Synthesis and functionalization of spirooxindoles using organic bases, organocatalytic and catalyst-free conditions

Thesis

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2nd Aug, 2021

CERTIFICATE

This is to certify that the thesis entitled ***"Synthesis and functionalization of spirooxindoles using organic bases, organocatalytic and catalyst-free conditions"*** submitted by **Kota Sathish** (Roll No. 716061) for the award of the degree of Doctor of Philosophy in Chemistry, National Institute of Technology, Warangal (T.S), under my guidance and supervision. This work has not been submitted earlier either in part or in full for any degree or diploma of any other Institute/University.

(Dr. D. Kashinath)

DECLARATION

I hereby declare that the matter embodied in this thesis entitled ***"Synthesis and functionalization of spirooxindoles using organic bases, organocatalytic and catalyst-free conditions"*** is based entirely on the results of the investigations and research work carried out by me under the supervision of **Dr. D. Kashinath,** Associate Professor, Department of Chemistry, National Institute of Technology, Warangal. I declare that this work is original and has not been submitted in part or full, for any degree or diploma to this or any other University/Institute.

(Kota Sathish)

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Date: 2nd Aug, 2021 **Kota Sathish**

ABBREVIATIONS

AMPA	:	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ACC	:	Acetyl-CoA carboxylase
Bn	:	Benzyl
Bcl-2	:	B-cell lymphoma 2
β-CD	:	β-cyclodextrin
$CDCl_3$	:	Deuterated chloroform
Cs_2CO_3	:	Cesium carbonate
CNS	:	Central nerves system
d	:	Doublets
dd	:	Doubly doublet
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DBU	:	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DES	:	Deep eutectic solvents
DIPEA`	:	*N*,*N*-Diisopropylethylamin
DMAP	:	4-Dimethylaminopyridine
DMF	:	Dimethylformamide
DMSO	:	Dimethyl sulfoxide
DMSO-d_6	:	Deuterated dimethyl sulfoxide
DMU	:	Dimethylurea
ee	:	Enantiomeric excess
EDC.HCl	:	Ethylcarbodiimide hydrochloride
ESI	:	Electro spray ionization
EtOH	:	Ethanol
EtOAc	:	Ethyl acetate
GABA	:	γ-amino butyric acid
h	:	Hours
HIV	:	Human immunodeficiency virus

HOBT	:	Hydroxybenzotriazole
HPLC	:	High Performance Liquid Chromatography
HRMS	:	High-resolution mass spectrometry
HZ	:	Hertz
IC_{50}	:	Half maximal inhibitory concentration
IL	:	Ionic Liquids
$InCl_3$	:	Indium chloride
J	:	Coupling constant
K_2CO_3	:	Potassium carbonate
m	:	Multiplet
MCRs	:	Multicomponent reactions
MeOH	:	Methanol
mg	:	milligram
min	:	Minutes
mL	:	Millilitre
mmol	:	milli mole
MP	:	Melting point
MWt	:	Molecular weight
ND	:	Not Detected
NHC	:	N-Heterocyclic Carbene
NMDA	:	N-methyl-*d*-aspartate
NMSM	:	N-Methyl-1-(methylthio)-2-nitroethenamine
NMR	:	Nuclear magnetic resonance
NSAID	:	Non-steroidal anti-inflammatory agents
Ph	:	Phenyl
ppm	:	parts per million
q	:	quartet
RT	:	Room temperature
S	:	Singlet
SAR	:	Structure activity relationships
t	:	Triplet

TEA	:	Triethylamine
THF	:	Terahydrofuran
TLC	:	Thin Layer Chromatography
TMS	:	Tetramethyl silane

TABLE OF CONTENTS

CHAPTER-I

Introduction to natural and biologically active heterocyclic molecules

CHAPTER-I

Molecules with more than one hetero atom (nitrogen, oxygen and sulfur) are widely spread in natural products and synthetic molecules and of immense important biologically as well as industry. Over more than 90% of new drugs contain atleast one hetero fragment in their structure. These molecules tested for biological activity and found comparable with the standard drugs. Considering the biological importance of heterocyclic molecules, we gave a brief introduction on biological importance of chromenes, spirochromenes, dinitrogen-fused pyrazolones, spirooxindoles, spirocyclopropanes and tetrahydrothiophenes which are part of this thesis. We believe that these molecules have significant importance in medicinal and drug discovery.

1. Introduction

Heterocyclic compounds are broadly involved in medicinal and agricultural fields.[1] Therefore, the development of methodologies useful for the assembly of molecules containing heterocyclic scaffolds has become one of the fascinating area in both the academic and industry research. Thus, organic and pharmaceutical chemists have been making extensive efforts to synthesize these molecules through developing versatile and efficient synthetic strategies. Since the aim of present work (thesis) is development of synthetic methods based on chromene & spirochromenes, isoxazole scaffolds, *N,N′* bicyclic pyrazolones, spirooxindoles, cyclopropanes and tetrahydrothiophenes. This chapter describes the importance of natural and pharmacological activities of these molecules along with the synthetic methods/modifications.

1.1 Introduction to biologically active chromenes and spirochromenes

The chromenes and spirochromenes are well-known scaffolds in medicinal chemistry. These compounds have been recognized as ideal medicinal scaffolds because of their unique pharmacological and biological activities. Chromene and its derivatives extensively used in the treatment of neurodegenerative (Parkinson, Huntington's and Alzheimer's) diseases.[2] The activities of chromenes also include anticancer,[3,4] antimicrobial,[5] anti-tubercular, antimalarial,[6] antibacterial,[7] anti-apoptotic (Bcl-2 proteins),[8] anti-fungal,[9] anti-rheumatic,[10] anti-hyperglycemic and α-glucosidase inhibitory activities.[11] In addition to this, these scaffolds also used for the treatment of asthma, ischemia, urinary incontinence. Some of these compounds play key role in central nervous system, possess excellent binding capacity towards many receptors in the biological systems and used as cosmetics, pigments and biodegradable agrochemicals (**Figure-**

1).[12a] The chromenes and spirochromenes are synthesized in many conditions including magnetic graphitic carbon nitride as heterogeneous catalyst,[12b] urea and choline chloride as deep eutectic solvent.[12c]

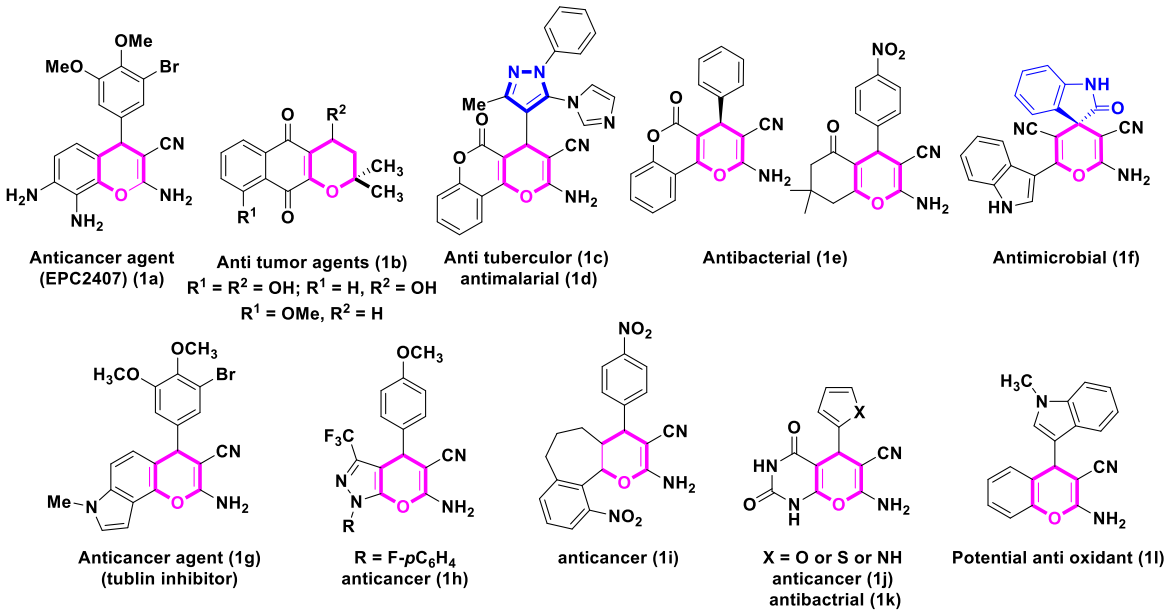

Figure-1: *Biologically active chromene & spirochromene heterocyclic compounds.*

1.2 Natural and biological active molecule of isoxazole moiety

Nitrogen containing heterocyclic compounds, especially isoxazole and its analogous extensively witnessed in natural products and bioactive molecules and were found to have multiple biological functions, such as to induce genes that support neuroendocrine and *β*-cell phenotypes or to act as cyclooxygenase inhibitors.[13] The reduction of nitro group (isoxazole) attached to the heteroaromatic core (**2a-2d**) on the conjugated system showing rapid fluorescent activity towards the detection of hydrogen sulfide (H_2S).[14] Isoxazole derivatives united with calixarenes and pyrroles rings were employed as chemo sensors for the efficient detection of anion sensors[15] or 'turn-off' sensors in micellar media[16] and metal ion analytes.[17] The delocalization of nitro group in isoxazole has employed to increase the binding affinity of any ligand to its putative target molecule.[18] Recently a variety of aryl isoxazole-oxindole hybrids have been synthesized and tested for the antiproliferative activity against human cancer cell lines [non-small cell lung (A549), cervical (HeLa), breast (MCF-7) and prostate (DU-145) cancer cell lines]. From these studies the electron donation groups (methoxy compound) (**2e**) is exhibited remarkable antiproliferative activity against A-549 (lung cancer) with an IC_{50} value 0.82 µM.[19] Isoxazole structure was

introduced in penicillin (*β*-lactam antibiotics) in order to improve the drug properties. As a result, cloxacillin (**2f-i**) show inhibitory activity towards many bacterial infections such as cellulitis, impetigo, otitis externa, pneumonia, septic *etc*., and became one of the best marketed drugs.[20] 3,4-Diarylisoxazole [Valdecoxib (**2j**)] scaffold is recurrently found in a wide variety of NSAIDs, protein kinase inhibitors, hypertensive agents, and oestrogen receptor (ER) and selective inhibitor for the COX-2 (cyclooxygenase-2).[21] These molecules also play role in central nervous system (CNS) particularly on the ionotropic transmembrane glutamate receptor and fast synaptic transmission; example AMPA (**2k**) is an ionotropic glutamate receptors (iGluRs) antagonist.[22] Both ibotenic (**2l**) acid[23a] and muscimol[23b] (**2m**) (a structural analogue of γ-aminobutyric acid, GABA) have been isolated from several fungal species including Amanita muscaria and are active CNS agents of the *N*-methyl-D-aspartate (NMDA) and GABA receptor systems respectively. Isoxazole moiety behaves as bio isostere for carbocycles and incorporated with many synthetic molecules for improving drug activity and structure activity relationships (SAR). Particularly leflunomide (**2n**) is an isoxazole derivative approved for the treatment of rheumatoid arthritis (RA)[24] and isoxicam (**2o**) is a nonsteroidal anti-inflammatory drug[25] (NSAID) and analgesic for reducing pain (**Figure-2**).

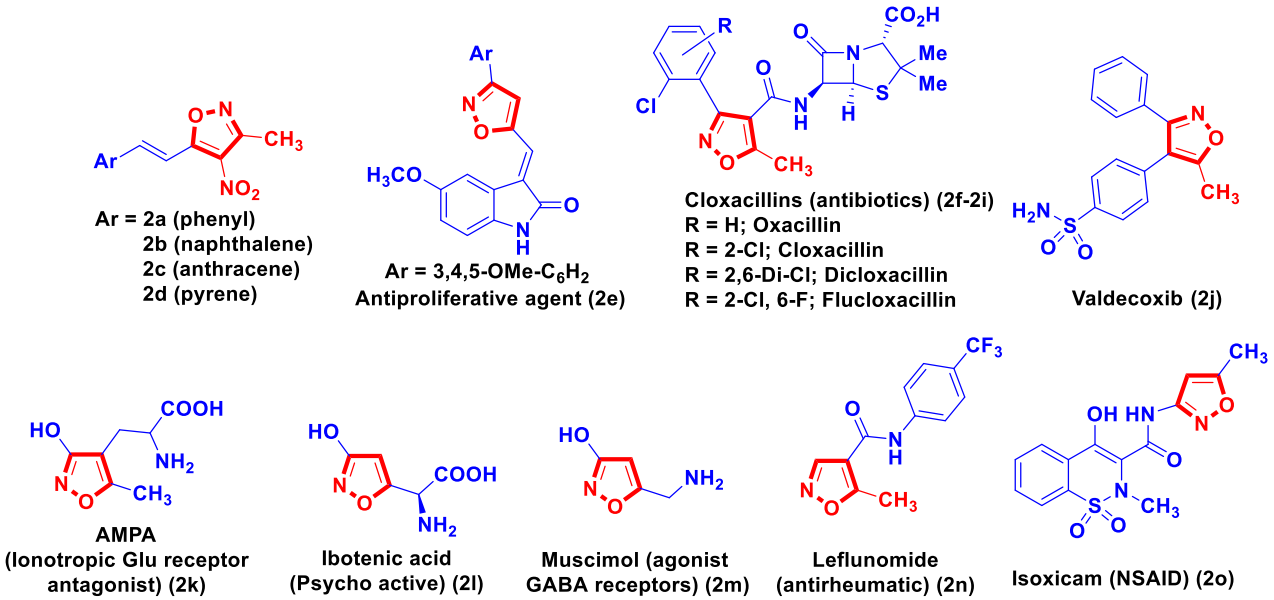

Figure-2: *Natural and biologically active molecules (**2a-2o**) with isoxazole moiety.*

1.3 Biological active molecules of dinitrogen-fused heterocyclics

Pyrazolone (pyrazole-5-one) is another useful scaffold commonly found in many biologically active molecules. The derivatives of pyrazolone such as morazone, phenazone, phenylbutazone (NSAIDs), tartrazine (anticancer), phenidone, BW357U (anorectic) are sold as commercial drugs (**Figure-3**).[26] Acyl substituted pyrazolone can undergo isomerization (proton exchange) and keto-enol tautomerism. These features make them useful synthons in organic chemistry for electrophilic and nucleophilic addition reactions.[27a-c] *N, N′*-Fused bicyclic pyrazolones are rare in the literature. These compounds were reported as γ-lactam antibiotics, antibacterial agents,[28a, b] acetyl-CoA carboxylase (ACC) inhibitors,[28c] sarcoplasmic reticulum Ca^{+2}–ATPase inhibitors,[28d] anticancer,[28e] also used as herbicides and pesticides in agriculture industry.[29]

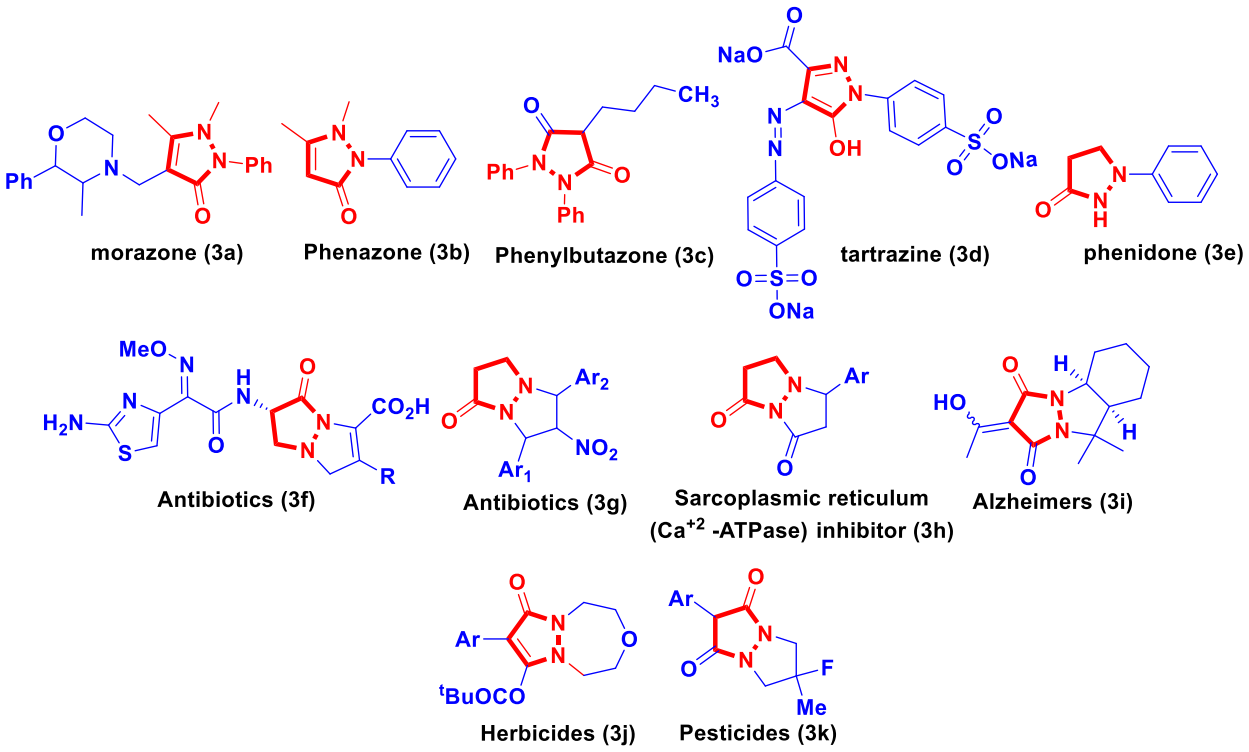

Figure-3: *Representative biologically importance of pyrazolones and pyrazolidinones (**3a-3k**).*

1.4 Natural and bioactive molecules of spirooxindoles

Spirooxindole alkaloids were first isolated from *Rubiaceae and Apocynaceae* plants and considered as a family member of oxindoles natural products in nature.[30] These spirooxindoles are structurally complex molecules with a tetra-substituted carbon (quaternary) at C-3 of the indole

nucleus, is considered as an important heterocyclic moiety that constructs the core structural unit of a large family of bioactive natural/unnatural spirooxindole molecules. The spirooxindole skeleton is present in many natural products like spirotryprostatin A & B (**4a & 4b**), rhynchophylline (**4d**), horsfiline (**4e**), Coerulescine(**4f**), (+)-elacomines (**4g**), gelsemine (**4h**), and marcfortine B (**4j**) *etc*., and show many biological properties (**Figure-4A**). Several spirooxindole-based natural/unnatural products display a wide range of biological activities such as progesterone receptor modulators,[31a] NITD609 as an antimalarial drug,[31b] anti-HIV,[31c] anticancer,[31d] antitubercular,[31e] antimalarial,[31f] and MDM2 inhibitor.[31g] Because of the structural complexity and biological prominence, these compounds attract the attention of synthetic chemist. Subsequently, many methods were developed over the years for their synthesis. The [3+2]-cycloaddition and tandem (one-pot), multicomponent reactions of isatin or its derivatives in presence of metal based and organocatalysis are some of the common methods employed.[32] In many cases the synthesized compounds were tested for biological activity and found comparable with the standard drugs. As a result, these compounds have become a promising scaffold in drug discovery.[33]

On the other hand, the chemistry of heterocycles fused with three-membered ring systems has played a vital role in the field of organic and medicinal chemistry. In particular, ring structure like cyclopropane has been given significant attention owing to its potential to deliver complex heterocyclic scaffolds. Spiro cyclopropane oxindoles are interesting scaffolds found in various drug molecules and exhibit a wide range of biological and pharmaceutical applications. For example, spirocyclopropyl compound (**4o**) showed nanomolar activity as an HIV-1 non-nucleoside reverse transcriptase inhibitor,[34] although compounds of type (**4p**) exhibited promising antitumor activity (**Figure-4B**).[35] In addition to this, these scaffolds also key intermediates for making valuable molecules and natural products (±)–strychnofoline and (–)–spirotryprostatin B.[36] However, the synthetic utility and highly dense biological applications of these molecules gaining much attention in both academic and industry.

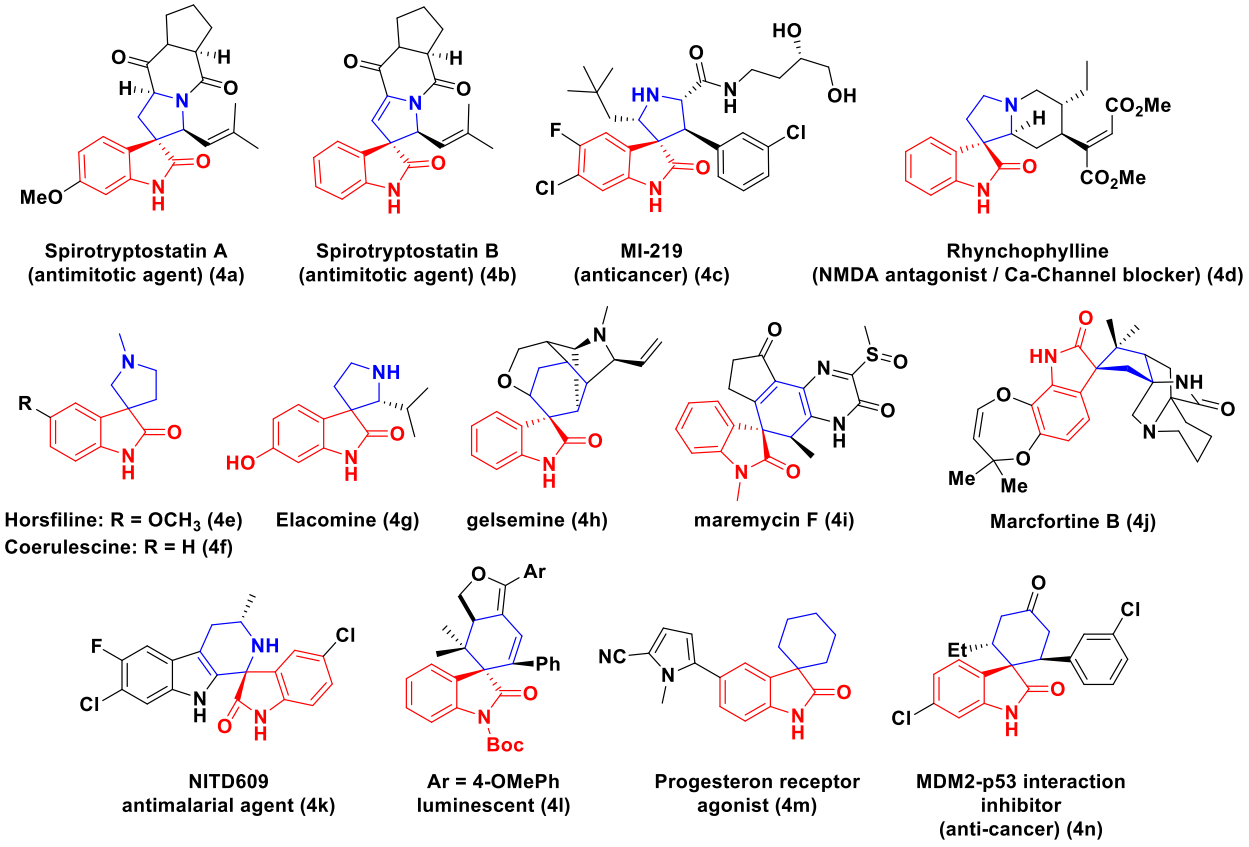

Figure-4A: *Representative biologically importance of five- and six-membered spirooxindoles.*

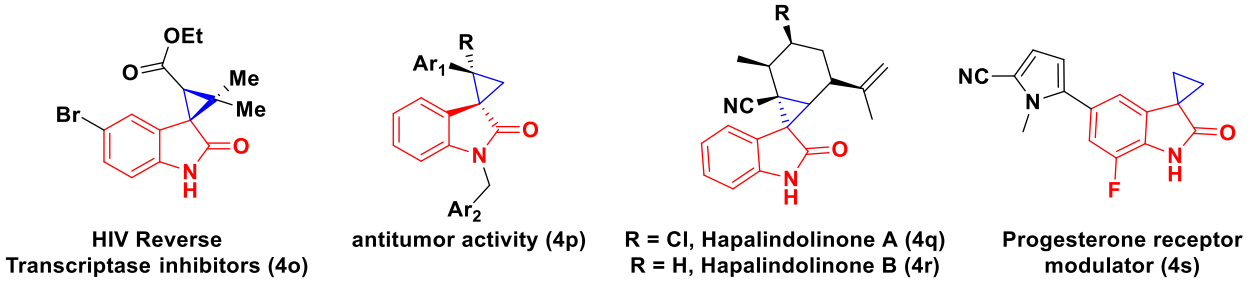

Figure-4B: *Representative biologically importance of spirocyclopropane oxindoles.*

1.5 Natural and bioactive molecules with sulfur-containing moiety

Sulfur-containing molecules are large class of significant natural products exhibit potent biological activities and pharmacological properties. These molecules are incorporated with other compounds for developing important drugs. Over 1000 sulfur-containing natural products are isolated from terrestrial organisms and other marine organisms.[37] The *Nuphar* thiaspiranes (**5a**) are a family of dimeric alkaloids that were isolated from fresh water plants *Nuphar sp*, these compounds exhibit potent *in-vitro* and *in-vivo* activity against various cancer cell lines.[38]

Dihydrothiophene sulfone (**5b**) is an another five-membered heterocycles, first isolated by Shen and co-workers[39] in 2009 from the bulbs of *Fritillaria anhuiensis* used to treat cough, and asthma. Tetrahydrothiophenes/sulfur-containing natural products (thionucleosides; **5c**) show potent antiviral activity[40a,b] antisense,[40c] antigene therapy,[40d] and enhancing the bacterial activity of *β*-lactam antibiotics (penicillin analogues; **5d**)[40e] and sulopenem (**5e**).[40f] Breynins A and B (**5f**) are novel sulfur-containing glycosides which were isolated[41a] from the Taiwanese plant *Breynia officinalis* display significant oral hypocholesterolemic activity.[41b] Biotin (**5g**) is a B-complex group of vitamins, which are synthesized by higher plants and most fungi and bacteria and play critical role in the intermediate metabolism of gluconeogenesis, fatty acid synthesis and amino acid catabolism (**Figure-5**).[42]

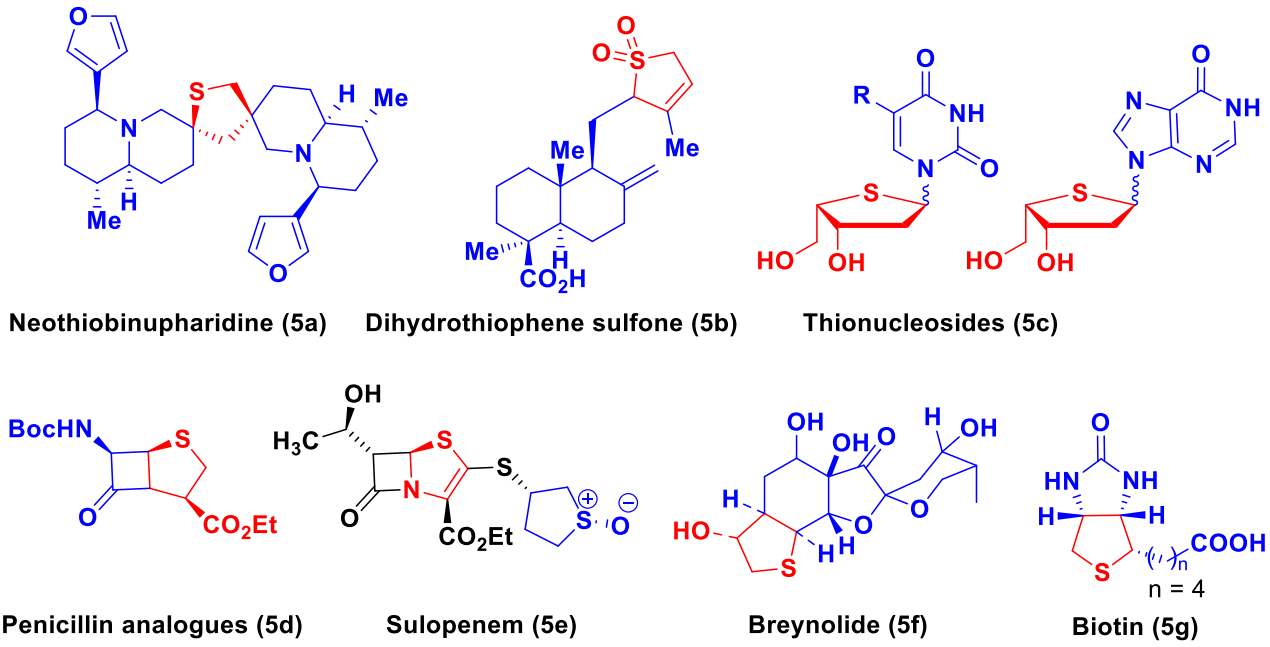

Figure-5: *Natural and biologically active sulfur-containing molecules.*

1.6 Regioselective-switchable reactions

Development of a regioselective method is highly desirable because it drastically improves the efficiency (economy, time and minimize the formation of byproduct) of a chemical process and allow the generation of complex molecules with structural diversity.[43] Switchable regioselective reactions enable the synthesis of library of molecules using similar set of starting materials by altering the reaction conditions, reagents or the catalysts.

1.7 Deep eutectic solvents (DES)

Development of environmentally benign methods is need of the hour. Over the years, many non-conventional reaction media like the use of water,[44a] glycerol,[44b] ionic liquids,[44c] perfluorinated,[44d] supercritical fluids[44e] and deep eutectic solvents (DES) have been developed. Among these, DES (popularly known as 21st century solvents) are gaining attention recently in biocatalysis,[45a] separation technology,[45b,c] electrochemistry[45d,e] and organic synthesis (cross-coupling,[45f] multicomponent, condensation and Michael addition reactions).[45g,h,i,j] DES are proven to be relatively cheaper, non-toxic and biodegradable[45a,b] compared to ionic liquids. DES are obtained by mixing of two or three safe hydrogen bond donors and hydrogen-bond acceptors as biodegradable components (from the natural source) in different ratio at room temperature or by heating (below 100 °C).[45]

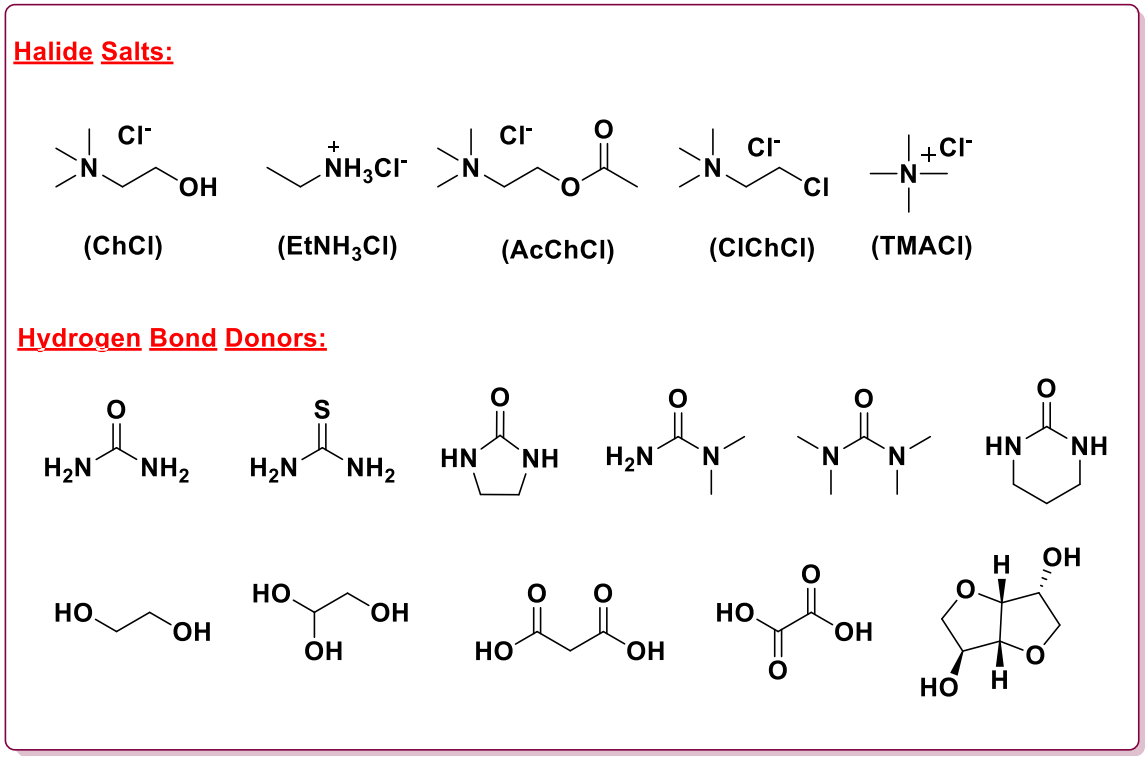

Figure-6: *Structures of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) of deep eutectic solvents (DES).*

1.8 Domino/cascade reactions

Michael addition reaction has been recognized as a powerful tool for the construction of C-C bond formation[46] whereas Domino/cascade reaction is a chemical process involving multiple bond-forming transformations occurs sequentially without adding additional catalyst or reagent, where the process of each step depends on the compounds/intermediates that are formed in previous step.[47] These reactions attracting in synthetic organic and medicinal chemistry for the preparation of complex molecules using simple starting materials, providing atom economy, reducing chemical waste and time, avoiding purification of intermediates and environmental friendliness. Recently domino/cascade reactions extensively used for the synthesis of natural products and other interesting scaffolds, total synthesis and processing chemistry.[48]

1.9 Catalyst-free conditions

Though many organic compounds are insoluble in water, the natural abundance, non-toxic, and non-flammable properties make water as a preferred reaction medium.[49-52] It is the first priority solvent because of the development of "on-water" and "in-water" concepts in which formation of aggregates *via* hydrophobic interactions with organic molecules is the key for the formation of product in organic trasformation.[51,53]

1.10 Organocatalysis

Organocatalysts are small organic compounds[54,55] consisting of carbon, hydrogen, sulfur and other nonmetal elements, plays vital role in both synthetic and medicinal chemistry because of low cost, large chiral pool, insensitive to moisture and environmental ecofriendly. Researchers reported several organo chiral catalysts such as *L*-proline, cinchona alkaloids, thiourea, squaramides, ionic liquids and various amino acids **(Figure-7)** show more enantioselectivity. There are various activation strategies including non-covalent catalysis *via* hydrogen-bonding,[56] phase transfer,[57] Bronsted acid,[58] Bronsted base[59] and covalent catalysis *via* Lewis base[60]. Among commonly used chiral organic molecules, amine–thiourea have been intensively investigated for promoting carbon–carbon and carbon–heteroatom bond formation *via* hydrogen-bonding interactions between substrates and catalysts.[61] Recently, urea (thiourea) or squaramide-based organocatalysts have been widely used in asymmetric catalysis due to their strong activation of carbonyl[62] and nitro[63] groups through efficient double-hydrogen-bonding interactions **(Figure-7)**.

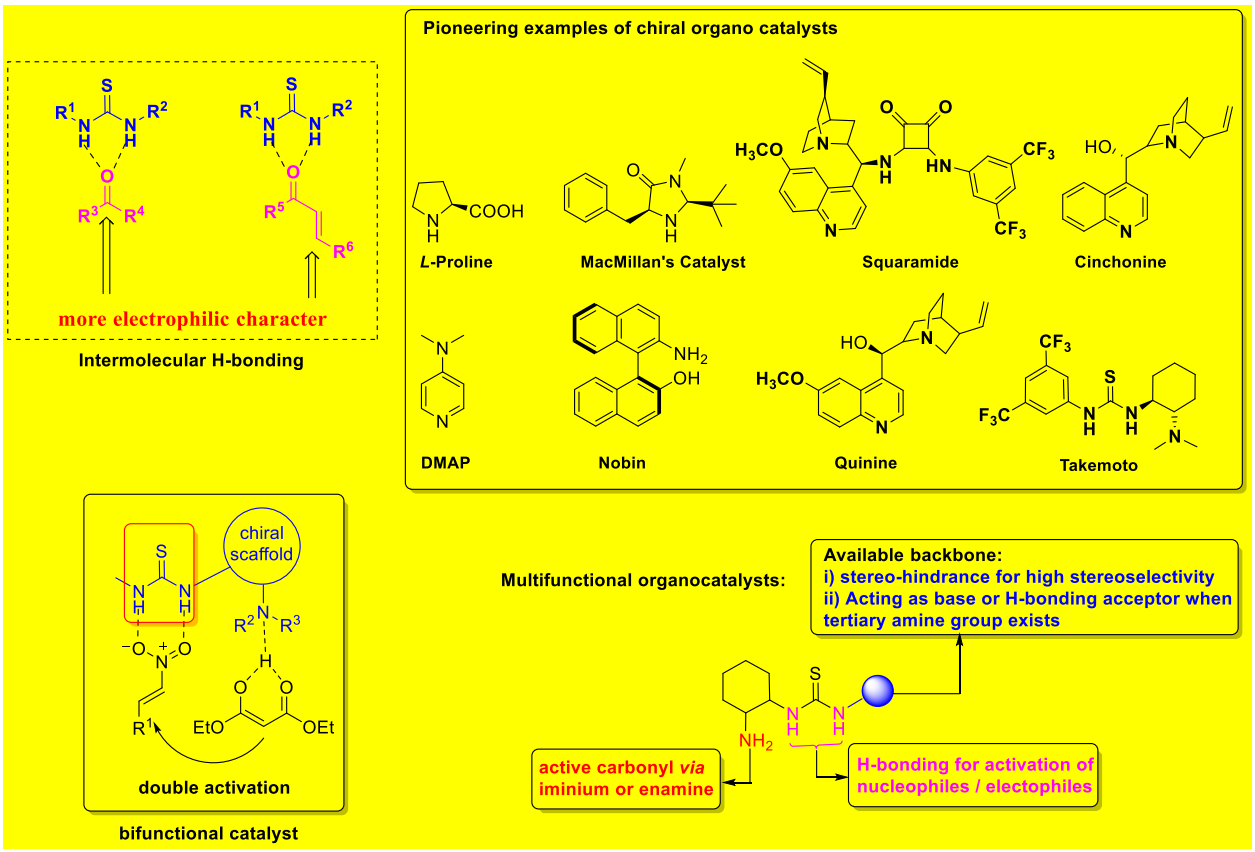

Figure-7: *Various activation strategies of chiral organocatalysis.*

1.11 Objectives of the thesis

Particularly, Spirooxindoles are possessing wide spectrum of biological activities and also play important role in synthetic organic, medicinal, material and pharmaceutical chemistry. Numerous methods have been reported for their synthesis with the aim of developing those molecules with superior biological activity. As a result, in recent years the heterocyclic synthetic organic chemistry has rapidly growing in both academic and industry. In this regard, green protocols such as one-pot approach, transition metal-free, alternative reaction media (Water, ionic liquids, deep eutectic solvents and organocatalysis) conditions are the emerging techniques for the synthesis heterocyclic compounds under the green chemistry principles. Hence, the development of new synthetic routes for synthesis of heterocyclic compounds using mild and non-toxic reagents is a crucial goal for chemist. In view of all these, the present thesis is aimed to the development of synthetic methods for the construction and functionalization of heterocyclic molecules based on chromenes, spirochromenes, dinitrogen-fused pyrazolones, spirooxindoles, spirocyclopropanes and tetrahydrothiophenes using green chemistry concepts (on-water, catalyst-free, one-pot and

multicomponent reactions), homogeneous catalysis conditions. Based on the chemistry, the thesis entitled ***"Synthesis and functionalization of spirooxindoles using organic bases, organocatalytic and catalyst-free conditions"*** is divided into following chapters as given below.

Chapter-II deals with the development of a synthetic method based on one-pot three-component reactions for the generation of 2-(methylamino)-3-nitrospiro-[chromene] and *N*-methyl-3-nitro-4*H* chromen-2-amines using deep eutectic solvent (DES) and water as reaction media.

In the **Chapter-III,** the synthesis of spiro pyrazolone-oxindole and bicyclic pyrazolone derivatives is described *via* solvent dependent regioselective aza-1,4/1,6-Michael and intramolecular cyclization under catalyst-free conditions.

Chapter-IV deals with the synthesis of spiro[indoline-3,2'-naphthalene]-4'-carbonitriles *via* regiodivergent domino protocol of isoxazole-oxindole styrenes and vinyl malononitriles.

Chapter-V is about base mediated synthesis of barbiturates/spirooxindole based cyclopropane hybrids using onium ylides at room temperature.

Chapter-VI is on the synthesis of aminoalkylnaphthol-based chiral organo catalysts and their applications for Michael, Aldol, vinylogous Henry-type and domino/cascade reactions.

The synthesis of the title compounds, present strategy, findings and experimental data will be discussed briefly in the following chapters and sections.

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CHAPTER-II

Dimethylurea/L-Tartaric acid as deep eutectic solvent for one-pot synthesis of 2-(methylamino)-3-nitrospiro-[chromene] and *N*-methyl-3-nitro-4*H* chromen-2-amines

CHAPTER-II

2.1 Introduction

The development of novel heterocyclic compounds from simple and easily accessible starting components is of significant importance in pharmaceutical and medicinal chemistry. Oxygen-containing heterocyclic compounds such as chromene and spirochromenes present in many natural products and biological active molecules (**Chapter-I; Figure-1**).[1a] During the past few decades, different type of methods have been reported in the literature for the synthesis of these molecules *via* (i) addition of malononitrile to olefins based phenols[1b] (ii) conjugate addition of nucleophiles on electrophilic 2-iminochromene[1c] (iii) addition of nucleophile on *α,α*-dicyanoolefins[1d] (iv) [4+2]-cycloaddition reactions using organocatalysts[1e] and (v) Knoevenagel-Michael-cyclization reactions.[1f] All these methods includes the use of Lewis acids or bases, heterogeneous catalysts, ionic liquids (ILs), chiral organocatalysts, catalyst-free and solvent-free conditions were employed for the synthesis of divergent heterocyclics.

2.1.1 Use of (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine for the synthesis of different heterocyclics and 4*H*-chromen-5-ones and spiro-4*H*-pyrans

(*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM)[2a] is fascinating building block for the synthesis of functionalized 1,4-dihydropyridines, pyridines, pyrimidines, pyridinones, pyrimidinones, pyrroles, quinoxalines, pyrroles, thiophenes, chromenes and spirochomenes (**Figure-2.2**). NMSM is an excellent and versatile amphipathic intermediate bearing electrophilic and nucleophilic nature because it contains both electron releasing alkylamino as well as an electron-withdrawing nitro group at the adjacent olefinic carbon (**Figure-2.1**).[2b] The unique properties of NMSM is useful for the construction of O-/N- heterocyclic compounds in one pot multicomponent approach.

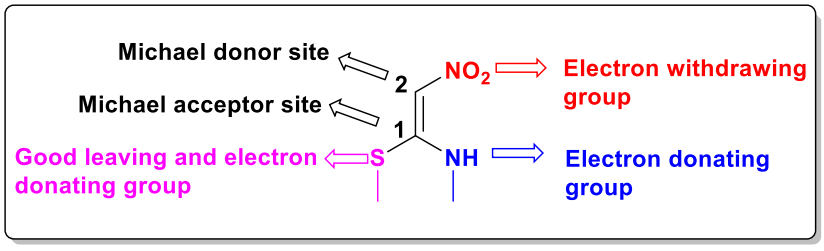


Figure-2.1: *The special reactive profile of NMSM.*

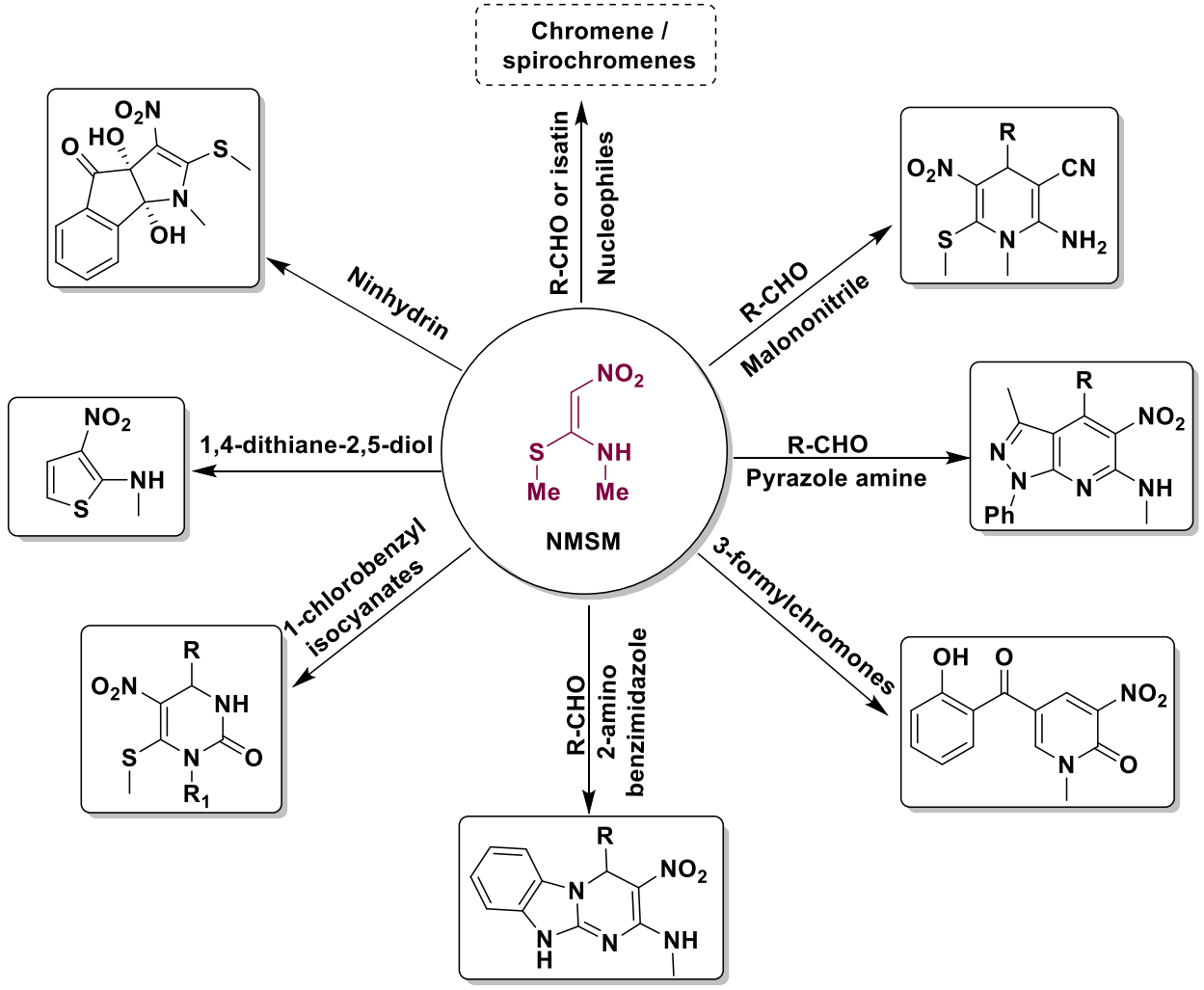
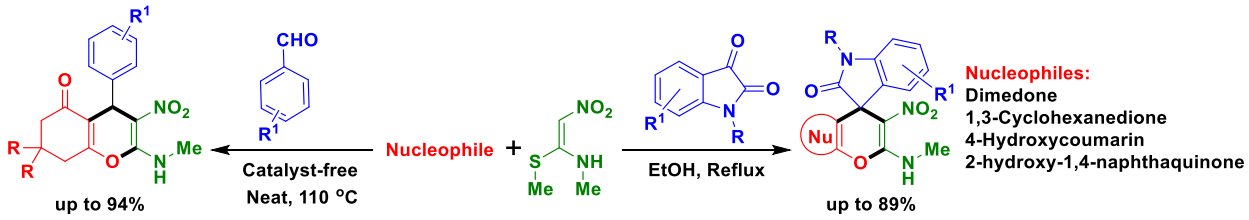


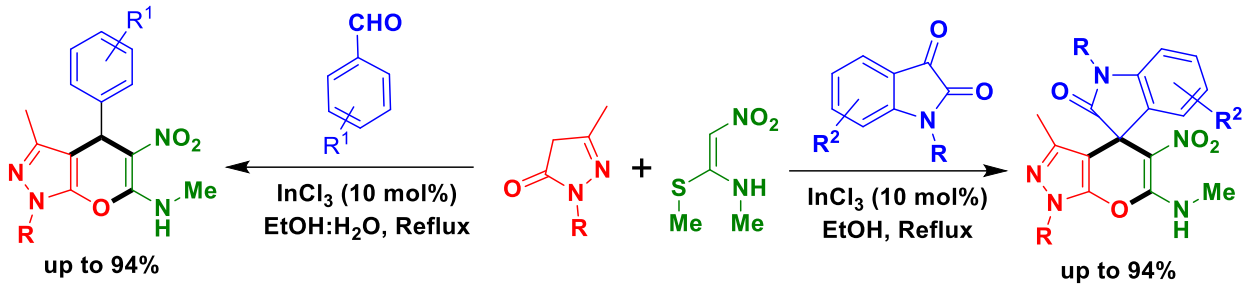
Figure-2.2: *Different methods for the synthesis of 5 and 6-membered heterocyclics using NMSM.*

In this connection, **Saigal** and his co-workers demonstrated to the synthesis of a short combinatorial library of 4*H*-chromen-5-ones using one-pot three component approach under catalyst and solvent-free conditions at 110 ^{o}C. The reaction occurred in between cyclic *β*-dicarbonyl, aryl aldehydes and NMSM in a short time with high yields.[3a] Later same group also developed an environmentally benign protocol for the synthesis of fused spiro-4*H*-pyran derivatives in good to excellent yields from the reaction of isatins, oxygen containing cyclic-1,3-dinucleophiles, and NMSM in the absence of the catalyst (**Scheme-2.1)**.[3b]



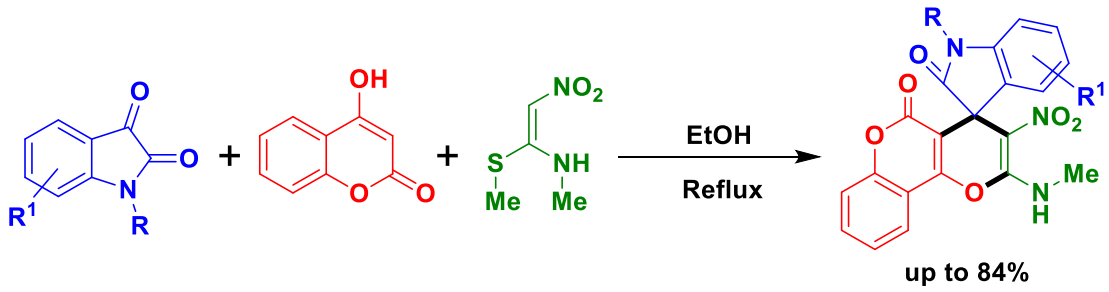
Scheme-2.1: *Synthesis of functionalized 4H-chromen-5-ones and spiro-4H-pyrans.*

Survase et al. developed a high-yielding $InCl_3$-mediated regioselective method for the synthesis of spiro-pyrans *via* a domino, one-pot reaction of aromatic aldehydes, pyrazolones and NMSM.[4a] On the other hand, **Poomathi et al.** introduced a new class of pyrazole-fused 4*H*-pyran derivatives using pyrazolones and NMSM with isatins in the presence of above mention catalyst in aqueous ethanol afforded excellent yields up to 94% (**Scheme-2.2)**.[4b]



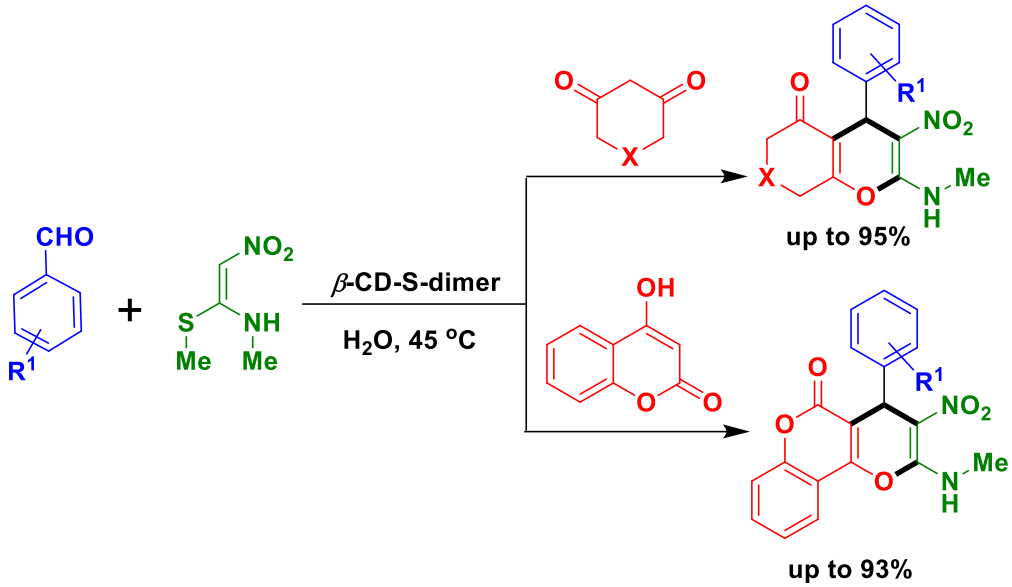
Scheme-2.2: *Synthesis of functionalized pyrazole-fused spiro pyran derivatives.*

S. Ghadiri et al. synthesized a new series of isatin-based spiro-fused compounds *via* three-component reaction of *N*-alkyl-1-(methylthio)-2-nitroethenamine derived from the addition of various amines to nitroketene dithioacetal with isatin derivatives and 4-hydroxycoumarin in ethanol as a solvent at reflux condition with good yields (**Scheme-2.3)**.[5]



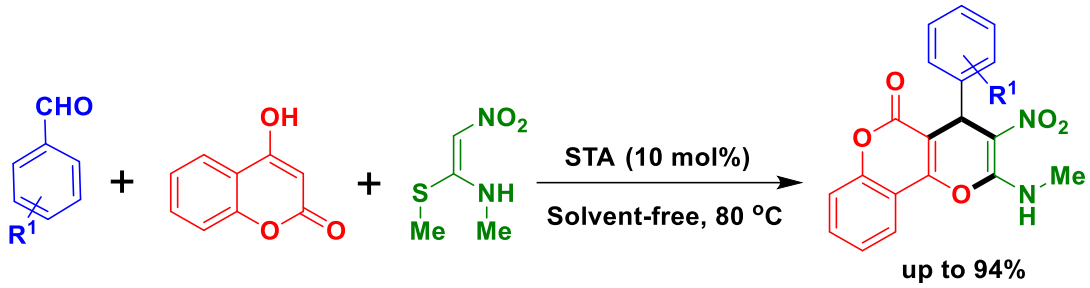
Scheme-2.3: *Synthesis of isatin-based spiro-fused compounds.*

Shinde and his co-workers reported the use of NMSM for the construction of biologically active chromenone and pyranochromene derivatives *via* a three-component reaction using 6,6'-thiobis-(methylene)-*β*-cyclodextrin dimer as a reusable catalyst in aqueous medium. They have also described the synthetic procedures of dimeric *β*-cyclodextrin linked by a thio-methylene bridge as a supramolecular host (**Scheme-2.4**).[6]



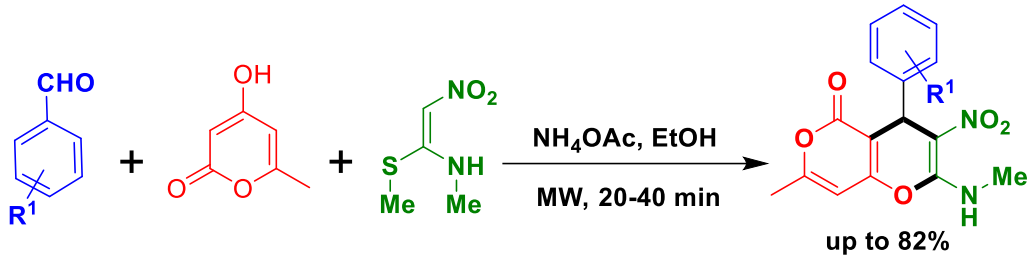
Scheme-2.4: *Synthesis of chromene and pyrano chromene derivatives.*

Later, **Jadhav** and his co-workers described a new approach for the synthesis of pyrano[3,2-*c*] chromen-5-ones using NMSM and aromatic aldehydes. The reaction was carried out under solvent-free condition in presence of silica supported tungstic acid (STA) in a catalytic amount and they also showed recyclability of the catalyst up to the 4th cycle and achieved excellent yields up to 94% (**Scheme-2.5**).[7]



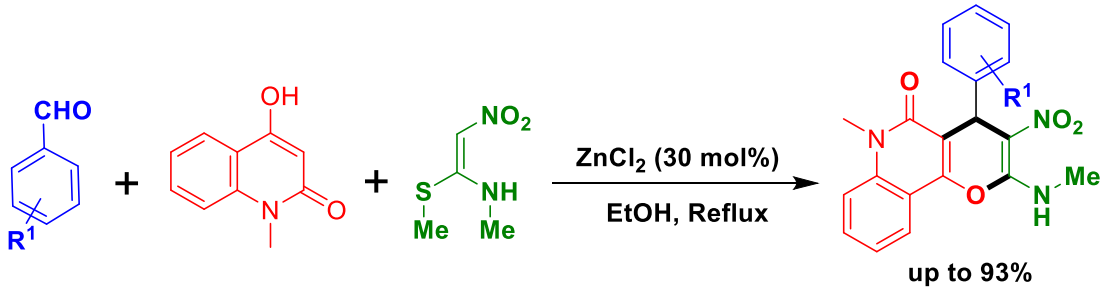
Scheme-2.5: *Synthesis of functionalized pyranochromen-5-one derivatives.*

Mao et al. developed an efficient method for the synthesis of new type of coumarin-fused pyrano[4,3-*b*] pyran-5-one derivatives using 4-hydroxy-6-methyl-2-pyrone, aromatic aldehydes and NMSM as a key substrate. The compounds were synthesized by irradiating the substrates in a microwave oven in the presence of ammonium acetate using EtOH as a solvent afforded with good yields (**Scheme-2.6)**.[8]



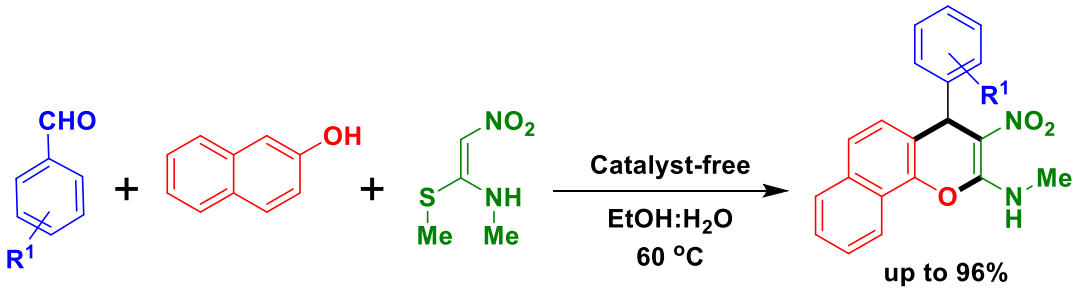
Scheme-2.6*: Synthesis of functionalized coumarin-fused pyran derivatives.*

Gunasekaran et al. applied NMSM for the construction of quinoline-fused pyrano chromene derivatives. The resulting compounds were synthesized using $ZnCl_2$-catalyzed three component reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one, aromatic aldehydes and NMSM in ethanol obtained with good to excellent yields (**Scheme-2.7)**.[9]



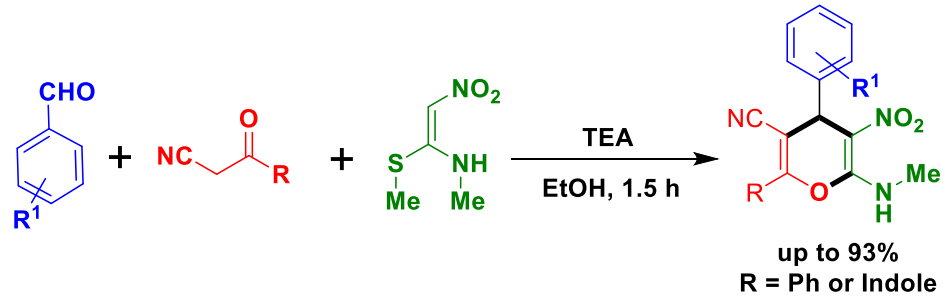
Scheme-2.7: *Synthesis of quinoline-fused pyran derivatives.*

Reddy et al. also reported a three-component reaction of various aromatic aldehydes, 2-naphthol and NMSM for the synthesis of benzo[*f*]chromen-3-amine derivatives (**Scheme-2.8)** under catalyst-free condition using a greener reaction medium (EtOH: H_2O mixture).[10]



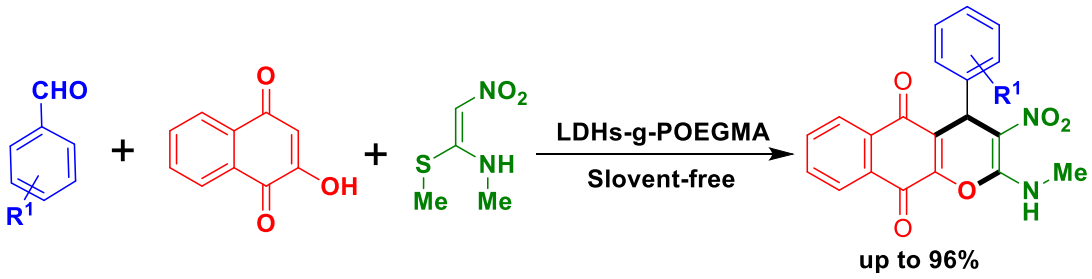
Scheme-2.8: *Synthesis of functionalized benzochromen derivatives.*

Sivakumar and his coworkers explored for the synthesis of simple 4*H*-pyrano chromenes. They were synthesized a series of novel 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro- 4-aryl-4*H*-pyran-3-carbonitriles and 6-(methylamino)-4-(aryl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitriles in the presence of TEA as a base *via* the three-component domino reactions of aryl aldehydes, α-cyano ketones and NMSM, respectively (**Scheme-2.9)**.[11]



Scheme-2.9*: Synthesis of indole-containing 4H-pyran derivatives.*

In 2018, **S. K. Krishnammagari et al.** demonstrated a simple protocol for the synthesis of benzo[*g*]chromene-5,10-diones under solvent-free conditions using poly (oligoethylene glycol methacrylate)-*g*-supported double hydroxides (LDHs-g-POEGMA) as a reusable heterogeneous catalyst. The scope of the reaction was also envisaged in the cyclic system (2-hydroxy-1,4-naphthoquinone) with aromatic aldehydes and NMSM and obtained the desired products with excellent yields (**Scheme-2.10)**.[12]



***Scheme-2.10**: Synthesis of the functionalized benzo[g]chromene-5,10-diones.*

Though these reports are good methods for the generation of complex chromene and spirochromene compounds using NMSM, there is a scope for further simplifying the reaction conditions under greener/better conditions. Considering this, and in continuation with our efforts of developing synthetic methods under homogeneous conditions,[13a,b] we applied our reported method (L-Proline and Melamine; 3:1 in DMSO, RT) for this reaction but the attempts were futile even at 80 °C (**Scheme-2.11**). Moreover, as mentioned in the introduction part (**Chapter-I**), the DES are finding lot of applications in organic synthesis and have been used for multicomponent reactions. However, to best of our knowledge, there is no report so far on the use of DES for the generation of spiro compounds using NMSM as starting material. In this context, herein we wish to report a new method for the construction of chromene and spirochromene/spirooxindole derivatives using deep eutectic solvent (DES)/water as green reaction medium in short reaction times (both methods) with excellent yields.

2.2 Present study

Considering the biological importance of chromene and spirochromenes and with the objective of developing simple and green conditions, herein, we describe an application of dimethyl urea and L-tartaric acid as deep eutectic solvent (DES) is demonstrated for the synthesis of 2-(methylamino)-3-nitrospiro[chromene] and *N*-methyl-3-nitro-4*H*-chromen-2-amines by a reaction of substituted isatins/pyrazole aldehydes, nucleophiles and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine. Systematic studies proved that the dimethyl urea and L-tartaric acid in 2:1 ratio at 80 °C gave the desired products in good yields in shorter period of reaction time. This method was extended for water as reaction medium and good yields of the products were obtained.

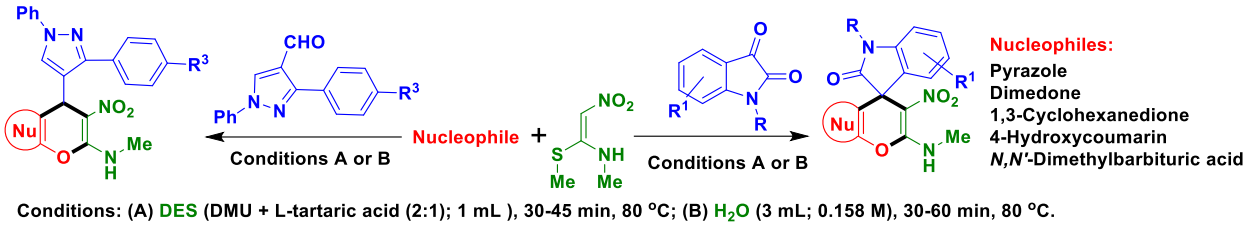
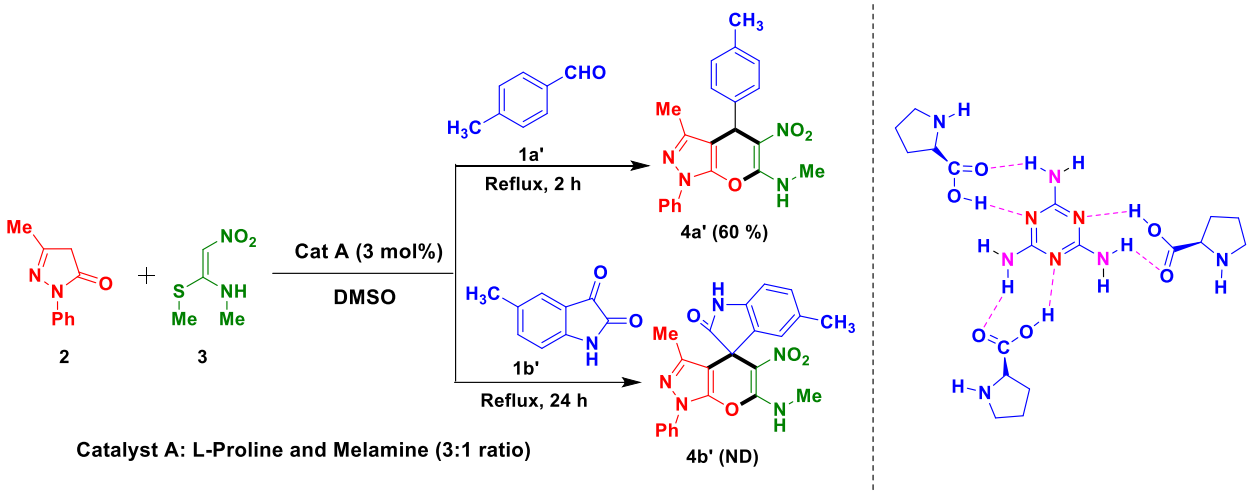


***Figure-2.3:** Synthesis of chromene and spirochromenes under green conditions.*

2.3 Results and Discussion

Owing to the biological importance of chromene and spirochromenes and in our continuous interest in sustainable organic transformations, we planned for the synthesis of chromene and spirochromenes using (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine. Initially, a model reaction of aldehyde (**1a'**), pyrazole (**2**) and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**3**) in presence of L-proline and melamine (3:1 ratio) as catalyst in DMSO at room temperature[13b] could not afford the desired product but the same reaction under heating conditions (80 ^{o}C) gave **4a'** in 60% yield in 2h. After confirmation of the product, similar condition was applied for isatin (**1b'**) but the desired product (**4b'**) was not formed even after prolonged reaction time (24 h) (**Scheme-2.11**). Then the above reaction was carried out in Ethanol under catalyst-free condition (50 °C in 6 h) leading to formation of the product **4b'** in 50% yield (**Table-2.1; entry-3**). The formation of the desired product was confirmed by ^{1}H, ^{13}C NMR and mass spectral data.



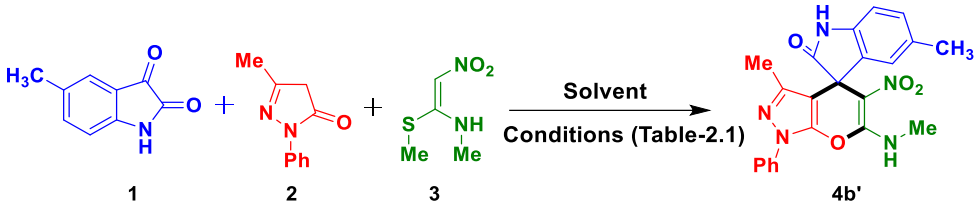
Scheme-2.11: *One-pot three-component synthesis of chromene and spirochromenes.*

After confirmation of the product, next task was to optimize the reaction conditions. Thus, the reaction was carried out in methanol and ethanol at 80 ^{o}C without catalyst (**Table-2.1; entries 4–5**) in which EtOH could give the desired product **4b'** in 70% yield in 6 h. Towards finding the best reaction conditions (time and yield), we choose deep eutectic solvent as reaction medium. Accordingly, above reaction was performed using urea-choline chloride and urea-$ZnCl_2$ as deep eutectic solvent (**Table-2.1; entries 6–8**). However, both the conditions fail to give the desired product (**4b'**). Then, efforts were continued using different combinations of DES [DMU + $ZnCl_2$, DMU + ChCl, $SnCl_2$ + ChCl, Ethylene glycol + ChCl, $ZnCl_2$ + ChCl, L-tartaric acid + ChCl,

Proline + Oxalic acid and Proline + L-tartaric acid] in different ratio (**Table-2.1; entries 9–22**), which afford desired product in 20-80% yields in 60 min at 80 ^{o}C. Following these results, changing the reaction medium to dimethyl urea + oxalic acid, dimethyl urea + citric acid and dimethyl urea + L-tartaric acid in different combinations gave product **4b**' in good yields in 30 min at 80 ^{o}C (**Table-2.1; entries 23–31**). Among the screened combinations, dimethyl urea + L-tartaric acid (2:1) was found to be superior in terms of product yield (90%) and reaction time (30 min) at 80 ^{o}C. To explore further to find green method, the same experiment was performed using water as solvent at 80 ^{o}C. To our delight, the product **4b**' was obtained in 95% yield in 1 h (**Table-2.1; entry-32**).

With the optimization condition in hand, protocol was explored for structurally different isatins (substitution on aromatic ring and nitrogen), nucleophiles (pyrazole, dimedone, 1,3-cyclohexanedione, 4-hydroxy coumarin and *N, N′*-dimethyl barbituric acid) and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine under both conditions (both in DES and water) to a library of spirochromene hybrids with good yields as shown in **Figure-2.4**. The structures of all the obtained products were confirmed by NMR and mass spectroscopic data. Keeping in view of the biological activity of pyrazole-chromene hybrids (**1c-d**) (**Chapter-I; Figure-1**), we extended this method for the synthesis of different chromene hybrids with pyrazole moiety. Thus, the reaction of pyrazole aldehyde (**7**; prepared *via* literature methods) dimedone (**2**), and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**3**) under the optimized reaction conditions in DES and water (as reaction media) gave the products with excellent yields up to 92% **(Figure-2.5)** in shorter reaction times. Later, various nucleophiles (dimedone, 1,3-cyclohexanedione and 4-hydroxy coumarin) were treated with pyrazole aldehyde and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine under optimized conditions to generate functionalized pyrazole-chromene hybrids with excellent yields both in DES and water (catalyst-free conditions). All the products obtained were characterized using spectroscopic data.

Table-2.1: Optimization of the reaction conditions for the synthesis of compound **4b'**[a]



1 2 3 4b'

Entry	Solvent	Temp (°C)	Time (h)	Yield (%) [b]
1	DMSO [L-proline and melamine (3:1)]	RT	24	ND
2	DMSO [L-proline and melamine (3:1)]	80	24	ND
3	EtOH	50	6	50
4	MeOH	80	6	Trace
5	EtOH	80	6	70
6	Urea + ChCl (1:1)	80	1	ND
7	Urea + ChCl (2:1)	80	1	ND
8	Urea + $ZnCl_2$ (2:1)	80	1	trace
9	DMU + $ZnCl_2$ (1:1)	80	1	20
10	DMU + $ZnCl_2$ (2:1)	80	1	55
11	DMU + $ZnCl_2$ (3:1)	80	1	40
12	DMU + ChCl (1:1)	80	1	70
13	DMU + ChCl (2:1)	80	1	60
14	DMU + ChCl (3:1)	80	1	50
15	$SnCl_2$ + ChCl (1:1)	80	1	50
16	$SnCl_2$ + ChCl (2:1)	80	1	80
17	$SnCl_2$ + ChCl (3:1)	80	1	70
18	Ethylene glycol + ChCl (2:1)	80	1	80
19	$ZnCl_2$ + ChCl (2:1)	80	1	25
20	L-tartaric acid + ChCl (2:1)	80	1	50
21	Proline + Oxalic acid (1:1)	80	1	30
22	Proline + L-tartaric acid (1:1)	80	1	70
23	DMU + Oxalic acid (1:1)	80	1	50
24	DMU + Oxalic acid (2:1)	80	1	60
25	DMU + Oxalic acid (3:1)	80	1	55
26	DMU + Citric acid (1:1)	80	0.5	75
27	DMU + Citric acid (2:1)	80	0.5	85
28	DMU + Citric acid (3:1)	80	0.5	80
29	DMU + L-tartaric acid (1:1)	80	0.5	80
30	**DMU + L-tartaric acid (2:1)**	**80**	**0.5**	**90**
31	DMU + L-tartaric acid (3:1)	80	0.5	85
32	**H_2O (3 mL; 0.158 M)**	**80**	**1**	**95**

[a] All the reactions were performed with 0.475 mmol of isatin. [b] Isolated yields.

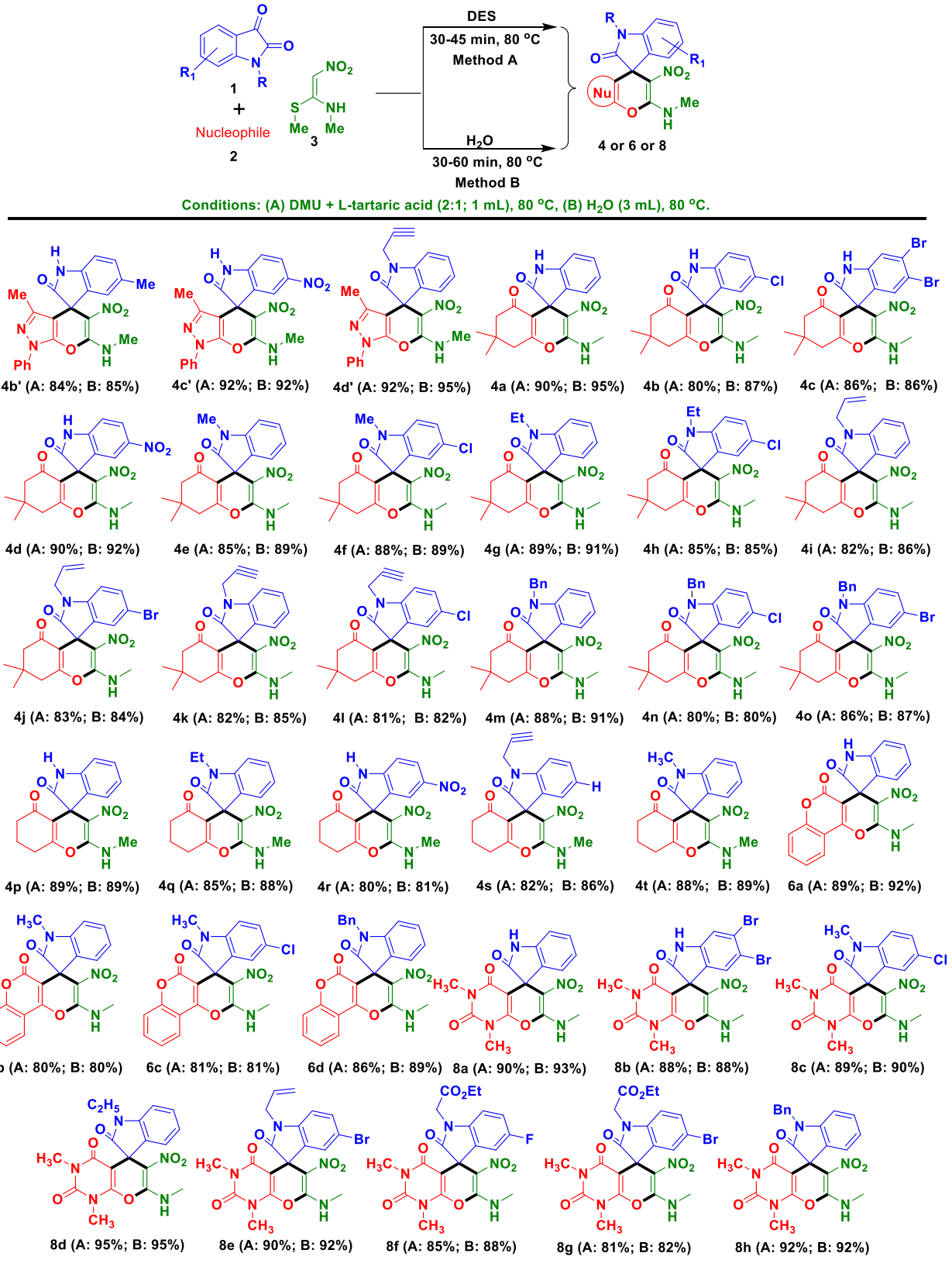


Figure-2.4: *Various spirochromene derivatives (**4-6**) under optimized reaction conditions.*

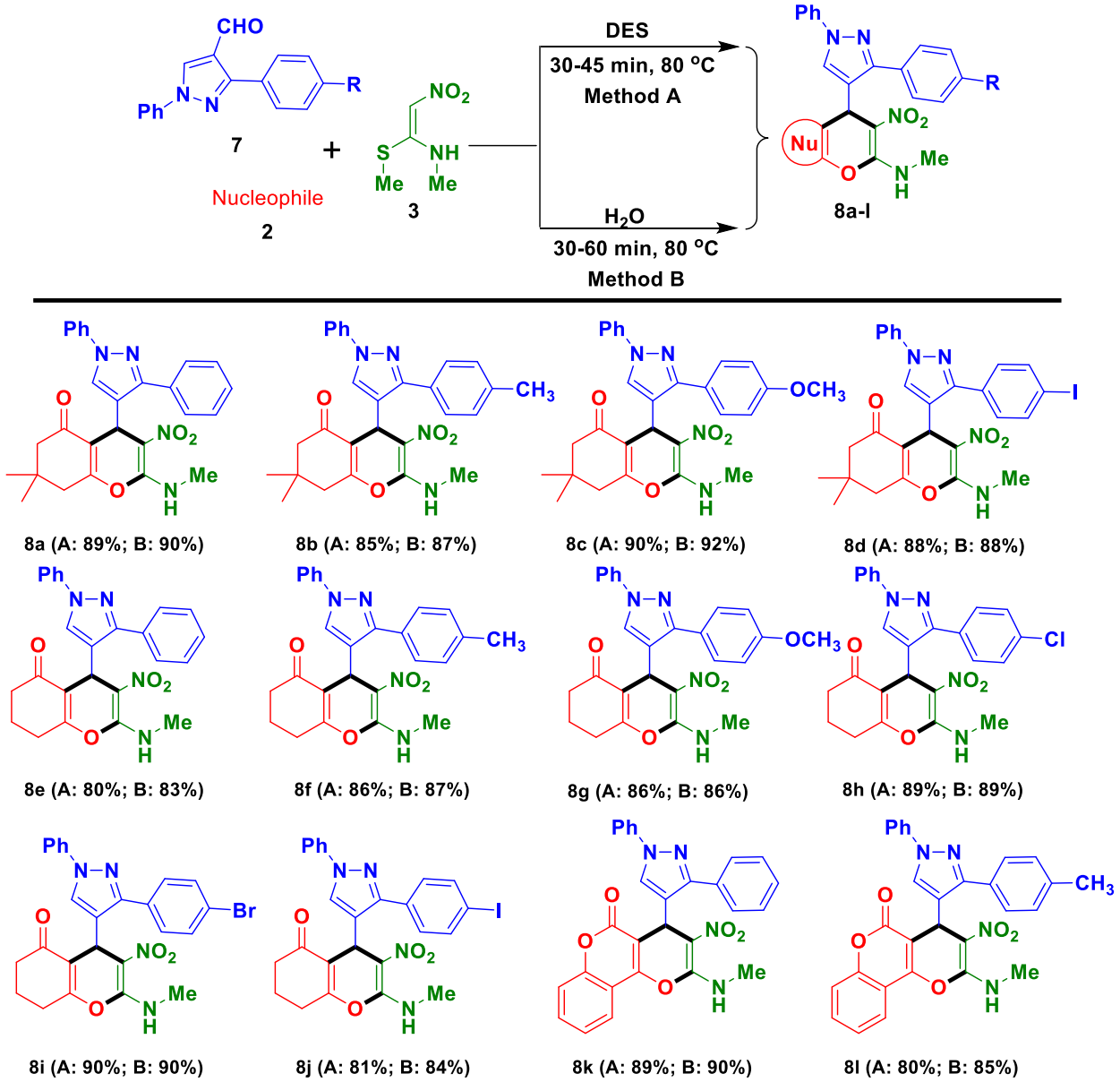


Figure-2.5: *Synthesis of chromene derivatives (**8a-l**) under optimized condition.*

Based on the experimental observations, we proposed a plausible mechanisms as shown in **Figure-2.6; A and B**. The DES induces the keto-enol tautomerism in dimedone. The activated dimedone (Enol form) undergo Knoevenagel condensation with isatin (The both carbonyl groups are accociated with DES *via* intermolecular hydrogen bonding) afforded intermediate (**I**), which act as Michael acceptor, the adduct (**I**) immediately undergoes Michael type addition with (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine to generate intermediate (**II**). Subsequent imine-enamine tautomerism of (**II**) afforded intermediate (**III**) followed by intramolecular *O*-cyclization

to give the product (**4a**). The water mediated reaction follow on-water concept.[14] The water induces enolization in dimedone. Simultaneously the isatin is activated and react with enolic form of dimedone to give Knoevenagel product followed by Michael addition, imine-enamine tautomerism and *O*-cyclization as shown in **Figure-2.6; B**.

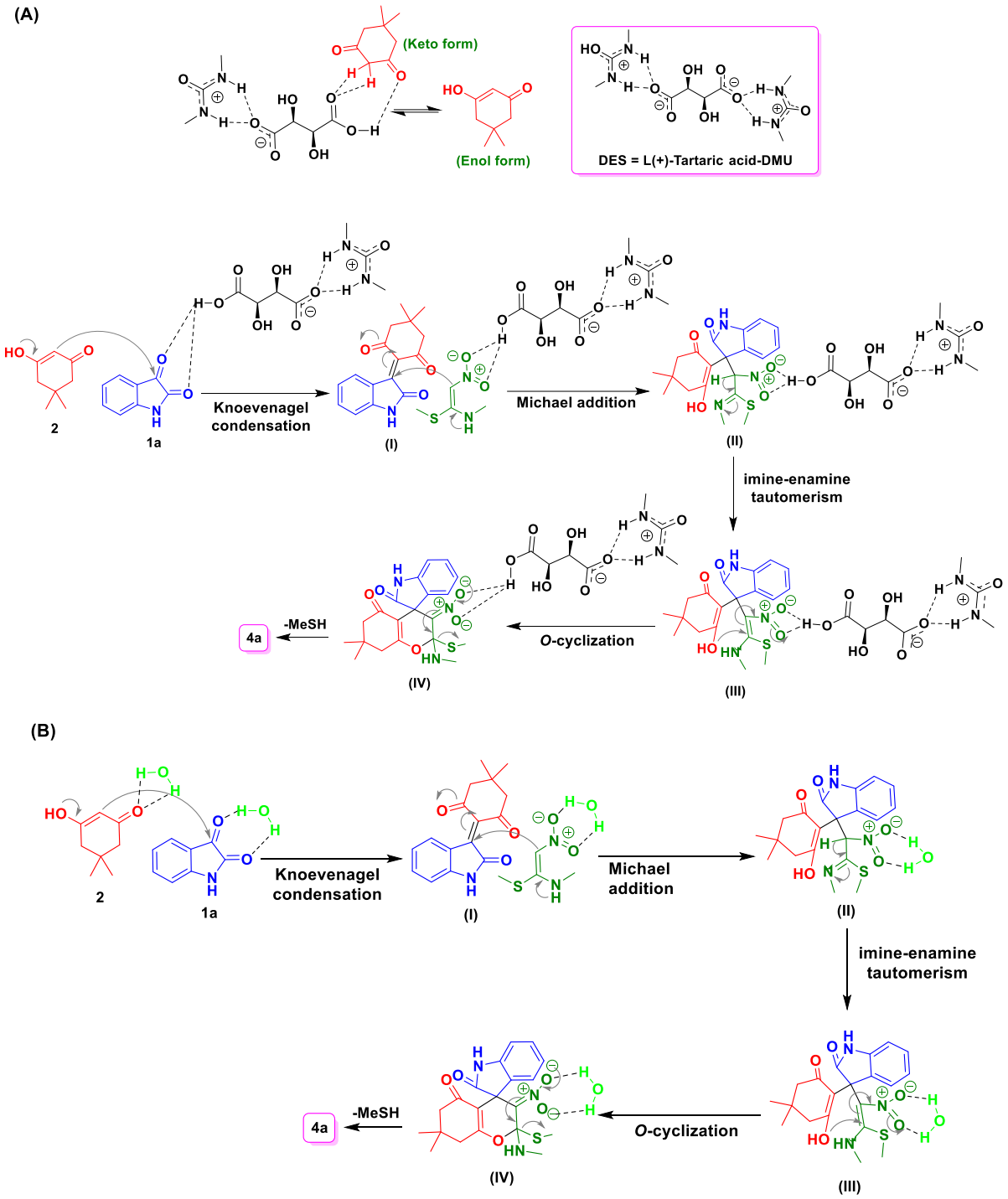


Figure-2.6: *Plausible mechanism for the reaction, (**A**) for DES and (**B**) for Water.*

2.4 Conclusion

In summary, we have developed a new efficient protocol for the synthesis of chromene and spirochromene derivatives using dimethylurea/L-tartaric acid as deep eutectic solvent. The reaction proceeds *via* Knoevenagel condensation, Michael addition, imine-enamine tautomerism followed by *O*-cyclization. This procedure offers notable advantages such as catalyst-free, environmentally benign reaction conditions and good yields of the products.

2.5 Experimental section

General: All the solvents and required chemicals were procured from SD-Fine, Sigma-Aldrich, and Spectrochem, and used without purification and distillation. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Avance 500 and 400 spectrometers using DMSO-d_6 as solvents and reported in δ ppm. The mass spectra of all the compounds were record using Agilent Technologies-6530.

2.5.1 General procedure

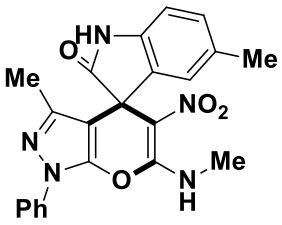
General procedure for the one-pot synthesis of chromene and spirochromenes

Method-A: A mixture of isatin/pyrazole aldehyde (0.475 mmol, 1 equiv), Nucleophile (0.475 mmol, 1 equiv) and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine (0.475 mmol, 1 equiv) was stirred at 80 °C in DMU+L-tartaric acid (2:1) (DES, 1mL). The progress of the reaction was monitored by TLC. After this period, the mixture was treated with water and extracted with EtOAc (2X10 mL). The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Evaporation of the solvent gave the crude product, which was further recrystallized from ethanol to afford the pure products.

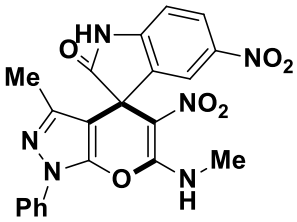
Method-B: A mixture of isatin/pyrazole aldehyde (0.475 mmol, 1 equiv), Nucleophile (0.475 mmol, 1 equiv) and (E)-*N*-methyl-1-(methylthio)-2-nitroethenamine (0.475 mmol, 1 equiv) was stirred at 80 °C in water (3 mL). The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled and filtered. Then the precipitate washed with cold water (2X5 mL) and the crude product was recrystallized from ethanol to afford the pure products.

2.6 Spectral data

3',5-dimethyl-6'-(methylamino)-5'-nitro-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c] pyrazol]-2-one (4b′): Yield = A: 84%; B: 85% (White solid); M.P: 248-250 °C, **Mass (ESI-MS):** m/z Calculated: 417.17; Observed: 418.1516 (M+1).

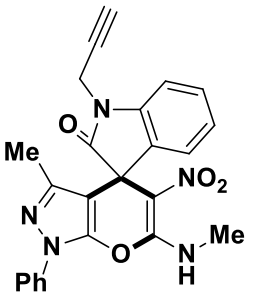


3'-methyl-6'-(methylamino)-5,5'-dinitro-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c] pyrazol]-2-one (4c′): Yield = A: 92%; B: 92% (White solid); M.P: 274-276 °C, **Mass (ESI-MS):** m/z Calculated: 448.11; Observed: 449.1216 (M+1).



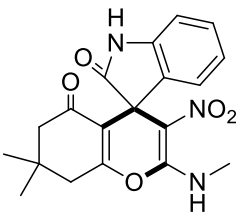
3'-methyl-6'-(methylamino)-5'-nitro-1'-phenyl-1-(prop-2-yn-1-yl)-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazol]-2-one (4d′):

Yield = A: 92%; B: 95% (White solid); M.P: 275-277 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.73 (d, *J* = 4.4 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.43 – 7.33 (m, 2H), 7.21 (dd, *J* = 19.2, 6.8 Hz, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 4.74 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.57 (dd, *J* = 17.6, 2.4 Hz, 1H), 3.32 (t, *J* = 2.4 Hz, 1H), 3.21 (d, *J* = 4.8 Hz, 3H), 1.57 (s, 3H). **Mass (ESI-MS):** m/z Calculated: 441.14; Observed: 442.1515 (M+1).

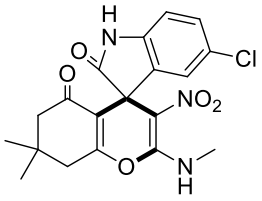


7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4a):

Yield = A: 90%; B: 95% (Light yellow solid); M.P: 302-304 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.47 (s, 1H), 10.44 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 3.11 (d, *J* = 4.4 Hz, 3H), 2.65 (q, *J* = 48.8 Hz, 2H), 2.13 (q, *J* = 53.6, 2H), 1.02 (s, 3H), 0.95 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.02, 178.26, 163.06, 157.59, 144.24, 130.99, 128.84, 122.86, 122.11, 113.07, 109.40, 107.88, 50.81, 49.18, 39.95, 31.85, 28.74, 27.92, 26.87. **Mass (ESI-MS):** m/z Calculated: 369.13; Observed: 395.1140 (M+Na).

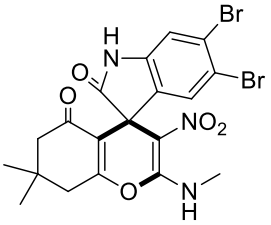


5'-chloro-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4b):



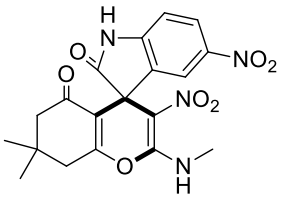
Yield = A: 80%; B: 87% (White solid); M.P: 275-277 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.59 (s, 1H), 10.50 (s, 1H), 7.22 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.11 (s, 3H), 2.65 (q, *J* = 17.6 Hz, 2H), 2.15 (q, *J* = 16.0 Hz, 2H), 1.02 (s, 3H), 0.97 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.04, 177.86, 163.38, 157.52, 143.44, 133.18, 128.50, 125.93, 123.05, 112.55, 110.53, 107.54, 50.77, 49.36, 31.90, 28.80, 27.67, 27.16. **Mass (ESI-MS):** m/z Calculated: 403.09; Observed: 426.0727 (M+Na).

5',6'-dibromo-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4c):



Yield = A: 86%; B: 86% (Light yellow solid); M.P: >310 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.91 (s, 1H), 10.51 (q, *J* = 4.4 Hz, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 3.11 (d, *J* = 5.2 Hz, 3H), 2.65 (q, *J* = 36.0 Hz, 2H), 2.16 (q, *J* = 25.6 Hz, 2H), 1.02 (s, 3H), 0.97 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 195.11, 176.76, 162.80, 157.29, 144.09, 135.10, 133.05, 125.21, 113.29, 112.80, 107.68, 102.22, 50.74, 50.26, 32.13, 29.00, 27.77, 27.46.

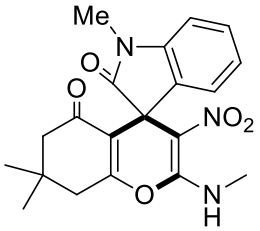
7,7-dimethyl-2-(methylamino)-3,5'-dinitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4d):



Yield = A: 90%; B: 92% (Light yellow solid); M.P: 275-277 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.59 (s, 1H), 10.50 (s, 1H), 7.22 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.11 (s, 3H), 2.65 (q, *J* = 17.6 Hz, 2H), 2.15 (q, *J* = 16.0 Hz, 2H), 1.02 (s, 3H), 0.97 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.02, 178.26, 163.06, 157.59, 144.24, 130.99, 128.84, 122.86, 122.11, 113.07, 109.40, 107.88, 50.81, 49.18, 39.95, 31.85, 28.74, 27.92, 26.87.

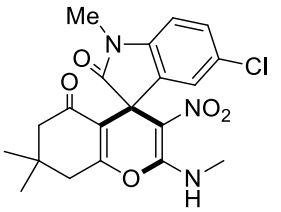
1',7,7-trimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4e):

Yield = A: 85%; B: 89% (Light yellow solid); M.P: 285-287 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.46 (d, *J* = 4.8 Hz, 1H), 7.23-7.17 (m, 1H), 7.07 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.93 – 6.86 (m, 2H), 3.14 (s, 3H), 3.11 (d, *J* = 4.8 Hz, 3H), 2.66 (dd, *J* = 42.4, 17.6 Hz, 2H), 2.10 (dd, *J* = 46.0, 16.0 Hz, 2H), 1.01 (s, 3H), 0.94 (s, 3H).**^{13}C NMR: (100 MHz, DMSO-d_6) δ** 194.80, 175.73, 162.31, 157.34, 146.33, 130.56, 128.72, 122.64, 121.99, 113.59, 107.81, 50.84, 48.51, 40.61, 40.40, 40.19, 39.98, 39.77, 39.56, 39.36, 32.10, 28.94, 28.03, 27.21, 26.95. **Mass (ESI-MS):** m/z Calculated: 383.15; Observed: 384.1456 (M+1).



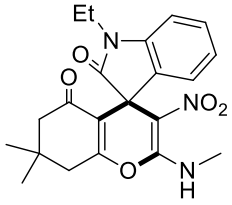
5'-chloro-1',7,7-trimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4f):

Yield = A: 88%; B: 89% (White solid); M.P: 309-311 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.51 (d, *J* = 4.8 Hz, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.15 (s, 3H), 3.12 (d, *J* = 4.8 Hz, 3H), 2.66 (q, *J* = 17.6 Hz, 2H), 2.13 (q, *J* = 16.0 Hz, 2H), 1.01 (s, 3H), 0.97 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 195.05, 175.56, 162.75, 157.38, 145.37, 132.67, 128.40, 126.10, 123.10, 112.97, 109.05, 107.49, 50.78, 48.68, 32.13, 28.97, 27.76, 27.53, 27.08. **Mass (ESI-MS):** m/z Calculated: 417.11; Observed: 440.0904 (M+Na).



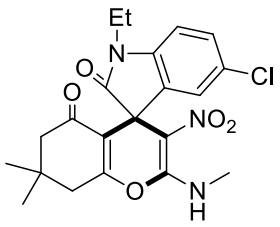
1'-ethyl-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4g):

Yield = A: 89%; B: 91% (White solid); M.P: 270-272 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.46 (q, *J* = 4.8 Hz, 1H), 7.19 (td, *J* = 8.0, 1.2 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 3.71 (q, *J* = 8.8 Hz, 2H), 3.11 (d, *J* = 5.2 Hz, 3H), 2.66 (dd, *J* = 45.6, 17.6 Hz, 2H), 2.20 – 2.02 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 3H), 0.94 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 194.75, 175.03, 162.30, 157.34, 145.32, 130.67, 128.69, 122.83, 121.74, 113.56, 107.79, 50.81, 48.56, 40.57, 40.36, 40.15, 39.94, 39.73, 39.52, 39.31, 34.82, 32.07, 28.92, 28.12, 27.12, 12.20. **Mass (ESI-MS):** m/z Calculated: 397.16; Observed: 398.1610 (M+1).



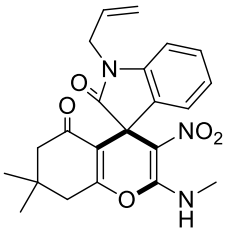
5'-chloro-1'-ethyl-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4h):

Yield = A: 85%; B: 85% (White solid); M.P: 279-281 °C**, ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.49 (s, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.25-7.20 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 3.70 (q, *J* = 7.2 Hz, 2H), 3.11 (d, *J* = 2.4 Hz, 3H), 2.65 (q, *J* = 18.0 Hz, 2H), 2.13 (q, *J* = 16.0 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 3H), 0.96 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 194.94, 174.84, 162.69, 157.37, 144.39, 132.82, 128.35, 125.84, 123.27, 112.96, 109.02, 107.58, 50.75, 48.71, 40.61, 40.40, 40.19, 39.98, 39.77, 39.56, 39.35, 34.98, 32.11, 28.97, 27.86, 27.46, 12.13**. Mass (ESI-MS):** m/z Calculated: 431.12; Observed: 454.1070 (M+Na).



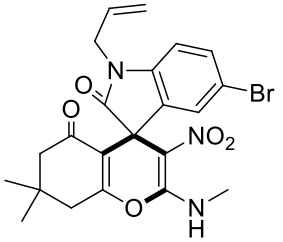
1'-allyl-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4i):

Yield = A: 82%; B: 86% (Light yellow solid); M.P: 236-238 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.49 (s, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12 – 7.08 (m, 1H), 6.91 – 6.86 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.95 – 5.84 (m, 1H), 5.53 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.19 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.36 – 4.23 (m, 2H), 3.12 (s, 3H), 2.67 (dd, *J* = 47.6, 18.0 Hz, 2H), 2.13 (dd, *J* = 51.6, 16.0 Hz, 2H), 1.03 (s, 3H), 0.94 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.20, 175.73, 162.65, 157.39, 145.41, 132.77, 130.45, 128.67, 122.72, 122.19, 117.50, 113.37, 108.58, 107.80, 50.78, 48.63, 43.08, 32.03, 28.89, 28.02, 27.09**. Mass (ESI-MS):** m/z Calculated: 409.16; Observed: 432.1483 (M+Na).

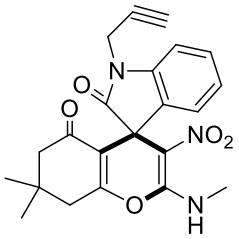


1'-allyl-5'-bromo-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4j):

Yield = A: 83%; B: 84% (White solid); M.P: 281-283 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.53 (d, *J* = 5.2 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.36 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.91-5.82 (m, 1H), 5.51 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.36 – 4.23 (m, 2H), 3.12 (d, *J* = 5.2 Hz, 3H), 2.67 (q, *J* = 17.6 Hz, 2H), 2.15 (q, *J* = 16.0 Hz, 2H), 1.02 (s, 3H), 0.98 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.13, 175.18, 162.86, 157.37, 144.96, 133.02, 132.58, 131.14, 125.82, 117.62, 113.85, 112.92, 110.30, 107.54, 50.73, 48.70, 43.10, 32.13, 29.00, 27.80, 27.49.

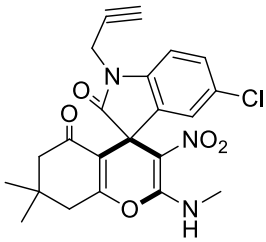


7,7-dimethyl-2-(methylamino)-3-nitro-1'-(prop-2-yn-1-yl)-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4k):



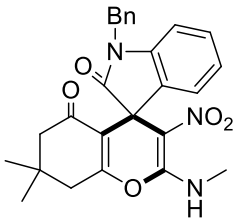
Yield = A: 82%; B: 85% (Light yellow solid); M.P: 270-272 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.46 (d, *J* = 4.0 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 4.49 (dd, *J* = 39.2, 17.6 Hz, 2H), 3.24 (s, 1H), 3.11 (d, *J* = 3.6 Hz, 3H), 2.67 (q, *J* = 45.6 Hz, 2H), 2.11 (q, *J* = 48.8 Hz, 2H), 1.02 (s, 3H), 0.94 (s, 3H**). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.36, 175.27, 162.87, 157.38, 144.29, 130.23, 128.83, 122.88, 122.71, 113.11, 108.55, 107.51, 78.25, 74.46, 50.67, 48.59, 32.00, 29.74, 28.85, 27.97, 27.05. **Mass (ESI-MS):** m/z Calculated: 407.15; Observed: 430.1304 (M+Na).

5'-chloro-7,7-dimethyl-2-(methylamino)-3-nitro-1'-(prop-2-yn-1-yl)-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4l):



Yield = A: 81%; B: 82% (Light yellow solid); M.P: 254-256 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.50 (d, *J* = 5.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 4.59-4.41 (m, 2H), 3.26 (t, *J* = 2.4 Hz, 1H), 3.11 (d, *J* = 4.8 Hz, 3H), 2.66 (q, *J* = 17.6 Hz, 2H), 2.14 (q, *J* = 16.0 Hz, 2H), 1.01 (s, 3H), 0.97 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.16, 174.78, 163.01, 157.32, 143.49, 132.50, 128.43, 126.61, 123.28, 112.66, 109.76, 107.24, 77.99, 74.85, 50.64, 48.74, 32.10, 29.87, 28.95, 27.75, 27.45. **Mass (ESI-MS):** m/z Calculated: 441.11; Observed: 442.1048 (M+1).

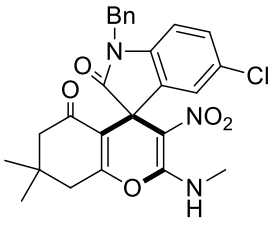
1'-benzyl-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4m):



Yield = A: 88%; B: 91% (Light yellow solid); M.P: 278-280 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.53 (d, *J* = 4.8 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 4.89 (dd, *J* = 75.2, 16.4 Hz, 2H), 3.13 (d, *J* = 5.2 Hz, 3H), 2.69 (dd, *J* = 48.8, 17.6 Hz, 2H), 2.16 (dd, *J* = 53.2, 16.0 Hz, 2H), 1.04 (s, 3H), 0.95 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.39, 176.35, 162.80, 157.45, 145.57, 137.02, 130.45, 128.83, 128.70, 127.73, 127.61, 122.84, 122.40, 113.39,

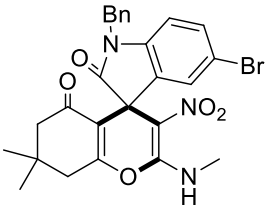
108.58, 107.75, 50.82, 48.73, 44.75, 32.03, 28.92, 28.04, 27.07. **Mass (ESI-MS):** m/z Calculated: 459.18; Observed: 482.1601 (M+Na).

1'-benzyl-5'-chloro-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4n):



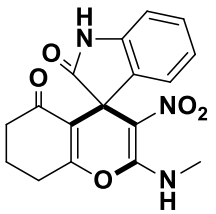
Yield = A: 80%; B: 80% (White solid); M.P: 309-311 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.57 (d, *J* = 5.2 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.32 (m, 3H), 7.31-7.24 (m, 1H), 7.19-7.12 (m, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 4.89 (dd, *J* = 73.2, 16.0 Hz, 2H), 3.13 (d, *J* = 4.8 Hz, 3H), 2.68 (q, *J* = 17.6 Hz, 2H), 2.18 (q, *J* = 16.0 Hz, 2H), 1.03 (s, 3H), 0.98 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.33, 175.94, 163.02, 157.42, 144.68, 136.77, 132.67, 128.85, 128.35, 127.72, 126.37, 123.27, 112.91, 109.71, 107.45, 50.77, 48.87, 44.76, 32.12, 29.01, 27.81, 27.44. **Mass (ESI-MS):** m/z Calculated: 493.14; Observed: 516.1188 (M+Na).

1'-benzyl-5'-bromo-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4o):



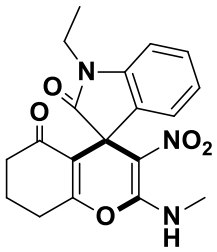
Yield = A: 86%; B: 87% (White solid); M.P: >310 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.56 (q, *J* = 4.4 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.30-7.25 (m, 2H), 6.55 (d, *J* = 8.4 Hz, 1H), 4.88 (dd, *J* = 72.4, 16.0 Hz, 2H), 3.13 (d, *J* = 5.2 Hz, 3H), 2.68 (q, *J* = 17.6 Hz, 2H), 2.18 (q, *J* = 16.0 Hz, 2H), 1.03 (s, 3H), 0.98 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 195.23, 175.77, 162.93, 157.41, 145.13, 136.82, 133.03, 131.19, 128.83, 127.72, 125.95, 114.03, 112.97, 110.28, 107.50, 50.78, 48.81, 44.73, 32.15, 29.03, 27.82, 27.48.

2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4p):



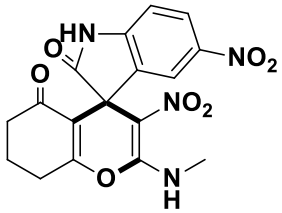
Yield = A: 89%; B: 89% (Brick red solid); M.P: 277-279 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.46 (d, *J* = 5.2 Hz, 1H), 10.43 (s, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 3.12 (d, *J* = 4.8 Hz, 3H), 2.76 (dd, *J* = 13.2, 7.2 Hz, 2H), 2.28 – 2.16 (m, 2H), 1.96 – 1.85 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 194.83, 177.11, 163.86, 157.20, 145.01, 131.51, 128.42, 123.00, 121.22, 114.82, 108.84, 108.23, 49.14, 37.40, 28.91, 27.01, 19.94. **Mass (ESI-MS):** m/z Calculated: 341.32; Observed: 364.0868 (M+Na).

1'-ethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4q):



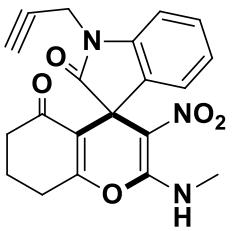
Yield = A: 85%; B: 88% (Light Yellow solid); M.P: 259-261 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.46 (d, *J* = 4.8 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.13 (d, *J* = 5.2 Hz, 3H), 2.76 (dd, *J* = 12.8, 6.8 Hz, 2H), 2.31 – 2.13 (m, 2H), 1.98 – 1.83 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 195.02, 175.21, 164.22, 157.23, 145.31, 130.77, 128.68, 122.98, 121.82, 114.59, 107.96, 107.71, 48.69, 37.28, 34.86, 28.90, 26.97, 19.88, 12.18. **Mass (ESI-MS):** m/z Calculated: 369.37; Observed: 392.1174 (M+Na).

2-(methylamino)-3,5'-dinitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4r):



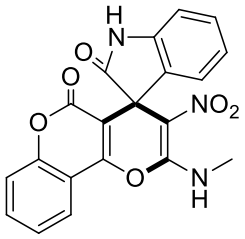
Yield = A: 80%; B: 81% (White solid); M.P: 321-323 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 11.23 (s, 1H), 10.55 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.14 (s, 3H), 2.84-2.71 (m, 2H), 2.32 – 2.20 (m, 2H), 1.99 – 1.88 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 195.38, 177.92, 165.01, 157.25, 151.59, 142.32, 132.71, 126.13, 119.07, 113.69, 108.67, 107.56, 49.16, 37.16, 29.04, 27.11, 19.87. **Mass (ESI-MS):** m/z Calculated: 386.32; Observed: 387.0891 (M+1).

2-(methylamino)-3-nitro-1'-(prop-2-yn-1-yl)-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4s):



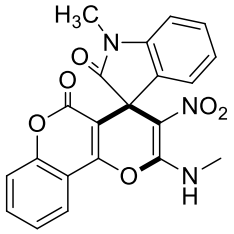
Yield = A: 82%; B: 86% (White solid); M.P: 305-307 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.46 (d, *J* = 4.8 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 4.59-4.41 (m, 2H), 3.23 (s, 1H), 3.13 (d, *J* = 4.8 Hz, 3H), 2.81-2.72 (m, 2H), 2.30 – 2.13 (m, 2H), 1.98-1.83 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 194.84, 174.93, 164.25, 157.12, 144.60, 130.57, 128.59, 123.02, 122.33, 114.48, 108.39, 107.68, 78.41, 74.65, 48.65, 37.19, 29.81, 28.97, 26.99, 19.93. **Mass (ESI-MS):** m/z Calculated: 379.37; Observed: 402.1014 (M+Na).

2'-(methylamino)-3'-nitro-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-2,5'-dione (5a):



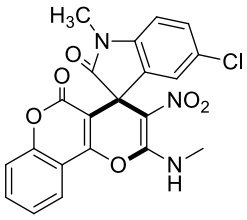
Yield = A: 89%; B: 92% (White solid); M.P: 299-300 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.70 (s, 1H), 10.64 (q, *J* = 4.4 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80-7.74 (m, 1H), 7.57 – 7.45 (m, 2H), 7.23-7.13 (m, 2H), 6.87-6.77 (m, 2H), 3.34 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 176.19, 157.58, 156.91, 153.35, 152.26, 145.09, 134.36, 130.27, 129.10, 125.64, 123.81, 121.63, 116.89, 112.48, 109.17, 107.52, 104.55, 49.72, 29.33. **Mass (ESI-MS):** m/z Calculated: 391.08; Observed: 414.0622 (M+Na).

1-methyl-2'-(methylamino)-3'-nitro-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-2,5'-dione (5b):



Yield = A: 80%; B: 80% (White solid); M.P: 304-306 °C**, ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.64 (d, *J* = 4.8 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 3.35 (s, 3H), 3.21 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 174.88, 157.66, 156.93, 153.51, 152.29, 146.43, 134.43, 129.48, 129.32, 125.68, 123.77, 123.60, 122.38, 116.93, 112.47, 108.07, 107.22, 104.35, 49.17, 29.36, 27.11. **Mass (ESI-MS):** m/z Calculated: 405.10; Observed: 428.0777 (M+Na).

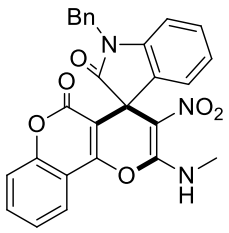
5-chloro-1-methyl-2'-(methylamino)-3'-nitro-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-2,5'-dione (5c):



Yield = A: 81%; B: 81% (White solid); M.P: >310 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.68 (d, *J* = 5.2 Hz, 1H), 8.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.58 – 7.48 (m, 3H), 7.33 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 3.35 (d, *J* = 5.2 Hz, 3H), 3.20 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 174.73, 157.84, 156.96, 153.86, 152.37, 145.42, 134.57, 131.45, 129.03, 126.53, 125.74, 124.05, 123.84, 116.99, 112.52, 109.38, 106.91, 103.63, 101.07, 49.29, 29.40, 27.25. **Mass (ESI-MS):** m/z Calculated: 439.06; Observed: 462.0355 (M+Na).

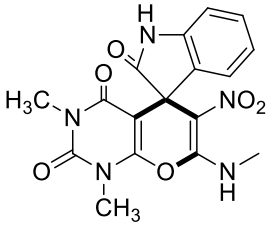
1-benzyl-2'-(methylamino)-3'-nitro-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-2,5'-dione (5d):

Yield = A: 86%; B: 89% (White solid); M.P: 297-299 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.70 (d, *J* = 4.8 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.25 (m, 4H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.96 (dd, *J* = 72.8, 16.0 Hz, 2H), 3.37 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 175.19, 157.76, 156.98, 153.61, 152.32, 145.85, 136.99, 134.50, 129.51, 129.19, 128.81, 127.87, 127.59, 125.71, 123.84, 122.52, 116.96, 112.49, 108.74, 107.20, 104.32, 49.37, 44.78, 29.42. **Mass (ESI-MS):** m/z Calculated: 481.13; Observed: 504.1049 (M+Na).



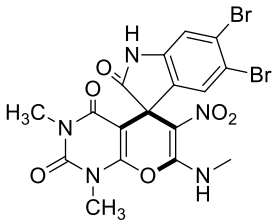
1',3'-dimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-2,2',4'(1'H,3'H)-trione (6a):

Yield = A: 90%; B: 93% (White solid); M.P: 293-295 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.52 (d, *J* = 4.8 Hz, 1H), 10.50 (s, 1H), 7.15 – 7.08 (m, 2H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 3.48 (s, 3H), 3.19 (d, *J* = 4.8 Hz, 3H), 3.03 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 176.70, 159.10, 156.71, 150.75, 149.78, 144.99, 130.95, 128.64, 123.43, 121.32, 108.96, 107.88, 90.06, 49.02, 30.08, 29.42, 28.29. **Mass (ESI-MS):** m/z Calculated: 385.10; Observed: 408.0826 (M+Na).



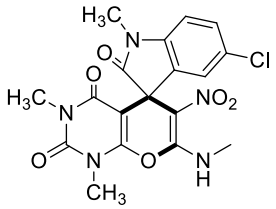
5,6-dibromo-1',3'-dimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-2,2',4'(1'H,3'H)-trione (6b):

Yield = A: 88%; B: 88% (Light grey solid); M.P: 307-309 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.99 (s, 1H), 10.57 (q, *J* = 4.8 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 3.47 (s, 3H), 3.19 (d, *J* = 5.2 Hz, 3H), 3.05 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 176.40, 159.30, 156.62, 150.99, 149.72, 144.07, 134.69, 133.27, 125.64, 113.40, 107.37, 102.29, 89.18, 50.23, 30.14, 29.54, 28.39.



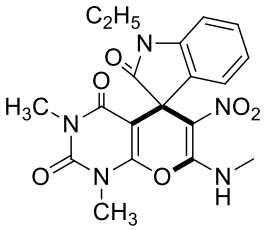
5-chloro-1,1',3'-trimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-2,2',4'(1'H,3'H)-trione (6c):

Yield = A: 89%; B: 90% (White solid); M.P: 287-289 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.55 (d, *J* = 5.2 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 3.47 (s, 3H), 3.19 (d, *J* = 4.8 Hz, 3H), 3.16 (s, 3H), 3.02 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 175.14, 159.25, 156.72, 151.01, 149.75, 145.33, 132.25, 128.59, 126.16, 123.58, 109.12, 107.22, 89.32, 48.64, 30.12, 29.51, 28.36, 27.14**. Mass (ESI-MS):** m/z Calculated: 433; Observed: 434 (M+1).



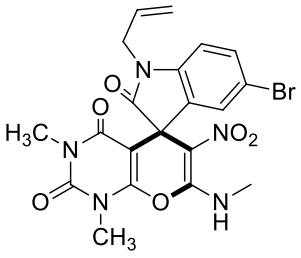
1-ethyl-1',3'-dimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-2,2',4'(1'H,3'H)-trione (6d):

Yield = A: 95%; B: 95% (White solid); M.P: 275-277 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.51 (q, *J* = 4.4 Hz, 1H), 7.24 – 7.15 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.90-6.85 (m, 1H), 3.82 – 3.64 (m, 2H), 3.48 (s, 3H), 3.19 (d, *J* = 4.8 Hz, 3H), 3.01 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 174.65, 159.12, 156.71, 150.87, 149.77, 145.35, 130.30, 128.84, 123.40, 121.79, 107.79, 89.91, 48.55, 34.94, 30.10, 29.45, 28.32, 12.28. Mass (ESI-MS): **Mass (ESI-MS):** m/z Calculated: 413.13; Observed: 436.1136 (M+Na).

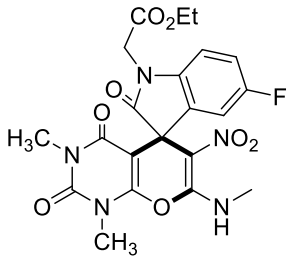


1-allyl-5-bromo-1',3'-dimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-2,2',4'(1'H,3'H)-trione (6e):

Yield = A: 90%; B: 92% (White solid); M.P: 300-302 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.58 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.86 (m, 1H), 5.51 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.20 (dd, *J* = 10.8, 1.6 Hz, 1H), 4.41 – 4.23 (m, 2H), 3.48 (s, 3H), 3.20 (d, *J* = 4.8 Hz, 3H), 3.03 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 174.77, 159.28, 156.70, 151.06, 149.74, 144.95, 132.62, 132.56, 131.33, 126.25, 117.67, 113.96, 110.36, 107.26, 89.29, 48.69, 43.16, 30.14, 29.54, 28.41. **Mass (ESI-MS):** m/z Calculated: 503.04; Observed: 526.0202 (M+Na).

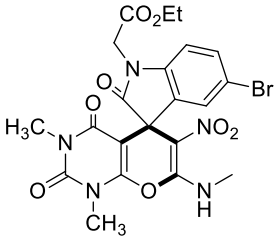


ethyl 2-(5-fluoro-1',3'-dimethyl-7'-(methylamino)-6'-nitro-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidin]-1-yl)acetate (6f):



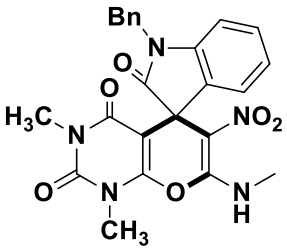
Yield = A: 85%; B: 88% (White solid); M.P: 267-269 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.51 (d, *J* = 5.2 Hz, 1H), 7.20 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.02-7.07 (m, 1H), 6.94-6.89 (m, 1H), 4.47 (dd, *J* = 37.6, 17.2 Hz, 2H), 4.18 – 4.10 (m, 2H), 3.47 (s, 3H), 3.19 (d, *J* = 4.8 Hz, 3H), 3.02 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 175.32, 167.97, 159.14, 157.75, 156.62, 150.98, 149.75, 141.68, 131.72, 114.81, 111.33, 109.21, 106.94, 89.40, 61.19, 48.86, 43.04, 30.12, 29.48, 28.35, 14.44. **Mass (ESI-MS):** m/z Calculated: 489; Observed: 490 (M+1).

ethyl 2-(5-bromo-1',3'-dimethyl-7'-(methylamino)-6'-nitro-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidin]-1-yl)acetate (6g):



Yield = A: 81%; B: 82% (Light pink solid); M.P: 280-282 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.53 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.48 (q, *J* = 16.8 Hz, 2H), 4.18 – 4.10 (m, 2H), 3.47 (s, 3H), 3.19 (d, *J* = 4.8 Hz, 3H), 3.02 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 175.06, 167.83, 159.20, 156.63, 151.04, 149.73, 144.74, 132.44, 131.32, 126.22, 114.19, 110.61, 106.87, 89.26, 61.23, 48.60, 42.91, 30.13, 29.50, 28.37, 14.43.

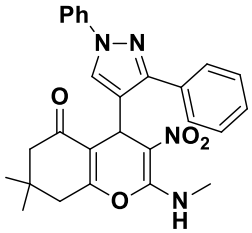
1-benzyl-1',3'-dimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-2,2',4'(1'H,3'H)-trione (6h):



Yield = A: 92%; B: 92% (Light yellow solid); M.P: 294-296 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.59 (d, *J* = 5.2 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 4.92 (dd, *J* = 105.6, 16.0 Hz, 2H), 3.51 (s, 3H), 3.23 (d, *J* = 4.8 Hz, 3H), 3.06 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 175.70, 159.25, 156.80, 150.93, 149.78, 145.72, 137.19, 130.20, 128.79, 127.80, 127.53, 123.40, 122.22, 108.53,

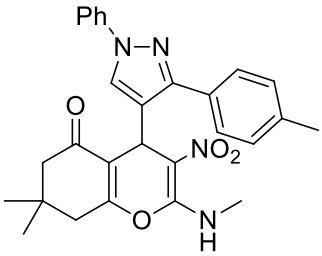
107.51, 90.00, 48.74, 44.77, 30.15, 29.53, 28.38. **Mass (ESI-MS):** m/z Calculated: 475.15; Observed: 498.1273 (M+Na).

4-(1,3-diphenyl-1H-pyrazol-4-yl)-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8a):



Yield = A: 89%; B: 90% (White solid); M.P: 238-240 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.16 (d, *J* = 5.2 Hz, 1H), 8.43 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.52-7.40 (m, 5H), 7.29 (t, *J* = 7.2 Hz, 1H), 5.10 (s, 1H), 2.99 (d, *J* = 4.8 Hz, 3H), 2.46 (d, *J* = 12.0 Hz, 2H), 2.21 (s, 2H), 1.03 (s, 3H), 0.99 (s, 3H**). ^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.21, 160.71, 157.41, 152.10, 139.83, 134.64, 129.92, 129.14, 128.46, 128.36, 128.07, 126.43, 123.89, 118.33, 115.23, 108.86, 50.49, 32.36, 28.58, 28.22, 28.08, 26.93. **Mass (ESI-MS):** m/z Calculated: 470.20; Observed: 471.1974 (M+1).

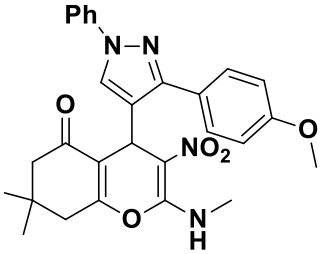
7,7-dimethyl-2-(methylamino)-3-nitro-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-7,8-dihydro-4H-chromen-5(6H)-one (8b):



Yield = A: 85%; B: 87% (White solid); M.P: 241-243 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.14 (d, *J* = 5.2 Hz, 1H), 8.39 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.30-7.23 (m, 3H), 5.09 (s, 1H), 2.98 (d, *J* = 4.8 Hz, 3H), 2.47 (d, *J* = 10.0 Hz, 2H), 2.39 (s, 3H), 2.21 (s, 2H), 1.03 (s, 3H), 0.99 (s, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.18, 160.66, 157.41, 152.08, 139.86, 137.24, 131.76, 129.90, 128.93, 128.35 128.35, 126.35, 123.85, 118.28, 115.30, 108.82, 50.47, 32.32, 28.53, 28.28, 28.00, 26.93, 21.39. **Mass (ESI-MS):** m/z Calculated: 484.21; Observed: 485.2129 (M+1).

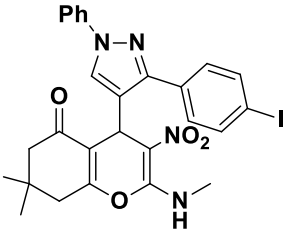
4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8c):

Yield = A: 90%; B: 92% (Light Yellow solid); M.P: 212-214 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.15 (d, *J* = 5.2 Hz, 1H), 8.38 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 5.08 (s, 1H), 3.84 (s, 3H), 3.00 (d, *J* = 5.2 Hz, 3H), 2.49 (d, *J* = 5.6 Hz, 2H), 2.21 (s, 2H), 1.03 (s, 3H), 0.99 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 196.19, 160.66, 159.36, 157.42, 151.90, 139.88, 130.33, 129.89, 128.29, 126.98, 126.30, 123.79, 118.25, 115.35, 113.81, 108.86, 55.60, 50.50, 32.36, 28.56, 28.27, 28.02, 26.93. **Mass (ESI-MS):** m/z Calculated: 500.21; Observed: 501.2075 (M+1).



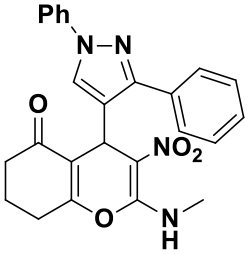
4-(3-(4-iodophenyl)-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8d):

Yield = A: 88%; B: 88% (White solid); M.P: 164-166 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.18 (d, *J* = 4.8 Hz, 1H), 8.42 (s, 1H), 7.86-7.79 (m, 4H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 5.06 (s, 1H), 3.04 (d, *J* = 5.2 Hz, 3H), 2.55 (s, 2H), 2.22 (d, *J* = 4.8 Hz, 2H), 1.05 (s, 3H), 1.00 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 196.34, 160.82, 157.33, 151.08, 139.76 137.27, 134.33, 131.13, 129.91, 128.50, 126.57, 124.47, 118.42, 115.42, 108.98, 94.48, 50.44, 32.43, 28.68, 28.39, 27.89, 26.88. **Mass (ESI-MS):** m/z Calculated: 596.09; Observed: 597.0925 (M+1).

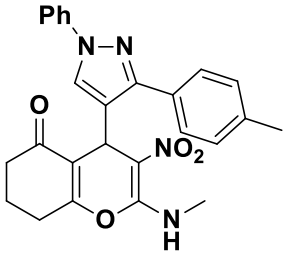


4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8e):

Yield = A: 80%; B: 83% (White solid); M.P: 250-252 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.11 (d, *J* = 4.8 Hz, 1H), 8.43 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.63-7.57 (m, 2H), 7.50-7.41 (m, 5H), 7.28 (t, *J* = 7.2 Hz, 1H), 5.09 (s, 1H), 2.95 (d, *J* = 5.2 Hz, 3H), 2.61 – 2.54 (m, 1H), 2.48-2.34 (m, 1H), 2.29 (t, *J* = 6.4 Hz, 2H), 1.99 – 1.82 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 196.22, 162.64, 157.23, 152.19, 139.83, 134.61, 129.89, 129.26, 128.54, 128.34, 128.13, 126.40, 123.63, 118.32, 116.04, 108.66, 36.64, 28.53, 26.93, 26.32, 20.00. **Mass (ESI-MS):** m/z Calculated: 442.16; Observed: 443.1667 (M+1).

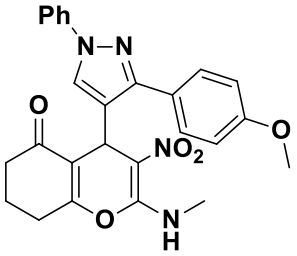


2-(methylamino)-3-nitro-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-7,8-dihydro-4H-chromen-5(6H)-one (8f):



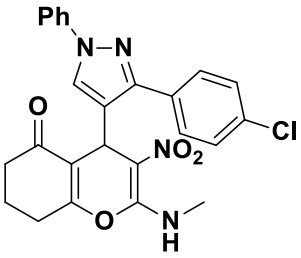
Yield = A: 86%; B: 87% (White solid); M.P: 213-215 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.10 (d, *J* = 4.8 Hz, 1H), 8.40 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.53 – 7.43 (m, 4H), 7.31-7.21 (m, 3H), 5.08 (s, 1H), 2.95 (d, *J* = 4.8 Hz, 3H), 2.62-2.53 (m, 1H), 2.45 (t, *J* = 5.2 Hz, 1H), 2.40 (s, 3H), 2.29 (t, *J* = 6.4 Hz, 2H), 1.98 – 1.83 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.21, 162.59, 157.23, 152.17, 139.85, 137.32, 131.70, 129.88, 129.13, 128.90, 128.44, 126.32, 123.64, 118.28, 116.14, 108.62, 36.64, 28.51, 26.92, 26.34, 21.39, 20.01. **Mass (ESI-MS):** m/z Calculated: 456.18; Observed: 457.1823 (M+1).

4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8g):



Yield = A: 86%; B: 86% (White solid); M.P: 258-260 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.12 (d, *J* = 4.0 Hz, 1H), 8.39 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.58 – 7.43 (m, 4H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.07 (s, 1H), 3.84 (s, 3H), 2.97 (d, *J* = 4.0 Hz, 3H), 2.52 (s, 2H), 2.30 (s, 2H), 1.93 (s, 2H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.22, 162.60, 159.41, 157.25, 151.99, 139.88, 130.46, 129.87, 128.38, 126.89, 126.28, 123.58, 118.26, 116.19, 113.79, 108.66, 55.63, 36.66, 28.51, 26.94, 26.36, 20.03. **Mass (ESI-MS):** m/z Calculated: 472.17; Observed: 473.1767 (M+1).

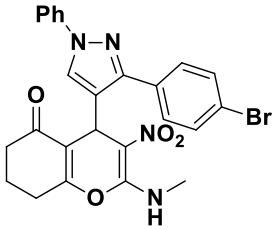
4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8h):



Yield = A: 89%; B: 89% (Light Yellow solid); M.P: 229-231 °C, **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.15 (d, *J* = 4.8 Hz, 1H), 8.42 (s, 1H), 7.87-7.78 (m, 4H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.06 (s, 1H), 3.02 (d, *J* = 4.8 Hz, 3H), 2.65-2.54 (m, 2H), 2.31 (t, *J* = 6.4 Hz, 2H), 2.00 – 1.90 (m, 2H**). ^{13}C NMR (100 MHz, DMSO-d_6) δ** 196.44, 162.77, 157.20, 150.95, 139.76, 133.65, 132.91, 130.84, 129.88, 128.58, 128.46,

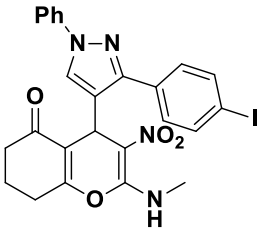
126.55, 124.38, 118.46, 116.44, 108.88, 36.65, 28.62, 26.86, 26.43, 20.07. **Mass (ESI-MS):** m/z Calculated: 476.12; Observed: 477.1276 (M+1).

4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8i):



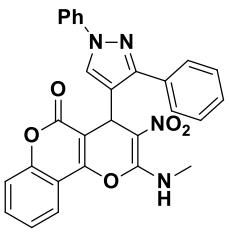
Yield = A: 90%; B: 90% (Yellow solid); M.P: 235-237 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.15 (d, *J* = 5.2 Hz, 1H), 8.42 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.06 (s, 1H), 3.02 (d, *J* = 4.8 Hz, 3H), 2.63-2.55 (m, 2H), 2.31 (t, *J* = 6.0 Hz, 2H), 2.00-1.88 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 196.44, 162.77, 157.20, 150.95, 139.75, 133.65, 132.91, 130.83, 129.88, 128.58, 128.46, 126.51, 124.38, 118.45, 116.44, 108.88, 36.65, 28.62, 26.86, 26.43, 20.07. **Mass (ESI-MS):** m/z Calculated: 521.05; Observed: 523.0748 (M+2).

4-(3-(4-iodophenyl)-1-phenyl-1H-pyrazol-4-yl)-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8j):



Yield = A: 81%; B: 84% (White solid); M.P: 255-257 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.14 (d, *J* = 5.2 Hz, 1H), 8.41 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 4H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.06 (s, 1H), 3.02 (d, *J* = 4.8 Hz, 3H), 2.64 – 2.55 (m, 2H), 2.31 (t, *J* = 6.0 Hz, 2H), 2.01 – 1.88 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 196.41, 162.73, 157.18, 151.13, 139.76, 137.24, 134.32, 131.23, 129.88, 128.61, 126.54, 124.32, 118.44, 116.39, 108.83, 94.51, 36.65, 28.66, 26.88, 26.42, 20.06. **Mass (ESI-MS):** m/z Calculated: 568.06; Observed: 569.0618 (M+1).

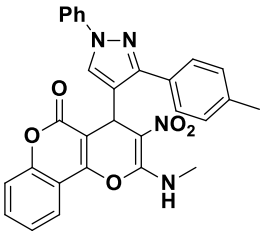
4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(methylamino)-3-nitropyrano[3,2-c]chromen-5(4H)-one (8k):



Yield = A: 89%; B: 90% (Light Yellow solid); M.P: 215-217 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.30 (d, *J* = 5.2 Hz, 1H), 8.57 (s, 1H), 7.90-7.80 (m, 3H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.53-7.43 (m, 4H), 7.40 – 7.34 (m, 3H), 7.27 (t, *J* = 7.6 Hz, 1H), 5.31 (s, 1H), 3.21 (d, *J* = 4.8 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 164.63, 161.47, 157.19, 157.16, 156.73,

144.53, 139.17, 138.22, 134.62, 133.77, 133.14, 132.89, 131.26, 130.09, 127.94, 127.45, 123.16, 121.75, 117.89, 113.03, 113.00, 111.20, 33.70, 33.24. **Mass (ESI-MS):** m/z Calculated: 492.14; Observed: 493.1455 (M+1).

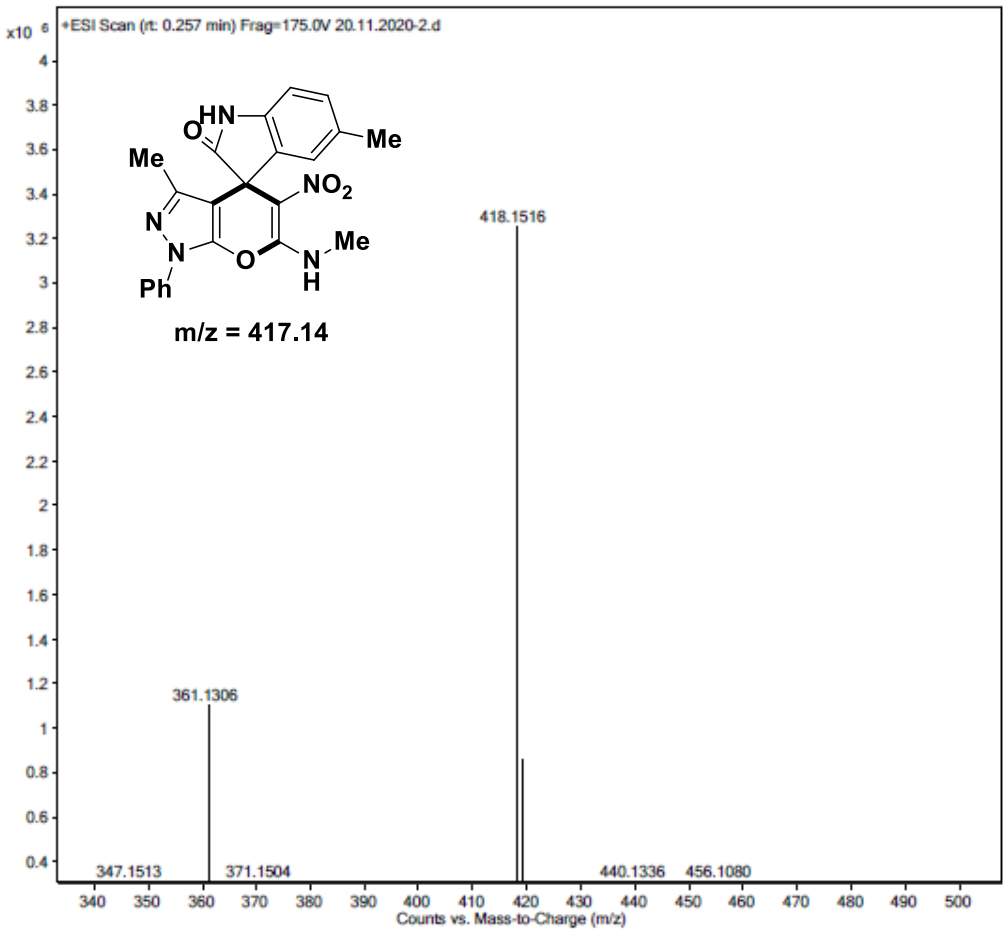
2-(methylamino)-3-nitro-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)pyrano[3,2-c]chromen-5(4H)-one (8l):



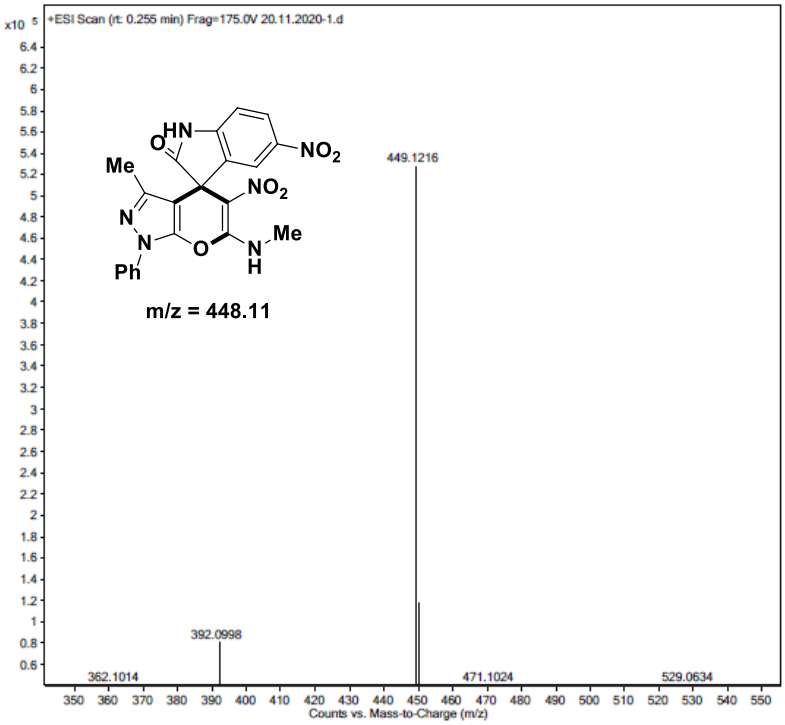
Yield = A: 80%; B: 85% (Yellow solid); M.P: 247-249 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.30 (d, *J* = 5.2 Hz, 1H), 8.55 (s, 1H), 7.89-7.80 (m, 3H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.53 – 7.43 (m, 6H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.29 (s, 1H), 3.22 (d, *J* = 4.8 Hz, 3H), 2.32 (s, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 156.68, 152.39, 151.98, 139.80, 137.41, 133.43, 131.49, 129.87, 128.92, 128.91, 126.45, 125.30, 123.16, 122.48, 118.37, 116.99, 113.14, 108.20, 106.33, 28.95, 28.50, 21.34. **Mass (ESI-MS):** m/z Calculated: 506.16; Observed: 507.1604 (M+1).

2.7 selected spectra

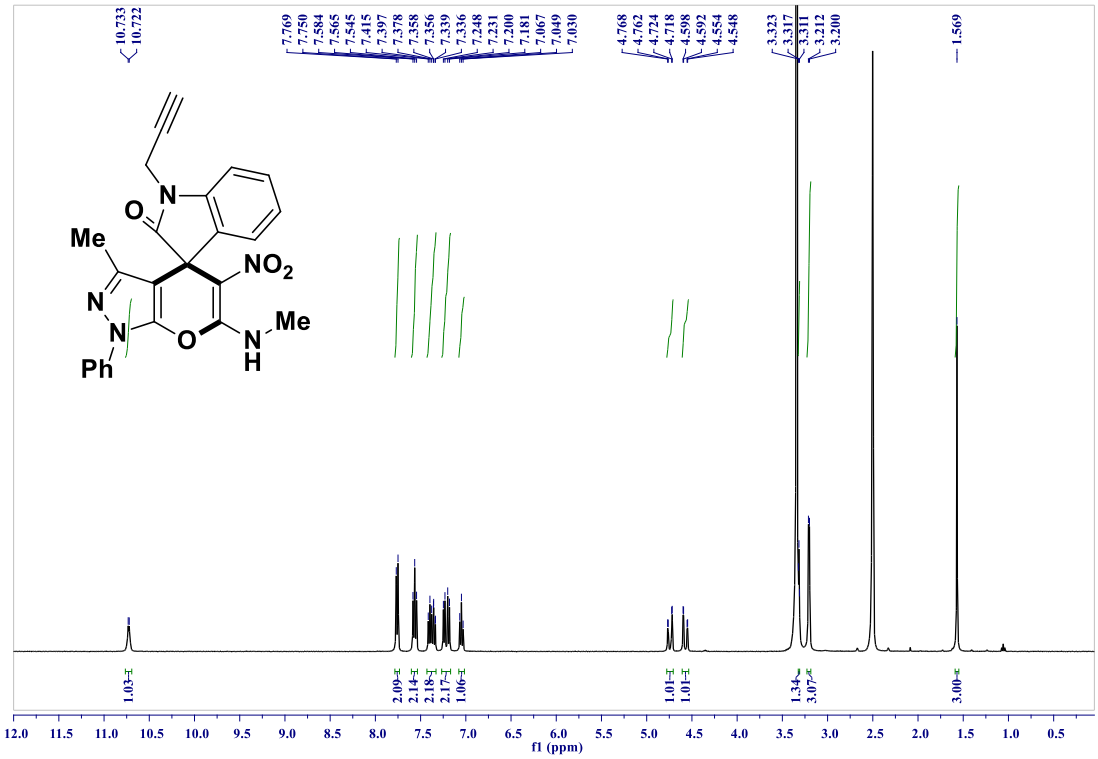
3',5-dimethyl-6'-(methylamino)-5'-nitro-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c] pyrazol]-2-one (4b'):

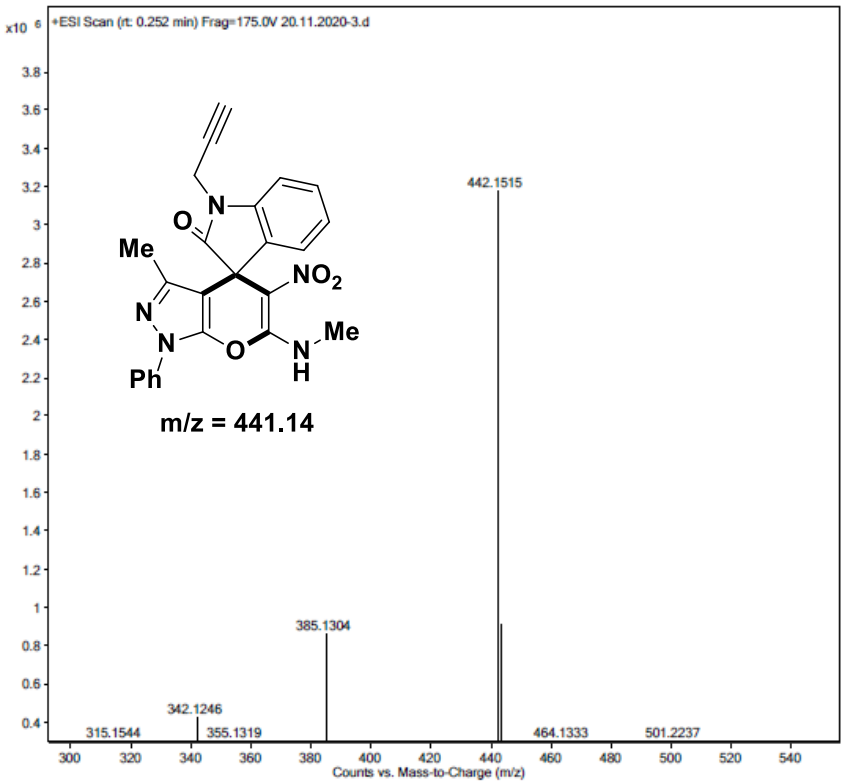


3'-methyl-6'-(methylamino)-5,5'-dinitro-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c] pyrazol]-2-one (4c'):

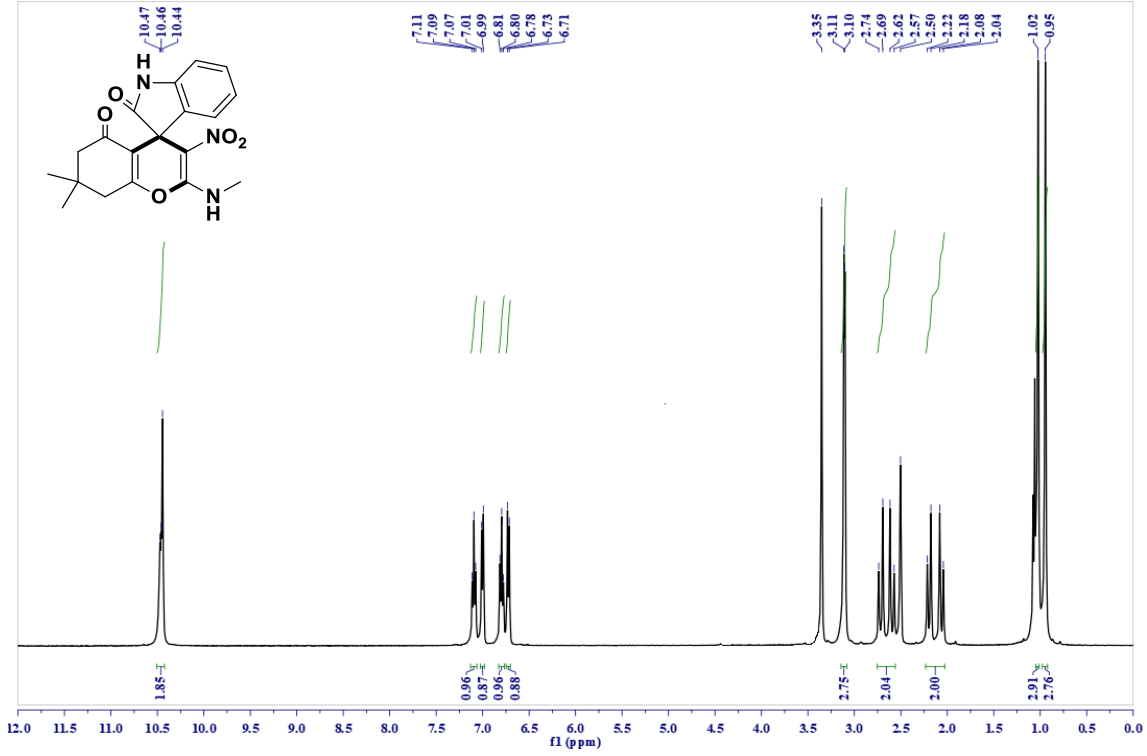


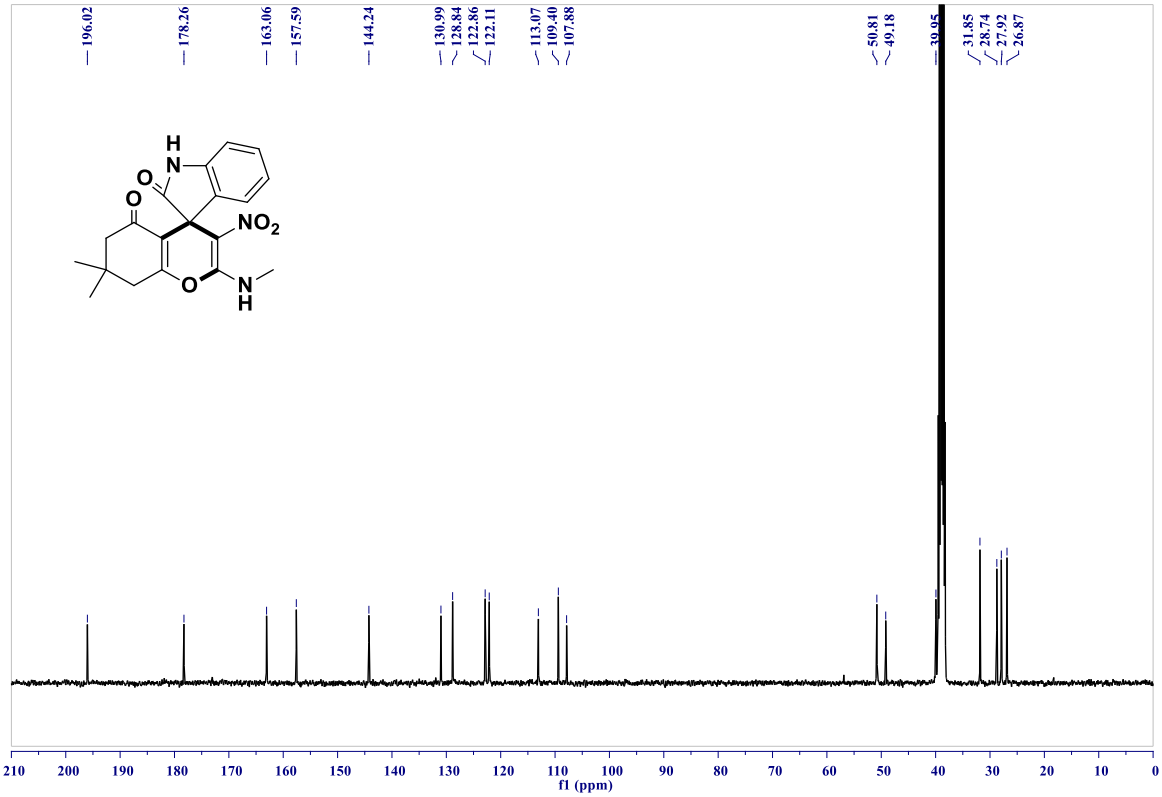
3'-methyl-6'-(methylamino)-5'-nitro-1'-phenyl-1-(prop-2-yn-1-yl)-1'H-spiro[indoline-3,4'-pyrano[2,3-c] pyrazol]-2-one (4d'):

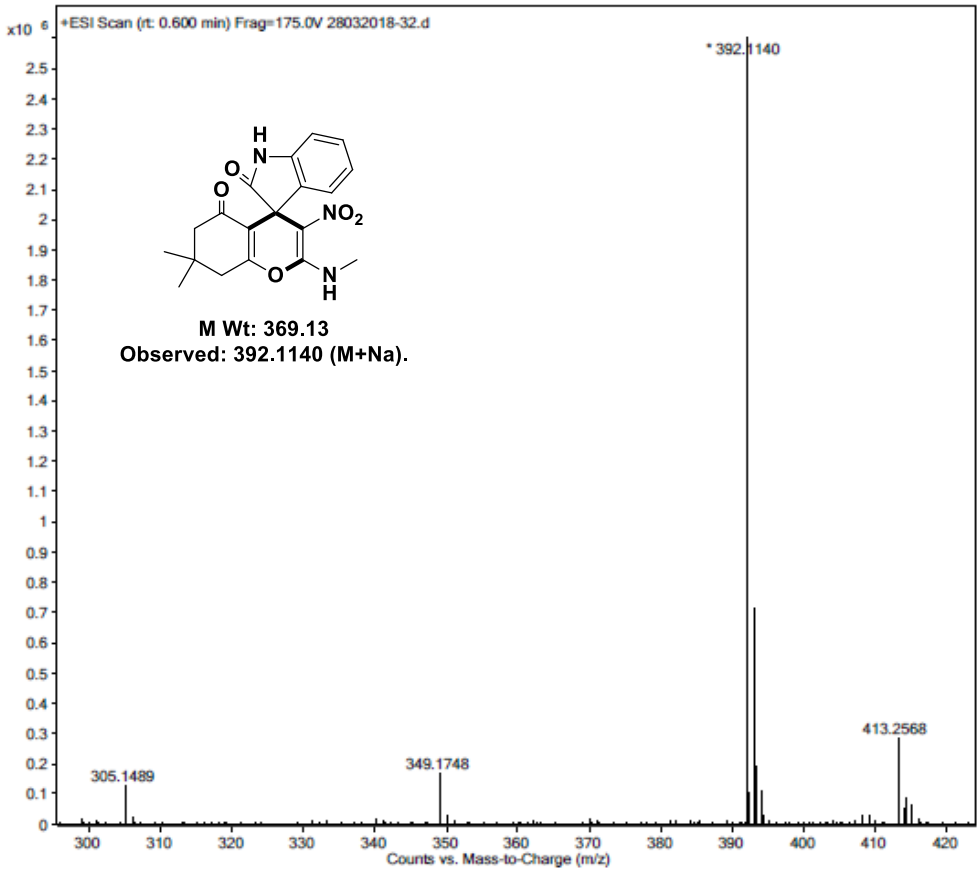




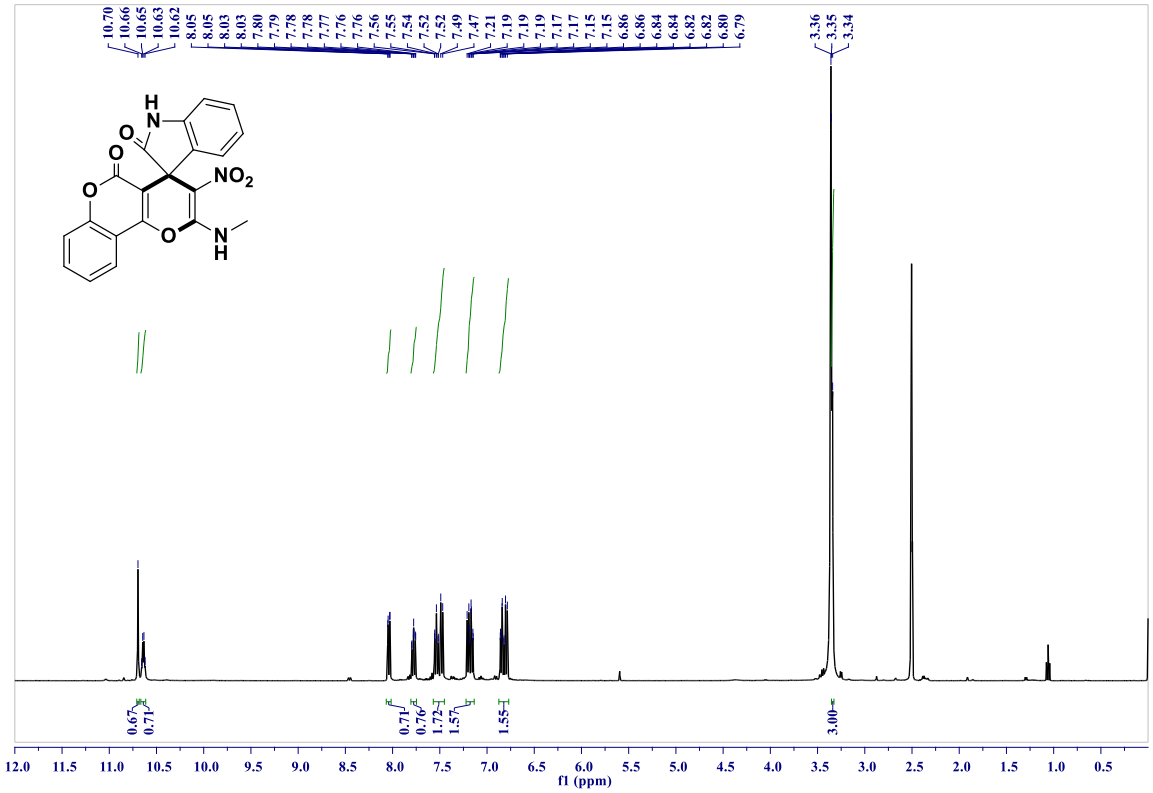
7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydrospiro[chromene-4,3'-indoline]-2',5(6H)-dione (4a):

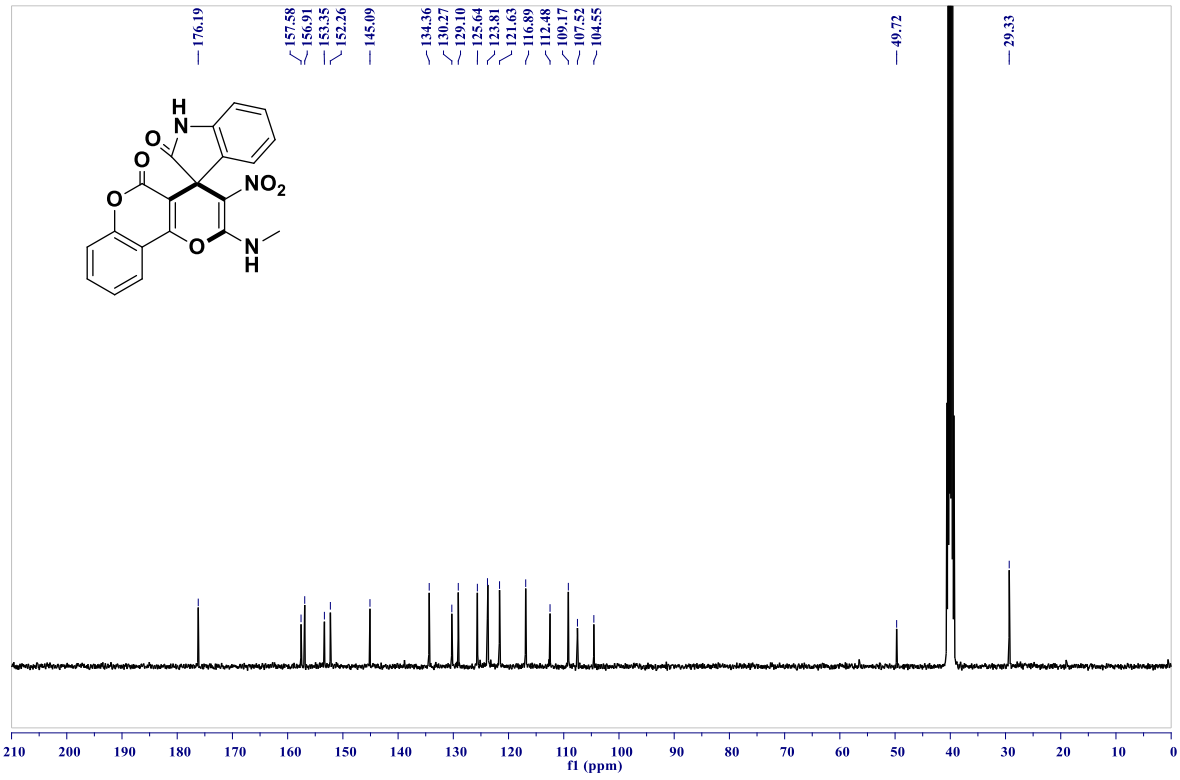


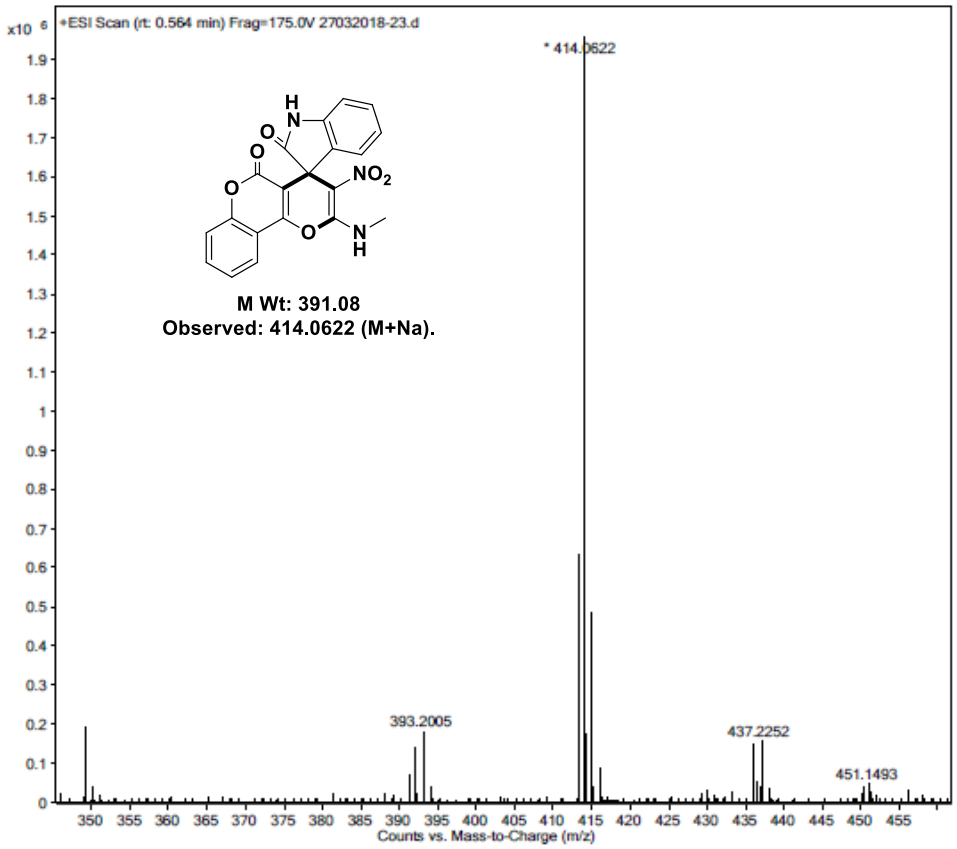

196.02
178.26
163.06
157.59
144.24
130.99
128.84
122.86
122.11
113.07
109.40
107.88
50.81
49.18
39.95
31.85
28.74
27.92
26.87
H
N
O
O
NO2
O
N
H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


x10 6
+ESI Scan (rt: 0.600 min) Frag=175.0V 28032018-32.d
* 392.1140
413.2568
349.1748
305.1489
H
N
O
O
NO2
O
N
H
M Wt: 369.13
Observed: 392.1140 (M+Na).
300 310 320 330 340 350 360 370 380 390 400 410 420
Counts vs. Mass-to-Charge (m/z)

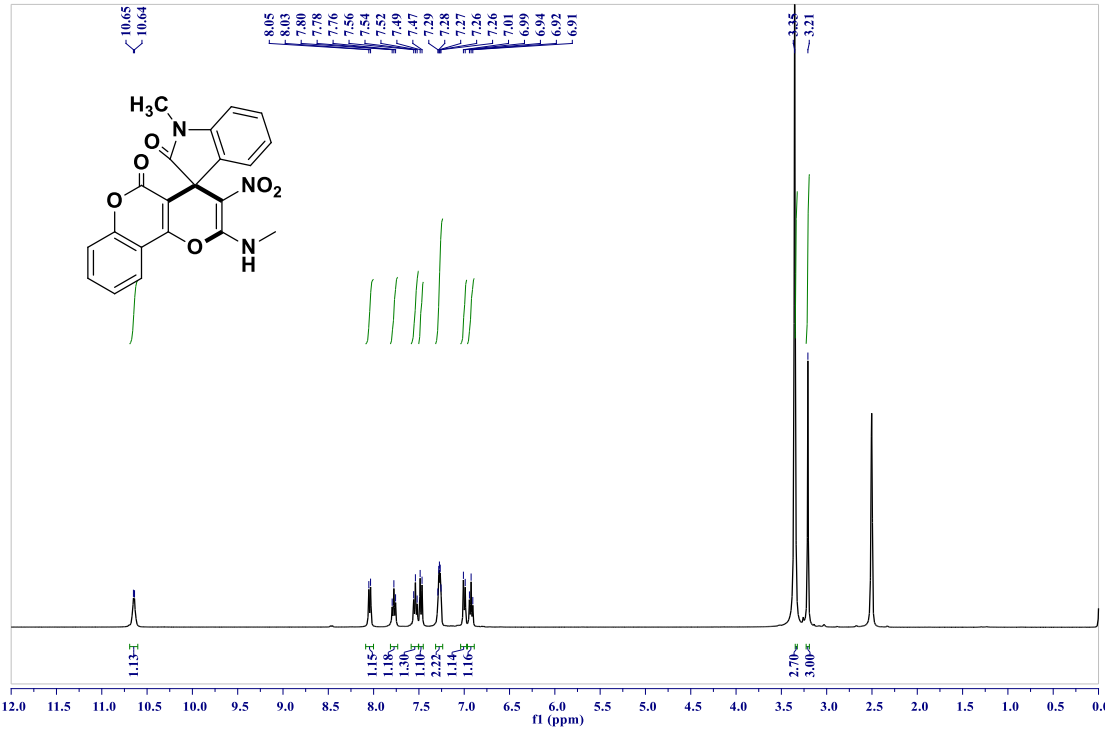
2'-(methylamino)-3'-nitro-5'H-spiro[indoline-3,4'-pyrano[3,2-c] chromene]-2,5'-dione (5a):

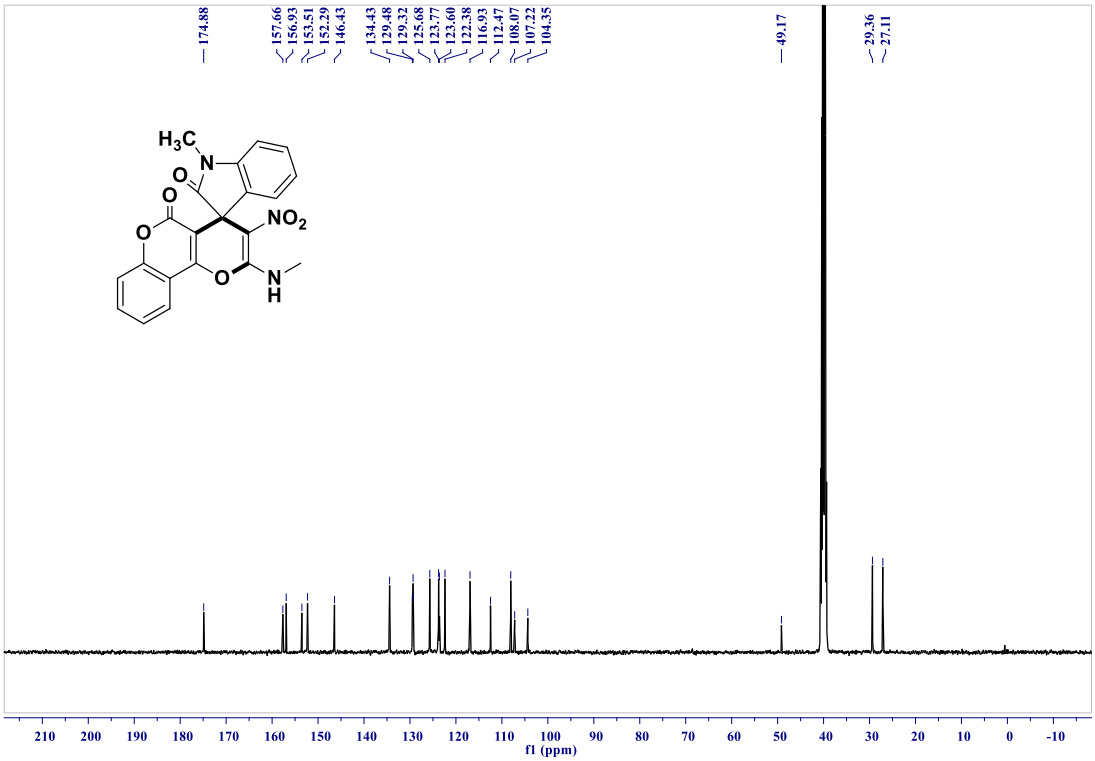


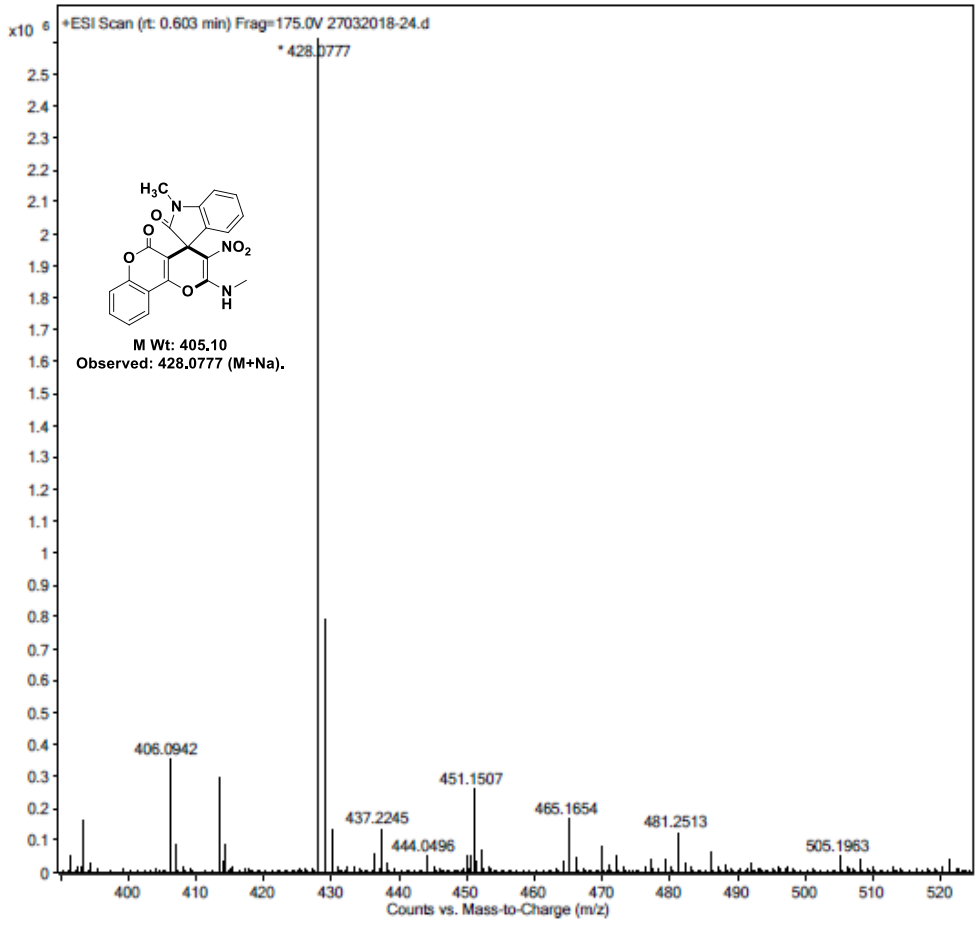




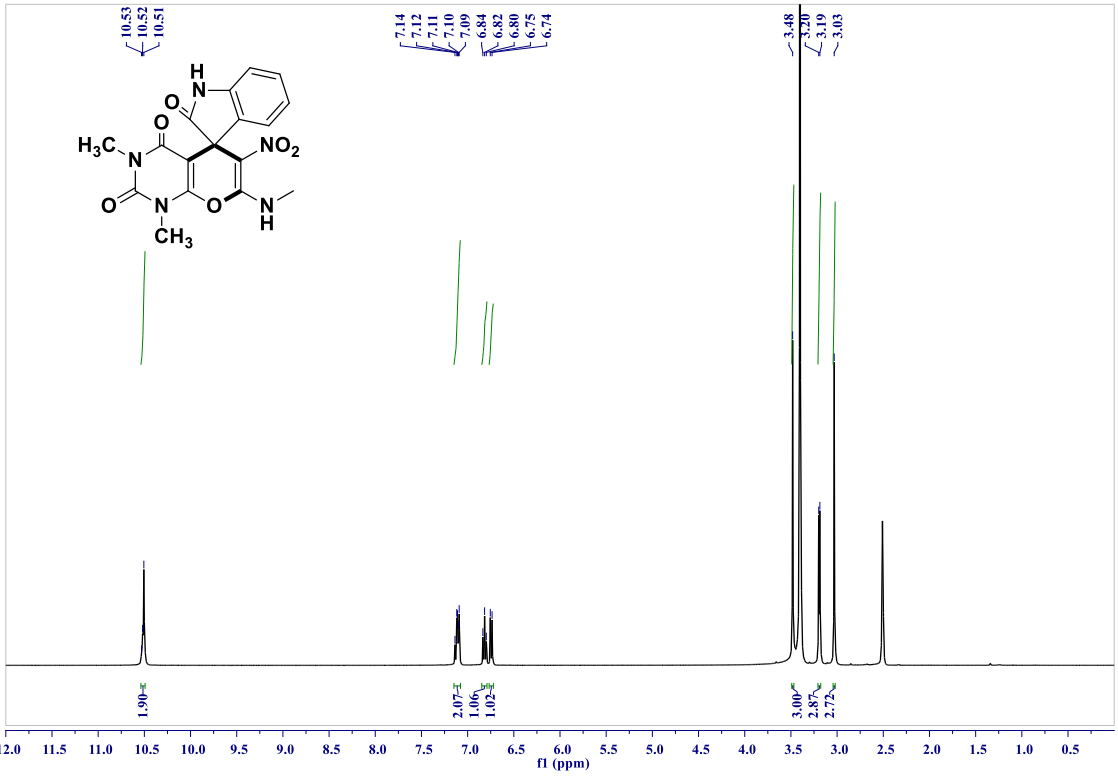
1-methyl-2'-(methylamino)-3'-nitro-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-2,5'-dione (5b):

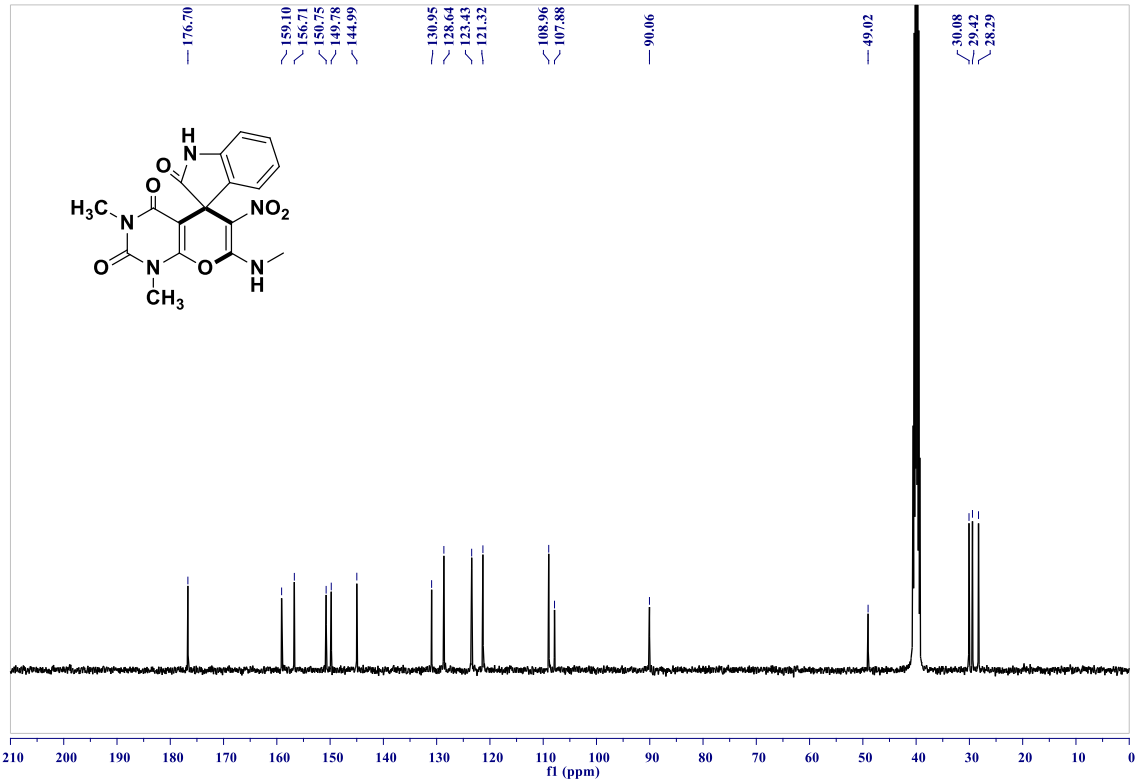


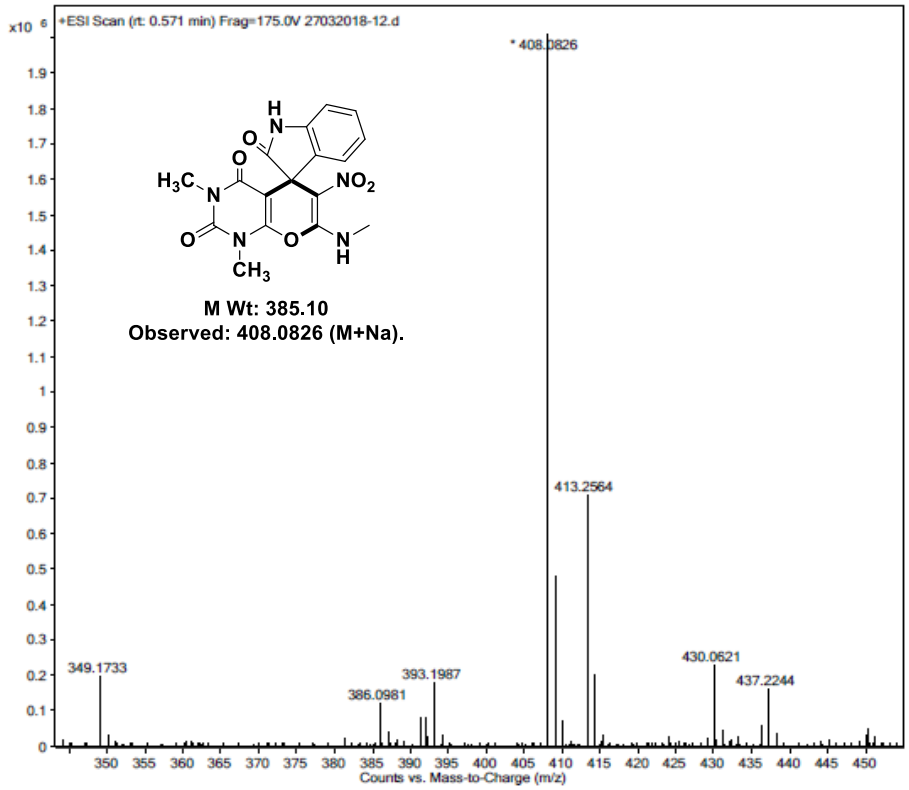

174.88
157.66
156.93
153.51
152.29
146.43
134.43
129.48
129.32
125.68
123.77
123.60
122.38
116.93
112.47
108.07
107.22
104.35
49.17
29.36
27.11
f1 (ppm)


x10 6
+ESI Scan (rt: 0.603 min) Frag=175.0V 27032018-24.d
* 428.0777
M Wt: 405.10
Observed: 428.0777 (M+Na).
406.0942
437.2245
444.0496
451.1507
465.1654
481.2513
505.1963
Counts vs. Mass-to-Charge (m/z)

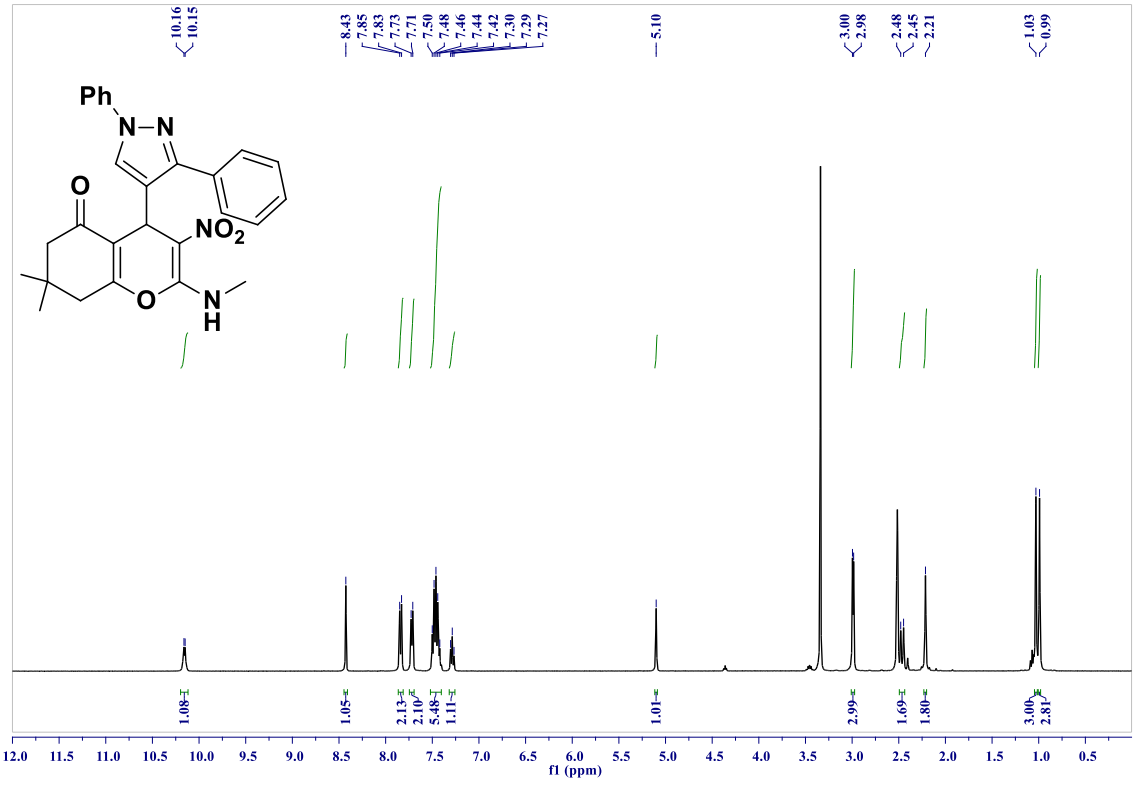
1',3'-dimethyl-7'-(methylamino)-6'-nitrospiro[indoline-3,5'-pyrano[2,3-d] pyrimidine]-2,2',4'(1'H,3'H)-trione (6a):

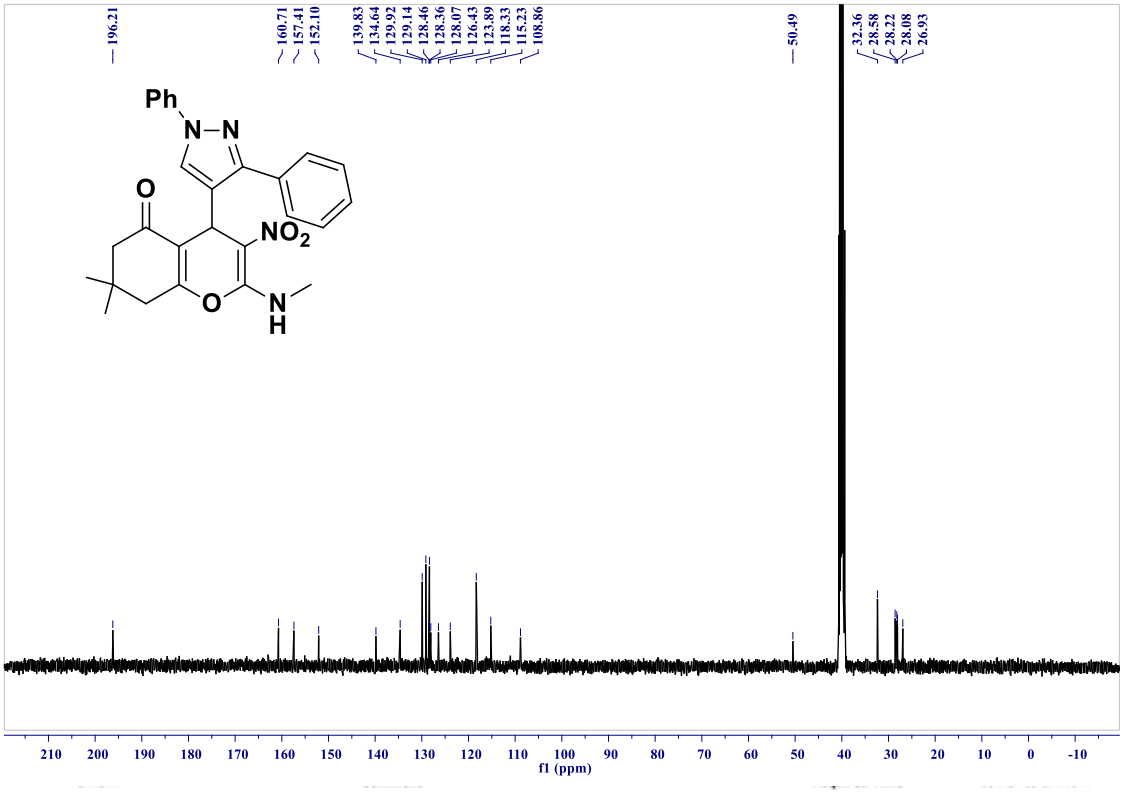


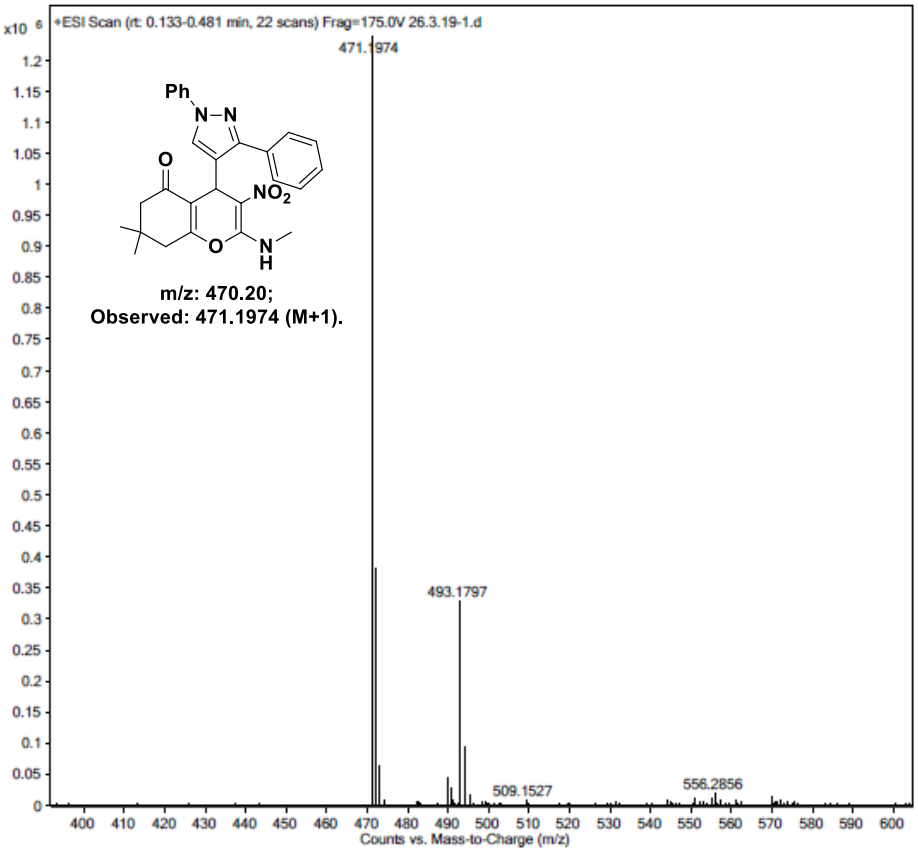




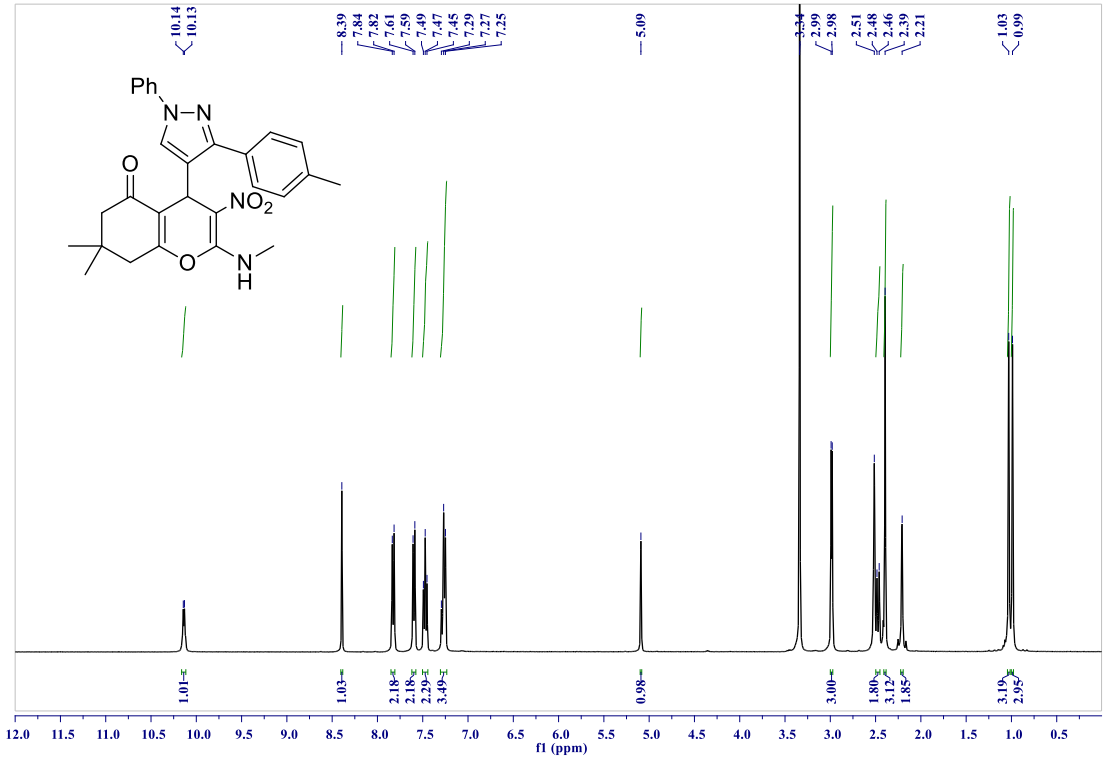
4-(1,3-diphenyl-1H-pyrazol-4-yl)-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8a):

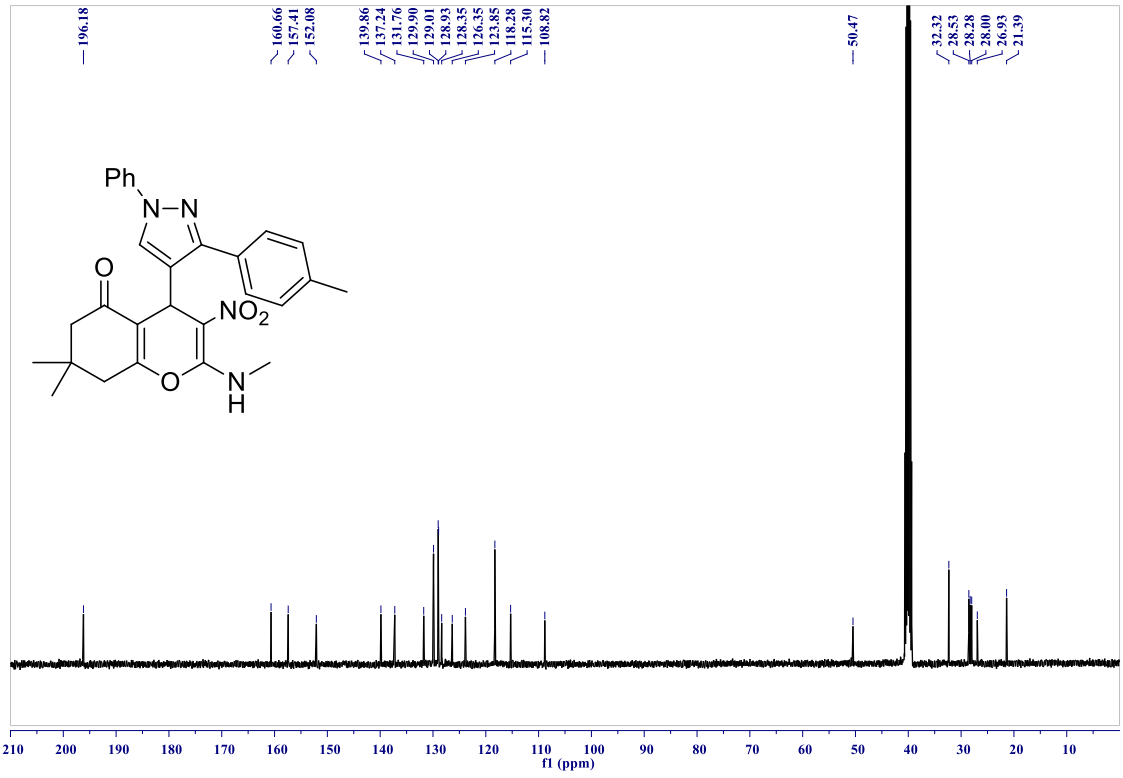


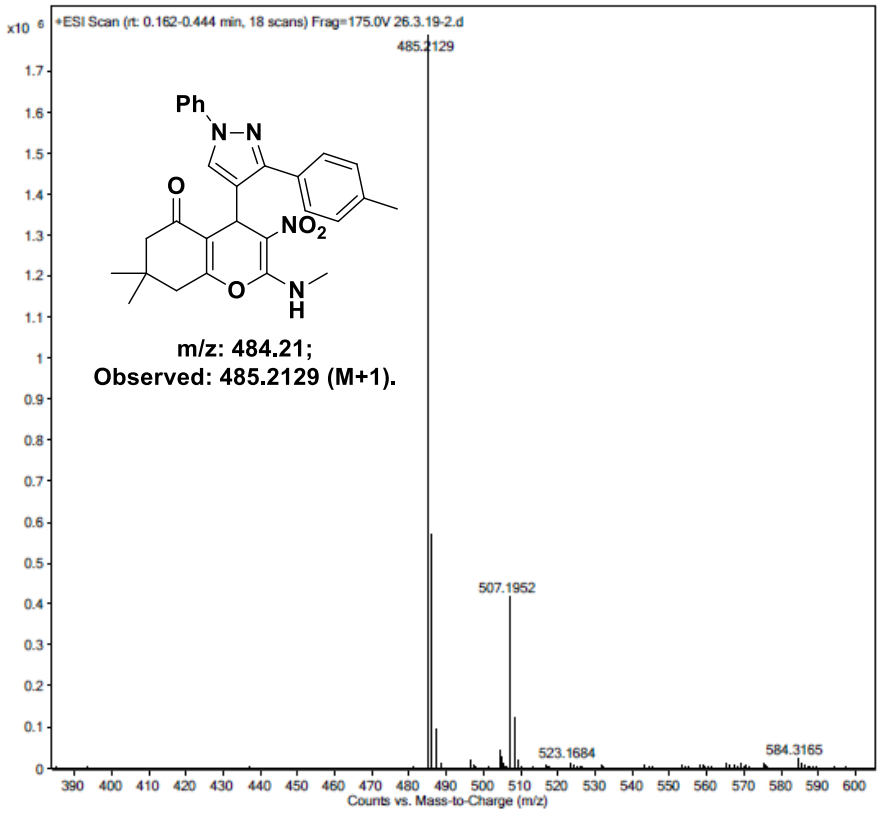

196.21
160.71
157.41
152.10
139.83
134.64
129.92
129.14
128.46
128.36
128.07
126.43
123.89
118.33
115.23
108.86
50.49
32.36
28.58
28.22
28.08
26.93
Ph
N–N
O
NO2
O
N
H
f1 (ppm)


x10 6
*ESI Scan (rt: 0.133-0.481 min, 22 scans) Frag=175.0V 26.3.19-1.d
471.1974
493.1797
509.1527
556.2856
m/z: 470.20;
Observed: 471.1974 (M+1).
Counts vs. Mass-to-Charge (m/z)

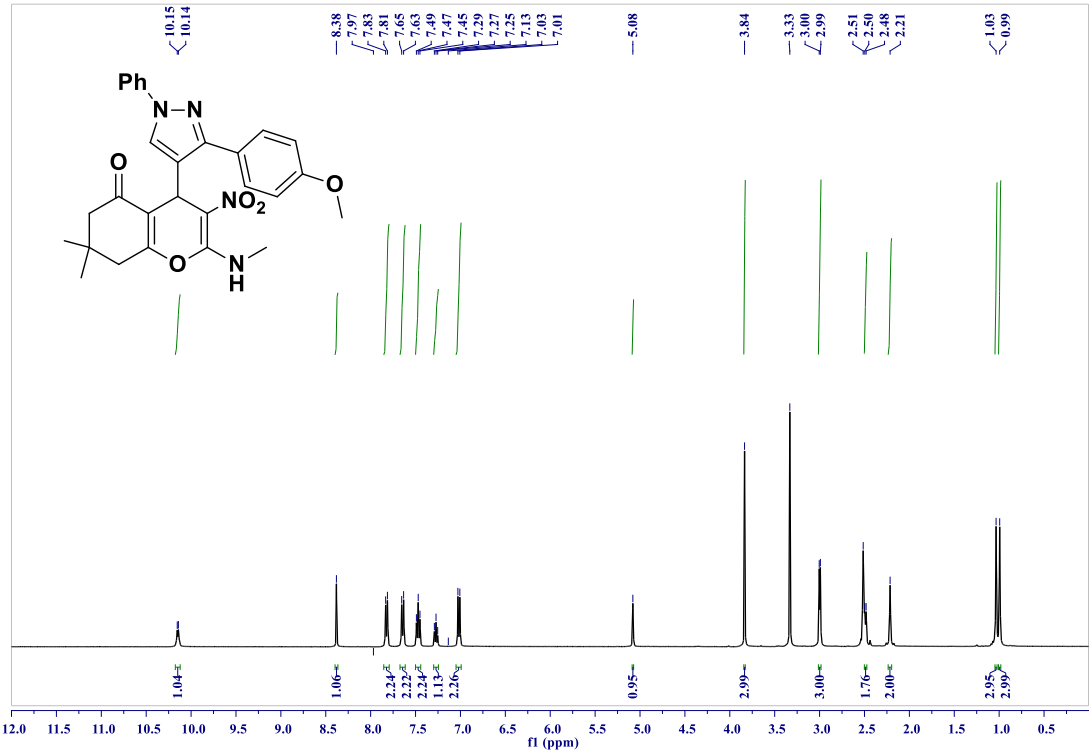
7,7-dimethyl-2-(methylamino)-3-nitro-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-7,8-dihydro-4H-chromen-5(6H)-one (8b):

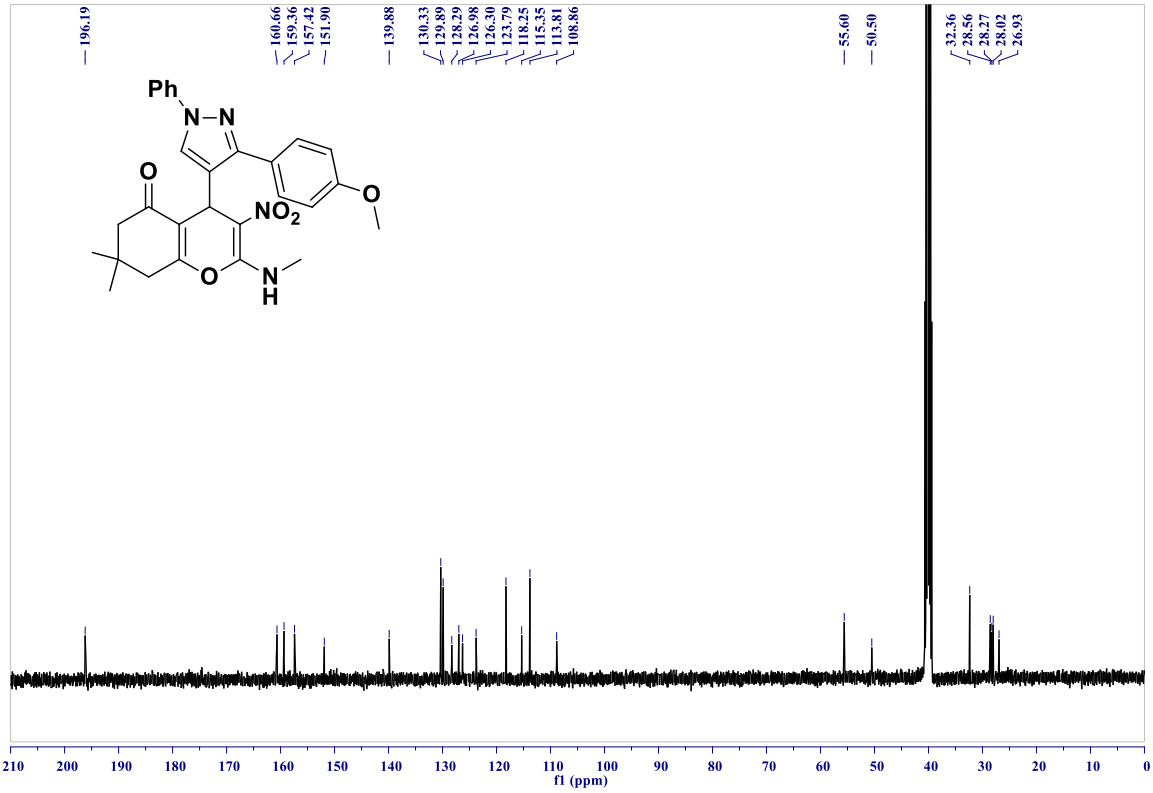


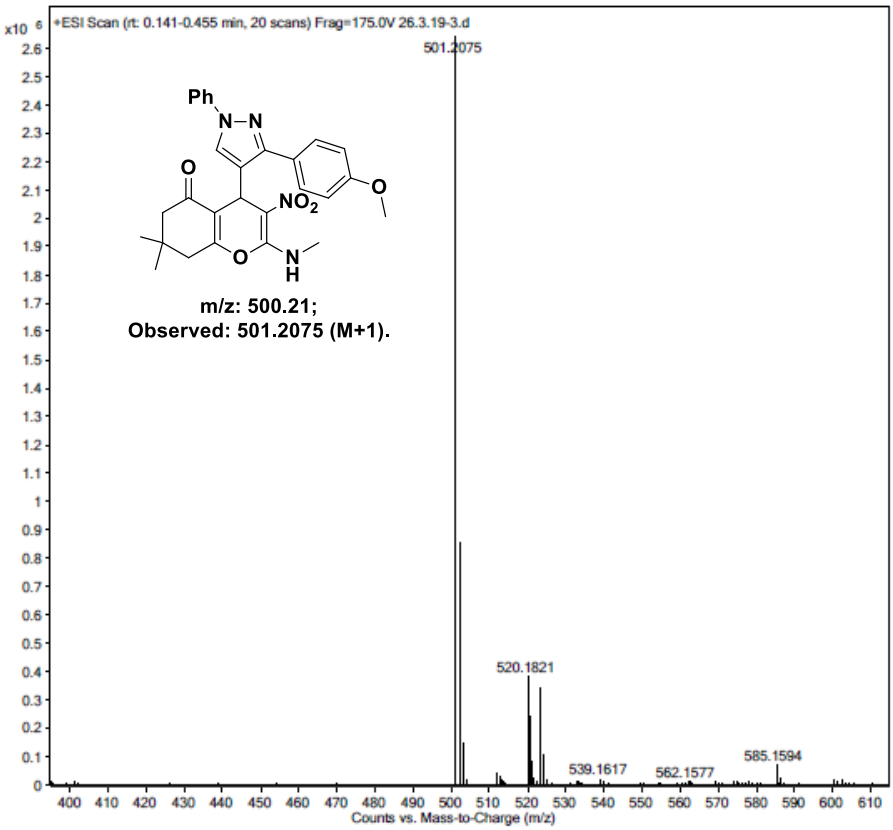




4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-2-(methylamino)-3-nitro-7,8-dihydro-4H-chromen-5(6H)-one (8c):




196.19
160.66
159.36
157.42
151.90
139.88
130.33
129.89
128.29
126.98
126.30
123.79
118.25
115.35
113.81
108.86
55.60
50.50
32.36
28.56
28.27
28.02
26.93
Ph
N–N
O
NO2
O
O
N
H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


x10 6
*ESI Scan (rt: 0.141-0.455 min, 20 scans) Frag=175.0V 26.3.19-3.d
501.2075
520.1821
539.1617
562.1577
585.1594
Ph
N–N
O
NO2
O
O
N
H
m/z: 500.21;
Observed: 501.2075 (M+1).
Counts vs. Mass-to-Charge (m/z)

2.8 References

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7. Jadhav, A. M.; Krishnammagari, S. K.; Kim, J. T.; Jeong, Y. T. *Tetrahedron* **2017,** *73,* 5163.
8. Mao, J.; Wang, J.; Zhang, W.; Li, Z.; Zhu, J.; Guo, C. *ARKIVOC,* **2016,** *(iii),* 171.
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12. Krishnammagari, S. K.; Lee, S. M.; Jeong, Y. T. *Res. Chem. Intermed.* **2018,** *44,* 517.
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CHAPTER-III

Synthesis of spiro pyrazolone-oxindole and bicyclic pyrazolone derivatives *via* solvent dependent regioselective aza-1,4/1,6-Michael and intramolecular cycloaddition under catalyst-free conditions

CHAPTER-III

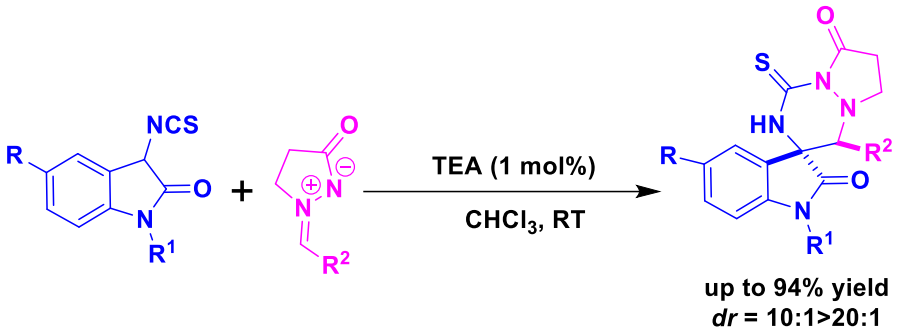
3.1 Introduction

3.1.1 Methods for the synthesis of dinitrogen-fused spirooxindoles

The cycloaddition reaction is a prevalent synthetic tool for the construction of valuable cyclic, polycyclic, and heterocyclic skeletons. In recent years, cycloaddition reactions have been the subject of significant research attention. Today, cycloaddition reactions have been extensively explored by transition-metal catalysis, photo-redox catalysis, asymmetric Lewis acid catalysis, C–H bond activation, and free radical-initiated cascades etc. Cycloaddition reactions [2+2], [3+2] and [4+2] are efficient methodologies in accessing challenging structures and extensively used by chemist for synthesizing natural, agrochemicals and other interesting pharmaceutical compounds. These strategies have many advantages, such as good atom-economy, abundance and modularity of starting materials and also attracted the attention of many organic chemists due to their promising reactivities such as excellent chemo- and stereoselectivities. Until now, several 1,3-dipoles, such as azomethine ylides, nitrones, *N*-Imides and pyridinium ylides have been studied and used for the synthesis of functionalized pyrrolidine, dihydrooxazole, and isoxazoles *via* 1,3-dipolar cycloaddition reactions (Michael addition, followed by Mannich type cyclization).[1] Among them, azomethine imines (acyclic and *N,N′*-cyclic) are readily accessible as quite stable compounds or intermediates for the synthesis of diverse five-membered heterocycles[2] by means of 1,3-dipolar cycloadditions (1,3-DC) under thermal[3a] or catalyzed[3b] conditions. The asymmetric processes have been performed using chiral substrates, chiral metal complexes[4] or organocatalysts.[5] However, the *N,N′*-cyclic azomethine ylides 1,3-dipoles were mainly prepared by the condensation of pyrazolidin-3-one with aldehydes. Different sorts of azomethine ylides for the diversity of reactions and compounds are still underdeveloped and highly desirable.

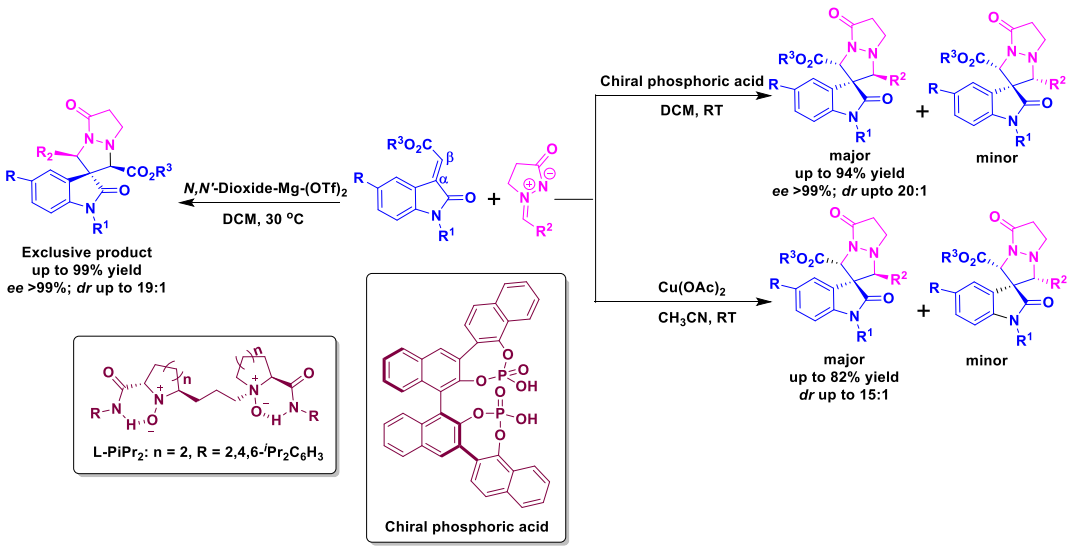
On the other hand, spirooxindole scaffolds, especially spiro heterocyclic oxindoles is an important research topic in organic and medicinal chemistry because of their key scaffolds found in various clinical pharmaceuticals and natural spirooxindole alkaloids with significant bioactive profile (As shown **Chapter-I & Figure-4A**). Accordingly, numerous elegant synthetic approaches have been developed for their synthesis over the past years and have been used in different therapeutic areas. Although spiro heterocyclic oxindoles fused with a five- or six-membered ring system at the C3-position have been well explored, there are still limited reports on the synthesis of spiro heterocyclic oxindoles through *N,N′*-cyclic azomethine imines.

In this connection, **Rui Wang** group demonstrated the base-catalyzed diastereoselective [3+3] annulations in between 3-isothiocyanatooxindoles and azomethine imines to give 3,3'-triazinnyl spirooxindoles at room temperature with high yields and diastereoselectives **(Scheme-3.1)**. [6]



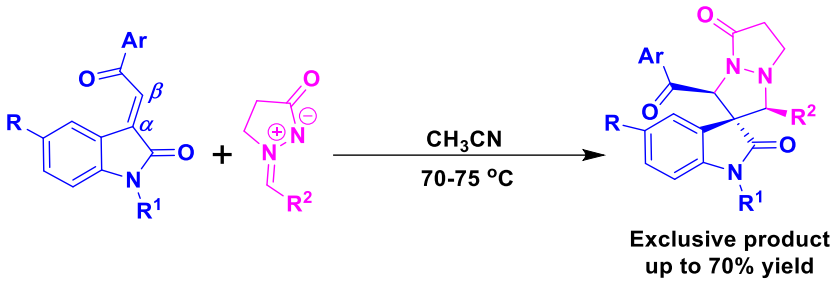
Scheme-3.1: *Base-catalyzed [3+3] cycloaddition of isothiocyanatooxindoles with azomethine imines.*

Later the same group achieved the synthesis of spiro[pyrazolidin-3,3′-oxindoles] by [3+2]-cycloaddition reaction (*β*-regioselective 1,4-aza Michael addition and intramolecular cyclization) of azomethine imines and methyleneindolinones in presence of chiral *bis*-phosphoric acid afforded with good yields.[7a] Next, **Feng** group carried out the same reaction in the presence of *N,N′*-dioxide–$Mg(OTf)_2$, the use of this catalyst afforded exclusive product with excellent yields and high enantioselectivities.[7b] Further, **J-T Sun** group demonstrated the use of the copper catalyst for 1,3-dipolar cycloaddition reaction of methyleneindolinones and *N,N′*-cyclic azomethine imines, the reaction has been developed under mild reaction conditions afforded with good yields (**Scheme-3.2**). [7c]



Scheme-3.2: *Synthesis of dinitrogen-fused spirooxindoles via β-regioselectivity.*

In a similar approach, **Yan** and co-workers reported a catalyst-free method for 1,3-dipolar cycloaddition of cyclic azomethine imines with 3-phenacyliceneoxindoles gave polysubstituted spiro[indoline-3,2′-pyrazolo[1,2-*a*] pyrazoles] in good yields and with high diastereoselectivity (**Scheme-3.3).** [8]



Scheme-3.3: *Synthesis of spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazoles].*

3.1.2 Methods for the synthesis of isoxazole based spirooxindoles

3-Methyl-4-nitro-5-isatylidenyl-isoxazole[9a] represents an excellent intermediate, having two reactive cites at α and β positions to the unsaturated double bond as shown in **Figure-3.1**. This feature has been applied for use as a dipolarophile for the construction of functionalized 3,3-Disubstituted oxindoles / spirocyclic oxindoles (*via* tandem Michael addition and Aldol/Mannich reactions)[9b-f] to give the desired product in good yields with excellent regio- and/or stereoselectivity. Recently the 3-methyl-4-nitro-5-isatylidenyl-isoxazole have been extensively used for various cycloaddition reactions.

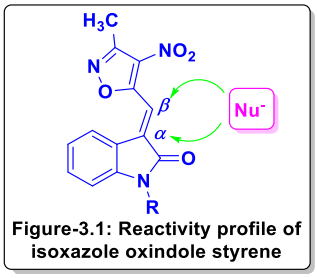
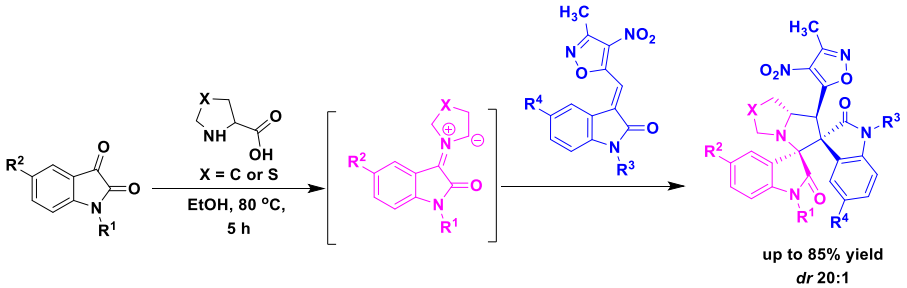


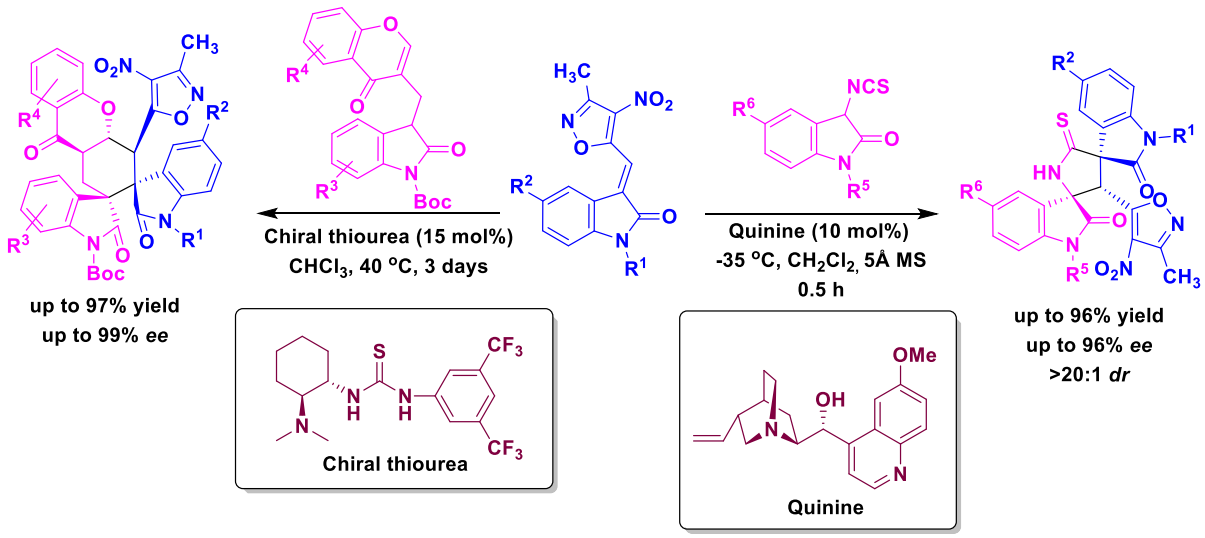
Figure-3.1: Reactivity profile of isoxazole oxindole styrene

In this regard, **Y. Zhou** and co-workers developed a one-pot three component method for the synthesis of *bis*-oxindole containing isoxazole-fused spiropyrrolidines *via* a catalyst-free cycloaddition reaction of azomethine ylides **(**Generated by the reaction of functionalized isatins and α- amino acids) and 3-methyl-4-nitro-5-styrylisoxazole[10] with up to 85% yields (**Scheme-3.4).**



Scheme-3.4: *Synthesis of bis-oxindole containing isoxazole-fused spiropyrrolidines.*

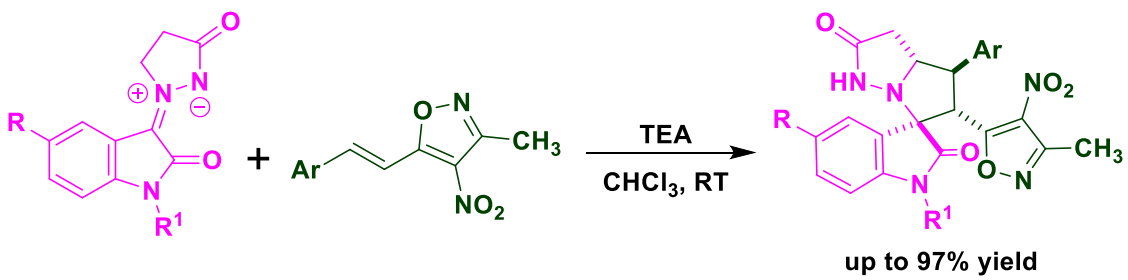
In an identical study, **Liu** and co-workers synthesized the isoxazole-dispirobisoxindole *via* β-regioselective [3+2]-cycloaddition reaction of 3-methyl-4-nitro-5-isatylidenyl-isoxazoles and 3-isothiocyanato oxindoles using quinine as an organo chiral catalyst. Later same group achieved the synthesis of bispirocyclic hexahydroxanthones *via* domino Michael/Michael addition reaction in between chromone-oxindoles and 3-methyl-4-nitro-5-isatylidenyl-isoxazoles and it offers excellent results (up to 91% yield, >20:1 *dr* and up to >99% *ee*) in presence of chiral thiourea as an organocatalyst.[11a,b]



Scheme-3.5: *Synthesis of isoxazole based dispirobisoxindole and bispirocyclic hexahydroxanthones.*

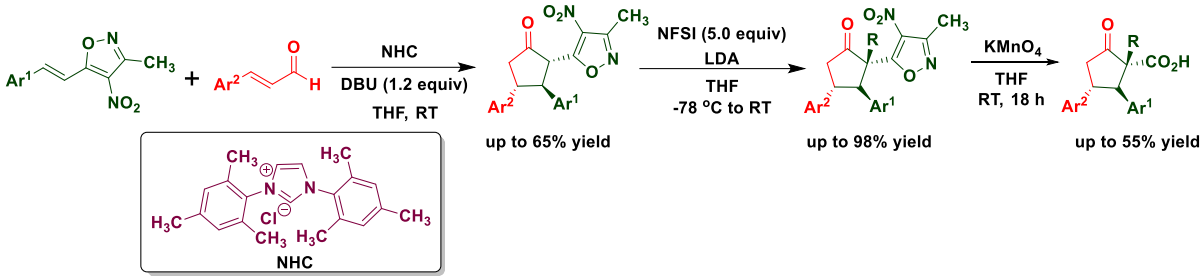
3.1.3 3-Methyl-4-nitro-5-styrylisoxazoles as a reactive partner in [3+2] cycloaddition reactions

In a recent report, **Chowhan** and his group demonstrated an unusual C–N–C [3+2]-cycloaddition of 3-methyl-4-nitro-5-styrylisoxazole and isatin *N,N'*-cyclic azomethine imines with high diastereoselectivity and upto 97% of excellent yield.[12a]



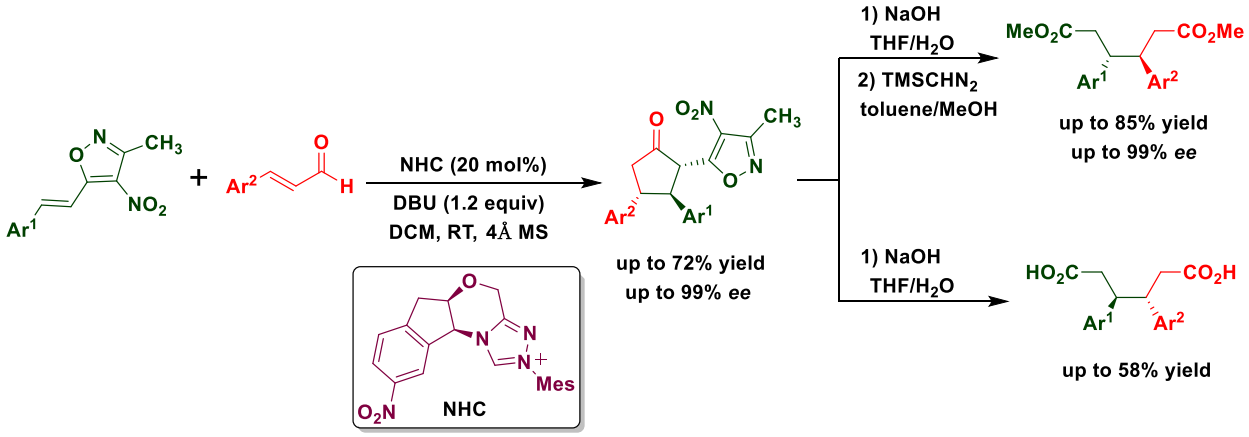
Scheme-3.6: *synthesis of isoxazole-containing spirooxindoles by an abnormal [3 + 2] cycloaddition.*

Adamo group described an *N*-heterocyclic carbene catalysed homoenolate addition to 4-nitro-5-styrylisoxazoles with cinnamaldehyde to give substituted cyclopentanones with moderate to good yields. Generated cyclopentanones were further used for α-fluorination followed by hydrolysis to give 1-fluoro-5-oxo-2,3-diarylcyclopentane carboxylic acids (**Scheme-3.7**).[12b]



Scheme-3.7: *Synthesis of functoinalised cyclopentanones using NHC as catalyst.*

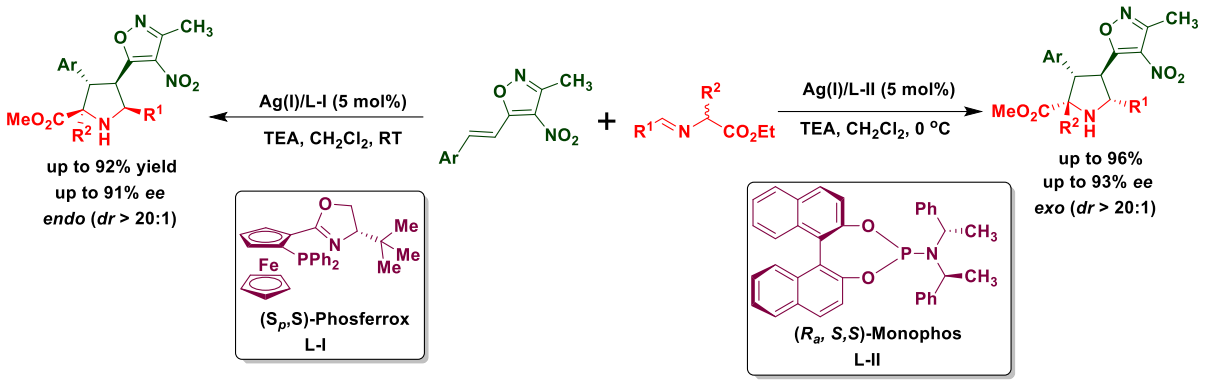
Later, similar strategy was developed by **Ender's** group by employing an asymmetric NHC-catalyzed [3+2] cycloaddition of enals with masked cinnammates in moderate to good yields and high stereoselectivities. They have also extended this strategy for the synthesis of 3*S*,4*S*-disubstituted adipic acid methyl esters and pharmaceutically useful gababutins by ring opening of isoxazole moiety (**Scheme-3.8**).[12c]



Scheme-3.8: *Synthesis of functionalized cyclopentanones using chiral NHC.*

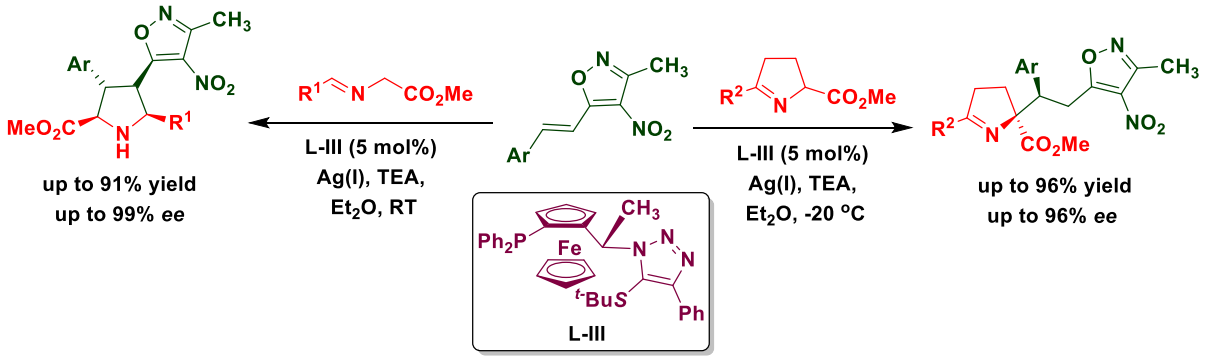
In 2018, **Wang** and co-workers reported the ligand and temperature controlled selective synthesis of tetra-substituted pyrrolidine derivatives *via* [3+2]-cycloaddition reaction of glycine-imine (as azomethine ylide equivalent) and isoxazole-styrene at 0 °C and RT. They screened many

combinations of chiral ligands in presence of copper and silver salts. They have been observed that the formation of endo isomer (*dr* >20:1) with AgOAc/(S_p,S)-Phosferrox (**L-I**) and exo isomer (*dr* >20:1) with AgOAc/Monophos (**L-II**) combination (**Scheme-3.9**).[12d]



Scheme-3.9: *Asymmetric synthesis of tetra substituted pyrrolidines using 3-methyl-4-nitro-5-styrylisoxazole and glycine-imines via [3+2]-cycloaddition reaction.*

Almost in the same period, **Fukuzawa** and co-workers demonstrated an application of (*R*,*Sp*)-ThioClickFerrophos (**L-III**)/AgOAc catalyst system for the synthesis of 1-pyrroline-5-carboxylates *via* 1,3-dipolar cycloaddition reaction of glycine-imines and isoxazole-styrenes in presence of TEA as a base at RT with moderate to excellent yields and high enantioselectivity. Similarly, cyclic iminoesters were reacted in Michael fashion with isoxazole-styrenes at -20 °C to give pyrrolidine derivatives to offer up to 96% of the yields and enantioselectivity up to 96% (**Scheme-3.10**).[12e]



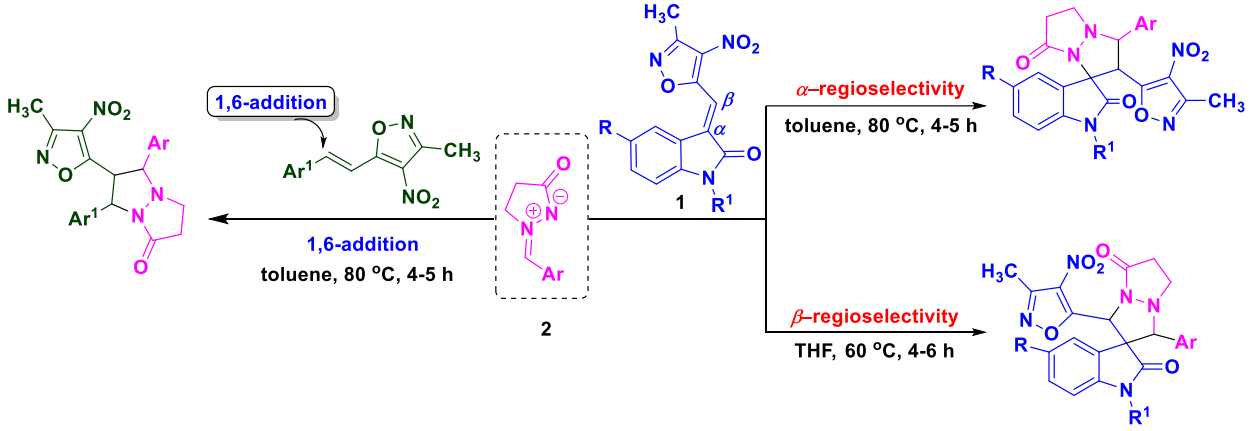
Scheme-3.10: *Asymmetric synthesis of functionalized isoxazole-pyrrolidine hybrids.*

All these methods have their own advantage in terms of regio/stereoselectivity and product yields. However, a switchable regioselective reaction has never been realised on 3-methyl-4-nitro-5-isatylidenyl-isoxazole. Considering the importance of spiro/bicyclic pyrazolones, herein we

report the first example of solvent dependent, regioselective-switchable reaction between *N, N′*-cyclic azomethine imines and 3-methyl-4-nitro-5-isatylidenyl-isoxazoles leading to complex dinitrogen-fused bicyclic and spirocyclic oxindoles with good yields.

3.2 Present study

Considering the biological prominence of dinitrogen-fused heterocyclics, herein we described first example of solvent dependent highly regioselective [3+2]-cycloaddition reaction of isoxazole-styrenes and azomethine imines under catalyst-free conditions to furnishing a library of pyrazolone-spirooxindole hybrids. Good regioselectivity for the isomeric structures were achieved in good yields by the reaction of isoxazole-oxindole-styrene (**1**) and azomethine imines (**2**) in different solvents and temperature. The developed method was extended for the synthesis of tri-substituted dinitrogen-fused pyrazolones by using 1,6-Michael addition reaction.

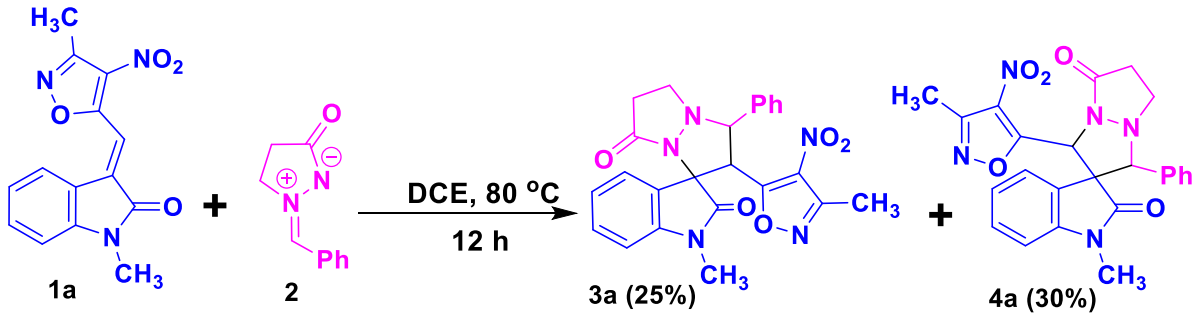


Scheme-3.11: Synthesis of *N, N′*-Fused spirooxindoles and diphenyltetrahydropyrazolo pyrazolones.

3.3 Results and Discussion

Towards achieving the synthesis of functionalized spirooxindole derivatives, we utilized 3-methyl-4-nitro-5-isatylidenyl-isoxazole (**1a**) and azomethine imine (**2**) as model substrates in dichloromethane (DCM) in the presence of organic bases (TEA and DABCO) and Lewis acids [$Zn(OTf)_3$, $AlCl_3$] at RT and heating (25 °C - 60 °C) did not yield the expected products (**Table-3.1; entries 1-5**). Then the same reaction was performed in 1,2-dichloroethane (DCE) at 80 °C, 12 h under catalyst-free condition. To our delight, the formation of products **3a** and **4a** were observed in 25% and 30% of yield respectively (**Table-3.1; entry 6**).

Encouraged by this result, and towards achieving the product selectivity, to reduce the reaction time and to get enhanced yields, above reaction was carried out in different solvents under catalyst-free conditions and the results were summarized in **Table-3.1** (**entries 7–26**). It is important to note that the polar solvents DMSO, DMF, CH_3CN, MeOH, EtOH and H_2O did not give the products even at elevated temperature. Even for the chlorinated solvents also the reactivity patterns were not consistent with overall yield of the products **3a** and **4a** [CH_2Cl_2 (no product), DCE (55%) and $CHCl_3$ (60%)] with respect to their boiling points and relative polarity. At this point, the other common solvents like toluene, xylene, ethylacetate, diethyl ether and tetrahydrofuran (from non-polar to medium polar) were tested for the reaction from 40 ^oC - 80 ^oC (without the catalyst). Surprisingly, the reaction in toluene and xylene at 80 ^oC gave **3a** in 84% and 70% respectively as major products along with **4a** in 5-10% as minor regio isomer (**Table-3.1; entries 14-15**). On the other hand, the reaction in tetrahydrofuran at 60 ^oC, gave the contrasting results *i.e.*, **4a** as major product (75%) and **3a** as minor product (15%) for 4 h (**Table-3.1; entry 21**). Both the isomers were characterized by ^1H, ^{13}C NMR and mass spectral data. The ^1H-NMR spectrum of the compound **3a** in $CDCl_3$ as two doublets at δ 5.05 (d, J = 10.8 Hz), and 4.49 (d, J = 10.8 Hz) ppm reveals that the phenyl and isoxazole ring containing protons are on adjacent carbons (**Figure-3.2**). Whereas for **4a** the two characteristic protons appeared as singlets at δ 5.97 and 4.12 ppm due to phenyl and isoxazole ring containing protons opposite to each other. The observed HRMS mass m/z of **3a** is 460.1614 (M+1) and **4a** is 460.1591 (M+1) further confirmed by the formation of the desired products.

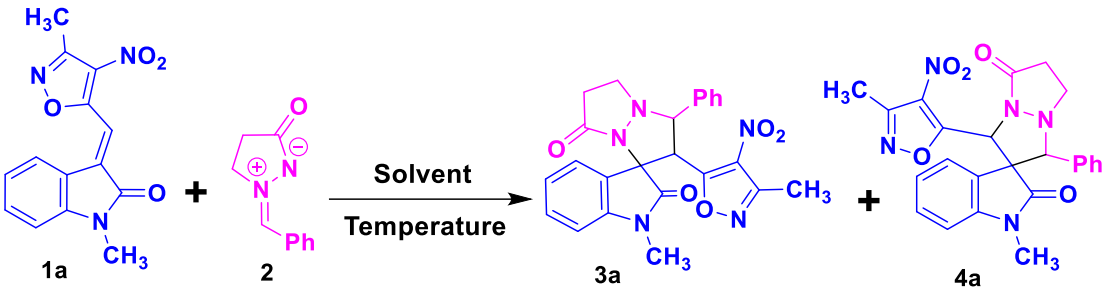


Scheme-3.12: *Synthesis of dinitrogen-fused spirooxindoles.*

At this juncture, we tried to understand the solvent effect on the outcome of the reaction. Towards this, different combinations of the solvents *i.e.*, toluene and tetrahydrofuran in different concentrations were studied and given in **Table-3.1** (**entries 22-26**). From these observations, we

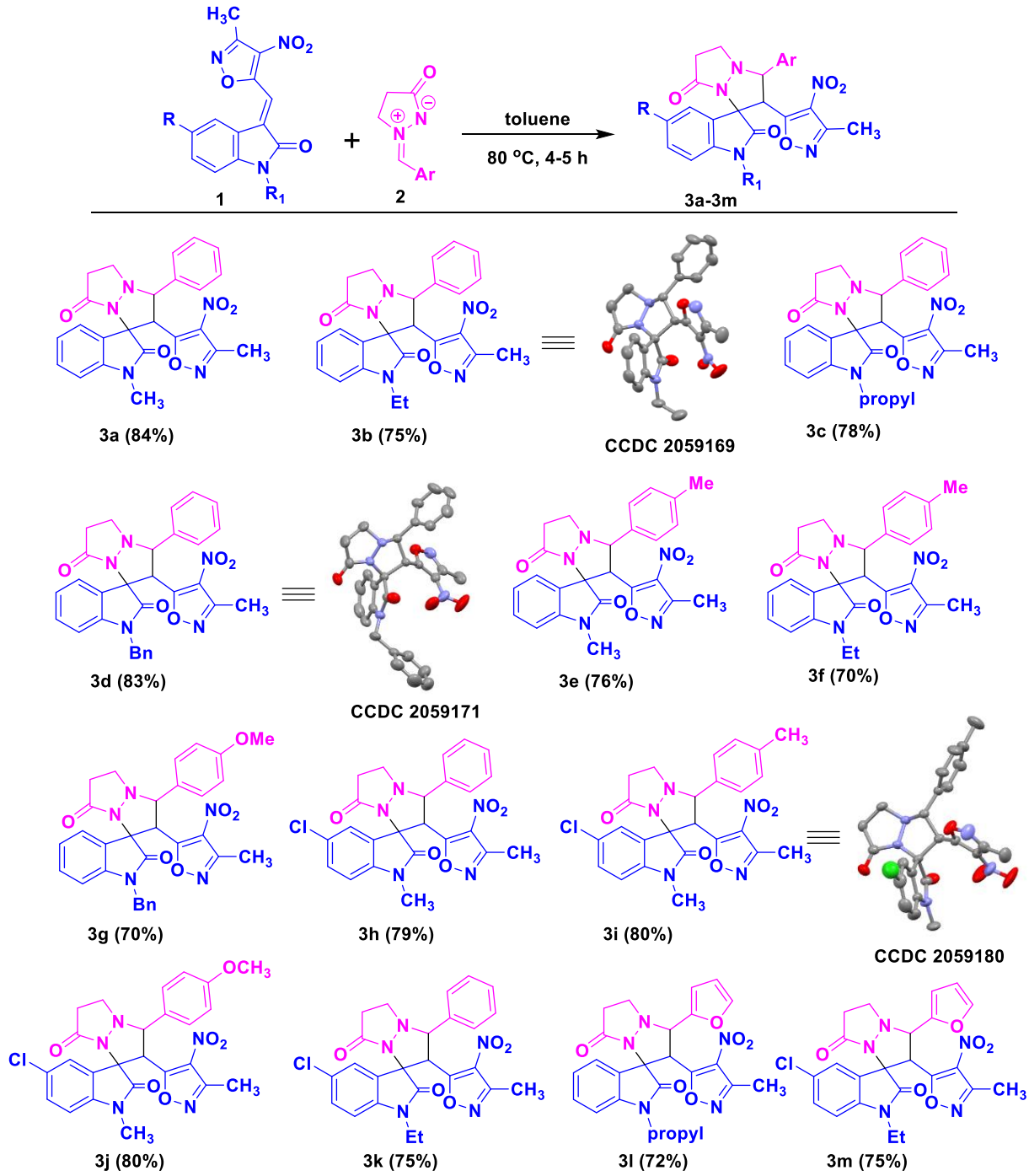
assume that polar chelating nature (solvation effect) of the tetrahydrofuran is helping to increase the electron density on the α-carbon of isoxazole-oxindole styrene which is facilitating the immediate attack of negatively charged nitrogen of azomethine imine **2** (1,3-dipole) to deliver the product **4a** as a major isomer.

Table-3.1: Optimization of Reaction Conditions. [a]



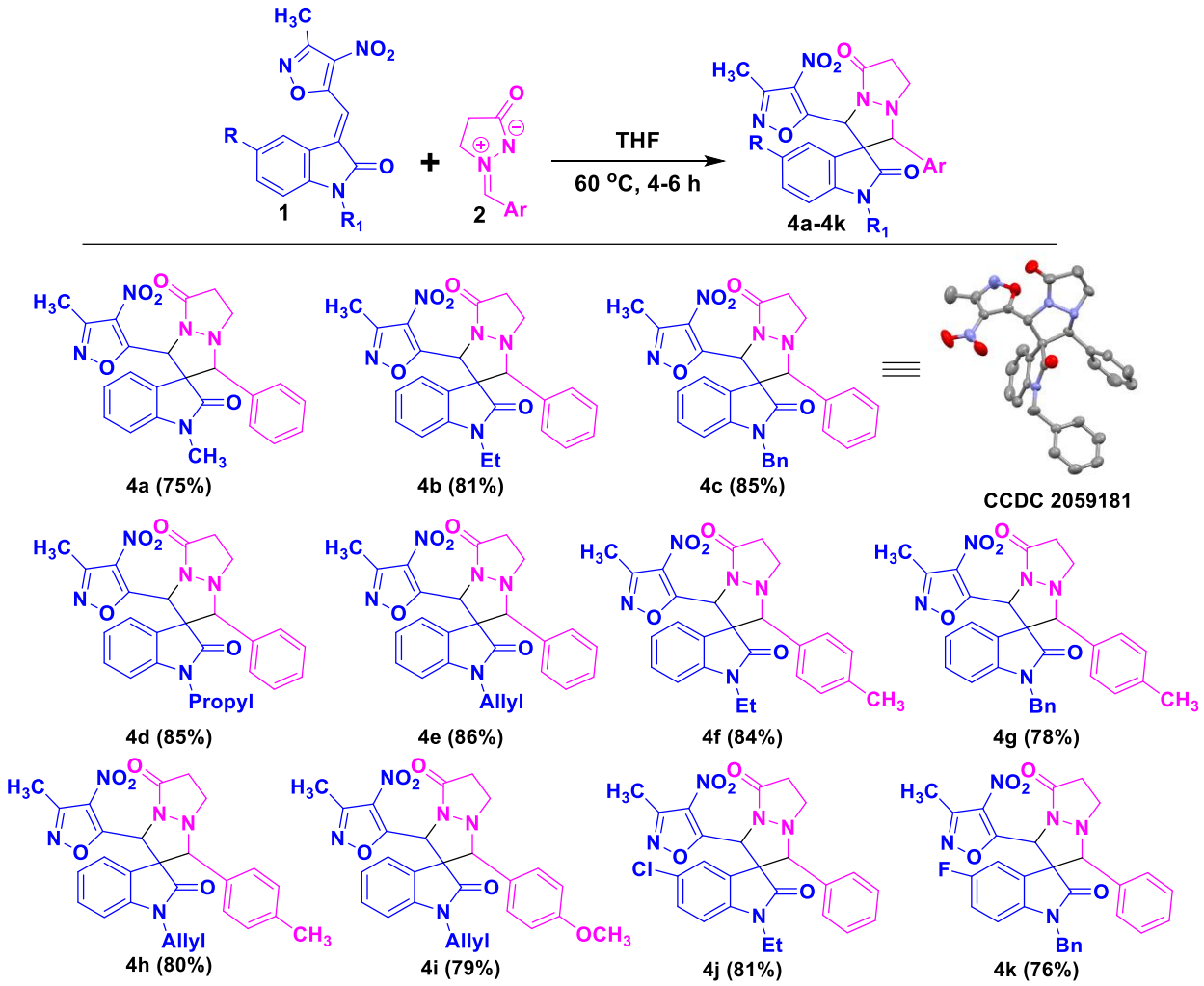
Entry	Solvent	Catalyst (20 mol%)	Temp (°C)	Time (h)	Yield (%) [b]	
					3a	4a
1	CH_2Cl_2	TEA	RT	12	ND	ND
2	CH_2Cl_2	DABCO	RT	12	ND	ND
3	CH_2Cl_2	Zn $(OTf)_3$	RT	12	ND	ND
4	CH_2Cl_2	$AlCl_3$	RT	12	ND	ND
5	CH_2Cl_2	-	60	12	ND	ND
6	DCE	-	80	12	25	30
7	$CHCl_3$	-	60	12	15	45
8	DMSO	-	80	12	ND	ND
9	DMF	-	80	12	ND	ND
10	CH_3CN	-	80	12	ND	trace
11	MeOH	-	80	12	ND	ND
12	EtOH	-	80	12	ND	ND
13	H_2O	-	80	12	ND	ND
14	**toluene**	**-**	**80**	**4**	**84**	**10**
15	xylene	-	80	4	70	5
16	toluene	-	RT	24	trace	ND
17	EtOAc	-	80	12	ND	ND
18	diethyl ether	-	40	4	ND	ND
19	THF	-	80	12	20	60
20	THF	-	RT	48	ND	60
21	**THF**	**-**	**60**	**4**	**15**	**75**
22	THF:tol	-	80	4	45	30[c]
23	THF:tol	-	80	4	55	20[d]
24	THF:tol	-	80	4	60	15[e]
25	THF:tol	-	80	4	30	40[f]
26	THF:tol	-	80	4	25	55[g]

[a]All the reactions were performed with **1a** (0.35 mmol) and **2** (0.35 mmol) in 4 mL of solvent. [b]Isolated yields. [c-g] The reactions were performed with 1:1, 1:2, 1:3, 2:1 and 3:1 ratio of THF and toluene.



Scheme-3.13: *Substrate scope for the synthesis of functionalized dinitrogen-fused spirooxindoles (**3a-3m**).*

After identifying the two optimal reaction conditions, we turned our attention towards substrate scope of the reactions. Accordingly, the substituted isatins (substitution on aromatic ring and nitrogen) and azomethine imines (aromatic and hetero aromatic) were reacted under optimized conditions (both in toluene and THF) to afford corresponding cycloaddition products (**3a-3m** and **4a-4k**) with good yields 70-86% (**Scheme-3.13 & Scheme-3.14**) in 4-6 h. All newly synthesized compounds were characterized using ^{1}H, ^{13}C-NMR and mass spectrometry. Further, towards establishing the regioselectivity, single crystal X-ray crystallographic data was obtained for the compounds **3b**, **3d**, **3i** and **4c**. The X-ray crystallographic data clearly indicating that the isoxazole and phenyl groups adjacent to each other in compounds of **Scheme-3.13** whereas in compounds of **Scheme-3.14** the rings were assigned opposite each other.



Scheme-3.14: *Substrate scope for the synthesis of functionalized dinitrogen-fused spirooxindoles (4a-4k).*

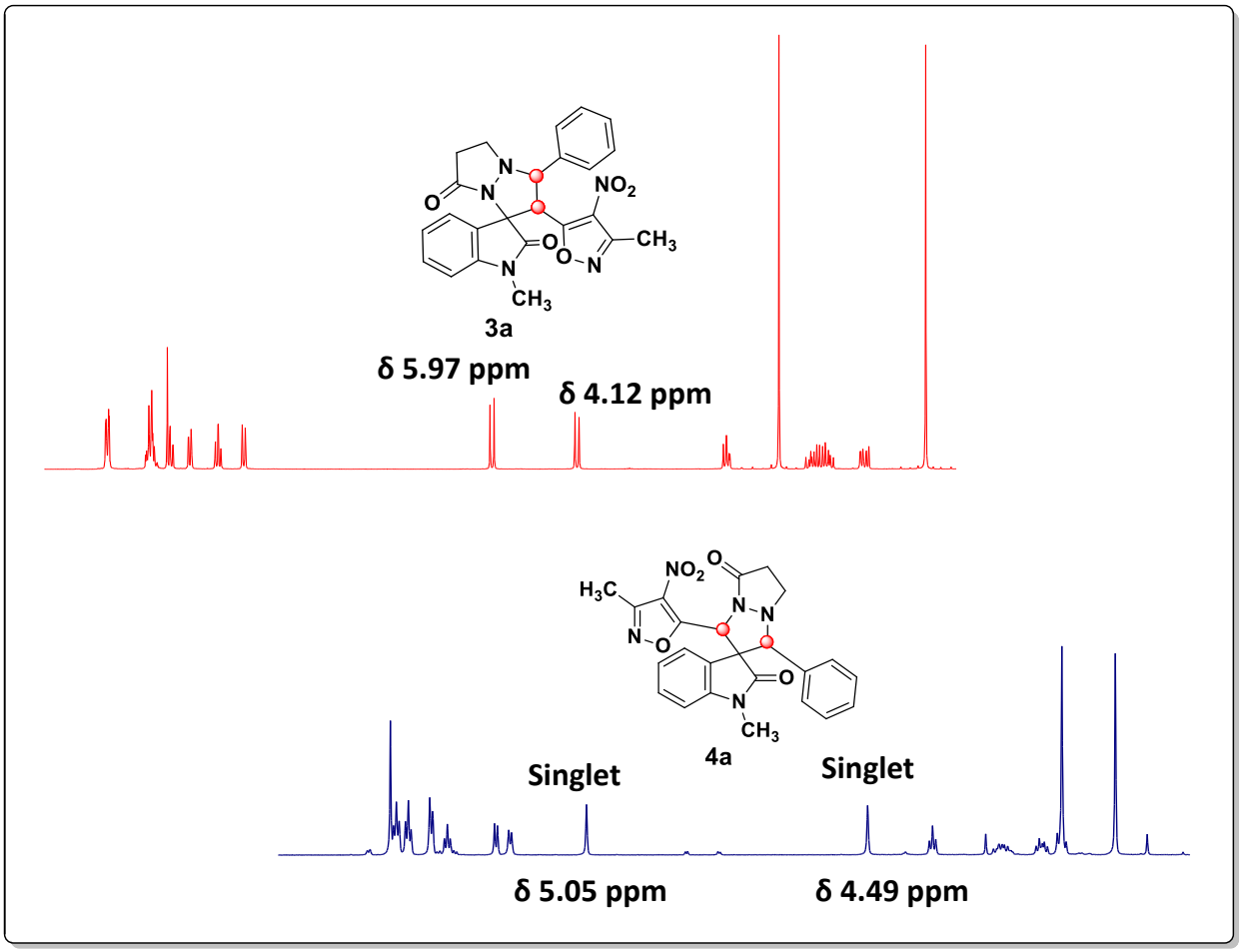


Figure-3.2**: Comparison of ^{1}H-NMR spectrum of **3a** and **4a.

Based on above results and single crystal data, a plausible mechanism was proposed for the [3+2]-cycloaddition reaction (**Figure-3.3**). Azomethine imine (**2**) reacts with 3-Methyl-4-nitro-5-isatylidenyl-isoxazole (**1**) *via* aza-1,6 Michael addition (of *α*-regioselectivity) to give adduct (**I**). This adduct will undergo intramolecular cyclization in presence of toluene (catalyst-free condition) to afford desired product **3**. Where as in THF the same reaction undergoes aza-1,4 Michael addition (of *β*-regioselectivity) followed by intramolecular cyclization to delivering the compound **4**.

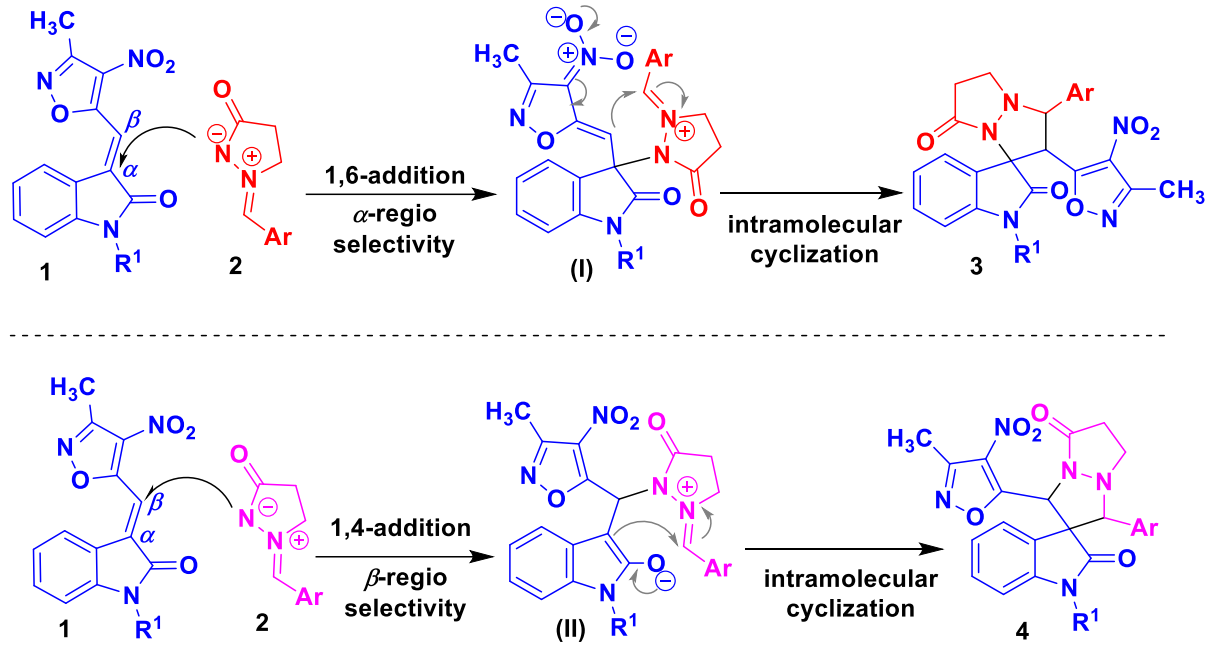


Figure-3.3: *Plausible mechanism of the reaction.*

Considering the biological importance of spirooxindoles, isoxazoles and pyrazolones (**Chapter-I; Figure-3)**, we extended our strategy for the synthesis of diphenyltetrahydropyrazolo pyrazolones (dinitrogen-fused heterocyclics). To achieve this, simple isoxazole-styrenes (**5**) were treated with azomethine imines (**2**) under optimized reaction conditions (in toluene and THF). To our surprise, the reaction was successful only in toluene (as reaction medium) to delivering isoxazole based dinitrogen-fused compounds (**6a-6k**) with good yields 65-90% in 4-5 h (**Figure-3.4**). Similar to above mechanism, in this case also the desired compounds (**6)** are formed by the reaction of isoxazole styrene **5** with azomethine imine (**2**) to afford adduct (**III**) *via* aza-1,6-Michael addition followed by intramolecular cyclization. The isoxazole moiety was also used as masked ester to generate carboxylic acid *via* ring opening under basic/oxidative conditions.[13] Finally the cycloadducts **3a** and **6b** were converted into carboxylic acids **7a** and **8b** by treating with aq. NaOH (ring opening of isoxazole moiety) in 78% and 85% respectively (**Schemes 3.15** and **3.16**). Then the carboxylic acid (**8b**) further functionalized into ester (**9b**) and amide (**10b**) derivatives with 65% and 85% of the yields using standard conditions (**Scheme-3.16**). These transformations (and other possible functional group interconversions of carboxylic acid) may lead to the generation of library of compounds, which may be useful in medicinal chemistry.

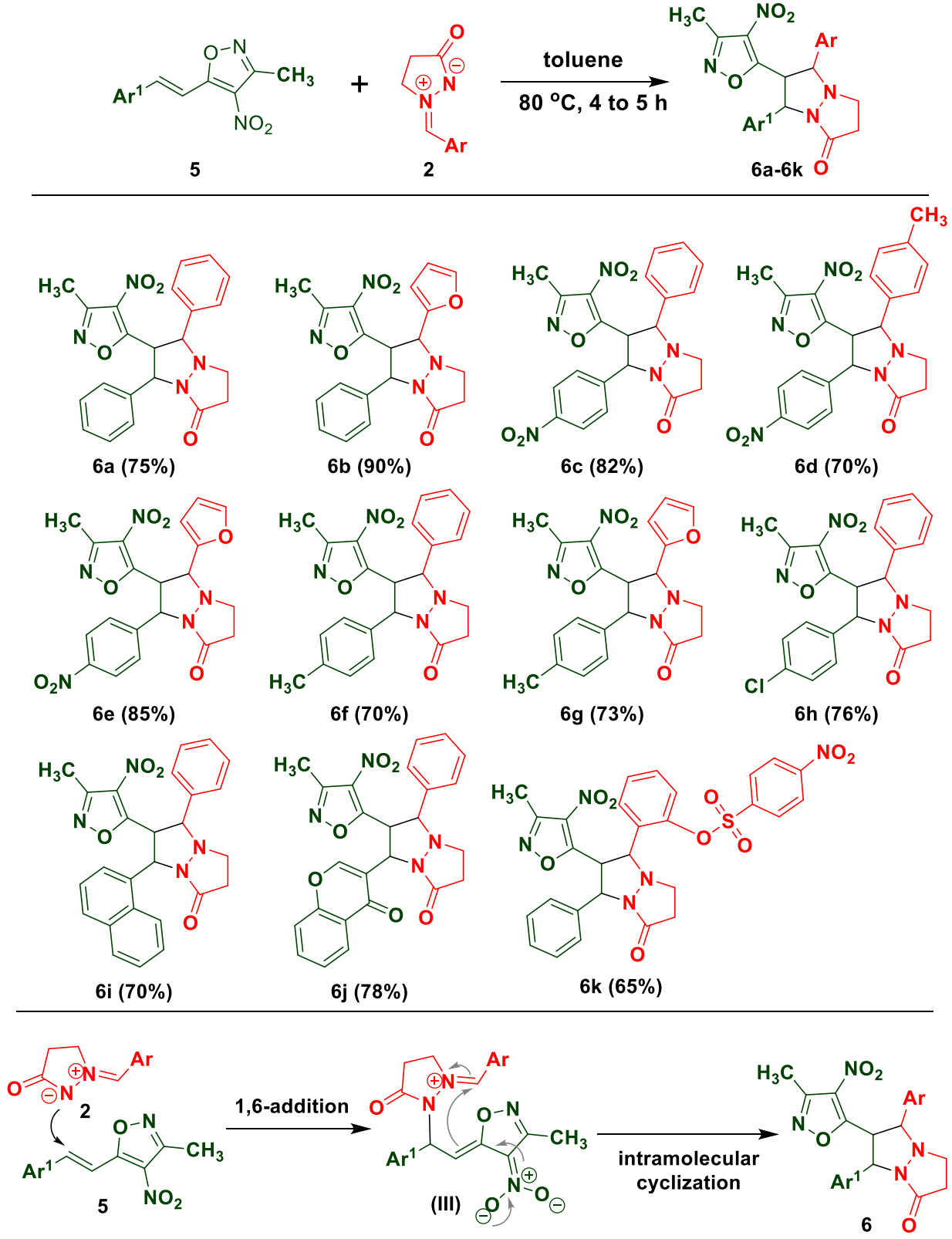
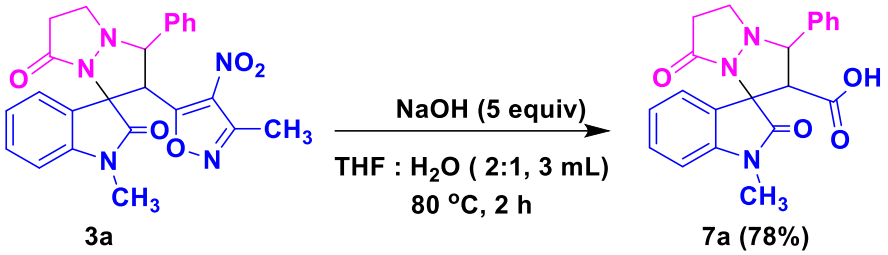
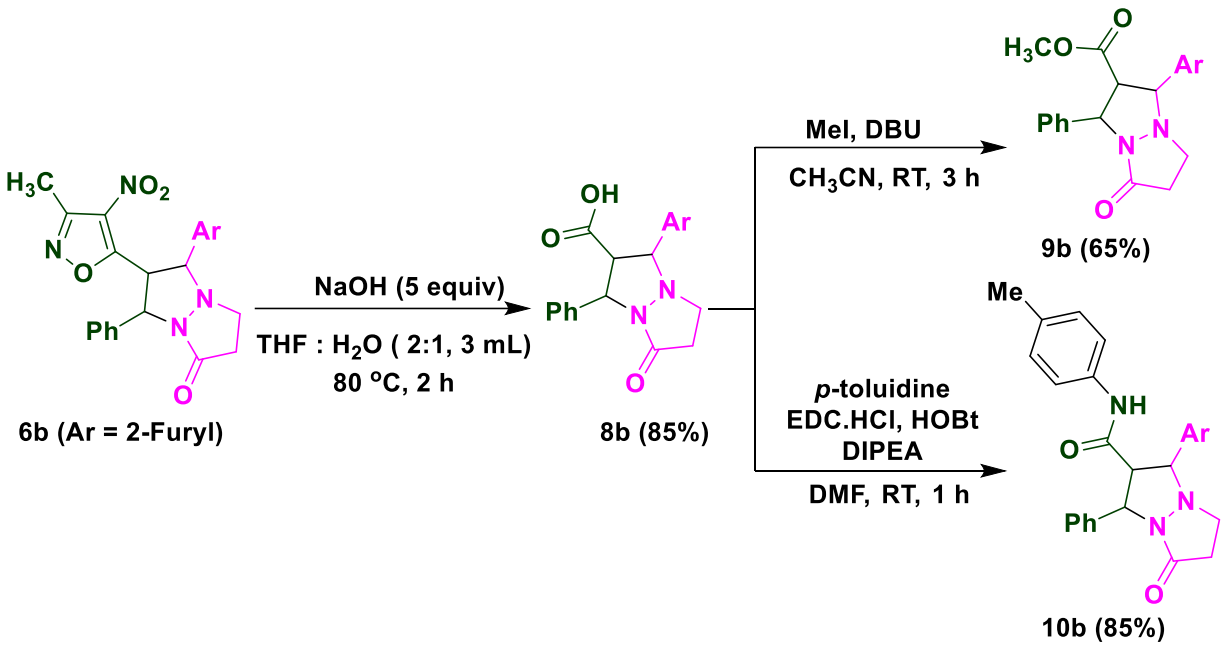


Figure-3.4: *Substrate scope for the synthesis of functionalized N, N'-Fused bicyclic pyrazolones and possible mechanism for the reaction.*



Scheme-3.15: *Synthesis of spirooxindole-pyrazolone carboxylic acid derivative* ***7a****.*



Scheme-3.16: *Functionalization of pyrazolo pyrazolone (****6b****).*

3.4 Conclusion

In summary, we have demonstrated a simple and catalyst-free [3+2]-cycloaddition reaction for the synthesis of dinitrogen-fused pyrazolone derivatives with moderate to good yields. The reaction proceeds *via* aza-1,4/1,6 (Michael) addition of azomethine imines on a conjugated system followed by intramolecular cyclization. Generated dinitrogen-fused heterocyclic compounds **3a** and **6b** were converted into pyrazolone-based carboxylic acids by hydrolysis of isoxazole ring. The carboxylic acid can be used as handle for making hybrid molecules using esterification or amide bond formation as shown in **Schemes-3.16** that may open significant importance of these molecules in medicinal chemistry.

3.5 Experimental

General: All the solvents and required chemicals were procured from SD-Fine, Sigma-Aldrich, and Spectrochem, and used without purification and distillation. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker Avance 400 or 500 MHz spectrometers using $CDCl_3$ and DMSO-d_6 as solvents and reported in δ ppm. The mass spectra of all the compounds were record using Agilent Technologies-6530.

3.5.1 General procedure

General (representative) procedure for the synthesis of [3+2] cycloaddition reaction:

To a solution of isoxazole-styrene (**1**) or (**5**) (0.35 mmol, 1 equiv) in THF/toluene (4 mL) was added azomethine imine (**2**) (0.35 mmol, 1 equiv) and the contents were heated (**Table-3.1**) for 4-6 h. After completion of reaction (monitored by TLC) the mixture was cooled to RT, solvent was evaporated and the crude product was purified by silica gel column chromatography. Elution of the column with Hexane/EtOAc (40-50%) gave the desired products **3/4/6**.

Procedure for synthesis of pyrazolo pyrazole carboxylic acids:

To a solution of cyclic adduct (**3a** or **6b**) (0.25 mmol, 1 equiv) in THF (2 mL) was added aq. NaOH [1.25 mmol, 5 equiv, 1 mL] and the resulting mixture heated at reflux for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 2N HCl at 0 ^{o}C. The mixture extracted into EtOAc (3X10 mL). The combined organic layers were dried using sodium sulfate. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography (Hexane/EtOAc) gave the desired products as white solids (**7a** or **8b**).

Procedure for synthesis of methyl 1-(furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-a] pyrazole-2-carboxylate (9b):

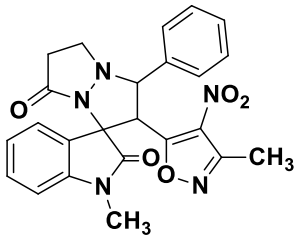
To a solution of carboxylic acid **8b** (0.32 mmol, 1 equiv) in CH_3CN (3 mL) was added DBU (0.32 mmol, 1 equiv) and MeI (0.38 mmol, 1.2 equiv). The reaction mixture was stirred at RT for 3 h. Then the crude product was purified over silica gel by column chromatography to afford the desired product **9b**.

Procedure for synthesis of 1-(furan-2-yl)-5-oxo-3-phenyl-N-(p-tolyl) hexahydropyrazolo[1,2-a] pyrazole-2-carboxamide (10b):

To a solution of the acid **8b** (0.32 mmol, 1 equiv) in DMF (3 mL) was added DIPEA (0.96 mmol, 3 equiv). The mixture was cooled to 0 ^{o}C and treated with EDC-HCl (0.64 mmol, 2 equiv), HOBt (0.64 mmol, 2 equiv) and the amine (0.38 mmol, 1.2 equiv). Then the reaction was stirred at RT for 1 h. After completion, the mixture was diluted with H_2O (15 mL) and extracted with EtOAc (15 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum. The resulting material was purified by silica gel column chromatography to provide the final product as a white solid **10b**.

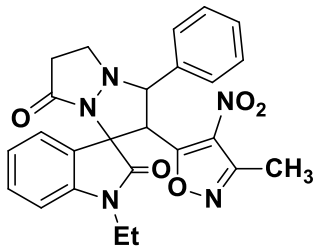
3.6 Spectral data

1-methyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3a):



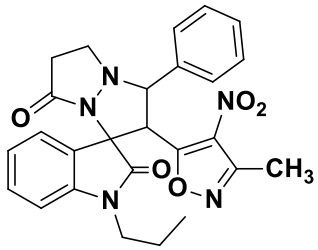
Yield = 134 mg (84%) Yellow solid; M.P: 183-185 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.59 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.04 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.89-6.82 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.17 (s, 3H), 2.99 – 2.80 (m, 2H), 2.64 – 2.57 (m, 1H), 2.20 (s, 3H**). ^{13}C NMR (100 MHz, CDCl$_3$) δ** 172.89, 167.35, 163.10, 155.70, 144.12, 133.83, 131.04, 130.76, 129.43, 129.18, 128.19, 124.08, 122.73, 122.01, 108.98, 70.96, 64.18, 59.54, 51.09, 36.15, 26.95, 11.17. **Mass (ESI-MS):** m/z Calculated for $C_{24}H_{21}N_5O_5$: 459.1543; Observed: 460.1614 (M+1).

1-ethyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3b):



Yield = 120 mg (75%) White solid; M.P: 168-170 °C **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.55 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.14 (m, 4H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 3.93 – 3.68 (m, 2H), 3.58 (t, *J* = 8.0 Hz, 1H), 2.97 (m 2H), 2.73 – 2.62 (m, 1H), 2.35 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 172.03, 166.93, 163.18, 155.75, 142.05, 133.57, 131.12, 130.70, 129.51, 129.23, 128.12, 127.96, 124.85, 123.98, 109.97, 70.88, 63.94, 59.06, 51.09, 36.13, 35.74, 12.01, 11.23. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{23}N_5O_5$ for: 473.1699; Observed: 474.1714 (M+1).

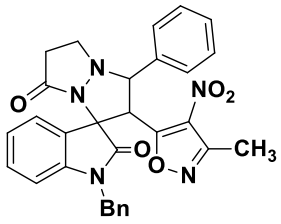
2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-1-propyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3c):



Yield = 121 mg (78%) Yellow solid; M.P: 168-170 °C **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.67 (d, *J* = 6.5 Hz, 2H), 7.39 (q, *J* = 6.4 Hz, 3H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.19 (d, *J* = 10.7 Hz, 1H), 4.59 (d, *J* = 10.7 Hz, 1H), 3.82 – 3.55 (m, 3H), 2.99 (dtd, *J* = 28.6, 13.1, 8.3 Hz, 2H), 2.68 (dd, *J* = 15.1, 6.6 Hz, 1H), 2.30 (s, 3H), 1.74 (td, *J* = 14.1, 6.9 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 172.81, 167.41, 162.99, 155.71, 143.93, 133.92, 130.68, 129.40, 129.17, 128.16, 127.41, 124.31, 122.47, 122.18, 109.21, 71.00, 64.15, 59.18, 51.12, 42.49, 36.23, 20.42, 11.35, 11.22. **Mass (ESI-MS):** m/z Calculated $C_{26}H_{25}N_5O_5$ for: 487.1856; Observed: 488.1971 (M+1).

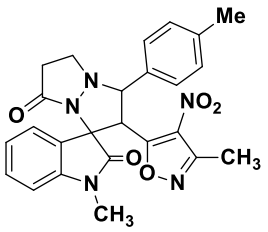
1-benzyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3d):

Yield = 123 mg (83%) White solid; M.P: 175-177 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.62-7.56 (m, 2H), 7.35 – 7.23 (m, 8H), 7.09 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.03 (td, *J* = 8.0, 1.2 Hz, 1H), 6.83 (td, *J* = 7.6, 0.8 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 5.23 (d, *J* = 16.0 Hz, 1H), 5.17 (d, *J* = 10.8 Hz, 1H), 4.59 (s, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 3.52 (t, *J* = 8.4 Hz, 1H), 3.04-2.92 (m, 1H), 2.91 – 2.82 (m, 1H), 2.61 (dd, *J* = 16.8, 7.6 Hz, 1H), 2.21 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 173.07, 167.30, 163.14, 155.72, 143.48, 134.71, 133.78, 131.09, 130.68, 129.46, 129.20, 128.86, 128.17, 127.57, 127.04, 124.19, 122.81, 122.17, 110.18, 70.93, 64.13, 59.33, 51.19, 44.66, 36.29, 11.23. **Mass (ESI-MS): Mass (ESI-MS):** m/z Calculated $C_{30}H_{25}N_5O_5$ for: 535.1856; Observed: 536.1940 (M+1).



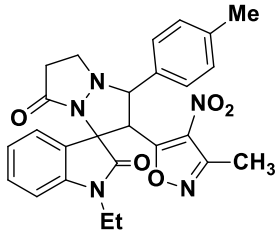
1-methyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-(p-tolyl)-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3e):

Yield = 126 mg (76%) Light yellow solid; M.P: 189-191 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.56 (d, *J* = 8.0 Hz, 2H), 7.27-7.19 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 4.56 (d, *J* = 10.4 Hz, 1H), 3.59 (t, *J* = 7.2 Hz, 1H), 3.26 (s, 3H), 3.09 – 2.87 (m, 2H), 2.69 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 172.91, 167.41, 163.09, 155.65, 144.10, 139.44, 131.07, 130.72, 130.67, 129.85, 128.08, 124.09, 122.71, 122.07, 108.95, 70.85, 64.16, 59.49, 51.06, 36.15, 26.94, 21.20, 11.17. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{23}N_5O_5$ for: 473.1699; Observed: 474.2758 (M+1).



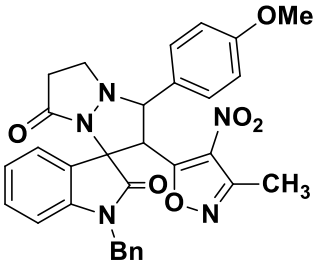
1-ethyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-(p-tolyl)-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3f):

Yield = 114 mg (70%) White solid; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.55 (d, *J* = 8.0 Hz, 2H), 7.26-7.18 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 3.93 – 3.68 (m, 2H), 3.58 (t, *J* = 8.0 Hz, 1H), 3.10-2.84 (m, 2H), 2.73 – 2.62 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ** 172.43, 167.42, 163.04, 155.70, 143.43, 133.90, 131.00, 130.72, 129.41, 129.18, 128.17, 124.37, 122.50, 122.27, 109.05, 71.00, 64.26, 59.13, 51.08, 36.19, 35.58, 12.08, 11.21. **Mass (ESI-MS):** m/z Calculated $C_{26}H_{25}N_5O_5$ for: 487.1856; Observed: 488.1868 (M+1).



1-benzyl-3'-(4-methoxyphenyl)-2'-(3-methyl-4-nitroisoxazol-5-yl)-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione: (3g):

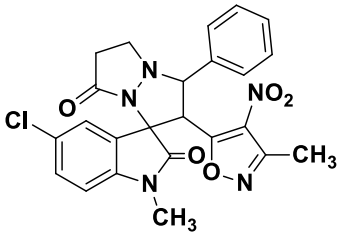
Yield = 109 mg (70%) White solid; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.51 (d, *J* = 8.6 Hz, 2H), 7.25 (m, 5H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 6.7 Hz, 3H), 6.47 (d, *J* = 7.8 Hz, 1H), 5.22 (d, *J* = 16.1 Hz, 1H), 5.14 (d, *J* = 10.7 Hz, 1H), 4.57 (d, *J* = 16.1 Hz, 1H), 4.50 (d, *J* = 10.7 Hz, 1H), 3.50 (t, *J* = 8.1 Hz, 1H), 3.40 (s, 3H), 3.02 – 2.81 (m, 2H), 2.61 (dd, *J* = 15.4, 7.1 Hz, 1H), 2.21 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 173.10, 167.39, 163.14, 160.45, 155.69, 143.43, 134.72, 131.13, 130.65, 129.37, 128.86, 127.57, 127.03, 125.34, 124.20, 122.81, 122.25, 114.58, 110.16, 70.58, 64.10, 59.24, 55.33, 51.16,



44.65, 36.27, 11.23. **Mass (ESI-MS):** m/z Calculated $C_{31}H_{27}N_5O_6$ for: 565.1961; Observed: 566.2041 (M+1).

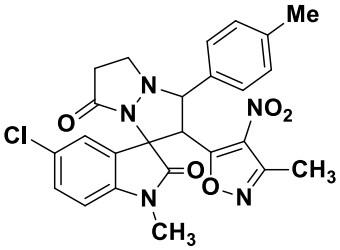
5-chloro-1-methyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3h):

Yield = 122 mg (79%) White solid; M.P: 166-168 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.64 (d, *J* = 6.4 Hz, 2H), 7.41-7.33 (m, 3H), 7.23 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 3.58 (t, *J* = 7.6 Hz, 1H), 3.23 (s, 3H), 3.07 – 2.89 (m, 2H), 2.73 – 2.65 (m, 1H), 2.32 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 172.49, 166.88, 163.23, 155.75, 142.76, 133.50, 131.18, 130.72, 129.53, 129.24, 128.21, 128.15, 124.59, 123.70, 109.91, 70.86, 63.88, 59.46, 51.11, 36.11, 27.08, 11.20. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{20}ClN_5O_5$ for: 493.1153; Observed: 494.2235 (M+1).



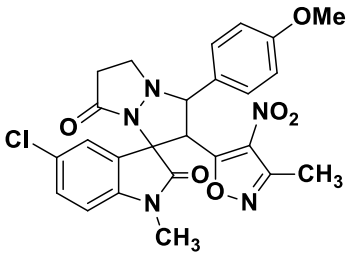
5-chloro-1-methyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-(p-tolyl)-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3i):

Yield = 127 mg (80%) White solid; M.P: 223-225 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.54 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 3.62-3.56 (m, 1H), 3.25 (s, 3H), 3.08-2.88 (m, 2H), 2.74 – 2.66 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 172.03, 166.93, 163.18, 155.75, 142.05, 133.57, 131.12, 130.70, 129.51, 129.23, 128.12, 127.96, 124.85, 123.98, 109.97, 70.88, 63.94, 59.06, 51.09, 36.13, 35.74, 12.01, 11.23. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{22}ClN_5O_5$ for: 507.1909; Observed: 508.2412 (M+1).



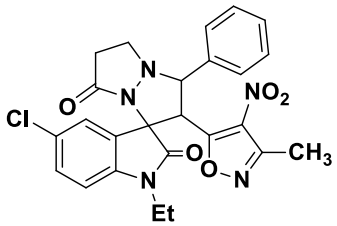
5-chloro-3'-(4-methoxyphenyl)-1-methyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3j):

Yield = 131 mg (80%) Light yellow solid; M.P: 194-196 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.58 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 10.8 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 3.81 (s, 3H), 3.63-3.54 (m, 1H), 3.25 (s, 3H), 3.08-2.87 (m, 2H), 2.74 – 2.66 (m, 1H), 2.34 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 172.50, 166.98, 163.20, 160.50, 155.70, 142.72, 131.22, 130.67, 129.35, 128.19, 125.06, 124.58, 123.78, 114.60, 109.86, 70.51, 63.84, 59.37, 55.33, 51.06, 36.08, 27.07, 11.20. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{22}ClN_5O_6$ for: 523.1259; Observed: 524.2379 (M+1).



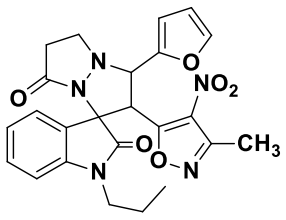
5-chloro-1-ethyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazole]-2,7'(3'H)-dione (3k):

Yield = 114 mg (75%) Light Yellow solid; M.P: 193-195 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.57 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.15 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 3.81-3.70 (m, 1H), 3.70-3.58 (m, 1H), 3.53-3.46 (m, 1H), 2.99 – 2.80 (m, 2H), 2.64 – 2.56 (m, 1H), 2.25 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 172.03, 166.93, 163.18, 155.75, 142.05, 133.57, 131.12, 130.70, 129.51, 129.23, 128.12, 127.96, 124.85, 123.98, 109.97, 70.88, 63.94, 59.06, 51.09, 36.13, 35.74, 12.01, 11.23. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{22}ClN_5O_5$ for: 507.1309; Observed: 508.1393 (M+1).



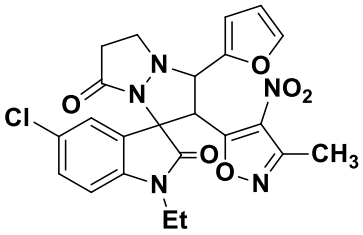
3'-(furan-2-yl)-2'-(3-methyl-4-nitroisoxazol-5-yl)-1-propyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3l):

Yield = 109 mg (72%) White solid; M.P: 180-183 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.45 (d, *J* = 0.8 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 6.39-6.35 (m, 1H), 5.47 (d, *J* = 10.4 Hz, 1H), 4.77 (d, *J* = 10.4 Hz, 1H), 3.81-3.69 (m, 2H), 3.68-3.60 (m, 1H), 3.11-2.91 (m, 2H), 2.72-2.61 (m, 1H), 2.34 (s, 3H), 1.82-1.70 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 172.35, 167.17, 163.06, 155.69, 146.68, 143.99, 143.88, 130.76, 124.23, 122.44, 122.09, 110.73, 110.15, 109.21,



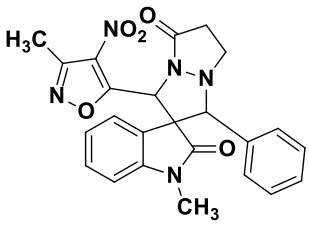
63.98, 63.89, 55.07, 51.43, 42.47, 36.00, 20.40, 11.32, 11.23. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{23}N_5O_6$ for: 477.1648; Observed: 478.2706 (M+1).

5-chloro-1-ethyl-3'-(furan-2-yl)-2'-(3-methyl-4-nitroisoxazol-5-yl)-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a] pyrazole]-2,7'(3'H)-dione (3m):



Yield = 111 mg (75%) White solid; M.P: 170-172 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.46 (d, *J* = 0.8 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.59 (s, 1H), 6.41-6.36 (m, 1H), 5.46 (d, *J* = 10.4 Hz, 1H), 4.75 (d, *J* = 10.4 Hz, 1H), 3.90-3.79 (m, 1H), 3.79-3.65 (m, 2H), 3.14 – 2.91 (m, 2H), 2.69 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.39 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.72, 166.81, 163.29, 155.75, 146.42, 144.00, 142.11, 131.03, 130.78, 127.95, 124.77, 123.90, 110.77, 110.40, 109.99, 63.84, 63.70, 54.95, 51.32, 35.90, 35.74, 12.00, 11.24 **Mass (ESI-MS):** m/z Calculated $C_{23}H_{20}ClN_5O_6$ for: 497.1102; Observed: 498.2188 (M+1).

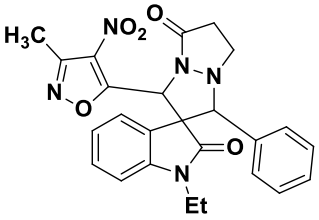
1-methyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4a):



Yield = 120 mg (75%) White solid; M.P: 161-162 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.22 (t, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 2H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 31.2 Hz, 1H), 5.97 (s, 1H), 4.12 (s, 1H), 3.69 (t, *J* = 8.4 Hz, 1H), 3.36-3.15 (m, 2H), 3.02 – 2.93 (m, 1H), 2.84 (s, 3H), 2.49 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 173.54, 167.82, 164.29, 156.16, 144.28, 130.35, 129.09, 128.30, 128.07, 127.59, 127.32, 123.01, 122.87, 122.48, 108.69, 77.28, 67.59, 54.07, 52.27, 36.63, 26.19, 11.31. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{21}N_5O_5$ for: 459.1543; Observed: 460.1591 (M+1).

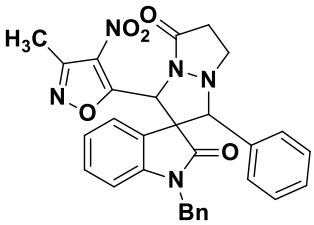
1-ethyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4b):

Yield = 128 mg (81%) White solid; M.P: 156-158 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 5.99 (s, 1H), 4.15 (s, 1H), 3.73 (t, *J* = 8.4 Hz, 1H), 3.67-3.55 (m, 1H), 3.34 – 3.19 (m, 2H), 3.09-2.96 (m, 1H), 2.92-2.82 (m, 1H), 2.51 (s, 3H), 0.68 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 173.07, 167.83, 164.22, 156.10, 143.43, 130.40, 130.27, 129.27, 129.02, 128.28, 127.34, 123.23, 123.13, 122.24, 108.73, 77.42, 67.46, 53.91, 52.20, 36.67, 34.53, 11.61, 11.31. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{23}N_5O_5$ for: 473.1699; Observed: 474.1714 (M+1).



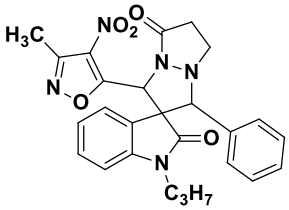
1-benzyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4c):

Yield = 125 mg (85%) Light Yellow solid; M.P: 160-162 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.36 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.19 – 7.14 (m, 1H), 7.14 – 7.06 (m, 5H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 2H), 6.37 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 1H), 5.09 (d, *J* = 16.4 Hz, 1H), 4.33 (d, *J* = 16.4 Hz, 1H), 4.26 (s, 1H), 3.76 (t, *J* = 8.4 Hz, 1H), 3.35 – 3.22 (m, 1H), 3.08 – 2.98 (m, 1H), 2.89 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 173.75, 167.69, 164.29, 156.10, 143.84, 143.53, 134.55, 130.58, 130.33, 129.17, 128.71, 128.63, 127.70, 127.24, 126.29, 123.09, 122.81, 122.46, 110.03, 77.24, 67.54, 54.59, 52.29, 43.91, 36.66, 11.29. **Mass (ESI-MS):** m/z Calculated $C_{30}H_{25}N_5O_5$ for: 535.1856; Observed: 536.1940 (M+1).



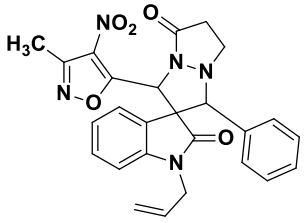
3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-1-propyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4d):

Yield = 132 mg (85%) Yellow solid; M.P: 155-157 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24 – 7.18 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 7.2 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 5.96 (s, 1H), 4.14 (s, 1H), 3.70 (t, *J* = 8.4 Hz, 1H), 3.55 – 3.46 (m, 1H), 3.31 – 3.13 (m, 2H), 3.03 – 2.92 (m, 1H), 2.85 (m, 1H), 2.49 (s, 3H), 1.22 – 1.07 (m, 2H), 0.58 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 173.40, 167.82, 164.23, 156.10, 144.06, 130.46, 130.26, 129.05, 128.34, 128.16, 127.41, 123.16, 122.96, 122.15, 108.93, 77.22, 67.37,



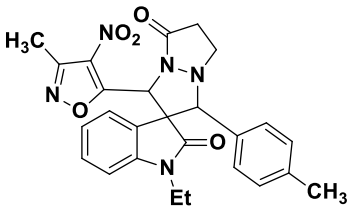
54.13, 52.28, 41.67, 36.65, 20.20, 11.31, 11.00. **Mass (ESI-MS):** m/z Calculated $C_{26}H_{25}N_5O_5$ for: 487.1856; Observed: 488.1971 (M+1).

1-allyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4e):



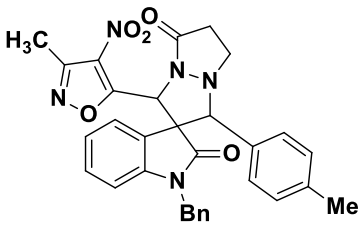
Yield = 134 mg (86%) White solid; M.P: 162-164 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 – 7.12 (m, 4H), 7.00 (d, *J* = 7.2 Hz, 2H), 6.93-6.87 (m, 1H), 6.53 (dd, *J* = 27.2, 7.6 Hz, 2H), 5.97 (s, 1H), 5.24 – 5.16 (m, 1H), 4.83 (d, *J* = 10.4 Hz, 1H), 4.32 (dd, *J* = 60.4, 17.6 Hz, 2H), 4.16 (s, 1H), 3.82 (dd, *J* = 16.4, 4.0 Hz, 1H), 3.70 (t, *J* = 8.4 Hz, 1H), 3.30 – 3.17 (m, 1H), 3.07-2.82 (m, 2H), 2.49 (s, 3H). **Mass (ESI-MS):** m/z Calculated $C_{26}H_{23}N_5O_5$ for: 485.1699; Observed: 486.2767 (M+1).

1-ethyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-(p-tolyl)-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4f):



Yield = 136 mg (84%) White solid; M.P: 203-205 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.06 (d, *J* = 7.6 Hz, 1H), 7.01-6.89 (m, 3H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 6.26 (s, 1H), 4.35 (s, 1H), 3.91-3.81 (m, 1H), 3.79-3.69 (m, 1H), 3.71-3.63 (m, 1H), 3.26-3.16 (m, 1H), 2.97 – 2.88 (m, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 174.50, 169.61, 160.76, 157.62, 155.55, 142.53, 138.26, 129.20, 128.74, 128.56, 127.28, 126.08, 124.30, 121.61, 108.23, 78.14, 66.01, 59.04, 45.91, 35.16, 30.34, 21.07, 12.15, 11.11. **Mass (ESI-MS):** m/z Calculated $C_{26}H_{25}N_5O_5$ for: 487.1856; Observed: 488.1868 (M+1).

1-benzyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-(p-tolyl)-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4g):

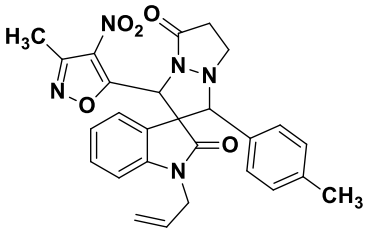


Yield = 118 mg (78%) Yellow solid; M.P: 166-168 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.15 (t, *J* = 7.2 Hz, 1H), 7.09 – 7.04 (m, 3H), 6.99 (q, *J* = 8.0 Hz, 4H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 7.2 Hz, 2H), 6.34 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 1H), 5.12 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 4.19 (s, 1H), 3.71 (t, *J* = 8.4 Hz, 1H), 3.34 – 3.19 (m, 1H),

3.05 – 2.93 (m, 1H), 2.86 (m, 1H), 2.48 (s, 3H), 2.34 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 173.85, 167.75, 164.28, 156.08, 143.54, 139.02, 134.63, 131.02, 130.25, 129.39, 128.47, 127.62, 127.47, 127.23, 126.42, 123.07, 122.91, 122.41, 109.99, 76.98, 67.49, 54.59, 52.25, 43.94, 36.65, 21.33, 11.29. **Mass (ESI-MS):** m/z Calculated $C_{31}H_{27}N_5O_5$ for: 549.2012; Observed: 550.2005 (M+1).

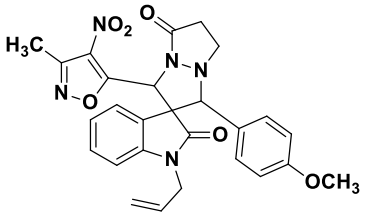
1-allyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-(p-tolyl)-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4h):

Yield = 128 mg (80%) White solid; M.P: 151-153 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.20 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.95-6.85 (m, 3H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.00 (s, 1H), 5.33-5.22 (m, 1H), 4.85 (d, *J* = 10.4 Hz, 1H), 4.42 – 4.27 (m, 2H), 4.15 (s, 1H), 3.85 (dd, *J* = 16.4, 5.2 Hz, 1H), 3.71 (t, *J* = 8.8 Hz, 1H), 3.32 – 3.19 (m, 1H), 3.04-2.93 (m, 1H), 2.86 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.51 (s, 3H), 2.27 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 173.36, 167.82, 164.23, 156.09, 143.56, 139.07, 130.99, 130.30, 130.16, 129.12, 127.39, 127.28, 123.04, 122.88, 122.36, 116.63, 109.66, 77.27, 67.53, 54.13, 52.20, 42.19, 36.64, 21.03, 11.30. **Mass (ESI-MS):** m/z Calculated $C_{27}H_{25}N_5O_5$ for: 499.1856; Observed: 500.1868 (M+1).

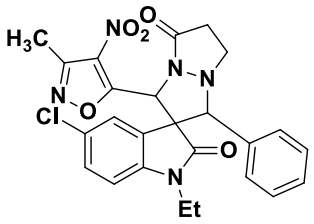


1-allyl-1'-(4-methoxyphenyl)-3'-(3-methyl-4-nitroisoxazol-5-yl)-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4i):

Yield = 130 mg (79%) White solid; M.P: 145-147 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.20 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 5.41-5.27 (m, 1H), 4.91 (d, *J* = 10.4 Hz, 1H), 4.50 (d, *J* = 17.2 Hz, 1H), 4.34 – 4.25 (m, 1H), 4.19 (s, 1H), 3.97-3.85 (m, 1H), 3.74 (s, 3H), 3.70 (d, *J* = 8.4 Hz, 1H), 3.30 – 3.18 (m, 1H), 3.07-2.95 (m, 1H), 2.88 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 173.42, 167.82, 164.23, 160.32, 156.10, 143.54, 130.98, 130.32, 130.16, 128.73, 123.01, 122.91, 122.37, 122.11, 116.81, 113.88, 109.68, 77.23, 67.49, 55.25, 54.13, 52.19, 42.22, 36.62, 11.31. **Mass (ESI-MS):** m/z Calculated $C_{27}H_{25}N_5O_6$ for: 515.1805; Observed: 516.1817 (M+1).

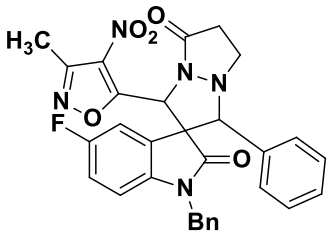


5-chloro-1-ethyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4j):



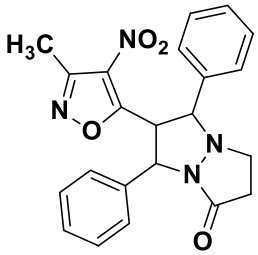
Yield = 123 mg (81%) Light yellow solid; M.P: 164-166 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.25 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.16 (m, 3H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.41 (s, 1H), 5.96 (s, 1H), 4.10 (s, 1H), 3.72 (t, *J* = 8.4 Hz, 1H), 3.65-3.54 (m, 1H), 3.30-3.21 (m, 2H), 3.04-2.94 (m, 1H), 2.92-2.83 (m, 1H), 2.55 (s, 3H), 0.66 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 172.63, 167.52, 164.25, 156.23, 141.98, 131.07, 130.22, 130.03, 129.26, 128.44, 127.51, 127.37, 124.82, 123.67, 109.59, 77.19, 67.55, 53.89, 52.16, 36.63, 34.71, 11.53, 11.15. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{22}ClN_5O_5$ for: 507.1309; Observed: 508.1324 (M+1).

1-benzyl-5-fluoro-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a] pyrazole]-2,5'(3'H)-dione (4k):



Yield = 110 mg (76%) White solid; M.P: 159-161 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.32 – 7.27 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.08 – 6.99 (m, 5H), 6.74-6.68 (m, 1H), 6.33 (d, *J* = 7.2 Hz, 2H), 6.25 – 6.17 (m, 2H), 5.96 (s, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 16.0 Hz, 1H), 4.11 (s, 1H), 3.66 (t, *J* = 8.4 Hz, 1H), 3.25 – 3.13 (m, 1H), 2.98-2.87 (m, 1H), 2.84-2.74 (m, 1H), 2.45 (s, 3H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ** 173.47, 167.32, 164.32, 159.76, 157.34, 156.19, 139.53, 134.18, 130.27, 129.37, 128.83, 128.72, 127.72, 127.40, 126.27, 116.94, 116.71, 111.27, 111.02, 77.16, 67.72, 54.44, 52.24, 44.05, 36.61, 11.25. **Mass (ESI-MS):** m/z Calculated $C_{30}H_{24}FN_5O_5$ for: 553.1761; Observed: 554.1669 (M+1).

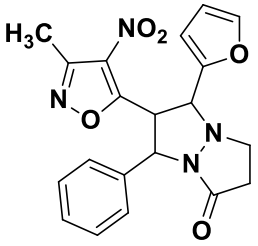
6-(3-methyl-4-nitroisoxazol-5-yl)-5,7-diphenyltetrahydropyrazolo[1,2-a] pyrazol-1(5H)-one (6a):



Yield = 131 mg (75%) White solid; M.P: 142-144 °C**, ^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.36 (m, 4H), 7.32 – 7.26 (m, 1H), 7.14 (m, 3H), 7.07 – 7.02 (m, 2H), 5.53 (d, *J* = 4.0 Hz, 1H), 4.88 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.51 (d, *J* = 6.8 Hz, 1H), 3.32 (t, *J* = 10.4 Hz, 1H), 3.05 (dd, *J* = 20.0, 10.0 Hz, 1H), 2.72 – 2.58 (m, 2H), 2.28 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 167.32, 155.89,

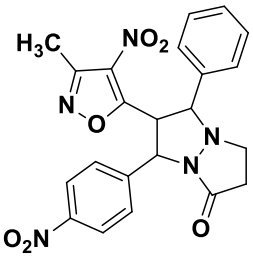
148.02, 144.92, 132.07, 130.65, 129.36, 128.98, 128.07, 127.80, 127.52, 124.53, 70.45, 57.03, 56.75, 49.65, 35.12, 10.59. **Mass (ESI-MS):** m/z Calculated $C_{22}H_{20}N_4O_4$ for: 404.1485; Observed: 405.1558 (M+1).

5-(furan-2-yl)-6-(3-methyl-4-nitroisoxazol-5-yl)-7-phenyltetrahydropyrazolo[1,2-a] pyrazol-1(5H)-one (6b):



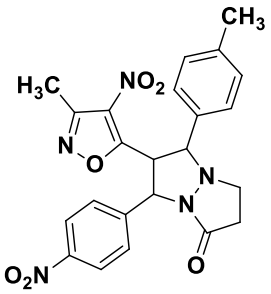
Yield = 154 mg (90%) Yellow semi solid; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.42 (d, *J* = 7.6 Hz, 2H), 7.33 (s, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.25 – 6.20 (m, 2H), 6.02 (d, *J* = 8.4 Hz, 1H), 4.99 (d, *J* = 6.8 Hz, 1H), 4.79 – 4.74 (m, 1H), 3.55 (dd, *J* = 22.0, 10.0 Hz, 1H), 3.12 (m, 1H), 2.39 (s, 3H), 1.78 – 1.61 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 168.98, 155.97, 147.99, 139.40, 130.66, 129.70, 128.97, 128.15, 127.44, 124.52, 124.42, 114.90, 70.15, 57.10, 56.62, 29.71, 21.11, 11.43. **Mass (ESI-MS):** m/z Calculated: 394.1277; Observed: 395.1369 (M+1).

6-(3-methyl-4-nitroisoxazol-5-yl)-7-(4-nitrophenyl)-5-phenyltetrahydropyrazolo[1,2-a] pyrazol-1(5H)-one (6c):



Yield = 133 mg (82%) White solid; M.P: 182-184 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.29 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.28 (m, 3H), 7.12 (d, *J* = 7.6 Hz, 2H), 5.76 (d, *J* = 4.0 Hz, 1H), 4.97 – 4.90 (m, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 3.41 (t, *J* = 11.2 Hz, 1H), 3.22 (dd, *J* = 20.0, 10.0 Hz, 1H), 2.76 – 2.63 (m, 2H), 2.38 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 168.90, 155.89, 148.02, 144.92, 132.07, 130.65, 129.36, 128.98, 128.07, 127.80, 127.52, 124.53, 70.45, 57.03, 56.75, 47.61, 35.12, 11.37. **Mass (ESI-MS):** m/z Calculated $C_{22}H_{19}N_5O_6$ for: 449.1335; Observed: 450.1403 (M+1).

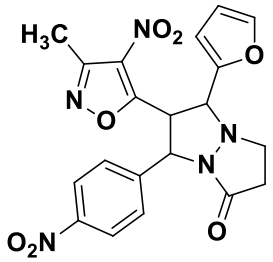
6-(3-methyl-4-nitroisoxazol-5-yl)-7-(4-nitrophenyl)-5-(p-tolyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6d):



Yield = 117 mg (70%) White solid; M.P: 179-181 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.27 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.79 (d, *J* = 4.4 Hz, 1H), 4.91 – 4.84 (m, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 3.33 (t, *J* = 10.4 Hz, 1H), 3.23 (dd, *J* = 19.2, 9.6 Hz, 1H), 2.61 (m, 2H), 2.38 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (125**

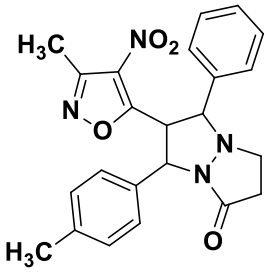
MHz, $CDCl_3$) δ 168.97, 155.97, 147.99, 139.40, 130.66, 129.71, 128.97, 128.15, 127.45, 124.52, 124.42, 114.91, 70.15, 57.10, 56.64, 34.70, 29.71, 21.12, 11.43. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{21}N_5O_6$ for: 463.1492; Observed: 464.1566 (M+1).

5-(furan-2-yl)-6-(3-methyl-4-nitroisoxazol-5-yl)-7-(4-nitrophenyl) tetrahydropyrazolo[1,2-a] pyrazol-1(5H)-one (6e):



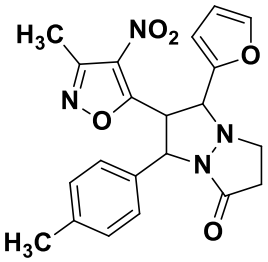
Yield = 135 mg (85%) Light yellow solid; M.P: 175-177 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.15 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.34 (s, 1H), 6.25 (m, 2H), 6.11 (d, *J* = 8.4 Hz, 1H), 5.01 (d, *J* = 6.8 Hz, 1H), 4.71 – 4.65 (m, 1H), 3.59 (dd, *J* = 22.0, 9.6 Hz, 1H), 3.20 – 3.10 (m, 1H), 2.41 (s, 3H), 2.38 – 2.32 (m, 1H), 1.64 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 168.97, 155.97, 147.99, 139.40, 130.66, 129.71, 128.97, 128.15, 127.45, 124.52, 124.42, 114.91, 70.15, 57.10, 56.64, 29.71, 21.12, 11.43. **Mass (ESI-MS):** m/z Calculated $C_{20}H_{17}N_5O_7$ for: 439.1128; Observed: 440.1188 (M+1).

6-(3-methyl-4-nitroisoxazol-5-yl)-5-phenyl-7-(p-tolyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6f):



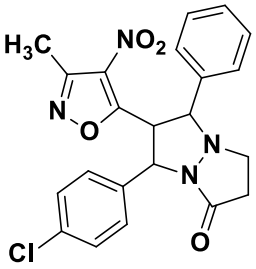
Yield = 119 mg (70%) White solid; M.P: 164-166 °C**, ^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.33 (d, *J* = 7.6 Hz, 2H), 7.22 (m, 5H), 7.14 – 7.09 (m, 2H), 5.53 (d, *J* = 3.6 Hz, 1H), 4.94 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.54 (d, *J* = 7.2 Hz, 1H), 3.39 (t, *J* = 8.4 Hz, 1H), 3.07 (dd, *J* = 20.4, 9.6 Hz, 1H), 2.86 – 2.65 (m, 2H), 2.36 (s, 3H), 2.34 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 169.00, 154.53, 137.51, 133.66, 131.54, 129.50, 129.01, 128.89, 127.98, 127.68, 126.84, 125.32, 69.35, 56.76, 56.25, 34.97, 28.68, 20.15, 10.36. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{22}N_4O_4$ for: 418.1641; Observed: 419.1713 (M+1).

5-(furan-2-yl)-6-(3-methyl-4-nitroisoxazol-5-yl)-7-(p-tolyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6g):



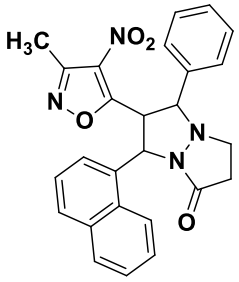
Yield = 122 mg (73%) Light Yellow semi solid; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.39 (d, *J* = 3.2 Hz, 2H), 7.36 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.31 – 6.28 (m, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 6.04 (d, *J* = 8.4 Hz, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 4.82 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.59 (dd, *J* = 22.0, 10.0 Hz, 1H), 3.21 – 3.13 (m, 1H), 2.47 (s, 1H), 2.45 (s, 3H), 2.44 – 2.38 (m, 1H), 2.32 (s, 3H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ** 174.34, 168.90, 156.06, 147.18, 144.10, 138.08, 136.60, 130.71, 129.73, 126.15, 112.20, 111.19, 62.26, 57.54, 55.05, 31.45, 29.71, 21.13, 11.52. **Mass (ESI-MS):** m/z Calculated $C_{21}H_{20}N_4O_5$ for: 408.1434; Observed: 409.1505 (M+1).

7-(4-chlorophenyl)-6-(3-methyl-4-nitroisoxazol-5-yl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6h):



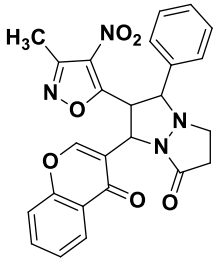
Yield = 126 mg (76%) White solid; M.P: 148-150 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.39 (s, 4H), 7.22 (m, 3H), 7.13 – 7.08 (m, 2H), 5.57 (d, *J* = 4.0 Hz, 1H), 4.91 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.56 (d, *J* = 7.2 Hz, 1H), 3.39 (m, 1H), 3.11 (q, *J* = 10.0 Hz, 1H), 2.70 (m, 2H), 2.35 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 169.50, 155.73, 136.21, 134.65, 132.13, 130.60, 129.48, 129.27, 128.90, 128.01, 127.90, 70.35, 57.37, 56.97, 35.40, 29.71, 11.38. **Mass (ESI-MS):** m/z Calculated $C_{22}H_{19}ClN_4O_4$ for: 438.1095; Observed: 439.1161 (M+1).

6-(3-methyl-4-nitroisoxazol-5-yl)-7-(naphthalen-1-yl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6i):



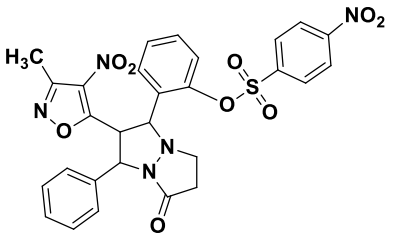
Yield = 113 mg (70%) White solid; M.P: 151-153 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.90 (t, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 6.8 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.24 – 7.17 (m, 3H), 7.09 (d, *J* = 6.8 Hz, 2H), 6.24 (d, *J* = 2.8 Hz, 1H), 4.96 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.47 (d, *J* = 6.8 Hz, 1H), 3.52 (m, 1H), 3.11 (m, 2H), 2.86 (m, 1H), 2.40 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 170.05, 165.10, 155.60, 134.33, 132.21, 132.17, 130.53, 129.99, 129.44, 129.32, 129.05, 128.62, 127.59, 127.06, 126.06, 125.32, 123.92, 121.71, 69.74, 56.61, 55.18, 36.85, 29.72, 11.47. **Mass (ESI-MS):** m/z Calculated $C_{26}H_{22}N_4O_4$ for: 454.1641; Observed: 455.1701 (M+1).

6-(3-methyl-4-nitroisoxazol-5-yl)-7-(4-oxo-4H-chromen-3-yl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6j):



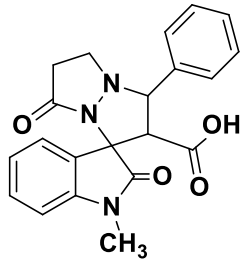
Yield = 123 mg (78%) White solid; M.P: 180-182 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.12 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.02 (s, 1H), 7.68 – 7.62 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.12 (m, 5H), 5.24 (d, *J* = 3.2 Hz, 1H), 5.14 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 3.43 (m, 1H), 2.98 – 2.86 (m, 2H), 2.73 (m, 1H), 2.27 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 175.42, 169.82, 164.87, 155.34, 154.37, 153.22, 133.22, 131.71, 129.30, 127.78, 127.48, 126.45, 124.65, 122.75, 118.23, 117.24, 69.84, 52.71, 52.31, 48.24, 35.34, 10.37. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{20}N_4O_6$ for: 472.1383; Observed: 473.1453 (M+1).

2-(2-(3-methyl-4-nitroisoxazol-5-yl)-7-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazol-1-yl)phenyl 4-nitrobenzenesulfonate (6k):



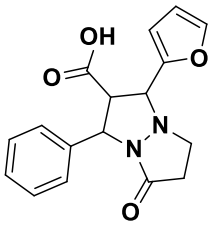
Yield = 170 mg (65%) Light Yellow Solid; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.41 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 4.0 Hz, 5H), 7.32 (dd, *J* = 5.4, 1.9 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.24 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 5.48 (d, *J* = 2.4 Hz, 1H), 5.01 (d, *J* = 6.4 Hz, 1H), 4.99 – 4.95 (m, 1H), 3.51 (t, *J* = 8.6 Hz, 1H), 3.21 (dd, *J* = 20.2, 9.8 Hz, 1H), 3.05-2.99 (m, 1H), 2.82 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.39 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.29, 164.87, 155.50, 151.21, 147.30, 141.14, 137.22, 130.64, 130.36, 129.57, 129.35, 128.89, 128.59, 127.73, 126.46, 126.43, 124.71, 122.36, 63.57, 58.53, 55.60, 49.52, 36.41, 11.37. **Mass (ESI-MS):** m/z Calculated $C_{28}H_{23}N_5O_9S$ for: 605.1216; Observed: 606.1297 (M+1).

1-methyl-2,7'-dioxo-3'-phenyl-3',5',6',7'-tetrahydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazole]-2'-carboxylic acid (7a);



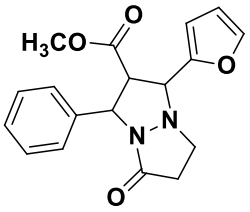
Yield = 64 mg (78%) Cream solid; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.56 (d, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.04 – 6.97 (m, 2H), 4.27 (d, *J* = 11.2 Hz, 1H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.15 (s, 3H), 3.02 – 2.94 (m, 1H), 2.80 – 2.71 (m, 1H), 2.42 - 2.29 (m, 2H). **Mass (ESI-MS):** m/z Calculated $C_{21}H_{19}N_3O_4$ for: 377.1376; Observed: 378.1460 (M+1).

1-(furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-2-carboxylic acid (8b):



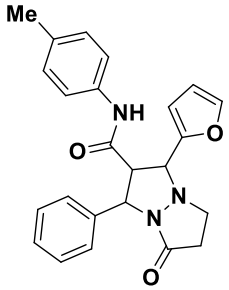
Yield = 67 mg (85%) Cream solid; M.P: 233-235 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 12.78 (s, 1H), 7.71-7.70 (d, *J* = 8.0 Hz 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 6.8 Hz, 1H), 6.53 – 6.52 (m, 1H), 6.46 (d, *J* = 2.8 Hz, 1H), 5.40 (d, *J* = 8.4 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 3.85 (t, *J* = 7.6 Hz, 1H), 3.43 (dd, *J* = 22.4, 10.0 Hz, 1H), 3.13 – 3.07 (m, 1H), 2.27 – 2.20 (m, 1H), 1.26 – 1.17 (m, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 175.41, 170.67, 149.21, 144.03, 141.93, 129.03, 127.87, 126.62, 111.95, 111.49, 61.24, 59.15, 58.48, 42.70, 30.70. **Mass (ESI-MS):** m/z Calculated $C_{17}H_{16}N_2O_4$ for: 312.1110; Observed: 313.1194 (M+1).

methyl 1-(furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-2-carboxylate (9b):



Yield = 67 mg (65%) Light yellow liquid; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.69 (d, *J* = 1.2 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.32 -7.28 (m, 1H), 6.53 (dd, *J* = 3.6, 2.0 Hz, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 5.43 (d, *J* = 8.0 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 3.99 (t, *J* = 8.0 Hz, 1H), 3.45 (s, 3H), 3.42 – 3.39 (m, 1H), 3.15 – 3.09 (m, 1H), 2.28 – 2.20 (m, 1H), 1.25 – 1.17 (m, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ** 174.94, 169.37, 148.48, 143.70, 141.11, 128.61, 127.53, 126.22, 111.52, 111.01, 60.66, 58.20, 57.99, 52.16, 42.30, 30.20. **Mass (ESI-MS):** m/z Calculated $C_{18}H_{18}N_2O_4$ for: 326.1267; Observed: 327.1350 (M+1).

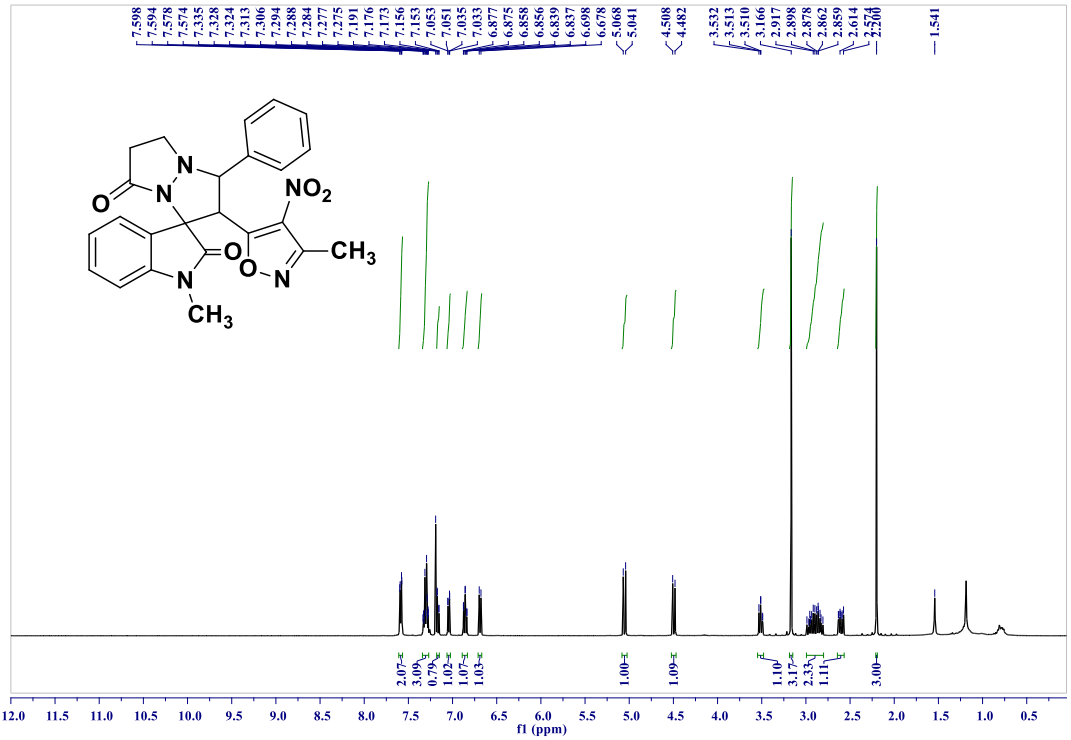
1-(furan-2-yl)-5-oxo-3-phenyl-N-(p-tolyl)hexahydropyrazolo[1,2-a]pyrazole-2-carboxamide (10b):

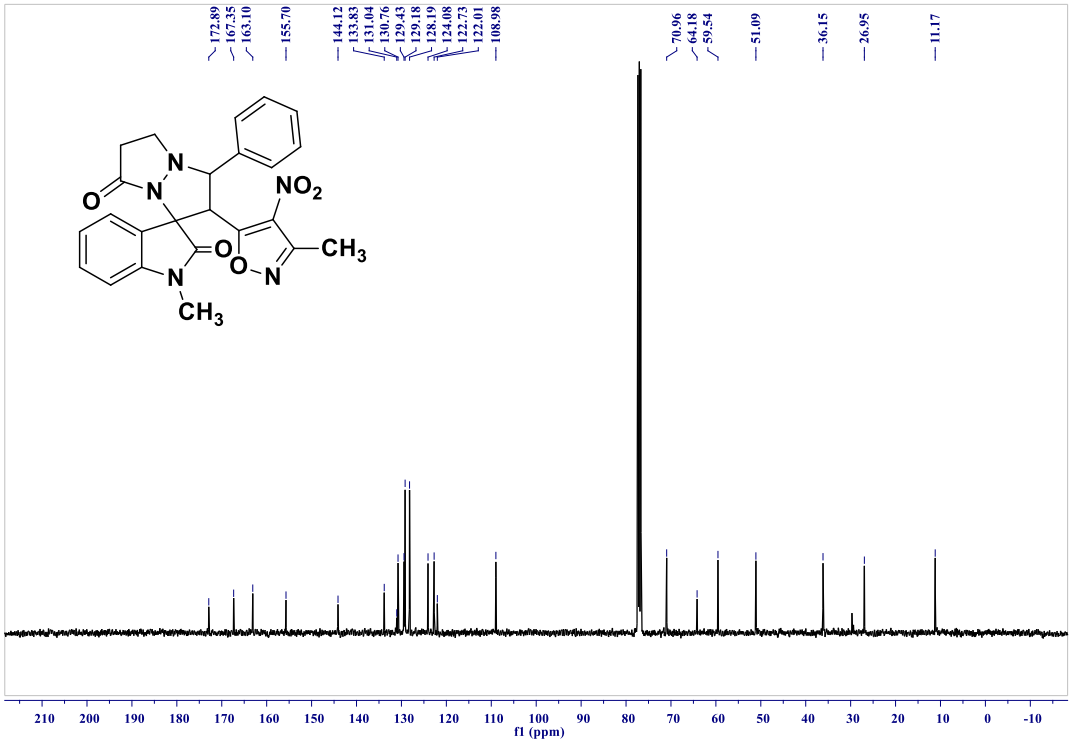


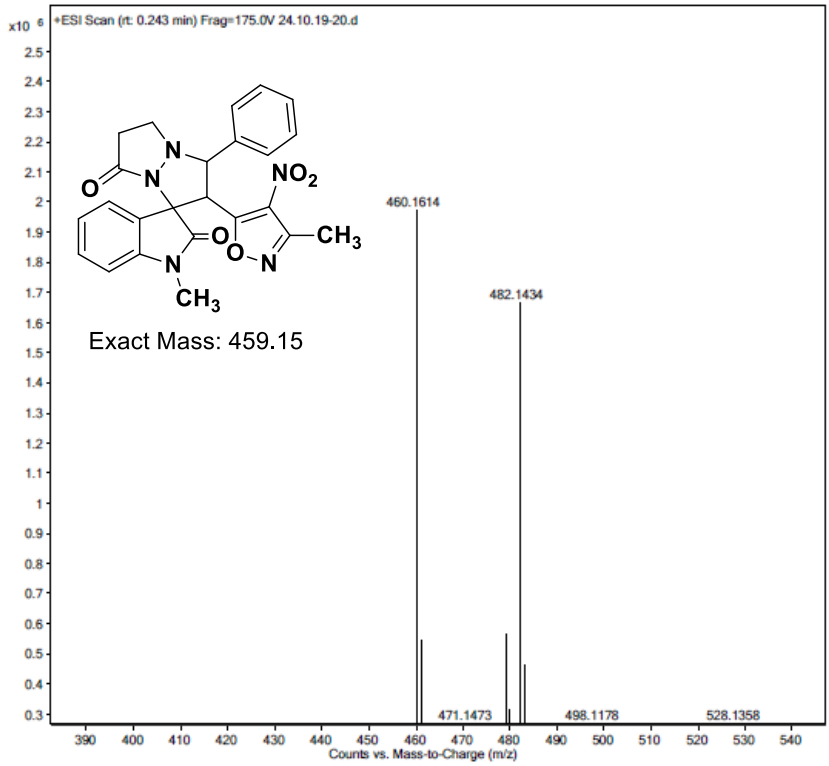
Yield = 109 mg (85%) White solid; M.P: 222-224 °C, **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 9.88 (s, 1H), 7.70 (d, *J* = 1.2 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 4H), 7.32 – 7.28 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.46 – 6.45 (m, 1H), 6.41 (d, *J* = 3.2 Hz, 1H), 5.64 (d, *J* = 8.4 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 1H), 3.82 (t, *J* = 7.6 Hz, 1H), 3.45 (dd, *J* = 22.0, 10.0 Hz, 1H), 3.15 – 3.08 (m, 1H), 2.35 – 2.20 (m, 1H), 2.20 (s, 3H), 1.45 – 1.33 (m, 1H). **^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ** 174.60, 165.32, 148.27, 143.99, 141.59, 135.96, 132.59, 129.04, 128.69, 127.38, 125.83, 119.59, 111.54, 111.12, 61.63, 60.77, 57.35, 42.53, 30.69, 20.40. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{23}N_3O_3$ for: 401.1739; Observed: 402.1829 (M+1).

3.7 Selected Spectra:

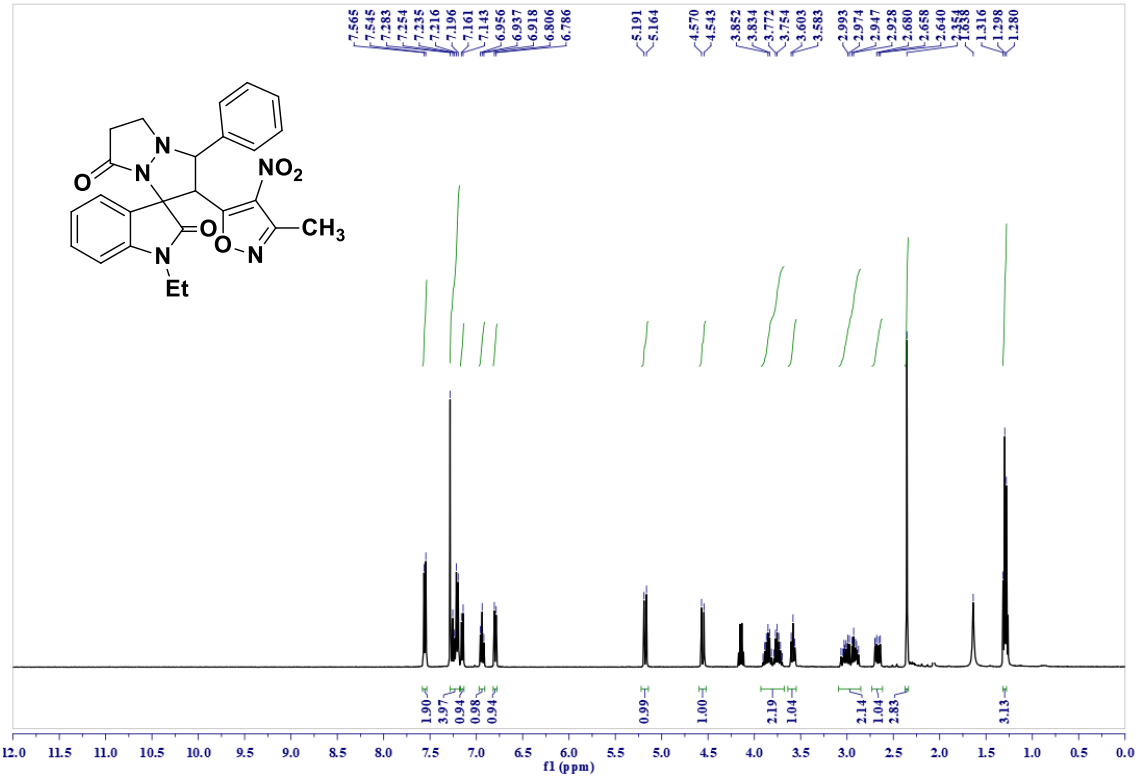
1-methyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazole]-2,7'(3'H)-dione (3a):

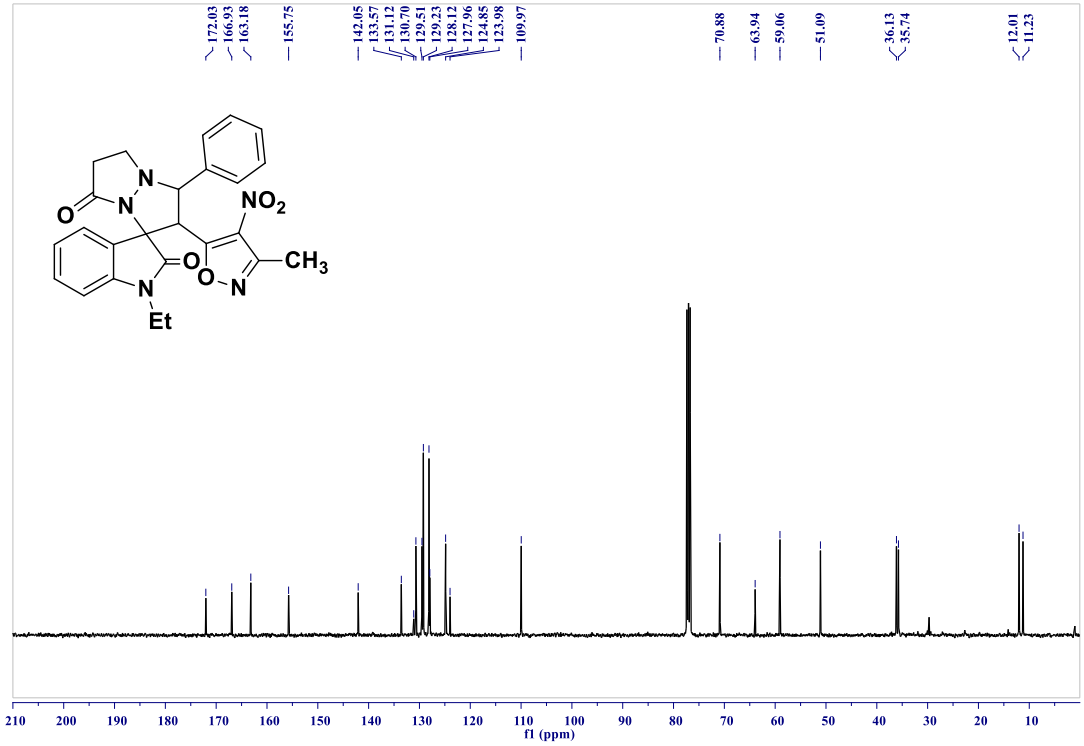


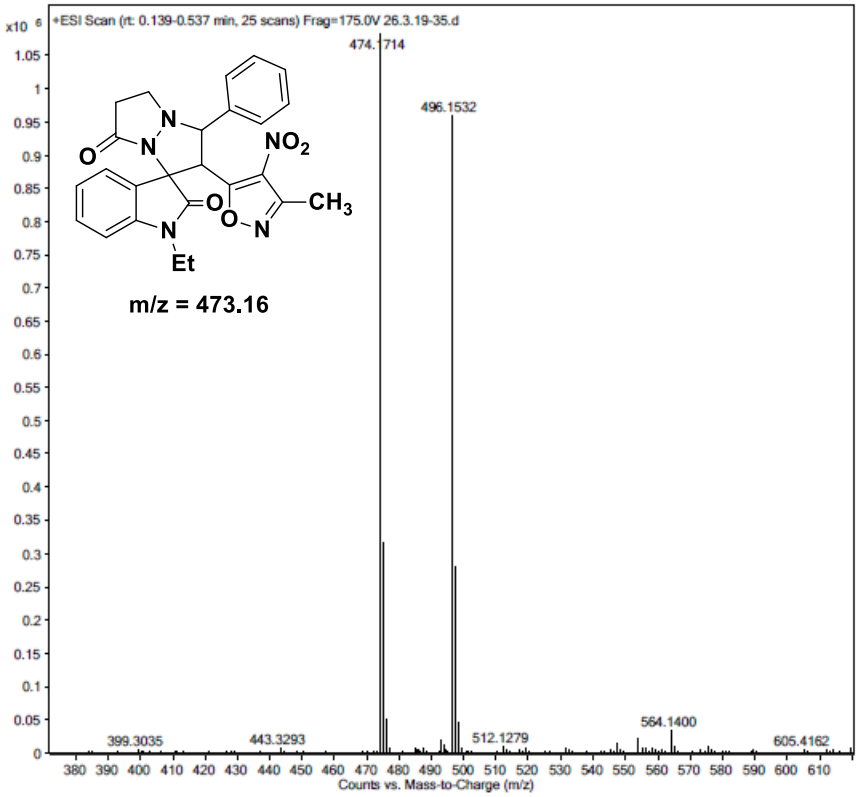




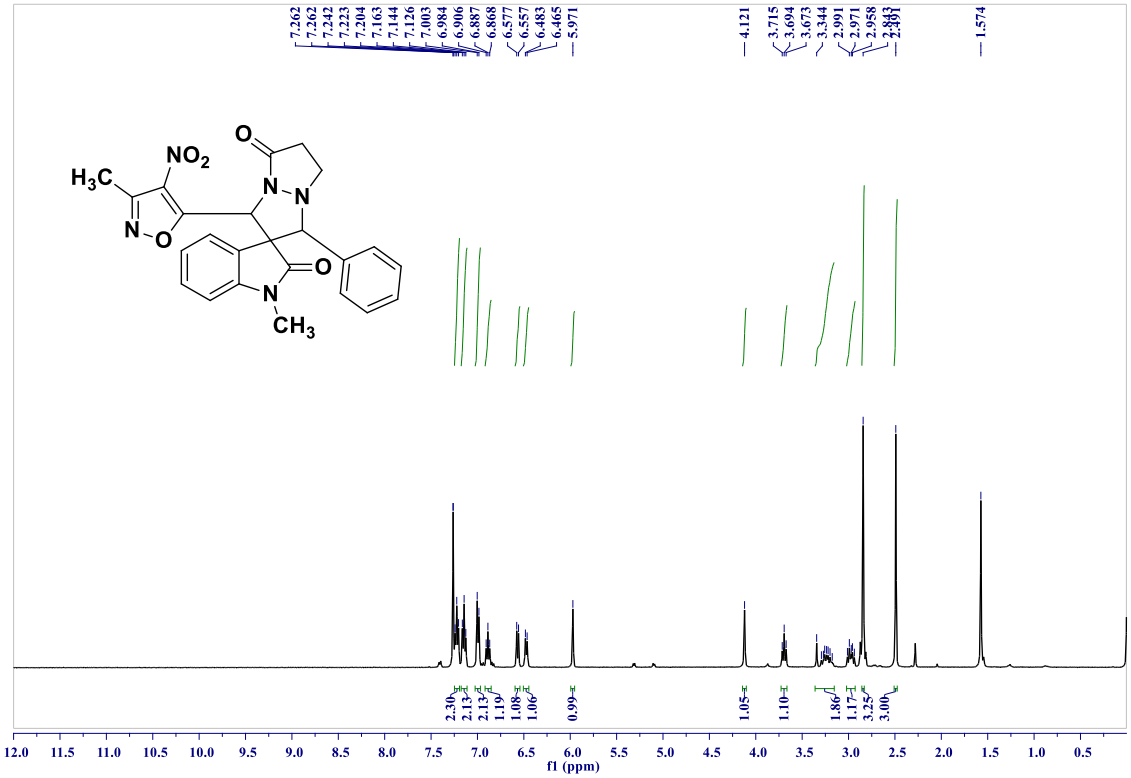
1-ethyl-2'-(3-methyl-4-nitroisoxazol-5-yl)-3'-phenyl-5',6'-dihydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazole]-2,7'(3'H)-dione (3b):

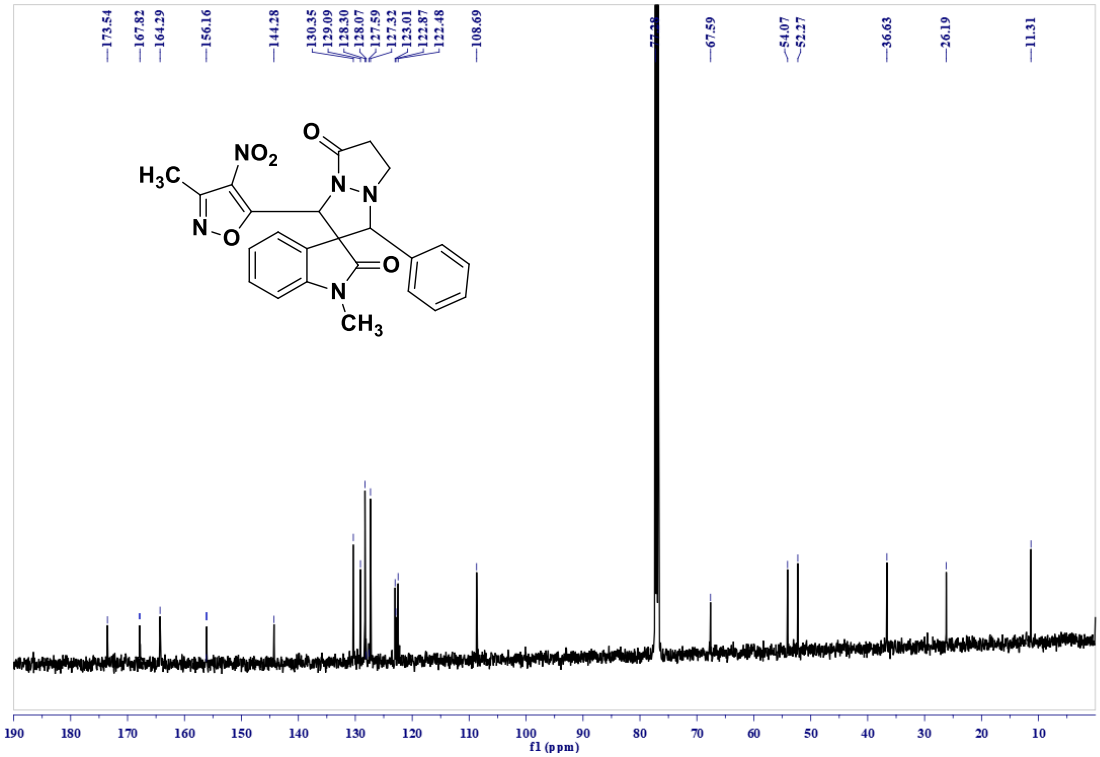


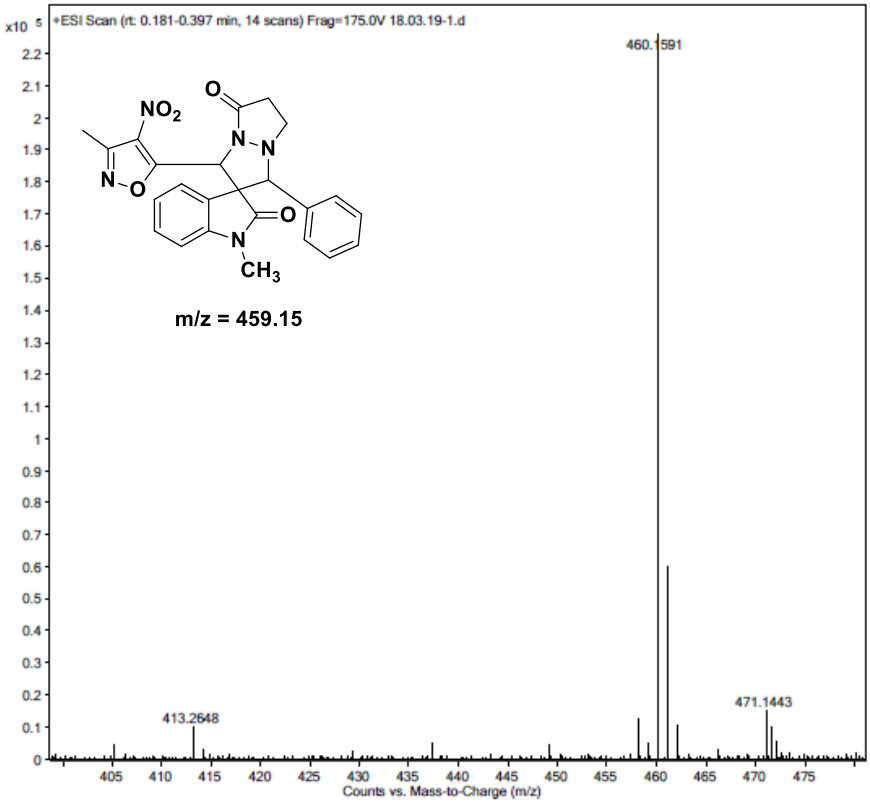

172.03
166.93
163.18
155.75
142.05
133.57
131.12
130.70
129.51
129.23
128.12
127.96
124.85
123.98
109.97
70.88
63.94
59.06
51.09
36.13
35.74
12.01
11.23
NO2
CH3
Et
f1 (ppm)


+ESI Scan (rt: 0.139-0.537 min, 25 scans) Frag=175.0V 26.3.19-35.d
x10 6
474.1714
496.1532
399.3035
443.3293
512.1279
564.1400
605.4162
NO2
CH3
Et
m/z = 473.16
Counts vs. Mass-to-Charge (m/z)

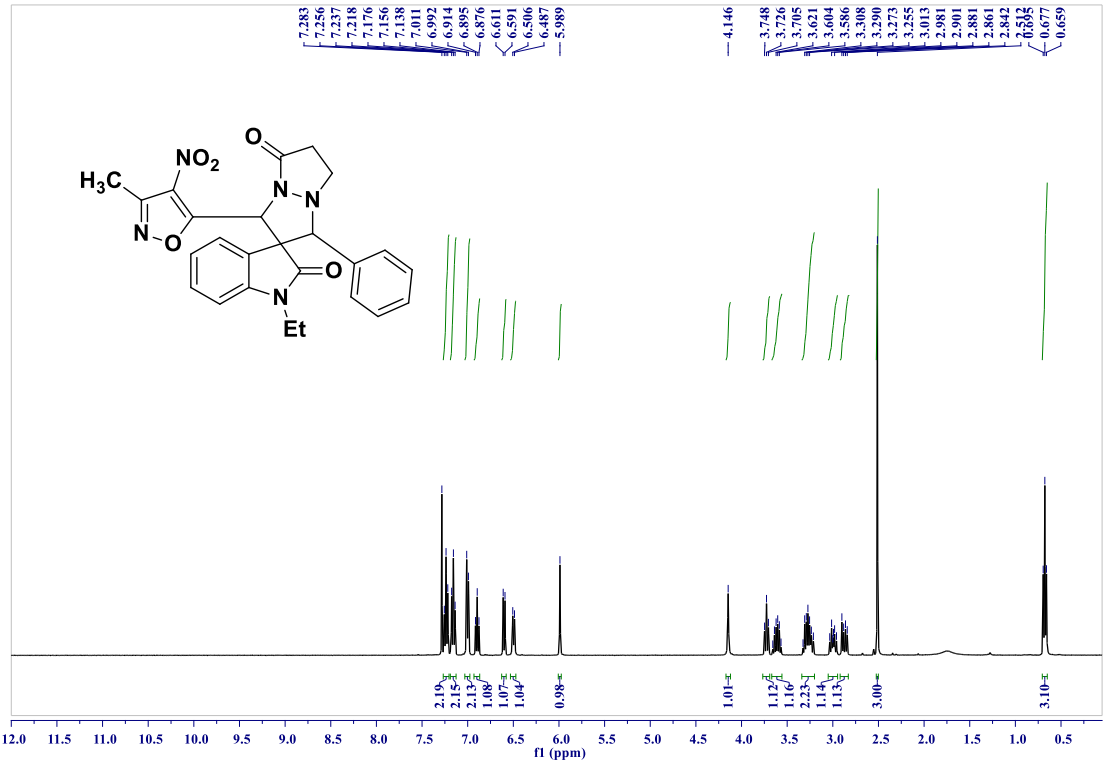
1-methyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a]pyrazole]-2,5'(3'H)-dione (4a):

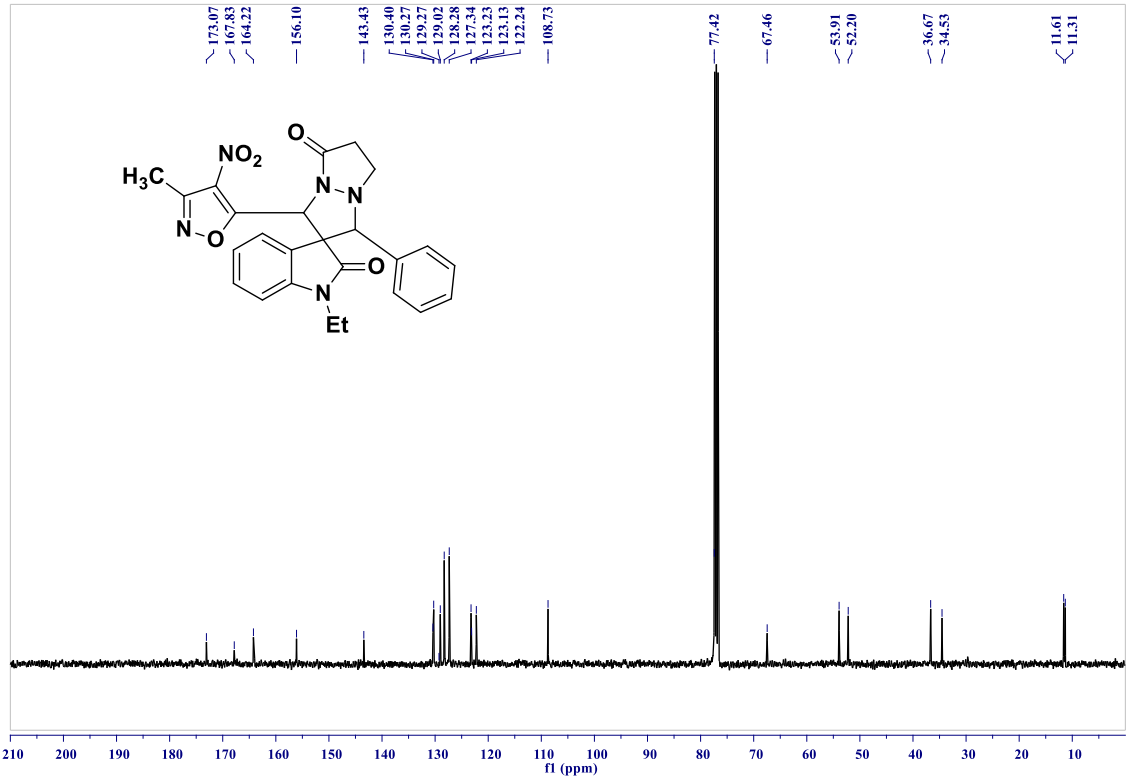






1-ethyl-3'-(3-methyl-4-nitroisoxazol-5-yl)-1'-phenyl-6',7'-dihydro-1'H-spiro[indoline-3,2'-pyrazolo[1,2-a]pyrazole]-2,5'(3'H)-dione (4b):

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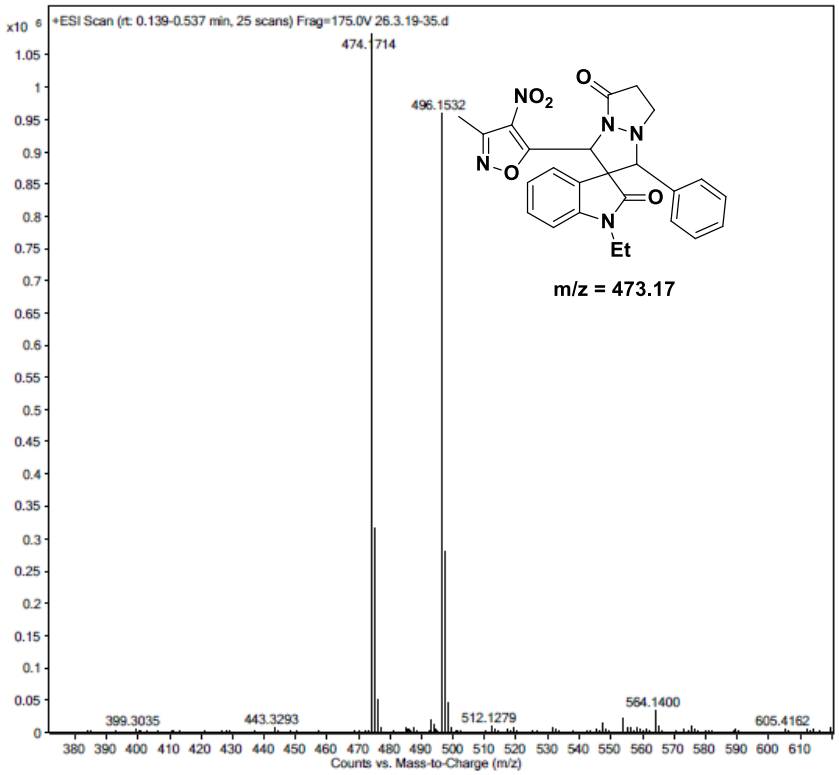
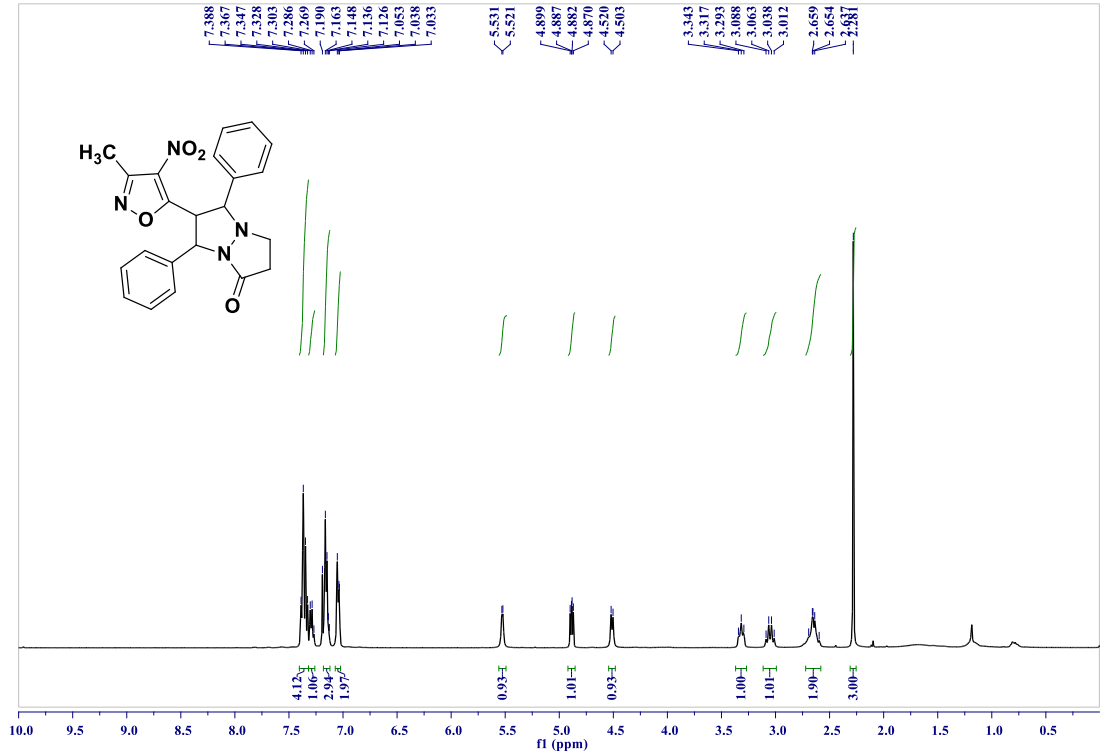
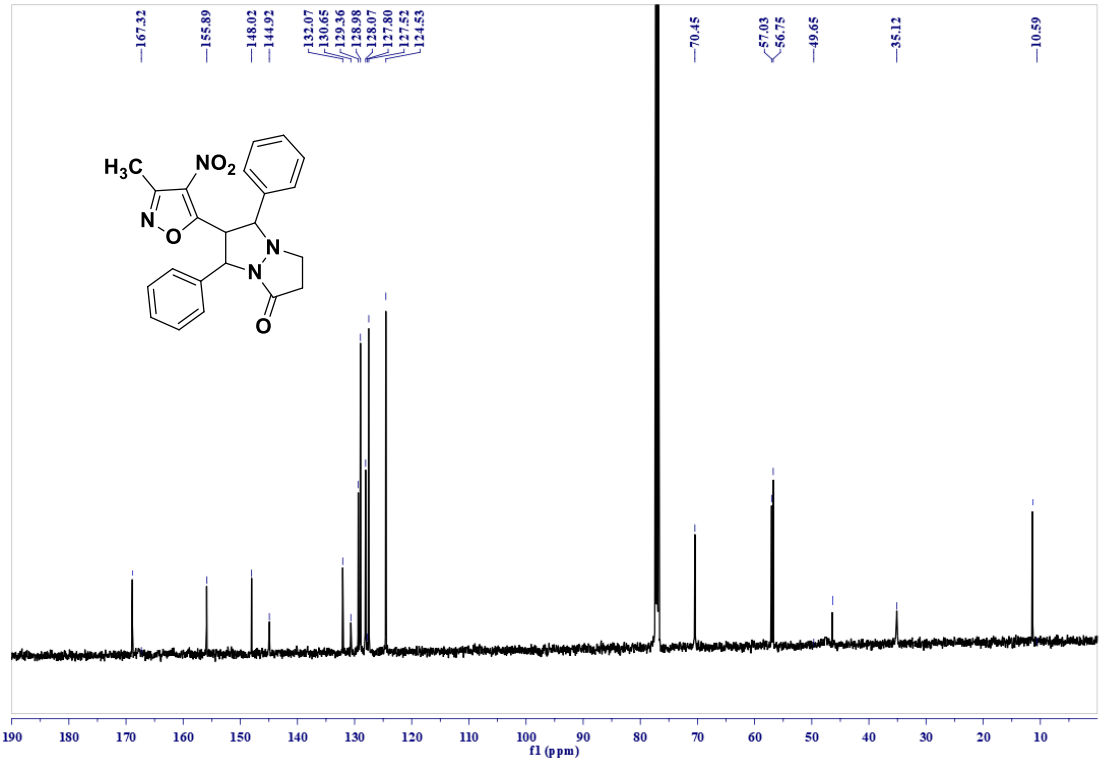
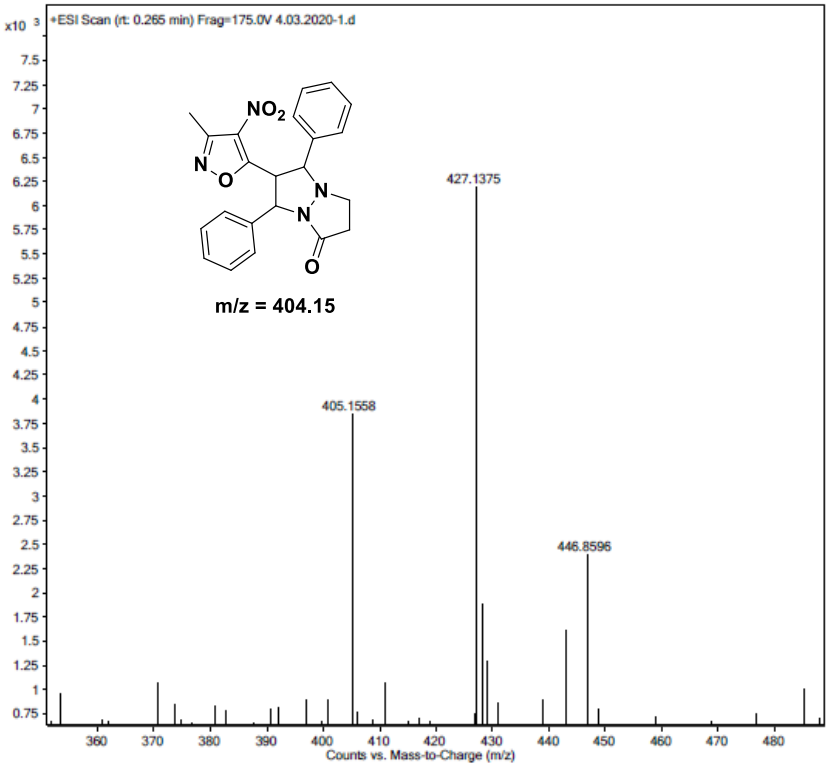
156.10
143.43
130.40
130.27
129.27
129.02
128.28
127.34
123.23
123.13
122.24
108.73
77.42
67.46
53.91
52.20
36.67
34.53
11.61
11.31
O
NO2
H3C
N
O
N
N
O
N
Et
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


x10 6
+ESI Scan (rt: 0.139-0.537 min, 25 scans) Frag=175.0V 26.3.19-35.d
474.1714
496.1532
NO2
O
N
N
O
N
O
Et
m/z = 473.17
399.3035
443.3293
512.1279
564.1400
605.4162
380 390 400 410 420 430 440 450 460 470 480 490 500 510 520 530 540 550 560 570 580 590 600 610
Counts vs. Mass-to-Charge (m/z)

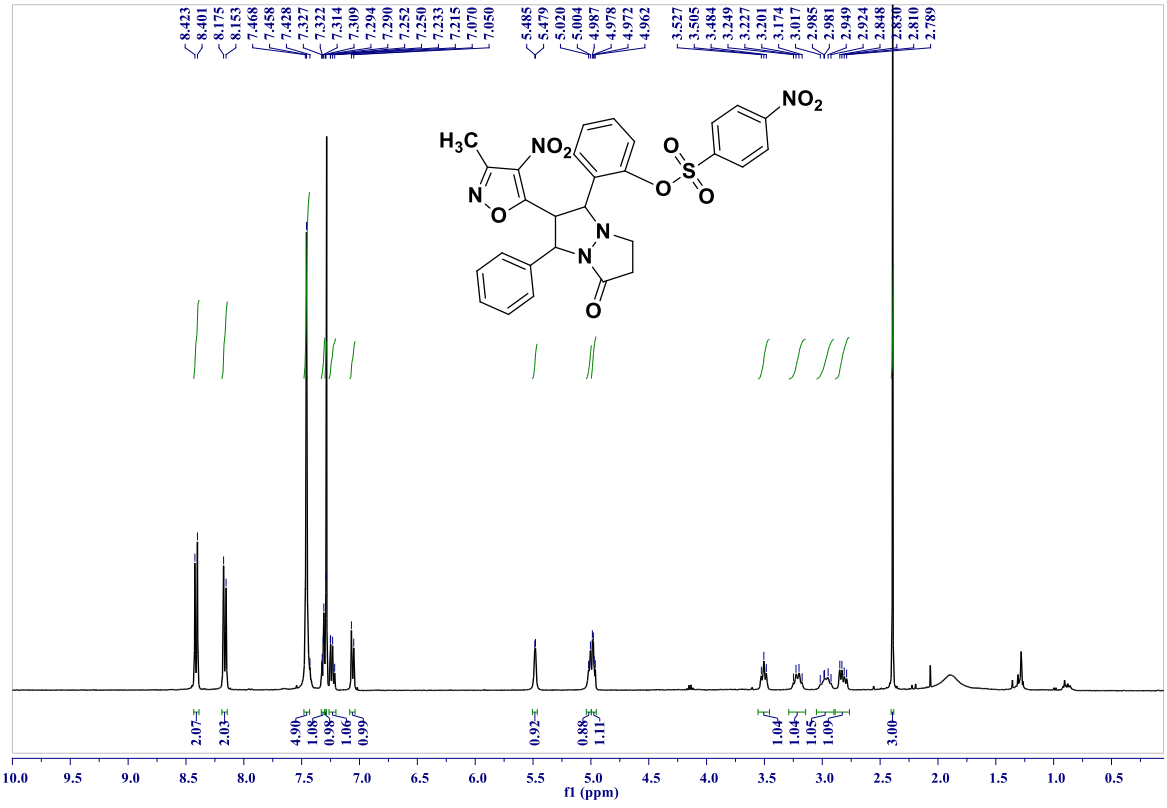
6-(3-methyl-4-nitroisoxazol-5-yl)-5,7-diphenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (6a):

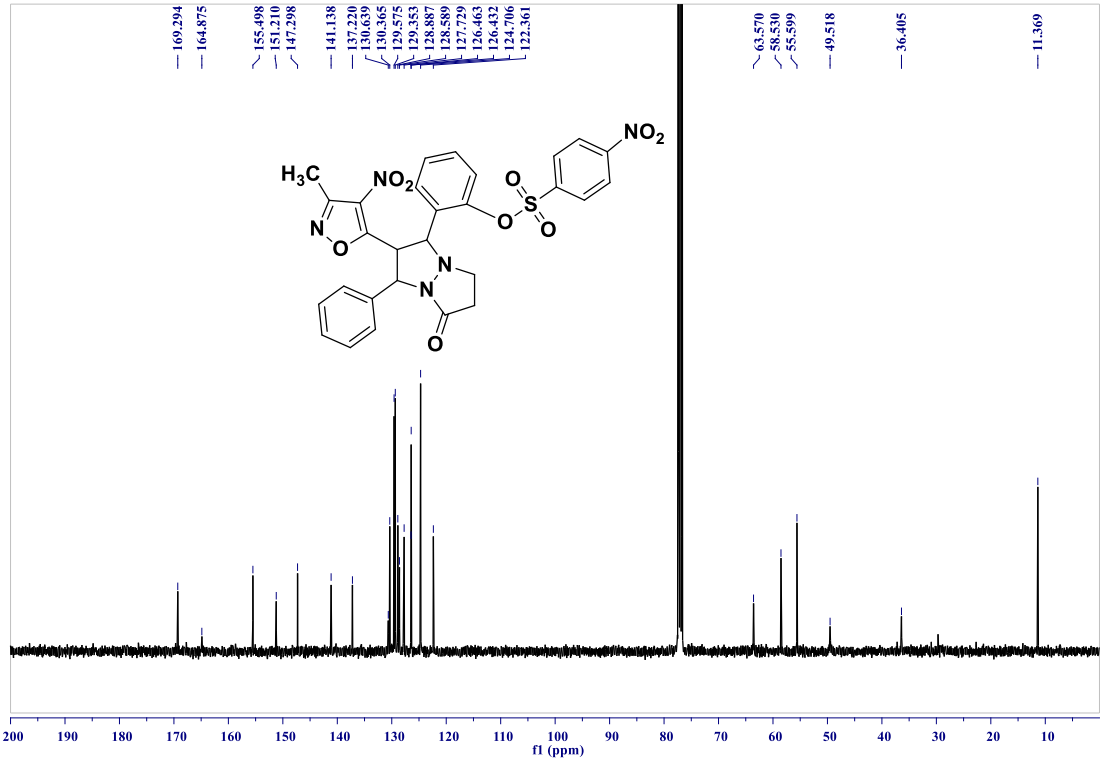






2-(2-(3-methyl-4-nitroisoxazol-5-yl)-7-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazol-1-yl)phenyl 4-nitrobenzenesulfonate (6k):




169.294
164.875
155.498
151.210
147.298
141.138
137.220
130.639
130.365
129.575
129.353
128.887
128.589
127.729
126.463
126.432
124.706
122.361
63.570
58.530
55.599
49.518
36.405
11.369
NO2
H3C
NO2
O
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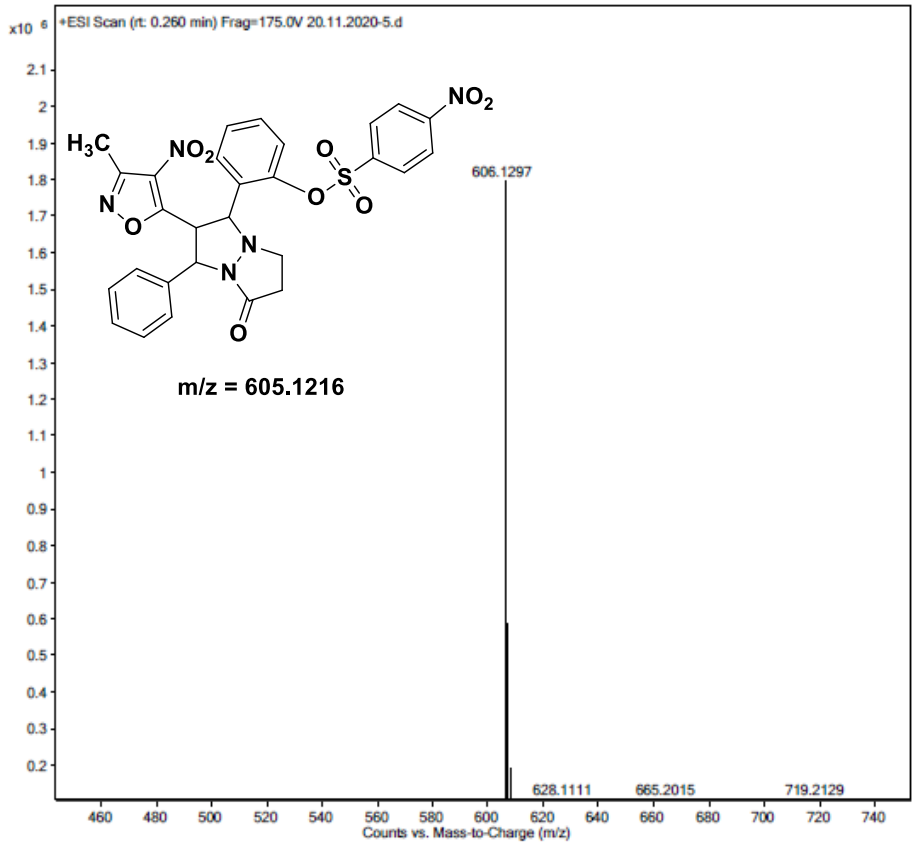
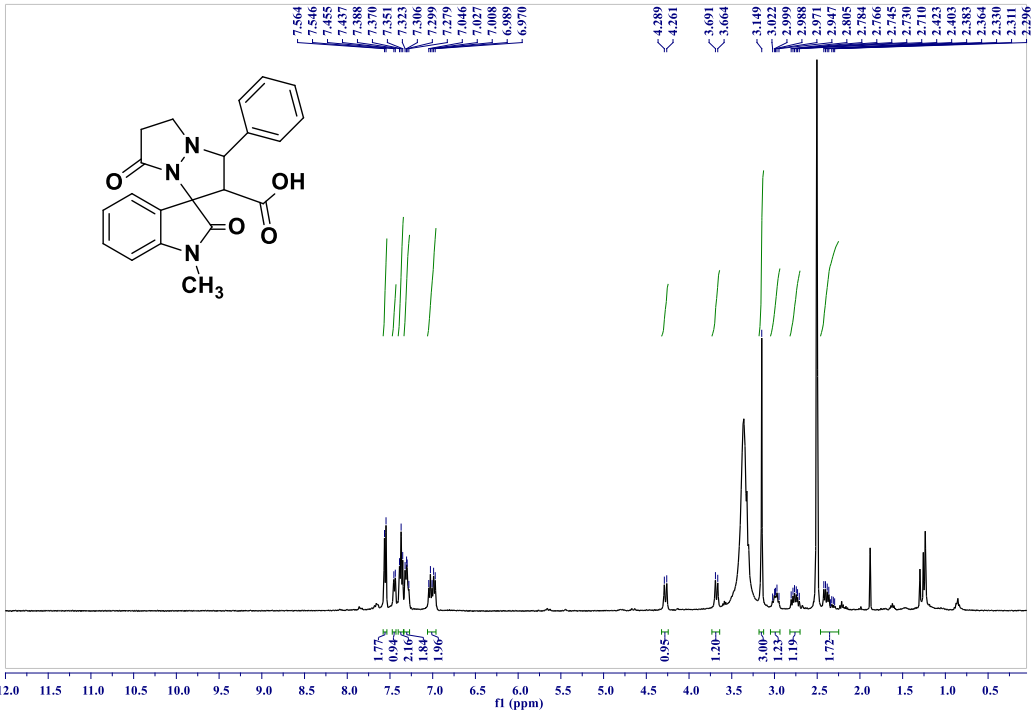
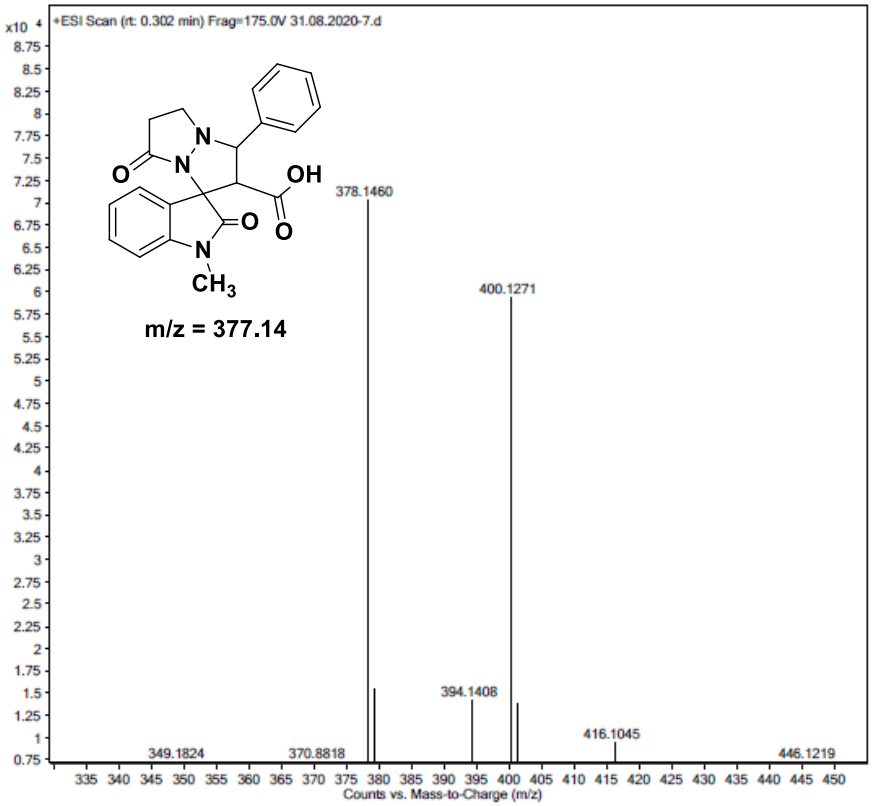
O
O
N
O
N
N
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

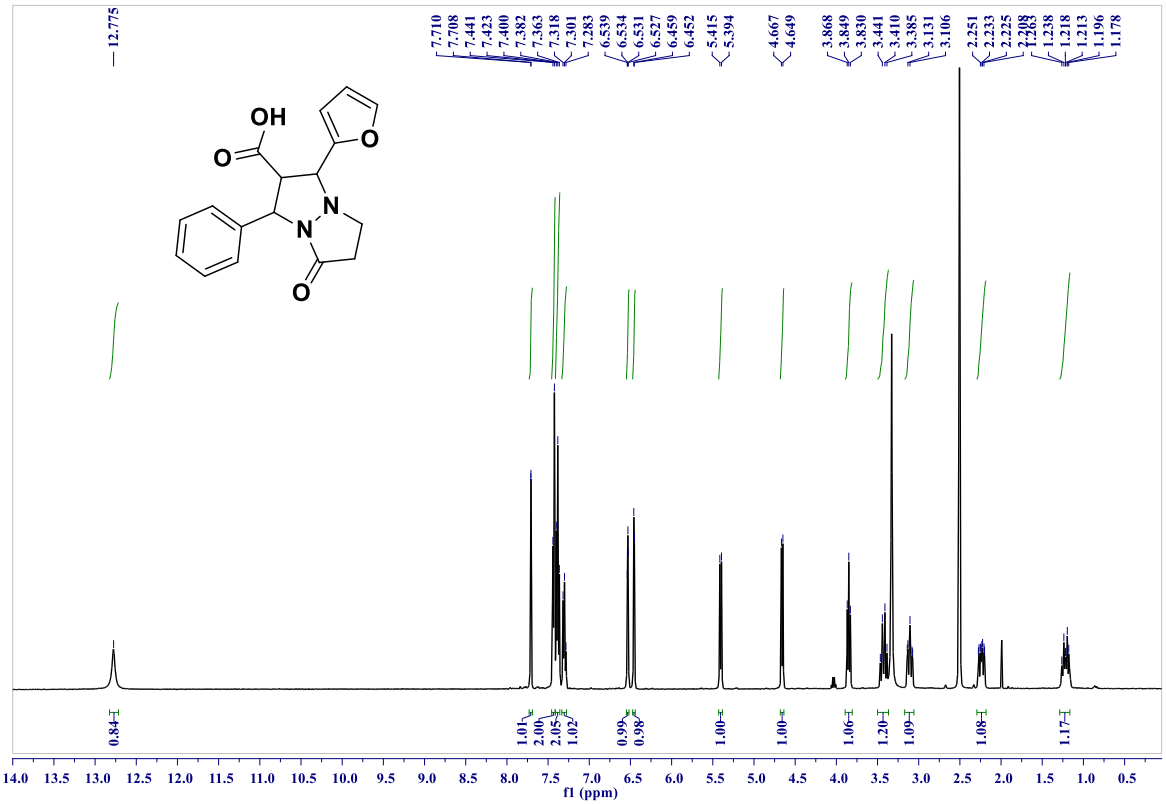

x10 6
*ESI Scan (rt: 0.260 min) Frag=175.0V 20.11.2020-5.d
NO2
H3C
NO2
O
S
O
O
N
O
N
N
O
606.1297
m/z = 605.1216
628.1111
665.2015
719.2129
460 480 500 520 540 560 580 600 620 640 660 680 700 720 740
Counts vs. Mass-to-Charge (m/z)

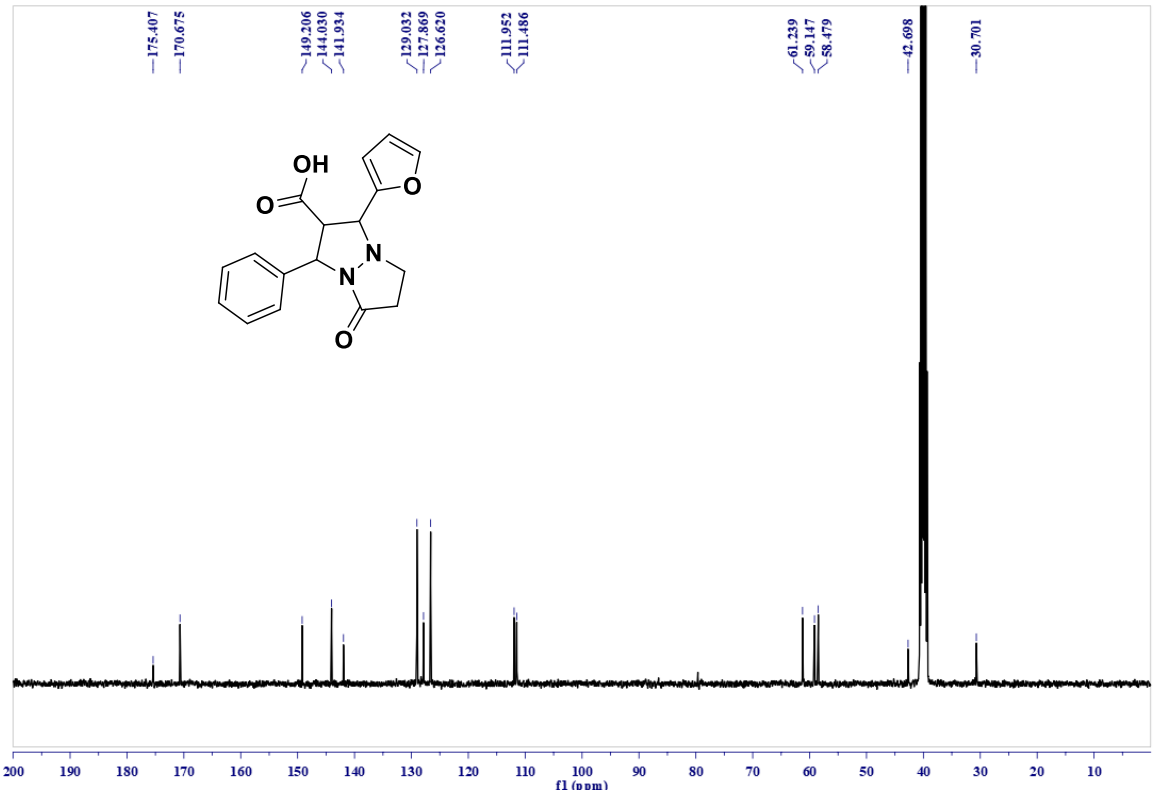
1-methyl-2,7'-dioxo-3'-phenyl-3',5',6',7'-tetrahydro-2'H-spiro[indoline-3,1'-pyrazolo[1,2-a]pyrazole]-2'-carboxylic acid (7a):

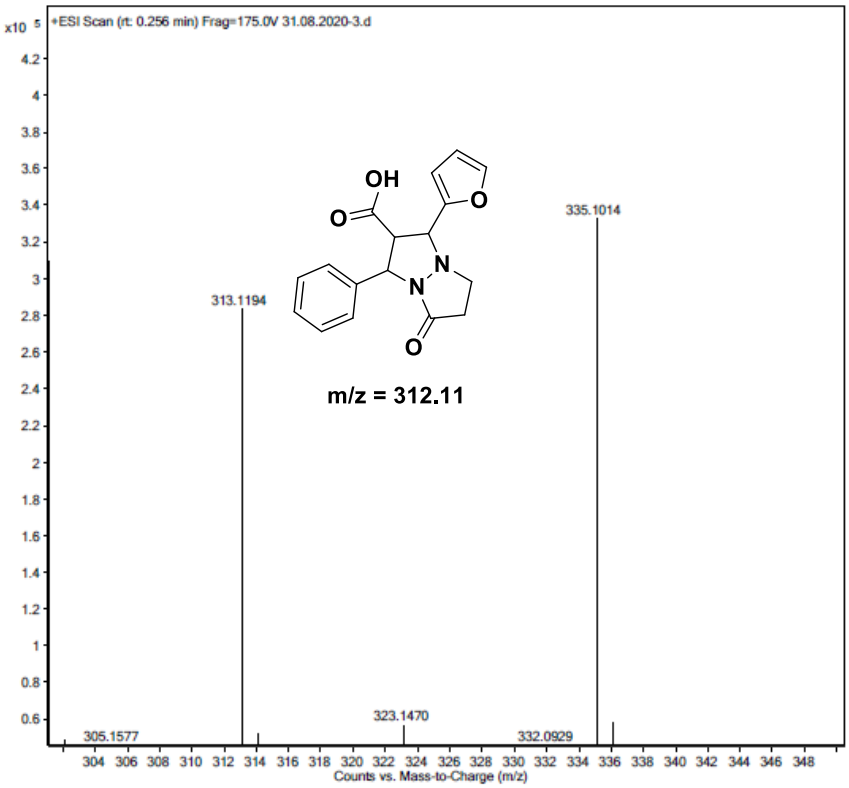




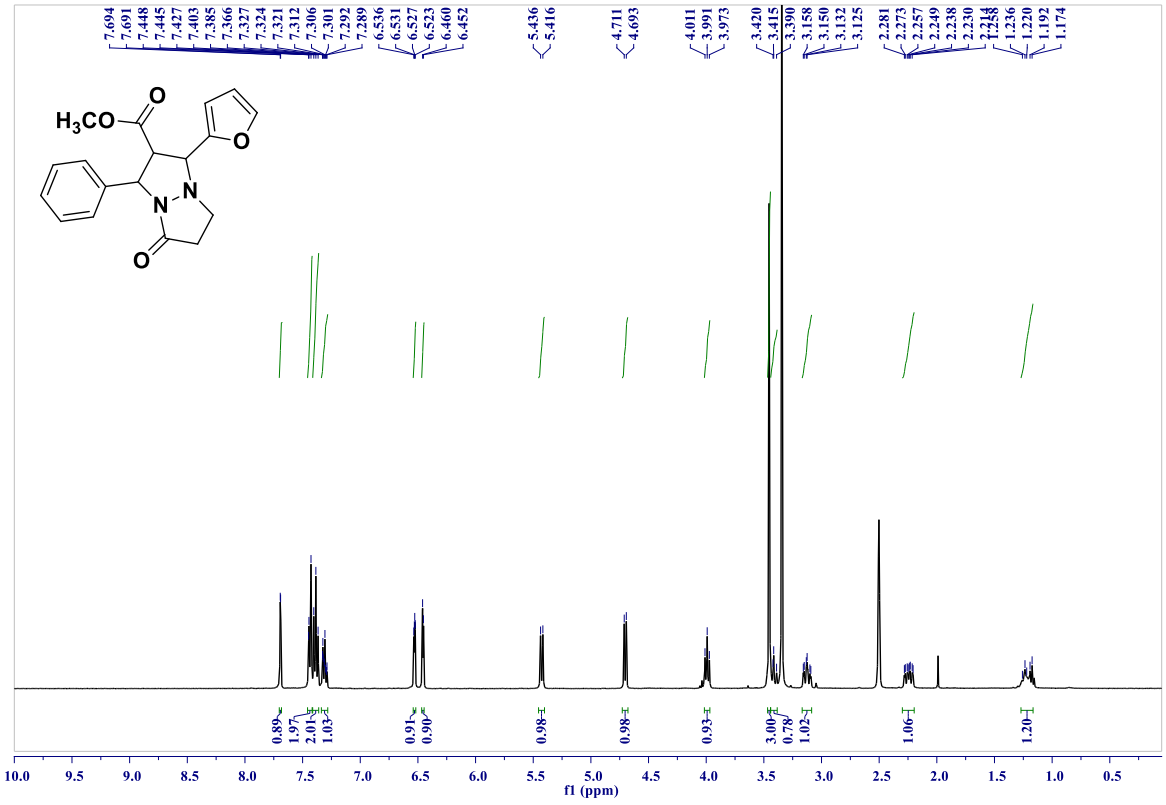
1-(furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-2-carboxylic acid (8b):

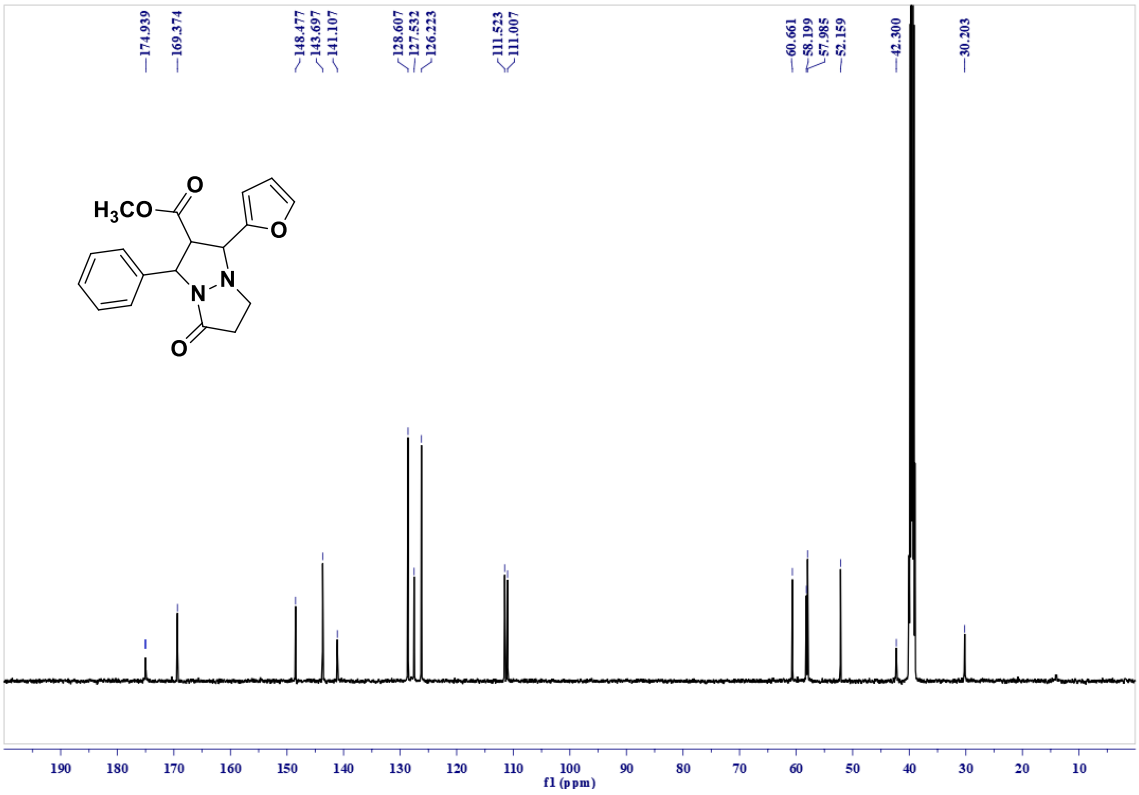


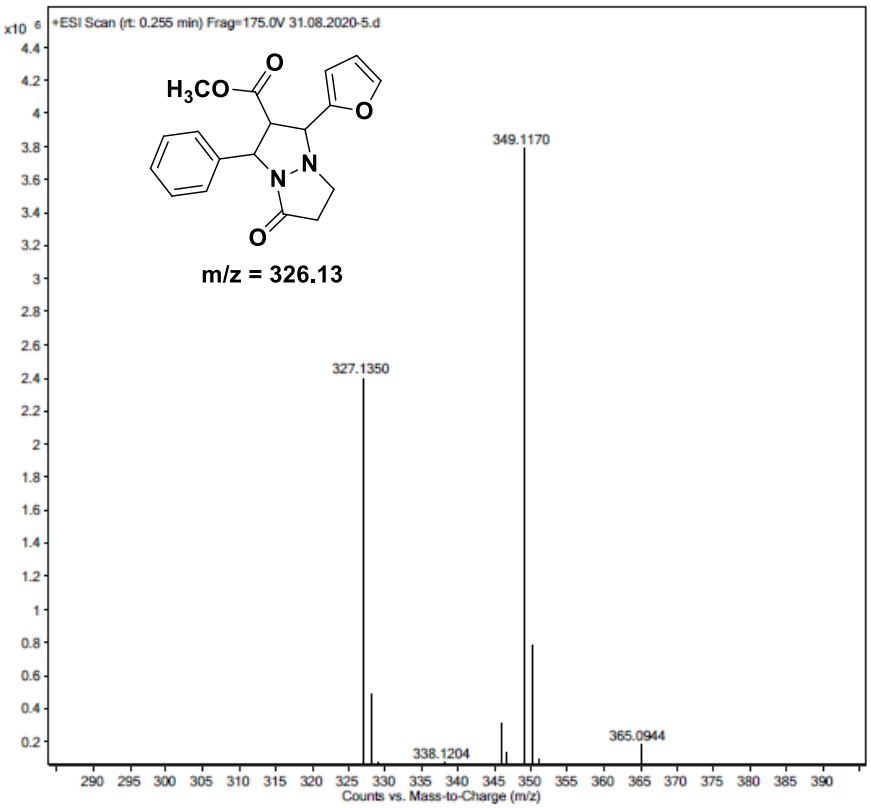




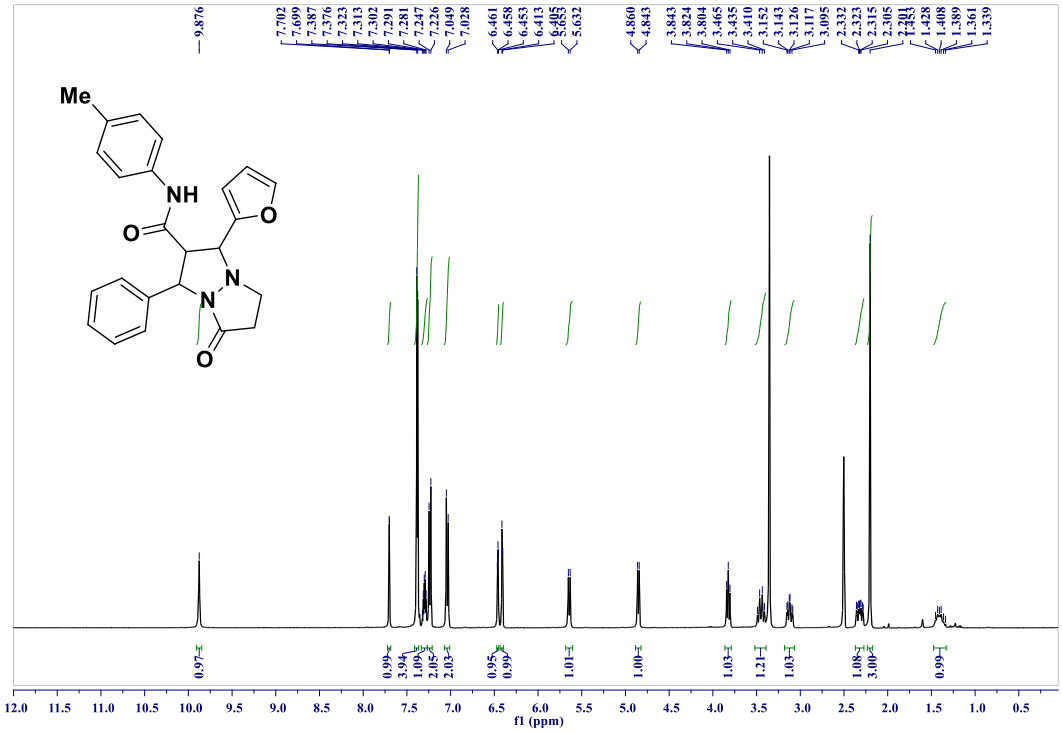
methyl 1-(furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-2-carboxylate (9b):

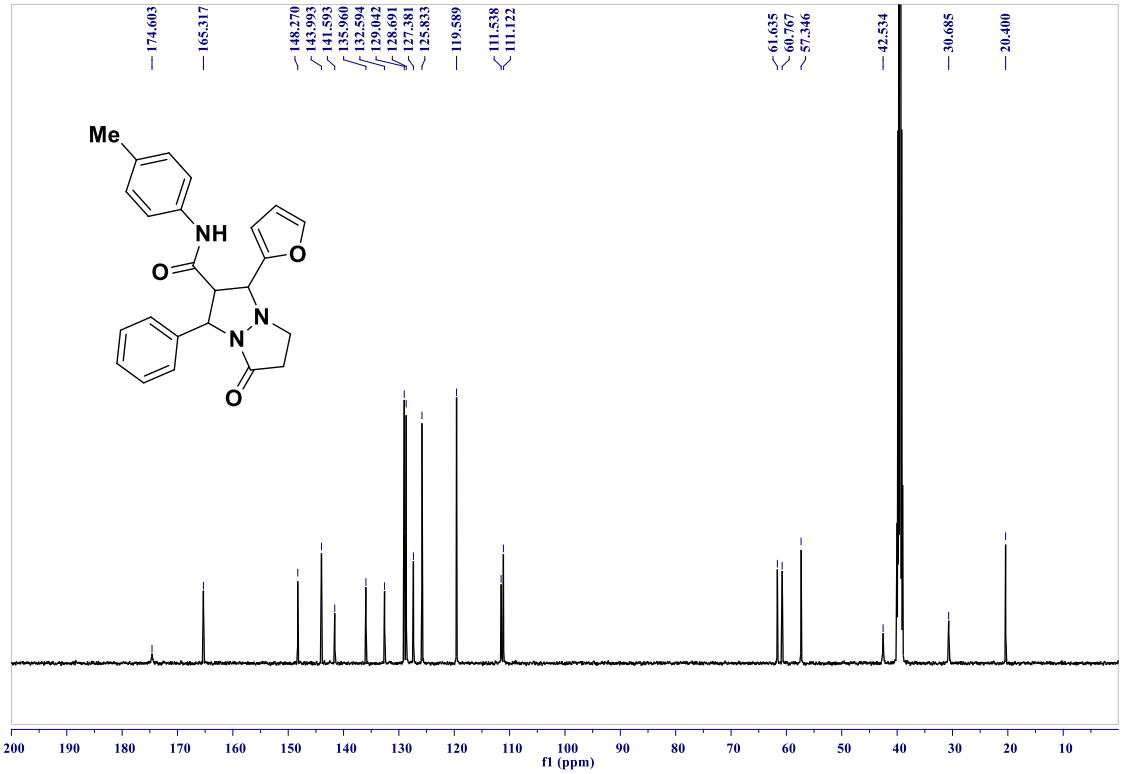


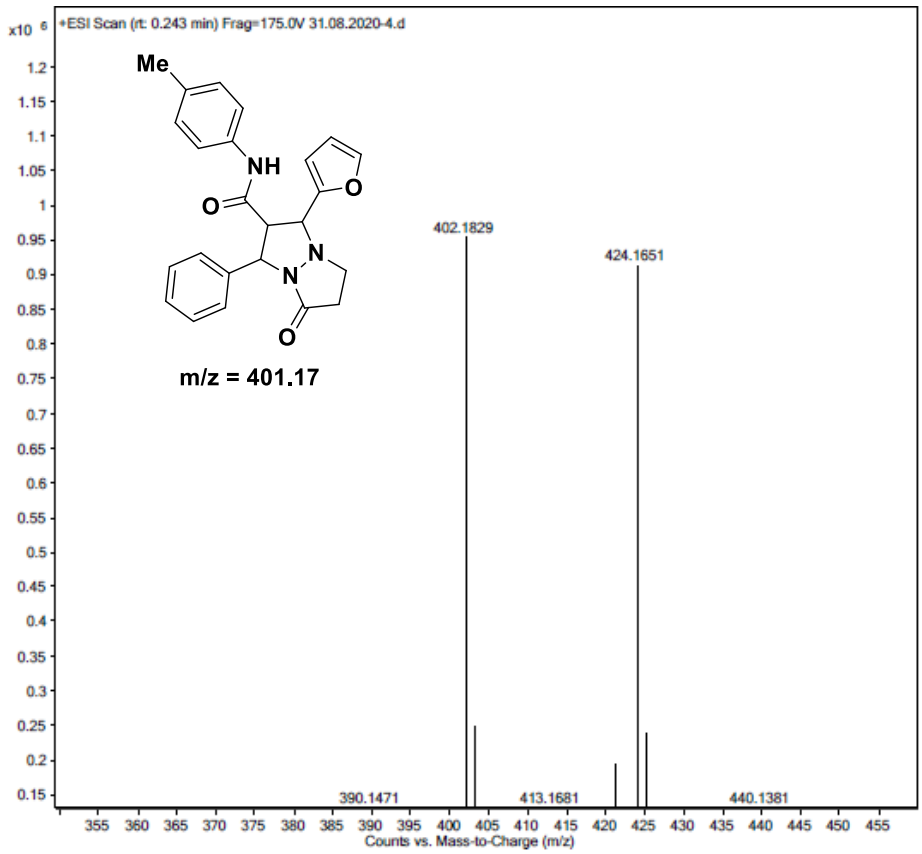

174.939
169.374
148.477
143.697
141.107
128.607
127.532
126.223
111.523
111.007
60.661
58.199
57.985
52.159
42.300
30.203
f1 (ppm)


x10 6
*ESI Scan (rt: 0.255 min) Frag=175.0V 31.08.2020-5.d
m/z = 326.13
349.1170
327.1350
338.1204
365.0944
Counts vs. Mass-to-Charge (m/z)

1-(furan-2-yl)-5-oxo-3-phenyl-N-(p-tolyl)hexahydropyrazolo[1,2-a]pyrazole-2-carboxamide (10b):







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CHAPTER-IV

Synthesis of spiro[indoline-3,2'-naphthalene]-4'-carbonitriles *via* regiodivergent domino protocol of isoxazole-oxindole styrenes and vinyl malononitriles

CHAPTER-IV

4.1 Introduction

4.1.1 Synthetic methods for the preparation of spirocyclic oxindoles (*via* domino reactions of vinyl malononitriles and various oxindole styrenes)

The vinylogous reactions have been recognized as a powerful and attractive tool for the construction of stereoselective carbon-carbon bond formation.[1] In this respect, the α,α-dicyanoolefins, which are readily available by the condensation of the corresponding carbonyl compounds and malononitrile and have been identified as versatile vinylogous donors in various reactions.[2a] The acidity of γ-C-H is greatly enhanced when the strong electron withdrawing groups are attached to C=C bonds, which allows easy generation of nucleophilic species by *in situ* deprotonation under mild conditions.[2b] The α,α-dicyanoolefins are electron deficient compounds, which can selectively function as acceptor. Due to their dense functionalities and versatile reactivity of α,α-dicyanoolefins have been widely used in various organic transformations (Michael, Michael/cyclization and cycloaddition reactions) for the synthesis of biologically active compounds.[2c-d] In recent years, significant progress has been made in the development of various organic transformations using the α,α-dicyanoolefins as electrophiles as well as nucleophiles.

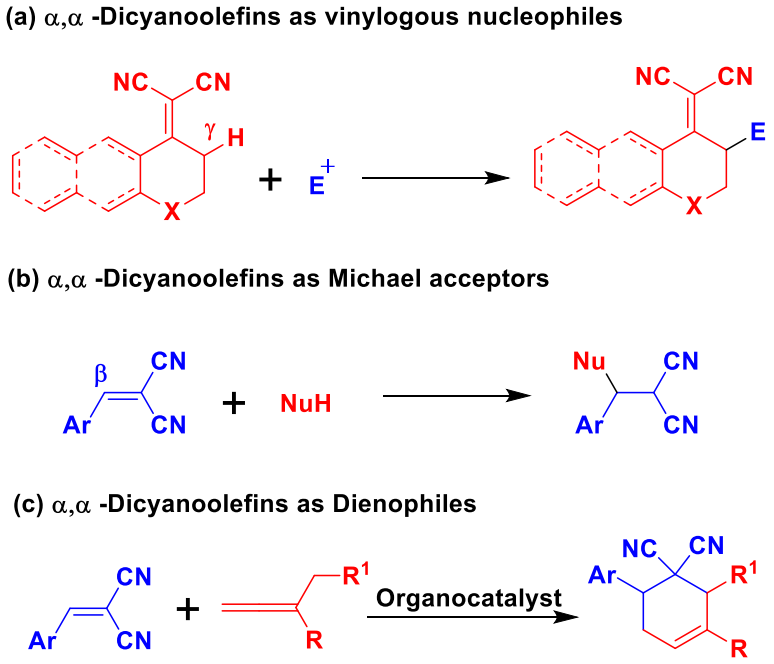
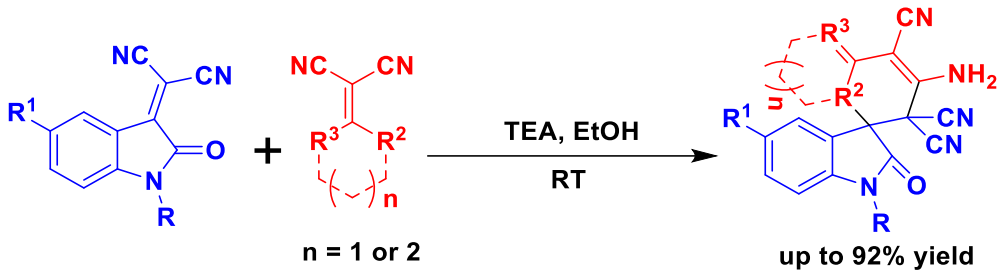


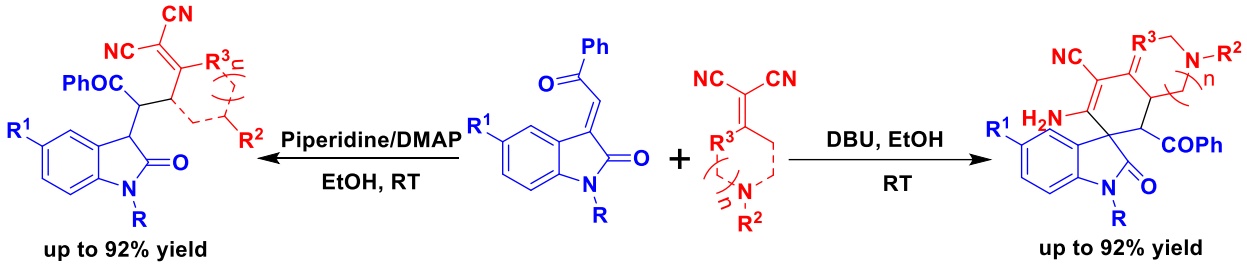
Figure-4.1: *Vinylogous nucleophilicity, electrophilicity and dienophilic nature of the α,α–dicyanoolefins.*

In this connection, **P.T. Perumal** group described one-pot tandem reaction of vinyl malononitriles with isatylidene malononitriles for the synthesis novel spirocyclic oxindole derivatives (**Scheme-4.1)** *via* vinylogous Michael addition followed by a sequential intramolecular addition and isomerization reaction with excellent yields (up to 92%).[3]



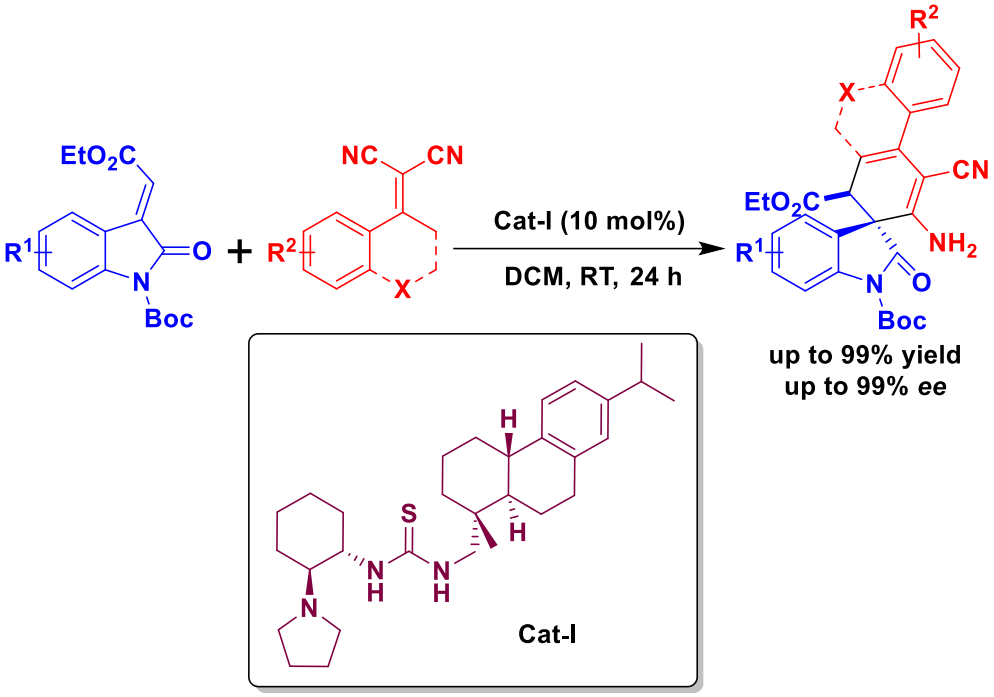
Scheme-4.1: *Synthesis of novel spirocyclic oxindoles.*

C.-G. Yan and his group systematically investigated the domino reaction of vinyl malononitriles with 3-phenacylideneoxindoles in ethanol in the presence of DBU as base to result in the functionalized spirocyclic oxindoles through the vinylogous Michael addition and intramolecular nucleophilic addition to cyano group. On the other hand, the similar reaction in the presence of piperidine as base afforded the simple Michael adducts in good yields (**Scheme-4.2)**.[4]



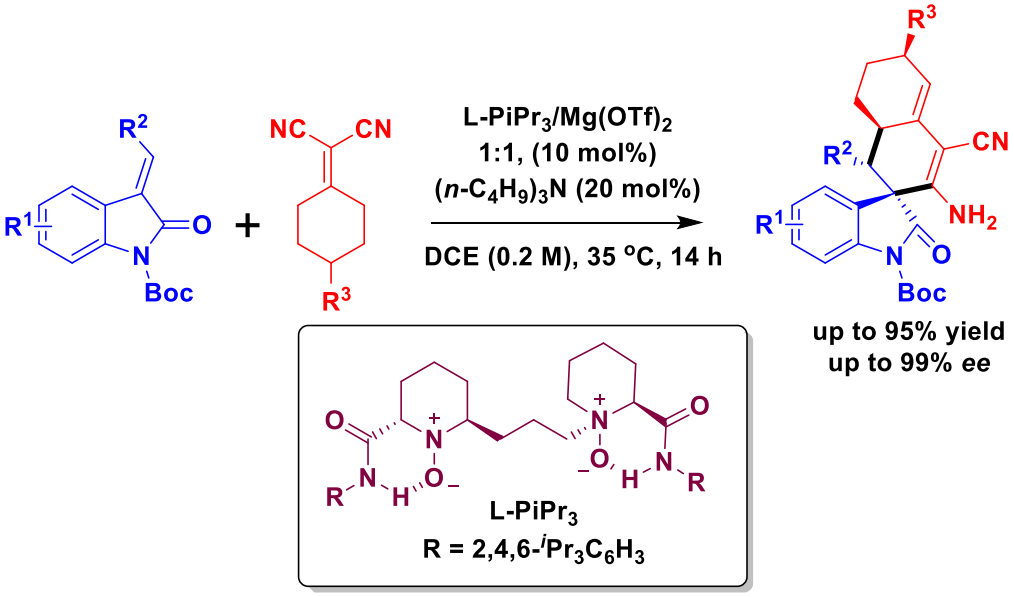
Scheme-4.2: *Synthesis of Michael addition products and spirocyclic oxindoles.*

Rui Wang reported the first example of organocatalytic asymmetric vinylogous Michael/cyclization reaction of α,α-dicyanoalkenes with 3-alkylideneoxindoles for synthesizing diversely structured spiro-oxindole skeletons (**Scheme-4.3)** with excellent yields and stereoselectivity (up to 99% yields, *dr* >20:1 and *ee* 91-99%).[5]



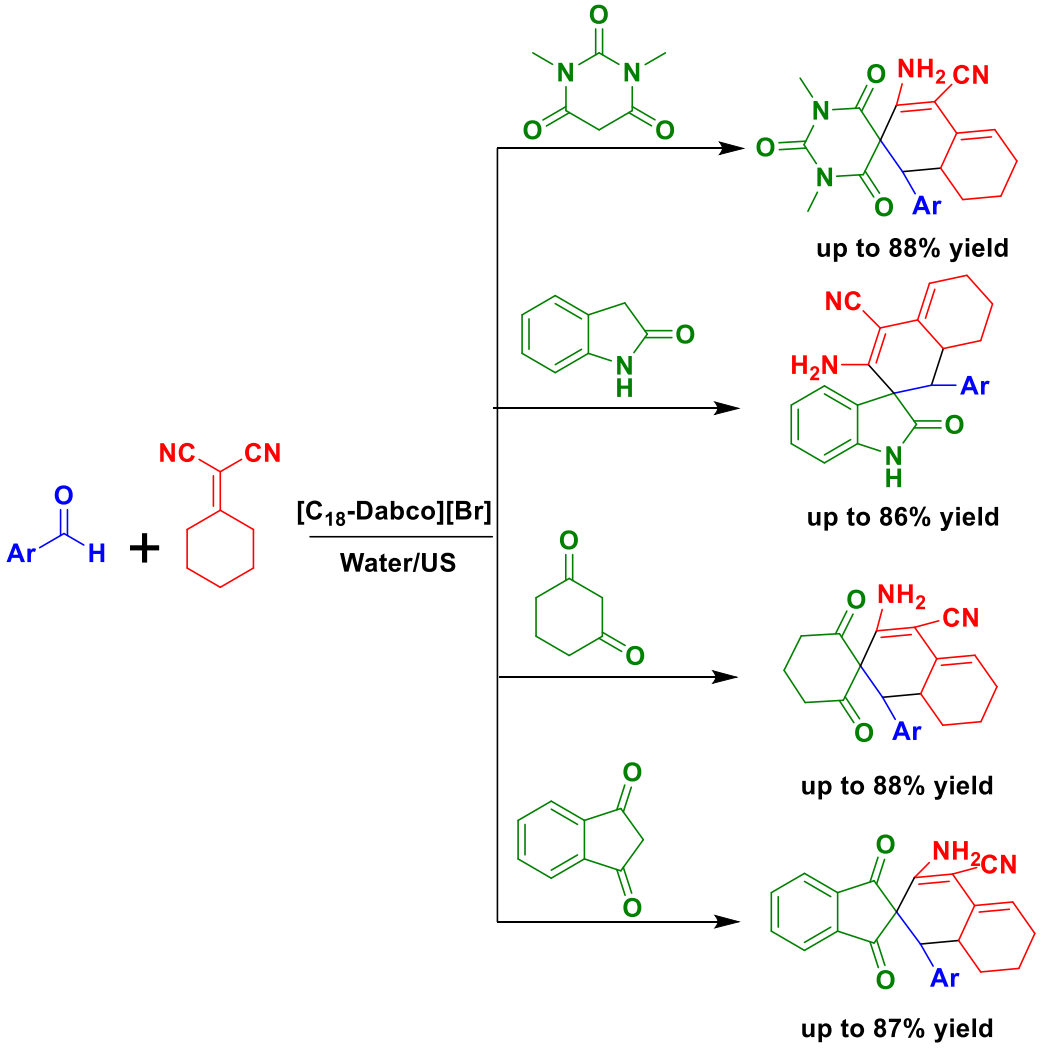
Scheme-4.3: *Asymmetric vinylogous Michael/cyclization cascade reaction of α,α-dicyanoalkenes with 3-alkylideneoxindoles.*

Lin and co-workers demonstrated the use of chiral *N, N'*-dioxide/Mg (II) complex and an organic base to catalyze the vinylogous Michael/cyclization cascade reaction of 4-substituted cyclic α,α-dicyanoalkenes and 3-methylene-indolinones to generate spiroindolinones bearing three adjacent stereogenic centers and a tertiary carbon center at remote site with excellent yields and high enantioselectivity (**Scheme-4.4**).[6]



Scheme-4.4: *The asymmetric vinylogous Michael/cyclization cascade reaction of α,α-dicyanoalkene with 3-alkylideneoxindole.*

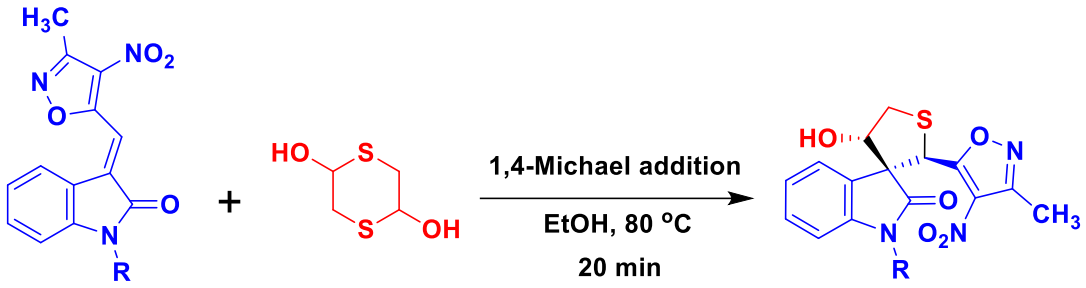
T. Lohar et al. developed an extremely simple, mild and clean synthetic protocol for the synthesis of spirocarbocycle derivatives *via* vinylogous Michael addition of cyclic nucleophiles with vinyl malononitrile and aldehydes using [C_{18}-DABCO][Br] as a cationic surfactant in water under ultrasonication afforded in good yields (**Scheme-4.5)**.[7]



Scheme-4.5: *Synthesis of spirocarbocycles using [C_{18}-Dabco][Br] surfactant in water.*

Our group also extensively working on 3-methyl-4-nitro-5-isatylidenyl-isoxazole for various organic transformation reactions. The synthesis of spirooxindole-isoxazole-tetrahydrothiophene hybrids (**Scheme-4.6)** were achieved by reaction of 3-methyl-4-nitro-5-isatylidenyl-isoxazoles and 1,4-dithiane-2,5-diol. The reaction proceeded *via* 1,4-thia-Michael

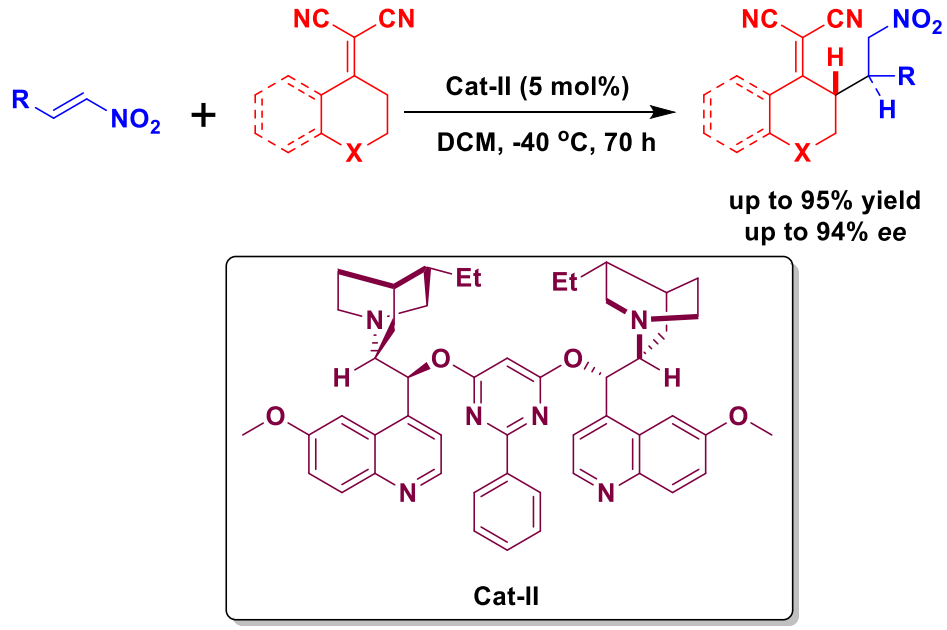
followed by intramolecular aldol reactions under catalyst-free conditions in excellent yields (up to 98%) in short reaction time (20 min).[8]



Scheme-4.6: *Synthesis of isoxazole based spiro-thiolane hybrids via (3+2)-cycloaddition reaction.*

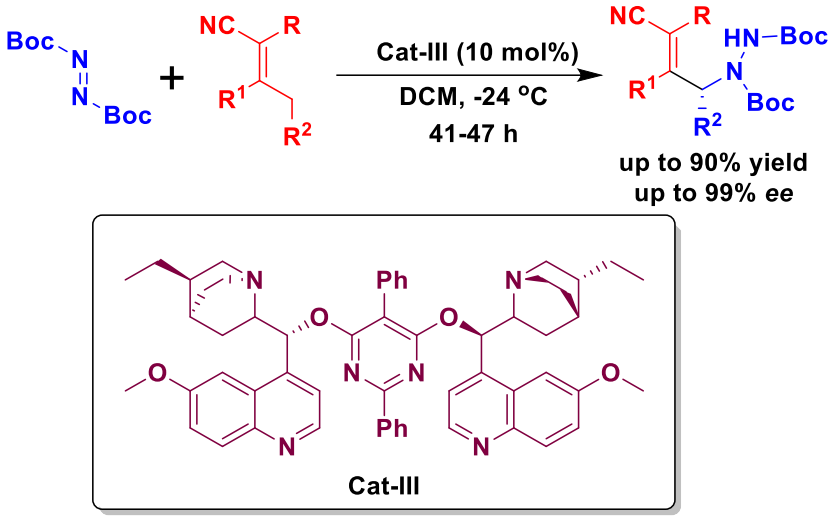
4.1.2 Vinylogous Michael addition reactions of vinyl malononitriles

Y.-C. Chen group reported the first example of organocatalytic and asymmetric direct vinylogous Michael reaction of electron-deficient vinyl malononitriles with nitro olefins in presence of catalytic amounts of $(DHQD)_2PYR$ to deliver multifunctional products with excellent yields and high levels of diastereoselectivity and enantioselectivity (**Scheme-4.7**).[9]



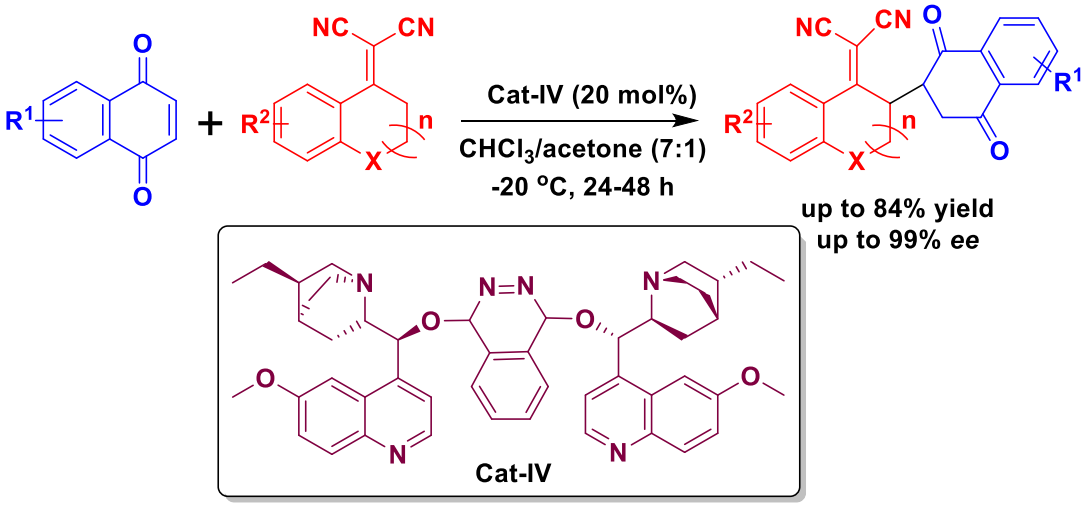
Scheme-4.7: Enantioselective vinylogous Michael addition of vinyl malononitriles to nitroolefins catalyzed by $[DHQD]_2PYR$.

K. A. Jørgensen's group, extended above strategy to diazodicarboxylates with alkylidene cyanoacetates/α,α-dicyano alkenes to deliver γ-aminated products with good yields and excellent enantioselectivity in presence of pseudoenantiomeric catalyst $(DHQ)_2PYR$ (**Scheme-4.8**).[10]



Scheme-4.8: *Organocatalytic enantioselective allylic amination of compounds of α,α-dicyano alkenes with di-tert-butyl azodicarboxylate.*

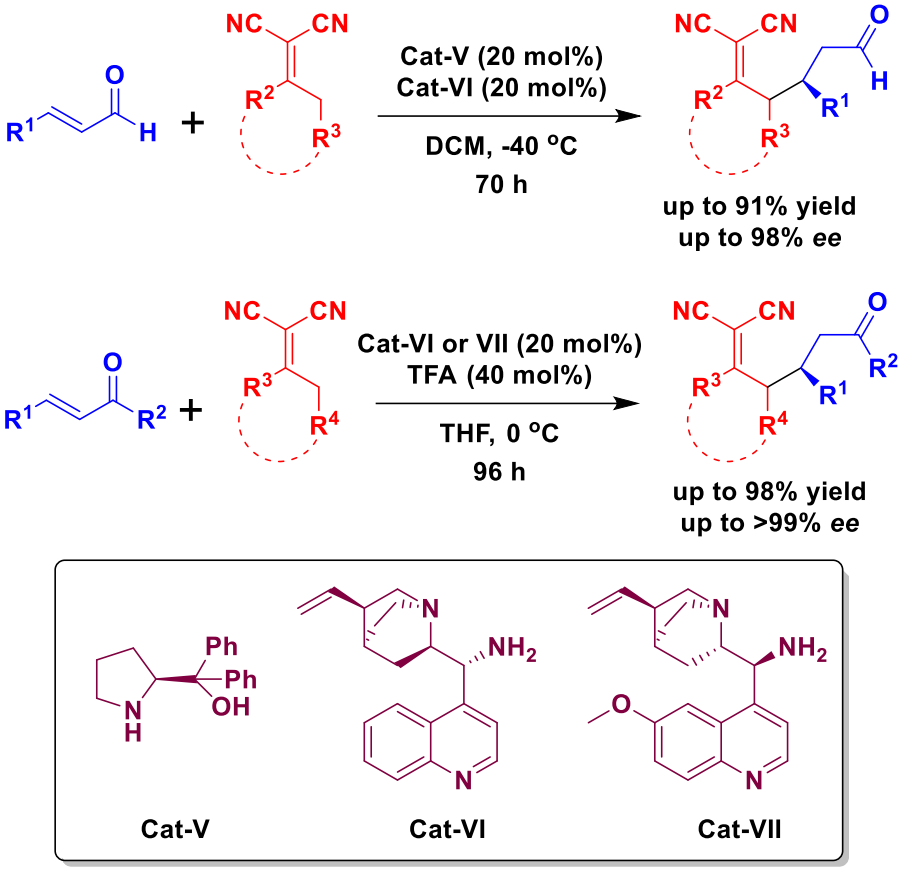
Later same group also described organocatalytic addition of dicyanoalkylidenes to quinones catalyzed by cinchona alkaloids leading to formation of 1,4-diketone derivatives with good yields, diastereoselectivities, and gives up to 99% *ee (***Scheme-4.9**).[11]



Scheme-4.9: *Benzoquinones in vinylogous Michael reactions with α,α-dicyano alkenes.*

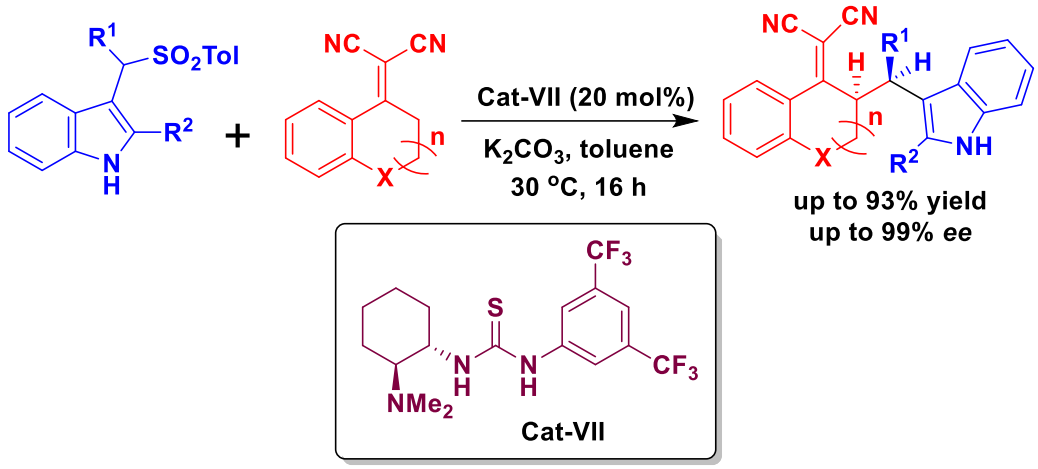
J.-G. Deng group described the highly regio-, chemo-, diastereo- and enantioselective direct vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes employing with readily available chiral α,α-diarylprolinol salts as iminium organocatalysts.[12] Later, the same group also demonstrated an asymmetric direct vinylogous Michael addition of α,α-dicyanoalkenes

with α,β-unsaturated ketones using chiral primary amines afforded with good to excellent yields and high enantioselectivity (**Scheme-4.10**).[13]



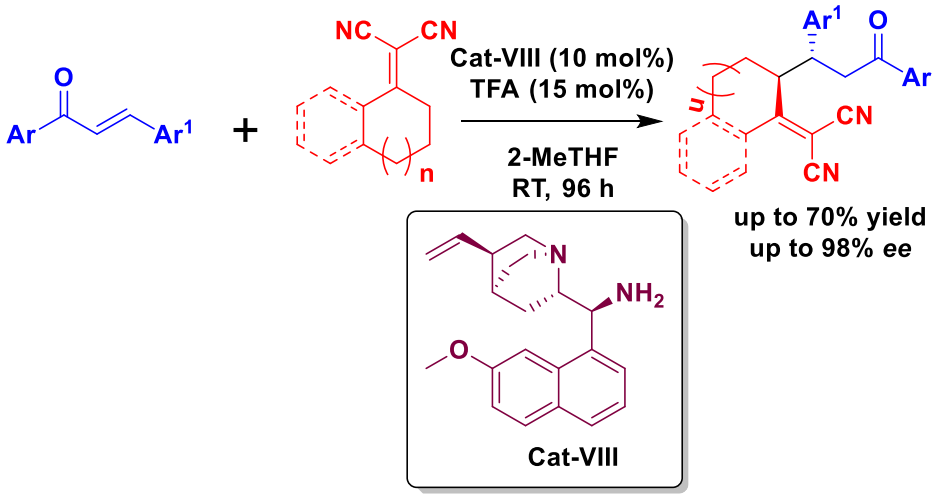
Scheme-4.10: *Direct vinylogous Michael reactions of α, α-dicyano alkenes with enals and enones.*

Jing and co-workers reported reactions of α,α-dicyano alkenes with arenesulfonylalkylindoles using Takemoto's amino thiourea catalyst under basic conditions to afforded highly functionalized C-3-alkyl-substituted indoles with high yields (up to 93%) and enantioselectivities (up to 99% *ee*) (**Scheme-4.11**).[14]



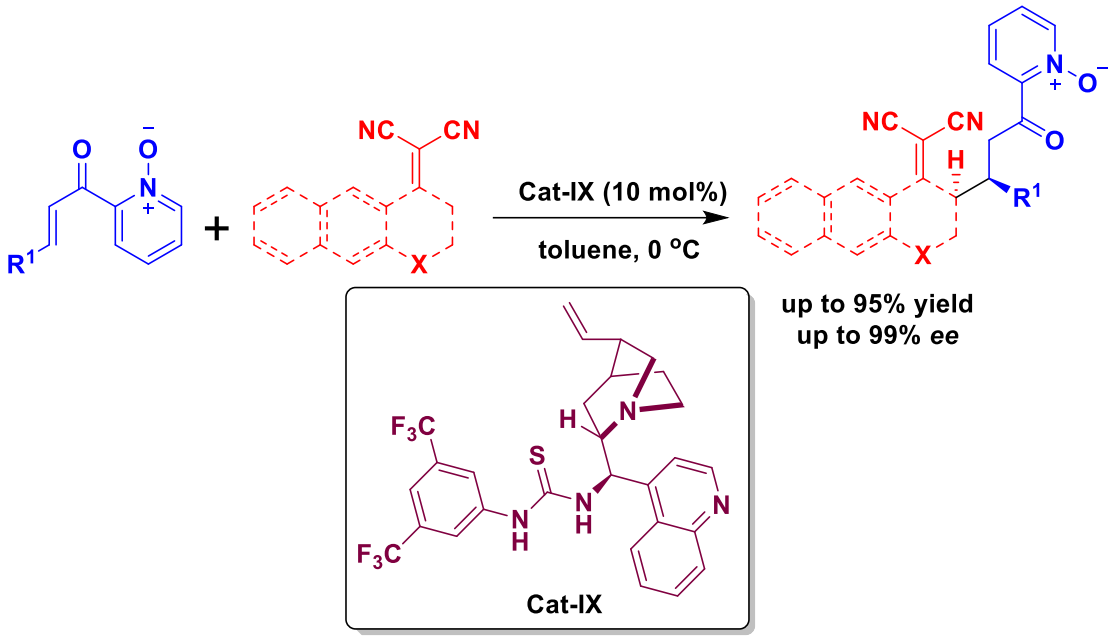
Scheme-4.11: *Vinylogous Michael reaction of α,α-dicyanoalkenes with arenesulfonylalkylindoles.*

L. S. R. Martelli et al. described the use of bifunctional catalyst derived from the cinchona alkaloid to perform the enantioselective Michael addition of α,α-dicyanoolefins with chalcones in presence of 2-MeTHF as solvent to provide various Michael adducts with good yields and excellent enantioselectivity (**Scheme-4.12**).[15]



Scheme-4.12: *Michael addition reaction of different chalcones with α,α-dicyanoolefins.*

V. K. Singh group described catalytic enantioselective direct vinylogous Michael addition of α,α-dicyanoalkenes to 2-enoylpyridine *N*-oxides with a bifunctional organocatalyst to deliver highly functionalized enantioenriched cyclohexylidenemalononitrile derivatives with excellent regio-, diastereo-, and enantioselectivity (**Scheme-4.13**).[16]



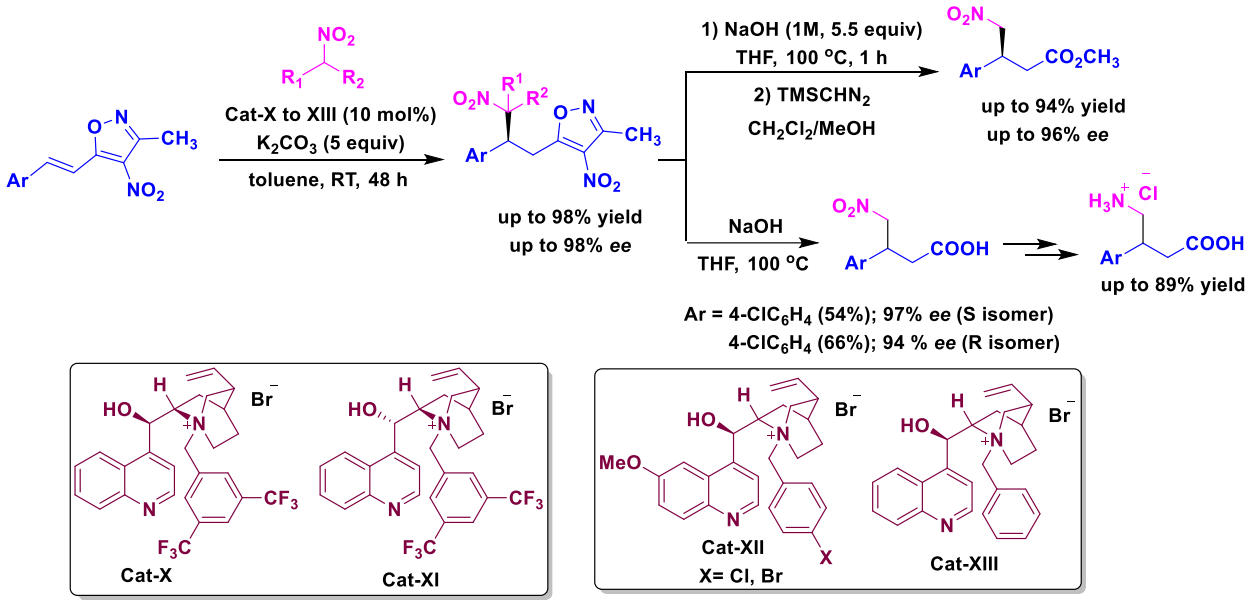
Scheme-4.13: *Direct vinylogous Michael reaction of α,α-dicyanoalkenes to 2-enoylpyridine N-oxides.*

4.1.3 1,6-Michael addition reactions of 3-methyl-4-nitro-5-styryl-isoxazoles

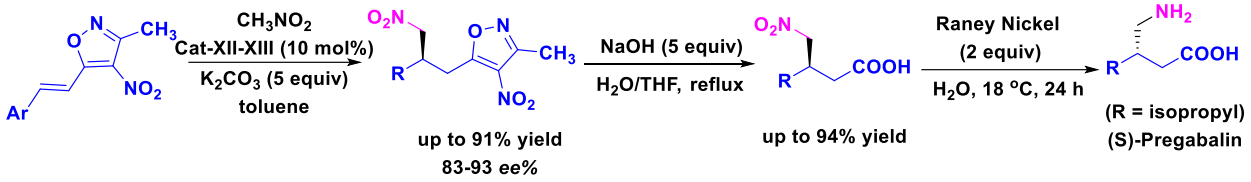
The 1,4-Michael addition reactions and their versions (1,4-Michael-domino/cascade reactions) are widely studied for the synthesis of various complex molecules. Along with this, 1,6-Michael addition also got much attention in the literature in past few decades. The presence of β- and δ- reactive positions in the starting material, electronic factors of conjugated system and controlling newly generated stereo genic system at δ-position are challenging tasks in 1,6-Michael addition reactions. This has been overcome by developing efficient designer catalysts which activate δ-position selectively and choosing suitable substrates with substitution at *β*-position.[17a-e] In this context, 3-methyl-4-nitro-5-styryl-isoxazole have been extensively used for the 1,6-Michael addition as Michael acceptor.[17f]

Adamo and his group was first to report an asymmetric Michael addition reaction of nitroalkane on isoxazole styrene by using cinchona alkaloids-based phase transfer catalysts (PTCs; **Cat-X to Cat-XIII**) at room temperature with good yields (50-98%) and excellent enantioselectivity (up to 98%). The resulting Michael adducts were converted into γ-nitro esters and γ-amino acids which can be useful as advanced intermediates in medicinal/pharmaceutical chemistry (**Scheme-4.14**).[18a] In continuation to this work, they have synthesized (*S*)-pregabalin [an epileptic drug] using alkyl substituted unsaturated isoxazole derivatives and nitromethane in

the of presence PTC (**Cat-XII, Cat-XIII**; 10 mol%) to afford Michael adducts with 89-91% yields and enantioselectivity (up to 93%). The resulting Michael adducts were treated for isoxazole ring opening and nitro reduction to give chiral γ-amino acids [one of the products is (*S*)-pregabalin] (**Scheme-4.15**).[18b]

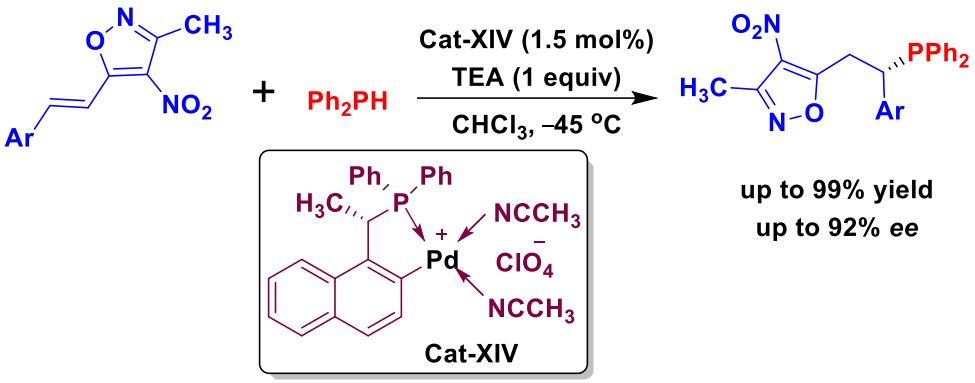


Scheme-4.14: *Asymmetric 1,6-Michael addition of isoxazole-styrenes and nitromethanes in presence of cinchona-based catalysts.*



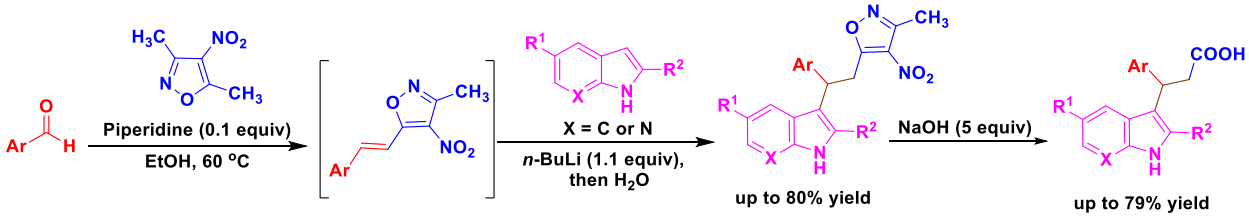
Scheme-4.15: *Synthesis of (S)-pregabalin via asymmetric 1,6-Michael addition reaction.*

R. J. Chew et al. developed an asymmetric synthesis of isoxazole containing tertiary phospanes by using 1,6-Michael addition reaction in between isoxazole-styrenes and diphenylphosphine in presence of chiral catalyst at mild reaction condition to offer good to excellent yields (93-99%) and enantioselectivity (up to 92% *ee)* (**Scheme-4.16**).[19]



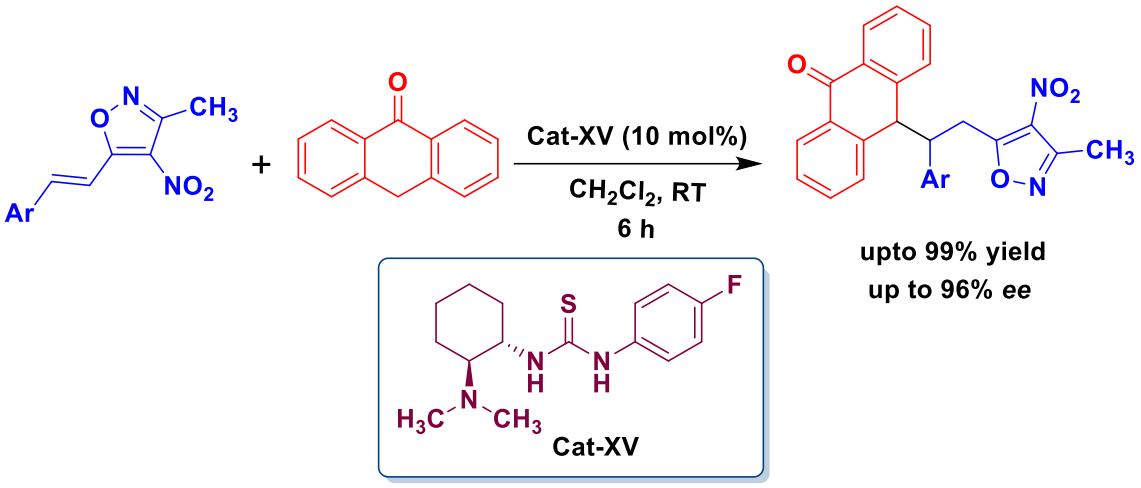
Scheme-4.16: *Asymmetric 1,6-Michael addition of diphenylphosphine on isoxazole-styrene.*

Later, the same group synthesized biologically important 3-indolyl propionic acids and 3-azaindolyl propionic acids. In this case, 3,5-dimethyl-4-nitroisoxazole and aldehydes were reacted in presence of piperidine to give isoxazole-styrenes followed by the addition of lithium slats of indoles/azaindoles **(**generated from the reaction of *n*-BuLi) to give 3-substitute isoxazole-indole hybrids in 70-80% yields. Further, ring opening of isoxazole moiety by treating with aqueous NaOH to delivered 3-indole propionic acids in 70-79% yields (**Scheme-4.17**).[20]



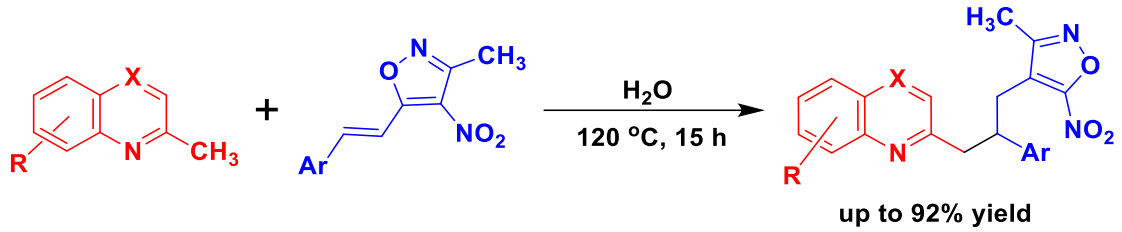
Scheme-4.17: *Synthesis of isoxazole-indole hybrids and 3-indolyl propionic acids.*

Yuan and co-workers reported an asymmetric 1,6-Michael addition of anthracen-9(10*H*)-one with isoxazole-styrene by using bifunctional chiral thiourea as organocatalyst at room temperature to give isoxazole-anthracen-9(10*H*)-one adducts in 57-99% yields and high enantioselectivity (up to 96%) (**Scheme-4.18**).[21]



Scheme-4.18: *Michael addition of anthracen-9(10H)-one on isoxazole-styrenes using bifunctional chiral thiourea as catalyst.*

M. N. Reddy group described the one-pot synthesis of functionalized azaarene-isoxazole hybrids using 2-methyl quinolone and 3-methyl-4-nitro-5-alkenyl-isoxazoles under catalyst-free (*via* sp^3 C-H activation) using "on-water" concept at 120 ^oC with moderate to excellent yields (**Scheme-4.19**).[22]



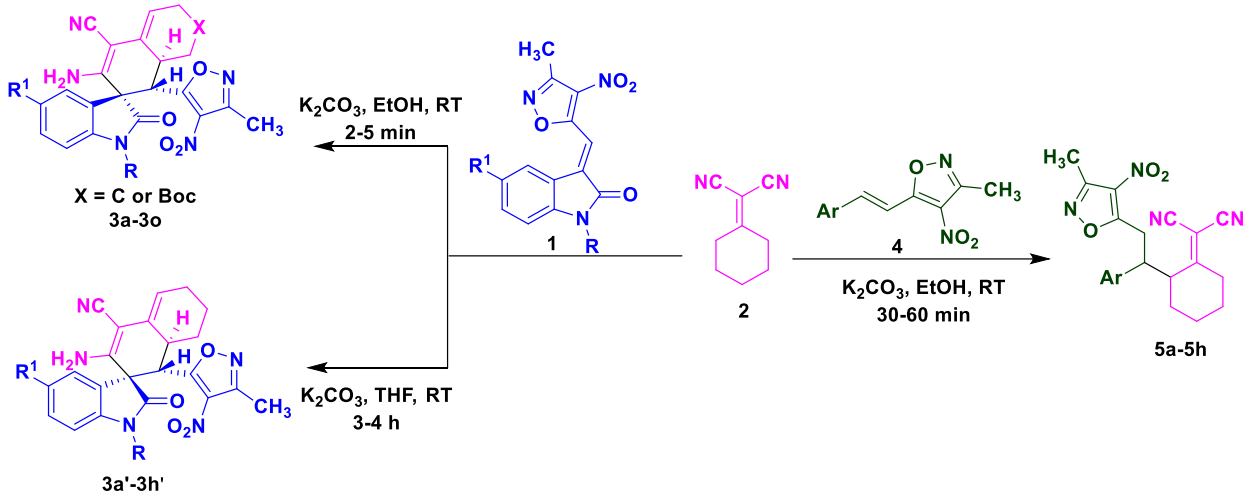
Scheme-4.19: *Reaction pathway for the Michael addition of azaarenes on isoxazole-styrenes.*

Nevertheless, 3-Methyl-4-nitro-5-isatylidenyl-isoxazoles have been poorly explored for domino Michael/Michael cyclization reactions. The only report by **Liu's** group described the asymmetric synthesis of bispirooxindole based hexahydroxanthones using chiral catalyst (**Chapter-III; Scheme-3.5**).[23] Recently, we have developed few efficient methods for the synthesis of 3,3-disubstituted oxindoles[24a] and spirocyclic oxindoles[24b] by using 3-methyl-4-nitro-5-isatylidenyl-isoxazole as key substrates. However, to the best of our knowledge there is no reports metal-free, base mediated, solvent dependent regiodivergent synthesis of spiro[indoline-

3,2'-naphthalene]-4'-carbonitrile using 3-methyl-4-nitro-5-isatylidenyl-isoxazoles with vinyl malononitriles.

4.2 Present study

Considering the biological prominence of isoxazole and oxindole in organic and medicinal chemistry, herein we describe a metal-free, base catalyzed reaction between 3-methyl-4-nitro-5-isatylidenyl-isoxazole (**1**) and vinyl malononitriles (**2**) *via* vinylogous Michael addition as the key step followed by a sequential tandem reaction. The reactivity of 3-methyl-4-nitro-5-styrylisoxazole (**4**) with vinyl malononitriles (**2**) is aslo discussed to afford simple Michael products. All the reactions proceeded under mild conditions with good to excellent yields.

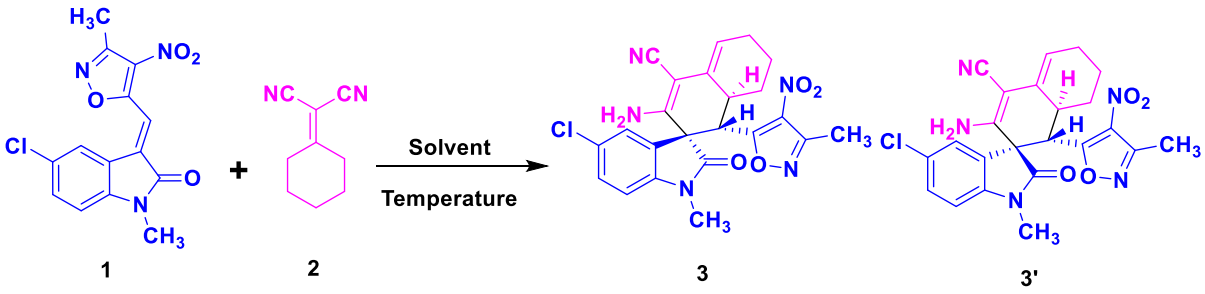


4.3 Results and Discussion

In our previous work (**Chapter-III**), we achieved the regioisomers of dinitrogen-fused spirooxindoles using the reaction of 3-methyl-4-nitro-5-isatylidenyl-isoxazole (**1**) with azomethine ylides by alerting the reaction conditions.[24b] Inspired by these results and in continuation of our efforts in developing synthetic methods for complex molecules (*via* vinylogous Michael, Michael/cyclization reactions), here we decided to synthesize spirocyclic compounds with isoxazole and oxindole moiety. To achieve this, we started our investigation by choosing 3-methyl-4-nitro-5-isatylidenyl-isoxazoles **1** and α,α-dicyanoolefin **2** as model substrates in dichloromethane (DCM) in presence of TEA as a base at room temperature (**Table-4.1; entry-1**). The formation of spirocyclic compound (**3**) was observed in 2 h with 40% of the yield as a sole product. Unexpectedly, the use of KO^{t}Bu led to mixture of diastereomers (**3** and **3'**) were observed on TLC with 30% and 25% of the conversions respectively (**Table-4.1; entry-6**). These results

are encouraged to us for further screening of the reaction conditions towards achieving the product selectivity, to reduce the reaction time and to get enhanced yields. A series of solvents such as DCM, EtOH, MeOH, CH_3CN, THF and toluene were screened in presence of DBU as a base and the results predicted in (**Table-4.1; entries 7-12**). In all these cases the formation of the product **3** was obtained as a single isomer with good to excellent yields (up to 95%) in short reaction time. Then we turned our attention to the choice of inorganic bases. Gratifyingly, the reaction promoted by K_2CO_3 in EtOH was clean and completed in less than 5 min, delivering **3** up to 98% of excellent yield. Somewhat to our surprise, when K_2CO_3, CS_2CO_3 and KO^{t}Bu treated in presence of THF, CH_3CN and toluene **3'** was generated as the major product up to 80% of the yield along with **3** also obtained in 10-20% of yield for 4 h. Both resulting isomers initially confirmed by ^1H, ^{13}C and 2D ^1H-^1H NOESY spectral analysis.

Table-4.1: Optimization of reaction condition[a]

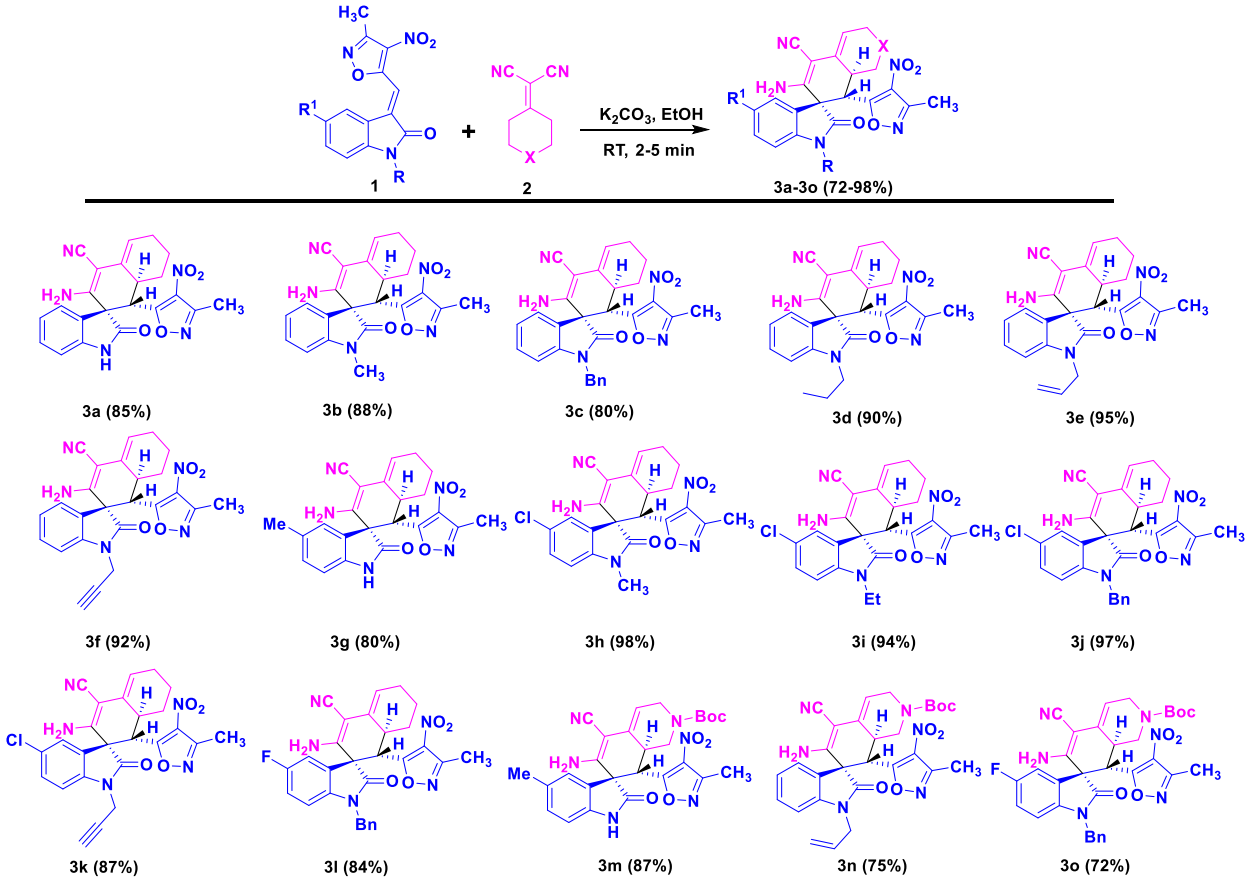


1 2 3 3'

Entry	Solvent	Catalyst (10 mol%)	Temp (°C)	Time (h)	Yield (%) [b] 3	3'
1	CH_2Cl_2	TEA	RT	4	40	ND
2	CH_2Cl_2	DABCO	RT	4	20	ND
3	CH_2Cl_2	piperidine	RT	4	70	ND
4	CH_2Cl_2	K_2CO_3	RT	4	20	trace
5	CH_2Cl_2	Cs_2CO_3	RT	4	30	trace
6	CH_2Cl_2	KO^{t}Bu	RT	4	30	25
7	CH_2Cl_2	DBU	RT	5min	88	ND
8	EtOH	DBU	RT	2min	95	ND
9	MeOH	DBU	RT	2min	90	ND
10	THF	DBU	RT	2min	92	ND
11	CH_3CN	DBU	RT	2min	85	ND

12	toluene	DBU	RT	2min	88	ND
13	**EtOH**	**K_2CO_3**	**RT**	**2min**	**98**	**ND**
14	**THF**	**K_2CO_3**	**RT**	**4**	**10**	**80**
15	THF	Cs_2CO_3	RT	5	10	70
16	THF	KO^{t}Bu	RT	5	20	65
17	CH_3CN	K_2CO_3	RT	5	10	30
18	toluene	K_2CO_3	RT	5	trace	45

[a]All the reactions were performed with **1a** (1 mmol), **2** (1 mmol), base (0.1 mmol) in 3 mL of solvent. [b]Isolated yields.

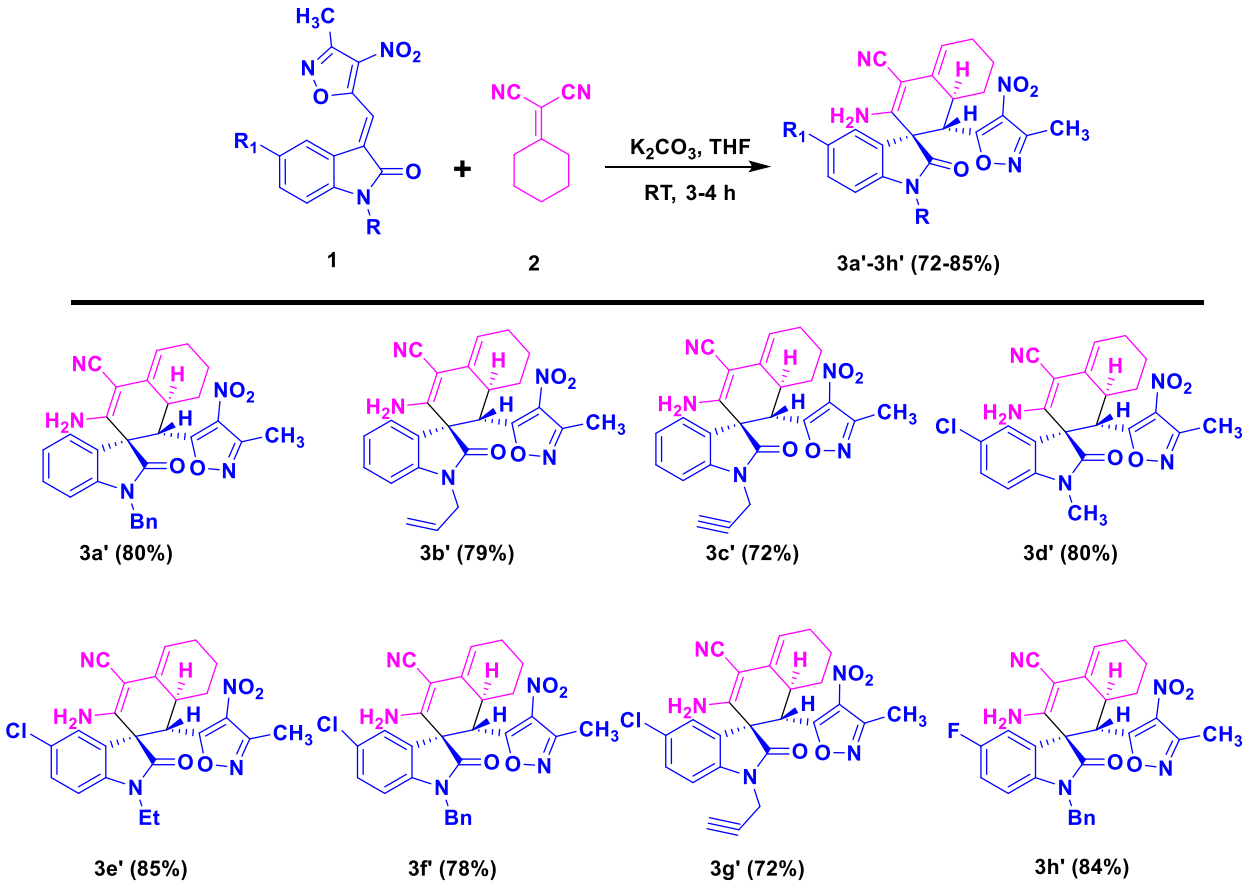


Scheme-4.20: *Substrate scope for the synthesis of spirocyclic oxindoles (**3a-3o**).*

With the optimal reaction conditions in hand, the scope of substrates was then investigated. Generally, the reaction proceeded smoothly to afford the desired products for most cases. The reaction of various isoxazole-oxindole styrenes **1** (substitution on aromatic ring and nitrogen of istain) with vinyl malononitrile were examined under optimized condition (both EtOH/THF;

K_2CO_3) to delivered the corresponding spirocyclicoxindoles in good to excellent yields (upto 98%) (**Scheme-4.20 & Scheme-4.21**). All newly synthesized compounds were characterized using NMR and mass spectroscopic data. Further, towards establishing the stereochemistry of the spirooxindoles **3e** and **3b'** are established by NMR spectroscopy, 2D ^{1}H–^{1}H NOESY experiments and X-ray diffraction analysis.

The ^{1}H-NMR (DMSO-d_6) spectrum of the compound **3e** characteristic –NH_2 protons appears at δ = 5.85 ppm, isoxazole adjacent proton appear as doublet at 4.40 - 4.37 (d, *J* = 12.4 Hz, 1H) and one multiplet (tertiary –CH) proton at 3.59 – 3.48 ppm. Another isomer **3b'** characteristic –NH_2 protons appears at δ = 6.27 ppm, isoxazole adjacent proton appear as doublet at 4.37 - 4.33 (d, *J* = 12.4 Hz, 1H) and one multiplet (tertiary –CH) proton at 3.19 – 3.04 ppm and the stereochemistry of the products **3e** and **3b'** was established on the basis of 2D ^{1}H–^{1}H NOESY, **3e** product clearly showed NOE cross-peak $H^a \leftrightarrow H^b$ and there is no cross peak between $H^c \leftrightarrow H^d$ for **3b'**. (**Figure-4.4 & 4.5**).



Scheme-4.21: *Substrate scope for the synthesis of spirocyclic oxindoles (**3a'-3h'**).*

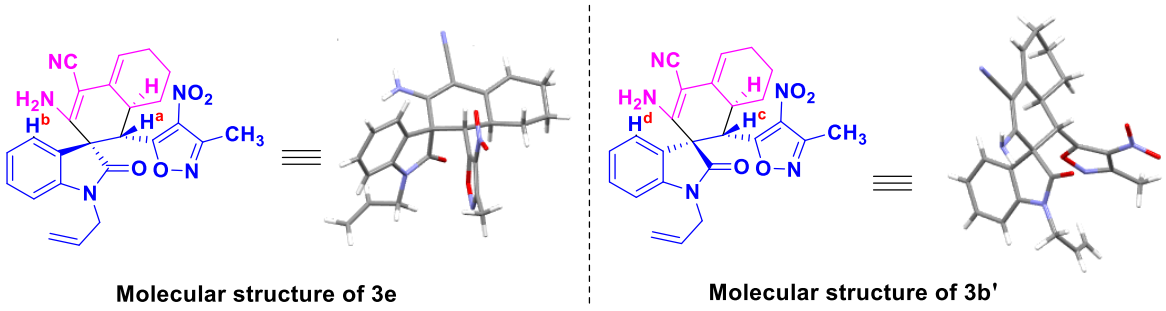
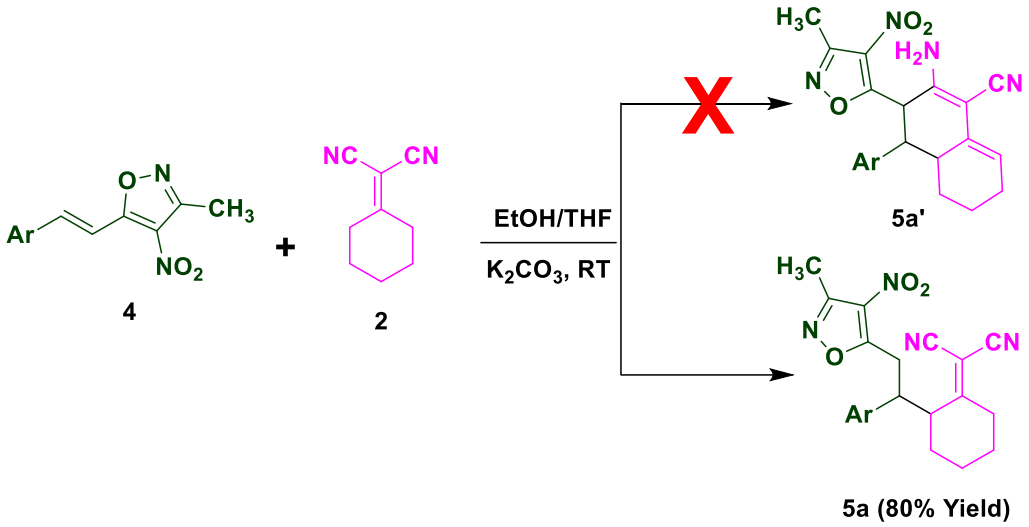


Figure-4.2: *X-ray structures of spirooxindoles* ***3e*** *and* ***3b'****.*

Based on above results and single crystal data and along with supporting the related reports of the vinyl malononitrile, we proposed a mechanism for the reaction in **Figure-4.3**; A. Initially under basic mild condition vinyl malononitrile possess facile deprotonation to afford vinylogous carbanion which is further attacks on isatin-isoxazole styrene (**1**) *via* 1,4 Michael addition followed by an intramolecular nucleophilic addition on CN group resulting in an imine (**II**). Finally, the spirocyclic oxindole (**3**) was formed by imino-enamine tautomerization.

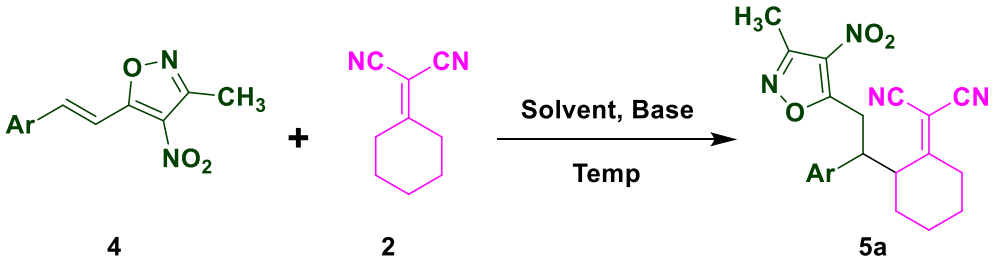


Scheme-4.23: *Attempts for the synthesis of double vinylogous product (****5a'****).*

Keeping in view of the biological importance of spirooxindoles, and isoxazoles (**Chapter-I; Figure-2)**, we extended our strategy on 3-methyl-4-nitro-5-styryl-isoxazole (**4**) moiety. For this, simple isoxazole-styrenes (**4**) were treated with α,α-dicyanoolefin **2** under optimized reaction conditions (in EtOH/THF; K_2CO_3). To our surprise, the reaction afforded only vinylogous Michael adduct **5a** instead of double vinylogous product **5a'** (**Table-4.2; entries 1-2**). The formation of

desired product further confirmed by NMR and Mass spectroscopic data. The ^{1}H NMR spectrum of the compound **5a** in $CDCl_3$, the characteristic $-CH_3$ proton appears at δ = 2.45 ppm, isoxazole adjacent two protons at 3.22 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.15 (d, *J* = 13.2 Hz, 1H), and phenyl adjacent one proton at 3.64 (td, *J* = 11.6, 4.0 Hz, 1H). Mass spectrum of the compound **5a** m/z Calculated $C_{21}H_{20}N_4O_3$ for: 376.1535; Observed: 377.1601 (M+1).

Table-4.2: Optimization of reaction condition[a]

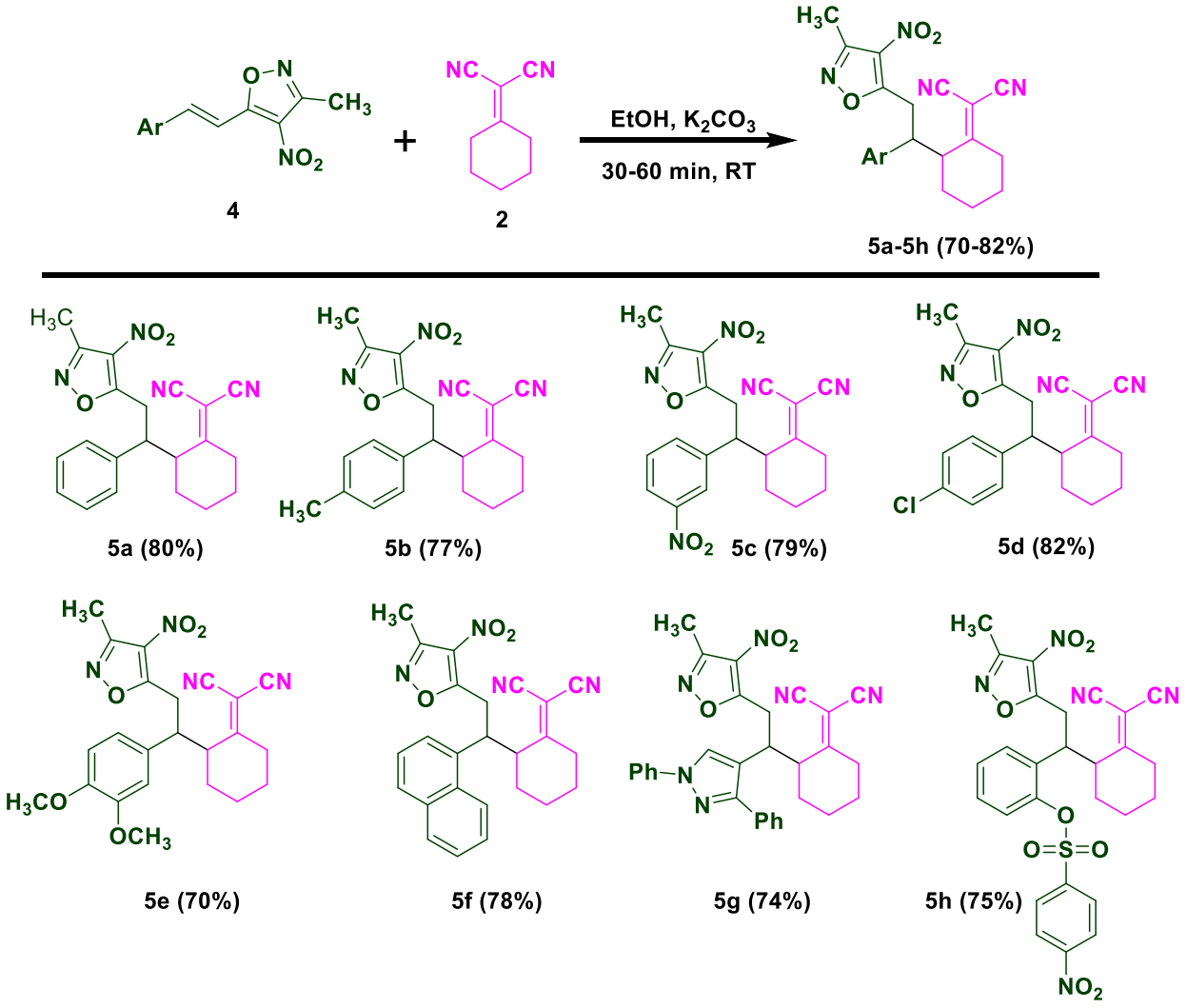


4 2 5a

Entry	Solvent	Catalyst (10 mol%)	Temp (ºC)	Time (h)	Yield (%) [b]
1	**EtOH**	**K_2CO_3**	**RT**	**1**	**82**
2	**THF**	**K_2CO_3**	**RT**	**1**	**75**
3	EtOH	TEA	RT	1	40
4	EtOH	DBU	RT	0.5	80
5	EtOH	piperdine	RT	0.5	55
6	EtOH	DABCO	RT	0.5	40
7	EtOH	Cs_2CO_3	RT	1	65
8	MeOH	DBU	RT	0.5	78
9	MeOH	K_2CO_3	RT	0.5	65
10	CH_2Cl_2	DBU	RT	0.5	75
11	CH_2Cl_2	K_2CO_3	RT	1	10
12	toluene	DBU	RT	0.5	70
13	toluene	K_2CO_3	RT	1	15
14	THF	DBU	RT	0.5	70

[a]All the reactions were performed with **1a** (1 mmol), **2** (1 mmol), base (0.1 mmol) in 3 mL of solvent. [b]Isolated yields.

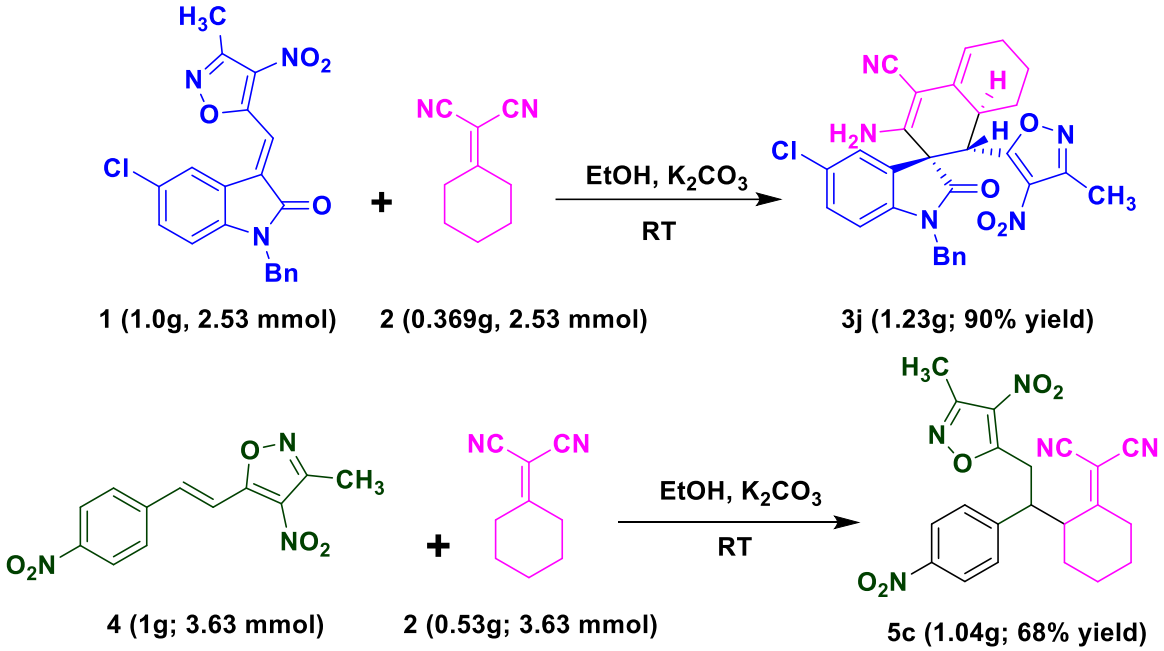
Later, we screened the above reaction with various solvents (polar, chlorinated and non-polar solvents) with different bases (inorganic and organic) to produce cycloaddition product **5a'** (**Table-4.2; entries 3-14**). But all the attempts were futile for giving the expected product **5a'**. Among screened conditions, the reaction promoted by K_2CO_3 (in EtOH) was efficient catalyst to delivering the various Michael adducts with good yields (70-82%). However, the yield of the product was decreases, when the reaction time increases or heating the reaction mixture. Depending on the structure of the substrate, the sequential/tandem step can stop at the middle step to produce simple Michael adducts (**Figure-4.3**; B).



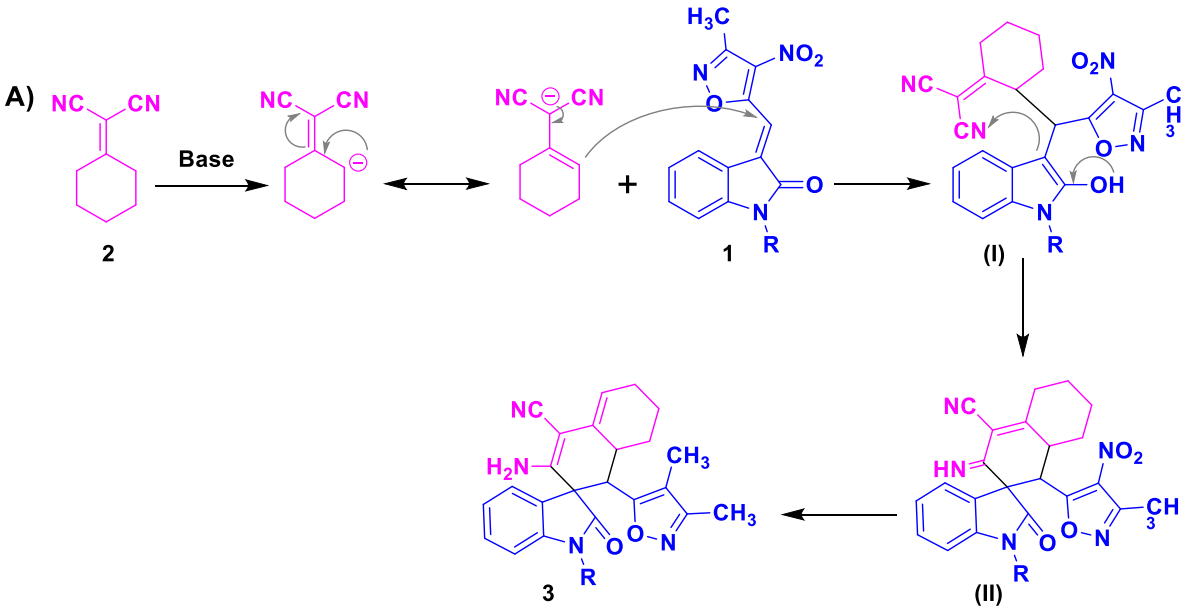
Scheme-4.24: *Substrate scope for the synthesis of Michael adducts (**5a-5h**).*

Gram Scale Reaction:

To explore synthetic potential of the reaction, a large-scale synthesis of **3j** and **5c** was carried out. When the reaction was performed in between isoxazole styrene **1 or 4** with vinyl malononitrile **2** under optimized condition (EtOH; K_2CO_3) to afford the corresponding desired products in 90% and 68% of the yields in short reaction time (for procedure, see experimental procedure).



Scheme-4.25: *A gram-scale preparation of adduct* ***3j/5c****.*



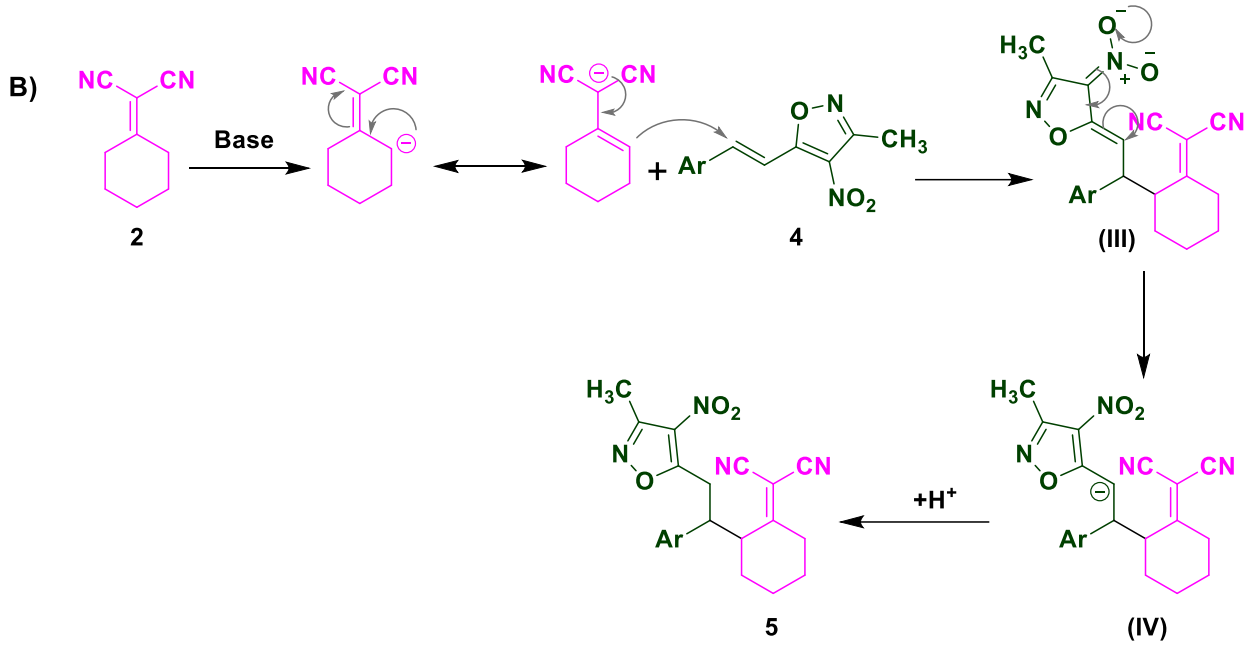


***Figure-4.3**: Plausible mechanism for the reaction. A) for Michael/cyclization; B) for Michael addition.*

4.4 Conclusion

In conclusion, we developed a simple and efficient method for the synthesis of novel isoxazole based spirooxindoles *via* domino reactions of vinyl malononitrile and isoxazole-oxindole styrenes under mild reaction conditions. The use of readily available starting materials, the short reaction times and easy purification with good to high yields are the advantages of the protocol.

4.5 Experimental Section

4.5.1 General procedure

General (representative) procedure for synthesis of spirooxindoles (3):

A mixture of vinyl malononitrile (**2**; 1.0 mmol), isoxazole-oxindole styrene (**1**; 1.0 mmol) and K_2CO_3 (0.1 mmol) in ethanol (3 mL) was stirred at room temperature for about 2-5 min. The resulting precipitate was collected by filtration and washed with cold alcohol to give the pure product for the analysis.

General (representative) procedure for synthesis of spirooxindoles (3'):

A mixture of vinyl malononitrile **2** (1.0 mmol) and isoxazole-oxindole styrene **1** (1.0 mmol) and K_2CO_3 (0.1 mmol) in THF (3 mL) was stirred at room temperature for about 3-4 h. After completion of reaction (monitored by TLC), solvent was evaporated and the crude product was purified by silica gel column chromatography. Elution of the column with Hexane/EtOAc (25-30%) gave the desired products

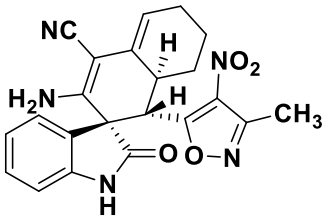
General (representative) procedure for synthesis of Michael adducts (5):

A mixture of vinyl malononitrile **2** (1.0 mmol) and styrene **4** (1.0 mmol) and K_2CO_3 (0.1 mmol) in ethanol (3 mL) was stirred at room temperature for about 30-60 min. After completion of reaction (monitored by TLC), solvent was evaporated and the crude product obtained was purified by silica gel column chromatography. Elution of the column with Hexane/EtOAc (5-10%) gave the desired product for the analysis.

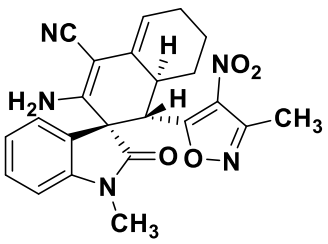
4.6 Spectral Data

(1'S,3R,8a'S)-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3a):

Yield = 54 mg (85%) Yellow solid; M.P: 252-254 °C; **^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ** 10.77 (s, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.80 (s, 2H), 5.66 (s, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 3.61 – 3.50 (m, 1H), 2.27 (s, 3H), 2.20 – 2.15 (m, 2H), 1.74 (d, *J* = 14.4 Hz, 1H), 1.50 – 1.42 (m, 1H), 1.25 – 1.23 (m, 1H), 1.07 (dd, *J* = 23.6, 11.2 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 175.20, 170.57, 155.56, 153.37, 142.92, 132.01, 130.74, 130.44, 127.09, 124.43, 122.59, 118.04, 117.76, 110.53, 81.36, 55.30, 45.75, 32.19, 27.10, 25.13, 21.73, 11.35. **Mass (ESI-MS):** m/z Calculated $C_{22}H_{19}N_5O_4$ for: 417.1437; Observed: 418.1524 (M+1).

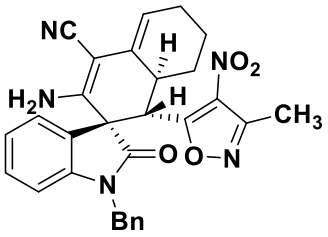


(1'S,3R,8a'S)-3'-amino-1-methyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3b):



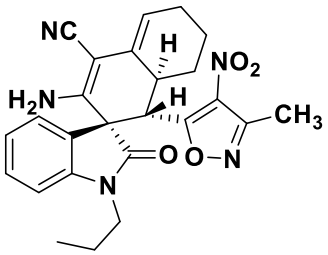
Yield = 57 mg (88%) Yellow solid; M.P: 246-248 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.27 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.86 (s, 2H), 5.67 (s, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 3.57 – 3. 46 (m, 1H), 3.02 (s, 3H), 2.24 (s, 3H), 2.22 – 2.12 (m, 2H), 1.74 (d, *J* = 13.2 Hz, 1H), 1.51 – 1.38 (m, 1H), 1.24 (d, *J* = 12.4 Hz, 1H), 1.11 – 1.00 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 173.35, 170.75, 155.06, 149.56, 143.85, 131.52, 130.84, 128.89, 125.13, 124.31, 123.60, 122.09, 116.78, 108.71, 86.94, 54.59, 45.66, 32.20, 29.69, 26.86, 25.20, 21.42, 11.45. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{21}N_5O_4$ for: 431.1594; Observed: 432.1673 (M+1).

(1'S,3R,8a'S)-3'-amino-1-benzyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3c):



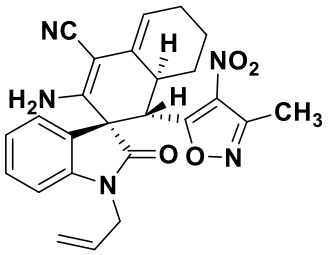
Yield = 56 mg (80%) White solid; M.P: 142-146 °C; **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.36 – 7.30 (m, 5H), 7.25 – 7.21 (m, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.03 (s, 1H), 5.10 (d, *J* = 14.8 Hz, 1H), 4.65 (dd, *J* = 28.4, 15.6 Hz, 2H), 4.08 (s, 2H), 3.96 – 3.85 (m, 1H), 2.37 (s, 3H), 2.31 – 2.32 (m, 2H), 1.84 (d, *J* = 12.8 Hz, 1H), 1.69 – 1.63 (m, 1H), 1.33 (dd, *J* = 12.0, 3.6 Hz, 1H), 1.20 (dd, *J* = 25.2, 13.2 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 172.62, 169.81, 155.18, 152.77, 142.59, 132.08, 130.49, 126.39, 124.48, 123.61, 118.19, 117.92, 110.23, 81.70, 55.12, 45.81, 32.37, 29.90, 27.07, 25.14, 21.69, 11.29. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{25}N_5O_4$ for: 507.1907; Observed: 508.1976 (M+1).

(1'S,3R,8a'S)-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-1-propyl-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3d):



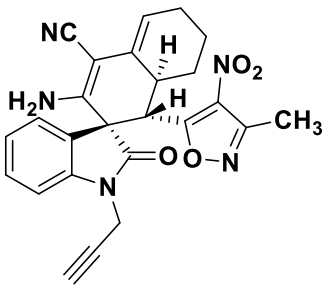
Yield = 60 mg (90%) Light Yellow Solid; M.P: 215-217 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.26 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.97 – 6.92 (m, 2H), 5.81 (s, 2H), 5.67 (s, 1H), 4.37 (d, *J* = 12.4 Hz, 1H), 3.64 – 3.50 (m, 2H), 3.45 – 3.40 (m, 1H), 2.25 (s, 3H), 2.22 – 2.08 (m, 2H), 1.75 (d, *J* = 12.4 Hz, 1H), 1.54 – 1.43 (m, 3H), 1.24 (d, *J* = 10.4 Hz, 1H), 1.07 – 1.042 (m, 1H), 0.86 (t, *J* = 7.6 Hz, 3H). **Mass (ESI-MS):** m/z Calculated $C_{25}H_{25}N_5O_4$ for: 459.1907; Observed: 458.1842 (M-1).

(1'S,3R,8a'S)-1-allyl-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3e):



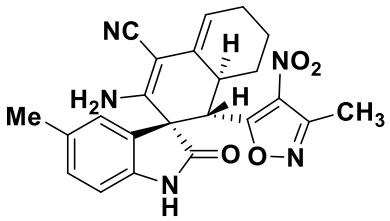
Yield = 63 mg (95%) Yellow solid; M.P: 230-232 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.26 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.85 (s, 2H), 5.75 – 5.63 (m, 2H), 5.23 – 5.15 (m, 2H), 4.39 (d, *J* = 12.4 Hz, 1H), 4.30 (dd, *J* = 16.4, 4.8 Hz, 1H), 4.11 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.59 – 3.48 (m, 1H), 2.26 (s, 3H), 2.21 – 2.15 (m, 2H), 1.75 (d, *J* = 14.4 Hz, 1H), 1.54 – 1.39 (m, 1H), 1.29 – 1.20 (m, 1H), 1.15 – 1.01 (m, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 173.24, 170.20, 155.62, 153.06, 143.54, 132.07, 131.73, 130.59, 130.45, 126.43, 124.32, 123.31, 118.33, 118.03, 117.97, 110.25, 81.56, 54.90, 45.79, 42.88, 32.37, 27.04, 25.13, 21.69, 11.31. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{23}N_5O_4$ for: 457.1750; Observed: 458.1836 (M+1).

(1'S,3R,8a'S)-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-1-(prop-2-yn-1-yl)-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3f):



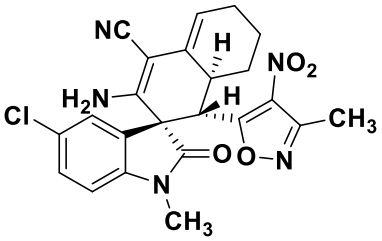
Yield = 61 mg (92%) White solid; M.P: 216-218 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.31 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.82 (s, 2H), 5.69 (s, 1H), 4.55 (dd, *J* = 17.6, 2.0 Hz, 1H), 4.37 (d, *J* = 12.4 Hz, 1H), 4.24 (dd, *J* = 18.0, 2.0 Hz, 1H), 3.57 – 3.41 (m, 1H), 3.21 (s, 1H), 2.24 (s, 3H), 2.25 - 2.10 (m, 2H), 1.83 – 1.69 (m, 1H), 1.56 – 1.46 (m, 1H), 1.34 – 1.20 (m, 1H), 1.16 – 1.00 (m, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 172.62, 169.81, 155.18, 152.77, 142.59, 132.08, 130.49, 126.39, 124.48, 123.61, 118.19, 117.92, 110.23, 81.70, 77.20, 75.26, 55.12, 45.81, 32.37, 29.90, 27.07, 25.14, 21.69, 11.29. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{21}N_5O_4$ for: 455.16; Observed: 456.1680 (M+1).

(1'S,3R,8a'S)-3'-amino-5-methyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3g):



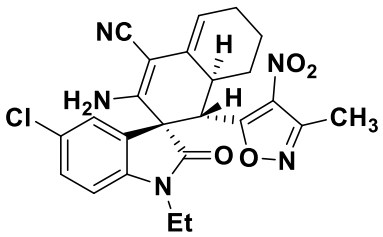
Yield = 52 mg (80%) Yellow solid; M.P: 260-262 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.65 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 5.79 (s, 2H), 5.66 (s, 1H), 4.28 (d, *J* = 12.4 Hz, 1H), 3.60 – 3.48 (m, 1H), 2.26 (s, 3H), 2.24 – 2.16 (m, 2H), 2.15 (s, 3H), 1.80 – 1.70 (m, 1H), 1.54 – 1.40 (m, 1H), 1.31 – 1.23 (m, 1H), 1.06 (dd, *J* = 24.0, 11.6 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 175.10, 170.44, 155.52, 153.38, 140.35, 132.16, 131.54, 130.74, 130.62, 127.16, 124.98, 118.03, 117.75, 110.22, 81.35, 55.42, 45.87, 32.05, 27.16, 25.12, 21.72, 20.89, 11.28. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{21}N_5O_4$ for: 431.16; Observed: 432.1681 (M+1).

(1'S,3R,8a'S)-3'-amino-5-chloro-1-methyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3h):



Yield = 66 mg (98%) White solid; M.P: 265-267 °C; **^{1}H NMR (400 MHz, CDCl$_3$+DMSO-*d*$_6$) δ** 7.35 – 7.30 (m, 2H), 6.93 – 6.88 (m, 1H), 6.00 (s, 2H), 5.68 (s, 1H), 4.36 (d, *J* = 12.4 Hz, 1H), 3.53 – 3.41 (m, 1H), 3.01 (s, 3H), 2.27 (s, 3H), 2.24 - 2.12 (m, 2H), 1.78 – 1.67 (m, 1H), 1.54 - 1.37 (m, 1H), 1.28 – 1.18 (m, 1H), 1.13 – 1.01 (m, 1H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 173.25, 169.87, 155.69, 152.40, 143.28, 132.23, 130.52, 130.23, 128.53, 127.30, 124.73, 118.00, 117.94, 111.00, 81.61, 55.09, 45.95, 32.21, 27.10, 27.05, 25.12, 21.68, 11.35. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{20}ClN_5O_4$ for: 465.12; Observed: 466.1284 (M+1).

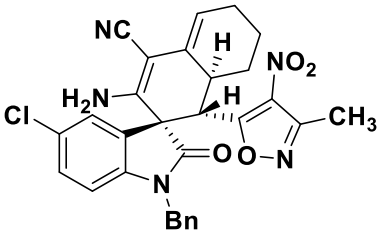
(1'S,3R,8a'S)-3'-amino-5-chloro-1-ethyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3i):



Yield = 64 mg (94%) Yellow solid; M.P: 273-275 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.35 – 7.29 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 5.96 (s, 2H), 5.67 (s, 1H), 4.37 (d, *J* = 12.4 Hz, 1H), 3.77 3.66 (m, 1H), 3.53 – 3.42 (m, 2H), 2.28 (s, 3H), 2.20 - 2.10 (m, 2H), 1.80 – 1.68 (m, 1H), 1.55 - 1.37 (m, 1H), 1.30 – 1.19 (m, 1H), 1.14 – 1.06 (m, 1H), 1.03 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 172.77, 169.92, 155.67, 152.44, 142.42, 132.20, 130.51, 130.27, 128.62, 127.15, 124.95, 118.02, 117.92,

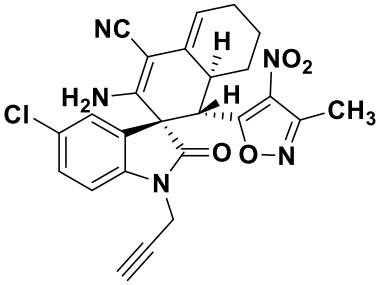
111.10, 81.58, 55.10, 45.64, 35.34, 32.24, 27.05, 25.13, 21.69, 12.12, 11.30. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{22}ClN_5O_4$ for: 479.1360; Observed: 480.1452 (M+1).

(1'S,3R,8a'S)-3'-amino-1-benzyl-5-chloro-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3j):



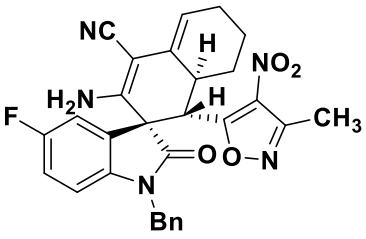
Yield = 71 mg (97%) Light Yellow solid; M.P: 148-150 °C; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.29 – 7.21 (m, 3H), 7.19 – 7.14 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.95 (s, 1H), 4.99 (d, *J* = 15.6 Hz, 1H), 4.59 (d, *J* = 15.6 Hz, 1H), 4.48 (d, *J* = 12.4 Hz, 1H), 3.98 (s, 2H), 3.80 - 3.70 (m, 1H), 2.32 (s, 3H), 2.25 – 2.12 (m, 2H), 1.79 – 1.67 (m, 1H), 1.29 – 1.10 (m, 4H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 173.58, 169.83, 155.69, 152.32, 142.59, 135.73, 132.28, 130.42, 130.37, 129.01, 128.28, 127.91, 127.65, 125.12, 118.16, 117.94, 111.73, 81.88, 55.10, 45.38, 44.30, 32.43, 27.04, 25.14, 21.71, 11.35. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{24}ClN_5O_4$ for: 541.15; Observed: 542.1608 (M+1).

(1'S,3R,8a'S)-3'-amino-5-chloro-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-1-(prop-2-yn-1-yl)-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3k):



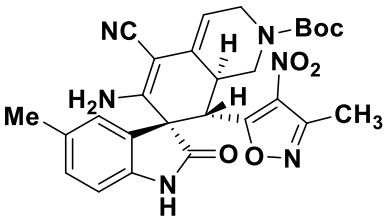
Yield = 60 mg (87%) White solid; M.P: 177-179 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.41 - 7.35 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 2H), 5.69 (s, 1H), 4.55 (dd, *J* = 18.0, 2.4 Hz, 1H), 4.38 (d, *J* = 12.8 Hz, 1H), 4.23 (dd, *J* = 17.6, 2.0 Hz, 1H), 3.52 – 3.39 (m, 1H), 3.23 (s, 1H), 2.26 (s, 3H), 2.24 – 2.11 (m, 2H), 1.81 – 1.70 (m, 1H), 1.55 – 1.38 (m, 1H), 1.30 – 1.20 (m, 1H), 1.13 – 1.00 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.98, 169.99, 155.01, 148.25, 140.46, 131.73, 130.88, 129.54, 128.45, 126.77, 124.99, 122.84, 116.43, 110.91, 87.49, 75.26, 73.44, 54.74, 45.46, 32.30, 30.03, 26.79, 25.19, 21.34, 11.44. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{20}ClN_5O_4$ for: 489.1204; Observed: 490.1284 (M+1).

(1'S,3R,8a'S)-3'-amino-1-benzyl-5-fluoro-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3l):



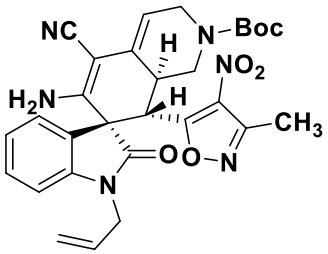
Yield = 61 mg (84%) White solid; M.P: 179-181 °C; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.29 – 7.19 (m, 4H), 7.17 (s, 1H), 6.94 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.82 (td, *J* = 8.4, 2.0 Hz, 1H), 6.49 (dd, *J* = 8.4, 4.0 Hz, 1H), 5.95 (s, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.54 (dd, *J* = 46.0, 15.6 Hz, 2H), 3.98 (s, 2H), 3.86 – 3.72 (m, 1H), 2.32 (s, 3H), 2.30 – 2.13 (m, 2H), 1.80 – 1.68 (m, 1H), 1.20 – 1.04 (m, 3H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 173.75, 169.91, 160.19, 157.81, 155.66, 152.51, 139.94, 135.91, 132.23, 130.49, 129.00, 128.04, 127.95, 127.89, 127.69, 118.10, 117.96, 117.10, 116.87, 112.99, 112.73, 111.34, 111.26, 81.85, 55.25, 45.33, 44.32, 32.47, 27.05, 25.15, 21.71, 11.35. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{24}FN_5O_4$ for: 525.1812; Observed: 526.1905 (M+1).

tert-butyl (3R,8'S,8a'S)-6'-amino-5'-cyano-5-methyl-8'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-8',8a'-dihydro-1'H-spiro[indoline-3,7'-isoquinoline]-2'(3'H)-carboxylate (3m):



Yield = 86 mg (87%) Light Yellow solid; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.71 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H), 5.59 – 5.55 (m, 1H), 4.33 (d, *J* = 12.6 Hz, 2H), 3.83 – 3.43 (m, 3H), 2.27 (s, 3H), 2.15 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (100 MHz, DMSO) δ** 174.72, 168.99, 155.69, 154.39, 154.08, 140.44, 132.19, 131.65, 130.80, 126.55, 125.33, 117.68, 110.33, 80.29, 79.74, 55.30, 43.94, 42.79, 31.48, 31.18, 28.42, 20.92, 11.26. **Mass (ESI-MS):** m/z Calculated $C_{27}H_{28}N_6O_6$ for: 532.2070; Observed: 555.1993 (M+Na).

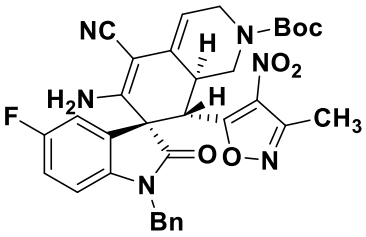
tert-butyl (3R,8'S,8a'S)-1-allyl-6'-amino-5'-cyano-8'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-8',8a'-dihydro-1'H-spiro[indoline-3,7'-isoquinoline]-2'(3'H)-carboxylate (3n):



Yield = 75 mg (75%) White solid; M.P: 174-176 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.31 – 7.21 (m, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.10 (s, 2H), 5.75 - 5.63 (m, 1H), 5.61 (s, 1H), 5.26 – 5.13 (m, 2H), 4.44 (d, *J* = 12.8 Hz, 1H), 4.30 (dd, *J* = 16.4, 4.8 Hz, 2H), 4.11 (dd, *J* = 16.4, 6.0 Hz, 1H), 3.86 – 3.43 (m, 4H), 2.27 (s, 3H), 1.38 (s, 9H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 172.86, 168.74, 155.76, 154.02, 143.63, 132.09, 131.63, 130.63, 125.82, 124.68, 124.59, 123.39, 118.36, 117.60,

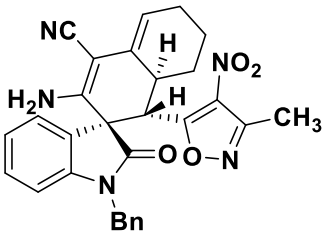
113.88, 110.34, 79.99, 79.78, 60.22, 54.77, 42.89, 42.69, 31.73, 31.15, 28.39, 11.24. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{30}N_6O_6$ for: 558.2227; Observed: 581.2145 (M+Na).

tert-butyl (3R,8'S,8a'S)-6'-amino-1-benzyl-5'-cyano-5-fluoro-8'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-8',8a'-dihydro-1'H-spiro[indoline-3,7'-isoquinoline]-2'(3'H)-carboxylate (3o):



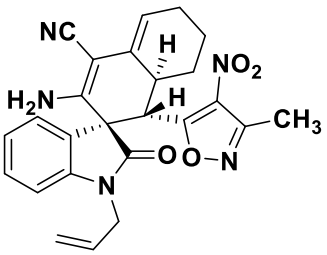
Yield = 74 mg (72%) White solid; M.P: 185-187 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.36 – 7.20 (m, 6H), 7.08 (td, *J* = 9.2, 1.2 Hz, 1H), 6.74 (s, 1H), 6.21 (s, 2H), 5.61 (s, 1H), 4.78 (dd, *J* = 33.2, 15.6 Hz, 2H), 4.53 (d, *J* = 12.8 Hz, 1H), 4.43 – 4.25 (m, 1H), 3.88 – 3.39 (m, 4H), 2.30 (s, 3H), 1.39 (s, 9H). **Mass (ESI-MS):** m/z Calculated $C_{33}H_{31}FN_6O_6$ for: 626.23; Observed: 649.2216 (M+Na).

(1'S,3S,8a'S)-3'-amino-1-benzyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3a')



Yield = 56 mg (80%) White solid; M.P: 302-304 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.58 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32 – 7.19 (m, 4H), 7.05 – 6.98 (m, 1H), 6.97 – 6.94 (m, 2H), 6.36 (s, 2H), 5.71 (s, 1H), 4.95 (d, *J* = 15.6 Hz, 1H), 4.38 (dd, *J* = 23.6, 12.8 Hz, 2H), 3.22 – 3.03 (m, 1H), 2.21 (s, 3H), 2.21 – 2.14 (m, 2H), 1.76 - 1.63 (m, 1H), 1.63 – 1.48 (m, 1H), 1.15 – 1.00 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 173.72, 168.95, 155.46, 152.89, 142.69, 136.00, 132.01, 130.77, 130.14, 129.79, 129.00, 128.02, 127.76, 127.42, 125.23, 118.29, 117.83, 111.73, 80.47, 55.70, 44.62, 34.14, 27.01, 25.13, 21.21, 11.55. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{25}N_5O_4$ for: 507.1907; Observed: 508.1976 (M+1).

(1'S,3S,8a'S)-1-allyl-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3b'):

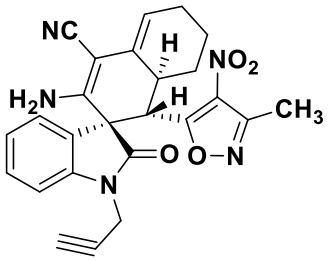


Yield = 53 mg (79%) White solid; M.P: 247-249 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.48 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.28 (s, 2H), 5.69 (s, 1H), 5.51 - 5.36 (m, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.72 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.36 (d, *J* = 12.8 Hz, 1H), 4.33 – 4.26 (m, 1H), 3.81 (dd, J = 16.4, 6.0 Hz 1H), 3.20 – 3.40 (m, 1H), 2.32 (s, 3H), 2.25 – 2.15 (m, 2H), 1.73 (d, *J* = 10.8 Hz,

1H), 1.61 – 1.45 (m, 1H), 1.27 – 1.06 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 173.40, 169.05, 155.62, 153.71, 143.47, 132.30, 131.56, 130.08, 129.97, 128.60, 125.21, 123.18, 117.97, 117.78, 117.40, 110.10, 79.95, 56.05, 44.95, 42.80, 33.86, 27.28, 25.14, 21.54, 11.26, 0.62. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{23}N_5O_4$ for: 457.1750; Observed: 458.1836 (M+1).

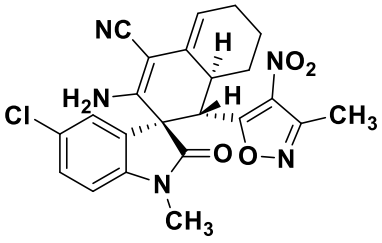
(1'S,3S,8a'S)-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-1-(prop-2-yn-1-yl)-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3c'):

Yield = 48 mg (72%) White solid; M.P: 239-241 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.47 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.29 (s, 2H), 5.69 (s, 1H), 4.48 (dd, *J* = 18.0, 2.4 Hz, 1H), 4.36 (d, *J* = 12.8 Hz, 1H), 3.98 (dd, *J* = 18.0, 2.4 Hz, 1H), 3.15 (t, *J* = 2.4 Hz, 1H), 3.13 – 3.01 (m, 1H), 2.31 (s, 3H), 2.26 – 2.13 (m, 2H), 1.79 – 1.66 (m, 1H), 1.61 – 1.46 (m, 1H), 1.27 – 1.18 (m, 1H), 1.11 (dd, *J* = 24.6, 12.0 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 172.58, 168.39, 155.65, 152.22, 141.47, 132.23, 130.48, 130.16, 129.78, 127.55, 125.12, 118.32, 117.80, 111.44, 80.68, 77.14, 74.29, 56.02, 45.24, 33.50, 29.83, 27.29, 25.16, 21.28, 11.50. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{21}N_5O_4$ for: 455.16; Observed: 456.1680 (M+1).



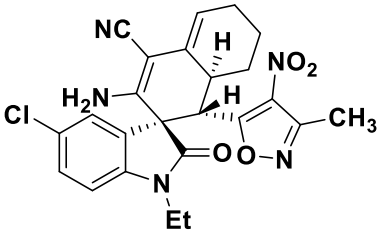
(1'S,3S,8a'S)-3'-amino-5-chloro-1-methyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3d'):

Yield = 54 mg (80%) White solid; M.P: 248-250 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.53 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.31 (s, 2H), 5.70 (s, 1H), 4.29 (d, *J* = 12.8 Hz, 1H), 3.19 - 3.02 (m, 1H), 2.86 (s, 3H), 2.34 (s, 3H), 2.24 – 2.15 (m, 2H), 1.78 – 1. 66 (m, 1H), 1.66 – 1.50 (m, 1H), 1.29 – 1.20 (m, 1H), 1.17 – 1.02 (m, 1H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 173.55, 168.65, 155.57, 152.64, 143.30, 132.12, 130.47, 130.15, 129.78, 127.24, 124.96, 118.30, 117.88, 111.13, 80.56, 56.24, 45.17, 33.55, 27.36, 27.03, 25.16, 21.32, 11.31. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{20}ClN_5O_4$ for: 465.12; Observed: 466.1284 (M+1).



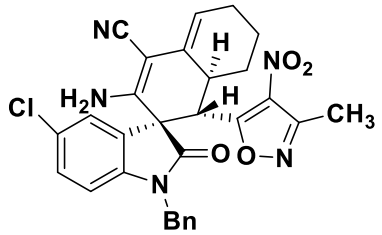
(1'S,3S,8a'S)-3'-amino-5-chloro-1-ethyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3e'):

Yield = 58 mg (85%) White solid; M.P: 232-234 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.52 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.29 (s, 2H), 5.70 (s, 1H), 4.30 (d, *J* = 12.9 Hz, 1H), 3.74 – 3.62 (m, 1H), 3.23 (dt, *J* = 13.9, 7.0 Hz, 1H), 3.10 (t, *J* = 11.8 Hz, 1H), 2.32 (s, 3H), 2.26 – 2.15 (m, 2H), 1.78 – 1.66 (m, 1H), 1.65 – 1.52 (m, 7.9 Hz, 1H), 1.32 - 1.23 (m, 1H), 1.22 – 1.05 (m, 1H), 0.70 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 173.09, 168.73, 155.58, 152.67, 142.41, 132.33, 130.73, 130.16, 129.83, 127.11, 125.09, 118.19, 117.84, 111.07, 80.47, 56.10, 45.16, 35.27, 33.50, 27.32, 25.16, 21.29, 11.84, 11.25. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{22}ClN_5O_4$ for: 479.1360; Observed: 480.1452 (M+1).



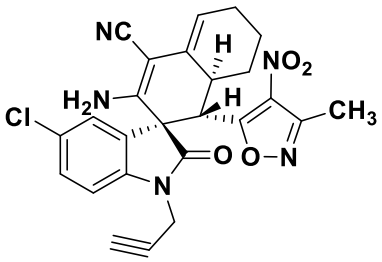
(1'S,3S,8a'S)-3'-amino-1-benzyl-5-chloro-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3f'):

Yield = 57 mg (78%) White solid; M.P: 234-236 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.60 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.30 – 7.20 (m, 3H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 6.8 Hz, 2H), 6.36 (s, 2H), 5.70 (s, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.39 (dd, *J* = 19.4, 14.2 Hz, 2H), 3.18 – 3.00 (m, 1H), 2.21 (s, 3H), 2.20 – 2.11 (m, 2H), 1.76 – 1.48 (m, 2H), 1.13 - 1.00 (m, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 173.73, 168.97, 155.46, 152.89, 142.69, 136.02, 132.01, 130.77, 130.14, 129.79, 129.00, 128.02, 127.77, 127.43, 125.23, 118.29, 117.83, 111.73, 80.48, 55.70, 44.62, 34.15, 27.01, 25.13, 21.22, 11.56. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{24}ClN_5O_4$ for: 541.15; Observed: 542.1608 (M+1).



(1'S,3S,8a'S)-3'-amino-5-chloro-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-1-(prop-2-yn-1-yl)-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3g'):

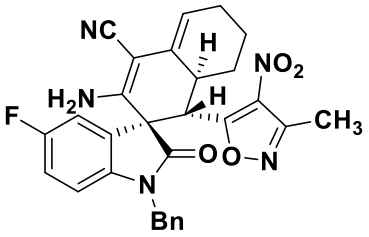
Yield = 50 mg (72%) White solid; M.P: 216-218 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 7.57 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.32 (s, 2H), 5.70 (s, 1H), 4.48 (dd, *J* = 18.0, 2.4 Hz, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.03- 3.95 (m, 1H), 3.19 (t, *J* = 2.4 Hz, 1H), 3.16 – 3. 04 (m, 1H), 2.32 (s, 3H), 2.23 – 2.11 (m, 2H), 1.74 – 1.53 (m, 2H), 1.27 - 1.19



(m, 1H), 1.09 (dd, *J* = 23.6, 10.8 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 172.58, 168.39, 155.65, 152.22, 141.47, 132.23, 130.48, 130.16, 129.78, 127.55, 125.12, 118.32, 117.80, 111.44, 80.68, 77.14, 74.29, 56.02, 45.24, 33.50, 29.83, 27.29, 25.16, 21.28, 11.50. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{20}ClN_5O_4$ for: 489.1204; Observed: 490.1284 (M+1).

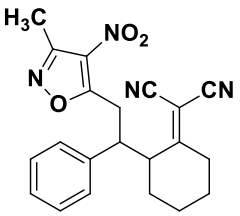
(1'S,3S,8a'S)-3'-amino-1-benzyl-5-fluoro-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3h'):

Yield = 61 mg (84%) White solid; M.P: 152-154 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 7.50 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.31 – 7.18 (m, 4H), 7.06 – 6.99 (m, 1H), 6.98 – 6.92 (m, 2H), 6.35 (s, 2H), 5.70 (s, 1H), 4.96 (d, *J* = 15.6 Hz, 1H), 4.39 (dd, *J* = 23.6, 12.8 Hz, 2H), 3.21 – 3.04 (m, 1H), 2.22 (s, 3H), 2.20 – 2.13 (m, 2H), 1.75 - 1.63 (m, 1H), 1.64 – 1.48 (m, 1H), 1.15 – 1.01 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 173.84, 169.07, 160.12, 157.75, 155.42, 153.06, 140.01, 136.19, 132.03, 130.51, 130.42, 129.90, 128.97, 127.95, 127.76, 118.11, 117.87, 116.60, 116.37, 113.55, 113.30, 111.18, 111.11, 80.41, 55.89, 44.63, 34.08, 27.04, 25.15, 21.28, 21.22, 11.55. **Mass (ESI-MS):** m/z Calculated $C_{29}H_{24}FN_5O_4$ for: 626.23; Observed: 649.2216 (M+Na).



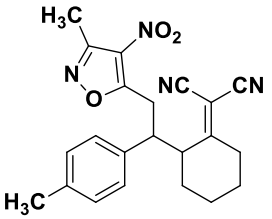
2-(2-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl)cyclohexylidene)malononitrile (5a):

Yield = 49 mg (80%) White semi solid; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.32 (m, 3H), 7.16 (d, *J* = 5.6 Hz, 2H), 3.64 (td, *J* = 11.6, 4.0 Hz, 1H), 3.51 – 3.45 (m, 2H), 3.22 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.75 (td, *J* = 13.2, 5.6 Hz, 1H), 2.45 (s, 3H), 2.29 – 2.20 (m, 1H), 1.70 – 1.49 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 186.27, 172.33, 155.34, 137.82, 129.34, 128.36, 127.67, 111.66, 111.23, 84.81, 48.55, 44.21, 32.58, 31.34, 30.40, 28.78, 19.63, 11.52. **Mass (ESI-MS):** m/z Calculated $C_{21}H_{20}N_4O_3$ for: 376.1535; Observed: 377.1601 (M+1).



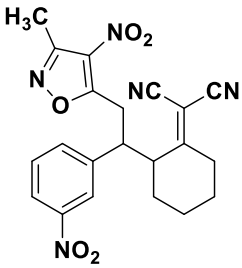
2-(2-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(p-tolyl)ethyl)cyclohexylidene)malononitrile (5b):

Yield = 48 mg (77%) Light yellow semi solid; **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.09 (d, *J* = 7.6 Hz, 2H), 7.01 (d, *J* = 6.4 Hz, 2H), 3.57 (td, *J* = 11.6, 4.0 Hz, 1H), 3.45 – 3.39 (m, 2H), 3.18 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.11 (d, *J* = 13.2 Hz, 1H), 2.73 (td, *J* = 13.2, 5.6 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 2.25 – 2.16 (m, 1H), 1.68 – 1.39 (m, 5H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 186.62, 172.55, 155.34, 138.06, 134.73, 130.13, 129.99, 127.54, 111.73, 111.31, 84.66, 48.72, 43.86, 32.65, 31.37, 30.44, 28.83, 21.11, 19.64, 11.56. **Mass (ESI-MS):** m/z Calculated $C_{22}H_{22}N_4O_3$ for: 390.1692; Observed: 413.1576 (M+Na).



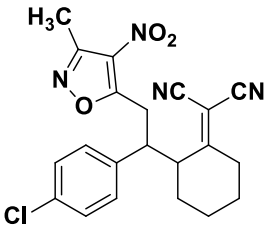
2-(2-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(3-nitrophenyl)ethyl)cyclohexylidene)malononitrile (5c):

Yield = 50 mg (79%) White solid; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 8.24 (s, 1H), 8.14 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 3.99 (td, *J* = 10.8, 4.0 Hz, 1H), 3.55 – 3.43 (m, 2H), 3.42 – 3.37 (m, 1H), 2.91 – 2.85 (m, 2H), 2.37 (s, 3H), 2.09 (d, *J* = 10.8 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.59 – 1.45 (m, 2H), 1.31 (t, *J* = 11.2 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 186.27, 172.33, 155.34, 137.82, 129.34, 128.36, 127.67, 111.66, 111.23, 84.81, 48.55, 44.21, 32.58, 31.34, 30.40, 28.78, 19.63, 11.52. **Mass (ESI-MS):** m/z Calculated $C_{21}H_{19}N_5O_5$ for: 421.14; Observed: 444.1271 (M+Na).

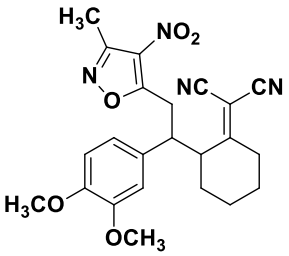


2-(2-(1-(4-chlorophenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)cyclohexylidene)malononitrile (5d):

Yield = 52 mg (82%) White solid; M.P: 184-186 °C; **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.29 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 2H), 3.61 (td, *J* = 11.6, 3.6 Hz, 1H), 3.45 – 3.37 (m, 2H), 3.20 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 2.74 – 2.66 (m, 1H), 2.46 (s, 3H), 2.23 – 2.19 (m, 1H), 1.63 – 1.45 (m, 5H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 185.63, 171.93, 155.45, 136.39, 134.27, 130.20, 129.62, 129.02, 111.60, 111.10, 85.07, 48.49, 43.57, 32.41, 31.30, 30.30, 28.69, 19.59, 11.53. **Mass (ESI-MS):** m/z Calculated $C_{21}H_{19}ClN_4O_3$ for: 410.11; Observed: 433.1027 (M+Na).

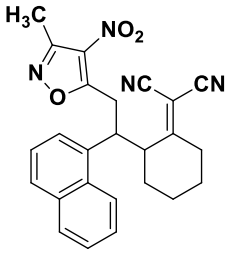


2-(2-(1-(3,4-dimethoxyphenyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)cyclohexylidene)malononitrile (5e):



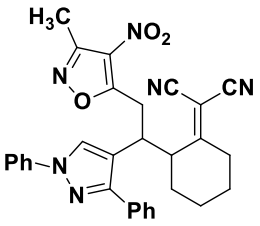
Yield = 45 mg (70%) Light yellow solid; M.P: 183-185 °C; **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.78 – 6.60 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.61 – 3.44 (m, 2H), 3.38 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.15 – 3.11 (m, 2H), 2.70 (td, *J* = 13.6, 5.6 Hz, 1H), 2.44 (s, 3H), 2.23 – 2.19 (m, 1H), 1.77 – 1.60 (m, 3H), 1.47 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 186.40, 172.39, 155.35, 149.53, 148.90, 130.20, 130.03, 111.75, 111.24, 84.74, 56.07, 55.84, 48.87, 43.96, 32.42, 31.40, 30.42, 28.78, 19.73, 11.57. **Mass (ESI-MS):** m/z Calculated $C_{23}H_{24}N_4O_5$ for: 436.1747; Observed: 459.1634 (M+Na).

2-(2-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(naphthalen-2-yl)ethyl)cyclohexylidene)malononitrile (5f):



Yield = 50 mg (78%) White solid; M.P: 128-130 °C**; ^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.85 – 7.80 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.46 – 7.40 (m, 2H), 4.76 (td, *J* = 11.2, 4.4 Hz, 1H), 3.70 (d, *J* = 12.4 Hz, 1H), 3.53 – 3.45 (m, 1H), 3.38 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.21 (d, *J* = 14.0 Hz, 1H), 2.91 (td, *J* = 13.2, 5.2 Hz, 1H), 2.27 – 2.24 (m, 1H), 2.22 (s, 3H), 1.73 – 1.46 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 186.38, 172.10, 155.01, 134.83, 133.78, 132.25, 129.41, 128.54, 126.69, 125.95, 125.86, 124.63, 120.84, 111.80, 111.29, 84.93, 49.29, 36.36, 33.77, 31.61, 30.52, 28.92, 20.61, 11.26. **Mass (ESI-MS):** m/z Calculated $C_{25}H_{22}N_4O_3$ for: 426.17; Observed: 449.1571 (M+1).

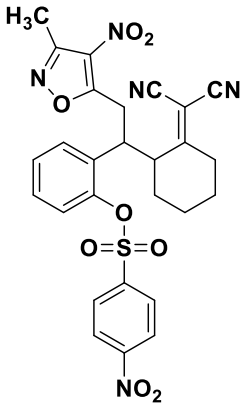
2-(2-(1-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)cyclohexylidene)malononitrile (5g):



Yield = 53 mg (74%) White solid; M.P: 178-180 °C; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 8.85 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.43 – 7.40 (m, 3H), 7.35 – 7.32 (m, 3H), 3.95 (td, *J* = 11.2, 4.0 Hz, 1H), 3.46 – 3.36 (m, 2H), 3.24 – 3.15 (m, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.30 (s, 3H), 2.03 (d, *J* = 15.6 Hz, 1H), 1.85 (d, *J* = 14.4 Hz, 1H), 1.60 – 1.43 (m, 3H), 1.323 – 1.30 (m, 1H). **^{13}C NMR (100 MHz, DMSO-d_6) δ** 186.76,

173.11, 155.74, 152.39, 139.71, 130.63, 130.03, 129.47, 129.04, 128.77, 128.42, 127.92, 126.95, 118.62, 112.53, 112.40, 84.50, 48.91, 34.03, 33.83, 31.65, 30.60, 28.68, 20.05, 11.46. **Mass (ESI-MS):** m/z Calculated $C_{30}H_{26}N_6O_3$ for: 518.21; Observed: 519.2139 (M+1).

2-(1-(2-(dicyanomethylene)cyclohexyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)phenyl 4-nitrobenzenesulfonate(5h):



Yield = 58 mg (75%) White solid; M.P: 181-183 °C; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 8.41 (d, *J* = 9.2 Hz, 2H), 8.04 (d, *J* = 9.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 3.73 (td, *J* = 11.2, 3.6 Hz, 1H), 3.43 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.28 – 3.19 (m, 2H), 2.91 – 2.75 (m, 2H), 2.38 (s, 3H), 1.77 – 1.57 (m, 2H), 1.55 – 1.41 (m, 2H), 1.29 (dd, *J* = 28.0, 13.2 Hz, 2H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 186.74, 172.96, 155.66, 151.49, 148.39, 139.52, 130.58, 130.49, 130.29, 125.32, 122.94, 112.51, 112.44, 84.50, 48.36, 43.18, 32.51, 31.47, 30.24, 28.62, 19.18, 11.56. **Mass (ESI-MS):** m/z Calculated $C_{27}H_{23}N_5O_8S$ for: 577.1267; Observed: 578.1237 (M+1).

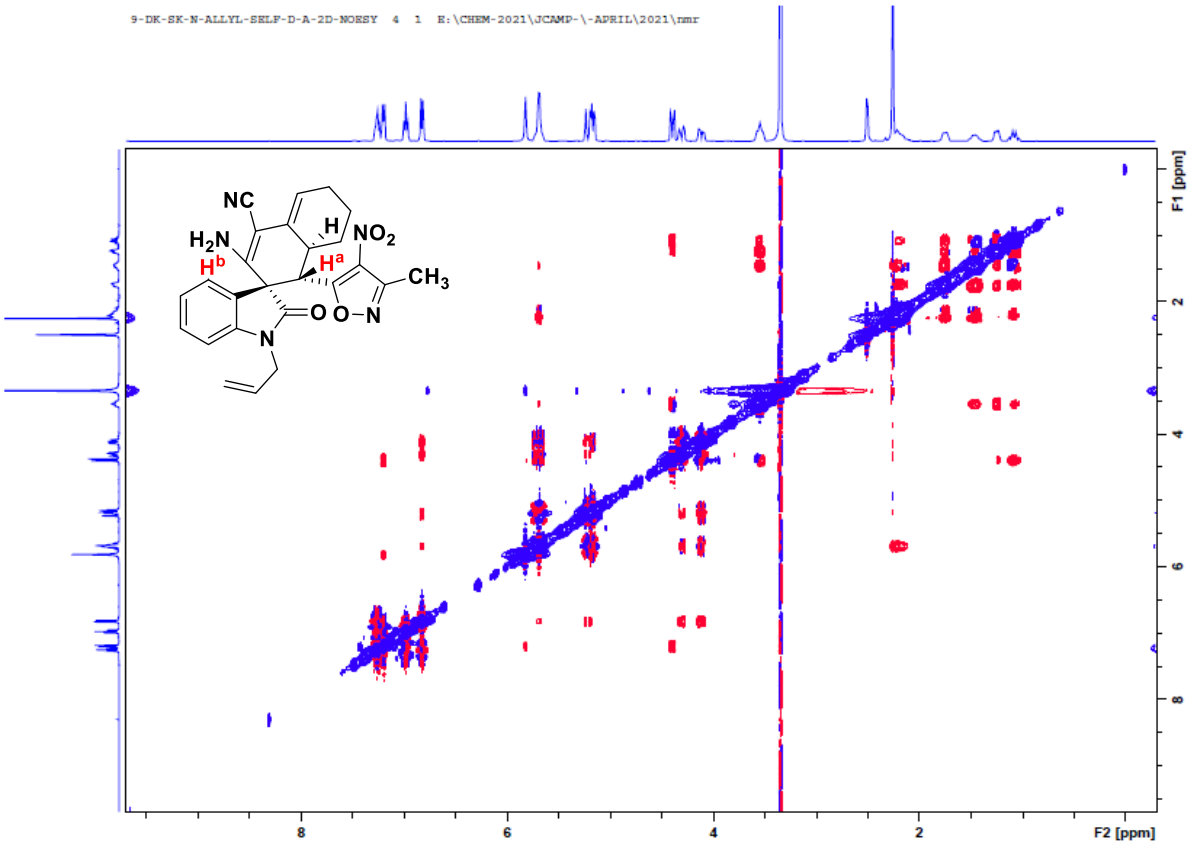


Figure-4.4: *NOESY spectrum of the compound* ***3e***

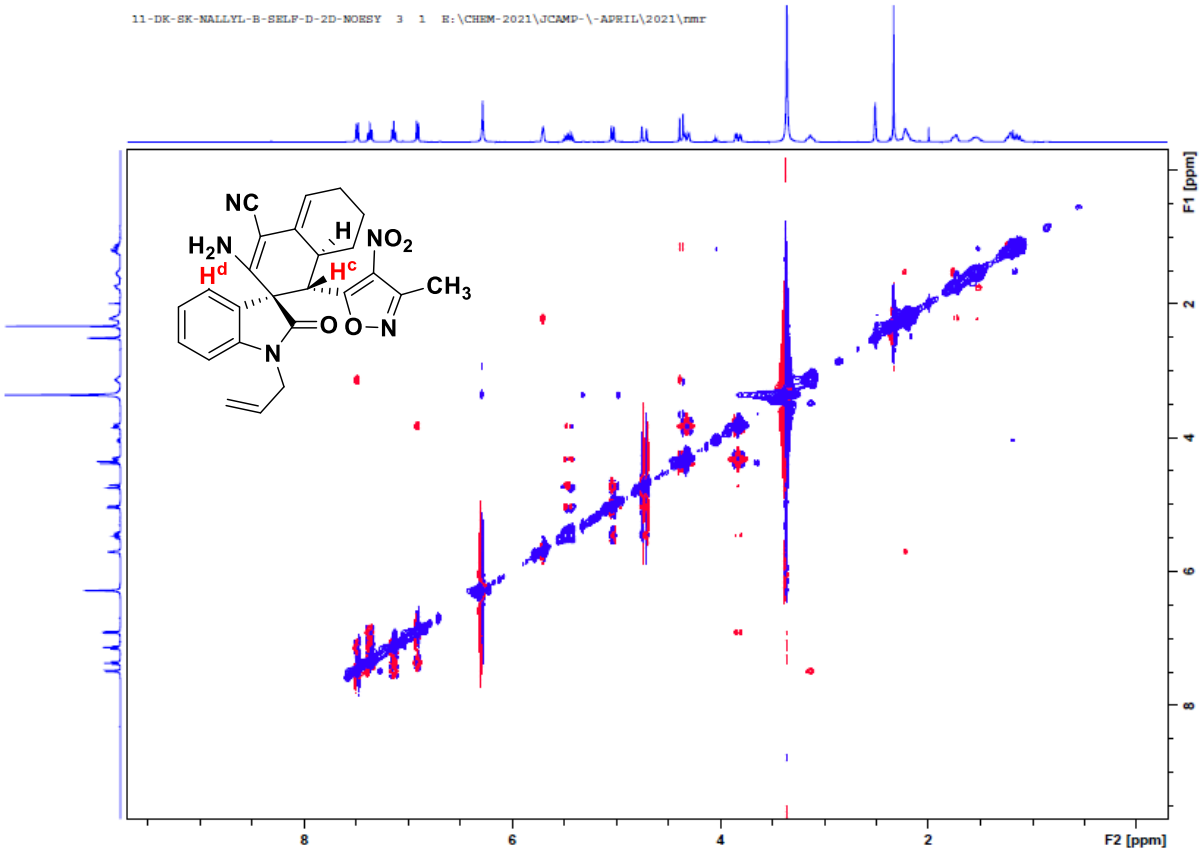
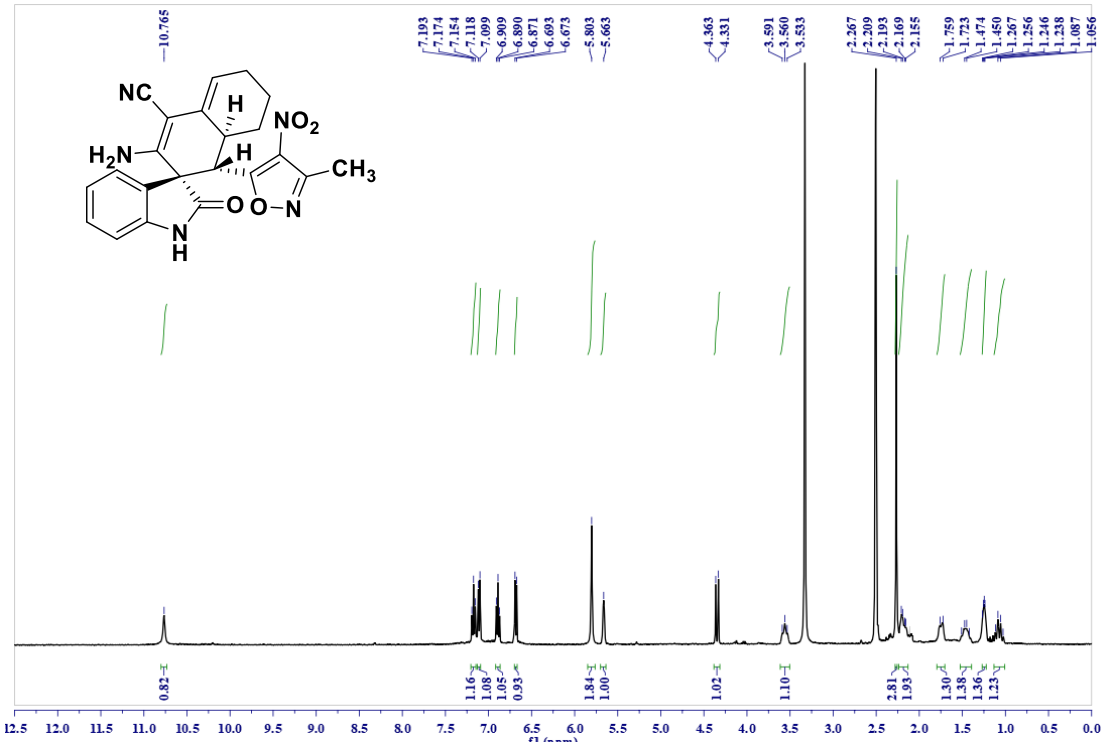
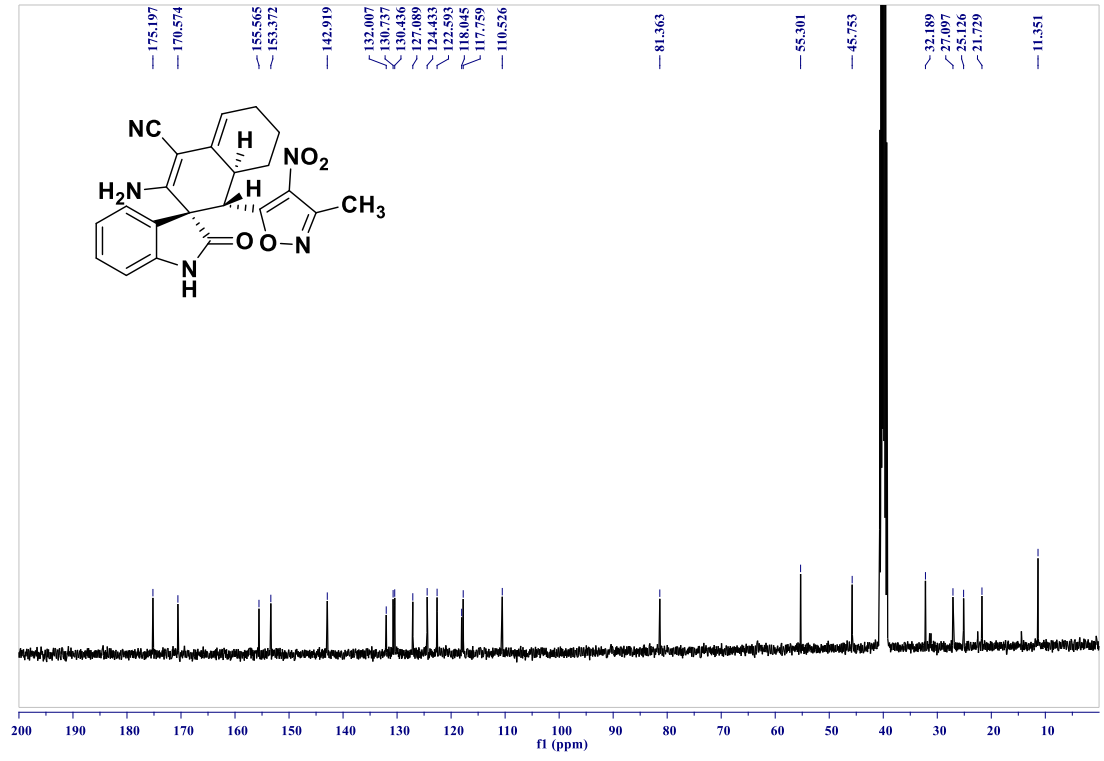


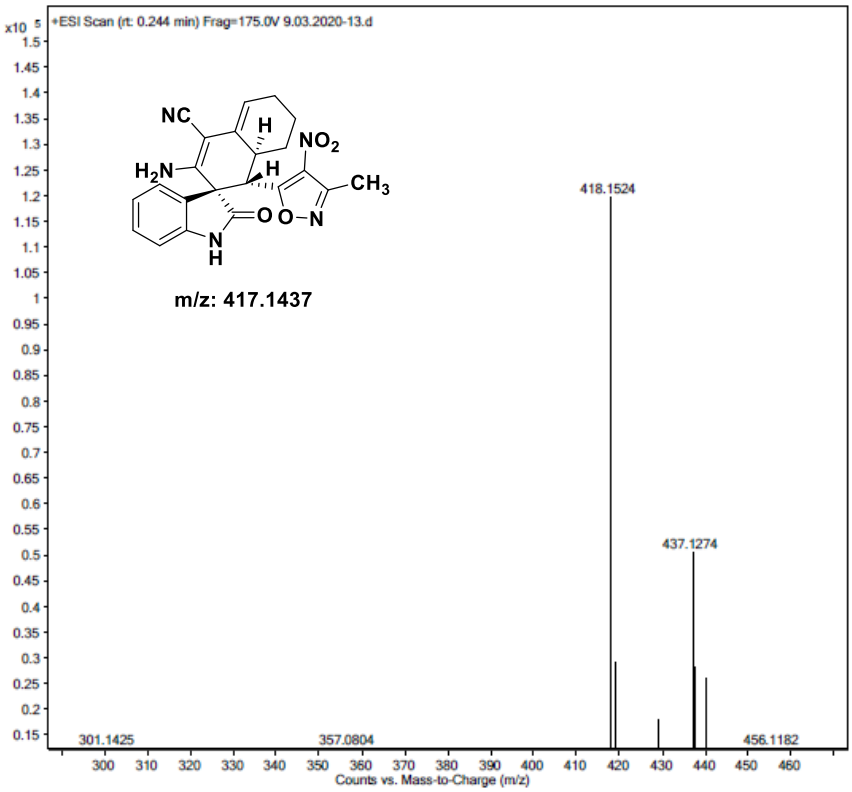
Figure-4.5: *NOESY spectrum of the compound* ***3b'***

4.7 Selected Spectra

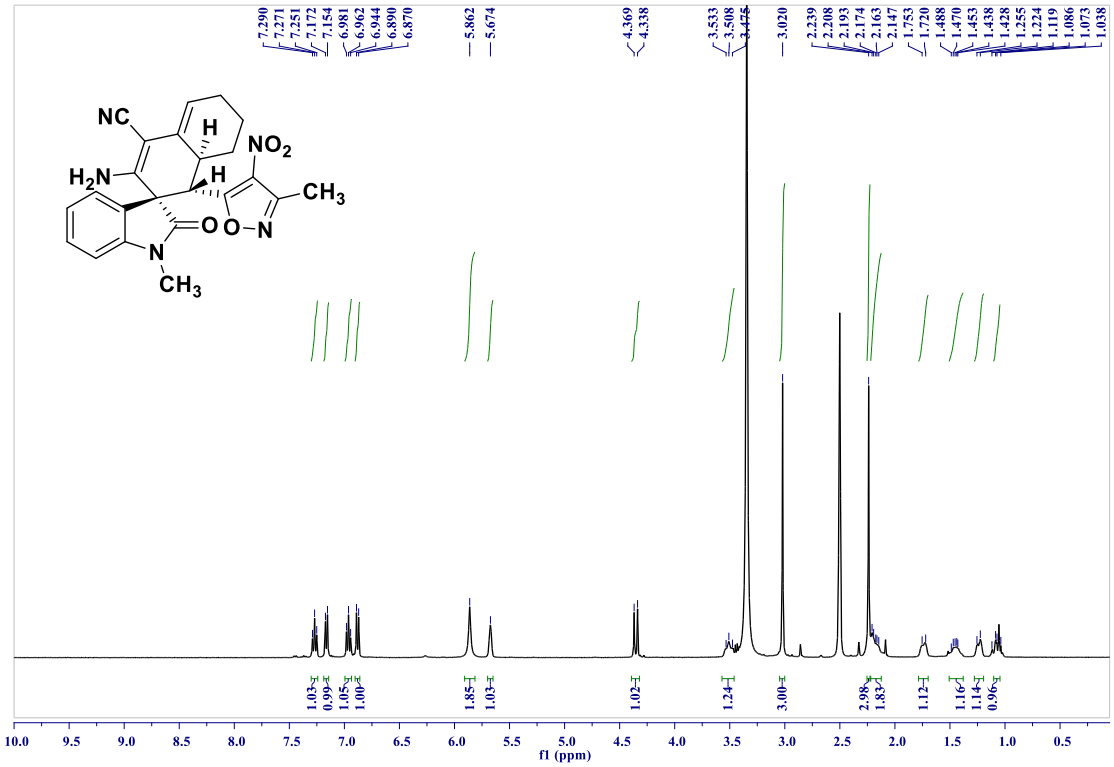
(1'S,3R,8a'S)-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3a):

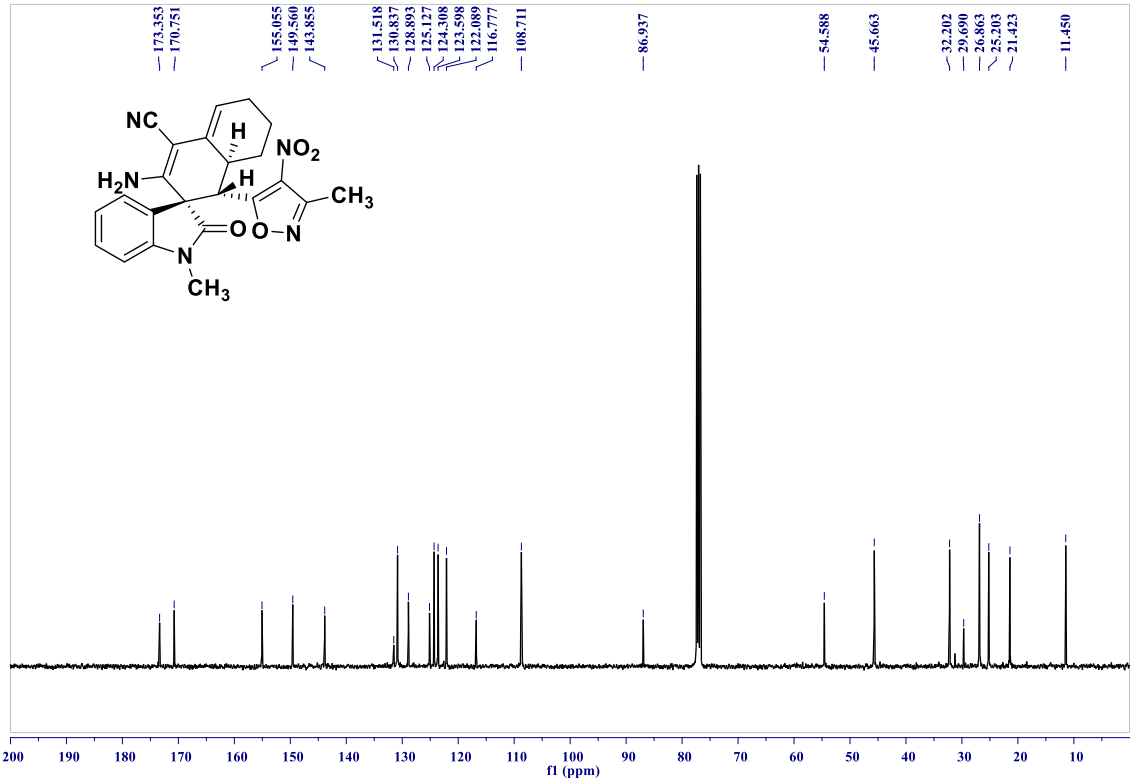


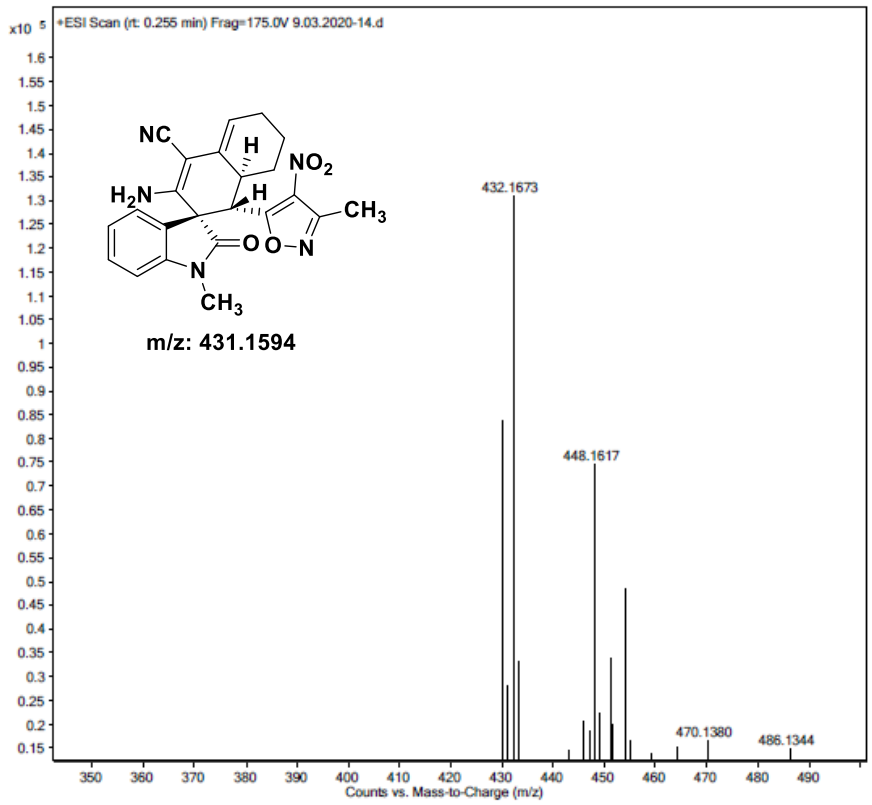




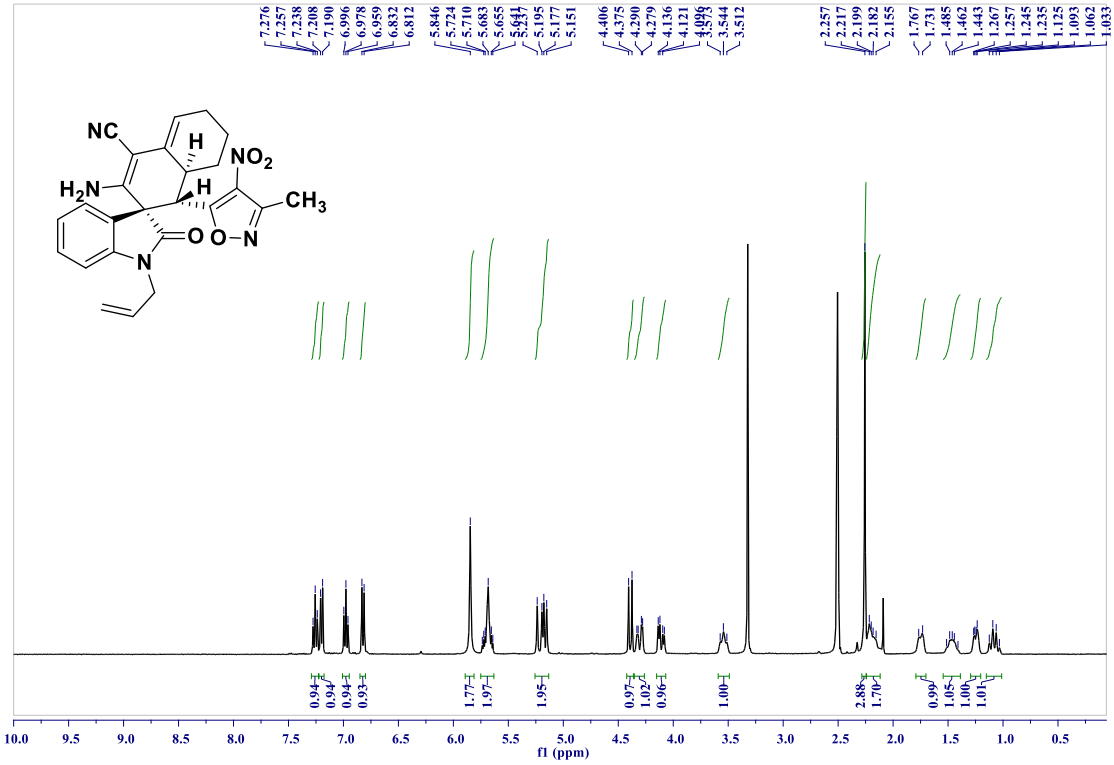
(1'S,3R,8a'S)-3'-amino-1-methyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3b):

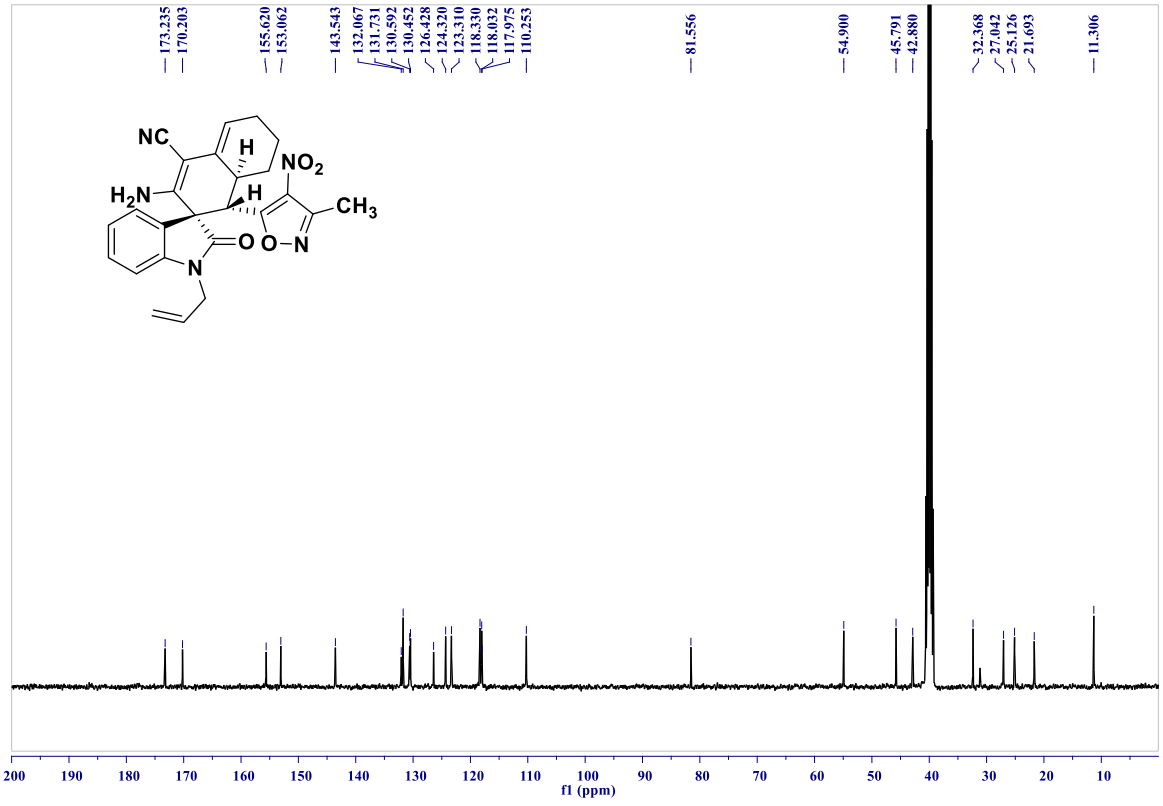


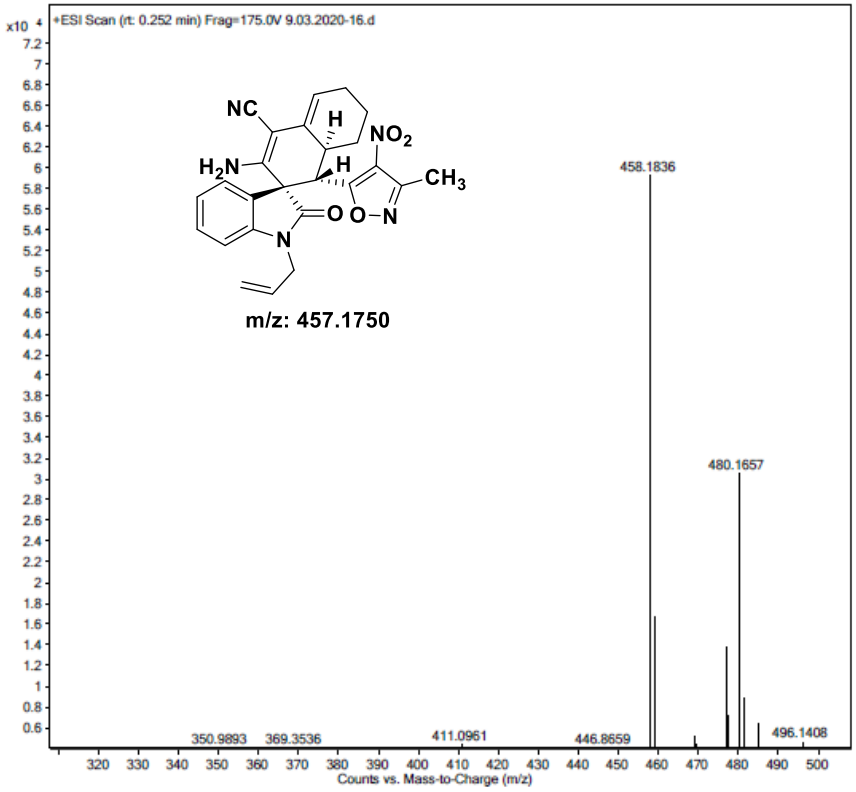

173.353
170.751
155.055
149.560
143.855
131.518
130.837
128.893
125.127
124.308
123.598
122.089
116.777
108.711
86.937
54.588
45.663
32.202
29.690
26.863
25.203
21.423
11.450
NC
H
NO2
H2N
H
CH3
O
O
N
N
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


x10 5
*ESI Scan (rt: 0.255 min) Frag=175.0V 9.03.2020-14.d
NC
H
NO2
H2N
H
CH3
O
O
N
N
CH3
m/z: 431.1594
432.1673
448.1617
470.1380
486.1344
Counts vs. Mass-to-Charge (m/z)

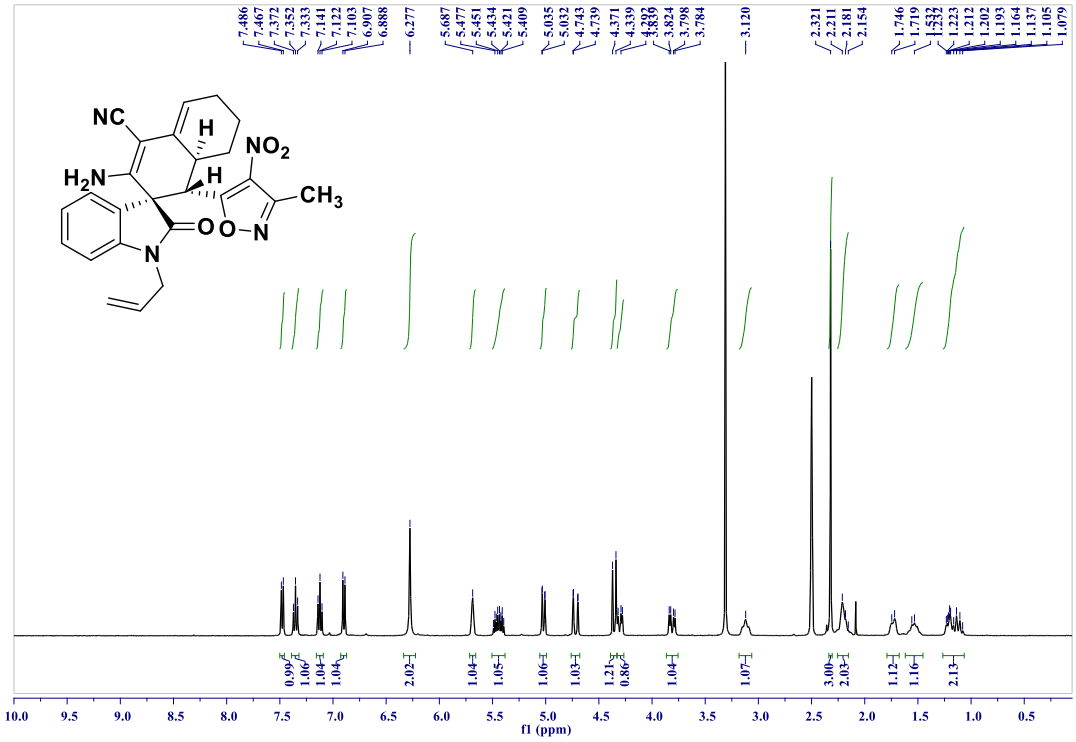
(1'S,3R,8a'S)-1-allyl-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3e):

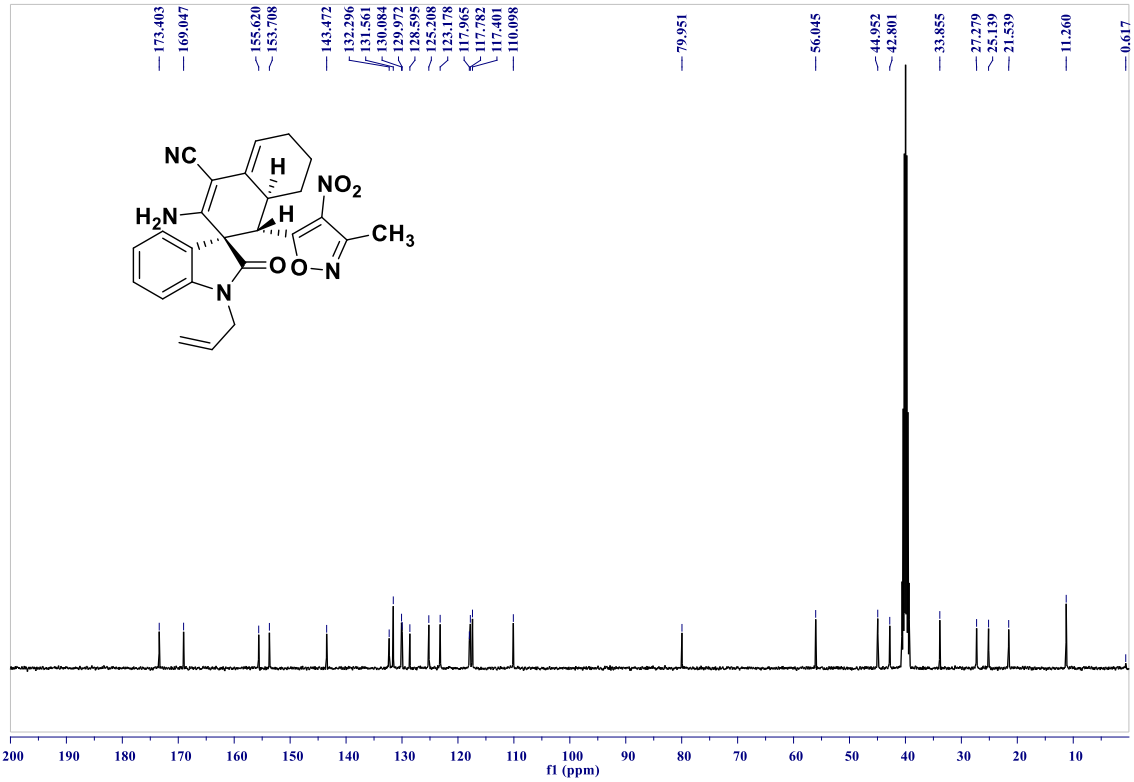


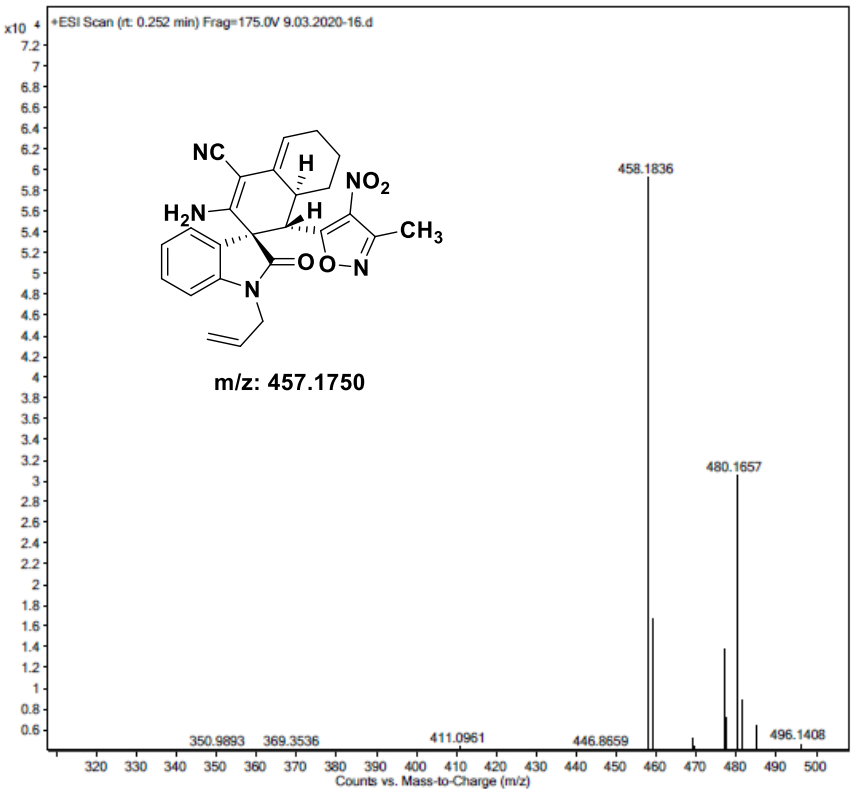




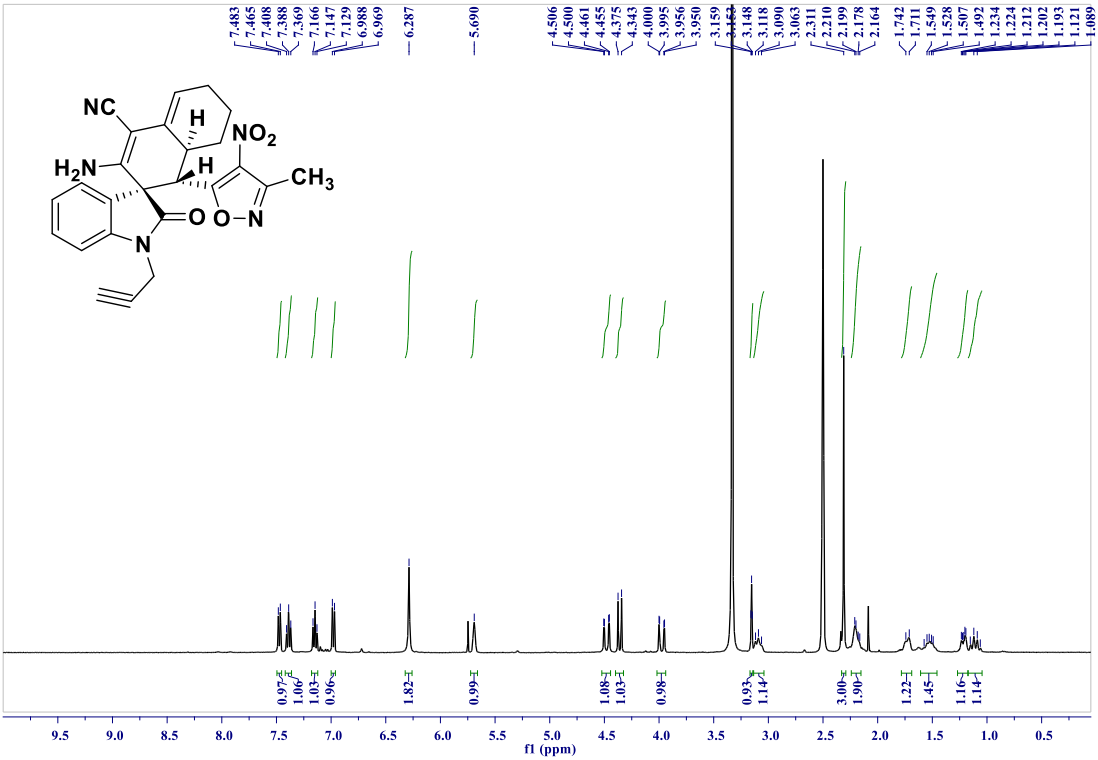
(1'S,3S,8a'S)-1-allyl-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3b'):

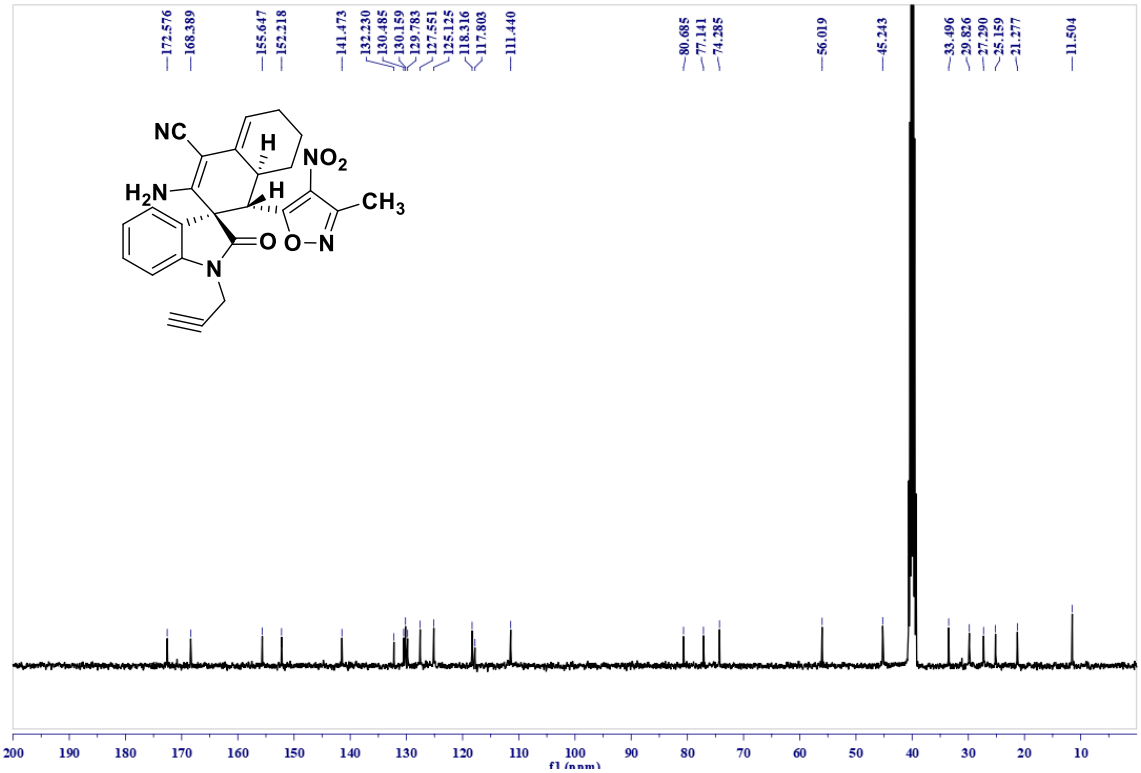


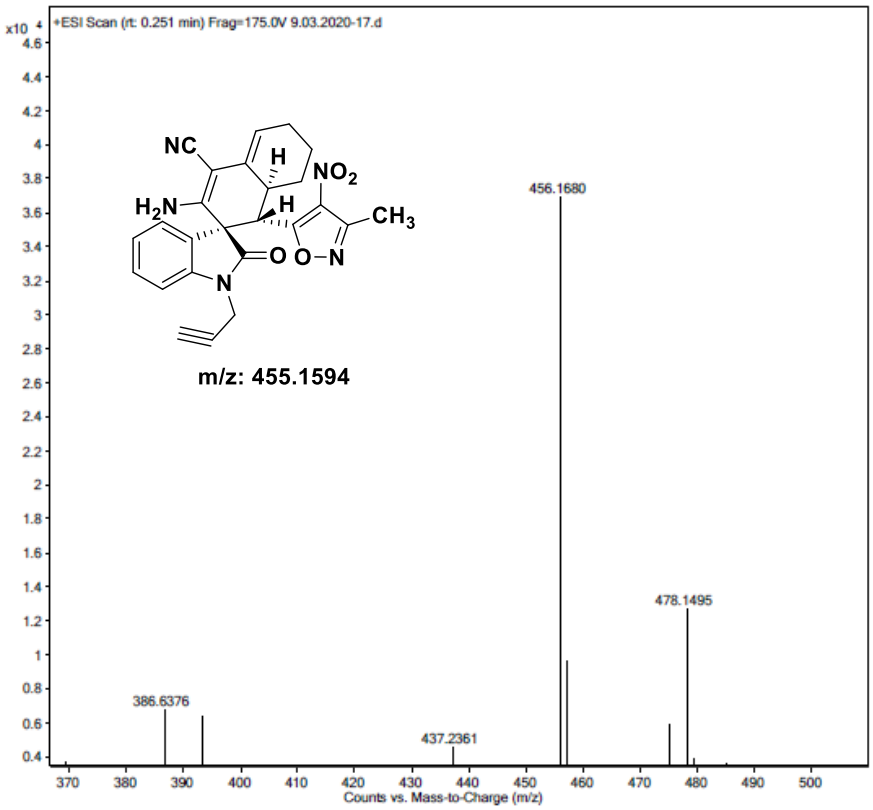

173.403
169.047
155.620
153.708
143.472
132.296
131.561
130.084
129.972
128.595
125.208
123.178
117.965
117.782
117.401
110.098
79.951
56.045
44.952
42.801
33.855
27.279
25.139
21.539
11.260
0.617
NC
H
NO2
H2N
H
CH3
O
O
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


x10 4
*ESI Scan (rt: 0.252 min) Frag=175.0V 9.03.2020-16.d
NC
H
NO2
H2N
H
CH3
O
O
N
N
m/z: 457.1750
458.1836
480.1657
350.9893
369.3536
411.0961
446.8659
496.1408
Counts vs. Mass-to-Charge (m/z)

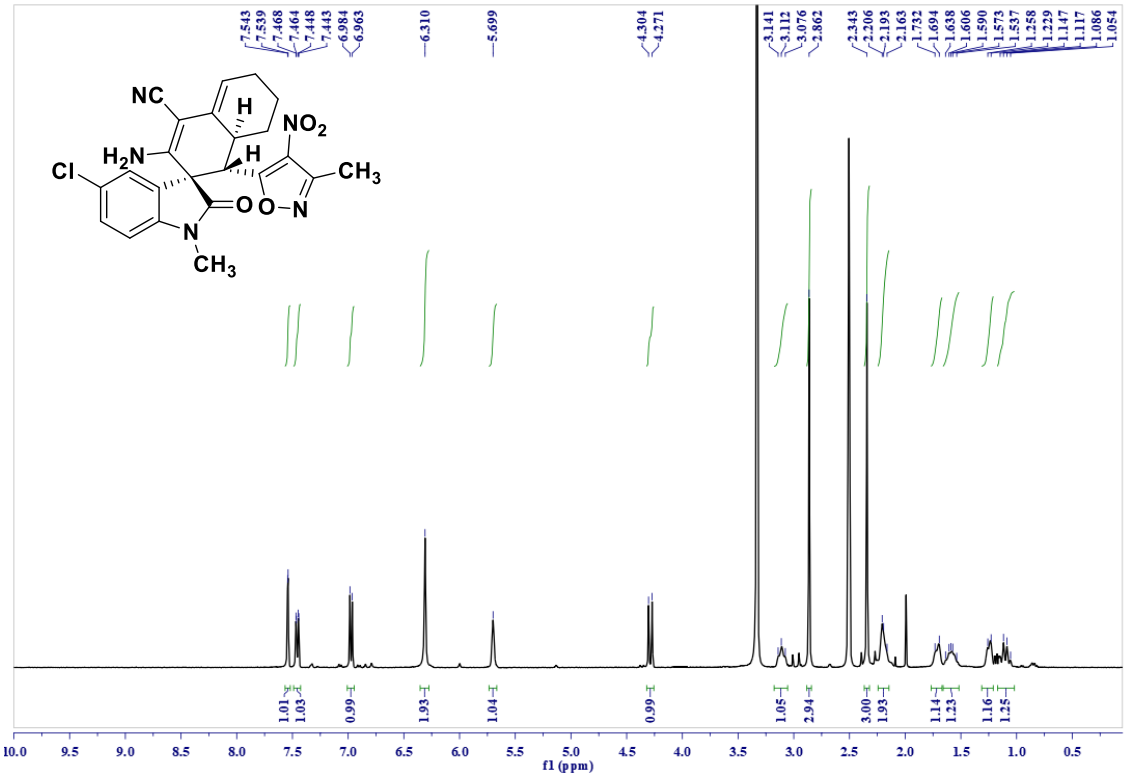
(1'S,3S,8a'S)-3'-amino-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-1-(prop-2-yn-1-yl)-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3c'):

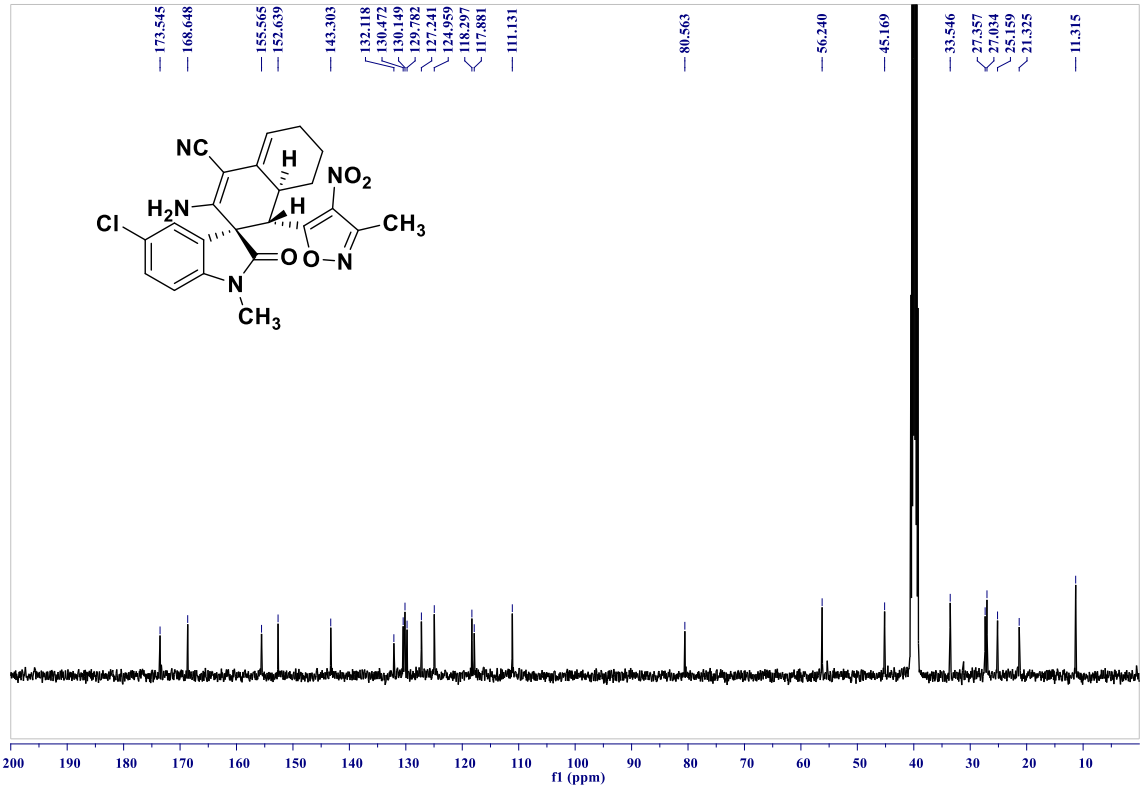


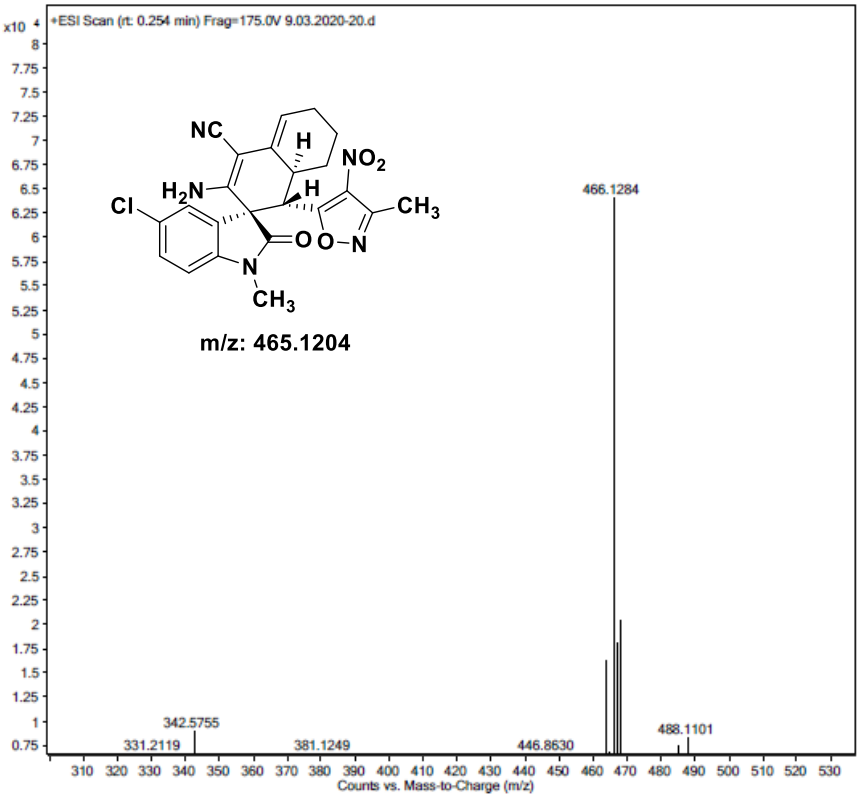




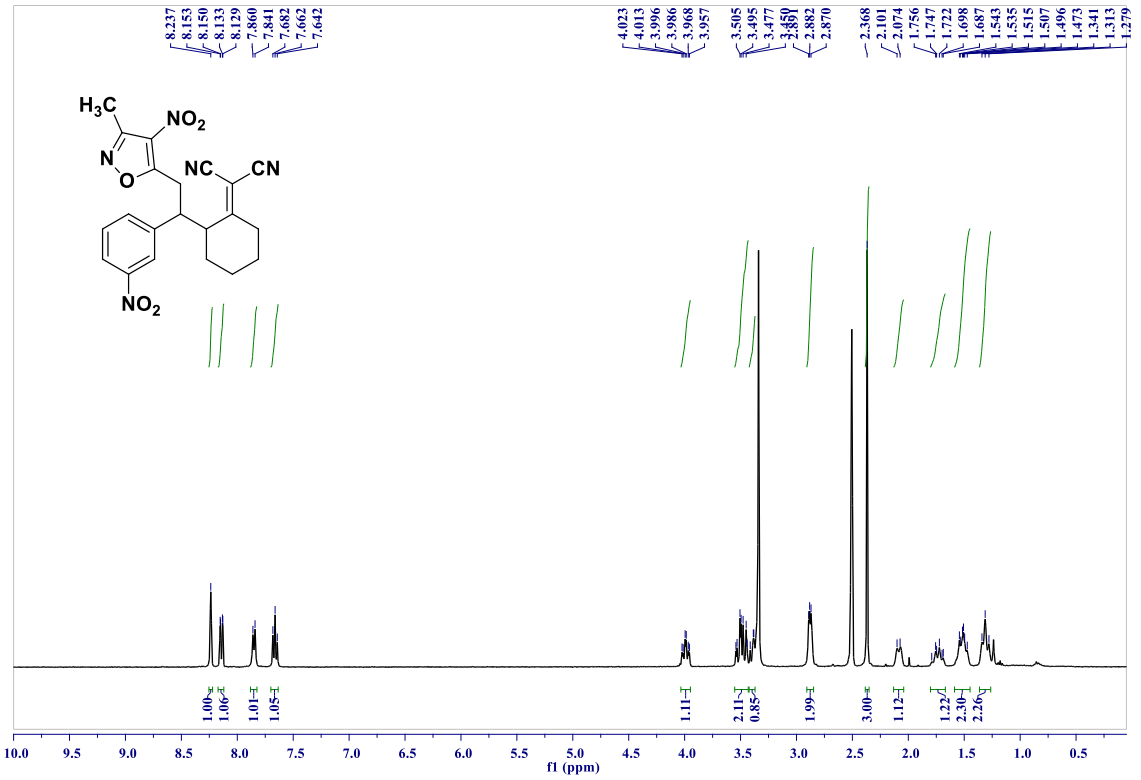
(1'S,3S,8a'S)-3'-amino-5-chloro-1-methyl-1'-(3-methyl-4-nitroisoxazol-5-yl)-2-oxo-6',7',8',8a'-tetrahydro-1'H-spiro[indoline-3,2'-naphthalene]-4'-carbonitrile (3d'):

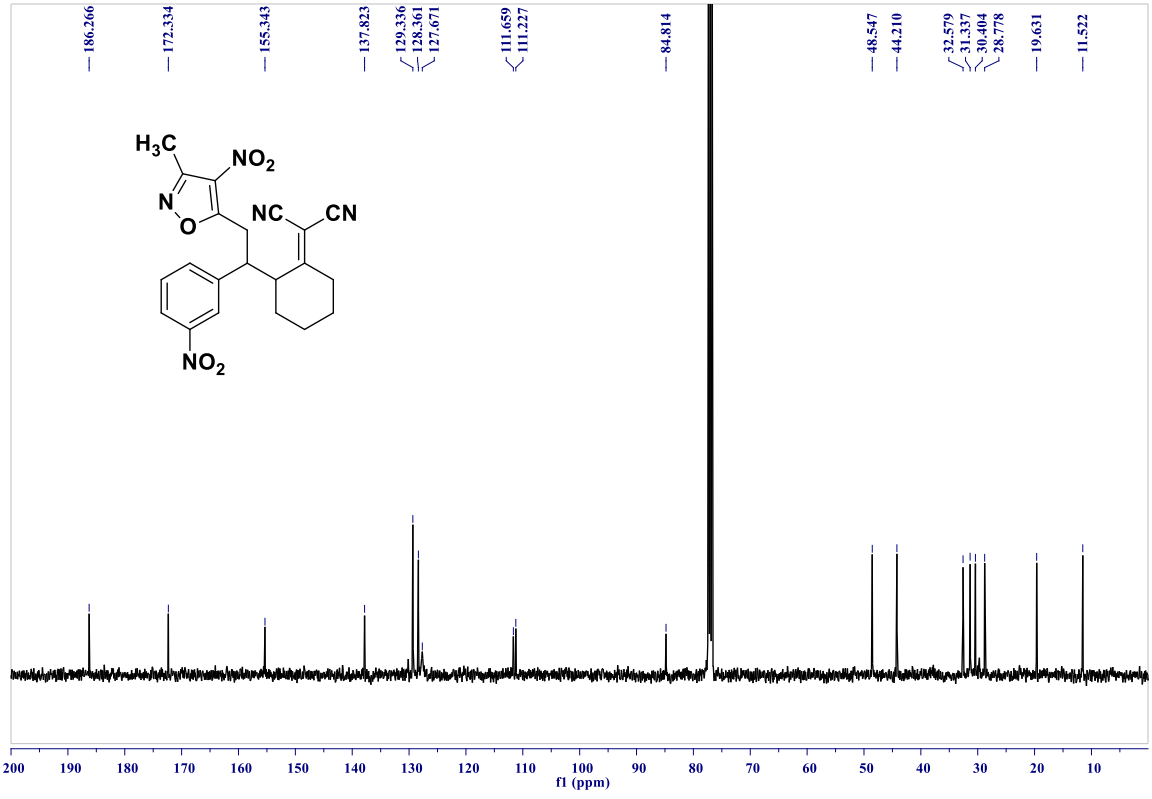


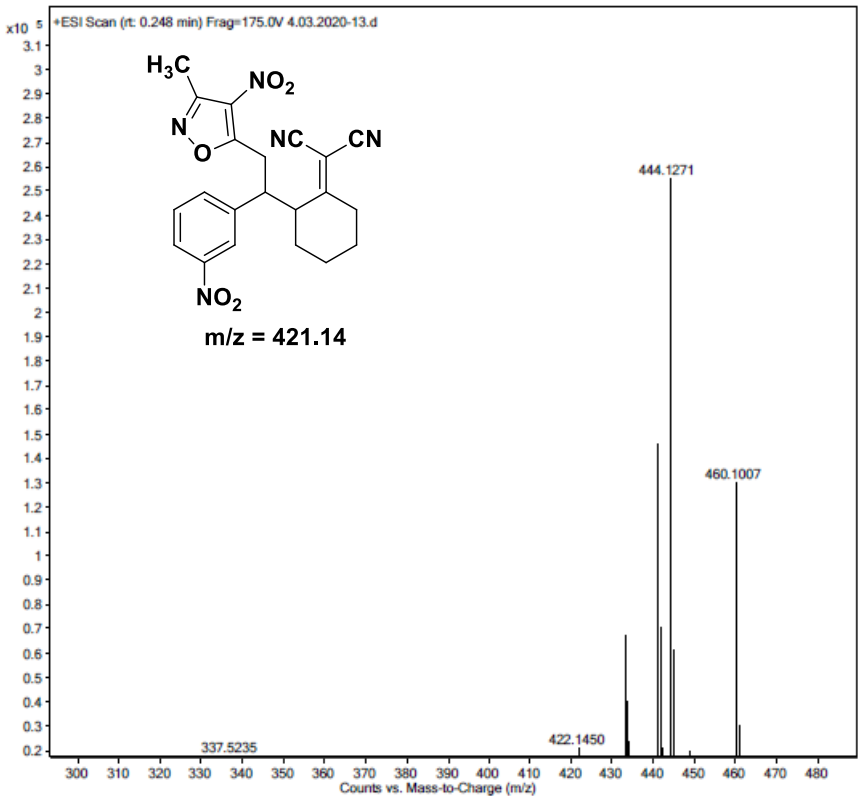

173.545
168.648
155.565
152.639
143.303
132.118
130.472
130.149
129.782
127.241
124.959
118.297
117.881
111.131
80.563
56.240
45.169
33.546
27.357
27.034
25.159
21.325
11.315
NC
H
NO2
H2N
H
Cl
CH3
O
O
N
N
CH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


x10 4
+ESI Scan (rt: 0.254 min) Frag=175.0V 9.03.2020-20.d
NC
H
NO2
H2N
H
Cl
CH3
O
O
N
N
CH3
m/z: 465.1204
466.1284
342.5755
331.2119
381.1249
446.8630
488.1101
Counts vs. Mass-to-Charge (m/z)

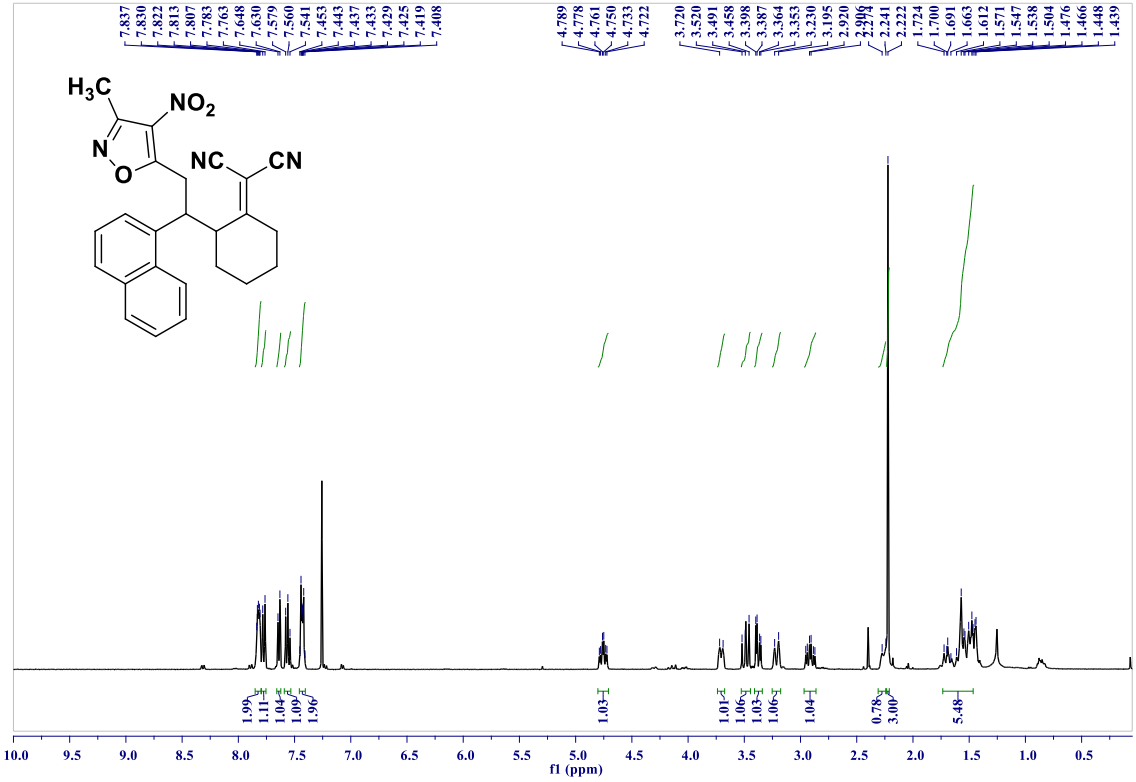
2-(2-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(3-nitrophenyl)ethyl)cyclohexylidene)malononitrile (5c):

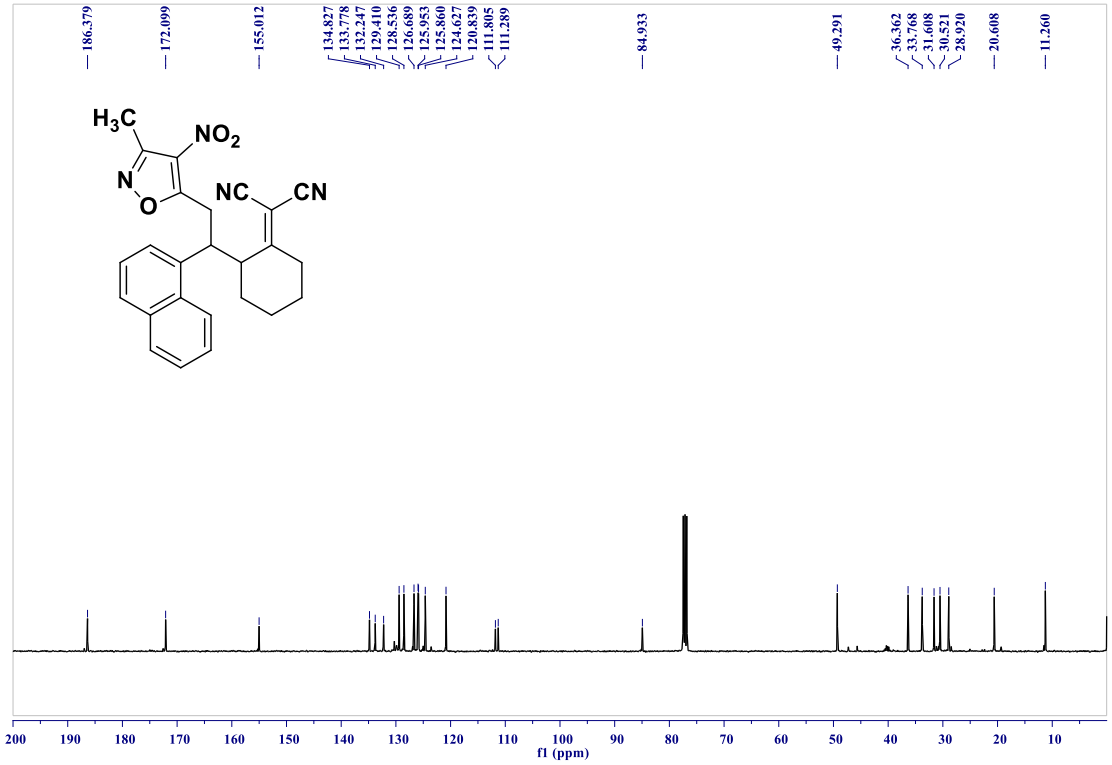


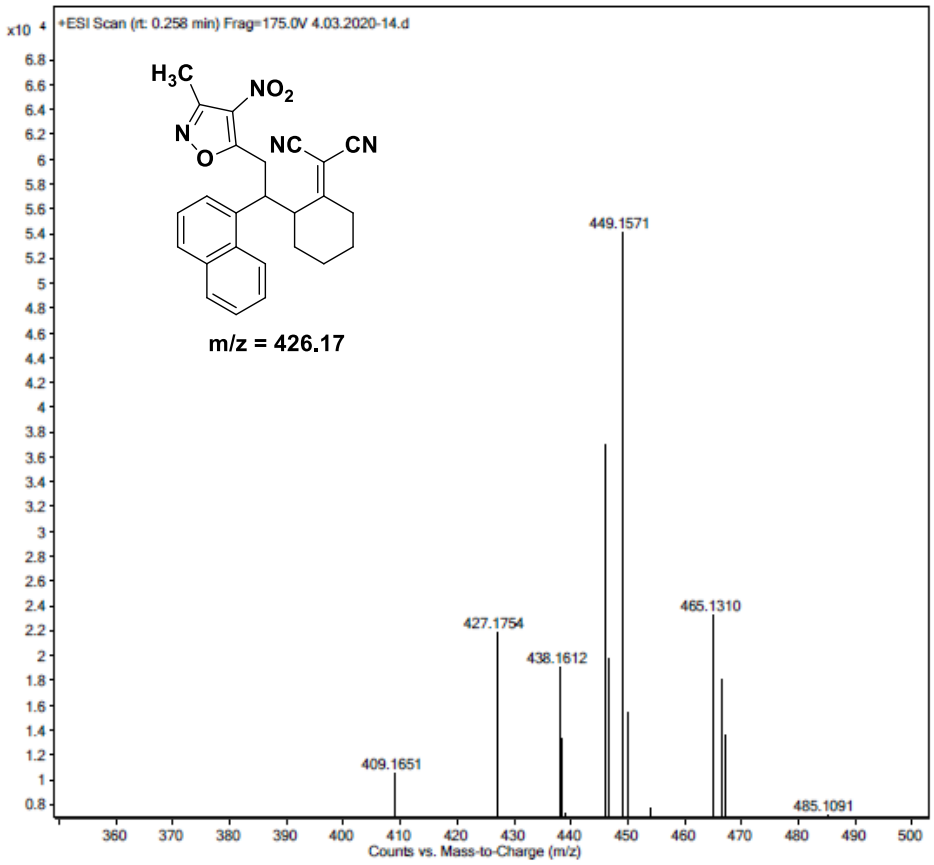




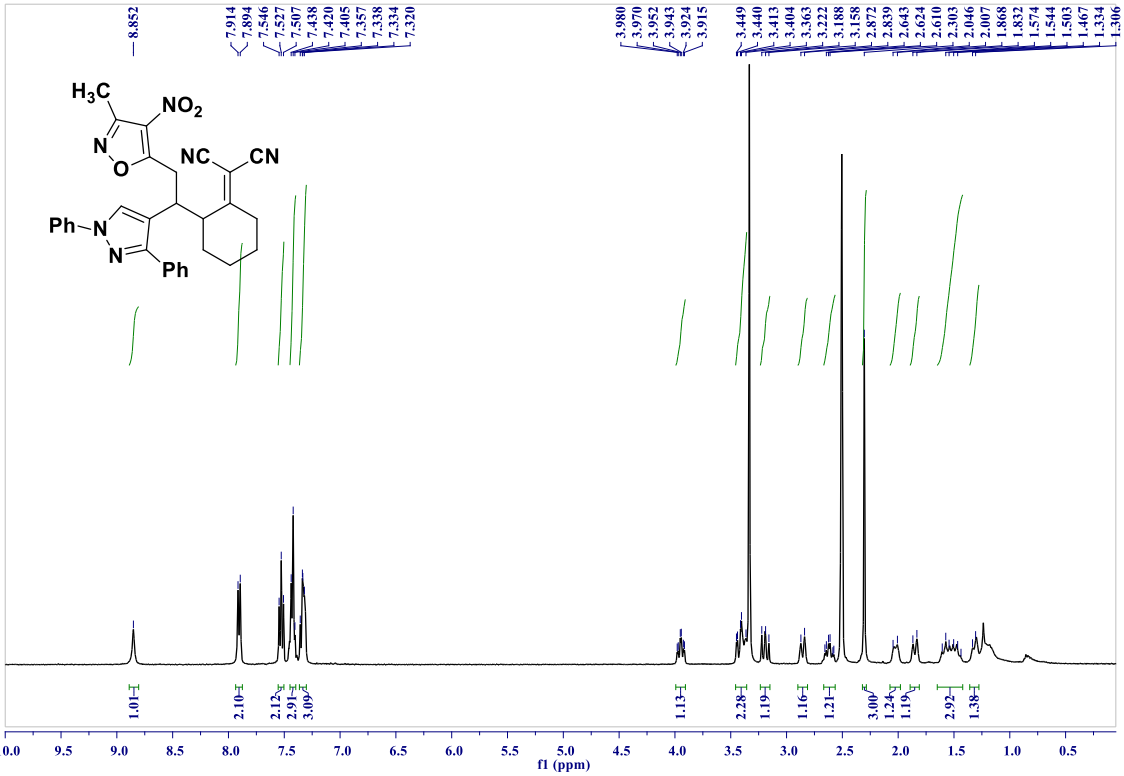
2-(2-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-(naphthalen-2-yl)ethyl)cyclohexylidene)malononitrile (5f):

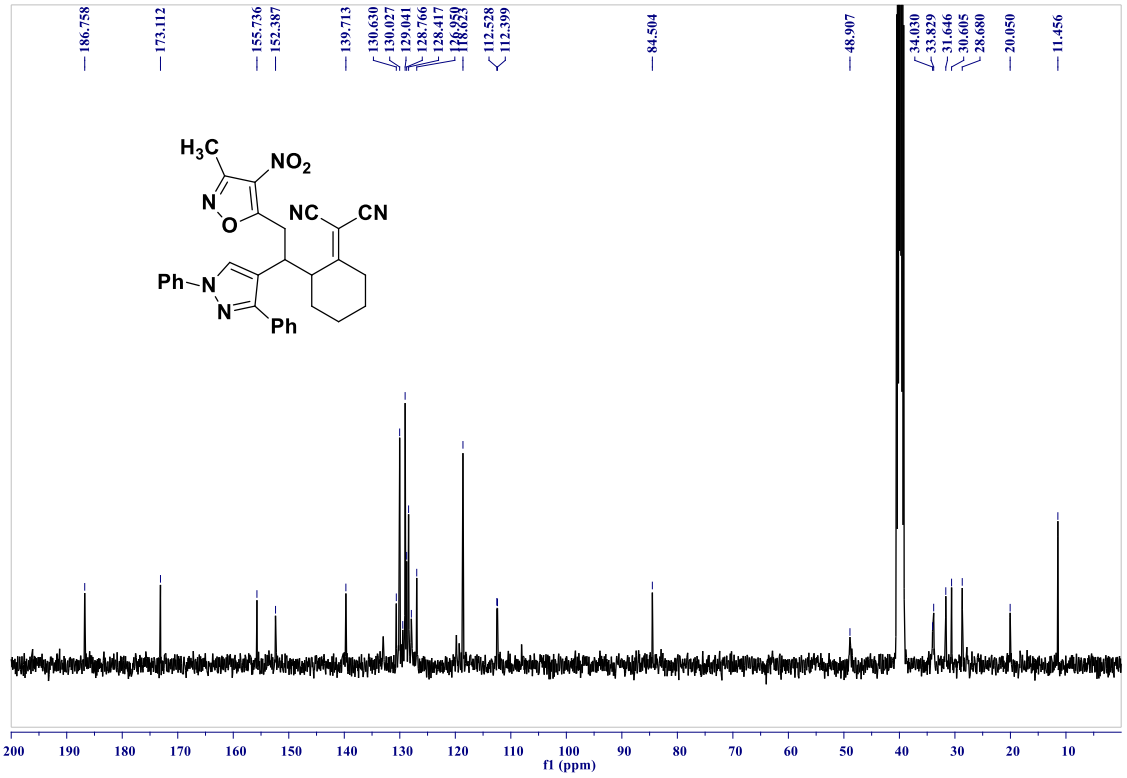


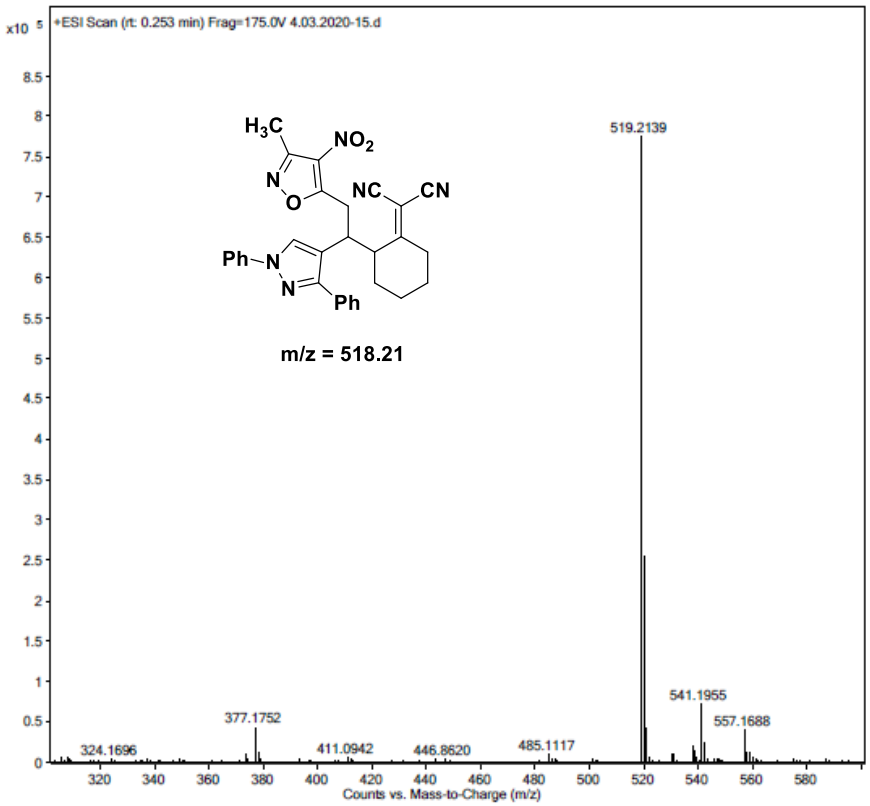

186.379
172.099
155.012
134.827
133.778
132.247
129.410
128.536
126.689
125.953
125.860
124.627
120.839
111.805
111.289
84.933
49.291
36.362
33.768
31.608
30.521
28.920
20.608
11.260
H3C
NO2
N
O
NC
CN
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


x10 4
+ESI Scan (rt: 0.258 min) Frag=175.0V 4.03.2020-14.d
H3C
NO2
N
O
NC
CN
m/z = 426.17
449.1571
465.1310
427.1754
438.1612
409.1651
485.1091
Counts vs. Mass-to-Charge (m/z)

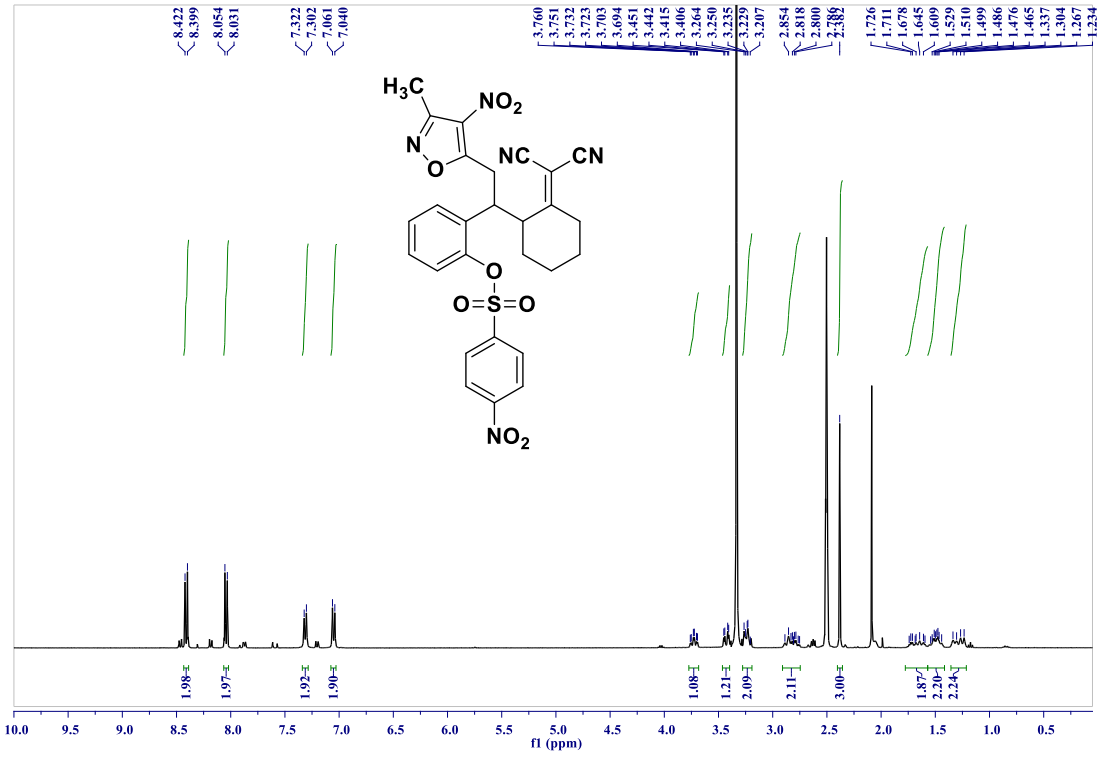
2-(2-(1-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)cyclohexylidene)malononitrile (5g):

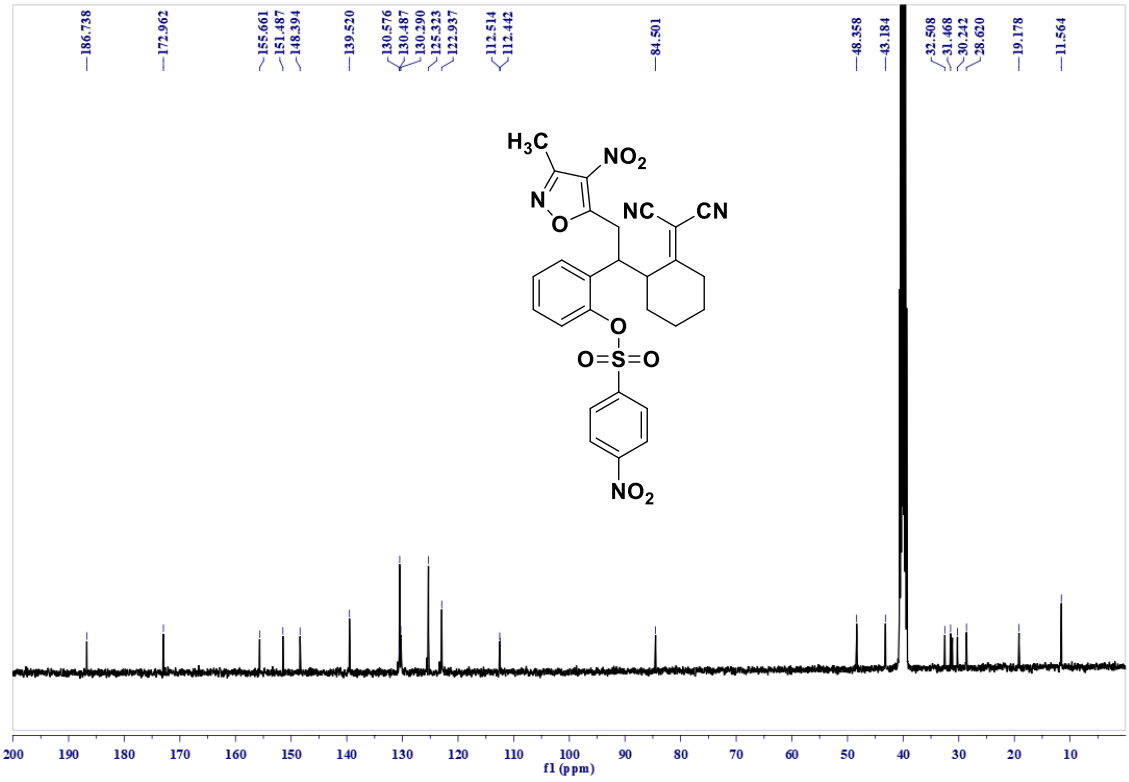






2-(1-(2-(dicyanomethylene)cyclohexyl)-2-(3-methyl-4-nitroisoxazol-5-yl)ethyl)phenyl 4-nitrobenzenesulfonate (5h):





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CHAPTER-V

Base mediated synthesis of spirooxindole-cyclopropane hybrids using onium ylides at room temperature

CHAPTER-V

5.1 Introduction

Cycloaddition reactions of cyclopropane and its analogues have been widely used in the rapid construction of cyclic, polycyclic, or bridged cyclic products; asymmetric synthesis of cyclic frameworks and building blocks for natural products. The cyclopropane subunit plays a significant role in organic and medicinal chemistry because of its distinctive reactivities. Cyclopropane and its derivatives also serve as versatile synthetic intermediates.[1] Barbiturate-fused spirocycles and spirocyclopropyl-oxindole motifs are widely present in clinical pharmaceuticals and bioactive compounds (**Chapter-I; Figure-4B**). For instance, these compounds act as inhibitors of dihydro-orotate dehydrogenase,[2a] nanomolar activity as an HIV-1 non-nucleoside reverse transcriptase inhibitor,[2b] and also exhibit promising antitumor activity.[2c] Over the past decades, several methodologies have been reported in the literature for the construction of spirocyclopropyl barbiturates/oxindoles skeletons using Michael-initiated organo-catalytic ring closure between 3-chloroindolin-2-ones and α,β-unsaturated carbonyl compounds,[3] transition metal assisted cyclopropanation of 3-diazoindolin-2-ones with olefins,[4] Michael-alkylation cascade reactions of alkyl halides and 3-alkylidene oxindoles[5] and bromo-nitro olefins and indolin-2-ones.[6]

Ylide chemistry first reported by Wittig in 1953 and have been developed into powerful synthetic tool in organic chemistry.[7] Ylide chemistry has served as the basis for constructing various structurally divergent, multi functionalized products and other useful important intermediates.[8] Synthesis based on 1,2-addition with ylides can rapidly generate various functionalized alkenes[9a] and small ring compounds such as epoxides, aziridines and cyclopropane ring molecules.[9b,c] Synthesis based on 1,4-addition of ylides with of α,β-unsaturated carbonyl or imine compounds to generate multi-substituted cyclopropane fragments *via* highly chemo selective [2+1] annulation.[9d] On the other hand, these α,β-unsaturated substrates allow effectively for the preparation of numerous five-membered heterocyclic compounds *via* [4+1] pathway instead of a challenging [2+1] pathway.

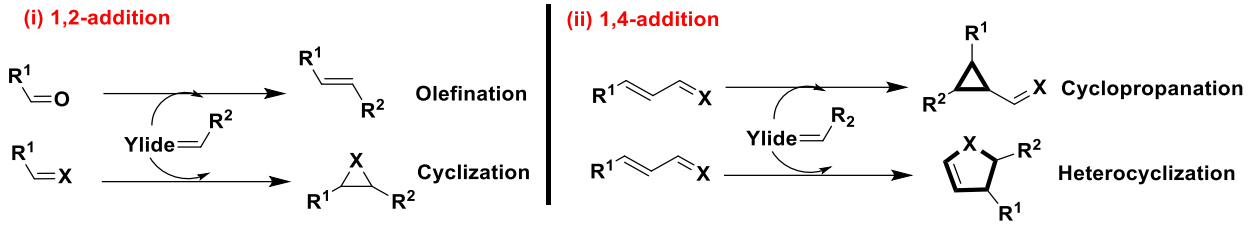
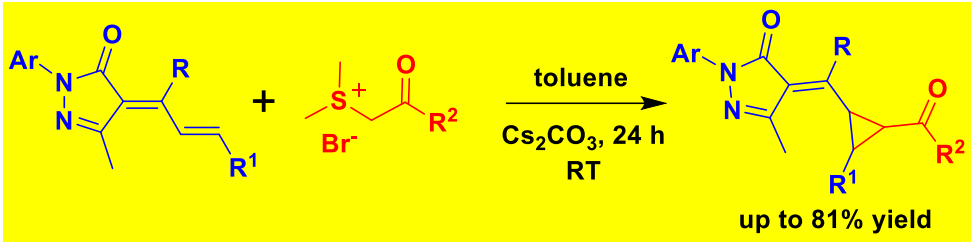


Figure-5.1: *Different addition patterns of ylide chemistry (X = O or N).*

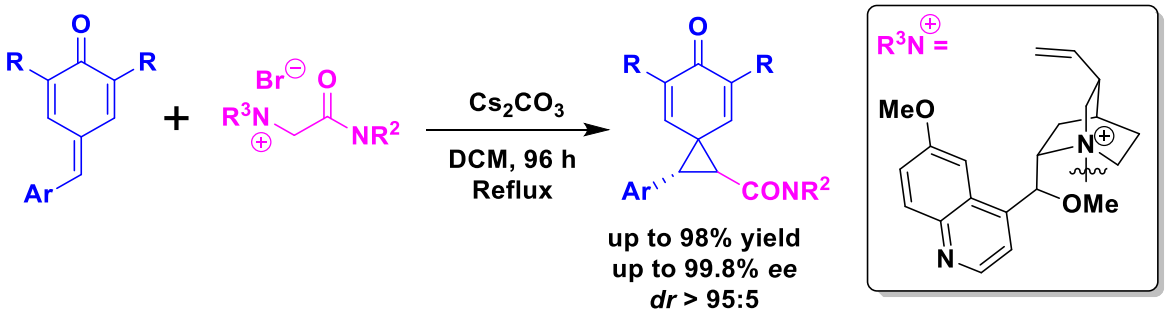
5.1.1 Methods for the synthesis of cyclopropane derivatives using onium ylides

In this connection, **C. Peng** group developed a cyclopropanation of α,β,γ,δ-unsaturated pyrazolones with sulfonium salts to construct the vinylcyclopropane-fused pyrazolones *via* remote 1,6-Michael addition followed by nucleophilic substitution under basic condition to afford excellent regio- and chemoselectivity, good yields (**Scheme-5.1**).[10]



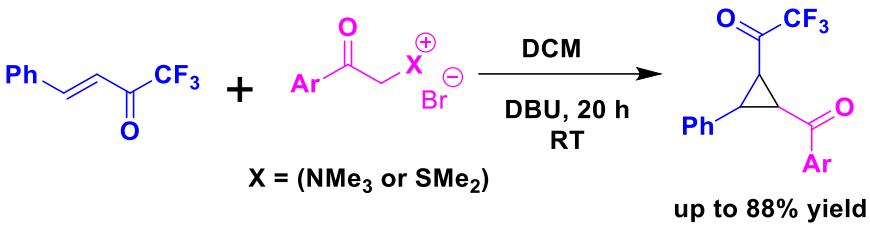
Scheme-5.1: *Synthesis of vinylcyclopropane-fused pyrazolones using sulfur ylides.*

M. Waser group have been developed a highly asymmetric and broadly applicable protocol for the straightforward synthesis of chiral spiro [2.5]-octa-4,7-dien-6-ones using *para*-quinone methides and cinchona alkaloid-based chiral ammonium ylides under basic condition in excellent yields (**Scheme-5.2**).[11]



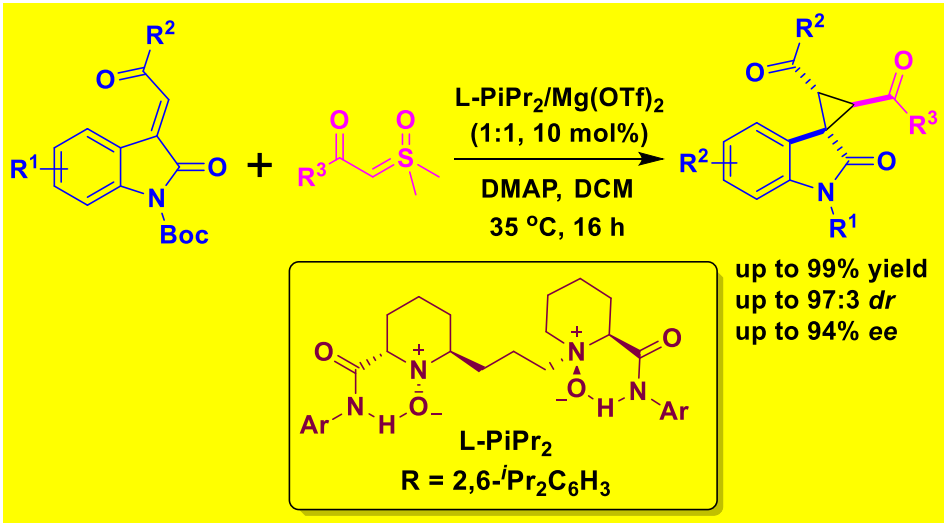
Scheme-5.2: *Ammonium ylide mediated asymmetric spirocyclopropanation of p-quinone methides.*

Later same group also demonstrated the use of carbonyl-stabilized ammonium and sulfonium ylides allows for the synthesis of highly-functionalized trifluoroacetyl-substituted cyclopropanes using DBU as organic base to provide moderate to good yields (**Scheme-5.3**).[12]



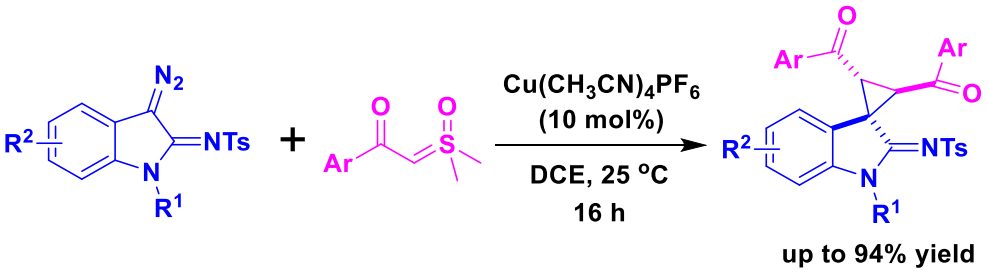
Scheme-5.3: *Ylide-mediated synthesis of trifluoroacetyl-containing cyclopropanes.*

Feng and co-workers reported a cyclopropanation of 3-alkenyl-oxindoles with sulfoxonium ylides and obtained a range of spirocyclopropyl oxindoles containing two or three continuous chiral carbon centers were obtained in high yields (up to 99%) with good *dr* (up to 97:3) and high *ee* values (up to 94% *ee*) (**Scheme-5.4**).[13]



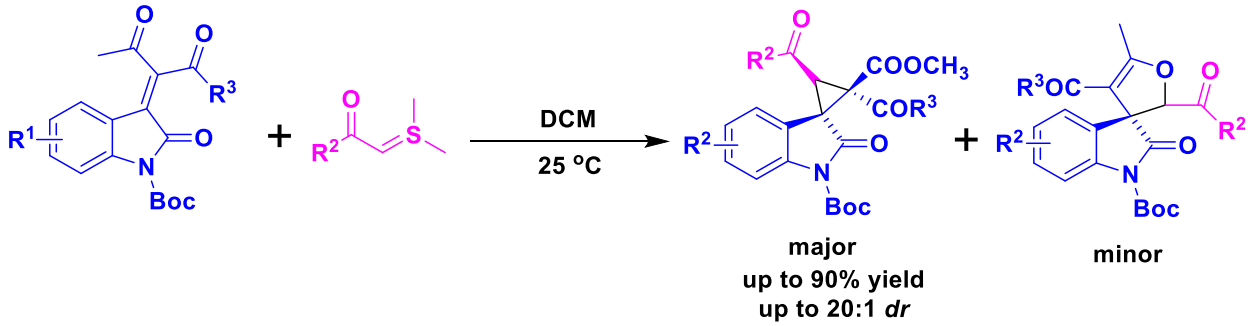
Scheme-5.4: *Synthesis of spirocyclopropyl oxindoles using sulfoxonium ylides.*

Y. Wang group developed copper-catalyzed dimerization of sulfoxonium ylides with 3-diazoindolin-2-imines to construct wide range of spiro[cyclopropane-1,3′-indolin]-2′-imines with good to excellent yields with high diastereoselectivity under mild reaction conditions (**Scheme-5.5**).[14]



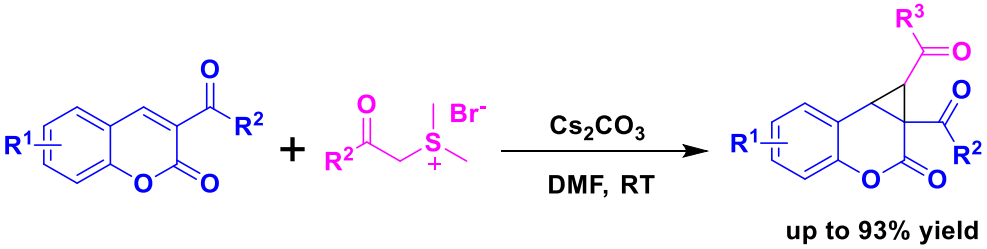
Scheme-5.5: *Synthesis of spiro[cyclopropane-1,3'-indolin]-2'-imines using sulfoxonium ylides with 3-diazoindolin-2-imines.*

Bo Han group achieved for the synthesis of multifunctional cyclopropane and dihydrofuran-fused spirooxindoles using tetra-substituted oxindole olefins and sulfur ylides. In this case cyclopropane oxindoles (as major isomers) were obtained up to 90% yield with up to 20:1 *dr*, under catalyst-free conditions (**Scheme-5.6**).[15]



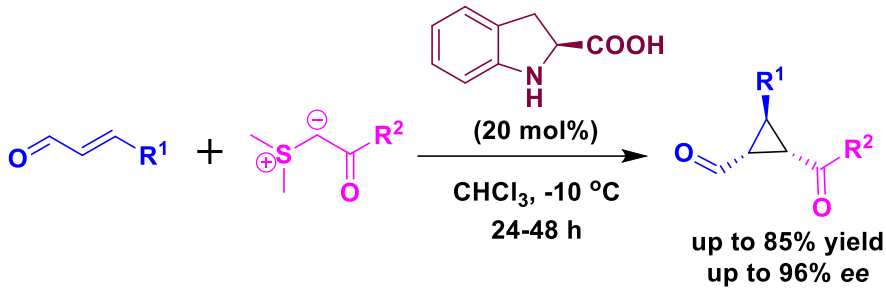
Scheme-5.6: *Synthesis of cyclopropane-fused spirooxindoles.*

D.-Q. Shi group developed a convenient and efficient stabilized sulfur ylide mediated cyclopropanation *via* [4+1] cycloaddition reaction of 3-acyl-2*H*-chromenones under mild condition in excellent yields (up to 93%) and excellent regio-selectivity (**Scheme-5.7**).[16]



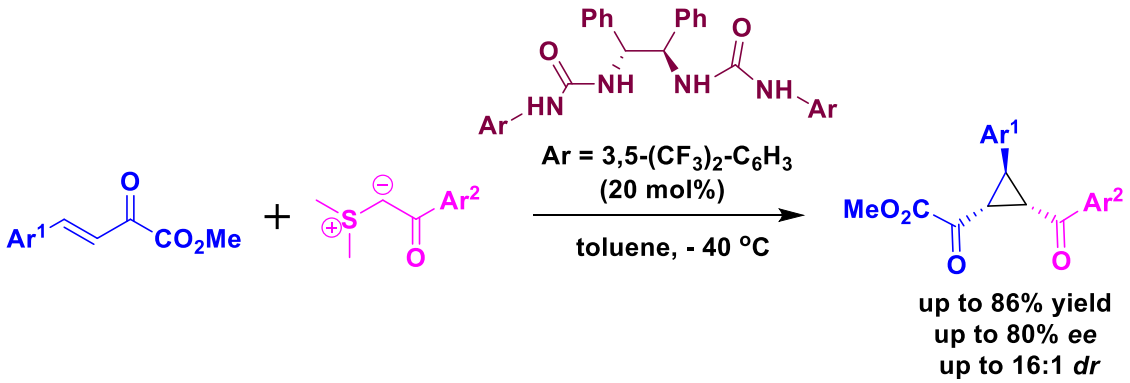
Scheme-5.7: *Sulphur ylide-mediated cyclopropanation for the synthesis of dihydrocyclopropane based chromenes.*

An amino catalyzed Corey-Chaykovsky type cyclopropanation was reported by **MacMillan and Kunz** using α,β-unsaturated aldehydes with sulfonium ylides to deliver corresponding cyclopropanes in good yields and high enantiomeric excess (**Scheme-5.8**).[17]



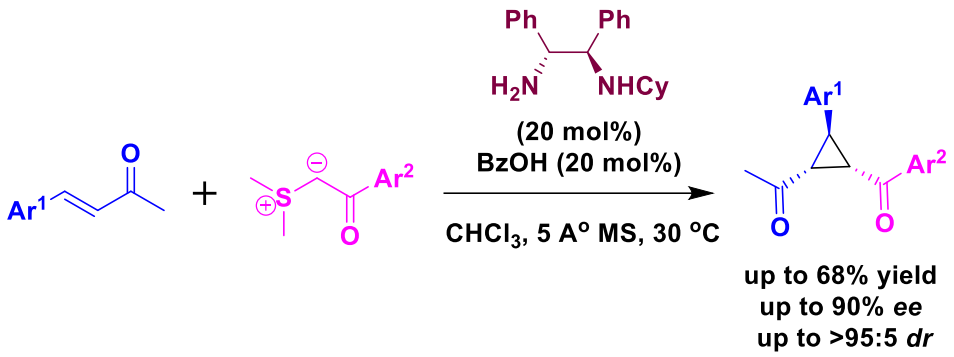
Scheme-5.8: *Asymmetric cyclopropanation of α,β-unsaturated aldehydes with sulfonium ylides catalyzed by 2-carboxylic acid dihydroindole.*

Sulfonium ylides have also been explored by **Xiao** and co-workers for the synthesis of asymmetric cyclopropanation of β,γ-unsaturated α-ketoesters with ylides for the synthesis of cyclopropane products with good yields and good enantioselectivity (up to 80%) (**Scheme-5.9**).[18]



Scheme-5.9: *Asymmetric cyclopropanation catalyzed by a bisurea as an organo catalyst.*

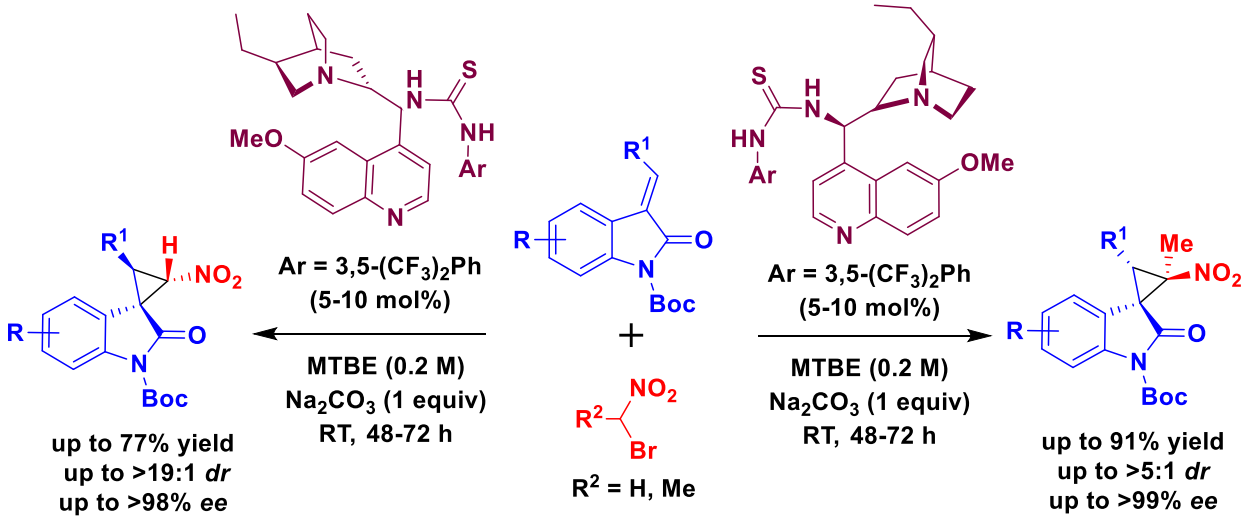
X. Feng group explained formation of cyclopropane derivatives using a simple chiral diamine catalyst for the asymmetric cyclopropanation of cinnamone derivatives with stabilized sulfur ylides. The desired products were obtained in moderate yields (up to 68%) with good enantioselectivities (up to 93% *ee*) and excellent diastereoselectivities (>95:5) under mild conditions (**Scheme-5.10**).[19]



Scheme-5.10: *Asymmetric cyclopropanation catalyzed by a diamine catalyst.*

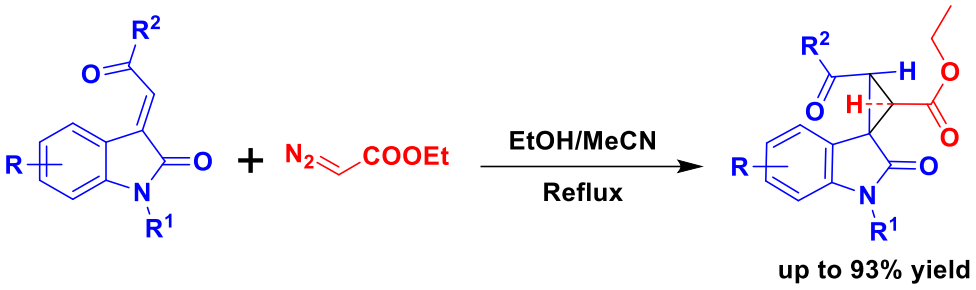
5.1.2 Synthetic methods for the preparation of cyclopropane derivatives using oxindole or barbiturate olefins

G. Bencivenni group have been developed the unprecedented organocatalyzed asymmetric synthesis of biologically encouraged spiro 3,3'-cyclopropyl oxindoles from readily available and simple starting materials such as bromonitromethane and *N*-Boc-protected oxindole with high yields and excellent enantioselectivity (**Scheme-5.11**).[20]



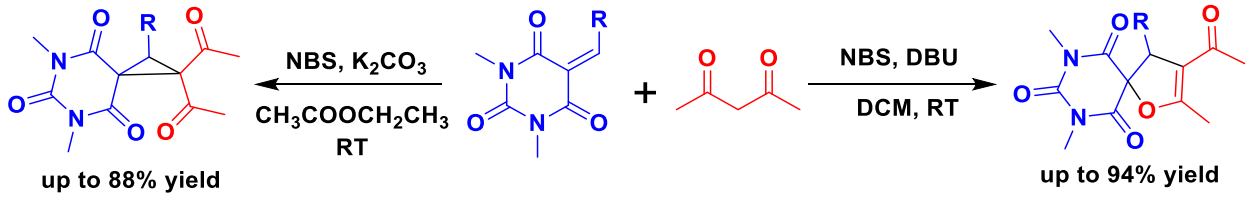
Scheme-5.11: *Synthesis of spiro nitrocyclopropyl oxindoles with two adjacent tertiary stereogenic centers.*

R. A. Maurya group explored the scope of the catalyst-free cyclopropanation of electron deficient alkenes with EDA to construct a number of spiro[cyclopropane-1,3'-indolin]-2'-ones in high yields with excellent diastereoselectivity (**Scheme-5.12**).[21]



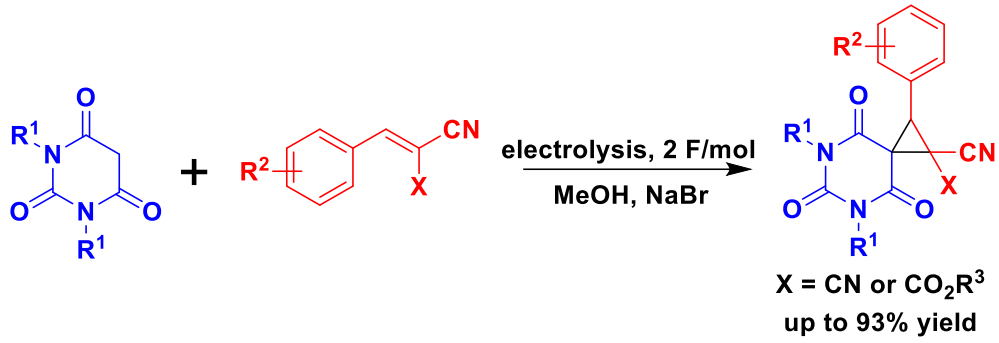
Scheme-5.12: *Catalyst-free diastereoselective synthesis of spiro-indoline derivatives.*

X. Yan and his group achieved the synthesis of spirodihydrofuryl barbiturates and spirocyclopropyl barbiturates selectively *via* cascade reactions of barbiturate-based olefins and acetylacetone with NBS under different basic conditions in moderate to excellent yields (**Scheme-5.13**).[3b]



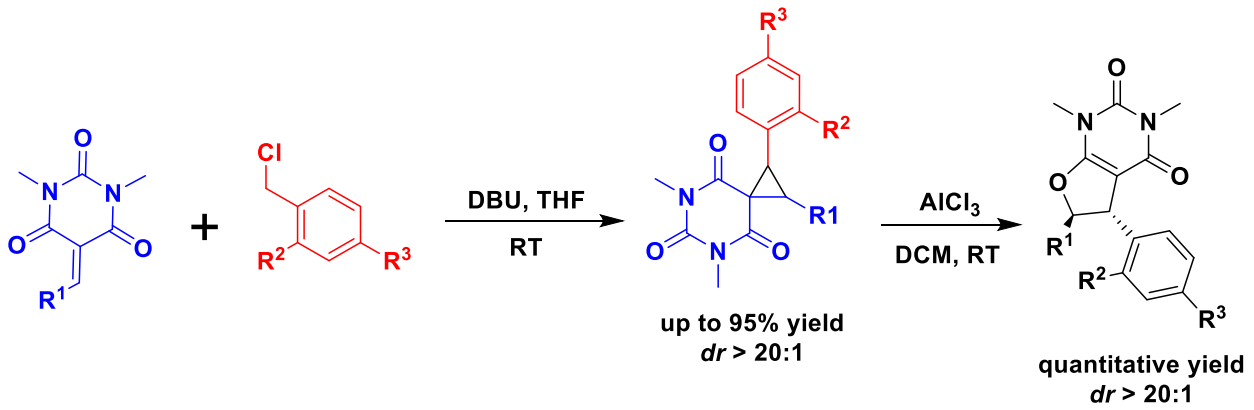
Scheme-5.13: *Synthesis of spirocyclopropyl barbiturates and spirodihydrofuryl barbiturates.*

E. O. Dorofeeva group explained the combined electrolysis of barbiturate olefins and benzylidenemalononitriles or benzylidenecyanoacetates in methanol in an undivided cell in the presence of sodium bromide results in the formation of corresponding spirocyclopropyl barbiturates up to 93% yield.[22]



Scheme-5.14: *The electrocatalytic transformation of barbituric acids and benzylidenemalononitriles.*

J. Chang group developed a method for the synthesis diastereoselective spirocyclopropanes using barbiturate-based olefins with 2,4-disubstituted benzyl chlorides in presence of DBU as an organo base afford in up to 95% of the yields with more than 20:1 *dr* in favor of anti-isomers. To explore synthetic utility of the spiro-products, a Lewis acid induced cyclopropane ring-expansion isomerization was also demonstrated.[23]

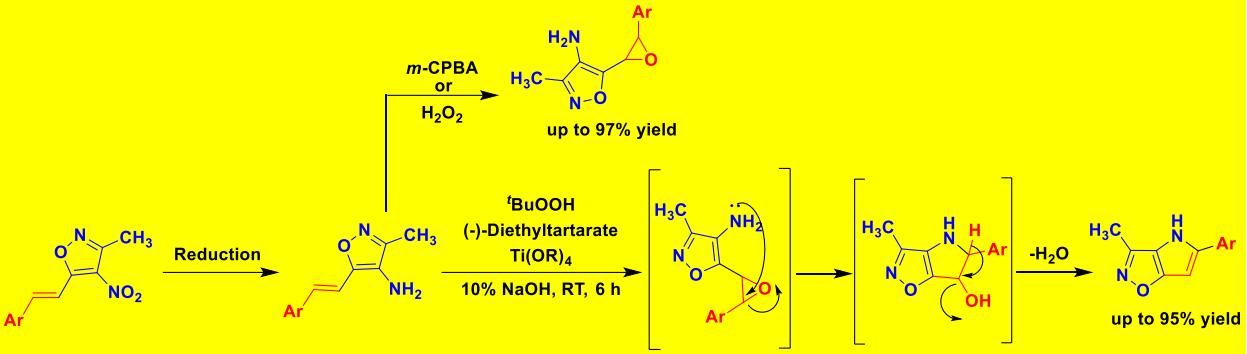


Scheme-5.15: *DBU-mediated diastereoselective synthesis of spirobarbiturate-cyclopropanes.*

5.1.3 3-Methyl-4-nitro-5-styrylisoxazoles as reactive partner in annulation reactions

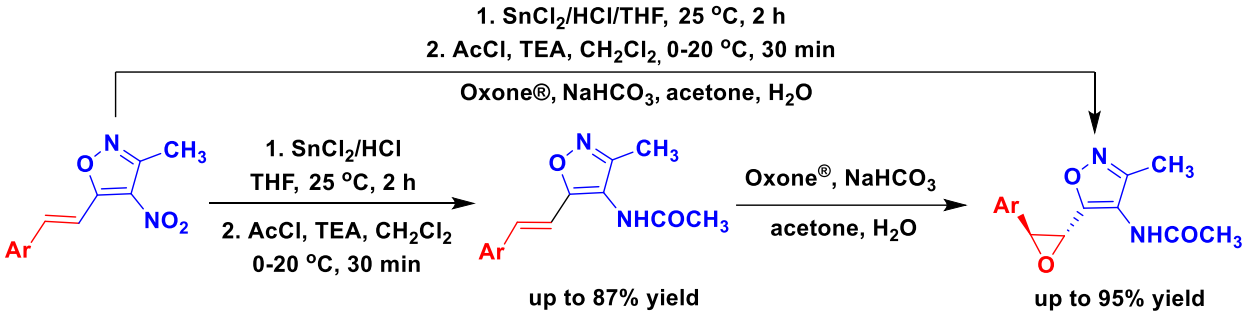
3-Membered cyclic structures such as epoxides, aziridines plays an important role in organic chemistry and can be used as handle for the preparation of 1,2-diols, 1,2-aminoalcohols (chiral and achiral versions). Similarly, 3-membered hydrocarbons like cyclopropanes show interesting structural and electronic properties. In this regard, the isoxazole based unsaturated molecules have been explored for the preparation of functionalized epoxides, aziridines, cyclopropanes *via* different annulation reactions to generate functionalised complex molecules.

Rajanarendar and his group first reported isoxazole-styrene as key substrates for the chemoselective reduction and epoxidation reaction (using *m*-CPBA or H_2O_2) to afford excellent yields (up to 97%). They, also developed one-pot method for the same transformation i.e., generation of epoxide (*in-situ*) using Sharpless epoxidation, then nucleophilic attack (intramolecular) of amine on epoxide (cyclization) followed by dehydration to give 3-methyl-5-aryl-4*H*-pyrrolo[2,3-*d*] isoxazoles with good to excellent yields (up to 95%) (**Scheme-5.16**).[24]



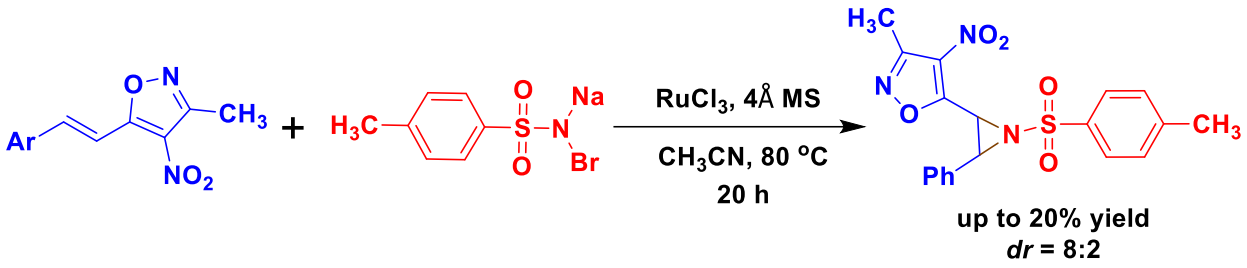
Scheme-5.16: *Epoxidation of 3-methyl-4-nitro-5-styrylisoxazole.*

Later, **Adamo et al.** reported the epoxidation on *N*-acetylamine in stepwise and one-pot method *via* reduction of nitro group [of 3-methyl-4-nitro-5-styrylisoxazole] to amine. Then epoxidation of *N*-acetylisoxazoles styrene using Oxone® in acetone to give desired epoxides (*N*-acetyl derivatives) up to 95% yields (**Scheme-5.17**).[25]

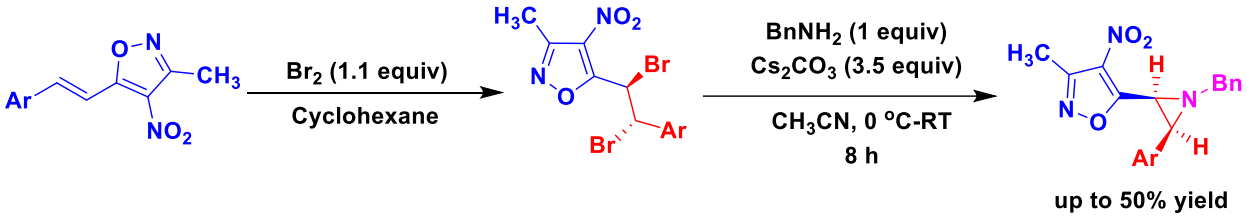


Scheme-5.17: *Epoxidation on 3-methyl-4-nitro-5-styrylisoxazole.*

Adamo and co-workers also reported for the synthesis of 3-membered aziridine sulphonamides using isoxazole-styrenes with bromamine-T as nitrene source in presence of $RuCl_3$ as a catalyst with 20% yields (**Scheme-5.17)**. In a similar report, they achieved the synthesis of *N*-benzyl aziridines (**Scheme-5.18**) *via* bromination of 3-methyl-4-nitro-5-styrylisoxazole followed by double nucleophilic substitution of NH_2 group of benzyl amine in presence of Cs_2CO_3 with moderate yields (up to 50%).[26]



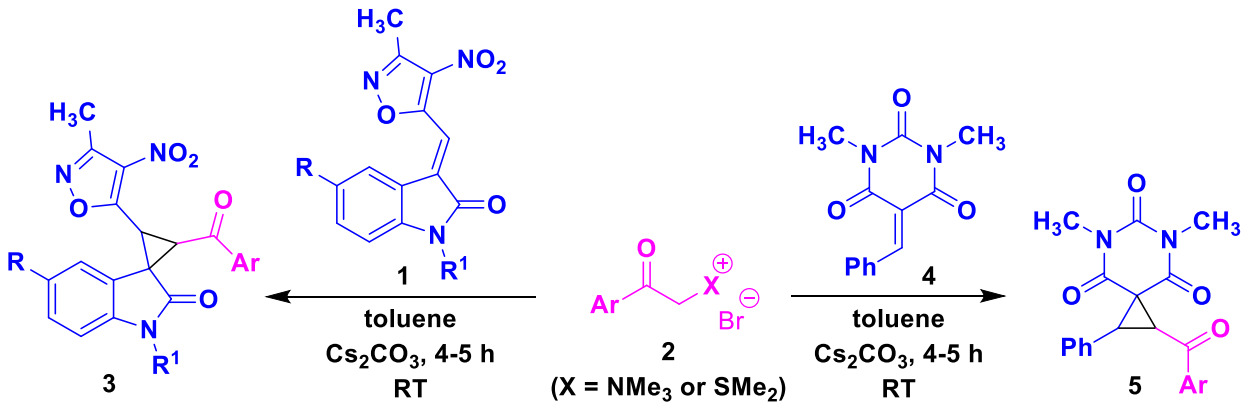
Scheme-5.17: *Synthesis of aziridinones using 3-methyl-4-nitro-5-styrylisoxazole.*



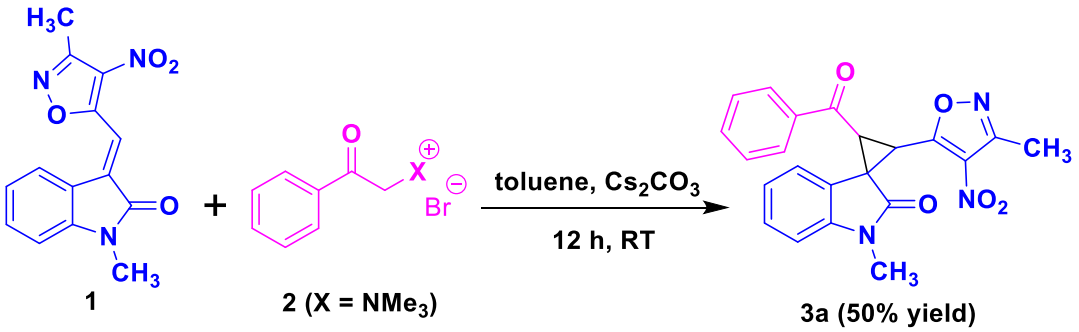
Scheme-5.18: *Synthesis of aziridinones from 3-methyl-4-nitro-5-styrylisoxazole.*

5.2 Present study

Considering the importance of small ring molecules (cyclopropanes, epoxides and aziridines) and their synthetic utility in various organic transformations, herein we described metal-free base mediated efficient construction of functionalized spirocyclopropanes using onium ylides (ammonium or sulfur) with oxindole or barbiturate olefins *via* 1,4/1,6-Micheal addition and nucleophilic substitution as key steps at room temperature afforded good yields for 4 to 5h.



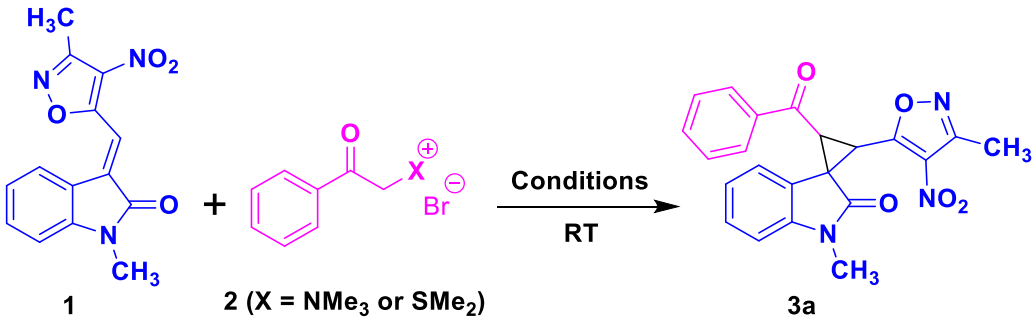
5.3 Results and Discussion



Scheme-5.19: Synthesis of spirocyclopropane oxindole using onium ylide.

We started our investigation by subjecting 3-methyl-4-nitro-5-isatylidenyl-isoxazole (**1**) with stabilized acetophenone-based ammonium salt (**2a**) in presence of 1.0 equiv of Cs_2CO_3 at room temperature was initially outlined. To our delight, the reaction proceeded smoothly and gave [2+1] annulation product **3a** with 50% of the yield in 12 h. (**Table 5.1; entry-1**). Encouraged by this result, we were planned to optimized the reaction conditions. For this, above experiment was done using different solvents with different bases (Cs_2CO_3, K_2CO_3, TEA, DBU and *t*-BuOK) as the results are summarized in (**Table-5.1; entries 1–16**). Lowering the amount of Cs_2CO_3 (0.5 equiv) resulted in reducing the yield of the product **3a** (**Table-5.1**; **entry-5**). Afterwards, the effect of solvents on the [2+1] annulation (*via* 1,4/1,6-Michael addition reaction) was investigated (**Table-5.1; entries 6-17**). Among screened conditions, it was observed that the toluene was proved to be the best solvent and gave the desired product **3a** in highest yield (**Table-5.1; entry-13**) in 4h. However, increasing or decreasing the reaction time could not result in a higher yield of the product **3a** (**Table-5.1; entries 18-19**).

Table-5.1: **Optimization of the reaction conditions for the synthesis of 3a**[a]



Entry	X	Solvent	Base	Time (h)	%Yield [b]
1	NMe_3	CH_2Cl_2	Cs_2CO_3	12	50
2	NMe_3	CH_2Cl_2	K_2CO_3	12	20
3	NMe_3	CH_2Cl_2	TEA	12	ND
4	NMe_3	CH_2Cl_2	DBU	12	trace
5	NMe_3	CH_2Cl_2	Cs_2CO_3	12	35[c]
6	NMe_3	$CHCl_3$	Cs_2CO_3	12	40
7	NMe_3	EtOH	Cs_2CO_3	12	ND
8	NMe_3	CH_3CN	K_2CO_3	12	30
9	NMe_3	CH_3CN	Cs_2CO_3	12	15
10	NMe_3	THF	K_2CO_3	12	20
11	NMe_3	THF	Cs_2CO_3	12	60
12	NMe_3	Et_2O	Cs_2CO_3	12	ND
13	**NMe_3**	**toluene**	**Cs_2CO_3**	**4**	**80**
14	NMe_3	toluene	K_2CO_3	12	30
15	NMe_3	toluene	^tBuOk	12	25
16	NMe_3	toluene	KOH	12	ND
17	NMe_3	toluene	TEA	12	ND
18	NMe_3	toluene	Cs_2CO_3	12	65
19	NMe_3	toluene	Cs_2CO_3	1	40
20	**SMe_2**	**toluene**	**Cs_2CO_3**	**4**	**78**
21	SMe_2	CH_2Cl_2	Cs_2CO_3	12	40
22	SMe_2	$CHCl_3$	Cs_2CO_3	12	25

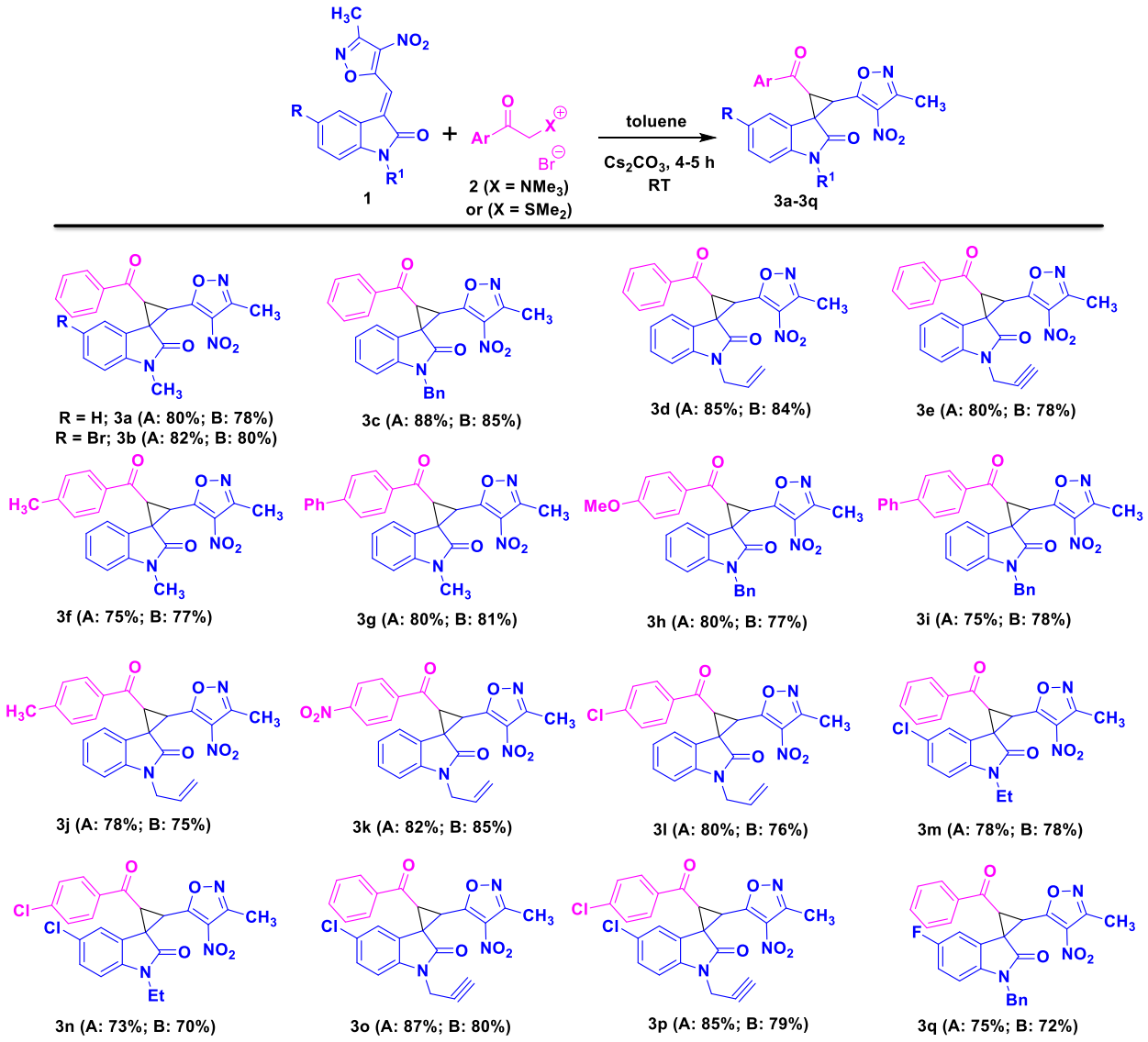
[a]All the reactions were performed with **1a** (0.32 mmol) and **2** (0.32 mmol) and base (1 equiv) in 4 mL of solvent. [b]Isolated yields. All reactions performed at room temperature. [c]Base (0.5 equiv).

The optimized reaction conditions [styrene **1a** (0.32 mmol), ammonium salt **2a** (0.32 mmol), 1.0 equiv of Cs_2CO_3 in 4 mL of toluene at room temperature] were applicable to the formal [2+1] annulation. Firstly, it was found that a variety of substituted isatins (Substitution on aromatic and nitrogen) with different ammonium ylides (electron withdrawing, donating and other substituted patterns on phenyl ring) were found to be suitable substrates for the formal [2+1] annulation, gave the desired products **3a**-**3q** in good yields (**Scheme-5.20;** 73-88% yields) for 4 to

5 h. In a next attempt, we used the sulfonium salt **2b** for this reaction (**Table-5.1; entries 20–22**) under optimized condition. Noteworthy, a similar outcome as for the ammonium salt **2a** was observed in presence toluene with Cs_2CO_3 conditions. In this case also the spirocyclopropane oxindoles were obtained in 4 to 5 h with good yields upto 85%. All newly synthesized compounds further confirmed by ^1H and ^{13}C NMR and Mass spectrometric analysis and the structure of the compound (**3c**) was also confirmed by single crystal X-ray diffraction analysis (**Figure-5.2**). ^1H NMR spectrum of the product **3a** which showed two doublets in the aliphatic region, the first one at 4.14 (d, *J* = 8.0 Hz, 1H), and the second one at 4.35 (d, *J* = 8.0 Hz, 1H). The observed HRMS mass m/z of **3a** is 404.1253 (M+1) is further confirmed the formation of the desired products.

Keeping in view of above all, considering the medicinal importance of the spiro-barbiturates and cyclopropanes. Next, we shifted our attention towards the synthesis of barbiturated-cyclopropanes using onium ylides **2** with barbiturate olefins **4**. In this case also the cyclopropanation products **5a** was obtained in 75% yield under similar optimized reaction condition. Experiments that probed the generality of the cyclopropanations were also performed. As summarized in **Scheme-5.21**, the reaction displays a broad scope for onium or sulfonium salts **2** and barbiturate olefins **4**, and in moderate to good yields are achieved. ^1H NMR spectrum of the product **5b** which showed two doublets in the aliphatic region, the first one at 4.23 (d, *J* = 9.2 Hz, 1H), the second one at 4.08 (d, *J* = 9.2 Hz, 1H) and two characteristic methyl protons (barbituric acid) appear at 3.26 (s, 3H), 3.18 (s, 3H) respectively.

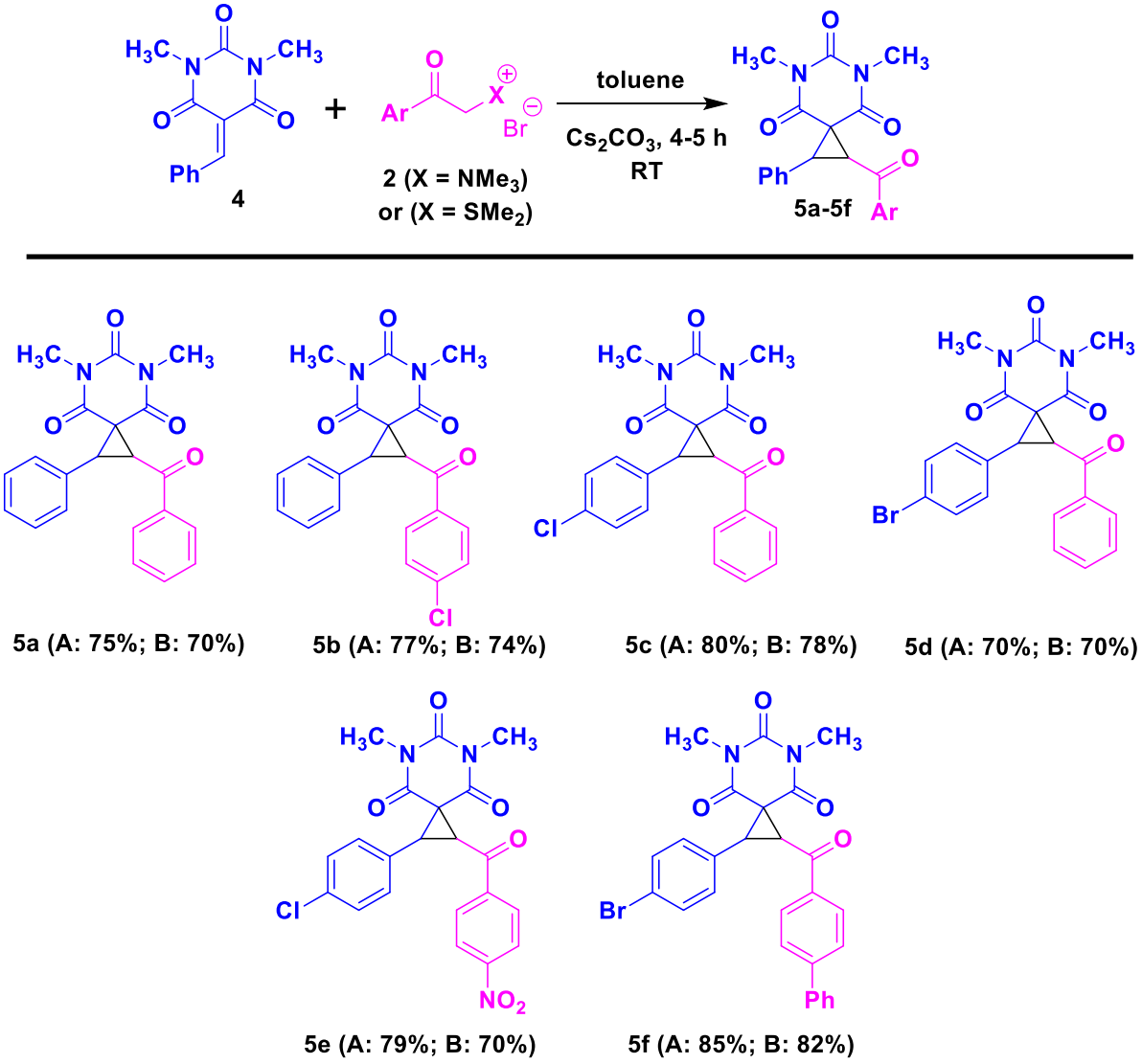
To evaluate the synthetic potential of this methodology, a gram scale reaction of **3k** carried out. **1** (1g, 3.2 mmol) reacted with onium ylide **2a** (0.97g, 3.2 mmol) smoothly, affording the desired product **3k** with 75% of the yield (1.14 g) (**Scheme-5.22**). Furthermore, treating the product **3k** with $NaBH_4$ in DCM: EtOH (1:1) at 0 ^oC to RT accessed **6k** in 90% of the yield for 30 min (**Scheme-5.23**).



Scheme-5.20: *Synthesis of isoxazole-spirocyclopropanes (**3a-3q**).*

Based on our experimental results and the related literature, a plausible reaction mechanism has been proposed (**Figure-5.3**) for the formal cyclopropanation reaction. Under basic condition onium ylide or sulfur ylide undergo facile deprotonation to generate carbanion ion, this will further react with isoxazole oxindole styerene **1** *via* Michael addition (1,4 or 1,6) reaction to afford intermediate (**I** or **III**). Then, the formal [2+1] annulation product **3** was obtained by the intramolecular nucleophilic substitution (**SN2**) cyclization and followed by elimination of trimethylamine or dimethyl sulfide. The similar mechanism also occurs in case of barbiturate olefins with onium ylides or sulfur ylides *via* 1,4-Michael addition, then followed by

intramolecular nucleophilic substitution (S_N2) cyclization with the leaving of trimethylamine or dimethyl sulfide to deliver corresponding spirocyclopropyl barbiturates (**Figure-5.3**).



Scheme-5.21: *Synthesis of spirocyclopropyl barbiturates (**5a-5f**).*

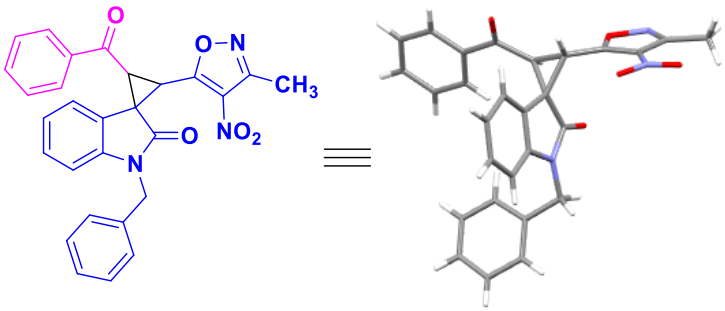
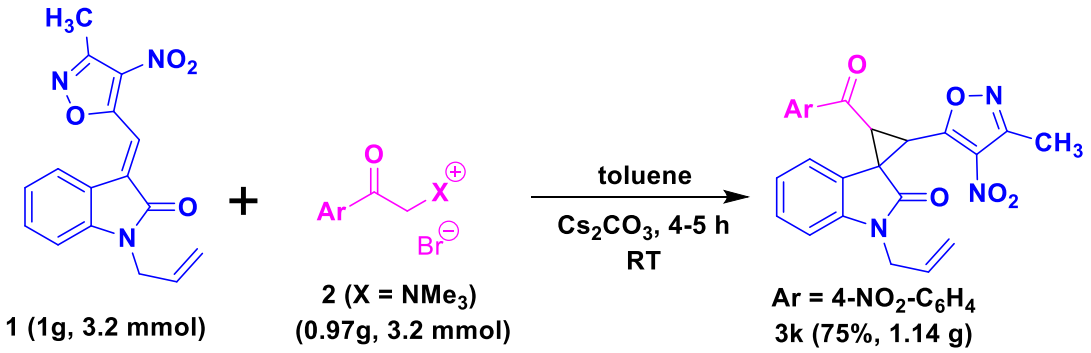
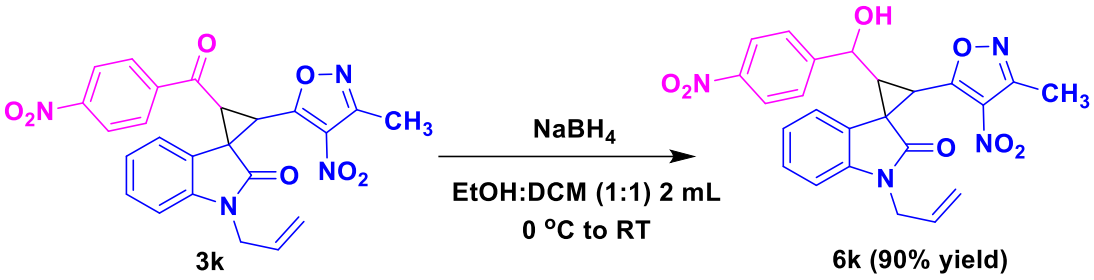


Figure-5.2: *X-ray crystallography of the compound **3c**.*



Scheme-5.22: *Gram scale reaction*



Scheme-5.23: *Reduction of spirocyclopropyl moiety* ***3k****.*

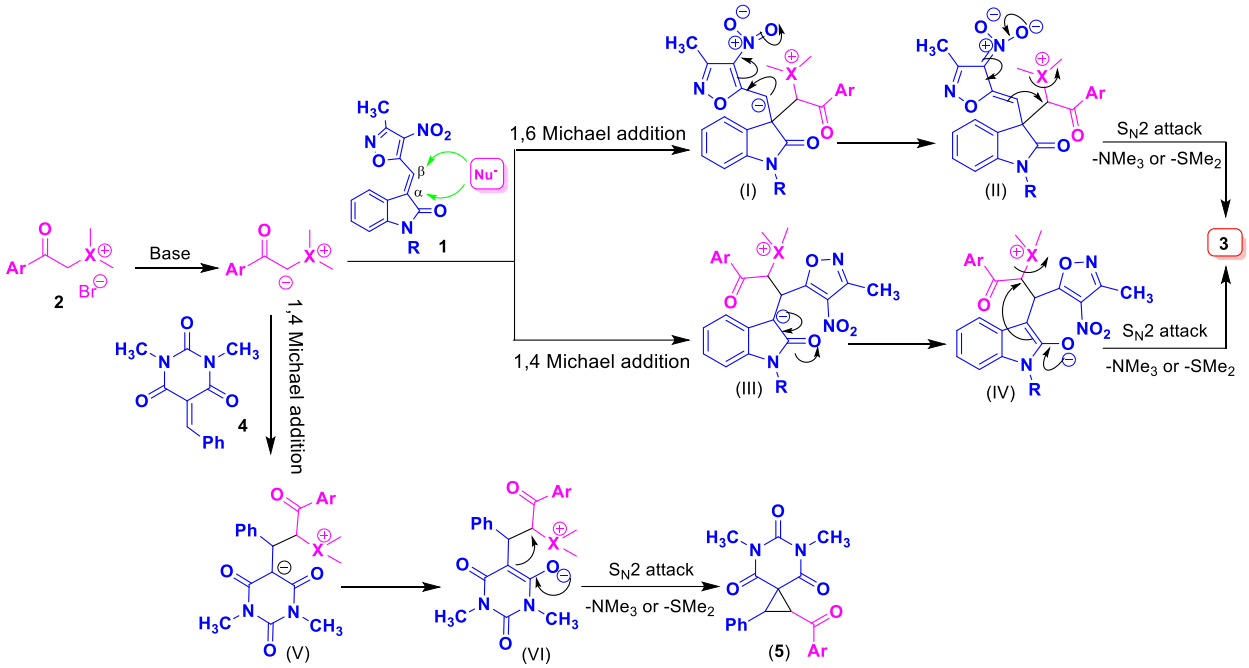


Figure-5.3: *Plausible mechanism for the reaction.*

5.4 Conclusion

In conclusion, we have developed a convenient and efficient method for the construction of highly functionalized oxindole/barbiturate-based cyclopropanes using ammonium or sulfur ylides (**2**) with styrenes (**1** or **4**) under basic condition in moderate to good yields *via* Michael/substitution cyclization reaction and it can be scaled up to gram synthesis. Currently, we are extending the newly synthesized cyclopropanes further convert into useful synthons and their biological evaluation is under process in our laboratory.

5.5 Experimental

5.5.1 General procedure

General procedure for the synthesis of spirocyclopropanes:

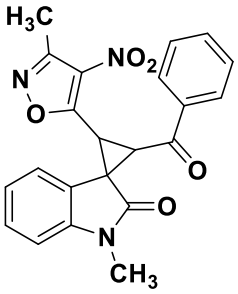
A mixture of styrene **1** or **4** (0.2 mmol) with onium ylide 2 (0.2 mmol, 1.0 equiv) in toluene (4 mL) was added Cs_2CO_3 (0.2 mmol, 1.0 equiv). The mixture was stirred at room temperature until the reaction was complete as observed by TLC analysis. Then the solution was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to afford compounds **3** or **5**, which were dried under vacuum and further analyzed by ^{1}H NMR, ^{13}C NMR and highresolution mass spectrometry.

5.5.2 Synthetic transformation of 6k:

To a stirred solution of **3k** in DCM : EtOH (1:1; 2mL) was added $NaBH_4$ in one portion at 0^oC. Then the reaction mixture was continued to stir at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was treated with water and extracted with EtOAc (2X10 mL). The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Evaporation of the solvent gave the crude product which was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product (**6k**).

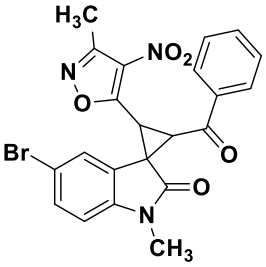
5.6 Spectral Data

2-benzoyl-1'-methyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3a):



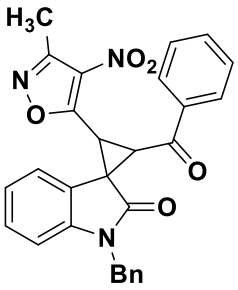
Yield = A: 80%; B: 78% (White solid); M.P: 187-188 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.87 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.19 (m, 2H), 6.96 (td, *J* = 7.6, 0.8 Hz, 1H)), 6.81 (d, *J* = 8.4 Hz, 1H), 4.35 (d, *J* = 8.0 Hz, 1H), 4.14 (d, *J* = 8.0 Hz, 1H), 3.17 (s, 3H), 2.51 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.95, 171.11, 167.91, 155.87, 144.14, 136.28, 134.21, 132.01, 128.92, 128.85, 128.64, 123.36, 123.04, 122.56, 108.66, 40.65, 38.32, 28.18, 26.87, 11.68. **Mass (ESI-MS):** m/z Calculated: 403.1168; Observed: 404.1257 (M+1).

2-benzoyl-5'-bromo-1'-methyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3b):



Yield = A: 82%; B: 80% (White solid); M.P: 243-244 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.92 – 7.88 (m, 2H), 7.56 – 7.51 (m, 1H), 7.43 – 7.33 (m, 4H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.35 (d, *J* = 8.0 Hz, 1H), 4.09 (d, *J* = 7.6 Hz, 1H), 3.14 (s, 3H), 2.51 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.66, 170.64, 167.44, 155.90, 143.24, 136.16, 134.40, 131.92, 131.77, 128.99, 128.73, 125.93, 125.39, 115.83, 109.98, 40.25, 38.34, 28.58, 26.96, 11.63. **Mass (ESI-MS):** m/z Calculated: 481.0273; Observed: 483.0259 (M+1).

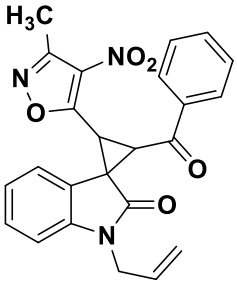
2-benzoyl-1'-benzyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3c):



Yield = A: 88%; B: 85% (White solid); M.P: 195-196 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.98 – 7.94 (m, 2H), 7.63 – 7.57 (m, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.27 – 7.26 (m, 1H), 7.23 – 7.17 (m, 3H), 7.63 – 7.57 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.96 (q, *J* = 16 Hz, 2H), 4.48 (d, *J* = 7.6 Hz, 1H), 4.27 (d, *J* = 7.6 Hz, 1H), 2.61 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.85, 171.39, 167.95, 155.87, 143.20, 136.24, 135.25, 134.24, 131.97, 128.92, 128.90, 128.80, 128.60, 127.77, 126.89, 123.29, 123.09, 122.49, 109.68, 44.22,

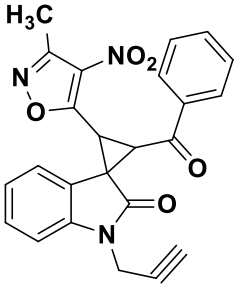
40.46, 38.84, 28.13, 11.66. **Mass (ESI-MS):** m/z Calculated: 479.1481; Observed: 480.1569 (M+1).

1'-allyl-2-benzoyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3d):



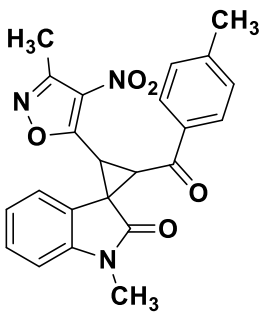
Yield = A: 85%; B: 84% (White solid); M.P: 165-166 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.97 (d, *J* = 9.5 Hz, 6H), 7.64 – 7.57 (m, 3H), 7.47 (t, *J* = 7.8 Hz, 6H), 7.37 – 7.31 (m, 6H), 7.10 (ddd, *J* = 15.3, 8.6, 4.2 Hz, 6H), 4.60 (dd, *J* = 17.7, 2.5 Hz, 3H), 4.47 (dd, *J* = 13.8, 3.9 Hz, 4H), 4.46 – 4.43 (m, 4H), 4.24 (d, *J* = 7.8 Hz, 3H), 2.60 (s, 9H), 2.27 (t, *J* = 2.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.89, 170.93, 167.91, 155.85, 143.30, 136.26, 134.23, 131.92, 130.78, 128.92, 128.76, 128.62, 123.31, 123.00, 122.55, 117.55, 109.57, 42.79, 40.46, 38.56, 28.15, 11.65. **Mass (ESI-MS):** m/z Calculated: 429.1325; Observed: 430.1389 (M+1).

2-benzoyl-3-(3-methyl-4-nitroisoxazol-5-yl)-1'-(prop-2-yn-1-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3e):



Yield = A: 80%; B: 78% (White solid); M.P: 200-201 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.00 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.30 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.58 (dd, *J* = 17.7, 2.5 Hz, 1H), 4.48 – 4.41 (m, 2H), 4.20 (d, *J* = 7.8 Hz, 1H), 2.61 (s, 3H), 2.29 (t, *J* = 2.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.69, 170.40, 167.63, 155.89, 142.25, 136.22, 134.27, 131.96, 128.94, 128.86, 128.65, 123.41, 123.26, 122.68, 109.65, 76.28, 72.76, 40.52, 38.58, 29.88, 28.38, 11.64. **Mass (ESI-MS):** m/z Calculated: 427.1168; Observed: 428.1253 (M+1).

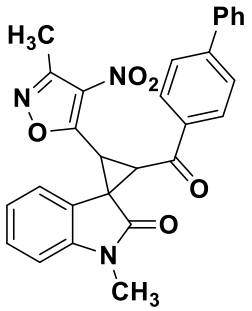
1'-methyl-2-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-methylbenzoyl)spiro[cyclopropane-1,3'-indolin]-2'-one (3f):



Yield = A: 75%; B: 77% (White solid); M.P: 198-199 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.78 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.94 (td, *J* = 8.0, 1.2 Hz, 1H), 6.81 – 6.77 (m, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 4.12 (d, *J* = 7.6 Hz, 1H), 3.16 (s, 3H), 2.50 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.38, 171.19, 168.03, 155.85,

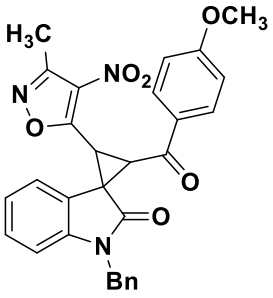
145.36, 144.12, 133.87, 131.89, 129.59, 128.78, 123.46, 123.01, 122.55, 108.60, 40.53, 38.29, 28.14, 26.84, 21.74, 11.67. **Mass (ESI-MS):** m/z Calculated: 417.1325; Observed: 418.1400 (M+1).

2-([1,1'-biphenyl]-4-carbonyl)-1'-methyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3g):



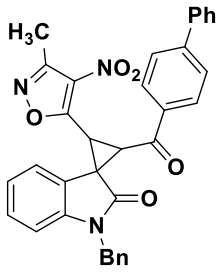
Yield = A: 80%; B: 81% (White solid); M.P: 200-201 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.95 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.28 (m, 1H), 7.26 – 7.19 (m, 2H), 6.99 – 6.92 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H), 4.15 (d, *J* = 7.6 Hz, 1H), 3.17 (s, 3H), 2.50 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.42, 171.16, 167.95, 155.88, 146.95, 144.16, 139.48, 134.95, 131.91, 129.26, 129.02, 128.86, 128.53, 127.52, 127.29, 123.40, 123.06, 122.58, 108.67, 40.67, 38.39, 28.20, 26.88, 11.67. **Mass (ESI-MS):** m/z Calculated: 479.1481; Observed: 480.1570 (M+1).

1'-benzyl-2-(4-methoxybenzoyl)-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3h):



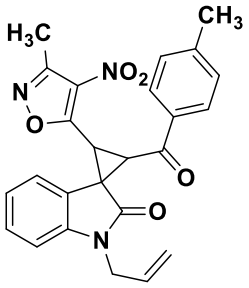
Yield = A: 80%; B: 77% (Light yellow solid); M.P: 205-206 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.79 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.19 (m, 3H), 7.16 – 7.09 (m, 4H), 6.91 (td, *J* = 7.6, 0.8 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.93 – 4.80 (m, 2H), 4.31 (d, *J* = 7.6 Hz, 1H), 4.15 (d, *J* = 7.6 Hz, 1H), 3.41 (s, 3H), 2.51 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 189.75, 171.26, 167.72, 155.89, 143.21, 140.93, 135.20, 134.53, 132.00, 129.93, 129.30, 128.94, 128.92, 127.84, 126.91, 123.12, 123.08, 122.38, 109.76, 50.88, 44.26, 40.45, 38.71, 28.12, 11.63. **Mass (ESI-MS):** m/z Calculated: 509.1587; Observed: 510.1573 (M+1).

2-([1,1'-biphenyl]-4-carbonyl)-1'-benzyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3i)



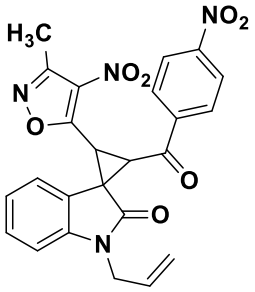
Yield = A: 75%; B: 78% (White solid); M.P: 192-194 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.93 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.24 – 7.07 (m, 7H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.94 – 4.81 (m, 2H), 4.41 (d, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 7.6 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.33, 171.44, 168.00, 155.88, 146.99, 143.23, 139.50, 135.27, 134.93, 132.00, 129.22, 129.04, 128.91, 128.81, 128.55, 127.78, 127.54, 127.30, 126.91, 123.36, 123.11, 122.54, 109.69, 44.24, 40.50, 38.89, 28.19, 11.66. **Mass (ESI-MS):** m/z Calculated: 555.1794; Observed: 556.1878 (M+1).

1'-allyl-2-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-methylbenzoyl)spiro[cyclopropane-1,3'-indolin]-2'-one (3j):



Yield = A: 78%; B: 75% (Light yellow solid); M.P: 152-153 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.87 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.23 (m, 4H), 7.03 (td, *J* = 7.6, 0.8 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.88 – 5.74 (m, 1H), 5.27 – 5.12 (m, 2H), 4.46 – 4.38 (m, 2H), 4.37 – 4.29 (m, 1H), 4.22 (d, *J* = 8.0 Hz, 1H), 2.60 (s, 3H), 2.41 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.31, 171.02, 168.03, 155.83, 145.39, 143.27, 133.85, 131.89, 130.81, 129.60, 128.75, 128.67, 123.40, 122.97, 122.53, 117.50, 109.51, 42.76, 40.34, 38.54, 28.09, 21.74, 11.64. **Mass (ESI-MS):** m/z Calculated: 443.1481; Observed: 444.1569 (M+1).

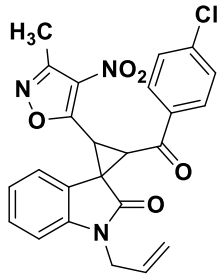
1'-allyl-2-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-nitrobenzoyl)spiro[cyclopropane-1,3'-indolin]-2'-one (3k):



Yield = A: 82%; B: 85% (Yellow solid); M.P: 174-175 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.31 (d, *J* = 9.2 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.08 – 7.02 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.88 – 5.76 (m, 1H), 5.27 – 5.13 (m, 2H), 4.49 – 4.42 (m, 1H), 4.40 (d, *J* = 7.6 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.23 (d, *J* = 7.6 Hz, 1H), 2.61 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 189.96, 170.54, 167.24, 155.93, 150.89, 143.37, 140.41, 131.99, 130.63, 129.62, 129.18,

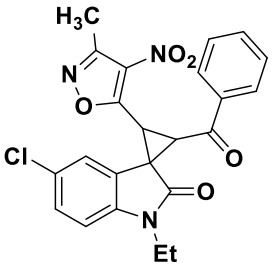
124.14, 123.13, 122.69, 122.36, 117.79, 109.84, 42.90, 40.81, 38.74, 28.28, 11.61. **Mass (ESI-MS):** m/z Calculated: 474.1175; Observed: 475.1267 (M+1).

1'-allyl-2-(4-chlorobenzoyl)-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3l):



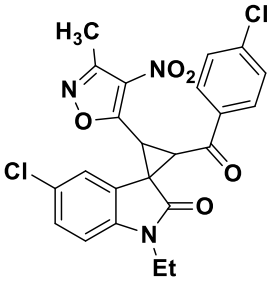
Yield = A: 80%; B: 76%; **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.90 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.06 – 7.01 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.88 – 5.74 (m, 1H), 5.27 - 5. 10(m, 2H), 4.46 – 4.39 (m, 1H), 4.37 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.29 (m, 1H), 4.21 (d, *J* = 8.0 Hz, 1H), 2.60 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 189.79, 170.81, 167.69, 155.88, 143.30, 140.94, 134.54, 131.99, 130.72, 129.96, 129.30, 128.90, 123.08, 123.04, 122.43, 117.62, 109.66, 42.82, 40.45, 38.43, 28.13, 11.64. **Mass (ESI-MS):** m/z Calculated: 463.0935; Observed: 464.1017 (M+1).

2-benzoyl-5'-chloro-1'-ethyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3m):



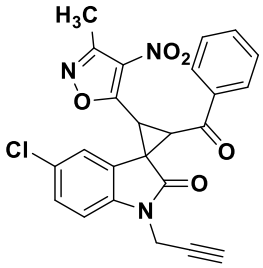
Yield = A: 78%; B: 78% (White solid); M.P: 185-186 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 8.01 – 7.98 (m, 2H), 7.65 – 7.60 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.41 (d, *J* = 7.6 Hz, 1H), 4.15 (d, *J* = 7.6 Hz, 1H), 3.89 – 3.78 (m, 1H), 3.77 – 3.66 (m, 1H), 2.61 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 189.66, 170.24, 167.32, 155.88, 141.81, 141.11, 134.46, 131.90, 130.06, 129.36, 128.92, 128.37, 125.11, 123.29, 109.73, 40.26, 38.25, 35.55, 28.44, 12.50, 11.62. **Mass (ESI-MS):** m/z Calculated: 451.0935; Observed: 452.1016 (M+1).

5'-chloro-2-(4-chlorobenzoyl)-1'-ethyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3n):



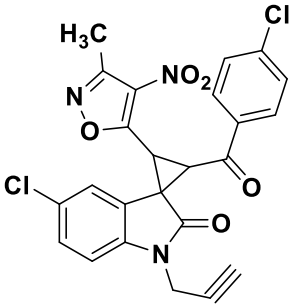
Yield = A: 73%; B: 70% (Light yellow solid); M.P: 199-200 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 8.01 – 7.98 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.41 (d, *J* = 7.7 Hz, 1H), 4.15 (d, *J* = 7.7 Hz, 1H), 3.83 (dq, *J* = 14.5, 7.2 Hz, 1H), 3.72 (dq, *J* = 14.3, 7.2 Hz, 1H), 2.61 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 189.66, 170.24, 167.32, 155.88, 141.81, 141.11, 134.46, 131.90, 130.06, 129.36, 128.92, 128.37, 125.11, 123.29, 109.73, 40.26, 38.25, 35.55, 28.44, 12.50, 11.62. **Mass (ESI-MS):** m/z Calculated: 485.0545; Observed: 486.0622 (M+1).

2-benzoyl-5'-chloro-3-(3-methyl-4-nitroisoxazol-5-yl)-1'-(prop-2-yn-1-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3o):



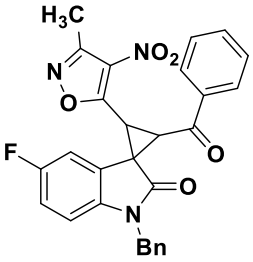
Yield = A: 87%; B: 80% (White solid); M.P: 188-189 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 8.00 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.39 – 7.30 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.58 (dd, *J* = 18.0, 2.4 Hz, 1H), 4.48 – 4.41 (m, 2H), 4.20 (d, *J* = 8.0 Hz, 1H), 2.61 (s, 3H), 2.29 (t, *J* = 2.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 190.50, 169.99, 167.19, 155.92, 140.82, 136.09, 134.47, 131.98, 129.02, 128.90, 128.75, 124.97, 123.36, 110.60, 75.84, 73.13, 40.24, 38.51, 29.99, 28.79, 11.63. **Mass (ESI-MS):** m/z Calculated: 461.0778; Observed: 462.0860 (M+1).

5'-chloro-2-(4-chlorobenzoyl)-3-(3-methyl-4-nitroisoxazol-5-yl)-1'-(prop-2-yn-1-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3p):



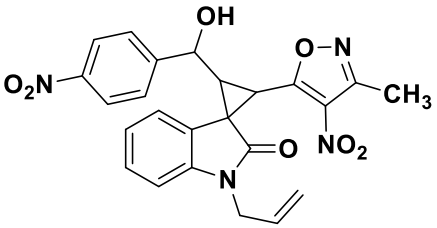
Yield = A: 85%; B: 79% **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.94 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.08 – 7.04 (m, 1H), 4.58 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.47 – 4.37 (m, 2H), 4.18 (d, *J* = 7.6 Hz, 1H), 2.60 (s, 3H), 2.29 (t, *J* = 2.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$) δ** 189.42, 169.87, 166.97, 155.95, 141.22, 140.81, 134.36, 132.01, 130.09, 129.40, 129.06, 129.02, 124.75, 123.27, 110.69, 75.79, 73.19, 40.24, 38.40, 30.01, 28.77, 11.62. **Mass (ESI-MS):** m/z Calculated: 495.0389; Observed: 496.0453 (M+1).

2-benzoyl-1'-benzyl-5'-fluoro-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3q):



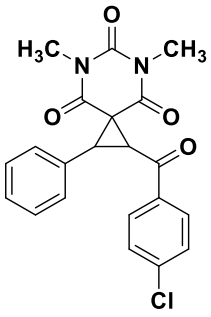
Yield = A: 75%; B: 72% (White solid); M.P: 189-190 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.96 (d, *J* = 6.8 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.28 – 7.25 (m, 1H), 7.24 – 7.16 (m, 3H), 7.04 – 6.98 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 5.02 – 4.91 (m, 2H), 4.47 (d, *J* = 7.6 Hz, 1H), 4.27 (d, *J* = 7.6 Hz, 1H), 2.61 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.61, 171.16, 167.59, 155.89, 139.18, 136.13, 134.91, 134.42, 132.02, 129.00, 128.96, 128.67, 127.89, 126.85, 124.97, 124.88, 115.36, 115.12, 111.17, 110.91, 110.27, 110.19, 44.37, 40.42, 38.72, 28.57, 11.63. **Mass (ESI-MS):** m/z Calculated: 497.1387; Observed: 498.1476 (M+1).

1'-allyl-2-(hydroxy(4-nitrophenyl) methyl)-3-(3-methyl-4-nitroisoxazol-5-yl) spiro[cyclopropane-1,3'-indolin]-2'-one (6k):



Yield = 90% (White solid); M.P: 189-190 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.17 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.66 (ddd, *J* = 22.1, 10.2, 5.1 Hz, 1H), 5.19 (d, *J* = 8.8 Hz, 1H), 5.09 (d, *J* = 10.3 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.21 (ddd, *J* = 21.7, 17.4, 5.0 Hz, 2H), 3.46 (d, *J* = 8.1 Hz, 1H), 3.08 (t, *J* = 8.5 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.73, 167.97, 155.77, 148.33, 147.86, 143.62, 131.61, 130.71, 128.83, 126.87, 124.25, 124.13, 122.83, 121.33, 117.59, 110.12, 70.75, 42.73, 40.90, 38.02, 29.62, 11.54. **Mass (ESI-MS):** m/z Calculated: 476.1332; Observed: 477.1276 (M+1).

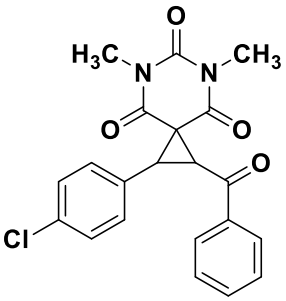
1-(4-chlorobenzoyl)-5,7-dimethyl-2-phenyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5b):



Yield = A: 77%; B: 74% (White solid); M.P: 167-169 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.91 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.39 – 7.33 (m, 5H), 4.23 (d, *J* = 9.2 Hz, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.26 (s, 3H), 3.18 (s,

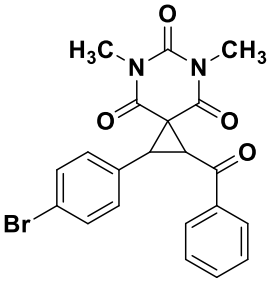
3H).**^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.25, 165.80, 163.42, 151.36, 140.31, 134.57, 130.95, 129.64, 129.59, 129.32, 128.88, 128.53, 48.01, 41.86, 40.91, 29.01, 28.97.

1-benzoyl-2-(4-chlorophenyl)-5,7-dimethyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5c):



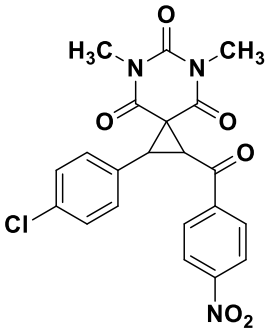
Yield = A: 80%; B: 78% (White solid); M.P: 170-172 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.94 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.34 (m, 5H), 4.22 (d, *J* = 9.2 Hz, 1H), 4.07 (d, *J* = 9.2 Hz, 1H), 3.25 (s, 3H), 3.18 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.23, 165.81, 163.43, 151.34, 140.30, 134.55, 130.96, 129.63, 129.60, 129.33, 128.89, 128.54, 48.00, 41.85, 40.93, 29.03, 28.99.

1-benzoyl-2-(4-bromophenyl)-5,7-dimethyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5d):



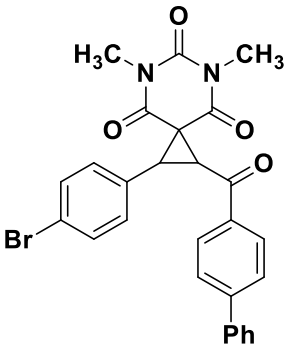
Yield = A: 70%; B: 70% (White solid); M.P: 166-168 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.87 (d, *J* = 9.6 Hz, 2H), 7.55 – 7.50 (m, 1H), 7.44 – 7.37 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.14 (d, *J* = 9.6 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 3.16 (s, 3H), 3.14 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$) δ** 206.91, 190.84, 165.53, 163.51, 151.31, 136.03, 133.90, 131.66, 131.28, 130.27, 128.98, 128.25, 123.00, 46.80, 41.53, 30.91, 29.04, 28.96. **Mass (ESI-MS):** m/z Calculated: 440.0372; Observed: 441.0460 (M+1).

1-(4-chlorophenyl)-5,7-dimethyl-2-(4-nitrobenzoyl)-5,7-diazaspiro[2.5]octane-4,6,8-trione (5e):



Yield = A: 79%; B: 70% (White solid); M.P: 207-209 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.26 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.17 (d, *J* = 9.2 Hz, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 3.17 (s, 3H), 3.14 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 206.89, 190.80, 165.51, 163.49, 151.28, 136.02, 133.88, 131.67, 131.27, 130.26, 128.97, 128.24, 123.00, 46.79, 41.55, 30.90, 29.03, 28.95. **Mass (ESI-MS):** m/z Calculated: 441.0728; Observed: 442.0713 (M+1).

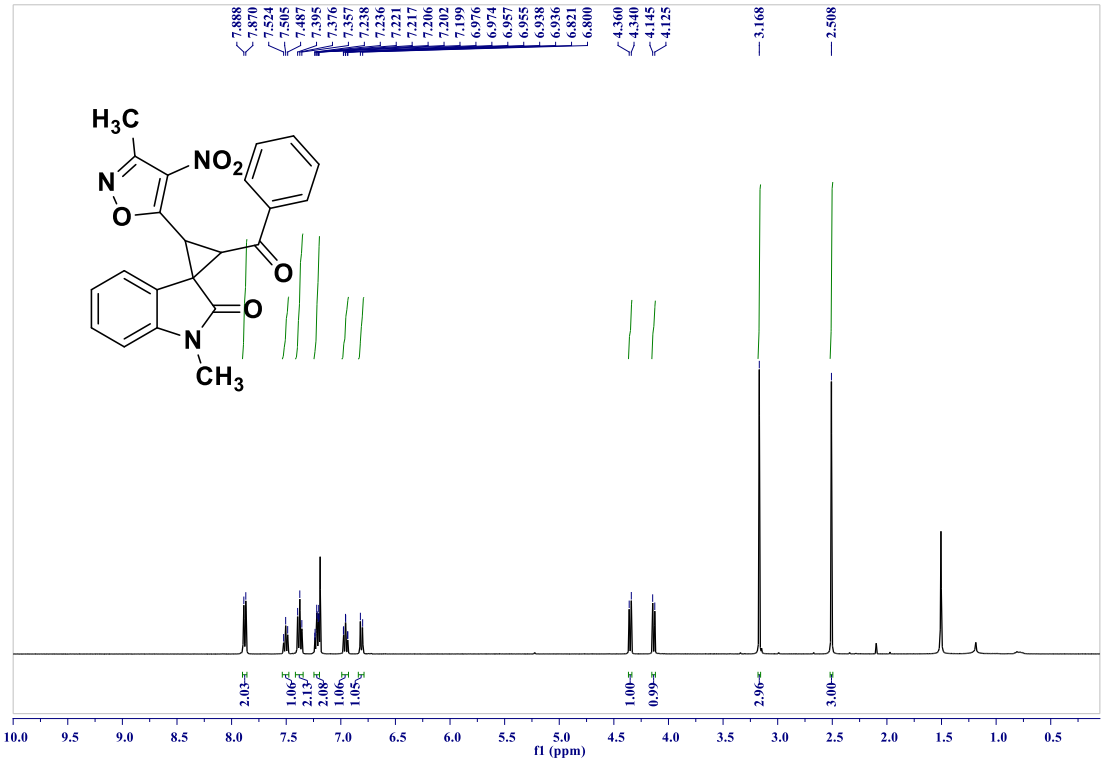
1-([1,1'-biphenyl]-4-carbonyl)-2-(4-bromophenyl)-5,7-dimethyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5f):

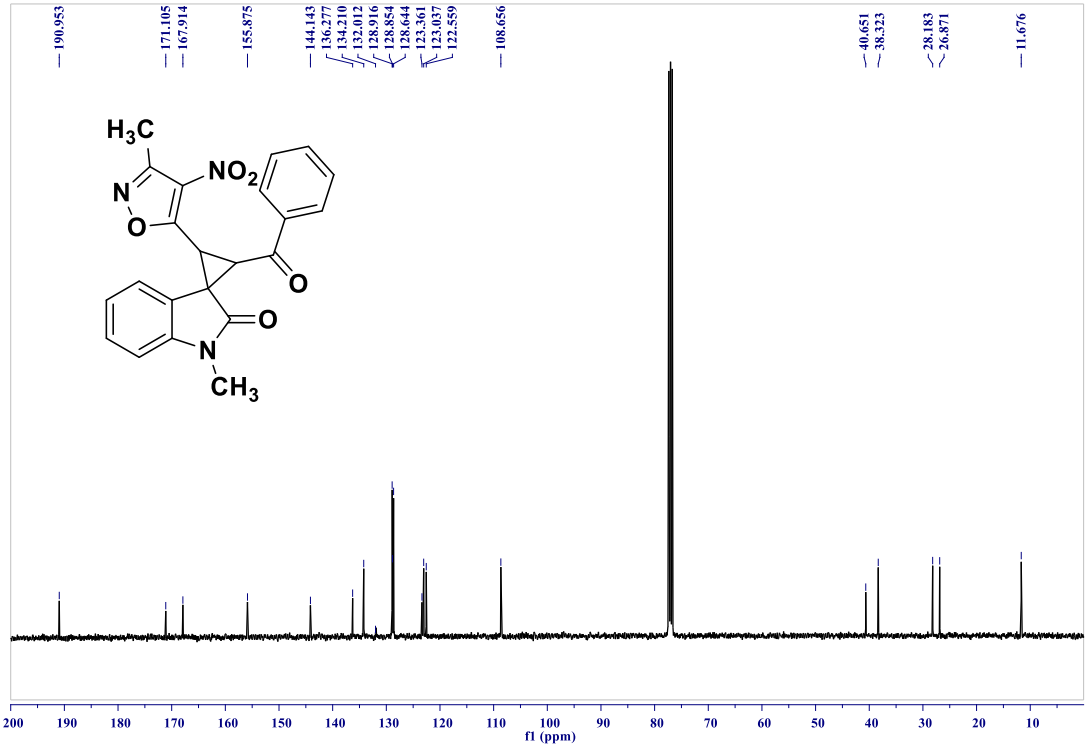


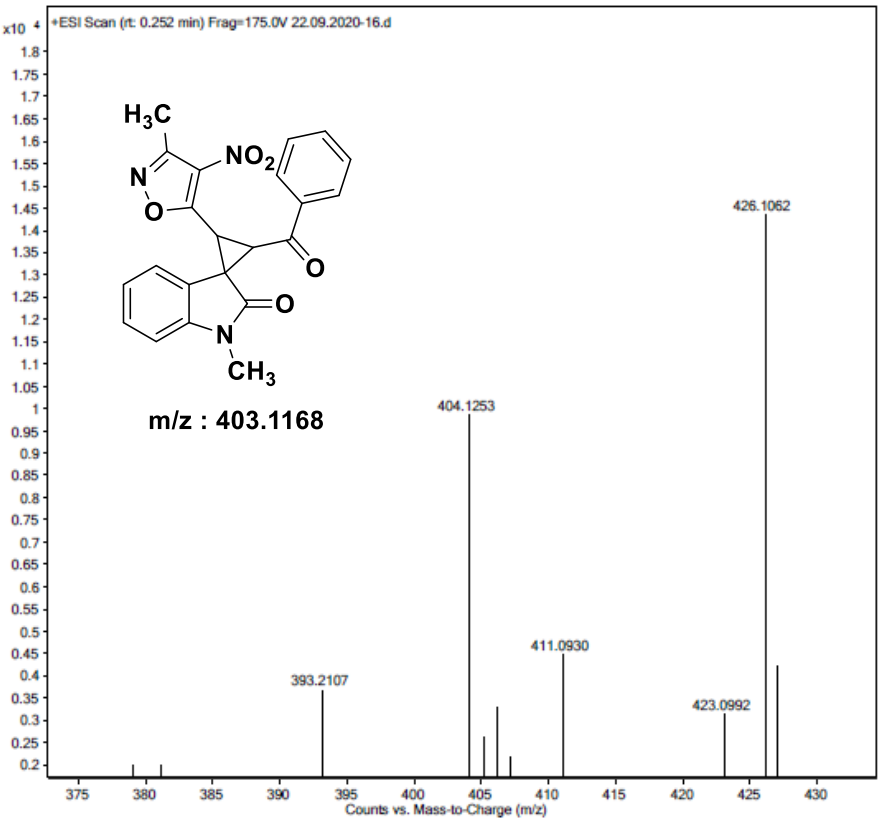
Yield = A: 85%; B: 82% (White solid); M.P: 201-203 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.94 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.36 – 7.31 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.17 (d, *J* = 9.6 Hz, 1H), 4.00 (d, *J* = 9.6 Hz, 1H), 3.18 (s, 3H), 3.15 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 190.44, 165.57, 163.55, 151.33, 146.61, 139.61, 134.74, 131.69, 131.30, 130.27, 129.02, 128.85, 128.47, 127.62, 127.28, 123.04, 46.90, 41.62, 30.92, 29.06, 29.01. **Mass (ESI-MS):** m/z Calculated: 516.0685; Observed: 517.0784 (M+1).

5.7 Selected Spectra

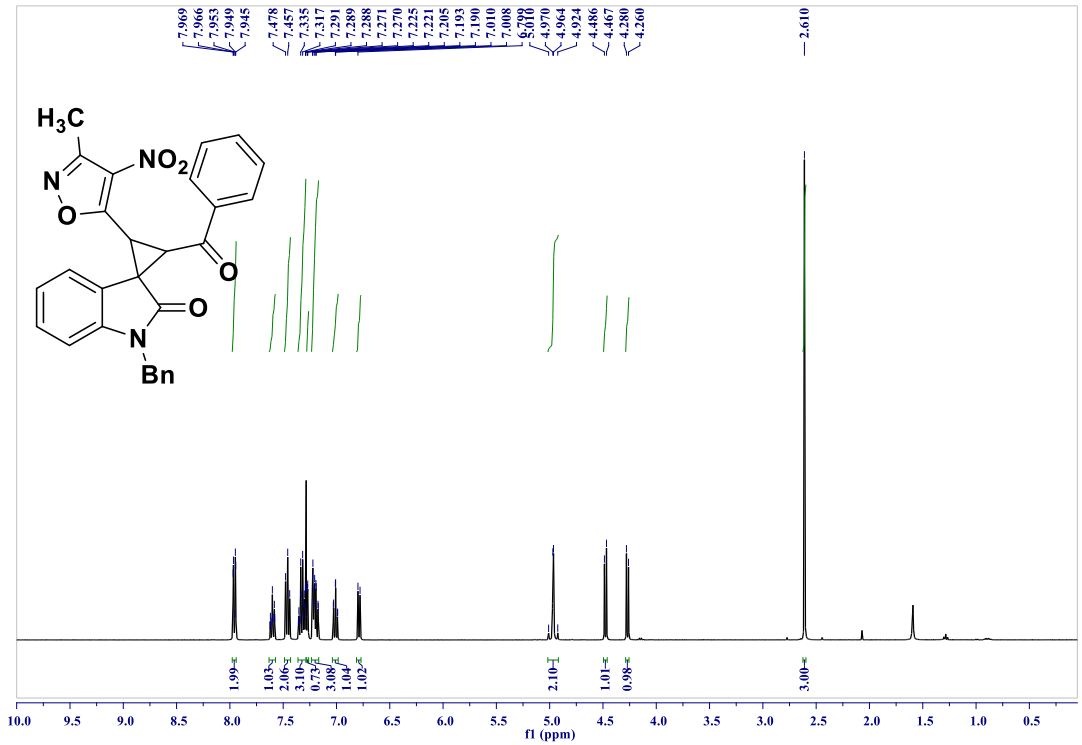
2-benzoyl-1'-methyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3a):

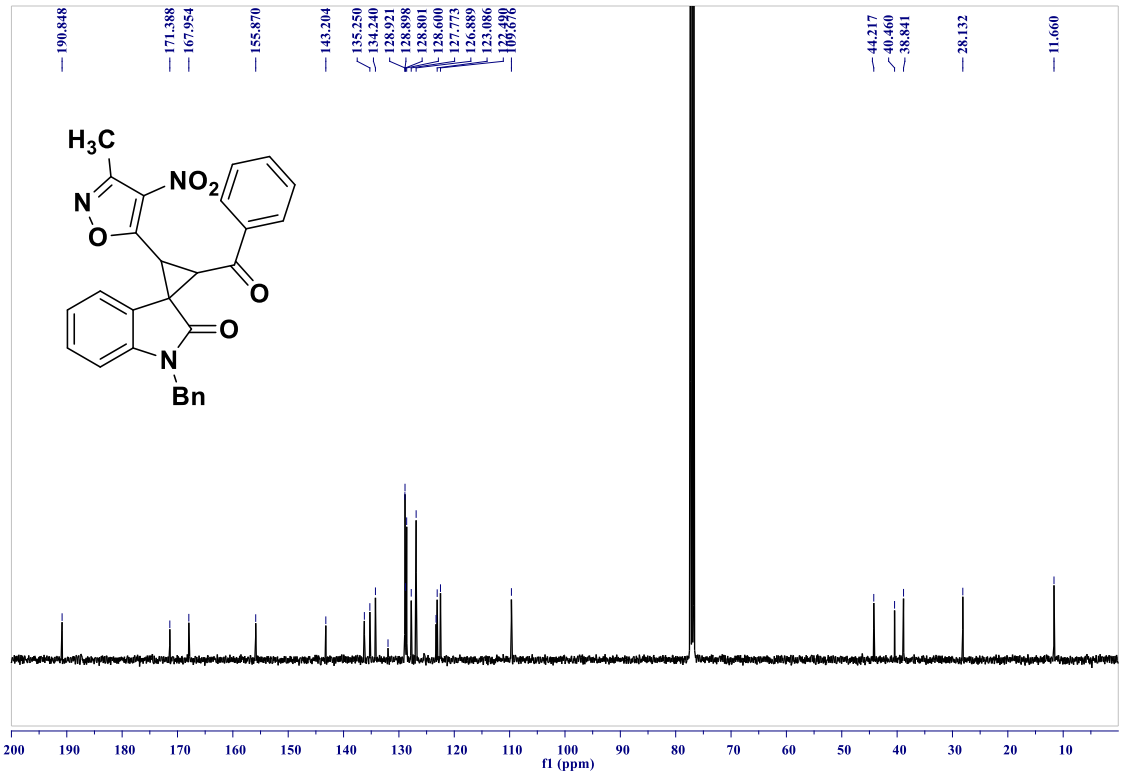


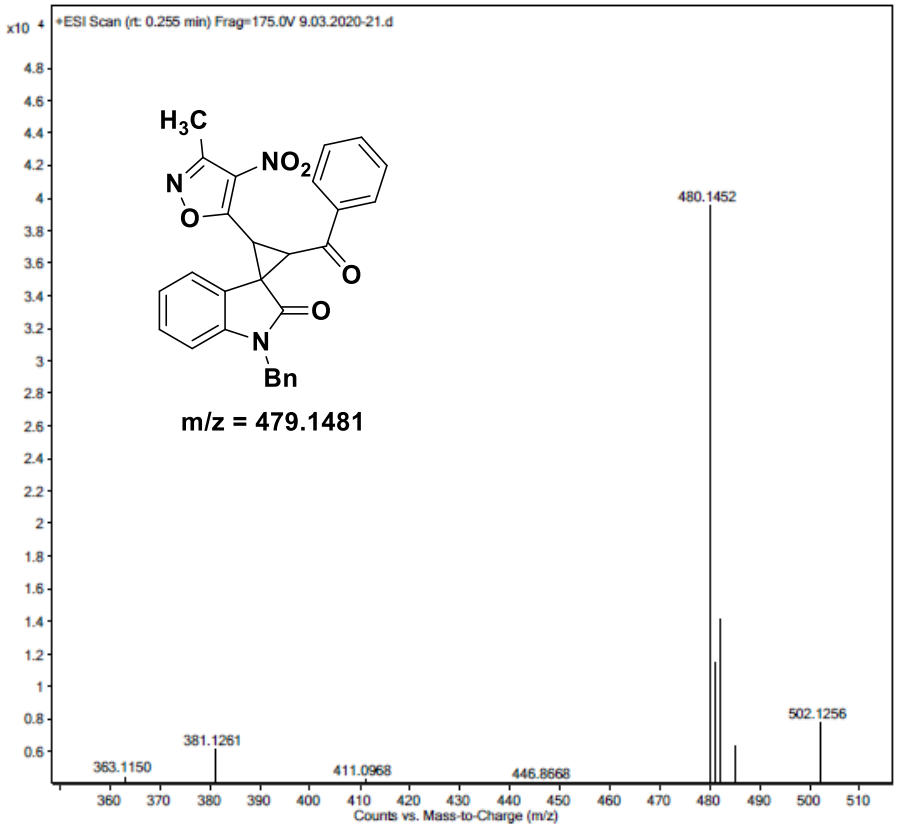




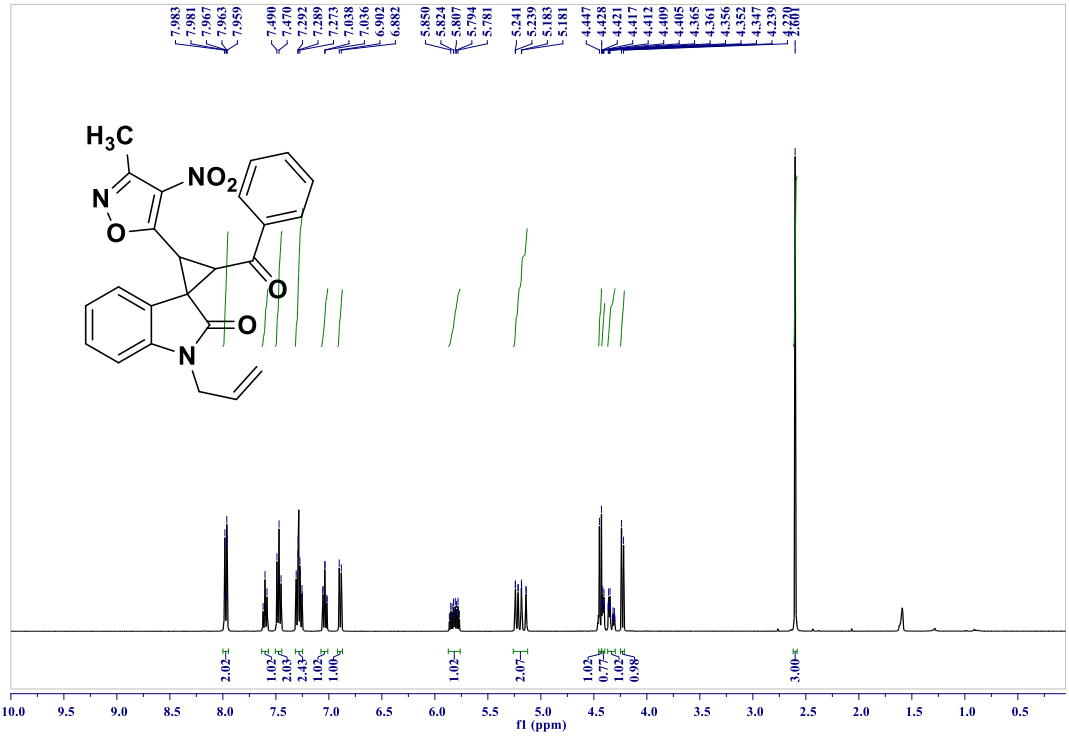
2-benzoyl-1'-benzyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3c):

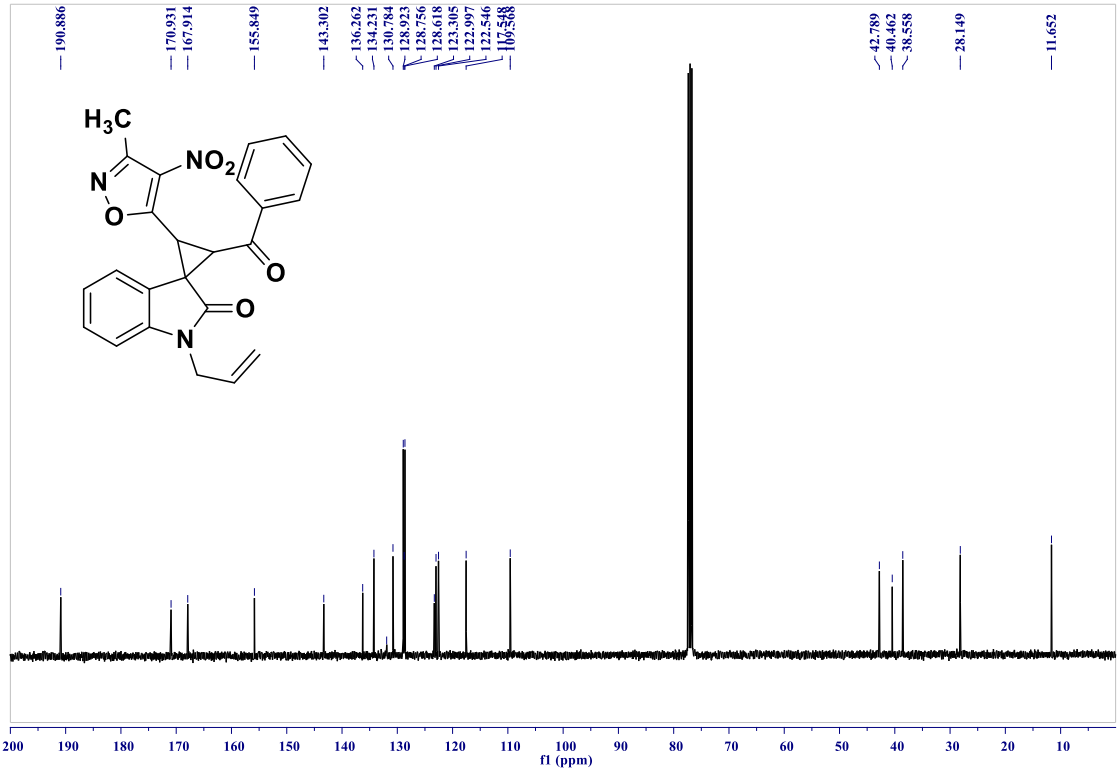

7.969
7.966
7.953
7.949
7.945
7.478
7.457
7.335
7.317
7.291
7.289
7.288
7.271
7.270
7.225
7.221
7.205
7.193
7.190
7.010
7.008
6.708
5.010
4.970
4.964
4.924
4.486
4.467
4.280
4.260
2.610
H3C
NO2
N
O
O
O
N
Bn
1.99
1.03
2.06
3.10
0.73
3.08
1.04
1.02
2.10
1.01
0.98
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

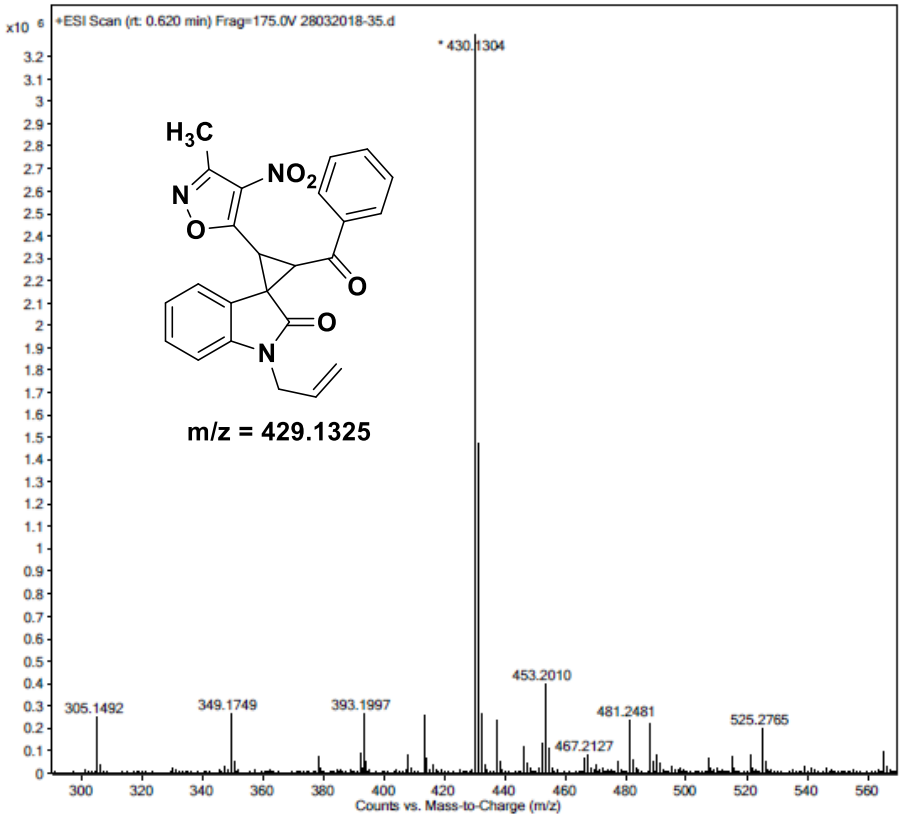

190.848
171.388
167.954
155.870
143.204
135.250
134.240
128.921
128.898
128.801
128.600
127.773
126.889
123.086
122.490
109.678
44.217
40.460
38.841
28.132
11.660
H3C
NO2
N
O
O
O
N
Bn
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)



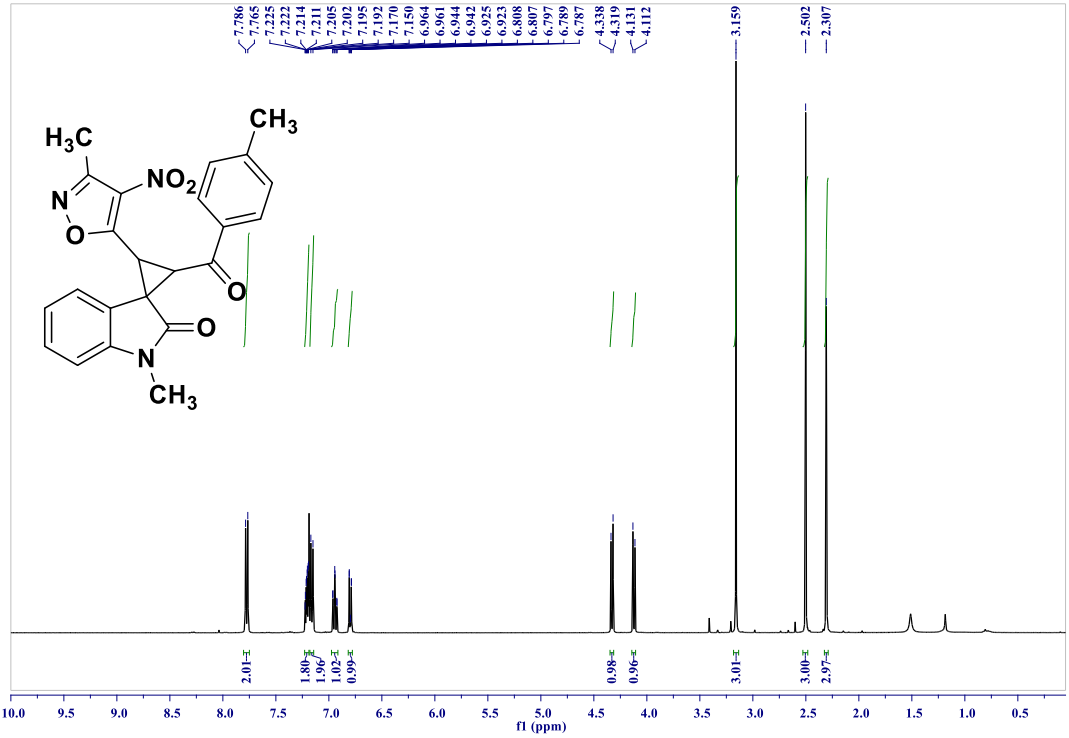
1'-allyl-2-benzoyl-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (3d):

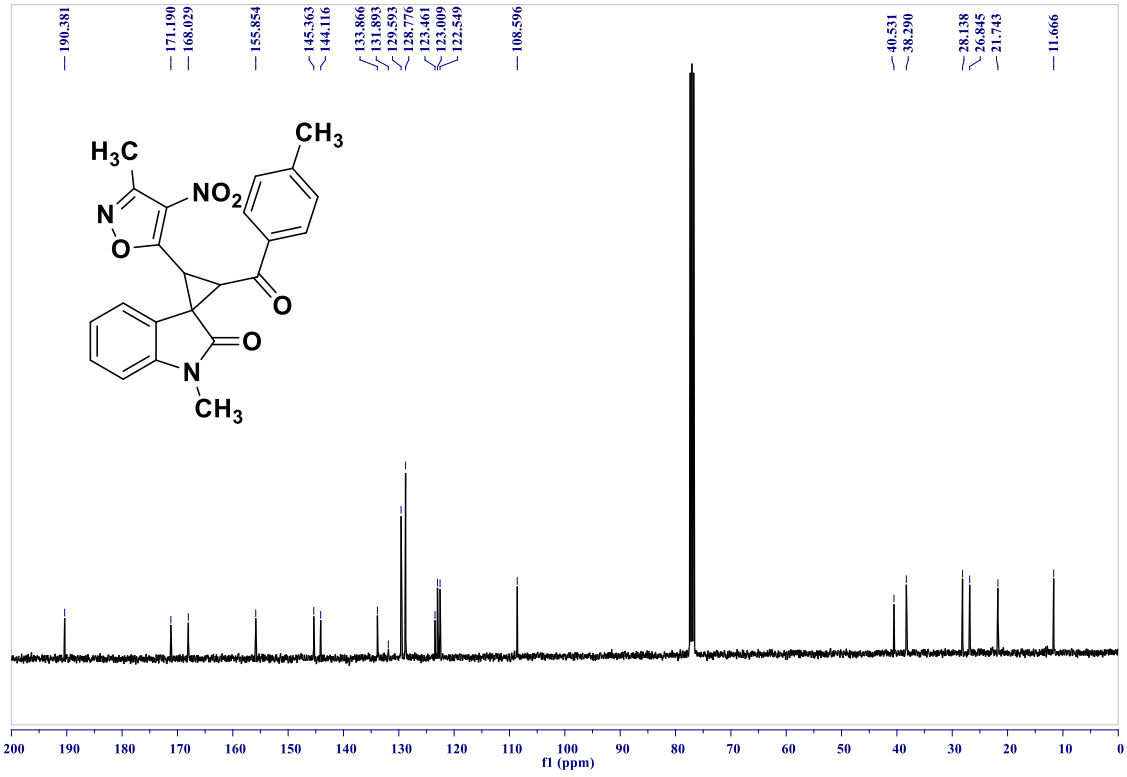


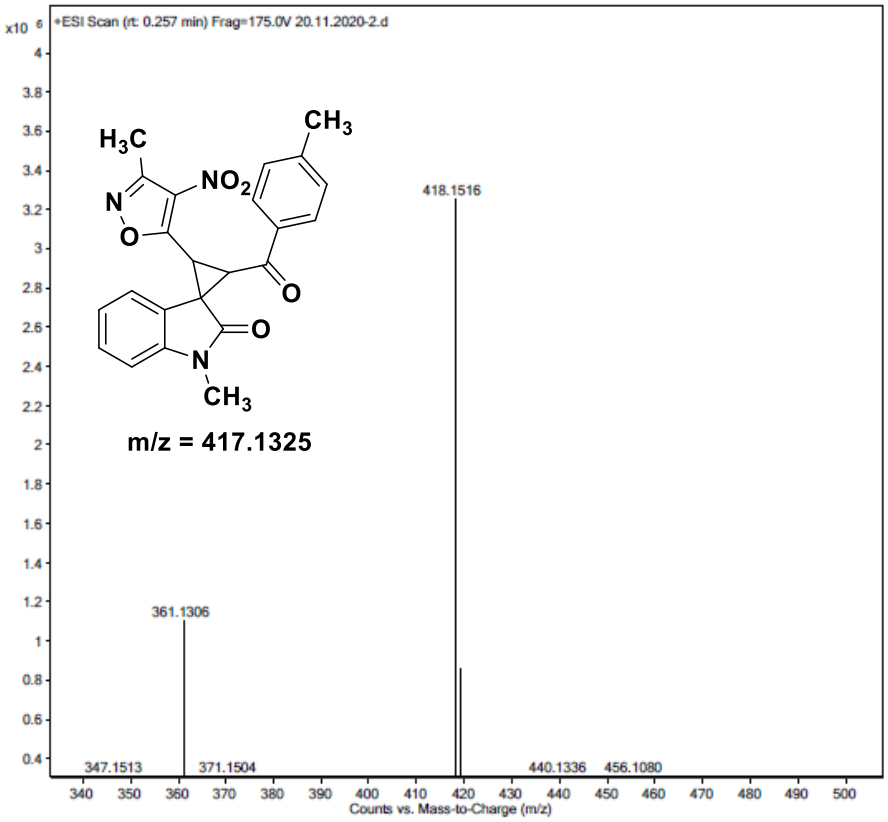




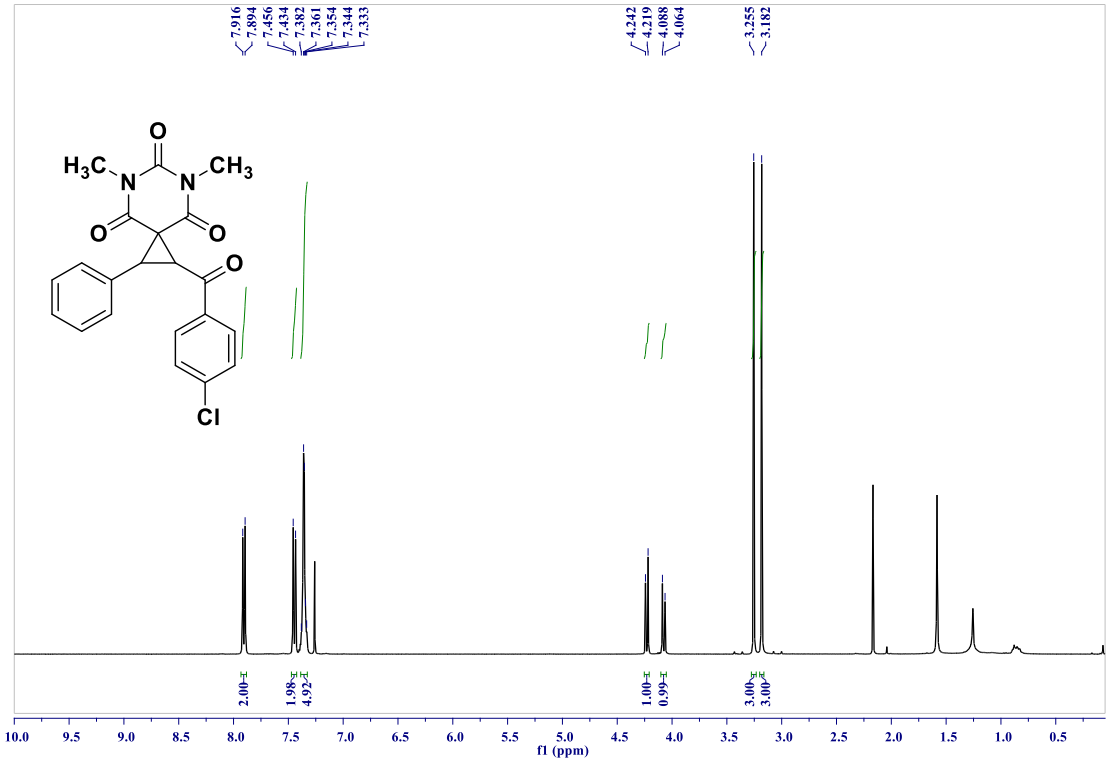
1'-methyl-2-(3-methyl-4-nitroisoxazol-5-yl)-3-(4-methylbenzoyl)spiro[cyclopropane-1,3'-indolin]-2'-one (3f):

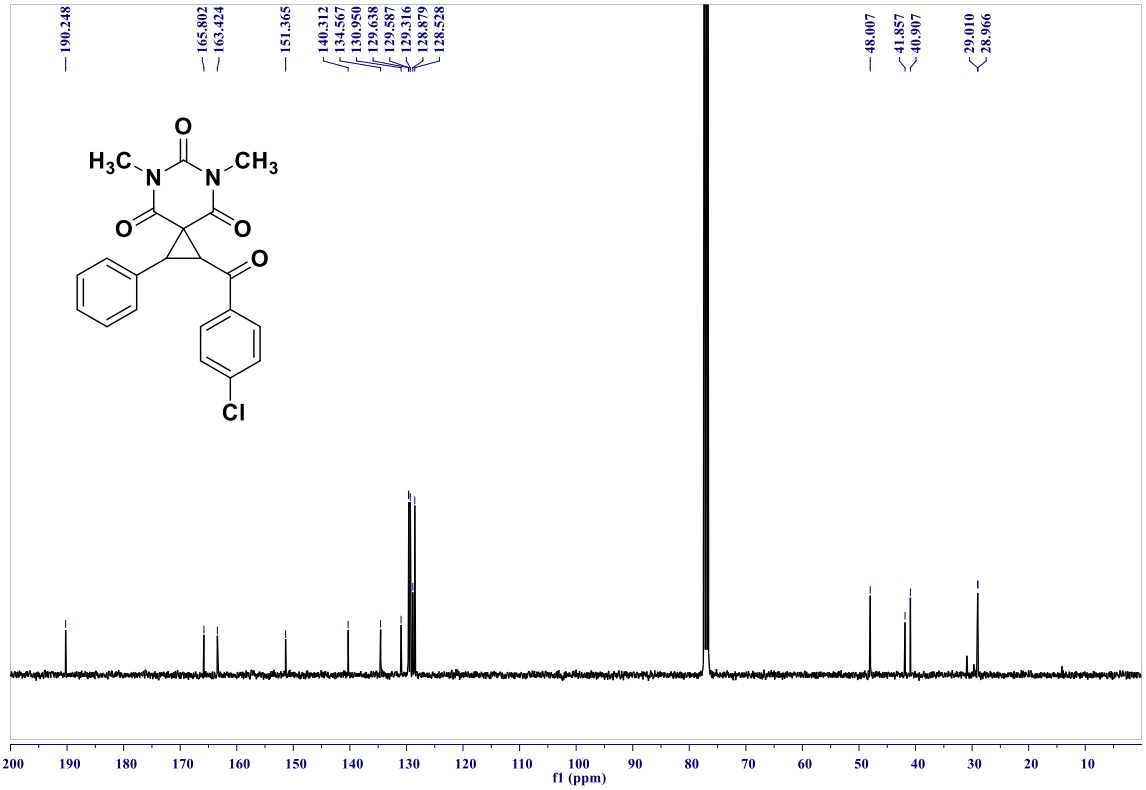

7.786
7.765
7.225
7.222
7.214
7.211
7.205
7.202
7.195
7.192
7.170
7.150
6.964
6.961
6.944
6.942
6.925
6.923
6.808
6.807
6.797
6.789
6.787
4.338
4.319
4.131
4.112
3.159
2.502
2.307
2.01
1.80
1.96
1.02
0.99
0.98
0.96
3.01
3.00
2.97
f1 (ppm)


190.381
171.190
168.029
155.854
145.363
144.116
133.866
131.893
129.593
128.776
123.461
123.009
122.549
108.596
40.531
38.290
28.138
26.845
21.743
11.666
f1 (ppm)

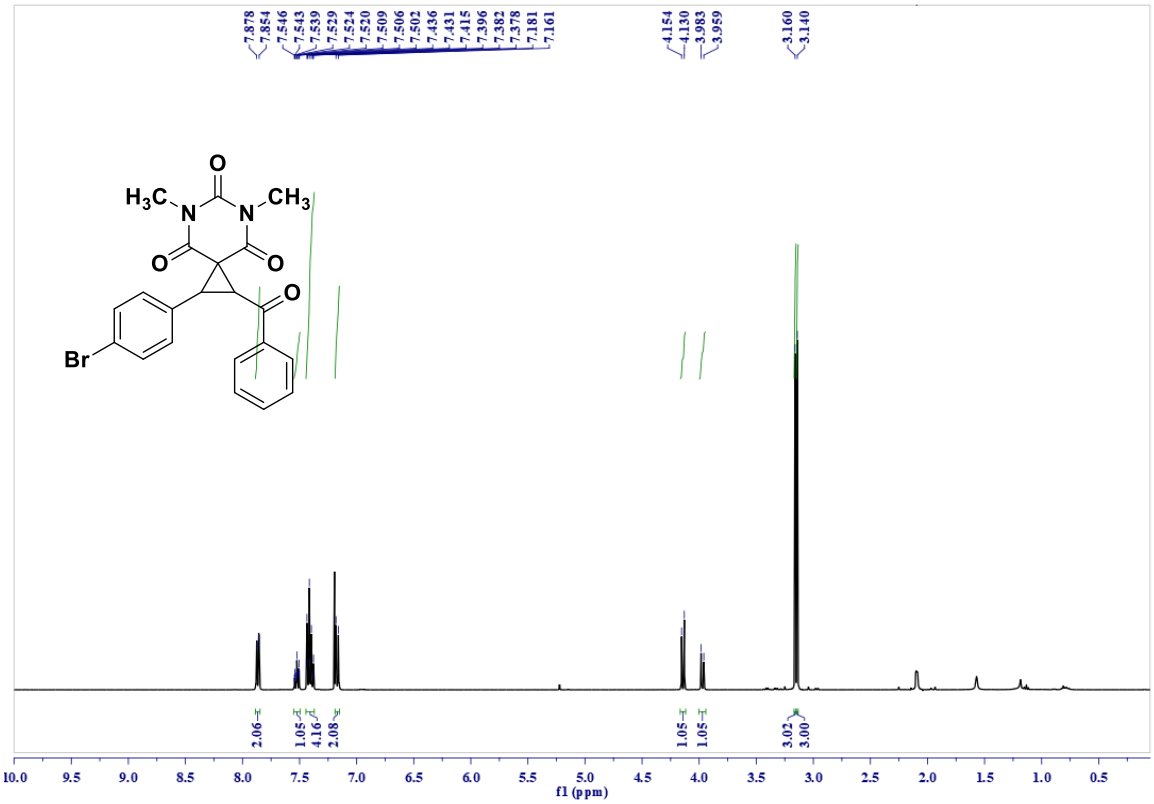


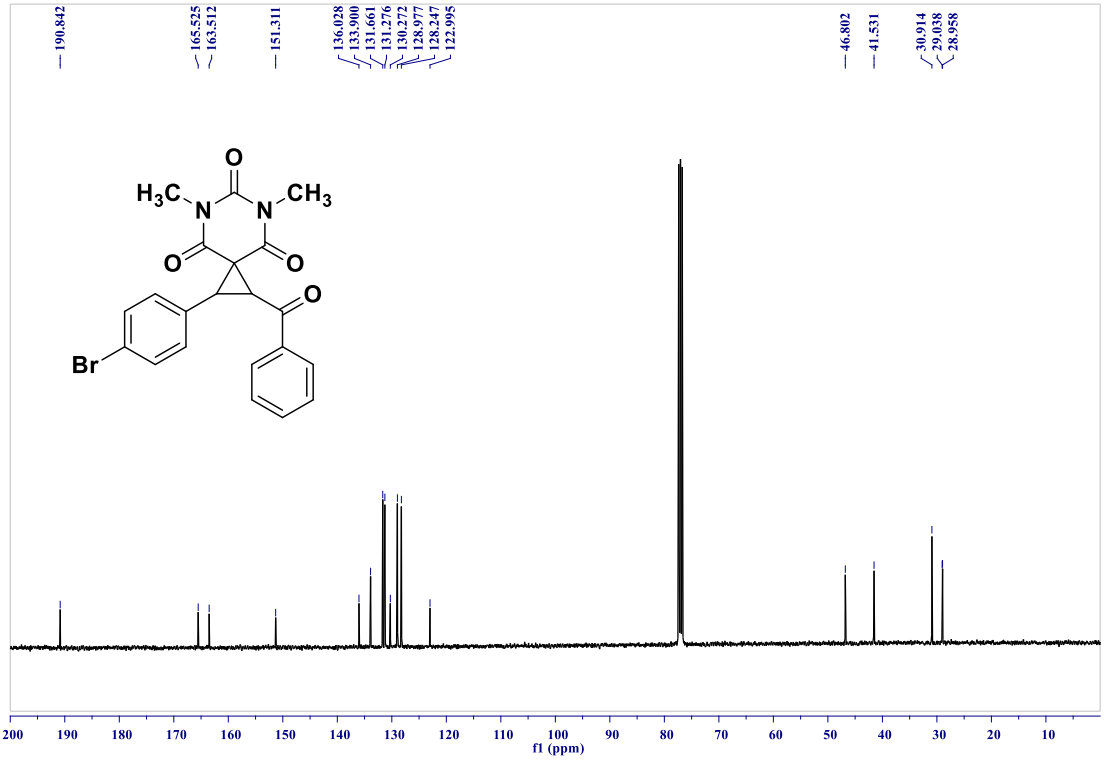
1-(4-chlorobenzoyl)-5,7-dimethyl-2-phenyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5b):



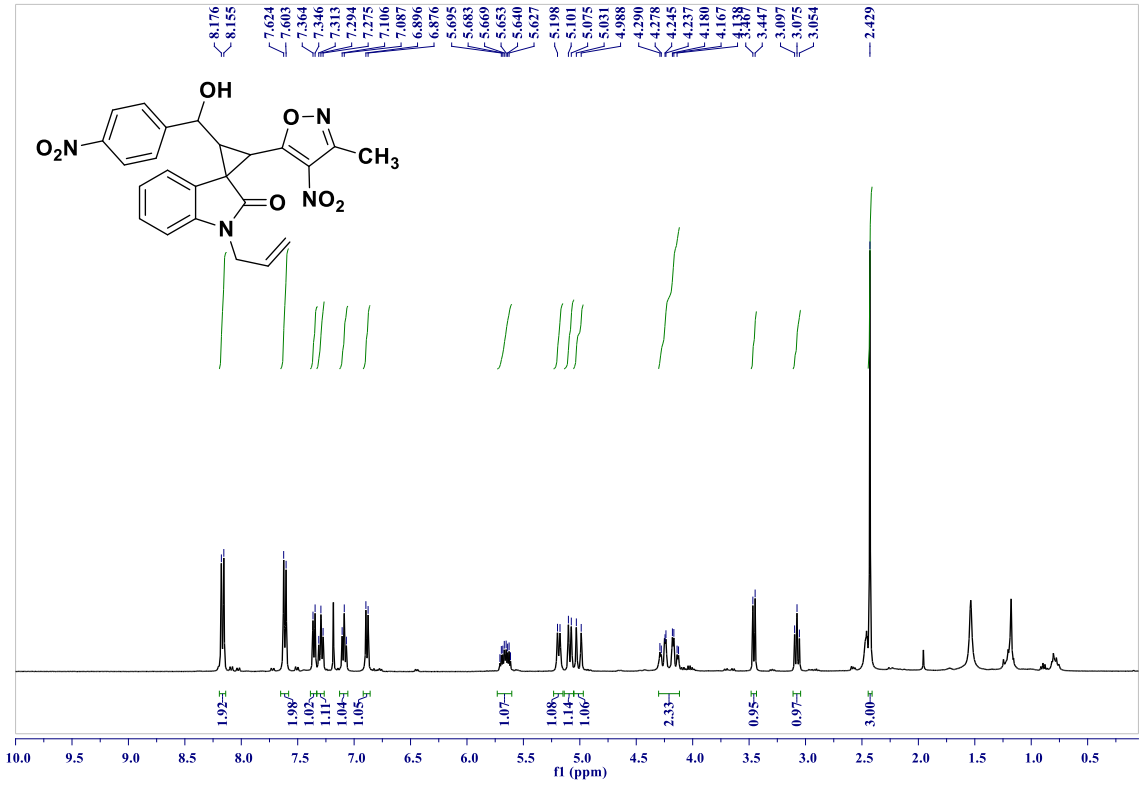


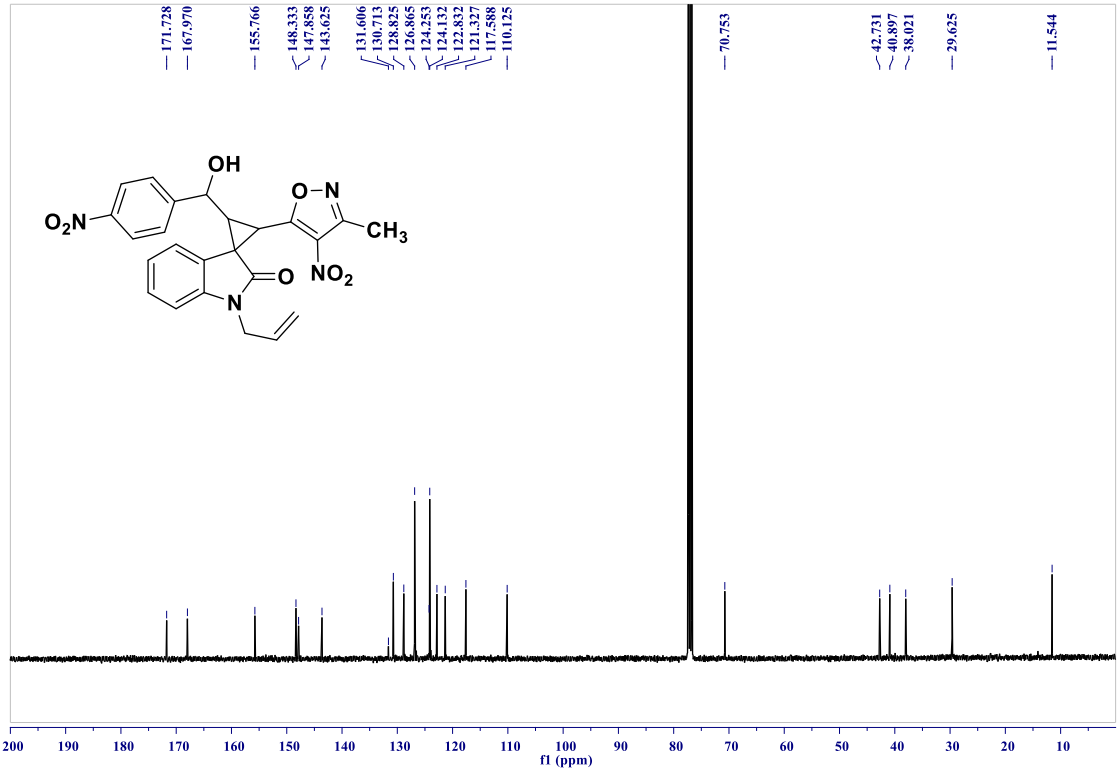
1-benzoyl-2-(4-bromophenyl)-5,7-dimethyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5d):

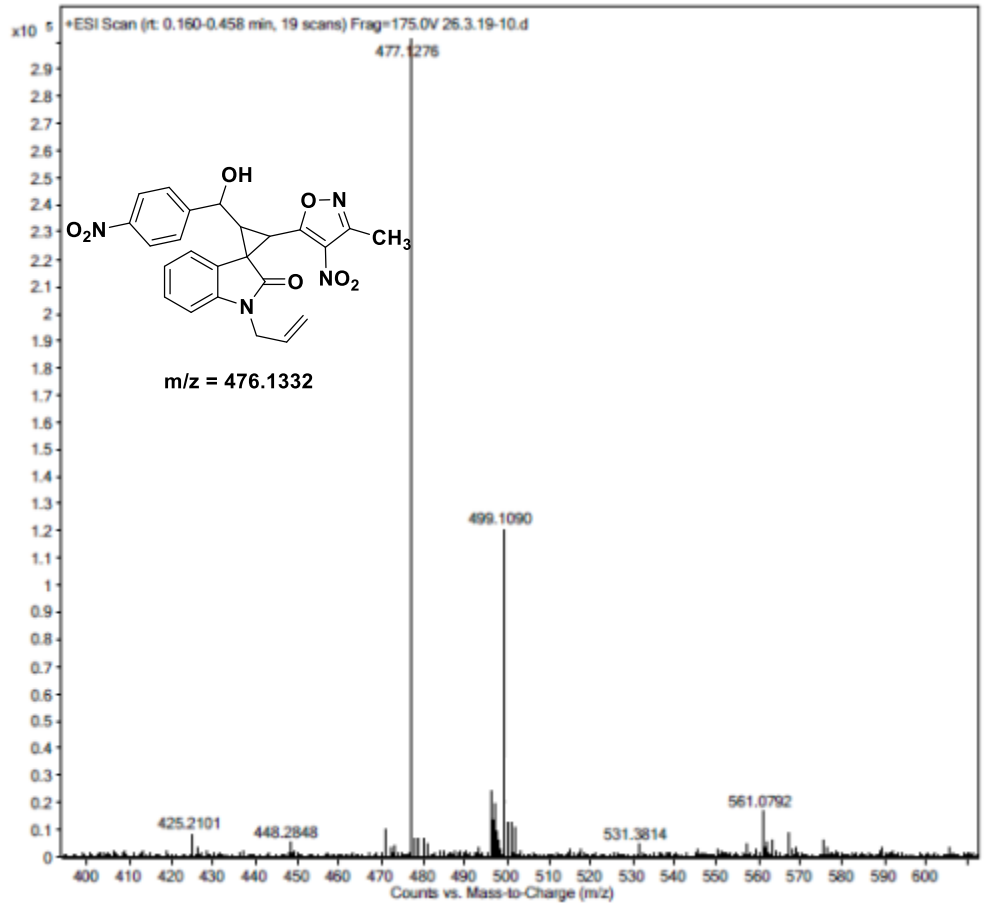




1'-allyl-2-(hydroxy(4-nitrophenyl)methyl)-3-(3-methyl-4-nitroisoxazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (6k):




171.728
167.970
155.766
148.333
147.858
143.625
131.606
130.713
128.825
126.865
124.253
124.132
122.832
121.327
117.588
110.125
70.753
42.731
40.897
38.021
29.625
11.544
OH
O2N
O–N
CH3
NO2
O
N
f1 (ppm)


x10 5
+ESI Scan (rt: 0.160-0.458 min, 19 scans) Frag=175.0V 26.3.19-10.d
477.1276
499.1090
425.2101
448.2848
531.3814
561.0792
m/z = 476.1332
Counts vs. Mass-to-Charge (m/z)

5.8 References

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4. (a) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013,** *15*, 42. (b) Magar, K. B. S.; Lee, Y. R.; Kim, S. H. *Molecular Diversity* **2013,** *17*, 679.
5. Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem. Eur. J.* **2011,** *17*, 2842.
6. Dou, X.; Lu, Y. *Chem. Eur. J.* **2012,** *18*, 8315.
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8. (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997,** *97*, 2341. (b) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004,** *37*, 611. (c) Lu, L.-Q.; Li, T.-R.; Wang, Q.; Xiao, W.-J. *Chem. Soc. Rev.* **2017,** *46*, 4135.
9. (a) Rein, T.; Pedersen, T. M. *Synthesis* **2002,** 579. (b) Illa, O.; Arshad, M.; Ros, A.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010,** *132*, 1828. (c) Illa, O.; Namutebi, M.; Saha, C.; Ostovar, M.; Chen, C. C.; Haddow, M. F.; Nocquet-Thibault, S.; Lusi, M.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013,** *135*, 11951. (d) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006,** *128*, 9730. (e) Zheng, J.-C.; Zhu, C.-Y.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2008,** *73*, 6909.
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11. Roiser, L.; Waser, M. *Org. Lett.* **2017,** *19*, 2338.

12. Winter, M.; Gaunersdorfer, C.; Roiser, L.; Zielke, K.; Monkowius, U.; Waser, M. *Eur. J. Org. Chem.* **2018,** 418.
13. Wang, L.; Cao, W.; Mei, H.; Hu, L.; Feng, X. *Adv. Synth. Catal.* **2018,** *360*, 4089.
14. Suleman, M.; Li, Z.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.* **2019,** 4447.
15. Kang, J. W.; Li, X.; Chen, F. Y.; Luo, Y.; Zhang, S. C.; Kang, B.; Peng, C.; Tian, X.; Han, B. *RSC Adv.* **2019,** *9*, 12255.
16. Meng, X. N.; Jiang, S.; Xu, X. Y.; Wu, Q. X.; Gu, Y. C.; Shi, D. Q. *Eur. J. Org. Chem.* **2016,** 4778.
17. Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005,** *127*, 3240.
18. Zlotin, S. G.; Kochetkov, S. V. *Russ. Chem. Rev.* **2015,** *84*, 1077.
19. Wang, J.; Liu, X.; Dong, S.; Lin, L.; Feng, X. *J. Org. Chem.* **2013,** *78*, 6322.
20. Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem. Eur. J.* **2011,** *17*, 2842.
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CHAPTER-VI

Synthesis of aminoalkylnaphthol-based chiral organo catalysts and their applications for Domino/cascade, Michael, Aldol, and Vinylogous henry type reactions

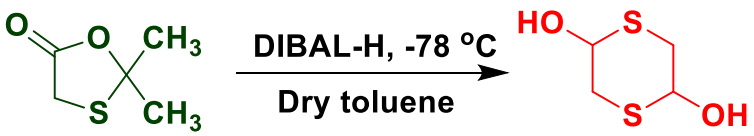
CHAPTER-VI

6.1 Introduction

6.1.1 Synthetic methods for the preparation of tetrahydrothiophene moiety

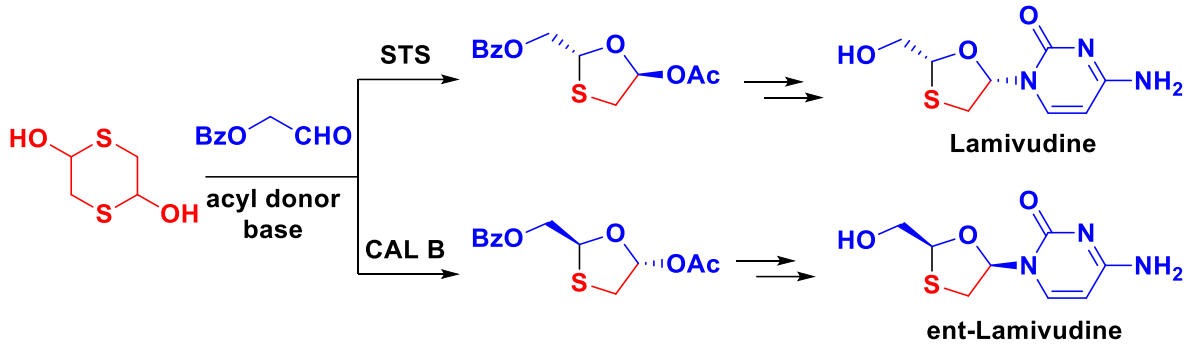
Sulfur containing heterocyclic molecules particularly tetrahydrothiophenes are limited in biology. However, the synthesis and isolation of some of the biologically active molecules with *β*-hydroxy tetrahydrothiophene unit are reported in the literature (**Chapter-1; Figure-5***).*[1a,b] Most of these methods involve either multiple step or complex protocol. Recently, the use of 1,4-dithiane-2,5-diol in combination with olefinic system have been emerged as one of the simple and convenient route for the synthesis of functionalized tetrahydrothiophenes *via in-situ* generation of mercaptoacetaldehyde under mild/basic conditions. It contains two-carbon synthon featuring both electrophilic and nucleophilic reactive cites (sulfur and aldehyde). This reagent firstly reported by Gewald and co-workers in 1966 for the preparation of thiazoles. Later the same reagent effectively used for domino reactions such as thia-Michael addition, Aldol, [3+3]-and [2+3]-cycloaddition reactions resulting in functionalized thiolane hybrids with three contiguous stereogenic centers involving C-C, C-S bond formation.[1c] Recently, 1,4-dithiane-2,5-diol also used for the synthesis of biologically active Lamivudine (3TC) and thiophene derivatives.[1c,d]

Preparation of 1,4-dithiane-2,5-diol: The reagent 1,4-dithiane-2,5-diol is reported by **J.M. McIntosh** group in 1983 using thiolactones by the treatment of DIBAL-H in dry toluene at -78 ^{o}C (**Scheme-6.1**).[2]



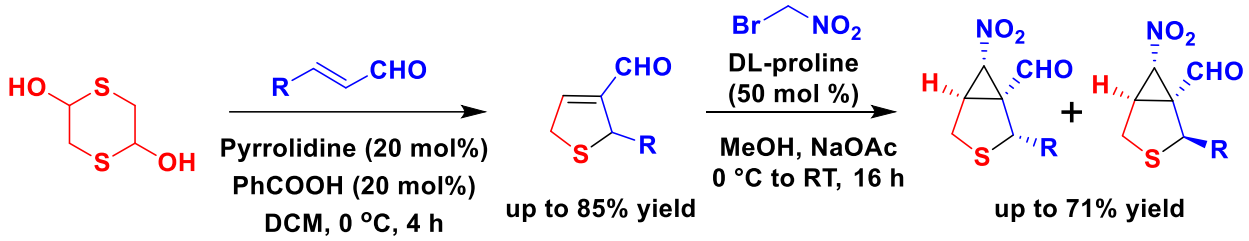
Scheme-6.1: *Preparation of 1,4-dithiane-2,5-diol from thiolactones.*

Ramström and his group described the use of 1,3-oxathiolanes for the synthesis of biologically active molecules like Lamivudine and ent-Lamivudine. Initially, they synthesized 1,3-oxathiolanes using 1,4-dithiane-2,5-diol and glycolaldehydes. Further, enzyme-catalyzed dynamic kinetic resolution of 1,3-oxathiolane derivatives gave key intermediates in pure form (stereoisomeric) which were converted into Lamivudine and ent-Lamivudine (**Scheme-6.2**).[1c,d]



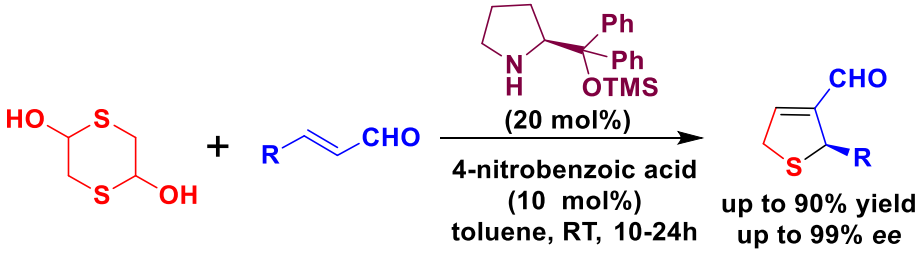
Scheme-6.2: *Enzyme-catalyzed asymmetric synthesis of Lamivudine and ent-Lamivudine.*

C. De. Risi group reported an unprecedented domino Michael/α-alkylation reaction between 2,5-dihydrothiophene-3-carbaldehydes and bromonitromethane catalyzed by DL-proline in the presence of NaOAc to provide access to novel nitrocyclopropanes derivatives in good yields with good to excellent diastereoselectivities (**Scheme-6.3A**).[3]



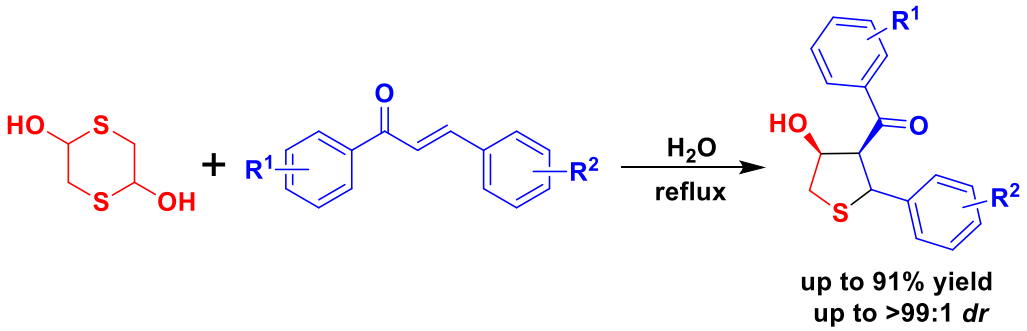
Scheme-6.3A: *Synthesis of nitrocyclopropanes using 1,4-dithiane-2,5-diol.*

In 2010, **Xu** and co-workers developed an organocatalytic domino thia-Michael/aldol condensation reaction of α,β-unsaturated aldehydes with 1,4-dithiane-2,5-diol catalyzed by chiral diphenylprolinol trimethylsilyl ether to provide chiral dihydrothiophenes with good yields and with excellent enantioselectivities (**Scheme-6.3B**).[4]



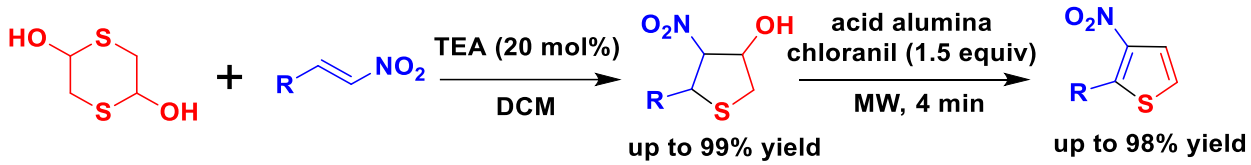
Scheme-6.3B: *Synthesis of chiral dihydrothiophenes via organocatalytic domino thia-Michael/aldol condensation of unsaturated aldehydes and 1,4-dithiane-2,5-diol.*

In 2014, **Ong et al.** reported an efficient, eco-friendly and catalyst-free method for the synthesis of trisubstituted tetrahydrothiophenes through thia-Michael/aldol cascade reaction in H_2O to deliver a series of tetrahydrothiophene derivatives with good to excellent yields (**Scheme-6.4**).[5]



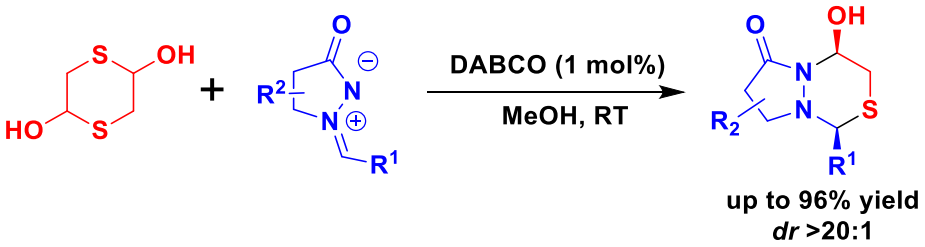
Scheme-6.4: *Synthesis of trisubstituted tetrahydrothiophenes via highly enantioselective cascade thia-Michael/aldol reaction.*

J. M. Southern and his group reported one-pot approach to the synthesis of 3-nitrothiophene and 3-nitro-2-substituted thiophenes using 1,4-dithane-2,5-diol with nitroalkenes in the presence of TEA as a base. Subsequent treatment of the generated intermediates with molecular sieves and combination of silica gel or acidic alumina with DDQ or chloranil formed 3-nitrothiophene or 3-nitro-2-substituted thiophenes. This reaction proceeds *via* tandem Michael-intramolecular Henry reaction followed by dehydration (**Scheme-6.5**).[6]



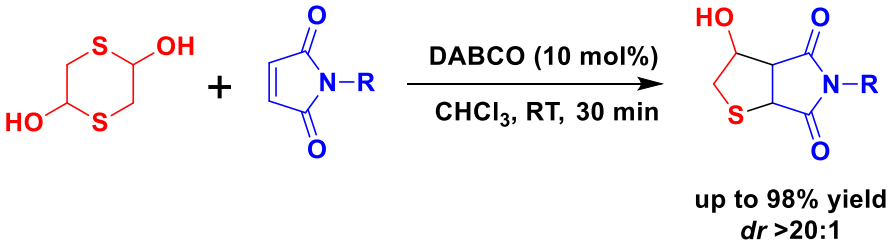
Scheme-6.5: *One-pot formation of nitrothiophenes using 1,4-dithane-2,5-diol.*

C.-J. Wang et al. reported diastereoselective synthesis of highly functionalized six-membered dinitrogen-fused heterocycles *via* [3+3]-cycloaddition of 1,4-dithiane-2,5-diol with azomethine imines catalyzed by DABCO in good yields with excellent diastereoselectivity (**Scheme-6.6**).[7]



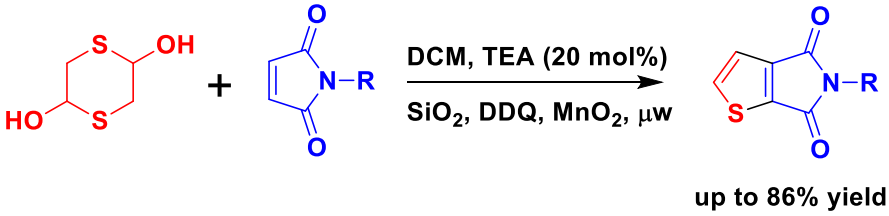
Scheme-6.6: *DABCO-catalyzed [3+3] cycloaddition of 1,4-dithiane-2,5-diol with azomethine imines.*

R. Wang et al. described highly diastereoselective intermolecular [3+2] annulation of 1,4-dithiane-2,5-diol with maleimides in presence of DABCO as a catalyst to provide a series of highly functionalized heterocyclic derivatives containing tetrahydrothiophene and pyrrolidine backbones in excellent yields and diastereoselectivities (up to 98% yield and >20:1 *dr*) (**Scheme-6.7A**).[8a]



Scheme-6.7A: *Synthesis of N-substituted maleimides.*

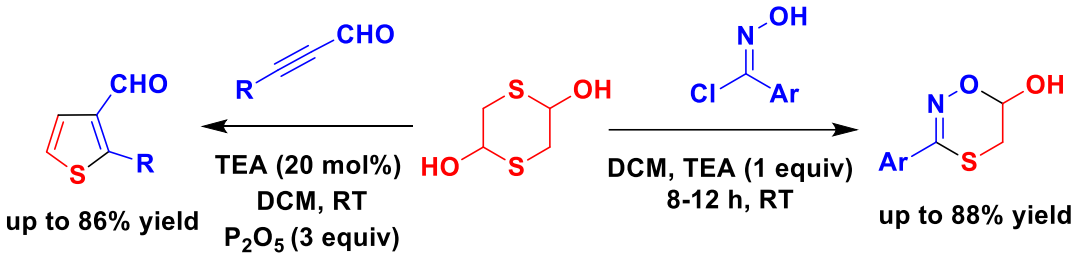
Later **J. Wang** group developed one-pot metal-free, formal [3+2]-annulation reaction of 1,4-dithiane-2,5-diol and *N*-substituted imides. This could furnish 2,3-thienoimides in good to high yields (**Scheme-6.7B**).[8b]



Scheme-6.7B: *One-pot synthesis of 2,3-thienoimides via formal [3+2] annulation reaction of 1,4-dithiane-2,5-diol and N-substituted imides.*

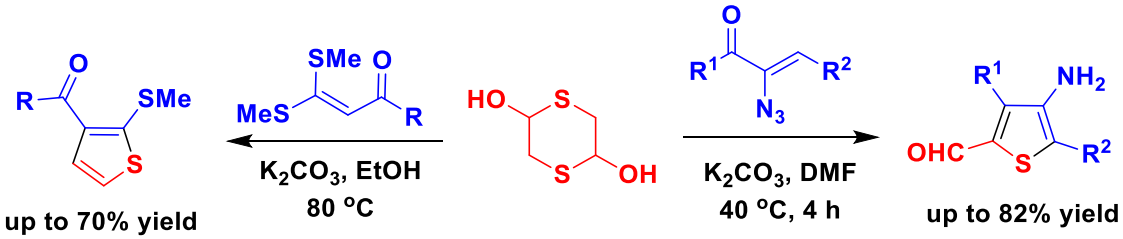
Shi et al. reported TEA-catalyzed [3+2]-cycloaddition reaction of 1,4-dithiane-2,5-diol with ynal to synthesize 3-aldehyde-2-substituted thiophenes in one portion in high yields.[9a] **Sundaravel** and his co-workers reported an efficient method for the synthesis of novel 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols[9b] from the reaction of (*E*)-*N*-hydroxyarylimidoyl chlorides and 1,4-

dithiane-2,5-diol in the presence of TEA. This transformation occurs with the formation of a C-S and C-O bond in a one pot operation (**Scheme-6.8**).



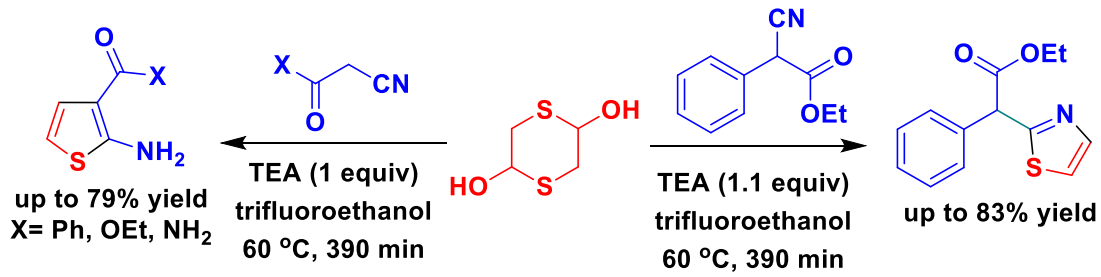
Scheme-6.8: *Synthesis of functionalized thiophenes and 5,6-dihydro-1,4,2-oxathiazines.*

H. Junjappa and his group reported a simple base catalyzed method for the synthesis of 2-(methylthio)-3-aroyl/heteroaryl thiophenes using the α-oxoketene dithioacetals with 1,4-dithiane-2,5-diol in presence of anhydrous K_2CO_3 in boiling ethanol to afford the corresponding products with moderate to good yields.[10a] **B. Chen et al.** developed a simple, highly efficient and ecofriendly method for the synthesis of 3,5-disubstituted 4-aminothiophene-2-carbaldehydes using vinyl azides and mercaptoacetaldehyde, allowing the generation of the desired products in good yields (**Scheme-6.9**).[10b]



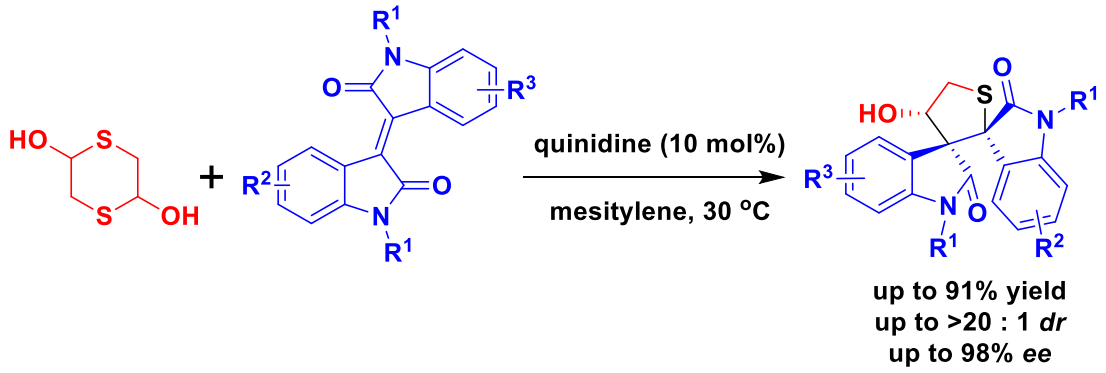
Scheme-6.9: *Synthesis of 2-methylthio-3-aroyl-/heteroaryl thiophenes and 3,5-disubstituted 4-aminothiophene-2-carbaldehydes.*

R. Baxendale described the use of 1,4-dithiane-2,5-diol with α-cyano carbonyl compounds in presence of TEA to synthesize 2-substituted thiazoles or 2-substituted aminothiophenes depending on the substitution of the α-carbon to the cyano group (**Scheme-6.10**).[11]



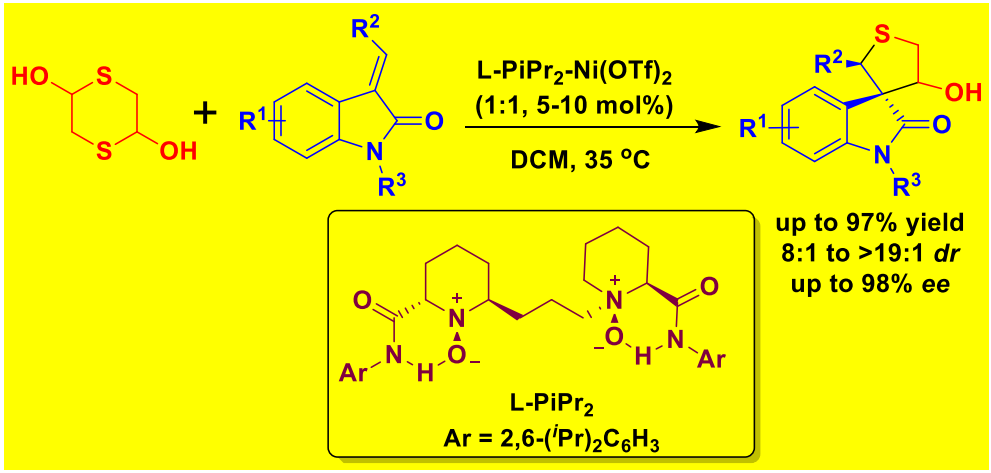
Scheme-6.10: *synthesis of 2-substituted thiazoles or 2-substituted aminothiophenes using 1,4-dithiane-2,5-diol.*

Y. Y. Gui et al. reported cinchona alkaloid catalyzed diastereoselective and enantioselective sulfa-Michael/aldol cascade reaction of mercaptoacetaldehyde and isoindigos in presence of quinidine as an organocatalyst to afford the highly congested bispirooxindole tetrahydrothiophenes (**Scheme-6.11**) with vicinal quaternary spirocenters in high yields (up to 91%), excellent diastereoselectivities (up to >20:1 *dr*) and good enantioselectivities (up to 98% *ee*).[12]



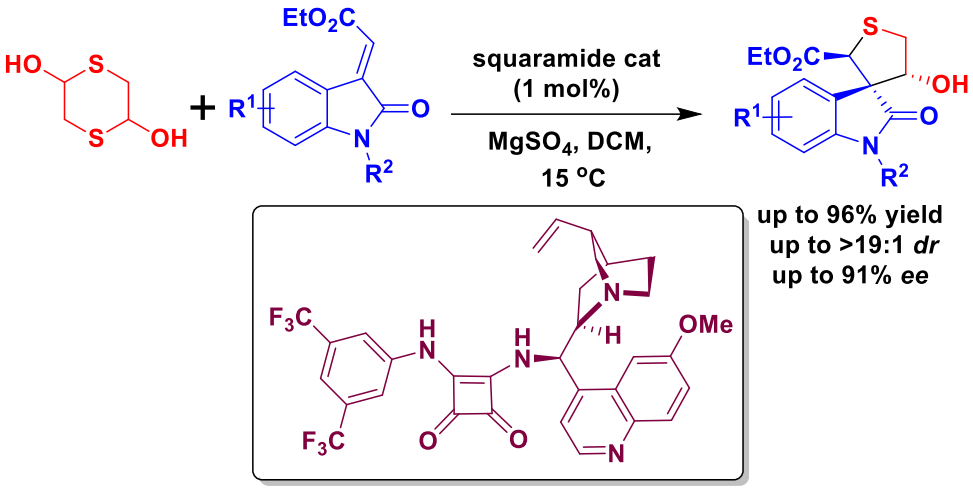
Scheme-6.11: *Cinchona alkaloid catalyzed enantioselective sulfa-Michael/aldol cascade reaction of isoindigos.*

X. Feng group demonstrated an efficient method for the synthesis of enantioenriched spirocyclic oxindole-fused tetrahydrothiophenes using *N,N'*-dioxide–nickel(II) catalyzed asymmetric domino thia-Michael/aldol cycloaddition reaction. A series of 3-alkenyloxindoles (**Scheme-6.12A**) underwent smoothly, affording the corresponding products in good yields with excellent enantioselectivities and diastereoselectivities (up to 97% yield, 98% *ee*, >19:1 *dr*).[13a]



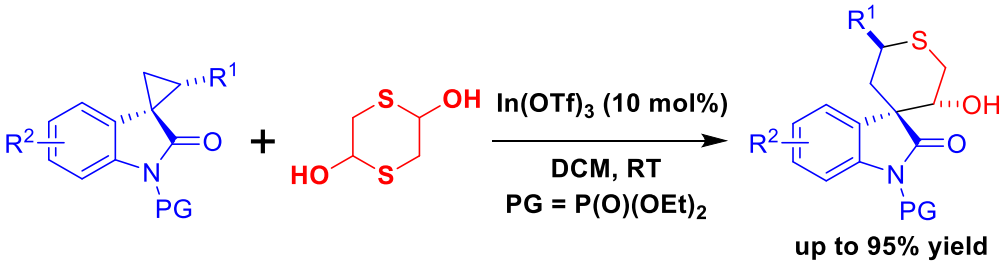
Scheme-6.12A: *Asymmetric synthesis of spirocyclic oxindole-fused tetrahydrothiophenes.*

W.-J. Xiao group reported an efficient asymmetric organocatalytic Michael-aldol cascade reaction for the synthesis of tetrahydrothiophene based spirocyclic oxindoles bearing three consecutive stereo genic centers in a highly stereoselective fashion *via* formal [3+2]-annulation (**Scheme-6.12B**).[13b]



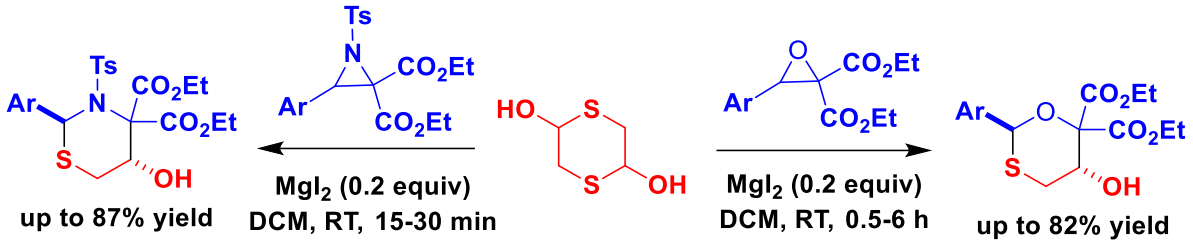
Scheme-6.12B: *Organocatalytic asymmetric Michael-aldol cascade reaction of 3-ylideneoxindoles and 1,4-dithiane-2,5-diol.*

Y. Hao et al. demonstrated $In(OTf)_3$-catalyzed [3+3]-annulation of spirocyclopropyl oxindoles and 1,4-dithiane-2,5-diol, for a facile preparation of spiro[indoline-3,4'-thiopyran]-2-ones bearing (tetrahydro)thiopyran skeleton (**Scheme-6.13**).[14]



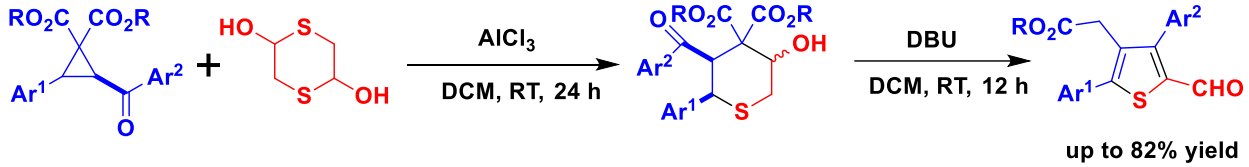
Scheme-6.13: *synthesis of sulfur-containing six-membered ring fused spirooxindoles.*

P. Banerjee and his group reported Lewis acid catalyzed [3+3]-annulation of *N*-tosylaziridine dicarboxylates and oxiranes with *in situ* generated sulfur aldehyde for the synthesis of functionalized thiazine and oxathiane derivatives with good yields (**Scheme-6.14**).[15]



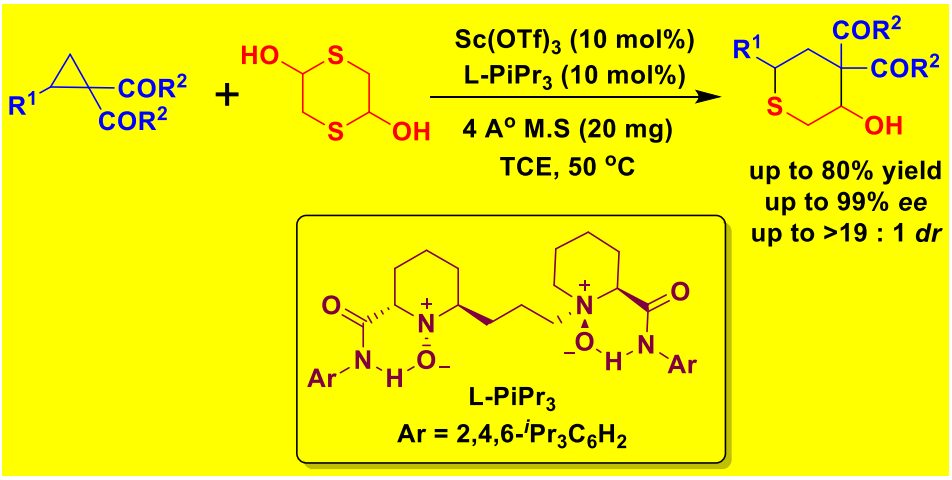
Scheme-6.14: *Synthesis of thiazines and oxathianes via [3+3] annulation of N-tosylaziridine dicarboxylates and oxiranes with 1,4-dithiane-2,5-diol.*

K. Srinivasan group developed a new two-step procedure for the synthesis of tetrasubstituted thiophenes using cyclopropanes and 1,4-dithiane-2,5-diol *via* $AlCl_3$-mediated [3+3]-annulation. The generated tetrahydrothiopyranols further converted into thiophenes with good yields (up to 82% yield) using DBU as organic base *via* rearrangement protocol (**Scheme-6.15**).[16]



Scheme-6.15: *Synthesis of tetrahydrothiopyranols and thiophenes.*

X. Feng group demonstrated highly diastereo- and enantioselective [3+3]-annulation of donor–acceptor cyclopropanes with mercaptoacetaldehyde in the presence of *N, N'*-dioxide–Sc (III) complex as the catalyst. Various aromatic cyclopropyl ketones reacted with mercaptoacetaldehyde providing the corresponding chiral tetrahydrothiopyranols in moderate yields and excellent enantioselectivity (**Scheme-6.16**).[17]

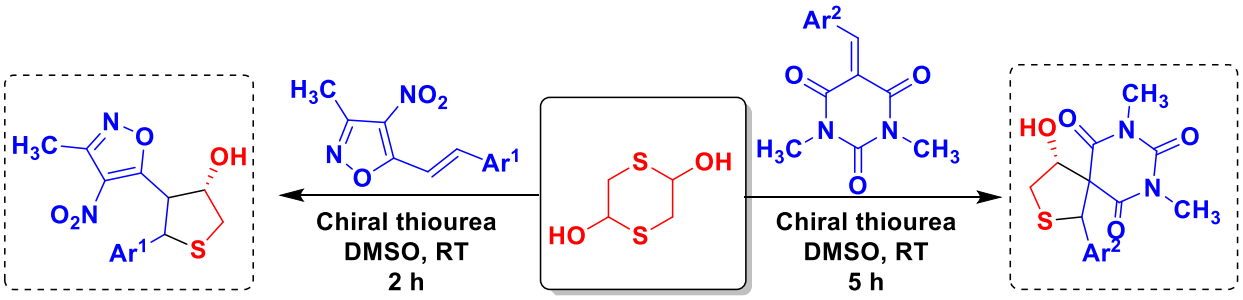


Scheme-6.16: *Catalytic asymmetric [3+3] annulation of cyclopropanes with 1,4-dithiane-2,5-diol.*

Organocatalysis[18] as an attractive platform for the asymmetric synthesis of important biologically active molecules and chiral building blocks, show wide range of applications in medicinal and drug discovery.[19] Organocatalysts have many advantages such low cost, large chiral pool, insensitive to moisture and environmental and ecofriendly in nature. Over last few dacades researchers demonstrated the applications of numerous organo chiral catalysts such as *L*-proline, cinchona alkaloids, thiourea, squaramides, ionic liquids and various amino acids for many named reactions (Aldol, Michael, Mannich, Morita-Baylis-Hillmann etc.) and applied for the synthesis of complex natural products in enantioselective fashion. There are various activation strategies/approaches adopted/developed including covalent and non-covalent catalysis, phase transfer, Brønsted acid, Brønsted base for the development of the catalysts. Under the noncovalent catalysis category, thiourea-based organocatalysts[20] have emerged as an efficient class of organocatalysts due to their unique dual hydrogen-bonding capacity. Considering the importance of small molecules (organocatalysis) in organic synthesis, here we reported novel organo chiral catalysts and their application to organic transformations (Domino/tandem, Aldol, Michael and Henry-type vinylogous reactions).

6.2 Present study

An asymmetric synthesis of functionalized tetrahydrothiophenes has been achieved by 1,4-dithiane-2,5-diol and isoxazole or barbiturate styrenes using chiral thiourea as an organocatalyst *via* domino sulfa-Michael/aldol condensation. The developed catalyst also extended for Domino/tandem, Aldol, Michael and Henry type vinylogous reactions afforded corresponding products with good to excellent yields.

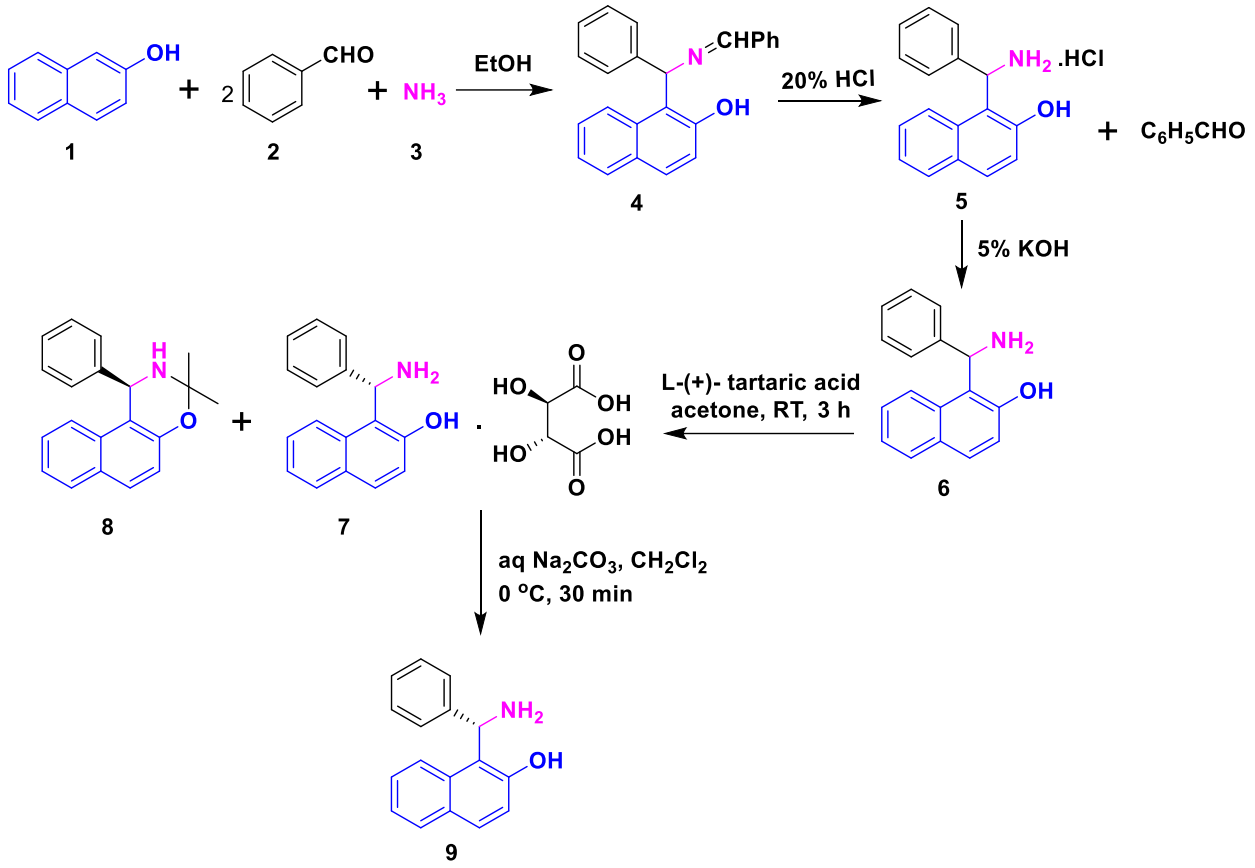


Scheme-6.17: Domino or cascade reactions promoted by chiral thiourea as an organo catalyst.

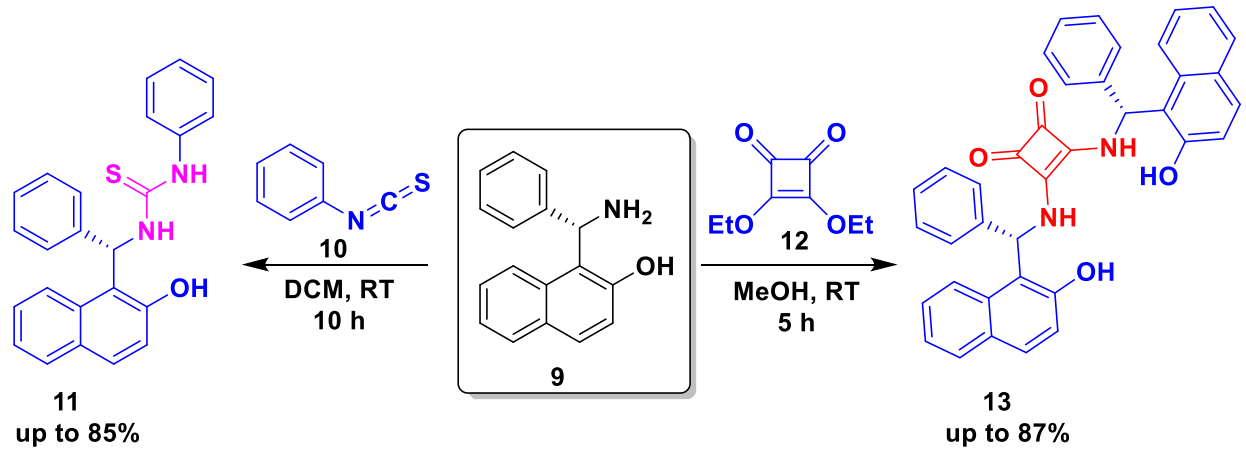
6.3 Results and Discussion

Asymmetric organocatalysis where small molecules (commercial or synthesized) are used as catalysts for the organic transformations has emerged as powerful tool for the asymmetric transformations. Pioneering work by Carlos Barbas III, MacMillan, Benjamin List, Andre Cobb, D. Ramachari, INN Namboothiri groups led to the development of different organocatalysts and their application for the simple and complex molecules including natural product synthesis[21] (based on Many reactions like Aldol, Diels-Alder, Michael addition, Mannich, Strecker and multicomponent reactions). Till now commercial or modularly designed catalysts like *L*-proline, cinchona alkaloids, cyclohexyl-amides, sulfonamides, chiral thiourea, squaramides, chiral peptides and ionic liquids are used as organocatalysts. Often commercially available chiral catalyst won't give the expected outcome when compared to modified catalyst in terms of enantioselectivity. To address this, many modularly designed catalysts are used in the literature.

Amidoalkylnapthols are gaining much importance in both academic and industry for the synthesis of natural products and synthetic pharmaceuticals. The main characteristic feature of these amidoalkylnaphthols is represented by a simple synthesis (Betti reaction) involving simple bench-top starting materials.[22] Though the amidoalkylnaphthols are used for asymmetric transformations, the outcome in terms of stereo selectivity was not encouraging. Thus, in this chapter, we planned to design and synthesis of new amidoalkylnaphthol-based organocatalysts and their application to asymmetric organic transformations. Towards this, the amidoalkylnaphthols were synthesized based on Betti reactions (racemic form) and resolved into pure form through Mannich reaction (**Scheme-6.18**)[23] and converted into bifunctional chiral thiourea (**11**) and squaramide catalysts (**13**) in 85% and 87% respectively (**Scheme-6.19**). These catalysts fully confirmed by ^{1}H, ^{13}C-NMR and Mass spectroscopic data.



Scheme-6.18: *Synthesis of chiral amidoalkylnaphthol.*



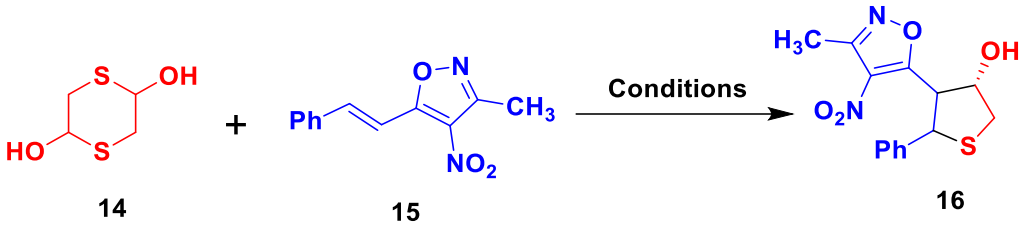
Scheme-6.19: *Synthesis of novel chiral thiourea (**11**) and squaramide catalyst (**13**).*

Later, we have examined on bench mark reactions and some of the reported reactions to test the efficiency of the catalyst in terms of reaction time and yield. For this, we initiated our investigation using 1,4-dithiane-2,5-diol (**14**) and isoxazole styrene (**15**) in the presence of 10 mol% catalyst (**Table-6.1; entry-1**). At first, chiral primary amine (**9**) was chosen to catalyze the

model reaction with 10 mol% catalyst loading in 3 mL of dichloromethane (CH_2Cl_2) at room temperature. The reaction could not afford expected product even after 24 h. The use of other solvents such as EtOH, THF, DMSO and toluene also proved to be disadvantageous leading to formation of the product **(Table-6.1; entries 3-6**). Then, we examined the use of other catalysts such as thiourea (**11**) and squaramide (**13**) in presence of various solvents. From these observations the formation of the product (**16**) could be obtained in 30-45% yield for 12 h (**Table-6.1; entries 11-12**). Encouraged by these results, then we explored the effect of additives for domino/cascade reaction of **14** and **15** in presence of thiourea **11** and squaramide **13** catalyst. Among screened conditions, DMSO with 10 mol% of catalyst (**11**) and benzoic acid supplied the best results, offering the highest yield in short period of reaction time (**Table-6.1; entry-13**). Having these results in hand, we moved to the substrate scope evaluation. First, we tested various isoxazole styrenes, which bearing different substituent groups on aryl ring were utilized to react with 1,4-dithiane-2,5-diol under the optimal conditions. The results show that whether the substituents were electron-donating or electron-withdrawing groups, the corresponding products can be obtained with satisfactory yields (70-88%).

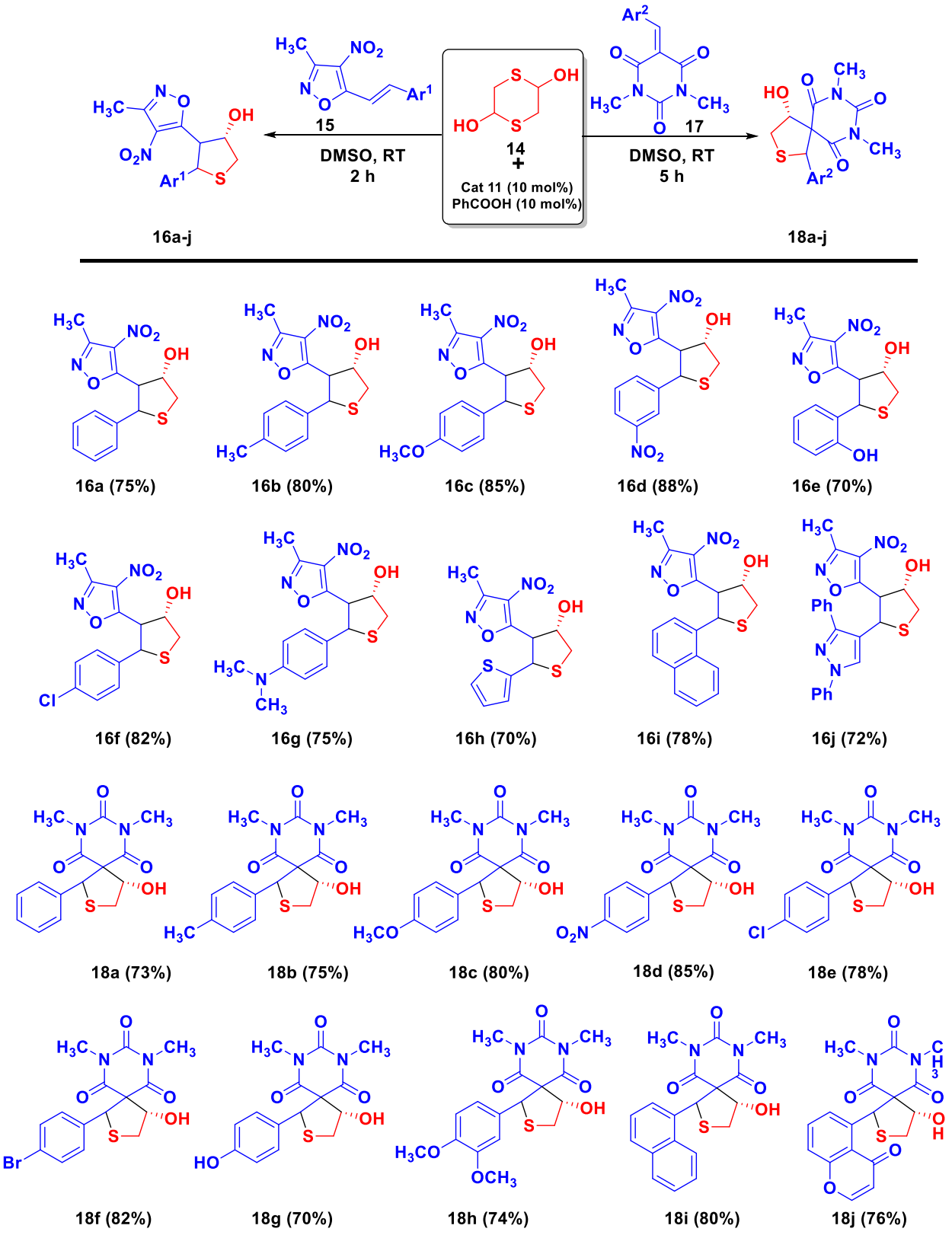
Barbiturates and its analogues, are remarkable scaffolds since they are prevalent in pharmacologically active compounds. Additionally, spirobarbiturates have continued to gain much attention in recent years because of their various pharmacological and biological properties, such as urease inhibitor, HIV-1 inhibitor, anticonvulsant, TACE inhibitor, MMP-13 inhibitor, and anticancer activities.[24] Considering the importance of spirobarbiturates in the biological point of view, our attention was shifted towards the synthesis of functionalized spirotetrahydrothiophenes. To achieve this, various barbiturate olefins were treated with 1,4-dithiane-2,5-diol under optimized condition to give the corresponding products (18a-18j) in 70-85% yields (**Scheme-6.20**), irrespective of electron donating (CH_3, OCH_3) or electron-withdrawing group substituted benzene ring (NO_2), halogens (-Cl) or naphthyl or heteroaryl substituted 3-formylchromones.

Table-6.1: Optimization of the reaction conditions for the synthesis of 16[a]



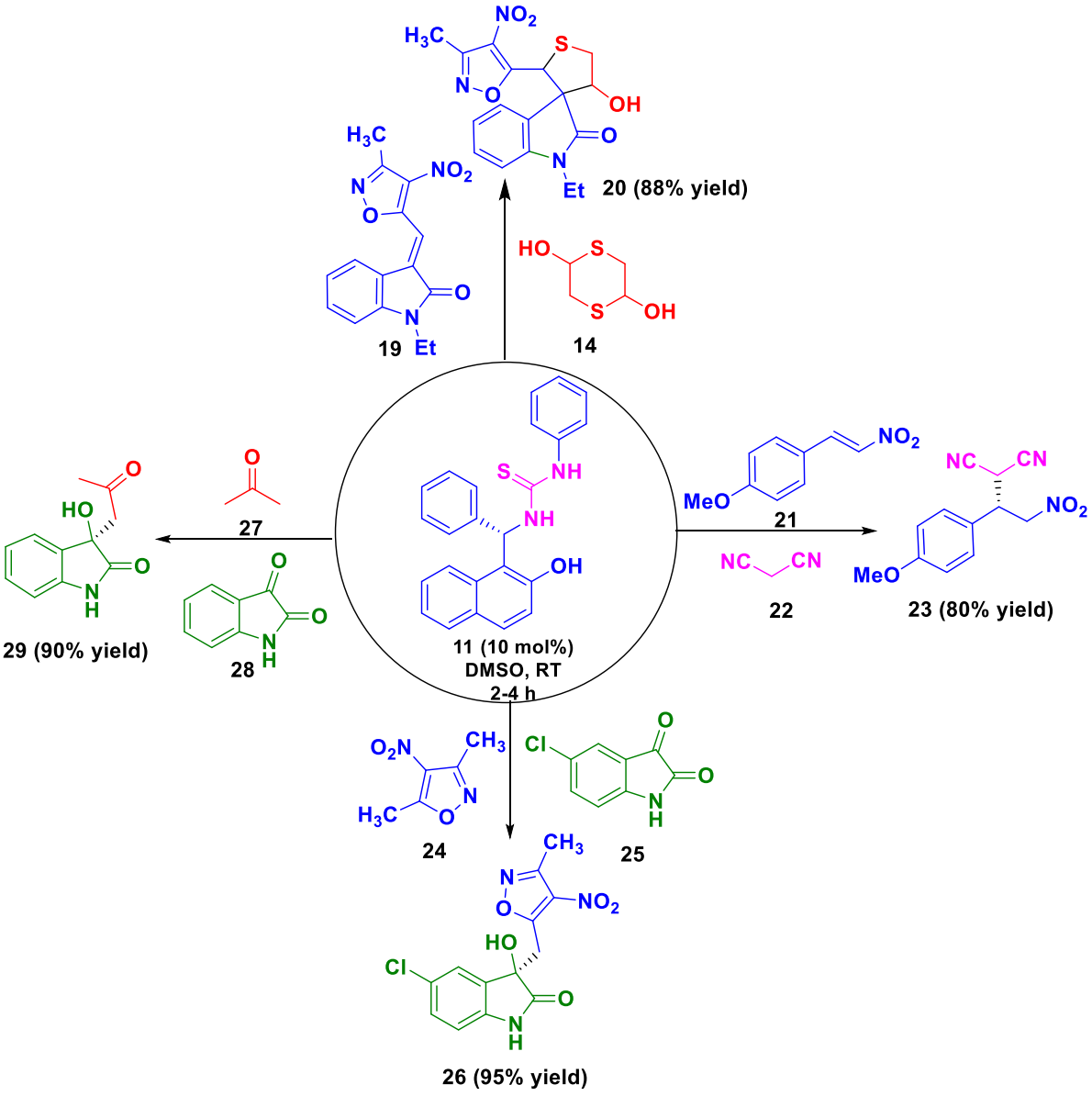
S.No	Solvent	Catalyst (10 mol%)	Additive (10 mol%)	Time (h)	Yield (%) [b]
1	DCM	9	-	24	ND
2	DCM	9	-	24	ND
3	EtOH	9	-	24	ND
4	THF	9	-	24	ND
5	DMSO	9	-	24	ND
6	toluene	9	-	24	ND
7	DCM	11	-	24	ND
8	EtOH	11	-	24	ND
9	THF	11	-	24	ND
10	toluene	11	-	24	ND
11	DMSO	11	-	12	45
12	DMSO	13	-	12	30
13	**DMSO**	**11**	**PhCOOH**	**2**	**75**
14	DMSO	11	TFA	12	60
15	DMSO	11	*p*TsOH	12	35
16	DMSO	11	C_6H_5OH	12	30
17	DMSO	13	PhCOOH	5	60
18	DMSO	13	TFA	12	45
19	DMSO	13	*p*TsOH	12	20
20	DMSO	13	C_6H_5OH	12	trace

[a]All the reactions were performed with **14** (1 mmol) and **15** (1 mmol), catalyst (10 mol%) and additive (10 mol%) in 3 mL of solvent. [b]Isolated yields.



Scheme-6.20: *Synthesis of tetrahydrothiophene derivatives using thiourea catalyst.*

Encouraged by the success of the asymmetric synthesis of tetrahydrothiophenes, we turned our attention to check the reactivity of catalyst efficiency for other reported reactions such as Domino/Cascade, Michael, Aldol and vinylogous Henry-type reactions under optimized condition (**Scheme-6.21**). In this case, the catalyst effectively working and delivering the corresponding products with good to excellent yields (up to 95% yield).



Scheme-6.21: *Domino/tandem, Aldol, Michael and Henry-type vinylogous reactions promoted by thiourea catalyst.*

Based on experimental results and previously reported methods, a plausible mechanism illustrated for above reaction (tetrahydrothiophenes). Both the substrates involved in the transition

state and activated by chiral thiourea catalyst as proposed and shown in **Figure-6.1**. Initially, 1,4-dithiane-2,5-diol converted into dimer of mercaptoacetaldehyde. This mercaptoacetaldehyde further undergo thia-1,6-Michael addition with isoxazole styrene followed by intramolecular aldol reaction to generate corresponding isoxazole based tetrahydrothiophenes. Similar mechanism also occurs in barbiturate olefins with 1,4-dithiane-2,5-diol *via* thia-1,4-Michael addition followed by intramolecular aldol reaction to afford spirotetrahydrothiophenes.

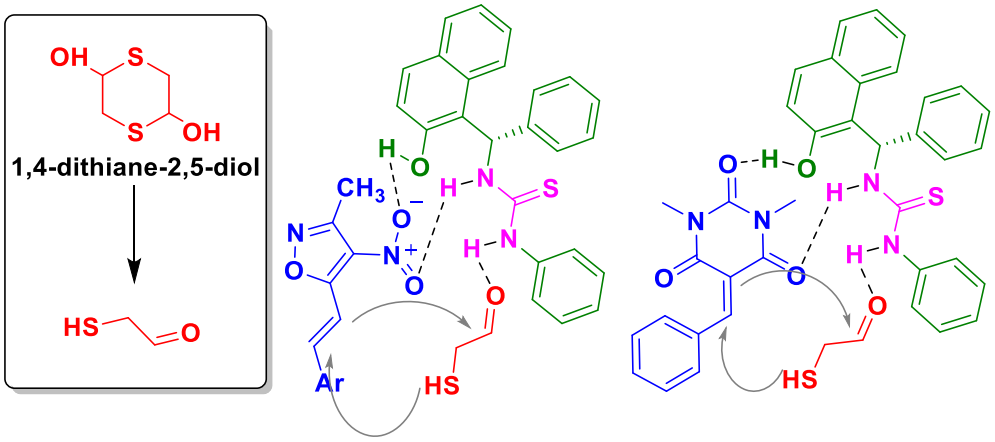


Figure-6.1: *Proposed mechanism for the reaction.*

6.4 Conclusion

In conclusion, we have developed a new class of chiral catalysts (thiourea and squaramide) for various organic transformations such as Michael, Aldol, vinylogous Henry-type and domino/cascade reactions under mild reaction conditions. Use of lower concentration of additive and catalyst at room temperature, with very good yields are advantages of the protocol. The enantioselectivity of these compounds is under process in our laboratory.

6.5 Experimental

6.5.1 General procedure

Typical procedure for the synthesis of chiral amidoalkylnaphthol (C-9):

Chiral amidoalkylnaphthol (C-9) prepared according to literature method.[18]

Typical procedure for the synthesis of chiral thiourea (C-11):

To a solution of **10** (1 mmol) in DCM: MeOH (1:1; 3 mL) was added chiral amine **9** in one portion and the reaction mixture was stirred at room temperature. After 10 h, the reaction mixture was

filtered. The precipitate was rinsed with cold MeOH (3 × 10 mL) to afford pure catalyst (**11**) with 85% yield.

Typical procedure for the synthesis of chiral squaramide (C-13):

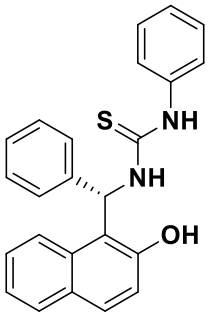
To a solution of **12** (1 mmol) in MeOH (3 mL) was added amine **9** (1 mmol) in one portion and the reaction mixture was stirred at room temperature under N_2 atmosphere. After 5 h, the reaction mixture was filtered. The precipitate was rinsed with cold MeOH (3X10 mL) to afford the pure catalyst (**13**) with 87% yield.

General procedure for the synthesis of tetrahydrothiophene hybrids:

To a stirred solution of styrene (1 mmol) in DMSO (3 mL), 1,4-dithiane-2,5-diol (0.5 mmol), catalyst-11 (10 mol%) and benzoic acid (10 mol%) were added. The reaction mixture was stirred at room temperature until disappearance of starting materials (confirming by TLC). Then saturated NH_4Cl solution (10 mL) was added to the reaction mixture and extracted with EtOAc (3X15mL). The solvent was evaporated and the crude product obtained was purified by column chromatography.

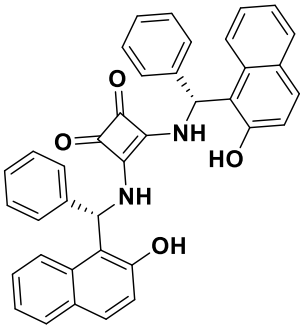
6.6 Spectral data

(S)-1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)-3-phenylthiourea (11):



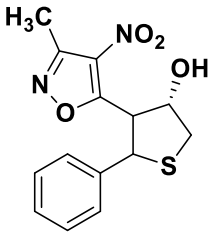
Yield = 85% White solid; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.16 (s, 1H), 10.19 (s, 1H), 8.69 (s, 1H), 8.14 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 18.0, 8.4 Hz, 2H), 7.51 (dd, *J* = 22.0, 7.3 Hz, 3H), 7.34 (dd, *J* = 13.6, 6.8 Hz, 3H), 7.29 – 7.11 (m, 7H). **^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 180.66, 153.61, 142.78, 139.40, 132.93, 129.98, 129.27, 129.10, 128.57, 127.46, 126.84, 126.30, 125.07, 123.80, 123.22, 122.88, 119.02, 118.93, 60.25. **Mass (ESI-MS):** m/z Calculated $C_{24}H_{20}N_2OS$ for: 384.1296; Observed: 383.1125 (M-1).

3-(((R)-(2-hydroxynaphthalen-1-yl)(phenyl)methyl)amino)-4-(((S)-(2-hydroxynaphthalen-1-yl)(phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (13):



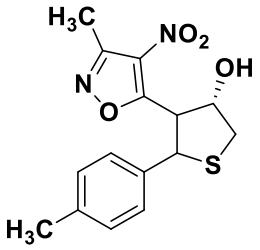
Yield = 87% White solid; **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** 10.13 (s, 1H), 10.03 (s, 1H), 8.84 (s, 2H), 7.99 (s, 2H), 7.88 (t, *J* = 7.7 Hz, 2H), 7.79 (dd, *J* = 15.4, 8.5 Hz, 2H), 7.58 (t, *J* = 9.5 Hz, 2H), 7.45 (dd, *J* = 15.9, 8.2 Hz, 2H), 7.37 – 7.31 (m, 3H), 7.30 - 7.19 (m, 7H), 7.18 – 7.10 (m, 4H).**^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ** 182.98, 182.92, 167.51, 167.47, 153.69, 153.55, 143.19, 143.10, 132.50, 132.41, 130.39, 130.24, 129.28, 129.19, 128.75, 128.69, 127.37, 127.32, 127.06, 126.90, 126.26, 126.04, 123.16, 123.08, 122.70, 122.47, 119.01, 118.82, 118.65, 53.50, 53.28.

***4-(3-methyl-4-nitroisoxazol-5-yl)-5-phenyltetrahydrothiophen-3-ol (16a)*:**



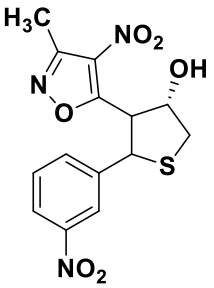
Yield = 75% (pale yellow semi solid); **^{1}H NMR (500 MHz, CDCl$_3$) δ** 7.50 – 7.27 (m, 5H), 5.35 (d, *J* = 10 Hz, 1H), 5.08 (s, 1H), 4.37 (d, *J* = 15 Hz, 1H), 3.77 (dd, *J* = 5, 5 Hz, 1H), 3.15 (d, *J* = 11.7 Hz, 1H), 2.77 (s, 1H), 2.51 (s, 3H); **^{13}C NMR (125 MHz, CDCl$_3$) δ** 170.83, 155.86, 138.22, 128.88, 128.14, 127.69, 56.61, 49.25, 40.75, 37.45, 11.62. **Mass (ESI-MS):** Calculated for: $C_{14}H_{14}O_4N_2S$, m/z 305.0547; Observed: 305.0590.

4-(3-methyl-4-nitroisoxazol-5-yl)-5-(p-tolyl) tetrahydrothiophen-3-ol (16b):



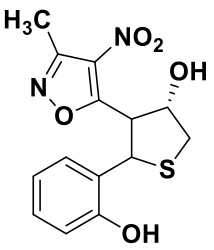
Yield = 80% (pale yellow semi solid); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.36 – 7.32 (m, 2H), 7.07 (d, *J* = 10 Hz, 2H), 5.31 (d, *J* = 10 Hz, 1H), 5.05 – 5.02 (m, 1H), 4.36 – 4.33 (m, 1H), 3.73 (dd, *J* = 5, 5 Hz, 1H), 3.13 (dd, *J* = 5, 5 Hz, 1H), 2.48 (s, 3H), 2.40 (d, *J* = 5 Hz, 1H), 2.27 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 170.88, 155.78, 138.05, 135.08, 129.55, 127.87, 76.94, 56.57, 48.98, 40.76, 21.06, 11.58. **Mass (ESI-MS):** Calculated for: $C_{15}H_{16}N_2O_4S$, m/z 319.0689; Observed: 319.0747.

4-(3-methyl-4-nitroisoxazol-5-yl)-5-(3-nitrophenyl)tetrahydrothiophen-3-ol (16d):



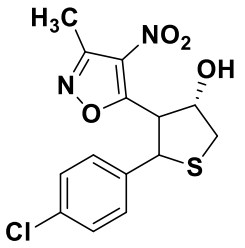
Yield = 88% (White powder); M.P. 140-142 ^{o}C; **^{1}H NMR (500 MHz, DMSO-d_6) δ** 8.33 (d, *J* = 34.9 Hz,1H), 8.05 (d, *J* = 15 Hz, 1H), 7.98 – 7.84 (m, 1H), 7.57 (t, *J* =5 Hz, 1H), 5.65 (d, *J* = 10 Hz, 1H), 5.02 (s, 1H), 4.36 (dd, *J* = 5, 5 Hz, 1H), 3.75 (dd, *J* = 5, 5 Hz, 1H), 3.10 (dd, *J* = 5, 5 Hz, 1H), 2.61 (d, *J* = 10 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6) δ** 170.93, 156.28, 148.35, 141.62, 135.61, 130.65, 123.31, 77.20, 75.51, 56.00, 48.66, 11.48. **Mass (ESI-MS):** Calculated for $C_{14}H_{13}N_3O_6S$: m/z 350.0438; Observed: 350.0441.

5-(2-hydroxyphenyl)-4-(3-methyl-4-nitroisoxazol-5-yl) tetrahydrothiophen-3-ol (16e):



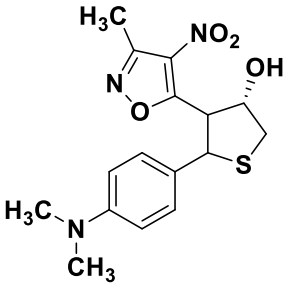
Yield = 70% (yellow semi solid); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.85 (d, *J* = 10 Hz, 1H), 7.73-7.55 (m, 2H), 7.41 (t, *J* =10 Hz, 1H), 5.72 (d, *J* = 10 Hz, 1H), 5.28 (d, *J* = 10 Hz, 1H), 5.11 (s, 1H), 4.64 – 4.55 (m, 1H), 3.72 (dd, *J* = 5, 5 Hz, 1H), 3.41 – 3.16 (m, 1H), 3.17 (dd, *J* = 5, 5 Hz, 5H), 2.47 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 170.23, 155.95, 150.17, 133.28, 130.85, 129.82, 128.92, 124.70, 124.18, 55.13, 44.12, 43.73, 40.57, 37.82, 11.55. **Mass (ESI-MS):** Calculated for $C_{14}H_{14}N_2O_5S$, m/z 321.0540; Observed: 321.0539.

5-(4-chlorophenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)tetrahydrothiophen-3-ol (16f):



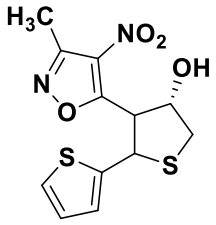
Yield = 82% (pale yellow semi solid); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.40 (d, *J* = 10 Hz, 1H), 7.27 (dd, *J* = 5, 5 Hz, 3H), 5.30 (d, *J* = 15 Hz, 1H), 5.04 (s, 1H), 4.27 (d, *J* = 10 Hz, 1H), 3.73 (d, *J* = 10 Hz, 1H), 3.11 (d, J = 10 Hz, 1H), 2.60 (s, 1H), 2.52 (s, 3H). **^{13}C NMR (125 MHz, DMSO-d_6) δ** 171.38, 156.44, 139.17, 131.95, 130.35, 121.46, 77.23, 55.21, 48.53, 36.94, 11.50. **Mass (ESI-MS):** Calculated for $C_{14}H_{13}ClN_2O_4S$, m/z 339.0211; Observed: 339.0200.

5-(4-(dimethylamino)phenyl)-4-(3-methyl-4-nitroisoxazol-5-yl)tetrahydrothiophen-3-ol (16g):



Yield = 75% (yellow semi solid); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.30 (d, *J* =10 Hz, 2H), 6.60 (d, *J* = 10 Hz, 2H), 5.27 (d, *J* = 10 Hz, 1H), 5.02 (s, 1H), 4.32 (dd, *J* = 5Hz, 1H), 3.72 (dd, *J* = 5, 5 Hz, 1H), 3.08 (d, *J* = 10 Hz, 1H), 2.88 (s, 6H), 2.45 (s, 3H), 2.39 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 171.34, 155.72, 150.31, 128.82, 124.91, 112.55, 112.04, 56.51, 53.85, 49.11, 40.52, 37.54, 11.61. **Mass (ESI-MS):** Calculated for $C_{16}H_{19}N_3O_4S$: 350.1168; Observed: 350.1169.

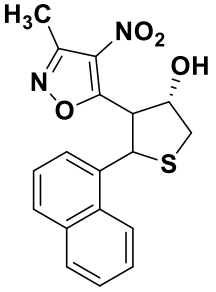
4-(3-methyl-4-nitroisoxazol-5-yl)-5-(thiophen-2-yl)tetrahydrothiophen-3-ol (16h):



Yield = 70% (White semi solid); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18 (d, *J* = 5. Hz, 1H), 7.01 (d, *J* = 5 Hz, 1H), 6.86 (dd, *J* = 5, 5 Hz, 1H), 5.65 (d, *J* = 10 Hz, 1H), 5.02 (s, 1H), 4.34 (dd, *J* = 5, 5 Hz, 1H), 3.75 (dd, *J* = 5, 5 Hz, 1H), 3.12 (dd, *J* = 5, 5 Hz, 1H), 2.63 (d, *J* = 10 Hz, 1H), 2.53 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 170.50, 155.93, 142.69, 127.00, 126.44, 125.55, 76.66, 57.60, 44.80, 40.56, 11.61. **Mass (ESI-MS):** Calculated for $C_{12}H_{12}N_2O_4S_2$: m/z 311.0154; Observed: 311.0154.

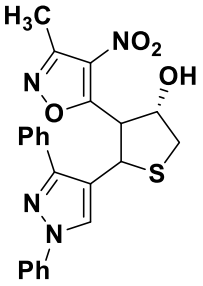
4-(3-methyl-4-nitroisoxazol-5-yl)-5-(naphthalen-1-yl)tetrahydrothiophen-3-ol (16i):

Yield = 78% (White solid); M.P. 134-136 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$) δ** 8.23 (d, *J* = 10 Hz, 1H), 7.83 (d, *J* = 10 Hz, 1H), 7.74 (d, *J* = 10 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.52 (t, *J* = 10 Hz, 1H), 7.35 (t, *J* = 10 Hz, 1H), 6.10 (d, *J* = 15 Hz, 1H), 5.13 (s, 1H), 4.82 (dd, *J* = 5, 5 Hz, 1H), 3.76 (dd, *J* = 5, 5 Hz, 1H), 3.20 (dd, *J* = 5, 5 Hz, 1H), 2.45 (s, 3H), 2.44 (s, 1H). **^{13}C NMR (125 MHz, CDCl$_3$) δ** 170.87, 155.72, 133.90, 131.90, 128.80, 126.65, 126.10, 125.50, 123.23, 53.24, 40.64, 11.56. **Mass (ESI-MS):** Calculated for $C_{18}H_{16}N_2O_4S$: m/z 355.0749; Observed: 355.0747.



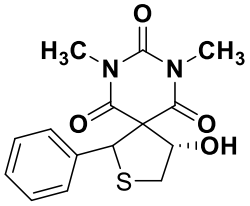
5-(1,3-diphenyl-1H-pyrazol-4-yl)-4-(3-methyl-4-nitroisoxazol-5-yl)tetrahydrothiophen-3-ol (16j):

Yield = 72% (White solid); M.P. 180-182 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$) δ** 8.04 (s, 1H), 7.67 (d, *J* = 5 Hz, 2H), 7.65 – 7.58 (t, *J* = 2 Hz 2H), 7.44 – 7.35 (m, 5H), 7.27 (t, *J* = 15 Hz, 1H), 5.44 (d, *J* = 10 Hz,1H), 4.90 (s, 1H), 4.44 (dd, *J* = 5, 5 Hz, 1H), 3.63 (dd, *J* = 5,5 Hz, 1H), 3.12 (d, *J* = 10 Hz, 1H), 2.45 (s, 3H), 2.44 (d, *J* = 5 Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$) δ** 170.51, 155.62, 152.26, 139.65, 132.56, 129.44, 128.70, 128.45, 126.72, 126.23, 119.41, 119.00, 54.85, 40.60, 40.30, 11.55: **Mass (ESI-MS):** Calculated for $C_{23}H_{20}N_4O_4S$: m/z 447.1117; Observed: 447.1121.

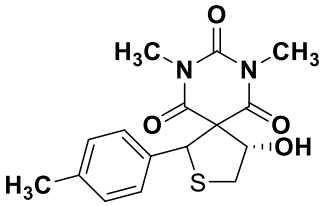


4-hydroxy-7,9-dimethyl-1-phenyl-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18a):

Yield = 73% (White solid); M.P: 135-137 °C, **^{1}H NMR (400 MHz, CDCl$_3$) δ** 7.26 (d, *J* = 7.2 Hz, 3H), 7.24 (d, *J* = 6.4 Hz, 2H), 5.37 (t, *J* = 8.8 Hz, 1H), 5.03 (s, 1H), 3.76 (t, *J* = 9.6 Hz, 1H), 3.40 (t, *J* = 8.8 Hz, 1H), 3.24 (s, 3H), 2.87 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** δ 169.10, 165.75, 150.00, 134.11, 129.54, 128.67, 127.80, 80.42, 67.63, 57.66, 36.37, 29.08, 28.12. **Mass (ESI-MS):** Calculated for $C_{15}H_{16}N_2O_4S$, m/z: 320; found: 319 (M-1).

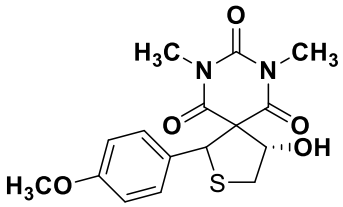


4-hydroxy-7,9-dimethyl-1-(p-tolyl)-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18b):



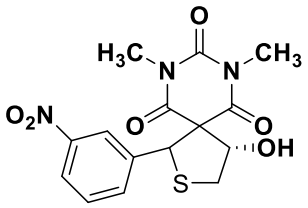
Yield = 75% (White solid); M.P: 179-181 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.11 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.36 (d, *J* = 6.3 Hz, 1H), 5.01 (s, 1H), 3.76 (t, *J* = 9.6 Hz, 1H), 3.43 (t, *J* = 8.9 Hz, 1H), 3.24 (s, 3H), 2.93 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.12, 165.87, 139.53, 130.87, 129.30, 127.70, 80.33, 67.64, 57.65, 36.43, 29.05, 28.14, 21.16. **Mass (ESI-MS):** Calculated for $C_{16}H_{18}N_2O_4S$, m/z: 334; found 333 (M-1).

4-hydroxy-1-(4-methoxyphenyl)-7,9-dimethyl-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18c):



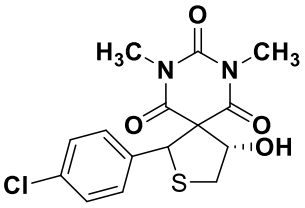
Yield = 80% (White solid); M.P: 180-1182 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.14 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.33 (t, *J* = 7.6 Hz, 1H), 5.02 (s, 1H), 3.83 – 3.68 (m, 4H), 3.37 (s, 1H), 3.23 (s, 3H), 2.94 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.24, 165.75, 160.32, 150.11, 129.08, 125.72, 113.90, 80.28, 67.65, 57.18, 55.33, 36.27, 29.08, 28.20. **Mass (ESI-MS):** Calculated for $C_{16}H_{18}N_2O_5S$, m/z: 350; found: 349 (M-1).

4-hydroxy-7,9-dimethyl-1-(3-nitrophenyl)-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18d):



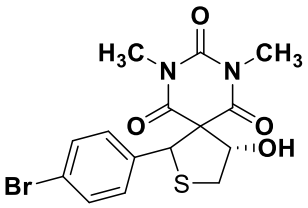
Yield = 85% (White solid); M.P: 152-153 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.15 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 8.1 Hz, 1H), 5.34-5.25 (m, 1H), 5.26 (s, 1H), 3.77 (t, *J* = 9.8 Hz, 1H), 3.44 (t, *J* = 9.6, 1H), 3.30 (s, 3H), 2.95 (s, 3H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ** 168.95, 165.10, 149.98, 148.20, 137.31, 134.26, 129.71, 124.10, 123.32, 81.73, 81.43, 77.37, 77.06, 76.74, 67.41, 55.03, 36.41, 29.35, 28.30. **Mass (ESI-MS):** Calculated for $C_{15}H_{15}N_3O_6S$, m/z: 365; found: 364 (M-1).

1-(4-chlorophenyl)-4-hydroxy-7,9-dimethyl-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18e):



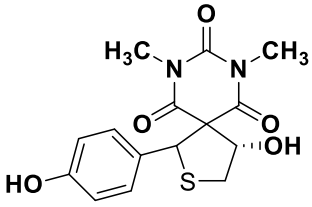
Yield = 78% (White solid); M.P: 135-137 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.30 (t, *J* = 8.8 Hz, 1H), 5.07 (s, 1H), 3.74 (t, *J* = 9.7 Hz, 1H), 3.37 (t, *J* = 8.5 Hz, 1H), 3.27 (s, 3H), 2.95 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.13, 165.45, 150.00, 135.18, 132.93, 129.34, 128.85, 81.08, 77.42, 77.08, 76.75, 67.45, 56.17, 36.35, 29.21, 28.22. **Mass (ESI-MS):** Calculated for $C_{15}H_{15}ClN_2O_4S$, m/z: 353; found: 353 (M).

1-(4-bromophenyl)-4-hydroxy-7,9-dimethyl-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18f):



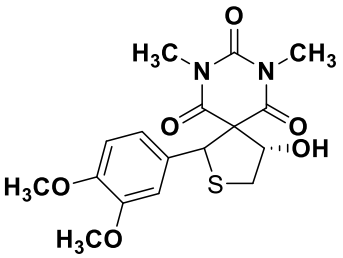
Yield = 82% (White solid); M.P:185-187 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.41 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.30 (q, *J* = 8.4 Hz, 1H), 5.05 (s, 1H), 3.76 (t, *J* = 9.7 Hz, 1H), 3.42 (t, *J* = 8 Hz, 1H), 3.30 (s, 1H), 3.27 (s, 3H), 2.95 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.11, 165.42, 149.98, 135.17, 132.90, 129.33, 128.81, 81.05, 77.44, 77.07, 76.73, 67.43, 56.15, 36.33, 29.20, 28.20. **Mass (ESI-MS):** Calculated for $C_{15}H_{15}BrN_2O_4S$, m/z: 399; found: 399 (M).

4-hydroxy-1-(4-hydroxyphenyl)-7,9-dimethyl-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18g):



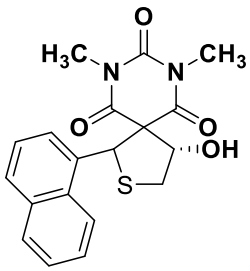
Yield = 70% (White solid); M.P: 175-177 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.07 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.34 (d, *J* = 6.1 Hz, 1H), 5.20 (d, *J* = 8.3 Hz, 1H), 5.12 (d, *J* = 3.4 Hz, 1H), 3.74 (t, *J* = 11.4 Hz, 1H), 3.28 (s, 1H), 2.97 (s, 3H), 2.55 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 165.30, 157.84, 129.00, 115.37, 80.84, 56.27, 40.40, 40.11, 39.77, 39.55, 36.00. **Mass (ESI-MS):** Calculated for $C_{15}H_{16}N_2O_5S$, m/z: 335; found: 335 (M).

1-(3,4-dimethoxyphenyl)-4-hydroxy-7,9-dimethyl-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18h):



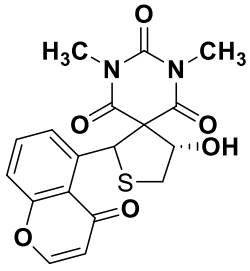
Yield = 74% (White solid); M.P: 114-116 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.84 (s, 1H), 6.70 (s, 2H), 5.36 (q, *J* = 9.1 Hz, 1H), 5.02 (s, 1H), 3.83 (d, *J* = 5.1 Hz, 6H), 3.74 (t, *J* = 9.6 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.26 (s, 3H), 2.95 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.22, 165.84, 150.07, 149.72, 148.96, 126.21, 120.33, 110.55, 80.47, 67.67, 57.60, 55.95, 36.47, 29.11, 28s.25. **Mass (ESI-MS):** Calculated for $C_{17}H_{20}N_2O_6S$, m/z: 380; found: 379 (M-1).

4-hydroxy-7,9-dimethyl-1-(naphthalen-1-yl)-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18i):



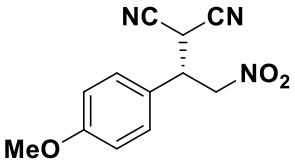
Yield = 80% (White solid); M.P: 153-155 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.97 (d, *J* = 7.2 Hz, 1H), 7.82 (dd, *J* = 19.2, 8.1 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.52-7.40 (m, 3H), 5.98 (s, 1H), 5.65 – 5.53 (m, 1H), 3.92 (t, *J* = 9.6 Hz, 1H), 3.52 (t, 8.4 Hz, 1H), 2.80 (s, 3H), 2.75 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.12, 166.03, 149.55, 133.53, 131.15, 129.85, 129.43, 127.22, 126.80, 126.02, 124.90, 121.46, 80.72, 67.08, 51.65, 36.38, 29.12, 28.00. **Mass (ESI-MS):** Calculated for $C_{19}H_{18}N_2O_4S$, m/z: 370; found: 369 (M-1).

4-hydroxy-7,9-dimethyl-1-(4-oxo-4H-chromen-3-yl)-2-thia-7,9-diazaspiro[4.5]decane-6,8,10-trione (18j):



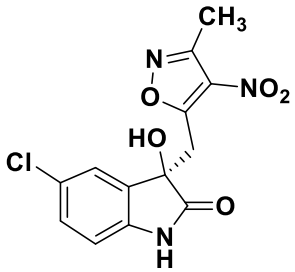
Yield = 76% (White solid); M.P: 192-194 °C, **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.40 (s, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 6.8 Hz, 1H), 7.43 – 7.38 (m, 1H), 5.35 (s, 1H), 5.32 (s, 3H), 5.13 (dd, *J* = 15.9, 6.5 Hz, 4H), 3.55 (d, *J* = 10.0 Hz, 4H), 3.46 (s, 14H), 3.17 (dd, *J* = 10.2, 6.2 Hz, 4H), 3.02 (s, 11H). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 177.30, 170.65, 166.64, 156.77, 156.78, 151.14, 134.16, 125.76, 125.64, 125.53, 122.55, 118.20, 84.45, 64.94, 46.87, 36.21, 29.44, 28.12. **Mass (ESI-MS):** Calculated for $C_{18}H_{16}N_2O_6S$, m/z: 388; found: 411 (M +Na).

2-(1-(4-methoxyphenyl)-2-nitroethyl)malononitrile (23):



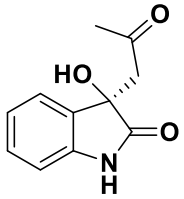
Yield = 80% (light yellow semi solid); **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.01 - 4.82 (m, 2H), 4.40 (d, *J* = 5.8 Hz, 1H), 4.04 (dd, *J* = 13.1, 7.0 Hz, 1H), 3.83 (s, 3H).

5-chloro-3-hydroxy-3-((3-methyl-4-nitroisoxazol-5-yl)methyl)indolin-2-one (26):



Yield = 95% (White solid), M.P: 95-97 ^oC; **^{1}H-NMR (500 MHz, MeOD)** δ 7.28 (t, *J* = 5 Hz, 2H), 6.88 (d, *J* = 5 Hz, 1H), 3.95 (d, *J* = 15 Hz, 1H), 3.73 (d, *J* = 15 Hz, 1H), 3.34 (s, 1H), 2.49 (s, 3H). **^{13}C- NMR (125 MHz, MeOD) δ** 178.16, 168.67, 155.34, 139.84, 131.89, 131.17, 129.68, 127.54, 124.19, 111.29, 74.81, 34.50, 10.08. **Mass (ESI-MS):** m/z Calculated: 323; Observed: 346 (M+ Na)

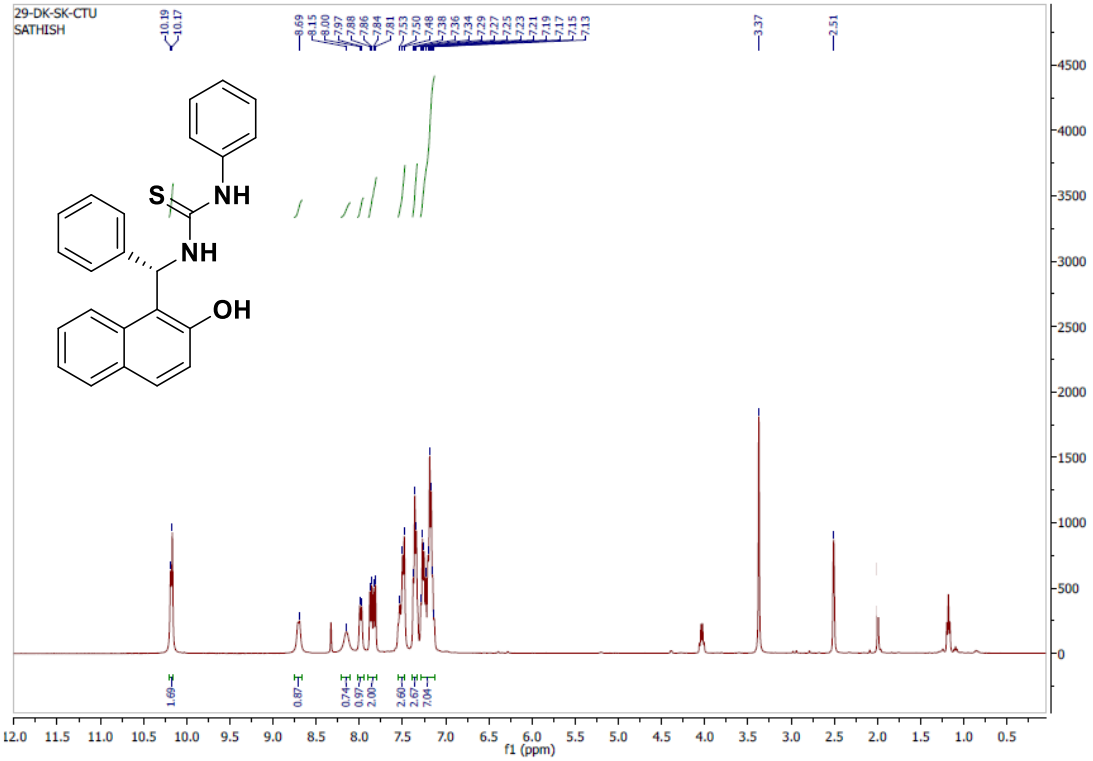
3-hydroxy-3-(2-oxopropyl)indolin-2-one (29):

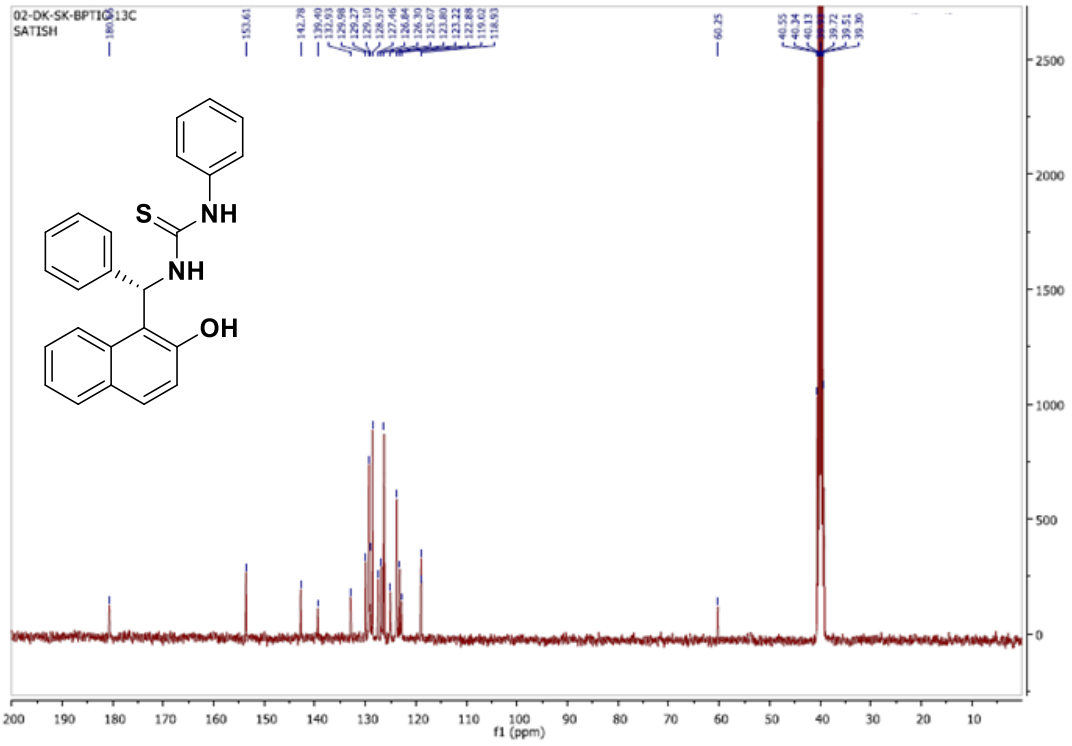


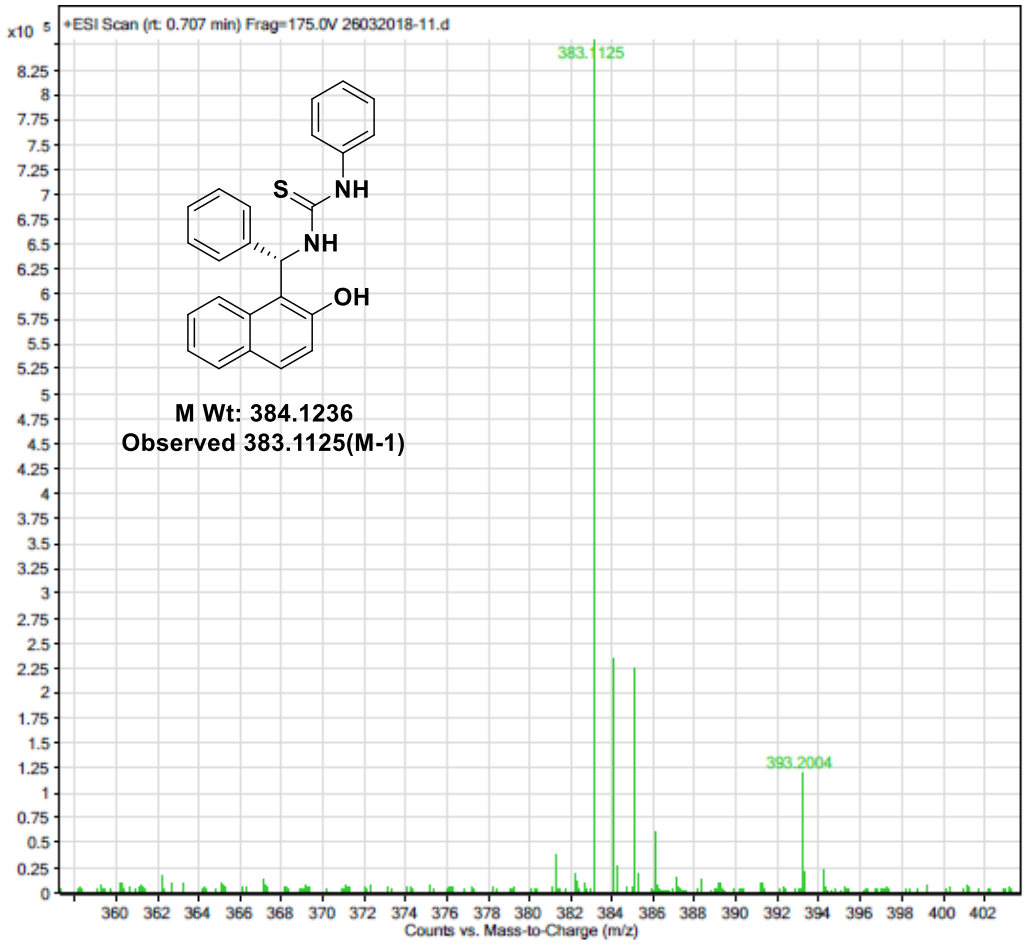
Yield = 90%; **^{1}H NMR (400 MHz, DMSO-d_6) δ** 10.22 (s, 1H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 5.98 (s, 1H), 3.27 (d, *J* = 16.6 Hz, 1H), 3.00 (d, *J* = 16.6 Hz, 1H), 2.00 (s, 3H).

6.7 Selected spectra

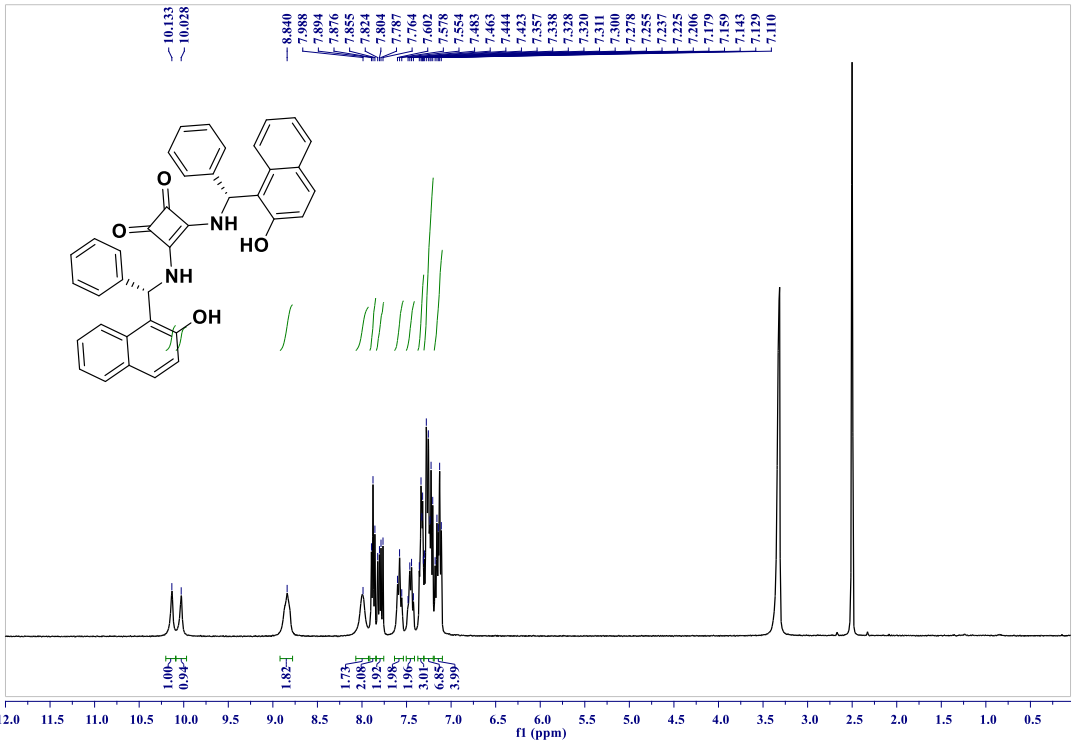
(S)-1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)-3-phenylthiourea (11):

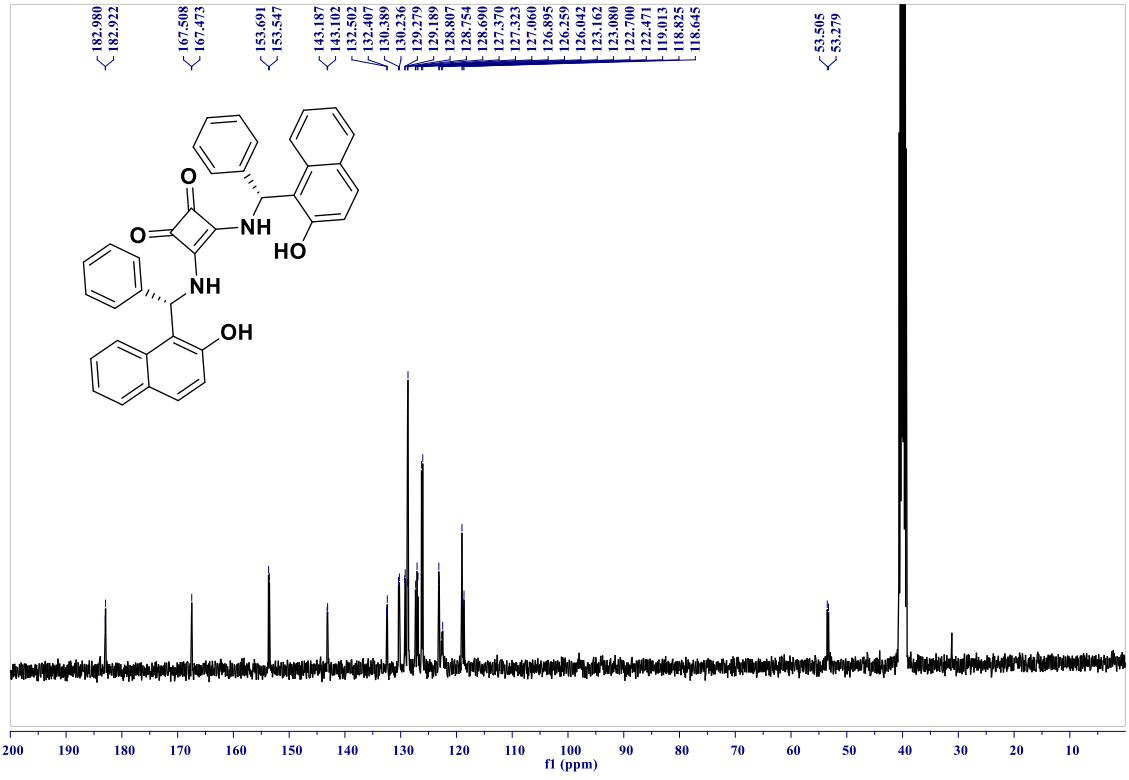




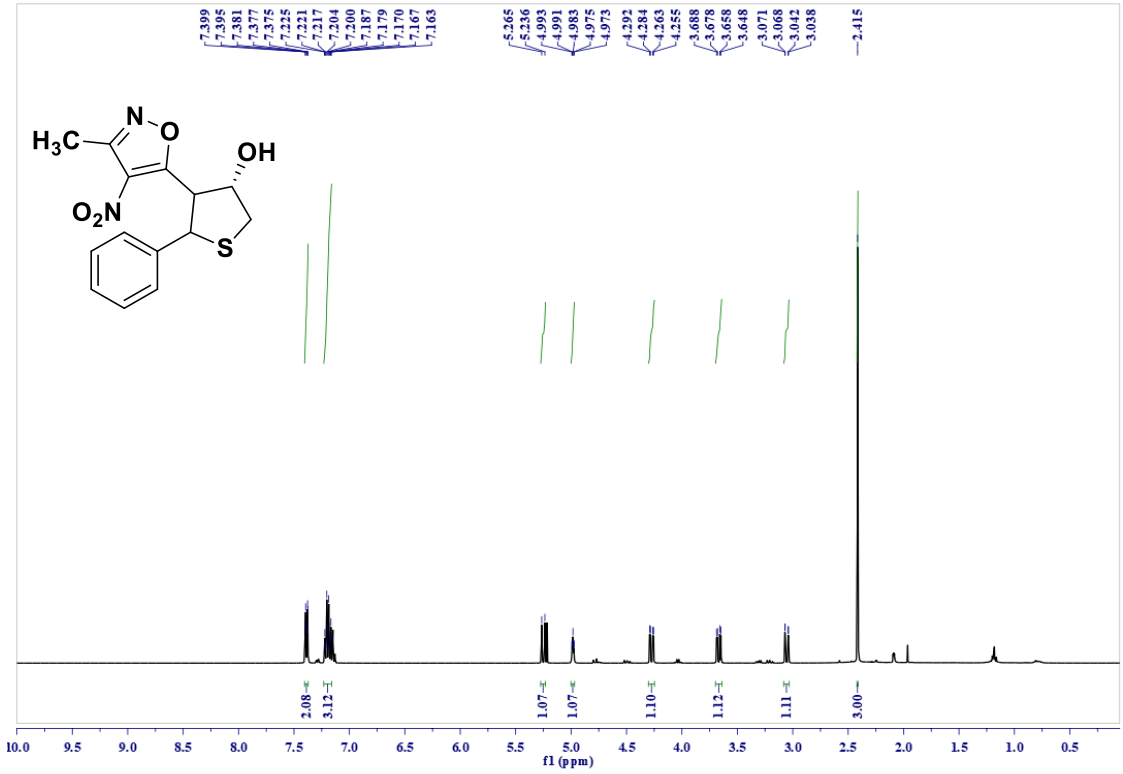

+ESI Scan (rt: 0.707 min) Frag=175.0V 26032018-11.d
x10 5
383.1125
393.2004
S
NH
NH
OH
M Wt: 384.1236
Observed 383.1125(M-1)
Counts vs. Mass-to-Charge (m/z)

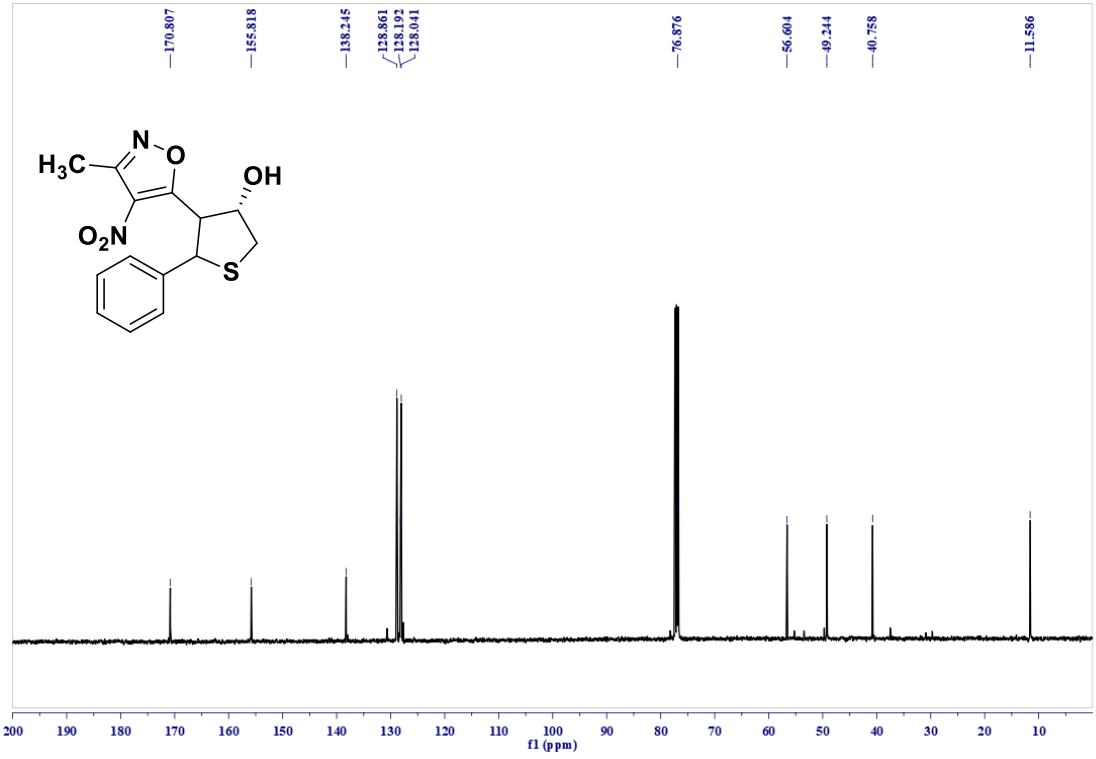
3-(((R)-(2-hydroxynaphthalen-1-yl)(phenyl)methyl)amino)-4-(((S)-(2-hydroxynaphthalen-1-yl)(phenyl)methyl)amino)cyclobut-3-ene-1,2-dione (13):



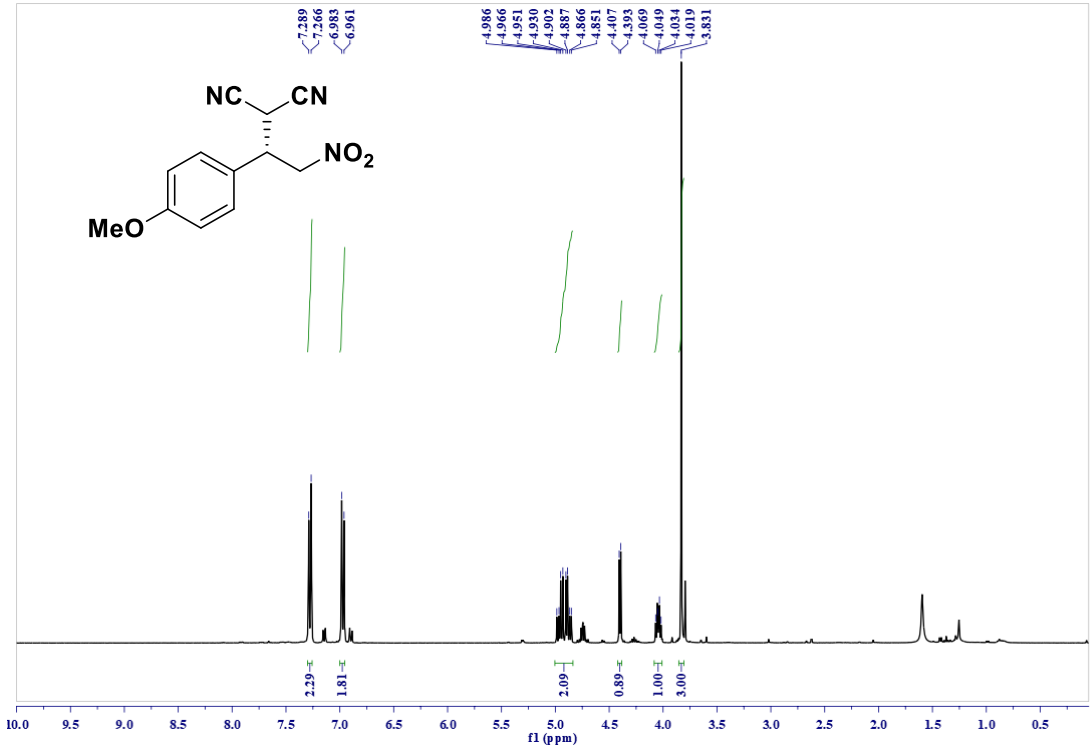


(3S)-4-(3-methyl-4-nitroisoxazol-5-yl)-5-phenyltetrahydrothiophen-3-ol

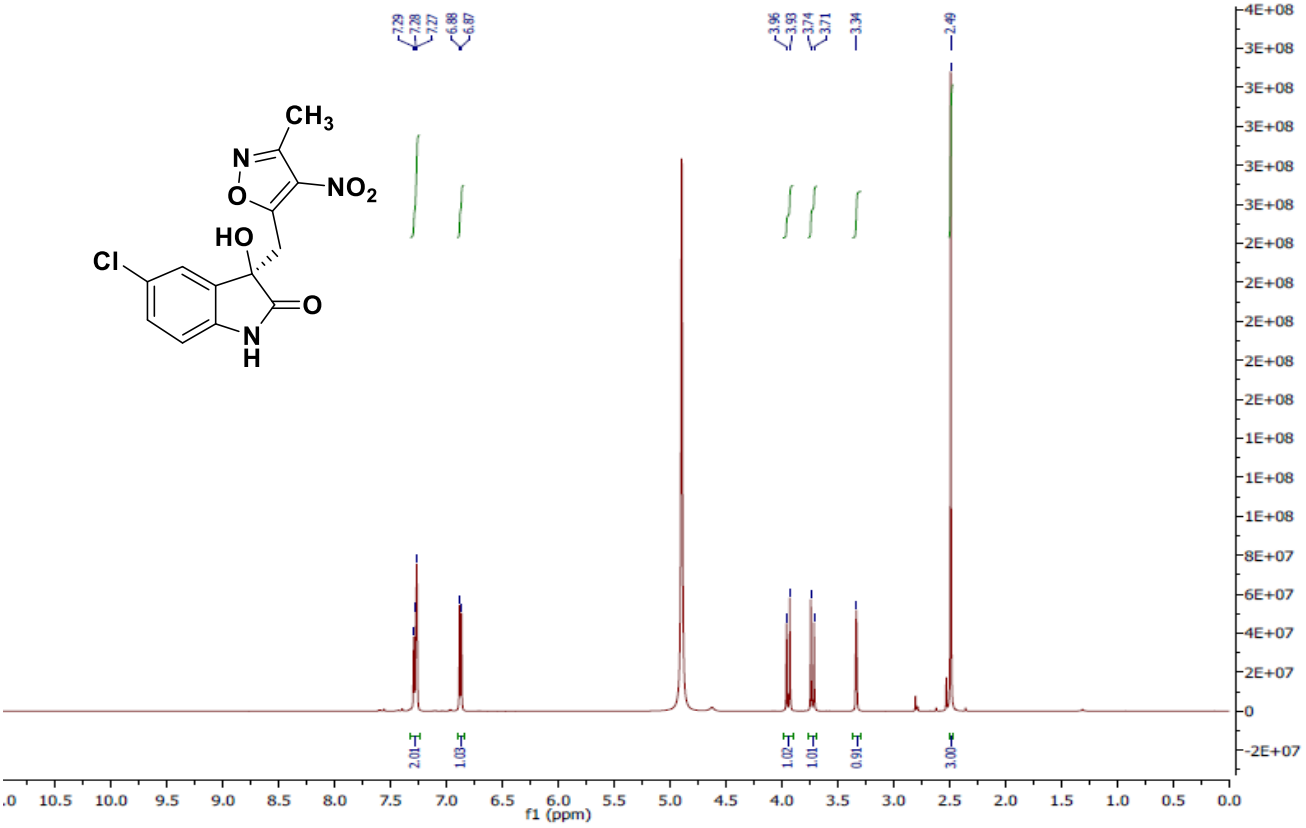


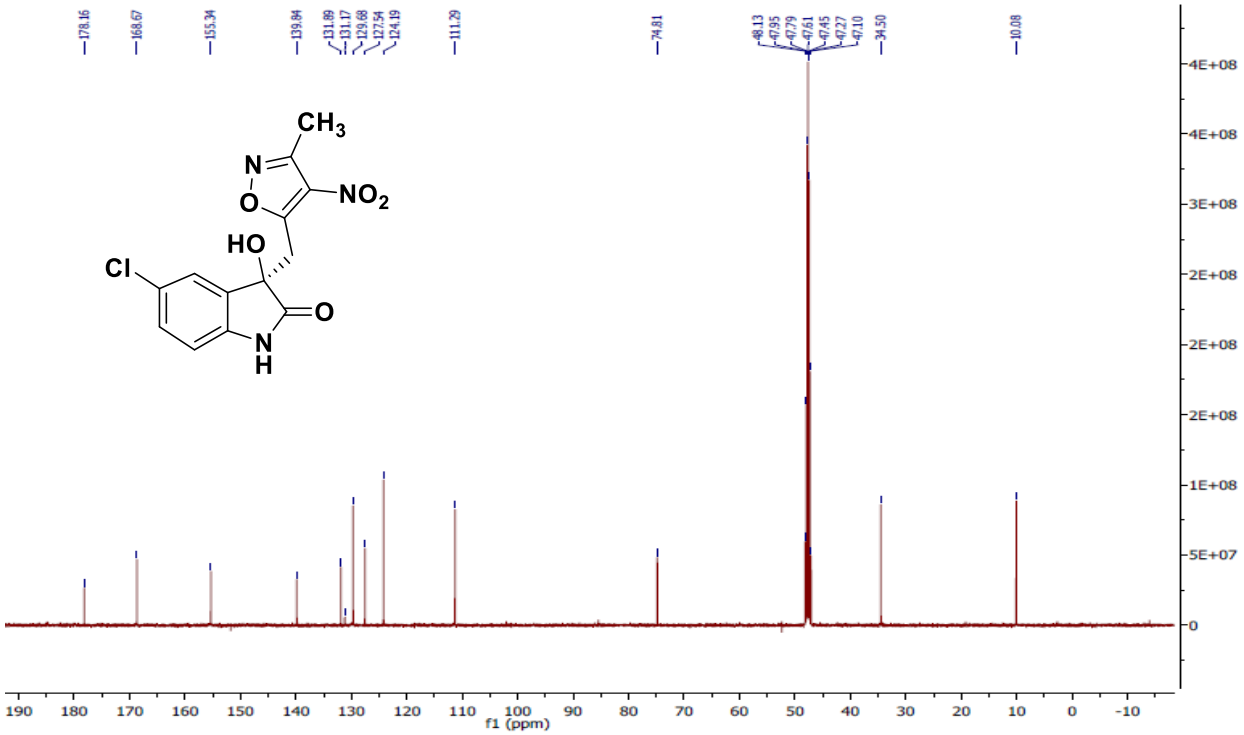


2-(1-(4-methoxyphenyl)-2-nitroethyl)malononitrile (23):

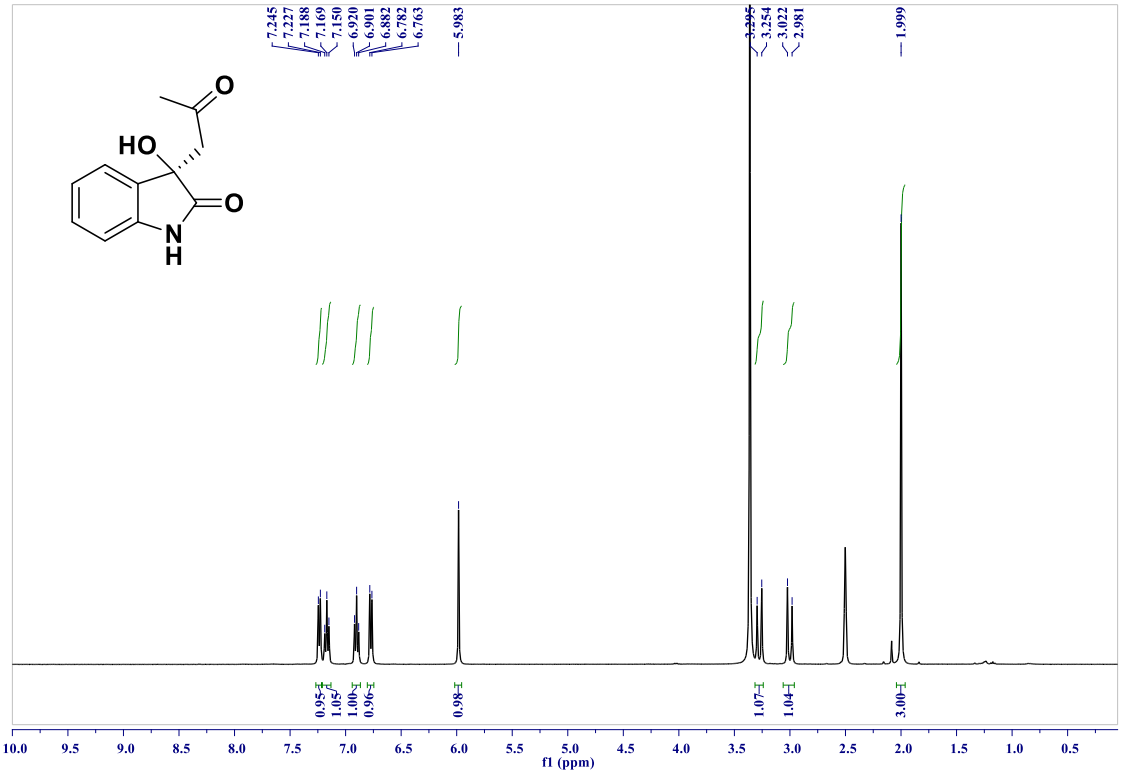


3-hydroxy-3-((3-methyl-4-nitroisoxazol-5-yl) methyl) indolin-2-one (26):





3-hydroxy-3-(2-oxopropyl)indolin-2-one (29):



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Summary and Conclusions

Summary and conclusions

CHAPTER-I

Introduction to natural and biologically active heterocyclic molecules

Heterocyclic compounds are broadly involved in medicinal and agricultural fields. Countless additives and modifiers based on heterocyclic molecules are used in industries as varied as reprography, cosmetics, information storage and plastics. Therefore, the development of methodologies useful for the assembly of molecules containing heterocyclic scaffolds has becoming one of the fascinating area in both the academic and industry. Thus, organic and pharmaceutical chemists have been making extensive efforts to synthesize those molecules through developing versatile and efficient synthetic strategies. Since the aim of present work (thesis) is development of synthetic methods based on chromene & spirochromenes, isoxazole scaffolds, *N,N′* bicyclic pyrazolones, spirooxindoles, cyclopropanes and tetrahydrothiophenes. This chapter also describes the importance of natural and pharmacological activities of these molecules.

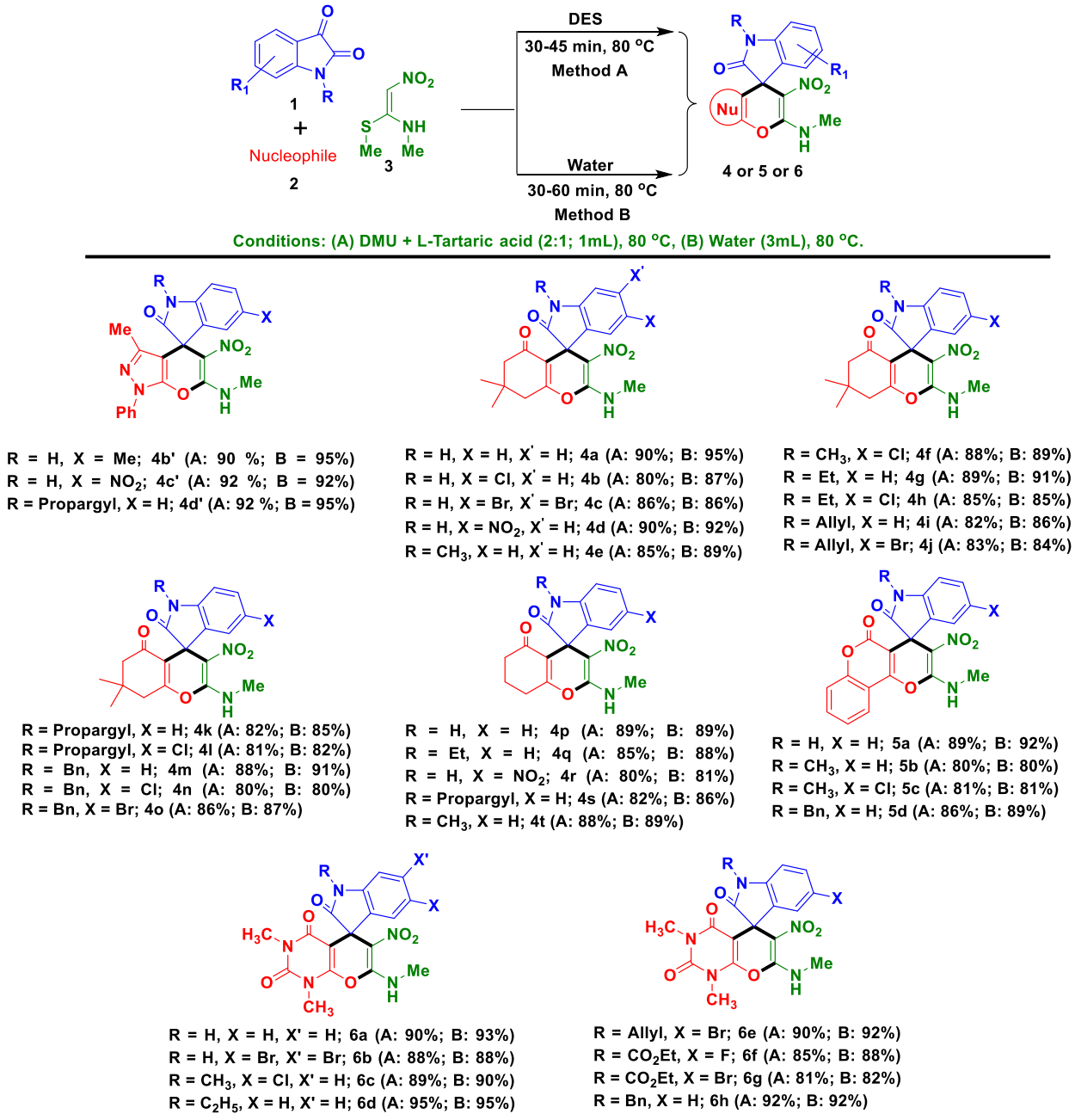
CHAPTER-II

Dimethylurea/L-Tartaric acid as deep eutectic solvent for one-pot synthesis of 2-(methylamino)-3-nitrospiro-[chromene] and N-methyl-3-nitro-4H chromen-2-amines

The chromenes and spirochromenes are well-known scaffolds in medicinal chemistry. Chromene derivatives show anticancer properties, antimicrobial, anti-tubercular, antimalarial, antibacterial, anti-apoptotic (Bcl-2 proteins), anti-fungal, anti-rheumatic, anti-hyperglycemic and α-glucosidase inhibitory activities. Some of these compounds play key role in central nervous system, possess excellent binding capacity towards many receptors in the biological systems and also used as cosmetics, pigments and biodegradable agrochemicals. The chromene and spirochromenes were synthesized in different conditions including catalyst-free, homogeneous and heterogeneous catalysts.

Considering the biological importance of chromene and spirochromenes, in the present work we described an application of dimethyl urea and L-tartaric acid as deep eutectic solvent (DES) for the synthesis of 2-(methylamino)-3-nitrospiro[chromene] by a reaction of substituted isatins, nucleophiles and (*E*)-N-methyl-1-(methylthio)-2-nitroethenamine. Systematic studies

proved that the dimethyl urea and L-tartaric acid in 2:1 ratio at 80 °C gave the desired products in good yields in shorter period of reaction time (45 min). To explore further to find out the green method the same reaction was carried out using water as reaction medium and good yields of the products were obtained in 1 h.

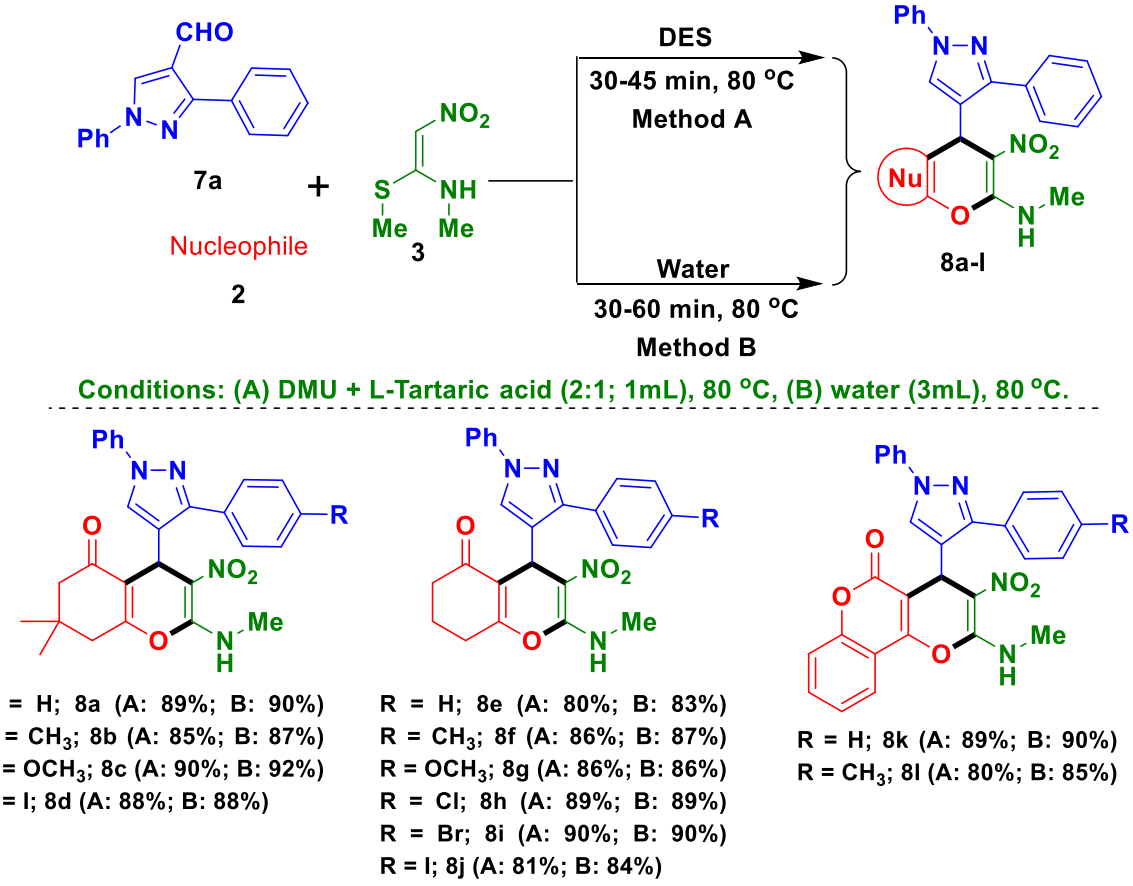


Scheme-2.1: Various spirochromene derivatives (**4-6**) under optimized reaction conditions.

Further, the same protocol was explored for the synthesis of functionalized spirochromenes, For this, different isatins (substitution on aromatic ring and nitrogen atom),

nucleophiles (pyrazole, dimedone, 1,3-cyclohexanedione, 4-hydroxy coumarin and *N,N'*-dimethyl barbituric acid) and (*E*)-N-methyl-1-(methylthio)-2-nitroethenamine under both conditions (in DES and water) to a library of spirochromene hybrids with excellent yields (upto 95%) as shown in (**Scheme-2.1)**.

Keeping in view of the biological activity of pyrazole-chromene hybrids, we extended this strategy for the synthesis of different chromene hybrids with pyrazole moiety. Thus, the reaction of pyrazole aldehyde (**7a**) with different nucleophiles (**2**), and (*E*)-N-methyl-1-(methylthio)-2-nitroethenamine (**3**) under the optimized reaction conditions in DES and water (as reaction media) at 80 °C gave the desired products with excellent yields up to 92% (**Scheme-2.2**). All synthesized compounds were characterized using ^{1}H, ^{13}C-NMR and mass spectroscopic data.



Scheme-2.2: Synthesis of pyrazole based chromene derivatives (**8a-l**) under optimized condition.

CHAPTER-III

Synthesis of spiro pyrazolone-oxindole and bicyclic pyrazolone derivatives via solvent dependent regioselective aza-1,4/1,6-Michael and intramolecular cycloaddition under catalyst-free conditions

N,N′-Fused bicyclic pyrazolones are useful scaffolds commonly found in many biologically active molecules. These compounds were reported as γ-lactam antibiotics, antibacterial agents, acetyl-CoA carboxylase (ACC) inhibitors, sarcoplasmic reticulum Ca^{+2}–ATPase inhibitors, anticancer, and as herbicides and pesticides in agriculture industry.

Considering the importance of spiro/bicyclic pyrazolones, herein we report the first example of solvent dependent, regioselective-switchable reaction between 3-methyl-4-nitro-5-isatylidenyl-isoxazoles (**1**) and *N,N′*-cyclic azomethine imines (**2**) in presence of toluene (80 ^{o}C) or THF (at 60 ^{o}C) leading to complex dinitrogen-fused bicyclic containing spirocyclic oxindoles with good yields for 4-6 h.

Further, we have extended the optimized protocol for the synthesis of various dinitrogen-fused spirocyclic oxindoles. To achieve this, the substituted isatins (substitution on aromatic ring and nitrogen) and azomethine imines (aromatic and hetero aromatic) were reacted under optimized conditions (both in toluene and THF) to afford corresponding cycloaddition products (**3a-3m** and **4a-4k**) with good yields 70-86% (**Scheme-3.1 & Scheme-3.2**) for 4-6 h. All newly synthesized compounds were characterized using ^{1}H, ^{13}C-NMR and Mass spectroscopic data. Further, towards establishing the regioselectivity, single crystal X-ray crystallographic data was obtained for the compounds **3b**, **3c**, **3i** and **4c**.

Later, we extended our strategy for the synthesis of diphenyltetrahydropyrazolo pyrazolones (dinitrogen-fused heterocyclics). For this, simple isoxazole-styrenes (**5**) were treated with azomethine imines (**2**) under optimized reaction conditions (in toluene and THF). To our surprise, the reaction was successful only in toluene (as reaction medium) to delivering isoxazole based dinitrogen-fused compounds (**6a-6k**) with good yields 65-90% in 4-5 h **(Scheme-3.3)**.

The isoxazole moiety was also used as masked ester to generate carboxylic acid *via* ring opening under basic/oxidative conditions. Finally, the cycloadducts **3a** and **6b** were converted into carboxylic acids **7a** and **8b** by treating with aq. NaOH (ring opening of isoxazole moiety) in 78% and 85% respectively (**Schemes 3.4**). Then the carboxylic acid (**8b**) further functionalized into

ester (**9b**) and amide (**10b**) derivatives with 65% and 85% of the yields using standard conditions (**Scheme-3.4**).

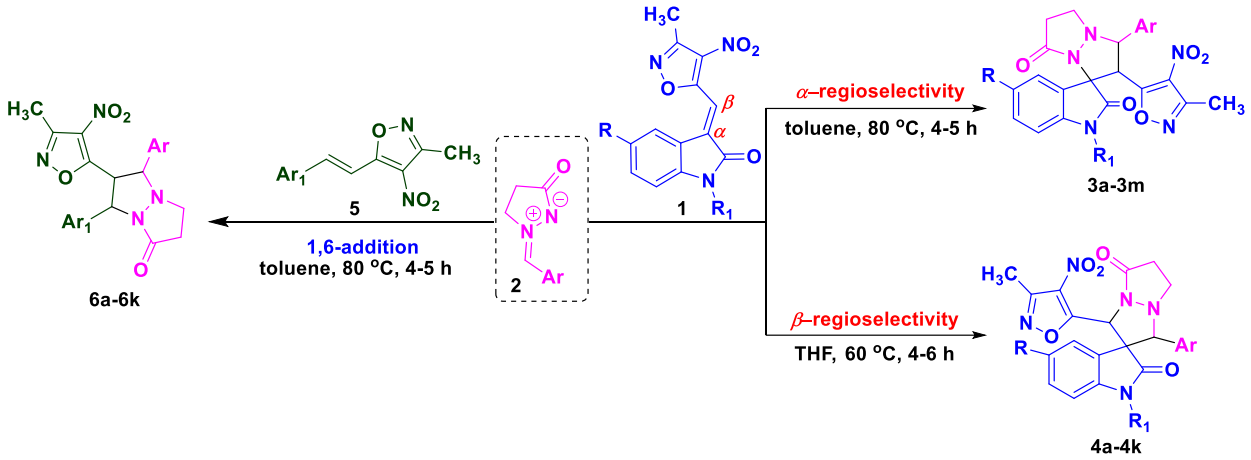
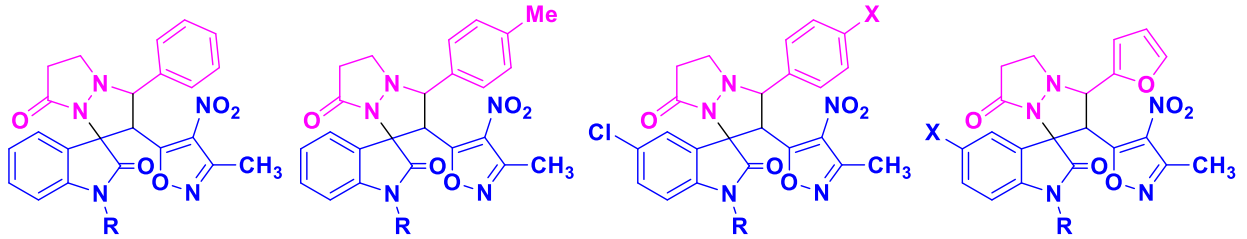
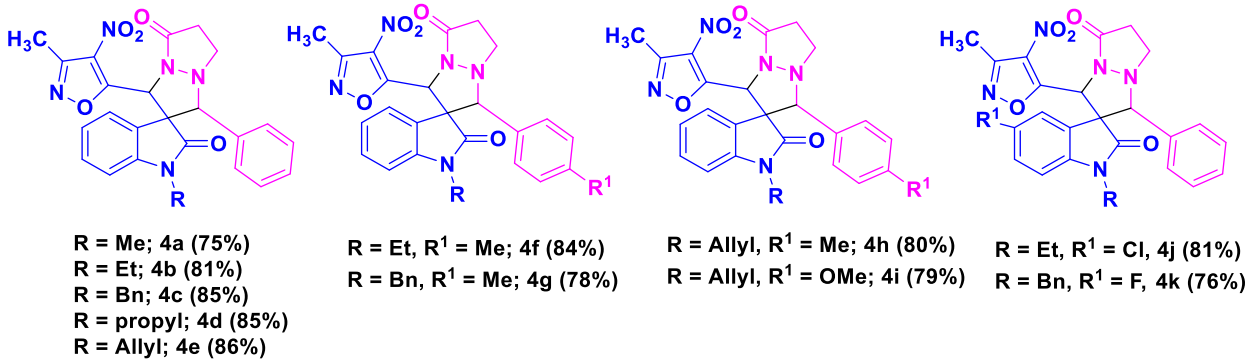


Figure-3.1: Synthesis of spiro pyrazolone-oxindole and bicyclic pyrazolone derivatives



Scheme-3.1: Substrate scope for the synthesis of functionalized dinitrogen-fused spirooxindoles (3a-3m).



Scheme-3.2: Substrate scope for the synthesis of functionalized dinitrogen-fused spirooxindoles (4a-4k).

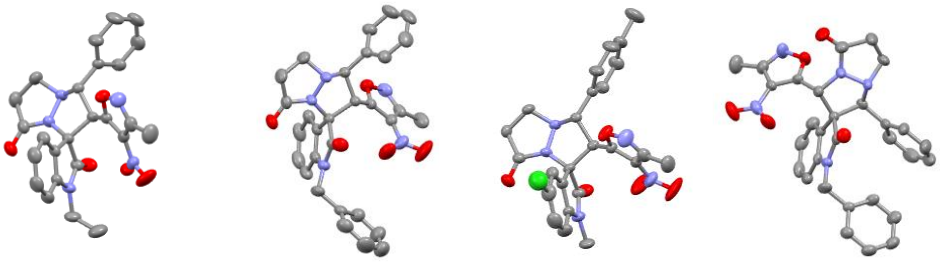
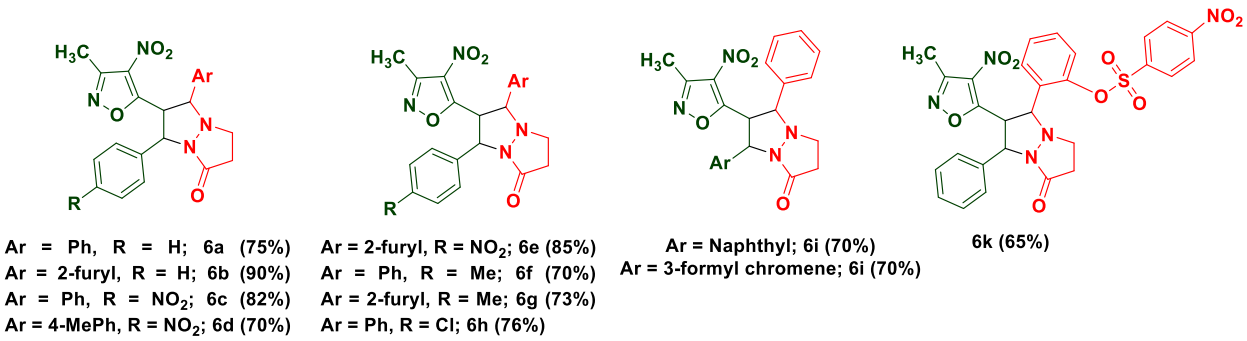
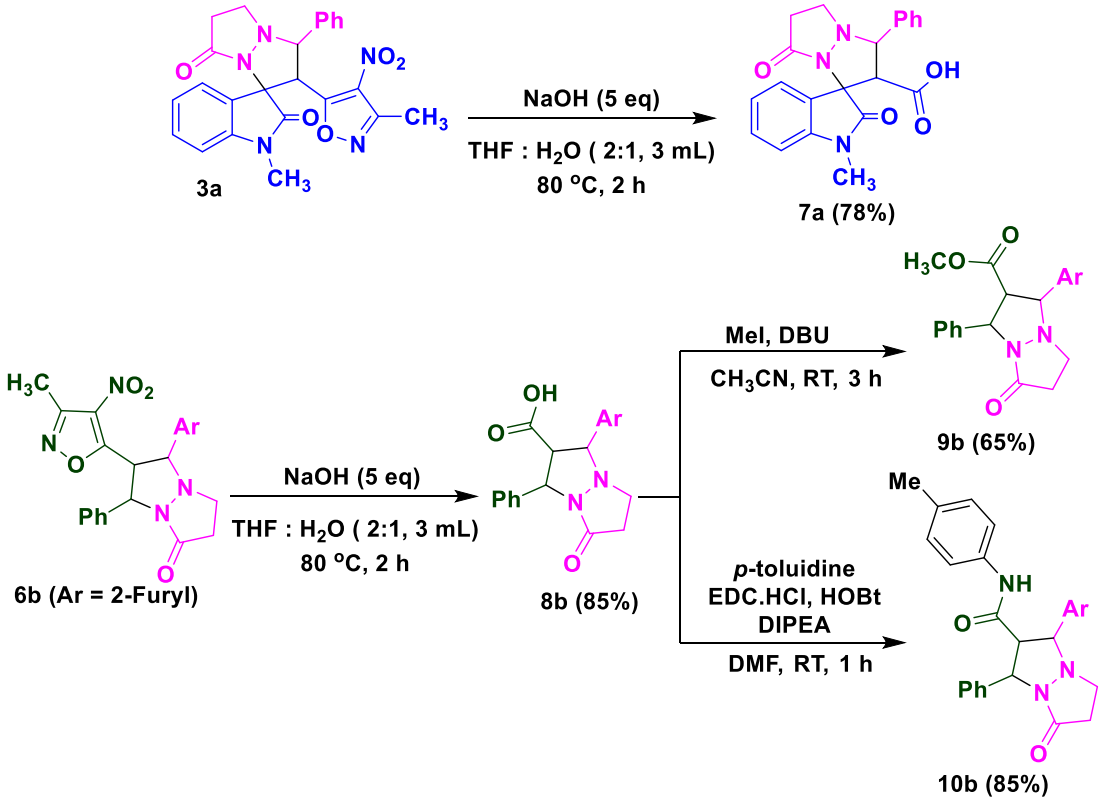


Figure-3.2: Molecular structure of the compounds **3b, 3c, 3i, 4c**



Sceme-3.3: Substrate scope for the synthesis of functionalized *N,N'*-Fused bicyclic pyrazolones.



Scheme-3.4: Further functionalization of pyrazolo pyrazolones **3a** and **6b.**

CHAPTER-IV

Synthesis of spiro[indoline-3,2'-naphthalene]-4'-carbonitriles via regiodivergent domino protocol of isoxazole-oxindole styrenes and vinyl malononitriles

Isatin and its C-3 derivatives are the most employed starting materials in the architecture of various spirocyclic 2-oxindoles. In this respect, isoxazole oxindole styrenes are the most important reagents because of their easy synthesis and versatile reactivity. Recently they have been reported in many synthetic reactions, such as 1,3-dipolar cycloaddition, domino/tandem and vinylogous henry-type reactions. In addition to this, α, α-dicyanoolefins (vinyl malononitriles) act as vinylogous donors and acceptors and recognized important starting materials in synthetic organic chemistry. Due to their dense functionalities and versatile reactivity of α, α-dicyanoolefins have been widely used in various organic transformations (Michael, Michael/cyclization and cycloaddition reactions) for the synthesis of structurally complex molecules.

In this present work, we have described a solvent-dependent and base catalyzed reaction in between 3-methyl-4-nitro-5-isatylidenyl-isoxazole (**1**) and vinyl malononitriles (**2**) *via* vinylogous Michael addition as the key step followed by sequential tandem reaction to afford diastereomers of spiro[indoline-3,2'-naphthalene]-4'-carbonitriles bearing isoxazole containing scaffolds.

Further, we have extended this protocol for the synthesis of functionalized spiro[indoline-3,2'-naphthalene]-4'-carbonitriles by using 3-methyl-4-nitro-5-isatylidenyl-isoxazole (**1**) and vinyl malononitriles (**2**) under optimized reaction conditions (both EtOH/THF; K_2CO_3) to afford desired products with good to excellent yield (**Scheme-4.1 & Scheme-4.2**). All newly synthesized compounds were characterized using NMR and mass spectroscopic data. Further, towards establishing the stereoselectivity, single crystal X-ray crystallographic data was obtained for the compounds **3e** and **3b' (Figure-4.2)**.

To check the reactivity of simple styrene system, we extended our method on 3-methyl-4-nitro-5-styryl-isoxazole (**4**) moiety. For this, simple isoxazole-styrenes (**4**) were treated with α, α-dicyanoolefin **2** in presence of different solvents using different bases (inorganic and organic). Among screened conditions, we concluded that the reaction promoted by K_2CO_3 (in EtOH) was efficient catalyst to delivering the various michael adducts (instead of double vinylogous products) with good yields (70-82%) in **Scheme-4.3**. Depending on the structure of substrate and reactivity, the sequential/tandem stem can stop at the middle step to give the michael products.

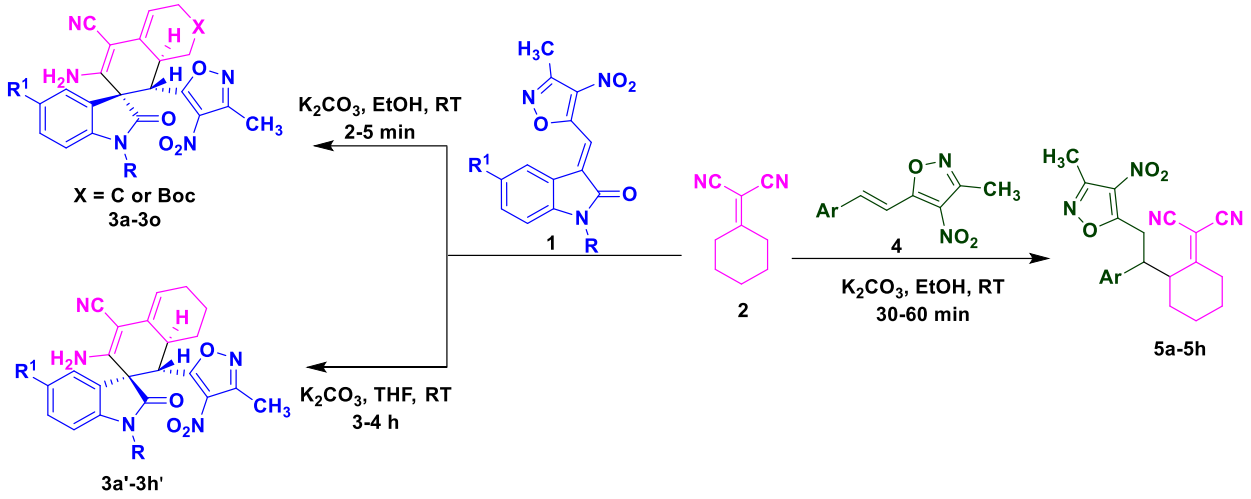
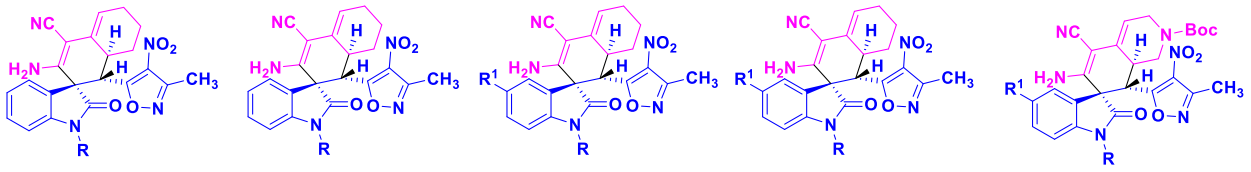
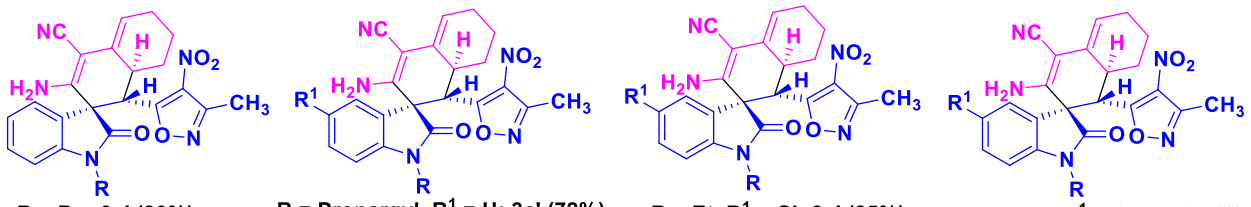


Figure-4.1: Synthesis of spirocyclic oxindoles and Michael adducts



Scheme-4.1: Substrate scope for the synthesis of spirocyclic oxindoles (3a-3o).



Scheme-4.2: Substrate scope for the synthesis of spirocyclic oxindoles (**3a'-3h'**).

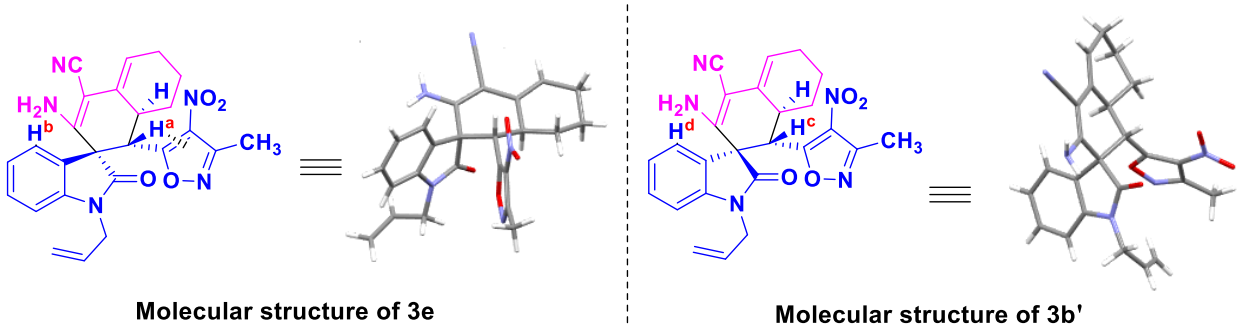
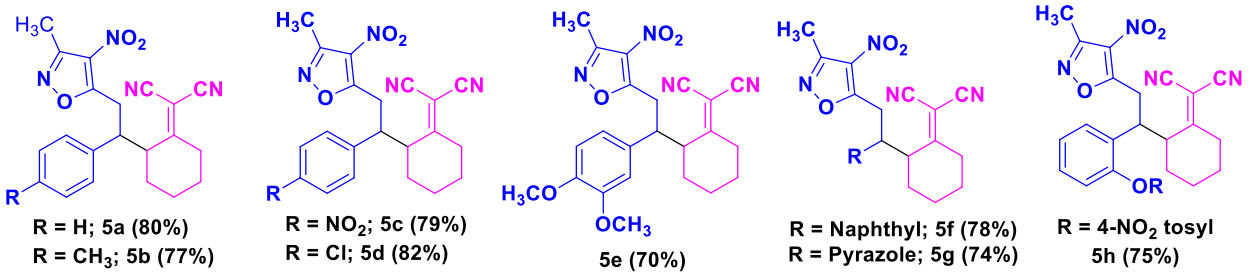


Figure-4.2: X-ray structures of spirooxindoles **3e** and **3b'.**



Scheme-4.3: Substrate scope for the synthesis of Michael adducts (**5a-5h**).

CHAPTER-V

Base mediated synthesis of spirooxindole-cyclopropane hybrids using onium ylides at room temperature

Barbiturate-fused spirocycles and spiro-cyclopropyl oxindole motifs are widely present in clinical pharmaceuticals and bioactive compounds. For instance, these compounds act as inhibitors of dihydro-orotate dehydrogenase, nanomolar activity as an HIV-1 non-nucleoside reverse transcriptase inhibitor, and also exhibit promising antitumor activity. In addition to this, these cyclo propanes also serve as valuable synthetic intermediates for the synthesis of wide range organic molecules.

Owing to the importance of the barbiturates, oxindoles and isoxazole moiety, in this context we report a metal-free base mediated efficient construction of functionalized spirocyclic propanes using onium ylides *via* 1,4/1,6-Micheal addition and nucleophilic substitution as key steps. In this regard, various 3-methyl-4-nitro-5-isatylidenyl-isoxazoles (**1**) treated with onium ylides (**2**) in toluene with CS_2CO_3 as base at room temperature to delivered corresponding spirocyclic oxindole derivatives with good yields (72-88%) for 4-5 h (**Scheme-5.1**). All newly synthesized compounds further confirmed by NMR and mass spectroscopic data and the structure of the compound (**3b**) was confirmed by single crystal X-ray diffraction analysis.

Keeping in view of above all, considering the medicinal importance of the spiro-barbiturates and cyclopropanes. Next, we turn our attention was shifted towards for the synthesis of barbiturated-cyclopropanes using onium ylides **2** and barbiturate olefins **4** under optimized reaction condition (toluene, Cs_2CO_3). Experiments that probed the generality of the cyclopropanations were also performed. As summarized in **Scheme-5.2**, the reaction displays a

broad scope for onium ylides (ammonium or sulfonium) **2** and barbiturate olefins **4**, and in moderate to good yields (70-85%) were achieved.

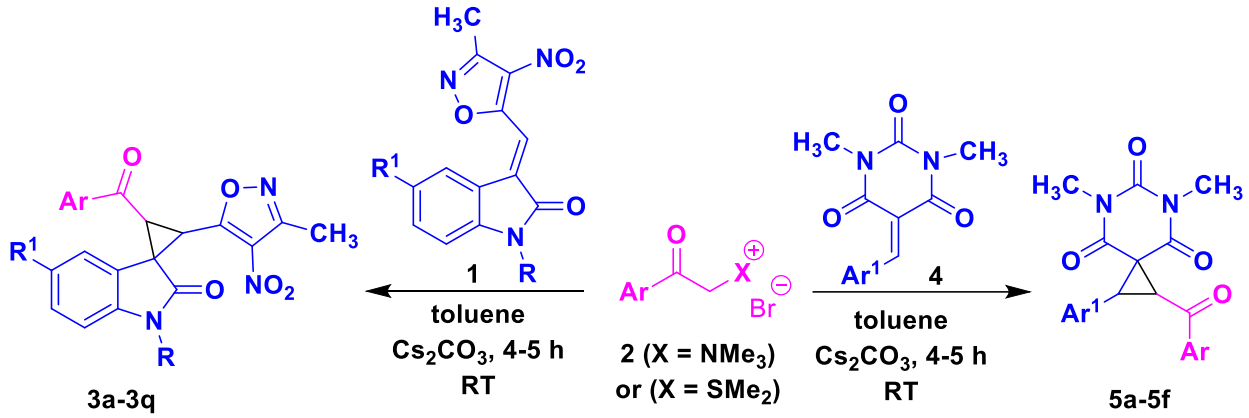
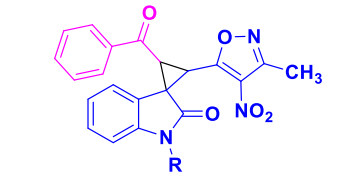
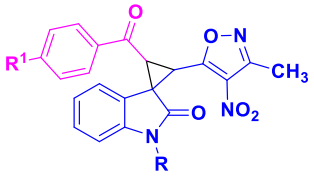


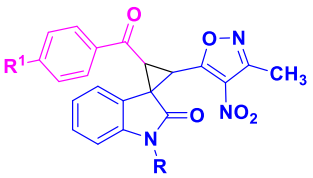
Figure-5.1: Synthesis of spirocyclopropanes using onium ylides



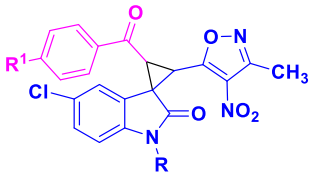
R = H; 3a (A: 80%; B: 78%)
R = Bn; 3b (A: 88%; B: 85%)
R = Allyl; 3c (A: 85%; B: 84%)
R = Propargyl; 3d (A: 80%; B: 78%)



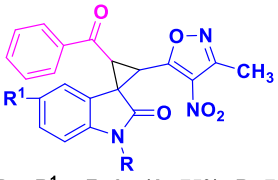
R = CH_3, R^1 = CH_3; 3e (A: 75%; B: 77%)
R = CH_3, R^1 = Ph; 3f (A: 80%; B: 81%)
R = Bn, R^1 = OMe; 3g (A: 80%; B: 77%)



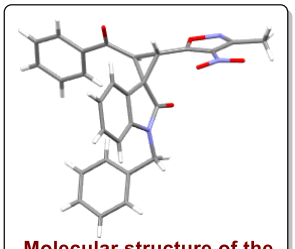
R = Bn, R^1 = Ph; 3h (A: 75%; B: 78%)
R = Allyl, R^1 = CH_3; 3i (A: 78%; B: 75%)
R = Allyl, R^1 = NO_2; 3j (A: 82%; B: 85%)
R = Allyl, R^1 = Cl; 3k (A: 80%; B: 76%)



R = Et, R^1 = H; 3l (A: 78%; B: 78%)
R = Et, R^1 = Cl; 3m (A: 73%; B: 70%)
R = Propargyl, R^1 = H; 3n (A: 87%; B: 80%)
R = Propargyl, R^1 = Cl; 3o (A: 85%; B: 79%)

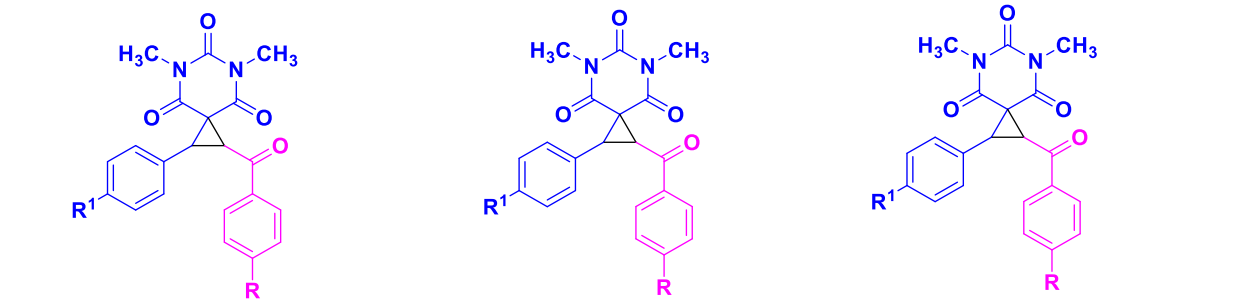


R = Bn, R^1 = F; 3p (A: 75%; B: 72%)
R = CH_3, R^1 = Br; 3q (A: 82%; B: 80%)



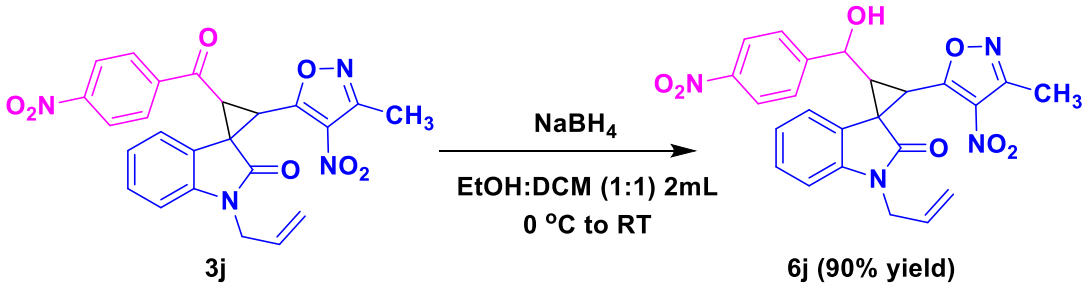
Molecular structure of the compound 3b

Scheme-5.1: synthesis of functionalized spirocyclic oxindoles in presence of toluene using Cs_2CO_3 at room temperature.



Scheme-5.2: synthesis of functionalized barbiturate cyclopropanes.

To evaluate the synthetic potential of this methodology, a gram scale reaction of **3j** carried out. **1j** (1g, 3.2 mmol) reacted with onium ylide **2a** (0.97g, 3.2 mmol) smoothly, affording the desired product **3j** with 75% of the yield (1.14 g). Furthermore, treating the product **3j** with $NaBH_4$ in DCM : EtOH (1:1) at 0 ºC to RT accessed **6j** in 90% of the yield for 30 min (**Scheme 4.4)**.



Scheme-5.3: Further functionalization of spirocyclic oxindole **6j.**

CHAPTER-VI

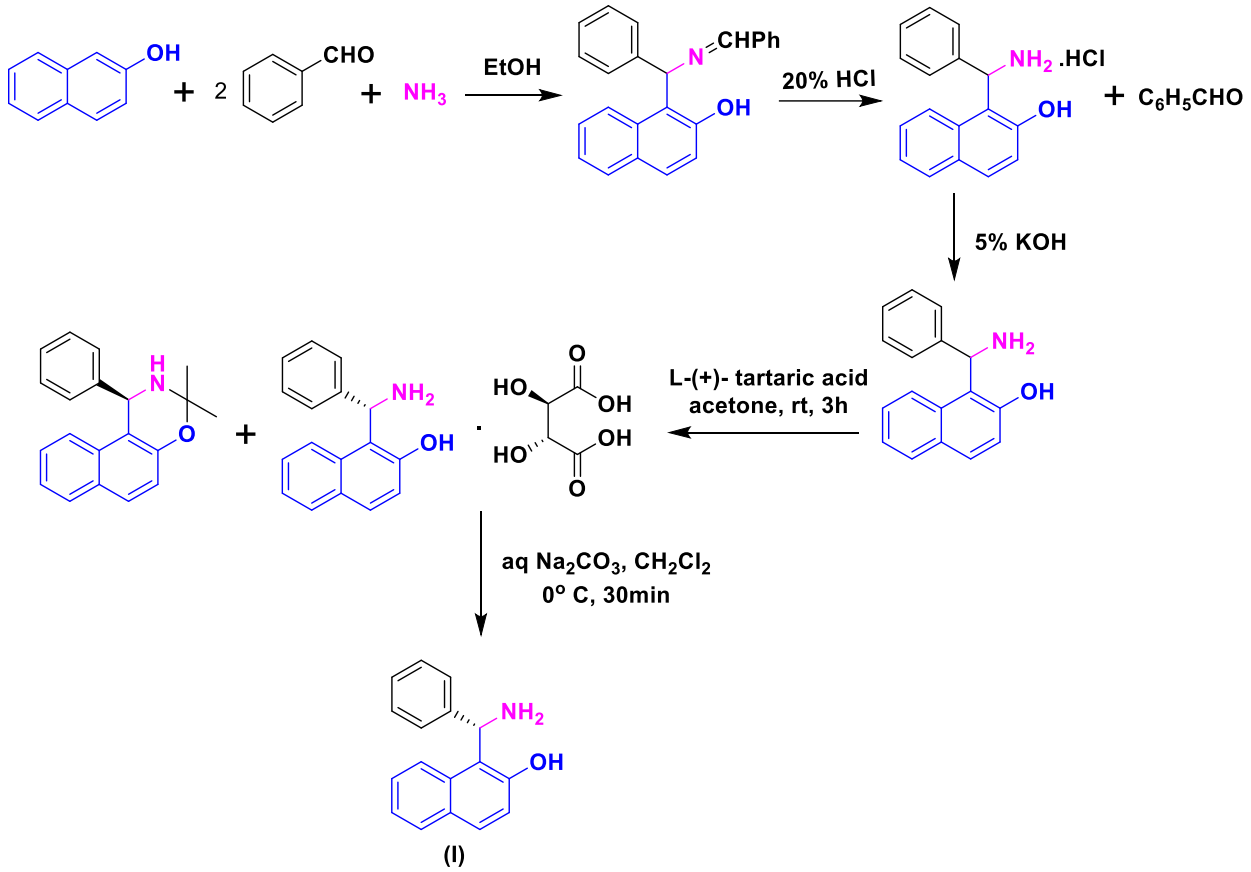
Synthesis of aminoalkylnaphthol-based chiral organo catalysts and their applications for Michael, Aldol, Vinylogous henry type and domino/cascade reactions

Last two decades belongs to asymmetric organocatalysis where small molecules (commercial or synthesized) is used as catalyst for the organic transformations were used as catalysts for the organic transformations (Aldol, Diels-Alder, Michael addition, Strecker, cross-coupling reactions and addition of diethyl zinc to carbonyl compounds etc.,) and for key reactions in natural product synthesis. Pioneering Carlos Barbas, MacMillan, Benjamin List, Andre Cobb, D. Ramachari, INN Namboothiri etc groups led to the development of different organocatalysts and their application for the simple and complex molecules including natural products synthesis.

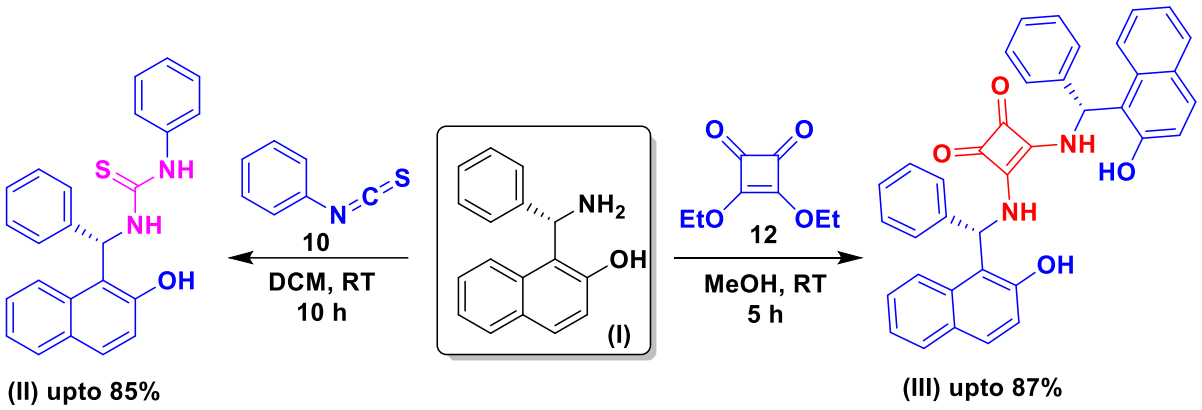
Till now commercial or modularly designed catalysts like *L*-proline, Cinchona alkaloids, cyclohexyl-amides, sulfonamides, chiral thiourea and squaramides, chiral peptides and ionic liquids are used as organocatalysts. Often commercially available chiral catalyst won't give expected outcome when compare to modified catalyst interns of enantioselectivity. To address this, many modularly designed catalysts are used in the literature.

Amidoalkylnapthols are gaining importance in both academic and industry for the synthesis of natural products and synthetic pharmaceuticals. The main characteristic feature of these amidoalkylnaphthols is represented by a simple synthesis (Betti reaction) involving simple bench-top starting materials. These amidoalkylnaphthols are used for asymmetric transformations but stereoselectivities were not encouraging. Thus, we propose the design and synthesis of new amidoalkylnaphthol-based organocatalysts and their application to asymmetric organic transformations.

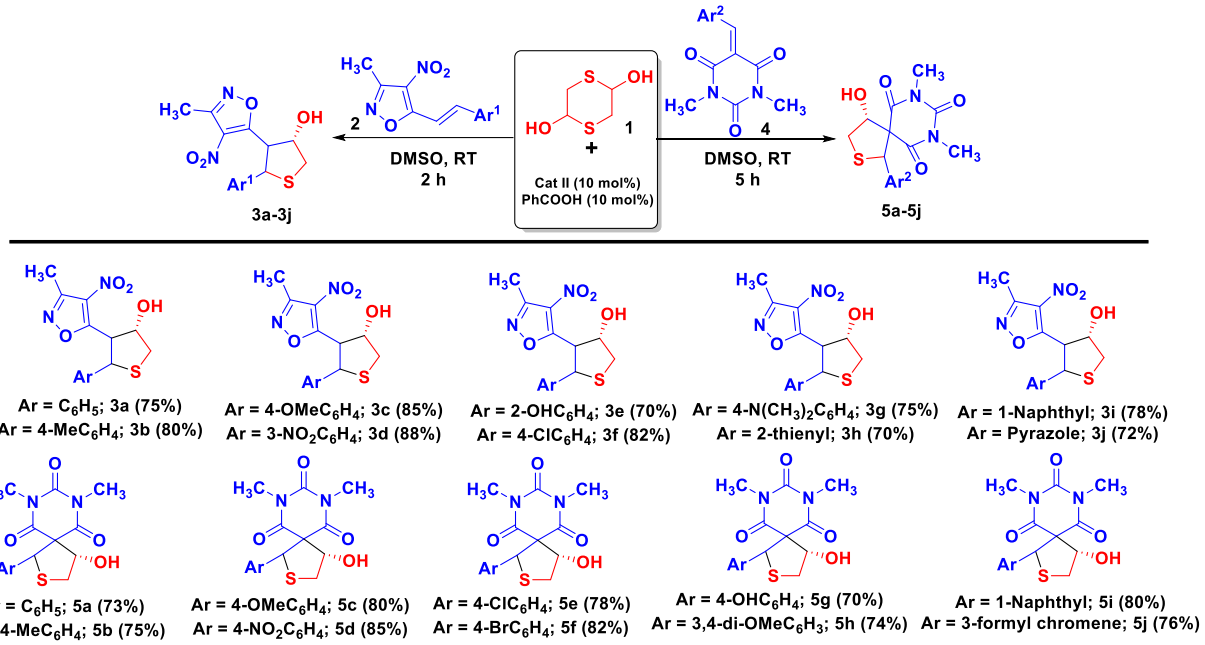
In this chapter, we were synthesized both the enantiomers of amidoalkylnaphthols (*R, S*) through mannich reaction using simple bench top chemicals and have been used for the synthesis of racemic amines. Amidoalkylnapthols were resolved into individual enantiomers in an optical pure form (*R, S*) by using simple resolution methods (**Scheme-6.1**). These chiral amines were used as catalyst and precursor to synthesize bifunctional chiral thiourea and squramide catalysts to afford good yields with 85% and 87% respectively (**Scheme-6.2**). Later, we have examined on bench mark reactions and some of the reported reactions to test the efficiency of the catalyst in terms of reaction time and yield. We have found that the benzoic acid was required as additive to enhance the yield and to reduce reaction time. Initially the catalyst was effectively used for the synthesis of tetrahydrothiophenes. To achieve this, the styrene (**2** or **4**) treated with 1 4-dithiane-2 5-diol (**1**) in DMSO using catalyst **II** (10 mol%) and benzoic acid (10 mol%) at room temperature afford good yields. With the preferred condition for the domino reaction in hand, we next examined the scope of the substrates and synthesized a library of compounds using similar condition for the synthesis of functionalized isoxazole based tetrahydrothiophenes and spiro tetrahydrothiophenes with good yields (70-88%) as shown in **scheme-6.3**. The catalyst (**II**) also efficiently working on Domino/Cascade, Michael, Aldol and vinylogous henry-type reactions under similar condition to gave corresponding products with good yields (**Scheme-6.4**).



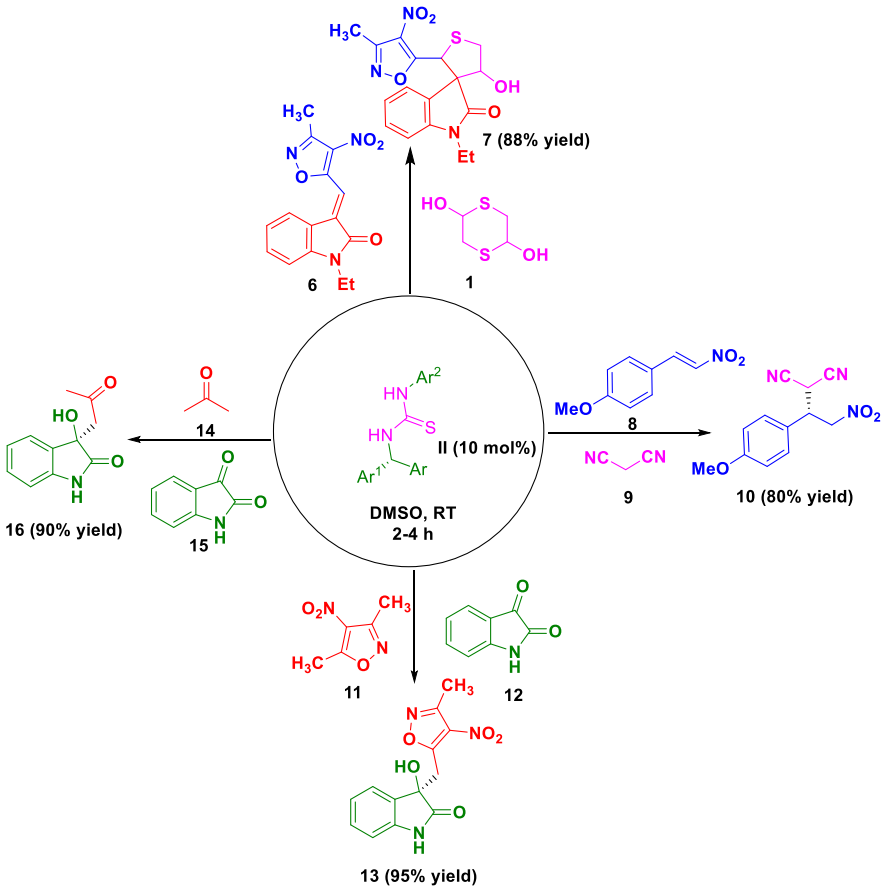
Scheme-6.1: Synthesis of chiral amidoalkylnaphthol.



Scheme-6.2: Synthesis of Novel chiral thiourea (**II**) and squaramide catalyst (**III**).



Scheme-6.3: Synthesis of tetrahydrothiophene derivatives using thiourea catalyst (II).



Scheme-6.4: Domino/tandem, Aldol, Michael and Henry-type vinylogous reactions promoted by thiourea catalyst.

Publications and Bio-Data

List of Publications

1. Nagaraju, S.; **Sathish. K**.; Kashinath, D. "Applications of 3,5-Dialkyl-4-nitroisoxazoles and Their Derivatives in Organic Synthesis" *ChemistrySelect*, **2021**, *6*, 7736.
2. **Sathish. K**.; Nagaraju, S.; Kashinath, D. "Dimethylurea/L-tartaric acid as deep eutectic solvent for one-pot synthesis of 2-(methylamino)-3-nitrospiro-[chromene] and *N*-methyl-3-nitro-4*H* chromen-2-amines" *Syn. Comn.* **2021**, *51*, 1242.
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Bio-Data

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