STUDIES ON THE SYNTHESIS AND EVALUATION OF BIOLOGICAL ACTIVITY OF NOVEL CHROMENES, DIHYDROPYRIDINES, PORPHYRINS AND PYRAZOLO-PHTHALAZINES

THESIS SUBMITTED TO

NATIONAL INSTITUTE OF TECHNOLOGY
WARANGAL

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

By

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AUGUST-2016

DECLARATION

I hereby declare that the research work presented in this thesis entitled **"Studies on the synthesis and evaluation of biological activity of novel chromenes, dihydropyridines, porphyrins and pyrazolo-phthalazines"** has been carried out by me under the supervision of **Dr. G. V. P. Chandramouli**, Professor, Department of Chemistry, National Institute of Technology, Warangal. I also affirm 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 or Institute.

Date:

Place: **(P. Sagar Vijay Kumar)**

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CERTIFICATE

The research work presented in this thesis entitled **"Studies on the synthesis and evaluation of biological activity of novel chromenes, dihydropyridines, porphyrins and pyrazolo-phthalazines"** submitted by **Mr. P. Sagar Vijay Kumar** for the award of the degree of **Doctor of Philosophy in Chemistry**, National Institute of Technology, Warangal (A.P.), under my guidance and supervision. This work has not been submitted earlier either in part or in full for any degree or diploma to this or any other university.

(G. V. P. Chandramouli)
Research Supervisor

Date:

Place:

ACKNOWLEDGEMENTS

It gives me immense pleasure and pride to express my deep sense of gratitude for my teacher and supervisor ***Dr. G. V. P. Chandramouli***, Professor, Department of Chemistry, National Institute of Technology, Warangal for his evergreen expertise and astute guidance. His unabated enthusiasm, which stems from his absolute command over the subject, has been a constant source of inspiring to me to work hard and the outcome is expressed in the form of this thesis. I consider myself fortunate that it would have been impossible to achieve this goal without his support and care.

I express my sincere thanks to ***Prof. T. Srinivasa Rao***, Director, National Institute of Technology, Warangal, for having given me the opportunity to carry out the work and allowing me to submit in the form of thesis.

Financial assistance from the ***Council of Scientific and Industrial Research (CSIR)***, New Delhi in the form of fellowship is gratefully acknowledged.

I wish to express my thanks to present and former Heads of our Department, ***Prof. V. Rajeswar Rao, Prof.(Ms.) B. Rajitha*** and ***Prof. K. Laxma Reddy*** for providing laboratory facilities to carry out the research work.

I express my thanks to Doctoral Scrutiny Committee (DSC) members, **Dr.** ***P. V. Srilakshmi***, Department of Chemistry and ***Prof. M. K. Mohan***, Professor of Metallurgical and Materials Engineering for their support and encouragement.

I would like to express my special thanks to ***Prof. B. V. Appa Rao***, ***Prof. A. Ramachandraiah***, ***Prof. P. Nageswar Rao***, ***Prof. I. Ajitkumar Reddy***, ***Dr. K. V. Gobi***, ***Dr. Venkatathri Narayanan***, ***Dr. Vishnu Shanker***, ***Dr. D. Kasinath*** and ***Dr. K. Hari Prasad*** for their valuable advice and encouragement.

I take this opportunity to express my thanks to ***Dr. B. Srinivas***, for interpretation of Single-Crystal X-ray diffraction data. I would like to express my sincere thanks to ***P. Omkar*** for evaluating biological activities and molecular docking studies

I wish to thank ***The Directors***, Indian Institute of Chemical Technology (IICT)-Hyderabad, University of Hyderabad and Sophisticated Test and Instrumentation Centre (STIC), Cochin University of Science &Technology-Kerala for providing library and instrumental facilities.

I wish to express my special thanks to ***Head***, ***Dept. of Biotechnology***, ***NIT Warangal***, for providing biological activities and molecular docking studies

I acknowledge with gratitude the keen and helpful guidance of ***Dr. M. Amaravathi*** throughout the research work for her constant encouragement.

I would like to express my sincere thanks to **Dr. D. Mohan rao, Managing Director, Symed Labs Ltd., Hyderabad**, for providing industrial project.

I thank all my seniors, ***Dr. B. Prasanna***, ***Dr. P. Naveen kumar***, ***Dr. A. Sunil Kumar***, and ***Dr. S. Kanakaraju*** for their valuable advice and encouragement throughout my research work.

With all happiness I acknowledge the cheerful assistance rendered by all my research colleagues, ***M. Narsihma Reddy***, ***K. Koteshwara Reddy***, ***G. Srinivasa Rao***, ***K. Vimal Kumar***, ***M. Nookaraju***, ***L. Suresh***, ***K. Chaitanya Kumar***, ***V. Ravibabu***, ***G. Rajitha***, ***G. Ramesh***, ***V. Krishnaiah***, ***G. Malikarjun***, ***P. Sreenu***, ***R. Rajkumar***, ***Tewodros Birhanu***, ***T. Surendar***, ***B. Thirupaiah***, ***L. Suresh***, ***M. Venkanna***, ***P. Mahendranath***, ***B. Paplol***, ***R. Hithavani***, ***S. Nagaraju***, ***B. Santosh Kumar***, ***P. Kavitha***, ***A. Rajini***, ***T. Ramesh***, ***M Satyanarayana***, ***A. Ajay Kumar***, ***K. Yugender***, ***E. Rajesh***, ***V. Amarnath***, ***Ch Srinivasa Rao***, ***Mayuri***, ***Varun***, ***Parameshwara chary***, ***Srikanth***, ***Sowmya***, ***Bharath***, ***Vinay***, ***Sujatha***, **Sanjay**, ***N. Satyanarayana***, ***Sunil***, ***Suman***, ***S. Suresh***, ***Ambedkar, Babji, Verendar Reddy***,and ***Ramaiya*** and other co-research scholar for their unstinted co-operation

Words are short to express my deep sense of gratitude to my family members: parents ***Jojappa*** and ***Suseela***, wife ***Varalakshmi***, brother ***Vinod***, sister ***Anusha***, for their constant support, cooperation, encouragement, inspiration, love and affection whose blessings made the journey worth effort. I owe everything to them.

I always remember and cherish the encouragement and inspiration provided by all my friends and well-wishers during the course of my research work

(P. Sagar Vijay Kumar)

ABBREVIATIONS

Ac	:	Acetyl
AcOH	:	Acetic acid
Anhyd.	:	Anhydrous
[BMIM]BF_4	:	1-Butyl-3-methylimidazolium tetrafluoroborate
[BMIM]Br	:	1-Butyl-3-methylimidazolium Bromide
[BMIM]PF_6	:	1-Butyl-3-methylimidazolium hexafluorophosphate
[BMIM]OH	:	1-Butyl-3-methylimidazolium hydroxide
[BSIM]Cl	:	1-butyl-3-sulfonic acid imidazolium chloride
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHP	:	Dihydropyridine
DMF	:	Dimethylformamide
[DMIM]HSO_4	:	1,3-Disulfonic acid imidazolium hydrogen sulfate
DMSO	:	Dimethyl sulfoxide
EDTA	:	Ethylenediaminetetraacetic acid
ESI	:	Electrospray ionization
[HMIM]TFA	:	1-Methylimidazolium trifluoroacetate
IC_{50}	:	Half maximal inhibitory concentration
ILs	:	Ionic liquids
MIC	:	Minimum inhibitory concentration
MWI	:	Microwave irradiation
NBS	:	*N*-Bromosuccinimide
4-NGP	:	4-nitrophenyl α-D-glucopyranoside
PEG	:	Polyethylene glycol
Powder-XRD	:	Powder X-Ray Diffraction
PPA	:	Polyphosphoric acid
rt	:	Room temperature
SAR	:	Structure–activity relationship
TEM	:	Transmission electron microscopy
THF	:	Tetrahydrofuran
P-TSA	:	*p*-Toluenesulfonic acid
TSILs	:	Task-specific ionic liquids

U.S.	:	Ultra sound
$VOSO_4$	:	Vanadyl sulfate
XPS	:	X-ray photoelectron spectroscopy

Dedicated to

…..My Beloved Parents

CHAPTER-I

INTRODUCTION

Introduction

Heterocyclic compounds comprise of one or more heteroatoms in their ring systems in addition to carbon. Though a number of heteroatoms are known to be part of the heterocyclic rings, the most common heteroatoms are nitrogen, oxygen, sulphur and selenium. They may be having simple aromatic or non-aromatic rings. Nearly half of the known organic compounds contain at least one heterocyclic ring. Many of the heterocyclic compounds occur naturally and are actively involved in biology *e.g.* nucleic acids (purine and pyrimidine bases), vitamins (thiamine B_1, riboflavin B_2, nicotinamide B_3, pyridoxol B_6 and ascorbic acid C), heme and chlorophyll, penicillins, cephalosporins, macrolides *etc*.[1] The majority of pharmaceuticals, agrochemicals, additives and modifiers used in industrial applications are heterocyclic in nature. A large number of alkaloids derived from heterocyclic molecules are used as drugs. Their applications in medicine, agriculture, photodiodes *etc*. have made them attractive synthetic targets.

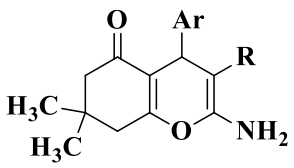
Many of the drugs possess heterocyclic units like chromenes, dihydropyridines, porphyrines, pyrazoles and phthalazines. A brief introduction and the applications of the above systems is discussed in this chapter. Many of them function as calcium channel modulators, antimicrobial, antiviral, anticancer, antioxidant, antitumor, anticonvulsant, antiinflammatory, antiallergic, antihypertensive, antineoplastic, antidepressant, antiproliferative, anticoagulant, antithyroid and anti-HIV agents.[2] They also have fungicidal, pesticidal, herbicidal and plant growth regulating properties.[3] Some of these compounds were also reported as inhibitors of enzymes like mitotic kinesin, CDC25 phosphatase, acetylcholinesterase (AChE), amino acid decarboxylase and histidine decarboxylase and act as antagonists of neuropeptide Y(NPY) and 5-HT_{2A} receptors.[4,5] A brief review of the literature on the importance of chromenes, dihydropyridines, porphyrines, pyrazoles and phthalazines is presented in the following section of this chapter.

Chromenes

The chromene ring systems are present in numerous natural products and are considered to be the most imperative molecules possessing wide spectrum of biological and pharmacological activities, that include spasmolytic, diuretic, clotting, antimicrobial, antiviral,

antitumoral, and antianaphylactic.[6] They are also used in pigments, photoactive materials and biodegradable agrochemicals.[6] These were also reported as anti-HIV,[7] antiinflammatory,[8] antileishmanial[9] and TNF-α inhibiting agents.[10]

Among the different types of chromene systems, tetrahydrobenzo[*b*]pyrans **(1)** are of considerable interest because of their wide range of biological properties, such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities.[11] They can also be used as cognitive enhancers not only for the treatment of schizophrenia and myoclonus but also for the treatment of neurodegenerative disease, including alzheimer's disease, amyotrophic lateral sclerosis, huntington's disease, parkinson's disease, AIDS associated dementia and down's syndrome.[12] cyano-chromene compounds **(2)**, are the first class of compounds which show fully selective inhibition of the human excitatory amino acid transporter subtype 1 (EAAT 1).[13] Many of the compounds having chromene based heterocyclic framework exhibit striking biological activities and a typical example of an approved drug is **amlexanox (3)**, which is a commonly prescribed antiallergic and typical antiulcer agent.[14] Many other similar compounds such as **4**, **5** and **6** exemplify the wide therapeutic and pharmacological properties[15] of the chromene molecules.



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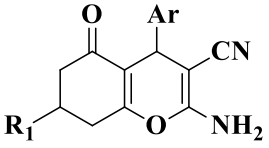

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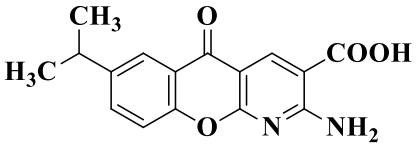
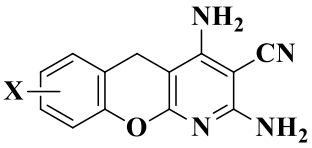


Amlexanox (3)



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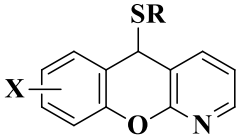

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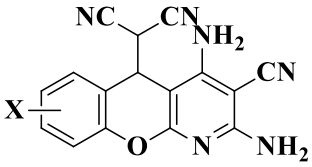
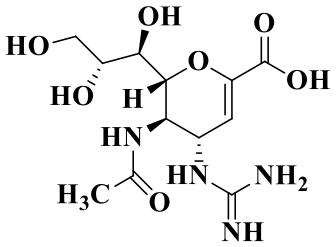


(6)

Ar = Aryl; R = Alkyl; R_1 = Alkyl/Alkoxyl; X = Halo

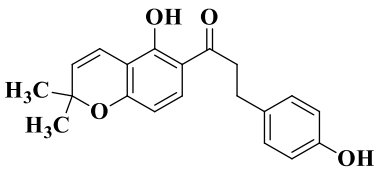
Zanamivir (7) is a neuraminidase inhibitor used for the treatment of infections caused by influenza A virus and influenza B virus. Zanamivir works by binding to the active site of the neuraminidase protein, rendering the influenza virus unable to escape its host cell and infect

others.[16] It also acts as an inhibitor of influenza virus *in vitro* and *in vivo*. In clinical trials, zanamivir was found to reduce the time-to-symptom resolution by 1.5 days if therapy was started within 48 hours of the onset of symptoms.

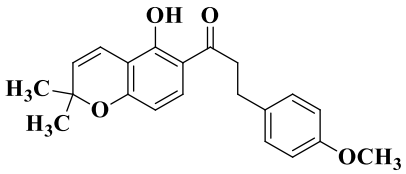


Zanamivir (7)

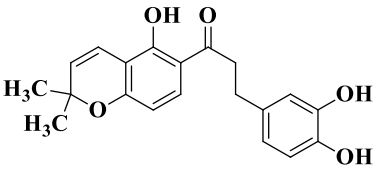
Narender *et al.*[17] described a convenient method for the synthesis of naturally occurring chromenochalcones such as **crotaramosmin (8)**, **crotaramin (9)** and **crotin (10)**, and evaluated their antileishmanial activity.



Crotaramosmin (8)

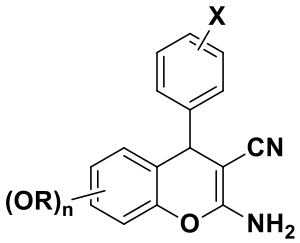


Crotaramin (9)



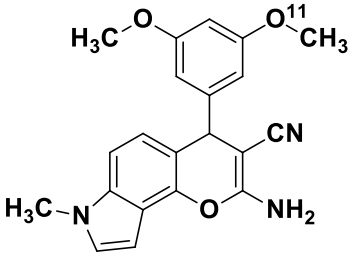
Crotin (10)

Shestopalov *et al.*[18] reported a series of polyalkoxy substituents containg chromenes (**11**) which exhibited strong cytotoxicity in the NC160 human tumor cell lines.



(11)

Gao *et al.*[19] identified carbon-11-labeled 4-aryl-4*H*-cromenes (**12** and **13**) as new PET agents for imaging of apoptosis in cancer.



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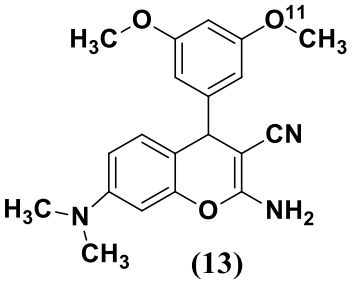
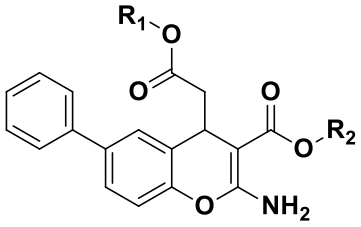


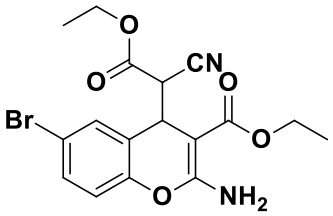
(13)

Aridos *et al.*[20] reported the synthesis of ethyl-2-amino-6-(3,5-dimethoxyphenyl)-4-(2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (CXL017) derivatives (**14**) and found that they could potentially kill cancer cell lines.



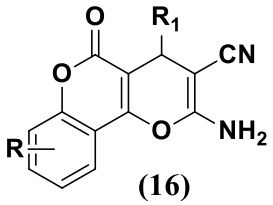
(14)

Doshi *et al.*[21] reported ethyl-2-amino-6-cyclopentyl-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (**15**, HA 14-1) as an antagonist of the antiapoptotic Bcl-2 proteins to overcome drug resistance in cancer.



(15)

Zhang *et al.*[22] synthesized a number of optically active pyranocoumarins (**16**) and 2-amino-4*H*-chromenes (**17**) through an organocatalytic Knoevenagel/Michael/cyclization sequence and studied preliminary antibacterial studies of these new heterocyclic compounds.



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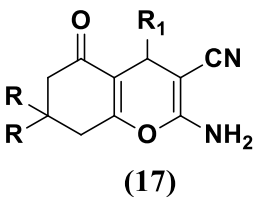

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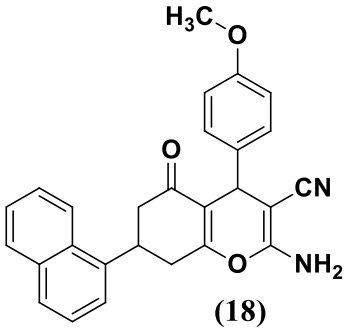
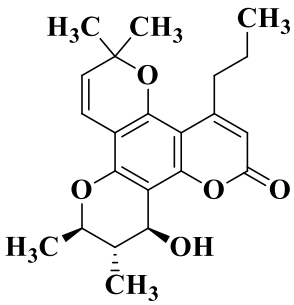
Jensen *et al.*[23] identified that compound (**18**) displayed nanomolar inhibitory activity against human excitatory amino acid transporter subtype 1 (EAAT1).



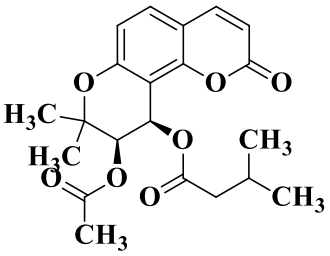
(18)

Calanolide A (19) is a new experimental non-nucleoside reverse transcriptase inhibitor (NNRTI) first extracted from *Calophyllum lanigerum* trees in Malaysia.[24-26]



Calanolide A (19)

Suksdorfin (20) a dihydroseselin type angular pyranocoumarin, which was isolated from the methanolic extract of *Lomatium suksdorfii* through a bioactivity-directed fractionation.[27]

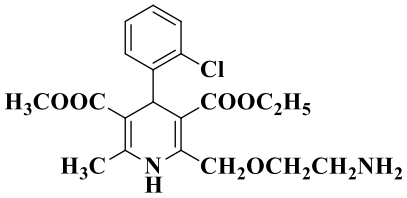


Suksdorfin (20)

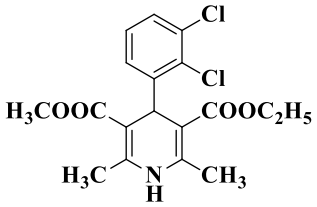
Dihydropyridines

Dihydropyridine ring is an important target in synthetic and medicinal chemistry as it is the key moiety in numerous biologically active compounds.[28] Some of them, such as **Amlodipine (21)**, **Felodipine (22)**, **Isradipine (23)**, **Lacidipine (24)**, **Nifedipine (25)** are

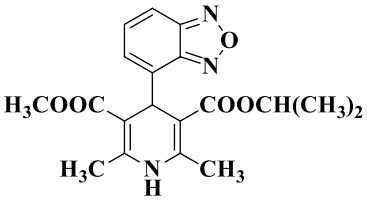
prominent drugs for the treatment of cardiovascular diseases and hypertension and they also act as effective calcium channel blockers.[29] 1,4-Dihydropyridines are good precursors for the synthesis of corresponding pyridine derivatives[30] and are useful as reducing agents for imines in the presence of catalytic amount of Lewis acid.[31]



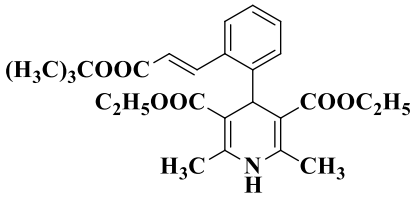
Amlodipine (21)



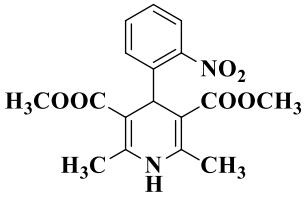
Felodipine (22)



Isradipine (23)

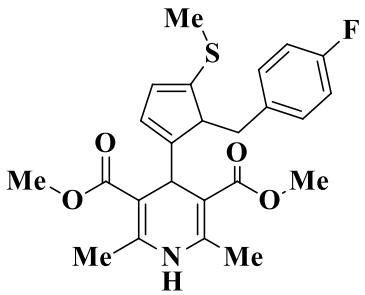


Lacidipine (24)



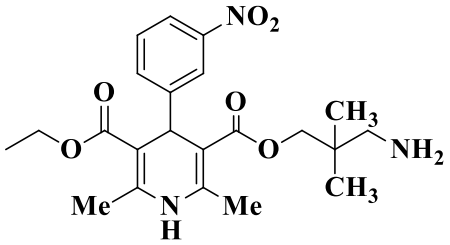
Nifidipine (25)

S.A. Mohajeri *et al.*[32] have reported a series of compounds based on 1,4-dihydropyridines bearing 1-(4-fluorobenzyl)-5-imidazolyl substituent at 4-position which were synthesized and tested for hypotensive activity in male rats (**26**).



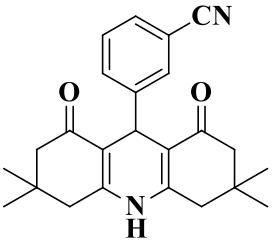
(26)

A.N. Balaev *et al.*[33] synthesized new 1,4-dihydropyridines containing 3-dialkylamino-2,2-dimethylpropyl fragment (**27**), which show greater hypotensive activity than nifedipine.



(27)

K.B. Ramesh *et al.*[34] reported that dihydropyridine derivatives **(28** and **29)** are potent anticancer agents against HepG2 and MCF-7 cell lines.



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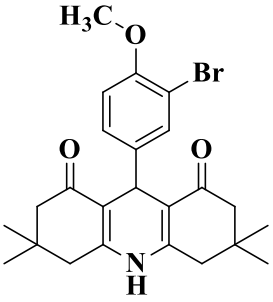
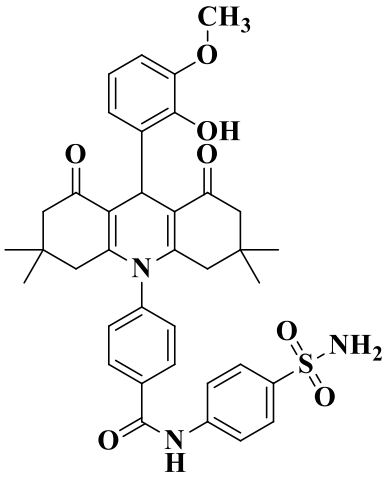


(29)

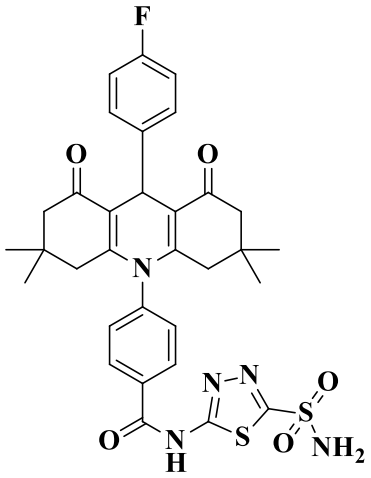
R. Ulus *et al.*[35] reported the synthesis of novel dihydropyridine (**30**) moieties and evaluated their cytosolic isoform hCA I inhibitory activities.



(30)

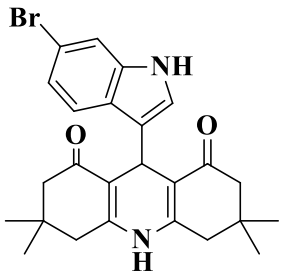
Ramazan Ulus *et al.*[36] synthesized dihydropyridine- acetazolamide analogues and screened for their *in vitro* human carbonic anhydrase isoforms hCA I, II, IV and VII activity. The fluoro

derivative **(31)** has shown good human carbonic anhydrase isoforms hCA I, II, IV and VII activity.



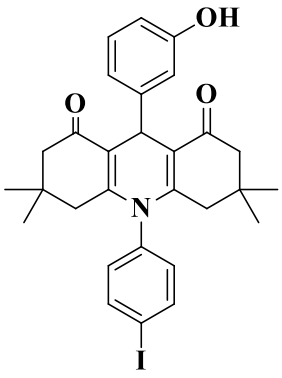
(31)

M.G. Gündüz *et al.*[37] reported the synthesis of novel indole moiety attached dihydropyridine derivatives and evaluated for their *in vitro* myorelaxant activity. Among all the compounds, bromo group derivative **(32)** displayed inhibitory activity against the noradrenaline precontracted tissues.



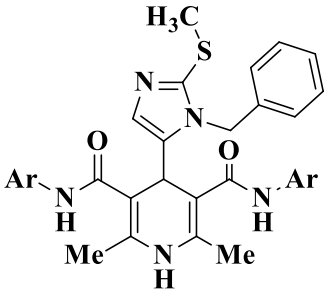
(32)

A. Nakhi *et al.*[38] reported that dihydropyridine derivative (**33**) exhibit sirtuin inhibitory potential *in vitro* studies.



(33)

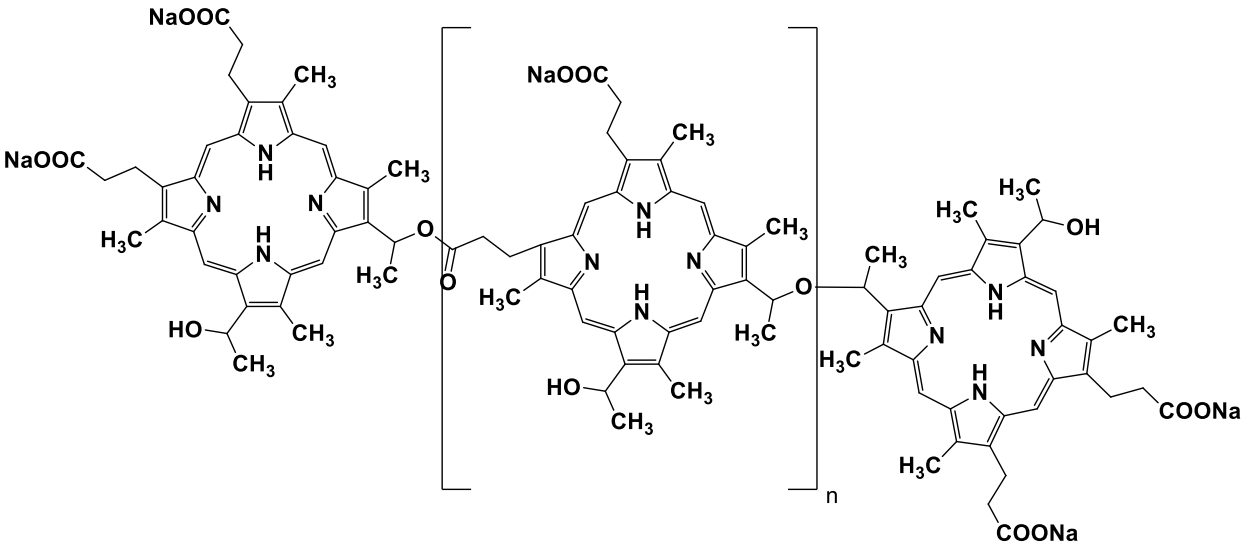
Afshin Fassihi *et al.*[39] found that a series of 4-substituted imidazolyl-2,6-dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides (**34**) are potent antitubercular agents against Mycobacterium tuberculosis H37Rv.



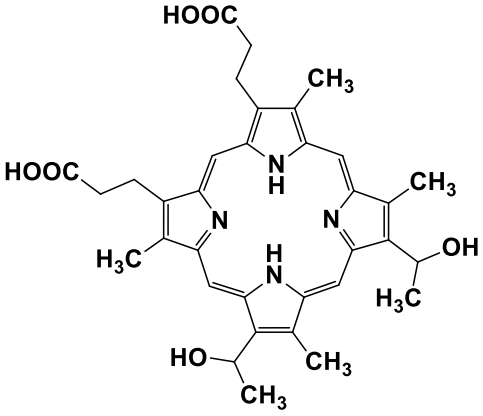
(34)

Porphyrins

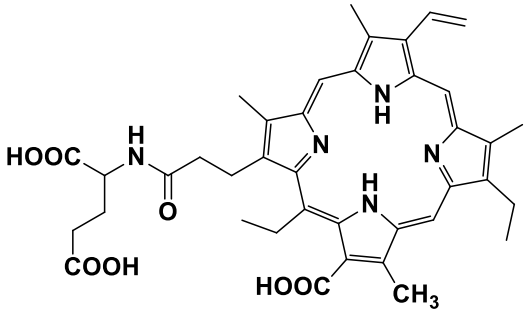
Porphyrins are flat 20-carbon aromatic macrocycles with four central nitrogen's attached to a single metal cation forming complexes or may be existing as a free-bases. There are two types of carbon atoms in the porphyrin ring that can undergo substitution. The linking methine carbons (positions α, β, γ, and δ) are designated the meso-positions and the pyrrolic carbons (positions 1, 2, 3, 4, 5, 6, 7 & 8) are defined as the β-positions. The nomenclature scheme for porphyrins is in line with conservative nomenclature prescribed by Hans Fischer. Porphyrinoid photosensitizers are the most clinically used photosensitizers in PDT. Porphyrins are tetrapyrrolic macrocycles with good photophysical and photosensitizing properties. Although the exact mechanism for selective photosensitizer biodistribution hasn't yet been elucidated, it is hypothesized that several physiological differences between tumor tissues and healthy tissues could be responsible for the preferential retention of photosensitizers in tumors. Currently there is one FDA approved drug, porfimer sodium **35** (Photofrin), which is approved and known to cause photodamage in various types of cancers (lung, esophageal, cervical, bladder).[40] Mono-Laspartyl chlorin e_6 **37** is used for skin and nasopharynx cancer.[41] Benzoporphyrin derivative **38** (Verteporfin) is a liposomal formulation used for the treatment of age-related macular generation and choroidal melanoma.[42] Tin ethyl etiopurpurin **39** (SnET2 or Purlytin) is being used for curing breast and prostate cancers.



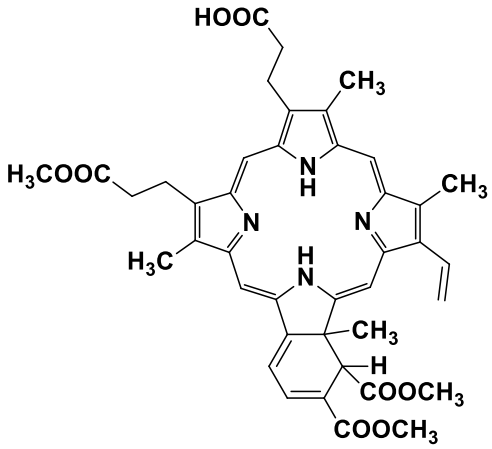
FDA approved drug photofrin **35**



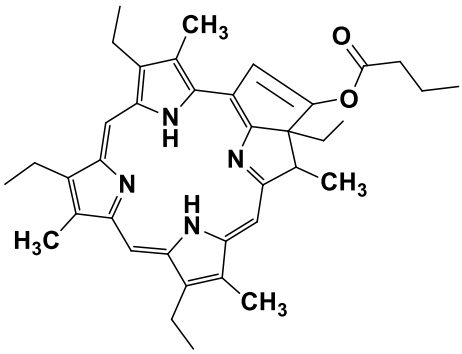
Hematoporphyrin (36)



Monoaspartyl chlorin e_6 (37)

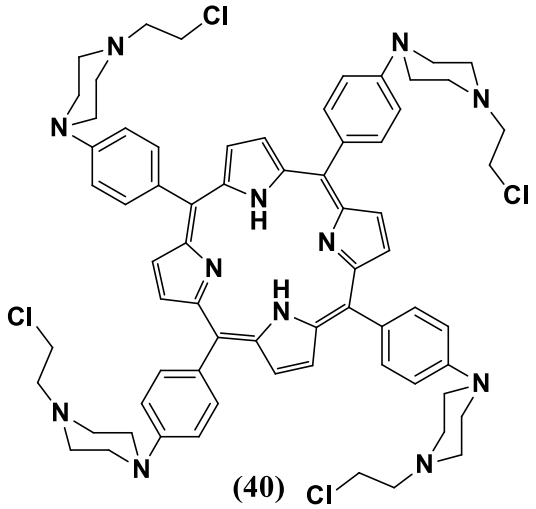


Verteporfin (38)



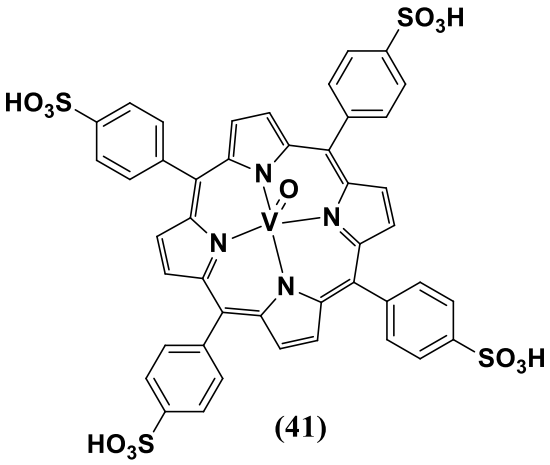
Puryltin (39)

C.C. Guo *et al.*[43] described the synthesis of novel chloroalkyl nitrogen mustard and piperazine porphyrin derivative (**40**) and evaluated their *in vitro* anticancer activity.

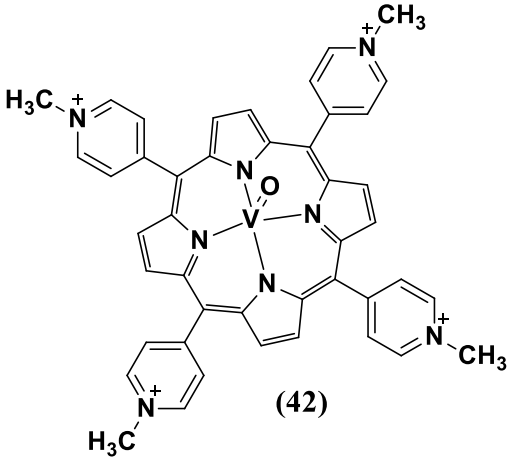


(40)

T.K. Saha *et al.*[44] synthesized [meso-tetrakis(4-sulfonatophenyl)porphyrinato]oxovanadate(IV) (**41**), [VO(tpps)] (**42**) and their *in vitro* insulin-mimetic activity.

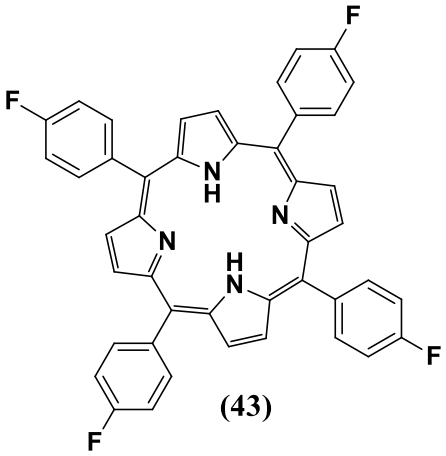


(41)



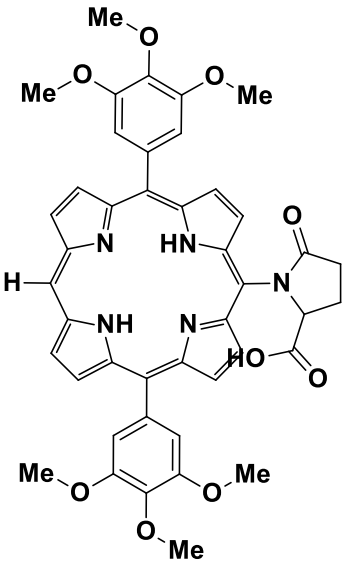
(42)

A. J. Alonso-Castro *et al.*[45] reported the synthesis of porphyrin derivatives and evaluated their anti-inflammatory and antinociceptive activities. Among all the compounds, 5,10,15,20-tetra(4-fluorophenyl)porphyrin (TpFPP) (**43**), displayed selective inhibitory activity exhibiting anti-inflammatory and antinociceptive activities



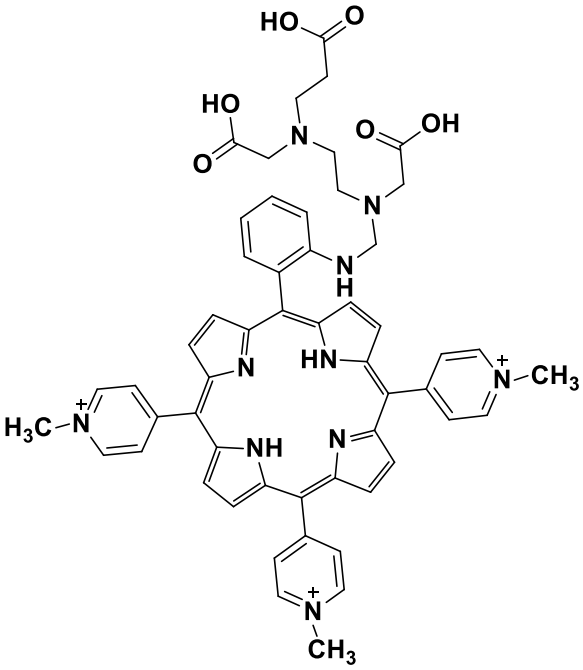
(43)

Zahra Abada *et al.*[46] synthesized porphyrin (**44**) and its derivatives which act as potential antiparasitic agents by interfering with heme metabolism.



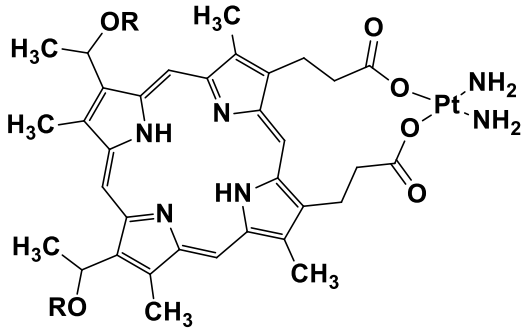
(44)

Schwach *et al.*[47] described that porphyrin-EDTA conjugate (**45**) exhibits a dose-dependent decrease in mitochondrial activity in MTC (MTC-SK and SHER-I cancer cell lines) with IC_{50} of 5.1 µM and 9.3 µM, respectively.



(45)

Lottner *et al.*[48] proved that porphyrin-platinum conjugate of (**46**) and the hematoporphyrin ligand is responsible for the penetration across the cell membranes and for the increased intracellular concentration.



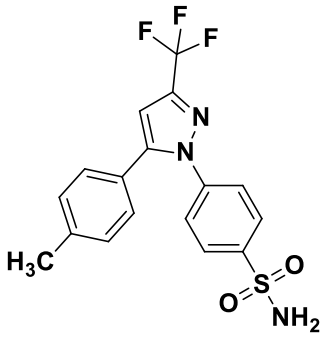
(46)

Pyrazoles

Many pharmaceuticals are synthetic compounds and a large number of them are heterocyclic in nature. Among them pyrazoles form an important class of compounds which are useful for new drug development that attracted much attention due to their broad spectrum of biological activities, like antimicrobial,[49] antifungal,[50] antiviral,[51] anticancer,[52] and anti-inflammatory[53] activities. Pyrazole derivatives also act as antiangiogenic agents,[54] work as kinase inhibitors for treatment of type-2 diabetes. They are also used in the treatment of

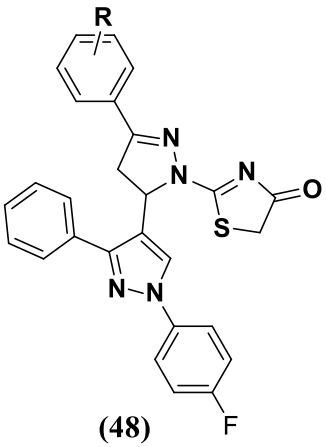
obesity[55] and for thrombopiotin mimetics.[56] Recently urea derivatives of pyrazoles have been reported as potent inhibitors of p38 kinase.[57] Some of the pyrazole derivatives also act as biocides, acaricides, herbicides, and fungicides.[58]

Celecoxib (47)[59] was identified as a highly selective COX-2 inhibitor which primarily inhibits isoform of cyclooxygenase (and thus causes inhibition of prostaglandin production).



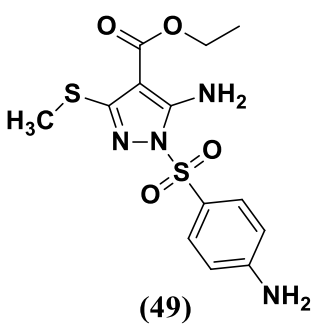
Celecoxib (47)

N. C. Desai *et al.*[60] synthesized a series of compounds 2-(5-(3-(4-fluorophenyl)-1-phenyl- 1*H*-pyrazol-4-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-ones (**48**) and screened them for in vitro antibacterial activity.



(48)

S. N. Thore *et al.*[61] described the synthesis of a novel ethyl-5-amino-3-methylthio-1*H*-pyrazole-4-carboxylates. The synthesized compounds were screened for in vivo analgesic and anti-inflammatory activities. Diclofenac sodium was used as a standard drug for comparison. Compounds **49**, **50** and **51** exhibited significant analgesic and anti-inflammatory activities.



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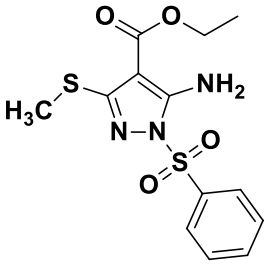
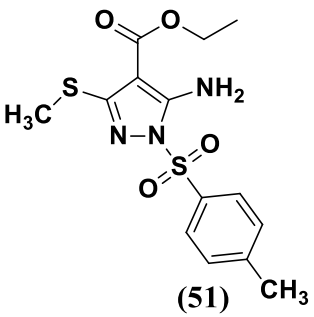
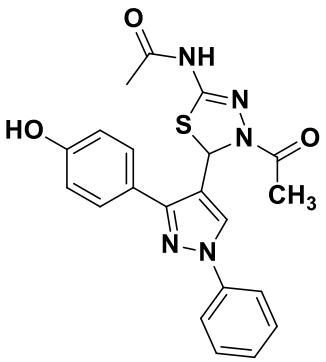


(50)



(51)

S. G. Alegaon *et al.*[62] reported the synthesis of 1,3,4-trisubstituted derivatives. These compounds were screened for the anti-inflammatory activity by carrageenan-induced paw edema method. Compounds **52** and **53** showed excellent anti-inflammatory activity (84.2% inhibition) compared to that of the standard drug diclofenac (86.72%).



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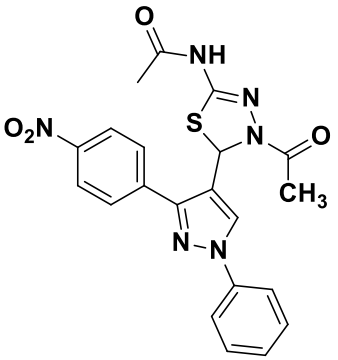
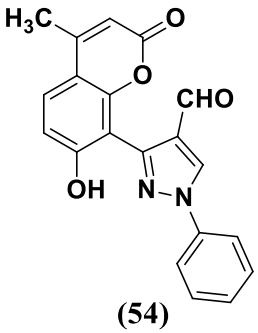


(53)

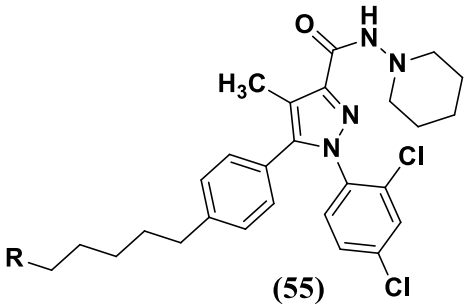
R. Nagamallu *et al.*[63] reported the synthesis of coumarin appended formyl-pyrazoles and screened for their in vitro antibacterial, antifungal activities. The compound **54** having chloro substitution exhibited promising antifungal and antibacterial activities.



(54)

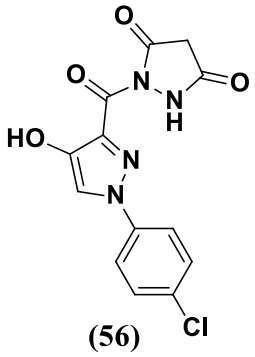
O. O. Alekseeva *et al.*[64] reported the synthesis of 5-substituted pyrazole derivatives from 4'-bromopropiophenone (**55**), utilizing a Suzuki-type coupling with an alkene. They are potent

CB1 antagonists and have binding affinities similar to SR 141716A. Like SR 141716A, they are proves to be clinically useful for the treatment of obesity.



(55)

S. A. Rostom *et al.*[65] synthesized two novel series of 1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazoles (**56**) linked to either poly-substituted 1*H*-pyrazole counterparts through a carbonyl bridge, or to some biologically active nitrogenous heterocycles by an amide linker. Some of the compounds have shown broad spectrum antitumor potential against most of the tested subpanel tumor cell lines at the GI50 and TGI levels, together with a mild cytotoxic (LC50) activity.



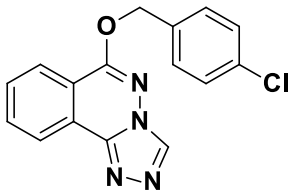
(56)

Phthalazines

The chemistry of phthalazines is very well known. These systems are widely used in organic chemistry as intermediates for the synthesis of numerous compounds. On the other hand; phthalazine derivatives were extensively studied as bioactive compounds. They possess remarkable biological activities.[66] According to literature survey, phthalazines have been reported to possess, anticonvulsant, cardio tonic, antimicrobial, antitumor, antihypertensive, antithrombotic, antidiabetic, antitrypanosomal, anti-inflammatory, and vasorelaxant activities.[67] Additionally, phthalazines have recently been reported to potentially inhibit serotonin reuptake

and are considered to be antidepression agents.[67] Phthalazine system is considered as an important biologically active pharmacophore present in many of the antidiabetic, antiallergic and anticancer drugs. A number of established drug molecules like Hydralazine, Budralazine, Azelastine, Ponalrestat and Zopolrestat are being prepared from the corresponding phthalazinones. The diverse biological activities of phthalazin-1(2H)-one, triazolothiadiazole and triazolo-thiadiazine pharmacophores encouraged many groups of researchers for the construction of new biologically active phthalazine molecules.[68]

Sun *et al.*[69] synthesized new series of 6- alkoxy-(1,2,4)-triazolo-(3,4*a*)-phthalazine (**57** and **58**) and evaluated their anticonvulsant activity and neurotoxicity by using MES test and Rota rod test.



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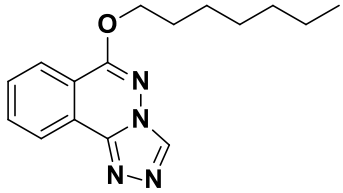
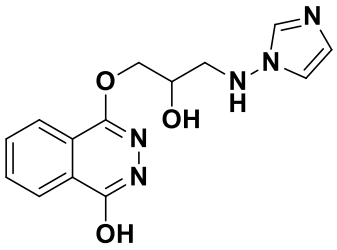
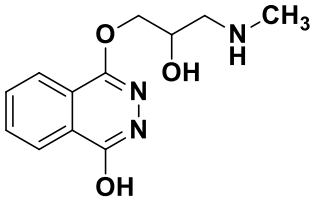


(58)

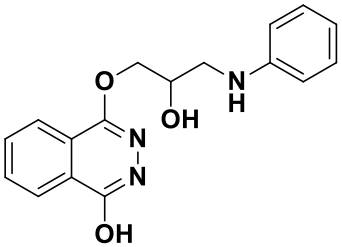
R. Sivakumar *et al.*[70] worked on synthesis of a series of 1-substituted-4-hydroxyphthalazines (**59**, **60**, **61** and **62**) and these compounds were assayed against seizures induced by maximal electroshock (MES), pentylenetetrazole (scMet) model and neurologic deficit by the rotarod test.



(59)



(60)



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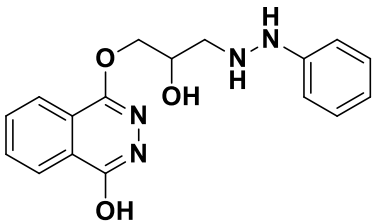
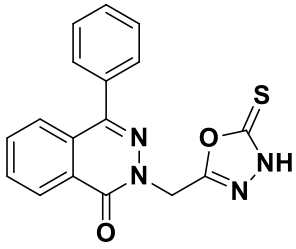


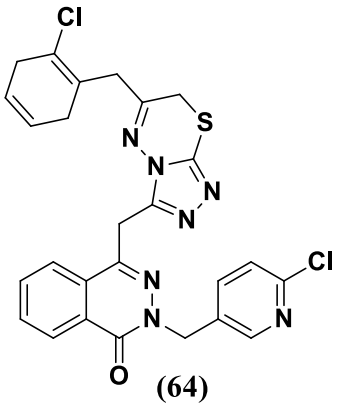
(62)

M. S. M. Abd alla *et al.*[71] described the synthesis and anti-inflammatory activity of different 4-(3,4-dimethyl-phenyl)-phthalazine-1(2*H*)-ones (**63**).



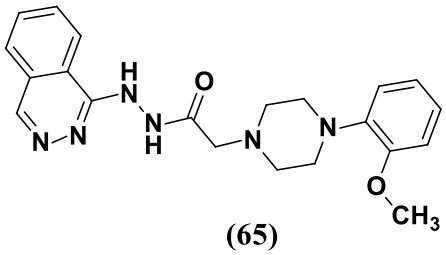
(63)

K.R Venugopala Reddy *et al.*[72] reported the synthesis of new 6-(chloropyridin-3-yl)methyl substituted phthalazine-1,2,4-triazolo-[3,4*b*]-1,3,4-thiadiazoles (**64**) and found that they possess antimicrobial potential.



(64)

Awadallah *et al.*[73] synthesized new phthalazine derivatives (**65**) and evaluated them for their vasorelaxant activity against nor-adrenaline- induced spam on thoracic rat aorta rings and compared to the reference drug prazosin.



(65)

Present work

Heterocyclic chemistry is a profile source for a large number of unusual, structurally complex and bioactive molecules. Over decades, the heterocyclic compounds emerged hold special appeal to synthetic chemist. In fact, chromenes, dihydropyridines, porphyrines, pyrazoles and phthalazines have attracted the attention of pharmaceutical community due to their therapeutic applications. This is reflected by the huge data available in the literature. The diverse pharmacological profile of these molecules and their derivatives, prompted us to undertake the synthesis of chromenes, dihydropyridines, porphyrines, pyrazoles and phthalazines by adopting simple and cost-effective procedures.

In view of this, we have taken up the research program entitled **"Studies on the synthesis and evaluation of biological activity of novel chromenes, dihydropyridines, porphyrins and pyrazolo-phthalazines"** which describes our contribution to the synthesis of novel class of chromenes, dihydropyridines, porphyrins and pyrazolo-phthalazines. The structures of the new compounds have been established by spectral parameters and elemental analyses. Some of the compounds have also been assayed for their antidiabetic, anticancer and antifungal activities. The docking simulation was also carried out using VLifeMDS 4.3 program to investigate the potential binding modes of some of the synthesized compounds. The biological assay data and molecular docking results suggested that a few of them could be used as the potential antidiabetic, anticancer and antifungal agents.

The division of the content of the actual work carried out is presented in the followed chapters of the thesis.

CHAPTER-II: Synthesis of novel fused chromenes by a green chemical method.

CHAPTER-III: This chapter is further divided into two sections.

***SECTION-A*:** Eco-friendly multicomponent synthesis of novel dihydropyridine derivatives.

***SECTION-B*:** Synthesis of new dihydropyridine derivatives using Eu_2O_3 modified CeO_2 nanoparticles.

CHAPTER-IV: Synthesis of novel A_2B_2 and A_4 type porphyrin derivatives.

CHAPTER-V: Synthesis of new pyrazolo-phthalazine derivatives using $[Bmim]BF_4$ ionic liquid.

CHAPTER-VI: Evaluation of biological activity.

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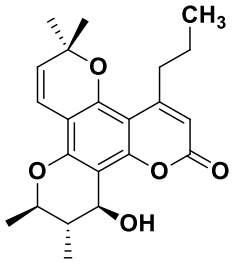
CHAPTER-II

SYNTHESIS OF NOVEL FUSED CHROMENES BY A GREEN CHEMICAL METHOD

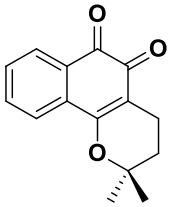
Synthesis of novel fused chromenes by a green chemical method

2.1. Introduction

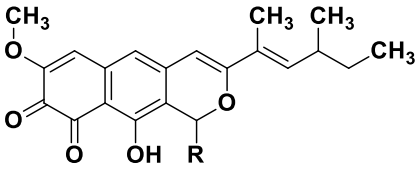
chromenes and chromenes-annulated heterocyclic scaffolds represent a "privileged" structural motif well distributed in naturally occurring compounds[1] with a broad spectrum of significant biological activities that include anticancer,[2] cytotoxic,[3] anti-HIV,[4] anti-inflammatory,[5] antimalarial,[6] antimicrobial,[7] antihyperglycemic and antidyslipidemic.[8] The chromeno drug molecules are also used in curing neuro degenerative disorders like Alzheimer's disease, Parkinson disease, Huntington's disease[9] and many more.[10] *Figure 2.1.1* represents a glimpse of some of the naturally occurring bioactive chromenes-annulated heterocyclic compounds exhibiting a diverse kind of pharmaceutical potentials.[11–16] Recently, a series of synthetic 2-amino-3-cyano-4*H*-chromenes (*Figure 2.1.2*) were evaluated for anticancer,[17–24] antibacterial, antifungal,[25–29] and antirheumatic[30] properties.



(+)-calanolide A - antiHIV[11-13]

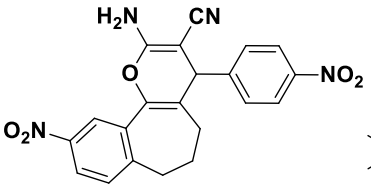


ß-lapachone - anticancer, anti inflammatory, antibiotics[13-15]

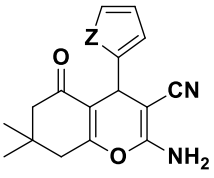


laccaridione A: R = OCH_3
laccaridione A: R = OCH_2CH_3
antiproliferative[16]

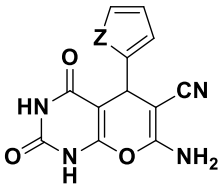
Figure 2.1.1. Some of the naturally occurring bioactive compounds bearing chromene-annulated scafolds



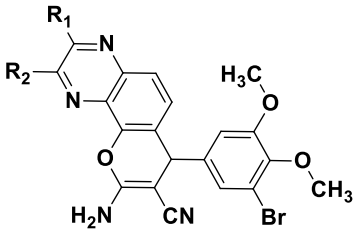
anticancer[18]



Z = NH, O, S (anticancer and antibacterial)[19,24]



Z = NH, O, S (anticancer and antibacterial)[19]

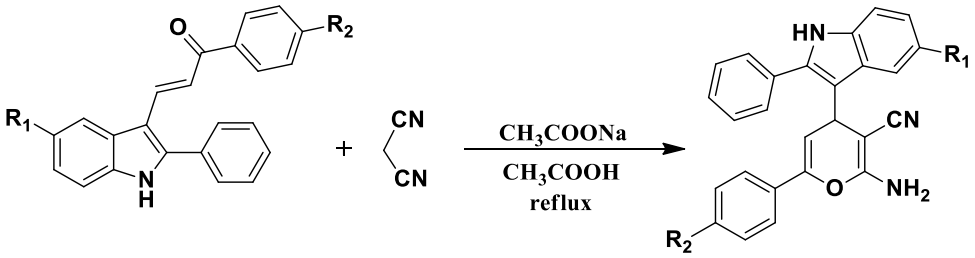


R_1,R_2 = H and
R_1,R_2 = CH_3
(anticancer)[17]

Figure 2.1.2. Representative examples of pharmacologically active synthetic fused 2-amino-3-cyano-4*H*-chromenes

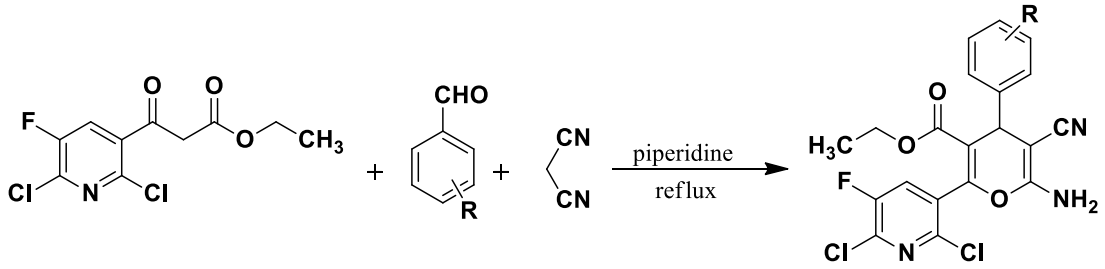
2.2. Earlier synthetic strategies for chromenes

A. R. Saundane *et al.*[31] reported cyclization of 3-(5'-Substituted 2'-phenyl-1*H*-indol-3'-yl)-1-arylprop-2-en-1-ones and malononitrile using a catalytic amount of sodium acetate in acetic acid to afford the corresponding 4*H*-pyrans derivatives in good yields (*Scheme 2.2.1*).



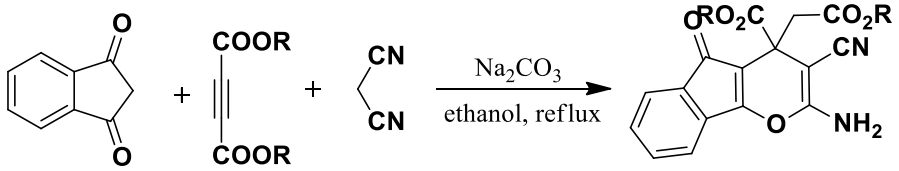
Scheme 2.2.1

C. Bingi *et al.*[32] achieved the one-pot synthesis of a series of new multihalogen-containing polyfunctionalized 4*H*-pyran derivatives by starting from 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate, aromatic aldehydes and malononitrile in the presence of piperidine (*Scheme 2.2.2*).



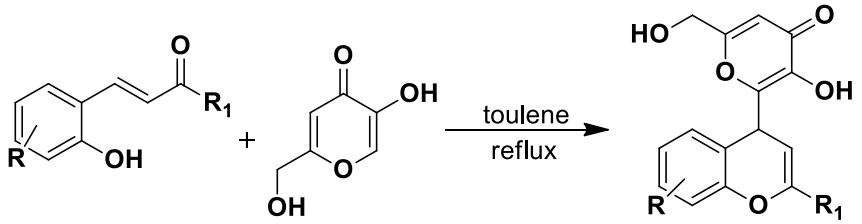
Scheme 2.2.2

B. Kazemi *et al.*[33] observed that the three-component reaction of 1,3-indanedione, various dialkyl acetylenedicarboxylates (DAADs), and malononitrile, catalyzed by sodium carbonate afforded various 4*H*-pyran scaffolds (*Scheme 2.2.3*).



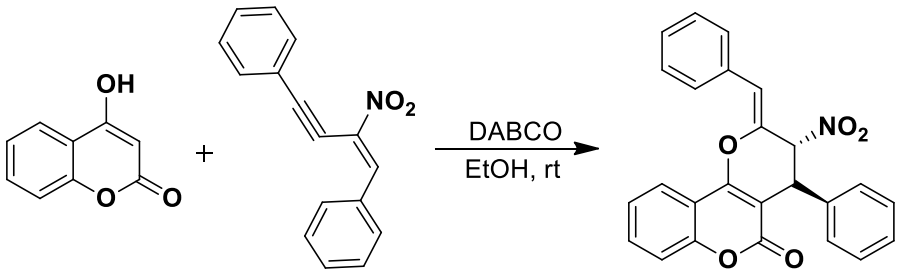
Scheme 2.2.3

C. Bingi *et al.*[34] reported that the reaction of 2-hydroxy chalcone and kojic acid under catalyst free condition in toluene medium at reflux temperature produced various 2-aryl/alkyl-4-kojic acid substituted 4*H*-pyran derivatives (*Scheme 2.2.4*).



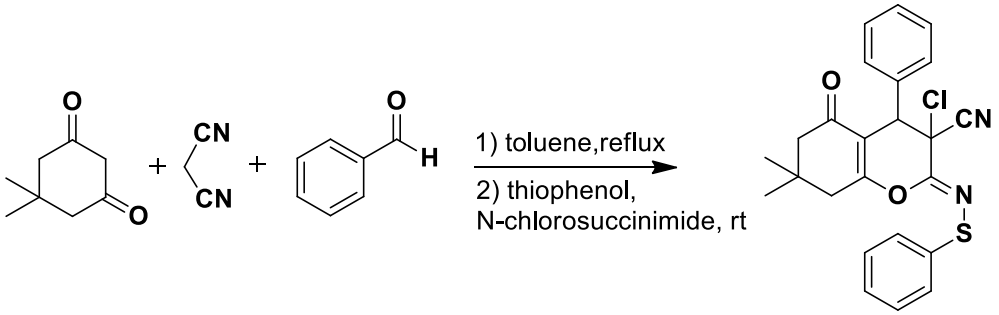
Scheme 2.2.4

Soumen Biswas *et al.*[35] have prepared chromene by condensation of 4-hydroxycoumarin and α-phenylacetylenyl-β-nitrostyrene in presence of DABCO at room temperature (*Scheme 2.2.5*)



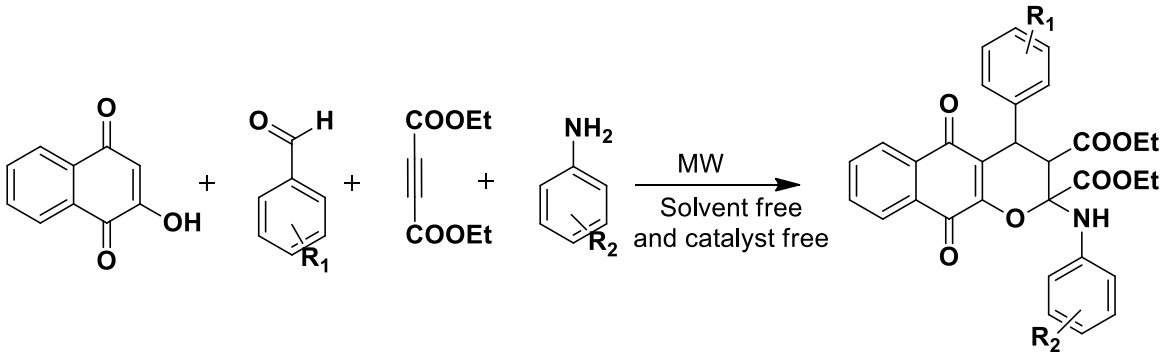
Scheme 2.2.5

Ashok Kale *et al.*[36] synthesized 2-sulfenylimine chromenes by a reaction between dimedone, malononitrile, aromatic aldehyde, thiophenol and NCS in presence of toluene at reflux for 3 hours (*Scheme 2.2.6*)



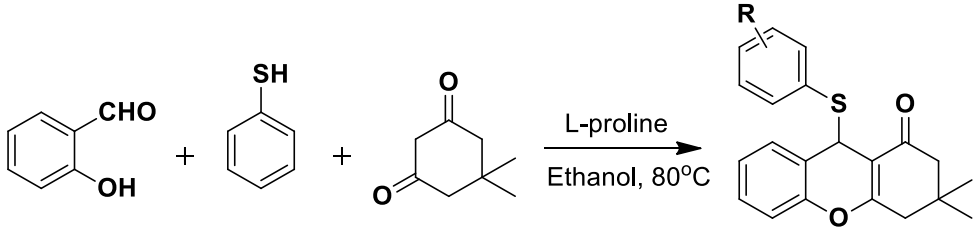
Scheme 2.2.6

Balasubramanian Devi Bala *et al.*[37] conducted the synthesis of chromenes by means of a multicomponent condensation of 2-hydroxynaphthalene-1,4-dione, aromatic aldehyde, DEAD and anilines by microwave irradiation (*Scheme 2.2.7*).



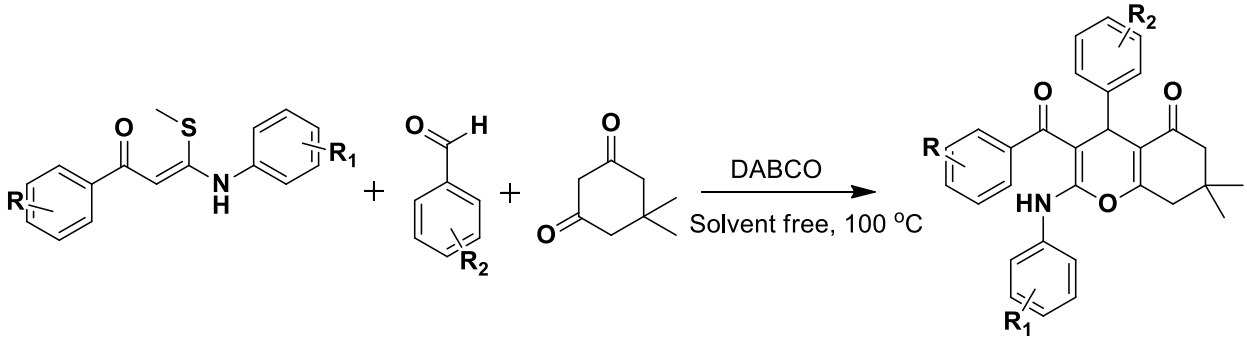
Scheme 2.2.7

Minghao Li *et al.*[38] developed L-proline catalyzed simple, one pot, and environmentally benign process for the synthesis of chromenes *via* three-component reaction of salicyladehyde, dimedone and substituted-thiophenols (*Scheme 2.2.8*).



Scheme 2.2.8

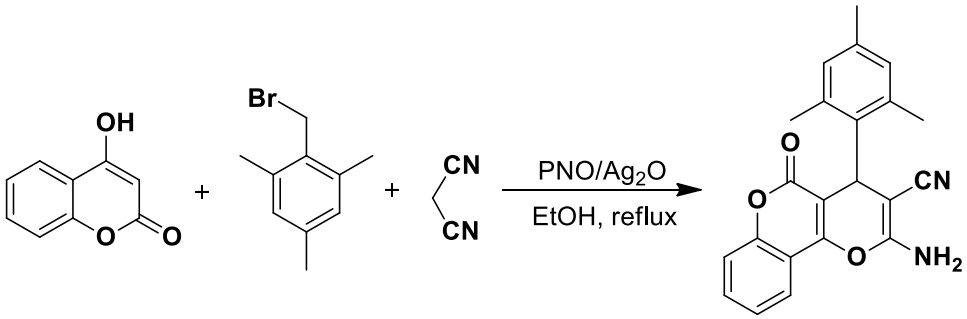
Maya Shankar Singh *et al.*[39] synthesized chromenes in high yields, by one-pot four-component condensation of aldehyde, dimedone, α-oxoketene-N,S-arylaminoacetal in the presence DABCO as catalyst under solvent-free condition at 100 ^{o}C (*Scheme 2.2.9*).



Scheme 2.2.9

Mallappa Beerappa *et al.*[40] developed an efficient and a novel one pot strategy for the synthesis of pyran analogues by in situ oxidation of benzyl halide into benzaldehyde followed

by the three component reaction of aldehyde, malanonitrile/ethylcyanoacetate and a hydroxy C–H acids in excellent yields (*Scheme 2.2.10*).



Scheme 2.2.10

2.3. present work

Green chemistry has become an essential inspiration for organic chemists to improve environmentally benign reagents and conditions for synthesis of organic compounds. It is a well-established fact that the sustainability of green chemistry greatly depends on (i) the use of environmentally benign solvents or solvent-free conditions, (ii) the development of less toxic and promising reagents/catalysts, (iii) the designing of cost effective and reliable methodologies and (iv) development of reusable catalysts. In view of these, the development of metal oxide nanoparticles has drawn much attention due to their operational simplicity, environmentally friendly, easy separation procedure, economically efficient and recyclability. In addition to this, use of water as a promising solvent for organic reactions has been established in considerable interest due to its green identifications such as low cost and easy availability. Besides, the network of hydrogen bonds, the high specific heat capacity, the large surface tension, the high polarity and high cohesive energy are some of the exclusive properties of water that can intensely influence the conversions in this medium.

Results and discussions

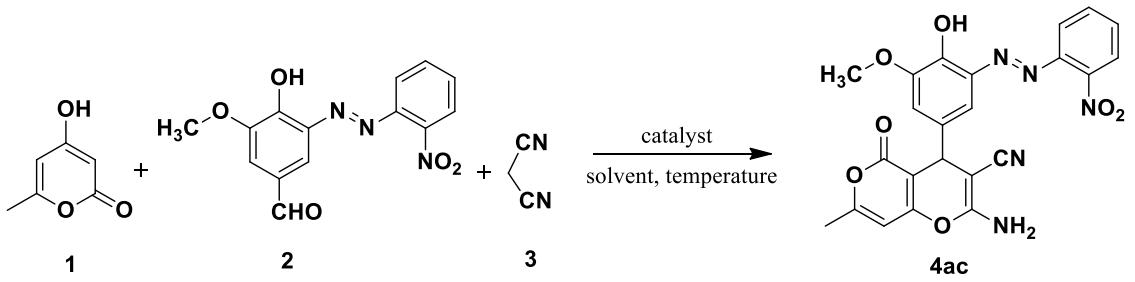
A green protocol was developed for the synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene-3-carbonitrile derivatives **4aa-bd** *via* a multicomponent approach from the reaction of 1,3-dicarbonyl compounds (**1a-e,** 1 mmol**)**, 4-hydroxy-3-methoxy-5-(substituted-phenyl diazenyl) benzaldehydes (**2a-f,** 1 mmol) and malononitrile (**3,** 1 mmol**)** in the presence of CeO_2–ZrO_2 nanoparticles (NPs) which act as a catalyst in aqueous medium at room temperature. Initial studies were carried out by reaction

among 4-hydroxy-6-methyl-2*H*-chromene-2-one **1a**, 4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)-benzaldehyde **2c** and malononitrile **3** as a model reaction in different solvents and catalysts. We have applied wide range of solvents such as methanol, ethanol, water, acetonitrile and dioxane (Table 2.3.1, entries 1-5). Water was proved to be the solvent of choice and improved for all imminent studies. To optimize the reaction conditions in terms of catalyst above model reaction was performed using different catalysts like KOH, triethylamine, piperidine, H_2SO_4, acetic acid (Table 2.3.1, entries 6-10) including nano catalysts like Fe_3O_4, ZnO, TiO_2, CeO_2, CeO_2–ZrO_2 (Table 2.3.1, entries 11-15). However, CeO_2–ZrO_2 (Cerium Zirconium Oxide) was identified as the suitable catalyst with **4ac** being isolated in maximum amounts (91%) and the yield of desired product was checked using different mol ratios (10, 20, 30 mol %). The maximum yield was obtained when the 20 mol % catalyst was used (Table 2.3.1, entry 16). Below the observed mol %, catalyst did not yield any encouraging result and when the reaction was attempted using 30 mol%, (Table 2.3.1, entry 17) it gave good yields of **4ac.** It is the same when 20 mol% used. In addition to this, we also studied the effect of temperature on the above reaction using different temperatures like 40°C, 50°C, 60°C and reflux temperature (Table 2.3.1, entries 18-21). Among these results, we found that at low temperature (room temperature) improved yields were obtained.

All these optimized conditions were then applied for all further experiments. Typically, a mixture of 1,3-dicarbonyl compounds (1 mmol**)**, (substituted-phenyl diazenyl) benzaldehydes (1 mmol), malononitrile (1 mmol**)** and 20 mol% of nano-CeO_2–ZrO_2 in 5 ml of water at room temperature for 3 hours, afforded a library of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene-3-carbonitrile derivatives **4aa-bd** in good to excellent yields (79-93%). To estimate the scope and generality of the procedure, 4-hydroxy-3-methoxy-5-(substituted-phenyl)diazenyl)-benzaldehydes (**2a-f**) namely 4-hydroxy-3-methoxy-5-(phenyldiazenyl)-benzaldehyde (**2a**), 4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)-benzaldehyde (**2b**), 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)-benzaldehyde (**2c**), 4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)-benzaldehyde (**2d**), 4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)-benzaldehyde (**2e**) and 3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxybenzaldehyde (**2f**) having both electron-donating and electron-withdrawing groups were reacted with 1,3-dicarbonyl compounds like 4-hydroxy-6-methyl-2*H*-chromene-2-one (**1a**), 4-hydroxycoumarin (**1b**), lawsone (**1c**), dimedone (**1d**) and 1,3-cyclohexanedione

(**1e**); and malononitrile (**3**) under optimized conditions, and results are summarized in **Table 2.3.2.**

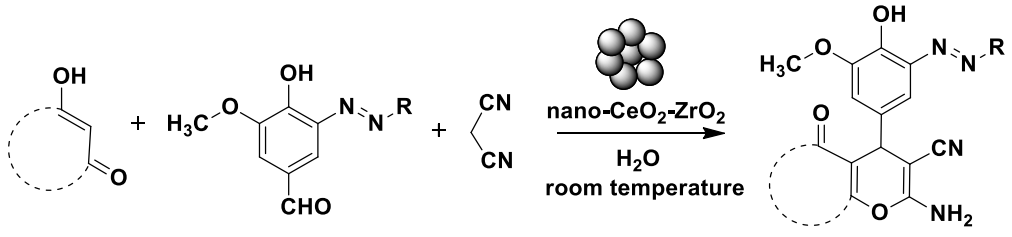
Table 2.3.1. Effect of solvent and catalysts on the synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyldiazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile **4ac**



entry[a]	catalyst (mol %)	solvent	temperature (°C)	time (h)	yield[b] (%)
1	----------	methanol	rt	24	10
2	----------	ethanol	rt	19	23
3	----------	water	rt	11	41
4	----------	acetonitrile	rt	13	21
5	----------	dioxane	rt	24	NR
6	KOH (10%)	water	rt	11	41
7	Triethylamine (10%)	water	rt	6	33
8	Piperidine (10%)	water	rt	6	39
9	H_2SO_4 (10%)	water	rt	6	51
10	Acetic acid(10%)	water	rt	6	46
11	Fe_3O_4 (10%)	water	rt	6	54
12	ZnO (10%)	water	rt	6	59
13	TiO_2 (10%)	water	rt	6	46
14	CeO_2 (10%)	water	rt	6	71
15	CeO_2–ZrO_2 (10%)	water	rt	3	81
16	**CeO_2–ZrO_2 (20%)**	**water**	**rt**	**2**	**91**
17	CeO_2–ZrO_2 (30%)	water	rt	2	90
18	CeO_2–ZrO_2 (20%)	water	40	2	80
19	CeO_2–ZrO_2 (20%)	water	50	2	73
20	CeO_2–ZrO_2 (20%)	water	60	2	51
21	CeO_2–ZrO_2 (20%)	water	reflux	2	49

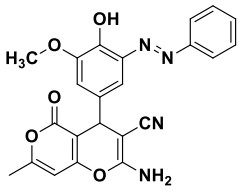
[a]Reaction conditions: 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde (1 mmol) and malononitrile (1 mmol), solvent (5 mL) and catalyst. [b]Yields of isolated products.

Table 2.3.2: Synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene -3-carbonitrile derivatives **4aa-bc**[a]

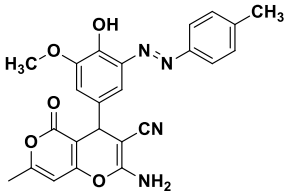


1a-e 2a-f 3 4aa-bd

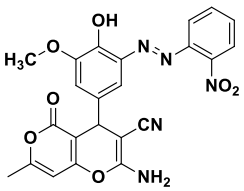
[b]yeild (%), time



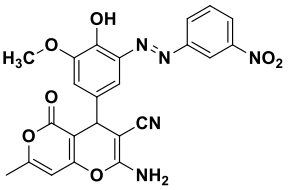
4aa
83%, 2 h



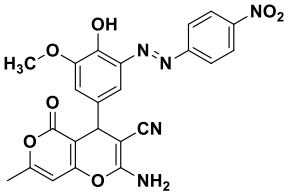
4ab
86%, 2.5 h



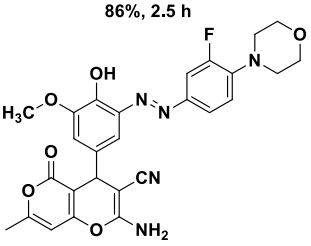
4ac
91%, 2 h



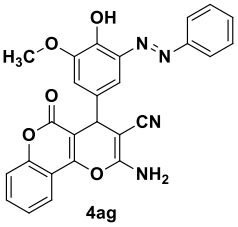
4ad
79%, 2 h



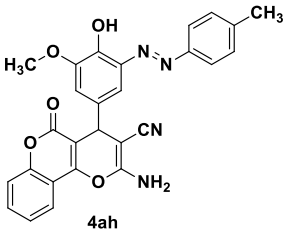
4ae
81%, 2.5 h



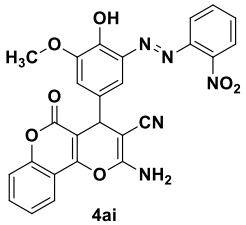
4af
85%, 3 h



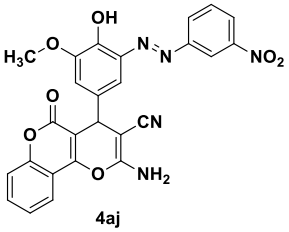
4ag
82%, 2 h



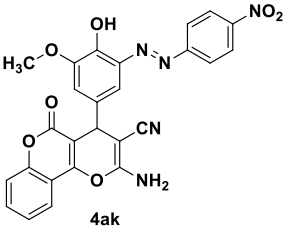
4ah
79%, 2 h



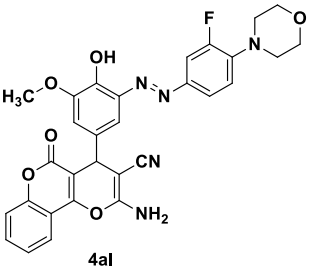
4ai
83%, 3 h



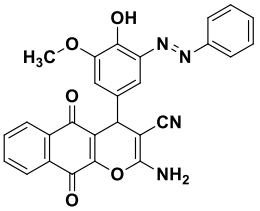
4aj
93%, 2 h



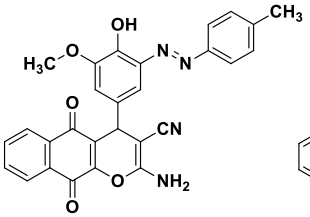
4ak
91%, 2.5 h



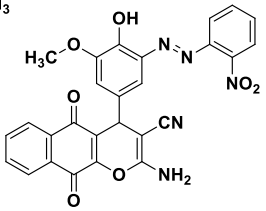
4al
87%, 2 h



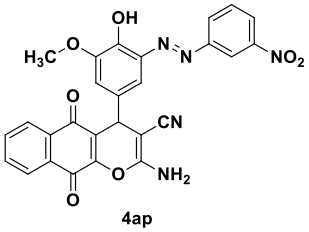
4am
81%, 2 h



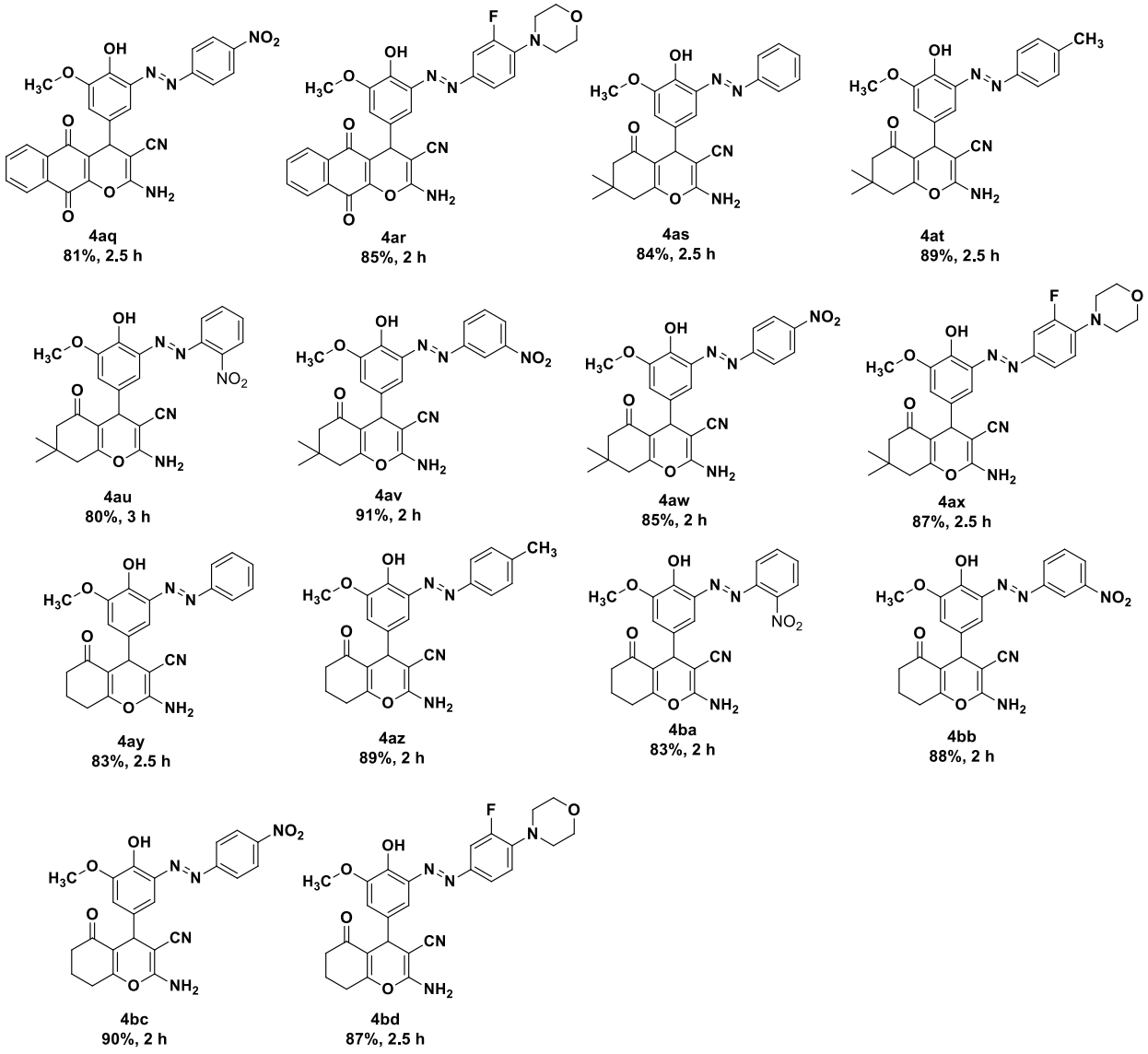
4an
89%, 3 h



4ao
84%, 3 h



4ap
83%, 2.5 h



[a]Reaction conditions: dicarbonyl compound (1 mmol), 4-hydroxy-3-methoxy-5-((substituted phenyl)diazenyl)benzaldehyde (1 mmol) and malononitrile (1 mmol), nano-CeO_2–ZrO_2 (20 mol %), water (5 mL). [b]Yields of isolated products.

To show the significance of nano sized-CeO_2–ZrO_2 catalyst, its reusability was tested upon the synthesis of compound **4ac** with 4-hydroxy-6-methyl-2H-chromene-2-one **1a**, 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde **2c** and malononitrile **3.** After each cycle, the reaction was followed by extraction of products and catalyst. The collected catalyst was washed with acetone for several times to remove organic substances and used for

the next run. The performance of the recycled catalyst was tested up to four successive runs and observed no significant loss in the reaction products **(Fig. 2.3.1**).

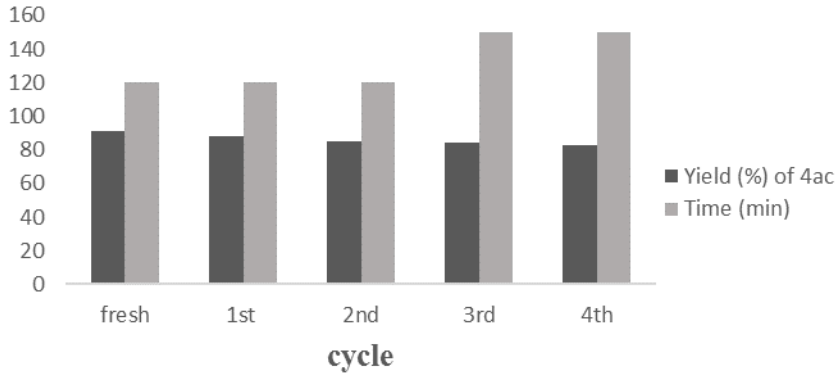
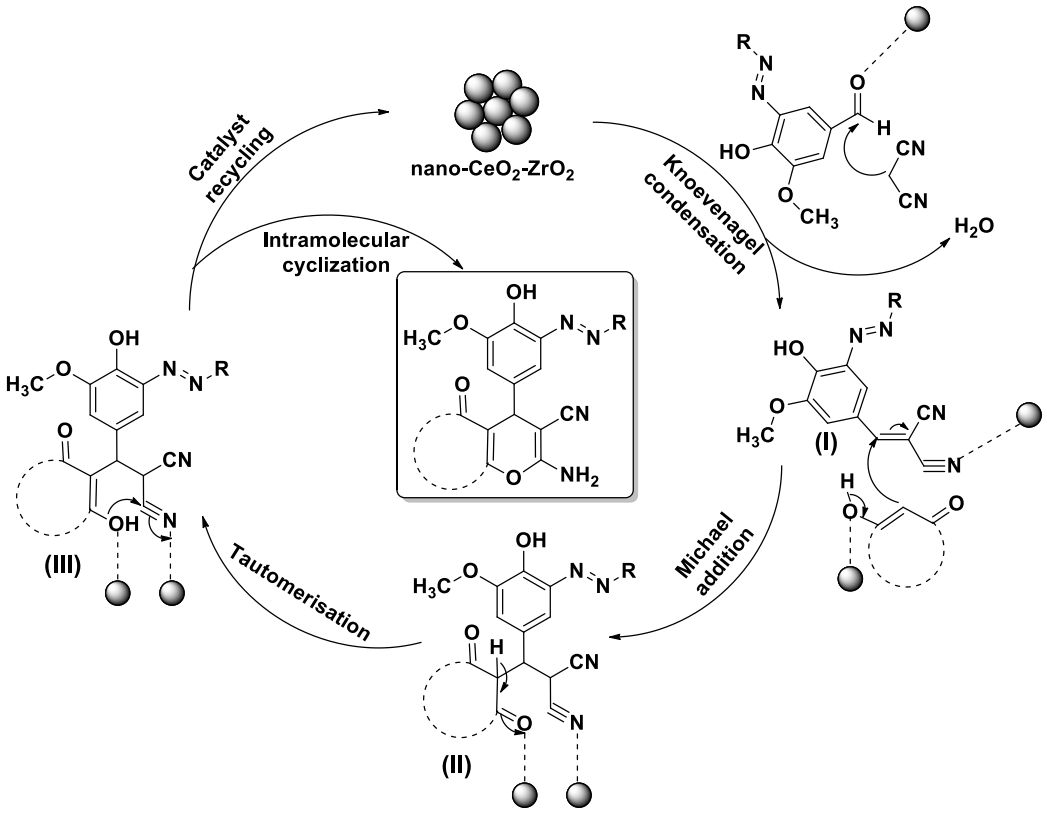


Fig. 2.3.1 Reusability studies of the nano-sized CeO_2-ZrO_2 catalyst for the synthesis of compound **4ac**

A plausible mechanism was suggested for the formation of title compounds which is shown in **scheme 2.3.1**.

Scheme 2.3.1: proposed mechanism for the multicomponent reaction using zirconium doped ceria nanoparticles



The reaction was supposed to proceed *via* first Knoevenagel condensation to produce 2-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)benzylidene)malononitrile (**I**). Consequently, the Michael addition reaction of the intermediate (**II**) with 1,3-dicarbonyl compounds followed by tautomerization and intramolecular cyclization provides the desired product. The structures of all the products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectrometry analysis.

Characterization of the catalyst

Powder-XRD: Fig. 2.3.3(a) shows the X-ray diffractograms of the zirconium doped ceria catalyst (CeO_2-ZrO_2). The main peaks (111), (200), (220) and (311) observed in this figure correspond to the typical cubic structure of ceria. No characterization peaks related to zirconium oxide were observed which confirm the formation of solid solution. The average crystallite size of CeO_2-ZrO_2 material is calculated by using the most intense peaks such as (111), (220) and (311) with the help of Sherrer equation and the obtained value is around 4.7 nm.

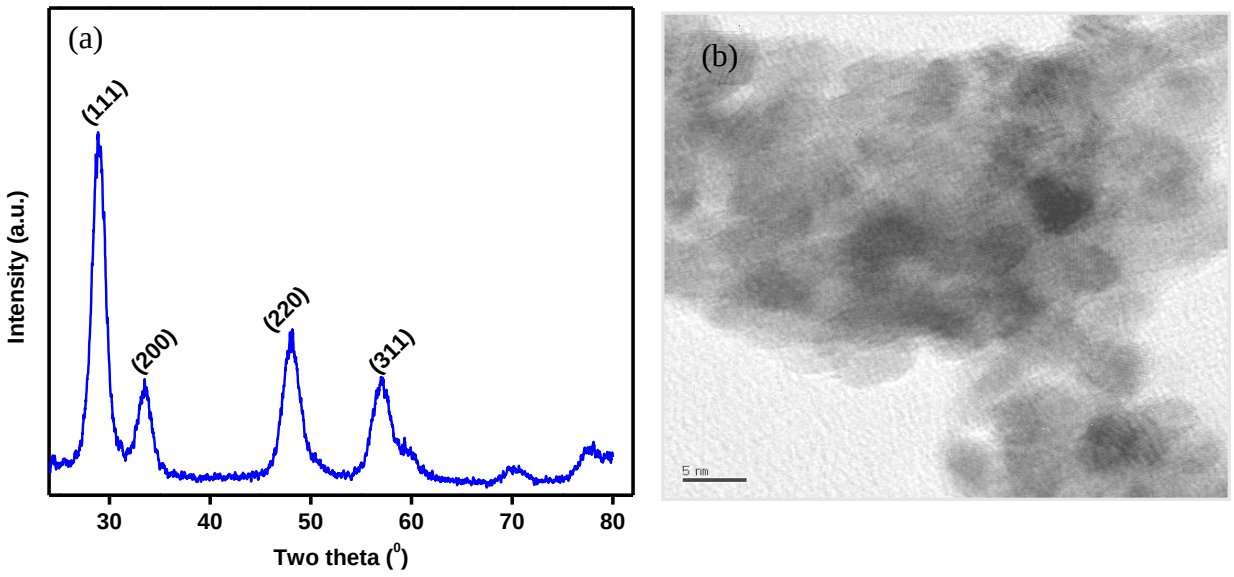


Fig. 2.3.3. (a) Powder X-ray diffraction patterns of zirconium doped ceria nanoparticles and (b) transmission electron microscopy image of zirconium doped ceria nanoparticles.

TEM: The TEM image of the CeO_2-ZrO_2 material (Fig. 2.3.3(b)) reveals that the average particle size of the prepared material is 4-6 nm, which is in agreement with the XRD results.

XPS: The results of XPS studies were carried out to identify the chemical states of the dopant and the host ions on the surface of the CeO_2-ZrO_2 are shown in Fig. 2.3.4

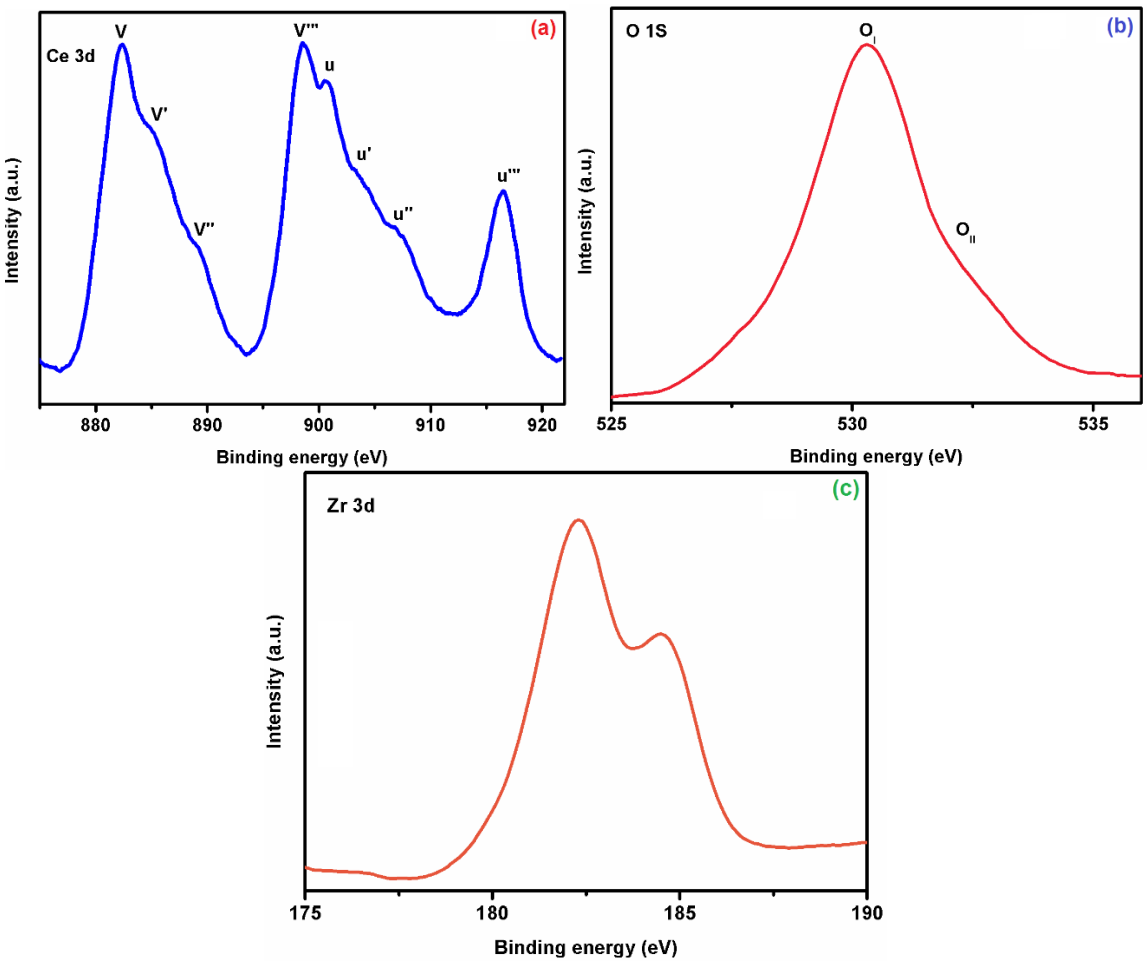


Fig. 2.3.4. XPS spectra of zirconium doped ceria nanoparticles

The Ce 3d XP spectrum of CeO_2-ZrO_2 is shown in Fig. 2.3.4(a), which suggests the coexistence of Ce^{3+} and Ce^{4+} which were characterized by two series of peaks: $3d_{3/2}$ and $3d_{5/2}$ labelled as u and v, respectively. The peaks designated as u, u″, u‴ and v, v″, v‴ can be assigned to Ce^{4+} while the peaks u′ and v′ belong to Ce^{3+}.[41]

The O 1s spectrum of CeO_2-ZrO_2 material is illustrated in Fig. 2.3.4(b). The peak centered at 530.3 eV is related to the lattice oxygen and the peak located at 532.3 eV is ascribed to adsorbed oxygen (O^-, O^{2-} or OH^-).[42]

Zr 3d XP spectrum of prepared CeO_2-ZrO_2 nanomaterial is shown in Fig. 2.3.4(c), reveals two peaks at 182.4 and 184.7 eV corresponding to Zr $3d_{5/2}$ and Zr $3d_{3/2}$ respectively, which are assigned to +4 oxidation state of the zirconium.[43] From the XPS studies, it is clear

that on the surface of the CeO_2-ZrO_2 material Ce exists in the 3+ and 4+ states and Zr in 4+ states along with the presence of two types of oxygen (lattice oxygen and adsorbed oxygen).

Experimental

All the reagents were procured from commercial sources and used without further purification. A Bruker WM-4 (X) spectrophotometer (577 model) was used for recording IR spectra (KBr). NMR spectra were recorded on a Bruker WM-500 spectrophotometer at 500 MHz (^{1}H), Bruker WM-400 spectrophotometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively, in DMSO-d_6 with TMS as an internal standard. Elemental analysis was performed on a Carlo Erba EA 1108 automatic elemental analyzer. Mass spectra (ESI) were taken on a jeo1 JMSD-300 spectrometer.

Single-crystal XRD: The single-crystal X-ray diffraction data of the crystals **4av** were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 293(2) K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The compound **4av** was crystallized from acetic acid to yield prismatic crystals.

Powder-XRD: Powder-XRD data was acquired in the 2θ range of 12–80° on a Rigaku Multiflex instrument using Cu Kα (λ = 1.5418 Å) radiation and a scintillation counter detector. Crystalline phases present in the samples were identified with the help of Powder Diffraction File-International Centre for Diffraction Data (PDF-ICDD). The average size of the crystalline domains (D) of the prepared materials were estimated with the help of the Scherrer equation (1) using the Powder-XRD data of all prominent lines.

$$D = K\,\lambda/\beta\cos\theta \qquad (1)$$

Where D denotes the crystallite size, λ is the X-ray wavelength (1.541 Å), K indicates the particle shape factor taken as 1, β represents the peak width (FWHM, full width at half maximum) in radians and θ is the Bragg diffraction angle.

TEM: TEM studies were made on a JEM-2010 (JEOL) instrument equipped with a slow-scan CCD camera at an accelerating voltage of 200 kV.

XPS: The XPS measurements were performed on a Shimadzu (ESCA 3400) spectrometer measurements were performed on a Shimadzu (ESCA 3400) spectrometer by using Al Kα (1486.7 eV) radiation as the excitation source. Charging effects of catalyst samples were corrected by using the binding energy of the adventitious carbon (C 1s) at 284.6 eV as internal

reference. The XPS analysis was done at ambient temperature and pressures usually in the order of less than 10−8 Pa.

Crystal structure determination

The single-crystal X-ray diffraction data of the crystals **4av** were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 293(2) K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL.[44] The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.[45] All the aromatic and aliphatic C−H hydrogens were generated by the riding model in idealized geometries. The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3 and X-Seed.[46]

Characterization of compound 4av by single crystal XRD

Further, the structure of compound **4av** was confirmed by single crystal X-ray diffraction method (**Fig. 2.3.2**, CCDC-1440722). The compound **4av** crystallizes in the centrosymmetric monoclinic C2/c space group with one molecule in the asymmetric unit. **Table 2.3.3** gives the pertinent crystallographic data.

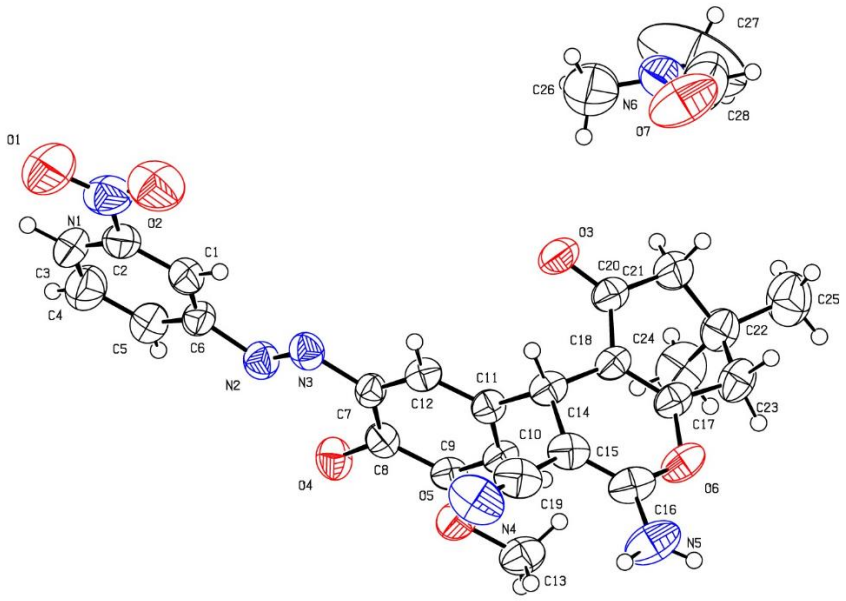


Fig. 2.3.2 ORTEP representation of compound **4av (**CCDC-1440722**)**. The thermal ellipsoids are drawn at 50% probability level.

Table 2.3.3. Salient crystallographic data and structure refinement parameters of compound **4av.**

	4av
Empirical formula	$C_{28}H_{29}N_6O_7$
Formula weight	561.57
Crystal system	Monoclinic
Space group	*C*2/c
T/K	296(2)
a/Å	13.5896(13)
b/Å	15.1701(14)
c/Å	27.316(3)
α/°	90
β/°	92.580(4)
γ/ °	90
Z	8
V/Å^3	5625.7(9)
D_{calc}/ Mg/cm^3	1.326
F(000)	2360
μ/mm^{-1}	0.097
θ/°	1.49 to 28.33
Index ranges	$-18 \leq h \leq 18$ $-16 \leq k \leq 20$ $-36 \leq l \leq 36$
N-total	23076
N-independent	6949
Parameters	373
R_1 ($I > 2\sigma(I)$)	0.0508
wR_2 (all data)	0.2159
GOF	1.017
CCDC	1440722

Spectral discussion

IR

The structures of the fused chromenes were confirmed by IR spectra which showed strong absorption bands at 3327-3498 cm^{-1} and 2183-2206 cm^{-1} due to NH_2 and CN groups respectively.

^{1}H NMR

The structure of the synthesized compounds **4aa-bd** were also characterized by ^{1}H NMR spectra. In ^{1}H NMR spectra of all the compounds, chromene proton (H-4) was observed as a singlet at δ 4.18-4.67 ppm which conformed the smooth cyclization. All aromatic and aliphatic protons were observed at expected regions.

^{13}C NMR

In addition, ^{13}C NMR spectra also confirmed the proposed structures **4aa-bd** due to the appearance of signal at δ 35.14-36.94 ppm due to chromene (C_4) carbon.

Mass

The mass spectra of the compounds 4aa-bd gave additional evidences for the proposed structures. In mass spectra almost all the compounds exhibited a charesteric M-1 peak, which were in agreement with their molecular weights.

For all the compounds, the elemental analyses values were in good agreement with the theoretical data.

Preparation of zirconium doped ceria nanoparticles

The CeO_2–ZrO_2 (CZ 1:1 mole ratio based on oxides) solid solution was synthesized by a modified coprecipitation method using appropriate amounts of the corresponding $Ce(NO_3)_3.6H_2O$ (Aldrich, AR grade), $ZrO(NO_3)_2 \cdot xH_2O$ (Fluka, AR grade) precursors. The desired amounts of the precursors were dissolved separately in double-distilled water under mild stirring conditions and mixed together. Dilute aqueous ammonia solution was added drop-wise over a period until the pH of the solution reached ~ 8.5. The resulting pale yellow colored slurry was decanted, filtered, and washed several times with double distilled water. The obtained precipitate was oven dried at 393 K for 12 h and calcined at 773 for 5 h at a heating rate of 5 K min^{-1} in air atmosphere.

Synthesis of 4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)benzaldehydes (2a-f)

3-methoxy-4-hydroxybenzaldehyde (3.8g, 25 mmol) was dissolved in 30 mL of 10% Na_2CO_3 solution and cooled to 0^{o}C. Meanwhile, a mixture of aniline (2.5 g, 27 mmol), conc. HCl (8 mL), and water (8 mL) was taken in a conical flask and cooled to 0^{o}C. To this, a cold $NaNO_2$ solution (2 g in 10 mL of water) was added gradually at 5^{o}C during stirring. This diazonium solution was added to the cold 3-methoxy-4-hydroxybenzaldehyde solution over a period of 30 min. Later, the reaction mixture was left at room temperature for 1 hour and filtered. The dark red colored product obtained was purified by column chromatography using the mixture of chloroform: hexane (6:4) as eluent to produce pure 4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)benzaldehydes (**2a-f**)

4-hydroxy-3-methoxy-5-(phenyldiazenyl)benzaldehydes (2a)

Dark red solid; m.p. 129-131 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 1688, 1596, 1483; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 4.02 (s, 3H, -OCH_3), 7.51 (s, 1H, ArH), 7.54-7.58 (m, 3H, ArH), 7.88-7.92 (m, 2H, ArH), 8.11 (s, 1H, ArH), 9.96 (s, 1H, -CHO), 14.25 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 190.34, 152.99, 151.16, 142.88, 138.58, 131.19, 128.62, 126.66, 123.42, 115.00, 36.87; **ESI-MS** (*m/z*): 255 (M-1); Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; Found: C, 65.55; H, 4.66; N, 10.71.

4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)benzaldehydes (2b)

Dark red solid; m.p. 138-140 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 1686, 1598, 1482; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 2.47 (s, 3H, -CH_3), 4.01 (s, 3H, -OCH_3), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.49 (s, 1H, ArH), 7.81 (d, J = 8.0 Hz, 2H, ArH), 8.07 (s, 1H, ArH), 9.95 (s, 1H, -CHO), 14.30 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 190.83, 153.40, 151.51, 143.29, 142.88, 138.58, 136.17, 134.55, 131.71, 129.15, 126.95, 123.72, 115.91, 36.64, 20.01; **ESI-MS** (*m/z*): 269 (M-1); Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36; Found: C, 66.51; H, 5.34; N, 10.28.

4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehydes (2c)

Dark red solid; m.p. 143-145 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3424, 1685, 1599, 1483; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 4.02 (s, 3H, -OCH_3), 7.50 (s, 1H, ArH), 7.54-7.59 (m, 2H, ArH), 7.88-7.92 (m, 2H, ArH), 8.10 (s, 1H, ArH), 9.96 (s, 1H, -CHO), 14.25 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 189.27, 153.75, 147.86, 144.01, 142.72, 139.46, 137.18, 134.90, 131.11, 128.29, 127.10, 122.73, 116.01, 35.70; **ESI-MS** (*m/z*): 300 (M-1); Anal. Calcd for $C_{14}H_{11}N_3O_5$: C, 55.82; H, 3.68; N, 13.95; Found: C, 55.73; H, 3.77; N, 13.81.

4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)benzaldehydes (2d)

Dark red solid; m.p. 134-136 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 1687, 1596, 1482; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 4.05 (s, 3H, -OCH_3), 7.52 (s, 1H, ArH), 7.88 (t, J = 8.0 Hz, 1H, ArH), 8.31 (s, 1H, ArH), 8.37 (d, J = 8.0 Hz, 1H, ArH), 8.47 (d, J = 8.0 Hz, 1H, ArH), 8.79 (s, 1H, ArH), 9.97 (s, 1H, -CHO), 14.31 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 190.00, 153.20, 151.02, 148.42, 142.79, 139.37, 137.32, 134.20, 131.77, 129.18, 127.34, 122.65, 116.28, 36.03; **ESI-MS** (*m/z*): 300 (M-1); Anal. Calcd for $C_{14}H_{11}N_3O_5$: C, 55.82; H, 3.68; N, 13.95; Found: C, 55.72; H, 3.79; N, 13.81.

4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)benzaldehydes (2e)

Dark red solid; m.p. 142-144 °C; **IR** (KBr, cm^{-1}) ν_{max}: 3428, 1686, 1600, 1486; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 4.02 (s, 3H, -OCH_3), 7.52 (d, *J* = 8.0 Hz, 2H, ArH), 7.49 (s, 1H, ArH), 7.81 (d, *J* = 8.0 Hz, 2H, ArH), 8.07 (s, 1H, ArH), 9.95 (s, 1H, -CHO), 14.30 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 189.27, 155.92, 152.70, 150.98, 143.65, 140.57, 138.23, 134.90, 131.85, 127.98, 122.59, 116.23, 36.06.; ESI-MS (*m/z*): 300 (M-1); Anal. Calcd for $C_{14}H_{11}N_3O_5$: C, 55.82; H, 3.68; N, 13.95; Found: C, 55.73; H, 3.77; N, 13.81.

3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxybenzaldehyde (2f)

Dark red solid; m.p. 129-131 °C; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 1685, 1598, 1487; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 3.24-3.27 (s, 4H), 3.89-3.91 (s, 4H), 4.00 (s, 3H, -OCH_3), 7.02 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.64 (d, 1H, ArH), 7.67 (s, 1H, ArH), 8.03 (s, 1H, ArH), 9.95 (s, 1H, -CHO), 13.93 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 188.17, 152.94, 150.00, 143.41, 141.30, 139.23, 131.19, 126.42, 120.79, 117.46, 115.40, 67.01, 50.34, 36.64; **ESI-MS** (*m/z*): 358 (M-1); Anal. Calcd for $C_{18}H_{18}FN_3O_4$: C, 60.16; H, 5.05; N, 11.69; Found: C, 60.32; H, 5.12; N, 11.73.

Synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene-3-carbonitrile derivatives (4aa-4bd)

A mixture of 1,3-dicarbonyl compound (1 mmol**)**, 4-hydroxy-3-methoxy-5-(substituted-phenyl diazenyl), benzaldehyde (1 mmol) and malononitrile (1 mmol**)** in water (5 mL) was taken in a 50 mL round bottom flask and nano-CeO_2–ZrO_2 was added. The resulting mixture was stirred for 2 hours at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction the product was separated from the catalyst by extracting with ethyl acetate, the extract was evaporated under vacuum. The product was purified by column chromatography using silica gel [ethyl acetate: n-hexane (5:5)] to afford the pure compounds (**4aa-4bd**).

2-amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4aa)

Dark red solid; m.p. 251-253 °C; **IR** (KBr, cm^{-1}) ν_{max}: 3414, 2203, 1698; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.27 (s, 3H, -CH_3), 3.94 (s, 3H, -OCH_3), 4.46 (s, 1H), 6.04 (s, 1H, ArH), 6.49 (s, 2H, -NH_2), 7.02 (s, 1H, ArH), 7.42 (s, 1H, ArH), 7.51-7.58 (m, 3H, ArH), 7.85-7.91 (m, 2H, ArH), 10.72 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.57, 161.89, 158.76, 158.65, 149.71, 147.21, 146.65, 143.97, 139.20, 135.19, 134.23, 131.81, 124.83, 119.80, 119.11,

116.17, 111.86, 100.72, 98.44, 79.63, 56.68, 36.32, 19.82; **ESI-MS** (*m/z*): 429 (M-1); Anal. Calcd for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02; Found: C, 64.52; H, 4.44; N, 13.38.

2-amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4ab)

Red solid; m.p. 264-266 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3398, 2201, 1707; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, -CH_3), 2.41 (s, 3H, -CH_3), 3.83 (s, 3H, -OCH_3), 4.33 (s, 1H), 6.29 (s, 1H, ArH), 6.96 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.22 (s, 2H, -NH_2), 7.38 (d, *J* = 8.0 Hz, 2H, ArH), 7.90 (d, *J* = 8.0 Hz, 2H, ArH), 10.97 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.42, 161.92, 158.60, 149.88, 149.29, 144.43, 142.12, 138.34, 134.90, 130.42, 123.18, 119.83, 115.06, 113.49, 100.98, 98.50, 79.42, 56.64, 36.49, 21.53, 19.82; **ESI-MS** (*m/z*): 443 (M-1); Anal. Calcd for $C_{24}H_{20}N_4O_5$: C, 64.86; H, 4.54; N, 12.61; Found: C, 64.92; H, 4.82; N, 12.93.

2-amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4ac)

Dark red solid; m.p. 257-259 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3394, 2200, 1714; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 2.27 (s, 3H, -CH_3), 3.96 (s, 3H, -OCH_3), 4.52 (s, 1H), 4.73 (s, 2H, -NH_2), 5.94 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.56 (t, *J* = 8.0 Hz, 1H, ArH), 7.73 (t, *J* = 8.0 Hz, 1H, ArH), 7.99 (d, *J* = 8.0 Hz, 1H, ArH), 8.12 (d, *J* = 8.0 Hz, 1H, ArH), 13.12 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.51, 161.90, 158.77, 158.62, 149.73, 147.20, 146.65, 143.97, 139.22, 135.19, 134.25, 131.81, 124.83, 119.80, 119.10, 116.16, 111.87, 100.72, 98.44, 79.65, 56.69, 36.34, 19.81; **ESI-MS** (*m/z*): 474 (M-1); Anal. Calcd for $C_{23}H_{17}N_5O_7$: C, 58.11; H, 3.60; N, 14.73; Found: C, 58.24; H, 3.43; N, 14.91.

2-amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4ad)

Dark brown solid; m.p. 231-233 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3392, 2205, 1702; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, -CH_3), 3.85 (s, 3H, -OCH_3), 4.34 (s, 1H), 6.30 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.23 (s, 2H, -NH_2), 7.87 (t, *J* = 8.0 Hz, 1H, ArH), 8.37 (d, *J* = 8.0 Hz, 1H, ArH), 8.46 (d, *J* = 8.0 Hz, 1H, ArH), 8.79 (s, 1H, ArH), 10.67 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.53, 161.89, 158.76, 158.62, 149.75, 147.20, 146.64, 143.98, 139.21, 135.19, 134.25, 131.81, 124.83, 119.80, 119.10, 116.14, 111.87, 100.70, 98.41, 79.64,

56.69, 36.34, 19.84; **ESI-MS** (*m/z*): 474 (M-1); Anal. Calcd for $C_{23}H_{17}N_5O_7$: C, 58.11; H, 3.60; N, 14.73; Found: C, 58.24; H, 3.43; N, 14.91.

2-amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4ae)

Dark red solid; m.p. 251-253 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3400, 2199, 1704; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, -CH_3), 3.85 (s, 3H, -OCH_3), 4.34 (s, 1H), 6.30 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.26 (s, 2H, -NH_2), 8.22 (d, J = 8.0 Hz, 2H, ArH), 8.41 (d, J = 8.0 Hz, 2H, ArH), 10.76 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.53, 161.91, 158.77, 158.63, 149.73, 147.20, 146.64, 143.98, 139.22, 135.19, 134.25, 131.81, 124.83, 119.83, 119.14, 116.16, 111.87, 100.72, 98.44, 79.64, 56.68, 36.34, 19.83; **ESI-MS** (*m/z*): 474 (M-1); Anal. Calcd for $C_{23}H_{17}N_5O_7$: C, 58.11; H, 3.60; N, 14.73; Found: C, 58.24; H, 3.43; N, 14.91.

2-amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4af)

Brown solid; m.p. 225-227 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3377, 2199, 1709; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, -CH_3), 3.18-3.21 (m, 4H), 3.73-3.90 (m, 4H), 3.96 (s, 3H, -OCH_3), 4.31 (s, 1H), 6.29 (s, 1H, ArH), 6.92 (s, 1H, ArH), 7.11 (s, 1H, ArH), 7.22 (s, 2H, -NH_2), 7.63 (d, J = 8.0 Hz, 1H, ArH), 7.76 (d, J = 8.0 Hz, 1H, ArH), 8.40 (s, 1H, ArH) 10.67 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.49, 161.92, 158.76, 158.61, 149.72, 147.20, 146.63, 143.97, 139.23, 135.19, 134.25, 131.83, 124.80, 119.82, 119.10, 116.16, 111.87, 100.72, 98.42, 79.67, 68.26, 56.68, 49.79, 36.34, 30.06, 27.68, 19.82; **ESI-MS** (*m/z*): 532 (M-1); Anal. Calcd for $C_{27}H_{24}FN_5O_6$: C, 60.78; H, 4.53; N, 13.13; Found: C, 60.52; H, 4.62; N, 13.22.

2-amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ag)

Red solid; m.p. 240-242 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3373, 2202, 1710; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.83 (s, 3H, -OCH_3), 4.52 (s, 1H), 7.06 (s, 1H, ArH), 7.23 (s, 1H, ArH), 7.46 (s, 2H, -NH_2), 7.46-7.59 (m, 5H, ArH), 7.73 (t, J = 8.0 Hz, 1H, ArH), 7.91 (d, J = 8.0 Hz, 1H, ArH), 7.98 (t, J = 8.0 Hz, 2H, ArH), 10.96 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.33, 158.37, 152.33, 148.73, 144.40, 143.42, 137.45, 134.09, 132.78, 131.28, 129.32, 124.55, 122.84, 122.46, 117.55, 116.50, 115.21, 113.13, 103.95, 78.96, 56.32, 36.81; **ESI-MS** (*m/z*): 465 (M-1); Anal. Calcd for $C_{26}H_{18}N_4O_5$: C, 66.95; H, 3.89; N, 12.01; Found: C, 66.67; H, 3.98; N, 12.23.

2-amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ah)

Dark red solid; m.p. 236-238 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3373, 2204, 1714; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, -CH_3), 3.83 (s, 3H, -OCH_3), 4.52 (s, 1H), 7.04 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.37 (d, *J* = 8.0 Hz, 2H, ArH), 7.43 (s, 2H, -NH_2), 7.48 (t, *J* = 8.0 Hz, 1H, ArH), 7.72 (t, *J* = 8.0 Hz, 2H, ArH), 7.87-7.93 (m, 3H, ArH), 11.03 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.80, 158.32, 152.75, 148.10, 144.89, 143.47, 137.97, 134.77, 132.47, 131.28, 129.51, 123.45, 123.13, 122.27, 117.93, 116.79, 115.00, 103.10, 78.73, 57.27, 49.09, 36.94, 19.77; **ESI-MS** (*m/z*): 479 (M-1); Anal. Calcd for $C_{27}H_{20}N_4O_5$: C, 67.49; H, 4.20; N, 11.66; Found: C, 67.80; H, 4.01; N, 11.83.

2-amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ai)

Red solid; m.p. 231-233 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3381, 2200, 1717; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.84 (s, 3H, -OCH_3), 4.50 (s, 1H), 7.10 (s, 1H, ArH), 7.44 (s, 2H, -NH_2), 7.47-7.52 (m, 2H, ArH), 7.73 (t, *J* = 10.0 Hz, 2H, ArH), 7.83 (t, *J* = 10.0 Hz, 1H, ArH), 7.91-7.97 (m, 3H, ArH), 8.10 (d, *J* = 10.0 Hz, 1H, ArH), 10.98 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 162.83, 160.93, 159.75, 157.46, 152.17, 149.79, 148.73, 146.21, 141.52, 138.37, 134.40, 132.33, 125.93, 125.01, 123.93, 122.15, 115.83, 114.48, 109.55, 106.03, 103.54, 76.96, 56.56, 36.18; **ESI-MS** (*m/z*): 510 (M-1); Anal. Calcd for $C_{26}H_{17}N_5O_7$: C, 61.06; H, 3.35; N, 13.69; Found: C, 61.32; H, 3.43; N, 13.90.

2-amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4aj)

Brown solid; m.p. 248-250 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3327, 2185, 1723; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.84 (s, 3H, -OCH_3), 4.51 (s, 1H), 7.08 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.45 (s, 2H, -NH_2), 7.46-7.52 (m, 2H, ArH), 7.72 (t, *J* = 10.0 Hz, 1H, ArH), 7.85 (t, *J* = 10.0 Hz, 1H, ArH), 7.90-7.96 (m, 2H, ArH), 8.35 (d, *J* = 10.0 Hz, 1H, ArH), 8.78 (s, 1H, ArH), 10.69 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 162.36, 160.66, 159.69, 157.30, 152.23, 149.55, 148.79, 146.09, 141.88, 138.39, 134.18, 132.99, 125.72, 125.04, 123.52, 122.05, 115.88, 114.55, 110.28, 106.07, 103.74, 77.68, 56.11, 36.83; **ESI-MS** (*m/z*): 510 (M-1); Anal. Calcd for $C_{26}H_{17}N_5O_7$: C, 61.06; H, 3.35; N, 13.69; Found: C, 61.31; H, 3.44; N, 13.88.

2-amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ak)

Dark red solid; m.p. 228-230 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3358, 2205, 1718; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, -OCH_3), 4.52 (s, 1H), 7.11 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.47 (s, 2H, -NH_2), 7.51 (t, *J* = 8.0 Hz, 1H, ArH), 7.73 (t, *J* = 8.0 Hz, 1H, ArH), 7.93 (t, *J* = 8.0 Hz, 2H, ArH), 8.21 (d, *J* = 8.0 Hz, 2H, ArH), 8.40 (d, *J* = 8.0 Hz, 2H, ArH), 10.79 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 162.80, 160.13, 158.52, 155.50, 153.94, 152.66, 149.88, 148.62, 146.91, 139.18, 134.74, 133.47, 125.37, 125.17, 124.24, 123.06, 119.71, 117.09, 116.38, 113.53, 110.87, 104.03, 79.65, 56.72, 36.28; **ESI-MS** (*m/z*): 510 (M-1); Anal. Calcd for $C_{26}H_{17}N_5O_7$: C, 61.06; H, 3.35; N, 13.69; Found: C, 61.32; H, 3.43; N, 13.90.

2-amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4al)

Brown solid; m.p. 220-222 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3411, 2227, 1731; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.16-3.21 (m, 4H), 3.76-3.79 (m, 4H), 3.96 (s, 3H, -OCH_3), 4.48 (s, 1H), 7.19-7.24 (m, 3H, ArH), 7.42 (s, 2H, -NH_2), 7.57 (s, 1H, ArH), 7.62 (d, *J* = 8.0 Hz, 1H, ArH), 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 7.90 (d, *J* = 8.0 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 11.03 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 163.15, 156.12, 153.50, 152.20, 150.06, 148.91, 146.59, 144.09, 142.74, 140.22, 139.30, 134.38, 130.43, 128.29, 126.75, 124.20, 122.25, 118.61, 115.06, 110.65, 108.10, 104.92, 78.63, 66.03, 56.04, 50.00, 37.37; **ESI-MS** (*m/z*): 568 (M-1); Anal. Calcd for $C_{30}H_{24}FN_5O_6$: C, 63.27; H, 4.25; N, 12.30; Found: C, 63.52; H, 4.33; N, 12.57.

2-amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4am)

Red solid; m.p. 265-267 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3453, 2190, 1723, 1657; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, -OCH_3), 4.67 (s, 1H), 7.07 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.35 (s, 2H, -NH_2), 7.54-7.59 (m, 3H, ArH), 7.83-7.87 (m, 2H, ArH), 7.89-7.92 (m, 1H, ArH), 7.97-8.00 (m, 2H, ArH), 8.04-8.08 (m, 1H, ArH), 10.97 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 183.21, 177.41, 158.87, 151.84, 149.57, 149.34, 144.75, 138.43, 134.98, 134.91, 134.59, 131.83, 131.57, 131.18, 129.88, 126.52, 126.31, 123.17, 121.96, 119.88, 115.39, 113.86, 79.65,

56.76, 36.85; **ESI-MS** (*m/z*): 477 (M-1); Anal. Calcd for $C_{27}H_{18}N_4O_5$: C, 67.78; H, 3.79; N, 11.71; Found: C, 67.51; H, 3.50; N, 11.93.

2-amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4an)

Red solid; m.p. 271-273 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3389, 2201, 1721, 1667; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, -CH_3), 3.84 (s, 3H, -OCH_3), 4.66 (s, 1H), 7.06 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.35 (s, 2H, -NH_2), 7.38 (d, *J* = 8.0 Hz, 1H, ArH), 7.83-7.91 (m, 6H, ArH), 8.04-8.07 (m, 1H, ArH), 11.05 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 183.81, 177.63, 158.97, 151.98, 150.80, 149.73, 144.97, 138.83, 135.76, 134.93, 134.40, 132.40, 132.01, 130.60, 129.56, 126.80, 126.39, 123.22, 121.84, 119.36, 115.85, 113.04, 79.74, 56.41, 36.54, 20.30; **ESI-MS** (*m/z*): 491 (M-1); Anal. Calcd for $C_{28}H_{20}N_4O_5$: C, 68.29; H, 4.09; N, 11.38; Found: C, 68.52; H, 4.14; N, 11.09.

2-amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4ao)

Red solid; m.p. 251-253 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3453, 2190, 1722, 1655; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, -OCH_3), 4.66 (s, 1H), 7.07 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.36 (s, 2H, -NH_2), 7.54-7.60 (m, 2H, ArH), 7.81-7.85 (m, 2H, ArH), 7.88-7.91 (m, 1H, ArH), 7.98 (d, *J* = 8.0 Hz, 2H, ArH), 8.04-8.08 (m, 1H, ArH), 10.96 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 183.21, 177.42, 158.87, 151.84, 149.57, 149.34, 144.74, 138.43, 134.99, 134.91, 134.59, 131.83, 131.57, 131.18, 129.89, 126.53, 126.32, 123.17, 121.97, 119.88, 115.39, 113.86, 79.65, 56.76, 36.84; **ESI-MS** (*m/z*): 522 (M-1); Anal. Calcd for $C_{27}H_{17}N_5O_7$: C, 61.95; H, 3.27; N, 13.38; Found: C, 61.82; H, 3.33; N, 13.21.

2-amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4ap)

Brown solid; m.p. 244-246 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3455, 2194, 1728, 1657; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, -OCH_3), 4.66 (s, 1H), 7.08 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.41 (s, 2H, -NH_2), 7.57-7.64 (m, 2H, ArH), 7.72 (s, 2H, ArH), 7.81-7.85 (m, 1H, ArH), 7.90 (d, *J* = 8.0 Hz, 2H, ArH), 7.95-7.99 (m, 1H, ArH), 11.05 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 183.75, 177.74, 159.00, 151.87, 149.81, 144.05, 138.04, 135.76, 135.18, 133.71, 131.70, 131.43, 129.69, 127.41, 126.52, 123.66, 121.07, 119.65, 115.65, 113.65, 79.95, 57.00,

36.60; **ESI-MS** (*m/z*): 522 (M-1); Anal. Calcd for $C_{27}H_{17}N_5O_7$: C, 61.95; H, 3.27; N, 13.38; Found: C, 61.80; H, 3.31; N, 13.22.

2-amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4aq)

Brown solid; m.p. 260-262 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 3454, 2198, 1723, 1653; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.92 (s, 3H, -OCH_3), 4.66 (s, 1H), 7.08 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.43 (s, 2H, -NH_2), 7.78 (d, 1H, *J* = 8.0 Hz, ArH), 8.02 (d, 1H, *J* = 8.0 Hz, ArH), 8.20 (d, 2H, *J* = 8.0 Hz, ArH), 8.42-8.47 (m, 4H, ArH), 11.02 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 183.10, 177.07, 158.68, 152.28, 150.69, 149.68, 144.96, 140.63, 138.34, 136.26, 134.33, 133.73, 132.46, 126.25, 125.69, 125.52, 125.34, 123.88, 118.27, 115.87, 113.52, 79.40, 56.40, 36.38; **ESI-MS** (*m/z*): 522 (M-1); Anal. Calcd for $C_{27}H_{17}N_5O_7$: C, 61.95; H, 3.27; N, 13.38; Found: C, 61.80; H, 3.35; N, 13.19.

2-amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4ar)

Brown solid; m.p. 242-244 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 3443, 2197, 1721, 1657; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.10-3.16 (m, 4H), 3.76-3.79 (m, 4H), 3.91 (s, 3H, -OCH_3), 4.65 (s, 1H), 7.77 (s, 1H, ArH), 7.89-7.91 (m, 3H, ArH), 8.01 (s, 1H, ArH), 8.31 (s, 2H, -NH_2), 8.38-8.46 (m, 3H, ArH), 8.79 (s, 1H, ArH), 10.75 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 183.77, 177.37, 161.24, 156.29, 153.84, 152.09, 150.10, 146.73, 143.18, 139.16, 134.87, 132.10, 129.90, 127.70, 124.88, 122.63, 118.83, 116.15, 115.27, 114.26, 110.71, 106.81, 104.17, 79.65, 66.48, 56.53, 50.42, 36.35; **ESI-MS** (*m/z*): 580 (M-1); Anal. Calcd for $C_{31}H_{24}FN_5O_6$: C, 64.02; H, 4.16; N, 12.04; Found: C, 64.32; H, 4.01; N, 12.21.

2-amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4as)

Red solid; m.p. 246-248 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 3452, 2190, 1676; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.02 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 2.09-2.33 (m, 4H), 3.83 (s, 3H, -OCH_3), 4.21 (s, 1H), 6.90 (s, 1H, ArH), 7.03 (s, 2H, -NH_2), 7.11 (s, 1H, ArH), 7.54-7.61 (m, 3H, ArH), 7.97 (d, *J* = 8.0 Hz, 2H, ArH), 10.74 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.29, 163.23, 158.95, 151.96, 149.44, 144.68, 138.65, 136.00, 131.76, 129.88, 123.17, 120.26, 114.72, 112.89, 111.92, 56.59, 50.48, 35.64, 32.28, 29.17, 26.96; **ESI-MS** (*m/z*): 443 (M-1); Anal. Calcd for $C_{25}H_{24}N_4O_4$: C, 67.55; H, 5.44; N, 12.60; Found: C, 67.41; H, 5.32; N, 12.82.

2-amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4at)

yellow solid; m.p. 247-249 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3437, 2189, 1735; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.01 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 2.09-2.31 (m, 2H), 2.41 (s, 3H, -CH_3), 2.52-2.73 (m, 2H), 3.82 (s, 3H, -OCH_3), 4.21 (s, 1H), 6.88 (s, 1H, ArH), 7.02 (s, 2H, -NH_2), 7.11 (s, 1H, ArH), 7.39 (d, *J* = 8.0 Hz, 2H, ArH), 7.88 (d, *J* = 8.0 Hz, 2H, ArH), 10.80 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.00, 162.87, 158.60, 149.63, 148.99, 143.94, 142.26, 141.73, 138.16, 135.60, 130.07, 122.79, 119.90, 114.14, 112.56, 112.01, 79.27, 56.23, 50.13, 35.27, 31.93, 28.78, 26.62, 21.17; **ESI-MS** (*m/z*): 457 (M-1); Anal. Calcd for $C_{26}H_{26}N_4O_4$: C, 68.11; H, 5.72; N, 12.22; Found: C, 68.32; H, 5.81; N, 12.46.

2-amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4au)

Dark red solid; m.p. 231-233 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3498, 2190, 1678; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.99 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 2.09-2.32 (m, 2H), 2.57-2.89 (m, 2H), 3.85 (s, 3H, -OCH_3), 4.18 (s, 1H), 6.94 (s, 1H, ArH), 6.96 (s, 1H, ArH), 7.04 (s, 2H, -NH_2), 7.74 (t, *J* = 8.0 Hz, 1H, ArH), 7.85 (t, *J* = 8.0 Hz, 1H, ArH), 7.97 (d, *J* = 8.0 Hz, 1H, ArH), 8.11 (d, *J* = 8.0 Hz, 1H, ArH), 10.73 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.58, 163.56, 159.17, 149.98, 147.67, 146.85, 139.75, 136.59, 134.43, 132.02, 124.96, 120.43, 119.33, 116.07, 112.96, 110.56, 79.88, 56.92, 50.73, 35.83, 32.48, 29.32, 27.37; **ESI-MS** (*m/z*): 488 (M-1); Anal. Calcd for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31; Found: C, 61.41; H, 4.51; N, 14.43.

2-amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4av)

Red solid; m.p. 249-251 ^{o}C; **IR** (KBr, cm^{-1}) ν_{max}: 3400, 2187, 1680; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.03 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 2.10-2.32 (m, 2H), 2.53-2.61 (m, 2H), 3.84 (s, 3H, -OCH_3), 4.20 (s, 1H), 6.93 (s, 1H, ArH), 7.05 (s, 2H, -NH_2), 7.12 (s, 1H, ArH), 7.88 (t, *J* = 8.0 Hz, 1H, ArH), 8.36 (d, *J* = 8.0 Hz, 1H, ArH), 8.44 (d, *J* = 8.0 Hz, 1H, ArH), 8.78 (s, 1H, ArH), 10.58 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 195.84, 162.86, 158.48, 152.29, 149.35, 148.81, 145.95, 138.52, 135.56, 133.27, 130.90, 130.44, 125.02, 119.78, 116.30, 115.86, 114.89, 112.30, 108.51, 104.94, 102.72, 56.07, 49.98, 35.17, 31.82, 28.74, 26.43; **ESI-**

MS (*m/z*): 488 (M-1); Anal. Calcd for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31; Found: C, 61.39; H, 4.54; N, 14.49.

2-amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4aw)

Dark red solid; m.p. 244-246 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3371, 2183, 1678; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.02 (s, 3H, -CH_3), 1.06 (s, 3H, -CH_3), 2.09-2.33 (m, 2H), 2.57-2.68 (m, 2H), 3.84 (s, 3H, -OCH_3), 4.21 (s, 1H), 6.95 (s, 1H, ArH), 7.04 (s, 2H, -NH_2), 7.11 (s, 1H, ArH), 8.20 (d, *J* = 8.0 Hz, 2H, ArH), 8.41 (d, *J* = 8.0 Hz, 2H, ArH), 10.65 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 195.76, 162.79, 158.47, 155.05, 149.33, 148.12, 146.24, 138.81, 136.63, 135.62, 124.90, 123.68, 119.69, 115.26, 112.27, 109.03, 56.09, 35.14, 31.77, 28.66, 26.43; **ESI-MS** (*m/z*): 488 (M-1); Anal. Calcd for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31; Found: C, 61.40; H, 4.52; N, 14.41.

2-amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4ax)

Brown solid; m.p. 236-238 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3373, 2187, 1677; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.01 (s, 3H, -CH_3), 1.05 (s, 3H, -CH_3), 2.09-2.31 (m, 2H), 2.56-2.89 (m, 2H), 3.17-3.21 (m, 4H), 3.72-3.81 (m, 4H), 3.96 (s, 3H, -OCH_3), 4.18 (s, 1H), 6.84 (s, 1H, ArH), 7.03 (s, 2H, -NH_2), 7.07 (s, 1H, ArH), 7.64 (d, *J* = 8.0 Hz, 1H, ArH), 7.75 (d, *J* = 8.0 Hz, 1H, ArH), 8.41 (s, 1H, ArH), 10.48 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 195.75, 162.69, 158.42, 155.95, 148.93, 144.28, 138.07, 135.39, 128.25, 124.67, 123.34, 122.16, 119.74, 118.36, 113.84, 112.40, 110.20, 77.96, 66.00, 56.02, 49.97, 35.16, 31.75, 28.67, 26.43; **ESI-MS** (*m/z*): 546 (M-1); Anal. Calcd for $C_{29}H_{30}FN_5O_5$: C, 63.61; H, 5.52; N, 12.79; Found: C, 63.42; H, 5.71; N, 12.61.

2-amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4ay)

Dark red solid; m.p. 206-208 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3402, 2194, 1665; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.88-2.01 (m, 2H), 2.27-2.33 (m, 2H), 2.60-2.67 (m, 2H), 3.84 (s, 3H, -OCH_3), 4.24 (s, 1H), 6.92 (s, 1H, ArH), 7.06 (s, 2H, -NH_2), 7.13 (s, 1H, ArH), 7.55-7.60 (m, 3H, ArH), 7.92-8.06 (m, 2H, ArH), 10.91 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.00, 164.49, 162.30, 158.54, 151.34, 148.85, 143.89, 137.94, 135.54, 131.27, 129.38, 122.96, 122.64, 119.79, 114.52, 113.56, 112.60, 56.14, 36.39, 35.11, 26.51, 19.84; **ESI-MS** (*m/z*): 415

(M-1); Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45; Found: C, 66.57; H, 4.62; N, 13.61.

2-amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4az)

Red solid; m.p. 249-251 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3405, 2194, 1681; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.90-2.00 (m, 2H), 2.29-2.33 (m, 2H), 2.41 (s, 3H, -CH_3), 2.60-2.69 (m, 2H), 3.83 (s, 3H, -OCH_3), 4.23 (s, 1H), 6.90 (s, 1H, ArH), 7.04 (s, 2H, -NH_2), 7.13 (s, 1H, ArH), 7.39 (d, *J* = 8.0 Hz, 2H, ArH), 7.90 (d, *J* = 8.0 Hz, 2H, ArH), 10.98 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.01, 164.47, 158.54, 149.35, 148.75, 143.55, 141.59, 137.78, 135.50, 129.93, 122.64, 119.79, 114.29, 113.59, 113.01, 56.12, 36.38, 35.09, 26.50, 21.02, 19.84; **ESI-MS** (*m/z*): 429 (M-1); Anal. Calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02; Found: C, 67.12; H, 5.44; N, 13.23.

2-amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4ba)

Dark red solid; m.p. 239-241 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3397, 2190, 1677; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.92-2.03 (m, 2H), 2.25-2.37 (m, 2H), 2.60-2.65 (m, 2H), 3.86 (s, 3H, -OCH_3), 4.21 (s, 1H), 6.97 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.03 (s, 2H, -NH_2), 7.74 (t, *J* = 8.0 Hz, 1H, ArH), 7.85 (t, *J* = 8.0 Hz, 1H, ArH), 8.00 (d, *J* = 8.0 Hz, 1H, ArH), 8.12 (d, *J* = 8.0 Hz, 1H, ArH), 10.82 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.53, 165.07, 159.02, 152.68, 149.72, 149.25, 146.13, 138.82, 136.05, 131.33, 130.78, 125.45, 120.27, 116.42, 115.63, 113.94, 109.95, 79.65, 56.59, 36.89, 35.65, 27.03, 20.35; **ESI-MS** (*m/z*): 460 (M-1); Anal. Calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18; Found: C, 60.12; H, 4.31; N, 14.99.

2-amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4bb)

yellow solid; m.p. 247-249 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3402, 2194, 1677; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.92-2.00 (m, 2H), 2.29-2.33 (m, 2H), 2.61-2.68 (m, 2H), 3.85 (s, 3H, -OCH_3), 4.23 (s, 1H), 6.95 (s, 1H, ArH), 7.05 (s, 2H, -NH_2), 7.15 (s, 1H, ArH), 7.88 (t, *J* = 8.0 Hz, 1H, ArH), 8.37 (d, *J* = 8.0 Hz, 1H, ArH), 8.47 (d, *J* = 8.0 Hz, 1H, ArH), 8.79 (s, 1H, ArH), 10.64 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.13, 165.36, 159.60, 152.44, 150.14, 149.54, 146.98, 138.63, 136.03, 131.11, 130.01, 125.45, 120.23, 116.75, 115.65, 113.07, 109.29, 79.95,

56.41, 36.60, 34.85, 27.39, 20.46; **ESI-MS** (*m/z*): 460 (M-1); Anal. Calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18; Found: C, 59.73; H, 4.30; N, 15.25.

2-amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4bc)

Red solid; m.p. 253-255 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3411, 2191, 1667; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.89-2.02 (m, 2H), 2.26-2.33 (m, 2H), 2.61-2.69 (m, 2H), 3.86 (s, 3H, -OCH_3), 4.24 (s, 1H), 6.97 (s, 1H, ArH), 7.05 (s, 2H, -NH_2), 7.13 (s, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 2H, ArH), 7.41 (d, *J* = 8.0 Hz, 2H, ArH), 10.75 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.56, 165.59, 159.69, 152.79, 150.31, 149.68, 146.21, 138.78, 136.87, 132.14, 130.34, 125.31, 120.60, 116.87, 115.00, 113.43, 109.34, 80.00, 56.83, 36.81, 34.66, 27.14, 20.30; **ESI-MS** (*m/z*): 460 (M-1); Anal. Calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18; Found: C, 59.78; H, 4.27; N, 15.31.

2-amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4bd)

Dark red solid; m.p. 241-243 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3409, 2197, 1669; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.91-1.97 (m, 2H), 2.28-2.32 (m, 2H), 2.60-2.65 (m, 2H), 3.17-3.21 (m, 4H), 3.72-3.78 (m, 4H), 3.95 (s, 3H, -OCH_3), 4.20 (s, 1H), 6.86 (s, 1H, ArH), 7.04 (s, 2H, -NH_2), 7.09 (s, 1H, ArH), 7.64 (d, *J* = 8.0 Hz, 1H, ArH), 7.75 (d, *J* = 8.0 Hz, 1H, ArH), 8.03 (s, 1H, ArH), 10.75 (s, 1H, -OH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 196.36, 166.77, 164.53, 158.51, 150.07, 148.89, 142.28, 137.90, 135.45, 132.52, 130.78, 123.35, 122.25, 118.40, 115.78, 113.56, 111.01, 79.30, 66.04, 56.05, 50.02, 36.41, 35.18, 26.54, 19.88; **ESI-MS** (*m/z*): 518 (M-1); Anal. Calcd for $C_{27}H_{26}FN_5O_5$: C, 62.42; H, 5.04; N, 13.48; Found: C, 62.73; H, 5.37; N, 13.21.

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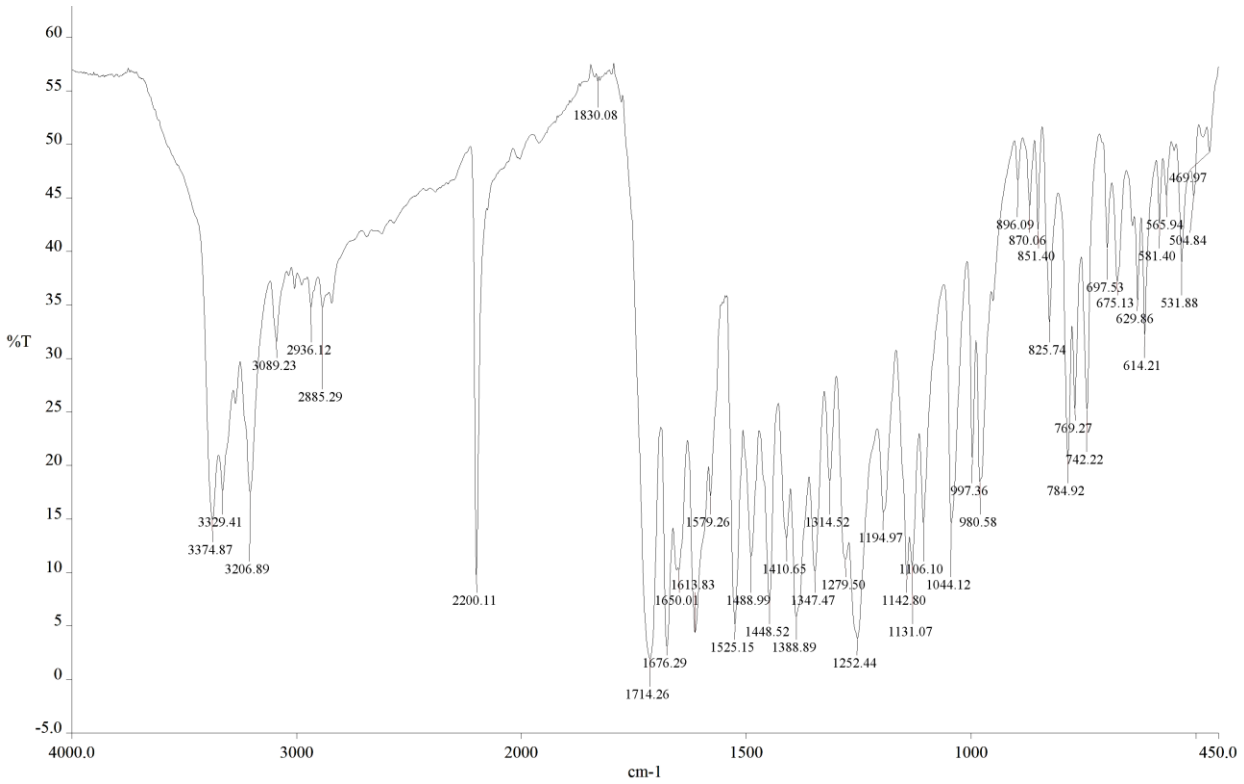
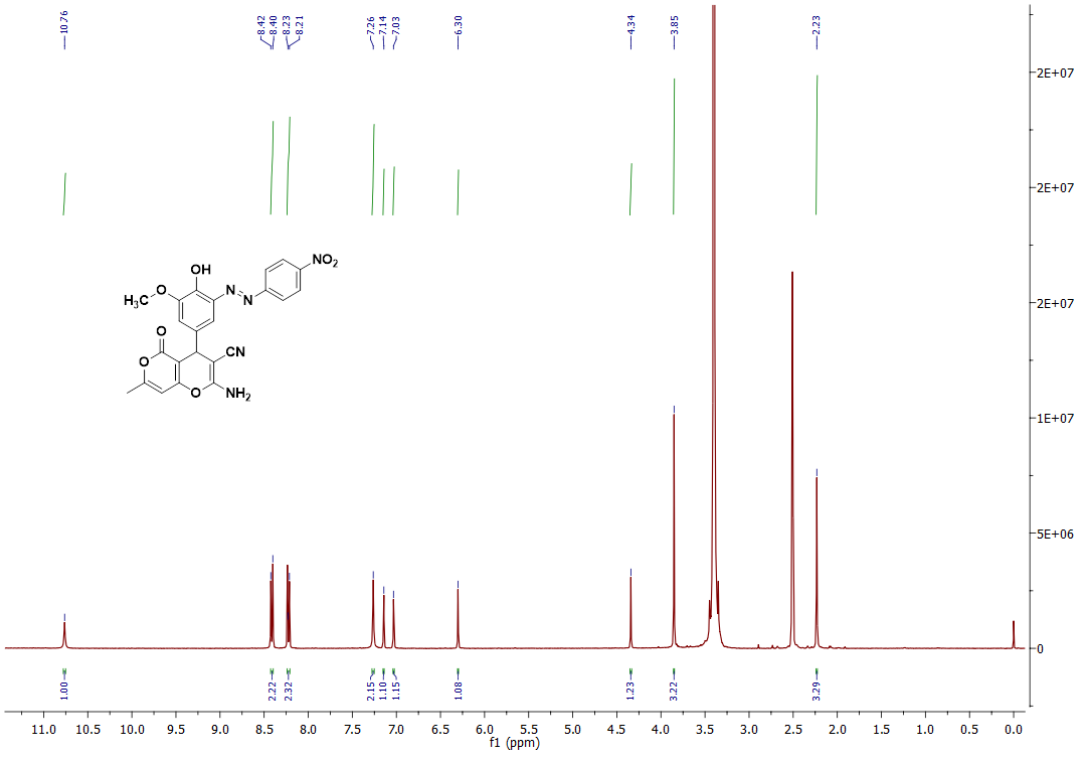
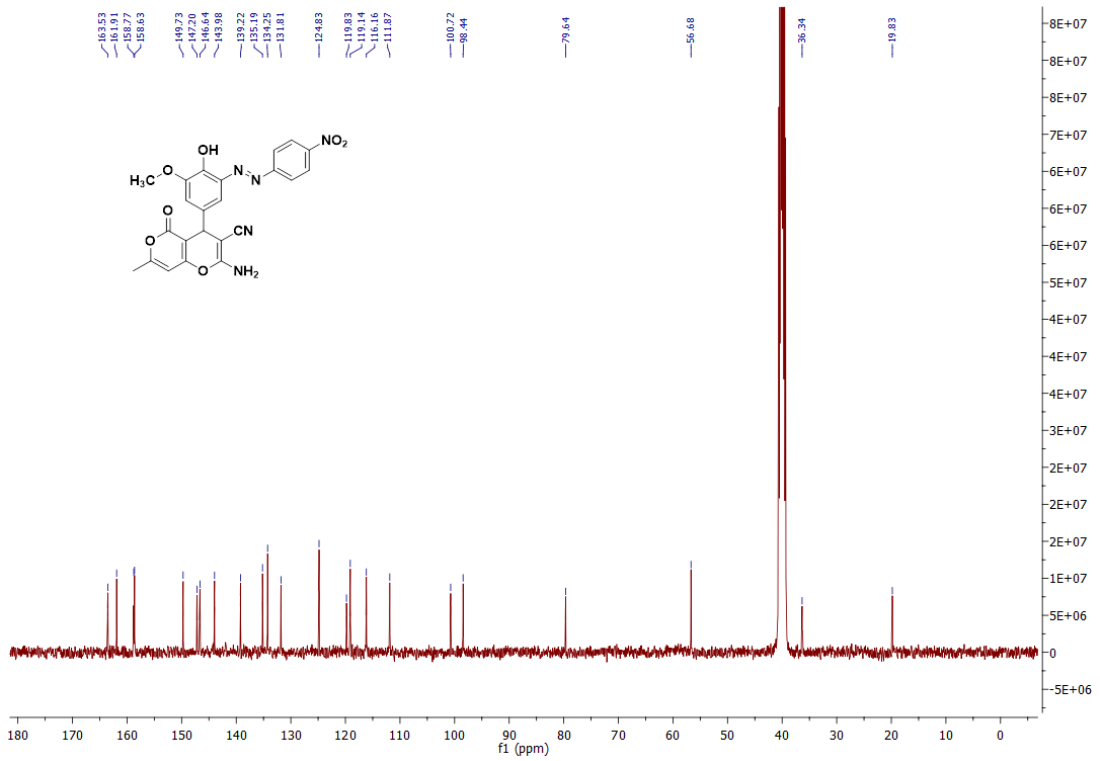


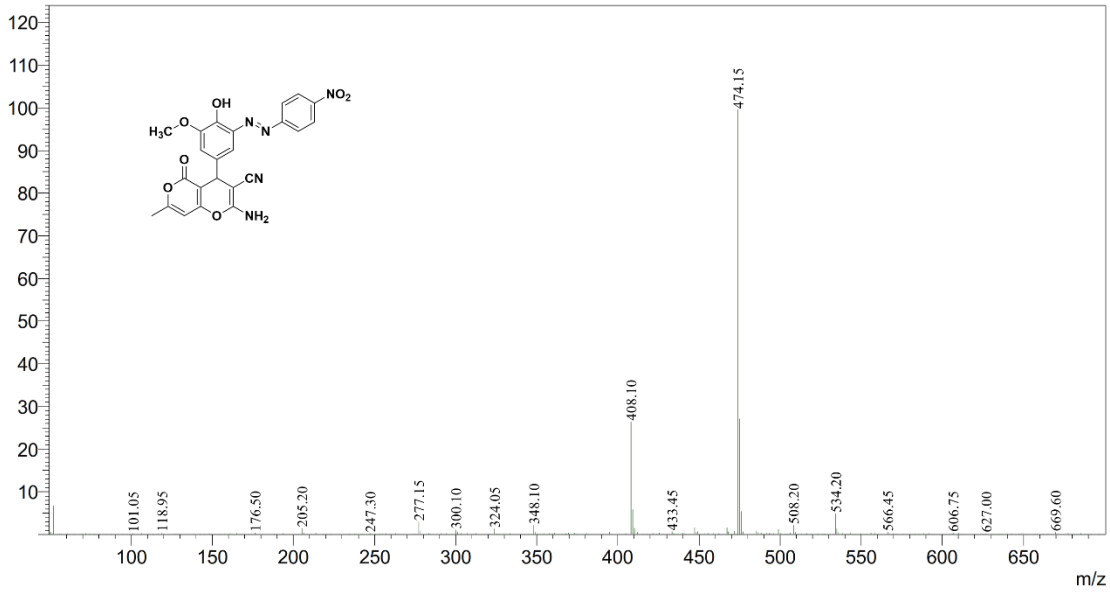
IR spectra of compound **4ae**



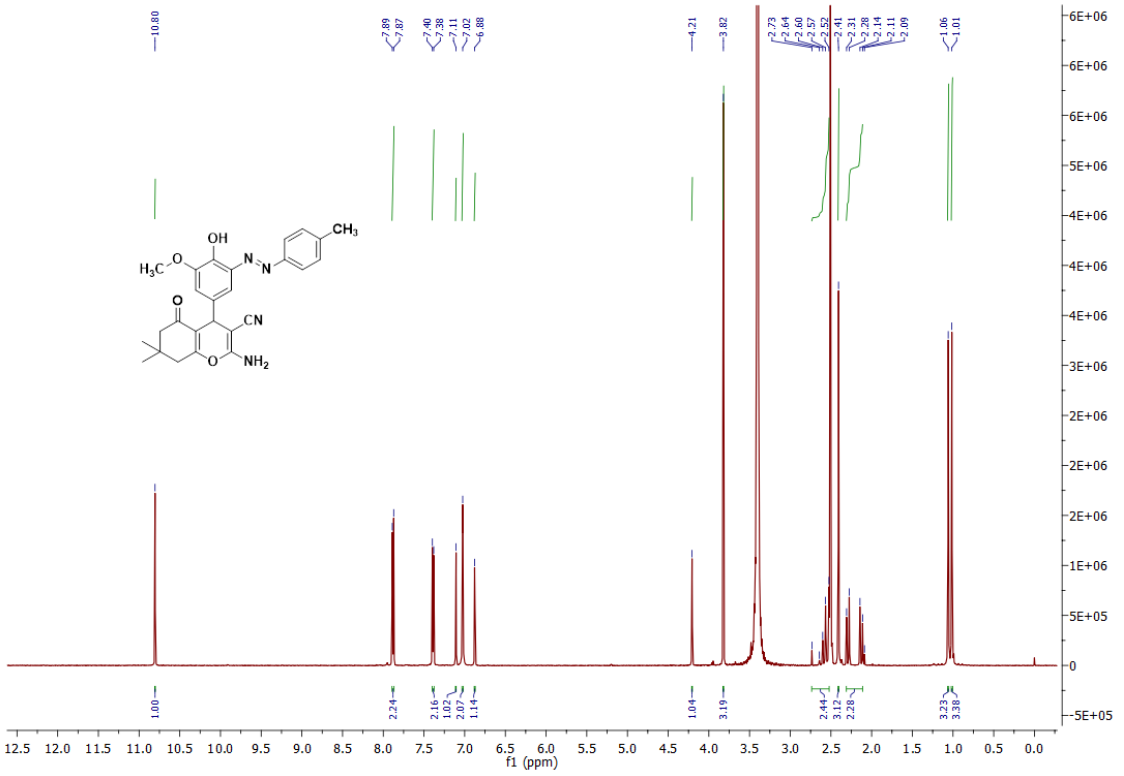
^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4ae**



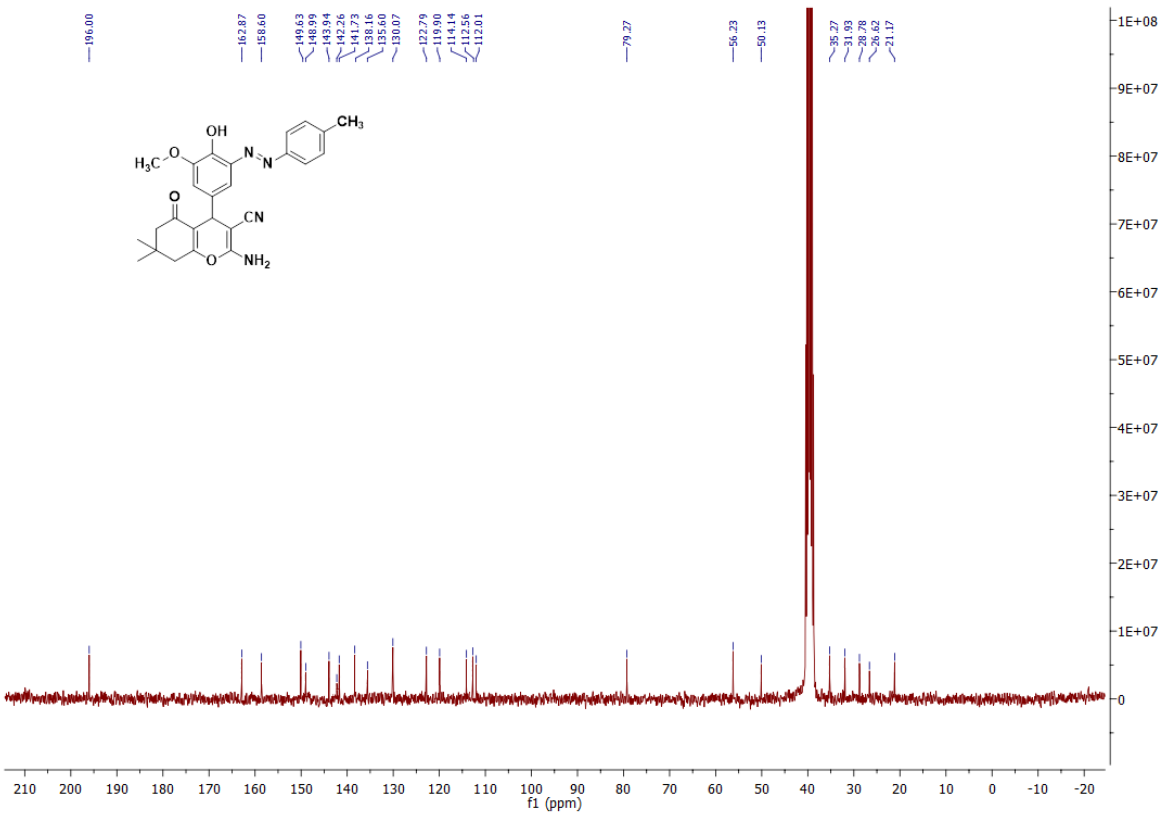
^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4ae**



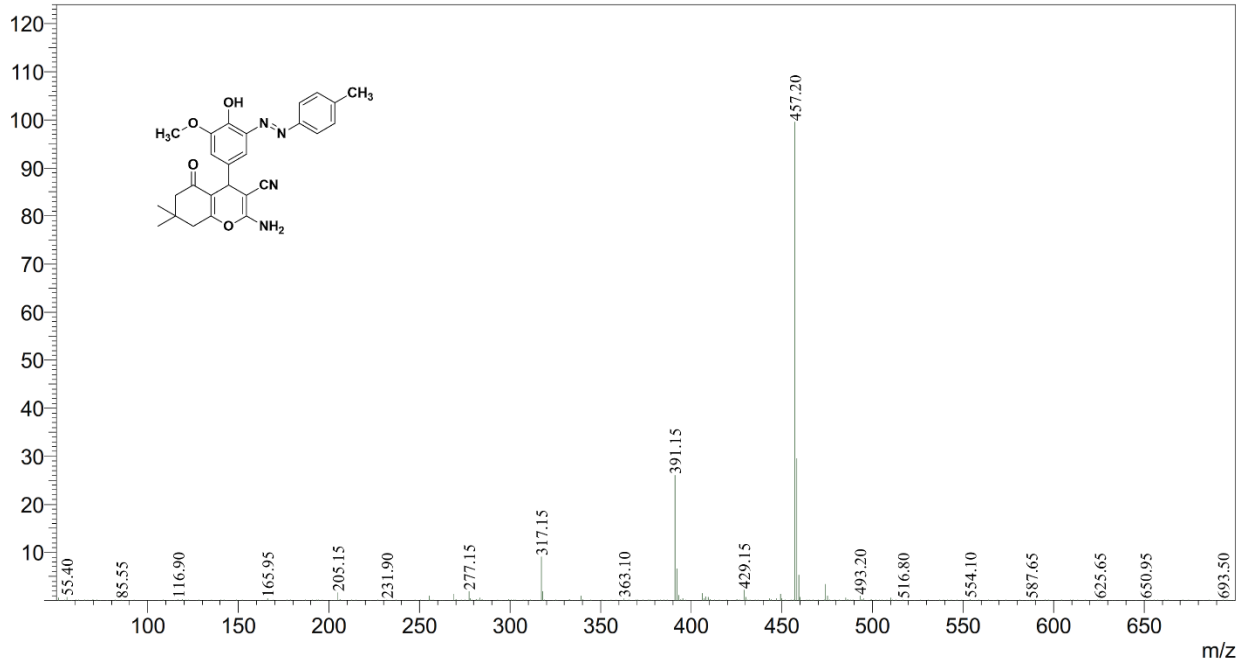
Mass spectrum of compound **4ae**



^{1}H NMR (400 MHz, DMSO-d_6)spectra of compound **4at**



^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4at**



Mass spectrum of compound **4at**

CHAPTER-III (SECTION-A)

ECO-FRIENDLY MULTICOMPONENT SYNTHESIS OF NOVEL DIHYDROPYRIDINE DERIVATIVES

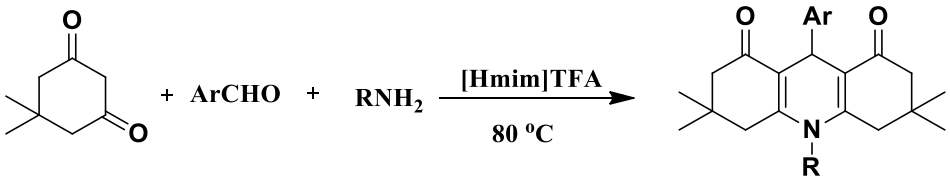
Eco-friendly multicomponent synthesis of novel dihydropyridine derivatives.

3a.1. Introduction

1,4-dihydropyridines (1,4DHP's) exhibit a wide range of biological properties,[1] acting as potent antihypertensives, antitumor, bronchodilators, vasodilators, antimutagenic, heptaprotective, geroprotective and antidiabetic agents.[2] Moreover, a number of DHP's act as calcium antagonists[3-5] and they have been introduced for the treatment of congestive heart failure. In addition to this 1,4-DHPs exhibit several other medicinal applications like platelet anti-aggregator,[6] neuroprotectant[7] activities as cerebral antiischemic agents in the treatment of Alzheimer's disease[8] and as a chemosensitizer in tumor therapy.[9]

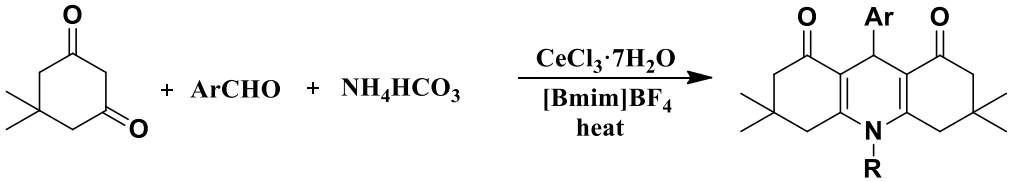
3a.2. Earlier synthetic strategies for dihydropyridines using ionic liquids

Minoo dabiri *et al.*[10] reported the synthesis of dihydropyridines *via* a three-component reaction involving 5,5-dimethyl-1,3-cyclohexanedione, aromatic aldehyde and primary amine in presence of [Hmim]TFA at 80 °C with good yields (*Scheme 3a.2.1*).



Scheme 3a.2.1

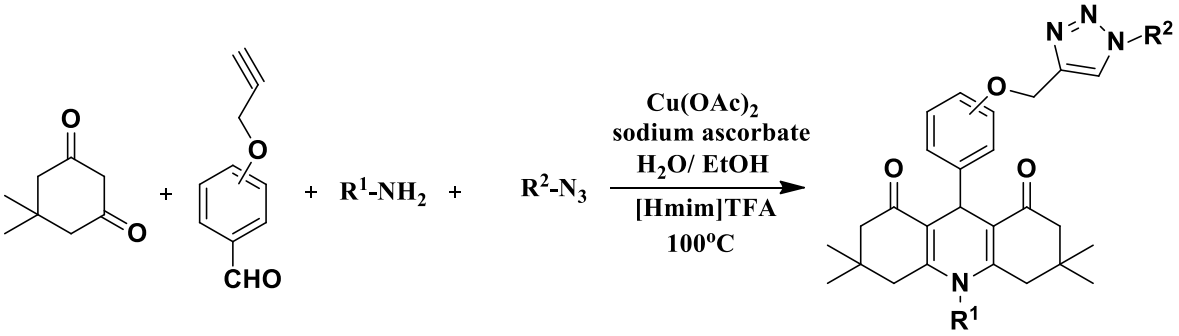
Xuesen Fan *et al.*[11] reported the synthesis of dihydropyridines from 5,5-dimethyl1,3-cyclohexandione, aromatic aldehyde and ammonium bicarbonate by adding a catalytic amount of cerium(III) chloride heptahydrate by using the ionic liquid, 1-butyl-3-methyl-imidazolium tetrafluoroborate ([Bmim]BF_4) as solvent (*Scheme 3a.2.2*).



Scheme 3a.2.2

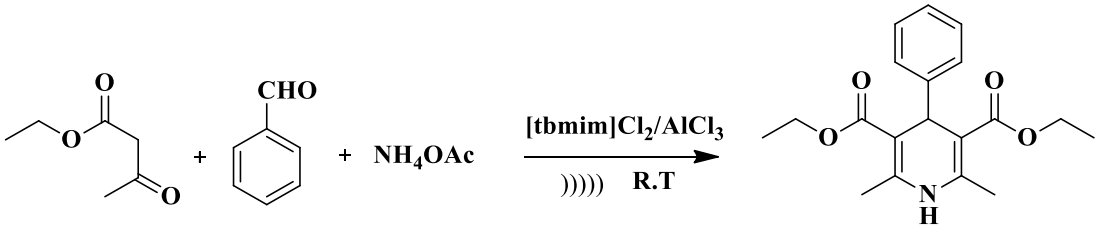
Minoo Dabiri *et al.*[12] designed the synthesis of dihydropyridine derivatives starting from dimedone, aromatic propargylated aldehyde, azide and aniline derivative or ammonium acetate

in the presence of $Cu(OAc)_2$, sodium ascorbate and 1-methylimidazolium triflouroacetate ([Hmim]TFA) with good yield (*Scheme 3a.2.3*).



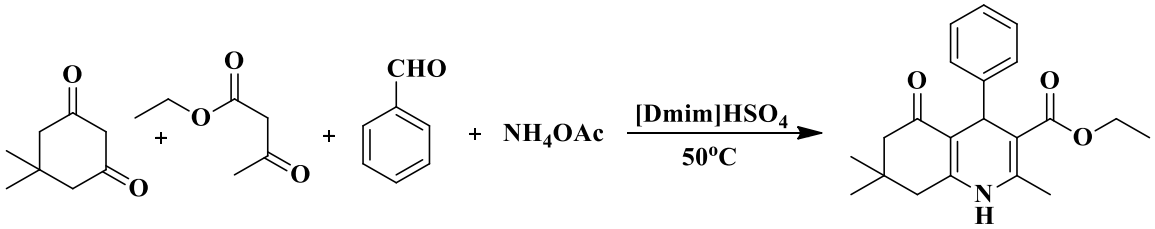
Scheme 3a.2.3

B. Palakshi Reddy *et al.*[13] described the synthesis of dihydropyridine derivatives through one-pot multicomponent reaction involving ethylacetoacetate, benzaldehyde and ammonium acetate catalyzed by $[tbmim]Cl_2/AlCl_3$ (*Scheme 3a.2.4*).



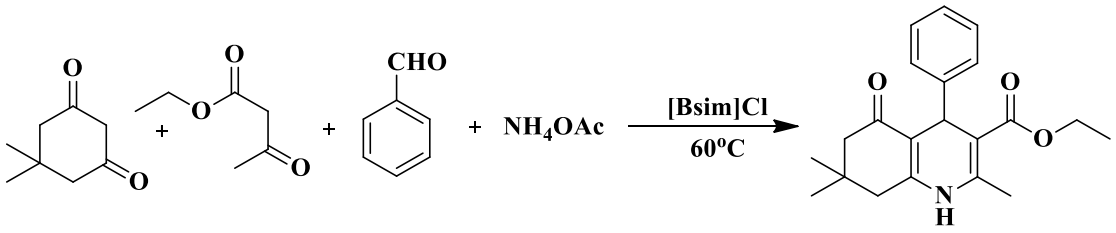
Scheme 3a.2.4

Abdolkarim Zare *et al.*[14] reported the synthesis of dihydropyridine derivatives from dimedone, ethylacetoacetate, benzaldehyde and ammonium acetate in the presence of $[Dmim]HSO_4$ under solvent-free conditions at 50°C (*Scheme 3a.2.5*).



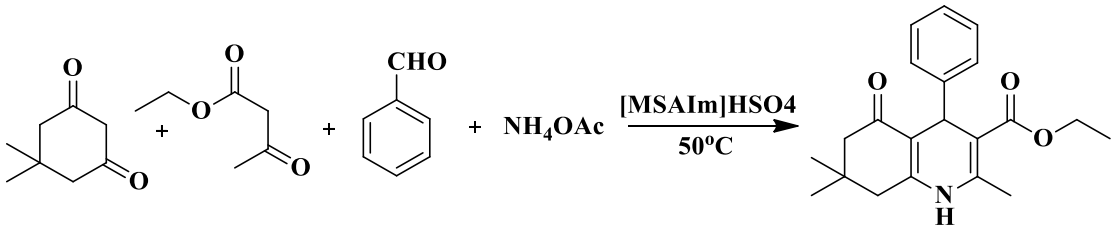
Scheme 3a.2.5

Mahdi Ghorbani *et al.*[15] developed a concise and efficient one-pot process from easily available dimedone, ethylacetoacetate, benzaldehyde and ammonium acetate for the synthesis of dihydropyridine derivatives in the presence of 1-butyl-3-sulfonic acid imidazolium chloride, [Bsim]Cl (*Scheme 3a.2.6*).



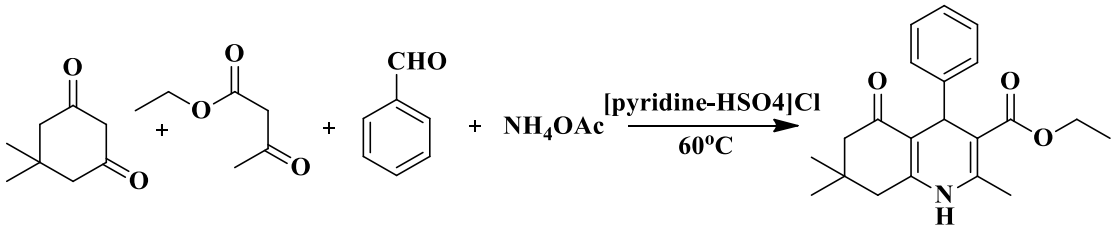
Scheme 3a.2.6

N. G. Khaligh *et al.*[16] reported the synthesis of dihydropyridine derivatives from dimedone, ethylacetoacetate, benzaldehyde and ammonium acetate in the presence of 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate [MSAIm]HSO_4 (*Scheme 3a.2.7*).



Scheme 3a.2.7

A. Khazaei *et al.*[17] developed a convenient method for the synthesis of dihydropyridines with dimedone, ethylacetoacetate, benzaldehyde and ammonium acetate in the presence of sulfonic acid functionalized pyridinium chloride (*Scheme 3a.2.8*).



Scheme 3a.2.8

3a.3. present work

As there is lot of focus on diversity, speed and efficiency, particularly in the drug discovery process, multi-component reactions (MCRs) have become very powerful tools in organic and medicinal chemistry. MCR in which three or more reactants are combined in single chemical operation, is one of the perfect solutions for sustainable manufacture.

Ionic liquids (ILs) have attracted considerable interest in the context of sustainable green synthesis during recent years, because they can also act as efficient media for organic syntheses. ILs possesses various attractive physicochemical properties such as non-volatility, low vapor

pressure, non-explosive, recyclable, easily operable and thermally stable over a wide range of temperatures. ILs can be considered as alternative green solvents for volatile organic solvents by virtue of their unique ionic character and structural organization. There are several reports about the applications of ionic liquids in organic reactions such as Beckmann rearrangement, Biginelli reaction, Diels-Alder reaction, Friedel-Crafts reaction, Pechmann condensation and Heck reaction.

Results and discussions

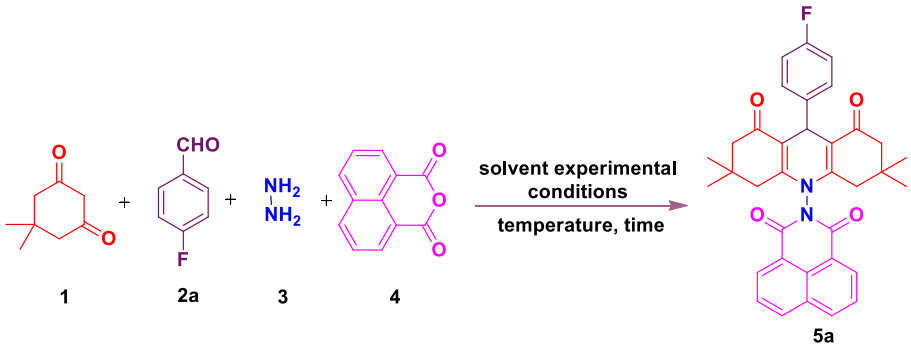
An environmentally benign protocol was used for the synthesis of naphthalimide based dihydropyridine derivatives *via* multicomponent process from the reaction of dimedone (**1**, 2 mmol), aromatic aldehydes (**2a-j**, 1 mmol), hydrazine hydrate (**3**, 1 mmol) and 1,8-naphthanoic anhydride (**4**, 1 mmol) in [bmim]HSO_4 (which act as eco-friendly green medium).

To avoid the drawbacks such as toxicity and volatility which exist in various organic solvents, the ionic liquid was employed in the multicomponent reaction as a green solvent medium. Firstly, a trial reaction was carried out using a multicomponent approach with dimedone (**1**), 4-fluorobenzaldehyde (**2a**), hydrazine hydrate (**3**) and 1,8-naphthanoic anhydride (**4**) as a simple model reaction in order to investigate the probability of the approach and to optimize the reaction conditions. However, the effects of reaction temperature and solvents were assessed from this model reaction, and the results are summarized in Table 3a.3.1.

During the optimization of reaction conditions, it was observed that the absence of solvent did not give the required products even after 24 hours under neat conditions. When the solvents such as methanol, ethanol, acetonitrile, acetone and acetic acid were used, their effect was only moderate (Table 3a.3.1, entry 2-6). But, when typical ionic liquids such as [bmim]Br, [bmim]PF_6, [bmim]BF_4 and [bmim]HSO_4 were used, it was observed that shorter reaction times and higher yields were obtained when compared to those of conventional solvents. Ionic liquid [bmim]HSO_4 proved to be considerably superior to the analogous bromide, hexafluorophosphate and tertafluoroborate ionic liquids for this reaction (Table 3a.3.1, entry 7-9). The yield of product **5a** was improved and the reaction time was reduced as the temperature was enhanced from room temperature to 60 ºC. No further improvement in the product yield was observed, when temperature was increased to 80 ºC (Table 3a.3.1, entry 10-13). Therefore, 60 ºC was chosen as the optimum reaction temperature for all these reactions.

In order to specify the scope of reaction, we have investigated the progress of the reaction under different conditions for dimedone (**1**), aromatic aldehydes (**2a-j**), hydrazine hydrate (**3**) and 1,8-naphthanoic anhydride (**4**). The naphthalimide based dihydropyridine derivatives (**5a-j)** were obtained in decent yields at 60°C in [bmim]HSO_4. The results are summarized in Table 3a.3.2. The protocol was effective with aromatic aldehydes having both electron-donating (-OMe) and electron-withdrawing (-F, -Cl, -Br) groups to produce the corresponding 10-(1.3-dioxo-1*H*-benzo[*de*] isoquinoline-2(3*H*)-yl)-9-aryl-hexahydroacridine-1,8-dione derivatives in good yields. The electron effects did not have any significant impact on the reaction rate.

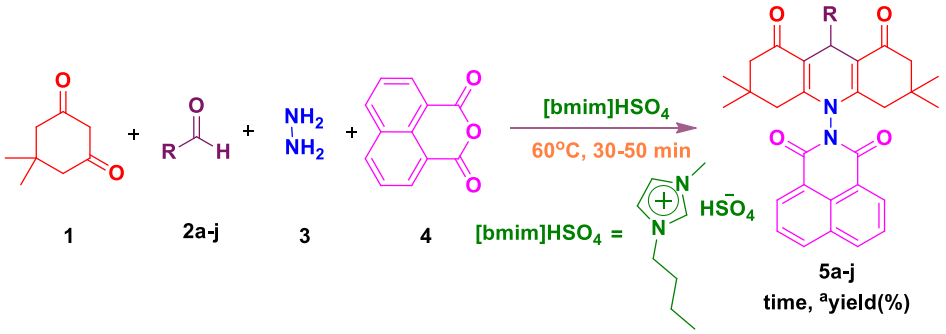
Table 3a.3.1: Optimization of reaction conditions for the synthesis of **5a**

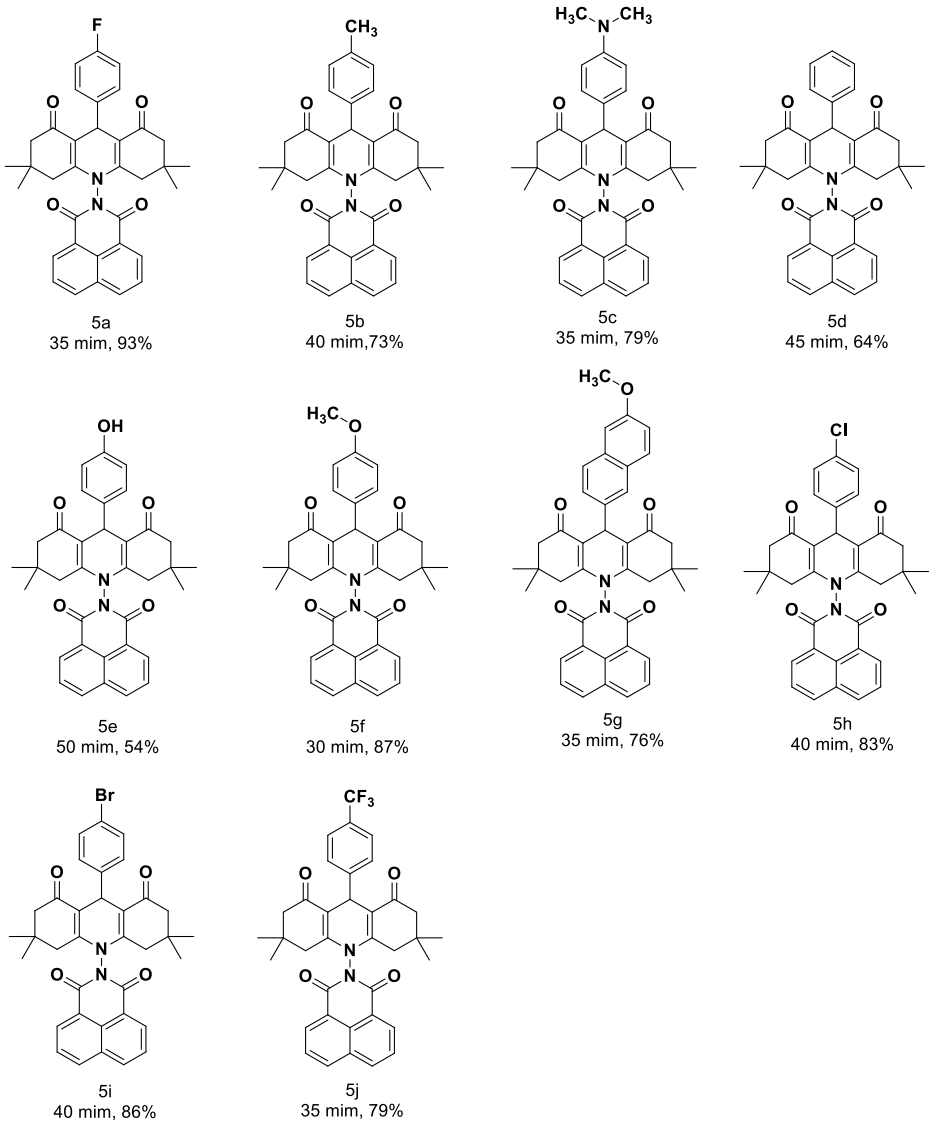


[a]Entries	solvent	Temperature (°C)	Time	[b]Yields (%)
1	neat	60	24 h	NR
2	Methanol	60	12 h	11
3	Ethanol	60	12 h	14
4	Acetonitrile	60	11 h	20
5	Acetone	60	16 h	16
6	Acetic acid	60	20 h	38
7	[bmim]Br	60	2 h	52
8	[bmim]PF_6	60	1.5 h	48
9	[bmim]BF_4	60	2 h	56
10	**[bmim]HSO_4**	**60**	**35 min**	**93**
11	[bmim]HSO_4	rt	1 h	54
12	[bmim]HSO_4	40	1 h	75
13	[bmim]HSO_4	80	35 min	94

[a]Reaction conditions: Dimedone (2 mmol), 4-fluoro benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), 1,8-naphthoic anhydride (1 mmol), solvent (1 mL). [b]Yields of the isolated products.

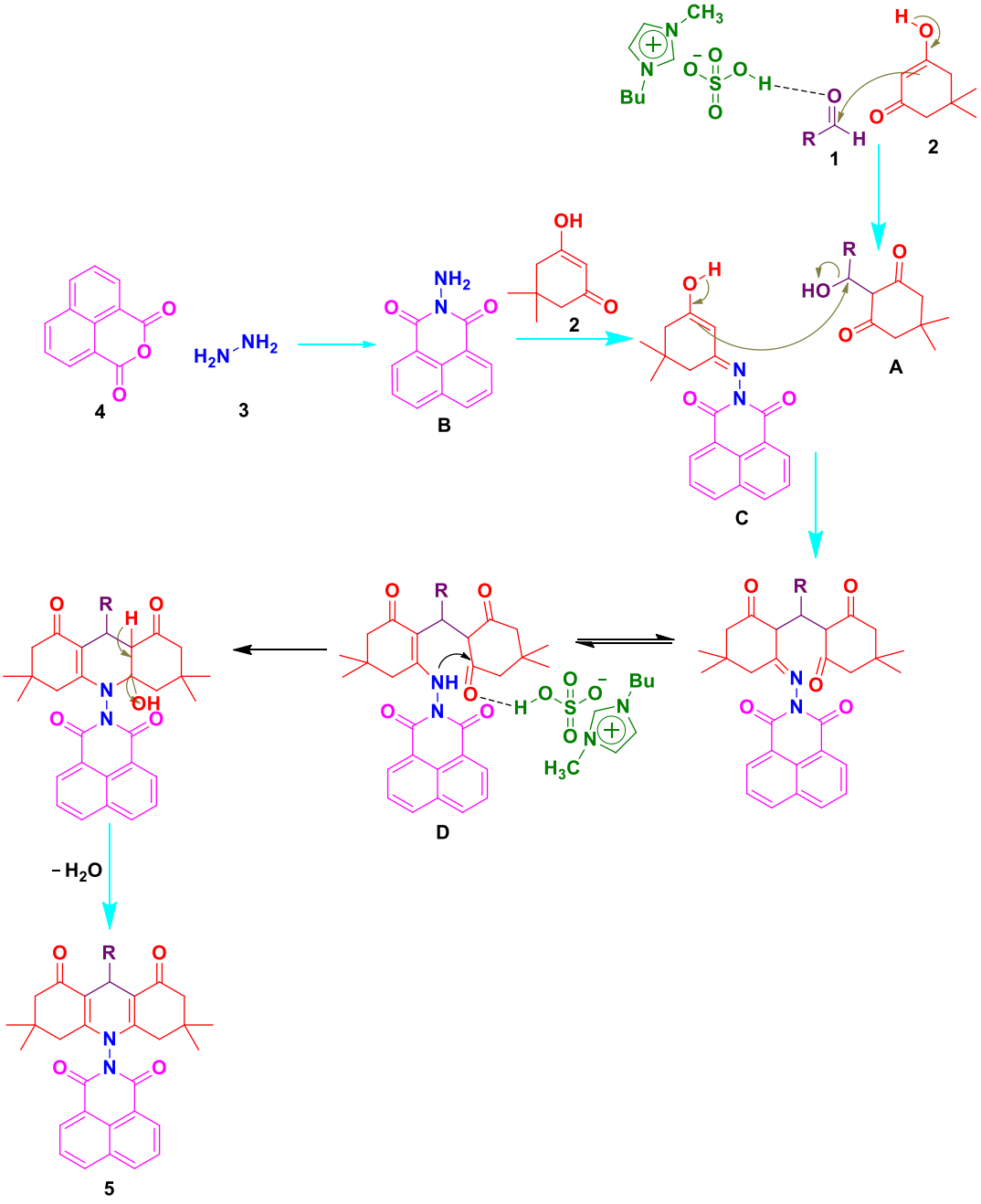
Table 3a.3.2: Synthesis of naphthalimide based dihydropyridine derivatives (**5a-j**)





Reaction conditions: Dimedone (2 mmol), 4-fluoro benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), 1,8-naphthoic anhydride (1 mmol), [bmim]HSO_4 (1 mL). [a]Yields of the isolated products.

Scheme 3a.3.1: Proposed mechanism for the formation of naphthalimide based dihydropyridine derivatives (**5a-j)**



We herein propose a mechanism in Scheme 3a.3.1 for the formation of naphthalimide based dihydropyridine derivatives in the presence of ionic liquid [bmim]HSO_4 which acts as a solvent and also as the catalyst. At first step, a hydrogen bond formation between the hydrogen atom of [bmim]HSO_4 and carbonyl group of aldehyde **2** produces a complex which upon

condensation with dimedone **1** forms a chalcone type intermediate (**A**). The formation of intermediate (**B**) takes place by a condensation between 1,8-naphthanoic anhydride **4** and hydrazine hydrate **3**. The dimedone **1** reacts with intermediate **B** forming another intermediate (**C**). Subsequently a Michael type addition occurs between intermediate **A** and **C** producing intermediate (**D**). Intermediate **D** undergoes intermolecular cyclization to afford the final product **5**. The reaction mixture was poured into ice cold water, the solid product obtained was isolated by filtration and the filtrate containing the ionic liquid [bmim]HSO_4 was extracted with ethyl acetate to remove the non-ionic organic impurities. Ionic liquid was recovered from water under reduced pressure, dried at 60-70 ºC and reused for subsequent reactions for additional four cycles. A slight decrease in its activity in terms of product yields (**fig. 3a.3.1**) was observed when the ionic liquid was used beyond four cycles.

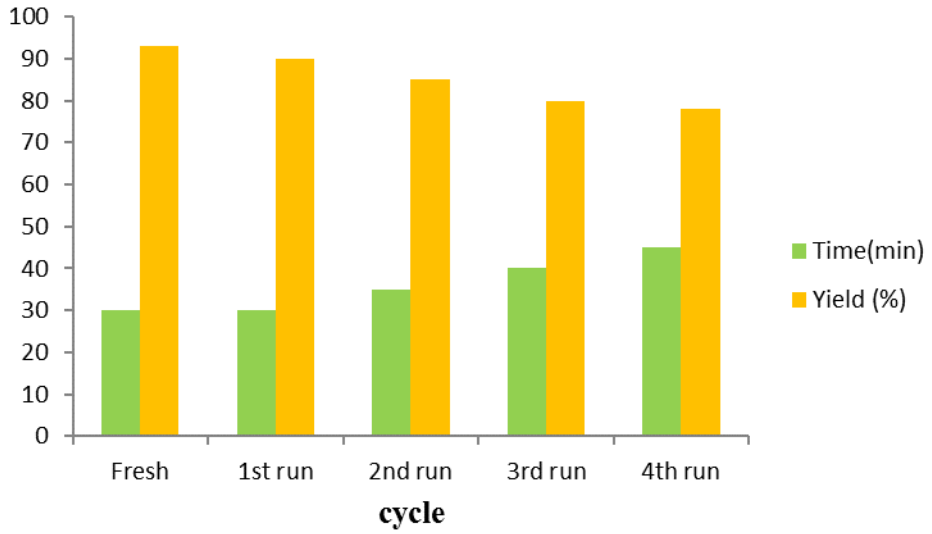


Fig. 3a.3.1: Recycling of the [bmim]HSO_4 ionic liquid used for the synthesis of compound **5a**

EXPERIMENTAL

General information

All the reagents were procured from commercial sources and used without further purification. A Bruker WM-4 (X) spectrophotometer (577 model) was used for recording IR spectra (KBr). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrophotometer at 400 MHz and 100 MHz respectively, in DMSO-d_6 with TMS as an internal standard. The chemical shifts were reported in ppm (δ). Elemental analysis was performed on a Carlo Erba EA 1108 automatic elemental analyzer. Mass spectra (ESI) were

recorded upon on a jeo1 JMSD-300 spectrometer. Compound **5a** was crystallized from acetic acid to yield prismatic crystals.

Spectral discussion

IR

The formation of dihydropyridine derivatives **5a-j** was confirmed by its IR spectra which showed absorption bands at 1700-1704 cm^{-1} and 1675-1678 cm^{-1} due to carbonyl groups respectively.

^{1}H NMR

The formation of dihydropyridine derivatives **5a-j** was confirmed by its ^{1}H NMR which showed a singlet at δ 4.95-5.10 ppm due to dihydropyridine proton. All other aromatic and aliphatic protons were observed at the expected regions.

^{13}C NMR

The formation of dihydropyridine derivatives **5a-j** was confirmed by its ^{13}C NMR which showed a signal at δ 50.01-50.30 ppm due to 3^{o} carbon and all other aromatic and aliphatic carbons

MASS

The mass spectra contained the expected molecular ion signals corresponding to respective molecular weight of synthesized compounds.

The elemental analyses values of synthesized compounds were in good agreement with the theoretical data.

Single Crystal X-ray Diffraction

The single-crystal X-ray diffraction data of the crystals **5a** were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 293(2) K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL.[18] The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.[19] All the aromatic and aliphatic C−H hydrogens were generated by the riding model in idealized geometries. The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3 and X-Seed.[20-22]

The structure of compound **5a** was confirmed by single crystal X-ray diffraction method (**fig. 3a.3.2**, CCDC-1415136). The compound **5a** crystallizes in the centrosymmetric monoclinic P21/c space group with one molecule in the asymmetric unit. The crystal structure analysis reveals that the molecules form a close packed structure with C–H···F and C–H···O hydrogen bonds. Two inversions related molecules combine via C–H···F hydrogen bonds and form a discrete dimer. These dimers are interconnected by C–H···O hydrogen bonds. The overall structure is close packed structure. **Table 3a.3.3** gives the pertinent crystallographic data, and **Table 3a.3.4** gives hydrogen bond parameters.

Table 3a.3.3. Salient crystallographic data and structure refinement parameters of compound **5a.**

	5a
Empirical formula	$C_{35}H_{31}FN_2O_4$
Formula weight	562.62
Crystal system	Monoclinic
Space group	$P2_1/n$
T/K	293(2)
a/Å	12.4943(12)
b/Å	17.1761(16)
c/Å	13.3901(13)
α/°	90
β/°	99.264(2)
γ/ °	90
Z	4
V/Å^3	2836.1(5)
D_{calc}/ g/cm^3	1.318
F(000)	1184
μ/mm^{-1}	0.091
θ/°	2.37 to 27.7
Index ranges	$-16 \le h \le 16$ $-22 \le k \le 21$ $-17 \le l \le 17$
N-total	32325
N-independent	6777
N-observed	5278
Parameters	383
R_1 ($I > 2\sigma(I)$)	0.0508
wR_2 (all data)	0.1408
GOF	1.046
CCDC	1415136

Table 3a.3.4. Geometrical parameters of hydrogen bonds in compound **5a**

D–H···A[a]	D···A (Å)	H···A (Å)	D–H···A (°)	Symmetry code
C(7)–H(7)···O(1)	3.138(2)	2.43	**122**	-1/2+x,1/2-y,-1/2+z
C(30)–H(30)···F(1)	3.423(2)	2.37	**163**	1-x,-y,1-z

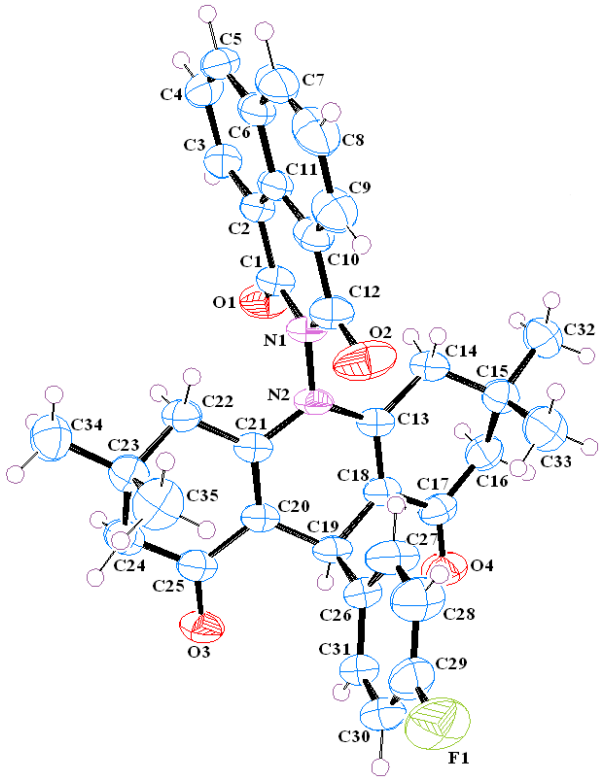


Fig. 3a.3.2. ORTEP representation of compound **5a**. The thermal ellipsoids are drawn at 50% probability level.

General procedure for the synthesis of (1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione derivatives (5a-j)

A mixture of aromatic aldehydes (1 mmol), 1,8-naphthoic anhydride (1 mmol), hydrazine hydrate (1 mmol), dimedone (2 mmol) in [bmim]HSO_4 (1 mL) was heated to 60 ºC. The progress of the reaction was monitored by TLC (eluent-ethyl acetate: n-hexane (2:8)), after completion of the reaction, reaction mixture was allowed to cool at room temperature and 10 mL of water was added to the mixture. The resultant precipitate was filtered and purified by column chromatography using silica gel [ethyl acetate: n-hexane (1:9)] to afford the pure compounds (**5a-j)**.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5a).

Pale yellow solid; m.p. 270-272 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2966, 1702, 1677, 1665, 1647; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.97–2.33 (m, 8H, CH_2), 4.95 (s, 1H), 7.07 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.61 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.66-8.76 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.05, 26.96, 28.68, 32.17, 50.17, 111.88, 118.16, 123.08, 126.27, 127.94, 129.47, 130.58, 139.27, 141.69, 146.47, 148.41, 148.77, 165.76, 194.68; **ESI-MS** (*m/z*): 563 (M+1); Anal. Calcd for $C_{35}H_{31}FN_2O_4$: C, 74.72; H, 5.55; N, 4.98; Found: C, 74.52; H, 5.44; N, 4.82.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5b).

White solid; m.p. 261-262 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2969, 1701, 1675, 1661, 1649; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.95 (s, 6H, CH_3), 1.01 (s, 6H, CH_3), 2.00–2.17 (m, 8H, CH_2), 2.38 (s, 3H, CH_3), 4.95 (s, 1H), 7.07 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.61 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.66-8.75 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.04, 26.97, 28.63, 32.13, 37.19, 50.13, 112.01, 118.15, 123.04, 126.26, 127.94, 129.46, 131.18, 139.12, 141.53, 146.47, 148.69, 165.79, 194.55; **ESI-MS** (*m/z*): 559 (M+1); Anal. Calcd for $C_{36}H_{34}N_2O_4$: C, 77.40; H, 6.13; N, 5.01; Found: C, 77.22; H, 6.14; N, 5.33.

9-(4-(dimethylamino)phenyl)-10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5c).

Pale red solid; m.p. 264-266 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2968, 1702, 1678, 1661, 1648; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.97–2.33 (m, 8H, CH_2), 3.19 (s, 6H, -N(CH_3)$_2$), 5.03 (s, 1H), 7.06 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.61 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.66-8.75 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.08, 26.65, 28.66, 32.21, 44.31, 50.16, 111.11, 118.21, 123.05, 126.23, 127.91, 129.47, 131.15, 139.14, 141.54, 146.43, 148.59, 148.75, 165.81, 195.05; **ESI-MS** (*m/z*): 588 (M+1); Anal. Calcd for $C_{37}H_{37}N_3O_4$: C, 75.65; H, 6.35; N, 7.15; Found: C, 75.96; H, 6.24; N, 7.36.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5d).

yellow solid; m.p. 271-273 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2959, 1701, 1676, 1663, 1647; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.98 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 1.97–2.33 (m, 8H, CH_2), 5.01 (s,

1H), 7.45 (t, *J* = 8.8 Hz, 2H, ArH), 7.92 (t, *J* = 7.2 Hz, 2H, ArH) 8.03–8.07 (m, 3H, ArH), 8.73-8.77 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.07, 26.93, 28.61, 32.15, 50.10, 111.97, 118.13, 123.05, 126.28, 127.91, 129.43, 130.99, 139.13, 141.55, 146.46, 148.71, 165.82, 194.63; **ESI-MS** (*m/z*): 545 (M+1); Anal. Calcd for $C_{35}H_{32}N_2O_4$: C, 77.18; H, 5.92; N, 5.14; Found: C, 77.32; H, 5.88; N, 5.31.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5e).

White solid; m.p. 257-259 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 3302, 2964, 1700, 1678, 1661, 1648; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.98–2.33 (m, 8H, CH_2), 4.03 (s, 1H, -OH), 4.96 (s, 1H), 7.07 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.61 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.66-8.76 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.05, 26.96, 28.68, 32.17, 50.30, 112.95, 118.84, 126.78, 126.98, 127.58, 128.99, 129.16, 129.48, 139.79, 140.51, 149.65, 164.10, 194.51; **ESI-MS** (*m/z*): 561 (M+1); Anal. Calcd for $C_{35}H_{32}N_2O_5$: C, 74.98; H, 5.75; N, 5.00; Found: C, 74.84; H, 5.72; N, 5.29.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5f).

Pale yellow solid; m.p. 268-270 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2963, 1701, 1678, 1660, 1645; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.98–2.33 (m, 8H, CH_2), 3.47 (s, 3H, -OCH_3), 4.96 (s, 1H), 7.06 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.61 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.66-8.76 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.05, 26.96, 28.68, 32.17, 50.17, 54.95, 112.08, 117.74, 125.62, 127.18, 128.23, 128.53, 129.25, 129.42, 131.90, 136.06, 148.53, 150.60, 164.99, 194.35; **ESI-MS** (*m/z*): 575 (M+1); Anal. Calcd for $C_{36}H_{34}N_2O_5$: C, 75.24; H, 5.96; N, 4.87; Found: C, 75.18; H, 5.94; N, 4.62.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-9-(6-methoxynaphthalen-2-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5g).

White solid; m.p. 284-286 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2969, 1704, 1678, 1665, 1642; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.98 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 2.09–2.25 (m, 8H, CH_2), 3.71 (s, 3H, -OCH_3), 5.10 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.91–8.03 (m, 4H, ArH), 8.22 (d, *J* = 8.0, 1H, ArH), 8.33 (s, 1H, ArH), 8.52-8.67 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 25.11, 28.86, 30.37, 34.83, 50.01, 54.91, 109.13, 116.26, 117.77, 119.16, 120.62, 122.45, 122.69, 126.12, 127.59, 128.35, 128.83, 129.45, 139.35, 141.24, 147.54,

148.79, 165.09, 195.76; **ESI-MS** (*m/z*): 625 (M+1); Anal. Calcd for $C_{40}H_{36}N_2O_5$: C, 76.90; H, 5.81; N, 4.48; Found: C, 76.76; H, 5.76; N, 4.57.

9-(4-chlorophenyl)-10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5h).

Pale yellow solid; m.p. 251-253 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2967, 1702, 1677, 1661, 1645; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.71 (s, 6H, CH_3), 0.86 (s, 6H, CH_3), 1.97–2.32 (m, 8H, CH_2), 5.01 (s, 1H), 7.06 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.60 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.67-8.77 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.09, 26.91, 28.59, 32.19, 50.09, 111.93, 118.17, 123.07, 126.30, 127.96, 129.45, 131.05, 139.15, 141.51, 146.47, 148.78, 165.81, 194.59; **ESI-MS** (*m/z*): 579 (M+1); Anal. Calcd for $C_{35}H_{31}ClN_2O_4$: C, 72.59; H, 5.40; N, 4.84; Found: C, 72.36; H, 5.48; N, 4.91.

9-(4-bromophenyl)-10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5i).

yellow solid; m.p. 274-276 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2968, 1701, 1675, 1660, 1641; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.08 (s, 6H, CH_3), 1.11 (s, 6H, CH_3), 2.09–2.29 (m, 8H, CH_2), 5.03 (s, 1H), 7.16 (t, *J* = 8.8 Hz, 2H, ArH), 7.50-7.55 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.65-8.69 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.11, 26.89, 28.55, 32.18, 50.11, 111.91, 118.16, 123.05, 126.33, 127.94, 129.47, 131.07, 139.14, 141.49, 146.46, 148.78, 165.83, 194.60; **ESI-MS** (*m/z*): 624 (M+2); Anal. Calcd for $C_{35}H_{31}BrN_2O_4$: C, 67.42; H, 5.01; N, 4.49; Found: C, 67.68; H, 5.15; N, 4.63.

10-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)-3,3,6,6-tetramethyl-9-(4-(trifluoromethyl)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5j).

Pale yellow solid; m.p. 304-306 ºC; **IR** (KBr, cm^{-1}) ν_{max}: 2977, 1703, 1677, 1660, 1646; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.97–2.33 (m, 8H, CH_2), 4.95 (s, 1H), 7.07 (t, *J* = 8.8 Hz, 2H, ArH), 7.57-7.61 (m, 2H, ArH), 7.99-8.04 (m, 2H, ArH), 8.66-8.76 (m, 4H, ArH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 24.10, 26.89, 28.60, 32.20, 50.08, 111.89, 118.12, 123.10, 126.28, 128.01, 129.42, 131.06, 139.14, 141.55, 146.50, 148.80, 165.79, 194.61; **ESI-MS** (*m/z*): 613 (M+1); Anal. Calcd for $C_{36}H_{31}F_3N_2O_4$: C, 70.58; H, 5.10; N, 4.57; Found: C, 70.28; H, 5.01; N, 4.81.

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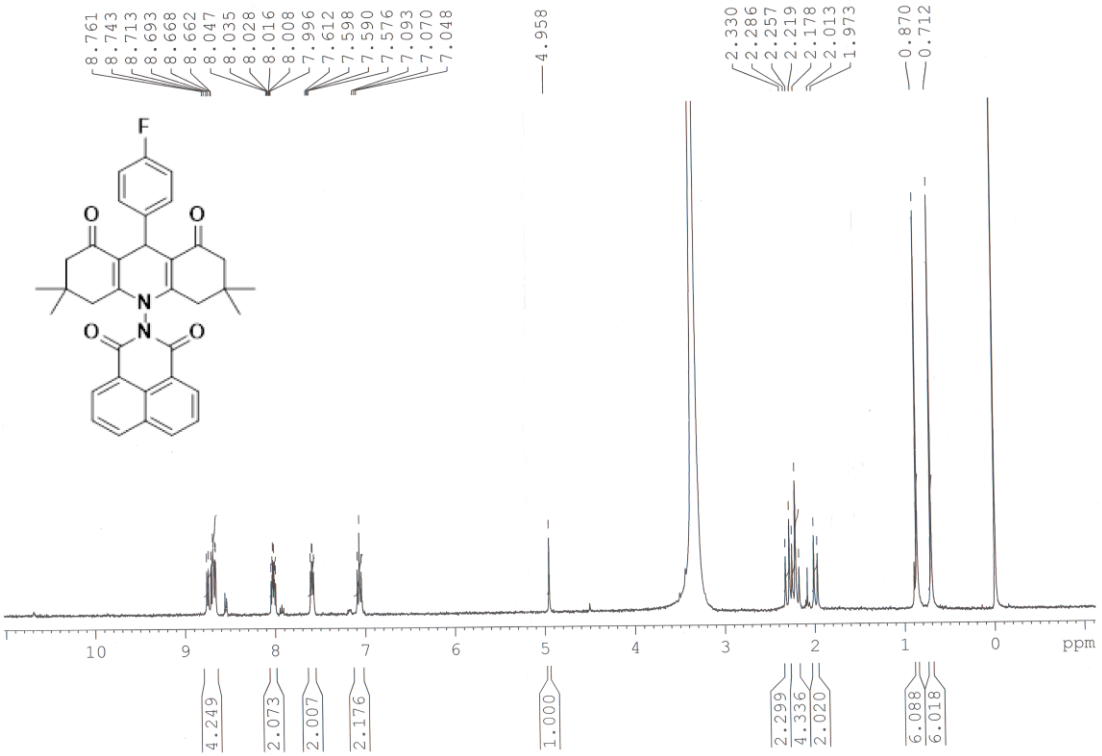
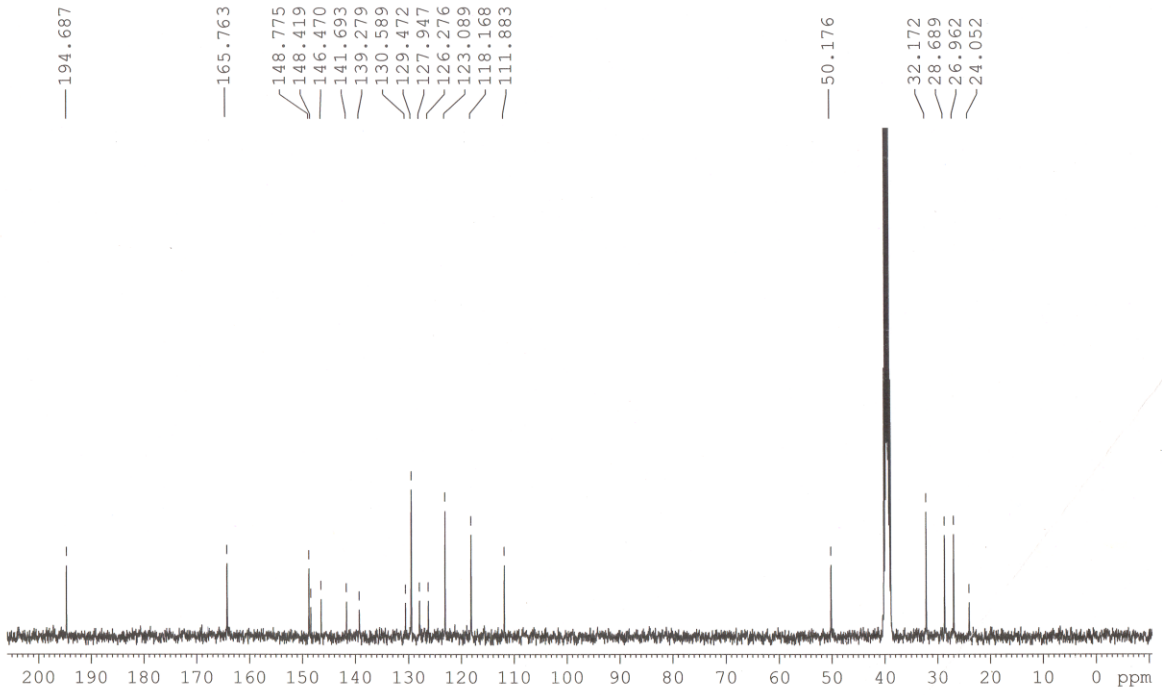
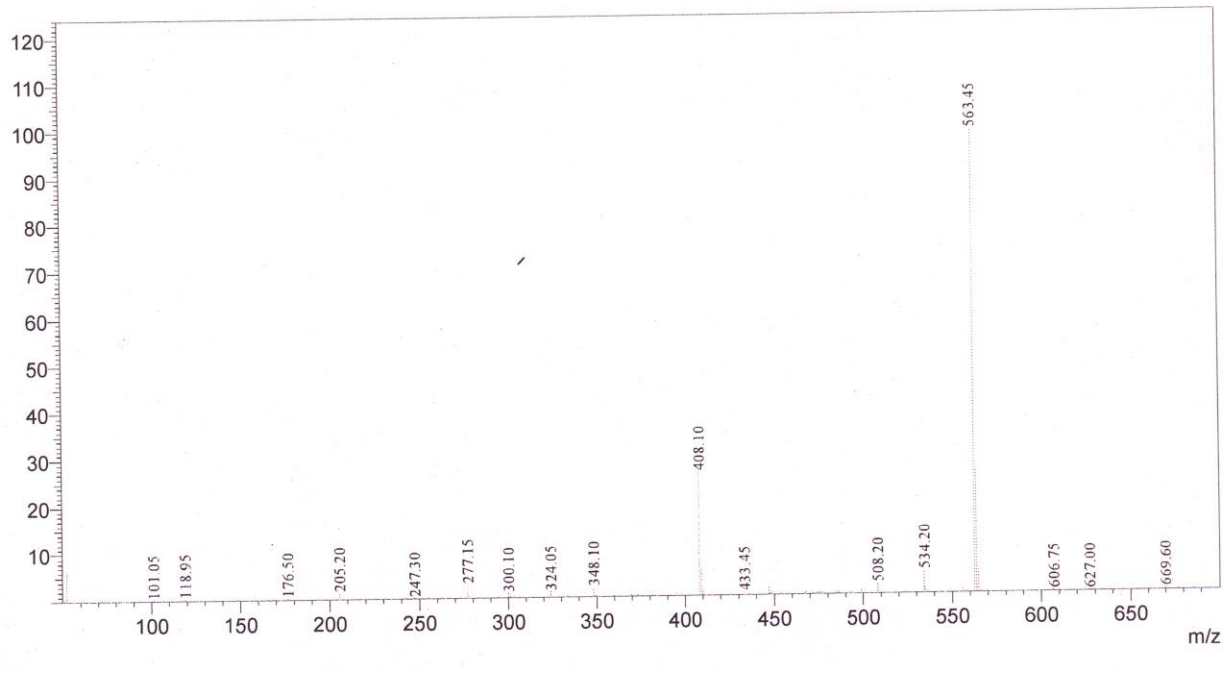


^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **5a**



^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **5a**



Mass spectrum of compound **5a**

CHAPTER-III (SECTION-B)

SYNTHESIS OF NEW DIHYDROPYRIDINE DERIVATIVES USING Eu_2O_3 MODIFIED CeO_2 NANOPARTICLES

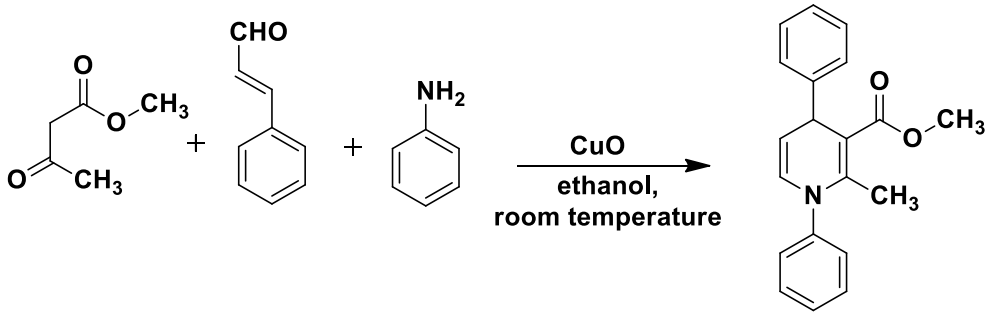
Synthesis of new dihydropyridine derivatives using Eu_2O_3 modified CeO_2 nanoparticles

3b.1. Introduction

Dihydropyridines represent a significant class of biologically active compounds, which have important attention from many of the medicinal and pharmaceutical chemists, because of their antibacterial,[1] myorelaxant,[2] antimalarial[3] and anticancer activities.[4]

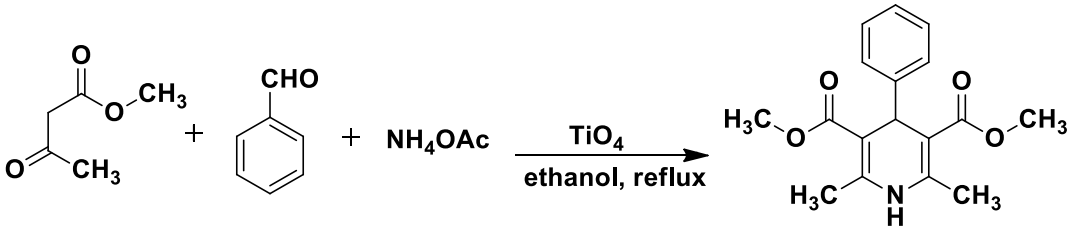
3b.2. Earlier synthetic strategies for dihydropyridine derivatives from nano metal oxides

M. Lakshmi Kantam *et al.*[5] reported the synthesis of dihydropyridines through three component reaction of aromatic amines, β-ketoesters and cinnamaldehyde using copper oxide nanoparticles as a catalyst in excellent yields (*Scheme 3b.2.1*).



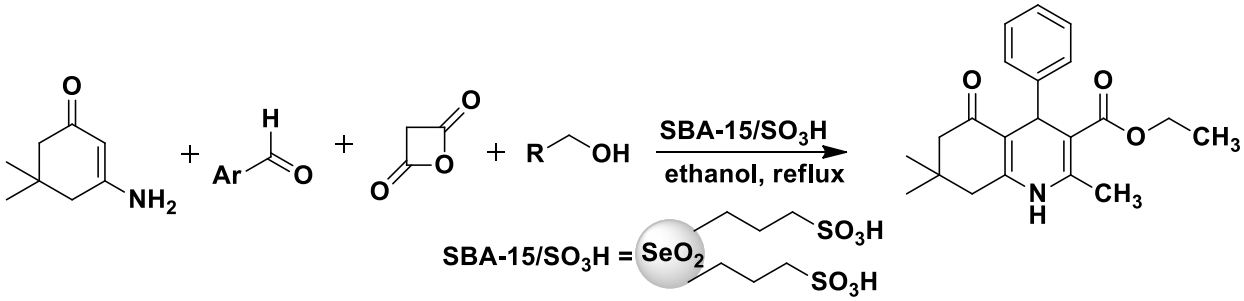
Scheme 3b.2.1

Mahmood Tajbakhsh *et al.*[6] described an efficient method for the synthesis of dihydropyridine derivatives *via* one-pot multicomponent reaction of aromatic aldehydes, ethyl acetoacetate and ammonium acetate in the presence of titanium oxide nanoparticles (*Scheme 3b.2.2*).



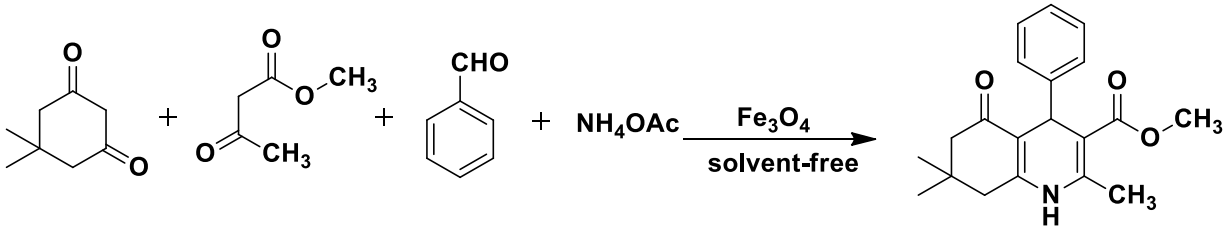
Scheme 3b.2.2

Sadegh Rostamnia *et al.* [7] have used SBA-15 sulfonic acid as a reusable catalyst for the synthesis of dihydropyridine derivatives by the reaction of diketene, alcohol, enamine, and aldehydes in ethanol under reflux condition (*Scheme 3b.2.3*).



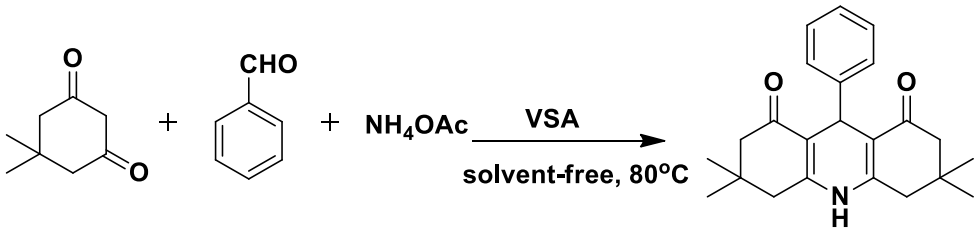
Scheme 3b.2.3

Masoud Nasr-Esfahani *et al.* [8] described an efficient method for the synthesis of dihydropyridine derivatives *via* multicomponent condensation of aldehyde, dicarbonyl compound and ammonium acetate catalyzed by Fe_3O_4 nanoparticles (*Scheme 3b.2.4*).



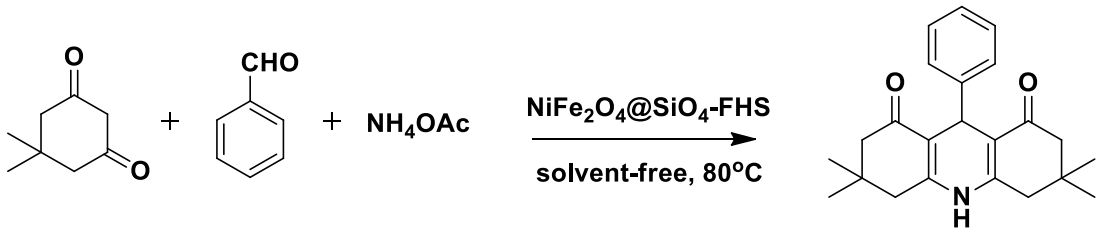
Scheme 3b.2.4

Masoud Nasr-Esfahani *et al.*[9] reported efficient method for the synthesis of dihydropyridines *via* three-component condensation of aromatic aldehyde, dimedone and ammonium acetate catalyzed by nanorod vanadate sulfuric acid under solvent-free condition (*Scheme 3b.2.5*).



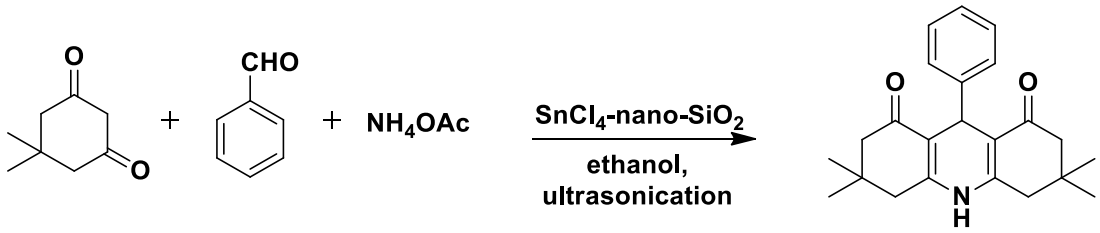
Scheme 3b.2.5

Amir Khojastehnezhad *et al.*[10] synthesized dihydropyridine derivatives using Ferric hydrogen sulfate supported on silica-coated nickel ferrite nanoparticles as efficient catalyst *via* one-pot three component condensation of aromatic aldehyde, dimedone and ammonium acetate in good yield (*Scheme 3a.2.6*).



Scheme 3b.2.6

Abdolhamid Bamoniri *et al.*[11] have synthesized dihydropyridine derivatives *via* one-pot, three component condensation of aromatic aldehyde, dimedone and ammonium acetate using nano-silica supported tin tetrachloride as a catalyst under ultrasonication (*Scheme 3b.2.7*).



Scheme 3b.2.7

3b.3. present work

Multicomponent reactions (MCRs) have been usually employed to quickly launch structurally varied and/or complex compounds from a number of simple starting materials in a one-pot approach.[12] These reactions are useful for a broad range of functional groups and provide an opportunity for performing a diversity of post-multicomponent reaction transformations, such as re-functionalization and cyclization.[13] MCRs in aqueous media are highly advantageous since, water is environmental friendly and it has exceptional physical and chemical properties which may lead to certain reactivity and selectivity usually unachievable by other organic solvents.[14]

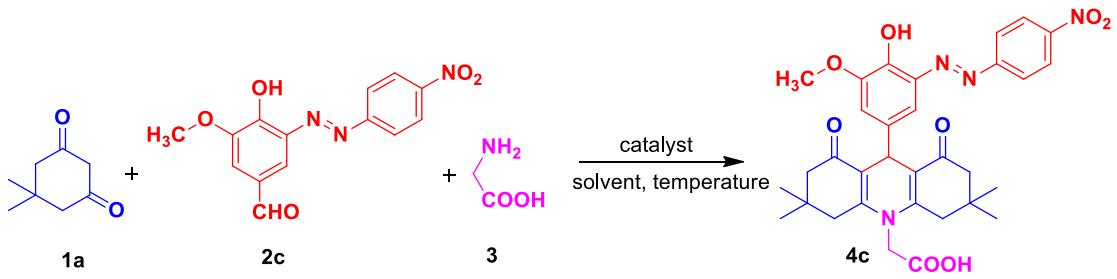
Nano metal oxide catalysis is a green chemistry approach to chemical conversions, because of its mild reaction conditions, high selectivity, formation of few by-products and low energy requirements. There is a need to search for promising new nano catalysts to reach eco-friendly reaction condition, to avoid the use of hazardous Lewis acids/bases to eliminate other harsh reaction conditions and to produce the required compounds in higher yields.[15]

Results and discussions

Encouraged by the importance of dihydropyridine derivatives, we developed a multicomponent nano-catalytic green chemical approach for the synthesis of novel dihydropyridine derivatives.

A green multicomponent synthesis of (4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-dihydropyridine-acetic acid derivatives was achieved by a reaction among 1,3-dicarbonyl compounds (**1a-b**, 2 mmol**)**, 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes (**2a-f,** 1 mmol) and glycine (**3,** 1 mmol**)** in the presence of CeO_2–Eu_2O_3 nanoparticles (NPs) acting as catalyst in aqueous medium at 80°C. A model reaction was conducted using 5,5-dimethylcyclohexane-1,3-dione **1a** and 4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)-benzaldehyde **2c** along with glycine **3** employing different solvents, catalysts at different temperatures for optimizing the reaction conditions.

Table.3b.3.1. Effect of solvent and catalysts in the synthesis of **4c**



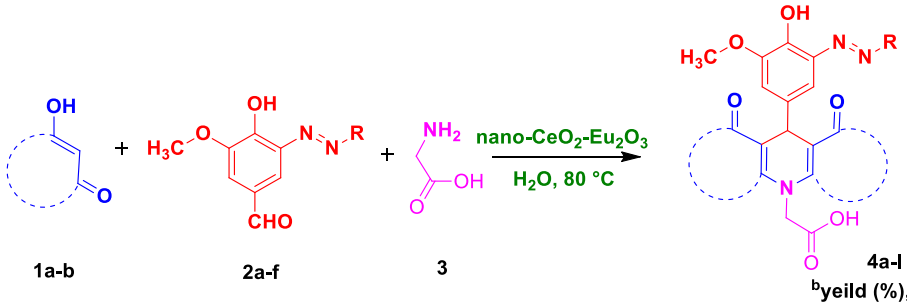
entry[a]	catalyst (mol %)	solvent	temperature (°C)	time (h)	yield[b] (%)
1	----------	methanol	80	24	5
2	----------	ethanol	80	24	12
3	----------	water	80	24	27
4	----------	acetonitrile	80	24	15
5	NaOH (10%)	water	80	15	36
6	Piperidine (10%)	water	80	8	31
7	Triethylamine (10%)	water	80	8	29
8	Acetic acid (10%)	water	80	8	63
9	$FeCl_3$(10%)	water	80	8	51
10	Fe_3O_4 (10%)	water	80	8	57
11	TiO_2 (10%)	water	80	8	44
12	CeO_2 (10%)	water	80	8	75
13	CeO_2–Eu_2O_3 (10%)	water	80	4	82
14	**CeO_2–Eu_2O_3 (20%)**	**water**	**80**	**2**	**90**
15	CeO_2–Eu_2O_3 (30%)	water	80	2	90
16	CeO_2–Eu_2O_3 (20%)	water	rt	2	55
17	CeO_2–Eu_2O_3 (20%)	water	40	2	71
18	CeO_2–Eu_2O_3 (20%)	water	60	2	79
19	CeO_2–Eu_2O_3 (20%)	water	reflux	2	83

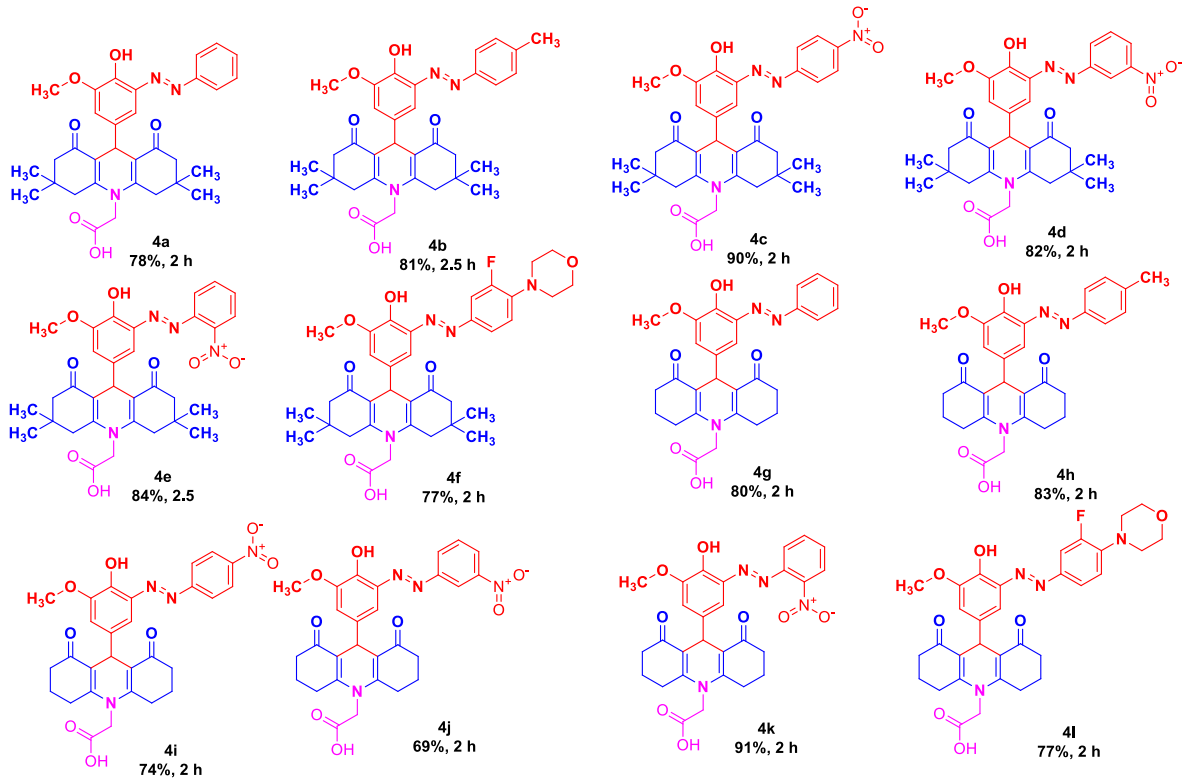
[a]Reaction conditions: 5,5-dimethylcyclohexane-1,3-dione (2 mmol), 4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)-benzaldehyde (1 mmol) and glycine (1 mmol), solvent (1 mL) and catalyst. [b]Yields of isolated products.

Initially the reaction was performed with a variety of solvents like methanol, ethanol, water, acetonitrile (Table.3b.3.1, entries 1-4) and it was observed that aqueous medium afforded better yields than other solvents. Further, we focused on the evaluation of different catalysts for the model reaction in water at 80°C. A wide range of catalysts like sodium hydroxide, piperidine, triethylamine, acetic acid, ferric chloride (Table.3b.3.1, entries 5-9) including nano catalysts like Fe_3O_4, TiO_2, CeO_2, CeO_2–Eu_2O_3 (Table.3b.3.1, entries 10-13) were employed to test their efficacy for the specific synthesis of compound **4c**. The results showed that in the presence of CeO_2–Eu_2O_3 (europium doped ceria nanoparticles), the desired product **4c** was obtained in 90% yield and the yield of the desired product was tested using different mol ratios (10, 20, 30 mol %). The maximum yield was found with the 20 mol % catalyst (Table.3b.3.1, entry 14). Lower than this, catalyst did not yield any promising result and when the reaction was tried using 30 mol%, (Table.3b.3.1, entry 15) no improvement was observed in the yields of **4c**. The results were **s**imilar with the reaction when 20 mol% catalyst was used. As an extension of the above, we also studied the effect of temperature on the above reaction at different temperatures like room temperature, 40°C, 60°C and reflux temperature (Table.3b.3.1, entries 16-19). Among these results, we found that 80° C temperature enhanced the reaction yields.

The well optimized one-step reaction protocol was adopted to create a diverse series of (4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-dihydropyridine-acetic acids **4a-l** in good to excellent yields (79-93%) with 1,3-dicarbonyl compounds **1a-b**, 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes **2a-f** and glycine **3** in the presence of CeO_2–Eu_2O_3 nanoparticles (NPs) as a catalyst in aqueous medium at 80° C. To estimate the scope and generality of the procedure, 4-hydroxy-3-methoxy-5-(substituted-phenyl)diazenyl)-benzaldehydes like 4-hydroxy-3-methoxy-5-(phenyldiazenyl)-benzaldehyde (**2a**), 4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)-benzaldehyde (**2b**), 4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)-benzaldehyde (**2c**), 4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)-benzaldehyde (**2d**), 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)-benzaldehyde (**2e**) and 3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxybenzaldehyde (**2f**) having both electron-donating and electron-withdrawing groups were reacted with 1,3-dicarbonyl compounds like 5,5-dimethyl-1,3-cyclohexanedione (**1a**) and 1,3-cyclohexanedione (**1b**); along with glycine (**3**) under optimized conditions, and results are summarized in Table.3b.3.2.

Table.3b.3.2. Synthesis of (4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-dihydropyridine-acetic acids **4a-l**[a]





[a]Reaction conditions: 1,3-dicarbonyl compounds (2 mmol), 4-hydroxy-3-methoxy-5-((4-substituted-phenyl)-diazenyl)-benzaldehyde (1 mmol) and glycine (1 mmol), water (1 mL) and nano-CeO_2–Eu_2O_3. [b]Yields of isolated products.

The recyclability is of excessive significance of applying a catalytic system in industrial processes. Therefore, the recyclability of the catalyst was investigated in the synthesis of

compound **4c** with 5,5-dimethylcyclohexane-1,3-dione **1a**, 4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)-benzaldehyde **2c** and glycine **3**. After completion of the reaction, the reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate. The catalyst was separated by filtration, washed with acetone, dried and used for the next run. The catalytic activity of the CeO_2–Eu_2O_3 was restored within the limits of the experimental errors for the four successive recycled runs (Fig.3b.3.1).

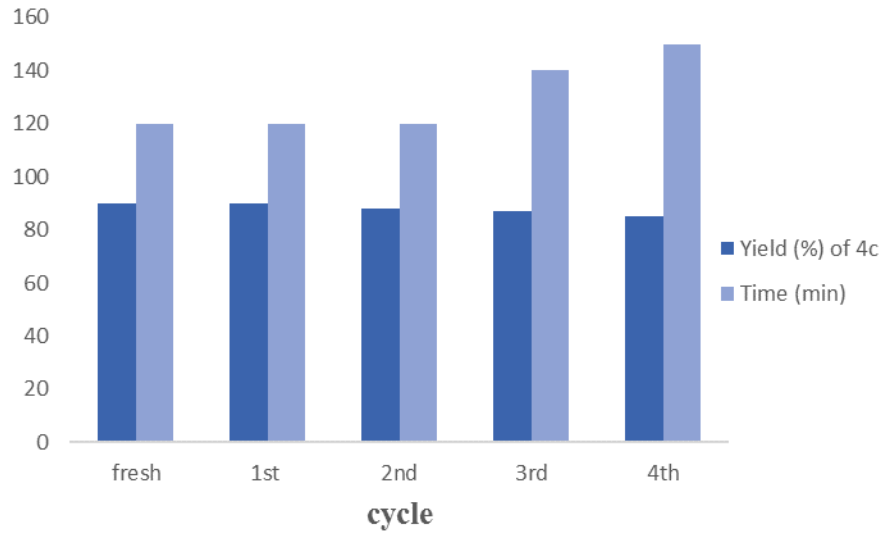
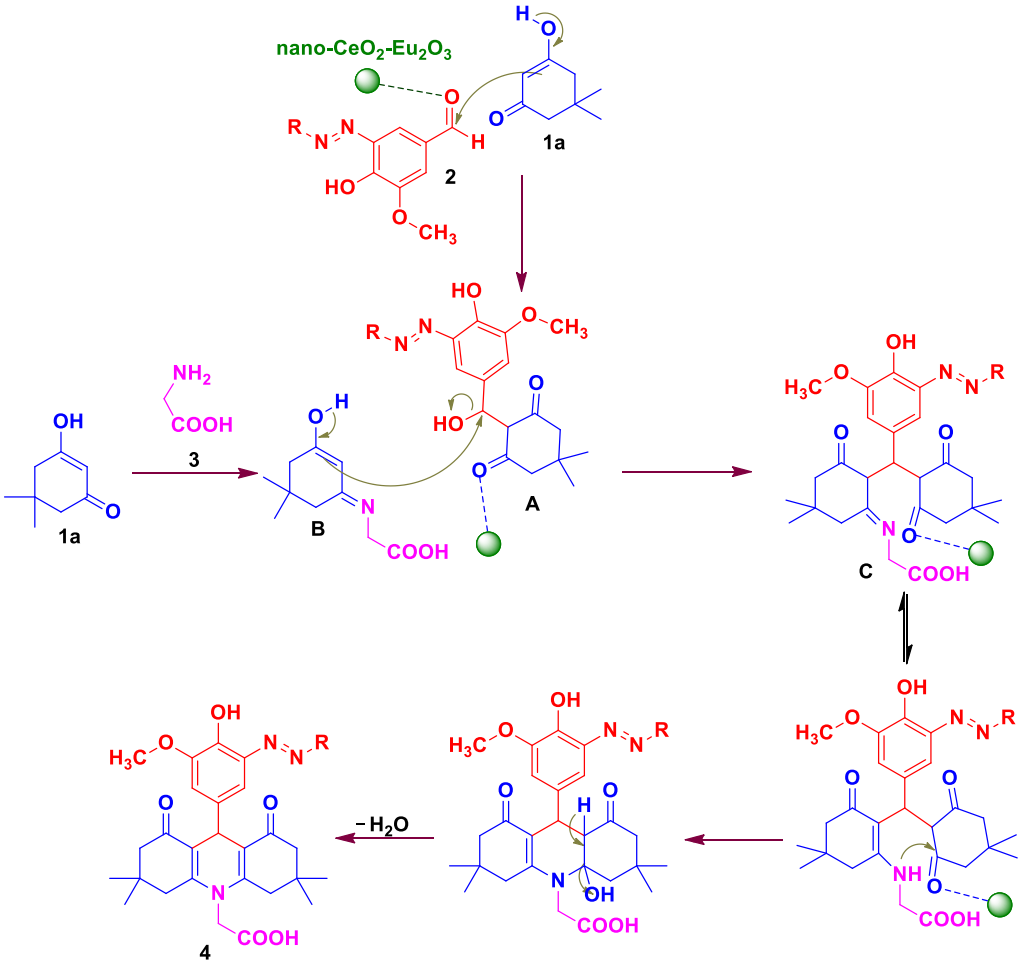


Fig.3b.3.1 Reusability studies of the nano-sized CeO_2-Eu_2O_3 catalyst for the synthesis of compound **4c**

A plausible reaction mechanism for the formation of dihydropyridines involves the activation of aldehyde **2** followed the attack of enol form of 1,3-dicarbonyl compound **1** to give the intermediate **A**. The formation of intermediate (**B**) takes place by a condensation between 1,3-dicarbonyl compound **1** and glycine **3**. Subsequently a Michael type addition occurs between intermediate **A** and **B** producing intermediate (**C**). Intermediate **C** undergoes intermolecular cyclization to afford the final product **5** as depicted in the **scheme.3b.3.1.** The structures of the synthesized compounds were well characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, mass spectrometry and elemental analysis.

Scheme 3b.3.1: Proposed mechanism for the formation of dihydropyridine derivatives (**4**)



Characterization of the catalyst

Powder-XRD: Fig.3b.3.2(a). shows the XRD of CE material. The planes are observed at 2θ = 28.4, 32.8, 47.3, 55.7°. From the analysis of XRD it is understood that only one type of crystalline phases is present in the prepared sample. Absence of the peaks corresponding to dopant oxide (Eu_2O_3) confirms the formation of solid solutions. The average crystallite size was calculated by the debye-sherrer equation using most intense peaks (111), (200), (220), and (311), which is 8.4 nm. The surface area of the material was measured using nitrogen adsorption-desorption method and was found to be 90 m^2/gm.

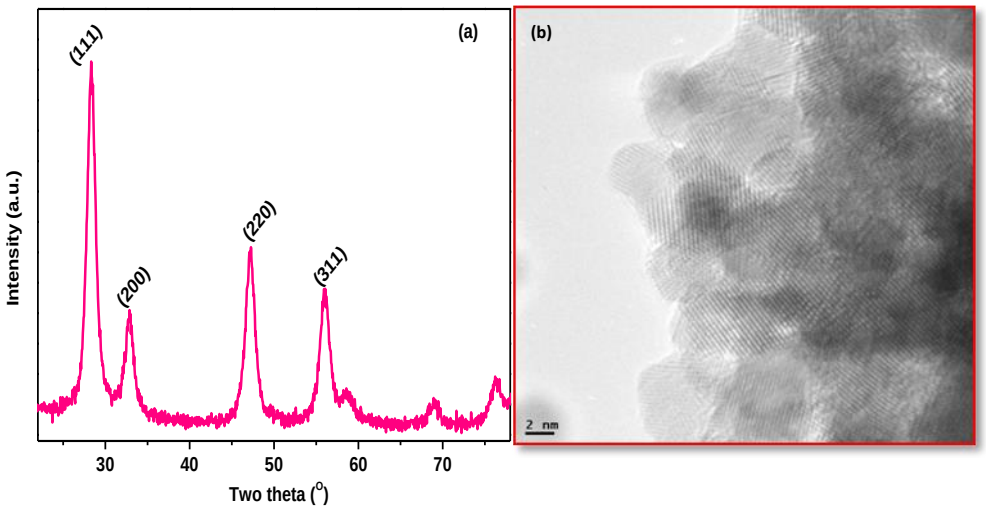


Fig.3b.3.2 (a) Powder X-ray diffraction patterns of europium doped ceria nanoparticles. **Fig.3b.3.2(b)** transmission electron microscopy image of europium doped ceria nanoparticles.

TEM: Fig.3b.3.2(b). shows the TEM images of the CE material. From the figure it is clear that, the average particle size was in the range of 8-10 nm which is well in agreement with XRD data.
XPS: XP spectra are used to know the oxidation states of the metal ions present on the surface of the solid solution. Fig.3b.3.3(a) and Fig.3b.3.3(b) represent the Ce 3d and O 1s spectra of CE material. Ce 3d spectra were deconvoluted into eight peaks corresponding to four pairs of spin-orbit doublets and the peaks were labeled as u and v refered to the $3d_{3/2}$ and $3d_{5/2}$ spin–orbit components, respectively. The peaks designated as u, u″, u‴ and v, v″, v‴ can be assigned to Ce^{4+} while the peaks u′ and v′ belong to Ce^{3+} suggesting the coexistence of Ce^{3+} and Ce^{4+} in the CE meterial.

O 1s spectra of prepared material calcined at 773 K is presented in Fig.3b.3.3(b). From the figure two peaks were observed, one is at 529.3 eV and other one is at 531.7 eV. The former can be related to lattice oxygen (O_I) and the latter to the adsorbed oxygen (O_{II}). It indicates that two types of oxygens are present in the CE material.

Eu 3d XP spectrum of prepared material is shown in Fig.3b.3.3(c). The peak observed at 1134 eV corresponds to Eu^{3+} and shows that the dopant is present in the trivalent state only[16] (Fig.3b.3.3(c)).

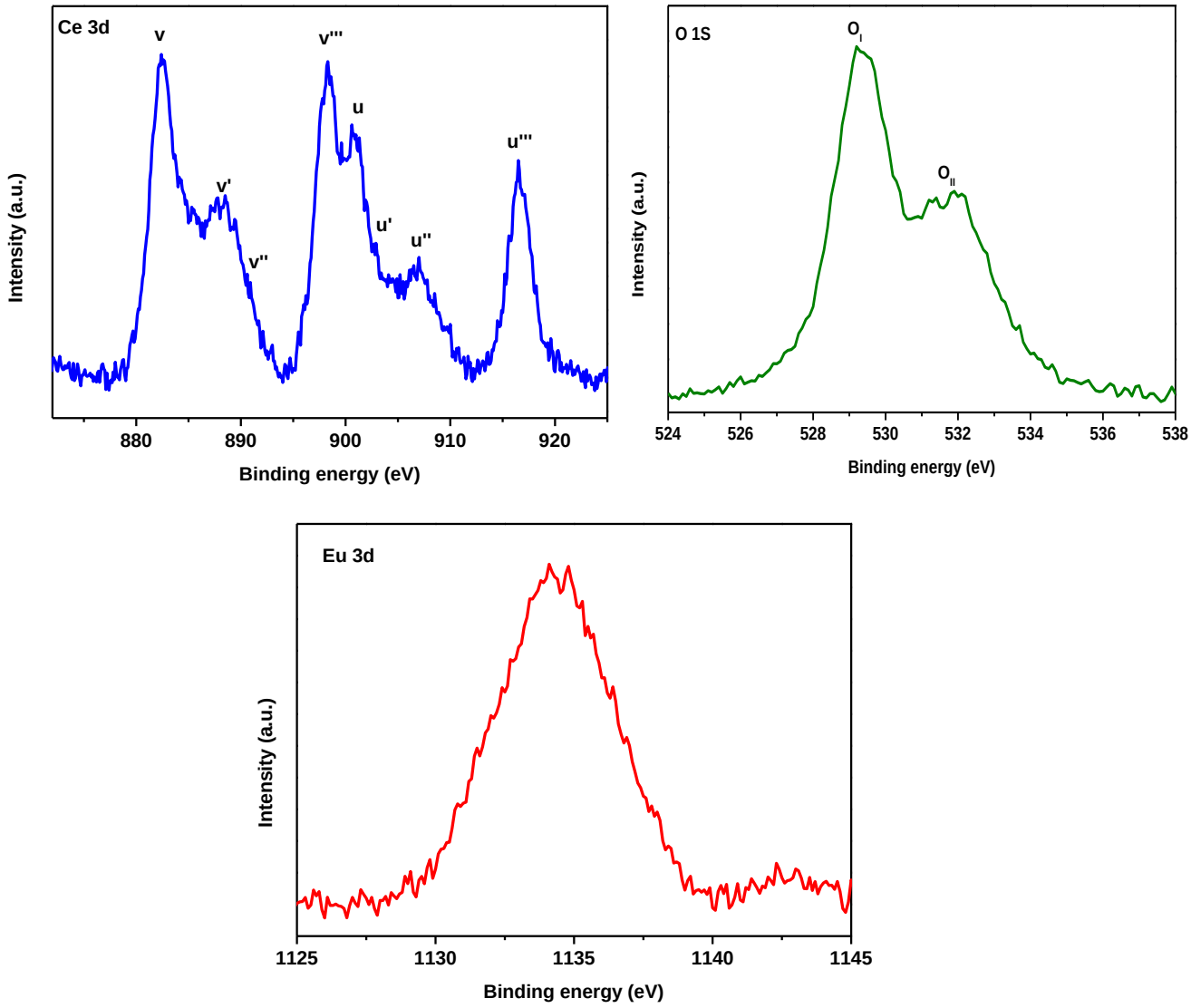


Fig.3b.3.3. XP spectra of Ce 3d, O1S and Eu 3d of europium doped ceria nanoparticles

Experimental

All the reagents were procured from commercial sources and used without further purification. A Bruker WM-4 (X) spectrophotometer (577 model) was used for recording IR spectra (KBr). NMR spectra were recorded on a Bruker WM-500 spectrophotometer at 400 MHz (^{1}H), Bruker WM-400 spectrophotometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively, in DMSO-d_6 with TMS as an internal standard. Elemental analysis was performed on a Carlo Erba EA 1108 automatic elemental analyzer. Mass spectra (ESI) were recorded on a jeo1 JMSD-300 spectrometer.

Powder-XRD: XRD data was acquired in the 2θ range of 12–80° on a Rigaku Multiflex instrument using Cu Kα (λ = 1.5418 Å) radiation and a scintillation counter detector. XRD phases present in the samples were identified with the help of the Powder Diffraction File-International Centre for Diffraction Data (PDF-ICDD). The average size of the crystalline domain (D) of CE was estimated with the help of the Scherrer equation (1) using the XRD data of all prominent lines.

$$D = K \lambda/\beta \cos\theta \quad (1)$$

Where D denotes the crystallite size, λ the X-ray wavelength (1.541 Å), K the particle shape factor taken as 1, β the peak width (FWHM, full width at half maximum) in radians, and θ the Bragg diffraction angle.

TEM: HRTEM studies were made on a JEM-2010 (JEOL) instrument equipped with a slow-scan CCD camera at an accelerating voltage of 200 kV.

XPS: The XPS measurements were performed on a Shimadzu (ESCA 3400) spectrometer by using Al Kα (1486.7 eV) radiation as the excitation source. Charging effects of catalyst samples were corrected by using the binding energy of the adventitious carbon (C 1s) at 284.6 eV as internal reference. The XPS analysis was done at ambient temperature and pressures usually in the order of less than 10^{-8} Pa.

Spectral discussion

IR

The structures of the dihydropyridines were confirmed by IR spectra which showed strong absorption bands at 3425-3427 cm^{-1} due to -COOH and -OH groups respectively.

^{1}H NMR

The structure of the synthesized compounds were also characterized by ^{1}H NMR spectra. In ^{1}H NMR spectra of all the compounds, pyrazole proton (H-9) was observed as a singlet at δ 4.18-5.59 ppm which conformed the smooth cyclization. All aromatic and aliphatic protons were observed at expected regions.

^{13}C NMR

In addition, ^{13}C NMR spectra also confirmed the proposed structures **4a-l** due to the appearance of signal at δ 31.39-37.01 ppm due to pyrazole (C_9) carbon.

Mass

Furthermore, the mass spectra of the compounds **4a-l** gave additional evidences for the proposed structures. In mass spectra of almost all the compounds showed M+1 peak, which were in agreement with their molecular weights.

For all the compounds, the elemental analyses values were in good agreement with the theoretical data.

Preparation of europium doped ceria nanoparticles

Nanosized $Ce_{0.8}Eu_{0.2}O_{2-\delta}$ (CE 8:2 mole ratio based on oxides) solid solutions were prepared by a modified co-precipitation method using appropriate amounts of the corresponding cerium (III) nitrate hexahydrate [$Ce(NO_3)_3 \cdot 6H_2O$, 99.99%, Aldrich] and europium (III) nitrate pentahydrate [$Eu(NO_3)_3 \cdot 5H_2O$, 99.9%, Aldrich] precursors respectively. The desired amounts of precursors were dissolved separately in double-distilled water under mild stirring conditions and mixed together. Dilute aqueous ammonia solution was added drop-wise over a period until the pH of the solution reached ~ 8.5 and CE hydroxide formed. The obtained light yellow colored precipitate was decanted, filtered, and washed with distilled water multiple times followed by oven drying at 393 K for 12 h. The oven dried samples were crushed using an agate mortar and calcined in air at 773 K for 5 h at a heating rate of 5 K min^{-1}.

Synthesis of 2-(9-(4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)phenyl)-1,8-dioxo-octahydroacridin-10(9H)-yl)acetic acid derivatives (4a-l)

A mixture of 1,3-dicarbonyl compound (2 mmol**)**, 4-hydroxy-3-methoxy-5-(substituted-phenyl diazenyl)-benzaldehyde (1 mmol) and glycine (1 mmol**)** in water (1 mL) was taken in a 50 mL round bottom flask and the catalyst of europium doped ceria nanoparticles was added. The resulting mixture was kept at 80°C for 2 - 2.5 hours until the full conversion was achieved (monitored by TLC). After completion of the reaction the product was separated from the catalyst by extraction with ethyl acetate, which was evaporated under vacuum. The product was purified by column chromatography using silica gel [ethyl acetate: n-hexane (6:4)] to afford the pure compounds (**4a-l**).

2-(9-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4a)

Dark red solid; m.p. 251-253 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 2950, 1728, 1669; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.02 (s, 6H, $-CH_3$), 1.06 (s, 6H, $-CH_3$), 2.32-2.44 (m, 10H), 3.86 (s, 3H, $-OCH_3$), 4.18 (s, 1H), 6.97 (s, 1H, ArH), 7.17 (s, 1H, ArH), 7.45-7.52 (m, 3H, ArH), 7.93 (d, 2H,

J = 8.0 Hz, ArH), 12.12 (s, 1H, -OH), 13.08 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 198.17, 195.57, 162.73, 159.55, 151.45, 148.63, 143.62, 137.44, 135.19, 132.70, 128.97, 124.17, 121.12, 115.77, 113.65, 55.78, 52.34, 49.46, 36.38, 32.99, 28.31, 25.73; **ESI-MS** (*m/z*): 558 (M+1); Anal. Calcd for $C_{32}H_{35}N_3O_6$: C, 68.92; H, 6.33; N, 7.54; Found: C, 68.72; H, 6.44; N, 7.38.

2-(9-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4b)

Dark red solid; m.p. 247-248 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 2949, 1732, 1667; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (s, 6H, $-CH_3$), 1.31 (s, 6H, $-CH_3$), 2.26-2.54 (m, 13H), 3.86 (s, 3H, $-OCH_3$), 5.59 (s, 1H), 6.75 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.33 (d, 2H, J = 8.0 Hz, ArH), 7.75 (d, 2H, J = 8.0 Hz, ArH), 12.09 (s, 1H, -OH), 13.19 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 198.32, 195.74, 162.36, 157.71, 148.05, 144.91, 140.78, 137.43, 135.60, 134.87, 122.00, 119.90, 114.14, 112.56, 112.01, 55.62, 50.86, 50.13, 34.55, 31.25, 29.55, 27.13, 21.62; **ESI-MS** (*m/z*): 572 (M+1); Anal. Calcd for $C_{33}H_{37}N_3O_6$: C, 69.33; H, 6.52; N, 7.35; Found: C, 69.42; H, 6.39; N, 7.21.

2-(9-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4c)

Dark red solid; m.p. 262-263 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 2948, 1729, 1670; **^{1}H NMR** (400 MHz, $CDCl_3$-d_6): δ 1.14 (s, 6H, $-CH_3$), 1.29 (s, 6H, $-CH_3$), 2.35-2.52 (m, 10H), 3.85 (s, 3H, $-OCH_3$), 5.55 (s, 1H), 6.78 (s, 1H, ArH), 7.28 (s, 1H, ArH), 7.94 (d, 2H, J = 8.0 Hz, ArH), 8.38 (d, 2H, J = 8.0 Hz, ArH), 12.04 (s, 1H, -OH), 12.87 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.86, 189.56, 153.51, 148.84, 148.40, 143.31, 137.34, 129.59, 125.02, 122.73, 122.52, 115.31, 115.23, 56.32, 47.10, 46.43, 32.33, 31.40, 29.78, 27.19; **ESI-MS** (*m/z*): 603 (M+1); Anal. Calcd for $C_{32}H_{34}N_4O_8$: C, 63.78; H, 5.69; N, 9.30; Found: C, 63.91; H, 5.89; N, 9.18.

2-(9-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4d)

Dark red solid; m.p. 269-270 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 2949, 1730, 1670; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.14 (s, 6H, $-CH_3$), 1.30 (s, 6H, $-CH_3$), 2.35-2.54 (m, 10H), 3.85 (s, 3H, $-OCH_3$), 5.56 (s, 1H), 6.80 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.71 (t, 1H, J = 8.0 Hz, ArH), 8.15 (d, 1H, J = 8.0 Hz, ArH), 8.32 (d, 1H, J = 8.0 Hz, ArH), 8.66 (s, 1H, ArH), 12.04 (s, 1H, -OH),

12.47 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.86, 189.59, 151.08, 149.17, 148.63, 141.68, 136.99, 130.27, 129.47, 128.96, 124.88, 122.71, 115.91, 115.27, 115.14, 56.35, 47.12, 46.45, 32.31, 31.49, 29.68, 27.26; **ESI-MS** (*m/z*): 603 (M+1); Anal. Calcd for $C_{32}H_{34}N_4O_8$: C, 63.78; H, 5.69; N, 9.30; Found: C, 63.99; H, 5.49; N, 9.55.

2-(9-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4e)

Dark red solid; m.p. 255-256 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 2947, 1725, 1669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.13 (s, 6H, $-CH_3$), 1.28 (s, 6H, $-CH_3$), 2.34-2.52 (m, 10H), 3.83 (s, 3H, $-OCH_3$), 5.51 (s, 1H), 6.68 (s, 1H, ArH), 7.13 (s, 1H, ArH), 7.53 (t, 1H, J = 8.0 Hz, ArH), 7.72 (t, 1H, J = 8.0 Hz, ArH), 7.97 (d, 1H, J = 8.0 Hz, ArH), 8.11 (d, 1H, J = 8.0 Hz, ArH), 12.05 (s, 1H, -OH), 13.18 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.77, 189.54, 149.61, 148.04, 143.81, 142.32, 137.73, 134.03, 129.47, 125.37, 122.14, 118.17, 115.17, 114.85, 56.25, 47.07, 46.43, 31.39, 30.97, 29.76, 27.21; **ESI-MS** (*m/z*): 603 (M+1); Anal. Calcd for $C_{32}H_{34}N_4O_8$: C, 63.78; H, 5.69; N, 9.30; Found: C, 63.90; H, 5.42; N, 9.51.

2-(9-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4f)

Dark red solid; m.p. 244-245 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 2953, 1750, 1670; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.14 (s, 6H, $-CH_3$), 1.30 (s, 6H, $-CH_3$), 2.35-2.54 (m, 10H), 3.20-3.24 (m, 4H), 3.83 (s, 3H, $-OCH_3$), 3.88-3.91 (m, 4H), 5.55 (s, 1H), 6.72 (s, 1H, ArH), 6.99 (d, 1H, J = 8.0 Hz, ArH), 7.24 (s, 1H, ArH), 7.74 (d, 1H, J = 8.0 Hz, ArH), 8.17 (s, 1H, ArH), 12.04 (s, 1H, -OH), 12.81 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.67, 189.51, 156.79, 154.32, 148.44, 146.24, 145.19, 142.48, 140.96, 136.83, 128.77, 123.32, 122.36, 122.24, 122.05, 117.93, 113.64, 107.61, 107.38, 66.81, 56.28, 50.38, 47.11, 46.44, 32.28, 31.42, 30.97, 29.75, 27.24; **ESI-MS** (*m/z*): 661 (M+1); Anal. Calcd for $C_{36}H_{41}FN_4O_7$: C, 65.44; H, 6.25; N, 8.48; Found: C, 65.31; H, 6.33; N, 8.62.

2-(9-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4g)

Dark red solid; m.p. 254-255 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 2949, 1749, 1669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.01-2.08 (m, 4H), 2.34-2.43 (m, 6H), 2.64-2.73 (m, 4H), 3.99 (s, 3H, $-OCH_3$), 4.82 (s, 1H), 7.24 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.46-7.53 (m, 3H, ArH), 7.83(d, 2H, ArH), 11.64 (s, 1H, -OH), 13.22 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 198.74, 195.83,

164.81, 162.49, 158.77, 151.52, 148.98, 144.08, 138.13, 135.70, 131.47, 129.66, 123.22, 122.32, 119.98, 114.78, 113.83, 112.79, 55.81, 47.06, 36.71, 34.87, 26.16, 23.48; **ESI-MS** (*m/z*): 502 (M+1); Anal. Calcd for $C_{28}H_{27}N_3O_6$: C, 67.05; H, 5.43; N, 8.38; Found: C, 67.22; H, 5.21; N, 8.59.

2-(9-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4h)

Dark red solid; m.p. 232-233 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 2948, 1748, 1670; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.90-2.00 (m, 4H), 2.29-2.33 (m, 6H), 2.41 (s, 3H, -CH_3), 2.60-2.69 (m, 4H), 3.83 (s, 3H, -OCH_3), 4.23 (s, 1H), 6.90 (s, 1H, ArH), 7.13 (s, 1H, ArH), 7.39 (d, 2H, J = 8.0 Hz, ArH), 7.90 (d, 2H, ArH), 10.98 (s, 1H, -OH), 12.88 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 198.41, 196.23, 164.75, 158.38, 149.54, 148.33, 143.38, 141.37, 137.62, 135.29, 129.59, 122.15, 119.33, 114.59, 113.87, 112.71, 55.47, 49.80, 36.71, 34.43, 26.10, 21.43, 19.31; **ESI-MS** (*m/z*): 516 (M+1); Anal. Calcd for $C_{29}H_{29}N_3O_6$: C, 67.56; H, 5.67; N, 8.15; Found: C, 67.39; H, 5.43; N, 8.33.

2-(9-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4i)

Dark red solid; m.p. 245-246 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 2950, 1749, 1671; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04-2.11 (m, 4H), 2.37-2.44 (m, 6H), 2.67-2.73 (m, 4H), 3.99 (s, 3H, -OCH_3), 4.81 (s, 1H), 7.24 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.96 (d, 2H, J = 8.0 Hz, ArH), 8.37 (d, 2H, ArH), 12.51 (s, 1H, -OH), 13.04 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.05, 189.86, 152.88, 150.27, 149.04, 145.34, 140.38, 138.20, 136.52, 135.36, 133.00, 130.79, 129.07, 126.75, 125.21, 122.92, 111.68, 56.65, 49.34, 37.01, 35.97, 27.32, 21.23; **ESI-MS** (*m/z*): 547 (M+1); Anal. Calcd for $C_{28}H_{26}N_4O_8$: C, 61.53; H, 4.80; N, 10.25; Found: C, 61.72; H, 4.93; N, 10.50.

2-(9-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4j)

Dark red solid; m.p. 229-230 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3427, 2951, 1743, 1669; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 1.94-2.02 (m, 4H), 2.27-2.34 (m, 6H), 2.64-2.74 (m, 4H), 3.83 (s, 3H, -OCH_3), 4.59 (s, 1H), 6.98 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.83 (t, 1H, J = 8.0 Hz, ArH), 8.22 (d, 1H, J = 8.0 Hz, ArH), 8.42 (d, 1H, J = 8.0 Hz, ArH), 8.74 (s, 1H, ArH), 11.72 (s, 1H, -OH), 12.44 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 197.02, 195.80, 155.43, 154.50,

149.43, 148.56, 145.31, 141.98, 138.60, 135.55, 132.25, 130.28, 125.40, 124.19, 56.48, 48.72, 36.91, 30.87, 26.96, 20.40; **ESI-MS** (*m/z*): 547 (M+1); Anal. Calcd for $C_{28}H_{26}N_4O_8$: C, 61.53; H, 4.80; N, 10.25; Found: C, 61.38; H, 4.62; N, 10.49.

2-(9-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4k)

Dark red solid; m.p. 276-277 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 2950, 1750, 1634; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.03-2.11 (m, 4H), 2.36-2.46 (m, 6H), 2.56-2.69 (m, 4H), 3.99 (s, 3H, -OCH_3), 4.82 (s, 1H), 7.21 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.51 (t, 2H, J = 8.0 Hz, ArH), 7.83 (d, 2H, J = 8.0 Hz, ArH), 11.61 (s, 1H, -OH), 13.22 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 198.45, 196.28, 164.57, 158.45, 152.30, 150.34, 148.71, 145.72, 139.65, 136.68, 132.24, 129.85, 124.95, 119.48, 117.25, 115.03, 113.25, 108.87, 56.09, 49.63, 37.36, 34.87, 26.36, 19.57; **ESI-MS** (*m/z*): 547 (M+1); Anal. Calcd for $C_{28}H_{26}N_4O_8$: C, 61.53; H, 4.80; N, 10.25; Found: C, 61.76; H, 4.94; N, 10.41.

2-(9-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)acetic acid (4l)

Dark red solid; m.p. 233-234 ^oC; **IR** (KBr, cm^{-1}) ν_{max}: 3425, 2950, 1748, 1670; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.02-2.08 (m, 4H), 2.36-2.41 (m, 6H), 2.68-2.74 (m, 4H), 3.20-3.25 (m, 4H), 3.88-3.91 (m, 4H), 3.98 (s, 3H, -OCH_3), 4.81 (s, 1H), 6.98 (d, 2H, J = 8.0 Hz, ArH), 7.18 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.62 (s, 1H, ArH), 11.78 (s, 1H, -OH), 12.98 (s, 1H, -COOH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.50, 196.97, 164.19, 148.06, 145.24, 141.54, 138.04, 136.91, 135.83, 134.96, 132.13, 122.66, 122.17, 117.95, 116.68, 116.14, 66.81, 56.54, 50.39, 48.03, 36.96, 27.20, 21.27, 20.32; **ESI-MS** (*m/z*): 605 (M+1); Anal. Calcd for $C_{32}H_{33}FN_4O_7$: C, 63.57; H, 5.50; N, 9.27; Found: C, 63.78; H, 5.38; N, 9.10.

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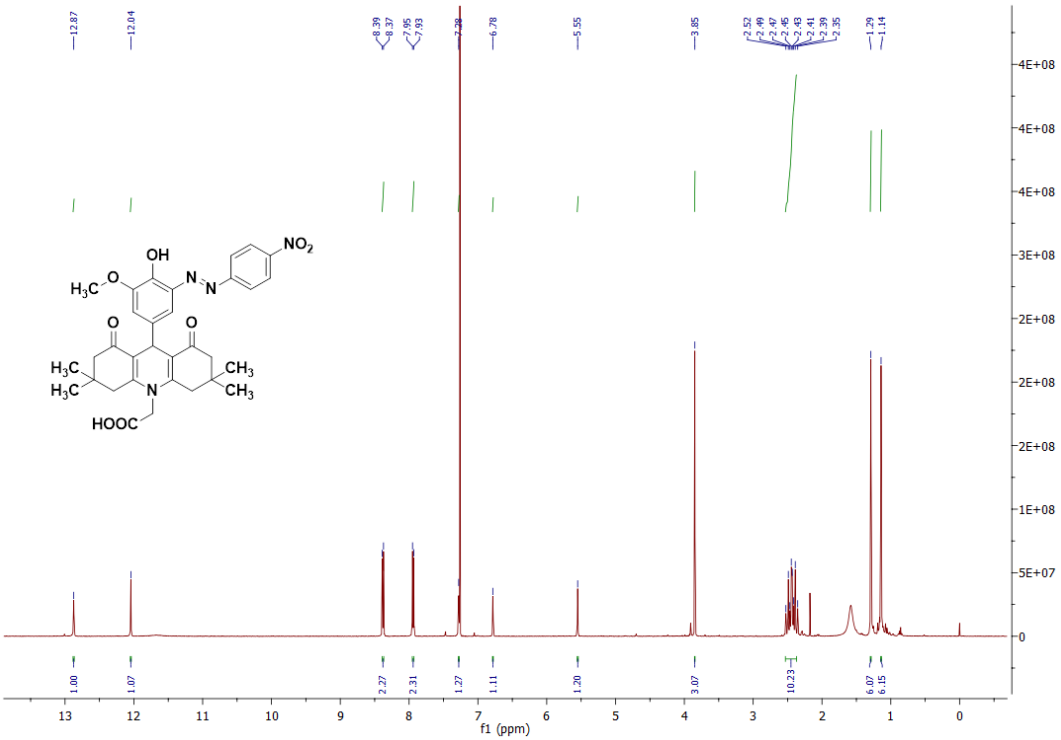
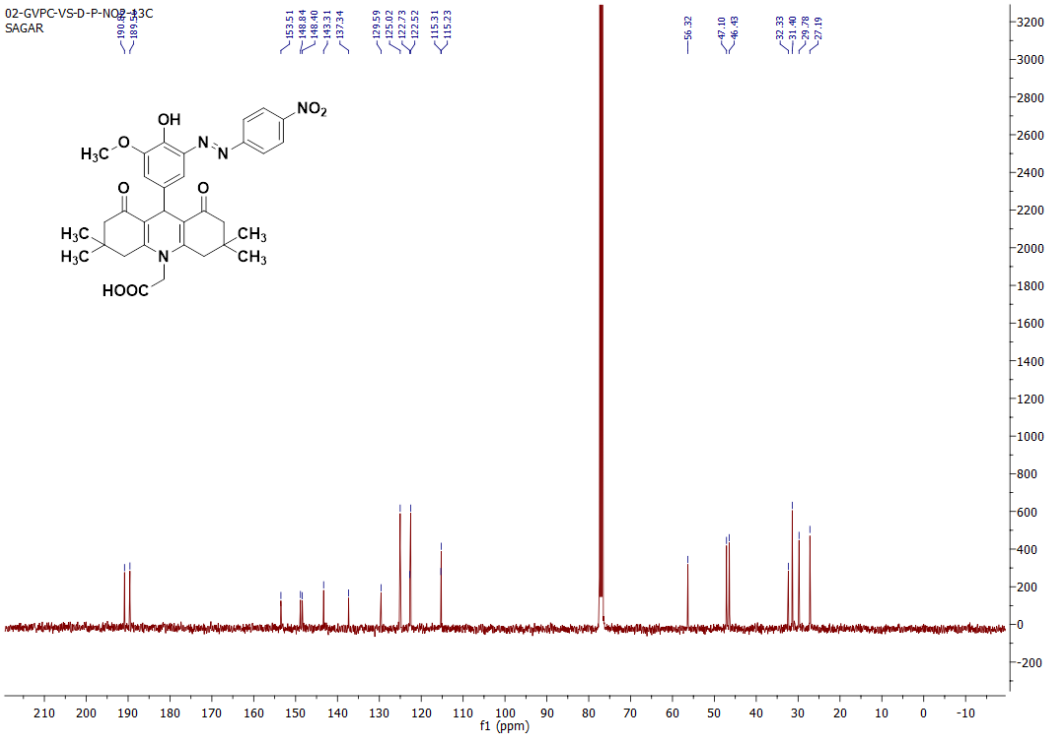
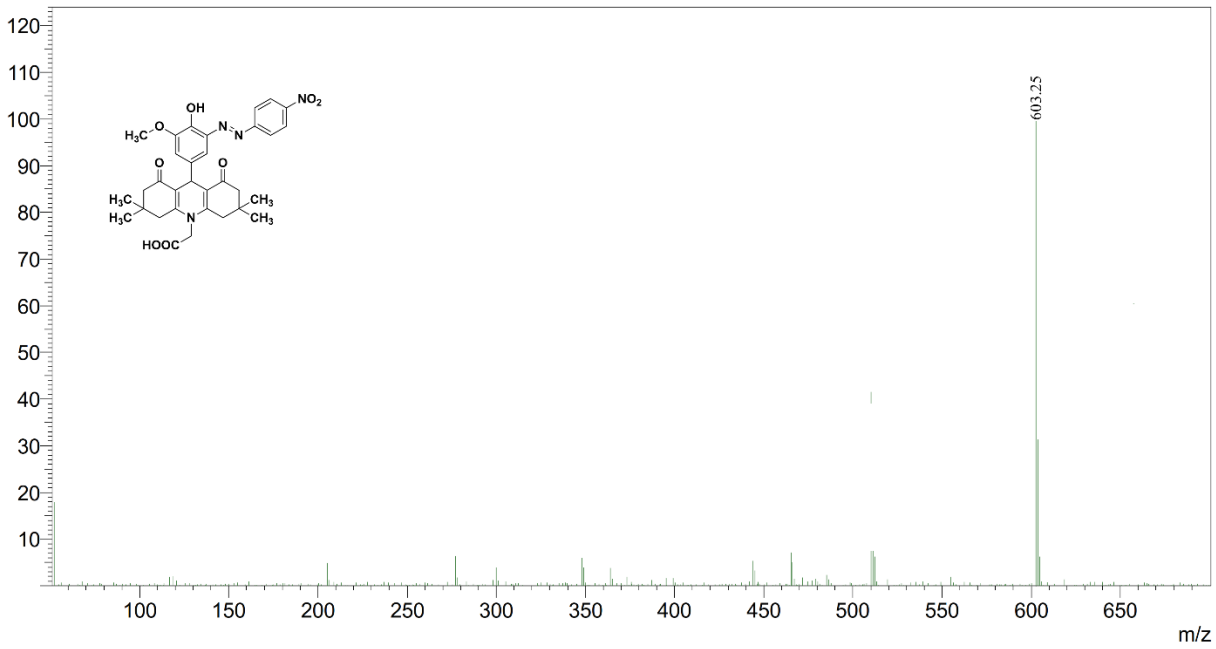


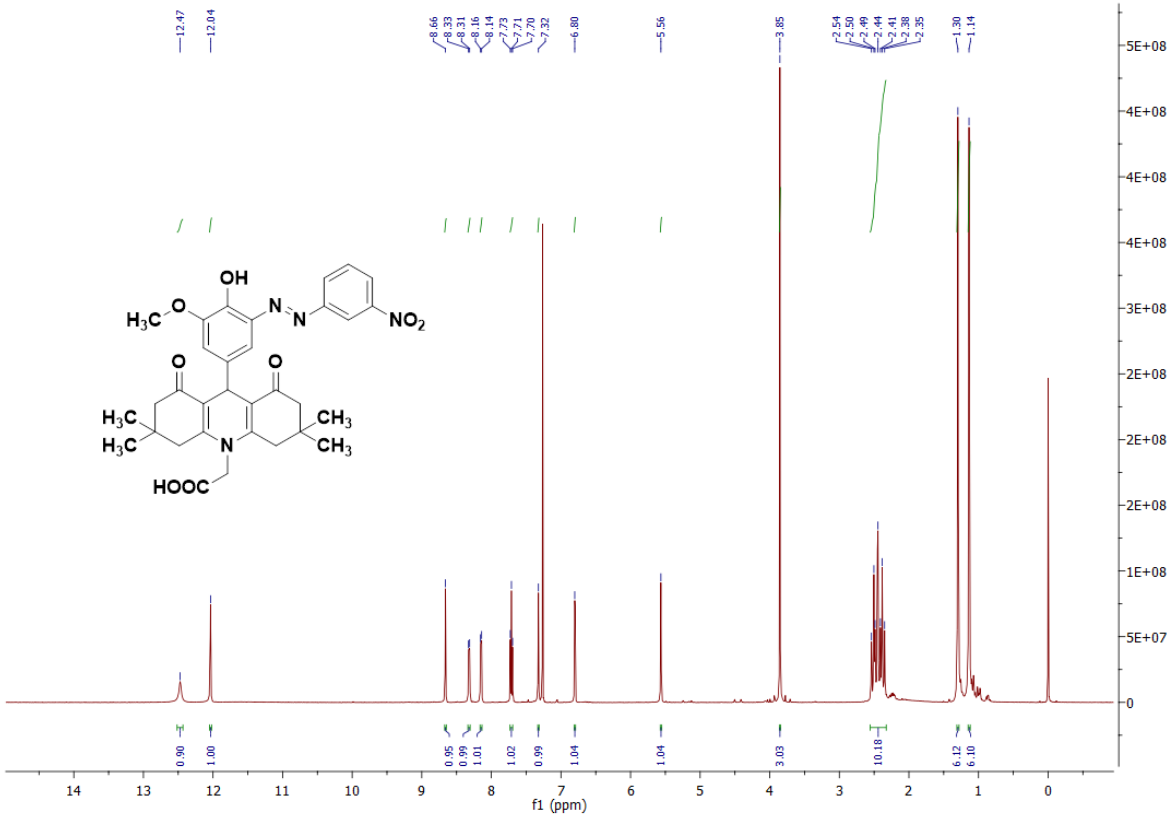
^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4c**



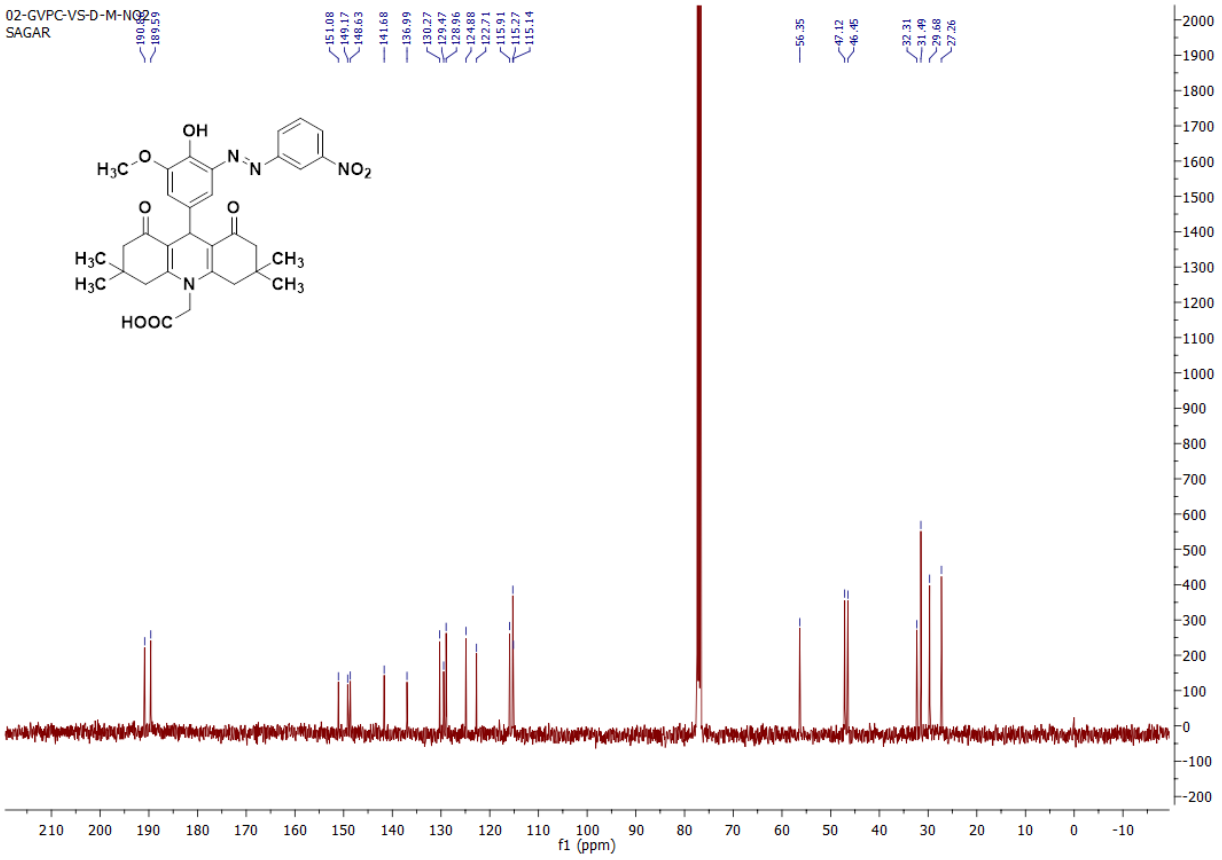
^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4c**



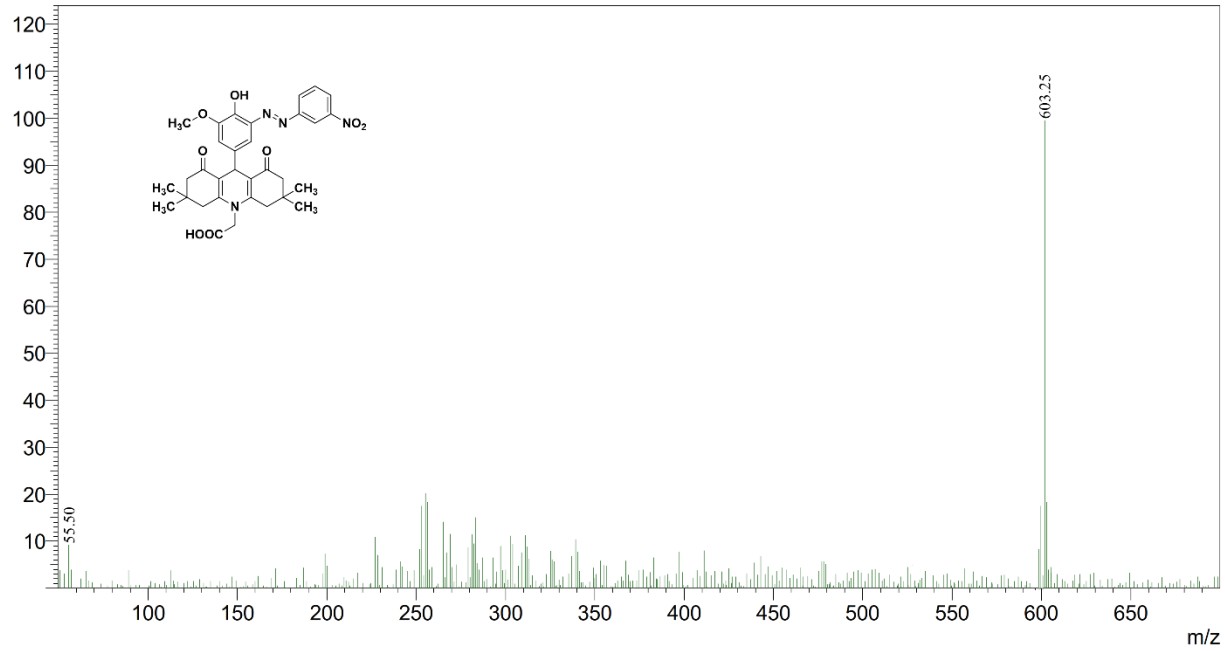
Mass spectrum of compound **4c**



^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4d**



^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4d**



Mass spectrum of compound **4d**

CHAPTER-IV

SYNTHESIS OF NOVEL A_2B_2 AND A_4 TYPE PORPHYRIN DERIVATIVES

Synthesis of novel A_2B_2 and A_4 type porphyrin derivatives

4.1. Introduction

The porphyrinic macrocyclic arrangement with four pyrrole rings connected by methine units was suggested more than a century ago and is extraordinarily stable. The nitrogen atoms at the interior form a central pocket ideally positioned to firmly incorporate metal atoms in a tetradentate fashion (Fe, Co or Mg prevail in biological systems). These anionic centres represent coordinately unsaturated units for charge transfer and ligation of adducts, which occurs with reversible changes of electronic configuration.

In the past decade, porphyrin systems have also become probably the most popular models which mimic many biological phenomena, as well as being targets for commercial exploitation of several catalytic processes of a type which are efficiently performed in Nature, for example in the chemical functionalization of hydrocarbons, transportation of oxygen, etc. The porphyrin macrocycle also provide an excellent chelating ligand for a variety of metal ions which can be studied in detail in order to reveal new features of inorganic and organometallic chemistry, as well as a wealth of molecules for medicinal, theoretical, physical, and spectroscopic investigations.

Porphyrin and their derivatives play a vital role in a number of biological processes and have considerable chemical and pharmacological importance. Recently, porphyrins have gained much importance as these compounds have been found to exhibit several biological activities, such as antidiabetic,[1] antimicrobial,[2] anticancer,[3] anti-inflammatory[4] and antiprotozoal[5] activities. Moreover, pyrazoles occupy a diverse place in heterocyclic chemistry and signify an important motif in medicinal chemistry due to their ability to show a range of bioactivities such as anticancer,[6] antimicrobial,[7] anti-inflammatory,[8] antimalarial,[9] anti-tubercular[10] and antidiabetic[11] activities. Here, we planned to develop a molecular system consisting of porphyrin and pyrazole moieties which may be having important biological applications (*Figure 4.1.1.*)

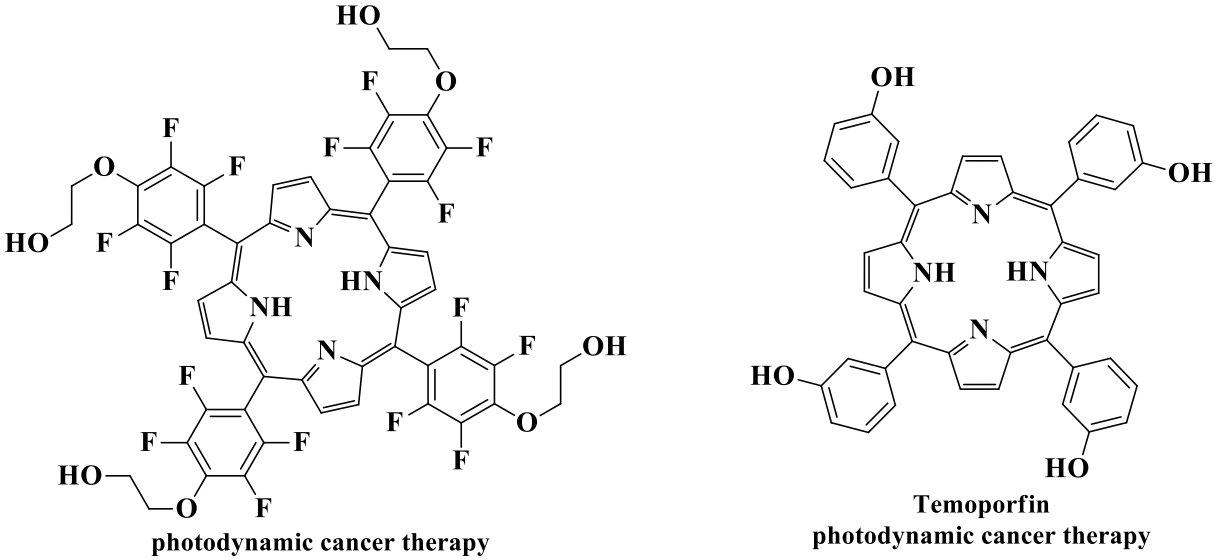
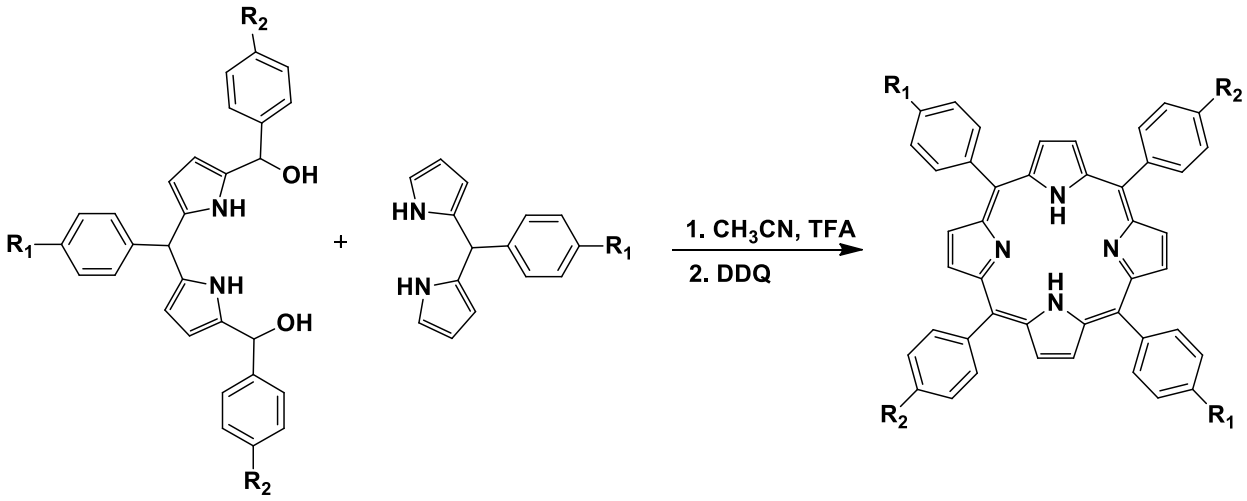


Figure 4.1.1. Representative examples of pharmacologically active synthetic porphyrin derivatives

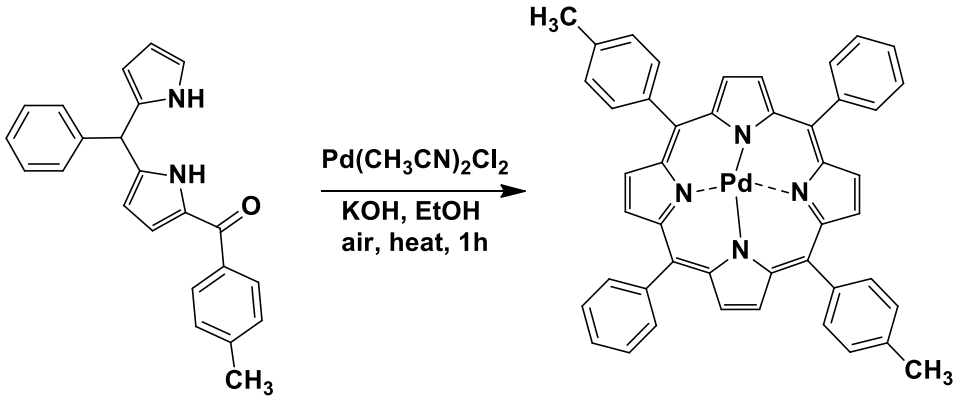
4.2. Earlier synthetic strategies for A_2B_2 and A_4 type porphyrins

Dorota Gryko *et al.*[12] studied the synthesis of A_2B_2 type porphyrins which were obtained by the treatment of dipyrromethane-dicarbinol and dipyrromethane in the presence of TFA in CH_3CN at room temperature for 5 min followed by oxidation with DDQ (*Scheme 4.2.1*).



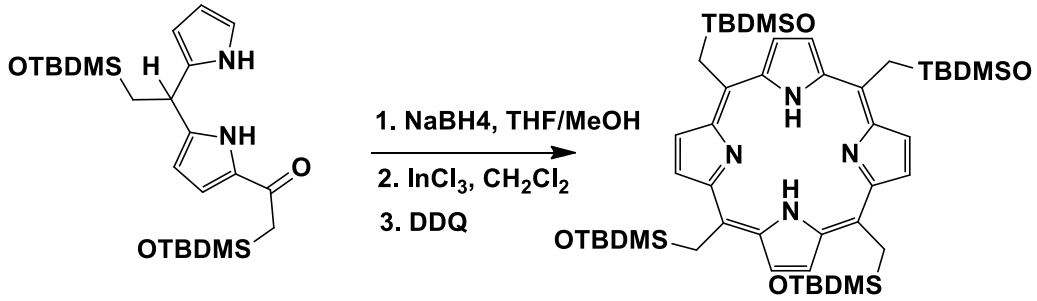
Scheme 4.2.1

Duddu S. Sharada *et al*[13] have achieved A_2B_2 type porphyrin using 1-acyldipyrromethane *via* a one-flask reaction (*Scheme 4.2.2*).



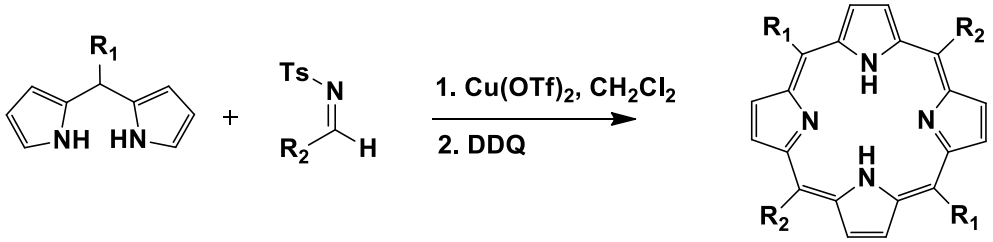
Scheme 4.2.2

Zhen Yao *et al*[14] synthesized A_4 type porphyrins by using 5-(tert-butyldimethylsiloxymethyl) dipyrromethane in the presence of sodium borohydride, indium chloride and DDQ (*Scheme 4.2.3*).



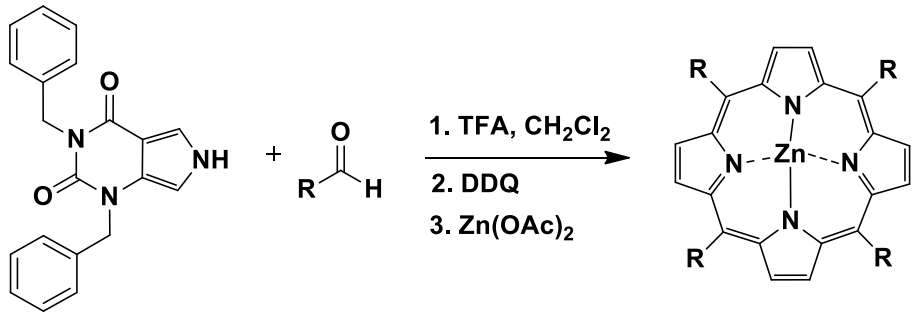
Scheme 4.2.3

Baris Temelli *et al*[15] prepared A_2B_2 type porphyrin derivatives by using 5-phenyldipyrromethane with N-benzylidene-4-methylbenzenesulfonamide in the presence of cupper triflate at room temperature (*Scheme 4.2.4*).



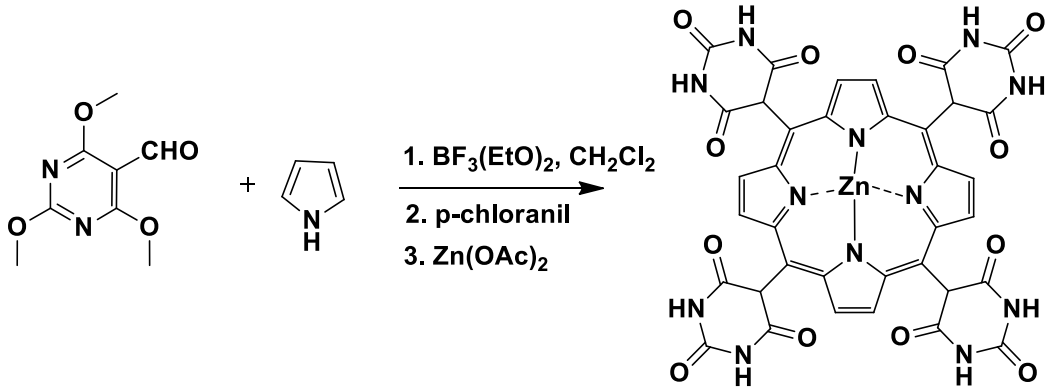
Scheme 4.2.4

C. M. B. Carvalho *et al*[16] reported the synthesis of A_4 type porphyrin derivatives with N-protected uracil-pyrrole and aldehydes (*Scheme 4.2.5*).



Scheme 4.2.5

Satoshi Arai *et al*[17] reported an efficient synthesis of A_4 type porphyrins using 5-formyl-2,4,6-trimethoxypyrimidine and pyrrole in the presence of BF_3 etherate (*Scheme 4.2.6*).



Scheme 4.2.6

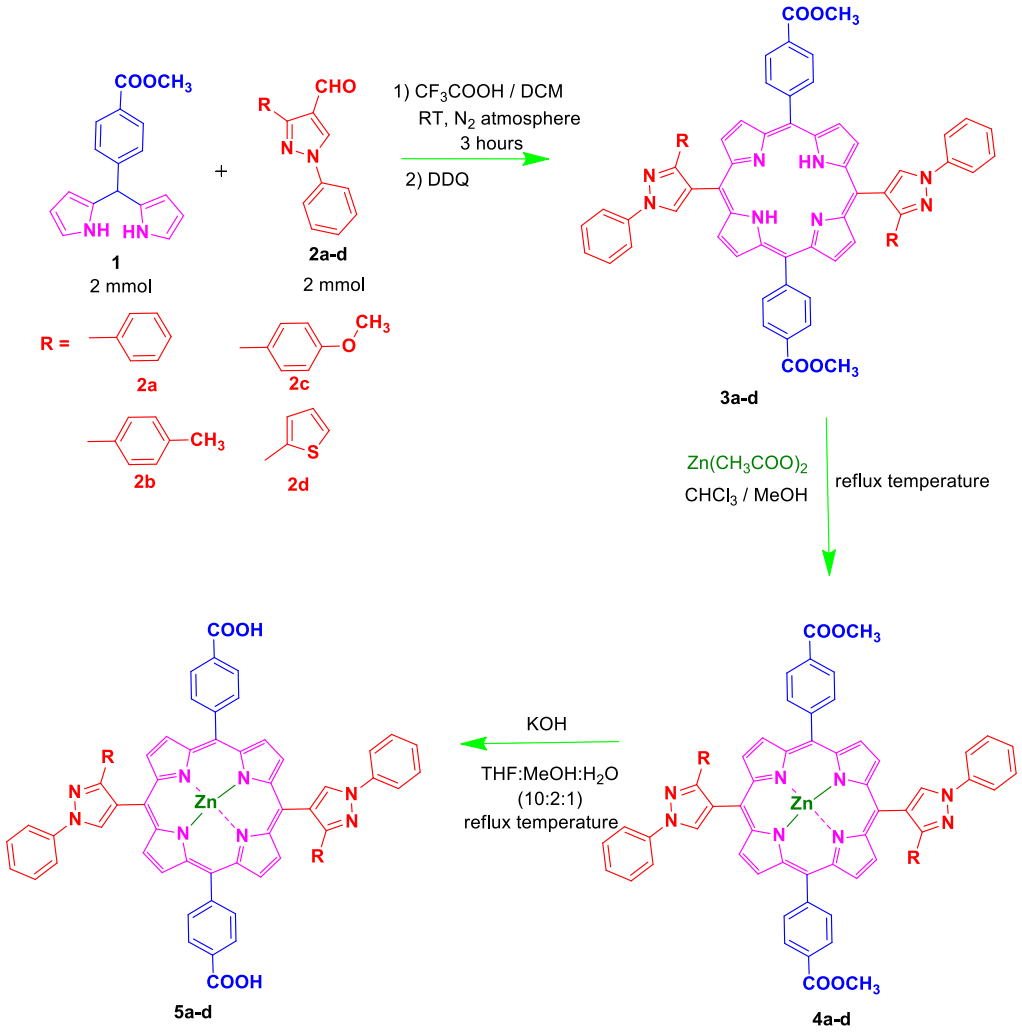
4.3 Present work

Results and Discussion:

The synthesis of Zn(II) complexs of 5,15-bis(1-phenyl-3-substitutedaryl-1*H*-pyrazol-4-yl)10,20-bis(4-carboxyphenyl)porphirins (**5a-d)** was depicted in ***Scheme 4.3.1***. The key intermediates required for the preparation of compounds **5a-d** were 5-(4-carbomethoxyphenyl)dipyrromethane (**1)** and 1-phenyl-3-substituted-aryl-4-formyl-1*H*-pyrazoles (**2a-d**). Dipyrromethane (**1)** was synthesized by reacting pyrrole (3 mols) with methyl-4-formylbenzoate (1 mol) in dilute HCl solution (1.8% HCl), in nitrogen atmosphere at room temperature. The 1-phenyl-3-substituted aryl-4-formyl-1*H*-pyrazoles (**2a-d**) were synthesized starting from 4-substituted acetophenones. The substituted acetophenones were treated with phenyl hydrazine in methanol in presence of catalytic amount of acetic acid for 2 hours to obtain the corresponding phenyl hydrazones which were later reacted with DMF-$POCl_3$ (1:1) mixture

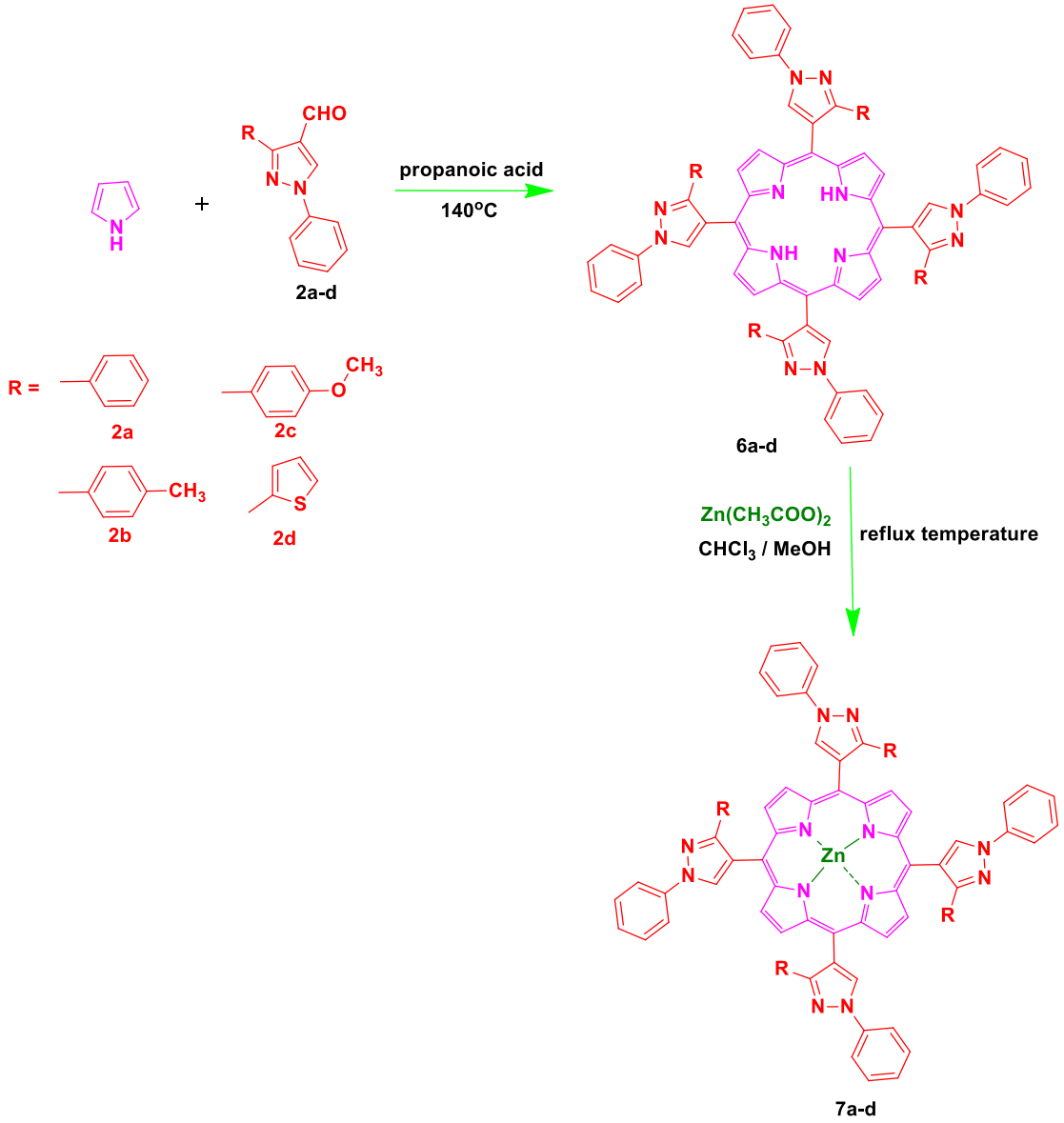
(Vilsmeier Hack reaction) at room temperature, while stirring was continued for 24 hours, in order to produce the required pyrazole aldehydes (**2a-d**) in 70-80% yield.

1-phenyl-3-substituted-aryl-4-formyl-1*H*-pyrazoles (**2a-d**) were treated with 5-(4-carbomethoxyphenyl)dipyrromethane (**1**) in presence of catalytic amount of TFA in dichloromethane at room temperature under nitrogen atmosphere, by Mac-Donald type 2+2 condensation. Further oxidation with DDQ gave 5,15-bis(1-phenyl-3-substitutedaryl-1H-pyrazol-4-yl)10,20-bis(4-carbomethoxyphenyl)porphirins (**3a-d)** in 22-25% yield**.** These porphyrins **(3a-d)** were refluxed with zinc acetate in $CHCl_3$-MeOH (2:1) to obtain zinc metallic porphyrins (**4a-d)** (85-90% yield), which upon hydrolysis with aq. KOH in THF-MeOH (2:1) solvent afforded the corresponding porphyrins (**5a-d**).



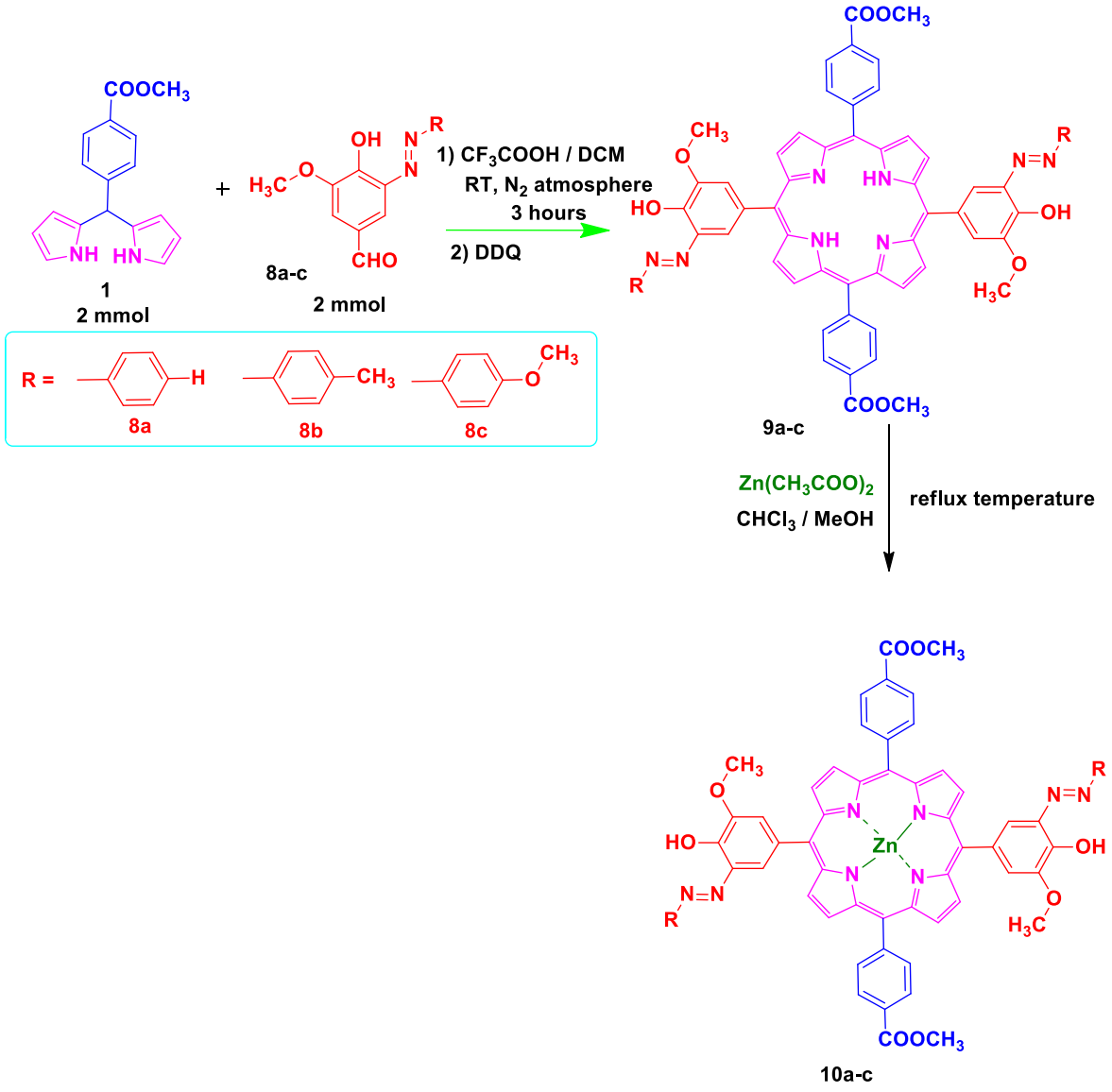
Scheme 4.3.1.

Furthermore, the synthesis of meso-tetrakis(1-phenyl-3-substitutedaryl-1H-pyrazol-4-yl)porphyrins (**6a-d**) were prepared by starting from 1-phenyl-3-substituted-aryl-4-formyl-1*H*-pyrazoles (**2a-d**) and pyrrole in propanoic acid at 140^{o}C for 6 hours. The zinc complexes (**7a-d**) were prepared by treating corresponding porphyrins **(6a-d)** with zinc acetate in chloroform and methanol (***Scheme 4.3.2***.).



Scheme 4.3.2.

4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes (**8a-c**) were treated with 5-(4-carbomethoxyphenyl)dipyrromethane (**1)** in presence of catalytic amount of TFA in dichloromethane at room temperature under nitrogen atmosphere, Further oxidation with DDQ gave 5,15-bis(4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)10,20-bis(4-carbomethoxyphenyl)porphirins (**9a-c)** in 31-33 % yield**.** These porphyrins **(9a-c)** were refluxed with zinc acetate in $CHCl_3$-MeOH (2:1) to obtain zinc metallic porphyrins (**10a-c)** (89-94% yield) (***Scheme 4.3.3***.). Further, the structures of all porphyrins were characterized by UV, IR, ^{1}H-NMR and MALDI-TOF spectrometric analysis.



Scheme 4.3.3.

Experimental:

All the reagents were procured from commercial sources and used without further purification. All the reactions were carried out in oven–dried glassware under an atmosphere of nitrogen. All chromatographic separations were conducted using silica–gel (220-400 mesh). The ^{1}H-NMR spectra were recorded ($CDCl_3$ or DMSO-D_6) at room temperature on Varian Oxford 300 MHz and Bruker AMX500 MHz spectrometers respectively and chemical shifts were reported in parts per million (ppm) with TMS as an internal standard. High resolution mass spectra were recorded in a Bruker Ultrafle Xtreme MALDI-TOF spectrometer. FT-IR spectra were measured on KBr pellets with a Perkin Elmer Spectrometer and reported in cm^{-1}. UV-Visible absorption spectra were obtained in THF or $CHCl_3$ on a Perkin Elmer Lambda-25 Specord 205 spectrophotometer. The emission spectra were measured on a JASCO FP-6500 fluorescence spectrophotometer (wavelength range 200-850).

Spectral discussion

IR

The structures of the porphyrin compounds were confirmed by IR spectra. Porphyrin compounds **3a-d** show strong absorption bands at 3432-3424 cm^{-1} and at 1701-1724 cm^{-1} due to pyrrole –NH and ester carbonyl group. Compounds **4a-d** show absorption band at 1701-1726 cm^{-1} due to ester carbonyl group. Compounds **5a-d** show absorption bands at 3373-3433 cm^{-1} and 1684-1702 cm^{-1} due to –COOH group. Compounds **6a-d** show absorption bands at 3435-3445 cm^{-1} due to pyrrole –NH stretching. Compounds **7a-d** show absorption bands at 2905-2913 cm^{-1} due to –CH stretching. Compounds **9a-c** show absorption bands at 3423-3433 cm^{-1} and 1722-1725 due to pyrrole –NH and ester carbonyl group. Compounds **10a-d** show absorption bands at 2905-2913 cm^{-1} and 1722-1725 due to –CH stretching and ester carbonyl group respectively.

^{1}H-NMR

The structure of the synthesized porphyrin compounds was also characterized by ^{1}H-NMR spectra. In ^{1}H-NMR spectra of the compounds **3a-d**, pyrrole-NH protons were observed as singlets at δ -2.61 to -2.65 ppm, ester–CH_3 protons were observed at δ 4.09-4.12 ppm, pyrazole–CH protons were observed at δ 8.64-8.67 ppm and pyrrole–CH protons were observed at δ 9.14-8.79 ppm. In ^{1}H-NMR spectra of the compounds **4a-d**, ester–CH_3 protons were found at δ 4.00-4.12 ppm, pyrazole–CH protons were present at δ 8.70-8.63 ppm and pyrrole–CH

protons were observed at δ 9.21-8.79 ppm. In ^{1}H-NMR spectra of the compounds **5a-d**, the -COOH protons were obtained at δ 13.32-13.17 ppm, pyrazole–CH protons were present at δ 9.40-9.30 ppm and pyrrole–CH protons were observed at δ 9.07-8.71 ppm. In ^{1}H-NMR spectra of the compounds **6a-d**, pyrrole-NH protons were observed as singlets at δ -2.44 to -2.46 ppm, pyrazole–CH protons were found at δ 8.59-8.67 ppm and pyrrole–CH protons were at δ 9.08-9.01 ppm. In ^{1}H-NMR spectra of the compounds **7a-d**, pyrazole–CH protons were observed at δ 8.62-8.73 ppm and pyrrole–CH protons were seen at δ 9.11-9.17 ppm. In ^{1}H-NMR spectra of the compounds **9a-d,** phenolic-OH protons were found at δ 13.73-13.75 ppm, pyrrole–CH protons were present at δ 9.04-8.82 ppm, ester–CH_3 protons were observed at δ 4.06-4.05 ppm and pyrrole-NH protons were seen as singlets at δ -2.71 to -2.70 ppm. In ^{1}H-NMR spectra of the compounds **10a-d,** phenolic-OH protons were observed at δ 13.67-13.60 ppm, pyrrole–CH protons were present at δ 9.14-9.13 ppm, ester–CH_3 protons were shown at δ 4.10-4.07 ppm.

MALDI-TOF-MS

Furthermore, the MALDI-TOF mass spectra of the porphyrin compounds gave additional evidences for the proposed structure.

General procedure for the synthesis of 5,15-Bis(1-phenyl-3-(4-substitutedphenyl)-1*H*-pyrazol-4-yl)10,20-bis(4-carbomethoxyphenyl)porphyrin derivatives (3a-d)

A solution of 1-phenyl-3-(4-substituted-phenyl)-4-formyl-1*H*-pyrazole (**2a-d**) (1 mmol) and 5-(4-carbomethoxyphenyl)dipyrromethane (**1**) (1 mmol) in 80 ml of dichloromethane was purged with nitrogen gas for 10 min. Then trifluoroacetic acid (0.3 ml, 3.8 mmol) was added and stirred in the dark under nitrogen atmosphere at room temperature. The reaction was monitored from time to time by TLC to confirm the complete disappearance of starting materials. After stirring for 2 hours, DDQ (300 mg) was added and stirred for overnight. The solvent was distilled; the black residues were passed through flash column chromatography using $CHCl_3$: MeOH (99:1) as eluent to give the pure dark violet coloured porphyrins (**3a-d**)

5,15-Bis(1,3-diphenyl-1*H*-pyrazol-4-yl)10,20-bis(4-carbomethoxyphenyl)porphyrin (3a): dark violet; 23.66% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3429, 2946, 1721; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.11 (s, 4H, pyrrole-H), 8.76 (s, 4H, pyrrole-H), 8.67 (s, 2H, pyrazole-H_5), 8.25-8.43 (m, 8H, Ar-H), 8.09-8.13 (m, 4H, Ar-H), 7.59-7.64 (m, 4H, Ar-H), 7.35-7.45 (m, 6H, Ar-H), 6.72-6.93 (m, 6H, Ar-H), 4.09 (s, 6H, -OCH_3), -2.65 (s, 2H, porphyrin-NH); **MALDI-TOF-**

MS: m/z: calculated for $C_{66}H_{46}N_8O_4$ 1014 (M^+); found 1012 (M-2); **UV-Vis**: λ_{max} nm: 424, 520, 554, 595, 655.

5,15-Bis{1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrin (3b): dark violet; 24.1% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3424, 2948, 1721; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.11 (s, 4H, pyrrole-H), 8.76 (s, 4H, pyrrole-H), 8.64 (s, 2H, pyrazole-H_5), 8.24-8.42 (m, 8H, Ar-H), 8.07-8.12 (m, 4H, Ar-H), 7.58-7.62 (m, 4H, Ar-H), 7.30-7.42 (m, 6H, Ar-H), 6.53-6.59 (m, 4H, Ar-H), 4.09 (s, 6H, -OCH_3), 2.00 (s, 3H, -CH_3), 1.97 (s, 3H, -CH_3), -2.64 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{68}H_{50}N_8O_4$ 1042 (M^+), found 1040 (M-2); **UV-Vis**: λ_{max} nm: 422, 520, 554, 594, 655.

5,15-Bis{1-phenyl-3-(4-methoxylphenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrin (3c): dark violet; 22.5% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3431, 2949, 1724, 1251; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.14 (s, 4H, pyrrole-H), 8.79 (s, 4H, pyrrole-H), 8.67 (s, 2H, pyrazole-H_5), 8.29-8.45 (m, 8H, Ar-H), 8.12-8.14 (m, 6H, Ar-H), 7.61-7.65 (m, 4H, Ar-H), 7.36-7.45 (m, 4H, Ar-H), 6.28-6.34 (m, 4H, Ar-H), 4.12 (s, 6H, O-CH_3), 3.48 (s, 6H, -OCH_3), 3.45 (s, 3H, -OCH_3), -2.61 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{68}H_{50}N_8O_6$ 1074 (M^+), found 1072 (M-2); **UV-Vis**: λ_{max} nm: 425, 519, 555, 594, 652.

5,15-Bis{1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrin (3d) :- dark violet; 23.4% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3432, 2947, 1722; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.12 (s, 4H, pyrrole-H); 8.80 (s, 4H, pyrrole-H); 8.67 (s, 2H, pyrazole-H_5); 8.25-8.43 (m, 8H, Ar-H), 8.08-8.11 (m, 4H, Ar-H), 7.59-7.63 (m, 4H, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 6.87-6.82 (m, 2H, Ar-H), 6.04-6.27 (m, 4H, Ar-H), 4.09 (s, 6H, O-CH_3), -2.63 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{62}H_{42}N_8O_4S_2$ 1026 (M^+), found 1024 (M-2); **UV-Vis**: λ_{max} nm: 424, 518, 553, 592, 654.

5,15-Bis{1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yGl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (4a-d)

Porphyrins (**3a-d**) (0.079 mmol) were dissolved in 30 ml of chloroform and added methanolic solution of $Zn(OAc)_2$ $2H_2O$ (0.6 g, 2.73 mmol in 15 ml methanol). The reaction mixture was refluxed for six hours under nitrogen atmosphere. The solvent was removed under

reduced pressure and 20 ml of water was added to the residue. The products were filtered and washed thoroughly with water and dried. The zinc porphyrins were purified by flash silica gel column chromatography using chloroform:methanol (99:1) as an eluent to obtain the pure porphyrins (**4a-d**)

5,15-Bis(1,3-diphenyl-1*H*-pyrazol-4-yl)10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (4a):- light purple solid; 87% yield; **IR** (KBr, cm^{-1}) ν_{max}: 2944, 1715; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.13 (s, 4H, pyrrole-H), 8.79 (s, 4H, pyrrole-H), 8.63 (s, 2H, pyrazole-H_5), 8.14-8.32 (m, 8H, Ar-H), 8.03-8.05 (d, 4H, Ar-H), 7.51-7.55 (m, 4H, Ar-H), 7.24-7.35 (m, 6H, Ar-H), 6.62-6.83 (m, 6H, Ar-H), 4.00 (s, 6H, O-CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{66}H_{44}N_8O_4Zn$ 1076 (M^+); found 1078 (M+2); **UV-Vis**: λ_{max} nm: 425, 551, 589.

5,15-Bis{1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (4b): purple solid; 82% yield; **IR** (KBr, cm^{-1}) ν_{max}: 2922, 1724; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.20 (s, 4H, pyrrole-H), 8.85 (s, 4H, pyrrole-H), 8.68 (s, 1H, pyrazole-H_5), 8.65 (s, 1H, pyrazole-H_5), 8.38-8.42 (m, 4H, Ar-H), 8.23-8.34 (m, 4H, Ar-H), 8.10-8.11 (d, 4H, Ar-H), 7.58-7.61 (m, 4H, Ar-H), 7.38-7.41 (m, 2H, Ar-H), 7.21-7.23 (m, 4H, Ar-H), 6.49-6.54 (m, 4H, Ar-H), 4.08 (s, 6H, -OCH_3), 1.96 (s, 3H, -CH_3), 1.95 (s, 3H, -CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{68}H_{48}N_8O_4Zn$ 1104 (M^+), found 1106 (M+2); **UV-Vis**: λ_{max} nm: 425, 551, 588.

5,15-Bis{1-phenyl-3-(4-methoxylphenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (4c) : purple solid; 88% yield; **IR** (KBr, cm^{-1}) ν_{max}: 2944, 1726, 1274; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.21 (s, 4H, pyrrole-H), 8.87 (s, 4H, pyrrole-H), 8.70 (s, 1H, pyrazole-H_5), 8.68 (s, 1H, pyrazole-H_5), 8.43-8.45 (m, 4H, Ar-H), 8.24-8.36 (m, 4H, Ar-H), 8.12-8.14 (d, 4H, Ar-H), 7.41-7.64 (m, 6H, Ar-H), 6.23-6.29 (m, 4H, Ar-H), 4.12 (s, 6H, O-CH_3), 3.44 (s, 6H, O-CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{68}H_{48}N_8O_6Zn$ 1136 (M^+), found 1138 (M^++2); **UV-Vis**: λ_{max} nm: 424, 551, 587.

5,15-Bis{1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (4d) : purple solid; 89.5% yield; **IR** (KBr, cm^{-1}) ν_{max}: 2949, 1701; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm: 9.21 (s, 4H, pyrrole-H), 8.89 (s, 4H, pyrrole-H), 8.69 (s, 2H, pyrazole-H_5), 8.24-8.41 (m, 8H, Ar-H), 8.09-8.11 (d, 4H, Ar-H), 7.40-

7.62 (m, 6H, Ar-H), 6.78-6.81 (m, 2H, Ar-H), 6.22-6.25 (m, 2H, Ar-H), 6.07-6.11 (m, 2H, Ar-H), 4.07 (s, 6H, O-CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{62}H_{40}N_8O_4S_2Zn$ 1088 (M^+), found 1090 (M+2); **UV-Vis**: λ_{max} nm: 424, 550, 587.

General procedure for the synthesis of 5,15-Bis{1-phenyl-3-(4-substituted-phenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carboxyphenyl)porphyrinato zinc (II) (5a-d)

A solution of zinc metallic porphyrins **(4a-d**) (0.035 mmol) in 20 ml THF-MeOH (1:1) was added 5 ml of aqueous KOH [0.052g, (0.93mmol) in 5 ml of water] and refluxed for 24 hours. Then the solvent was removed under reduced pressure and 20 ml of water was added to the residue. On acidification with 10N HCl solution, the porphyrins were precipitated as bright violet colored solids. The solids were filtered and washed with water three times (10ml of water each time) to remove the inorganic impurities. The compounds were filtered and dried in vacuum to give **5a-d**

5,15-Bis(1,3-diphenyl--1*H*-pyrazol-4-yl)10,20-bis(4-carboxyphenyl)porphyrinato zinc (II) (5a): purple solid; 80% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3426, 2924, 1691; **^{1}H-NMR** (DMSO-D_6, 400 MHz) **δ** (ppm); 13.26 (s, 2H, -COOH), 9.39 (s, 2H, pyrazole-C_5), 9.07 (d, 4H, pyrrole-H), 8.74 (d, 4H, pyrrole-H), 8.24-8.39 (m, 12H, Ar-H), 7.65-7.70 (m, 4H, Ar-H), 7.43-7.48 (m, 2H, Ar-H), 7.26-7.33 (m, 4H, Ar-H), 6.88-6.93(m, 2H, Ar-H), 6.72-6.80 (m, 4H, Ar-H); **MALDI-TOF-MS**: m/z: calculated for $C_{64}H_{40}N_8O_4Zn$ 1048(M^+), found 1049 (M+1); **UV-Vis**: λ_{max} nm: 429, 559, 599.

5,15-Bis{1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carboxyphenyl)porphyrinato zinc (5b): purple solid; 80% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3433, 2920, 1684; **^{1}H-NMR** (DMSO-D_6, 400 MHz) **δ** (ppm): 13.17 (s, 2H, -COOH), 9.31 (s, 2H, pyrazole-C_5), 9.05 (d, 4H, pyrrole-H), 8.71 (d, 4H, pyrrole-H), 8.26-8.37 (m, 12H, Ar-H), 7.63-7.79 (m, 4H, Ar-H), 7.42-7.46 (m, 2H, Ar-H), 7.10-18 (m, 4H, Ar-H), 6.53-6.61 (m, 4H, Ar-H), 1.92 (s, 3H, -CH_3), 1.91 (s, 3H, -CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{66}H_{44}N_8O_4Zn$ 1076 (M^+), found 1079 (M+3); **UV-Vis**: λ_{max} nm: 429, 559, 599.

5,15-Bis(1-phenyl-3-(4-methoxylphenyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carboxyphenyl)porphyrinato zinc (5c): purple solid; 80% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3387, 2929, 1702, 1244; **^{1}H-NMR** (DMSO-D_6, 400 MHz) **δ** (ppm): 13.22 (s, 2H, 2 x COOH), 9.30 (s,

2H, pyrazole-C_5), 9.03 (d, 4H, pyrrole-H), 8.72 (d, 4H, pyrrole-H), 8.25-8.32 (m, 12H, Ar-H), 7.63-7.67 (m, 4H, Ar-H), 7.41-7.46 (m, 2H, Ar-H), 7.18 (d, 4H, Ar-H), 6.30-6.34 (m, 4H, Ar-H), 3.36 (s, 3H, -OCH_3), 3.35 (s, 3H, -OCH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{66}H_{44}N_8O_6Zn$ 1108 (M^+), found 1110(M+2); **UV-Vis**: λ_{max} nm: 429, 559, 599.

5,15-Bis{1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (5d): purple solid; 89.5% yield; **IR** (KBr, cm^{-1}) ν_{max}: 3373, 2923, 1699; **^{1}H-NMR** (DMSO-D_6, 400 MHz) **δ** (ppm): 13.32 (s, 2H, -COOH), 9.40 (s, 2H, pyrazole-C_5), 9.05 (d, 4H, pyrrole-H), 8.76 (d, 4H, pyrrole-H), 8.24-8.32 (m, 12H, Ar-H), 7.64-7.69 (m, 4H, Ar-H), 7.42-7.47 (m, 2H, Ar-H), 7.06-7.10 (m, 2H, Ar-H), 6.22-6.28 (m, 2H, Ar-H), 5.77-5.84 (m, 2H, Ar-H); **MALDI-TOF-MS**: m/z: calculated for $C_{60}H_{36}S_2N_8O_4Zn$ 1060 (M^+), found 1063 (M+3) and 1062 (M+2); **UV-Vis**: λ_{max} nm: 428, 558, 599.

General procedure for the synthesis of meso-tetrakis(1-phenyl-3-(4-sustituted-phenyl)-1*H*-pyrazol-4-yl)porphyrin (6a-d)

1-phenyl-(3-substituted phenyl)-4-formyl-1*H*-pyrazole (**2a-d**) (0.248 g, 1 mmol) and pyrrole (0.280g, 1 mmol) in 15 ml propionic acid taken in a three necked round-bottomed flask fitted with a reflux condenser and purged with nitrogen gas, the reaction mixture was refluxed for 2 hours. The reaction mixture was cooled, distilled the propionic acid and neutralized with $NaHCO_3$ solution. The black solids were allowed to settle then filtered, dried and purified on a silica column using CH_2Cl_2 and MeOH (98:2) as eluent to give pure porphyrins **6a-d.**

meso-tetrakis(1,3-diphenyl-1*H*-pyrazol-4-yl)porphyrin (6a): dark violet; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.02 (s, 8H, pyrrole-H), 8.59-8.64 (m, 4H, pyrazole-H_5), 8.06-8.11 (m, 10H, Ar-H), 7.56-7.71 (m, 9H, Ar-H), 7.29-7.43 (m, 10H, Ar-H), 6.86-6.92 (m, 5H, Ar-H), 6.68-6.79 (m, 6H, Ar-H), -2.46 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{80}H_{54}N_{12}$, 1182; found 1183 (M+1); **UV-Vis**: λ_{max} nm: 419, 515, 551, 589, 651.

meso-tetrakis(1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl)porphyrin (6b): dark violet; **^{1}H-NMR** ($CDCl_3$, 500 MHz) **δ** (ppm): 9.04 (s, 8H, pyrrole-H), 8.60-8.65 (m, 4H, pyrazole-H_5), 8.06-8.10 (m, 8H, Ar-H), 7.55-7.60 (m, 9H, Ar-H), 7.28-7.40 (m, 9H, Ar-H), 7.19-7.24 (m, 3H, Ar-H), 6.51-6.59 (m, 7H, Ar-H), 1.97-2.02 (m, 12H, -CH_3), -2.45 (s, 2H, porphyrin-NH);

MALDI-TOF-MS: m/z: calculated for $C_{80}H_{54}N_{12,}$ 1238; found 1239 (M+1); **UV-Vis**: λ_{max} nm: 427, 525, 565, 596, 660.

meso-tetrakis(1-phenyl-3-(4-methoxylphenyl)-1*H*-pyrazol-4-yl)porphyrin (6c): dark violet; **^{1}H-NMR** ($CDCl_{3,}$ 500 MHz) **δ** (ppm): 9.01-9.05 (m, 8H, pyrrole-H), 8.58-8.64 (m, 4H, pyrazole-H_5), 8.05-8.09 (m, 8H, Ar-H), 7.55-7.60 (m, 10H, Ar-H), 7.32-7.39 (m, 10H, Ar-H), 6.24-6.33 (m, 8H, Ar-H), 3.43-3.48 (m, 12H, -OCH_3), -2.46 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{84}H_{62}N_{12}O_{4,}$ 1304; found 1305 (M+1); **UV-Vis**: λ_{max} nm: 427, 523, 566, 596, 660.

meso-tetrakis(1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl)porphyrin (6d): dark violet; **^{1}H-NMR** ($CDCl_{3,}$ 500 MHz) **δ** (ppm): 9.08 (s, 8H, pyrrole-H), 8.63-8.67 (m, 4H, pyrazole-H_5), 8.06-8.09 (m, 8H, Ar-H), 7.56-7.60 (m, 8H, Ar-H), 7.38-7.41 (m, 5H, Ar-H), 6.81-6.86 (m, 4H, Ar-H), 6.05-6.27 (m, 7H, Ar-H), -2.44 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{72}H_{46}N_{12}S_{4,}$ 1206; found 1207 (M+1); **UV-Vis**: λ_{max} nm: 426, 524, 565, 595, 660.

General procedure for the synthesis of meso-tetrakis(1-phenyl-3-(4-sustituted-phenyl)-1*H*-pyrazol-4-yl)porphyrinato]zinc(II) (7a-d)

Porphyrins (**6a-d**) (0.079 mmol) were dissolved in 30 ml of chloroform and added methanolic solution of $Zn(OAc)_2$ $2H_2O$ (0.6 g, 2.73 mmol in 15 ml methanol). The reaction mixture was refluxed for six hours under nitrogen atmosphere. The solvent was removed under reduced pressure and 20 ml of water was added to the residue. The products were filtered and washed thoroughly with water and dried. The zinc porphyrins were purified by flash silica gel column chromatography using chloroform:methanol (99:1) as an eluent to obtain the pure porphyrins (**7a-d**)

[meso-tetrakis(1,3-diphenyl--1*H*-pyrazol-4-yl)porphyrinato]zinc(II) (7a): dark violet; **^{1}H-NMR** ($CDCl_{3,}$ 400 MHz) **δ** (ppm): 9.13 (d, 8H, pyrrole-H), 8.65-8.71 (m, 4H, pyrazole-H_5), 8.09 (d, 8H, Ar-H), 7.56-7.60 (m, 8H, Ar-H), 7.28-7.41 (m, 12H, Ar-H), 6.83-6.89 (m, 4H, Ar-H), 6.66-6.74 (m, 8H, Ar-H); **MALDI-TOF-MS**: m/z: calculated for $C_{80}H_{52}N_{12}Zn_{,}$ 1244; found 1246 (M+2); **UV-Vis**: λ_{max} nm: 425, 523, 567.

[meso-tetrakis(1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl)porphyrinato]zinc(II) (7b): dark violet; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 9.11-9.13 (t, 8H, pyrrole-H), 8.62-8.71 (m, 4H, pyrazole-H_5), 8.08-8.10 (d, 8H, Ar-H), 7.57-7.60 (t, 8H, Ar-H), 7.37-7.40 (m, 4H, Ar-H), 7.16-7.23 (m, 8H, Ar-H), 6.49-6.54 (m, 8H, Ar-H), 1.95-1.99 (m, 12H, -CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{84}H_{60}N_{12}Zn$, 1302; found 1302 (M^+); **UV-Vis**: λ_{max} nm: 426, 525, 566.

[meso-tetrakis(1-phenyl-3-(4-methoxylphenyl)-1*H*-pyrazol-4-yl)porphyrinato]zinc(II) (7c): dark violet; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 9.11-9.14 (d, 8H, pyrrole-H), 8.64-8.70 (m, 4H, pyrazole-H_5), 8.08-8.10 (d, 8H, Ar-H), 7.56-7.58 (d, 8H, Ar-H), 7.36-7.40 (m, 5H, Ar-H), 7.19-7.23 (t, 7H, Ar-H), 6.20-6.27 (m, 8H, Ar-H), 3.41-3.46 (m, 12H, -CH_3); **MALDI-TOF-MS**: m/z: calculated for $C_{84}H_{60}N_{12}O_4Zn$, 1366; found 1366 (M^+); **UV-Vis**: λ_{max} nm: 422, 521, 563.

[meso-tetrakis(1-phenyl-3-(2-thienyl)-1*H*-pyrazol-4-yl)porphyrinato]zinc(II) (7d): dark violet; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 9.17-9.18 (d, 8H, pyrrole-H), 8.69-8.73 (m, 4H, pyrazole-H_5), 8.08-8.09 (d, 8H, Ar-H), 7.57-7.61 (t, 8H, Ar-H), 7.38-7.42 (m, 4H, Ar-H), 6.76-6.80 (m, 4H, Ar-H), 6.23-6.26 (m, 4H, Ar-H), 6.09-6.14 (m, 4H, Ar-H); **MALDI-TOF-MS**: m/z: calculated for $C_{72}H_{44}N_{12}S_4Zn$, 1270; found 1271 (M+1); **UV-Vis**: λ_{max} nm: 423, 525, 565.

General procedure for the synthesis of 5,15-Bis(4-hydroxy-3-methoxy-5-(4-substituted-phenyldiazenyl)phenyl)10,20-bis(4-carbomethoxyphenyl)porphyrin derivatives (9a-c)

A solution of 4-hydroxy-3-methoxy-5-((substituted phenyl)diazenyl)benzaldehyde (**8a-c**) (1 mmol) and 5-(4-carbomethoxyphenyl)dipyrromethane (**1**) (1 mmol) in 80 ml of dichloromethane was purged with nitrogen gas for 10 min. Then trifluoroacetic acid (0.3 ml, 3.8 mmol) was added and stirred in the dark under nitrogen atmosphere at room temperature. The reaction was monitored time to time by TLC to confirm the complete disappearance of starting materials. After stirring for 2 hours, DDQ (300 mg) was added and stirred for overnight. The solvent was distilled; the black residues were passed through flash column chromatography using $CHCl_3$: MeOH (99:1) as eluent to give the pure dark violet coloured porphyrins (**9a-c**)

5,15-Bis(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)10,20-bis(4-carbomethoxyphenyl)porphyrin (9a): dark violet; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 13.75 (s, 2H, -OH) 9.03-9.04 (s, 4H, pyrrole-H), 8.82-8.83 (s, 4H, pyrrole-H), 8.43-8.47 (m, 8H,

Ar-H), 8.28-8.32 (m, 4H, Ar-H), 7.84-7.86 (m, 6H, Ar-H), 7.34-7.36 (m, 4H, Ar-H), 4.10 (m, 6H, $-OCH_3$), 4.05 (s, 6H, $-OCH_3$), -2.71 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{62}H_{46}N_8O_8$, 1031 (M^+); found 1032 (M+1). **UV-Vis**: λ_{max} nm: 275, 428, 519, 555, 592, 650.

5,15-Bis{4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl}10,20-bis(4-carbomethoxyphenyl)porphyrin (9b): dark violet; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 13.73 (s, 2H, -OH) 9.03-9.04 (s, 4H, pyrrole-H), 8.83-8.84 (s, 4H, pyrrole-H), 8.42-8.46 (m, 6H, Ar-H), 8.29-8.33 (m, 4H, Ar-H), 7.85-7.87 (m, 6H, Ar-H), 7.33-7.35 (m, 4H, Ar-H), 4.11 (m, 6H, $-OCH_3$), 4.06 (s, 6H, $-OCH_3$), 2.45 (s, 6H, $-CH_3$), -2.71 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{64}H_{50}N_8O_8$ 1059 (M^+), found 1061 (M+2); **UV-Vis**: λ_{max} nm: 275, 428, 519, 555, 592, 653.

5,15-Bis{4-hydroxy-3-methoxy-5-(p-methoxydiazenyl)phenyl}10,20-bis(4-carbomethoxyphenyl)porphyrin (9c): dark violet, **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 13.74 (s, 2H, -OH) 9.03-9.04 (s, 4H, pyrrole-H), 8.82-8.83 (s, 4H, pyrrole-H), 8.41-8.45 (m, 6H, Ar-H), 8.29-8.33 (m, 4H, Ar-H), 7.84-7.86 (m, 6H, Ar-H), 7.33-7.35 (m, 4H, Ar-H), 4.11 (m, 6H, $-OCH_3$), 4.06 (s, 12H, $-OCH_3$), -2.70 (s, 2H, porphyrin-NH); **MALDI-TOF-MS**: m/z: calculated for $C_{64}H_{50}N_8O_{10}$, 1091 (M^+), found 1093 (M+2); **UV-Vis**: λ_{max} nm: 274, 428, 519, 554, 592, 654.

5,15-Bis{4-hydroxy-3-methoxy-5-(4-substituted-phenyldiazenyl)phenyl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (10a-c)

Porphyrins (**9a-c**) (0.079 mmol) were dissolved in 30 ml of chloroform and added methanolic solution of $Zn(OAc)_2$ $2H_2O$ (0.6 g, 2.73 mmol in 15 ml methanol). The reaction mixture was refluxed for six hours under nitrogen atmosphere. The solvent was removed under reduced pressure and 20 ml of water was added to the residue. The products were filtered and washed thoroughly with water and dried. The zinc porphyrins were purified by flash silica gel column chromatography using chloroform:methanol (99:1) as an eluent to obtain the pure porphyrins (**10a-c**)

5,15-Bis(4-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (10a): purple solid; **^{1}H-NMR** ($CDCl_3$, 400 MHz)

δ (ppm): 13.63 (s, 2H, -OH) 9.13-9.14 (s, 4H, pyrrole-H), 8.93-8.95 (s, 4H, pyrrole-H), 8.40-8.46 (m, 6H, Ar-H), 8.29-8.34 (m, 4H, Ar-H), 7.87-7.90 (m, 6H, Ar-H), 7.44-7.51 (m, 4H, Ar-H), 4.07 (m, 6H, $-OCH_3$), 4.05 (s, 6H, $-OCH_3$); **MALDI-TOF-MS**: m/z: calculated for $C_{62}H_{44}N_8O_8Zn$, 1094 (M^+); found 1095 (M+1); **UV-Vis**: λ_{max} nm (log €): 276, 431.

5,15-Bis{4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (10b): purple solid; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 13.67 (s, 2H, -OH) 9.13-9.14 (s, 4H, pyrrole-H), 8.93-8.94 (s, 4H, pyrrole-H), 8.39-8.43 (m, 7H, Ar-H), 8.29-8.33 (m, 5H, Ar-H), 7.85-7.88 (m, 3H, Ar-H), 7.76-7.81 (m, 4H, Ar-H), 4.08 (m, 6H, $-OCH_3$), 4.05 (s, 6H, $-OCH_3$), 2.39 (s, 6H, $-CH_3$); **MALDI-TOF-MS**: m/z: calculated for $C_{64}H_{48}N_8O_8Zn$, 1122 (M^+), found 1123 (M+1); **UV-Vis**: λ_{max} nm: 274, 428.

5,15-Bis{4-hydroxy-3-methoxy-5-(p-methoxydiazenyl)phenyl}10,20-bis(4-carbomethoxyphenyl)porphyrinato zinc (II) (10c): purple solid; **^{1}H-NMR** ($CDCl_3$, 400 MHz) **δ** (ppm): 13.60 (s, 2H, -OH) 9.13-9.14 (s, 4H, pyrrole-H), 8.91-8.93 (s, 4H, pyrrole-H), 8.41-8.45 (m, 6H, Ar-H), 8.29-8.33 (m, 4H, Ar-H), 7.84-7.90 (m, 6H, Ar-H), 6.95-7.00 (m, 4H, Ar-H), 4.10 (m, 6H, $-OCH_3$), 4.05 (s, 6H, $-OCH_3$), 3.86 (s, 6H, $-OCH_3$); **MALDI-TOF-MS**: m/z: calculated for $C_{64}H_{48}N_8O_{10}Zn$, 1152 (M^+), found 1153 (M+1); **UV-Vis**: λ_{max} nm: 274, 428.

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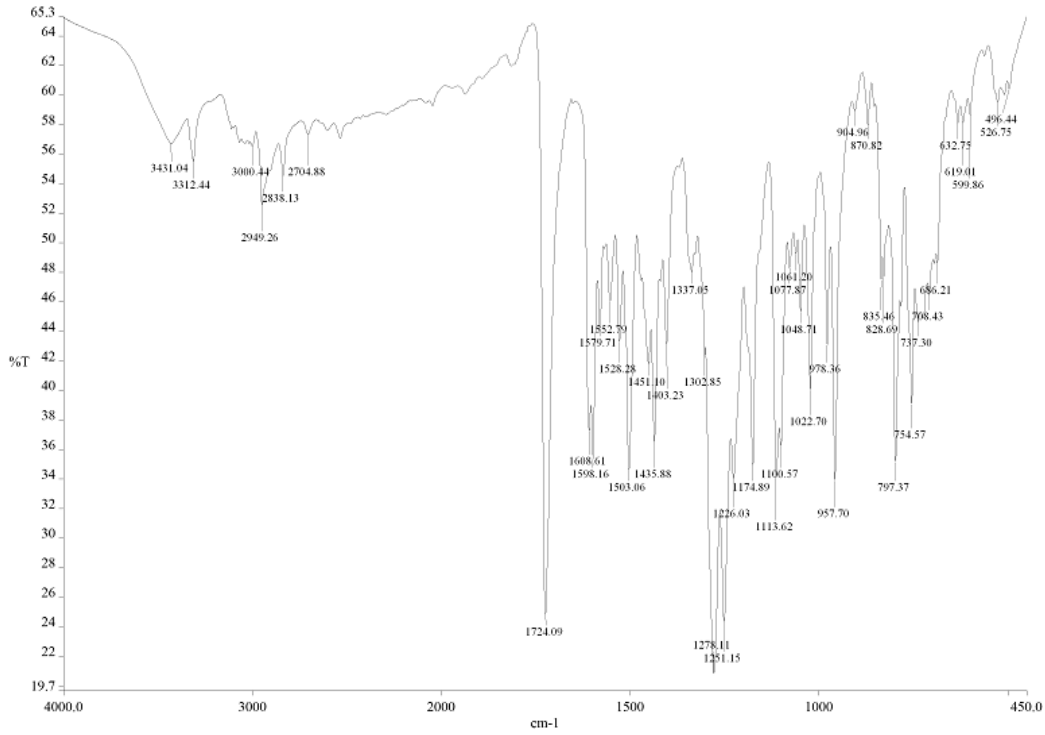
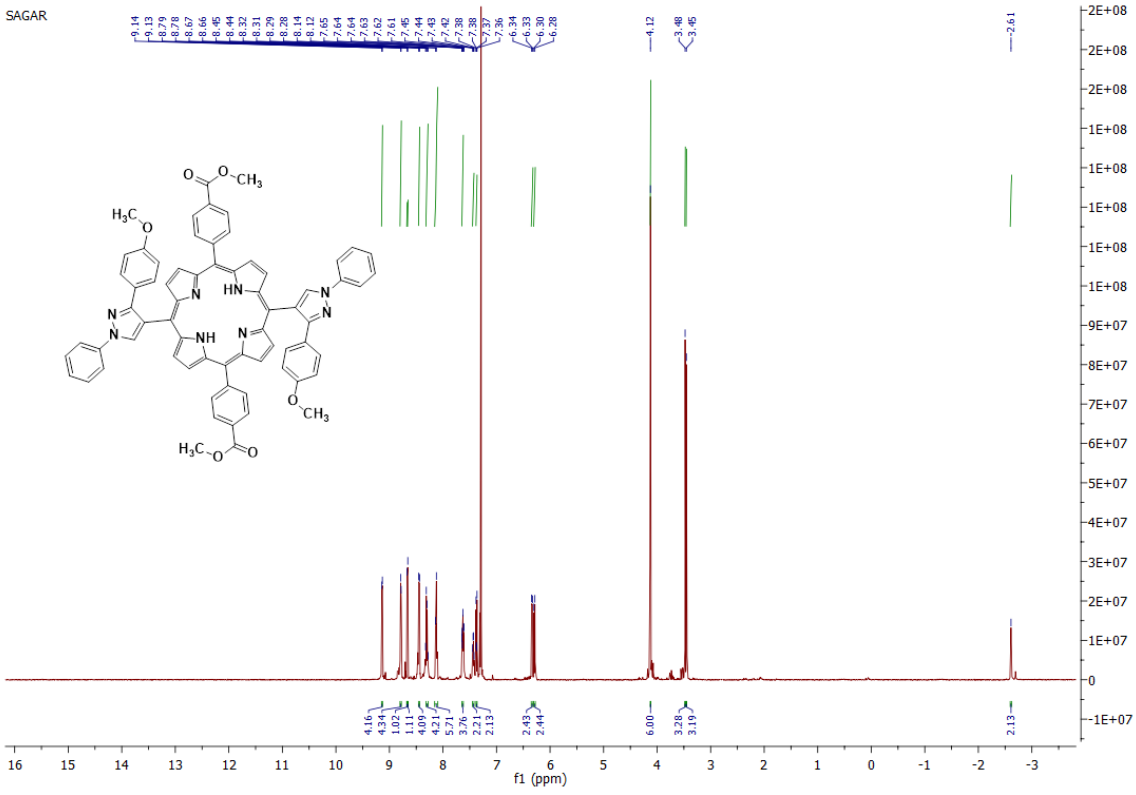


IR spectra of compound 3c



^{1}H-NMR spectra of compound 3c

PROF GVP CHANDRA MOULI , MA-15

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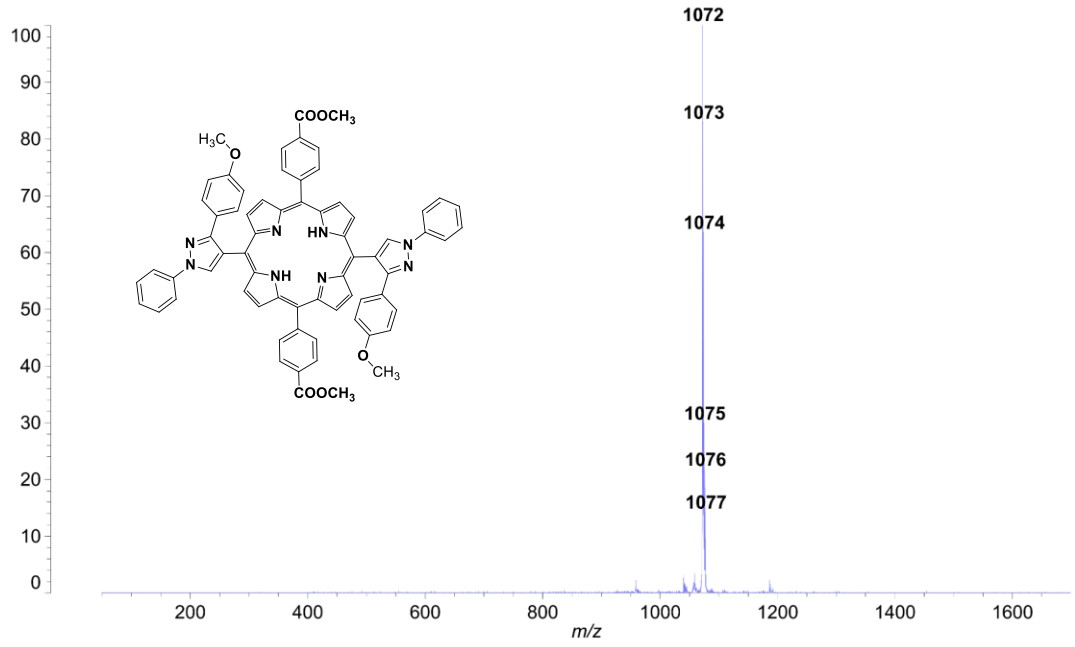
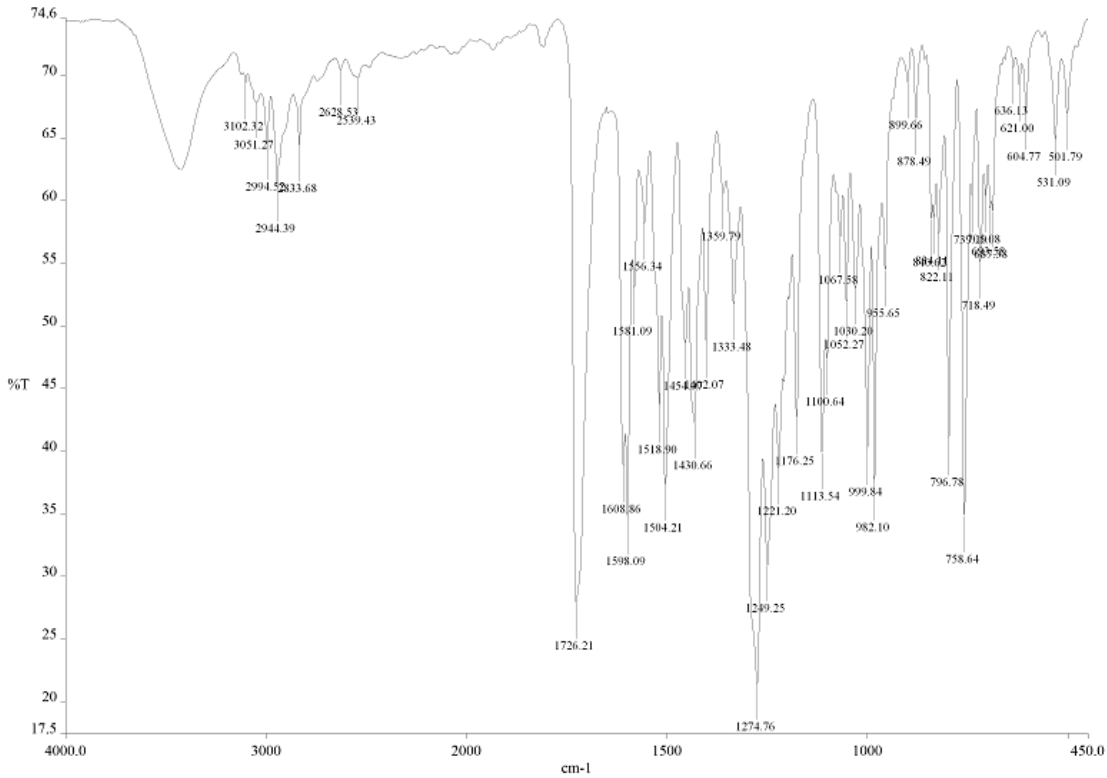


MALDI-TOF-MS spectra of compound 3c



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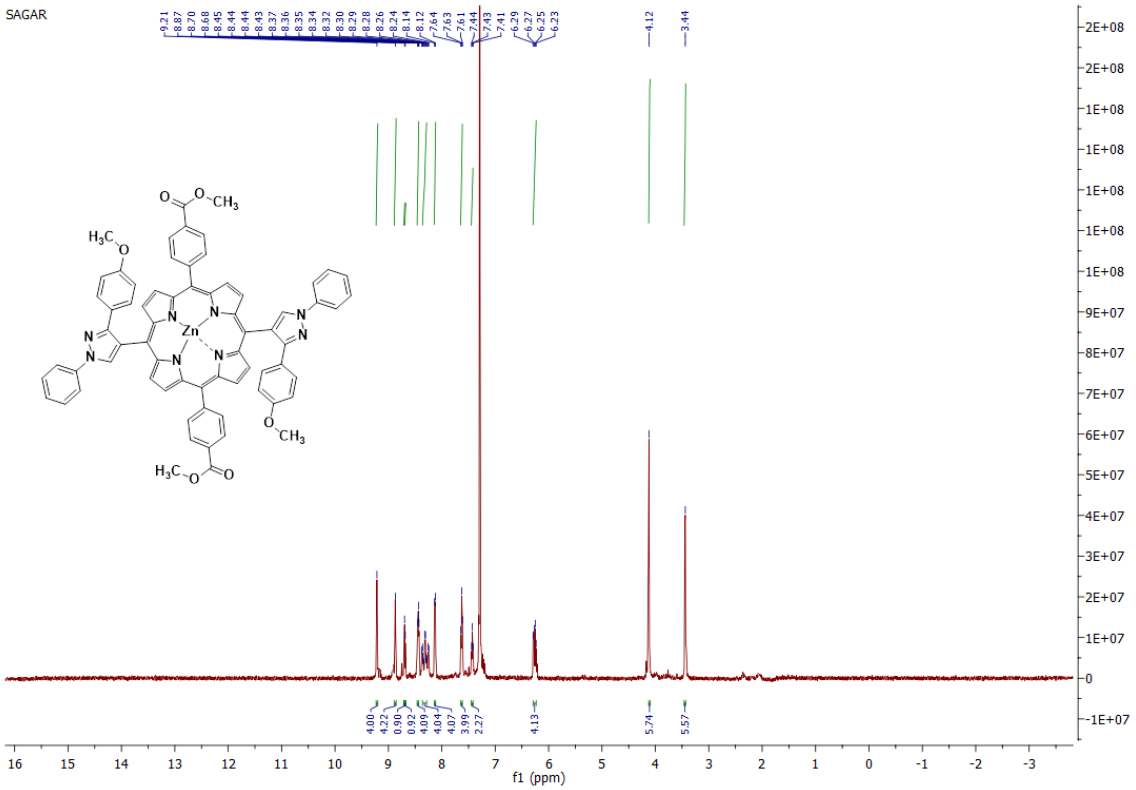

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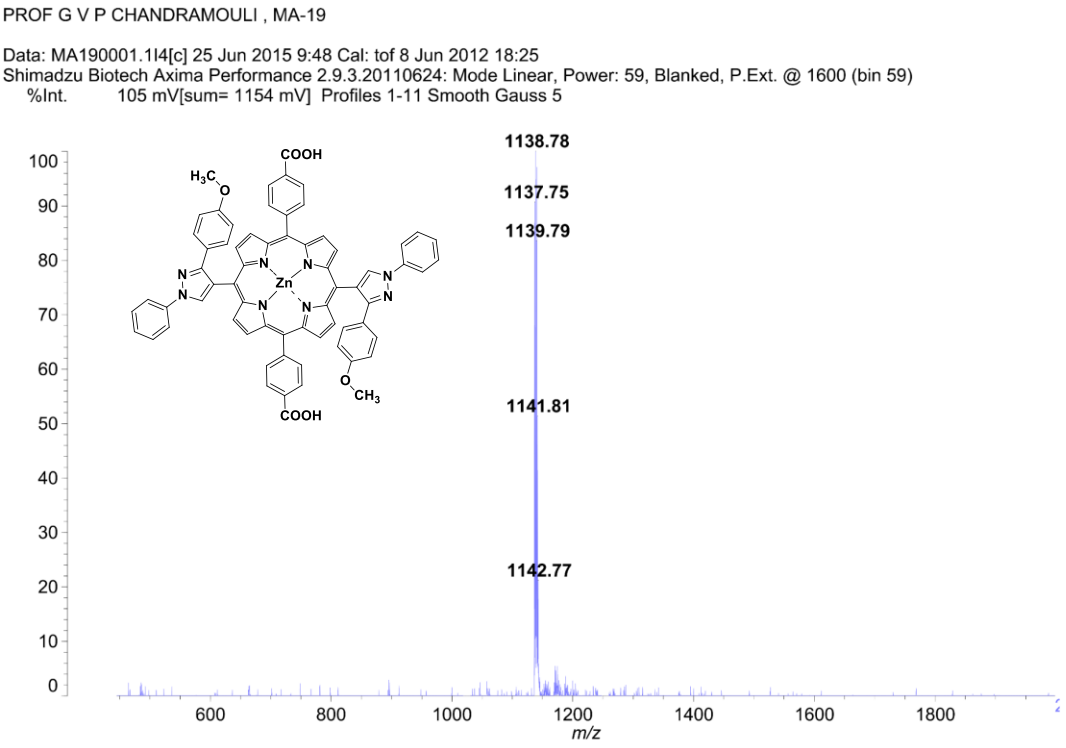
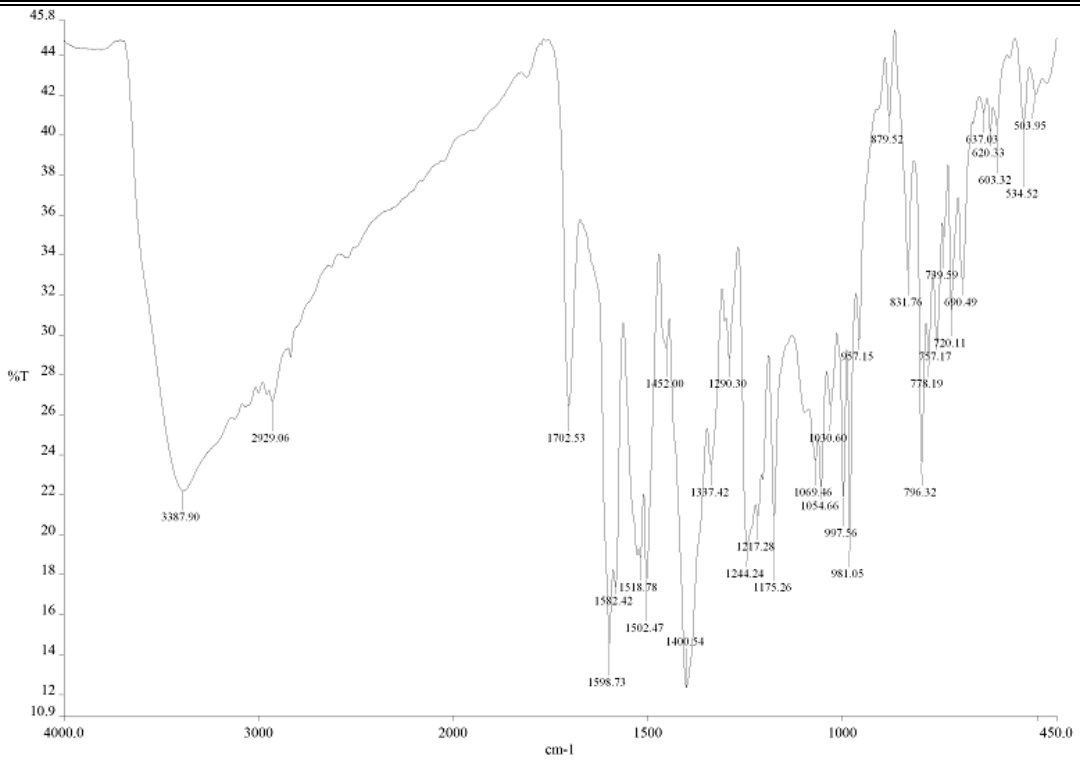


MALDI-TOF-MS spectra of compound 4c



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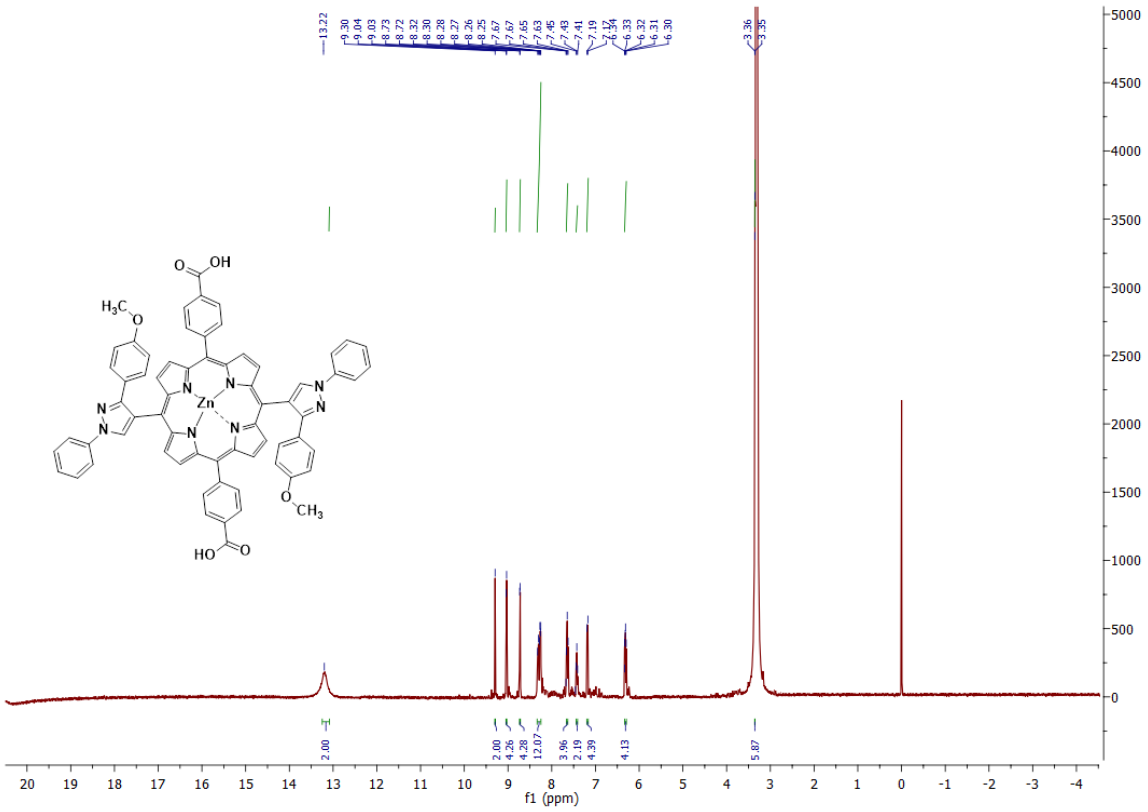
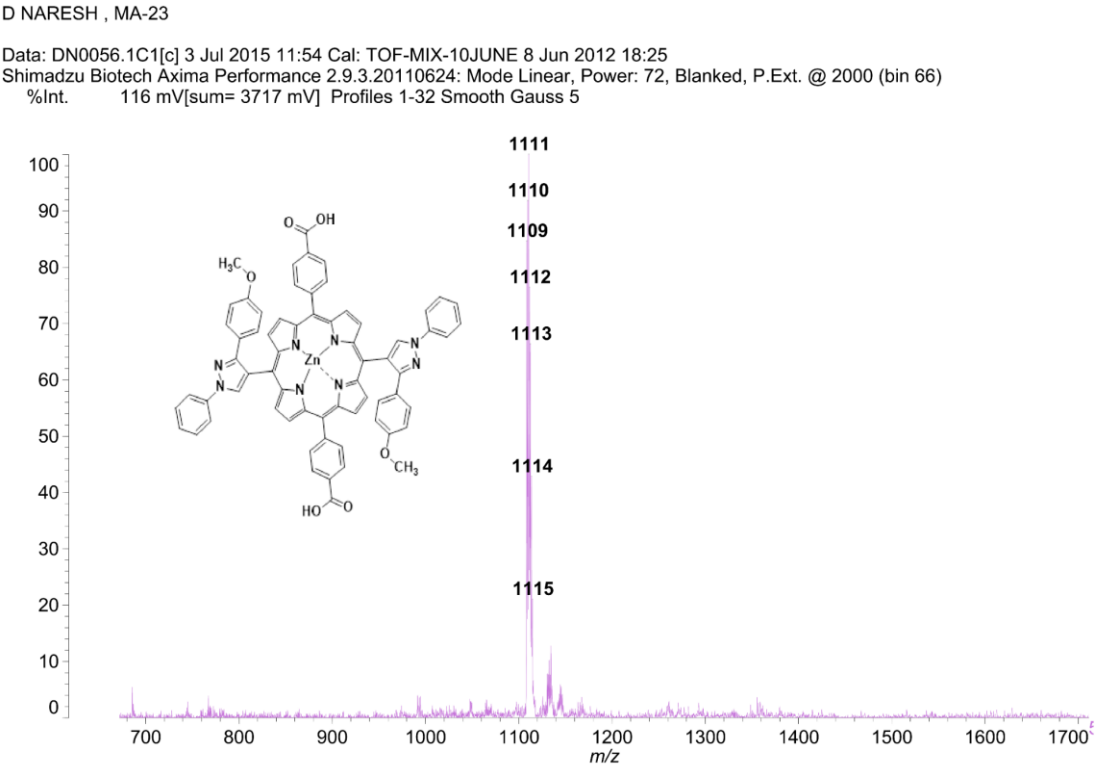
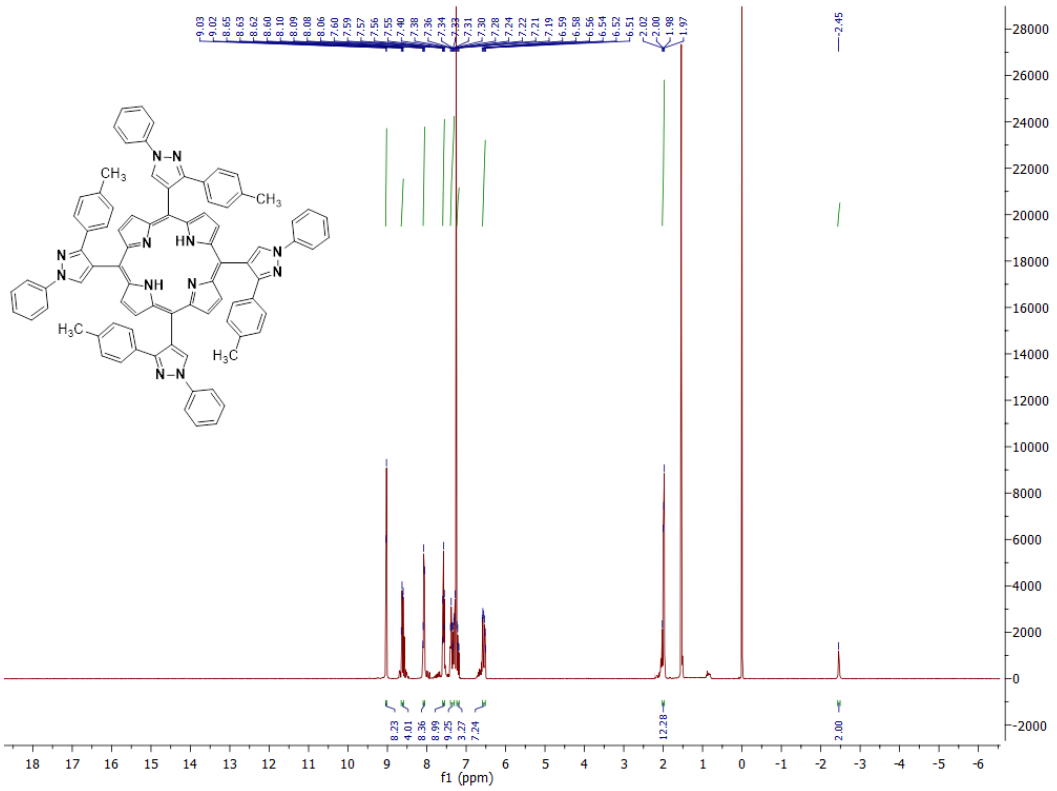


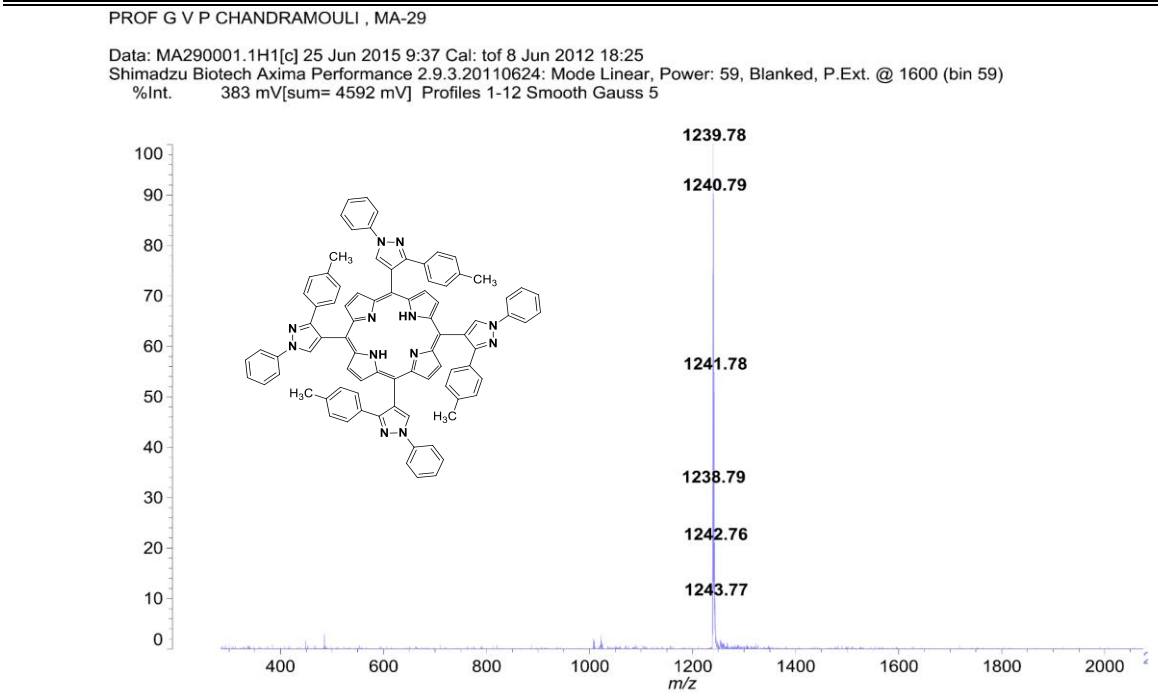
^{1}H-NMR spectra of compound 4c



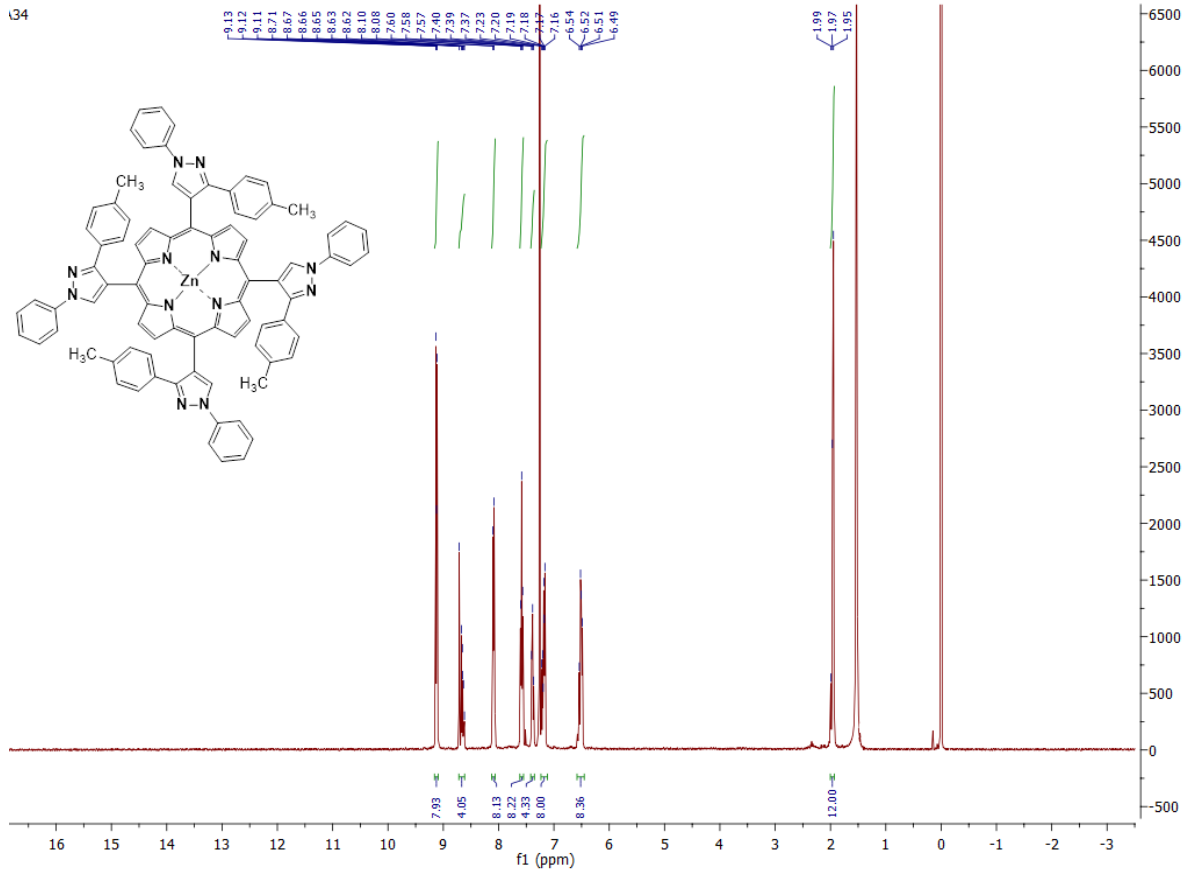
MALDI-TOF-MS spectra of compound 5c



^{1}H-NMR spectra of compound 6b



MALDI-TOF-MS spectra of compound 6b



^{1}H-NMR spectra of compound 7b

PROF C CHANDRAMOULI , MA-34, NIT, WARANGAL

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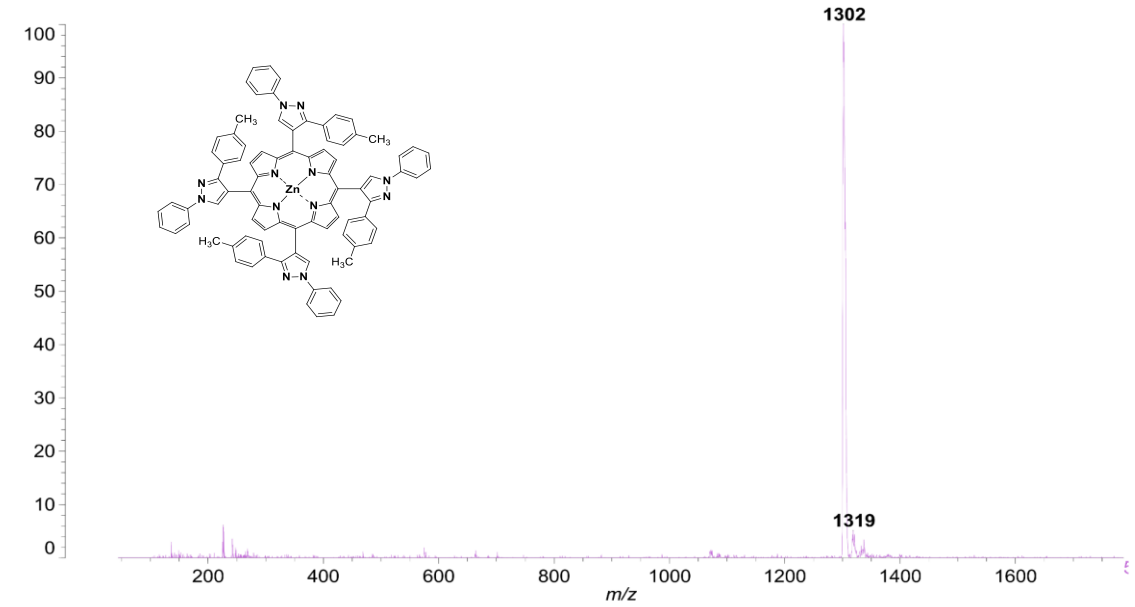
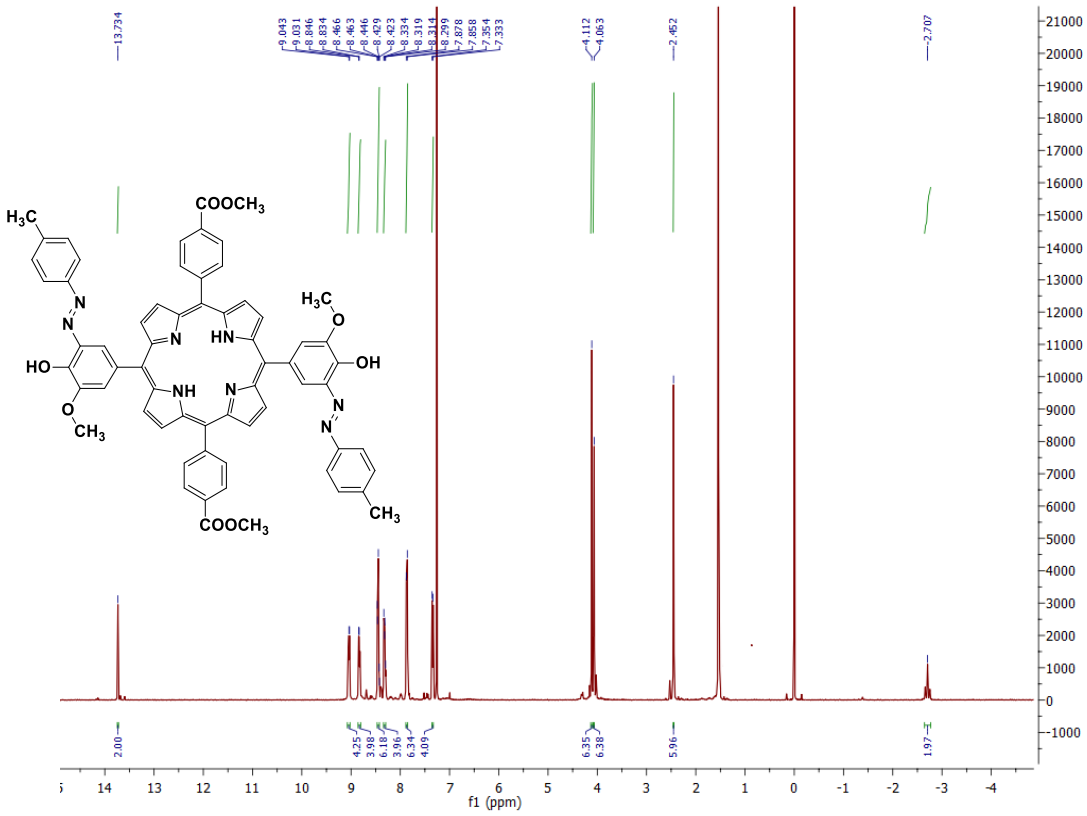
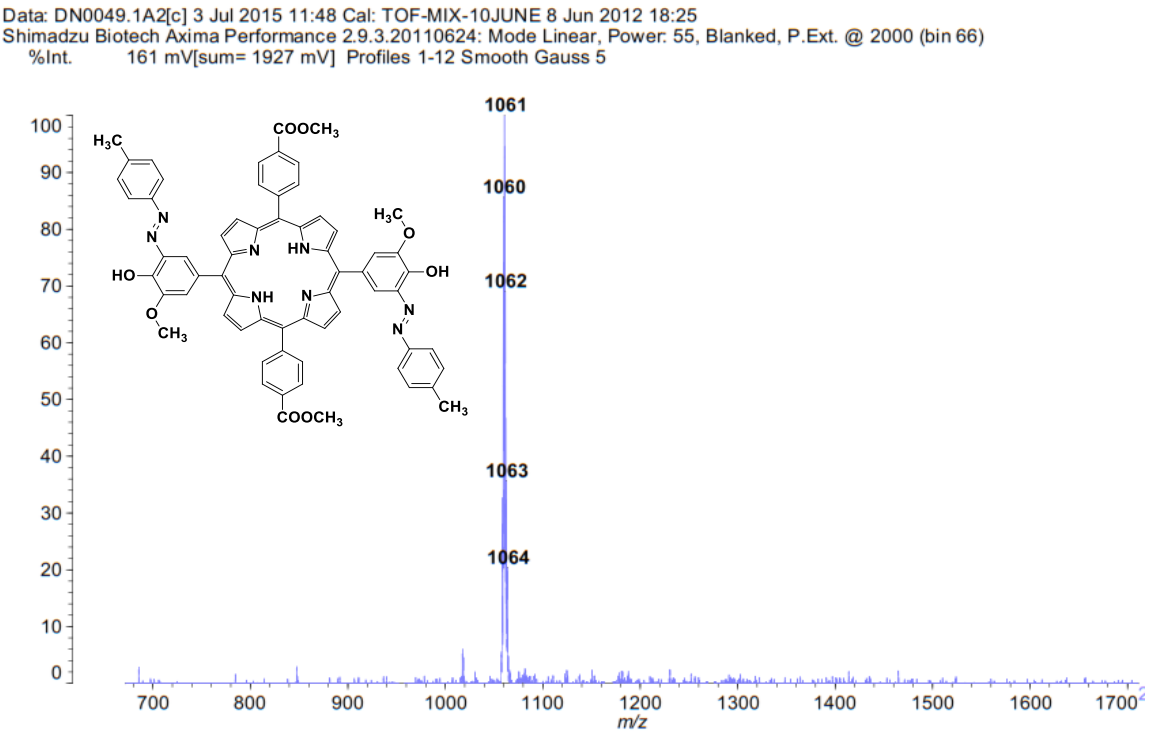


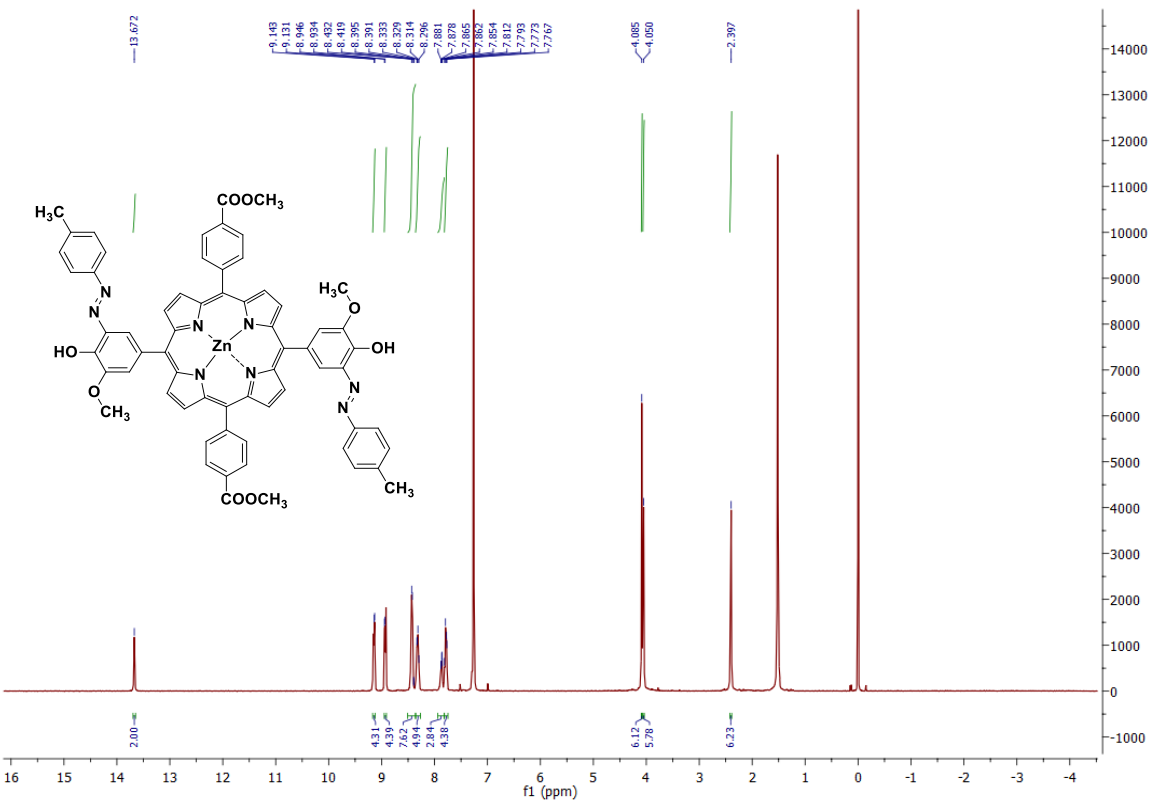
MALDI-TOF-MS spectra of compound 7b



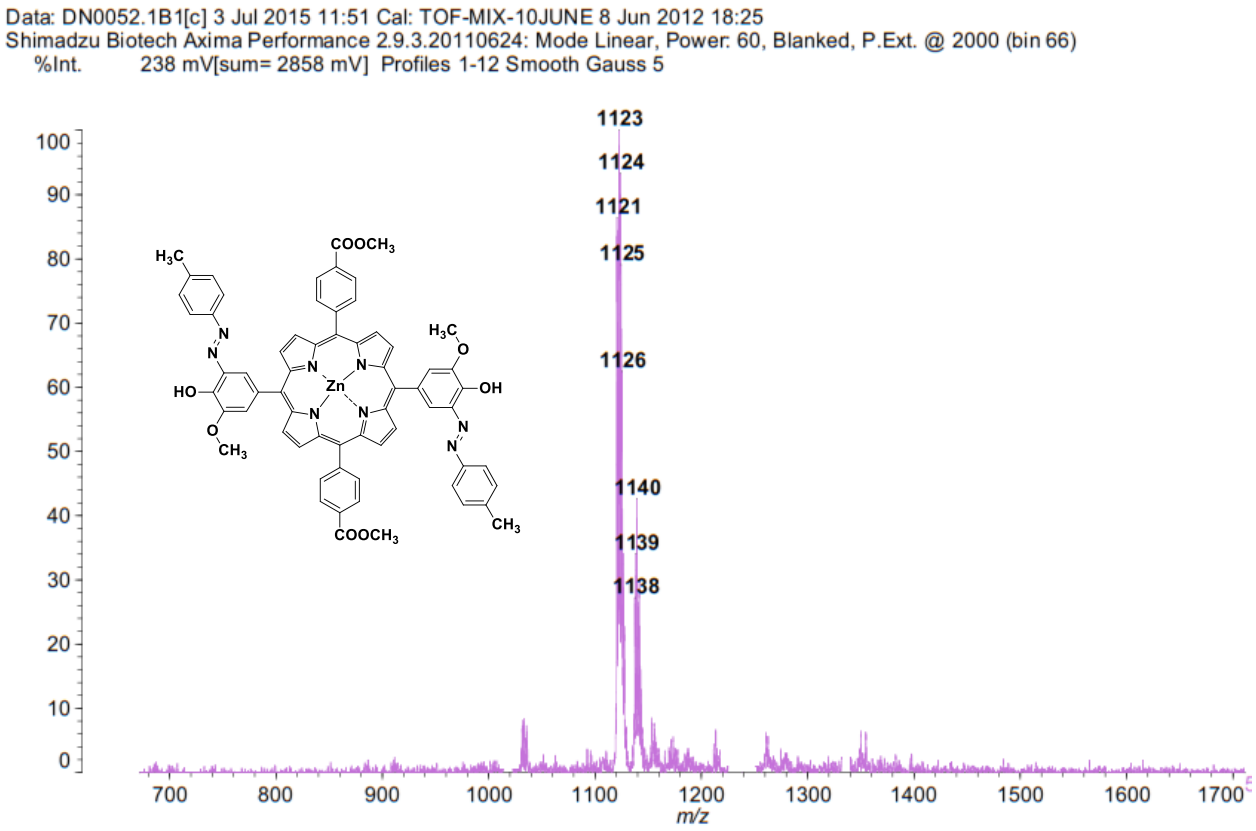
^{1}H-NMR spectra of compound 9b



MALDI-TOF-MS spectra of compound 9b



^{1}H-NMR spectra of compound 10b



MALDI-TOF-MS spectra of compound 10b

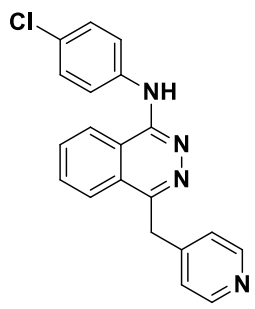
CHAPTER-V

SYNTHESIS OF NEW PYRAZOLO-PHTHALAZINE DERIVATIVES USING [Bmim]BF_4 IONIC LIQUID.

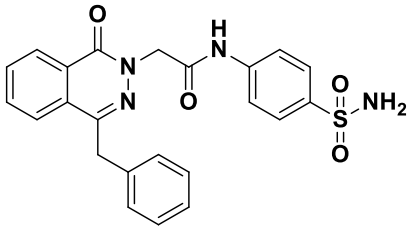
Synthesis of new pyrazolo-phthalazine derivatives using [Bmim]BF_4 ionic liquid.

5.1. Introduction

Phthalazines are significant heterocyclic compounds due to their pronounced biological and pharmaceutical properties such as anticonvulsant,[1] cardiotonic,[2] vasorelaxant,[3] antimicrobial, antifungal,[4] anticancer[5] and anti-inflammatory activities.[6] Pyrazole and its derivatives are well known to be important structural unit for the development of pharmaceuticals and agrochemicals. Pyrazoles also exhibit antimicrobial, antinflammatory, analgesic, anticonvulsant, anticancer and herbicidal activities.[7]



Vatalanib
VEGFR inhibitor



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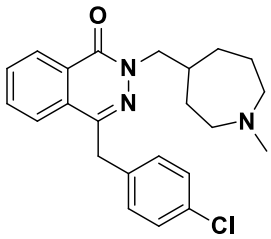
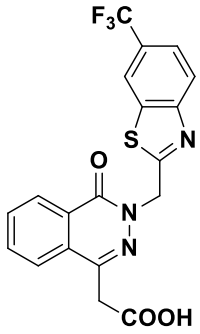
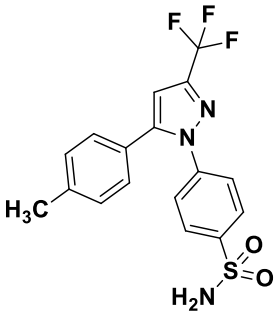


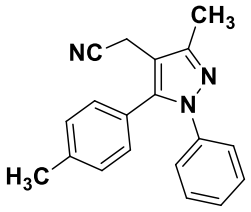
AzelastineMY5445



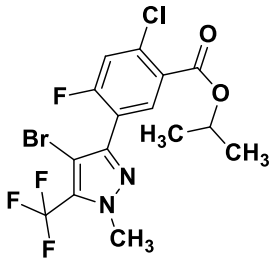
Zopolrestat



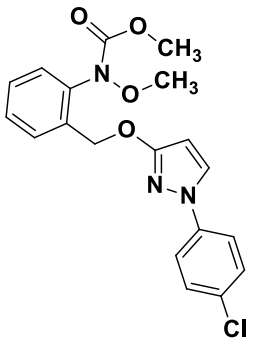
Celecoxib



PNU-32945



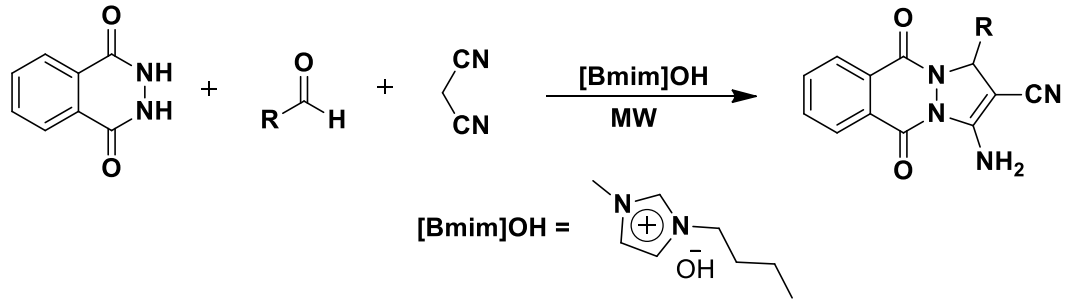
Fluazolate



Pyraclostrobin

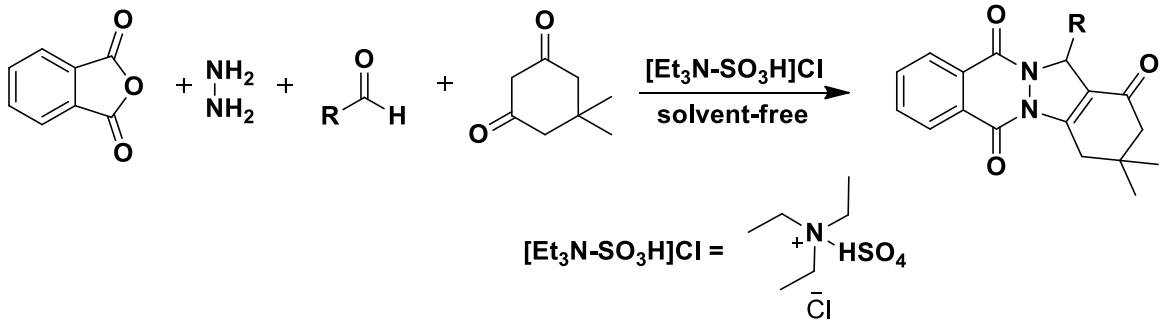
5.2. Earlier synthetic strategies for pyrazolo-phthalazine derivatives using ionic liquids

D. S. Raghuvanshi *et al.*[8] reported an efficient one-pot synthesis of pyrazolophthalazine derivatives by three component condensation reaction of phthalhydrazide, aromatic aldehydes and malononitrile in presence of [bmim]OH under microwave irradiation (*Scheme.5.2.1*).



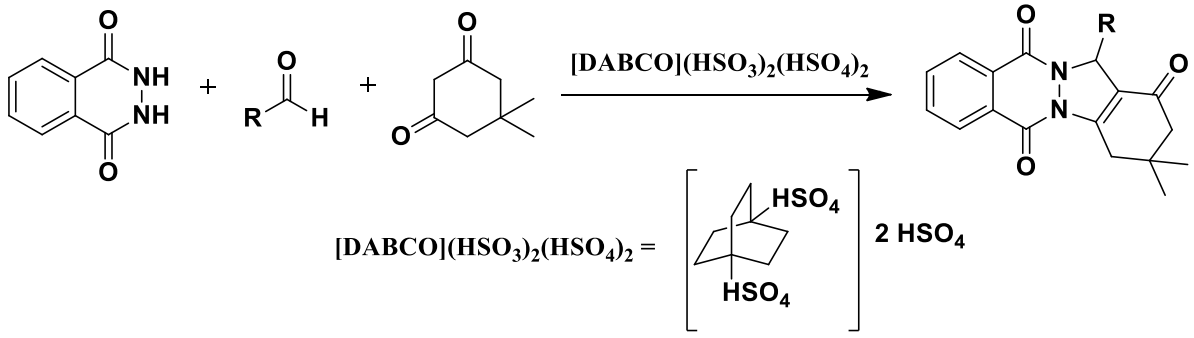
Scheme.5.2.1

B. Pouramiri *et al.*[9] described an efficient method for the synthesis of a series of pyrazolophthalazine derivatives via a condensation reaction of aromatic aldehydes, dimedone, hydrazine hydrate, and succinic anhydride in the presence of $[Et_3N–SO_3H]Cl$ under solvent-free condition (*Scheme.5.2.2*).



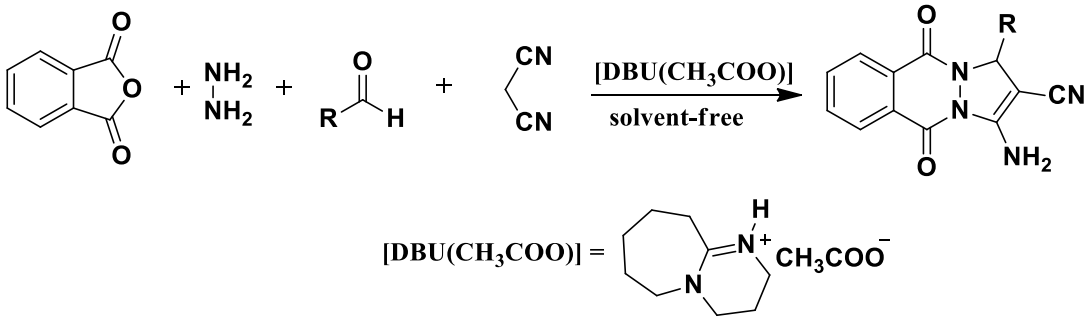
Scheme.5.2.2

Farhad Shirini *et al.*[10] synthesized a series of pyrazolophthalazines by the condensation of aromatic aldehydes, phthalhydrazide and dimedone was studied in the presence of $[DABCO](HSO_3)_2(HSO_4)_2$ (*Scheme.5.2.3*).



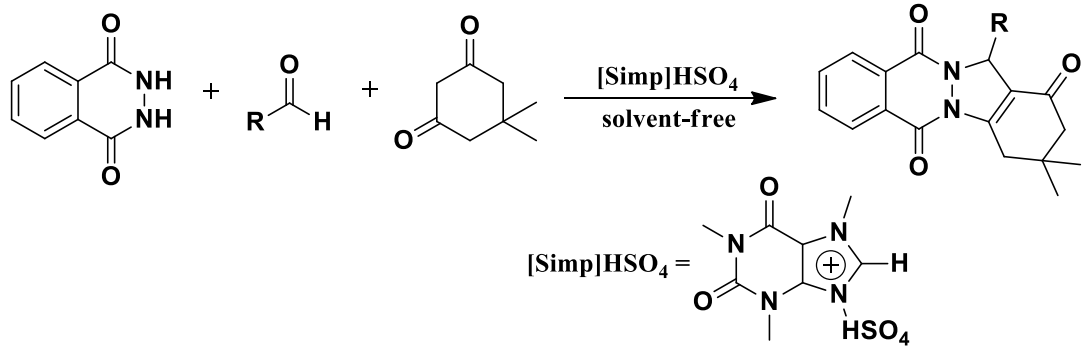
Scheme.5.2.3

Hamid Reza Shaterian *et al.*[11] reported the synthesis of a series of pyrazolophthalazines by the reaction of aromatic aldehydes, dimedone, hydrazine hydrate, and succinic anhydride in the presence of [DBU(CH3COO)] (*Scheme.5.2.4*).



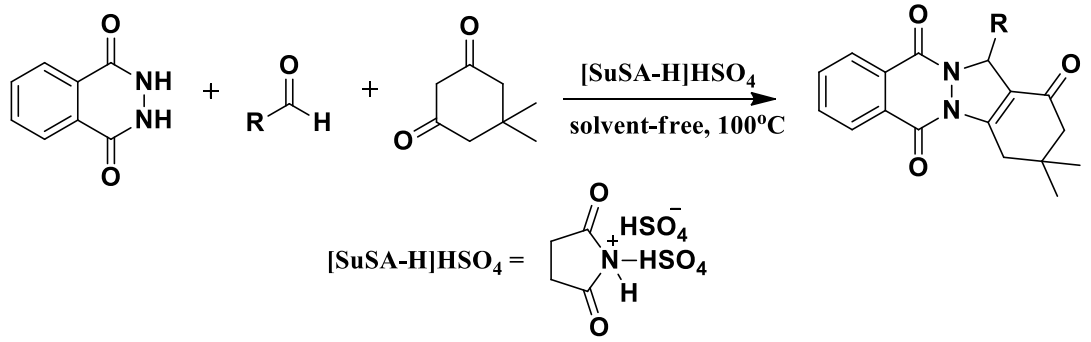
Scheme.5.2.4

Reza Tayebee *et al.*[12] described an efficient synthetic approach for pyrazolophthalazines via a one pot reaction between aromatic aldehydes, phthalhydrazide and dimedone in presence of [Simp]HSO_4 (*Scheme.5.2.5*).



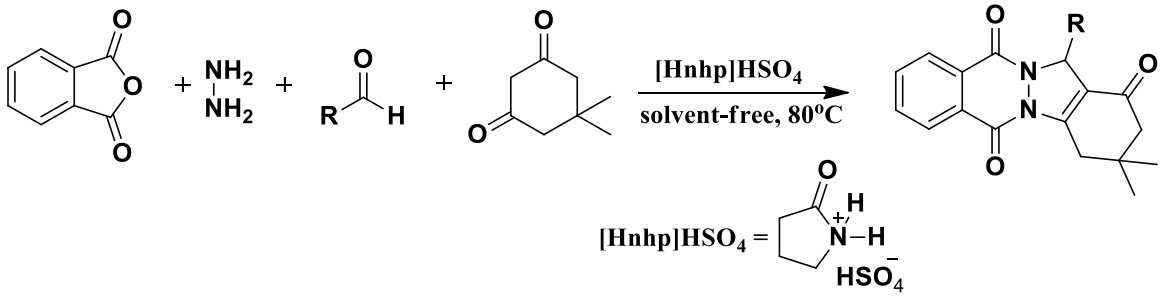
Scheme.5.2.5

Masoumeh Abedini *et al.*[13] synthesized a series of pyrazolophthalazines *via* multicomponent reaction of aromatic aldehydes, phthalhydrazide and dimedone using [SuSA-H]HSO_4 as a catalyst with good yields (*Scheme.5.2.6*).



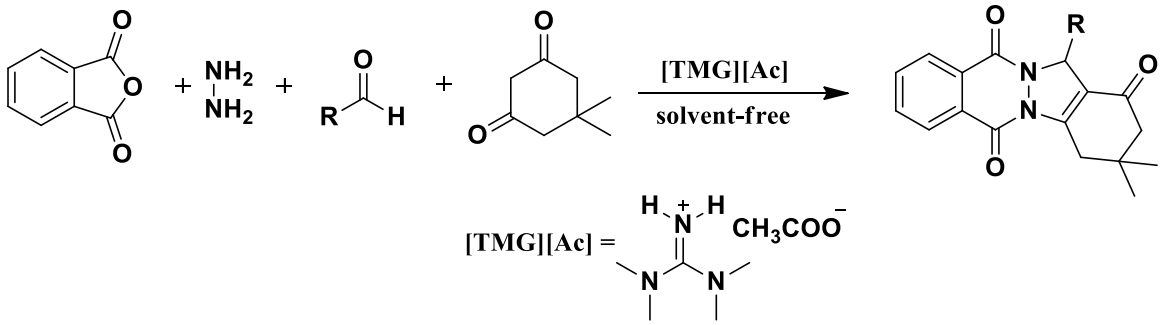
Scheme.5.2.6

Hamid Reza Shaterian *et al.*[14] studied the synthesis of pyrazolophthalazine derivatives by a one pot four component condensation reaction of aromatic aldehydes, phthalhydrazide and dimedone in the presence of [Hnhp]HSO_4 as a catalyst under solvent-free condition (*Scheme.5.2.7*).



Scheme.5.2.7

Hojat Veisi *et al.*[15] have synthesized pyrazolophthalazine derivatives *via* one-pot three component condensation of aromatic aldehydes, phthalhydrazide and dimedone using [TMG][Ac] as a catalyst (*Scheme.5.2.8*).



Scheme.5.2.8

5.3. Present work

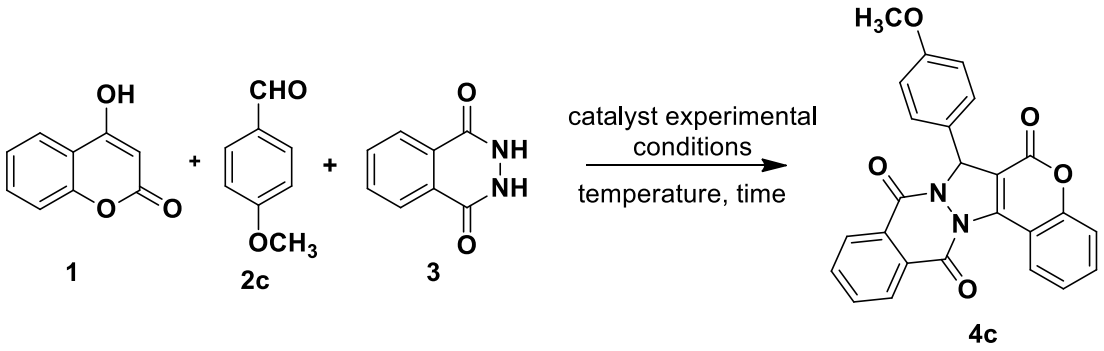
Multi-component processes is a combination of at least three reactants in a single pot to produce a product containing all atoms of the preliminary materials.[16] Multi-component reactions (MCRs) have recently gained considerable attention because of atom efficacy, mild conditions, economy, great convergence and reaction design. The green synthesis concept struggles to understand the scientific tasks of both preserving human health and the environment and has become a significant theme of discussion. A green chemical process for supportable growth always takes into consideration such aspects as using economical catalysts without any additives along with employing a solvent-free method. More recently, ionic liquids have

attracted much response from synthetic organic chemists and have been widely applied for a glut of organic reactions as catalysts because of their relative non-toxicity and recyclability.[17,18]

Results and Discussion

In the course of present work, we designed a multicomponent green chemical method for the synthesis of pyrazolo-phthalazine derivatives. A series of pyrazolophthalazine derivatives (**4a-t**) were synthesized by single-pot reaction of 4-hydroxy coumarin, aromatic aldehydes, phthalhydrazide in the presence of [Bmim]BF_4 ionic liquid, which acts as a catalyst and solvent. To optimize the reaction conditions in terms of catalyst, a model reaction was performed with 4-hydroxycoumarin, 4-methoxybenzaldehyde, and phthalhydrazide using different catalysts like acetic acid, triethyl amine, piperidine, L-Proline, p-TSA and [Bmim]BF_4. In these catalysts [Bmim]BF_4 under solvent free conditions was found to be a more efficient catalyst for this reaction, and acetic acid, L-Proline, p-TSA were less active while triethyl amine and piperidine were inactive. To optimize the reaction conditions in terms of [Bmim]BF_4 ionic liquid the above reaction was repeated using different mol ratios of [Bmim]BF_4 (10, 20, 30 mol%) Table 5.3.1. The desired product (**4c**) was obtained in maximum yield when the ionic liquid was used in 20 mol%. Below 20 mol% the ionic liquid did not yield any encouraging result and when the reaction was attempted, 30 mol% of [Bmim]BF_4 gave good yields of **4c**. It is the same as when 20 mol% of ionic liquid is used. It is concluded that 20 mol% of ionic liquid could not affect the reaction time and product yield. These optimal conditions of using 20 mol % of catalyst at 80 ^oC under solvent free condition were employed for the same reaction employing different aldehydes as shown in scheme 5.3.1. After completion of the reaction, the [Bmim]BF_4 was recovered under reduced pressure, washed with ethyl acetate, dried out and reused for subsequent reactions for further four cycles. However, a slight decrease in its activity was noticed in terms of product yield (Fig. 5.3.1).

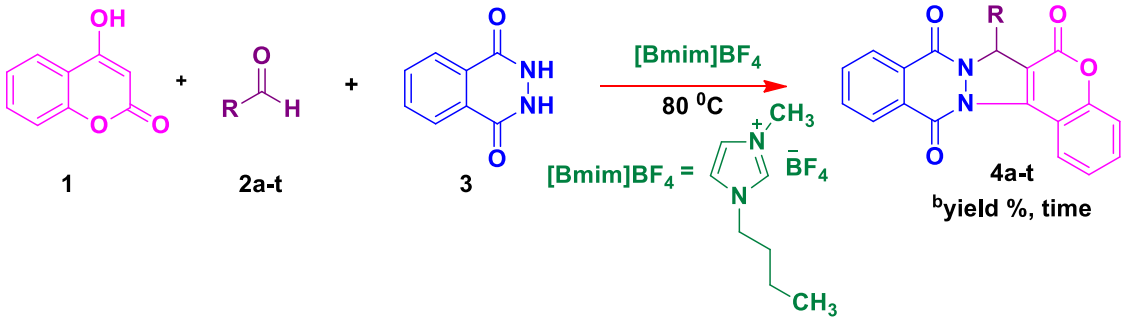
Table 5.3.1: Optimization of reaction conditions for the one-pot synthesis of **4c**

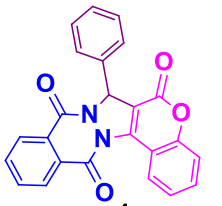


[a]Entries	catalyst	Catalyst loading (mol %)	Temperature (^oC)	Time (min)	[b]Yields (%)
1	No catalyst	----------	rt	90	NR
2	No catalyst	----------	80	90	NR
3	Acetic acid	20	80	65	20
4	L-proline	20	80	60	23
5	p-TSA	20	80	60	47
6	Triethyl amine	20	80	90	NR
7	piperidine	20	80	90	NR
8	$[Bmim]BF_4$	10	80	45	70
9	$[Bmim]BF_4$	20	80	45	91
10	$[Bmim]BF_4$	30	80	45	91

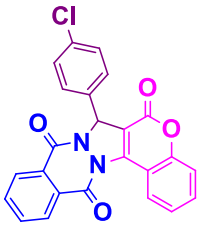
[a]**Reaction conditions**: 4-methoxy benzaldehydes (1 mmol), phthalhydrazide (1 mmol), 4-hydroxy coumarin (1 mmol). [b]Yields of isolated products.

Scheme 5.3.1. Synthesis of pyrazolophthalazine derivatives **4a-t**[a]

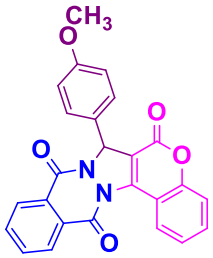




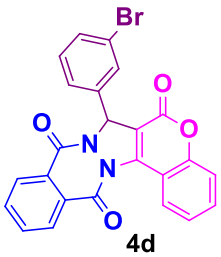
4a
84%, 30 min



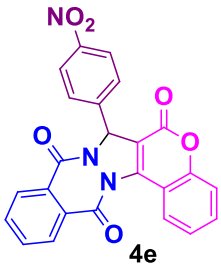
4b
80%, 35 min



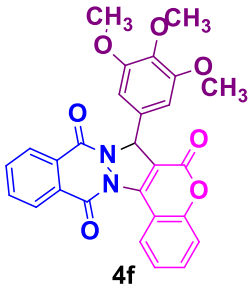
4c
91%, 45 min



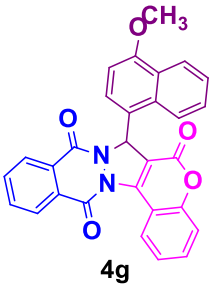
4d
87%, 30 min



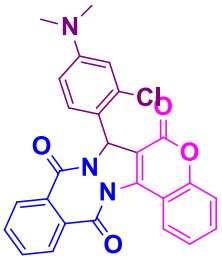
4e
87%, 30 min



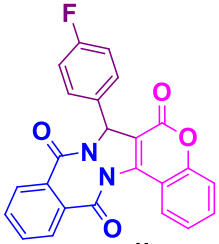
4f
96%, 30 min



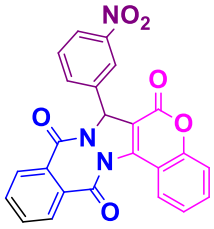
4g
81%, 30 min



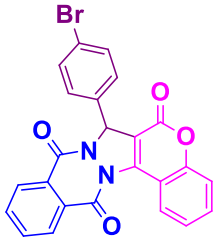
4h
92%, 45 min



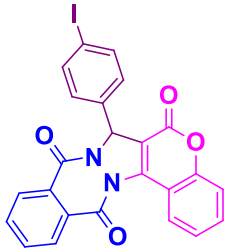
4i
83%, 30 min



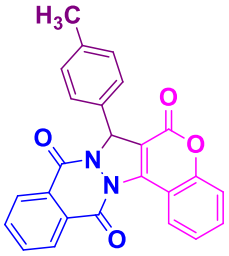
4j
72%, 45 min



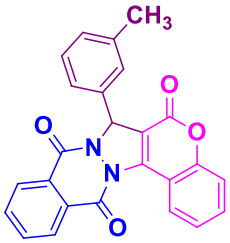
4k
81%, 35 min



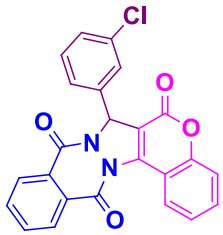
4l
84%, 35 min



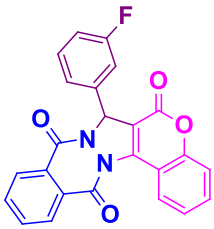
4m
85%, 30 min



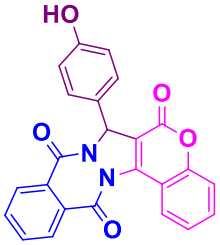
4n
81%, 30 min



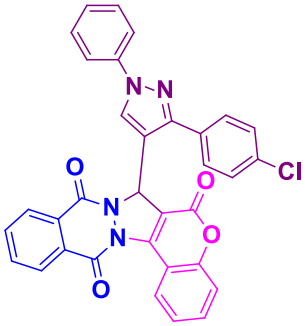
4o
79%, 30 min



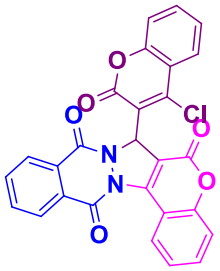
4p
82%, 35 min



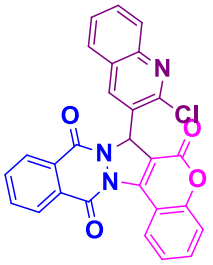
4q
75%, 45 min



4r
89%, 30 min



4s
90%, 35 min

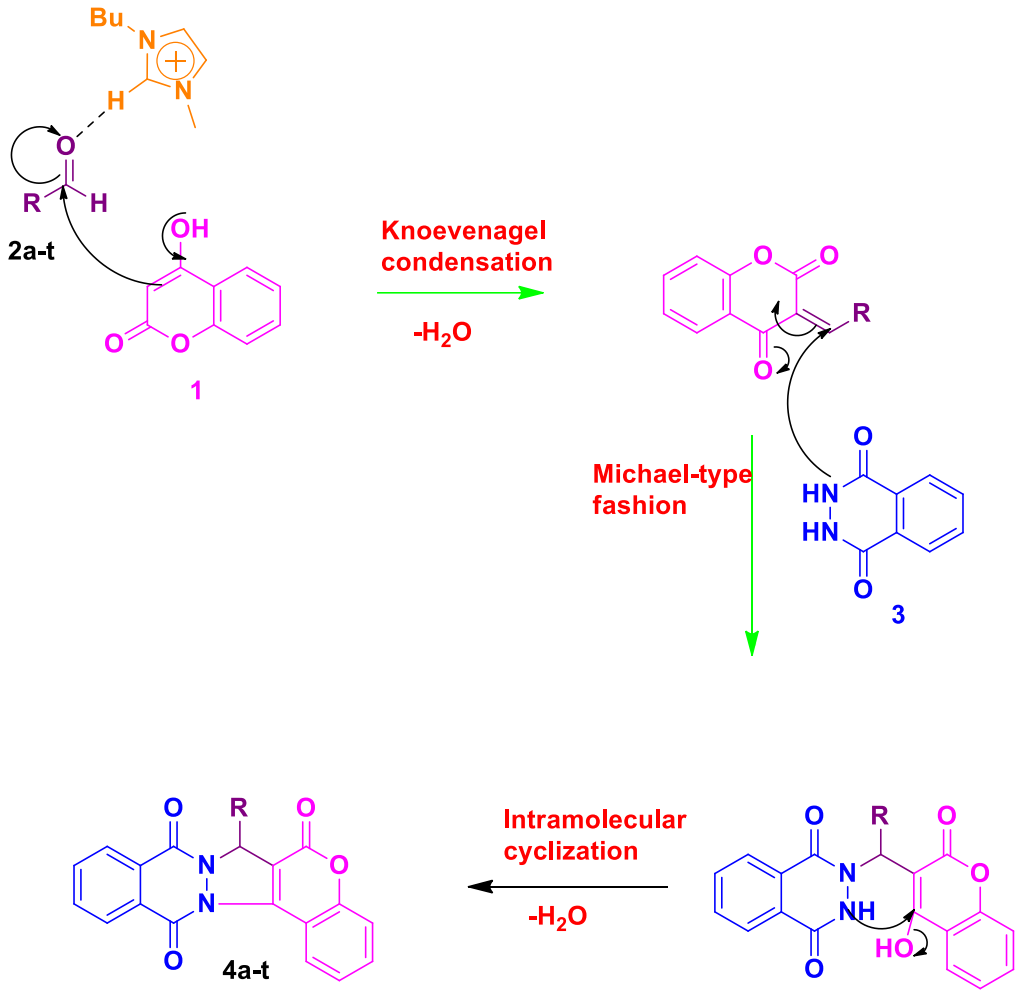


4t
85%, 40 min

[a]**Reaction conditions**: aromatic aldehydes, phthalhydrazide, 4-hydroxy coumarin and [Bmim]BF_4 (20 mole %) solvent free at 80 ^{0}C. [b]Yields of isolated products.

A probable reaction mechanism for the formation of 7-(substituted phenyl) chromeno-pyrazolo [1,2-*b*]phthalazine-6,9,14(7*H*)-trione derivatives (**4a-t**) in the presence of [Bmim]BF_4 is proposed in scheme 5.3.2. The electron deficient hydrogen atom of [Bmim]BF_4, forms hydrogen bonding interaction with the carbonyl function of aldehydes, wherein it assists in the formation of chalcone type moiety via dehydrolative condensation of 4-hydroxy coumarin and aldehydes. Freshly formed chalcone reacts with phthalhydrazide to form chromeno-pyrazolo [1,2-*b*]phthalazine-6,9,14(7*H*)-trione derivatives via Michael-type fashion followed by intra-molecular cyclization respectively.

Scheme 5.3.2. proposed reaction mechanism



EXPERIMENTAL

General information

All the reagents were commercially available and were used without further purification. Reaction progress was observed by thin layer chromatography (TLC) making use of aluminum sheets pre-coated with silica gel 60F254, purchased from Merck. Column chromatography was performed using silica gel column of mesh 100-200. Infrared spectra were recorded using a Bruker WM-4(X) spectrometer (577 model) in KBr from 400 to 4000 cm-1. 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were measured at room temperature on Bruker WM-400 spectrometers, respectively using DMSO-d6 as a solvent. Mass spectra (ESI) were recorded

on a JEOL SX-102 spectrometer. CHN analyses were performed on Carlo Erba EA 1108 automatic elemental analyzer.

Spectral discussion

IR

The formation of pyrazolo-phthalazine derivatives **4a-t** was confirmed by its IR spectra which showed absorption bands at 1781-1797 cm^{-1} and 1655-1670 cm^{-1} due to carbonyl groups respectively.

^{1}H NMR

The formation of pyrazolo-phthalazine derivatives **4a-t** was confirmed by its ^{1}H NMR which showed a singlet at δ 4.92-6.41 ppm due to 3^{o} carbon proton and all other aromatic and aliphatic protons were observed at the expected regions.

^{13}C NMR

The formation of pyrazolo-phthalazines **4a-t** was confirmed by its ^{13}C NMR which showed at δ 25.30-36.15 ppm due to 3^{o} carbon and all other aromatic and aliphatic carbons were identified depending upon their values.

MASS

The mass spectra contain the expected molecular ion peaks corresponding to respective molecular weights of the synthesized compounds.

The elemental analyses values of synthesized compounds were in good agreement with the theoretical data.

General procedure for the synthesis of chromeno-pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione derivatives (4a-t)

A mixture of aldehydes (1 mmol), 2,3-dihydro-1,4-phthalazinedione (1 mmol), 4-hydroxy -coumarin (1 mmol) in [Bmim]BF_4 was heated under reflux for an appropriate time as mentioned in Table 5.3.1. The completion of reaction was monitored by TLC. After disappearance of starting materials the reaction mixture was cooled to room temperature and poured into ice cold water. The solid separated was filtered, washed with water, dried and purified by column chromatography using silica gel (ethyl acetate: hexane (1:1) to afford the title compounds **4a-t**

7-phenyl- chromeno[4',3':3,4]pyrazolo [1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4a)

White solid; mp 218-219 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2955, 1792, 1667, 1605; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.17 (s, 1H), 7.22-7.33 (m, 2H, ArH), 7.41 (d, J = 7.6 Hz, 3H, ArH), 7.61-7.65 (m, 4H, ArH), 8.01 (d, 2H, J = 7.6 Hz, ArH), 8.07 (d, 2H, J= 8 Hz, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 36.15, 104.19, 113.53, 116.00, 117.92, 123.35, 123.61, 126.92, 130.89, 131.57, 152.26, 164.83, 165.36; **MS**: m/z 395 (M+H); Anal. Calcd for $C_{24}H_{14}N_2O_4$: C, 73.09; H, 3.58; N, 7.10; Found: C, 73.12; H, 3.54; N, 7.13.

7-(4-chloro-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4b)

White solid; mp 266-267 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2963, 1793, 1667, 1613; **^{1}H NMR** (400 MHz, DMSO-d6): 6.27 (s, 1H), 6.66-6.72 (m, 2H, ArH), 6.80 (d, 2H, J = 8.4 Hz, ArH), 7.29-7.34 (m, 4H, ArH), 7.56-7.60 (m, 2H, ArH), 7.90 (t, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.70, 103.89, 115.97, 116.16, 118.01, 123.73, 123.95, 127.94, 130.11, 131.94, 139.35, 152.27, 164.69, 165.51; **MS**: m/z 429 (M+H); Anal. Calcd for $C_{26}H_{13}ClN_2O_6$: C, 67.22; H, 3.06; N, 6.53; Found: C, 67.14; H, 3.24; N, 6.62.

7-(4-methoxyphenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4c)

White solid; mp. 251-253 ^{o}C; IR (KBr, cm-1) $_{vmax}$: 2955, 1793, 1667, 1604; **^{1}H NMR** (400 MHz, DMSO-d6): δ 3.69 (s, 3H, OCH_3), 6.25 (s, 1H), 6.77 (d, 2H, J = 8.8 Hz, ArH), 7.03 (d, 2H, J = 8.8 Hz, ArH), 7.27-7.33 (m, 4H, ArH), 7.54-7.58 (m, 2H, ArH), 7.85-7.87 (m, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.23, 54.94, 104.39, 115.95, 117.82, 123.76, 123.85, 127.75, 131.35, 131.89, 152.16, 157.32, 164.79, 165.02; **MS**: m/z 425 (M+H); Anal. Calcd for $C_{25}H_{16}N_2O_5$: C, 70.75; H, 3.80; N, 6.60; Found: C, 70.72; H, 3.84; N, 6.62.

7-(3-bromo-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4d)

White solid; mp 258-259 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2984, 1793, 1668, 1603,1309; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.26 (s, 1H), 7.12 (s, 2H, ArH), 7.23-7.33 (m, 6H, ArH), 7.55 (d, 2H, J = 6.8, ArH), 7.85 (d, J = 6.8, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.85, 103.81, 115.87, 119.65, 123.82, 123.93, 128.02, 128.93, 130.17, 132.05, 140.02, 152.45, 164.81, 165.35; **MS**: m/z 474 (M+H); Anal. Calcd for $C_{24}H_{13}BrN_2O_4$: C, 60.91; H, 2.77; N, 5.92; Found: C, 60.84; H, 2.89; N, 6.09.

7-(4-Nitro-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4e)

White solid; mp 264-265 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2981, 1795, 1667, 1607; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.26 (s, 1H), 6.77(t, 2H, ArH), 7.04 (d, J = 7.2, 2H, ArH), 7.28-7.35 (m, 4H, ArH), 7.55-7.59 (m, 2H, ArH), 7.86-7.89 (m, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6):

δ 27.28, 109.38, 113.89, 116.16, 116.60, 122.32, 122.61, 123.91, 124.70, 132.10, 132.46, 136.21, 152.89, 164.82, 165.53; **MS**: m/z 440 (M+H); Anal. Calcd for $C_{24}H_{13}N_3O_6$: C, 65.61; H, 2.98; N, 9.56; Found: C, 65.84; H, 2.89; N, 9.39.

7-(2,3,4-trimethoxy-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4f)

White solid; mp 291-292 ºC; **IR** (KBr, cm-1) vmax: 2963, 1793, 1667, 1613; **^{1}H NMR** (400 MHz, DMSO-d6): δ 3.47 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.28 (s, 1H), 7.14 (d, 2H, J = 8.4 Hz, ArH), 7.23-7.33 (m, 4H, ArH), 7.56 (t, 2H, ArH), 7.86 (d, 2H, J = 8.4 Hz, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 28.25, 55.92, 56.01, 60.99, 108.31, 114.08, 116.03, 116.81, 121.30, 122.41, 123.74, 124.73, 131.89,132.27, 136.49, 151.90, 152.01, 156.61, 157.50, 164.62, 165.43; **MS**: m/z 485 (M+H); Anal. Calcd for $C_{27}H_{20}N_2O_7$: C, 66.94; H, 4.16; N, 5.78; Found: C, 66.81; H, 4.23; N, 5.66.

7-(4-methoxy-naphthyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4g)

White solid; mp 254-255 ºC; **IR** (KBr, cm-1) $_{vmax}$: 2959, 1794, 1668, 1602; **^{1}H NMR** (400 MHz, DMSO-d6): δ 3.83 (s, 3H, OCH_3), 6.41 (s, 1H), 7.03-7.05 (m, 1H, ArH), 7.22-7.35 (m, 6H, ArH), 7.52-7.68 (m, 5H, ArH), 7.85 (d, 2H, J = 7.6 Hz, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 36.13, 55.07, 104.15, 105.62, 115.91, 118.10, 118.18, 123.62, 123.92, 124.27, 126.47, 128.44, 129.05, 131.75, 132.67, 135.38, 152.27, 156.74, 164.76, 165.56; **MS**: m/z 475 (M+H); Anal. Calcd for $C_{29}H_{18}N_2O_5$: C, 73.41; H, 3.82; N, 5.90; Found: C, 73.46; H, 3.78; N, 5.91.

7-(2-chloro-4-(Dimethylamino)phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4h)

yellow solid; mp 254-255 ºC; **IR** (KBr, cm-1) $_{vmax}$: 2954, 1793, 1669, 1603; **^{1}H NMR** (400 MHz, DMSO-d6): δ 3.11 (s, 6H), δ 6.27 (s, 1H), 7.21-7.28 (m, 6H, ArH), 7.35 (s, 1H, ArH), 7.49-7.53 (m, 2H, ArH), 7.79-7.81 (m, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.91, 45.46, 103.02, 115.54, 119.62, 122.98, 124.07, 128.14, 131.11, 152.49, 164.40, 167.53; **MS**: m/z 472 (M+H); Anal. Calcd for $C_{26}H_{18}ClN_3O_4$: C, 66.18; H, 3.84; N, 8.90; Found: C, 66.27; H, 3.73; N, 8.89.

7-(4-floro-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4i)

White solid; mp 257-258 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2964, 1792, 1663, 1610; **^{1}H NMR** (400 MHz, DMSO-d6): 6.28 (s, 1H), 6.65-6.71 (m, 2H, ArH), 6.79 (d, 2H, J = 8.4 Hz, ArH), 7.30-7.35 (m, 4H, ArH), 7.55-7.61 (m, 2H, ArH), 7.89 (t, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.71, 103.87, 115.99, 116.15, 118.05, 123.77, 123.91, 127.99, 130.13, 131.97, 139.34, 152.24, 164.67, 165.55; **MS**: m/z 413 (M+H); Anal. Calcd for $C_{24}H_{13}FN_2O_4$: C, 69.90; H, 3.18; N, 6.79; Found: C, 69.94; H, 3.24; N, 6.66.

7-(3-nitro-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4j)

White solid; mp 263-264 ^{o}C; **IR** (KBr, cm-1) vmax: 2985, 1790, 1665, 1604; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.27 (s, 1H), 7.10 (s, 2H, ArH), 7.21-7.31 (m, 6H, ArH), 7.54 (d, 2H, J = 6.8, ArH), 7.83 (d, J = 6.8, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.83, 103.79, 115.89, 119.63, 123.81, 123.90, 128.00, 128.89, 130.21, 132.10, 140.21, 152.23, 164.32, 165.33; MS: m/z 440 (M+H); Anal. Calcd for $C_{24}H_{13}N_3O_6$: C, 65.61; H, 2.98; N, 9.56; Found: C, 65.84; H, 2.87; N, 9.40.

7-(4-bromo-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4k)

White solid; mp 273-274 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2961, 1797, 1666, 1618; **^{1}H NMR** (400 MHz, DMSO-d6): 6.24 (s, 1H), 6.63-6.75 (m, 2H, ArH), 6.80 (d, 2H, J = 8.4 Hz, ArH), 7.32-7.38 (m, 4H, ArH), 7.56-7.63 (m, 2H, ArH), 7.90 (t, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.77, 103.86, 115.97, 116.11, 118.07, 123.75, 123.98, 127.94, 130.16, 131.91, 139.33, 152.26, 164.69, 165.51; **MS**: m/z 473 (M+H); Anal. Calcd for $C_{24}H_{13}BrN_2O_4$: C, 60.91; H, 2.77; Br, 16.88; N, 5.92; Found: C, 69.79; H, 2.54; N, 16.69.

7-(4-iodo-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4l)

White solid; mp 263-264 ^{o}C; **IR** (KBr, cm-1) $_{vmax}$: 2967, 1791, 1669, 1611; **^{1}H NMR** (400 MHz, DMSO-d6): 6.30 (s, 1H), 6.64-6.70 (m, 2H, ArH), 6.79 (d, 2H, J = 8.4 Hz, ArH), 7.30-7.35 (m, 4H, ArH), 7.53-7.61 (m, 2H, ArH), 7.89 (t, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.65, 103.90, 115.93, 116.17, 118.09, 123.72, 123.93, 127.91, 130.20, 131.89, 139.43, 152.29, 164.70, 165.49; **MS**: m/z 520 (M+H); Anal. Calcd for $C_{24}H_{13}IN_2O_4$: C, 55.40; H, 2.52; N, 5.38; Found: C, 55.24; H, 2.34; N, 5.52.

7-(4-methyl-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4m)

White solid; mp 245-246 ^{o}C; **IR** (KBr, cm-1) vmax: 2967, 1790, 1661, 1617; **^{1}H NMR** (400 MHz, DMSO-d6): 2.29 (s, 3H), 6.29 (s, 1H), 6.65-6.73 (m, 2H, ArH), 6.79 (d, 2H, J = 8.4 Hz, ArH), 7.30-7.35 (m, 4H, ArH), 7.54-7.59 (m, 2H, ArH), 7.93 (t, 2H, ArH); **^{13}C NMR** (100

MHz, DMSO-d6): δ 19.12, 35.67, 103.91, 115.89, 116.17, 118.11, 123.83, 123.52, 127.43, 130.14, 131.87, 139.29, 152.27, 164.62, 165.54; **MS**: m/z 409 (M+H); Anal. Calcd for $C_{25}H_{16}N_2O_4$: C, 73.52; H, 3.95; N, 6.86; Found: C, 73.31; H, 3.74; N, 6.59.

7-(3-methyl-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4n)

White solid; mp 249-250 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 2967, 1790, 1661, 1617; **^{1}H NMR** (400 MHz, DMSO-d6): 2.29 (s, 3H), δ 6.30 (s, 1H), 7.13 (s, 2H, ArH), 7.23-7.32 (m, 6H, ArH), 7.53 (d, 2H, J = 6.8, ArH), 7.84 (d, J = 6.8, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 19.12, 35.62, 103.79, 115.92, 116.19, 118.14, 123.76, 123.43, 127.65, 130.21, 131.91, 139.30, 152.26, 164.59, 165.61; **MS**: m/z 409 (M+H); Anal. Calcd for $C_{25}H_{16}N_2O_4$: C, 73.52; H, 3.95; N, 6.86; Found: C, 73.31; H, 3.74; N, 6.59.

7-(3-chloro-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4o)

White solid; mp 253-254 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 2962, 1794, 1667, 1612; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.27 (s, 1H), 7.11 (s, 2H, ArH), 7.22-7.31 (m, 6H, ArH), 7.52 (d, 2H, J = 6.8, ArH), 7.83 (d, J = 6.8, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.67, 103.88, 115.91, 116.13, 118.01, 123.72, 123.95, 127.94, 130.11, 131.96, 139.28, 152.19, 164.54, 165.52; **MS**: m/z 429 (M+H); Anal. Calcd for $C_{26}H_{13}ClN_2O_6$: C, 67.22; H, 3.06; N, 6.53; Found: C, 67.14; H, 3.24; N, 6.62.

7-(3-floro-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4p)

White solid; mp 267-268 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 2959, 1791, 1670, 1609; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.24 (s, 1H), 7.13 (s, 2H, ArH), 7.21-7.30 (m, 6H, ArH), 7.55 (d, 2H, J = 6.8, ArH), 7.81 (d, J = 6.8, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.70, 103.91, 115.87, 116.15, 118.04, 123.67, 123.92, 127.81, 130.14, 131.99, 139.31, 152.14, 164.49, 165.60; **MS**: m/z 413 (M+H); Anal. Calcd for $C_{24}H_{13}FN_2O_4$: C, 69.90; H, 3.18; N, 6.79; Found: C, 69.94; H, 3.24; N, 6.66.

7-(4-hydroxy-phenyl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4q)

White solid; mp 251-252 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 3431, 2962, 1793, 1665, 1611; **^{1}H NMR** (400 MHz, DMSO-d6): 4.23 (s, 1H), 6.30 (s, 1H), 6.63-6.71 (m, 2H, ArH), 6.80 (d, 2H, J = 8.4 Hz, ArH), 7.31-7.36 (m, 4H, ArH), 7.55-7.60 (m, 2H, ArH), 7.91 (t, 2H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.70, 103.95, 115.91, 116.23, 118.04, 123.79, 123.43, 127.51, 130.13,

131.83, 139.25, 152.23, 155.13, 164.59, 165.49; **MS**: m/z 411 (M+H); Anal. Calcd for $C_{24}H_{14}N_2O_5$: C, 70.24; H, 3.44; N, 6.83; Found: C, 70.46; H, 3.67; N, 6.53.

7-(4-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4r)

Pale yellow solid; mp 279-280 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 2918, 1781, 1655, 1618, 1312; **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.32 (s, 1H), 7.09-7.12 (m, 2H, ArH), 7.22-7.27 (m, 5H, ArH), 7.40-7.46 (m, 4H, ArH), 7.49-7.53 (m, 2H, ArH), 7.75-7.78(m, 2H, ArH), 7.81-7.84(t, 2H, ArH), 8.22(s, 1H, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 28.52, 103.76, 115.61, 117.79, 123.37, 123.74, 125.73, 127.33, 127.82, 128.97, 129.35, 131.46, 131.85, 139.45, 152.04, 164.53, 165.41; **MS**: m/z 572 (M+H); Anal. Calcd for $C_{33}H_{19}ClN_4O_4$: C, 69.42; H, 3.35; N, 9.81; Found: C, 69.78; H, 3.85; N, 9.72.

7-[4-Chloro-2-oxo-2*H*-chromen-3-yl]-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4s)

Pale yellow solid; mp 334-335 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 2977, 1803, 1727, 1667, 1607, 1310; **^{1}H NMR** (400 MHz, DMSO-d6): δ 5.55 (s, 1H), 7.30-7.39 (m, 2H, ArH), 7.50-7.63 (m, 5H, ArH), 7.76 (t, 2H, J = 7.6 Hz, ArH), 8.03 (d, 1H, J = 8 Hz, ArH), 8.40 (d, 2H, J = 8 Hz, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 25.30, 102.33, 112.90, 116.08, 116.16, 116.51, 123.02, 123.93, 124.83, 132.33, 133.01, 151.92, 152.27, 154.69, 159.61, 161.06, 162.04; **MS**: m/z 497 (M+H); Anal. Calcd for $C_{27}H_{13}ClN_2O_6$: C, 65.27; H, 2.64; N, 5.64; Found: C, 64.78; H, 2.89; N, 5.91.

7-(2-Chloroquinolin-3-yl)-chromeno[4',3':3,4]pyrazolo[1,2-*b*]phthalazine-6,9,14(7*H*)-trione (4t)

White solid; mp 311-312 ^oC; **IR** (KBr, cm-1) $_{vmax}$: 2964, 1792, 1661, 1615, 1315; **^{1}H NMR** (400 MHz, DMSO-d6): δ 4.92 (s, 1H), 7.18-7.20 (m, 1H, ArH), 7.29 (d, 1H, J = 8 Hz, ArH), 7.45-7.57 (m, 5H, ArH) 7.75-7.81 (m, 3H, ArH), 8.14 (s, 1H, ArH), 8.43 (d, 2H, J = 8 Hz, ArH); **^{13}C NMR** (100 MHz, DMSO-d6): δ 35.12, 103.05, 105.63, 115.89, 118.13, 118.19, 123.65, 123.88, 124.25, 126.44, 128.46, 129.09, 131.74, 132.69, 135.40, 152.30, 164.82, 165.63; **MS**: m/z 480 (M+H); Anal. Calcd for $C_{27}H_{14}ClN_3O_4$: C, 67.58; H, 2.94; N, 8.76; Found: C, 67.75; H, 2.87; N, 8.91.

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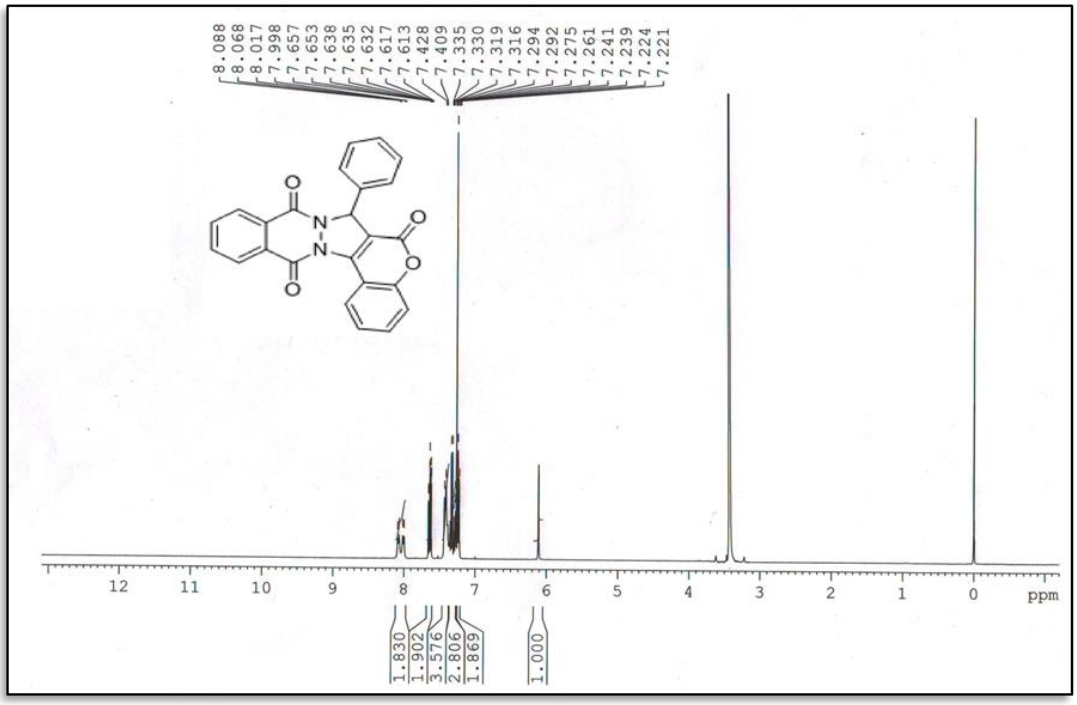
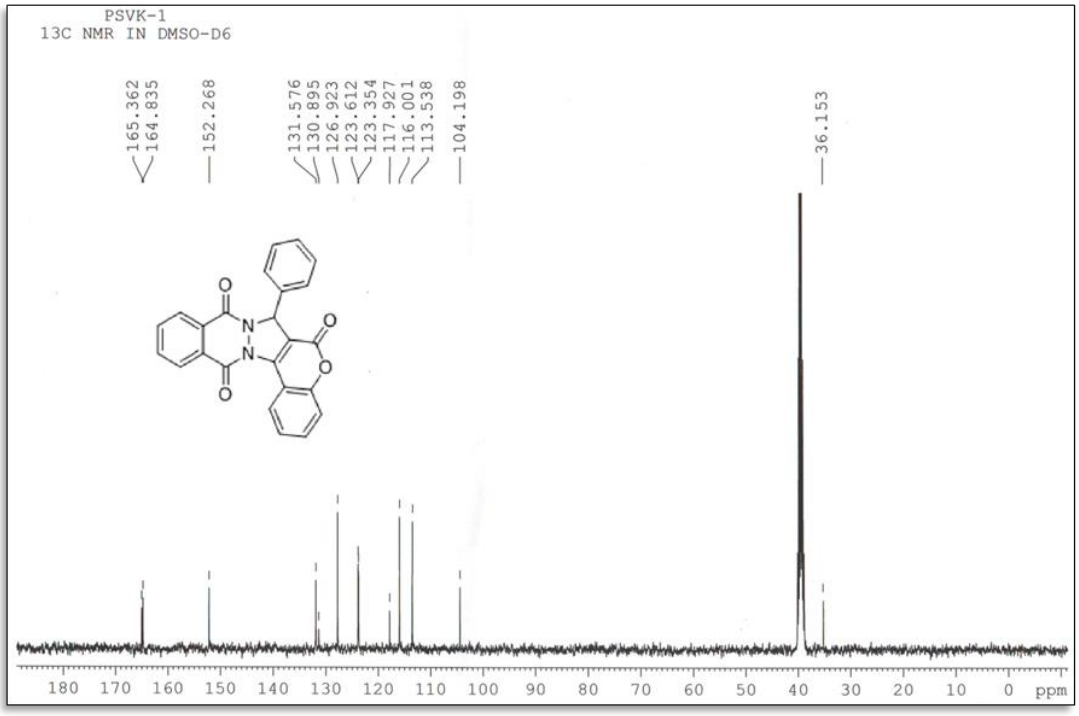
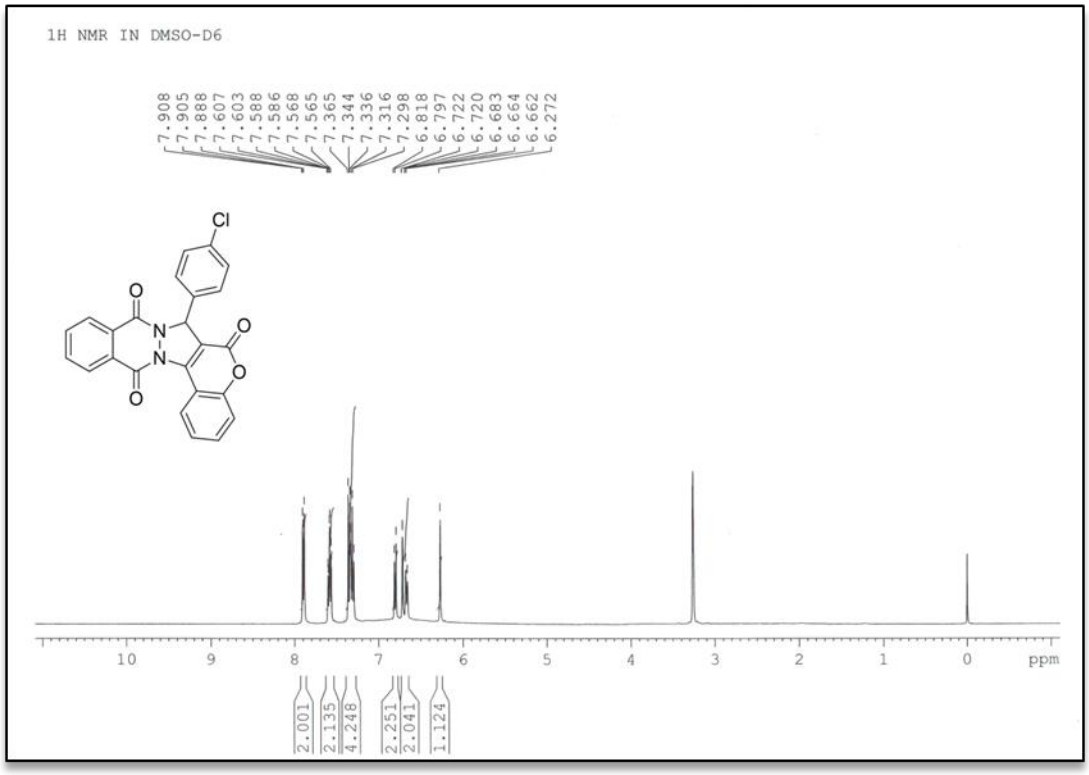


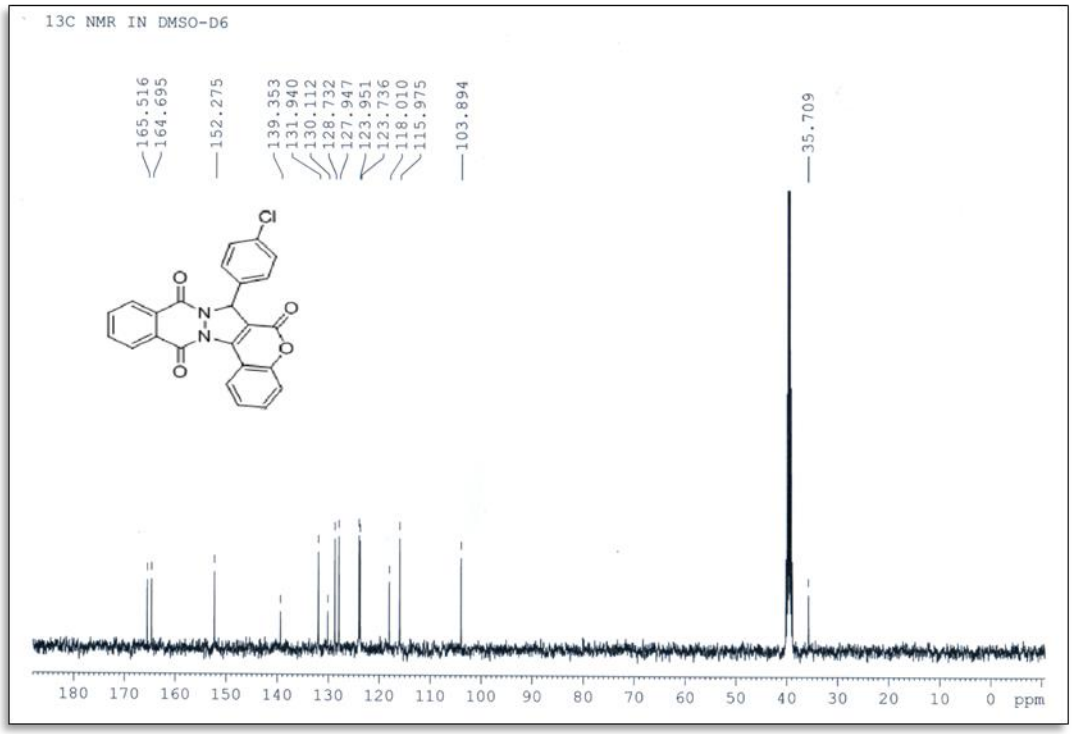
^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4a**



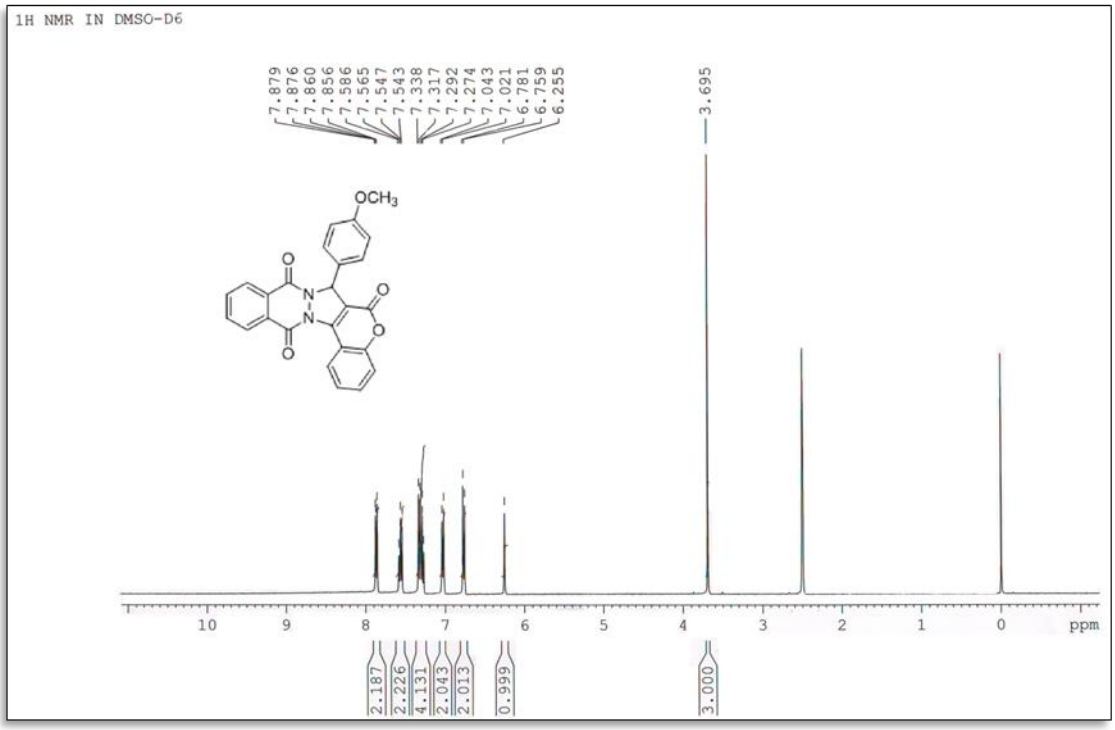
^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4a**



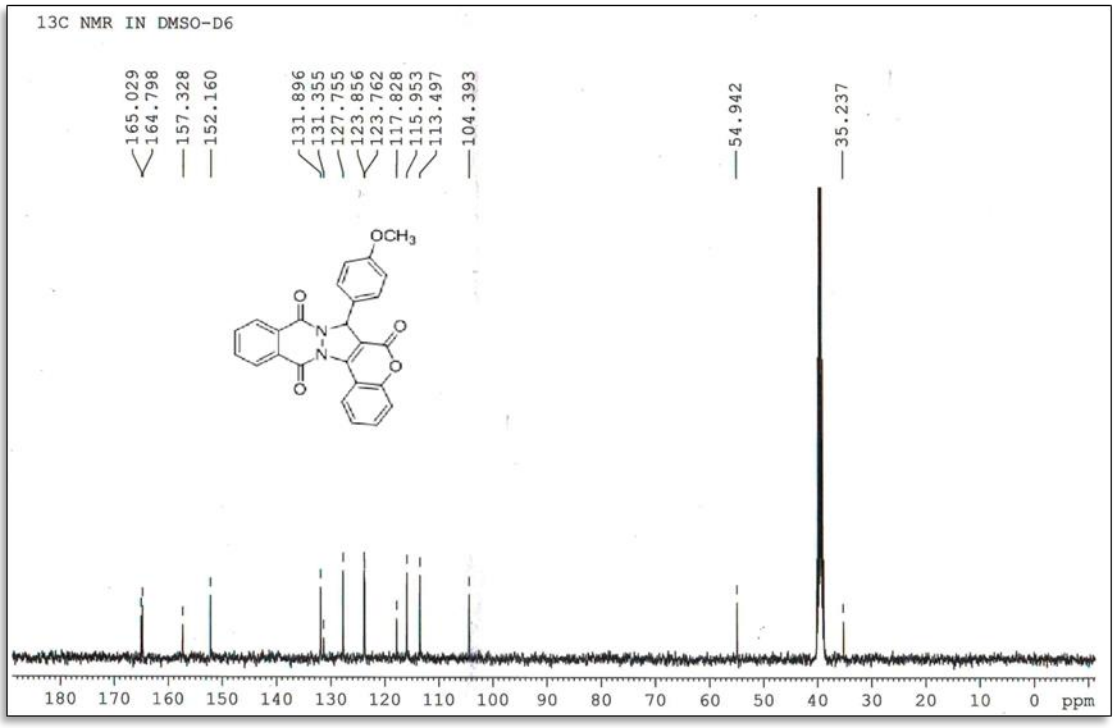
^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4b**



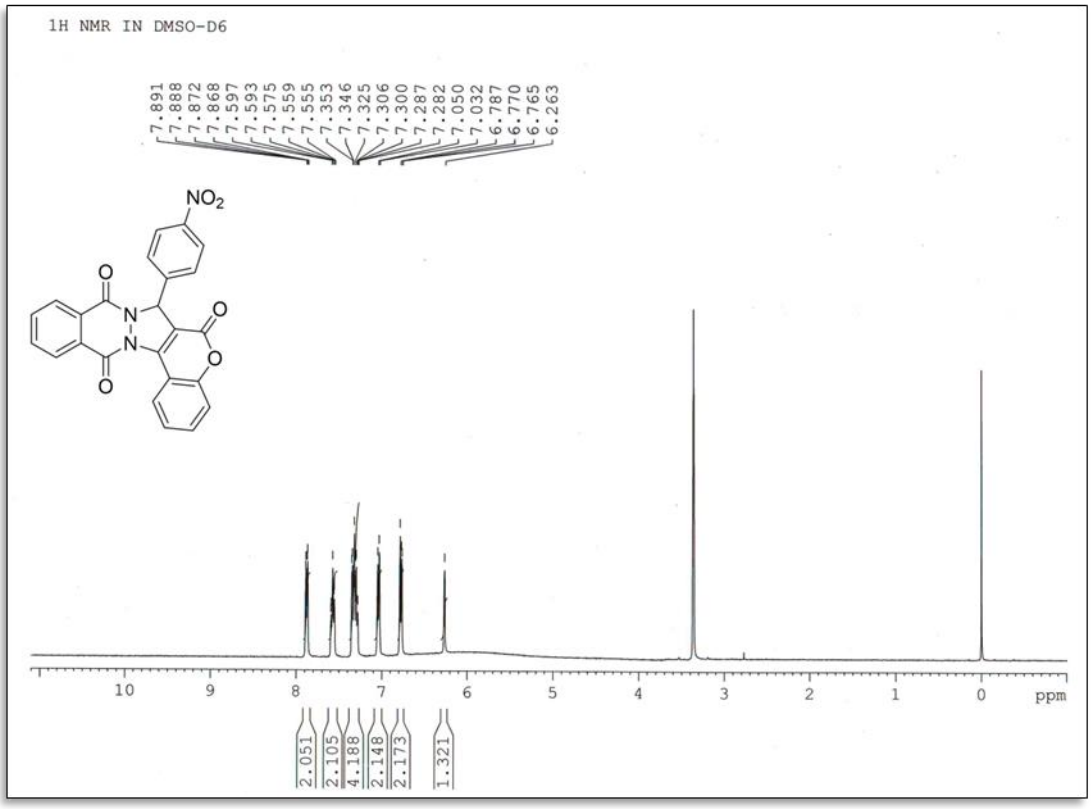
^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4b**



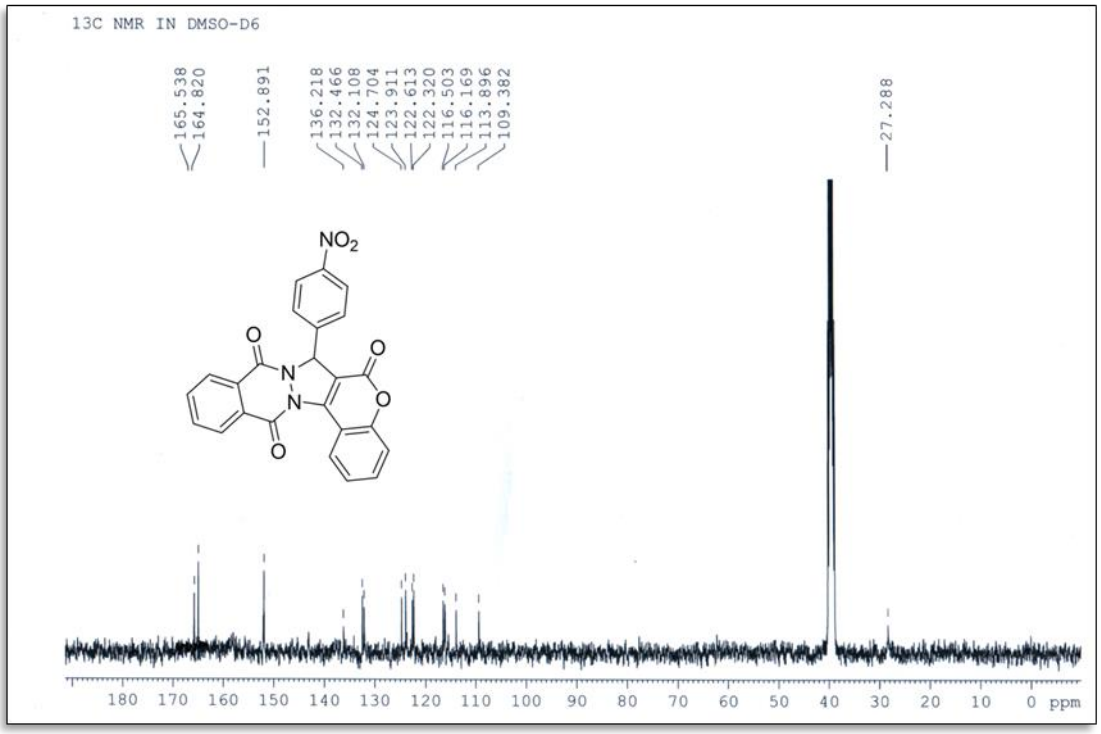
^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4c**



^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4c**



^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **4e**



^{13}C NMR (100 MHz, DMSO-d_6) spectra of compound **4e**

CHAPTER-VI

EVALUATION OF BIOLOGICAL ACTIVITY

Evaluation of biological activity

6.1. Introduction

Type 2 diabetes (T2DM) is characterized by chronic hyperglycemia and the development of micro-angiopathic problems such as neuropathy, nephropathy along with retinopathy. α-glucosidase is a vital enzyme in the metabolism of sugar. α-glucosidase hydrolyses terminal non-reducing 1-4 linked α-glucose residues to release an α-glucose molecule.[1,2] By hindering the breakdown of intricate carbohydrates, post prandial glucose concentration *in vivo* could be lessened thus regulating blood sugar levels. Hence α-glucosidase inhibition is appropriate for the management of T2DM.

Cancer is a disease in which cells can be aggressive (grow and divide beyond normal limits), invasive (invade and destroy adjacent tissues) and metastatic (spread to other locations in body). These three malignant properties of cancer differentiate them from benign tumors, which are self-limited in their growth and do not invade or metastasize. Cancer may affect people at all ages, even fetuses, but risk for the more common varieties tends to increase with age. Cancer causes about 13% of all deaths. According to the American cancer society, 7.6 million people died from cancer in the world during 2007. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. With the current chemotherapy, lack of selectivity of chemotherapeutic agents against cancerous cells is a significant problem.[3]

During the past two decades, the rate of aggressive and general fungal infections has increased dramatically,[4-9] There is an urgent demand for the expansion of new alternative antifungal agents,[10-12] due to several offensive mycotic infections in humans. It has become necessary to develop new compounds to suppress the infections caused mainly by *Candida* and *Aspergillus* species. However, besides these known fungal species, new emerging fungal pathogens appear every year as the cause of morbidity and life-threatening infections in the immunocompromised hosts.

6.2. Present work

It is a known fact that many of the heterocyclic compounds exhibit a variety of pharmacological activities including antidiabetic, anticancer and antifungal activities. The important biological applications of heterocyclic molecules attracted our attention to synthesize and to study their biological activities. Therefore, some of the compounds which were newly synthesized during

the course of the present program were screened for their antidiabetic, anticancer and antifungal activities. The screening results reveled that some of these compounds have shown moderate to good activities.

In the present study, some of the newly synthesized compounds which were already described in the earlier chapters (chapter II, IIIA, IIIB, IV and V) were evaluated for antidiabetic, anticancer and antifungal activities. We have also done the docking studies on the synthesized compounds with their target enzymes in order to predict the possible antidiabetic and antifungal mechanisms of the newly synthesized compounds.

Biological protocol

Antidiabetic activity (α-glucosidase inhibition activity)

α-amylase assay:

α-amylase inhibitory activity of the enzyme (EC 3.2.1.1 from porcine pancreas) was measured using starch as substrate.[13] The liberated reducing groups (calculated as maltose) were measured by the reduction of 3, 5-dinitrosalicylic acid and immediately quantified spectrometriaclly on a Jasco Visible spectrophotometer at 37°C, 540nm. The substrate stock solution 0.5% (w/v) starch was prepared. The inhibitor compounds were dissolved in Dimethyl sulfoxide (DMSO) and diluted to the corresponding concentration. The reaction mixture containing 400µl of substrate, 100µl enzyme, was incubated at 37ºC for 10 min., 250µl of coloring reagent (sodium potassium tartrate and 3, 5-dinitrosalicylic acid (DNS)) was added and the mixture was boiled at 70ºC upon a water bath for 15 min. Later 2.5ml of deionized water was added to the assay mixture followed by measuring absorbance at 540nm.

α-glucosidase assay

α-glucosidase inhibitory activity of the enzyme (EC 3.2.1.20 from Baker's Yeast) was measured using 4-nitrophenyl α-D-glucopyranoside (4-NGP) as substrate.[14] The liberated 4-nitrophenol was immediately quantified spectrometrically on a BIORAD Model 680 microplate reader at 37°C, 410nm for 10 min. The enzyme stock solution (2 mg dissolved in 1 ml of 10mM Tris-HCl buffer, pH 7.0) was prepared. The inhibitor compounds were dissolved in DMSO and diluted to the corresponding concentration. The assay was carried out in a 96 well plate. The reaction mixture containing 25µl of 4-NGP (substrate stock solution 10mM 4-NGP), 25µl of α-glucosidase enzyme and 950µl deionized H_2O was added to the wells and was incubated at

37°C, for 10 min. The percentage inhibition was calculated for each compound using the following formula:

$$\%\ inhibition = 100 - \left(\frac{OD\ sample}{OD\ control}\right) \times 100$$

The inhibitory effects of the tested compounds were shown as the concentrations that inhibited 50% of enzyme activity (IC_{50}).

Enzyme inhibition Kinetic studies and determination of IC_{50} values[15]

IC_{50} value is defined as the concentration of inhibitor molecule inhibiting 50% of α-glucosidase activity under the standard assay conditions. For determination of IC_{50} values, the enzyme inhibition assays were carried out by varying concentration (10µM to 500µM) of new compounds, using acarbose as reference. The enzyme reaction was performed by incubating the mixture at 37°C for 30 min. and optimum concentration of the inhibitors were determined based on the results from inhibitory activity assay as described earlier. For those molecules which showed significant inhibition, the mode of inhibition of inhibitor against α-glucosidase activity was measured with increasing concentrations of 4-NGP (0.25, 0.4, 0.6, 0.8, 1.0, 1.25, 1.5 and 2.0 mM) as substrate in the absence or presence of the inhibitor molecules at two different concentrations (25 and 50µM). Mode of inhibition was determined by Lineweaver-Burk plot analysis of the data calculated following Michaelis-Menten kinetics and the values were determined by linear regression by fitting in to a sigmoidal dose-response equation with variable slope. All the values are represented as Mean ± Standard Deviation.

Anticancer activity

The cellular viability of the synthesized compounds against Hep-G2 (hepatocellular liver carcinoma), HeLa (human epitheloid cervix carcinoma) and MCF-7 (breast cancer) cell lines were determined by MTT-microcultured tetrazolium assay following reported protocol.[16] Hep-G2, HeLa and MCF-7 cells were plated into a 96-well plate at a density of 1×104 cells/well. Cells were grown overnight in the medium and then switched to the low serum media. DMSO was used as control. After 48 hours of treatment with different concentrations of test compounds, the cells were incubated with MTT (2.5 mg/ml) in the CO2 chamber for 2 hours. The medium was then removed and 100 µL of DMSO was added into each well to dissolve formazan crystals. After carefully mixing, the plates were read at 570 nm for optical density which is directly linked with cell quantity. The results were characterized as percentage of

cytotoxicity/viability. All the experiments were carried out in triplicates. The IC50 values were calculated from the percentage of cytotoxicity and compared with the reference Doxorubicin. The response parameter calculated was the IC50 value, which resembles to the concentration required for 50% inhibition of cell viability.

Antifungal activity assay

Aspergillus niger and *Candida albicans* were used for evaluating the antifungal activity of all synthesized compounds. The media was altered Sabouraud-chloramphenicol agar containing 2% glucose, 1% peptone and solid media in addition to 15% agar. All the synthesized compounds were dissolved in DMSO as stoke solutions. The antifungal activity was evaluated by disc diffusion method.[17] The inhibition action was tested after incubating for 48 h at 37 °C and the minimum inhibitory concentrations (MICs, µM) were recorded. fluconazole was used as a standard drug.

Docking studies

Computer aided molecular modelling has become a crucial drug-designing technique. Such studies typically involve modelling of the putative inhibitors and exploring its docking into a known enzyme receptor cavity, permitting elucidation of the interactions involved in the enzyme receptor-inhibitor complex.

Preparation of Ligands

All the 2D structures of ligand molecules were drawn, converted to 3D structures and energy minimization was done by using MMFF (*Merck Molecular Force Field*)[18-23] with RMS (root mean square) gradient of 0.001 Å of VLife MDS v 4.3 that works based on MM3 force fields until reaching global minima.

Preparation of Receptors

Crystal structures of secreted aspartic proteinase of *Candida albicans*[24] were obtained from Protein Data Bank (PDB IDs: 1EAG). The one ligand of 1EAG namely A70 (C42 H70 N6 O5) was excised off from the receptors before docking using a Biopredicta module of VLife MDS v 4.3 in order to avoid ligand competition for active site. The crystal structure of *Saccharomyces cerevisiae* maltase (α-glucosidase) MAL12 (uniprot id P53341) is yet to be made available in the public domain. So, a homology model was built using Biopredicta module to carryout docking studies with the ligand structures of the test compounds. The MAL12

protein sequence (target) was retrieved from uniprot database (Seq id P53341). Local BLAST with default matrix BLOSUM62 was used to search for potential templates using the target sequence against the PDB database. The top ten hits with their percentage identity, positives and gaps were analyzed and the potential template PDB 3AJ7 (Crystal Structure of isomaltase from *Saccharomyces cerevisiae*) was chosen. The chosen template had 72% identity (423/587) residues, 85% positives (499/587) residues, and 0% literally negligible gaps (5/587) residues.

The template 3D structure PDB id: 3AJ7 was retrieved from the RCSB PDB database and examined for the presence of incomplete, modified, missing, and cris-cross residues. Subsequently, the template structure was used for building the model of Yeast maltase MAL12 protein using the Biopredicta module.

Docking using VLife v4.3

In order to verify the results obtained by Hex and iGEMDOCK, again molecular docking was performed by VLife MDS, which have a facility to dock dissimilar ligands in protein binding sites preferred by the user. VLife MDS Biopredicta docking wizard consists of both flexible (torsional flexibility to ligand with rigid protein) and rigid (no torsional flexibility of protein as well as ligand) docking of the molecules. When a drug binds in the receptor's (usually protein) pocket, its biological activity is exerted. Molecules exhibit chemical and geometric complementarily, which are essential for successful drug activity in their binding conformations. The computational process of searching for a suitable ligand that is able to fit both energetically and geometrically into the binding site of a protein is called as molecular docking. Molecular docking helps in studying receptor/ protein or drug/ ligand interactions by initial identification of suitable active sites in protein while obtaining the best geometry of ligand - receptor complex followed by calculating the energy of interaction for different ligands to design more effective ligands. The molecular docking tool has been developed based on different scoring functions viz. the sum of electrostatic and steric (parameters of Merck Molecular Force Field). Only electrostatics and Dock Score are to be obtained for a favoured interactive geometry of ligand - receptor complexes with minimum interaction energy. To minimize the interaction energy between ligand – receptor, VLifeMDS uses a genetic algorithm (GA), Piecewise Linear Pairwise Potential (PLP) and Grid algorithms.

Result and discussions

Chapter-II: Chromene derivatives

Evaluation of the chromene derivatives were conducted for their enzyme inhibitory activities against taking yeast MAL12 α-glucosidase as a model enzyme. The enzyme assay was carried out following a standard protocol from literature by analyzing the hydrolysis of nitrophenyl glucoside spectrometrically. The inhibitory activity of chromene derivatives (**4aa-bd**) at 5mM concentration against α-glucosidase are shown in Fig.6.2.1

On comparison, the inhibition of α-glucosidase activity by chromene derivatives (**4aa-bd**) was found to be much higher than the inhibition of α-amylase activity. All the 30 inhibitors tested showed variable amount of α-glucosidase inhibition with IC_{50} values ranging from 46.46 µM to 189.35 µM (Table.6.2.1.). Acarbose was selected as the reference inhibitor. The IC_{50} value for acarbose under same assay conditions was found to be 33.95 µM. Among all the tested inhibitors, **4bd** has shown the minimal IC_{50} value of 46.46 µM and **4ay** showed the maximal IC_{50} value of 189.35 µM. Similarly, **4aw** (81.40±4.74µM), **4bb** (71.83±4.13µM), **4bc** (76.79±4.78µM) and **4bd** (46.46±5.22µM) have shown the top four minimal IC_{50} values for α-glucosidase inhibition activity. These top 4 inhibitors were selected for studying the mode of inhibition against α-glucosidase.

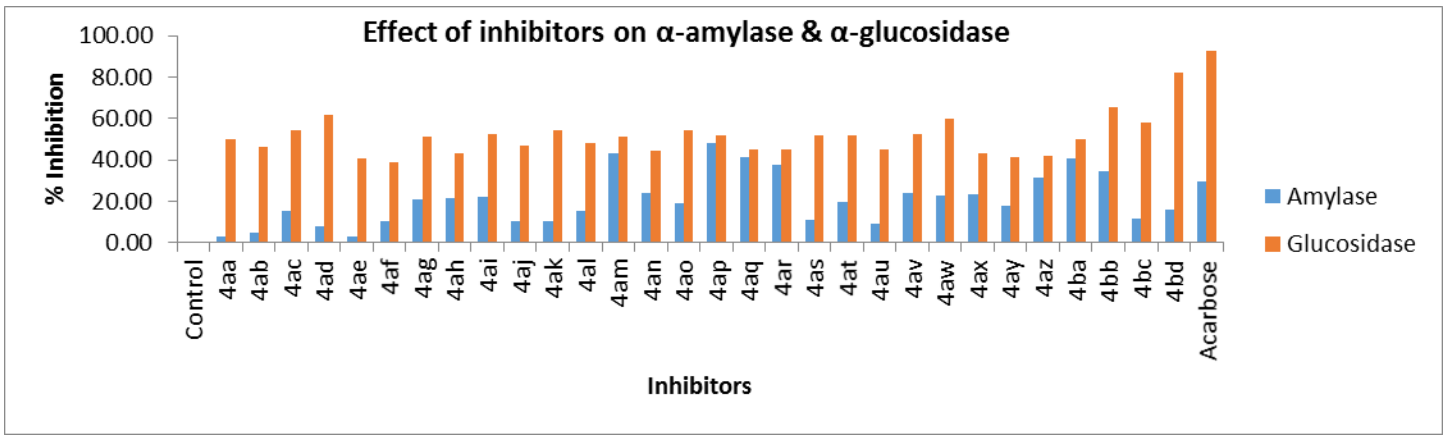


Fig.6.2.1. Inhibition profile of α-amylase and α-glucosidase by chromene derivatives (**4aa-bd**) at 5 mM concentration.

Table.6.2.1. chromene derivatives (**4aa-bd**) with the assay produced IC_{50} values.

Compounds	IC_{50} (µM)
4aa	137.68±3.57
4ab	151.95±4.27
4ac	121.90±2.12
4ad	84.18±3.08
4ae	187.02±5.66
4af	171.43±3.69
4ag	129.58±8.20
4ah	186.65±4.70
4ai	96.91±4.61
4aj	146.05±4.55
4ak	95.73±5.05
4al	117.39±6.34
4am	111.49±3.58
4an	165.40±4.13
4ao	94.60±4.68
4ap	100.83±3.82
4aq	117.54±4.44
4ar	143.49±5.09
4as	111.59±4.12
4at	112.53±3.43
4au	134.90±4.06
4av	97.98±4.71
4aw	81.40±4.74
4ax	172.87±3.19
4ay	189.35±2.50
4az	169.05±3.93
4ba	127.16±5.25
4bb	71.83±4.13
4bc	76.79±4.78
4bd	46.46±5.22
STDEV	
Acarbose	33.95±3.20

The mode of inhibition of the selected inhibitors were determined by comparing the Michaelis-Menten kinetic constants K_m and V_{max} obtained from the experimental investigations carried out by varying concentrations of inhibitors. Among the four selected inhibitors, **4aw** has

shown a mixed-uncompetitive mode of inhibition while the other three compounds **4bb**, **4bc**, and **4bd** have shown a non-competitive mode of inhibition. The results of K_m and V_{max} of α-glucosidase in the presence of all the four inhibitors **4aw**, **4bb**, **4bc**, and **4bd** are shown in Table.6.2.2.

Chromene derivatives **(4aa-bd)** exhibited a more selective inhibition towards α-glucosidase than α-amylase. Increasing the concentration of all the tested compounds showed a tendency to lessen the activity of α-glucosidase but the same was not observed for α-amylase. This selective affinity for the inhibition of α-glucosidase as compared to α-amylase is in a way beneficial because non-specific inhibition of both α-glucosidase and α-amylase might contribute towards the accretion of partially digested complex carbohydrates, which consecutively could result in abdominal discomfort including cramping, diarrhea and flatulence.

Kinetic Measurements and Mechanism of Inhibition:

All tested inhibitors displayed an analogous relationship between enzyme activity and concentration. The related data for the most active inhibitors **4bd, 4bb, 4bc** and **4aw** are shown in Fig.6.2.2 The enzyme inhibition activities of the 2-amino-phenyldiazenyl-4*H*-chromene derivatives **4bd, 4bb, 4bc** and **4aw** were demonstrated by means of double reciprocal plot in kinetic studies. This investigation revealed that the values of K_m and V_{max} calculated from Lineweaver–Burk plot got decreased as the inhibitor concentration of **4aw** was increased, however K_m was almost constant and V_{max} decreased as the inhibitor concentration of **4bb**, **4bc** and **4bd** were increased. It is clear from the graph that families of 1/V versus 1/[S] regression line showed signature slopes as estimated for non-competitive inhibition behavior for **4bb**, **4bc** and **4bd** and a mixed un-competitive inhibition for **4aw**. The following equations generalize the trends of the inhibition.

Michaelis-Menten equation:

$$V = \frac{Vmax\ [S]}{Km + [S]}$$

Lineweaver-Burk equation:

$$\frac{1}{V} = \frac{Km}{Vmax}\frac{1}{[S]} + \frac{1}{Vmax}$$

Where *V* is velocity (rate of the reaction), K_m is the Michaelis-Menten constant, V_{max} is the maximum velocity of the reaction and [S] is the concentration of the substrate.

A recent study (Deng et al., 2015) has also reported a similar mode of mixed inhibition of α-glucosidase by Pu-erh tea polysaccharide (PTPS). The mode of inhibition of compounds **4bb**, **4bc** and **4bd** were similar to the inhibition of α-glucosidase by luteolin inhibitors.

Table.6.2.2. IC_{50}, K_{im} and inhibition mode of 4aw, 4bb, 4bc and 4bd K_m and V_{max} of α-glucosidase (8.56 µM and 65.07 µM/min) 4-NGP without inhibitor.

Compound	IC_{50} (µM)	K_{im} (µM)			V_{max} (µM/min)			Mode of inhibition
		i1	i2	i3	i1	i2	i3	
4aw	81.40±4.74	2.421	1.108	0.726	20.878	13.161	9.381	Mixed-Uncompetitive
4bb	71.83±4.13	8.244	8.582	8.324	47.073	38.991	31.761	Non-Competitive
4bc	76.79±4.78	8.512	8.582	8.613	51.328	36.051	32.232	Non-Competitive
4bd	46.46±5.22	8.533	8.616	8.370	49.225	37.834	33.389	Non-Competitive

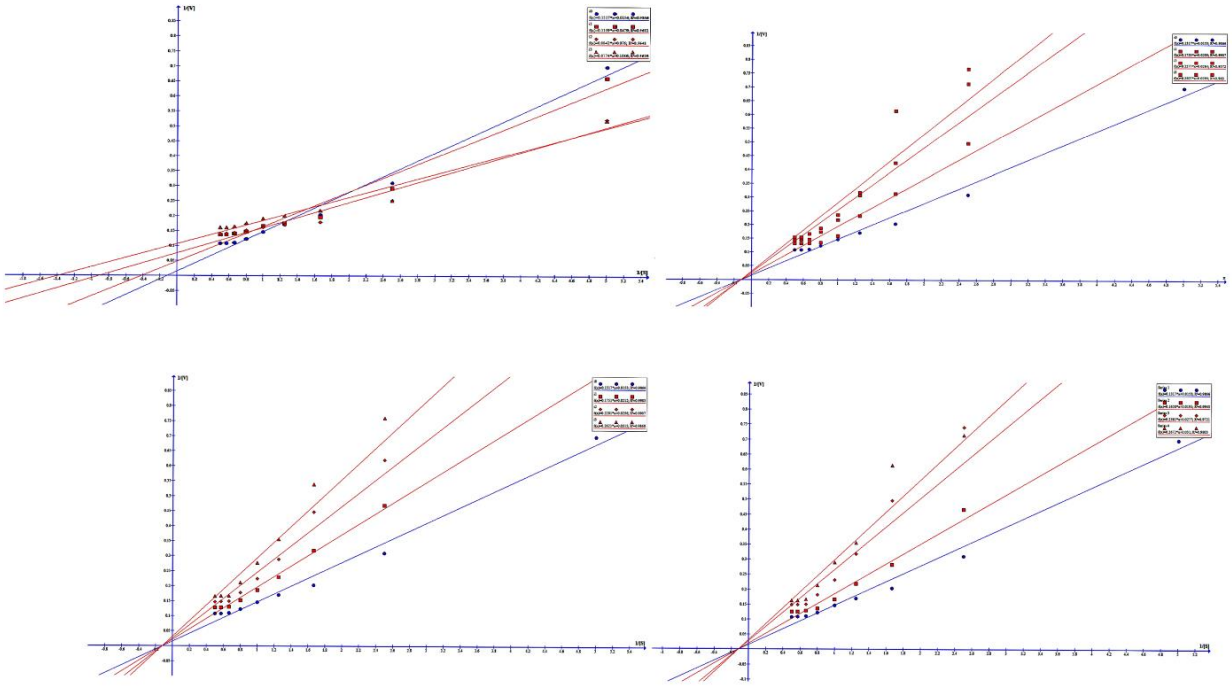


Fig.6.2.2. Lineweaver-Burk double reciprocal plot for the mode of inhibition of α-glucosidase by 4aw, 4bb, 4bc and 4bd.

Docking studies

In support of the *in vitro* screening results, docking studies were performed with the homology model of MAL12 and the 2-amino-phenyldiazenyl-4*H*-chromene derivatives (**4aa-bd**). The binding modes and contacts between the active site of the homology model of MAL12 and the 2-amino-phenyldiazenyl-4*H*-chromene derivatives (**4aa-bd**) were evaluated.

All the tested ligands occupied the same region of the binding pocket as that of acarbose forming similar contacts with the enzyme. Further analysis of the ligands with the interaction viewer module revealed additionally significant residues including PHE157, HIS279, SER239 and ARG312 in addition to the active site residues ASP214, GLU276, and ASP349 involved in the α-glucosidase inhibition. The above mentioned residues were found interacting with one or more tested ligand atoms. Interactions between MAL12 and the 2-amino-phenyldiazenyl-4*H*-chromene derivatives (**4aa-bd**) are summarized and given in Table.6.2.3.

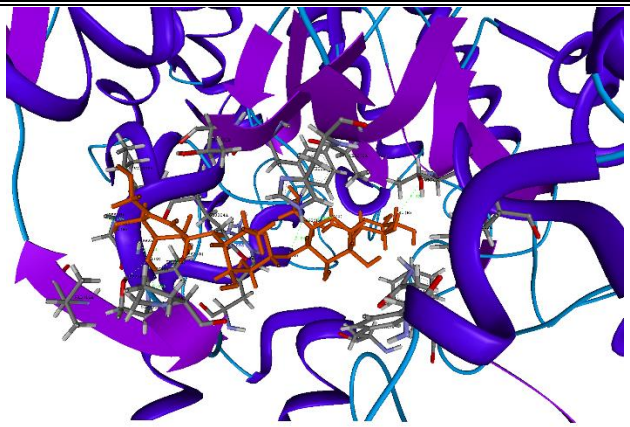
Among all the ligands that exhibited multiple interactions, **4bd**, **4bc**, **4bb** and **4aw** were found to be potent and promising ligands. Maximum interactions were exhibited by compound **4bd**. In addition to numerous hydrophobic interactions the ligand **4bd** formed two aromatic interactions with PHE157 and HIS279 and two hydrogen bonds with SER239 and ARG312 within the binding pocket. Aromatic interactions were observed between 11C and PHE157 (5.1Å), 21C and HIS279 (4.3Å). H-bonds were observed between 28O and SER239 (1.9 Å) and 13O and ARG312 (2.0 Å). All the interactions were observed in close vicinity and adjacent to the active site residues ASP214, GLU276, and ASP349. The 2D and 3D interactions are shown in Fig.6.2.3.

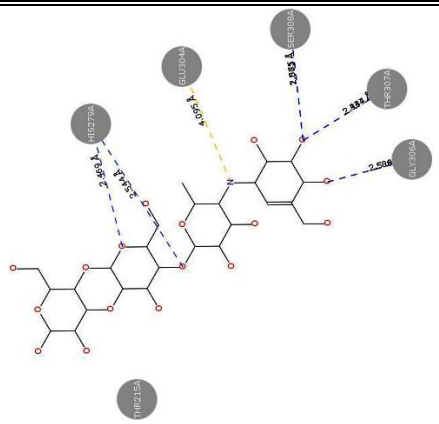
All these interactions showed that amino acid residue HIS279 might be crucial for interaction between strong inhibitors and α-glucosidases. The keto group on the cyclohexanone ring of the ligands were consistently forming hydrogen bond with the same amino acid residue ARG312, emphasizing the importance of the residue for the α-glucosidases inhibitory activity. Also the amino acid residue HIS279 interactions with electron withdrawing groups (nitro, fluro and morpholin moieties) attached to phenyl ring forming aromatic interaction/π-π interaction correlated with improved α-glucosidases inhibitory activity.

Table.6.2.3. Docking interactions between yeast (MAL12) homology model and 2-amino-phenyldiazenyl-4*H*-chromene derivatives 4aw, 4bb, 4bc, 4bd and Acarbose

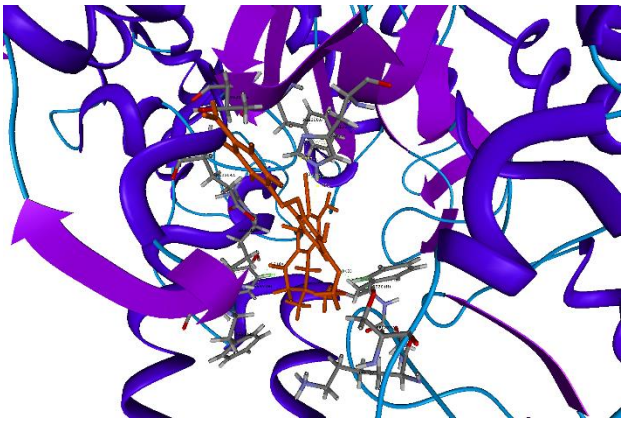
Residue	Atom	Ligand	Ligand Atom	Distance (Å)	Interaction Type
PHE157	2516C	4bd	11C	5.169	AROMATIC_INTERACTION
HIS279	4452C		21C	4.310	AROMATIC_INTERACTION
SER239	3820H		28O	1.970	HYDROGENBOND_INTERACTION
ARG312	4947H		13O	2.021	HYDROGENBOND_INTERACTION
HIS279	4452C	4bc	11C	5.401	AROMATIC_INTERACTION
HIS279	4452C		21C	4.844	AROMATIC_INTERACTION
HIS279	4463H		31N	1.723	HYDROGENBOND_INTERACTION
ARG312	4947H		13O	2.446	HYDROGENBOND_INTERACTION
HIS279	4452C	4bb	11C	5.101	AROMATIC_INTERACTION
HIS279	4452C		21C	4.999	AROMATIC_INTERACTION
HIS279	4463H		31N	1.914	HYDROGENBOND_INTERACTION
ARG312	4947H		13O	2.409	HYDROGENBOND_INTERACTION
HIS279	4452C	4aw	11C	4.951	AROMATIC_INTERACTION
HIS279	4452C		21C	5.087	AROMATIC_INTERACTION
SER239	3820H		28O	2.090	HYDROGENBOND_INTERACTION
HIS279	4463H		33N	1.919	HYDROGENBOND_INTERACTION
ARG312	4947H		13O	2.375	HYDROGENBOND_INTERACTION
GLU304	4829O	Acarbose	19N	4.095	CHARGE_INTERACTION
THR215	3435O		81H	2.527	HYDROGENBOND_INTERACTION
HIS279	4463H		1O	2.544	HYDROGENBOND_INTERACTION
HIS279	4463H		3O	2.469	HYDROGENBOND_INTERACTION
GLY306	4851N		82H	2.539	HYDROGENBOND_INTERACTION
GLY306	4855H		13O	2.586	HYDROGENBOND_INTERACTION
THR307	4863O		80H	2.337	HYDROGENBOND_INTERACTION
THR307	4865H		11O	2.444	HYDROGENBOND_INTERACTION
SER308	4872N		80H	2.065	HYDROGENBOND_INTERACTION
SER308	4882H		11O	1.571	HYDROGENBOND_INTERACTION

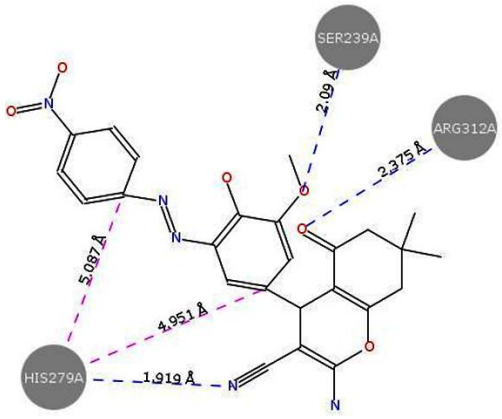
Acarbose



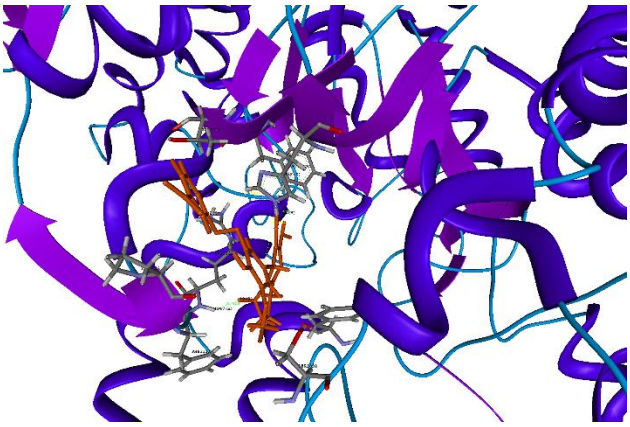


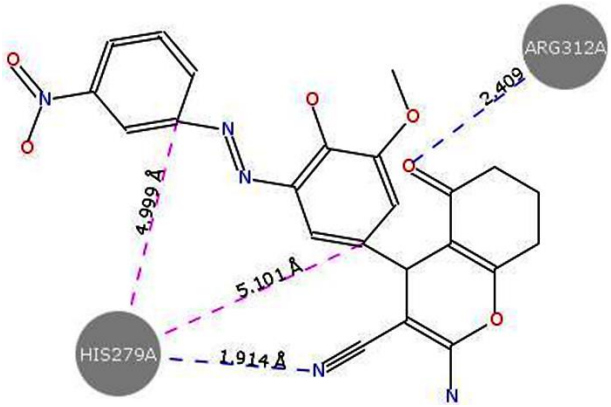
4aw



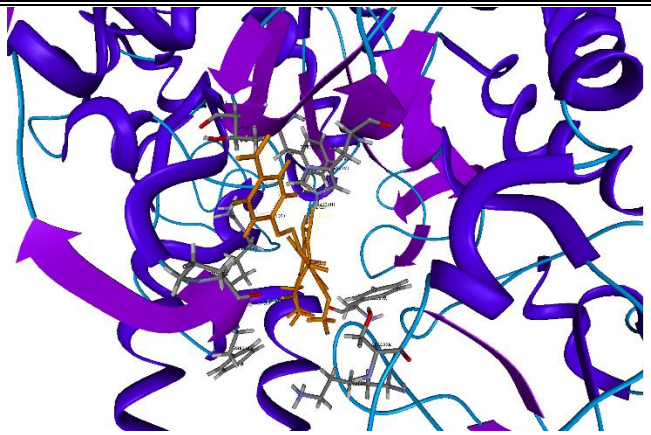


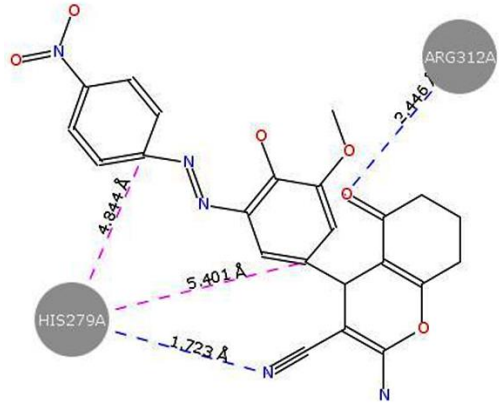
4bb



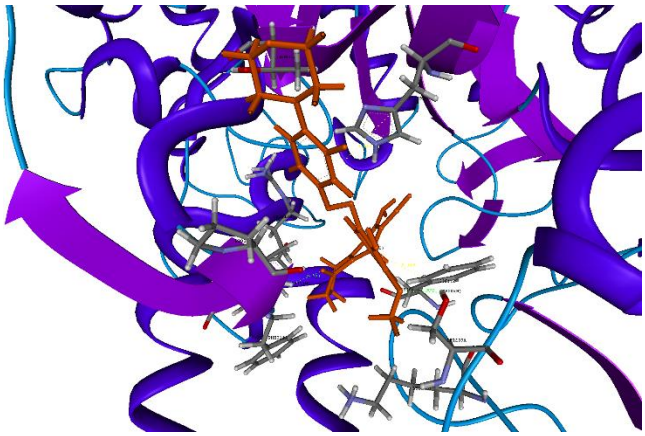


4bc





4bd



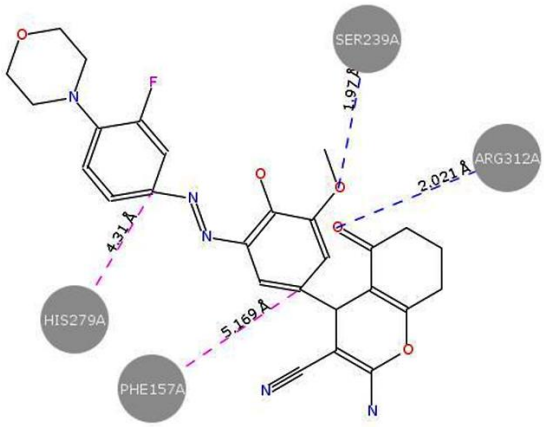
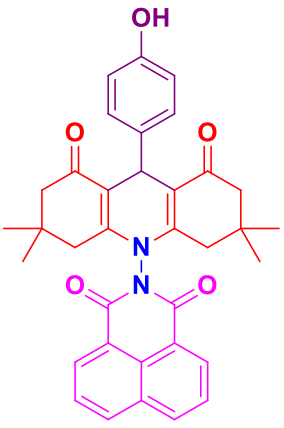


Fig.6.2.3. 3D and 2D docking interactions for Acarbose, 4aw, 4bb, 4bc and 4bd inside the active site cavity of MAL12 homology Model.

Chapter-III A: dihydropyridine derivatives

All the synthesized compounds **(5a-j)** were screened for *in-vitro* anticancer activity against MCF-7, Hep-G2 and HeLa cell lines by MTT assay. *In-vitro* anticancer activity results revealed that all the compounds were active against all the three tested cell lines. Among them, the compound **5e** has shown broad spectrum activity against MCF-7, HepG2 & HeLa with IC50 values 14.02 ± 0.9, 12.12 ± 0.6 & 17.99 ± 0.4 µM respectively. 6-methoxy-2- naphthalene benzaldehyde *i.e* **5g** has shown broad spectram activity against MCF-7, Hep G2 and HeLa with IC_{50} values 19.12 ± 0.2, 12.60 ± 0.2 and 40.07 ± 0.5 µM respectively. The compound derived from p-methoxybenzaldehyde *i.e* 5f against MCF-7, Hep G2 and HeLa with IC_{50} values 23.76 ± 0.4, 15.76 ± 0.8 and 29.06 ± 0.6 µM respectively. The compound derived from p-

methoxybenzaldehyde *i.e* 5f against MCF-7 and Hep G2 with IC_{50} values 33.12 ± 0.1 and 22.60 ± 0.2 µM respectively displayed prominent activity when compared with the standard drug Doxorubicin. Remaining all compounds have shown moderate activity against the three cell lines. (**Table.6.2.4.)**



5e

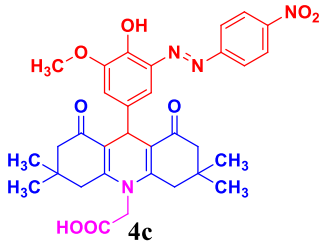
	IC_{50}
MCF-7	**14.02 ± 0.9 µM**
HepG2	**12.12 ± 0.6 µM**
HeLa	**17.99 ± 0.4 µM**

Table.6.2.4. *In-vitro* anticancer activity of compounds 5a-j against cancer cell lines MCF-7, HepG2 and HeLa

S.No	Compounds	IC_{50} MCF-7(µM)	IC_{50} HepG2 (µM)	IC_{50} HeLa (µM)
1	5a	30.03 ± 0.8	27.11 ± 0.4	50.97 ± 01
2	5b	64.23 ± 0.3	23.57 ± 0.7	70.75 ± 0.9
3	5c	18.09 ± 0.5	35.80 ± 0.3	30.64 ± 0.2
4	5d	89.19 ± 0.5	33.82 ± 0.3	52.82 ± 0.5
5	5e	14.02 ± 0.9	12.12 ± 0.6	17.99 ± 0.4
6	5f	23.76 ± 0.4	15.76 ± 0.8	29.06 ± 0.6
7	5g	19.12 ± 0.2	12.60 ± 0.2	40.07 ± 0.5
8	5h	70.18 ± 0.7	38.99 ± 0.5	51.72 ± 0.5
9	5i	33.32 ± 1.0	18.06 ± 0.7	25.04 ± 0.4
10	5j	31.29 ± 0.8	24.34 ± 0.5	27.18 ± 0.6
11	Doxorubicin	3.00 ± 03	1.09 ± 0.3	1.38 ± 0.7

Chapter-III B: dihydropyridine derivatives

Evaluation of the dihydropyridine derivatives for their enzyme inhibitory activities against yeast MAL12 α-glucosidase as a model enzyme. The enzyme assay was carried out following a standard protocol from literature by analyzing the hydrolysis of nitrophenyl glucoside spectrometrically. On comparison, the inhibition of α-glucosidase activity by dihydropyridine derivatives (**4a-l**) was found to be much higher than the inhibition of α-amylase activity. All the 12 inhibitors tested showed variable amount of α-glucosidase inhibition with IC_{50} values ranging from 63.53 µM to 110.74 µM (**Table.6.2.5.**). Acarbose was selected as the reference inhibitor. The IC_{50} value for acarbose under same assay conditions was found to be 33.95 µM. Among all the tested inhibitors, **4c** has shown the minimal IC_{50} value of 63.53±1.64 µM and **4b** showed the maximal IC_{50} value of 110.74±0.71 µM. Similarly, **4c** (63.53±1.64 µM), **4f** (64.75±1.34 µM), **4j** (67.66±0.78 µM) and **4l** (78.57±1.77 µM) have shown the top four minimal IC_{50} values for α-glucosidase inhibition activity.



4c

IC_{50} 63.53 ± 1.64

Table.6.2.5. dihydropyridine derivatives (**4a-l**) with the assay produced IC_{50} values for α-glucosidase inhibition activity.

S:No	Compounds	IC_{50} (uM)	Deviation (Error)
1	4a	76.14	3.27
2	4b	110.74	0.71
3	4c	63.53	1.64
4	4d	94.92	4.40
5	4e	83.99	2.20
6	4f	64.75	1.34
7	4g	80.32	0.75
8	4h	85.64	3.70
9	4i	88.62	3.54
10	4j	67.66	0.78
11	4k	96.72	2.41
12	4l	78.57	1.77
13	Acarbose	33.95	3.20

Chapter-IV: porphyrin derivatives

All the synthesized compounds (**3a-d, 4a-d, 5a-d, 6a-d, 7a-d, 9a-c, 10a-c**) were screened for their *in-vitro* antidiabetic activity against α-glucosidase enzyme with respect to standard antidiabetic drug acarbose. The Porphyrin compounds were evaluated for their potent glycosidase inhibitory activity. *Saccharomyces cerevisiae* α-glucosidase and porcine pancreatic α-amylase were used to test the glycosidase inhibitory activities of the compounds. All tested compounds have shown varying and appreciable levels of inhibitory activity for both the enzymes. usually most of the porphyrin compounds possess potent lipase inhibitory activity. Hence the synthesized porphyrin compounds were also tested for Lipase inhibitory activity using *Candida antartica* lipase. However, the compounds showed nearly negligible inhibitory activity for lipase. The complete details of the enzyme assay methods are included in the experimental section. The percentage inhibition for all the compounds at 5mM concentration against all the three enzymes are shown **Figure.6.2.4.** The α-glucosidase inhibitory drug Acarbose was used as the reference. All the compounds showed varying levels of α-glucosidase inhibition with a maximum and minimum IC_{50} values of 31.36µM and 111.64 µM respectively. The IC_{50} are shown in the **Table.6.2.6.** **The most potent compound 6c showed better inhibitory activity (31.36µM) as compared to the reference Acarbose (33.95µM) under matching assay conditions**.

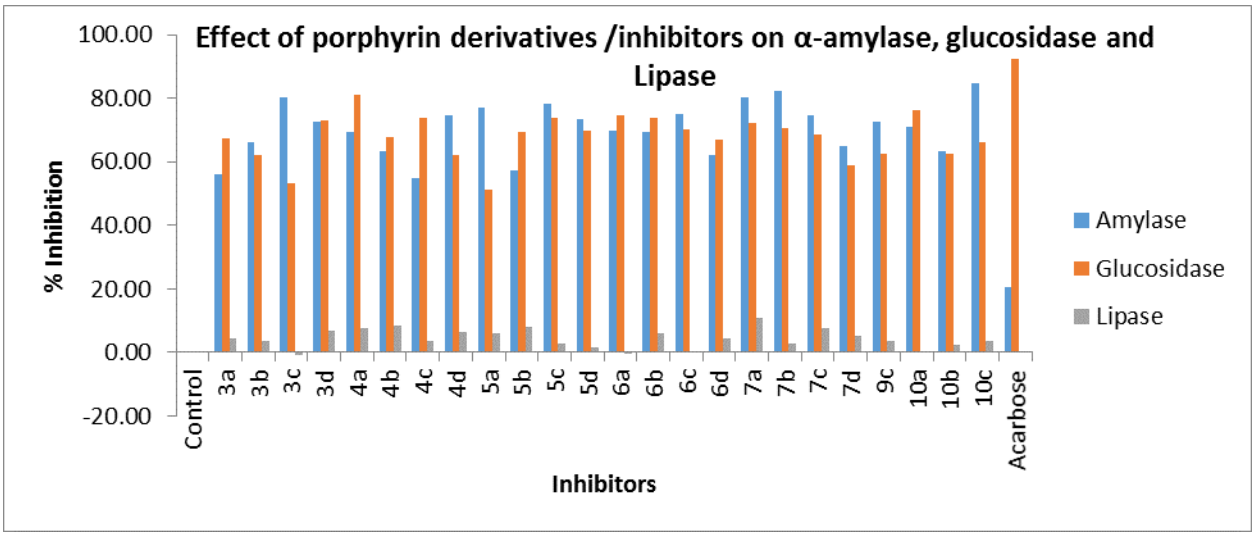


Figure.6.2.4. The percentage inhibition of fused Porphyrin compounds at 5mM concentration against α-amylase, α-glucosidase and Lipase

Table.6.2.6. Half inhibitory maximal value (IC_{50}) for the fused porphyrin compounds.

Sl. No.	Compound	IC_{50} (μM)	Deviation (Error)
1	3a	93.74	3.51
2	3b	95.40	4.07
3	3c	86.86	3.49
4	3d	56.84	0.97
5	4a	111.11	1.55
6	4b	97.30	2.76
7	4c	93.22	2.34
8	4d	111.64	1.21
9	5a	92.22	1.99
10	5b	76.52	1.91
11	5c	67.17	4.30
12	5d	57.89	1.33
13	6a	94.31	0.82
14	6b	79.40	3.95
15	6c	31.36	2.86
16	6d	47.07	2.17
17	7a	67.57	4.03
18	7b	41.35	1.67
19	7c	58.68	3.12
20	7d	83.13	2.04
21	Acarbose	33.95	3.20

Kinetic studies were carried out for the most potent compound **6c** against α-glucosidase using Michaelis-Menten kinetics and the kinetic constants K_m and V_{max} were calculated. The analysis of the values of K_m and V_{max} calculated from Lineweaver–Burk plot showed decrease in the values of both constants as the inhibitor concentration of **6c** was increased demonstrating a mixed un-competitive mode of inhibition. The Lineweaver-Burk plot for α-glucosidase

inhibition is shown in **Fig.6.2.5.** The plot 1/V vs. 1/[S] shows slope as expected for a mixed un-competitive mode of inhibition for **6c**.

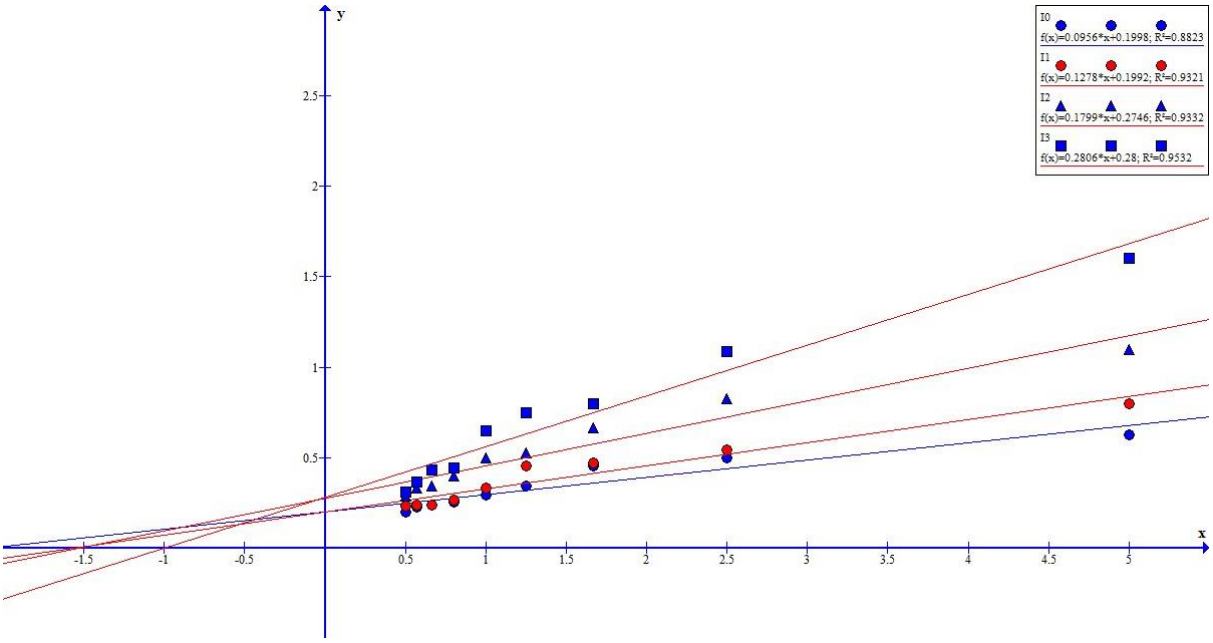


Fig.6.2.5. The Lineweaver-Burk plot for K3 against α-glucosidase enzyme

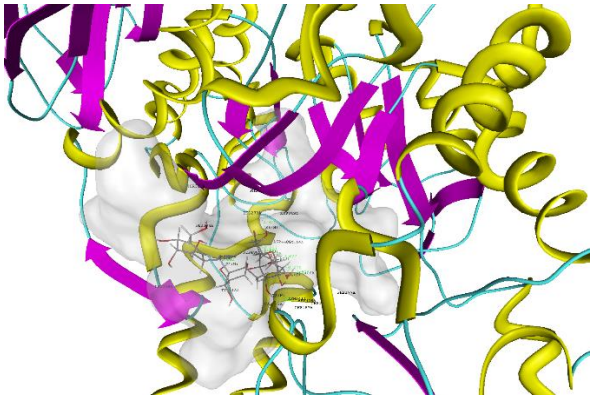
***In silico* studies: Binding analysis:**

The pyrazole moieties fused to the porphyrin scaffold were aligned in the core direction within the interacting cavity. This alignment facilitated the group to interact strongly with key residues within the active site. The porphyrin scaffold allows for the formation of both enhanced and firm complexes between the multiple fused pyrazole moieties and the amino acid side chains within the active cavity. The most active molecule **6c** showed multiple hydrogen bonds and aromatic (pi-pi) bond interactions with key amino acid side chains within the binding site. For the most active compound **6c** four hydrogen bonds were observed between (99) oxygen and (95) hydrogen of the compound and side chains of amino acid residue Asn214, Thr303 and His279 respectively. In addition to the hydrogen bonds aromatic interactions which are also called as the π-π stacking interactions facilitated the binding of the compound to the active site. In total eleven π-π stacking interactions were observed between the carbon in the rings of the most active molecule **6c** and amino acids side chain rings namely Phe157, His279, phe300,

phe311 and His348. The complete interactions for the most potent molecules K3, K4, K6 and reference Acarbose are shown below in the **Table.6.2.7.**

Fig.6.2.6. 3D interactions of a. Acarbose, b. K3 c. K4 and d. k6 with MAL12 protein model.

a



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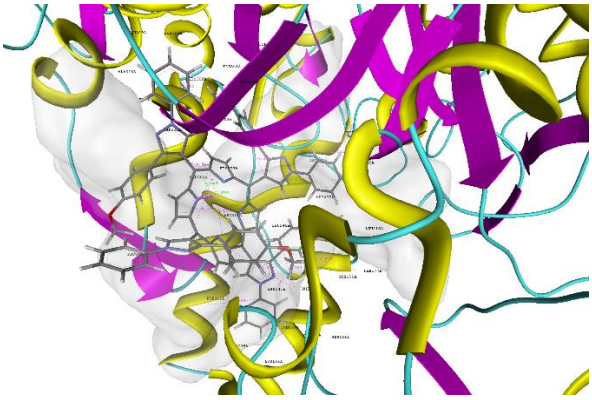

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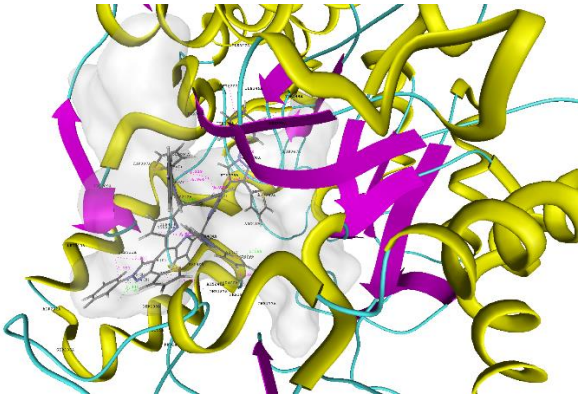

d

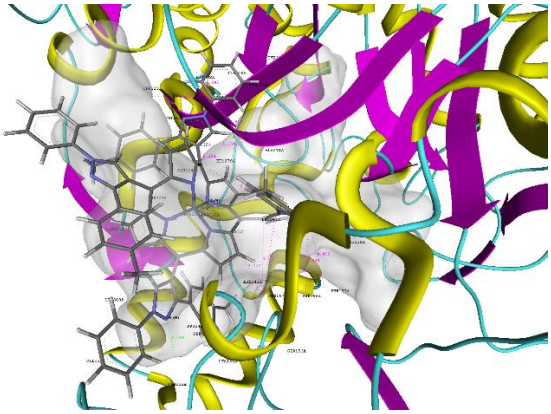

Table.6.2.7. Molecular docking interactions between MAL12 protein model and the most potent molecules K3, K4, K6 and reference Acarbose

Compounds	Residue	Atom	Ligand Atom	Distance Å	INTERACTION
K3	PHE157A	2516C	37C	4.995	AROMATIC_INTERACTION
	PHE157A	2516C	70C	4.787	AROMATIC_INTERACTION
	PHE177A	2847C	70C	4.613	AROMATIC_INTERACTION
	HIS279A	4452C	20C	4.108	AROMATIC_INTERACTION
	HIS279A	4452C	27C	5.401	AROMATIC_INTERACTION
	HIS279A	4452C	28C	4.525	AROMATIC_INTERACTION
	HIS279A	4452C	37C	4.675	AROMATIC_INTERACTION
	PHE300A	4760C	26C	4.007	AROMATIC_INTERACTION
	HIS302A	4794C	81C	4.050	AROMATIC_INTERACTION
	PHE311A	4921C	69C	4.334	AROMATIC_INTERACTION
	HIS348A	5547C	40C	5.283	AROMATIC_INTERACTION
	ASN241A	3847H	99O	1.727	HYDROGENBOND_INTERACTION
	HIS279A	4453N	110H	2.524	HYDROGENBOND_INTERACTION
	HIS279A	4456N	110H	1.598	HYDROGENBOND_INTERACTION
	THR303A	4816H	95O	1.421	HYDROGENBOND_INTERACTION
K6	PHE157A	2516C	20C	4.252	AROMATIC_INTERACTION
	PHE157A	2516C	28C	4.927	AROMATIC_INTERACTION
	PHE157A	2516C	37C	4.861	AROMATIC_INTERACTION
	PHE158A	2534C	38C	4.934	AROMATIC_INTERACTION
	PHE177A	2847C	28C	5.019	AROMATIC_INTERACTION
	PHE177A	2847C	38C	4.458	AROMATIC_INTERACTION
	HIS279A	4452C	25C	5.191	AROMATIC_INTERACTION
	HIS279A	4452C	37C	4.991	AROMATIC_INTERACTION
	PHE300A	4760C	25C	5.370	AROMATIC_INTERACTION
	PHE300A	4760C	69C	4.804	AROMATIC_INTERACTION
	HIS302A	4794C	69C	4.049	AROMATIC_INTERACTION
	TRP323A	5140C	69C	5.415	AROMATIC_INTERACTION
	GLU304A	4829O	5N	4.486	CHARGE_INTERACTION
	GLU304A	4829O	18N	2.420	CHARGE_INTERACTION
	GLU304A	4829O	97Zn	3.879	CHARGE_INTERACTION
	SER239A	3816H	66N	2.456	HYDROGENBOND_INTERACTION
K4	PHE157A	2516C	39C	3.762	AROMATIC_INTERACTION

	PHE177A	2847C	60C	5.105	AROMATIC_INTERACTION
	HIS279A	4452C	20C	4.028	AROMATIC_INTERACTION
	HIS279A	4452C	66C	4.364	AROMATIC_INTERACTION
	HIS279A	4452C	67C	5.218	AROMATIC_INTERACTION
	PHE300A	4760C	20C	4.442	AROMATIC_INTERACTION
	PHE300A	4760C	37C	4.875	AROMATIC_INTERACTION
	PHE300A	4760C	38C	4.598	AROMATIC_INTERACTION
	HIS302A	4794C	38C	3.600	AROMATIC_INTERACTION
	PHE311A	4921C	26C	5.285	AROMATIC_INTERACTION
	PHE311A	4921C	40C	3.850	AROMATIC_INTERACTION
	TYR313A	4965C	25C	4.491	AROMATIC_INTERACTION
	TYR313A	4965C	59C	3.927	AROMATIC_INTERACTION
	TYR344A	5478C	38C	4.551	AROMATIC_INTERACTION
	LYS155A	2496H	34N	2.464	HYDROGENBOND_INTERACTION
	LYS155A	2497H	35N	2.440	HYDROGENBOND_INTERACTION
	GLU304A	4829O	98H	2.048	HYDROGENBOND_INTERACTION
	ARG439A	7051H	76S	2.065	HYDROGENBOND_INTERACTION
Acarbose	GLU304A	4829O	19N	4.499	CHARGE_INTERACTION
	PHE157A	2512O	73H	1.986	HYDROGENBOND_INTERACTION
	GLU304A	4829O	72H	1.558	HYDROGENBOND_INTERACTION
	ASP349A	5562O	86H	1.422	HYDROGENBOND_INTERACTION
	ASP406A	6498O	84H	2.476	HYDROGENBOND_INTERACTION
	ASP406A	6499O	84H	2.005	HYDROGENBOND_INTERACTION
	ARG439A	7030N	85H	2.287	HYDROGENBOND_INTERACTION
	ARG439A	7041H	8O	2.448	HYDROGENBOND_INTERACTION
	ARG439A	7041H	16O	2.422	HYDROGENBOND_INTERACTION
	ARG439A	7049H	16O	2.023	HYDROGENBOND_INTERACTION

Chapter-V: pyrazolo-phthalazine derivatives

The synthesized fused pyrazolo-phthalazine derivatives were evaluated there *in vitro* antifungal activity against *Aspergillus niger* and *Candida albicans*. Regarding antifungal tests against *Candida albicans*, compounds of series **4a-t** have showed promising inhibitory activity (**Table.6.2.8.**). Compounds of series **4a-k**, specially, **4f** (MIC = 10.25 µM), **4k** (MIC = 13.42 µM) have displayed good activity compared to other synthesized compounds. Moderate activity was observed for **4g** (MIC = 19.01 µM), **4i** (MIC = 20.91 µM), **4h** (MIC = 21.53 µM), **4j** (MIC = 22.09 µM), **4c** (MIC = 33.94 µM) and less active compounds were **4b** (MIC = 50.32 µM), 4e (MIC = 100.34 µM), 4d (MIC = 125.92 µM). Compound **4a** did not display any biological activity under the concentration tested.

From the antifungal activity data (**Table.6.2.8.**) against *Aspergillus niger*, it is clearly observed that many of the synthesized compounds show prominent antifungal activity. The compound **4f** (MIC = 15.27 µM) has exhibited good activity compared to other synthesized compounds. Moderate activity was observed for five compounds **4k** (MIC = 20.41 µM), 4j (MIC = 23.19 µM), **4g** (MIC = 25.13 µM), **4c** (MIC = 30.35 µM) and **4i** (MIC = 30.83 µM) against *Aspergillus niger*. Compounds **4d**, **4b**, **4e** and **4h** showed less activity and **4a** did not display any biological activity.

3.3. Molecular docking

To gain a better understanding of the potency of the ligand analogue molecules, we proceeded to examine the interaction of fused chromeno-pyrazolo-phthalazine derivatives docked into the catalytic site of receptors 1EAG. Dock runs of ligands on enzyme *VLifeMDS v 4.3* resulted in the evaluation of antifungal efficacy of a compound, which could be evaluated based on their binding compatibility [docked energy (kcal/mol)]. The docking experimental results are summarized in **Table.6.2.9.**

In GRIP docking of *VLifeMDS*, the ligand can be either in rigid or flexible conformation. Docking analysis by treating ligand as both rigid and flexible gives the interaction profile with the active site of the receptor as a function of Van der Wall (VDW), hydrophobic, charged and hydrogen bond interactions **(Fig.6.2.7.)**.

Table.6.2.9. Antifungal activity of synthesized pyrazolo-phthalazine derivatives (**4a-t**)

S:No	Compounds	Candida albicans (uM)	Aspergillus niger (uM)
1	4a	> 250	> 250
2	4b	50.32	61.22
3	4c	33.94	30.35
4	4d	125.92	54.05
5	4e	100.34	93.37
6	4f	10.25	15.27
7	4g	19.01	25.13
8	4h	21.53	120.35
9	4i	20.91	30.83
10	4j	22.09	23.19
11	4k	13.42	20.41
12	4l	37.39	51.23
13	4m	46.41	70.71
14	4n	73.40	41.98
15	4o	33.39	77.65
16	4p	41.03	32.17
17	4q	63.47	84.05
18	4r	54.22	59.87
19	4s	59.63	88.19
20	4t	72.12	54.12
21	Fluconazole	3.51	4.09

The present experimental results for antifungal activity analysis clearly indicate that the ligand molecule **4f** has highest binding energy of - 82.745574 Kcal/mol against the receptor secreted aspartic proteinase (SAP) of *Candida albicans* (1EAG) when all the ligands were treated as flexible. It generated the interaction profile of VDW interactions with VAL 12A, TYR 84A, GLY 85A, ASP 86A, ILE 119A, ILE 123A, THR 221A, THR 222A, ILE 223A, TYR 225A, ASN 301A, ALA 303A, ILE 305A; hydrophobic interactions with GLY 85A, THR 221A, THR 222A, ILE 223A; one aromatic interaction with TYR 225A and one hydrogen bond interaction with TYR 225A. The importance of the binding with GLY 85A was in agreement with key role of such amino acids as the anchoring point in SAP2 active site. The docking analysis of **4f** characterised by a hydrophobic interaction and VDW interaction between phthalamide carbonyl group and GLY 85A amide proton. On the other hand all the rigid

ligands interacted with the same receptor and compound **4f** has shown the highest affinity towards the aspartic proteinase (SAP) of *Candida albicans* (1EAG) and resulted only in VDW interactions with ASP 32A, TYR 84A, GLY 85A, ASP 86A, ILE 123A, GLY 220A, THR 221A, THR 222A, ILE 223A, TYR 225A, ASN 301A, ALA 303A, ILE 305A; hydrophobic interactions with ASP 86A, THR 222A, ILE 223A and aromatic interaction with TYR 84A, TYR 225A with binding energy of – 71.509335 Kcal/mol. This molecular docking result suggests that compound **4f** is a potential inhibitor of secreted aspartic proteinase (SAP) of *Candida albicans* (1EAG).

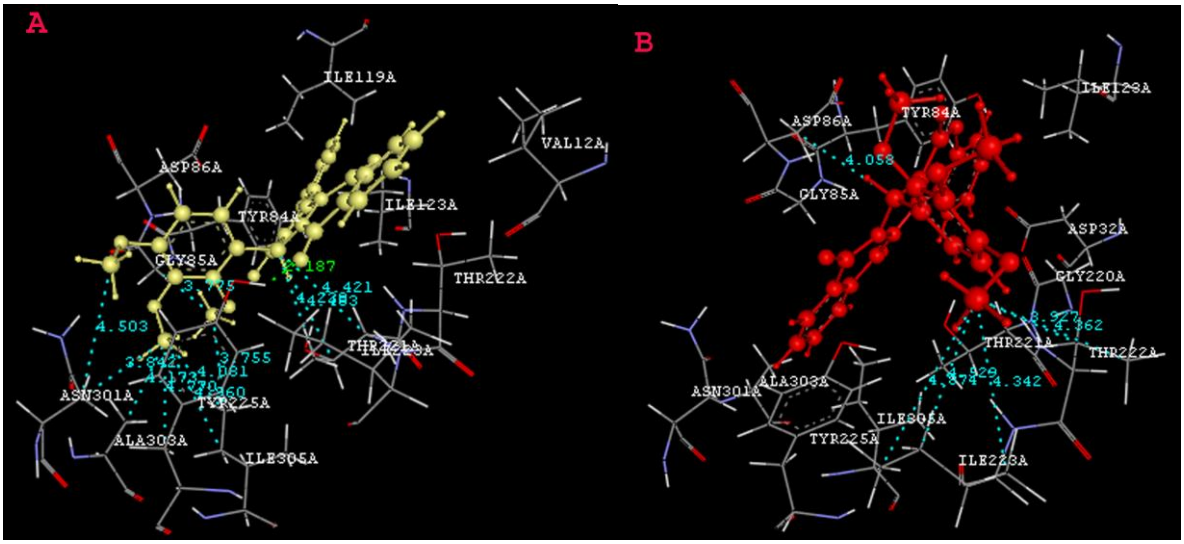

Fig.6.2.7. Ligand-Receptor interaction profiles by Molecular Docking (A) Interactions between 1EAG and **4f** (ligand flexible) (B) Interactions between 1EAG and **4f** (ligand rigid)

Legand: H-bond interactions, green dashed line: Hydrophobic interactions, blue dashed line.

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SUMMARY

Summary

The thesis entitled **"Studies on the synthesis and evaluation of biological activity of novel chromenes, dihydropyridines, porphyrins and pyrazolo-phthalazines"** is divided into six chapters. The titles of all chapters are given below.

CHAPTER-I: Introduction.

CHAPTER-II: Synthesis of novel fused chromenes by a green chemical method.

CHAPTER-III: This chapter is further divided into two sections.

***SECTION-A*:** Eco-friendly multicomponent synthesis of novel dihydropyridine derivatives.

***SECTION-B*:** Synthesis of new dihydropyridine derivatives using Eu_2O_3 modified CeO_2 nanoparticles.

CHAPTER-IV: Synthesis of novel A_2B_2 and A_4 type porphyrin derivatives.

CHAPTER-V: Synthesis of new pyrazolo-phthalazine derivatives using [Bmim]BF_4 ionic liquid.

CHAPTER-VI: Evaluation of biological activity.

CHAPTER-I

INTRODUCTION

A brief introduction of chromenes, dihydropyridines, porphyrins and pyrazolo-phthalazines is presented in this chapter. These molecules have broad pharmacological applications as they are integral parts of several drugs. Applications of these heterocyclic units inculcated enthusiasm in us to synthesize novel molecules containing one or more of the above pharmacophores employing green conditions/ aqueous medium or by conventional method.

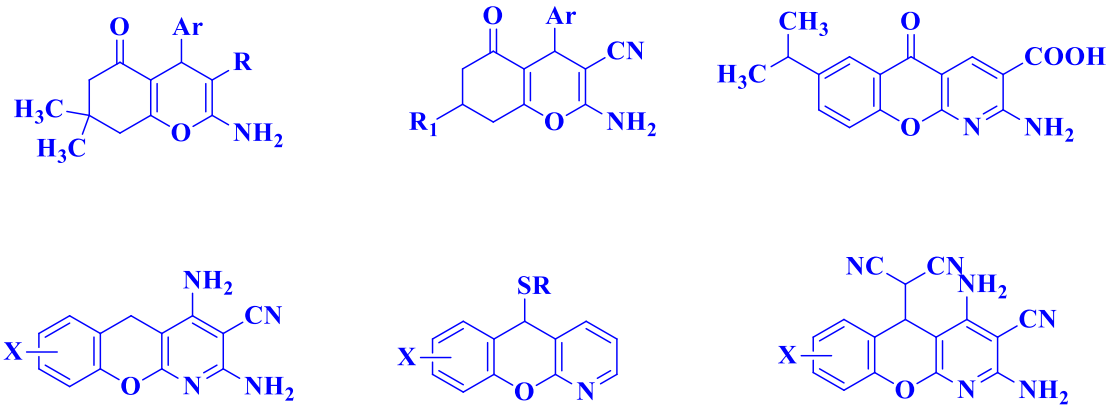
General introduction to heterocycles

Many heterocyclic compounds occur naturally and are actively involved in biology *e.g.* nucleic acids (purine and pyrimidine bases), vitamins (thiamine B_1, riboflavin B_2, nicotinamide B_3, pyridoxol B_6 and ascorbic acid C), heme, chlorophyll, penicillins, cephalosporins, macrolides *etc*. The majority of pharmaceuticals, agrochemicals, additives and modifiers used in industrial applications are heterocyclic in nature. A large number of alkaloids derived from heterocyclic molecules are used as drugs. Their applications in medicine, agriculture, photoelectronics *etc*. made them attractive synthetic targets.

Chromenes

The chromene ring systems are present in numerous natural products and are considered to be the most imperative molecules possessing wide spectrum of biological and pharmacological activities, that include spasmolytic, diuretic, clotting, antimicrobial, antiviral, antitumoral, and antianaphylactic activities. They are also used in pigments, photoactive materials, and biodegradable agrochemicals. These were also reported as anti-HIV, antiinflammatory, antileishmanial and TNF-α inhibiting agents.

They can also be used as cognitive enhancers not only for the treatment of schizophrenia and myoclonus but also for the treatment of neurodegenerative disease, including alzheimer's disease, amyotrophic lateral sclerosis, huntington's disease, parkinson's disease, AIDS associated dementia, and down's syndrome. Similar compounds have shown fully selective inhibition of the human excitatory amino acid transporter subtype 1 (EAAT 1). A typical example of an approved chromene drug is **amlexanox**, which is a commonly prescribed antiallergic and typical antiulcer drug. Many other compounds also exhibit a wide therapeutic and pharmacological properties[10] (**Fig 1**).



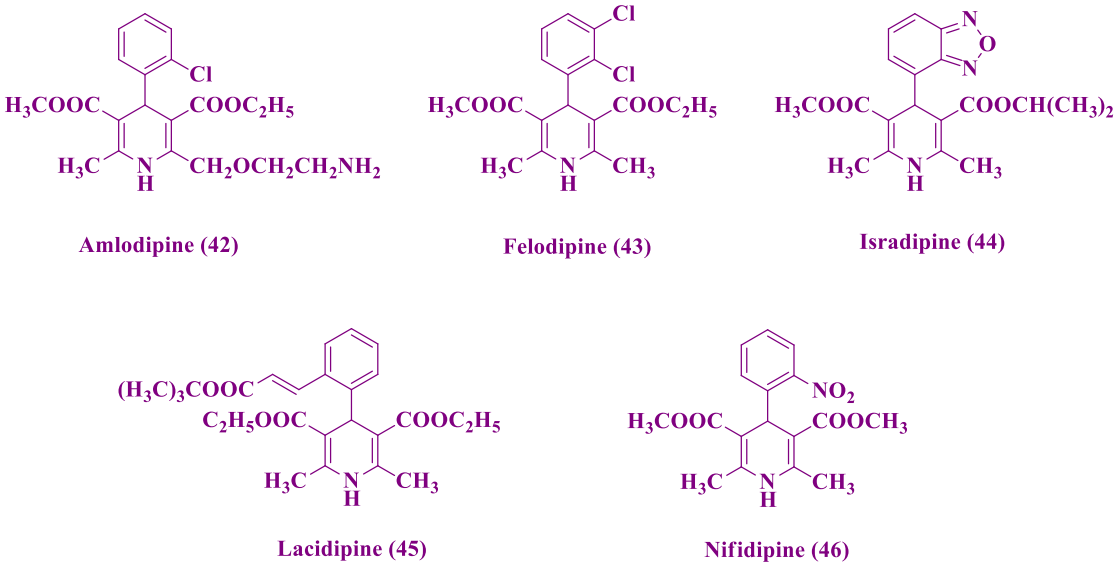
Ar = Aryl; R = Alkyl; R_1 = Alkyl/Alkoxyl; X = Halo

Fig. 1

Dihydropyridines

Dihydropyridine ring is an important target in synthetic and medicinal chemistry as it is the key moiety in numerous biologically active compounds. The molecules containing dihydropyridines such as **Amlodipine**, **Felodipine**, **Isradipine**, **Lacidipine** and **Nifedipine** are prominent drugs for the treatment of cardiovascular diseases and hypertension as effective calcium channel blockers **(Fig. 2).**

1,4-Dihydropyridines are good precursors for the synthesis of corresponding pyridine derivatives and are useful as reducing agents for imines in the presence of catalytic amount of Lewis acid.



Amlodipine (42) Felodipine (43) Isradipine (44)

Lacidipine (45) Nifidipine (46)

Fig. 2

Porphyrins

The porphyrinic macrocyclic arrangement with four pyrrole rings connected by methine units was suggested more than a century ago, and is extraordinarily stable. The nitrogen atoms at the interior form a central pocket ideally positioned to firmly incorporate metal atoms in a tetradentate fashion (Fe, Co or Mg prevail in biological systems). These anionic centres represent coordinatively unsaturated units for charge transfer and ligation of adducts, which occurs with reversible changes of electronic configuration.

In the past decade, porphyrin systems have also become probably the most popular model with which to mimic many biological phenomena, as well as being targets for commercial exploitation of several catalytic processes of a type which are efficiently performed in Nature, for example in the chemical functionalization of hydrocarbons, transportation of oxygen, etc. The porphyrin macrocycle also provides an excellent chelating ligand for a variety of metal ions which can be studied in detail in order to reveal new features of inorganic and organometallic chemistry, as well as a wealth of molecules for medicinal, theoretical, physical, and spectroscopic investigations (**Fig. 3)**.

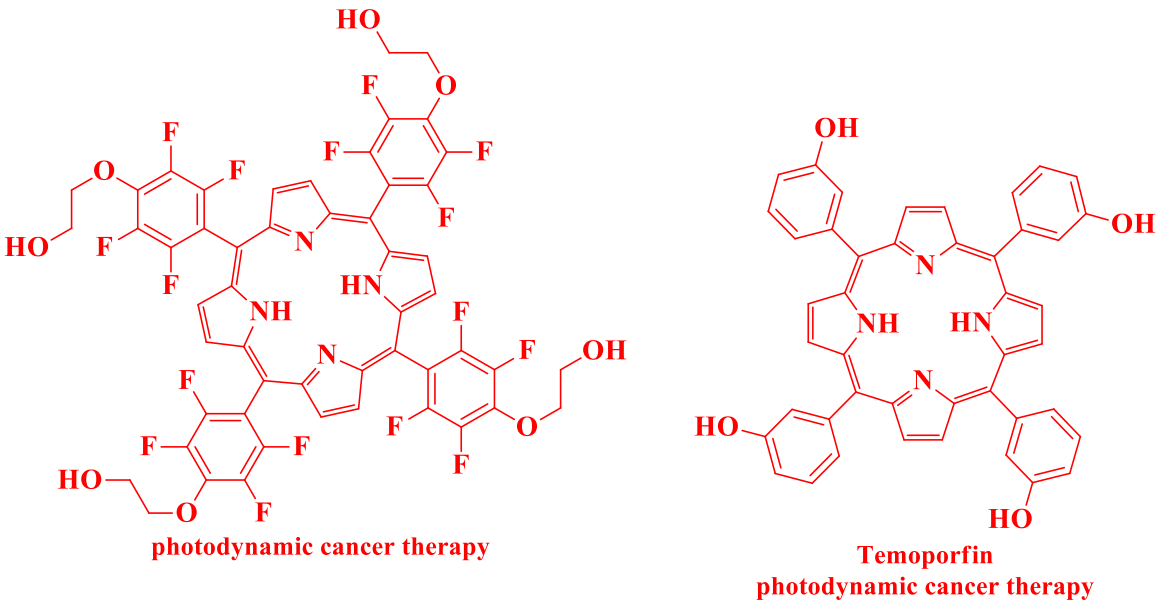


Fig. 3

Pyrazolo-phthalazines

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to pharmaceuticals, agrochemicals, and functional materials are becoming more and more important. Pyrazoles constitute an important class of compounds for new drug development, as they provide core structure for numerous biologically active compounds,

including blockbuster drugs such as celecoxib, viagra, pyrazofurine, and many others. Similarly, heterocycles containing a phthalazine moiety are of current interest due to their pharmacological and biological activities, for example, pyrazolo-phthalazine is described as antimicrobial, anti-inflammatory, analgesic, anti-hypoxic, and anti-pyretic agent (**Fig. 4**). Phthalazine derivatives are also found to possess anticonvulsant, cardiotonic and vasorelaxant activities.

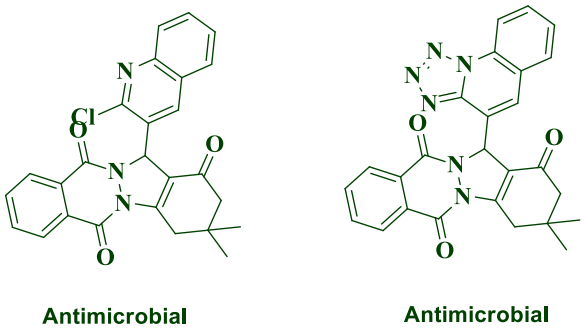


Fig. 4

Encouraged by the above reports, we got inspired to take up the synthesis of the title compounds.

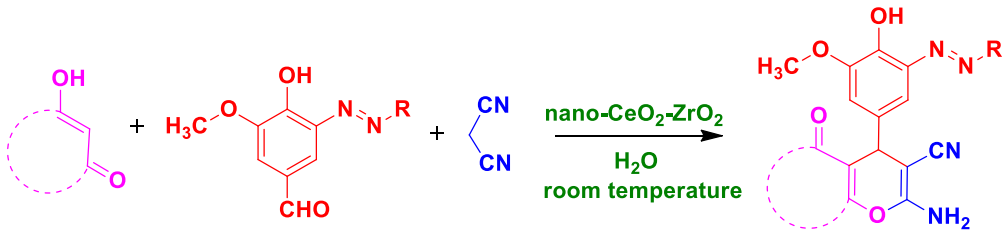
CHAPTER-II

SYNTHESIS OF NOVEL FUSED CHROMENES BY A GREEN CHEMICAL METHOD

Chromene derivatives have received considerable interest from the pharmaceutical industry due to their wide range of biological and therapeutic properties such as antiallergic, antibacterial, antifungal, antioxidant, antitumor, anti-inflammatory, antiviral and anticancer activities.

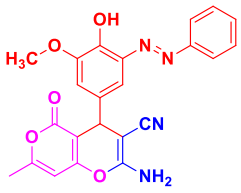
In view of the pharmaceutical importance of chromenes, we have developed simple, efficient and eco-friendly methods for the synthesis of a new series of fused chromenes **(4aa-bd)** *via* a three-component cyclocondensation reaction. The reaction is among 1,3-dicarbonyl compounds, 4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-benzaldehydes and malononitrile in presence of zirconium doped ceria nanoparticles (CeO_2-ZrO_2) in excellent yields **(Table 1)**.

Table 1: Synthesis of chromene derivatives **4aa-bc**[a]

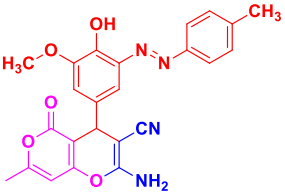


1a-e 2a-f 3 4aa-bd

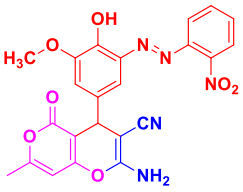
[b]yeild (%), time



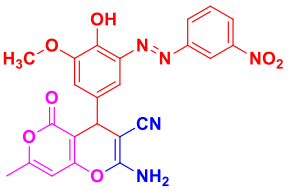
4aa
83%, 2 h



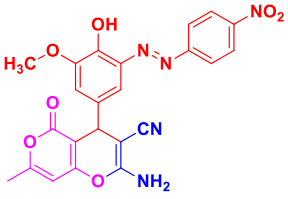
4ab
86%, 2.5 h



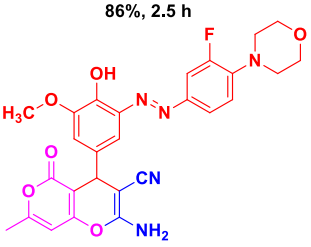
4ac
91%, 2 h



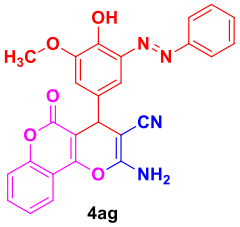
4ad
79%, 2 h



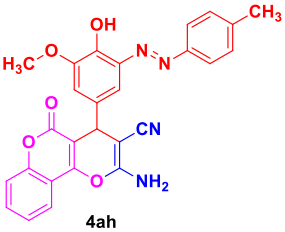
4ae
81%, 2.5 h



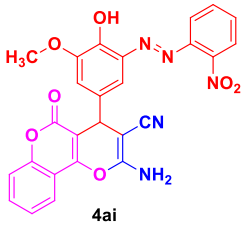
4af
85%, 3 h



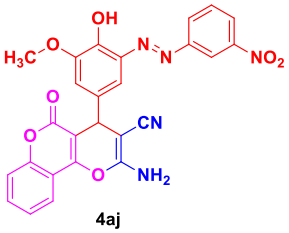
4ag
82%, 2 h



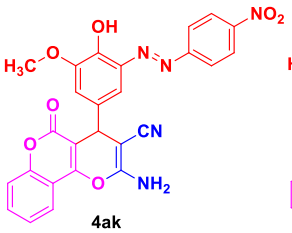
4ah
79%, 2 h



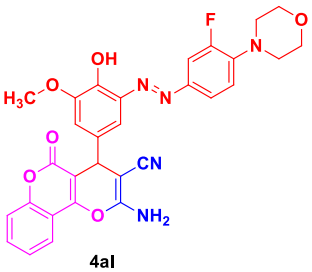
4ai
83%, 3 h



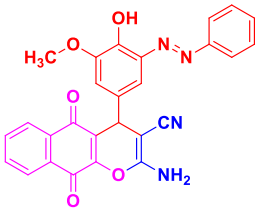
4aj
93%, 2 h



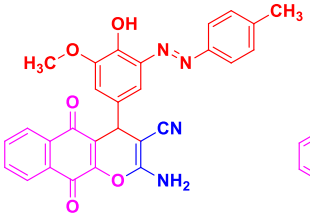
4ak
91%, 2.5 h



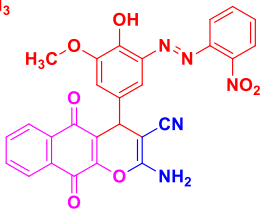
4al
87%, 2 h



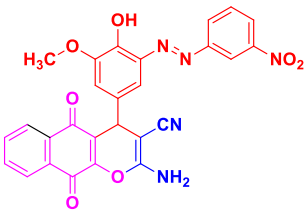
4am
81%, 2 h



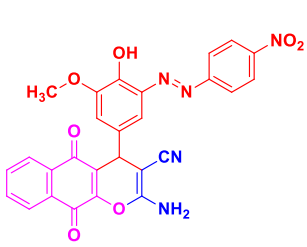
4an
89%, 3 h



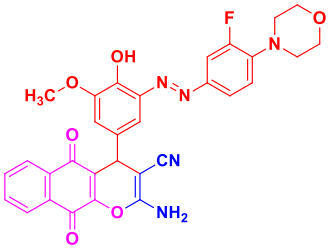
4ao
84%, 3 h



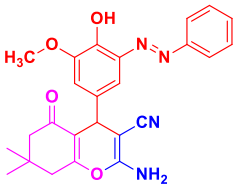
4ap
83%, 2.5 h



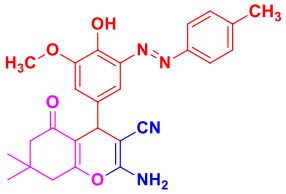
4aq
81%, 2.5 h



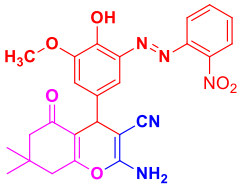
4ar
85%, 2 h



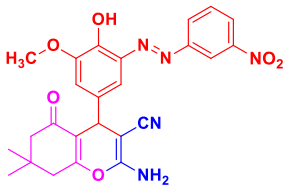
4as
84%, 2.5 h



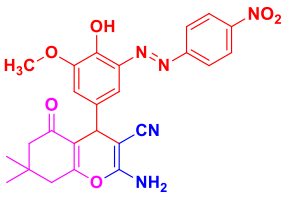
4at
89%, 2.5 h



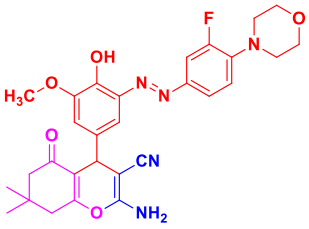
4au
80%, 3 h



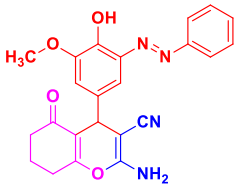
4av
91%, 2 h



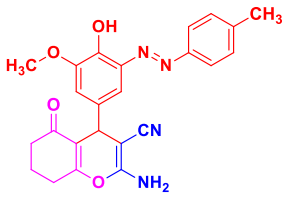
4aw
85%, 2 h



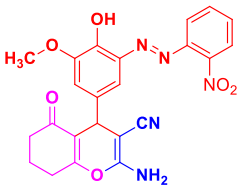
4ax
87%, 2.5 h



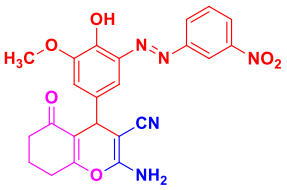
4ay
83%, 2.5 h



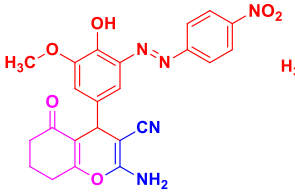
4az
89%, 2 h



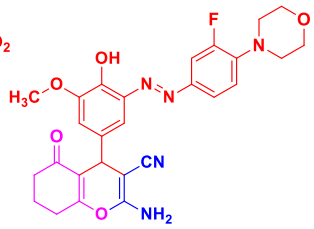
4ba
83%, 2 h



4bb
88%, 2 h



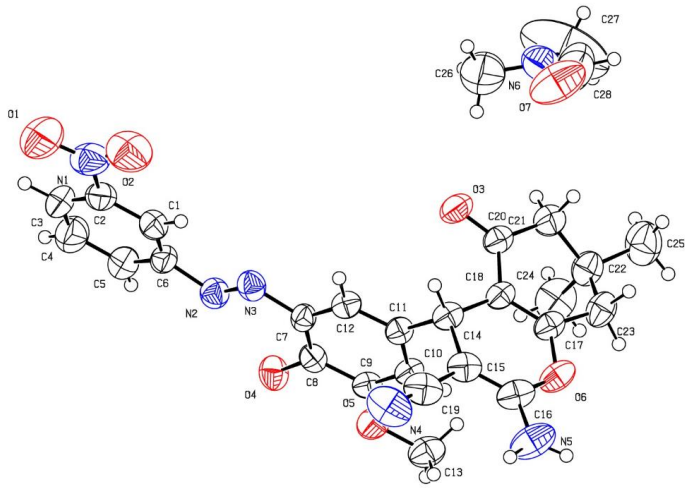
4bc
90%, 2 h



4bd
87%, 2.5 h

[a]Reaction conditions: dicarbonyl compound (1 mmol), 4-hydroxy-3-methoxy-5-((substituted phenyl)diazenyl)benzaldehyde (1 mmol) and malononitrile (1 mmol), nano-CeO_2–ZrO_2 (20 mol %), water (5 mL). [b]Yields of isolated products.

All the synthesized compounds were confirmed by their analytical and spectral studies. A single crystal structure of a representative compound **4av** proved the products formation. The crystal structure of **4av** was determined as "monoclinic". The ORTEP representation of the molecular structure of **4av** which was drawn at 50% probability level is shown in **Fig. 5**.



4av

Fig. 5.

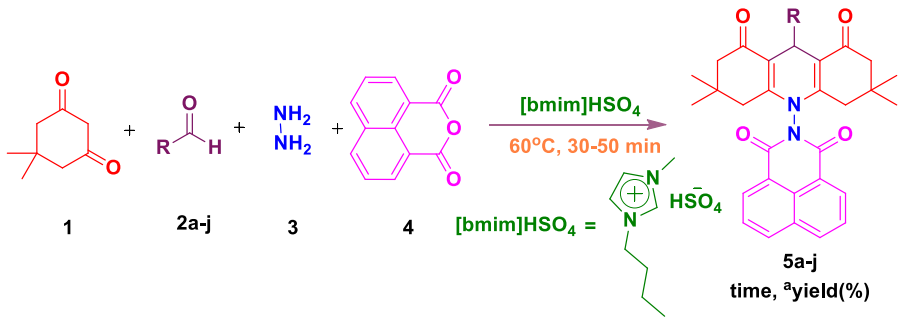
The above protocols described have advantages such as high yields of products in short reaction times, simple work-up procedure, easy isolation of the catalyst from the reaction mixture, reusability of the catalyst and environmentally benign in nature.

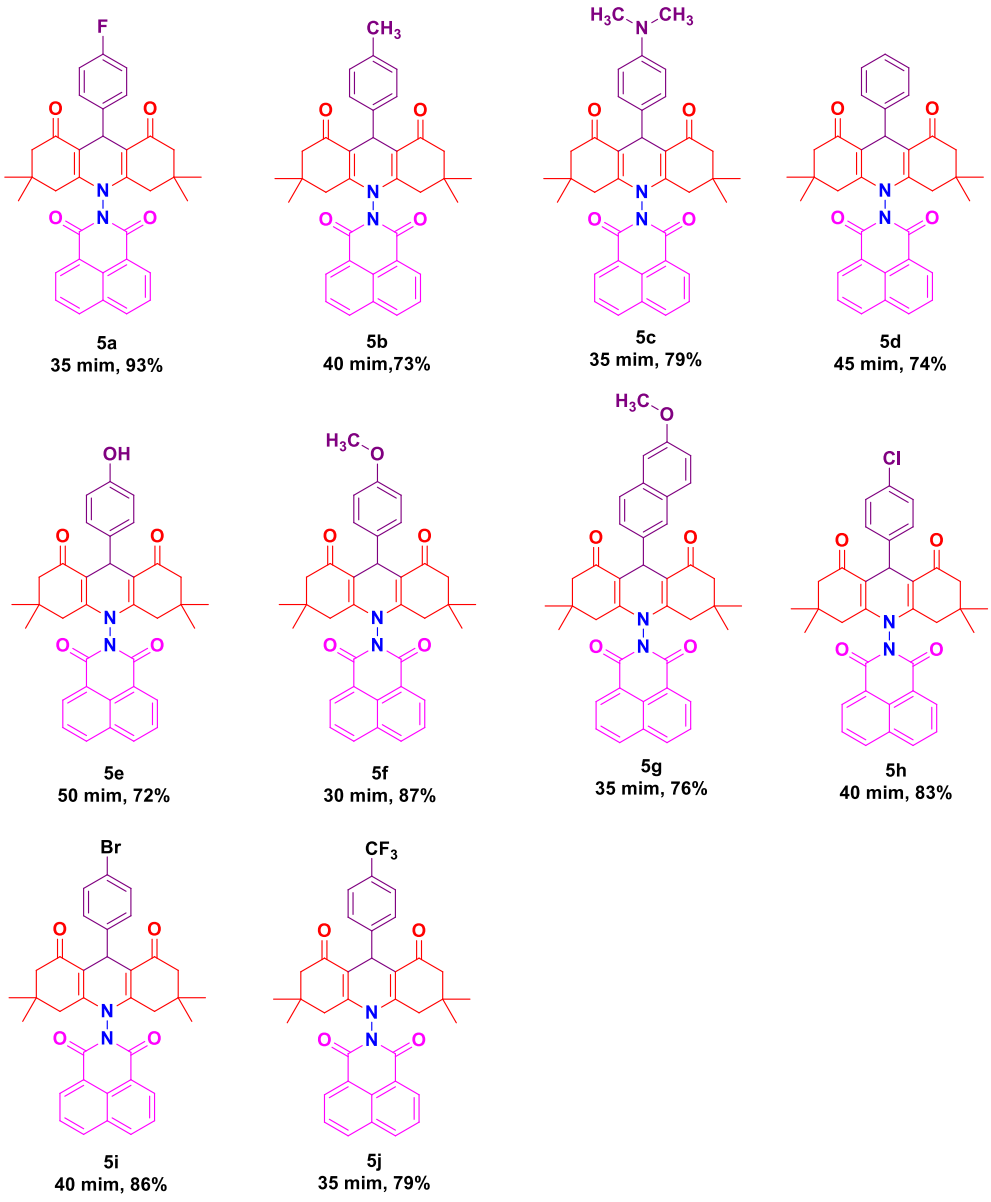
CHAPTER-III (SECTION-A)

ECO-FRIENDLY MULTICOMPONENT SYNTHESIS OF NOVEL DIHYDROPYRIDINE DERIVATIVES

Literature survey revealed that dihydropyridines possess a high degree of bio-activity. Therefore, we elicit the synthesis of various novel dihydropyridines utilizing inexpensive, eco-friendly and reusable ionic liquid, [bmim]HSO_4. Dimedone, aromatic aldehydes, hydrazine hydrate and 1,8-naphthanoic anhydride were reacted in the presence of [bmim]HSO_4 ionic liquid at 60^oC to afford the corresponding dihydropyridine derivatives in good yields **(Table 2)**.

Table 2: Synthesis of naphthalimide based acridine-1,8-dione derivatives (**5a-j**)





Reaction conditions: Dimedone (2 mmol), 4-fluoro benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), 1,8-naphthoic anhydride (1 mmol), [bmim]HSO_4 (1 mL). [a]Yields of the isolated products.

Spectral studies, as well as single crystal X-ray data of a representative compound **5a** confirmed the structure of all the reaction products. The crystal structure of **5a** was determined as "monoclinic". The ORTEP representation of the molecular structure of **5a** which was drawn at 50% probability level is shown in **Fig. 6**.

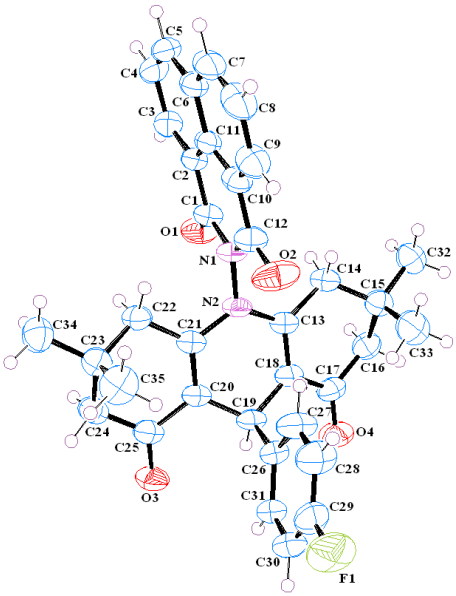


Fig. 6.

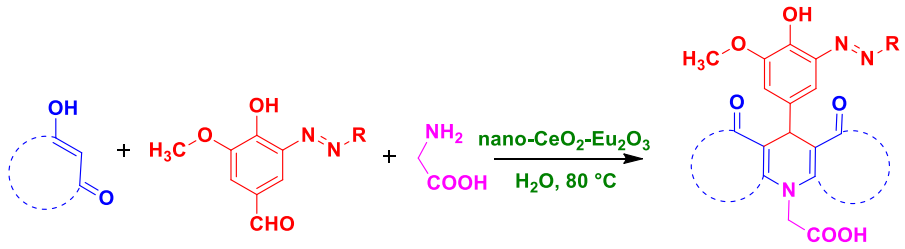
In conclusion, we reported the synthesis of various dihydropyridine derivatives utilizing an efficient, eco-friendly and reusable ionic liquid [bmim]HSO_4 catalyst.

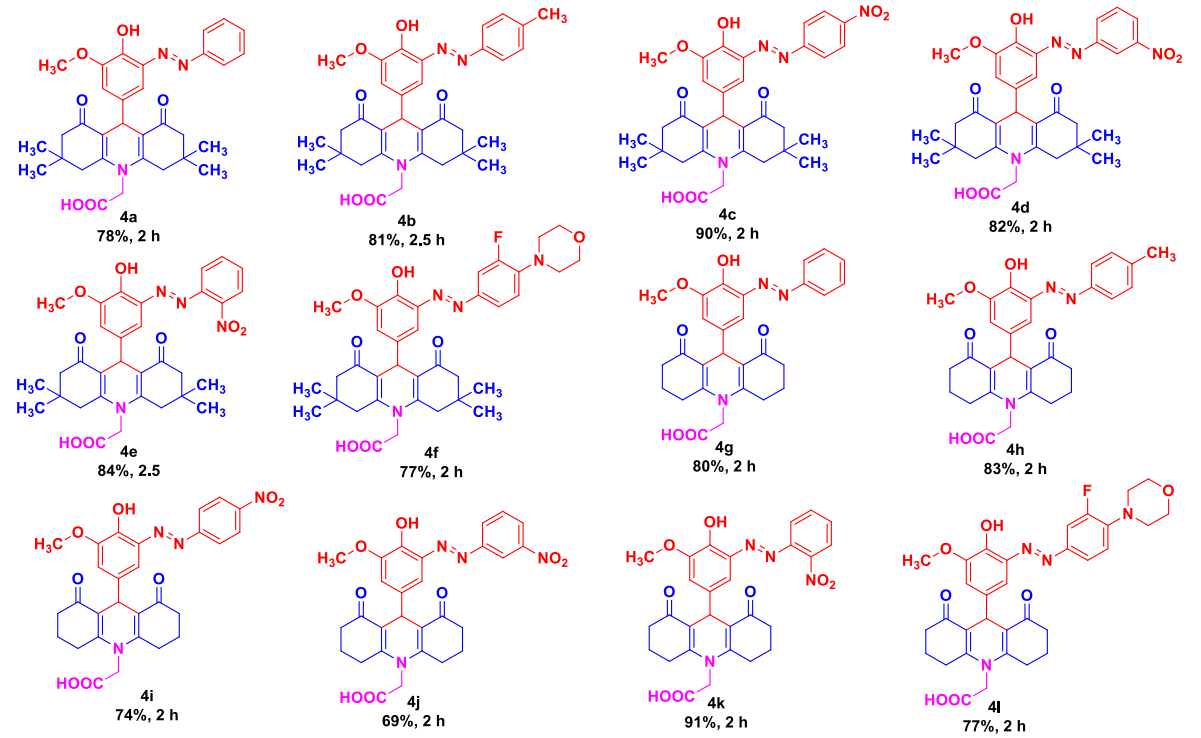
CHAPTER-III (SECTION-B)

SYNTHESIS OF NEW DIHYDROPYRIDINE DERIVATIVES USING Eu_2O_3 MODIFIED CeO_2 NANOPARTICLES

In this section, we have developed a facile method for the synthesis of dihydropyridine derivatives by the reaction of 1,3-dicarbonyl compounds, 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes and glycine in the presence of Eu_2O_3 modified CeO_2 nanoparticles using as a catalyst in aqueous medium at 80^oC **(Table 3)**. All the synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR and mass spectral data as well as elemental analyses.

Table 3: Synthesis of dihydropyridine derivatives **4a-l**[a]





[a]Reaction conditions: 1,3-dicarbonyl compounds (2 mmol), 4-hydroxy-3-methoxy-5-((4-substituted-phenyl)-diazenyl)-benzaldehyde (1 mmol) and glycine (1 mmol), water (1 mL) and nano-CeO_2–Eu_2O_3. [b]Yields of isolated products.

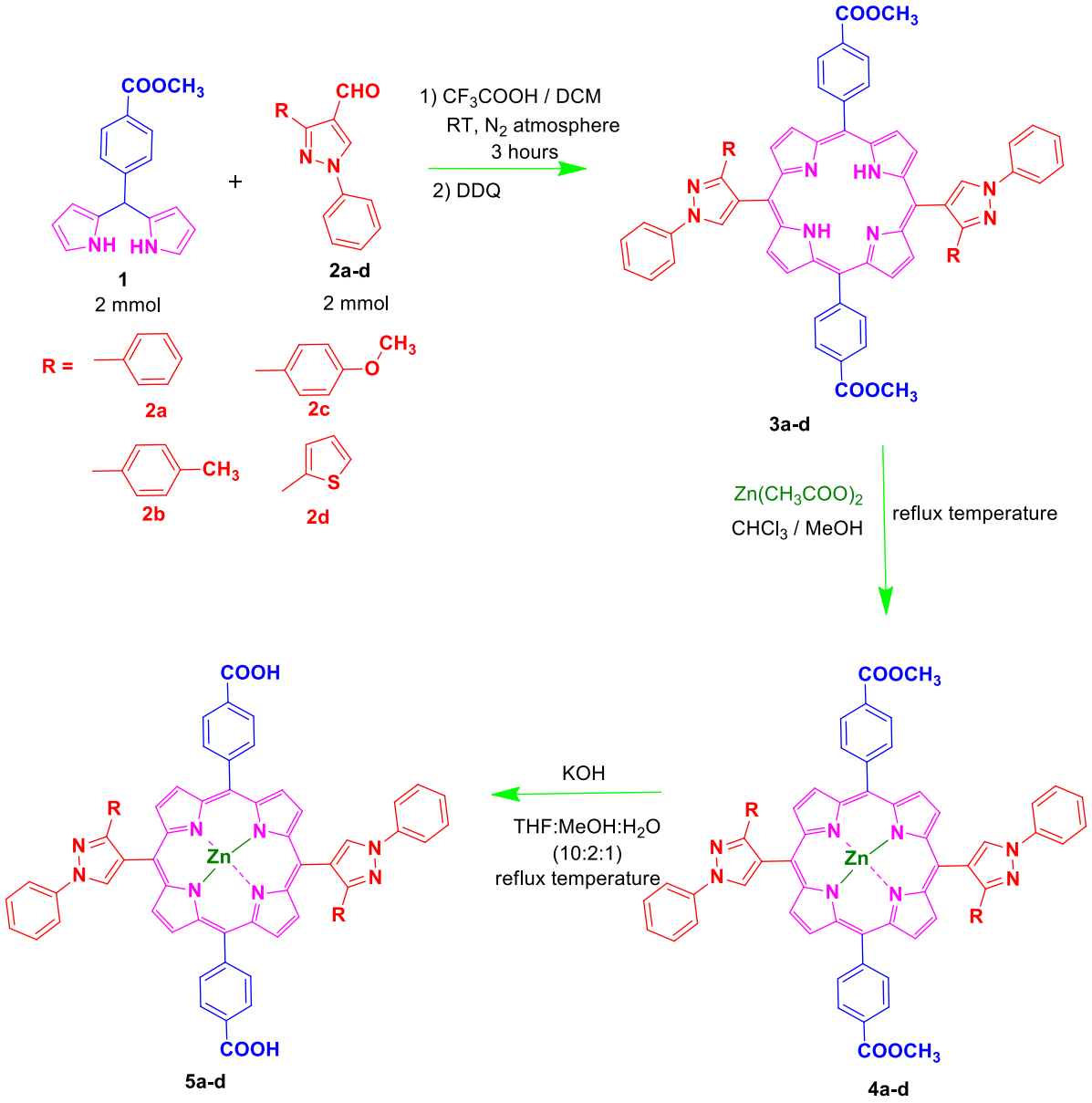
This protocol offers several advantages over other procedures, including higher yields, shorter reaction times, easy work-up procedure, and analytically pure products. We believe that, this protocol may have industrial utility for manufacturing dihydropyridines.

CHAPTER-IV

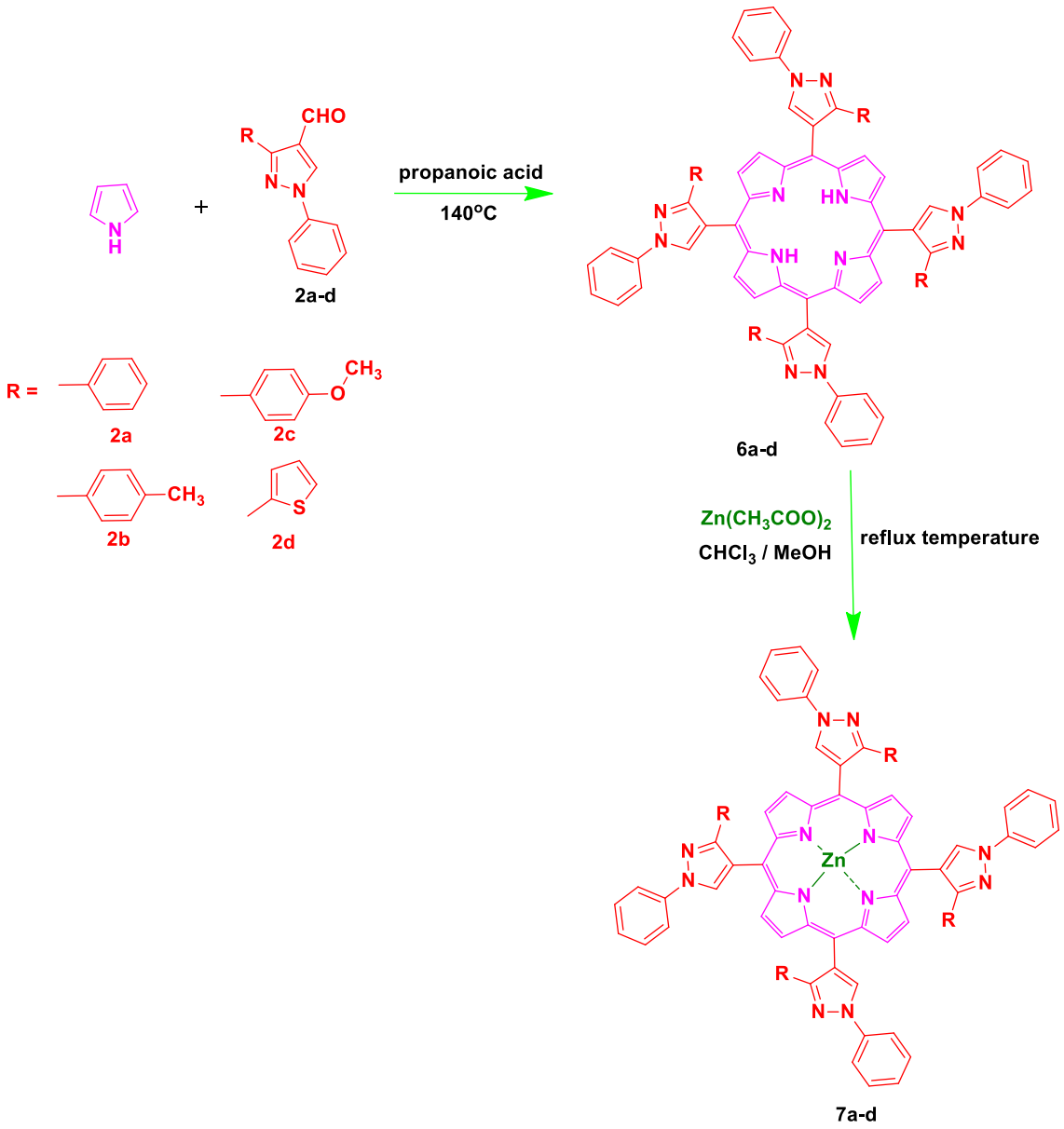
SYNTHESIS OF NOVEL A_2B_2 AND A_4 TYPE PORPHYRIN DERIVATIVES

We observed that porphyrins possess a wide range of applications in medicine and in engineering. Now-a-days they are also used in solar cell development. This chapter deals with the synthesis of different A_2B_2 and A_4 porphyrins. 1-phenyl-3-substituted-aryl-4-formyl-1*H*-pyrazoles (**2a-d**) were treated with 5-(4-carbomethoxyphenyl)dipyrromethane (**1)** in presence of catalytic amount of TFA in dichloromethane at room temperature under nitrogen atmosphere, by Mac-Donald type 2+2 condensation. Further oxidation with DDQ gave 5,15-bis(1-phenyl-3-substitutedaryl-1H-pyrazol-4-yl)10,20-bis(4-carbomethoxyphenyl)porphirins (**3a-d)** in 22-25% yield**.** These porphyrins **(3a-d)** were refluxed with zinc acetate in $CHCl_3$-MeOH (2:1) to obtain zinc metallic porphyrins (**4a-d)** (85-90% yield), which upon hydrolysis with aq. KOH in THF-MeOH (2:1) solvent afforded the corresponding porphyrins (**5a-d**) (**scheme 1**). Furthermore, the synthesis of meso-tetrakis(1-phenyl-3-substitutedaryl-1H-pyrazol-4-yl)porphyrins (**6a-d**) were prepared by starting from 1-phenyl-3-substituted-aryl-4-formyl-1*H*-pyrazoles (**2a-d**) and pyrrole in propanoic acid at 140^{o}C for 6 hours. The zinc complexes (**7a-d**) were prepared by treating corresponding porphyrins **(6a-d)** with zinc acetate in chloroform and methanol (**scheme 2**). Further, the structures of all porphyrins were characterized by UV, IR, ^{1}H-NMR and MALDI-TOFF spectrometric analysis.

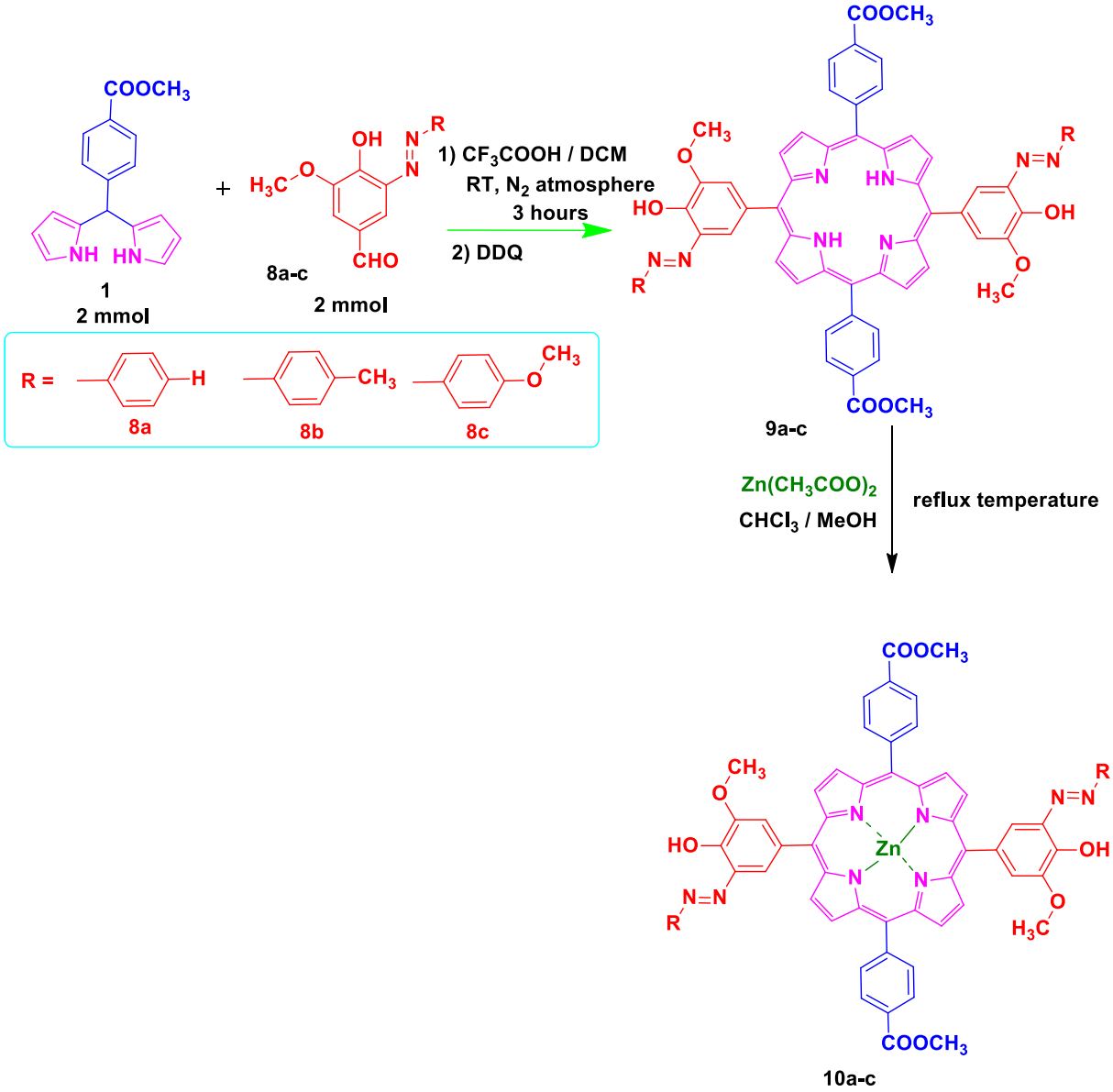
4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes (**8a-c**) were treated with 5-(4-carbomethoxyphenyl)dipyrromethane (**1)** in presence of catalytic amount of TFA in dichloromethane at room temperature under nitrogen atmosphere, Further oxidation with DDQ gave 5,15-bis(4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)10,20-bis(4-carbomethoxyphenyl)porphirins (**9a-c)** in 31-33 % yield**.** These porphyrins **(9a-c)** were refluxed with zinc acetate in $CHCl_3$-MeOH (2:1) to obtain zinc metallic porphyrins (**10a-c)** (89-94% yield) (**scheme 3**). Further, the structures of all porphyrins were characterized by UV, IR, ^{1}H-NMR and MALDI-TOFF spectrometric analysis.


COOCH3
CHO
R
N
N
NH
HN
1
2 mmol
2a-d
2 mmol
+
1) CF3COOH / DCM
RT, N2 atmosphere
3 hours
2) DDQ
R =
2a
2c
CH3
O
2b
CH3
2d
S
3a-d
Zn(CH3COO)2
CHCl3 / MeOH
reflux temperature
COOH
5a-d
KOH
THF:MeOH:H2O
(10:2:1)
reflux temperature
Zn
4a-d

Scheme 1


propanoic acid
140°C
2a-d
R =
2a
2c
2b
2d
6a-d
Zn(CH3COO)2
CHCl3 / MeOH
reflux temperature
7a-d

Scheme 2



Scheme 3

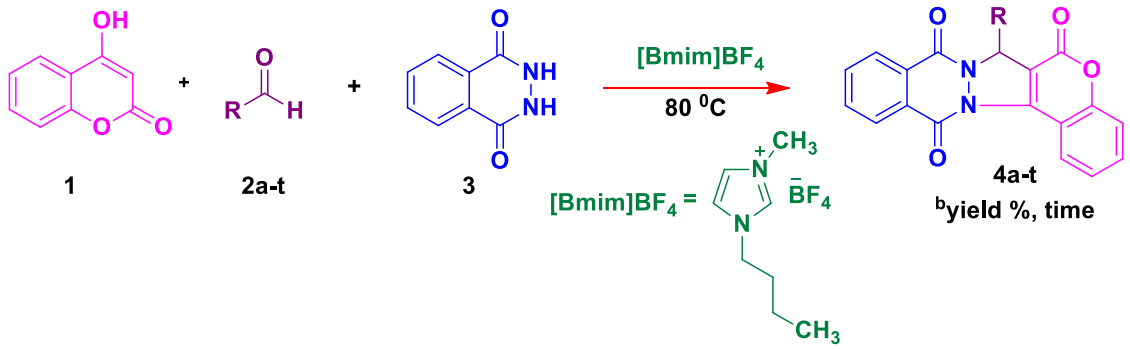
CHAPTER-V

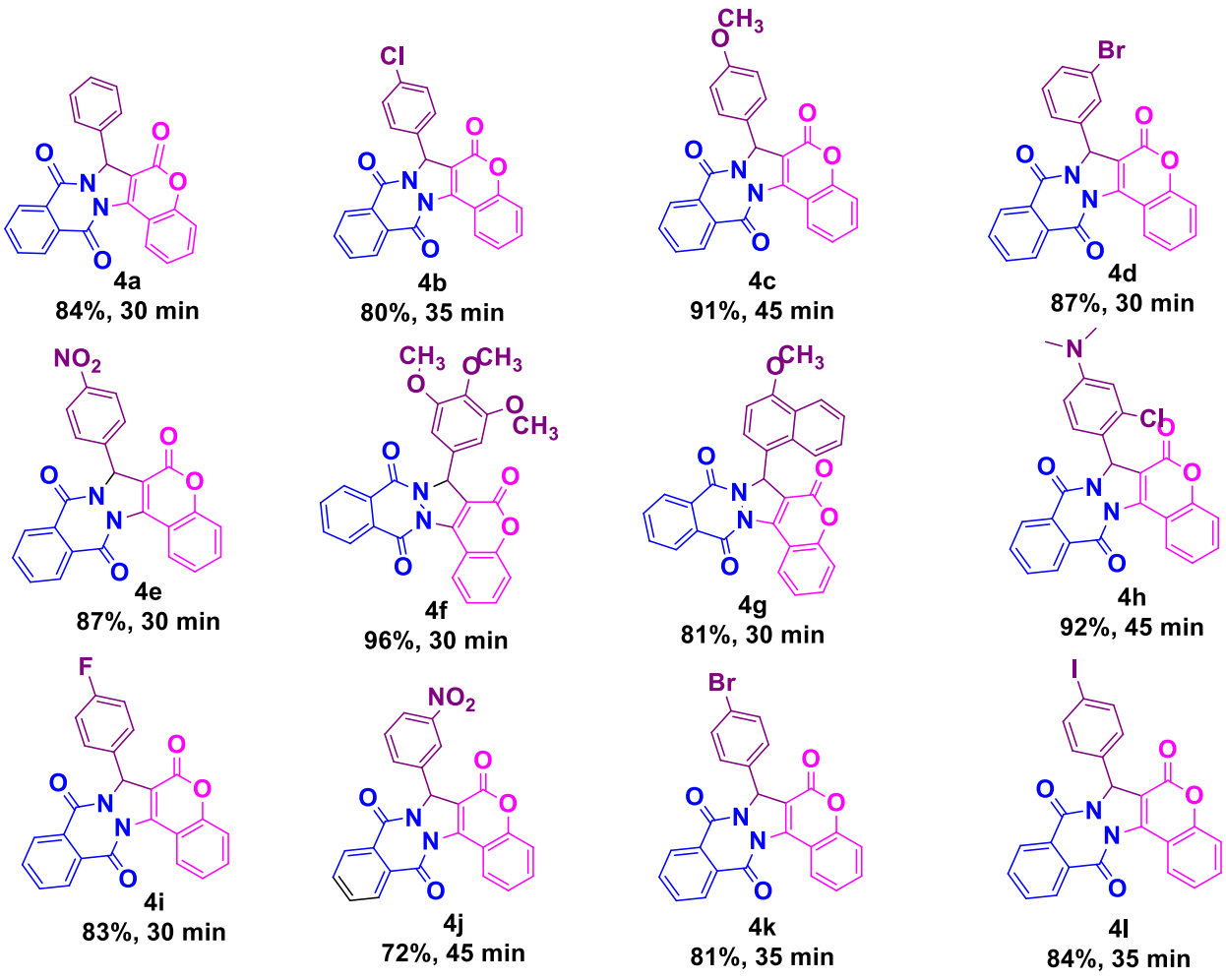
SYNTHESIS OF NEW PYRAZOLO-PHTHALAZINE DERIVATIVES USING [BMIM]BF_4 IONIC LIQUID

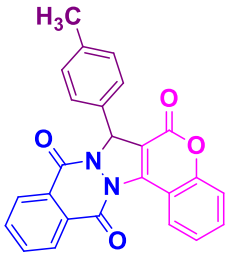
In recent years, much attention has been directed towards the synthesis of pyrazolo-phthalazines because of their diverse therapeutic and pharmacological properties.

Here in, we describe an eco-synthesis of pyrazolo-phthalazines **(4a-t)** *via* multicomponent condensation of 4-hydroxycoumarin, aromatic aldehydes, phthalhydrazide utilizing an efficient, eco-friendly and recyclable [Bmim]BF_4 as catalyst with excellent yields. All the products were characterized by analytical and spectral studies.

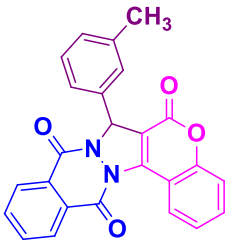
Table 4. Synthesis of pyrazolophthalazine derivatives **4a-t**[a]



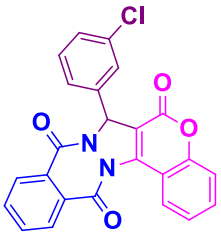




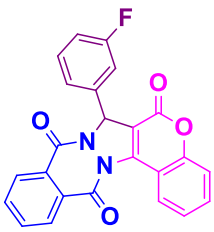
4m
85%, 30 min



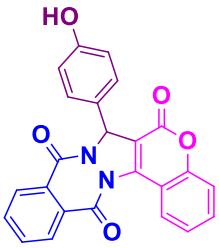
4n
81%, 30 min



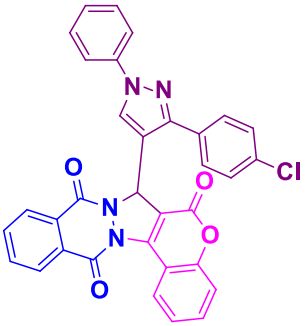
4o
79%, 30 min



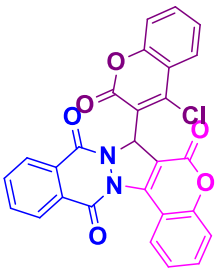
4p
82%, 35 min



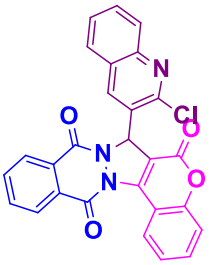
4q
75%, 45 min



4r
89%, 30 min



4s
90%, 35 min



4t
85%, 40 min

[a]**Reaction conditions**: aromatic aldehydes, phthalhydrazide, 4-hydroxy coumarin and [Bmim]BF_4 (20 mol %) solvent free at 80 ^{0}C. [b]Yields of isolated products.

CHAPTER-VI

Evaluation of biological activity

This chapter deals with biological evaluation of newly synthesized compounds which were presented in Chapter-II, Chapter-III, Chapter-IV and Chapter-V. The newly synthesized compounds in Chapter-II, Chapter-IIIB, Chapter-IV were subjected to *in-vitro* antidiabetic testing against α-glucosidase enzyme. All the synthesized compounds in Chapter-IIIB were screened for *in-vitro* anticancer activity and synthesized compounds in Chapter-V were screened for *in-vitro* antifungal activity.

Chapter-II: Chromene derivatives

All the synthesized compounds (**4aa-bd**) were screened for their *in-vitro* antidiabetic activity against α-glucosidase enzyme with respect to standard antidiabetic drug acarbose. The antidiabetic screening data revealed that, the compound **4bd** (46.46 ± 5.22 µM) have shown very good activity when compared to the standard drug acarbobe (33.95±3.20 µM) **(Fig. 7).**

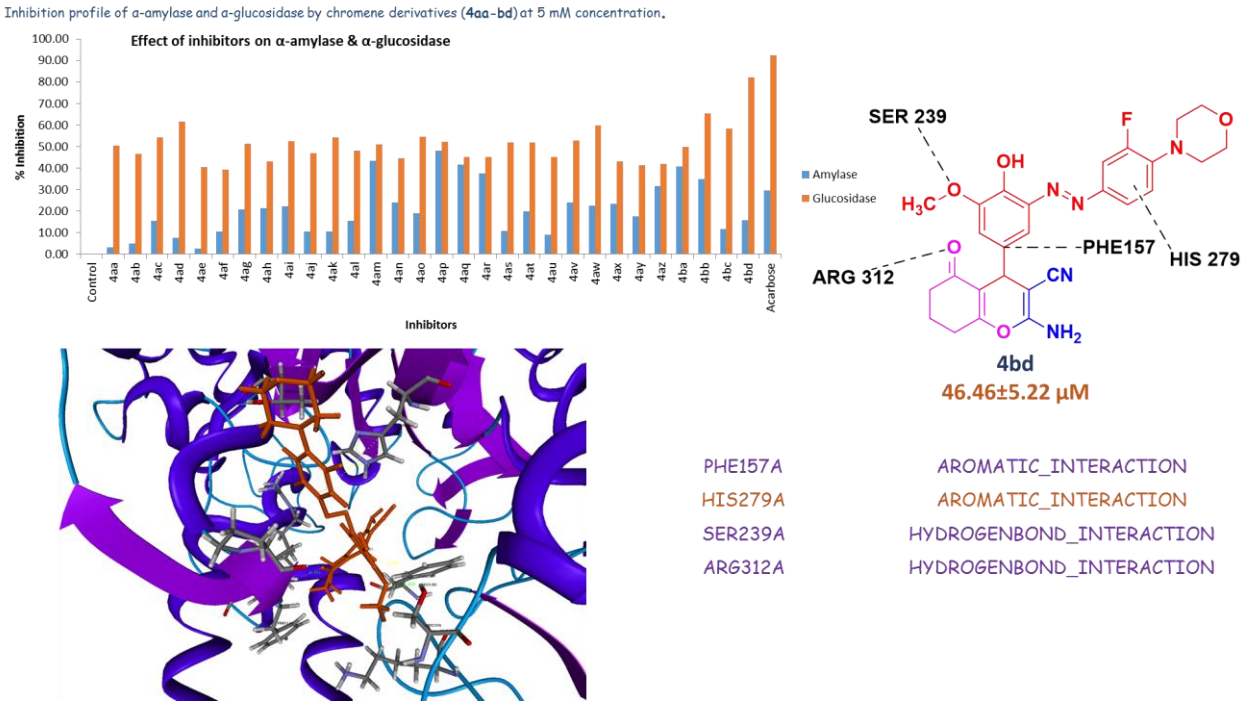
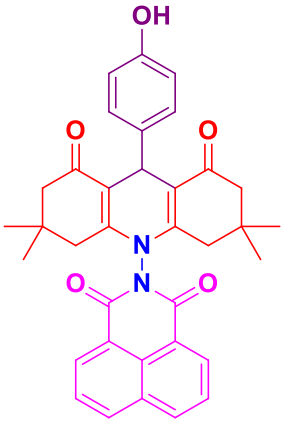


Fig. 7

Chapter-III A: dihydropyridine derivatives

All the synthesized compounds **(5a-j)** were screened for *in-vitro* anticancer activity against MCF-7, Hep-G2 and HeLa cell lines by MTT assay. *In-vitro* anticancer activity results revealed that all the compounds were active against all the three tested cell lines. Among them, the compound **5e** has shown broad spectrum activity against MCF-7, HepG2 & HeLa with IC50 values 14.02 ± 0.9, 12.12 ± 0.6 & 17.99 ± 0.4 µM respectively **(Fig. 8).**



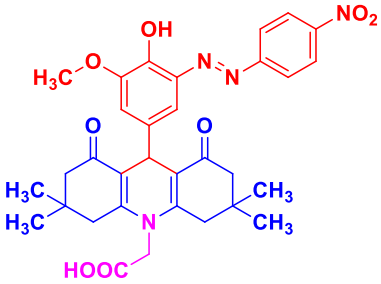
	IC50
MCF-7	14.02 ± 0.9 µM
HepG2	12.12 ± 0.6 µM
HeLa	17.99 ± 0.4 µM

5e

Fig. 8

Chapter-III B: dihydropyridine derivatives

All the synthesized compounds (**4a-l**) were screened for their *in-vitro* antidiabetic activity against α-glucosidase enzyme with respect to standard antidiabetic drug acarbose. The antidiabetic screening data revealed that, the compound **4c** (63.53 ± 1.64 µM) have shown very good activity with respect to the standard drug acarbobe (33.95±3.20 µM) **(Fig. 9)**.



4c

IC50 63.53 ± 1.64

Fig. 9

Chapter-IV: porphyrin derivatives

All the synthesized compounds (**3a-d, 4a-d, 5a-d, 6a-d, 7a-d, 9a-c, 10a-c**) were screened for their *in-vitro* antidiabetic activity against α-glucosidase enzyme with respect to standard antidiabetic drug acarbose. The antidiabetic screening data revealed that, the compound **6c** (31.36 ± 2.86 µM) have shown very good activity in comparison with the standard drug acarbobe (33.95±3.20 µM) **(Fig. 10).**

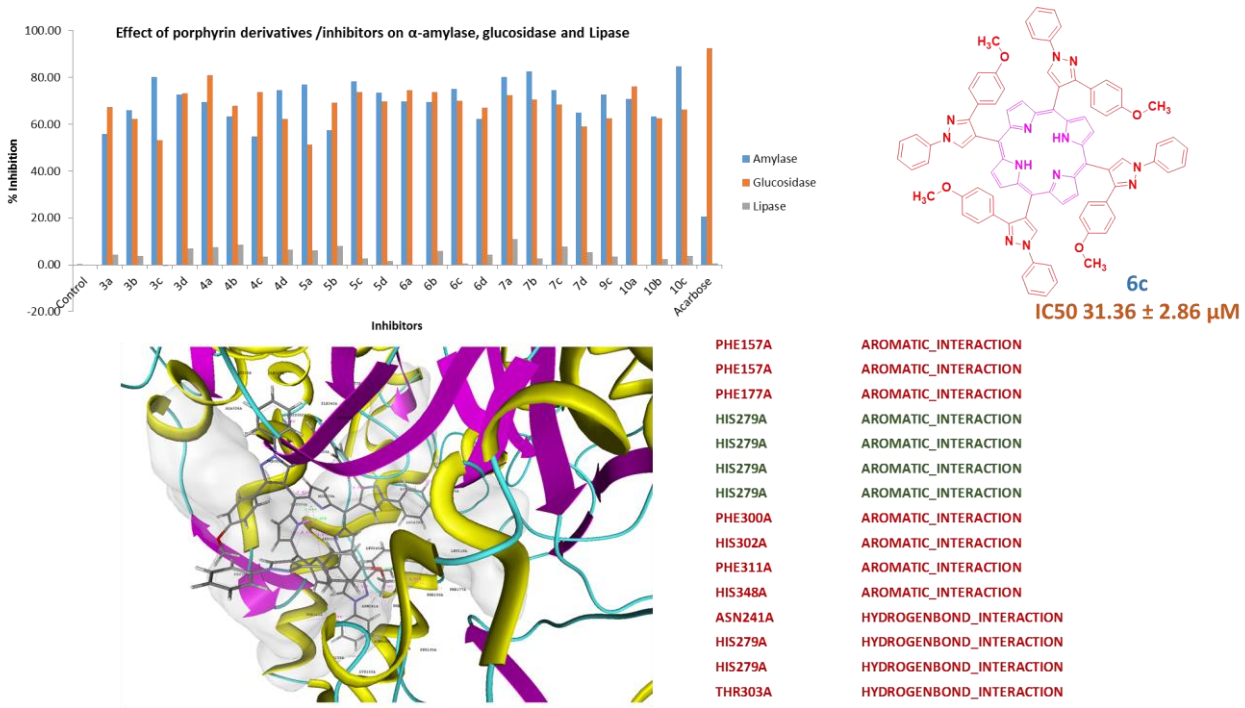
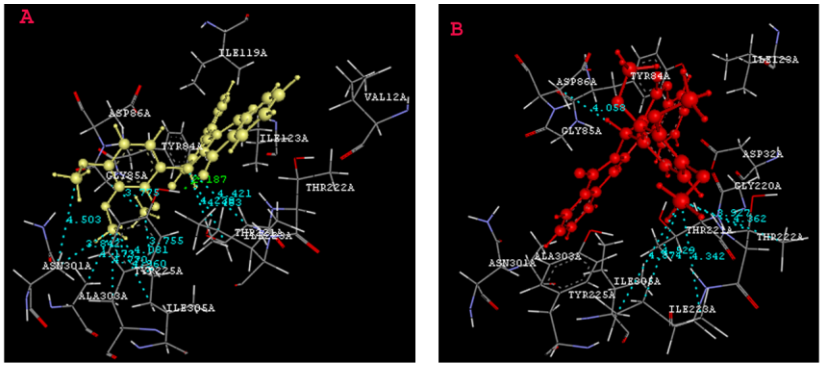


Fig. 10

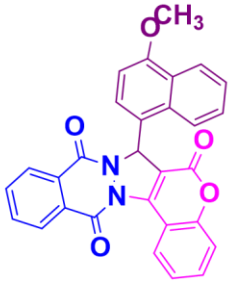
Chapter-V: pyrazolo-phthalazine derivatives

The synthesized fused chromeno-pyrazolo-phthalazine derivatives were evaluated there *in vitro* antifungal activity against *Aspergillus niger* and *Candida albicans.* Regarding antifungal tests against *Candida albicans*, compounds of series **4a-t** have showed promising inhibitory activity. Compounds of series **4a-t**, specially, **4f** (MIC = 10.25 µM) have displayed good activity compared to other synthesized compounds.

From the antifungal activity data against *Aspergillus niger*, it is clearly observed that many of the synthesized compounds show prominent antifungal activity. The compound **4f** (MIC = 15.27 µM) has exhibited good activity compared to other synthesized compounds **(Fig. 11)**.



Ligand-Receptor interaction profiles by Molecular Docking (A) Interactions between 1EAG and **4f** (ligand flexible) (B) Interactions between 1EAG and **4f** (ligand rigid)
Legand: H-bond interactions, green dashed line: Hydrophobic interactions, blue dashed line.



4f

Candida albicans	MIC = 10.25 µM
Aspergillus niger	MIC = 15.27 µM

Fig. 11

1. Zirconium Doped Ceria Nanoparticles: An Efficient and Reusable Catalyst for a Green Multicomponent Synthesis of Novel Phenyldiazenyl–Chromene Derivatives Using Aqueous Medium.
   P. Sagar Vijay Kumar, L. Suresh, T. Vinodkumar, Benjaram. M. Reddy, and G. V. P. Chandramouli.
   ***ACS Sustainable Chemistry & Engineering*, 2016, 4 (4), pp 2376–2386**

2. Ionic Liquid-Promoted Green Protocol for the Synthesis of Novel Naphthalimide-Based Acridine-1,8-dione Derivatives via a Multicomponent Approach.
   P. Sagar Vijay Kumar, Suresh lingala, bhargavi g, srinivas basavoju, G.V.P. Chandramouli.
   ***ACS Sustainable Chemistry & Engineering,* 2015,3 (11), pp 2944–2950**

3. Ionic liquid catalyzed multicomponent synthesis, antifungal activity, docking studies and in-silico ADMET properties of novel fused chromeno-pyrazolo-phthalazine derivatives
   P. Sagar Vijay Kumar, Suresh lingala, G.V.P. Chandramouli.
   Journal of Saudi Chemical Society, 2015, doi:10.1016/j.jscs.2015.08.001

4. An expeditious four-component domino protocol for the synthesis of novel thiazolo[3,2-a]thiochromeno[4,3-*d*]pyrimidine derivatives as antibacterial and antibiofilm agents
   Lingala Suresh, **P. Sagar Vijay Kumar,** Y. Poornachandra, C. Ganesh Kumar, Nanubolu Jagadeesh Babu, G.V.P. Chandramouli.
   Bioorganic & Medicinal Chemistry 24 (2016) 3808–3817

5. Ionic liquid-promoted multicomponent synthesis of fused tetrazolo[1,5-*a*]pyrimidines as α-glucosidase inhibitors
   Lingala Suresh, P. Onkara, **P. Sagar Vijay Kumar**, Y. Pydisetty, G. V. P. Chandramouli
   Bioorganic & Medicinal Chemistry Letters 26 (2016) 4007–4014

6. Heterogeneous recyclable nano-CeO_2 catalyst: efficient and eco-friendly synthesis of novel fused triazolo and tetrazolo pyrimidine derivatives in aqueous medium.
   Lingala Suresh, **P. Sagar Vijay Kumar**, T. Vinodkumar and G. V. P. Chandramouli.
   RSC Adv., 2016, 6, 68788

7. Design, synthesis, and in vitro antimicrobial evaluation of fused pyrano [3,2-*e*] tetrazolo [1,5-*c*] pyrimidines and diazepines.
   S. Kanakaraju, **P. Sagar Vijay Kumar**, G.V.P. Chandramouli
   ISRN organic chemistry, 2013

ACS Sustainable Chemistry & Engineering

Research Article

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Ionic Liquid-Promoted Green Protocol for the Synthesis of Novel Naphthalimide-Based Acridine-1,8-dione Derivatives via a Multicomponent Approach

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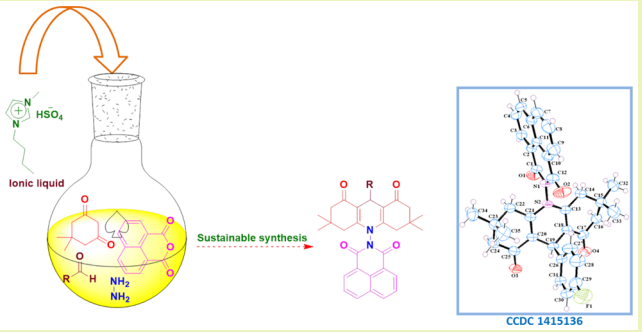
Supporting Information

ABSTRACT: An efficient, one-pot multicomponent synthesis of novel naphthalimide-based acridine-1,8-dione derivatives was achieved by condensation of dimedone, aromatic aldehydes, hydrazine hydrate, and 1,8-naphthanoic anhydride in the presence of a [bmim]HSO_4 ionic liquid, which acts as a green solvent medium. Mild conditions with excellent conversions and a simple isolation procedure are noteworthy advantages of this method. The recovery and recyclability of the ionic liquid make this protocol environmentally desirable.



KEYWORDS: *Ionic liquid, Multicomponent reaction, Naphthalimide-based acridine-1,8-dione derivatives, [bmim]HSO_4, Environmentally friendly protocol*

INTRODUCTION

As there is lot of focus on diversity, speed, and efficiency, particularly in the drug discovery process, multicomponent reactions (MCRs) have become very powerful tools in organic and medicinal chemistry.[1,2] A MCR in which three or more reactants are combined in a single chemical operation is one of the perfect solutions for sustainable manufacture.[3−5] Isoquinolindione (naphthalimide) derivatives have been assessed as anticancer agents,[6−10] and particular analogues, such as amonafide and mitonafide, have exhibited notable anticancer activity both preclinically and in clinical trials.[11−14] On the other hand, acridines make up a known significant class of organic molecules, which have attracted attention from many medicinal and pharmaceutical chemists, because of their anticancer activity.[15−17] Here, we planned to develop a molecular system consisting of naphthalimide and acridine moieties that may be having important biological applications.

Ionic liquids (ILs)[18−20] have attracted considerable interest in the context of sustainable green synthesis during recent years, because they can also act as efficient media for organic syntheses. ILs possess various attractive physicochemical properties such as nonvolatility, low vapor pressure, nonexplosiveness, recyclability, easy operation, and thermal stability over a wide range of temperatures. ILs can be considered as alternative green solvents because of their unique ionic character and structural organization. There are several reports about the applications of ionic liquids in organic reactions such as Beckmann rearrangement,[21] Biginelli reaction,[22] Diels−Alder reaction,[23] Friedel−Crafts reaction,[24] Pechmann condensation,[25] Heck reaction,[26] and other reactions.[27−29]

In continuation of our efforts toward the development of novel heterocyclic compounds using ionic liquids,[30−32] herein we report a facile synthesis of naphthalimide-based acridine-1,8-dione derivatives. To the best of our knowledge, this is the first report of the synthesis of naphthalimide-based acridine-1,8-dione derivatives via multicomponent reaction of dimedone, aromatic aldehydes, hydrazine hydrate, and 1,8-naphthanoic anhydride in the presence of [bmim]HSO_4 (1-butyl-3-methylimidazolium hydrogen sulfate).

RESULTS AND DISCUSSION

An environmentally benign protocol was used for the synthesis of naphthalimide-based acridine-1,8-dione derivatives via a multicomponent process from the reaction of dimedone (**1**, 2 mmol), aromatic aldehydes (**2a−j**, 1 mmol), hydrazine hydrate (**3**, 1 mmol), and 1,8-naphthanoic anhydride (**4**, 1 mmol) in [bmim]HSO_4, which act as an eco-friendly green medium.

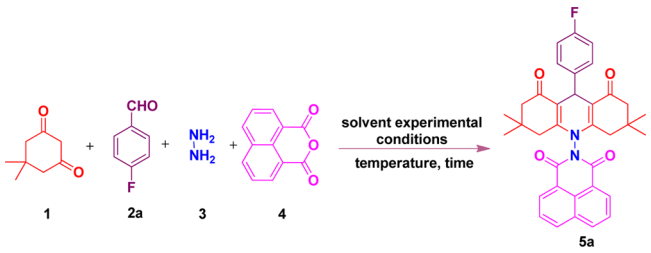
To avoid the drawbacks such as the toxicity and volatility of various organic solvents, the ionic liquid was employed in the multicomponent reaction as a green solvent medium. First, a trial reaction was conducted using a multicomponent approach with dimedone (**1**), 4-fluorobenzaldehyde (**2a**), hydrazine

Received: August 19, 2015
Revised: September 18, 2015
Published: September 27, 2015

DOI: 10.1021/acssuschemeng.5b00900
ACS Sustainable Chem. Eng. 2015, 3, 2944−2950

hydrate (**3**), and 1,8-naphthanoic anhydride (**4**) as a simple model reaction to investigate the probability of the approach and to optimize the reaction conditions. However, the effects of reaction temperature and solvents were assessed from this model reaction, and the results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions for the Synthesis of 5a



entry[a]	solvent	temp (°C)	time	yield[b] (%)
1	neat	60	24 h	NR
2	methanol	60	12 h	11
3	ethanol	60	12 h	14
4	acetonitrile	60	11 h	20
5	acetone	60	16 h	16
6	acetic acid	60	20 h	38
7	[bmim]Br	60	2 h	52
8	[bmim]PF_6	60	1.5 h	48
9	[bmim]BF_4	60	2 h	56
10	**[bmim]HSO_4**	**60**	**35 min**	**93**
11	[bmim]HSO_4	rt	1 h	54
12	[bmim]HSO_4	40	1 h	75
13	[bmim]HSO_4	80	35 min	94

[a]Reaction conditions: dimedone (2 mmol), 4-fluorobenzaldehyde (1 mmol), hydrazine hydrate (1 mmol), 1,8-naphthoic anhydride (1 mmol), and solvent (1 mL). [b]Yields of the isolated products.

During the optimization of reaction conditions, it was observed that the absence of solvent did not give the required products even after 24 h under neat conditions. When solvents such as methanol, ethanol, acetonitrile, acetone, and acetic acid were used, their effect was only moderate (Table 1, entries 2–6), but when typical ionic liquids such as [bmim]Br, [bmim]PF_6, [bmim]BF_4, and [bmim]HSO_4 were used, shorter reaction times and higher yields compared to those of conventional solvents were observed. Ionic liquid [bmim]HSO_4 proved to be considerably superior to the analogous bromide, hexafluorophosphate, and tertafluoroborate ionic liquids for this reaction (Table 1, entries 7–9). The yield of product **5a** was improved, and the reaction time was reduced as the temperature was enhanced from room temperature to 60 °C. No further improvement in the product yield was observed, when the temperature was increased to 80 °C (Table 1, entries 10–13). Therefore, 60 °C was chosen as the optimal reaction temperature for all these reactions.

To specify the scope of the reaction, we have investigated the progress of the reaction under different conditions for dimedone (**1**), aromatic aldehydes (**2a–j**), hydrazine hydrate (**3**), and 1,8-naphthanoic anhydride (**4**). The naphthalimide-based acridine-1,8-dione derivatives (**5a–j**) were obtained in decent yields at 60 °C in [bmim]HSO_4. The results are summarized in Table 2. The protocol was effective with aromatic aldehydes having either electron-donating (-OMe) or electron-withdrawing (-F, -Cl, or -Br) groups to produce the corresponding 10-[1.3-dioxo-1*H*-benzo[*de*]isoquinoline-2(3*H*)-yl]-9-aryl-hexahydroacridine-1,8-dione derivatives in good yields. The electron effects did not have any significant impact on the reaction rate. We herein propose a mechanism in Scheme 1 for the formation of naphthalimide-based acridine-1,8-dione derivatives in the presence of ionic liquid [bmim]-HSO_4, which acts as a promoter. As the first step, a hydrogen bond between the hydrogen atom of [bmim]HSO_4 and the carbonyl group of aldehyde **2** produces a complex which upon condensation with dimedone **1** forms a chalcone-type intermediate (**A**). The formation of intermediate **B** takes place by a condensation between 1,8-naphthanoic anhydride **4** and hydrazine hydrate **3**. Dimedone **1** reacts with intermediate **B** forming another intermediate (**C**). Subsequently, a Michael-type addition occurs between intermediates **A** and **C**, producing intermediate **D**. Intermediate **D** undergoes intermolecular cyclization to afford the final product **5**. The reaction mixture was poured into ice-cold water; the obtained solid product was isolated by filtration, and the filtrate containing ionic liquid [bmim]HSO_4 was extracted with ethyl acetate to remove the nonionic organic impurities. The ionic liquid was recovered from water under reduced pressure, dried at 60–70 °C, and reused for subsequent reactions for four additional cycles. A slight decrease in its activity in terms of product yields (Figure 1) was observed when the ionic liquid was used beyond four cycles.

The structures of the synthesized compounds were well-characterized by infrared (IR), ^{1}H nuclear magnetic resonance (NMR), and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Further, the structure of compound **5a** was confirmed by the single-crystal X-ray diffraction method (Figure 2, CCDC-1415136). Compound **5a** crystallizes in centrosymmetric monoclinic space group $P21/c$ with one molecule in the asymmetric unit. Crystal structure analysis reveals that the molecules form a closely packed structure with C–H···F and C–H···O hydrogen bonds. Two inversion-related molecules combine via C–H···F hydrogen bonds and form a discrete dimer. These dimers are interconnected by C–H···O hydrogen bonds. The overall structure is a closely packed structure. Table 3 gives the pertinent crystallographic data, and Table 4 gives hydrogen bond parameters.

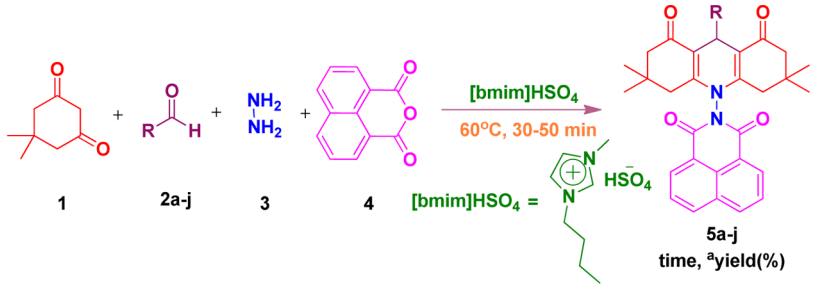
EXPERIMENTAL SECTION

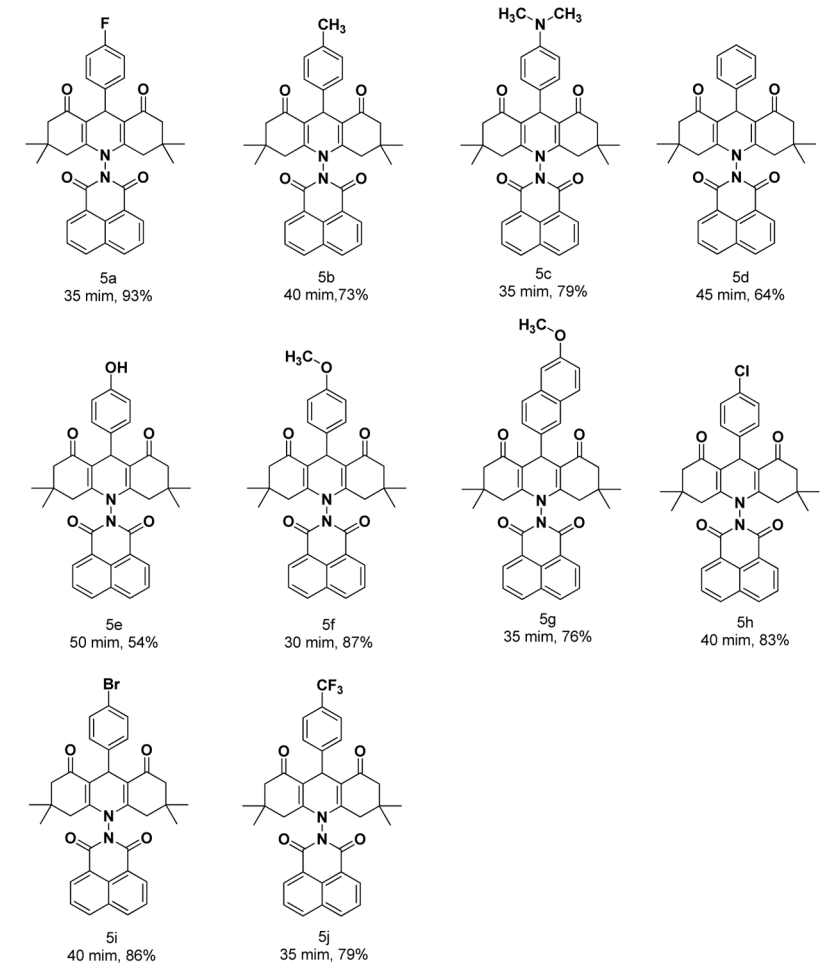
General Information. All reagents were procured from commercial sources and used without further purification. A Bruker WM-4 (X) spectrophotometer (577 model) was used for recording IR spectra (KBr). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrophotometer at 400 and 100 MHz, respectively, in DMSO-d_6 with TMS as an internal standard. The chemical shifts are reported in parts per million (δ). Elemental analysis was performed on a Carlo Erba EA 1108 automatic elemental analyzer. Mass spectra (ESI) were conducted on a jeo1 JMSD-300 spectrometer. Compound **5a** was crystallized from acetic acid to yield prismatic crystals.

Single-Crystal X-ray Diffraction. The single-crystal X-ray diffraction data of the crystals **5a** were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 293(2) K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using SHELXTL.[33] The crystal structures were determined by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.[34] All the aromatic and aliphatic C–H hydrogens were generated by the riding model in idealized geometries.

DOI: 10.1021/acssuschemeng.5b00900
ACS Sustainable Chem. Eng. 2015, 3, 2944–2950

Table 2. Synthesis of Naphthalimide-Based Acridine-1,8-dione Derivatives (5a–j)[b]





[a]Yields of the isolated products. [b]Reaction conditions: dimedone (2 mmol), 4-fluorobenzaldehyde (1 mmol), hydrazine hydrate (1 mmol), 1,8-naphthoic anhydride (1 mmol), and [bmim]HSO_4 (1 mL).

Mercury 2.3 (Build RC4), ORTEP-3, and X-Seed[35−37] were used to prepare material for publication.

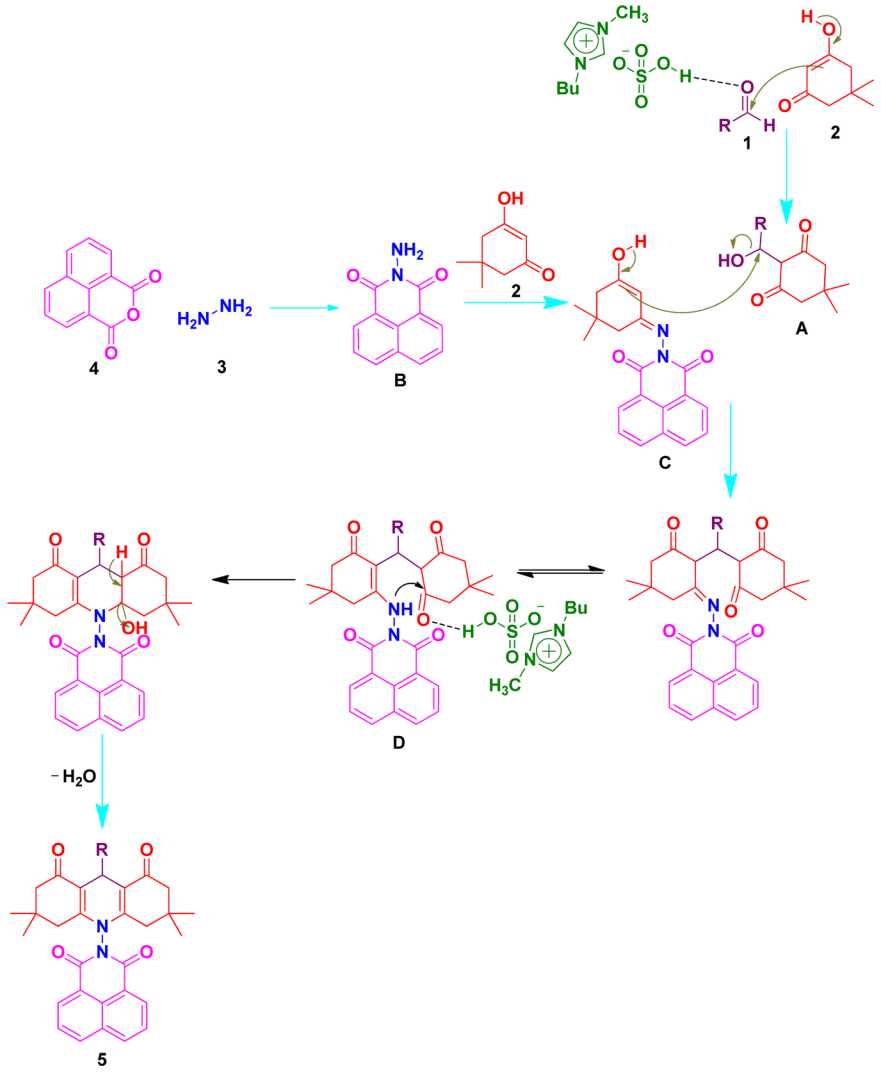
*General Procedure for the Synthesis of [1,3-Dioxo-1H-benzo-[de]isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione Derivatives (**5a–j**).* A mixture of aromatic aldehydes (1 mmol), 1,8-naphthoic anhydride (1 mmol), hydrazine hydrate (1 mmol), and dimedone (2 mmol) in [bmim]-HSO_4 (1 mL) was heated to 60 °C. The progress of the reaction was monitored by TLC [eluent, ethyl acetate/*n*-hexane (2:8)]; after completion of the reaction, the reaction mixture was allowed to cool to room temperature, and 10 mL of water was added to the mixture. The resultant precipitate was filtered and purified by column chromatography using silica gel [ethyl acetate/*n*-hexane (1:9)] to afford the pure compounds (**5a–j**).

*10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (**5a**).* Pale yellow solid: mp 270−272 °C; IR (KBr) ν_{max} 2966, 1702, 1677, 1665, 1647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.97−2.33 (m, 8H, CH_2), 4.95 (s, 1H), 7.07 (t, J = 8.8 Hz, 2H, ArH), 7.57−7.61 (m, 2H, ArH), 7.99−8.04 (m, 2H, ArH), 8.66−8.76 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.05, 26.96, 28.68, 32.17, 50.17, 111.88, 118.16, 123.08, 126.27, 127.94, 129.47, 130.58, 139.27, 141.69, 146.47, 148.41, 148.77, 165.76, 194.68; ESI-MS m/z 563 (M + 1). Anal. Calcd for $C_{35}H_{31}FN_2O_4$: C, 74.72; H, 5.55; N, 4.98. Found: C, 74.52; H, 5.44; N, 4.82.

*10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-9-(p-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5b**).* White solid: mp 261−262 °C; IR (KBr) ν_{max} 2969, 1701, 1675, 1661, 1649 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.95 (s, 6H, CH_3), 1.01 (s, 6H, CH_3), 2.00−2.17 (m, 8H, CH_2), 2.38 (s, 3H, CH_3), 4.95 (s, 1H), 7.07 (t, J = 8.8 Hz, 2H, ArH), 7.57−7.61 (m, 2H, ArH), 7.99−8.04 (m, 2H, ArH), 8.66−8.75 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.04, 26.97, 28.63, 32.13, 37.19, 50.13, 112.01,

DOI: 10.1021/acssuschemeng.5b00900
ACS Sustainable Chem. Eng. 2015, 3, 2944−2950

Scheme 1. Proposed Mechanism for the Formation of Naphthalimide-Based Acridine-1,8-dione Derivatives (5a–j)



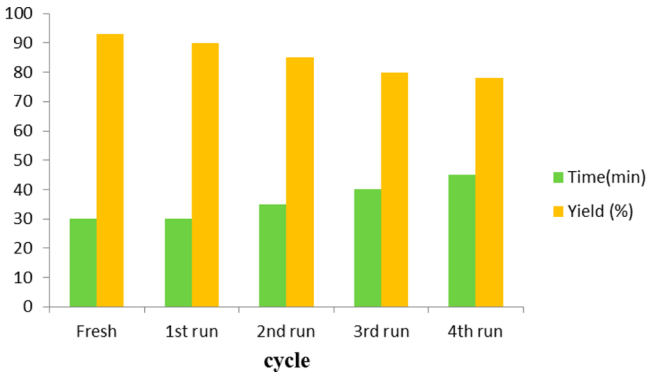


Figure 1. Recycling of the [bmim]HSO_4 ionic liquid used for the synthesis of compound **5a**.

118.15, 123.04, 126.26, 127.94, 129.46, 131.18, 139.12, 141.53, 146.47, 148.69, 165.79, 194.55; ESI-MS *m/z* 559 (M + 1). Anal. Calcd for $C_{36}H_{34}N_2O_4$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.22; H, 6.14; N, 5.33.

9-[4-(Dimethylamino)phenyl]-10-[1,3-dioxo-1H-benzo[de]-isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (***5c***). Pale red solid: mp 264–266 °C; IR (KBr) ν_{max} 2968, 1702, 1678, 1661, 1648 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.97–2.33 (m, 8H, CH_2), 3.19 [s, 6H, -N(CH_3)$_2$], 5.03 (s, 1H), 7.06 (t, *J* = 8.8 Hz, 2H, ArH), 7.57–7.61 (m, 2H, ArH), 7.99–8.04 (m, 2H, ArH), 8.66–8.75 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.08, 26.65, 28.66, 32.21, 44.31, 50.16, 111.11, 118.21, 123.05, 126.23, 127.91, 129.47, 131.15, 139.14, 141.54, 146.43, 148.59, 148.75, 165.81, 195.05; ESI-MS *m/z* 588 (M + 1). Anal. Calcd for $C_{37}H_{37}N_3O_4$: C, 75.65; H, 6.35; N, 7.15. Found: C, 75.96; H, 6.24; N, 7.36.

10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (***5d***). Yellow solid: mp 271–273 °C; IR (KBr) ν_{max} 2959, 1701, 1676, 1663, 1647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 1.97–2.33 (m, 8H, CH_2), 5.01 (s, 1H), 7.45 (t, *J* = 8.8 Hz, 2H, ArH), 7.92 (t, *J* = 7.2 Hz, 2H, ArH), 8.03–8.07 (m, 3H, ArH), 8.73–8.77 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.07, 26.93, 28.61, 32.15, 50.10, 111.97, 118.13, 123.05, 126.28, 127.91, 129.43, 130.99, 139.13, 141.55, 146.46, 148.71, 165.82, 194.63; ESI-MS *m/z* 545 (M + 1). Anal. Calcd for $C_{35}H_{32}N_2O_4$: C, 77.18; H, 5.92; N, 5.14. Found: C, 77.32; H, 5.88; N, 5.31.

10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (***5e***). White solid: mp 257–259 °C; IR (KBr) ν_{max} 3302, 2964, 1700, 1678, 1661, 1648 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.98–2.33 (m, 8H, CH_2), 4.03 (s, 1H, -OH), 4.96 (s, 1H), 7.07 (t, *J* = 8.8 Hz, 2H, ArH), 7.57–7.61 (m, 2H, ArH), 7.99–8.04 (m, 2H, ArH), 8.66–8.76 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.05, 26.96, 28.68, 32.17, 50.30, 112.95, 118.84, 126.78, 126.98, 127.58, 128.99, 129.16,

DOI: 10.1021/acssuschemeng.5b00900
ACS Sustainable Chem. Eng. 2015, 3, 2944–2950

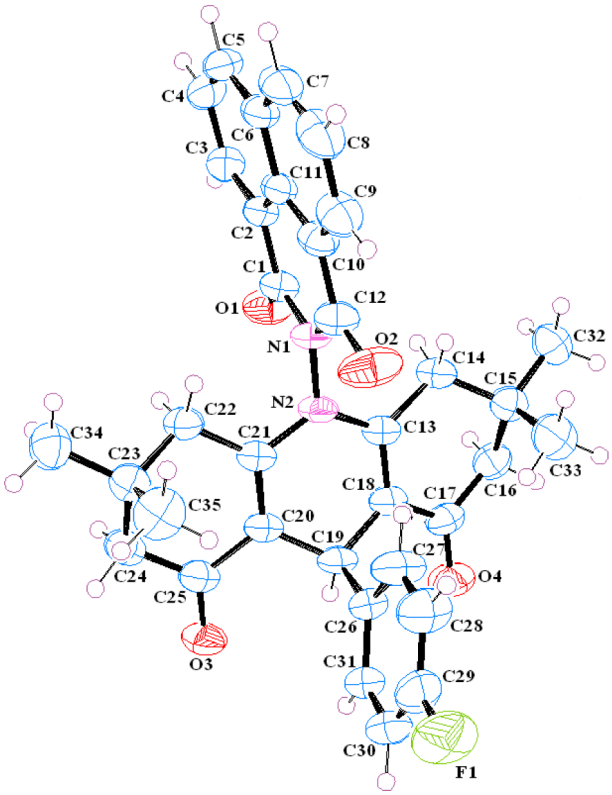


Figure 2. ORTEP representation of compound **5a**. The thermal ellipsoids are drawn at the 50% probability level.

Table 3. Salient Crystallographic Data and Structure Refinement Parameters of Compound 5a

empirical formula	$C_{35}H_{31}FN_2O_4$
formula weight	562.62
crystal system	monoclinic
space group	$P2_1/n$
T (K)	293(2)
a (Å)	12.4943(12)
b (Å)	17.1761(16)
c (Å)	13.3901(13)
α (deg)	90
β (deg)	99.264(2)
γ (deg)	90
Z	4
V (Å^3)	2836.1(5)
D_{calc} (g/cm^3)	1.318
$F(000)$	1184
μ (mm^{-1})	0.091
θ (deg)	2.37−27.7
index ranges	$-16 \le h \le 16$
	$-22 \le k \le 21$
	$-17 \le l \le 17$
total no. of reflections	32325
no. of independent reflections	6777
no. of observed reflections	5278
no. of parameters	383
R_1 $[I > 2\sigma(I)]$	0.0508
wR_2 (all data)	0.1408
GOF	1.046
CCDC	1415136

Table 4. Geometrical Parameters of Hydrogen Bonds in Compound 5a

D−H···A	D···A (Å)	H···A (Å)	D−H···A (deg)	symmetry code
C(7)−H(7)···O(1)	3.138(2)	2.43	122	$-^1/_2 + x, ^1/_2 - y, -^1/_2 + z$
C(30)−H(30)···F(1)	3.423(2)	2.37	163	$1 - x, -y, 1 - z$

129.48, 139.79, 140.51, 149.65, 164.10, 194.51; ESI-MS m/z 561 (M + 1). Anal. Calcd for $C_{35}H_{32}N_2O_5$: C, 74.98; H, 5.75; N, 5.00. Found: C, 74.84; H, 5.72; N, 5.29.

10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (***5f***). Pale yellow solid: mp 268−270 °C; IR (KBr) ν_{max} 2963, 1701, 1678, 1660, 1645 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.98−2.33 (m, 8H, CH_2), 3.47 (s, 3H, -OCH_3), 4.96 (s, 1H), 7.06 (t, J = 8.8 Hz, 2H, ArH), 7.57−7.61 (m, 2H, ArH), 7.99−8.04 (m, 2H, ArH), 8.66−8.76 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.05, 26.96, 28.68, 32.17, 50.17, 54.95, 112.08, 117.74, 125.62, 127.18, 128.23, 128.53, 129.25, 129.42, 131.90, 136.06, 148.53, 150.60, 164.99, 194.35; ESI-MS m/z 575 (M + 1). Anal. Calcd for $C_{36}H_{34}N_2O_5$: C, 75.24; H, 5.96; N, 4.87. Found: C, 75.18; H, 5.94; N, 4.62.

10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-9-(6-methoxynaphthalen-2-yl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (***5g***). White solid: mp 284−286 °C; IR (KBr) ν_{max} 2969, 1704, 1678, 1665, 1642 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (s, 6H, CH_3), 1.05 (s, 6H, CH_3), 2.09−2.25 (m, 8H, CH_2), 3.71 (s, 3H, -OCH_3), 5.10 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.91−8.03 (m, 4H, ArH), 8.22 (d, J = 8.0 Hz, 1H, ArH), 8.33 (s, 1H, ArH), 8.52−8.67 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.11, 28.86, 30.37, 34.83, 50.01, 54.91, 109.13, 116.26, 117.77, 119.16, 120.62, 122.45, 122.69, 126.12, 127.59, 128.35, 128.83, 129.45, 139.35, 141.24, 147.54, 148.79, 165.09, 195.76; ESI-MS m/z 625 (M + 1). Anal. Calcd for $C_{40}H_{36}N_2O_5$: C, 76.90; H, 5.81; N, 4.48. Found: C, 76.76; H, 5.76; N, 4.57.

9-(4-Chlorophenyl)-10-[1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (***5h***). Pale yellow solid: mp 251−253 °C; IR (KBr) ν_{max} 2967, 1702, 1677, 1661, 1645 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 6H, CH_3), 0.86 (s, 6H, CH_3), 1.97−2.32 (m, 8H, CH_2), 5.01 (s, 1H), 7.06 (t, J = 8.8 Hz, 2H, ArH), 7.57−7.60 (m, 2H, ArH), 7.99−8.04 (m, 2H, ArH), 8.67−8.77 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.09, 26.91, 28.59, 32.19, 50.09, 111.93, 118.17, 123.07, 126.30, 127.96, 129.45, 131.05, 139.15, 141.51, 146.47, 148.78, 165.81, 194.59; ESI-MS m/z 579 (M + 1). Anal. Calcd for $C_{35}H_{31}ClN_2O_4$: C, 72.59; H, 5.40; N, 4.84. Found: C, 72.36; H, 5.48; N, 4.91.

9-(4-Bromophenyl)-10-[1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8-(2H,5H)-dione (***5i***). Yellow solid: mp 274−276 °C; IR (KBr) ν_{max} 2968, 1701, 1675, 1660, 1641 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (s, 6H, CH_3), 1.11 (s, 6H, CH_3), 2.09−2.29 (m, 8H, CH_2), 5.03 (s, 1H), 7.16 (t, J = 8.8 Hz, 2H, ArH), 7.50−7.55 (m, 2H, ArH), 7.99−8.04 (m, 2H, ArH), 8.65−8.69 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.11, 26.89, 28.55, 32.18, 50.11, 111.91, 118.16, 123.05, 126.33, 127.94, 129.47, 131.07, 139.14, 141.49, 146.46, 148.78, 165.83, 194.60; ESI-MS m/z 624 (M + 2). Anal. Calcd for $C_{35}H_{31}BrN_2O_4$: C, 67.42; H, 5.01; N, 4.49. Found: C, 67.68; H, 5.15; N, 4.63.

10-[1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl]-3,3,6,6-tetramethyl-9-[4-(trifluoromethyl)phenyl]-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (***5j***). Pale yellow solid: mp 304−306 °C; IR (KBr) ν_{max} 2977, 1703, 1677, 1660, 1646 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 (s, 6H, CH_3), 0.87 (s, 6H, CH_3), 1.97−2.33 (m, 8H, CH_2), 4.95 (s, 1H), 7.07 (t, J = 8.8 Hz, 2H, ArH), 7.57−7.61 (m, 2H, ArH), 7.99−8.04 (m, 2H, ArH), 8.66−8.76 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.10, 26.89, 28.60, 32.20, 50.08, 111.89, 118.12, 123.10, 126.28, 128.01, 129.42, 131.06, 139.14, 141.55, 146.50, 148.80, 165.79, 194.61; ESI-MS m/z 613 (M + 1). Anal. Calcd for $C_{36}H_{31}F_3N_2O_4$: C, 70.58; H, 5.10; N, 4.57. Found: C, 70.28; H, 5.01; N, 4.81.

DOI: 10.1021/acssuschemeng.5b00900
ACS Sustainable Chem. Eng. 2015, 3, 2944−2950

CONCLUSION

In conclusion, we have demonstrated a very concise, efficient, environmentally benign, atom economical, and facile protocol for the synthesis of a novel naphthalimide-based acridine-1,8-dione derivative in the presence of [bmim]HSO_4 via a multicomponent reaction. This new chemistry would provide a simple, compatible, and potentially powerful method for the modular construction of naphthalimide-based acridine-1,8-dione derivatives. The prominent advantages of this method are mild reaction conditions, high atom economy, shorter reaction times, and higher yields. Meanwhile, the reusability of ionic liquid [bmim]HSO_4 makes this an environmentally friendly protocol amenable for scale-up.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b00900.

^{1}H NMR, ^{13}C NMR, and mass spectra of the obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful to the Director, National Institute of Technology, Warangal, for providing facilities. P.S.V.K. is grateful to Council of Scientific & Industrial Research (CSIR), New Delhi, India [File 09/922 (0005)2012/EMR-I], for financial assistance.

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Zirconium Doped Ceria Nanoparticles: An Efficient and Reusable Catalyst for a Green Multicomponent Synthesis of Novel Phenyldiazenyl−Chromene Derivatives Using Aqueous Medium

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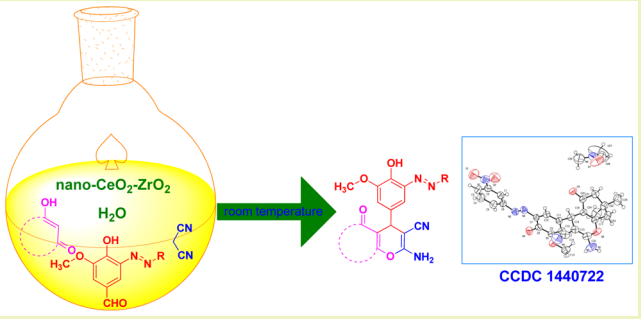
Supporting Information

ABSTRACT: Zirconium doped ceria nanoparticles are found to be efficient heterogeneous catalysts for the multicomponent reaction of 1,3-dicarbonyl compounds with 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl) benzaldehydes and malononitrile to yield the corresponding 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-chromene-3-carbonitrile derivatives in water medium. The results show that nanosized CeO_2−ZrO_2 is a potential catalytic material for synthesis of title compounds in high yields. The used catalyst was recovered and reused several times without significant loss of catalytic activity, which is an essential parameter of green synthesis. The formation, size, and oxidation state of the metal ions present in the material is confirmed by powdered X-ray diffraction, transmission electron spectroscopy, and X-ray photoelectron spectroscopy techniques.



KEYWORDS: *Zirconium doped ceria nanoparticles, Multicomponent reaction, Phenyldiazenyl−chromene, Aqueous medium*

INTRODUCTION

Green chemistry has become an essential inspiration for organic chemists to improve environmentally benign reagents and conditions for synthesis of organic compounds.[1] It is well established fact that the sustainability of green chemistry greatly depends on (i) the use of benign solvents or solvent-free conditions, (ii) the development of less toxic and promising reagents/catalysts, (iii) the design of cost-effective and reliable methodologies, and (iv) development of reusable catalysts. In view of these, the development of nano metal oxide catalysts has drawn much attention due to their operational simplicity, environmental friendliness, easy separation procedure, economic efficiency, and recyclability.[2,3] In recent years, zirconium doped ceria catalysts have been proposed as promising materials for energy and environmentally related applications such as catalysts, fuel cells, gas sensors, generation of solar fuels, oxidation of carbon monoxide, soot, etc. All these applications are due to the presence of more oxygen defects, high reduction properties, good acid−base properties, etc.[4−6] In addition to this, the use of water as a promising solvent for organic reactions has been established in considerable interest due to its green identifications such as low cost and easy availability. Besides, the factors like network of hydrogen bonds, high specific heat capacity, large surface tension, high polarity, and high cohesive energy have been highlighted as some of the characteristic properties of water that can intensely influence the organic conversions in this medium.[7]

Multicomponent reactions (MCRs) have drawn great interest in enjoying an unresolved status in modern organic synthesis and medicinal chemistry. Multicomponent reaction protocols offer incredible advantages such as high selectivity, high yields and structural diversity of drug scafolds.[8,9] Theoretically, MCRs are potential candidates for use of water as solvent since the multiple hydrophobic reactants are carried in closer proximity due to hydrophobic interactions.[10]

The chromene moiety often appears as an important structural component in compounds exhibiting antimicrobial,[11] anticancer,[12] antitubercular,[13] antioxidant,[14] antiproliferation,[15] and antimalarial[16] activities. On the other hand, azo compounds are highly significant as synthetic dyes. They also have diverse applications in several fields such as medicinal chemistry and dyeing textile fiber.[17,18] In recent years, azo compounds have been intensively studied, due their activities such as antifungal agents,[19] anticancer agents,[20] tyrosinase inhibitors,[21] and vesicular glutamate transporter inhibitors.[22] Therefore, synthesis of an azo group containing chromene derivatives using green protocols attracted significant attention. In continuation of our efforts toward the development of novel heterocyclic compounds using green protocols[23,24] herein, we report a facile synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-

Received: January 10, 2016
Revised: February 17, 2016
Published: February 29, 2016

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376−2386

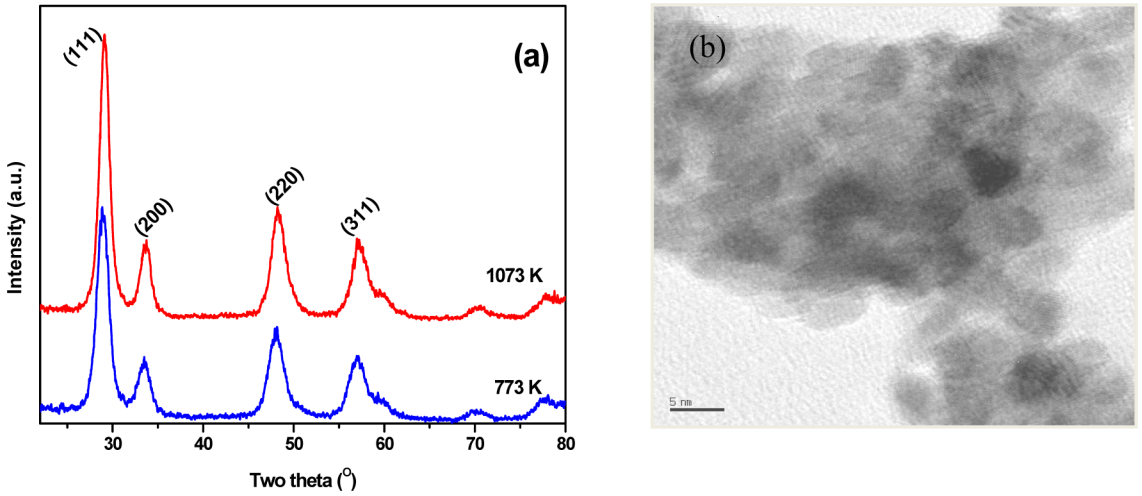


Figure 1. (a) Powder X-ray diffraction patterns of zirconium doped ceria nanoparticles calcined at 773 and 1073 K. (b) Transmission electron microscopy image of zirconium doped ceria nanoparticles calcined at 773 K.

phenyldiazenyl)-pyran-3-carbonitrile derivatives. To the best of our knowledge, for the first time, an ecofriendly process was developed for the synthesis of novel 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-pyran-3-carbonitrile scaffold from 1,3-dicarbonyl compounds, 4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl) benzaldehydes, and malononitrile in the presence of zirconium doped ceria nanoparticles (CeO_2–ZrO_2). The used material was prepared by coprecipitation method and characterized using powdered-X-ray diffraction (XRD), transmission electron microscopy (TEM), and X-ray photoelectron spectroscopy (XPS) techniques.

RESULTS AND DISCUSSIONS

The CeO_2–ZrO_2 (CZ 1:1 mol ratio based on oxides) solid solution was synthesized by a modified coprecipitation method using appropriate amounts of the corresponding $Ce(NO_3)_3 \cdot 6H_2O$ (Aldrich, AR grade) and $ZrO(NO_3)_2 \cdot xH_2O$ (Fluka, AR grade) precursors. The desired amounts of the precursors were dissolved separately in double-distilled water under mild stirring conditions and mixed together. Dilute aqueous ammonia solution was added dropwise over a period until the pH of the solution reached ~8.5. The resulting pale yellow colored slurry was decanted, filtered, and washed several times with double distilled water until it was free from anion impurities. The obtained precipitate was oven-dried at 393 K for 12 h and calcined at 773 and 1073 K for 5 h at a heating rate of 5 K min^{-1} in an air atmosphere.

Figure 1a shows the X-ray diffractograms of the zirconium doped ceria catalysts (CeO_2–ZrO_2) calcined at 773 and 1073 K. The main peaks (111), (200), (220), and (311) observed in this figure correspond to the typical cubic structure of ceria. No characterization peaks related to zirconium oxide were observed which confirm the formation of solid solution. The average crystallite size of CeO_2–ZrO_2 materials is calculated by using the most intense peaks such as (111), (220), and (311) with the help of Sherrer equation, and the obtained value is around 4.7 nm at 773 K and 5.5 nm at 1073 K. From Figure 1a, it is apparent that, the material is stable even at 1073 K.

The TEM image of the CeO_2–ZrO_2 material (Figure 1b) reveals that the average particle size of the prepared material is 4–6 nm, which is in agreement with the XRD results.

To identify the chemical states of the dopant and the host ions on the surface of the CeO_2–ZrO_2 material XPS study was carried out and shown in Figure 2.

The Ce 3d XP spectrum of CeO_2–ZrO_2, shown in Figure 2a, suggests the coexistence of Ce^{3+} and Ce^{4+} and characterized by two series of peaks: $3d_{3/2}$ and $3d_{5/2}$ labeled as *u* and *v*, respectively. The peaks designated as *u*, *u*″, *u*‴ and *v*, *v*″, *v*‴ can be assigned to Ce^{4+} while the peaks *u*′ and *v*′ belonging to Ce^{3+}.[25]

The O 1s spectrum of CeO_2–ZrO_2 material is illustrated in Figure 2b. The peak centered at 530.3 eV is related to the lattice oxygen and the peak located at 532.3 eV is ascribed to adsorbed oxygen (O^-, O^{2-}, or OH^-).[26]

Zr 3d XP spectrum of prepared CeO_2–ZrO_2 nanomaterial is shown in Figure 2c, reveals two peaks at 182.4 and 184.7 eV corresponding to Zr $3d_{5/2}$ and Zr $3d_{3/2}$ respectively, which are assigned to +4 oxidation state of the zirconium.[27] From the XPS studies, it is clear that on the surface of the CeO_2–ZrO_2 material Ce exists in the 3+ and 4+ states and Zr in 4+ states along with the presence of two types of oxygen (lattice oxygen and adsorbed oxygen).

To show the merits of CeO_2–ZrO_2 nanoparticles in organic synthesis, we applied this catalyst for multicomponent reaction. A green protocol was used for the synthesis of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-chromene-3-carbonitrile derivatives **4aa–bd** via a multicomponent approach from the reaction of 1,3-dicarbonyl compounds (**1a–e**, 1 mmol), 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes (**2a–f**, 1 mmol) and malononitrile (**3**, 1 mmol) in the presence of CeO_2–ZrO_2 nanoparticles (NPs) as a catalyst in aqueous medium at room temperature. Initial studies were carried out by reaction between 4-hydroxy-6-methyl-2*H*-chromene-2-one **1a**, 4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)-benzaldehyde **2c**, and malononitrile **3** as a model reaction in different solvents and catalysts. We have applied wide range of solvents such as methanol, ethanol, water, acetonitrile, and dioxane (Table 1, entries 1–5). Water was proved to be the solvent of choice and improved for all imminent studies. To optimize the reaction conditions in terms of catalyst above model reaction was performed using different catalysts like KOH, triethylamine, piperidine, H_2SO_4, acetic acid (Table 1, entries 6–10) including nano catalysts i.e.,

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376–2386

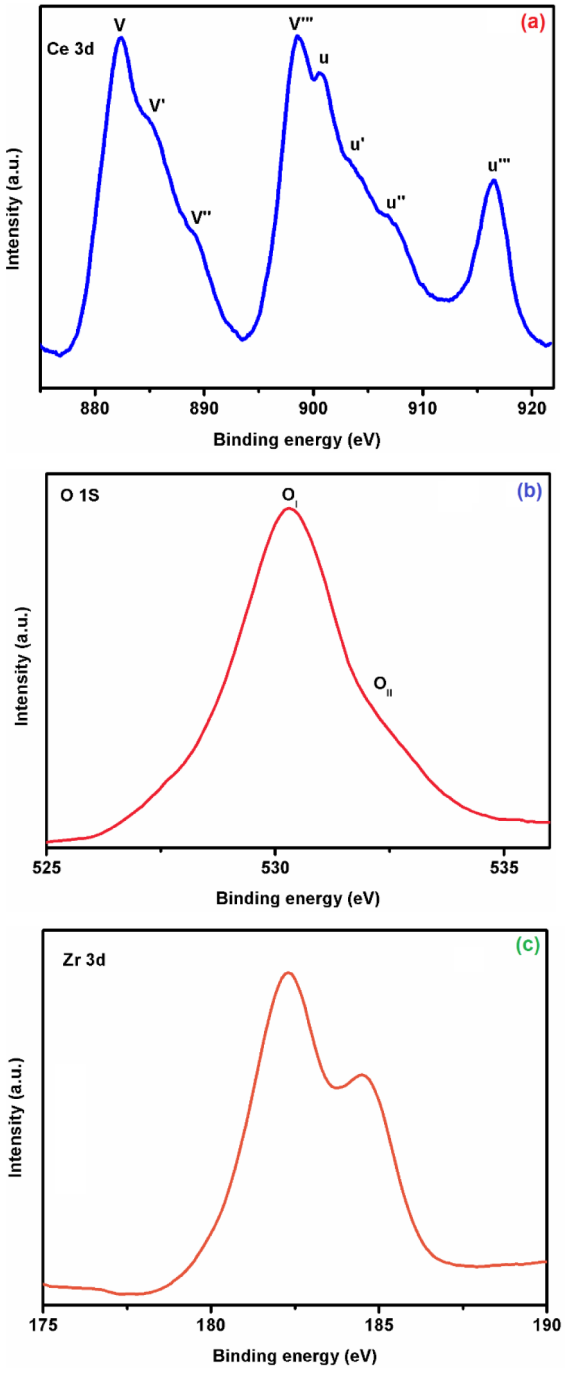


Figure 2. XPS spectra of zirconium doped ceria nanoparticles calcined at 773 K.

Fe_3O_4, ZnO, TiO_2, CeO_2, CeO_2–ZrO_2 (Table 1, entries 11–15). However, CeO_2–ZrO_2 (cerium zirconium oxide) was identified as the suitable catalyst with **4ac** being isolated maximum amounts (91%) and the yield of desired product was checked using different mol ratios (10, 20, 30 mol %). The maximum yield was obtained when the 20 mol % catalyst was used (Table 1, entry 16). Below this, catalyst did not yield any encouraging result and when the reaction was attempted using 30 mol %, (Table 1, entry 17) it gave good yields of **4ac**. It is the same when 20 mol % used. In addition to this, we also studied the effect of temperature on the above reaction using different temperatures like 40, 50, 60 °C and reflux temperature (Table 1, entries 18–21). Among these results, we found that low temperature (room temperature) improved the reaction yields.

All these optimized conditions were then applied for all further experiments. Typically, a mixture of 1,3-dicarbonyl compounds (1 mmol), (substituted-phenyl-diazenyl)-benzaldehydes (1 mmol), malononitrile (1 mmol), and 20 mol % of nano-CeO_2–ZrO_2 in 5 mL of water at room temperature for 3 h, which afforded a library of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-chromene-3-carbonitrile derivatives **4aa–bd** in good to excellent yields (79–93%). To estimate the scope and generality of the procedure, 4-hydroxy-3-methoxy-5-(substituted-phenyl)diazenyl)-benzaldehydes like 4-hydroxy-3-methoxy-5-(phenyldiazenyl)-benzaldehyde (**2a**), 4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)-benzaldehyde (**2b**), 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)-benzaldehyde (**2c**), 4-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)-benzaldehyde (**2d**), 4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)-benzaldehyde (**2e**), and 3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxybenzaldehyde (**2f**) having both electron-donating and electron-withdrawing groups were reacted with 1,3-dicarbonyl compounds like 4-hydroxy-6-methyl-2*H*-chromene-2-one (**1a**), 4-hydroxycoumarin (**1b**), 2-hydroxy-1,4-naphthoquinone (**1c**), 5,5-dimethyl-1,3-cyclohexanedione (**1d**), and 1,3-cyclohexanedione (**1e**) and malononitrile (**3**) under optimized conditions, and results are summarized in Table 2.

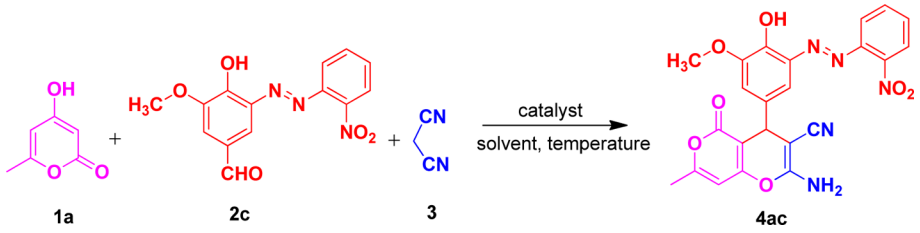
To show the significance of nanosized CeO_2–ZrO_2 catalyst, its reusability was tested upon the synthesis of compound **4ac** with 4-hydroxy-6-methyl-2*H*-chromene-2-one **1a**, 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde **2c**, and malononitrile **3**. After each cycle, the reaction was followed by extraction of products and catalyst. The collected catalyst was washed with acetone for several times to remove organic substances and used for the next run. The performance of the recycled catalyst was tested up to four successive runs and observed no significant loss in the reaction products (Figure 3). A plausible mechanism was suggested in Scheme 1. The reaction was supposed to continue via first Knoevenagel condensation to proceed 2-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)benzylidene)malononitrile (**I**). Consequently, the Michael addition reaction of the intermediate (**II**) with 1,3-dicarbonyl compounds followed by tautomerization and intramolecular cyclization providing the desired product. The structures of all the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry analysis. Further, the structure of compound **4av** was confirmed by single crystal X-ray diffraction method (Figure 4, CCDC-1440722). The compound **4av** crystallizes in the centrosymmetric monoclinic *C*2/*c* space group with one molecule in the asymmetric unit. Table 3 gives the pertinent crystallographic data

EXPERIMENTAL RESULTS

Materials and Method. All reagents were procured from commercial sources and used without further purification. A Bruker WM-4 (X) spectrophotometer (577 model) was used for recording IR spectra (KBr). NMR spectra were recorded on a Bruker WM-500 spectrophotometer at 500 MHz (^{1}H), Bruker WM-400 spectrophotometer at 400 MHz (^{1}H), and 100 MHz (^{13}C), respectively, in DMSO-d_6 with TMS as an internal standard. Elemental analysis was performed on a Carlo Erba EA 1108 automatic elemental analyzer. Mass spectra (ESI) were carried out on a Jeol JMSD-300 spectrometer. The compound **4av** was crystallized from DMF to yield prismatic crystals. XRD data was acquired in the 2θ range of 12–80° on a Rigaku Multiflex instrument using Cu Kα (λ = 1.5418 Å)

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376–2386

Table 1. Effect of Solvent and Catalysts on the Synthesis of 2-Amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyldiazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile 4ac



entry[a]	catalyst (mol %)	solvent	temperature (°C)	time (h)	yield[b] (%)
1		methanol	rt	24	10
2		ethanol	rt	19	23
3		water	rt	11	41
4		acetonitrile	rt	13	21
5		dioxane	rt	24	NR
6	KOH (10%)	water	rt	11	41
7	triethylamine (10%)	water	rt	6	33
8	piperidine (10%)	water	rt	6	39
9	H_2SO_4 (10%)	water	rt	6	51
10	acetic acid (10%)	water	rt	6	46
11	Fe_3O_4 (10%)	water	rt	6	54
12	ZnO (10%)	water	rt	6	59
13	TiO_2 (10%)	water	rt	6	46
14	CeO_2 (10%)	water	rt	6	71
15	CeO_2–ZrO_2 (10%)	water	rt	3	81
16	**CeO_2–ZrO_2 (20%)**	**water**	**rt**	**2**	**91**
17	CeO_2–ZrO_2 (30%)	water	rt	2	90
18	CeO_2–ZrO_2 (20%)	water	40	2	80
19	CeO_2–ZrO_2 (20%)	water	50	2	73
20	CeO_2–ZrO_2 (20%)	water	60	2	51
21	CeO_2–ZrO_2 (20%)	water	reflux	2	49

[a]Reaction conditions: 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde (1 mmol), and malononitrile (1 mmol), solvent (5 mL) and catalyst. [b]Yields of isolated products.

radiation and a scintillation counter detector. Crystalline phases present in the samples were identified with the help of Powder Diffraction File-International Centre for Diffraction Data (PDF-ICDD). The average size of the crystalline domains (D) of the prepared materials were estimated with the help of the Scherrer eq 1 using the XRD data of all prominent lines.

$$D = K\lambda/\beta \cos\theta \quad (1)$$

Where D denotes the crystallite size, λ is the X-ray wavelength (1.541 Å), K indicates the particle shape factor taken as 1, β represents the peak width (fwhm, full width at half-maximum) in radians, and θ is the Bragg diffraction angle. TEM studies were made on a JEM-2010 (JEOL) instrument equipped with a slow-scan CCD camera at an accelerating voltage of 200 kV. The XPS measurements were performed on a Shimadzu (ESCA 3400) spectrometer by using Al Kα (1486.7 eV) radiation as the excitation source. Charging effects of catalyst samples were corrected by using the binding energy of the adventitious carbon (C 1s) at 284.6 eV as an internal reference. The XPS analysis was done at ambient temperature and pressures usually in the order of less than 10^{-8} Pa.

Crystal Structure Determination. The single-crystal X-ray diffraction data of the crystals **4av** were collected on a Bruker Kappa APEX-II CCD DUO diffractometer at 293(2) K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). No absorption correction was applied. The lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SHELXTL.[28] The crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.[29] All the aromatic and aliphatic C–H hydrogens were generated by the riding model in idealized geometries. The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3, and X-Seed.[30−32]

Synthesis of 2-Amino-4-(4-hydroxy-3-methoxy-5-(substituted phenyldiazenyl)-chromene-3-carbonitrile Derivatives (4aa–4bd). A mixture of 1,3-dicarbonyl compound (1 mmol), 4-hydroxy-3-methoxy-5-(substituted-phenyl diazenyl), benzaldehyde (1 mmol), and malononitrile (1 mmol) in water (5 mL) was taken in a 50 mL round-bottom flask and nano-CeO_2–ZrO_2 was added. The resulting mixture was stirred for 2 h at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction the product was separated from the catalyst by extracted with ethyl acetate, which was evaporated under vacuum. The product was purified by column chromatography using silica gel [ethyl acetate: *n*-hexane (5:5)] to afford the pure compounds (**4aa–4bd**).

2-Amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)-phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4aa). Dark red solid. mp 251–253 °C. IR (KBr, cm^{-1}) ν_{max}: 3414, 2203, 1698. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H, $-CH_3$), 3.94 (s, 3H, $-OCH_3$), 4.46 (s, 1H), 6.04 (s, 1H, ArH), 6.49 (s, 2H, $-NH_2$), 7.02 (s, 1H, ArH), 7.42 (s, 1H, ArH), 7.51–7.58 (m, 3H, ArH), 7.85–7.91 (m, 2H, ArH), 10.72 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.57, 161.89, 158.76, 158.65, 149.71, 147.21, 146.65, 143.97, 139.20, 135.19, 134.23, 131.81, 124.83, 119.80, 119.11, 116.17, 111.86, 100.72, 98.44, 79.63, 56.68, 36.32, 19.82. ESI-MS (m/z): 429 (M − 1). Anal. calcd for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.52; H, 4.44; N, 13.38.

2-Amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)-phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4ab). Red solid. mp 264–266 °C. IR (KBr, cm^{-1}) ν_{max}: 3398, 2201, 1707. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H,

DOI: 10.1021/acssuschemeng.6b00056
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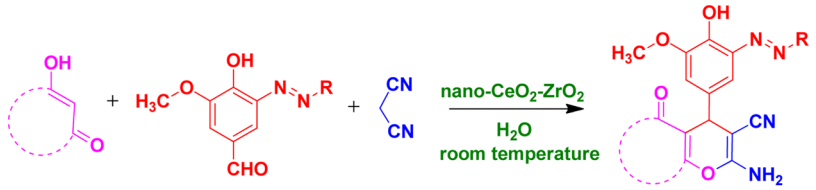
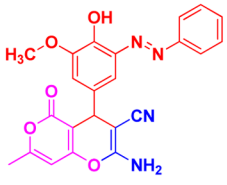
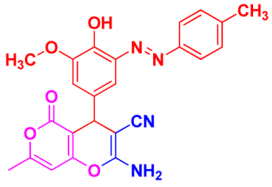
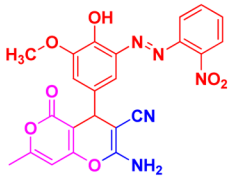
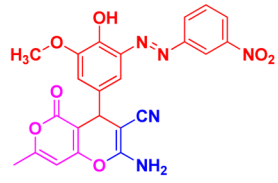
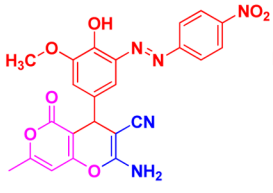
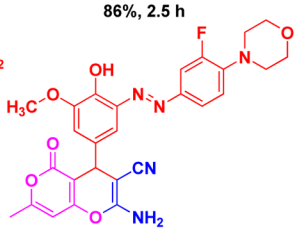
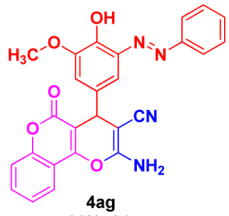
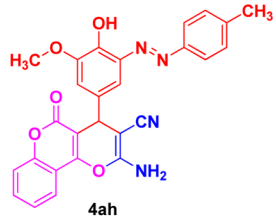
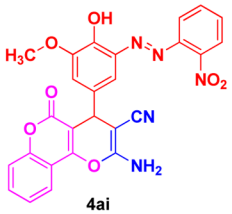
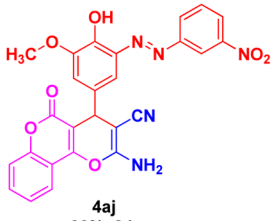
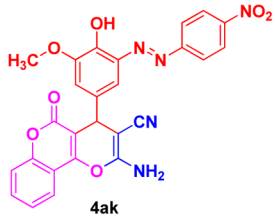
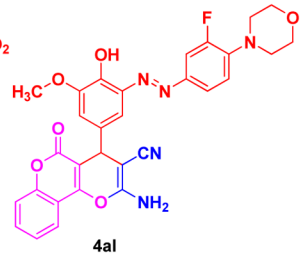
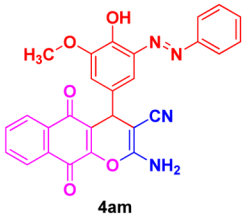
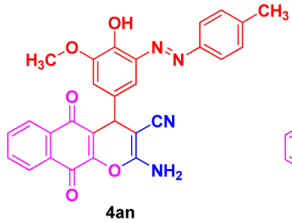
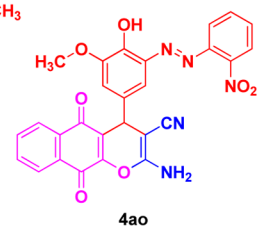
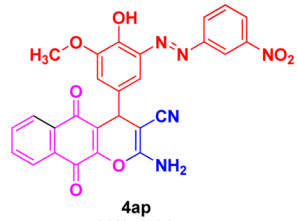
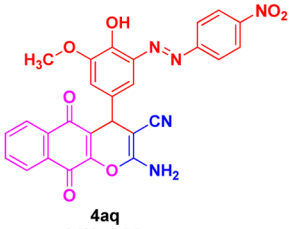
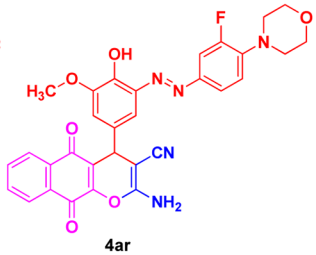
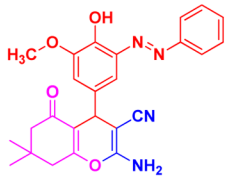
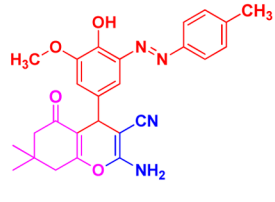
Table 2. Synthesis of 2-Amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-chromene-3-carbonitrile Derivatives 4aa–bc[a]



1a-e 2a-f 3 4aa-bd

[b]yeild (%), time

 4aa 83%, 2 h	 4ab 86%, 2.5 h	 4ac 91%, 2 h	 4ad 79%, 2 h
 4ae 81%, 2.5 h	 4af 85%, 3 h	 4ag 82%, 2 h	 4ah 79%, 2 h
 4ai 83%, 3 h	 4aj 93%, 2 h	 4ak 91%, 2.5 h	 4al 87%, 2 h
 4am 81%, 2 h	 4an 89%, 3 h	 4ao 84%, 3 h	 4ap 83%, 2.5 h
 4aq 81%, 2.5 h	 4ar 85%, 2 h	 4as 84%, 2.5 h	 4at 89%, 2.5 h

DOI: 10.1021/acssuschemeng.6b00056
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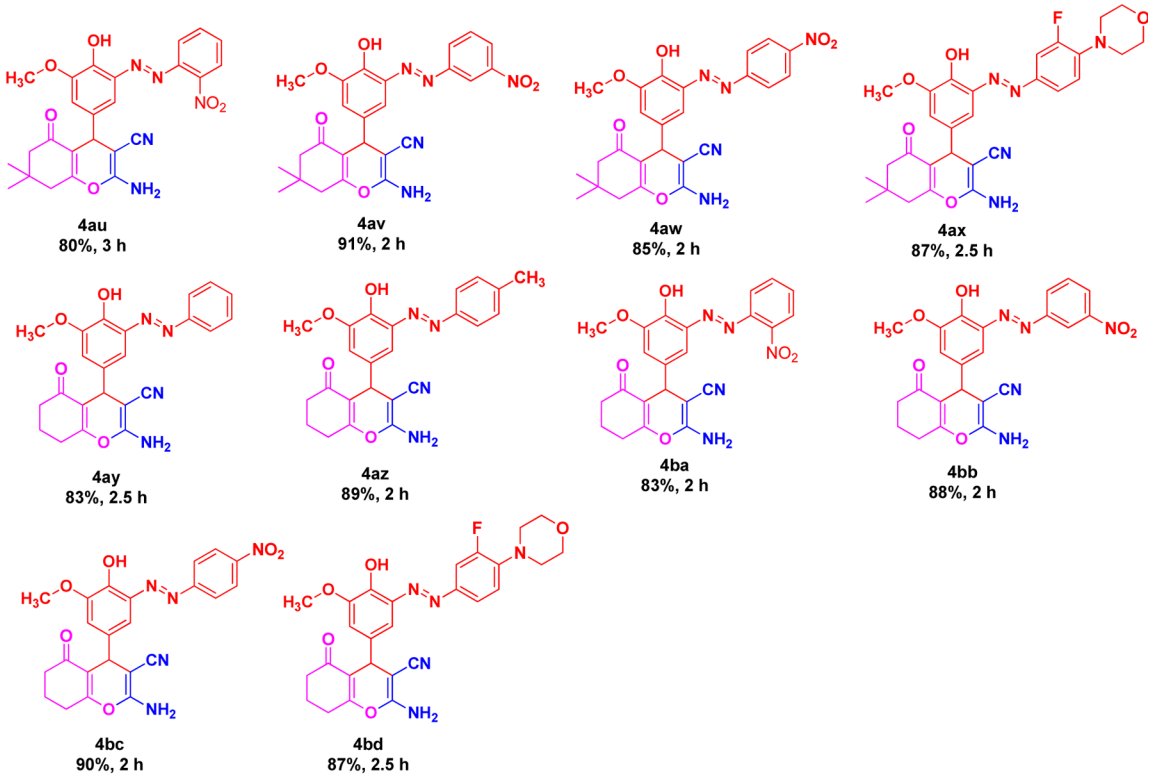
Table 2. continued



[a]Reaction conditions: dicarbonyl compound (1 mmol), 4-hydroxy-3-methoxy-5-((substituted phenyl)diazenyl)benzaldehyde (1 mmol) and malononitrile (1 mmol), nano-CeO_2–ZrO_2 (20 mol %), water (5 mL). [b]Yields of isolated products.

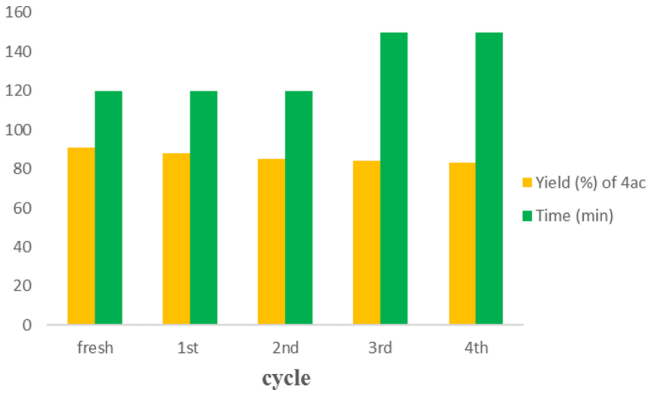


Figure 3. Reusability studies of the nanosized CeO_2–ZrO_2 catalyst for the synthesis of compound **4ac**.

–CH_3), 2.41 (s, 3H, –CH_3), 3.83 (s, 3H, –OCH_3), 4.33 (s, 1H), 6.29 (s, 1H, ArH), 6.96 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.22 (s, 2H, –NH_2), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.90 (d, J = 8.0 Hz, 2H, ArH), 10.97 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.42, 161.92, 158.60, 149.88, 149.29, 144.43, 142.12, 138.34, 134.90, 130.42, 123.18, 119.83, 115.06, 113.49, 100.98, 98.50, 79.42, 56.64, 36.49, 21.53, 19.82. ESI-MS (m/z): 443 (M – 1). Anal. calcd for $C_{24}H_{20}N_4O_5$: C, 64.86; H, 4.54; N, 12.61. Found: C, 64.92; H, 4.82; N, 12.93.

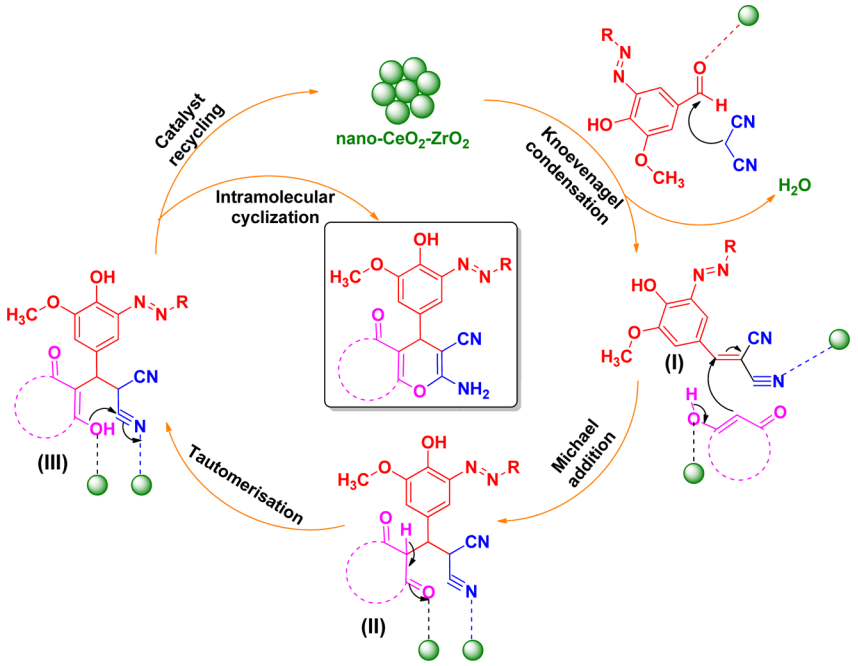
2-Amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]-pyran-3-carbonitrile (4ac). Dark red solid. mp 257–259 °C. IR (KBr, cm^{-1}) ν_{max}: 3394, 2200, 1714. ^{1}H NMR (400 MHz, $CDCl_3$-d_6): δ 2.27 (s, 3H, –CH_3), 3.96 (s, 3H, –OCH_3), 4.52 (s, 1H), 4.73 (s, 2H, –NH_2), 5.94 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.56 (t, J = 8.0 Hz, 1H, ArH), 7.73 (t, J = 8.0 Hz, 1H, ArH), 7.99 (d, J = 8.0 Hz, 1H, ArH), 8.12 (d, J = 8.0 Hz, 1H, ArH), 13.12 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.51, 161.90, 158.77, 158.62, 149.73, 147.20, 146.65, 143.97, 139.22, 135.19, 134.25, 131.81, 124.83, 119.80, 119.10, 116.16, 111.87, 100.72, 98.44, 79.65, 56.69, 36.34, 19.81. ESI-MS (m/z): 474 (M – 1). Anal. calcd for $C_{23}H_{17}N_5O_7$: C, 58.11; H, 3.60; N, 14.73. Found: C, 58.24; H, 3.43; N, 14.91.

2-Amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)-diazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]-pyran-3-carbonitrile (4ad). Dark brown solid. mp 231–233 °C. IR (KBr, cm^{-1}) ν_{max}: 3392, 2205, 1702. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, –CH_3), 3.85 (s, 3H, –OCH_3), 4.34 (s, 1H), 6.30 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.23 (s, 2H, –NH_2), 7.87 (t, J = 8.0 Hz, 1H, ArH), 8.37 (d, J = 8.0 Hz, 1H, ArH), 8.46 (d, J = 8.0 Hz, 1H, ArH), 8.79 (s, 1H, ArH), 10.67 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.53, 161.89, 158.76, 158.62, 149.75, 147.20, 146.64, 143.98, 139.21, 135.19, 134.25, 131.81, 124.83, 119.80, 119.10, 116.14, 111.87, 100.70, 98.41, 79.64, 56.69, 36.34, 19.84. ESI-MS (m/z): 474 (M – 1). Anal. calcd for $C_{23}H_{17}N_5O_7$: C, 58.11; H, 3.60; N, 14.73. Found: C, 58.24; H, 3.43; N, 14.91.

2-Amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]-pyran-3-carbonitrile (4ae). Dark red solid. mp 251–253 °C. IR (KBr, cm^{-1}) ν_{max}: 3400, 2199, 1704. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, –CH_3), 3.85 (s, 3H, –OCH_3), 4.34 (s, 1H), 6.30 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.26 (s, 2H, –NH_2), 8.22 (d, J = 8.0 Hz, 2H, ArH), 8.41 (d, J = 8.0 Hz, 2H, ArH), 10.76 (s, 1H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.53, 161.91, 158.77, 158.63, 149.73, 147.20, 146.64, 143.98, 139.22, 135.19, 134.25, 131.81, 124.83, 119.83, 119.14, 116.16, 111.87, 100.72, 98.44, 79.64, 56.68, 36.34, 19.83. ESI-MS (m/z): 474 (M – 1). Anal. calcd for $C_{23}H_{17}N_5O_7$: C, 58.11; H, 3.60; N, 14.73. Found: C, 58.24; H, 3.43; N, 14.91.

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376–2386

Scheme 1. Proposed Mechanism for the Multicomponent Reaction Using Zirconium Doped Ceria Nanoparticles



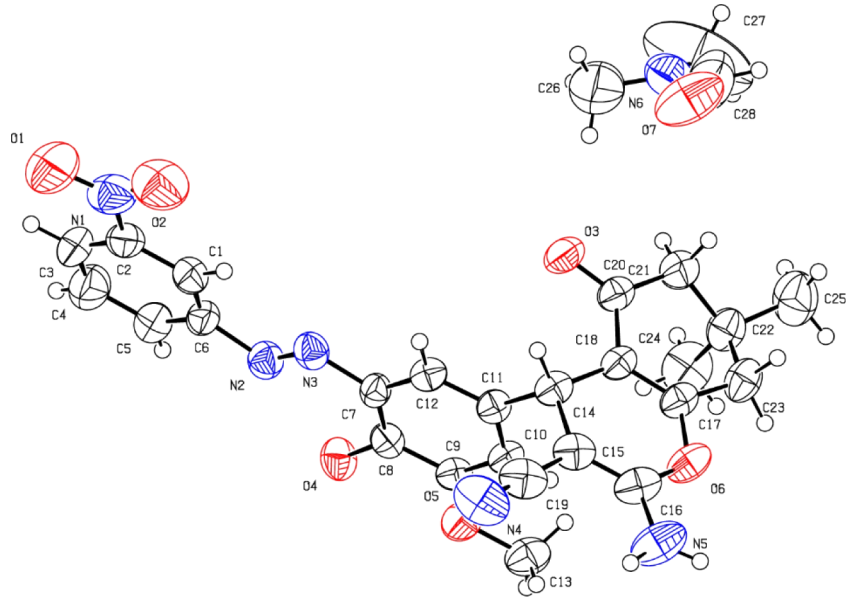


Figure 4. ORTEP representation of compound **4av** (CCDC-1440722). The thermal ellipsoids are drawn at 50% probability level.

2-Amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-*b*]pyran-3-carbonitrile (4af). Brown solid. mp 225–227 °C. IR (KBr, cm^{-1}) ν_{max}: 3377, 2199, 1709. ^1H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, $-CH_3$), 3.18–3.21 (m, 4H), 3.73–3.90 (m, 4H), 3.96 (s, 3H, $-OCH_3$), 4.31 (s, 1H), 6.29 (s, 1H, ArH), 6.92 (s, 1H, ArH), 7.11 (s, 1H, ArH), 7.22 (s, 2H, $-NH_2$), 7.63 (d, J = 8.0 Hz, 1H, ArH), 7.76 (d, J = 8.0 Hz, 1H, ArH), 8.40 (s, 1H, ArH) 10.67 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.49, 161.92, 158.76, 158.61, 149.72, 147.20, 146.63, 143.97, 139.23, 135.19, 134.25, 131.83, 124.80, 119.82, 119.10, 116.16, 111.87, 100.72, 98.42, 79.67, 68.26, 56.68, 49.79, 36.34, 30.06, 27.68, 19.82; ESI-MS (m/z): 532 (M − 1). Anal. calcd for $C_{27}H_{24}FN_5O_6$: C, 60.78; H, 4.53; N, 13.13. Found: C, 60.52; H, 4.62; N, 13.22.

2-Amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)-phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ag). Red solid. mp 240–242 °C. IR (KBr, cm^{-1}) ν_{max}: 3373, 2202, 1710. ^1H NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H, $-OCH_3$), 4.52 (s, 1H), 7.06 (s, 1H, ArH), 7.23 (s, 1H, ArH), 7.46 (s, 2H, $-NH_2$), 7.46–7.59 (m, 5H, ArH), 7.73 (t, J = 8.0 Hz, 1H, ArH), 7.91 (d, J = 8.0 Hz, 1H, ArH), 7.98 (t, J = 8.0 Hz, 2H, ArH), 10.96 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.33, 158.37, 152.33, 148.73, 144.40, 143.42, 137.45, 134.09, 132.78, 131.28, 129.32, 124.55, 122.84, 122.46, 117.55, 116.50, 115.21, 113.13, 103.95, 78.96, 56.32, 36.81. ESI-MS (m/z): 465 (M − 1). Anal. calcd for $C_{26}H_{18}N_4O_5$: C, 66.95; H, 3.89; N, 12.01. Found: C, 66.67; H, 3.98; N, 12.23.

2-Amino-4-(4-hydroxy-3-methoxy-5-(*p*-tolyldiazenyl)-phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ah). Dark red solid. mp 236–238 °C. IR (KBr, cm^{-1}) ν_{max}: 3373, 2204, 1714; ^1H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, $-CH_3$), 3.83 (s, 3H, $-OCH_3$), 4.52 (s, 1H), 7.04 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.37 (d, J = 8.0 Hz, 2H, ArH), 7.43 (s, 2H, $-NH_2$), 7.48 (t, J = 8.0 Hz, 1H, ArH), 7.72 (t, J = 8.0 Hz, 2H, ArH), 7.87–7.93 (m,

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376–2386

Table 3. Salient Crystallographic Data and Structure Refinement Parameters of Compound 4av

	4av
empirical formula	$C_{28}H_{29}N_6O_7$
formula weight	561.57
crystal system	monoclinic
space group	*C*2/c
T/K	296(2)
a/Å	13.5896(13)
b/Å	15.1701(14)
c/Å	27.316(3)
α/deg	90
β/deg	92.580(4)
γ/deg	90
Z	8
V/Å^3	5625.7(9)
D_{calc}/Mg/cm^3	1.326
F(000)	2360
μ/mm^{-1}	0.097
θ/deg	1.49−28.33
index ranges	$-18 \le h \le 18$
	$-16 \le k \le 20$
	$-36 \le l \le 36$
N-total	23076
N-independent	6949
parameters	373
R_1 ($I > 2\sigma(I)$)	0.0508
wR_2 (all data)	0.2159
GOF	1.017
CCDC	1440722

3H, ArH), 11.03 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.80, 158.32, 152.75, 148.10, 144.89, 143.47, 137.97, 134.77, 132.47, 131.28, 129.51, 123.45, 123.13, 122.27, 117.93, 116.79, 115.00, 103.10, 78.73, 57.27, 49.09, 36.94, 19.77. ESI-MS (*m*/*z*): 479 (M − 1). Anal. calcd for $C_{27}H_{20}N_4O_5$: C, 67.49; H, 4.20; N, 11.66. Found: C, 67.80; H, 4.01; N, 11.83.

2-Amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ai). Red solid. mp 231−233 °C. IR (KBr, cm^{-1}) ν_{max}: 3381, 2200, 1717. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.84 (s, 3H, −OCH_3), 4.50 (s, 1H), 7.10 (s, 1H, ArH), 7.44 (s, 2H, −NH_2), 7.47−7.52 (m, 2H, ArH), 7.73 (t, *J* = 10.0 Hz, 2H, ArH), 7.83 (t, *J* = 10.0 Hz, 1H, ArH), 7.91−7.97 (m, 3H, ArH), 8.10 (d, *J* = 10.0 Hz, 1H, ArH), 10.98 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.83, 160.93, 159.75, 157.46, 152.17, 149.79, 148.73, 146.21, 141.52, 138.37, 134.40, 132.33, 125.93, 125.01, 123.93, 122.15, 115.83, 114.48, 109.55, 106.03, 103.54, 76.96, 56.56, 36.18. ESI-MS (*m*/*z*): 510 (M − 1). Anal. calcd for $C_{26}H_{17}N_5O_7$: C, 61.06; H, 3.35; N, 13.69. Found: C, 61.32; H, 3.43; N, 13.90.

2-Amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)-diazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4aj). Brown solid. mp 248−250 °C. IR (KBr, cm^{-1}) ν_{max}: 3327, 2185, 1723. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.84 (s, 3H, −OCH_3), 4.51 (s, 1H), 7.08 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.45 (s, 2H, −NH_2), 7.46−7.52 (m, 2H, ArH), 7.72 (t, *J* = 10.0 Hz, 1H, ArH), 7.85 (t, *J* = 10.0 Hz, 1H, ArH), 7.90−7.96 (m, 2H, ArH), 8.35 (d, *J* = 10.0 Hz, 1H, ArH), 8.78 (s, 1H, ArH), 10.69 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.36, 160.66, 159.69, 157.30, 152.23, 149.55, 148.79, 146.09, 141.88, 138.39, 134.18, 132.99, 125.72, 125.04, 123.52, 122.05, 115.88, 114.55, 110.28, 106.07, 103.74, 77.68, 56.11, 36.83. ESI-MS (*m*/*z*): 510 (M − 1). Anal. calcd for $C_{26}H_{17}N_5O_7$: C, 61.06; H, 3.35; N, 13.69. Found: C, 61.31; H, 3.44; N, 13.88.

2-Amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4ak). Dark red solid. mp 228−230 °C. IR (KBr, cm^{-1}) ν_{max}: 3358, 2205, 1718. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, −OCH_3), 4.52 (s, 1H), 7.11 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.47 (s, 2H, −NH_2), 7.51 (t, *J* = 8.0 Hz, 1H, ArH), 7.73 (t, *J* = 8.0 Hz, 1H, ArH), 7.93 (t, *J* = 8.0 Hz, 2H, ArH), 8.21 (d, *J* = 8.0 Hz, 2H, ArH), 8.40 (d, *J* = 8.0 Hz, 2H, ArH), 10.79 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.80, 160.13, 158.52, 155.50, 153.94, 152.66, 149.88, 148.62, 146.91, 139.18, 134.74, 133.47, 125.37, 125.17, 124.24, 123.06, 119.71, 117.09, 116.38, 113.53, 110.87, 104.03, 79.65, 56.72, 36.28. ESI-MS (*m*/*z*): 510 (M − 1). Anal. calcd for $C_{26}H_{17}N_5O_7$: C, 61.06; H, 3.35; N, 13.69. Found: C, 61.32; H, 3.43; N, 13.90.

2-Amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]-chromene-3-carbonitrile (4al). Brown solid. mp 220−222 °C. IR (KBr, cm^{-1}) ν_{max}: 3411, 2227, 1731. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16−3.21 (m, 4H), 3.76−3.79 (m, 4H), 3.96 (s, 3H, −OCH_3), 4.48 (s, 1H), 7.19−7.24 (m, 3H, ArH), 7.42 (s, 2H, −NH_2), 7.57 (s, 1H, ArH), 7.62 (d, *J* = 8.0 Hz, 1H, ArH), 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 7.90 (d, *J* = 8.0 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 11.03 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.15, 156.12, 153.50, 152.20, 150.06, 148.91, 146.59, 144.09, 142.74, 140.22, 139.30, 134.38, 130.43, 128.29, 126.75, 124.20, 122.25, 118.61, 115.06, 110.65, 108.10, 104.92, 78.63, 66.03, 56.04, 50.00, 37.37. ESI-MS (*m*/*z*): 568 (M − 1). Anal. calcd for $C_{30}H_{24}FN_5O_6$: C, 63.27; H, 4.25; N, 12.30. Found: C, 63.52; H, 4.33; N, 12.57.

2-Amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)-phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4am). Red solid. mp 265−267 °C. IR (KBr, cm^{-1}) ν_{max}: 3453, 2190, 1723, 1657. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, −OCH_3), 4.67 (s, 1H), 7.07 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.35 (s, 2H, −NH_2), 7.54−7.59 (m, 3H, ArH), 7.83−7.87 (m, 2H, ArH), 7.89−7.92 (m, 1H, ArH), 7.97−8.00 (m, 2H, ArH), 8.04−8.08 (m, 1H, ArH), 10.97 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.21, 177.41, 158.87, 151.84, 149.57, 149.34, 144.75, 138.43, 134.98, 134.91, 134.59, 131.83, 131.57, 131.18, 129.88, 126.52, 126.31, 123.17, 121.96, 119.88, 115.39, 113.86, 79.65, 56.76, 36.85. ESI-MS (*m*/*z*): 477 (M − 1). Anal. calcd for $C_{27}H_{18}N_4O_5$: C, 67.78; H, 3.79; N, 11.71. Found: C, 67.51; H, 3.50; N, 11.93.

2-Amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)-phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4an). Red solid. mp 271−273 °C. IR (KBr, cm^{-1}) ν_{max}: 3389, 2201, 1721, 1667. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, −CH_3), 3.84 (s, 3H, −OCH_3), 4.66 (s, 1H), 7.06 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.35 (s, 2H, −NH_2), 7.38 (d, *J* = 8.0 Hz, 1H, ArH), 7.83−7.91 (m, 6H, ArH), 8.04−8.07 (m, 1H, ArH), 11.05 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.81, 177.63, 158.97, 151.98, 150.80, 149.73, 144.97, 138.83, 135.76, 134.93, 134.40, 132.40, 132.01, 130.60, 129.56, 126.80, 126.39, 123.22, 121.84, 119.36, 115.85, 113.04, 79.74, 56.41, 36.54, 20.30. ESI-MS (*m*/*z*): 491 (M − 1). Anal. calcd for $C_{28}H_{20}N_4O_5$: C, 68.29; H, 4.09; N, 11.38. Found: C, 68.52; H, 4.14; N, 11.09.

2-Amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]-chromene-3-carbonitrile (4ao). Red solid. mp 251−253 °C. IR (KBr, cm^{-1}) ν_{max}: 3453, 2190, 1722, 1655. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, −OCH_3), 4.66 (s, 1H), 7.07 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.36 (s, 2H, −NH_2), 7.54−7.60 (m, 2H, ArH), 7.81−7.85 (m, 2H, ArH), 7.88−7.91 (m, 1H, ArH), 7.98 (d, *J* = 8.0 Hz, 2H, ArH), 8.04−8.08 (m, 1H, ArH), 10.96 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.21, 177.42, 158.87, 151.84, 149.57, 149.34, 144.74, 138.43, 134.99, 134.91, 134.59, 131.83, 131.57, 131.18, 129.89, 126.53, 126.32, 123.17, 121.97, 119.88, 115.39, 113.86, 79.65, 56.76, 36.84. ESI-MS (*m*/*z*): 522 (M − 1). Anal. calcd for $C_{27}H_{17}N_5O_7$: C, 61.95; H, 3.27; N, 13.38. Found: C, 61.82; H, 3.33; N, 13.21.

2-Amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)-diazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]-chromene-3-carbonitrile (4ap). Brown solid. mp 244−246 °C. IR (KBr, cm^{-1}) ν_{max}: 3455, 2194, 1728, 1657. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, −OCH_3), 4.66 (s, 1H), 7.08 (s, 1H, ArH), 7.30 (s, 1H, ArH), 7.41 (s, 2H, −NH_2), 7.57−7.64 (m, 2H, ArH), 7.72

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376−2386

(s, 2H, ArH), 7.81−7.85 (m, 1H, ArH), 7.90 (d, J = 8.0 Hz, 2H, ArH), 7.95−7.99 (m, 1H, ArH), 11.05 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.75, 177.74, 159.00, 151.87, 149.81, 144.05, 138.04, 135.76, 135.18, 133.71, 131.70, 131.43, 129.69, 127.41, 126.52, 123.66, 121.07, 119.65, 115.65, 113.65, 79.95, 57.00, 36.60. ESI-MS (m/z): 522 (M − 1). Anal. calcd for $C_{27}H_{17}N_5O_7$: C, 61.95; H, 3.27; N, 13.38. Found: C, 61.80; H, 3.31; N, 13.22.

2-Amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)phenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]-chromene-3-carbonitrile (4aq). Brown solid. mp 260−262 °C. IR (KBr, cm^{-1}) ν_{max}: 3454, 2198, 1723, 1653; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.92 (s, 3H, −OCH_3), 4.66 (s, 1H), 7.08 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.43 (s, 2H, −NH_2), 7.78 (d, 1H, J = 8.0 Hz, ArH), 8.02 (d, 1H, J = 8.0 Hz, ArH), 8.20 (d, 2H, J = 8.0 Hz, ArH), 8.42−8.47 (m, 4H, ArH), 11.02 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.10, 177.07, 158.68, 152.28, 150.69, 149.68, 144.96, 140.63, 138.34, 136.26, 134.33, 133.73, 132.46, 126.25, 125.69, 125.52, 125.34, 123.88, 118.27, 115.87, 113.52, 79.40, 56.40, 36.38. ESI-MS (m/z): 522 (M − 1). Anal. calcd for $C_{27}H_{17}N_5O_7$: C, 61.95; H, 3.27; N, 13.38. Found: C, 61.80; H, 3.35; N, 13.19.

2-Amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile (4ar). Brown solid. mp 242−244 °C. IR (KBr, cm^{-1}) ν_{max}: 3443, 2197, 1721, 1657. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10−3.16 (m, 4H), 3.76−3.79 (m, 4H), 3.91 (s, 3H, −OCH_3), 4.65 (s, 1H), 7.77 (s, 1H, ArH), 7.89−7.91 (m, 3H, ArH), 8.01 (s, 1H, ArH), 8.31 (s, 2H, −NH_2), 8.38−8.46 (m, 3H, ArH), 8.79 (s, 1H, ArH), 10.75 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.77, 177.37, 161.24, 156.29, 153.84, 152.09, 150.10, 146.73, 143.18, 139.16, 134.87, 132.10, 129.90, 127.70, 124.88, 122.63, 118.83, 116.15, 115.27, 114.26, 110.71, 106.81, 104.17, 79.65, 66.48, 56.53, 50.42, 36.35. ESI-MS (m/z): 580 (M − 1). Anal. calcd for $C_{31}H_{24}FN_5O_6$: C, 64.02; H, 4.16; N, 12.04. Found: C, 64.32; H, 4.01; N, 12.21.

2-Amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4as). Red solid. mp 246−248 °C. IR (KBr, cm^{-1}) ν_{max}: 3452, 2190, 1676. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 3H, −CH_3), 1.06 (s, 3H, −CH_3), 2.09−2.33 (m, 4H), 3.83 (s, 3H, −OCH_3), 4.21 (s, 1H), 6.90 (s, 1H, ArH), 7.03 (s, 2H, −NH_2), 7.11 (s, 1H, ArH), 7.54−7.61 (m, 3H, ArH), 7.97 (d, J = 8.0 Hz, 2H, ArH), 10.74 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.29, 163.23, 158.95, 151.96, 149.44, 144.68, 138.65, 136.00, 131.76, 129.88, 123.17, 120.26, 114.72, 112.89, 111.92, 56.59, 50.48, 35.64, 32.28, 29.17, 26.96. ESI-MS (m/z): 443 (M − 1). Anal. calcd for $C_{25}H_{24}N_4O_4$: C, 67.55; H, 5.44; N, 12.60. Found: C, 67.41; H, 5.32; N, 12.82.

2-Amino-4-(4-hydroxy-3-methoxy-5-(p-tolyldiazenyl)-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4at). Yellow solid. mp 247−249 °C. IR (KBr, cm^{-1}) ν_{max}: 3437, 2189, 1735. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (s, 3H, −CH_3), 1.06 (s, 3H, −CH_3), 2.09−2.31 (m, 2H), 2.41 (s, 3H, −CH_3), 2.52−2.73 (m, 2H), 3.82 (s, 3H, −OCH_3), 4.21 (s, 1H), 6.88 (s, 1H, ArH), 7.02 (s, 2H, −NH_2), 7.11 (s, 1H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 7.88 (d, J = 8.0 Hz, 2H, ArH), 10.80 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.00, 162.87, 158.60, 149.63, 148.99, 143.94, 142.26, 141.73, 138.16, 135.60, 130.07, 122.79, 119.90, 114.14, 112.56, 112.01, 79.27, 56.23, 50.13, 35.27, 31.93, 28.78, 26.62, 21.17. ESI-MS (m/z): 457 (M − 1). Anal. calcd for $C_{26}H_{26}N_4O_4$: C, 68.11; H, 5.72; N, 12.22. Found: C, 68.32; H, 5.81; N, 12.46.

2-Amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4au). Dark red solid. mp 231−233 °C. IR (KBr, cm^{-1}) ν_{max}: 3498, 2190, 1678. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 3H, −CH_3), 1.06 (s, 3H, −CH_3), 2.09−2.32 (m, 2H), 2.57−2.89 (m, 2H), 3.85 (s, 3H, −OCH_3), 4.18 (s, 1H), 6.94 (s, 1H, ArH), 6.96 (s, 1H, ArH), 7.04 (s, 2H, −NH_2), 7.74 (t, J = 8.0 Hz, 1H, ArH), 7.85 (t, J = 8.0 Hz, 1H, ArH), 7.97 (d, J = 8.0 Hz, 1H, ArH), 8.11 (d, J = 8.0 Hz, 1H, ArH), 10.73 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.58, 163.56, 159.17, 149.98, 147.67, 146.85, 139.75, 136.59, 134.43, 132.02, 124.96, 120.43, 119.33, 116.07, 112.96, 110.56, 79.88, 56.92, 50.73, 35.83, 32.48, 29.32, 27.37. ESI-MS (m/z): 488 (M − 1). Anal. calcd for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.41; H, 4.51; N, 14.43.

2-Amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)-diazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4av). Red solid. mp 249−251 °C. IR (KBr, cm^{-1}) ν_{max}: 3400, 2187, 1680. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 3H, −CH_3), 1.06 (s, 3H, −CH_3), 2.10−2.32 (m, 2H), 2.53−2.61 (m, 2H), 3.84 (s, 3H, −OCH_3), 4.20 (s, 1H), 6.93 (s, 1H, ArH), 7.05 (s, 2H, −NH_2), 7.12 (s, 1H, ArH), 7.88 (t, J = 8.0 Hz, 1H, ArH), 8.36 (d, J = 8.0 Hz, 1H, ArH), 8.44 (d, J = 8.0 Hz, 1H, ArH), 8.78 (s, 1H, ArH), 10.58 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.84, 162.86, 158.48, 152.29, 149.35, 148.81, 145.95, 138.52, 135.56, 133.27, 130.90, 130.44, 125.02, 119.78, 116.30, 115.86, 114.89, 112.30, 108.51, 104.94, 102.72, 56.07, 49.98, 35.17, 31.82, 28.74, 26.43. ESI-MS (m/z): 488 (M − 1). Anal. calcd for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.39; H, 4.54; N, 14.49.

2-Amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4aw). Dark red solid. mp 244−246 °C. IR (KBr, cm^{-1}) ν_{max}: 3371, 2183, 1678. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 3H, −CH_3), 1.06 (s, 3H, −CH_3), 2.09−2.33 (m, 2H), 2.57−2.68 (m, 2H), 3.84 (s, 3H, −OCH_3), 4.21 (s, 1H), 6.95 (s, 1H, ArH), 7.04 (s, 2H, −NH_2), 7.11 (s, 1H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 8.41 (d, J = 8.0 Hz, 2H, ArH), 10.65 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.76, 162.79, 158.47, 155.05, 149.33, 148.12, 146.24, 138.81, 136.63, 135.62, 124.90, 123.68, 119.69, 115.26, 112.27, 109.03, 56.09, 35.14, 31.77, 28.66, 26.43. ESI-MS (m/z): 488 (M − 1). Anal. calcd for $C_{25}H_{23}N_5O_6$: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.40; H, 4.52; N, 14.41.

2-Amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4ax). Brown solid. mp 236−238 °C. IR (KBr, cm^{-1}) ν_{max}: 3373, 2187, 1677. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (s, 3H, −CH_3), 1.05 (s, 3H, −CH_3), 2.09−2.31 (m, 2H), 2.56−2.89 (m, 2H), 3.17−3.21 (m, 4H), 3.72−3.81 (m, 4H), 3.96 (s, 3H, −OCH_3), 4.18 (s, 1H), 6.84 (s, 1H, ArH), 7.03 (s, 2H, −NH_2), 7.07 (s, 1H, ArH), 7.64 (d, J = 8.0 Hz, 1H, ArH), 7.75 (d, J = 8.0 Hz, 1H, ArH), 8.41 (s, 1H, ArH), 10.48 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.75, 162.69, 158.42, 155.95, 148.93, 144.28, 138.07, 135.39, 128.25, 124.67, 123.34, 122.16, 119.74, 118.36, 113.84, 112.40, 110.20, 77.96, 66.00, 56.02, 49.97, 35.16, 31.75, 28.67, 26.43. ESI-MS (m/z): 546 (M − 1). Anal. calcd for $C_{29}H_{30}FN_5O_5$: C, 63.61; H, 5.52; N, 12.79. Found: C, 63.42; H, 5.71; N, 12.61.

2-Amino-4-(4-hydroxy-3-methoxy-5-(phenyldiazenyl)-phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4ay). Dark red solid. mp 206−208 °C. IR (KBr, cm^{-1}) ν_{max}: 3402, 2194, 1665. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88−2.01 (m, 2H), 2.27−2.33 (m, 2H), 2.60−2.67 (m, 2H), 3.84 (s, 3H, −OCH_3), 4.24 (s, 1H), 6.92 (s, 1H, ArH), 7.06 (s, 2H, −NH_2), 7.13 (s, 1H, ArH), 7.55−7.60 (m, 3H, ArH), 7.92−8.06 (m, 2H, ArH), 10.91 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.00, 164.49, 162.30, 158.54, 151.34, 148.85, 143.89, 137.94, 135.54, 131.27, 129.38, 122.96, 122.64, 119.79, 114.52, 113.56, 112.60, 56.14, 36.39, 35.11, 26.51, 19.84. ESI-MS (m/z): 415 (M − 1). Anal. calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.57; H, 4.62; N, 13.61.

2-Amino-4-(4-hydroxy-3-methoxy-5-(*p*-tolyldiazenyl)-phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4az). Red solid. mp 249−251 °C. IR (KBr, cm^{-1}) ν_{max}: 3405, 2194, 1681. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90−2.00 (m, 2H), 2.29−2.33 (m, 2H), 2.41 (s, 3H, −CH_3), 2.60−2.69 (m, 2H), 3.83 (s, 3H, −OCH_3), 4.23 (s, 1H), 6.90 (s, 1H, ArH), 7.04 (s, 2H, −NH_2), 7.13 (s, 1H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 7.90 (d, J = 8.0 Hz, 2H, ArH), 10.98 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.01, 164.47, 158.54, 149.35, 148.75, 143.55, 141.59, 137.78, 135.50, 129.93, 122.64, 119.79, 114.29, 113.59, 113.01, 56.12, 36.38, 35.09, 26.50, 21.02, 19.84. ESI-MS (m/z): 429 (M − 1). Anal. calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02. Found: C, 67.12; H, 5.44; N, 13.23.

2-Amino-4-(4-hydroxy-3-methoxy-5-((2-nitrophenyl)-diazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-

DOI: 10.1021/acssuschemeng.6b00056
ACS Sustainable Chem. Eng. 2016, 4, 2376−2386

carbonitrile (4ba). Dark red solid. mp 239−241 °C. IR (KBr, cm^{-1}) ν_{max}: 3397, 2190, 1677. ^1H NMR (400 MHz, DMSO-d_6): δ 1.92−2.03 (m, 2H), 2.25−2.37 (m, 2H), 2.60−2.65 (m, 2H), 3.86 (s, 3H, $-OCH_3$), 4.21 (s, 1H), 6.97 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.03 (s, 2H, $-NH_2$), 7.74 (t, J = 8.0 Hz, 1H, ArH), 7.85 (t, J = 8.0 Hz, 1H, ArH), 8.00 (d, J = 8.0 Hz, 1H, ArH), 8.12 (d, J = 8.0 Hz, 1H, ArH), 10.82 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.53, 165.07, 159.02, 152.68, 149.72, 149.25, 146.13, 138.82, 136.05, 131.33, 130.78, 125.45, 120.27, 116.42, 115.63, 113.94, 109.95, 79.65, 56.59, 36.89, 35.65, 27.03, 20.35. ESI-MS (m/z): 460 (M − 1). Anal. calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18. Found: C, 60.12; H, 4.31; N, 14.99.

2-Amino-4-(4-hydroxy-3-methoxy-5-((3-nitrophenyl)-diazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4bb). Yellow solid. mp 247−249 °C. IR (KBr, cm^{-1}) ν_{max}: 3402, 2194, 1677. ^1H NMR (400 MHz, DMSO-d_6): δ 1.92−2.00 (m, 2H), 2.29−2.33 (m, 2H), 2.61−2.68 (m, 2H), 3.85 (s, 3H, $-OCH_3$), 4.23 (s, 1H), 6.95 (s, 1H, ArH), 7.05 (s, 2H, $-NH_2$), 7.15 (s, 1H, ArH), 7.88 (t, J = 8.0 Hz, 1H, ArH), 8.37 (d, J = 8.0 Hz, 1H, ArH), 8.47 (d, J = 8.0 Hz, 1H, ArH), 8.79 (s, 1H, ArH), 10.64 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.13, 165.36, 159.60, 152.44, 150.14, 149.54, 146.98, 138.63, 136.03, 131.11, 130.01, 125.45, 120.23, 116.75, 115.65, 113.07, 109.29, 79.95, 56.41, 36.60, 34.85, 27.39, 20.46. ESI-MS (m/z): 460 (M − 1). Anal. calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18. Found: C, 59.73; H, 4.30; N, 15.25.

2-Amino-4-(4-hydroxy-3-methoxy-5-((4-nitrophenyl)-diazenyl)phenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4bc). Red solid. mp 253−255 °C. IR (KBr, cm^{-1}) ν_{max}: 3411, 2191, 1667. ^1H NMR (400 MHz, DMSO-d_6): δ 1.89−2.02 (m, 2H), 2.26−2.33 (m, 2H), 2.61−2.69 (m, 2H), 3.86 (s, 3H, $-OCH_3$), 4.24 (s, 1H), 6.97 (s, 1H, ArH), 7.05 (s, 2H, $-NH_2$), 7.13 (s, 1H, ArH), 7.22 (d, J = 8.0 Hz, 2H, ArH), 7.41 (d, J = 8.0 Hz, 2H, ArH), 10.75 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.56, 165.59, 159.69, 152.79, 150.31, 149.68, 146.21, 138.78, 136.87, 132.14, 130.34, 125.31, 120.60, 116.87, 115.00, 113.43, 109.34, 80.00, 56.83, 36.81, 34.66, 27.14, 20.30. ESI-MS (m/z): 460 (M − 1). Anal. calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18. Found: C, 59.78; H, 4.27; N, 15.31.

2-Amino-4-(3-((3-fluoro-4-morpholinophenyl)diazenyl)-4-hydroxy-5-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4bd). Dark red solid. mp 241−243 °C. IR (KBr, cm^{-1}) ν_{max}: 3409, 2197, 1669. ^1H NMR (400 MHz, DMSO-d_6): δ 1.91−1.97 (m, 2H), 2.28−2.32 (m, 2H), 2.60−2.65 (m, 2H), 3.17−3.21 (m, 4H), 3.72−3.78 (m, 4H), 3.95 (s, 3H, $-OCH_3$), 4.20 (s, 1H), 6.86 (s, 1H, ArH), 7.04 (s, 2H, $-NH_2$), 7.09 (s, 1H, ArH), 7.64 (d, J = 8.0 Hz, 1H, ArH), 7.75 (d, J = 8.0 Hz, 1H, ArH), 8.03 (s, 1H, ArH), 10.75 (s, 1H, −OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.36, 166.77, 164.53, 158.51, 150.07, 148.89, 142.28, 137.90, 135.45, 132.52, 130.78, 123.35, 122.25, 118.40, 115.78, 113.56, 111.01, 79.30, 66.04, 56.05, 50.02, 36.41, 35.18, 26.54, 19.88. ESI-MS (m/z): 518 (M − 1). Anal. calcd for $C_{27}H_{26}FN_5O_5$: C, 62.42; H, 5.04; N, 13.48. Found: C, 62.73; H, 5.37; N, 13.21.

CONCLUSION

In summary, an efficient and one-pot multicomponent reaction in aqueous medium using zirconium doped ceria nanoparticles acting as heterogeneous catalyst has been developed for the synthesis of a novel phenyldiazenyl-chromene derivatives by starting with 1,3-dicarbonyl compounds, 4-hydroxy-3-methoxy-5-(substituted-phenyl diazenyl) benzaldehydes, and malononitrile. This protocol has the advantages of a wide scope of operational simplicity, ease separation, easy of handling, high catalytic activity, and reusability of the catalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.6b00056.

Copies of ^1H, ^{13}C NMR, and mass spectra of the obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are thankful to the Director, National Institute of Technology, Warangal, for providing facilities. One of the authors PSVK also grateful to council of scientific & industrial research (CSIR), New Delhi [File no. 09/922 (0005)2012/EMR-I], India, for the award of senior research fellowship. We are also thankful to STIC Cochin for single crystal X-ray diffraction facility.

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