SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS USING MULTICOMPONENT APPROACH

THESIS SUBMITTED

TO

NATIONAL INSTITUTE OF TECHNOLOGY

WARANGAL

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

BY

KODAM SUJATHA

ROll NO. 701446

UNDER SUPERVISION OF

PROF. V. RAJESWAR RAO

DEPARTMENT OF CHEMISTRY

NATIONAL INSTITUTE OF TECHNOLOGY-WARANGAL

WARANGAL-506004, TELANGANA, INDIA

SEPTEMBER-2019

Dedicated to

…..My parents and guide

Dr. V. Rajeswar Rao
Professor
Email: vrajesw@yahoo.com

Department of Chemistry
National Institute of Technology
Warangal - 506 004
Telangana, India.

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis of New Heterocyclic Compounds using Multicomponent Approach"** submitted by **Ms. Kodam Sujatha** for the award of the degree of **Doctor of Philosophy in Chemistry**, National Institute of Technology, Warangal (T.S), under my guidance and supervision. This work has not been submitted earlier either in part or in full for any degree or diploma of any other University.

(Prof. V. Rajeswar Rao)

DECLARATION

I hereby declare that the matter embodied in this thesis entitled **"Synthesis of New Heterocyclic Compounds using Multicomponent Approach"** is based entirely on the results of the investigations and research work carried out by me under the supervision of **Prof. V. Rajeswar Rao**, Department of Chemistry, National Institute of Technology-Warangal. I declare that this work is original and has not been submitted in part or full, for any degree or diploma to this or any other university.

(Kodam Sujatha)

Date: Warangal

Place: September, 2019

ACKNOWLEDGEMENTS

The work presented in this thesis would not have been possible without help many people. I take this opportunity to extend my sincere gratitude and appreciation to all those who made this Ph. D., thesis possible.

It gives me immense pleasure and delight to express my deep sense of gratitude to my teacher and research guide ***Dr. V. Rajeswar Rao***, Professor, Former Head Department of Chemistry, National Institute of Technology, Warangal for his inspiring and valuable guidance. His unfailing attention, constant encouragement and co-operation have helped me in attaining my goal. It would have been impossible to achieve this goal without his support and valuable advice. I consider myself fortunate that he has given me a significant acceleration to my career. I will be thankful to him throughout my lifetime.

I am greatly indebted to ***Prof. N. V. Ramana Rao***, Director, National Institute of Technology, Warangal for allowing me to submit my research work in the form of a thesis. I express my gratitude to ***Prof. T. Srinivasa Rao*** and ***Prof. G. R. C. Reddy***, former Directors, National Institute of Technology, Warangal for giving me the opportunity to carry out the research work.

My special thanks to ***Prof. P. V. Srilakshmi,*** Head, Department of Chemistry and ***Prof. K. V. Gobi, Prof. B. Rajitha,*** former Heads, Department of Chemistry, National Institute of Technology, Warangal for their valuable advice and support.

I express my sincere thanks to the Doctoral Scrutiny Committee (DSC) members, ***Prof. P. V. Srilakshmi, Dr. K. Hariprasad***, Department of Chemistry and ***Prof. J. V. Ramana Murthy***, Department of Mathematics for their support and encouragement.

I take this opportunity to express thanks to ***Prof. A. Ramachandraiah***, ***Prof. K. Laxma Reddy, Dr. Vishnu Shanker***, ***Dr. Venkatathri Narayanan***, ***Dr. D. Kashinath***, ***Dr. B. Srinivas, Dr. Raghu Chitta, Dr. S. Nagarajan, Dr. M. Raghasudha, Dr. C. Jugun Prakash, Dr. Ravinder Pawar*** for their suggestions and encouragement. It also an appropriate time to remember all my teachers and professors who helped me at various stages of my education carrier and encouraged me to reach this level.

I wish to express my sincere thanks to ***Dr. Kesava Rao D S*** for his valuable advice in drafting my thesis.

Financial assistance from the Government of India, Ministry of Human Resource Development ***(MHRD)*** in the form of fellowship is gratefully acknowledged.

It is a pleasant task to thank all my seniors ***Dr. Tewodros Birhanu, Dr. R. Rajkumar, Dr. B. Thirupaiah, Dr. V. Krishnaiah and Dr. P. Srinivas*** for their encouragement throughout my research work.

I am thankful to all my fellow research scholars, ***Dr. K. Vimal Kumar, Dr. B. Janardhan, Dr. B. Rajitha, Dr. S. Kanaka Raju, Dr. M. Satyanarayana, Dr. T. Surendar, Dr. G. Ramesh, Dr. V. Ravi Babu, Dr. L. Suresh, Dr. P. Sagar Vijay Kumar, M. Narsimha Reddy, Dr. K. Koteshwara Reddy, Dr. T. Surender, Dr. T. Ramesh, Dr. G. Srinivasa Rao, Dr. A. Ajay Kumar, K. Venkata Bharath, M. Srikanth, J. Parameswara chary, Ch. Raju, T. Dhanunjay Rao, N. Satyanarayana, A. Rajini, B. Mayuri, K. Vijendar reddy, P. Babji, N. Sunil Kumar, P. Mahendranath, P. Vinay, A. Bhargava Sai, B. Sowmya, T. Sanjay, K. Ramaiah, M. Venkanna, M. Saikumar, A. Naveen Reddy, Ch. Suman, R. Hithavani, R. Venkatesh, S. Suresh, K. Shekar, G. Ambedhkar, K. Satish, G. Sivaparvathi, G. Srinath, G. Sripal Reddy, M. Sirisha, P. Venkatesham, B. Sravanthi*** for their help and creating a nice atmosphere in and outside of the laboratory.

Finally, I would like to express my deep sense of gratitude to my family members Parents ***Kodam Ilaiah*** and ***Sarojana***, my brother ***Ravinder***, sisters **Vanitha, Sunitha** and **Sumalatha**, brothers-in-laws **Laxman, Srinivas and Kiran kumar,** sister-in-law ***Lavanya***, nephews **Vinay, Vikas, Kaushik, Rishith** and **Venkata Vivek** for their constant support, cooperation, encouragement, inspiration, love and affection whose blessings made the journey worth effort. I owe everything to them.

Finally, I take this opportunity to thank one and all who directly or indirectly helped me in completing this task.

(Kodam Sujatha)

TABLE OF CONTENTS

CHAPTER-I

A MICRO REVIEW ON MULTICOMPONENT CONDENSATION REACTIONS AND THEIR USES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

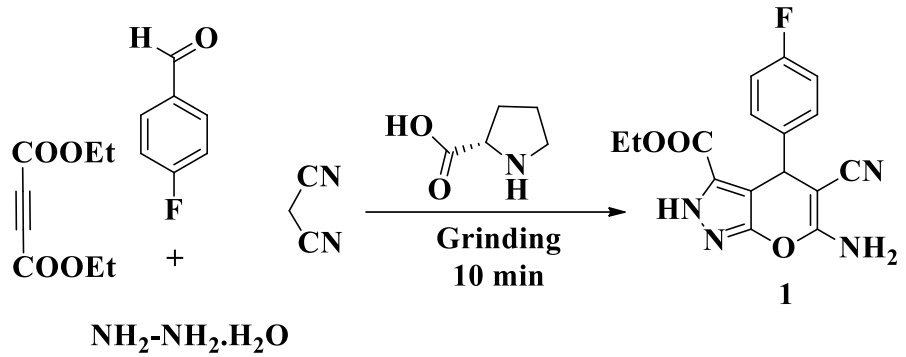
INTRODUCTION

In this chapter, a brief introduction to multicomponent reactions is presented.

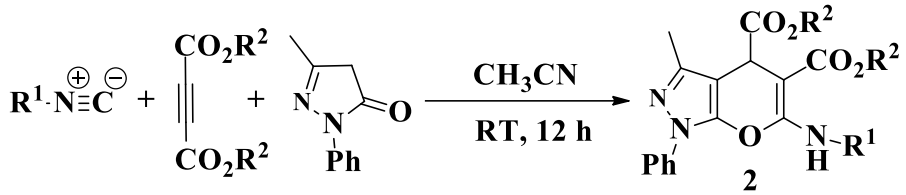
Multicomponent reactions (MCRs) are the chemical reactions which involve three or more reactants combine to form a product which retains a majority of the atoms of all the reactants. The MCRs provide rapid access to molecular diversity by combining several reactants into functionalized molecules. Hence, they drag greater attention in generating chemical molecules of drug type of heterocyclic systems. The MCRs have been known for over 160 years with the Strecker synthesis of α- amino cyanides in 1850 from which α-amino acids could be derived. During this period, some noteworthy achievements have been taken into account of the discovery of Biginelli condensation of ethyl acetoacetate, benzaldehyde and urea. Mannich reaction is an amino alkylation of acidic hydrogen of carbonyl compound using HCHO, 1^0 or 2^0 amine or NH_3. Passerine reaction is a reaction between isocyanide, aldehyde (or ketone) and carboxylic acid to form α-acyloxy amide. The reagents employed may be different molecules or they may be different functional groups of the same reagent. Planning of MCRs which results in giving many bonds at once is an important aspect in recent times to the organic chemists.[1(a-e)] This methods reduce time and costly purification process, as well as protection and deprotection steps. They show atom economy and they are inherently more environmentally benign.[2(a,b)] Speed, diversity, efficiency and environmental amiability are the key features of this class of reactions. MCRs follow green chemistry principles so that these are useful, effective green tools for the synthesis of organic transformations and complex drug molecules. These are mainly used for the formation of several bonds in a single step of operation.[3,4] The multicomponent reactions are important because of their utility in the synthesis of many heterocyclic compounds and new synthetic methodologies. The multicomponent reactions become more interesting area of research.

Recent Literature of Multi-Component Reactions

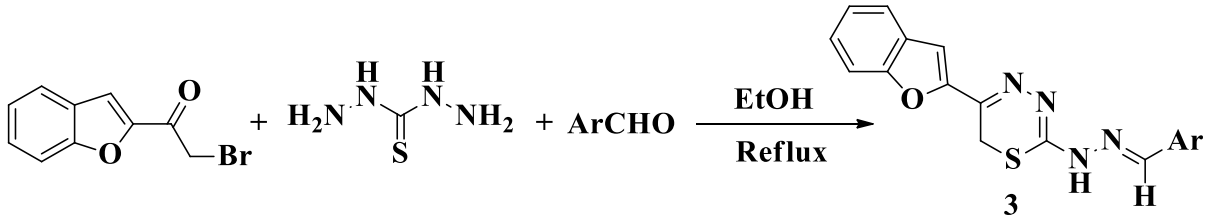
Ambethkar *et al.*[5] described the synthesis of **1** by condensation of 4-fluorobenzaldehyde with malononitrile, hydrazine hydrate and diethyl acetylenedicarboxylate. The reaction mixture was ground under solvent free condition and in the presence of L-proline.



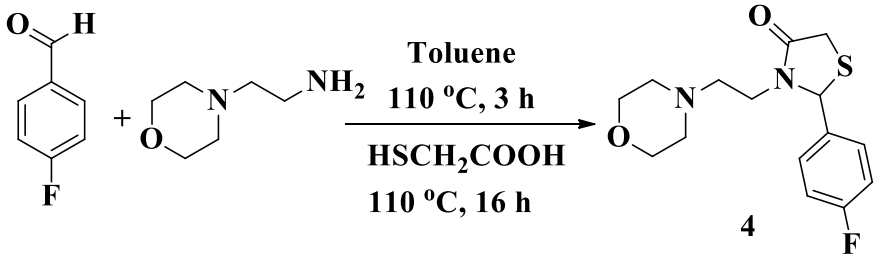
Shaabani *et al.*[6] reported the synthesis of 6-(cyclohexylamino)-1,4-dihydro-3-methyl-1-phenylpyrano[2,3-*c*]pyrazole-4,5-dicarboxylate (**2**) via a multicomponent reaction of phenyl-1*H*-pyrazol-5(4*H*)-one, dimethyl acetylenedicarboxylate and cyclohexyl isocyanide.



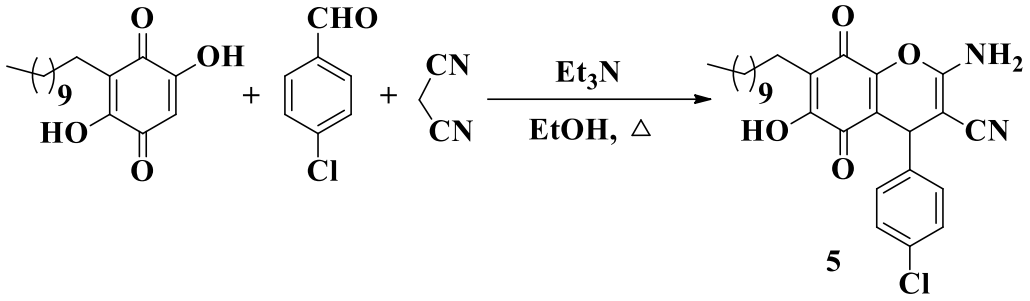
Ramagiri *et al.*[7] synthesized 5-(benzofuran-2-yl)-2-(2-(3,4,5-trimethoxybenzylidine)hydrazinyl)-6*H*-1,3,4-thiadiazine (**3**) from 2-(2-bromoacetyl)benzofuran, thiocarbohydrazide and 3,4,5-trimethoxybenzaldehyde in ethanol under reflux.



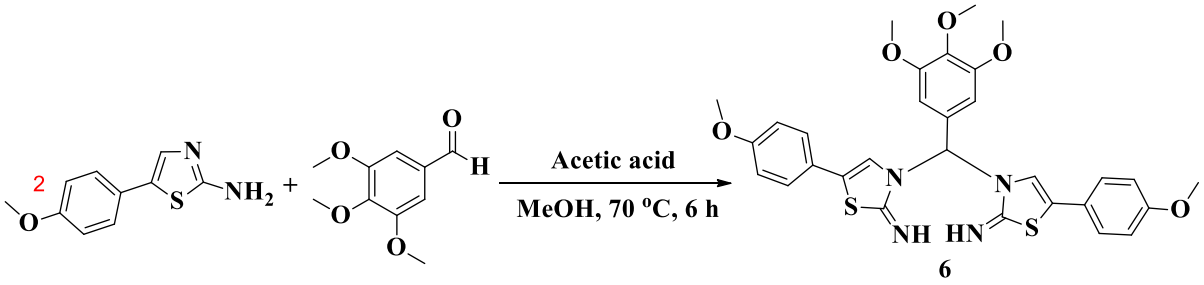
Gouvea *et al.*[8] synthesized 2-(4-fluorophenyl)-3-(2-morpholinoethyl)thiazolidin-4-one (**4**) from the reaction of 2-morpholinoethylamine, 4-fluorobenzaldehyde and mercaptoacetic acid.



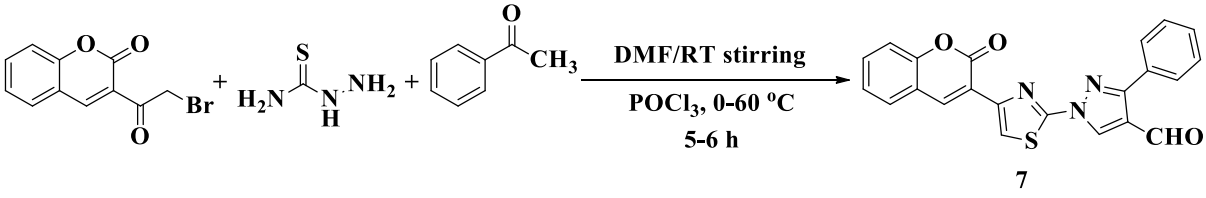
Martin-Acosta *et al.*[9] reported the synthesis of 2-amino-4-(4-chlorophenyl)-6-hydroxy-5,8-dioxo-7-undecyl-5,8-dihydro-4*H*-chromene-3-carbonitrile (**5**) by reacting embellin, 4-chlorobenzaldehyde and malononitrile in ethanol and triethylamine under reflux.



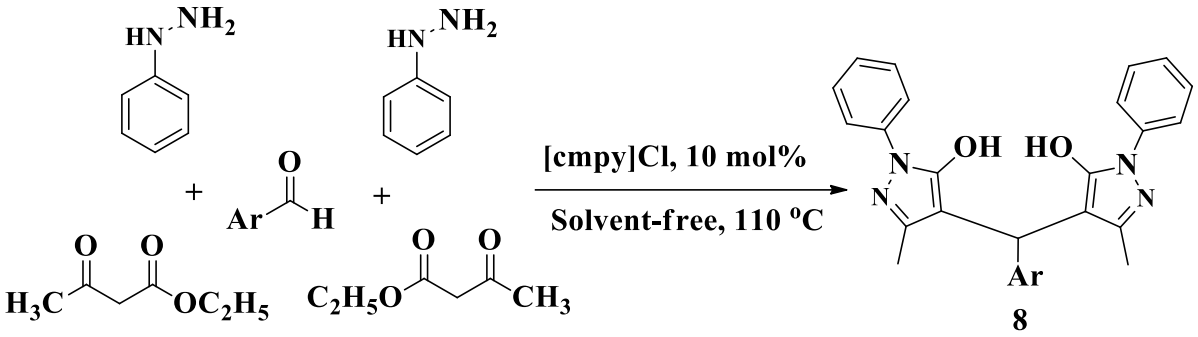
Synthesis of 3,3[1]-((3,4,5-trimethoxyphenyl)methylene)bis(5-(4-methoxyphenyl)thiazol-2(3*H*)-imine) was achieved by Abraham *et al.*[10]. In this reaction, 4-Methoxy phenyl-2-amino thiazole and 3,4,5-trimethoxy benzaldehyde were allowed to react in one-pot to afford **6**.



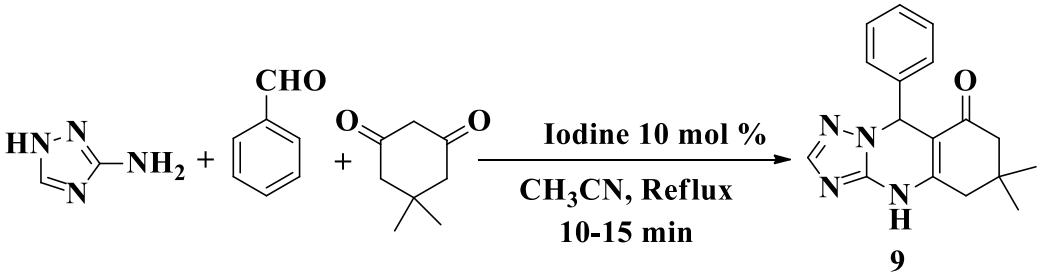
The compound **7** was synthesized by Vaarla *et al.*[11] through condensation of 3-(2-bromoacetyl)coumarin, hydrazinecarbothioamide and phenyl methyl ketone using Vilsmeier-Haack reaction.



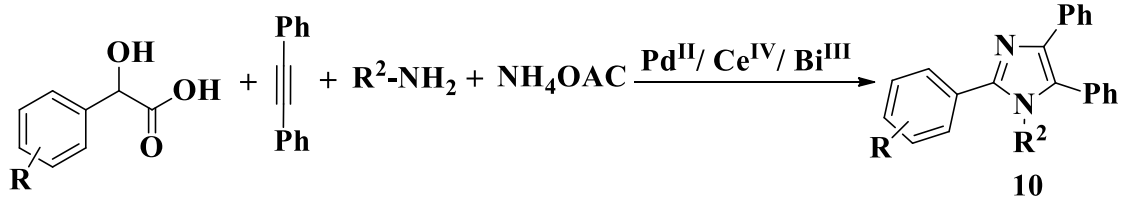
Moosavi-Zare *et al.*[12] described 4-4[1]-(arylmethylene)-bis(3-methyl-1-phenylpyrazol-5-ols) (**8**) via a multicomponent condensation of phenyl hydrazine, ethylacetoacetate and aromatic aldehyde using 1-(carboxymethyl)pyridinium chloride {[cmpy]Cl} as homogenous organic catalyst under solvent-free condition.



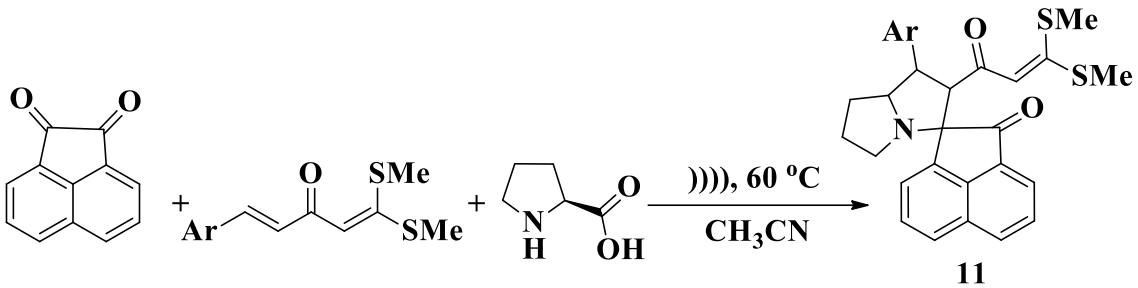
Puligoundla *et al.*[13] synthesized **9** by applying multicomponent reaction of 3-amino-1,2,4-triazole, benzaldehyde and dimedone with molecular iodine as a catalyst.



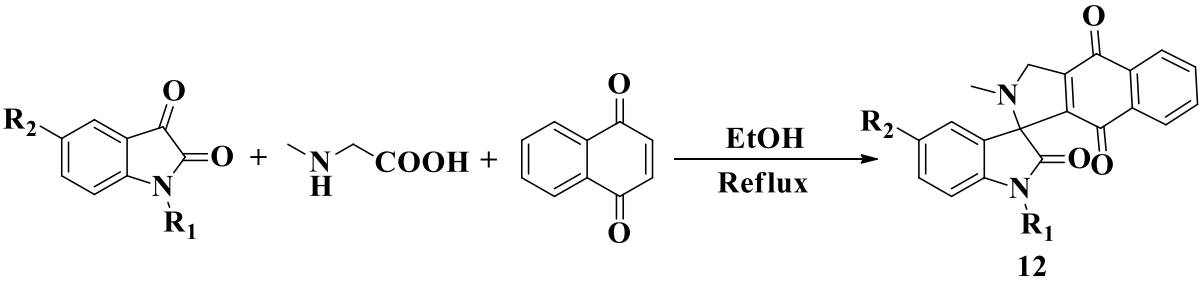
Synthesis of 2,4,5-triphenyl-1*H*-imidazoles (**10**) by Sun *et al.*[14] via a multicomponent reaction of 1,2-diphenylacetylene, 2-hydroxyl phenyl acetic acid, primary amine and ammonium acetate. Pd(II)/ Ce(IV)/ Bi(III) catalysts were used.



Synthesis of 2^1-(3,3,-bis(methylthio)acryloyl)-1^1,2^1,5^1,6^1,7^1,$7a^1$-hexahydro-2*H*-spiro[acenaphthalene-1,3^1-pyrrolizin]-2-one (**11**) via a multicomponent reaction of α-aroylidine ketene dithioacetals, acenaphthalene-1,2-dione and L-proline in acetonitrile under ultrasound irradiation was described by Thimmarayaperumal *et al.*[15]

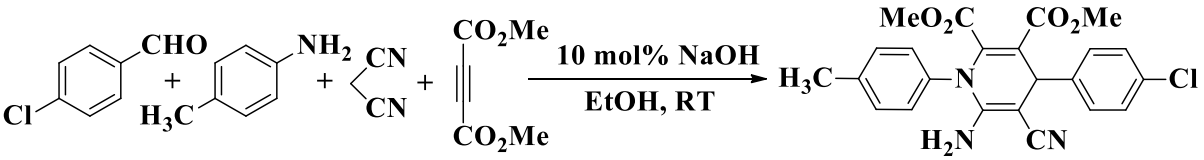


2-Methyl-2,3-dihydrospiro[benzo[f]isoindole-1,3[1]-indoline]-2[1]-4,9-trione (**12**) was reported by Bhaskar *et al.*[16] through a multicomponent reaction of isatin, sacrosine and 1,4-naphthoquinone in ethanol under reflux.



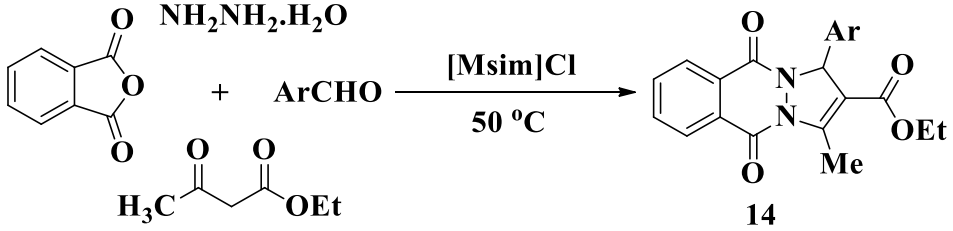
12

Pal *et al.*[17] reported the synthesis of dimethyl 5[1]-amino-4-chloro-6[1]-cyano-4[11]-methyl-1[1],4[1]-dihydro-[1,1[1],4[1],1[11]-terphenyl]-2[1],3[1]-dicarboxylate (**13**) via a multicomponent reaction of 4-chlorobenzaldehyde, malononitrile, 4-methylaniline and dimethyl acetylenedicarboxylate in the presence of 10% ethanolic sodium hydroxide.



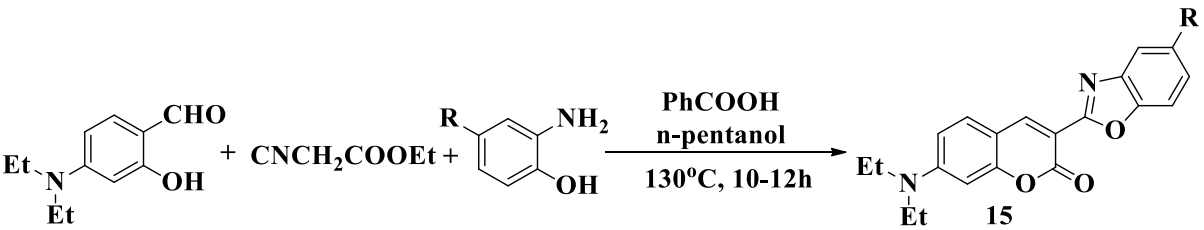
13

Ethyl-3-methyl-5,10-dioxo-1-phenyl-5,10-dihydro-1*H*-pyrazole[1,2-*b*]phthalazines-2-carboxylate (**14**) was synthesized by Pouramiri *et al.*[18] by condensing ethyl acetoacetate, aromatic aldehyde, phthalic anhydride and hydrazine hydrate in an ionic liquid.



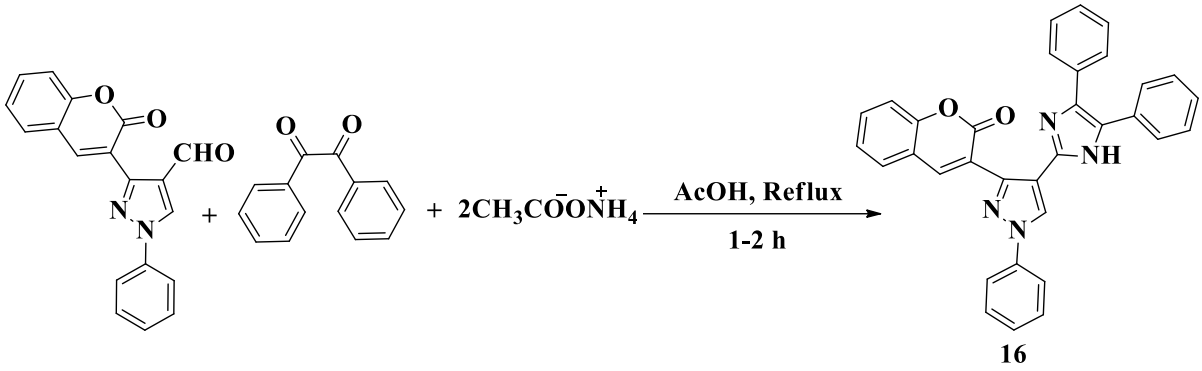
14

Ye *et al.*[19] synthesized **15** with the reaction of 4-diethylamino salicylaldehyde with ethyl cyanoacetate and 4-substituted 2-amino phenol in n-pentanol and benzoic acid under reflux.



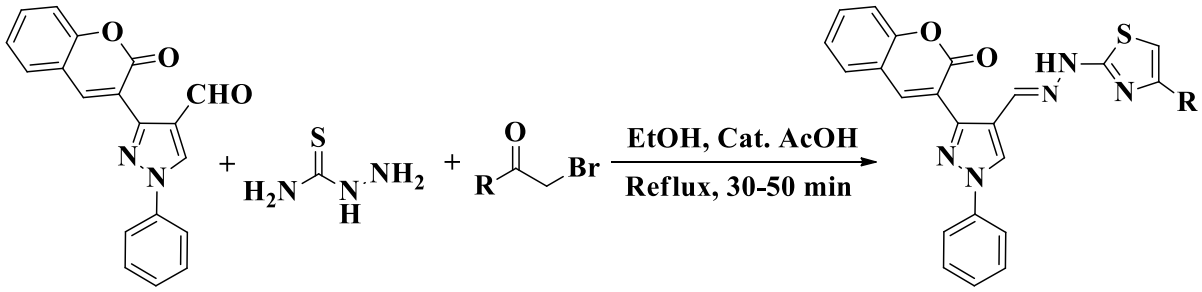
15

Chaudhry *et al.*[20] synthesized compound **16** from 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole, benzil and ammonium acetate in acetic acid.



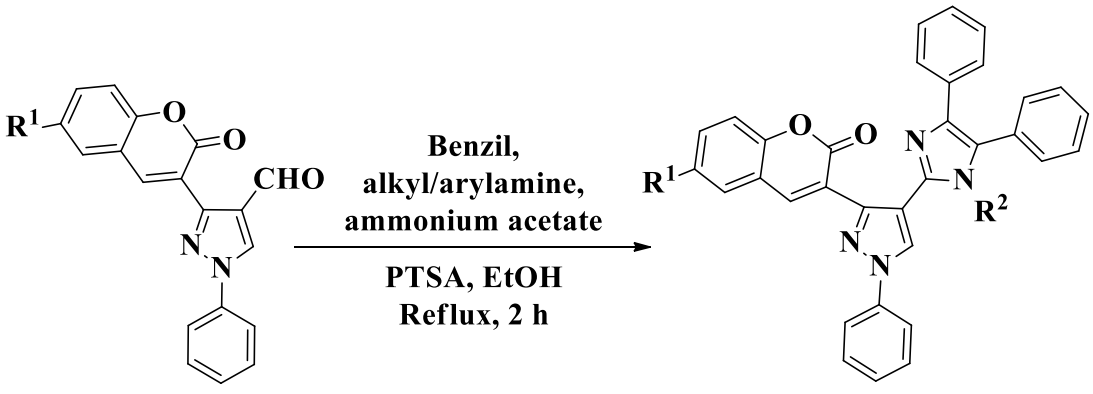
16

Gondru *et al.*[21] synthesized **17** through condensation of 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole, hydrazinecarbothioamide and various α-halo carbonyl compounds under following given conditions



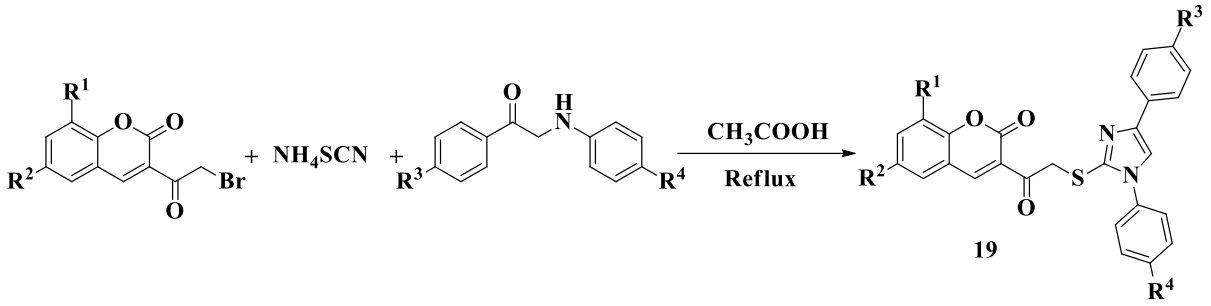
17

Chaudhry *et al.*[22] synthesized 4a, 8a-dihydro-2*H*-chromen-2-ones (**18**) through a reaction between substituted 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole, benzil, ammonium acetate and 4-chloro aniline in presence of PTSA in ethanol.

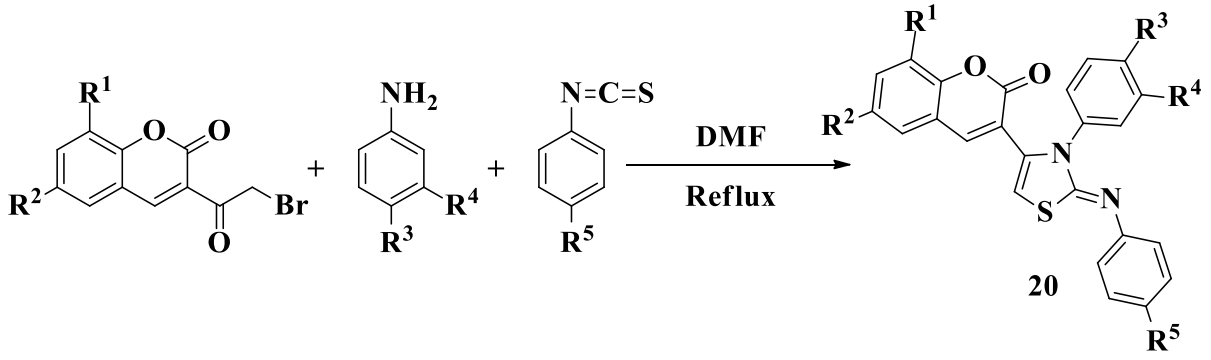


18

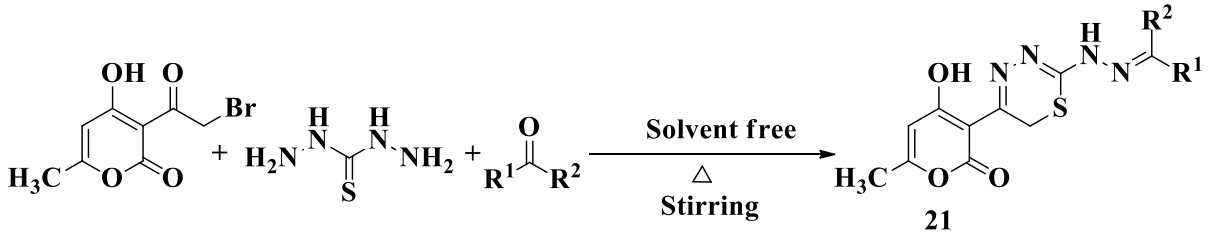
Compounds **19** were synthesized by Ramagiri *et al.*[23] by condensation of 3-(2-bromoacetyl)coumarin, NH_4SCN and phenacylaniline in CH_3COOH.



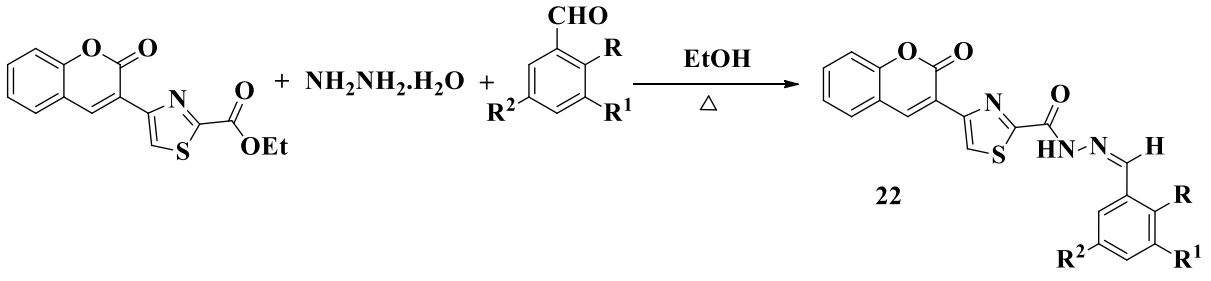
Ramagiri *et al.*[24] synthesized **20** in one pot condensation of 3-(2-bromoacetyl)coumarins, primary amines and phenyl isothiocyanate in presence of DMF.



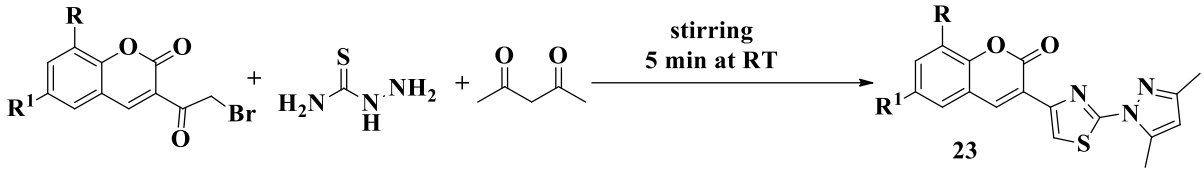
Penta *et al.*[25] devised a synthesis for compounds **21** starting from bromo dehydro acetic acid, thicarbohydrazide and carbonyl compounds.



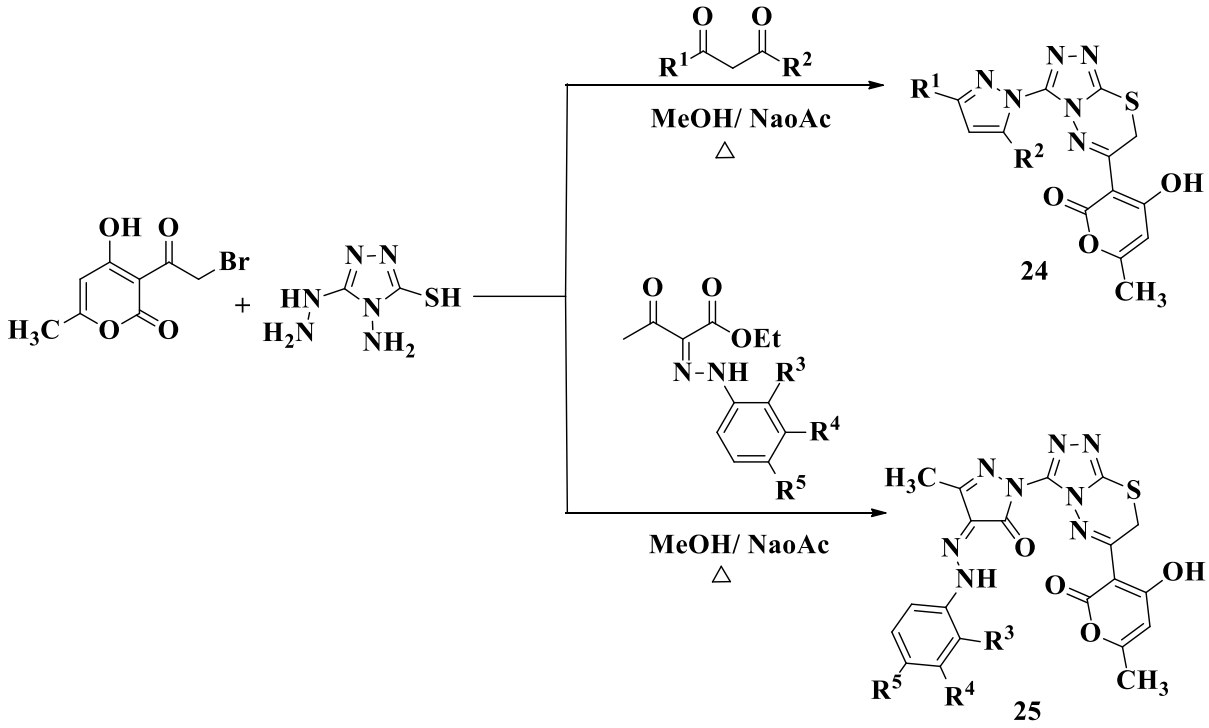
Products **22** synthesis was given by Wang *et al.*[26] through a condensation of 2-carbethoxy-4-(2*H*-1-benzopyran-2-one-3-yl)thiazole, NH_2-$NH_2.H_2O$ and substituted araldehydes.



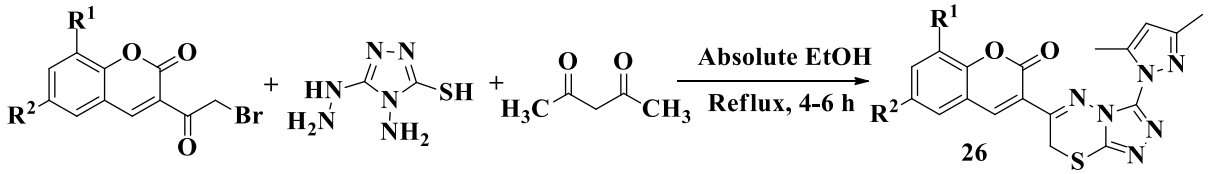
Srimanth *et al.*[27] synthesized compounds **23** by reacting acetyl acetone, thiosemicarbazide and 3-(2-bromoacetyl)coumarins.



Penta *et al.*[28] synthesized compounds **24** and **25** by condensation of bromo dehydro acetic acid with purpald and acetyl acetone or ethyl 2-(2-aryl hydrazono)-3-oxo butanoates in methanol and sodium acetate.

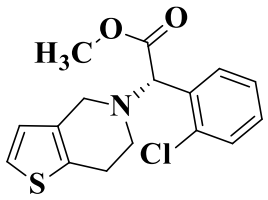


Pavurala *et al.*[29] synthesized **26** by the condensation of 3-(2-bromo acetyl)coumarins, purpald and acetyl acetone.



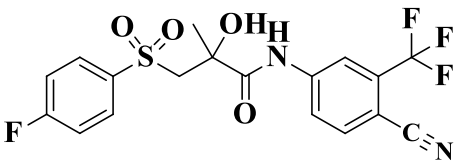
Applications in generating drugs through MCRs:

By using MCR approach (S)-Clopidogrel (**27**) and bicalutamide[30] (**28**) were synthesized by using Ugi and Passerine reactions.[31,32]



(S)-Clopidogrel

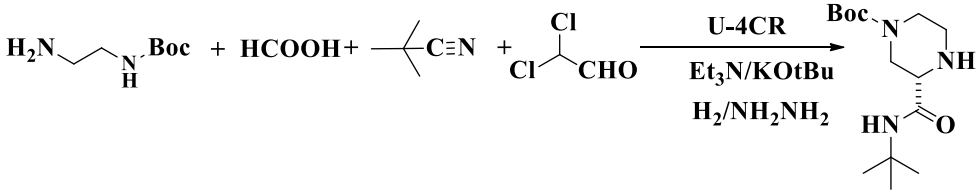
27



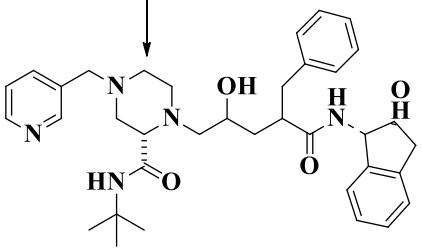
Bicalutamide

28

Crixivan intermediate (**29**) synthesis has been described by Rossen *et al.*[33] It is a HIV-protease inhibitor. The heterocyclic ring piperazine was obtained from N-Boc-ethylenediamine, dichloroacetaldehyde, tert-butyl isocyanide and formic acid.



29

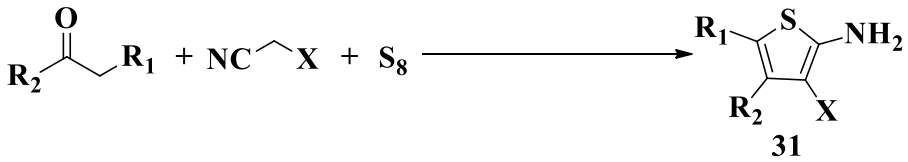


30

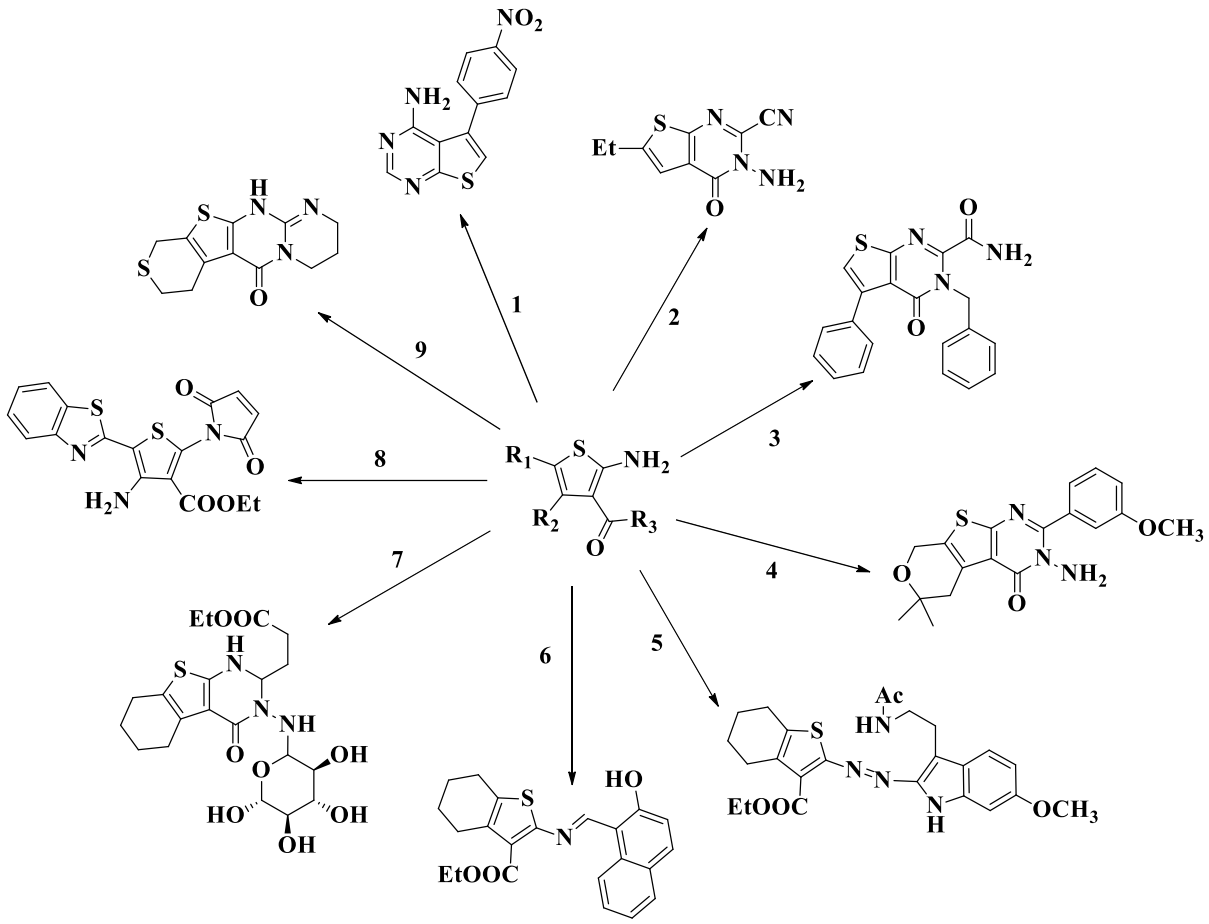
Applications in combinatorial chemistry:

Small drug like molecules are synthesized by combinatorial chemistry. Combinatorial chemistry involves the rapid synthesis of the computer simulation of a large number of different but simultaneously related molecules. Combinatorial method can give many molecules at a time.[34] Three points of diversity (R_1, R_2 and R_3) of molecules can generate $NR_1XNR_2XNR_3$ possible structures. Where NR_1, NR_2 and NR_3 are the different number of substituents utilized as shown below.

Diversity of secondary reactions based on the Gewald-MCR:



31



Chemical diversity, drugs and drug like structures, good pharmaco kinetic properties, preparative yields, environmentally benign and atom-economic are some features which draw my attention to exploit MCRs in developing new methodologies and generating a library of different heterocyclic entities.

PRESENT WORK

From the above mentioned review, it can be understood that MCRs play an important role in synthesizing heterocyclic compounds.

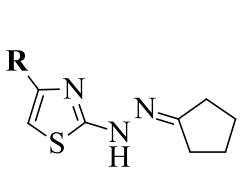
The research work is intended to develop efficient synthetic methodologies for new heterocyclic compounds by the application of MCRs.

Objectives of the research:

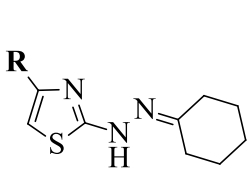
1. To establish new methods for the synthesis of heterocyclic compounds.
2. Identification of structures of new compounds by spectral data.

Chapter-I deals with review on multi-component condensation reactions and their use in the synthesis of biologically active compounds.

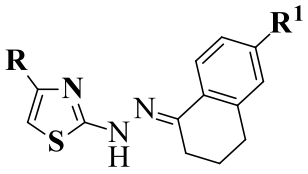
Chapter-II describes the synthesis of following thiazole derivatives without using solvent.



32

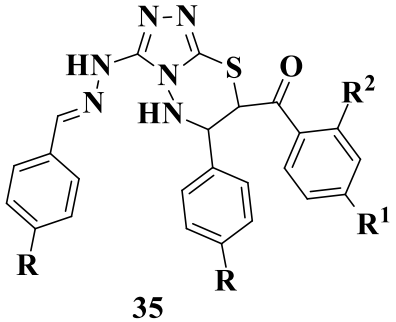


33

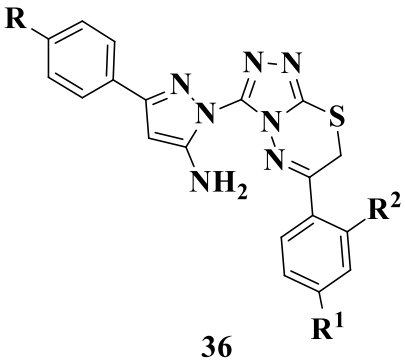


34

Chapter-III reports an efficient multicomponent synthesis of 35 and 36 compounds.

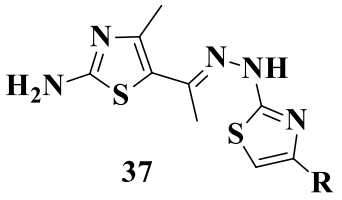


35

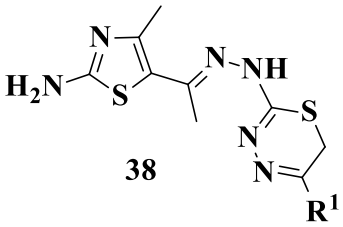


36

Chapter-IV deals with one step multicomponent synthesis of compounds **37** and **38**.

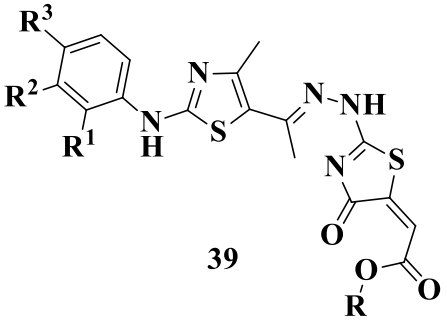


37

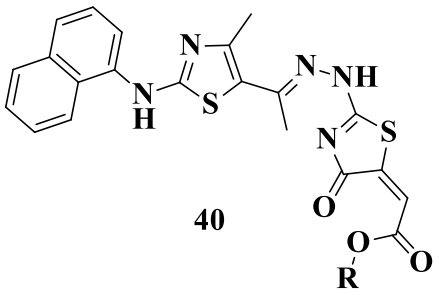


38

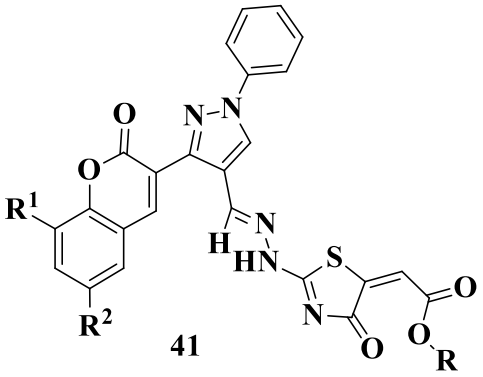
Chapter-V portrays the one-vessel, five component synthesis of the following new heterocyclic compounds **39**, **40, 41** and **42**.



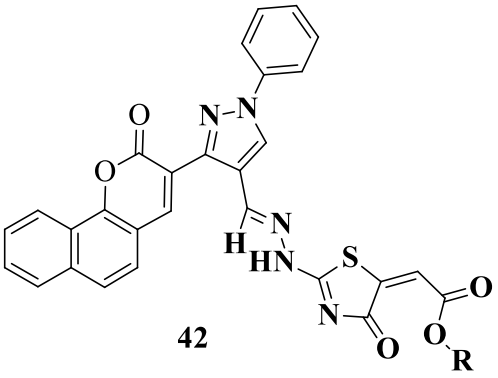
39



40

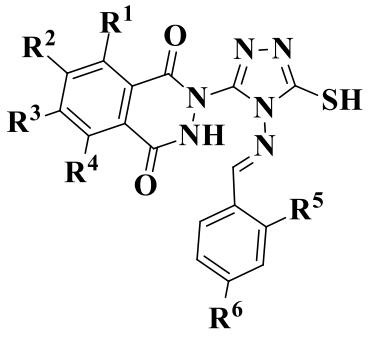


41



42

Chapter-VI deals with the one-vessel three component synthesis of **43** compounds.



43

Spectral characteristics of the compounds **32** to **43** were given.

References:

[1] (a) Zhu, J.; Bienayme, H. 'Multicomponent Reactions', 1st Edition; *Wiley-VCH, Weinheim, Germany*. **2005**, 7-8. (b) Ngouansavanh, T.; Zhu, J. *Angew Chem Int Ed.* **2007**, *46*, 5775-5778. (c) Laurent, E. K.; Marie, G.; Laurence, G.; Julie, O. *Org. Lett.* **2006**, *8*, 4019-4021. (d) Tempest, P. A. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776-788. (e) Lu, K.; Luo, T.; Xiang, Z.; You, Z.; Fathi, R.; Chen, J.; Yang, Z. *J. Comb. Chem.* **2005**, *7*, 958-967.

[2] (a) Trost, B. M. *Angew Chem Int Ed.* **1995**, *107*, 285-307. (b) Trost, B. M. *Angew Chem Int Ed.* **1995**, *34*, 259-281.

[3] Jangale, A. D.; Dalal, D. S. *Chemistry Select.* **2019**, *4*, 1323-1329.

[4] Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969-4009.

[5] Ambethkar, S.; Padmini, V.; Bhuvanesh, N. *J. Adv. Res.* **2015**, *6*, 975-985.

[6] Shaabani, A.; Sarvary, A.; Rezayan, A. H.; Keshipour, S. *Tetrahedron*. **2009**, *65*, 3492-3495.

[7] Ramagiri, R. K.; Vaarla, K.; Vedula, R. R. *Synth. Commun.* **2016**, *46*, 1499-1506.

[8] Gouvea, D. P.; Vasconcellos, F. A.; Berwaldt, G. A.; Neto, A. C. P. S.; Fischer, G.; Sakata, R. P.; Almeida, W. P.; Cunico, W. *Eur. J. Med. Chem.* **2016**, *118*, 259-265.

[9] Martin-Acosta, P.; Haider, S.; Amesty, A.; Aichele, D.; Jose, J.; Etevez-Braun, A. *Eur. J. Med. Chem.* **2018**, *144*, 410-423.

[10] Abraham, R.; Periakaruppan, P. *Tetrahedron Lett.* **2017**, *58*, 3057-3063.

[11] Vaarla, K.; Kesharwani, R. K.; Santosh, K.; Vedula, R. R.; Koramraju, S.; Toopurani, M. K. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5797-5803.

[12] Moosavi-Zare, A. R.; Zolfigol, M. A.; Noroozizadeh, E.; Khaledian, O.; Shaghasemi, B. S. *Res Chem Intermed*. **2016**, *42*, 4759-4772.

[13] Puligoundla, R. G.; Karnakanti, S.; Bantu, R.; Kommu, N.; Kondra, S. B.; Nagarapu, L. *Tetrahedron Lett.* **2013**, *54*, 2480-2483.

[14] Sun, W.; Zhang, M.; Li, P.; Li, Y. *Synthesis.* **2019**, *51*, A-J.

[15] Thimmarayaperumal, S.; Shanmugam, S. *New J. Chem.* **2018**, *42*, 4061-4066.

[16] Bhaskar, G.; Arun, Y.; Balachandran, C.; Saikumar, C.; Perumal, T. P. *Eur. J. Med. Chem.* **2012**, *51*, 79-91.

[17] Pal, S.; Choudhury, L. H.; Parvin, T. *Synth. Commun.* **2013**, *43*, 986-992.

[18] Pouramiri, B.; Far, R. G.; Zahedifar, M. *Chem Heterocycl Compd.* **2018**, *54*, 1056-1060.

[19] Ye, F. F.; Gao, J. R.; Sheng, W. J.; Jia, J. H. *Dyes Pigm.* **2008**, *77*, 556-558.

[20] Chaudhry, F.; Naureen, S.; Huma, R.; Shaukat, A.; al-Rashida, M.; Asif, N.; Ashraf, M.; Munawar, M. A.; Khan, M. A. *Bioorg Chem.* **2017**, *71*, 102-109.

[21] Gondru, R.; Banoth, J.; Thatipamula, R. K.; Hussain SK, A.; Bavantula, R. *RSC Adv.* **2015**, *5*, 33562-33569.

[22] Chaudhry, F.; Choudhry, S.; Huma, R.; Ashraf, M.; al-Rashida, M.; Munir, R.; Sohail, R.; Jahan, B.; Munawar, M. A.; Khan, M. A. *Bioorg Chem.* **2017**, *73*, 1-9.

[23] Ramagiri, R. K.; Thupurani, M. K.; Vedula, R. R. *J. Heterocycl. Chem.* **2015**, *52*, 1713-1717.

[24] Ramagiri, R. K.; Vedula, R. R. *Synth. Commun.* **2014**, *44*, 1301-1306.

[25] Penta, S.; Vedula, R. R. *J. Sulphur Chem.* **2011**, *32*, 327-333.

[26] Wang, G.; He, D.; Li, X.; Li, J.; Peng, Z. *Bioorg Chem.* **2016**, 167-174.

[27] Vedula, R. R.; Srimanth, K. *J. Chem. Research (S).* **2002**, 420-421.

[28] Penta, S.; Gadidasu, K. K.; Basavoju, S.; Rao, V. R. *Tetrahedron Lett.* **2013**, *54*, 5663-5666.

[29] Pavurala, S.; Vaarla, K.; Vedula, R. R. *J. Heterocycl. Chem.* **2015**, *52*, 1503-1505.

[30] (a) Gurbel, P. A.; O'Connor, C. M.; Cummings, C. C.; Serebruany, V. L. *Pharm. Res.* **1999**, *40*, 107-111. (b) Jacobson, A. K. *Best Pract. Res. Clin. Haematol.* **2004**, *17*, 55-64.

[31] Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synthesis.* **2008**, *24*, 4007-4011.

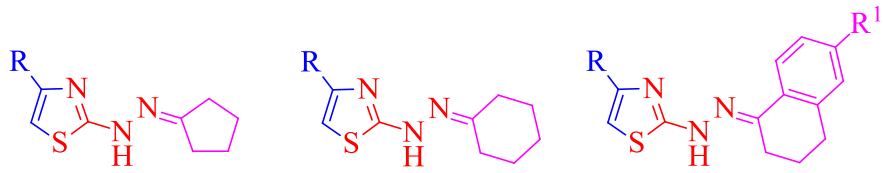
[32] Savi, P.; Zachayus, J. L.; Delesque-Touchard, N.; Labouret, C.; Herve, C.; Uzabiaga, M. F.; Pereillo, J. M.; Culouscou, J. M.; Bono, F.; Ferrara, P.; Herbert, J. M. *Proc Natl Acad Sci USA.* **2006**, *103*, 11069-11074.

[33] Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823-6826.

[34] Wang, K.; Kim, D.; Domling, A. *J. Comb. Chem.* **2010**, *12*, 111-118.

CHAPTER-II

A NOVEL ONE-POT EXPEDITIOUS SYNTHESIS OF 2,4-DISUBSTITUTED THIAZOLES VIA A THREE COMPONENT REACTION UNDER SOLVENT-FREE CONDITIONS



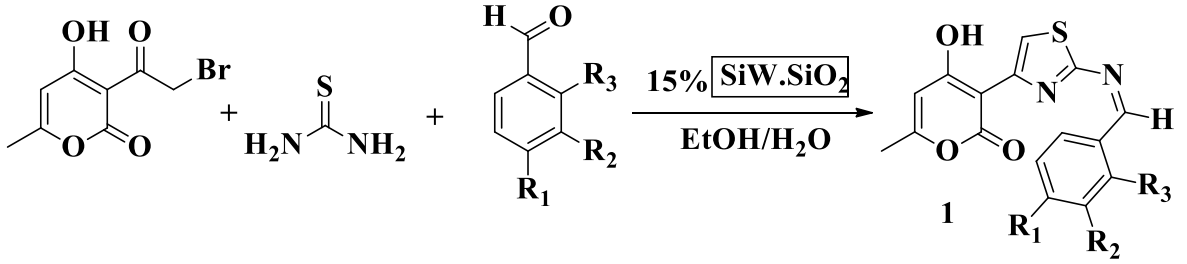
INTRODUCTION

Thiazoles are unique structural motifs, which are abundantly found in nature.[1] Due to their versatility, they are very important in the organic chemistry as well as in medicinal chemistry.[2]

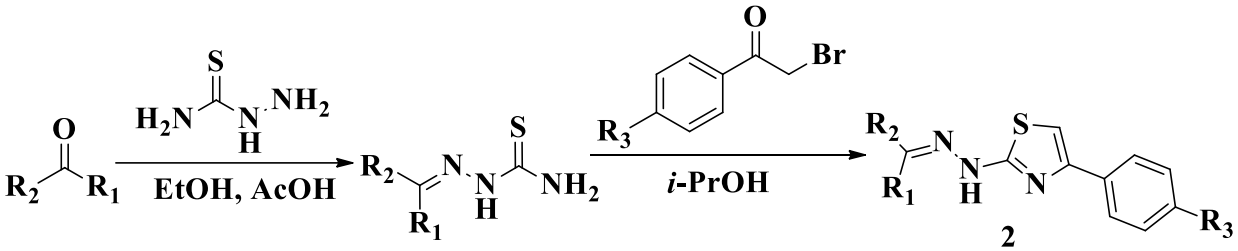
Thiazoles are present in some of the useful antibiotics[3] and synthetic organic molecules with biological activities like insecticides,[4] antibacterial,[5] florescent dyes,[6] anti-oxidant,[7] antimalarial,[8] anti HIV[9] and anti-cancer.[10]

The literature report indicated that there are various reports on the synthesis of thiazoles. Thiazole molecules are mainly synthesized from Hantzsch thiazole synthesis, in which carbonyl compounds and thiourea are starting materials. The various methods of synthesis of 2,4-disubstituted thiazoles are given.

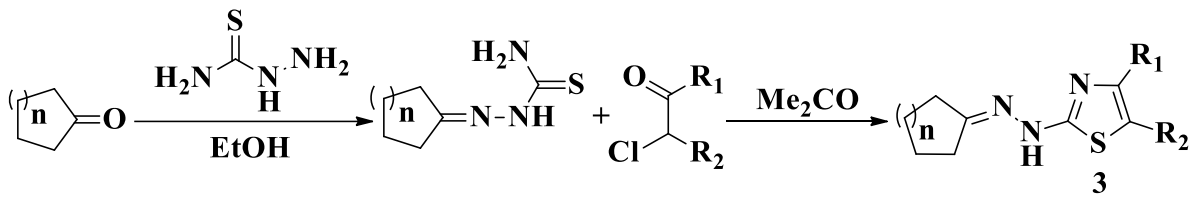
Houria Bouherrou *et al.*[11] reported the synthesis of substituted thiazole derivatives (**1**) using bromo dehydro acetic acid, thiourea and benzaldehydes.



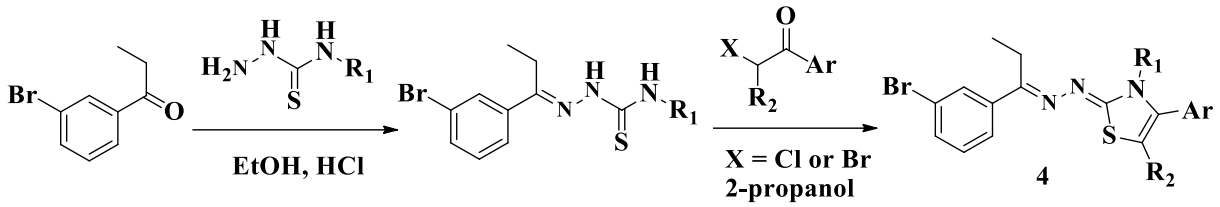
Lino *et al.*[12] synthesized 2-hydrazino-4-aryl thiazoles (**2**) by the condensation of aldehyde or ketone with thiosemicarbazide and phenacyl bromides. The intermediates are thiosemicarbazones of carbonyl compounds.



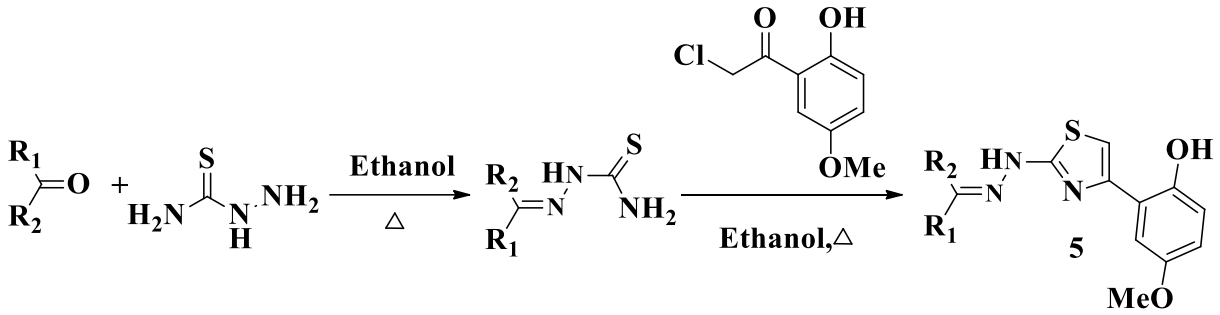
Cristina Nastasa *et al.*[13] synthesized aryliden-hydrazono thiazoles (**3**) by stepwise condensation of cycloalkylidine thiosemicarbazones with α or γ- halo carbonyl compounds.



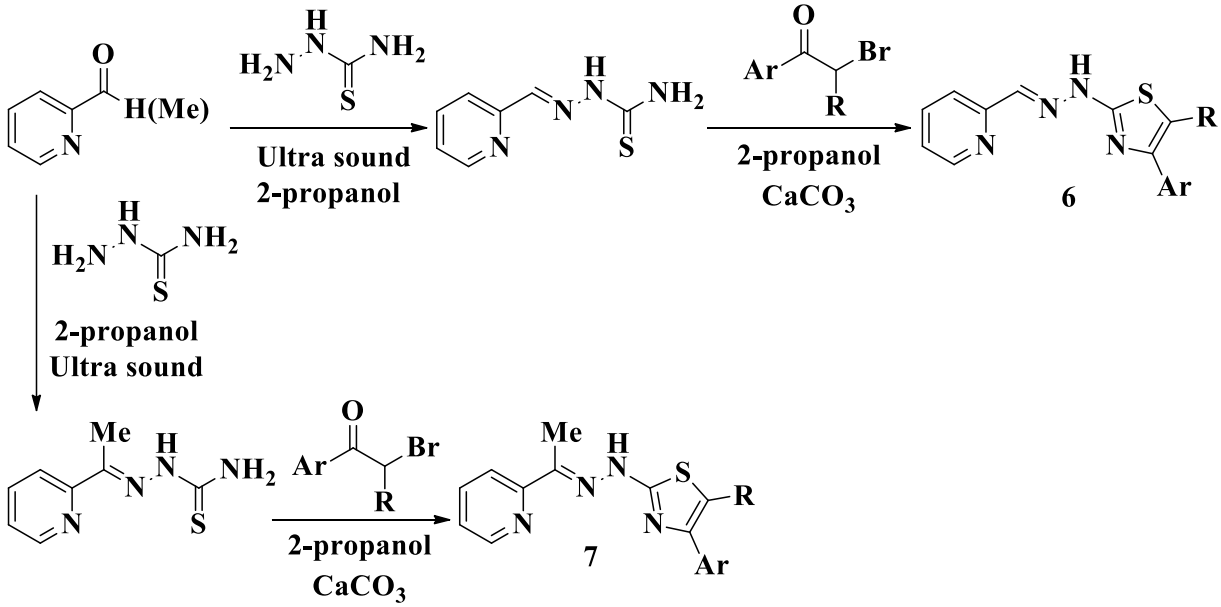
Moraes Gomes *et al.*[14] reported the 3-(bromo propiophenone)hydrazinyl-1,3-thiazoles (**4**) with the reaction of 1-(3-bromophenyl)propan-1-one, thiosemicarbazide and α-haloketones.



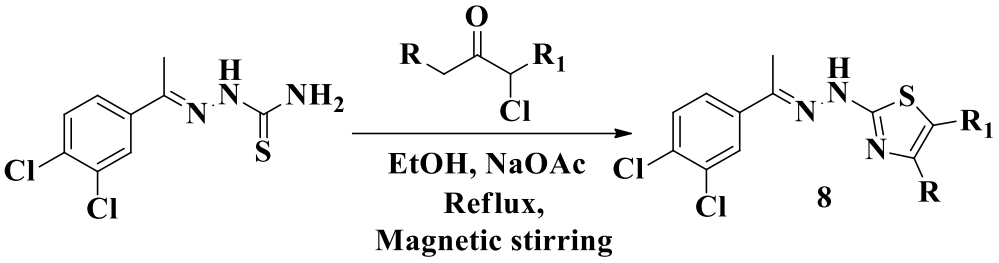
Various 2,4-disubstituted thiazoles (**5**) were synthesized by Maillard *et al.*[15] starting from thiosemicarbazone and 2-hydroxy-5-methoxy phenacyl chloride.



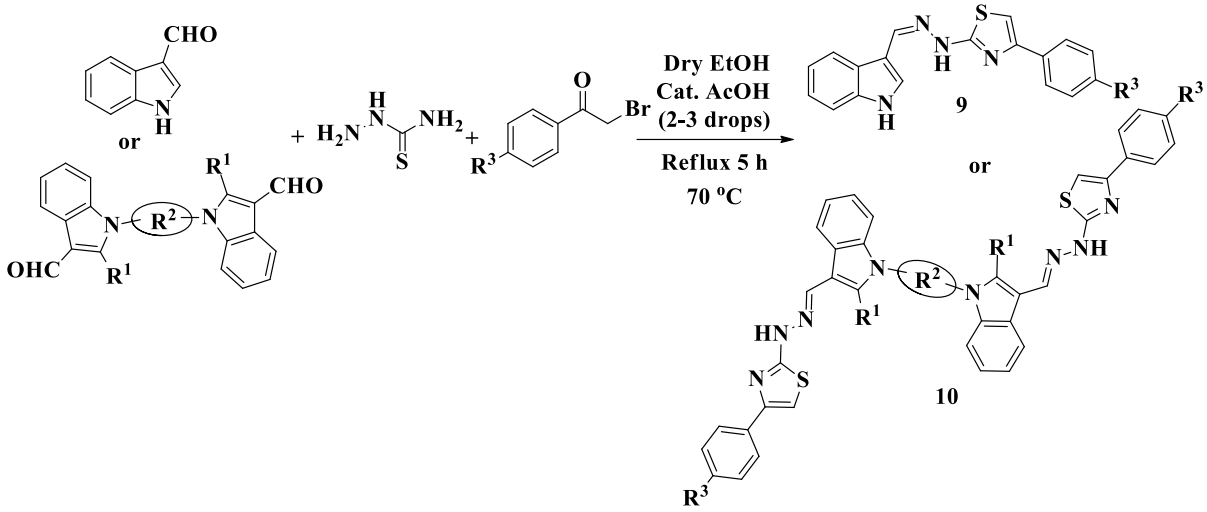
Cardoso *et al.*[16] synthesized thiazoles (**6**) and (**7**) by condensation of thiosemicarbazones derived from pyridine-2-aldehyde or 2-acetyl pyridine with phenacyl bromides.



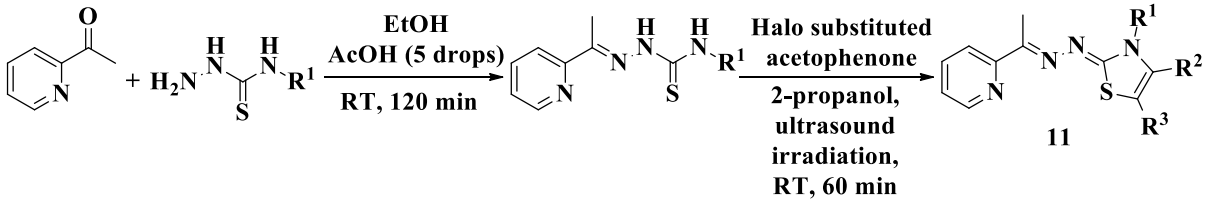
Oliveira Filho *et al.*[17] synthesized 2-[1-(3,4-dichlorophenyl)ethylidenohydrazinyl]-4-methyl-1,3-thiazoles. Reaction of thiosemicarbazide with 3, 4-dichloroacetophenone in ethanol and H_2SO_4 gave the thiosemicarbazone. The thiosemicarbazone was heated with 2-chloro substituted acetone or acetophenone to yield 2-[1-(3,4-dichlorophenyl)ethylidenohydrazinyl]-4-methyl-1,3-thiazoles (**8**).



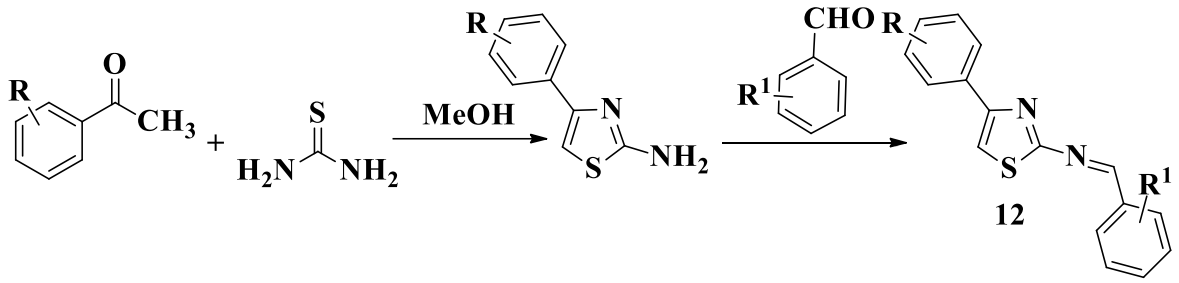
Mahmoodi *et al.*[18] described the synthesis of indol-3-ylhydrazinyl thiazoles. In this reaction thiosemicarbazone intermediate formed from indole-3-carbaldehyde and thiosemicarbazide was reacted with phenacyl bromides to give final compounds (**9**) and (**10**).



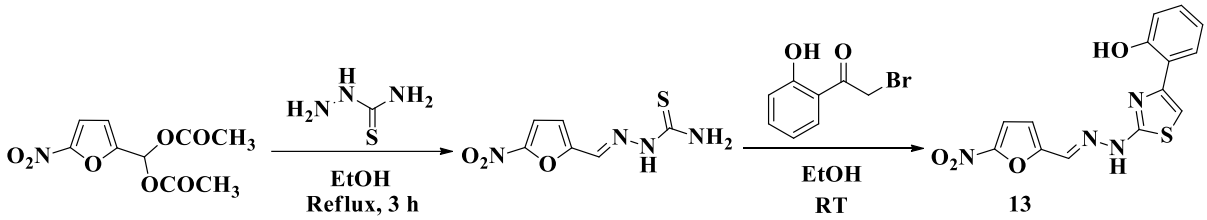
Synthesis of new thiazoles (**11**) was described by Silva *et al.*[19] by interaction of acetyl-2-pyridine and 4-methyl-3-thiosemicarbazide or 4-phenyl-3-thiosemicarbazide in ethanol and 5 drops of acetic acid leads to the formation of thiosemicarbazone. This upon treatment with halo substituted acetophenone in isopropanol under ultrasound irradiation yielded thiazole derivatives (**11**).



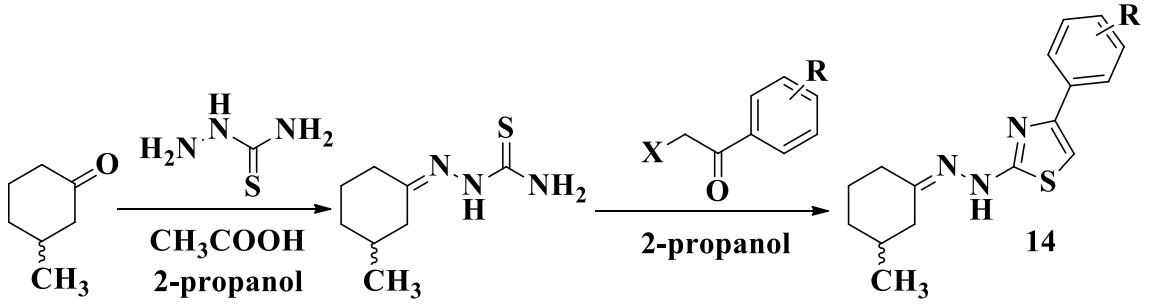
Synthesis of *N*-benzylidene-4-phenylthiazol-2-amines (**12**) was described by Brito *et al.*[20] starting from acetophenone, thiourea and iodine.



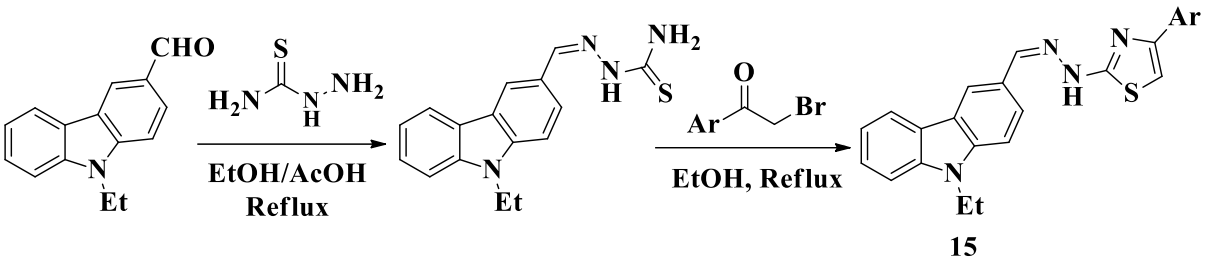
Synthesis of (*E*)-2-(2-(2-((5-nitrofuran-2-yl)methylene)hydrazinyl)thiazol-4-yl)phenol (**13**) by Yurttas *et al.*[21]. Reaction of 5-nitro-2-furaldehyde diacetate and thiosemicarbazide led to the formation of thiosemicarbazone. This on further cyclization with 2-hydroxy α-bromoarylethanone gave (*E*)-2-(2-(2-((5-nitrofuran-2-yl)methylene)hydrazinyl)thiazol-4-yl)phenol.



Chimenti *et al.*[22] synthesized 1-(4-arylthiazol-2-yl)-2-(3-methylcyclohexylidene)hydrazines (**14**) by the condensation of various phenacyl bromides with thiosemicarbazone derived by cyclohexanone.



Carbazole based thiazoles (**15**) were synthesized by Tran Nguyen *et al.*[23] Reaction of 9-ethyl-9*H*-carbazole-3-carbaldehyde with thiosemicarbazone in ethanol resulted in the formation of thiosemicarbazone. The thiosemicarbazone on further cyclocondensation with α-bromo ketones to yield title compounds



CURRENT WORK

Based on the importance of hydrazones and thiazoles as physiological active moieties we would like to synthesize the compounds having these two entities in a single molecular structure.

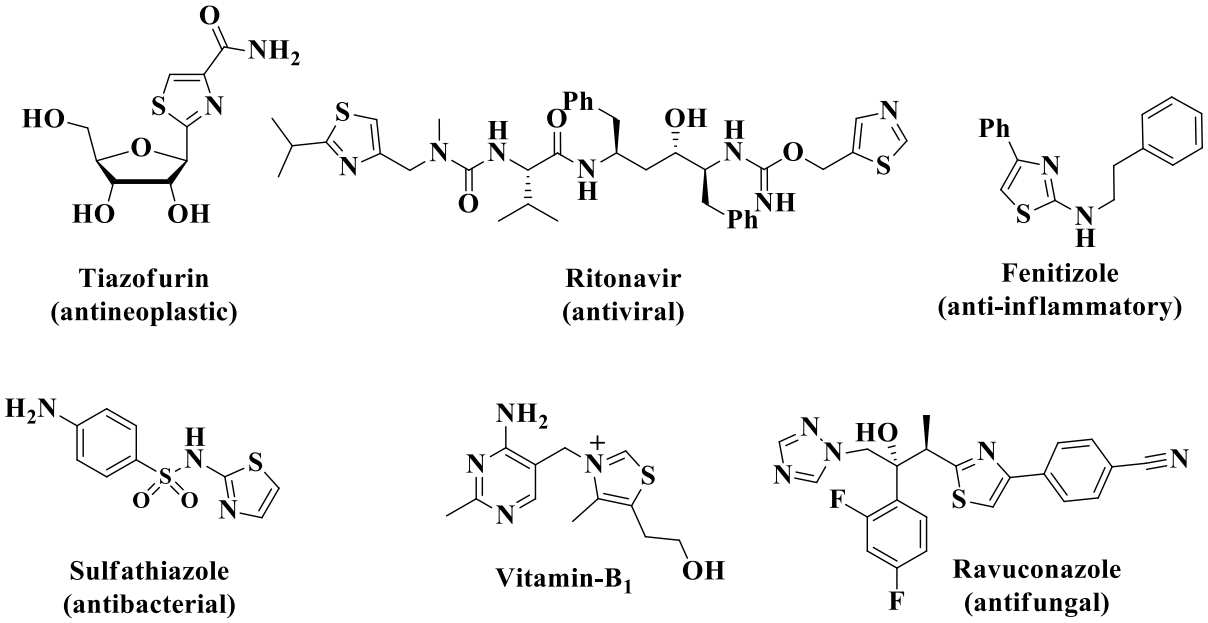
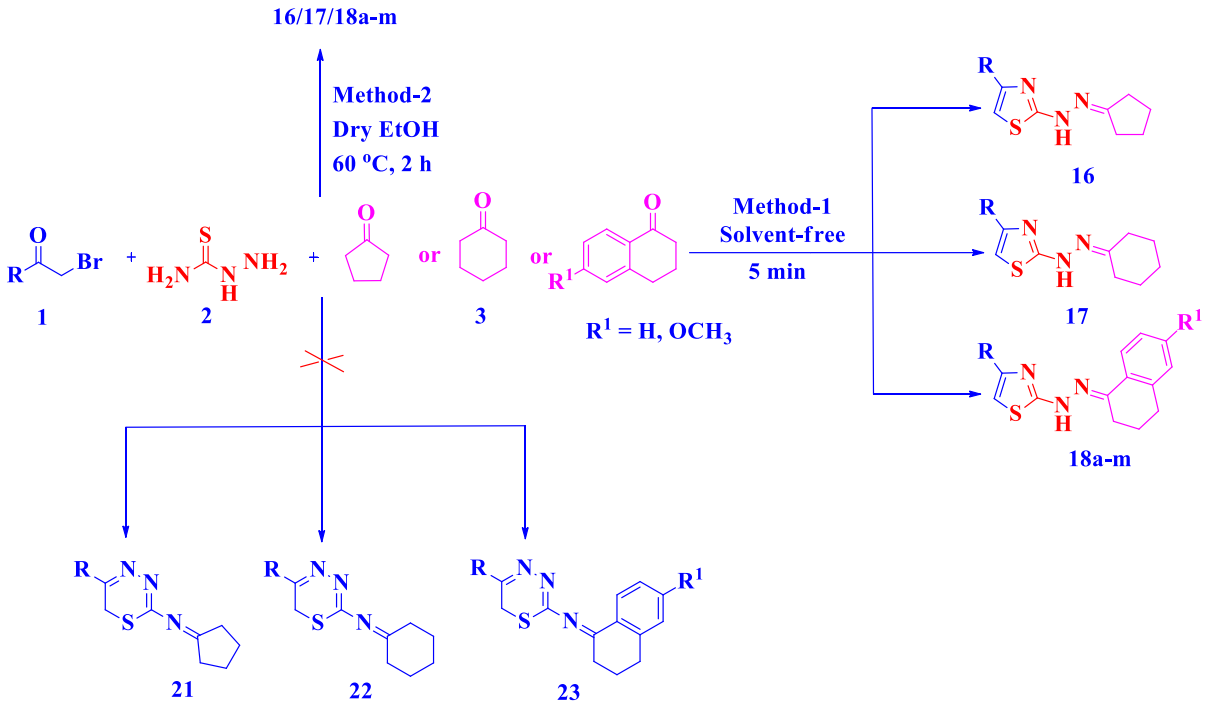


Fig.1. Examples of biologically important molecules having thiazole units.

Hence, in continuation of our research in this direction, we synthesized new hybrid molecules. A series of novel 2,4-disubstituted thiazole derivatives prepared and synthetic route for the preparation of target compounds (**16**, **17**, **18**) is summarized in a scheme-1.

These compounds were synthesized by using modified Hantzsch thiazole. In this synthetic method, phenacyl bromides or 3-(2-bromoacetyl)coumarins, thiosemicarbazide and cyclic ketone were stirred for 5 min at room temperature gave corresponding 2,4-disubstituted thiazoles with good to excellent yields.

Method-1 is solvent-free synthesis, it is believed that the phenacyl bromides or 3-(2-bromoacetyl)coumarins react with thiosemicarbazide gave 2-hydrazino-4-substituted thiazoles as intermediates followed by the reaction with cyclic ketones gave **16**, **17** and **18**.



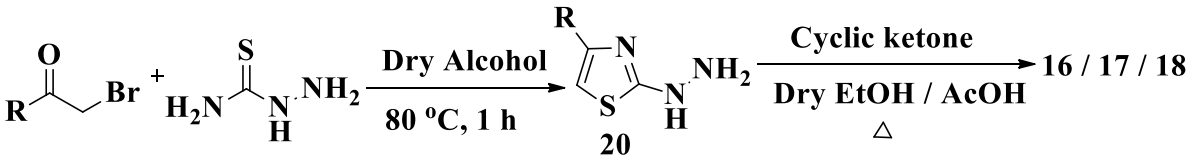
Scheme-1. Outline of synthesis of **16**, **17** and **18a-m**.

Table-1. Different substituents of the products (**16**, **17** and **18a-m**).

Entry	Product	R	R^1	Time (min)
1	16	Phenacyl	-	5
2	17	6,8-Dibromo-3-coumarinyl	-	4
3	18a	Phenacyl	H	4
4	18b	4-Bromo phenacyl	H	4
5	18c	4-Chloro phenacyl	H	4
6	18d	2,4-Dichloro phenacyl	H	3.5
7	18e	4-Nitro phenacyl	H	4
8	18f	6-Bromo-3-coumarinyl	H	4
9	18g	6,8-Dibromo-3-coumarinyl	H	4
10	18h	8-Methoxy-3-coumarinyl	H	4
11	18i	Phenacyl	6-OCH_3	5
12	18j	4-Chloro phenacyl	6-OCH_3	4
13	18k	4-Nitro phenacyl	6-OCH_3	4
14	18l	6,8-Dibromo-3-coumarinyl	6-OCH_3	4
15	18m	6-bromo-8-methoxy-3-coumarinyl	6-OCH_3	4

We also synthesized compounds **16**, **17** and **18** by a one-pot condensation of three reactants in ethanol (solvent) at 60 ºC (Method-2) and also we carried out the synthesis of **16**, **17** and **18** by unambiguous method (Method-3). In the method-3 condensation of various phenacyl bromides or 3-(2-bromoacetyl) coumarins with thiosemicarbazide gave corresponding 2-hydrazino-4-substituted thiazoles (**20**). These on treatment with cyclic

ketones resulted in the formation of **16**, **17** and **18** via a two-step process. The compounds produced in all the three methods were same on the basis of their mixed M.Ps, identical-TLC and Infrared spectra. In the current study first method was used to synthesize the target molecules **16**, **17** and **18** as it has more advantages such as higher yields, shorter reaction times, milder reaction conditions, one-pot, solvent-free and easy reaction workup.

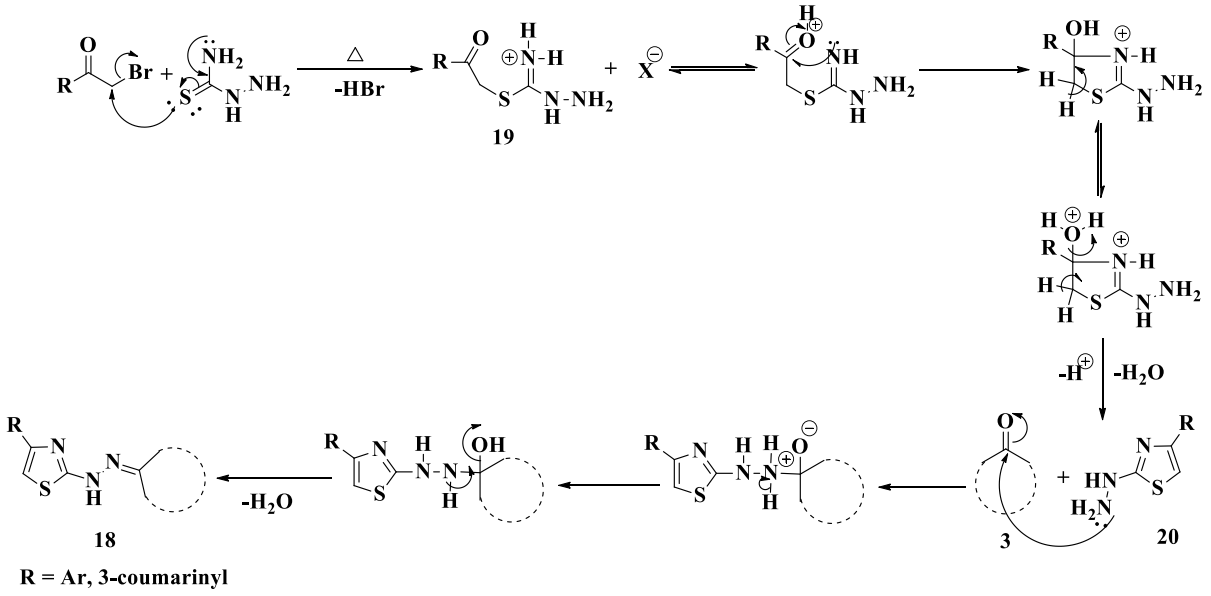


Scheme-2. Method-3. Synthesis of 2,4-disubstituted thiazoles by an unambiguous method

Reaction between phenacyl bromide or 3-(2-bromoacetyl) coumarin, thiosemicarbazide and cyclic ketone is expected to give the compound **16**/**17**/**18** or corresponding N-cyclopentylidine (**21**), cyclohexylidene (**22**) and 3,4-dihydronaphthalene-1(2*H*)-ylidene-5-substituted-6*H*-1,3,4-thiadiazines (**23**) or both depending on the mode of cyclization and reaction conditions used. In the present investigation the reaction between phenacyl bromide and thiosemicarbazide proceeds selectively in such a way that the thioamide of thiosemicarbazide undergoes cyclization gave only 2,4-disubstituted thiazoles. The reaction conditions played a crucial role in the selective hetero cyclization. The alternate products **21**, **22** and **23** can be rejected on the ground of spectral studies.

Mechanism:

From the mechanism, it is clear that the substitution of the α-bromine atom of the phenacyl bromide / 3-(2-bromoacetyl)coumarin by the sulphur atom of the thioamide part of thiosemicarbazide occurs first to give an open chain α-thioketone (**19**), which under trans protonation proceeds to yield 4-hydroxy-2-thiazoline derivative. This further loses the water and proton to give **20**. This intermediate undergoes intermolecular condensation reaction with cyclic ketone gave final compounds (**16**, **17** and **18**).



Scheme-3. The plausible reaction mechanism for 2,4-disubstituted thiazoles.

CONCLUSION

We have successfully prepared a new 2,4-disubstituted thiazole derivatives through a multicomponent approach under solvent free reaction conditions. The method had the advantages of mild reaction conditions, better to excellent yields, one-pot and operational simplicity.

EXPERIMENTAL SECTION

Starting materials:

Different 3-acetyl coumarins,[24,25] 3-(2-bromoacetyl) coumarins[26] synthesized by reported method. Various phenacyl bromides, hydrazinecarbothioamide, cyclopentanone, cyclohexanone, tetralone, 6-methoxy tetralone have been obtained from the source of commercial.

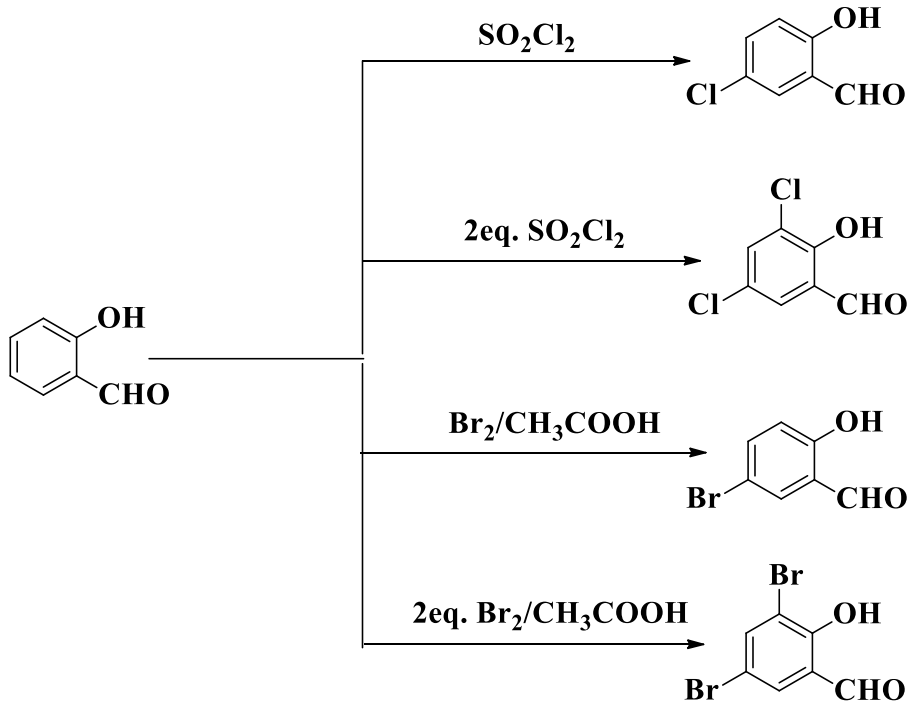
Preparation of coumarins

Present study involves the preparation of substituted 3-(2-(bromoacetyl)coumarins. By using them new heterocyclic molecules were constructed. Preparation of 3-(2-(bromoacetyl) coumarins involves the following methods.

(i). Preparation of 2-hydroxy benzaldehyde derivatives

Salicylaldehydes have been prepared by different procedures. Bromination of salicylaldehyde using bromine in acetic acid gave 5-bromo isomer as a single product.[27] Salicylaldehyde on treatment with two equivalents of bromine gave dibromosalicilaldehyde.[28] 5-Chloro salicylaldehyde was prepared by treating one equivalent of SO_2Cl_2 with

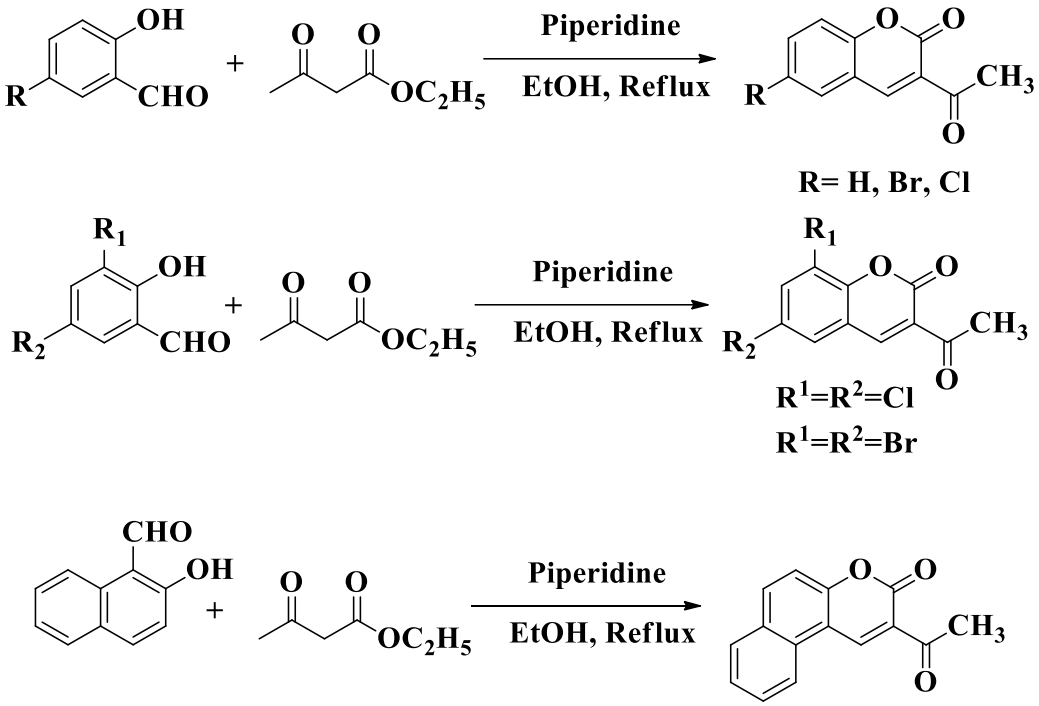
salicylaldehyde. 3,5-Dichlorosalicylaldehyde was prepared with the addition of two equivalents of SO_2Cl_2 to salicylaldehyde to give exclusive product.[29]



Similarly, few of the *o*-hydroxy aldehydes like o-Vanillin and 2-hydroxy-1-naphthaldehyde were purchased from commercial sources.

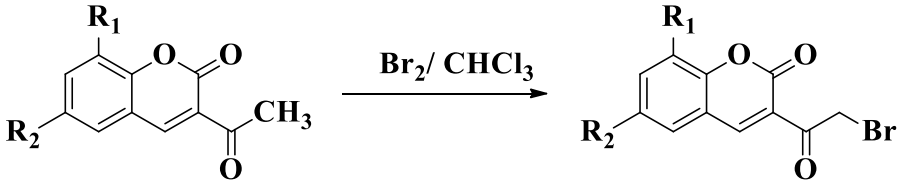
(ii). Preparation of 3-acetl-2*H*-1-benzopyran-2-ones

Substituted 3-acetyl-2*H*-1-benzopyran-2-ones were synthesized by condensing salicylaldehydes with ethylacetoacetate[30-32]



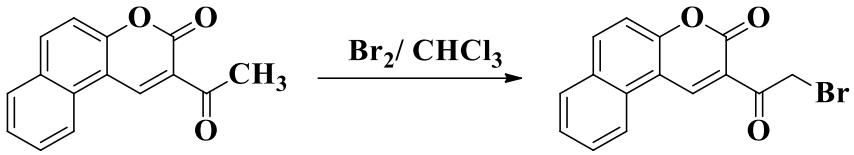
(iii). **Bromination of 3-acetyl-2*H*-1-benzopyran-2-ones**

3-Acetyl coumarins on bromination afforded substituted 3-(2-bromoacetyl)-2*H*-1-benzopyran-2-ones[26] using $Br_2/CHCl_3$.

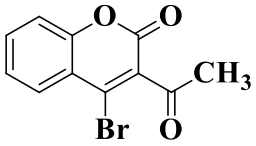


1. $R^1=R^2=H$ **4. $R^1=R^2=Cl$**
2. $R^1=H$, $R^2=Cl$ **5. $R^1=R^2=Br$**
3. $R^1=H$, $R^2=Br$

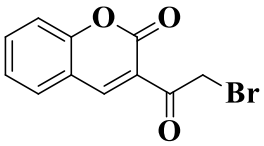
In the same way, 5,6-benzoanalogue of 3-(2-bromoacetyl)coumarin was prepared.



Earlier preparation methods reported that the bromination of 3-acetyl coumarin with bromine gave the 3-acetyl-4-bromo-2*H*-chromen-2-one wherein nuclear derivative as the main product.[33]



The above structure of the bromo-compound was discarded by Koelsch,[34] who has brominated the 3-acetyl coumarin in alcohol free chloroform with bromine and he had conducted the degradation experiments, finally he proved that the following structure is correct.

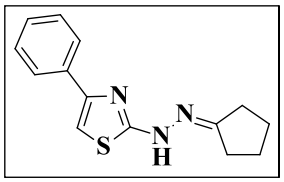


Synthesis of 2,4-disubstituted thiazoles (16, 17, 18a-m):

A mixture of phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)-2*H*-1-benzopyran-2-one (1 mmol), thiosemicarbazide (1 mmol) and cyclopentanone (1 mmol)/cyclohexanone (1 mmol)/ tetralone (1 mmol) was reacted and agitated at ambient temperature for required time and progress of the reaction checked by the TLC. After completion of the reaction, the product was cooled, filtered and recrystallized from methanol.

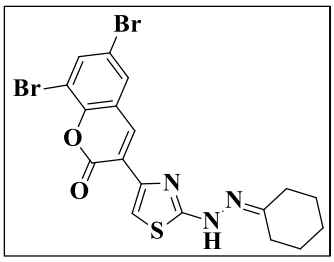
SPECTRAL DATA

2-(2-Cyclopentylidenehydrazinyl)-4-phenylthiazole (16).



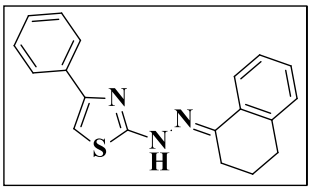
Color: black solid; mp: 142-143 °C; yield: (0.27g, 95%); IR (KBr, Wave number, cm^{-1}): 3437-3053 (NH), 1628 (C=N); PMR (400 MHz, $CDCl_3$): δ 1.80-1.87 (m, 2H), 1.90-1.96 (m, 2H), 2.5–2.57 (m, 4H), 6.74 (s, 1H), 7.38-7.42 (m, 1H), 7.44-7.48 (m, 2H, ArH), 7.74 (d, J = 7.6 Hz, 2H) ppm; CMR (100 MHz, $CDCl_3$): δ 24.83, 24.95, 29.91, 33.28, 101.67, 125.60, 129.13, 129.33, 129.79, 143.69, 168.90, 169.27 ppm; ESI-MS: *m/z* 258 $[M+H]^+$; Anal. calcd. for $C_{14}H_{15}N_3S$, C, 65.34; H, 5.87; N, 16.33; S, 12.46%. Found: C, 65.30, H, 5.84; N, 16.39; S, 12.42%.

6, 8-Dibromo-3-(2-(2-cyclohexylidenehydrazinyl) thiazol-4-yl)-2*H*-chromen-2-one (17).



Color: yellow solid; mp: 172-173 °C; yield: (0.523g, 95%); IR (KBr, Wave number, cm^{-1}): 3448-3061 (NH), 1733 (C=O), 1609 (C=N); PMR (400 MHz, DMSO-d_6): δ 1.59-1.64 (m, 6H), 2.26 (s, 2H), 2.45 (s, 2H), 7.74 (s, 1H), 8.11 (s, 2H), 8.40 (s, 1H), 10.98 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 22.19, 25.33, 26.91, 34.86, 110.42, 116.96, 121.98, 122.50, 123.63, 131.29, 136.86, 138.63, 144.95, 147.07, 148.92, 158.23, 175.30 ppm; ESI-MS: m/z 498 $[M+H]^+$; Anal. Calcd. for $C_{18}H_{15}Br_2N_3O_2S$, C, 43.48; H, 3.04; Br, 32.14; N, 8.45; S, 6.45%. Found: C, 43.53; H, 3.12; Br, 32.19; N, 8.49; S, 6.41%.

2-(2-(3, 4-Dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)-4-phenylthiazole (18a).

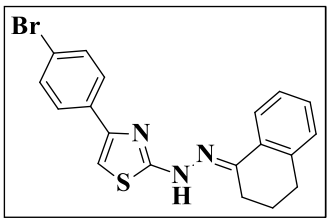


Color: black solid; mp: 157-159 °C; yield: (0.332g, 96%); PMR (400 MHz, $CDCl_3$): δ 1.89-1.95 (m, 2H), 2.57 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.0 Hz, 2H), 6.92 (s, 1H), 7.15 (d, J = 4.4 Hz, 1H), 7.27-7.29 (m, 3H), 7.33 (d, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.82 (d, J = 7.6 Hz, 2H), 8.16 (t, J = 4.8 Hz, 1H) ppm; CMR (100 MHz, $CDCl_3$): δ 21.41, 25.68, 29.41, 103.58, 124.62, 125.96, 126.57, 127.96, 128.44, 128.76, 128.92, 132.12, 134.34, 139.32, 147.23, 150.58, 170.17 ppm; Anal. calcd. for $C_{19}H_{17}N_3S$, C, 71.44; H, 5.36; N, 13.15; S, 10.04. Found: C, 71.49; H, 5.31; N, 13.19; S, 10.14%.

4-(4-Bromophenyl)-2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole (18b).

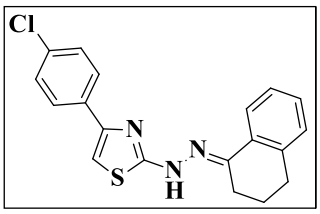
Color: yellow solid; mp: 227-228 °C; yield: (0.437g, 91%); IR (KBr, Wave number, cm^{-1}): 3440-3033 (NH), 1608 (C=N); PMR (DMSO-d_6, 400 MHz): δ 1.85 (t, J = 5.6 Hz, 2H), 2.70

(t, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.0 Hz, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 7.26 (t, *J* = 4.4 Hz, 2H), 7.42 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.99 (t, *J* = 4.8 Hz, 1H), 8.33 (s, 1H) ppm; CMR (DMSO-d_6, 100 MHz): δ 21.74, 26.51, 29.31, 105.46, 124.41, 126.79, 128.04, 129.07, 129.87, 130.29, 130.75, 131.55, 131.78, 132.0, 132.61, 139.82, 170.51 ppm; ESI-MS: m/z 398 $[M+H]^+$; Anal. calcd. for $C_{19}H_{16}BrN_3S$, C, 57.29; H, 4.05; Br, 20.06, N, 10.55; S, 8.05. Found: C, 57.33; H, 4.13; Br, 20.17, N, 10.51; S, 8.12%.



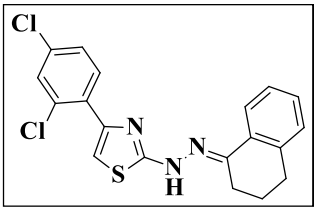
4-(4-Chlorophenyl)-2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole (18c).

Color: off white solid; mp: 220-221 °C; yield: (0.392g, 90%); IR (KBr, Wave number, cm^{-1}): 3450-3030 (NH), 1609 (C=N); PMR (400 MHz, $CDCl_3$): δ 2.04 (t, *J* = 5.2 Hz, 2H), 2.82 (s, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 6.77 (s, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.29 (s, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 12.34 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.74, 26.51, 29.32, 105.37, 124.41, 126.79, 127.73, 128.64, 128.87, 129.09, 130.02, 130.47, 132.60, 133.93, 139.73, 147.32, 170.51 ppm; ESI-MS: m/z 354 $[M+H]^+$; Anal. calcd. for $C_{19}H_{16}ClN_3S$, C, 64.49; H, 4.56; Cl, 10.02, N, 11.87; S, 9.06. Found: C, 64.44; H, 4.52; Cl, 10.12, N, 11.83; S, 9.14%.



4-(2,4-Chlorophenyl)-2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole (18d).

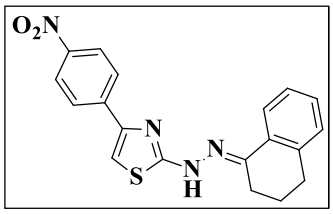
Color: pale brown solid; mp: 188-189 °C; yield: (0.404g, 96%); IR (KBr, Wave number, cm^{-1}): 3347-3019 (NH), 1628 (C=N); PMR (400 MHz, $CDCl_3$): δ 1.95-2.01 (m, 2H), 2.70 (t, *J* = 6.4 Hz, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 7.16 (d, *J* = 9.6 Hz, 2H), 7.28-7.34 (m, 4H), 7.49 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H) ppm; CMR (100 MHz, $CDCl_3$): δ 21.51, 26.40, 29.40, 108.43, 124.85, 126.62, 127.71, 128.63, 128.95, 129.70, 130.54, 131.34, 131.40, 132.62, 134.96, 139.98, 141.75, 150.80, 168.98 ppm; ESI-MS: m/z 388 $[M+H]^+$; Anal. calcd. for $C_{19}H_{15}Cl_2N_3S$, C, 58.77; H, 3.89; Cl, 18.26; N, 10.82; S, 8.26. Found: C, 58.70; H, 3.81; Cl, 18.22; N, 10.77; S, 8.67%.



2-(2-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)-4-(4-nitrophenyl)thiazole (18e).

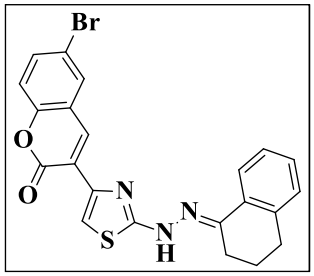
Color: brown solid; mp: 200-201 °C; yield: (0.383g, 95%); IR (KBr, Wave number, cm^{-1}): 3421-3334 (NH), 1598 (C=N); PMR (400 MHz, $CDCl_3$): δ 2.03 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 5.6 Hz, 2H), 2.89 (t, *J* = 6.4 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H),

7.34 (d, *J* = 7.2 Hz, 1H), 7.49 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 2H), 12.07 (s, 1H, NH) ppm; CMR (100 MHz, $CDCl_3$): δ 21.73, 26.58, 29.48, 108.60, 123.57, 124.13, 124.46, 124.60, 126.50, 126.61, 128.70, 128.93, 132.27, 139.58, 146.72, 147.90, 170.70 ppm; ESI-MS: m/z 365 $[M+H]^+$; Anal. calcd. for $C_{19}H_{16}N_4O_2S$, C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.65; H, 4.48; N, 15.32; S, 8.84%.



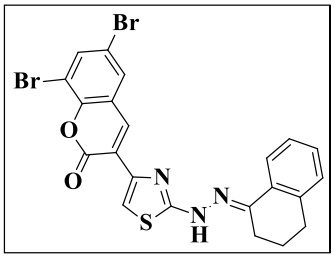
6-Bromo-3-(2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazol-4-yl)-2*H*-chromen-2-one (18f).

Color: brown solid; mp: 239-240 °C; yield: (0.485g, 96%); IR (KBr, Wave number, cm^{-1}): 3440-3450 (NH), 1616 (C=N); PMR (400 MHz, DMSO-d_6): δ 1.86 (t, *J* = 6.0 Hz, 2H), 2.70-2.77 (m, 4H), 7.19-7.20 (m, 1H), 7.26 (t, *J* = 4.0 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.82 (s, 1H), 7.99 (t, *J* = 5.2 Hz, 1H), 8.09 (s, 1H), 8.49 (s, 1H), 11.30 (s, 1H); CMR (100 MHz, DMSO-d_6): δ 21.73, 26.60, 29.30, 116.84, 118.89, 120.99, 123.30, 124.47, 126.84, 129.08, 131.27, 132.38, 133.95, 135.15, 135.38, 139.90, 142.76, 143.49, 147.86, 152.75, 157.24, 170.20 ppm; ESI-MS: m/z 468 $[M+2]^+$; Anal. calcd. for $C_{21}H_{15}BrN_3O_2S$, C, 55.64; H, 3.34; Br, 17.63; N, 9.27; S, 7.07. Found: C, 55.61; H, 3.38; Br, 17.68; N, 9.22; S, 7.13%.



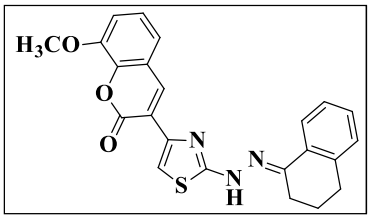
6,8-Dibromo-3-(2-(2-(3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazol-4-yl)-2*H*-chromen-2-one (18g).

Color: brown solid; mp: 209-210 °C; yield: (0.586g, 93%); IR (KBr, Wave number, cm^{-1}): 3450-3367 (NH), 1734 (C=O), 1636 (C=N); PMR (400 MHz, DMSO-d_6): δ 1.86 (s, 2H), 2.74 (t, *J* = 7.4 Hz, 4H), 7.20-7.25 (m, 2H), 7.65 (s, 1H), 7.84 (s, 1H), 7.98 (s, 1H), 8.42 (s, 2H), 8.76 (s, 1H), 11.31 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.73, 26.53, 29.32, 110.18, 111.29, 113.08, 116.79, 122.62, 122.79, 124.31, 126.77, 129.06, 130.69, 132.53, 135.96, 136.21, 136.43, 139.67, 143.99, 148.45, 158.11, 169.89 ppm; Anal. calcd. for $C_{22}H_{15}Br_2N_3O_2S$, C, 48.46; H, 2.77; Br, 29.31; N, 7.71; S, 5.88. Found: C, 48.42; H, 2.72; Br, 29.34; N, 7.68; S, 5.82%.



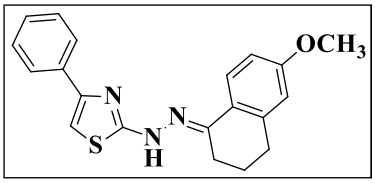
3-(2-(2-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazol-4-yl)-8-methoxy-2*H*-chromen-2-one (18h).

Color: yellow solid; mp: 219-220 °C; yield: (0.453g, 92%); IR (KBr, Wave number, cm^{-1}): 1733 (C=O), 1616 (C=N); PMR (400 MHz, DMSO-d_6): δ 1.86 (t, J = 5.2 Hz, 2H), 2.69-2.75 (m, 4H), 3.93 (s, 3H), 7.18-7.20 (m, 1H), 7.25-7.26 (m, 2H), 7.34-7.36 (m, 2H), 7.79 (s, 1H), 7.98 (s, 1H), 8.15 (s, 1H), 8.54 (s, 1H), 11.31 (s, 1H) ppm; ESI-MS: m/z 418 $[M+H]^+$; Anal. calcd. for $C_{23}H_{19}N_3O_3S$, C, 66.17; H, 4.59; N, 10.07; S, 7.68. Found: C, 66.13; H, 4.52; N, 10.13; S, 7.62%.



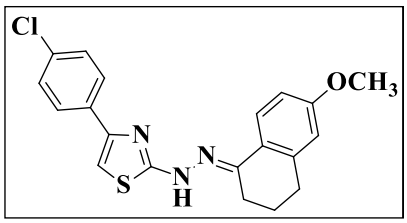
2-(2-(6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)-4-phenylthiazole (18i).

Color: brown solid; mp: 204-205 °C; yield: (0.359g, 97%); IR (KBr, Wave number, cm^{-1}): 3400-2900 (NH), 1614 (C=N); PMR (400 MHz, $CDCl_3$): δ 1.25 (s, 1H), 1.98 (t, J = 6.0 Hz, 2H), 2.77 (d, J = 5.6 Hz, 4H), 3.83 (s, 3H), 6.66 (s, 1H), 6.78 (s, 1H), 6.82 (d, J = 8.8 Hz, 1H), 7.37-7.40 (m, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.75 (d, J = 7.6 Hz, 2H), 8.04 (d, J = 8.8 Hz, 1H) ppm; CMR (100 MHz, $CDCl_3$): δ 21.63, 26.58, 29.70, 55.28, 102.61, 112.50, 113.41, 124.36, 125.68, 126.60, 128.76, 128.95, 131.57, 141.82, 146.08, 150.85, 160.65, 169.81 ppm; ESI-MS: m/z 350 $[M+H]^+$; Anal. calcd. for $C_{20}H_{19}N_3OS$, C, 68.74; H, 5.48; N, 12.02; S, 9.18. Found: C, 68.71; H, 5.41; N, 12.14; S, 9.13%.

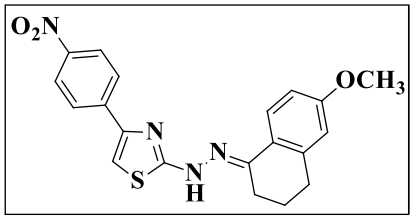


4-(4-Chlorophenyl)-2-(2-(6-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazole (18j).

Color: white solid; mp: 225-226 °C; yield: (0.411g, 93%); IR (KBr, wave number, cm^{-1}): 3400-3044 (NH), 1624 (C=N); PMR (400 MHz, $CDCl_3$): δ 2.02 (t, J = 6.0 Hz, 2H), 2.79 (t, J = 5.6 Hz, 2H), 2.90 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 6.68 (s, 1H), 6.73 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.8 Hz, 1H), 12.49 (s, 1H); CMR (100 MHz, $CDCl_3$): δ 21.64, 27.77, 29.73, 55.39, 101.14, 112.63, 113.74, 123.26, 125.81, 126.89, 127.15, 129.92, 136.57, 139.62, 143.15, 156.52, 161.67, 169.42 ppm; ESI-MS: m/z 384 $[M+H]^+$; Anal. calcd. for $C_{20}H_{18}ClN_3OS$, C, 62.57; H, 4.73; Cl, 9.24; N, 10.95; S, 8.35. Found: C, 62.52; H, 4.79; Cl, 9.28; N, 10.90; S, 8.39%.

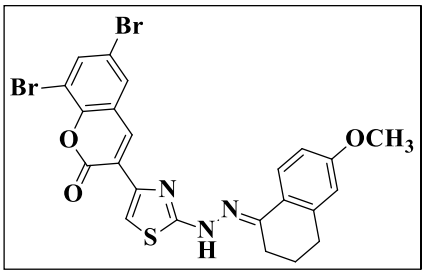


2-(2-(6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)-4-(4-nitrophenyl)thiazole (18k).



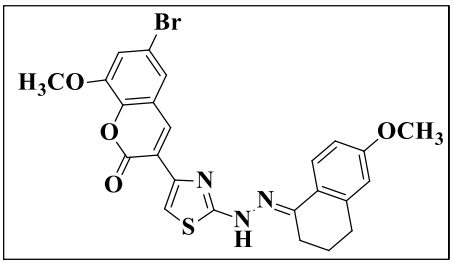
Color: brown solid; mp: 220-221 °C; yield: (0.414g, 95%); IR (KBr, Wave number, cm^{-1}): 3343-3037 (NH), 1625 (C=N); PMR (400 MHz, DMSO-d_6): δ 1.84 (t, J = 6.0 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 5.6 Hz, 2H), 3.77 (s, 3H), 6.76 (s, 1H), 6.85 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 8.4 Hz, 2H), 11.23 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.82, 26.46, 29.61, 55.61, 109.19, 112.97, 113.81, 124.59, 126.06, 126.77, 141.30, 141.60, 146.58, 147.78, 148.94, 160.14, 170.95 ppm; ESI-MS: m/z 395 $[M+H]^+$; Anal. calcd. for $C_{20}H_{18}N_4O_3S$, C, 60.90; H, 4.60; N, 14.20; S, 8.13. Found: C, 60.95; H, 4.65; N, 14.25; S, 8.18%.

6,8-Dibromo-3-(2-(2-(6-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazol-4-yl)-2*H*-chromen-2-one (18l).

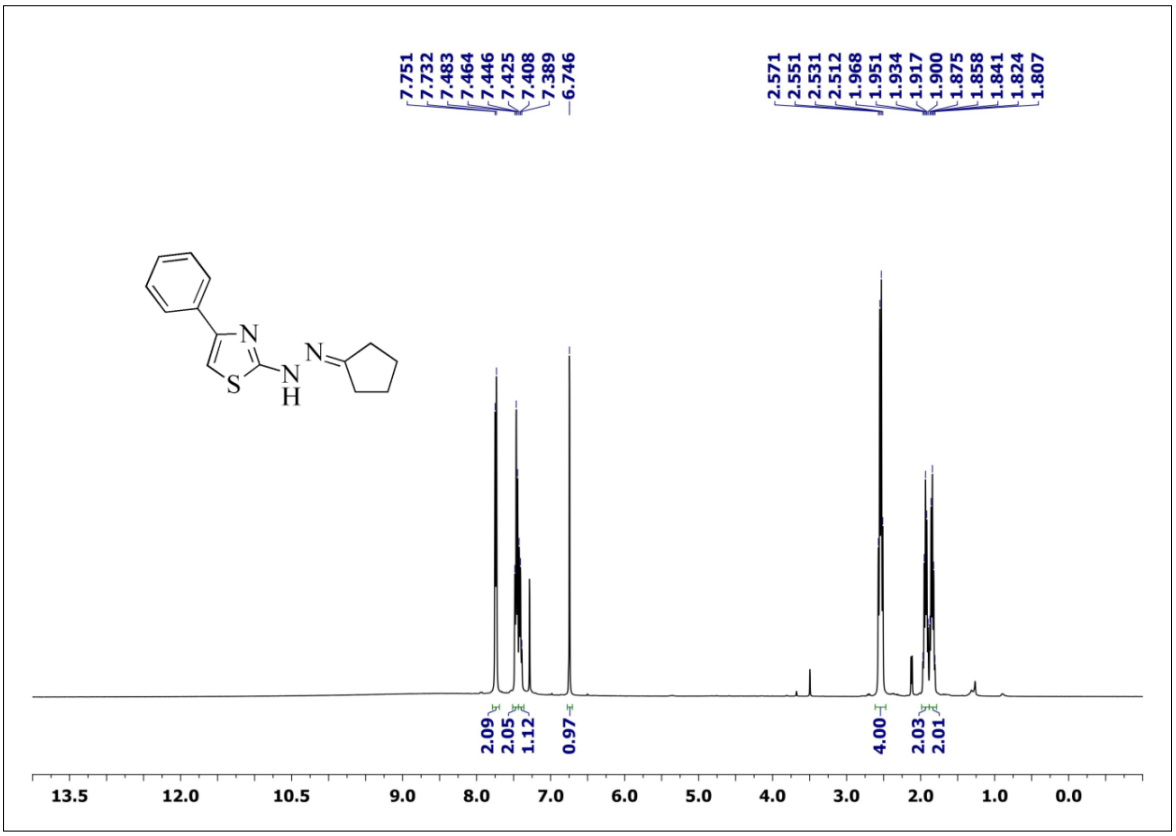


Colour: yellow solid; mp: 233-234 °C; yield: (0.625g, 92%); IR (KBr, Wave number, cm^{-1}): 3431-3152 (NH), 1738 (lactone carbonyl stretching), 1631(-C=N); PMR (400 MHz, DMSO-d_6): δ 1.84 (t, J = 5.6 Hz, 2H), 2.68 (t, J = 6.0 Hz, 2H), 2.73 (t, J = 5.6 Hz, 2H), 3.77 (s, 3H), 6.75 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 8.10 (s, 2H), 8.42 (s, 1H), 11.15(s, 1H) ppm; ESI-MS: m/z 576 $[M+H]^+$; Anal. calcd. for $C_{23}H_{17}Br_2N_3O_3S$, C, 48.02; H, 2.98; Br, 27.78; N, 7.30; S, 5.57. Found: C, 48.10; H, 2.93; Br, 27.72; N, 7.35; S, 5.53%.

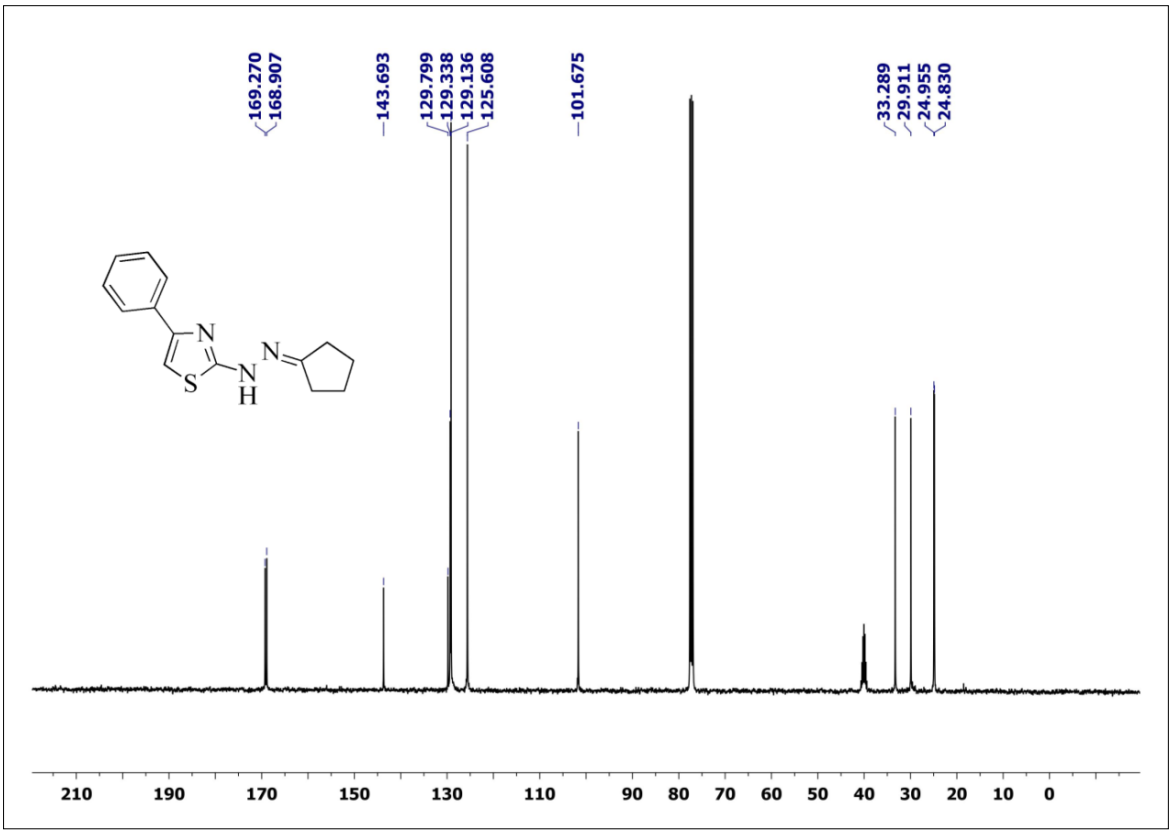
6-Bromo-8-methoxy-3-(2-(2-(6-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)hydrazinyl)thiazol-4-yl)-2*H*-chromen-2-one (18m).



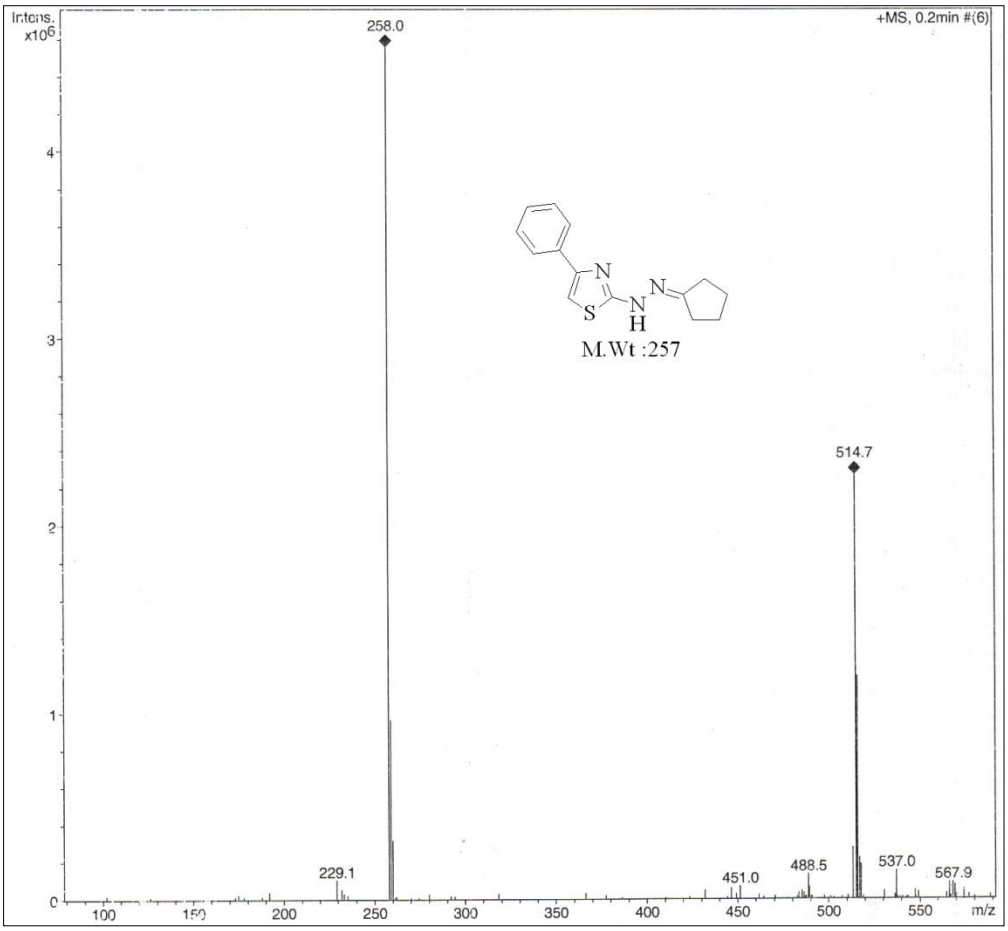
Color: brown solid; mp: 214-215 °C; yield: (0.618g, 85%); PMR (400 MHz, DMSO-d_6): δ 1.83 (s, 1H), 2.27 (s, 1H), 2.67-2.72 (m, 2H), 3.77 (s, 2H), 3.94 (s, 6H) 6.75 (s, 1H), 6.84 (d, J = 9.6 Hz, 1H), 7.42-7.44 (m, 2H), 7.79-7.83 (m, 1H), 7.91 (d, J = 8.8 Hz, 1H), 8.43 (s, 1H), 11.53 (s, 1H, NH) ppm; ESI-MS: m/z 528 $[M+2]^+$; Anal. calcd. for $C_{24}H_{20}BrN_3O_4S$, C, 54.76; H, 3.83; Br, 15.18; N, 7.98; S, 6.09. Found: C, 54.72; H, 3.87; Br, 15.14; N, 7.94; S, 6.12%.



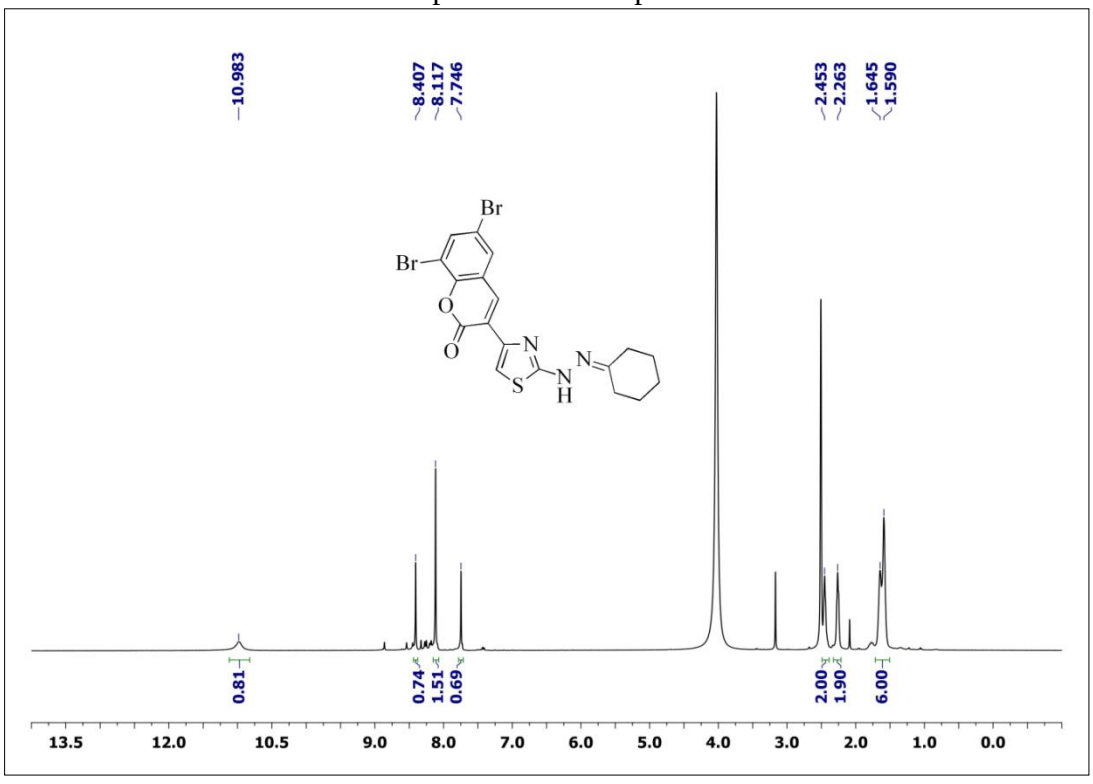
PMR Spectrum of compound **16**



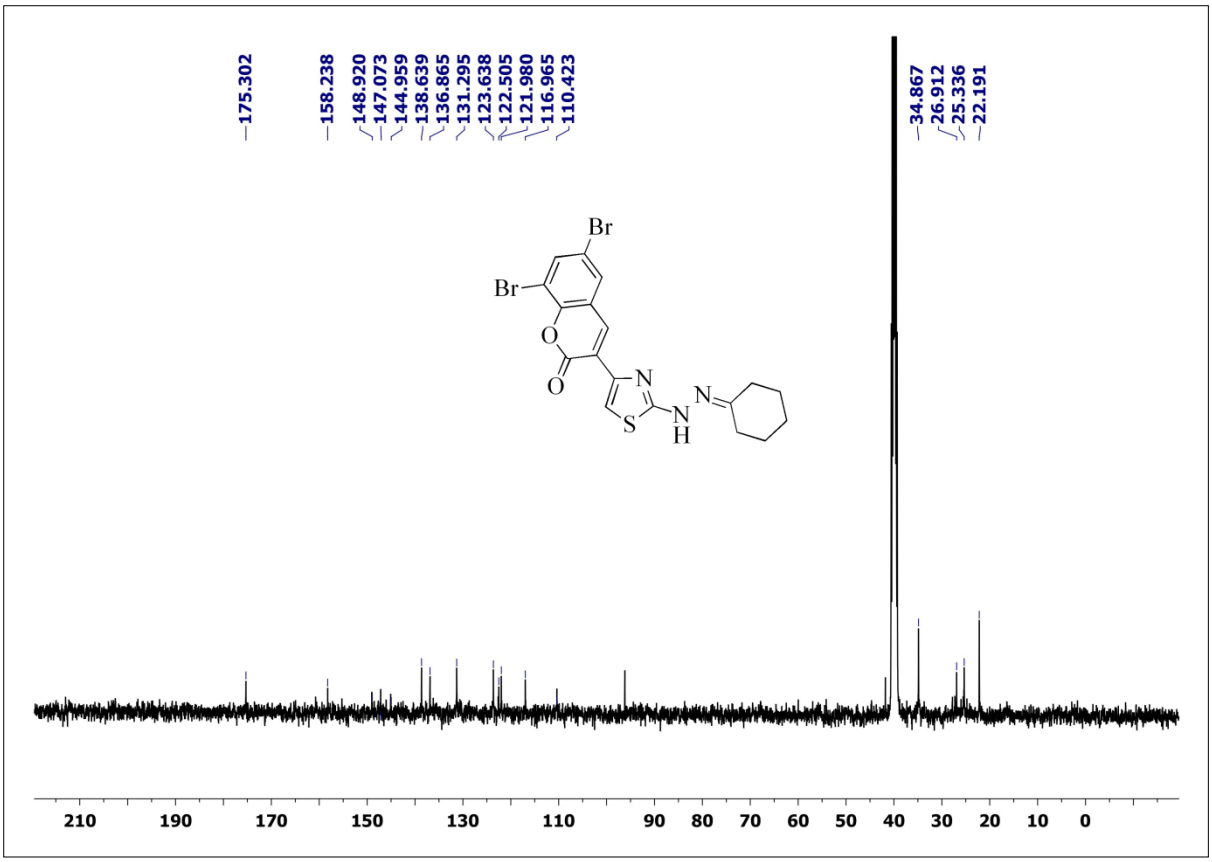
CMR Spectrum of compound **16**



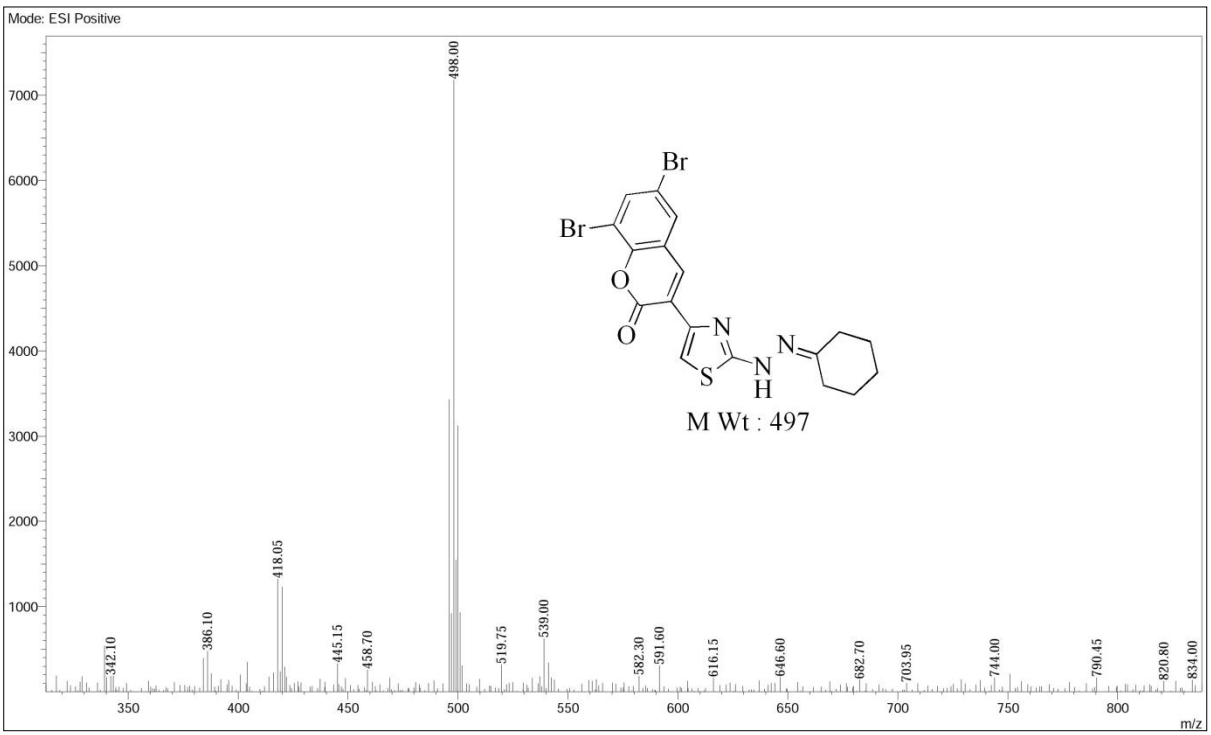
Mass Spectrum of compound **16**



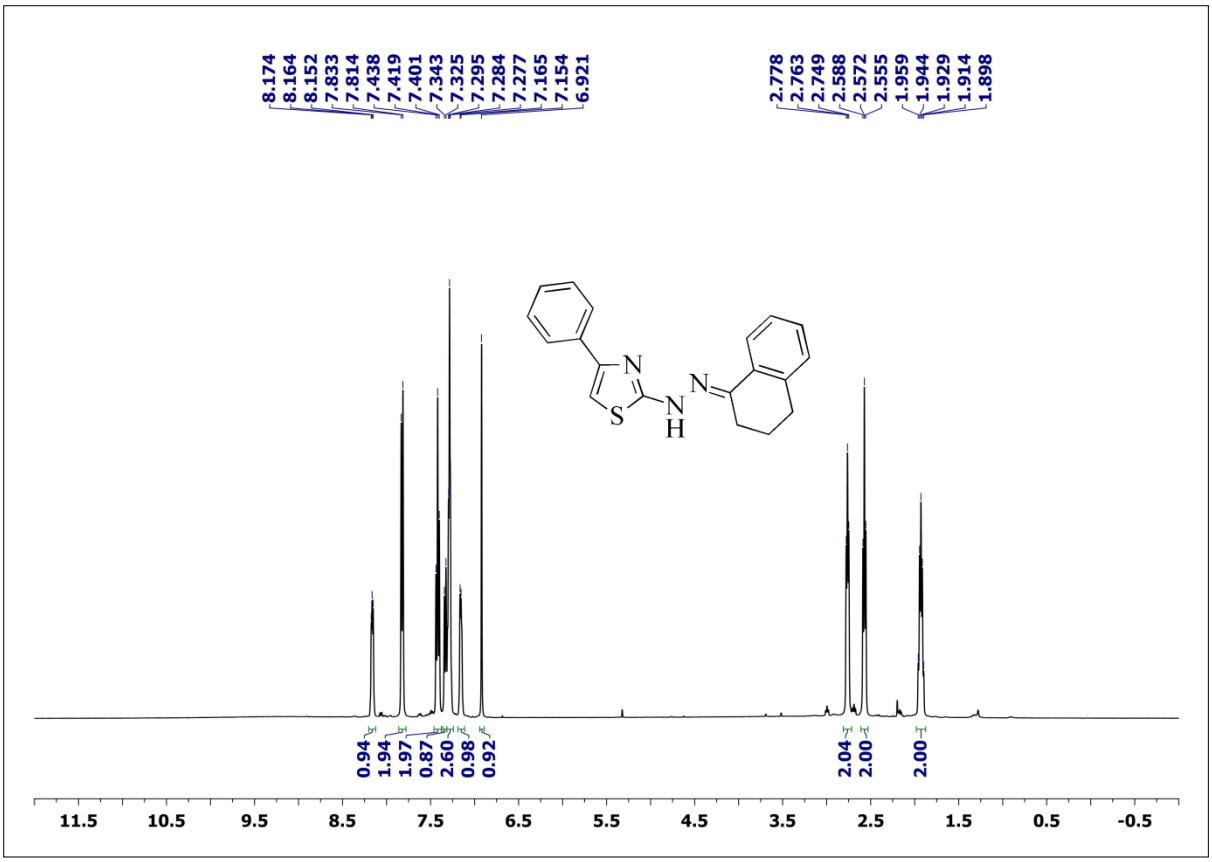
PMR Spectrum of compound **17**



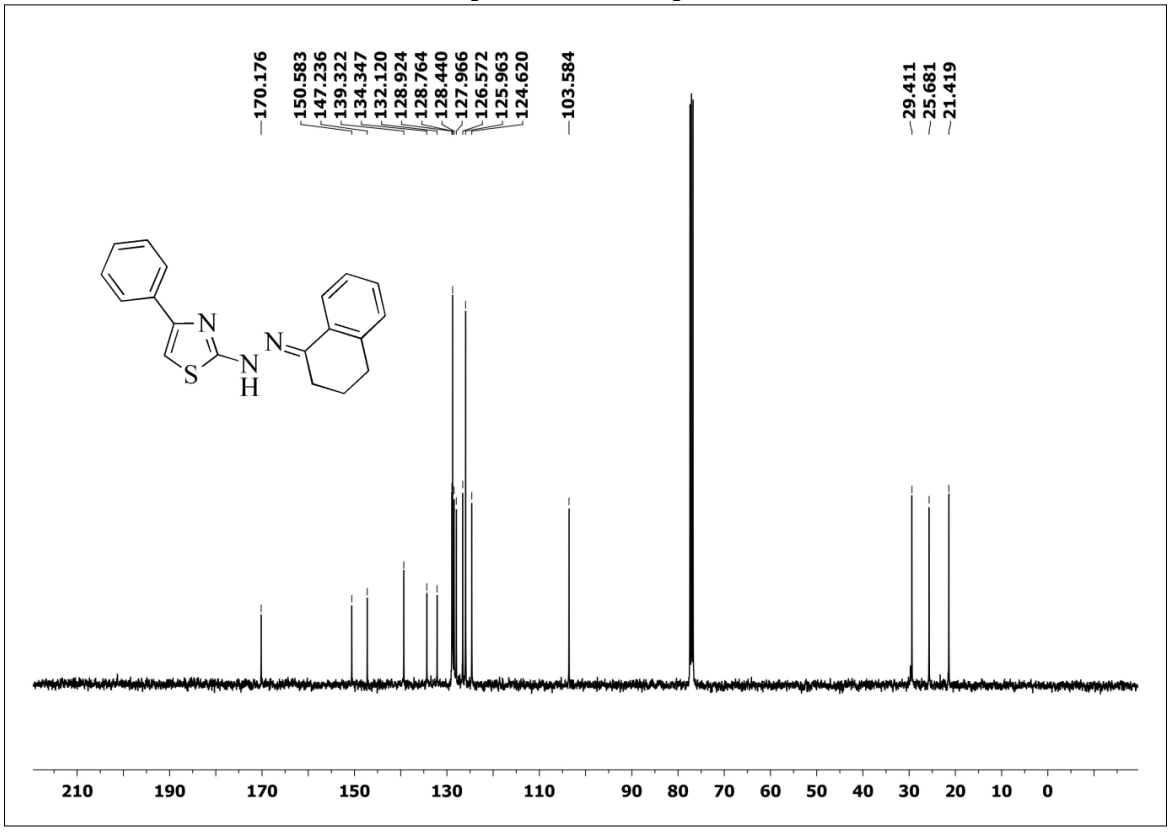
CMR Spectrum of compound **17**



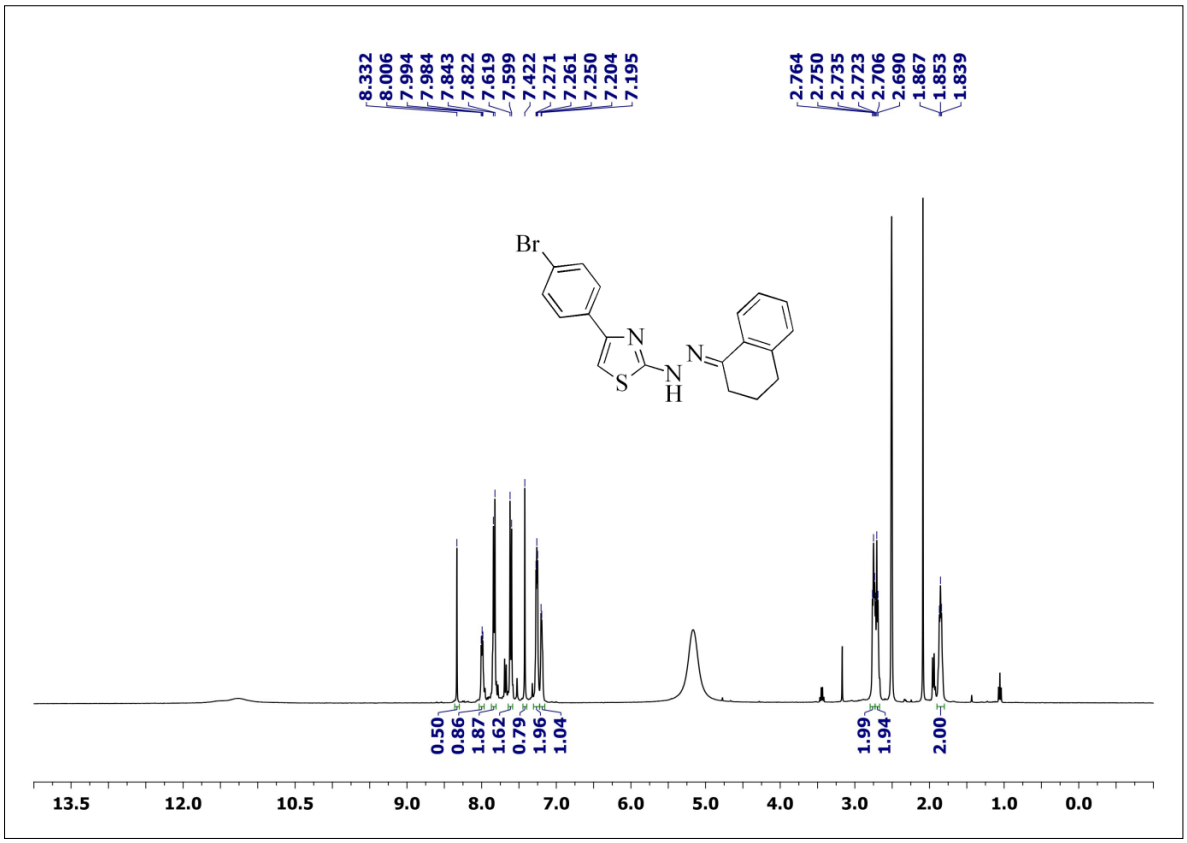
Mass Spectrum of compound **17**



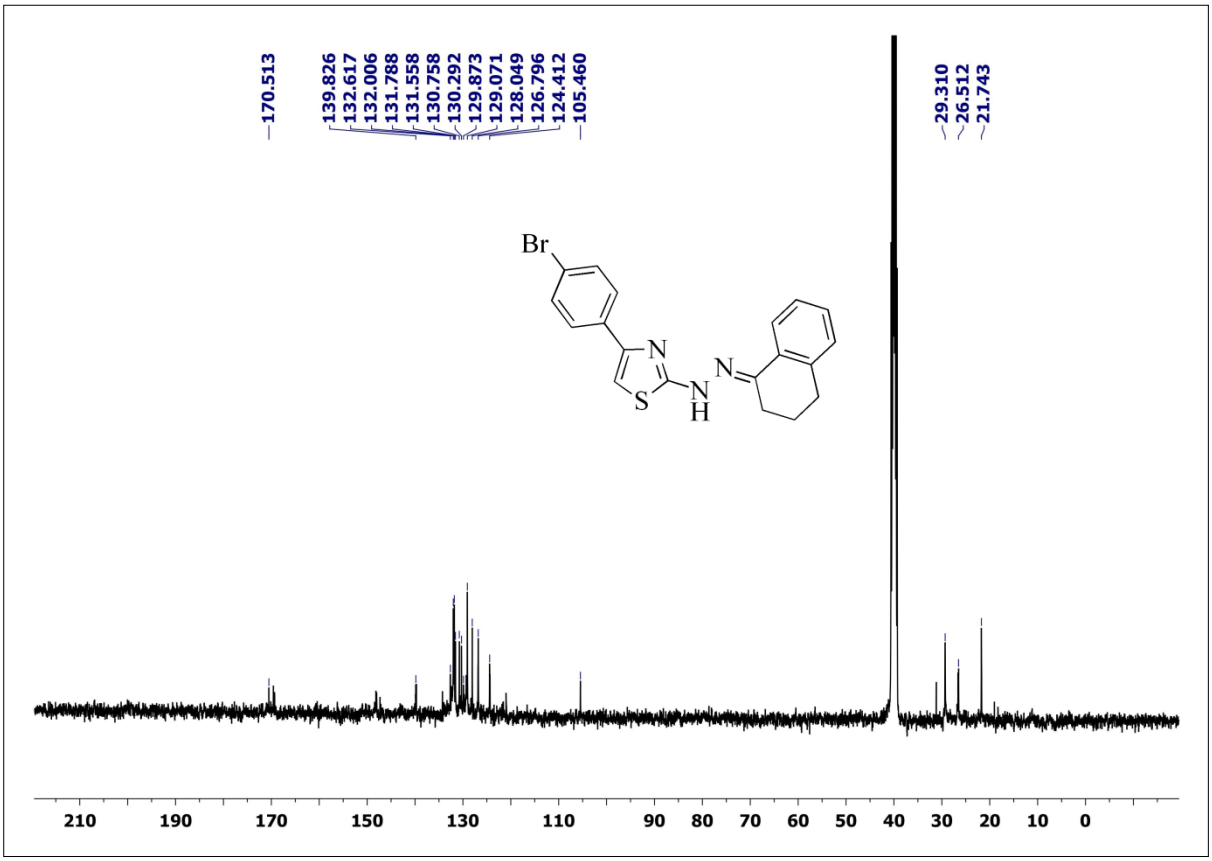
PMR Spectrum of compound **18a**



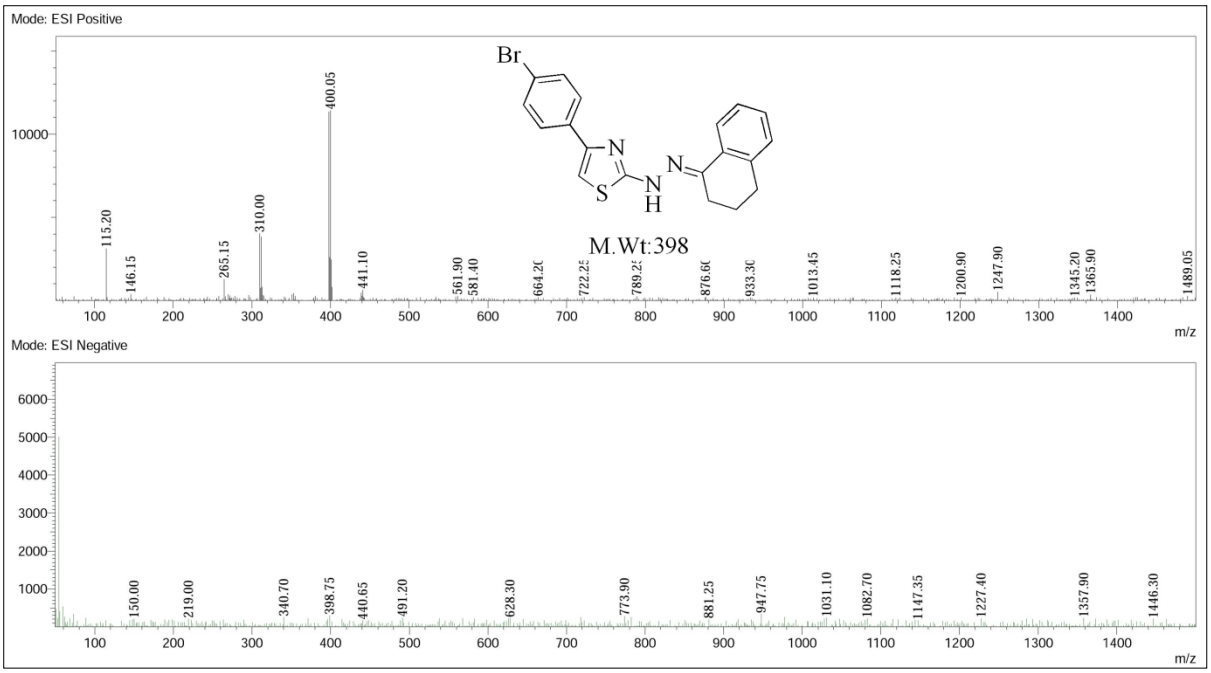
CMR Spectrum of compound **18a**



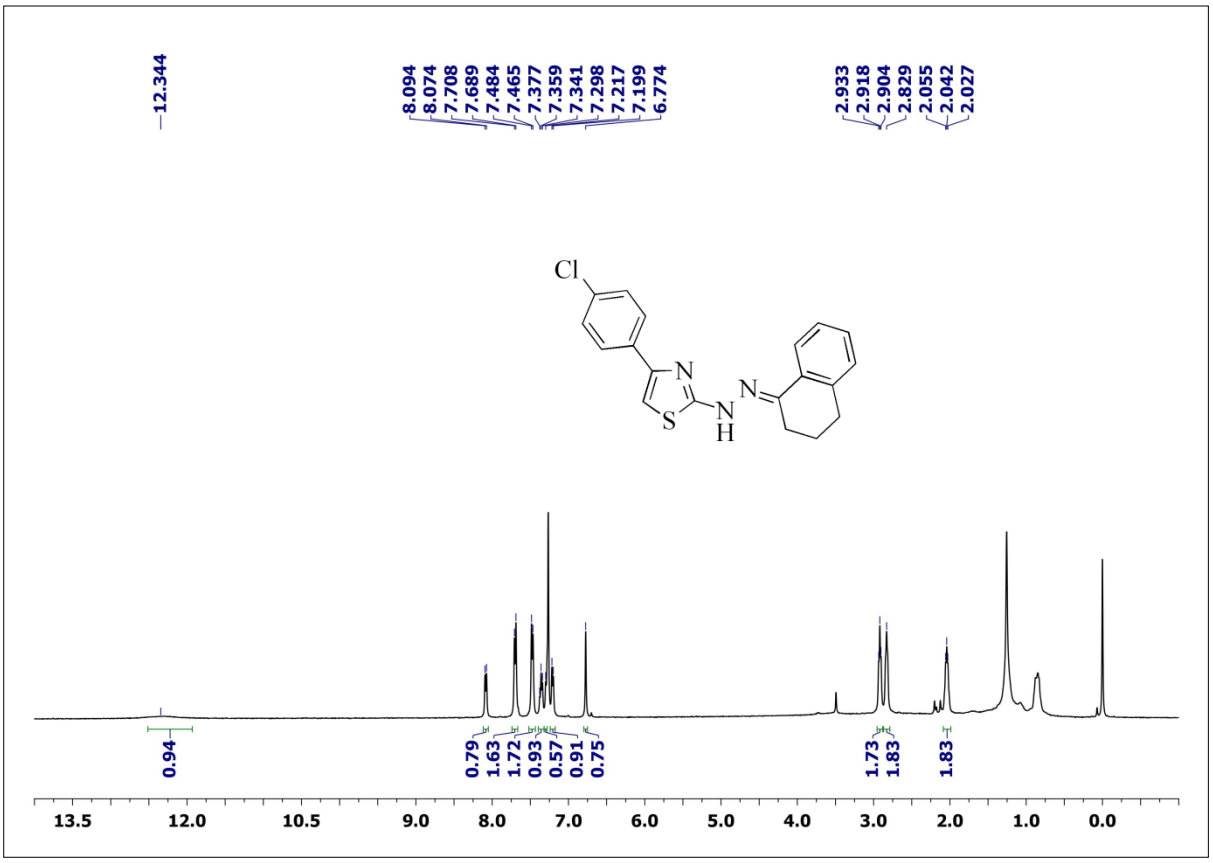
PMR Spectrum of compound **18b**



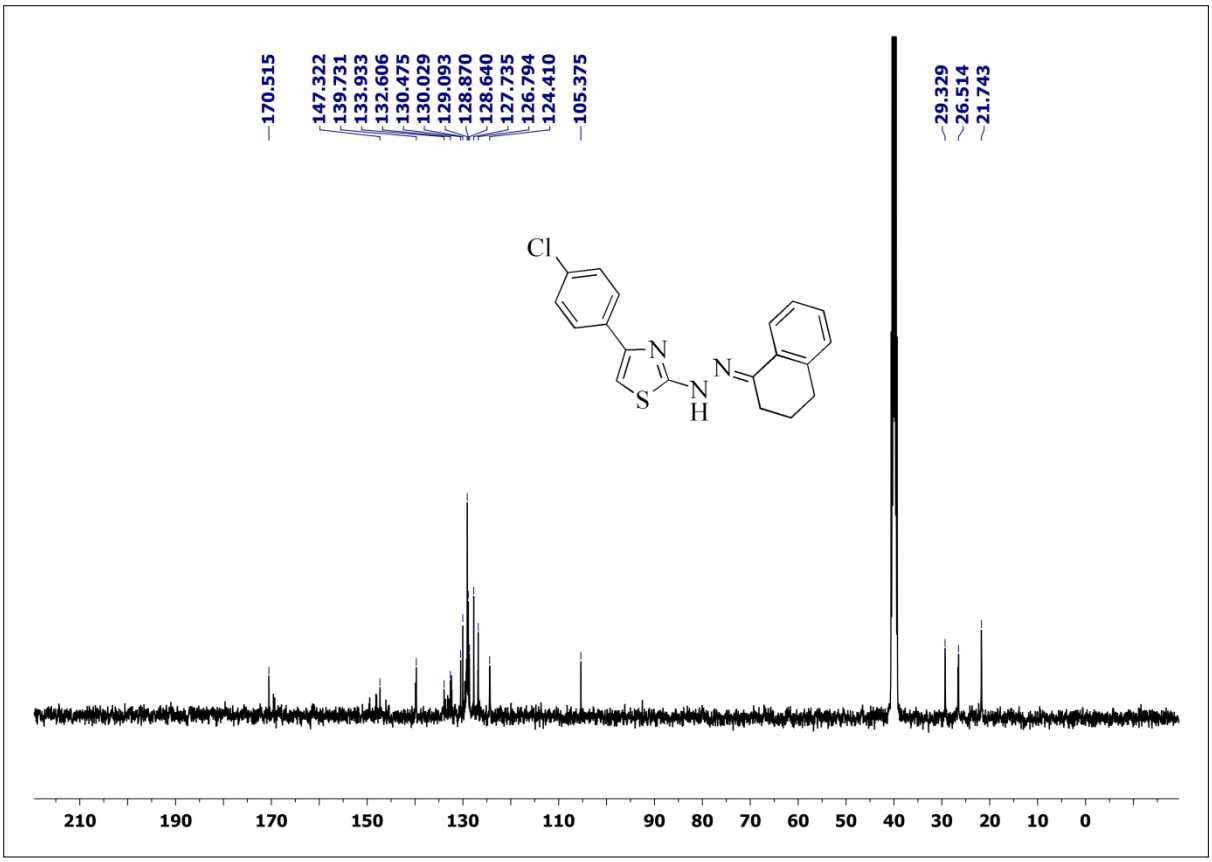
CMR Spectrum of compound **18b**



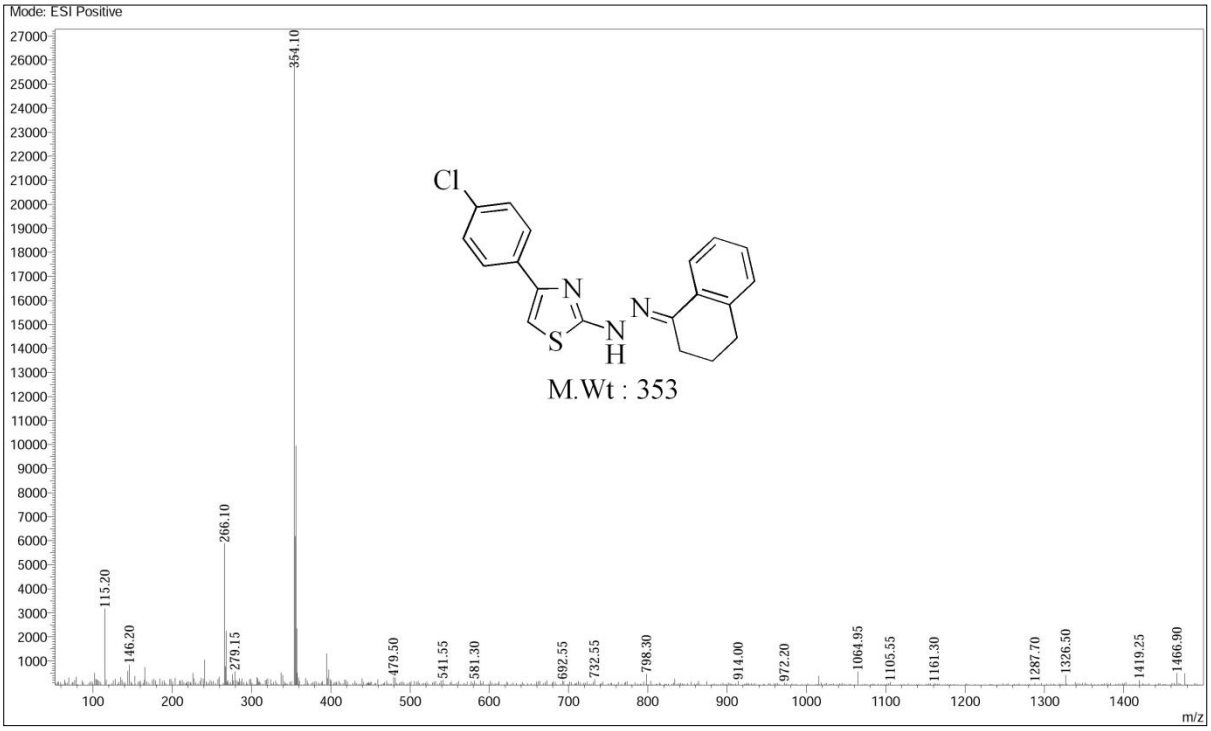
Mass Spectrum of compound **18b**



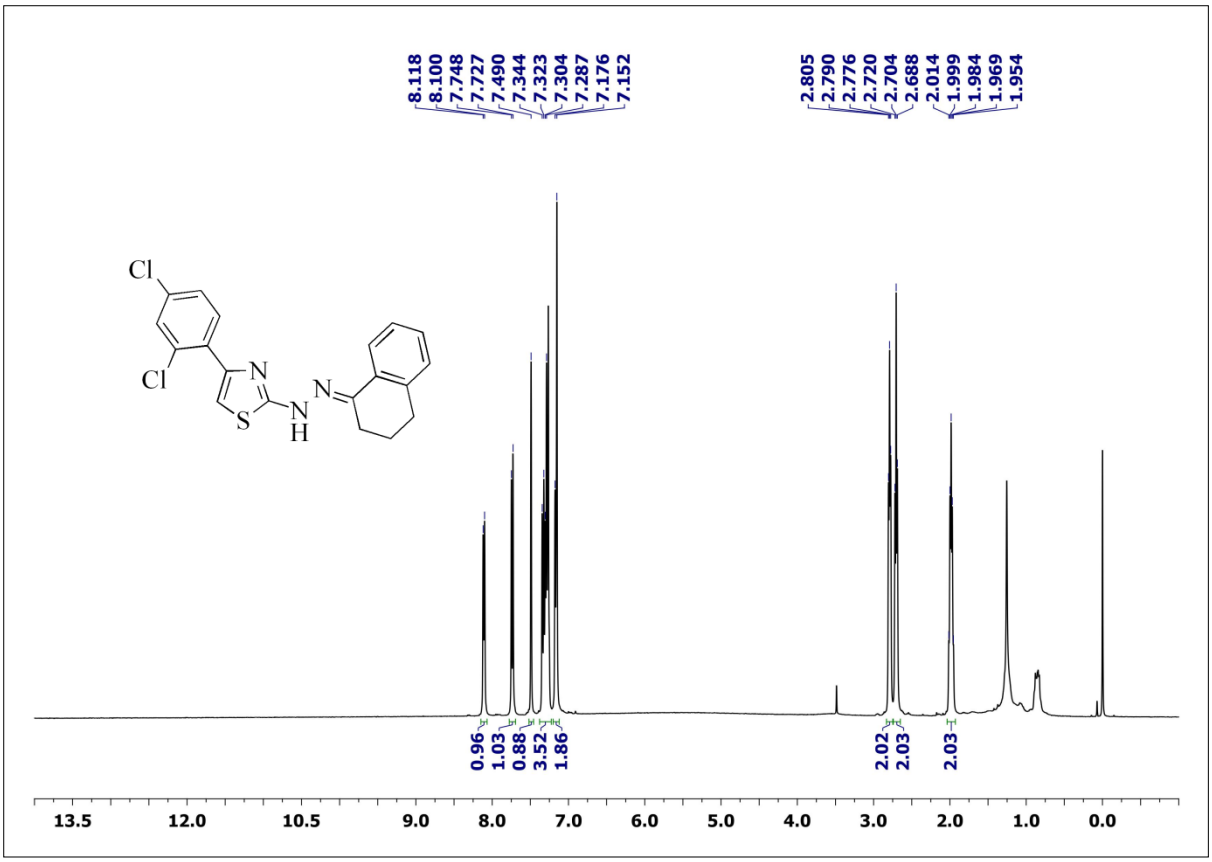
PMR Spectrum of compound **18c**



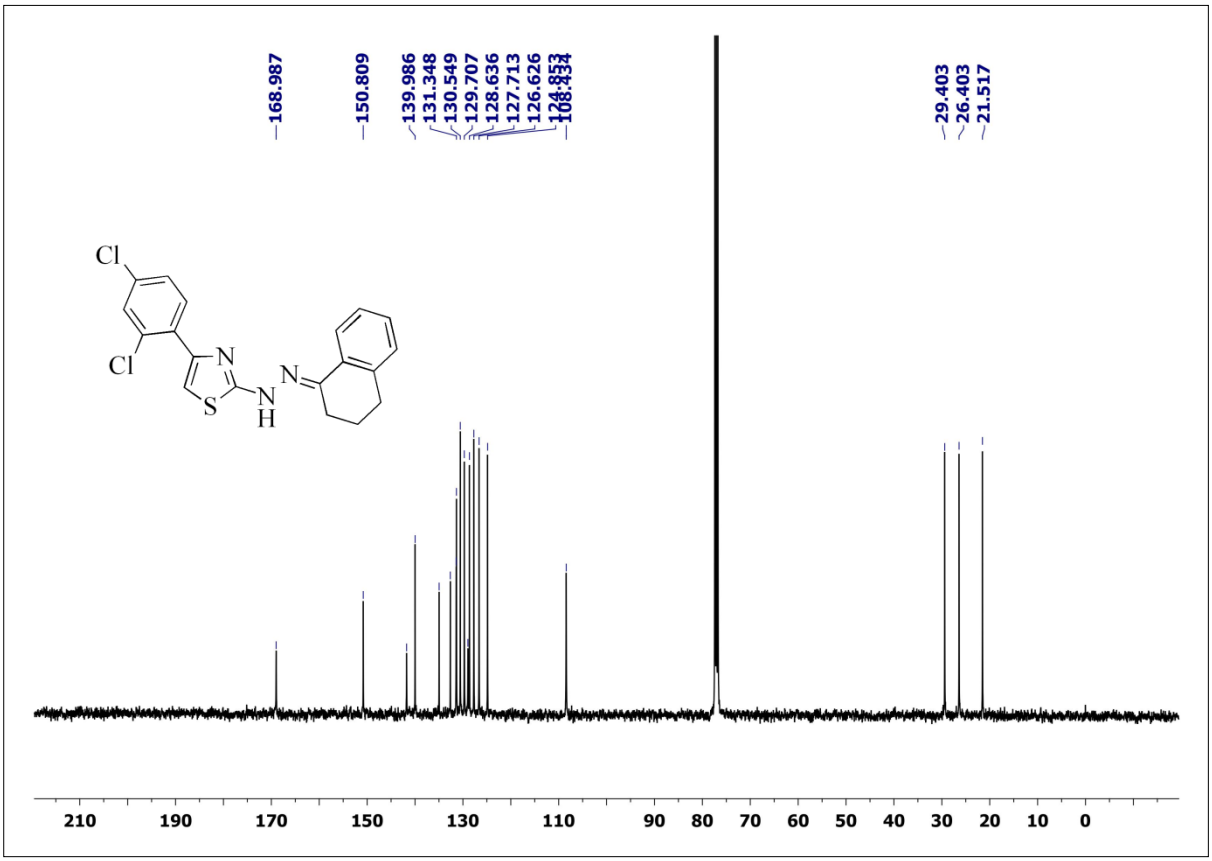
CMR Spectrum of compound **18c**



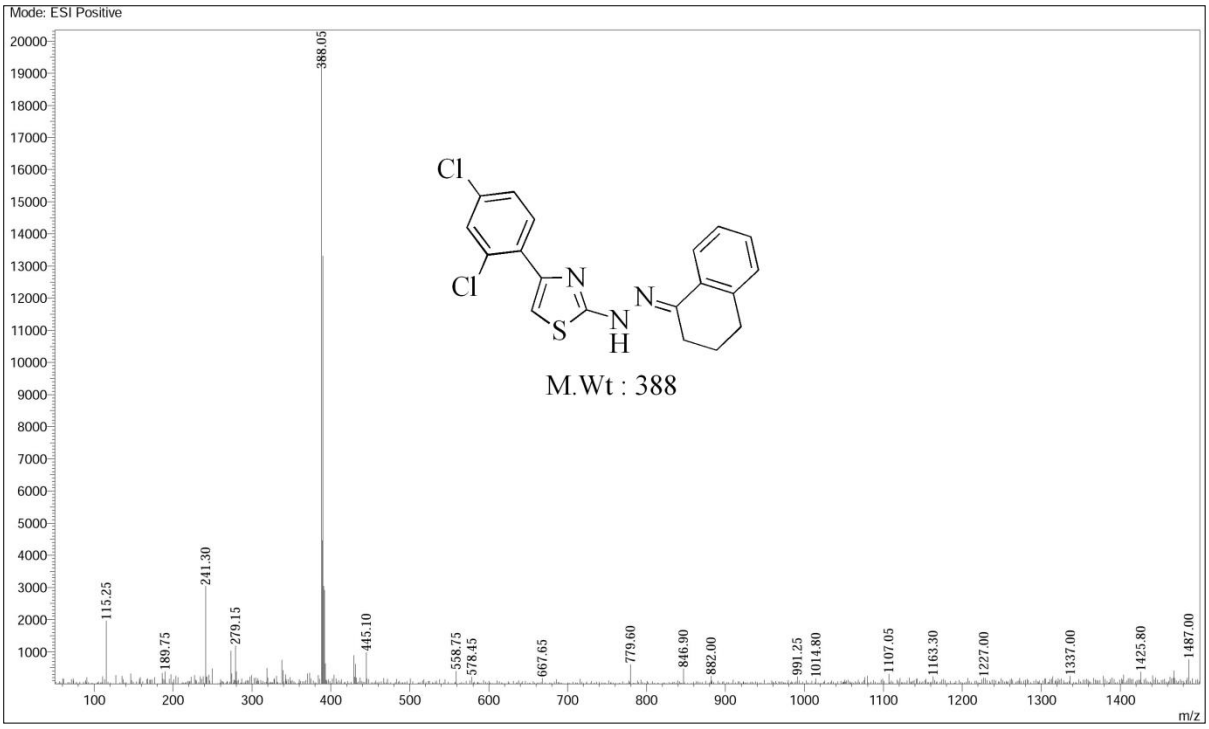
Mass Spectrum of compound **18c**



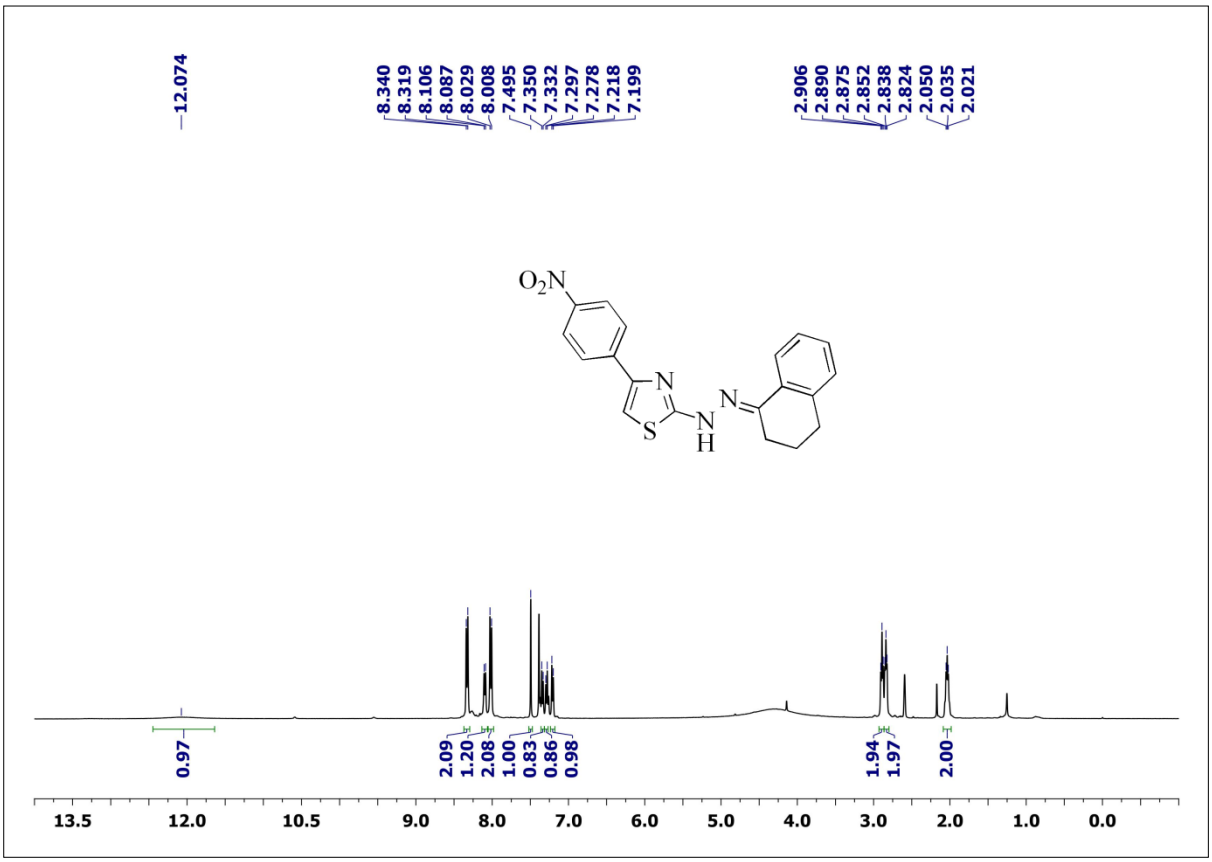
PMR Spectrum of compound **18d**



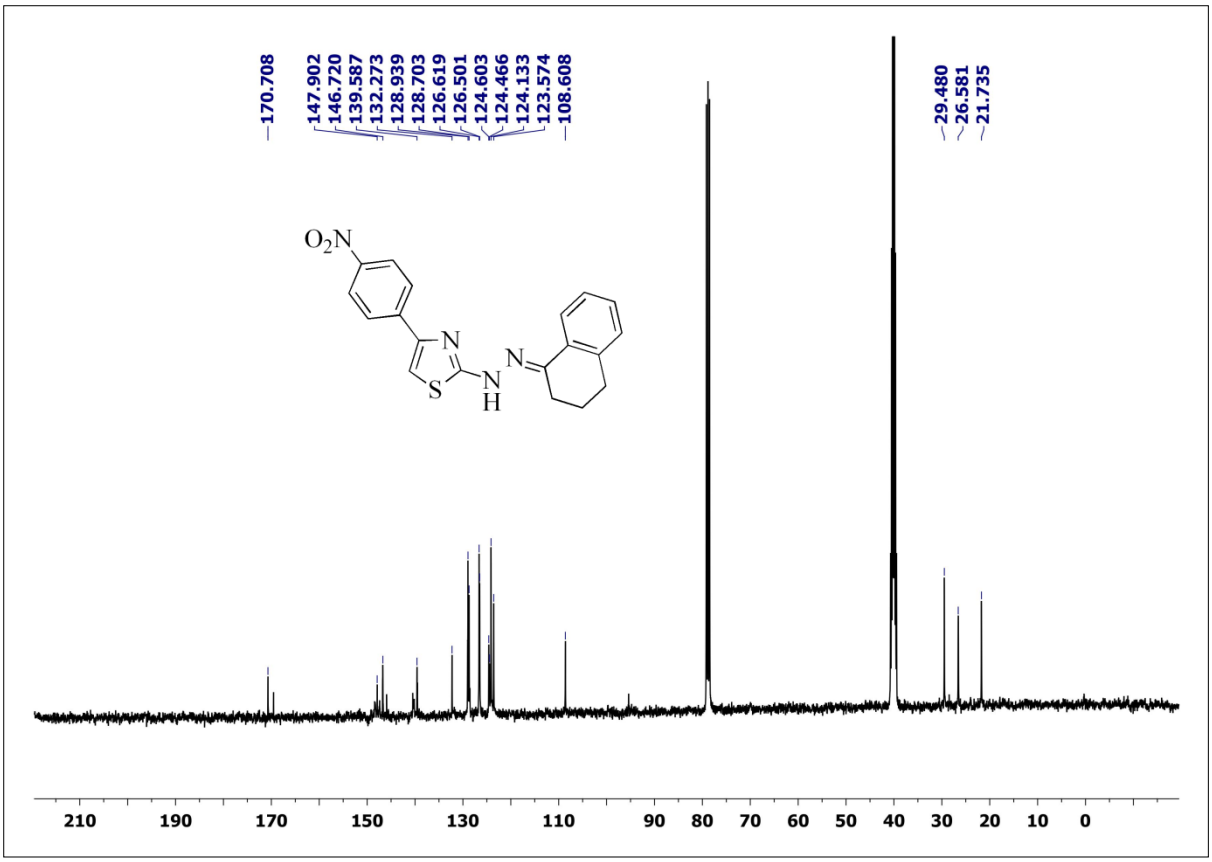
CMR Spectrum of compound **18d**



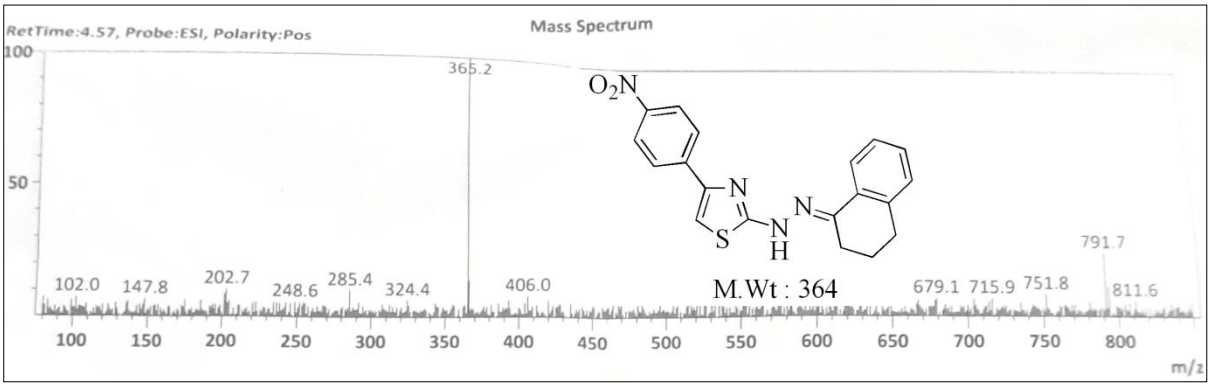
Mass Spectrum of compound **18d**



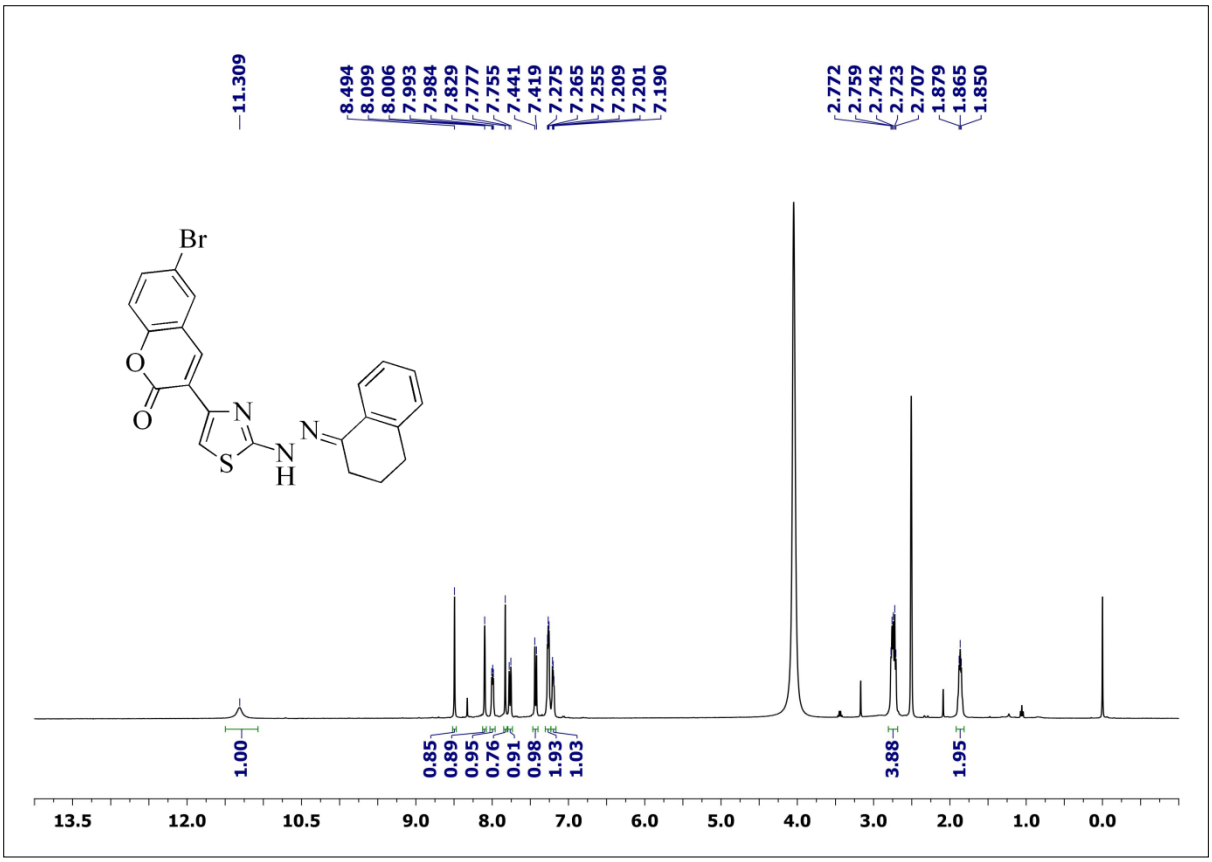
PMR Spectrum of compound **18e**



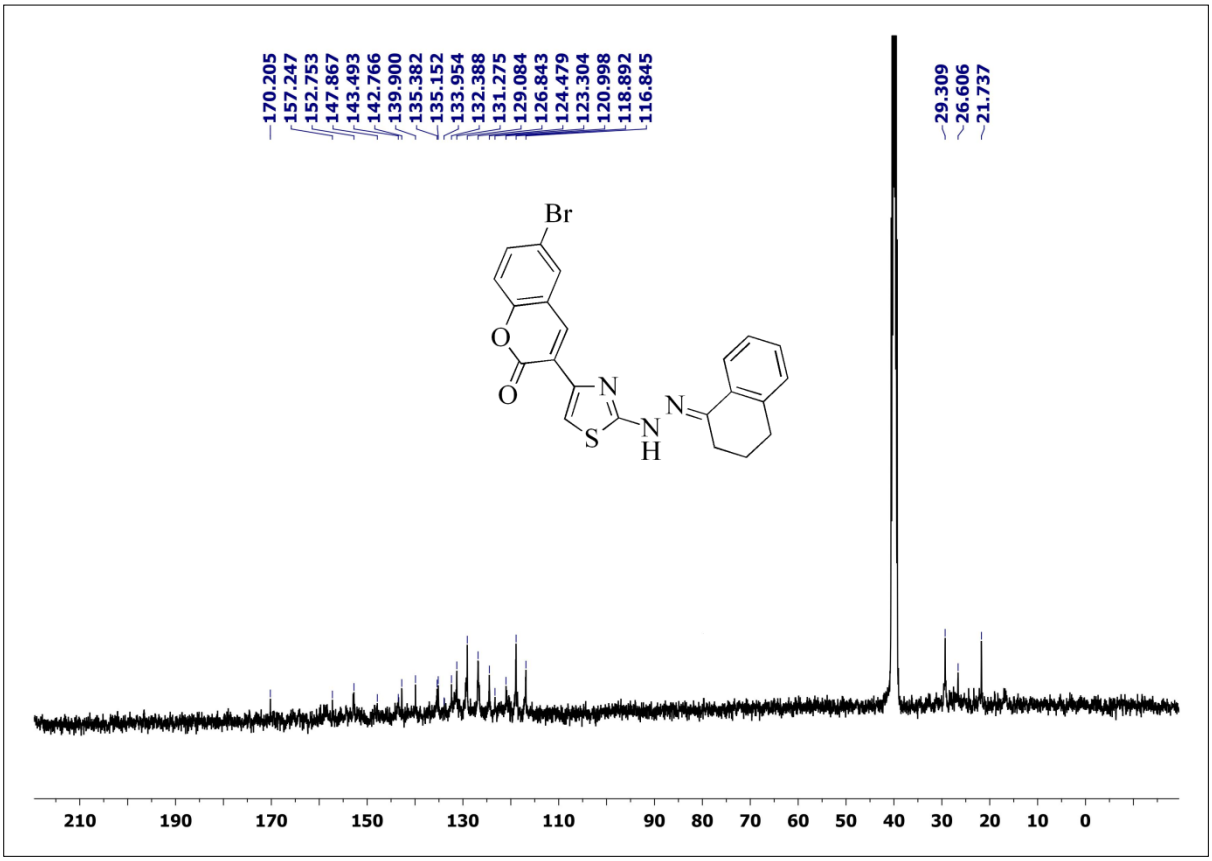
CMR Spectrum of compound **18e**



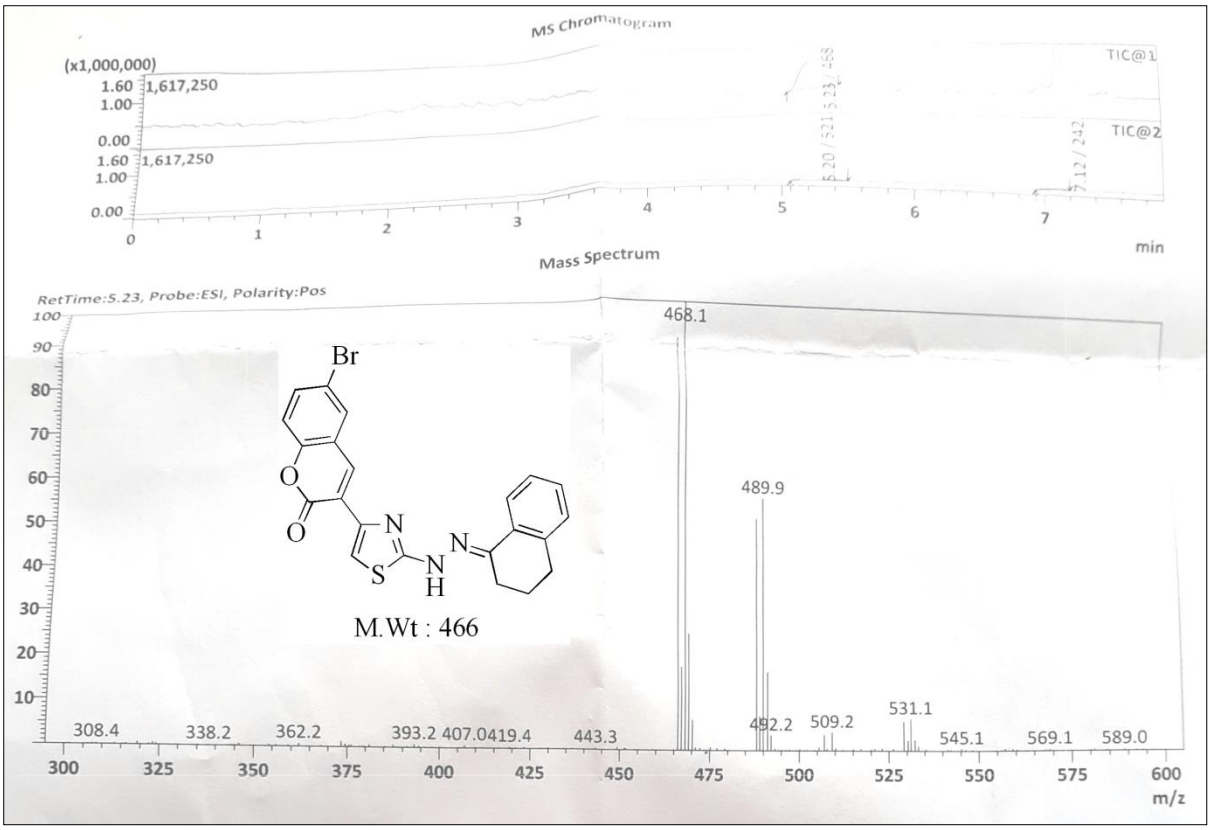
Mass Spectrum of compound **18e**



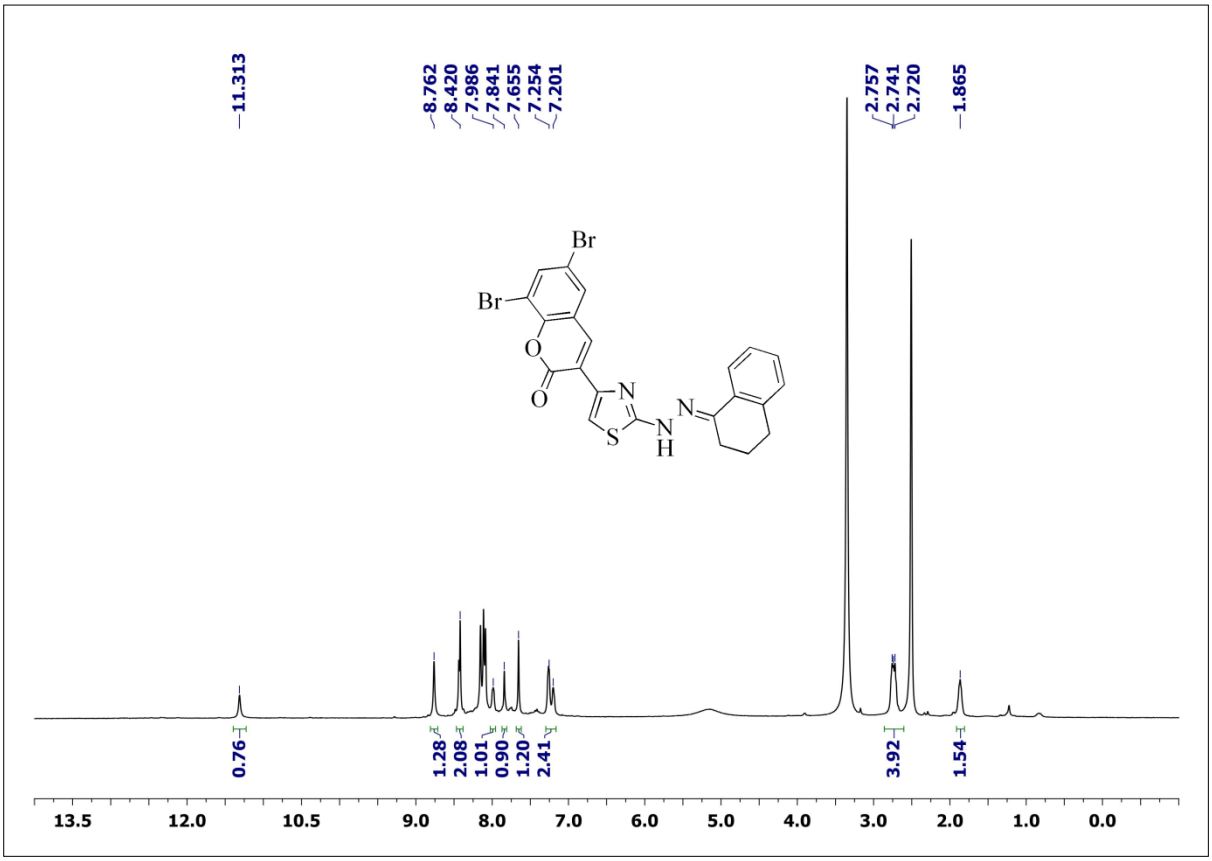
PMR Spectrum of compound **18f**



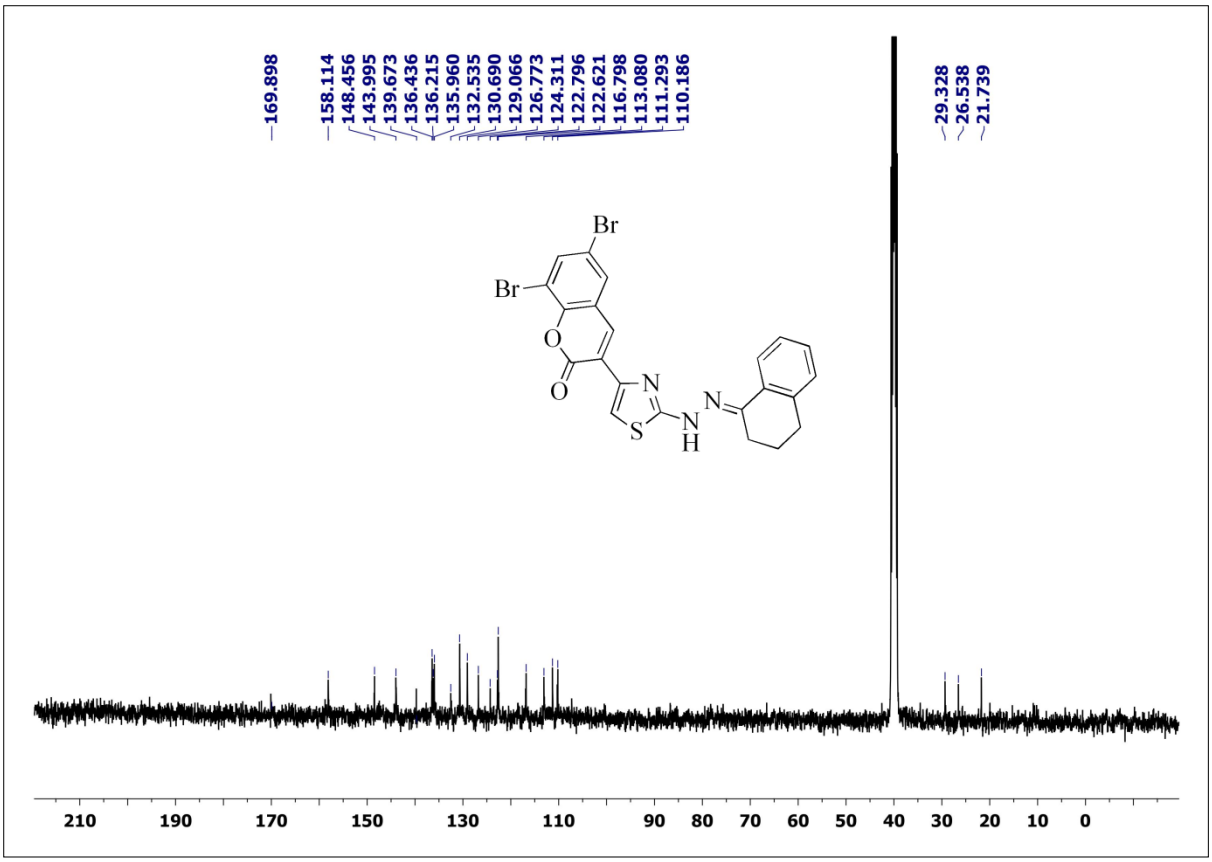
CMR Spectrum of compound **18f**



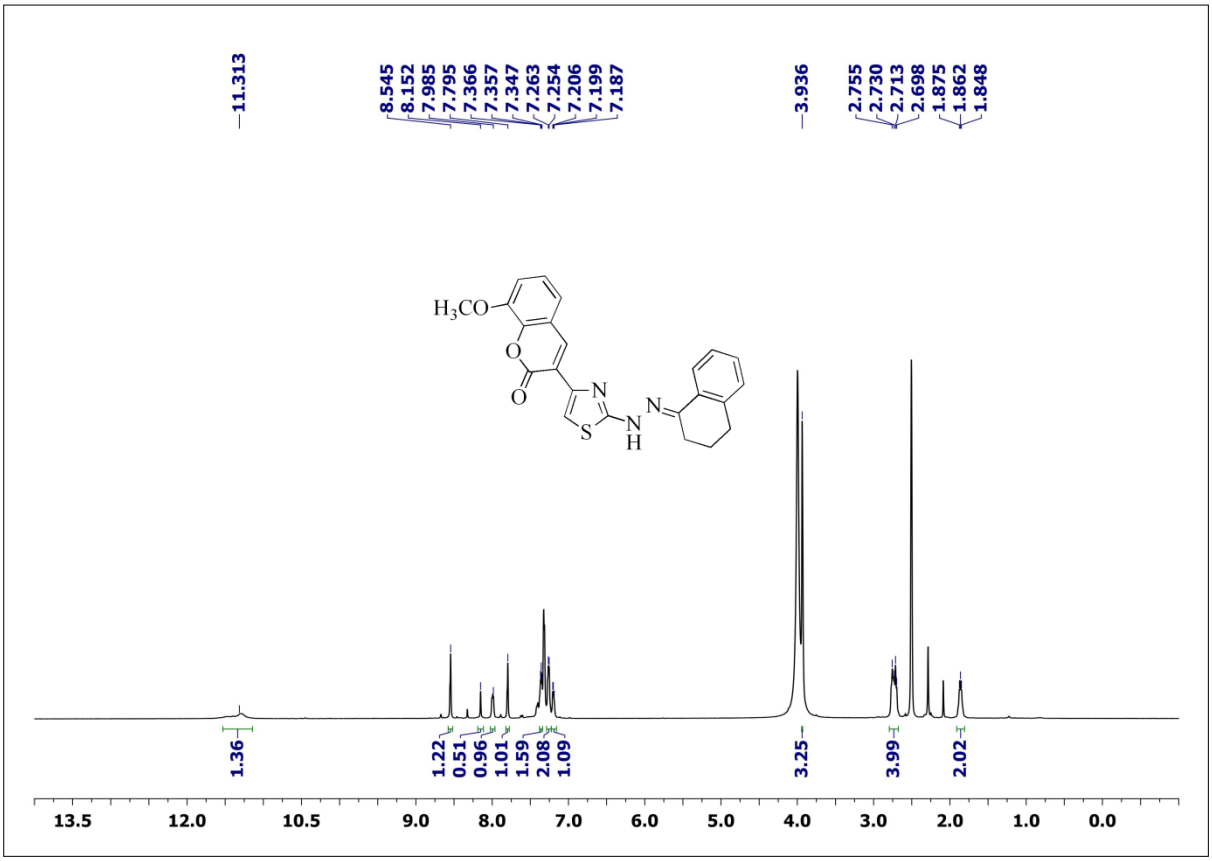
Mass Spectrum of compound **18f**



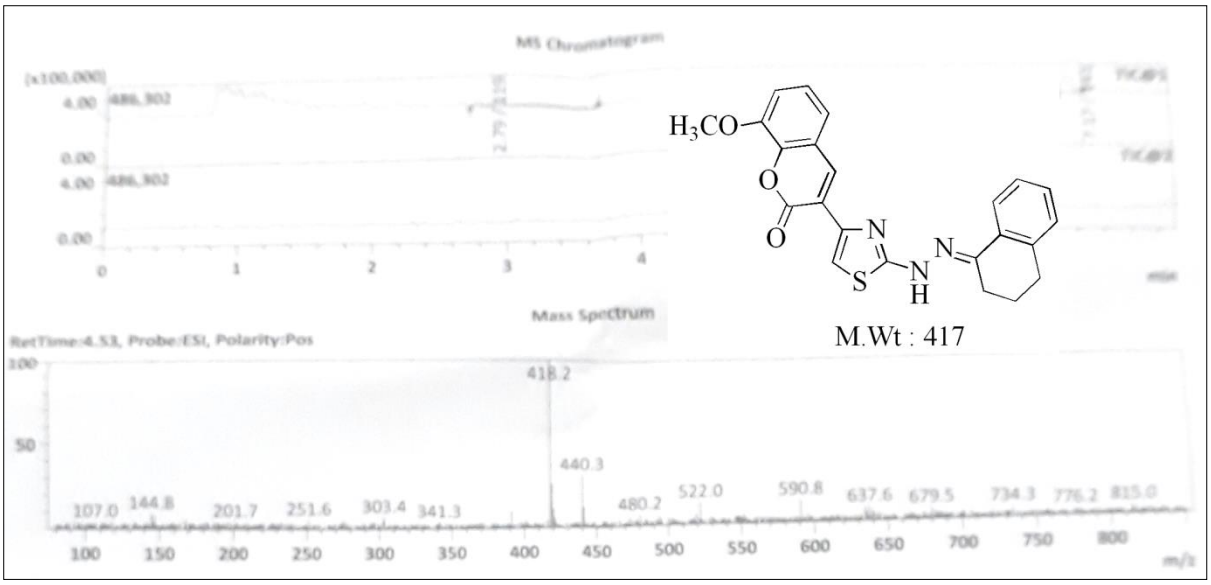
PMR Spectrum of compound **18g**



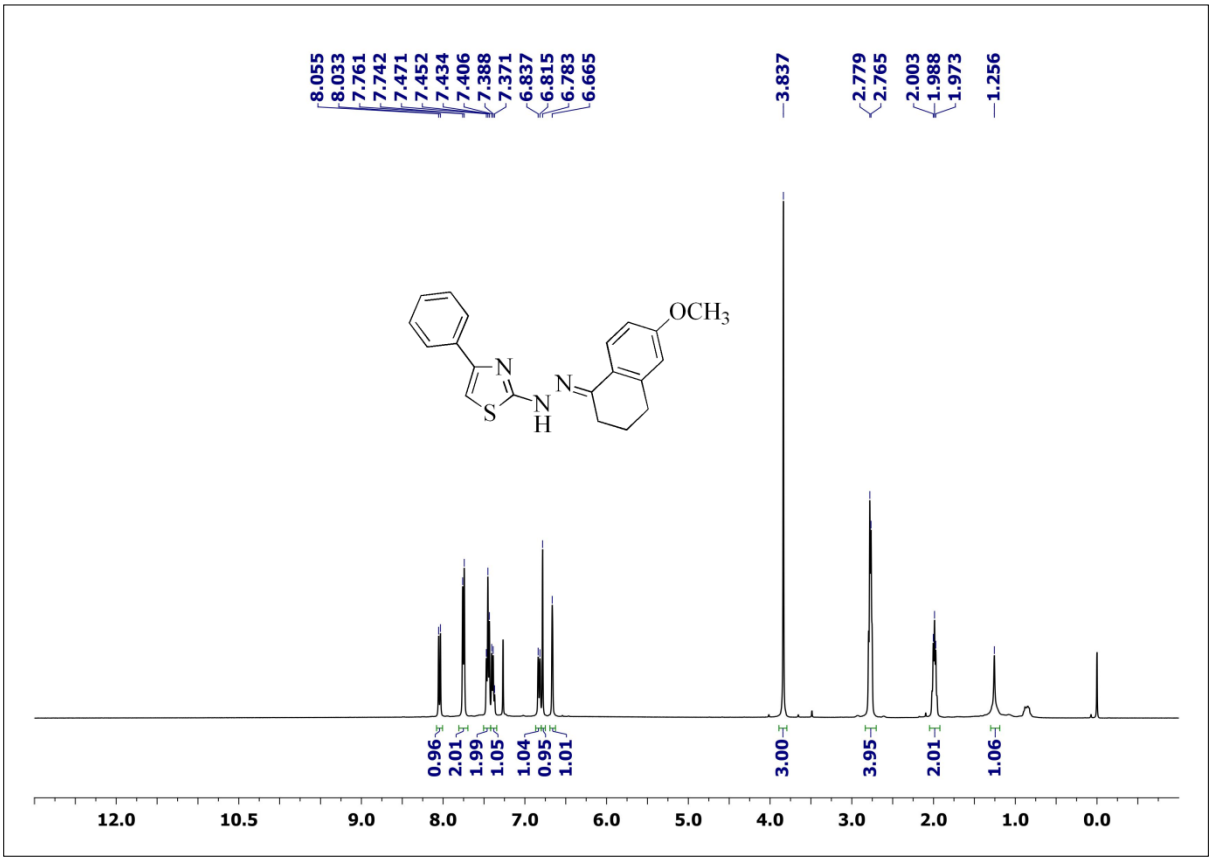
CMR Spectrum of compound **18g**



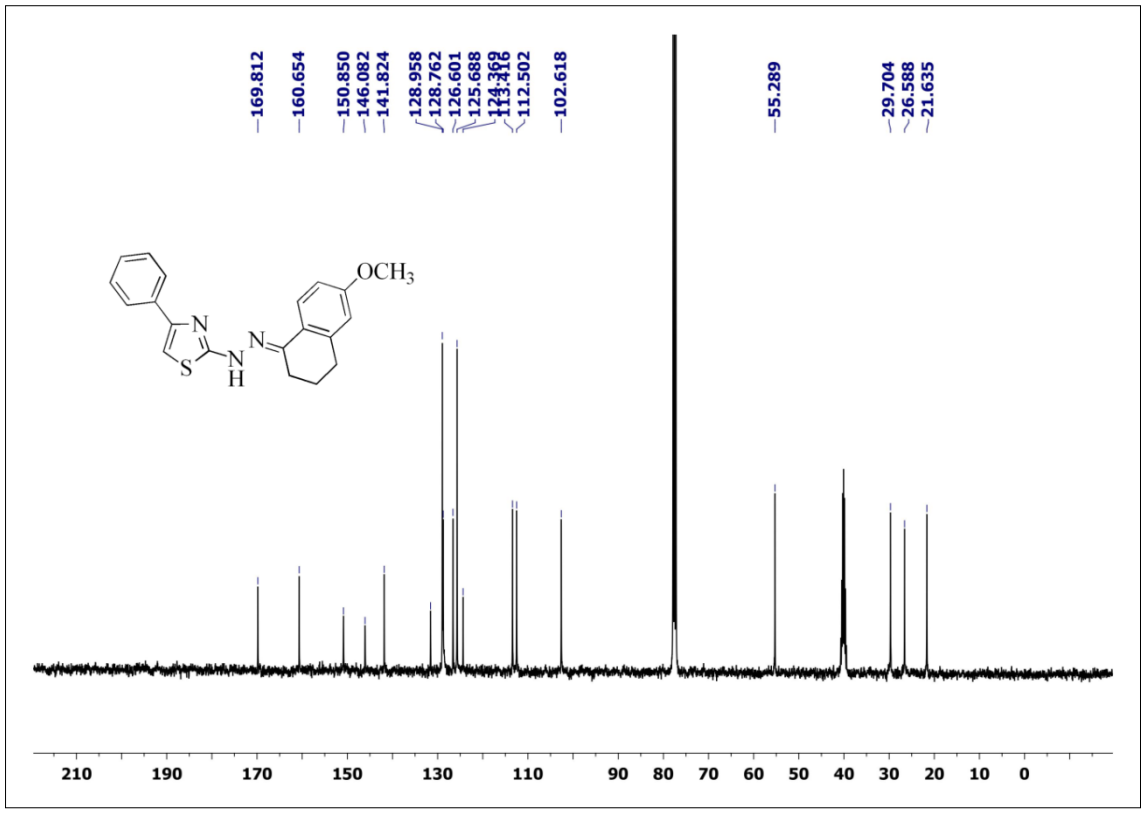
PMR Spectrum of compound **18h**



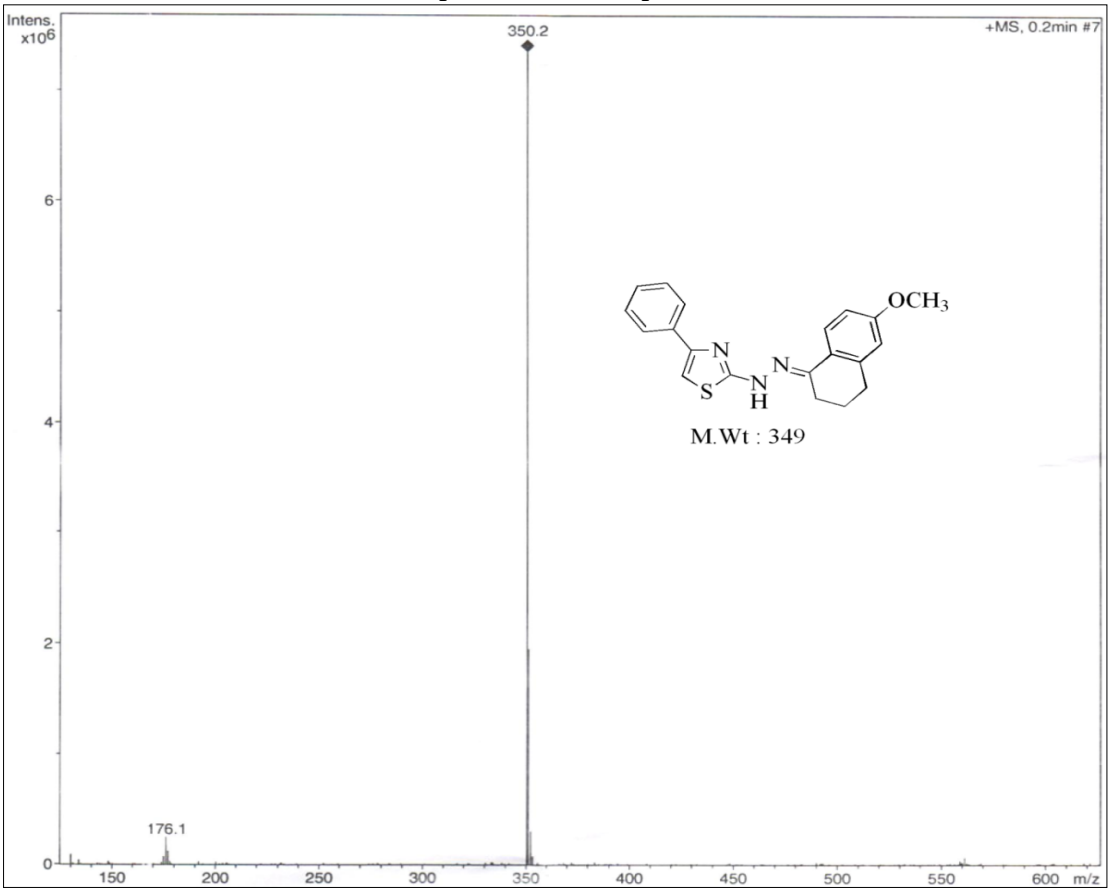
Mass Spectrum of compound **18h**



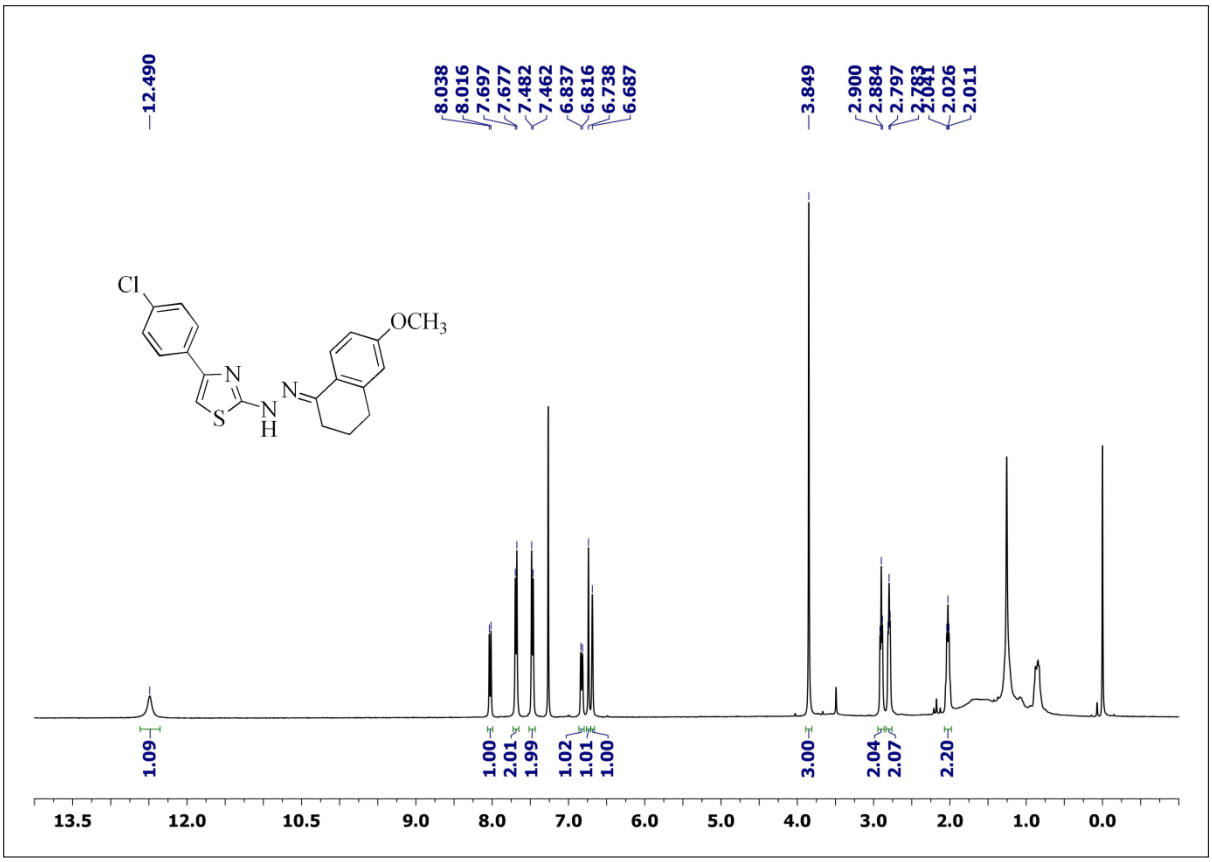
PMR Spectrum of compound **18i**



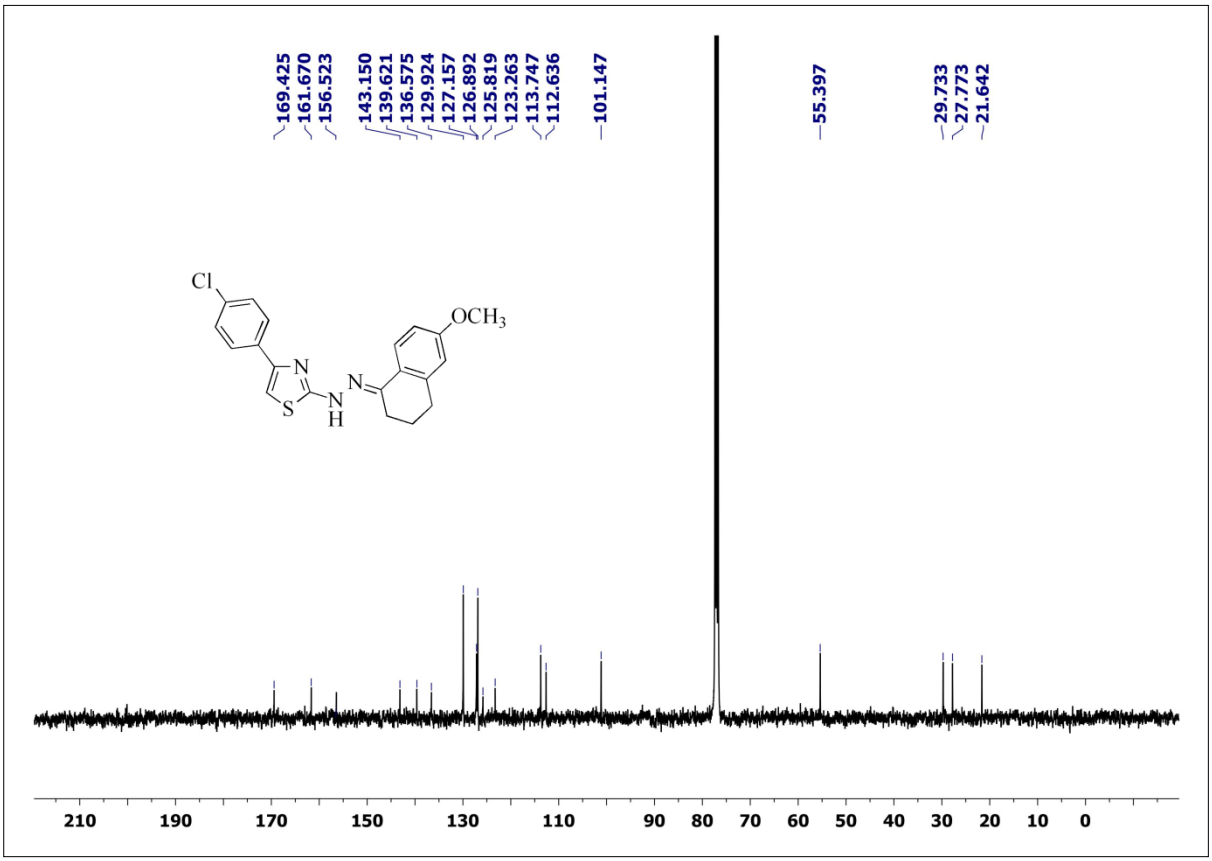
CMR Spectrum of compound **18i**



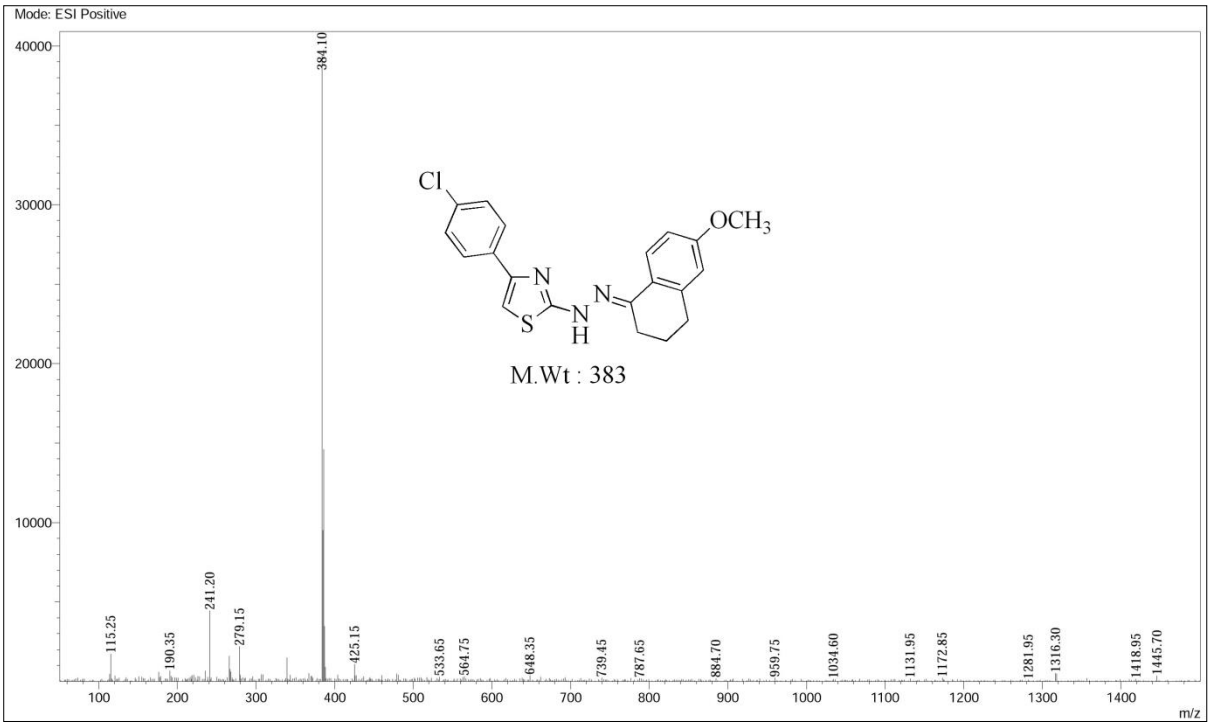
Mass Spectrum of compound **18i**



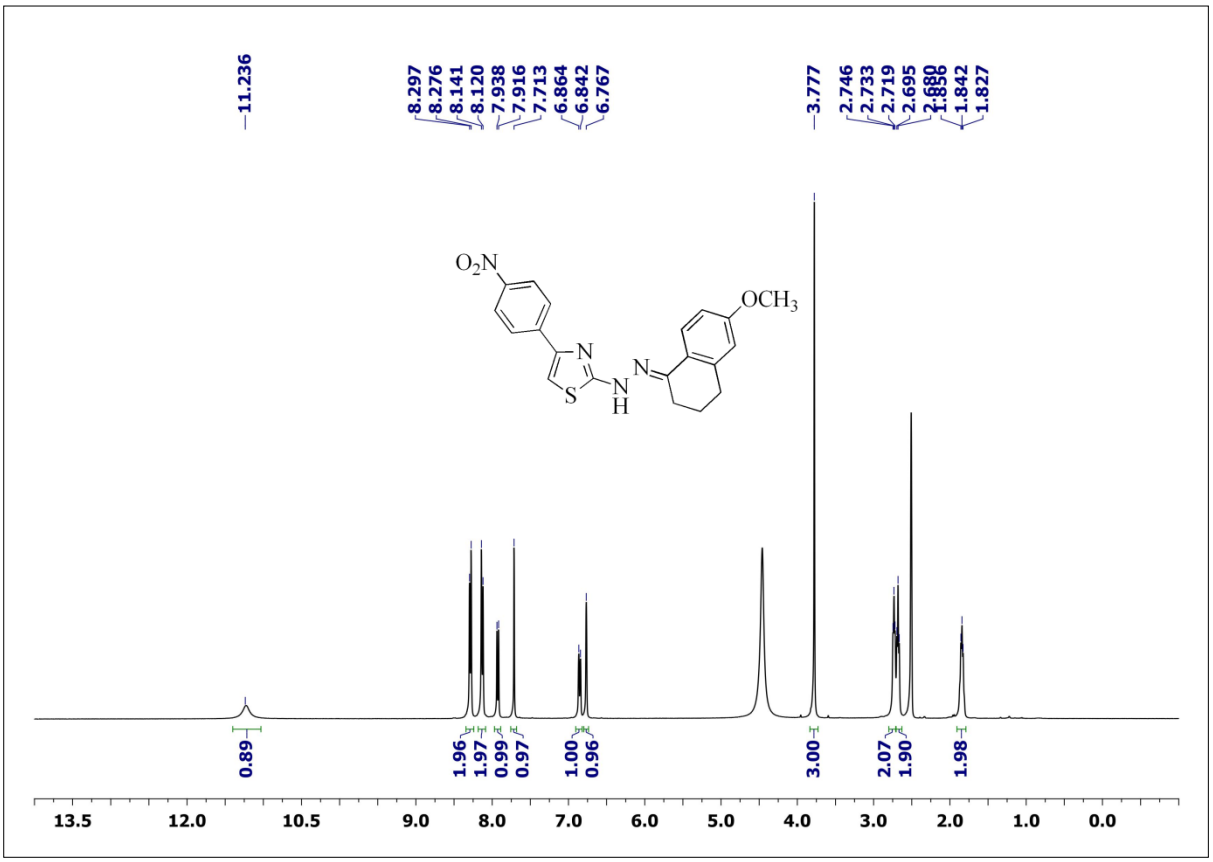
PMR Spectrum of compound **18j**



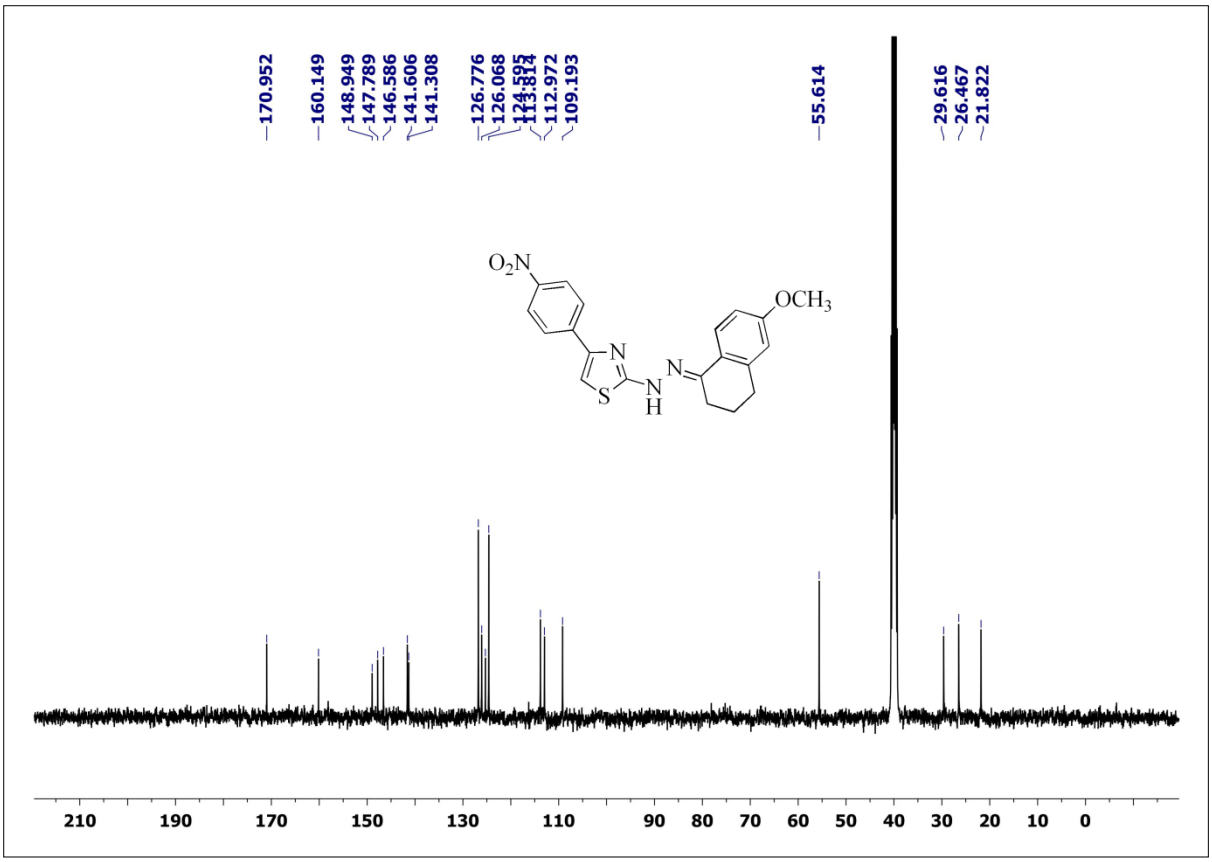
CMR Spectrum of compound **18j**



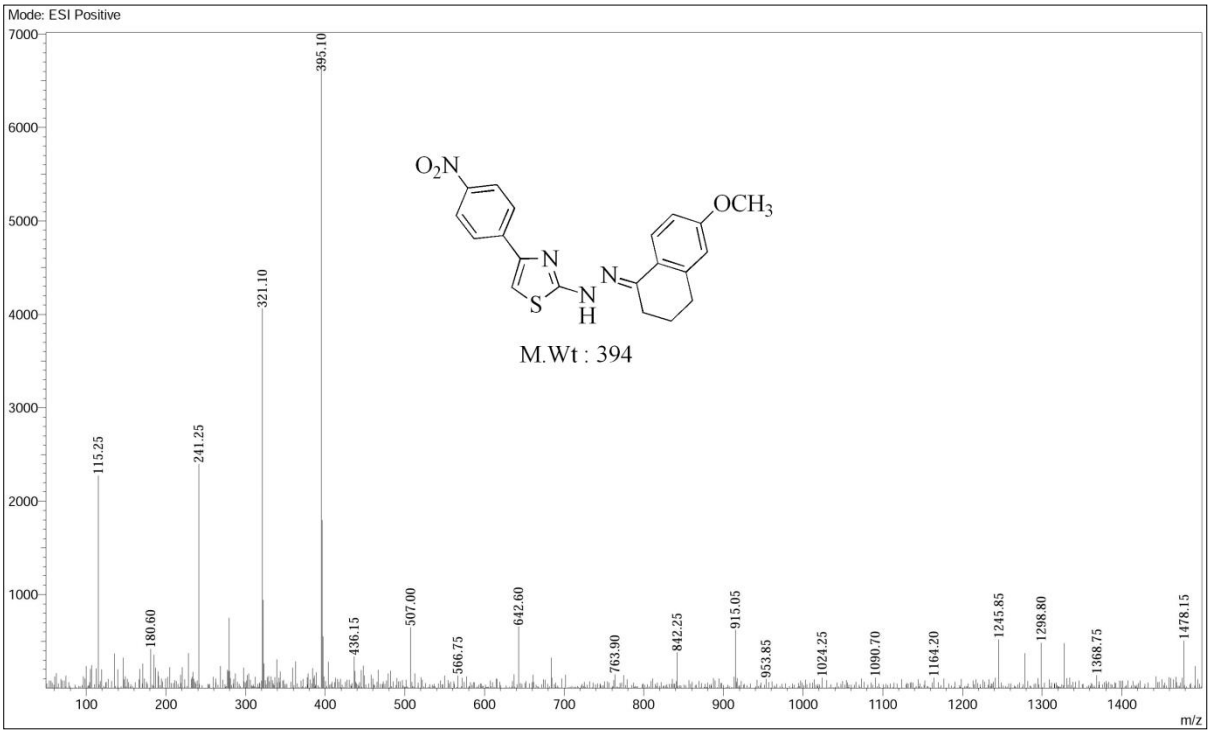
Mass Spectrum of compound **18j**



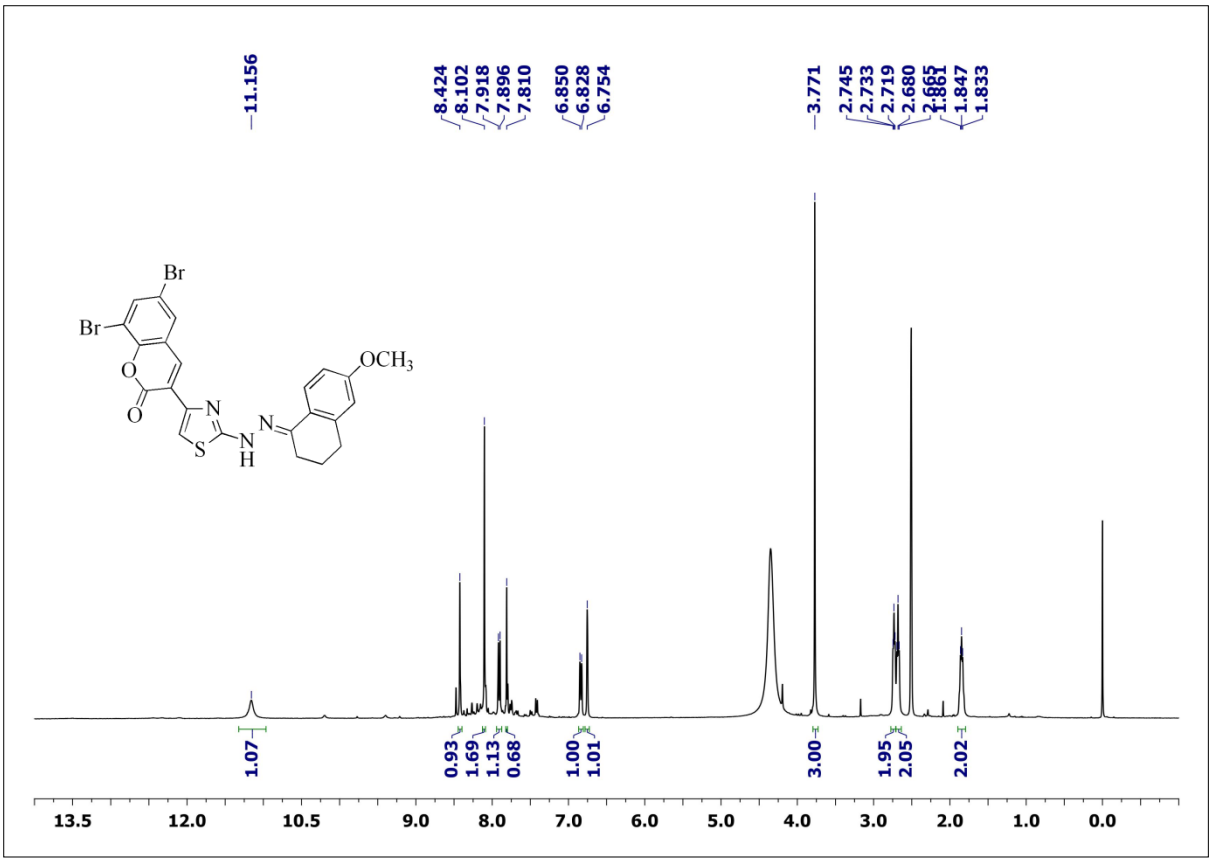
PMR Spectrum of compound **18k**



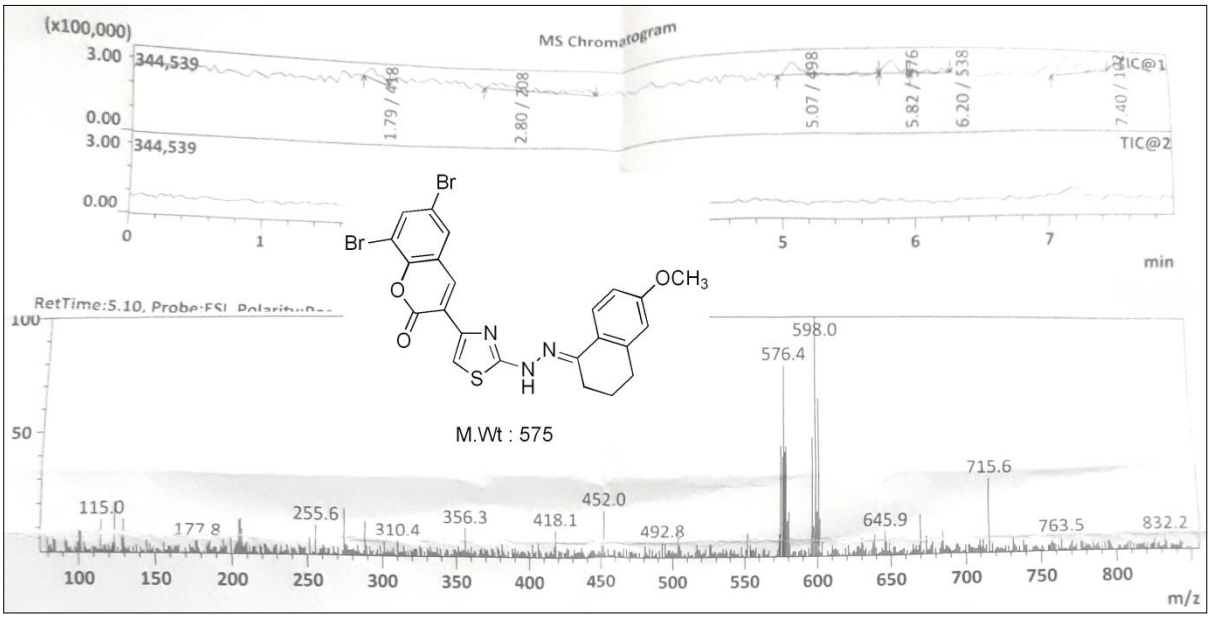
CMR Spectrum of compound **18k**



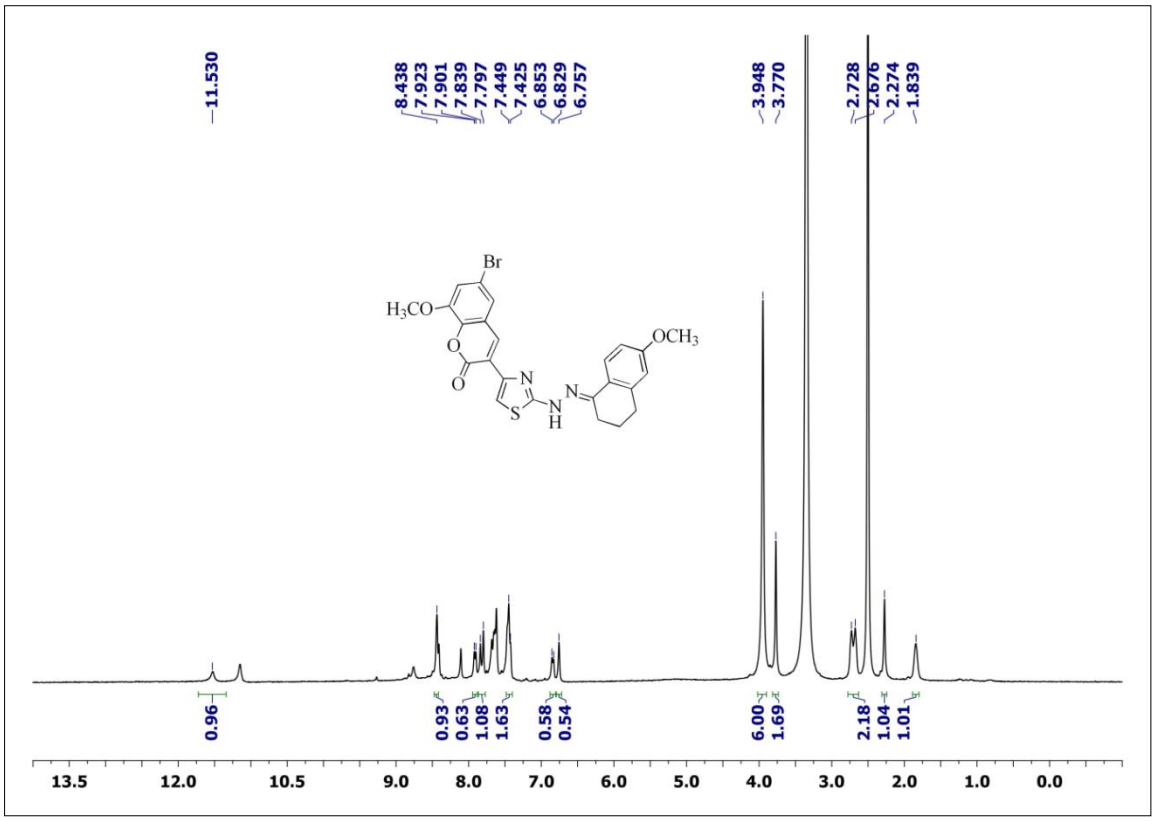
Mass Spectrum of compound **18k**



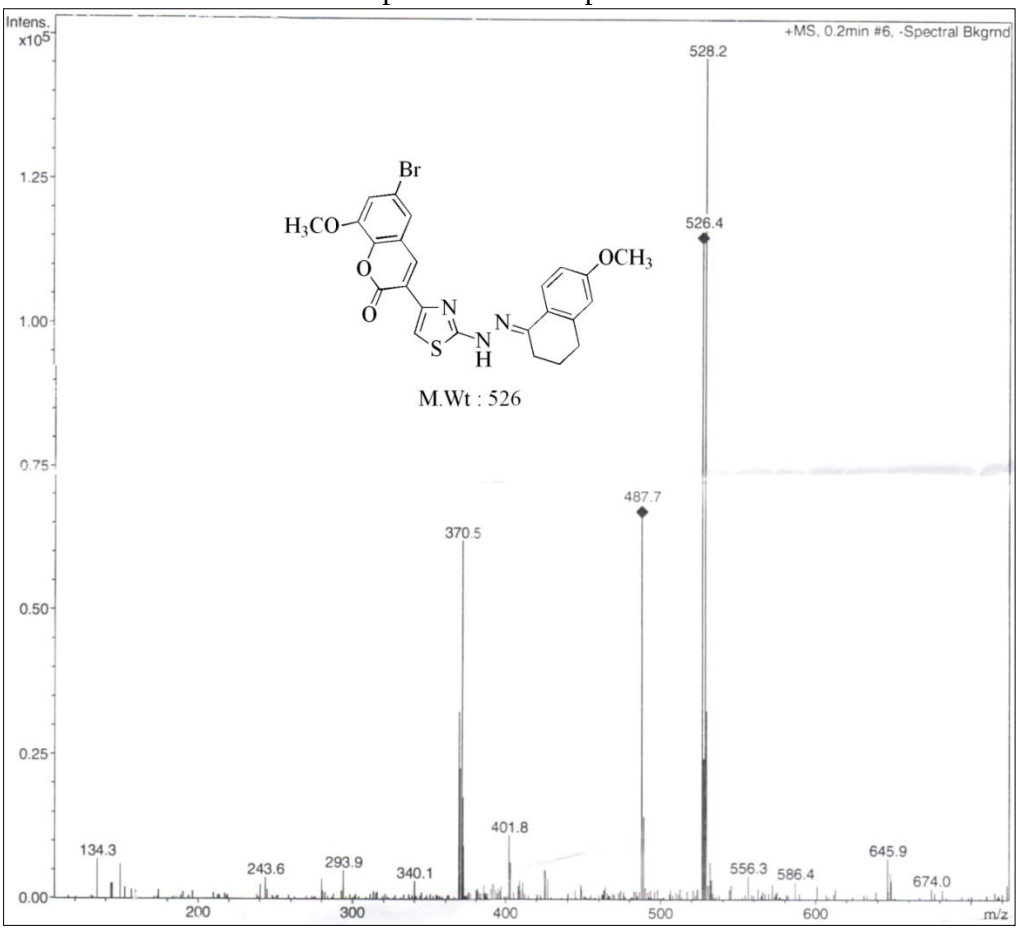
PMR Spectrum of compound **18l**



Mass Spectrum of compound **18l**



PMR Spectrum of compound **18m**



Mass Spectrum of compound **18m**

References:

[1] Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143-1191.

[2] Chhabria, M. T.; Patel, S.; Modi, P.; Brahmkshatriya, P. S. *Curr Top Med Chem.* **2016**, *16*, 2841-2862.

[3] Aulakh, V. S.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 5750-5753.

[4] Yu, H.; Qin, Z.; Dai, H.; Zhang, X.; Qin, X.; Wang, T.; Fang, J. *J. Agric. Food Chem.* **2008**, *56*, 11356-11360.

[5] Hassan, A. A.; Ibrahim, Y. R.; EI-Sheref, E. M.; Abdel-Aziz, M.; Brase, S.; Nieger, M. *Arch. Pharm. Chem. Life Sci.* **2013**, *346*, 562-570.

[6] Yu-Jing, L.; Qiang, D.; Jin-Qiang, H.; Dong-Ping, H.; Zheng-Ya, W.; Kun, Z.; Leonard, G. L.; Wing-Leung, W.; Cheuk-Fai, C. *ACS Chem. Biol.* **2016**, *11*, 1019-1029.

[7] Bhaskara Reddy, M. V.; Srinivasulu, D.; Peddanna, K.; Apparao, Ch.; Ramesh, P. *Synth. Commun.* **2015**, *45*, 2592-2600.

[8] Bueno, J. M.; Carda, M.; Crespo, B.; Cunat, A. C.; de Cozar, C.; Leon, M. L.; Marco, J. A.; Roda, N.; Sanz-Cervera, J. F. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3938-3944.

[9] Madni, M.; Hameed, S.; Ahmed, M. N.; Tahir, M. N.; Al-Masoudi, N. A.; Pannecouque, C. *Med Chem Res.* **2017**, *26*, 2653-2665.

[10] Zheng, S.; Zhong, Q.; Xi, Y.; Mottamal, M.; Zhang, Q.; Schroeder, R. L.; Sridhar, J.; He, L.; McFerrin, H.; Wang, G. *J. Med. Chem.* **2014**, *57*, 6653-6667.

[11] Bouherrou, H.; Saidoun, A.; Abderrahmani, A.; Abdellaziz, L.; Rachedi, Y.; Dumas, F.; Demenceau, A. *Molecules.* **2017**, *22*, 757.

[12] Lino,C.I.; de Souza, I. G.; Borelli, B. M.; Matos, T. T. S.; Teixeira, I. N. S.; Ramos, J. P.; Fagundes, E. M. S.; Fernandes, P. O.; Maltarollo, V. G.; Johann, S.; Oliveira, R. B. *Eur. J. Med. Chem.* **2018**, *151*, 248-260.

[13] Nastasa, C.; Tiperciuc, B.; Oniga, S.; Pirnau, A.; Ionescu, M.; Tarlungeanu, D.; Palage, M.; Verite, P.; Oniga, O. *Farmacia.* **2013**, *61*, 5

[14] Moraes Gomes, P. A. T.; Barbosa, M. O.; Santiago, E. F.; Cardoso, M. V. O.; Costa, N. T.C.; Hernandes, M. Z.; Moreira, D. R. M.; Silva, A. C.; Santos, T. A. R.; Pereira, V. R. A.; Santosd, F. A. B.; Pereira, G. A. N.; Ferreira, R. S.; Leite, A. C. L. *Eur. J. Med. Chem.* **2016**, *121*, 387-398.

[15] Maillard, L. T.; Bertout, S.; Quinonero, O.; Akaline, G.; Turan-Zitouni, G.; Fulcrand, P.; Demirci, F.; Martinez, J.; Masurier, N. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1803-1807.

[16] Cardoso, M. V. O.; Siqueira, L. R. P.; Silva, E. B.; Costa, L. B.; Hernandes, M. Z.; Rabello, M. M.; Ferreira, R. S.; Cruz, L. F.; Moreira, D. R. M.; Pereira, V. R. A.; Castro, M. C. A. B.; Bernhardt, P. V.; Leite, A. C. L. *Eur. J. Med. Chem.* **2014**, *86*, 48-59.

[17] de Oliveira Filho, G. B.; de Oliveira Cardoso, M. V.; Espindola, J. W. P.; Silva, D. A. O.; Ferreira, R. S.; Coelho, P. L.; Anjos, P. S.; Santos, E. S.; Meira, C. S.; Moreira, D. R. M.; Soares, M. B. P.; Leite, A. C. L. *Eur. J. Med. Chem.* **2017**, *141*, 346-361.

[18] Mahmoodi, N. O.; Khalili, B.; Rezaeianzade, O.; Ghavidast, A.; *Res Chem Intermed.* **2016**, *42*, 6531-6542.

[19] Silva, E. B. Silva, D. A. O.; Oliveira, A. R.; Mendes, C. H. S.; Santos, T. A. R.; Silva, A. C.; Castro, M. C. A.; Ferreira, R. S.; Moreira, D. R. M.; Cardoso, M. V. O.; Simone, C. A.; Pereira, V. R. A.; Leite, A. C. L. *Eur. J. Med. Chem.* **2017**, *130*, 39-50.

[20] Brito, C. C.B.; Silva, H. V. C.; Brondani, D. J.; Faria, A. R.; Ximenes, R. M.; Silva, I. M.; Albuquerque, J. F. C.; Castilho, M. S. *J. Enzyme inhib. Med. Chem.* **2019**, *34*, 333-342.

[21] Yurttas, L.; Sahin, Z.; Er, S.; Demirayak, S. *Acta Pharm. Sci.* **2016**, *54*, 43-51.

[22] Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Carradori, S.; Yanez, M.; Orallo, F.; Luisa Sanna, M.; Gallinella, B.; Cirilli, R. *J. Med. Chem.* **2010**, *53*, 6516-6520.

[23] Tran Nguyen, M. A.; Mungara, A. K.; Kim, J. A.; Lee, K. D.; Park, S. *Phosphorus Sulfur Silicon Relat Elem.* **2015**, *190*, 191-199.

[24] Aggarwal, R.; Kumar, S.; Kaushik, P.; Kaushik, D.; Gupta, G. K. *Eur. J. Med. Chem.* **2013**, *62*, 508-514.

[25] Arshad, A.; Osman, H.; Bagley, M. C.; Lam, C. K.; Mohamad, S.; Zahariluddin, A. S. M. *Eur. J. Med. Chem.* **2011**, *46*, 3788-3794.

[26] Rajeswar Rao, V.; Padmanabha Rao, T. V. *Indian J. Chem.* **1986**, *25B*, 413.

[27] Raiford, L. C.; Tanzer, L. K. *Org. Chem.* **1941**, *6*, 722-731.

[28] Brewster, C. M. *J. Am. Chem. Soc.* **1924**, *46*, 2463-2468.

[29] Stept, B. I. *Chem. Ber.* **1994**, *37*, 4022-4027.

[30] Pangal, A.; Shaikh, J. A.; Muiz, G.; Mane, V.; Ahmed, K. *Int. Res. J. Pharm.* **2013**, *4*, 108-110.

[31] Valizadeh, H.; Shockravi, A.; Gholipur, H. *J. Hetrocyclic Chem.* **2007**, *44*, 867-870.

[32] Mohamed, S. B.; Rachedi, Y.; Hamdi, M.; Bideau, F. L.; Dejean, C.; Dumas, F. *Eur. J. Org. Chem.* **2016**, 2628-2636.

[33] Rap. *Gazz. Chim. Ital.* **1897**, *27*, II, 500-506

[34] Koelsch, C. F. *J. Am. Chem. Soc.* **1950**, *72*, 2993-2995.

CHAPTER-III

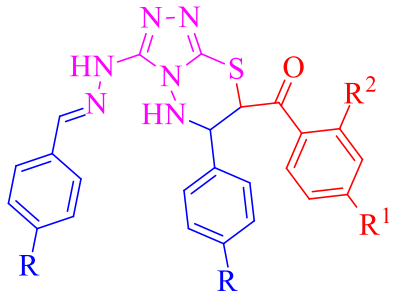
EFFICIENT MULTICOMPONENT SYNTHESIS OF NEW (*E*)-(3-(2-(4-METHOXYBENZYLIDENE)HYDRAZINYL)-6-(4-METHOXYPHENYL)-6,7-DIHYDRO-5*H*-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZIN-7-YL)(PHENYL)METHANONES

AND

A FACILE ONE-POT SYNTHESIS OF 3-(4-CHLOROPHENYL)-1-(6-PHENYL-7*H*-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZIN-3-YL)-1*H*-PYRAZOL-5-AMINES VIA MULTICOMPONENT APPROACH

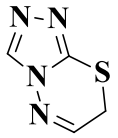
SECTION-A

EFFICIENT MULTICOMPONENT SYNTHESIS OF NEW (*E*)-(3-(2-(4-METHOXYBENZYLIDENE)HYDRAZINYL)-6-(4-METHOXYPHENYL)-6,7-DIHYDRO-5*H*-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZIN-7-YL)(PHENYL)METHANONES



INTRODUCTION

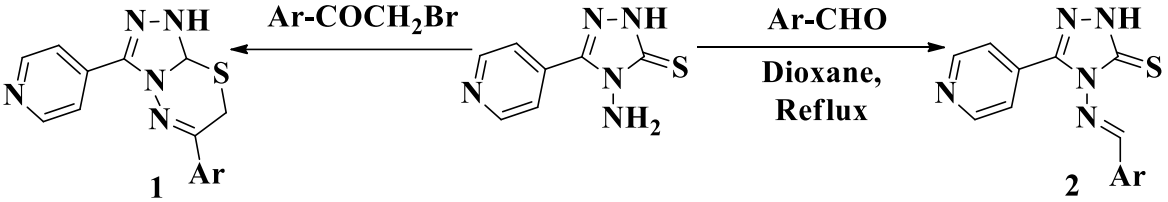
. Triazolothiadiazines are fused with 5, 6-membered heterocyclic compounds containing nitrogen and sulphur heteroatoms. Triazolothiadiazines possess importance in drugs and related compounds[1] and exhibit extensively good anti-microbial,[2] anti-inflammatory,[3] antiviral,[4] anti-leishmanial,[5] anti-HIV and antitumor,[6] antibacterial, antifungal,[7] analgesic,[8] anthelmintic[9] and anticancer activities.[10]



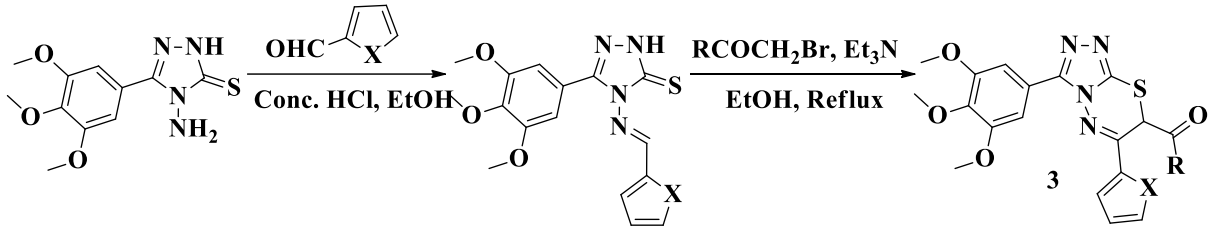
Schiff bases possess good biological activity.[11] In particular, Schiff bases bearing heterocyclic molecules show enhanced therapeutic and pharmacological,[12] antifungal,[13] antibacterial,[14] antitumor, antiviral,[15] antitubercular,[16] antioxidant,[17] antimicrobial,[18] anticancer[19] and anti-HIV activities.[20]

Different methods of synthesis of [1,2,4]triazolo[3,4-*b*]thiadizines.

Hussein *et al.*[21] synthesized compound **1** using 3-(4-pyridyl)-4-amino-5-mercapto-1,2,4-triazole and phenacyl bromide in absolute ethanol. Compound (**2**) were synthesised by the reaction of aryl aldehyde with 3-(4-pyridyl)-4-amino-5-mercapto-1,2,4-triazole in dioxane.

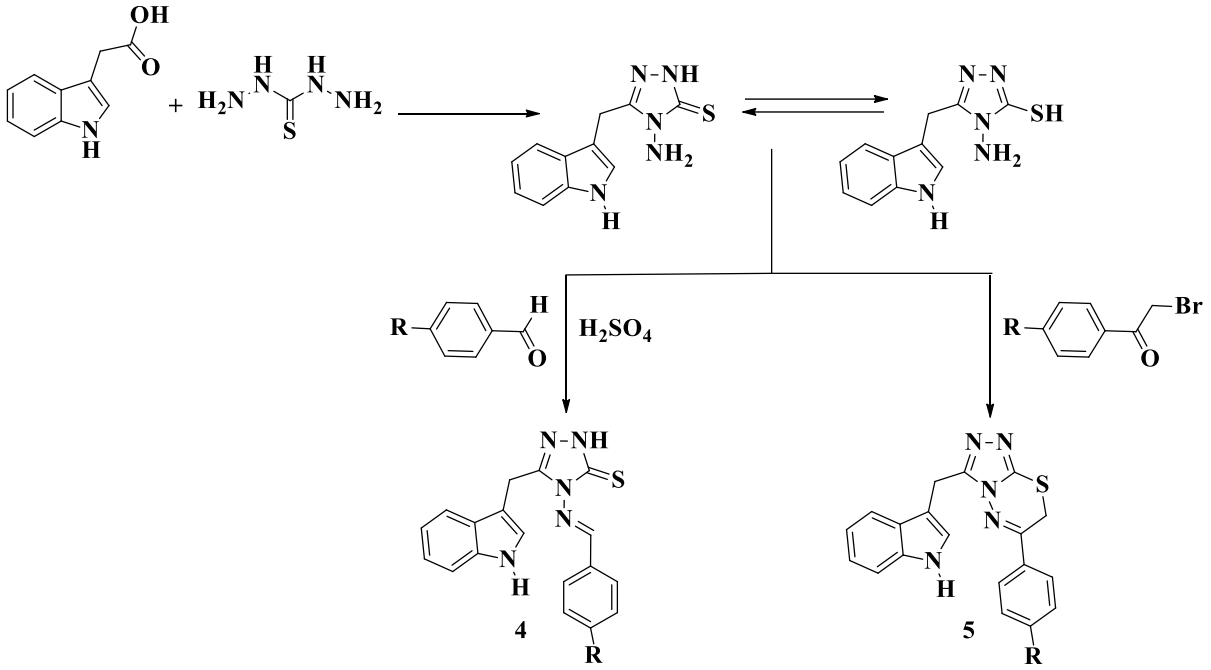


Zhang *et al.*[22] synthesized compound **3** by condensation of Schiff bases derived from 4-amino-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione, phenacyl bromide and triethylamine in ethanol. The Schiff bases were obtained by the reaction of furan or thiophene-2-carbaldehyde with 4-amino-3-(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione.

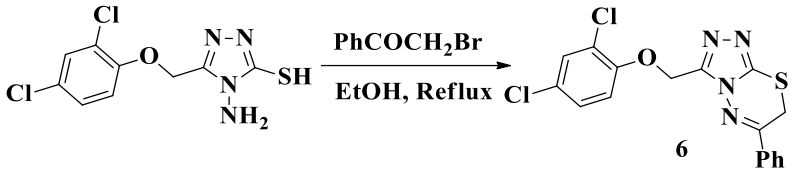


Kaplancikli *et al.*[23] reported the condensation of indole acetic acid with thiocarbohydrazide to give amino mercapto triazole system. This on further reaction with aryl aldehyde in ethanol

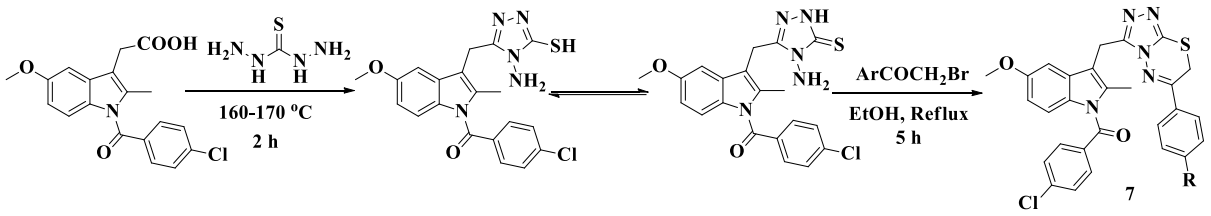
and catalytic amount of H_2SO_4 afforded **4**. Cyclocondensation of triazole with phenacyl bromide in dry ethyl alcohol gave **5**.



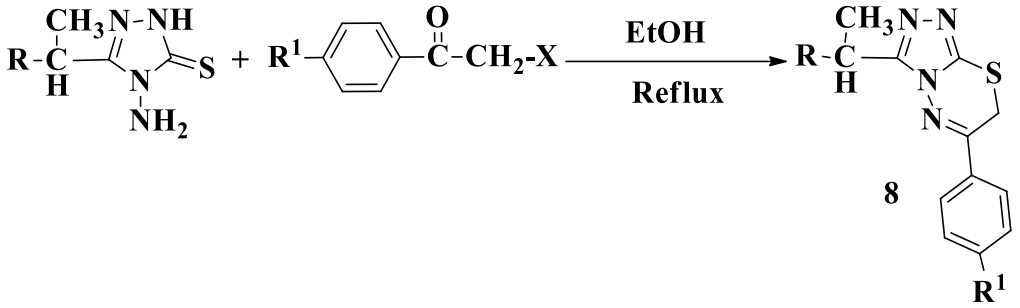
El-Shehry *et al.*[24] described the synthesis of 3-((2,4-dichlorophenoxy)methyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (**6**) by the reaction of substituted amino mercapto triazole with 2-bromo-1-phenylethanones in ethanol.



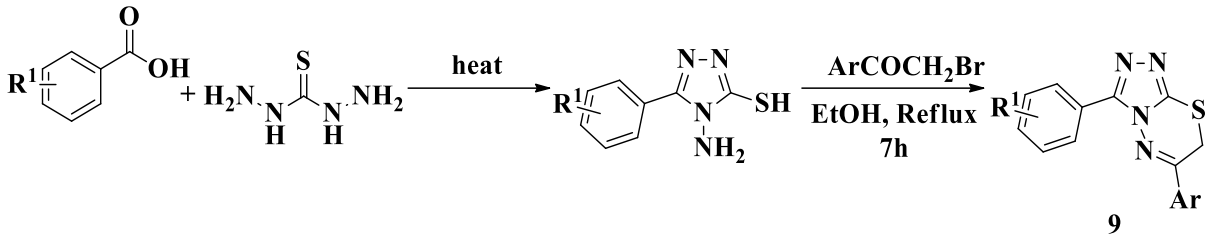
Synthesis of compounds[25] **7** were carried out by reacting 4-amino-5-[(5-methoxy-2-methyl-1-(4-chlorobenzoyl)-1*H*-indol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-thione with phenacyl bromides in ethanol.



Compounds[26] **8** synthesis were carried out from phenacyl halides and 4-amino-3-aryl-1,2,4-triazole-5-thione.

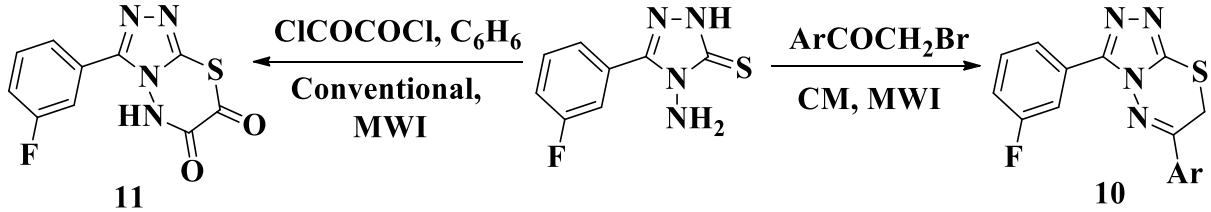


Compounds[27] (**9**) synthesis were done from 4-amino-1,2,4-triazole-3-thiol and phenacyl bromides. The intermediate 5-aryl-4-amino-3-mercapto triazole was obtained by reacting thiocarbohydrazide with aromatic acids.

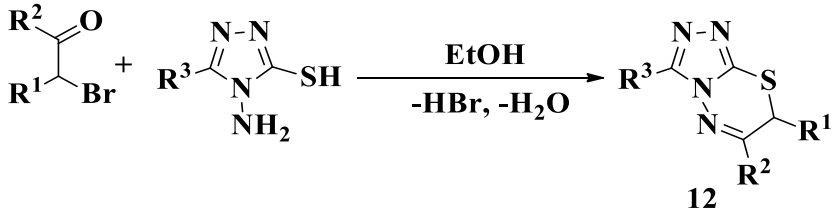


The compounds[28] (**10**) preparation was carried out from 4-amino-5-(3-fluorophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and phenacyl bromides in two different methods.

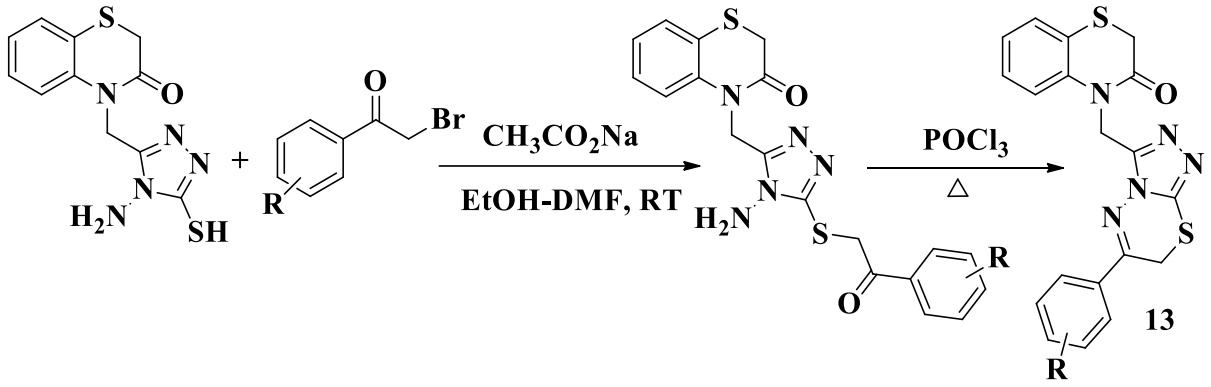
The compound (**11**) was also synthesized from 5-aryl-4-amino-3-mercapto-1,2,4-triazole and oxalyl chloride.



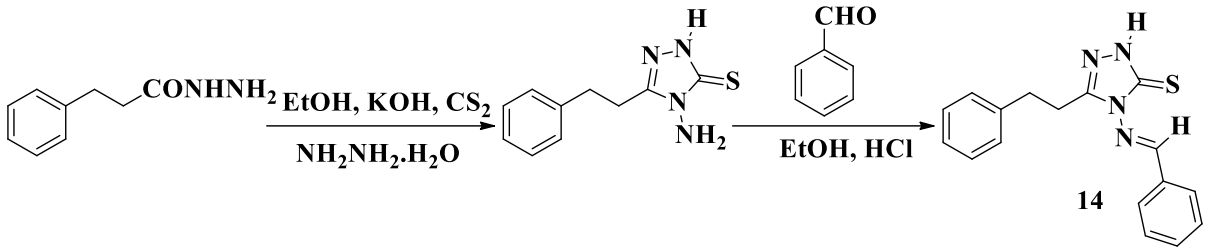
Knak *et al.*[29] synthesized 2,3-diphenyl-1,2,4-triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines (**12**) from 4-amino-5-sulfanyl-1,2,4-triazole and 2-bromo-1,2-diphenylethan-1-one in ethanol.



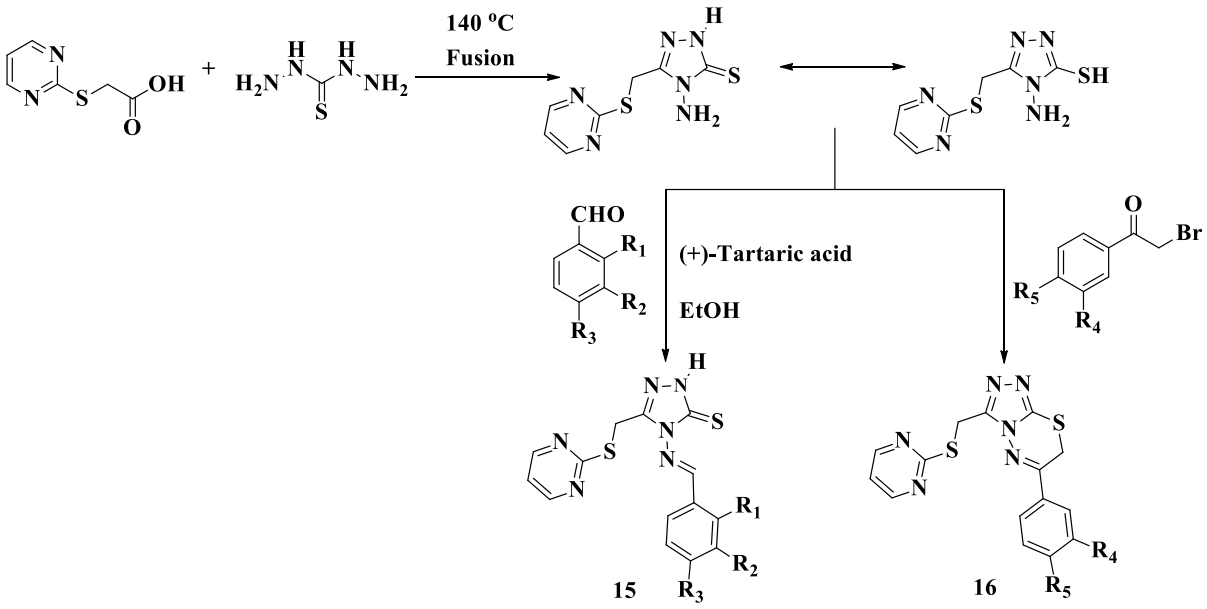
Goveas *et al.*[30] synthesized **13** from the reaction of an equimolar amount of 4-[(4-amino-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)methyl]-2*H*-1,4-benzothiazin-3-(4*H*)-one with phenacyl bromides and dry alcohol to give 4-[(4-amino-5-{[2-(4-substituted phenyl)-2-oxoethyl]sulfanyl}-4*H*-1,2,4-triazol-3-yl)methyl]-2*H*-1,4-benzothiazin-3(4*H*)-one, which was further treated with $POCl_3$ under reflux resulted in the formation of title compounds.



Alghamdi *et al.*[31] synthesized **14** by a multi step method. Condensation of hydrazide derived from phenyl propionic acid with CS_2 in alcoholic KOH solution using NH_2-NH_2.H_2O to yield 4-amino-5-(2-phenyleth-1-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione. This on further condensation with benzaldehyde in ethanol gave the title compound with good yield

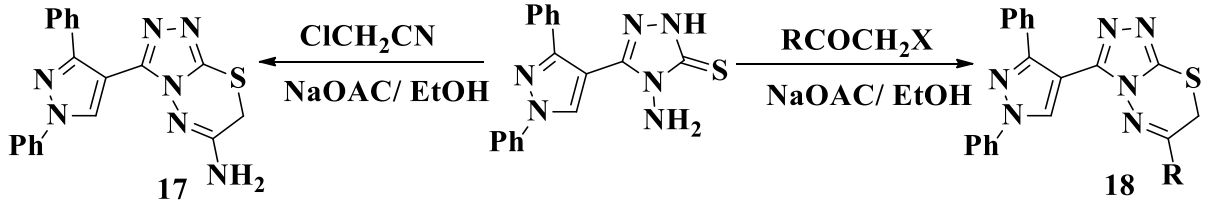


Sim *et al.*[32] synthesized **15** involving the condensation of 4-amino-3-mercapto-5-(2-thiomethylpyrimidyl)-1,2,4-triazole with araldehydes utilising (+)-tartaric acid as catalyst. Compounds **16** were synthesized from reaction of 4-amino-3-mercapto-5-(2-thiomethylpyrimidyl)-1,2,4-triazole with different phenacyl bromides.

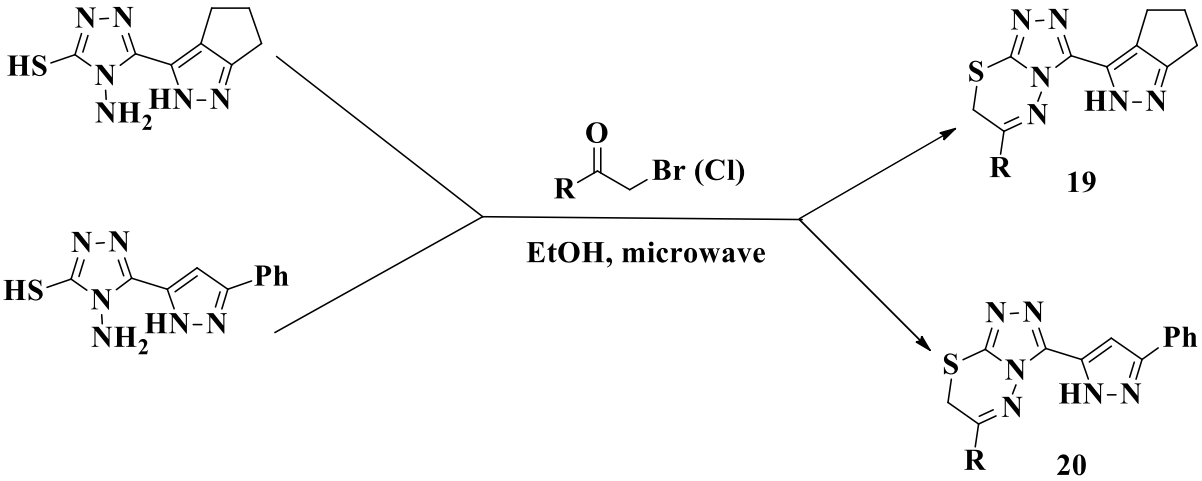


Pyrazoles are good structural motifs present in various drug molecules. Pyrazole derivatives are exhibiting good biological and pharmacological activities[33] such as anti tubercular,[34] anti malarial,[35] anti cancer,[36] anti microbial,[37] anti convulsant,[38] anti viral[39] and anti depressant activity.[40] Pyrazole in combination with triazolothiadiazine increases their biological activity and acts as CXCR2 receptor antagonists,[41] non-purine xanthine oxidase inhibitor[42] and anti proliferative activity.[43]

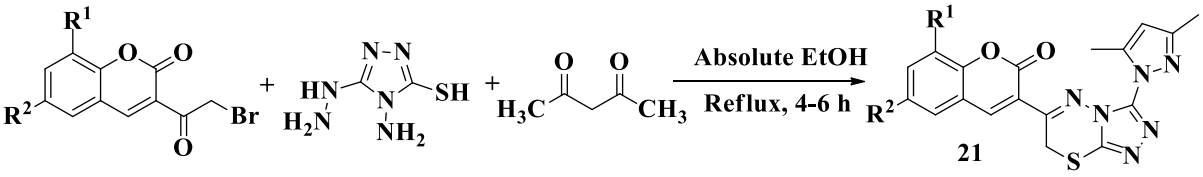
Compounds[44] **17** were synthesized from the reaction of 4-amino-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)[1,2,4]triazole thione and chloroacetonitrile in ethanol containing fused sodium acetate. 4-Amino-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)[1,2,4]triazole thione with chloroacetone and α-bromo acetophenones in alcohol yielded **18**.



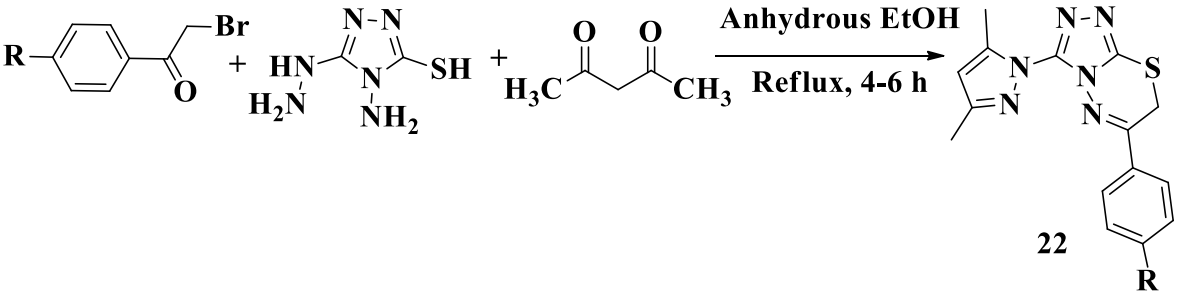
La Porte *et al.*[45] synthesized **19**, **20** by the reaction of 4-amino-5-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol or 4-amino-5-(3-phenyl-1*H*-pyrazol-5-yl)-4*H*-1,2,4-triazole-3-thiol with various substituted 2-chloro or 2-bromo-1-phenylethan-1-ones in ethanol under microwave conditions. Then cooling to room temperature gave the title compounds.



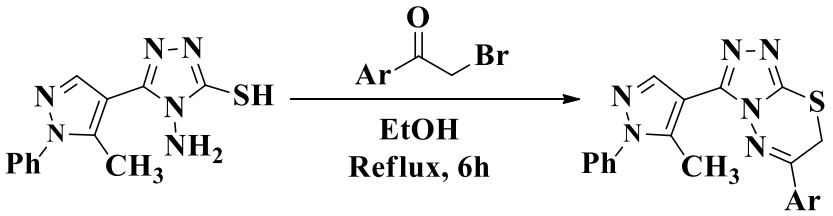
Compound **21** synthesis was described by Pavurala *et al.*[46] 3-(2-Bromo acetyl) coumarins, purpald and acetyl acetone were reacted to yield final compound **21**.



Aychiluhim *et al.*[47] synthesized compounds **22** by using various phenacyl bromides, purpald and acetyl acetone.



Sanjeeva Reddy *et al.*[48] synthesized compounds **23**. In this 4-amino-5-(-methyl-1-phenyl-1*H*-4-pyrazolyl)-4*H*-1,2,4-triazol-3yl hydrosulfide were reacted with phenacyl bromide in absolute ethanol under reflux.



23

SECTION-A

PRESENT WORK

Based on the importance of triazolothiadiazines we are reporting here with the synthesis of **27** by using simple starting materials.

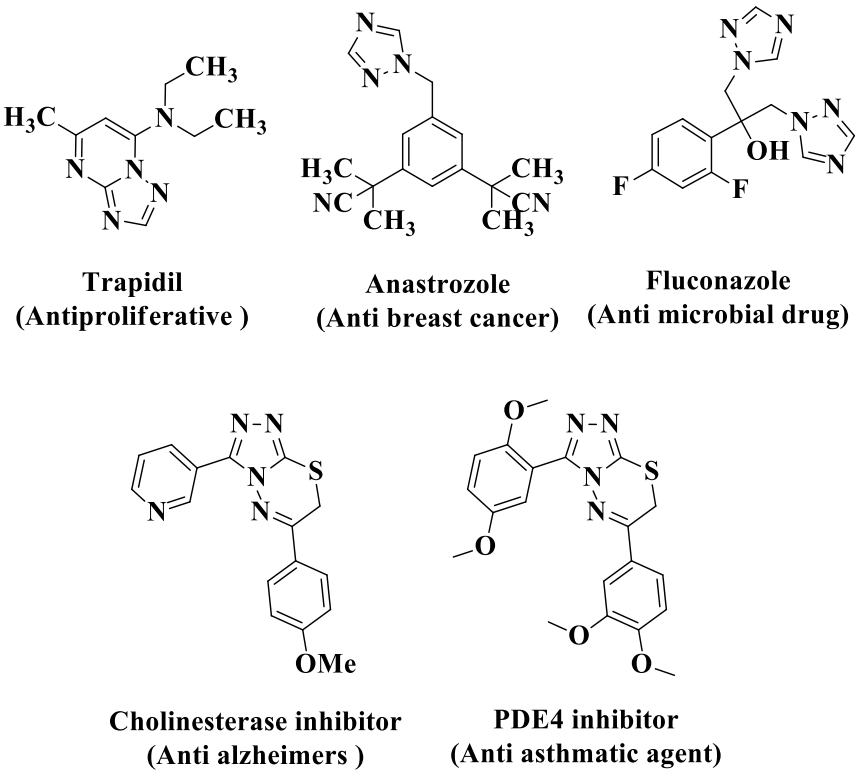
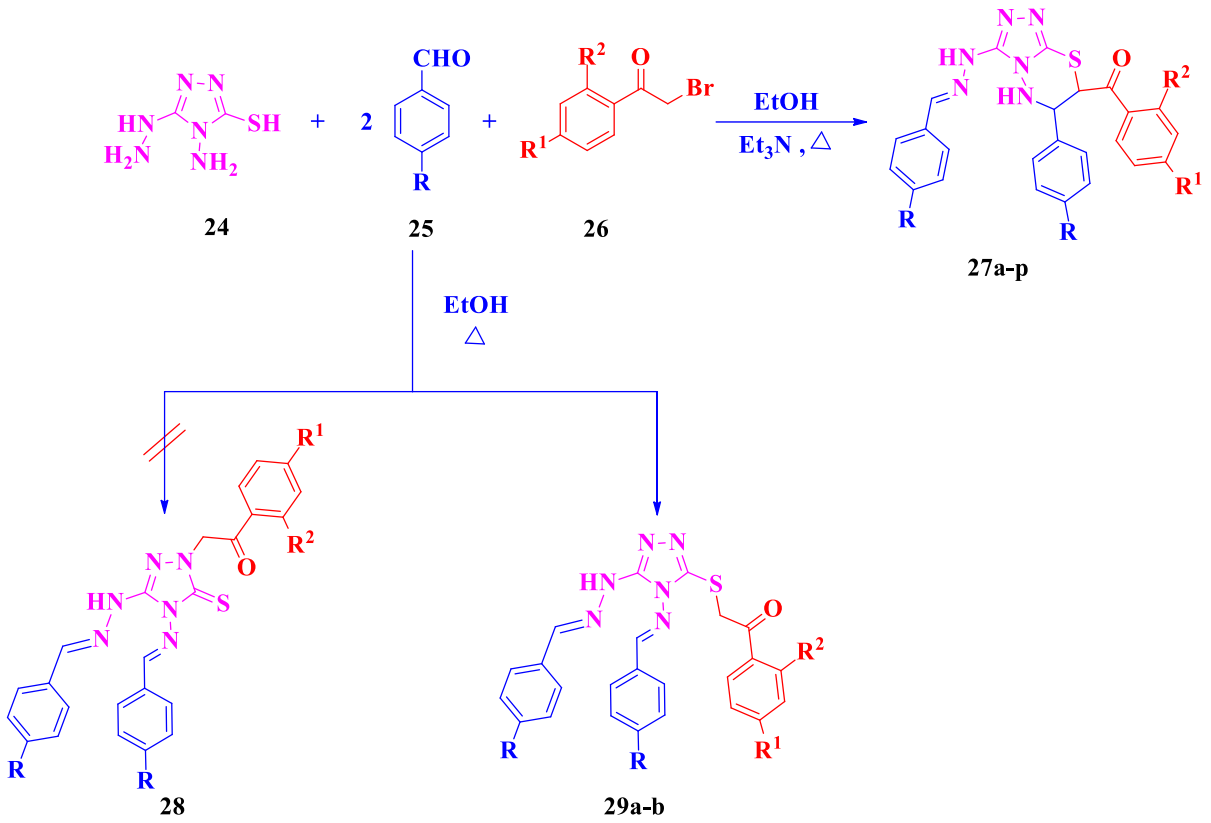


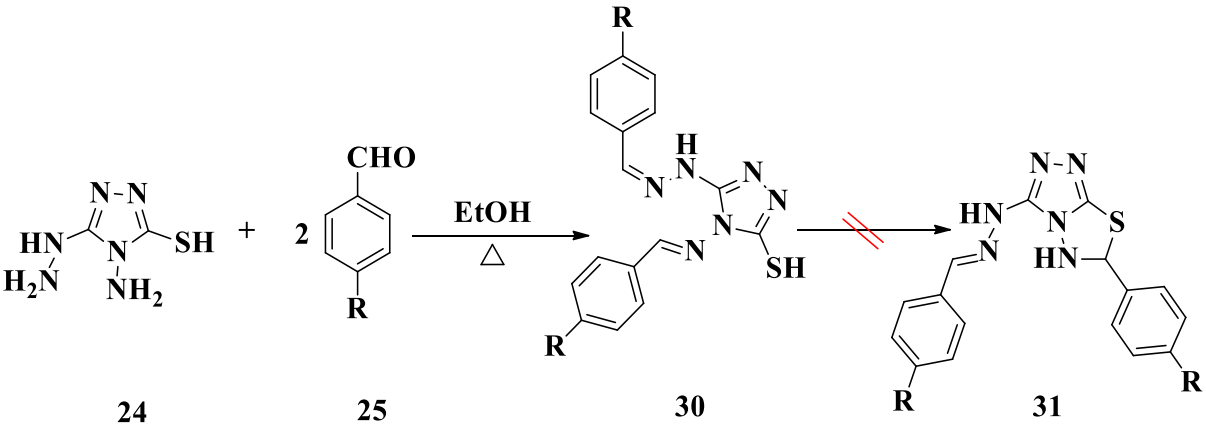
Fig.1. The triazole, triazolo thiadiazine containing biologically active drug molecules.

As a preliminary experiment, purpald (**24**) was treated with two equivalents of aromatic aldehydes (**25**) and phenacyl bromide (**26**) at 40 ^{o}C in dry ethanol and two equivalents of Et_3N. The reaction was found to be sluggish at room temperature and did not give any product. However, at an elevated temperature (70 ^{o}C), the reaction conditions yielded product in less time. Initially one equivalent of Et_3N was used to carry out the reaction between **24**, **25** and **26** by using anhydrous EtOH as solvent. But the reaction did not proceed to give the product.

Synthesis of compounds **27a-p** were achieved by reacting purpald (**24**) with two equivalents of aromatic aldehydes (**25**) and various phenacyl bromides (**26**) in absolute ethanol and two equivalents of Et_3N (Scheme-1).



Scheme 1. Synthesis of triazolo thiadiazine derivatives **27a-p**.



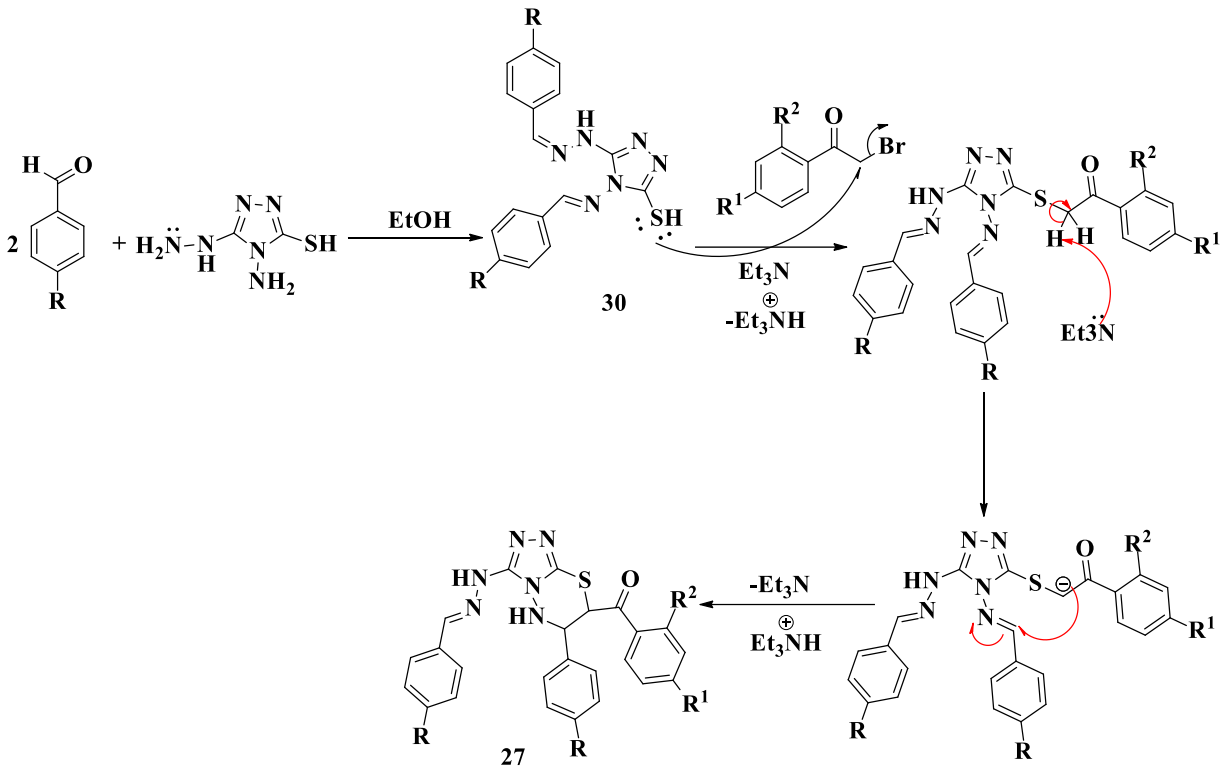
Scheme 2. Synthesis of dianil derivatives (**30**).

Table-1. Different substituents of the products (**27a-p**, **29a-b** and **30a-b**).

Entry	Product	R	R^1	R^2	Time (h)
1	27a	OCH_3	H	H	4
2	27b	OCH_3	Br	H	3.5
3	27c	OCH_3	Cl	H	4
4	27d	OCH_3	Cl	Cl	4
5	27e	OCH_3	F	H	4
6	27f	OCH_3	CH_3	H	4
7	27g	OCH_3	OCH_3	H	4
8	27h	OCH_3	NO_2	H	4.5
9	27i	CH_3	H	H	4
10	27j	CH_3	Br	H	3.5
11	27k	CH_3	Cl	H	4
12	27l	CH_3	Cl	Cl	4
13	27m	CH_3	F	H	4
14	27n	CH_3	CH_3	H	4
15	27o	CH_3	OCH_3	H	4
16	27p	CH_3	NO2	H	4.5
17	29a	OCH_3	OCH_3	H	4
18	29b	OCH_3	F	H	4
19	30a	OCH_3	-	-	1
20	30b	CH_3	-	-	1

The mechanism for the formation of (**27)** can be explained readily. Initially, two equivalents of aldehyde molecules undergo condensation reaction with the 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol (**24**) to give the dianil derivatives. These on further reaction with phenacyl bromides and triethylamine yield the compound (**27**). During the reaction the thiol group of dianil replaces the bromine atom of phenacyl bromide followed by nucleophile addition of carbanion generated *in situ* on carbon atom of imino group adjacent to cyclic nitrogen atom of triazole moiety. The speciality of this reaction is that simultaneous condensation of two equivalents of aldehydes on hydrazino and amino functional groups of (**24**) followed by ring closure reaction in presence of two equivalents of Et_3N. When the reaction is carried out in the absence of phenacyl bromide by using absolute alcohol simple condensation of **24** with two equivalents of aldehyde, it resulted in the formation of dianil (**30**) (Scheme-2) exclusively without formation of any cyclised product (**31**) involving both thiol and imine functionalities. The structure of dianil has been confirmed by IR spectra, in which new stretching bands appeared for –C=N and disappearance of characteristic peaks for $–NH_2$ stretching frequencies.

The mechanism for the formation of dianils and triazolothiadiazine derivatives (**27)** has been established as shown in the following scheme-3.



Scheme-3. Mechanism for the formation of dianil (**30**) and triazolothiadiazine derivatives (**27**).

On the other hand, when (**24)** is reacted with two equivalents of the aromatic aldehyde and one equivalent of phenacyl bromide resulted in the formation of phenacyl thio dianil compound (**29)**. The condensation between **24** with two equivalents of aldehyde and one equivalent of phenacyl bromide may result in the formation of different types of products *N*-phenacylated compound (**28)** and/or *S*-phenacylated compound (**29)**. In our case, only one product (**29)** was observed (as evidenced by TLC). The formation of *S*-phenacylated (**29)** product over *N*-phenacylated (**28)** product can be explained by more nucleophilicity of thiol group. The structures of *S*-phenacylated products were confirmed by their analytical and spectral data.

Later the same reaction was tried with two equivalents of Et_3N in dry ethanol under reflux that gave the products in good to excellent yields. With these optimized reaction conditions a series (*E*)-(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)(phenyl)methanones **27**a-p has been synthesized to investigate the generality of the reaction. The reaction proceeded in such a way to give the products with high yields with substituted aldehydes and phenacyl bromides.

CONCLUSION

We have developed a novel pseudo four component condensation method for the preparation of title compounds in a simple procedure. This proceeds through a four component condensation reaction and is expected to be a more convenient protocol to produce compound **27**. This can be used for biologically active scaffolds. The speciality of this reaction is the shorter reaction time, good yields, simple experimental conditions, easy work, operational simplicity and clean reaction profiles.

EXPERIMENTAL SECTION

Starting materials:

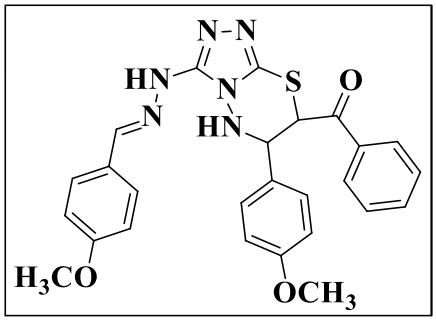
Purpald[49] was procured from reported method.

Preparation of compounds 27a-p.

Purpald (1 mmol), aromatic aldehyde (2 mmol) and phenacyl bromide (1 mmol) were refluxed 4 h in absolute ethanol (5 ml) using Et_3N (2 mmol). After completion of reaction (monitored by TLC), the mass was cooled to room temperature and placed in ice cold water. Solid product was filtered, dried and purified by recrystallization from ethanol.

SPECTRAL DATA

(*E*)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)(phenyl)methanone (27a).

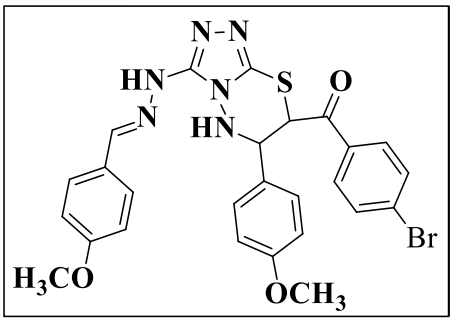


Color: colorless solid; mp: 196-198 °C; yield: (0.555g, 90%); IR (KBr, Wave number, cm^{-1}): 3280 (NH), 2959 (CH), 1680 (C=O), 1609 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H,OCH_3), 3.78 (s, 3H, OCH_3), 4.87 (t, J = 7.2 Hz, 1H, CH of thiadiazine), 5.73 (d, J = 6.4 Hz, 1H, CH of thiadiazine), 6.88 (t, J = 8.0 Hz, 3H, ArH), 6.97 (d, J = 8.8 Hz, 2H, Ar H), 7.49 (d, J = 8.4 Hz, 2H, ArH), 7.54-7.59 (m, 4H, ArH), 7.71 (t, J = 7.2 Hz, 1H, ArH), 8.0 (d, J = 7.6 Hz, 2H, ArH), 8.22 (s, 1H, -CH=N proton), 10.38 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 195.2, 160.4, 159.4, 152.2, 143.3, 134.9, 134.7, 129.6, 129.3, 129.1, 128.1, 114.6, 114.3, 59.1, 55.6, 55.5, 43.8 ppm; ESI-MS: m/z 501 $[M+H]^+$; Anal. calcd. for $C_{26}H_{24}N_6O_3S$, C, 62.38; H, 4.83; N, 16.79; S, 6.41; Found: C, 62.15; H, 4.80; N, 16.71; S, 6.45%.

(*E*)-(4-Bromophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)methanone (27b).

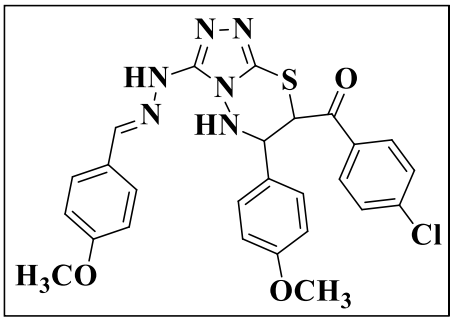
Color: colorless solid; mp: 204-206 °C; yield: (0.629g, 92%); IR (KBr, Wave number, cm^{-1}): 3277 (NH), 1679 (C=O), 1607 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.715 (s, 3H, OCH_3),

3.79 (s, 3H, OCH_3), 4.90 (t, *J* = 6.8 Hz, 1H), 5.71 (d, *J* = 5.6 Hz, 1H), 6.86-6.91 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.22 (s, 1H, -CH=N proton), 10.38 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 194.7, 160.4, 159.4, 143.5, 134.0, 132.6, 131.1, 130.9, 129.2, 129.1, 128.9, 128.2, 114.6, 114.3, 58.7, 55.6, 55.5, 43.9 ppm; Anal. calcd. for $C_{26}H_{23}BrN_6O_3S$, C, 53.89; H, 4.00; Br, 13.79; N, 14.50; S, 5.53; Found: C, 53.82; H, 3.96; Br, 13.84; N, 14.53, S, 5.57%.



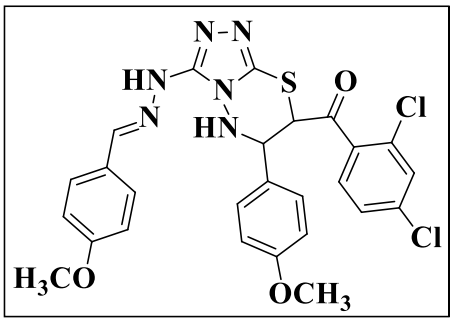
(*E*)-(4-Chlorophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)methanone (27c).

Color: colorless solid; mp: 206-208 °C; yield: (0.557g, 96%); IR (KBr, Wave number, cm^{-1}): 3277 (NH), 1678 (C=O), 1608 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.92 (t, *J* = 6.0 Hz, 1H), 5.73 (d, *J* = 5.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 8.23 (s, 1H, -CH=N proton), 10.55 (s, 1H, NH) ppm; ESI-MS: m/z 535 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}ClN_6O_3S$, C, 58.37; H, 4.33; Cl, 6.63; N, 15.71; S, 5.99; Found: C, 58.31; H, 4.38; Cl, 6.60; N, 15.75; S, 5.87%.



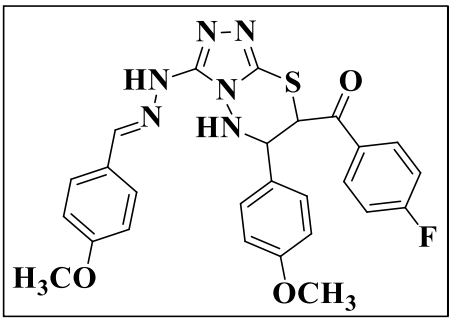
(*E*)-(2,4-Dichlorophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)methanone (27d).

Color: colorless solid; mp: 163-165 °C; yield: (0.639g, 89%); IR (KBr, Wave number, cm^{-1}): 3253 (NH), 1684 (C=O), 1608 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.34 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 1H, NH), 4.80 (t, *J* = 7.2 Hz, 1H), 5.51 (t, *J* = 6.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.84-6.90 (m, 1H), 6.97-6.99 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz,1H), 7.39-7.50 (m, 1H), 7.54-7.59 (m, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.20-8.31 (m, 1H), 10.36 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 196.7, 163.2, 162.6, 160.4, 159.1, 148.8, 145.3, 133.0, 131.3, 129.2, 128.6, 128.2, 125.2, 114.9, 114.6, 98.7, 59.6, 55.9, 55.6, 55.4 ppm; ESI-MS:



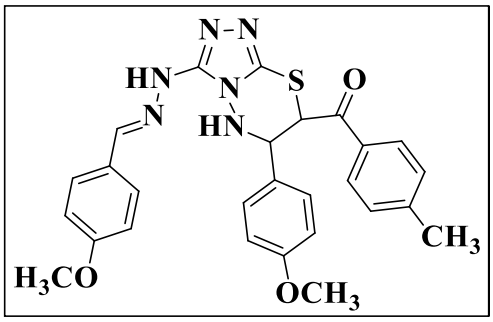
m/z 569 $[M+H]^+$; Anal. calcd. for $C_{26}H_{22}Cl_2N_6O_3S$, C, 54.80; H, 3.80; Cl, 12.40; N, 14.70; S, 5.60; Found: C, 53.9; H, 3.84; Cl, 12.46; N, 14.82; S, 5.24%.

(*E*)-(4-Fluorophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)methanone (27e).



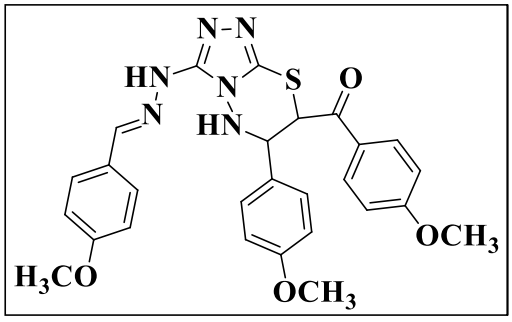
Color: colorless solid; mp: 200-202 °C; yield: (0.545g, 95%); IR (KBr, Wave number, cm^{-1}): 3278 (NH), 1673 (C=O), 1596 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.89 (t, J = 7.2 Hz, 1H), 5.72 (d, J = 6.0 Hz, 1H), 6.86-6.91 (m, 3H), 6.97 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 8.6 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 8.09-8.12 (m, 2H), 8.22 (s, 1H, -CH=N proton), 10.37 (s, 1H, NH) ppm; ESI-MS: m/z 519 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}FN_6O_3S$, C, 60.22; H, 4.47; N, 16.21; S, 6.18; Found: C, 60.26, H, 4.42, N, 16.26, S, 6.13%.

(*E*)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)(*p*-tolyl)methanone (27f).



Color: colorless solid; mp: 215-217 °C; yield: (0.565g, 91%); IR (KBr, Wave number, cm^{-1}): 3275 (NH), 1676 (C=O), 1608 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.84 (t, J = 7.6 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.84-6.90 (m, 3H), 6.97 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 7.6 Hz, 2H), 8.22 (s, 1H, -CH=N proton) 10.35 (s, 1H, NH) ppm; ESI-MS: m/z 515 $[M+H]^+$; Anal. calcd. for $C_{27}H_{26}N_6O_3S$, C, 63.02; H, 5.09; N, 16.33; S, 6.23; Found: C 63.12; H, 5.14; N, 16.37; S, 6.28%.

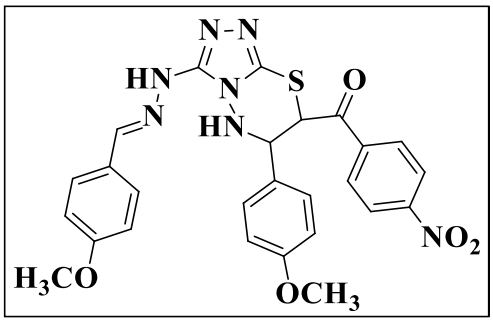
(*E*)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) (4-methoxy phenyl)methanone (27g).



Color: colorless solid; mp: 203-205 °C; yield: (0.563g, 94%); IR (KBr, Wave number, cm^{-1}): 3275 (NH), 1676 (C=O), 1608 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.81 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 8.4 Hz,

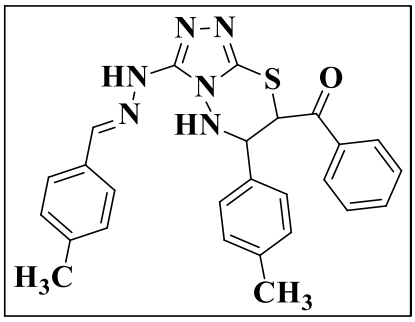
1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.96 (t, *J* = 8.8 Hz, 2H), 8.21 (s, 1H, -CH=N proton), 8.26 (d, *J* = 6.8 Hz, 1H), 10.35 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 193.4, 164.5, 160.4, 159.4, 152.1, 143.3, 137.3, 131.6, 129.3, 128.4, 128.1, 128.0, 127.6, 114.8, 114.6, 114.3, 59.5, 56.2, 55.6, 55.5 ppm; ESI-MS: m/z 531 $[M+1]^+$; Anal. calcd. for $C_{27}H_{26}N_6O_4S$, C, 61.12; H, 4.94; N, 15.84; S, 6.04; Found: C, 61.18; H, 4.91; N, 15.79; S, 6.16%.

(*E*)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) (4-nitro phenyl)methanone (27h).



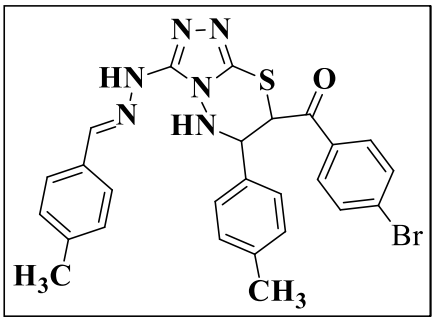
Color: light yellow solid; mp: 198-200 °C; yield: (0.612g, 89%); IR (KBr, Wave number, cm^{-1}): 3282 (NH), 1683 (C=O), 1602 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.98 (t, *J* = 6.0 Hz, 1H), 5.79 (d, *J* = 4.8 Hz, 1H), 6.89 (t, *J* = 8.0 Hz, 3H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 8.25 (d, *J* = 9.6 Hz, 3H), 8.36 (d, *J* = 8.4 Hz, 2H), 10.38 (s, 1H, NH) ppm; ESI-MS: m/z 546 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}N_7O_5S$, C, 57.24; H, 4.25; N, 17.97; S, 5.88; Found: C, 57.29; H, 4.29; N, 17.92; S, 5.83%.

(*E*)-3-(2-(4-Methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) methanone (27i).



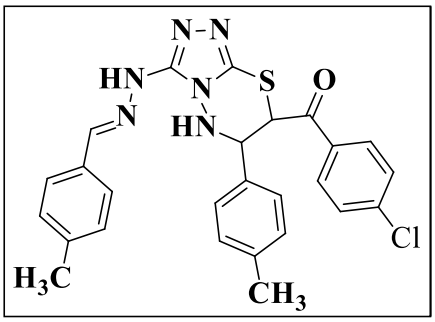
Color: colorless solid; mp: 223-225 °C; yield: (0.544g, 86%); IR (KBr, Wave number, cm^{-1}): 3307 (NH), 1687 (C=O), 1610 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.92 (t, *J* = 6.8 Hz, 1H), 5.75 (d, *J* = 6.4 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 2H), 8.25 (s, 1H), 10.47 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 195.2, 152.1, 143.4, 139.0, 137.9, 137.1, 134.9, 134.7, 134.4, 132.7, 129.7, 129.5, 129.2, 129.0, 127.9, 127.0, 126.6, 59.1, 43.6, 21.4, 21.1 ppm; ESI-MS: m/z 469 $[M+H]^+$; Anal. calcd. for $C_{26}H_{24}N_6OS$, C, 66.64; H, 5.16; N, 17.94; S, 6.84; Found: C, 66.69; H, 5.13; N, 17.91; S, 6.83%.

(*E*)-(4-Bromophenyl)(3-(2-(4-methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)methanone (27j).



Color: colorless solid; mp: 206-208 °C; yield: (0.607g, 90%); IR (KBr, Wave number, cm^{-1}): 3277 (NH), 1679 (C=O), 1591 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.95 (t, *J* = 6.4 Hz, 1H), 5.72 (d, *J* = 5.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H), 8.25 (s, 1H), 10.45 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 194.7, 152.0, 143.5, 139.0, 137.9, 137.0, 134.3, 134.0, 132.6, 131.2, 130.9, 129.7, 129.5, 128.9, 127.8, 127.0, 126.6, 58.7, 43.6, 21.4, 21.0 ppm; ESI-MS: m/z 549 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}BrN_6OS$, C, 57.04; H, 4.23; Br, 14.60; N, 15.35; S, 5.86; Found: 57.14; H, 4.28; Br, 14.68; N, 15.39; S, 5.81%.

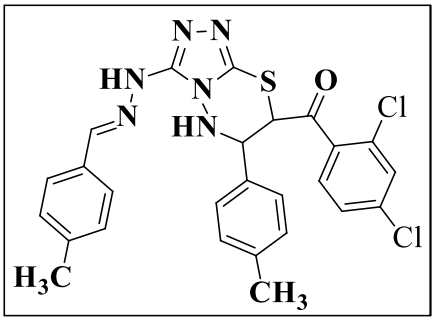
(*E*)-(4-Chlorophenyl)(3-(2-(4-methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) methanone (27k).



Color: colorless solid; mp: 206-208 °C; yield: (0.529g, 95%); IR (KBr, Wave number, cm^{-1}): 3277 (NH), 1673 (C=O), 1598 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.95 (t, *J* = 6.8 Hz, 1H), 5.72 (d, *J* = 5.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 HZ, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.5 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 8.25 (s, 1H,-CH=N proton), 10.45 (s, 1H, NH) ppm; ESI-MS: m/z 503 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}ClN_6OS$, C, 62.08; H, 4.61; Cl, 7.05; N, 16.71; S, 6.37; Found: C, 62.14; H, 4.67; Cl, 7.10; N, 16.67; S, 6.33%.

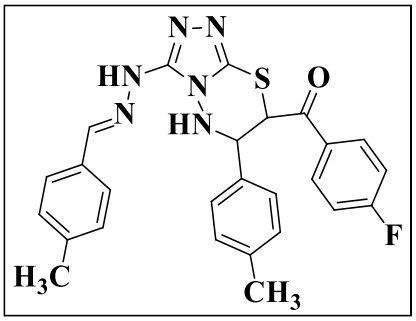
(*E*)-(2,4-Dichlorophenyl)(3-(2-(4-methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) methanone (27l).

Color: colorless solid; mp: 172-174 °C; yield: (0.553g, 97%); IR (KBr, Wave number, cm^{-1}): 3278 (NH), 1698 (C=O), 1580 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.87 (t, J = 6.8 Hz, 1H), 5.52 (d, J = 6.O Hz, 1H), 7.04 (d, J = 6.4 Hz, 1H), 7.1 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 6.8 Hz, 2H), 7.33-7.39 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 6.4 Hz, 3H), 7.74 (d, J = 12.4 Hz, 1H), 8.34 (s, 1H), 10.24 (s, 1H) 10.46 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 196.6, 152.3, 146.1, 143.3, 138.9, 137.3, 135.4, 133.8, 133.0, 132.8, 131.6, 130.4, 129.7, 129.4, 128.0, 127.8, 127.3, 126.6, 79.6, 59.4, 21.4 ppm; ESI-MS: m/z 537 $[M+H]^+$; Anal. calcd. for $C_{26}H_{22}Cl_2N_6OS$, C, 58.10; H, 4.13; Cl, 13.19; N, 15.64; S, 5.97; Found: C, 58.15; H, 4.16; Cl, 13.25; N, 15.70; S, 5.92%.



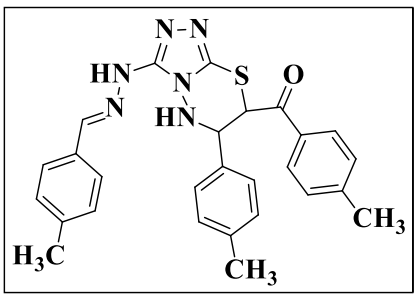
(*E*)-(4-Fluorophenyl)(3-(2-(4-methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) methanone (27m).

Color: colorless solid; mp: 202-204 °C; yield: (0.511g, 95%); IR (KBr, Wave number, cm^{-1}): 3276 (NH), 1676 (C=O), 1594 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.93 (t, J = 6.8 Hz, 1H), 5.73 (d, J = 5.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 8.10-8.13 (m, 2H), 8.25 (s, 1H, -CH=N proton), 10.44(s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 194.0, 167.3, 164.7, 152.1, 137.9, 134.4, 132.3, 129.7, 129.5, 127.8, 126.6, 116.7, 116.5, 59.0, 43.6, 21.4, 21.0 ppm; ESI-MS: m/z 487 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}FN_6O_6S$, C, 64.18; H, 4.76; N, 17.27; S, 6.59; Found: C, 64.22; H, 4.71; N, 17.24; S, 6.55%.



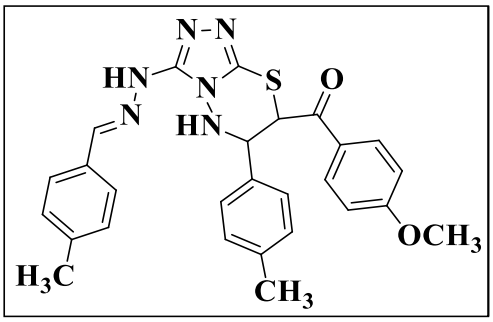
(*E*)-(3-(2-(4-Methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)(p-tolyl)methanone (27n).

Color: colorless solid; mp: 200-202 °C; yield: (0.535g, 90%); IR (KBr, Wave number, cm^{-1}): 3275 (NH), 1671 (C=O stretching), 1594 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.00 (d, J = 8.4 Hz, 1H), 5.70 (d, J = 5.6 Hz, 1H), 6.86-6.96 (m, 1H), 7.0 (d, J = 6.4 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.22 (s, 3H), 7.33 (d, J = 6.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 6.8 Hz,



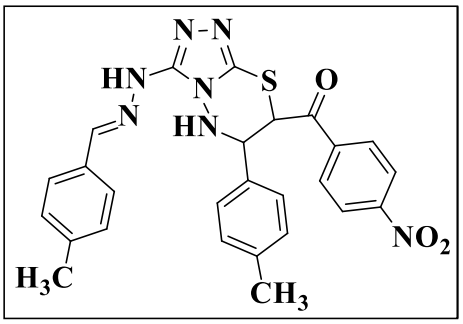
1H), 7.5 (d, *J* = 7.2 Hz, 1H), 7.5 (d, *J* = 6.4 Hz, 1H), 7.85-7.91 (m, 2H), 8.26 (d, *J* = 17.2 Hz, 1H), 10.28 (s, 1H, NH) ppm; ESI-MS: m/z 481 $[M+H]^+$; Anal. calcd. for $C_{27}H_{26}N_6OS$, C, 67.20; H, 5.43; N, 17.41; S, 6.64; Found: C, 67.26; H, 5.48; N, 17.48; S, 6.69%.

(*E*)-(4-Methoxyphenyl)(3-(2-(4-methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) methanone (27o).



Color: colorless solid; mp: 214-216 °C; yield: (0.535g, 93%); IR (KBr, Wave number, cm^{-1}): 3280 (NH), 1673 (C=O), 1598 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.85 (t, *J* = 7.2 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 8.23 (s, 1H, -CH=N proton), 10.44 (s, 1H, NH) ppm; CMR (100 MHz, DMSO-d_6): δ 193.5, 164.5, 152.1, 143.4, 134.5, 131.6, 129.7, 129.5, 127.9, 127.6, 126.6, 114.8, 59.6, 56.1, 43.2, 21.4, 21.1 ppm; ESI-MS: m/z 497 $[M+H]^+$; Anal. calcd. for $C_{27}H_{26}N_6O_2S$, C, 65.04; H, 5.26; N, 16.86; S, 6.43; Found: C, 65.14; H, 5.22; N, 16.81; S, 6.49%.

(*E*)-(3-(2-(4-Methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl) (4-nitro phenyl)methanone (27p).

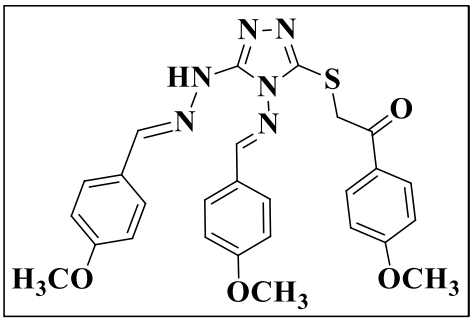


Color: light yellow solid; mp: 203-205 °C; yield: (0.563g, 91%); IR (KBr, Wave number, cm^{-1}): 3274 (NH), 1683 (C=O), 1593 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.04 (t, *J* = 5.6 Hz, 1H), 5.80 (d, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.47-7.53 (m, 4H), 8.27 (d, *J* = 7.6 Hz, 3H), 8.37 (d, *J* = 8.0 Hz, 2H), 10.49 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 194.7, 150.7, 143.5, 139.8, 139.0, 137.9, 136.8, 134.2, 132.7, 130.7, 129.7, 129.5, 127.7, 127.1, 126.6, 124.4, 58.2, 44.4, 21.4, 21.0 ppm; ESI-MS: m/z 514 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}N_7O_3S$, C, 60.81; H, 4.51; N, 19.09; S, 6.24; Found: C, 60.87; H, 4.56; N, 19.14; S, 6.20%.

General procedure for the synthesis of compounds (29a, b).

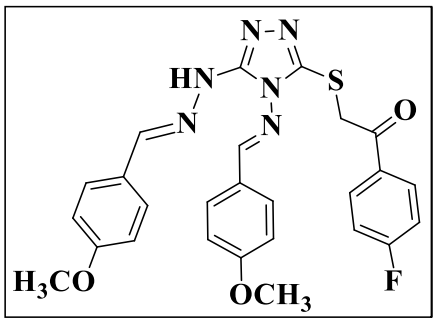
A mixture of purpald (1 mmol), aromatic aldehyde (2 mmol) and phenacyl bromide (1 mmol) was taken in 5 ml of absolute alcohol and refluxed for 3 h. After completion of the reaction (monitored by TLC). The solid separated was filtered and purified by recrystallization from ethanol.

2-((4-((*E*)-(4-Methoxybenzylidene)amino)-5-((*E*-2-(4-methoxybenzylidene)hydrazinyl)-4*H*-1, 2, 4-triazol-3-yl) thio)-1-(4-methoxyphenyl)ethanone (29a).



Color: colorless solid; mp: 119-121 °C; yield: (0.557g, 95%); IR (KBr, Wave number, cm^{-1}): 3400 (NH), 2964 (CH), 1673 (C=O), 1599 (C=N); PMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.72 (s, 2H, CH_2), 6.77 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 4H), 7.28 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 8.86 (d, J = 8.4 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 191.2, 169.5, 164.3, 164.2, 161.8, 149.7, 147.7, 145.8, 132.2, 131.3, 129.7, 128.2, 126.3, 124.0, 115.2, 114.7, 114.5, 56.2, 56.1, 55.8 ppm; ESI-MS: m/z 531 $[M+H]^+$; Anal. calcd. for $C_{27}H_{26}N_6O_4S$, C, 61.12; H, 4.94; N, 15.84; S, 6.04; Found: C, 61.19; H, 4.98; N, 15.81; S, 6.12%.

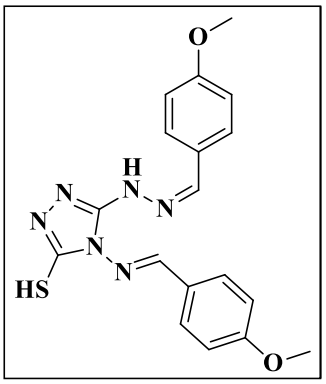
1-(4-Fluorophenyl)-2-((4-((*E*)-(4-methoxybenzylidene) amino)-5-((*E*-2-(4-methoxybenzylidene)hydrazinyl)-4*H*-1, 2, 4-triazol-3-yl) thio) ethanone (29b).



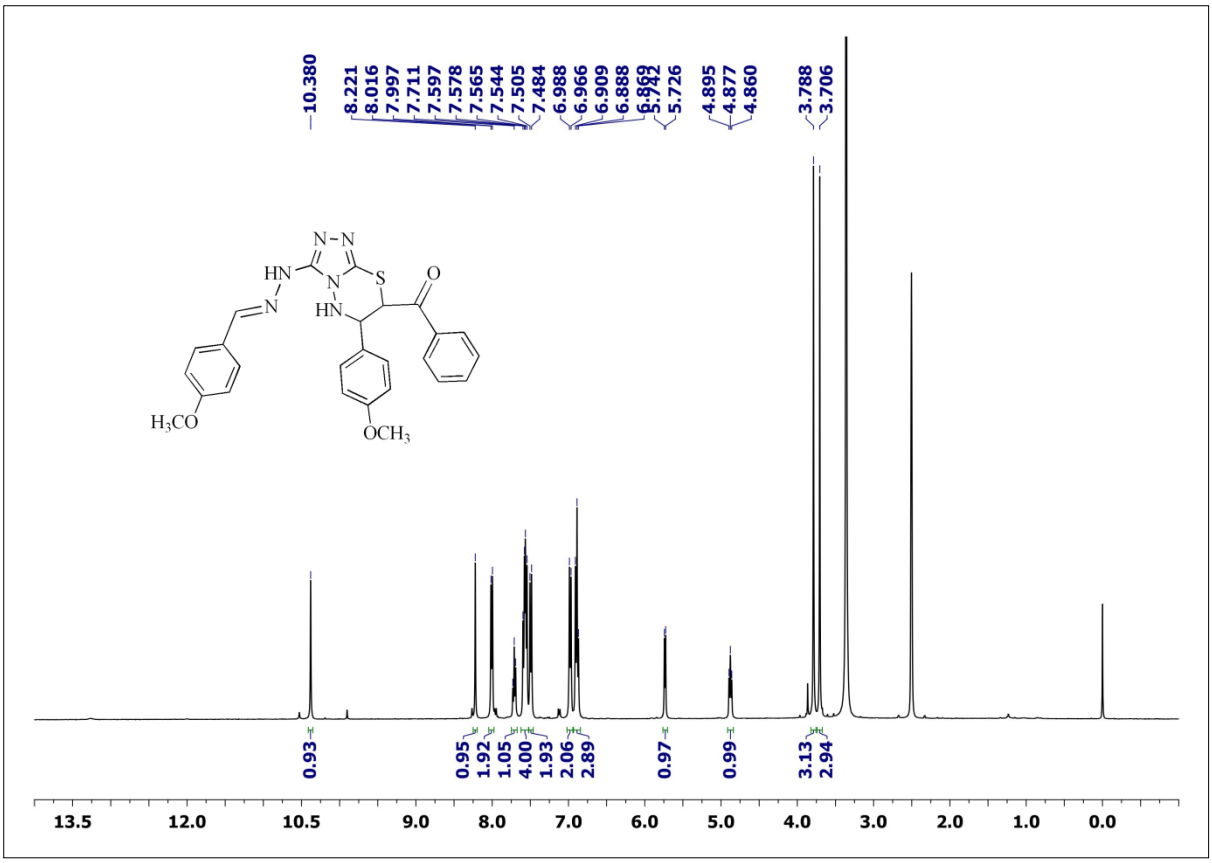
Color: colorless solid; mp: 212-214 °C; yield: (0.556g, 93%); IR (KBr, Wave number, cm^{-1}): 3400 (NH), 2945 (CH), 1691 (C=O), 1599 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.47 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.00 (s, 2H, CH_2), 6.28 (s, 2H), 7.03 (d, J = 8.4 Hz, 3H), 7.42 (t, J = 8.8 Hz, 3H), 7.79 (d, J = 8.4 Hz, 3H), 8.17 (t, J = 8 Hz, 2H), 8.36 (s, 1H), 12.67 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 191.9, 161.7, 151.3, 150.7, 149.3, 132.0, 132.0, 131.3, 129.7, 126.2, 116.8, 116.5, 116.3, 114.7, 55.8, 23.6 ppm; ESI-MS: m/z 519 $[M+H]^+$; Anal. calcd. for $C_{26}H_{23}FN_6O_3S$, C, 60.22; H, 4.47; N, 16.21; S, 6.18; Found: C, 60.28; H, 4.42; N, 16.26; S, 6.13%.

General procedure for the synthesis of 4-((*E*)-(4-methoxybenzylidene) amino)-5-((*Z*)-2-(4-methoxybenzylidene) hydrazinyl)-4*H*-1, 2, 4-triazole-3-thiol (30).

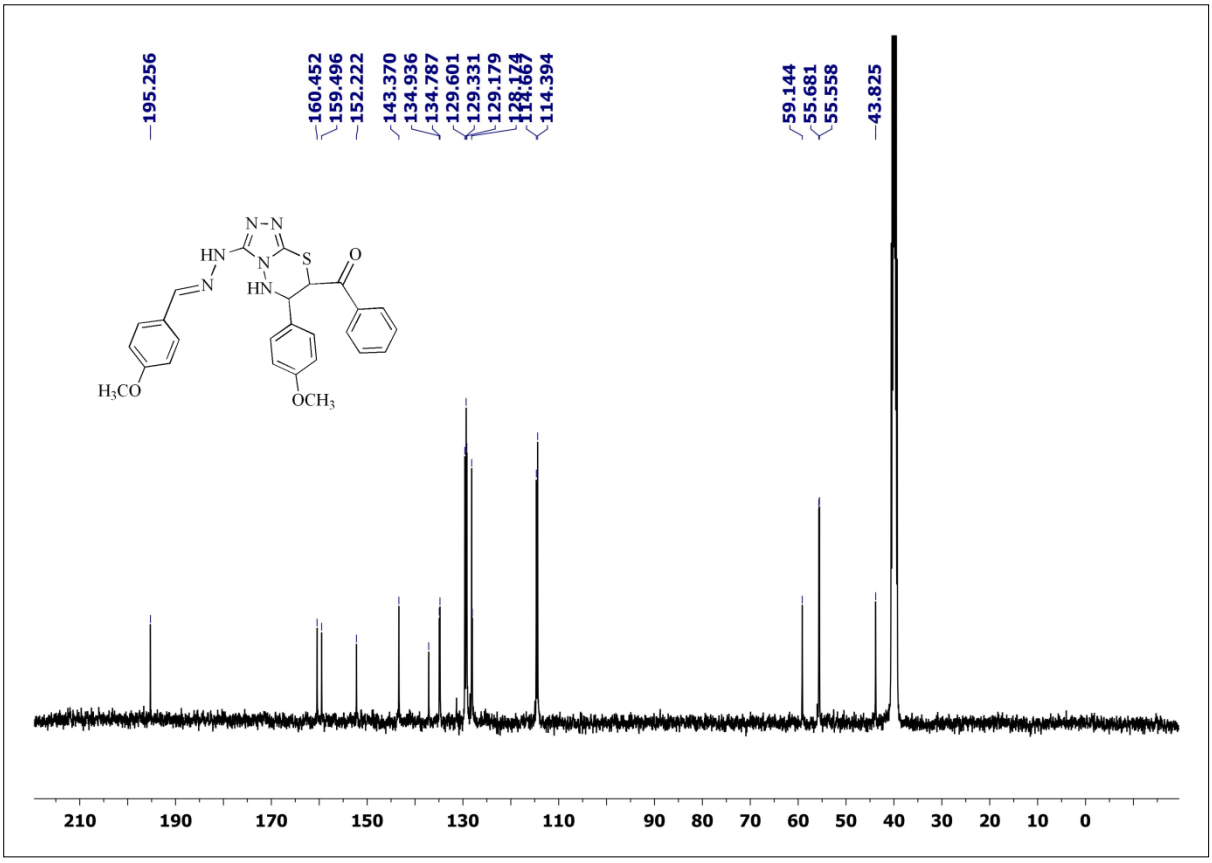
A mixture of purpald (1 mmol), 4-methoxybenzaldehyde (2 mmol) in 5 ml of absolute alcohol was refluxed for 1 h (monitored through TLC). The mass produced was cooled to



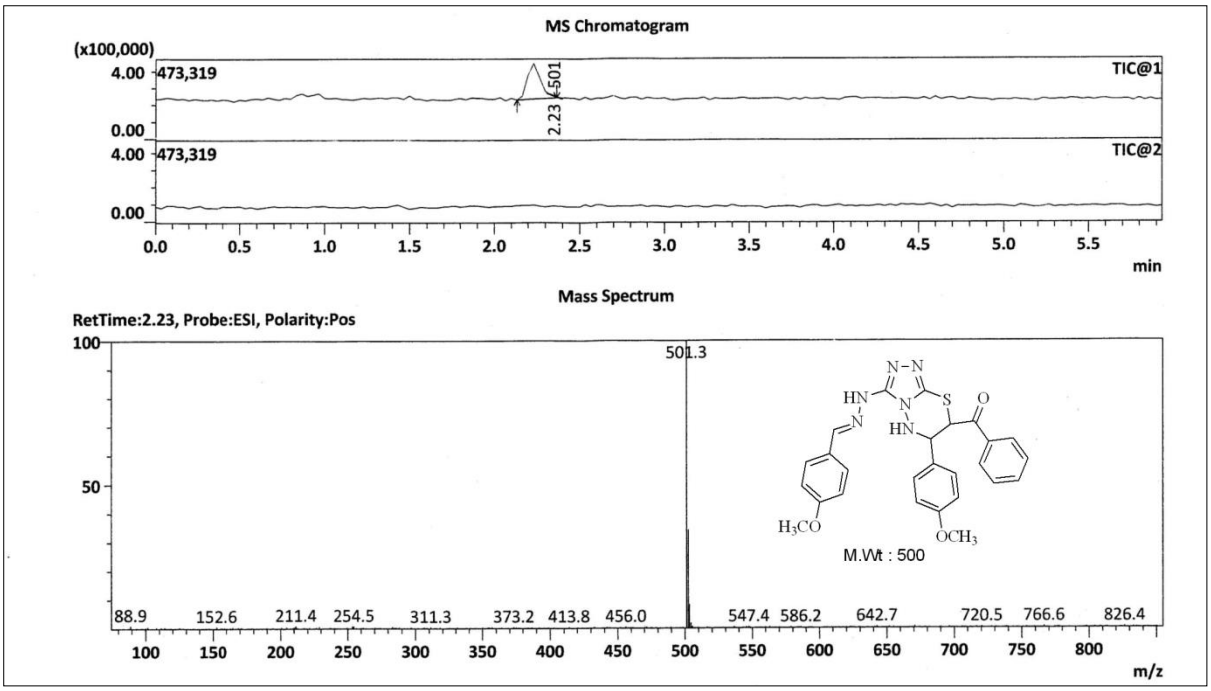
room temperature. The solid separated was filtered and washed with water and recrystallized using methanol. Color: colorless solid; mp: 241-243 °C; yield: (0.397g, 96%); IR (KBr, Wave number, cm^{-1}): 1636 (C=N), 2610 (SH); PMR (400 MHz, DMSO-d_6): δ 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.98 (d, J = 8.4Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 8.27 (s, 1H), 9.90 (s, 1H), 10.52 (s, 1H), 13.26 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 163.1, 162.6, 160.8, 159.8, 148.7, 145.3, 131.3, 128.4, 127.5, 125.2, 114.9, 114.7, 56.0, 55.7 ppm; ESI-MS: m/z 383 $[M+H]^+$; Anal. calcd. for $C_{18}H_{18}N_6O_2S$, C, 56.53; H, 4.74; N, 21.97; S, 8.38; Found: C, 56.59; H, 4.79; N, 21.93; S, 8.32%.



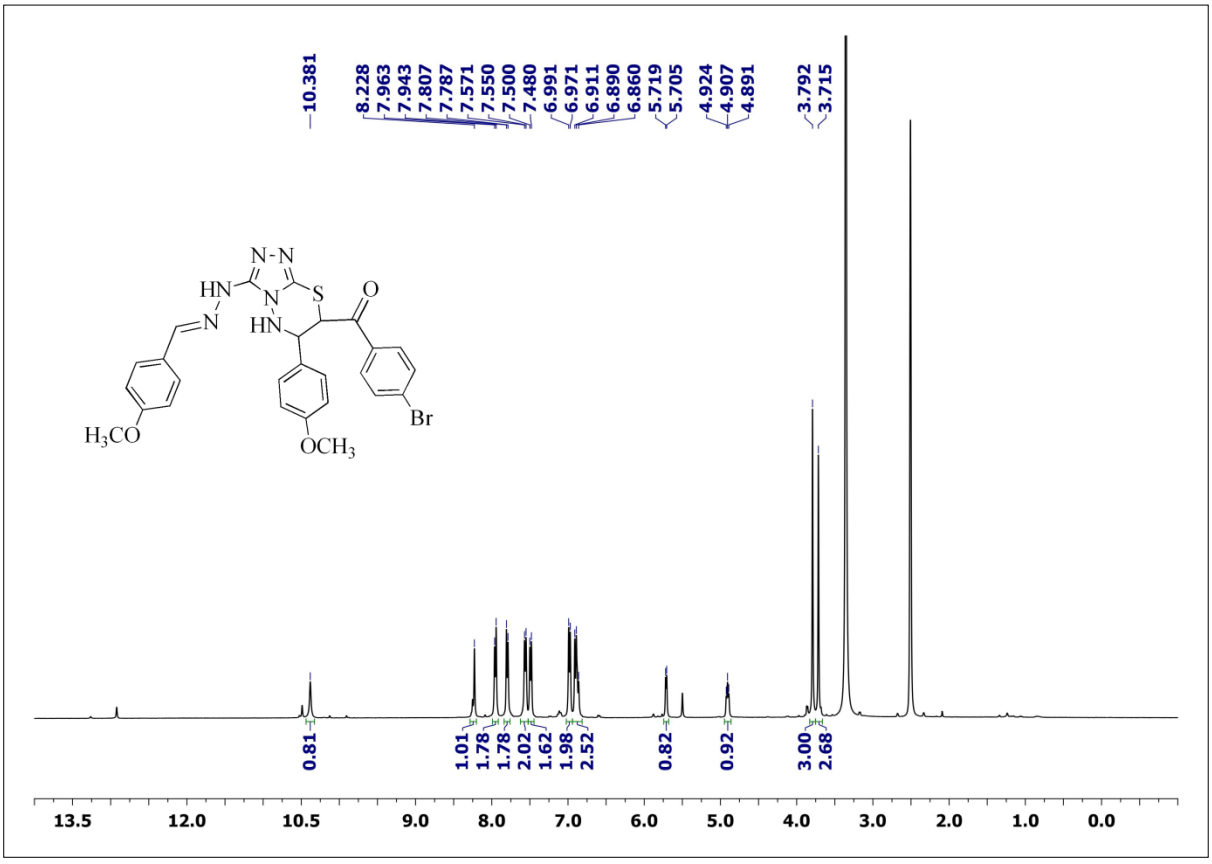
PMR Spectrum of compound **27a**



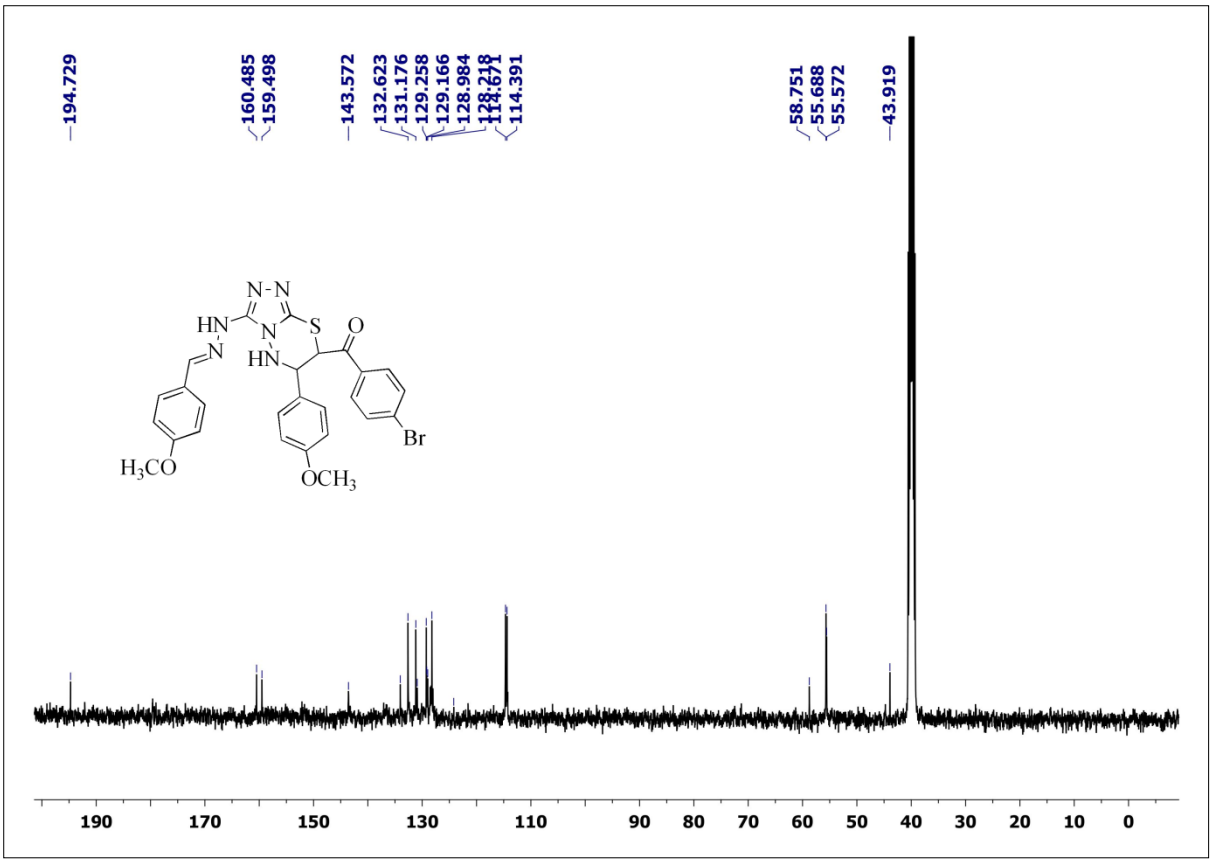
CMR Spectrum of compound **27a**



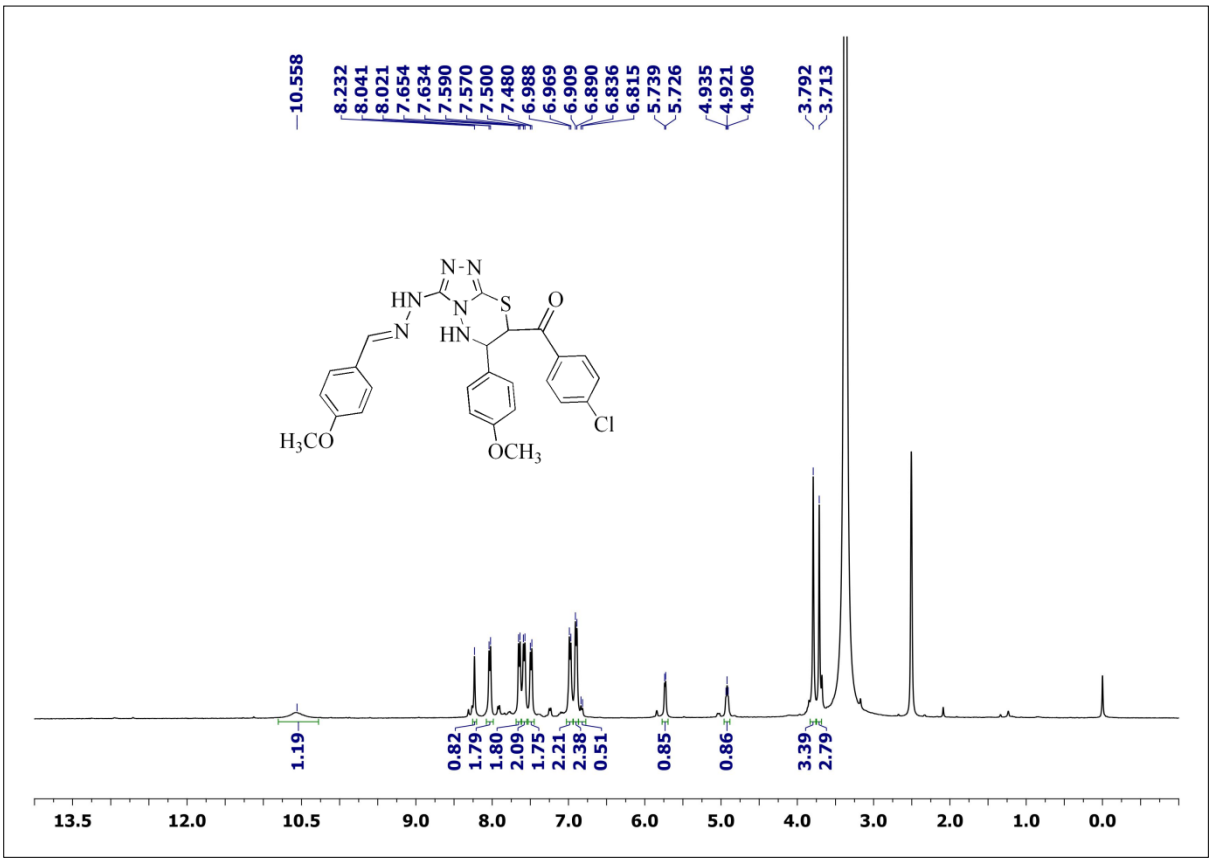
Mass Spectrum of compound **27a**



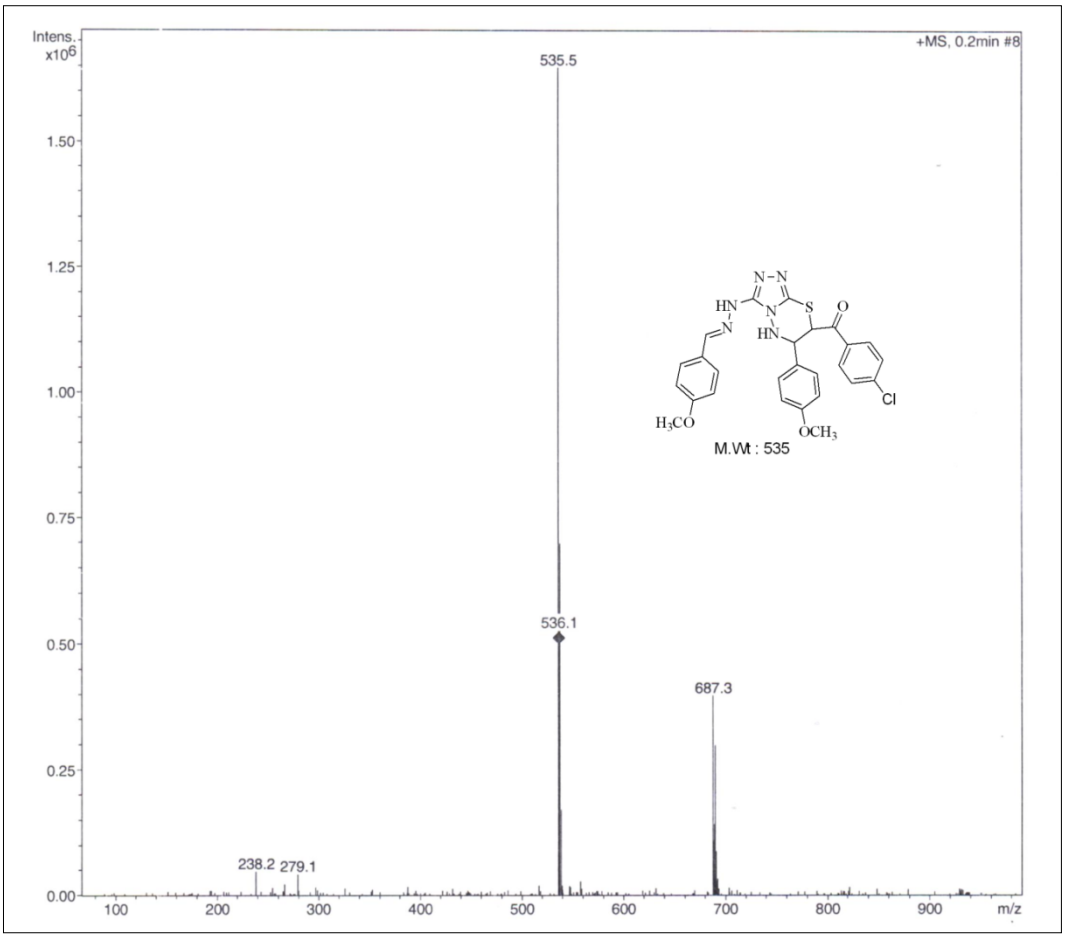
PMR Spectrum of compound **27b**



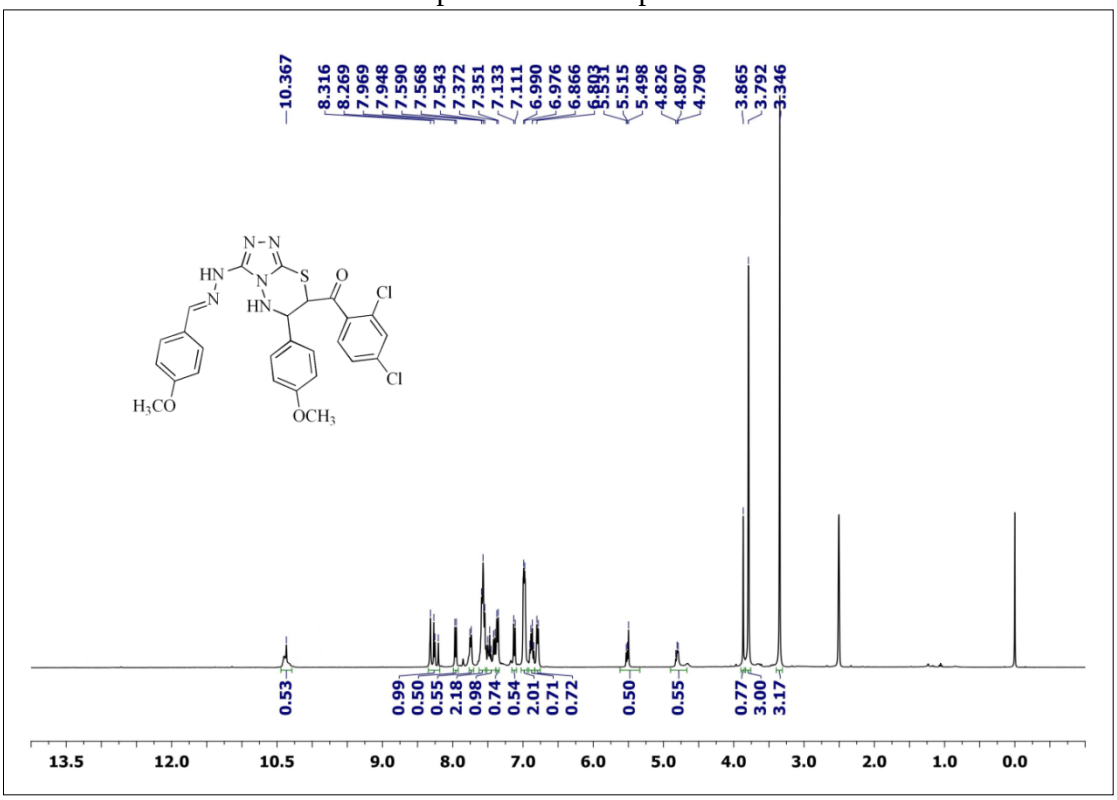
CMR Spectrum of compound **27b**



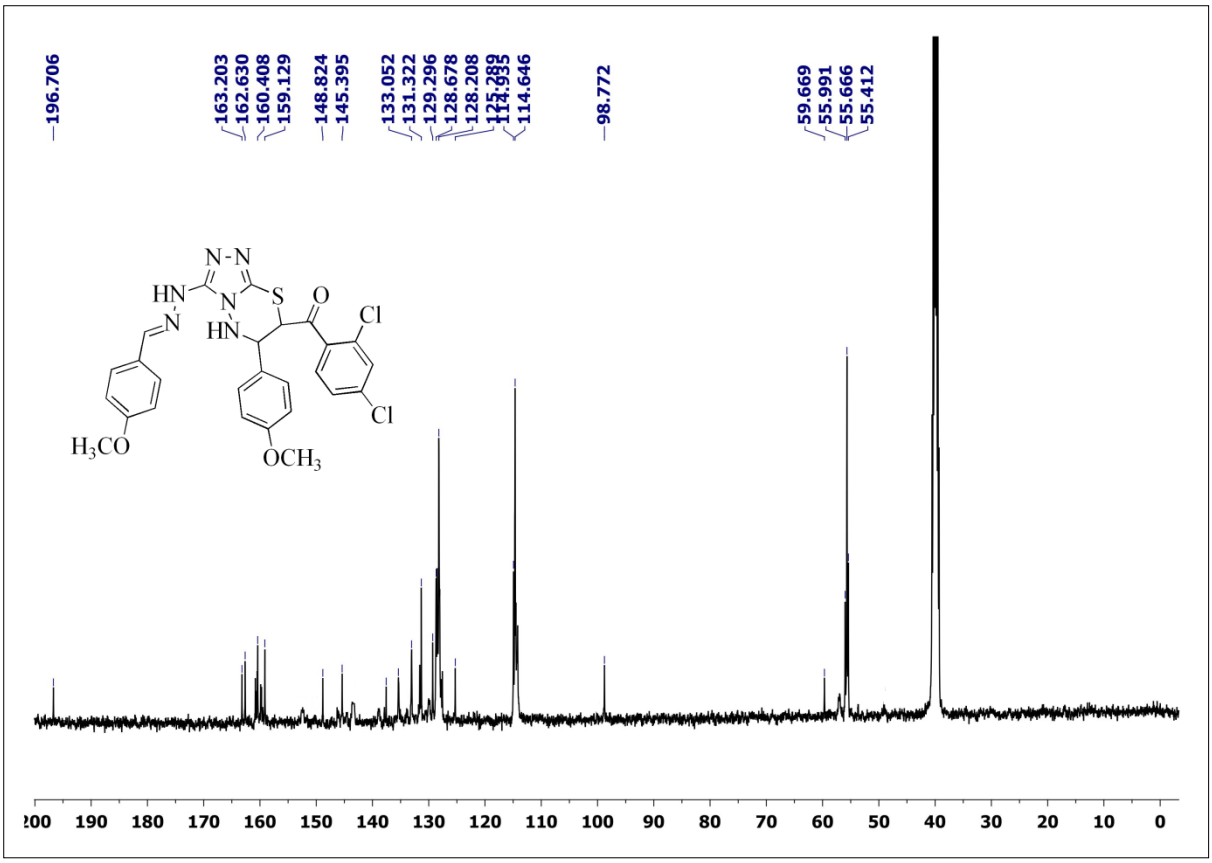
PMR Spectrum of compound **27c**



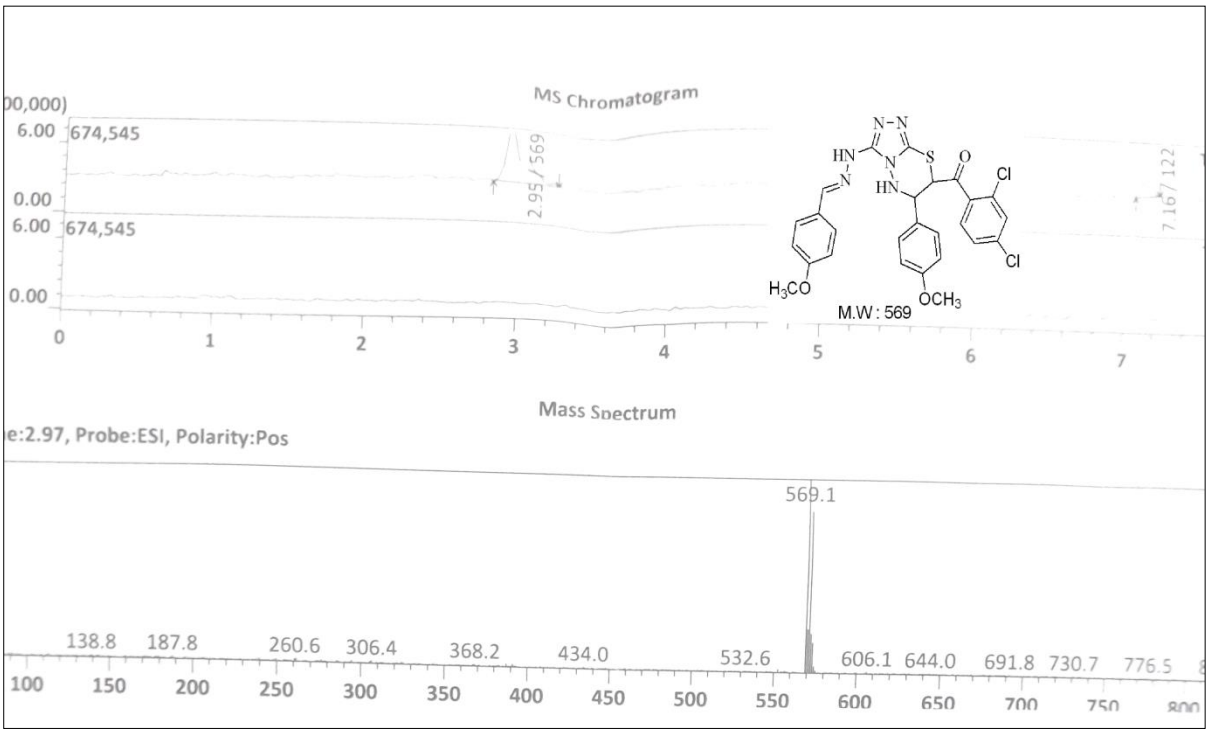
Mass Spectrum of compound **27c**



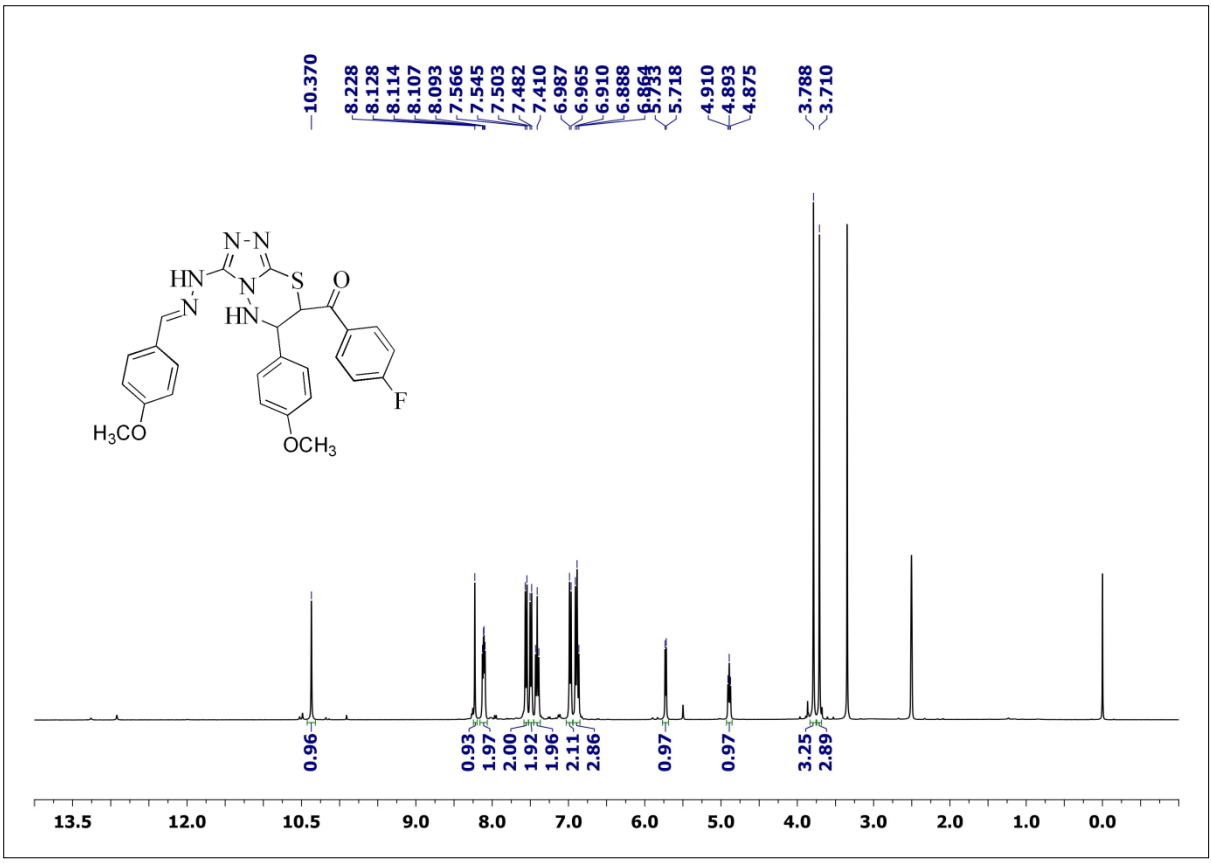
PMR Spectrum of compound **27d**



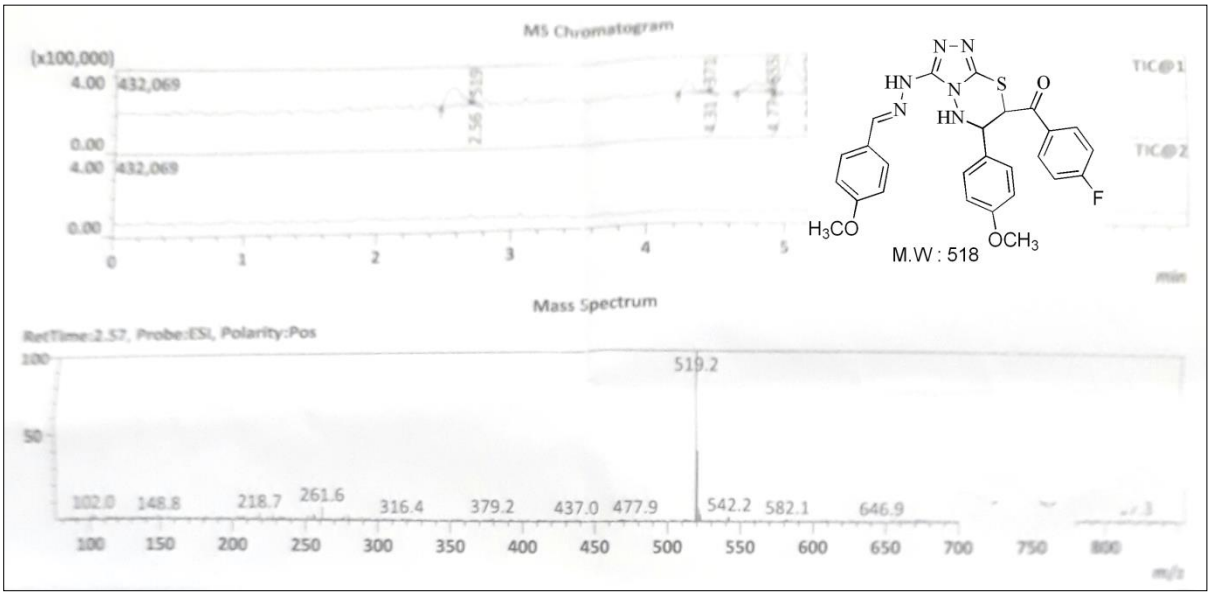
CMR Spectrum of compound **27d**



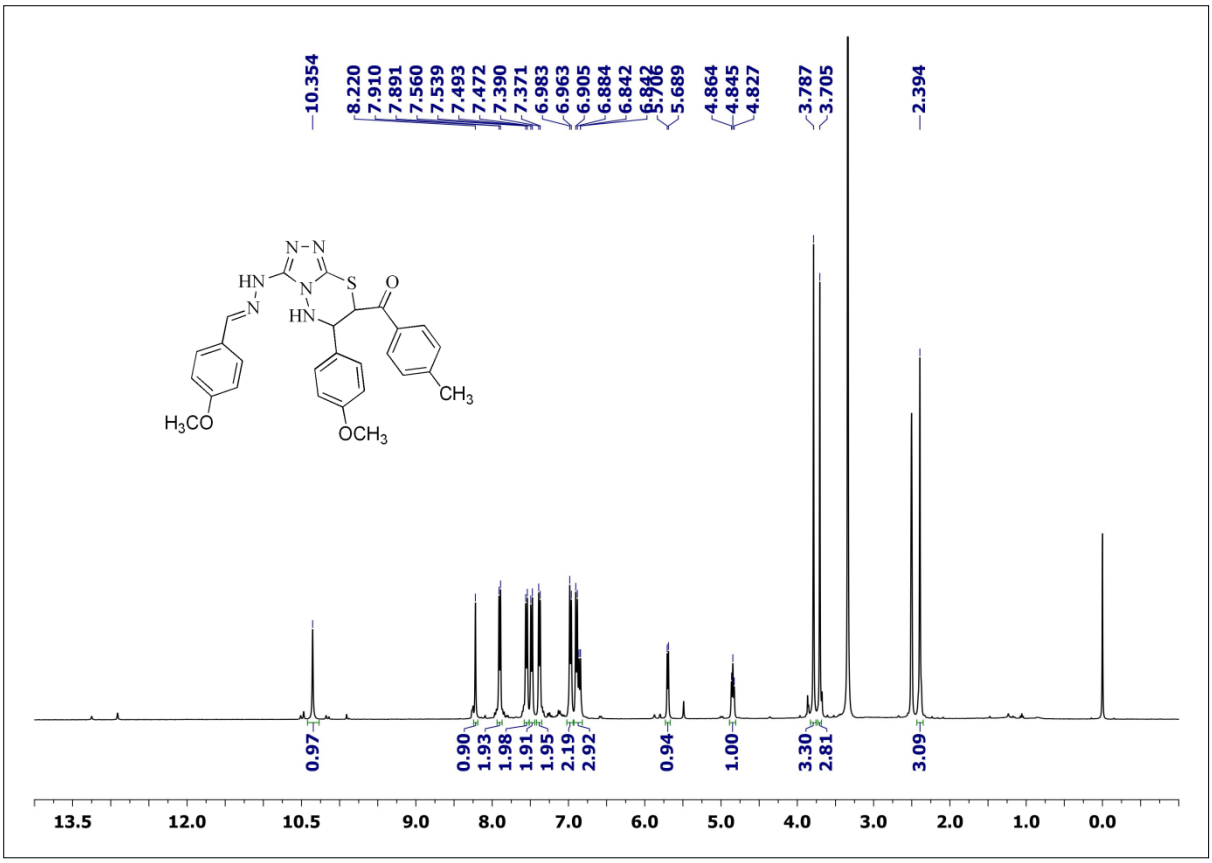
Mass Spectrum of compound **27d**



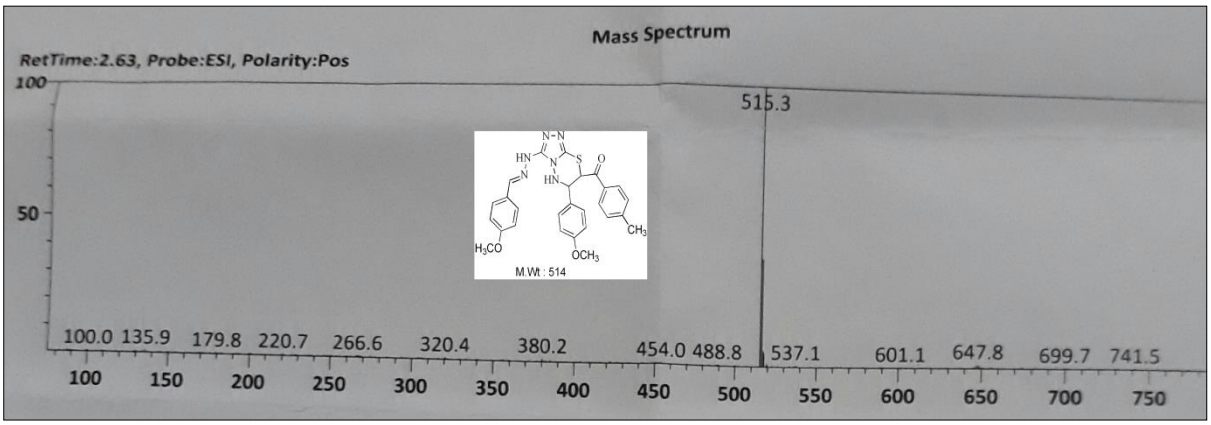
PMR Spectrum of compound **27e**



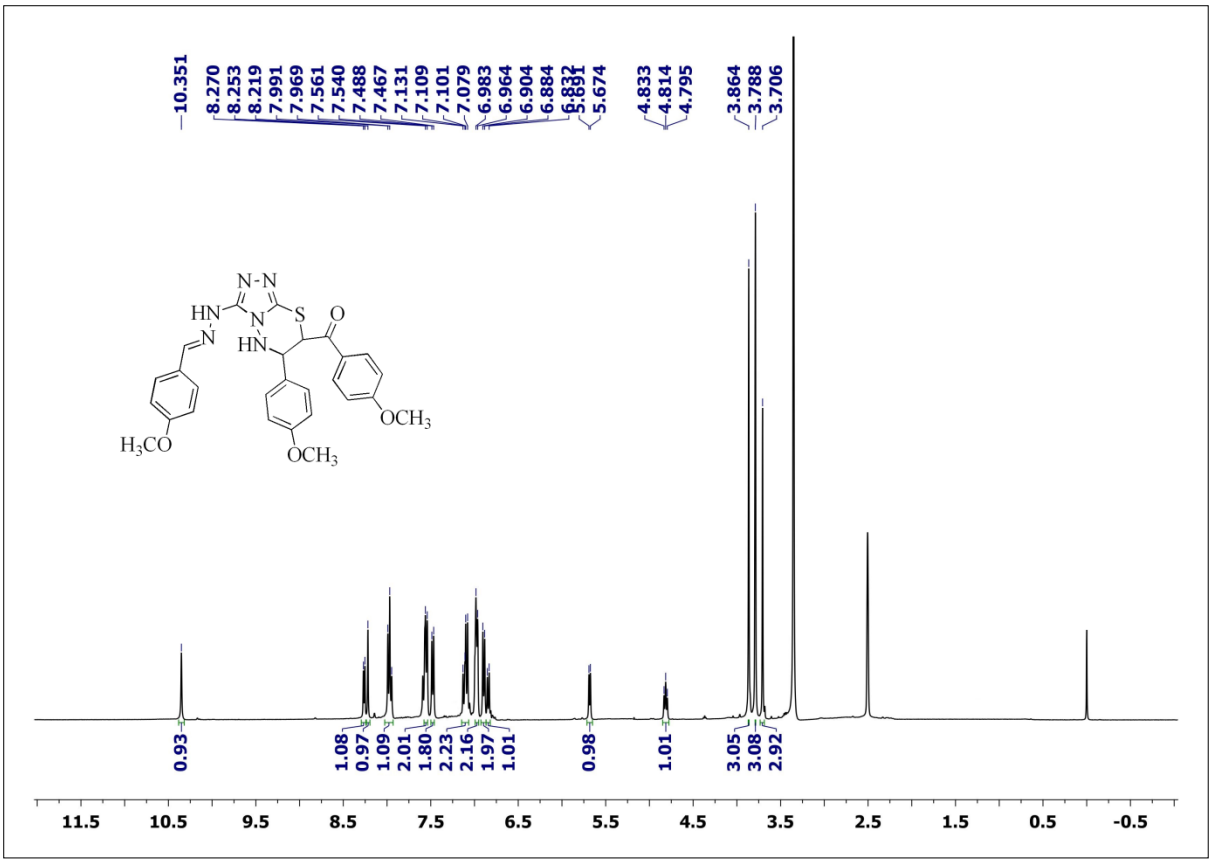
Mass Spectrum of compound **27e**



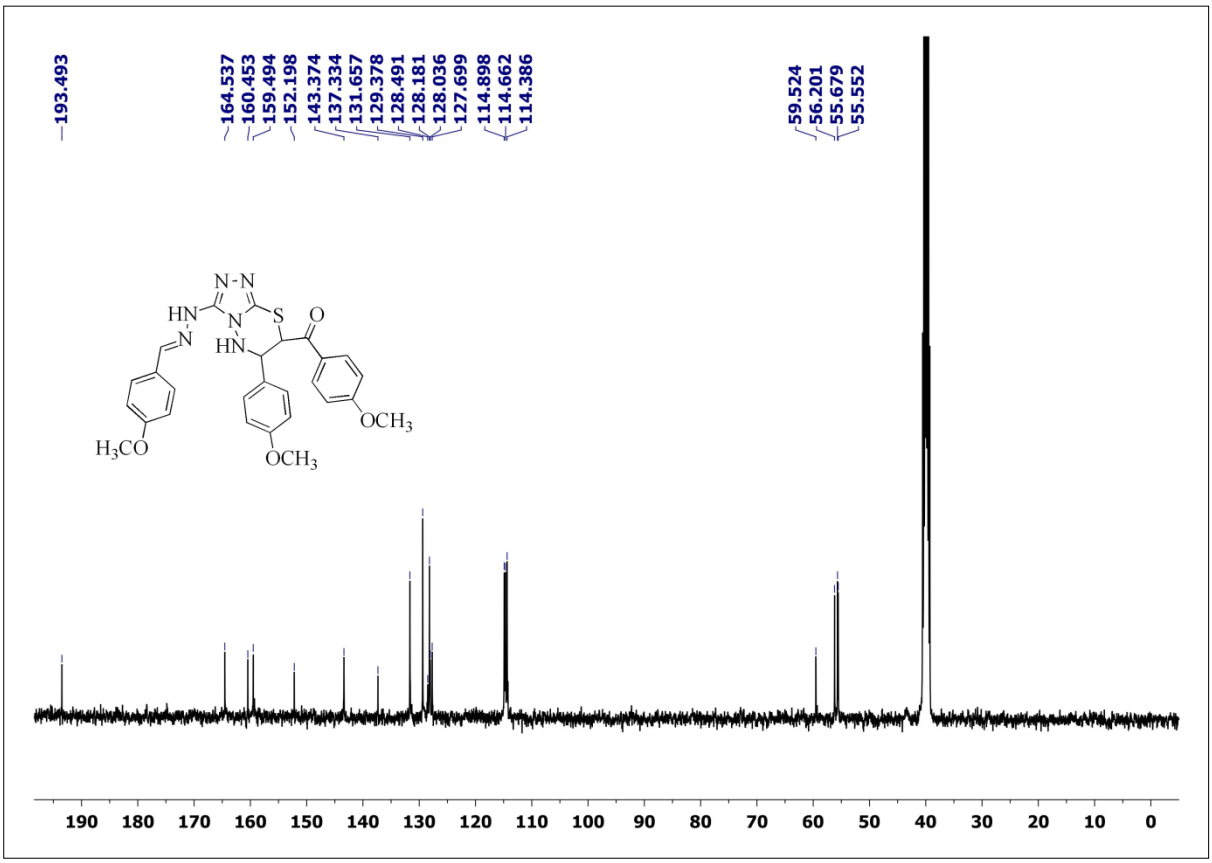
PMR Spectrum of compound **27f**



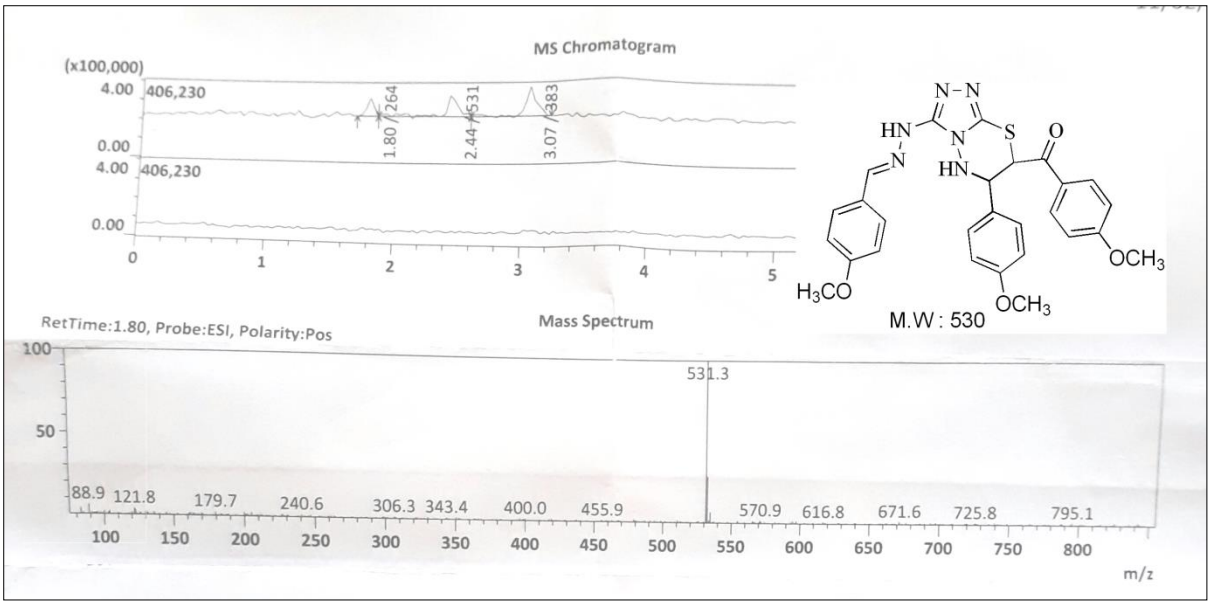
Mass Spectrum of compound **27f**



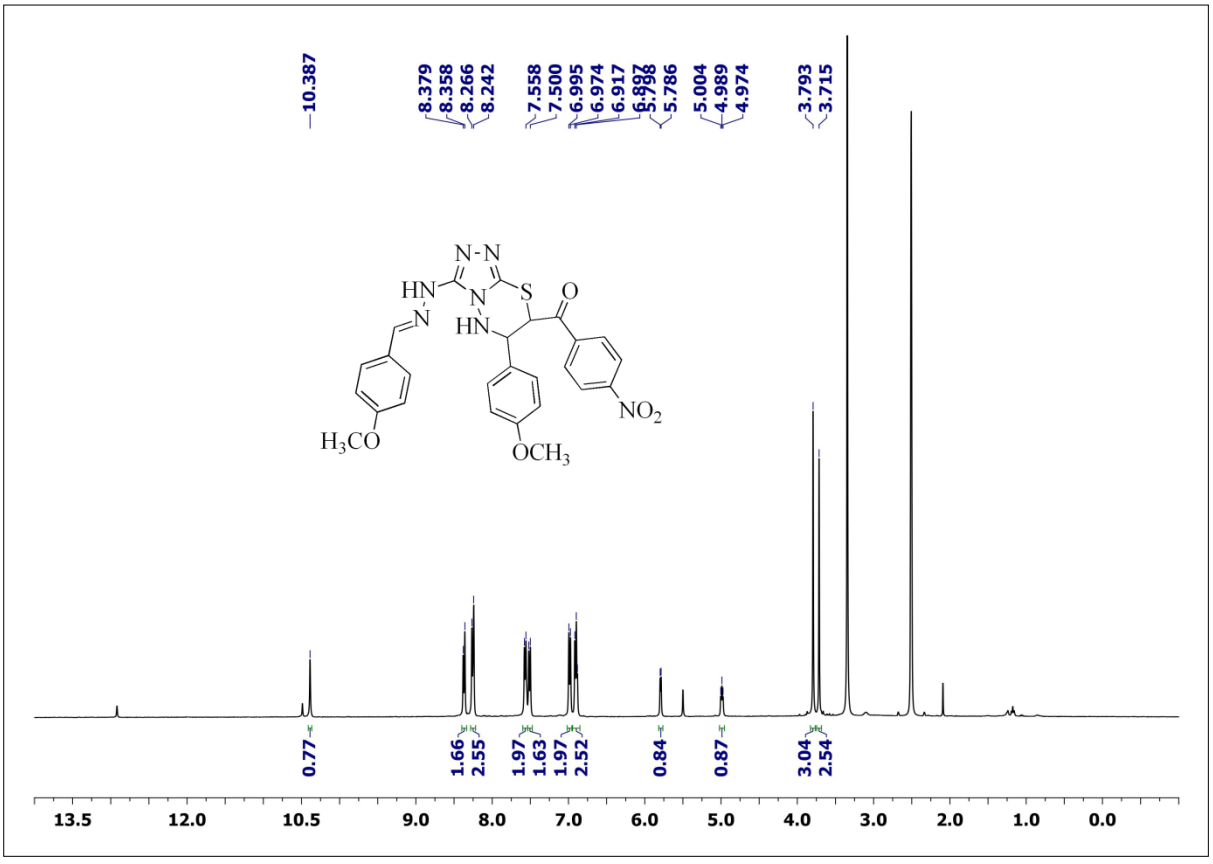
PMR Spectrum of compound **27g**



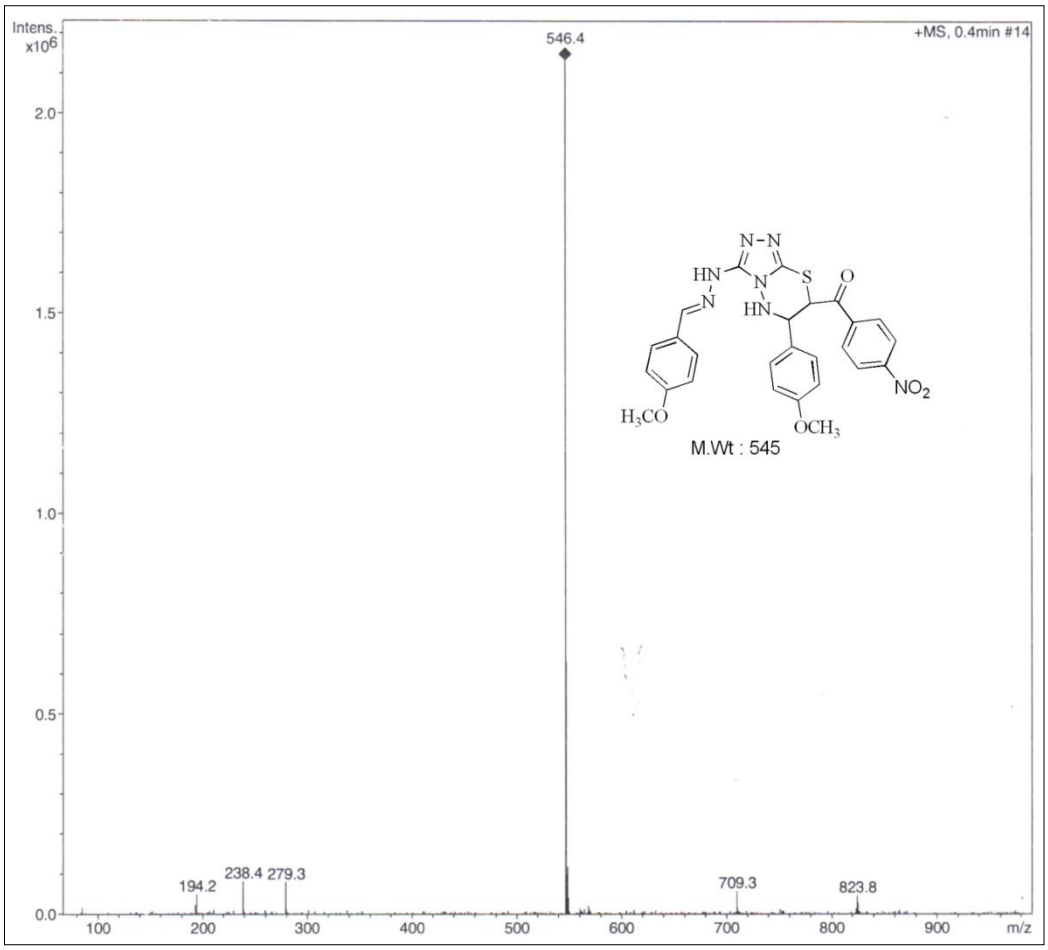
CMR Spectrum of compound **27g**



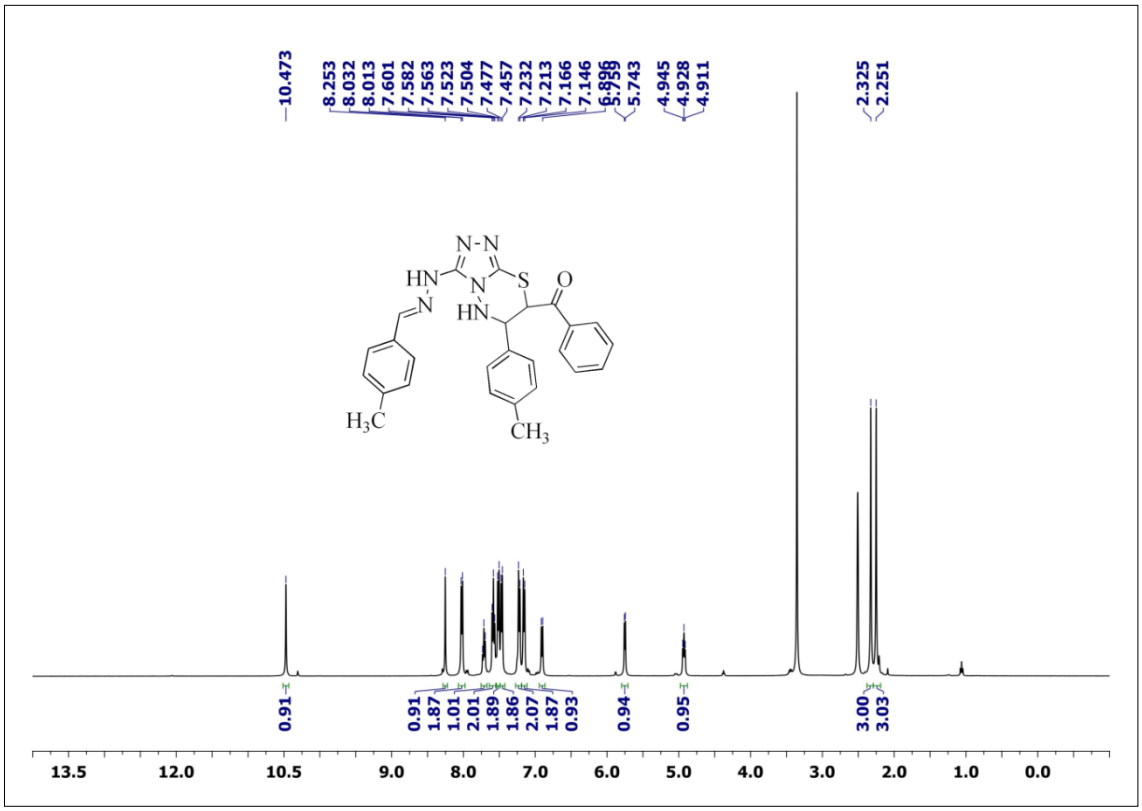
Mass Spectrum of compound **27g**



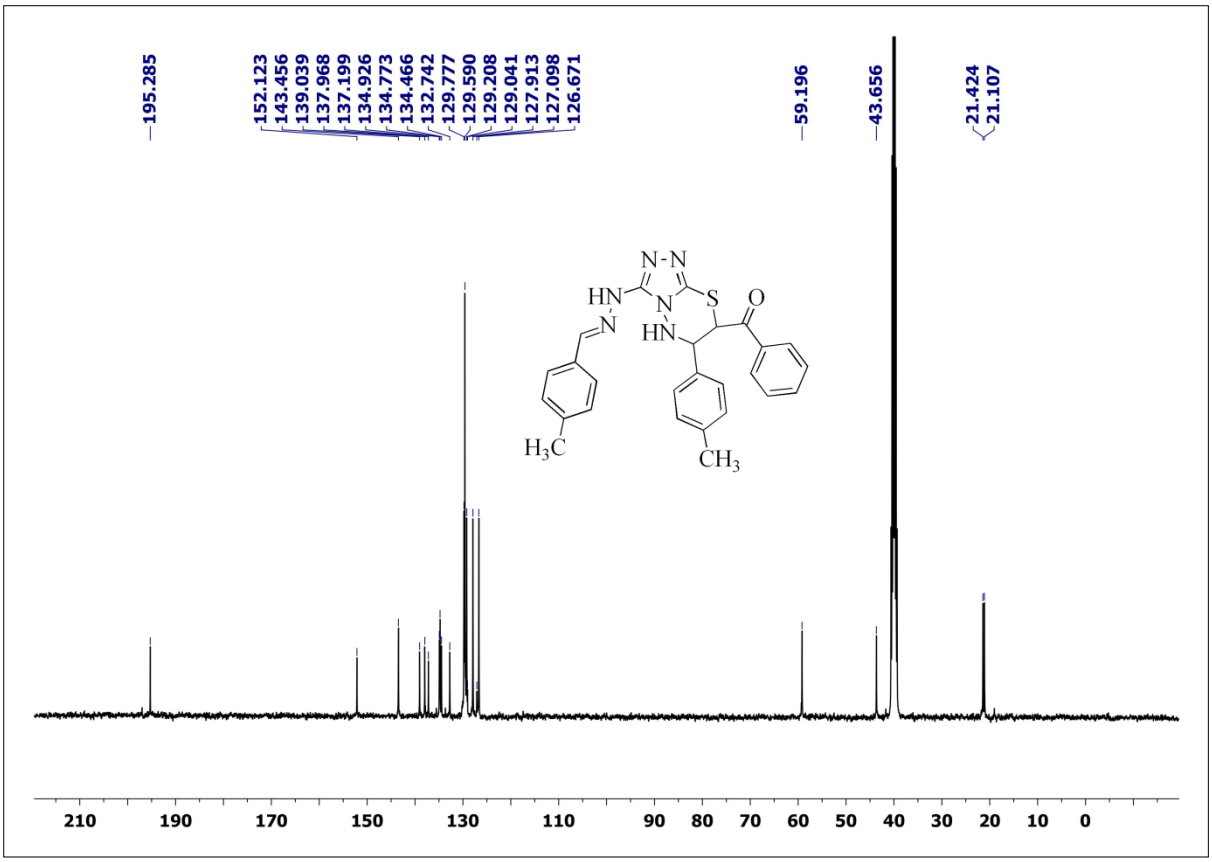
PMR Spectrum of compound **27h**



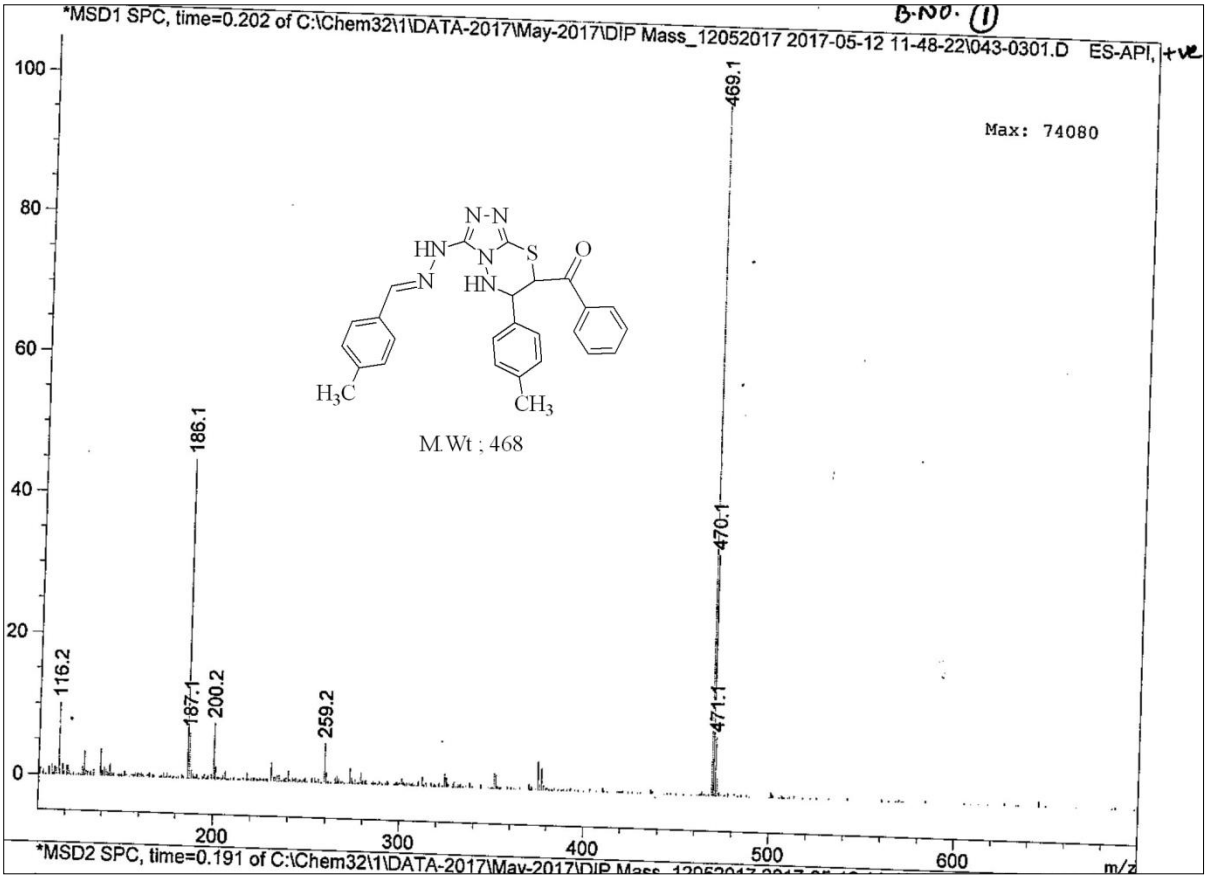
Mass Spectrum of compound **27h**



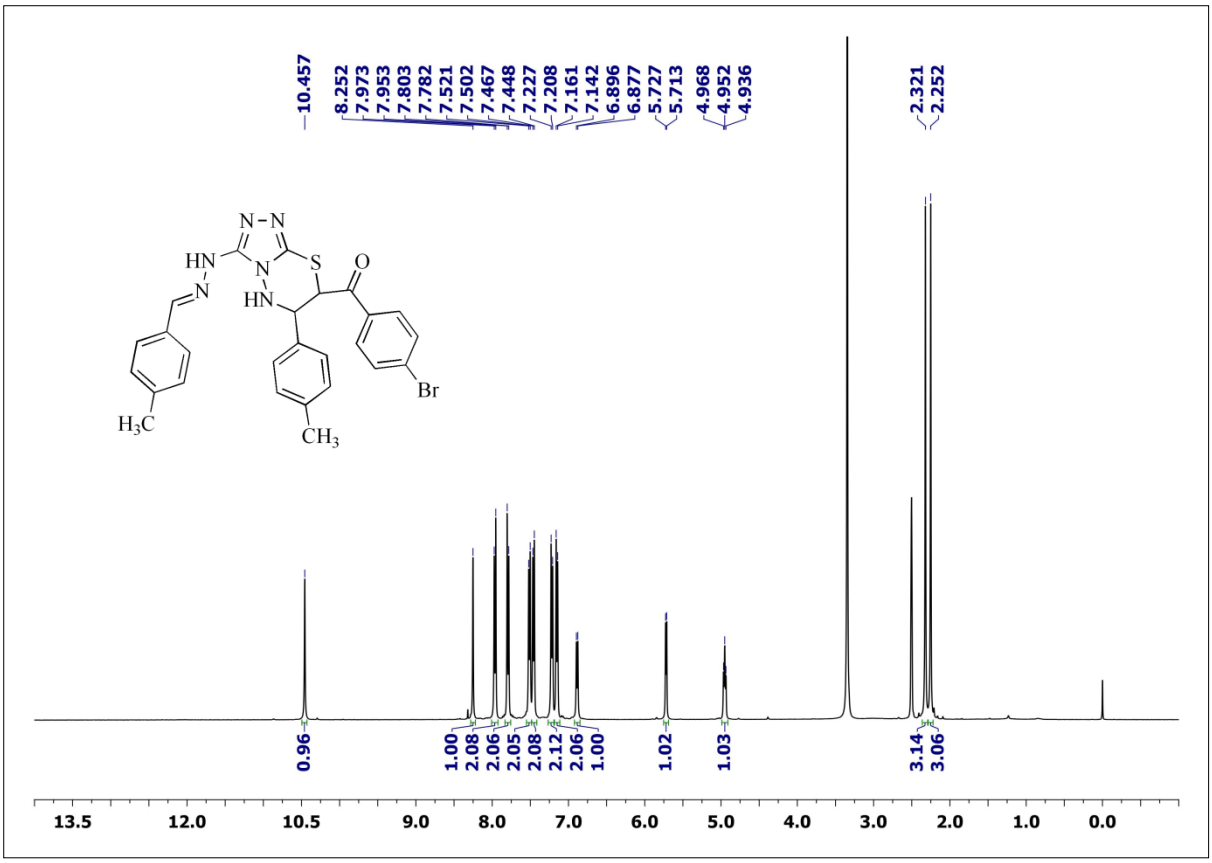
PMR Spectrum of compound **27i**



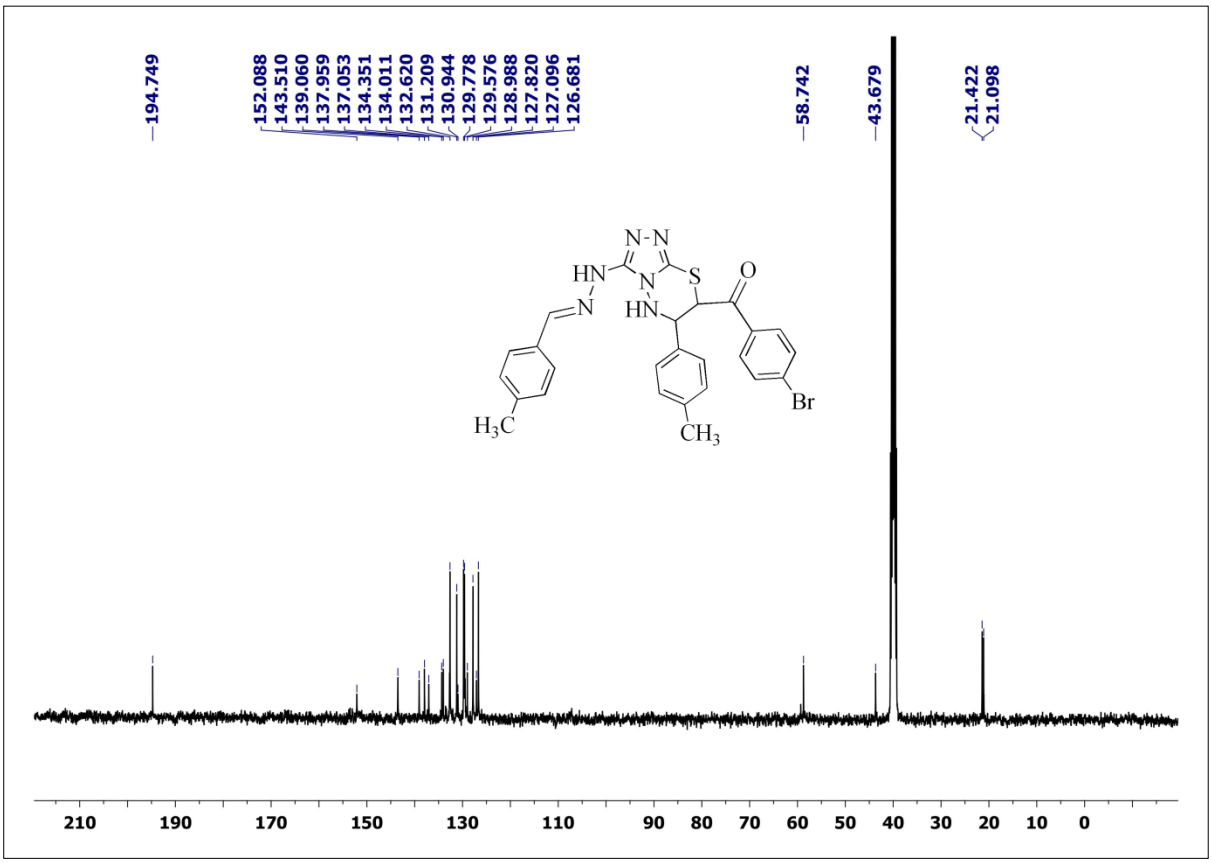
CMR Spectrum of compound **27i**



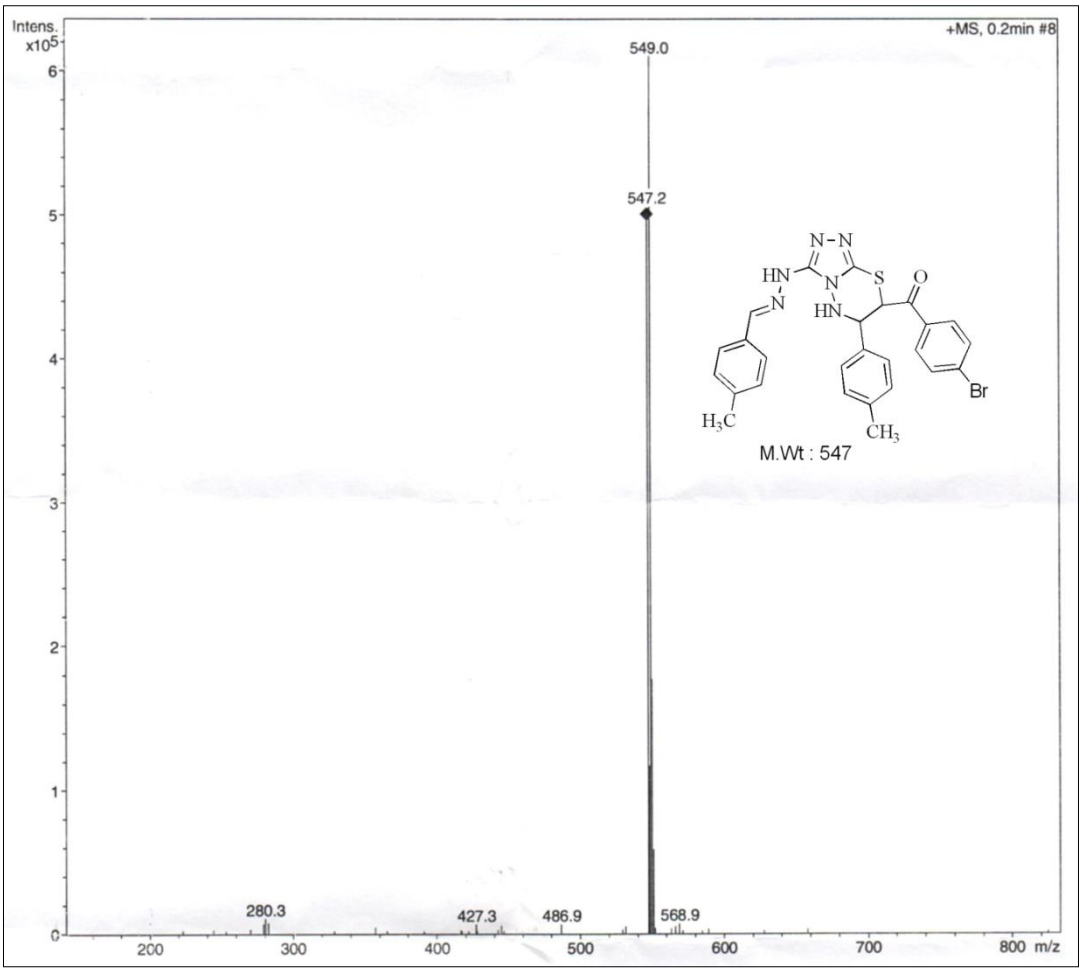
Mass Spectrum of compound **27i**



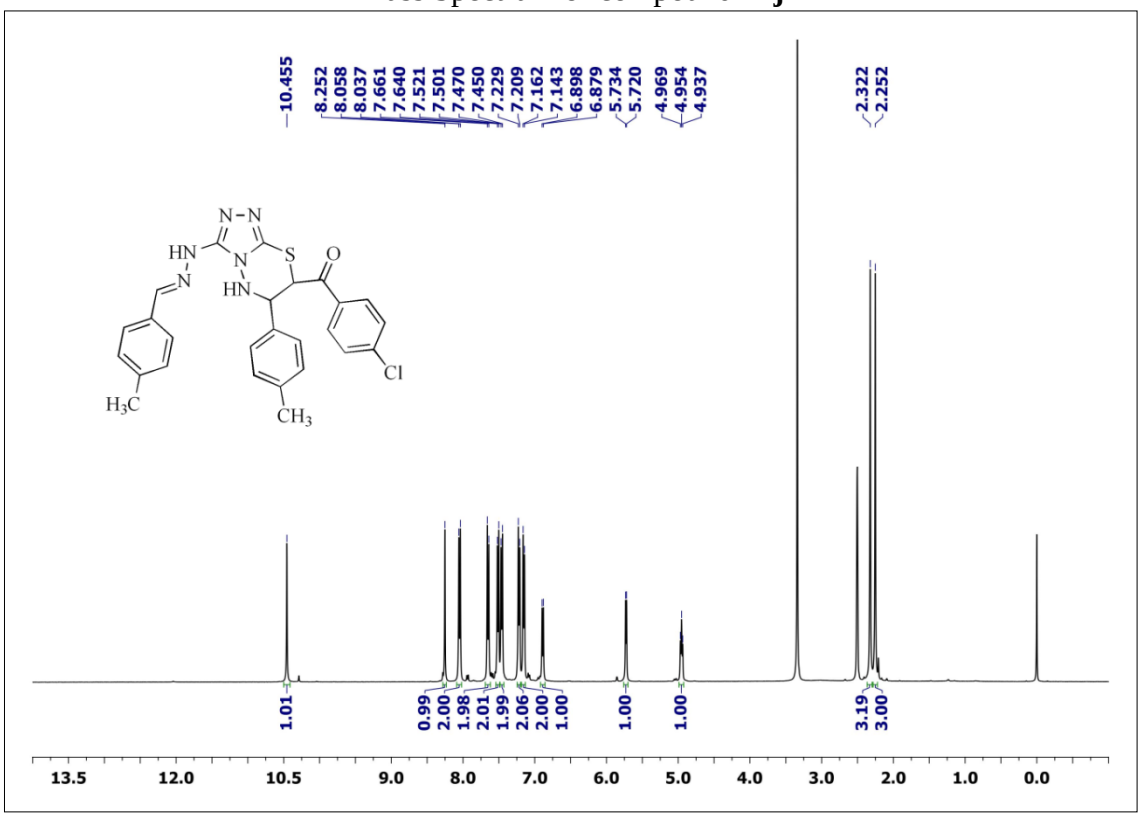
PMR Spectrum of compound **27j**



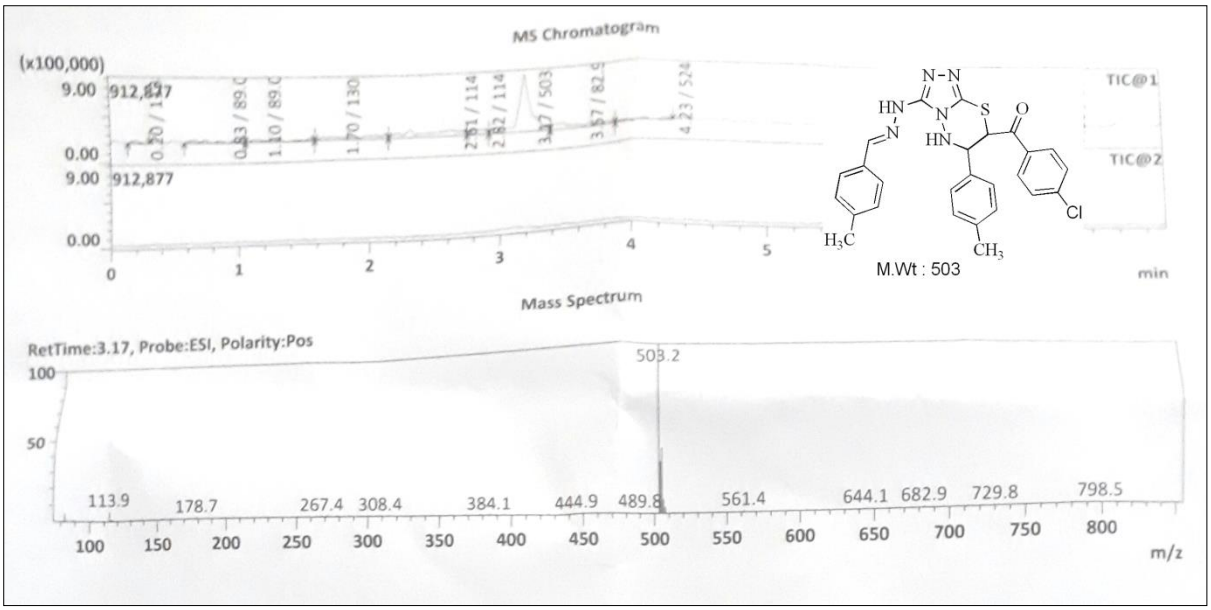
CMR Spectrum of compound **27j**



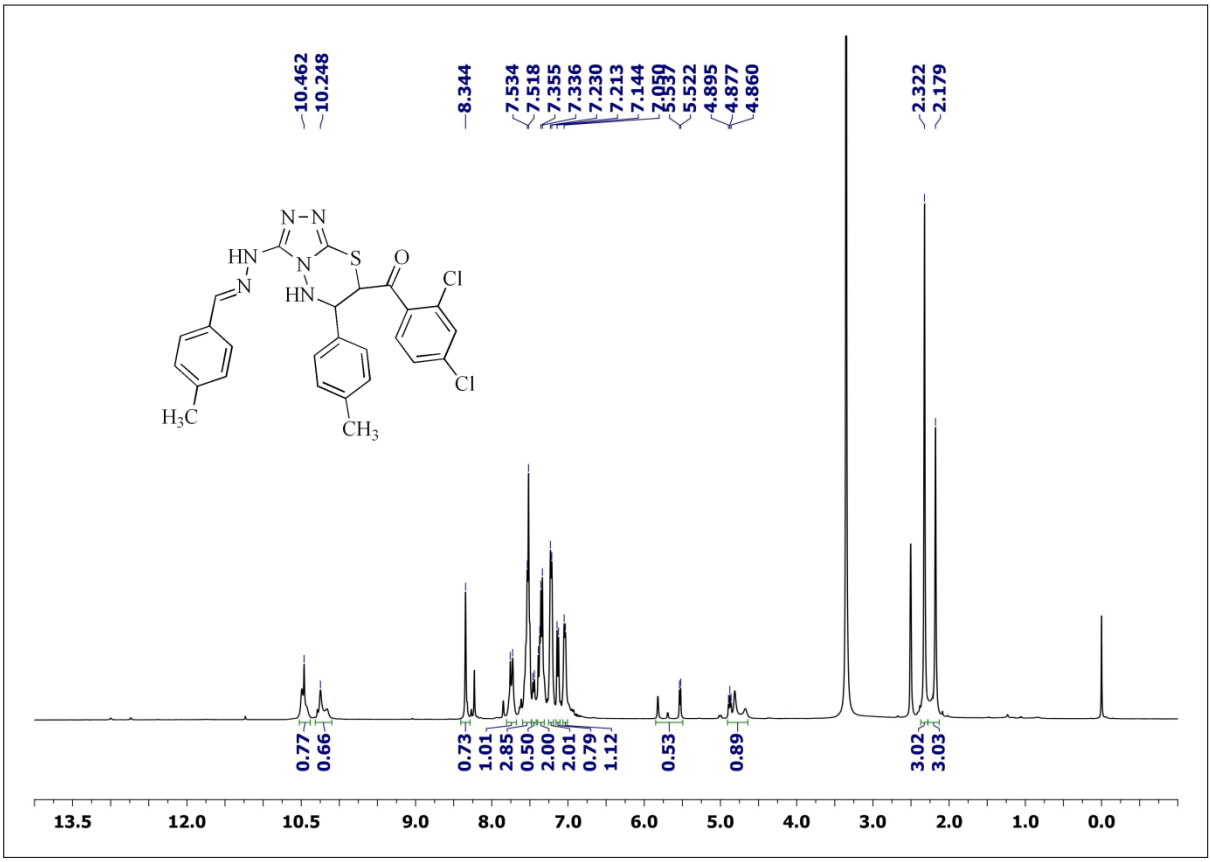
Mass Spectrum of compound **27j**



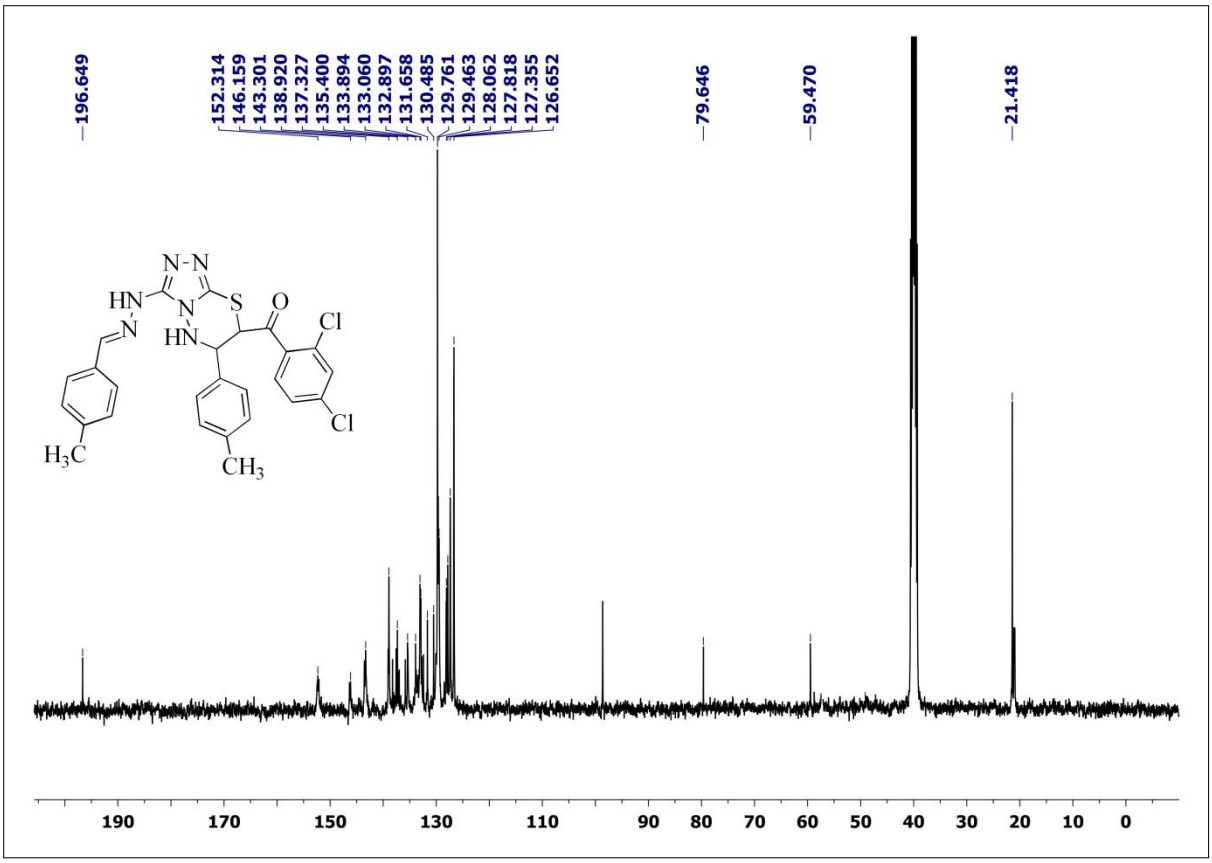
PMR Spectrum of compound **27k**



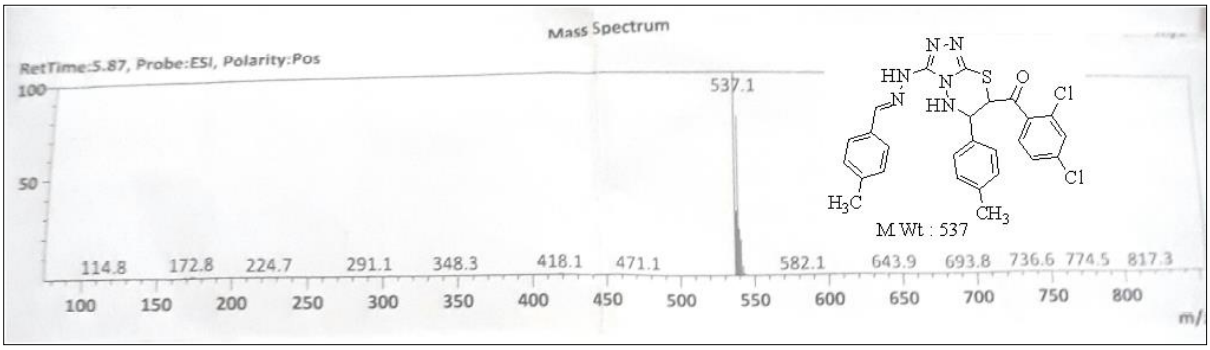
Mass Spectrum of compound **27k**



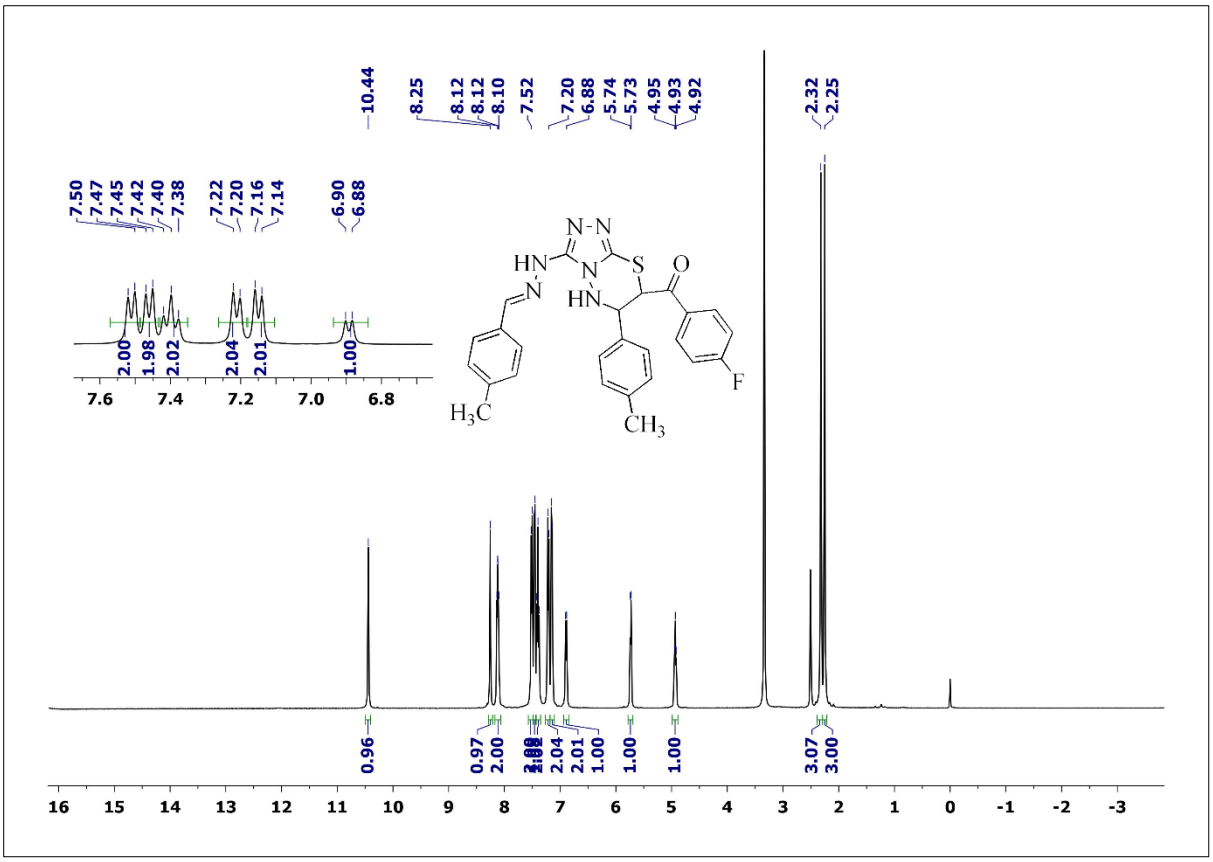
PMR Spectrum of compound **27l**



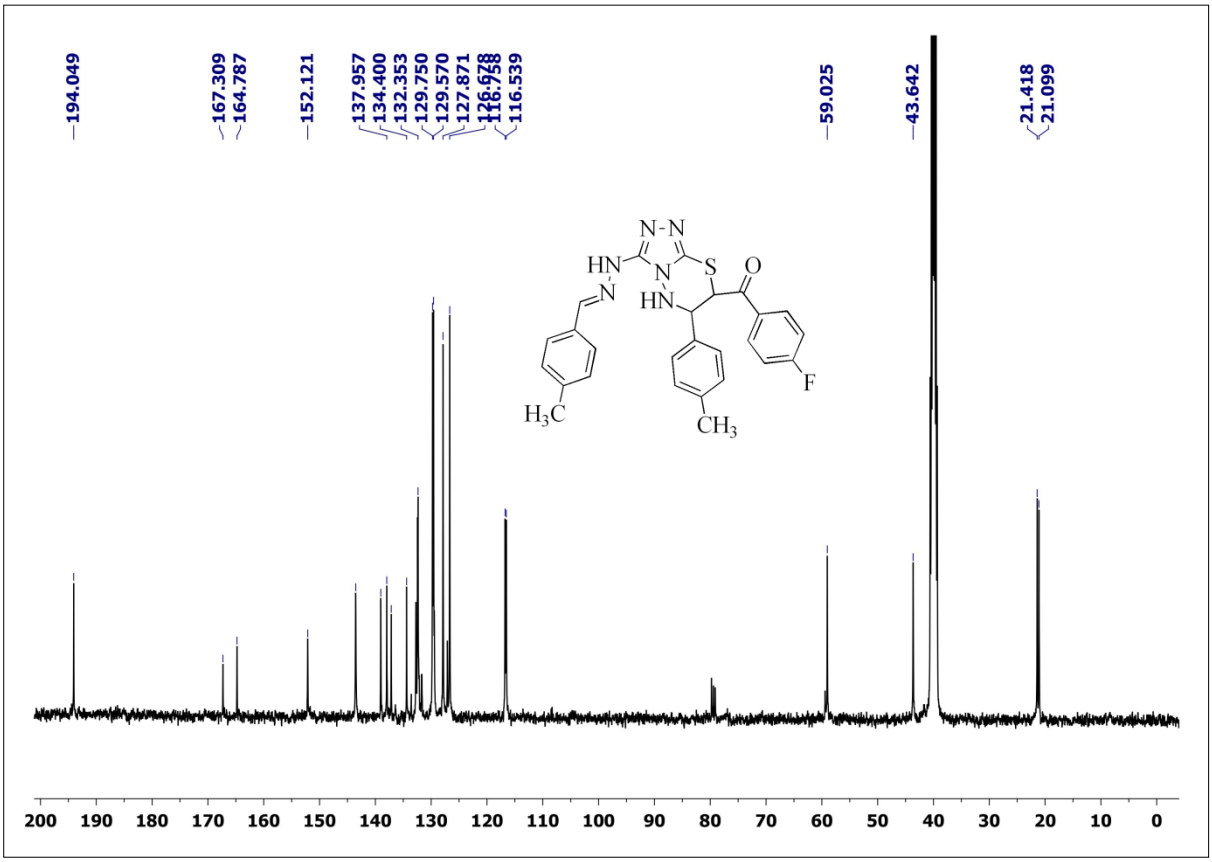
CMR Spectrum of compound **27l**



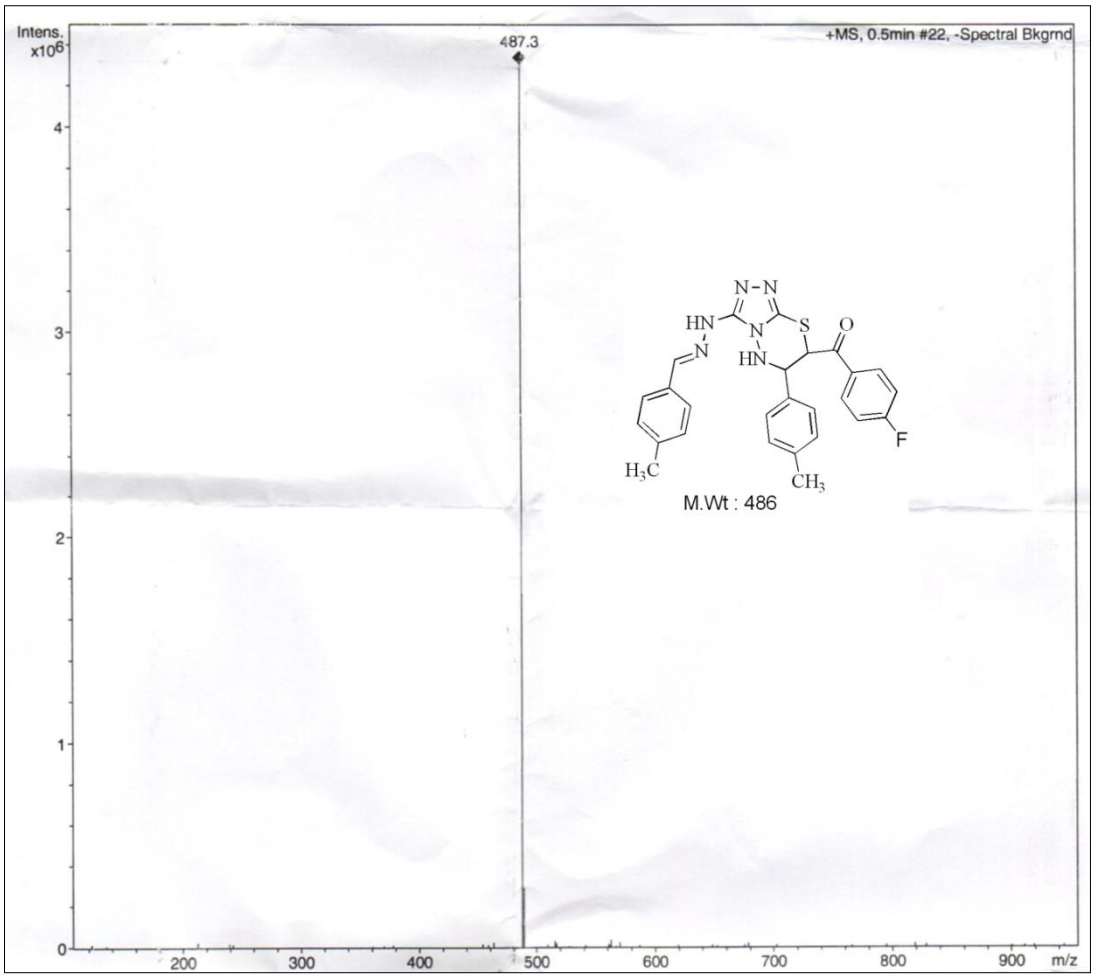
Mass Spectrum of compound **27l**



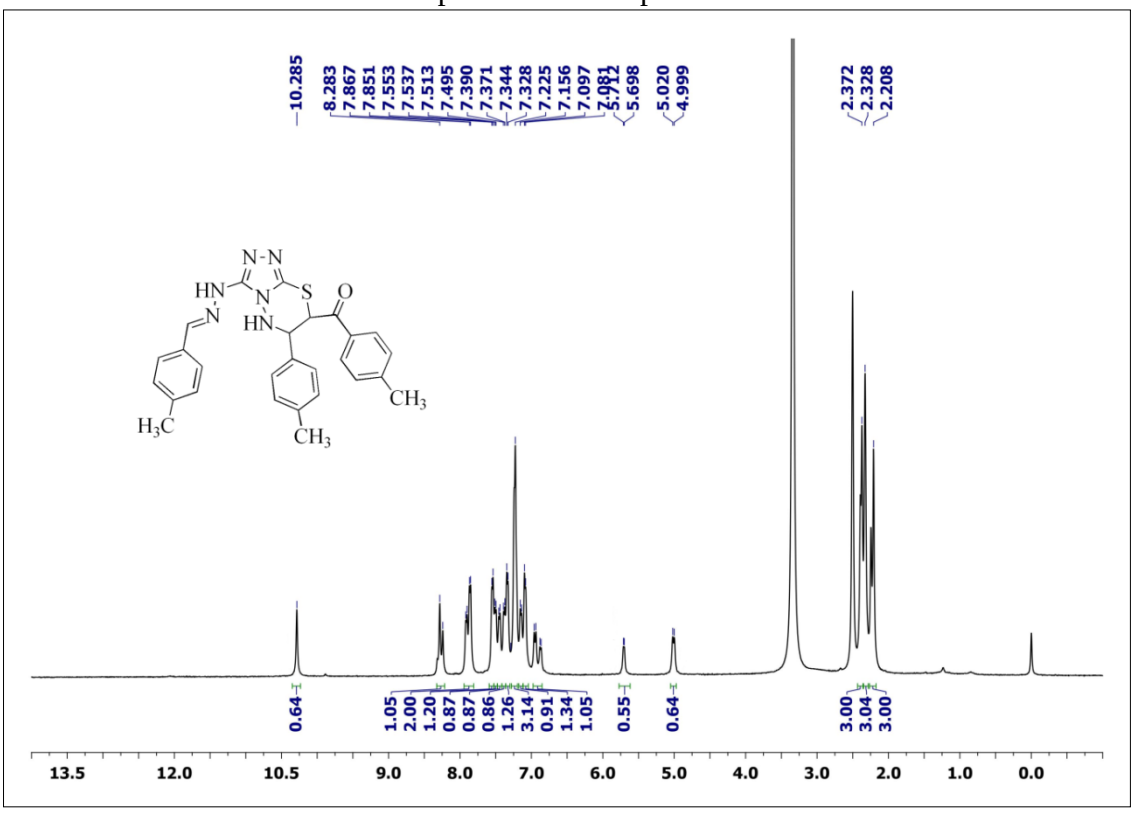
PMR Spectrum of compound **27m**



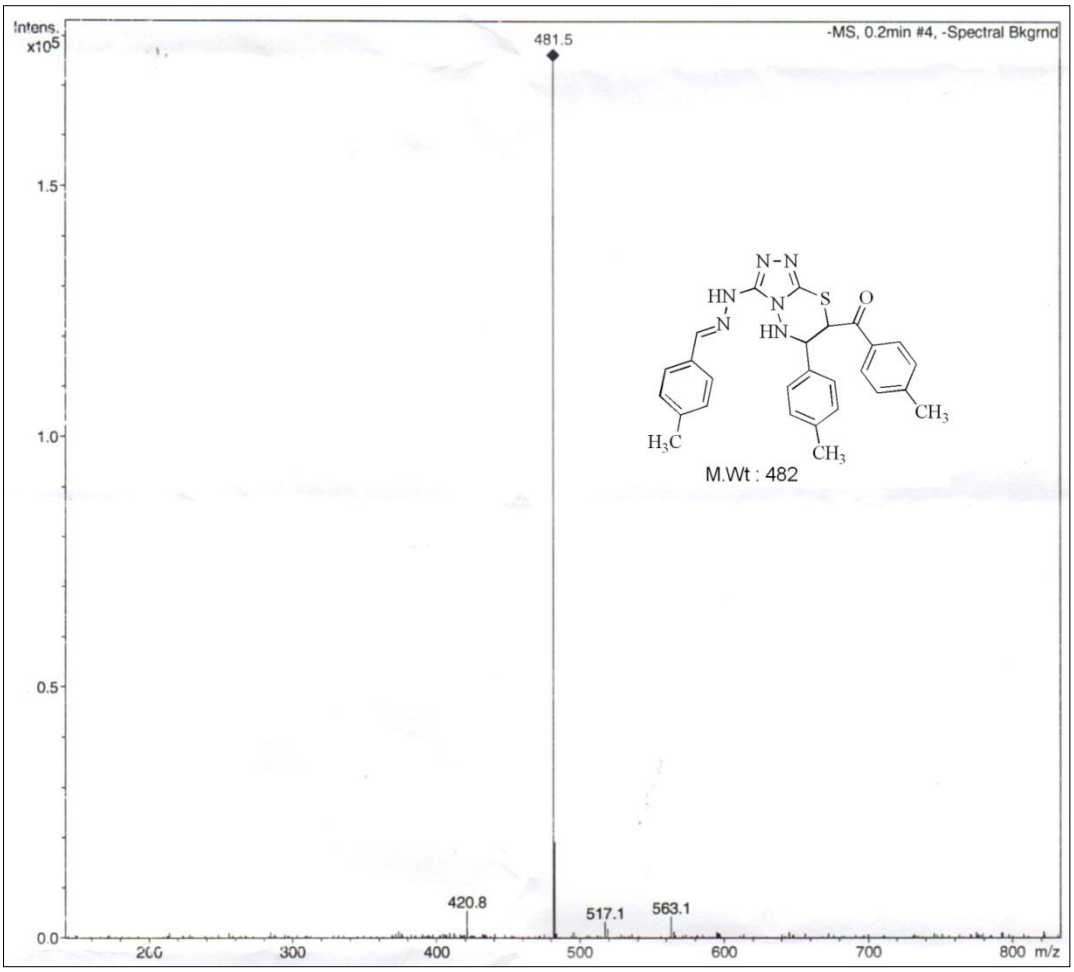
CMR Spectrum of compound **27m**



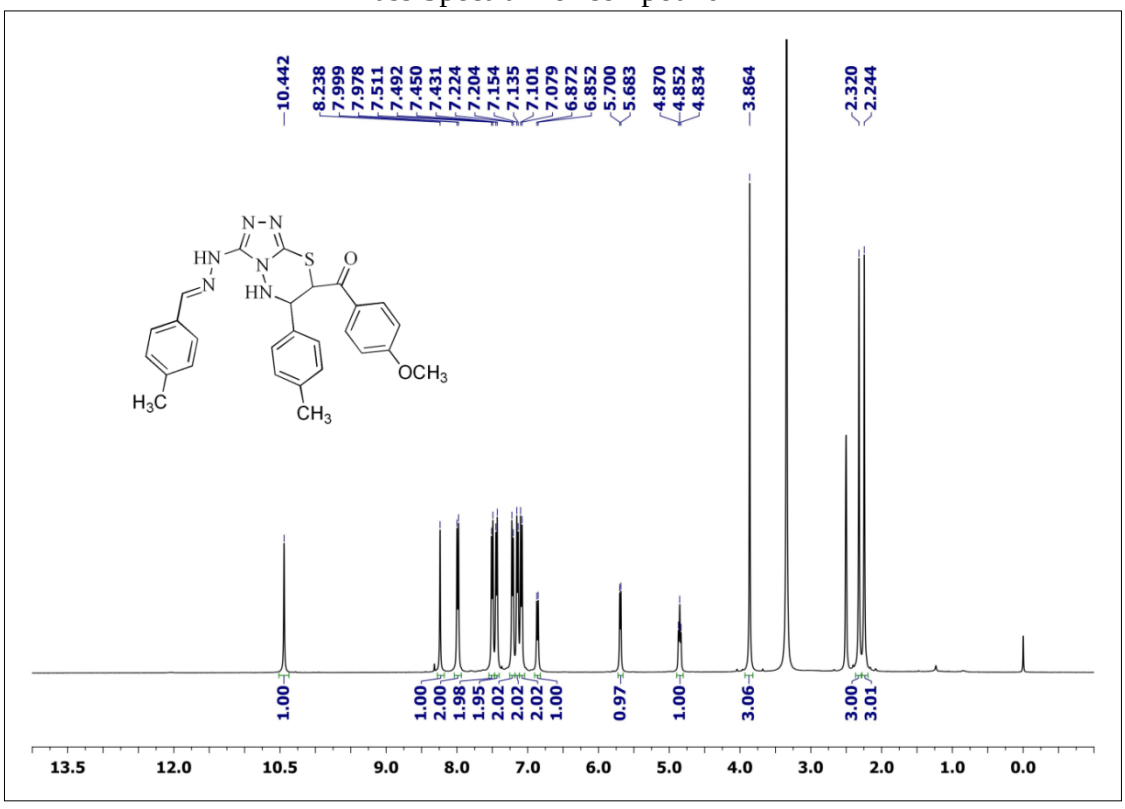
Mass Spectrum of compound **27m**



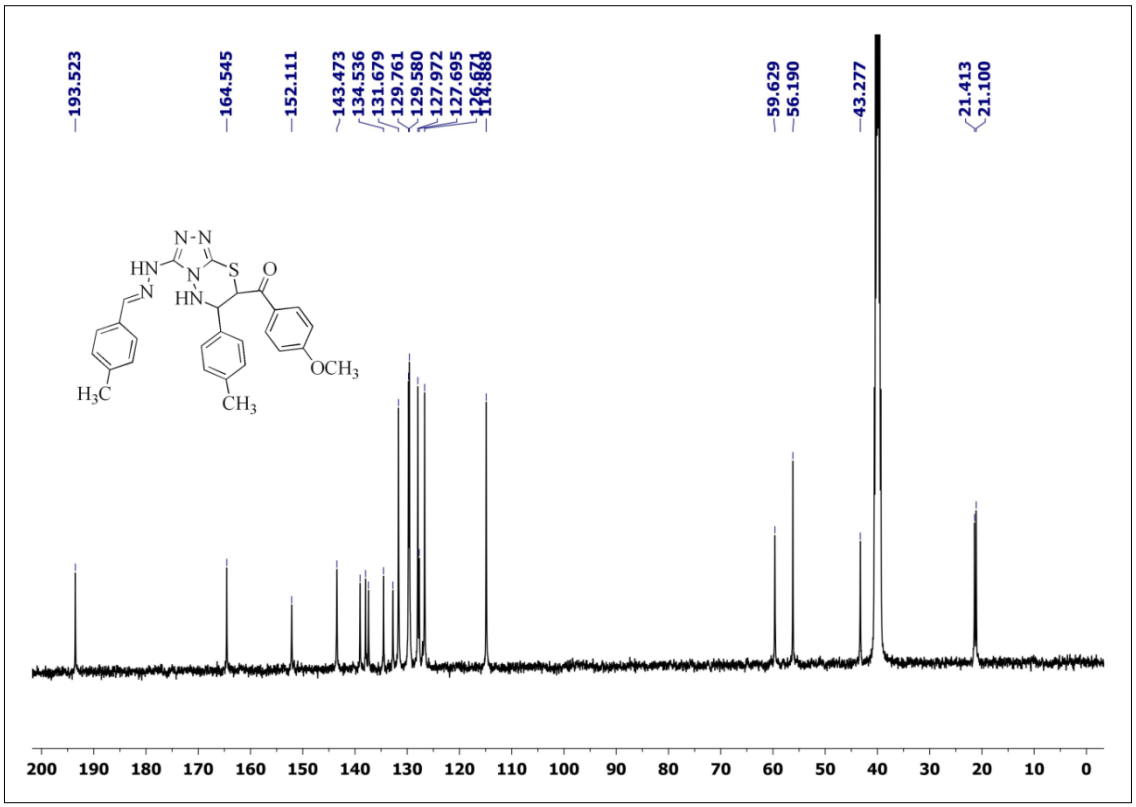
PMR Spectrum of compound **27n**



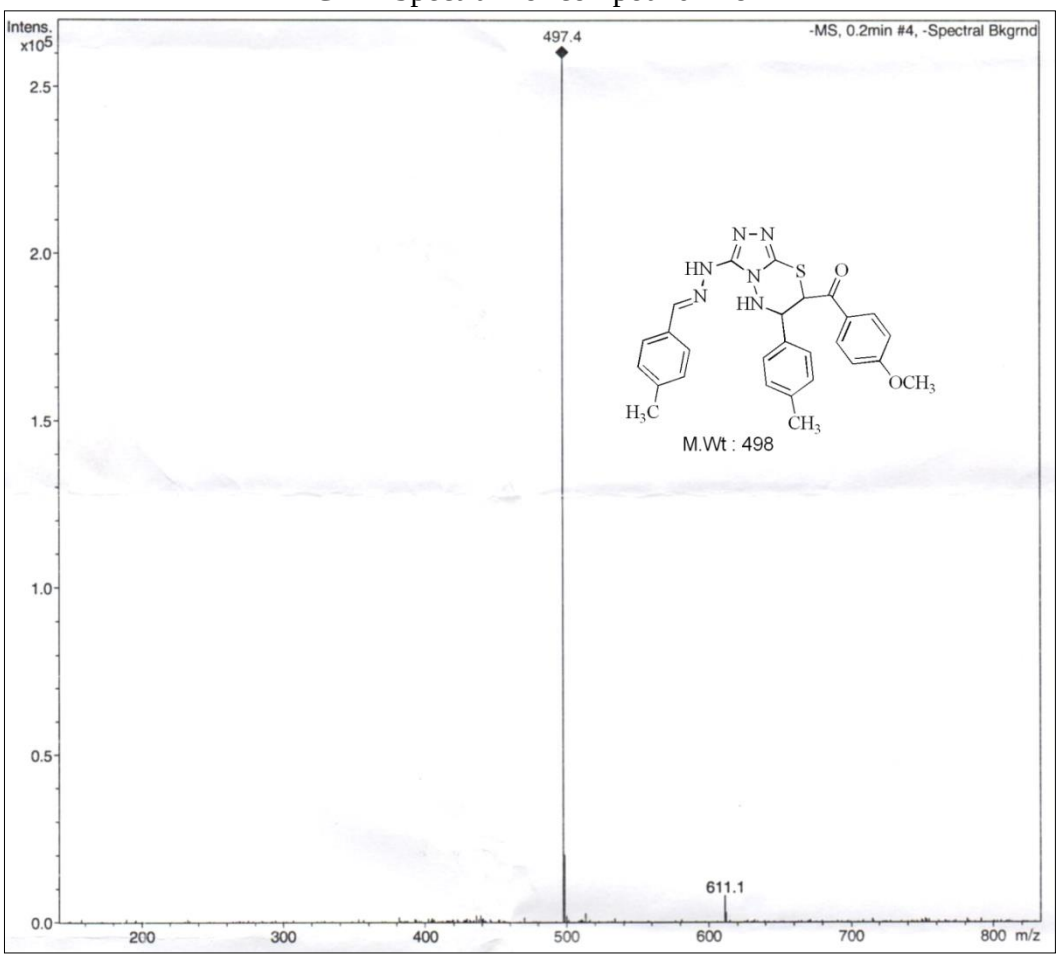
Mass Spectrum of compound **27n**



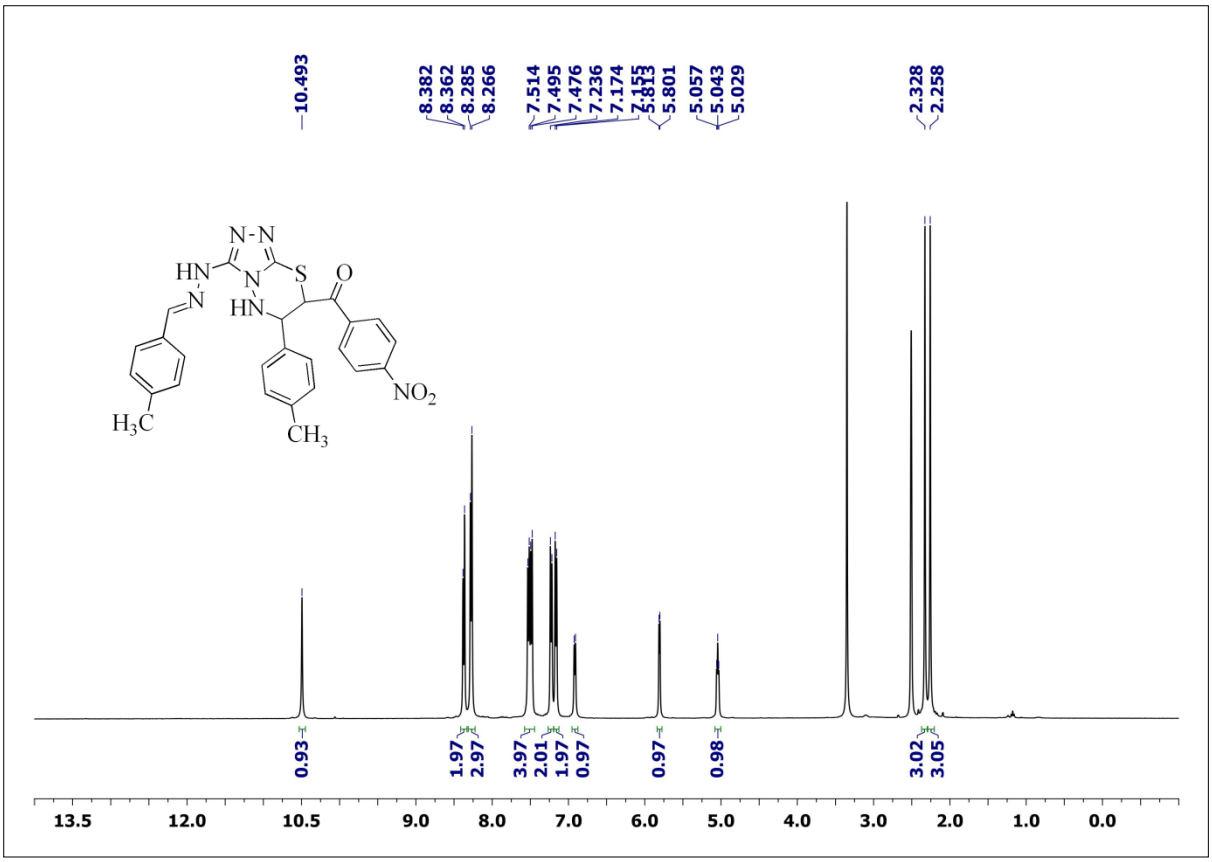
PMR Spectrum of compound **27o**



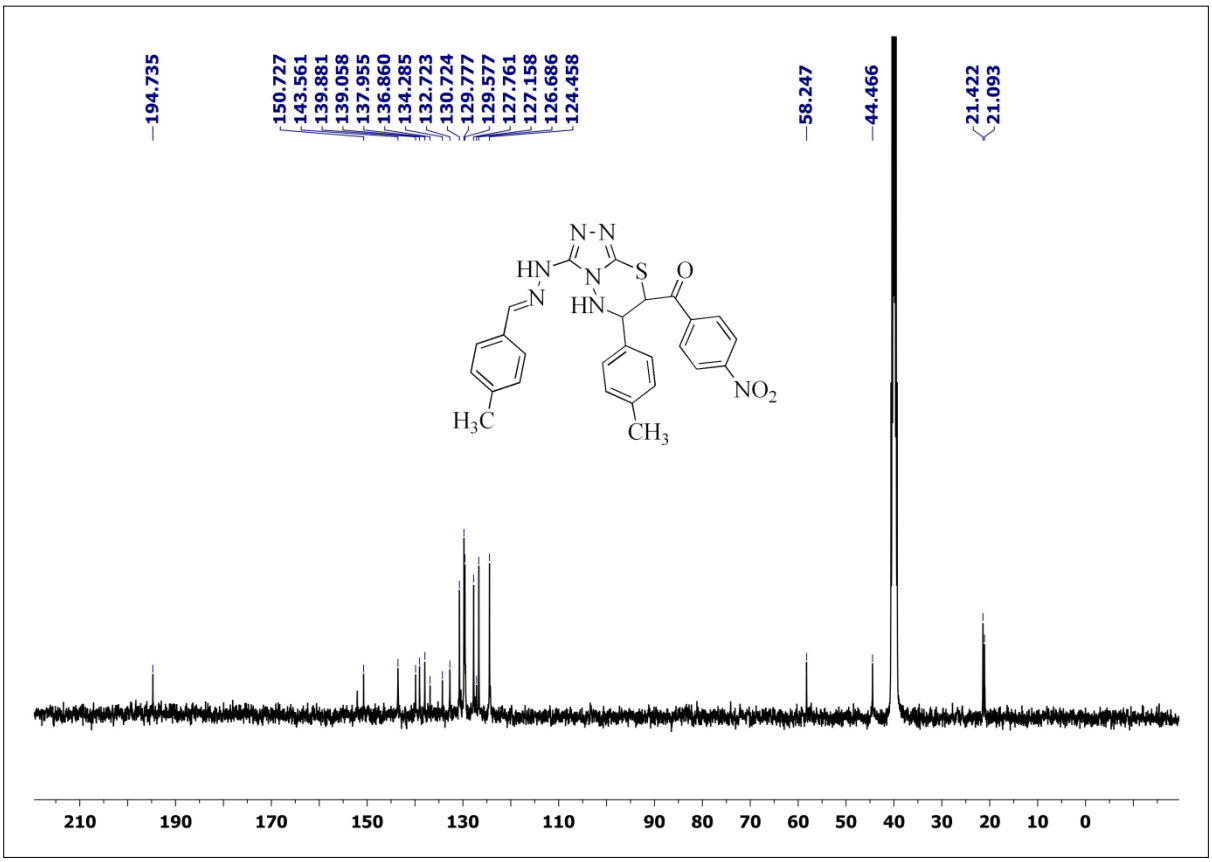
CMR Spectrum of compound **27o**



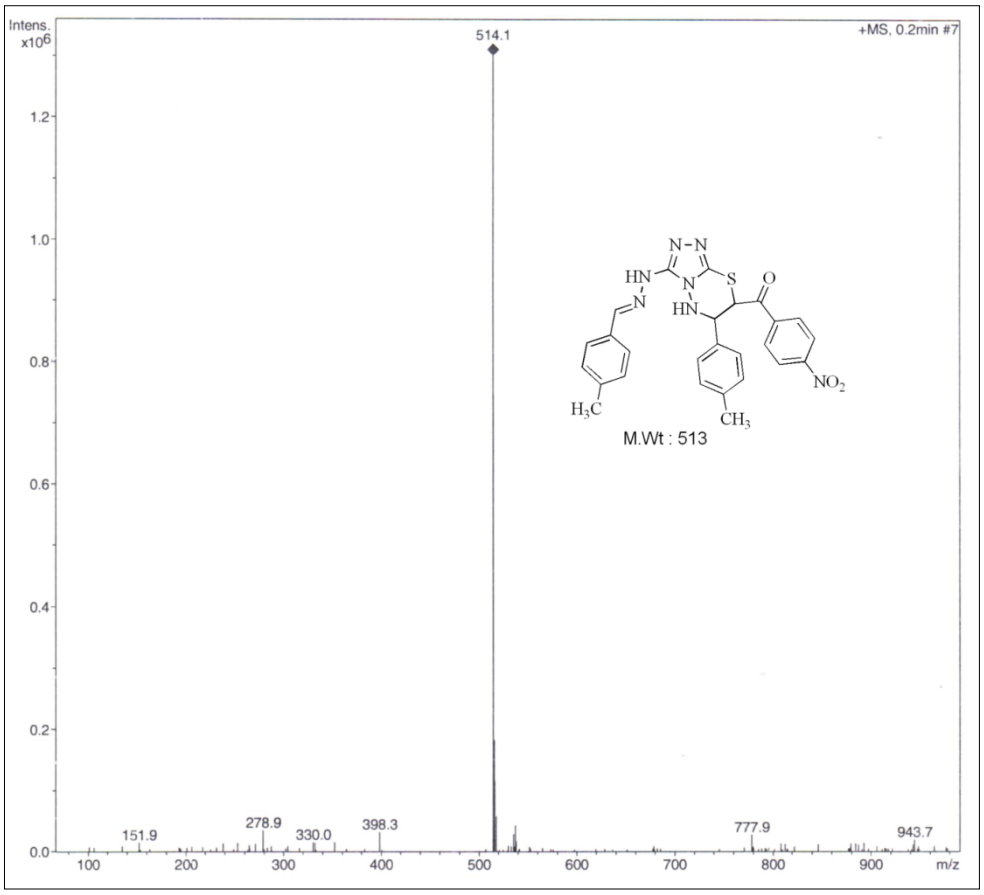
Mass Spectrum of compound **27o**



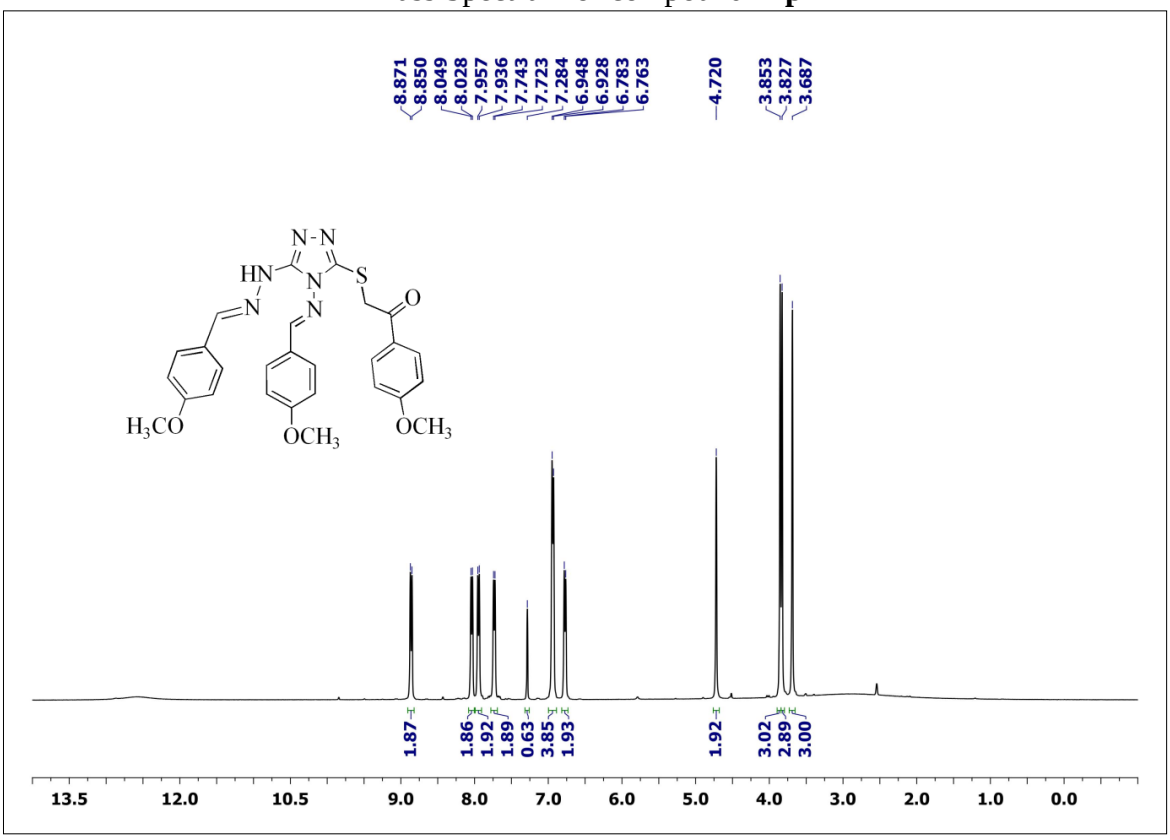
PMR Spectrum of compound **27p**



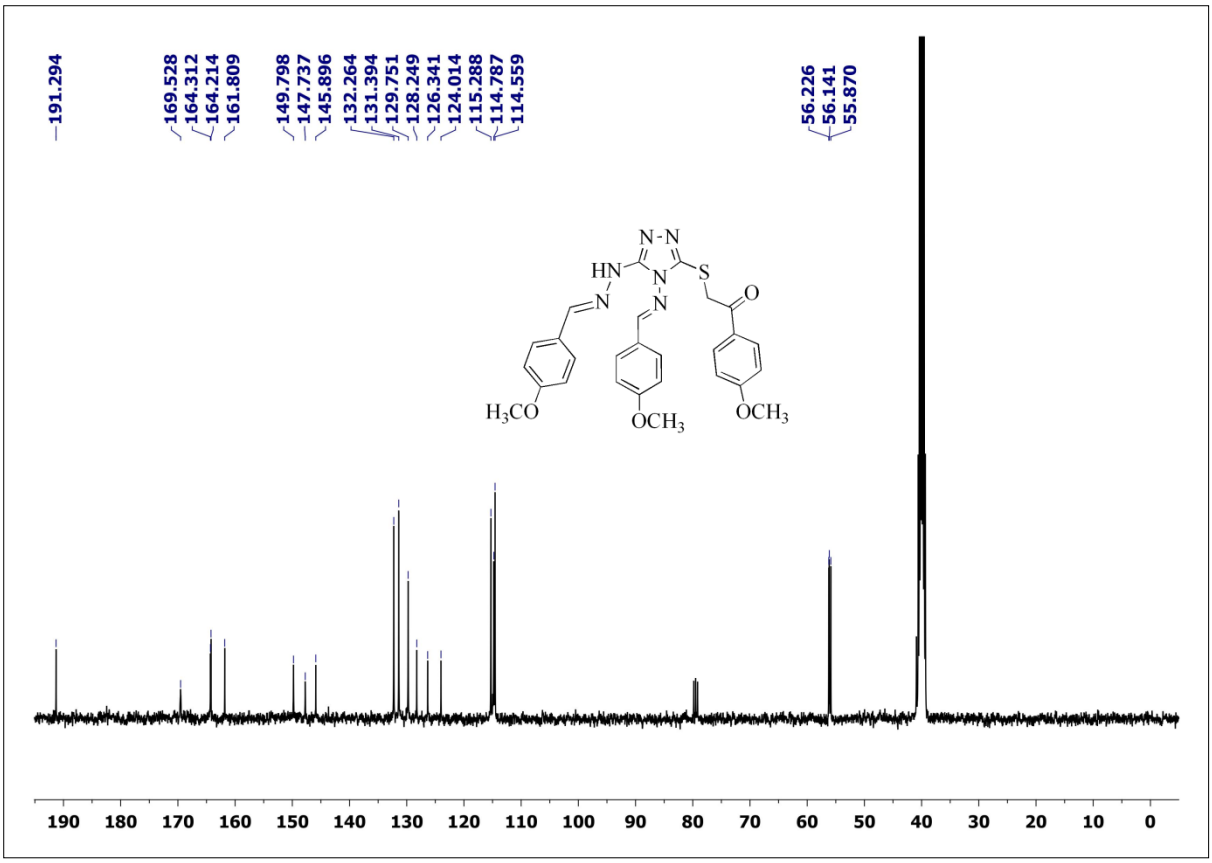
CMR Spectrum of compound **27p**



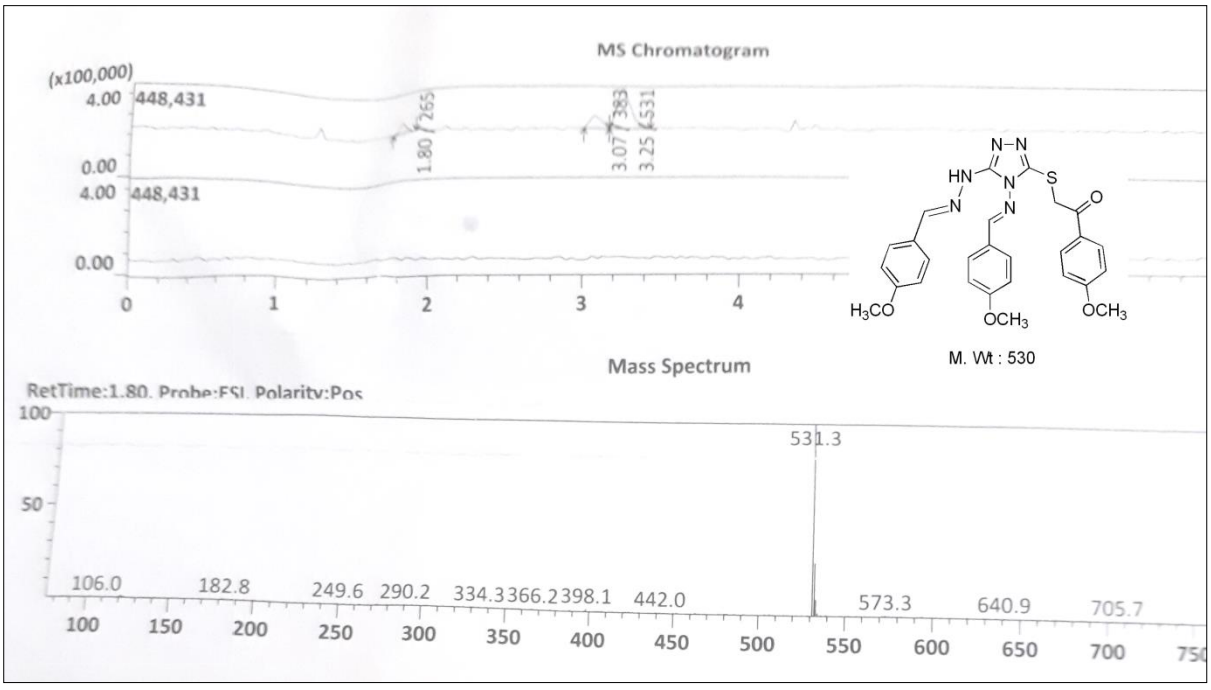
Mass Spectrum of compound **27p**



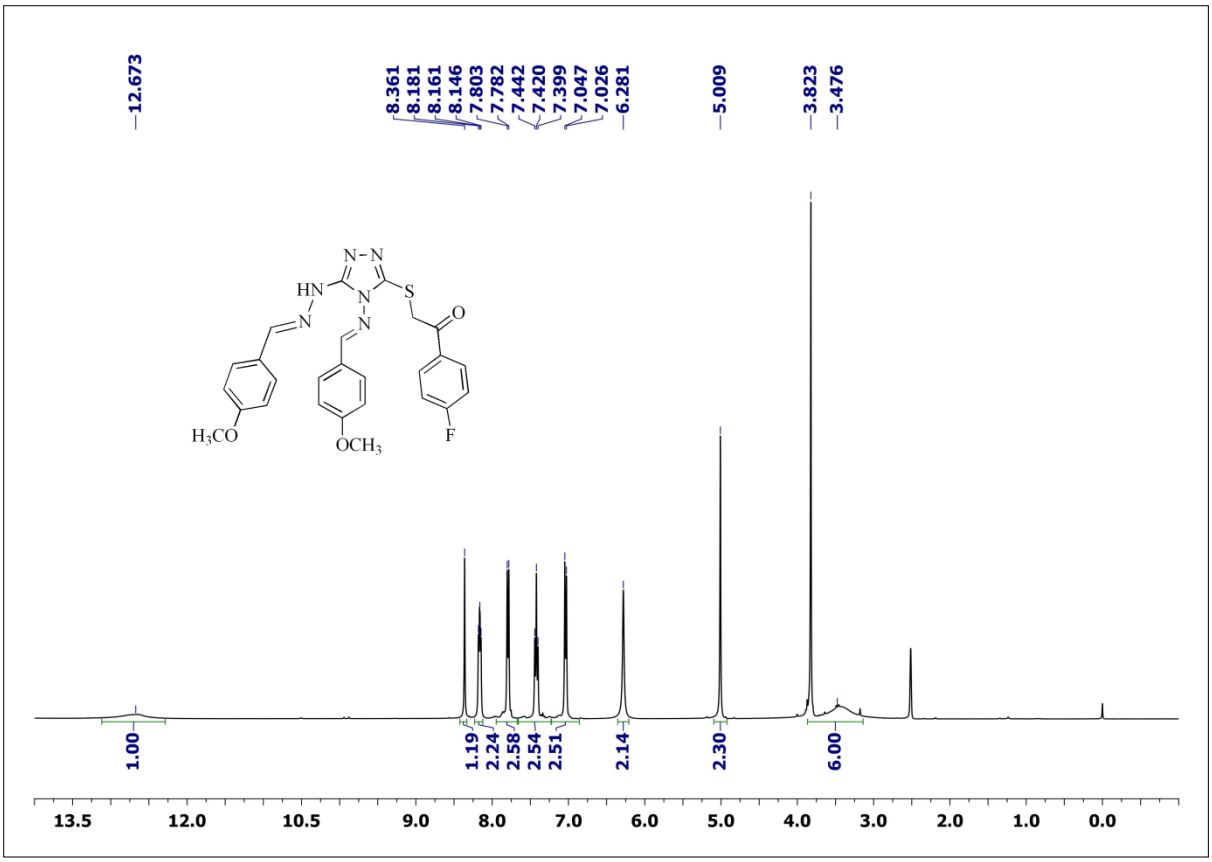
PMR Spectrum of compound **29a**



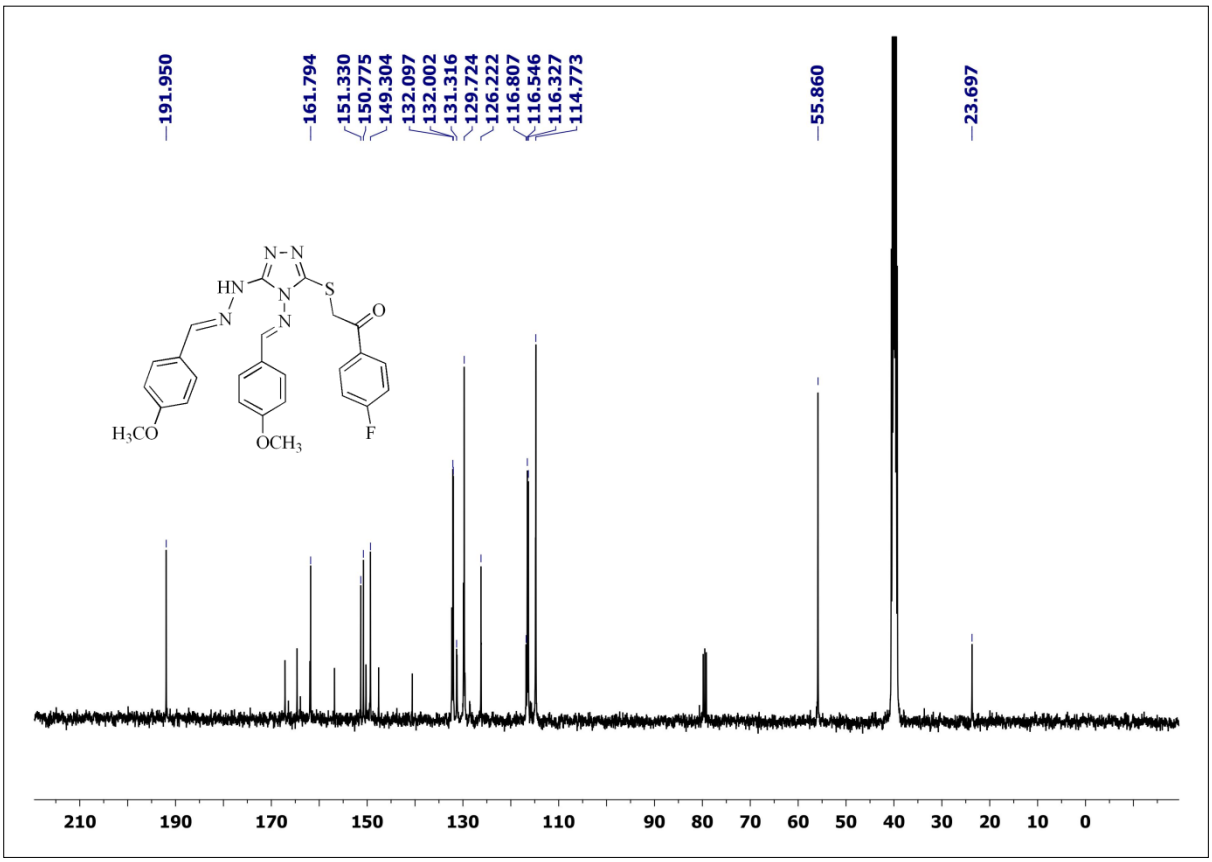
CMR Spectrum of compound **29a**



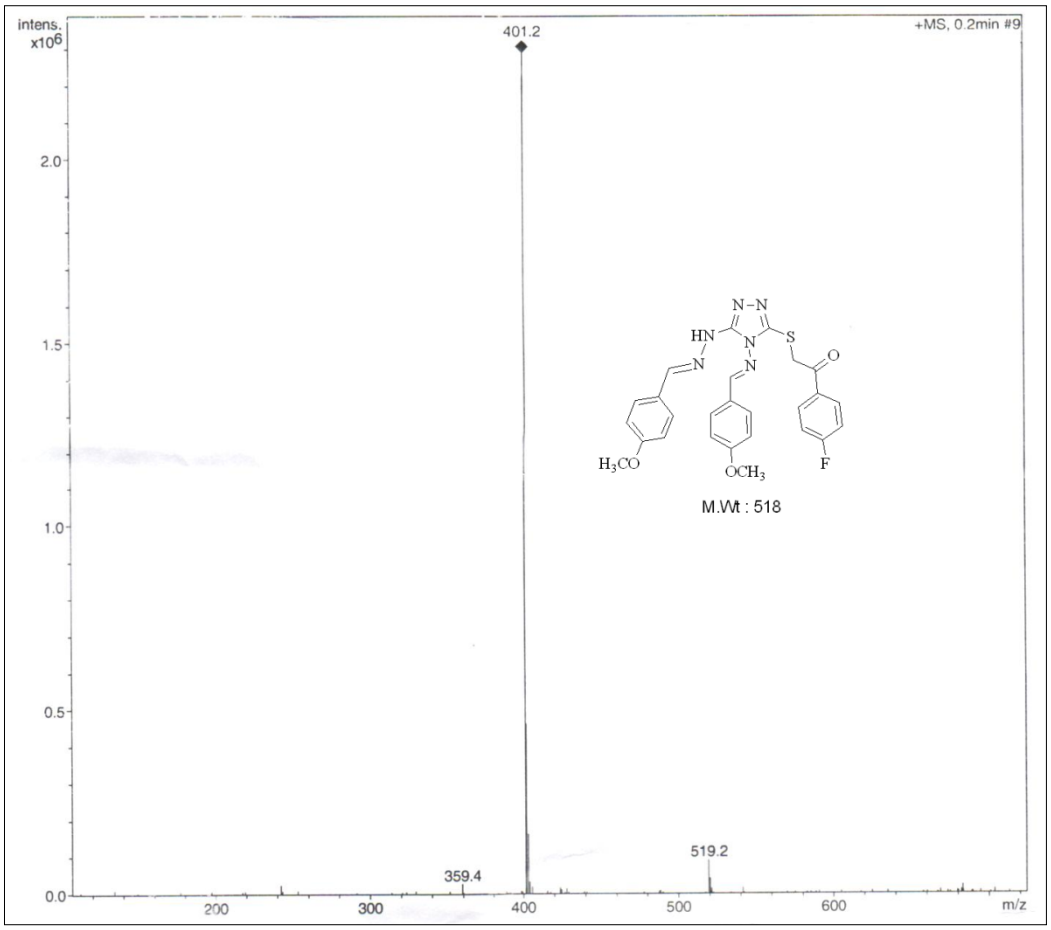
Mass Spectrum of compound **29a**



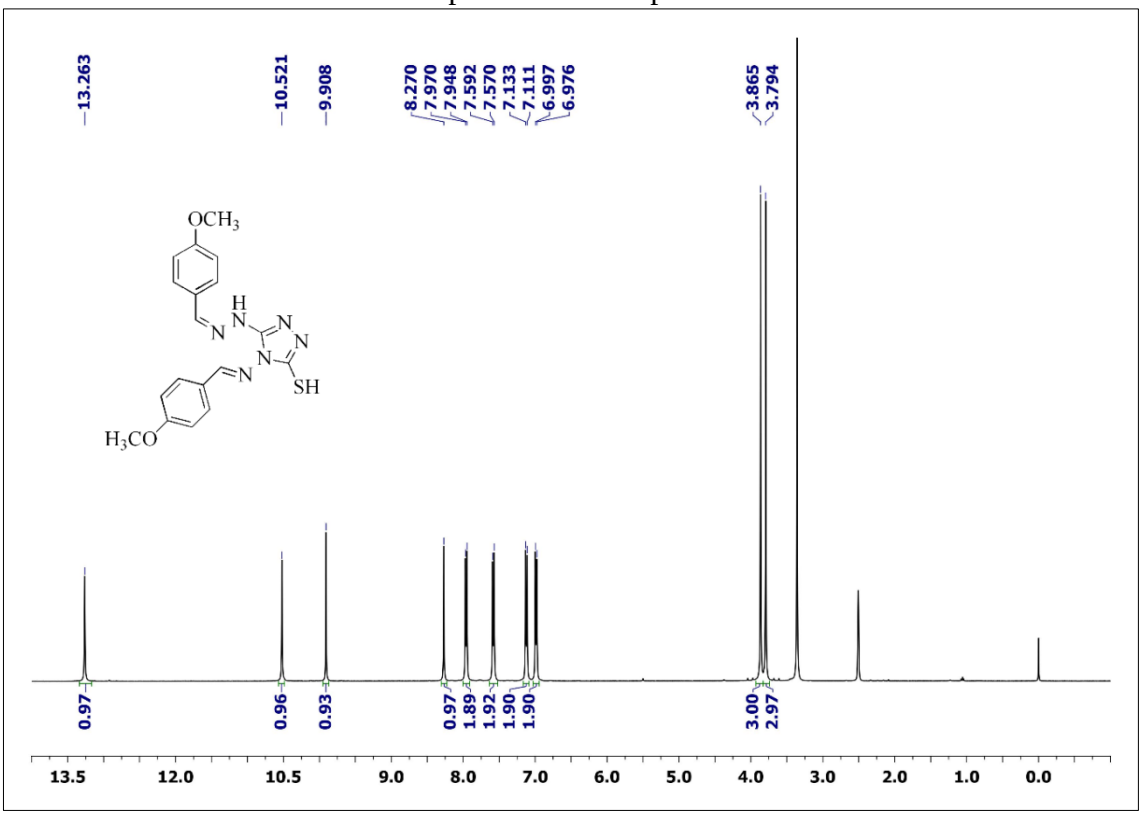
PMR Spectrum of compound **29b**



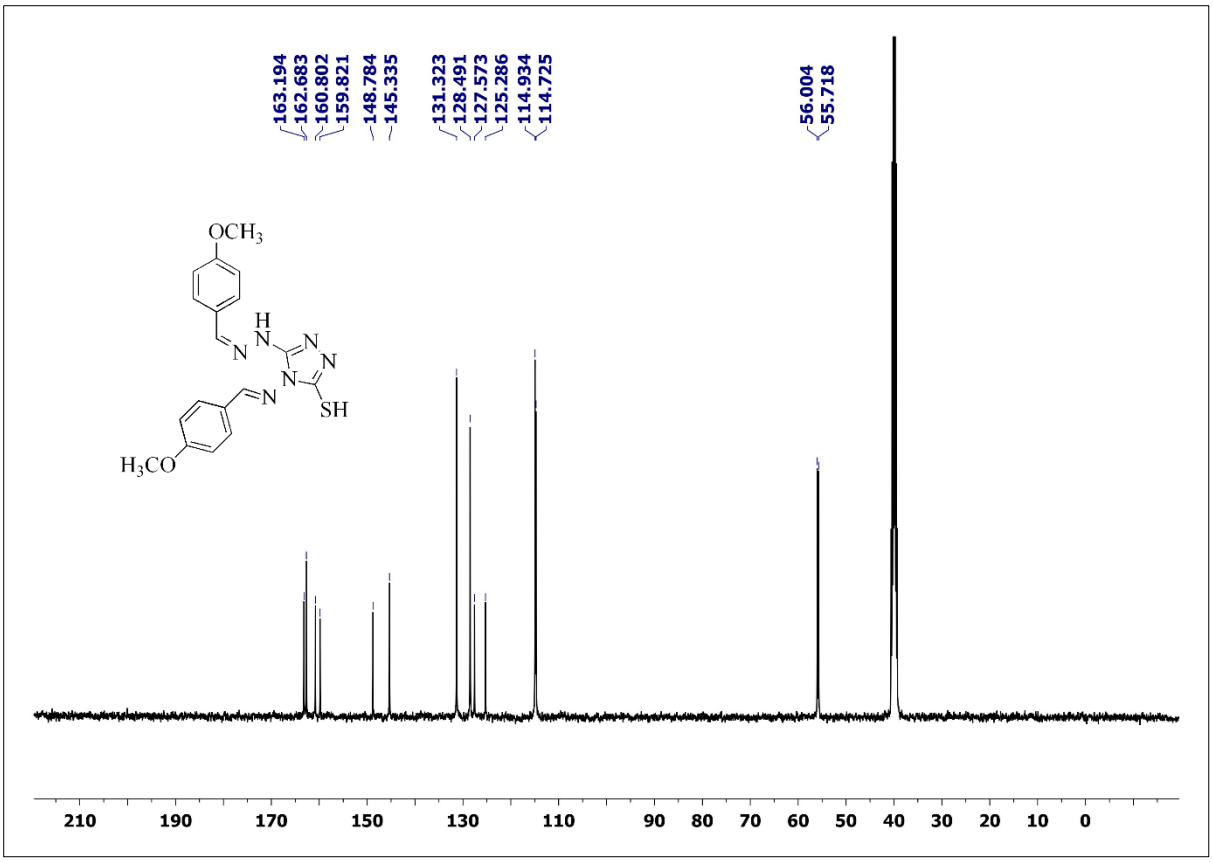
CMR Spectrum of compound **29b**



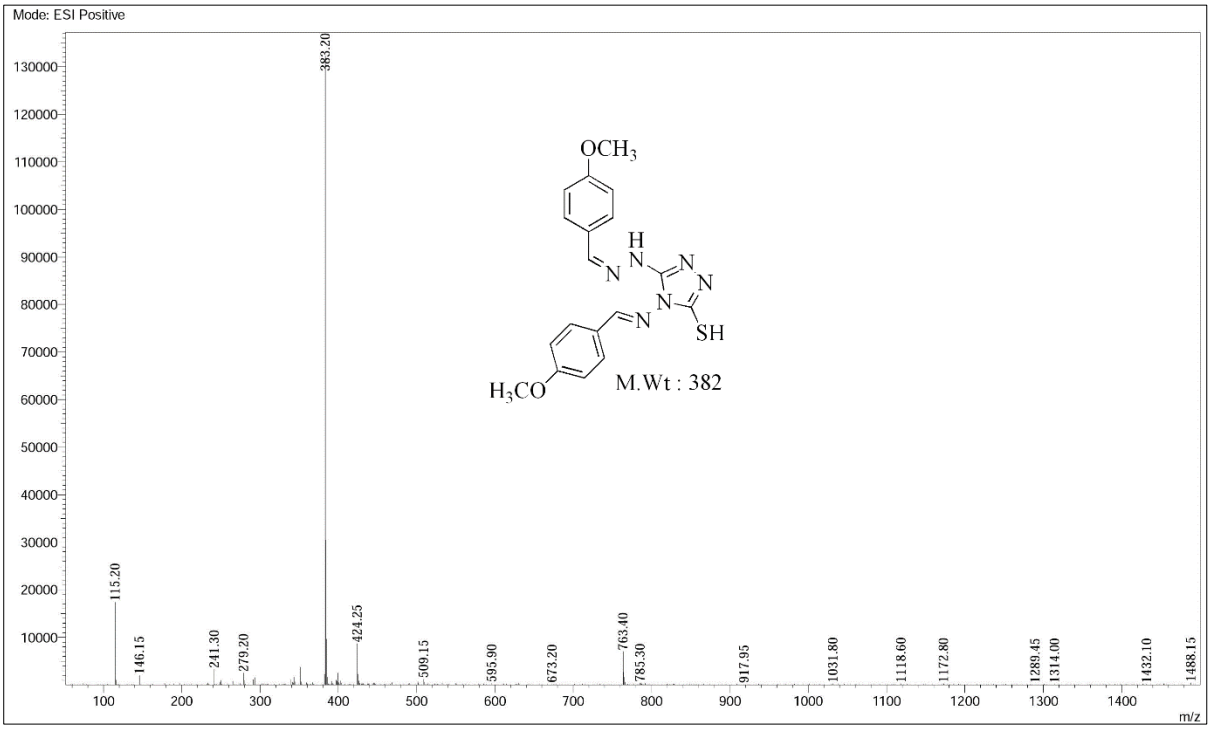
Mass Spectrum of compound **29b**



PMR Spectrum of compound **30**



CMR Spectrum of compound **30**

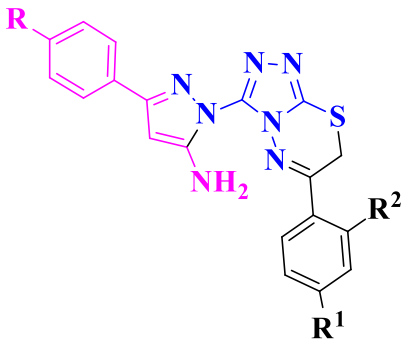


Mass Spectrum of compound **30**

CHAPTER-III

SECTION-B

A FACILE ONE-POT SYNTHESIS OF 3-(4-CHLOROPHENYL)-1-(6-PHENYL-7*H*-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZIN-3-YL)-1*H*-PYRAZOL-5-AMINES VIA MULTICOMPONENT APPROACH



SECTION-B

PRESENT WORK

Keeping the importance of triazolothiadiazinyl pyrazole amines, an efficient method has been described for the synthesis of novel heterocyclic systems like **33** and **36**.

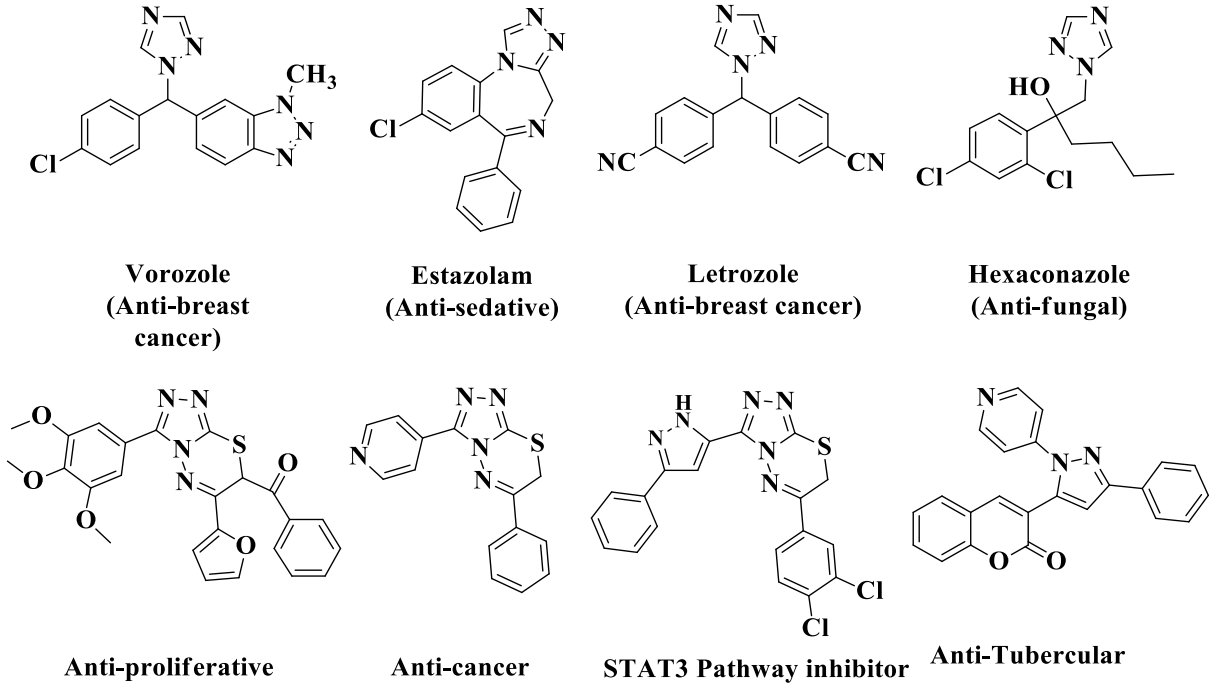
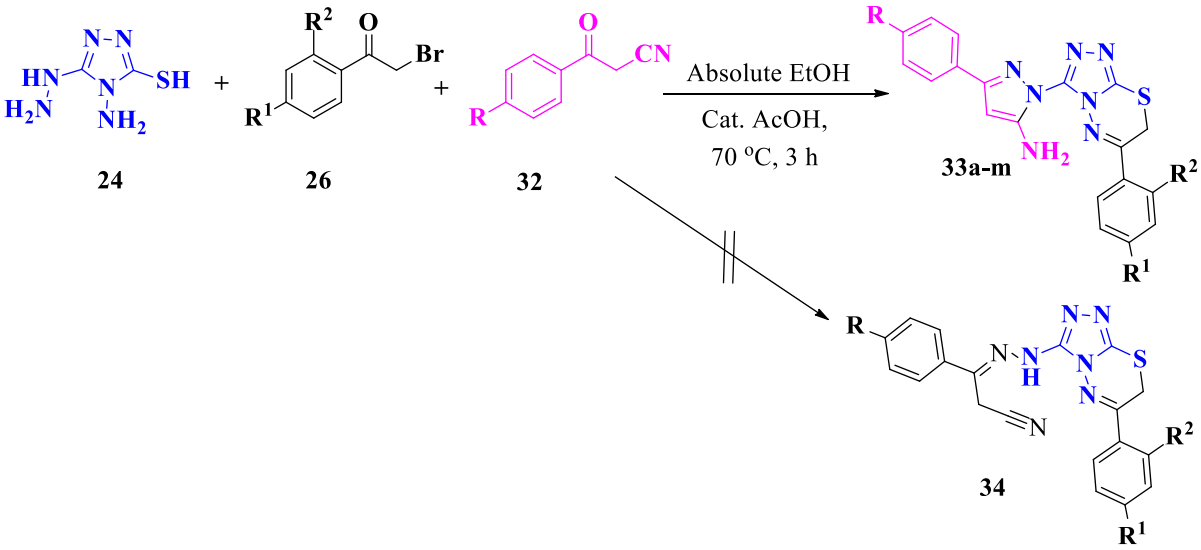


Fig.1. Biologically active molecules with triazolothiadiazine, pyrazolotriazolothiadiazines and pyrazolocoumarin scaffolds.

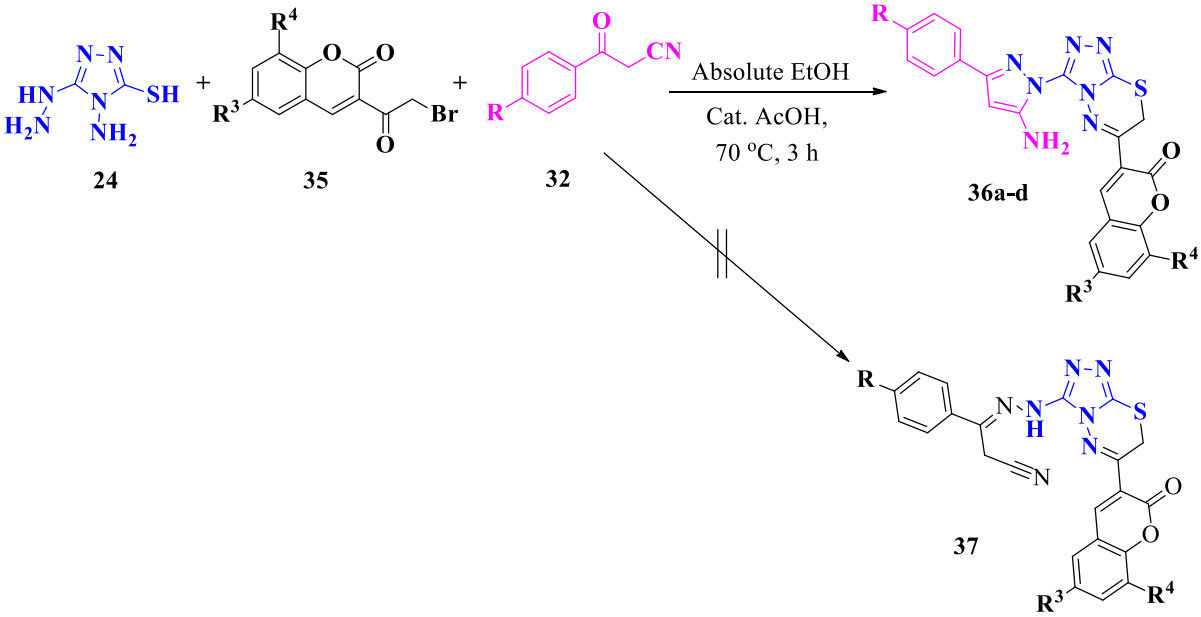
Purpald can be taken as a useful tool in building triazolothiadiazinylpyrazoles. One of the intermediate purpald is prepared from thiourea with NH_2-NH_2.H_2O under reflux conditions on water bath. Condensation of purpald, various phenacyl bromides or 3-(2-bromoacetyl)coumarins and benzoylacetonitriles in absolute alcohol containing trace of acetic acid resulted in the formation of (**33**) and (3**6)**.

Reaction between purpald, phenacyl bromide or 3-(2-bromoacetyl)coumarin and phenacyl cyanide is expected to produce compound (**34**) and (**37)** depending on the mode of cyclization. The formation of compound (**34)** and (**37)** can be ruled on the basis of spectral studies. In the present investigation, both NH_2 and SH of purpald at a time undergoes condensation with either phenacyl bromide or 3-(2-bromoacetyl)coumarin leading to first hetero cyclization. Then the hydrazino group of purpald reacts with phenacyl cyanide to give the compound **33**. The desired product was achieved in each case good to excellent yield. The importance of the synthesis is that different hetero atom connectivities such as 2N=C, C-S

and N-C (Compounds **33** and **36**) are obtained concomitantly in one-vessel resulting in new hetero cyclization having no other products.



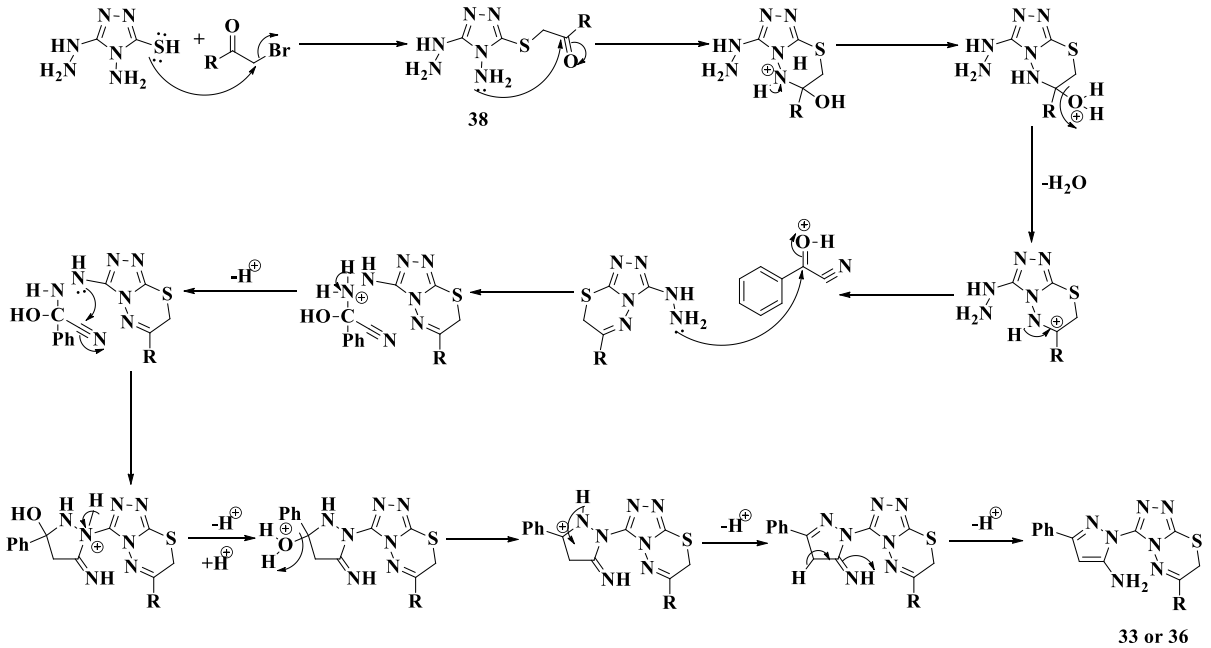
Scheme-4. Synthesis of compounds **33a-m**.



Scheme-5. Synthesis of compounds **36a-d**.

Table-1. Different substitutions of the compounds **33a-m** and **36a-d.**

Entry	compound	R	R^1	R^2	R^3	R^4	Time in hours
1	33a	Cl	H	H	-	-	2
2	33b	Cl	CH_3	H	-	-	3
3	33c	Cl	Cl	H	-	-	2
4	33d	Cl	F	H	-	-	2
5	33e	Cl	OCH_3	H	-	-	2
6	33f	H	H	H	-	-	2.5
7	33g	H	Br	H	-	-	2
8	33h	H	CH_3	H	-	-	2
9	33i	H	Cl	Cl	-	-	2
10	33j	H	F	H	-	-	2.5
11	33k	H	OCH_3	H	-	-	2
12	33l	Cl	Ph	H	-	-	3
13	33m	H	H	CH_3	-	-	2
14	36a	H	-	-	H	OEt	2
15	36b	Cl	-	-	Cl	-	2.5
16	36c	Cl	-	-	H	OEt	2
17	36d	Cl	-	-	Br	OCH_3	2



Scheme-6. Mechanism for the formation of **33** or **36**.

In the formation of fused thiadiazine ring on triazole, the highly nucleophilic sulphur atom of mercapto group of purpald attacks on the carbon atom of the (CH_2-Br) of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one gave an open chain α-thioketone (**38**). Then it undergoes intra molecular cyclization with the elimination of water molecules leading

to the formation of hydrazino triazolothiadiazine derivative. The hydrazino group of triazolothiadiazine undergoes cyclocondensation reaction with benzoylacetonitrile resulted in the formation of title compounds with better yields.

CONCLUSION

In conclusion, we have synthesized **33** and **36** by a three-component condensation and it involves the usage of readily available starting materials. This synthetic method has more advantages such as shorter reaction time, without use of harsh reaction conditions, easy work up procedure and good to excellent yields of the products.

EXPERIMENTAL SECTION

Starting materials:

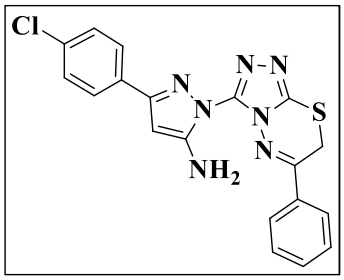
Purpald and various 3-(2-bromoacetyl)-2*H*-1-benzopyran-2-ones have been synthesized by following literature method. Various phenacyl bromides, benzoylacetonitriles were obtained from market.

General procedure for the synthesis of compounds (33a-m and 36a-d).

An equimolar amount of purpald (1 mmol), phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)coumarin (1 mmol) in 5 ml of ethanol with two drops of CH_3COOH was heated for 1 hour. Then the reaction mixture was treated with benzoylacetonitrile (1 mmol) and further refluxed for 1 hour. The reaction mixture was cooled to room temperature. The solid separated was filtered and recrystallized from methanol to give final product.

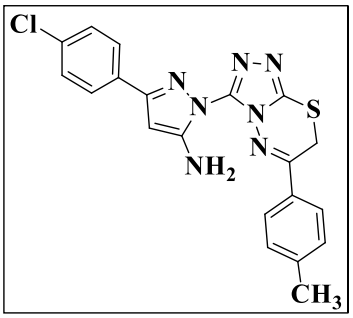
SPECRAL DATA

3-(4-Chlorophenyl)-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33a)



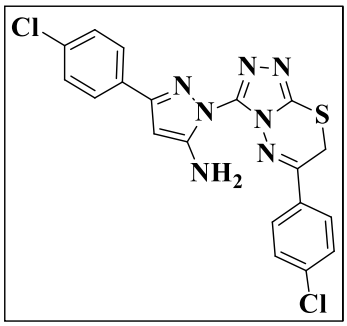
Color: pale yellow solid; mp: 240-241 °C; yield: (0.442g, 92%); IR (KBr, Wave number, cm^{-1}): 3411 (NH_2), 1618 (C=N); PMR (400 MHz, DMSO-d_6): δ 4.49 (s, 2H, CH_2), 5.90 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.51-7.60 (m, 3H ArH and 2H NH_2), 7.79 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 7.2 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 23.5, 84.9, 127.5, 128.0, 129.1, 129.5, 130.7, 132.6, 133.1, 133.6, 142.8, 146.3, 151.9, 152.3, 156.6 ppm; ESI-MS: m/z 408 $[M+H]^+$; Anal. calcd. for $C_{19}H_{14}ClN_7S$: C, 55.95; H, 3.46; Cl, 8.69; N, 24.04; S, 7.86. Found: C, 55.90; H, 3.41; Cl, 8.62; N, 24.10; S, 7.82%.

3-(4-Chlorophenyl)-1-(6-(p-tolyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33b)



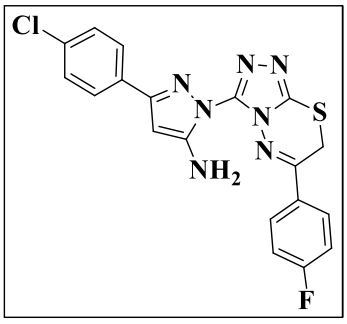
Color: white solid; mp: 265-266 °C; yield: (0.438g, 96%); IR (KBr, Wave number, cm^{-1}): 3435 (NH_2), 1614 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH3), 4.46 (s, 2H, CH_2), 5.90 (s, 1H), 6.03 (s, 2H, NH_2), 7.35 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.78-7.84 (m, 4H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.5, 23.3, 84.9, 127.5, 128.0, 128.4, 129.1, 130.1, 130.8, 132.2, 133.1, 142.9, 146.4, 151.9, 152.3, 156.4 ppm; ESI-MS: m/z 422 $[M+H]^+$; Anal. calcd. for $C_{20}H_{16}ClN_7S$: C, 56.94; H, 3.82; Cl, 8.40; N, 23.24; S, 7.60. Found: C, 56.90; H, 3.86; Cl, 8.47; N, 23.20; S, 7.67%.

3-(4-Chlorophenyl)-1-(6-(4-chlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33c)



Color: yellow solid; mp: 197-198 °C; yield: (0.491, 90%); IR (KBr, Wave number, cm^{-1}): 3418 (NH_2), 1614 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 4.50 (s, 2H, CH_2), 6.18 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 6.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 8.02-8.08 (m, 2H ArH and 2H NH_2) ppm; CMR (100 MHz, DMSO-d_6): δ 23.3, 85.0, 127.5, 129.1, 129.6, 129.7, 132.1, 132.4, 133.2, 137.5, 142.8, 146.4, 151.9, 152.4, 155.5 ppm; ESI-MS: m/z 442 $[M]^+$; Anal. calcd. for $C_{19}H_{13}Cl_2N_7S$: C, 51.59; H, 2.96; Cl, 16.03; N, 22.17; S, 7.25. Found: C, 51.54; H, 2.91; Cl, 16.12; N, 21.14; S, 7.29%.

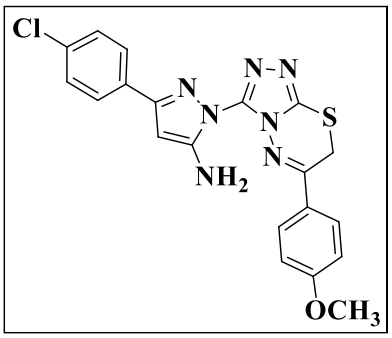
3-(4-Chlorophenyl)-1-(6-(4-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33d)



Color: pale yellow solid; mp: 247-248 °C; yield: (0.447g, 95%); IR (KBr, Wave number, cm^{-1}): 3414 (NH_2), 1608 (C=N); PMR (400 MHz, DMSO-d_6): δ 4.48 (s, 2H, CH_2), 5.90 (s, 1H), 6.04 (s, 2H, NH_2), 7.41 (t, J = 8.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 5.2 Hz, 1H), 8.01 (d, J = 5.6 Hz, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 23.4, 84.9, 116.6, 116.8, 127.5, 129.1, 130.6, 130.7, 132.2, 133.1, 142.7, 146.4, 151.9, 152.4, 155.5, 163.5, 166.0 ppm; ESI-MS: m/z 426 $[M+H]^+$; Anal. calcd. for $C_{19}H_{13}ClFN_7S$: C, 53.59; H, 3.08; Cl, 8.32; N, 23.02; S, 7.53. Found: C, 53.55; H, 3.10; Cl, 8.37; N, 23.10; S, 7.58%.

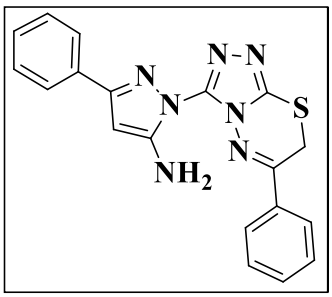
3-(4-Chlorophenyl)-1-(6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33e)

Color: white solid; mp: 255-256 °C; yield: (0.46g, 95%); IR (KBr, Wave number, cm^{-1}): 3372 (NH_2), 1610 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3) 4.44 (s, 2H, CH_2), 5.90 (s, 1H), 6.01 (s, 2H, NH_2) 7.09 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 23.2, 56.0, 84.9, 114.9, 125.6, 127.5, 129.1, 129.9, 132.2, 133.1, 142.8, 146.2, 151.9, 152.3, 156.0, 162.8 ppm; ESI-MS: m/z 438 $[M+H]^+$; Anal. calcd. for $C_{20}H_{16}ClN_7OS$: C, 54.86; H, 3.68; Cl, 8.10; N, 22.39; S, 7.32. Found: C, 54.81; H, 3.62; Cl, 8.15; N, 22.36; S, 7.38%.



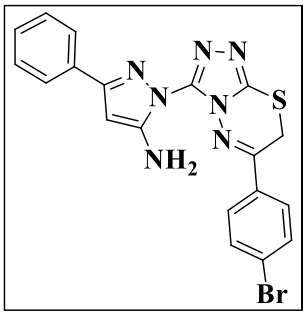
3-Phenyl-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33f)

Color: white solid; mp: 218-219 °C; yield: (0.401g, 93%); IR (KBr, Wave number, cm^{-1}): 3410 (NH_2), 1569 (C=N); PMR (400 MHz, DMSO-d_6): δ 4.49 (s, 2H, CH_2), 5.89 (s, 1H), 6.25 (s, 2H, NH_2) 7.33 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.2 Hz, 3H), 7.52-7.61 (m, 3H), 7.77 (d, J = 6.8 Hz, 1H), 7.94 (d, J = 6.8 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ C 23.5, 84.9, 125.8, 128.0, 128.7, 129.0, 129.5, 132.5, 133.2, 133.6, 142.8, 146.5, 151.7, 153.5, 156.5 ppm; ESI-MS: m/z 374 $[M+H]^+$; Anal. calcd. for $C_{19}H_{15}N_7S$: C, 61.11; H, 4.05; N, 26.26; S, 8.59. Found: C, 61.15; H, 4.11; N, 26.20; S, 8.52%.



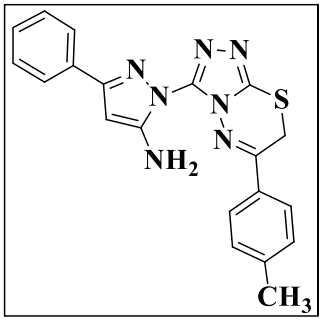
1-(6-(4-Bromophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-3-phenyl-1*H*-pyrazol-5-amine (33g)

Color: pale yellow solid; mp: 215-216 °C; yield: (0.496g, 91%); IR (KBr, Wave number, cm^{-1}): 3413 (NH_2), 1610 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 4.48 (s, 2H, CH_2), 5.89 (s, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 3H), 7.87 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 23.3, 85.0, 123.4, 125.8, 126.4, 129.1, 129.4, 129.9, 131.5, 132.5, 134.7, 146.5, 151.7, 153.5, 155.6 ppm; ESI-MS: m/z 454 $[M+2]^+$; Anal. calcd. for $C_{19}H_{14}BrN_7S$: C, 50.45; H, 3.12; Br, 17.66, N, 21.68; S, 7.09. Found: C, 50.49; H, 3.16; N, 21.61; S, 7.13%.



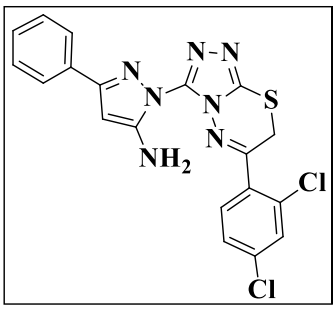
3-Phenyl-1-(6-(p-tolyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33h)

Color: white solid; mp: 196-197 °C; yield: (0.407g, 95%); IR (KBr, Wave number, cm^{-1}): 3435 (NH_2), 1615 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 5.89 (s, 1H), 6.00 (s, 2H, NH_2), 7.34 (d, J = 7.6 Hz, 3H), 7.41 (t, J = 7.6 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.5, 23.3, 84.9, 125.8, 128.0, 128.6, 129.0, 130.1, 130.8, 133.3, 142.8, 142.8, 146.5, 151.7, 153.4, 156.4 ppm; ESI-MS: m/z 388 $[M+H]^+$; Anal. calcd. for $C_{20}H_{17}N_7S$: C, 62.00; H, 4.42; N, 25.30; S, 8.28. Found: C, 62.10; H, 4.47; N, 25.35; S, 8.22%.



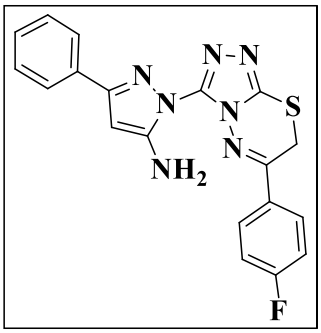
1-(6-(2,4-Dichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-3-phenyl-1*H*-pyrazol-5-amine (33i)

Color: yellow solid; mp: 199-200 °C; yield: (0.496g, 89%); IR (KBr, Wave number, cm^{-1}): 3440 (NH_2), 1608 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 4.37 (s, 2H, CH_2), 5.83 (s, 1H), 7.32-7.41 (m, 3H), 7.61 (d, J = 8.4 Hz, 2H), 7.72-7.77 (m, 2H), 7.86 (s, 2H), 7.94 (d, J = 8.0 Hz, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 26.3, 85.0, 125.8, 128.4, 128.8, 129.0, 130.2, 132.0, 132.7, 133.1, 136.9, 143.0, 144.2, 146.5, 151.7, 153.5, 156.6 ppm; ESI-MS: m/z 442 $[M]^+$; Anal. calcd. for $C_{19}H_{13}Cl_2N_7S$: C, 51.59; H, 2.96; Cl, 16.03; N, 22.17; S, 7.25. Found: C, 51.55; H, 2.92; Cl, 16.12; N, 22.12; S, 7.21%.



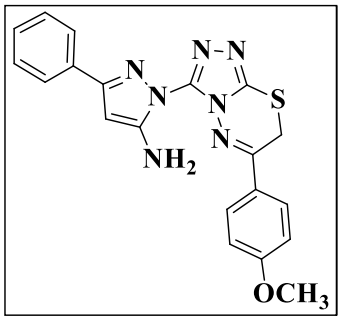
1-(6-(4-Fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-3-phenyl-1*H*-pyrazol-5-amin (33j)

Color: white solid; mp: 200-201 °C; yield: (0.403g, 97%); IR (KBr, Wave number, cm^{-1}): 3415 (NH_2), 1599 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.62 (s, 2H, NH_2), 4.06 (s, 2H, CH_2), 5.96 (s, 1H), 7.18 (t, J = 8.4 Hz, 2H), 7.33-7.41 (m, 3H), 7.80 (d, J = 8.0 Hz, 2H), 7.99-8.02 (m, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 23.4, 84.9, 116.5, 116.7, 125.8, 128.6, 129.0, 130.2, 130.2, 130.6, 130.7, 133.3, 142.6, 146.5, 151.7, 153.5, 155.5, 163.5, 166.0 ppm; ESI-MS: m/z 392 $[M+H]^+$; Anal. calcd. for $C_{19}H_{14}FN_7S$: C, 58.30; H, 3.61; N, 25.05; S, 8.19. Found: C, 58.35; H, 3.67; N, 25.10; S, 8.15%.



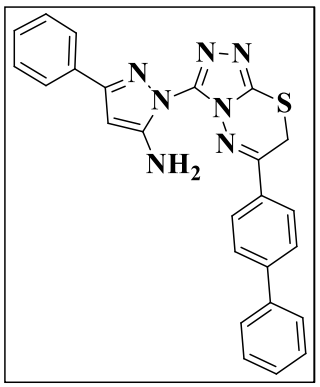
1-(6-(4-Methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-3-phenyl-1*H*-pyrazol-5-amine (33k)

Color: brown solid; mp: 150-151 °C; yield: (0.438g, 92%); IR (KBr, Wave number, cm^{-1}): 3432 (NH_2), 1606 (-C=N-); PMR (400 MHz, DMSO-d_6, ppm): δ 3.82 (s, 3H, OCH_3), 4.27 (s, 2H, NH_2), 4.45 (s, 2H, CH_2), 5.89 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.77 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H); CMR (100 MHz, DMSO-d_6, ppm): δ 23.2, 56.0, 84.9, 114.9, 125.8, 127.6, 128.6, 129.0, 129.9, 133.2, 142.8, 146.3, 151.7, 153.4, 156.0, 162.8; ESI-MS: m/z 404 $[M+H]^+$; Anal. calcd. for $C_{20}H_{17}N_7OS$: C, 59.54; H, 4.25; N, 24.30; S, 7.95. Found: C, 59.50; H, 4.29; N, 24.35; S, 7.91%.



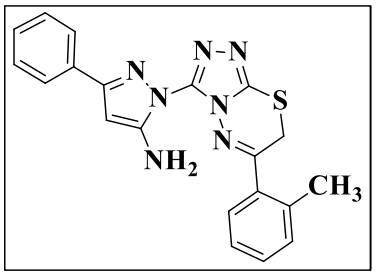
1-(6-([1,1[1]-Biphenyl]-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-3-(4-chlorophenyl)-1*H*-pyrazol-5-amine (33l)

Color: pale yellow solid; mp: 210-211 °C; yield: (0.498g, 90%); IR (KBr, Wave number, cm^{-1}): 3421 (NH_2), 1604 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 4.53 (s, 1H), 5.95 (s, 1H), 7.43-7.49 (m, 5H), 7.72-7.88 (m, 6H ArH and 2H NH_2), 8.02 (d, J = 7.6 Hz, 1H), 8.13 (d, J = 8.0 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.5, 85.1, 127.3, 127.5, 127.8, 129.1, 129.5, 130.6, 132.0, 133.2, 133.4, 139.0, 139.5, 144.4, 146.3, 149.4, 151.0, 151.9, 172.4 ppm; ESI-MS: m/z 484 $[M+H]^+$; Anal. calcd. for $C_{25}H_{18}ClN_7S$: C, 62.04; H, 3.75; Cl, 7.33; N, 20.26; S, 6.63. Found: C, 62.12; H, 3.70; Cl, 7.37; N, 20.21; S, 6.68%.

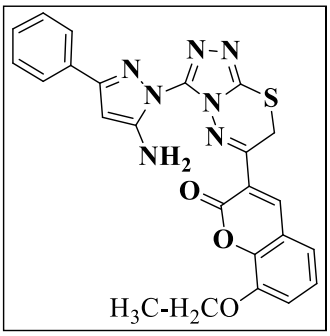


3-Phenyl-1-(6-(o-tolyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amine (33m)

Color: brown solid; mp: 136-138 °C; yield: (0.455g, 85%); IR (KBr, Wave number, cm^{-1}): 3451 (NH_2), 1614 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 5.93 (s, 1H), 7.34-7.47 (m,6H ArH and 2H NH_2), 7.56 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 20.7, 26.3, 85.1, 125.7, 126.6, 128.8, 129.1, 129.3, 131.0, 131.7, 133.0, 134.7, 136.9, 143.1, 146.4, 151.7, 153.6, 159.2 ppm; ESI-MS: m/z 388 $[M+H]^+$; Anal. calcd. for $C_{20}H_{17}N_7S$: C, 62.00; H, 4.42; N, 25.30; S, 8.28. Found: C, 62.10; H, 4.46; N, 23.25; S, 8.25%.

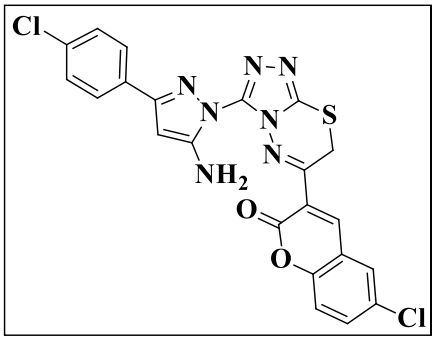


3-(3-(5-Amino-3-phenyl-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-8-ethoxy-2H-chromen-2-one (36a)



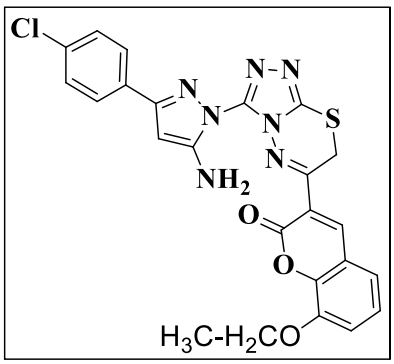
Color: brown solid; mp: 219-220 °C; yield: (0.505g, 96%); IR (KBr, Wave number, cm^{-1}): 3467 (NH_2), 1722 (lactone C=O), 1614 (C=N); PMR (400 MHz, DMSO-d_6, ppm): δ 1.40 (t, J = 6.8 Hz, 3H), 4.19 (d, J = 6.8 Hz, 2H), 4.35 (s, 2H), 5.85 (s, 1H), 6.02 (s, 2H), 7.31-7.35 (m, 3H), 7.39 (t, J = 6.0 Hz, 3H), 7.75 (d, J = 7.2 Hz, 1H), 8.32 (s, 1H), 8.43 (s, 1H); ESI-MS: m/z 486 $[M+H]^+$; Anal. calcd. for $C_{24}H_{19}N_7O_3S$: C, 59.37; H, 3.94; N, 20.19; S, 6.60. Found: C, 59.32; H, 3.93; N, 20.15; S, 6.65.

3-(3-(5-Amino-3-(4-chlorophenyl)-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-6-Chloro-2*H*-chromen-2-one (36b)



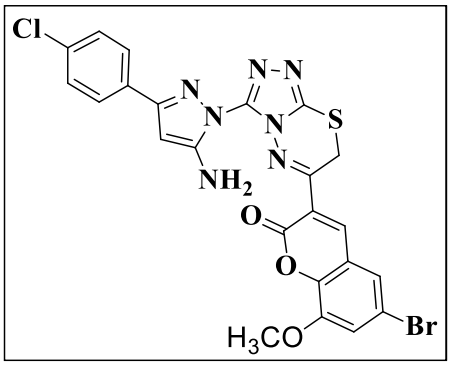
Color: yellow solid; mp: 228-229 °C; yield: (0.554g, 92%); IR (KBr, Wave number, cm^{-1}): 3436 (NH_2), 1722 (lactone C=O), 1617 (-C=N-); PMR (400 MHz, DMSO-d_6): δ 4.35 (s, 1H), 5.92 (s, 1H), 6.75 (s, 1H), 7.40-7.55 (m, 3H), 7.65-7.87 (m, 3H), 8.16-8.68 (m, 3H), 9.37 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 24.8, 79.6, 118.7, 120.0, 123.8, 126.1, 127.5, 129.0, 129.7, 130.2, 133.8, 134.2, 134.4, 139.4, 143.9, 150.8, 153.0, 155.9, 158.6, 165.8 ppm; ESI-MS: m/z 510 $[M]^+$; Anal. calcd. for $C_{22}H_{13}Cl_2N_7O_2S$: C, 51.77; H, 2.57; Cl, 13.89; N, 19.21; S, 6.28. Found: C, 51.73; H, 2.53; Cl, 13.84; N, 19.25; S, 6.24%.

3-(3-(5-Amino-3-(4-chlorophenyl)-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-8-ethoxy-2*H*-chromen-2-one (36c)

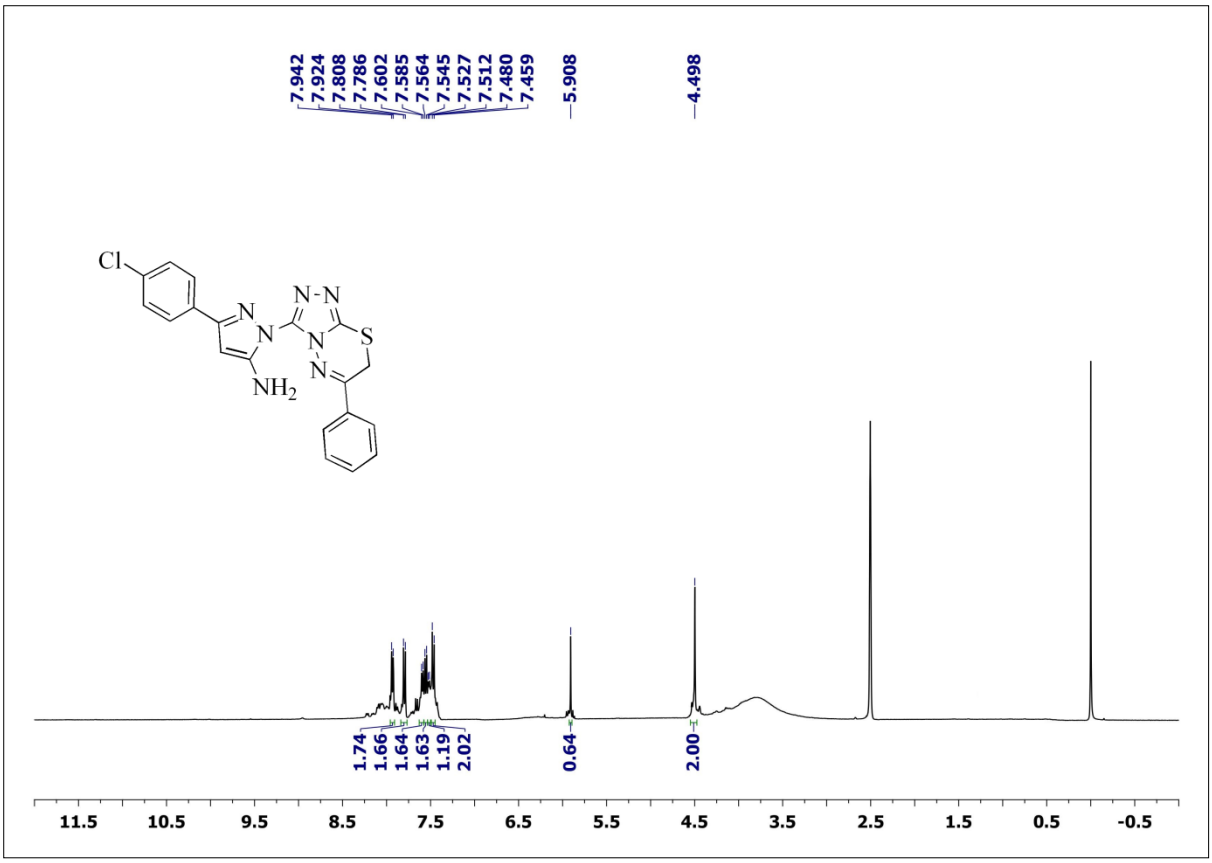


Color: yellow solid; mp: 209-210 °C; yield: (0.535g, 97%); IR (KBr, Wave number, cm^{-1}): 3454 (NH_2), 1725 (lactone C=O), 1614 (C=N); PMR (400 MHz, DMSO-d_6): δ 1.40 (t, J = 6.8 Hz, 3H), 4.19 (q, J = 6.8 Hz, 2H), 4.35 (s, 2H), 5.87 (s, 1H), 6.04 (s, 2H), 7.29-7.35 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 8.42 (s, 1H) ppm; ESI-MS: m/z 520 $[M+H]^+$; Anal. calcd. for $C_{24}H_{18}ClN_7O_3S$: C, 55.44; H, 3.49; Cl, 6.82; N, 18.86; S, 6.17. Found: C, 55.40; H, 3.42; Cl, 6.87; N, 18.81; S, 6.20%.

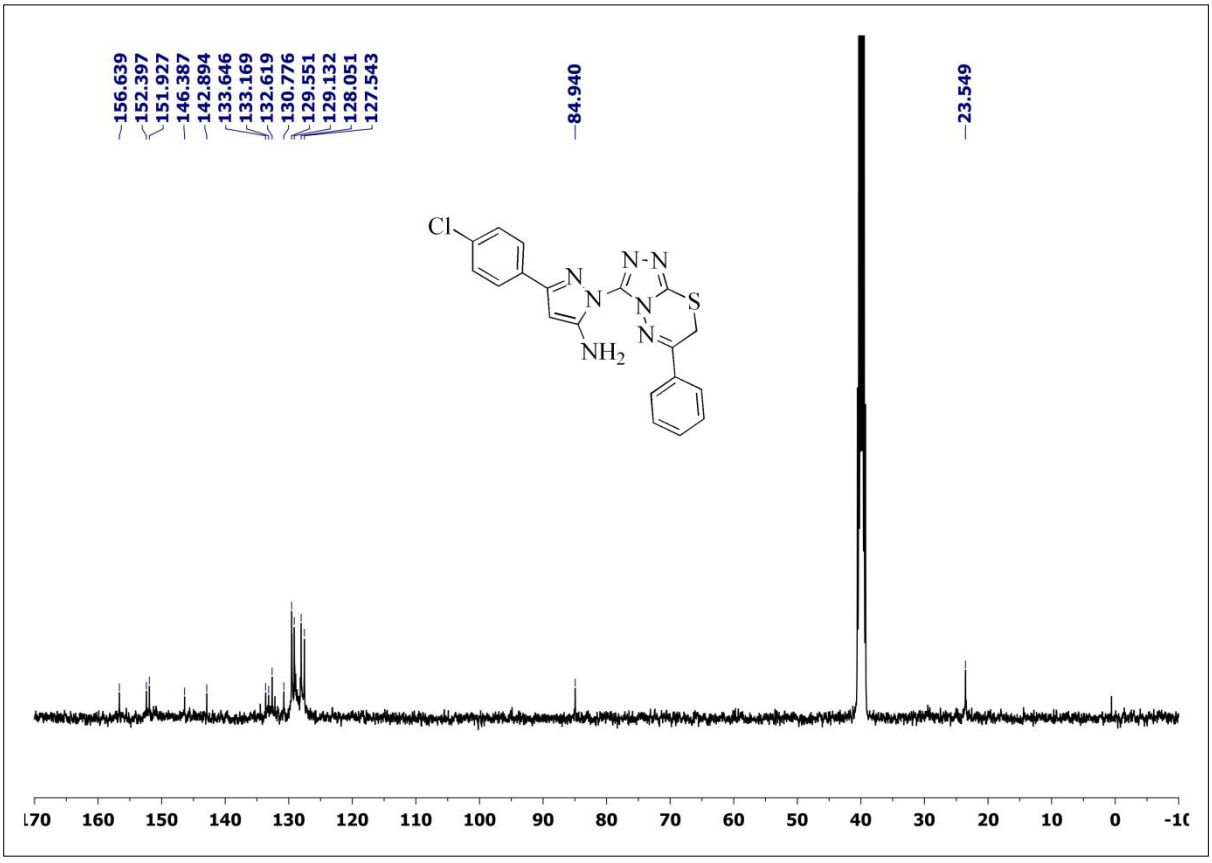
3-(3-(5-Amino-3-(4-chlorophenyl)-1*H*-pyrazol-1-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-6-bromo-8-methoxy-2*H*-chromen-2-one (36d)



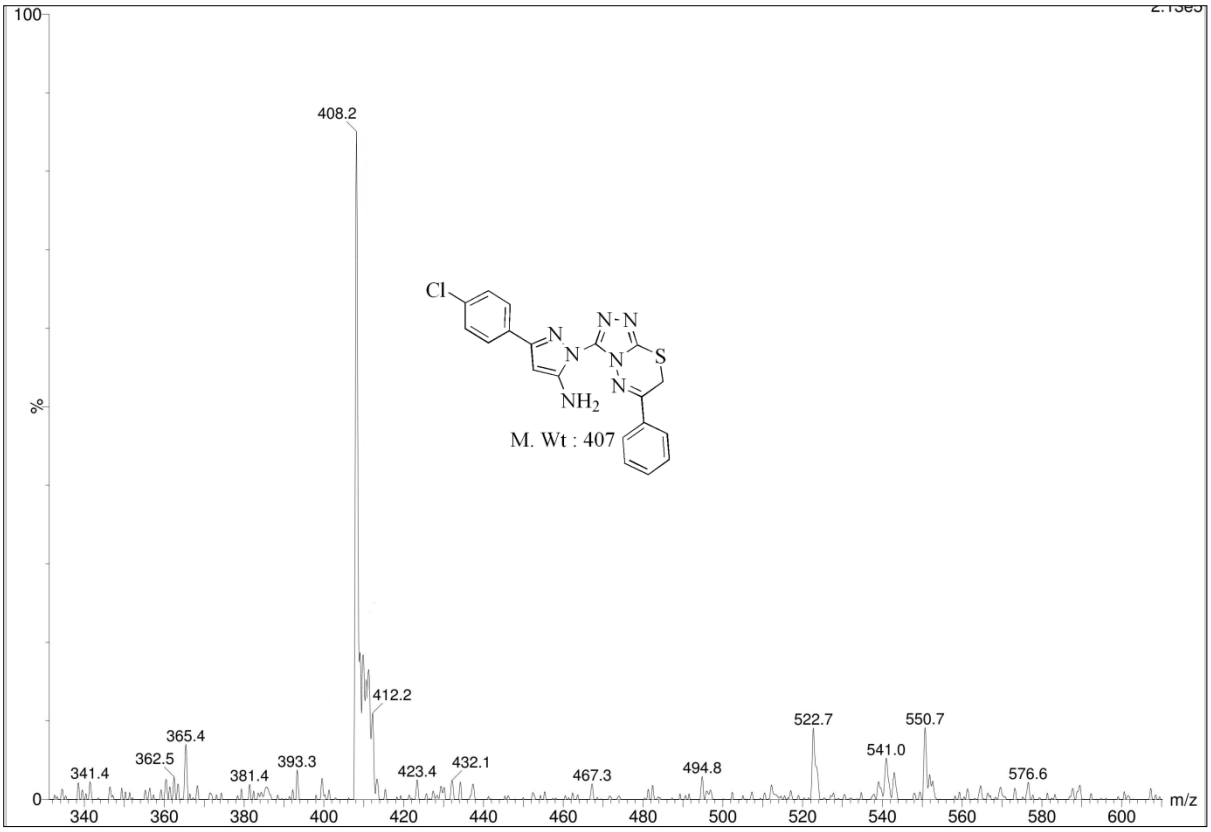
Color: pale yellow solid; mp: 196-197 °C; yield: (0.627g, 93%); IR (KBr, Wave number, cm^{-1}): 3437 (NH_2), 1735 (lactone C=O), 1601 (C=N); PMR (400 MHz, DMSO-d_6): δ 3.97 (s, 3H, OCH_3), 4.78 (s, 1H), 5.36 (s, 2H), 5.94 (s, 1H) 7.11 (s, 1H), 7.47-7.81 (m, 4H), 8.39 (s, 1H), 8.74 (s, 1H), 9.39 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 28.8, 57.3, 94.9, 100.3, 102.6, 110.5, 117.0, 120.2, 124.0, 129.1, 133.7, 135.2, 137.9, 142.6, 147.6, 149.8, 150.8, 154.2, 160.1, 160.9, 166.7 ppm; ESI-MS: m/z 584 $[M]^+$; Anal. calcd. for $C_{23}H_{15}BrClN_7O_3S$: C, 47.24; H, 2.59; Cl, 6.06; N, 16.76; S, 5.48. Found: C, 47.29; H, 2.52; Cl, 6.12; N, 16.72; S, 5.44%.



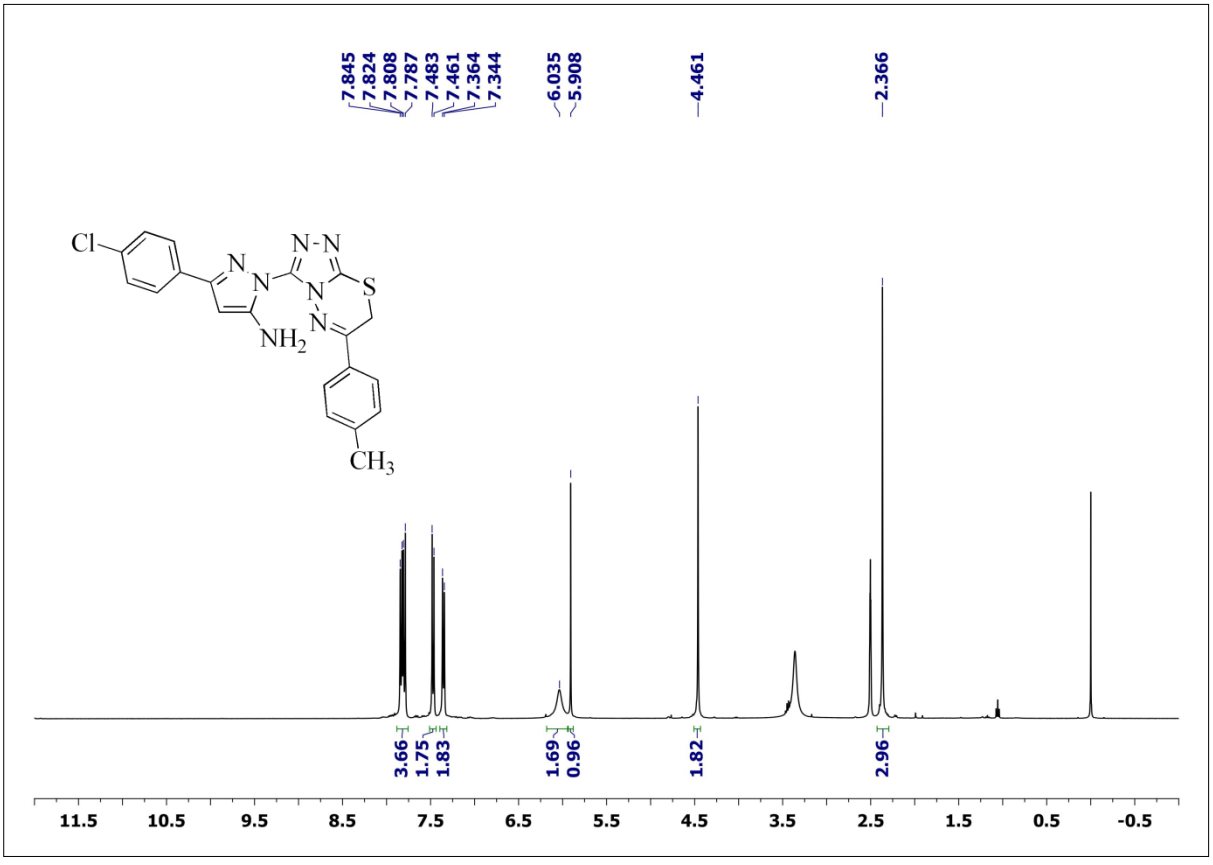
PMR Spectrum of compound **33a**



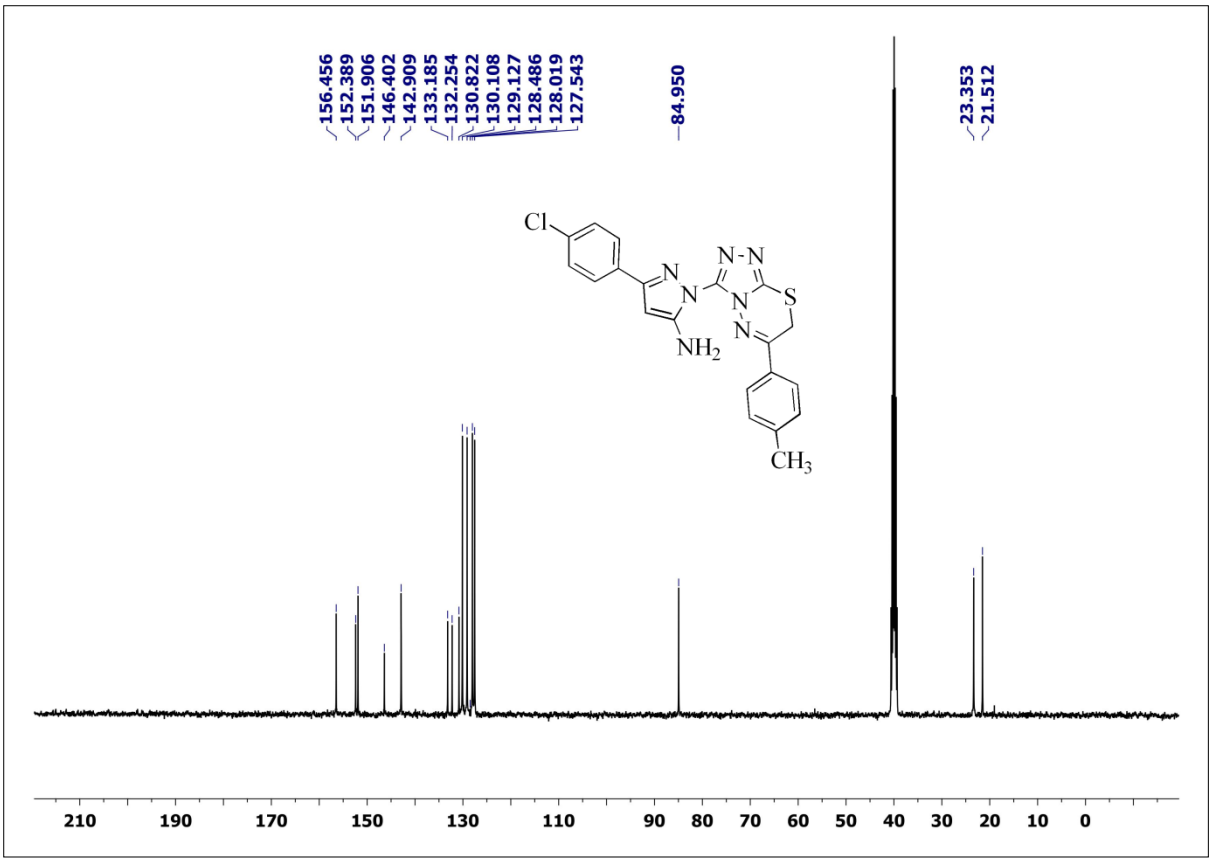
CMR Spectrum of compound **33a**



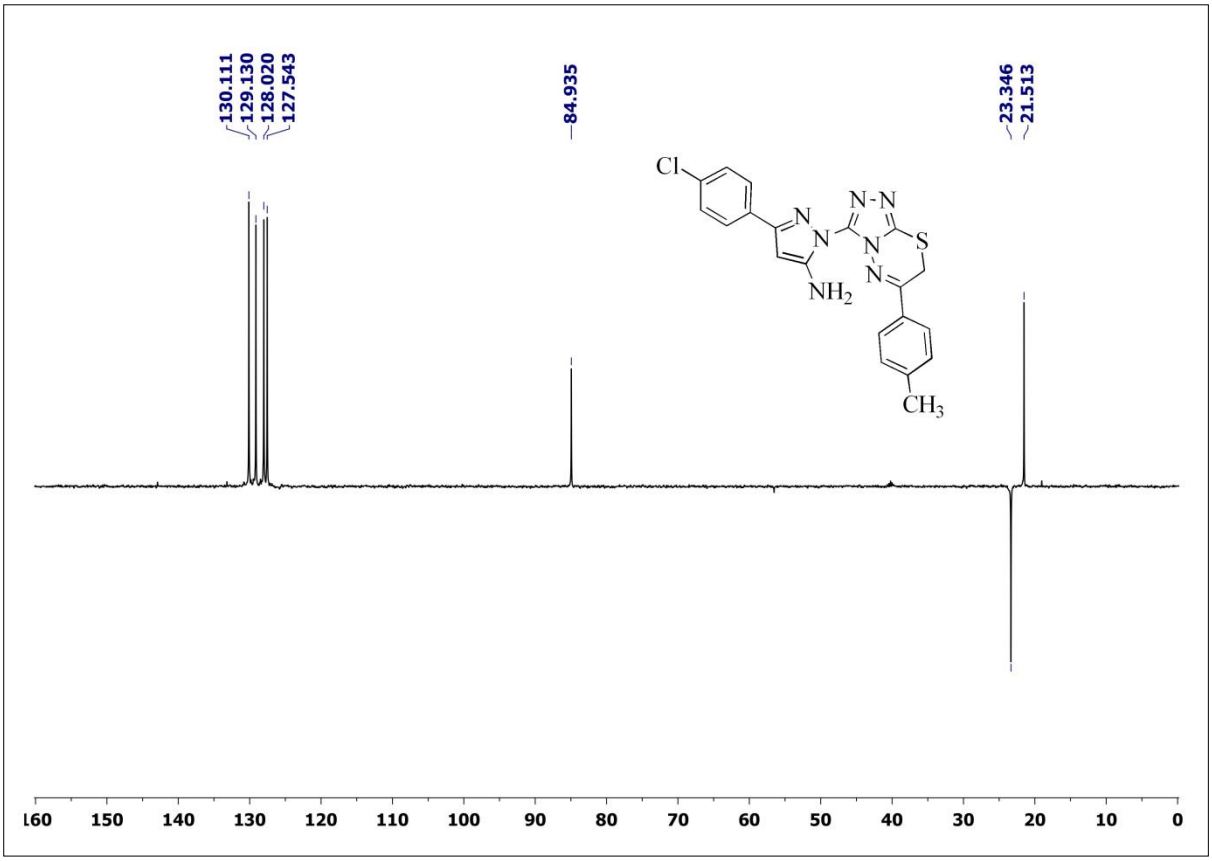
Mass Spectrum of compound **33a**



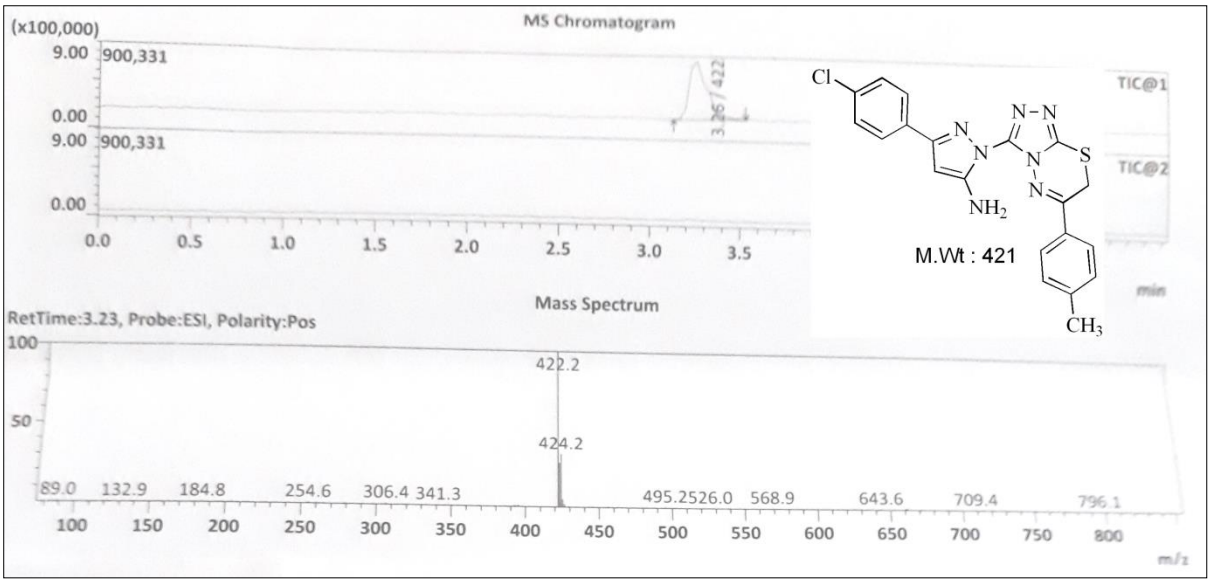
PMR Spectrum of compound **33b**



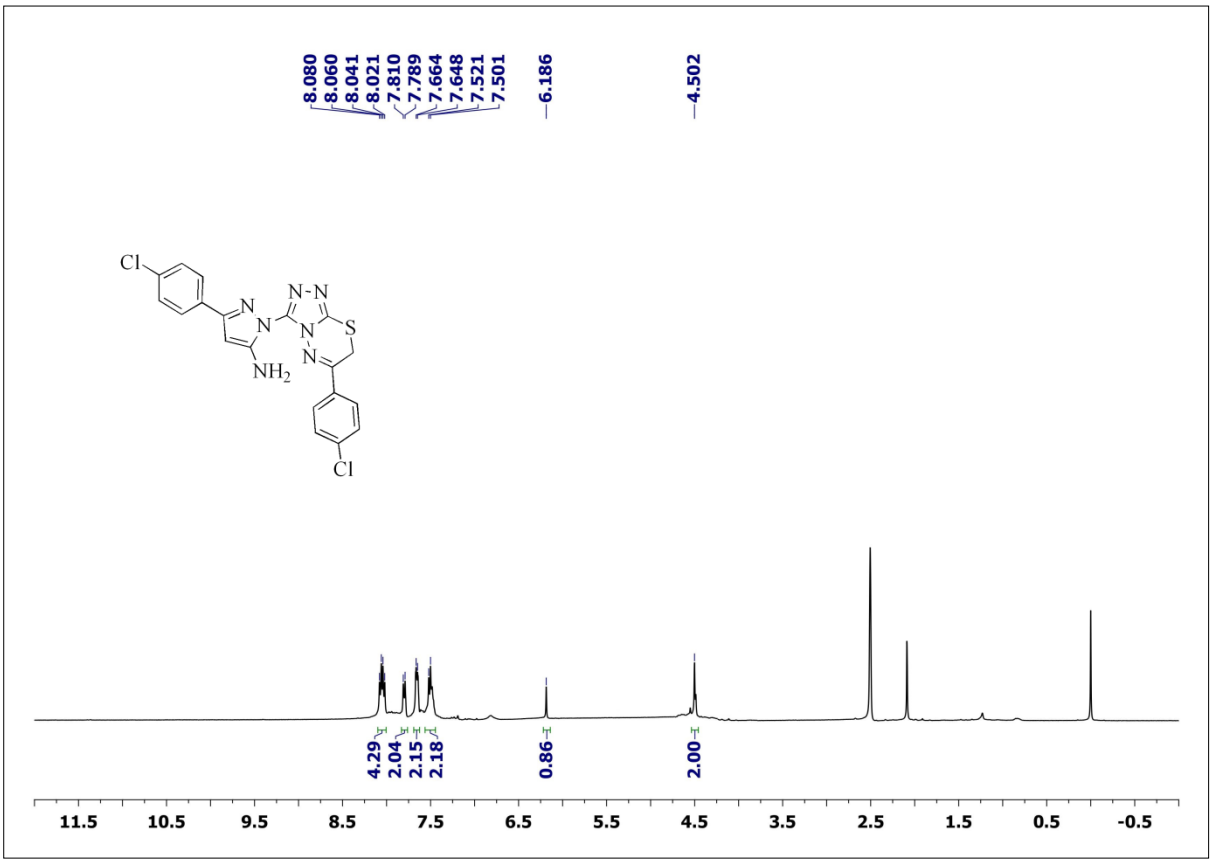
CMR Spectrum of compound **33b**



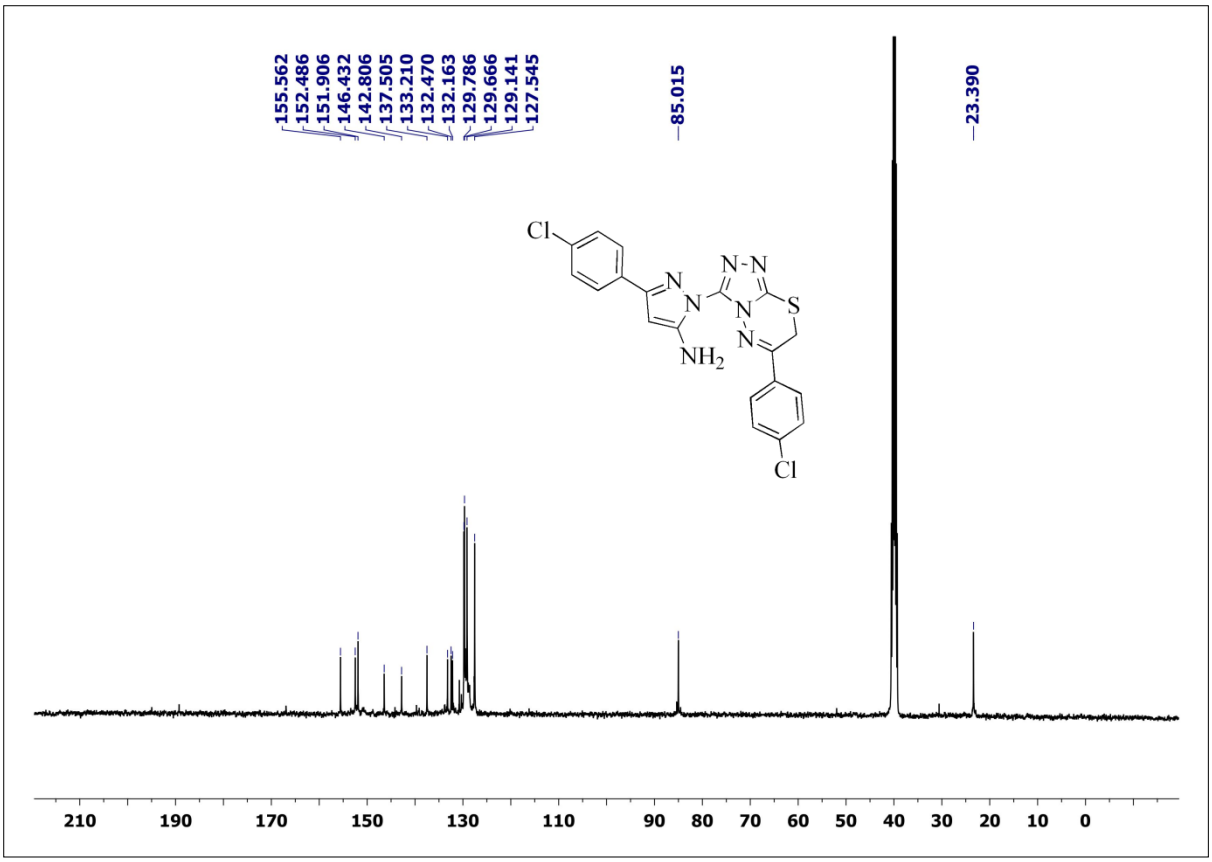
DEPT Spectrum of compound **33b**



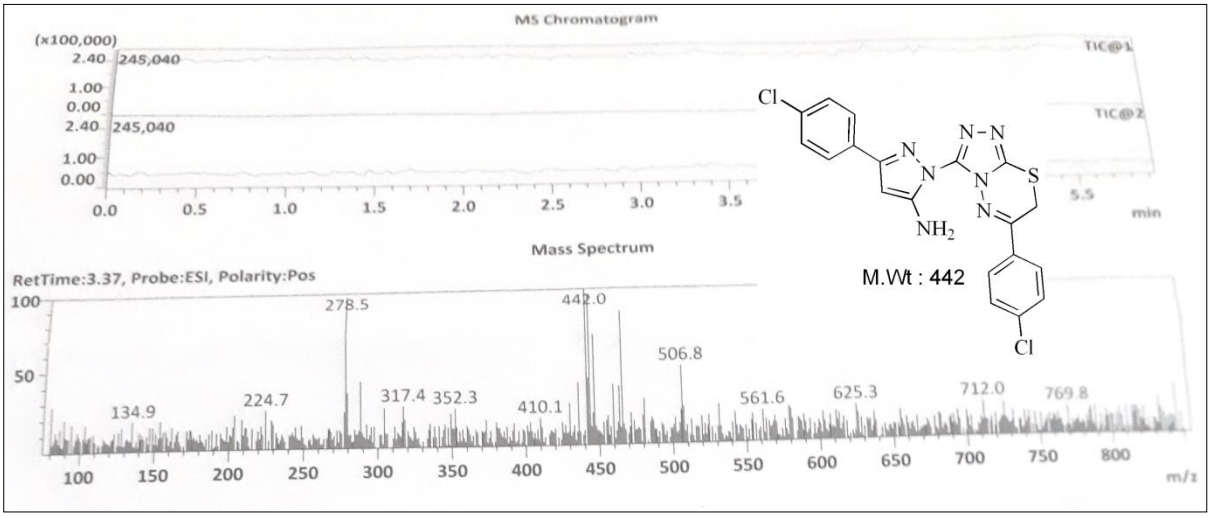
Mass Spectrum of compound **33b**



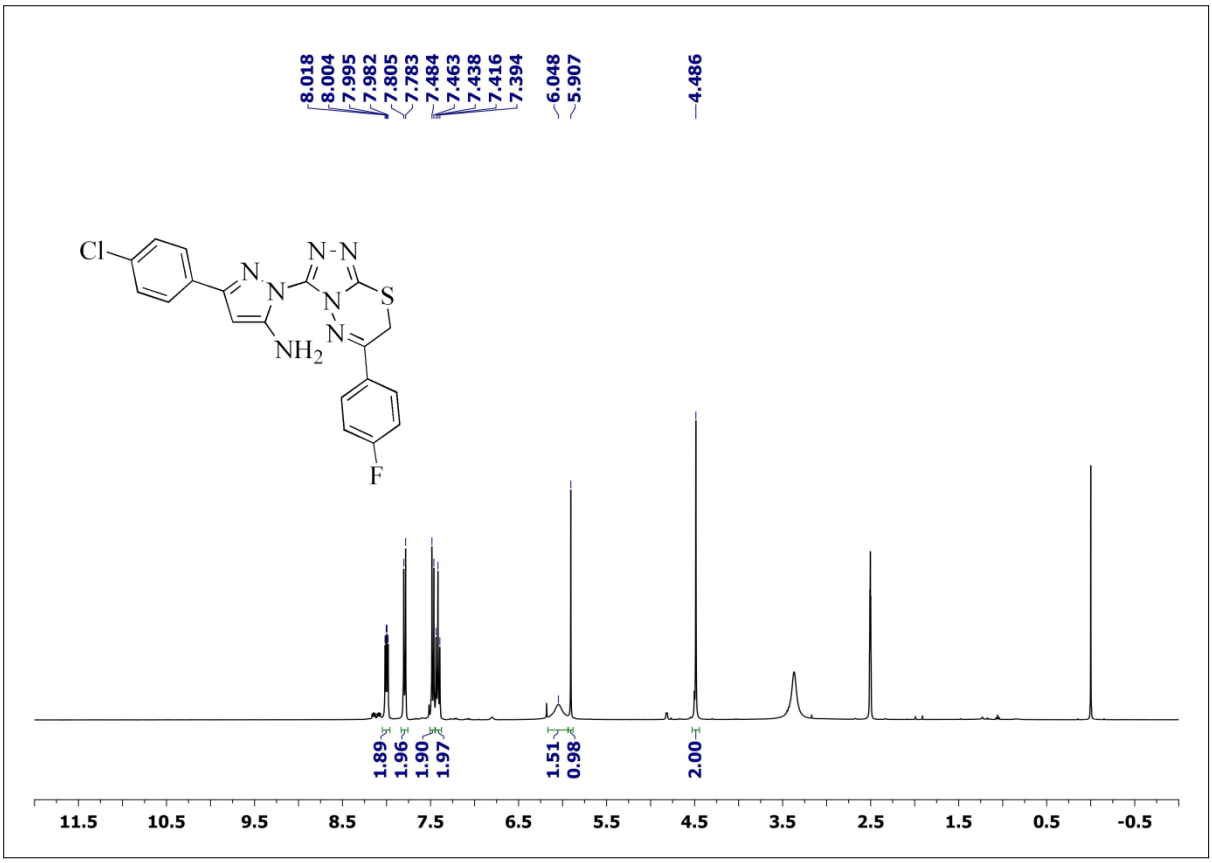
PMR Spectrum of compound **33c**



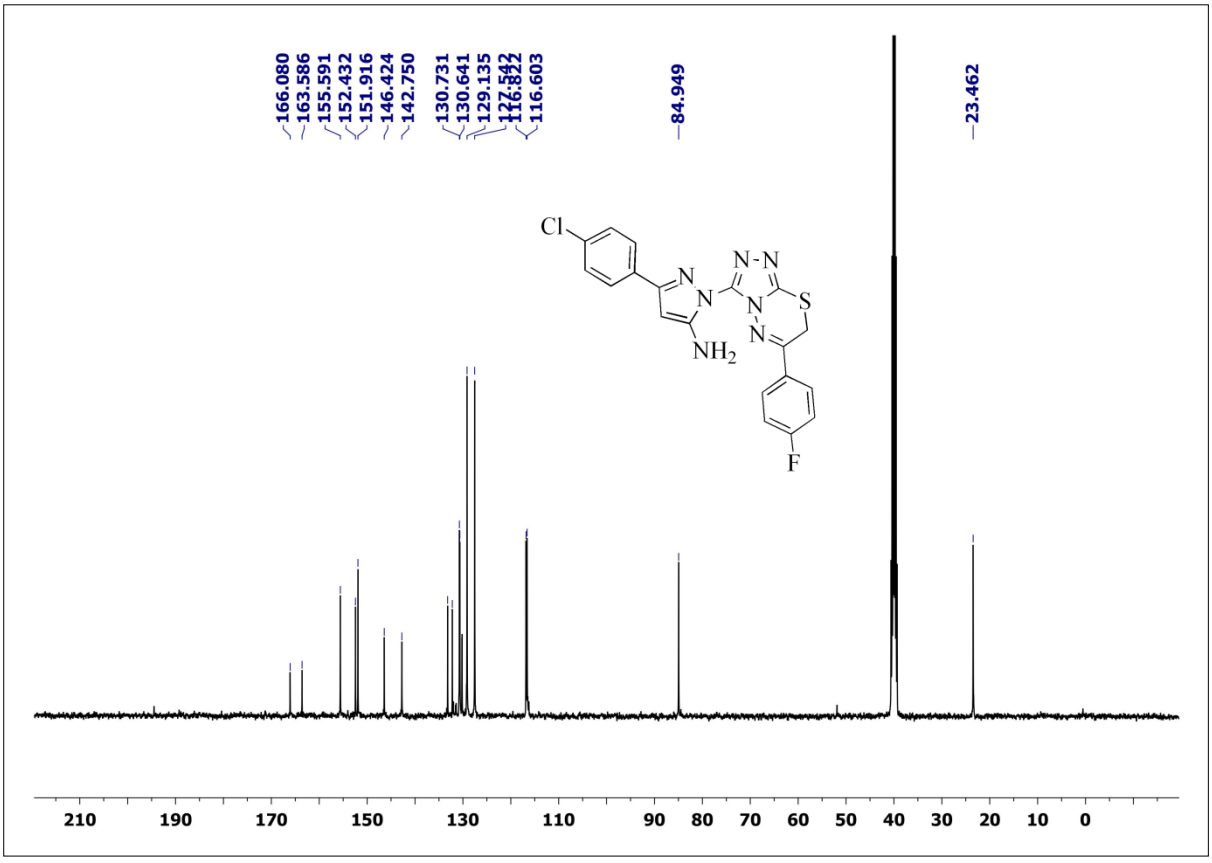
CMR Spectrum of compound **33c**



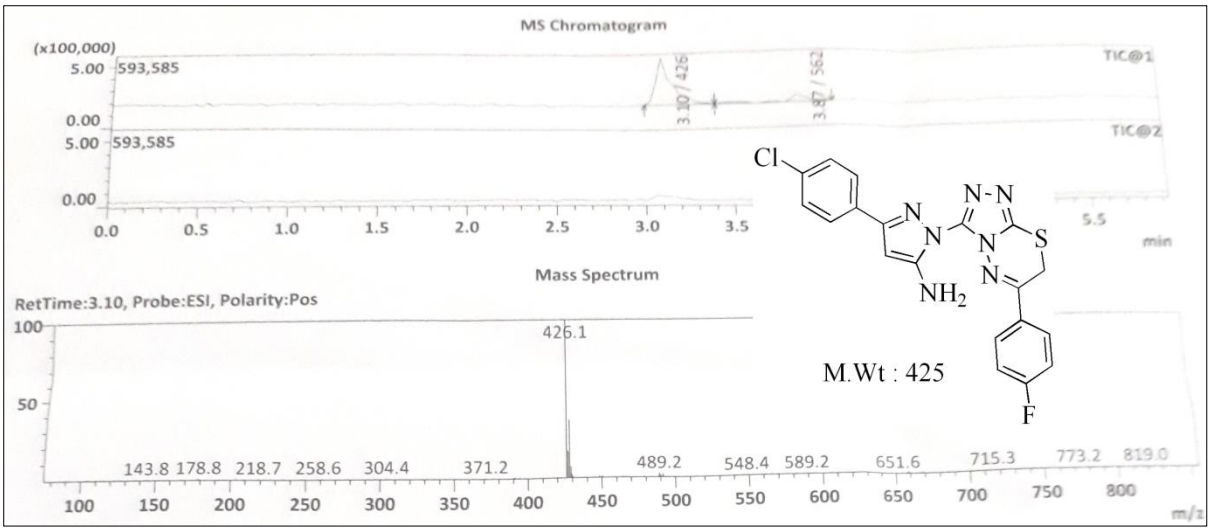
Mass Spectrum of compound **33c**



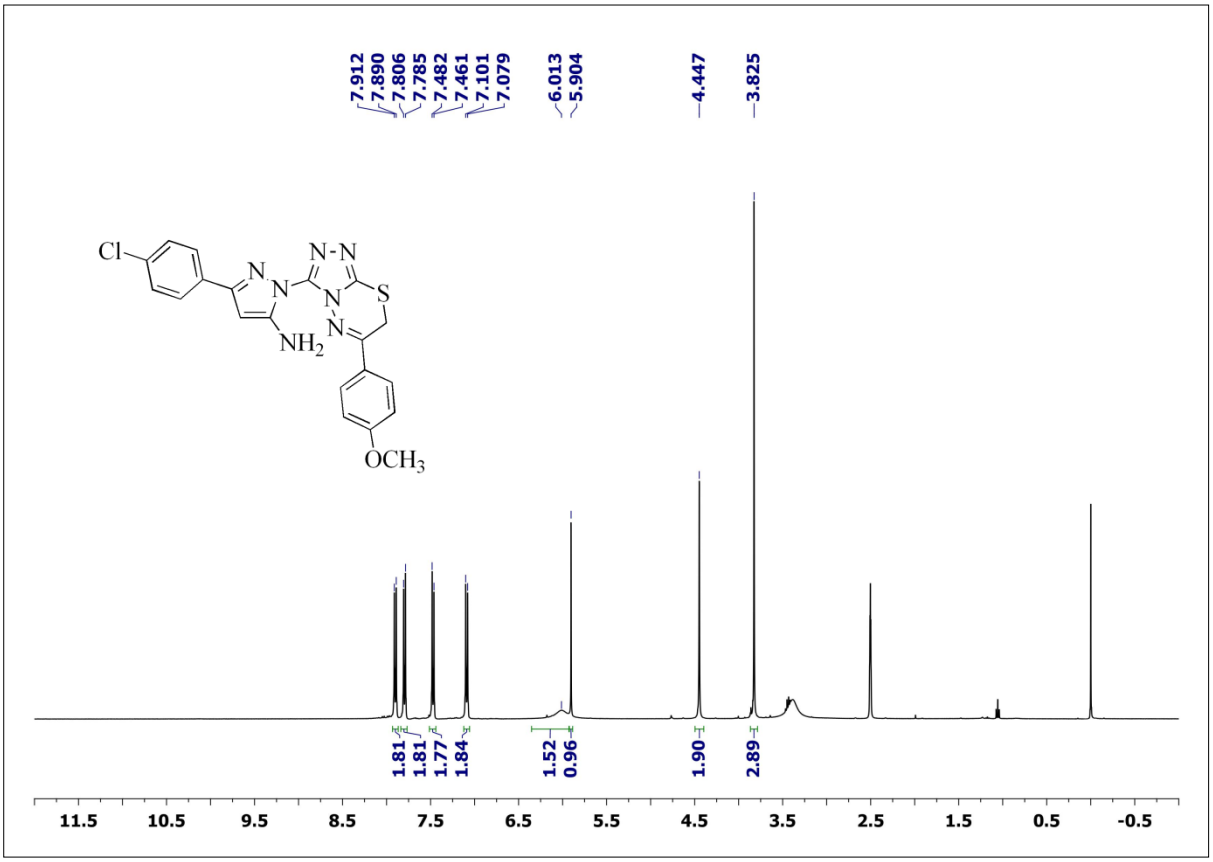
PMR Spectrum of compound **33d**



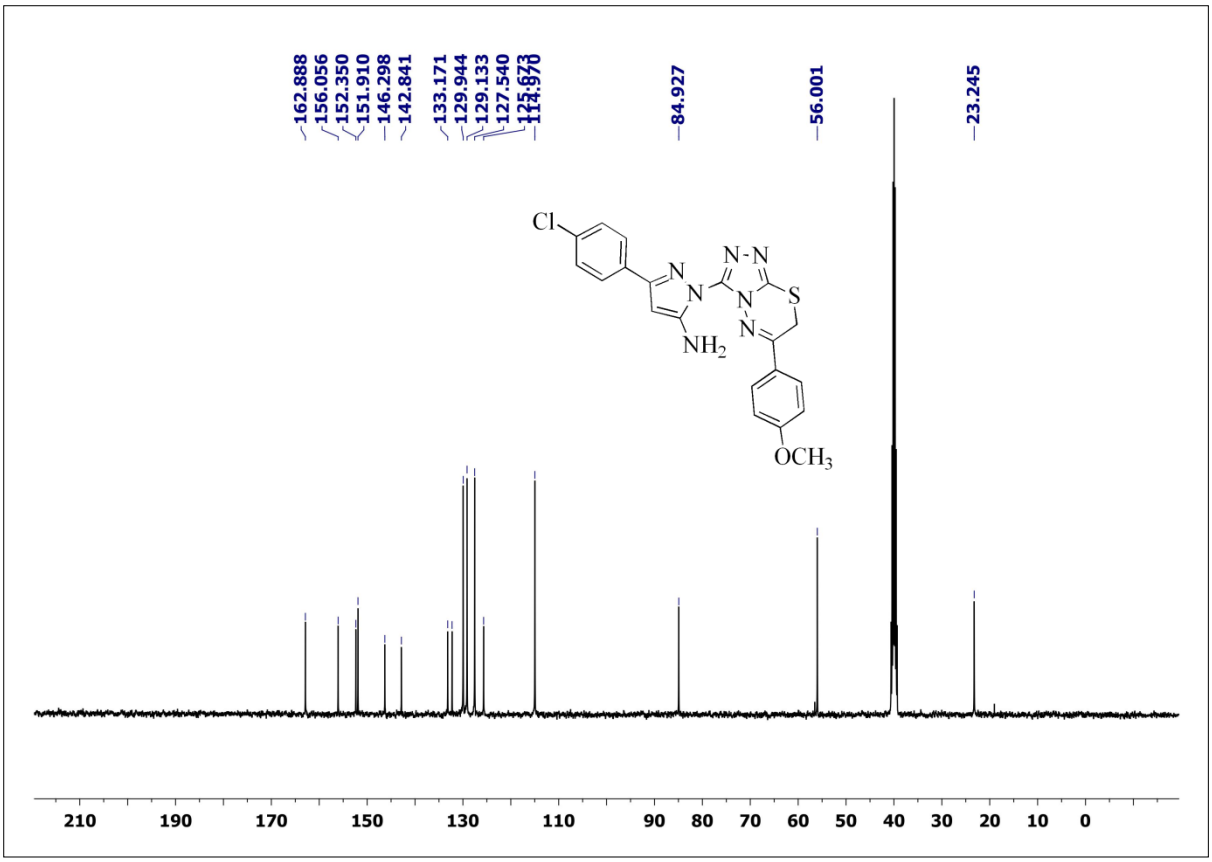
CMR Spectrum of compound **33d**



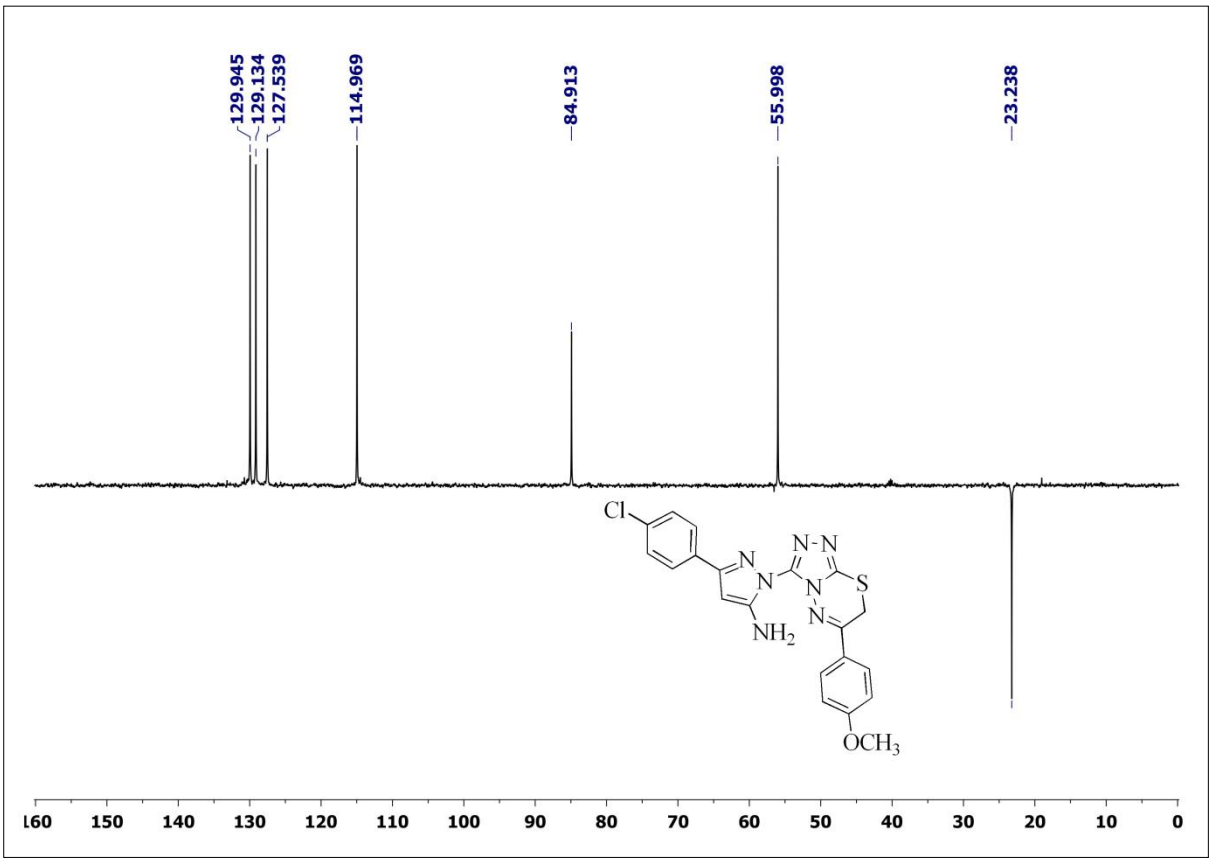
Mass Spectrum of compound **33d**



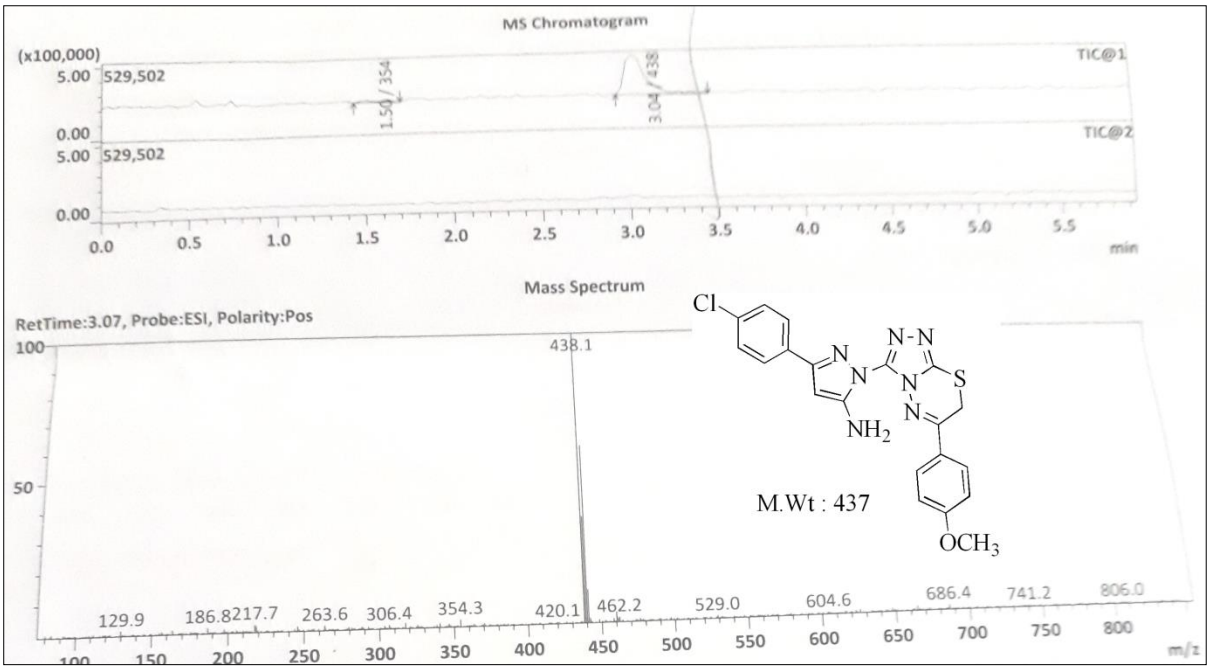
PMR Spectrum of compound **33e**



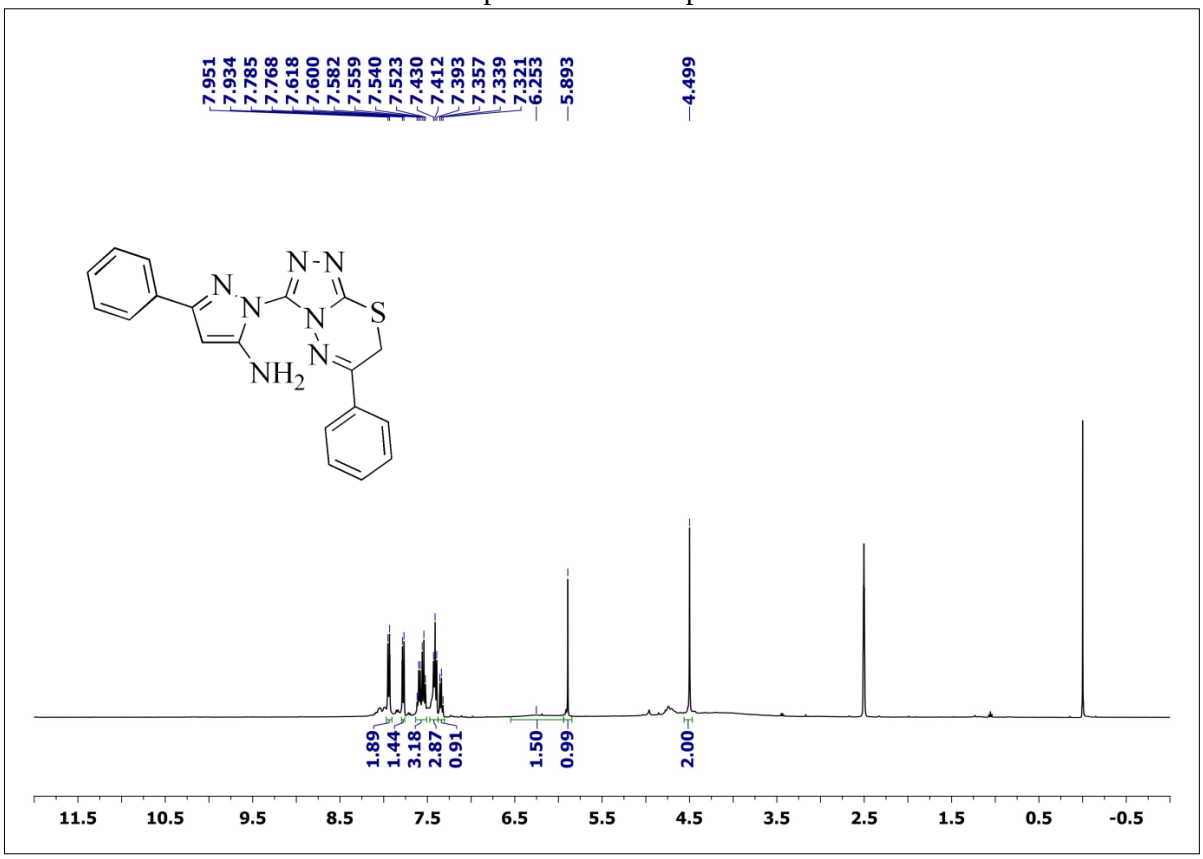
CMR Spectrum of compound **33e**



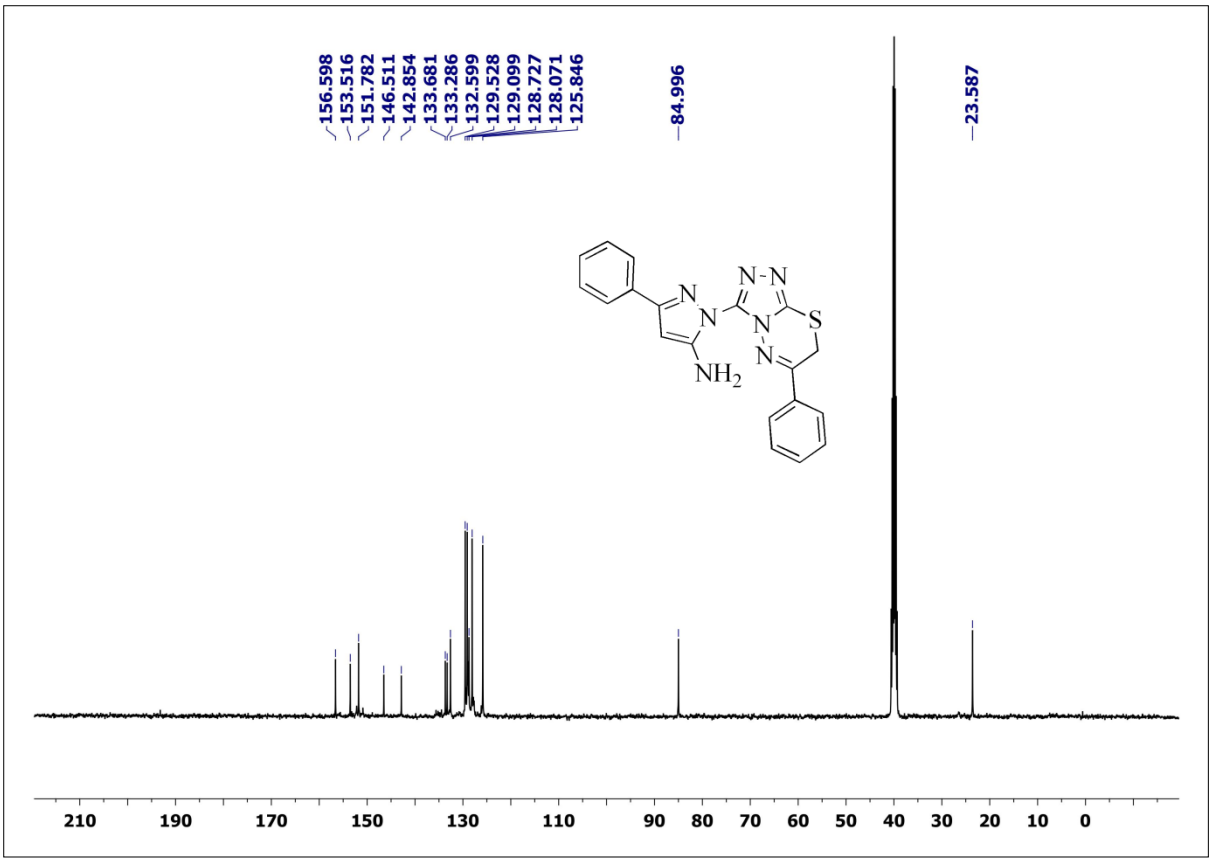
DEPT Spectrum of compound **33e**



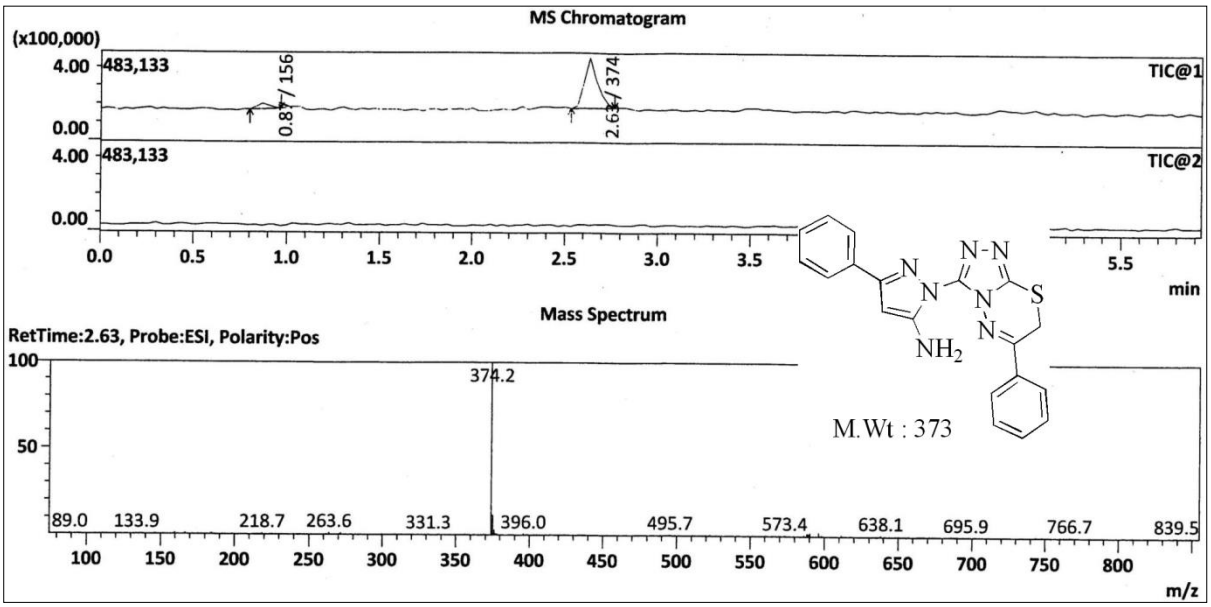
Mass Spectrum of compound **33e**



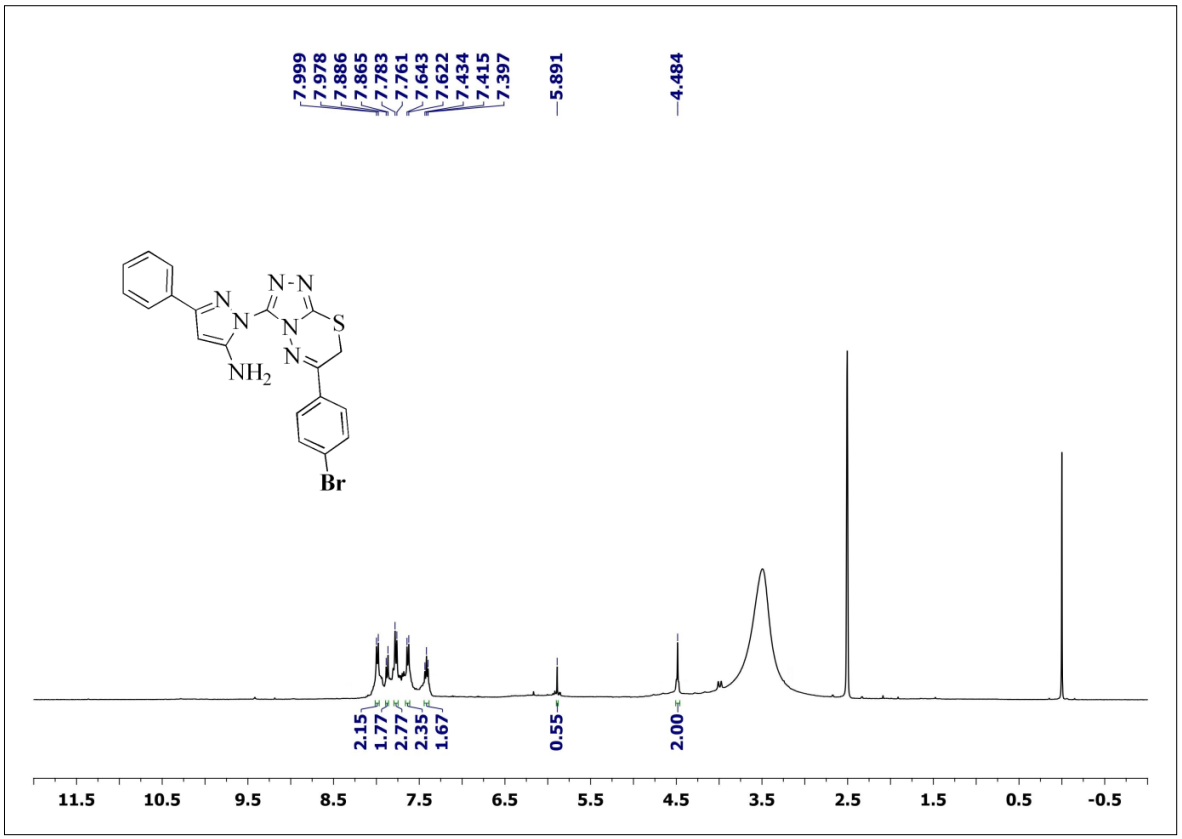
PMR Spectrum of compound **33f**



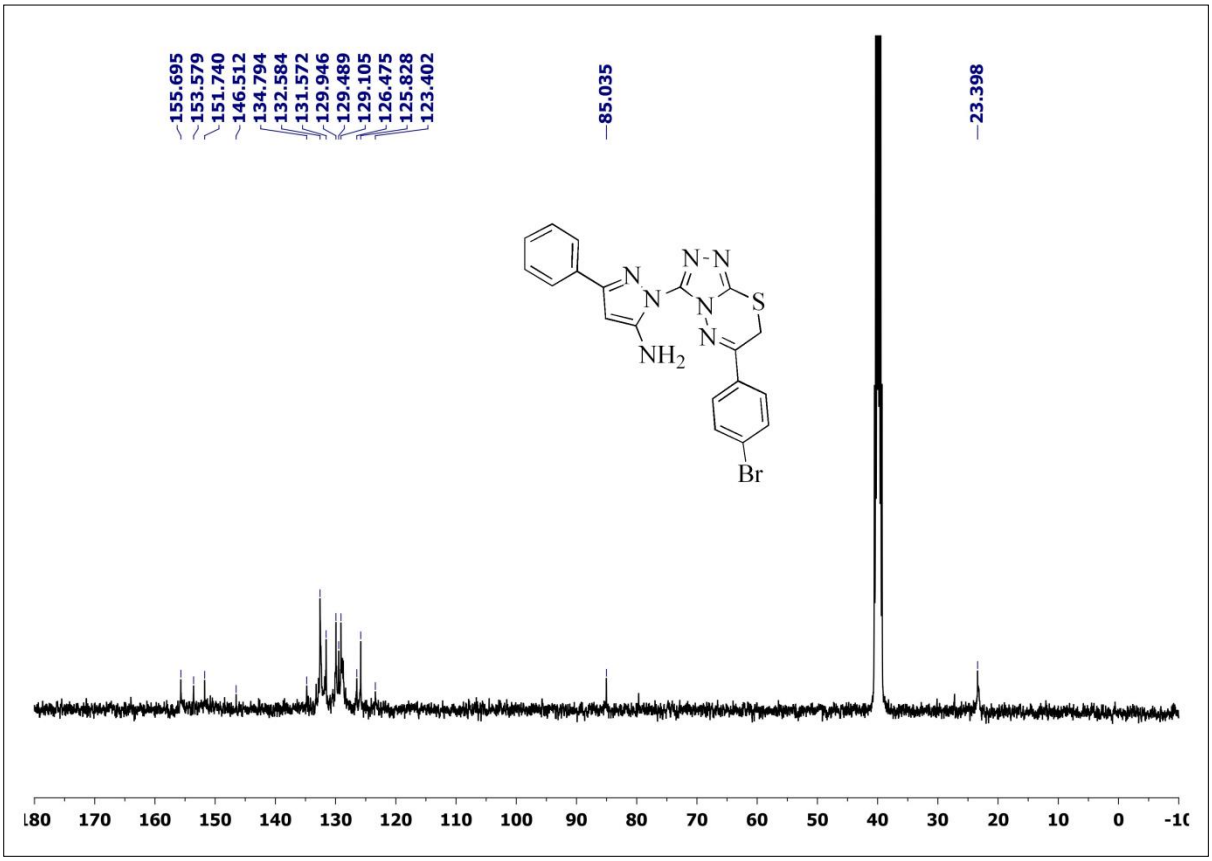
CMR Spectrum of compound **33f**



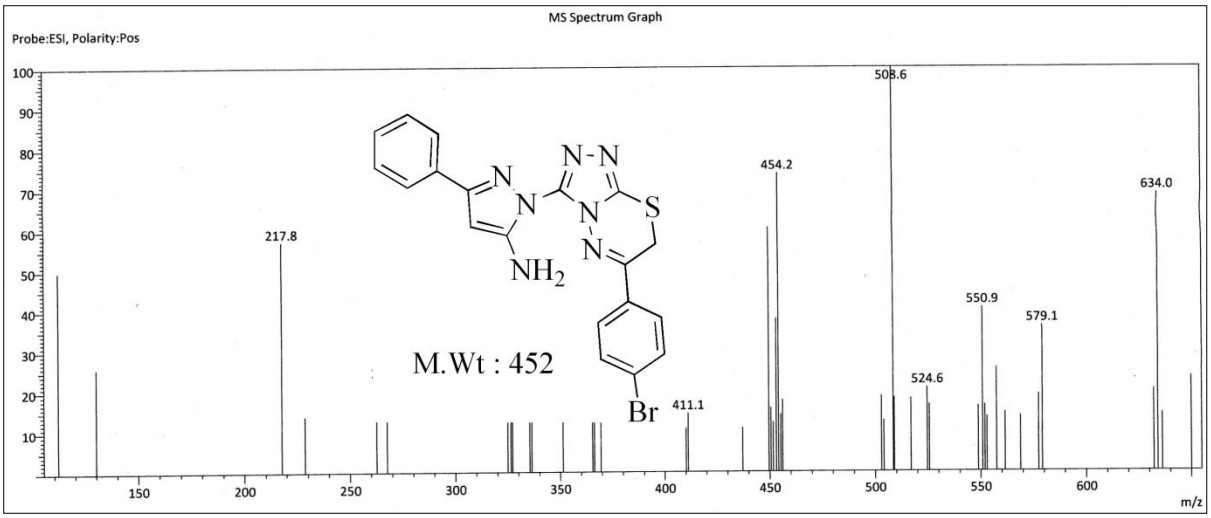
Mass Spectrum of compound **33f**



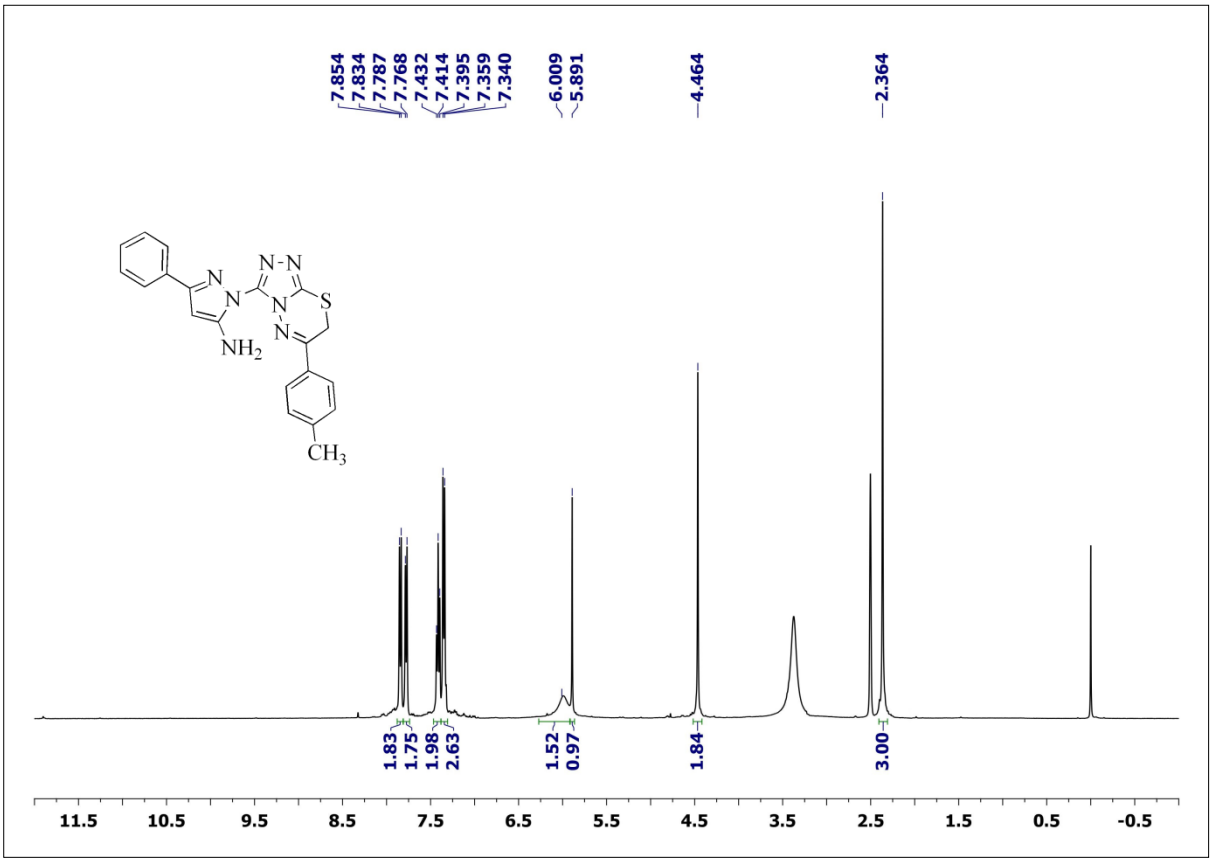
PMR Spectrum of compound **33g**



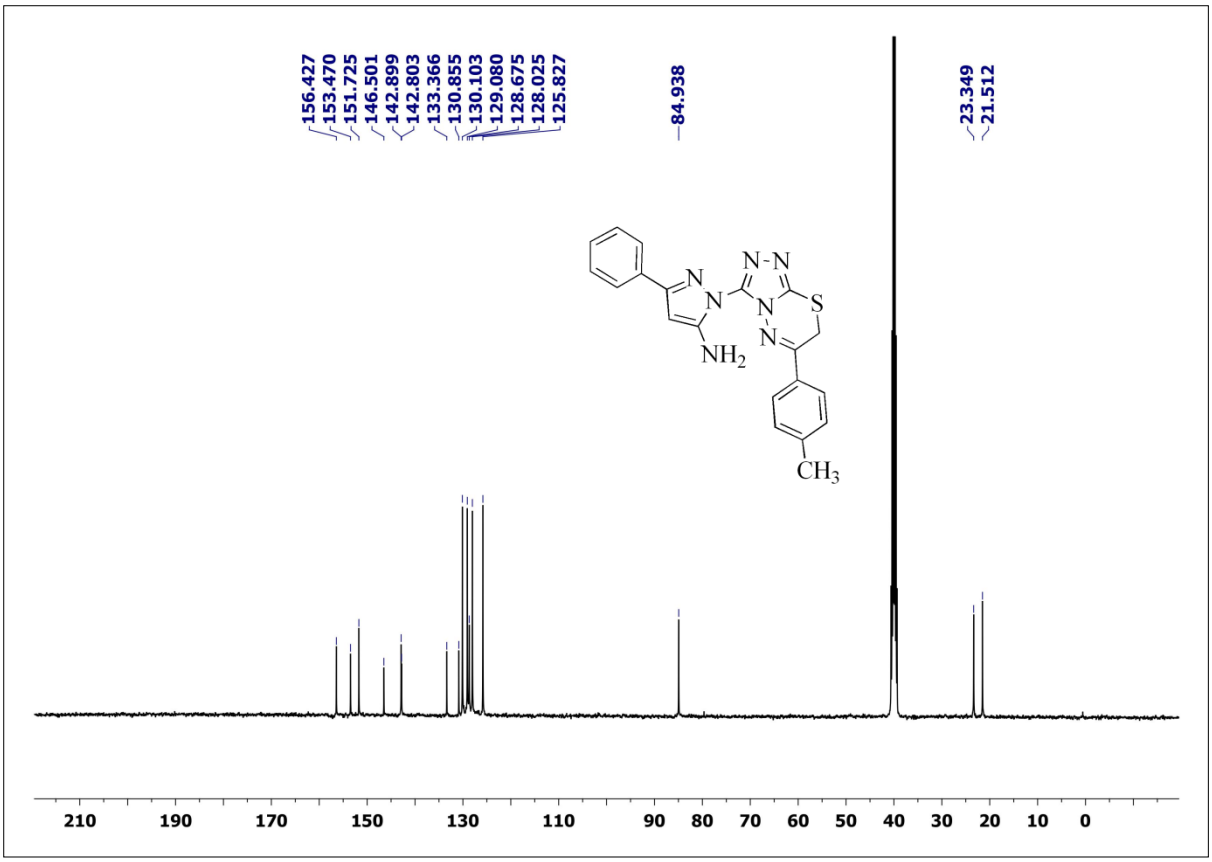
CMR Spectrum of compound **33g**



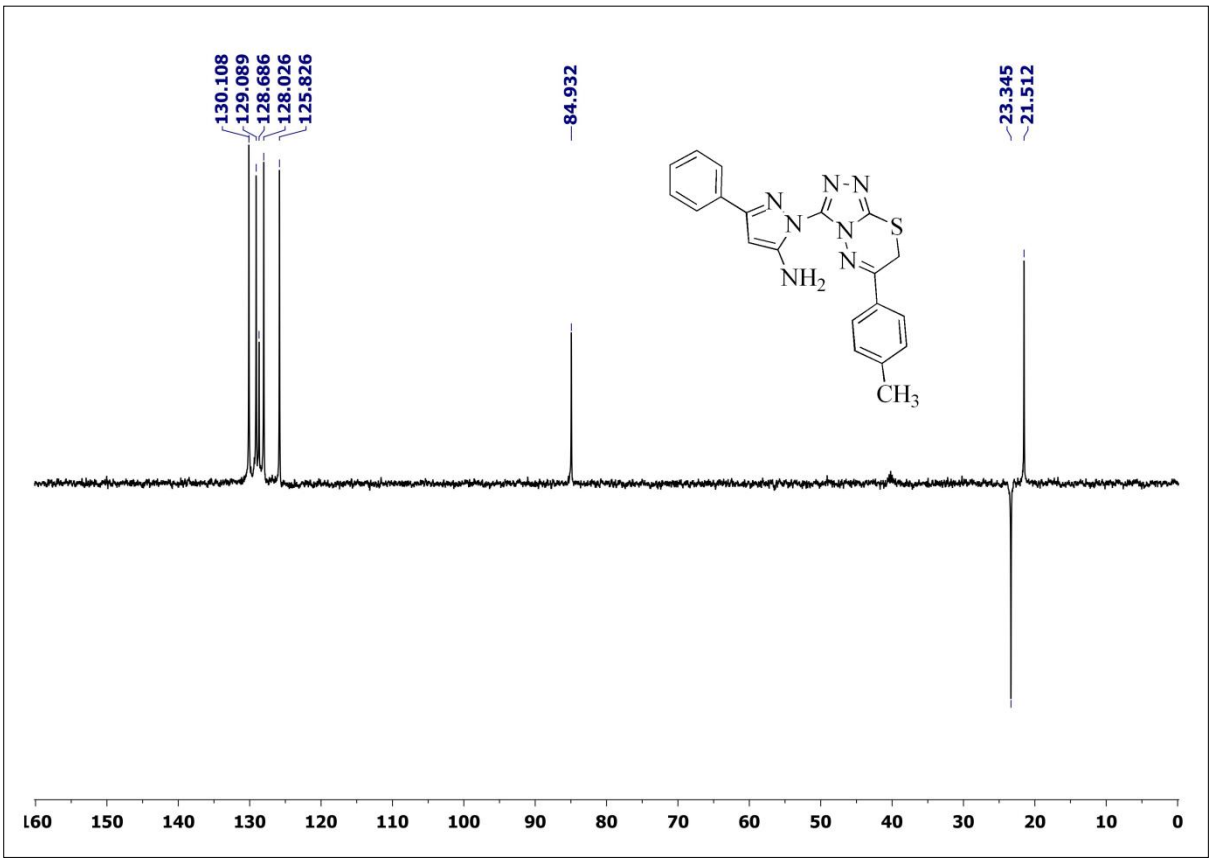
Mass Spectrum of compound **33g**



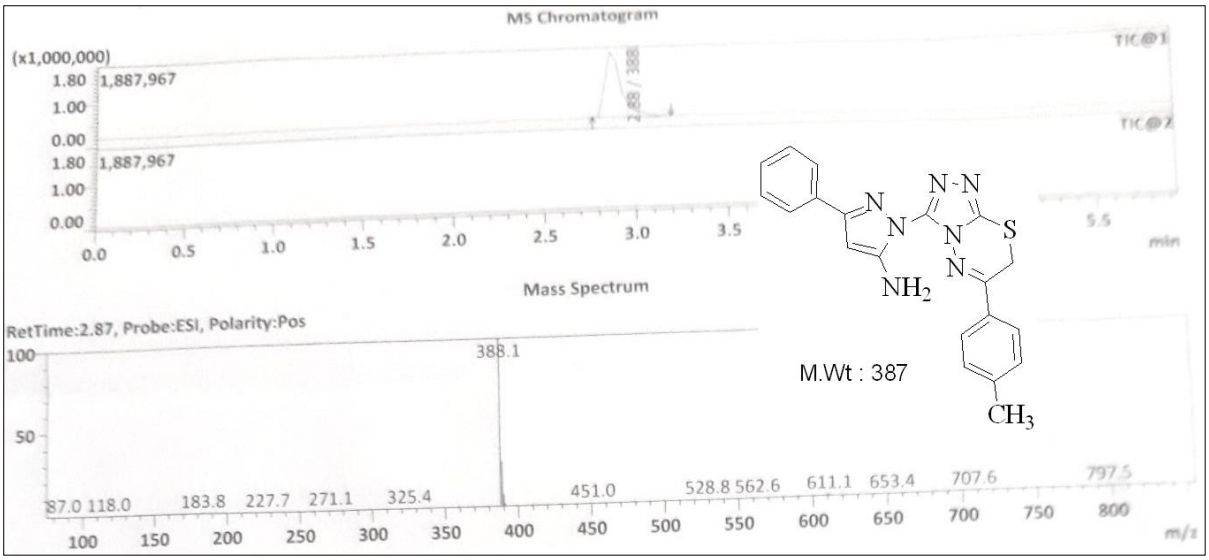
PMR Spectrum of compound **33h**



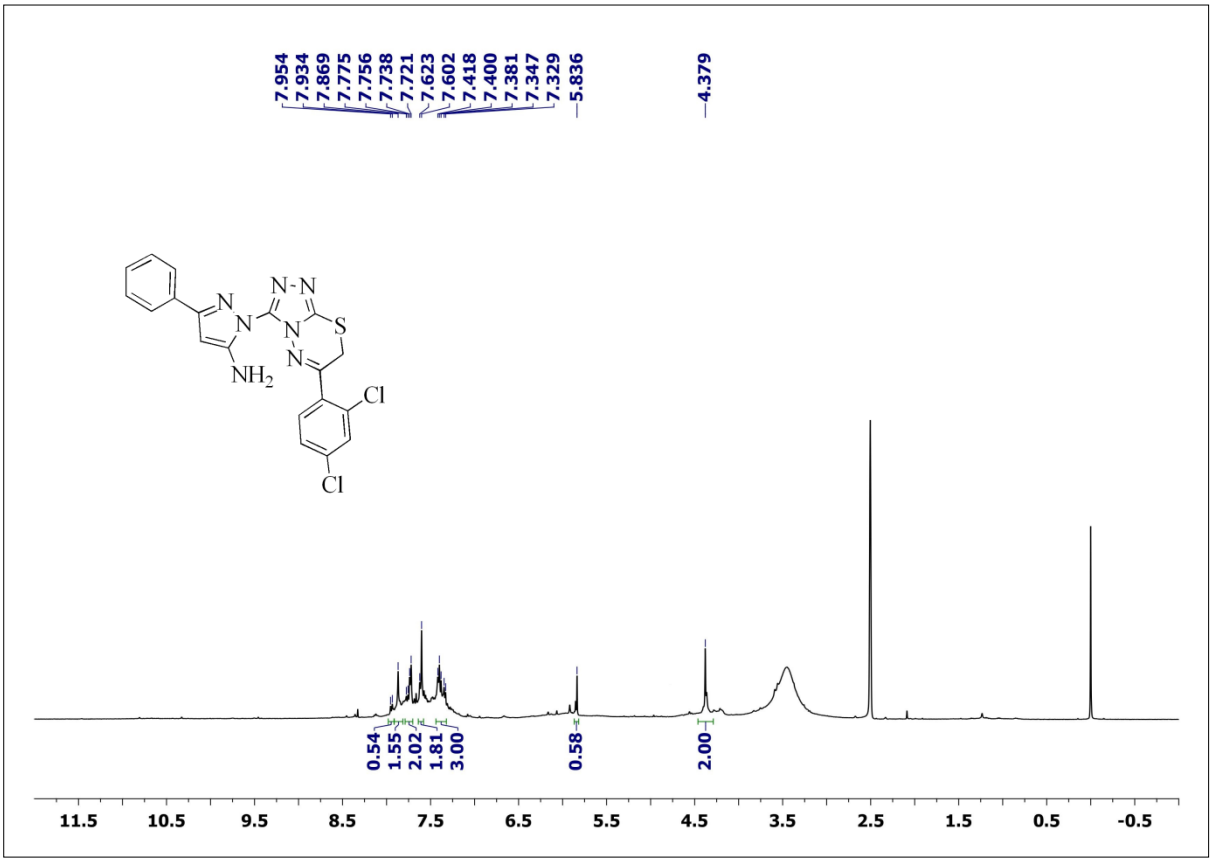
CMR Spectrum of compound **33h**



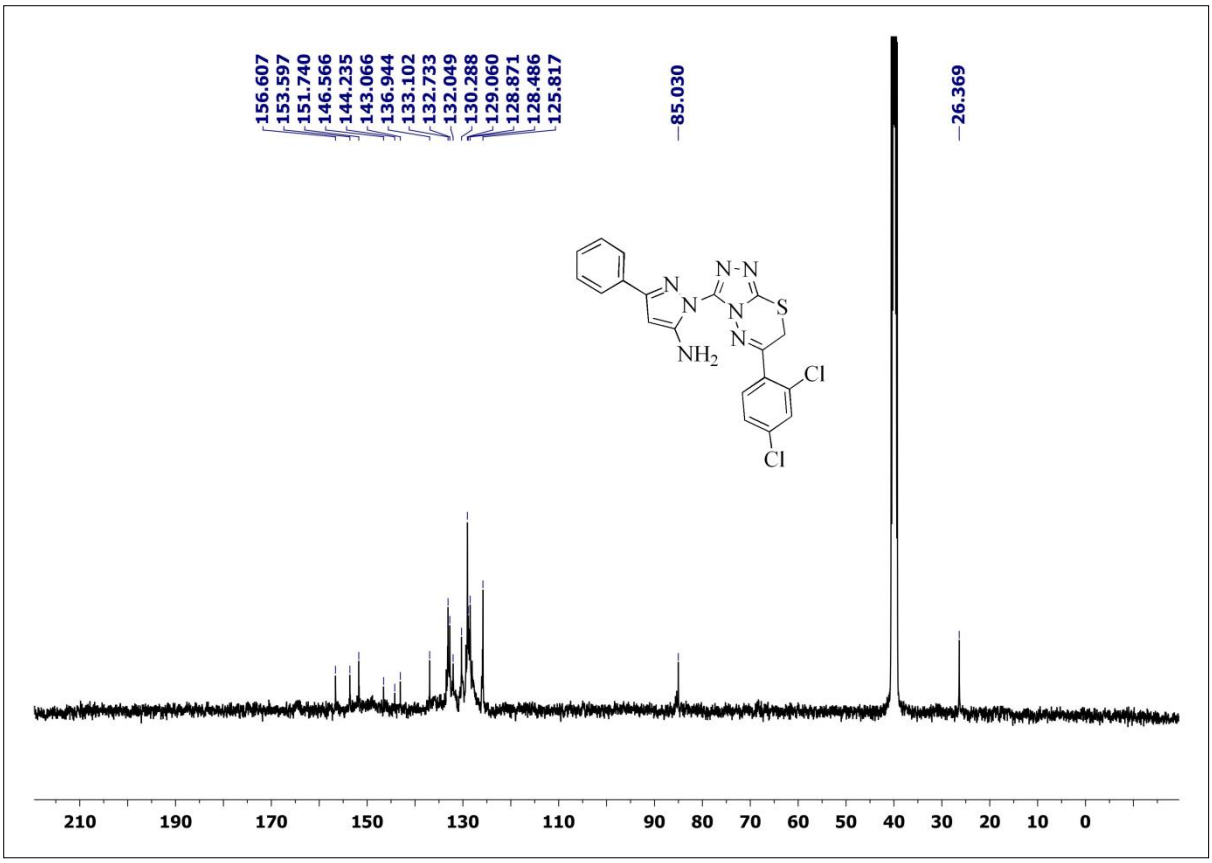
DEPT Spectrum of compound **33h**



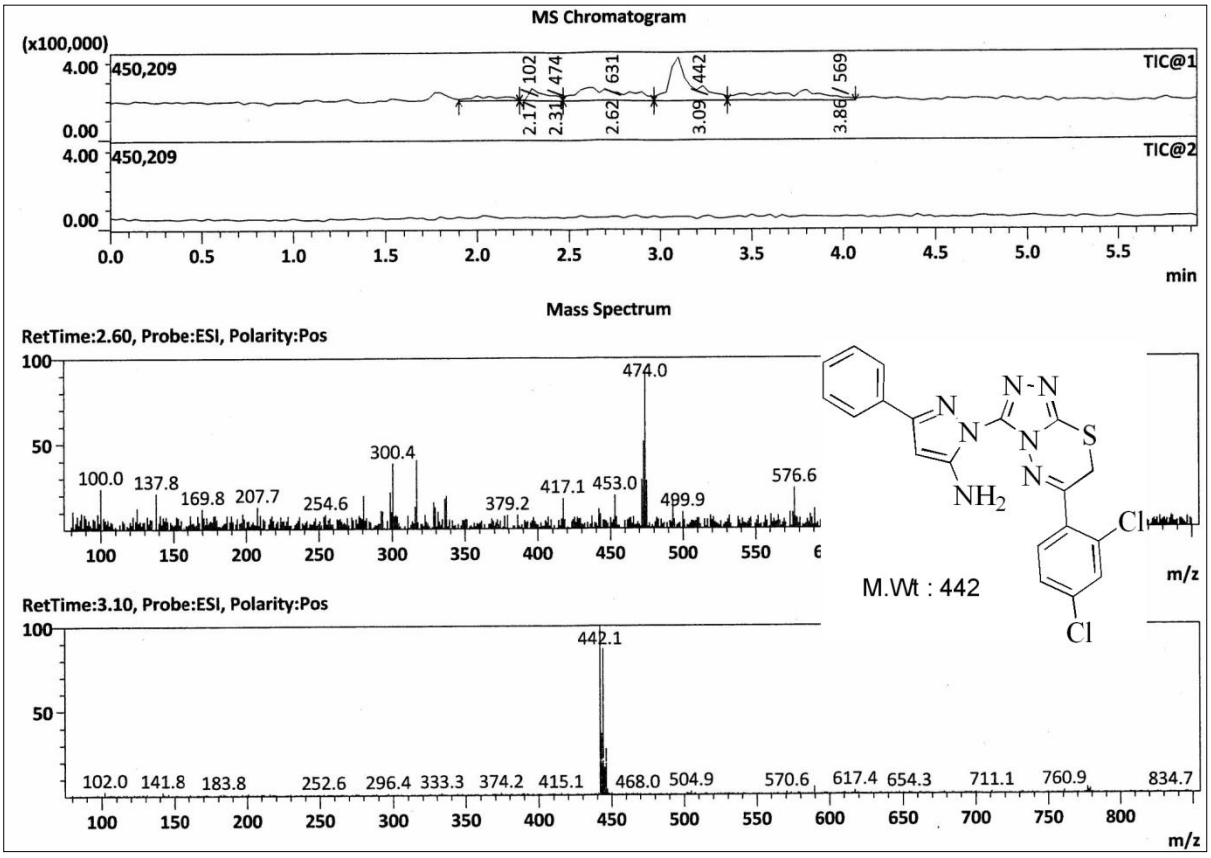
Mass Spectrum of compound **33h**



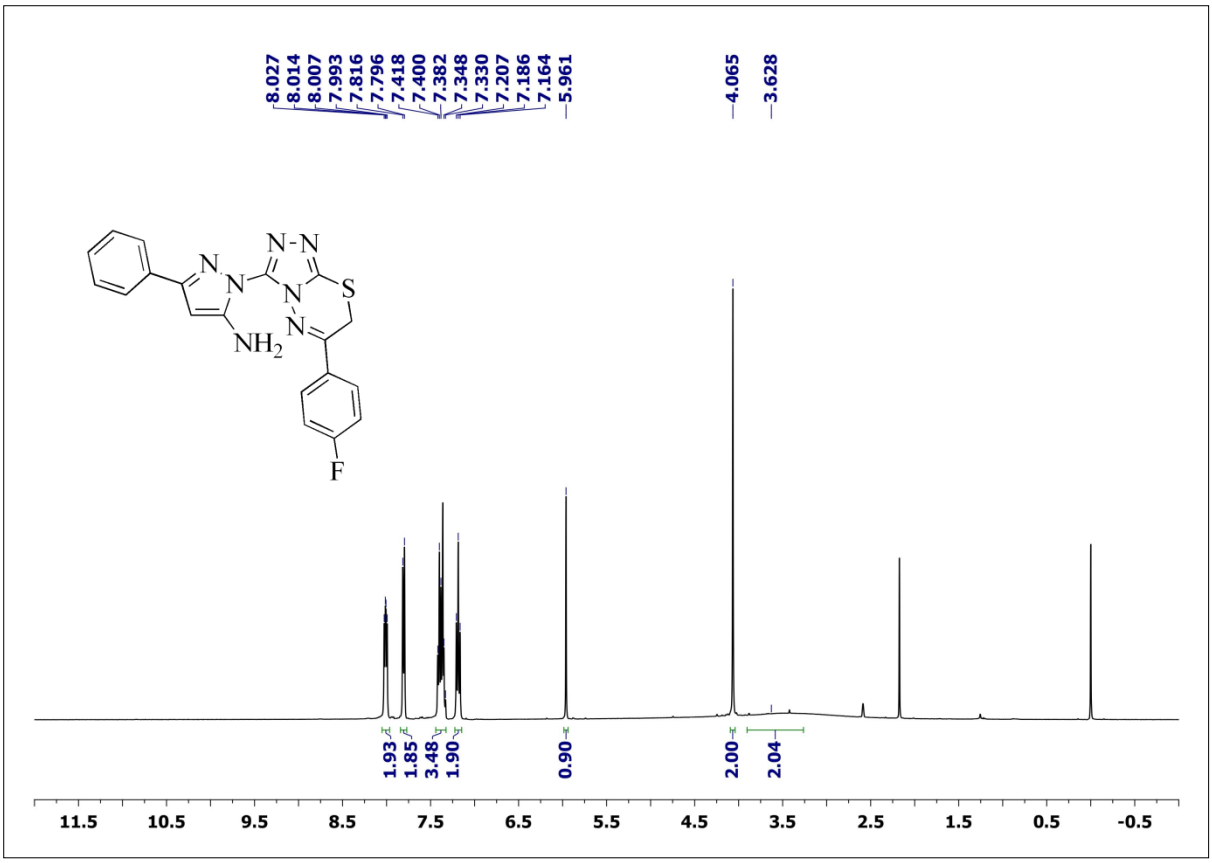
PMR Spectrum of compound **33i**



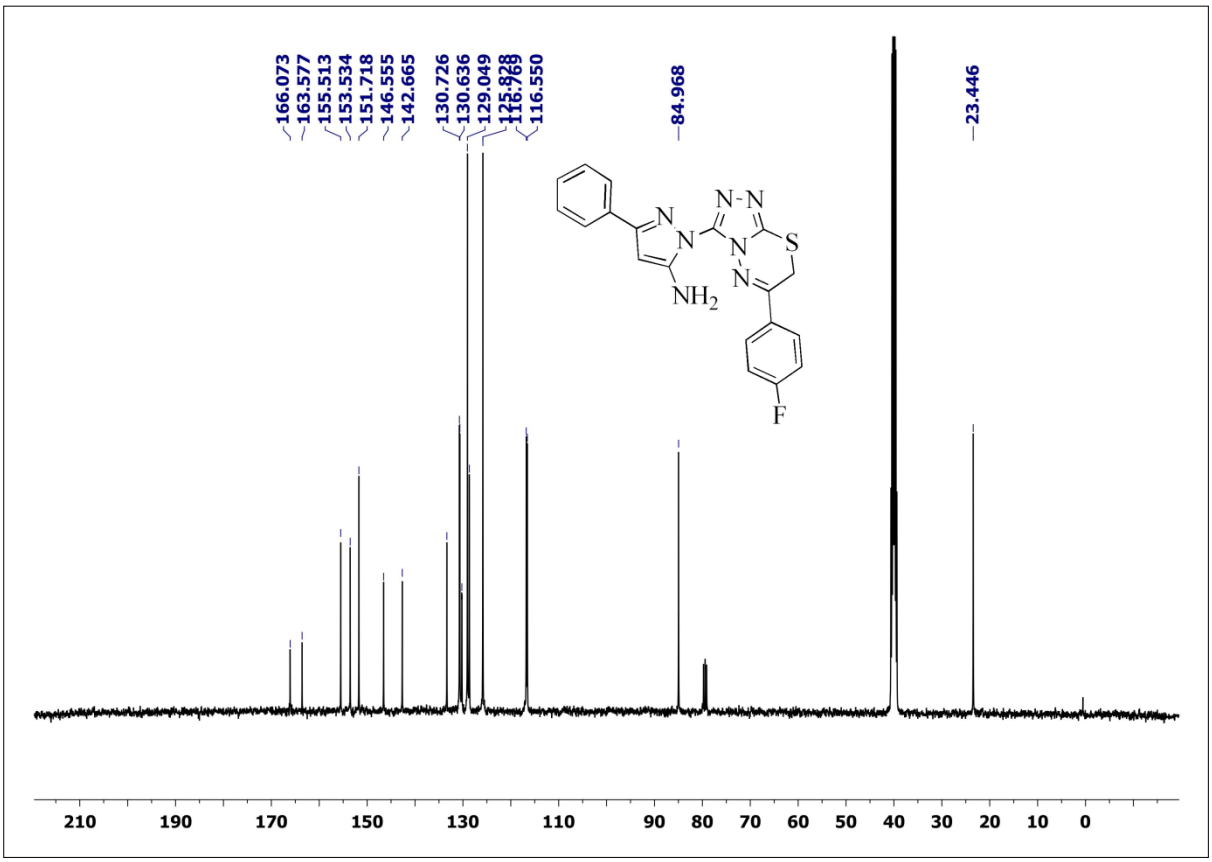
CMR Spectrum of compound **33i**



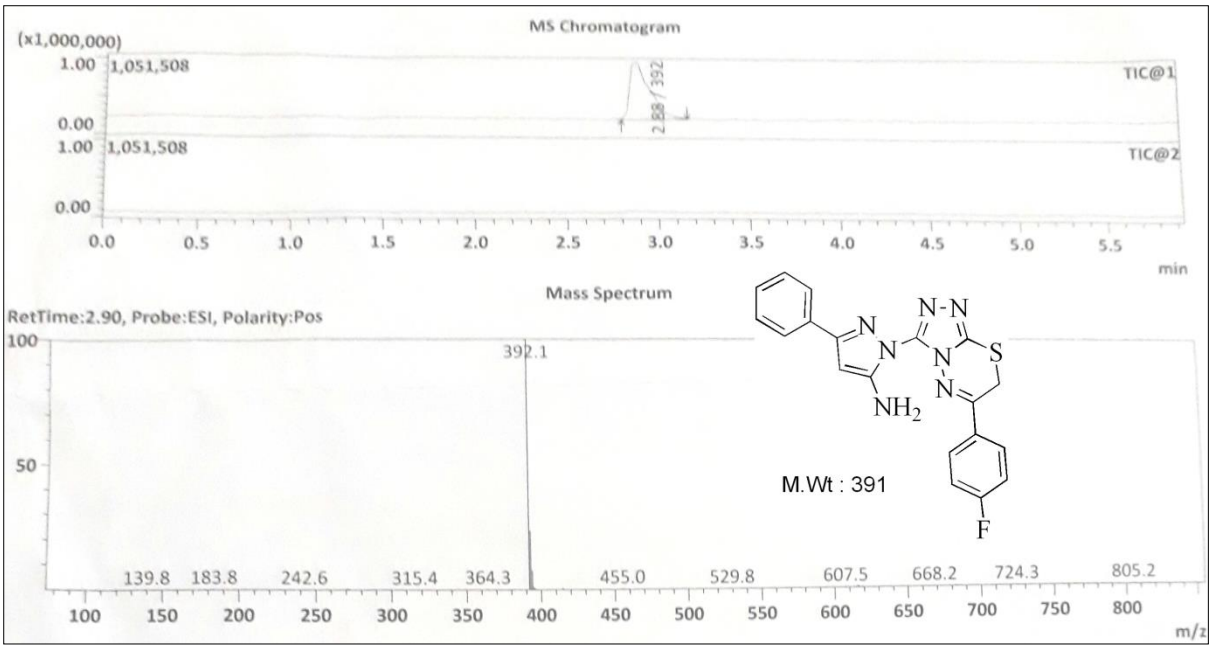
Mass Spectrum of compound **33i**



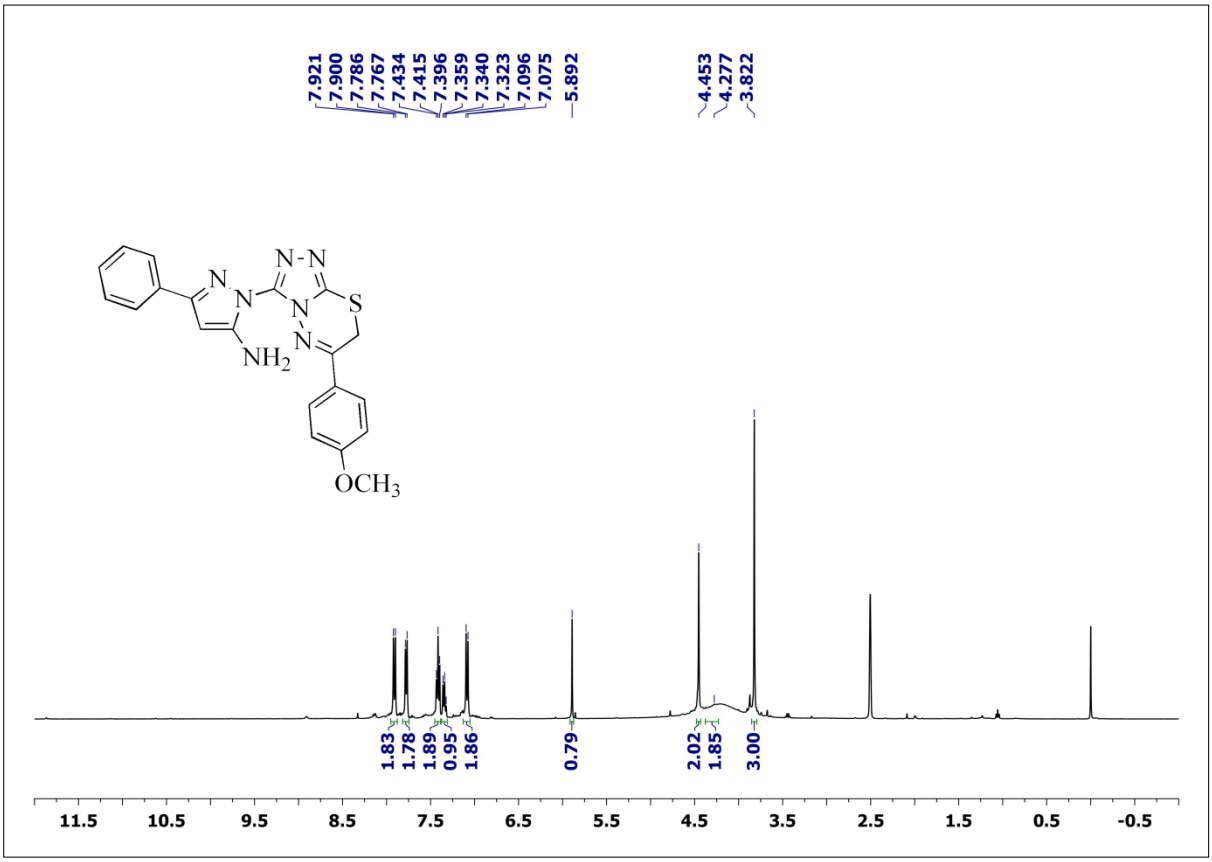
PMR Spectrum of compound **33j**



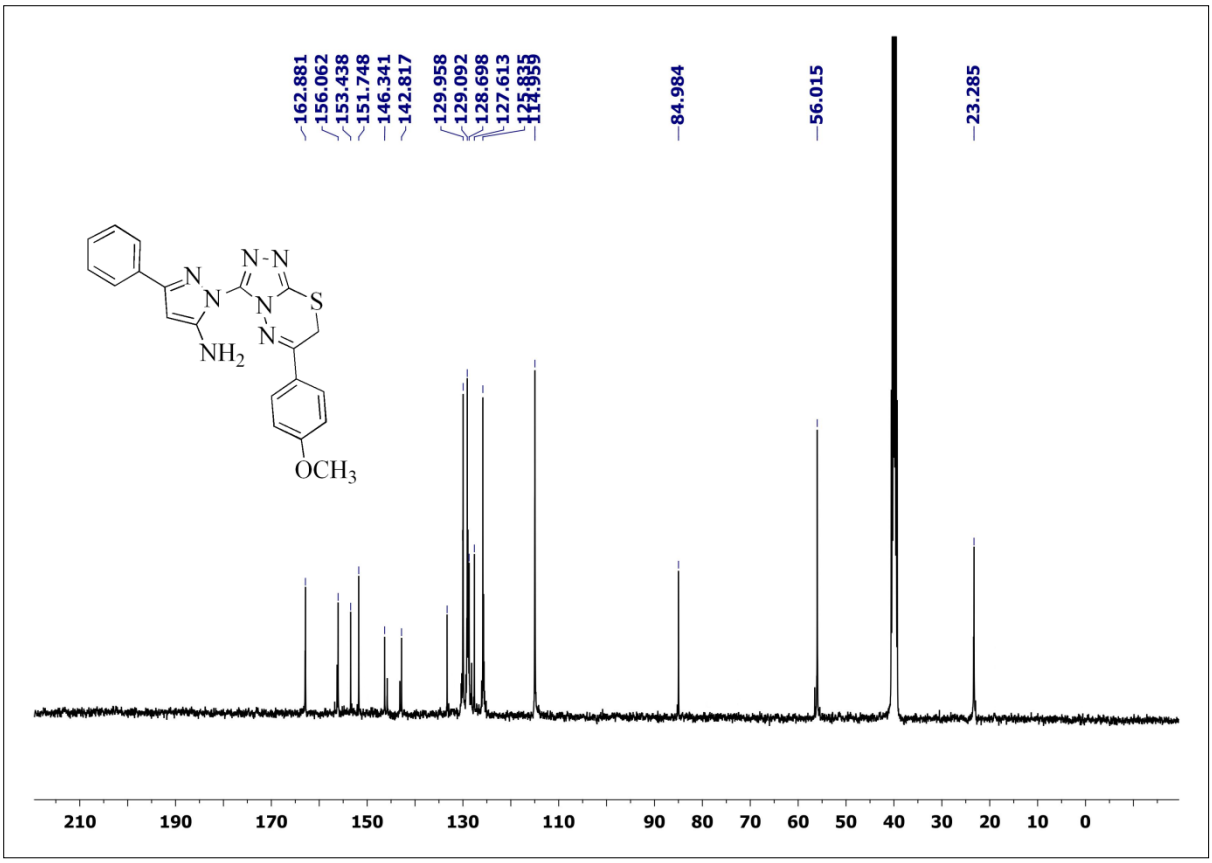
CMR Spectrum of compound **33j**



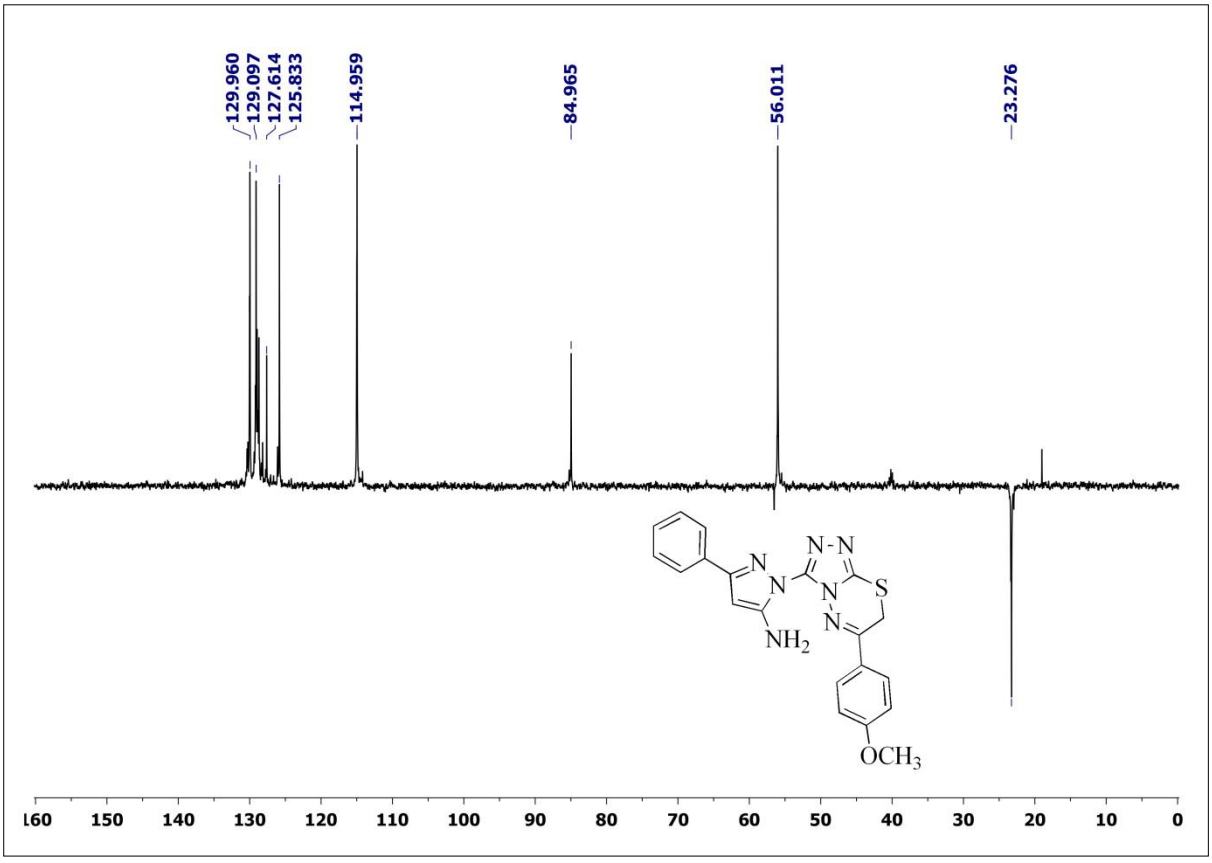
Mass Spectrum of compound **33j**



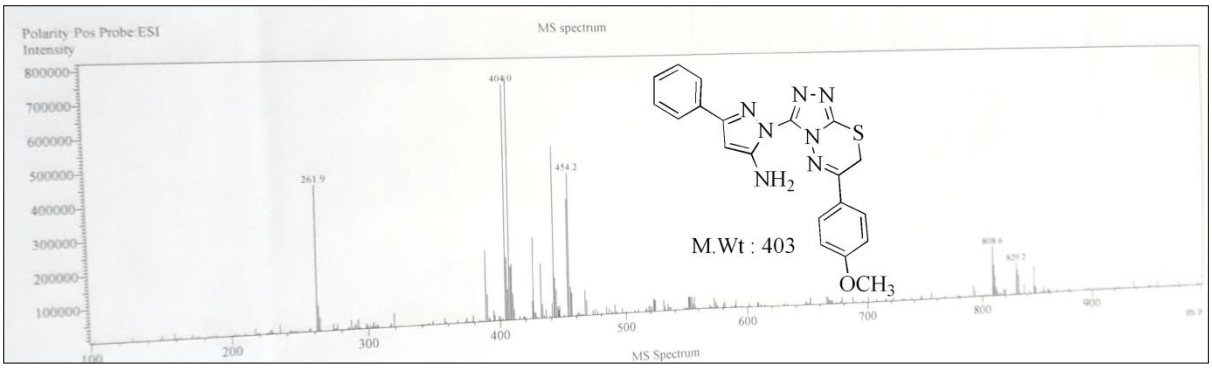
PMR Spectrum of compound **33k**



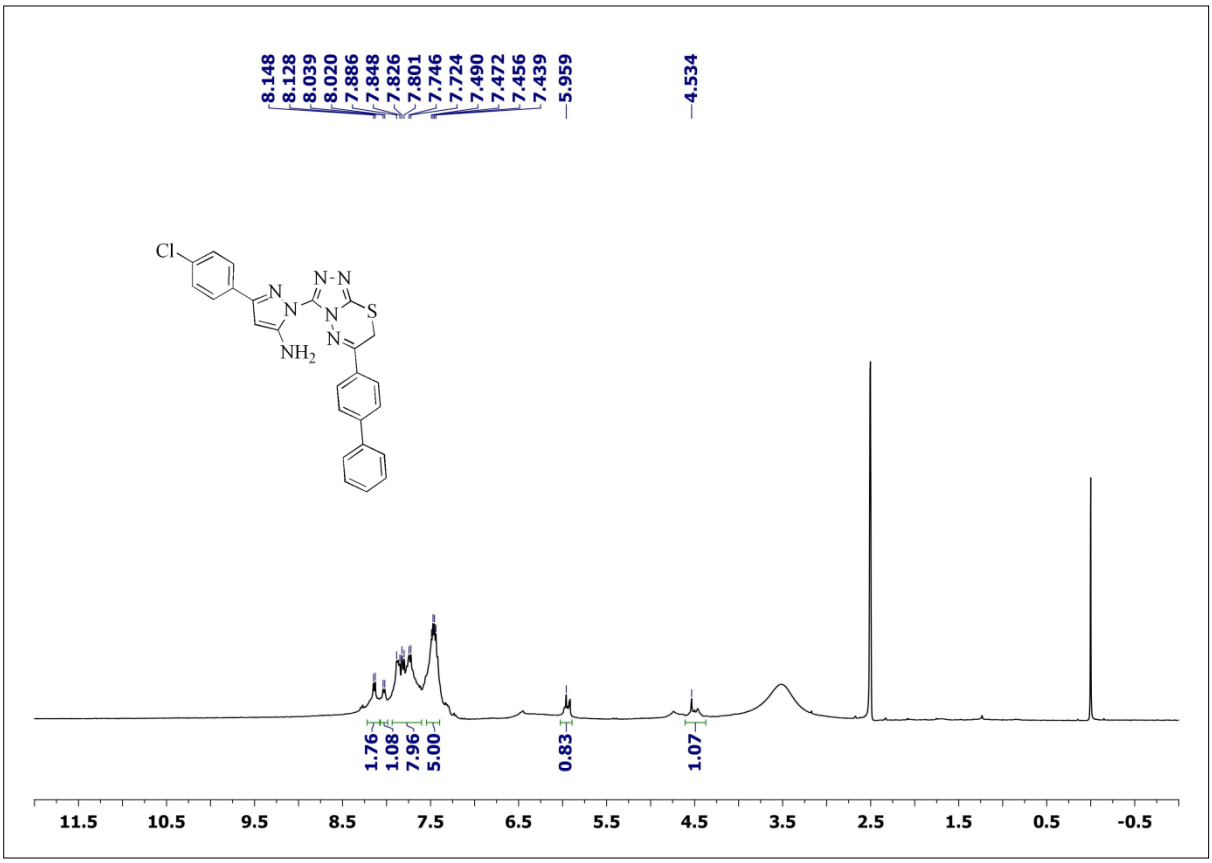
CMR Spectrum of compound **33k**



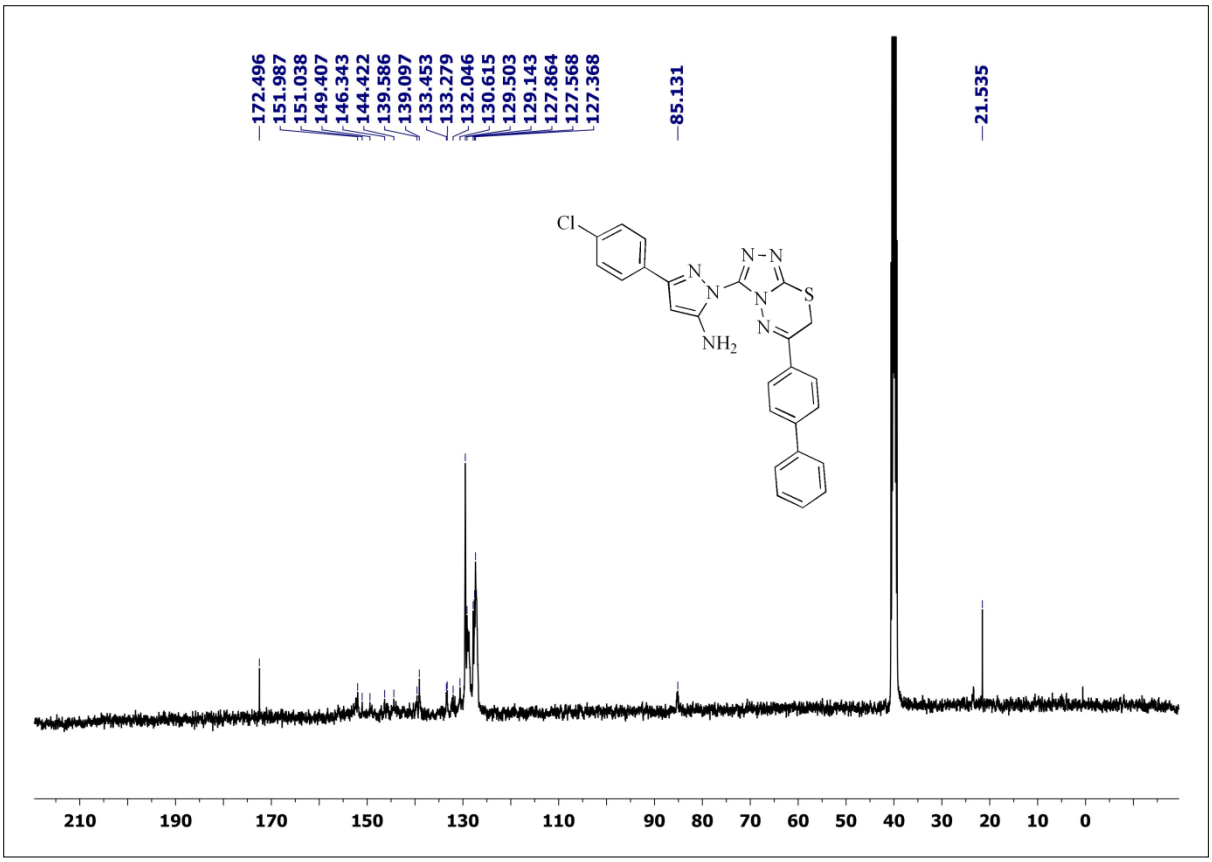
DEPT Spectrum of compound **33k**



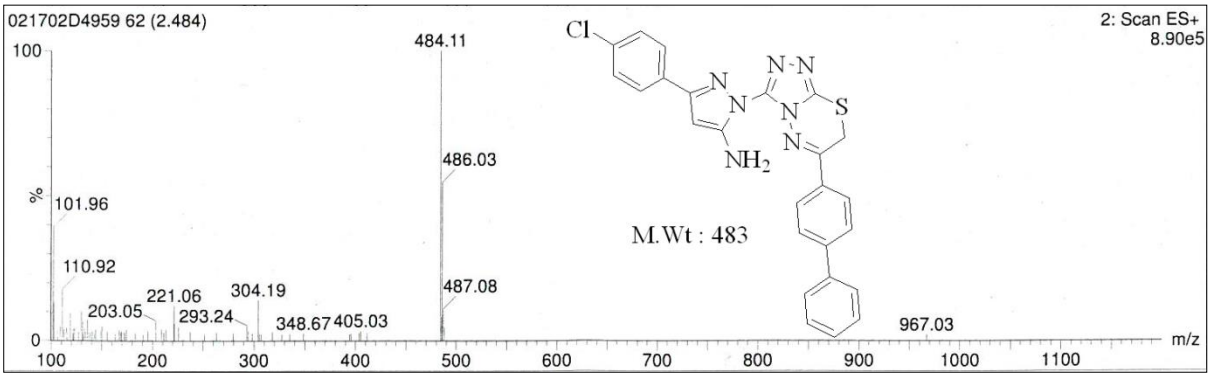
Mass Spectrum of compound **33k**



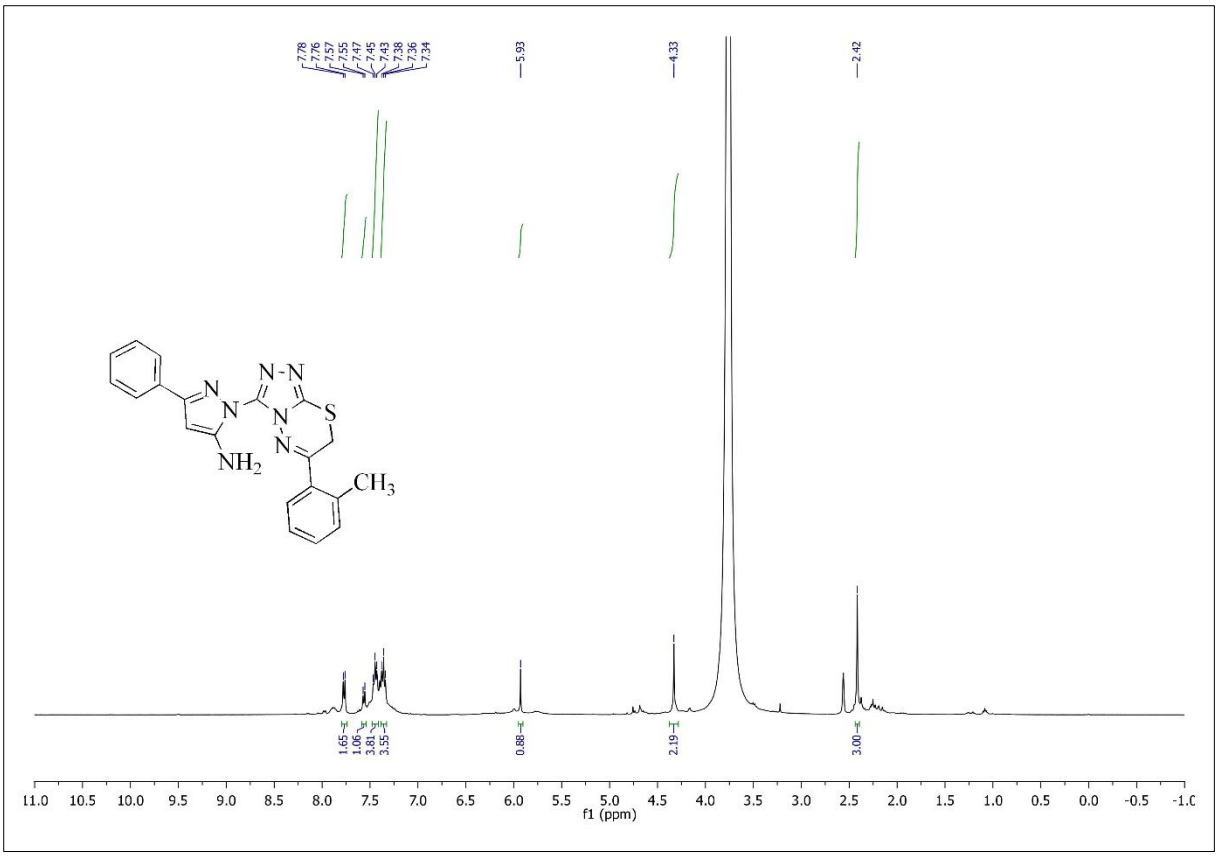
PMR Spectrum of compound **33l**



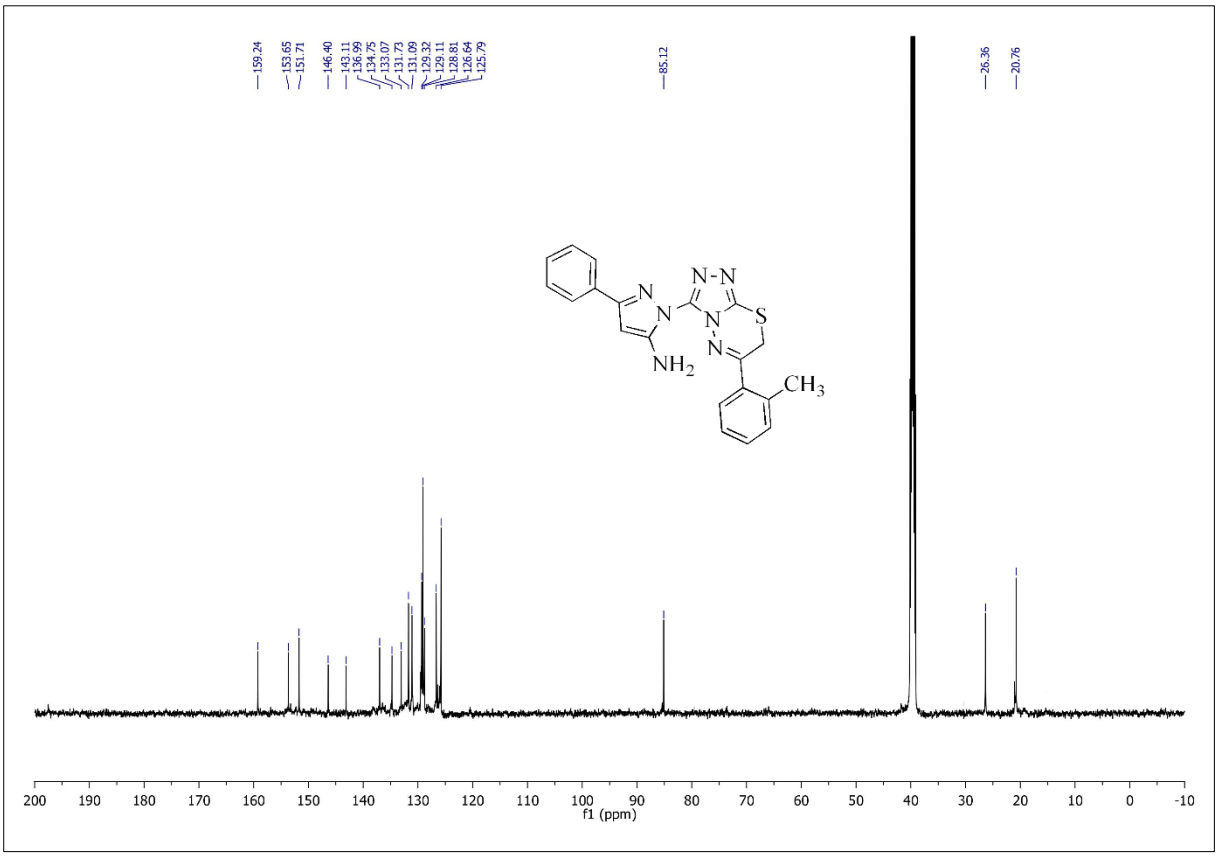
CMR Spectrum of compound **33l**



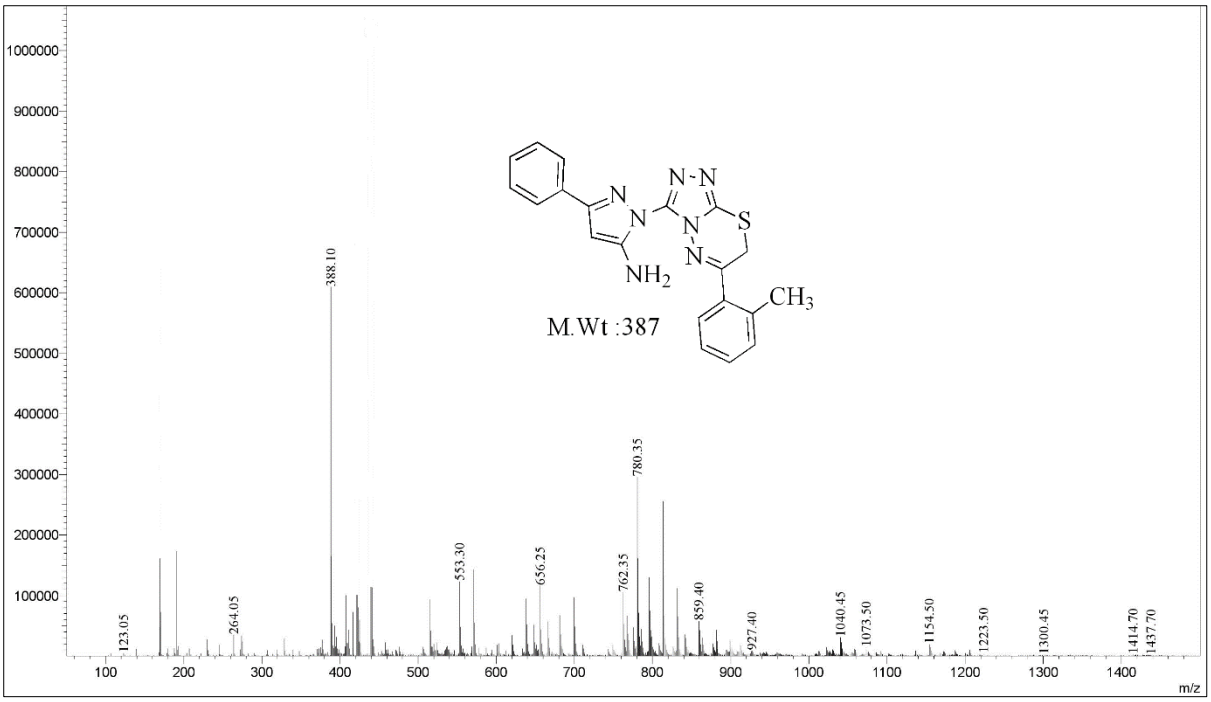
Mass Spectrum of compound **33l**



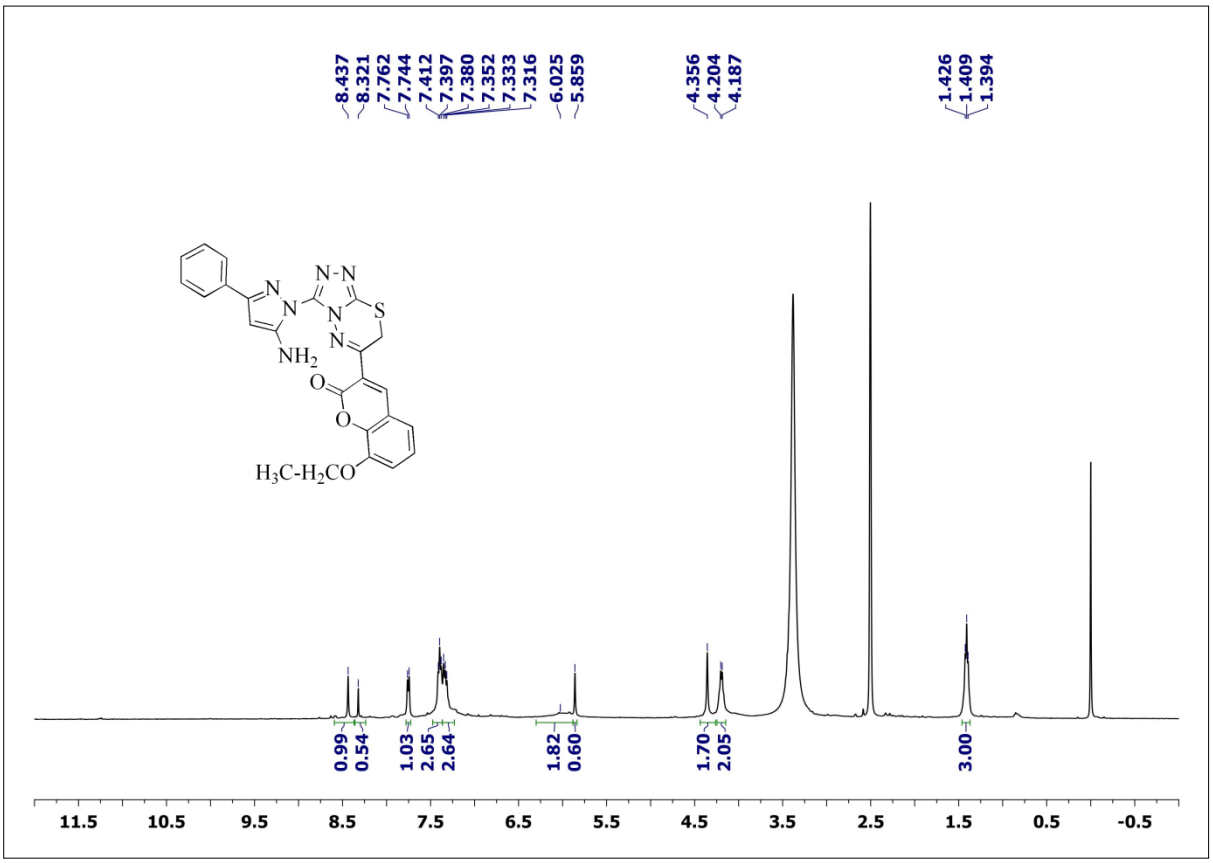
PMR Spectrum of compound **33m**



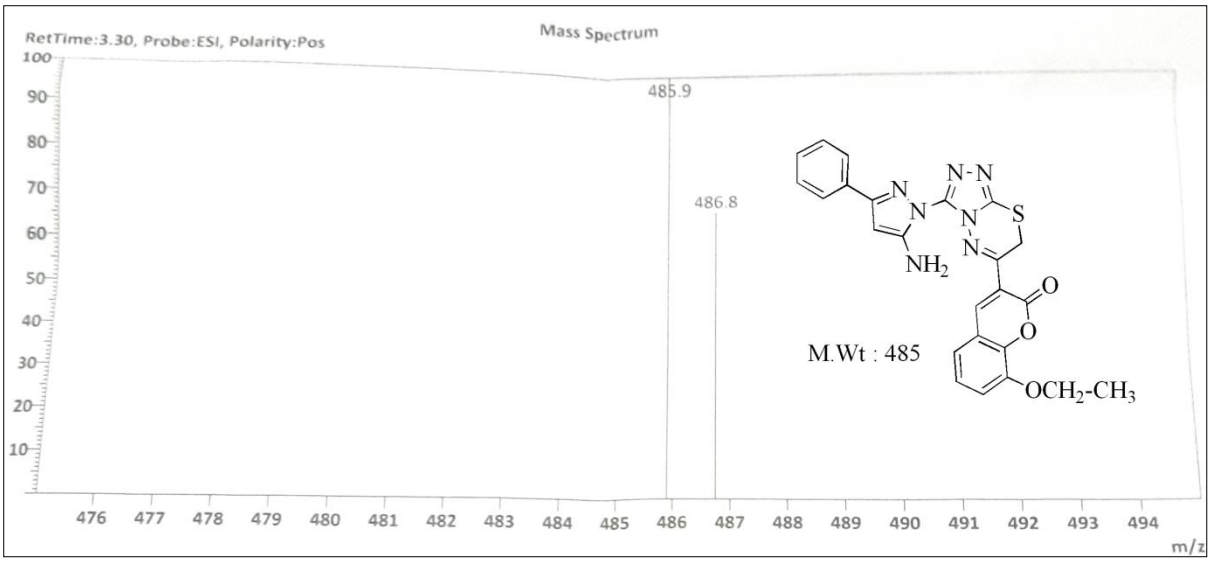
CMR Spectrum of compound **33m**



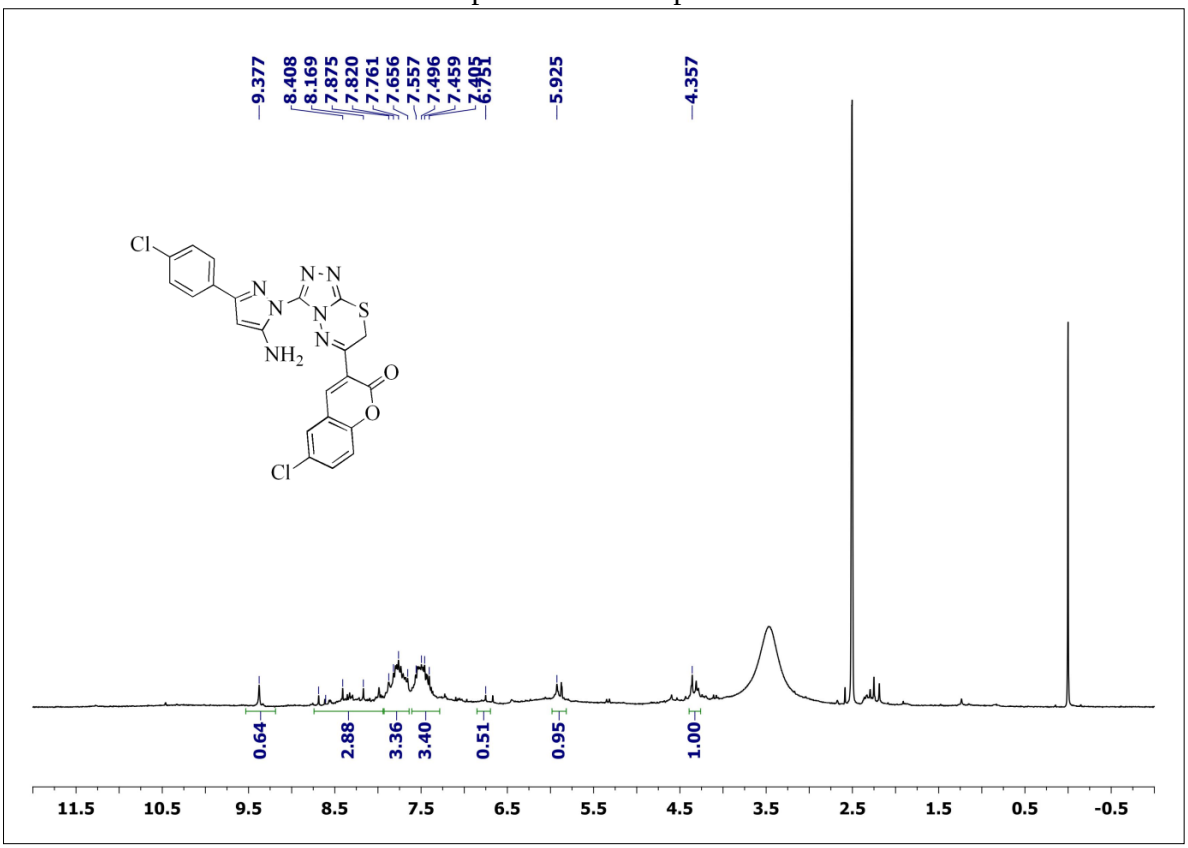
Mass Spectrum of compound **33m**



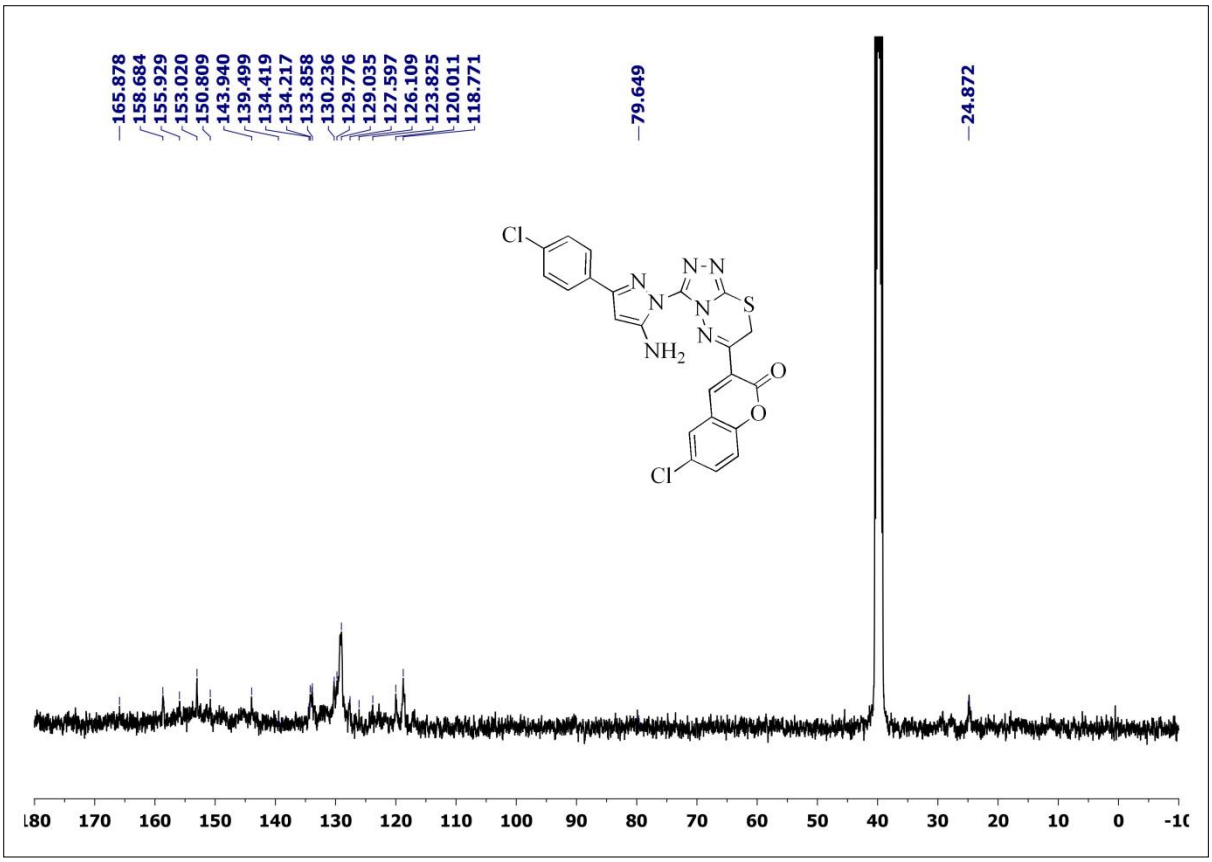
PMR Spectrum of compound **36a**



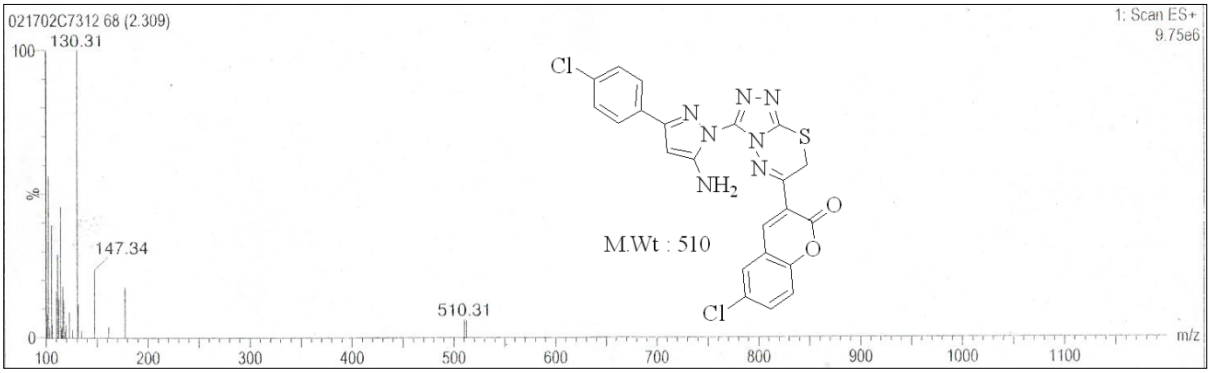
Mass Spectrum of compound **36a**



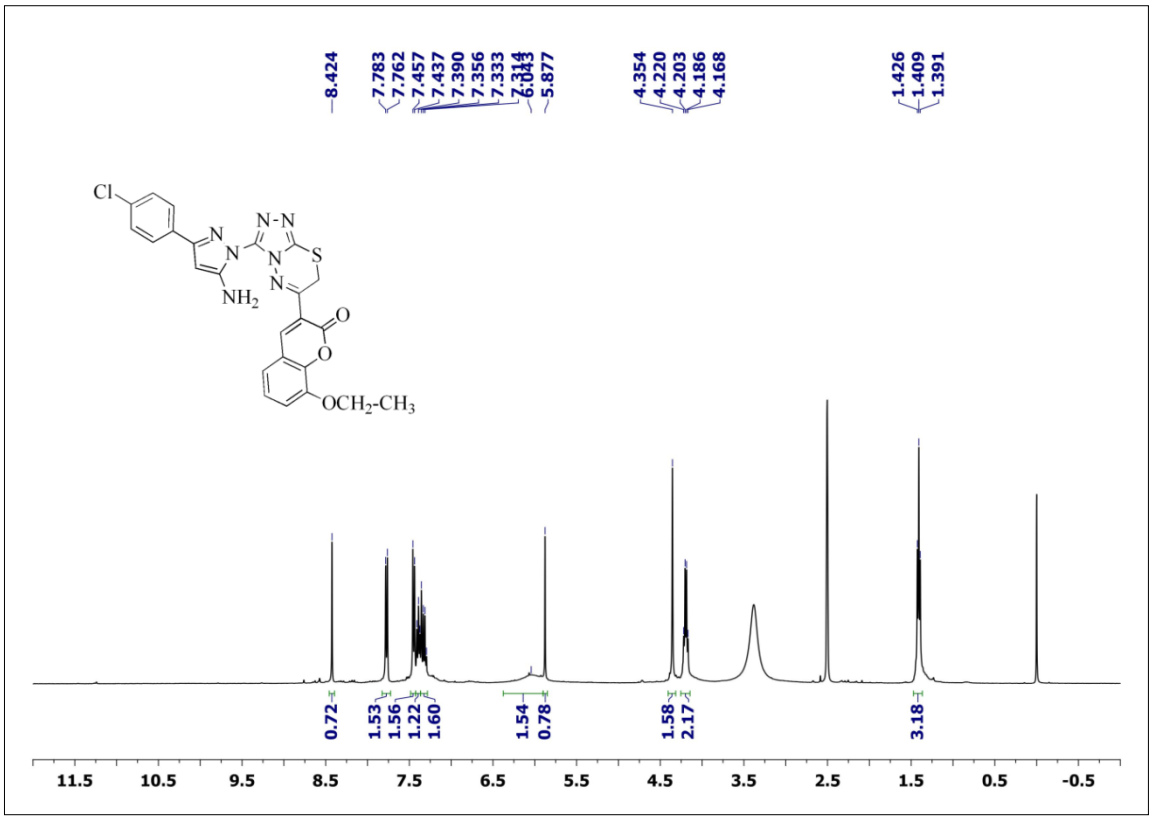
PMR Spectrum of compound **36b**



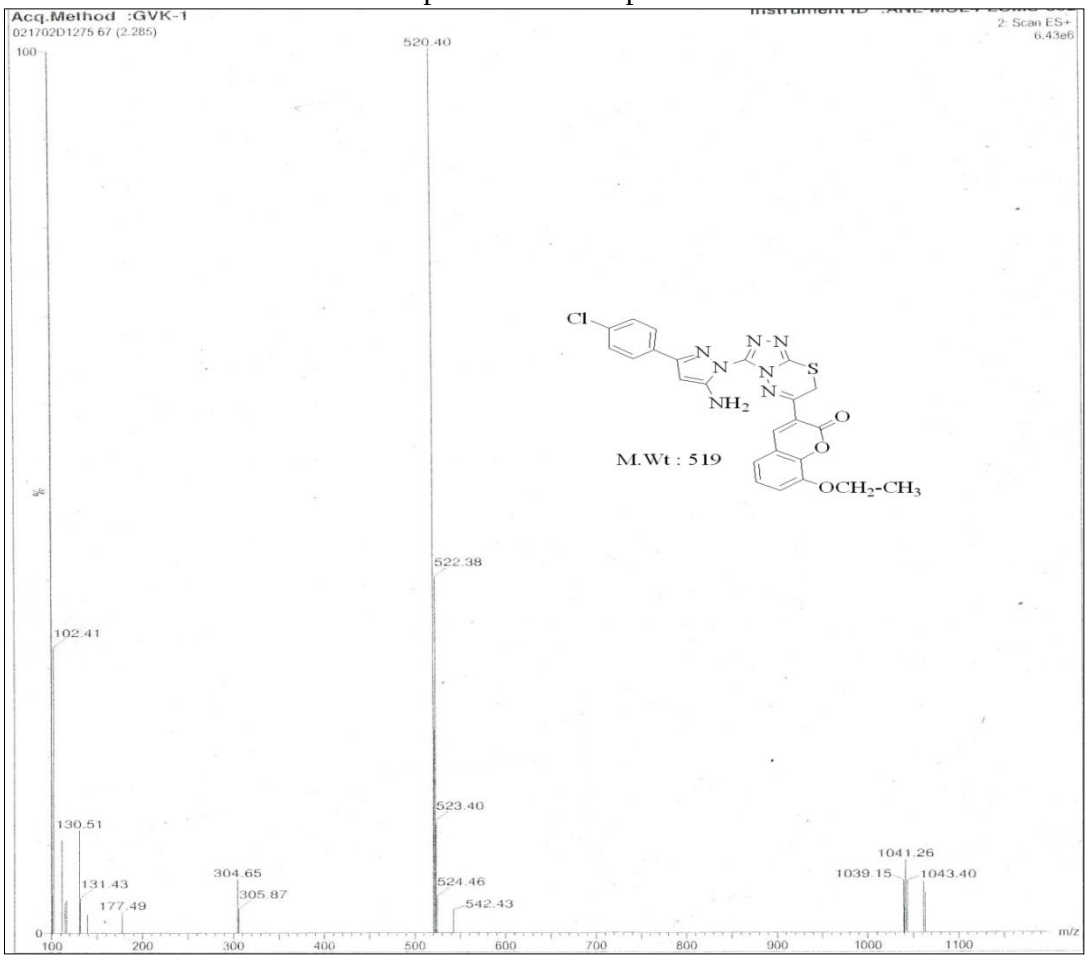
CMR Spectrum of compound **36b**



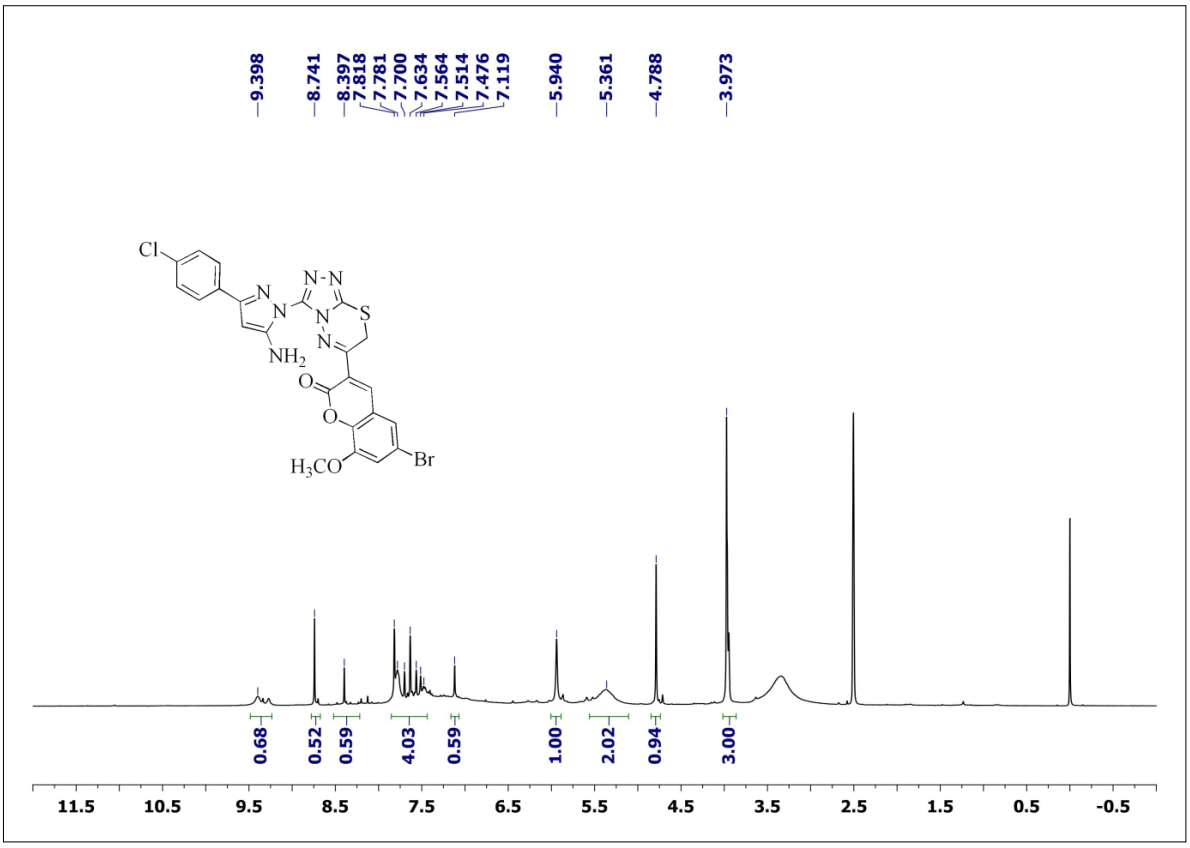
Mass Spectrum of compound **36b**



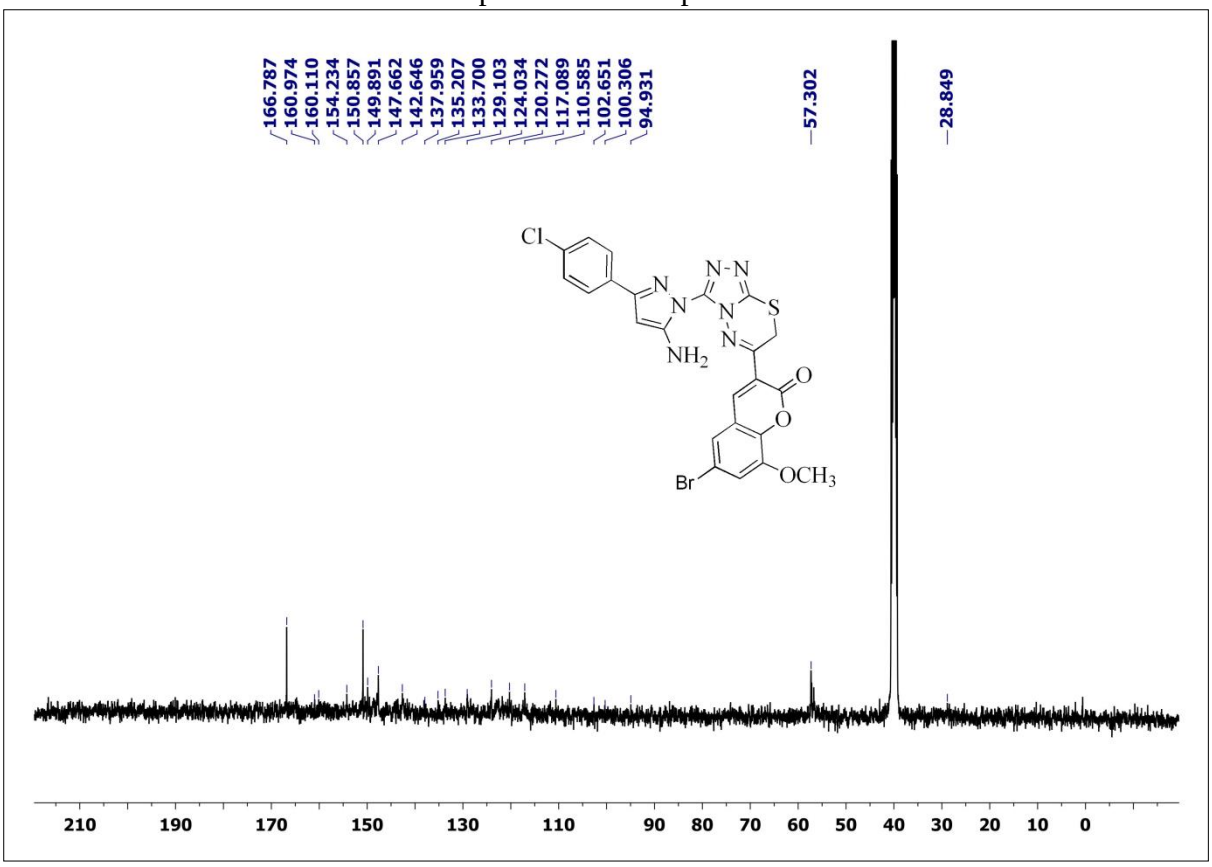
PMR Spectrum of compound **36c**



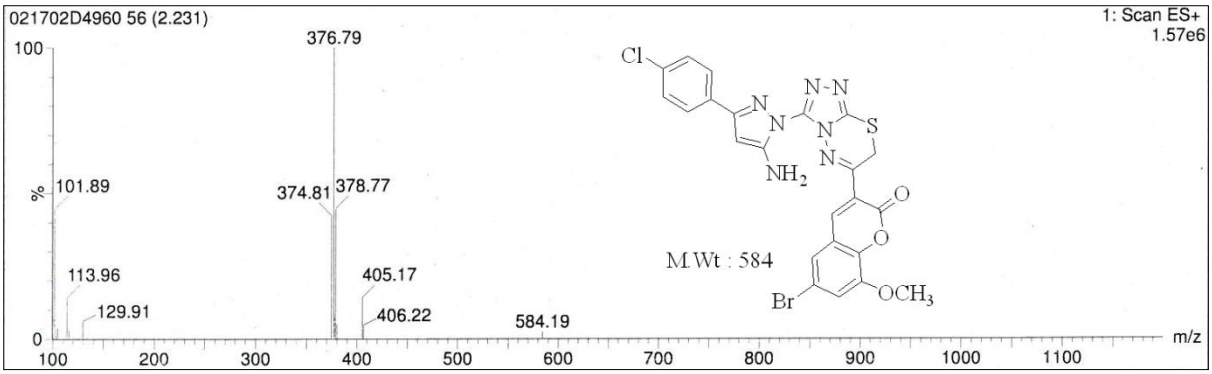
Mass Spectrum of compound **36c**



PMR Spectrum of compound **36d**



CMR Spectrum of compound **36d**



Mass Spectrum of compound **36d**

References:

[1] Zhou, S.; Zhang, L.; Jin, J.; Zhang, A.; Lei, X.; Lin, J.; He, J.; Zhang, H. *Phosphorus, Sulfur Silicon Relat Elem.* **2007**, *182*, 419-432.

[2] Prakash, O.; Aneja, D. K.; Hussain, K.; Lohan, P.; Ranjan, P.; Arora, S.; Sharma, C. Aneja, K. R. *Eur. J. Med. Chem.* **2011**, *46*, 5065-5073.

[3] Singh, R. J.; Singh, D. K. *Int. J. Chem Tech Res.* **2009**, *1*, 1239-1243.

[4] Pavurala, S.; Vaarla, K.; Kesharwani, R.; Naesens, L.; Liekens, S.; Vedula, R. R. *Synth. Commun.* **2018**, *48*, 1494-1503.

[5] Ibrar, A.; Zaib, S.; Jabeen, F.; Iqbal, J.; Saeed, A. *Arch. Pharm. Chem. Life Sci.* **2016**, *349*, 1-13.

[6] Al-Soud, Y. A.; Al-Masoudi, N. A.; Loddo, R.; Colla, P. L. *Arch. Pharm. Chem. Life Sci.* **2008**, *341*, 365-369.

[7] Abdelhameed, R. M.; El-Sayed, H. A.; El-Shahat, M.; El-Sayed, A. A.; Darwesh, O. M. *Curr. Bioact. Compd.* **2018**, *14*, 169-179.

[8] Shashikala Devi, K.; Ramaiah, M.; Vanita, G. K.; Veena, K.; Vaidya, V. P. *J. Chem. Pharm. Res.* **2011**, *3*, 445-451.

[9] Nadkarni, B. A.; Kamat, V. R.; Khadse, B. G. *Arzneimittelforschung.* **2001**, *51*, 569-573.

[10] Hussain, A.; Rashid, M.; Shaharyar, M.; Siddiqui, A. A.; Mishra, R. *Eur. J. Med. Chem.* **2013**, *62*, 785-798.

[11] Xiao-Xia, Y.; Zhen-Fei, C.; An-Jiang, Z.; Li-Xue, Z. *Molecules.* **2007**, *12*, 1202-1209.

[12] Kandile, N. G.; Mohamed, M. I.; Ismaeel, H. M. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 119-129.

[13] Chohan, Z. H.; Hanif, M. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 944-953.

[14] Nastasa, C.; Vodnar, D. C.; Ionut, I.; Stana, A.; Benedec, D.; Tamaian, R.; Oniga, O.; Tiperciuc, B. *Int. J. Mol. Sci.* **2018**, *19*, 222.

[15] Al-Soud, Y. A.; Al-Dweri, M. N.; Al-Masoudi, N. A. *Il Farmaco.* **2004**, *59*, 775-783.

[16] Singh, R.; Kashaw, S. K.; Mishra, V. K.; Mishra, M.; Rajoriya, V.; Kashaw, V. *Indian J. Pharm. Sci.* **2018**, *80*, 36-45.

[17] Unver, Y.; Deniz, S.; Celik, F.; Akar, Z.; Kucuk, M.; Sancak, K. *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 89-95.

[18] Sharma, V.; Mehta, D. K.; Das, R.; Kaur, P. K. *Int J Pharm Pharm Sc*i. **2016**, *8*, 28-31.

[19] Kaur, R.; Dwivedi, A. R.; Kumar, B.; Kumar, V. *Anticancer Agents Med Chem.* **2016**, *16*, 465-489.

[20] Al-Masoudi, N. A.; Aziz, N. M.; Mohammed, A. T. *Phosphorus, Sulfur Silicon Relat Elem.* **2009**, *184*, 2891-2901.

[21] Hussein, M. A,; Shaker, R. M.; Ameen, M. A.; Mohammed, M. F. *Arch Pharm Res.* **2011**, *34*, 1239-1250.

[22] Bei, Z.; Yan-Hong, L.; Yang, L.; Yu-Rong, C.; En-Shan, P.; Wen-Wei, Y.; Pei-Liang, Z. *Eur. J. Med. Chem.* **2015**, *103*, 335-342.

[23] Kaplancikli, Z. A.; Turan-Zitouni, G.; Ozdemir, A.; Revial, G. *Eur. J. Med. Chem.* **2008**, *43*, 155-159.

[24] El Shehry, M. F.; Abu-Hashem, A. A.; El-Telbani, E. M. *Eur. J. Med. Chem.* **2010**, *45*, 1906-1911.

[25] Sever, B.; Altintop, M. D.; Kus, G.; Ozkurt, M.; Ozdemir, A.; Kaplancikli, Z. A. *Eur. J. Med. Chem.* **2016**, *113*, 179-186.

[26] Aytac, P. S.; Durmaz, I.; Houston, D. R.; Cetin-Atalay, R.; Tozkoparan, B. *Bioorg. Med. Chem.* **2016**, *24*, 858-872.

[27] Khan, I.; Bakht, S. M.; Ibrar, A.; Abbas, S.; Hameed, S.; White, J. M.; Rana, U. A.; Zaib, S.; Shahide, M.; Iqbal, J. *RSC Adv.* **2015**, *5*, 21249-21267.

[28] Aouad, M. R.; Al-Saedi, A. M. H.; Ali, A. A.; Rezki, N.; Messali, M. *Org Prep Proced Int.* **2016**, *48*, 355-370.

[29] Knak, S.; Pfeiffer, W. D.; Dollinger, H.; Saghyan, A. S.; Langer, P. *J. Heterocyclic Chem.* **2015**, *52*, 463-467.

[30] Goveas, J.; Khader, A. M. A.; Kalluraya, B.; Sheik, S.; Chandrashekar, K. R. *Der Pharma Chemica.* **2015**, *7*, 248-255.

[31] Alghamdi, A. F.; Rezki, N. *J Taibah Univ Sci.* **2017**, *11*, 759-767.

[32] Kooi-Mow, S.; Pei-Qie, C.; Xin-Lik, B.; Ker-Sin, H.; Kah-Whei, L.; Kah-Cheng, T. *Lett Org Chem.* **2018**, *15*, 575-582.

[33] Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y. N.; Al-aizari, F. A.; Ansar, M. *Molecules.* **2018**, *23*, 134.

[34] Meta, E.; Brullo, C.; Tonelli, M.; Franzblau, S. G.; Wang, Y.; Ma, R.; Baojie, W.; Orena, B. S.; Pasca, M. R.; Bruno, O. *Med Chem.* **2019**, *15*, 17-27.

[35] Domingueza, J. N.; Charrisa, J. E.; Caparellib, M.; Riggionec, F. *Arzneimittelforschung.* **2002**, *52*, 482-488.

[36] El-Sayed, W. A.; Flefel, E. M.; Morsy, E. M. H. *Der Pharma Chemica.* **2012**, *4*, 23-32.

[37] Abunada, N. M.; Hassaneen, H. M.; Kandile, N. G.; Miqdad, O. A. *Molecules*. **2008**, *13*, 1501-1517.

[38] Kocyigit-Kaymakcioglu, B.; Aker, R. G.; Tezcan, K.; Sakalli, E.; Ketenci, S.; Oruc-Emre, E. E.; Akin, D.; Gurbanova, A.; Terzioglu, B.; Onat, F.; Rollas, S. *Med Chem Res.* **2011**, *20*, 607-614.

[39] Tantawy, A. S.; Nasr, M. N. A.; El-Sayed, M. A. A. Tawfik, S. S. *Med Chem Res.* **2012**, *21*, 4139-4149.

[40] Abdel-Aziz, M.; Abuo-Rahma, G. E. A. Hassan, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 3480-3487.

[41] Porter, D. W.; Bradley, M.; Brown, Z.; Canova, R.; Charlton, S.; Cox, B.; Hunt, P.; Kolarik, D.; Lewis, S.; O'Connor, D.; Reilly, J.; Spanka, C.; Tedaldi, L.; Watson, S. J.; Wermuth, R.; Press, N. J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 72-76.

[42] Nepali, K.; Singh, G.; Turan, A.; Agarwal, A.; Sapra, S.; Kumar, R.; Banerjee, U. C.; Verma, P. K.; Satti, N. K.; Gupta, M. K.; Suri, O. P.; Dhar, K. L. *Bioorg. Med. Chem. Lett.* **2011**, *19*, 1950-1958.

[43] Mojzych, M.; Tarasiuk, P.; Karczmarzyk, Z.; Juszczak, M.; Rzeski, W.; Fruzinski, A.; Wozny, A. *Med Chem.* **2018**, *14*, 53-59.

[44] Farghaly, A. R.; Clercq, E. D.; El-Kashef, H. *Arkivoc.* **2006**, *X*, 137-151.

[45] LaPorte, M. G.; Wang, Z.; Colombo, R.; Garzan, A.; Peshkov, V. A.; Liang, M.; Johnston, P. A.; Schurdak, M. E.; Sen, M.; Camarco, D. P.; Hua, Y.; Pollock, N. I.; Lazo, J. S.; Grandis, J. R.; Wipf, P.; Huryn, D. M. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3581-3585.

[46] Pavurala, S.; Vedula, R. R. *J. Heterocyclic Chem.* **2015**, *52*, 306-309.

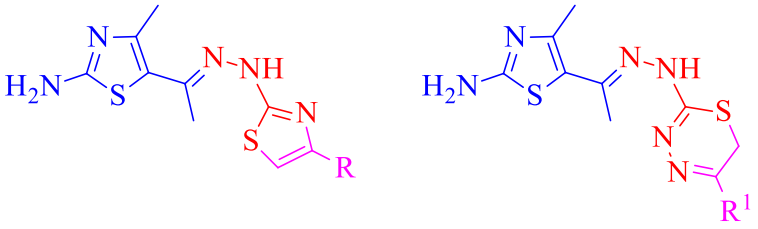
[47] Aychiluhim, T. B.; Vedula, R. R. *Synth. Commun.* **2014**, *44*, 1422-1429.

[48] Sanjeeva Reddy, Ch.; Sanjeeva Rao, L. Sunitha, B.; Nagaraj, A. *Indian J. Chem.* **2015**, *54B*, 1283-1289.

[49] Amer, A. A.; Moustafa, A. H. *Synlett.* **2016**, *27*, 1703-1706.

CHAPTER-IV

ONE-POT MULTICOMPONENT SYNTHESIS OF THIAZOLYL HYDRAZONO THIAZOLAMINES AND 1,3,4-THIADIAZINYL HYDRAZONO THIAZOLAMINES



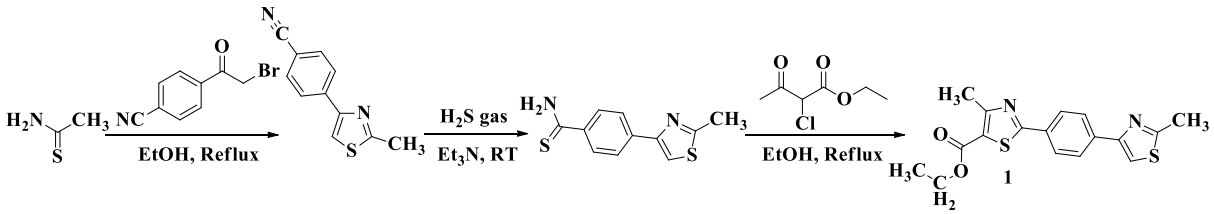
INTRODUCTION

Thiazoles are well known molecules in drug industry. Thiazole structural core nucleus is present in many natural products, chemical drugs and antibiotics.[1,2] They are exhibiting more biological activities such as anti-tumour,[3] anti-malarial,[4] antifungal,[5] antiviral,[6] antibacterial,[7] anticancer,[8] antimicrobial,[9] insecticidal[10] and anti-inflammatory.[11]

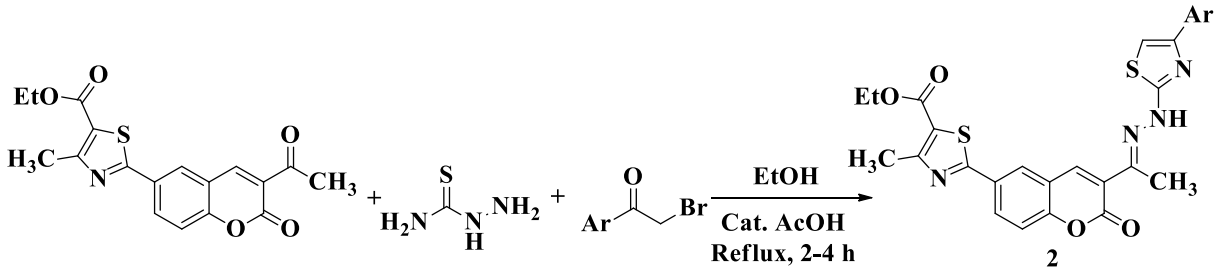
1,3,4-Thiadiazines are nitrogen and sulphur containing six membered heterocyclic compounds. It contains sulphur and nitrogen at 1 and 3, 4 positions. 1,3,4-Thiadiazines and its derivatives show various biological and pharmaceutical activities such as antiviral,[12] antiHIV,[13] antimicrobial,[14] anticancer,[15] anti-oxidative and antifungal activities.[16]

Different methods for the synthesis of thiazoles and 1,3,5-thiadiazines.

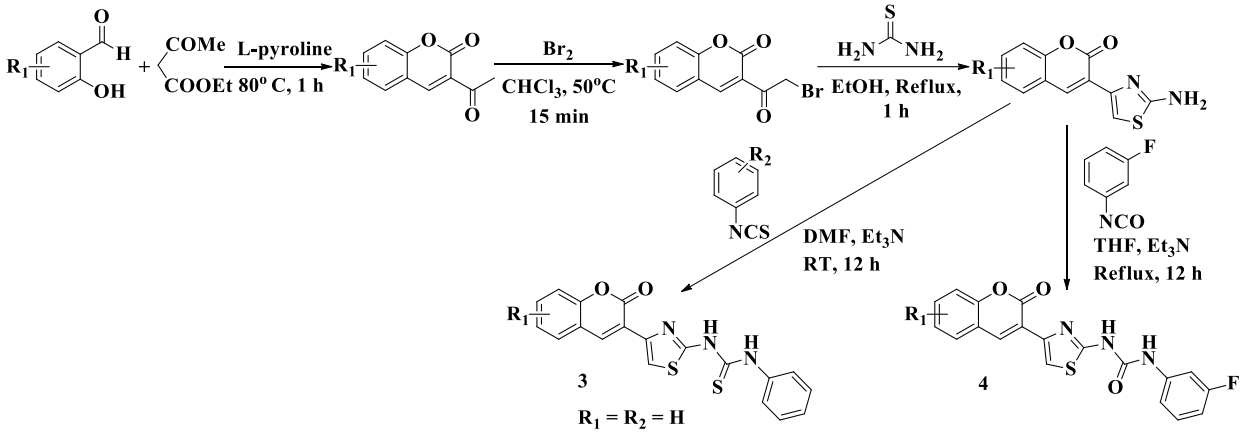
Borcea *et al.*[17] synthesized ethyl 4-methyl-2-(4-(2-methylthiazol-4-yl)phenyl)thiazole-5-carboxylate (**1**) from 4-(2-methylthiazol-4-yl)benzothioamide and ethyl 2-chloroacetoacetate. The required intermediate 2-methyl-4-(2-methyl thiazol-4-yl) benzonitrile was in turn obtained by condensation of thiourea with 4-(2-bromo acetyl) benzonitrile.



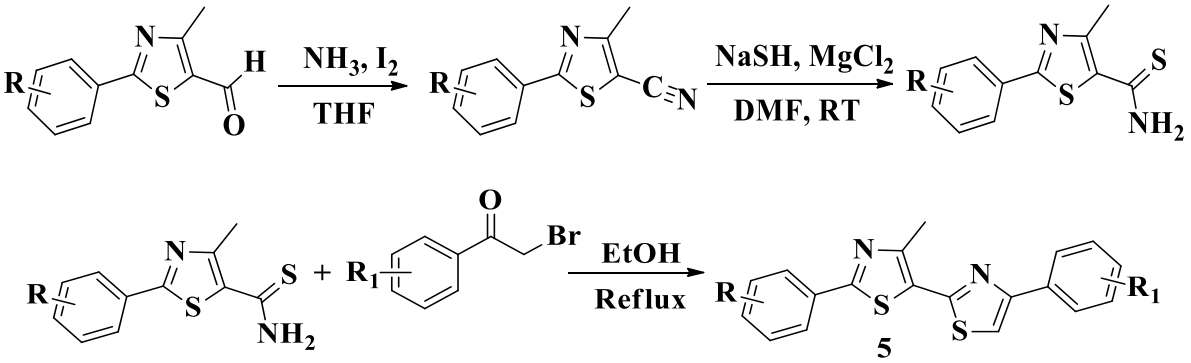
Compounds[18] **2** were synthesized by the condensation of 6-thiazolyl-3-acetyl coumarin, thiosemicarbazide and phenacyl bromides or 3-(2-bromoacetyl) coumarins.



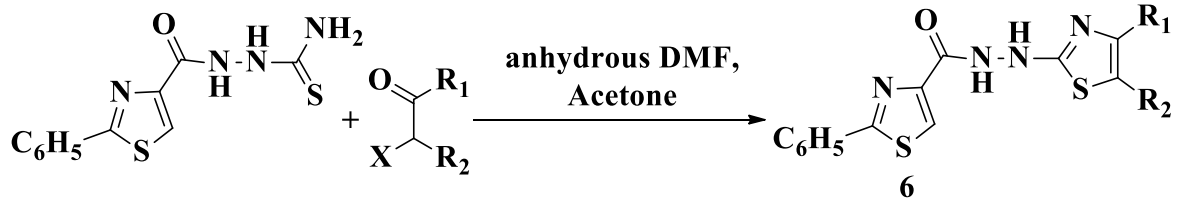
Kurt *et al.*[19] synthesized compounds **3** and **4** starting from substituted salicylaldehydes and ethyl 3-oxobutanoate as indicated in the following sequence of reactions.



4-Aryl-4[1]-methyl-2[1]-aryl-2,5[1]-bisthiazoles (**5**) synthesis was reported by Abhale *et al.*[20] by the reaction of 4-methyl-2-phenylthiazole-5-carbothioamide and phenacyl bromide. The thioamide intermediates were obtained by the reaction of 4-methyl-2-phenylthiazole-5-carbonitrile with NaSH. The required 4-methyl-2-phenylthiazole-5-carbonitriles in turn were obtained by the reaction of 4-methyl-2-phenylthiazol-5-carbaldehyde with NH_3/ I_2 in THF.

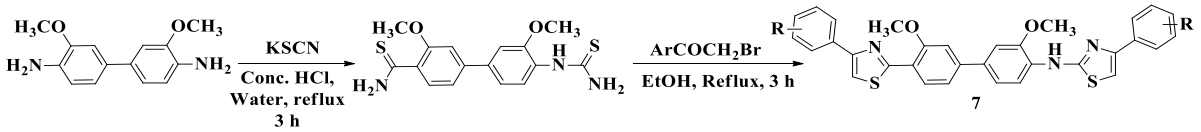


Zaharia *et al.*[21] synthesized hydrazino-bisthiazoles (**6**) through cyclocondensation of 4-(2-phenyl-1,3-thiazolo-4-carbonyl)-thiosemicarbazide and α-halogeno carbonyl compounds in anhydrous dimethylformamide and acetone.

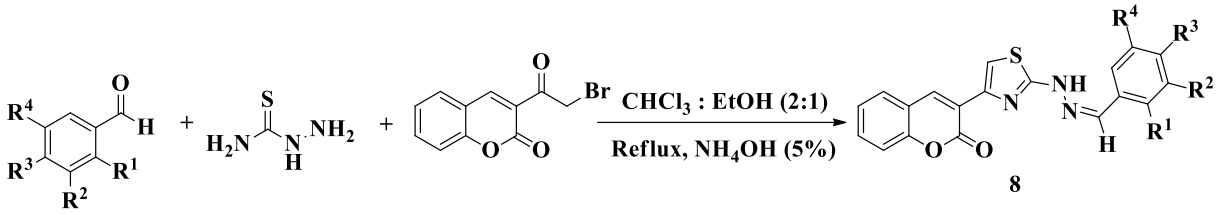


Turan-Zitouni *et al.*[22] synthesized a novel 3,3[1]-dimethoxy-N[4],N[41]-bis(4-phenylthiazol-2-yl)-[1,10-biphenyl]-4,4[1]-diamine (**7**). Reaction of 3, 3[1]-dimethoxybiphenyl-4,4[1]-diamine with KSCN, Conc. HCl in water resulted in the formation of 1,1[1]-(3,3[1]-dimethoxybiphenyl-4,4[1]-

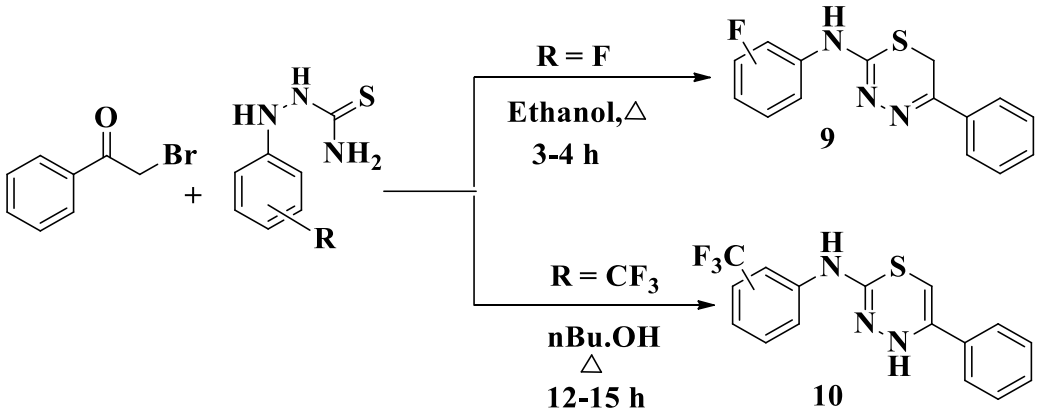
diyl)bis(thiourea). This intermediate on further reaction with substituted phenacyl bromides gave the title bis-thiazole derivatives.



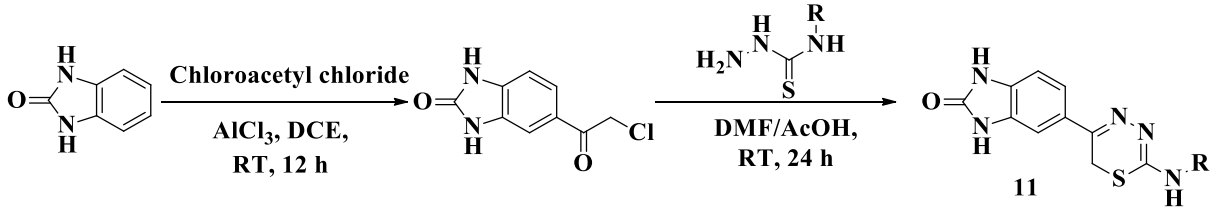
Arshad *et al.*[23] reported the synthesis of **8** from the condensation of various substituted aldehydes with thiosemicarbazide to thiosemicarbazone derivatives. These on cyclocondensation with 3-(2-bromoacetyl)coumarins gave title compounds with good yields.



Shchegol'kov *et al.*[24] synthesized fluorinated 2-amio-5-phenyl-1,3,4-thiadiazines from the reaction of α-bromo acetophenone and thiosemicarbazide in ethanol.



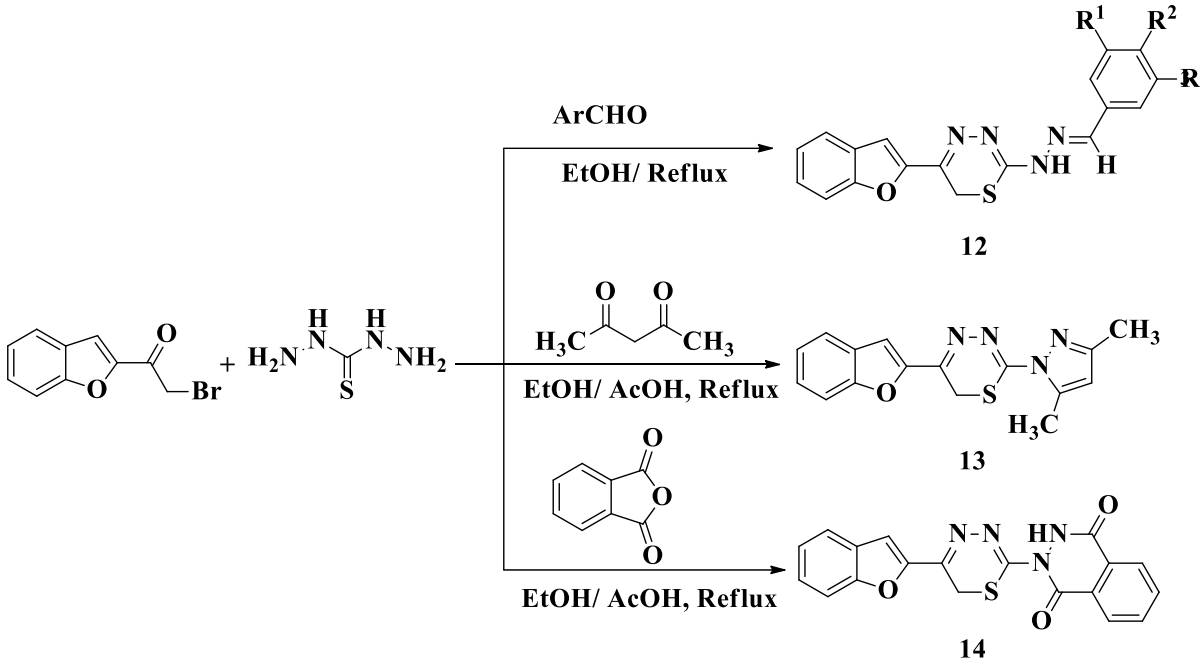
Kumar *et al.*[25] gave the synthesis of selective *N*-benzyl-5-(benzo[*d*]imidazol-2(3*H*)-one)-6*H*-1,3,4-thiadiazin-2-amines. Reaction of 1*H*-benzo[*d*]imidazole-2(3*H*)-one, chloroacetyl chloride and $AlCl_3$ in DCE at RT for 12 h gave 5-(2-chloroacetyl)-1*H*-benzo[*d*]imidazole-2(3*H*)-one. This on further reaction with *N*-alkyl thiosemicarbazides in DMF/AcOH gave 1,3,4-thiadiazines (**11**).



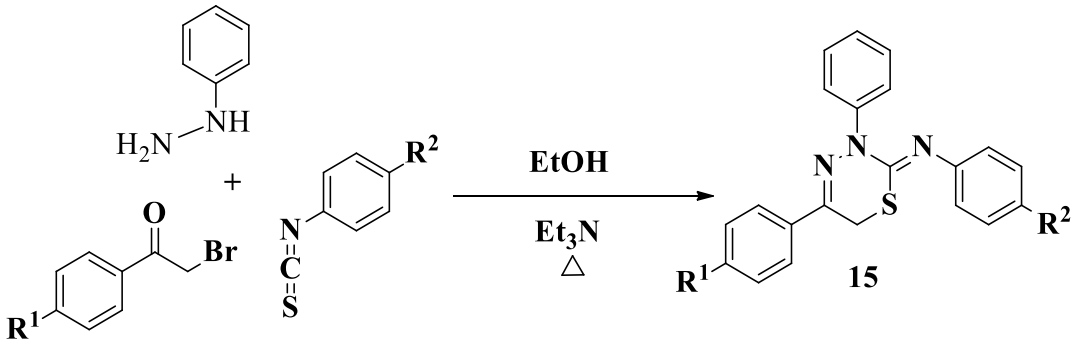
Ramagiri *et al.*[26] outlined the synthesis of 2,5-disubstituted-1,3,4-thiadiazines by the condensation of 2-(2-bromoacetyl)benzofuran, thiocarbohydrazide and different aldehydes in ethanol, refluxed for 4 hours gave corresponding thiadiazines (**12**).

Condensation of 2-(2-bromoacetyl) benzofuran, thiocarbohydrazide and acetyl acetone gave the compound **13**.

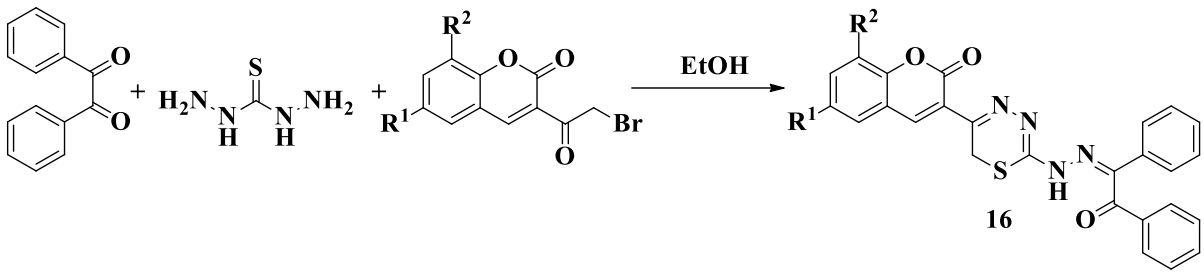
Cyclocondensation of 2-(2-bromoacetyl)benzofuran, thiocarbohydrazide and isobenzofuran-1,3-dione in alcohol having acetic acid upon heating gave corresponding compounds **14**.



Moghimi *et al.*[27] synthesized **15** starting from phenyl hydrazine, α-bromo aryl ketone and aryl isothiocyanates in ethanol and catalytic amount of triethylamine.



Cyclocondensation of 3-(2-bromoacetyl) coumarins, thiocarbohydrazide and benzil in ethanol gave compounds.[28](**16**)



PRESENT WORK

The synthesis of nitrogen and sulphur containing five and six membered heterocyclic systems play a vital role in drug discovery to identify new chemical entities (NCEs) of immense therapeutic potential. Thiazoles and 1,3,5-thiadiazines are most privileged structures that are widely explored for their range of pharmacological properties. As a part of our continuous search for potential bioactive molecules, a series of compounds having two thiazoles, one thiadiazine attached to thiazole were synthesized.

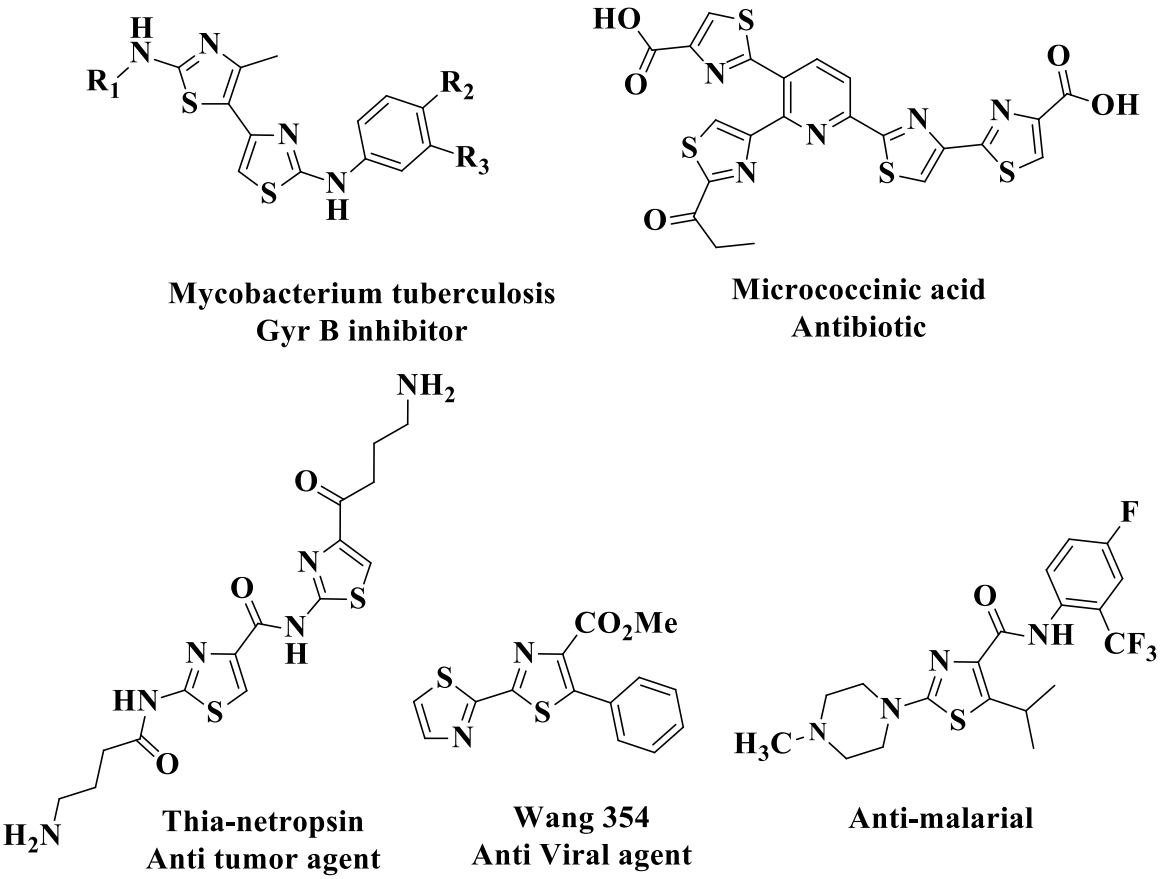
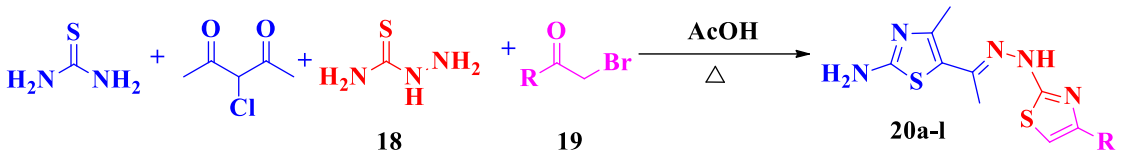


Fig.1. Biologically active molecules.

The pharmacological potency of bithiazoles and thiazole having thiadiazine drew our attention to synthesize these compounds containing both these heterocyclic units in a single molecule.

In this chapter, we are reporting the synthesis of bithiazoles by a 4CC reaction of thiourea, 3-chloroacetyl acetone, thiosemicarbazide and phenacyl bromide or 3-(2-bromoacetyl)coumarins in acetic acid (Scheme-1, method-1). In this method, the intermediate formed in the first step 2-amino-4-methyl-5-acetyl thiazole reacts with thiosemicarbazide and phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones gave final products **20**.

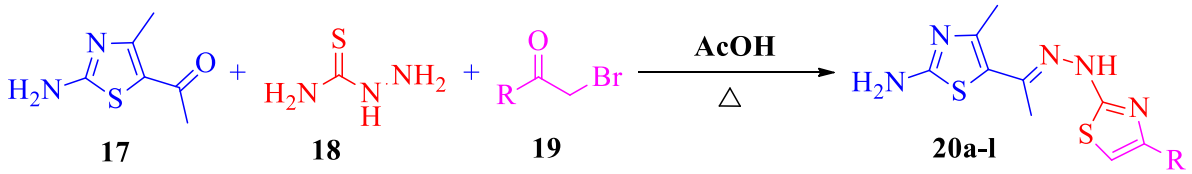


Scheme-1. Method-1: Synthesis of **20**.

Bi-thiazoles were also synthesized by a one-pot multicomponent method (Scheme-2, method-2) using 2-amino-4-methyl-5-acetylthiazole, thiosemicarbazide, phenacyl bromide or 3-(2-bromoacetyl)coumarins.

The 2-amino-4-methyl-5-acetylthiazole first reacts with thiosemicarbazide to give corresponding thiosemicarbazone of 2-amino-4-methyl-5-acetylthiazole. The *in situ* formed thiosemicarbazones react with phenacyl bromides or 3-(2-bromoacetyl)coumarins to give final product **20** by Hantzsch thiazole synthesis (Scheme-2). The yields of method-1 are good (93%) compared to method-2 (80%). The products obtained by both the methods are identical on examination of spectra of these compounds.

Among the two methods discussed above 1st method was more useful because of its less time and easy workup and general acceptability. The important features of the synthesis was that four hetero atom bonds like 2N-C, C=N and C-S bonds formed at once.

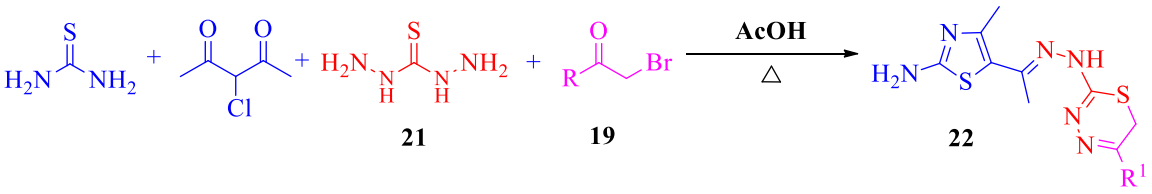


Scheme-2. Method-2: synthesis of bithiazoles

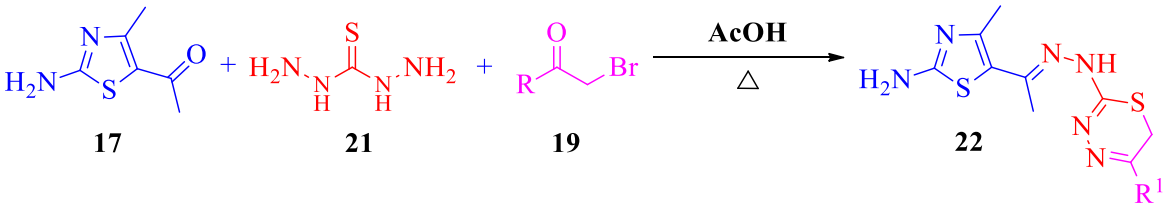
Table-1. Type of substituents and time taken to form **20a-l**

Entry	Product	R	Time (h) (Method-1)
1	20a	Phenacyl	4
2	20b	4-Fluoro phenacyl	4
3	20c	2,4-Dichloro phenacyl	3.5
4	20d	4-Bromo phenacyl	3.5
5	20e	4-Nitro phenacyl	3.5
6	20f	4-Methyl phenacyl	4
7	20g	4-Methoxy phenacyl	4
8	20h	3-Coumarinyl	4
9	20i	6-Bromo-3-coumarinyl	4
10	20j	6-Chloro-3-coumarinyl	3.5
11	20k	6,8-Dibromo-3-coumarinyl	4
12	20l	8-Methoxy-3-coumarinyl	4

Similarly condensation of thiourea, 3-chloroacetyl acetone, thiocarbohydrazide, phenacyl bromide or 3-(2-bromoacetyl)coumarins in acetic acid afforded the products **22**. This is a four component condensation reaction (Scheme-3, method-1).



Scheme-3. Method-1: one-pot multicomponent synthesis of compound **22**.



Scheme-4. Method-2: Synthesis of thiazolothiadiazines by three component condensation.

Table-2. Type of the substituents and reaction time of **22a-k**

Entry	Compound	R^1	Time in hours (Method-1)
1	22a	Phenacyl	4
2	22b	4-Nitro phenacyl	3.5
3	22c	4-Fluoro phenacyl	3.5
4	22d	2,4-Dichloro phenacyl	3.5
5	22e	4-Bromo phenacyl	4
6	22f	4-Methoxy phenacyl	4
7	22g	4-Phenyl phenacyl	4
8	22h	3-Coumarinyl	4
9	22i	6-Bromo-3-coumarinyl	4
10	22j	6,8-Dibromo-3-coumarinyl	4
11	22k	8-Methoxy-6-nitro-3-coumarinyl	4

Compound **22** may also be formed by another method involving condensation of 2-amino-4-methyl-5-acetylthiazole which on reaction with thiocarbohydrazide gives thiocarbohydrazone of 2-amino-4-methyl-5-acetylthiazole. The *in situ* formed thiocarbohydrazone of 2-amino-4-methyl-5-acetylthiazole undergoes cyclization with α-halo ketones such as phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones to yield the target compound **22** as given in scheme-4. Advantage of our reaction is that without isolation of intermediate thiosemicarbazone of **17** or thiocarbohydrazone of **17**, we have synthesized the final products (**20** and **22**) in a single step. In addition to this, the reaction involves concomitant formation of C=N, C-N and C-S bonds. The yields of the products are 92%. The method-1 involves less time, simple workup and is of more applicability.

The compounds formed in first and second method are same. In the current process first method was found to be more useful than second method. The structure of **22** was confirmed by their analytical and spectral data.

CONCLUSION

In conclusion, we have developed a straight forward thiazolyl hydrazono thiazolamines (**20**) and 1,3,4-thiadiazinylidene hydrazono thiazolamines (**22**) synthesis. The present process involves no harsh conditions, no complex workup, no column chromatographic purification and good to better yields.

EXPERIMENTAL SECTION

Starting materials: 2-Amino-4-methyl-5-acetylthiazole, thiosemicarbazide and phenacyl bromides were procured from commercial source. Different 3-(2-bromoacetyl)coumarins were prepared by following reported method.

General procedure for the preparation of 20.

Method-1: Four component reaction:

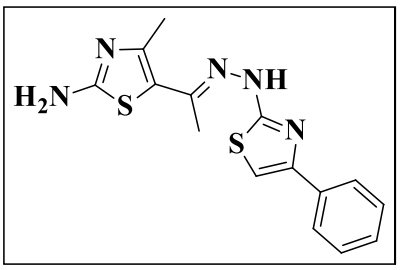
An equimolar amount of thiourea (1 mmol), 3-chloroacetyl acetone (1 mmol) was taken in acetic acid (4 ml) and refluxed at 70 ^{o}C for 2 hours (conformed by TLC by using ethyl acetate and n-hexane 40%), then thiosemicarbazide (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl) coumarin (1 mmol) has been added and reflux was continued for 2 hours. The product separated was subjected to filtration, dried and purified from methanol.

Method-2: Three component reaction:

An equimolar amount of 2-amino-4-methyl-5-acetylthiazole (1 mmol), hydrazinecarbothioamide (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)coumarin (1mmol) were reacted in acetic acid (2 ml) at 70 ^{o}C for 2 hours. (monitored by TLC). Solid formed was filtered, dried and recrystallized from methanol to yield **20**.

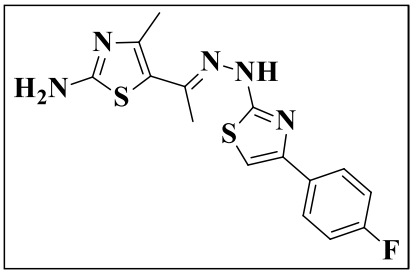
SPECTRAL DATA

4-Methyl-5-(1-(2-(4-phenylthiazol-2-yl)hydrazono)ethyl)thiazol-2-amine (20a).



Color: white solid; mp: 195-196 $^{\circ}$C; yield: (0.365g, 90%); IR (KBr, Wave number, cm^{-1}): 3448 (NH_2), 1619 (C=N), 1578 (C=C); PMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.30-7.33 (m, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 9.39 (s, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.1, 15.8, 104.4, 119.1, 125.9, 128.1, 129.1, 133.8, 134.5, 141.9, 149.8, 167.8, 169.5 ppm; ESI-MS: m/z 330 $[M+H]^+$; Anal. Calcd. for $C_{15}H_{15}N_5S_2$: C, 54.69; H, 4.59; N, 21.26; S, 19.47. Found: C, 54.62; H, 4.63; N, 21.21; S, 19.42%.

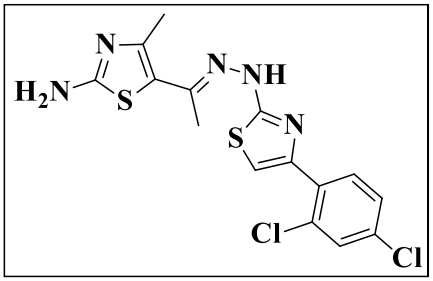
5-(1-(2-(4-(4-Fluorophenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (20b).



Color: white solid; mp: 211-213 $^{\circ}$C; yield: (0.428g, 81%); IR (KBr, Wave number, cm^{-1}): 3442 (NH_2), 1621 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.25 (t, J = 8.8 Hz, 2H), 7.32 (s, 1H), 7.41 (t, J = 8.8 Hz, 1H), 7.87-7.90 (m, 2H), 7.95-7.99(m, 1H), 13.36(s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.1, 15.8, 115.6, 115.8, 116.0, 116.4, 116.7, 128.0, 130.0, 130.1, 150.8, 164.5, 167.7 ppm; ESI-MS: m/z 348 $[M+H]^+$; Anal. Calcd. for

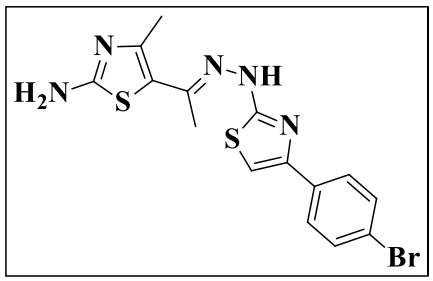
$C_{15}H_{14}FN_5S_2$: C, 51.85; H, 4.06; N, 20.16; S, 18.46. Found: C, 51.81; H, 4.12; N, 20.20; S, 18.41%.

5-(1-(2-(4-(2,4-Dichlorophenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (20c).



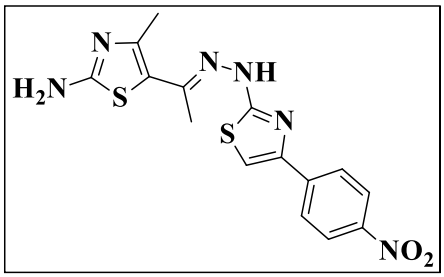
Color: white solid; mp: 170-172 °C; yield: (0.457g, 87%); IR (KBr, Wave number, cm^{-1}): 3448 (NH_2), 1624 (C=N); PMR (400 MHz, DMSO-d_6, ppm): δ 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.40 (s, 1H), 7.50-7.53 (m, 1H), 7.70 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 9.37 (s, 2H), 11.56(s, 1H); CMR (100 MHz, DMSO-d_6, ppm): δ 14.3, 15.8, 110.1, 118.8, 127.9, 130.2, 132.0, 132.4, 132.6, 133.0, 134.6, 141.9, 146.05, 167.7, 168.7; ESI-MS: m/z 416 $[M+NH_4]^+$; Anal. Calcd. for $C_{15}H_{13}Cl_2N_5S_2$: C, 45.23; H, 3.29; N, 17.58; S, 16.10. Found: C, 45.27; H, 3.23; N, 17.52; S, 16.17%.

5-(1-(2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (20d).



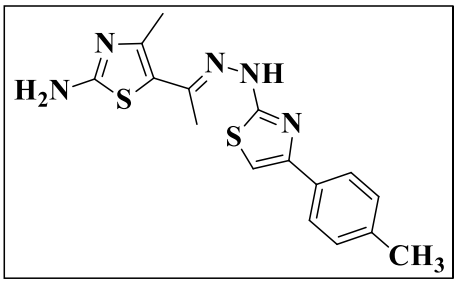
Color: white solid; mp: 185-187 °C; yield: (0.443g, 92%); IR (KBr, Wave number, cm^{-1}): 3427 (NH_2), 1624 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.41 (s, 1H), 7.61 (d, J = 11.6 Hz, 2H), 7.78-7.83 (m, 3H), 9.29 (s, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 13.8, 15.3, 104.9, 120.6, 127.5, 128.9, 131.5, 132.0, 133.5, 133.9, 141.4, 164.0, 167.3, 169.1, 171.9 ppm; ESI-MS: m/z 410 $[M+2]^+$; Anal. Calcd. for $C_{15}H_{14}BrN_5S_2$: C, 44.12; H, 3.46; N, 17.15; S, 15.71. Found: C, 44.16; H, 3.41; N, 17.11; S, 15.76%.

4-Methyl-5-(1-(2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-amine (20e).



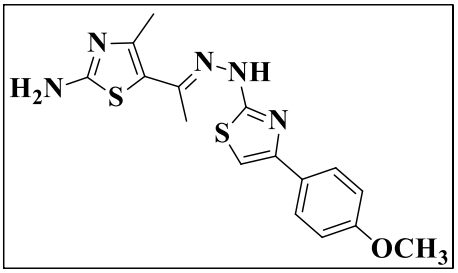
Color: white solid; mp: 207-209 °C; yield: (0.415g, 90%); IR (KBr, Wave number, cm^{-1}): 3430 (NH_2), 1638 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.70 (s, 1H), 8.07-8.15 (m, 4H), 8.28 (d, J = 8.8 Hz, 2H), 11.37 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.2, 16.4, 109.3, 118.8, 124.5, 126.7, 141.1, 143.2, 146.6, 155.2, 156.7, 167.4, 170.1 ppm; ESI-MS: m/z 375 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{14}N_6O_2S_2$: C, 48.11; H, 3.77; N, 22.44; S, 17.13. Found: C, 48.16; H, 3.71; N, 22.40; S, 17.10%.

4-Methyl-5-(1-(2-(4-(p-tolyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-amine (20f).



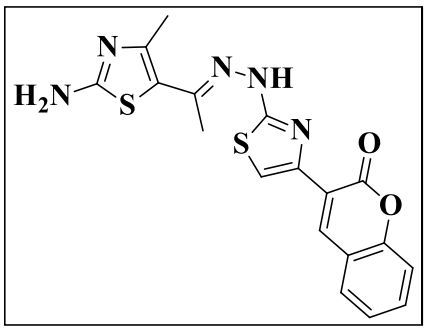
Color: white solid; mp: 213-215 °C; yield: (0.403g, 85%); IR (KBr, Wave number, cm^{-1}): 3436 (NH_2), 1622 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.97 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 9.38 (s, 2H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.1, 15.8, 21.2, 103.4, 125.9, 129.6, 130.0, 131.8, 133.7, 142.1, 151.7, 167.7, 169.2, 169.8 ppm; ESI-MS: m/z 344 $[M+1]^+$; Anal. Calcd. for $C_{16}H_{17}N_5S_2$: C, 55.95; H, 4.99; N, 20.39; S, 18.67. Found: C, 55.91; H, 4.92; N, 20.31; S, 18.64%.

5-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (20g).



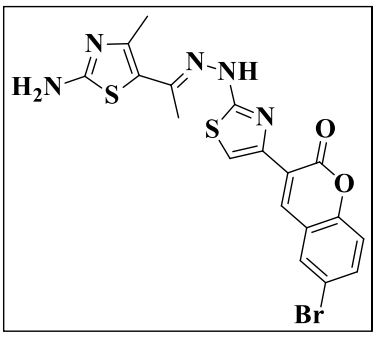
Color: white solid; mp: 188-190 °C; yield: (0.437g, 82%); IR (KBr, Wave number, cm^{-1}): 3420 (NH_2), 1615 (C=N); PMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.89 (s, 1H, NH), 6.97 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 9.38 (s, 2H); CMR (100 MHz, DMSO-d_6, ppm): δ 14.1, 15.7, 55.6, 102.1, 114.4, 115.1, 119.1, 127.2, 130.5, 132.4, 133.2, 133.7, 141.9, 159.3, 167.8, 169.5; ESI-MS: m/z 360 $[M+1]^+$; Anal. Calcd. for $C_{16}H_{17}N_5OS_2$: C, 53.46; H, 4.77; N, 19.48; S, 17.84. Found: C, 53.49; H, 4.71; N, 19.42; S, 17.88%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)thiazol-4-yl)-2*H*-chromen-2-one (20h).



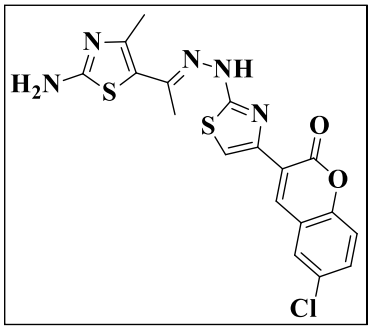
Color: white solid; mp: 255-257 °C; yield: (0.426g, 93%); IR (KBr, Wave number, cm^{-1}): 3401 (NH_2), 1706 (lactone C=O), 1577 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.40 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.81 (t, J = 7.6 Hz, 2H), 8.54 (s, 1H), 9.17 (s, 2H) 11.59 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.5, 15.8, 111.6, 116.3, 118.9, 119.5, 120.8, 125.2, 129.2, 132.2, 135.0, 138.5, 152.7, 159.1, 167.7, 168.9 ppm; ESI-MS: m/z 398 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{15}N_5O_2S_2$: C, 54.39; H, 3.80; N, 17.62; S, 16.13. Found: C, 54.33; H, 3.84; N, 17.67; S, 16.17%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)thiazol-4-yl)-6-bromo-2*H*-chromen-2-one (20i).



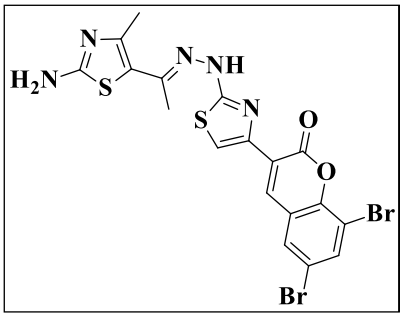
Color: white solid; mp: 209-211 °C; yield: (0.523g, 91%); IR (KBr, Wave number, cm^{-1}): 3400 (NH_2), 1718 (lactone C=O), 1629 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.42 (d, J = 8.8 Hz, 1H), 7.75-7.77 (m, 1H), 7.83 (s, 1H), 8.07 (s, 1H), 8.44 (s, 1H), 9.20 (s, 2H) 11.62 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 15.9, 112.6, 116.9, 118.5, 121.5, 130.9, 131.2, 134.4, 136.9, 137.4, 144.2, 151.7, 158.6, 167.7, 169.0, 169.8, 172.5 ppm; ESI-MS: m/z 476 $[M]^+$; Anal. Calcd. for $C_{18}H_{14}BrN_5O_2S_2$: C, 45.38; H, 2.96; N, 14.70; S, 13.46. Found: C, 45.41; H, 3.00; N, 14.73; S, 13.41%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)thiazol-4-yl)-6-chloro-2*H*-chromen-2-one (20j).



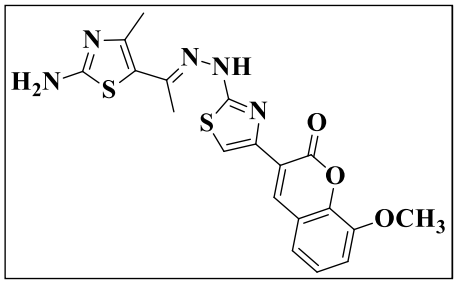
Color: white solid; mp: 203-205 °C; yield: (0.478g, 90%); IR (KBr, Wave number, cm^{-1}): 3397 (NH_2), 1723 (lactone C=O), 1623 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.49 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.83 (s, 1H), 7.96 (s, 1H), 8.46 (s, 1H), 8.96 (s, 2H), 11.57 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.6, 16.0, 102.0, 105.9, 109.0, 112.5, 112.7, 118.2, 119.0, 120.9, 128.0, 131.6, 135.3, 137.3, 144.4, 151.3, 159.9, 169.1 ppm; ESI-MS: m/z 432 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{14}ClN_5O_2S_2$: C, 50.05; H, 3.27; N, 16.21; S, 14.85. Found: C, 50.12; H, 3.24; N, 16.16; S, 14.88%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)thiazol-4-yl)-6,8-dibromo-2*H*-chromen-2-one (20k).



Color: white solid; mp: 238-240 °C; yield: (0.652g, 85%); IR (KBr, Wave number, cm^{-1}): 3392 (NH_2), 1723 (lactone C=O), 1630 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.83 (s, 1H), 8.08-8.11 (m, 2H), 8.38 (s, 1H), 9.07 (s, 2H), 11.58 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.6, 15.8, 110.2, 113.2, 116.9, 119.0, 122.4, 130.5, 135.3, 136.1, 136.3, 141.8, 143.9, 148.4, 157.9, 167.7, 168.9, 172.3 ppm; ESI-MS: m/z 555 $[M]^+$; Anal. Calcd. for $C_{18}H_{13}Br_2N_5O_2S_2$: C, 38.93; H, 2.36; Br, 28.78; N, 12.61; S, 11.55. Found: C, 38.97; H, 2.31; N, 12.66; S, 11.50%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)thiazol-4-yl)-8-methoxy-2*H*-chromen-2-one (20l).



Color: white solid; mp: 216-218 °C; yield: (0.496g, 86%); IR (KBr, Wave number, cm^{-1}): 3407 (NH_2), 1710 (lactone C=O), 1624 (C=N); PMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 7.33 (t, J = 7.2Hz, 3H), 7.80 (s, 1H), 8.15 (s, 1H), 8.51 (s, 1H), 9.14 (s, 2H); ESI-MS: m/z 426 $[M-1]^+$; Anal. Calcd. for $C_{19}H_{17}N_5O_3S_2$: C, 53.38; H, 4.01; N, 16.38; S, 15.00. Found: C, 55.32, H, 4.12; N, 16.32; S, 14.96%.

General procedure for the synthesis of compounds (22)

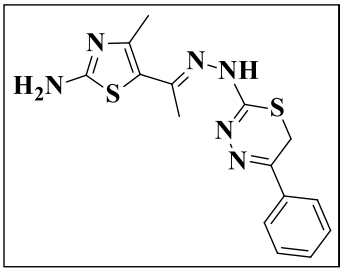
Method-1: Four component reaction:

An equimolar amount of thiourea (1 mmol), 3-chloroacetyl acetone (1 mmol) was refluxed in acetic acid (4 ml) at 70 °C approximately 2 hours (checked by TLC). Later thiocarbohydrazide (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)coumarin (1 mmol) addition was done and refluxed at 70 °C for 2 hours. After separation of solid, it was filtered and recrystallized from methanol to yield **22**.

Method-2: Three component reaction:

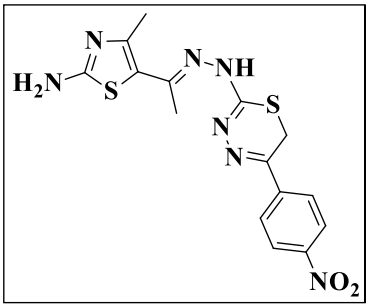
An equimolar mixture of 2-amino-4-methyl-5-acetylthiazole (1 mmol), thiocarbohydrazide (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)coumarin (1 mmol) was refluxed in acetic acid (2 ml) at 70 °C approximately 2 hours. (checked by TLC). Separated solid was subjected to filtration, dried and recrystallized from methanol to give **22**.

4-Methyl-5-(1-(2-(5-phenyl-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)thiazol-2-amine (22a).



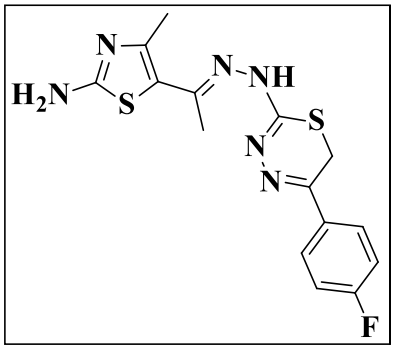
Color: white solid; mp: 230-232 °C; yield: (0.386g, 89%); IR (KBr, Wave number, cm^{-1}): 3400 (NH_2), 1605 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.94 (s, 2H, CH_2 of thiadiazine), 7.45-7.46 (m, 3H), 7.79-7.81 (m, 2H), 8.53 (s, 2H), 11.47 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 15.9, 18.7, 22.2, 120.4, 126.3, 129.1, 130.0, 135.3, 147.0, 152.3, 160.9, 168.0, 170.9 ppm; ESI-MS: m/z 343 $[M-1]^+$; Anal. Calcd. for $C_{15}H_{16}N_6S_2$: C, 52.30; H, 4.68; N, 24.40; S, 18.62. Found: C, 52.34; H, 4.61; N, 24.45; S, 18.65%.

4-Methyl-5-(1-(2-(5-(4-nitrophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)thiazol-2-amine (22b)



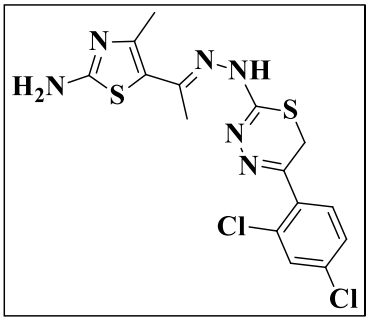
Color: white solid; mp: 194-196 °C; yield: (0.422g, 92%); IR (KBr, Wave number, cm^{-1}): 3400 (NH_2), 1663 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.04 (s, 2H, CH_2 of thiadiazine), 8.04 (d, J = 9.2 Hz, 2H), 8.30 (d, J = 9.2 Hz, 2H), 8.66 (s, 2H), 11.84 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 15.9, 18.6, 29.9, 120.2, 121.7, 124.3, 127.2, 141.5, 143.9, 147.9, 153.1, 157.8, 159.5, 168.1, 170.9 ppm; ESI-MS: m/z 390 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{15}N_7O_2S_2$: C, 46.26; H, 3.88; N, 25.18; S, 16.47. Found: C, 46.22; H, 3.82; N, 25.14; S, 16.52%.

5-(1-(2-(5-(4-Fluorophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (22c)



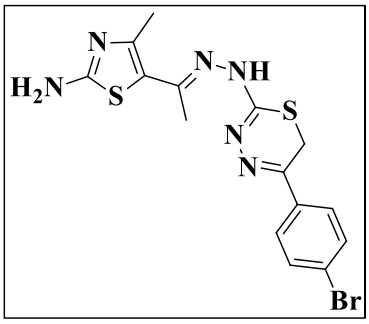
Color: white solid; mp: 204-206 °C; yield: (0.402g, 90%); IR (KBr, Wave number, cm^{-1}): 3437 (NH_2), 1626 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.96 (s, 2H, CH_2 of thiadiazine), 7.31 (t, J = 8.8 Hz, 2H), 7.84-7.87 (m, 2H), 9.17 (s, 2H), 11.58 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.6, 15.6, 22.3, 116.0, 116.2, 120.4, 128.6, 128.7, 131.8, 135.8, 146.2, 151.6, 161.7, 164.6, 168.1 ppm; ESI-MS: m/z 363 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{15}FN_6S_2$: C, 49.71; H, 4.17; N, 23.19; S, 17.69. Found: C, 49.67; H, 4.21; N, 23.15; S, 17.73%.

5-(1-(2-(5-(2,4-Dichlorophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (22d)



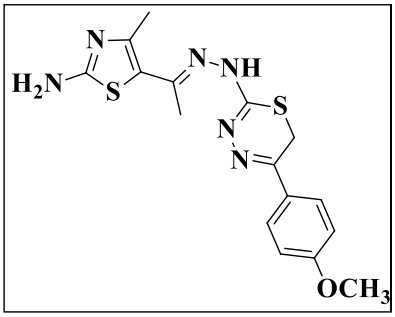
Color: white solid; mp: 211-213 °C; yield: (0.474g, 87%); IR (KBr, Wave number, cm^{-1}): 3431 (NH_2), 1627 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.79 (s, 2H, CH_2 of thiadiazine), 7.48-7.51 (m, 3H), 7.75 (s, 1H), 11.43 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.4, 17.5, 25.4, 120.2, 128.1, 129.8, 132.5, 132.8, 135.3, 146.3, 149.6, 153.6, 159.9, 162.8, 168.2 ppm; ESI-MS: m/z 413 $[M+1]^+$; Anal. Calcd. for $C_{15}H_{14}Cl_2N_6S_2$: C, 43.59; H, 3.41; N, 20.33; S, 15.51. Found: C, 43.55; H, 3.47; N, 20.37; S, 15.56%.

5-(1-(2-(5-(4-Bromophenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (22e)



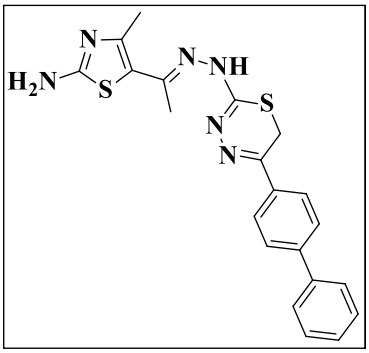
Color: white solid; mp: 193-195 °C; yield: (0.497g, 85%); IR (KBr, Wave number, cm^{-1}): 3400 (NH_2), 1624 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.92 (s, 2H, CH_2 of thiadiazine), 7.65 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 8.03 (s, 2H), 11.46 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.2, 17.0, 21.9, 120.3, 123.3, 128.2, 132.0, 134.7, 143.5, 145.6, 153.1, 159.8, 167.9 ppm; Anal. Calcd. for $C_{15}H_{15}BrN_6S_2$: C, 42.56; H, 3.57; N, 19.85; S, 15.15. Found: C, 42.62; H, 3.52; N, 19.81; S, 15.19%.

5-(1-(2-(5-(4-Methoxyphenyl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (22f)



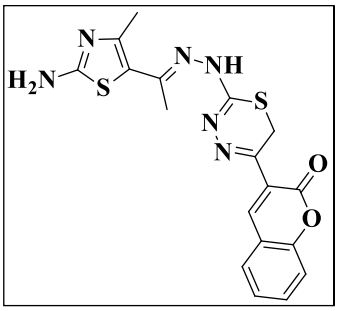
Color: white solid; mp: 240-242 °C; yield: (0.44g, 85%); IR (KBr, Wave number, cm^{-1}): 3380 (NH_2), 1604 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2 of thiadiazine), 7.01 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 9.07 (s, 2H), 11.42 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.3, 15.1, 21.8, 55.3, 114.0, 120.0, 127.1, 127.4, 135.8, 146.8, 150.8, 160.4, 161.6, 167.6 ppm; ESI-MS: m/z 375 $[M+1]^+$; Anal. Calcd. for $C_{16}H_{18}N_6OS_2$: C, 51.32; H, 4.84; N, 22.44; S, 17.12. Found: C, 51.35; H, 4.80; N, 22.47; S, 17.16%.

5-(1-(2-(5-([1,1^1-Biphenyl]-4-yl)-6*H*-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (22g)



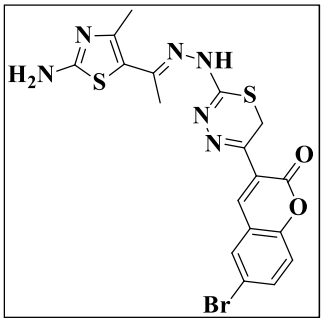
Color: white solid; mp: 236-238 °C; yield: (0.488g, 86%); IR (KBr, Wave number, cm^{-1}): 3434 (NH_2), 1627 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.01 (s, 2H, CH_2 of thiadiazine), 7.41 (d, J = 6.8 Hz, 2H), 7.49 (t, J = 7.2 Hz, 2H), 7.73-7.79 (m, 4H), 7.91 (d, J = 8.0 Hz, 1H), 9.30 (s, 2H), 11.65 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.3, 16.7, 29.7, 127.1, 128.3, 129.5, 139.6, 168.2, 169.9, 189.5 ppm; ESI-MS: m/z 421 $[M+1]^+$; Anal. Calcd. for $C_{21}H_{20}N_6S_2$: C, 59.97; H, 4.79; N, 19.98; S, 15.25. Found: C, 60.00; H, 4.13; N, 19.94; S, 15.20%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6*H*-1,3,4-thiadiazin-5-yl)-2*H*-chromen-2-one (22h).



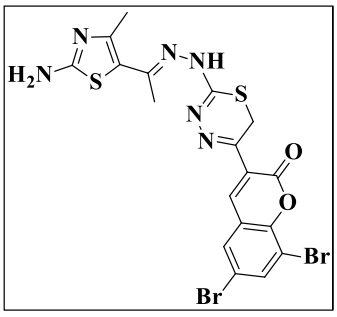
Color: white solid; mp: 214-216 °C; yield: (0.457g, 90%); IR (KBr, Wave number, cm^{-1}): 3392 (NH_2), 1710 (lactone C=O), 1605 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.43 (s, NH), 3.86 (s, 2H, CH_2 of thiadiazine), 7.30-7.40 (m, 3H, ArH), 7.65- 7.75 (m, 3H, 1 ArH and NH_2), 8.45 (s, 1H, coumarin 4th proton) ppm; CMR (100 MHz, DMSO-d_6): δ 16.6, 17.7, 23.5, 116.1, 118.9, 119.9, 123.7, 125.0, 129.4, 132.7, 141.3, 144.3, 146.7, 153.5, 153.6, 159.2, 159.4, 167.6 ppm; ESI-MS: m/z 413 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{16}N_6O_2S_2$: C, 52.41; H, 3.91; N, 20.37; S, 15.55. Found: C, 52.45; H, 3.95; N, 20.32; S, 15.51%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6*H*-1,3,4-thiadiazin-5-yl)-6-bromo-2*H*-chromen-2-one (22i).



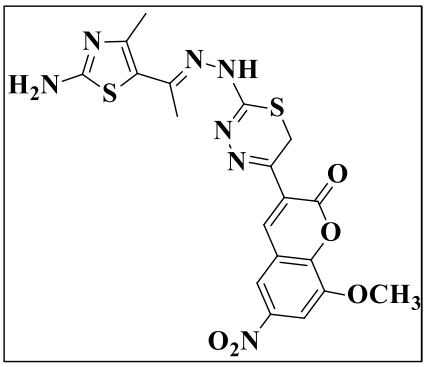
Color: white solid; mp: 219-221 °C; yield: (0.545g, 90%); IR (KBr, Wave number, cm^{-1}): 3421 (NH_2), 1722 (lactone C=O), 1623 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.86 (s, 2H, CH_2 of thiadiazine), 7.44 (d, J = 8.8 Hz, 2H), 8.14 (s, 1H), 8.25 (s, 1H), 8.65 (s, 2H), 11.73 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.7, 15.7, 23.7, 116.9, 11.8, 120.3, 121.2, 125.0, 131.6, 135.3, 140.4, 144.4, 149.6, 152.2, 152.9, 159.2, 161.5, 168.2 ppm; ESI-MS: m/z 490 $[M-1]^+$; Anal. Calcd. for $C_{18}H_{15}BrN_6O_2S_2$: C, 44.0; H, 3.08; Br, 16.26, N, 17.10; S, 13.05. Found: C, 39.96; H, 3.12; N, 17.15; S, 12.96%.

3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6*H*-1,3,4-thiadiazin-5-yl)-6,8-dibromo-2*H*-chromen-2-one (22j).

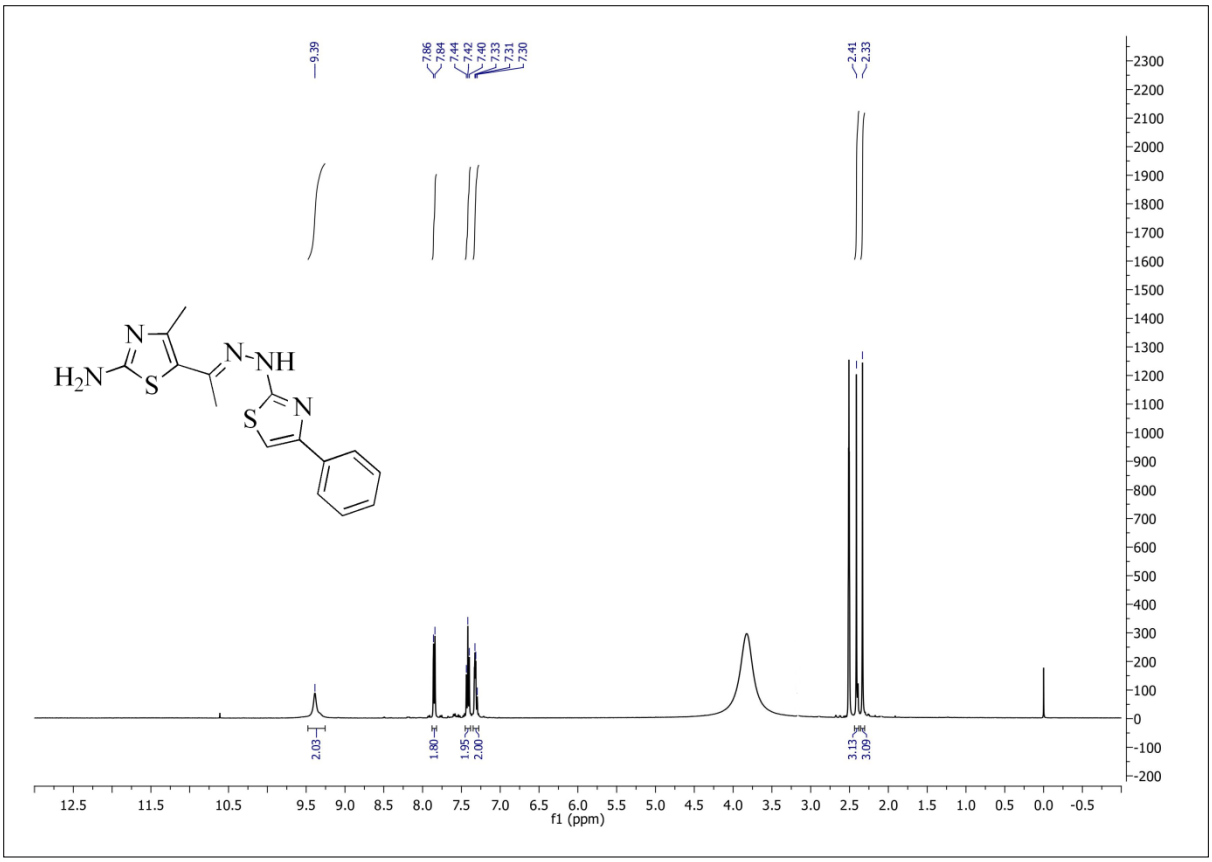


Color: white solid; mp: 226-228 °C; yield: (0.619g, 92%); IR (KBr, Wave number, cm^{-1}): 3394 (NH_2), 1730 (lactone C=O), 1623 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.85 (s, 2H, CH_2 of thiadiazine), 8.05 (s, 1H), 8.16 (s, 1H), 8.28 (s, 1H), 8.72 (s, 2H), 11.75 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 15.3, 16.0, 23.6, 110.5, 116.9, 120.4, 122.2, 125.7, 131.3, 135.3, 137.2, 139.8, 141.5, 143.7, 149.8, 153.0, 158.6, 168.1 ppm; ESI-MS: m/z 571 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{14}Br_2N_6O_2S_2$: C, 37.91; H, 2.47; N, 14.74; S, 11.25. Found: C, 37.96; H, 2.42; N, 14.72; S, 11.29%.

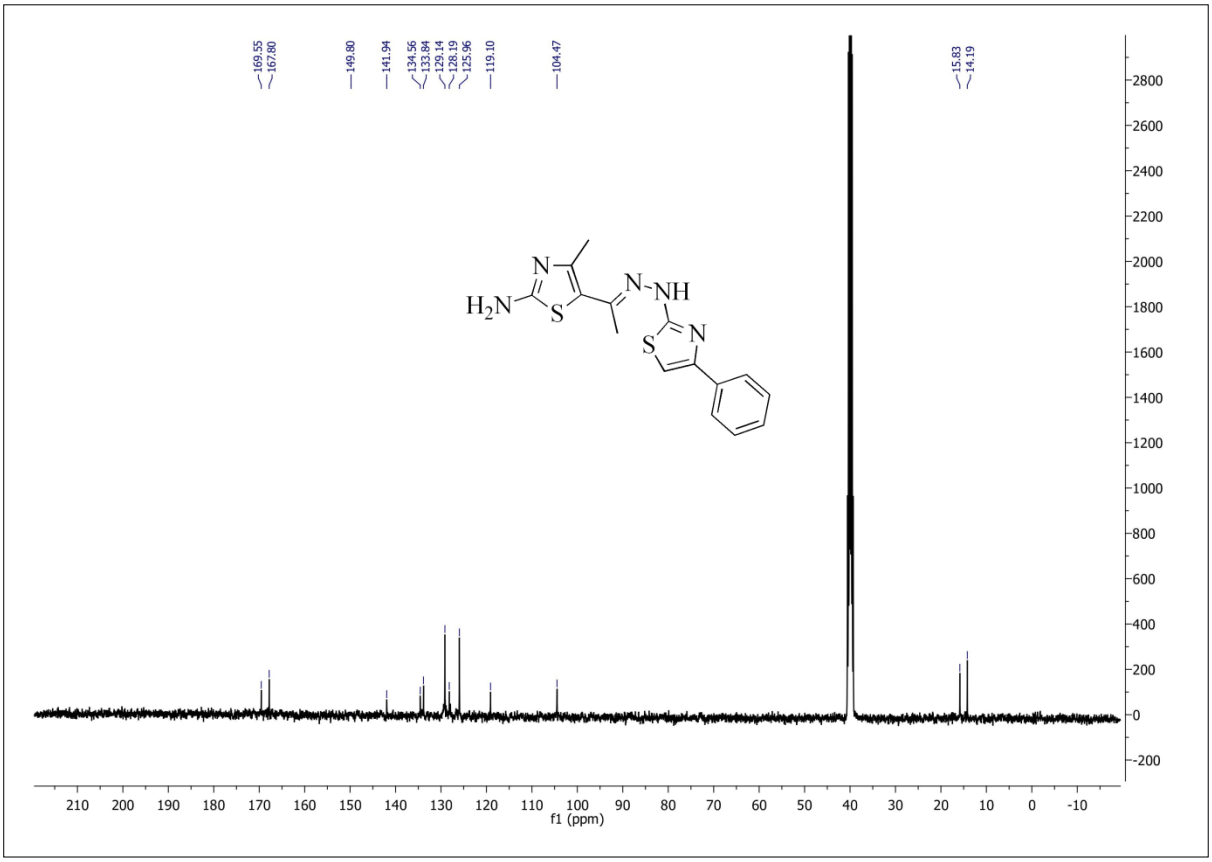
3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6*H*-1,3,4-thiadiazin-5-yl)-8-methoxy-6-nitro-2*H*-chromen-2-one (22k).



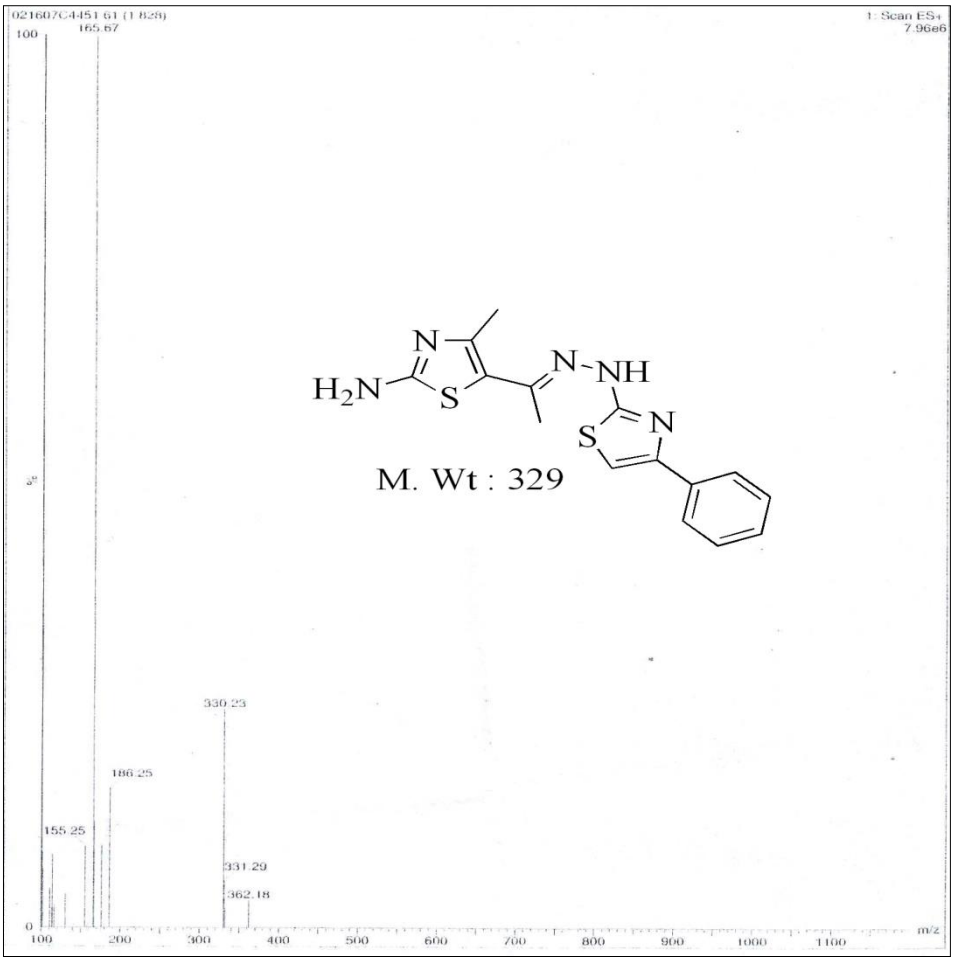
Color: white solid; mp: 234-236 °C; yield: (0.566g, 86%); IR (KBr, Wave number, cm^{-1}): 3400 (NH_2), 1734 (lactone C=O), 1602 (C=N); PMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.94 (s, 2H, CH_2 of thiadiazine), 4.05 (s, 3H, OCH_3), 7.56 (s, 1H), 7.83 (s, 2H), 8.26 (s, 1H), 8.48 (s, 1H), 8.70 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.2, 18.7, 29.8, 56.8, 112.6, 116.7, 119.5, 121.7, 125.7, 139.9, 144.1, 147.3, 148.4, 153.5, 153.9, 158.0, 167.7, 170.9, 188.7 ppm; ESI-MS: m/z 488 $[M+1]^+$; Anal. Calcd. for $C_{19}H_{17}N_7O_5S_2$: C, 46.81; H, 3.51; N, 20.11; S, 13.15. Found: C, 46.85; H, 3.35; N, 20.15; S, 13.18%.



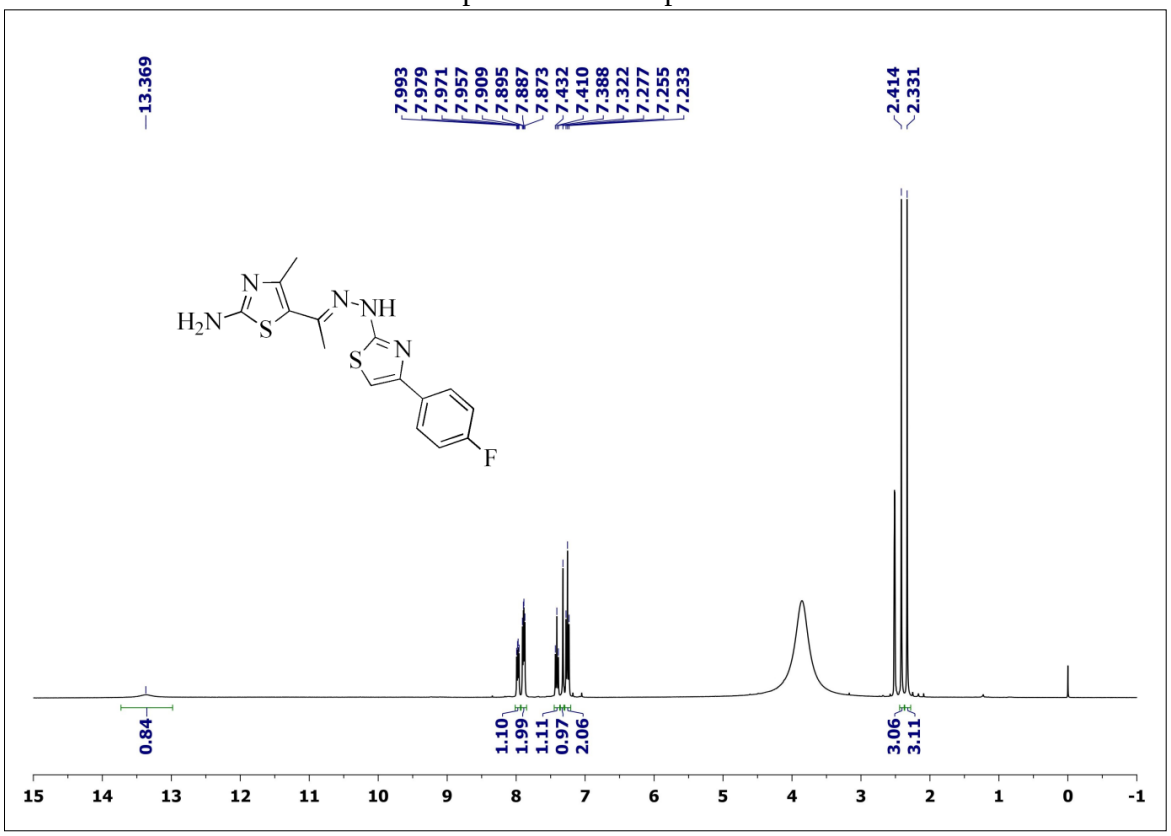
PMR Spectrum of compound **20a**



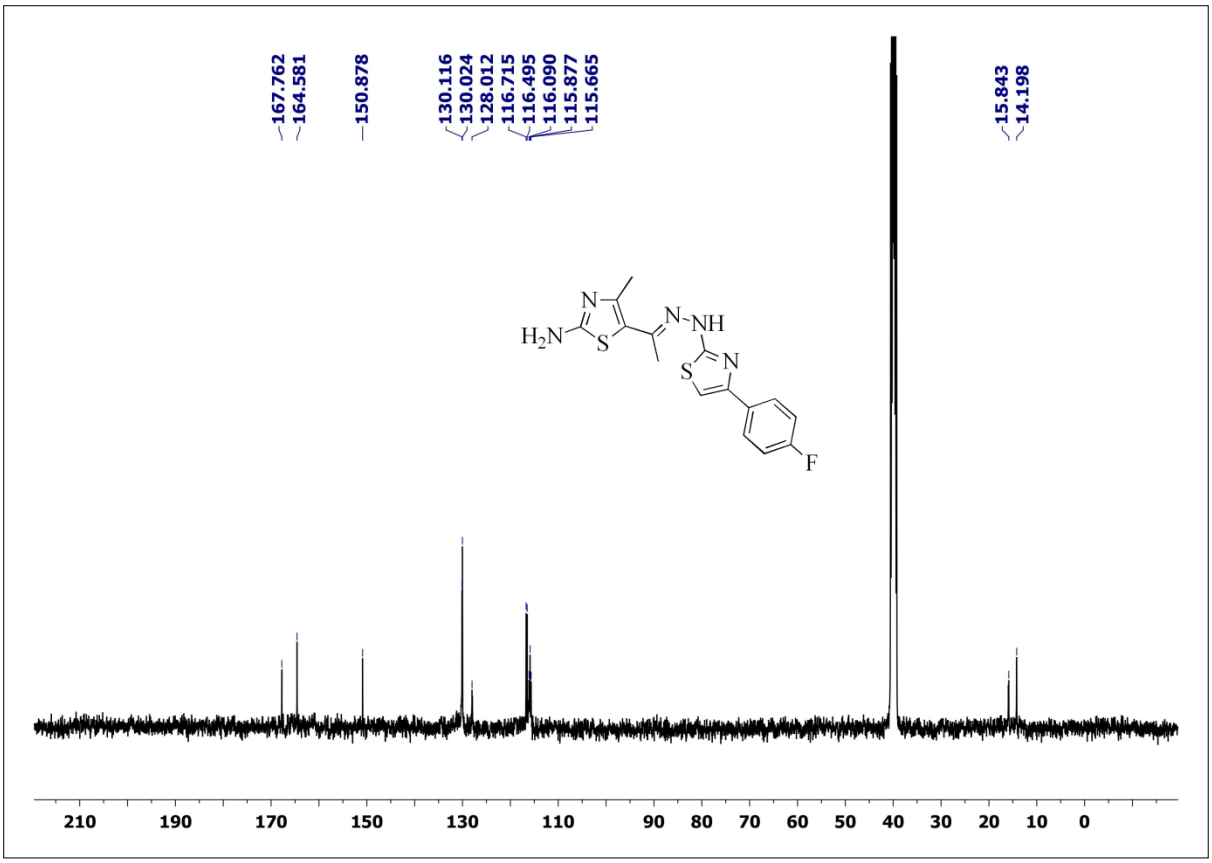
CMR Spectrum of compound **20a**



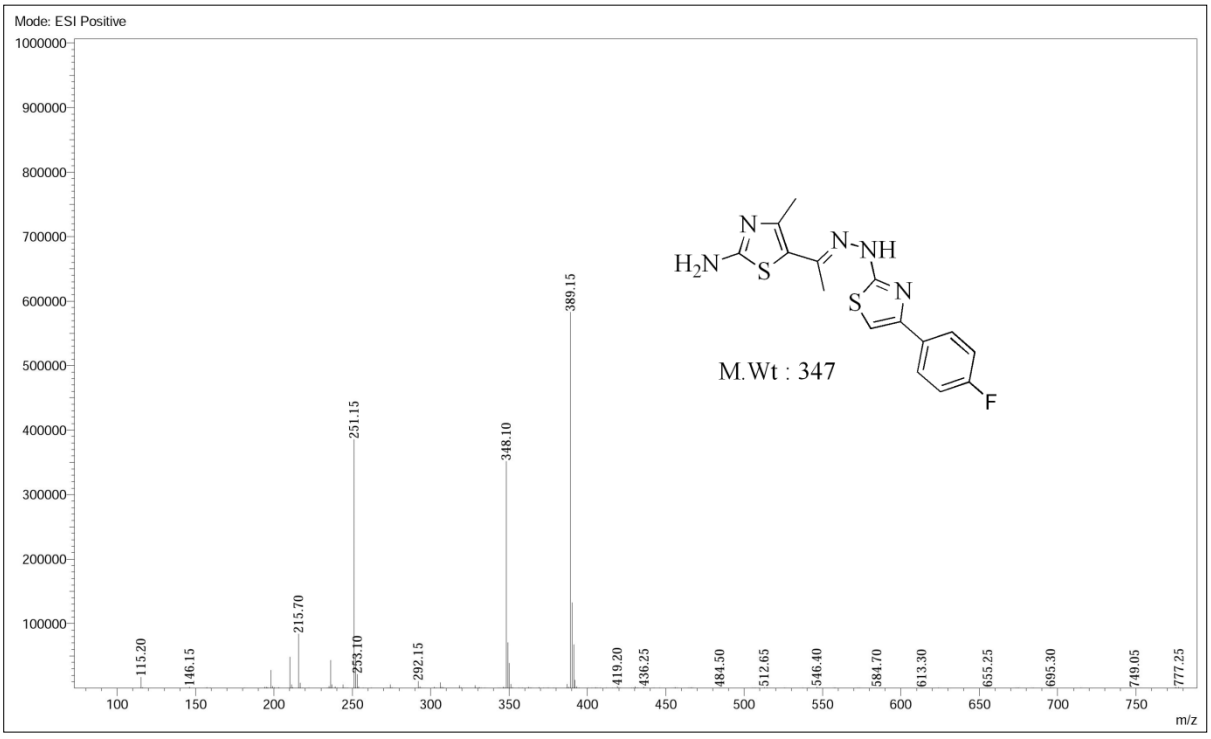
Mass Spectrum of compound **20a**



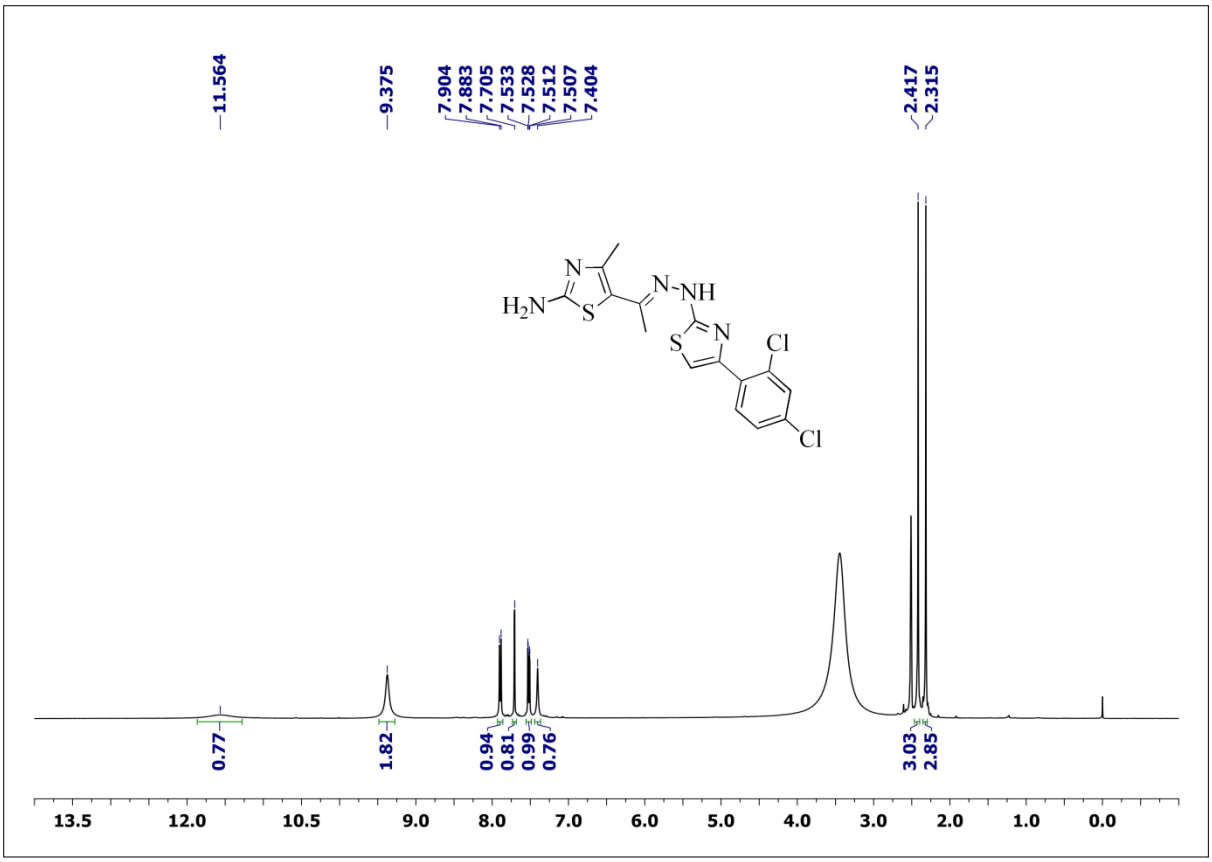
PMR Spectrum of compound **20b**



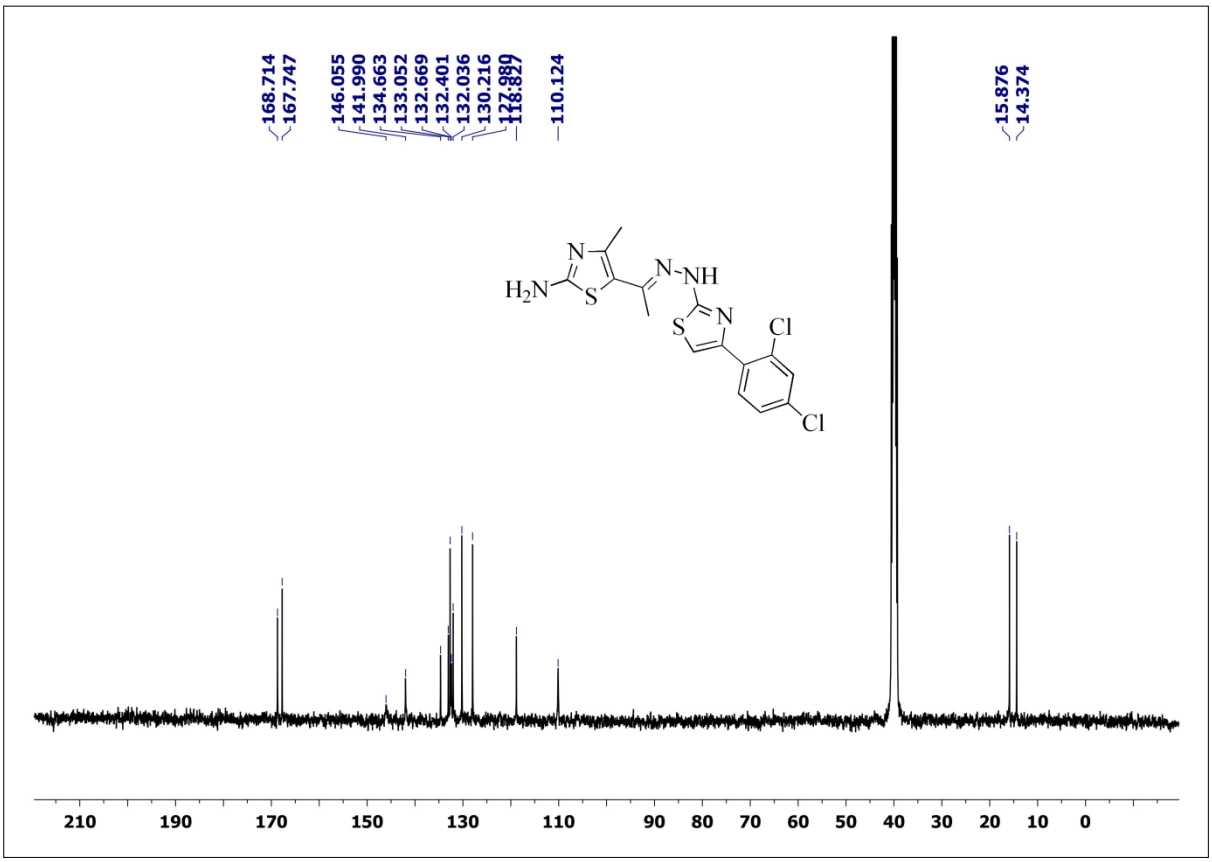
CMR Spectrum of compound **20b**



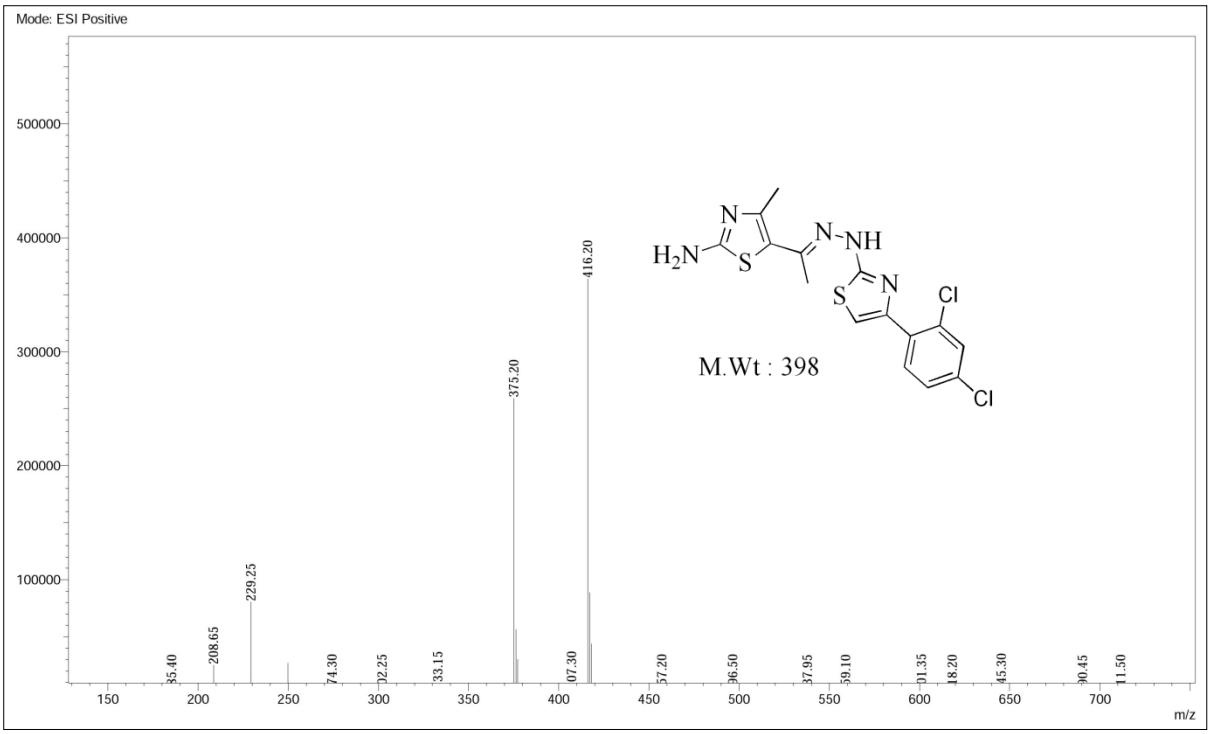
Mass Spectrum of compound **20b**



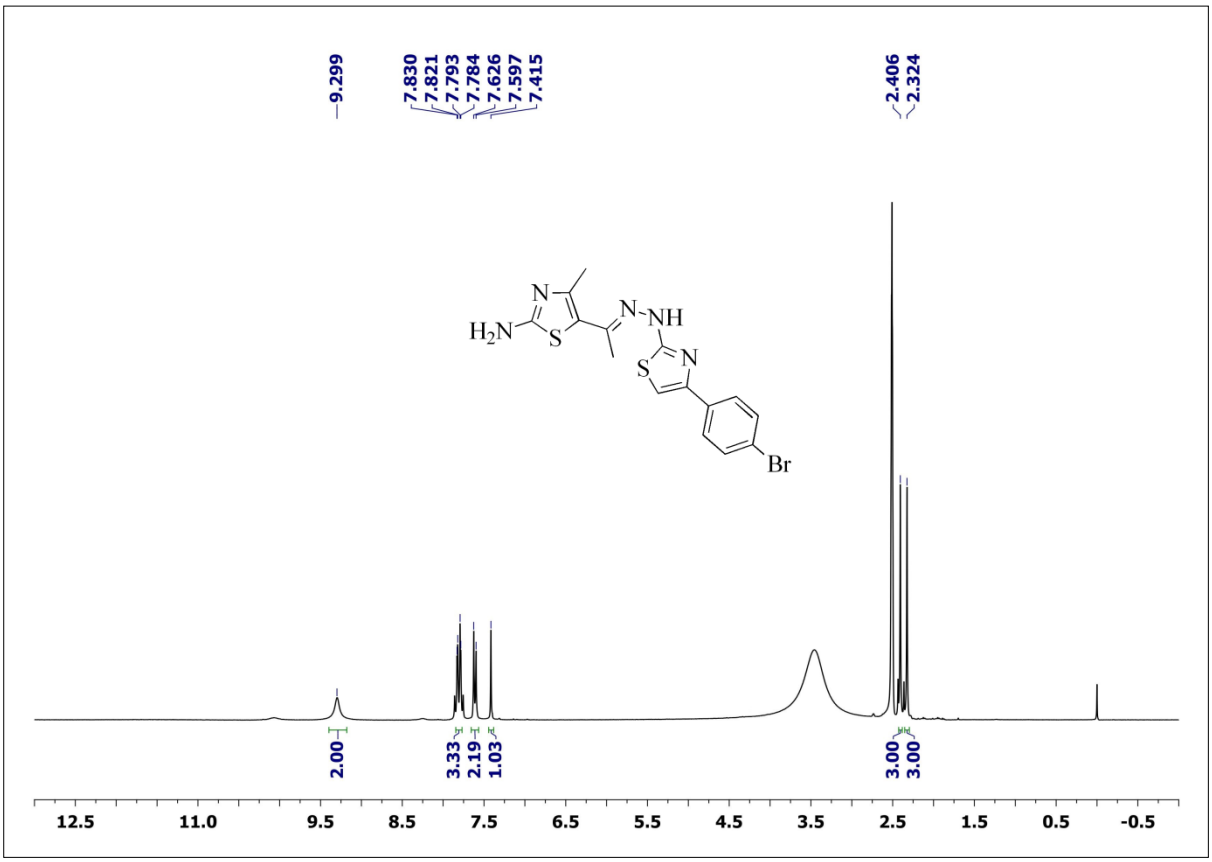
PMR Spectrum of compound **20c**



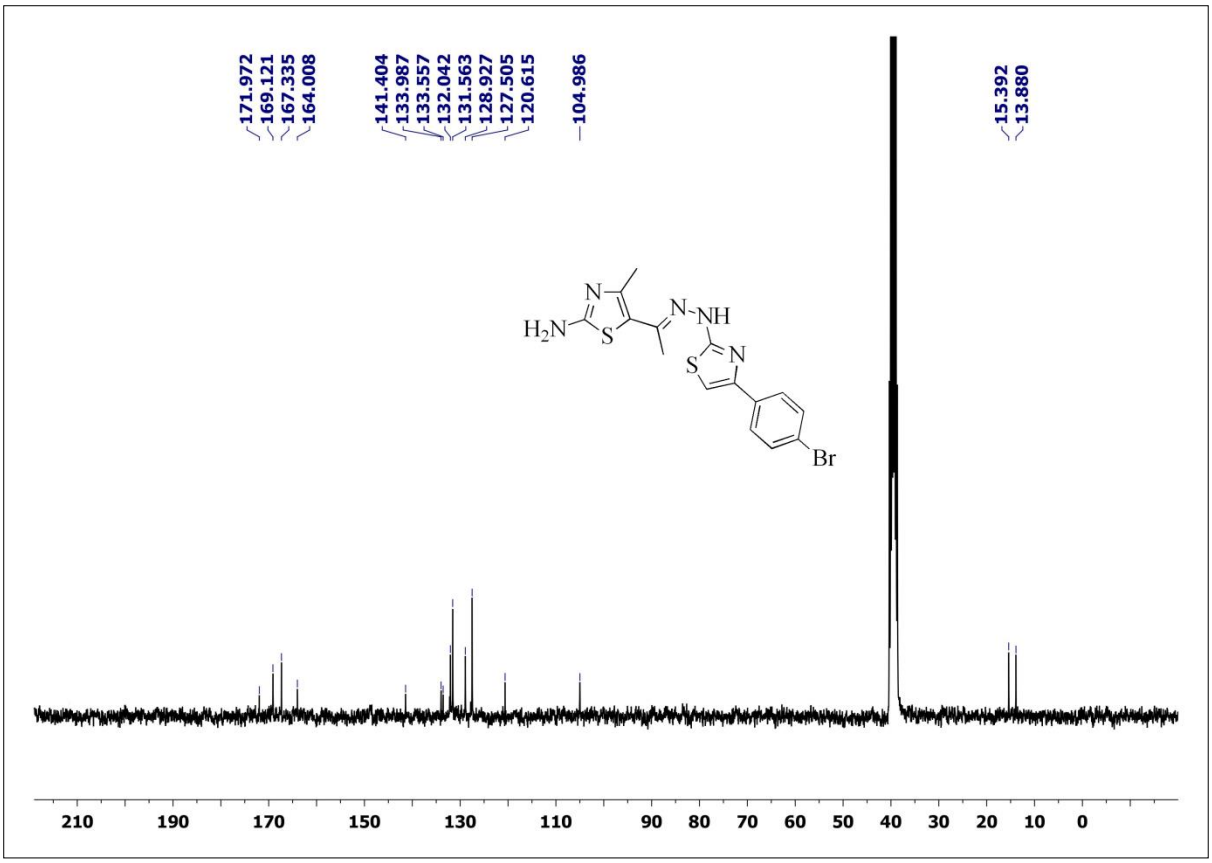
CMR Spectrum of compound **20c**



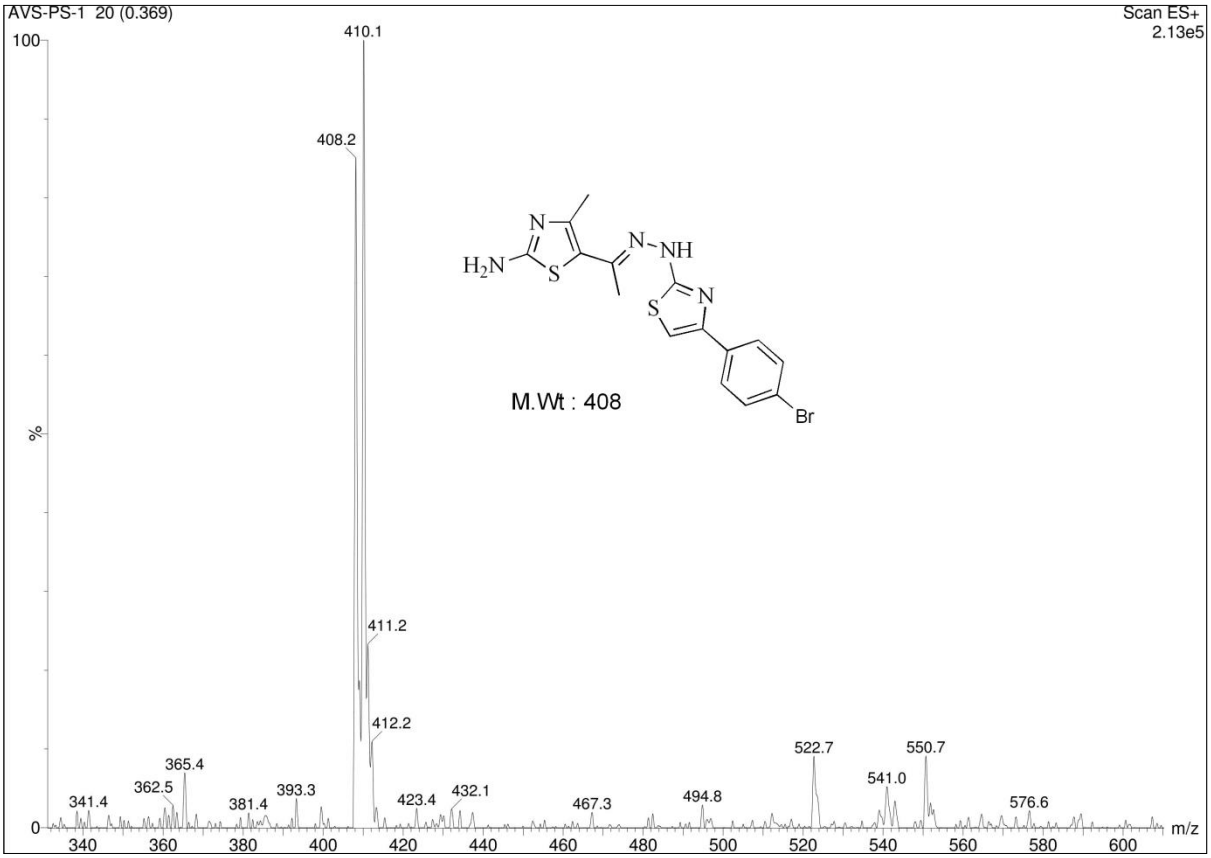
Mass Spectrum of compound **20c**



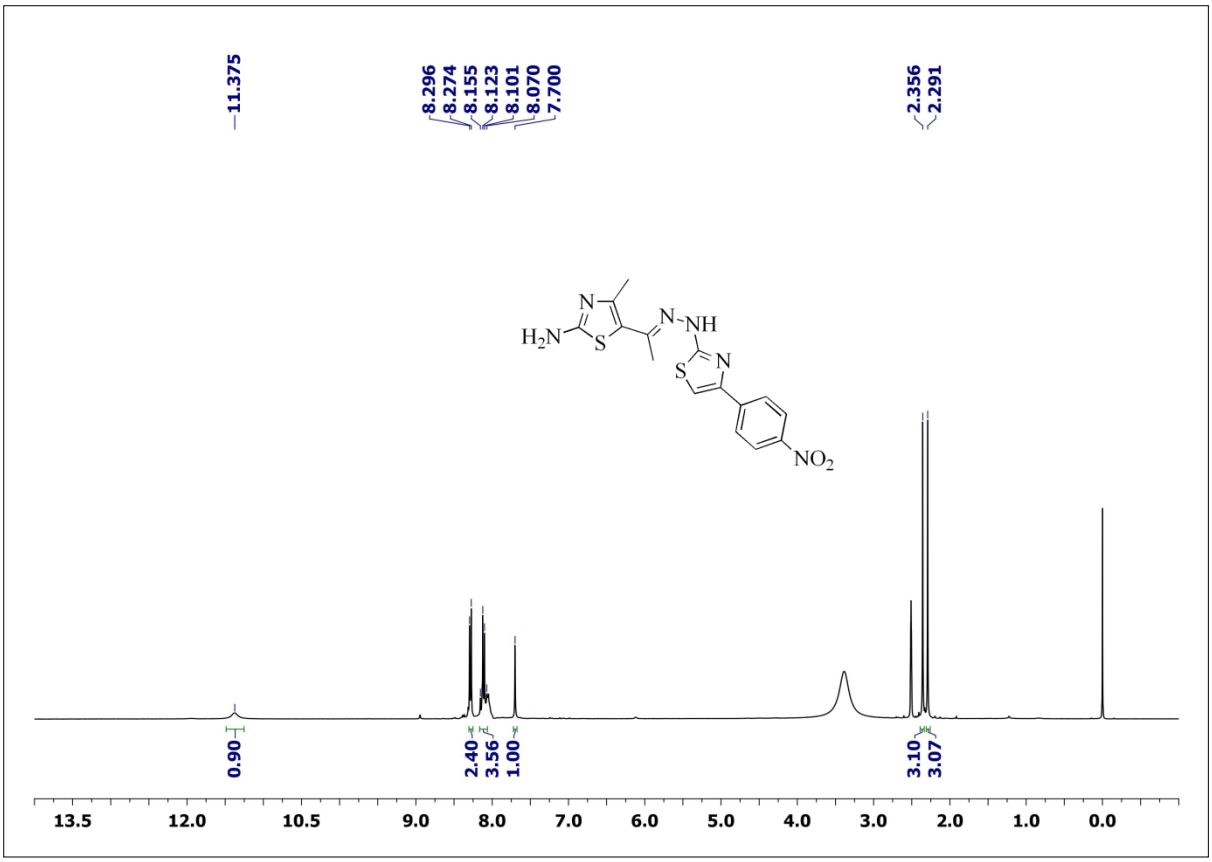
PMR Spectrum of compound **20d**



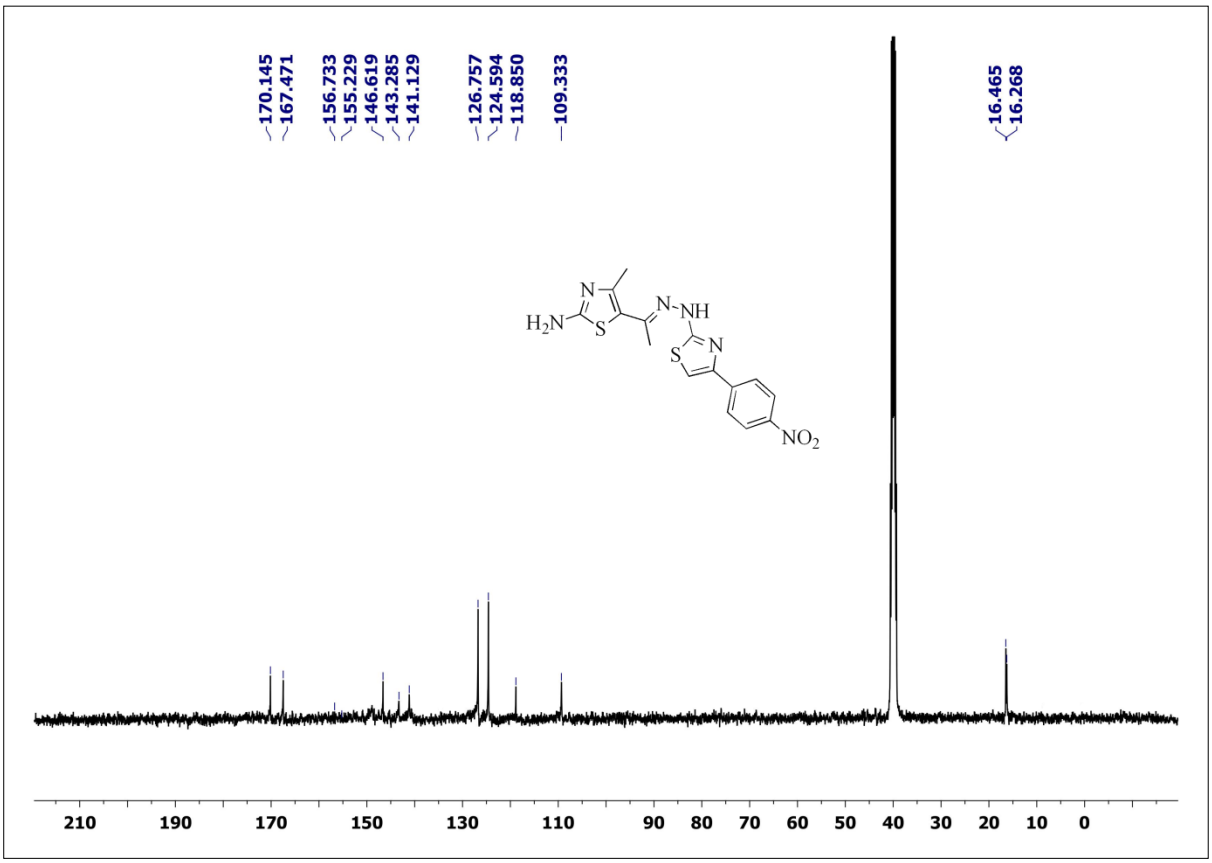
CMR Spectrum of compound **20d**



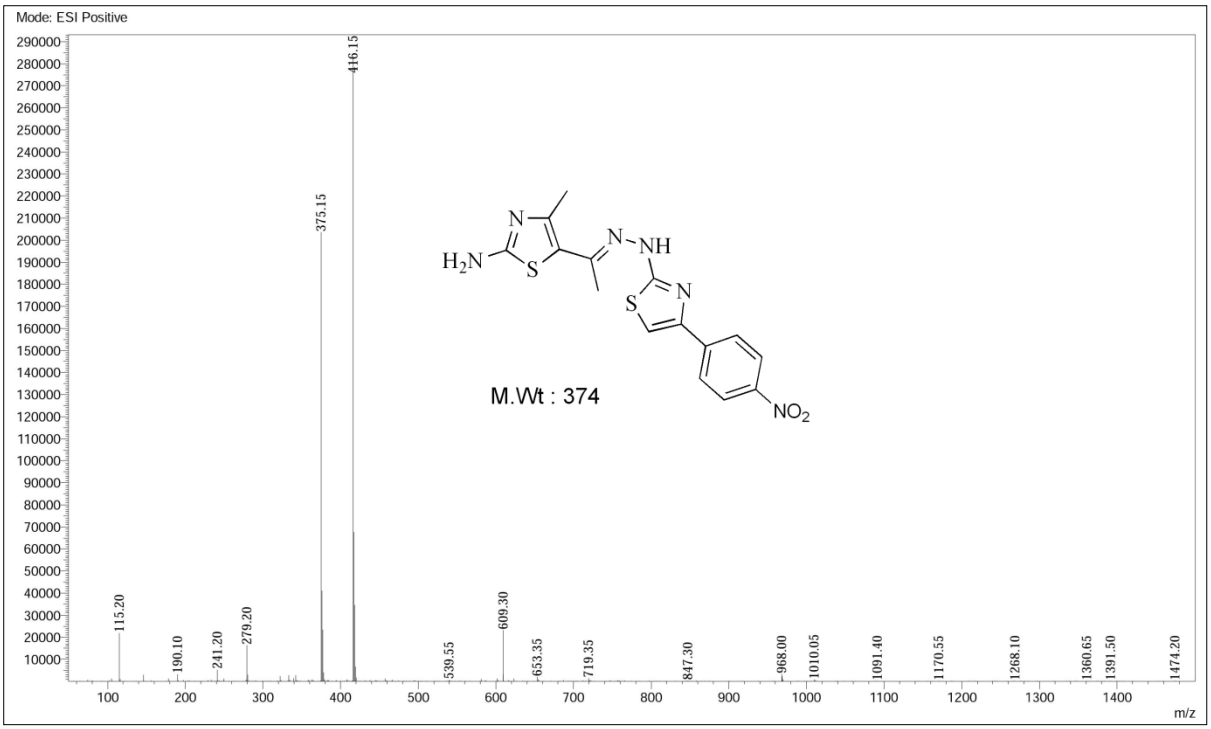
Mass Spectrum of compound **20d**



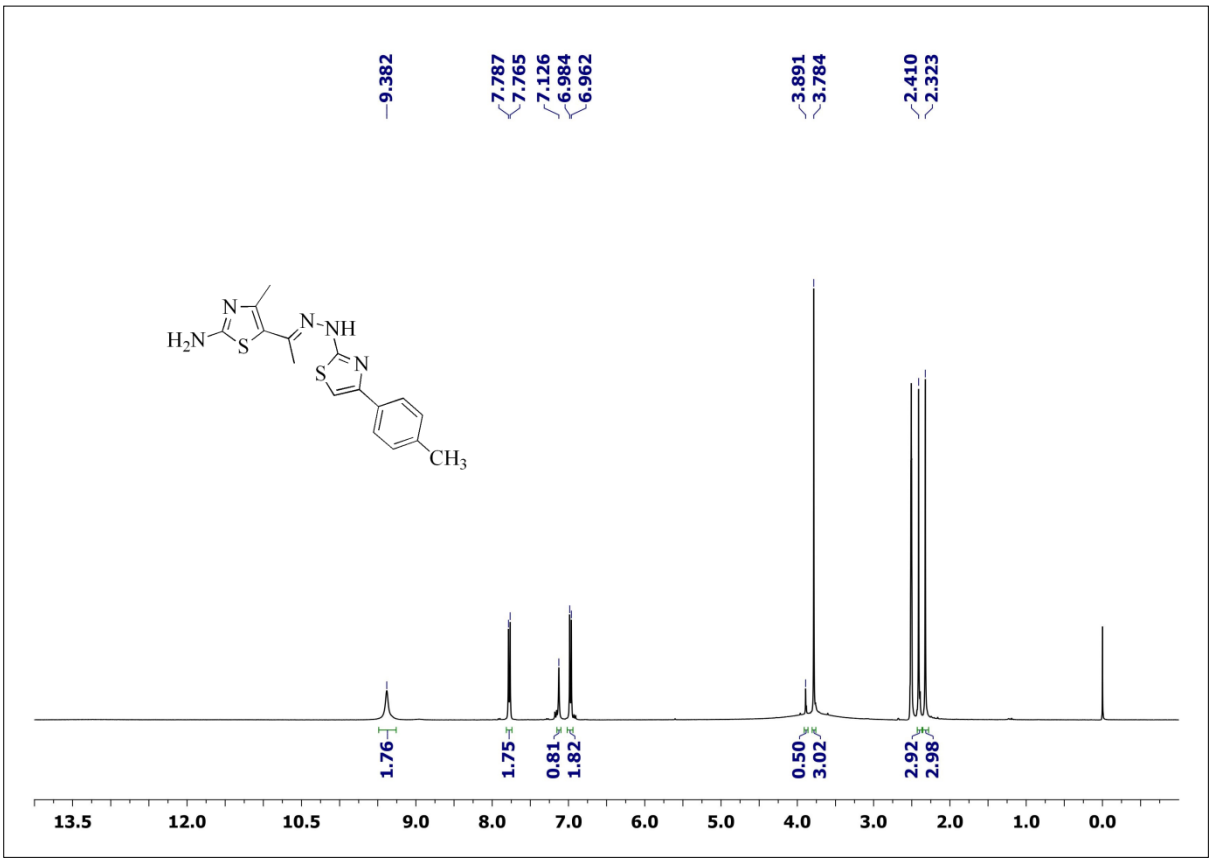
PMR Spectrum of compound **20e**



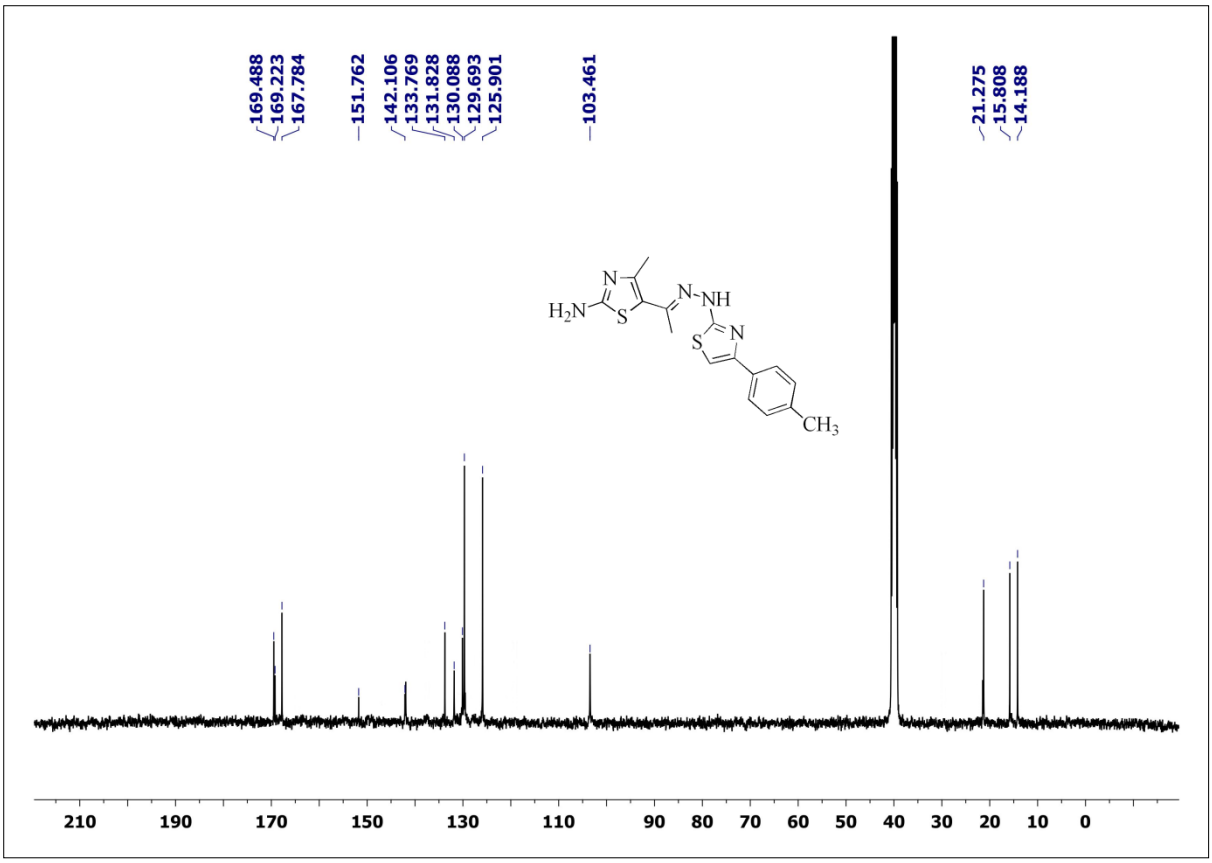
CMR Spectrum of compound **20e**



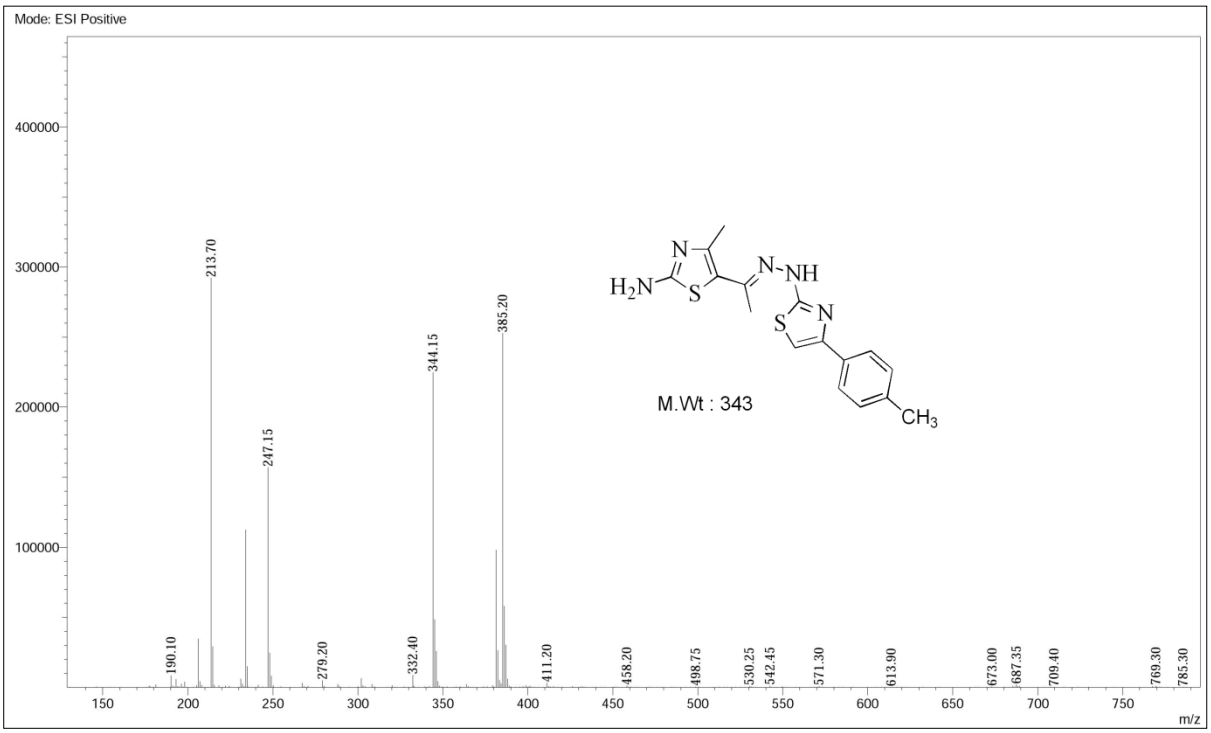
Mass Spectrum of compound **20e**



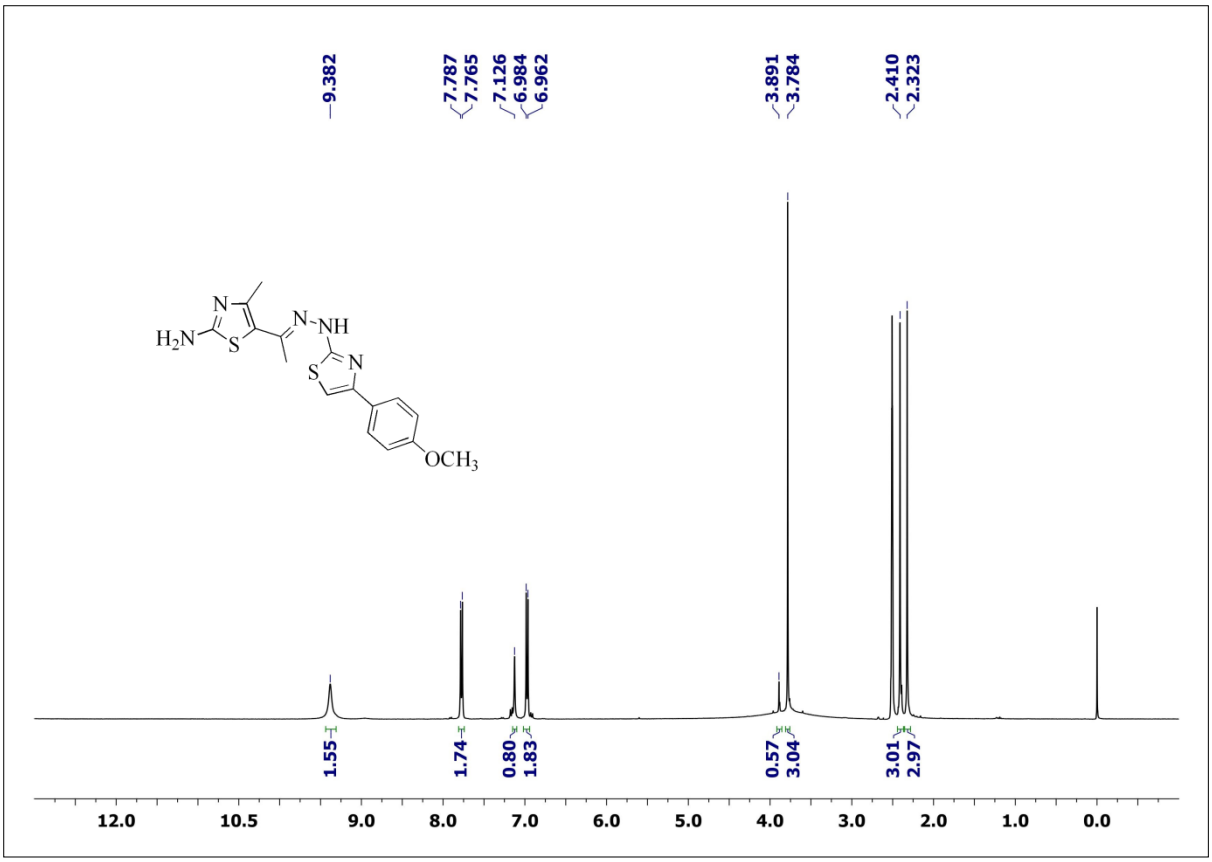
PMR Spectrum of compound **20f**



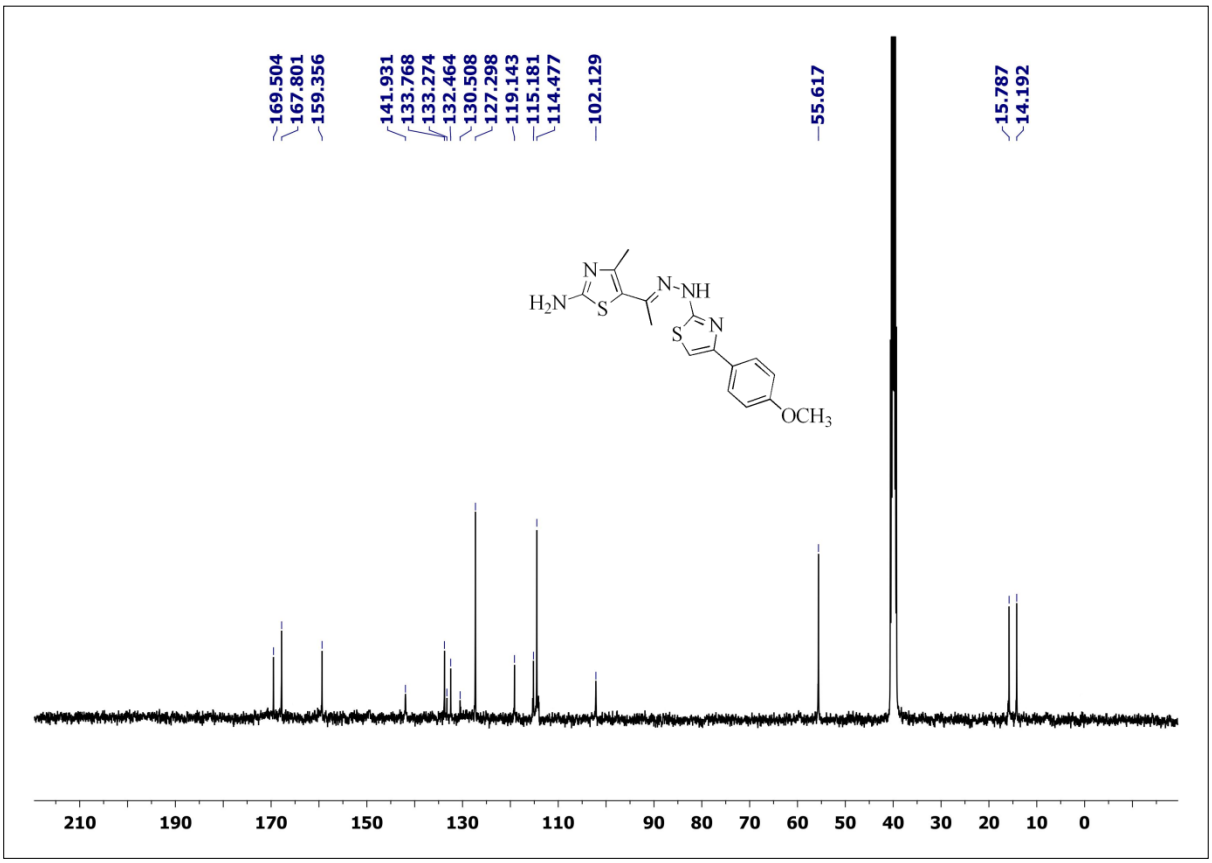
CMR Spectrum of compound **20f**



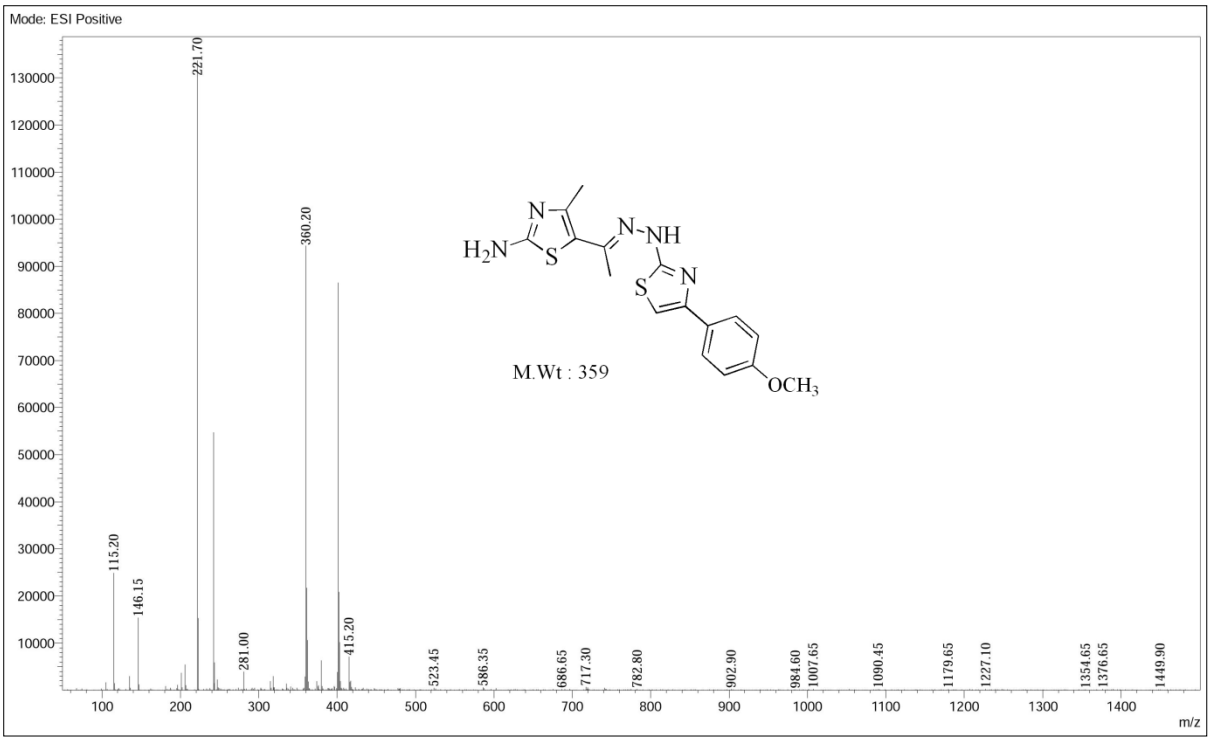
Mass Spectrum of compound **20f**



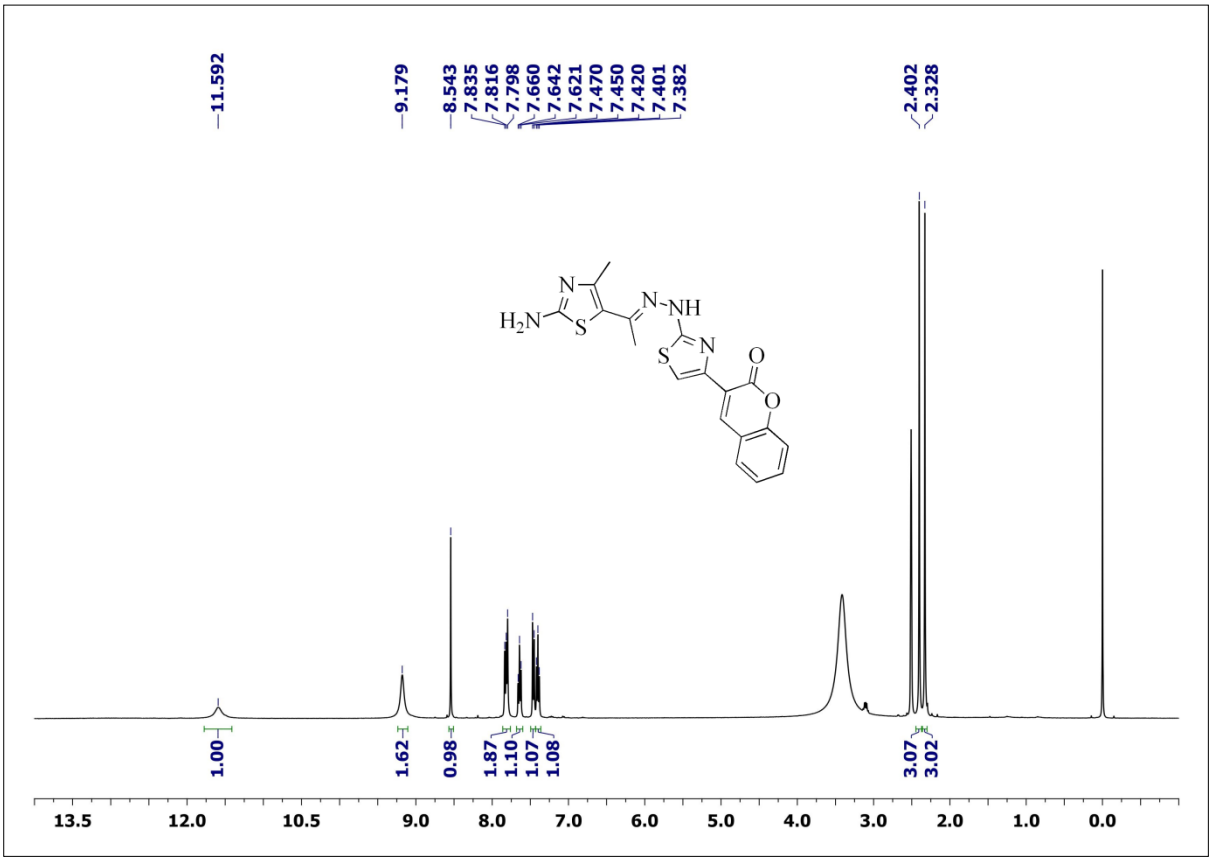
PMR Spectrum of compound **20g**



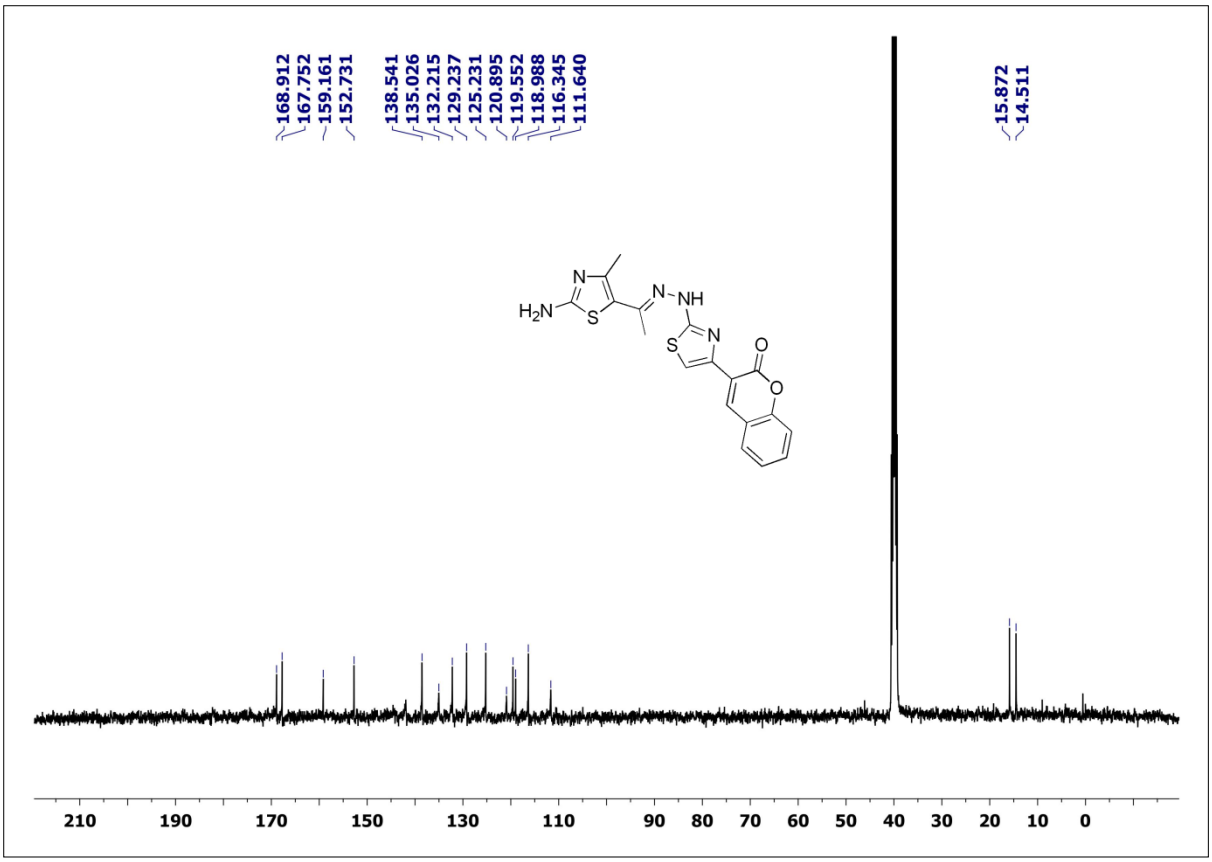
CMR Spectrum of compound **20g**



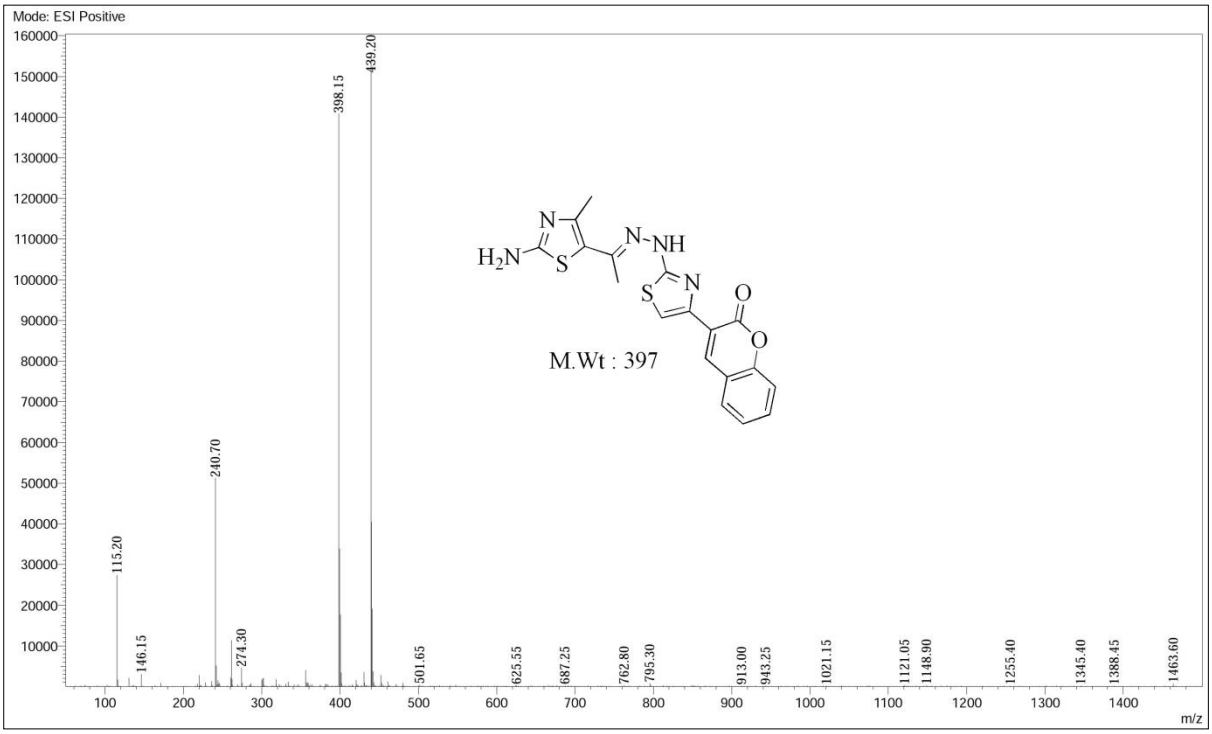
Mass Spectrum of compound **20g**



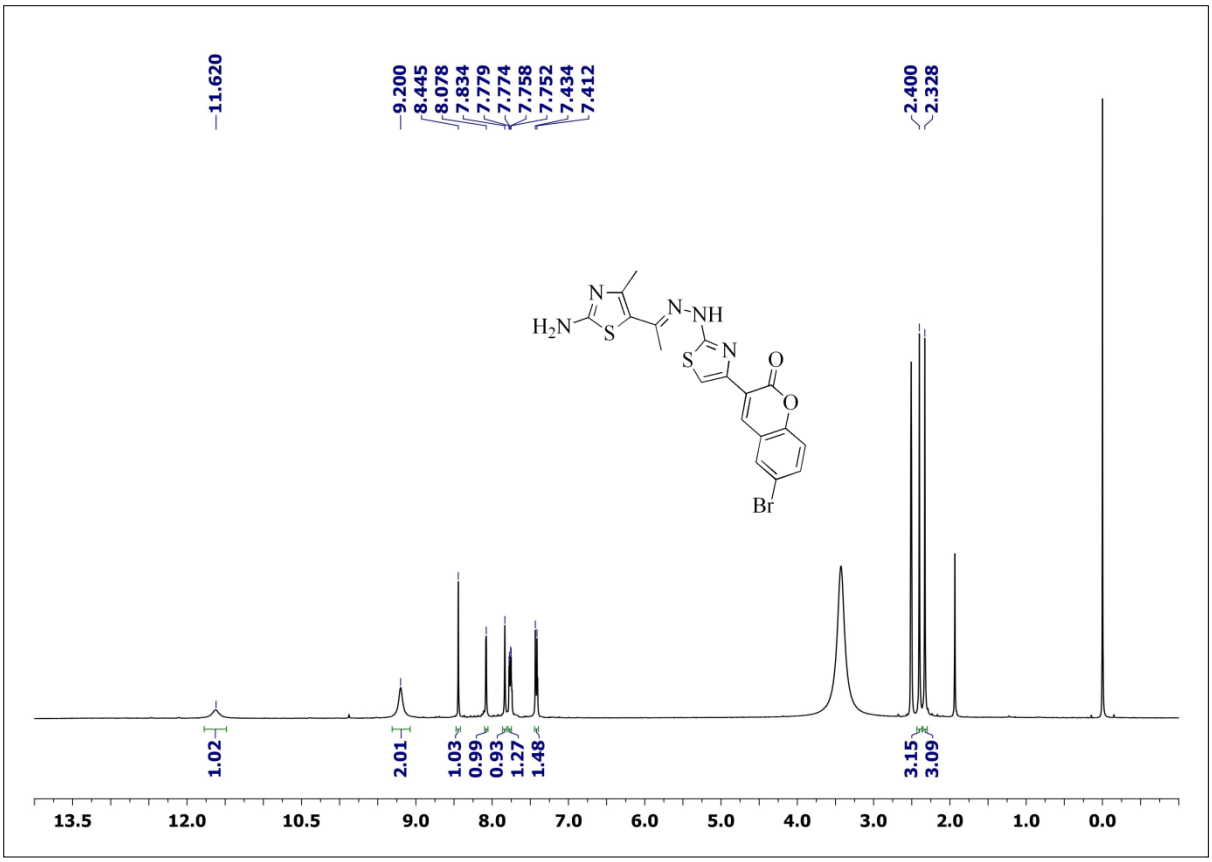
PMR Spectrum of compound **20h**



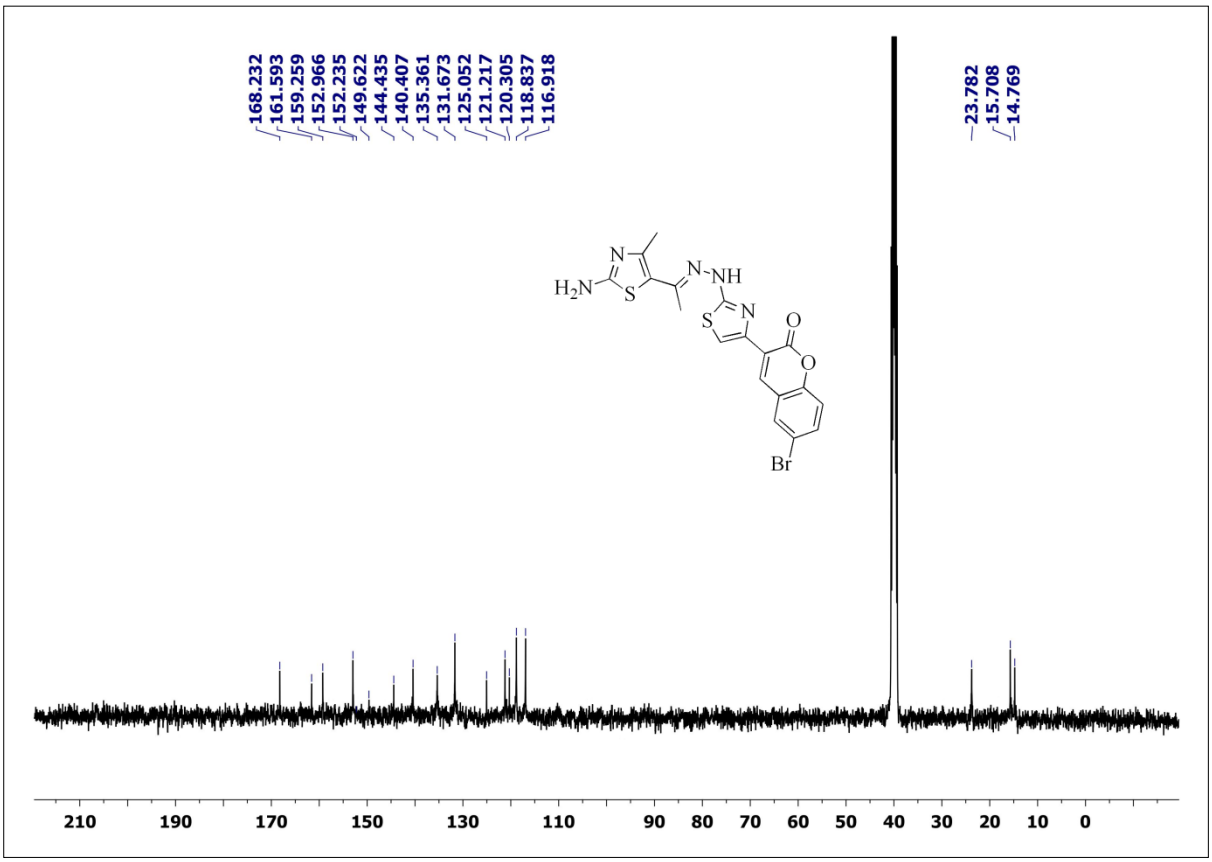
CMR Spectrum of compound **20h**



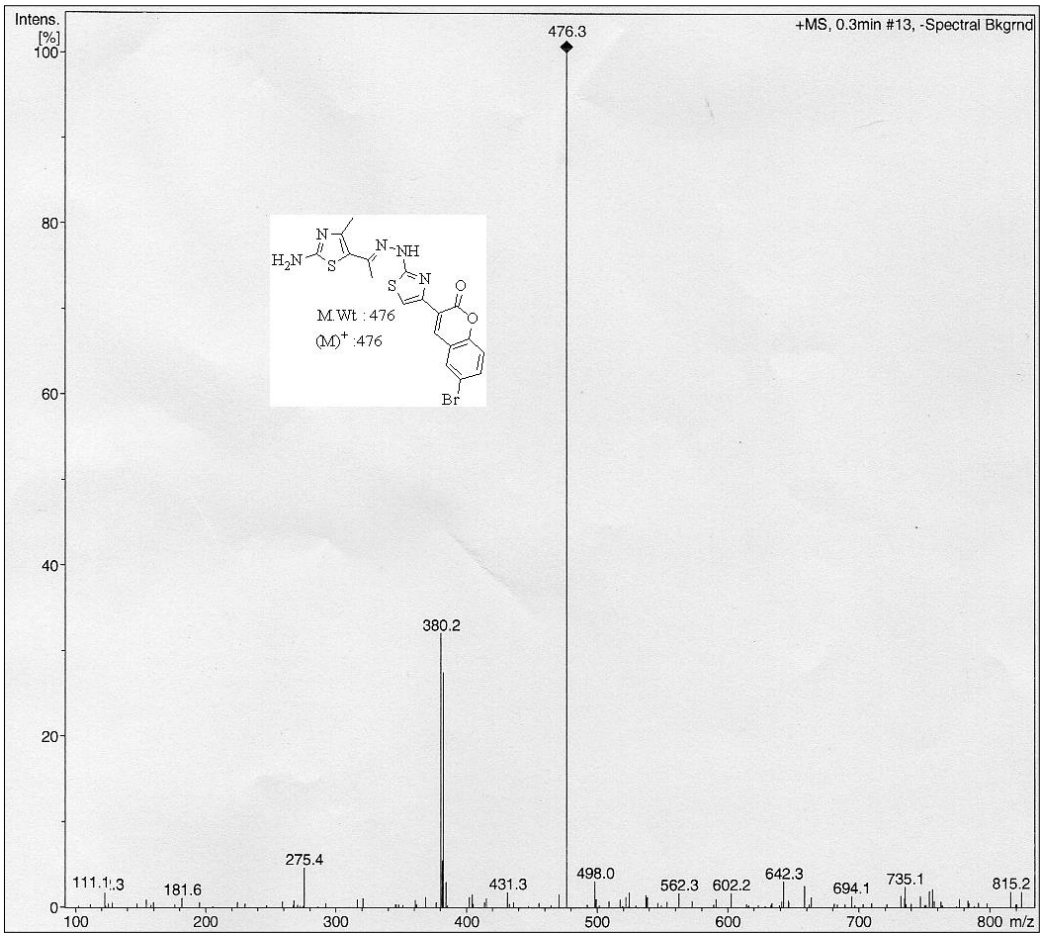
Mass Spectrum of compound **20h**



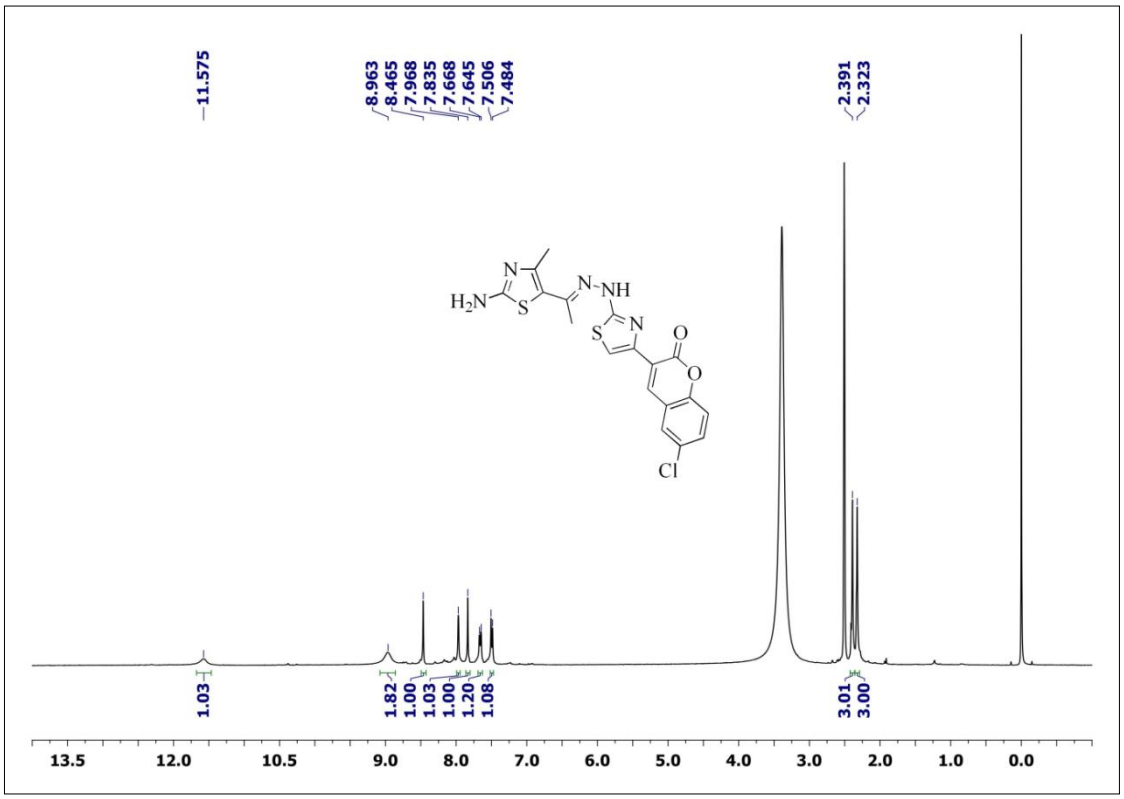
PMR Spectrum of compound **20i**



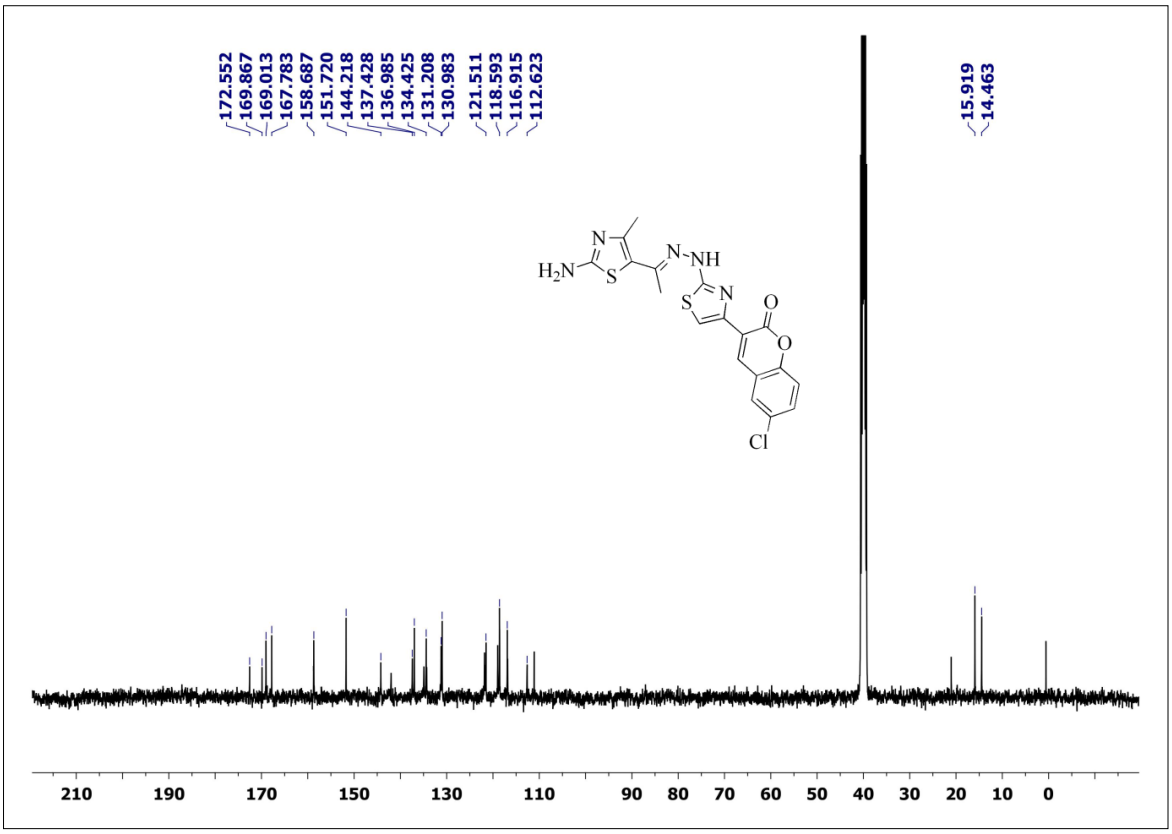
CMR Spectrum of compound **20i**



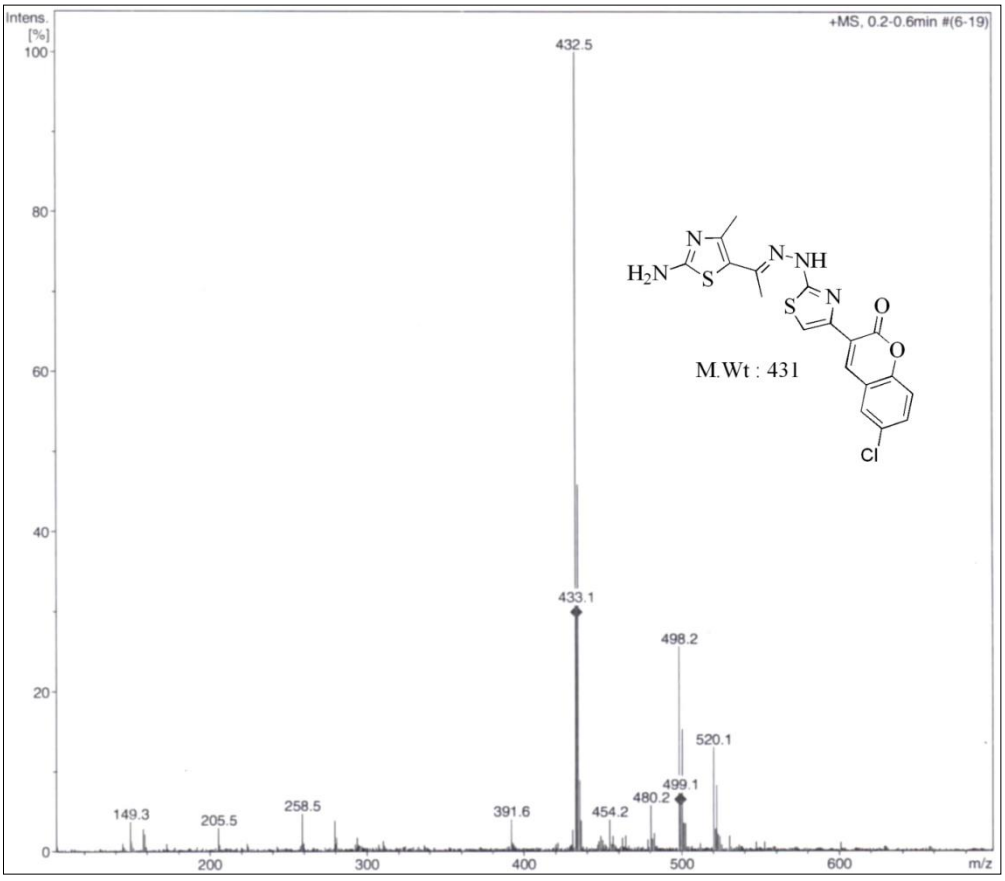
Mass Spectrum of compound **20i**



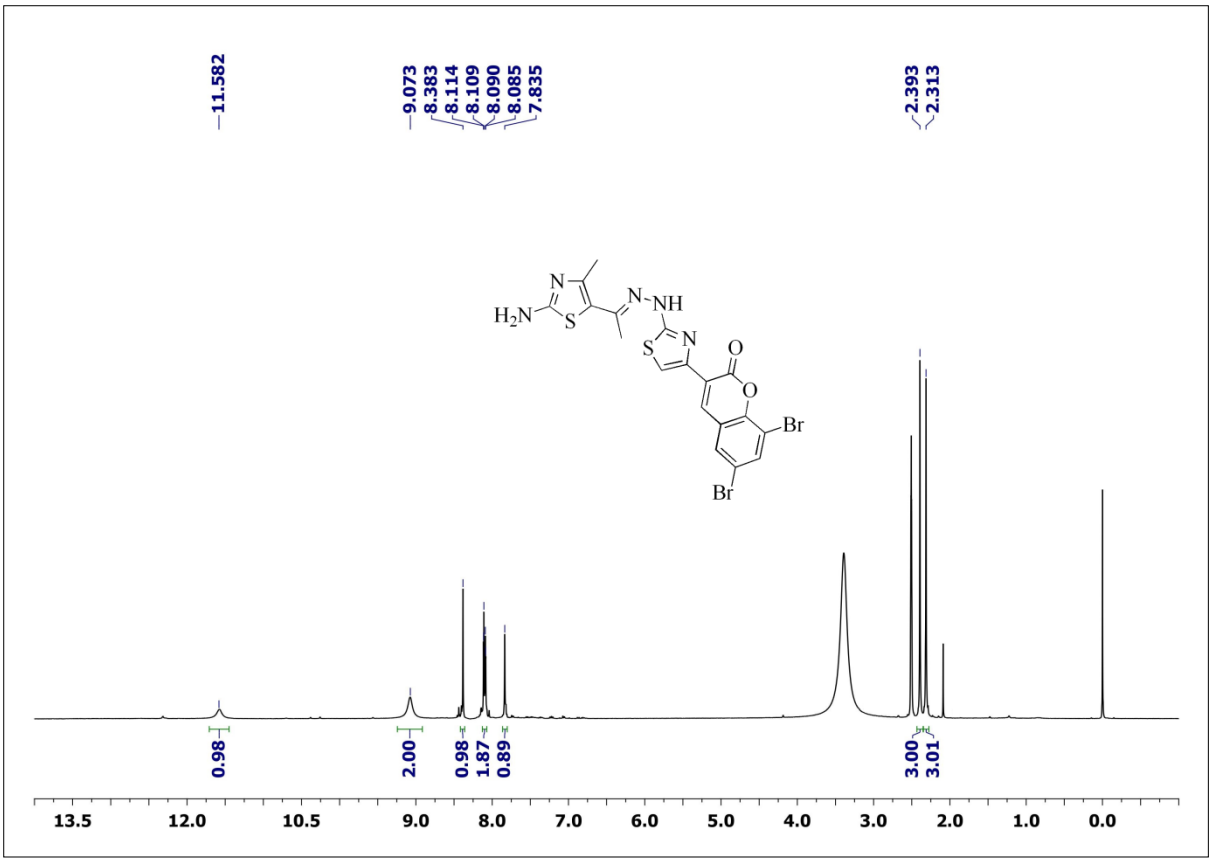
PMR Spectrum of compound **20j**



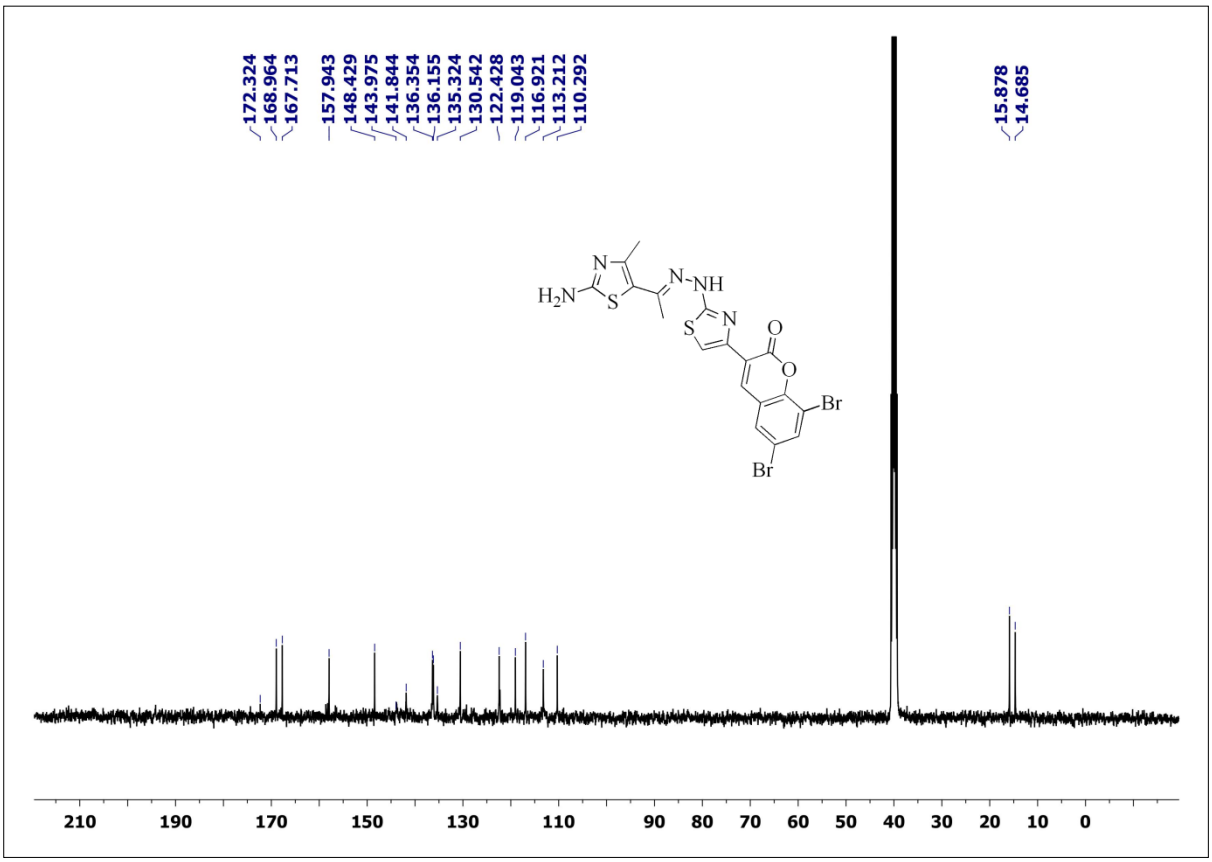
CMR Spectrum of compound **20j**



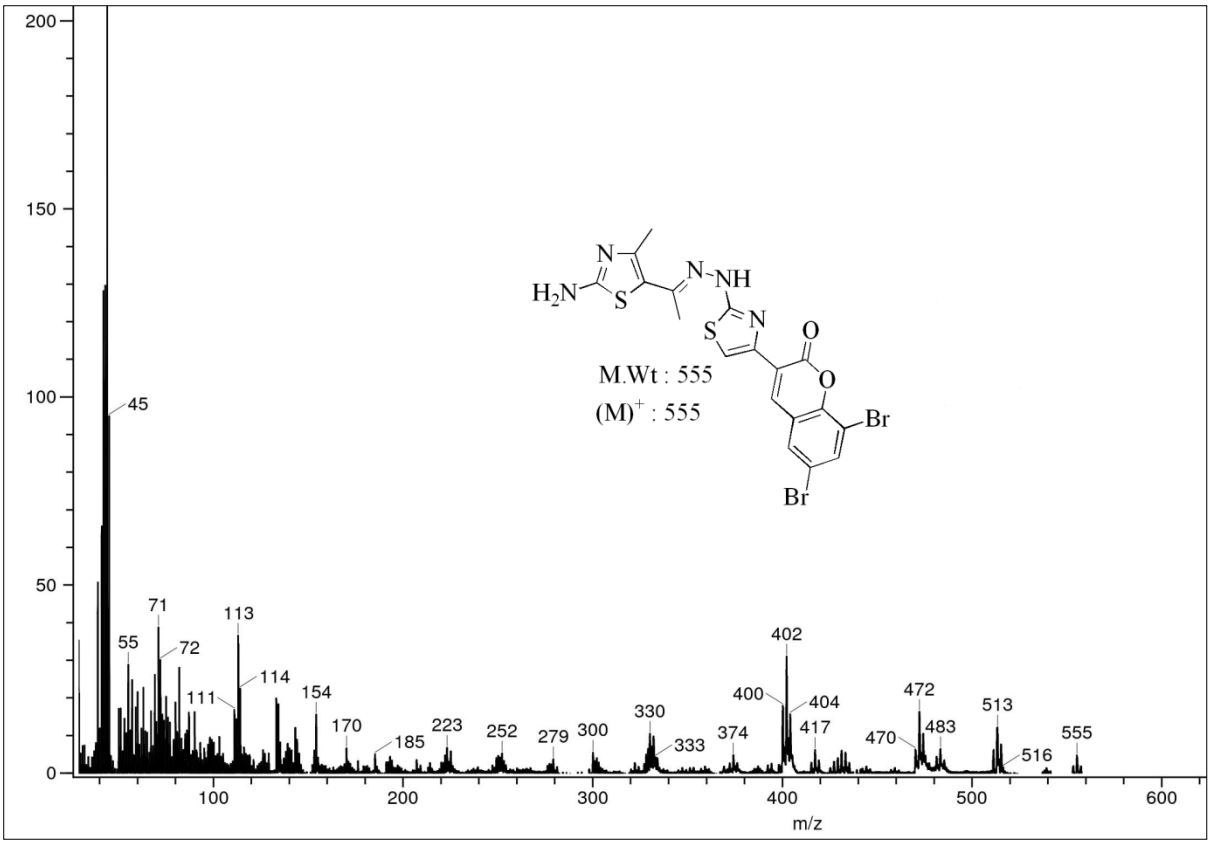
Mass Spectrum of compound **20j**



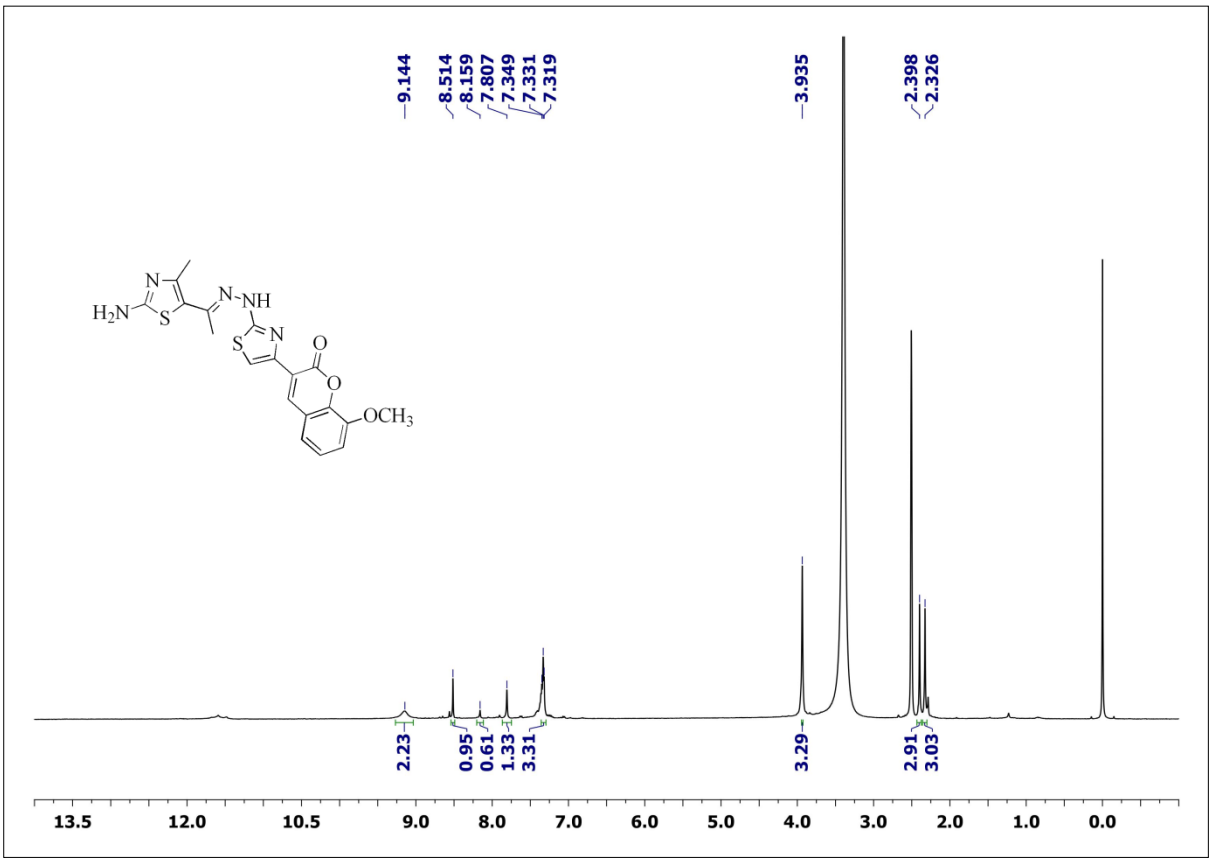
PMR Spectrum of compound **20k**



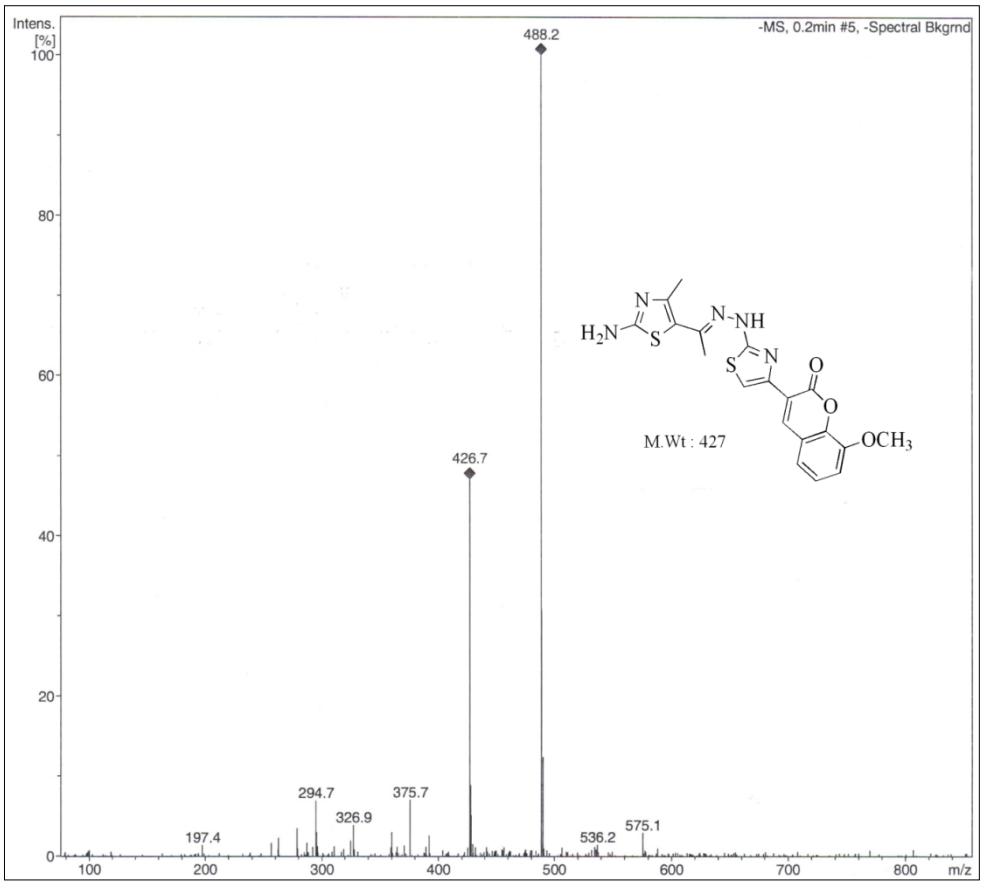
CMR Spectrum of compound **20k**



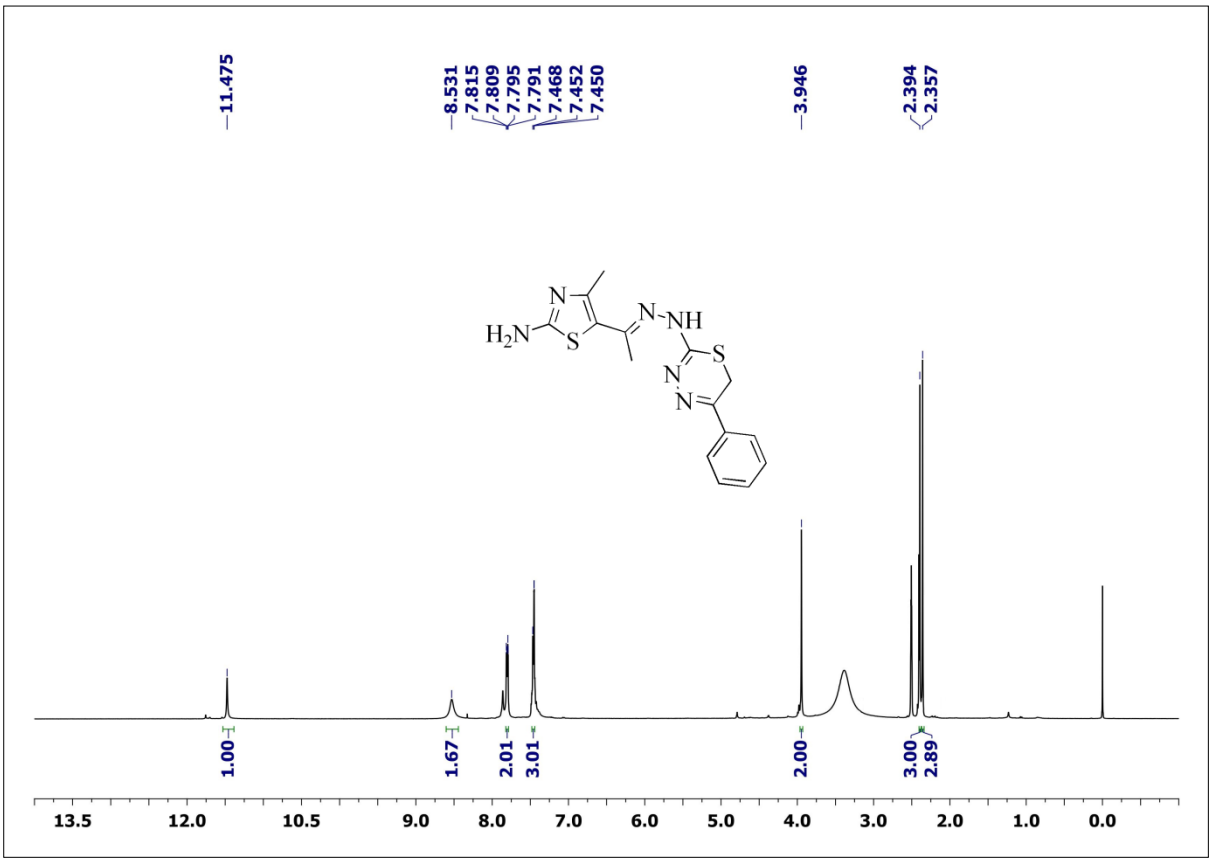
Mass Spectrum of compound **20k**



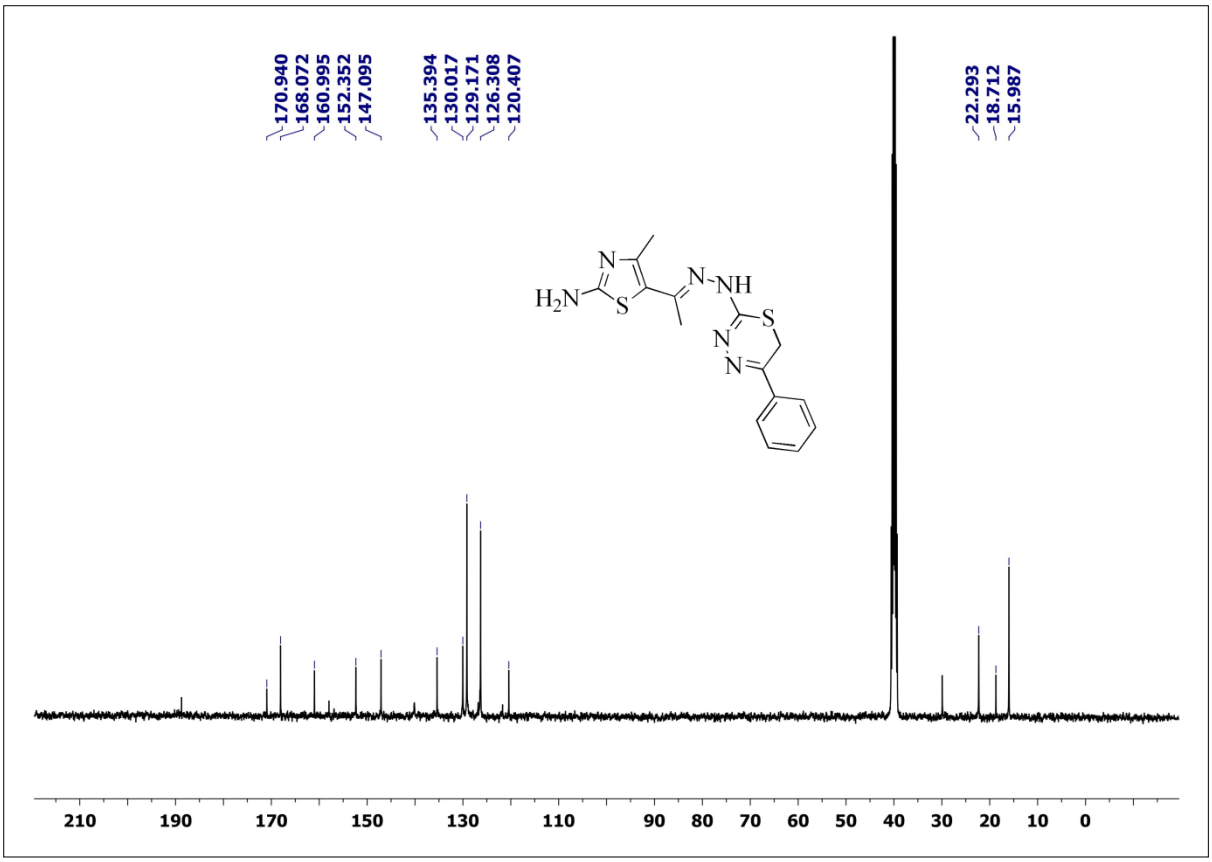
PMR Spectrum of compound **20l**



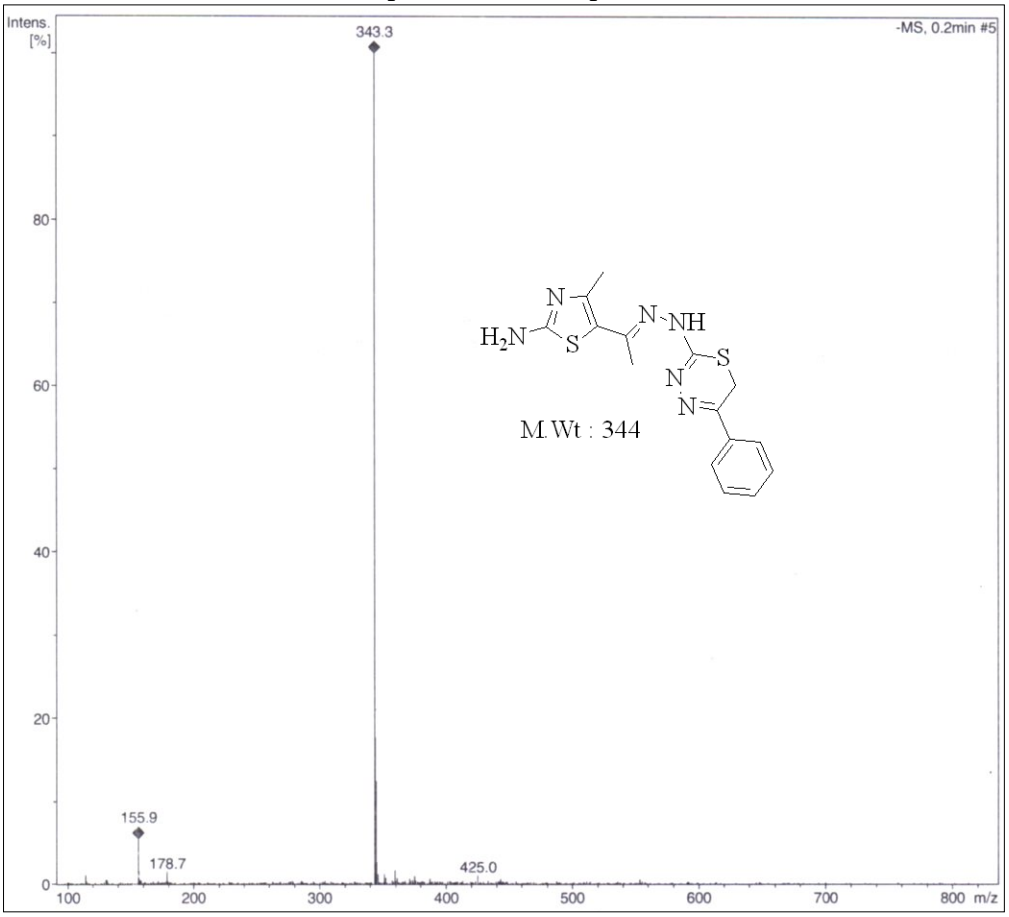
Mass Spectrum of compound **20l**



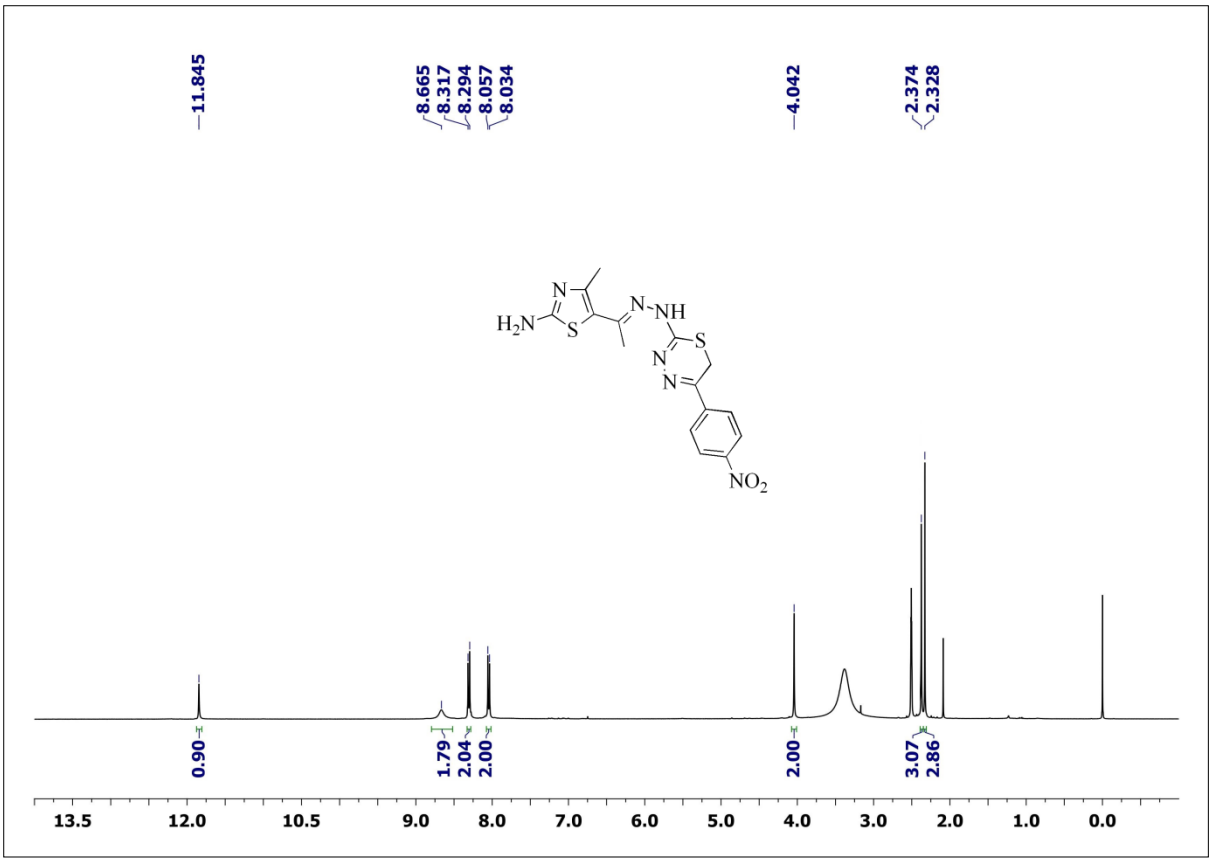
PMR Spectrum of compound **22a**



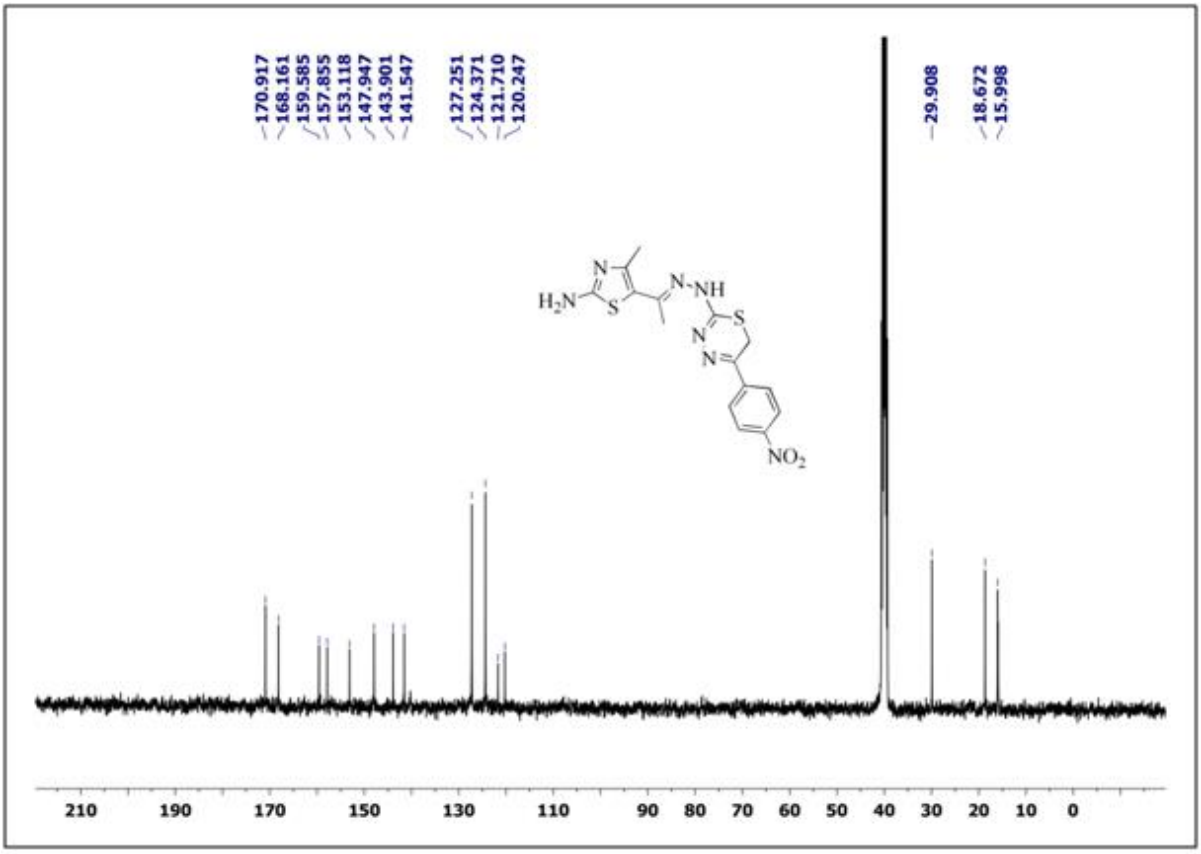
CMR Spectrum of compound **22a**



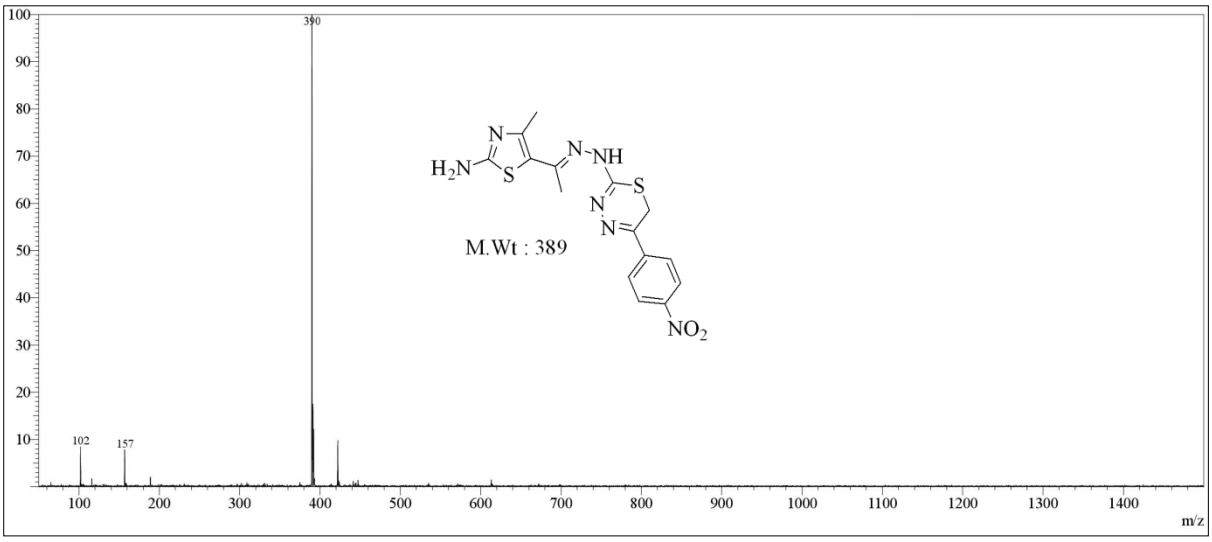
Mass Spectrum of compound **22a**



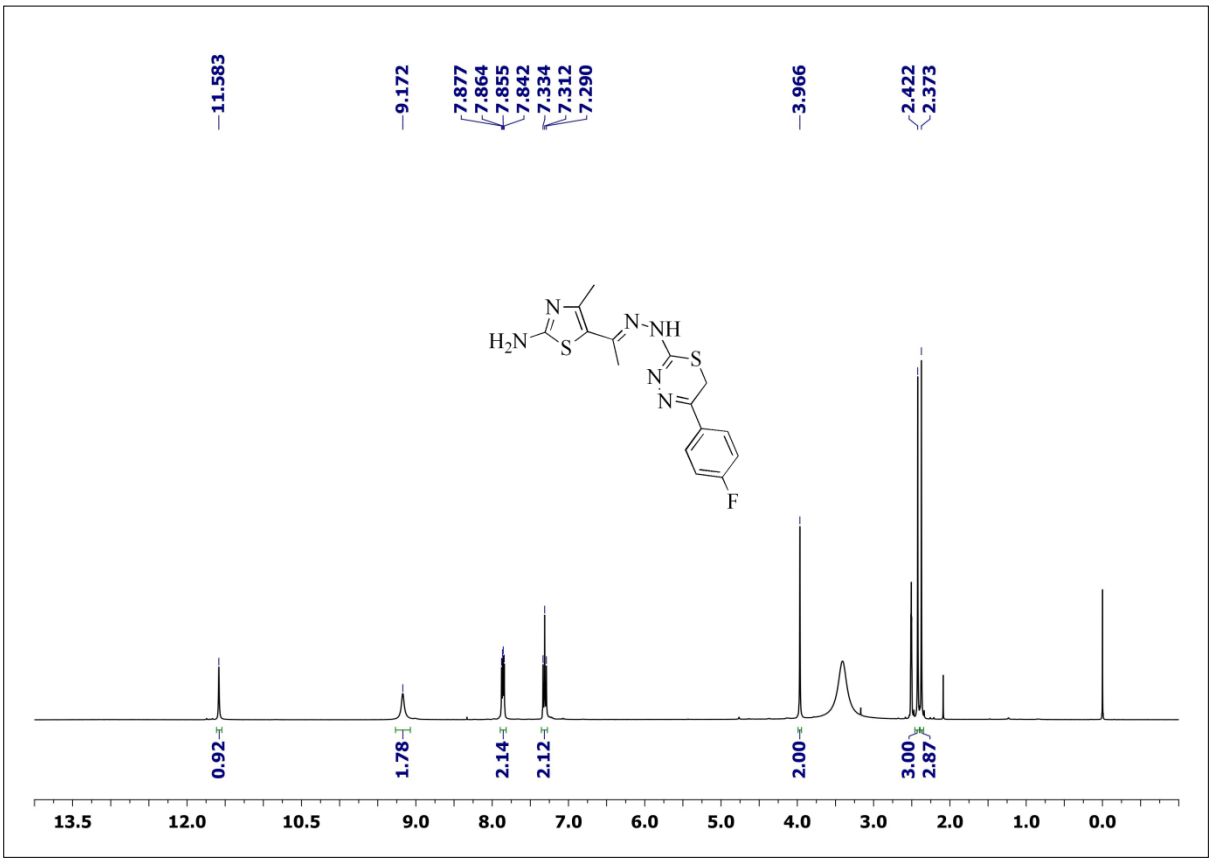
PMR Spectrum of compound **22b**



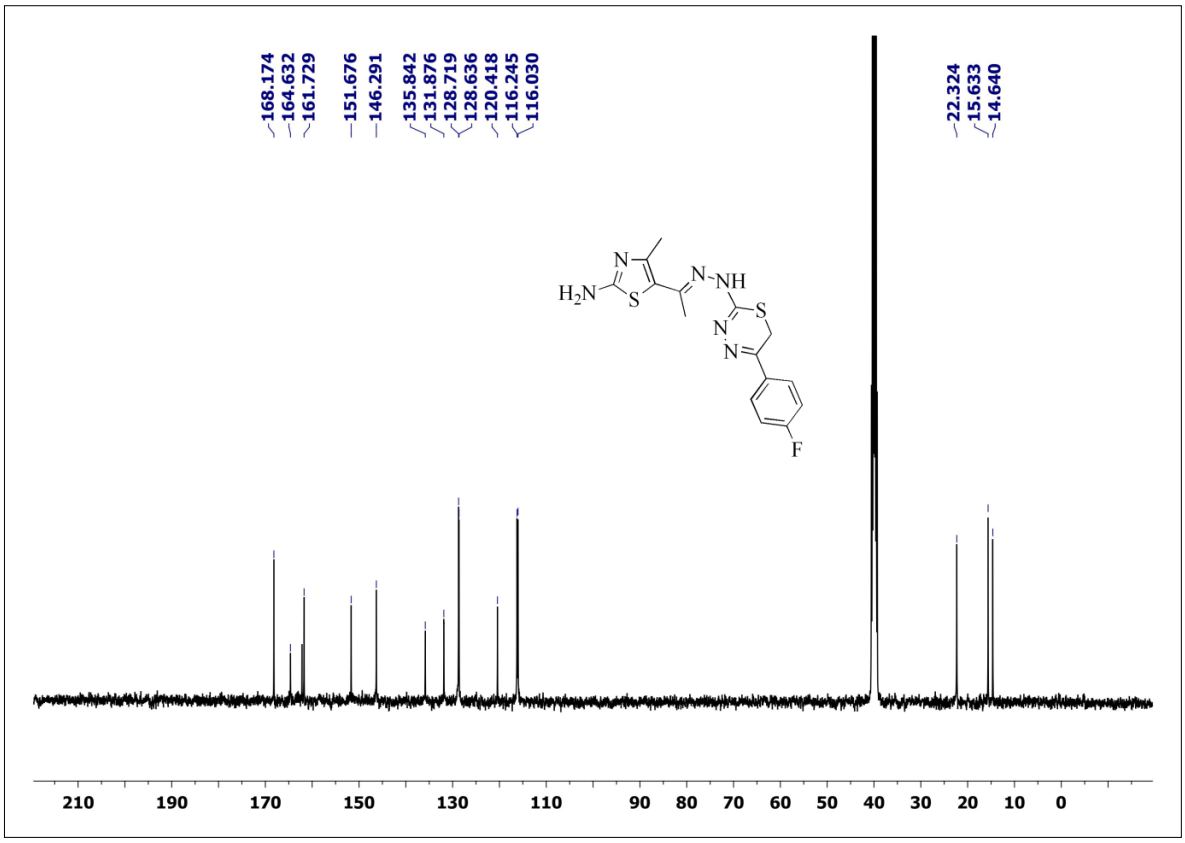
CMR Spectrum of compound **22b**



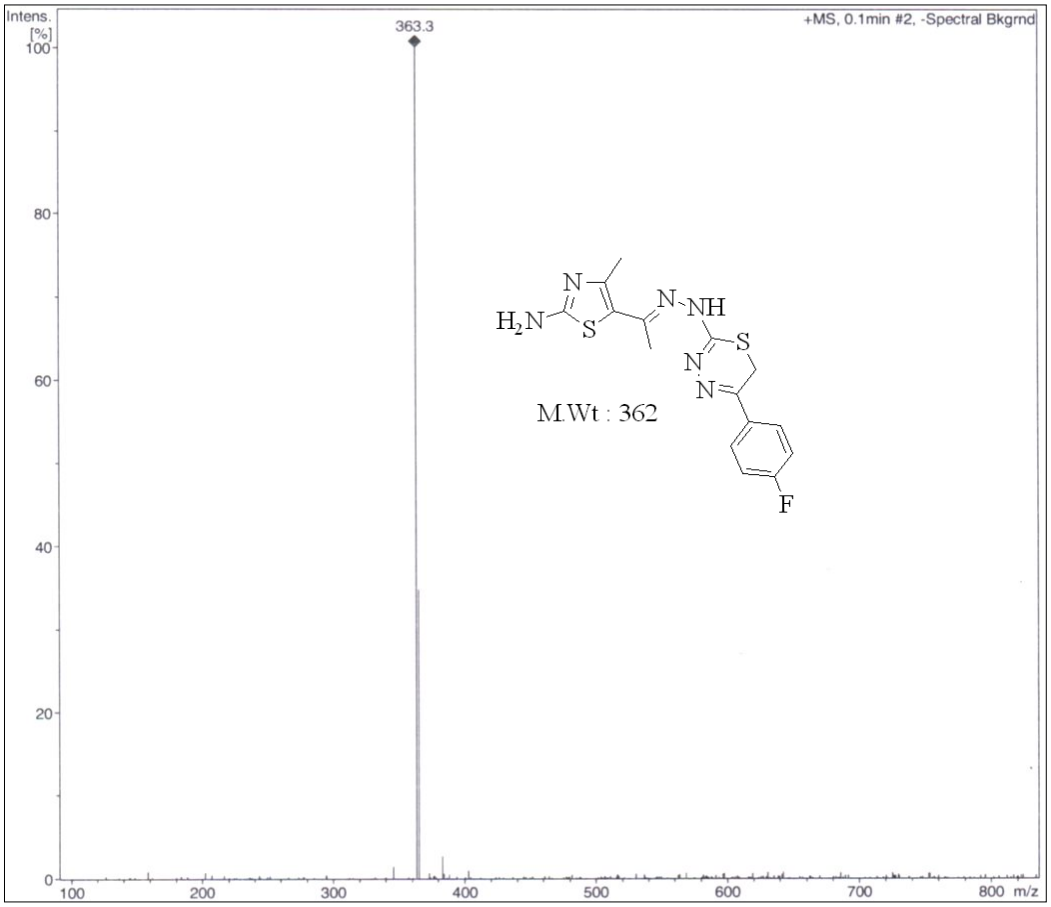
Mass Spectrum of compound **22b**



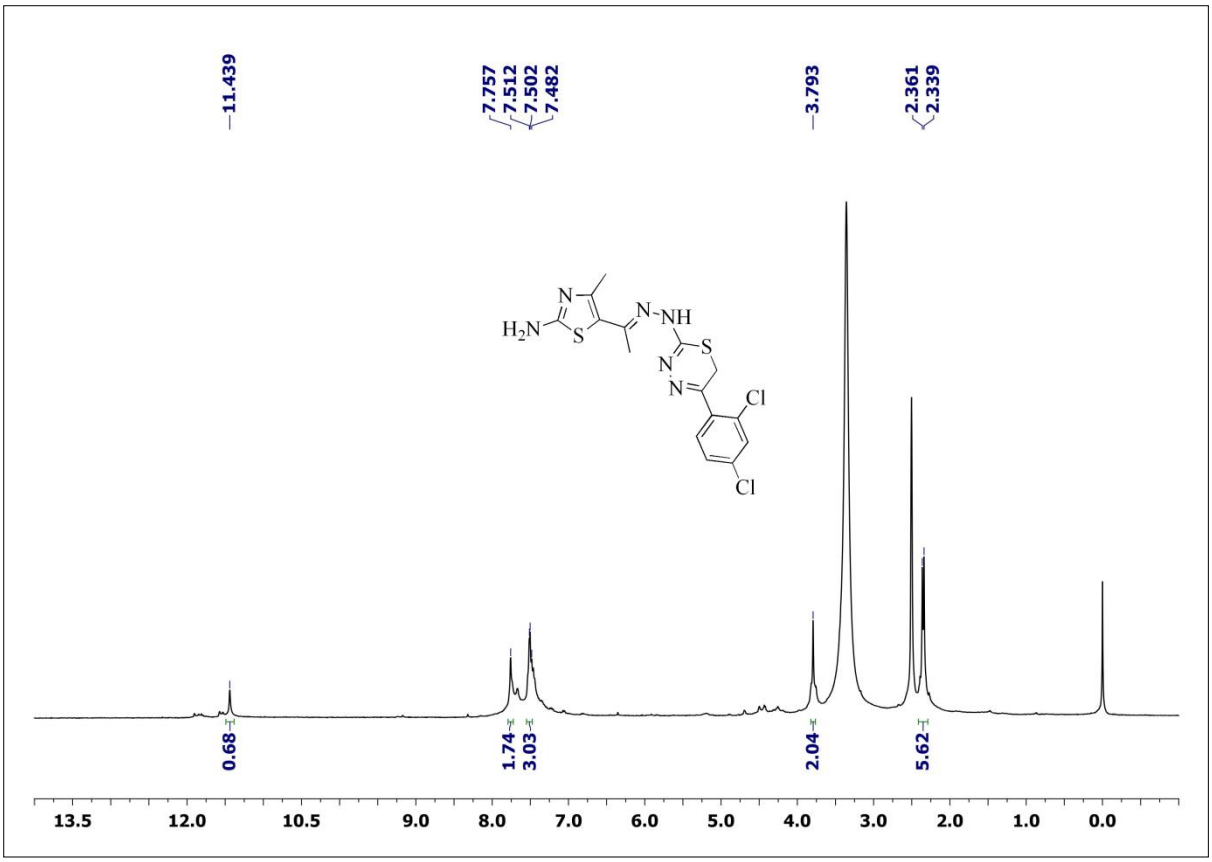
PMR Spectrum of compound **22c**



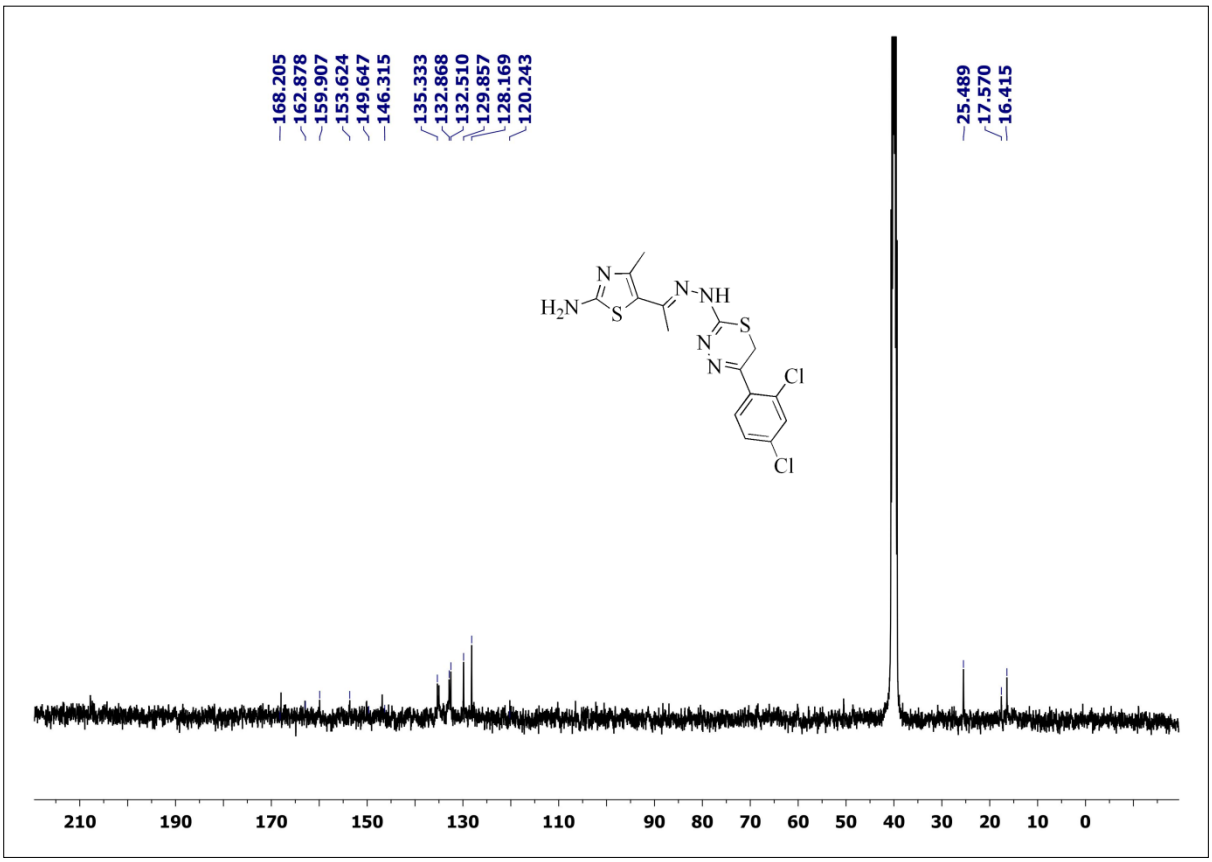
CMR Spectrum of compound **22c**



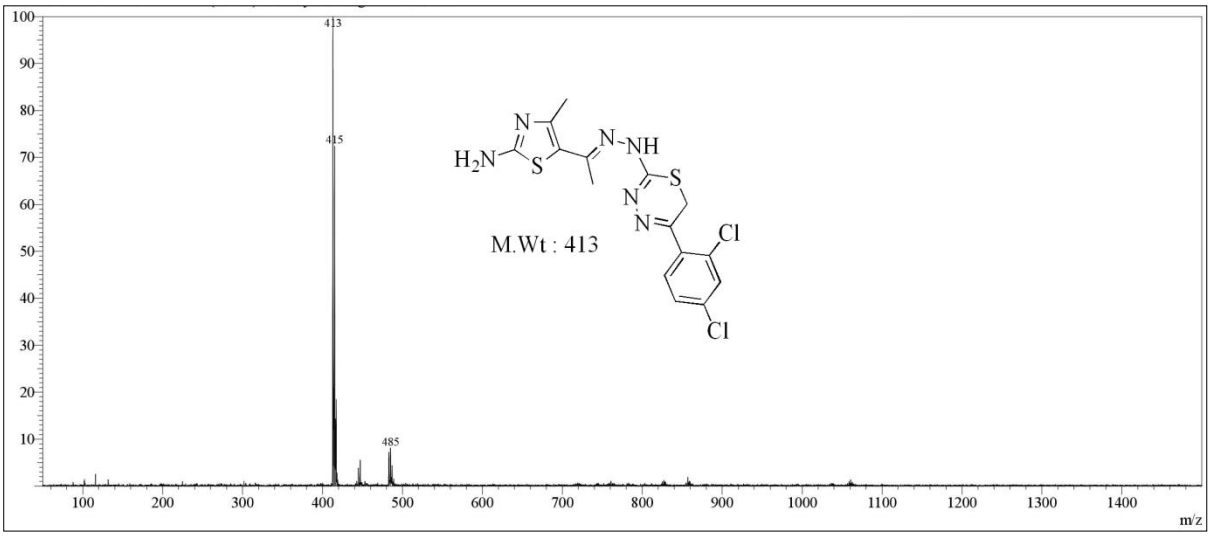
Mass Spectrum of compound **22c**



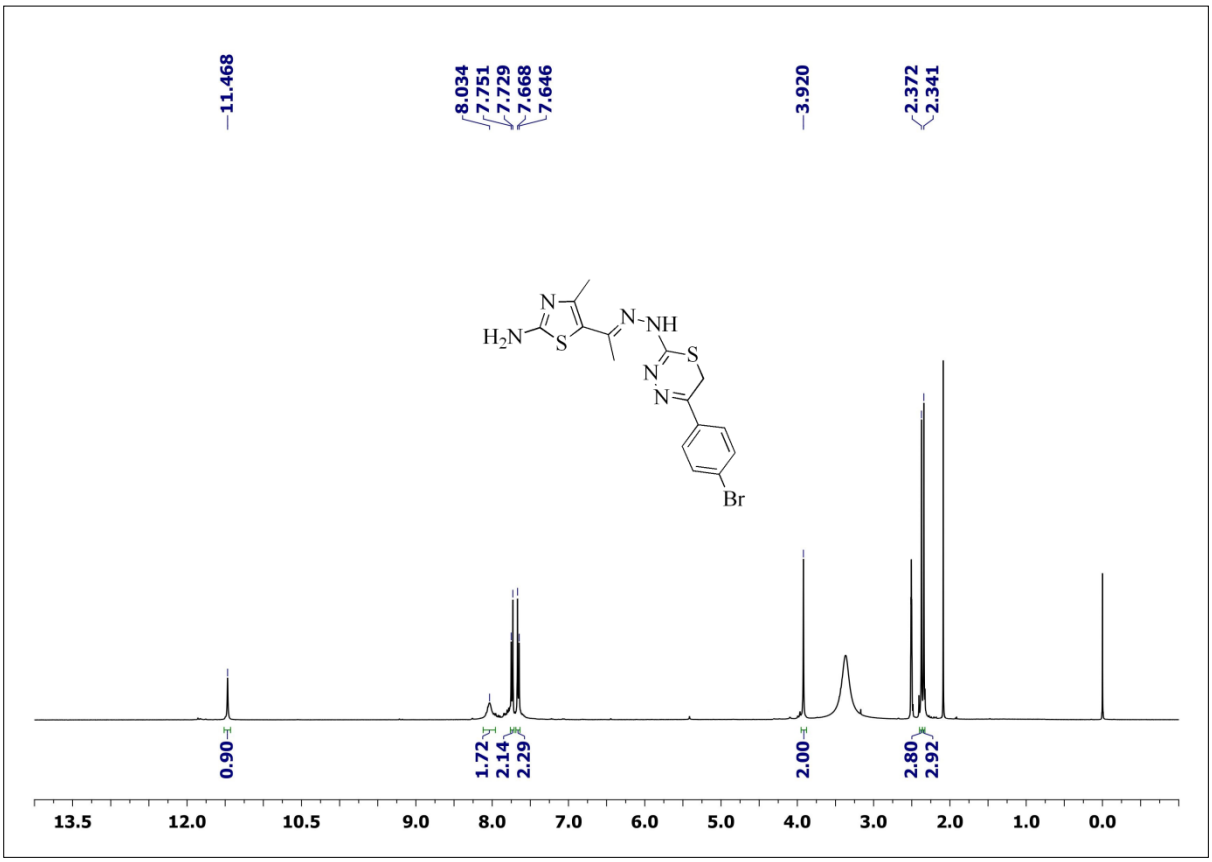
PMR Spectrum of compound **22d**



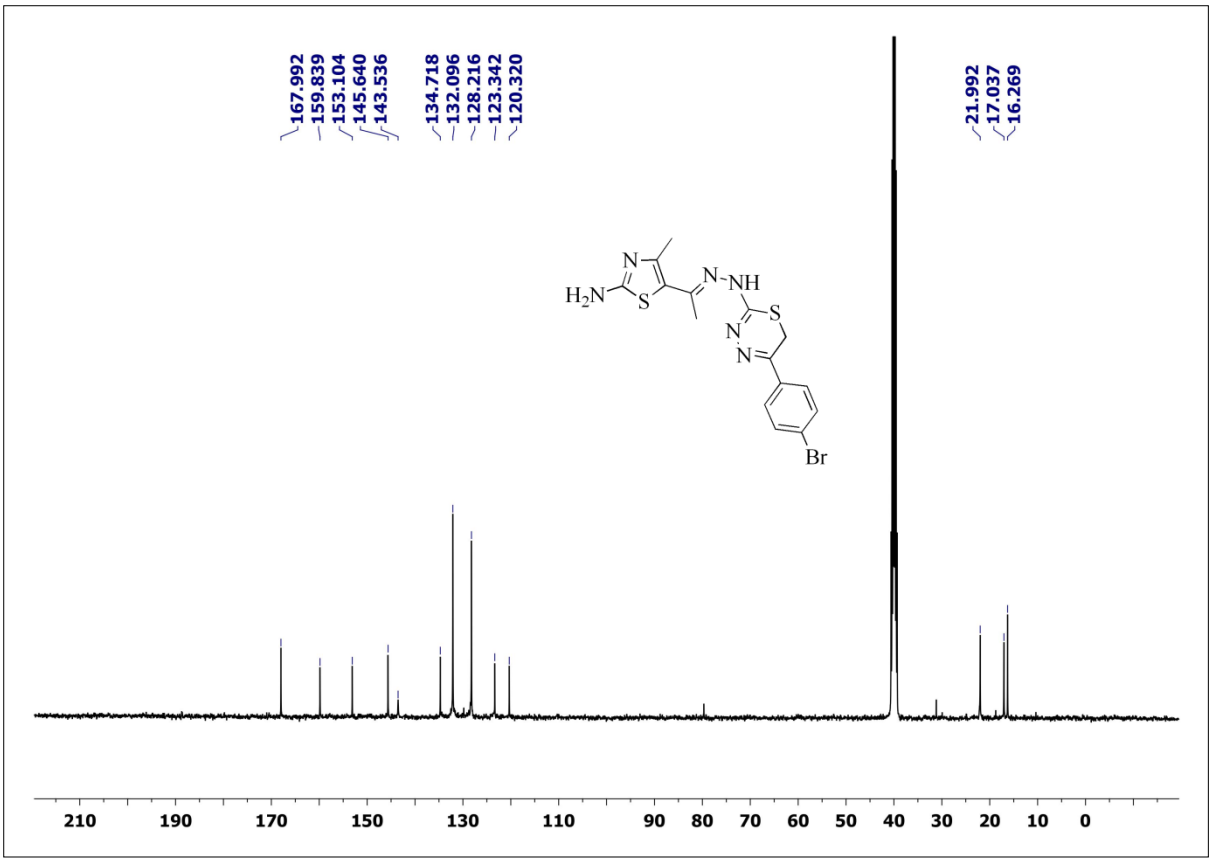
CMR Spectrum of compound **22d**



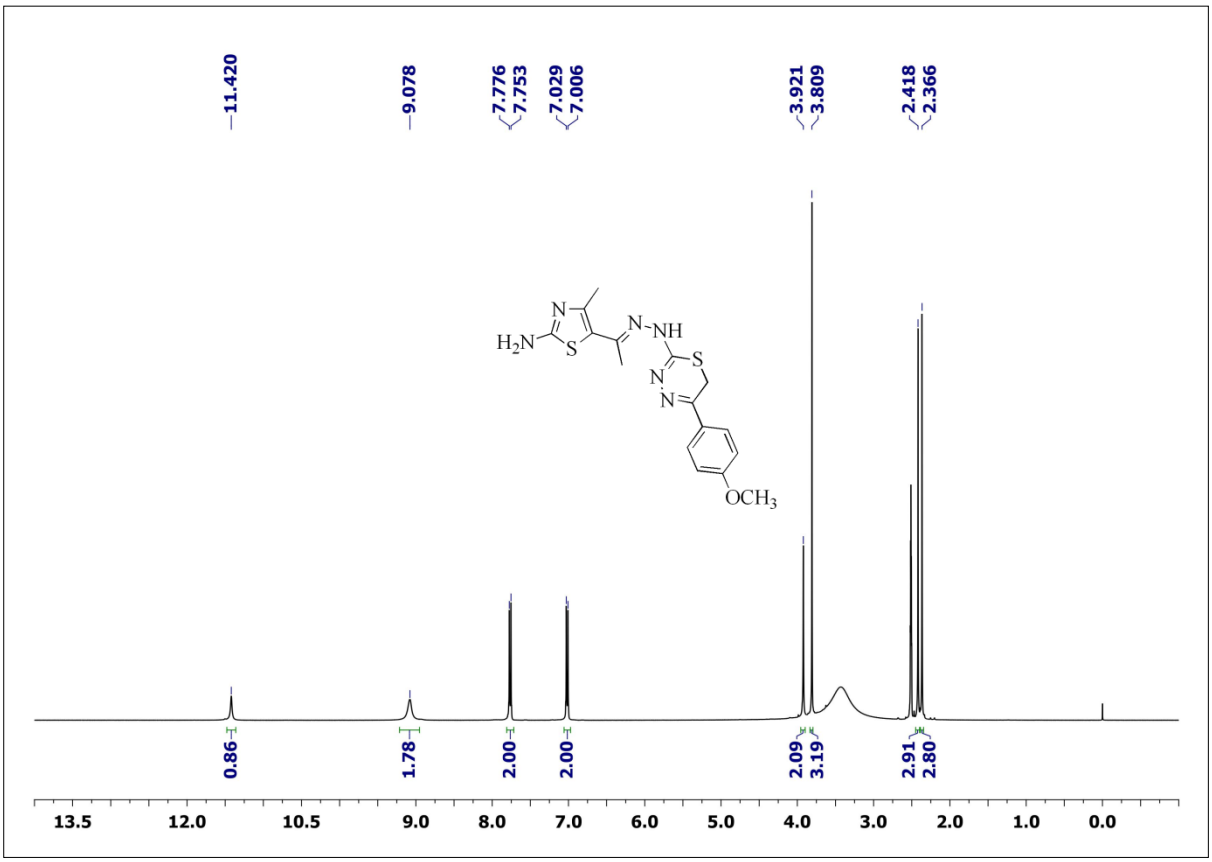
Mass Spectrum of compound **22d**



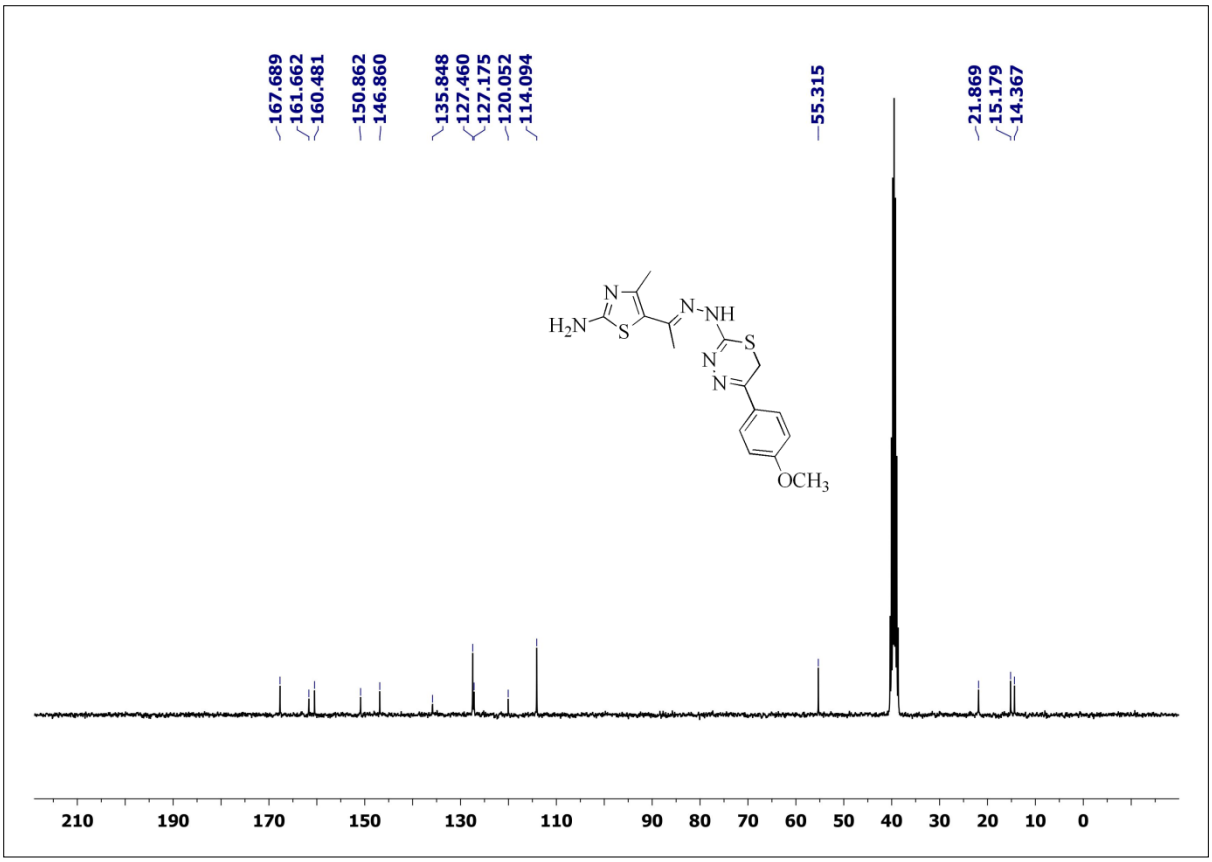
PMR Spectrum of compound **22e**



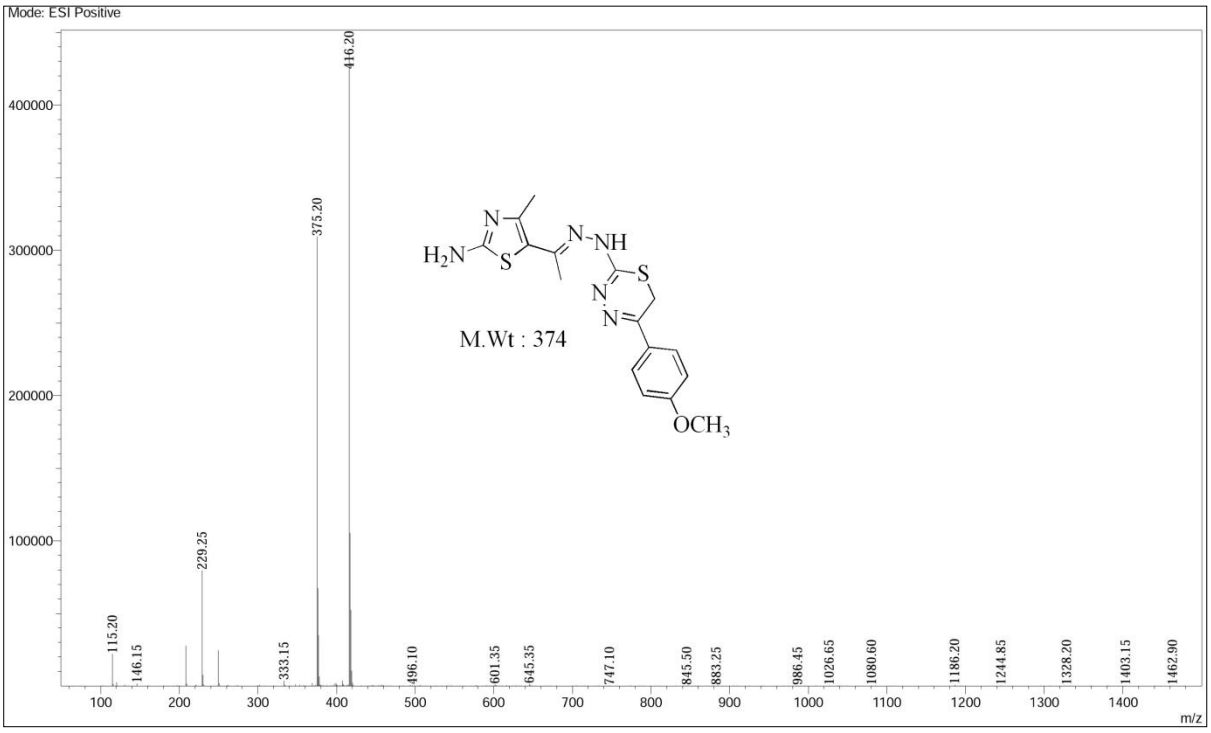
CMR Spectrum of compound **22e**



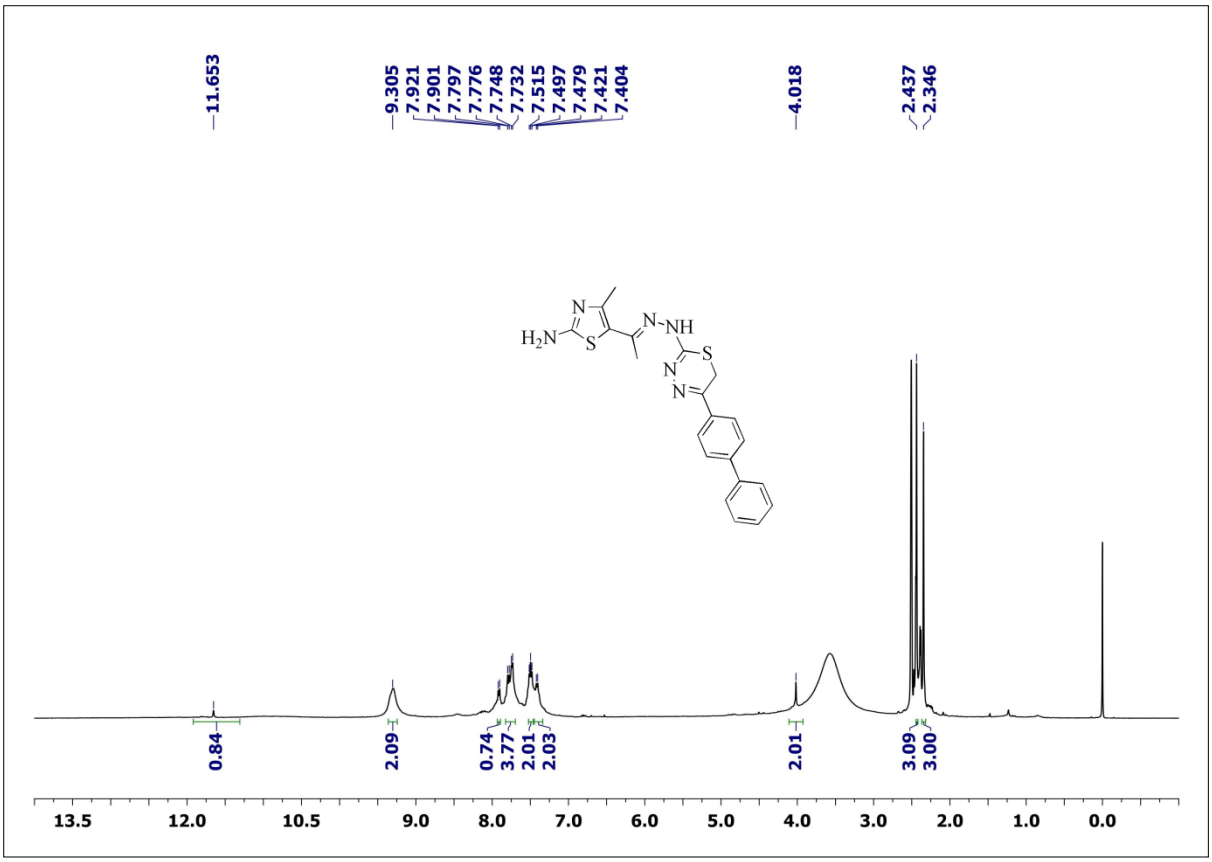
PMR Spectrum of compound **22f**



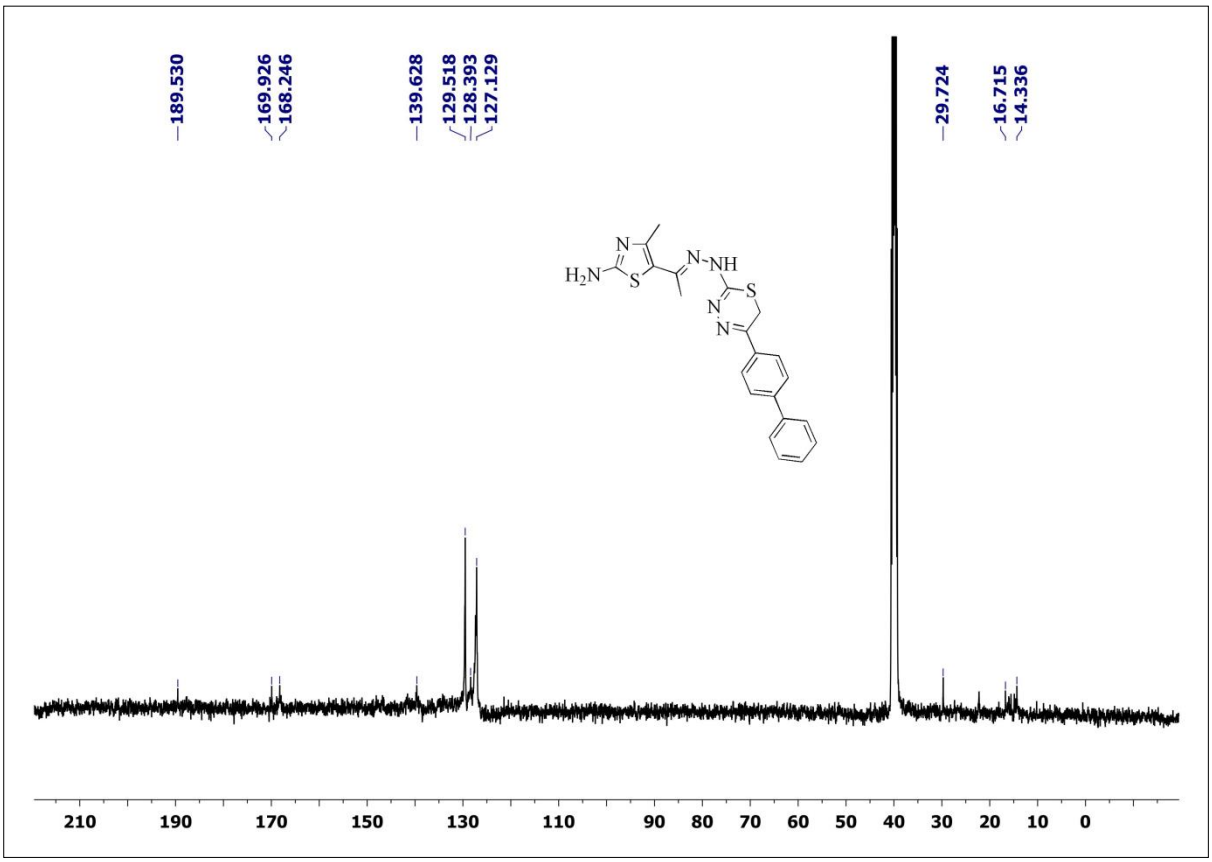
CMR Spectrum of compound **22f**



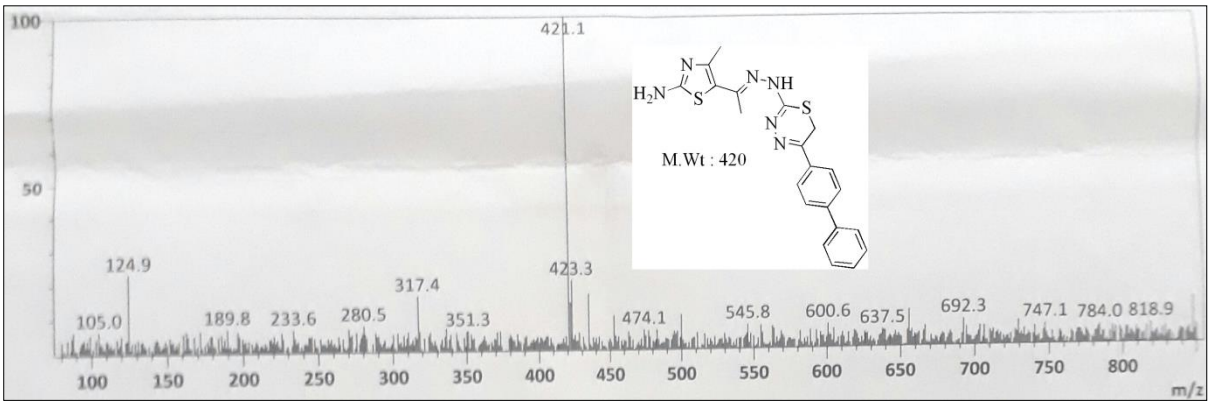
Mass Spectrum of compound **22f**



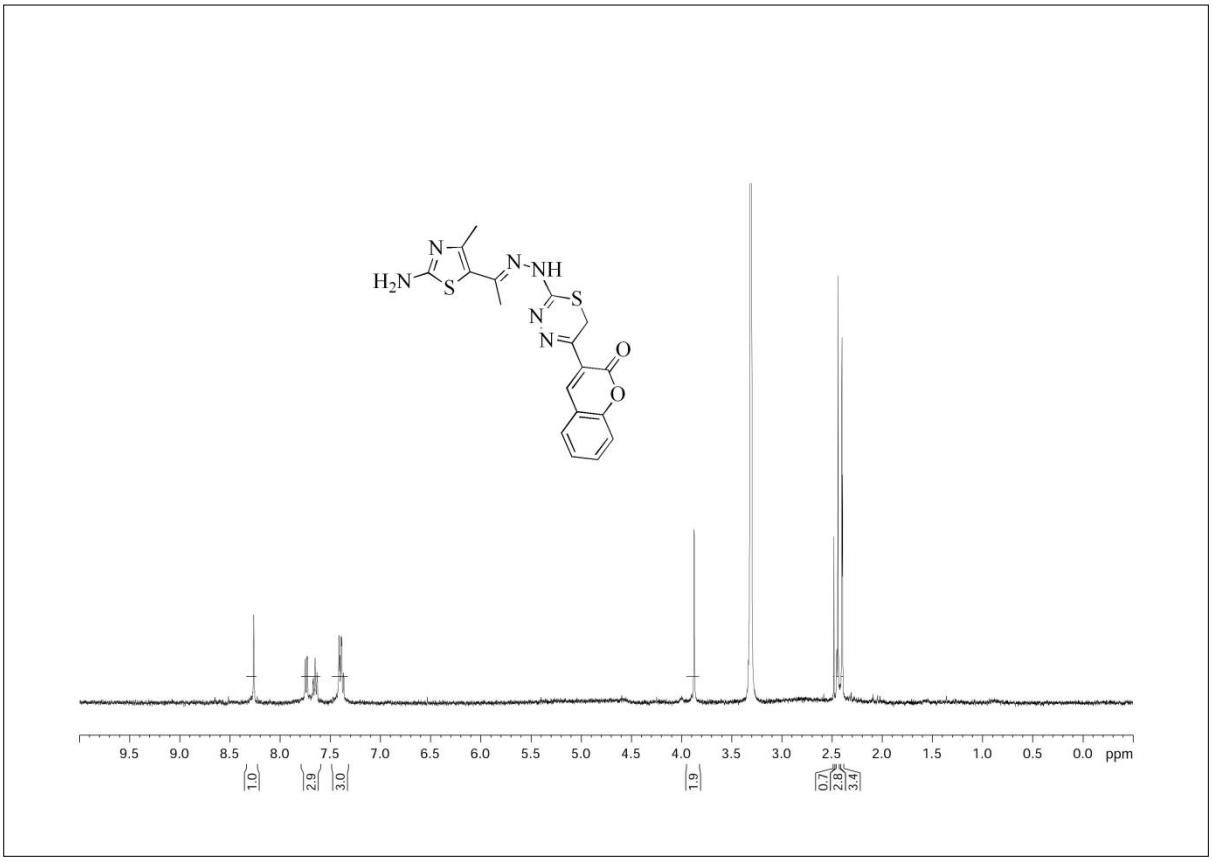
PMR Spectrum of compound **22g**



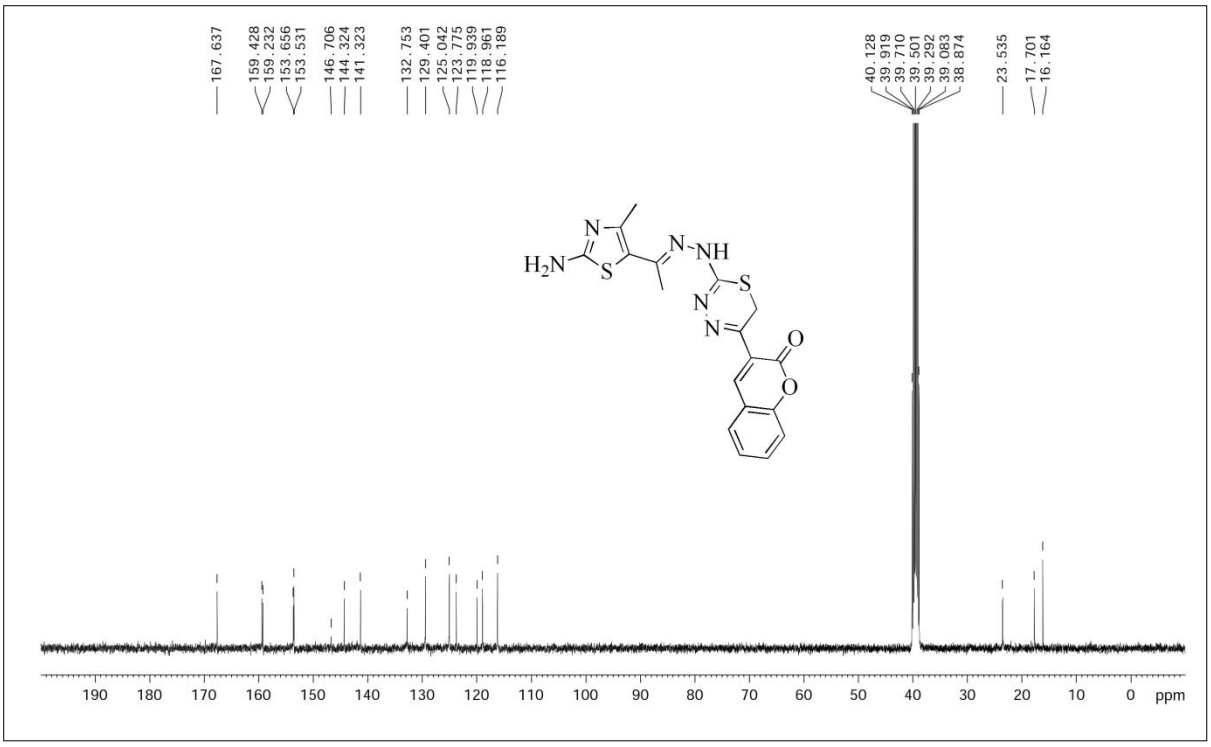
CMR Spectrum of compound **22g**



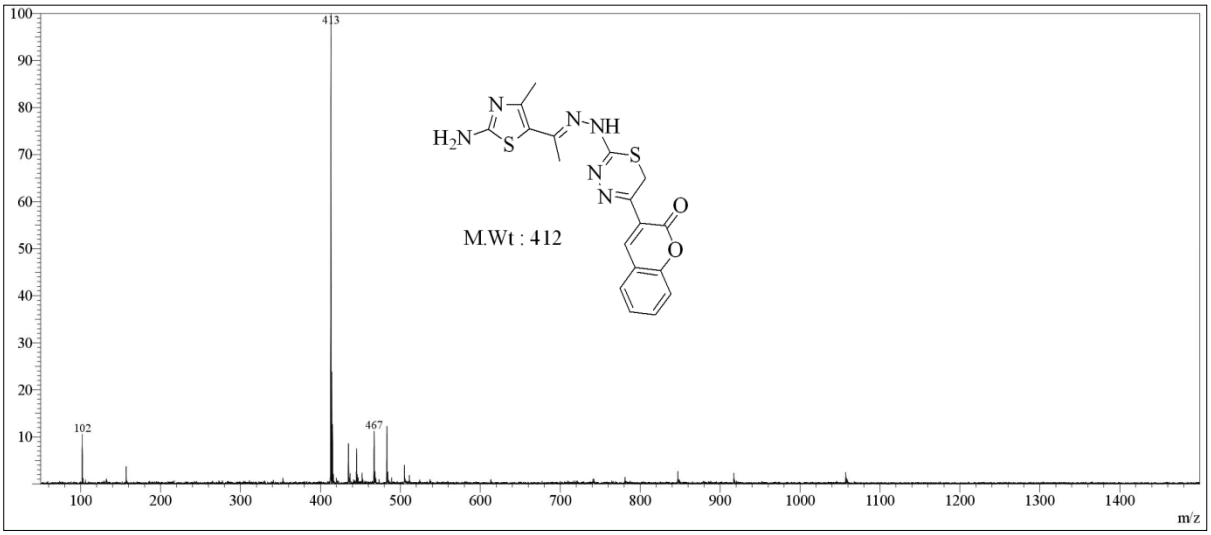
Mass Spectrum of compound **22g**



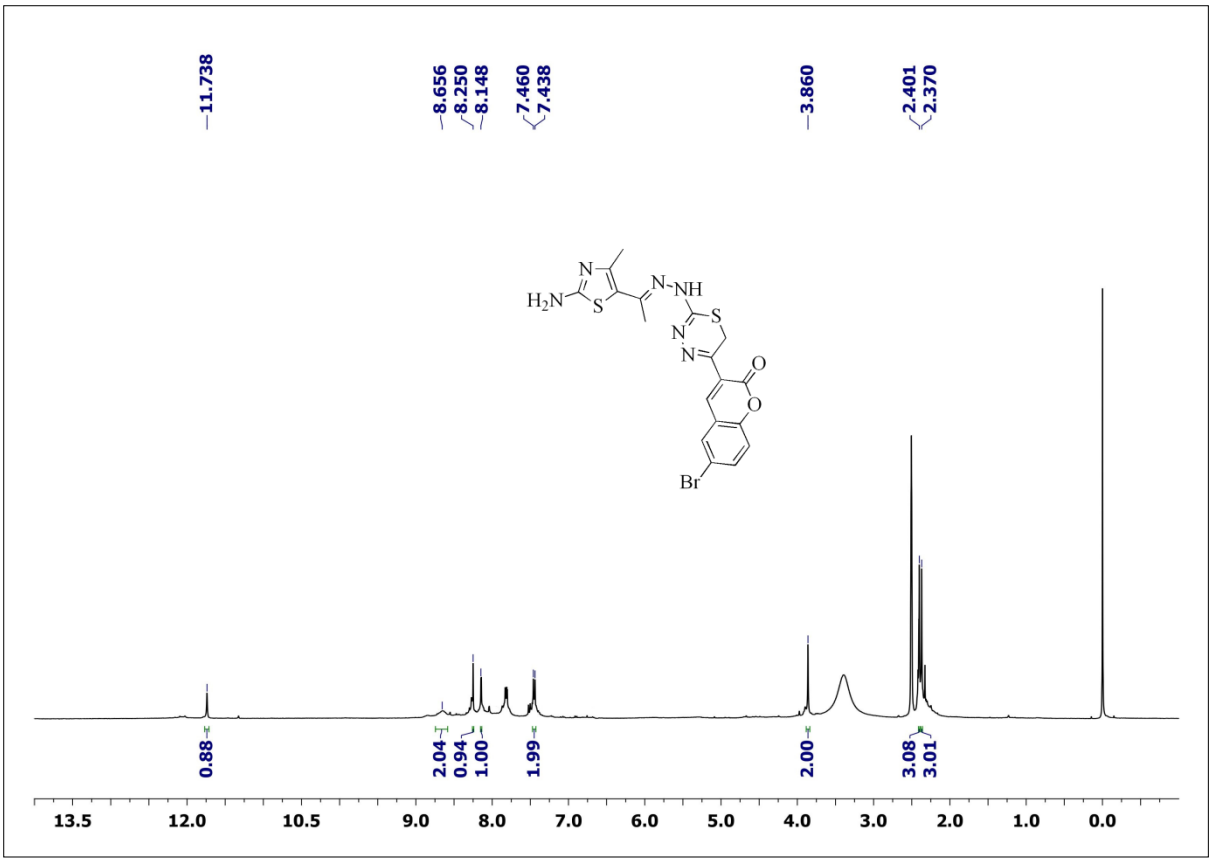
PMR Spectrum of compound **22h**



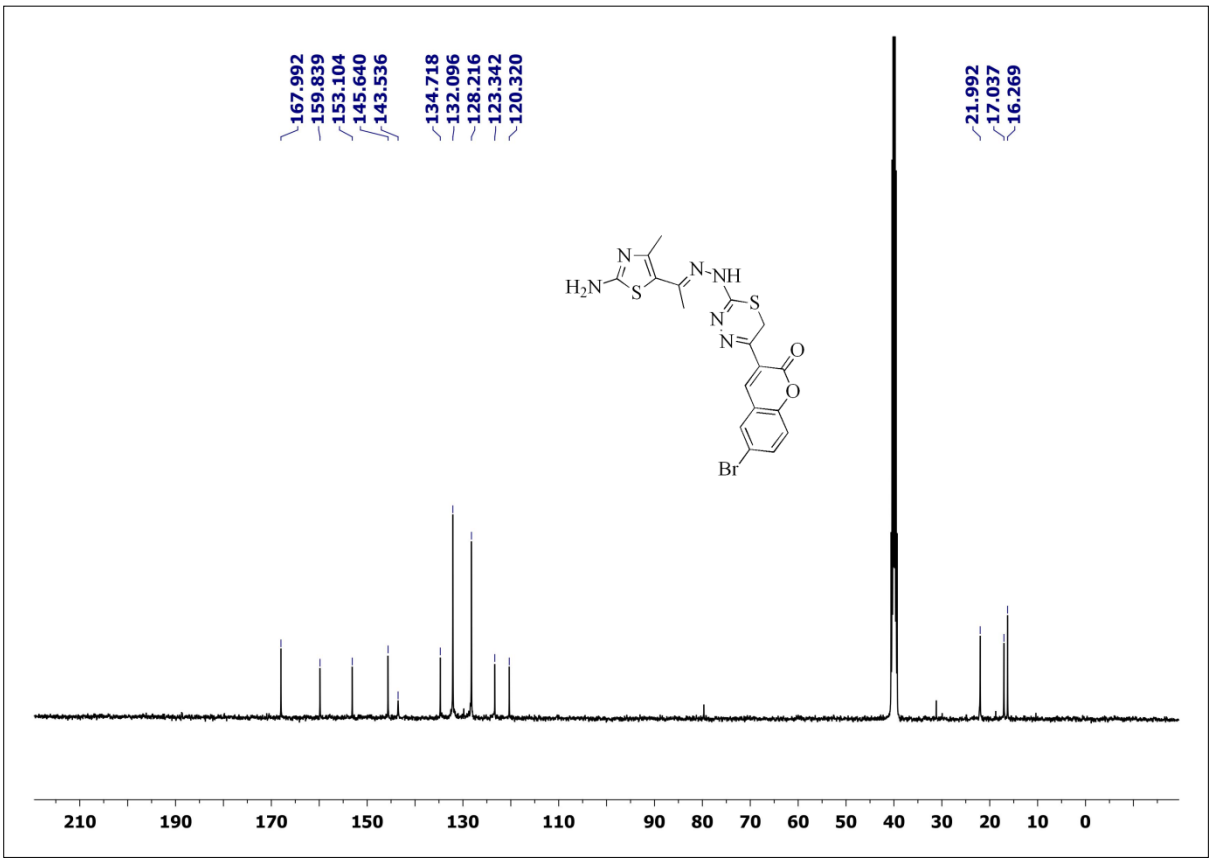
CMR Spectrum of compound **22h**



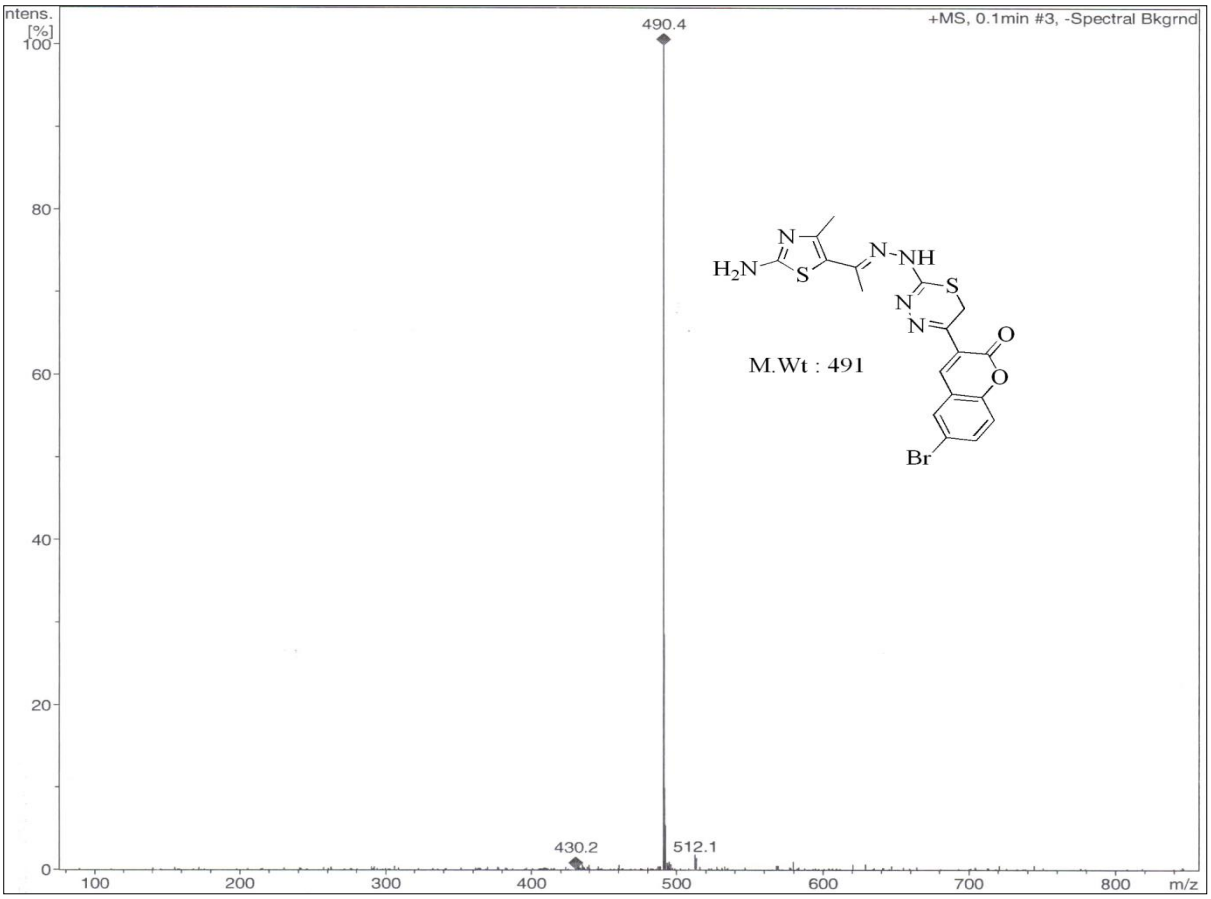
Mass Spectrum of compound **22h**



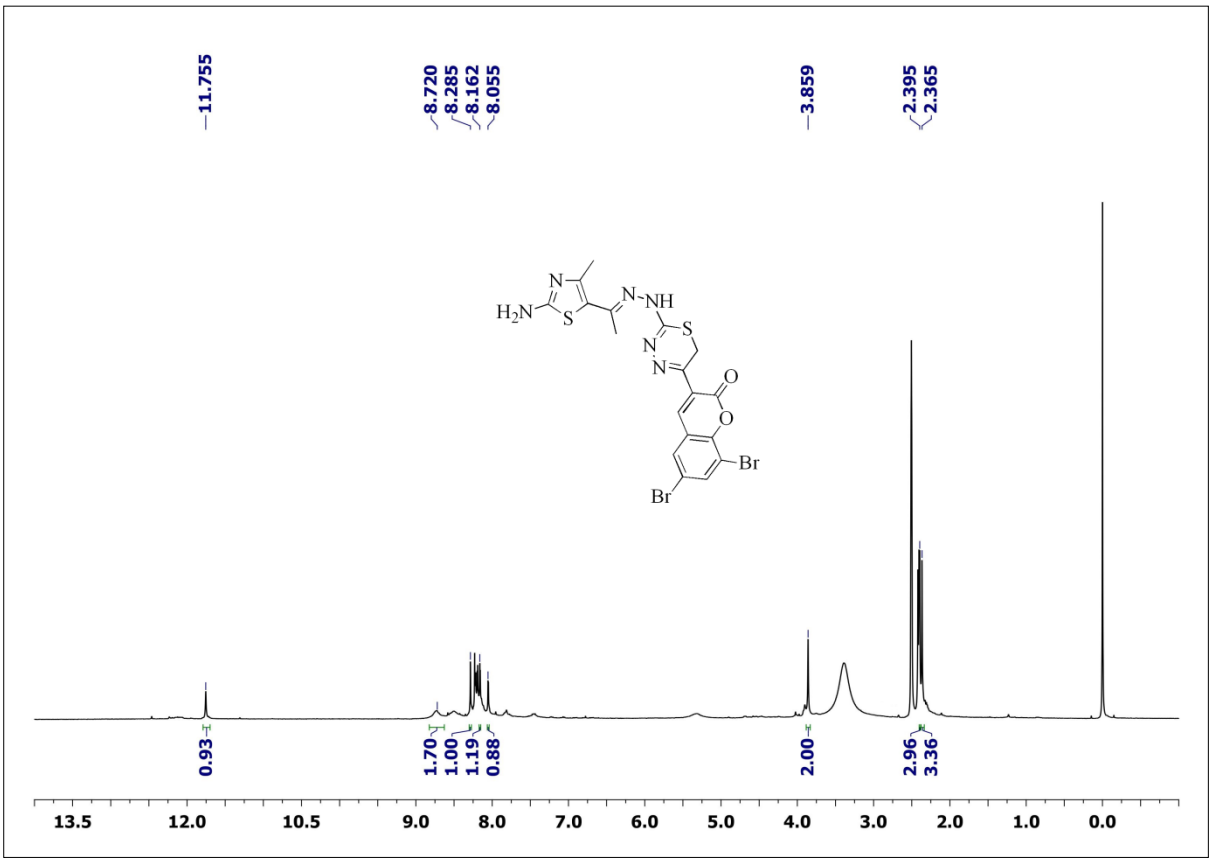
PMR Spectrum of compound **22i**



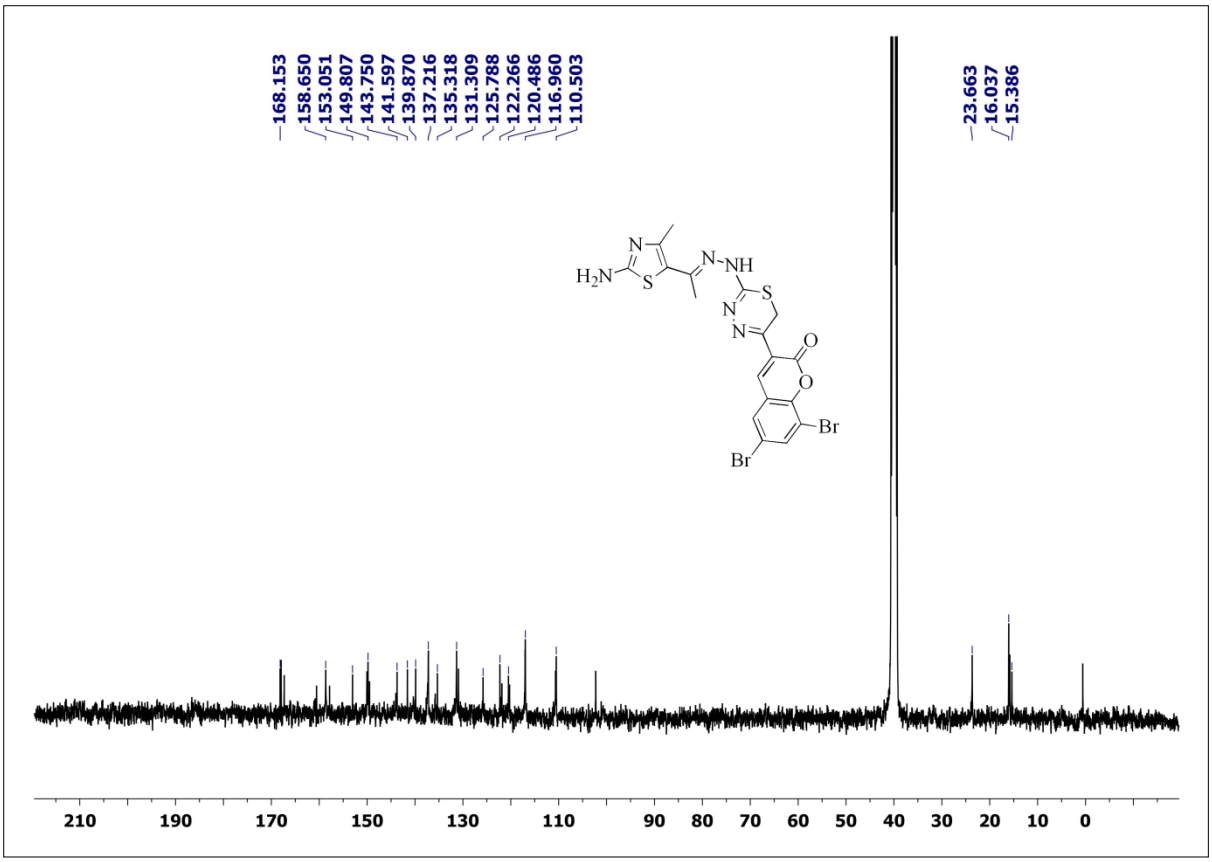
CMR Spectrum of compound **22i**



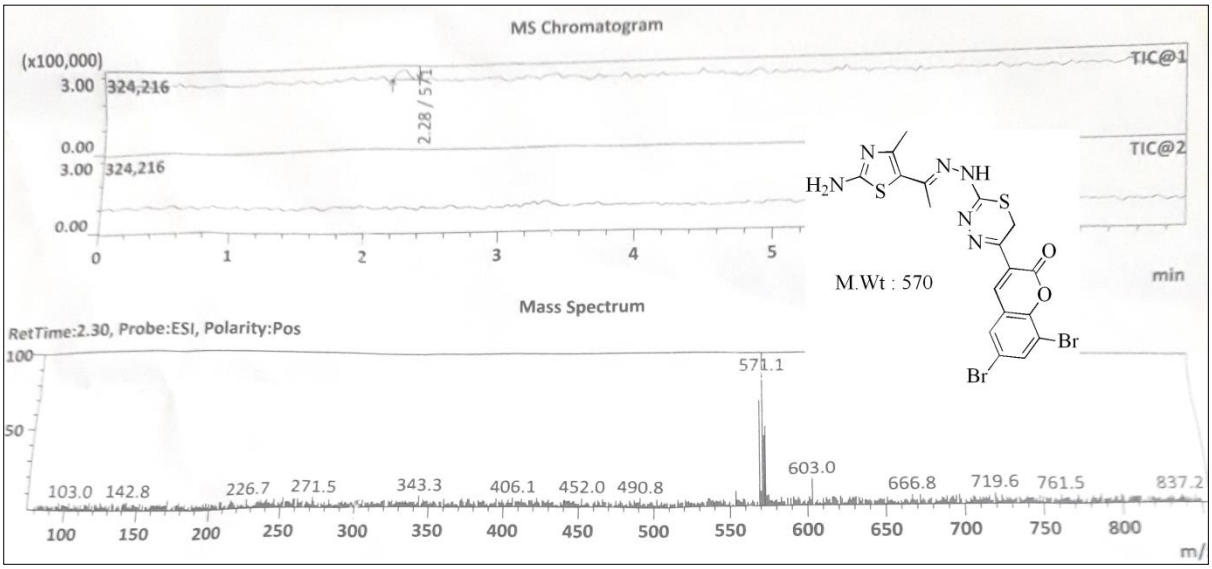
Mass Spectrum of compound **22i**



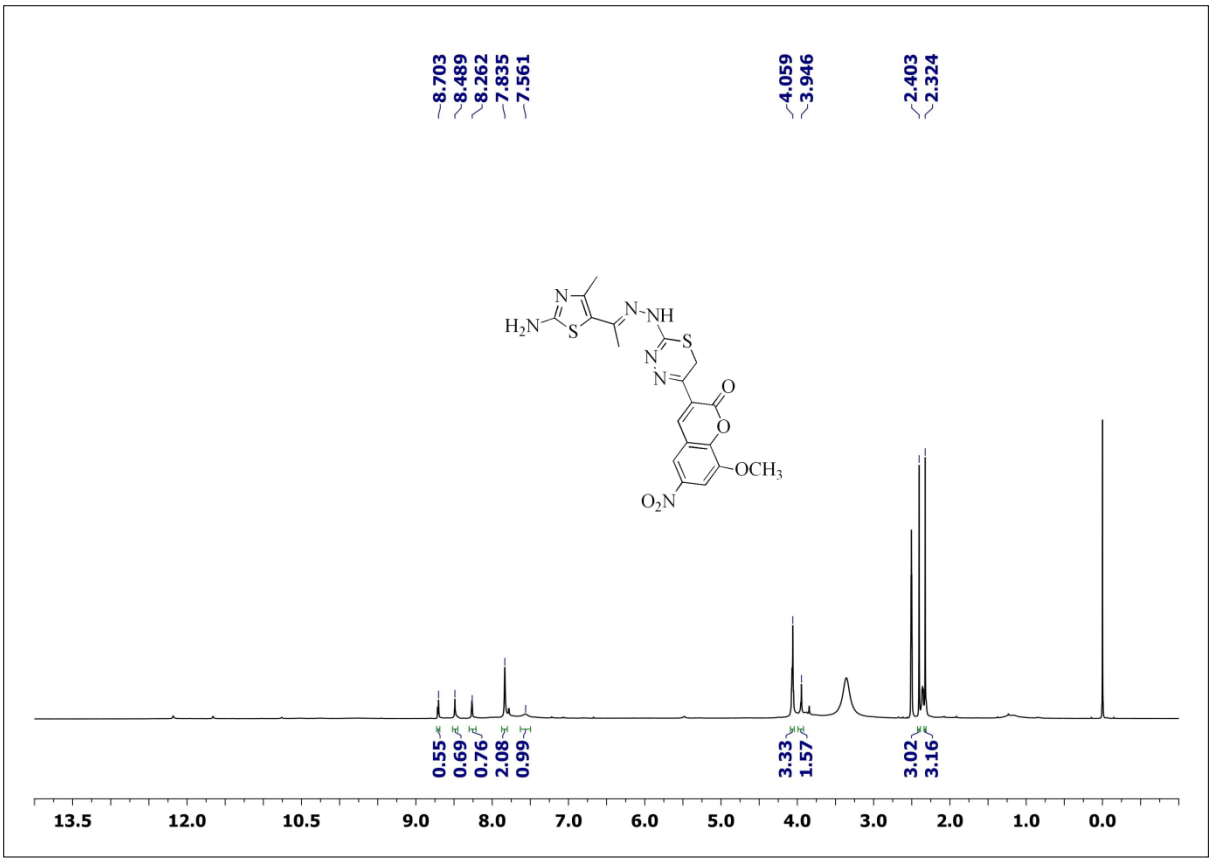
PMR Spectrum of compound **22j**



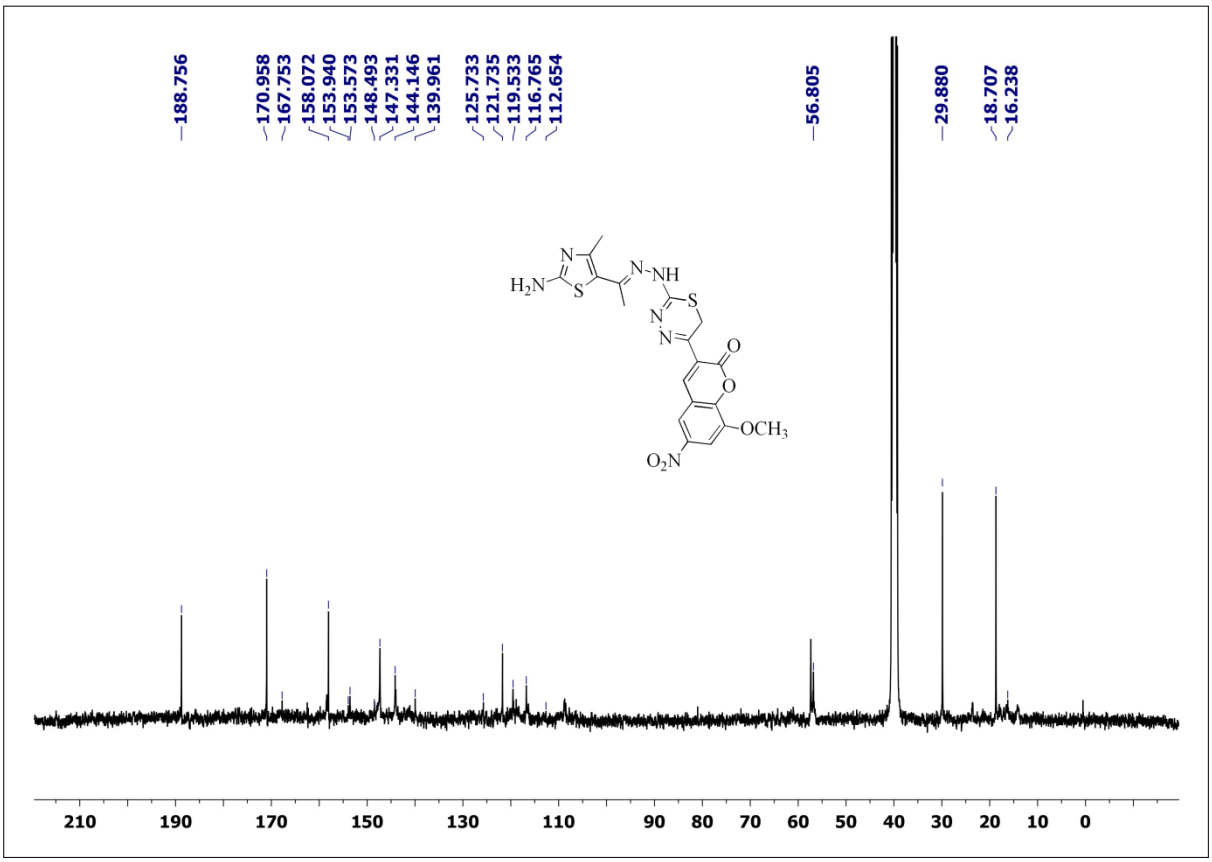
CMR Spectrum of compound **22j**



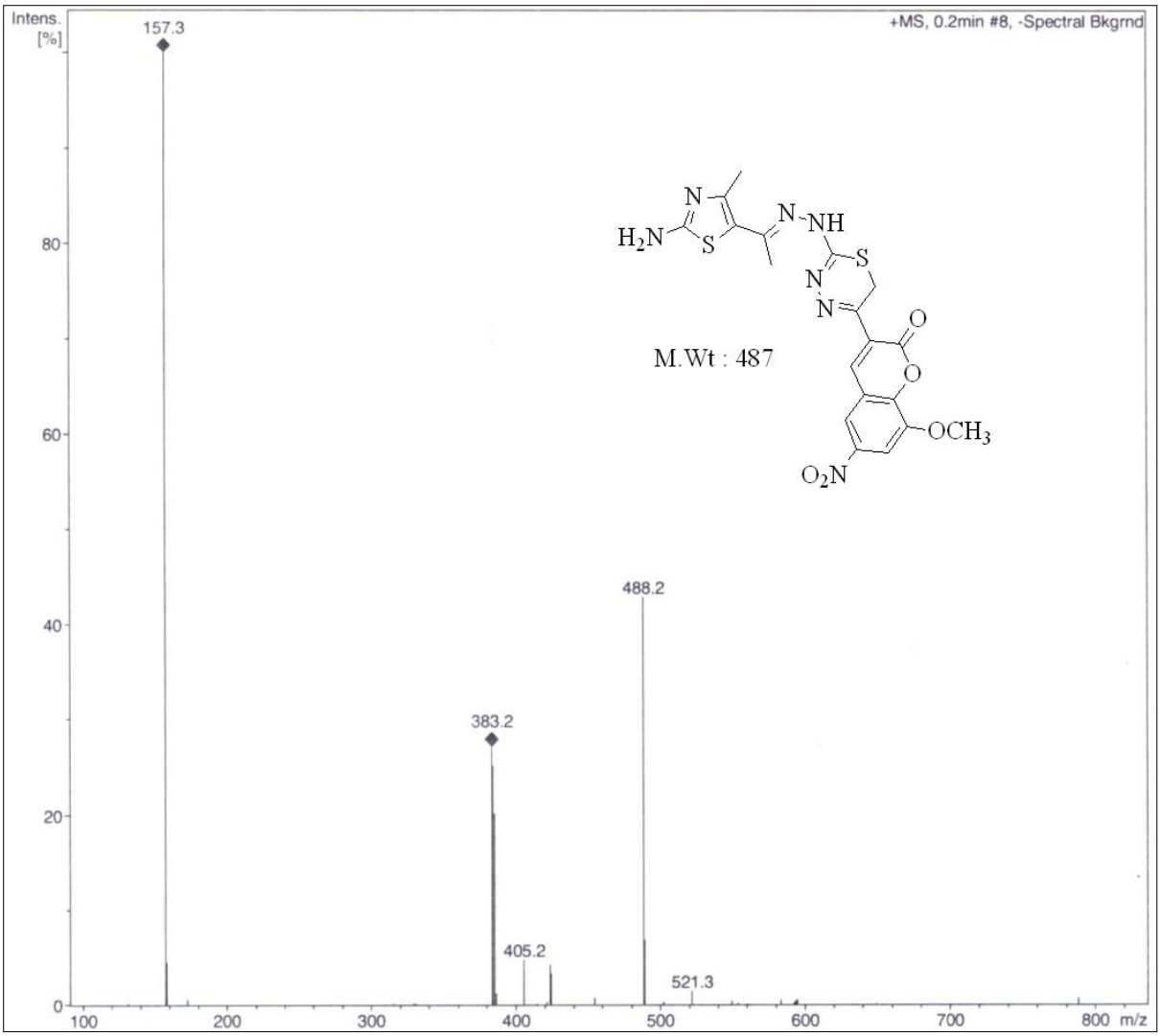
Mass Spectrum of compound **22j**



PMR Spectrum of compound **22k**



CMR Spectrum of compound **22k**



Mass Spectrum of compound **22k**

REFERENCES

[1] Fu, P.; MacMillan, J. B. *J. Nat. Prod.* **2015**, *78*, 548-551.

[2] Zhang, C.; Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Zink, D. L.; Occi, J.; Birdsall, G.; Venugopal, J.; Ushio, M.; Burgess, B.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *J. Nat. Prod.* **2009**, *72*, 841-847.

[3] He, H.; Wang, X.; Shi, L.; Yin, W.; Yang, Z.; He, H.; Liang, Y. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3263-3270.

[4] Bueno, J. M.; Carda, M.; Crespo, B.; Cunat, A. C.; de Cozar, C.; Leon, M. L.; Marco, J. A.; Roda, N.; Sanz-cervera, J. F. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3938-3944.

[5] Guo, X.; Zhao, B.; Fan, Z.; Yang, D.; Zhang, N.; Wu, Q.; Yu, B.; Zhou, S.; Kalinina, T. A.; Belskaya, N. P. *J. Agric. Food Chem.* **2019**, *67*, 1647-1655.

[6] Wang, N. Y.; Xu, Y.; Zuo, W. Q.; Xiao, K. J.; Liu, L.; Zeng, X. X.; You, X. Y.; Zhang, L. D.; Gao, C.; Liu, Z. H.; Ye, T. H.; Xia, Y.; Xiong, Y.; Song, X. J.; Lei, Q.; Peng, C. T.; Tang, H.; Yang, S. Y.; Wei, Y. Q.; Yu, L. T. *J. Med. Chem.* **2015**, *58*, 2764-2778.

[7] Abu-Melha, S. *Molecules.* **2018**, *23*, 434.

[8] Shao, H.; Shi, S.; Huang, S.; Hole, A. J.; Abbas, A. Y.; Baumli, S.; Liu, X.; Lam, F.; Foley, D. W.; Fischer, P. M.; Noble, M.; Endicott, J. A.; Pepper, C.; Wang, S. *J. Med. Chem.* **2013**, *56*, 640-659.

[9] El-sayed, E. H.; Fadda, A. A. *J. Heterocyclic Chem.* **2018**, *55*, 2251-2260.

[10] Cao, S.; Liu, A.; Liu, W.; Liu, X.; Ren, Y.; Pei, H.; Huang, L.; Zheng, X.; Huang, M.; Wu, D. *J. Heterocyclic Chem.* **2017**, *54*, 3395-3402.

[11] Muhammad, Z. A.; Masaret, G. S.; Amin, M. M.; Abdallah, M. A.; Farghaly, T. A. *Med Chem.* **2017**, *13*, 226-238.

[12] Yang, Y.; Feng, Z.; Jiang, J.; Yang, Y.; Pan, X.; Zhang, P. *Chem. Pharm. Bull.* **2011**, *59*, 1016-1019.

[13] Xin-Yong, L.; Ren-zhang, Y.; Yan, W.; Peng, Z.; Erik De, C.; Christophe, P.; Myriam, W.; Maria, T. M.; Salvador, V. *Arch. Pharm. Chem. Life Sci.* **2008**, *341*, 216-222.

[14] Abdel-Aziem, A. *J. Heterocyclic Chem.* **2015**, *52*, 251-259.

[15] Abdel-Rahman, T. M. *Phosphorus, Sulfur Silicon Relat Elem.* **2006**, *181*, 1737-1754.

[16] Milan, C.; Valentina, P.; Maja, M.; Bojan, S.; Elizabeta, H. S. *Molecules.* **2014**, *19*, 1163-1177.

[17] Borcea, A. M.; Marc, G.; Ionut, I.; Vodnar, D. C.; Vlase, L.; Gligor, F.; Pricopie, A.; Pirnau, A.; Tiperciuc, B.; Oniga, O. *Molecules.* **2019**, *24*, 184.

[18] Velpula, R.; Gondru, R.; Velivela, Y.; Bavantula, R.; *Synth. Commun.* **2015**, *45*, 578-585.

[19] Kurt, B. Z.; Gazioglu, I.; Sonmez, F.; Kucukislamoglu, M. *Bioorg Chem.* **2015**, *59*, 80-90.

[20] Abhale, Y. K.; Shinde, A. D.; Deshmukh, K. K.; Nawale, L.; Sarkar, D.; Choudhari, P. B.; Kumbhar, S. S.; Mhaske, P. C. *Med Chem Res*. **2017**, *26*, 2889-2899.

[21] Zaharia, V.; Ignat, A.; Palibroda, N.; Ngameni, B.; Kuete, V.; Fokunang, C. N.; Moungang, M. L.; Ngadjui, B. T. *Eur. J. Med. Chem.* **2010**, *45*, 5080-5085.

[22] Turan-Zitouni, G.; Altintop, M. D.; Ozdemir, A.; Kaplancikli, Z. A.; Ciftci, G. A.; Temel, H. E. *Eur. J. Med. Chem.* **2016**, *107*, 288-294.

[23] Arshad, A.; Osman, H.; Bagley, M. C.; Lam, C. K.; Mohamad, S.; Zahariluddin, A. S. M. *Eur. J. Med. Chem.* **2011**, *46*, 3788-3794.

[24] Shchegol'kov.; Burgart, Ya. V.; Saloutin, V. I.; Chupakhin, O. N. *Russ. Chem. Bull., Int. Ed.* **2013**, *62*, 220-222.

[25] Kumar, K.; Man-Un Ung, P.; Wang, P.; Wang, H.; Li, H.; Andrews, M. K.; Stewart, A. F.; Schlessinger, A.; DeVita, R. J. *Eur. J. Med. Chem.* **2018**, *157*, 1005-1016.

[26] Ramagiri, R. K.; Vaarla, K.; Vedula, R. R. *Synth. Commun.* **2016**, *46*, 1499-1506.

[27] Moghimi, S.; Shiri, M.; Heravi, M . M.; Kruger, H. G. *Tetrahedron Lett.* **2013**, *54*, 6215-6217.

[28] Pavurala, S.; Vaarla, K.; Vedula, R. R. *Phosphorus, Sulfur Silicon Relat Elem.* **2017**, *192*, 69-72.

CHAPTER-V

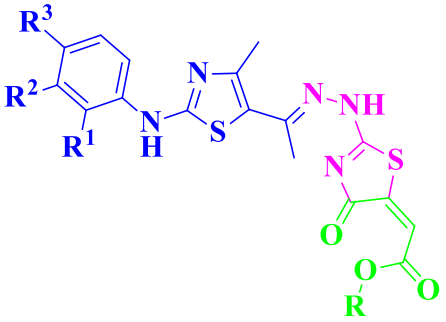
ONE-POT, FIVE COMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(2-((*E*)-2-(1-(4-METHYL-2-(PHENYLAMINO)THIAZOL-5YL)ETHYLIDENE) HYDRAZINYL)-4-OXOTHIAZOL-5(4*H*)-YLIDENE)ACETATES

AND

ONE POT MULTICOMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(4-OXO-2-((*E*)-2-((3-(2-OXO-2*H*-CHROMEN-3-YL)-1-PHENYL-1*H*-PYRAZOL-4-YL)METHYLENE)HYDRAZINYL)THIAZOL-5(4*H*)-YLIDENE)ACETATES

SECTION-A

ONE-POT, FIVE COMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(2-((*E*)-2-(1-(4-METHYL-2-(PHENYLAMINO)THIAZOL-5YL)ETHYLIDENE) HYDRAZINYL)-4-OXOTHIAZOL-5(4*H*)-YLIDENE)ACETATES



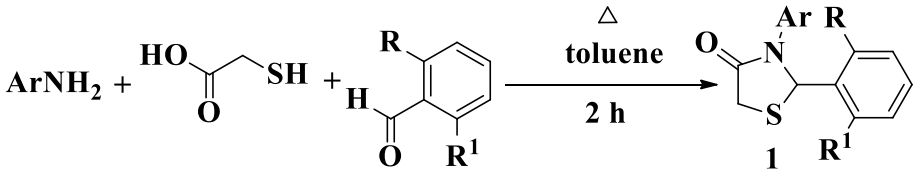
INTRODUCTION

Thiazoles and their derivatives are abundantly found in nature.[1] Thiazole core nucleus found in many drugs, acts as intermediate in many organic synthetic reactions.[2] These possess a wide range of biological activities[3] such as antitubercular,[4] anticancer,[5] antiviral,[6] antimalarial,[7] antibacterial,[8] antitumor[9] and anti-inflammatory,[10] antidiabetic,[11] anti-oxidant activities.[12]

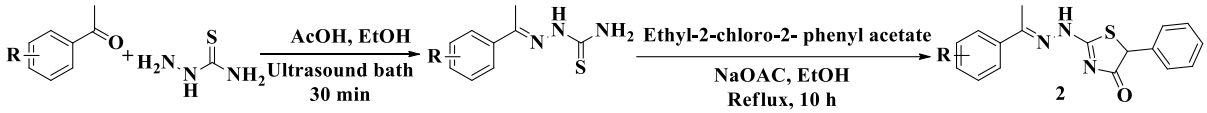
Thiazolidinones are found in many drugs and heterocyclic compounds. Thiazolidinones show diversified biological activities[13] such as antifungal,[14] antibacterial,[15] anticancer,[16] anti-HIV,[17] anti-oxidant,[18] anti-inflammatory,[19] antiviral,[20] antidiabetic,[21] antimicrobial activities.[22]

The following is a brief review of literature on synthetic methods of thiazolidinones.

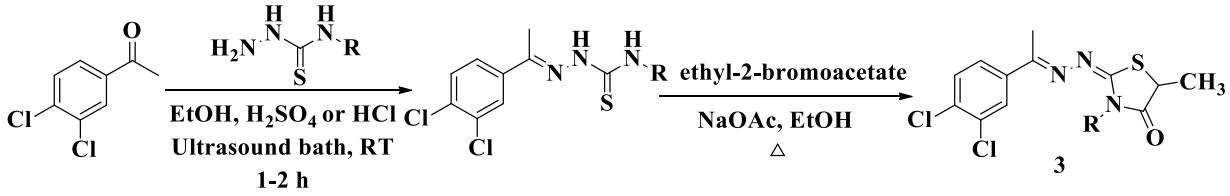
Barreca *et al.*[23] synthesized 2,3-diaryl-1,3-thiazolidin-4-ones (**1**) by using an equimolar amount of 2,6-dihalo-substituted benzaldehyde with aromatic amine and excess of mercapto acetic acid in toluene.



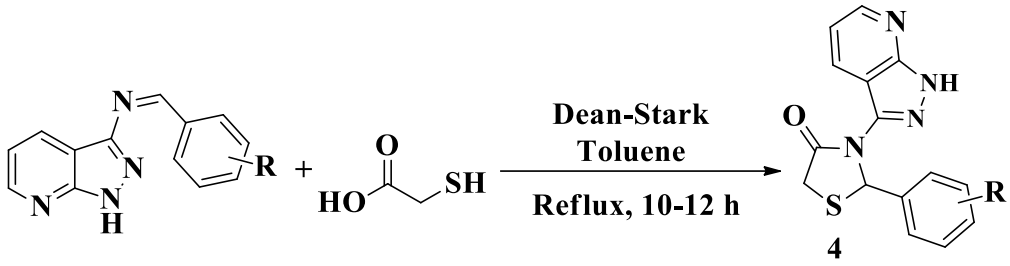
Moreira *et al.*[24] synthesized thiazolidinones by the condensation reaction of aryl ketone with thiosemicarbazide in presence of acetic acid, ethanol under ultrasound to give arylthiosemicarbazone. This on further treatment with ethyl-2-chloro-2-phenylacetate in ethanol and sodium acetate gave the corresponding thiazolidinones (**2**).



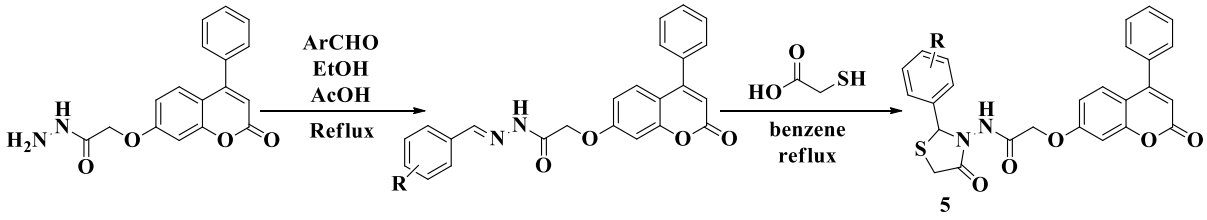
Filho *et al.*[25] reported the synthesis of 2-[1-(3,4-dichlorophenyl)ethylidenohydrazone]thiazolidin-4-one (**3**) by using 3,4-dichloroacetophenone with thiosemicarbazide in ethanol and presence of H_2SO_4 or HCl to give thiosemicarbazone. This on further reaction with ethyl-2-bromoacetate in ethanol and sodium acetate under reflux gave title compound.



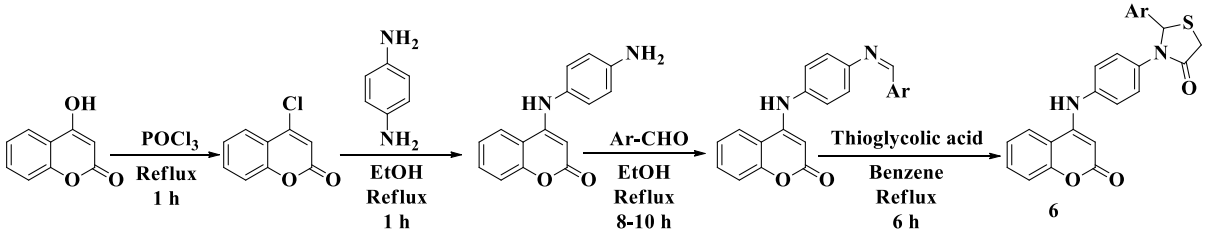
Compounds (**4**) were synthesized by Kundariya *et al.*[26] using (*Z*)-N-benzylidene-1*H*-pyrazolo[3,4-*b*]pyridine-3-amine with mercaptoacetic acid in toluene under reflux.



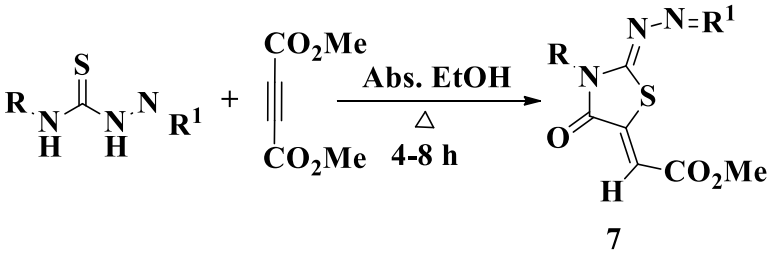
Batran *et al.*[27] prepared 2-(2-oxo-4-phenyl-2*H*-chromen-7-yloxy)-*N*-(2-(4fluorophenyl)-4-oxothiazolidin-3-yl)acetamides (**5**) by the reaction of Schiff bases 2-((2-oxo-4-phenyl-2*H*-chromen-7-yl)oxy)acetohydrazides with thioglycolic acid in dry benzene under reflux. The schiff bases of 2-((2-oxo-4-phenyl-2*H*-chromen-7-yl)oxy)acetohydrazide were obtained by condensation of aromatic aldehyde with 2-((2-oxo-4-phenyl-2*H*-chromen-7-yl)oxy)acetohydrazide in a mixture of ethanol and acetic acid.



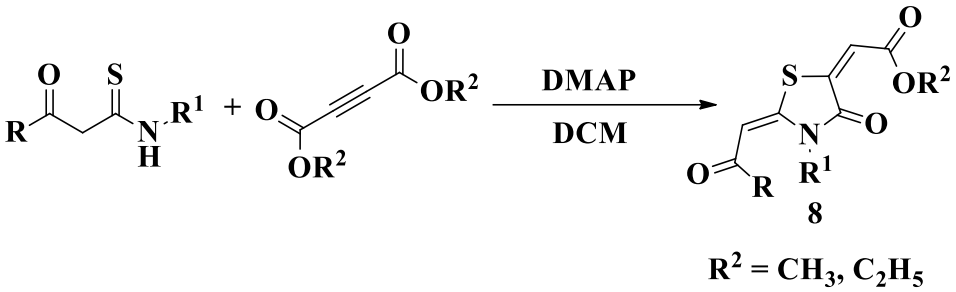
Patel *et al.*[28] synthesized 3-[4-(2-oxo-2*H*-chromen-4-ylamino)-phenyl]-2-phenyl-thiazolidin-4-ones (**6**). 4-Hydroxycoumarin reacts with $POCl_3$ to give 4-chlorocoumarin, which on further treatment with p-phenylene diamine in ethanol and triethylamine gave 4-[(4-aminophenyl)amino]-2*H*-chromen-2-one. This compound reacts with aldehydes in absolute ethanol, catalytic amount of piperidine under reflux to afford Schiff bases. These on treatment with thioglycolic acid in dry benzene gave final compounds (**6**).



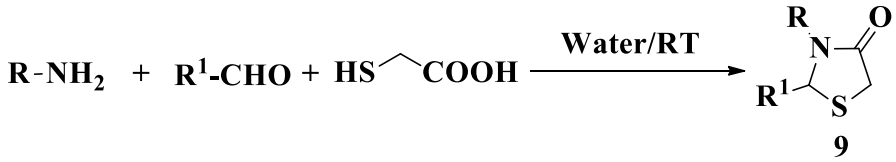
(*Z*)-Methyl-2-((*Z*)-3-(cyclopentylideneamino)-4-oxo-2-(phenylimino)thiazolidin-5-ylidene)acetates (**7**) were synthesized by Hassan *et al.*[29] they have condensed alkylidene-*N*-substituted hydrazinecarbothioamides with dimethyl acetylene dicarboxylate in ethanol under reflux to yield **7**.



Functionalized thiazolidinones (**8**) synthesis was reported by Verma *et al.*[30] β-Keto thioamides and dialkylacetylene dicarboxylates were reacted in presence of DMAP to produce the compounds **8**.



Thakare *et al.*[31] described the preparation of 4-thiazolidinones (**9**) using aliphatic or aromatic amine, aromatic aldehydes and mercaptoacitic acid in water.



SECTION-A

PRESENT WORK

Thiazoles and thiazolidinones are biologically important compounds and hence large demand is there for their synthesis.

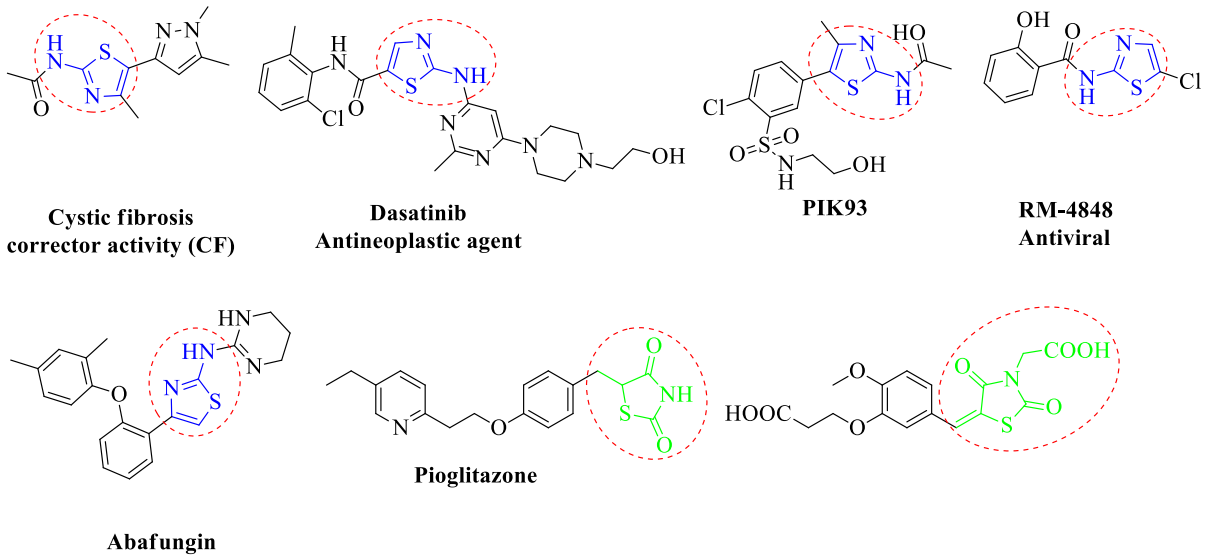
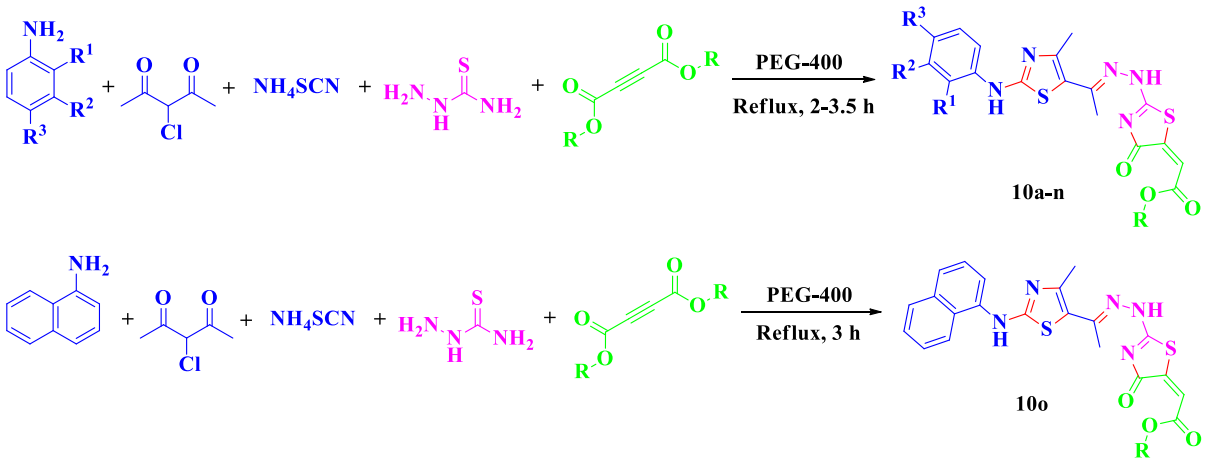


Fig. 1. Thiazole and thiazolidinones of biological importance

In this part, we are describing a five component condensation using readily available starting materials aromatic amines, ammonium thiocyanate, 3-chloropentan-2,4-dione, thiosemicarbazide and DMAD or DEAD in PEG-400 (Scheme-**1**, method-**1**).

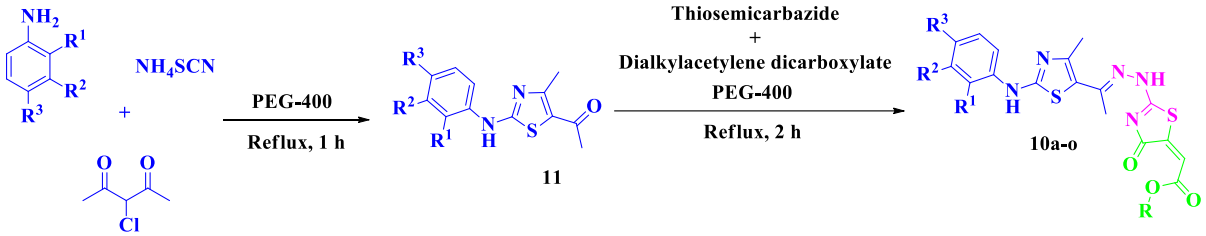


Scheme-1. Method-1: showing one-pot multicomponent synthesis of **10a-o.**

The above reaction is carried out in two methods. The method-1 is more versatile because it involves less time, no harsh conditions are needed and it can be used readily. In this synthesis many connectivities such as 2C=N, 2C-N, 3C-S and one cyclic N-C=O were obtained concomitantly. The speciality of the reaction is that no side products are formed.

Compound **10** may also be formed by another path wherein aromatic amines, NH_4SCN, 3-chloroacetylacetone were reacted in PEG-400 to give **11** (isolated). Compounds 11 on reaction with thiosemicarbazide and dialkylacetylene dicarboxylate yielded **10** (70-80% yield) by a stepwise process as given below.

During the formation of **10** from **11** it is believed that the intermediate is thiosemicarbazone of **11** which was not isolated. The compounds **10** obtained by both the methods were found to be same. This was evidenced from their spectra.



Scheme-2. Method-2: Two step synthesis of **10a-o**

Table-1 showing conditions of optimization for the preparation of **10b.**

S. No.	Reaction condition	Solvent	Catalyst (10 mol %)	Time (h)	Yields (%) of 10b
1	Reflux	DMF	-	24	-
2	Reflux	DMF + EtOH	-	24	40
3	Reflux	CH_3OH	-	12	52
4	Reflux	Acetone	-	12	50
5	Reflux	THF	-	24	-
6	Reflux	H_2O	-	24	-
7	Reflux	EtOH	KOH	12	-
8	Reflux	EtOH	NaOH	12	-
9	Reflux	EtOH	$NaHCO_3$	12	-
10	Reflux	EtOH	NH_4OH	12	-
11	Reflux	EtOH	K_2CO_3	12	-
12	Reflux	PEG-400	-	3	96

Among the above conditions tried PEG-400 was best condition for the formation of product **10**.

PEG-400 prevents the environment pollution and hence we have used this greener solvent. PEG-400 may be recovered and used several times (4 runs) without loss of its reactivity. First run, percentage of yield was 96, 93 in second run, 91 in third run and in the last run it showed very little change of the yield 90%.

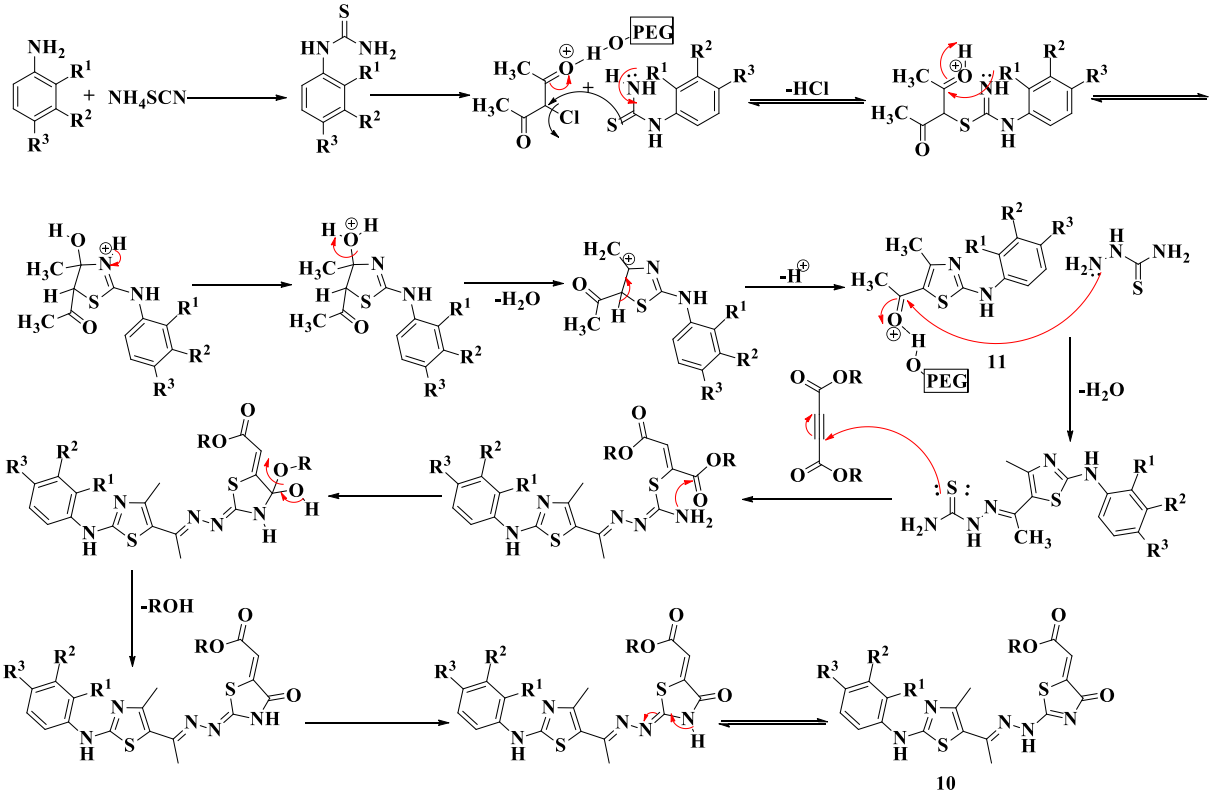
After separation of the end product, H_2O was removed by distillation and polymer of ethylene glycol-400 was washed with ether (2 times, each time 3 ml). The isolated PEG-400 was used for next 4 runs. There was no much loss of efficacy and with almost no practical loss of PEG-400.

The substrate scope with amino group in the aromatic ring having both +I and -I substituents gave the final products. α-Naphthyl amine (bulky) also undergoes this reaction.

The products obtained are less soluble in common organic solvents. Later on we have understood that this reaction is invalid with aliphatic amino compounds.

Table-2 indicating substitution pattern and time (**10a-o)**.

S. No.	Compound	R	R^1	R^2	R^3	Time (h)
1	**10a**	OEt	H	H	H	3
2	**10b**	OEt	H	H	CH_3	3
3	**10c**	OEt	CH_3	CH_3	H	2.5
4	**10d**	OEt	H	OCH_3	H	3
5	**10e**	OEt	H	H	OCH_3	3.5
6	**10f**	OEt	H	OH	H	3
7	**10g**	OEt	H	Cl	H	2.5
8	**10h**	OEt	H	H	Cl	3
9	**10i**	OEt	H	NO_2	H	3.5
10	**10j**	OCH_3	H	H	H	2.5
11	**10k**	OCH_3	H	OCH_3	H	3
12	**10l**	OCH_3	H	OH	H	3.5
13	**10m**	OCH_3	H	Cl	H	3
14	**10n**	OCH_3	H	H	Cl	3
15	**10o**	OCH_3	-	-	-	3



Scheme-3. Mechanism for the formation of **10a-o**.

From the above mechanism it is clear that for the formation of **11** from the reactants takes place by Hantzsch thiazole synthesis. Later on the thiosemicarbazone of **11** formed reacts with dialkylacetylene dicarboxylate to form final compounds **10**.

CONCLUSION

The above domino reaction takes place in PEG-400

A straight forward preparation of compounds **10** by five component condensation reaction involving greener solvent has been described. Several specialities of this method are less time, metal-free, easy work up, no columns chromatography application, utilization of no hazardous organic solvents, ease of recovery of solvent and its reuse.

EXPERIMENTAL SECTION

Starting materials:

Various aromatic amines, NH_4SCN, 3-chloropentan-2,4-dione, thiosemicarbazide, DMAD and DEAD, polyethylene glycol were purchased from market.

General procedure for the synthesis of (10a-o)

A mixture of aromatic amine (1 mmol), 3-chloropentan-2,4-dione (1 mmol) and ammonium thiocyanate (1 mmol) in 5 ml of polyethylene glycol-400 was heated for 1h (monitored by TLC). When the reaction completed, thiosemicarbazide (1 mmol) and diethyl acetylenedicarboxylate or dimethyl acetylenedicarboxylate (1 mmol) were added and refluxed for 1-2 h (monitored by TLC). The product formed after filtration was subjected to alcohol recrystallization.

Synthesis of 1-(4-methyl-2-(phenylamino)thiazol-5-yl)ethanone (11)

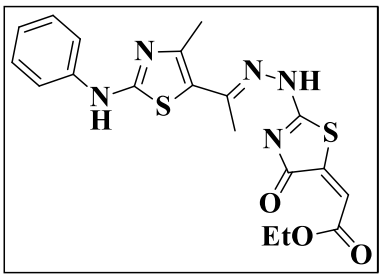
In 5 ml of polyethylene glycol-400, aromatic amine (1 mmol), ammonium thiocyanate (1 mmol) and 3-chloropentan-2,4-dione (1 mmol) were taken and heated for 1 h. The product formed after filtration was subjected to alcohol recrystallization.

Synthesis of (10) from (11)

In polyethylene glycol-400 (5ml), **11** (1 mmol), thiosemicarbazide (1 mmol) was placed and heated for 0.5 h (maintained by TLC). Later on DMAD or DEAD (1 mmol) was added and heated for 1 h. After cooling the reaction mass was placed in crushed ice. The product formed after filtration was subjected to alcohol recrystallization.

SPECTRAL DATA

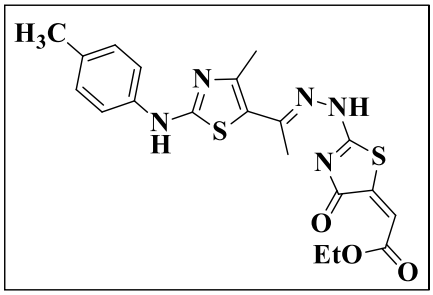
(*E*)-Ethyl 2-(2-((*E*)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10a).



Color: orange solid; mp: 307-309 $^{\circ}C$; yield: (0.483g, 92%); IR (KBr, Wave number, cm^{-1}): 1693 cm^{-1} (C=O), 3199 cm^{-1} (NH); PMR (400 MHz, DMSO-d_6): δ 1.28 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.25 (q, J = 8.0 Hz,

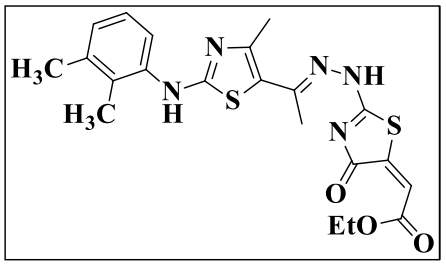
2H), 6.62 (s, 1H,), 7.00 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 10.46 (s, 1H), 12.80 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 16.9, 19.2, 61.6, 114.4, 117.9, 120.7, 122.3, 129.4, 141.0, 143.6, 151.5, 157.7, 159.0, 163.3, 165.9, 166.0 ppm; ESI-MS: m/z 430 $[M+H]^+$; Anal. calcd. for $C_{19}H_{19}N_5O_3S_2$: C, 53.13; H, 4.46; N, 16.31; S, 14.93. Found: C, 53.18; H, 4.40; N, 16.38; S, 14.90%.

(*E*)-Ethyl 2-(2-((*E*)-2-(1-(4-methyl-2-(*p*-tolylamino)thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10b).



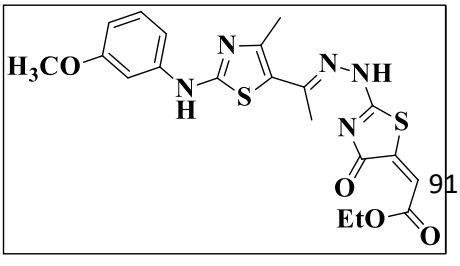
Color: orange solid; mp: 244-246 °C; yield: (0.478g, 96%); IR (KBr, Wave number, cm^{-1}): 1692 (C=O), 3196 (NH); PMR (400 MHz, DMSO-d_6): δ 1.26 (t, *J* = 4.0 Hz, 3H), 2.28 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.23 (q, *J* = 4.0 Hz, 2H), 4.65 (s, 3H), 6.60 (s, 1H,), 7.16 (d, *J* = 4.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 10.65 (s, 1H), 12.80 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.5, 16.8, 18.6, 20.9, 61.7, 114.6, 118.9, 120.1, 130.0, 132.2, 138.0, 143.5, 149.9, 157.9, 158.8, 164.0, 165.8, 166.0 ppm; ESI-MS: m/z 444 $[M+H]^+$; Anal. calcd. for $C_{20}H_{21}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79; S, 14.46. Found: C, 54.10; H, 4.72; N, 15.73, S, 14.41%.

(*E*)-Ethyl 2-(2-((*E*)-2-(1-(2-((2,3-dimethyl phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10c).



Color: orange solid; mp: 292-294 °C; yield: (0.525g, 90%); IR (KBr, Wave number, cm^{-1}): 1687 (C=O), 3221 (NH); PMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 8.0 Hz, 3H), 2.15 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.23 (q, *J* = 4.0 Hz, 2H), 6.60 (s, 1H,), 7.04 (d, *J* = 4.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 9.66 (s, 1H), 12.76 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.3, 14.5, 15.8, 17.0, 19.2, 20.7, 61.7, 102.9, 111.0, 112.7, 114.7, 122.3, 126.3, 127.6, 130.9, 138.2, 143.9, 150.7, 159.4, 162.0, 165.7 ppm; Anal. calcd. for $C_{21}H_{23}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79; S, 14.46. Found: C, 54.19; H, 4.72; N, 15.73; S, 14.40%.

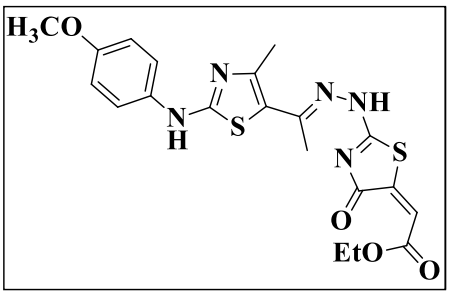
(*E*)-Ethyl 2-(2-((*E*)-2-(1-(2-((3-methoxy phenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10d).



Color: orange solid; mp: 287-289 °C; yield: (0.5g, 95%); IR (KBr, Wave number, cm^{-1}): 1694 (C=O),

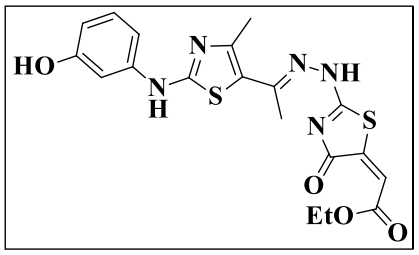
3208 (NH); PMR (400 MHz, DMSO-d_6): δ 1.28 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.60 (t, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.40 (s, 1H), 10.46 (s, 1H), 12.80 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 16.8, 19.2, 55.4, 61.6, 103.9, 107.5, 110.4, 114.4, 120.8, 130.1, 142.1, 143.6, 151.3, 157.9, 158.9, 160.3, 163.2, 165.9, 166.0 ppm; ESI-MS: m/z 460 $[M+H]^+$; Anal. calcd. for $C_{20}H_{21}N_5O_4S_2$: C, 52.27; H, 4.61; N, 15.24; S, 13.96. Found: C, 52.22; H, 4.65; N, 15.20; S, 13.92%.

(*E*)-Ethyl 2-(2-((*E*)-2-(1-(2-((4-methoxy phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10e).



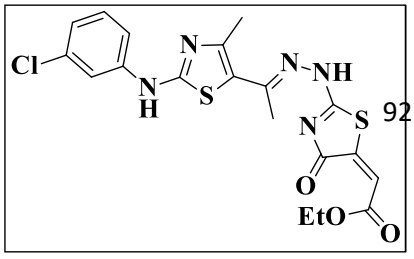
Color: orange solid; mp: 236-238 °C; yield: (0.5g, 95%); IR (KBr, Wave number, cm^{-1}): 1690 (C=O), 3130 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, J = 8.0 Hz, 3H), 2.45 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.61 (s, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 10.25 (s, 1H), 12.78 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 16.8, 19.2, 55.6, 61.6, 114.5, 114.7, 119.9, 134.4, 135.5, 143.7, 151.7, 155.0, 157.4, 159.0, 164.0, 165.9, 166.0 ppm; ESI-MS: m/z 460 $[M+H]^+$; Anal. calcd. for $C_{20}H_{21}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72; S, 14.39. Found: C, 51.27; H, 4.35; N, 15.78; S, 14.44%.

(*E*)-Ethyl 2-(2-((*E*)-2-(1-(2-((3-hydroxy phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10f).



Color: orange solid; mp: 300-302 °C; yield: (0.495g, 93%); IR (KBr, Wave number, cm^{-1}): 1686 (C=O), 3149 (NH); PMR (400 MHz, DMSO-d_6): δ 1.28 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.41 (d, J = 12.0 Hz, 1H), 6.62 (s, 1H), 7.01 (d, J = 12.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.18 (s, 1H), 9.43 (s, 1H), 10.32 (s, 1H), 12.80 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 16.9, 19.2, 61.6, 106.2, 108.9, 109.6, 114.4, 120.5, 130.0, 141.9, 143.6, 151.5, 157.6, 158.3, 159.0, 163.3, 165.9, 166.0 ppm; ESI-MS: m/z 444 $[M-H]^+$; Anal. calcd. for $C_{19}H_{19}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72; S, 14.39. Found: C, 51.26; H, 4.36; N, 15.75; S, 14.32%.

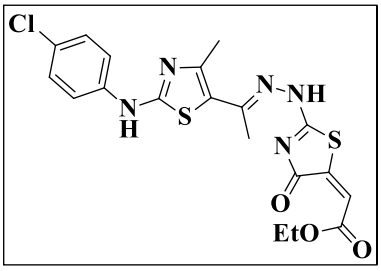
(*E*)-Ethyl 2-(2-((*E*)-2-(1-(2-((3-chloro phenyl)amino)-4-methylthiazol-5-



yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10g).

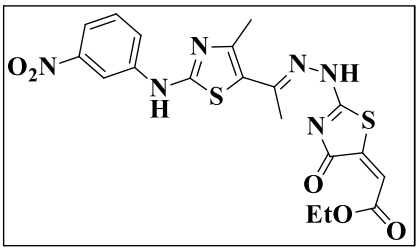
Color: orange solid; mp: 254-256 °C; yield: (0.526g, 91%); IR (KBr, Wave number, cm^{-1}): 1691 (C=O), 3061 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.23 (q, J = 8.0 Hz, 2H), 6.61 (s, 1H), 7.02-7.04 (m, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.50-7.52 (m, 1H), 7.89 (t, J = 4.0 Hz, 1H), 10.62 (s, 1H), 12.80 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.5, 16.8, 19.2, 61.7, 114.6, 116.3, 117.1, 121.6, 121.7, 131.0, 133.8, 142.3, 143.6, 151.2, 158.2, 158.9, 162.8, 165.9, 166.0 ppm; ESI-MS: m/z 464 $[M+H]^+$; Anal. calcd. for $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.09; S, 13.82. Found: C, 49.15; H, 3.95; N, 15.12; S, 13.88%.

(*E*)-Ethyl 2-(2-((*E*)-2-(1-(2-((4-chloro phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10h).



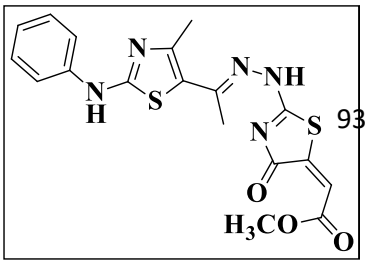
Color: orange solid; mp: 305-307 °C; yield: (0.504g, 95%); IR (KBr, Wave number, cm^{-1}): 1694 (C=O), 3189 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.24 (q, J = 8.0 Hz, 2H), 6.61 (s, 1H), 7.38 (d, J = 12.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 10.57 (s, 1H), 12.81 (s, 1H) ppm; ESI-MS: m/z 464 $[M+H]^+$; Anal. calcd. for $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.09; S, 13.82. Found: C, 49.15; H, 3.96; N, 15.14; S, 13.88%.

(*E*)-Ethyl 2-(2-((*E*)-2-(1-(4-methyl-2-((3-nitrophenyl)amino)thiazole-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10i).



Color: orange solid; mp: 296-298 °C; yield: (0.550g, 89%); IR (KBr, Wave number, cm^{-1}): 1694 (C=O), 3253 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, J = 8.0 Hz, 3H), 2.47 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.24 (q, J = 8.0 Hz, 2H), 6.60 (s, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.76 (s, 1H), 10.91 (s, 1H), 12.82 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 16.7, 19.2, 61.6, 114.3, 119.2, 121.3, 125.5, 129.2, 139.9, 143.6, 151.2, 158.0, 158.8, 162.9, 165.8, 166.0 ppm; ESI-MS: m/z 475 $(M+H)^+$; Anal. calcd. for $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; S, 13.51. Found: 48.10; H, 3.88; N, 17.76; S, 13.58%.

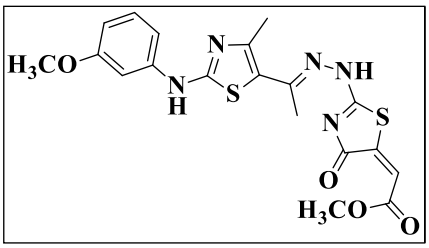
(*E*)-Methyl 2-(2-((*E*)-2-(1-(4-methyl-2-(phenylamino)thiazol-5-



yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10j).

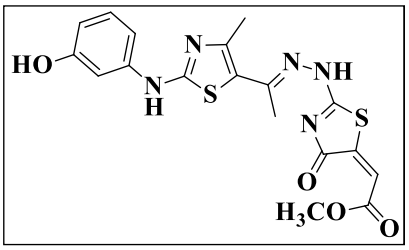
Color: orange solid; mp: 312-314 °C; yield: (0.427g, 97%); IR (KBr, Wave number, cm^{-1}): 1693 (C=O), 3083 (NH); PMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.65 (s, 1H,), 7.00 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 10.44 (s, 1H), 12.81 (s, 1H) ppm; ESI-MS: m/z 414 $[M-H]^+$; Anal. calcd. for $C_{18}H_{17}N_5O_3S_2$: C, 52.03; H, 4.12; N, 16.86; S, 15.43. Found: C, 52.12; H, 4.17; N, 16.82; S, 15.47%.

(*E*)-Methyl 2-(2-((*E*)-2-(1-(2-((3-methoxyphenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetates (10k).



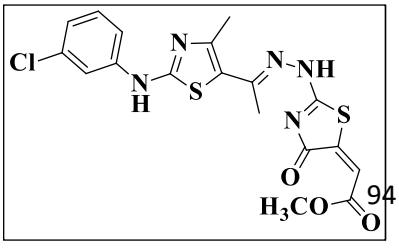
Color: red solid; mp: 310-312 °C; yield: (0.483g, 92%); IR (KBr, Wave number, cm^{-1}): 1693 (C=O), 3145 (NH); PMR (400 MHz, DMSO-d_6, ppm): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.59 (t, J = 8.0 Hz, 1H), 6.65 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.41 (s, 1H), 10.45 (s, 1H), 12.82 (s, 1H); CMR (100 MHz, DMSO-d_6, ppm): δ 16.8, 19.2, 52.6, 55.4, 103.8, 107.7, 110.5, 113.8, 114.1; 120.9, 130.5, 131.7; 132.1; 138.2; 142.0, 158.9, 160.3, 163.3, 166.3; ESI-MS: m/z 446 $[M+H]^+$; Anal. calcd. for $C_{19}H_{19}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72; S, 14.39. Found: C, 51.27; H, 4.34; N, 15.67; S, 14.35%.

(*E*)-Methyl 2-(2-((*E*)-2-(1-(2-((3-hydroxyphenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (10l).



Color: red solid; mp: 295-297 °C; yield: (0.478g, 90%); IR (KBr, Wave number, cm^{-1}): 1688 (C=O), 3145 (NH); PMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.41 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.19 (s, 1H), 9.43 (s, 1H), 10.32 (s, 1H), 12.81 (s, 1H) ppm; ESI-MS: m/z 430 $(M-H)^+$; Anal. calcd. for $C_{18}H_{17}N_5O_4S_2$: C, 50.10; H, 3.97; N, 16.23; S, 14.86. Found: C, 50.14; H, 3.92; N, 16.28; S, 14.82%.

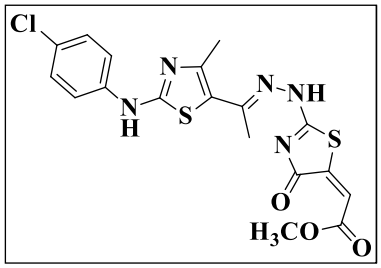
(*E*)-Methyl 2-(2-((*E*)-2-(1-(2-((3-chlorophenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (10m).



Color: orange solid; mp: 308-310 °C; yield: (0.528g, 85%); IR (KBr, Wave number, cm^{-1}): 1697 (C=O), 3186 (NH);

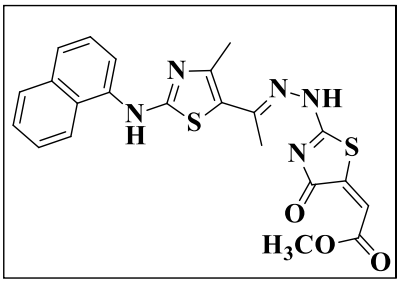
PMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.65 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 12.0 Hz, 1H), 7.91 (s, 1H), 10.63 (s, 1H), 12.83 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.7, 19.2, 52.7, 114.2, 116.2, 117.1, 121.6, 123.3, 131.0, 133.8, 142.3, 143.8, 151.1, 158.1, 158.9, 162.8, 166.0, 166.4 ppm; ESI-MS: m/z 450 $[M+H]^+$; Anal. calcd. for $C_{18}H_{16}ClN_5O_3S_2$: C, 48.05; H, 3.58; N, 15.57; S, 14.25. Found: C, 48.18; H, 3.52; N, 15.51; S, 14.29%.

(*E*)-Methyl 2-(2-((*E*)-2-(1-(2-((4-chlorophenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (10n).



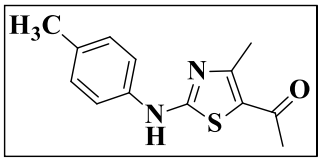
Color: orange solid; mp: 307-309 °C; yield: (0.482g, 93%); IR (KBr, Wave number, cm^{-1}): 1693 (C=O), 3189 (NH); PMR (400 MHz, DMSO-d_6): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.64 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.7 (d, *J* = 8.0 Hz, 2H), 10.57 (s, 1H), 12.82 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.7, 19.2, 52.7, 114.1, 119.3, 121.3, 125.5, 129.2, 139.9, 143.8, 151.3, 158.0, 158.9, 162.9, 166.0, 166.4 ppm; ESI-MS: m/z 450 $[M+H]^+$; Anal. calcd. for $C_{18}H_{16}ClN_5O_3S_2$: C, 48.05; H, 3.58; N, 15.57; S, 14.25. Found: C, 48.19; H, 3.51; N, 15.61; S, 14.20%.

(*E*)-Methyl 2-(4-oxo-2-((*E*)-2-((3-(2-oxo-2*H*-benzo[h]chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazinyl)thiazol-5(4*H*)-ylidene)acetate (10o).



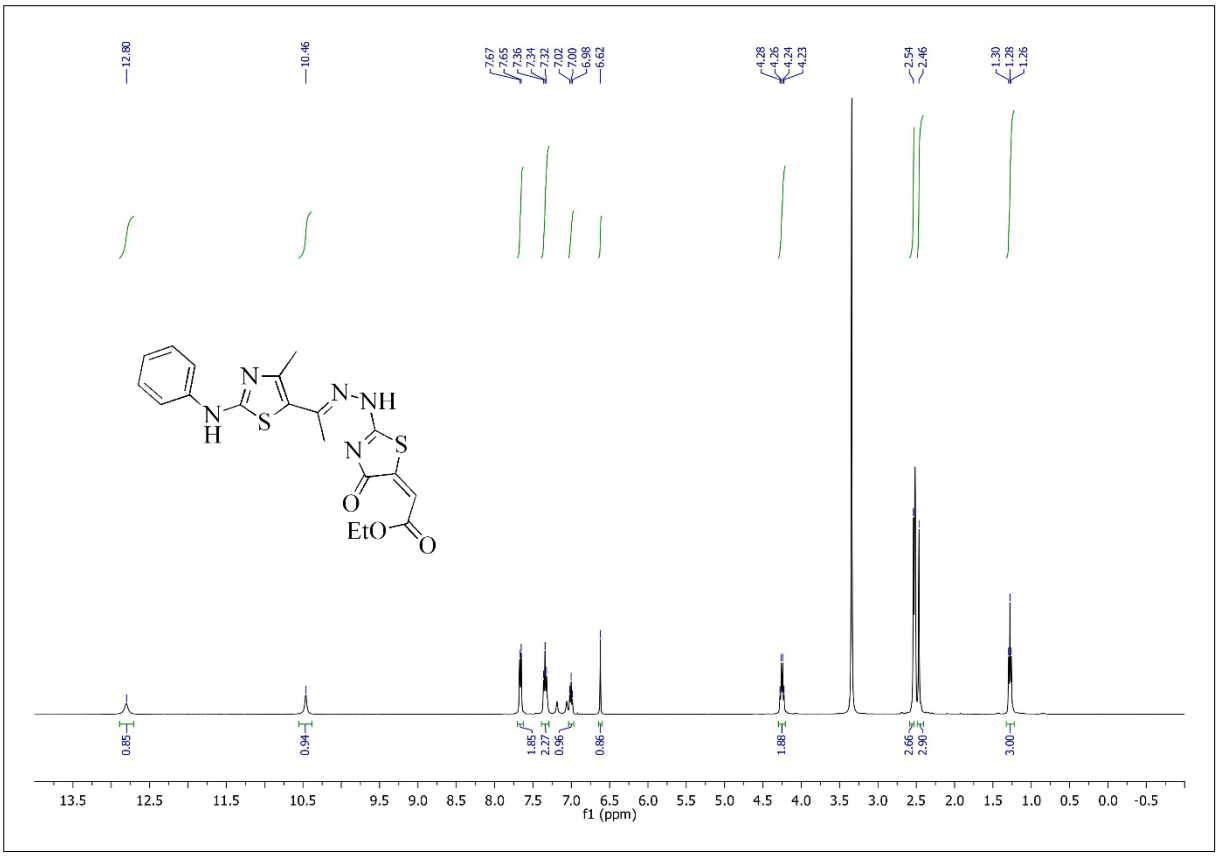
Color: orange solid; mp: 302-304 °C; yield: (0.484g, 96%); IR (KBr, Wave number, cm^{-1}): 1702 (C=O), 3053 (NH); PMR (400 MHz, DMSO-d_6): δ 2.45 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.65 (s, 1H), 7.53-7.59 (m, 3H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.96-7.98 (m, 1H), 8.12-8.13 (m, 1H), 8.24-8.25 (m, 1H), 10.37 (s, 1H), 12.77 (s, 1H) ppm; ESI-MS: m/z 464 $[M-H]^+$; anal. calcd. for $C_{29}H_{19}N_5O_5S$: C, 63.38; H, 3.48; N, 12.74; S, 5.83. Found: C, 63.32; H, 3.43; N, 12.70; S, 5.87.

1-(4-Methyl-2-(p-tolylamino)thiazol-5-yl)ethanones (11).

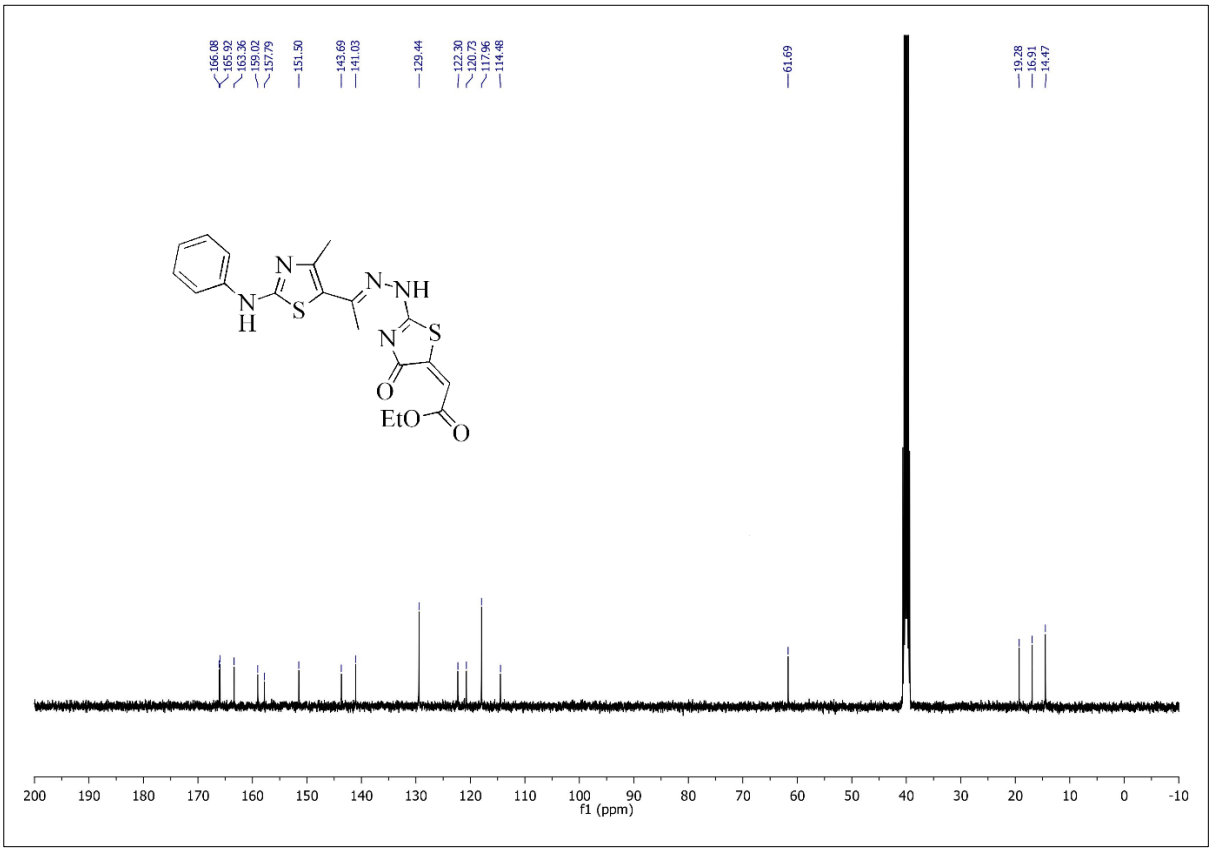


Color: white solid; mp: 189-191 °C; yield: (0.253g, 97%); PMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.07 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 9.73 (s,

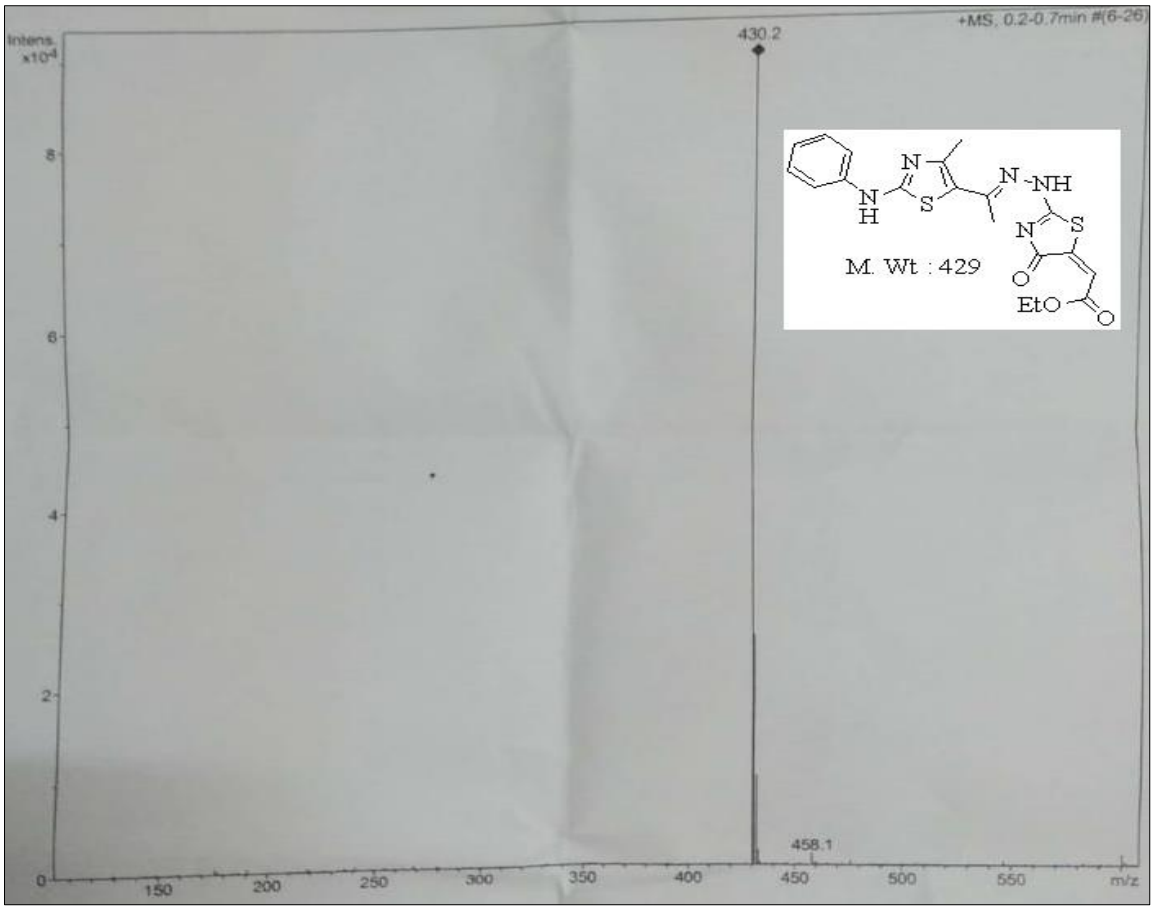
1H) ppm; ESI-MS: m/z 247 $[M+H]^+$.



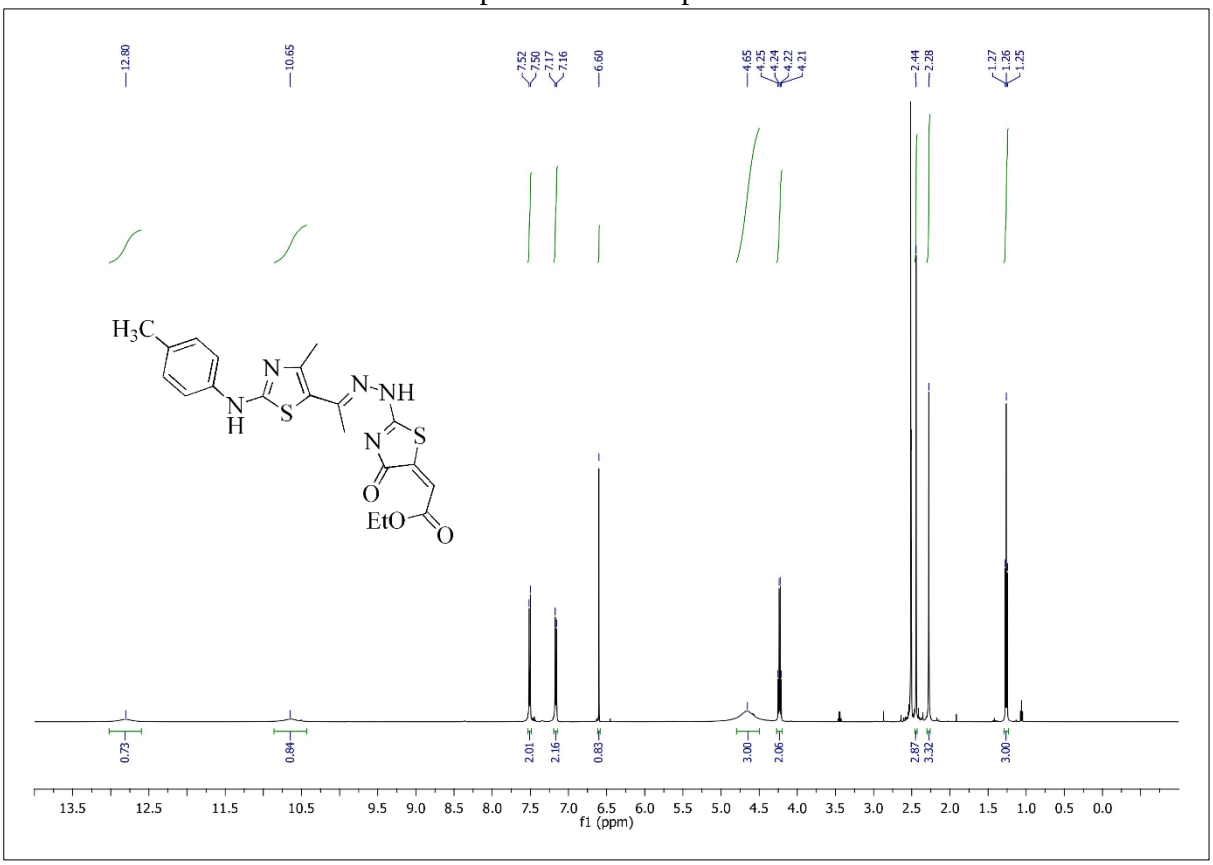
PMR Spectrum of compound **10a**



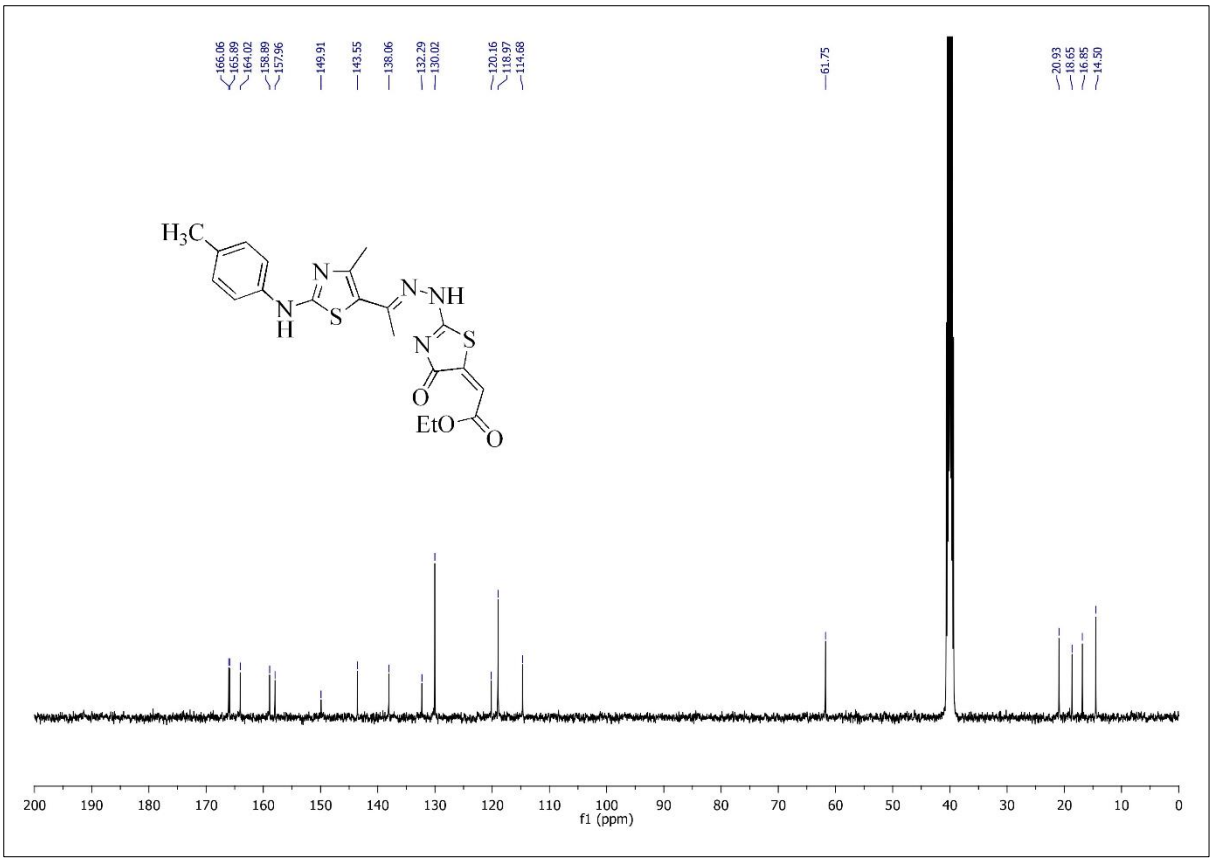
CMR Spectrum of compound **10a**



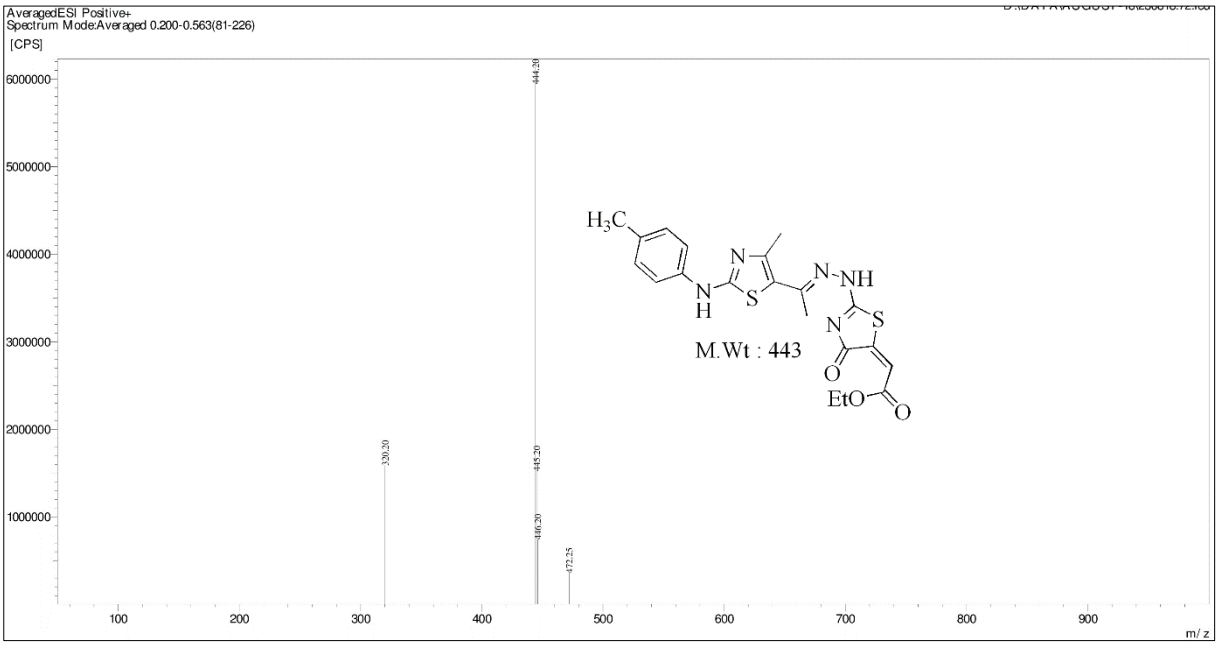
Mass Spectrum of compound **10a**



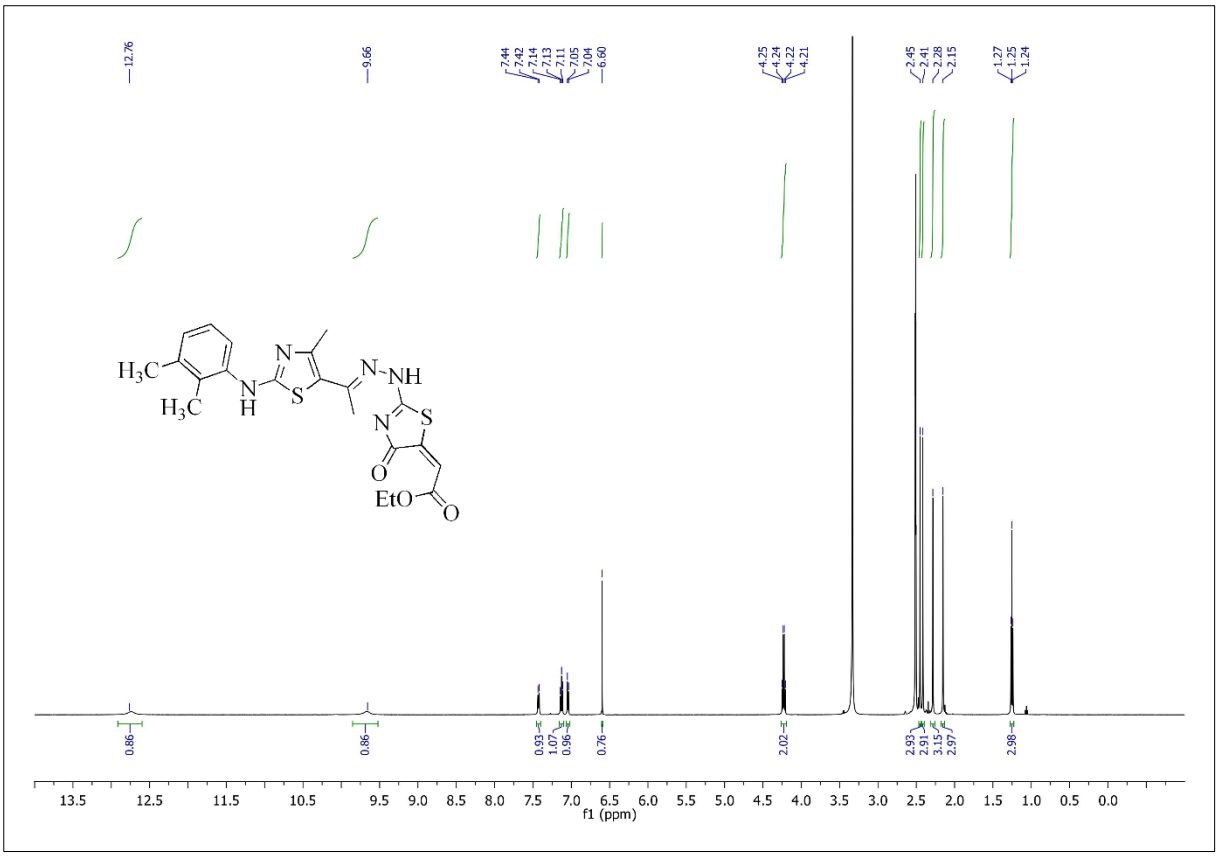
PMR Spectrum of compound **10b**



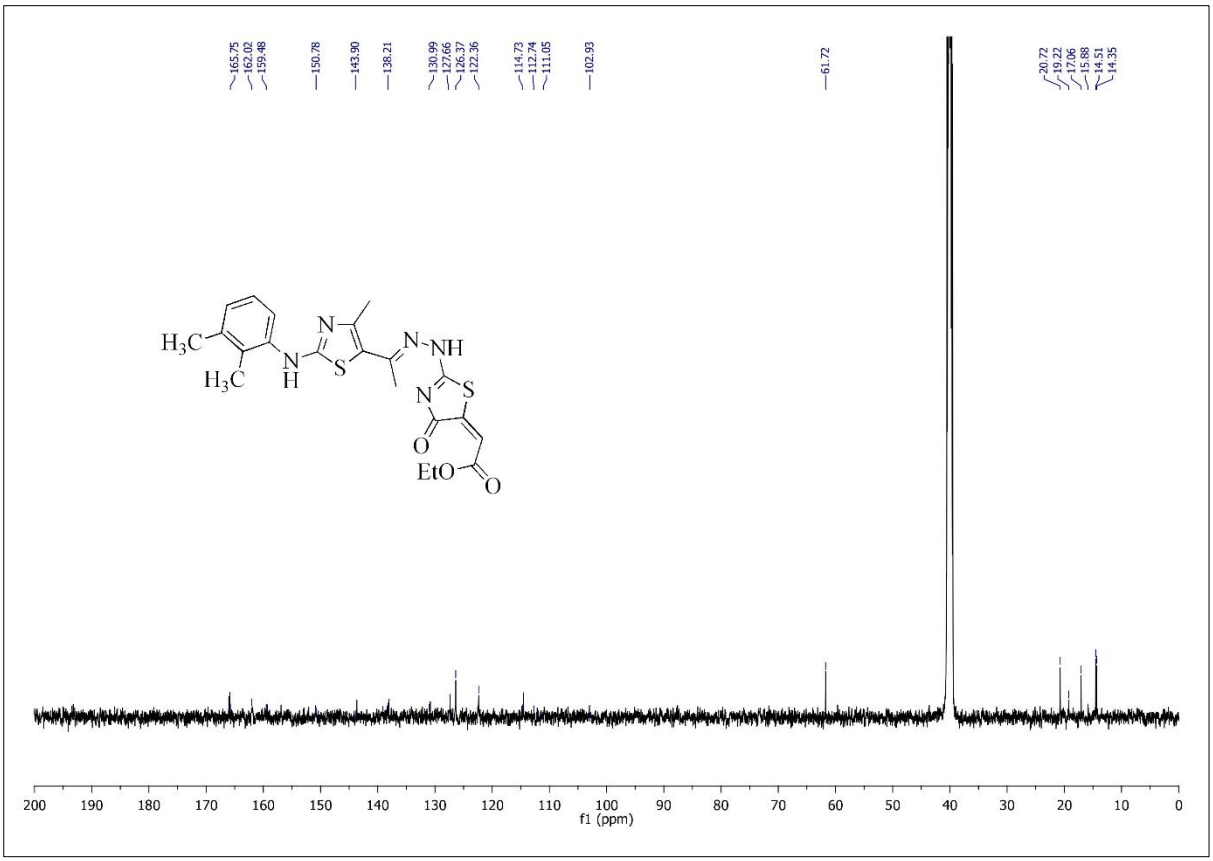
CMR Spectrum of compound **10b**



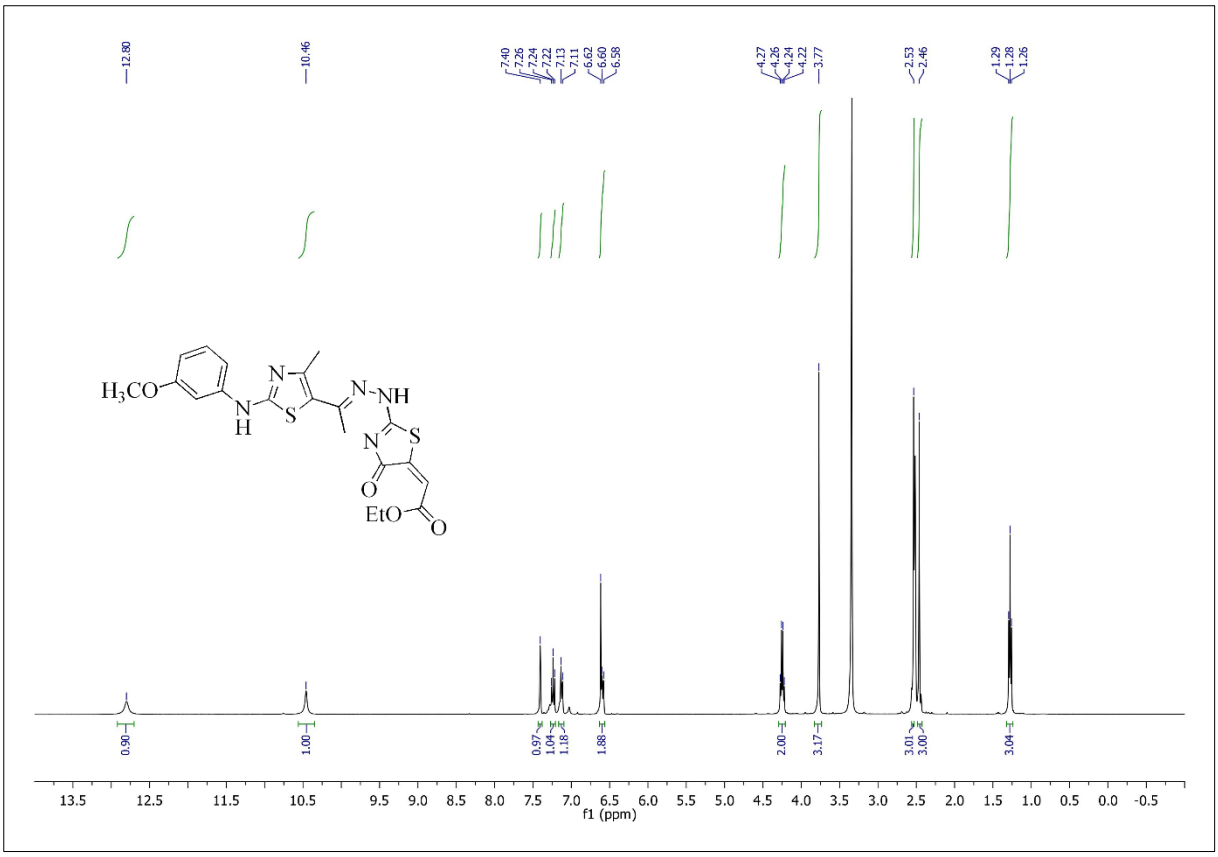
Mass Spectrum of compound **10b**



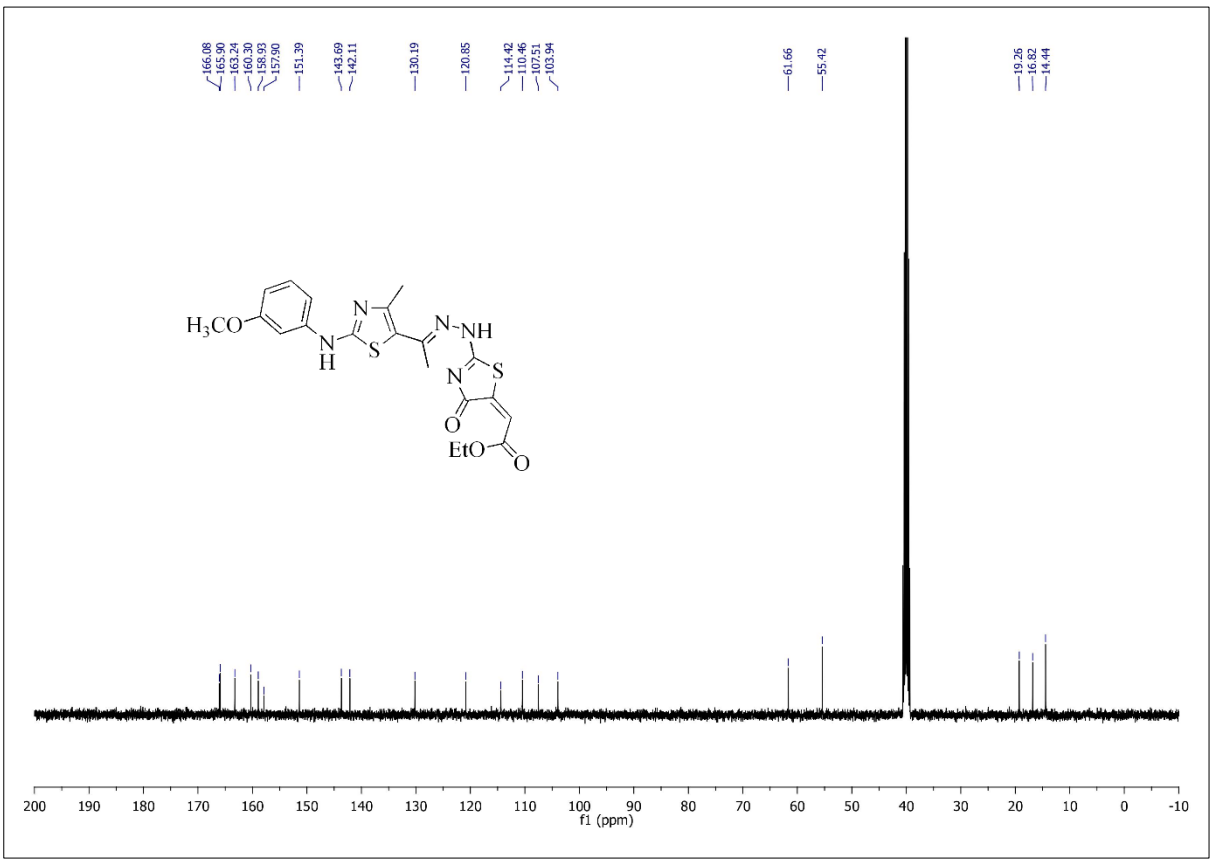
PMR Spectrum of compound **10c**



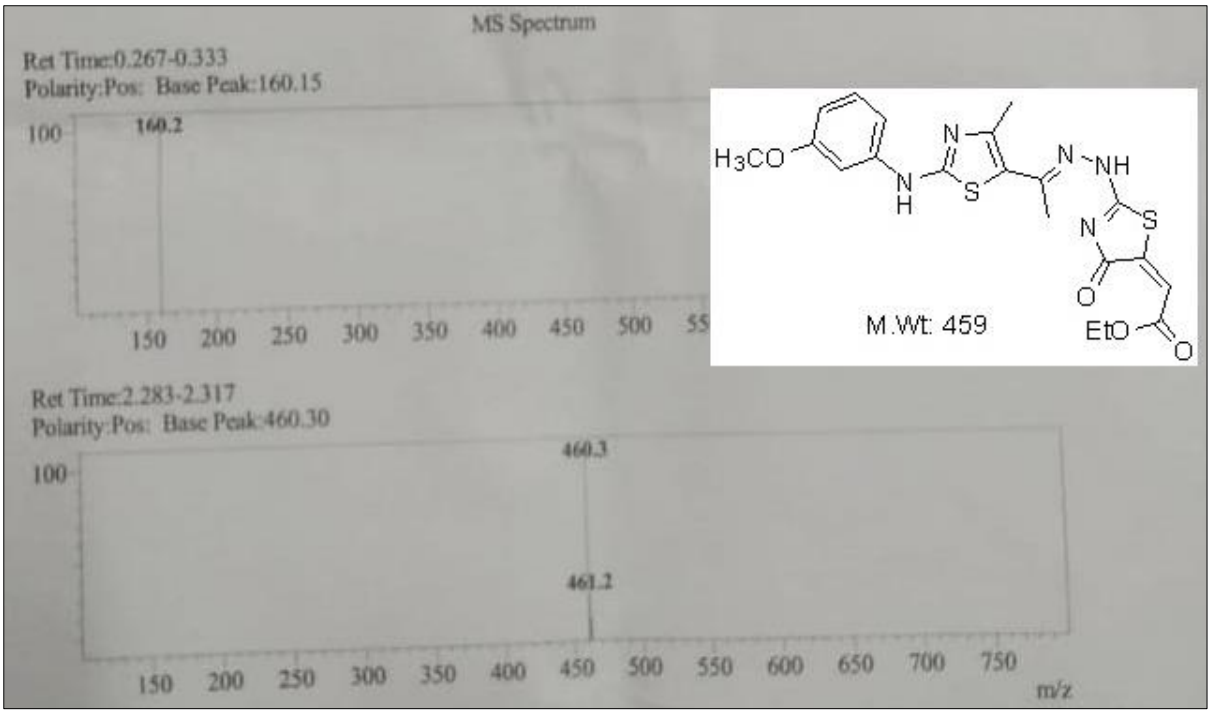
CMR Spectrum of compound **10c**



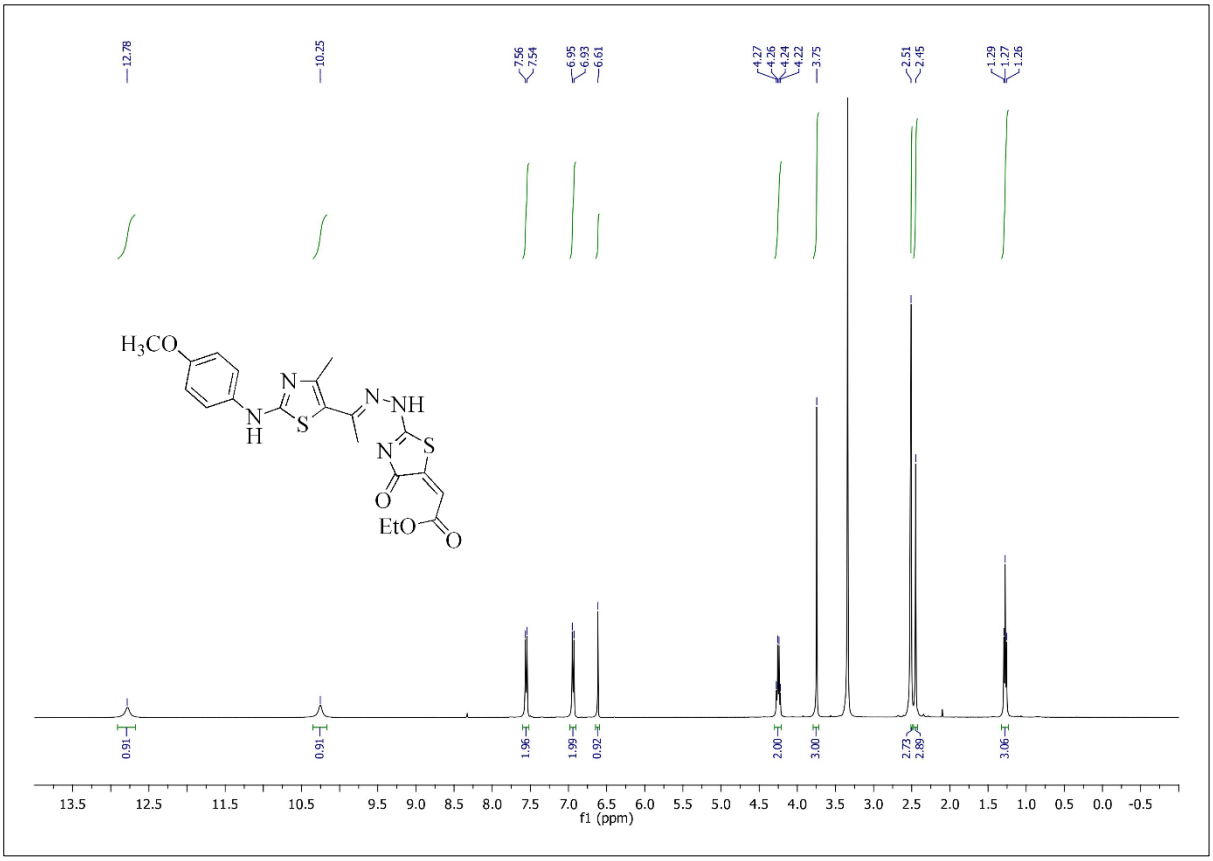
PMR Spectrum of compound **10d**



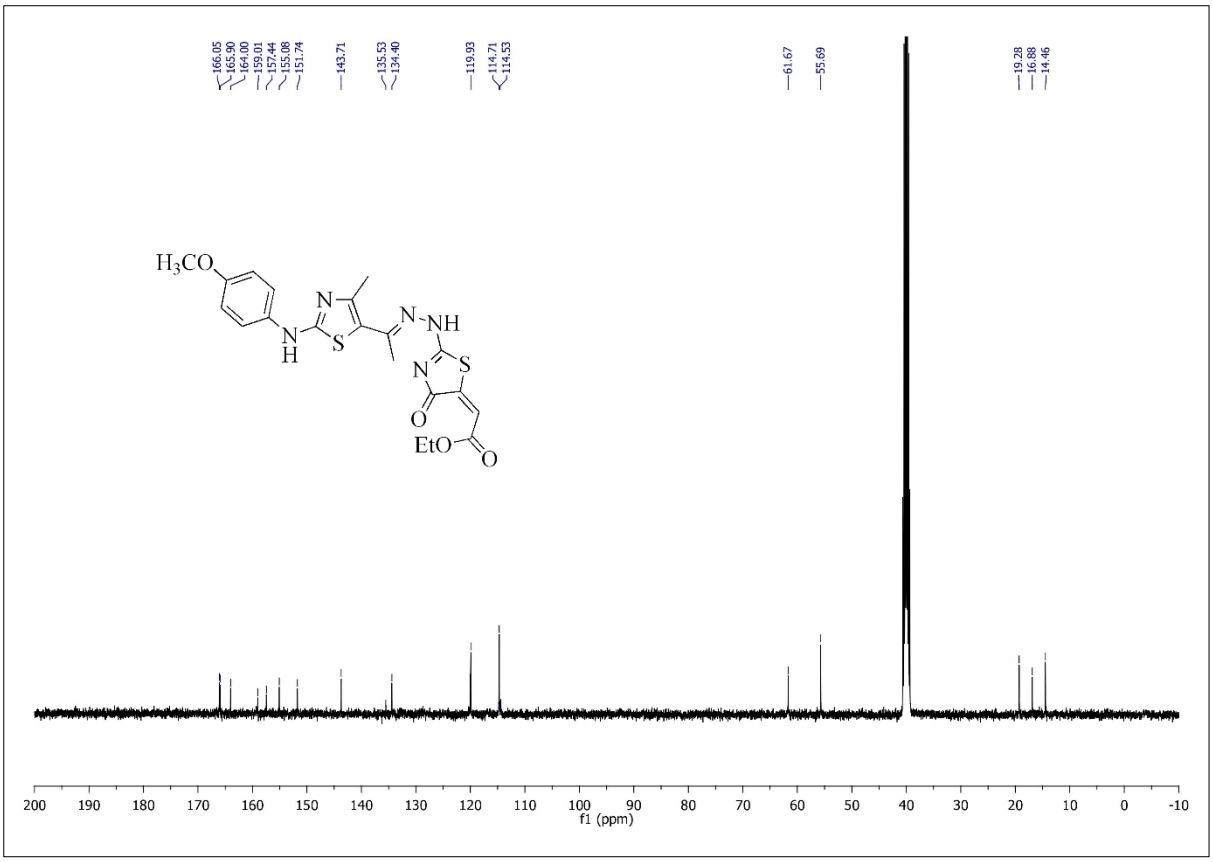
CMR Spectrum of compound **10d**



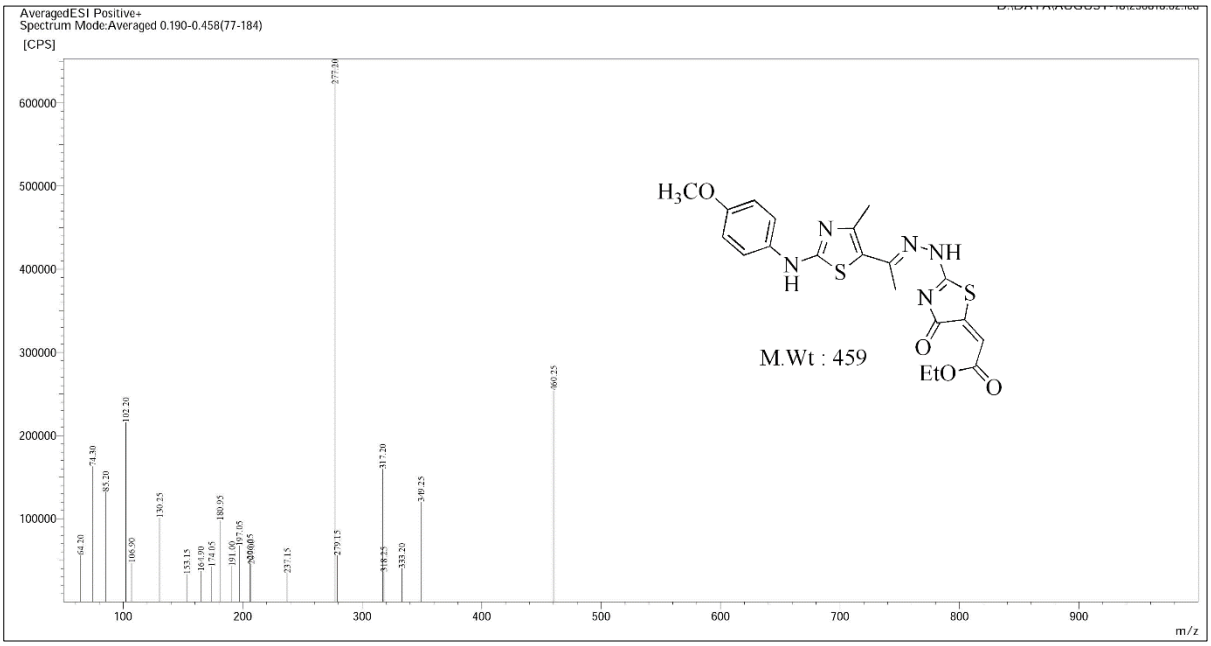
Mass Spectrum of compound **10d**



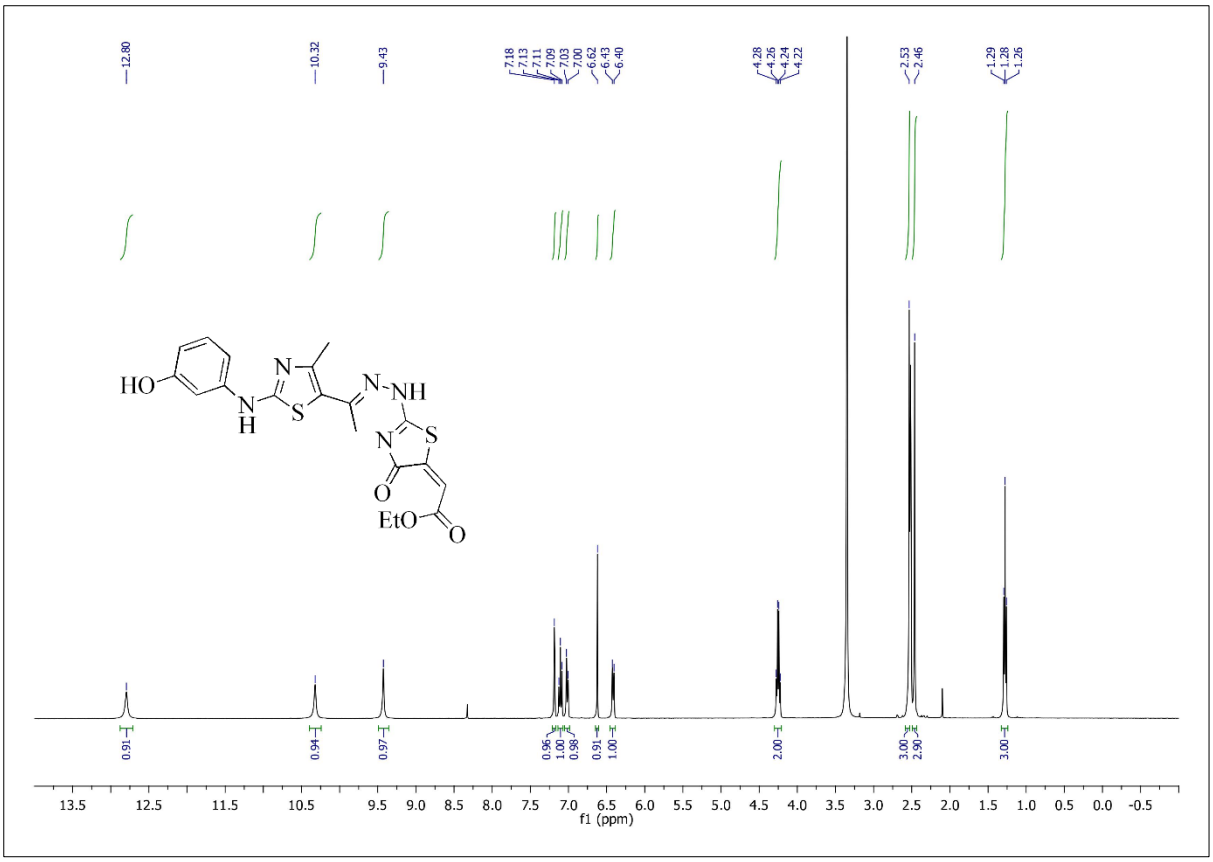
PMR Spectrum of compound **10e**



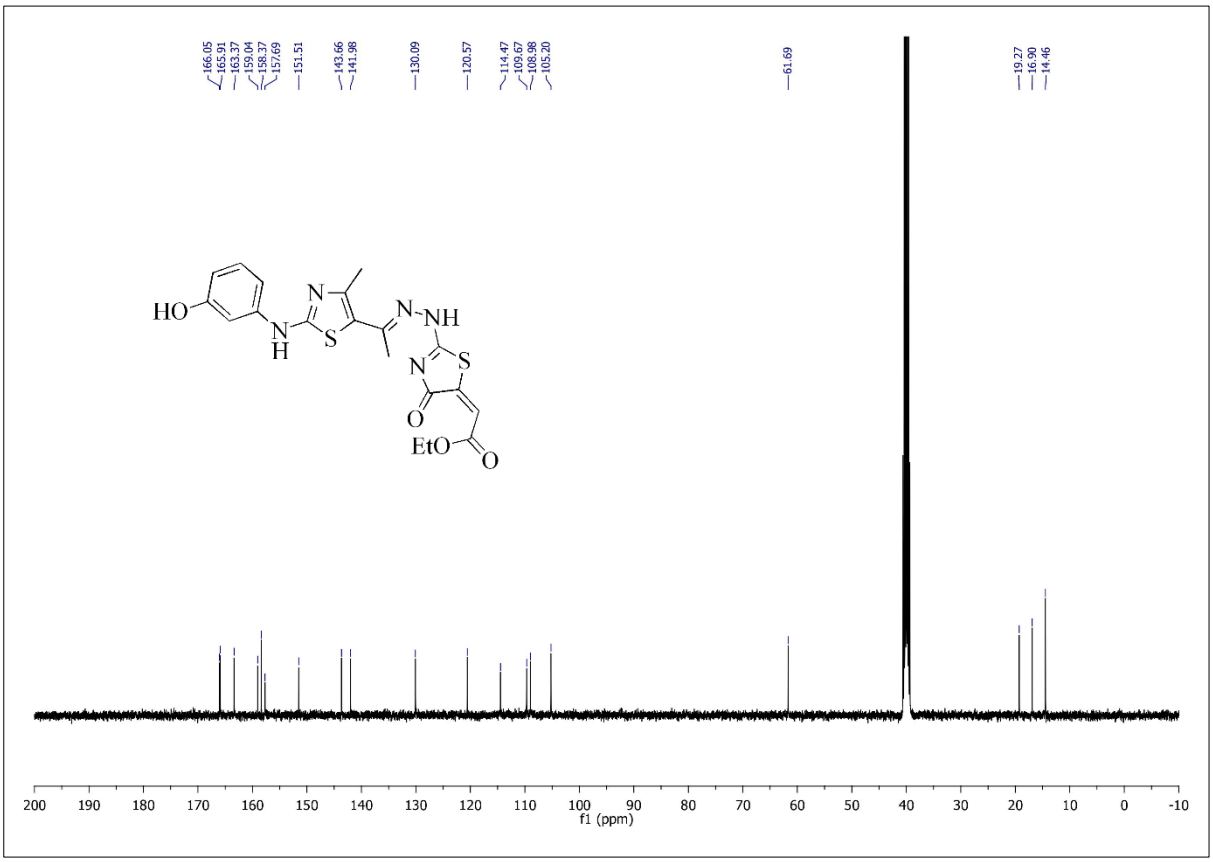
CMR Spectrum of compound **10e**



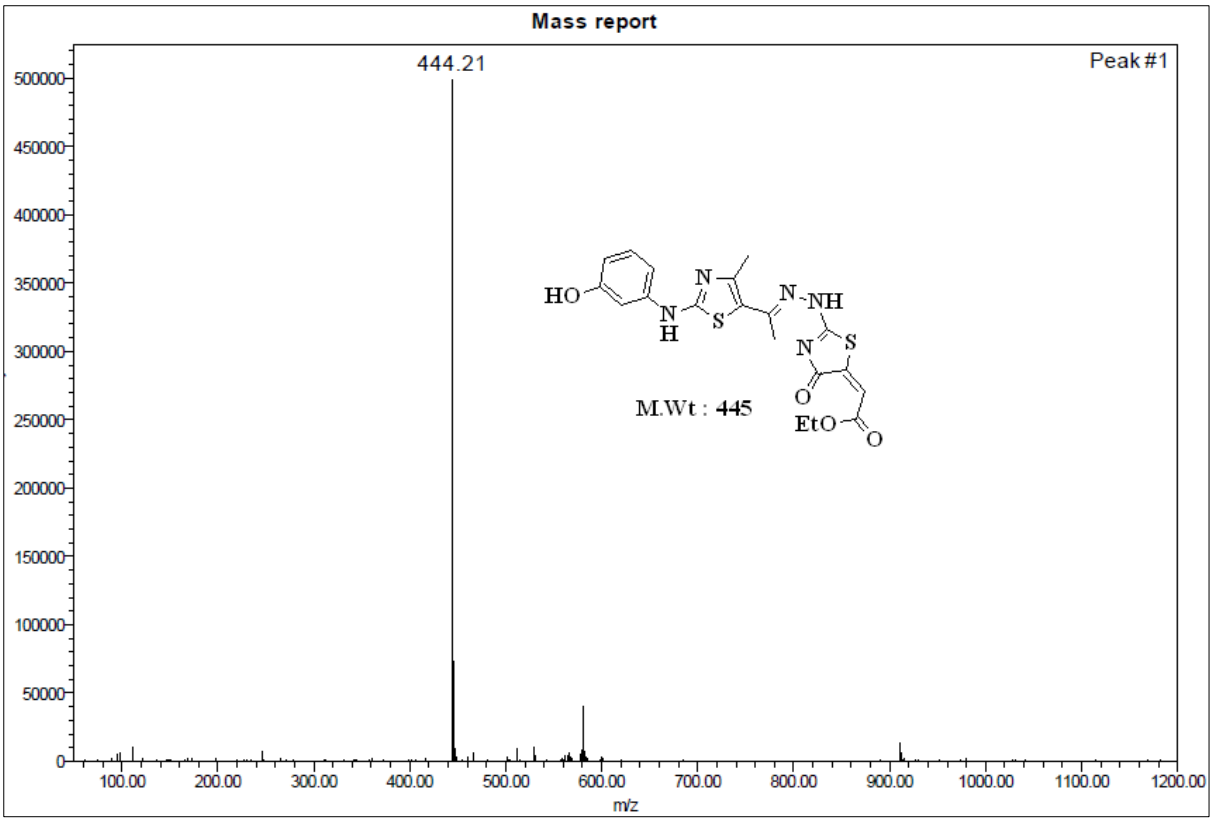
Mass Spectrum of compound **10e**



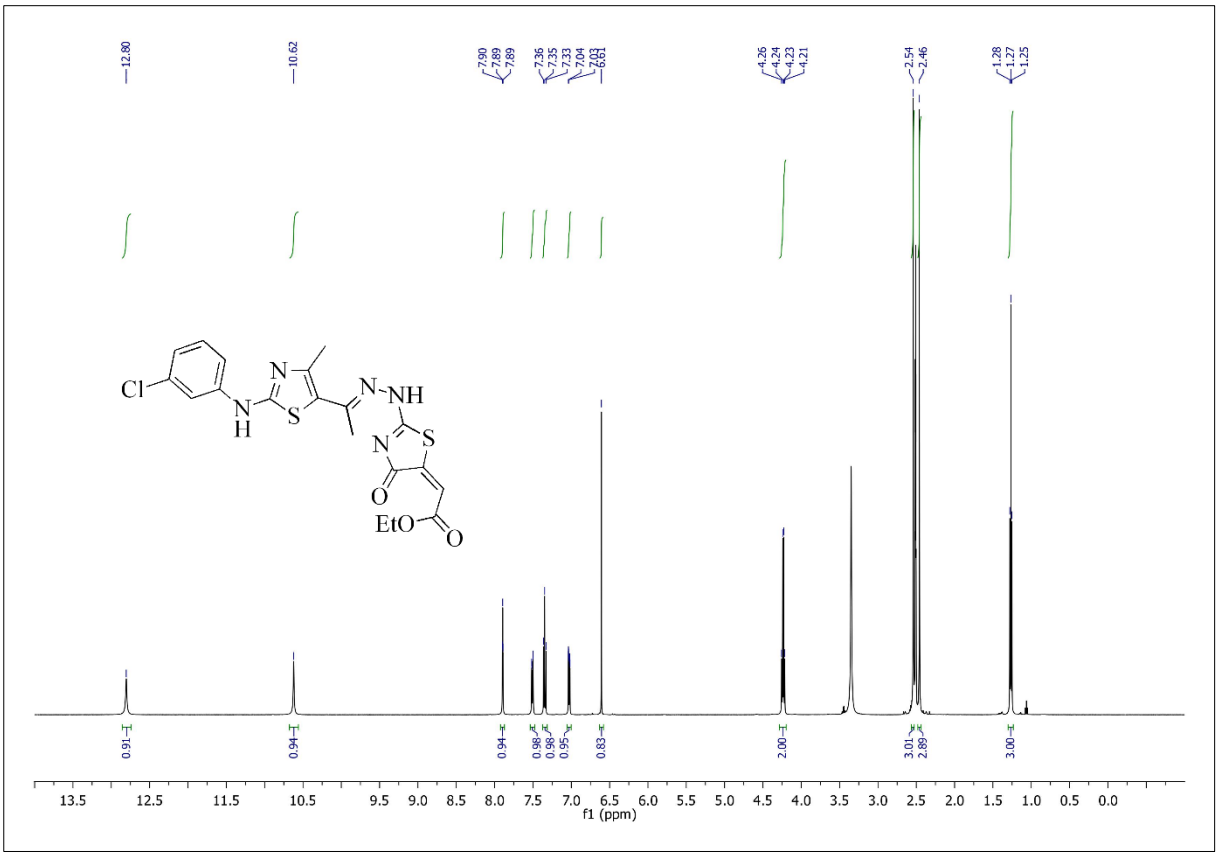
PMR Spectrum of compound **10f**



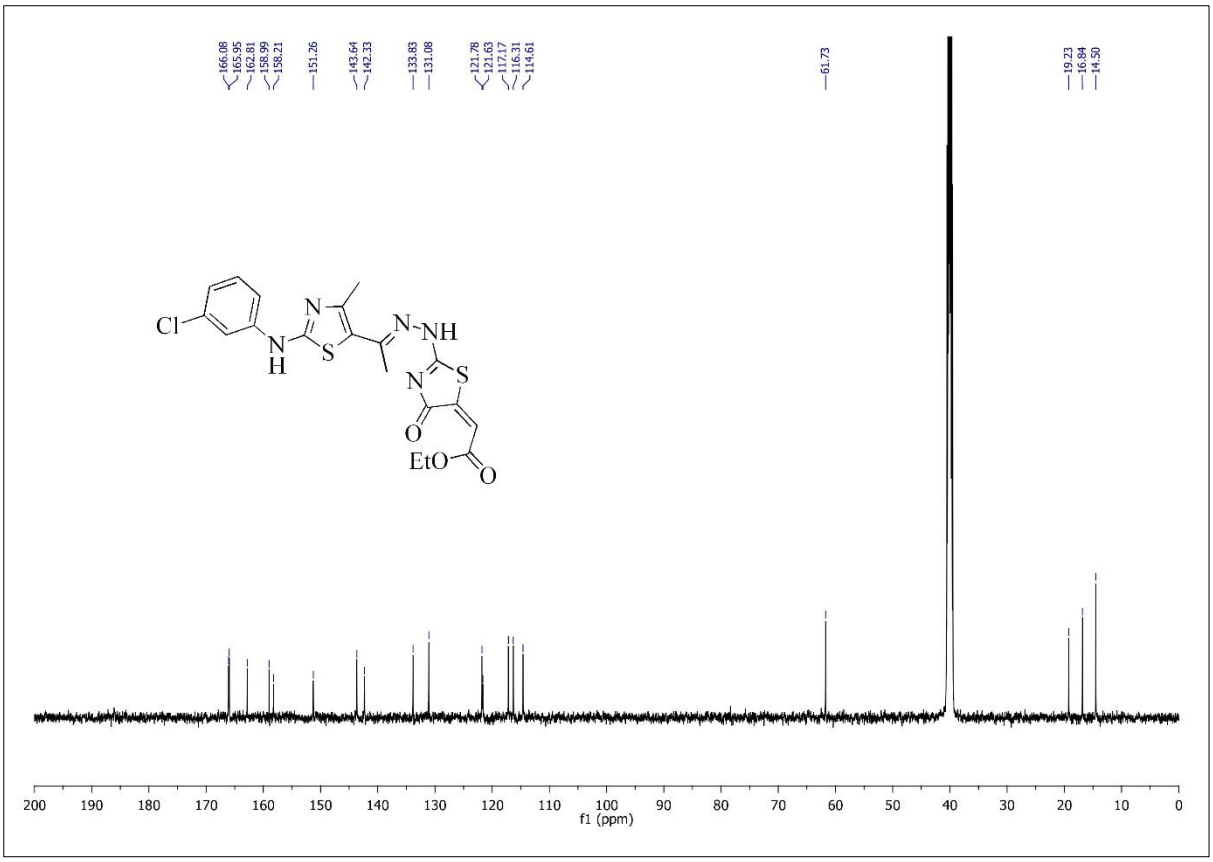
CMR Spectrum of compound **10f**



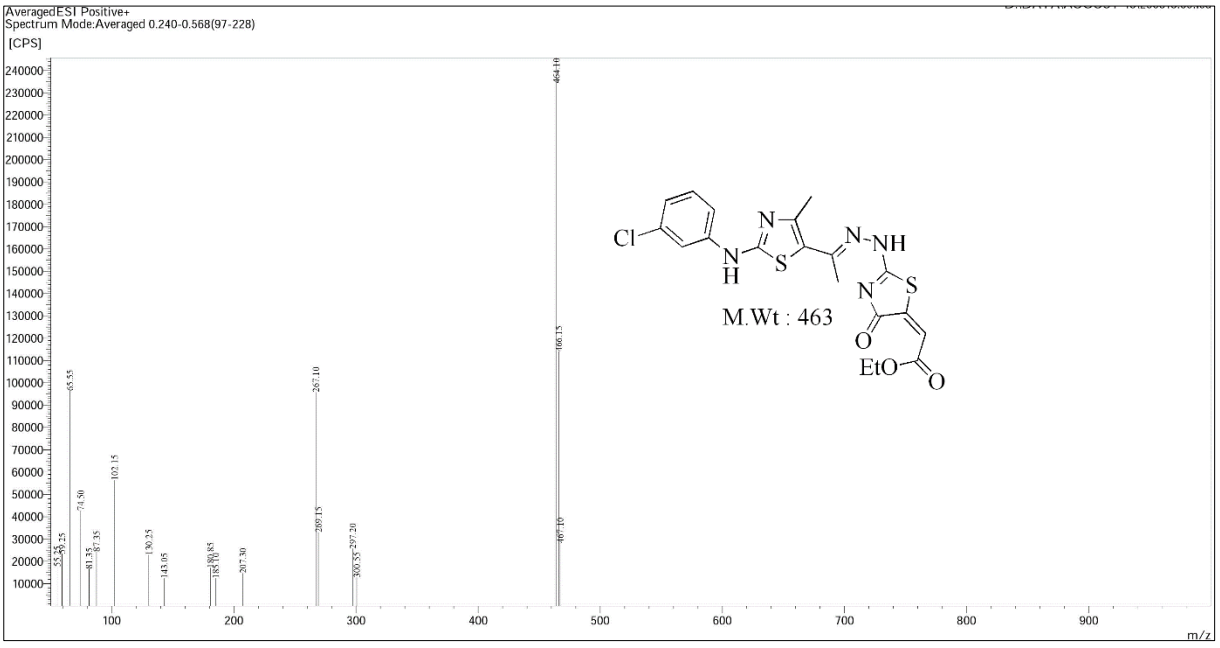
Mass Spectrum of compound **10f**



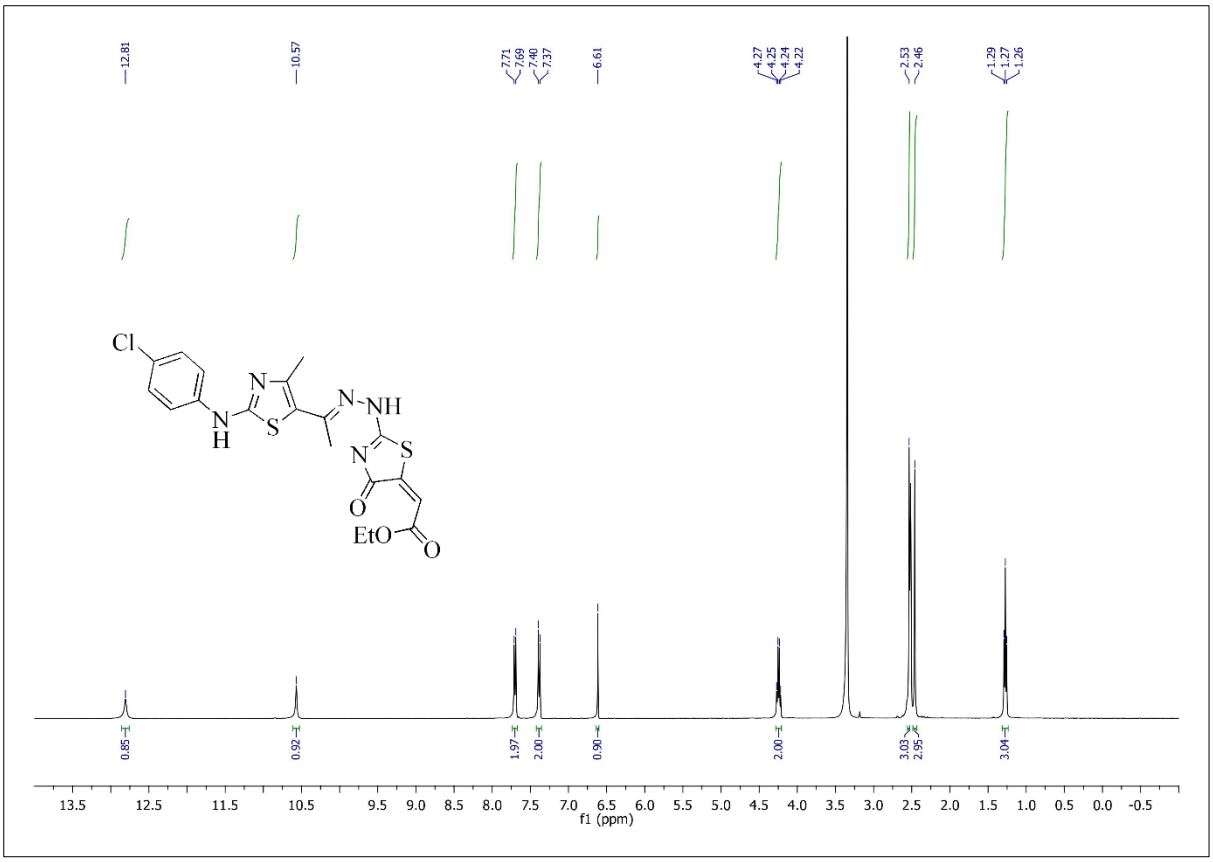
PMR Spectrum of compound **10g**



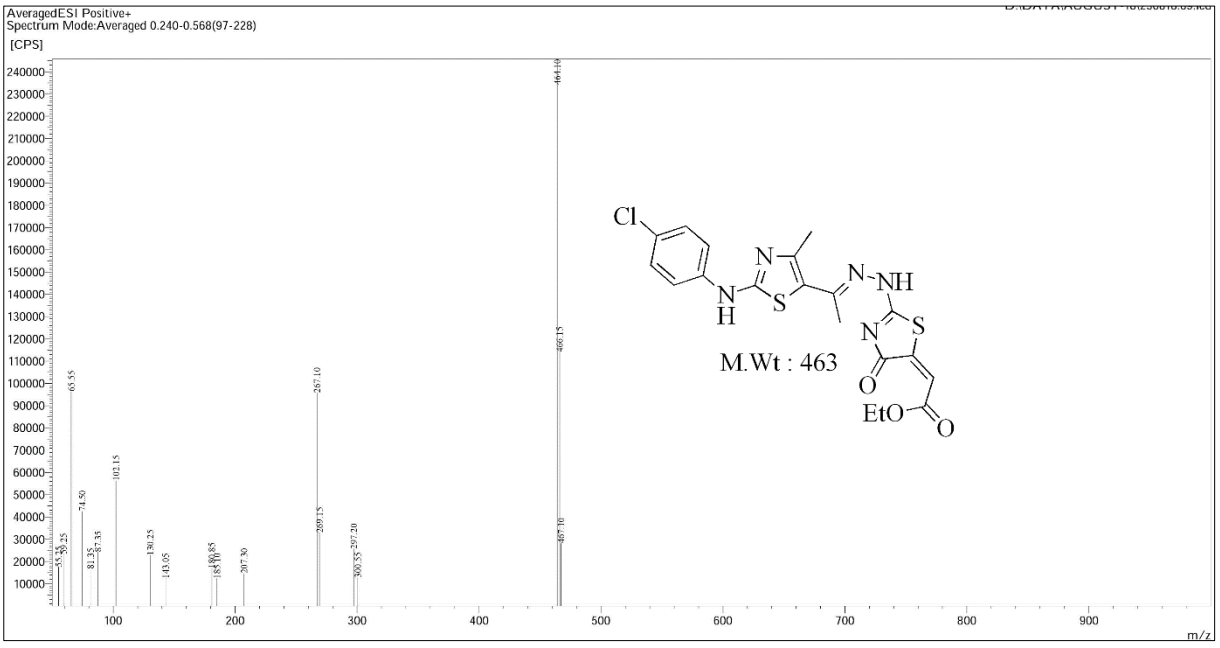
CMR Spectrum of compound **10g**



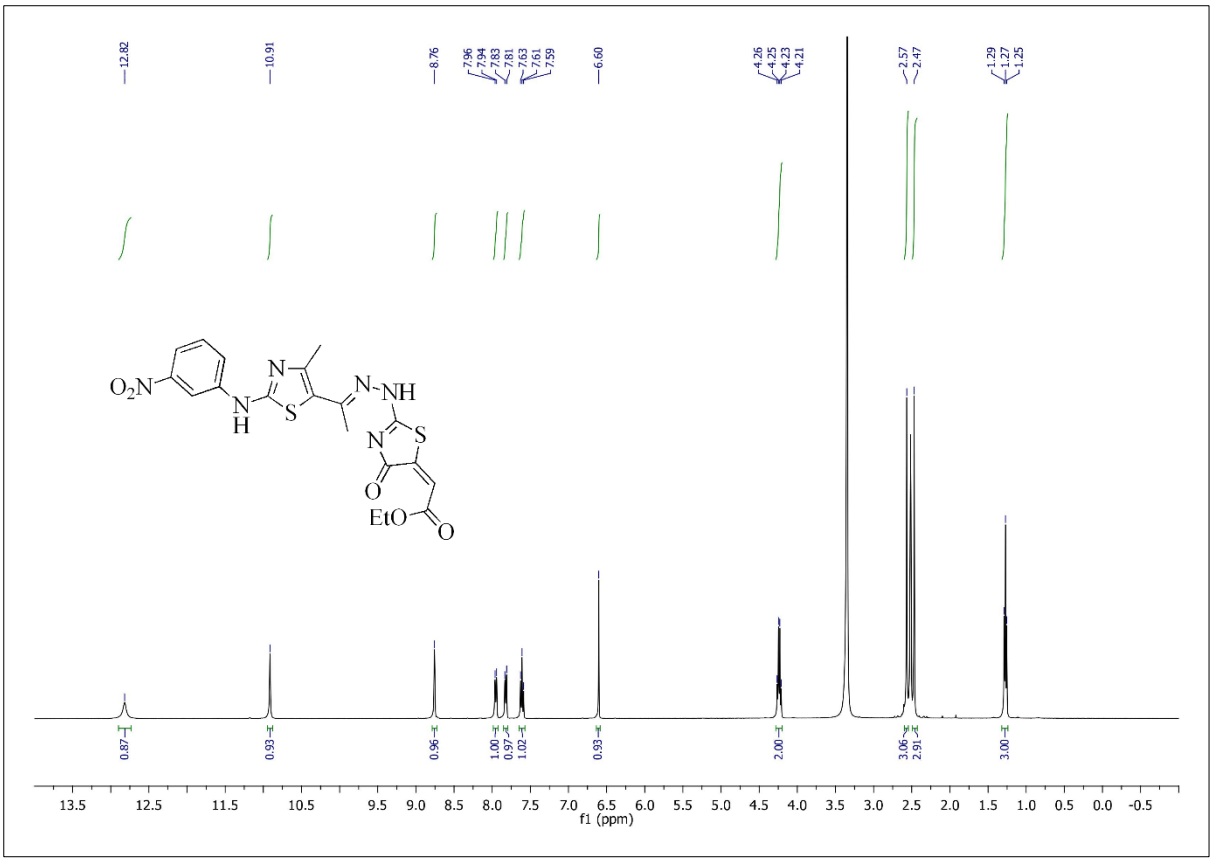
Mass Spectrum of compound **10g**



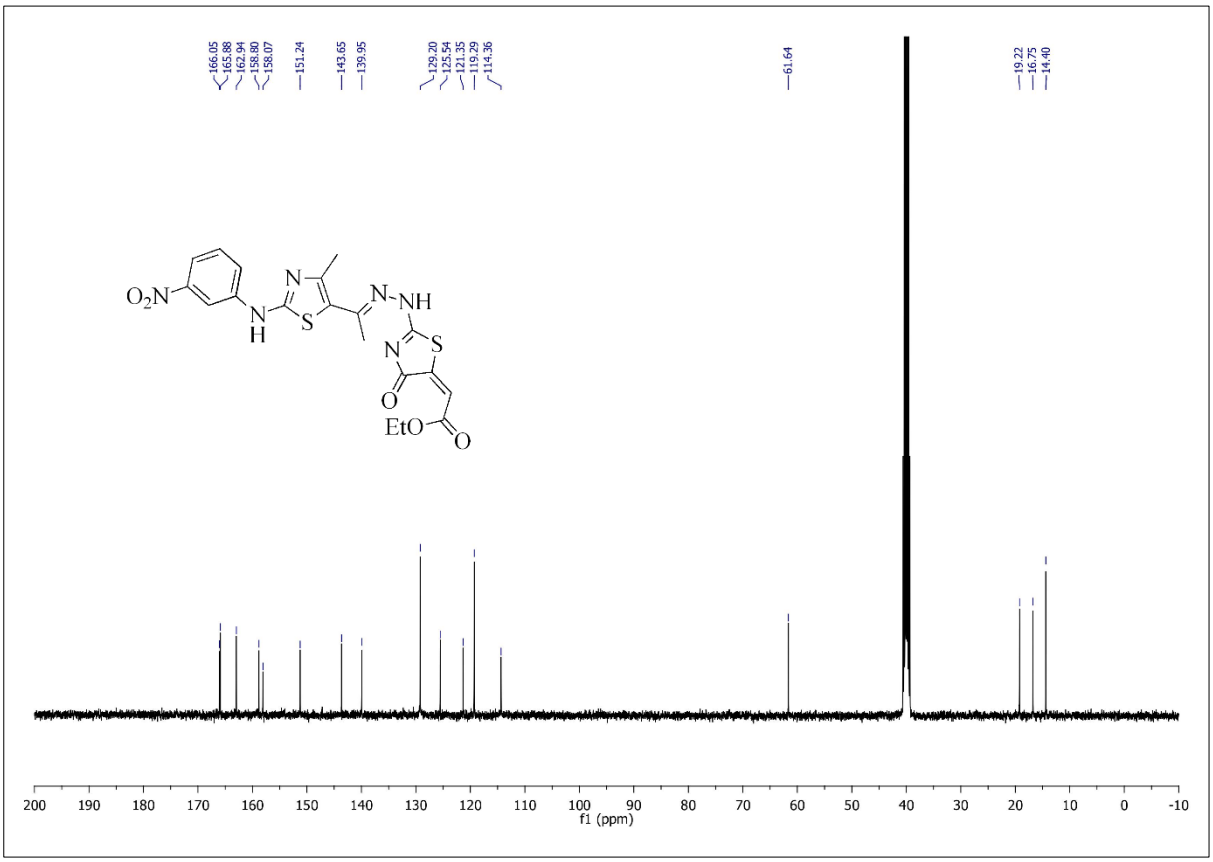
PMR Spectrum of compound **10h**



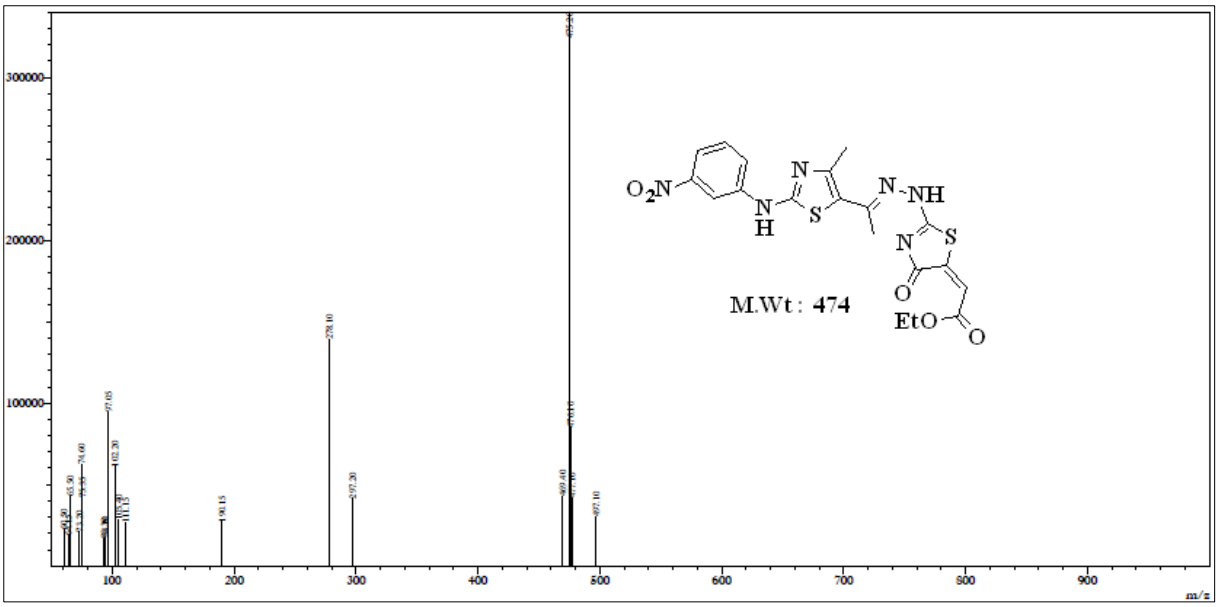
Mass Spectrum of compound **10h**



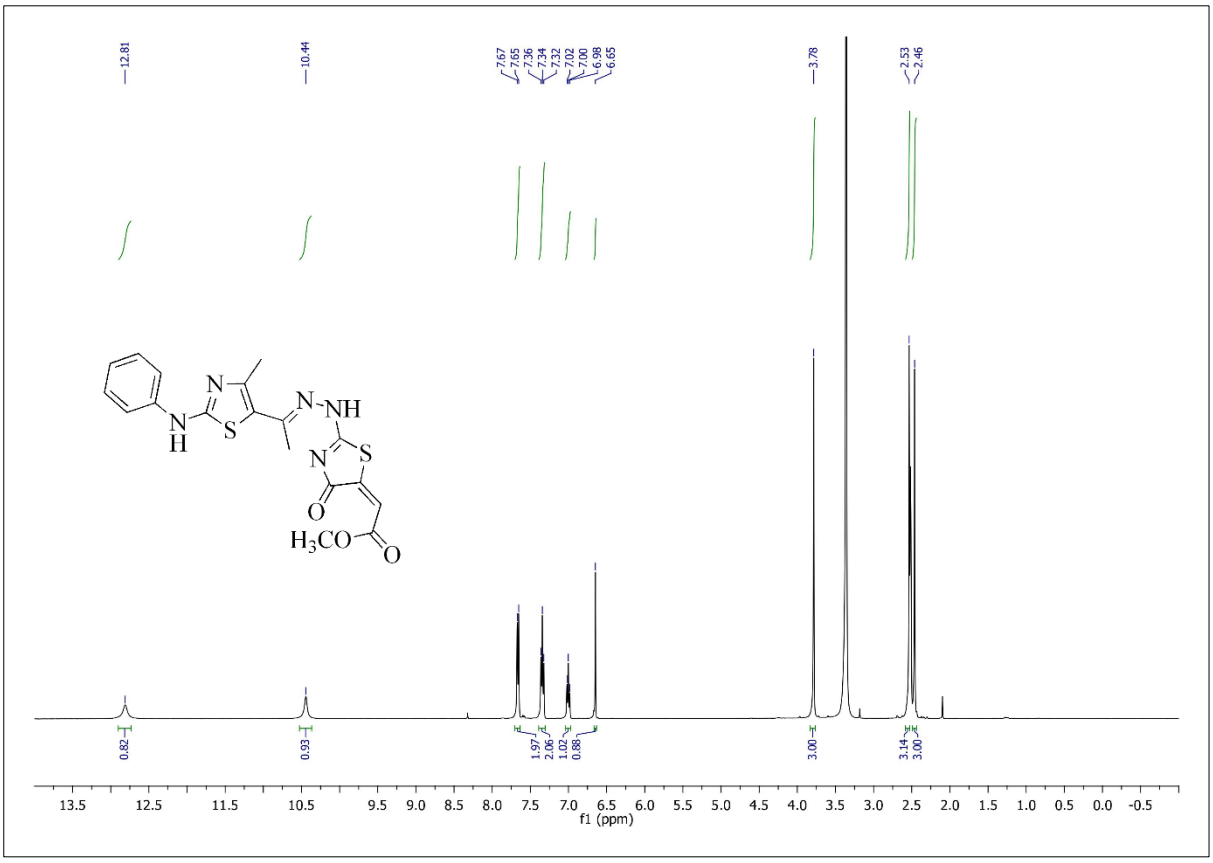
PMR Spectrum of compound **10i**



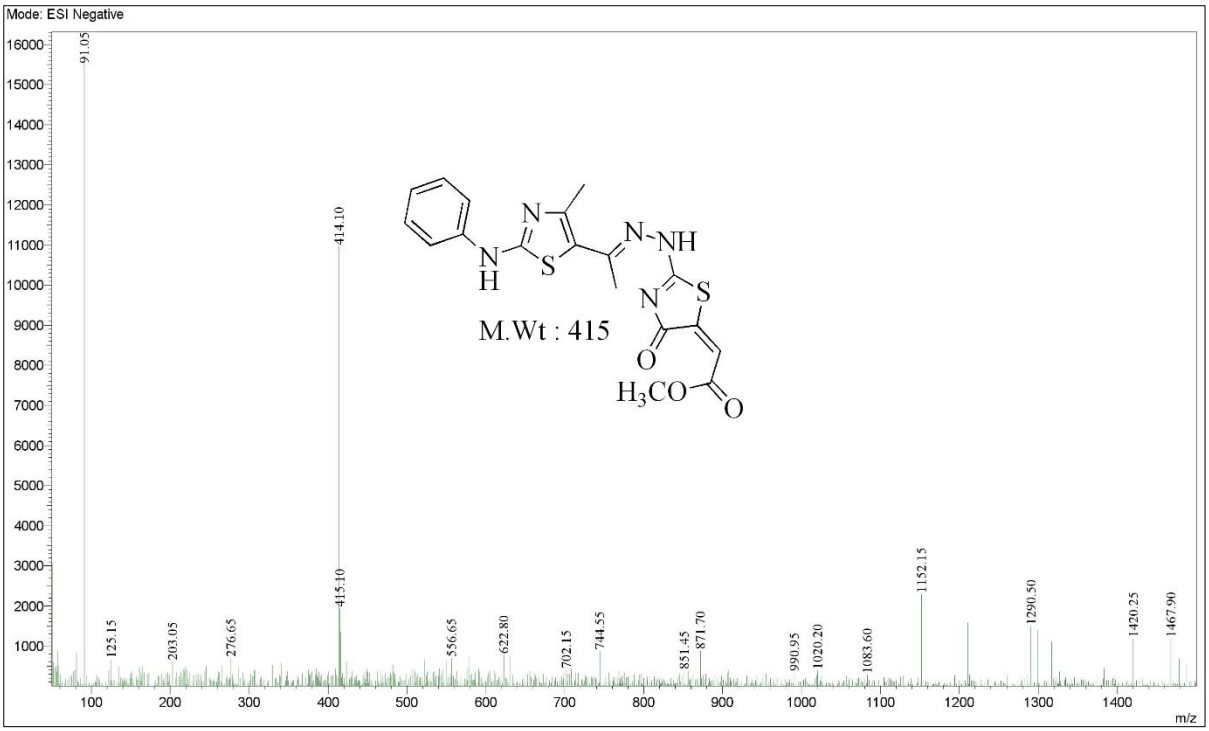
CMR Spectrum of compound **10i**



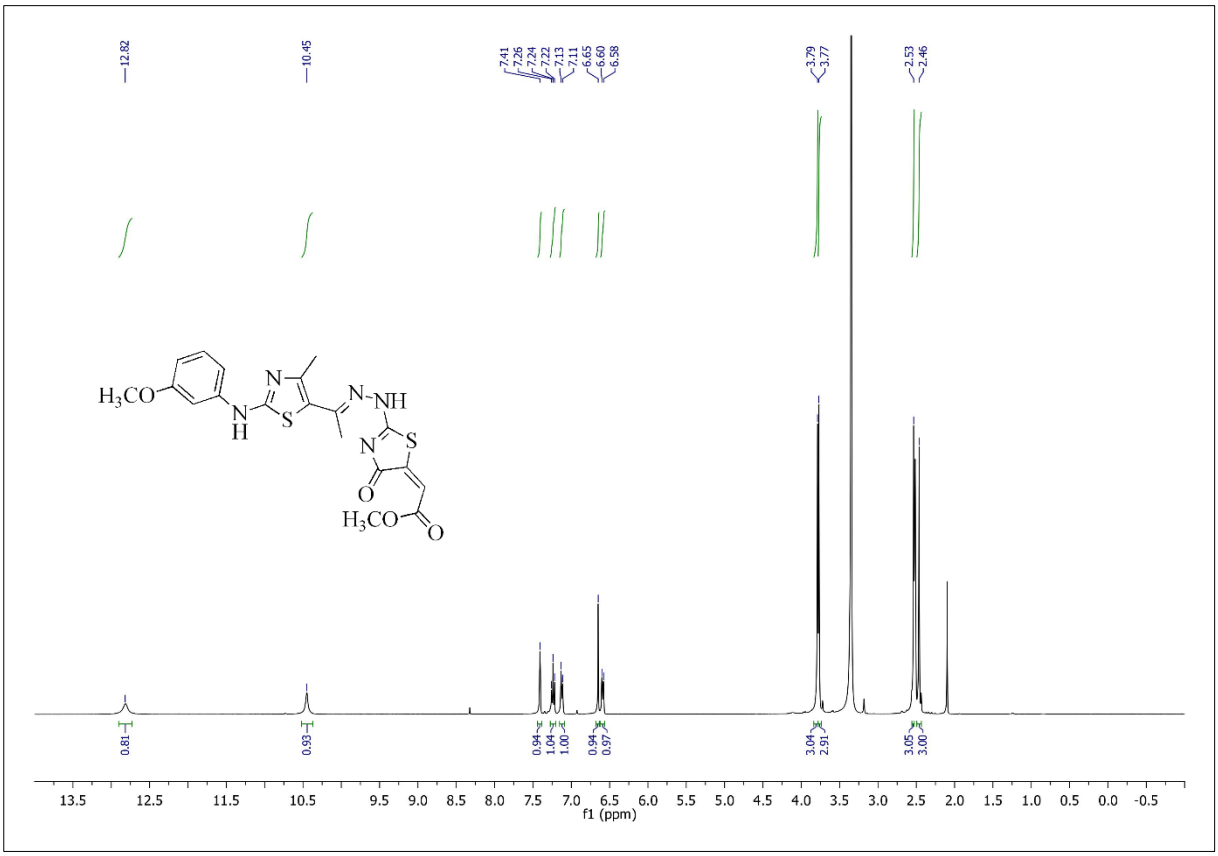
Mass Spectrum of compound **10i**



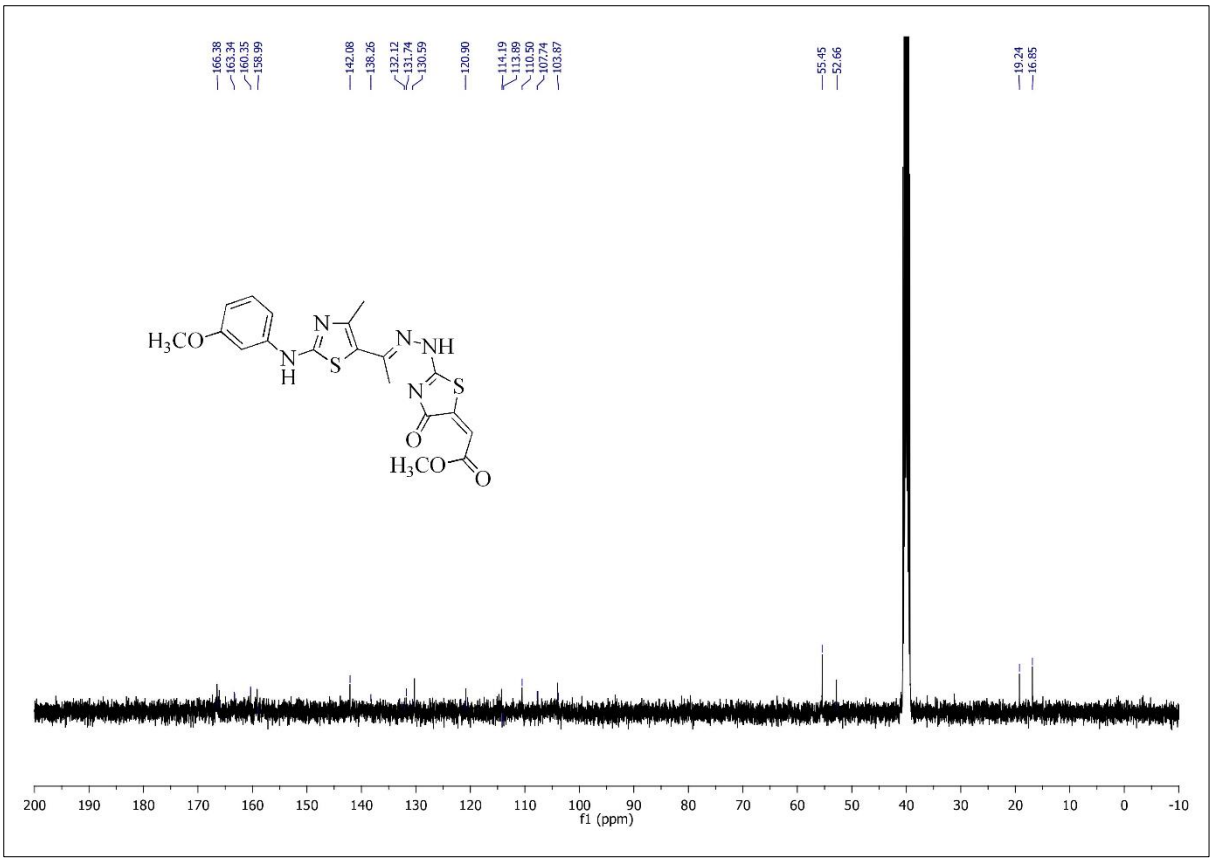
PMR Spectrum of compound **10j**



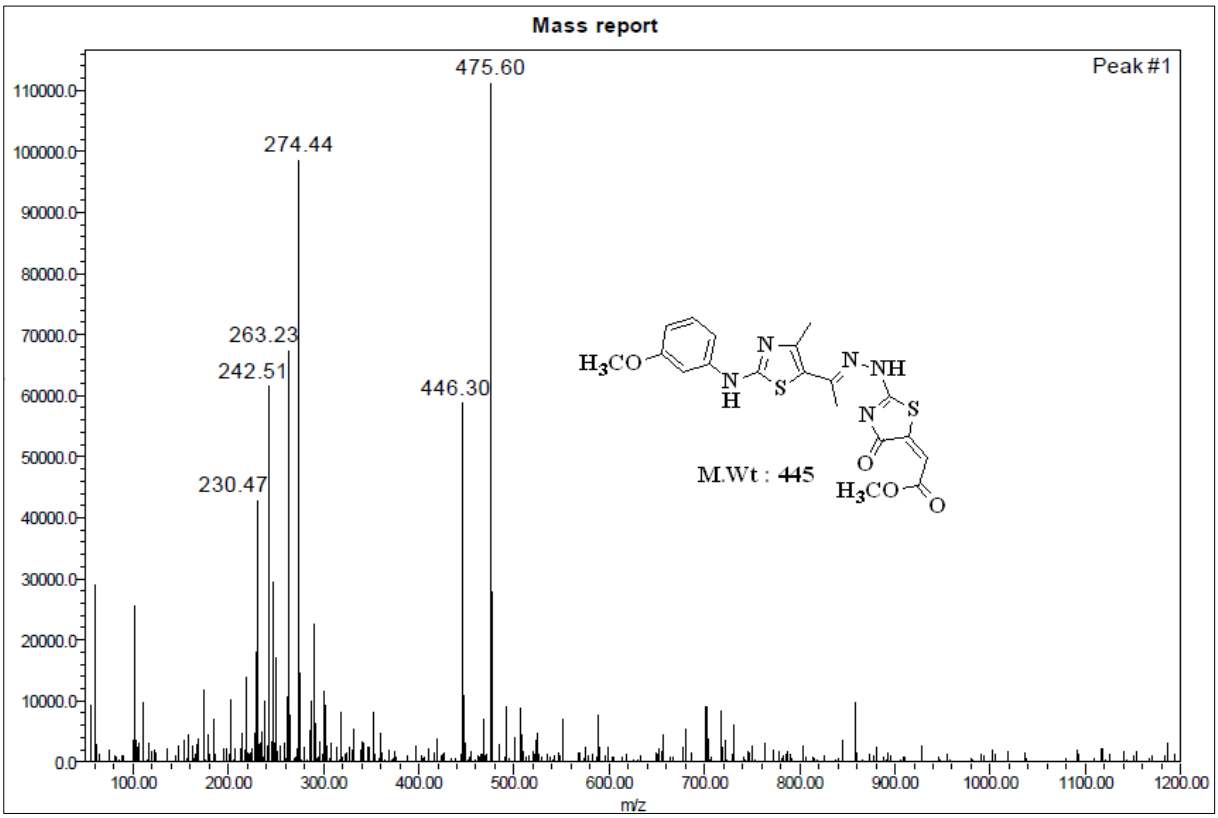
Mass Spectrum of compound **10j**



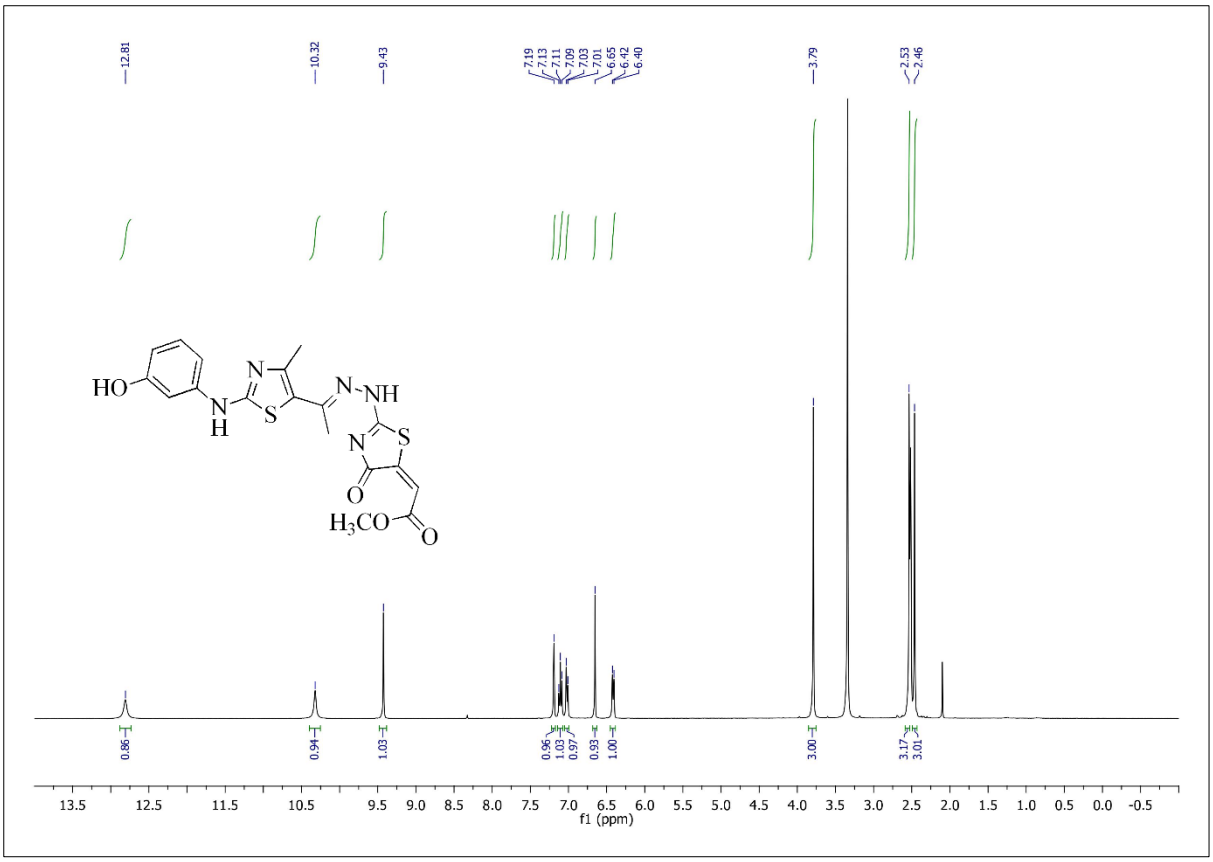
PMR Spectrum of compound **10k**



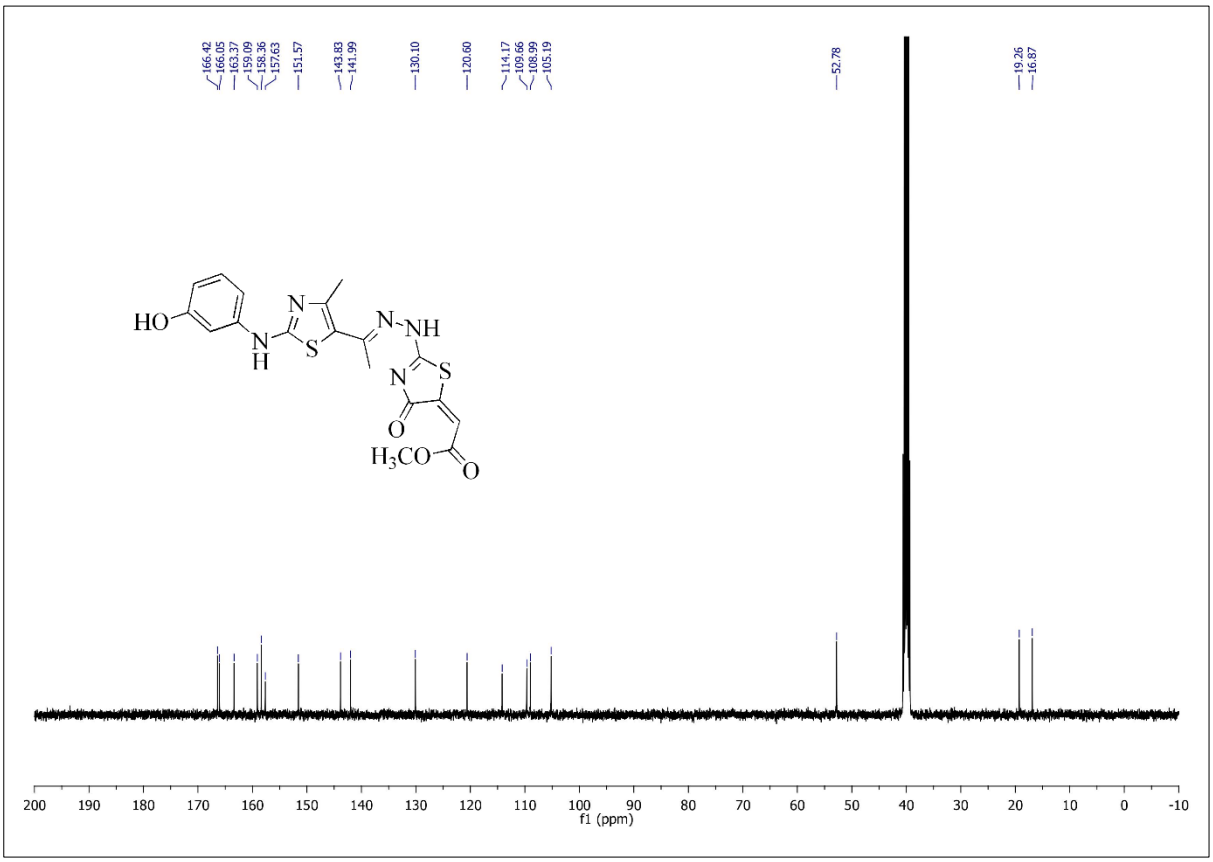
CMR Spectrum of compound **10k**



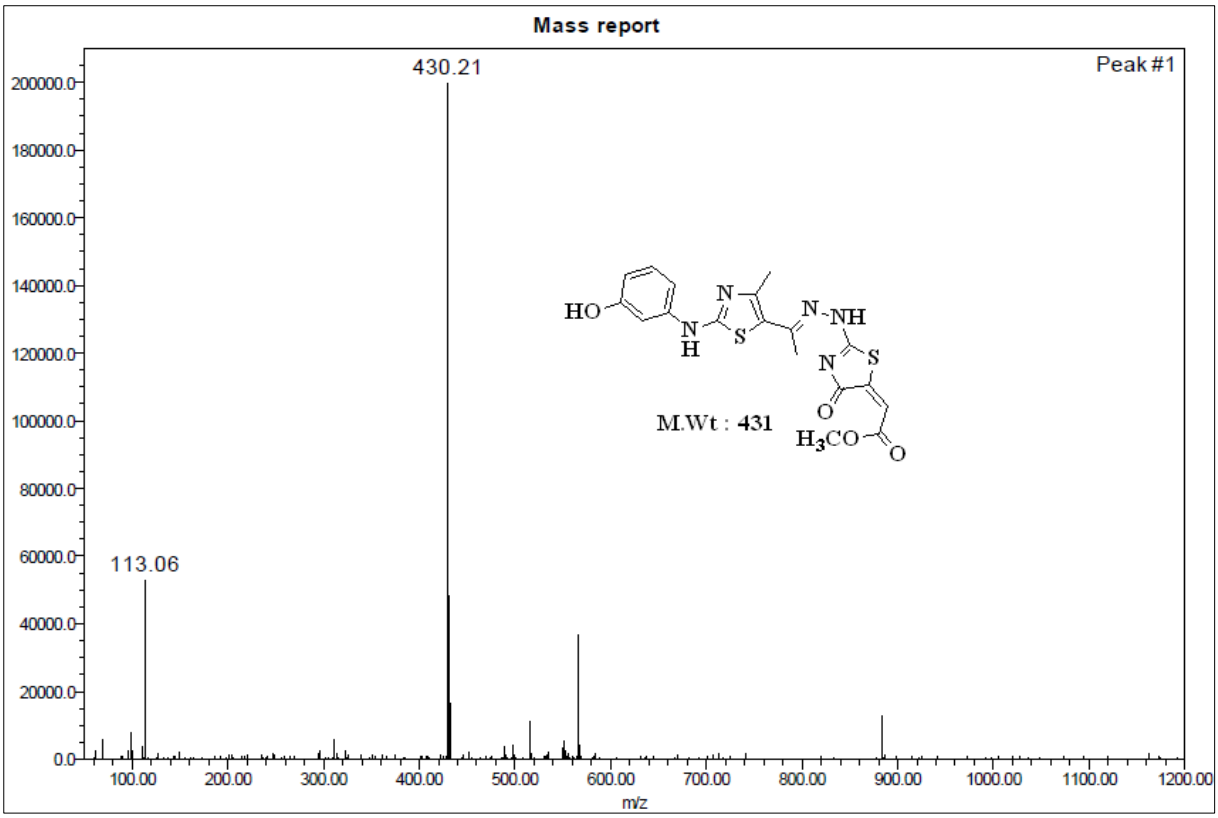
Mass Spectrum of compound **10k**



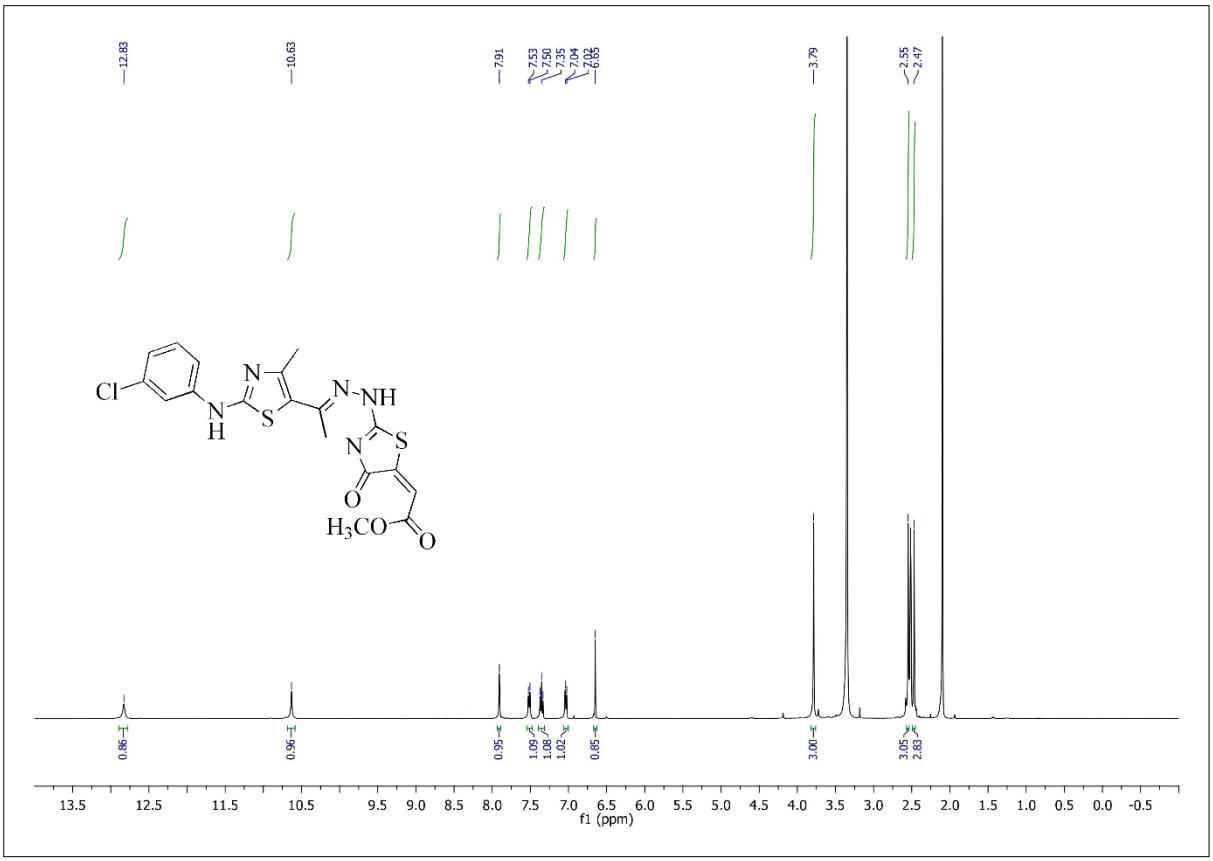
PMR Spectrum of compound **10l**



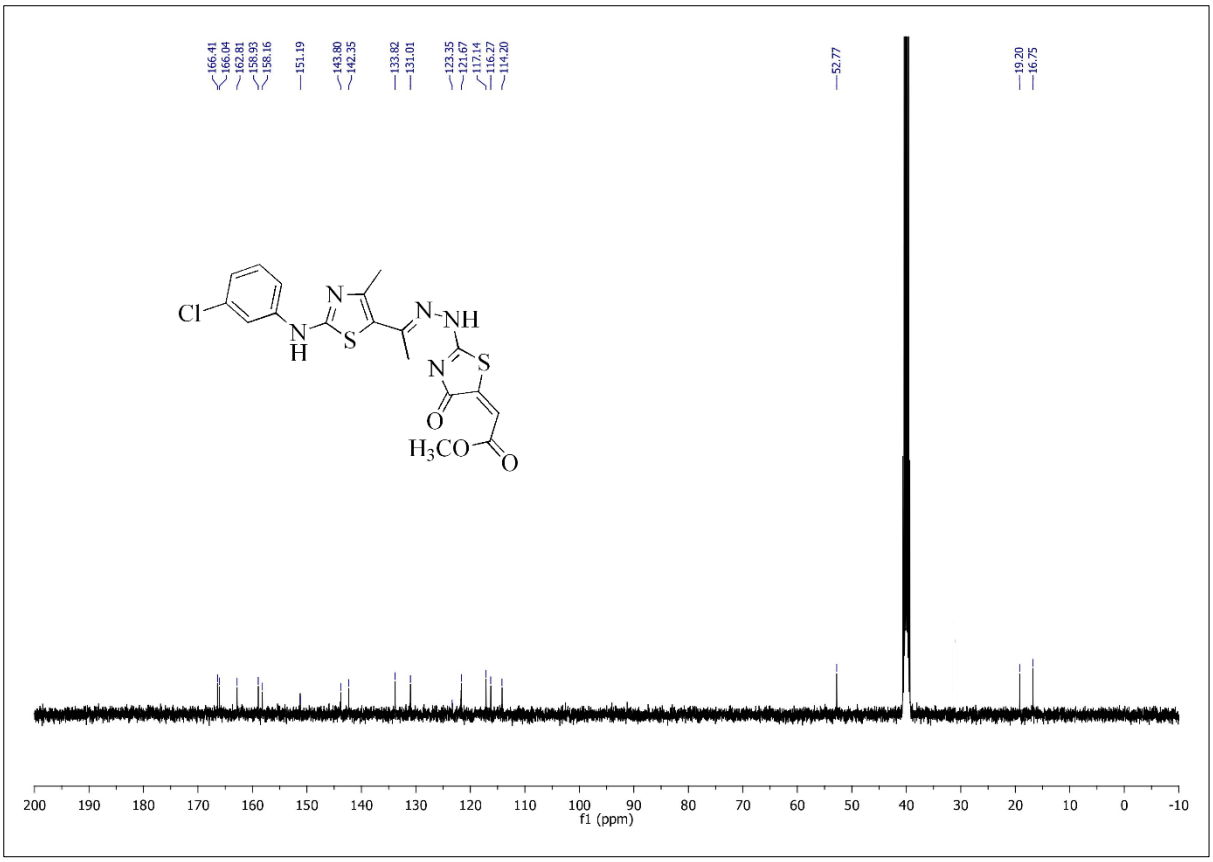
CMR Spectrum of compound **10l**



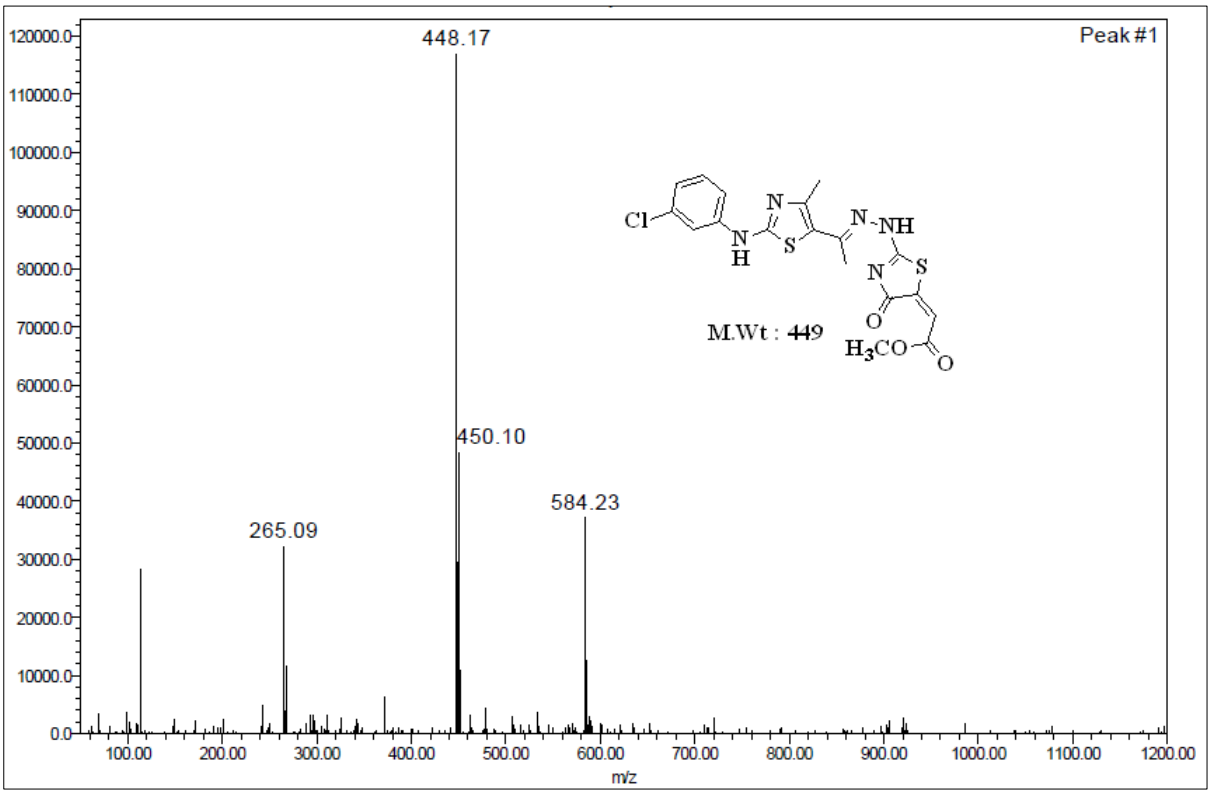
Mass Spectrum of compound **10l**



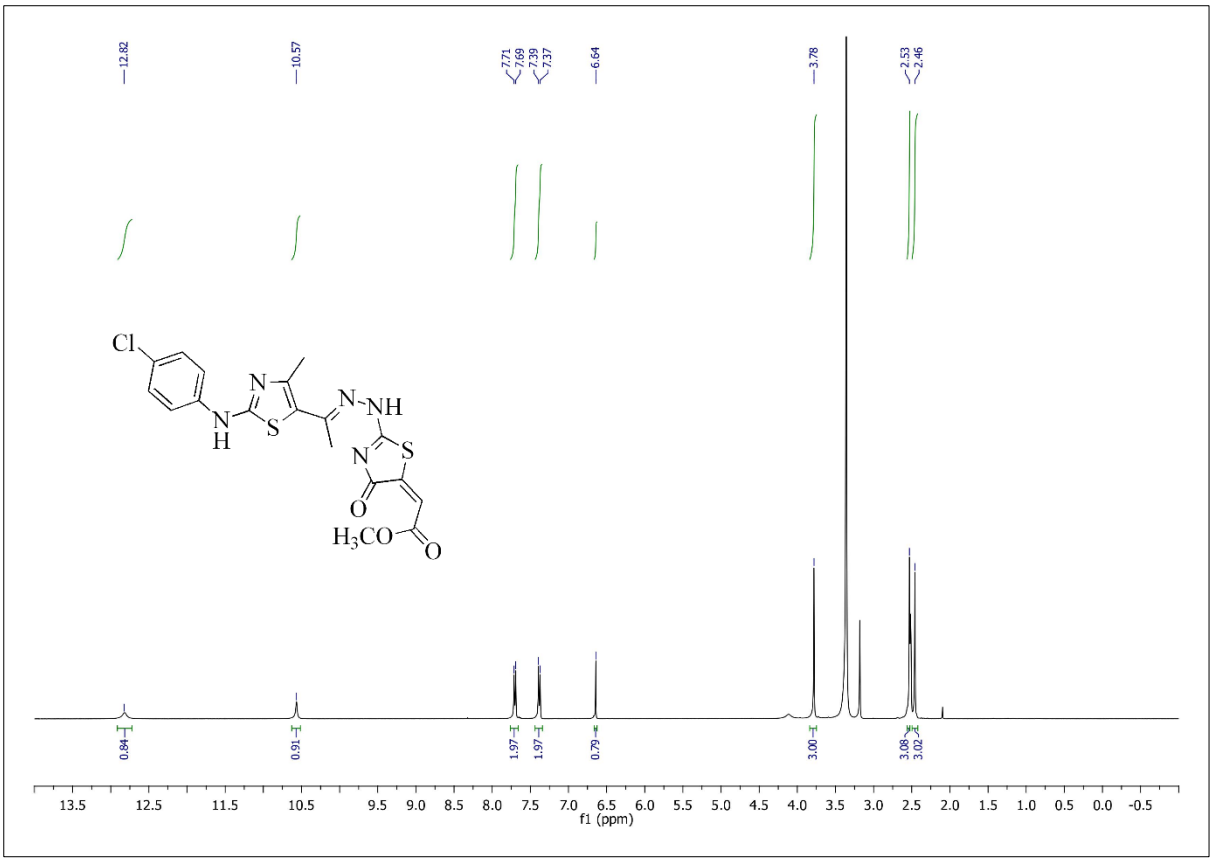
PMR Spectrum of compound **10m**



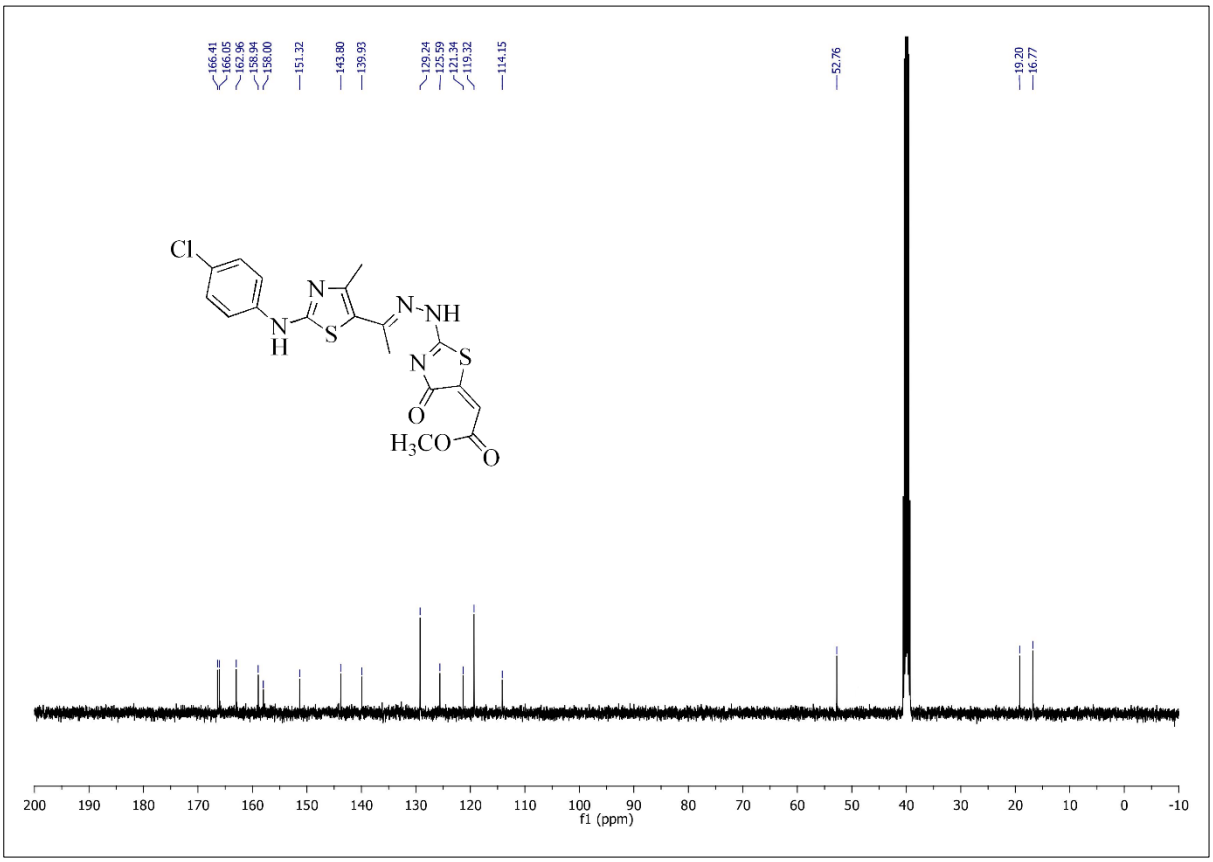
CMR Spectrum of compound **10m**



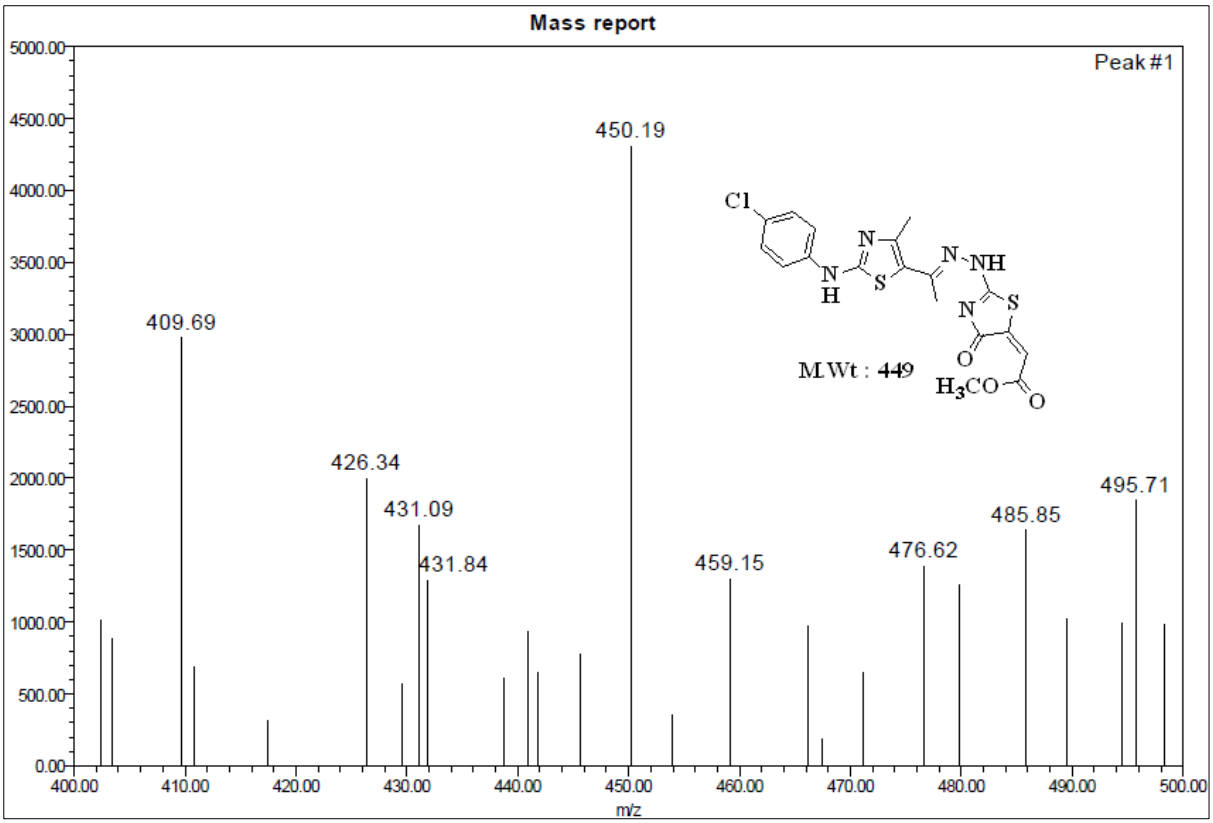
Mass Spectrum of compound **10m**



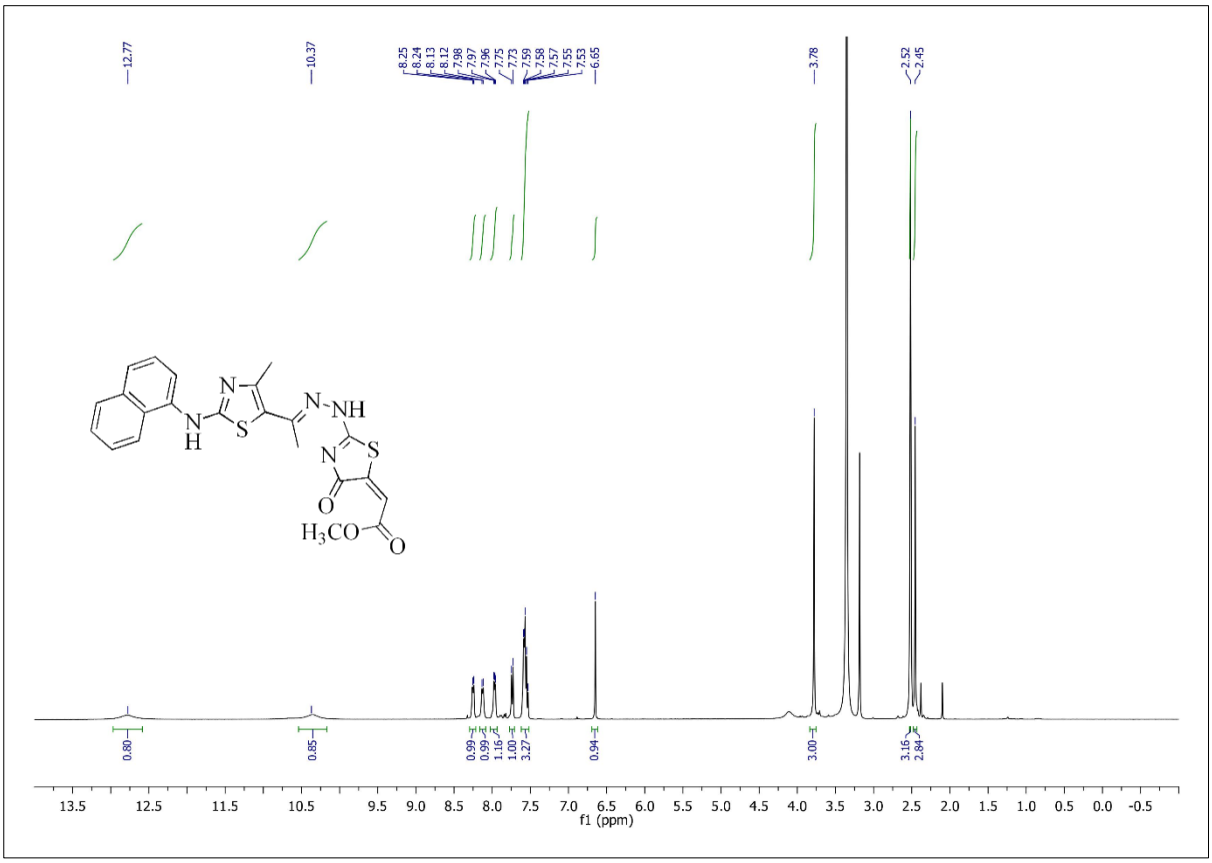
PMR Spectrum of compound **10n**



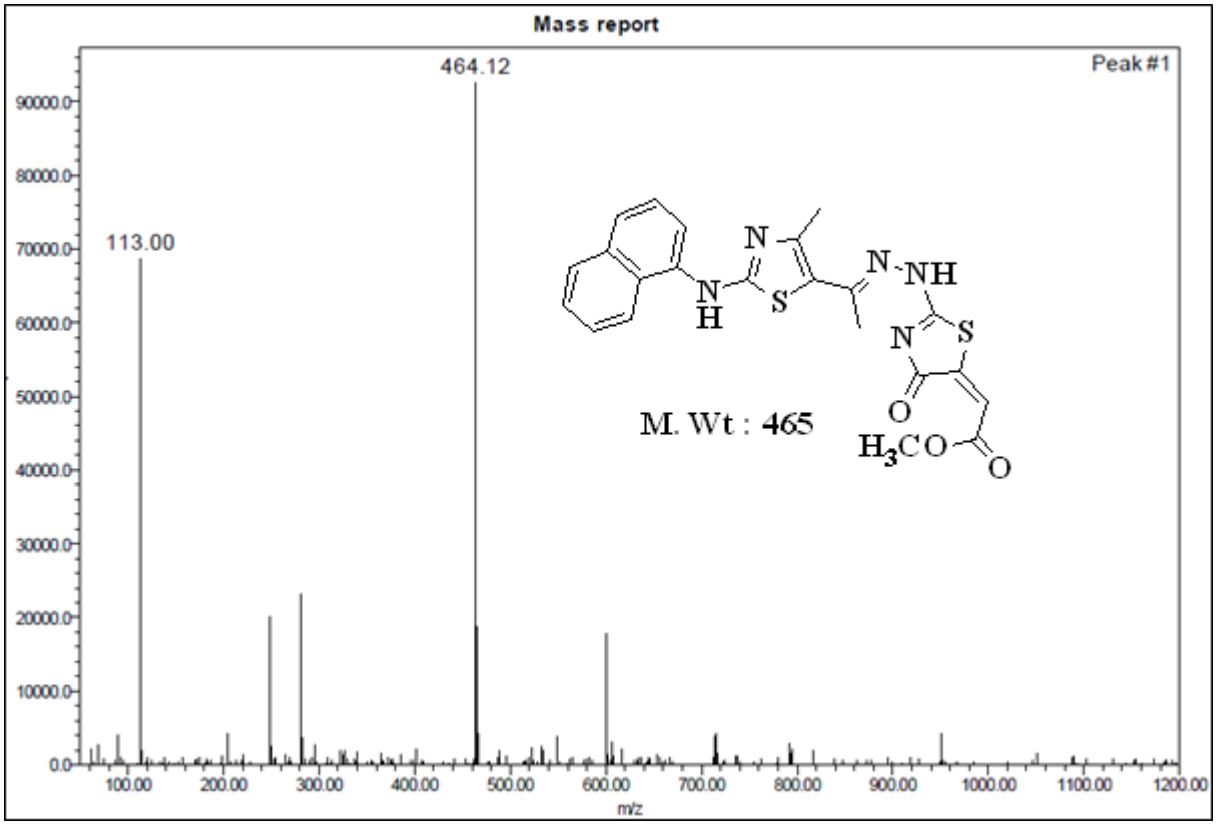
CMR Spectrum of compound **10n**



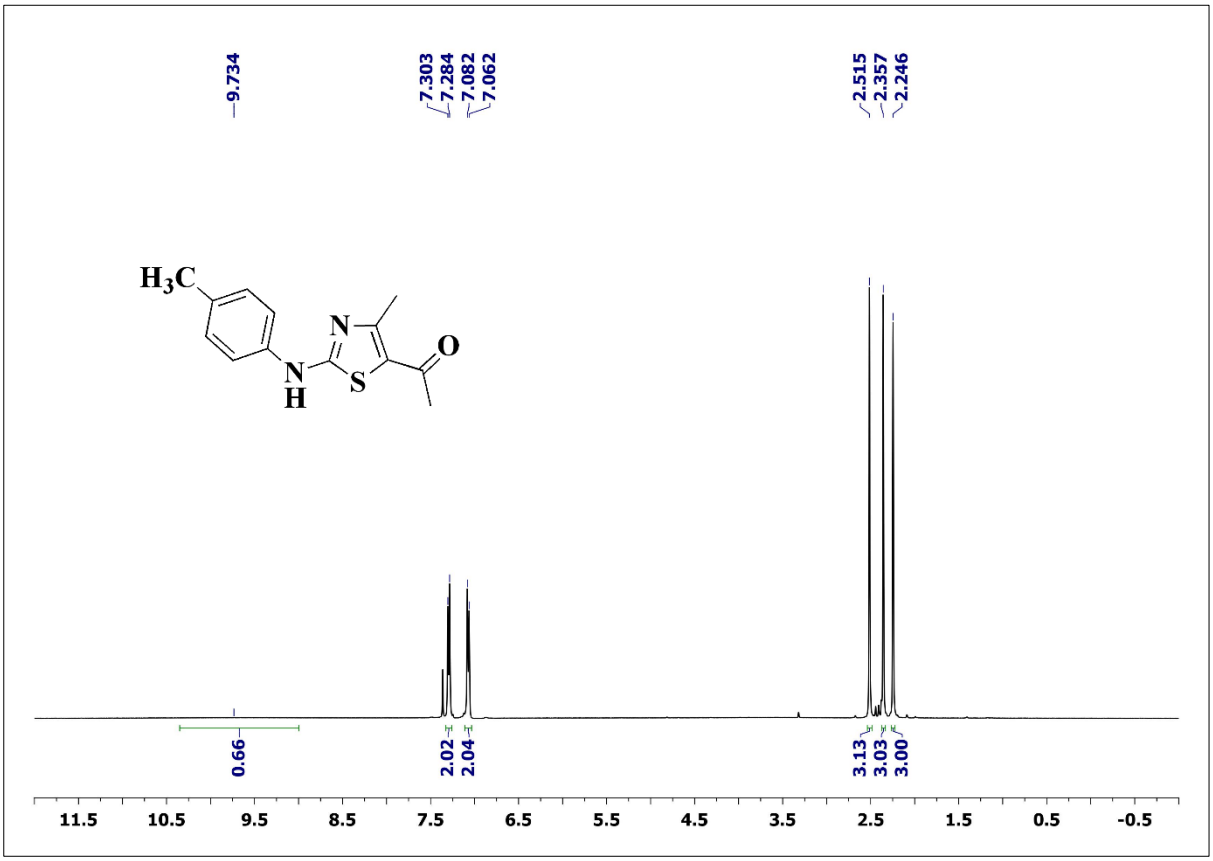
Mass Spectrum of compound **10n**



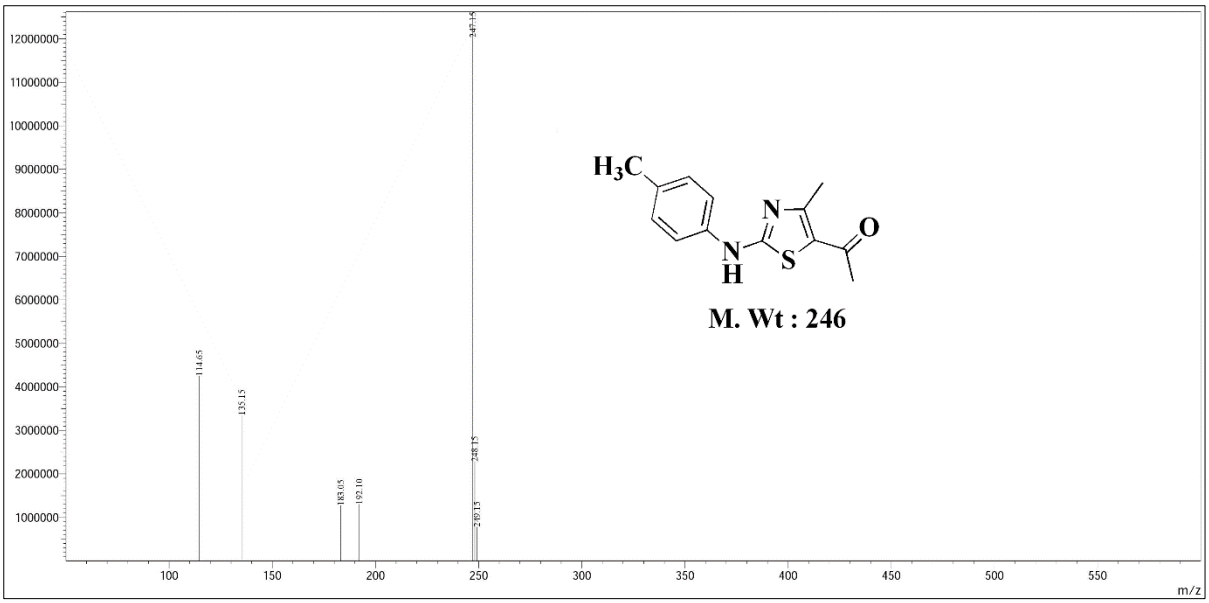
PMR Spectrum of compound **10o**



Mass Spectrum of compound **10o**



PMR Spectrum of compound **11**

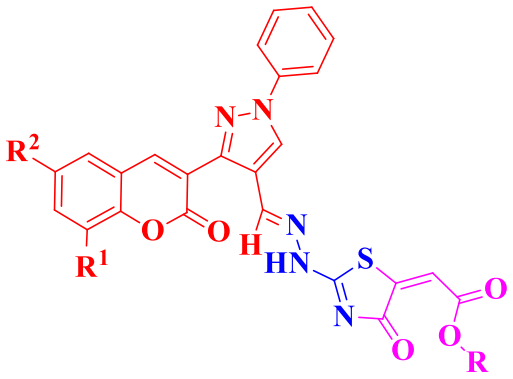


Mass Spectrum of compound **11**

CHAPTER-V

SECTION-B

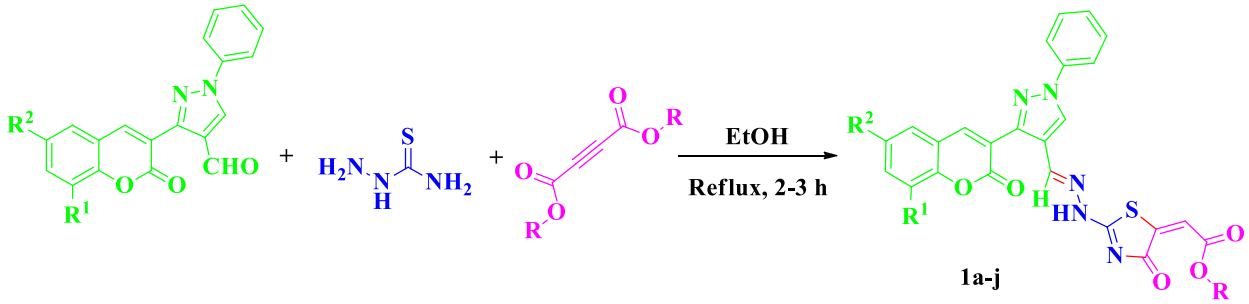
ONE POT MULTICOMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(4-OXO-2-((*E*)-2-((3-(2-OXO-2*H*-CHROMEN-3-YL)-1-PHENYL-1*H*-PYRAZOL-4-YL)METHYLENE)HYDRAZINYL)THIAZOL-5(4*H*)-YLIDENE)ACETATES

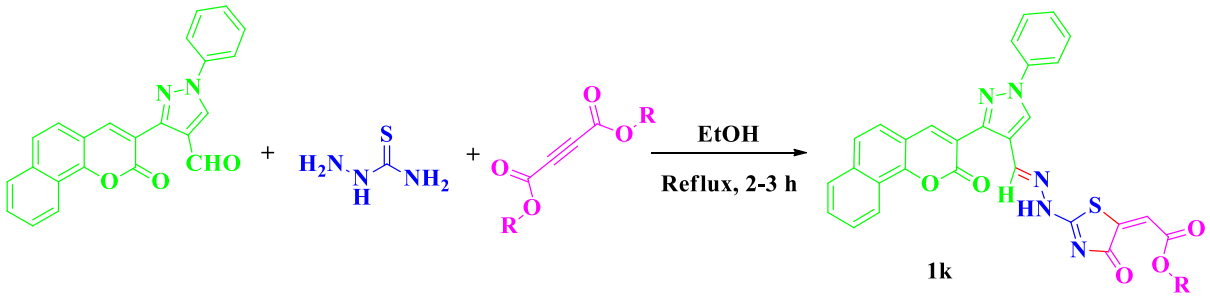


SECTION-B

PRESENT WORK

This chapter deals with the synthesis of (*E*)-ethyl-2-(4-oxo-2-((*E*)-2-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)thiazol-5(4*H*)-ylidene)acetates (1a-k). 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole, thiosemicarbazide and dialkylacetylene dicarboxylates were condensed in ethanol to afford 1a-k as shown in the scheme-1 and Table-1.





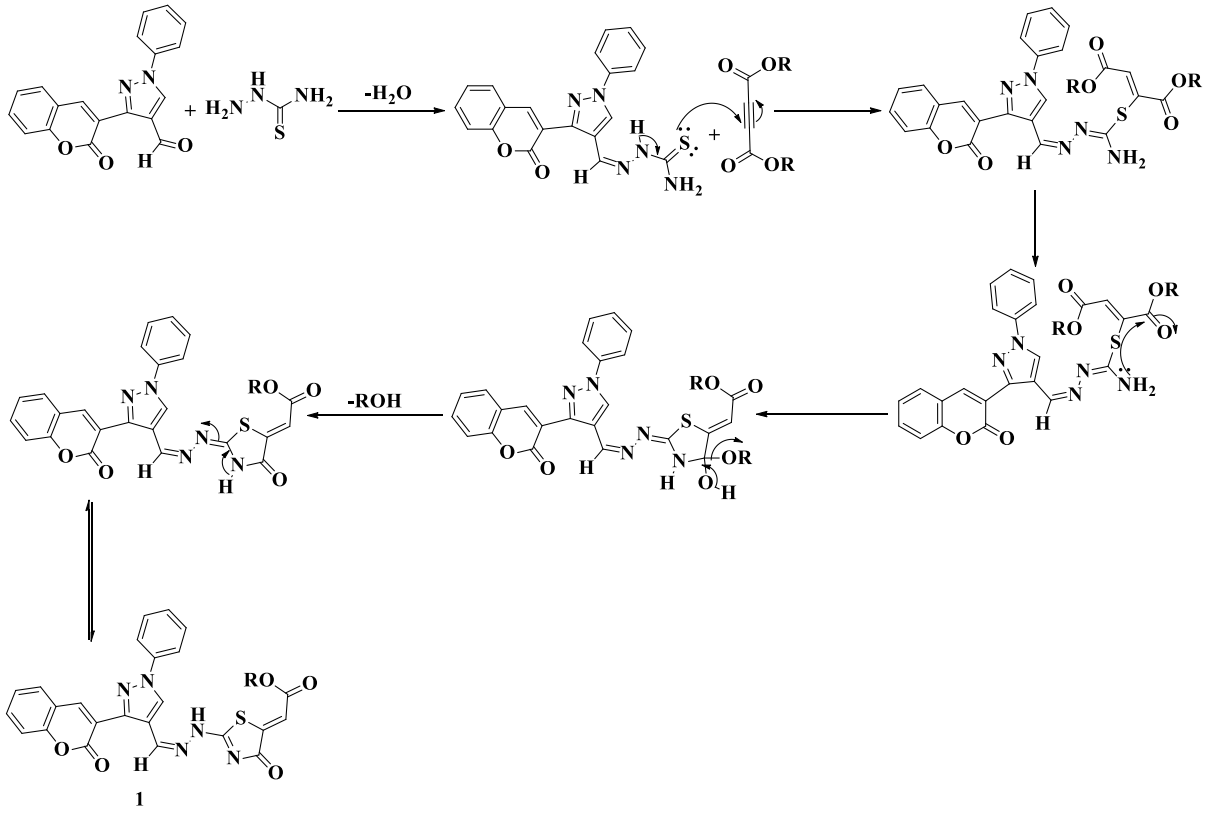
Scheme-1. Synthesis of compounds **1a-k**.

Table-1. Reaction time and substitution pattern of **1a-k**.

Entry	Product	R	R^1	R^2	Time (h)
1	1a	OEt	H	H	3
2	1b	OEt	H	Cl	3
3	1c	OEt	H	Br	2
4	1d	OEt	OCH_3	H	2.5
5	1e	OEt	OEt	H	3
6	1f	OCH_3	H	H	3
7	1g	OCH_3	H	Cl	2
8	1h	OCH_3	H	Br	3
9	1i	OCH_3	OCH_3	H	2.5
10	1j	OCH_3	OEt	H	2

11	1k	OCH_3	Naphthyl	-	3

1a-k formation mechanism was given in the scheme-2. Amino group of thiosemicarbazide attacks on the C=O functionality of 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole to form thiosemicarbazone of 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole. In the next step the intermediate on cyclization with dialkylacetylene dicarboxylate afforded thiazolidinone 1.



Scheme-2. Mechanism for the formation of **1a-k**.

CONCLUSION

In gist, we have developed a new methodology for the synthesis of a series of 1a-k through a multicomponent method. The advantages of this reaction are operational simplicity, green solvent medium, mild reaction condition, easy workup procedure, no columns chromatography for the purification of compounds good to excellent yields and catalyst-free conditions.

EXPERIMENTAL SECTION

Starting materials:

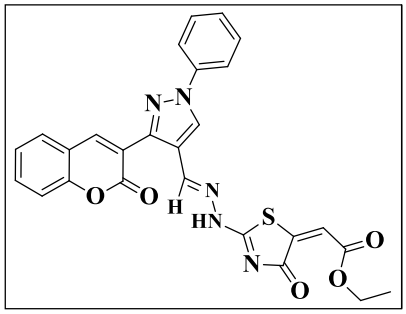
Different 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazoles were prepared by known methodology. Thiosemicarbazide and dialkylacetylene dicarboxylates were procured from market.

General procedure for the synthesis of compounds (1a-k).

Equi milli molar amount of 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole, thiosemicarbazide and dialkylacetylene dicarboxylate was suspended in absolute ethanol (5 ml) and refluxed for 2-3 hours. The solid formed was subjected to filtration and compound was recrystallized from methanol.

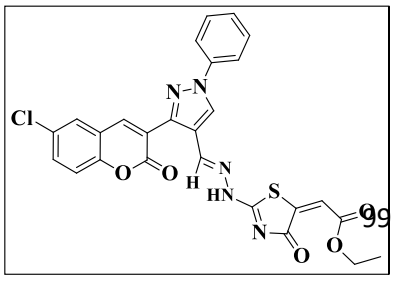
SPECTRAL DATA

(*E*)-Ethyl 2-(4-oxo-2-((*E*)-2-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)thiazol-5(4*H*)-ylidene)acetate (1a).



Color: yellow solid; mp: 290-292 °C; yield: (0.610g, 84%); IR (KBr, Wave number, cm^{-1}): 1692 (C=O of amide), 1731 (-C=O of ester), 3418 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, J = 8.0 Hz, 3H), 4.22 (q, J = 8.0 Hz, 2H), 6.59 (s, 1H,), 7.40-7.45 (m, 2H), 7.50 (d, J = 12 Hz, 1H), 7.59 (t, J = 8.0 Hz, 2H), 7.68 (t, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 2H), 8.39 (s, 1H), 8.51 (s, 1H), 9.04 (s, 1H), 12.75 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.5, 61.6, 114.6, 117.0, 118.7, 119.3, 119.4, 121.4, 122.9, 125.1, 127.8, 129.2, 130.1, 132.6, 139.2, 143.2, 143.4, 147.2, 152.0, 154.0, 159.5, 165.6, 166.1, 173.7 ppm; ESI-MS: m/z 514 $[M+H]^+$; Anal. calcd. for $C_{26}H_{19}N_5O_5S$: C, 60.81; H, 3.73; N, 13.64; S, 6.24. Found: C, 60.85; H, 3.77; N, 13.60; S, 6.28%.

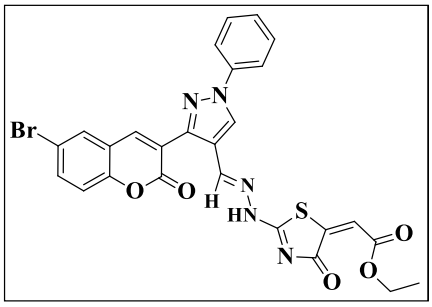
(*E*)-Ethyl-2-(2-((*E*)-2-((3-(6-chloro-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1b).



Color: yellow solid; mp: 304-306 °C; yield: (0.621g, 88%); IR (KBr, Wave number, cm^{-1}): 1692 (C=O of amide), 1735 (-C=O of ester), 3431 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, J =

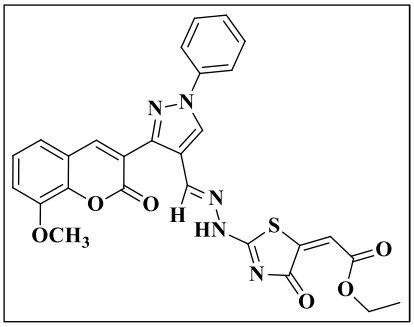
8.0 Hz, 3H), 4.22 (q, *J* = 8.0 Hz, 2H), 6.56 (s, 1H,), 7.43 (t, *J* = 8.0 Hz, 1H), 7.53-7.61 (m, 3H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 3H), 8.33 (s, 1H), 8.51 (s, 1H), 9.04 (s, 1H), 12.76 (s, 1H) ppm; CMR (DMSO-d_6): δ 14.5, 61.6, 114.5, 116.6, 118.6, 119.0, 119.3, 119.6, 120.7, 121.6, 123.1, 127.7, 128.4, 129.0, 130.2, 132.5, 135.8, 139.3, 142.4, 146.0, 152.5, 159.2, 165.7, 178.1 ppm; ESI-MS: m/z 548 $[M+H]^+$; Anal. calcd. for $C_{26}H_{18}ClN_5O_5S$: C, 56.99; H, 3.31; N, 12.78; S, 5.85. Found: C, 56.94; H, 3.35; N, 12.73; S, 5.81%.

(*E*)-Ethyl-2-(2-((*E*)-2-((3-(6-bromo-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1c).



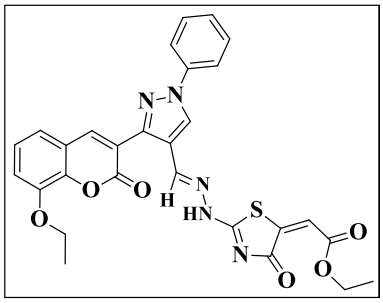
Color: yellow solid; mp: 297-299 °C; yield: (0.643g, 92%); IR (KBr, Wave number, cm^{-1}): 1692 (C=O of amide), 1735 (-C=O of ester), 3429 (NH); PMR (400 MHz, DMSO-d_6): δ 1.27 (t, *J* = 8.0 Hz, 3H), 4.22 (q, *J* = 8.0 Hz, 2H), 6.55 (s, 1H,), 7.43 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.90-7.97 (m, 2H), 8.06-8.23 (m, 3H), 8.34 (s, 1H), 8.54 (s, 1H), 9.05 (s, 1H), 12.79 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 16.6, 68.9, 110.6, 116.9, 119.1, 119.7, 122.1, 124.0, 127.8, 128.4, 130.2, 131.1, 133.2, 135.8, 137.3, 138.9, 139.2, 141.9, 145.5, 147.0, 149.9, 158.7, 178.1, 186.0 ppm; ESI-MS: m/z 591 $[M-H]^+$; Anal. calcd. for $C_{26}H_{18}BrN_5O_5S$: C, 52.71; H, 3.06; N, 11.82; S, 5.41. Found: C, 52.75; H, 3.12; N, 11.86; S, 5.45%.

(*E*)-Ethyl-2-(2-((*E*)-2-((3-(8-methoxy-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1d).



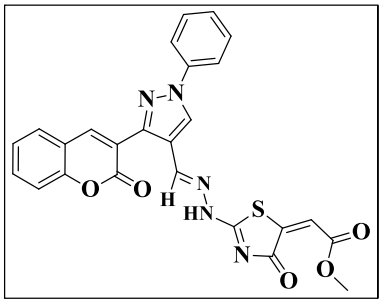
Color: yellow solid; mp: 309-311 °C; yield: (0.571g, 95%); IR (KBr, Wave number, cm^{-1}): 1645 (C=O of amide), 1727 (-C=O of ester), 3434 (NH); PMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 8.0 Hz, 3H), 3.94 (s, 3H), 4.19 (q, *J* = 8.0 Hz, 2H), 6.59 (s, 1H,), 7.33-7.44 (m, 4H), 7.58 (t, *J* = 8.0 Hz, 2H), 8.0 (d, *J* = 8.0 Hz, 2H), 8.39 (s, 1H), 8.51 (s, 1H), 9.03 (s, 1H), 12.76 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.4, 52.7, 56.5, 115.0, 119.5, 120.5, 121.3, 126.9, 127.8, 130.1, 133.0, 139.2, 140.7, 143.6, 147.1, 147.3, 150.2, 151.8, 152.2, 154.7, 156.8, 159.4, 166.1 ppm; Anal. calcd. for $C_{27}H_{21}N_5O_6S$: C, 59.66; H, 3.89; N, 12.88; O, 17.66; S, 5.90. Found: C, 59.61; H, 3.85; N, 12.82; S, 5.95%.

(*E*)-Ethyl-2-(2-((*E*)-2-((3-(8-ethoxy-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1e).



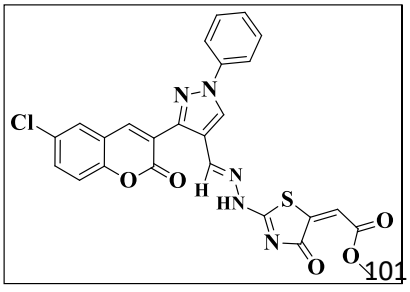
Color: yellow solid; mp: 310-312 °C; yield: (0.586g, 95%); IR (KBr, Wave number, cm^{-1}): 1694 (C=O of amide), 1725 (-C=O of ester), 3430 (NH); PMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 8.0 Hz, 3H), 1.42 (t, *J* = 8.0 Hz, 3H), 4.17-4.23 (m, 4H), 6.60 (s, 1H,), 7.35-7.43 (m, 4H), 7.58 (t, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.39 (s, 1H), 8.51 (s, 1H), 9.03 (s, 1H), 12.79 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 14.5, 15.1, 61.5, 64.8, 114.7, 116.0, 118.7, 119.5, 120.0, 120.5, 121.1, 125.1, 126.0, 127.8, 129.5, 130.1, 133.2, 134.9, 139.2, 143.3, 143.6, 143.7, 146.2, 147.4, 159.5, 165.5 ppm; ESI-MS: m/z 558 $[M+H]^+$; Anal. calcd. for $C_{28}H_{23}N_5O_6S$: C, 60.31; H, 4.16; N, 12.56; S, 5.75. Found: C, 60.36; H, 4.19; N, 12.50; S, 5.71%.

(*E*)-Eethyl-2-(4-oxo-2-((*E*)-2-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)thiazol-5(4*H*)-ylidene)acetate (1f).



Color: yellow solid; mp: 310-312 °C; yield: (0.554g, 90%); IR (KBr, Wave number, cm^{-1}): 1646 (C=O of amide), 1725 (-C=O of ester), 3439 (NH); PMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H), 6.62 (s, 1H,), 7.40-7.44 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.0 (d, *J* = 8.0 Hz, 2H), 8.39 (s, 1H), 8.51 (s, 1H), 9.04 (s, 1H), 12.77 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 52.7, 114.4, 117.0, 118.7, 119.3, 119.4, 121.4, 123.1, 125.1, 127.8, 129.2, 130.1, 132.7, 136.7, 140.8, 143.3, 145.9, 147.2, 152.0, 154.1, 157.4, 159.5, 166.0 ppm; ESI-MS: m/z 500 $(M+H)^+$; Anal. calcd. for $C_{25}H_{17}N_5O_5S$: C, 60.11; H, 3.43; N, 14.02; S, 6.42. Found: C, 60.15; H, 3.47; N, 14.10; S, 6.48%.

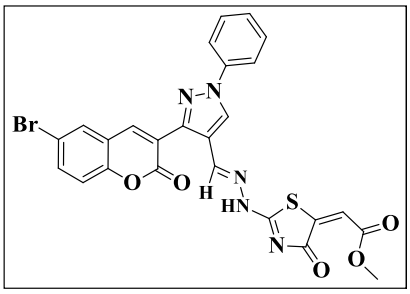
(*E*)-Methyl-2-(2-((*E*)-2-((3-(6-chloro-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1g).



Color: yellow solid; mp: 312-314 °C; yield: (0.567g, 94%); IR (KBr, Wave number, cm^{-1}): 1649 (C=O of amide), 1728 (-C=O of ester), 3430 (NH); PMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H), 6.59 (s, 1H,), 7.43 (t, *J* = 8.0 Hz, 1H), 7.54-7.61 (m, 3H),

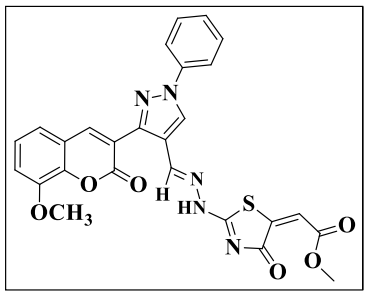
7.72 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 3H), 8.34 (s, 1H), 8.52 (s, 1H), 9.04 (s, 1H), 12.79 (s, 1H) ppm; ESI-MS: m/z 534 $[M+H]^+$; Anal. calcd. for $C_{25}H_{16}ClN_5O_5S$: C, 56.24; H, 3.02; N, 13.12; S, 6.01. Found: C, 54.20; H, 3.12; N, 13.16; S, 5.95%.

(*E*)-Methyl-2-(2-((*E*)-2-((3-(6-bromo-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1h)



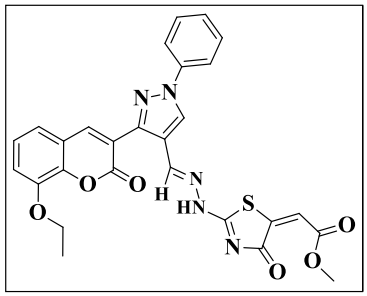
Color: yellow solid; mp: 312-314 °C; yield: (0.642g, 90%); IR (KBr, Wave number, cm^{-1}): 1686 (C=O of amide), 1743 (-C=O of ester), 3432 (NH); PMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H), 6.58 (s, 1H,), 7.43 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 3H), 8.14 (s, 1H), 8.21 (s, 1H), 8.35 (s, 1H), 8.54 (s, 1H), 9.05 (s, 1H), 12.79 (s, 1H) ppm; Anal. calcd. for $C_{25}H_{16}BrN_5O_5S$: C, 51.91; H, 2.79; N, 12.11; S, 5.54. Found: C, 51.95; H, 2.75; N, 12.15; S, 5.59%.

(*E*)-Methyl-2-(2-((*E*)-2-((3-(8-methoxy-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1i)



Yellow solid; mp: 320-322 °C; yield: (0.556g, 95%); IR (KBr, Wave number, cm^{-1}): 1692 (C=O of amide), 1718 (-C=O of ester), 3433 (NH); PMR (400 MHz, DMSO-d_6): δ 3.73 (s, 3H), 3.94 (s, 3H), 6.61 (s, 1H,), 7.35-7.45 (m, 4H), 7.58 (t, *J* = 8.0 Hz, 2H), 8.0 (d, *J* = 8.0 Hz, 2H), 8.39 (s, 1H), 8.51 (s, 1H), 9.03 (s, 1H), 12.78 (s, 1H) ppm; Anal. calcd. for $C_{26}H_{19}N_5O_6S$: C, 58.97; H, 3.62; N, 13.23; S, 6.06. Found: C, 58.93; H, 3.64; N, 13.27; S, 5.94%.

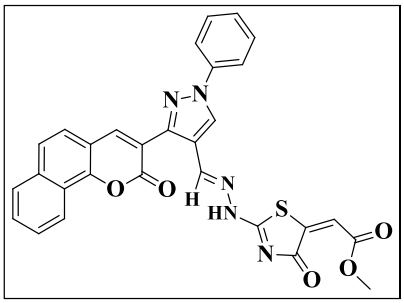
(*E*)-Methyl-2-(2-((*E*)-2-((3-(8-ethoxy-2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (1j)



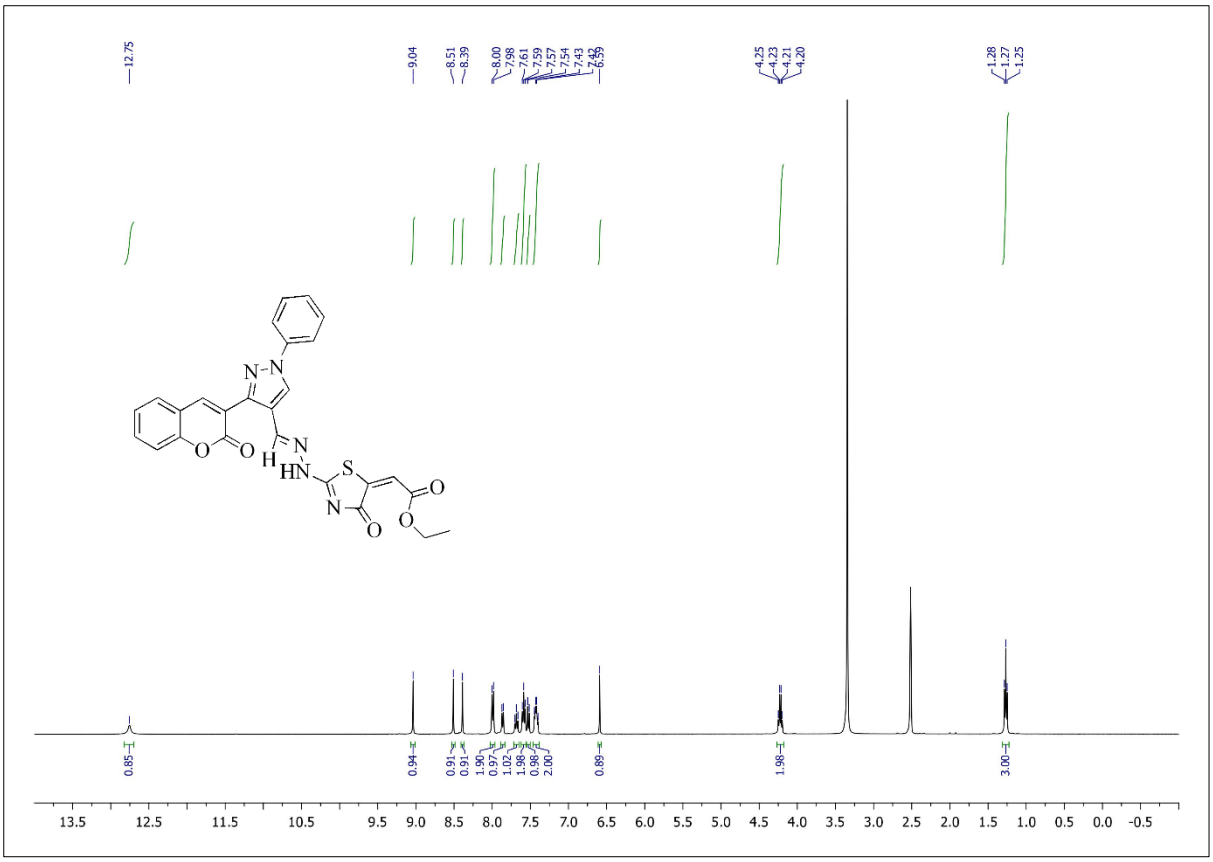
Color: yellow solid; mp: 305-307 °C; yield: (0.631g, 86%); IR (KBr, Wave number, cm^{-1}): 1646 (C=O of amide), 1725 (-C=O of ester), 3431 (NH); PMR (400 MHz, DMSO-d_6): δ 1.42 (t, *J* = 8.0 Hz, 3H), 3.73 (s, 3H), 4.21 (q, *J* = 8.0 Hz, 2H), 6.62 (s, 1H,), 7.35 (t, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.39 (s, 1H), 8.51 (s, 1H), 9.03 (s,

1H), 12.81 (s, 1H) ppm; ESI-MS: m/z 544 $[M+H]^+$; Anal. calcd. for $C_{27}H_{21}N_5O_6S$: C, 59.66; H, 3.89; N, 12.88; S, 5.90. Found: C, 59.62; H, 3.85; N, 12.83; S, 5.95%.

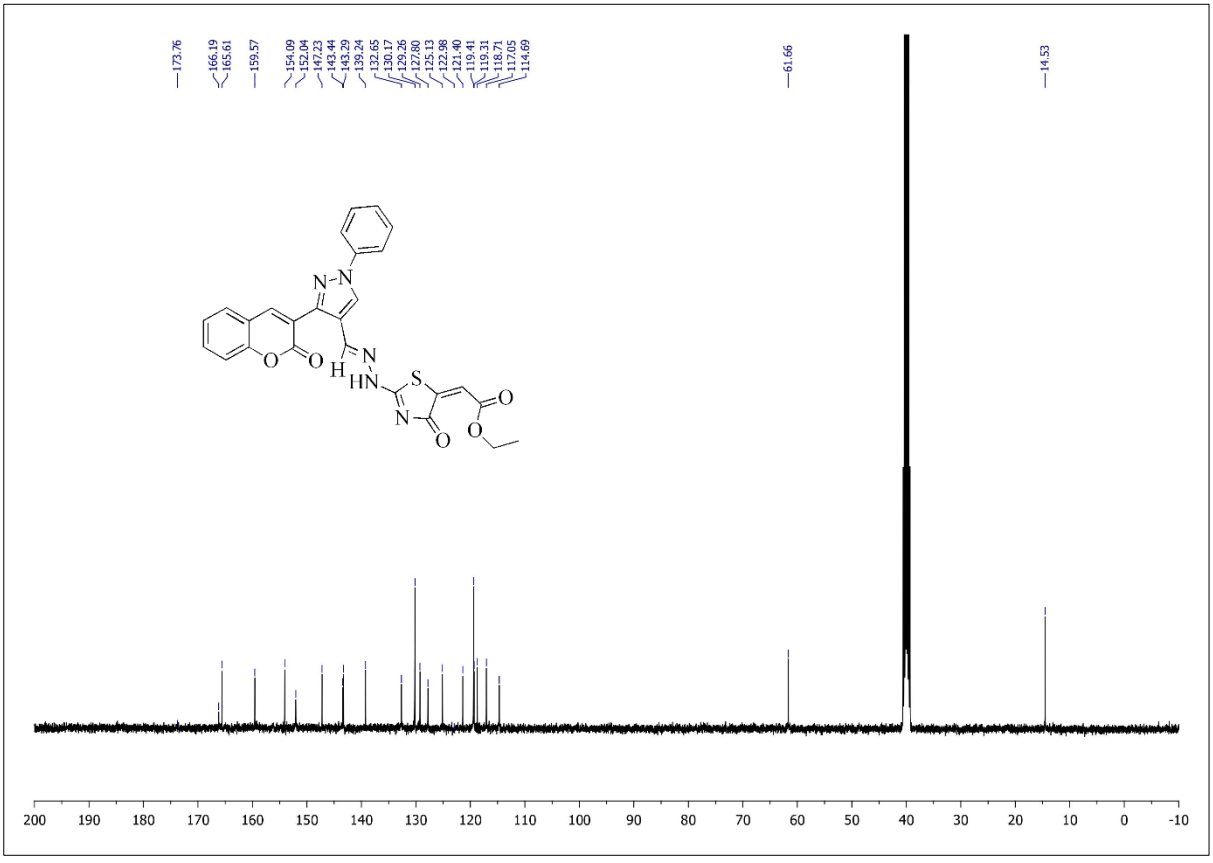
(*E*)-Methyl-2-(4-oxo-2-((*E*)-2-((3-(2-oxo-2*H*-benzo[*h*]chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-thiazol-5(4*H*)-ylidene)acetate (1k)



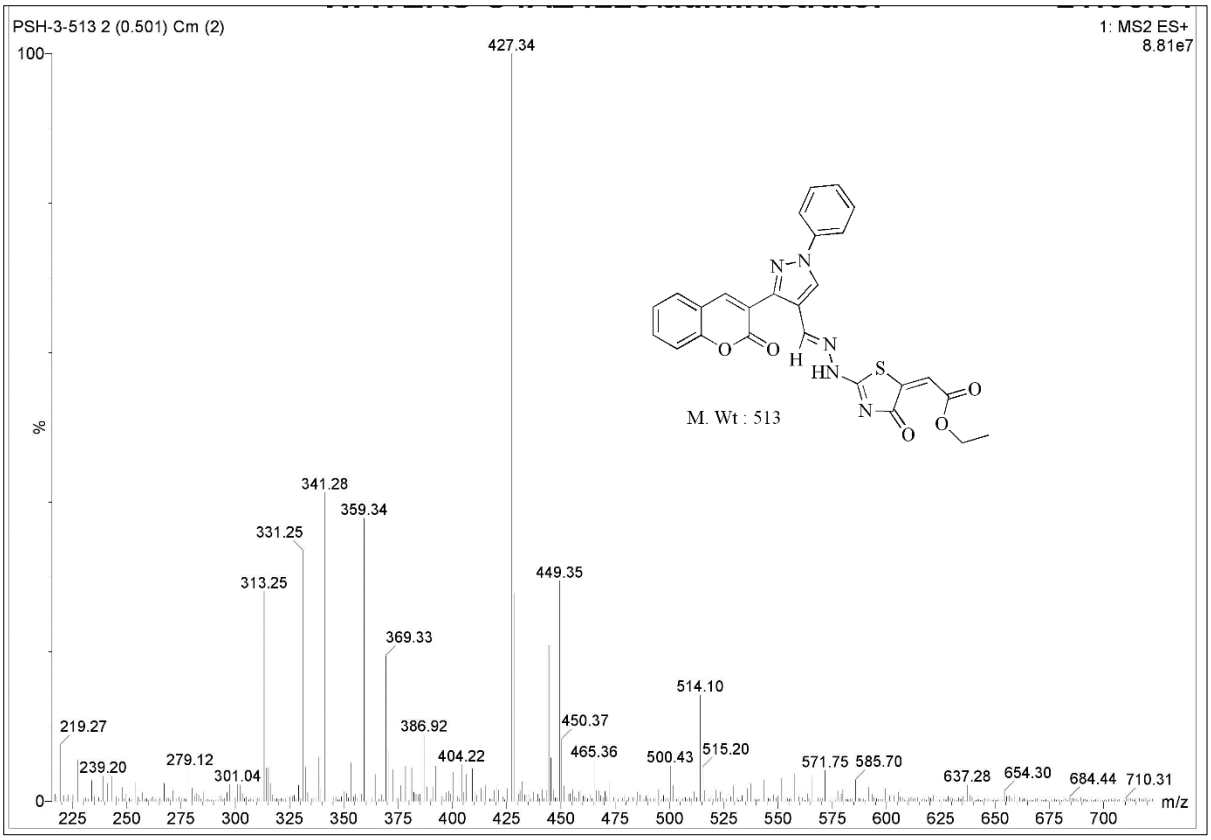
Color: yellow solid; mp: 250-252 °C; yield: (0.590g, 93%); IR (KBr, Wave number, cm^{-1}): 1639 (C=O of amide), 1719 (-C=O of ester), 3440 (NH); PMR (400 MHz, DMSO-d_6): δ 3.69 (s, 3H), 6.57 (s, 1H,), 7.44 (s, 1H), 7.60 (t, *J* = 8.0 Hz, 2H), 7.69-7.72 (m, 2H), 7.96-8.11 (m, 4H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.55 (s, 1H), 8.71 (d, *J* = 8.0 Hz, 1H), 9.07 (s, 1H), 9.16-9.22 (m, 1H),12.76 (s, 1H) ppm; ESI-MS: m/z 550 $[M+H]^+$; Anal. calcd. for $C_{29}H_{19}N_5O_5S$: C, 63.38; H, 3.48; N, 12.74; S, 5.83. Found: C, 63.34; H, 3.43; N, 12.70; S, 5.88%.



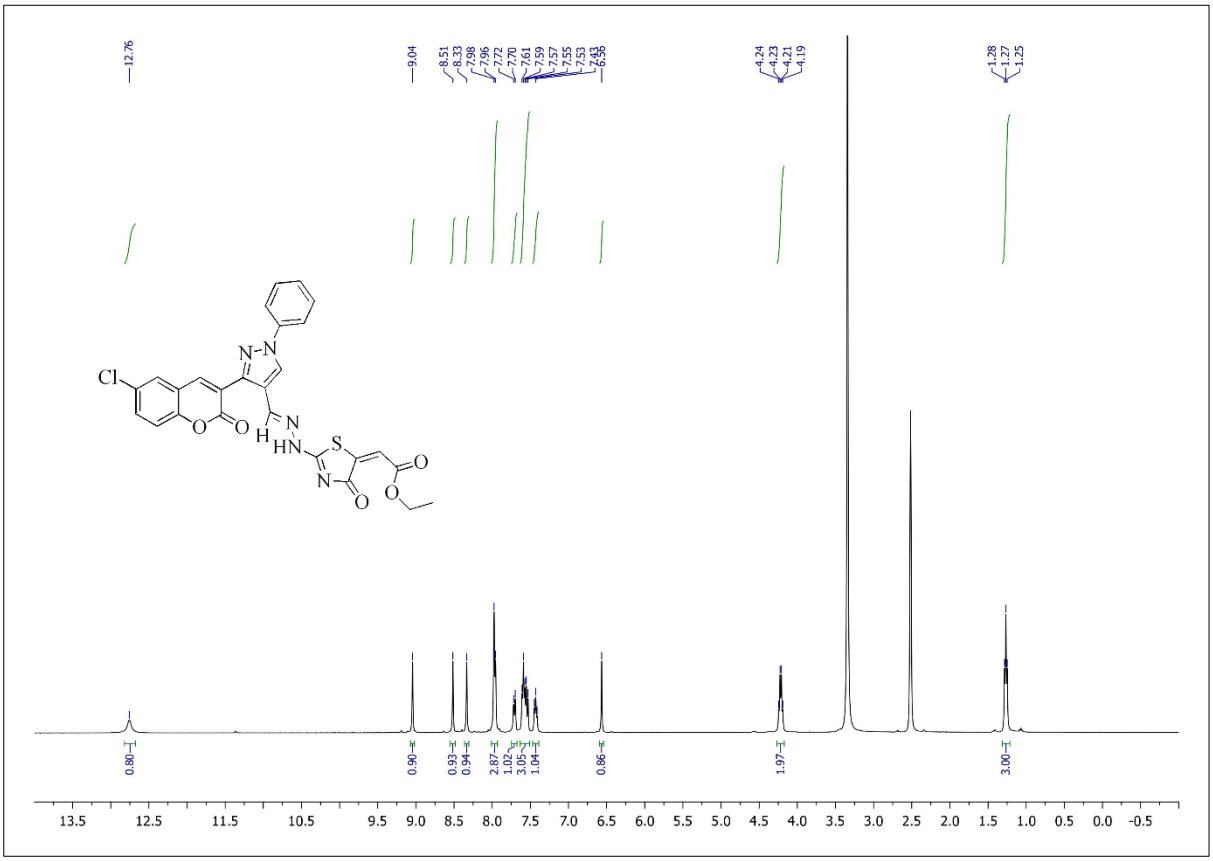
PMR Spectrum of compound **1a**



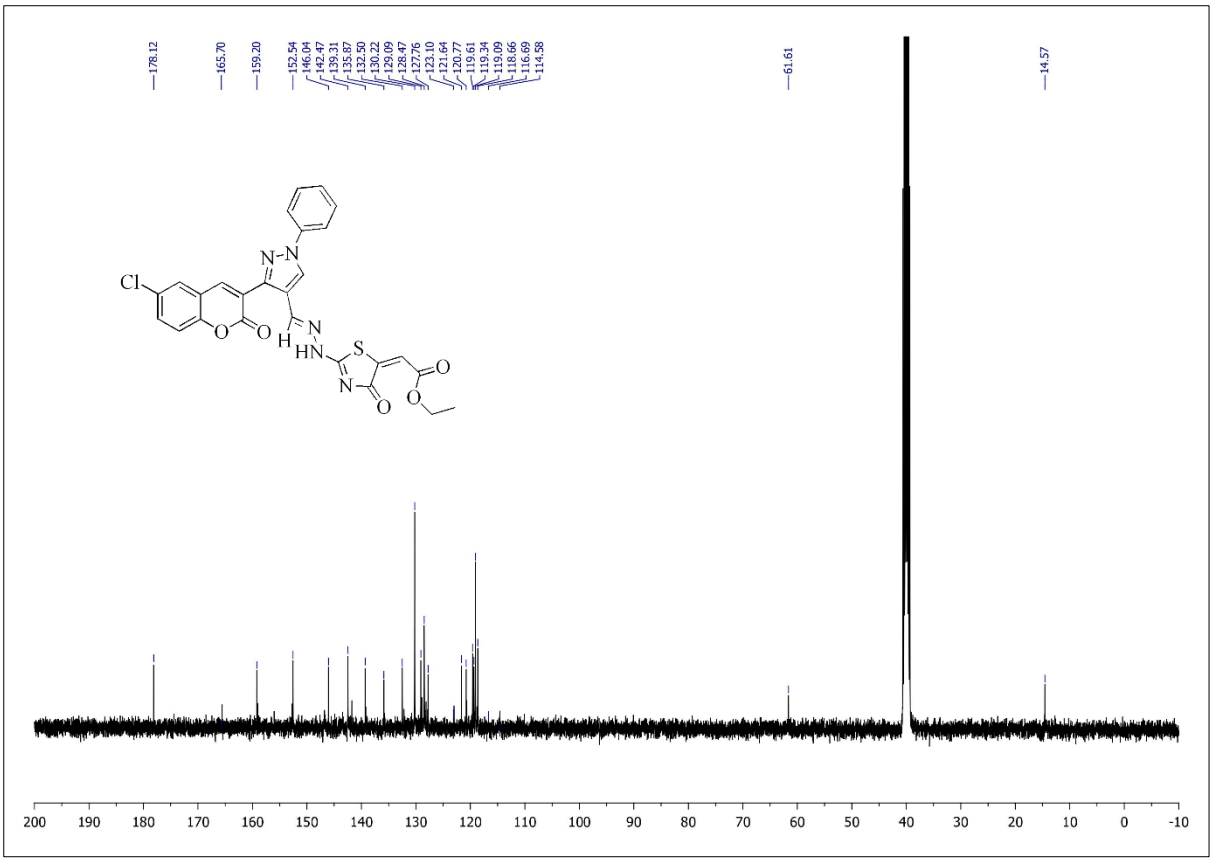
CMR Spectrum of compound **1a**



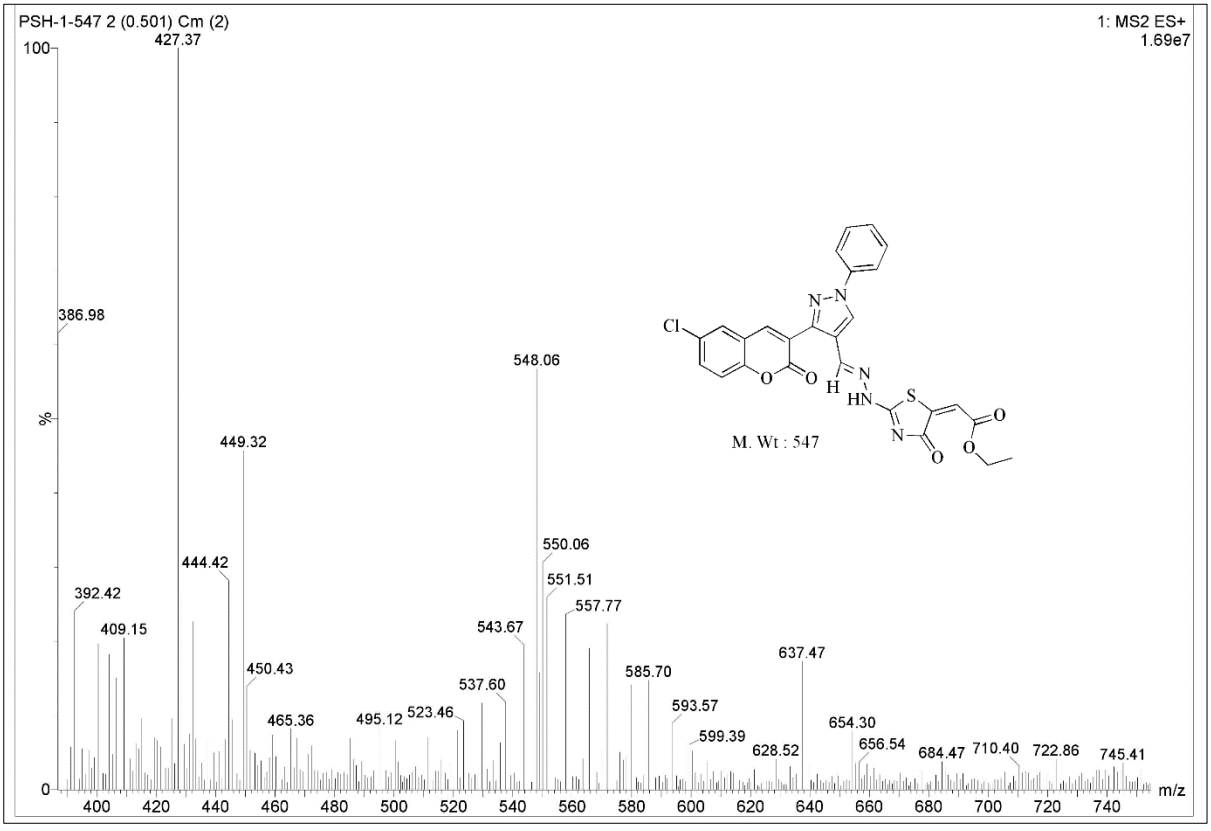
Mass Spectrum of compound **1a**



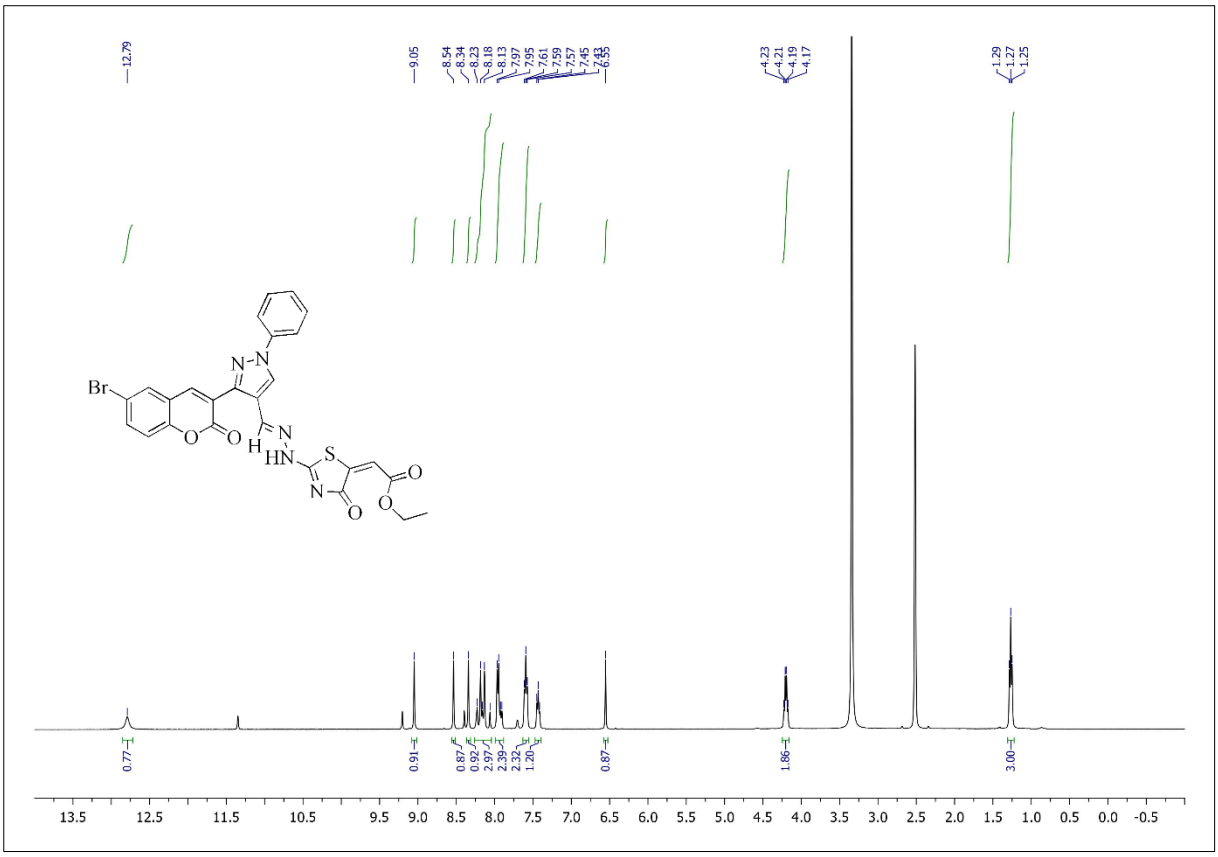
PMR Spectrum of compound **1b**



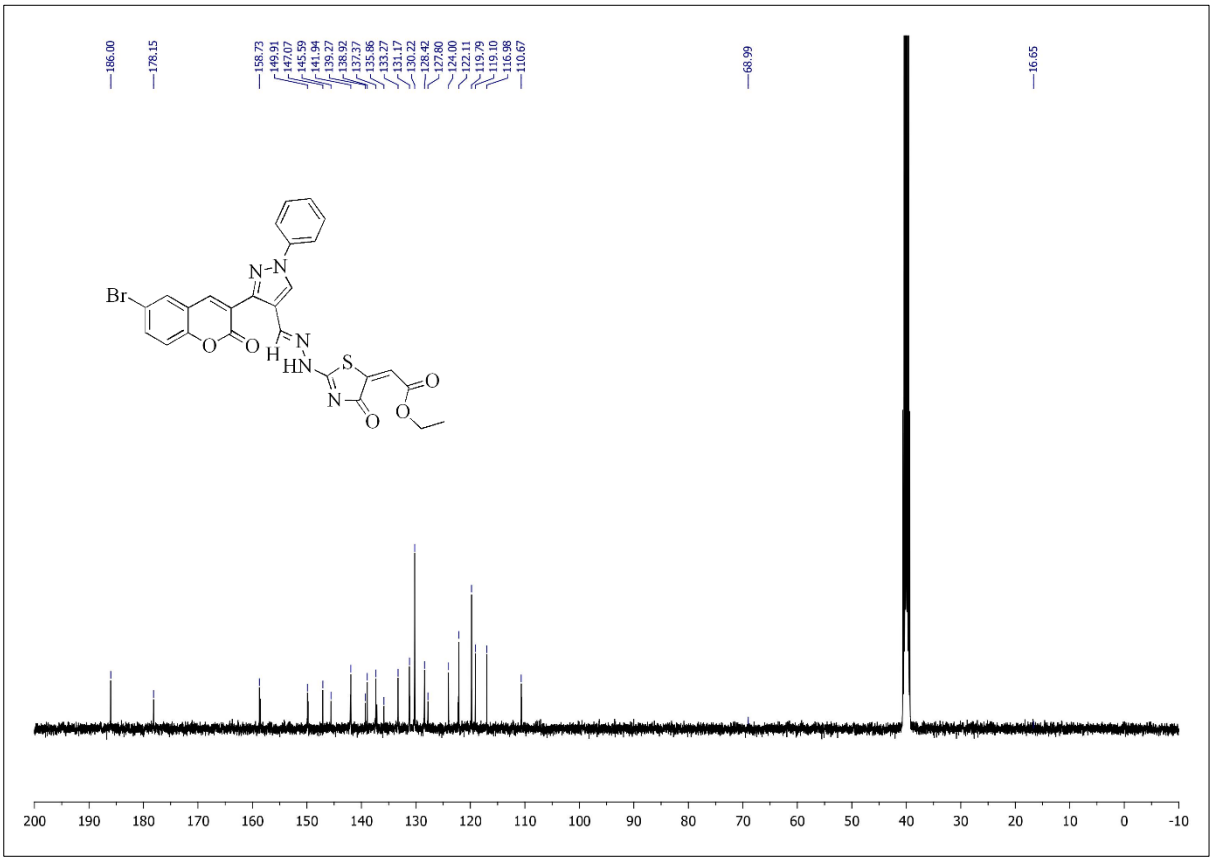
CMR Spectrum of compound **1b**



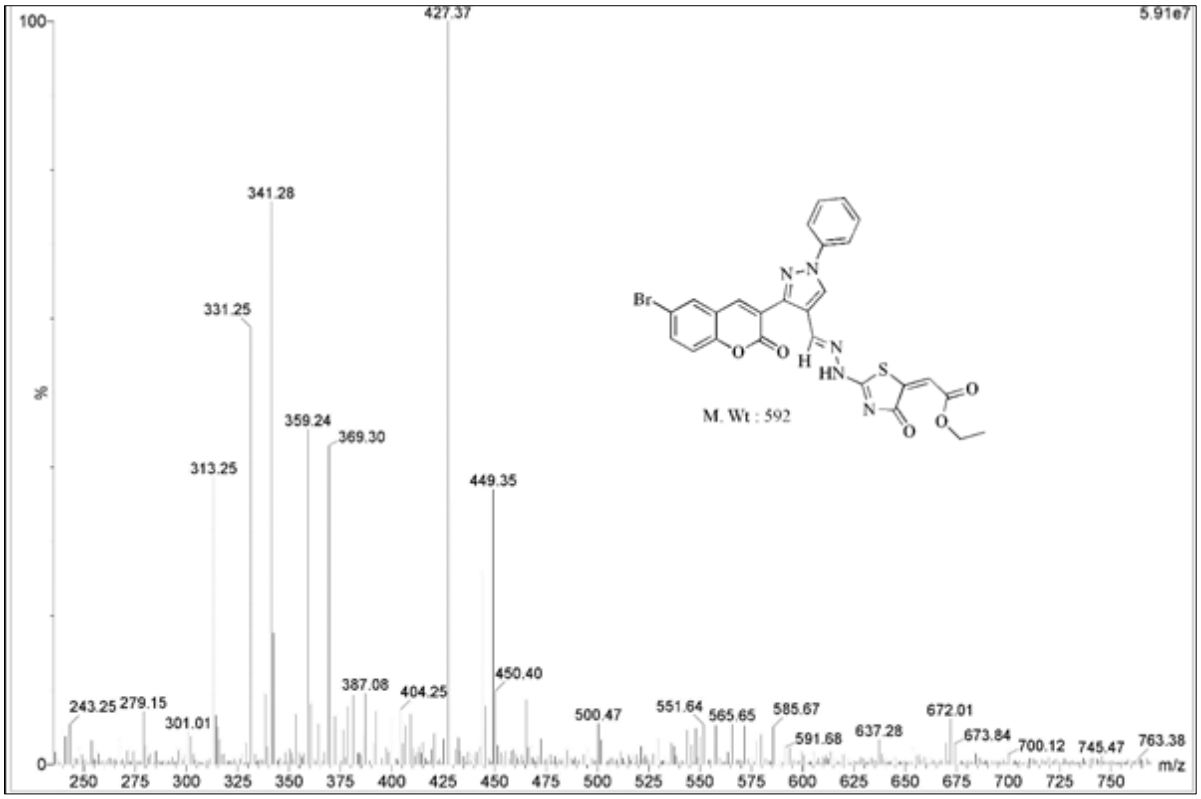
Mass Spectrum of compound **1b**



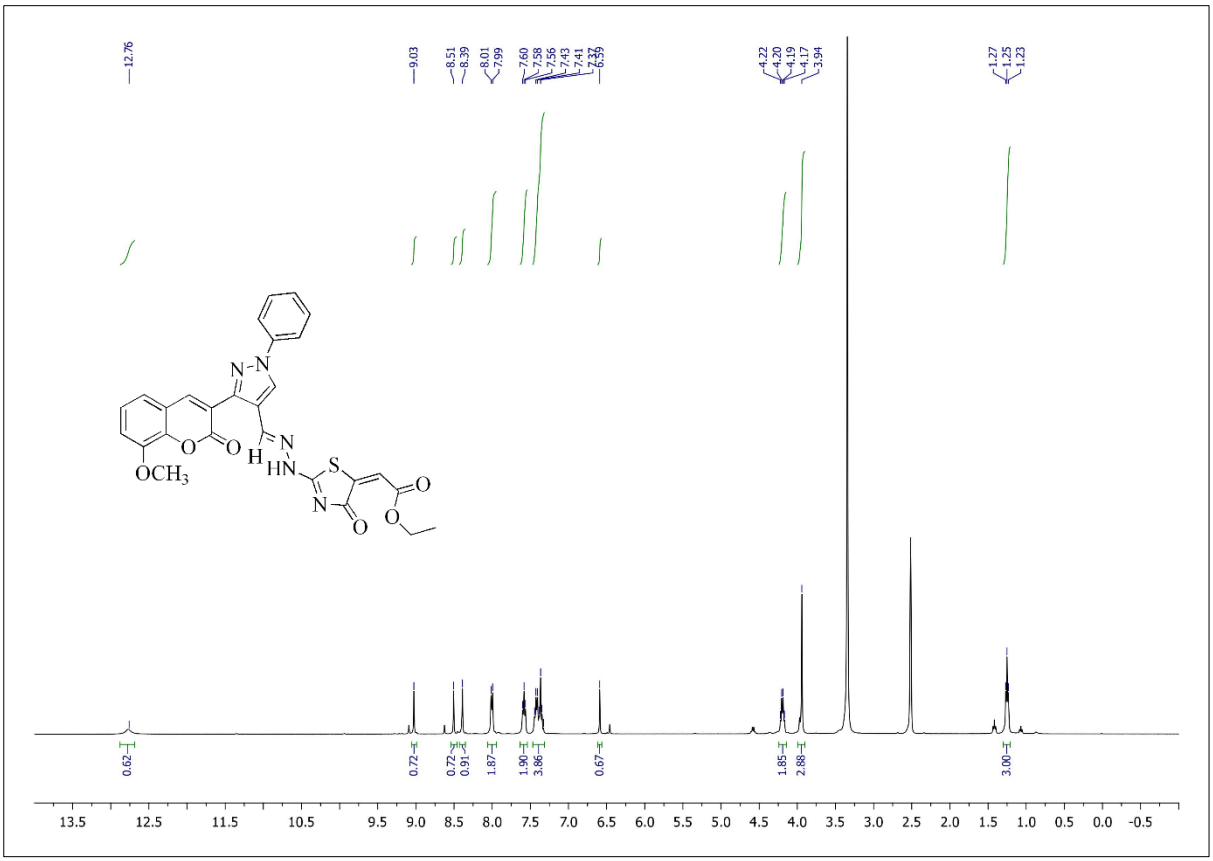
PMR Spectrum of compound **1c**



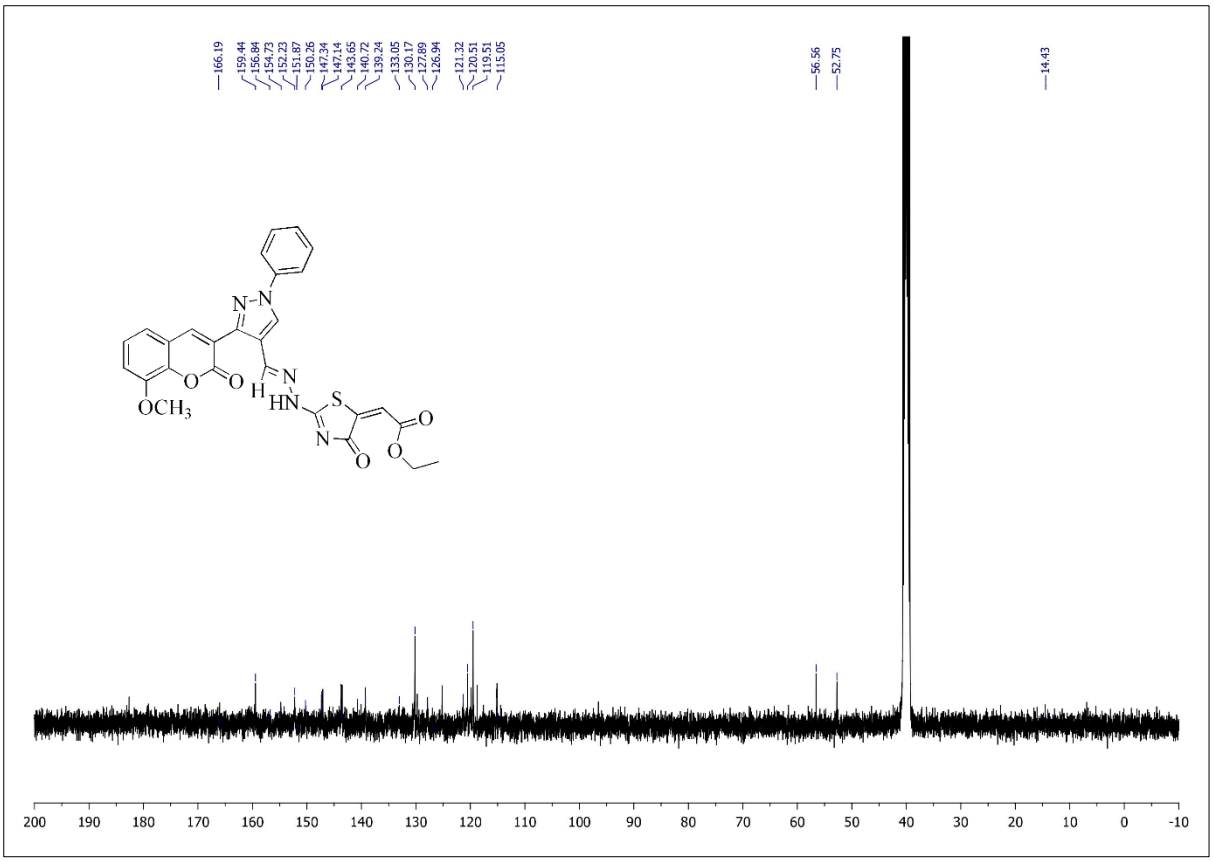
CMR Spectrum of compound **1c**



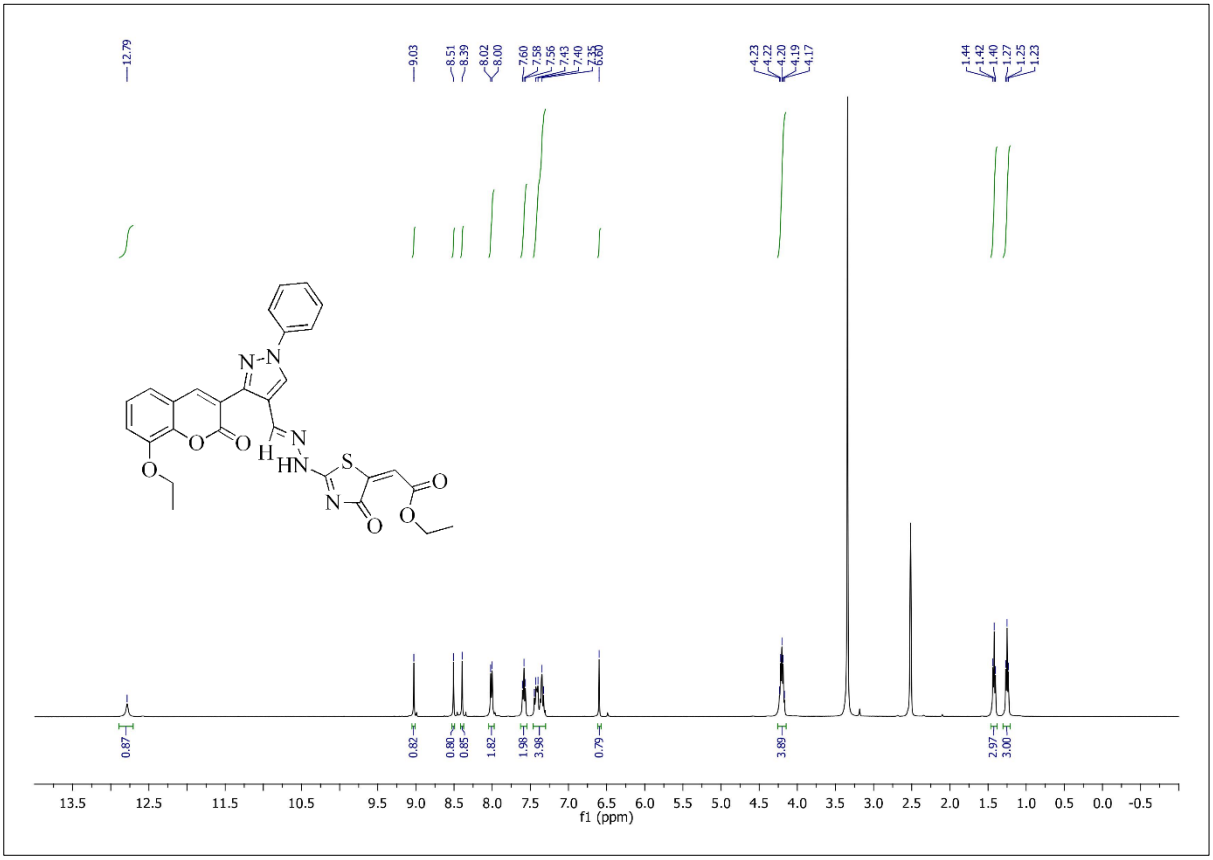
Mass Spectrum of compound **1c**



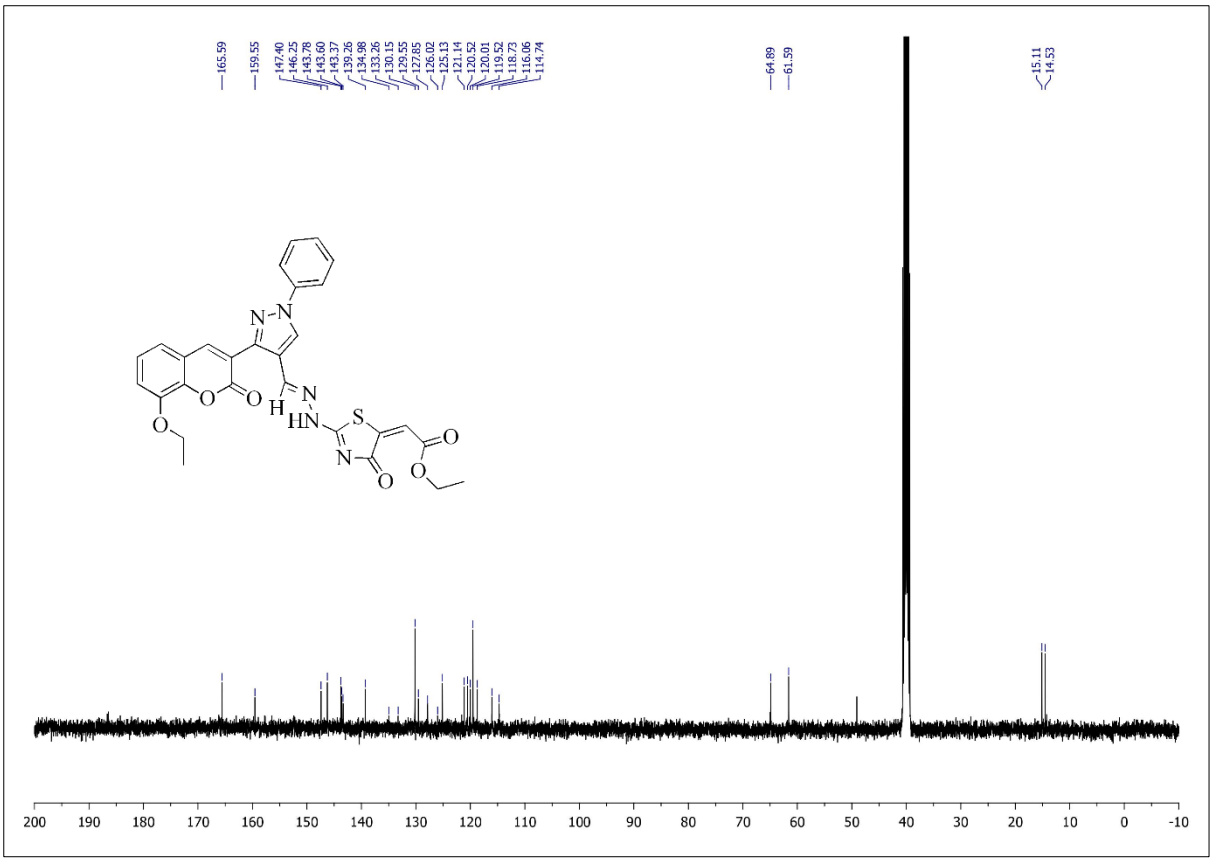
PMR Spectrum of compound **1d**



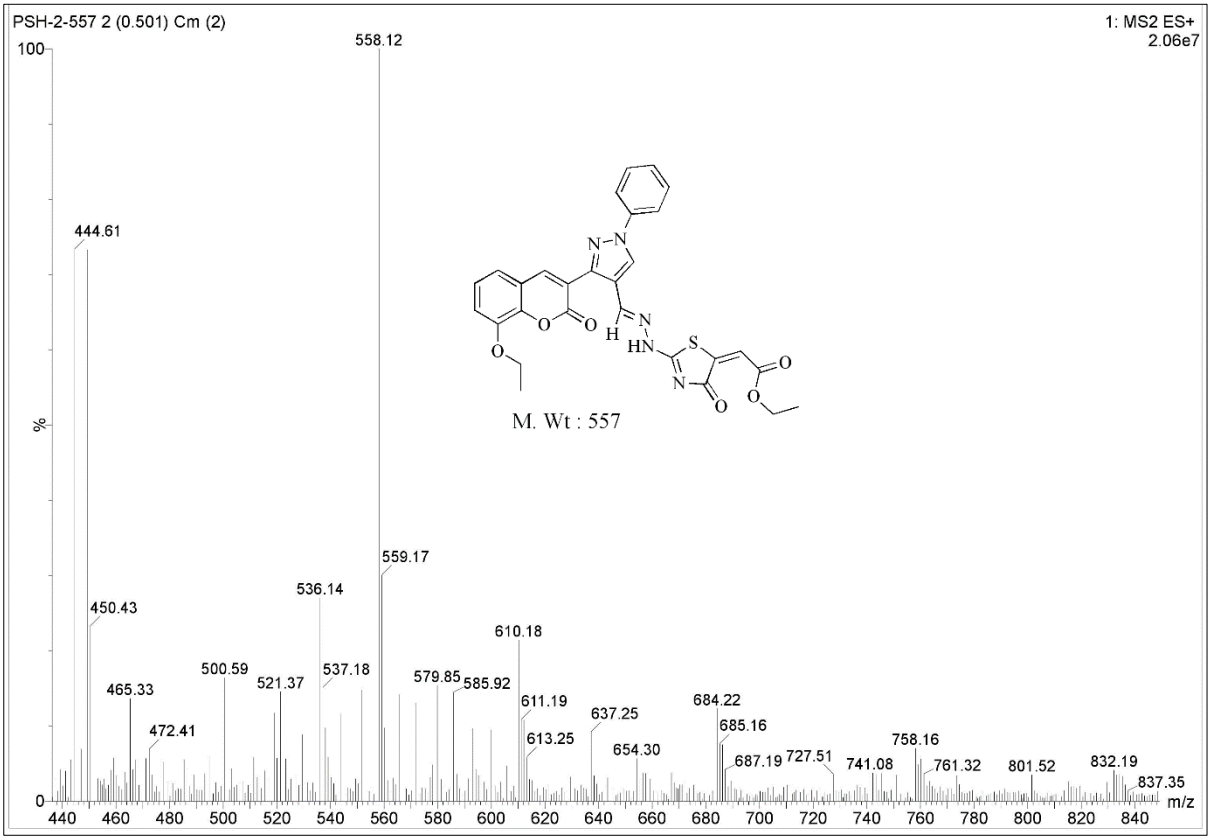
CMR Spectrum of compound **1d**



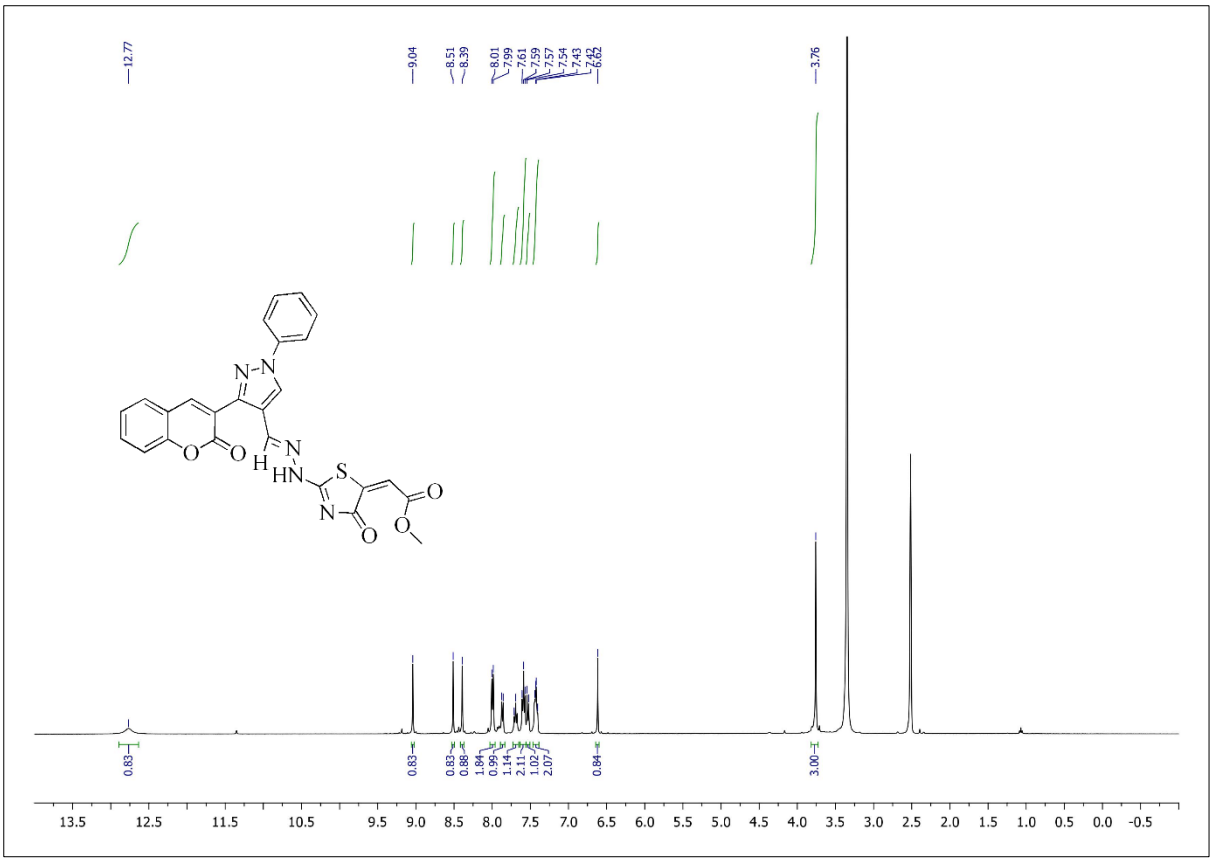
PMR Spectrum of compound **1e**



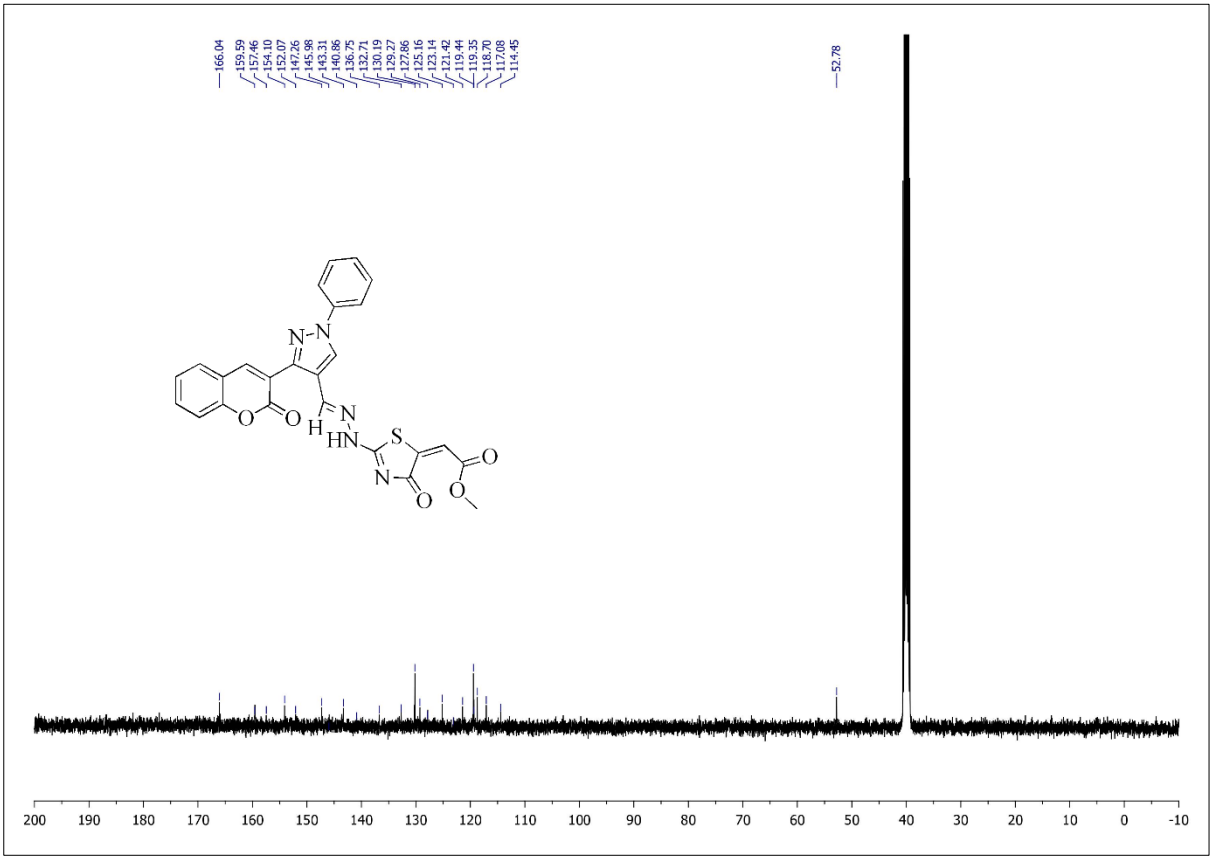
CMR Spectrum of compound **1e**



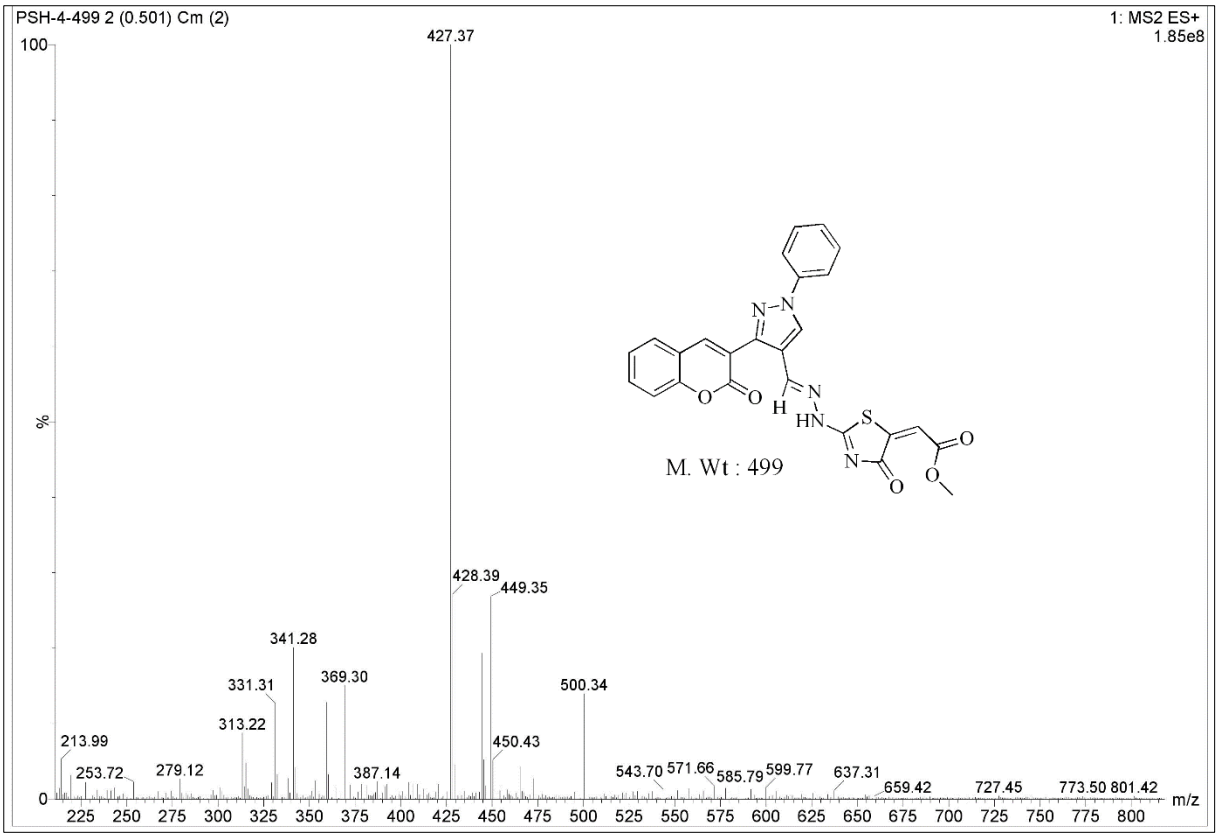
Mass Spectrum of compound **1e**



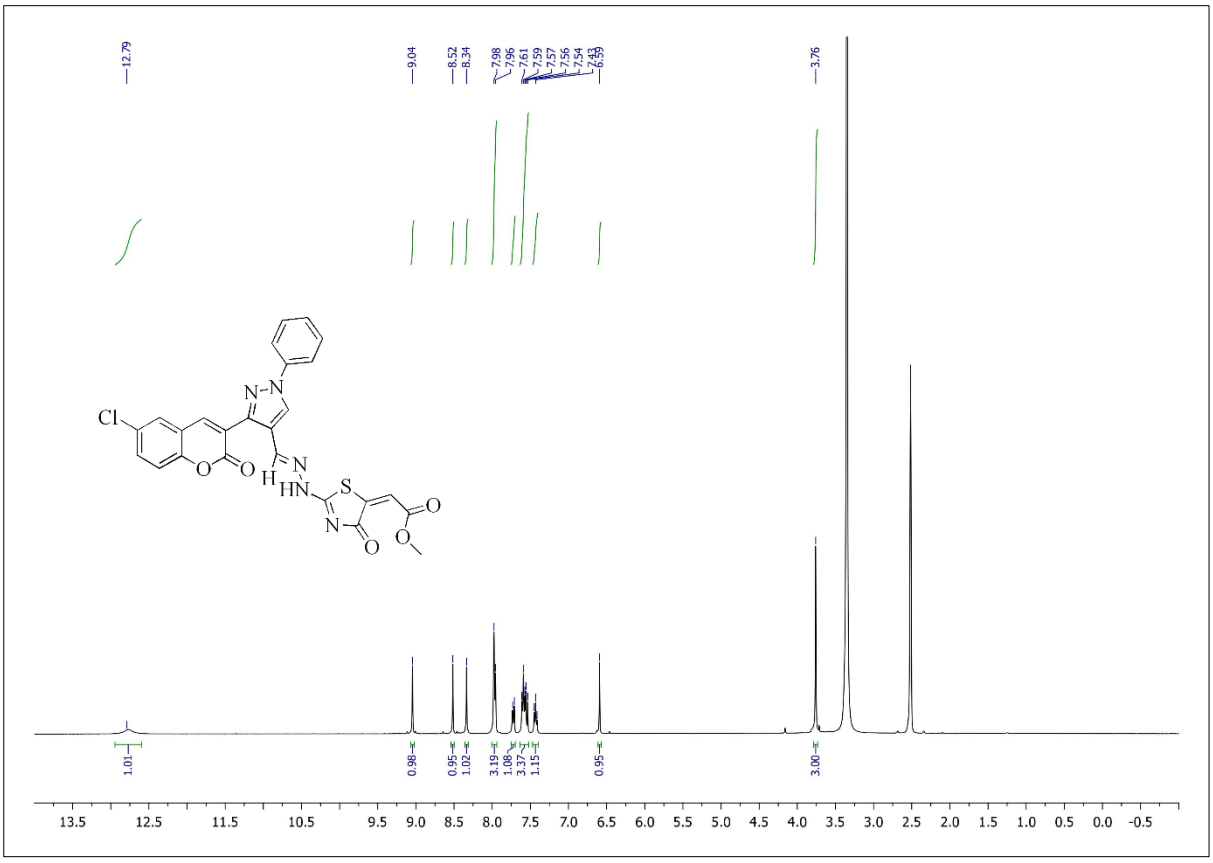
PMR Spectrum of compound **1f**



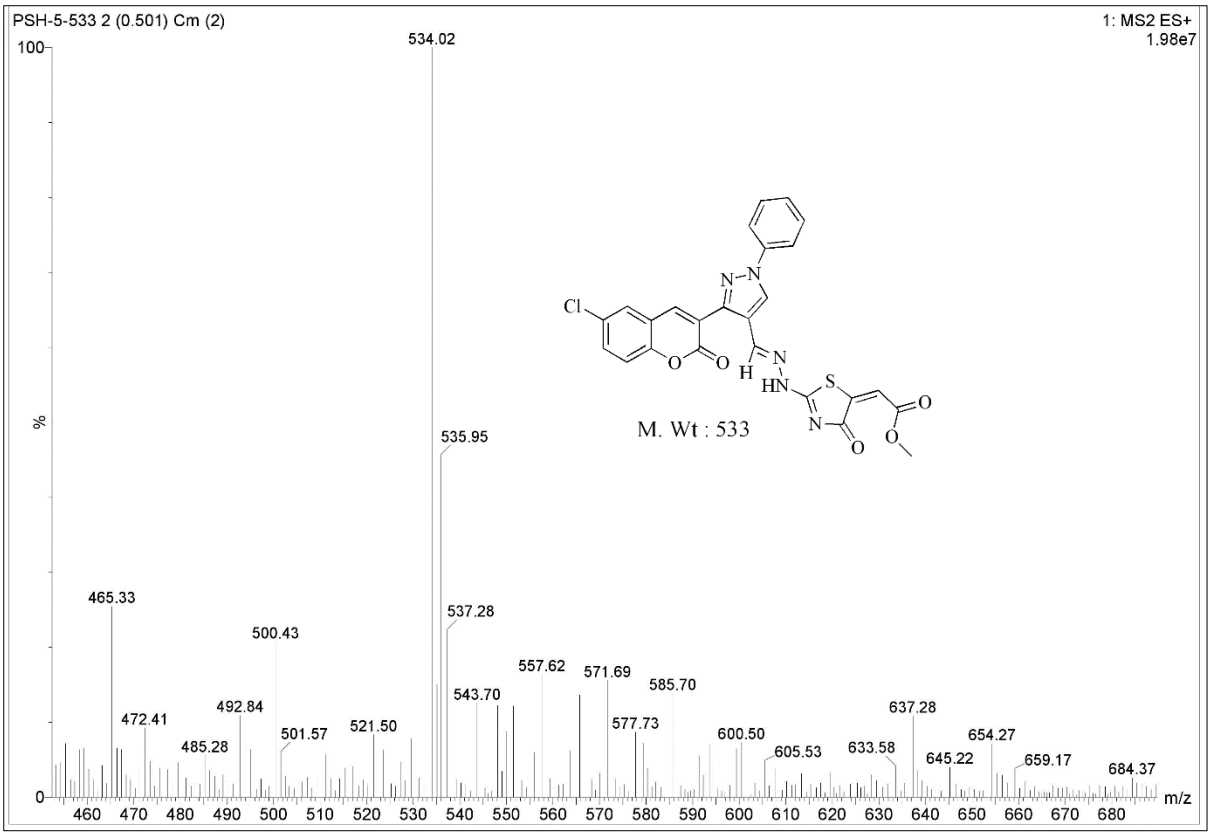
CMR Spectrum of compound **1f**



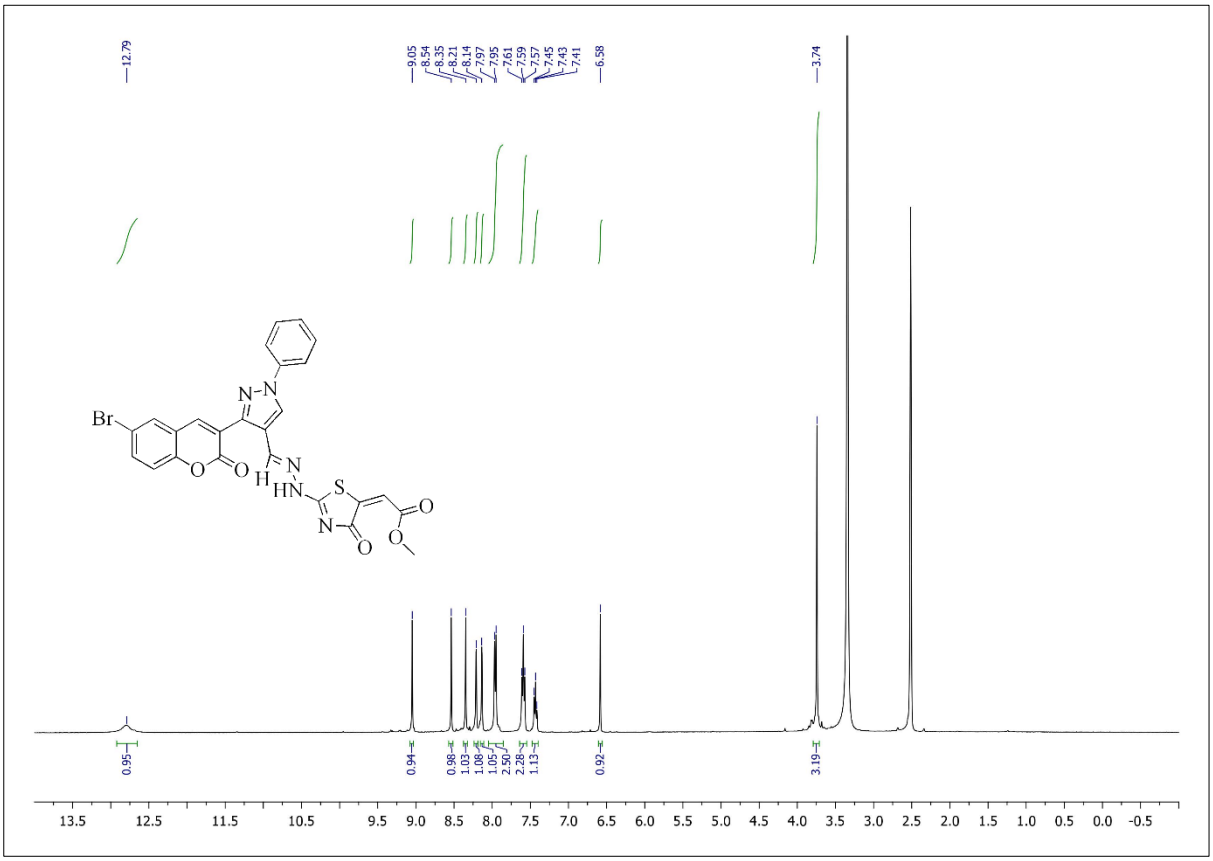
Mass Spectrum of compound **1f**



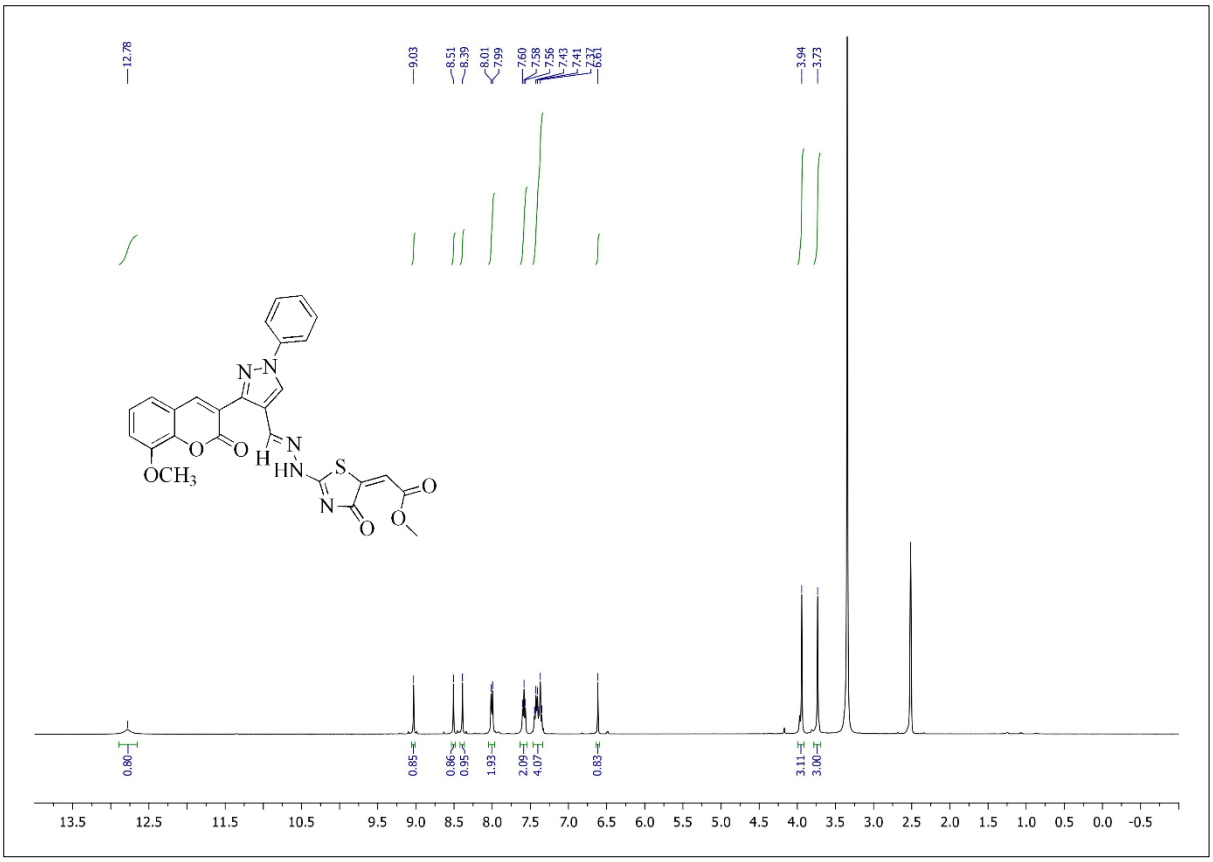
PMR Spectrum of compound **1g**



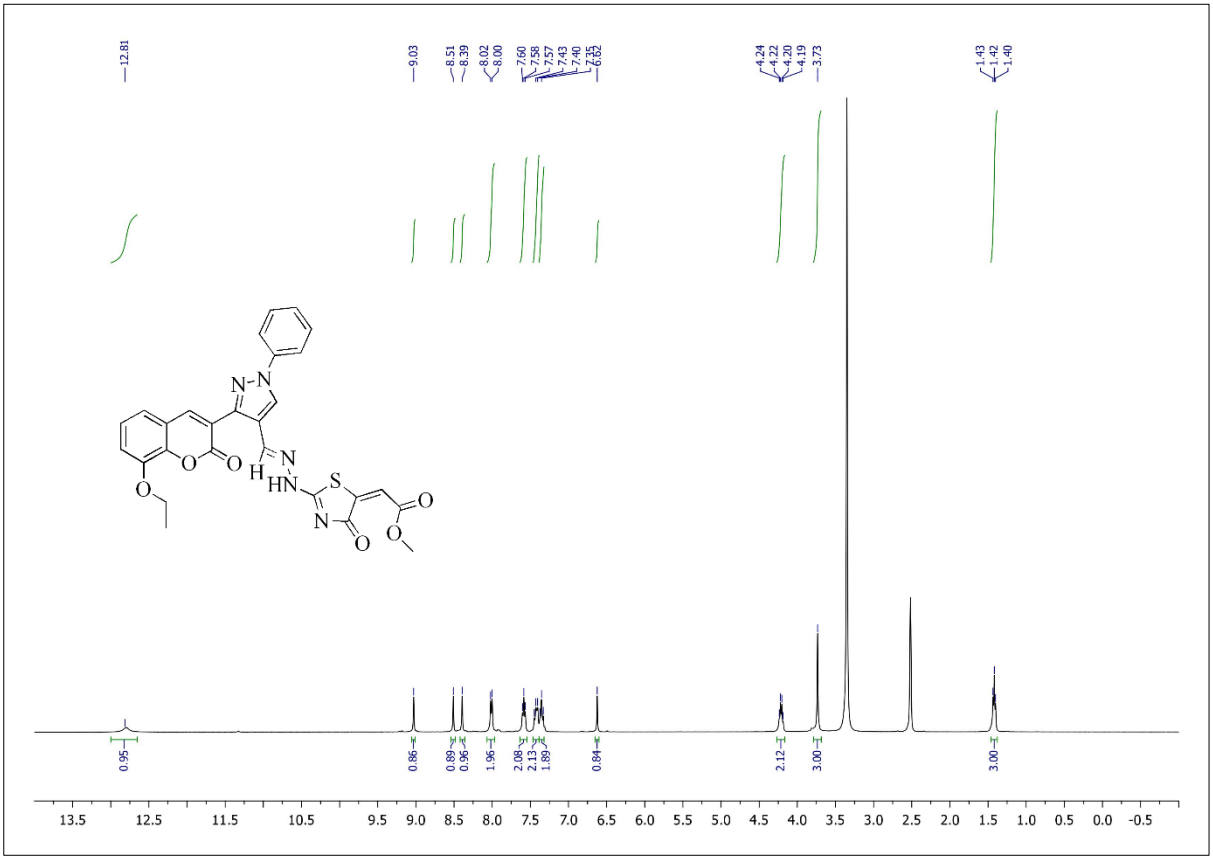
Mass spectrum of compound **1g**



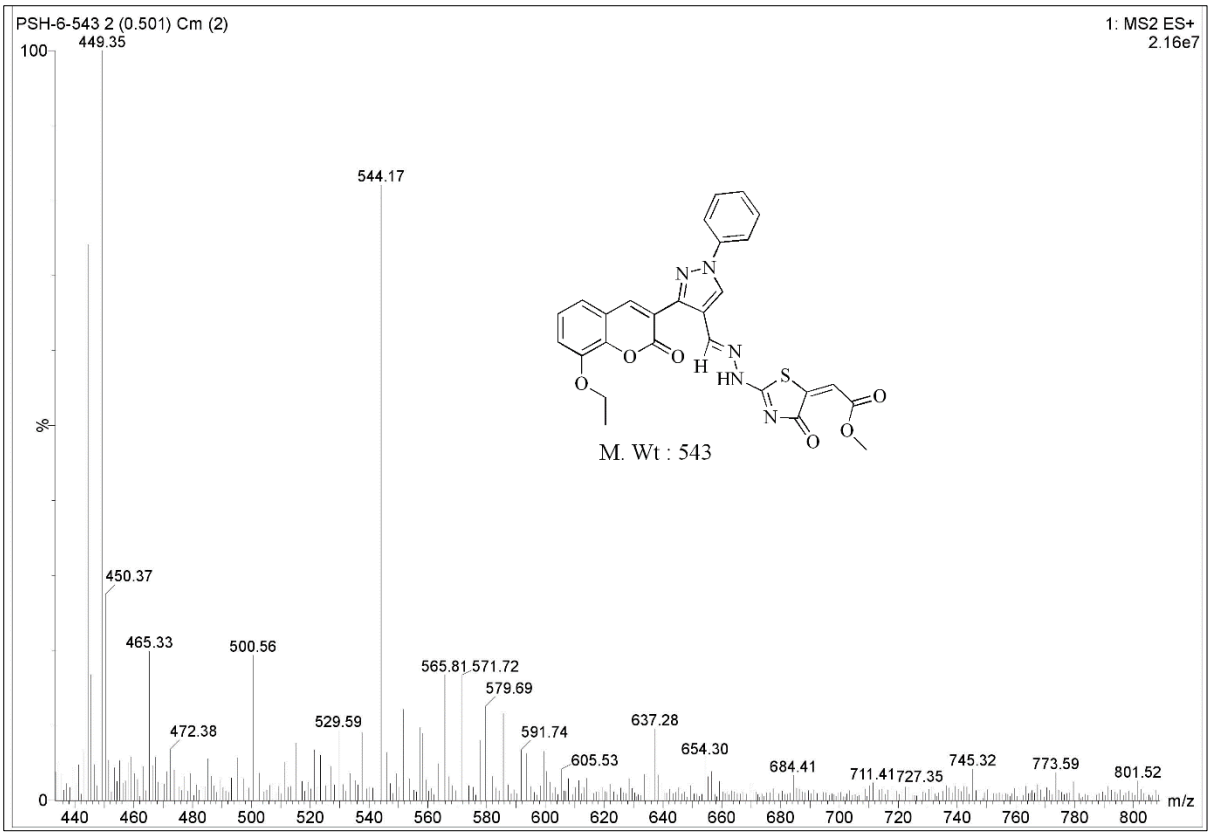
PMR Spectrum of compound **1h**



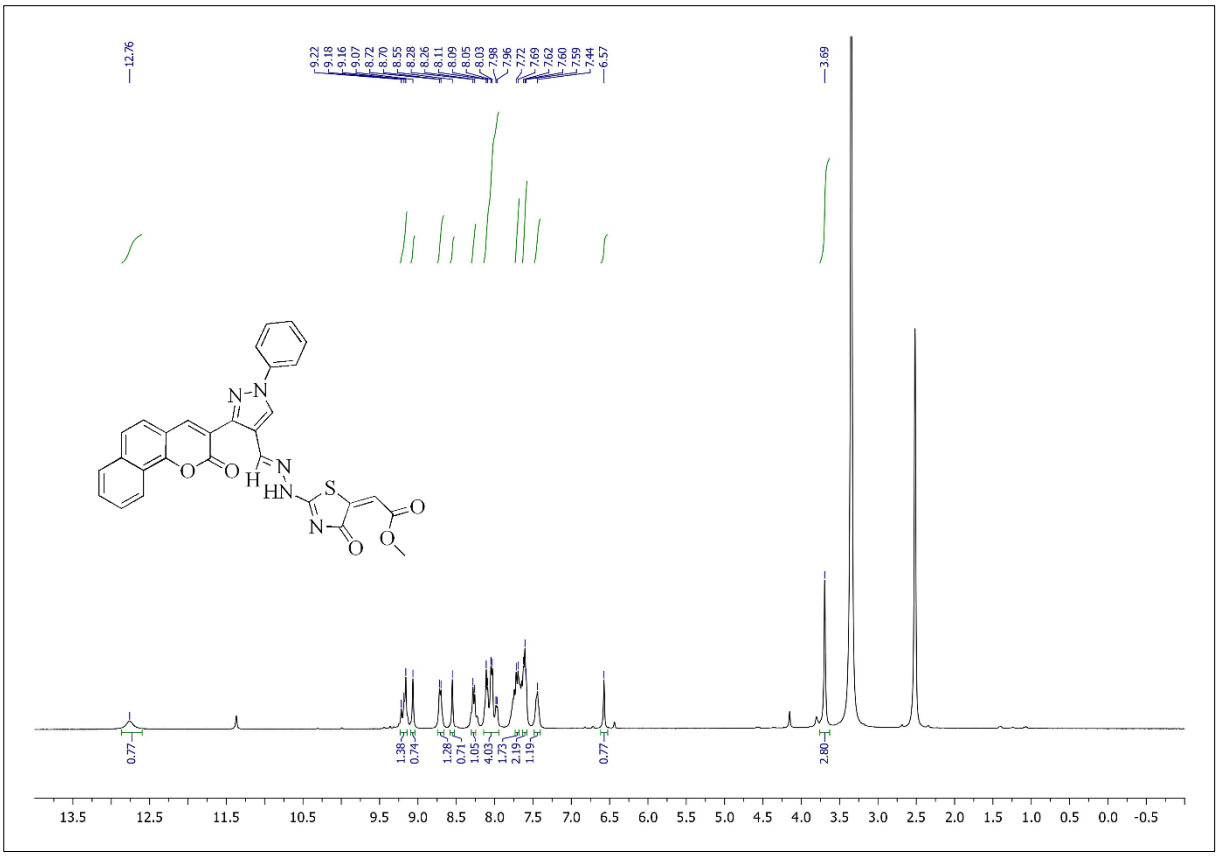
PMR Spectrum of compound **1i**



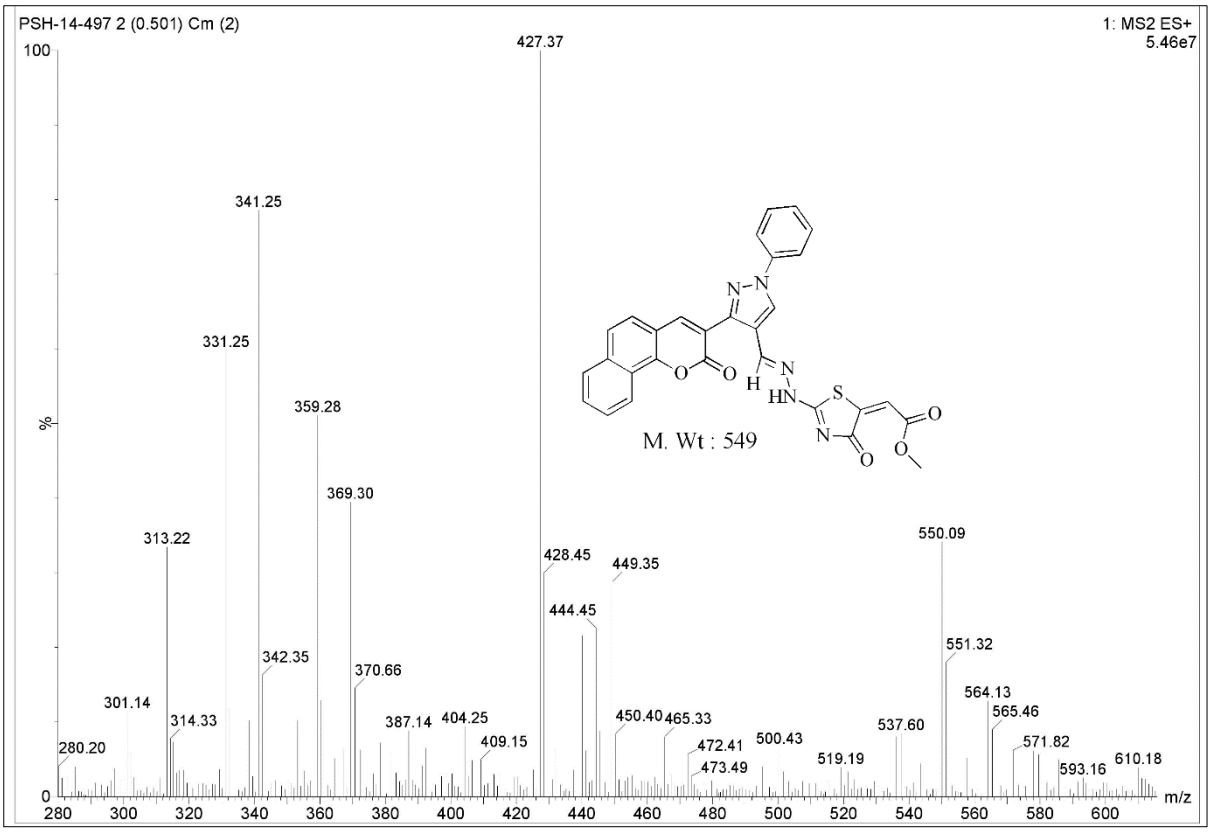
PMR Spectrum of compound **1j**



Mass Spectrum of compound **1j**



PMR Spectrum of compound **1k**



Mass Spectrum of compound **1k**

References:

[1] Hencken, C. P.; Jones-Brando, L.; Bordon, C.; Stohler, R.; Mott, B. T.; Yolken, R.; Posner, G. H.; Woodard, L. E. *J. Med. Chem.* **2010**, *53*, 3594-3601.

[2] Ye-Ji, K.; Hye-Jin, K.; Si-Yeon, H.; Young-Dae, G. *ACS Comb. Sci.* **2019**, *21*, 380-388.

[3] Zhu, J.; Han, L.; Diao, Y.; Ren, X.; Xu, M.; Xu, L.; Li, S.; Li, Q.; Dong, D.; Huang, J.; Liu, X.; Zhao, Z.; Wang, R.; Zhu, L.; Xu, Y.; Qian, X.; Li, H. *J. Med. Chem.* **2015**, *58*, 1123-1139.

[4] Moraski, G. C.; Seeger, N.; Miller, P. A.; Oliver, A. G.; Boshoff, H. I.; Cho, S.; Mulugeta, S.; Anderson, J. R.; Franzblau, S. G.; Miller, M. J. *ACS Infect. Dis.* **2016**, *2*, 393-398.

[5] Radwan, A. S.; Khalid, M. A. A. *J. Heterocyclic Chem.* **2019**, *56*, 1063-1074.

[6] Sokolova, A. S.; Yarovaya, o. I.; Bormotov, N. I.; Shishkina, L. N.; Salakhutdinov, N. F. *Med. Chem. Commun.* **2018**, *9*, 1746-1753.

[7] Bueno, J. M.; Carda, M.; Crespo, B.; Cunat, A. C.; de Cozar, C.; Leon, M. L.; Marco, J. A.; Roda, N.; Sanz-Cervera, J. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3938-3944.

[8] Khalil, A. M.; Berghot, M. A.; Gouda,M. A. *Eur. J. Med. Chem.* **2009**, *44*, 4434-4440.

[9] Spano, V.; Attanzio, A.; Cascioferro, S.; Carbone, A.; Montalbano, A.; Barraja, P.; Tesoriere, L.; Cirrincione, G.; Diana, P.; Parrino, B. *Mar. Drugs.* **2016**, *14*, 226.

[10] Deb, P. K.; Kaur, R.; Chandrasekaran. B.; Bala, M.; Gill, D.; Kaki, V. R.; Akkinepalli, R. R.; Mailavaram, R. *Med Chem Res.* **2014**, *23*, 2780-2792.

[11] Sravanthi, T. V.; Lulu, S. S.; Vino, S.; Jayasri, M. A.; Mohanapriya, A.; Manju, S. L. *Med Chem Res.* **2017**, *26*, 1306-1315.

[12] Vijaya Bhaskara Reddy, M.; Srinivasulu, D.; Peddanna, K.; Apparao, Ch.; Ramesh, P. *Synth. Commun.* **2015**, *45*, 2592-2600.

[13] Nirwan, S.; Chahal, V.; Kakkar, R. *J. Heterocyclic Chem.* **2019**, *56*, 1239-1253.

[14] Omar, K.; Geronikaki, A.; Zoumpoulakis, P.; Camoutsis, C.; Sokovic, M.; Ciric, A.; Glamoclija, J. *Bioorg. Med. Chem. Lett.* **2010**, *18*, 426-432.

[15] Dwivedi, J.; Devi, K.; Asmat, Y.; Jain, S.; Sharma, S.; *J Saudi Chem Soc.* **2016**, *20*, S16-S20.

[16] Szychowski, K. A.; Leja, M. L.;Kaminskyy, D. V.; Kryshchyshyn, A. P.; Binduga, U. E.; Pinyazhko, O. R.; Lesyk, R. B.; Tobiasz, J.; Gminski, J. *Eur. J. Med. Chem.* **2017**, *141*, 162-168.

[17] Suryawanshi, R.; Jadhav, S.; Makwana, N.; Desai, D.; Chaturbhuj, D.; Sonawani, A.; Idicula-Thomas, S.; Murugesan, V.; Katti, S. B.; Tripathy, S.; Paranjape, R.; Kulkarni, S. *Bioorg Chem.* **2017**, *71*, 211-218.

[18] Djukic, M.; Fesatidou, M.; Xenikakis, I.; Geronikaki, A.; Angelova, V. T.; Savic, V.; Pasic, M.; Krilovic, B.; Djukic, D.; Gobeljic, B.; Pavlica, M.; Djuric, A.; Stanojevic, I.; Vojvodic, D.; Saso, L. *Chem Biol Interact.* **2018**, *286*, 119-131.

[19] Hu, J.; Wang, Y.; Wei, X.; Wu, X.; Chen, G.; Cao, G.; Shen, X.; Zhang, X.; Tang, Q.; Liang, G.; Li, X. *Eur. J. Med. Chem.* **2013**, *64*, 292-301.

[20] Cihan-Ustundag, G.; Gursoy, E.; Naesens, L.; Ulusoy-Guzeldemirci, N.; Capan, G. *Bioorg. Med. Chem.* **2016**, *24*, 240-246.

[21] Ezer, M.; Yildirim, L. T.; Bayro, O.; Verspohl, E. J.; Dundar, O. B. *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 419-427.

[22] Patel, N. B.; Shaikh, F. M. *Saudi Pharm J.* **2010**, *18*, 129-136.

[23] Barreca, M. L.; Balzarini, J.; Chimirri, A.; Clercq, E. D.; Luca, L. D.; Holtje, H. D.; Holtje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappala, M. *J. Med. Chem.* **2002,** *45*, 5410-5413.

[24] Moreira, D. R. M.; Santos, D. S.; Santo, R. F. E.; Santos, F. E.; Filho, G. B. O.; Leite, A. C. L.; Soares, M. B. P.; Villarreal, C. F. *Chem Biol Drug Des.* **2017**, *90*, 297-307.

[25] Filho, G. B. O.; Cardoso, M. V. O.; Espindola, J. W. P.; Ferreira, L. F. G. R.; Simone, C. A.; Ferreira, R. S.; Coelho, P. L.; Meira, C. S.; Moreira, D. R. M.; Soares, M. B. P.; Leite, A. C. L. *Bioorg. Med. Chem.* **2015**, *23*, 7478-7486.

[26] Kundariya, D. S.; Patel, P. K.; Bheshdadia, B. M. *Der Chemica Sinica.* **2014**, *5*, 138-143.

[27] Batran, R. Z.; Kassem, A. F.; Abbas, E. M. H.; Elseginy, S. A.; Mounier, M. M. *Bioorg. Med. Chem.* **2018**, *26*, 3474-3490.

[28] Patel, D.; Kumari, P.; Patel, N. *Arch. Appl. Sci. Res.* **2010**, *2*, 68-75.

[29] Hassan, A. A.; Mohamed, S. K.; Mohamed, N. K.; El-Shaieb, K. M. A.; Abdel-Aziz, A. T.; Mague, J. T.; Akkurt, M. *J. Heterocyclic Chem.* **2017**, *54*, 2043-2053.

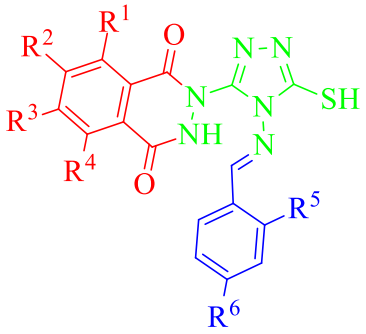
[30] Verma, G. K.; Shukla, G.; Nagaraju, A.; Srivastava, A.; Raghuvanshi, K.; Singh, M. S. *RSC Adv.* **2014**, *4*, 11640-11647.

[31] Thakare, M. P.; Shaikh, R.; Tayade, D. *RSC Adv.* **2016**, *6*, 28619-28623.

[32] Srikrishna, D.; Dubey, P. K. *Der Pharma Chemica*. **2014**, *6*, 57-60.

CHAPTER-VI

ONE-POT MULTICOMPONENT SYNTHESIS OF (*E*)-2-(BENZYLIDENEAMINO)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-3-YL)-2,3-DIHYDROPHTHALAZINE-1,4-DIONES



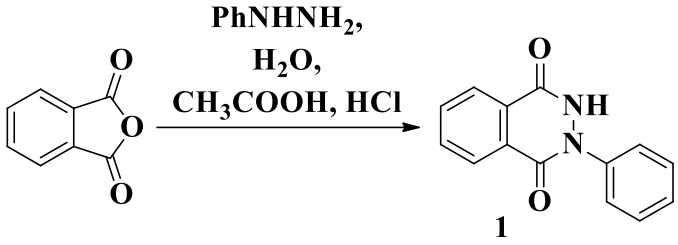
INTRODUCTION

Phthalazines are nitrogen containing heterocyclic compounds. These scaffolds had significant importance in drug discovery, medicinal, synthetic and material chemistry.[1,2] Phthalazines bearing triazole show enhanced therapeutic activity[3] and possess anti-inflammatory,[4] anticancer,[5] antibacterial,[6] anticonvulsant,[7] antitumor,[8] antimicrobial,[9] antitrypanosomal,[10] vasorelaxant[11] and anti-Alzheimer activities.[12]

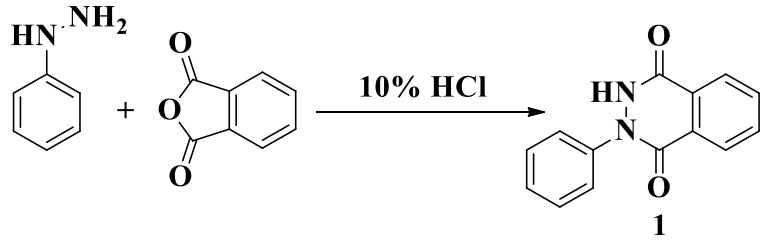
The following is short review of related literature.

General methods of synthesis of phthalic anhydrides.

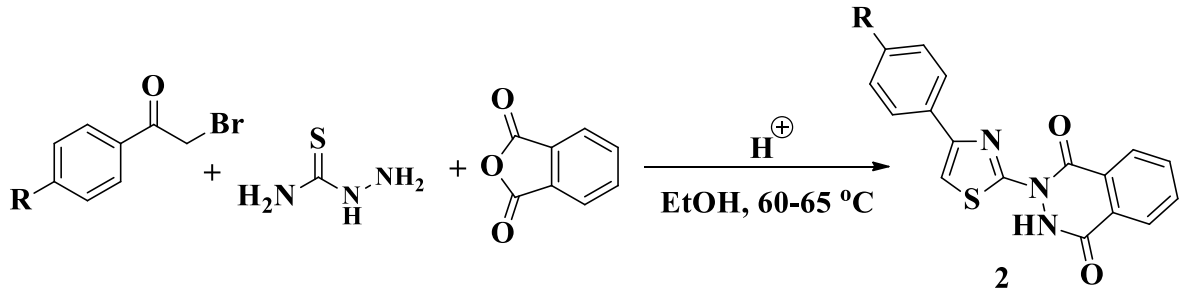
`Bayoumi *et al.*[13] synthesized 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**1**) by using phthalic anhydride with phenyl hydrazine in presence of aqueous ethanolic acid and HCl.



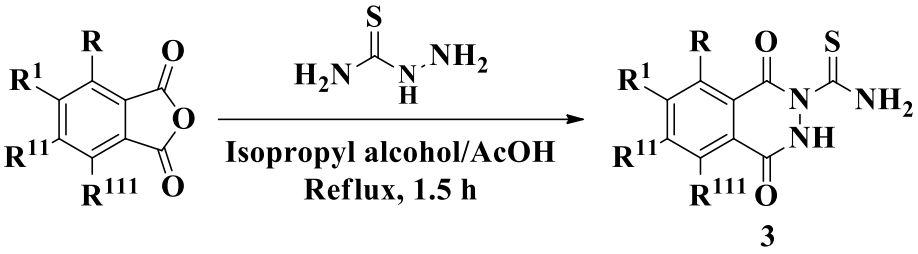
Poli *et al.*[14] synthesized 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**1**) starting from phenyl hydrazine and phthalic anhydride.



2-[4-(4-Methylphenyl)thiazol-2-yl]-2,3-dihydrophthalazine-1,4-diones (**2**) were synthesized by Chunduru *et al.*[15] 2-Bromo-1-phenyl ethanone was condensed with thiosemicarbazide and phthalic anhydride in a mixture of ethanol and small amount of ethanoic acid to give **2**.

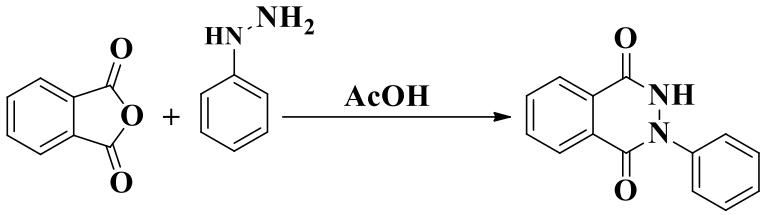


1,4-Dioxo-3,4-dihydrophthalazine-2(1*H*)-carbothioamides (**3**) were synthesized by Cardia *et al.*[16] by reacting phthalic anhydride with thiosemicarbazide in acetic acid and isopropyl alcohol under reflux.



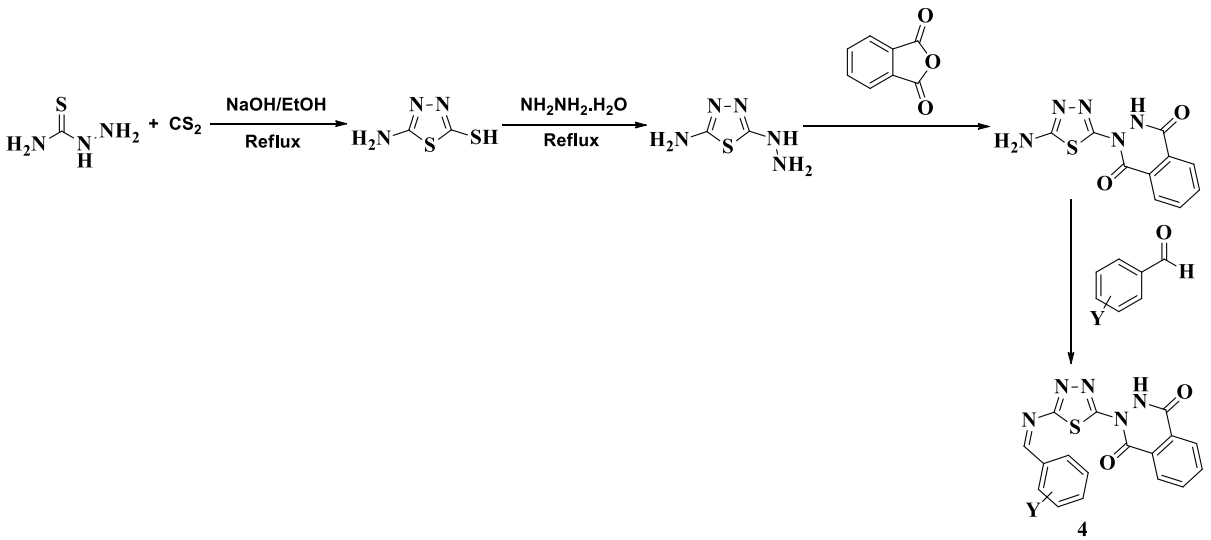
3

Prime *et al.*[17] found phthalic anhydride and phenyl hydrazine are useful for the synthesis of 2-phenyl-2,3-dihydrophthalazine-1,4-diones (**1**).



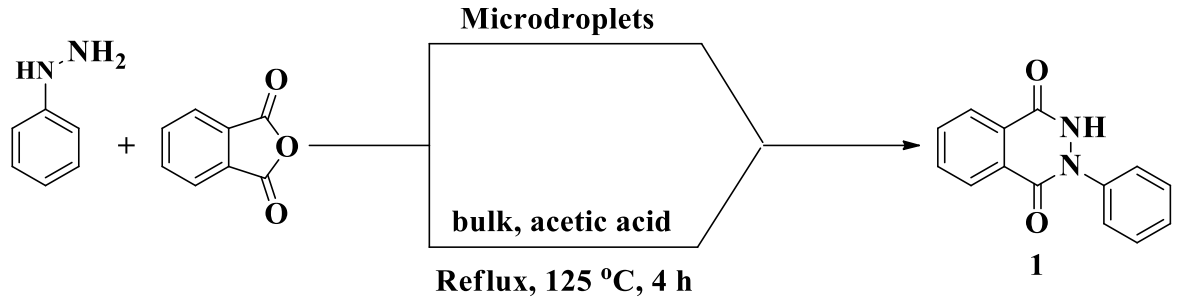
1

Hamad *et al.*[18] prepared (*Z*)-2-(5-(benzylideneamino)-1,3,4-thiadiazol-2yl)-2,3-dihydrophthalazine-1,4-diones (**4**). Reaction of thiosemicarbazide with carbon disulfide in sodium hydroxide, ethanol under reflux gave 2-amino-5-mercapto-1,3,4-thiadiazole, which on treatment with hydrazine hydrate to afford 2-amino-5-hydrazine-1,3,4-thiadiazole. This on further reaction with phthalic anhydride gave 2-amino-5-(1,2-dihydro phthalazines-3,6-dione-1-yl)-1,3,4-thiadiazole. Finally the 2-amino-5-dihydro phthalizines-3,6-dione-1-yl)-1,3,4-thiadiazole on treatment with aromatic aldehydes gave the title compound.



4

Gao *et al.*[19] studied the reaction between phenyl hydrazine and phthalic anhydride in micro droplets and in ethanoic acid to give 2-phenyl-2,3-dihydrophthalazine-1,4-dione (**1**).



PRESENT WORK

In the present work we are reporting a series of (*E*)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-diones (**8a-l**) as shown in the scheme-1. The following figure indicates biologically active molecules having triazole and phthalazines ring systems.

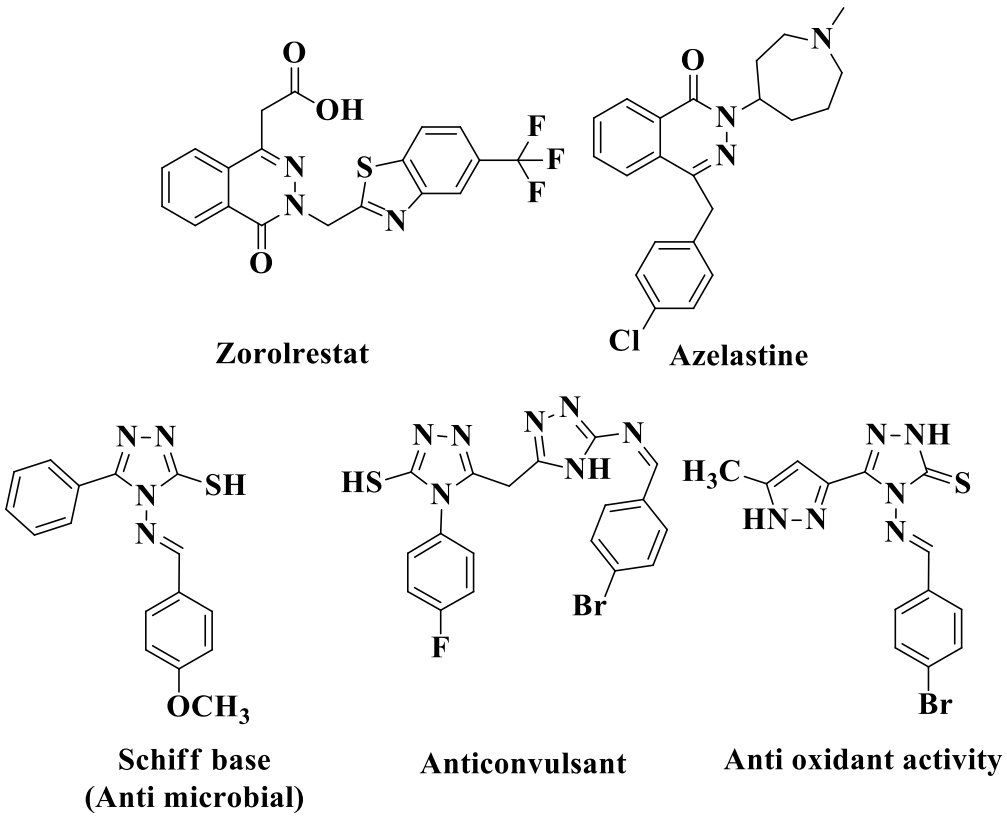
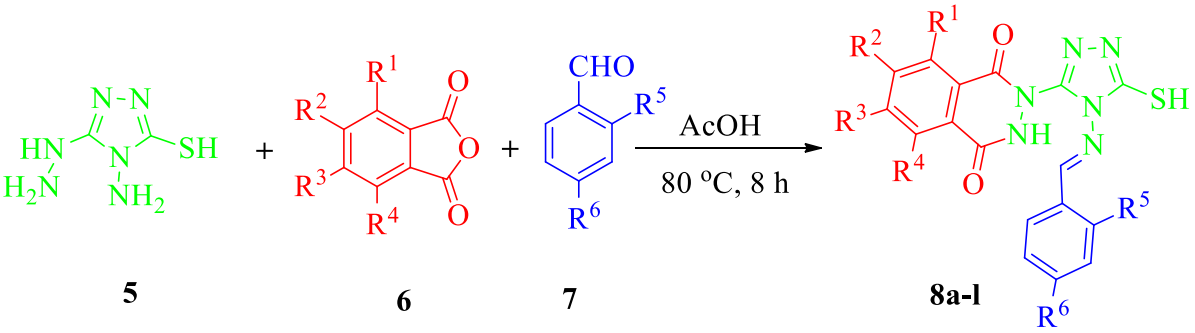


Fig.1. Biologically active molecules containing phthalazines and triazole moieties.

In the present work, we have condensed **5**, **6** and **7** compounds in ethanoic acid to give final products (**8a-l**).



5 **6** **7** **8a-l**

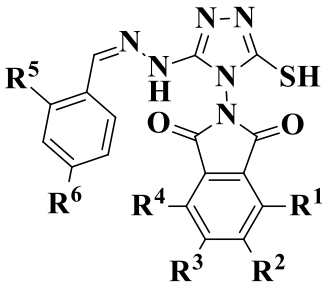
Scheme-1. Synthesis of compounds **8a-l**.

Reaction of (**5**), (**6**) and (**7**) in dry alcohol under heating afforded 15% of product. Additionally, the reaction was tried in methanol, methanol and catalytic amount of acetic acid, methanol and catalytic amount of HCl respectively. Except in ethanoic acid in remaining solvents the products are formed in low yields. Therefore, the favourable condition for the generation of **8** in ethanoic acid.

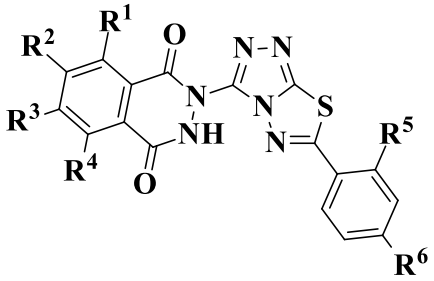
Table-1. Different substituents and time to form **8a-l.**

Entry	Product	R^1	R^2	R^3	R^4	R^5	R^6	Time (h)
1	8a	H	H	H	H	H	CH_3	8
2	8b	H	H	H	H	H	OCH_3	7.5
3	8c	H	H	H	H	H	OH	8
4	8d	H	H	H	H	OH	OEt	7.5
5	8e	H	H	H	H	H	CN	7.5
6	8f	H	H	H	H	H	F	8
7	8g	H	H	H	H	Cl	H	8
8	8h	H	H	H	H	H	Cl	8
9	8i	H	H	H	H	Cl	Cl	7.5
10	8j	H	H	H	H	H	Br	8
11	8k	Br	Br	Br	Br	H	CH_3	8
12	8l	Br	Br	Br	Br	Cl	H	8

Reaction between compound (**5**), Phthalic anhydride (**6**) and aldehyde (**7**) is expected to give compound (**9**) and (**10**) or a mixture of **9** and **10** also based on the way in which ring closure occurs. But in the present study the reaction occurred in such a manner in which the –NH-NH_2 of **5** undergone reaction with **6** accompanied by further reaction of amino functionality of **5** with aromatic aldehyde. This ultimately produced **8a-l** (single product by TLC). The significant feature of this scheme is that three new linkages like one N=C and two –N-C=O are formed at a time under mild conditions. The yields of the products were 82-93%. From this it is evident that the nature of the solvent and reaction conditions played an important role in the selective heterocyclization reaction. The structure (**9**) and (**10**) can be discarded based on the spectra.

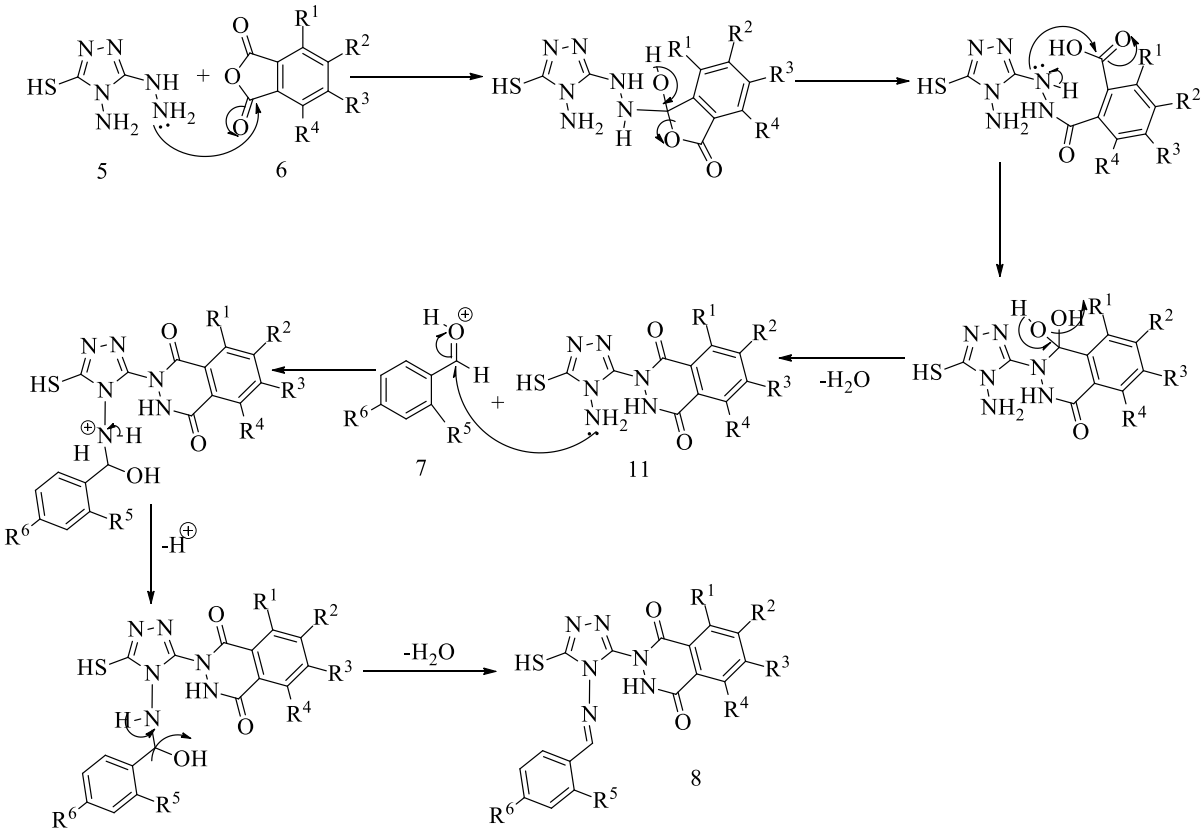


9



10

Final product (**8**) formation is proposed below. In the first step, condensation of (**5**) with phthalic anhydride (**6**) resulted in the formation of intermediate (**11**). This on further reaction with aromatic aldehyde loses water molecule leading to the formation of final product (**8**).



Scheme-2. Mechanism for the formation of **8a-l**.

CONCLUSION

This work describes a novel (*E*)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives synthesis**.** This reaction gave good to excellent yields and all the products were purified by recrystallization.

EXPERIMENTAL SECTION

Starting materials:

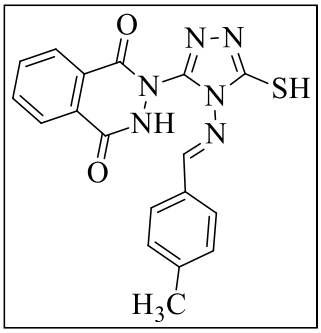
Purpald was prepared by the procedure discussed in the chapter-III. Various aromatic aldehydes were procured from commercial source.

General procedure for 8a-l compounds synthesis

An equi milli molar amount of purpald, phthalic anhydride and aromatic aldehyde was suspended in ethanoic acid. The reaction mixture was refluxed at 80 ^{o}C for about 8 h. The solid produced was filtered and recrystallized from methanol.

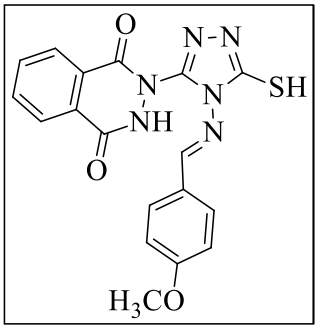
SPECTRAL DATA

(*E*)-2-(5-Mercapto-4-((4-methylbenzylidene)amino)-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8a).



Color: white solid; mp: 245-247 $^{\circ}$C; yield: (0.441g, 85%); IR (KBr, Wave number, cm^{-1}): 1604 (C=N), 1738 (carbonyl), 2550 (SH), 3336 (NH); PMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.37 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.96-8.03 (m, 4H), 10.07 (s, 1H), 10.16 (s, 1H), 13.37 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.7, 124.4, 127.0, 129.2, 129.62, 129.9, 130.1, 136.0, 143.4, 149.1, 161.0, 162.2, 165.7 ppm; ESI-MS: m/z 379 $[M+H]^+$; Anal. calcd. for $C_{18}H_{14}N_6O_2S$: C, 57.13; H, 3.73; N, 22.21; S, 8.47. Found: C, 57.17; H, 3.78; N, 22.25; S, 8.43%.

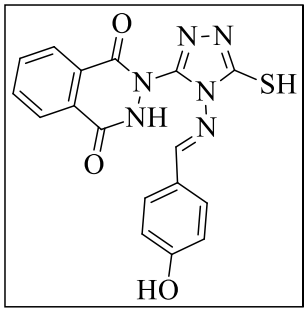
(*E*)-2-(5-Mercapto-4-((4-methoxybenzylidene)amino)-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8b).



Color: white solid; mp: 237-239 $^{\circ}$C; yield: (0.463g, 85%); IR (KBr, Wave number, cm^{-1}): 1626 (C=N), 1736 (carbonyl), 2550 (SH), 3445 (NH); PMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H, CH_3), 7.09 (d, J = 6.8 Hz, 2H), 7.89 (d, J = 7.2 Hz, 2H), 7.95-8.01 (m, 4H), 9.99 (s, 1H), 10.04 (s, 1H), 13.33 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 56.0, 115.0, 124.3, 125.0, 129.6, 131.2, 136.0, 149.1, 161.0, 162.5, 163.3, 165.7 ppm; ESI-MS: m/z 395 $[M+H]^+$; Anal. calcd. for $C_{18}H_{14}N_6O_3S$: C, 54.81; H, 3.58; N, 21.31; S, 8.13. Found: C, 54.85; H, 3.54; N, 21.37; S, 8.00%.

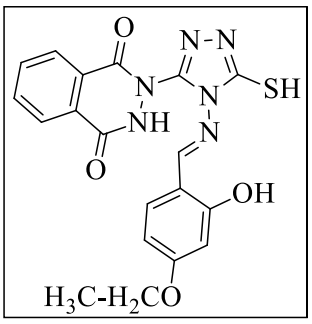
(*E*)-2-(4-((4-Hydroxybenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8c).

Color: white solid; mp: 245-247 °C; yield: (0.463g, 82%); IR (KBr, Wave number, cm^{-1}): 1614 (C=N), 1738 (carbonyl), 2550 (SH), 3247 (NH); PMR (400 MHz, DMSO-d_6): δ 5.48 (s, 1H), 6.8 (d, J = 8.0 Hz, 3H), 7.45 (d, J = 8.0 Hz, 3H), 8.21 (s, 2H), 9.79 (s, 1H), 10.36 (s, 1H), 12.89 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 116.0, 126.2, 128.5, 145.0, 150.2, 159.1, 164.7 ppm; ESI-MS: m/z 381 $[M+H]^+$; Anal. calcd. for $C_{17}H_{12}N_6O_3S$: C, 53.68; H, 3.18; N, 22.09; S, 8.43. Found: C, 53.65; H, 3.15; N, 22.10; S, 8.46%.



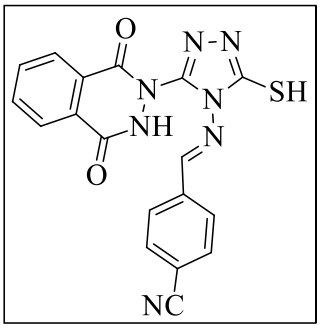
(*E*)-2-(4-((3-Ethoxy-2-hydroxybenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8d).

Color: white solid; mp: 243-245 °C; yield: (0.493g, 86%); IR (KBr, Wave number, cm^{-1}): 1635 (C=N), 1736 (carbonyl), 2540 (SH), 3318 (NH); PMR (400 MHz, DMSO-d_6): δ 1.40 (t, J = 8.0 Hz, 3H), 4.08 (q, J = 8.0 Hz, 2H), 6.81 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 4H), 9.25 (s, 1H), 9.84 (s, 1H), 10.49 (s, 1H), 13.11 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ 15.0, 64.8, 116.9, 118.9, 119.3, 119.6, 124.3, 129.6, 135.9, 147.7, 148.8, 149.2, 158.3, 160.9, 165.6 ppm; ESI-MS: m/z 425 $[M+H]^+$; Anal. calcd. for $C_{19}H_{16}N_6O_4S$: C, 53.77; H, 3.80; N, 19.80; S, 7.55. Found: C, 053.73; H, 3.84; N, 19.85; S, 7.58%.



(*E*)-4-(((3-(1,4-Dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)imino)methyl)benzonitrile (8e).

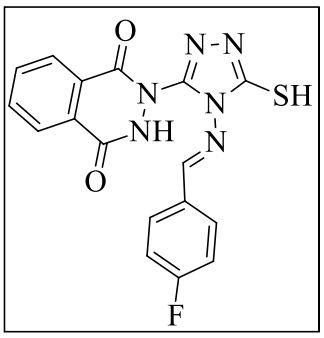
Color: yellow solid; mp: 250-252 °C; yield: (0.432g, 90%); IR (KBr, Wave number, cm^{-1}): 1623 (C=N), 1736 (carbonyl), 2774 (SH), 3355 (NH); PMR (400 MHz, DMSO-d_6): δ 7.97-8.05 (m, 6H), 8.18 (d, J = 8.0 Hz, 2H), 10.23 (s, 1H), 10.56 (s, 1H), 13.48 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 114.7, 118.8, 124.4, 129.6, 129.7, 133.3, 136.0, 137.0, 149.2, 158.3, 161.0, 165.6 ppm; ESI-MS: m/z 390 $[M+H]^+$; Anal. calcd. for $C_{18}H_{11}N_7O_2S$: C, 55.52; H, 2.85; N, 25.18; S, 8.23. Found: C, 55.58; H, 2.81; N, 25.14; S, 8.27%.



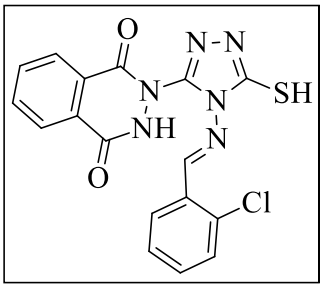
(*E*)-2-(4-((4-Fluorobenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8f).

Color: white solid; mp: 260-262 °C; yield: (0.415g, 92%); IR (KBr, Wave number, cm^{-1}): 1614 (C=N), 1736 (carbonyl), 2550 (SH), 3430 (NH); PMR (400 MHz, DMSO-d_6): δ 7.42 (t,

J = 8.0 Hz, 2H), 7.96-8.07 (m, 6H), 10.13 (s, 1H), 10.23 (s, 1H), 13.40 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 116.6, 116.8, 124.4, 129.3, 129.6, 131.8, 131.8, 136.0, 149.1, 160.9, 161.0, 163.8, 165.7, 166.3 ppm. ESI-MS: m/z 383 $[M+H]^+$; Anal. calcd. for $C_{17}H_{11}FN_6O_2S$: C, 53.40; H, 2.90; N, 21.98; S, 8.39. Found: C, 53.44; H, 2.87; N, 21.94; S, 8.34%.

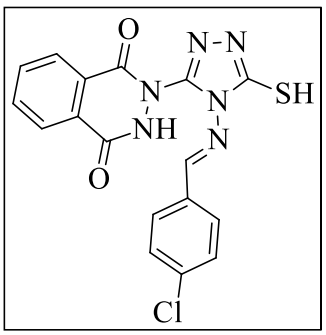


(*E*)-2-(4-((2-Chlorobenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8g).



Color: white solid; mp: 258-260 °C; yield: (0.442g, 90%); IR (KBr, Wave number, cm^{-1}): 1637 (C=N), 1733 (carbonyl), 2550 (SH), 3438 (NH); PMR (400 MHz, DMSO-d_6): δ 7.54 (t, *J* = 8.0 Hz, 1H), 7.62-7.67 (m, 2H), 7.97-8.05 (m, 4H), 8.38 (d, *J* = 8.0 Hz, 1H), 10.21 (s, 1H), 11.07 (s, 1H), 13.48 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 124.4, 128.1, 128.5, 129.6, 130.5, 130.6, 134.4, 135.6, 136.0, 149.3, 155.1, 160.8, 165.6 ppm; ESI-MS: m/z 399 $[M+H]^+$; Anal. calcd. for $C_{17}H_{11}ClN_6O_2S$: C, 51.20; H, 2.78; N, 21.07; S, 8.04. Found: C, 51.23; H, 2.75; N, 21.12; S, 8.12%.

(*E*)-2-(4-((4-Chlorobenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8h).

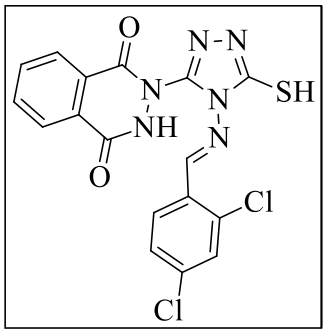


Color: white solid; mp: 248-250 °C; yield: (0.427g, 93%); IR (KBr, Wave number, cm^{-1}): 1632 (C=N), 1737 (carbonyl), 2550 (SH), 3445 (NH); PMR (400 MHz, DMSO-d_6): δ 7.47-7.50 (m, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.96-7.98 (m, 2H), 8.00-8.02 (m, 2H), 10.14 (s, 1H), 10.31 (s, 1H), 13.41 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 124.4, 128.6, 129.6, 129.6, 130.9, 131.6, 136.0, 137.7, 149.1, 160.3, 161.0, 165.6 ppm; ESI-MS: m/z 399 $[M+H]^+$; Anal. calcd. for $C_{17}H_{11}ClN_6O_2S$: C, 51.20; H, 2.78; N, 21.07; S, 8.04. Found: C, 51.24; H, 2.74; N, 21.10; S, 8.12%.

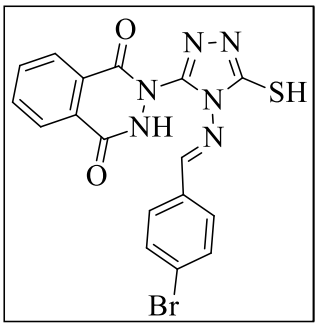
(*E*)-2-(4-((2,4-Dichlorobenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8i).

Color: white solid; mp: 261-263 °C; yield: (0.481g, 90%); IR (KBr, Wave number, cm^{-1}): 1637 (C=N), 1731 (carbonyl), 2550 (SH), 3448 (NH); PMR (400 MHz, DMSO-d_6): δ 7.48-7.51 (m, 1H), 7.65-7.71 (m, 2H), 7.87-8.03 (m, 3H), 8.54 (s, 1H), 11.11 (s, 1H), 11.23 (s, 1H), 13.27 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 124.4, 128.0, 128.4, 129.7, 130.2,

131.2, 133.5, 134.8, 136.0, 139.3, 149.2, 160.8, 165.5, 169.1 ppm; ESI-MS: m/z 433 $[M+H]^+$; Anal. calcd. for $C_{17}H_{10}Cl_2N_6O_2S$: C, 47.13; H, 2.33; N, 19.40; S, 7.40. Found: C, 47.17; H, 2.37; N, 19.44; S, 7.35%.

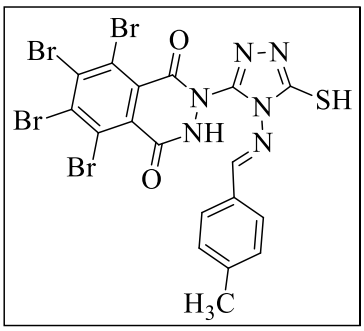


(*E*)-2-(4-((4-Bromobenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8j).



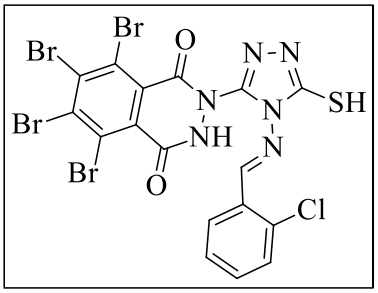
Color: white solid; mp: 264-266 °C; yield: (0.527g, 84%); IR (KBr, Wave number, cm^{-1}): 1632 (C=N), 1737 (carbonyl), 2670 (SH), 3445 (NH); PMR (400 MHz, DMSO-d_6): δ 5.52 (s, 1H), 7.56-7.63 (m, 4H), 7.79 (t, J = 8.0 Hz, 1H), 7.91-8.03 (m, 2H), 8.29 (s, 1H), 10.79 (s, 1H), 12.98 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 122.7, 124.4, 128.7, 129.6, 131.0, 132.2, 132.6, 134.4, 136.0, 143.1, 149.9, 165.0 ppm; ESI-MS: m/z 445 [M+2]; Anal. calcd. for $C_{17}H_{11}BrN_6O_2S$: C, 46.06; H, 2.50; N, 18.96; S, 7.23. Found: C, 46.12; H, 2.54; N, 18.92; S, 7.20%.

(*E*)-5,6,7,8-Tetrabromo-2-(5-mercapto-4-((4-methylbenzylidene)amino)-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8k).

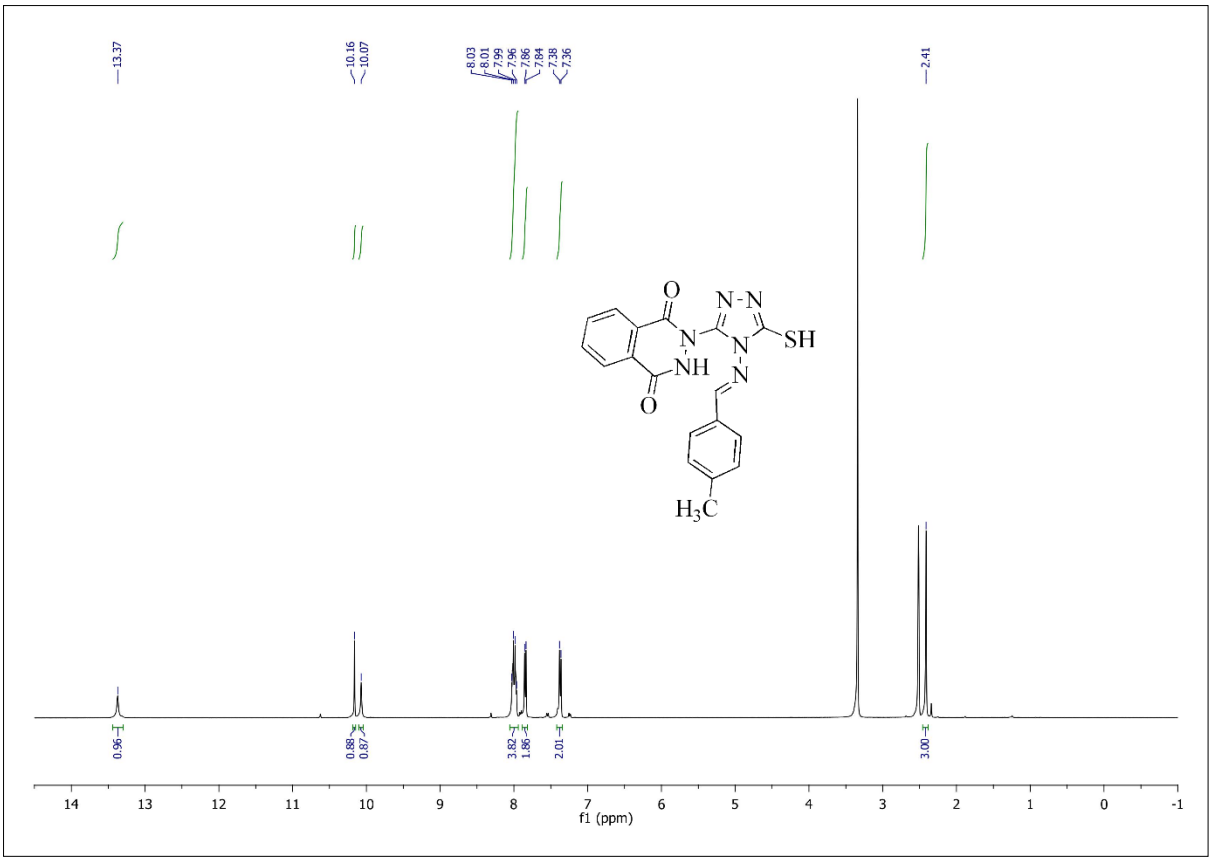


Color: pale yellow solid; mp: >300 °C; yield: (0.815g, 85%); IR (KBr, Wave number, cm^{-1}): 1639 (C=N), 1748 (carbonyl), 2660 (SH), 3435 (NH); PMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH3), 7.32 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 9.88 (s, 1H), 10.32 (s, 1H), 13.47 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6): δ 21.8, 121.9, 129.0, 129.1, 129.6, 129.9, 138.1, 143.6, 148.5, 161.0, 161.8, 163.6 ppm; ESI-MS: m/z 694 $[M+H]^+$; Anal. calcd. for $C_{18}H_{10}Br_4N_6O_2S$: C, 31.15; H, 1.45; N, 12.11; S, 4..62. Found: C, 31.18; H, 1.48; N, 12.14; S, 4.67%.

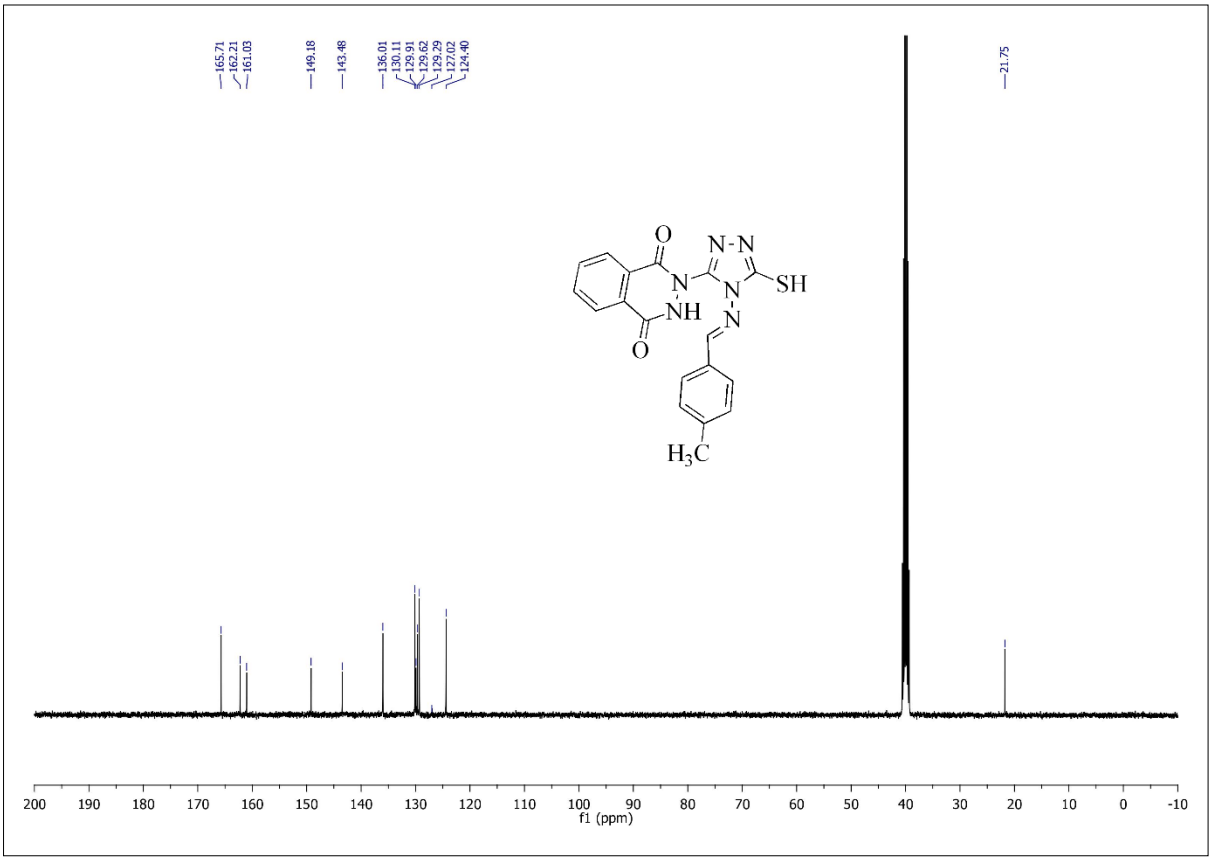
(*E*)-5,6,7,8-Tetrabromo-2-(4-((2-chlorobenzylidene)amino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (8l).



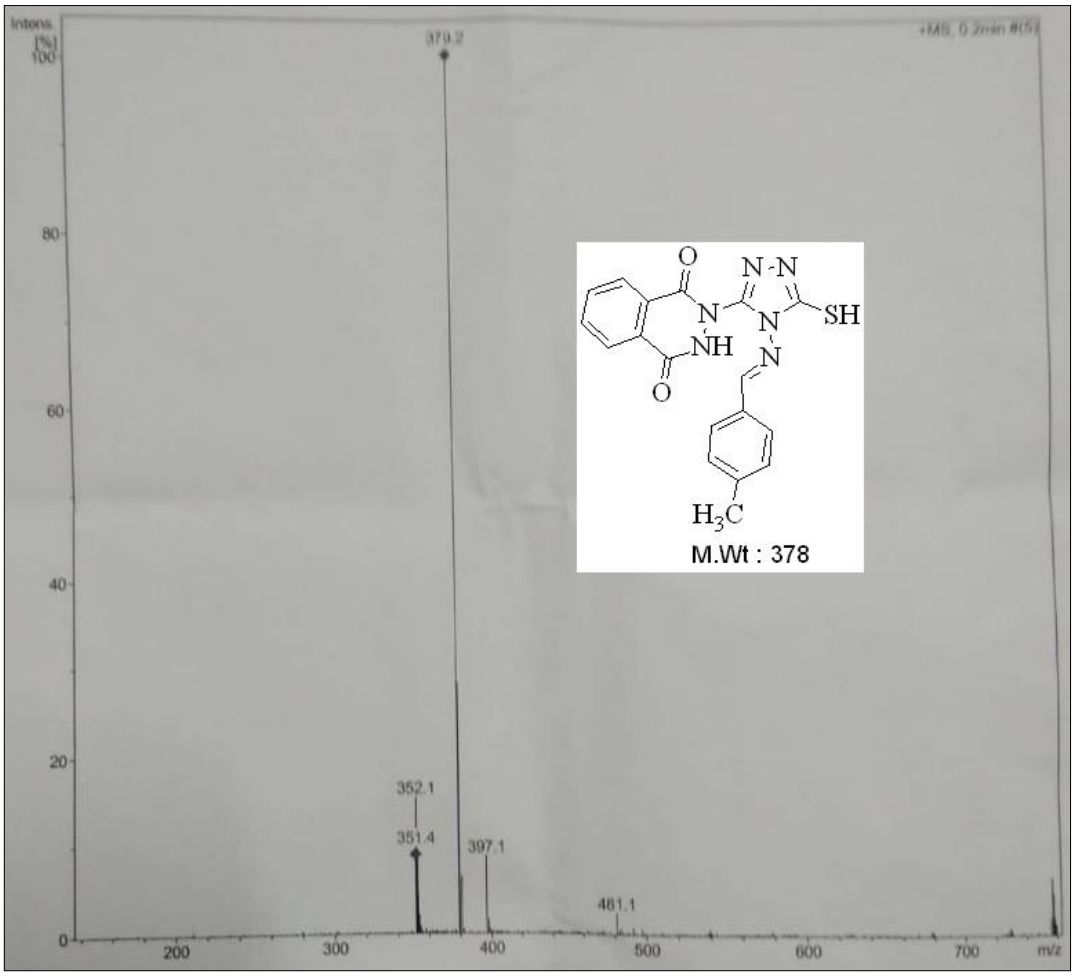
Color: white solid; mp: >300 °C; yield: (0.793g, 90%); IR (KBr, Wave number, cm^{-1}): 1628 (C=N), 1727 (carbonyl), 2550 (SH), 3412 (NH); PMR (400 MHz, DMSO-d_6): δ 7.29 (s, 1H), 7.42 (s, 2H), 8.2 (d, J = 8.0 Hz, 1H), 9.61 (s, 1H), 11.13 (s, 1H), 13.08 (s, 1H) ppm; CMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ 122.0, 128.0, 128.4, 129.0, 130.3, 130.5, 134.3, 135.6, 138.2, 148.9, 155.6, 160.9, 161.7 ppm; ESI-MS: m/z 714 $[M+H]^+$; Anal. calcd. for $C_{17}H_7Br_4ClN_6O_2S$: C, 28.58; H, 0.99; N, 11.76; S, 4.49. Found: C, 28.52; H, 1.03; N, 11.73; S, 4.45%.



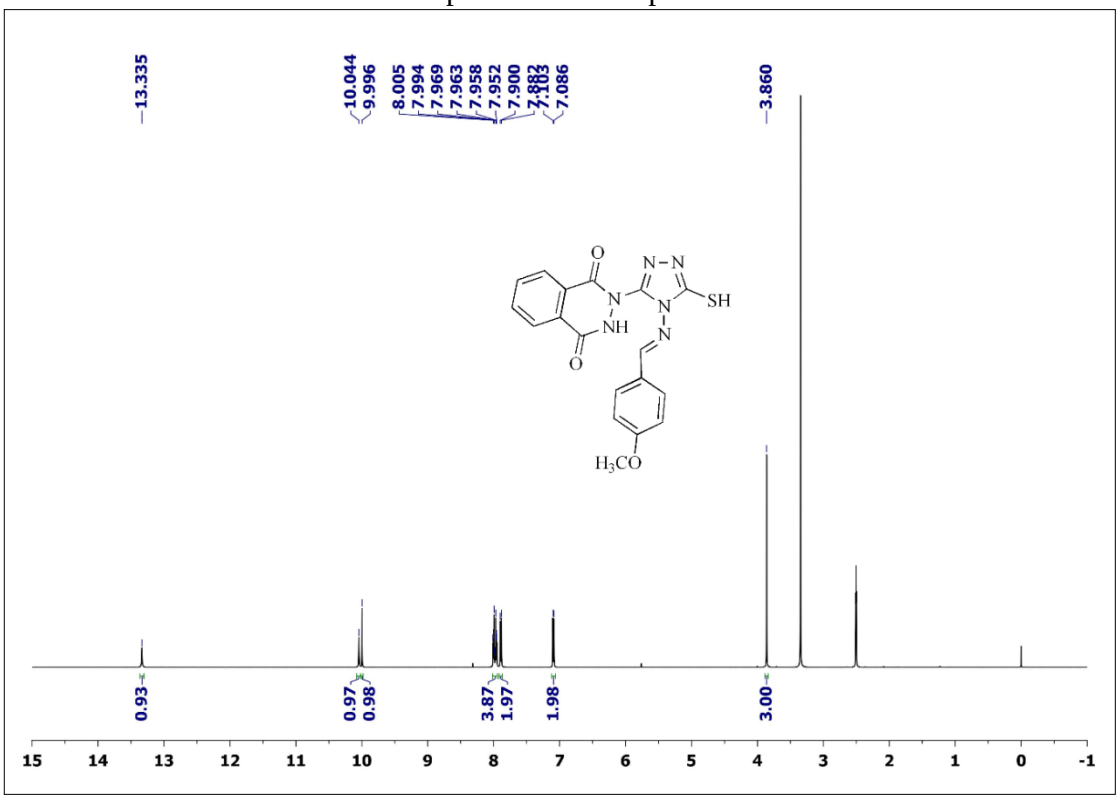
PMR Spectrum of compound **8a**



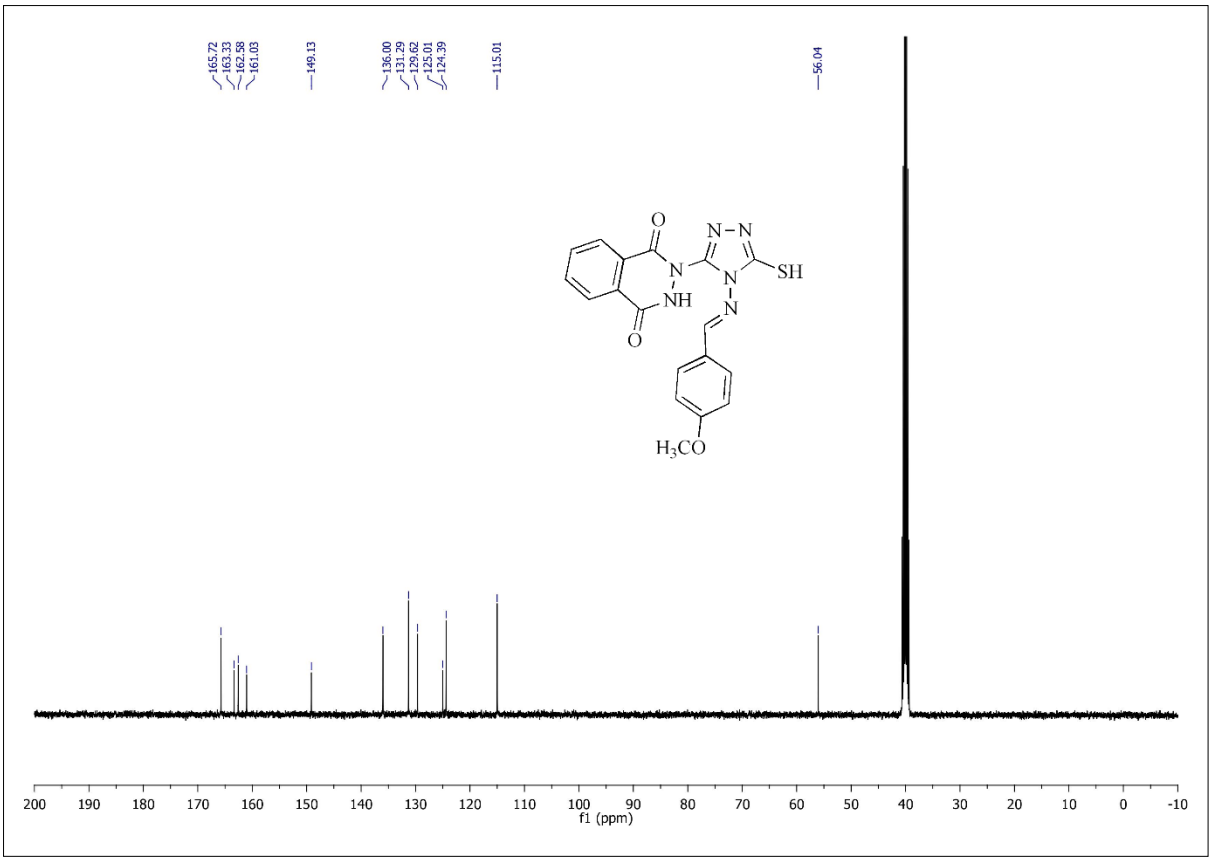
CMR Spectrum of compound **8a**



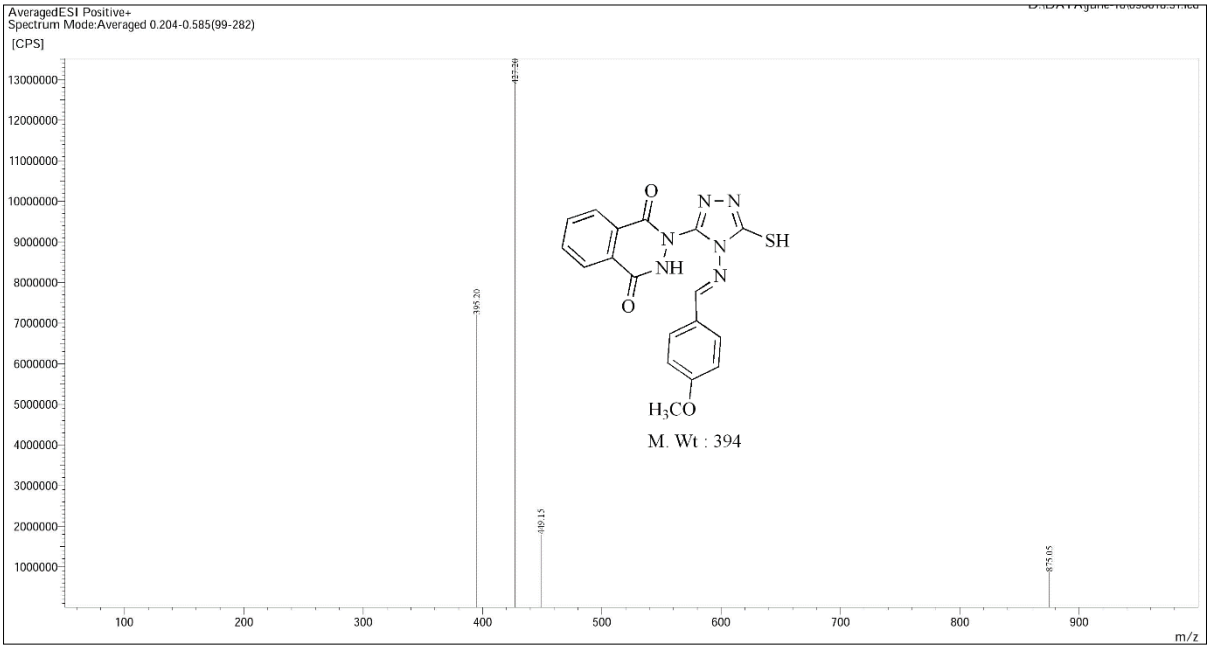
Mass Spectrum of compound **8a**



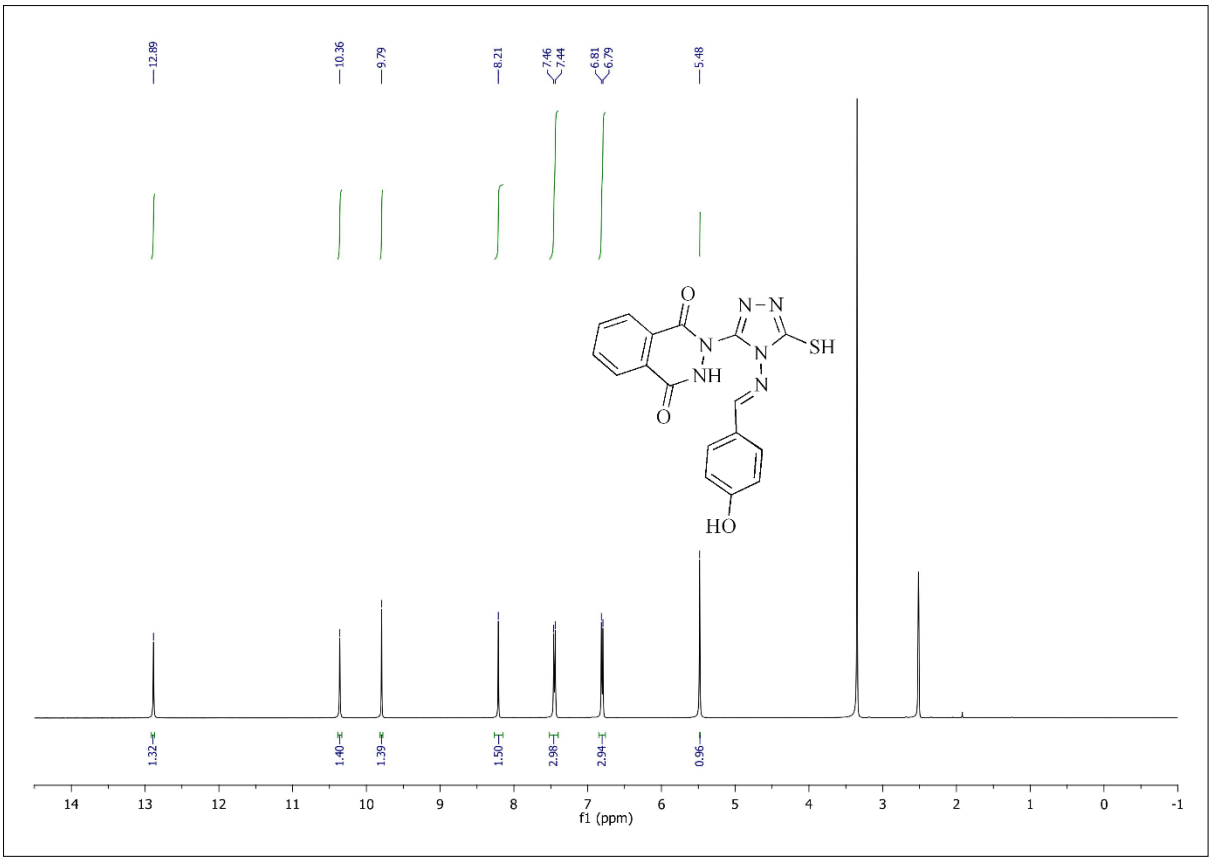
PMR Spectrum of compound **8b**



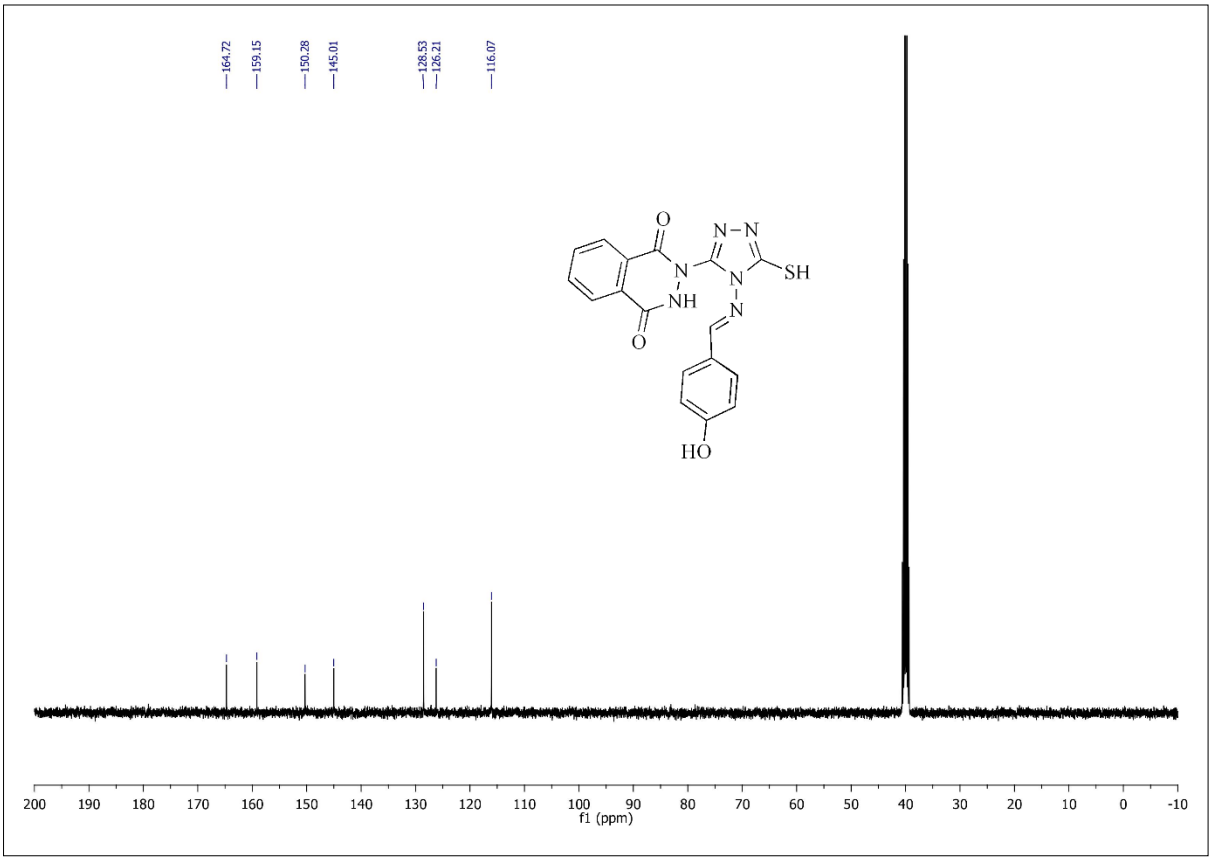
CMR Spectrum of compound **8b**



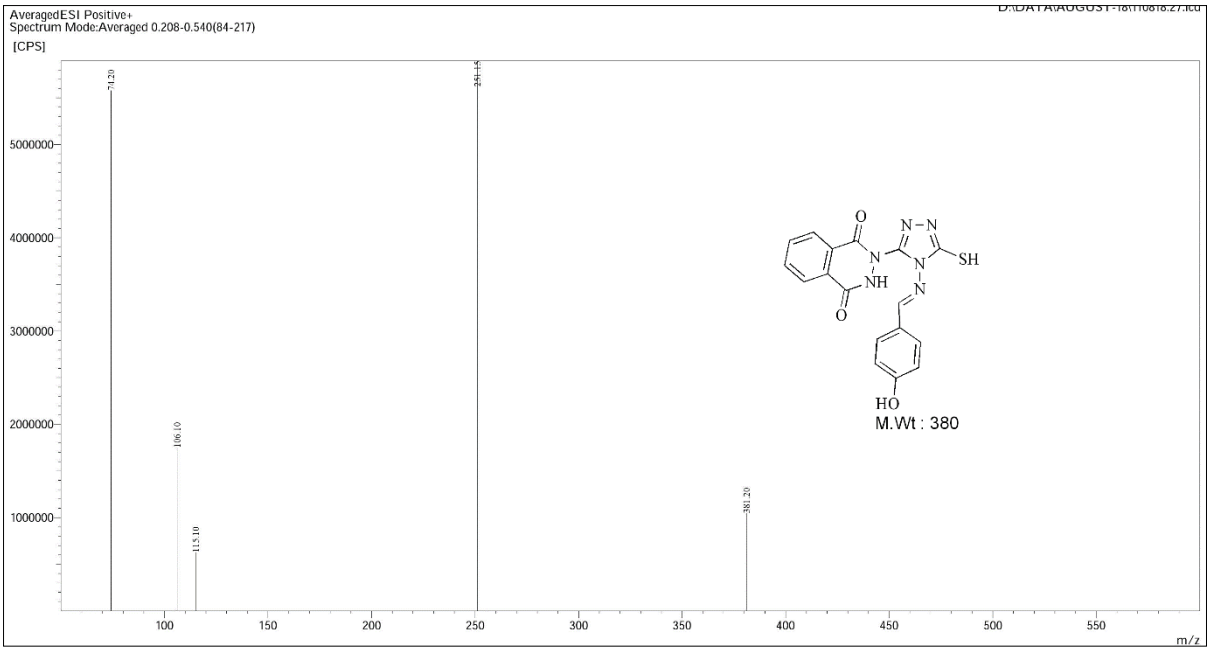
Mass Spectrum of compound **8b**



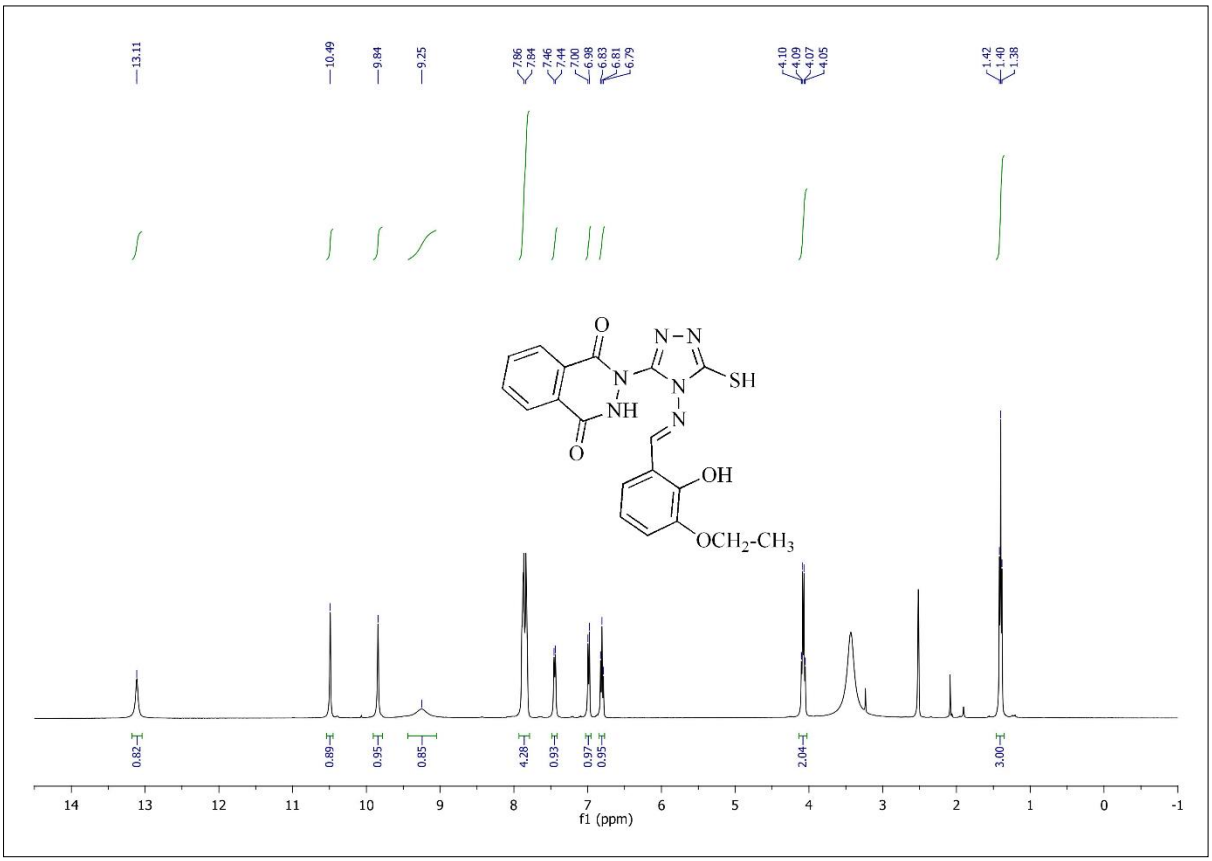
PMR Spectrum of compound **8c**



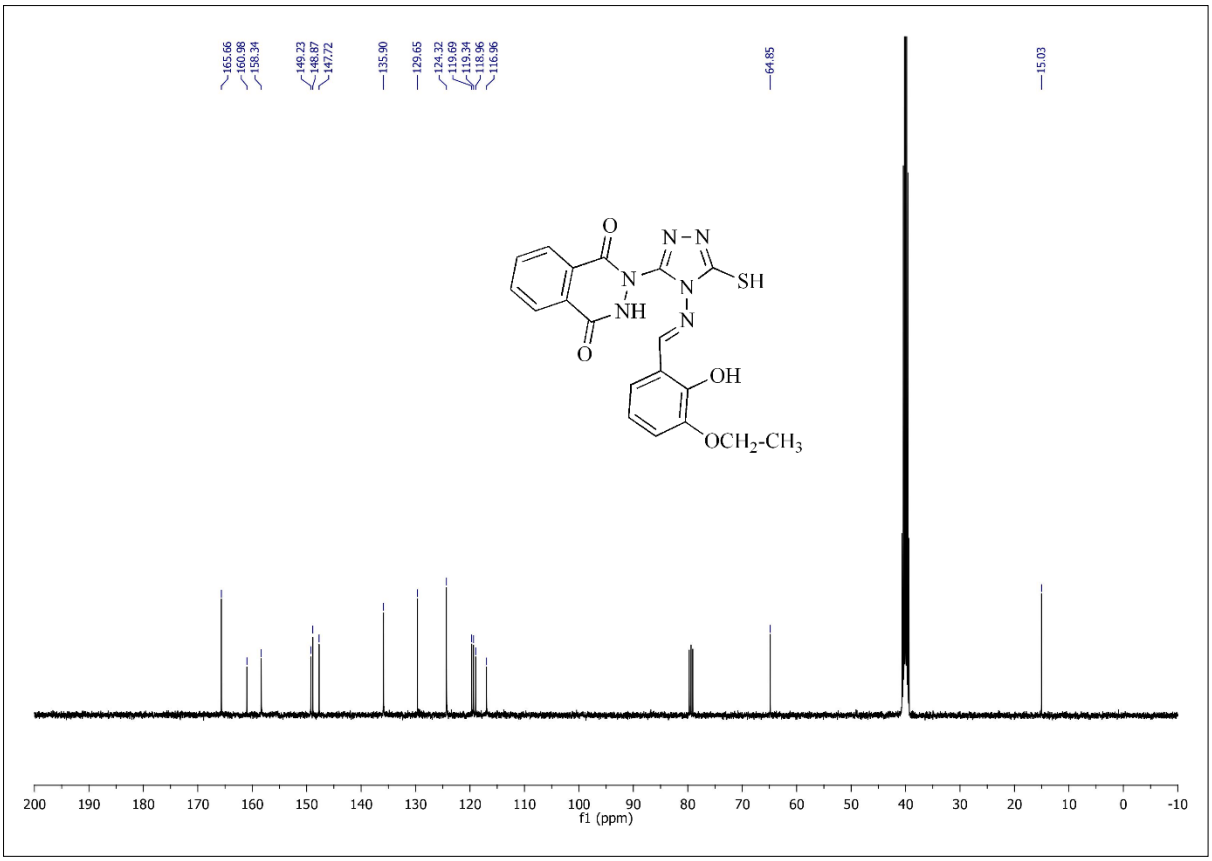
CMR Spectrum of compound **8c**



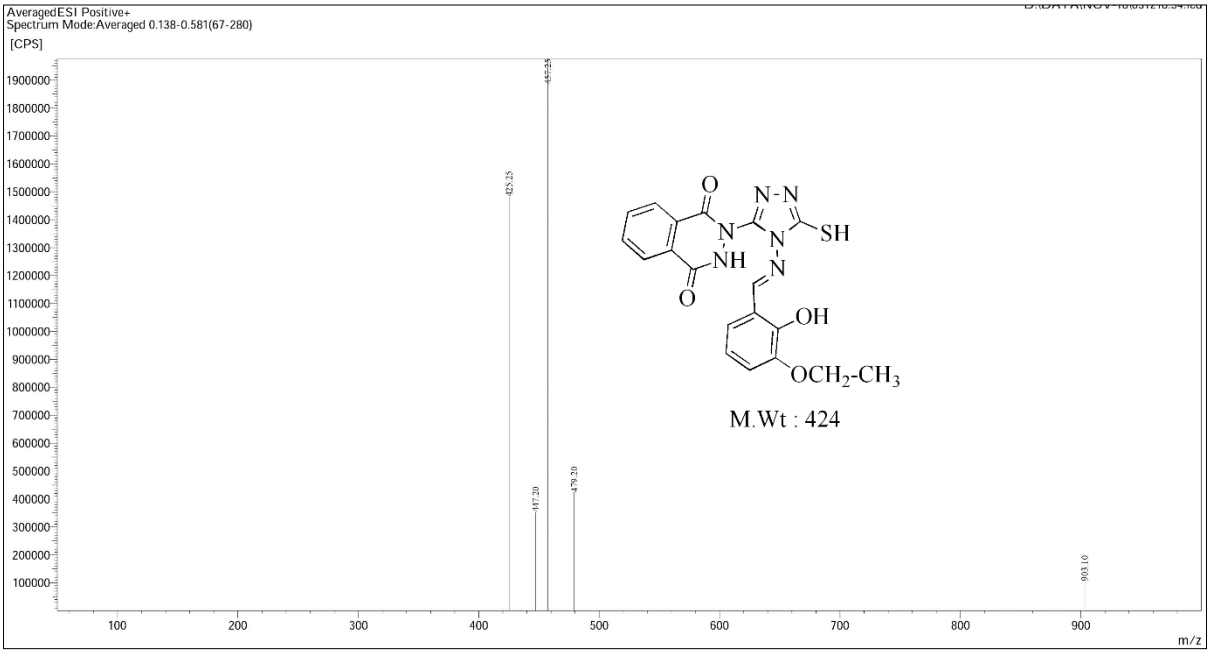
Mass Spectrum of compound **8c**



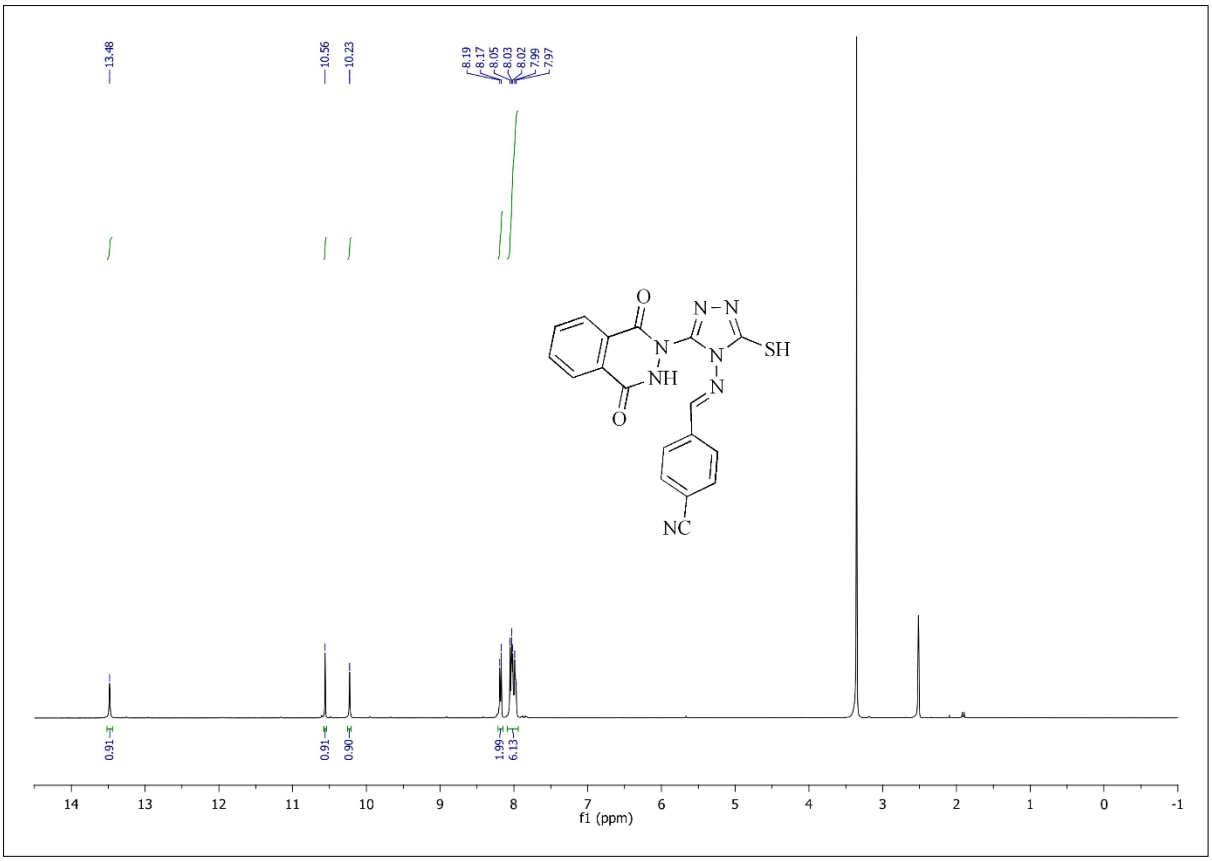
PMR Spectrum of compound **8d**



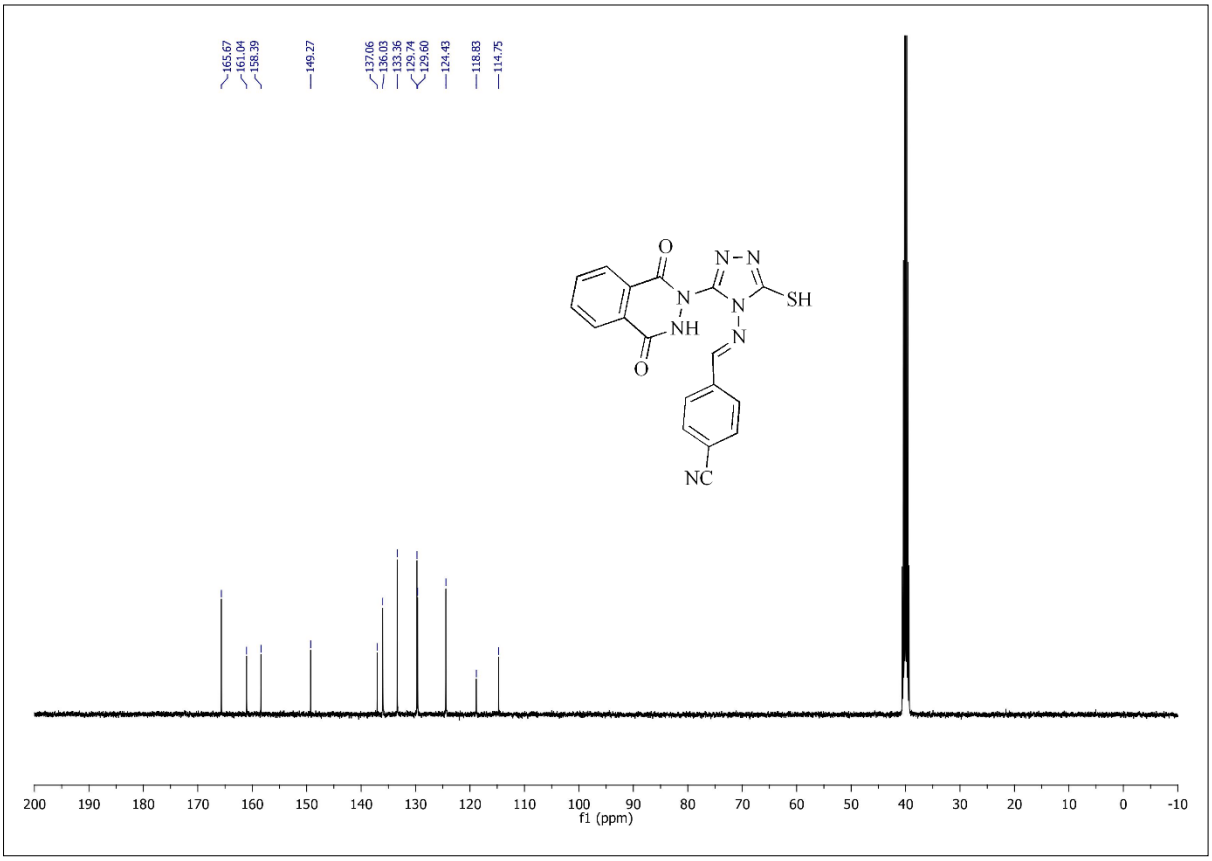
CMR Spectrum of compound **8d**



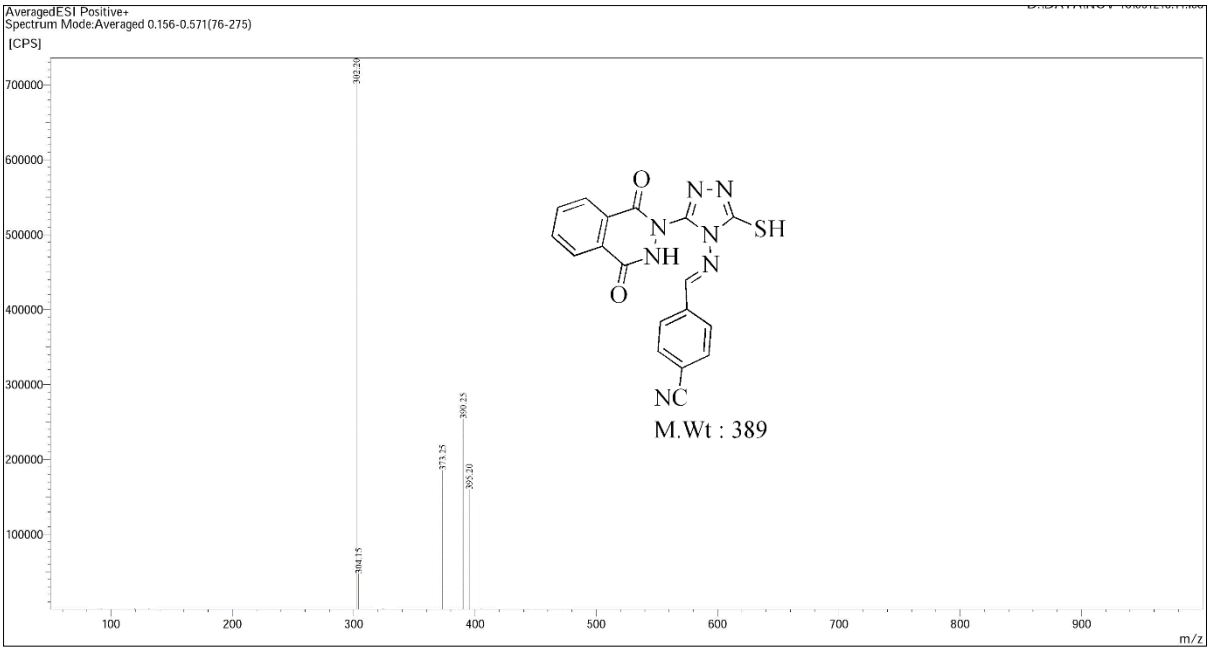
Mass Spectrum of compound **8d**



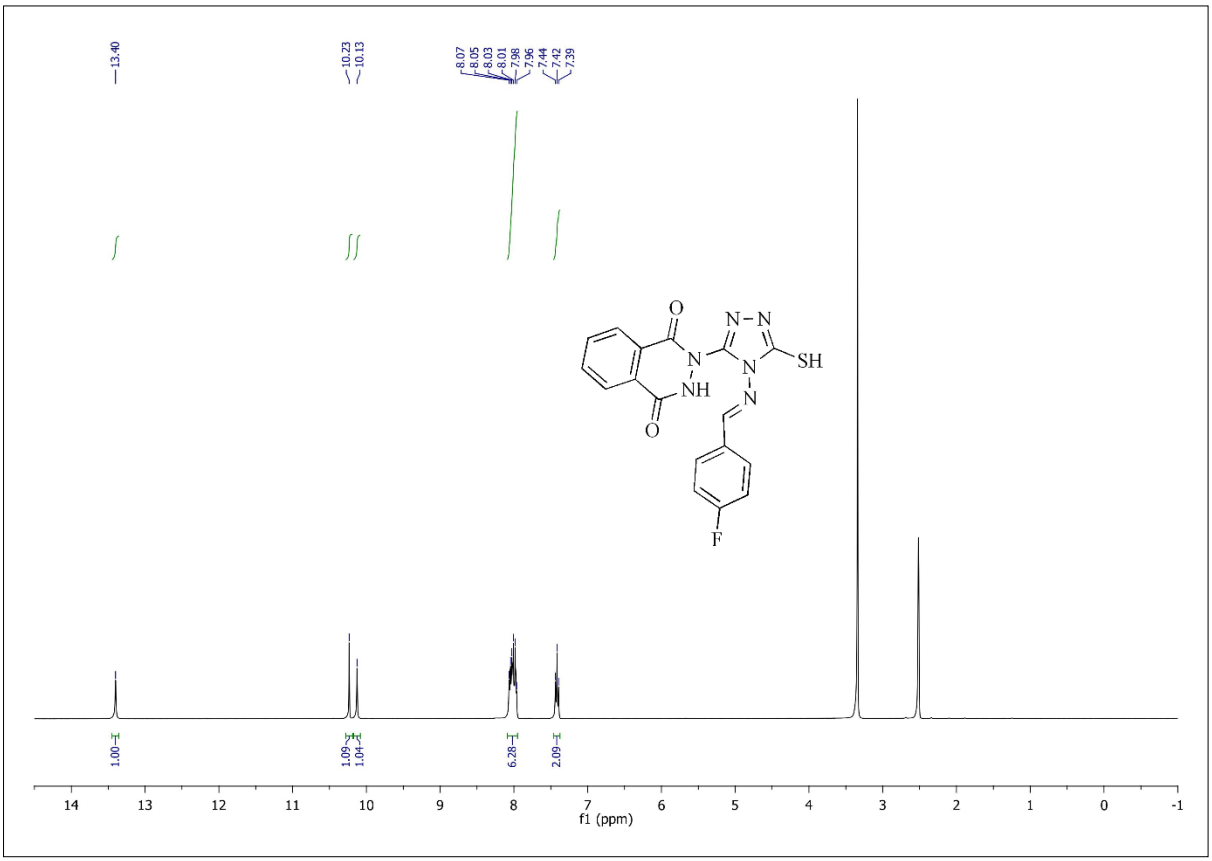
PMR Spectrum of compound **8e**



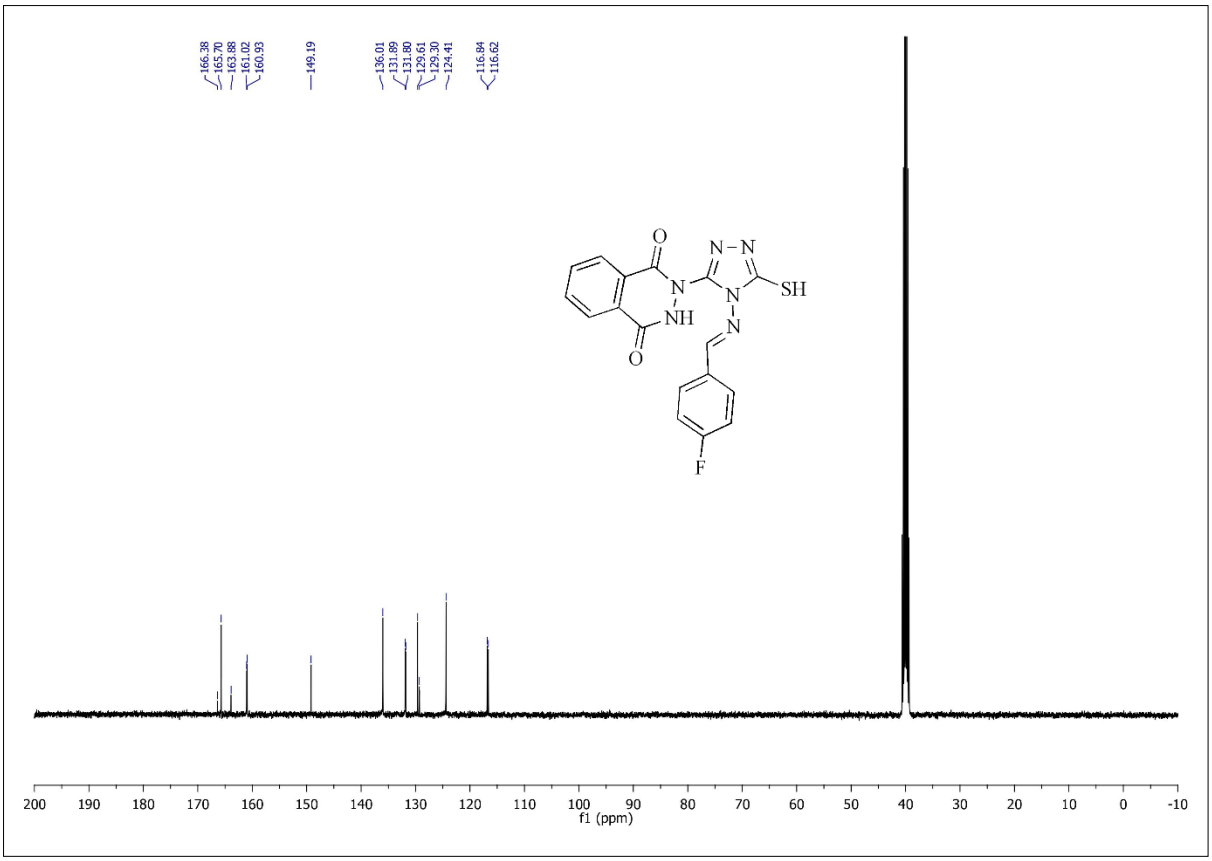
CMR Spectrum of compound **8e**



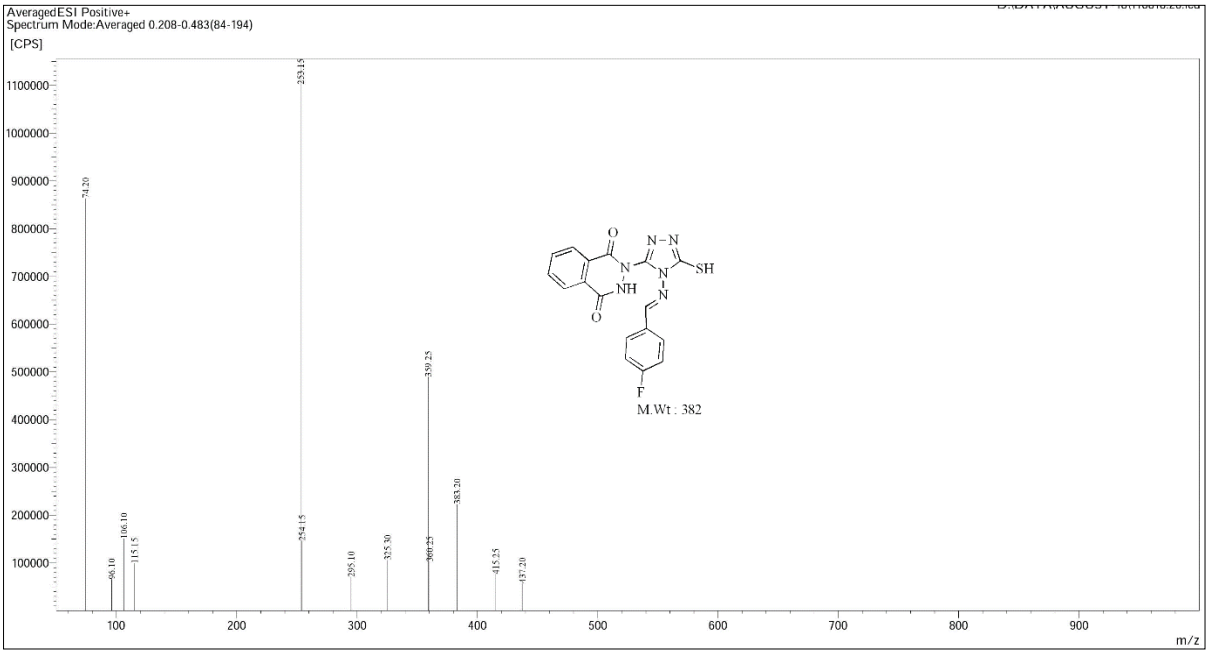
Mass Spectrum of compound **8e**



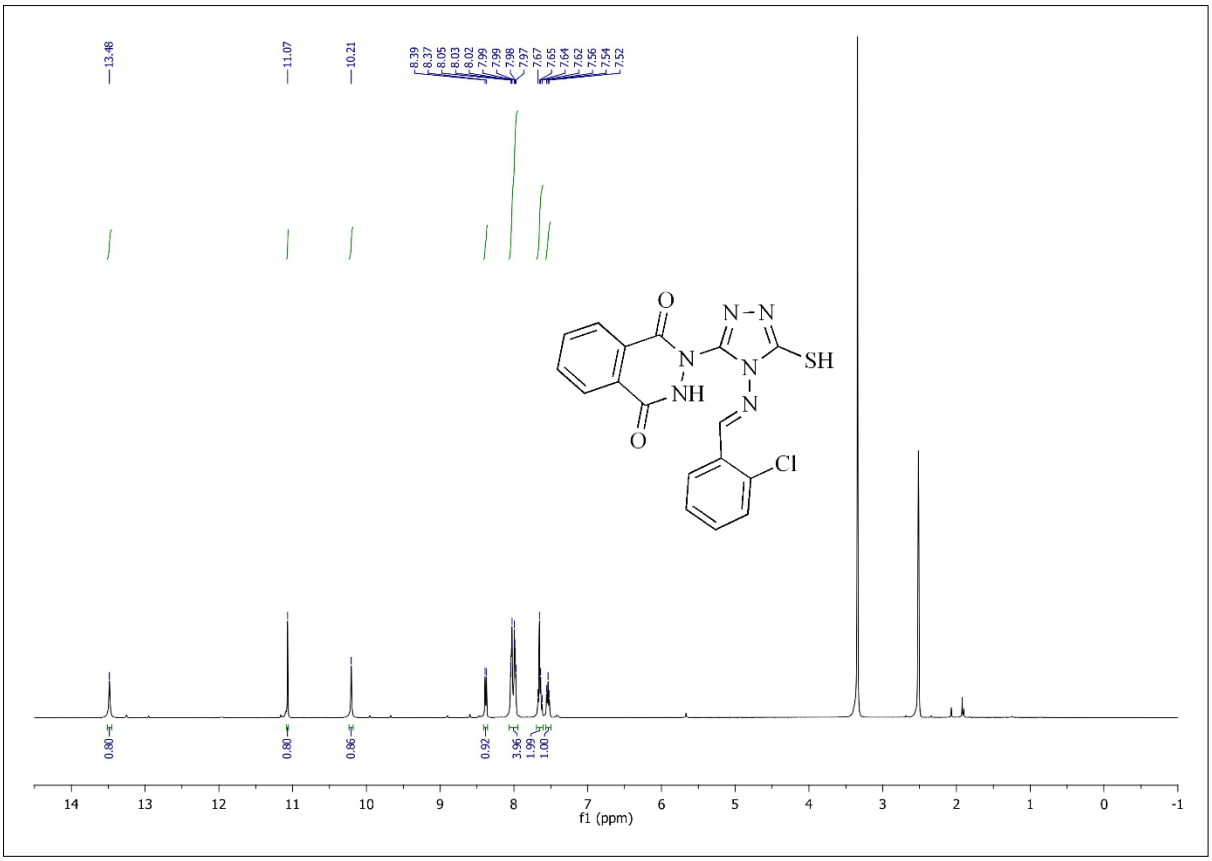
PMR Spectrum of compound **8f**



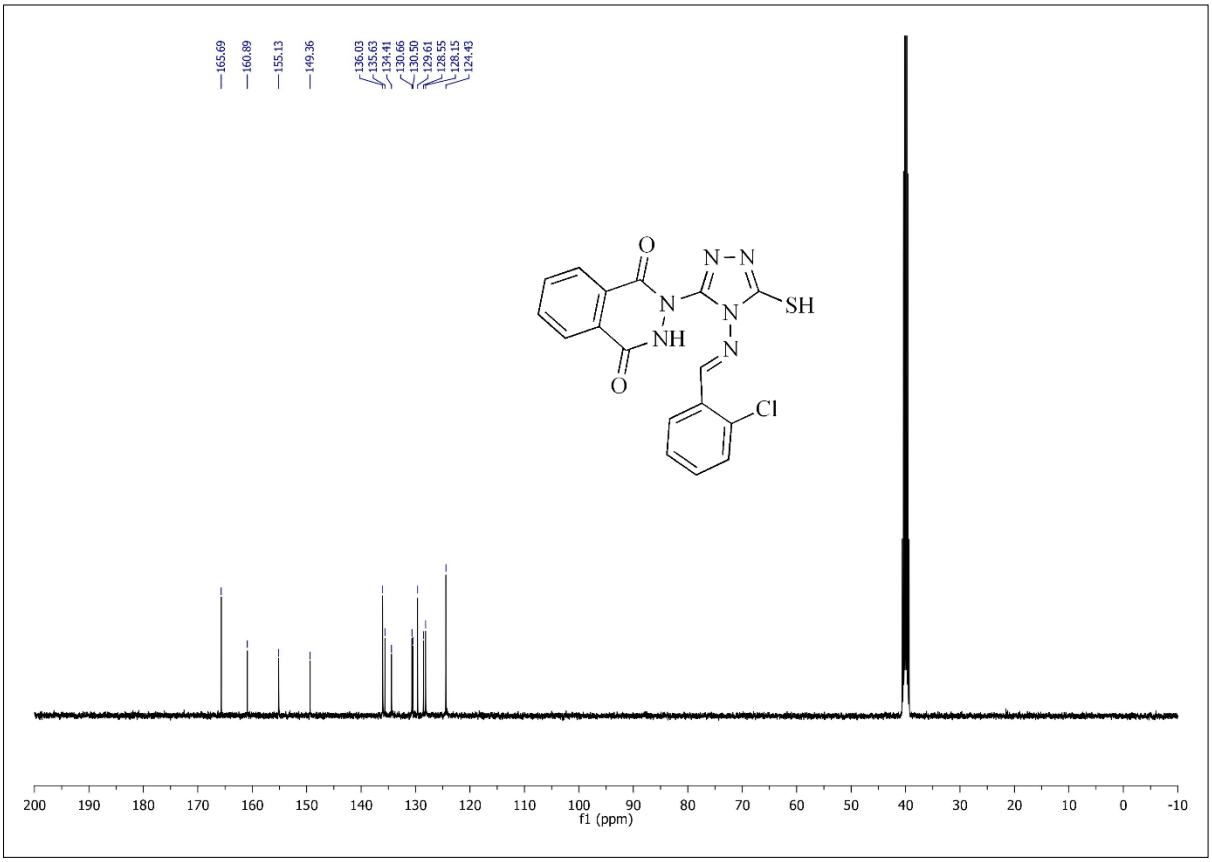
CMR Spectrum of compound **8f**



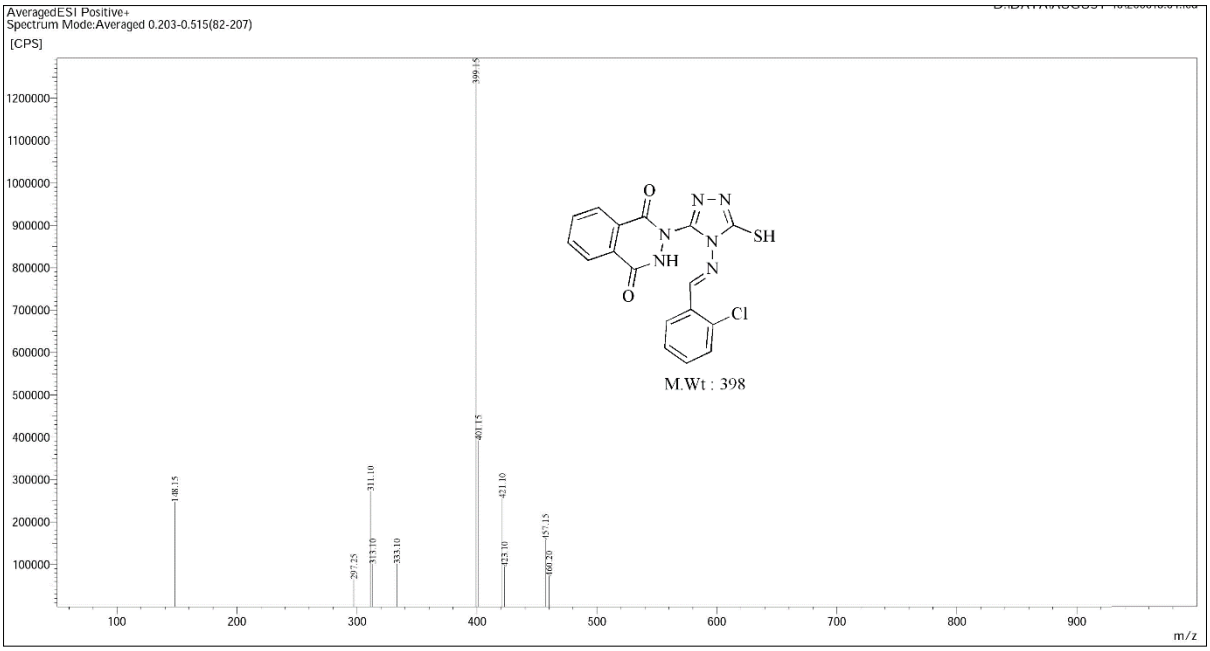
Mass Spectrum of compound **8f**



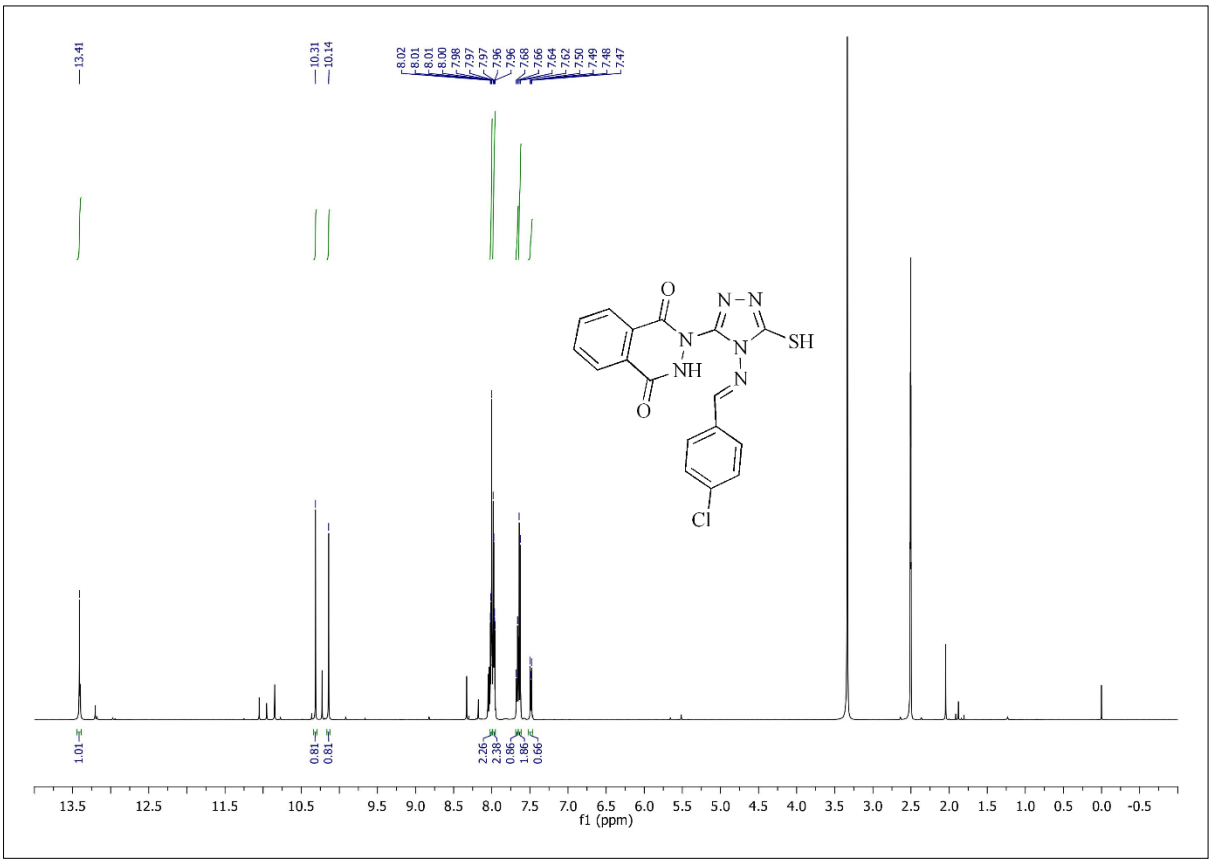
PMR Spectrum of compound **8g**



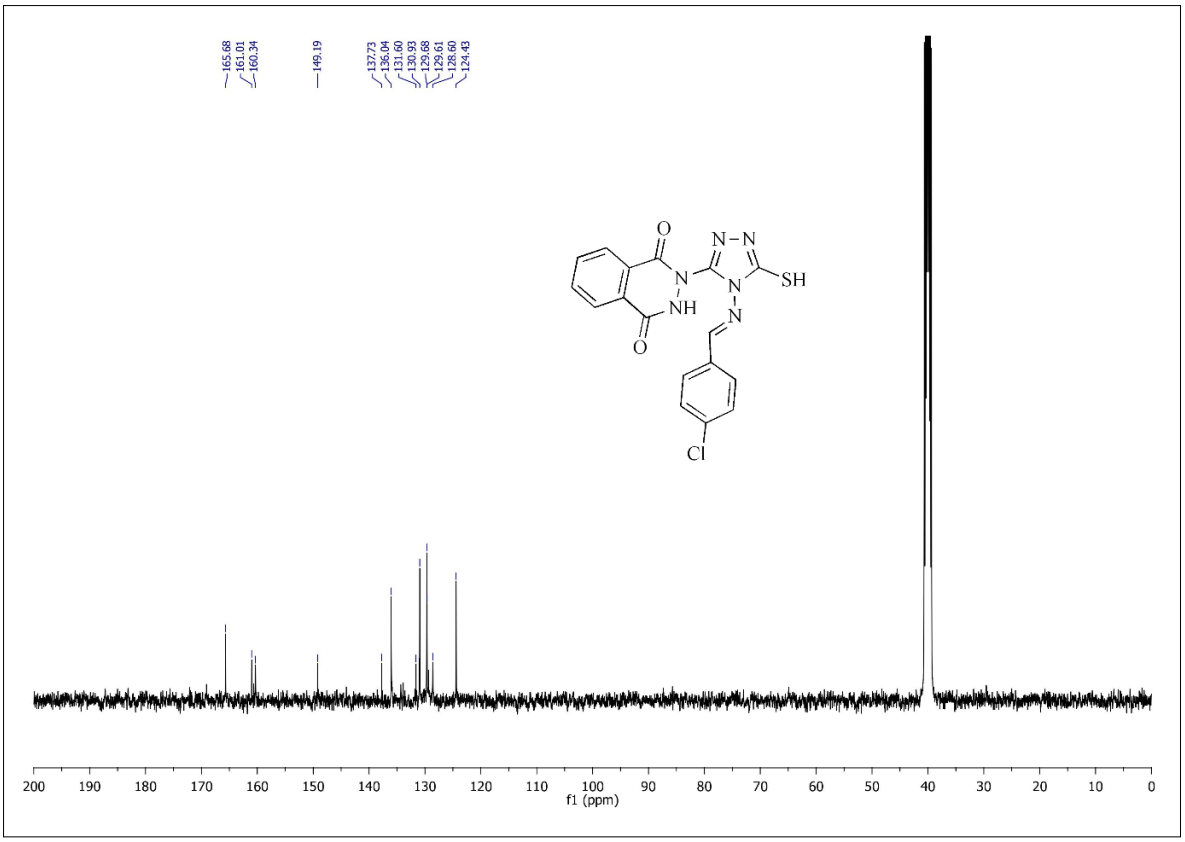
CMR Spectrum of compound **8g**



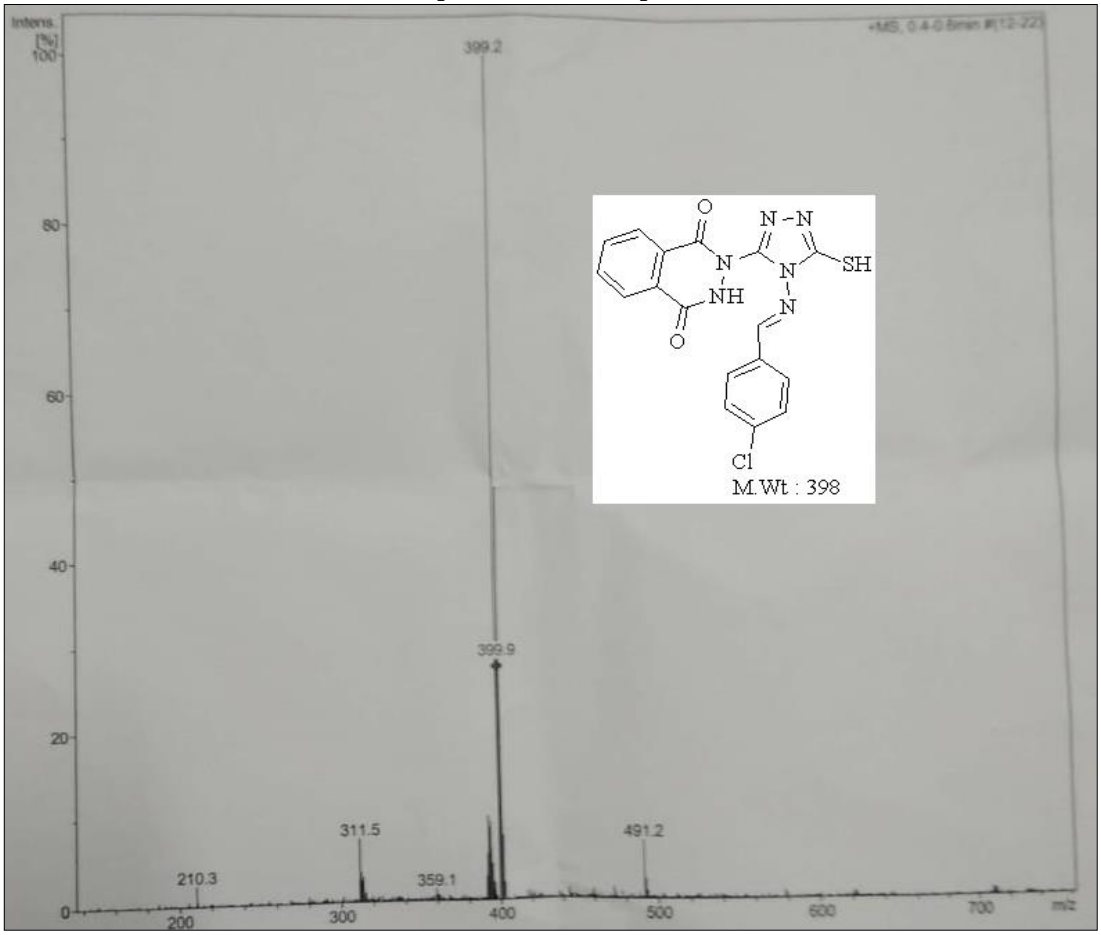
Mass Spectrum of compound **8g**



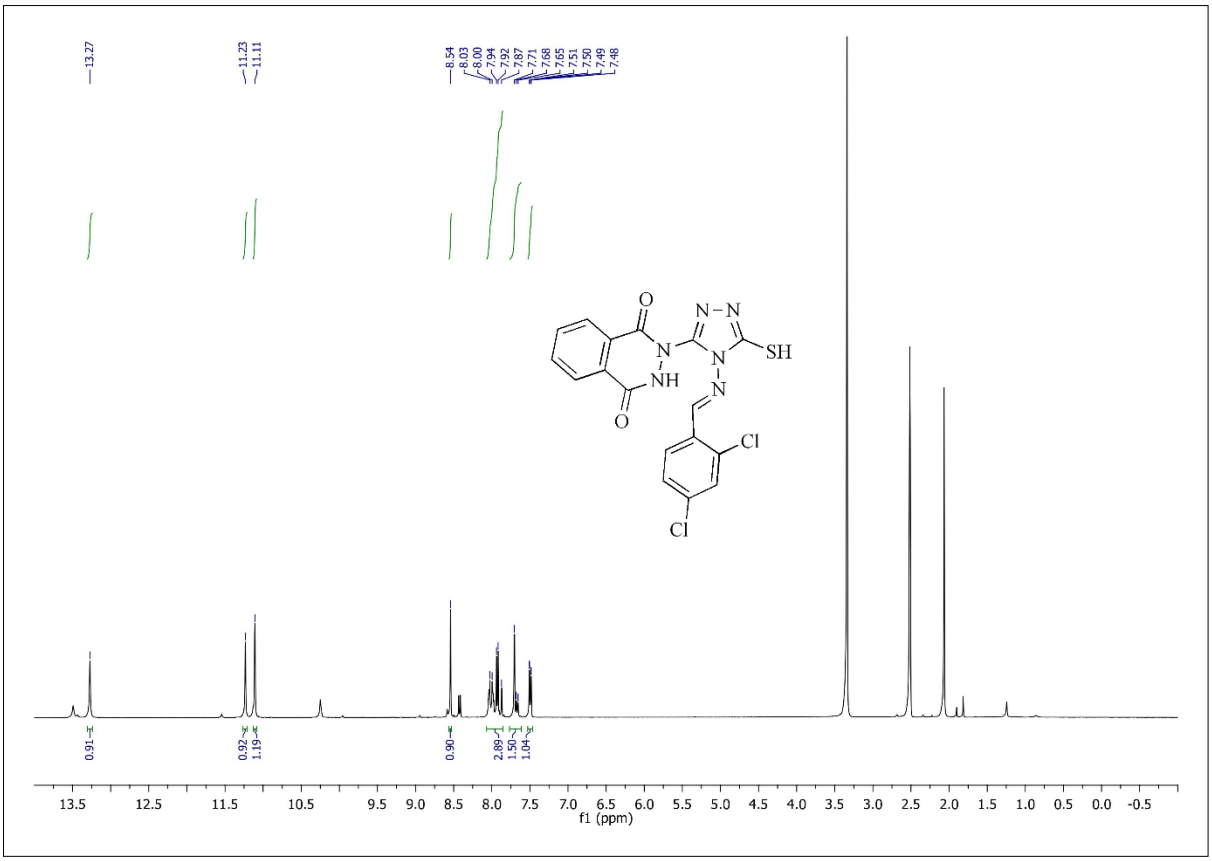
PMR Spectrum of compound **8h**



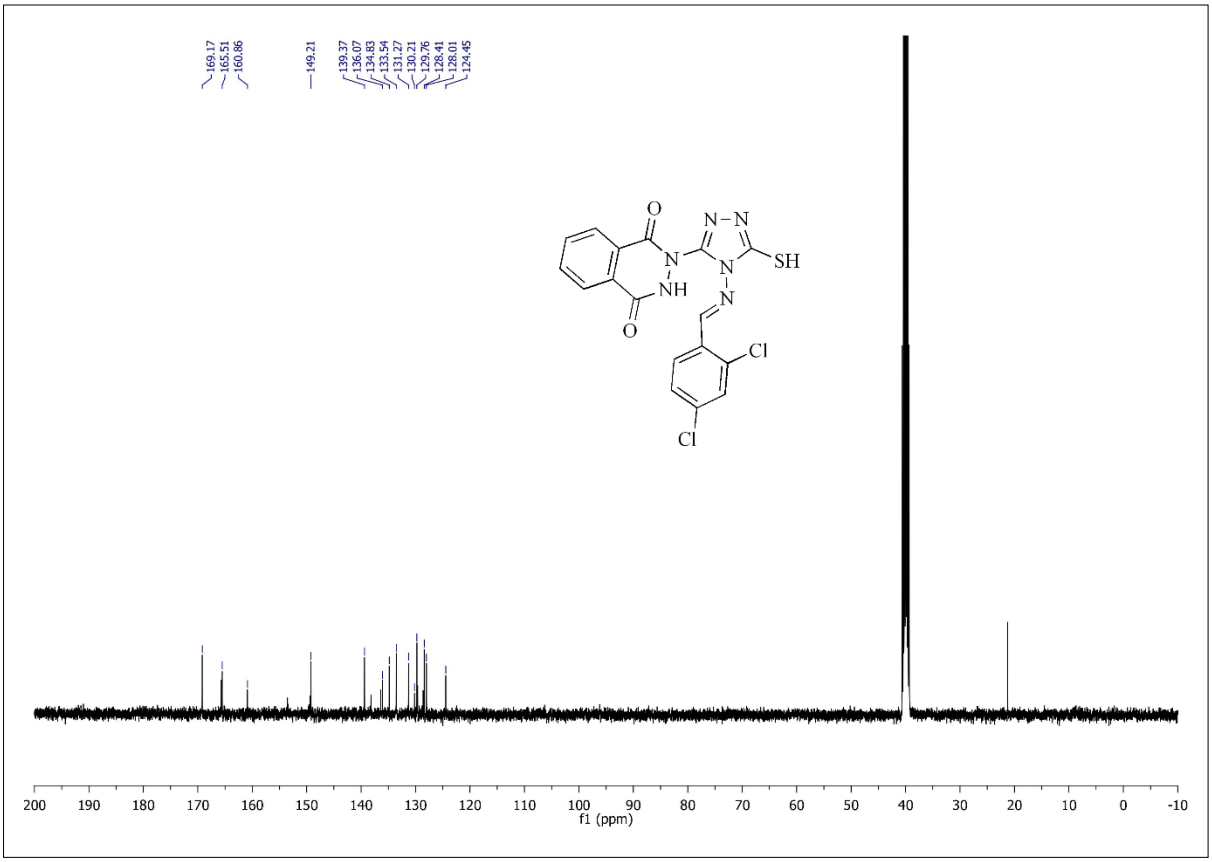
CMR Spectrum of compound **8h**



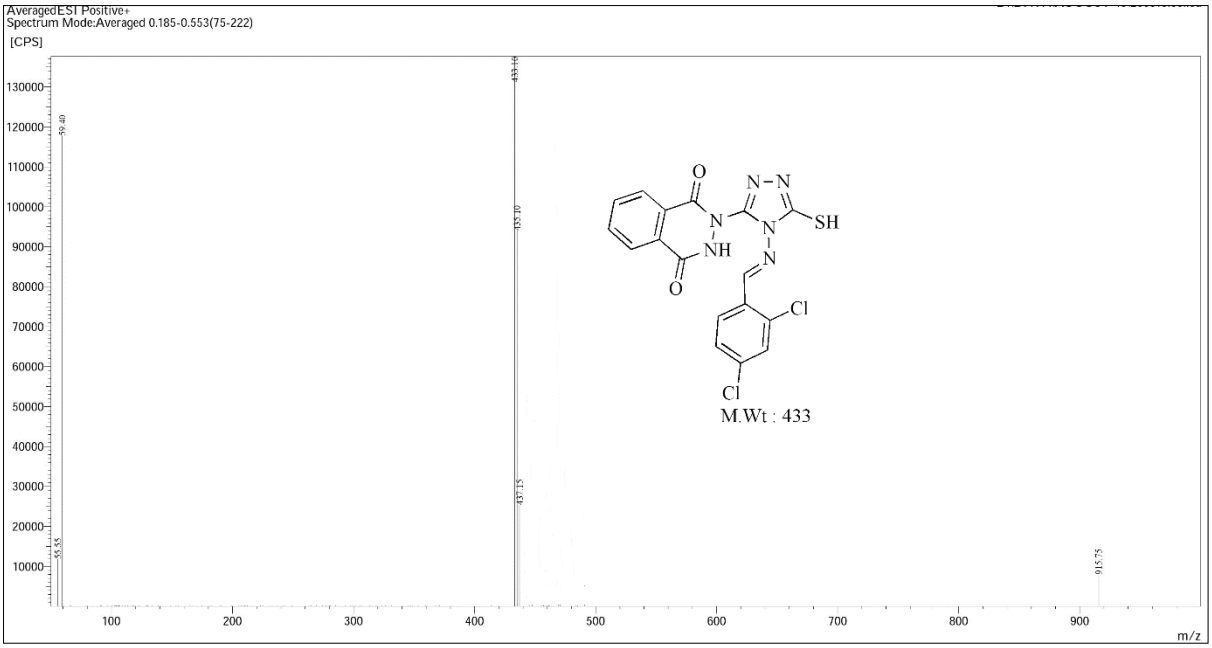
Mass Spectrum of compound **8h**



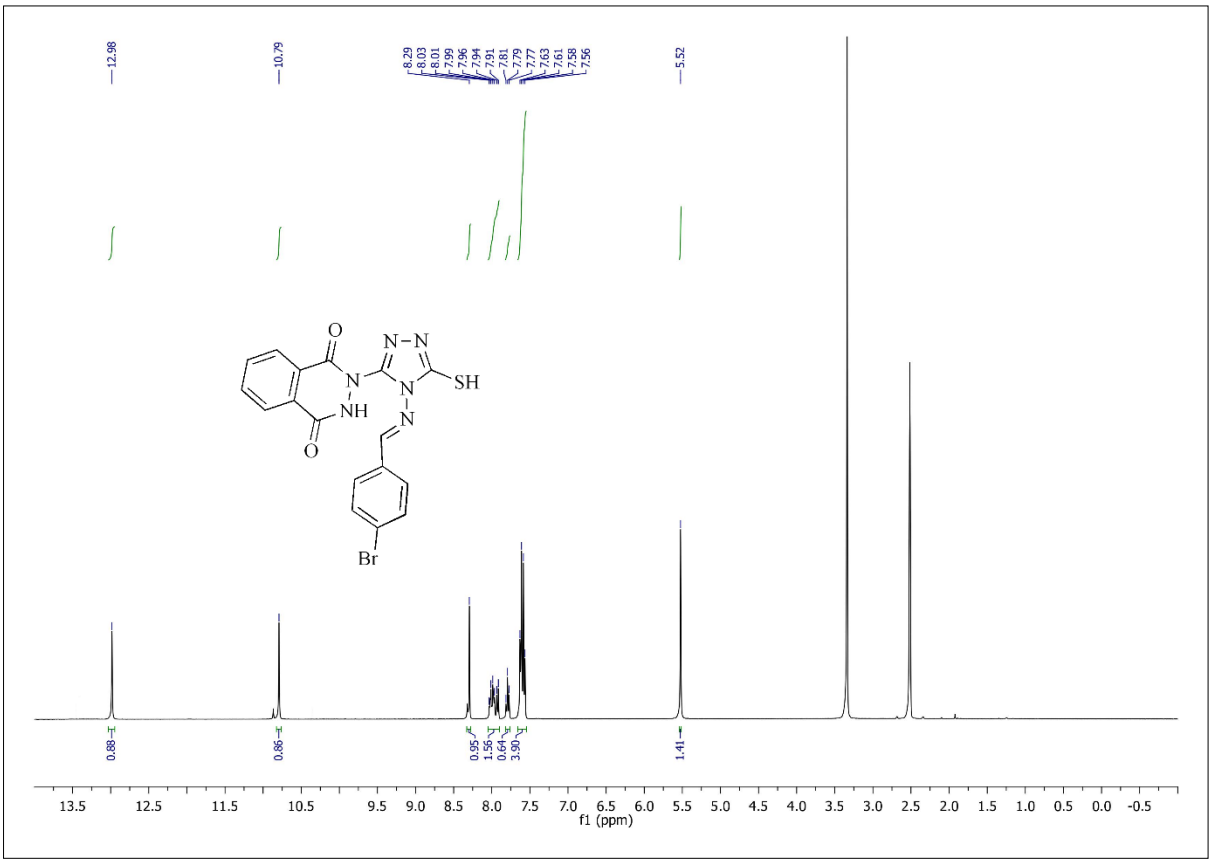
PMR Spectrum of compound **8i**



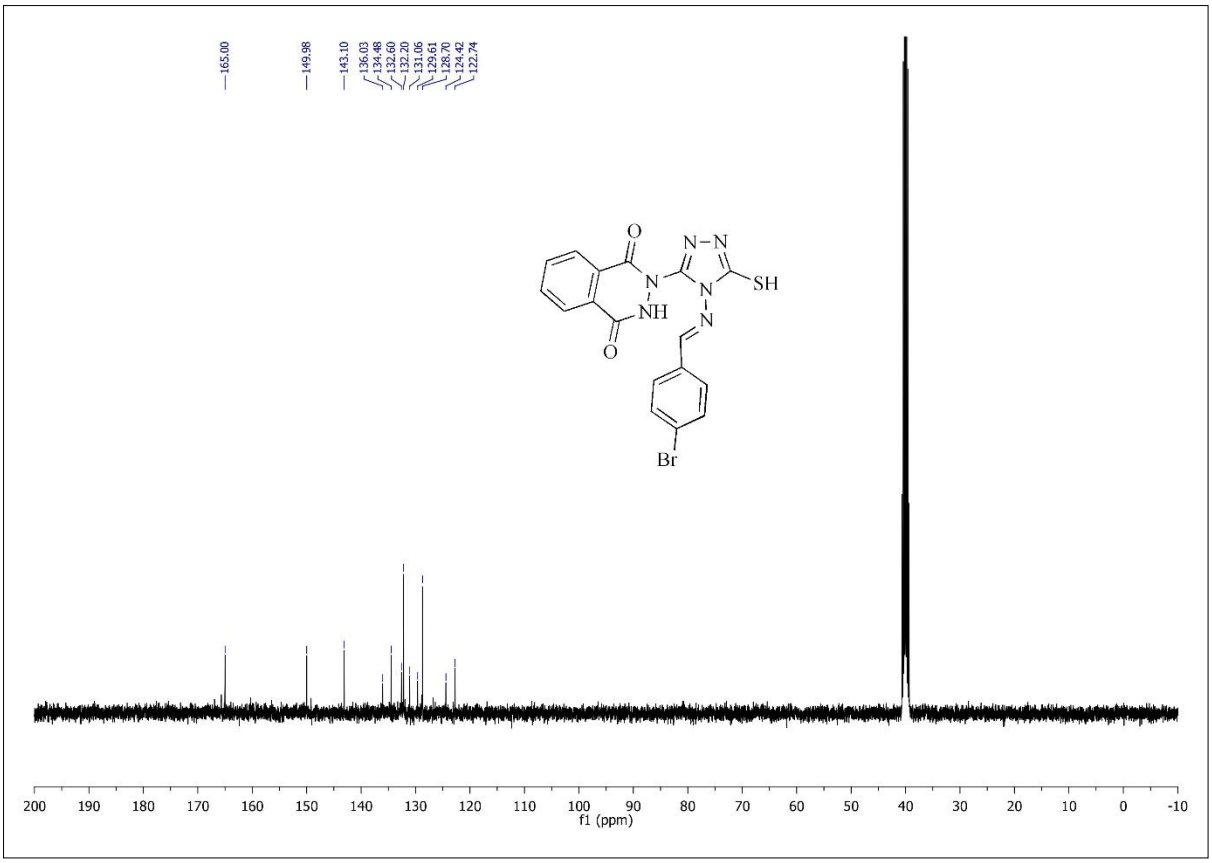
CMR Spectrum of compound **8i**



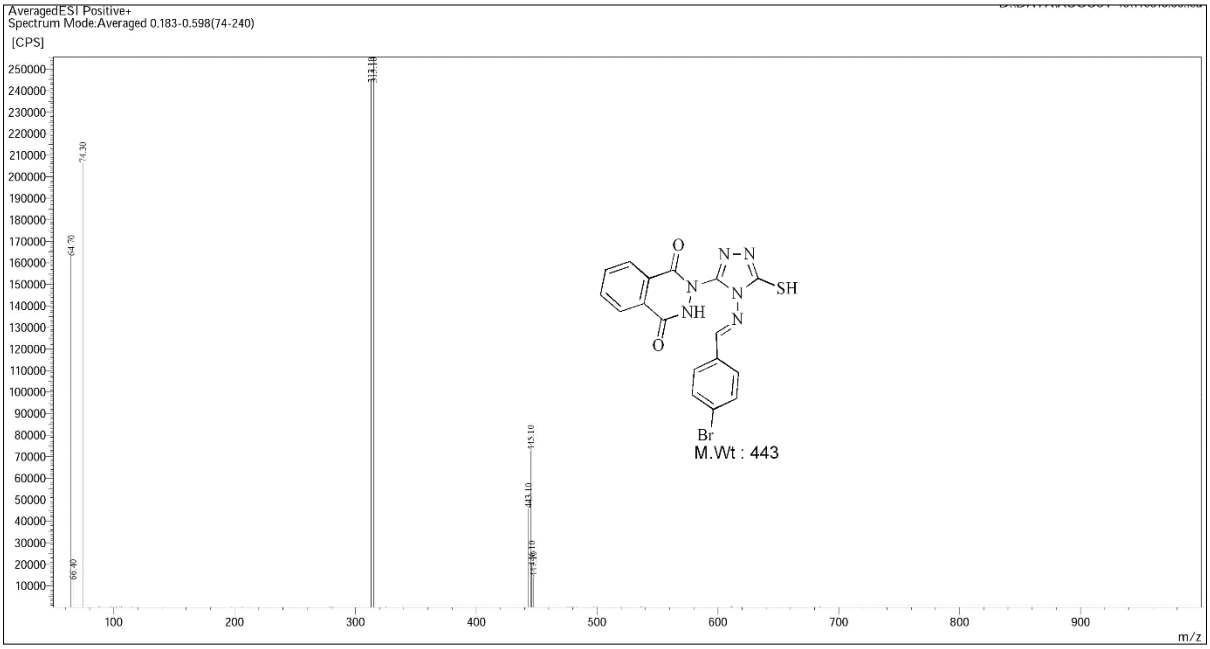
Mass Spectrum of compound **8i**



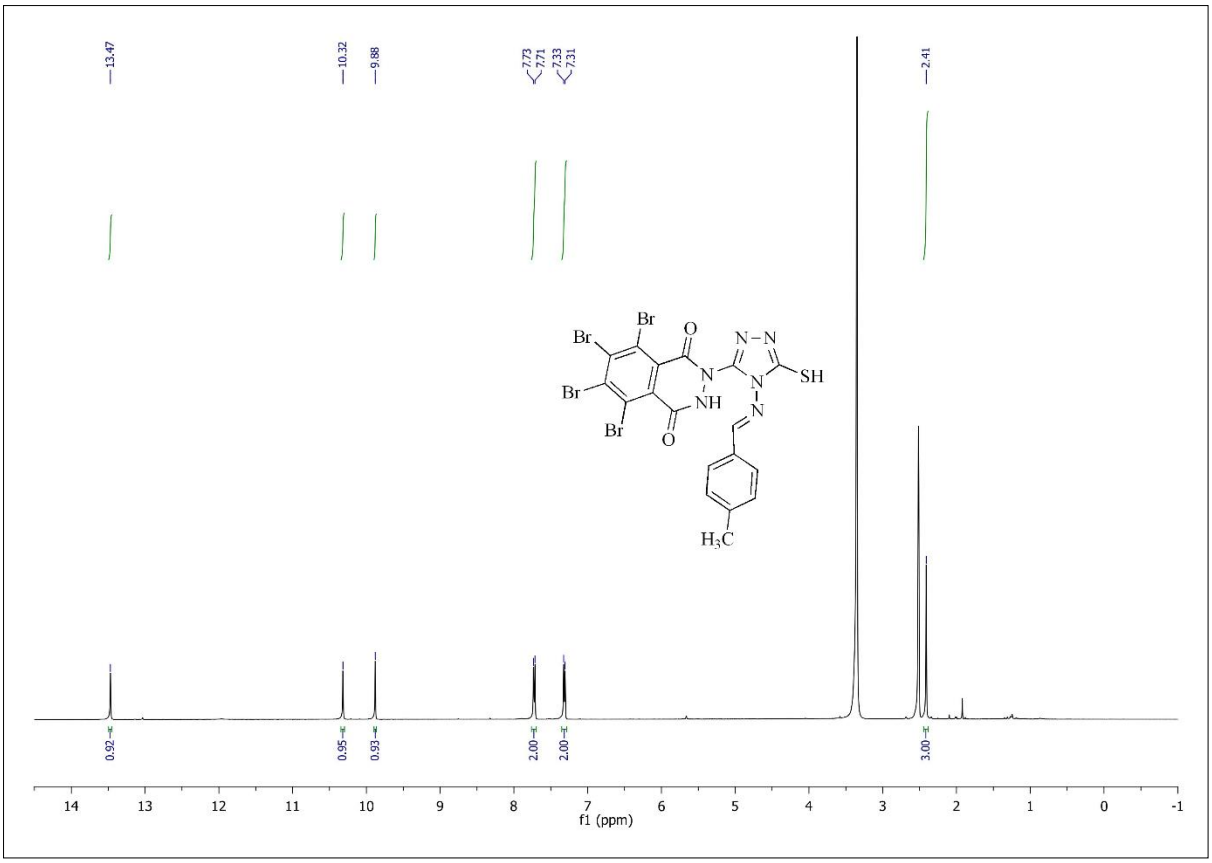
PMR Spectrum of compound **8j**



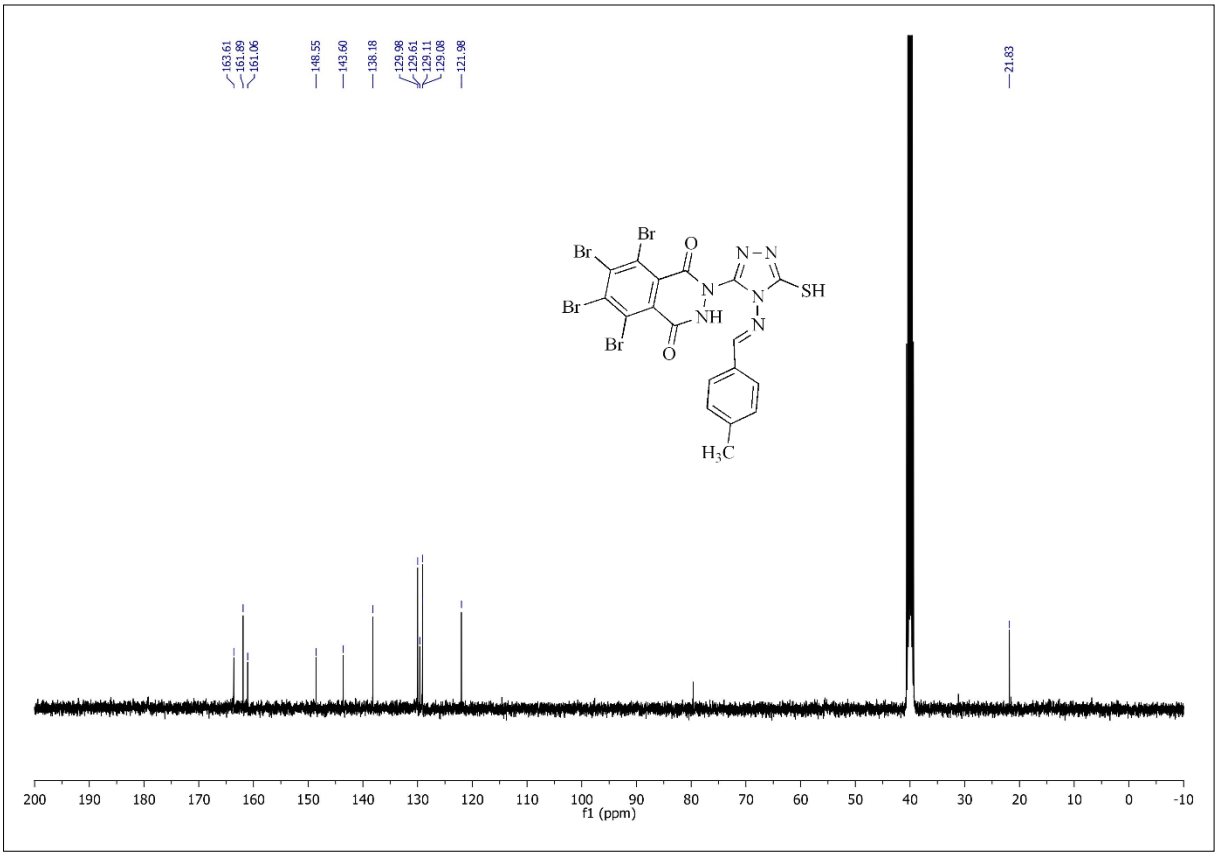
CMR Spectrum of compound **8j**



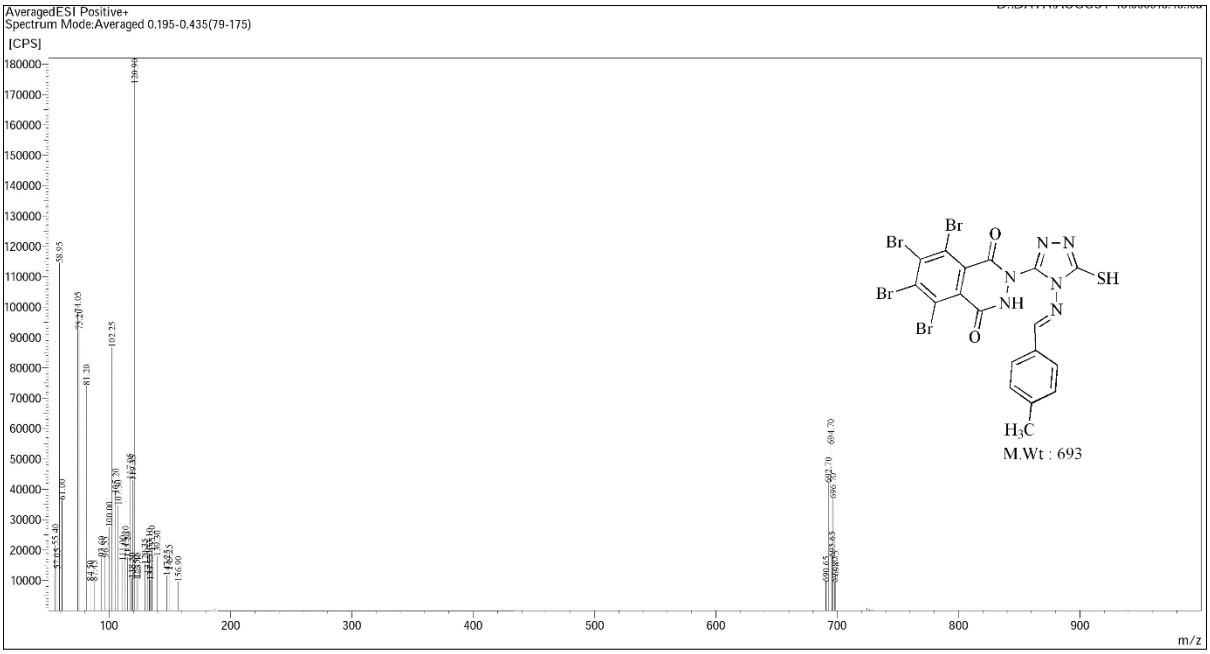
Mass Spectrum of compound **8j**



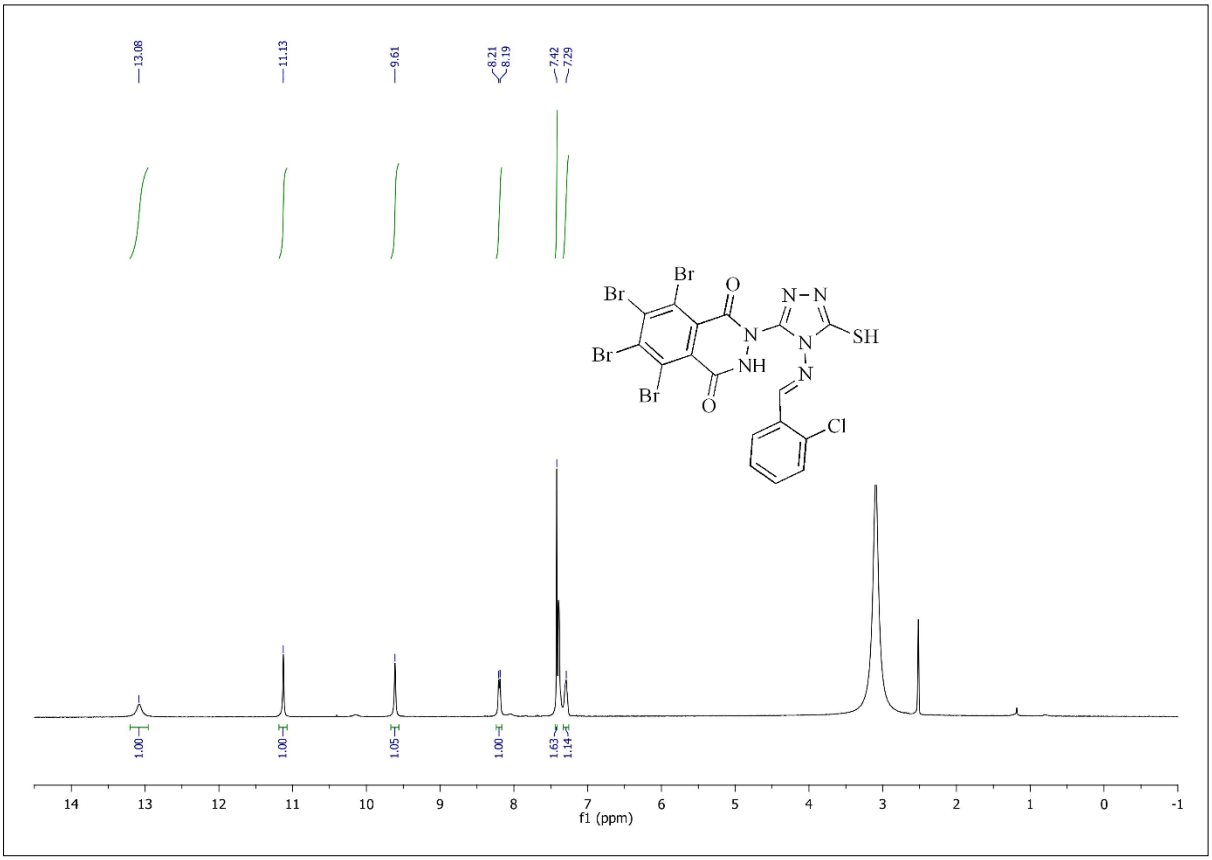
PMR Spectrum of compound **8k**



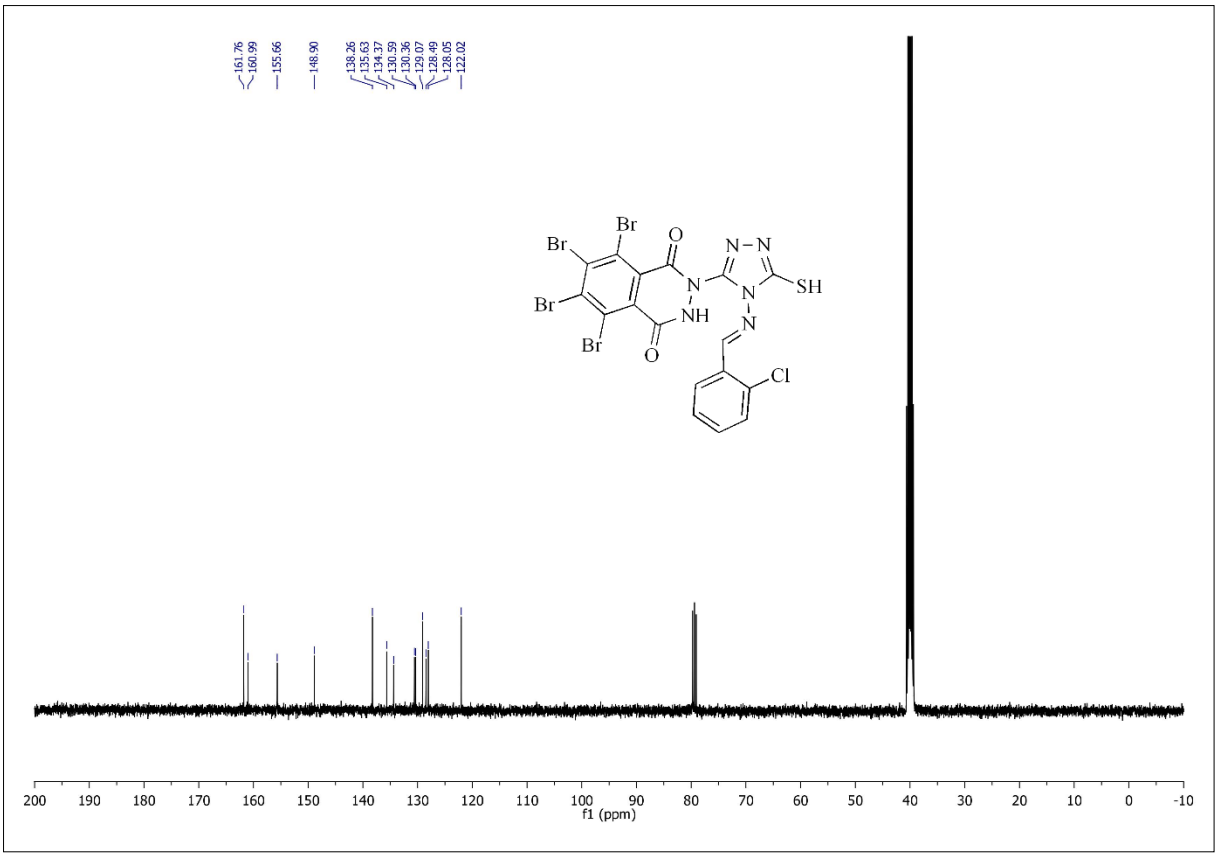
CMR Spectrum of compound **8k**



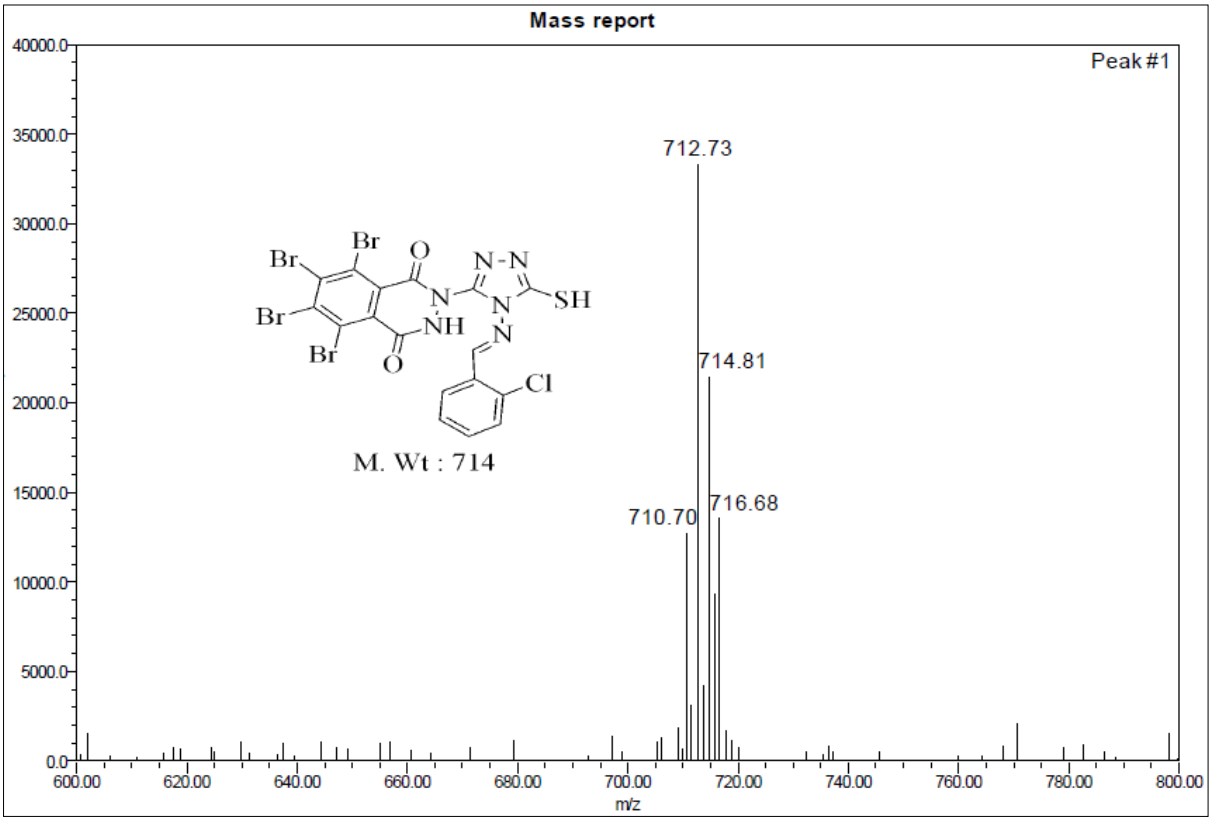
Mass Spectrum of compound **8k**



PMR Spectrum of compound **8l**



CMR Spectrum of compound **8l**



Mass Spectrum of compound **8l**

References:

[1] Vila, N.; Besada, P.; Costas, T.; Costas-Lago, M. C. Teran, C. *Eur. J. Med. Chem.* **2015**, *97*, 462-482.

[2] Teran, C.; Besada, P.; Vila, N.; Costas-Lago, M. C. *Eur. J. Med. Chem.* **2019**, *161*, 468-478.

[3] Sivakumar, R.; Gnanasam, S. K.; Ramachandran, S.; Leonard, J. T. *Eur. J. Med. Chem.* **2002**, *37*, 793-801.

[4] Liu, D. C.; Gong, G. H.; Wei, C. X.; Jin, X. J.; Quan, Z. S. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1576-1579.

[5] Xue, D. Q.; Zhang, X. Y.; Wang, C. J.; Ma, L. Y.; Zhu, N.; He, P.; Shao, K. P.; Chen, P. J.; Gu, Y. F.; Zhang, X. S.; Wang, C. F.; Ji, C. H.; Zhang, Q. R.; Liu, H. M. *Eur. J. Med. Chem.* **2014**, *85*, 235-244.

[6] Ibrahim, H. S.; Eldehna, W. M.; Abdel-Aziz, H. A.; Elaasser, M. M.; Abdel-Aziz, M. M. *Eur. J. Med. Chem.* **2014**, *85*, 480-486.

[7] Bian, M.; Deng, X. Q.; Gong, G. H.; Wei, C. X.; Quan, Z. S. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 792-800.

[8] Marzouk, M. I.; Shaker, S. A.; Hafiz, A. A. A.; El-Baghdady, K. Z. *Biol. Pharm. Bull.* **2016**, *39*, 239-251.

[9] Zhang, Q. R.; Xue, D. Q.; He, P.; Shao, K. P.; Chen, P. J.; Gu, Y. F.; Ren, J. L.; Shan, L. H.; Liu, H. M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1236-1238.

[10] Olmo, F.; Gomez-Contreras, F.; Navarro, P.; Marin, C.; Yunta, M. J. R.; Cano, C.; Campayo, L.; Martin-Oliva, D.; Rosales, M. J.; Sanchez-Moreno, M. *Eur. J. Med. Chem.* **2015**, *106*, 106-119.

[11] Munin, J.; Quezada, E.; Cuinas, A.; Campos-Toimil, M.; Uriarte, E.; Santana, L.; Vina, D. *Eur. J. Med. Chem.* **2014**, *82*, 407-417.

[12] Jalili-Baleh, L.; Nadri, H.; Moradi, A.; Bukhari, S. N. A.; Shakibaie, M.; Jafari, M.; Golshani, M.; Moghadam, F. H.; Firoozpour, L.; Asadipour, A.; Emami, S.; Khoobi, M.; Foroumadi, A. *Eur. J. Med. Chem.* **2017**, *139*, 280-289.

[13] Bayoumi, W. A.; Barghash, A. E. M.; Gineinah, M. M.; Massoud, M. A.; Abdelal, A. M. *Der Pharma Chemica.* **2014**, *6*, 89-102.

[14] Poli, D.; Catarzi, D.; Colotta, V.; Varano, F.; Filacchioni, G.; Daniele, S.; Trincavelli, L.; Martini, C.; Paoletta, S.; Moro, S. *J. Med. Chem.* **2011**, *54*, 2102-2113.

[15] Chunduru, V. S. R.; Vedula, R. R. *Chem Heterocycl Compd.* **2013**, *49*, 586-590.

[16] Cardia, M. C.; Distinto, S.; Maccioni, E.; Bonsignore, L.; DeLogu, A. *J. Heterocycl. Chem.* **2003**, *40*, 1011-1015.

[17] Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; Saal, W. V.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth, M. *J. Med. Chem.* **2011**, *54*, 312-319.

[18] Hamad, A. S.; Najem, R. S. *Tikrit J Pure Sci.* **2013**, *18*(3).

[19] Gao, D.; Jin, F.; Yan, X.; Zare, R. N. *Chem. Eur. J.* 10.1002/chem.201805585.

SUMMARY

The thesis is entitled **"Synthesis of New Heterocyclic Compounds using Multicomponent Approach"** and it consists of six chapters, out of which five chapters (**II/III/IV/V/VI**) deal with the synthesis of different heterocyclic compounds relying on the use of multicomponent approach as a common theme. The introduction part (**Chapter-I**) gives brief overview of multicomponent reactions, highlighting their applications in organic synthesis and their uses in the synthesis of biologically active compounds.

CHAPTER-I

A micro review on multicomponent condensation reactions and their uses in the synthesis of biologically active compounds

INTRODUCTION

A reaction in which three or more reactants[1] come together in a reaction vessel and forms a product which contains, portions of all the reactants is called multicomponent condensation reaction (MCR). The multicomponent reaction strategies offer significant advantages over conventional linear type of synthesis to provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry.[2,3] The multicomponent reaction can be carried out either in solid phase or in solution phase to achieve the target products in very fast and efficient manner without the isolation of any intermediate. As a result, it has been recognized as environmental friendly and acceptable from 'Green chemistry' perspective. It is obvious that the implementation of such strategies allows minimization of both waste production and expenditure of human labor.[4,5] In recent years, the discovery of novel protocols using multicomponent strategy has become an increasingly active area of research for generating new chemical scaffolds for drug discovery program,[6] bioactive molecules[7] and natural product synthesis.[8,9] Thus, we have selected the development of new methodologies by applying multicomponent strategy as our research program.

3-Acetyl coumarins,[10,11] phenacyl bromides,[12,13] 3-(2-bromoacetyl)coumarin,[14] 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol,[15] thiocarbohydrazide[16] and 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole[17] are key intermediates in the synthesis of heterocyclic systems. The reactivity of these key intermediates is also discussed.

In this research program, we have synthesized a number of heterocyclic molecules through multicomponent strategy and developed novel synthetic methodologies for these transformations successfully. The total research contribution is formatted into thesis.

Objectives of the present work are mentioned and outlines of the work carried out in the present investigations are given.

CHAPTER-II

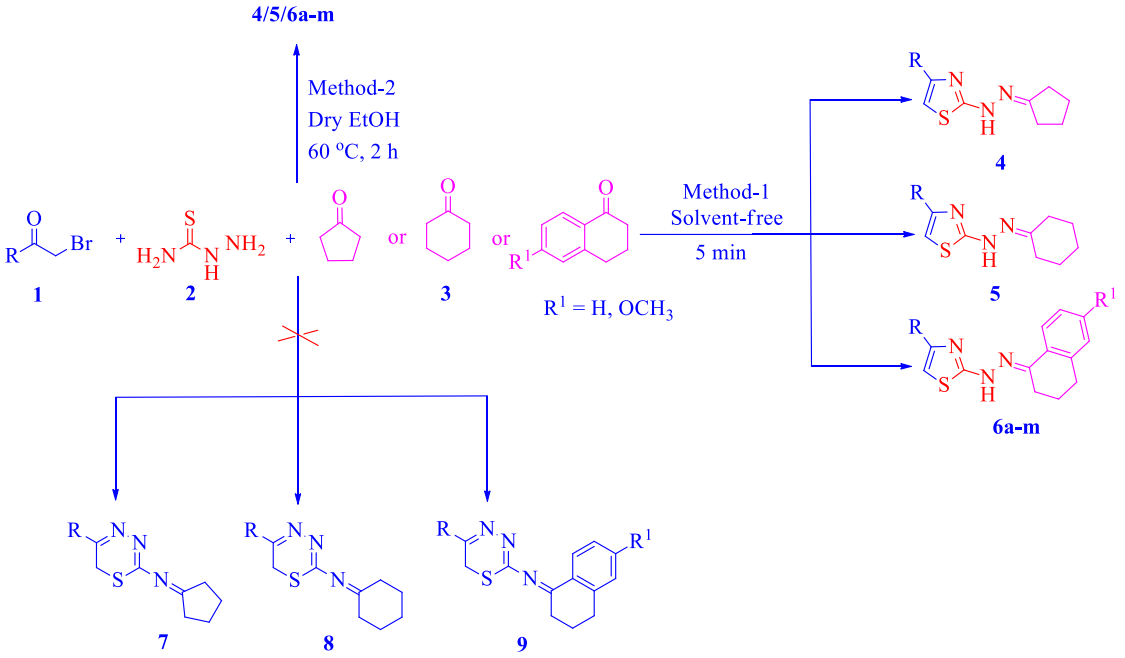
A NOVEL ONE-POT EXPEDITIOUS SYNTHESIS OF 2,4-DISUBSTITUTED THIAZOLES VIA A THREE COMPONENT REACTION UNDER SOLVENT-FREE CONDITIONS

This chapter includes a short review of related literature on the synthesis and importance of 2,4-disubstituted thiazoles.

A convenient one-pot method for the synthesis of 2,4-disubstituted thiazoles (**4/5/6a-m**) gave good to excellent yields. Cyclocondensation reaction of an equimolar amount of phenacyl bromide or 3-(2-bromoacetyl) coumarin, thiosemicarbazide and cyclic ketone under solvent-free conditions at room temperature afforded the corresponding 2,4-disubstituted thiazoles (**4/5/6a-m**).

In the one step solvent free synthesis (Scheme-1, method-1), it is believed that the phenacyl bromides or 3-(2-bromoacetyl)coumarin react with thiosemicarbazide to give the corresponding intermediate 2-hydrazino-4-substituted thiazoles followed by the reaction with cyclic ketones to afford the target compounds (**4**, **5** and **6**).

Scheme-1:



The alternative possible condensed products **(7)**, **(8)**, **(9)** from **(1)**, **(2)**, **(3)** can be rejected on the basis of the analytical and spectral data.

Entry	Product	R	R^1
1	4	Phenacyl	-
2	5	6,8-Dibromo-3-coumarinyl	-
3	6a	Phenacyl	H
4	6b	4-Bromo phenacyl	H
5	6c	4-Chloro phenacyl	H
6	6d	2,4-Dichloro phenacyl	H
7	6e	4-Nitro phenacyl	H
8	6f	6-Bromo-3-coumarinyl	H
9	6g	6,8-Dibromo-3-coumarinyl	H
10	6h	8-Methoxy-3-coumarinyl	H
11	6i	Phenacyl	6-OCH_3
12	6j	4-Chloro phenacyl	6-OCH_3
13	6k	4-Nitro phenacyl	6-OCH_3
14	6l	6,8-Dibromo-3-coumarinyl	6-OCH_3
15	6m	6-bromo-8-methoxy-3-coumarinyl	6-OCH_3

In conclusion, we have successfully synthesized a novel 2,4-disubstituted thiazoles via a multicomponent approach involving without solvent. The method had the advantages of mild reaction conditions, good to excellent yields, one-pot and operational simplicity.

CHAPTER-III

EFFICIENT MULTICOMPONENT SYNTHESIS OF NEW (*E*)-(3-(2-(4-METHOXYBENZYLIDENE)HYDRAZINYL)-6-(4-METHOXYPHENYL)-6,7-DIHYDRO-5*H*-[1,2,4]TRIAZOLO[3,4-*B*][1,3,4]THIADIAZIN-7-YL)(PHENYL)METHANONES AND A FACILE ONE-POT SYNTHESIS OF 3-(4-CHLOROPHENYL)-1-(6-PHENYL-7*H*-[1,2,4]TRIAZOLO[3,4-*B*][1,3,4]THIADIAZIN-3-YL)-1*H*-PYRAZOL-5-AMINES VIA MULTICOMPONENT APPROACH

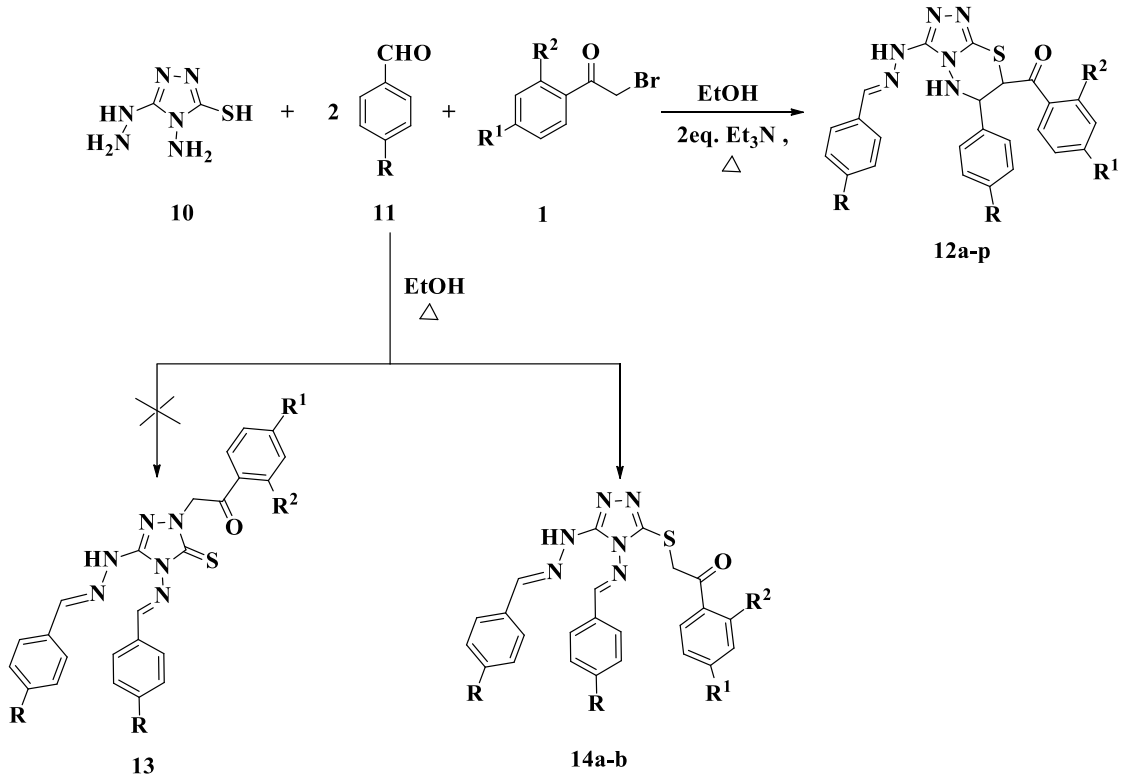
This chapter is divided into two sections.

SECTION-A

EFFICIENT MULTICOMPONENT SYNTHESIS OF NEW (*E*)-(3-(2-(4-METHOXYBENZYLIDENE)HYDRAZINYL)-6-(4-METHOXYPHENYL)-6,7-DIHYDRO-5*H*-[1,2,4]TRIAZOLO[3,4-*B*][1,3,4]THIADIAZIN-7-YL)(PHENYL)METHANONES

Condensation of purpald (**10**) with two equivalents of aromatic aldehydes (**11**) and various phenacyl bromides (**1**) in absolute ethanol and catalytic amount of Et_3N at 60 ^oC gave [1,2,4]triazolo[3,4]thiadiazines (**12a-p**) with good to excellent yields (Scheme-2). Similarly condensation of purpald (**10**) with two equivalents of aromatic aldehydes (**11**) and various phenacyl bromides gave corresponding Schiff bases (**14a-b**).

Scheme-2:



The alternative possible condensation products such as (**13)** from the reaction between (**10)**, (**11)** and (**1)** can be ruled out on the basis of their analytical and spectral data.

Entry	Product	R	R^1	R^2
16	12a	OCH_3	H	H
17	12b	OCH_3	Br	H
18	12c	OCH_3	Cl	H
19	12d	OCH_3	Cl	Cl
20	12e	OCH_3	F	H
21	12f	OCH_3	CH_3	H
22	12g	OCH_3	OCH_3	H
23	12h	OCH_3	NO_2	H
24	12i	CH_3	H	H
25	12j	CH_3	Br	H
26	12k	CH_3	Cl	H
27	12l	CH_3	Cl	Cl
28	12m	CH_3	F	H
29	12n	CH_3	CH_3	H
30	12o	CH_3	OCH_3	H
31	12p	CH_3	NO_2	H
32	14a	OCH_3	OCH_3	H
33	14b	OCH_3	F	H

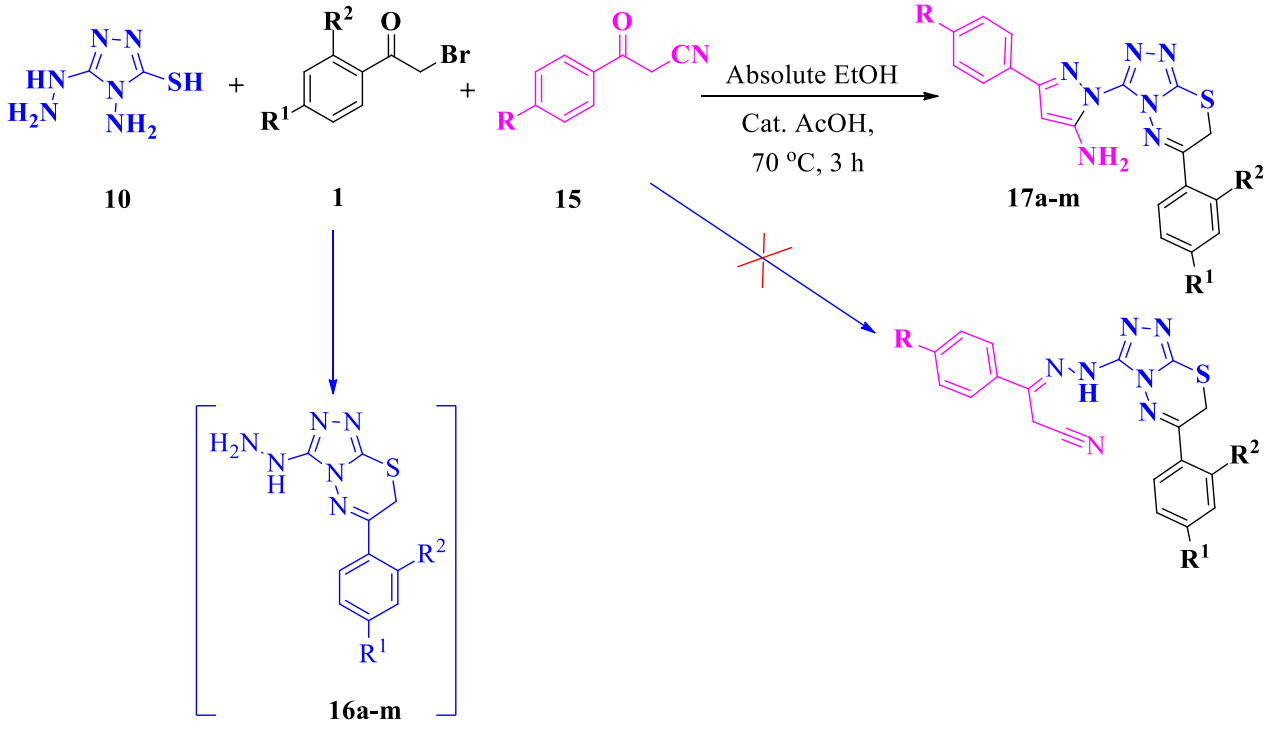
In summary, we described an efficient MCR for the synthesis of title compounds in a simple procedure. The speciality of this reaction is that it involves shorter reaction time, good yields, simple experimental conditions, easy work, operational simplicity and clean reaction profiles.

SECTION-B

A FACILE ONE-POT SYNTHESIS OF 3-(4-CHLOROPHENYL)-1-(6-PHENYL-7*H*-[1,2,4]TRIAZOLO[3,4-*B*][1,3,4]THIADIAZIN-3-YL)-1*H*-PYRAZOL-5-AMINES VIA MULTICOMPONENT APPROACH

Condensation of purpald (**10**) with phenacyl bromides (**1**) in ethanol, at 70 °C resulted in the formation of 3-hydrazinyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (**16a-m**). The *in situ* formed intermediate (**16**) reacts with phenacyl nitriles and one or two drops of acetic acid to afford the 3-(4-chlorophenyl)-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amines **(17a-m**) (Scheme-3). This reaction involves in the formation of fused triazolothiadiazine and pyrazole rings simultaneously in one pot operation.

Scheme-3:



Entry	Product	R	R^1	R^2
34	17a	Cl	H	H
35	17b	Cl	CH_3	H
36	17c	Cl	Cl	H
37	17d	Cl	F	H
38	17e	Cl	OCH_3	H
39	17f	H	H	H
40	17g	H	Br	H
41	17h	H	CH_3	H
42	17i	H	Cl	Cl
43	17j	H	F	H
44	17k	H	OCH_3	H
45	17l	Cl	Ph	H
46	17m	H	H	CH_3

3-(4-chlorophenyl)-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amines (**17a-m**) are obtained by using readily available starting materials. This synthetic method has more advantages such as shorter reaction time, no use of harsh reaction conditions, easy work up procedure and good to excellent yields of the products.

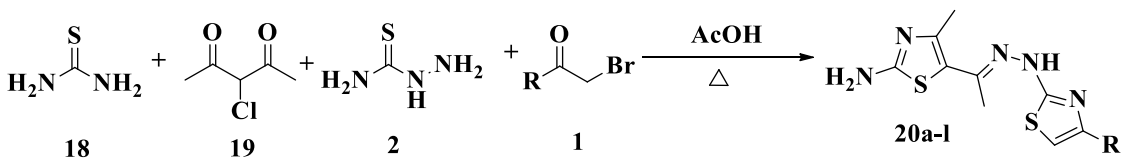
CHAPTER-IV

ONE-POT MULTICOMPONENT SYNTHESIS OF THIAZOLYL HYDRAZONO THIAZOLAMINES AND 1,3,4-THIADIAZINYL HYDRAZONO THIAZOLAMINES

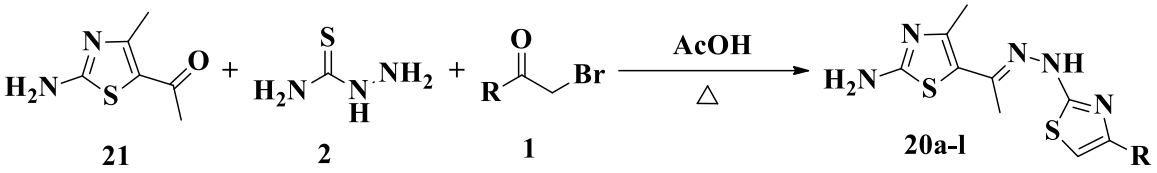
In this chapter a brief introduction to the synthetic methods of thiazolyl hydrazono thiazolamines and 1,3,4-thiadiazinyl hydrazono thiazolamines has been given.

The synthesis of thiazolyl hydrazono thiazolamines by a one-pot four component reaction has been reported by the condensation of thiourea, 3-chloroacetyl acetone, thiosemicarbazide and phenacyl bromide or 3-(2-bromoacetyl)coumarins in acetic acid (Scheme-4, method-1). In this method the intermediate formed in the first step 2-amino-4-methyl-5-acetyl thiazole reacts with thiosemicarbazide and phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones to give final products **20a-l**.

Scheme-4. Method-1: One-pot multicomponent synthesis of 20a-l. (Four component condensation)



Scheme-5. Method-2: Step wise or unambiguous synthesis of 20a-l. (A three component condensation)



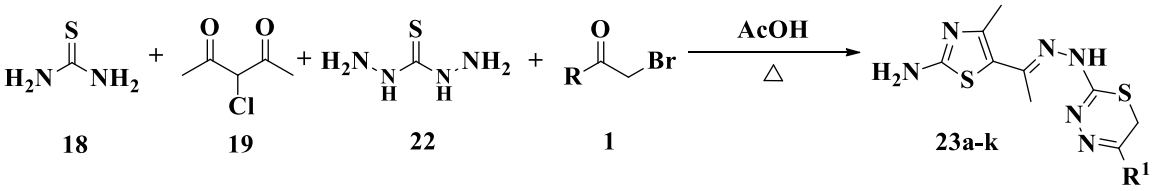
Entry	Product	R
47	20a	Phenacyl
48	20b	4-Fluoro phenacyl
49	20c	2,4-Dichloro phenacyl
50	20d	4-Bromo phenacyl
51	20e	4-Nitro phenacyl
52	20f	4-Methyl phenacyl
53	20g	4-Methoxy phenacyl
54	20h	3-Coumarinyl
55	20i	6-Bromo-3-coumarinyl
56	20j	6-Chloro-3-coumarinyl
57	20k	6,8-Dibromo-3-coumarinyl
58	20l	8-Methoxy-3-coumarinyl

Reaction of 2-amino-4-methyl-5-acetylthiazole, thiosemicarbazide, phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in acetic acid under reflux conditions gave the corresponding cycloproducts thiazolyl hydrazono thiazolamines (Scheme-5, method-2).

The yields of method-1 are good (93%) compared to method-2 (80%). The products obtained by both the methods are same on the basis of their mixed melting points, identical TLC and infrared spectra. In the present case first method was more preferable than second method. This is due to advantages in first method.

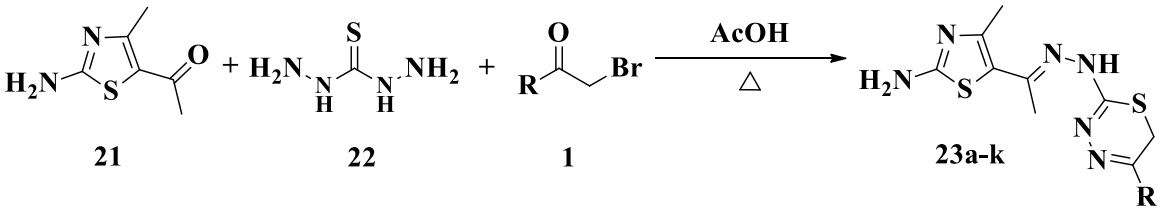
In a similar way, the synthesis of 1,3,4-thiadiazinyl hydrazono thiazolamines (**23**) was also described. Condensation of thiourea, 3-chloroacetyl acetone, thiocarbohydrazide, phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in acetic acid resulted in the formation of products **23** (Scheme-6, method-1).

Scheme-6. Method-1: One-pot multicomponent synthesis of 23a-k (Four component condensation)



Condensation of equimolar amounts of 2-amino-4-methyl-5-acetyl thiazole, thiocarbohydrazide and phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in acetic acid under reflux conditions gave the target products (**23**) (Scheme-7, method-2).

Scheme-7. Method-2: Stepwise or unambiguous synthesis of 23a-k (A three component condensation)



Entry	Product	R^1
59	23a	Phenacyl
60	23b	4-Nitro phenacyl
61	23c	4-Fluoro phenacyl
62	23d	2,4-Dichloro phenacyl
63	23e	4-Bromo phenacyl
64	23f	4-Methoxy phenacyl
65	23g	4-Phenyl phenacyl
66	23h	3-Coumarinyl
67	23i	6-Bromo-3-coumarinyl
68	23j	6,8-Dibromo-3-coumarinyl
69	23k	8-Methoxy-6-nitro-3-coumarinyl

The products formed by both the methods were found to be same on checking melting points, co-TLC and infrared spectra. In the present study method-1 was preferable over method-2. This is due to advantages in method-1. The structures of new products were established based on their spectra.

In gist, we have developed novel thiazolyl hydrazono thiazolamines and 1,3,4-thiadiazinyl hydrazono thiazolamines via a one pot multi component approach. The method had the advantages of mild reaction conditions, easy work up, no column chromatographic purification and good to better yields.

CHAPTER-V

ONE-POT, FIVE COMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(2-((*E*)-2-(1-(4-METHYL-2-(PHENYLAMINO)THIAZOL-5YL)ETHYLIDENE)HYDRAZINYL)-4-OXOTHIAZOL-5(4*H*)-YLIDENE)ACETATES AND ONE POT MULTICOMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(4-OXO-2-((*E*)-2-((3-(2-OXO-2*H*-CHROMEN-3-YL)-1-PHENYL-1*H*-PYRAZOL-4-YL)METHYLENE)HYDRAZINYL)THIAZOL-5(4*H*)-YLIDENE)ACETATES

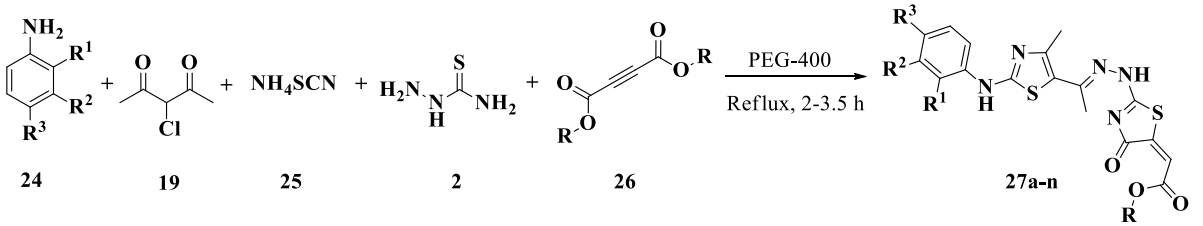
This chapter is divided into two sections.

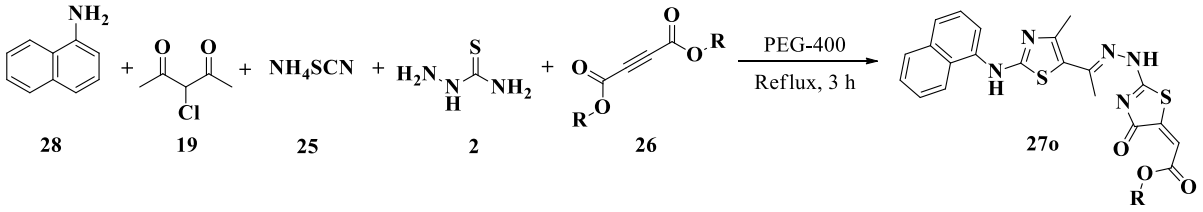
SECTION-A

ONE-POT, FIVE COMPONENT SYNTHESIS OF (*E*)-ETHYL2-(2-((*E*)-2-(1-(4-METHYL-2-(PHENYLAMINO)THIAZOL-5YL)ETHYLIDENE)HYDRAZINYL)-4-OXOTHIAZOL-5(4*H*)-YLIDENE)ACETATES

Reaction of one mole of each aromatic amine, ammonium thiocyanate, 3-chloroacetylacetone in polyethylene glycol under reflux condition afforded **28** as an intermediate (not isolated). Later on addition of one mole of each thiosemicarbazide and dialkylacetylene dicarboxylate under reflux gave target compounds with good yields (scheme-8 and 9). This is a five component condensation reaction to produce highly functionalized thiazolothiazolidinones.

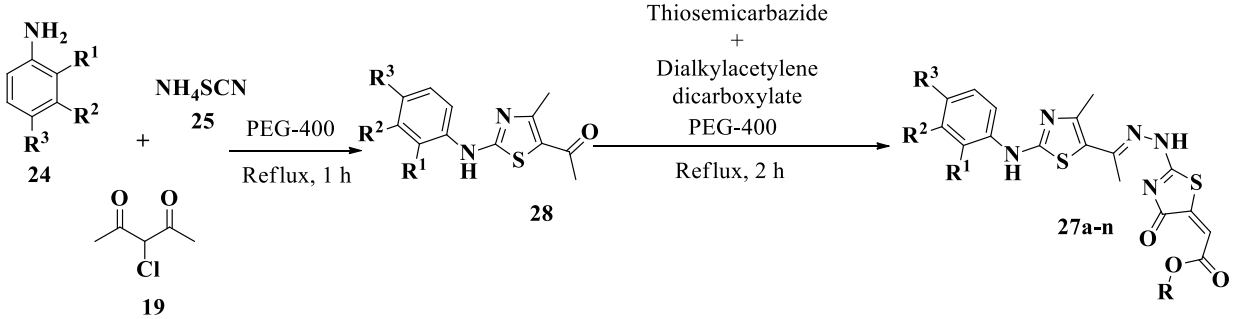
Scheme-8. Method-1: One pot multicomponent synthesis of compounds 27a-o





Condensation of 2-arylamino-4-methyl-5-acetyl thiazoles with thiosemicarbazide and dialkylacetylene dicarboxylates resulted in the formation of products **27a-n**.

Scheme-9: Method-2. Stepwise or unambiguous synthesis of 27a-n (A three component condensation).



Entry	Product	R	R^1	R^2	R^3
70	27a	OEt	H	H	H
71	27b	OEt	H	H	CH_3
72	27c	OEt	CH_3	CH_3	H
73	27d	OEt	H	OCH_3	H
74	27e	OEt	H	H	OCH_3
75	27f	OEt	H	OH	H
76	27g	OEt	H	Cl	H
77	27h	OEt	H	H	Cl
78	27i	OEt	H	NO_2	H
79	27j	OCH_3	H	H	H
80	27k	OCH_3	H	OCH_3	H
81	27l	OCH_3	H	OH	H
82	27m	OCH_3	H	Cl	H
83	27n	OCH_3	H	H	Cl
84	27o	OCH_3	-	-	-

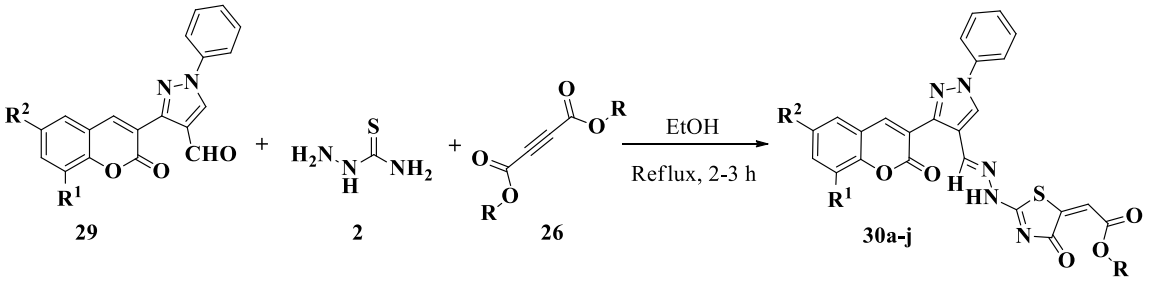
We have achieved a straight forward one-pot five component synthesis of **27** using PEG-400 as a greener solvent with high yields. Several specialities of this domino reaction are less time, metal-free, easy work up, no columns chromatography application, utilisation of no hazardous organic solvents, ease of recovery of solvent and its reuse.

SECTION-B

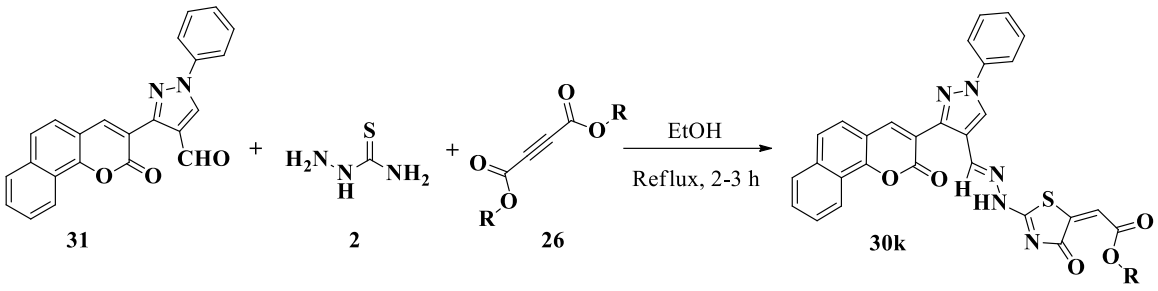
ONE POT MULTICOMPONENT SYNTHESIS OF (*E*)-ETHYL 2-(4-OXO-2-((*E*)-2-((3-(2-OXO-2*H*-CHROMEN-3-YL)-1-PHENYL-1*H*-PYRAZOL-4-YL)METHYLENE)HYDRAZINYL)THIAZOL-5(4*H*)-YLIDENE)ACETATES.

Condensation of 1-phenyl-3-(2*H*-1-benzopyran-2-one-3yl)-4-formylpyrazole with thiosemicarbazide and dialkylacetylene dicarboxylates in dry ethanol under reflux led to the formation of title compounds in good to excellent yields as shown in scheme-10.

Scheme-10:



29 2 26 30a-j



31 2 26 30k

Entry	Product	R	R^1	R^2
85	30a	OEt	H	H
86	30b	OEt	H	Cl
87	30c	OEt	H	Br
88	30d	OEt	OCH_3	H
89	30e	OEt	OEt	H
90	30f	OCH_3	H	H
91	30g	OCH_3	H	Cl
92	30h	OCH_3	H	Br
93	30i	OCH_3	OCH_3	H
94	30j	OCH_3	OEt	H
95	30k	OCH_3	Naphthyl	-

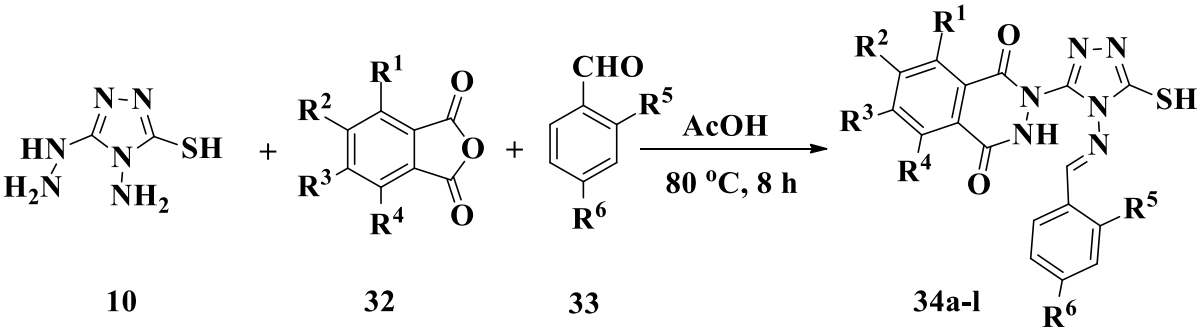
The advantages of the above reactions are operational simplicity, green solvent medium, mild reaction condition, easy workup procedure, no column chromatography for the purification of compounds, good to excellent yields and catalyst-free conditions.

CHAPTER-VI

SYNTHESIS OF (*E*)-2-(BENZYLIDENEAMINO)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-3-YL)-2,3-DIHYDROPHTHALAZINE-1,4-DIONES THROUGH ONE-VESSEL MULTICOMPONENT METHOD.

Reaction of purpald, phthalic anhydride and aromatic aldehyde in acetic acid gave the final products (*E*)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-diones (Scheme-11) with good yields.

Scheme-11:



10 32 33 34a-l

Entry	Product	R^1	R^2	R^3	R^4	R^5	R^6
96	34a	H	H	H	H	H	CH_3
97	34b	H	H	H	H	H	OCH_3
98	34c	H	H	H	H	H	OH
99	34d	H	H	H	H	OH	OEt
100	34e	H	H	H	H	H	CN
101	34f	H	H	H	H	H	F
102	34g	H	H	H	H	Cl	H
103	34h	H	H	H	H	H	Cl
104	34i	H	H	H	H	Cl	Cl
105	34j	H	H	H	H	H	Br
107	34k	Br	Br	Br	Br	H	CH_3
108	34l	Br	Br	Br	Br	Cl	H

The reaction gave good to excellent yields and all the products were purified by recrystallization.

REFERENCES

[1] Gonzalez-Olvera, R.; Roman-Rodriguez, V.; Negron-Silva, G. E.; Espinoza-Vazquez, A.; Rodriguez-Gomez, F. J.; Santillan, R. *Molecules.* **2016**, 21, 250.

[2] Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759-3762.

[3] Mironov, M. A. *Russ. J. Gen. Chem.* **2010**, *80*, 2628-2646.

[4] Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958-2975.

[5] Carranco, I.; Diaz, J. L.; Jimenez, O.; Vendrell, M.; Albericio, F.; Royo, M.; Lavilla, R. *J. Comb. Chem.* **2005**, *7*, 33-41.

[6] Slobbe, P.; Ruijter, E.; Orru, R. V. A. *Med. Chem. Commun.* **2012**, *3*, 1189-1218.

[7] Rossen, K. Pye, P. J.; DiMichelc, L. M.; Volante, R. P.; Reider, P. L. *Tetrahedron Lett.* **1998**, *39*, 6823-6826.

[8] Nandaluru, P. R.; Bodwell, G. J. *Org. Lett.* **2012**, *14*, 310-313.

[9] Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594-1595.

[10] Aggarwal, R.; Kumar, S.; Kaushik, P.; Kaushik, D.; Gupta, G. K. *Eur. J. Med. Chem.* **2013**, *62*, 508-514.

[11] Arshad, A.; Osman, H.; Bagley, M. C.; Lam, C. K.; Mohamad, S.; Zahariluddin, A. S. M. *Eur. J. Med. Chem.* **2011**, *46*, 3788-3794.

[12] Sket, B.; Zupan, M. *Synth. Commun.* **1989**, *19*, 2481-2487.

[13] Jiang, Q.; Sheng, W.; Guo, C. *Green Chem.* **2013**, *15*, 2175-2179

[14] Rajeswar Rao, V.; Padmanabha Rao, T. V. *Indian J. Chem.* **1986**, *25B*, 413.

[15] Amer, A. A.; Moustafa, A. H. *Synlett.* **2016**, *27*, 1703-1706.

[16] Audrieth, L. F.; Scott, E. S.; Kippur, P. S. *J. Org. Chem.* **1954**, *19*, 733-741.

[17] Srikrishna, D.; Dubey, P. K. *Der Pharma Chemica.* **2014**, *6*, 57-60.

PUBLICATIONS

LIST OF PUBLICATIONS

1. **Kodam Sujatha,** Rajeswar Rao Vedula*, Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three component reaction under solvent free conditions, *Synth. Commun.* **2018**, *48*, 302–308.
2. **Kodam Sujatha,** Ravindra Pramod Deshpande, Rajesh Kumar Kesharwani, Phanithi Prakash Babu and Rajeswar Rao Vedula*, An efficient one-pot expeditious synthesis of 3-phenyl-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1H-pyrazol-5-amines via multicomponent approach, *Synth. Commun.* **2019**, *49*, 49–55.
3. **Kodam Sujatha,** Rajeswar Rao Vedula*, Multicomponent Efficient Synthesis of New [1,2,4]Triazolo[3,4]thiadiazines, *J. Heterocycl. Chem.* **2019,** *56*, 832-838.
4. **Kodam Sujatha,** Rajeswar Rao Vedula*, Polyethylene glycol (PEG-400) promoted one-pot five-component synthesis of (*E*)-ethyl-2-(2-((*E*)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl)ethylidene)hydrazinyl-4-oxothiazol-5(4*H*)-ylidene)acetates, *Mol. Divers.* **2019,** 1-9. DOI:10.1007/s11030-019-09962-3
5. Bade Thirupaiah, **Kodam Sujatha,** Rajeswar Rao Vedula*, One pot multicomponent synthesis of 4-hydroxy-6-methyl -3-(3-pheylthiazolo[2,3-*c*][1,2,4]triazol-5-yl)-2*H*-pyran-2-ones, *Indian J Chem.* **2017**, *56B*, 1089-1093.
6. **Kodam Sujatha,** Naidu Babu Ommi, Anwita Mudiraj, Phanithi Prakash Babu* and Rajeswar Rao Vedula*, Synthesis of thiazolyl hydrazono thiazolamines and 1,3,4-thiadiazinyl hydrazono thiazolamines as a class of anti-malarial agents, *Arch Pharm Chem Life Sci.***2019**. DOI: 10.1002/ardp.201900079.
7. **Kodam Sujatha,** Rajeswar Rao Vedula*, Novel one-pot multicomponent synthesis of (*E*)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives, *Synth. Commun. 50,* 129–135. DOI: 10.1080/00397911.2019.1689571
8. **Kodam Sujatha,** Bade Thirupaiah, Rajeswar Rao Vedula*, An efficient one pot multicomponent synthesis of coumarino pyrazolyl thiazolidinones, *J. Heterocycl. Chem.* (under review, 2019)**.**

PRESENTATION & PARTICIPATION IN SYMPOSIA

1. Presented a poster in National Conference on "**Emerging Trends in Instrumental Methods of Chemical Analysis (ETIMCA)-2019**" 30th-31th January **2019**, held at Department of Chemistry, **National Institute of Technology Warangal**.
2. Presented a poster in Conference on "**Innovations in pharmaceutical Technologies & Workshop on GLP/GMP Compliance (IPT)-2019**" 24th-25th January **2017**, held at **National Institute of Pharmaceutical Education and Research (NIPER)**, Balanagar, Hyderabad.
3. Presented a paper in National Seminar on "**Recent Trends and Challenges in Chemical Sciences (RTCCS)**" 24th-25th March **2017**, held at Department of Chemistry, **Kakatiya University,** Warangal.
4. Participated in the One day National Conference on "**Recent Advances in Organic Synthesis**" 29th June **2016**, held at Department of Chemistry, **National Institute of Technology Warangal**.
5. Participated in the One day National Conference on "**Recent Advances in Organic Synthesis**" 29th June **2016**, held at Department of Chemistry, **National Institute of Technology,** Warangal.
6. Participated in one day Workshop on "**Waste Water Treatment Technologies**" 24th July **2016**, held at Department of Chemical Engineering, **National Institute of Technology,** Warangal.
7. Presented a paper in National Seminar on "**Green Chemistry for Sustainable Development (GCSD)**" 6th-7th April **2017**, held at Department of Chemistry, **Government Degree College, Jammikunta**, Dist. Karimnagar.
8. Presented a poster in National Conference on "**Recent Developments in Chemical Sciences and Allied Technology**" 29th-30th June **2017**, held at Department of Chemistry, **National Institute of Technology,** Warangal.
9. Presented a poster in "**21st CRSI National Symposium in Chemistry-2017**" 14th-16th July **2017**, held at **CSIR-Indian Institute of Chemical Technology,** Hyderabad.

10. Participated in a one week faculty development workshop on "**Teaching and Learning Chemical Spectroscopy through Hands-On Experience**" 11th-16th September **2017**, held at Department of Chemistry, **National Institute of Technology,** Warangal.
11. Presented a paper in "**Research Conclave'17"** 19th March **2017**, held at **National Institute of Technology,** Warangal.
12. Presented a poster in "**International Conference on Advanced Functional Materials (ICAFM)-2017**" 18th-20th December **2017**, held at RGUKT, Basar.
13. Participated in a Two day workshop on "**Research Methodology and Scholarly Writing Skills**" 25th-26th January **2014**, organized by the SC/ ST Cell, **National Institute of Technology,** Warangal.
14. Participated in a Two day workshop on "**Bioinformatics and its Applications (BAIA-2014)**" 3rd-4th April **2014**, organized by Department of Bio Technology, **National Institute of Technology,** Warangal.
15. Participated in the National Seminar on "**Recent Advances in Chemistry (RAC-2015)**" 30th-31th March **2015**, held at Department of Chemistry, **Kakatiya University,** Warangal.
16. Presented a paper in National Conference on "**Drug Discovery and Development in Chemistry-Applications in Pharma Industry (DDDC-2015)**" 14th-15th September **2015**, held at Department of Chemistry, **Sri Venkateswara University**, Tirupati.
17. Participated in the 7th IEEE International Conference on "**Technology for Education (T4E 2015)**" 10th-12th December **2015**, organized by **National Institute of Technology,** Warangal.
18. Presented a paper in National Conference on "**Frontiers in Chemical Sciences and Technologies (FCST)**" 28th-29th January **2016**, held at Department of Chemistry, **National Institute of Technology,** Warangal.

Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three-component reaction under solvent free conditions

Kodam Sujatha & Rajeswar Rao Vedula

To cite this article: Kodam Sujatha & Rajeswar Rao Vedula (2018) Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three-component reaction under solvent free conditions, Synthetic Communications, 48:3, 302-308, DOI: 10.1080/00397911.2017.1399422

To link to this article: https://doi.org/10.1080/00397911.2017.1399422

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 3, 302–308
https://doi.org/10.1080/00397911.2017.1399422

Taylor & Francis
Taylor & Francis Group

Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three-component reaction under solvent free conditions

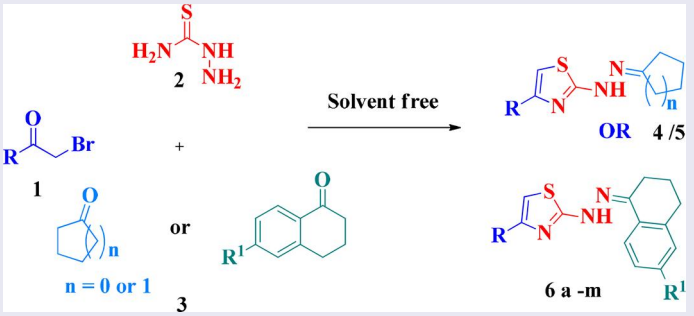
Kodam Sujatha and Rajeswar Rao Vedula

Department of Chemistry, National Institute of Technology, Warangal, India

ABSTRACT

An expeditious one pot method has been developed for the synthesis of 2,4-disubstituted thiazoles under solvent free conditions via a multicomponent approach. Substituted thiazoles were synthesized with high yields by the reaction of cyclic ketones, thiosemicarbazide, and phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in a shorter reaction time with high purity via simple purification technique.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 6 September 2017

KEYWORDS
2,4-Disubstituted thiazoles; cyclic ketones; cyclocondensation; multicomponent reactions; phenacyl bromides; thiosemicarbazone

Introduction

Multicomponent reactions are simple efficient,[1] convergent, diversity oriented reactions,[2,3] in which three are more reactants come together in a single reaction operation to form a desired novel product in which all the reactants are incorporated into the product. One-pot multicomponent approach is the best method of synthesis of complex heterocyclic molecules,[4,5] it involves minimum number of steps, there is no isolation of intermediate, without use of noxious solvents, shorter reaction time, easy work up procedure to give good to excellent yields.

Coumarins are important pharmacophores in medicinal chemistry and have biological activities,[6] such as cytotoxic, anti-inflammatory,[7] antituberculosis,[8] antibacterial,[9] antiviral,[10] herbicidal,[11] anti-HIV agent,[12] and antioxidant.[13] Significantly coumarin

CONTACT Rajeswar Rao Vedula rajeswarnitw@gmail.com Department of Chemistry, National Institute of Technology, Warangal-506004, Telangana, India.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.

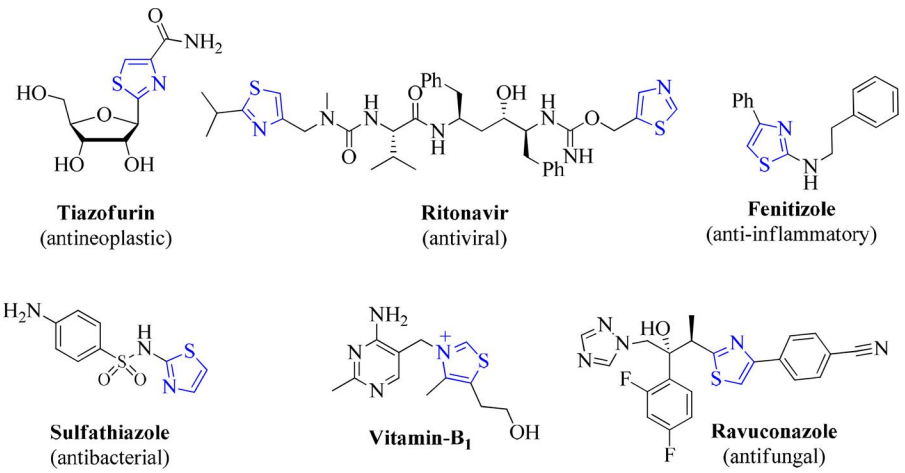


Figure 1. Some of the representative examples of biologically potent compounds bearing thiazole scaffold.

derivatives are used as luminescent materials,[14] inhibition of platelet aggregation,[15] allosteric MEK1 inhibitor[16] and also acts as free radical scavengers.[17]

In the recent years, thiazole[18,19] and its derivatives attained considerable interest due to their wide variety of biological and pharmacological activities,[20], such as antiproliferative,[21] anticancer,[22] antimalarial,[23] anti-HIV,[24] antimicobacterial,[25] anti-inflammatory[26] and antihypertensive agents. Moreover thiazole and its derivatives being a structural framework in variety of biologically important natural, semi-synthetic, and synthetic drugs[27] (Fig. 1). Besides, actinomycete member's producing complex naturally occurring antibiotics which are thiazole embedding secondary metabolites.[28]

In view of various physiological activities associated with coumarins and thiazoles, our current studies are focused on the development of new routes for the synthesis of thiazoles incorporating both aryl and coumarin moieties. We have developed a one-pot multicomponent reaction for the synthesis of title compounds assuming that the resulting compounds may possess good biological activities.

2,4-Disubstituted thiazoles were generally synthesized by various methods. The most common method involves the Hantzsch thiazole synthesis. This involves condensation of α -halogeno ketones with thiourea or thioamides.[29,30] King and co-workers[31–33] synthesized 2,4-disubstituted thiazoles by replacing α-halogenoketones with ketone and halogen. Despite of this modification, the method of King and co-workers is cumbersome and time taking process (24–25 h).

Results and discussion

By considering the importance of the heterocyclic moieties and in continuation of our earlier work on the development of biologically important heterocyclic compounds containing nitrogen and sulfur atoms,[34,35] we designed synthesis of novel 2,4-disubstituted thiazoles, using a multicomponent approach involving modified Hantzsch thiazole synthesis at room temperature. An equimolar mixture of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one, thiosemicarbazide and cyclic ketone

was stirred for 5 min at room temperature to afford the corresponding 2,4-disubstituted thiazoles (**4, 5**, and **6a–m**) with good to excellent yields (85–95%) (Table 1).

In the one step solvent free synthesis (Scheme 1, method 1), it is believed that the phenacyl bromides or 3-(2-bromoacetyl) coumarins react with thiosemicarbazide to give the corresponding intermediate 2-hydrazino-4-substituted thiazoles followed by the reaction with cyclic ketones to afford the target compounds (**4, 5**, and **6**).

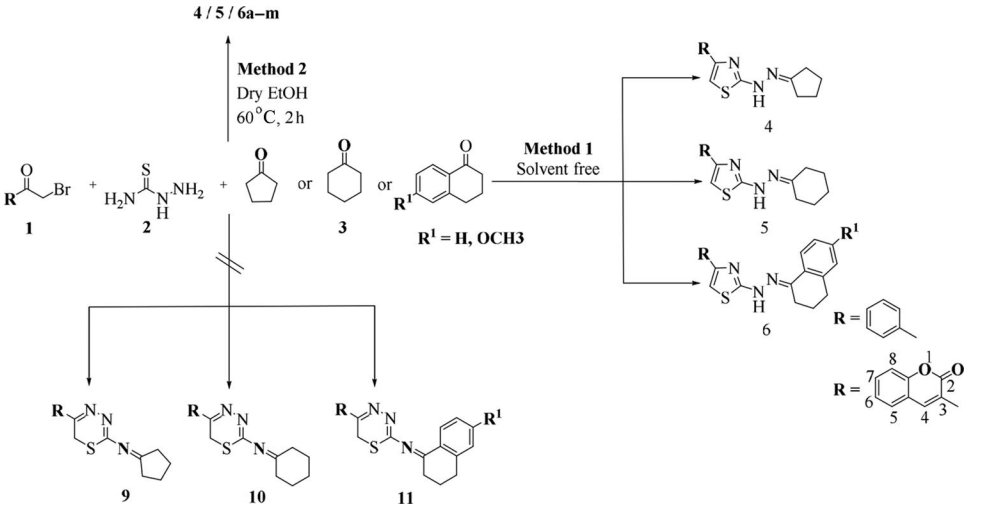
We have synthesized compounds **4, 5**, and **6** by a one pot condensation of three reactants in ethanol at 60 °C (method 2) and also we have performed the synthesis of **4, 5**, and **6** by unambiguous method (Scheme 2, method 3). In the method 3, condensation of various phenacyl bromides or 3-(2-bromoacetyl) coumarins with thiosemicarbazide to give corresponding 2-hydrazino-4-substituted thiazoles (**8**). These on treatment with cyclic ketones resulted in the formation of **4, 5**, and **6** through a two-step process. The products obtained by all the three methods were found to be identical by their mixed melting point measurements, co-TLC, and IR spectra. In the present investigation, method 1 was used as it has more advantages, such as higher yields, shorter reaction times, milder reaction conditions, one pot, solvent free and easy reaction workup. In method 2 the overall yields were 75–85% and this method was not used for the synthesis of title compounds. The intermediates 2-hydrazino-4-aryl thiazoles and 2-hydrazino-4-coumarinyl thiazoles were synthesized by following the literature procedures.[36,37]

Method 3

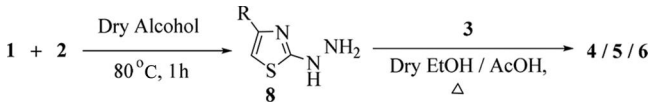
Reaction between phenacyl bromide or 3-(2-bromoacetyl) coumarin, thiosemicarbazide and cyclic ketone is expected to give the compound **4/5/6** or corresponding *N*-cyclopentylidine (**9**), cyclohexylidene (**10**), and 3,4-dihydronaphthalene-1(2*H*)-ylidene-5-substituted-6*H*-1,3,4-thiadiazines (**11**) or both depending on the mode of cyclization and reaction conditions used. In the present investigation the reaction between 1 and 2 proceeds selectively in such a way that the thioamide of 2 undergoes cyclization to give only 2,4-disubstituted thiazoles. The reaction conditions played a crucial role in the selective hetero cyclization. The alternate products **9, 10**, and **11** can be rejected on the basis of spectral studies (IR, NMR, ^{13}C, and Mass).

Table 1. Synthesis of compounds (**4**, **5**, and **6a–m**) and their corresponding yields.

Entry	R	R1	Yields (%) (method 1)
4	Phenacyl	—	95
5	6,8-Dibromo-3-coumarinyl	—	95
6a	Phenacyl	H	96
6b	4-Bromo phenacyl	H	91
6c	4-Chloro phenacyl	H	90
6d	2,4-Dichloro phenacyl	H	96
6e	4-Nitro phenacyl	H	95
6f	6-Bromo-3-coumarinyl	H	96
6g	6,8-Dibromo-3-coumarinyl	H	93
6h	8-Methoxy-3-coumarinyl	H	92
6i	Phenacyl	6-OCH_3	97
6j	4-Chloro phenacyl	6-OCH_3	93
6k	4-Nitro phenacyl	6-OCH_3	95
6l	6,8-Dibromo-3-coumarinyl	6-OCH_3	92
6m	6-Bromo-8-methoxy-3-coumarinyl	6-OCH_3	85

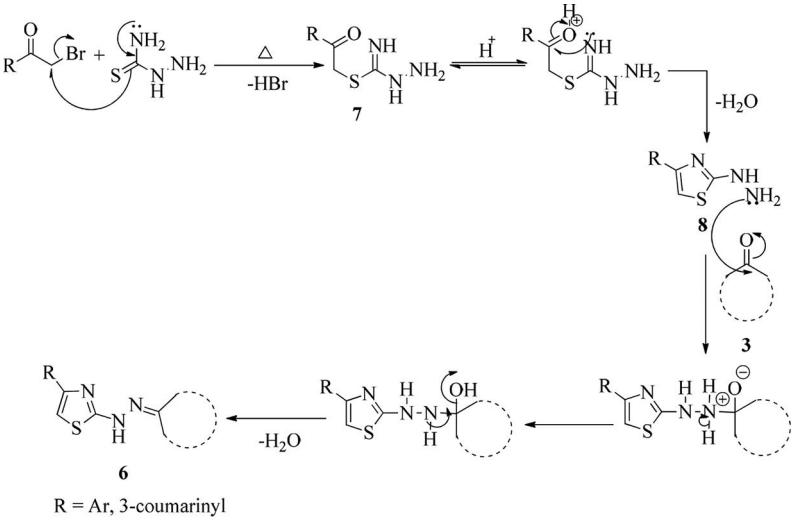


Scheme 1. Synthesis of 2,4-disubstituted thiazoles via multicomponent approach.



Scheme 2. Unambiguous synthesis of 2,4-disubstituted thiazoles.

The formation of the products (**4, 5**, and **6**) can be explained (Scheme 3), by the intra molecular cyclization of α-thioketone (**7**) to give 2-hydrazino-4-substituted thiazole (**8**). This intermediate undergoes intermolecular condensation reaction with cyclic ketone to give final compounds (**4, 5**, and **6**).



Scheme 3. Plausible mechanism for the synthesis of 2,4-disubstituted thiazoles.

All the structures of newly synthesized compounds have been confirmed by their spectral data. The IR spectrum of compound **6c** shows prominent peaks at 3450–3030 cm^{-1} (b, m to different NH stretchings), 1609 cm^{-1} (C=N–) stretching vibrations, respectively. The ^{1}H-NMR spectrum of compound **6c** gave prominent peaks for three CH_2 protons of tetralone at δ 2.04 (t, $J = 5.2$ Hz, 2H), 2.82 (s, 2H) and 2.91 (t, $J = 6.0$ Hz, 2H), respectively. Thiazole proton appeared as singlet at δ 6.77. The NH proton appeared at δ 12.34. The peaks of the remaining aromatic protons were observed in the usual region. ^{13}C NMR spectrum of **6c** shows three non-equivalent methylene carbons of tetralone ring at δ 21.74, 26.51, and 29.32 ppm respectively and thiazole carbon appeared at δ 105.37 ppm. Whereas the remaining aromatic carbons were observed in the usual region. The mass spectrum of **6c** exhibited $[M+H]^+$ peak at *m/z* 354 as base peak.

Experimental section

All the chemicals which were used in the present study were purchased from commercial sources and used further without any purification. Melting points were determined in open capillaries with a Stuart melting point apparatus (Mumbai, India) and were uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100S spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker WM-400 spectrometer in δ ppm using TMS as the standard, ESI-MS spectra were recorded on JEOL JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer, compounds purity was checked by TLC plates (E Merck, Mumbai, India). The supplemental materials contain ^{1}H and ^{13}C NMR spectra of products **4, 5**, and **6**.

General procedure for the synthesis of 2,4-disubstituted thiazoles (method 1)

An equimolar amount of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one, thiosemicarbazide and cyclopentanone/cyclohexanone/tetralone were taken in a round bottom flask and stirred at room temperature for about 5 min. The progress of the reaction was monitored through TLC using ethyl acetate and *n*-hexane (40%). After completion of the reaction, the separated solid was filtered, washed with ether to remove unreacted cyclic ketone and dried. The product was purified by recrystallization from methanol.

2-(2-Cyclopentylidenehydrazinyl)-4-phenylthiazole (4)

Phenacyl bromide (199 mg, 1 mmol), thiosemicarbazide (91 mg, 1 mmol), and cyclopentanone (0.5 mL, 4 mmol) were stirred at room temperature for 5 min. The solid separated was filtered and washed with ether to remove unreacted cyclic ketone. The product was recrystallized from methanol. Black solid; mp 142–143 °C; yield (95%); IR (KBr, ν_{max}, cm^{-1}): 3437–3053 (b, m to different NH stretching), 1628 (–C=N–); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80–1.87 (m, 2H), 1.90–1.96 (m, 2H), 2.5–2.57 (m, 4H), 6.74 (s, 1H), 7.38–7.42 (m, 1H), 7.44–7.48 (m, 2H, ArH), 7.74 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.83, 24.95, 29.91, 33.28, 101.67, 125.60, 129.13, 129.33, 129.79, 143.69, 168.90, 169.27. ESI-MS, *m/z* (%): 258 $(M+H)^+$; anal. calcd for $C_{14}H_{15}N_3S$, C, 65.34; H, 5.87; N, 16.33; S, 12.46%. Found: C, 65.30, H, 5.84; N, 16.39; S, 12.42.

6,8-Dibromo-3-(2-(2-cyclohexylidenehydrazinyl) thiazol-4-yl)-2h-chromen-2-one (5)

6,8-Dibromo-3-(2-bromoacetyl)-2*H*-chromen-2-one (425 mg, 1 mmol), thiosemicarbazide (91 mg, 1 mmol) and cyclohexanone (0.5 mL, 4 mmol) were stirred at room temperature for 5 min. The solid separated was filtered and washed with ether to remove unreacted cyclic ketone. The product was recrystallized from methanol. Yellow solid; mp 172–173 °C; yield (95%); IR (KBr, ν_{max}, cm^{-1}): 3448–3061 (b, m to different NH stretching vib.), 1733 (C=O of lactone), 1609 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.59–1.64 (m, 6H), 2.26 (s, 2H), 2.45 (s, 2H), 7.74 (s, 1H), 8.11 (s, 2H), 8.40 (s, 1H), 10.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.19, 25.33, 26.91, 34.86, 110.42, 116.96, 121.98, 122.50, 123.63, 131.29, 136.86, 138.63, 144.95, 147.07, 148.92, 158.23, 175.30. ESI- MS, *m/z* (%): 498 $(M+H)^+$; anal. calcd for $C_{18}H_{15}Br_2N_3O_2S$, C, 43.48; H, 3.04; Br, 32.14; N, 8.45; S, 6.45%. Found: C, 43.53; H, 3.12; Br, 32.19; N, 8.49; S, 6.41.

2-(2-(3,4-Dihydronaphthalen-1(2h)-ylidene)hydrazinyl)-4-phenylthiazole (6a)

Phenacyl bromide (199 mg, 1 mmol), thiosemicarbazide (91 mg, 1 mmol) and tetralone (0.5 mL, 4 mmol) were stirred at room temperature for 5 min. The solid separated was filtered and washed with ether to remove unreacted cyclic ketone. The product was recrystallized from methanol. Black solid; mp 157–159 °C; yield (96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89–1.95 (m, 2H), 2.57 (t, $J = 6.8$ Hz, 2H), 2.76 (t, $J = 6.0$ Hz, 2H), 6.92 (s, 1H), 7.15 (d, $J = 4.4$ Hz, 1H), 7.27–7.29 (m, 3H), 7.33 (d, $J = 7.2$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.82 (d, $J = 7.6$ Hz, 2H), 8.16 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.41, 25.68, 29.41, 103.58, 124.62, 125.96, 126.57, 127.96, 128.44, 128.76, 128.92, 132.12, 134.34, 139.32, 147.23, 150.58, 170.17. Anal. calcd for $C_{19}H_{17}N_3S$, C, 71.44; H, 5.36; N, 13.15; S, 10.04%. Found: C, 71.49; H, 5.31; N, 13.19; S, 10.14.

Conclusion

In conclusion, we have successfully synthesized a novel 2,4-disubstituted thiazole derivatives through a multi component approach under solvent free reaction conditions. The method had the advantages of mild reaction conditions, better to excellent yields, one pot operational simplicity.

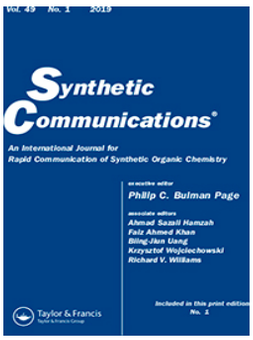
Acknowledgments

The authors are thankful to the Director, National Institute of Technology, Warangal, Telangana, India for providing the facilities. K. S. thanks to the MHRD, India for fellowship.

References

[1] D'Souza, D. M.; Muller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*(7), 1095–1108.
[2] Haji, M. *Beilstein J. Org. Chem.* **2016**, *12*, 1269–1301.
[3] Jain, V.; Bijani, S.; Ambasana, P.; Mehariya, K.; Bhoya, U.; Pandey, B.; Shah, A. *Synth. Commun.* **2016**, *46*, 63–72.
[4] Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
[5] Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246.
[6] Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*(8), 887–916.

[7] Mohareb, R. M.; Abdo, N. Y. M. *Molecules* **2015**, *20*, 11535–11553.
[8] Bhila, V. G.; Patel, C. V.; Patel, N. H.; Brahmbhatt, D. I. *Med. Chem. Res.* **2013**, *22*(9), 4338–4346.
[9] de Souza, S. M.; Monache, F. D.; Smania Jr, A. Z. *Naturforsch.* **2005**, *60c*, 693–700.
[10] Hassan, M. Z.; Osman, H.; Ali, M. A.; Ahsan, M. J. *Eur. J. Med. Chem.* **2016**, *123*, 236–255.
[11] Purohit, N. V. *Indian J. Chem.* **2001**, *40B*, 222–227.
[12] Garro, H. A.; Pungitore, C. R. *Curr. Drug Discov. Technol.* **2015**, *12*(2), 66–79.
[13] Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*(30), 3813–3833.
[14] Bullock, S. J.; Felton, C. E.; Fennessy, R. V.; Harding, L. P.; Andrews, M.; Pope, S. J. A.; Rice, C. R.; Riis-Johannessen, T. *Dalton Trans.* **2009**, *47*, 10570–10573
[15] Di Braccio, M.; Grossi, G.; Roma, G.; Signorello, M. G.; Leoncini, G. *Eur. J. Med. Chem.* **2004**, *39*, 397–409.
[16] Han, S.; Zhou, V.; Pan, S.; Liu, Y.; Hornsby, M.; McMullan, D.; Klock, H. E.; Haugen, J.; Lesley, S. A.; Gray, N.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5467–5473.
[17] Kancheva, V. D.; Boranova, P. V.; Nechev, J. T.; Manolov, I. I. *Biochimie* **2010**, *92*(9), 1138–1146.
[18] Rouf, A.; Tanyeli, C. *Eur. J. Med. Chem.* **2015**, *97*, 911–927.
[19] Chhabria, M. T.; Patel, S.; Modi, P.; Brahmkshatriya, P. S. *Curr. Top. Med. Chem.* **2016**, *16*, 2841–2862.
[20] Ayati, A.; Emami, S.; Asadipour, A.; Shafiee, A.; Foroumadi, A. *Eur. J. Med. Chem.* **2015**, *97*, 699–718.
[21] Laczkowski, K. Z.; Misiura, K.; Switalska, M.; Wietrzyk, J.; Laczkowska, A. B.; Fernandez, B.; Paneth, A.; Plech, T. *Anticancer Agents Med. Chem.* **2014**, *14*(9), 1271–1281.
[22] Turan-Zitouni, G.; Altintop, M. D.; Ozdemir, A.; Kaplancikli, Z. A.; Ciftci, G. A.; Temel, H. E. *Eur. J. Med. Chem.* **2016**, *107*, 288–294.
[23] Cabrera, D. G.; Douelle, F.; Feng, T. S.; Nchinda, A. T.; Younis, Y.; White, K. L.; Wu, Q.; Ryan, E.; Burrows, J. N.; Waterson, D.; *J. Med. Chem.* **2011**, *54*(21), 7713–7719.
[24] Curreli, F.; Kwon, Y. D.; Zhang, H.; Scacalossi, D.; Belov, S. D. S.; Tikhonov, A. A.; Andreev, I. A.; Altieri, A.; Kurkin, A. V.; Kwong, P. D.; *J. Med. Chem.* **2015**, *58*(17), 6909–6927.
[25] Hampannavar, G. A.; Karpoormath, R.; Palkar, M. B.; Shaikh, M. S.; Chandrasekaran, B. *ACS Med. Chem. Lett.* **2016**, *7*(7), 686–691.
[26] Helal, M. H. M.; Salem, M. A.; El-Gaby, M. S. A.; Aljahdali, M. *Eur. J. Med. Chem.* **2013**, *65*, 517–526.
[27] Xinjiang, W.; Fekadu, K.; Volker, M. S. *Mutat. Res.* **2005**, *589*, 81–102.
[28] Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022–1037.
[29] Hantzsch, A.; Weber, H. J. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118.
[30] Hantzsch, A. *Justus Leibigs Ann. Chem.* **1988**, *249*, 1.
[31] Dodson, R. M.; King, L. C. *J. Am. Chem. Soc.* **1945**, *67*(12), 2242–2243.
[32] King, L. C.; Hlavacek, R. J. *J. Am. Chem. Soc.* **1950**, *72*, 3722–3725.
[33] Koelsch, C. F. *J. Am. Chem. Soc.* **1950**, *72*(7), 2993–2995.
[34] Santhosh, P.; Kranthi Kumar, G.; Srinivas, B.; Rajeswar Rao, V. *Tetrahedron Lett.* **2013**, *54*, 5663–5666.
[35] Krishnaiah, V.; Rajesh Kumar, K.; Santosh, K.; Rajeswar Rao, V.; Srigiridhar, K.; Murali Krishna, T. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5797–5803.
[36] Subrahmanya Bhat, K.; Shivarama Holla, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1019–1026.
[37] Santhosh, P.; Rajeswar Rao, V. *Indian J. Chem.* **2014**, *53B*, 115–119.



Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

An efficient one-pot expeditious synthesis of 3-phenyl-1-(6-phenyl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazin-3-yl)-1H-pyrazol-5-amines via multicomponent approach

Kodam Sujatha, Ravindra Pramod Deshpande, Rajesh Kumar Kesharwani, Phanithi Prakash Babu & Rajeswar Rao Vedula

To cite this article: Kodam Sujatha, Ravindra Pramod Deshpande, Rajesh Kumar Kesharwani, Phanithi Prakash Babu & Rajeswar Rao Vedula (2019) An efficient one-pot expeditious synthesis of 3-phenyl-1-(6-phenyl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazin-3-yl)-1H-pyrazol-5-amines via multicomponent approach, Synthetic Communications, 49:1, 49-55, DOI: 10.1080/00397911.2018.1537398

To link to this article: https://doi.org/10.1080/00397911.2018.1537398

Published online: 12 Dec 2018.

SYNTHETIC COMMUNICATIONS®
2019, VOL. 49, NO. 1, 49–55
https://doi.org/10.1080/00397911.2018.1537398

Taylor & Francis
Taylor & Francis Group

An efficient one-pot expeditious synthesis of 3-phenyl-1-(6-phenyl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazin-3-yl)-1H-pyrazol-5-amines via multicomponent approach

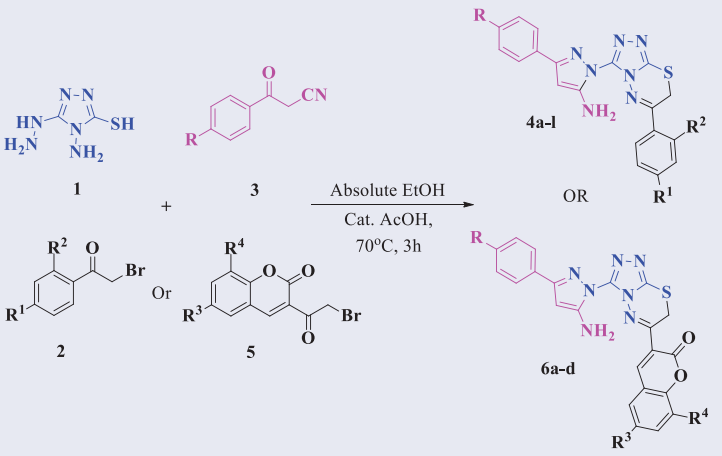
Kodam Sujatha[a], Ravindra Pramod Deshpande[b], Rajesh Kumar Kesharwani[c], Phanithi Prakash Babu[b], and Rajeswar Rao Vedula[a]

[a]Department of Chemistry, National Institute of Technology, Warangal, India; [b]Department of Biotechnology and Bioinformatics, School of Life Sciences, University of Hyderabad, Hyderabad, India; [c]Department of Advanced Science & Technology, NIET, Nims University Rajasthan, Jaipur, India

ABSTRACT

An efficient synthesis of 3-phenyl-1-(6-phenyl-7*H*-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amines was accomplished by a simple, atom-economical, and multicomponent approach. Reaction of 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol with various phenacyl bromides and benzoylacetonitriles in ethanol and catalytic amount of acetic acid afforded the titled compounds. The structures of newly synthesized compounds were confirmed by their analytical and spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and Mass) data.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 17 July 2018

KEYWORDS
Multicomponent reaction; phenacyl bromide; 3-(2-bromoacetyl)-2H-chromen-2-one; triazolothiadiazine

Introduction

Triazoles are important class of heterocyclic compounds for organic chemists on account of their implications in the biological, pharmacological, medicinal, agricultural,

CONTACT Rajeswar Rao Vedula rajeswarnitw@gmail.com Department of Chemistry, National Institute of Technology, Warangal, Telangana 506 004, India.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

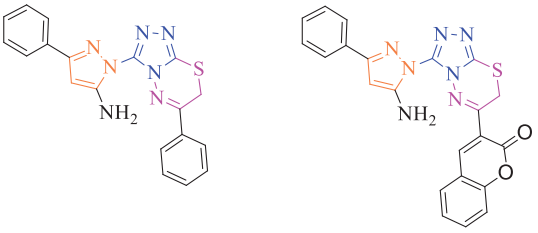
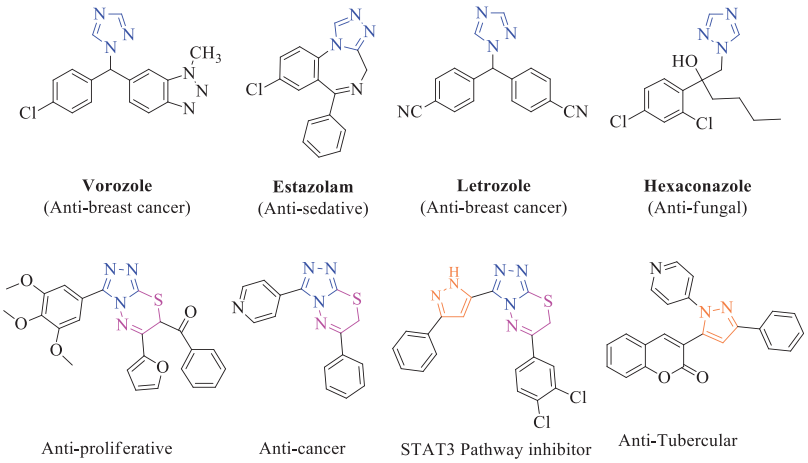


Figure 1. Design strategy of synthesized molecules.

and industry.[1,2] When triazole ring is fused with a 5-membered or with a 6-membered heterocyclic ring its enhance the biological activity of the lead molecule[3,4] and triazolothiadiazines were associated with different biological activities such as anti-cancer,[5,6] anti-tubercular,[7] anti-candidal,[8] and anti-microbial activity.[9] Triazolothiadiazines having substituent's such as substituted aryl, coumarin moieties are reported with better biological activity.[10,11]

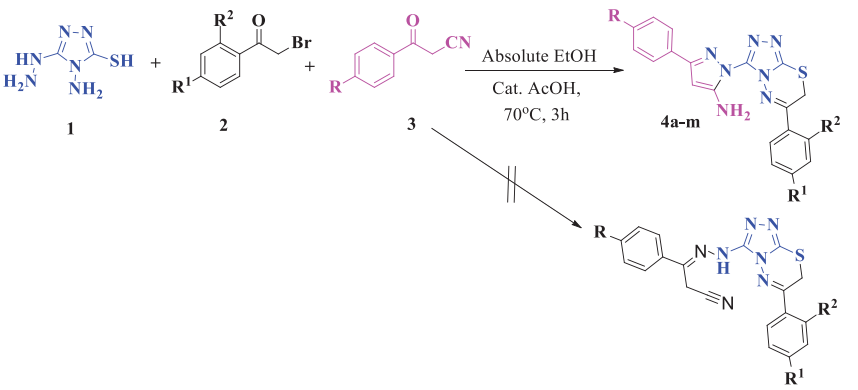
Pyrazoles are also important heterocyclic molecules.[12,13] Pyrazoles and their derivatives are having predominant biological and pharmacological activities,[14–17] such as anti-hyperglycaemic,[18] anticonvulsant, anti-depressant,[19] anti-tubercular, anti-bacterial,[20] anti-viral,[21,22] anti-fungal,[23,24] anti-histaminic,[25] anti-inflammatory,[26] anti-diabetic[27] and anti-leukaemia agent.[28] The existing literature revealed that pyrazole ring directly linked to the 1,2,4-triazolo-[3,4-b]thiadiazines showed human (h) A_3 adenosine receptor[29] and better anti-proliferative activity (Figure 1).[30,31]

Multicomponent reactions are widely used in organic synthesis due to advantages such as high efficiency, atom economy, high yields, clear reactions, and simple procedures resulting in the formation of new structures.[32]



Some of the reported biologically active molecules with triazolothiadiazine, pyrazolotriazolothiadiazines, and pyrazolocoumarin scaffolds.

Keeping the importance of triazoles, pyrazoles, and triazolothiadiazines, our present study is focused on the development of new methodologies for the synthesis of thiadiazine fused to triazole and having pyrazole.



Scheme 1. Synthesis of compounds **4a–4m**.

In continuation of our earlier work on MCR,[33,34] we have developed a one-pot multicomponent reaction for the synthesis of title compounds intending that these compounds may have good biological activities (Schemes 1 and 2).

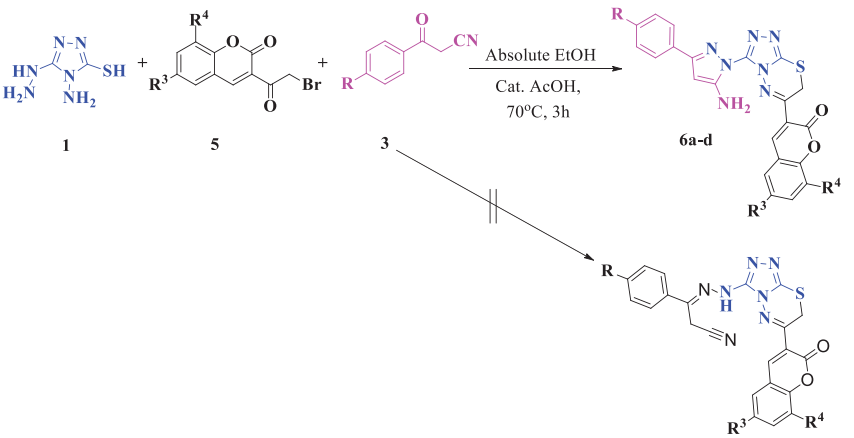
Results and discussion

4-Amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol can be taken as useful tool in building triazolothiadiazinylpyrazoles. It is prepared by reaction of thiourea with hydrazine hydrate under reflux conditions on water bath.[35] Condensation of 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol (**1**), various phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**2**), and benzoylacetonitriles (**3**) resulted in the formation of **4** and **6**.

Reaction between compound **1**, phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one and phenacyl cyanide is expected to produce compound **7** and **8** depending on the mode of cyclization. The formation of compound **7** and **8** can be ruled on the basis of spectral studies. In the present investigation, both NH_2 and SH of **1** at a time undergoes condensation with either **2** or **5** leading to first hetero cyclization. Then, the hydrazino group of **1** reacts with phenacyl cyanide to give the title compound. The desired product was achieved in each case good to excellent yield. The work may trigger an interesting chemistry involving new methodology. The very noticeable feature of the synthesis is that different hetero atom bonds like C–S, 2N = C, and N–C (compounds **4** and **6**) are formed concomitantly in one pot leading to selective new hetero cyclization without formation of any other products (Table 1).

In the formation of fused thiadiazine ring on triazole, the highly nucleophilic sulfur atom of mercapto group of 1 attacks on the carbon atom of the (CH_2-Br) of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one to give an open chain α-thioketone. Then, it undergoes intra molecular cyclization, leading to the formation of thiadiazine ring. The hydrazino group of triazolothiadiazine undergoes cyclocondensation reaction with benzoylacetonitrile leading to the formation of title compounds with better yields.

The structures of all the newly synthesized compounds were confirmed by their analytical and spectral data and are summarized in supporting information. The IR spectrum of Compound **4a** shows prominent peaks at 3411 cm^{-1} (NH_2 Stretching), 1618 cm^{-1} (–C = N– stretching). The ^{1}H-NMR spectrum of the compound **4a** showed a



Scheme 2. Synthesis of compounds **6a–6d**.

characteristic peak at δ 4.49 ppm corresponds to CH_2 of thiadiazine and δ 5.90 ppm corresponds to pyrazole proton. The 13C NMR of the **4a** exhibits a characteristic peak at δ 23.5 ppm. This is due to carbon atom of CH_2 of thiadiazine. The compound **4a** exhibited the molecular ion peak at m/z 407.

Experimental

All the chemicals which were used in the present study were purchased from commercial sources and used further without any purification. Melting points were determined in open capillaries with a Stuart melting point apparatus Mumbai, India and were uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100 s. ^{1}H-NMR spectra were recorded on Bruker WM-400 spectrometer in δ ppm using TMS as the standard, ESI-MS spectra were recorded on Jeol JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer, compounds purity was checked by TLC plates (E Merck, Mumbai, India). The Supplemental Materials contain ^{1}H and ^{13}C NMR spectra of products **4**, **6**.

General procedure for the synthesis of compounds (4a–m and 6a–d)

An equimolar amount of 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol) in ethanol (5 ml) and catalytic amount of acetic acid (2 drops) was refluxed for 1 h. Then, the reaction mixture was treated with benzoylacetonitrile (1 mmol) and further refluxed for 1 h. The reaction mixture was cooled to room temperature. The solid separated was filtered and recrystallized from methanol to give final product.

Table1. Different substitutions of the compounds **4a–4m** and **6a–6d**.

Entry	Product	R	R^1	R^2	R^3	R^4	Yields (%)
1	**4a**	Cl	H	H	–	–	92
2	**4b**	Cl	CH_3	H	–	–	96
3	**4c**	Cl	Cl	H	–	–	90
4	**4d**	Cl	F	H	–	–	95
5	**4e**	Cl	OCH_3	H	–	–	95
6	**4f**	H	H	H	–	–	93
7	**4g**	H	Br	H	–	–	91
8	**4h**	H	CH_3	H	–	–	95
9	**4i**	H	Cl	Cl	–	–	89
10	**4j**	H	F	H	–	–	97
11	**4k**	H	OCH_3	H	–	–	92
12	**4l**	Cl	Ph	H	–	–	90
13	**4m**	H	H	CH_3	–	–	85
14	**6a**	H	–	–	H	OEt	96
15	**6b**	Cl	–	–	Cl	–	92
16	**6c**	Cl	–	–	H	OEt	97
17	**6d**	Cl	–	–	Br	OCH_3	93

3 -(4-Chlorophenyl)-1-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-1H-pyrazol-5-amine (4a)

Pale yellow solid; mp 240–241 °C; Yield (92%); IR (KBr, ν_{max}, cm^{-1}): 3411 (NH_2 Stretching), 1618 (–C = N– stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.49 (s, 2 H, CH_2), 5.90 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.51–7.60 (m, 3 H ArH and 2 H NH_2), 7.79 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 7.2 Hz, 2H); 13C NMR (100 MHz, DMSO-d_6, ppm): δ 23.5, 84.9, 127.5, 128.0, 129.1, 129.5, 130.7, 132.6, 133.1, 133.6, 142.8, 146.3, 151.9, 152.3, 156.6. ESI-MS, *m/z* (%): 408 $(M + H)^+$; anal. calcd. for $C_{19}H_{14}ClN_7S$: C, 55.95; H, 3.46; Cl, 8.69; N, 24.04; S, 7.86. Found: C, 55.90; H, 3.41; Cl, 8.62; N, 24.10; S, 7.82.

3 -(3-(5-Amino-3-phenyl-1H-pyrazol-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-8-ethoxy-2H-chromen-2-one (6a)

Brown solid; mp 219–220 °C; Yield (96%); IR (KBr, ν_{max}, cm^{-1}): 3467 (NH_2 Stretching), 1722 (lactone C = O stretching), 1614 (–C = N– stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.40 (t, J = 6.8 Hz, 3H), 4.19 (d, J = 6.8 Hz, 2H), 4.35 (s, 2H), 5.85 (s, 1H), 6.02 (s, 2H), 7.31–7.35 (m, 3H), 7.39 (t, J = 6.0 Hz, 3H), 7.75 (d, J = 7.2 Hz, 1H), 8.32 (s, 1H), 8.43 (s, 1H). ESI-MS, *m/z* (%): 486 $(M + H)^+$; anal. calcd. for $C_{24}H_{19}N_7O_3S$: C, 59.37; H, 3.94; N, 20.19; S, 6.60. Found: C, 59.32; H, 3.93; N, 20.15; S, 6.65.

Conclusion

In conclusion, we report a novel one-pot multicomponent synthesis of some 3-phenyl-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amines by using readily available starting materials. This synthetic method has more advantages such as shorter reaction time, no use of harsh reaction conditions, easy work-up procedure, and good to excellent yields of the products.

Acknowledgments

The authors are thankful to the Director, National Institute of Technology, Warangal, Telangana, India for providing the facilities. K. S thanks to the MHRD, India for fellowship.

ORCID

Ravindra Pramod Deshpande http://orcid.org/0000-0002-4634-9967
Phanithi Prakash Babu http://orcid.org/0000-0002-1528-8575

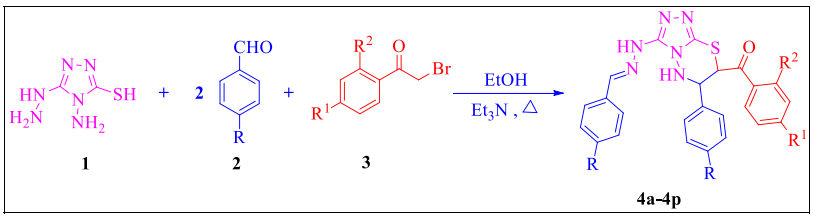
References

[1] Al-Masoudi, I. A.; Al-Soud, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 1377–1403.
[2] Potts, K. T. *Chem. Rev.* **1961**, *61*, 87–127.
[3] Pran Kishore, D.; Balakumar, C.; Raghuram Rao, A.; Roy, P. P.; Roy, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 818–823.
[4] Abdelrazek, F. M.; Gomha, S. M.; Shaaban, M. E. B.; Lotfi, A. I.; El-Shemy, H. N. *Synth. Commun* **2018**, *48*, 32–37.
[5] Aytac, P. S.; Durmaz, I.; Houston, D. R.; Cetin-Atalay, R.; Tozkoparan, B. *Bioorg. Med. Chem.* **2016**, *24*, 858–872.
[6] Kamel, M. M.; Megally Abdo, N. Y. *Eur. J. Med. Chem.* **2014**, *86*, 75–80.
[7] Li, Z.; Bai, X.; Deng, Q.; Zhang, G.; Zhou, L.; Liu, Y.; Wang, J.; Wang, Y. *Bioorg. Med. Chem.* **2017**, *25*, 213–220.
[8] Altintop, M. D.; Kaplancikli, Z. A.; Turan-Zitouni, G.; Ozdemir, A.; Iscan, G.; Akalin, G.; Yildirim, S. U. *Eur. J. Med. Chem.* **2011**, *46*, 5562–5566.
[9] Kaplancikli, Z. A.; Turan-Zitouni, G.; Ozdemir, A.; Revial, G. *Eur. J. Med. Chem.* **2008**, *43*, 155–159.
[10] Hasui, T.; Matsunaga, N.; Ora, T.; Ohyabu, N.; Nishigaki, N.; Imura, Y.; Igata, Y.; Matsui, H.; Motoyaji, T.; Tanaka, T.; et al. *J. Med. Chem.* **2011**, *54*, 8616–8631.,
[11] Kumar, Pm.; Ravi, T.; Chawla, R.; Bhuvana, S.; Sonia, G.; Gopalakrishnan, S. *Indian J. Pharm. Sci.* **2010**, *72*, 357
[12] Amer, A.; Moustafa, A. *Synlett.* **2016**, *27*, 1703–1706.
[13] Gomha, S. M.; Edrees, M. M.; Faty, R. A. M.; Muhammad, Z. A.; Mabkhot, Y. N. *Chem. Cent. J.* **2017**, *11*, 37
[14] Hu, G. Q.; Hou, L. L.; Yang, Y.; Yi, L.; Xie, S. Q.; Wang, G. Q.; Duan, N. N.; Chao, T. Y.; Wen, X. Y.; Huang, W. L. *Chinese Chem. Lett.* **2011**, *22*, 804–806.
[15] Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. *New J. Chem.* **2017**, *41*, 16–41.
[16] Gomha, S. M.; Badrey, M. G.; Abdalla, M. M.; Arafa, R. K. *Med. Chem. Commun.* **2014**, *5*, 1685–1692.
[17] Gomha, S. M.; Khalil, K.; Abdel-Aziz, H.; Abdalla, M. *Heterocycles.* **2015**, *91*, 1763–1773.
[18] Kenchappa, R.; Bodke, Y. D.; Chandrashekar, A.; Aruna Sindhe, M.; Peethambar, S. K. *Arab. J. Chem.* **2017**, *10*, S3895–S3906.
[19] Abdel-Aziz, M.; Abuo-Rahma, G. E.-D. A.; Hassan, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 3480–3487.
[20] Nayak, N.; Ramprasad, J.; Dalimba, U. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5540–5545.
[21] Larsen, J. S.; Zahran, M. A.; Pedersen, E. B.; Nielsen, C. *Monatshefte Fuer. Chemie.* **1999**, *130*, 1167–1173.
[22] Gomha, S.; Abdallah, M.; Abd El-Aziz, M.; Serag, N. *Turk. J. Chem.* **2016**, *40*, 484–498.
[23] Gupta, M.; Paul, S.; Gupta, R. *Eur. J. Med. Chem.* **2011**, *46*, 631–635.
[24] Abdelhamid, A. O.; Shawali, A. S.; Gomha, S. M. *Heterocycles.* **2015**, *91*, 2126–2142.

[25] Yildirim, I.; Ozdemir, N.; Akcamur, Y.; Dincer, M.; Andac, O. *Acta Crystallogr. Sect. E Struct. Reports Online* **2005**, *61*, o256–o258.
[26] El-Moghazy, S. M.; Barsoum, F. F.; Abdel-Rahman, H. M.; Marzouk, A. A. *Med. Chem. Res.* **2012**, *21*, 1722–1733.
[27] Ahn, J. H.; Kim, H. M.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Yang, S. D.; Cheon, H. G.; Kim, S. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4461–4465.
[28] Chou, L.-C.; Huang, L.-J.; Yang, J.-S.; Lee, F.-Y.; Teng, C.-M.; Kuo, S.-C. *Bioorg. Med. Chem.* **2007**, *15*, 1732–1740.
[29] Cheong, S. L.; Dolzhenko, A. V.; Paoletta, S.; Lee, E. P. R.; Kachler, S.; Federico, S.; Klotz, K.-N.; Dolzhenko, A. V.; Spalluto, G.; Moro, S.; et al. *Bioorg. Med. Chem.* **2011**, *19*, 6120–6134.
[30] LaPorte, M. G.; Wang, Z.; Colombo, R.; Garzan, A.; Peshkov, V. A.; Liang, M.; Johnston, P. A.; Schurdak, M. E.; Sen, M.; Camarco, D. P.; et al. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3581–3585.,
[31] Rashdan, H. R. M.; Gomha, S. M.; El-Gendey, M. S.; El-Hashash, M. A.; Soliman, A. M. M. *Green Chem. Lett. Rev.* **2018**, *11*, 264–274.
[32] Marek, I. *Tetrahedron.* **2005**, *61*, 11309.
[33] Aychiluhim, T. B.; Rao, V. R. *Synth. Commun.* **2014**, *44*, 1422–1429.
[34] Pavurala, S.; Vedula, R. R. *J. Heterocyclic Chem.* **2015**, *52*, 306–309.
[35] Dickinson, R. G.; Jacobsen, N. W. *Org. Prep. Proced. Int.* **1974**, *6*, 156–157.

Kodam Sujatha and Rajeswar Rao Vedula*

Department of Chemistry, National Institute of Technology, Warangal 506 004, Telangana, India
*E-mail: rajeswarnitw@gmail.com
Received August 27, 2018
DOI 10.1002/jhet.3458
Published online 28 January 2019 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel triazolo thiadiazines were synthesized by a simple, highly efficient, one-pot pseudo four component approach involving the condensation of 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (**1**), aromatic aldehydes (**2**), and various phenacyl bromides (**3**) with good yields. The structures of compounds were confirmed by analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR) data.

J. Heterocyclic Chem., **56**, 832 (2019).

INTRODUCTION

Multicomponent reactions are the reactions in which sequential assembling of two or more starting materials in a single reaction vessel forms the final product. Multicomponent reactions are the useful platform for the synthesis of simple to complex heterocyclic molecules in minimum number of steps to get diversity-oriented products and having much important in chemical as well as biological aspects [1–5]. The advantages of MCRs are atom economy, simplicity, and time-saving process [6].

1,2,4-Triazole derivatives are very good structural entity present in many of the drugs and had been paid much attention in the fields of pharmaceutical and medicinal chemistry. They show good biological activities such as antifungal [7], antitrypanosomal activity [8], benzodiazepine receptor agonist [9], and also antiviral [10]. In the other hand, thiadiazines are also important structural motif. Compounds having thiadiazines exhibit antidepressant [11]. Compounds containing 1,2,4-triazoles are widely used as drug molecules [12] and are shown in Figure 1.

1,2,4-Triazole ring fused with the 6-membered ring enhances their antimicrobial activity [13,14]. Fused triazolo thiadiazines show anti-HIV-1, molluscicidal [15], anti-inflammatory [16], antitumor [17], antibacterial [18], cholinesterase inhibitory activity [19], PDE4 inhibitors [20], and anti-diabetic activity [21]. Several triazole ring bearing Schiff bases showed good antimicrobial activity [22].

Generally fused triazolo thiadiazines were synthesized by condensation of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiols with α-halogeno ketones [23]. In continuation of our earlier research work on nitrogen and sulfur heterocyclic systems involving MCRs [24,25], herein, we report a new method for synthesis of novel fused triazolo thiadiazines by a multicomponent approach.

RESULTS AND DISCUSSION

The compounds **4a**–**4p** were synthesized by reaction of 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (**1**) with two equivalents of aromatic aldehydes (**2**) and various phenacyl bromides (**3**) in absolute ethanol and catalytic amount of Et_3N. These compounds were formed in good to excellent yields (Scheme 1; Table 1).

The mechanism for the formation of **4** can be explained readily. Initially, two equivalents of aldehyde molecules undergo condensation reaction with the 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (**1**) to give the dianil derivatives. These on further reaction with phenacyl bromides and triethylamine yield the compound (**4**). During the reaction, the thiol group of dianil replaces the bromine atom of phenacyl bromide followed nucleophile addition of carbanion generated *in situ* on carbon atom of imino group adjacent to cyclic nitrogen atom of triazole moiety. The speciality of this reaction is the simultaneous condensation of two equivalents of aldehydes on hydrazino and amino functional groups of **1**, followed by ring closure reaction in presence of **2** equivalents of Et_3N. When the reaction is carried out in the absence of phenacyl bromide by using absolute alcohol, simple condensation of **1** with two equivalents of aldehyde

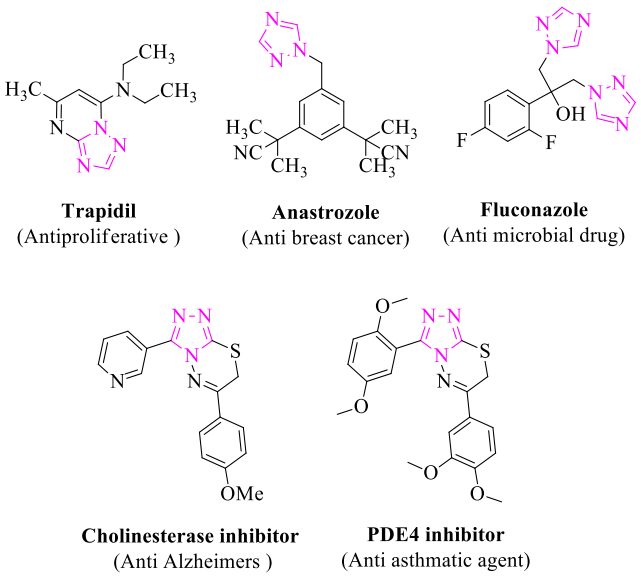
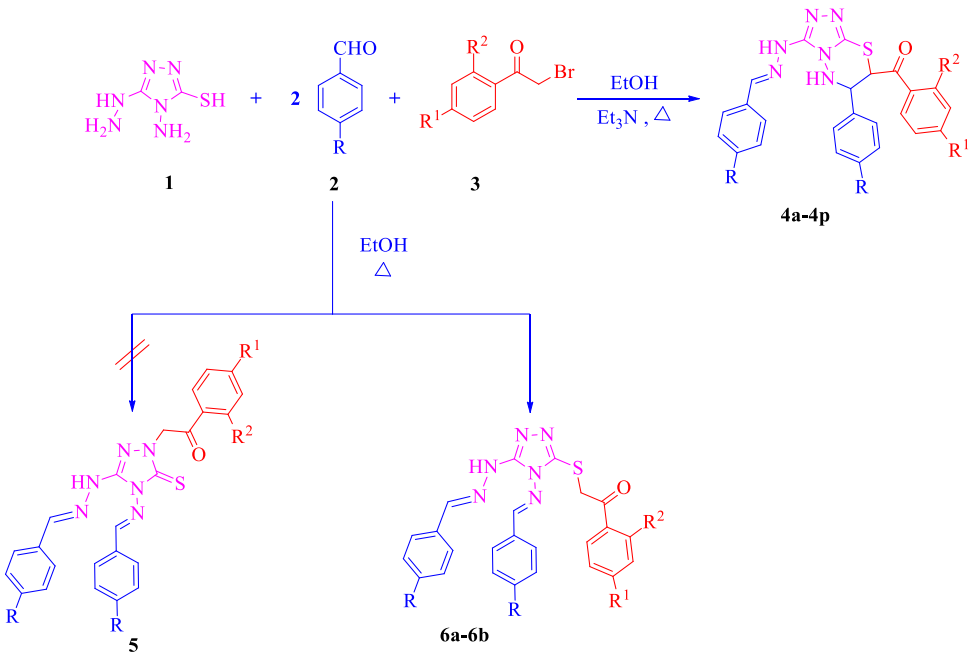


Figure 1. The triazole, triazolothiadiazine containing biologically active drug molecules. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthesis of triazolo thiadiazine derivatives **4a–4p**. [Color figure can be viewed at wileyonlinelibrary.com]



resulted in the formation of dianil (**7**) (Scheme 2) exclusively without formation of any cyclized product (**8**) involving both thiol and imine functionalities. The structure of dianil has been confirmed by IR spectra, in which new stretching bands are appeared for —C=N and disappearance of characteristic peaks for $-NH_2$ stretching frequencies.

The mechanism for the formation of dianils and triazolo thiadiazine derivatives (**4**) has been established as shown in Scheme 3.

On the other hand, when **1** is reacted with two equivalents of the aromatic aldehyde and **1** equivalent of phenacyl bromide resulted in the formation of phenacyl thio dianil compound **6**. The condensation between **1** with two equivalents of aldehyde and **1** equivalent of phenacyl bromide may result in the formation of different types of products *N*-phenacylated compound (**5**) and/or *S*-phenacylated compound (**6**). In our case, only one product (**6**) was observed (as evidenced by TLC). The formation of *S*-phenacylated (**6**) product over

Table 1

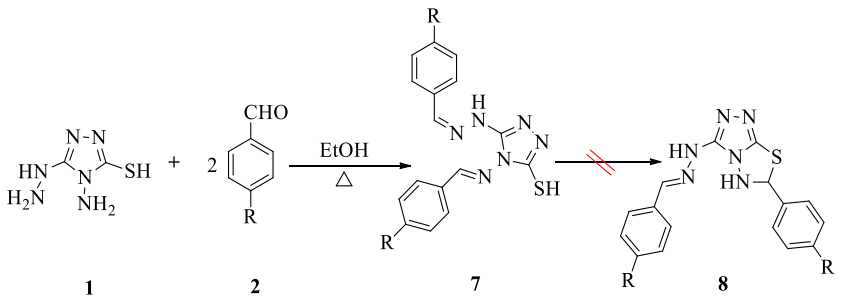
Yields of the products (**4a–4p**, **6a–6b**, and **7a–7b**).

Entry	Product	R	R^1	R^2	Yields (%)
1	**4a**	OCH_3	H	H	90
2	**4b**	OCH_3	Br	H	92
3	**4c**	OCH_3	Cl	H	96
4	**4d**	OCH_3	Cl	Cl	89
5	**4e**	OCH_3	F	H	95
6	**4f**	OCH_3	CH_3	H	91
7	**4g**	OCH_3	OCH_3	H	94
8	**4h**	OCH_3	NO_2	H	89
9	**4i**	CH_3	H	H	86
10	**4j**	CH_3	Br	H	90
11	**4k**	CH_3	Cl	H	95
12	**4l**	CH_3	Cl	Cl	97
13	**4m**	CH_3	F	H	95
14	**4n**	CH_3	CH_3	H	90
15	**4o**	CH3	OCH3	H	93
16	**4p**	CH3	NO2	H	91
17	**6a**	OCH_3	OCH_3	H	95
18	**6b**	OCH_3	F	H	93
19	**7a**	OCH_3	—	—	96
20	**7b**	CH_3	—	—	93

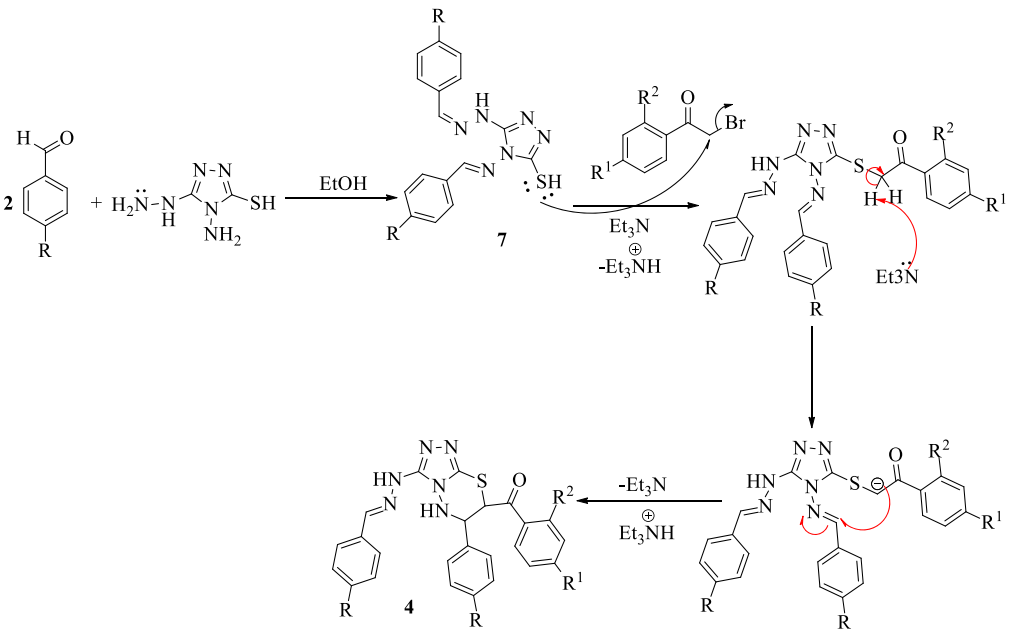
N-phenacylated (**5**) product can be explained by the fact that the more nucleophilicity of thiol group. The structures of *S*-phenacylated products were confirmed by their analytical and spectral data.

All the structures of newly synthesized compounds have been confirmed by their spectral data. The IR spectrum of compound **4a** shows prominent peaks at 3280 cm^{-1} (NH), 2959 cm^{-1} (CH), 1680 cm^{-1} (C═O), and 1609 cm^{-1} (C═N—) stretching frequencies. The ^1H NMR spectrum of compound **4a** gave prominent peaks for the CH protons of thiadiazine at δ 4.87 and 5.73. The NH proton appeared as singlet at 10.38. The peaks of the remaining aromatic protons were observed in the usual region. ^{13}C NMR spectrum of **4a** shows two carbons of thiadiazine ring observed at δ 55.6 and 59.1, whereas the remaining aromatic carbons were observed in the usual region. The mass spectrum of **4a** exhibited $[M + H]^+$ peak at *m/z* 501.

Scheme 2. Synthesis of dianil derivatives (**7**). [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Mechanism for the formation of dianil (**7**) and triazolo thiadiazine derivatives (**4**). [Color figure can be viewed at wileyonlinelibrary.com]



CONCLUSION

We have developed an efficient MCR for the synthesis of title compounds in a simple procedure. The speciality of this reaction is the shorter reaction time, good yields, simple experimental conditions, easy work, operational simplicity, and clean reaction profiles.

EXPERIMENTAL

The starting material 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol was prepared by literature procedure [26]. All the chemicals were purchased from commercial sources. Melting points were determined in open capillaries with a Stuart melting point apparatus (Mumbai, India) and were uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100 s. ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as the standard. ESI-MS spectra were recorded on Jeol JMSD-300 spectrometer, and the elemental analyses were done by Carlo Erba EA 1108 automatic elemental analyzer; compounds purity were checked by TLC plates (E. Merck, Mumbai, India). The Supporting Information contains sample ^{1}H and ^{13}C NMR spectra of products **4a**–**4p**.

General procedure for the synthesis of compounds 4a–4p. 4-Amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (1 mmol), aromatic aldehyde (2 mmol), and phenacyl bromide (1 mmol) were taken in a round bottom flask and treated with 5 mL of absolute ethanol, Et_3N (2 mmol), and refluxed for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and poured onto crushed ice. The resulting solid was filtered, dried, and purified by recrystallization from ethanol.

(E)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(phenyl)methanone (4a). Colorless solid; mp 196–198°C; IR (KBr) ν_{max} (cm^{-1}): 3280 (NH stretching), 2959 (CH stretching), 1680 (C═O stretching), 1609 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.87 (t, *J* = 7.2 Hz, 1H, CH of thiadiazine), 5.73 (d, *J* = 6.4 Hz, 1H, CH of thiadiazine), 6.88 (t, *J* = 8.0 Hz, 3H, ArH), 6.97 (d, *J* = 8.8 Hz, 2H, ArH), 7.49 (d, *J* = 8.4 Hz, 2H, ArH), 7.54–7.59 (m, 4H, ArH), 7.71 (t, *J* = 7.2 Hz, 1H, ArH), 8.0 (d, *J* = 7.6 Hz, 2H, ArH), 8.22 (s, 1H, ─CH═N proton), 10.38 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.2, 160.4, 159.4, 152.2, 143.3, 134.9, 134.7, 129.6, 129.3, 129.1, 128.1, 114.6, 114.3, 59.1, 55.6, 55.5, 43.8; ESI-MS, *m/z* (%): 501 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{24}N_6O_3S$: C, 62.38; H, 4.83; N, 16.79; S, 6.41; found: C, 62.15; H, 4.80; N, 16.71; S, 6.45.

(E)-(4-Bromophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4b). Colorless solid; mp 204–206°C; IR (KBr) ν_{max} (cm^{-1}): 3277 (NH stretching), 1679 (C═O stretching), 1607 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.715 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.90 (t, *J* = 6.8 Hz, 1H), 5.71 (d, *J* = 5.6 Hz, 1H), 6.86–6.91 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 8.22 (s, 1H, ─CH═N proton), 10.38 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.7, 160.4, 159.4, 143.5, 134.0, 132.6, 131.1, 130.9, 129.2, 129.1, 128.9, 128.2, 114.6, 114.3, 58.7, 55.6, 55.5, 43.9; *Anal*. Calcd for $C_{26}H_{23}BrN_6O_3S$: C, 53.89; H, 4.00; Br, 13.79; N, 14.50; S, 5.53; found: C, 53.82; H, 3.96; Br, 13.84; N, 14.53, S, 5.57.

(E)-(4-Chlorophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4c). Colorless solid; mp 206–208°C; IR (KBr) ν_{max} (cm^{-1}): 3277 (NH stretching), 1678 (C═O stretching), 1608 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.92 (t, *J* = 6.0 Hz, 1H), 5.73 (d, *J* = 5.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 8.23 (s, 1H, ─CH═N proton), 10.55 (s, 1H, NH); ESI-MS, *m/z* (%): 535 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}ClN_6O_3S$: C, 58.37; H, 4.33; Cl, 6.63; N, 15.71; S, 5.99; found: C, 58.31; H, 4.38; Cl, 6.60; N, 15.75; S, 5.87.

(E)-(2,4-Dichlorophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4d). Colorless solid; mp 163–165°C; IR (KBr) ν_{max} (cm^{-1}): 3253 (NH stretching), 1684 (─C═O stretching), 1608 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.34 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 1H, NH), 4.80 (t, *J* = 7.2 Hz, 1H), 5.51 (t, *J* = 6.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.84–6.90 (m, 1H), 6.97–6.99 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz,1H), 7.39–7.50 (m, 1H), 7.54–7.59 (m, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.20–8.31 (m, 1H), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.7, 163.2, 162.6, 160.4, 159.1, 148.8, 145.3, 133.0, 131.3, 129.2, 128.6, 128.2, 125.2, 114.9, 114.6, 98.7, 59.6, 55.9, 55.6, 55.4; ESI-MS, *m/z* (%): 569 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{22}Cl_2N_6O_3S$: C, 54.80; H, 3.80; Cl, 12.40; N, 14.70; S, 5.60; found: C, 53.9; H, 3.84; Cl, 12.46; N, 14.82; S, 5.24.

(E)-(4-Fluorophenyl)(3-(2-(4-methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4e). Colorless solid; mp 200–202°C; IR (KBr) ν_{max} (cm^{-1}):

3278 (NH stretching), 1673 (C═O stretching), 1596 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.89 (t, J = 7.2 Hz, 1H), 5.72 (d, J = 6.0 Hz, 1H), 6.86–6.91 (m, 3H), 6.97 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 8.6 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 8.09–8.12 (m, 2H), 8.22 (s, 1H, ─CH═N proton), 10.37 (s, 1H, NH); ESI-MS, m/z (%): 519 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}FN_6O_3S$: C, 60.22; H, 4.47; N, 16.21; S, 6.18; found: C, 60.26, H, 4.42, N, 16.26, S, 6.13.

(E)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(p-tolyl)methanone (4f). Colorless solid; mp 215–217°C; IR (KBr) ν_{max} (cm^{-1}): 3275 (NH stretching), 1676 (C═O stretching), 1608 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.84 (t, J = 7.6 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.84–6.90 (m, 3H), 6.97 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 7.6 Hz, 2H), 8.22 (s, 1H, ─CH═N proton), 10.35 (s, 1H, NH); ESI-MS, m/z (%): 515 (M + H)$^+$; *Anal*. Calcd for $C_{27}H_{26}N_6O_3S$: C, 63.02; H, 5.09; N, 16.33; S, 6.23; found: C, 63.12; H, 5.14; N, 16.37; S, 6.28.

(E)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(4-methoxyphenyl)methanone (4g). Colorless solid; mp 203–205°C; IR (KBr) ν_{max} (cm^{-1}): 3275 (NH stretching), 1676 (C═O stretching), 1608 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.81 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.96 (t, J = 8.8 Hz, 2H), 8.21 (s, 1H, ─CH═N proton), 8.26 (d, J = 6.8 Hz, 1H), 10.35 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.4, 164.5, 160.4, 159.4, 152.1, 143.3, 137.3, 131.6, 129.3, 128.4, 128.1, 128.0, 127.6, 114.8, 114.6, 114.3, 59.5, 56.2, 55.6, 55.5; ESI-MS, m/z (%): 531 (M + 1)$^+$; *Anal*. Calcd for $C_{27}H_{26}N_6O_4S$: C, 61.12; H, 4.94; N, 15.84; S, 6.04; found: C, 61.18; H, 4.91; N, 15.79; S, 6.16.

(E)-(3-(2-(4-Methoxybenzylidene)hydrazinyl)-6-(4-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(4-nitrophenyl)methanone (4h). Light yellow solid; mp 198–200°C; IR (KBr) ν_{max} (cm^{-1}): 3282 (NH stretching), 1683 (C═O stretching), 1602 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.98 (t, J = 6.0 Hz, 1H), 5.79 (d, J = 4.8 Hz, 1H), 6.89 (t, J = 8.0 Hz, 3H), 6.98 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 8.25 (d, J = 9.6 Hz, 3H), 8.36 (d, J = 8.4 Hz, 2H), 10.38 (s, 1H, NH); ESI-MS, m/z (%): 546 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}N_7O_5S$: C, 57.24; H, 4.25; N, 17.97; S, 5.88; found: C, 57.29; H, 4.29; N, 17.92; S, 5.83.

(E)-3-(2-(4-Methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl) methanone (4i). Colorless solid; mp 223–225°C; IR (KBr) ν_{max} (cm^{-1}): 3307 (NH stretching), 1687 (C═O stretching), 1610 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.92 (t, J = 6.8 Hz, 1H), 5.75 (d, J = 6.4 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 7.6 Hz, 2H), 8.25 (s, 1H), 10.47 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.2, 152.1, 143.4, 139.0, 137.9, 137.1, 134.9, 134.7, 134.4, 132.7, 129.7, 129.5, 129.2, 129.0, 127.9, 127.0, 126.6, 59.1, 43.6, 21.4, 21.1; ESI-MS, m/z (%): 469 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{24}N_6OS$: C, 66.64; H, 5.16; N, 17.94; S, 6.84; found: C, 66.69; H, 5.13; N, 17.91; S, 6.83.

(E)-(4-Bromophenyl)(3-(2-(4-methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4j). Colorless solid; mp 206–208°C; IR (KBr) ν_{max} (cm^{-1}): 3277 (NH stretching), 1679 (C═O stretching), 1591 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.95 (t, J = 6.4 Hz, 1H), 5.72 (d, J = 5.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H), 8.25 (s, 1H), 10.45 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.7, 152.0, 143.5, 139.0, 137.9, 137.0, 134.3, 134.0, 132.6, 131.2, 130.9, 129.7, 129.5, 128.9, 127.8, 127.0, 126.6, 58.7, 43.6, 21.4, 21.0; ESI-MS, m/z (%): 549 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}BrN_6OS$: C, 57.04; H, 4.23; Br, 14.60; N, 15.35; S, 5.86; found: 57.14; H, 4.28; Br, 14.68; N, 15.39; S, 5.81.

(E)-(4-Chlorophenyl)(3-(2-(4-methylbenzylidene) hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4k). Colorless solid; mp 206–208°C; IR (KBr) ν_{max} (cm^{-1}): 3277 (NH stretching), 1673 (C═O stretching), 1598 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.95 (t, J = 6.8 Hz, 1H), 5.72 (d, J = 5.6 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6HZ, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.5 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.25 (s, 1H, ─CH═N proton), 10.45 (s, 1H, NH); ESI-MS, m/z (%): 503 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}ClN_6OS$: C, 62.08; H, 4.61; Cl, 7.05; N, 16.71; S, 6.37; found: C, 62.14; H, 4.67; Cl, 7.10; N, 16.67; S, 6.33.

(E)-(2,4-Dichlorophenyl)(3-(2-(4-methylbenzylidene) hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)methanone (4l). Colorless solid; mp 172–174°C; IR (KBr) ν_{max} (cm^{-1}): 3278 (NH stretching),

1698 (C═O stretching), 1580 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.87 (t, J = 6.8 Hz, 1H), 5.52 (d, J = 6.OHz, 1H), 7.04 (d, J = 6.4 Hz, 1H), 7.1 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 6.8 Hz, 2H), 7.33–7.39 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 6.4 Hz, 3H), 7.74 (d, J = 12.4 Hz, 1H), 8.34 (s, 1H), 10.24 (s, 1H), 10.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.6, 152.3, 146.1, 143.3, 138.9, 137.3, 135.4, 133.8, 133.0, 132.8, 131.6, 130.4, 129.7, 129.4, 128.0, 127.8, 127.3, 126.6, 79.6, 59.4, 21.4; ESI-MS, *m/z* (%): 537 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{22}Cl_2N_6OS$: C, 58.10; H, 4.13; Cl, 13.19; N, 15.64; S, 5.97; found: C, 58.15; H, 4.16; Cl, 13.25; N, 15.70; S, 5.92.

(E)-(4-Fluorophenyl)(3-(2-(4-methylbenzylidene) hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-7-yl)methanone (4m). Colorless solid; mp 202–204°C; IR (KBr) ν_{max} (cm^{-1}): 3276 (NH stretching), 1676 (C═O stretching), 1594 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.93 (t, J = 6.8 Hz, 1H), 5.73 (d, J = 5.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 8.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 8.10–8.13 (m, 2H), 8.25 (s, 1H, ─CH═N proton), 10.44 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.0, 167.3, 164.7, 152.1, 137.9, 134.4, 132.3, 129.7, 129.5, 127.8, 126.6, 116.7, 116.5, 59.0, 43.6, 21.4, 21.0; ESI-MS, *m/z* (%): 487 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}FN_6O_6S$: C, 64.18; H, 4.76; N, 17.27; S, 6.59; found: C, 64.22; H, 4.71; N, 17.24; S, 6.55.

(E)-(3-(2-(4-Methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(p-tolyl) methanone (4n). Colorless solid; mp 200–202°C; IR (KBr) ν_{max} (cm^{-1}): 3275 (NH stretching), 1671 (C═O stretching), 1594 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.00 (d, J = 8.4 Hz, 1H), 5.70 (d, J = 5.6 Hz, 1H), 6.86–6.96 (m, 1H), 7.0 (d, J = 6.4 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.22 (s, 3H), 7.33 (d, J = 6.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 6.8 Hz, 1H), 7.5 (d, J = 7.2 Hz, 1H), 7.5 (d, J = 6.4 Hz, 1H), 7.85–7.91 (m, 2H), 8.26 (d, J = 17.2 Hz, 1H), 10.28 (s, 1H, NH); ESI-MS, *m/z* (%): 481 (M + H)$^+$; *Anal*. Calcd for $C_{27}H_{26}N_6OS$: C, 67.20; H, 5.43; N, 17.41; S, 6.64; found: C, 67.26; H, 5.48; N, 17.48; S, 6.69.

(E)-(4-Methoxyphenyl)(3-(2-(4-methylbenzylidene) hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-7-yl)methanone (4o). Colorless solid; mp 214–216°C; IR (KBr) ν_{max} (cm^{-1}): 3280 (NH stretching), 1673 (C═O stretching), 1598 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.85 (t, J = 7.2 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 7.6 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.23 (s, 1H, ─CH═N proton), 10.44 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.5, 164.5, 152.1, 143.4, 134.5, 131.6, 129.7, 129.5, 127.9, 127.6, 126.6, 114.8, 59.6, 56.1, 43.2, 21.4, 21.1; ESI-MS, *m/z* (%): 497 (M + H)$^+$; *Anal*. Calcd for $C_{27}H_{26}N_6O_2S$: C, 65.04; H, 5.26; N, 16.86; S, 6.43; found: C, 65.14; H, 5.22; N, 16.81; S, 6.49.

(E)-(3-(2-(4-Methylbenzylidene)hydrazinyl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(4-nitrophenyl)methanone (4p). Light yellow solid; mp 203–205°C; IR (KBr) ν_{max} (cm^{-1}): 3274 (NH stretching), 1683 (C═O stretching), 1593 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.04 (t, J = 5.6 Hz, 1H), 5.80 (d, J = 4.8 Hz, 1H), 6.91 (d, J = 6.8 Hz, 1H), 7.16 (d, J = 7.6 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 7.47–7.53 (m, 4H), 8.27 (d, J = 7.6 Hz, 3H), 8.37 (d, J = 8.0 Hz, 2H), 10.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.7, 150.7, 143.5, 139.8, 139.0, 137.9, 136.8, 134.2, 132.7, 130.7, 129.7, 129.5, 127.7, 127.1, 126.6, 124.4, 58.2, 44.4, 21.4, 21.0; ESI-MS, *m/z* (%): 514 (M + H)$^+$; *Anal*. Calcd for $C_{26}H_{23}N_7O_3S$: C, 60.81; H, 4.51; N, 19.09; S, 6.24; found: C, 60.87; H, 4.56; N, 19.14; S, 6.20.

General procedure for the synthesis of compounds (6a, b). 4-Amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (1 mmol), aromatic aldehyde (2 mmol), and phenacyl bromide (1 mmol) were taken in a round bottom flask containing 5 mL of absolute alcohol and refluxed for 3 h. The progress of the reaction was monitored through TLC using ethyl acetate and n-hexane (40%). After completion of the reaction, the reaction mixture was cooled to room temperature, and the solid separated was filtered and purified by recrystallization from ethanol.

2-((4-((E)-(4-Methoxybenzylidene)amino)-5-((E-2-(4-methoxybenzylidene)hydrazinyl)-4H-1,2,4-triazol-3-yl)thio)-1-(4-methoxyphenyl)ethanone (6a). Colorless solid; mp 119–121°C; IR (KBr) ν_{max} (cm^{-1}): 3400 (NH stretching), 2964 (CH stretching), 1673 (C═O stretching), 1599 (C═N stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.72 (s, 2H, CH_2), 6.77 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 4H), 7.28 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 8.86 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.2, 169.5, 164.3, 164.2, 161.8, 149.7, 147.7, 145.8, 132.2, 131.3, 129.7, 128.2, 126.3, 124.0, 115.2, 114.7, 114.5, 56.2, 56.1, 55.8; ESI-MS, *m/z* (%): 531 (M + H)$^+$; *Anal*. Calcd for $C_{27}H_{26}N_6O_4S$: C, 61.12; H, 4.94; N, 15.84; S, 6.04; found: C, 61.19; H, 4.98; N, 15.81; S, 6.12.

1-(4-Fluorophenyl)-2-((4-((E)-(4-methoxybenzylidene) amino)-5-((E-2-(4-methoxybenzylidene)hydrazinyl)-4H-1,2,4-triazol-3-yl)thio)ethanone (6b). Colorless solid; mp 212–214°C; IR (KBr) ν_{max} (cm^{-1}): 3400 (NH stretching), 2945 (CH stretching), 1691 (C═O stretching), 1599

(C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.47 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.00 (s, 2H, CH_2), 6.28 (s, 2H), 7.03 (d, J = 8.4 Hz, 3H), 7.42 (t, J = 8.8 Hz, 3H), 7.79 (d, J = 8.4 Hz, 3H), 8.17 (t, J = 8 Hz, 2H), 8.36 (s, 1H), 12.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 191.9, 161.7, 151.3, 150.7, 149.3, 132.0, 132.0, 131.3, 129.7, 126.2, 116.8, 116.5, 116.3, 114.7, 55.8, 23.6; ESI-MS, *m/z* (%): 519 $(M + H)^+$; *Anal*. Calcd for $C_{26}H_{23}FN_6O_3S$: C, 60.22; H, 4.47; N, 16.21; S, 6.18; found: C, 60.28; H, 4.42; N, 16.26; S, 6.13.

General procedure for the synthesis of 4-((*E*)-(4-methoxybenzylidene)amino)-5-((*Z*)-2-(4-methoxybenzylidene) hydrazinyl)-4*H*-1,2,4-triazole-3-thiol (7). 4-Amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (1 mmol) and 4-methoxybenzaldehyde (2 mmol) were taken in a round bottom flask containing 5 mL of absolute alcohol and refluxed for about 1 h. The progress of the reaction was monitored through TLC using ethyl acetate and n-hexane (40%). After completion of the reaction, the reaction mixture was cooled to room temperature. The solid separated was filtered and washed with water. The crude product was recrystallized from methanol. Colorless solid; mp 241–243°C; IR (KBr) ν_{max} (cm^{-1}): 1636 (C=N stretching), 2610 (SH stretching); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.98 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 8.27 (s, 1H), 9.90 (s, 1H), 10.52 (s, 1H), 13.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 162.6, 160.8, 159.8, 148.7, 145.3, 131.3, 128.4, 127.5, 125.2, 114.9, 114.7, 56.0, 55.7; ESI-MS, *m/z* (%): 383 $(M + H)^+$; *Anal*. Calcd for $C_{18}H_{18}N_6O_2S$: C, 56.53; H, 4.74; N, 21.97; S, 8.38; found: C, 56.59; H, 4.79; N, 21.93; S, 8.32.

Acknowledgments. The authors are thankful to the Director, National Institute of Technology, Warangal, Telangana, India, for providing the facilities. S. K. thanks the MHRD, India, for fellowship.

REFERENCES AND NOTES

[1] Parchinsky, V. Z.; Koleda, V. V.; Shuvalova, O.; Kravchenko, D. V.; Krasavin, M. Tetrahedron Lett 2006, 47, 6891.

[2] Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. Chem - An Asian J 2318, 2010, 5.

[3] Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Angew Chem Int Ed 2011, 50, 6234.

[4] Groenendaal, B.; Ruijter, E.; Orru, R. V. A. Chem Commun 2008, 43, 5474.

[5] Domling, A.; Wang, W.; Wang, K. Chem Rev 2012, 112, 3083.

[6] Tam, A.; Armstrong, I. S.; La Cruz, T. E. Org Lett 2013, 15, 3586.

[7] Lebouvier, N.; Pagniez, F.; Duflos, M.; Le Pape, P.; Na, Y. M.; Le Baut, G.; Le Borgne, M. Bioorg Med Chem Lett 2007, 17, 3686.

[8] Papadopoulou, M. V.; Bloomer, W. D.; Rosenzweig, H. S.; Wilkinson, S. R.; Szular, J.; Kaiser, M. Eur J Med Chem 2016, 123, 895.

[9] Akbarzadeh, T.; Tabatabai, S. A.; Khoshnoud, M. J.; Shafaghi, B.; Shafiee, A. Bioorg Med Chem 2003, 11, 769.

[10] Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N.; Papakonstantinou-Garoufalias, S.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. II Farm 2002, 57, 253.

[11] Sarapultsev, A.; Chupakhin, O.; Sarapultsev, P.; Sidorova, L.; Tseitler, T. Pharmaceuticals 2016, 9, 27.

[12] Kucukguzel, S. G.; Cikla-Suzgun, P. Eur J Med Chem 2015, 97, 830.

[13] Sahu, J.; Kaushik, A.; Ganguly, S. J Adv Pharm Technol Res 2014, 5, 90.

[14] Khan, I.; Ibrar, A.; Abbas, N. Eur J Med Chem 2013, 63, 854.

[15] El Shehry, M. F.; Abu-Hashem, A. A.; El-Telbani, E. M. Eur J Med Chem 2010, 45, 1906.

[16] Karegoudar, P.; Prasad, D. J.; Ashok, M.; Mahalinga, M.; Poojary, B.; Holla, B. S. Eur J Med Chem 2008, 43, 808.

[17] Kamal, A.; Khan, M. N. A.; Srikanth, Y. V. V.; Srinivasa Reddy, K.; Juvekar, A.; Sen, S.; Kurian, N.; Zingde, S. Bioorg Med Chem 2008, 16, 7804.

[18] Hussein, M. A.; Shaker, R. M.; Ameen, M. A.; Mohammed, M. F. Arch Pharm Res 2011, 34, 1239.

[19] Khan, I.; Ibrar, A.; Zaib, S.; Ahmad, S.; Furtmann, N.; Hameed, S.; Simpson, J.; Bajorath, J.; Iqbal, J. Bioorg Med Chem 2014, 22, 6163.

[20] Skoumbourdis, A. P.; LeClair, C. A.; Stefan, E.; Turjanski, A. G.; Maguire, W.; Titus, S. A.; Huang, R.; Auld, D. S.; Inglese, J.; Austin, C. P.; Michnick, S. W.; Xia, M.; Thomas, C. J. Bioorg Med Chem Lett 2009, 19, 3686.

[21] Kaushik, N.; Kumar, N.; Kumar, A. Immunol Endocr Metab Agents Med Chem 2016, 16, 70.

[22] Amer, S.; El-Wakiel, N.; El-Ghamry, H. J Mol Struct 2013, 1049, 326.

[23] Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad, S. K. Eur J Med Chem 2012, 57, 407.

[24] Vaarla, K.; Kesharwani, R. K.; Santosh, K.; Vedula, R. R.; Kotamraju, S.; Toopurani, M. K. Bioorg Med Chem Lett 2015, 25, 5797.

[25] Penta, S.; Gadidasu, K. K.; Basavoju, S.; Rajeswar Rao, V. Tetrahedron Lett 2013, 54, 5663.

[26] Dickinson, R. G.; Jacobsen, N. W. Org Prep Proced Int 1974, 6, 156.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Molecular Diversity
https://doi.org/10.1007/s11030-019-09962-3

ORIGINAL ARTICLE

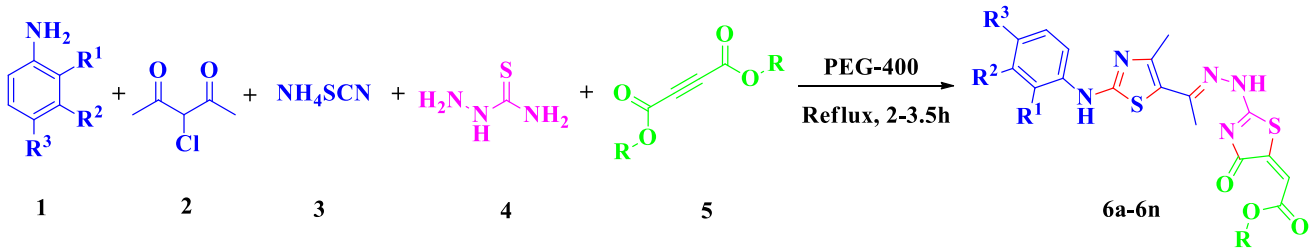
Polyethylene glycol (PEG-400) promoted one-pot, five-component synthesis of (E)-ethyl2-(2-((E)-2-(1-(4-methyl-2-(phenylamino) thiazol-5yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene) acetates

Kodam Sujatha[1] · **Rajeswar Rao Vedula**[1]

Received: 3 April 2019 / Accepted: 16 May 2019

Abstract
A facile, inexpensive and eco-friendly synthesis of functionalised (E)-ethyl2-(2-((E)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl)ethylidene)hydrazinyl)14-oxothiazol-5(4*H*)-ylidene)acetates has been developed via one-pot five-component approach. The title compounds were synthesized by the reaction of anilines, 3-chloropentane-2,4-dione, ammoniumthiocyanate, thiosemicarbazide and dialkylacetylene dicarboxylate using polyethylene glycol as green and recyclable solvent. The domino reaction proceeded smoothly in good-to-excellent yields.

Graphical abstract



Keywords Ammoniumthiocyanate · Anilines · 3-Chloroacetylacetone · Dialkylacetylene dicarboxylates · PEG-400

Introduction

Thiazoles are versatile precursors for the synthesis of biologically active heterocyclic molecules. Thiazoles and their analogues represent an important class of heterocycles, which is abundant in various natural products [1]. Thiazoles exhibit diverse range of biological activities like anticancer [2], anti-inflammatory [3], antifungal [4], antiviral [5], antitubercular [6], antimalarial activity [7] and anticandida activity [8]. The striking drug activity of these compounds not only attracted chemists to synthesize heterocyclic nucleus but also became an active research area of continuing interest [9].

Meanwhile, thiazolidinones are good structural motif found in many biologically active compounds [10]. Thiazolidinones and their derivatives also exhibit anti-inflammatory [11], antifungal, antibacterial [12], antiviral [13], antioxidant, antibacterial [14] and antimalarial activity [15] (Fig. 1).

Inspired by biological profile of thiazoles, thiazolidinones and their increasing importance in pharmaceutical

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-019-09962-3) contains supplementary material, which is available to authorized users.

✉ Rajeswar Rao Vedula
rajeswarnitw@gmail.com

[1] Department of Chemistry, National Institute of Technology, Warangal, Telangana 506 004, India

Published online: 23 May 2019

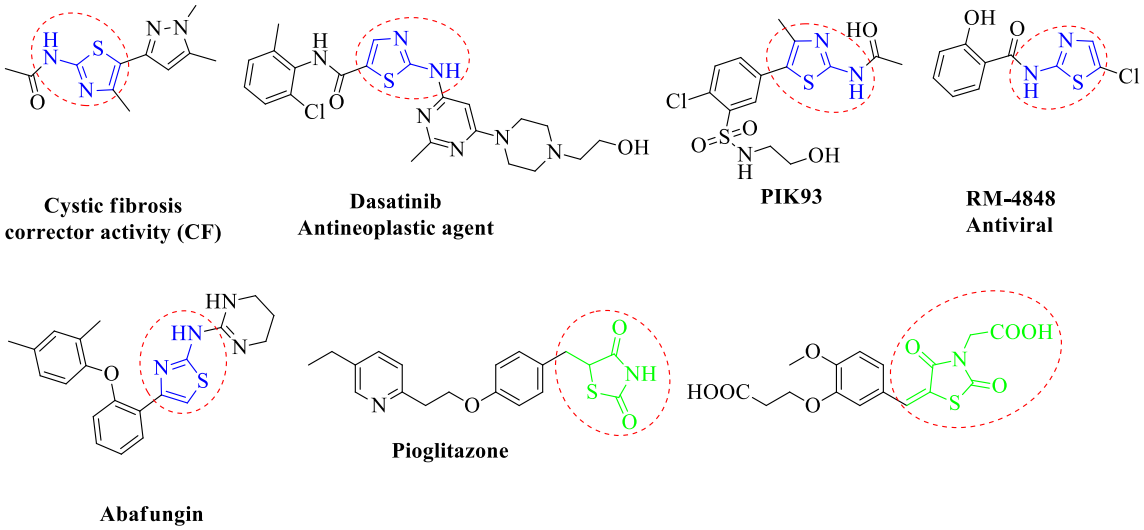


Fig. 1 Biologically active molecules on thiazole and thiazolidinones

and biological fields [16, 17], we would like to synthesize the title compounds.

Notably, synthesis of diversified heterocyclic molecules from simple and readily available starting materials in a low-cost and time-effective manner is durable challenge for organic chemists [18]. MCRs, where three or more reactants are combined together in a single reaction vessel to generate a product incorporating most of the atoms contained in the reactants, are considered as an effective tool for this challenge [19, 20]. These reactions are applicable both green chemistry and economic point of view. They are useful for generating combinatorial libraries of complex organic molecules in a very short time. MCRs have acquired great interest in recent time [21].

Polyethylene glycol has gained much importance as a powerful green solvent for many organic reactions [22]. Most importantly, it is an inexpensive, nontoxic, thermally stable, easy to handle and recyclable medium. Due to these qualities, we were inspired to examine the usefulness of PEG-400 in multicomponent reactions for the synthesis of title compounds.

In continuation of our ongoing research to develop new synthetic methodologies for the synthesis of diverse heterocycles using multicomponent reactions [23–25] and in order to enhance the biological activity of both thiazole and thiazolidinones, it was thought of interest to accommodate thiazole and thiazolidinones moieties in a single framework to obtain a new class of compounds with potential biological activity.

Results and discussion

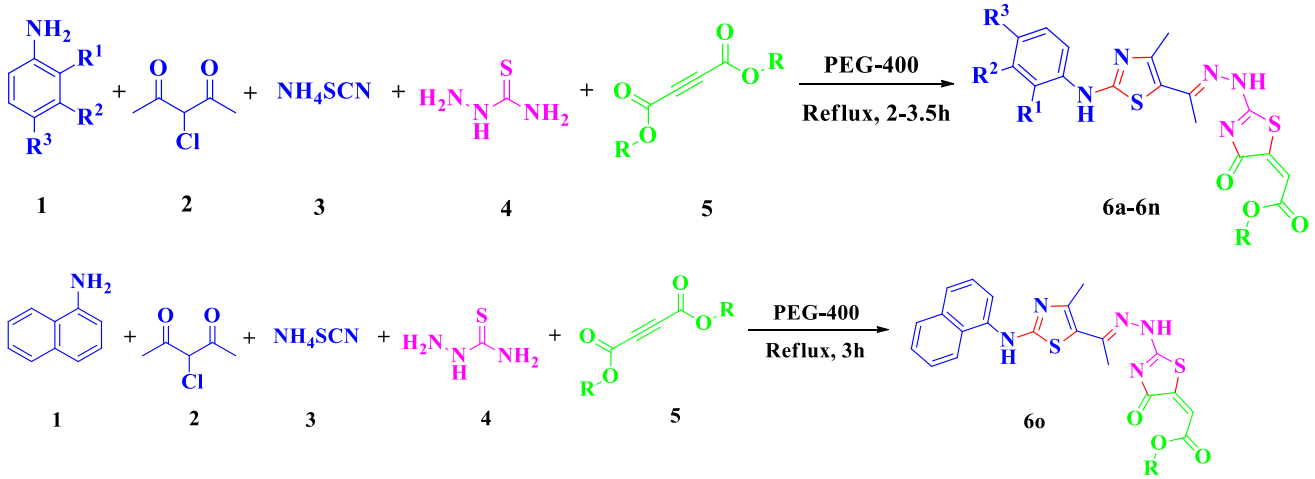
In this article firstly, we wish to report the synthesis of highly substituted thiazolyl thiazolidinones via the five-component reaction of aromatic amines, ammoniumthiocyanate, 3-chloroacetylacetone, thiosemicarbazide and dialkylacetylene dicarboxylates in polyethylene glycol (Scheme 1, method-**1**).

Reaction of equimolar mixture of aromatic amine, ammoniumthiocyanate and 3-chloroacetylacetone in polyethylene glycol under reflux condition afforded an intermediate 7 (not isolated). To this on further addition of equimolar amount of thiosemicarbazide and dialkylacetylene, dicarboxylate under reflux gave compound **6**.

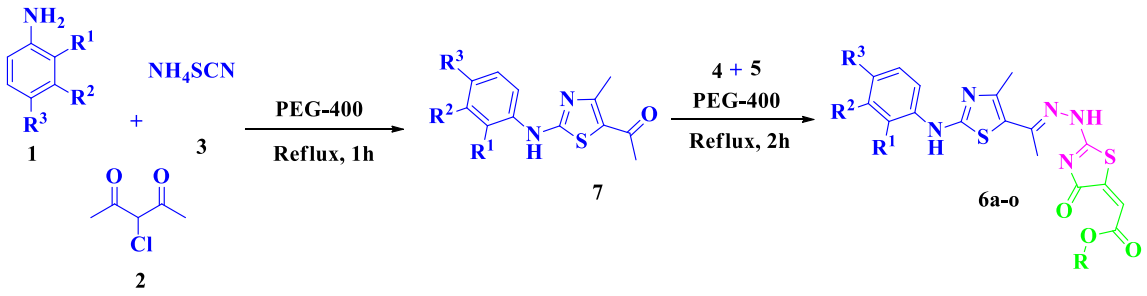
The method-**1** is less time-consuming, and it involves a simple workup procedure and is of general applicability. The reaction takes place under mild conditions. This work may trigger on interesting chemistry involving new methodology. The main feature of the synthesis is that eight heteroatom bonds like 3C-S, 2C=N, 2C-N bond and one cyclic N–C=O are formed simultaneously in one pot leading to selective novel heterocyclization without formation of any side products.

Compound **6** can also be synthesized by an alternative method involving condensation of aromatic amines, NH_4SCN and 3-chloroacetylacetone in polyethylene glycol to yield the corresponding substituted 1-(4-methyl-2-(*p*-tolylamino)thiazol-5-yl)ethanones **7** (isolated).

These on reaction with thiosemicarbazide and dialkylacetylene dicarboxylate resulted in the formation of cyclocondensation products (yield 70–80%) **6** via a two-step process (Scheme 2, method-**2**) of the cyclocondensation that proceeds in such a way that the intermediate thiosemicarbazone of **7** reacts with dialkylacetylene dicarboxylate to give the final products **6**. The products obtained by both the methods were found to be identical by their mixed melting point measurements, co-TLC and IR spectra. In the present investigation, method-**1**



Scheme 1 Method-**1**, one-pot multicomponent synthesis of compounds **6a–6o**



Scheme 2 Method-**2**, stepwise or unambiguous synthesis of compounds **6a–6o** from intermediate **7**

Table 1 Optimization of reaction conditions for the synthesis of **6b**

Entry	Reaction condition	Solvent	Catalyst (10 mol%)	Time (h)	Yields (%) of **6b**
1	Reflux	DMF	–	24	–
2	Reflux	DMF + EtOH	–	24	40
3	Reflux	CH_3OH	–	12	52
4	Reflux	Acetone	–	12	50
5	Reflux	THF	–	24	–
6	Reflux	H_2O	–	24	–
7	Reflux	EtOH	KOH	12	–
8	Reflux	EtOH	NaOH	12	–
9	Reflux	EtOH	$NaHCO_3$	12	–
10	Reflux	EtOH	NH_4OH	12	–
11	Reflux	EtOH	K_2CO_3	12	–
12	Reflux	PEG-400	–	3	96

was preferred over method-**2** because of advantages in method-**1**. The structures of **6** and **7** were confirmed by their analytical and spectral data such as IR, NMR, ^{13}C and MS spectra (Table 1).

Initially, the reaction of 4-methyl aniline (1.0 equivalent), NH_4SCN (1.0 equivalent), 3-chloroacetylacetone (1.0 equivalent), thiosemicarbazide (1.0 equivalent) and dialkylacetylene dicarboxylate was tested in the presence of DMF at reflux condition. The reaction did not proceed. The reaction was tried in various solvents such as DMF + EtOH, CH_3OH, acetone, THF and water. The reaction did not proceed for completion. Different base catalysts such as KOH, NaOH, $NaHCO_3$, NH_4OH and K_2CO_3 were screened (10 mol%) in ethanol under reflux to find out the optimum condition. The reaction did not yield any product. Ultimately, we investigated that the reaction in polyethylene glycol under reflux gave the desired product. Thus, among all the solvents, polyethylene glycol was found to be the best solvent for this MCR.

Thus, to avoid the environmental pollution, we have used the greener reaction medium. Among various solvents tried, PEG-400 was found to be an efficient reaction medium in terms of reaction time as well as yield. In addition, the recyclability of the PEG-400 was investigated and revealed the important observation that PEG-400 was recovered and reused for four times without loss of its activity. We observed that in the first run percentage of yield was 96, in the second run 93%, in the third run 91% and in the fourth run a very slight change of 90%.

After isolation of the product, water was removed through direct distillation and PEG-400 was washed with diethyl ether (two times, every time 3 ml). The recovered PEG-400 was used in consecutive runs (four times) without much loss of efficiency and with a negligible loss of PEG-400.

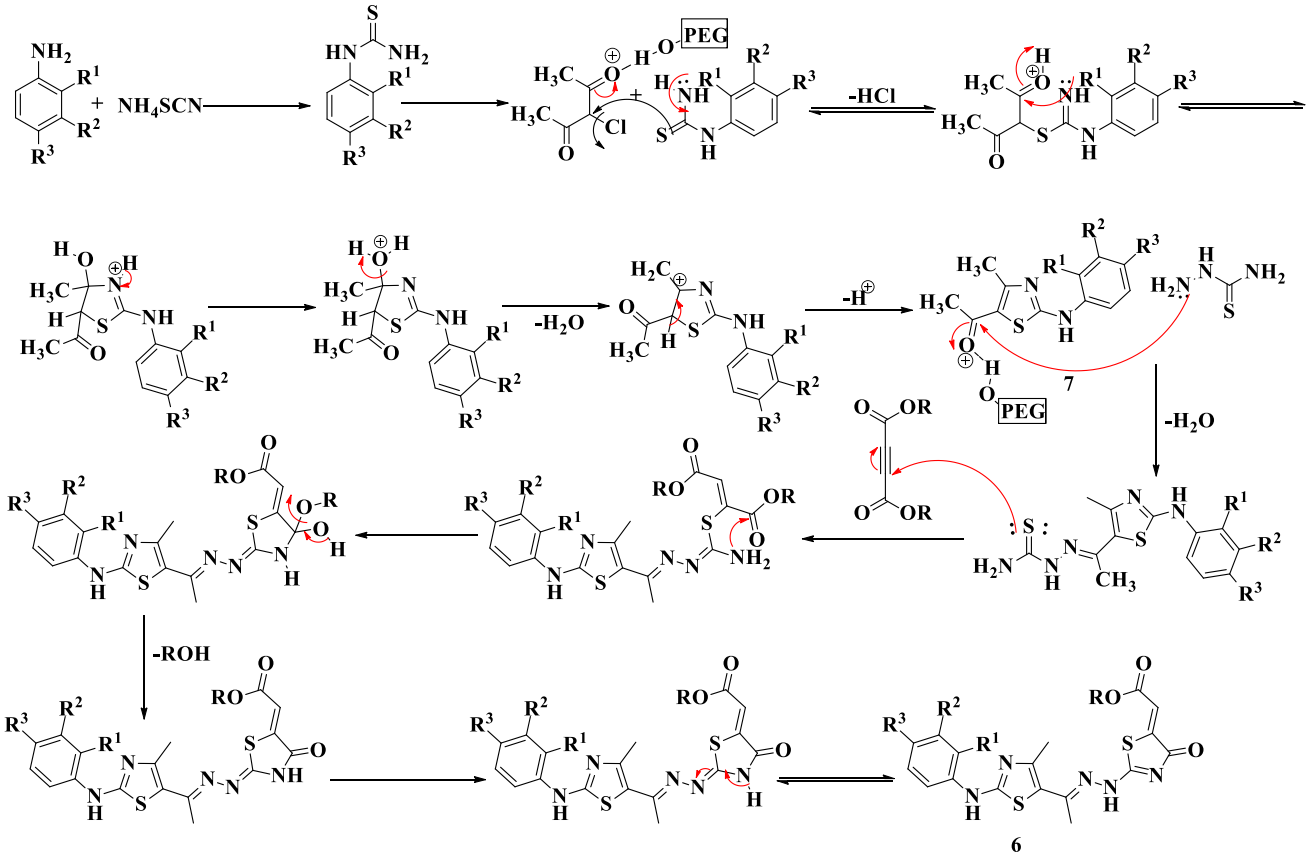
Under the optimized reaction conditions, a study on the substrate scope was carried out and the results are summarized. It can be found from the results that a wide range of aromatic amines are suitable for this multicomponent reaction. Aromatic amines tethered with both electron donating and electron withdrawing substituents afforded the desired products in good yields. Bulky amine such as α-naphthyl amine also underwent this five-component reaction smoothly to provide the final product. But these compounds are practically sparingly soluble in routine solvents. Next we realized that this protocol is not so useful for aliphatic amines (Table 2).

We believe the mechanism of the reaction goes via the Hantzsch thiazole condensation of aromatic amines, ammoniumthiocyanate and 3-chloroacetylacetone to give intermediate **7**. Simultaneously, thiosemicarbazide reacts with **7** to give corresponding thiosemicarbazone of **7**. The next step is the cyclocondensation of added dialkylacetylene dicarboxylate to yield the final compounds **6** (Scheme 3).

The structures of all the newly synthesized title compounds were confirmed by their spectral data. The IR spectrum of compound **6a** showing prominent peaks at 1693 cm^{-1} is due to C=O stretching vibration. The peak 3199 cm^{-1} is due to –NH– stretching vibration frequency. The ^1H NMR spectrum of compound **6a** showed characteristic singlet for CH_3 at δ 1.28, quartet for OCH_2 at 4.25, and NH at δ 12.80 ppm and ^{13}C NMR spectrum of compound **6a** showed characteristic CH_3 carbon at δ 14.4 ppm. The other carbon atoms appear at the expected region. The compound **6a** exhibited the $[M+H]^+$ peak at *m*/*z* 430.

Table 2 Different substitutions of the compounds (**6a–6o**)

Entry	Product	R	R^1	R^2	R^3	Time (h)	Yields (%)
1	**6a**	OEt	H	H	H	3	94
2	**6b**	OEt	H	H	CH_3	3	96
3	**6c**	OEt	CH_3	CH_3	H	2.5	90
4	**6d**	OEt	H	OCH_3	H	3	95
5	**6e**	OEt	H	H	OCH_3	3.5	95
6	**6f**	OEt	H	OH	H	3	93
7	**6g**	OEt	H	Cl	H	2.5	91
8	**6h**	OEt	H	H	Cl	3	95
9	**6i**	OEt	H	NO_2	H	3.5	89
10	**6j**	OCH_3	H	H	H	2.5	97
11	**6k**	OCH_3	H	OCH_3	H	3	92
12	**6l**	OCH_3	H	OH	H	3.5	90
13	**6m**	OCH_3	H	Cl	H	3	85
14	**6n**	OCH_3	H	H	Cl	3	93
15	**6o**	OCH_3	–	–	–	3	96



Scheme 3 Plausible mechanism for the synthesis of **6a–6o**

Conclusion

In conclusion, we have developed a facile and efficient one-pot five-component protocol for the synthesis of highly substituted thiazolo thiazolidinones using PEG-400 as a green reaction medium with high yields. This domino reaction proceeded smoothly in good-to-excellent yields and afforded several advantages such as short reaction time, metal free, simple experimental procedure, easy workup, simple purification and greener aspects such as lack of hazardous organic solvent, ease of recovery and reuse of reaction medium.

Experimental section

All the reagents and chemicals which were used in the present study were purchased from commercial sources and used further without any purification. Melting points were determined in open capillaries with a Stuart melting point apparatus, Mumbai, India, and were uncorrected. IR spectra were recorded on PerkinElmer Spectrum 100 s. ^{1}H-NMR spectra were recorded on Bruker WM-400 spectrometer in δ ppm using TMS as the standard, and ESI–MS spectra were recorded on Jeol JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer, and compounds purity was checked by TLC plates (E Merck, Mumbai, India). Supplemental Materials contain ^{1}H and ^{13}C NMR spectra of products **6a–6o**.

General procedure for compounds (6a–6o) Amixture of substituted aniline (1 mmol), 3-chloroacetylacetone (1 mmol) and ammoniumthiocyanate (1 mmol) was taken in 5 ml of polyethylene glycol-400 and refluxed for 1 h by monitoring TLC (ethyl acetate and *n*-hexane 2:8). After completion of the reaction, to the reaction mixture thiosemicarbazide (1 mmol) and dialkylacetylene dicarboxylate (1 mmol) were added. The reaction mixture was refluxed for another 1–2 h by monitoring TLC. The mixture was cooled to room temperature and poured into ice-cold water. The precipitate formed was filtered off and washed with water, and the crude product was purified by recrystallization from methanol to get the pure product **6a–6o**.

General procedure for the synthesis of substituted 1-(4-methyl-2-(p-tolylamino)thiazol-5-yl)ethanone (7) Amixture of aromatic amine (1 mmol), ammoniumthiocyanate (1 mmol) and 3-chloroacetylacetone (1 mmol) was taken 5 ml of polyethylene glycol and refluxed for 1 h. The solid

separated was collected by filtration and recrystallized from ethanol. White solid; mp 189–191 °C (lit [26] 190–192 °C).

General procedure for the synthesis of (6) from (7) Amixture of compound **7** (1 mmol) and thiosemicarbazide (1 mmol) was taken in 5 ml of polyethylene glycol and refluxed for half an hour (by monitoring TLC) and to this dialkylacetylene dicarboxylate (1 mmol) was added and refluxed for 1 h. The mixture was cooled to room temperature and poured into ice-cold water. The precipitate formed was filtered off and washed with water, and the crude product was purified by recrystallization from methanol to get the pure products **6a**–**6o**.

(E)-ethyl2-(2-((E)-2-(1-(4-methyl-2-(phenylamino)thiazol-5yl) ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6a) Orange solid; mp 307–309 °C; Yield (92%); IR (KBr, ν_{max}, cm^{-1}):1693 cm^{-1} (C=O stretching), 3199 cm^{-1} (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.28 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.62 (s, 1H,), 7.00 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 10.46 (s, 1H), 12.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.4, 16.9, 19.2, 61.6, 114.4, 117.9, 120.7, 122.3, 129.4, 141.0, 143.6, 151.5, 157.7, 159.0, 163.3, 165.9, 166.0; ESI–MS, *m/z* (%): 430 $(M+H)^+$; Anal. calcd. for $C_{19}H_{19}N_5O_3S_2$: C, 53.13; H, 4.46; N, 16.31; S, 14.93. Found: C, 53.18; H, 4.40; N, 16.38; S, 14.90.

(E)-ethyl2-(2-((E)-2-(1-(4-methyl-2-(p-tolylamino)thiazol-5yl) ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6b) Orange solid; mp 244–246 °C; Yield (96%); IR (KBr, ν_{max}, cm^{-1}): 1692 (C=O stretching), 3196 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.26 (t, J = 4.0 Hz, 3H), 2.28 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.23 (q, J = 4.0 Hz, 2H), 4.65 (s, 3H), 6.60 (s, 1H,), 7.16 (d, J = 4.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 10.65 (s, 1H), 12.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.5, 16.8, 18.6, 20.9, 61.7, 114.6, 118.9, 120.1, 130.0, 132.2, 138.0, 143.5, 149.9, 157.9, 158.8, 164.0, 165.8, 166.0; ESI–MS, *m/z* (%): 444 $(M+H)^+$; Anal. calcd. for $C_{20}H_{21}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79; S, 14.46. Found: C, 54.10; H, 4.72; N, 15.73, S, 14.41.

(E)-ethyl2-(2-((E)-2-(1-(2-((2,3-dimethyl phenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6c) Orange solid; mp 292–294 °C; Yield (90%); IR (KBr, ν_{max}, cm^{-1}): 1687 (C=O stretching), 3221 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.25 (t, J = 8.0 Hz, 3H), 2.15 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.23 (q, J = 4.0 Hz, 2H), 6.60 (s, 1H,), 7.04 (d, J = 4.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 9.66 (s, 1H), 12.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.3, 14.5, 15.8, 17.0, 19.2, 20.7, 61.7, 102.9, 111.0, 112.7, 114.7, 122.3, 126.3, 127.6, 130.9, 138.2, 143.9, 150.7, 159.4, 162.0, 165.7; Anal. calcd. for $C_{21}H_{23}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79; S, 14.46. Found: C, 54.19; H, 4.72; N, 15.73; S, 14.40.

(E)-ethyl2-(2-((E)-2-(1-(2-((3-methoxy phenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6d) Orange solid; mp 287–289 °C; Yield (95%); IR (KBr, ν_{max}, cm^{-1}): 1694 (C=O stretching), 3208 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.28 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.60 (t, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.40 (s, 1H), 10.46 (s, 1H), 12.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ14.4, 16.8, 19.2, 55.4, 61.6, 103.9, 107.5, 110.4, 114.4, 120.8, 130.1, 142.1, 143.6, 151.3, 157.9, 158.9, 160.3, 163.2, 165.9, 166.0; ESI–MS, *m/z* (%): 460 $(M+H)^+$; Anal. calcd. for $C_{20}H_{21}N_5O_4S_2$: C, 52.27; H, 4.61; N, 15.24; S, 13.96. Found: C, 52.22; H, 4.65; N, 15.20; S, 13.92.

(E)-ethyl2-(2-((E)-2-(1-(2-((4-methoxy phenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6e) Orange solid; mp 236–238 °C; Yield (95%); IR (KBr, ν_{max}, cm^{-1}): 1690 (C=O stretching), 3130 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.27 (t, J = 8.0 Hz, 3H), 2.45 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.61 (s, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 10.25 (s, 1H), 12.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.4, 16.8, 19.2, 55.6, 61.6, 114.5, 114.7, 119.9, 134.4, 135.5, 143.7, 151.7, 155.0, 157.4, 159.0, 164.0, 165.9, 166.0; ESI–MS, *m/z* (%): 460 $(M+H)^+$; Anal. calcd. for $C_{20}H_{21}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72; S, 14.39. Found: C, 51.27; H, 4.35; N, 15.78; S, 14.44.

(E)-ethyl2-(2-((E)-2-(1-(2-((3-hydroxy phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6f) Orange solid; mp 300–302 °C; Yield (93%); IR (KBr, ν_{max}, cm^{-1}): 1686 (C=O stretching), 3149 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.28 (t, J = 8.0 Hz, 3H), 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.25 (q, J = 8.0 Hz, 2H), 6.41 (d, J = 12.0 Hz, 1H), 6.62 (s, 1H), 7.01 (d, J = 12.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.18 (s, 1H), 9.43 (s, 1H), 10.32 (s, 1H), 12.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.4, 16.9, 19.2, 61.6, 106.2, 108.9, 109.6, 114.4, 120.5, 130.0, 141.9, 143.6, 151.5, 157.6, 158.3, 159.0, 163.3, 165.9, 166.0; ESI–MS, *m/z* (%): 444 $(M-H)^+$; Anal. calcd.

for $C_{19}H_{19}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72; S, 14.39. Found: C, 51.26; H, 4.36; N, 15.75; S, 14.32.

(E)-ethyl2-(2-((E)-2-(1-(2-((3-Chloro phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6g) Orange solid; mp 254–256 °C; Yield (91%); IR (KBr, ν_{max}, cm^{-1}): 1691 (C=O stretching), 3061 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.27 (t, $J=8.0$ Hz, 3H), 2.46 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.23 (q, $J=8.0$ Hz, 2H), 6.61 (s, 1H), 7.02–7.04 (m, 1H), 7.35 (t, $J=8.0$ Hz, 1H), 7.50–7.52 (m, 1H), 7.89 (t, $J=4.0$ Hz, 1H), 10.62 (s, 1H), 12.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.5, 16.8, 19.2, 61.7, 114.6, 116.3, 117.1, 121.6, 121.7, 131.0, 133.8, 142.3, 143.6, 151.2, 158.2, 158.9, 162.8, 165.9, 166.0; ESI–MS, *m/z* (%): 464 $(M+H)^+$; Anal. calcd. for $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.09; S, 13.82. Found: C, 49.15; H, 3.95; N, 15.12; S, 13.88.

(E)-ethyl2-(2-((E)-2-(1-(2-((4-Chloro phenyl)amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6h) Orange solid; mp 305–307 °C; Yield (95%); IR (KBr, ν_{max}, cm^{-1}): 1694 (C=O stretching), 3189 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.27 (t, $J=8.0$ Hz, 3H), 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.24 (q, $J=8.0$ Hz, 2H), 6.61 (s, 1H), 7.38 (d, $J=12.0$ Hz, 2H), 7.70 (d, $J=8.0$ Hz, 2H), 10.57 (s, 1H), 12.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.4, 16.8, 19.2, 61.6, 114.4, 119.3, 121.3, 125.5, 129..2, 139.9, 143.6, 151.2, 158.0, 158.8, 162.9, 165.9, 166.0; ESI–MS, *m/z* (%): 464 $(M+H)^+$; Anal. calcd. for $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.09; S, 13.82. Found: C, 49.15; H, 3.96; N, 15.14; S, 13.88.

(E)-ethyl2-(2-((E)-2-(1-(4-methyl-2-((3-nitrophenyl)amino)thiazole-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene) acetates (6i) Orange solid; mp 296–298 °C; Yield (89%); IR (KBr, ν_{max}, cm^{-1}): 1694 (C=O stretching), 3253 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.27 (t, $J=8.0$ Hz, 3H), 2.47 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.24 (q, $J=8.0$ Hz, 2H), 6.60 (s, 1H), 7.61 (t, $J=8.0$ Hz, 1H), 7.82 (d, $J=8.0$ Hz, 1H), 7.95 (d, $J=8.0$ Hz, 1H), 8.76 (s, 1H), 10.91 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.4, 16.7, 19.2, 61.6, 114.3, 119.2, 121.3, 125.5, 129.2, 139.9, 143.6, 151.2, 158.0, 158.8, 162.9, 165.8, 166.0; ESI–MS, *m/z* (%): 475 $(M+H)^+$; Anal. calcd. for $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; S, 13.51. Found: 48.10; H, 3.88; N, 17.76; S, 13.58.

(E)-methyl 2-(2-((E)-2-(1-(4-methyl-2-(phenylamino)thiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene) acetates (6j) Orange solid; mp 312–314 °C; Yield (97%); IR (KBr, ν_{max}, cm^{-1}): 1693 (C=O stretching), 3083 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.65 (s, 1H,), 7.00 (t, $J=8.0$ Hz, 1H), 7.34 (t, $J=8.0$ Hz, 2H), 7.66 (d, $J=8.0$ Hz, 2H), 10.44 (s, 1H), 12.81 (s, 1H); ESI–MS, *m/z* (%): 414 $(M-H)^+$; Anal. calcd. for $C_{18}H_{17}N_5O_3S_2$: C, 52.03; H, 4.12; N, 16.86; S, 15.43. Found: C, 52.12; H, 4.17; N, 16.82; S, 15.47.

(E)-Methyl 2-(2-((E)-2-(1-(2-((3-methoxyphenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetates (6k) Red solid; mp 310–312 °C; Yield (92%); IR (KBr, ν_{max}, cm^{-1}): 1693 (C=O stretching), 3145 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.59 (t, $J=8.0$ Hz, 1H), 6.65 (s, 1H), 7.12 (d, $J=8.0$ Hz, 1H), 7.24 (t, $J=8.0$ Hz, 1H), 7.41 (s, 1H), 10.45 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ16.8, 19.2, 52.6, 55.4, 103.8, 107.7, 110.5, 113.8, 114.1; 120.9, 130.5, 131.7; 132.1; 138.2; 142.0, 158.9, 160.3, 163.3, 166.3; ESI–MS, *m/z* (%): 446 $(M+H)^+$; Anal. calcd. for $C_{19}H_{19}N_5O_4S_2$: C, 51.22; H, 4.30; N, 15.72; S, 14.39. Found: C, 51.27; H, 4.34; N, 15.67; S, 14.35.

(E)-methyl 2-(2-((E)-2-(1-(2-((3-hydroxyphenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetate (6l) Red solid; mp 295–297 °C; Yield (90%); IR (KBr, ν_{max}, cm^{-1}): 1688 (C=O stretching), 3145 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.41 (d, $J=8.0$ Hz, 1H), 6.65 (s, 1H), 7.02 (d, $J=8.0$ Hz, 1H), 7.11 (t, $J=8.0$ Hz, 1H), 7.19 (s, 1H), 9.43 (s, 1H), 10.32 (s, 1H), 12.81 (s, 1H); ESI–MS, *m/z* (%): 430 $(M-H)^+$; Anal. calcd. for $C_{18}H_{17}N_5O_4S_2$: C, 50.10; H, 3.97; N, 16.23; S, 14.86. Found: C, 50.14; H, 3.92; N, 16.28; S, 14.82.

(E)-methyl 2-(2-((E)-2-(1-(2-((3-chlorophenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetate (6m) Orange solid; mp 308–310 °C; Yield (85%); IR (KBr, ν_{max}, cm^{-1}): 1697 (C=O stretching), 3186 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.47 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.65 (s, 1H), 7.03 (d, $J=8.0$ Hz, 1H), 7.35 (t, $J=8.0$ Hz, 1H), 7.51 (d, $J=12.0$ Hz, 1H), 7.91 (s, 1H), 10.63 (s, 1H), 12.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ16.7, 19.2, 52.7, 114.2, 116.2, 117.1, 121.6, 123.3, 131.0, 133.8, 142.3, 143.8, 151.1, 158.1, 158.9, 162.8, 166.0, 166.4; ESI–MS, *m/z* (%): 450 $(M+H)^+$; Anal. calcd. for $C_{18}H_{16}ClN_5O_3S_2$: C, 48.05; H, 3.58; N, 15.57; S, 14.25. Found: C, 48.18; H, 3.52; N, 15.51; S, 14.29.

(E)-methyl 2-(2-((E)-2-(1-(2-((4-chlorophenyl) amino)-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)-ylidene)acetate (6n) Orange solid; mp 307–309 °C; Yield (93%); IR (KBr, ν_{max}, cm^{-1}): 1693 (C=O stretching), 3189 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.46 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.64 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.7 (d, J = 8.0 Hz, 2H), 10.57 (s, 1H), 12.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ16.7, 19.2, 52.7, 114.1, 119.3, 121.3, 125.5, 129.2, 139.9, 143.8, 151.3, 158.0, 158.9, 162.9, 166.0, 166.4; ESI–MS, *m/z* (%): 450 $(M+H)^+$; Anal. calcd. for $C_{18}H_{16}ClN_5O_3S_2$: C, 48.05; H, 3.58; N, 15.57; S, 14.25. Found: C, 48.19; H, 3.51; N, 15.61; S, 14.20.

(E)-methyl 2-(4-oxo-2-((E)-2-((3-(2-oxo-2H-benzo[h]chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl)thiazol-5(4H)-ylidene)acetate (6o) Orange solid; mp 302–304 °C; Yield (96%); IR (KBr, ν_{max}, cm^{-1}): 1702 (C=O stretching), 3053 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.45 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.65 (s, 1H), 7.53–7.59 (m, 3H), 7.74 (d, J = 8.0 Hz, 1H), 7.96–7.98 (m, 1H), 8.12–8.13 (m, 1H), 8.24–8.25 (m, 1H), 10.37 (s, 1H), 12.77 (s, 1H); ESI–MS, *m/z* (%): 464 $(M-H)^+$; Anal. calcd. for $C_{29}H_{19}N_5O_5S$: C, 63.38; H, 3.48; N, 12.74; S, 5.83. Found: C, 63.32; H, 3.43; N, 12.70; S, 5.87.

1-(4-methyl-2-(p-tolylamino)thiazol-5-yl)ethanones (7) White solid; mp 189–191 °C; Yield (97%); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.24 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.07 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 9.73 (s, 1H); ESI–MS, *m/z* (%): 247 $(M+H)^+$.

Acknowledgements The authors are thankful to the Director of the National Institute of Technology, Warangal Telangana, India, for providing financial support and facilities.

References

1. Alsharif ZA, Alam MA (2017) Modular synthesis of thiazoline and thiazole derivatives by using a cascade protocol. RSC Adv 7:32647–32651
2. de Santana TL, Barbosa MO, Gomes PATM, da Cruz ACN, da Silva TG, Leite ACL (2018) Synthesis, anticancer activity and mechanism of action of new thiazole derivatives. Eur J Med Chem 144:874–886
3. Sinha S, Doble M, Manju SL (2018) Design, synthesis and identification of novel substituted 2-amino thiazole analogues as potential anti-inflammatory agents targeting 5-lipoxygenase. Eur J Med Chem 158:34–50
4. Lino CI, de Souza IG, Borelli BM, Matos TTS, Teixeira INS, Ramos JP, de Souza Fagundes EM, Fernandes PO, Maltarollo VG, Johann S, de Oliveira RB (2018) Synthesis, molecular modeling studies and evaluation of antifungal activity of a novel series of thiazole derivatives. Eur J Med Chem 151:248–260
5. Sharma SK, Tandon M, Lown JW (2000) Design and synthesis of novel thiazole-containing cross-linked polyamides related to the antiviral antibiotic distamycin. J Org Chem 65(4):1102–1107
6. Karuvalam RP, Haridas KR, Nayak SK, Guru Row TN, Rajeesh P, Rishikesan R, Kumari NS (2012) Design, synthesis of some new (2-aminothiazol-4-yl)methylester derivatives as possible antimicrobial and antitubercular agents. Eur J Med Chem 49:172–182
7. Kumawat MK (2018) Thiazole containing heterocycles with antimalarial activity. Curr Drug Discov Technol 15:196–200
8. Maillard LT, Bertout S, Quinonero O, Akalin G, Turan-Zitouni G, Fulcrand P, Demirci F, Martinez J, Masurier N (2013) Synthesis and anti-Candida activity of novel 2-hydrazino-1,3-thiazole derivatives. Bioorg Med Chem Lett 23:1803–1807
9. Hai-Bo S, Shi-Jie Z, Qiu-Fu G, Dian-Wu G, Chao-Ming C, Wei-Xiao H (2010) Synthesis and anticancer evaluation of thiazolylchalcones. Bioorg Med Chem Lett 20:6555–6559
10. Sucheta, Tahlan S, Verma PK (2017) Biological potential of thiazolidinedione derivatives of synthetic origin. Chem Cent J 11:130
11. Apostolidis I, Liaras K, Geronikaki A, Hadjipavlou-Litina D, Gavalas A, Sokovic M, Glamoclija J, Ciric AC (2013) Synthesis and biological evaluation of some 5-arylidene-2-(1,3-thiazol-2-ylimino)-1,3-thiazolidin-4-ones as dual anti-inflammatory/antimicrobial agents. Bioorg Med Chem 21:532–539
12. Kouatli O, Athina G, Panagiotis Z, Charalabos C, Marina S, Ana C, Jasmina G (2010) Novel 4-thiazolidinone derivatives as potential antifungal and antibacterial drugs. Bioorg Med Chem 18:426–432
13. Saeed A, Al-Masoudi NA, Latif M (2013) Synthesis and antiviral activity of new substituted methyl [2-(arylmethylene-hydrazino)-4-oxo-thiazolidin-5-ylidene]acetates. Arch Pharm Chem Life Sci 346:618–625
14. Asghari A, Pourshab M, Mohseni M (2018) Synthesis, characterization, and evaluation of antioxidant and antibacterial activities of novel indole-hydrazono thiazolidinones. Monatsh Chem Chem Mon 149:2327–2336
15. Rojas Ruiz FA, Garcia-Sanchez RN, Estupinan SV, Gomez-Barrio A, Torres Amado DF, Perez-Solorzano BM, Nogal-Ruiz JJ, Martinez-Fernandez AR, Kouznetsov VV (2011) Synthesis and antimalarial activity of new heterocyclic hybrids based on chloroquine and thiazolidinone scaffolds. Bioorg Med Chem 19:4562–4573
16. Liaras K, Fesatidou M, Geronikaki A (2018) Thiazoles and thiazolidinones as COX/LOX inhibitors. Molecules 23:685
17. Bondock S, Khalifa W, Fadda AA (2007) Synthesis and antimicrobial evaluation of some new thiazole, thiazolidinone and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde. Eur J Med Chem 42:948–954
18. Domling A (2006) Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev 106:17–89
19. Zhu J, Bienaym H (2005) Multicomponent reactions. Wiley-VCH, Weinheim
20. Tietze LF, Brasche G, Gericke KM (2006) Domino reactions in organic synthesis. Wiley-VCH, Weinheim
21. Ibarra IA, Islas-Jacome A, Gonzalez-Zamora E (2018) Synthesis of polyheterocycles via multicomponent reactions. Org Biomol Chem 16:1402–1418
22. Chandrasekhar S, Narsihmulu Ch, Shameem Sultana S, Ramakrishna Reddy N (2002) Poly(ethylene glycol) (PEG) as a reusable solvent medium for organic synthesis. Application in the Heck reaction. Org. Lett. 4(25):4399–4401
23. Sujatha K, Vedula RR (2018) Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three component reaction under solvent free conditions. Synth Commun 48:302–308
24. Sujatha K, Deshpande RP, Kesharwani RK, Prakash Babu P, Vedula RR (2019) An efficient one-pot expeditious synthesis of

3-phenyl-1-(6-phenyl-7H-[1, 2, 4] triazolo[3,4-b][1, 3, 4] thiadiazin-3-yl)-1H-pyrazol-5-amines via multicomponent approach. Synth Commun 49:49–55
25. Sujatha K, Vedula RR (2019) Multicomponent efficient synthesis of new [1, 2, 4]triazolo[3, 4] thiadiazines. J Heterocycl Chem 56:832–838
26. Hai-Bo S, Shi-Jie Z, Yan-Fang L, Wei-Xiao H, Chao-Ming C (2011) Study on condensation of *N*-aryl thioureas with 3-bromo-acetylacetone: synthesis of aminothiazoles and iminodihydrothiazoles, and their in vitro antiproliferative activity on human cervical cancer cells. J Hetrocycl Chem 48:1061–1066

Indian Journal of Chemistry
Vol. 56B, October 2017, pp. 1089-1093

One pot multicoponent synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo [2,3*c*][1,2,4]triazol-5-yl)-2*H*-pyran-2-ones

Bade Thirupaiah, Kodam Sujatha & Vedula Rajeswar Rao*

Department of Chemistry, National Institute of Technology, Warangal 506 004, India
E-mail: vrajesw@yahoo.com

Received 27 March 2017; accepted (revised) 5 September 2017

An efficient one pot multicomponent reaction for the synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-*c*][1,2,4]triazol-5-yl)-2*H*-pyran-2-ones with good to excellent yields has been described. Reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), thiosemicarbazide (**2**) and various aromatic carboxylic acids (**3a-j**) in dry toluene and $POCl_3$ affords 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-*c*][1,2,4]triazol-5-yl)-2*H*-pyran-2-ones. All the synthesized compounds have been characterized by their analytical and spectral data.

Keywords: Dehydroacetic acid, benzoic acid, thiosemicarbazide, thiazole, thiazolo triazole, multicomponent reaction

Multi component reactions are the reactions in which two or more starting materials sequentially combine to form the final compound in a single reaction vessel. MCRs are efficient, atom economic and selective reactions because of lesser number of steps, shorter reaction time, good yields, and therefore, play an important role in modern organic chemistry[1-3].

The thiazole ring system is an important structural moiety found in a number of biologically active molecules. In recent years thiazoles have received much attention in the field of medicinal chemistry because of their pharmacological activities like antifungal[4], anti microbial[5], anti bacterial[6], anti inflammatory[7], anticancer[8] and anti-HIV[9]. On the other hand synthesis of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one and its derivatives has attracted considerable attention from organic and medicinal chemists[10] for many year due to their wide range of applications in the medical field in the form of fungicidal[11], complexing agent[12], anti microbial[13], good cosmetic[14], herbicidal[15] and insecticidal activities[16]. Thiazolo triazoles are an important class of heterocyclic molecules in which two fused rings of thiazole and triazole exist in isomeric forms and possess good biological activities[17-21].

In view of the pharmacological significance of thiazolotriazolyl pyrans and in continuation of our earlier research work[22-26] in the field of multi component synthesis of biologically active hetero cyclic compounds, herein we report the synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-*c*][1,2,4] triazol-5-yl)-2*H*-pyran-2-ones (**4**) *via* a multi component approach.

Results and Discussion

A few years ago triazolo-thiazoles were synthesized by Rao *et al*.[27] by two methods. These methods have limitations like harsh reaction conditions, multiple step synthesis, has longer reaction times, application of expensive metal catalyst and gave low yields. In the present method we have developed a new synthesis of title compounds *via* a multi component approach .This method gives greater yield of the products, a single step process with shorter duration, and does not require any metal catalyst.

Two methods of synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-*c*][1,2,4]triazol-5-yl)-2*H*-pyran-2-one derivatives (**4**) are given. Method I is a one-pot multi component synthesis. Reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), thiosemicarbazide (**2**) and various aromatic carboxylic acids (**3**) in dry toluene and $POCl_3$ under reflux gave a fused system 4-hydroxy-6-methyl-3-(3-phenyl-thiazolo[2,3-*c*][1,2,4]triazol-5-yl)-2*H*-pyran-2-one (**4**) (Scheme I).

Method II is a two-step procedure. Reaction of bromodehydroacetic acid (**1**) with thiosemicarbazide (**2**) in acetic acid under reflux gave the corresponding 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran- 2-one (**5**). This intermediate, on reactions with

substituted benzoic acids (**3a-j**) in the presence $POCl_3$ gave 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-*c*] [1,2,4] triazol-5-yl)-2*H*-pyran-2-one derivatives (**4a-j**) (Scheme II). The products obtained by both methods were found to be identical by mixed melting point measurements, co-TLC and their analytical and spectral data.

A plausible mechanism for the formation of title compounds **4** is proposed in Scheme III. The initial step is the formation of 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **5** from 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **1** and thiosemicarbazide **2**. Intermediate **5** reacts with various aromatic acids **3** to give corresponding title compounds **4**.

In the IR spectrum of **4a**, the OH functional group appeared at 3389 cm^{-1}, lactone –C=O group at 1724 cm^{-1} and –C=N at 1599 cm^{-1} respectively. ^{1}H NMR spectrum of compound **3a** exhibited characteristic peaks for $–CH_3$ of pyran as singlet at δ 2.22, pyran proton as singlet at δ 6.15, thiazole proton as singlet at δ 7.27, aromatic protons appears as multiplets in the region δ 7.46-7.50, 7.90-7.98 and -OH proton appeared as singlet at δ 12.68 respectively. ^{13}C NMR spectrum exhibited characteristic lactone carbonyl carbon at δ 193.5. The mass spectrum of the compound **4a** shows $[M+H]^+$ ion peak at *m/z* 326. From the spectral data we assigned the structure **4** for the synthesized molecules.

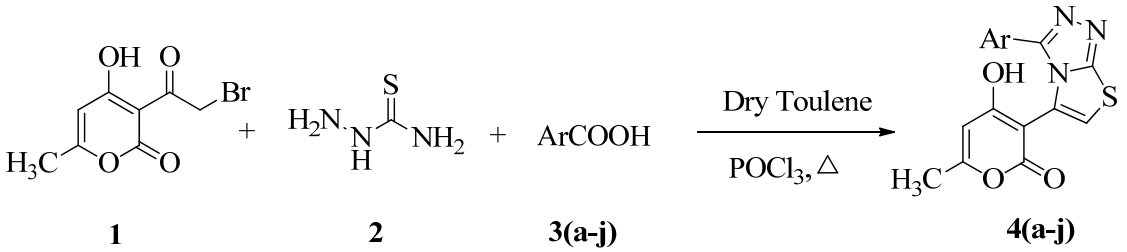
Experimental Section

General procedure for preparation of compounds (4a-j)

A mixture of substituted 3-(2-bromoacetyl) -4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), thiosemicarbazide (1 mmol) and aromatic carboxylic acid (1 mmol) was taken in a round bottom flask containing 15 mL of dry toluene and 5 mL of $POCl_3$, refluxed for about 3-4 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled to RT and poured onto crushed ice. The resulting solid product was filtered, washed with $NaHCO_3$ solution (5%), followed by cold water. It was dried and purified by recrystalization from ethanol.

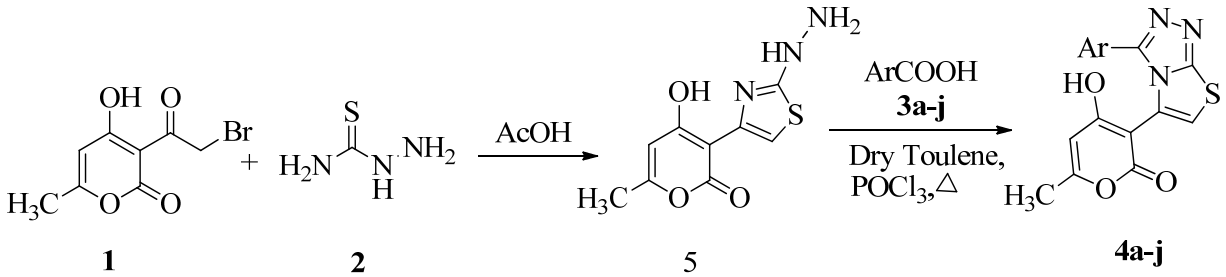
4-Hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c] [1,2,4] triazol-5-yl)-2*H*-pyran-2-one, 4a: Yellow solid. Yield 89%. m.p.173-75°C. IR (KBr): 3389 (OH), 1724 (lactone –C=O), 1599 cm^{-1} (–C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3 of pyran), 6.15 (s, 1H, pyran), 7.27 (s, 1H, CH of thiazole), 7.46–7.50 (m, 2H, ArH), 7.90–7.98 (m, 3H, ArH), 12.68 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d_6): δ 22.2, 98.6, 103.3, 121.1, 127.9, 129.1, 131.8, 133.2, 136.2, 146.6, 151.9, 153.5, 163.1, 193.5; ESI-MS: *m/z* (%) 326 $(M+H)^+$. Anal. Calcd for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 59.00; H, 3.37; N, 12.87%.

3-(3-(2-Chlorophenyl)thiazolo[2,3-c][1,2,4]triazol -5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4b: Yellow solid. Yield 89%. m.p. 203-205°C. IR (KBr): 3398



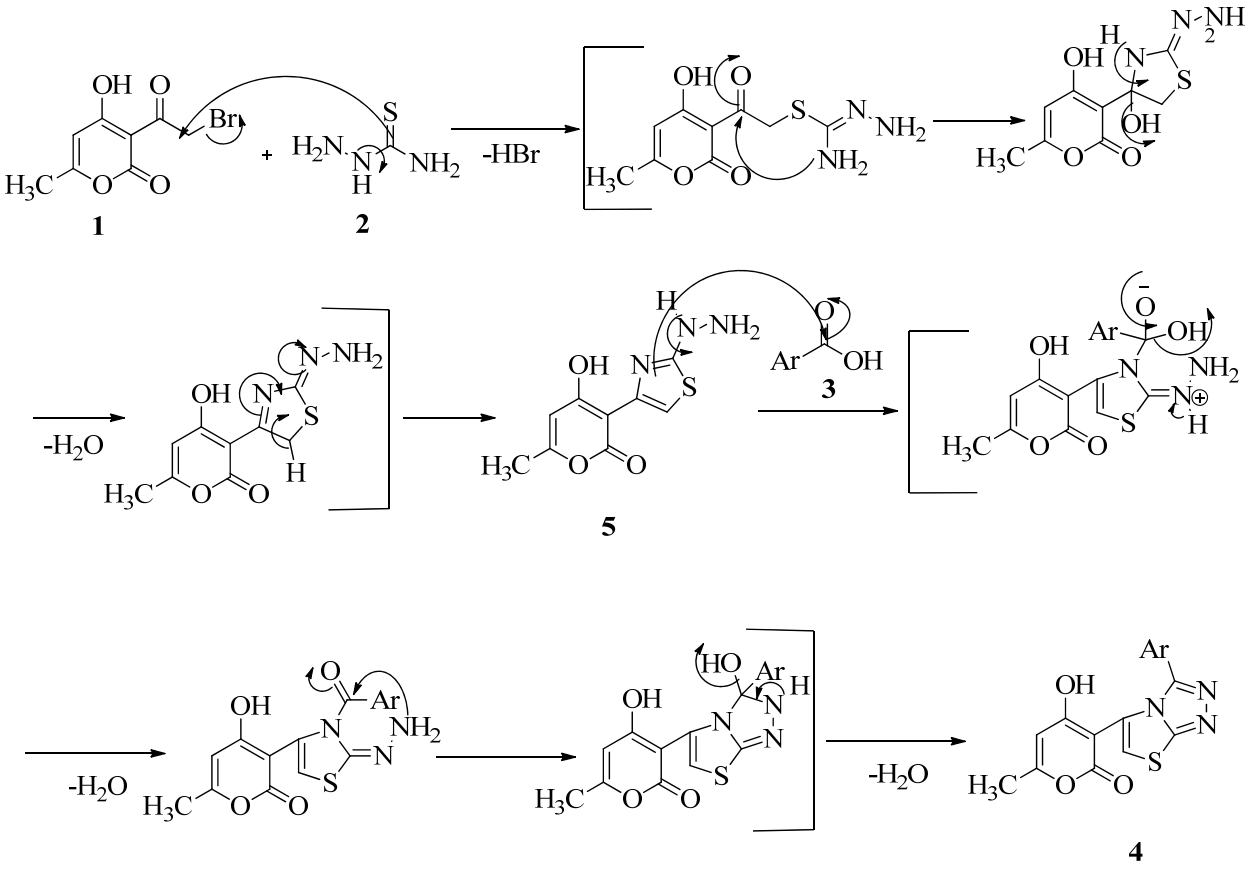
1 **2** **3(a-j)** **4(a-j)**

Scheme I — One pot synthesis of 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-ones



1 **2** 5 **4a-j**

Scheme II — Two step synthesis of 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-ones



Scheme III — Generation of the target molecule 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one

(OH), 1717 (lactone C=O), 1599 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3 of pyran), 6.17 (s, 1H, pyran), 7.32-7.56 (m, 1H thiazole, 4H ArH), 12.72 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3, 98.9, 103.5, 119.2, 127.3, 128.4, 129.3, 130.7, 133.5, 134.2, 138.6, 146.0, 151.7, 155.4, 163.2, 192.3; ESI-MS: *m/z* (%) 360 $(M+H)^+$. Anal. Calcd for $C_{16}H_{10}ClN_3O_3S$: C, 53.41; H, 2.80; N, 11.68. Found: C, 53.37; H, 2.73; N, 11.63%.

4-Hydroxy-6-methyl-3-(3-(*p*-tolyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-2*H*-pyran-2-one, 4c: Yellow solid. Yield 85%. m.p.151-153°C. IR (KBr): 3406 (OH), 1727 (lactone C=O), 1599 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.36 (s, 3H, CH_3 of pyran), 6.15 (s, 1H, pyran), 7.31 (s, 1H, CH of thiazole), 7.66 (d, J = 8.8Hz, 2H, ArH), 8.36 (d, J = 9.2, 3H, ArH), 12.74 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d_6): δ 22.2, 23.1, 98.8, 104.1, 119.6, 125.5, 128.5, 130.7, 133.1, 135.2, 144.9, 152.1, 154.8, 162.9, 193.0; ESI-MS: *m/z* (%) 340 $(M+H)^+$. Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 60.11; H, 3.80; N, 12.30%.

3-(3-(3,5-Dinitrophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4d: Yellow solid. Yield 88%. m.p.147-149°C. IR (KBr): 3434 (OH), 1720 (lactone C=O), 1600 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3 of pyran), 6.13 (s, 1H, pyran), 7.28 (s, 1H, CH of thiazole), 8.60–8.75 (m, 3H, ArH), 12.83 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d_6): δ 22.2, 100.4, 105.5, 118.2, 119.7, 128.6, 129.5, 132.5, 144.1, 149.3, 152.5, 155.1, 163.5, 192.5. Anal. Calcd for $C_{16}H_9N_5O_7S$: C, 46.27; H, 2.18; N, 16.86. Found: C, 46.19; H, 2.13; N, 16.81%.

3-(3-(2-Aminophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4e: Yellow solid. Yield 82%. m.p.216-218°C. IR (KBr): 3417 (OH), 1722 (lactone C=O), 1612 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3 of pyran), 3.82 (s, 2H, NH_2), 6.18 (s, 1H, pyran), 6.72-6.80 (m, 2H, ArH), 7.29–7.34 (m, 1H thiazole, 2H ArH), 12.61 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d_6): δ 22.2, 99.1, 105.4, 110.5, 117.1, 119.8, 121.6, 128.0, 131.2, 132.9, 144.7, 147.2, 152.4, 155.1, 164.3, 192.8. Anal.

Calcd for $C_{16}H_{12}N_4O_3S$: C, 56.46; H, 3.55; N, 16.46. Found: C, 56.50; H, 3.49; N, 16.40%.

4-Hydroxy-3-(3-(4-hydroxyphenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-6-methyl-2*H*-pyran-2-one, 4f: Yellow solid. Yield 80%. m.p.188-190°C. IR (KBr): 3413 (OH), 1727 (lactone C=O), 1602 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 6.17 (s, 1H, pyran), 7.19 (s, 1H thiazole), 7.49 (d, J = 8.0, 2H ArH), 8.03 (d, 2H, ArH); ^{13}C NMR (100MHz, DMSO-d_6): δ 22.0, 99.4, 103.4, 117.3, 121.6, 127.8, 129.4, 133.7, 146.5, 152.8, 155.3, 159.7, 164.3, 193.1. Anal. Calcd for $C_{16}H_{11}N_3O_4S$: C, 56.30; H, 3.25; N, 12.31. Found: C, 56.25; H, 3.19; N, 12.26%.

3-(3-(4-Bromophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4g: Yellow solid. Yield 85%. m.p.177-179°C. IR (KBr): 3400 (OH), 1719 (lactone C=O), 1605 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 6.20 (s, 1H, pyran), 7.26 (s, 1H, CH of thiazole), 7.84 (d, J = 8.8Hz, 2H, ArH), 8.23 (d, J = 8.0,2H, ArH), 12.82 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d_6): δ 22.2, 99.3, 105.1, 119.9, 123.1, 130.0, 132.7, 133.5, 135.4, 145.5, 152.8, 155.5, 162.6, 193.1. Anal. Calcd for $C_{16}H_{10}BrN_3O_3S$: C, 47.54; H, 2.49; N, 10.39. Found: C, 47.47; H, 2.42; N, 10.31%.

3-(3-(3,5-Dichlorophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4h: Yellow solid. Yield 85%. m.p.161-163°C. IR (KBr): 3412 (OH), 1711 (lactone C=O), 1609 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3 of pyran), 6.18 (s, 1H, pyran), 7.30 (s, 1H, CH of thiazole), 7.83-7.96 (m, 3H, ArH), 12.90 (s, 1H, OH); ^{13}C NMR (100MHz, DMSO-d_6): δ 21.8, 100.6, 105.2, 118.9, 126.4, 130.3, 132.2, 134.9, 136.1, 147.0, 151.3, 155.4, 164.2, 192.9. Anal. Calcd for $C_{16}H_9Cl_2N_3O_3S$: C, 48.75; H, 2.30; N, 10.66. Found: C, 48.69; H, 2.25; N, 10.61%.

4-Hydroxy-3-(3-(3-methoxyphenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-6-methyl-2*H*-pyran-2-one, 4i: Yellow solid. Yield 86%. m.p.139-142°C. IR (KBr): 3406 (OH), 1724 (lactone C=O), 1601 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.12 (s, 1H, pyran), 6.90-6.99 (m, 2H, ArH), 7.28-7.32 (m, 1H thiazole, 2H ArH), 12.71 (s, 1H, OH). Anal. Calcd for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82. Found: C, 57.41; H, 3.62; N, 11.77%.

4-Hydroxy-6-methyl-3-(3-(3-nitrophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-2*H*-pyran-2-one, 4j: Yellow solid. Yield 82%. m.p.201-203°C. IR (KBr): 3414 (OH), 1728 (lactone C=O), 1606 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3 of pyran), 6.11 (s, 1H, pyran), 7.32 (s, 1H thiazole), 8.34-8.44 (m, 4H ArH), 12.82 (s, 1H, OH). Anal. Calcd for $C_{16}H_{10}N_4O_5S$: C, 51.89; H, 2.72; N, 15.13. Found: C, 51.83; H, 2.65; N, 15.07%.

General procedure for synthesis of compound 5

3-(2-Hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one

A mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1mmol) and thiosemicarbazide was refluxed with 5 mL of acetic acid for about 1hour. The reaction mixture was cooled, the solid product separated was filtered and washed with water. It was dried and purified from acetic acid.

General procedure for synthesis of compound 4a-j from 5

A mixture compound (5) (1mmol) and 3 (1mmol) was refluxed with 5 mL of $POCl_3$ for 4hours, the reaction mixture was cooled and the excess of $POCl_3$ was distilled off and the remaining mass poured onto crushed ice. The resulting solid product was filtered, washed with $NaHCO_3$ solution (5%) followed by cold water. It was dried and purified by recrystallisation from ethanol. The products were identified to be the same as those prepared by three component reaction.

3-(2-Hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one: Yellow solid. Yield 90%. m.p.135-137°C. IR (KBr): 3434 (OH), 3298 (NH_2), 3179 (NH), 1717 (lactone C=O), 1610 cm^{-1} (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3 of pyran), 6.19 (s, 1H, pyran), 7.33 (s, 1H thiazole), 10.01 (s, 2H, NH_2), 10.34 (s, 1H, NH), 14.62 (s, 1H, OH). Anal. Calcd for $C_9H_9N_3O_3S$: C, 45.17; H, 3.79; N, 17.56. Found: C, 45.11; H, 3.73; N, 17.49%.

Conclusion

In conclusion, we have described the synthesis of thiazolo-triazolyl derivatives. The reaction proceeded by two methods. The first method is a multi-component reaction and second method is a two-step reaction. The advantages of this synthetic protocol are mild reaction conditions, shorter reaction times, easy work-up and excellent yields.

Acknowledgments

The authors are very much thankful to the Director of the National Institute of Technology,

Warangal, T.S., India, for providing financial support and research facilities.

References

1 Trost B M, *Acc Chem Res*, 35 (2002) 695.
2 Duraisamy C & Ramarajan R, *RSC Advances*, 4 (2014) 41314.
3 Wen-Tai L, Wan-Hsun W, Chien-Hsiang T, Ready T & Shui-Tein C, *ACS Comb Sci*, 13 (2011) 72.
4 Narayan B, Vijaya Raj K K, Ashalatha B V & Suchetha N K, *Indian J Chem*, 45B (2006) 1704.
5 Holla B S, Karegoudar P, Karthikeyan M S, Prasad D J, Mahalinga M & Kumari N S, *Eur J Med Chem*, 43 (2008) 261.
6 Sharma P K, Swonhney S N, Gupta A, Singh G B & Bani S, *Indian J Chem*, 37B (1998) 371.
7 Quin Y J, Wang P F, Makawana J A, Wang Z C, Wang Z N, Gu Y, Jiang A Q & Zhu H L, *Bioorg Med Chem Lett*, 24 (2014) 5279.
8 Koppireddi S, Chilaka D R K, Avula S, Komsani J R, Kotamraju S & Yadla R, *Bioorg Med Chem Lett*, 24 (2014) 5428.
9 Bell F W, Cantrell A S, Hog berg M, Jaskunas S R, Johansson N G, Jordan C L, Kinnick M D, Lind P & Morin Jr J M, *J Med Chem*, 38 (1995) 4929.
10 Abdi Y, Boutemeur-Kheddis B, Hamdi M, Talhi O, Bachari K, Kirsch G & Silva A M S, *Synlett*, 27 (2016) A.
11 Venkateswar Rao P & Venkata Narasaiah A, *Indian J Chem*, 42A (2003) 1896.
12 Fouad D M, Ismail N M, El-Gahami M A & Ibrahim S A, *Spectrochimica Acta*, *Part A*, 67 (2007) 564.
13 Bennassi C A, Semenzato A, Lucchiari M & Bettero A, *Int J Cosmet Sci*, 10 (1988) 20.
14 Mikami E, Goto T, Ohno T, Matsumoto H & Nishida M, *J Pharm Biomed Anal*, 28 (2002) 261.
15 Schleiffenbaum B, Spertini O & Tedder Thomas F, *J Cell Biol*, 119 (1) (1992) 229.
16 Stanley VG, Woldesenbet S & Gray Cassandra, *Poultry Sci*, 75(1) (1996) 42.
17 Potts K T & Husain S, *J Org Chem*, 36 (1971) 1.
18 El-Sherif H A H, Mahmoud A M, Sarhan A A O, Hozien Z A & Habib O M A, *J Sulfur Chem*, 27 (1) (2006) 65.
19 Barbuceanu S F, Almajan G L, Saramet I, Draghici C, Tarcomnicu A I & Bancescu G, *Eur J Med Chem*, 44 (2009) 4752.
20 Davoodnia A, Ameli SH & Hoseini T, *Asian J Chem*, 23(8) (2011) 3707.
21 Jag Mohan, *Indian J Chem*, 42 (2003) 401.
22 Venkata sreenivasa Rao C & Rajeswar Rao V, *Synth Commun*, 42 (2012) 1154.
23 Venkata Sreenivasa Rao C & Rajeswar Rao V, *Indian J Chem*, 51B (2012) 1417.
24 Aychiluhim T B & Rajeswar Rao V, *Org Prep Proced Int*, 46 (2014) 66.
25 Thirupaiah B & Rajeswar Rao V, *Synth Commun*, 44 (2014) 3183.
26 Sreenu P, Krishnaiah V & Rajeswar Rao V, *Phosphorus Sulfur and Silicon*, 192 (1) (2017) 69.
27 Aditya Vardhan V, Ravi Kumar V & Rajeswar Rao V, *Indian J Chem*, 38B (1999) 18.

Received: 26 March 2019 | Revised: 14 August 2019 | Accepted: 1 September 2019

DOI: 10.1002/ardp.201900079

DPhG ARCH PHARM
Archiv der Pharmazie

FULL PAPER

Synthesis of thiazolyl hydrazonothiazolamines and 1,3,4-thiadiazinyl hydrazonothiazolamines as a class of antimalarial agents

Kodam Sujatha[1] | Naidu Babu Ommi[2] | Anwita Mudiraj[2] | Phanithi Prakash Babu[2] | Rajeswar Rao Vedula[1]

[1]Department of Chemistry, National Institute of Technology, Warangal, Telangana, India

[2]Department of Biotechnology and Bioinformatics, School of Life Sciences, University of Hyderabad, Hyderabad, Telangana, India

Correspondence
Phanithi Prakash Babu, Department of Biotechnology and Bioinformatics, School of Life Sciences, University of Hyderabad, Hyderabad, Telangana 500046, India.
Email: prakash@uohyd.ac.in

Rajeswar Rao Vedula, Department of Chemistry, National Institute of Technology, Warangal, Telangana 506004, India.
Email: rajeswarnitw@gmail.com

Abstract

Novel thiazolyl hydrazonothiazolamines and 1,3,4-thiadiazinyl hydrazonothiazolamines were synthesized by a facile one-pot multicomponent approach by the reaction of 2-amino-4-methyl-5-acetylthiazole, thiosemicarbazide or thiocarbohydrazide and phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in acetic acid with good to excellent yields. These new compounds were screened in vitro for their antimalarial activity; among them, four compounds, **4h**, **4i**, **4k**, **4l**, showed moderate activity with half-maximal inhibitory concentration (IC_{50}) values of 3.2, 2.7, 2.7, and 2.8 and 3.2, 3.2, 3.1, and 3.5 μM against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*, respectively. Compound **4l** inhibited the ring stage growth of *P. falciparum* 3D7 at an IC_{90} concentration of 12.5 μM in a stage-specific assay method, where the culture is incubated with specific stages of *P. falciparum* for 12 hr, and no activity was found against the trophozoite and schizont stages, confirming that **4l** may have potent action against the ring stage of *P. falciparum*.

KEYWORDS

2-amino-4-methyl-5-acetylthiazole, antimalarial activity, bithiazoles, multicomponent reactions, thiazolothiadiazines

1 | INTRODUCTION

Malaria is a parasitic disease transmitted to humans by the female *Anopheles* mosquito and continues to remain a lethal infectious disease. According to WHO 2017 report,[1] an estimated 216 million cases of malaria occurred worldwide in 2016, and India accounts for 6% of it. *Plasmodium falciparum*, the most virulent species of this parasite has developed resistance to most available antimalarial drugs. This has been a constant challenge to malaria control initiatives necessitating the search for novel and structurally diverse antimalarial drugs as a viable strategy to combat this issue.

Multicomponent reactions (MCRs) are modern methods for the synthesis of drug molecules.[2] The advantages of MCRs are convergent, one pot and sequential assembling of starting materials to get the final product in a short time. MCRs play a vital role in modern organic synthesis. MCRs are good synthetic approaches for functionalized heterocyclic compounds without any side products.[3,4]

Thiazole scaffolds (Figure 1) are found in many natural products[5] and possess diverse medicinal and pharmaceutical applications such as antitubercular,[6,7] anticonvulsant,[8] anticancer,[9] antiviral,[10] antimicrobial,[11] antimalarial[12] and anti-inflammatory activity.[13]

Coumarin is an important pharmacophore having many applications in the fields of medicinal chemistry as well as pharmaceuticals like antifungal,[14] anti-HIV agents,[15] anti-Alzheimers[16]and also acts as a luminescent material.[17] When the coumarin ring is attached with the thiazole ring, it exhibits improved biological activities like being an anti-inflammatory and anti-analgesic agent.[18] On the other hand, thiadiazines are also versatile biologically important heterocyclic molecules[19] with proven applications as antidepressant,[20] antihypertensive[21] and antiproliferative agents.[22]

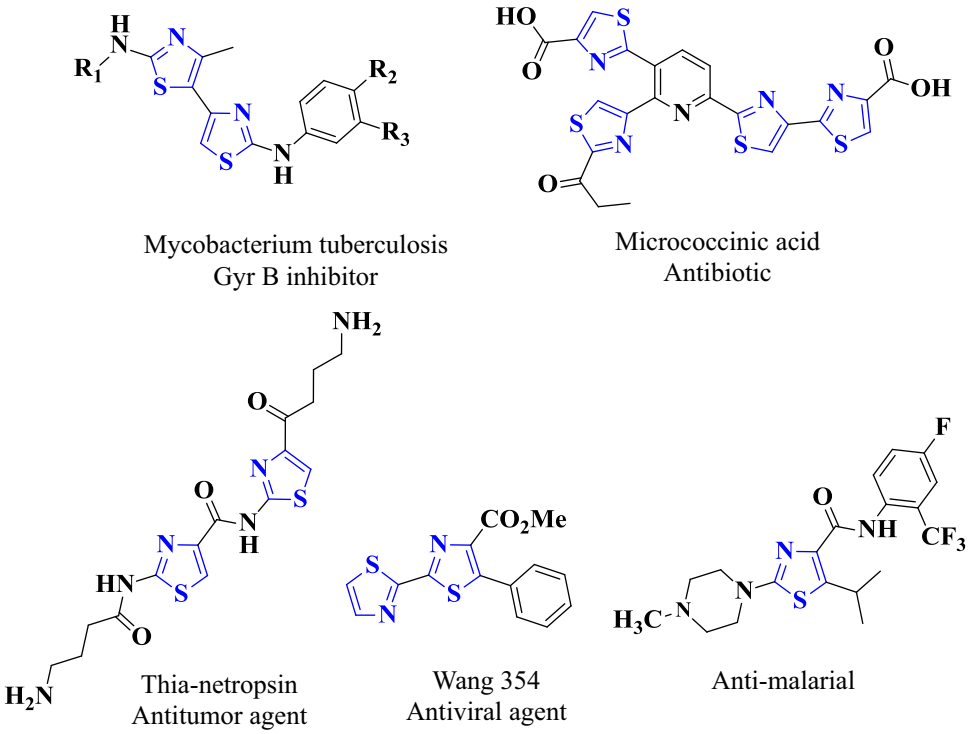


FIGURE 1 Biologically active molecules

Furthermore, thiazoles attached to coumarins, thiadiazine, and thiosemicarbazones are documented to exhibit an enhanced spectrum of biological activities.[23,24] To the best of our knowledge, coumarinyl hydrazino thiazole and coumarinyl hydrazino thiadiazine moieties and their antiplasmodial activity are hitherto unreported.

In continuation of our earlier work on nitrogen and sulphur heterocycles,[25,26] we are now reporting the synthesis of thiazolyl hydrazonothiazolamines and 1,3,4-thiadiazinyl hydrazonothiazolamines having aryl/3-coumarinyl moieties via a one-pot multicomponent method and their antimalarial activity against *P. falciparum* in vitro.

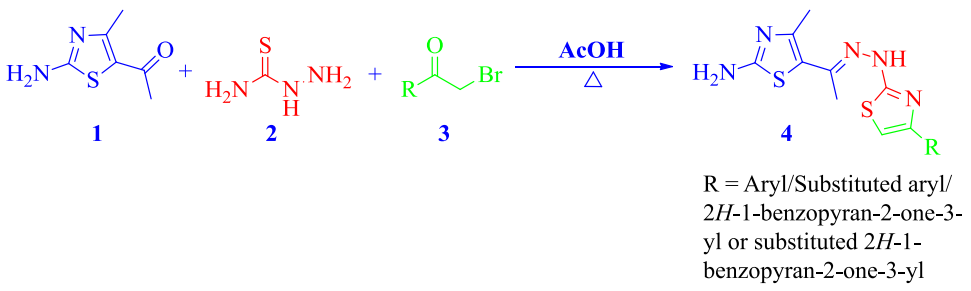
2 | RESULTS AND DISCUSSION

2.1 | Chemistry

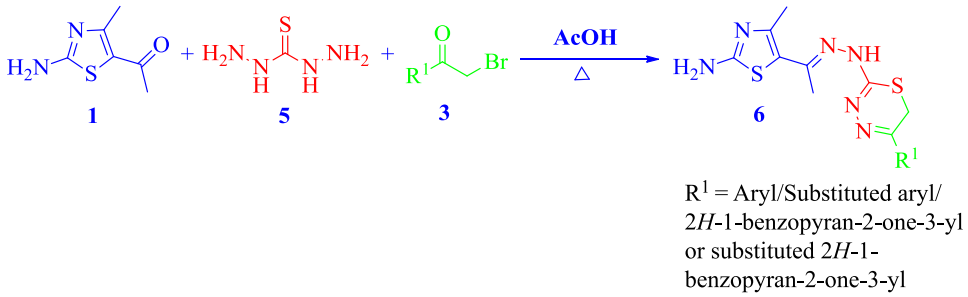
Thiazolyl hydrazonothiazolamines were synthesized by a one-pot multicomponent method using 2-amino-4-methyl-5-acetylthiazole, thiosemicarbazide, phenacyl bromide, or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in good yields.

This is a three-component condensation reaction. In this reaction, the 2-amino-4-methyl-5-acetylthiazole first reacts with thiosemicarbazide to give the corresponding thiosemicarbazone of 2-amino-4-methyl-5-acetylthiazole. The in-situ formed thiosemicarbazones react with phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones to give final product **4** by Hantzsch thiazole synthesis (Scheme 1).

In contrast, 2-amino-4-methyl-5-acetylthiazole on reaction with thiocarbohydrazide gave the thiocarbohydrazone of 2-amino-4-methyl-5-acetylthiazole. This undergoes cyclization with α-halo ketones such as phenacyl bromides or 3-(2-bromoacetyl) coumarins to yield the target compound **6**, as given in Scheme 2. The advantage of our reaction is that without isolation of intermediate thiosemicarbazone of **1** or thiocarbohydrazone of **1,** we have synthesized the final products (**4** and **6**) in a single step. In addition to this, the reaction involves concomitant formation of C=N, C–N, and C–S bonds.



SCHEME 1 Synthesis of thiazolyl hydrazonothiazolamines



SCHEME 2 Synthesis of 1,3,4-thiadiazinyl hydrazonothiazolamines

The structures of all the newly synthesized compounds were confirmed by their spectral data and are summarized in the Supporting Information. The infrared (IR) spectrum of compound **4f** showed peaks at 3,436 and 1,622 cm^{-1} due to amino and –C═N– groups, respectively. The ^{1}H NMR spectrum of the compound **4f** showed a characteristic singlet peak at δ 7.12 ppm corresponding to the newly formed thiazole CH proton and the remaining protons were observed in the usual expected region. ^{13}C NMR of compound **4f** gave a characteristic peak at 103.4, which further confirms the newly formed thiazole carbon. The compound **4f** exhibited the molecular ion peak at *m/z* 344 $(M+1)^{+}$.

The IR spectrum of compound **6a** showed prominent peaks at 3,400 and 1,605 cm^{-1} for amino and –C═N– groups, respectively. The ^{1}H NMR spectrum of the compound **6a** showed a characteristic singlet peak at δ 3.94 ppm, corresponding to newly formed thiadiazine CH_2 protons, and the remaining protons were observed in the usual expected region. ^{13}C NMR of compound **6a** gave a characteristic peak at 22.2, corresponding to newly formed thiadiazine CH_2 carbon. Compound **6a** exhibited a molecular ion peak at *m/z* 343 $(M-1)^{+}$.

2.2 | Biological evaluation

2.2.1 | In vitro antimalarial activity and cytotoxicity of compounds

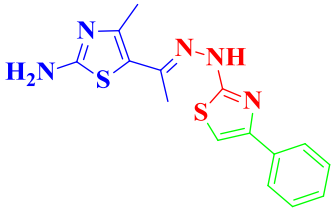
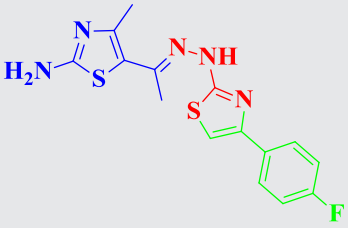
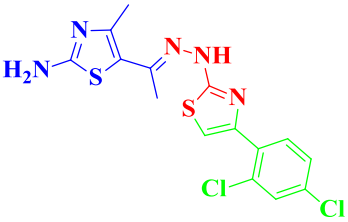
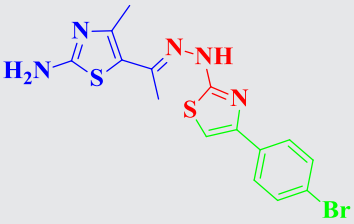
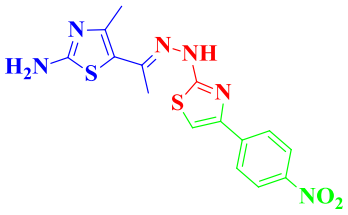
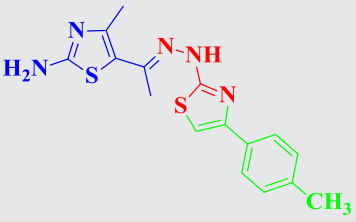
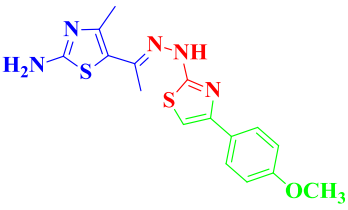
The antimalarial property of all derivatives were evaluated in vitro against the chloroquine (CQ)-resistant (Dd2) and CQ-sensitive (3D7) strains of *P. falciparum* parasite. Thirteen compounds exhibited half-maximal inhibitory concentration (IC_{50}) values below 6.30 μM against both sensitive and resistant 3D7 and Dd2 strains. All IC_{50} values against CQ-sensitive and -resistant strains are tabulated in Table 1. Compound **6g** showed an IC_{50} value of 12.5 ± 0.12 μM and the remaining nine compounds showed no activity (>24 μM) in the 3D7 strain. Four compounds **4h**, **4i**, **4k**, **4l** showed reasonable activity with an IC_{50} value of 3.2, 2.7, 2.7, and 2.8 μM against the CQ-sensitive strain of *P. falciparum*. These compounds also showed inhibition of the CQ-resistant strain with an IC_{50} value of 3.25, 3.25, 3.13, and 3.5 μM (Table 1). Furthermore, lactate dehydrogenase (LDH) assay was conducted to measure the cytotoxicity of **4h**, **4i**, **4k**, and **4l** against synchronized *P. falciparum* 3D7 culture in vitro. These four compounds showed IC_{50} at 3.12 μM concentration against *P. falciparum* 3D7 culture (SI data). In general, the thiazolyl hydrazonothiazolamine series having halogenated and electron-rich coumarin substituents showed good activity compared with simple phenyl substituted thiazolyl hydrazonothiazolamines. Presence of electron-withdrawing $-NO_2$ group on the benzene ring in **4e** compound caused a complete loss of antimalarial activity in the 3D7 strain compared with analogs having halogen atoms and electron-donating groups. In contrast, the simple phenyl or coumarin substituted 1,3,4-thiadiazinyl hydrazonothiazolamine series showed no activity. Only three compounds from this series (**6b**, **6c**, and **6e**) showed activity around 6.15–6.25 μM against the CQ-sensitive strain of *P. falciparum*. Hence, in both series, the active compounds were **4h**, **4i**, **4k**, and **4l**. The IC_{50} of chloroquine against 3D7 is 26 ± 2.5 nM and that of Dd2 is 184 ± 10.6 nM; whereas the antimalarial activity of these four compounds cannot be compared to that of chloroquine, the functional group modifications at thiazole or coumarin moiety have tremendous prospects in further development and this work is in progress in this laboratory.

To check the toxicity of the compounds against normal cell cytotoxicity, tests were carried out against mice macrophage J774.2 cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric method. Compounds **4i** and **4k** had a cytotoxic concentration 50 (CC_{50}) of 500 μM, whereas **4h** and **4l** showed a CC_{50} of 250 μM, respectively (Table 2).

2.2.2 | Inhibition of β-hematin crystallization

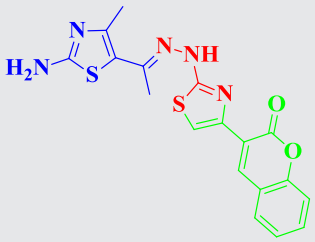
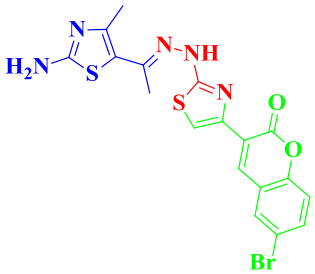
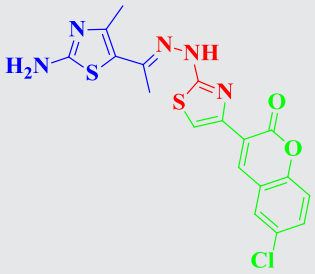
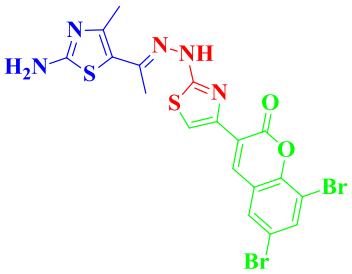
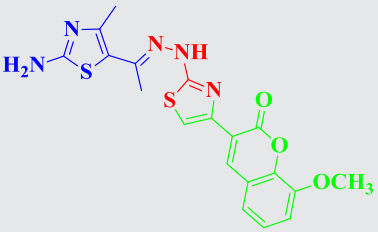
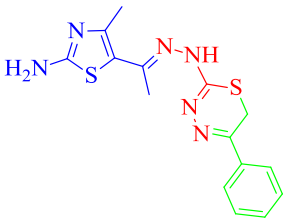
Hemozoin formation is unique to *Plasmodium*. *P. falciparum* is an intraerythrocytic parasite that grows and multiplies by converting the toxic by-product heme (ferriprotoporphyrin IX) released from hemoglobin degradation into nontoxic hemozoin. This occurs in the digestive food vacuole of the parasite, and inhibition of hemozoin formation proves fatal for the parasite, and thus forms an attractive antimalarial drug target. The inhibition of β-hematin formation was evaluated for active compounds. Results showed that compound **4h** inhibited β-hematin formation with an IC_{50} value of 62.5 μM similar to that of chloroquine, whereas the other compounds did not show any activity against β-hematin crystallization like the negative control of pyrimethamine (Figure 2).

TABLE 1 Compound structures (**4a–l**, **6a–k**) and half-maximal inhibitory concentration (IC_{50}) values with 3D7 strain and Dd2 strain

Compound code	Compound structure	IC_{50} (μM) 3D7 strain	IC_{50} (μM) Dd2 strain
4a		6.37 ± 0.87	6.783 ± 0.21
4b		5.375 ± 0.37	6.23 ± 0.15
4c		5.7917 ± 0.39	5.85 ± 0.83
4d		5.375 ± 0.37	6.25 ± 0.41
4e		>50	nd
4f		4.166 ± 0.83	5.23 ± 0.35
4g		4.166 ± 0.83	5.12 ± 0.20

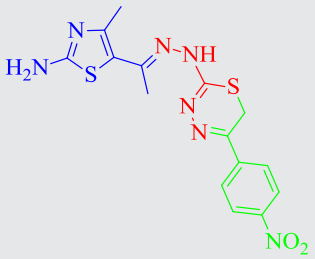
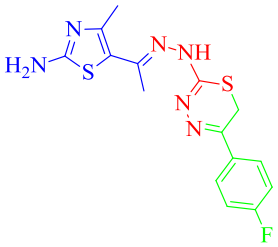
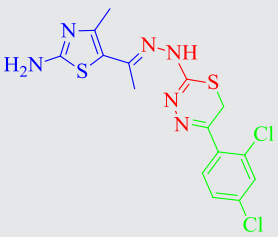
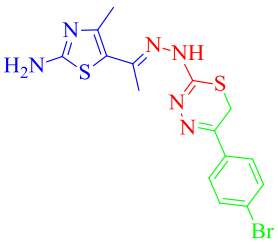
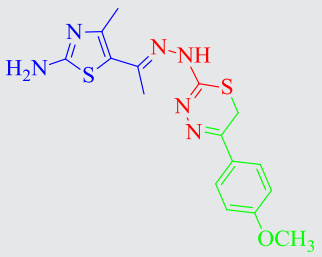
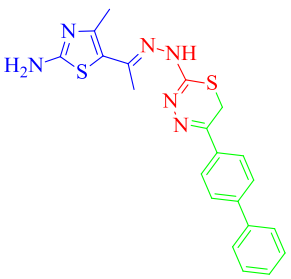
(Continues)

TABLE 1 (Continued)

Compound code	Compound structure	IC_{50} (μM) 3D7 strain	IC_{50} (μM) Dd2 strain
4h		3.208 ± 0.43	3.25 ± 0.88
4i		2.706 ± 0.20	3.251 ± 0.42
4j		5.375 ± 0.37	6.12 ± 0.20
4k		2.708 ± 0.20	3.138 ± 0.42
4l		2.85 ± 0.20	3.521 ± 0.31
6a		25	nd

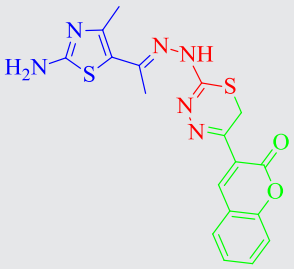
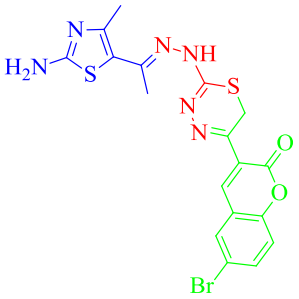
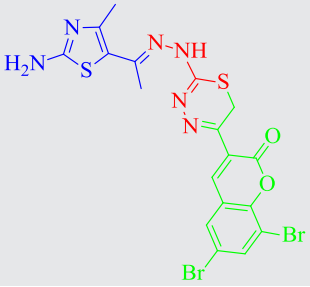
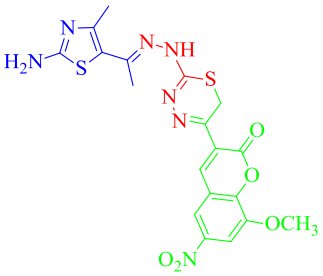
(Continues)

TABLE 1 (Continued)

Compound code	Compound structure	IC_{50} (μM) 3D7 strain	IC_{50} (μM) Dd2 strain
6b		6.15 ± 0.28	7.32 ± 0.43
6c		6.15 ± 0.10	6.534 ± 0.22
6d		26 ± 0.44	nd
6e		6.25 ± 0.78	nd
6f		25.8 ± 0.26	nd
6g		12.5 ± 0.12	nd

(Continues)

TABLE 1 (Continued)

Compound code	Compound structure	IC_{50} (μM) 3D7 strain	IC_{50} (μM) Dd2 strain
6h		26.2 ± 0.40	nd
6i		24 ± 0.36	nd
6j		25.2 ± 0.24	nd
6k		24 ± 0.13	nd

Note: IC_{50} of chloroquine against 3D7 is 26 ± 2.5 nM and Dd2 is 184 ± 10.6 nM.
Abbreviation: nd, not determined.

2.2.3 | Effect of compound 4l on the growth of *P. falciparum* 3D7 culture

To check the growth inhibition activity of compound **4l** against *P. falciparum*, the parasite culture was treated with an IC_{90} concentration of 12.5 μM at their corresponding stages, that is, ring (R), trophozoite (T), and schizont (S) stages for 12 hr. The compound was removed after 12 hr by several washes and supplemented with complete Roswell Park Memorial Institute (RPMI) media for further growth of the parasite. The parasitemia was estimated from Giemsa stained smears. Figure 3a shows that there is no increase of parasitemia at 48 hr in the ring stage treated culture (R + **4l**) similar to unremoved culture (UR + **4l**) when compared to control. The survived parasites of ring stage treated and unremoved cultures were further grown and infected fresh red blood cell (RBC) forming rings at 48 hr after removal of the compound (Figure 3b), but we found they could not grow further, and the morphology remained at the ring stage even after 60 and 72 hr when compared with the control. The control attained the trophozoite stage at a similar cycle time. Trophozoite (T + **4l**) and schizont (S + **4l**) stage treated parasites have more parasitemia than the ring stage treated culture and their growth morphology is similar to control at 60 and 72 hr. The compounds **4h** and **4k** have shown ring stage growth inhibition of the parasite in unremoved culture (S.I) and because of their highest IC_{90}

TABLE 2 Antimalarial activities of active compounds against blood-stage parasites and in vitro cytotoxicity

Compound	IC_{50} (μM)[a]		CC_{50} (μM)[b]
	pf3D7	pfDd2	J774.2
4h	3.208 ± 0.43	3.25 ± 0.88	250
4i	2.706 ± 0.20	3.251 ± 0.42	500
4k	2.708 ± 0.20	3.138 ± 0.42	500
4l	2.85 ± 0.20	3.521 ± 0.31	250

Abbreviations: CC_{50}, cytotoxic concentration 50; IC_{50}, half-maximal inhibitory concentration.

[a]Blood-stage antiplasmodial activity was determined against the CQ-sensitive strain 3D7 and CQ-resistant strain Dd2 of *P. falciparum*.

[b]Cytotoxicity was determined against a mouse macrophage (J774.2) cell line; data are expressed as the CC_{50}, which is the concentration required to reduce cell viability by 50%.

concentration they did not show growth inhibition in transiently treated cultures at the specific stage of the parasite with 12.5 μM concentration. These results show that the compound **4l** is more active in inhibiting the growth of the ring stage of the *P. falciparum* 3D7.

3 | CONCLUSIONS

In conclusion, we have developed novel thiazolyl hydrazonothiazolamines and 1,3,4-thiadiazinyl hydrazonothiazolamine derivatives via a one pot multicomponent approach and evaluated their antimalarial activity. Four compounds showed good antimalarial potency with low cytotoxicity as observed in macrophage cell lines. The method had the advantages of mild reaction conditions, easy workup, no column chromatographic purification and good to better yields.

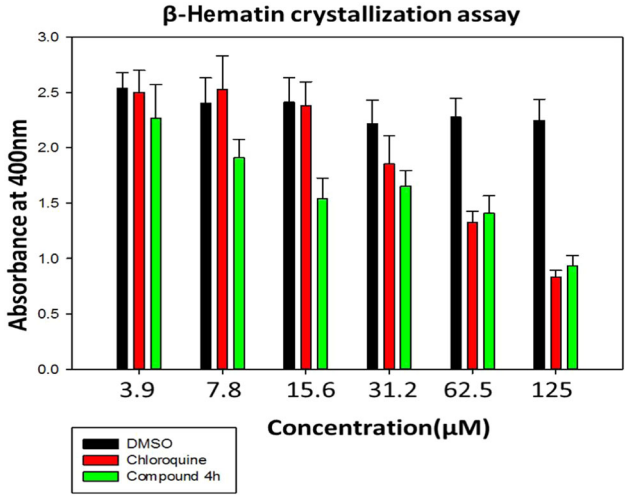


FIGURE 2 β-Hematin crystallization assay. NP-40 polymerizes free synthetic hemin into β-hematin, which was dissolved in 0.36 M NaOH, 2% (wt/vol) sodium dodecyl sulfate and has absorbance at 400 nm. Increasing the concentration of **4h** inhibits the polymerization reactions, which have shown less absorbance and are plotted against the respective concentration

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

3-(2-Bromoacetyl) coumarins were prepared by bromination of different 3-acetyl coumarins in dry chloroform. The remaining chemicals used in the present work were purchased from commercial sources and used without any purification. Melting points were determined in open capillaries with a Stuart melting point apparatus (Mumbai, India) and were uncorrected. IR spectra were recorded on a PerkinElmer Spectrum 100 s (Perkin Elmer corporate office Waltham, MA). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as the standard (Switzerland), ESI-MS spectra were recorded on a Jeol JMSD-300 spectrometer (Tokyo, Japan). Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer (France), compound purity was checked with TLC plates (E. Merck, Mumbai, India).

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | General procedure for the synthesis of compounds 4

An equimolar amount of 2-amino-4-methyl-5-acetylthiazole (1 mmol), thiosemicarbazide (1 mmol), and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol) was taken in a round bottom flask and refluxed in acetic acid (2 ml) at 70°C for about 2 hr. The progress of the reaction was monitored through TLC using ethyl acetate and *n*-hexane (40%). After completion of the reaction, the solid separated was filtered, dried and recrystalized from methanol to give **4**.

*(E)-4-Methyl-5-(1-(2-(4-phenylthiazol-2-yl)hydrazono)ethyl)thiazol-2-amine (**4a**)*

Yield 90%. White solid, mp: 195–196°C; IR (KBr, ν_{max}, cm^{-1}): 3,448 (NH_2 stretching), 1,619 (–C═N– stretching), 1,578 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.30–7.33 (m, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 9.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.1, 15.8, 104.4, 119.1, 125.9, 128.1, 129.1, 133.8, 134.5, 141.9, 149.8, 167.8, 169.5; MS (ESI) *m/z*: 330 (M+H)$^+$; Anal. calcd. for $C_{15}H_{15}N_5S_2$: C, 54.69; H, 4.59; N, 21.26; S, 19.47. Found: C, 54.62; H, 4.63; N, 21.21; S, 19.42.

*(E)-5-(1-(2-(4-(4-Fluorophenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**4b**)*

Yield 81%. White solid, mp: 211–213°C; IR (KBr, ν_{max}, cm^{-1}): 3,442 (NH_2 stretching), 1,621 (–C═N– stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.33 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.25 (t, J = 8.8 Hz, 2H), 7.32 (s, 1H), 7.41 (t, J = 8.8 Hz, 1H), 7.87–7.90 (m, 2H), 7.95–7.99 (m, 1H), 13.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.1, 15.8, 115.6, 115.8, 116.0, 116.4, 116.7, 128.0, 130.0, 130.1, 150.8, 164.5, 167.7; MS (ESI) *m/z*: 348 (M+H)$^+$; Anal. calcd. for

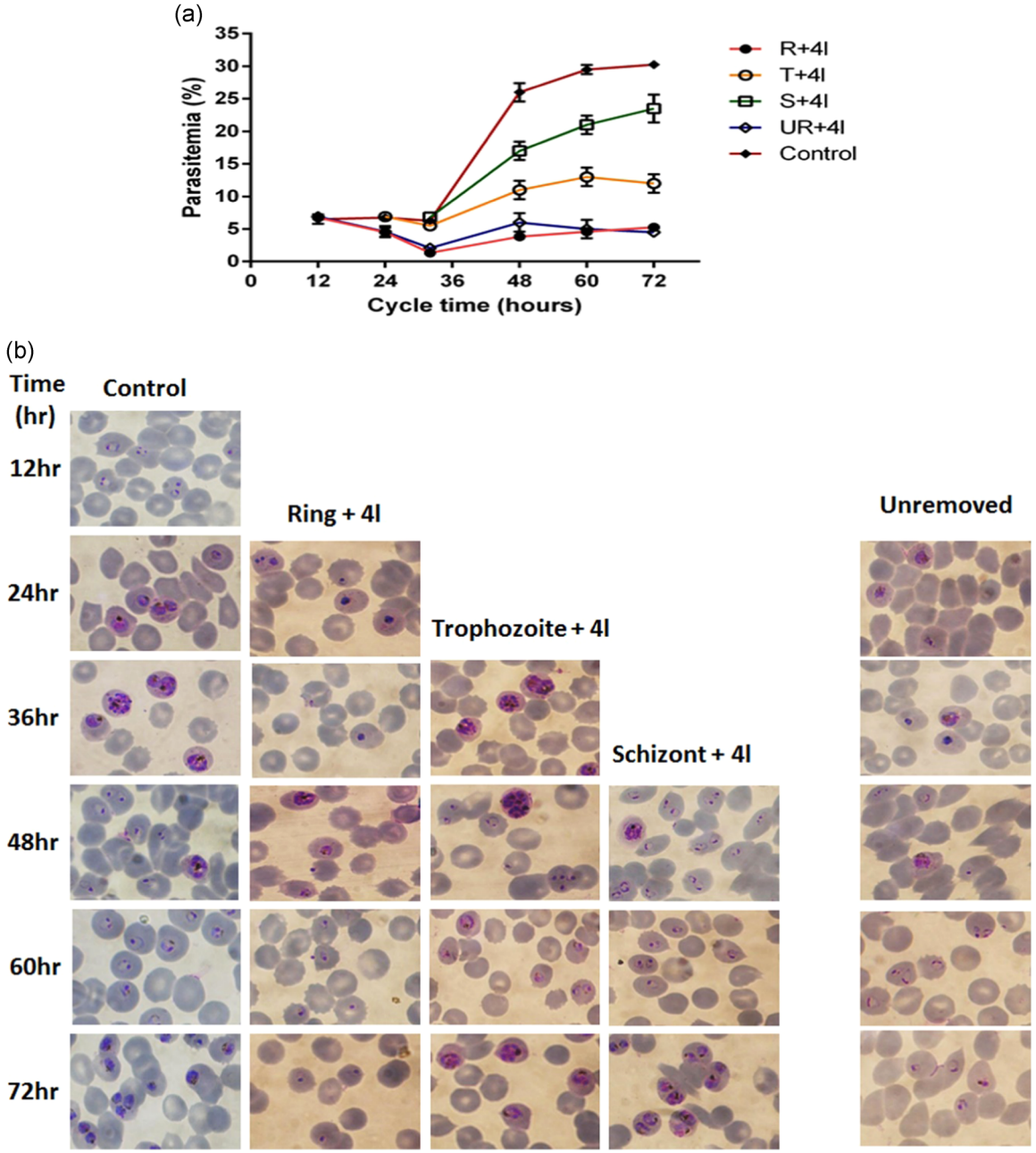


FIGURE 3 Effect of short term treatment of compound **4l** at various plasmodial stages. (**a**) Growth of parasitemia after treatment with compound **4l** at various *Plasmodium falciparum* 3D7 growth stages; 12 hr postinfection cultures were treated with compound **4l** at various stages corresponding to ring (R + **4l**), trophozoite (T + **4l**) and schizont (S + **4l**) stages. After that, the compound was removed and the parasitemia was monitored for up to 72 hr postinfection. Results are represented as the mean of three individual experiments ± standard error. (**b**) Giemsa stained images represent the morphology of the parasite at the corresponding stages. Representation used is R + **4l** (closed circles), T + **4l** (open circles), S + **4l** (open square), unremoved **4l** (open diamond), control (closed diamond)

$C_{15}H_{14}FN_5S_2$: C, 51.85; H, 4.06; N, 20.16; S, 18.46. Found: C, 51.81; H, 4.12; N, 20.20; S, 18.41.

*(E)-5-(1-(2-(4-(2,4-Dichlorophenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**4c**)*

Yield 87%. White solid, mp: 170–172°C; IR (KBr, ν_{max}, cm^{-1}): 3,448 (NH_2 stretching), 1,624 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.40 (s, 1H), 7.50–7.53 (m, 1H), 7.70 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 9.37 (s, 2H), 11.56 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.3, 15.8, 110.1, 118.8, 127.9, 130.2, 132.0, 132.4, 132.6, 133.0, 134.6, 141.9, 146.05, 167.7, 168.7; MS (ESI) *m/z*: 416 $(M+NH_4)^+$; Anal. calcd. for $C_{15}H_{13}Cl_2N_5S_2$: C, 45.23; H, 3.29; N, 17.58; S, 16.10. Found: C, 45.27; H, 3.23; N, 17.52; S, 16.17.

*(E)-5-(1-(2-(4-(4-Bromophenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**4d**)*

Yield 92%. White solid, mp: 185–187°C; IR (KBr, ν_{max}, cm^{-1}): 3,427 (NH_2 stretching), 1,624 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.41 (s, 1H), 7.61 (d, J = 11.6 Hz, 2H), 7.78–7.83 (m, 3H), 9.29 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 13.8, 15.3, 104.9, 120.6, 127.5, 128.9, 131.5, 132.0, 133.5, 133.9, 141.4, 164.0, 167.3, 169.1, 171.9; MS (ESI) m/z: 410 $(M+2)^+$; Anal. calcd. for $C_{15}H_{14}BrN_5S_2$: C, 44.12; H, 3.46; N, 17.15; S, 15.71. Found: C, 44.16; H, 3.41; N, 17.11; S, 15.76.

*(E)-4-Methyl-5-(1-(2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazono)ethyl)-thiazol-2-amine (**4e**)*

Yield 90%. White solid, mp: 207–209°C; IR (KBr, ν_{max}, cm^{-1}): 3,430 (NH_2 stretching), 1,638 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.29 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.70 (s, 1H), 8.07–8.15 (m, 4H), 8.28 (d, J = 8.8 Hz, 2H), 11.37 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 16.2, 16.4, 109.3, 118.8, 124.5, 126.7, 141.1, 143.2, 146.6, 155.2, 156.7, 167.4, 170.1; MS (ESI) m/z: 375 $(M+1)^+$; Anal. calcd. for $C_{15}H_{14}N_6O_2S_2$: C, 48.11; H, 3.77; N, 22.44; S, 17.13. Found: C, 48.16; H, 3.71; N, 22.40; S, 17.10.

*(E)-4-Methyl-5-(1-(2-(4-(p-tolyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-amine (**4f**)*

Yield 85%. White solid, mp: 213–215°C; IR (KBr, ν_{max}, cm^{-1}): 3,436 (NH_2 stretching), 1,622 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.97 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 9.38 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.1, 15.8, 21.2, 103.4, 125.9, 129.6, 130.0, 131.8, 133.7, 142.1, 151.7, 167.7, 169.2, 169.8; MS (ESI) m/z: 344 $(M+1)^+$; Anal. calcd. for $C_{16}H_{17}N_5S_2$: C, 55.95; H, 4.99; N, 20.39; S, 18.67. Found: C, 55.91; H, 4.92; N, 20.31; S, 18.64.

*(E)-5-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**4g**)*

Yield 82%. White solid, mp: 188–190°C; IR (KBr, ν_{max}, cm^{-1}): 3,420 (NH_2 stretching), 1,615 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.89 (s, 1H, NH), 6.97 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 9.38 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.1, 15.7, 55.6, 102.1, 114.4, 115.1, 119.1, 127.2, 130.5, 132.4, 133.2, 133.7, 141.9, 159.3, 167.8, 169.5; MS (ESI) m/z: 360 $(M+1)^+$; Anal. calcd. for $C_{16}H_{17}N_5OS_2$: C, 53.46; H, 4.77; N, 19.48; S, 17.84. Found: C, 53.49; H, 4.71; N, 19.42; S, 17.88.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-thiazol-4-yl)-2H-chromen-2-one (**4h**)*

Yield 93%. White solid, mp: 255–257°C; IR (KBr, ν_{max}, cm^{-1}): 3,401 (NH_2 stretching), 1,706 (lactone C═O stretching), 1,577 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.40 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.81 (t, J = 7.6 Hz, 2H), 8.54 (s, 1H), 9.17 (s, 2H), 11.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.5, 15.8, 111.6, 116.3, 118.9, 119.5, 120.8, 125.2, 129.2, 132.2, 135.0, 138.5, 152.7, 159.1, 167.7, 168.9; MS (ESI) m/z: 398 $(M+1)^+$; Anal. calcd. for $C_{18}H_{15}N_5O_2S_2$: C, 54.39; H, 3.80; N, 17.62; S, 16.13. Found: C, 54.33; H, 3.84; N, 17.67; S, 16.17.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-thiazol-4-yl)-6-bromo-2H-chromen-2-one (**4i**)*

Yield 91%. White solid, mp: 209–211°C; IR (KBr, ν_{max}, cm^{-1}): 3,400 (NH_2 stretching), 1,718 (lactone C═O stretching), 1,629 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.42 (d, J = 8.8 Hz, 1H), 7.75–7.77 (m, 1H), 7.83 (s, 1H), 8.07 (s, 1H), 8.44 (s, 1H), 9.20 (s, 2H), 11.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.4, 15.9, 112.6, 116.9, 118.5, 121.5, 130.9, 131.2, 134.4, 136.9, 137.4, 144.2, 151.7, 158.6, 167.7, 169.0, 169.8, 172.5; MS (ESI) m/z: 476 $(M)^+$; Anal. calcd. for $C_{18}H_{14}BrN_5O_2S_2$: C, 45.38; H, 2.96; N, 14.70; S, 13.46. Found: C, 45.41; H, 3.00; N, 14.73; S, 13.41.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-thiazol-4-yl)-6-chloro-2H-chromen-2-one (**4j**)*

Yield 90%. White solid, mp: 203–205°C; IR (KBr, ν_{max}, cm^{-1}): 3,397 (NH_2 stretching), 1,723 (lactone C═O stretching), 1,623 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.49 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.83 (s, 1H), 7.96 (s, 1H), 8.46 (s, 1H), 8.96 (s, 2H), 11.57 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.6, 16.0, 102.0, 105.9, 109.0, 112.5, 112.7, 118.2, 119.0, 120.9, 128.0, 131.6, 135.3, 137.3, 144.4, 151.3, 159.9, 169.1; MS (ESI) m/z: 432 $(M+1)^+$; Anal. calcd. for $C_{18}H_{14}ClN_5O_2S_2$: C, 50.05; H, 3.27; N, 16.21; S, 14.85. Found: C, 50.12; H, 3.24; N, 16.16; S, 14.88.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-thiazol-4-yl)-6,8-dibromo-2H-chromen-2-one (**4k**)*

Yield 85%. White solid, mp: 238–240°C; IR (KBr, ν_{max}, cm^{-1}): 3,392 (NH_2 stretching), 1,723 (lactone C═O stretching), 1,630 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.83 (s, 1H), 8.08–8.11 (m, 2H), 8.38 (s, 1H), 9.07 (s, 2H), 11.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.6, 15.8, 110.2, 113.2, 116.9, 119.0, 122.4, 130.5, 135.3, 136.1, 136.3, 141.8, 143.9, 148.4, 157.9, 167.7, 168.9, 172.3; MS (ESI) m/z: 555 $(M)^+$; Anal. calcd. for $C_{18}H_{13}Br_2N_5O_2S_2$: C, 38.93; H, 2.36; Br, 28.78; N, 12.61; S, 11.55. Found: C, 38.97; H, 2.31; N, 12.66; S, 11.50.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-thiazol-4-yl)-8-methoxy-2H-chromen-2-one (**4l**)*

Yield 86%. White solid, mp: 216–218°C; IR (KBr, ν_{max}, cm^{-1}): 3,407 (NH_2 stretching), 1,710 (lactone C═O stretching), 1,624 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 7.33 (t, J = 7.2 Hz, 3H), 7.80 (s, 1H), 8.15 (s, 1H), 8.51 (s, 1H), 9.14 (s, 2H); MS (ESI) m/z: 426 $(M-1)^+$; Anal. calcd. for $C_{19}H_{17}N_5O_3S_2$: C, 53.38; H, 4.01; N, 16.38; S, 15.00. Found: C, 55.32, H, 4.12; N, 16.32; S, 14.96.

4.1.3 | General procedure for the synthesis of compounds 6

Equimolar amounts of 2-amino-4-methyl-5-acetylthiazole (1 mmol), thiocarbohydrazide (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol) were taken in a round bottom flask and refluxed in acetic acid (2 ml) at 70°C for about 2 hr. The progress of the reaction was monitored through TLC using ethyl acetate and *n*-hexane (40%). After completion of the reaction, the solid separated was filtered, dried and recrystalized from methanol to give **6**.

*(E)-4-Methyl-5-(1-(2-(5-phenyl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)-ethyl)thiazol-2-amine (**6a**)*

Yield 89%. White solid, mp: 230–232°C; IR (KBr, ν_{max}, cm^{-1}): 3,400 (NH_2 stretching), 1,605 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.94 (s, 2H, CH_2 of thiadiazine), 7.45–7.46 (m, 3H), 7.79–7.81 (m, 2H), 8.53 (s, 2H), 11.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 15.9, 18.7, 22.2, 120.4, 126.3, 129.1, 130.0, 135.3, 147.0, 152.3, 160.9, 168.0, 170.9; MS (ESI) *m/z*: 343 $(M-1)^+$; Anal. calcd. for $C_{15}H_{16}N_6S_2$: C, 52.30; H, 4.68; N, 24.40; S, 18.62. Found: C, 52.34; H, 4.61; N, 24.45; S, 18.65.

*(E)-4-Methyl-5-(1-(2-(5-(4-nitrophenyl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)thiazol-2-amine (**6b**)*

Yield 92%. White solid, mp: 194–196°C; IR (KBr, ν_{max}, cm^{-1}): 3,400 (NH_2 stretching), 1,663 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.04 (s, 2H, CH_2 of thiadiazine), 8.04 (d, J = 9.2 Hz, 2H), 8.30 (d, J = 9.2 Hz, 2H), 8.66 (s, 2H), 11.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 15.9, 18.6, 29.9, 120.2, 121.7, 124.3, 127.2, 141.5, 143.9, 147.9, 153.1, 157.8, 159.5, 168.1, 170.9; MS (ESI) *m/z*: 390 $(M+1)^+$; Anal. calcd. for $C_{15}H_{15}N_7O_2S_2$: C, 46.26; H, 3.88; N, 25.18; S, 16.47. Found: C, 46.22; H, 3.82; N, 25.14; S, 16.52.

*(E)-5-(1-(2-(5-(4-Fluorophenyl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)-ethyl)-4-methylthiazol-2-amine (**6c**)*

Yield 90%. White solid, mp: 204–206°C; IR (KBr, ν_{max}, cm^{-1}): 3,437 (NH_2 stretching), 1,626 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.96 (s, 2H, CH_2 of thiadiazine), 7.31 (t, J = 8.8 Hz, 2H), 7.84–7.87 (m, 2H), 9.17 (s, 2H), 11.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.6, 15.6, 22.3, 116.0, 116.2, 120.4, 128.6, 128.7, 131.8, 135.8, 146.2, 151.6, 161.7, 164.6, 168.1; MS (ESI) *m/z*: 363 $(M+1)^+$; Anal. calcd. for $C_{15}H_{15}FN_6S_2$: C, 49.71; H, 4.17; N, 23.19; S, 17.69. Found: C, 49.67; H, 4.21; N, 23.15; S, 17.73.

*(E)-5-(1-(2-(5-(2,4-Dichlorophenyl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**6d**)*

Yield 87%. White solid, mp: 211–213°C; IR (KBr, ν_{max}, cm^{-1}): 3,431 (NH_2 stretching), 1,627 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.79 (s, 2H, CH_2 of thiadiazine), 7.48–7.51 (m, 3H), 7.75 (s, 1H), 11.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 16.4, 17.5, 25.4, 120.2, 128.1, 129.8, 132.5, 132.8, 135.3, 146.3, 149.6, 153.6, 159.9, 162.8, 168.2; MS (ESI) *m/z*: 413 $(M+1)^+$; Anal. calcd. for $C_{15}H_{14}Cl_2N_6S_2$: C, 43.59; H, 3.41; N, 20.33; S, 15.51. Found: C, 43.55; H, 3.47; N, 20.37; S, 15.56.

*(E)-5-(1-(2-(5-(4-Bromophenyl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)-ethyl)-4-methylthiazol-2-amine (**6e**)*

Yield 85%. White solid, mp: 193–195°C; IR (KBr, ν_{max}, cm^{-1}): 3,400 (NH_2 stretching), 1,624 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.92 (s, 2H, CH_2 of thiadiazine), 7.65 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 8.03 (s, 2H), 11.46 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 16.2, 17.0, 21.9, 120.3, 123.3, 128.2, 132.0, 134.7, 143.5, 145.6, 153.1, 159.8, 167.9; Anal. calcd. for $C_{15}H_{15}BrN_6S_2$: C, 42.56; H, 3.57; N, 19.85; S, 15.15. Found: C, 42.62; H, 3.52; N, 19.81; S, 15.19.

*(E)-5-(1-(2-(5-(4-Methoxyphenyl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**6f**)*

Yield 85%. White solid, mp: 240–242°C; IR (KBr, ν_{max}, cm^{-1}): 3,380 (NH_2 stretching), 1,604 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.36 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.92 (s, 2H, CH_2 of thiadiazine), 7.01 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 9.07 (s, 2H), 11.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.3, 15.1, 21.8, 55.3, 114.0, 120.0, 127.1, 127.4, 135.8, 146.8, 150.8, 160.4, 161.6, 167.6; MS (ESI) *m/z*: 375 $(M+1)^+$; Anal. calcd. for $C_{16}H_{18}N_6OS_2$: C, 51.32; H, 4.84; N, 22.44; S, 17.12. Found: C, 51.35; H, 4.80; N, 22.47; S, 17.16.

*(E)-5-(1-(2-(5-([1,1^1-Biphenyl]-4-yl)-6H-1,3,4-thiadiazin-2-yl)hydrazono)ethyl)-4-methylthiazol-2-amine (**6g**)*

Yield 86%. White solid, mp: 236–238°C; IR (KBr, ν_{max}, cm^{-1}): 3,434 (NH_2 stretching), 1,627 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.34 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.01 (s, 2H, CH_2 of thiadiazine), 7.41 (d, J = 6.8 Hz, 2H), 7.49 (t, J = 7.2 Hz, 2H), 7.73–7.79 (m, 4H), 7.91 (d, J = 8.0 Hz, 1H), 9.30 (s, 2H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.3, 16.7, 29.7, 127.1, 128.3, 129.5, 139.6, 168.2, 169.9, 189.5; MS (ESI) *m/z*: 421 $(M+1)^+$; Anal. calcd. for $C_{21}H_{20}N_6S_2$: C, 59.97; H, 4.79; N, 19.98; S, 15.25. Found: C, 60.00; H, 4.13; N, 19.94; S, 15.20.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6H-1,3,4-thiadiazin-5-yl)-2H-chromen-2-one (**6h**)*

Yield 90%. White solid, mp: 214–216°C; IR (KBr, ν_{max}, cm^{-1}): 3,392 (NH_2 stretching), 1,710 (lactone C═O stretching), 1,605 (–C═N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm):δ; 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.43 (s, NH), 3.86 (s, 2H, CH_2 of thiadiazine), 7.30–7.40 (m, 3H, ArH), 7.65–7.75 (m, 3H, 1 ArH and NH_2), 8.45 (s, 1H, coumarin 4th proton); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 16.6, 17.7, 23.5, 116.1, 118.9, 119.9, 123.7, 125.0, 129.4, 132.7, 141.3, 144.3, 146.7, 153.5, 153.6, 159.2, 159.4, 167.6; MS (ESI) *m/z*:

413 $(M+1)^+$; Anal. calcd. for $C_{18}H_{16}N_6O_2S_2$: C, 52.41; H, 3.91; N, 20.37; S, 15.55. Found: C, 52.45; H, 3.95; N, 20.32; S, 15.51.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6H-1,3,4-thiadiazin-5-yl)-6-bromo-2H-chromen-2-one (**6i**)*
Yield 90%. White solid, mp: 219–221°C; IR (KBr, ν_{max}, cm^{-1}): 3,421 (NH_2 stretching), 1,722 (lactone C=O stretching), 1,623 (–C=N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.86 (s, 2H, CH_2 of thiadiazine), 7.44 (d, J = 8.8 Hz, 2H), 8.14 (s, 1H), 8.25 (s, 1H), 8.65 (s, 2H), 11.73 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 14.7, 15.7, 23.7, 116.9, 11.8, 120.3, 121.2, 125.0, 131.6, 135.3, 140.4, 144.4, 149.6, 152.2, 152.9, 159.2, 161.5, 168.2; MS (ESI) *m/z*: 490 $(M-1)^+$; Anal. calcd. for $C_{18}H_{15}BrN_6O_2S_2$: C, 44.0; H, 3.08; Br, 16.26, N, 17.10; S, 13.05. Found: C, 39.96; H, 3.12; N, 17.15; S, 12.96.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6H-1,3,4-thiadiazin-5-yl)-6,8-dibromo-2H-chromen-2-one (**6j**)*
Yield 92%. White solid, mp: 226–228°C; IR (KBr, ν_{max}, cm^{-1}): 3,394 (NH_2 stretching), 1,730 (lactone C=O stretching), 1,623 (–C=N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.85 (s, 2H, CH_2 of thiadiazine), 8.05 (s, 1H), 8.16 (s, 1H), 8.28 (s, 1H), 8.72 (s, 2H), 11.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 15.3, 16.0, 23.6, 110.5, 116.9, 120.4, 122.2, 125.7, 131.3, 135.3, 137.2, 139.8, 141.5, 143.7, 149.8, 153.0, 158.6, 168.1; MS (ESI) *m/z*: 571 $(M+1)^+$; Anal. calcd. for $C_{18}H_{14}Br_2N_6O_2S_2$: C, 37.91; H, 2.47; N, 14.74; S, 11.25. Found: C, 37.96; H, 2.42; N, 14.72; S, 11.29.

*(E)-3-(2-(2-(1-(2-Amino-4-methylthiazol-5-yl)ethylidene)hydrazinyl)-6H-1,3,4-thiadiazin-5-yl)-8-methoxy-6-nitro-2H-chromen-2-one (**6k**)*
Yield 86%. White solid, mp: 234–236°C; IR (KBr, ν_{max}, cm^{-1}): 3,400 (NH_2 stretching), 1,734 (lactone C=O stretching), 1,602 (–C=N– stretching); ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 2.32 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.94 (s, 2H, CH_2 of thiadiazine), 4.05 (s, 3H, OCH_3), 7.56 (s, 1H), 7.83 (s, 2H), 8.26 (s, 1H), 8.48 (s, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 16.2, 18.7, 29.8, 56.8, 112.6, 116.7, 119.5, 121.7, 125.7, 139.9, 144.1, 147.3, 148.4, 153.5, 153.9, 158.0, 167.7, 170.9, 188.7; MS (ESI) *m/z*: 488 $(M+1)^+$; Anal. calcd. for $C_{19}H_{17}N_7O_5S_2$: C, 46.81; H, 3.51; N, 20.11; S, 13.15. Found: C, 46.85; H, 3.35; N, 20.15; S, 13.18.

4.2 | Biology

4.2.1 | Antiplasmodial activity against *P. falciparum* 3D7 and Dd2 strains

P. falciparum 3D7 and Dd2, chloroquine-sensitive and -resistant strains, respectively, were maintained at 37°C by the bell jar candle method in RPMI 1640 medium supplemented with HEPES 25 mM, AlbumAX I 0.5% (wt/vol), hypoxanthine 100 μM, gentamicin 12.5 μg/ml and sodium bicarbonate 1.77 mM. IC_{50} of the compounds against *P. falciparum* strains was determined using the SYBR Green fluorescence-based method.[27] Briefly, parasite culture was synchronized with 5% sorbitol at the ring stage and further transferred to complete RPMI media till it reached the mature trophozoites. In 96-well plates, compounds were incubated with mature trophozoite culture in a proportion of 2% hematocrit and 1% parasitemia in a total volume of 200 μl for 48 hr in triplicate. After incubation, 100 μl of resuspended culture was transferred to 96-well flat-bottom plates already containing 100 μl of SYBR Green I lysis buffer (2XSYBR Green, 20 mM Tris base pH 7.5, 20 mM EDTA, 0.008% w/v saponin, 0.08% wt/vol Triton X-100). The plates were incubated for 1 hr at 37°C, fluorescence associated with SYBR Green I-intercalated parasitic DNA was measured at 490 nm excitation and 540 nm emission using a TECAN Infinite F-200 spectrophotometer (Tecan Trading AG, Switzerland) and IC_{50} of compounds was calculated from three independent experiments.

4.2.2 | Cytotoxicity assays (MTT)

Cytotoxicity of compounds was determined by using MTT.[28] The compounds were seeded at 1×10^4 cells in each well of 96-well plates. After 24 hr, the cells were treated with different concentrations of compounds (0.48–500 μM) in twofold serial dilution or vehicle (0.25% DMSO) for 24 hr. After 24 hr of treatment, 200 μl of medium containing MTT (0.5 mg/ml) was added to each well of a 96-well plate and incubated for 4 hr in a CO_2 chamber at 37°C. Reduced formazan crystals were dissolved in 100 μl of DMSO and absorbance was measured at 570 nm on a multiplate reader (Tecan infinite-200).

4.2.3 | NP-40 mediated β-hematin crystallization assay

Compounds were incubated with 100 μM hematin, 1 M acetate buffer of pH-4.8 and 30.55 μM NP-40 in a 96-well plate at 37°C and shaken at 55 rpm for 4 hr, the incubation plate was centrifuged at 1,100*g* for 1 hr at 25°C[29] and after discarding the supernatant, 200 μl of 0.15 M sodium bicarbonate containing 2% sodium dodecyl sulfate (SDS) was added to each well and centrifugation was repeated, and the supernatant containing free heme was discarded. Then, 200 μl 0.36 M sodium hydroxide and 2% SDS was added to dissolve the synthesized β-hematin. The absorbance was measured at 400 nm using a multiplate reader (Tecan infinite-200). β-Hematin crystallization inhibition IC_{50} concentrations of active compounds were measured by comparing their absorbance values with chloroquine absorbance, a positive control of the β-hematin crystallization inhibitor.

4.2.4 | LDH assay

LDH assay was conducted to measure the cytotoxicity of compounds **4h**, **4i**, **4k**, and **4l** against synchronized *P. falciparum* 3D7 culture in vitro. The culture was adjusted to 1–1.5% parasitemia and 2% hematocrit in a 96-well plate containing serially diluted compounds

and grown for 48 hr. Later, the percentage of cytotoxicity was estimated using a Cayman's LDH cytotoxicity assay kit, where the LDH released from the *P. falciparum* due the action compounds reduces NAD^+ to NADH and H^+ by oxidation of lactate to pyruvate. Using NADH and H^+, diaphorase reduces a tetrazolium salt (INT) to colored formazan, which has maximum absorbance at 490–520 nM.

4.2.5 | Stage-specific growth inhibition assay

Tightly synchronous ring (12 hr), trophozoite (24 hr and schizont (36 hr) stage *Plasmodium*-infected erythrocytes were incubated for 12 hr[30] at every individual stage with an IC_{90} concentration of the compound from the same synchronized culture, after that, the compound was removed by various washes and supplemented with complete RPMI media for further growth. Being untreated and presence of the compound with culture until the completion of the experiment (unremoved) were taken as controls. The experiment was continued up to 72 hr from postinfection of the RBC by a parasite. The smear was prepared for every 12 hr, stained with Giemsa and examined around 1,000 parasite-infected RBC to assess the stage-specific growth of the parasite and the percentage of parasitemia.

ACKNOWLEDGMENTS

The authors are thankful to the Director, National Institute of Technology, Warangal, Telangana, India for providing facilities. K.S. thanks the MHRD, India for the fellowship.

ORCID

Rajeswar Rao Vedula http://orcid.org/0000-0002-9762-0868

REFERENCES

[1] WHO, *World malaria report 2017*. Geneva: World Health Organization, 2017.
[2] L. Weber, *Curr. Med. Chem.* **2002**, *9*, 2085.
[3] H. Zheng, Y. J. Mei, K. Du, X. T. Cao, P. F. Zhang, *Molecules* **2013**, *18*, 13425.
[4] C. C. Musonda, D. Taylor, J. Lehman, J. Gut, P. J. Rosenthal, K. Chibale, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3901.
[5] U. Kazmaier, A. Persch, *Org. Biomol. Chem.* **2010**, *8*, 5442.
[6] V. U. Jeankumar, J. Renuka, P. Santosh, V. Soni, J. P. Sridevi, P. Suryadevara, P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem.* **2013**, *70*, 143.
[7] P. Makam, R. Kankanala, A. Prakash, T. Kannan, *Eur. J. Med. Chem.* **2013**, *69*, 564.
[8] J. G. Ghogare, S. V. Bhandari, K. G. Bothara, A. R. Madgulkar, G. A. Parashar, B. G. Sonawane, P. R. Inamdar, *Eur. J. Med. Chem.* **2010**, *45*, 857.
[9] I. Kayagil, S. Demirayak, *Phosphorus Sulfur Silicon Relat. Elem.* **2009**, *184*, 2197.
[10] K. M. Dawood, T. M. A. Eldebss, H. S. A. El-Zahabi, M. H. Yousef, *Eur. J. Med. Chem.* **2015**, *102*, 266.
[11] S. Bondock, T. Naser, Y. A. Ammar, *Eur. J. Med. Chem.* **2013**, *62*, 270.
[12] J. M. Bueno, M. Carda, B. Crespo, A. C. Cuñat, C. de Cozar, M. L. León, J. A. Marco, N. Roda, J. F. Sanz-Cervera, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3938.
[13] M. H. M. Helal, M. A. Salem, M. S. A. El-Gaby, M. Aljahdali, *Eur. J. Med. Chem.* **2013**, *65*, 517.
[14] S. Sardari, Y. Mori, K. Horita, R. G. Micetich, S. Nishibe, M. Daneshtalab, *Bioorg. Med. Chem.* **1999**, *7*, 1933.
[15] P. Zhou, Y. Takaishi, H. Duan, B. Chen, G. Honda, M. Itoh, Y. Takeda, O. K. Kodzhimatov, K. H. Lee, *Phytochemistry* **2000**, *53*, 689.
[16] P. Anand, B. Singh, N. Singh, *Bioorg. Med. Chem.* **2012**, *20*, 1175.
[17] S. J. Bullock, C. E. Felton, R. V. Fennessy, L. P. Harding, M. Andrews, S. J. A. Pope, C. R. Rice, T. Riis-Johannessen, *Dalton Trans.* **2009**, *47*, 10570.
[18] A. Ibrar, Y. Tehseen, I. Khan, A. Hameed, A. Saeed, N. Furtmann, J. Bajorath, J. Iqbal, *Bioorg. Chem.* **2016**, *68*, 177.
[19] R. Echemendía, O. Fernández, J. Coro, M. Suárez, D. G. Rivera, *Tetrahedron Lett.* **2017**, *58*, 1784.
[20] A. Sarapultsev, O. Chupakhin, P. Sarapultsev, L. Sidorova, T. Tseitler, *Pharmaceuticals* **2016**, *9*, 27.
[21] D. Wang, W. Liu, F. Yi, Y. Zhao, J. Chen, *Org. Biomol. Chem.* **2016**, *14*, 1921.
[22] A. Guerra, P. Gonzalez-Naranjo, N. E. Campillo, J. Varela, M. L. Lavaggi, A. Merlino, H. Cerecetto, M. González, A. Gomez-Barrio, J. A. Escario, C. Fonseca-Berzal, G. Yaluf, J. Paniagua-Solis, J. A. Páez, *Eur. J. Med. Chem.* **2017**, *136*, 223.
[23] A. Ayati, S. Emami, A. Asadipour, A. Shafiee, A. Foroumadi, *Eur. J. Med. Chem.* **2015**, *97*, 699.
[24] C. M. Moldovan, O. Oniga, A. Pârvu, B. Tiperciuc, P. Verite, A. Pîrnău, O. Crişan, M. Bojiţă, R. Pop, *Eur. J. Med. Chem.* **2011**, *46*, 526.
[25] K. Sujatha, R. R. Vedula, *Synth. Commun.* **2018**, *48*, 302.
[26] K. Sujatha, R. P. Deshpande, R. K. Kesharwani, P. P. Babu, R. Rao Vedula, *Synth. Commun.* **2019**, *49*, 49.
[27] M. Smilkstein, N. Sriwilaijaroen, J. X. Kelly, P. Wilairat, M. Riscoe, *Antimicrob. Agents Chemother.* **2004**, *48*, 1803.
[28] M. Ferrari, M. C. Fornasiero, A. M. Isetta, *J. Immunol. Methods* **1990**, *131*, 165.
[29] J. M. Pisciotta, I. Coppens, A. K. Tripathi, P. F. Scholl, J. Shuman, S. Bajad, V. Shulaev, D. J. Sullivan, *Biochem. J.* **2007**, *402*, 197.
[30] C. Moneriz, P. Marín-García, A. García-Granados, J. M. Bautista, A. Diez, A. Puyet, *Malar. J.* **2011**, *10*, 82.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Sujatha K, Ommi NB, Mudiraj A, Babu PP, Vedula RR. Synthesis of thiazolyl hydrazonothiazolamines and 1,3,4-thiadiazinyl hydrazonothiazolamines as a class of antimalarial agents. *Arch Pharm Chem Life Sci*. 2019;e1900079. https://doi.org/10.1002/ardp.201900079

Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Novel one-pot multicomponent synthesis of (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives

Kodam Sujatha & Rajeswar Rao Vedula

To cite this article: Kodam Sujatha & Rajeswar Rao Vedula (2019): Novel one-pot multicomponent synthesis of (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives , Synthetic Communications, DOI: 10.1080/00397911.2019.1689571

To link to this article: https://doi.org/10.1080/00397911.2019.1689571

Published online: 12 Nov 2019.

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1689571

Novel one-pot multicomponent synthesis of (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives

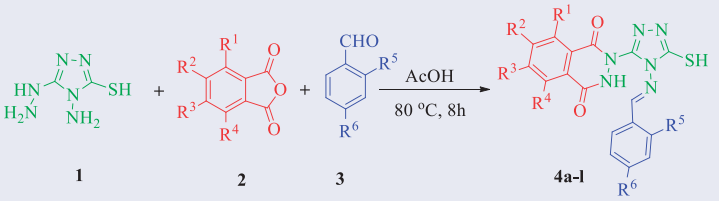
Kodam Sujatha and Rajeswar Rao Vedula

Department of Chemistry, National Institute of Technology, Warangal, India

ABSTRACT

An expeditious, one-pot multicomponent reaction has been developed for the synthesis of (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives. Condensation of 4-amino-5-hydrazino-4*H*-1,2,4-triazole-3-thiol with phthalic anhydride and aromatic aldehyde afforded the (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-diones in acetic acid medium with excellent yields. All the synthesized compounds were characterized by their analytical and spectral data.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 12 March 2019

KEYWORDS
4-Amino-5-hydrazino-4*H*-1,2,4-triazole-3-thiol; 2,3-dihydrophthalazine-1,4-dione; aromatic aldehyde; Schiff base

Introduction

Multicomponent reactions are important strategies to reach ecofriendly and sustainable transformations in modern chemistry. These reactions have several advantages when compared to stepwise linear synthesis such as atom economy, less waste production time and energy saving, easy purification and high convergence among others.[1]

Triazoles are important heterocyclic molecules in current organic synthesis,[2–4] the core nucleus of triazole is found in many drugs and it exhibits numerous pharmacological and biological activities such as anti-inflammatory,[5] antifungal,[6] antioxidant,[7] anti tubercular and microbial agent[8] and anticancer activity.[9]

Nitrogen containing heterocyclic molecules such as phthalazines possess good pharmaceutical activities such as anti-analgesic,[10] anti-inflammatory,[11] anti-diabetic,[12] anti-

CONTACT Rajeswar Rao Vedula rajeswarnitw@gmail.com Department of Chemistry, National Institute of Technology, Warangal, Telangana 506004, India.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.

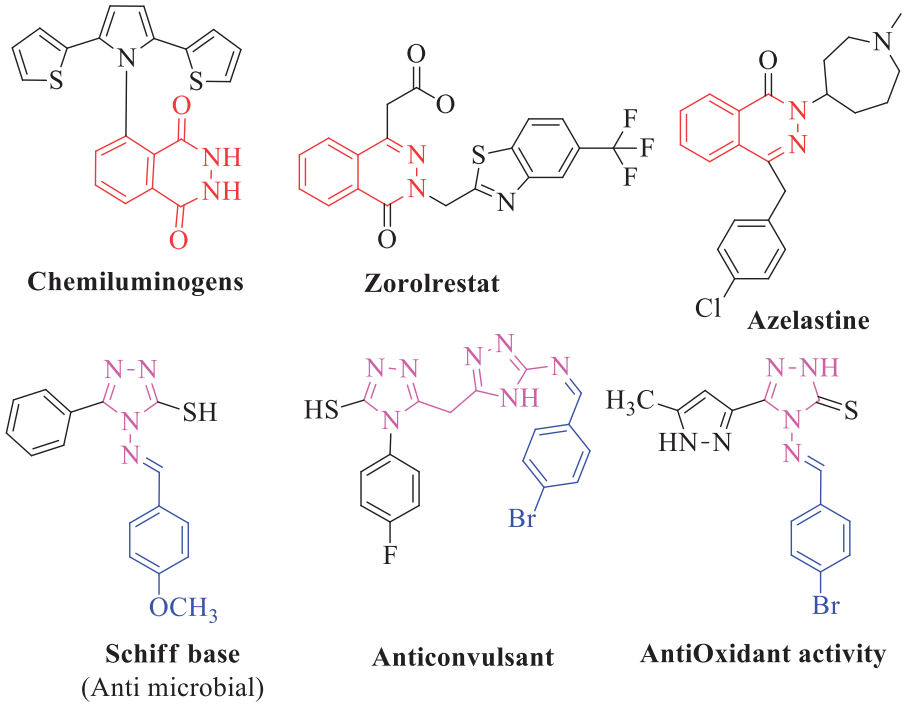


Figure 1. Biologically active molecules containing phthalazines and triazole moieties.

microbial,[13] anti-viral,[14] anti-tumor,[15] antineoplastic,[16] insecticidal[17] antifungal,[18] anti-bacterial,[19] anticonvulsant,[20] anti-proliferative[21] and vasorelaxant activities.[22]

Triazolo phthalazines were also good heterocyclic molecules in organic synthesis and also exhibit good biological activities such as anti-tubercular,[23] anti-inflammatory,[24,25] antimicrobial,[26] anticancer[27] and anticonvulsant properties.[28,29]

Schiff bases are important class of organic compounds.[30] Schiff bases are known to exhibit good biological activities like anti-fungal,[31] antioxidant and antimicrobial,[32] antibacterial (Fig. 1).[33]

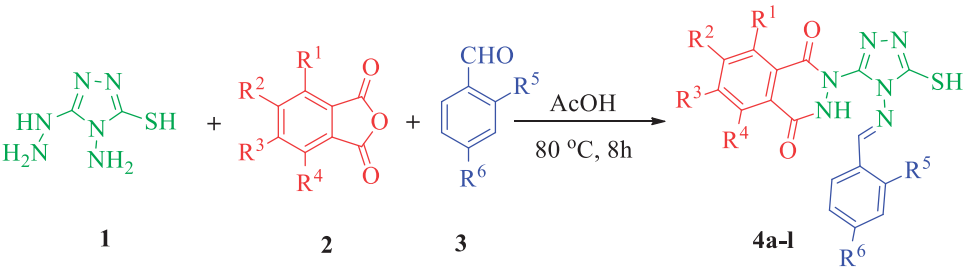
Keeping in view of numerous biological activities associated with triazoles, phthalazines and Schiff's bases, our present study is focused on the development of new methodologies for the synthesis of phthalazines having triazole and Schiff bases.

In continuation of our earlier work,[34–36] we had developed a one-pot MCR for the synthesis of title compounds expecting that these compounds may possess good biological activities.

Results and discussion

Reaction of an equimolar amount of 4-amino-5-hydrazino-4*H*-1,2,4-triazole-3-thiol, phthalic anhydride and aromatic aldehyde in acetic acid gave the final products (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-diones (Scheme 1) with good yields.

Reaction of **1**, **2** and **3** in absolute ethanol under reflux gave only 15% of expected product. Additionally, when the same reaction is examined by the various other solvents



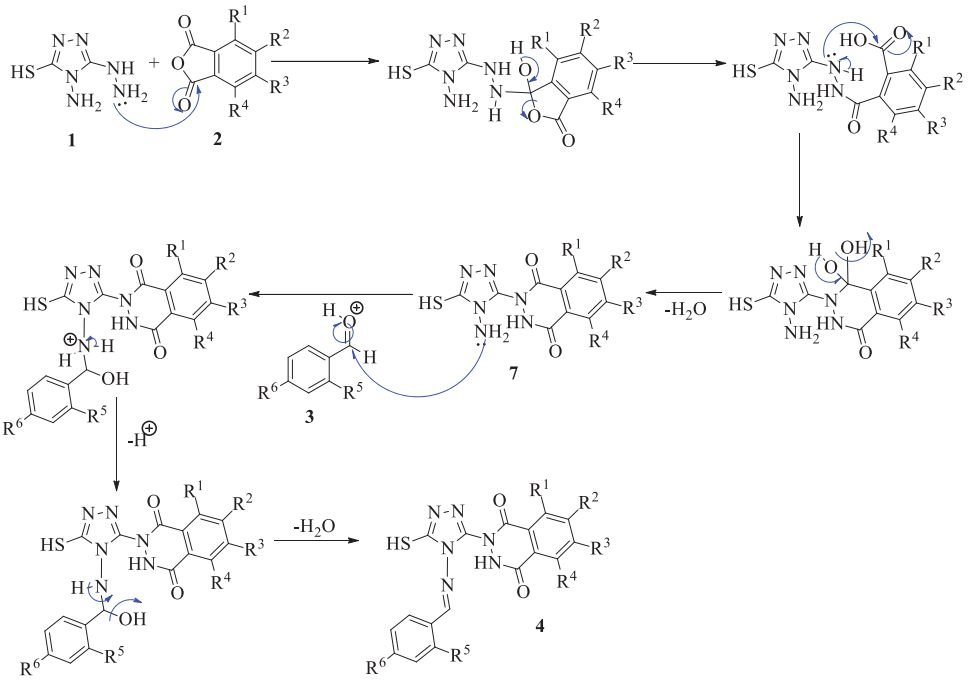
Scheme 1. Synthesis of compounds **4a–l**.

Table 1. Different substitutions of the compounds **4a–l**.

Entry	Product	R^1	R^2	R^3	R^4	R^5	R^6	Yields (%)
1	**4a**	H	H	H	H	H	CH_3	85
2	**4b**	H	H	H	H	H	OCH_3	85
3	**4c**	H	H	H	H	H	OH	82
4	**4d**	H	H	H	H	OH	OEt	86
5	**4e**	H	H	H	H	H	CN	90
6	**4f**	H	H	H	H	H	F	92
7	**4g**	H	H	H	H	Cl	H	90
8	**4h**	H	H	H	H	H	Cl	93
9	**4i**	H	H	H	H	Cl	Cl	90
10	**4j**	H	H	H	H	H	Br	84
11	**4k**	Br	Br	Br	Br	H	CH_3	85
12	**4l**	Br	Br	Br	Br	Cl	H	90

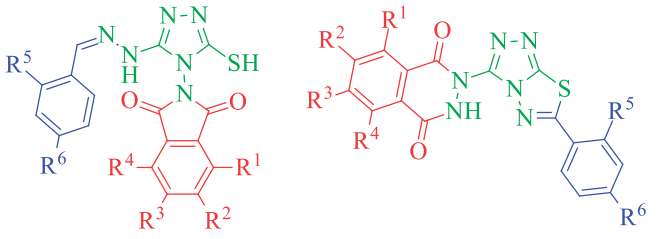
such as methanol, methanol and catalytic amount of acetic acid, methanol and catalytic amount of HCl produced low yields of the products when compared to acetic acid. Therefore, the optimized condition for the heterocyclization and condensation is the acetic acid under reflux condition (Table 1).

Reaction between compound **1**, phthalic anhydride and aldehyde is expected to give compounds **5** and **6** or both depending on the process of cyclization. In the present investigation, the reaction takes place in such a way that only hydrazino part of compound **1** underwent cyclocondensation with **2** followed by further condensation of N-amino group of compound **1** with aromatic aldehyde leading to the formation of final products (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-diones (**4**) (only one product based on TLC). The significant feature of this scheme is that three new hetero atom bonds like one N=C and two –N–C=O are formed at a time under mild conditions. The yields of the products were 82–93%. From the above, it is apparent that the solvent and reaction conditions have played an important role in the selective heterocyclization reaction. During multicomponent reaction, we have condensed compound-**1** first with phthalic anhydride, and then, we have added aldehyde in a sequential manner. Hence, there is no possibility of formation of compound-**5**. Compound-**5** structure can be rejected on the basis of spectral evidence. The nucleophilicity of C_5 hydrazino group of 1 is more compared to the ring N-amino group. 5-Hydrazino group of 1 readily attacks on electrophilic carbon atom of carbonyl group of phthalic anhydride. Under mild acidic conditions phthalazines are formed as shown in the mechanism. This is supported by authors earlier work.[37–39] Later on the $N–NH_2$ attacks on the Carbon atom of electrophilic aldehyde followed by loss of water to give final compound **4**. The reaction stops at the stage of Schiff base 4. This is



Scheme 2. Mechanism for the formation of **4a–l**.

supported by spectral evidence. There is a free SH group in the final compound **4**. The compound **5** might be formed on reversal addition of reactants like aldehyde followed by phthalic anhydride on 1, not the conditions which we have applied. We have tried for growing single crystal to the compound 4 but we could not succeed. We have tried to cyclize the compound **4** into 6 using PTSA/DMF and also by using SiO_2/DMF. But the reaction did not proceed at all. The compound after work up gave only 4. The alternative products **5** and **6** can be rejected on the basis of spectral studies.



5 **6**

A plausible mechanism for the formation of final product **4** is proposed in Scheme 2. In the first step, condensation of **1** with phthalic anhydride resulted in the formation of intermediate **7**. This on further reaction with aromatic aldehyde loses water molecule leading to the formation of final product **4**.

All the structures of newly synthesized compounds were confirmed by their spectral data. The IR spectrum of compound **4a** shows prominent peaks at 1604 cm^{-1} (C=N), 1738 cm^{-1} (carbonyl stretching), 2550 cm^{-1}(SH stretching), 3336 cm^{-1} (NH stretching), whereas the

^{1}H NMR spectrum of compound **4a** showed characteristic singlet for CH_3 of aldehyde at δ 2.41, NH at δ 10.07 and SH at δ 13.37 ppm and 13C NMR spectrum of compound **4a** showed characteristic CH_3 carbon at δ 21.7 ppm. The other carbon atoms appear at the expected region. The compound **4a** exhibited the molecular ion peak at *m/z* 379.

Experimental

All the reagents and chemicals which were used in the present study were purchased from commercial sources and used further without any purification. 4-Amino-5-hydrazinyl 4*H*-1,2,4 triazole-3-thiol is a starting compound, it is prepared by the literature procedure.[40] Melting points were determined in open capillaries with a Stuart melting point apparatus Mumbai, India and were uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100s. ^{1}H-NMR spectra were recorded on Bruker WM-400 spectrometer in δ ppm using TMS as the standard, ESI-MS spectra were recorded on Jeol JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer, compounds purity was checked by TLC plates (E Merck, Mumbai, India). The Supplemental Materials contain ^{1}H and ^{13}C NMR spectra of products **4a–l**.

General procedure for the synthesis of compounds (4a–l)

An equimolar amount of 4-amino-5-hydrazino-4*H*-1,2,4-triazole-3-thiol (1 mmol), phthalic anhydride (1 mmol) and aromatic aldehyde (1 mmol) was taken in glacial acetic acid. The reaction mixture was heated at 80 °C for about 8 h and cooled to room temperature. The solid obtained was filtered and recrystallized from methanol to give final product.

(E)-2-(5-mercapto-4-((4-methylbenzylidene)amino)-4H-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione (4a)

White solid; mp 245–247 °C; Yield (85%); IR (KBr, ν_{max}, cm^{-1}): 1604 (C=N), 1738 (carbonyl stretching), 2550 (SH stretching), 3336 (NH stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.41 (s, 3H, CH3), 7.37 (d, $J = 8.0$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 2H), 7.96–8.03 (m, 4H), 10.07 (s, 1H), 10.16 (s, 1H), 13.37 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 21.7, 124.4, 127.0, 129.2, 129.62, 129.9, 130.1, 136.0, 143.4, 149.1, 161.0, 162.2, 165.7. ESI-MS, *m/z* (%): 379 $(M + H)^+$; anal. calcd. for $C_{18}H_{14}N_6O_2S$: C, 57.13; H, 3.73; N, 22.21; S, 8.47. Found: C, 57.17; H, 3.78; N, 22.25; S, 8.43.

Conclusion

In conclusion, we have developed a novel one-pot multicomponent method for the synthesis of (E)-2-(benzylideneamino)-5-mercapto-4*H*-1,2,4-triazol-3-yl)-2,3-dihydrophthalazine-1,4-dione derivatives. This reaction gave good to excellent yields and all the products were purified by recrystallization.

Acknowledgments

The authors are thankful to the Director, National Institute of Technology, Warangal, Telangana, India for providing the facilities.

Funding

K. S. thanks to the MHRD, India for fellowship.

References

[1] Haline, G. O. A.; Eufranio, N. S. J.; Brenno, A. D. N. *RSC Adv.* **2014**, *4*, 54282–54299.
[2] Sherif, Y. E.; Alansari, R.; Gouda, M. A. *Antiinflamm. Antiallergy Agents Med. Chem.* **2018**, *17*, 3–15. doi:10.2174/1871523017666180413111321.
[3] Yanan, L.; Bin, W.; Pei, C.; Jianjian, H.; Tao, Yinglei, W.; Bozhou, W. *RSC Adv.* **2018**, *8*, 13755–13763.
[4] Abdulaziz, A.; Mervat, M. A.; Mohamed, A. R.; Solwan, M. I.; Kamal, U. S. *J. Heterocycl. Chem.* **2018**, *55*, 1804–1808.
[5] Hao, X.; Shuang, M.; Yuanqing, X.; Longxiang, B.; Tao, D.; Xiaomin, F.; Wenkai, Z.; Yanrong, R. *J. Org. Chem.* **2015**, *80*, 1789–1794.
[6] Rajeev, K.; Prabodh, C. S.; Mohammed, S. Y. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1–21.
[7] Pokuri, S.; Singla, R. K.; Bhat, V. G.; Shenoy, G. G. *Curr. Drug Metab.* **2014**, *15*, 389–397. doi:10.2174/1389200215666140908101958.
[8] Hany, A. M. E. S.; Mohamed, A. A.; Hamdy, M. A. R. *J. Adv. Biomed. Pharm. Sci.* **2018**, *1*, 1–5.
[9] Singh, R.; Kashaw, S. K.; Mishra, V. K.; Mishra, M.; Rajoriya, V.; Kashaw, V. *Indian J. Pharm. Sci.* **2018**, *80*, 36–45.
[10] El-Sherief, H. A. M.; Youssif, B. G. M.; Bukhari, S. N. A.; Abdel-Aziz, M.; Abdel-Rahman, H. M. *Bioorg. Chem.* **2018**, *76*, 314–325. doi:10.1016/j.bioorg.2017.12.013.
[11] El-Shamy, I. E.; Abdel-Mohsen, A.; Alsheikh, A. A.; Fouda, M. M.; Al-Deyab, S. S.; El-Hashash, M. A.; Jancar, J. *Dyes Pigm.* **2015**, *113*, 357. doi:10.1016/j.dyepig.2014.08.026.
[12] Madhavan, G. R.; Chakrabarti, R.; Kumar, S. K.; Misra, P.; Mamidi, R. N.; Balraju, V.; Kasiram, K.; Babu, R. K.; Suresh, J.; Lohray, B. B.; et al. *Eur. J. Med. Chem.* **2001**, *36*, 627.
[13] Roxana, M. B.; Maria, D. C.; Vasilichia, B.; Margareta, U.; Antonia, P.; Cristina, T.; Margareta, F.; Ionel, I. M. *J. Heterocycl. Chem.* **2007**, *44*, 1149.
[14] Moustafa, A. H.; El-Sayed, H. A.; Abd El-Hady, R. A.; Haikal, A. Z.; El-Hashash, M. *J. Heterocycl. Chem.* **2016**, *53*, 789. doi:10.1002/jhet.2316.
[15] Zhang, S. L.; Liu, Y. J.; Zhao, Y. F.; Guo, Q. T.; Gong, P. *Chin. Chem. Lett.* **2010**, *21*, 1071. doi:10.1016/j.cclet.2010.04.004.
[16] Costantino, G.; Macchiarulo, A.; Camaioni, E.; Pellicciari, R. *J. Med. Chem.* **2001**, *44*, 3786. doi:10.1021/jm010116l.
[17] Aly, M. R. E.; Ibrahim, M. M.; Okael, A. M.; Gherbawy, Y. A. M. H. *Russ. J. Bioorg. Chem.* **2014**, *40*, 214–227. doi:10.1134/S1068162014020022.
[18] Chung-Kyu, R.; Rae-Eun, P.; Mi-Young, M.; Ji-Hee, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2577–2580.
[19] Khalil, A. M.; Berghot, M. A.; Gouda, M. A. *Eur. J. Med. Chem.* **2009**, *44*, 4448–4454. doi:10.1016/j.ejmech.2009.06.003.
[20] Ming, B.; Xian-Qing, D.; Guo-Hua, G.; Cheng-Xi, W.; Zhe-Shan, Q. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 792–800.
[21] Rashdan, H. R. M.; Gomha, S. M.; El-Gendey, M. S.; El-Hashash, M. A.; Soliman, A. M. M. *Green Chem. Lett. Rev.* **2018**, *11*, 264–274. doi:10.1080/17518253.2018.1474270.

[22] Watanabe, N.; Kabasawa, Y.; Takase, Y.; Matsukura, M.; Miyazak, K.; Ishihara, H.; Kodama, K.; Adachi, H. *J. Med. Chem.* **1998**, *41*, 3367. doi:10.1021/jm970815r.
[23] Veau, D.; Krykun, S.; Mori, G.; Orena, B. S.; Pasca, M. R.; Frongia, C.; Lobjois, V.; Chassaing, S.; Lherbet, C.; Baltas, M. *Chem. Med. Chem.* **2016**, *11*, 1078–1089. doi:10.1002/cmdc.201600085.
[24] Liu, D. C.; Gong, G. H.; Wei, C. X.; Jin, X. J.; Quan, Z. S. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1576–1579. doi:10.1016/j.bmcl.2016.02.008.
[25] Xian-Yu, S.; Chuan, H.; Xian-Qing, D.; Cheng-Xi, W.; Zhi-Gang, S.; Zhe-Shan, Q. *Eur. J. Med. Chem.* **2010**, *45*, 4807–4812. doi:10.1016/j.ejmech.2010.07.049.
[26] Habib, N. S.; Farghaly, A. M.; Ashour, F. A.; Bekhit, A. A.; El Razik, H. A. A.; El Azeim, T. A. *Arch. Pharm. Pharm. Med. Chem.* **2011**, *344*, 530–542. doi:10.1002/ardp.201100053.
[27] Prithwiraj, D.; Michel, B.; Delphine, L. T.; Celine, B.; Robert, K.; Florence, B. B.; Nathalie, S. *Bioorg. Med. Chem. Lett.* **2010**, *18*, 2537–2548.
[28] Lei, Z.; Li-Ping, G.; Ian-Yu, S.; Cheng-Xi, W.; Kyu-Yun, C.; Zhe-Shan, Q. *Chem. Biol. Drug Des.* **2009**, *73*, 313–319.
[29] Cheng-Xi, W.; Zhou, G.; Fu-Nan, L.; Zhe-Shan, Q. *Asian J. Chem.* **2011**, *23*, 127–131.
[30] Kandile, N. G.; Mohamed, M. I.; Ismaeel, H. M. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 119–129. doi:10.1080/14756366.2016.1238365.
[31] Ruyi, J.; Jingli, L.; Guanghui, Z.; Jiajia, L.; Shuan, Z.; Hui, G. *Chem. Biodivers.* **2018**, *15*, e1800263. doi:10.1002/cbdv.201800263.
[32] Unver, Y.; Deniz, S.; Celik, F.; Akar, Z.; Kucuk, M.; Sancak, K. *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 89–95. doi:10.1080/14756366.2016.1206088.
[33] Yusra, H. A.; Jawad, K. S. H.; Ahmad, N. A. A. A. *J. Sci.* **2015**, *5*, 293–299.
[34] Sujatha, K.; Vedula, R. R. *Synth. Commun.* **2018**, *48*, 302–308. doi:10.1080/00397911.2017.1399422.
[35] Sujatha, K.; Deshpande, R. P.; Kesharwani, R. K.; Prakash Babu, P.; Vedula, R. R. *Synth. Commun.* **2019**, *49*, 49–55. doi:10.1080/00397911.2018.1537398.
[36] Thirupaiah, B.; Sujatha, K.; Vedula, R. R. *Indian J. Chem.* **2017**, *56B*, 1089–1093.
[37] Chunduru, V. S. R.; Vedula, R. R. *Synth. Commun.* **2013**, *43*, 923–929.
[38] Chunduru, V. S. R.; Vedula, R. R. *Chem Heterocycl. Compd.* **2013**, *4*, 628–632.
[39] Thirupaiah, B.; Vedula, R. R. *Synth. Commun.* **2014**, *44*, 513–519. doi:10.1080/00397911.2013.817584.
[40] Dickinson, R. G.; Jacobsen, N. W. *Org. Prep. Proced. Int.* **1974**, *6*, 156–157. doi:10.1080/00304947409355092.