NOVEL SYNTHETIC AND BIOLOGICAL STUDIES ON BENZOTHIAZOLES, BENZIMIDAZOLES, OXAZOLIDINONES AND PYRAZOLOPYRIMIDINE

A THESIS

Submitted by

BHARATH YARLAGADDA

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GUNTUR – 522213, ANDHRA PRADESH, INDIA

MAY 2017

Dedicated

To

My Beloved Parents

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Prof. Mandava Venkata Basaveswara Rao
Research Guide
Professor, Dept. of chemistry,
Krishna University, Machilipatnam,
Andhra Pradesh, India

Dr.D.Nagaraju
Research Co-Guide
Professor, Dept. of Science and humanities
VFSTR University, Andhra Pradesh, India

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ABSTRACT

NOVEL SYNTHETIC AND BIOLOGICAL STUDIES ON BENZOTHIAZOLES, BENZIMIDAZOLES, OXAZOLIDINONES AND PYRAZOLOPYRIMIDINE

Heterocyclic compounds are important building blocks used to build up compounds of biological or medicinal chemistry interest to chemists. A huge number of heterocyclic building blocks have applications in pharmaceutical research, agriculture, and drug discovery. Keeping in view of the importance of the hetero cyclic ring containing compounds, in the present thesis describes the synthetic and biological studies on some of the important category of drug substances particularly Benzothiazole , Benzimidazole ,oxazolidinones and pyrazolopyrimidine containing hetero cyclic ring. Here the thesis containing research work on novel benzothiazole scaffolds , new synthetic method for the preparation of benzimidazole has been developed using a new catalyst Gd (OTf) $_3$ under microwave irradiation, C-ring modified and C-5 Substituted new oxazolidino amide/sulfonamides conjugates and the ultrasound assisted synthesis of a series of 2- alkynyl pyrazolo[1,5-*a*] pyrimidine derivatives . The total work carried out in the present research programme is being presented in six chapters.

Chapter 1: This chapter describes a general introduction on benzothiazoles and oxazolidinones, mechanism of action, pharmacological aspects of Benzothiazoles, Benzimidazole and oxazolidinones. It also covers the preface about the Benzothiazole, Benzimidazole and oxazolidinones and their medicinal importance.

Chapter 2: The second chapter describes the review on heterocyclic compounds and its importance in drug discovery.

Chapter 3: Chapter three describes the synthesis of biologically active compounds which consist of two distinct pharmocophores; benzothiazoles and triazoles, Facile synthesis of *N*-(benzyl-1*H*-1,2,3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides *via* click chemistry.

Chapter 4: Efficient method Microwave irradiation for synthesis of 2-substituted benzimidazole from *1*, *2*- phenylenediamine and *β*-keto esters /1, 3-di ketones using Gd $(OTf)_3$ as a Catalyst.

Chapter 5: This chapter deals with the importance of oxazolidinones in medicinal research, Structural Modification of Oxazolidinones *via* Multistep synthesis and their impact on antitubercular and antibacterial activity**.** Experimental procedures are also included. The activity data of compounds are included.

Chapter 6: The method development for the 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine framework might provide a template for the discovery of novel and potential anticancer agents, environmentally benign method for the preparation of pyrazolo-pyrimidine rings and experimental procedures were described .

KEYWORDS: Hetero cyclic compounds, benzothiazole, benzimidazole, oxazolidinones and 2-alkynyl pyrazolopyrimidine.

GENERAL REMARKS

1. Infrared spectra were recorded on Perkin-Elmer-683 series spectrometer with KBr optics.
2. Proton Nuclear Magnetic Resonance spectra were recorded on Bruker Avance 300, Varian Unity 400 and Avance 500 spectrometers using tetramethylsilane (TMS) as an internal standard and chemical shifts are shown in δ scale.
3. Electron Impact (EI), ESI, HR MS and Chemical ionization mass spectra (CIMS) were recorded on VG micro mass 70-70 H instrument 70 ev.
4. Melting points were recorded on Buchi-510 melting point apparatus and are uncorrected.
5. Elemental analyses were carried out on Elemental Vario Micro Cube Elementar instrument (Germany) apparatus.
6. Microwave irradiations were carried out on 300W (CEM-discover, model number-908010).
7. Silica gel 60/120(120-125 micron) mesh and 100/200 (75-120 micron) mesh used for column chromatography was purchased from Avra synthesis chemical company.
8. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60G F_{254} (20x20 cm.) (Merck); spots were visualized with UV light (254 nm).

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List of Abbreviations

ADP	Adenosine Diphosphate
ATP	Adenosine Triphosphate
AIDS	Acquired Immune Deficiency Syndrome
BZO	1,4-Benzoxazepine
CAN	Ceric Ammonium Nitrate
CJM-126	2-(4-Aminophenyl)Benzothiazole
$CHCl_3$	Chloroform
CNS	Central Nervous System
CO	Carbon Monoxide
CuAAC	Copper Catalyzed Azide-Alkyne Cyclo-Addition
DCM	Dichloromethane
DIPEA	Di-Isopropyl Ethyl Amine
DMA	*N*, *N*-Dimethylacetamide
DMF	*N*, *N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide
equiv	Equivalent
EtOAc	Ethyl Acetate
g	Grams
HCl	Hydrochloric Acid
H_2O_2	Hydrogen Peroxide
H_3PO_3	Phosphorous Acid
HOBt	Hydroxy benzotriazole
hrs	Hours
IR	Infrared Spectrometer
Lit/LIT	Literature
MCF-7	*Human Breast Adenocarcinoma Cell Line*
MDA 468	*Human Breast Adenocarcinoma Cell Line*
mg	Milligram
min	Minutes(S)

mmol	Milli Mole
MHz	Mega Hertz
MsCl	Methyl Sulfonyl Chloride
MWI	Microwave Irradiation
ml	Mile Liter
MIC	Minimum Inhibition Concentration
mp	Melting Point
$NaHCO_3$	Sodium Bicarbonate
NaCL	Sodium Chloride
NaN_3	Sodium Azide
Na_2SO_4	*Sodium Sulfate*
NH_4CL	Ammonium Chloride
NMP	N-Methyl Pyrolidione
NMR	Nuclear Magnetic Resonance
OBN	Benzoxyl
-OTf	Trifluoromethanesulfonate
Ph	Phenyl
PPA	Poly Phosphoric Acid
Pd	Palladium
PPH_3	Triphenylphosphine
PPM	Parts Per Million
RT	Room Temperature
$SnCL_2$	Stannous Chloride
TFA	Triflouro Acetic Acid
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TMS	Tetra Methyl Silane
TBAP	Tetrabutyl Ammonium Permanganate
TMEDA	Tetramethylethylenediamine
WHO	World Health Organization

CHAPTER 1

Introduction

1.1. Benzothiazoles:

The German bacteriologist Paul Ehrlich and his student Sahachiro Hata developed Salvarsanin 1910for the treatment of Syphilis, and this was the first synthetic chemotherapeutic agent. Alexander Fleming isolated Penicillinin 1929 which was the world first antibiotic from *penicillium notatum.* At the same time the first sulfa drug was synthesised, and Streptomycin (an antituberculosis agent), Tetracycline and other antibiotics with excellent antimicrobial efficacy were found one after another.

Antimicrobial agents, since their discovery have substantially reduced the threats posed by infectious diseases. The use of these "wonder drugs" has led to a dramatic drop in deaths from diseases that were previously widespread, untreatable and frequently fatal. Over the years, antimicrobial have saved the lives and eased the suffering of millions of people. But today's main concern is the emergence and spreads of microbes those are resistant to economical and effective first-line drugs. The bacterial infections which contribute most to human diseases are also those in which emerging and microbial resistance is most evident. Some important examples include diarrhoeal diseases, respiratory tract infections, meningitis, penicillin-resistant*Streptococcus Pneumoniae, vancomycin*-resistant *entercocci*, and multi-resistant*Mycobacterium Tuberculosis.* When infections become resistant to first lineantimicrobials, treatment has to be switched to second or third line drugs which are nearly always much more expensive and more toxic as well e.g. the drug needed to treat multi drug-resistant form of tuberculosis are over 100 times more expensive than the first line drugs used to treat non-resistant forms.

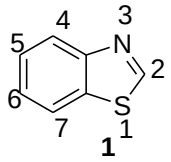
Most alarming of all are diseases where resistance is developing for all currently available drugs; current trends suggest that some diseases will have no effective therapies within the next ten years. So, there is a requirement to develop new replacement drug immediately which is effective against resistant bacteria having lesser toxicity as well as economical also.[1] In view of the biological importance of the benzothiazole nucleus containing compounds, in the present work, it is plan to synthesize benzothiazoles by developing methodology.

After a gap of 30-40 years Benzothiazoles were found as new class of compounds widely prescribed for the treatment of infections in humans. Currently Benzothiazoles are the most interesting group of antibacterial drugs made amajor impact on the field of antimicrobial chemotherapy with broad spectrum of activity.

1.2. Importance of benzothiazole nucleus:

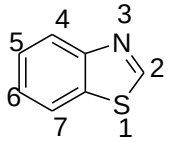
Benzothiazole is a privileged bicyclic ring system. It contains a benzene ring fused to a thiazole ring. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like- antimicrobial, antitubercular, antitumor, antimalarial, anticonvulsant, anthelmintic, analgesic and anti-inflammatory activity.[2]In addition, the benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Due to their importance in pharmaceutical utilities, the synthesis of various benzothiazole derivatives is of considerable interests.

1.3. Characteristics of nucleus:



1

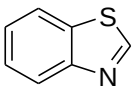
Benzothizoles

Structure	
IUPAC Name	1,3-Benzothiazole
Molecular Formula	C_7H_5NS
Molecular Weight	136.19
Boiling Point	227-228^{O}C
Melting Point	2^{O}C
Density	1.644 g/ml
Physical appearance	colorless, slightly viscous liquid

Benzothiazoles are bicyclic ring system (Chaudhary et al, 2010) a number of 2-aminobenzothiazoles have been studied as central muscle relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments (Bryson et al, 1996).

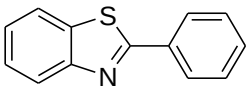
Benzothiazole ring made from thiazole ring fused with benzene ring. Thiazole ring is a five-member ring consists of one nitrogen and one sulphur atom in the ring. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. It was found to be possessing pharmacological activities such as anti-viral, anti-bacterial, anti-microbial and fungicidal activities (Singh et al , 1988).Benzothiazole nucleus containing molecules are also reported as anti-allergic, (Musser et al ,1984) anti-diabetic, (Pattan et al ,2005) antitumor, (Yoshida et al ,2005) anti-inflammatory, anti-helmintic, and anti-HIV agents. 2-aryl substituted benzothiazoles show antitumor activity while condensed pyrimido-benzothiazoles and benzothiazolo-quinazolines showed anti-viral activity (Bradshaw et al, 2002 and Hutchinson et al, 2002).Substituted 6-nitro and 6-aminobenzothiazoles have been reported for antimicrobialactivity.

However, in recent years, 2-arylbenzothiazoles (**2**) have emerged as an important pharmacophore in the development of antitumor agents. The promising biological profile and synthetic accessibility have been attractive in the design and development of new benzothiazoles and their conjugate systems as potential chemotherapeutics.



Benzothiazole

1



2-arylbenzothiazole

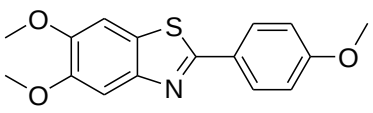
2

Antitumor 2-arylbenzothiazoles:

Benzothiazoles are fused bicyclic systems possessing diverse biological properties such as neuron protective (Lagunin et al, 2000 and Nogradi et al, 2001), anticonvulsive, (Amnerkar et al, 2010 and Deng et al, 2010)antiglutamate (Jimonet et al, 1999),antimalarial (Burger et al, 1986), anthelmintic (Hori et al, 1992), antitubercular (Huang et al, 2009 and Patel et al, 2010) , analgesic, anti-inflammatory (Lee et al, 2011 and Jin et al, 2010)) antimicrobial (Al-Tel et al, 2011, Stella et al ,2011 and Franchini et al, 2009) and anticancer effects (Kamal et al, 2011 ,Trapani et al, 2001, Khokra et al, 2011 and Kumbhare et al,2011). In the past two decades, benzothiazoles demonstrated interesting pharmacological activities (Chaudhary et al,

2010 and Yadav et al, 2011) and have been extensively studied particularly for their antitumor activities (Yates et al, 1991).

Stevens and co-workers inspired from a crystallographic analysis of 5, 6-dimethoxy-2-(4-methoxyphenyl) benzothiazole (Stevens et al, 1994) (**3**) and synthesized polyhydroxylated 2-phenylbenzothiazole (**4**) and compared their cytotoxicity as well as pharmacological properties with the naturally occurring bioactive flavonoidquercetin and isoflavone genistein. They believed that planar polyhydroxylated 2-phenylbenzothiazoles might mimic the adenosine triphosphate (ATP) antagonistic effects of those natural products and displayed tyrosine kinase inhibitory properties, but were not successful in discovering active polyhydroxylated compound with exploitable antitumor activities (Shi et al, 1996) They have identified planar aryl amine with unique selective properties and reported 2-(4-aminophenyl)benzothiazole (CJM 126, 3) as an original lead compound from this series that exhibited nanomolar in vitro inhibitory activity against a panel of human sensitive breast cancer cell lines such as MCF-7 and MDA 468. Furthermore, the activity against these cancer cell lines was characterized by a biphasic dose response relationship. Structure activity relationship (SAR) studies revealed that compound having methyl or halogen substituent at 3-position of amino phenyl ring is especially potent than the unsubstituted amine CJM 126 (3), extending the spectrum of in vitro anticancer activity to ovarian, lung, renal and colon carcinoma cell lines with a remarkable selectivity profile (Sreenivasa et al,1998).



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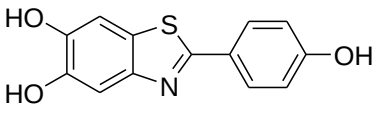

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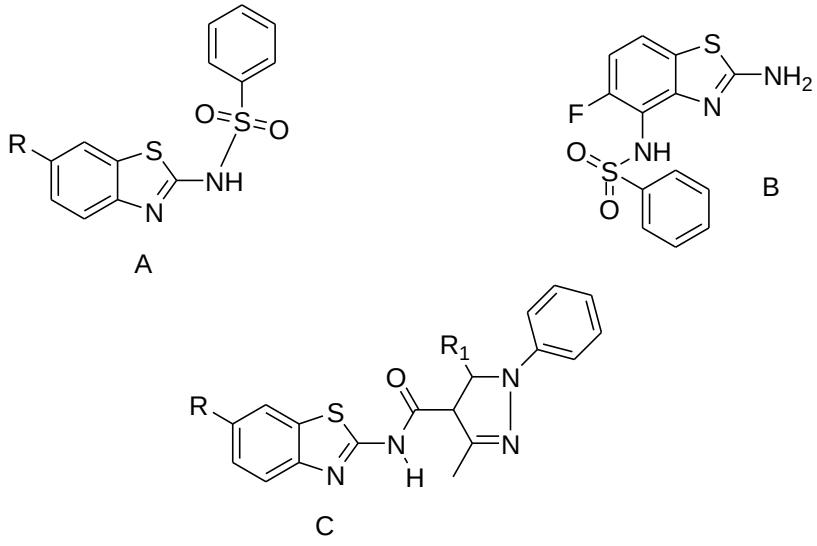
1.4. APPLICATION:

(i) Antimicrobial activity:

Microbes are the causative agents for various types of diseases like pneumonia, ameobiasis, typhoid, malaria, common cough, cold and various infections and cause some severe diseases like tuberculosis, influenza, syphilis, and AIDS etc.

Benzothiazoles show a chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles. 2-(substitutedarylsulfonamido)-6-substituted (A, **Scheme 1.1**) have reported for their anti-bacterial activity against *Bacillus subtilis*, *Salmonella typhi* and*S. dysentery* (Gopkumar et al, 2001).



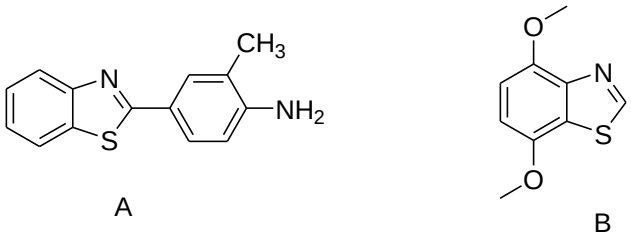
Scheme 1.1: Anti-bacterial benzothiazole derivatives

Another, derivative i.e. N-(2-amino-6-fluorobenzo[d]thiazol-7-yl)benzene sulfonamide (B, **Scheme 1.1**) was synthesized and studied for their antibacterial and anti-fungal activities and it showed moderate activity against S. aureus, S. albus and C.ablicans. Various benzothiazolyl carboxamido pyrazoline derivatives (C, **Scheme1.1**) were prepared and studied their anti-microbial activity (Trapani et al, 2003).It was found that when$R=CH_3$ and R_1 =*o*-$OCH_3C_6H_4$, compound showed no activity and when R= Cl and R_1= *p*-$OCH_3C_6H_4$, the compound was active against *S. aureus* and the compounds which are left has showed activity against, *S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus mirabilis*. In other words it can be stated thatbenzothiazole moiety serves as a royal warrior against almost all types of microbes.

(ii) Antitumor activity:

The benzothiazole moiety with various substitutions has shown antitumor activity. The aminomethylphenyl derivatives (**A, Scheme 1.2**) and 4, 7-dimethoxy benzothiazole (**B, Scheme 1.2**) shows selective growth inhibitory properties against

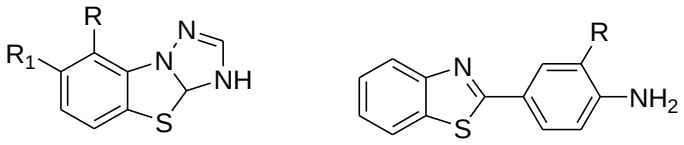
human cancer cell lines and proliferation of cells respectively. Chlorinated and fluorinated derivatives of this moiety exhibit good *in vitro* as well as *in vivo* antitumor activity. Substituted 2-(4-aminophenyl) benzothiazoles examined, *in vitro* , shows antitumor activity in ovarian, breast, lung, renal and colon carcinoma human cell line 2-(4-aminophenyl)-benzothiazoles consists of a novel mechanistic class of antitumor agents. Pyrimido benzothiazole and benzothiazolo quinoline derivatives, imidazo benzothiazoles and polymerized benzothiazoles have posses anti-tumour activity. Some fluorinated analogues of 2-(4-aminophenyl)-benzothiazoles were reported to block the C-oxidation. The 2-cyano derivatives of benzothiazole exhibit interesting *invitro* anti-tumour activity.



Scheme 1.2: Some antitumor benzothiazole derivatives

(iii) Anthelmintic activity:

Benzimidazoles recent reports of resistance have been forced the researchers to develop new drugs with anthelmintic activity, to fight against helminthiasis, which is causing untold misery to the infected individuals. Benzothiazole derivatives have been synthesized, which is sulphur isostere of benzimidazole, reported for better anthelmintic activity. A 8-fluoro-9-substituted benzothiazolo 1, 3, 4-triazoles (A, **Scheme 1.3**) compounds have been studied for their anthelmintic activity againstearthworm, *Perituma posthuma* and showed a good activity. A compound with R=*o*-nitro anilino substituent was found to possess excellent anthelmintic activity, thanthe other compounds, Some substituted imidazo benzothiazoles were examined *in vivo* anthelmintic activity against *H. nana* infection and were found to show good to moderate activity.



R= Aniline, Nitro aniline

R_1= F,Br

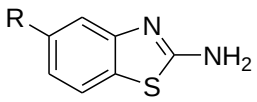
R= H,CH_3,Cl,Br

Scheme 1.3: Structure of reported anthelmintic substituted-2-benzothiazolamine

(iv) Anticonvulsant activity:

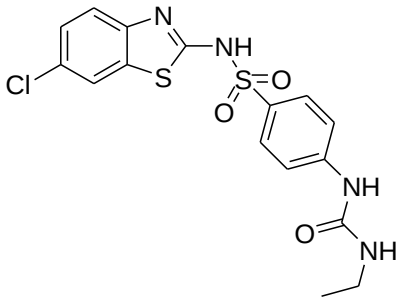
For anticonvulsant activity a large number of benzothiazole derivatives were evaluated and found to possess significant activity against various types of seizures. In the search of new anticonvulsant agents having benzothiazole nucleus, Amit, B. N. et al synthesized a lot of substituted-2-benzothiazolamines **(Scheme 1.4).**

Benzothiazoles were first observed in 1978 as anticonvulsive agents against pentylenetetrazole induced convulsions on 2-(-4-arylthiosemicarbazidocarbonylthio) benzothiazoles and then several benzothiazoles containing sulphonamide derivatives (**Scheme 1.5**), benzothiazolamines were synthesized and evaluated for their activity against electroshock and pentylenetetrazole induced seizures. This review revealed that benzothiazole moiety as a dynamic agent against convulsive seizures. Sulphonamide derivatives having benzothiazole nucleus is synthesized by treating 2-(4-aminophenylsulphonamido)-6-halo/alkyl benzothiazoles with alkyl isothiocyanate and were evaluated for their anticonvulsant activity. A 2-(4-arylthiosemicarbazidocarbonylthio) benzothiazoles were screened for their anticonvulsant activity against pentylenetetrazole induced convulsions in mice and found that all the compounds possess measurable anticonvulsant activity. A large number of 2- (3*H*) -benzothiazolo derivatives have been synthesized and evaluated for theire anticonvulsant activity in mice and were found to be singinificantly anticonvulsant activity.



R = CH_3, C_2H_5,CF_3,OC_2H_5

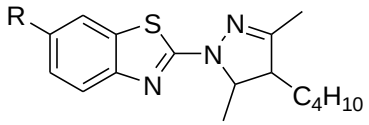
Scheme 1.4: Structure of reported anticonvulsant substituted-2-benzothiazolamines



Scheme1.5: Structure of reported anticonvulsant substituted-2-benzothiazolamines sulphonamide.

(v) Anti-inflammatory activity:

Pyrazolones and pyrazolinones are more valuable non-steroidal anti-inflammatory agents. Phenylbutazone and its congeners incorporating a pyrazoline-3, 5-dione structure are more potent anti-inflammatory agents. In the recent years a number of benzothiazole derivatives have been synthesized and found to possess anti-inflammatory activity. Some new 2-(4'-butyl-3',5'-dimethylpyrazol-1'-yl)-6-substitutedbenzothiazole were found to posses significant anti-inflammatory activity (Viegas-Junior et al, 2007). A series of 2-(2-alkoxy -6-pentadecylphenyl) methylthio-1*H*- Benzimidazoles / benzothiazoles and benzoxazoles from an anacardic acid (Xie et al, 2011), for their ability to inhibit human cycloxygenase-2-enzyme (COX-2).



Scheme 1.6: Structure benzothiazol-pyrazolone derivatives

That, replacement of the urea moiety by benzothiazoles inhibitors of HIV-1 protease with improved potency andOther report showed sulfonamide showed anti-viral activities.

1.5. Recent advancements

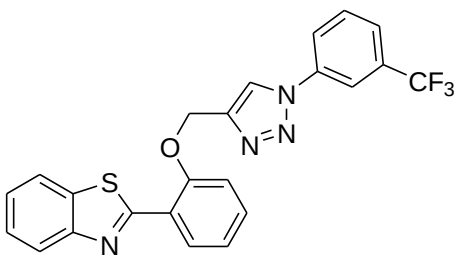
The literature of recent years in this area demonstrates that benzothiazoles are attaining great practical significance. They have been investigated with regard to their mode of action, 1, 2, 3-triazole derivatives also possess variously analgesic,

antipyretic and antiphlogistic properties. Few examples of biologically active benzothiazole and 1, 2, 3-triazole derivatives.

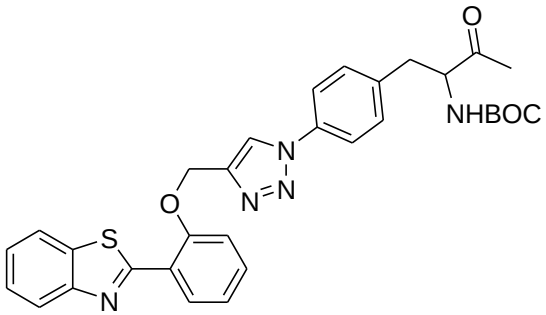
Hybrids of Benzothiazole

In recent years, molecular hybridization of two or more active pharmocophores within a single molecule has become one of the successful and promising approaches in drug discovery including cancer chemotherapy (Decker et al, 2011 and Breen et al, 2010) the hybrid approach can also be used to optimize biological effects including efficacy and specificity. However, a suitable way to chemically connect the drug component or pharmacophore and an approach to enhance the biological activity remain the challenging task of hybrid molecule strategy. A variety of hybrid molecules have been designed and developed in the past few years to unravel their intricacies with respect to their effectiveness and usefulness. These hybrid molecules have displayed profound and improved biopharmaceutical properties including efficacy profiles by additive or synergistic effect. The advantages of employing hybrid molecules over combination therapy and multicomponent drugs involve cost-effective hybrid drugs and lower risk of drug adverse interactions. In addition, the pharmacokinetic profile of a hybrid molecule is comparatively more predictable than using, combination of drugs or single component.

Kumbhare et .al reported new series triazoles linked 2-phenyl benzothiazole were synthesized and evaluated for their anticancer activity. These compounds have been tested for their cytotoxicity against three cancer cell lines. Among the compounds tested, compound (**A**) showed good cytotoxicity against Colo-205 and A549 cells.



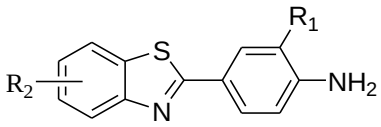
A



B

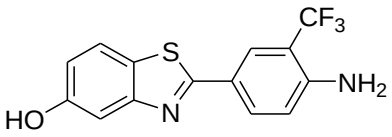
Further compound **A** has been at a 2-position reacts with azide containing molecule (**B**) cold form florescent adducts.

In recent years polyheterocycles, linked or fused, have received increasing attention due to their potential biological properties and considerable efforts have been undertaken to exploit synthetic routes and biological activities of these compounds. Imidazolo[2,l-b]benzothiazoles, pyrimido[2,l-*b*]benzothiazolones and pyrimido[2,l-*b*]benzothiazoles have been synthesized (Mehta et al, 2002), to evaluate their possible synthetic route. Small and simple heterocycle structures often have surprisingly complex biological properties. Antitumour 2-(4-aminophenyl)benzothiazoles, are a case in point, their development from humble beginnings, synthetic intermediates in a programmed searching for tyrosine kinase inhibitor to their present status as agents in advance preclinical development is a remarkable one. Structure-activity relationship studies based on the initial lead compound 2-(4-aminophenyl) benzothiazole established that certain substituents (CH_3, CI) in the third position of the phenyl group produces novel agents with potent activity in certain breast, ovarian, renal, colon and lungs cell lines in vitro (Eva et al, 1999). Particularly, noteworthy futures of this series were the unique in vitro selectivity fingerprint and highly unusual biphasic dose response relationship. On the basis of superior in vivo activity, 2-(4-amino-3-methylphenyl) benzothiazoles (DF- 203; NSC 674495) was initially selected as the lead compound for the study.

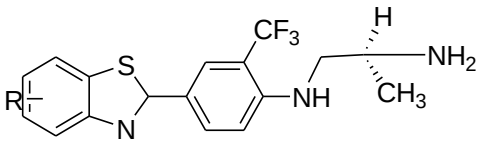


Mechanistic studies have been established the crucial role metabolism, mediating the antitumour effects of this class of agents. The major metabolite of compound 3b in vitro was found to be the corresponding 6-hydroxy analogue (Cyrille et al, 2002) and enzyme responsible for this biotransformation to be the P450 isoform CYPlAl (Shi et al, 1996). The identification of the 6-hydroxy metabolite, however, presented problems in terms of potential preclinical advancement of the project. The compound 4 was found to be both inactive in cell lines sensitive to parent compound and antagonize CYPIAI activation step crucial to the antitumor activity of lb (thus

occurring, at least in part, for the biphasic dose response relationship). One medicinal chemistry approach to circumvent this activating metabolism centered on the synthesis of various fluorinated analogues, from which 2-(4-amino-S-methyl phenyl)-5-fluorobenzothiazoles (5F 203; NSC 703786) emerged as the most potent analogue in vitro evaluation.Intriguingly, this agent unlike the corresponding 6-fluoro isomer (6F 203) abolished the biphasic dose response relationship seen in vitro, presumably by inhibiting the formation of inactive exportable hydroxylated metabolites.



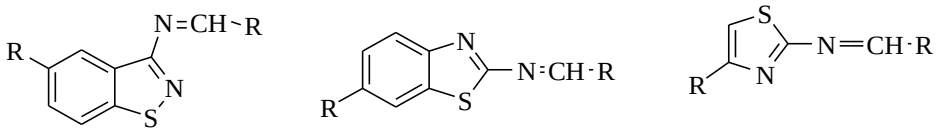
A series of water insoluble L-Lysel and L-Alanyl prodrugs 2-(4-araino phenyl) benzothiazoles have been synthesized and tested for antitumour activity. The prodrugs exhibited the required pharmaceutical properties (Bradshaw et al 1998).



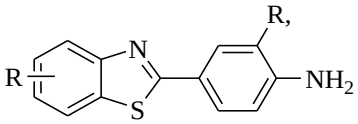
(Chua et al, 2000), have synthesized 2-(4-arylaminophenyl) benzothiazoles and investigated the role of acylation in antitumour activities of parent amines. The parent compounds have displayed potent and selective antitumour activity against interalia breast, ovarian, colon and renal cell lines. But their mechanism of action is not yet defined, may be novel. Based on 2-methyl-4-nitro-2*f*/-pyrazole-3-carboxylic acid [2-(cyclohexane carbonyl amino) benzothiazol-6-yl] amide, this shows selective cytotoxicity against tumourigenic cell lines.

Three new series of Benzisothiazole, benzothiazole and thiazole Schiff's bases were synthesized and tested in vitro. With the aim of identifying novel lead compounds active against emergent and re-emergent human and cattle infection diseases (AIDS, hepatitis B and C, tuberculosis, bovine viral diarrhea) or against drug resistant cancers (leukemia, carcinoma, melanoma, MDR tumors) for which no definitive cure are efficacies vaccine is available at present. In particular, these compounds were evaluated in vitro against representatives of different virus classes such as HIV-I (Retrovirus), a HBV (Hepadnavirus) and the single-stranded RNA viruses, yellow fever virus (YFV) and Bovine viral diarrhea virus (BVDV), both

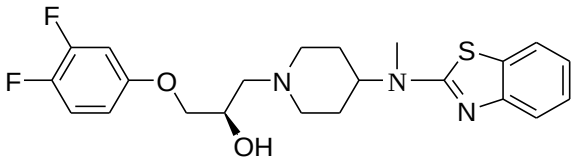
belonging to Flaviviridae. The benzo [isothiazole compounds showed a marked cytotoxicity (CC50 = 4-9 against CD4 lymphocytes (MT-4) that were used to support HIV-I growth. For this reason, the most cytotoxic compounds of this series were evaluated for their anti-proliferative activity against a panel of human cell lines derived from hematological and solid tumors. The results highlighted that all the benzoisothiazole derivatives inhibited the growth of leukemia cell lines, whereas only one of the above mentioned compound showed antiproliferative activity against two solid tumors derived cell lines.



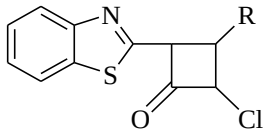
(Hutchinson et al, 2000), have synthesized 3'-cyano and 3'-alkynyl-substituted-2-(4'-aminophenyl) benzothiazoles as new potent and selective analogues in vitro against MCF-7 and MBA-468 human cancer cell lines. One of the compounds was found to be potent and selective analogue



A series of sulfamate salt derivatives of the potent and selective 2-(4- aminophenyl) benzothiazole antitumor agents have been prepared by She et al, 1996. And their evaluation as potential prodrugs for parenteral administration carried out. The salts were sparingly soluble under aqueous condition at PH 4-9 and degradation to the active free amine was shown to occur under strongly acidic conditions. The salts were found to be markedly less active than their parent amines against sensitive human tumor cell lines in vitro. Peters et al, 1995, have synthesized (+)-(*S*)-l-{4-[(2-benzothiazolyl) (methyl) amino] piperidyl}-3-(3,4-difluorophenoxy)-2-propanol (Lubeluzole) a novel benzothiazole derivative which has shown tumor colony number reducing effectin natural cells and interleukin-2. Besides other pharmacological effects, the neuroprotective compound Lubeluzole blocks low voltage activated and high voltage activated calcium channel currents.



The condensation of various 2-aminobenzothiazoles with chlorosulfonylacetylchloride has been carried out that offered 3-novel tricyclic benzothiazolo[2,3-*c*]thiadiazines (Hutchinson et al, 2003)They have been found as platelet ADP receptor antagonists that bind reversibly and with high affinity to platelet receptors. The ant inflammatory activities of the compounds will be assessed by inhibition of edema formation in hind paw of rats. Several molecules have been evaluated for their ant inflammatory activity. The present drugs available in the market are known to possess anti inflammatory activity but with side-effects. In an attempt to synthesize side-effects free and non-steroidal ant inflammatory agents (Hiroki et al, 1974), have synthesized 2- substituted-5-benzothiazole acetic acid analogues and some of them was found to be active. Ten new derivatives of l-benzothiazol-2-yl-3-chloro-4-substituted-azetidin-2- ones (Paola et al, 2003), have been synthesized using various Schiff's bases. Some of them have been screened for anti-inflammatory activity in vivo using carrageen an induced rat paw edema model. All the tested compounds exhibited considerable anti-inflammatory activities.



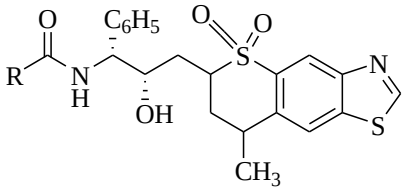
A new series of manoglycoloyl amino derivatives have been synthesized by the treatment of corresponding aromatic monoamine derivatives with glycoloyl chloride derivatives in pyridine or dichloromethane in presence of the base. Hydrolysis of acetoxy compounds in aqueous ammonia and methanol solution produced hydroxyl derivatives (goldfrab et al , 2000) .it has been tested for antiallergic and antiinflammatory activities. Benzothaizole and benzonitrile derivatives exhibited marked inhibition.

(Hafez et al, 1998) have synthesized three types of amino derivatives 6-R_2-2-aminobenzothiazoles, 6-amino-2-R_3-thiabenzothiazoles and hydrazide derivatives, and tested for their antibacterial activity. A series of sulfonamides and S-benzyl

derivatives of substituted/ unsubstituted Striazole-[3,4-*b*]benzothiazole-3-thiones were synthesized and evaluated for antitubercular activity against H37RV strain of Mycobacterium tuberculosis. Most of the compounds of this series showed promising activity.

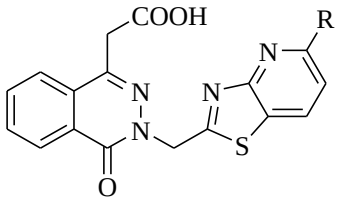
The influence of nosocarnial infections by the yeast like fungi strains has surged over the past decade for the most common cause of nausocorneal bloodstream infection in the general hospital population. The discoveries of azole antifungal compounds have been allowed for broader spectrum of antifungal treatment and duration. These drugs act by inhibiting cytochrome P-450 dependent ergosterol synthesis and cytochrome-oxidative and per oxidative enzymes. The disruption of enzyme process ultimately lead to fungal death*N*-3-(l, 2, 4] dithiazole-5-(thione)-P-resorcylcarbothiamide (DTRTA) have been synthesized and investigated for their antifungal activity by (Niewiadomy et al, 2005). Some of the tested compounds exhibited MIC's ranging between 50-200 *mg*/ml against Candida albicans and Candida tropical.

The human immuno deficiency virus (HIV) has been shown to be causative agent for AIDS. The HIV virus encodes for a unique as partyl protease that is essential for production of enzymes and proteins in the final stages of maturation. Protease inhibitors have been useful in combating the disease. The inhibitors incorporate a variety of isosteres including the hydroxy ethyl urea at protease cleaves site. (Srinivasan et al, 2003), have shown that the replacement of t-butylurea moiety by benzothiazole sulfonamide provided inhibitors with improved potency and antiviral activities. Some of the compounds have shown good oral bioavailability and half-life in rats.



The role aldose reductase mediated glucose metabolism in the etiology of diabetic complication and therapeutic potential aldose reductase inhibitors (ARI's) have been extensively reviewed. Among the clinically important ARI's, Sorbonil was first one to enter broad scale clinical testing and it is being shown to demonstrate efficacy in diabetic painful neuropathy. (Banavara et al, 1992) has synthesized ARI-1 and ARI-2,

which are currently being tested in the clinic for the treatment of diabetic complications. In addition to this they have modified ARM and ARI-2 with special focus on benzothiazole side chain.



Recently, (Van Zandt et al, 2005), discovered 3-[(4, 5, 7-trifluoro-benzothiazol-2- yl) methyl] indole-*N*-acetic acid (Lidorestat) and congeners as highly potent and selective inhibitors of aldose reeducates for the treatment of chronic diabetic complications. It lowers nerve and lens sorbital levels in the STZ-induced diabetic rat model. It normalizes polyols and reduces the motor nerve condition velocity deficit by 59 % relative to diabetic controls. It has a favorable pharmacokinetic profile with good penetration in target tissues.

Malaria is a major heath concern particularly which has got about 90 % of the worldwide annual clinical cases. The increasing number of drug resistant Plasmodium falciparum justifies the search for new drugs in this field. The antimalarial activity of 2- substitute 6-nitro and 6-aminobenzothiazole and their anthranillic acids has been tested. An in vitro study has been performed on W2 and 3D7 strains of Plasmodium falciparum and on clinical isolates from malaria infected patients. Toxicity has been assessed on THPl human monocytic cells. For the most active drug candidates, the in vitro study was followed by in stage dependency and the mechanism of action of derivatives tested in vitro, two had specific antimalarial properties. Each compound was active on all stages of the parasite, but one was markedly active on mature schizonts, while the other was more active on young schizont forms. Both drugs were also active on mitochondrial membrane potency. In vivo data confirmed efficiency with a sustained decrease of parasitaemia. Some of the compounds of this series considered as potential antimalarial worthy of further chemical and biological research.

1.5. Benzimidazoles:

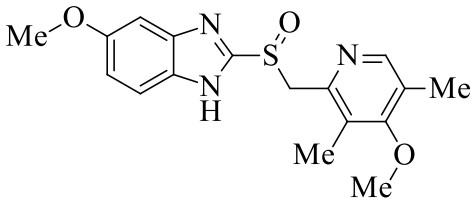
The development of antimicrobial agents to treat infections has been one of the most important medical accomplishments of the past century. Despite significant progress inantimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to the rapid development of resistance to the existing antimicrobial drugs. The increased useof antibacterial and antifungal drugs in recent years has resulted in the development of resistance to theseagents (Abbanat et al, 2003) and possible microbialimplications for morbidity, mortality and health care costs have become a serious fear. Even though, there are large numbers of antimicrobial drugs available for medical use, there will always be a vital need to discover new agents due to antimicrobial (Goldstein et al, 2007).

The benzimidazole ring is an important pharmacophore in modern drug discovery and their synthesis remains a main focus of medicinal research. The benzimidazole ring system as a nucleus from which to develop potential chemotherapeutic agents was established in 1950s when it was found as an integral part of the structure vitamin B12 (Barker et al, 1960 and Macchiarulo et al, 2002).The discovery of thiabendazole(Brown et al,1961) in 1961 further spurred chemists around the world to design and synthesize several thousands of benzimidazole molecules for anthelmintic activity and they are very important intermediates in organic reactions.[97]

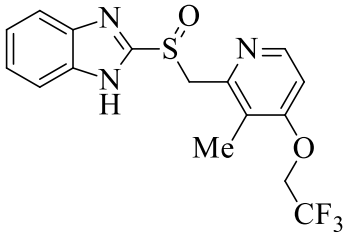
1.6. Importance of benzimidazole derivatives:

a) Antiulcer agents:

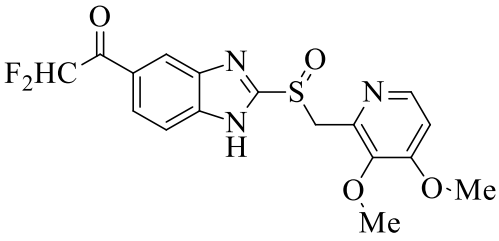
The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux-oesophagitis and nonsteroidal anti-inflammatory drug-induced lesions (Carcanague et al, 2002). In human body many tissuesare responsible for the imbalance between aggressive factors (like acid, pepsin, *H.pylori* infection) and local mucosa defense (secretion of bicarbonates, mucus and prostaglandin) results in acid-peptic and duodenal ulcer, gastroesophageal reflux disease, Zolinger-ellision syndrome and gastritis. This disease seems to have very prominent share in health disorder in current scenario of globalization.



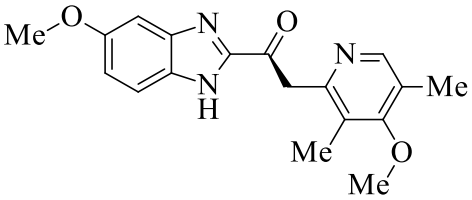
Omeprazole



Lansoprazole



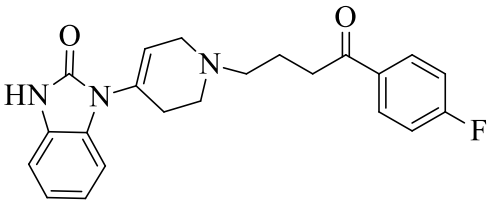
Pantoprazole



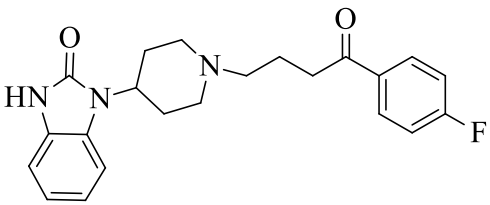
Esomeprazole

b) Antipsychotic agents:

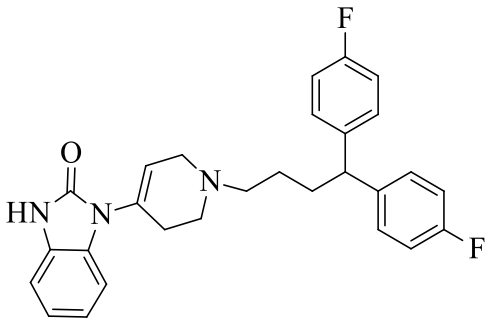
Benzimidazoles containing piperdinyl moiety (Ingle et al, 2011)are useful as antipsychotic agents and as analgesic.



Droperidol



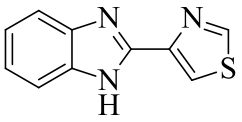
Benperidol



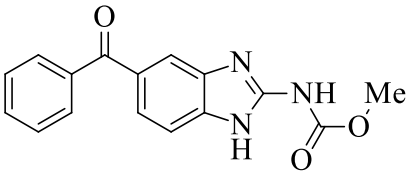
Pimozide

c) Antihelmintic drugs:

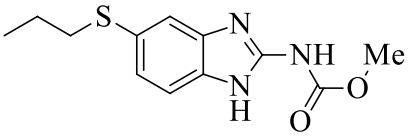
Benzimidazolesare most promising drugs as antihelmintic agents. Thiabendazole and mebendazoleare highly effective asbroad-spectrum antihelmintic agents. They are used for the treatment of nematode infestations and treatment of proto myxzoa infestations. Albendazole is effective against roundworms, tapeworm and flukes of domestic animals and human.



Thiabendazole



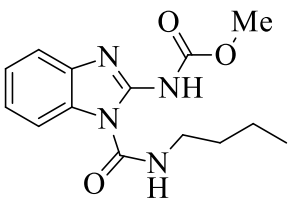
Mebendazole



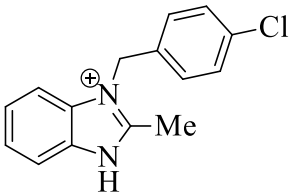
Albendazole

d) Antimicrobial andfungicidal drugs:

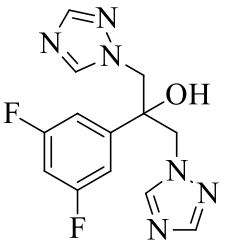
Infectious diseases have been serious and growing threatens to human health during the past few decades. Several research groups are working in this direction with a focus to prepare or invent new class of drugs which can withstand to bacterial resistance strains. Fluconazole is the first line of triazole based antifungal drug recommended by WHO duo to its pharmacokinetics characteristics. Tri halogen benzimidazoles exhibited the most potent antibacterial activity with MIC 3.12 µg/ml against *S.aureus*(Tuncbilek et al, 2009).Number of benzimidazole derivatives have commercial application for fungal infections.



Benomyl



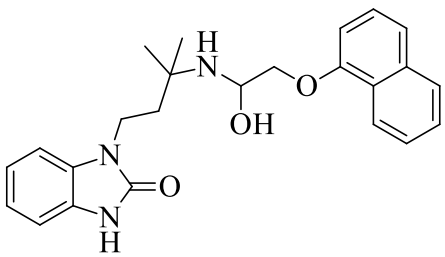
Chlormidazole



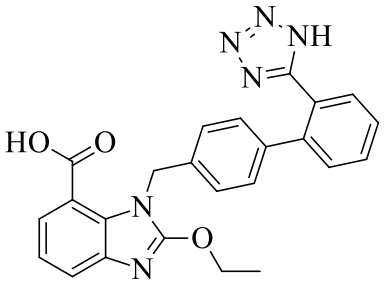
Fluconazole

e) Anti hypertensive drugs:

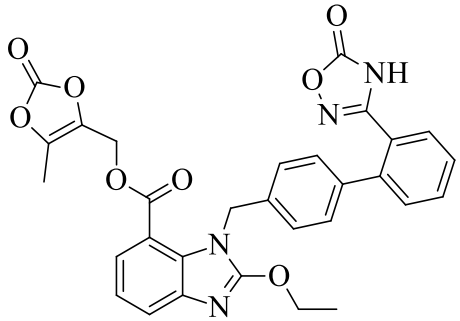
Benzimidazoles are considered as promising as anti hypertensive drugs (Kohara et al ,1996). Adimol is an anti hypertensive agent which acts as anon selective α_1-, α_2-, β-adrenergic receptor antagonist. Azilsartan medoxomil and Candesartan are acts as angiotension-II receptor antagonist, which are benzimidazole nucleus containing compounds.



Adimolol



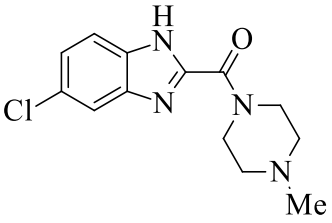
Candesartan



Azisartan medoxomil

f) Anti-inflammatory drugs:

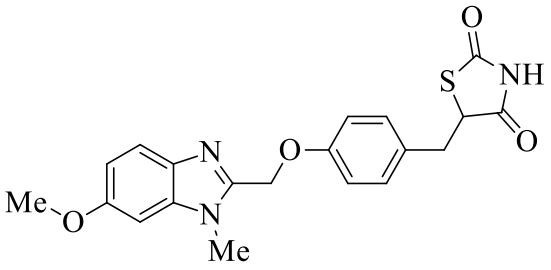
Some of the benzimidazole derivatives act as anti inflammatory agents, like VUF-6002 a potent and selective antagonist at the histamine H4 receptor (Zhang et al, 2007). It has anti-inflammatory and analgesic effects in animal studies of acute inflammation (Coruzzi et al, 2007).



VUF-6002

g) Antidiabetic drugs:

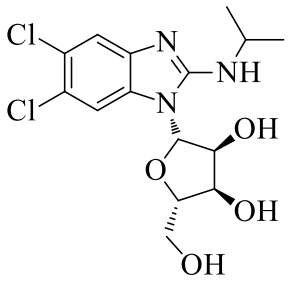
Rivoglitazone is a thiazolidine dione which contain benzimidazole nucleus was under the research for the use in the treatment of type-II diabetes (Shoichi et al, 2009).



Rivoglitazone

h) Antiviral drugs:

Maribavir is an oral anti viral drug which is the benzimidazole derivative; it is used for the prevention and treatment of human cytomeglo virus (HCMV) disease in hematopoietic stem cell/ bone marrow transplant patients. The mechanism by which inhibits HCMV replication is by inhibition of an HCMV encoded protein kinase enzyme called UL97 or pUL (Porcari et al, 1998).



Maribavir

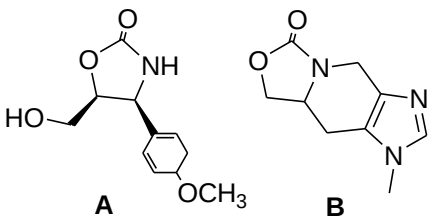
1.7. Oxazolidinones:

The development of antimicrobial agents to treat infections has been one of the most important medical accomplishments of the past century. Despite significant progress inantimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to the rapid development of resistance to the existing antimicrobial drugs. The increased useof antibacterial and antifungal drugs in recent years has resulted in the development of resistance to theseagentsand possible microbialimplications for morbidity, mortality and health care costs have become a

serious fear. Even though, thereare large numbers of antimicrobial drugs available for medical use, there will always be a vital need to discover new agents due to antimicrobial.

Heterocyclic molecules are well recognized due to their wide spread existence in nature. Almost two thirds of the currently recommended drugs, antibacterial, defoliants, fungicides, herbicides, and other such preparations include heterocyclic moiety. Oxazolidinones, the cyclic analogs of carbonates, contain both nitrogen and oxygen atom in their five membered heterocyclic ring. They are common heterocyclic motifs in a variety of biologically active and pharmaceutically interesting molecules and have wide range of applications in pharmacology, biology, paint and varnish industry,lubricants, herbicides and fungicides in agrochemical industry, in organic synthesis as chiral synthons, protecting groupsand as chiral auxiliaries in many organic reactions (Cicchi et al, 2001) .

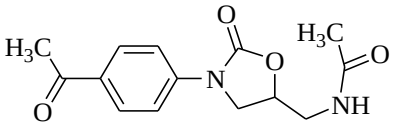
The 2-oxazolidinone ring is formed in many naturally occurring and synthetic molecules often with significant biological activity, like cytoxazone (**A)** an alkaloid isolated from a Streptomycessp. (Sp. Stands for species). This oxazolidinone is an immunomodulator that inhibits intercellular communication between macrophages. An oxazolidinone analogue of the muscarinic agonist pilocarpine (**B**) is used for the treatment of glaucoma. Spiro-oxazolidinones have been found to be a strong agonist used in the treatment of neurodegenerative diseases. The N-aryloxazolidinone scaffold is a constituent of a number of compounds, which shows interesting biological effects as antibacterial agents. They are used in developing novel drugs especially antibiotics of low toxicity for the host but effective against penicillin-resistant pathogens (Malamas et al, 1996).



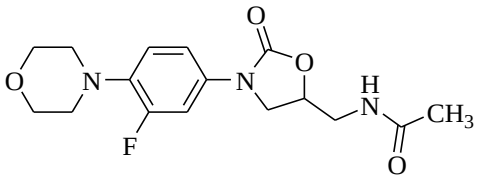
A **B**

Aryl-oxazolidinones were first described by E. I. du Pont de Nemours and company in 1987 as a novel class of synthetic antimicrobial agents.[126] The first representative, DuP 721 showed promising pharmacological properties such as

its oral activity against multidrug-resistant Gram-positive bacteria and a low occurrence of resistance development. DuP 721 (**A)** and derivatives, however, did not advance to phase II human clinical trials (Kearney et al, 1999).Instead, the new analogs eperezolid and linezolid were developed by Pharmacia and Upjohn (Adams patent, 1993). Linezolid is the first antibiotic containing oxazolidinone which exhibits an antimicrobial spectrum encompassing a broad range of susceptible and multidrug resistant Gram-positive coci.Linezolid (**B**) has been used successfully for the treatment of patients with endocarditic, bacteraemia, osteomyelitis, joint infections and tuberculosis and it is often used for treatment of complicated infections when other therapies have failed (Middleton patent 1972).

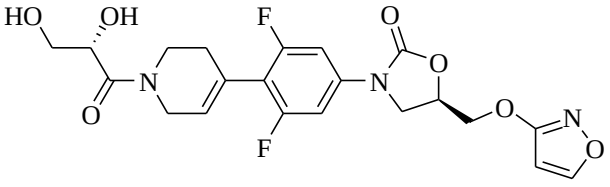


A



B

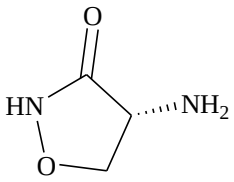
A number of studies are going on to develop oxazolidinone derivatives with improved potency and antibacterial spectrum. The oxazolidinones are also active against Gram-positive anaerobes such as Clostridium spp. [spp. stands for plural of species], Peptostreptococcus spp. and ropionibacterium acnes. AstraZeneca introduced AZD2563, a new oxazolidinone which has a spectrum and potency against Gram-positive organisms, including antimicrobial-resistant isolates regardless of resistance to otherclasses of antibiotics(Wookey et al, 2004).AZD2563 has a similar structure to linezolid, differing only at positions 3 and 4 of thearyl ring and on the C-5 side chain.



A

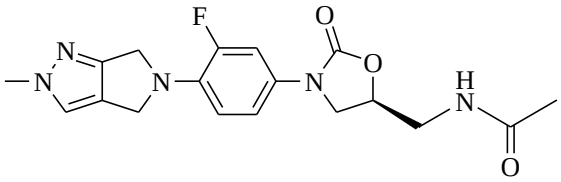
At a concentration of 2 mg/L, AZD2563 (**A**) can inhibit 98% of most of the Gram-positive bacteria tested in vitro including susceptible and resistant isolates

(Muller et al,2000 and Jones et al, 2002).Radezolid is a novel oxazolidinone with broader spectrum of coverage and increased activity against Gram-positive organisms as compared to other oxazolidinones. Radezolid has recently ompleted successfully two Phase 2 clinical trials: one for community acquired pneumonia and the second for uncomplicated skin and skin structure infections. Cycloserine (**A**) (4-amino-3-isoxazolidinone) is a drug sold under the brand name Seromycin (Lemaire et al, 2010).



A

It is an antibiotic effective against Mycobacterium tuberculosis (Brickner et al, 1996, Ford et al, 1997 and Slee et al, 1987) .D-Cycloserine is a broad-spectrum antibiotic used with other antibiotics to treat various forms of tuberculosis RWJ-416457 (32) (systematic name: N-{(5S)-3-[4-(5,6-dihydro-2H,4H-2-methylpyrrolo [3,4-c]pyrazol-5-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}acetamide), is an investigational pyrrolopyrazolyl-substituted oxazolidinone with activity against antibiotic-susceptible and resistant Gram-positive pathogens (Stevens et al, 2004) .



A

The unique mode of action combined with a high potential of antimicrobial activity of oxazolidinones, has prompted us to investigate new molecules with enhanced activity based on them. In this present investigation an attempt has been made to synthesize a novel series of C-ring modified and C-5 arm modified oxazolidino-arylamido/sulphonamides analogs. In the present work the main focus has been on improving the activity and limiting the cytotoxicity of oxazolidinone based derivatives. The present work describes the synthesis and evaluation of bacterial and

anti-tubercular activity of oxazolidino-aryl amides and sulphonamide conjugates particularly for drug resistance bacteria.

On continuation of our interest to synthesis the heterocyclic compounds, the present work is focused on synthesis of some novel Benzothiazole derivatives, Oxazolidinone derivatives, triazoles derivatives and pyrazolopyrimidine derivatives and to evaluate for their Bio-logical activities.

1.8. Current strategies:

The major problem in the recent times was the resistance of bacterial strains towards certain Benzothiazoles and other antibacterial agents across the world. In order to meet this problem several strategies were planned to synthesize new class of compounds such as combination of two active pharmocophores to make the hybrid molecules or fusion of two active ring systems to make hetero ring fused bioactive molecules. The hybrid molecules concept was first adopted by Lescher[146]and his co-workers for antimalarial activity with an idea that presence of two pharmocophores in single molecule may enhance the activity. Other strategy was to prepare hetero ring fused benzimadazoles and oxazolidinones.

1.9. Present work:

Present work has been designed for the preparation of novel Heterocyclic fusedHybrids molecules andevaluation of their activity wasconveniently divided in to 6 chapters:

Chapter 1: This chapterdescribes a benzothiazoles and oxazolidinones, mechanism ofaction, pharmacological aspectsofBenzothiazoles and oxazolidinones. It alsocovers the introduction about the benzothiazoles, oxazolidinones and their medicinal importance.

Chapter 2: The second chapter describes the review on heterocyclic compounds and its importance in drug discovery.

Chapter 3: Chapter threedescribes thesynthesis of biologically active compounds which consist of two distinct pharmocophores; benzothiazoles and triazoles, Facile

synthesis of *N*-(benzyl-1*H*-1, 2,3-triazol-5-yl)methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides *via* clickchemistry.

Chapter 4: Efficient method Microwave irradiation for synthesis of 2-substituted benzimidazole from*1,2*- phenylenediamine andβ-keto esters /1, 3-di ketones using $Gd(OTf)_3$ as aCatalyst .

Chapter 5: This chapter deals with the importance of oxazolidinones in medicinal research, Structural Modification of Oxazolidinones via Multistep synthesis and their impact on antitubercular and antibacterial activity**.** Experimental procedures are also included. The activity data of compounds are included.

Chapter 6: The method development for the 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine framework might provide a template for the discovery of novel and potential anticancer agents,environmentally benign method for the preparation of pyrazolo-pyrimidine rings and experimental procedures were described.

CHAPTER 2

Micro Review on Heterocyclic Compounds

Micro Review on Heterocyclic Compounds

2.1 Introduction

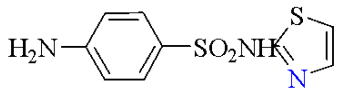
Heterocyclic compounds having a special place among pharmaceutically significant natural products and synthetic compounds. The significant ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmocophores has basically contributed to their unique value as conventional key elements of numerous drugs (De Leon et al, 1997) .[1]Heterocycles afford a large area for new lead molecules and for generation of activity relationship with biological targets. For these reasons, it is not surprising that this structural class has received unique concentration in drug discovery.

The molecules containing a ring self-possessed of two or more different kinds of atoms commonly known as carbon [C], nitrogen [N], oxygen [O] and sulfur[S] like indole, oxadiazole, chroman, pyran, furan, thiophene, pyrrole and thiazole etc. are called as heterocyclic moieties. Heterocyclic rings have hydrogen bond donors and acceptors in a semi-rigid scaffold and they can therefore present a various range of pharmocophores. The convenience of heterocyclic is due to their combination of compact and robust molecular structures with high degree of molecular diversity that results in properties which can be finally adjusted to the need of complicated applications. Derivatization of heterocyclic pharmocophores with different groups or substituent's represents an flexible approach to generate chemical diversity for lead identification and optimization of drug target probables.

Large number of naturally occurring substances that are essential for the living cells such as the pyrimidine and purine bases of the genetic material DNA; important amino acids such as proline, histidine, tryptophan; vitamins and coenzyme precursor thiamine, riboflavin, pyridoxime, folic acid, biotin; the B_{12} and E families of vitamin; photosynthesizing pigment chlorophyll; oxygen carrying pigment hemoglobin and its breakdown products; the bile pigments; the hormones kinetin, heteroauxine, scrotonin and histamine together with most of the sugars contain different heterocyclic nuclei.

A variety of natural products such as antibiotics, penicillin, indolmycin and cephalosporins; alkaloids like vinblastine, ellipticine, morphine, reserpine; cyclopeptides, cyclicdepsipeptides, macrolides, polyketides, steroids, saponins and glycosides all have heterocyclic moieties. It can be esteemed by looking the structures

of many marketed drugs that are currently in therapeutic use such as an psicofaranine and tubercidin; aminoglycosidal antibiotics such as streptomycin and kanamycin; sulfa drugs as Sulphathiazole [1] used against a wide range of bacteria; antidiabetic drug, Pioglitazone [2]; antiprotozoal drug, Tinidazole [3]; CNS stimulant drug, Mazindaol [4]; antithyroid drug, Carbimazole [5]; anti-inflammatory drug, Indomethacin [6]; diuretics as Ethoxzolamide [7] and antihistamine drug, Trimeprazine [8] all these molecules contain different heterocyclic moities.



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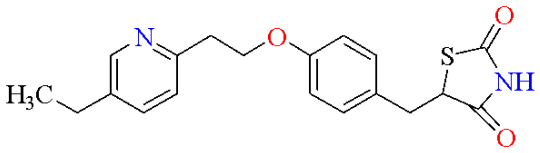

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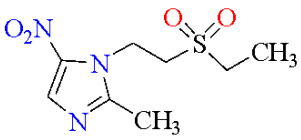

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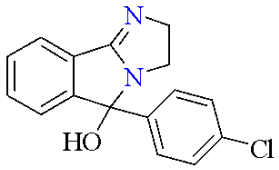

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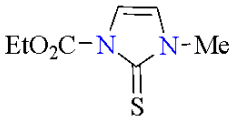

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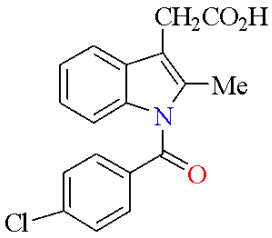

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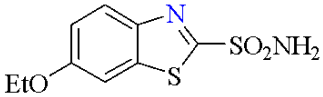

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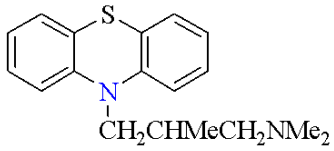


(8)

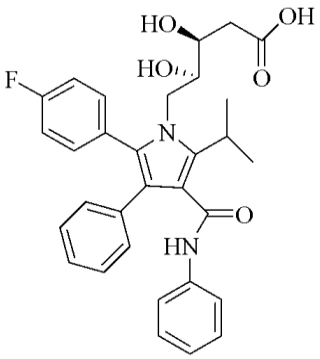
2.2 NITROGEN CONTAINING HETEROCYCLES

Nitrogen containing Heterocycles are abundant in nature and are of great importance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and alkaloids, as well as pharmaceuticals herbicides, dyes and several more compounds (Paula et al,2002) .[2]

2.2.1. Pyrrole and its benzo derivatives (Indole).

Pyrrole is the central building block for all naturally happening porphyrins,including haem chlorophyll ,phycobilin and cobalamine .Its derivatives are very important and displays a variety of physiological activities, particularly, 1,2,3,5- tetra substituted

pyrrole derivatives are known to display antibacterial (Daidone et al,1990) ,[3] anti viral (Almerico et al, 1998) , [4] anti inflammatory (Kaiser et al,1972) [5] and antioxidant activities and to inhibit cytokine-mediated disease (Tilfordet al,1971). [6]Additionally they have been found to demonstrate potent inhibition of platelet aggregation [7] and anti hypertensive activities (Naemati et al, 1998). The drug Atorvastatin (Schaefer et al, 2004) [9] is used for the treatment of cardiovascular disorder, Bisdistamycin [10] used as anti-HIV (Deidda et al, 1998), the compound BM 212 (Kikuchi et al,1999) [11] shows anti mycobacterial activity against multi drug-resistant tuberculosis.



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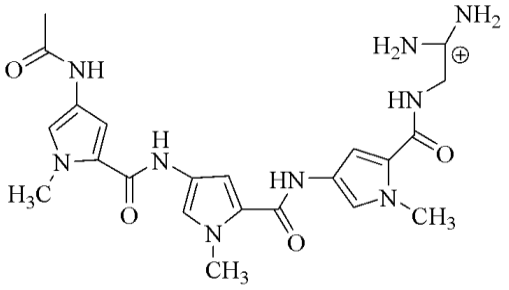

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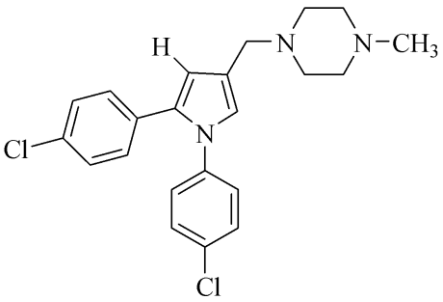
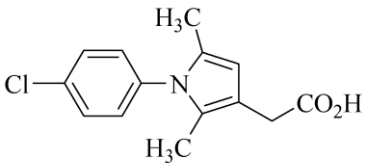


(11)

Benzene rings provide the aromatic nucleus for the majority of the NSAIDs (Non steroidal anti-inflammatory drugs). A propionic acid attached to its 2nd positions provides the side chain for most of these compounds .One such compound is Clopirac [12].

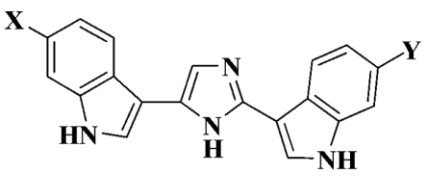


(12)

Benzopyrrole or more commonly identified as indole and its derivatives are another class of heterocycles which have been the subject of great interest for their biological activities (Hurdle et al, 2005). The indole scaffold probably represents one of the most important structural subunits for the discovery of new drug candidates. The demonstration that many alkaloids contain the indole nucleus, the recognition of the importance of essential amino acid tryptophan in human nutrition and the discovery of the plant hormones served to bring about a massive search on indole chemistry, giving rise to a enormous number of biologically active natural and synthetic products, with a wide range of therapeutic targets, such as anti-inflammatories, phosphodiesterase inhibitors, 5-hydroxytryptamine receptor agonist and antagonists, cannabinoid receptors agonists and HMG- CoA reductase inhibitors. Many of these target receptors fit into the class of GPCRS (integral membrane G-protein coupled receptors) and possess a conserved building pocket that is predictable by the indole scaffold in a "common" harmonizing binding domain, explaining the great number of drugs that contain the indole substructure, such as indomethacin, ergotamine, frovatriptan, ondansetron, tadalafil, among many others.

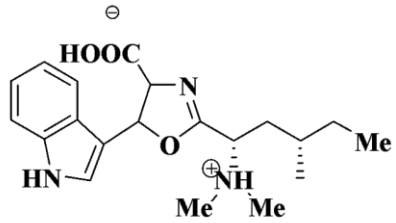
Indole is a well known heterocyclic skeleton, a common and important feature of a variety of natural products and medicinal agents (Gu et al, 1999) . Compounds carrying the indole residue, exhibit antibacterial, antifungal, antiviral and anti-estrogenic properties (Takahashi et al, 1998) . A large number of natural products containing the indole ring have been identified such as antitumoral, Nortopsentins (Meseguer et al, 1999) [13], potent inhibitor of lipid peroxidation, Martefragin A (van Loevezijin et al, 2001) [14], protein kinase C activator, Indololactum V (Reinicke et al,1997) [15] and Fumitre morgin(Heinelt et al,2001) as a specific reversal agent for the breast cancer resistance protein. Indole is present in drugs with a remarkable range of activities demonstrated by the steroidal anti inflammatory agent Indomethacin (Gubin et al, 1992) [16] and potent and selective factor of X_a inhibitor (Robinson et al, 1996). Some indole related heterocycles eg. Indolizines shows anti arrhytmic

(Petrounia et al, 1994), oxindoles exhibit anti-rheumatic properties and are inhibitor of mandelonitrile lyase (Bermudez et al, 1990). Derivatised indulines are known to be potent and selective 5-HT_3 receptor anatagonists (Bennett et al, 1989).



(13)

X, Y= H, OH, Br



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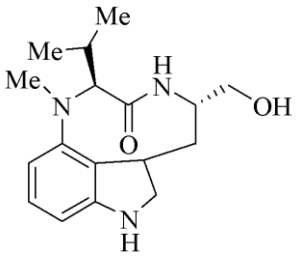

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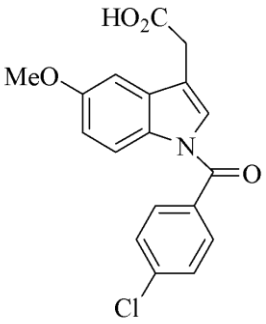


(16)

2.2.2. Azoles and its derivatives

Azoles are compounds having heterocyclic ring containing two or more nitrogen atoms. They have emerged as a best class of effective antifungal and antibacterial agents for common and life threatening infections. Well-known azole derivatives have a gem- phenyl-(1*H*-imidazol-1-yl methyl) moiety (fig-1), which is thought to be largely responsible for imparting antifungal activity, for e.g:- Chloromidazole [17], Miconazole [18], Ketoconazole [19] and Flucanzole [20] have all been developed for clinical uses. SAR studies revealed that imidazole and phenyl rings which are also pharmacophoric segment of all these molecules can be replaced by triazoles (Orjales et al, 1997).

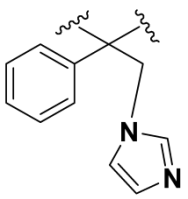
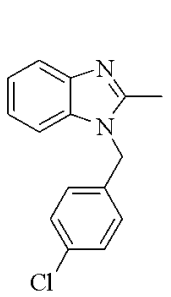


Fig- 1. Structure of gem-phenyl-(1*H* imidazol-1-yl methyl) moiety.



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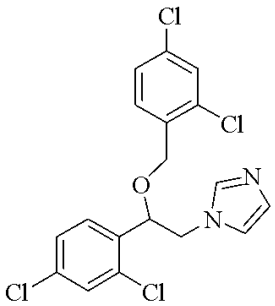

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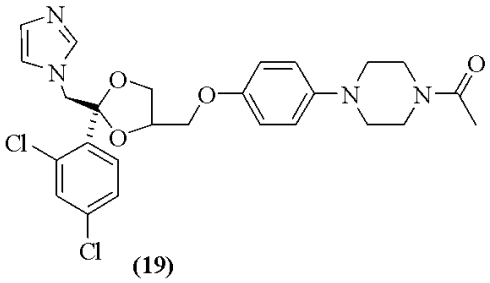

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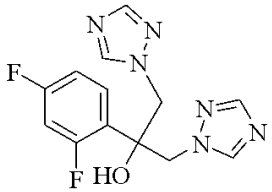
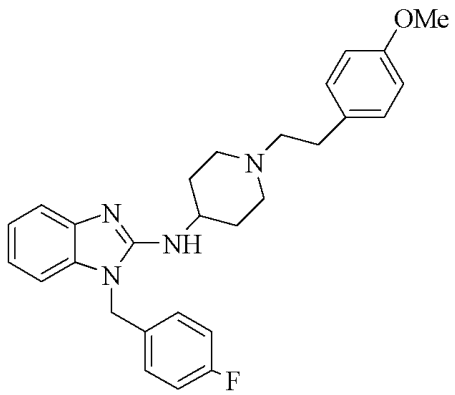


(20)

(i) Benzimidazoles

Benzimidazoles derivatives comprise of imidazole ring fused to benzene and are reported to be physiologically and pharmacologically active. They find application in the treatment of several diseases like epilepsy, diabetes, antimicrobial, anticancer etc (Sparatore et al, 1991). remarkable clinical examples being the antihistamine compound, Astemizole [20] and the proton pump inhibitor, Omeprazole [21], Lansoprazole [22], Pantoprazole [23].



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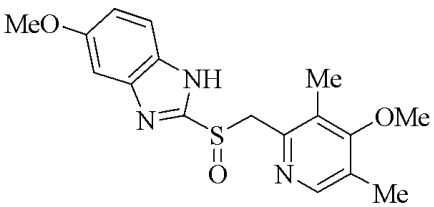

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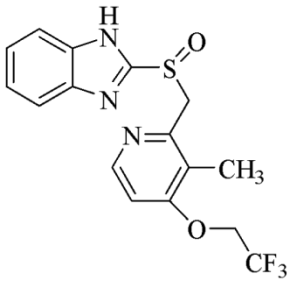

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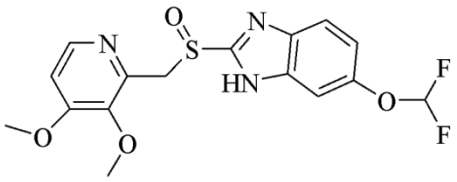
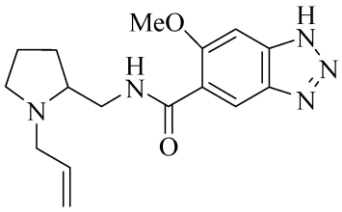


(23)

(ii) Benzotriazoles

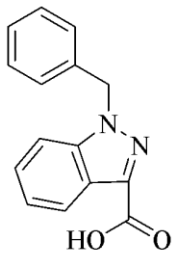
Benzotriazole derivatives having a 3-nitrogen containing ring fused to benzene represent a novel sequence of bioactive compounds that have found application as antiemetic. Alizapride [24] is a benzotriazole derivative used for treatment of side effects caused by cisplastin chemotherapy (Li et al, 2003).



(24)

(iii) Indazoles

The indazole nucleus is an essential pharmaceutical moiety and constitutes the key subunit in many drug substances with a broad range of pharmacological activities like antitumor, antimicrobial, and antiplatelet activities. Indazole containing Lonidamide [25] shows anticancer activity, whereas compound Bendazac (Gazit et al, 1996) [26] and Benzydamine [27] marketed as drug for anti-inflammatory activity.



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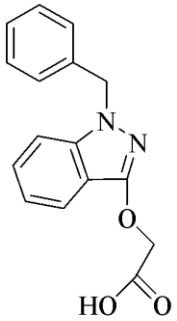

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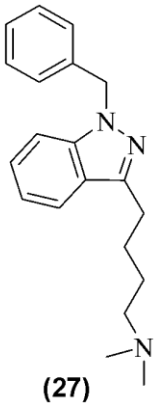
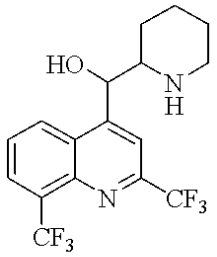


(27)

2.2.3.Quinolines and Isoquinolines

Quinoline and Isoquinoline as well as their tetrahydroderivatives are a widespread structural design found in many biologically active natural and synthetic compounds. For e.g:- it is present in the HIV protease inhibitor, Sanquinavir [28], antimalarial drug, Mefloquine [29], Levofloxacin [30] and Trovafloxacin [31], wide spectrum antibacterial agents (Chao et al,1999), Ciprofloxacin that can also be used to treat anthrax, antidepressant drug ,Nomifensive [32] and inhibitor of angiotensin converting enzyme, Quinapil [33]. Chloroquine [34], a well known antimalarial drug (Vlahov et al, 1990) also has a quinoline nucleus. Many quinoline containing compounds have been found application as anti-inflammatory agents, antitumoral and as analgesics. Distant from this, these heterocycles have shown potential as ligands for the human glucocorticoid receptor (Witt et al, 2003).



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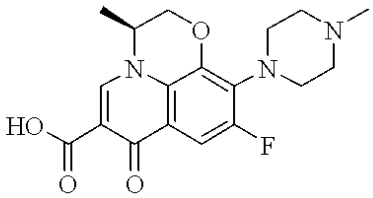

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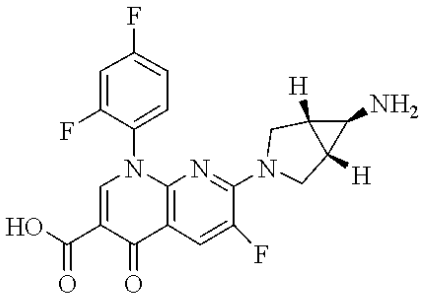

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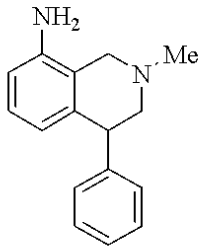

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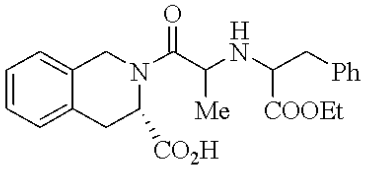

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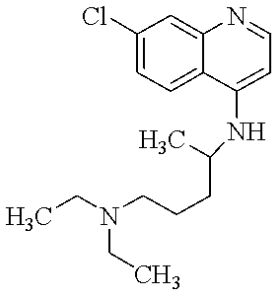
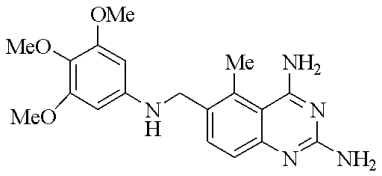


(34)

2.2.4. Quinazolines

Quinazoline (Benzo[*d*]pyrimidine) and their derivatives are building blocks for more or less, 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, microorganisms and animals (Spencer et al, 1994). This heterocycle is present in Trimetrexate [35], drug used for treatment of pneumonia caused by *Pneumocystis carinii*, in Prazosin [36], for treatment of benign prostatic hyperplasia (BPH) and in the anti hypertensive agent Ketanserin. Quinazoline derivatives exhibit wide range of biological properties such as antitumorals [37], potent non-nucleoside reverse transcriptase inhibitor of HIV-1 antibacterial [38], antagonist for the human adenosine A(3) receptor (van Muijlwyk- Koezen et al, 2000), anti-inflammatory, anti-asthmatic and anti-ischemic agents.



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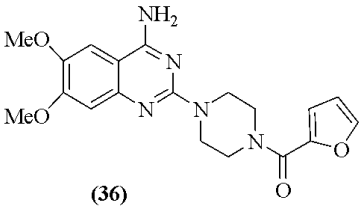

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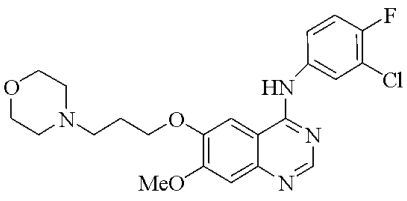

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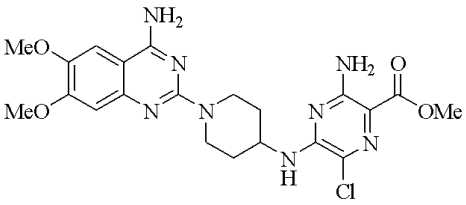
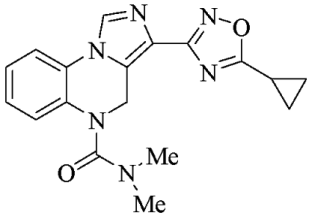


(38)

2.2.5. Quinoxalines

Quinoxaline represents one more class of N-containing compounds. Quinoxaline di-*N*-oxide shows antitrypanosomal activity in vitro against epimastigote forms of *Trypanosoma cruze* (Jacobsen et al, 1999). Some analogues of imidazo [1, 5-*a*] quinoxaline [39] and [40] show antixiolytic activity due to high affinity of the *γ*-aminobutyric acid A (GABA). Chloro-quinoxaliyl with phenoxy propionic acid group (XK 469) [41] (Hazeldine et al, 2001) is broadly active against mammary adenocarcinoma-17/ Adr tumors. Many biologically active quinoxaline compounds have angiotensin II receptor antagonist 57 and adenosine receptor antagonistic activity (Sarges et al, 1990).



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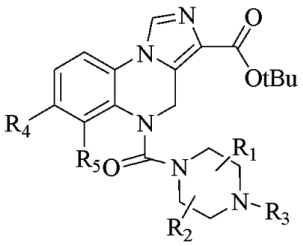

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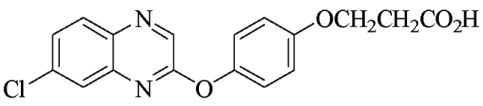
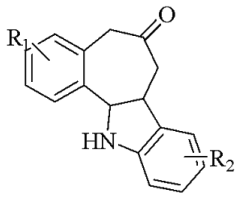


(41)

2.2.6. Benzazepines

Benzazepines are benzoannulated heterocyclic compounds having nitrogen atom in a 7- membered ring system. A series of 7, 12-dihydroindolo-[3,2-*d*] [1] benzazepin-6(5*H*)-one derivatives [42] and related heterocycles [43] are reported to act as cyclin-

dependent kinase (CDK) inhibitors (Link et al, 1998). Other compounds having this moiety have shown biological activity as central selective acetyl cholinesterase inhibitors (Ishihara et al, 2000), vasopressin receptor antagonists and particular bradycardiac agent. Eg- Zatebradine [44] (Bom et al, 2001).



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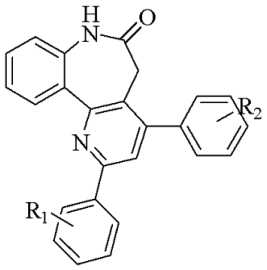

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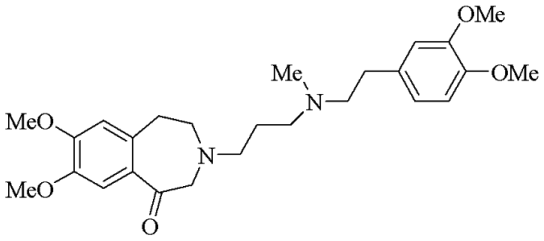
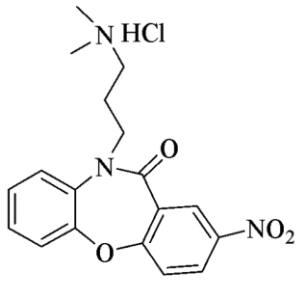


(44)

2.2.7. Benzoxapines

Several physiologically active compounds contain benzoxazepine ring system for example nitoxazepine [45] and related compounds exhibit pronounced antidepressant activity (Kamei et al, 2001). A new class of 1,4-benzoxazepine (BZO) derivative [46] has been detailed as a effective and selective 5- HT_{1A} agonist, exhibiting vastly potent antiischemic effect.



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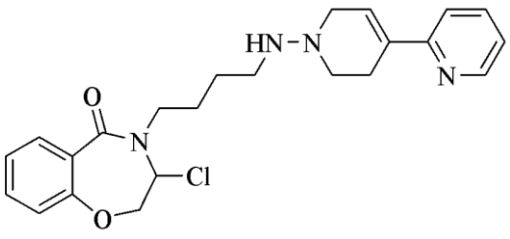
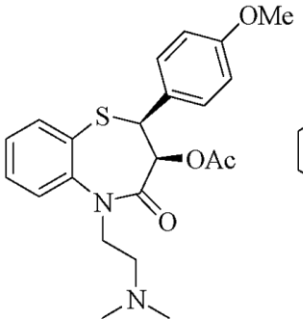


(46)

2.2.8. Benzothiazepines

Compounds containing benzothiazepine moiety are known as angiotensin converting enzyme inhibitors (Slade et al, 1985) Dilitiazen (Kantoci et al, 1996) [47], a well

known 1,5-benzothiazepine-4-one is among the most widely used drugs in the treatment of cardiovascular disorders due to its role as calcium channel blocker. JMV 1645 [48] and [49] have novelty been reported as potent and selective bradykinin antagonists (Bedos et al, 2000).



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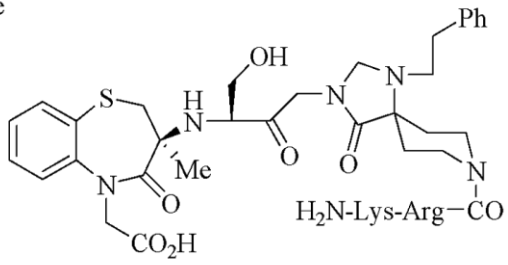

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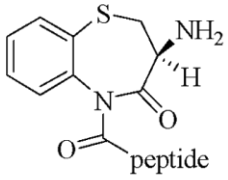
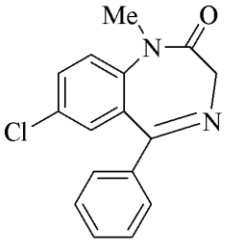


(49)

2.2.8. Benzodiazepines

Benzodiazepines are benzo annulated heterocyclic compounds having nitrogen atom embedded in 7-membered ring system. Various benzodiazepine derivatives display diverse pharmacological activities such as antiarrhytmics (Selnick et al, 1997) , vasopressin antagonists (Albright et al, 1998), HIV reverse transcriptase inhibitors, cholecystokinin antagonists etc. The therapeutic application of Diazepam [50], Triazolam [51], and Midazolam [52] containing benzodiazepine nucleus are well known as anxiolytic (Hanley et al, 2000), sedative and anticonvulsants. A number of natural products have also been reported to incorporate the 1,4-benzodiazepine-2,5-dione core structure (Rahback et al, 1999) .



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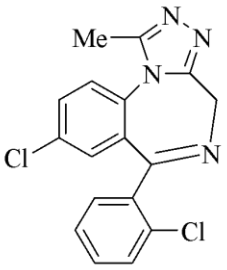

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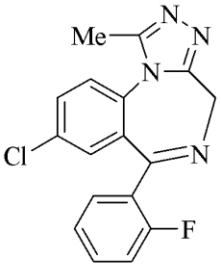
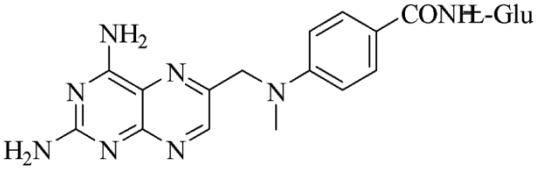


(52)

2.2.9. Pteridines

Pteridines have two fused six membered heterocyclic rings namely pyrazine and pyrimidine. They have been reported to show a variety of biological activities and constitute the backbone of several marketed drugs, for example, the anti folate drug methotrexate (Khaled et al, 1984) (MTX) [53] is used as an antitumor agent and compound SCI-208 [54] is used as antihepatitis agent by inhibiting TGFB-R_1 Kinase. Other pteridines are reported to have activities against biological targets such as alkyltransferase, adenosinekinase (Gomstsyan et al, 2004), mycobacterial FtsZ, xanthine oxidase, and neuronal nitric oxide synthase (Momparler et al, 2000).



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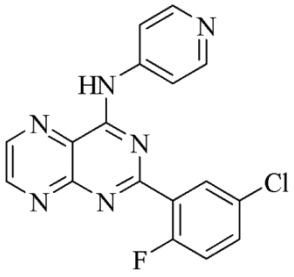
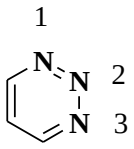


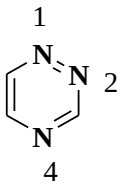
(54)

2.2.10. Triazines and Its Benzoderivatives

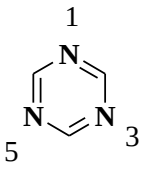
Triazines are aromatic compounds analogues to benzene ring but with the carbon replaced by nitrogens. The three isomers of triazine are distinguished from each other by position of their nitrogen atoms.



1,2,3- Triazine



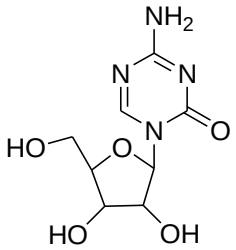
1,2,4- Triazine



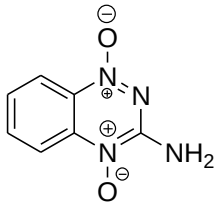
1,3,5- Triazine

A large number of synthetic compounds containing the triazine ring show biological activity and are in use as pharmaceuticals (Smith et al, 2000). 1,3,5-triazine-2-one derivatives include well known anticancer drugs (Kelson et al, 1998), 5-azacytidine (4-amino-1-B-D-ribofuranosyl-1,3,5-triazine-2(H)-one, [55] a synthetic analogue of the natural pyrimidine nucleoside cystidine has strong antileukemic activity (Rosowsky et al, 1973). Tirapazamine (Guerrera et al, 1993) (TPZ 1, 2, 4-benzotriazin-3-amine 1,4-dioxide), [56] is most advance bioreductive drug that is selectively toxic to hypoxic cells, hence, it is a useful adjunct to radiotherapy and

chemotherapy which often fails to eliminate hypoxic cells within tumors. Some of the phenyl dihydrotriazines have been used therapeutically as antimalarial (Rosenblatt et al, 1992), antifungal (Stevenson et al, 1998) and antiparasitic agent (Karatas et al, 2006).



(55)



(56)

2.3. OXYGEN CONTAINING HETEROCYCLES

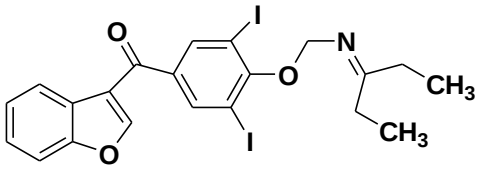
Heterocyclic compounds containing an oxygen atom are most widely distributed and occur in large number of natural products. Many natural or synthetic compounds having oxygen hetero ring system form a family of active compounds and show a wide range of physiological and pharmacological properties. This class of heterocycles display anticoagulant, antipsoriasis, viral proteases inhibitory activity, antibacterial, antitumoral, anti-oxidant, antipoliferative, estrogen agonist and/ or antagonist and CNS modulating activities. Different types of oxo-heterocyclic compounds are listed as follows:

2.3.1.Furans and Benzofurans

Furan and its analogues constitute a major group of naturally occurring compounds that are of particular interest because of their biological activity and the role they play in defense system (Habermann et al, 1999). They find applications as oxidants, antioxidants, as brightening agents, for drugs and in other field of chemistry and agriculture (Guiraudou et al, 2004). Amiodarone [57] an iodinated lipophilic benzofuran derivative is widely used in the treatment of ventricular tachyarrhythmia and artrial fibrillation (McEvoy et al, 1987) , it also possess coronary and peripheral vasodilator effects(Gonzalez-Gomez et al,2005) . Benzofuran derivatives form another important class of heterocyclic molecules known to possess many important pharmacological properties. Benzofuran containing structures are found among naturally occurring furocoumarins, such as Psoralen [58] and Methoxalen [59]

isolated from seed of *Ammi majus L* and are used for the treatment of psoriasis (Dalla Via et al,2001) and other dermal diseases (Ingolfsdotter et al,2002) . Another important application of Psoralen is in field of photo chemotherapy where Psoralens are capable of undergoing photo addition with thymine units present in DNA (Kundu et al, 1997). Usnic acid [60] containing benzofuran moiety is one of the most common and abundant lichen metabolite, well known as an antibiotic. It is also endowed with other interesting pharmacological properties such as antimicrobial and in the control of tumor proliferation (Hoeksema et al, 1956). Nitrofuran [61] and Nidroxyzone [62] both having furan nucleus act as antibacterial and hydrophilic congener respectively.

Dantrolene [63] is a muscle relaxant that acts by abolishing excitation- contraction coupling in muscle cells by action on ryanodine receptor and is an effective treatment for malignant hyperthermia. Ranitidine [64] is a histamine H_2- receptor antagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (Refouvelet et al, 2004) (GERD).



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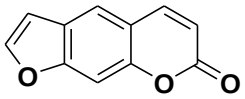

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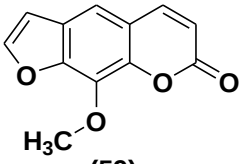

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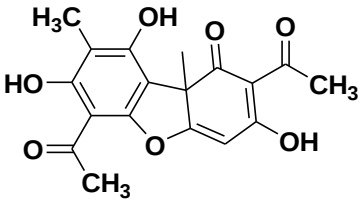

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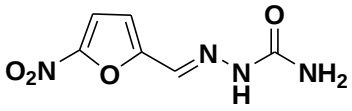

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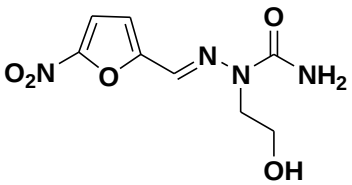

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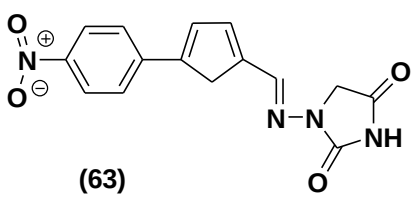

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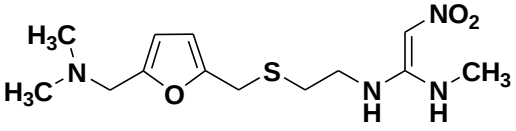
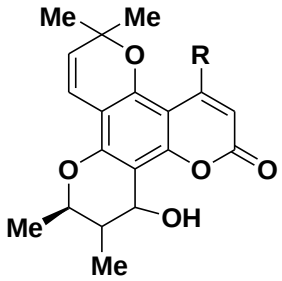


(64)

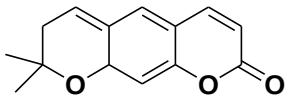
2.3.2. Coumarins

Coumarins are natural or synthetic benzopyran-2-one derivatives that form a family of active compounds with a wide range of pharmacological proper ties. Coumarin derivatives display anticoagulant, antioxidant (Roelens et al, 2005), antipoliferative, estrogen- agonist effects (Usui et al, 2006) and / or central nervus system modulating activities. The discovery of coumarin compounds with weak estrogenic activity has been of potential medicinal interest since such derivatives could be used as therapeutic agents to prevent the emergence of adverse effects associated with menopause such as osteoporosis, cardiovascular risks (atherosclerosis) and cognitive deficiency (Mali et al, 2002). Recently it has been reported that some coumarin derivatives like Calanolide [65] and Inophyllum [66] isolated from Calophyllum genus (Guttiferae) showed strong activity against human immunodeficiency virus type I (HIIV-I).

Two naturally occurring pyranocoumarin derivatives like Xanthyletin (Vilar et al, 2006) [67] and Seselin [68] have shown antifungal, insecticidal, anticancer, and anti-HIV activities. Seselin is also used as a photoactive drug for skin disorders (Gebauer et al, 2007). Drug molecules like Carbochromen [69], a potent specific coronary vasodilator have been used for many years in the treatment of angina pectoris. Warfarin [70] another coumarin derivative shows potent anticoagulant activity and a good pharmacokinetic profile (Konkoy et al, 2000).



(65) R=Pr
(66) R=Ph



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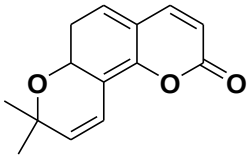

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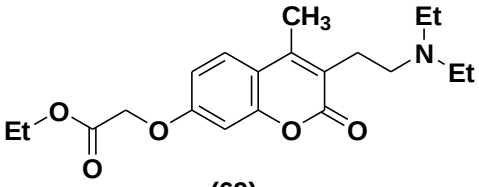

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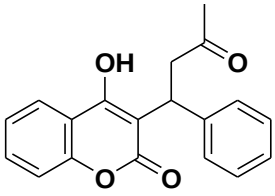
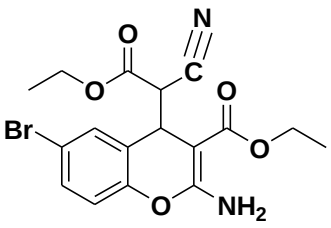


(70)

2.3.3 Chromans and Chromenes

Chromans and chromenes represent an important class of oxygen containing heterocyclic compounds. They possess awide range of biological activities, such as, spasmolytic, diuretic, anticoagulant, anticancer and anti-anaphylactic. In addition, they can be used as a cognitive and enhances for the treatment of neurodegenerative diseases like Alizheimer's, Huntington's or Parkinson's diseases, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus. A number of 2-amino-4H-pyrans are useful as photoactive materials. Chromenes have been used as an antagonist for antiapoptotic Bcl-2 proteins to overcome drug resistance in cancer [71] (Jain et al, 2006), and as anti-inflammatory Quercinol [72] (Chimenti et al, 2007) . Recently many chromene and chroman derivatives have emerged as a novel class of drugs called selective estrogen receptor modulators (SERMs) [73, 74, 75] (Wang et al, 2005).



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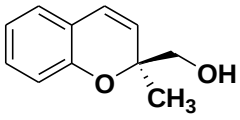

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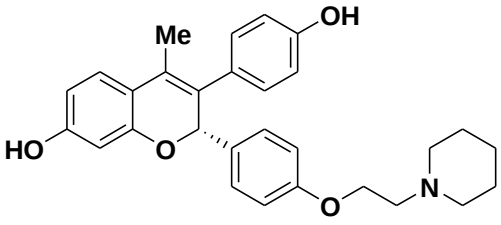

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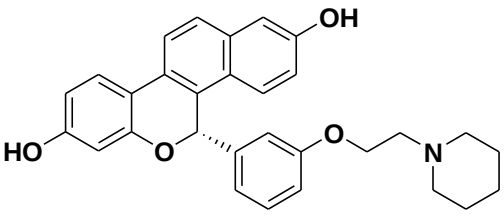

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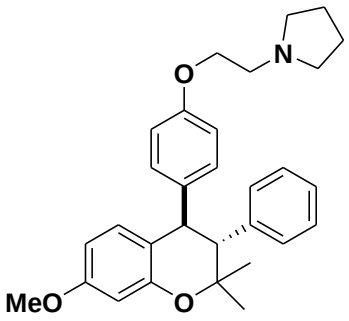
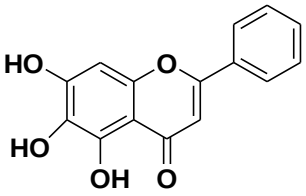


(75)

2.3.4. Flavonoids

Flavonoids are a group of [4000 naturally occurring compounds] aryl substituted benzo-pyrones or chromononesbased on a common three- ring nucleus. They are ubiquitous in all vascular plants and important constituents of the human diet.

Flavonoids have been found to possess antitumoral (Engler et al, 2004), antidiabetic (Ogundaini et al, 1996), [123] anti-atherosclerotic cardio protective, anti-inflammatory, antiperoxidant (Rahman et al, 2002) ,[126] antiosteoprotic, antimicrobial and antiviral characteristics. The most beneficial and the most studied health effect of Flavonoids is their antioxidant impact. (In anticancer area, flavonoids can inhibit the metabolism of the carcinogen benzo[a] pyrene by hamster embryo cells in tissue culture and markedly augment the cytotoxicity of TNF (tumoral necrosis factor-a). Flavonoids are also found to have tyrosinase inhibitory activity, moderate aromatase inhibitory activity and inhibition of estradiol induced DNA synthesis. Flavonoids containing moieties such as Baicalein [76] is a potent, in vitro inhibitor of platelet 12-human lipoxygenase, Karanjin [77] as hypoglycemic and antifungal and compounds [78] and [79] show anticancer activity (Zhou et al, 2004) .



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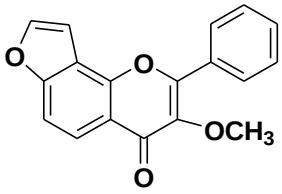

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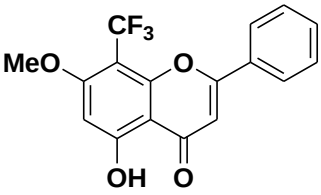

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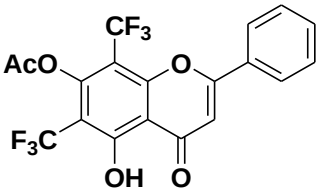
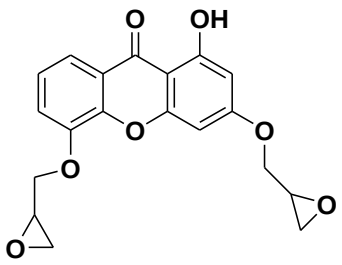


(79)

2.3.5. Xanthones and Xanthenes

The interesting structural scaffold and biological efficacy of xanthones enforced many scientists to isolate or synthesize new xanthone derivatives for the development of prospective new drug candidates. They show very diverse biological profiles including anti-hypertensive, anti-oxidative, anti-thrombotic, anticancer, activity based on their molecular structures (Sanugul et al, 2005). Polyoxygenated xanthones [80], either synthetic or isolated from natural resources showed inhibitory activity against several cancer cell lines. Psorospermin [81], isolated from African plant

Psorospermum febrifugem showed good anti-cancer activity against human and murine cancer cell lines. Recent studies have indicated that some xanthone derivatives such as Mangiferin, a xanthone C-glucoside act as potent α-glycoside inhibitor, Sch 56036 [82] shows potent antifungal activity. α –Mangostin [83], another derivative of xanthone shows activities like competitive antagonist of the histamine H1 receptor, inhibition of topoisomerases I and II, antibacterial activity against Helicobacter pylori, anti-inflammatory activity and inhibition of oxidative damage of human LDL. Astroviridin [84] is a tetracyclic polyhydroxylated xanthone recently isolated from the stem bark of Garcinia atroviridis, and has been traditionally used for earache (Hideo et al, 1981).



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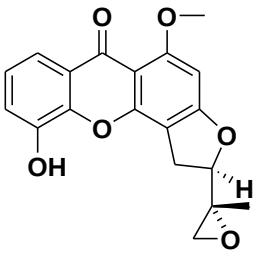

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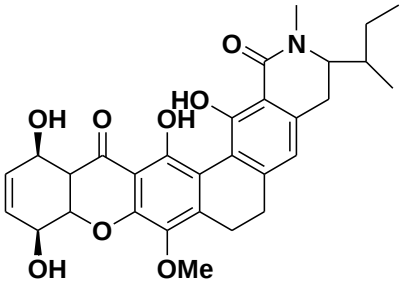

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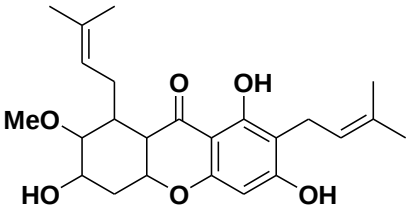

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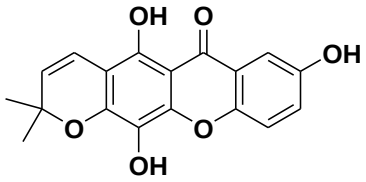


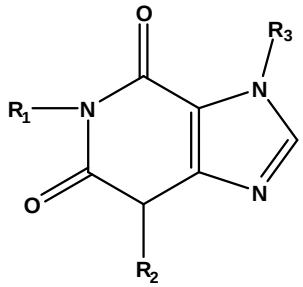
(84)

Derivatives of Xanthine are collectively known as Xanthenes, are a group of alkaloids commonly used for their effects as mild stimulants and as bronchodilator, notably in treating symptoms of asthma. Due to widespread effects, the therapeutic range of xanthenes is narrow, making them merely a second-line asthma treatment. Methylated xanthenes include Caffeine, Aminophylline, IBMX, Paraxanthine, Pentoxifylline, Theobromine and Theophylline. These drugs act as both:-

a. Competitive nonselective phosphodiesterase inhibitors which raise intracellular cAMP, activate PKA, inhibit TNF- alpha and leukotriene synthesis and reduce inflammation and innate immunity.

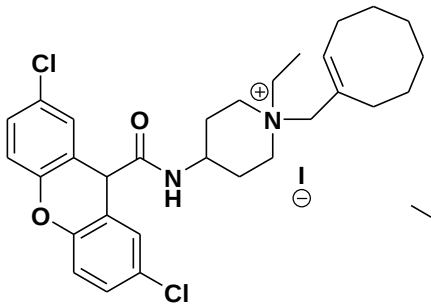
And,

b. Non- selective adenosine receptor antagonists which inhibit sleepiness-inducing adenosine.



R_1= R_2=R_3=CH_3; Caffeine.
R_1=H, R_2= R_3= CH_3; Theobromine
R_1= R_2= CH_3, R_3= H; Theophylline

Xanthene derivatives show wide range of biological and pharmaceutical properties such as antiviral, antibacterial and anti-inflammatory activities. Examples of biologically active xanthenes include novel CCR1 receptor agonist [85], chemosensitizers [86, 87, 88] against chloroquine resistant *Plasmodium falciparum.* Furthermore, these compounds are used as dyes, in laser technology, pH-sensitive flurorescent materials for the visualization of biomolecular assemblies. It is also noteworthy that dibenzoxanthene derivatives are candidates as sensitizers in photodyanamic therapy.



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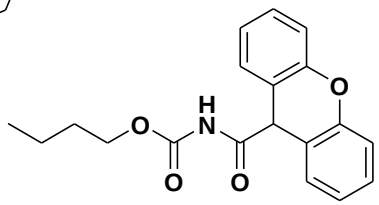

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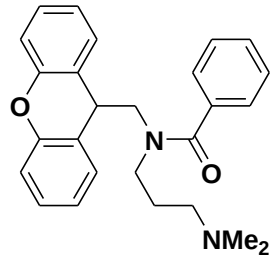

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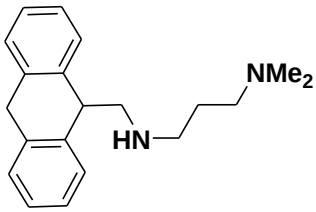


(88)

2.4. Sulfur Containing Heterocycles

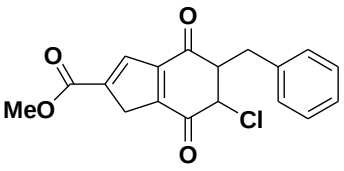
The sulfur containing heterocycles are also present in a large number of biological active compounds and it was proven by discovery of many drugs such as sulphonamides and sulfones that had appreciable antimalarial, antimycobacterial, antibacterial, antifungal and several other biological activities. Drug molecules having sulfur hetero ring system as Raloxefene, a benzothiophene nucleus derived drug is used in the treatment of osteoporosis, Chloroprothixene containing thioxanthene, used psycotropic drug and thiadiazole derived drug, Cezopram used as antibiotic.

2.4.1. Thiophenes and Benzothiophene

The thiophene ring structure is widespread in nature and many of these compounds are biologically active. Thiophene derivatives are widely utilized as functional materials in dyes, liquid crystals and as components of organic conducting polymers. Many of thiophene containing compounds has been found to show nematocidal, insecticidal, antibacterial, antifungal and antiviral activities.

Recently some 4,7-dioxobenzo(b)thiophene [89] derivatives have shown antifungal activity (Krajewski et al, 2006) , DDE934 [90] and NSC-380292 [91] are used as anti-HIV agent and are more potent than Nevirapine (De Nanteuil et al, 2003) , another

compound [92] acts as protein tyrosine phosphatase 1B inhibitor. Benzothiophene compounds have emerged as an important class of pharmacophores in medicinal chemistry as exemplified by the successful launch of Raloxifene [93] and Arzoxifene [94] as bone resorption inhibitors and representatives of a novel class of compounds known as selective estrogen receptor modulators (SERMs).



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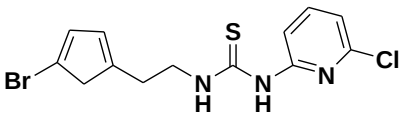

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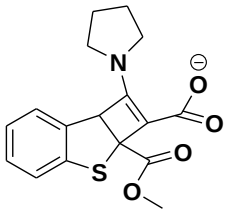

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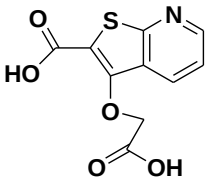

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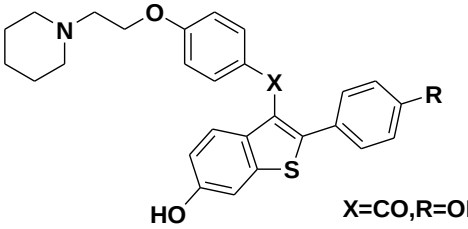


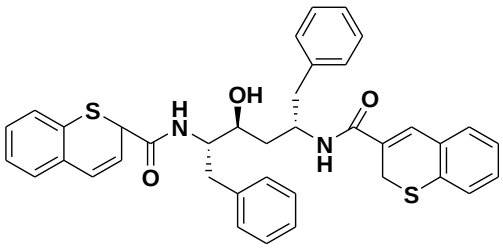
X=CO,R=OH, (93)

X=O,R=OMe, (94)

2.4.2. Thiochromenes

The thiochromenes (2H-1-benzothiopyran) group is an important structural motif in the preparation of pharmaceuticals and its derivatives exhibit interesting biological properties such as modulators of estrogen receptors and inhibitors of cyclo oxygenase-2.

It has been reported that thiochromene derivatives show better biological activity as compared to their oxygen counterpart, benzopyran moiety in the preparation of drugs. Thiochromene analog [95] of Ritanovir (A) [96] is a potent HIV-I protease inhibitor (Jeyaseeli et al, 2006).



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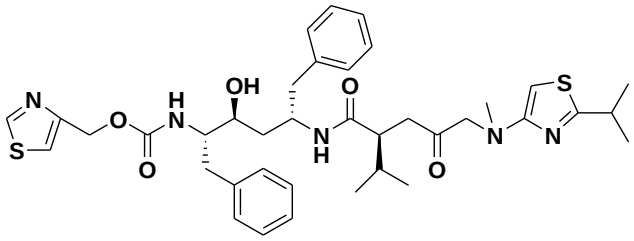
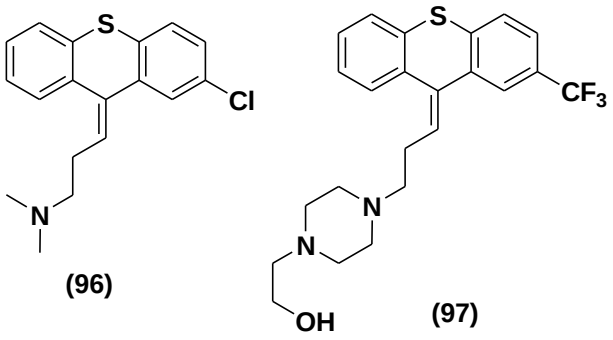


(96)

2.4.3. Thioxanthenes

This class of compounds form a significant part of one of the most extensive and well-studied group of drugs known as tricyclic pharmaceuticals and have found extensive use in treatment of various mental and physical disorders, such as psychosis, depression, epilepsy, parkinson's disease and various kinds of allergies. Examples of drug molecules that are in clinical practice are psychotropic drug, Chlorprothixene [96] (Glennon et al, 2004), antimicrobial drug, Flupenthixol [97] (Panek et al, 2000) and neuroprotector drug, Clopenthixol [98] (D'Ambrosio et al, 1996). However, these drugs also have some other clinical useful properties such as anti tumour agent, as positive allostric modulators of m Glut receptor, σ_1 receptor ligands, anti-emetic, anti-nausea, antihistamine and potentiate analgesics sedative and general anaesthetic action.



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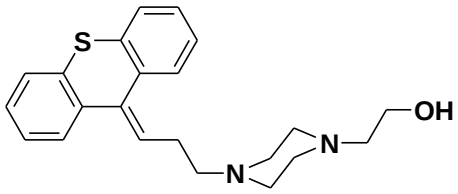

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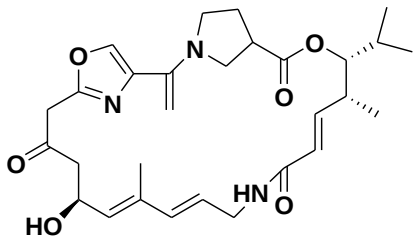
2.5. HETEROCYCLIC MOLECULES WITH MORE THAN ONE ATOM

2.5.1. Oxazoles

Oxazoles are compounds having a five membered heterocyclic ring containing oxygen and nitrogen atom. They are key building blocks of natural products, pharmaceuticals, and synthetic intermediates. The 2, 4-disubstituted oxazole is a motif found in many natural products, which display biological activity over a wide range of therapeutic areas. In the last two decades, various natural products containing C2- C4' linked poly oxazole moieties such as Telomestatin and Ulapualide A have been isolated and reported to possess different biological activities. Virginiamycin M_2 [99] is an antibiotic, Hennoxazole A [100] is an antiviral agent and Leucascandrolide A [101] is a cytotoxic and antifungal agent. Recently BMS-337197 [102] has been reported as a potent inhibitor of inosine monophosphate dehydrogenase (MPDH) (Kalagutkar et al, 2003) for anti-poliferative activity.



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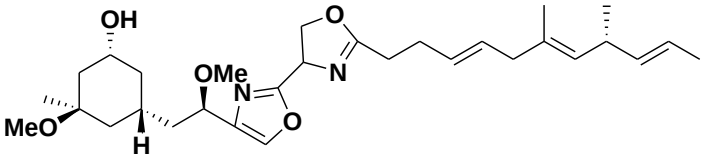

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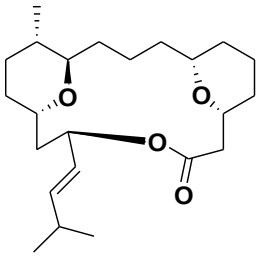

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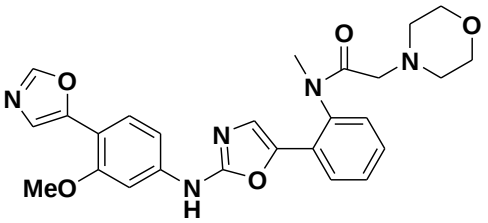
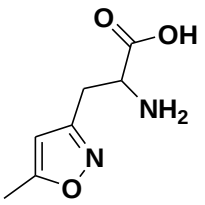


(102)

2.5.2. Isoxazoles

Like oxazoles, isomeric isoxazoles are also well known as versatile building block in organic synthesis and they have long been targeted in synthetic investigation for their biological and pharmacological properties such as hypoglycemic analgesic, anti-inflammatory and antibacterial activities. Hydroxy substituted isoxazole have been exploited particularly for the design of CNS drugs like (S)-2-Amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid [AMPA, 103] and (*S*)-2-Amino-3-(3-hydroxy-5-phenyl-4-isoxazolyl)propionic acid [APPA, 104], where the 3-hydroxy oxazole unit acts as an effective biosteric and conformationally restricted substitute for the 7-carboxylic group of glutamate the major excitatory amino acid neurotransmitter. Recently a different series of isoxazole derivatives have been synthesized and screened for anti-inflammatory, antitumor, anti-HIV, anti thrombotic, antibacterial and 5-HT inhibitory activities. Leflunomide [105] (Yamamoto et al, 2007) is an orally active disease modifying anti-inflammatory agent for the treatment of advanced rheumatoid arthritis, XU065 [106] another potent compound showed antiplatelet effect, ki- 6425 (107) has been recently reported as lysophosphatidic acid (LPA) antagonist.



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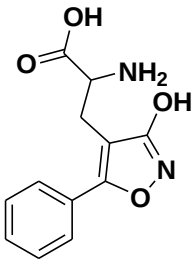

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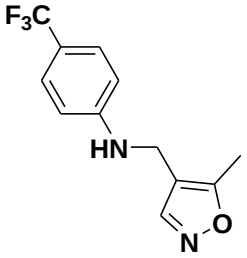

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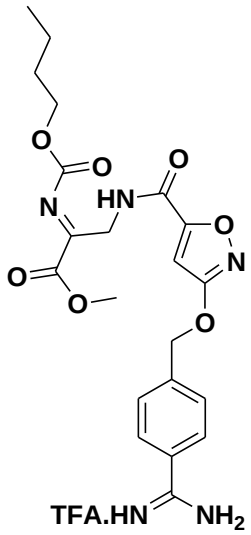

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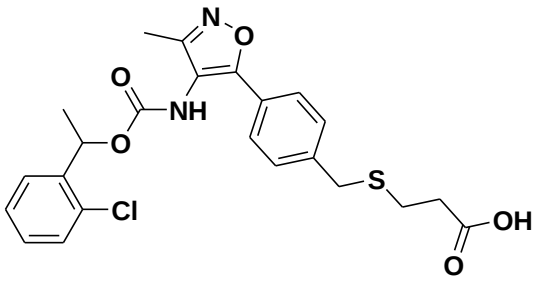
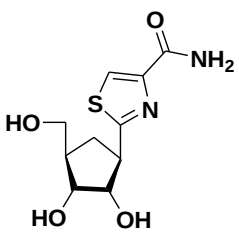


(107)

2.5.3. Thiazoles

Thiazoles are another class of five membered heterocyclic compounds containing sulfur and nitrogen atoms. They play a prominent role in nature, for example thiazole moiety exists in thiamine, a coenzyme required for the oxidative decarboxylation of α-keto acids. Tetrahydro thiazole appears in the skeleton of penicillin which is one of the first and still most important of the broad spectrum antibiotics. Many thiazole derivatives have attracted continuing interest over the years because of their varied biological activities in the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial HIV infections, and hypnotics and more recently for the treatment of pain. Aminothiazoles are known as ligands for estrogen receptors as well as a novel class of adenosine receptor antagonists, as fungicides, herbicides etc. Tiazofurin [108] an antitumor drug used for inhibition of ionosin5”-monophosphate

(IMP) enzyme plays a significant role in the cell proliferation, Leinamycin [109], a DNA damaging natural product with potent antimour activity, GW501516 [110] has been reported as the most potent and selective PPAR b/d agonist.(Fawzi et al, 2001)



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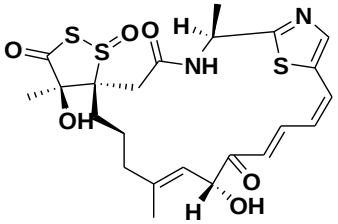

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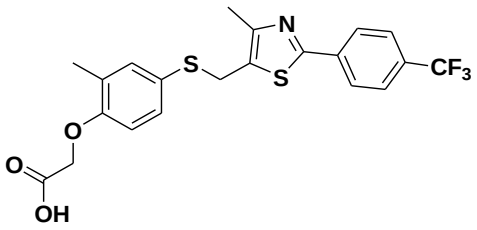

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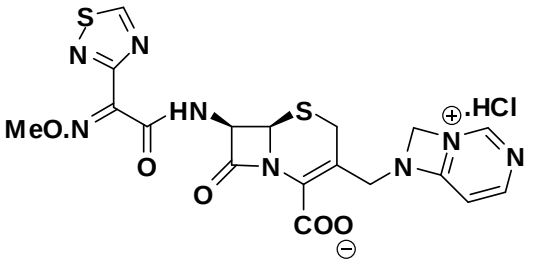
2.5.4. Thiadiazoles

Very interesting therapeutic applications have been found in the 1, 2, 4-thiadiazole ring system with a number of synthetic compounds showing a broad range of biological activities.[175] The antibiotic cefozopram [111], and SCH-202676 [112] as a promising allosteric modulator of G-protein coupled receptors, KC12291 [113] as cardioprotective. More recently, the small heterocyclic thiadiazolidinones TDZD-8 [114] were described as the frist non-ATP competitive glycogen synthase kinase *3β* inhibitors (Hartmann et al, 1998). A number of derivatives of thiadiazoles have been prepared in order to improve the pharmacological properties of these interesting lead compounds. The usefulness of 1, 2, 4-thiadiazole as pharmacophore in medicinal chemistry has promted synthetic advances on the chemistry of this system.



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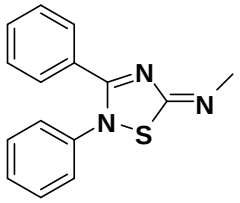

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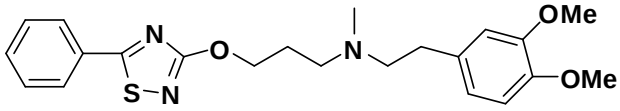

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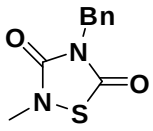
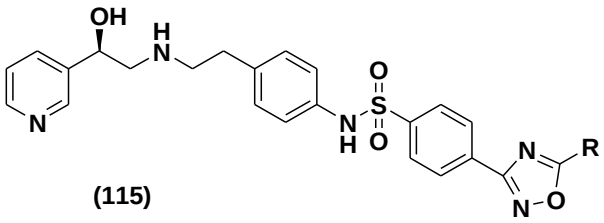


(114)

2.5.5. Oxadiazoles

1, 2, 4-oxadiazoles have received considerable attention in the pharmaceutical industry as heterocyclic amide and ester isoesters. They have also been employed in the design of numerous biologically active templates such as muscarinic agonists, tryrosin kinase inhibitors, anti inflammatory agents, histamine H3 antagonists, antitumor agents and monoamine oxidase inhibitors. Recent reports have shown that 5-alkyl oxadiazole substituted benzene sulphonamide [115] act as adrenergic receptor agonist SB-236057 [116] show high affinity, selectivity and inverse agonist activity at human 5-HT_{1B} receptor, MK-0518 [117] as a potent anti-HIV agent and compound [118] shows tryptase inhibitor activity (Swaney et al, 1998).



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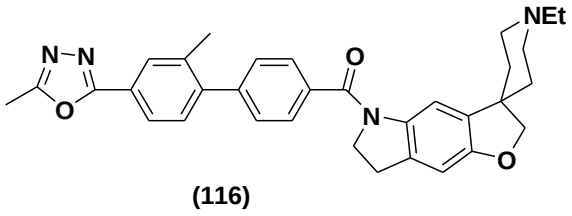

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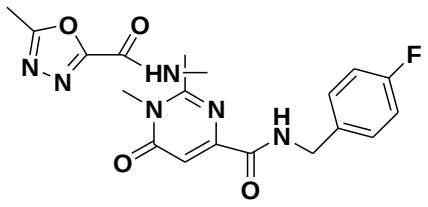

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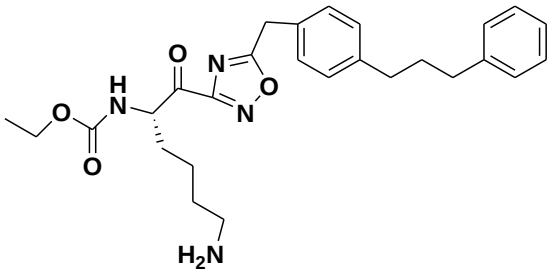

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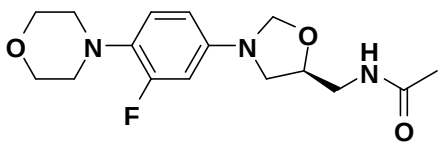
2.5.6. Oxazolidinones

Oxazolidinones are an important class of heterocyclic compounds, which have been found to have a large range of applications as intermediates in organic synthesis. Methodologies using chiral 2-oxazolidinones have been highly successful in the stereoselective construction of a number of natural products, antibiotics and medicinally important compounds with antidepressant, antihistaminic, antifungal, antihypertensive, or antibacterial activity.

Discovery of oxazolidinones as a new class of synthetic antibacterial has opened up an exciting avenue of antibiotic research because of its activity against resistant Gram positive organisms such as methicilin- resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE). Oxazolidinones bind selectively to 50S ribosomal subunit thereby inhibiting bacterial protein biosynthesis at an early stage. Linezolid [119], the first oxazolidinone to receive regulatory approval, has become an important clinical option in the treatment of serious Gram- positive bacterial infections, including those caused by multi-drug resistant pathogens such as MRSA and VRE. Other oxazolidinones that have advanced into clinical trials include piperazine analog epezolid [120].



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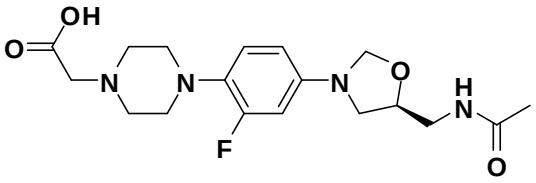

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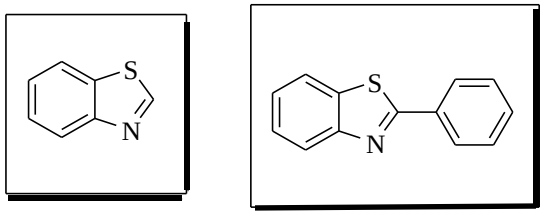
CHAPTER 3

Facile Synthesis of *N*-(Benzyl-1*H*-1, 2, 3-Trizole-5-yl-Methyl)-4-(6-Methoxy benzo [*d*] Thiazol-2-yl) -2-Nitro benzamides via Click Chemistry.

3.1. Introduction:

Benzothiazole scaffold comprises a bicyclic ring classification and is known as to exhibit a wide range of biological properties including antimicrobial and anticancer activities. Benzothiazole derivatives have long been therapeutically used for the treatment of a variety of diseases. However, in recent years, 2-arylbenzothiazoles have emerged as a significant pharmacophore in the development of antitumor agents. The promising biological profile and synthetic convenience have been attractive in the design and development of innovative benzothiazoles and their conjugate systems as potential chemotherapeutics.

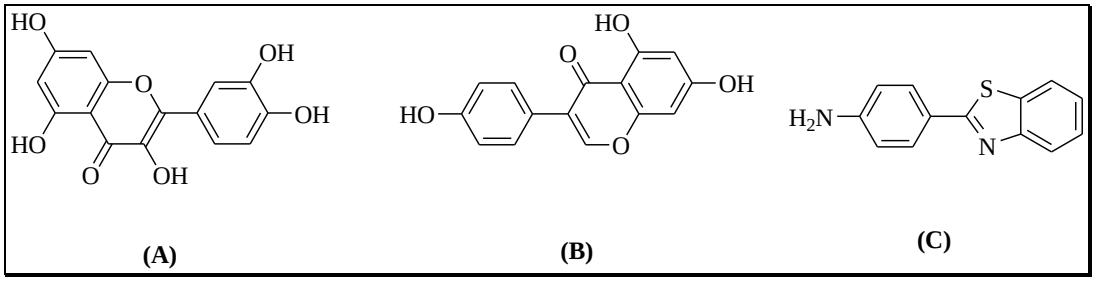


3.1.1 Antitumor 2-arylbenzothiazoles:

Benzothiazoles are fused bicyclic systems possessing various biological properties such as neuron protective (Lagunin et al, 2000, Nogradi et al, 2001 and Bae et al,2000) anticonvulsive (Amnerkar et al, 2010, Deng et al, 2010, Chopade et al, 2002 and Siddiqui et al ,2009) antiglutamate (Jimonet et al ,1999), antimalarial (Burger et al ,1986), anthelmintic (Hori et al,1992), antitubercular (Palmer et al, 1971, Huang et al ,2009 Waisser et al ,1988, and Patel et al ,2010), analgesic, anti-inflammatory (Lee et al,2011, Jin et al, 2010 and Paramashivappa et al, 2003), antimicrobial (Al-Tel et al ,2011, Stella et al ,2011, Nam et al , 2011, Gilani et al, 2011, Franchini et al ,2009, Latrofa et al, 2005, Youssef et al ,2007, Singh et al , 2006, Gagos et al, 2005, Chohan et al, 2003 and Bujdakova et al, 1993) and anticancer effects (Havrylyuk et al, 2010, Kamal et al, 2011, Trapani et al ,2011, Amino et al ,2006, Huang et al, 2008 and Kumbhare et al ,2011). In the past two decades, benzothiazoles confirmed motivating pharmacological activities (Khokra et al, 2011, Chaudhary et al, 2010, Sanap et al, 2010, Priyanka et al, 2010 and Yadav et al, 2011) and have been widely studied mostly for their antitumor activities (Caleta et al, 2009).

Stevens and co-workers inspired from a crystallographic analysis of 5, 6-dimethoxy-2-(4-methoxyphenyl) benzothiazole and synthesized polyhydroxylated 2-

phenylbenzothiazoles (Yates et al, 1991) and compared their cytotoxicity as well as pharmacological properties with the naturally occurring bioactive flavonoid quercetin**(A)** and isoflavone genistein**(B)**. They supposed that planar polyhydroxylated 2-phenyl benzothiazoles might mimic the adenosine triphosphate (ATP) antagonistic effects of those natural products and displayed tyrosine kinase inhibitory properties, but were not successful in discovering active polyhydroxylated compound with utilizable antitumor activities (Stevens et al, 1994). They have identified planar arylamine with unique selective properties and reported 2-(4-aminophenyl)benzothiazole (CJM 126, **C**) as an original lead compound from this series that exhibited nanomolar in vitro inhibitory activity against a panel of human sensitive breast cancer cell lines such as MCF-7 and MDA 468. Furthermore, the activity against these cancer cell lines was characterized by a biphasic dose response relationship. Structure activity relationship (SAR) studies revealed that compound having methyl or halogen substituent at 3-position of amino phenyl ring is particularly potent than the unsubstituted amine CJM 126 (3), extending the spectrum of in vitro anticancer activity to ovarian, lung, renal and colon carcinoma cell lines with a outstanding selectivity profile.



(A) **(B)** **(C)**

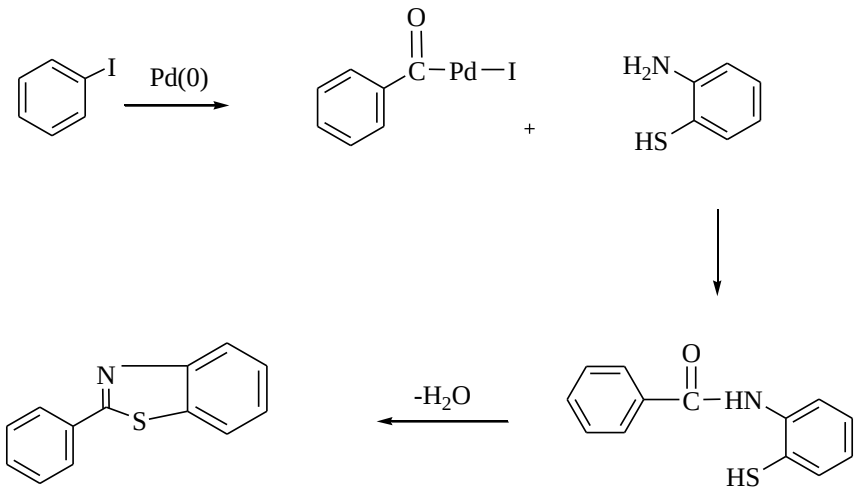
3.2. General Methods for the Synthesis of Benzothiazoles and Its Derivatives:

1) Synthesis of 2-pheny1 benzothiazole (**Stauding et *al*. approach)**

Benzothiazole is prepared by the reaction of an aromatic / aliphatic aldehyde or acid or acid chloride with 2-aminothiophenol. This reaction proceeds *via* the dihydro intermediate that arise from the cyclisation on aerial oxidation or in the presence of oxidation reagent gives rise to 2-phenyl benzothiazole. The mechanism of benzothiazole formation is shown in below scheme.

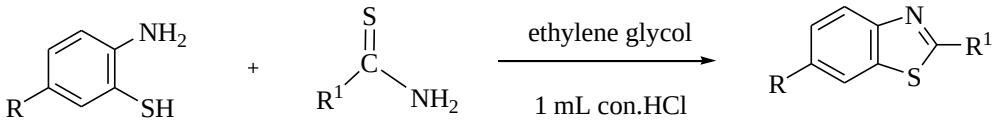
2) Synthesis of 2-arylbenzothiazole using Pd catalyst **(Steen *et al,* 1991)**

Steen *et al.* reported the synthesis of 2- arylbenzothiazoles by the reaction of halo aromatic compounds with 2-aminothiophenol in the presence of 95% of CO, a palladium catalyst and 2, 6-lutidine N_3-dimethylaccetamide (DMA).



3) Synthesis of benzothiazole from thioamides (**Vaughan *et al,* 1961**)

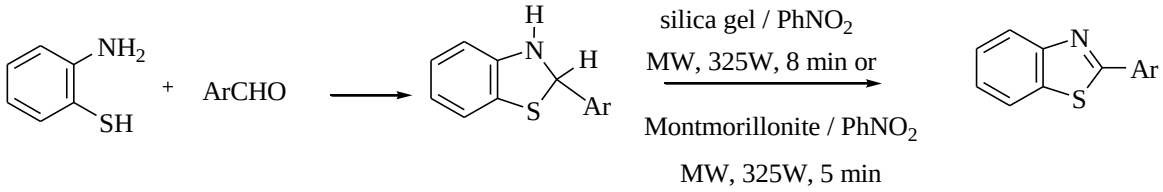
Kishore *et al.* reported the condensation of thioamides with substituted 2-aminothiophenols in ethylene glycol containing 1mL conc.HCl to give substituted benzothiazoles in good yields.



R = H, Me, Cl, COOH, COOMe etc.
R^1 = Me, Ph, CH_2OPh, CH_2OCOPh, CH_2CN etc.

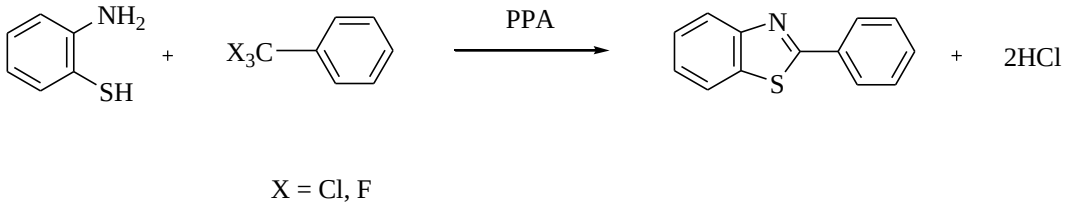
4) Synthesis of 2-arylbenzothiazoles under MW (**Ben-Alloum *et al*. approach)**

Ben-Alloum *et al.* reported the condensation of aldehydes with 2-aminothiophenol on silica gel / nitrobenzene or montmorillonite K10 / nitrobenzene under microwave irradiation to give 2-arylbenzothiazoles.



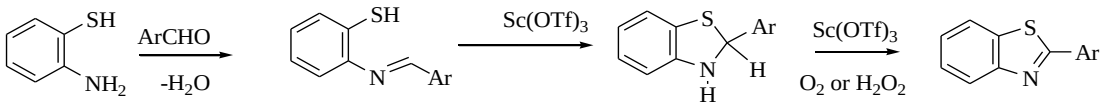
5) Synthesis of 2-arylbenzothiazoles from trichloro or fluoromethy1 aromatic compounds (**Ying – Hung *et al* approach)**

Ying-Hung *et al.* synthesized 2-arylbenzothiazoles by the reaction of α, α, α- trichloro or fluoromethy1 aromatic compounds with 2-aminothiophenol in presence of polyphosphoric acid.



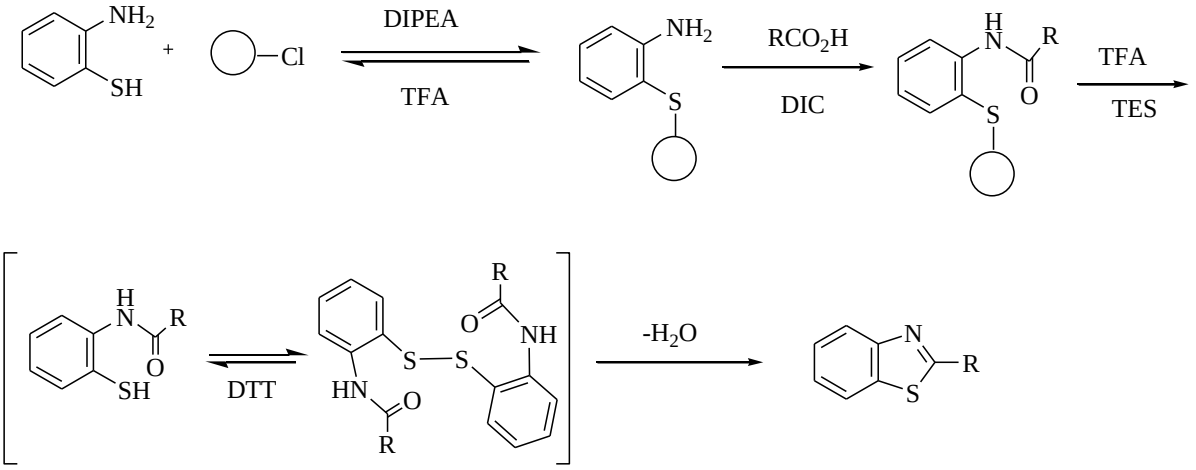
6) Synthesis of 2-arylbenzothiazoles using Samarium (III) Triflate (**Ingle et *al*. approach)**

Ingle *et al.* reported, The reaction of 2-aminothiophenol with an arylaldehyde reacted to give a benzothiazoline *via* an imine intermediate , and the benzothiazoline was aromatized by oxygen or hydrogen peroxide to give 2-arylbenzothiazole in the presence of a catalytic amount of Samarium triflate .

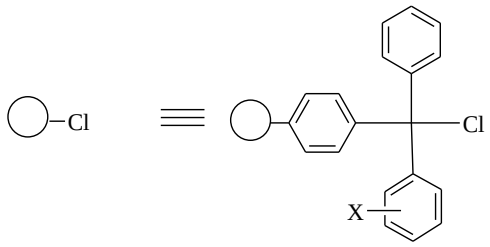


7) Solid phase synthesis of benzothiazoles (**Mourtas *et al*. approach)**

Mourtas *et al.* reported 2- aminothiophenol bound through its thiol function to the 2-chlorotrity1, trity1, 4-methyltrity1 and 4-methoxytrity1 resins, was acylated at the amino function by aliphatic and aromatic acids. The obtained 2-*N*-acy1-aminothiophenols were cleaved from the resin by treatment with trifluoroacetic acid. 2-*N*-acy1-aminothiophenols released from the resin were cyclised to the corresponding 2-substituted benzothiazoles, by dithiothreitol in DMF or methanol.



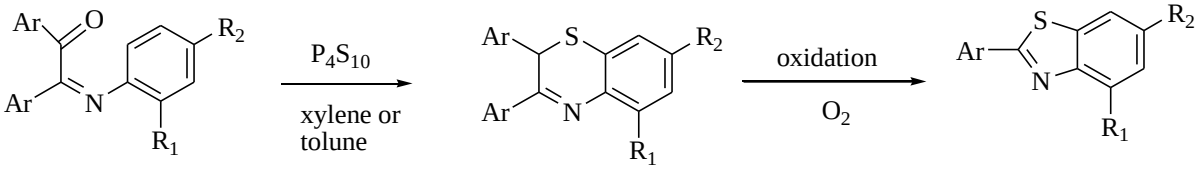
R = CH_3, C_6H_5, C_6H134-Cl-C_6H_4, 2-Cl-C_6H_4 etc



X = 2-Cl, H, 4-CH_3, 4-CH_3O

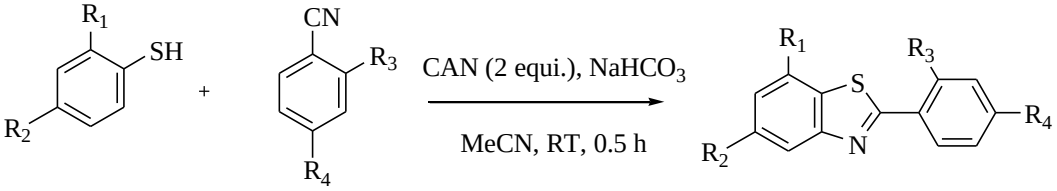
8) Synthesis of 2-arylbenzothiazoles from benzyl aryl imines (**Charrier *et al.* approach)**

Charrier *et al.* reported benzil monoarylimines were treated with phosphorus pentasulfide in refluxing toluene or xylene gave 2*H*-benzo-1, 4-thiazines gave benzothiazoles.



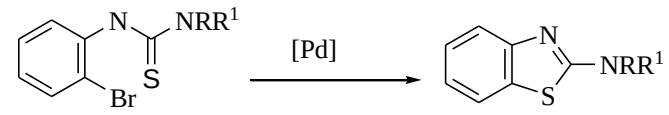
9) Synthesis of 2-arylbenzothiazoles mediated by cericammonium nitrate (**Tale *et al.* approach)**

Tale *et al.* reported the oxidative coupling between thiophenols and aromatic nitriles in the presence of ceric ammonium nitrate leads to the formation of 2-arylbenzothiazoles.



10) Synthesis of 2-substituted-benzothiazoles from *o*-bromophenlthioureas and *o*-bromo phenylthioamides (**Benedi *et al*. approach)**

Benedi *et al.* have synthesized 2-substituted-benzothiazoles by palladium catalyzed intramolecular cycliztion of *o*-bromophenylthioureas and *o*-bromopheny1 thioamides.

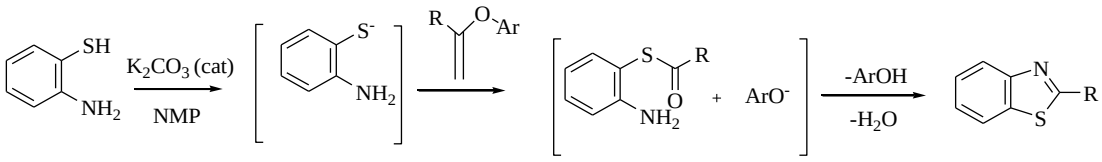


R = H, Me etc

R^1 = Me, Ph etc

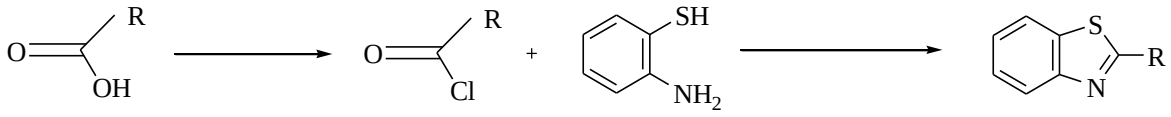
11) Synthesis of 2-substituted benzothiazoles from phenolic esters (**Chakraborti *et al*. approach)**

Chakraborti *et al.* reported phenolic esters are efficiently converted to 2-substituted benzothiazoles by treatment with 2-aminothiophenol in the presence of a catalytic amount of K_2CO_3 in *N*-methy1-2-pyrrolidone (NMP) at 100° C.



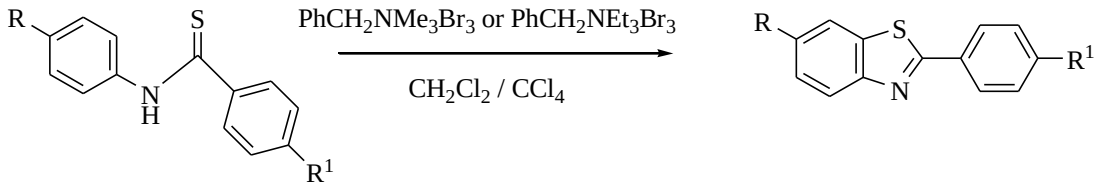
12) Synthesis of benzothiazoles from carboxylic acids (**Rudrawar *et al*. approach)**

Rudrawar et al. reported carboxylic acids are converted to benzothiazoles in a one pot reaction with thiony1 chloride followed by treatment with 2-aminothiophenol under acid and catalyst-free conditions.



13) Synthesis of benzothiazoles by oxidative cyclization of thiobenzanilides (**Moghaddam *et al*. reported)**

Moghaddam *et al.* reported *N*-benzy1-DABCO tribromide, a stable, crystalline organic ammonium tribromide ($PhCH_2NMe_3Br_3$ or $PhCH_2NEt_3Br_3$), as electrophilic bromine source for the efficient oxidative cyclization of thiobenzanilides to the corresponding benzothiazoles under mild conditions.



Objectives

i) To synthesize nucleus containing benzothiazoles, potent anti-bacterial compounds of

Heterocyclic compounds and synthesis of benzthiozole- trizoles hybrid molecules from alkynes and aromatic azides by using click reaction.

ii) The development of a procedure for using commercially available inexpensive catalyst.

iii) To obtain highly pure benzthiozole- trizoles derivatives without using tedious Chromatographic techniques.

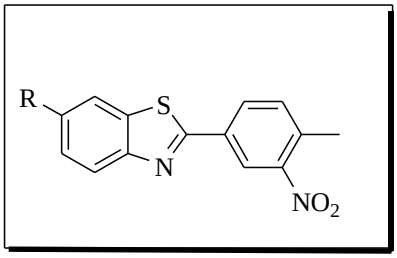
iv) To establish the structure on the basis of melting point, infrared spectra, NMR spectra and mass spectra.

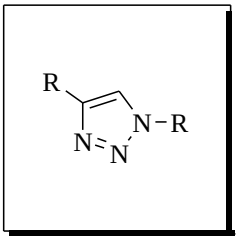
v) To evaluate compounds for antimicrobial activity.

3.3. PRESENT WORK:

Although the demand for new chemical materials and biologically active molecules continues to grow, chemists have hardly begun to discover the enormous pool of potentially active compounds. In the scenario of a persistent request especially from the pharmaceuticals companies for better drugs, it has become a challenging task for medicinal chemists to prepare new patentable molecules that combine high activity and selectivity, drug-likeness, and good pharmacokinetic properties.

As part of our continuing interest in the synthesis of biologically active compounds we have successfully synthesized such derivatives which consist of two distinct pharmacophores; benzothiazoles and trizoles, each certainly, possessing a wide range of biological and pharmacological activities.





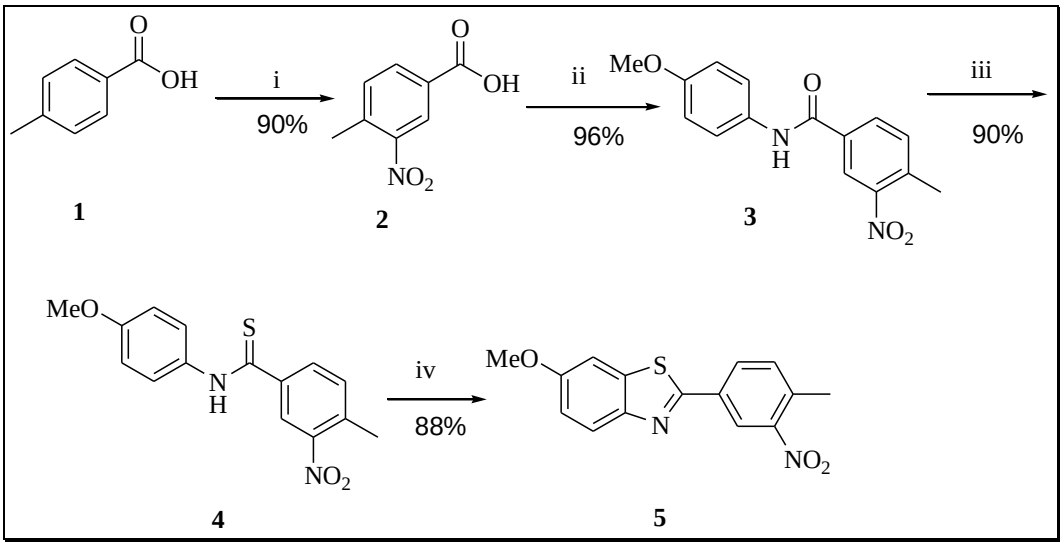
Benzothiazole scaffold derivatives consist of fused bicyclic ring systems. Benzothiazoles are an important class of potential organic molecules in medicinal chemistry due to their extensive range of activity such as neuron protective, anti-convulsive, anti-glutamate, anti-malarial, anthelmintic, anti-tubercular, analgesic, anti-inflammatory, anti-microbial, and anti-cancer to name a few . In this context, synthetically accessible molecules having new benzothiazole scaffold with promising biological profile have attracted the attention of medicinal organic chemists for their applications in potential chemotherapeutics.

As one of the best click reactions to date, the copper-catalyzed azide-alkyne cycloaddition features an enormous rate acceleration of 10^7 to 10^8 compared to the uncatalyzed 1, 3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization. The active Cu (I) catalyst can be generated from Cu (I) salts or Cu (II) salts using sodium ascorbate as the reducing agent. Addition of a slight excess of sodium ascorbate prevents the formation of oxidative homocoupling products. Disproportionation of a Cu (II) salt in presenc of a Cu wire can also be used to form active Cu (I). Instead, a copper acetylide forms, after which the azide displaces another ligand and binds to the copper. Then, an unusual six-membered copper (III) metallacycle was formed. The barrier for this process has been calculated to be considerably lower than the one for the uncatalyzed reaction (Liu et al, 2011), Azide–alkyne [3+2] cyclo-addition illustrates that it bring about many of the necessitous. It is well known that, many of the simple mono substituted alkynes and organic azides are accessible commercially. Many others can effortlessly be synthesized with an extensive range of functional groups, those cyclo-addition reactions selectively gives 1, 2, 3-triazoles. In fact, a Cu (I) catalyzed alternative that follows a divergent mechanism and insensitive to oxygen and water.These click reactions proceed under mild conditions and not required any protecting groups. Additionally, the [3+2] cyclo-addition also well known as Husigen cyclo-addition of alkynes and azides to form 1, 4 -disubstituted [1, 2, 3]-trizoles. These copper (I) catalyzed [3+2] reactions comply fully with the sense of click chemistry. Hence Azide-alkyne cyclo-addition has put a focus on as a prototype click chemistry reaction. It is important to existence that click reactions achieve their required characteristics by having a high thermodynamic driving force, usually greater than 20 kcal mol^{-1}. Such processes proceed rapidly to completion and also tend to be highly selective for a single product. We recognize the convenient of inter-molecular Azide-alkyne [3+2] cyclo-addition in order to construct *N*-((l-benzyl-l*H*-1,2,3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides. Herein, we describe the click chemistry and approach for the constructed by copper catalyzed Azide-alkyne cyclo-addition(CuAAC) reaction and their biological activity studies of *N*-((l-benzyl-l*H*-l, 2, 3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides.

3.3.1. Chemistry, Results and Discussion:

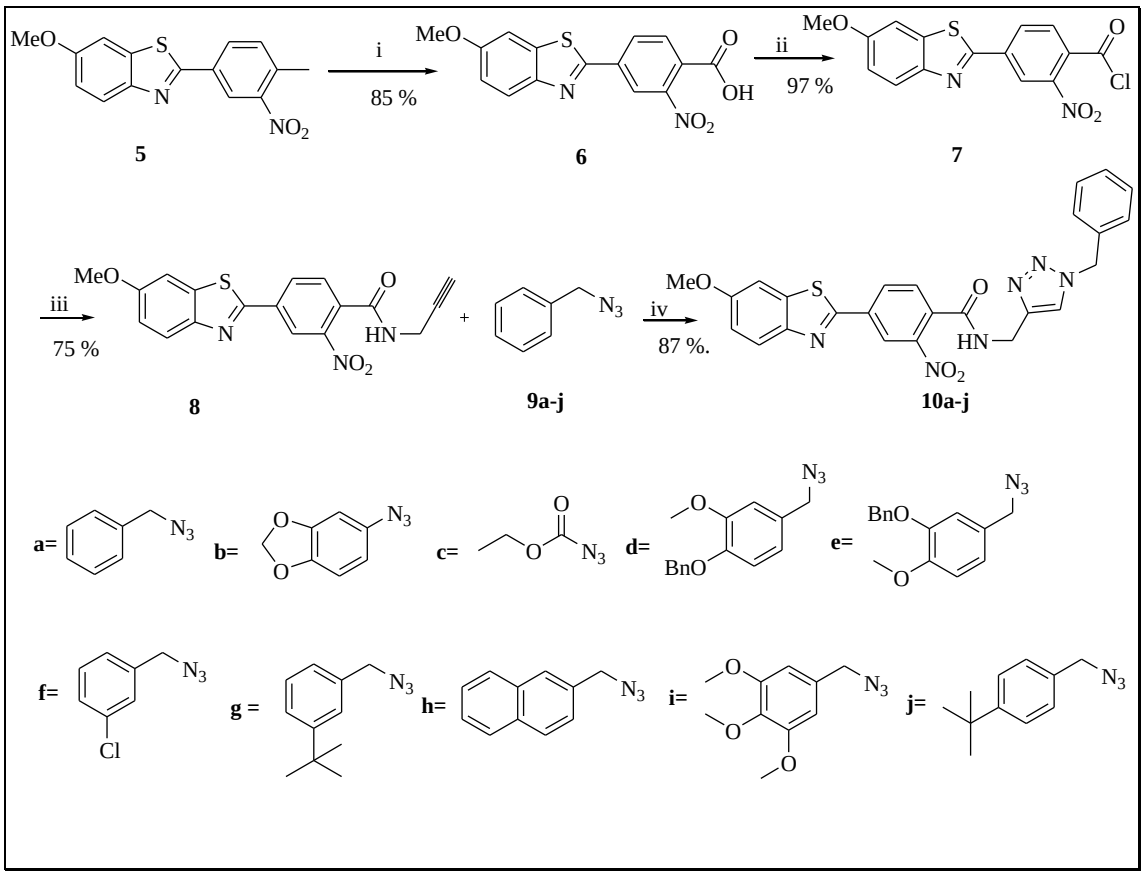
The synthetic scheme for the synthesis of 6-methoxy-2-(4-methyl-3-nitrophenyl) benzo[*d*]thiazole (**5**) (Scheme **1)** was started from readily available *p*-toluic acid. The nitration of *p*-toluic acid **1** was carried with HNO_3 in the presence of concentrated H_2SO_4 in CH_2Cl_2 at 0 °C to give colorless white solid 4-methyl-3-nitrobenzoic acid **2** in 90 % yield. 4-methyl-3-nitrobenzoic acid **2** was converted to its acid chloride by treating with thionyl chloride which was condensed with the readily available *p*-anisidine in the presence of triethyl amine to afford light brown crystals of amide **3** in 87 % yield. The formation of amide **3** was characterized with its ^{1}H NMR spectrum which showed two singlets of methyl and methoxy groups at δ 2.61 and δ 3.75 respectively. It was further characterized with the characteristic amide NH appeared as a singlet at δ 10.13.Its ESI-MS peak appeared at 287 (M+H).

The next step was the functional group transformation from amide **3** to thioamide **4** was treated with Lawesson's reagent in dry toluene under reflux condition to obtain thioamide **4** as pale yellow crystals in 90 % yield. ^{1}H NMR spectrum of compound **4** showed characteristic thioamide NH singlet appeared deshielded at δ 11.87 compared to that of NH of amide **2**. Its ESI-MS spectrum showed a peak at 303 (M+H). Intramolecular free-radical cyclization of thioamide **4** by using Dess-Martin periodinane (DMP) (Veeresa et al, 2004, Syed et al, 2012 and Idrees et al, 2006) in DCM at room temperature within 15 minutes afforded the 2-arylbenzothiazole **5** as a light yellow solid in 88 % yield. ^{1}H NMR spectrum of compound **5** showed two singlets at δ 2.62 and δ 3.86 corresponding to benzylic-CH_3 and -OCH_3 respectively and a deshielded hindered proton singlet at δ 8.49-8.58 corresponding to the aromatic proton present at 2nd position adjacent to the nitro group. It was further characterized by ^{13}C NMR and its ESI-MS showed peak at 301 (M+H).



Scheme-1

Reagents and conditions: (i) HNO_3, conc. H_2SO_4, CH_2C1_2, 0 °C, rt, 4-5 h (ii) $SOC1_2$, cat. DMF, CH_2C1_2 (a) *P*-Anisidine, Et_3N, THF, 0 °C, rt (b) 4- fluoro aniline, Et_3N, THF, 0 °C, rt (iii) Lawesson's Reagent, toluene, 95 °C (iv) DMP, CH_2C1_2, rt , 20 min.



Scheme-2

***Reagents and conditions**:* (i) Tetrabutyl Ammonium Permanganate (TBAP), dry Pyridine, (ii) $SOC1_2$, and cat. DMF, CH_2C1_2 (iii) Propargyl amine, Et_3N, dry THF, 0 °C, rt (iv) 0.25-2 mol % $CuSO_4.5H_2O$, 5-10 mol % Sodium ascorbate, t-BuOH:H_2O (1:1) , rt , 30 min.

The synthetic scheme for the synthesis of *N*-((1-benzyl-l*H*-l, 2, 3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides(10a-j) shown in (Scheme-2), Compound **5** upon treatment with freshly prepared Tetrabutylammonium permanganate (TBAP) in dry pyridine at room temperature afforded 6-methoxy-2-(4-methyl-3-nitrophenyl) benzo [*d*] thiazole **6** as a light yellow solid in 85 % yield. ^{1}H NMR spectrum of **6** showed a broad singlet at δ 10.25-10.81 corresponding to acidic proton, also the disappearance of singlet for methyl group at δ 2.62. It was further confirmed by the appearance of a peak at 331 (M+H) in ESI-MS. Its IR spectrum showed bands at 2924, 1714 and 1225 cm^{-1} (corresponding to OH stretching, C=O stretching, and O-C stretching of -COOH functionality) and bands at 1538 cm^{-1} as well as at 1368 cm^{-1} (N=O nitro asymmetric and symmetric stretching). Quantitative yield was obtained only by Tetrabutylammonium permanganate (TBAP). Nitro acid **6** was converted to its acid chloride **7** with thionyl chloride, which was condensed with Propargyl amine in the presence of triethyl amine to obtain nitro amide **8** containing triple bond in 85 % yield, as a brownish solid. ^{1}H NMR spectrum of compound **8** showed two singlets for -OCH_3 group and terminal acetylenic proton at δ 3.93 and δ 2.59 respectively. It also showed triplet for CH_2 group at δ 4.10-4.24. It was further confirmed with a characteristic amide NH appeared as a broad singlet at δ 8.97. Its ESI-MS peak appeared at 368 (M+H). Compound **8** and benzyl azides **9a-j** in the presence of 0.5 mol% $CuSO_4.5H_2O$ and 10 mol% sodium ascaorbate afforded the triazole.The reactionisregioselectiveonly in the presence of Cu (I)or Cu (II) salts as a catalyst, because Cu (I) as a catalyst strongly activate the terminal acetylenes toward 1,3-dipole in azide to give the desired 1,4-disubstituted [1,2,3]-triazolederivatives **10a-j** in good yields (85-87%) *via* click Chemistry . Structures were confirmed by utilizing spectral data and Elemental Analysis.

3.4. Experimental Procedure:

Melting points were determined using Buchi-510 instrument. IR spectra were recorded on Perkin-Elmer-683 series spectrometer with KBr optics, and ^{1}H NMR (300

MHz) were recorded on BrukerAvance 400 spectrometer using TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70 H instrument. CHN analysis was carried out using Vario Micro Cube Elementar instrument.

4-Methyl-3-Nitrobenzoic Acid (2):

HNO_3 (10.05 g, 125.64 mmol, 1 equiv.) was added to a stirred solution of 4-methylbenzoic acid (18 g, 132.35 mmol, 1 equiv.) in Dichloromethane and stirred for 10-15 minutes. Then conc. H_2SO_4 (24.46 ml, 249.66 mmol,) was added to the above reaction mixture drop wise at 0 °C for a period of 15-20 minutes with vigorous stirring. Stirring was continued at room temperature for a period of 4-5 hours till TLC showed the completion of the reaction. The reaction mixture was quenched with ice cold water (200 mL) and then allowed to return rt. The organic layer was separated and evaporated in vacuo under reduced pressure. The resulting residue was washed with water several times to remove acidic impurities. It was filtered off to give crude solid which on Recrystallization using EtOAc: petroleum ether afforded colorless prisms of **2** (21 g) in 90 % yield, m.p. 178-180 °C; ^{1}H NMR (300MHz, DMSO-d_6, TMS) δ 2.65 (s, 3H), 5.36 (broad singlet, 1H), 7.41-7.49 (d, 1H,J = 7.73 Hz), 8.08-8.16 (dd, 1H,J_1 = 1.55Hz), 8.51-8.54 (d, 1H, 1.55Hz),9.5-9.64(s,-COOH).

***N*-(4-Methoxyphenyl)-4-Methyl-3-Nitrobenzamide (3)**

Compound **2** (20 g, 110.49 mmol, 1 equiv.) was converted to its acid chloride (21.10 g, 110.45 mmol, 1 equiv.) using $SOCl_2$ (12.02 g, 101.00 mmol, 1.5 equiv.) and dry benzene at 80 °C in the presence of catalytic amount of DMF (2-3 drops) in 96 % yield. This freshly prepared acid chloride was added drop wise to stirred solution of *p*-anisidine (13.04 g, 106.01 mmol, 1 equiv.) and Et_3N (16.09 g, 159.00 mmol, 1.5 equiv.) in dry THF (35 mL) at 0 °C and the stirring was continued at room temperature for a period of 2-3 hours. Solvent THF was removed by rotaevaporator under reduced pressure. The crude solid was washed with a saturated solution of $NaHCO_3$, 1N HC1 and cold water to remove if any unreacted starting materials were present. The crude solid was filtered off through Buchner funnel and crystallized using methanol to obtain light yellow crystals of **3** (27.49 g) in 87 % yield, m.p. 150-152 °C; ^{1}H NMR (AVANCE 300 MHz, DMSO-d_6, TMS) δ 2.61 (s, 3H, CH_3), 3.75 (s, 3H, OCH3), 6.74-6.88 (d, 2H, J = 9.06 Hz, Ar-H), 7.44-7.54 (d, 1H, J= 8.12 Hz,

Ar-H), 7.55-7.67 (d, 2H, J = 9.06 Hz, Ar-H), 8.11-8.21 (dd, 1H, J_1= 7.93 Hz, J_2 = 1.70 Hz, Ar-H), 8.56-8.64 (m, 1H, Ar-H), 10.13 (broad singlet, 1H, NH). IR (Neat): Vmax 3414.52, 3090.79, 2934.81, 2832.99, 1666.22, 1619.42, 1598.87, 1534.21, 1510.67, 1458.68, 1413.18, 1352.42, 1321.02, 1232.38, 1178.51, 1114.44, 1031.37, 837.52, 735.01, 691.51, 597.49, 521.77, 472.48, 419.67cm^{-1}.

_N_-(4-Methoxyphenyl)-4-Methyl-3-Nitrobenzothioamide (4)

To a stirred solution of amide **3** (21 g, 73.42 mmol, 1 equiv.) in dry toluene (50 mL), Lawesson's reagent (14.75 g, 36.71 mmol, 0.5 equiv.) was added at 90 °C. The reaction mixture was refluxed for 2-3 hrs. After completion of the reaction (monitored by TLC) solvent toluene was removed by vacuo under reduced pressure. The resulting reaction mixture was quenched with 10 mL of Sodium hypochlorite aqueous solution and ice-cubes were added to it. Then the reaction mixture was filtered through Buchner funnel to get dark yellow coloured crude product. Purification of the crude solid by column chromatography on silica gel using EtOAc: petroleum ether (2:5) afforded pure pale yellow coloured compound **4** (19.95 g) in 90 % yield. M.p. 132-134 °C; ^{1}H NMR (AVANCE 300 MHz, DMSO-d_6, TMS) δ 2.57 (s, 3H, CH3), 3.79 (s, 3H, OCH3), 6.92-7.10 (d, 2H, J = 9.07 Hz, Ar-H), 7.53-7.64 (d, 1H, J= 7.97 Ar-H), 7.67-7.79 (d, 2H, J= 9.07 Hz, Ar-H), 8.00-8.17 (dd, 1H, J = 9.07 Hz, J = 1.92 Hz, Ar-H), 8.35-8.51 (m, 1H, Ar-H), 11.87 (broad singlet, 1H, NH).^{13}C NMR (AVANCE 75 MHz, DMSO-d_6, TMS) δ 19.43, 55.25, 113.60, 123.20, 125.62, 131.70, 132.49, 132.66, 135.13, 140.87, 148.17, 157.40, 193.37. IR (KBr): V max 3447.07, 3147.42, 2971.32, 1612.48, 1560.53, 1529.30, 1447.68, 1348.66, 1307.89, 1251.97, 1163.40, 1107.83, 1074.32, 1030.76, 993.29, 899.47, 820.07, 794.90, 748.48, 712.96, 670.17, 603.20, 535.78, 508.70, 448.10 cm^{-1}.

6-Methoxy-2-(4-Methyl-3-Nitrophenyl)- 1 , 3-Benzothiazole (5)

Dess-Martin periodinane (25.27 g, 59.59 mmol, 1.2 equiv.) was added to a stirred solution of thioformanilide **4** (15.00 g, 49.66 mmol, 1 equiv.) in dichloromethane (100 mL) at room temperature. The progress of the reaction was monitored by TLC. After the completion, the reaction mixture was quenched with H_2O (2 x 10 mL) and it was extracted with CH_2Cl_2 (3 x 10 mL). All organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo, to afford the crude product. Then it was purified by column chromatography on silica gel using EtOAc: petroleum

ether (1:3) to get the 2-aryl benzothiazole **5** as light yellow colored solid in 91 % yield. M.p. 141-143 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.62 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.00-7.11 (dd, 1H, J_1 = 8.87 Hz, J2 = 2.26 Hz, Ar-H), 7.37-7.45 (d, 1H, J_2 = 2.26 Hz, Ar-H), 7.46-7.55 (d, 1H, J = 7.93 Hz, Ar-H), 7.80-7.94 (d, 2H, J = 8.68 Hz, Ar-H), 8.05-8.16 (dd, 1H, J_1 = 7.93 Hz, J_2 = 1.13 Hz, Ar-H), 8.49-8.58 (m, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.5, 55.8, 104.0, 116.2, 123.0, 124.0, 130.8, 132.9, 133.4, 135.4, 136.4, 148.4, 149.5, 158.1, 162.3. IR (KBr): V max 3424.14, 2931.95, 2839.13, 1601.01, 1564.11, 1529.41, 1481.37, 1434.69, 1378.07, 1345.46, 1293.52, 1265.45, 1227.44, 1159.38, 1117.44, 1058.59, 1025.21, 985.94, 910.60, 877.25, 839.99, 817.13, 756.64, 726.24, 666.23, 595.64, 510.69, 438.16 cm^{-1}. ESI-MS: *m/z* (%) = 301 (M^{+}+H, 100).

4-(6-Methoxy-1, 3-Benzothiazole-2-yl)-2-Nitrobenzoic Acid (6)

Freshly prepared Tetrabutylammonium Permanganate (TBAP) (25.34 g, 70.00 mmol, 2.1 equiv.) was added to a solution of 2-arylbenzothiazole **5** (10 g, 33.33 mmol, 1.0 equiv.) in dry pyridine (50 mL) at room temperature. It was observed that the reaction was so exothermic, the reaction mixture started to reflux for 5-10 minutes even at room temperature. The reaction was continued to stir at room temperature for a period of 12 hours. The completion of reaction was monitored by TLC. This reaction mixture was poured into a mixture of $NaHCO_3$ and cold dilutes Hcl. Then, the reaction mixture was extracted with ethyl acetate (3x10 mL). The combined organic layer was removed by vacuo under reduced pressure to afford crude compound. Recrystallization using EtOAc : petroleum ether resulted into a free flowing light yellow colored solid **6** (9.34 g) in 85 % yield, m.p. 221-222 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 3.91 (s, 3H), 7.06-7.15 (dd, 1H, J_1 = 8.85 Hz, J_2=2.72 Hz), 7.41-7.45 (m, 1H), 7.90-7.98 (m, 2H), 8.20-8.27 (d, 1H, J = 8.17 Hz), 8.42 (s, 1H). IR (KBr): V max 3423.37, 2928.18, 2544.91, 1696.03, 1599.79, 1543.71, 1469.33, 1409.32, 1370.30, 1307.72, 1284.36, 1257.68, 1172.13, 1026.26, 947.54, 901.28, 837.02, 759.32, 728.52, 693.19, 654.59, 610.92, 560.89, 516.88 cm^{-1}. ESI-MS: *m/z* 331 $(M+H)^{+}$.

4-(6-Methoxybenzo [*d*]Thiazol-2-yl)-2-Nitro-*N*-(Prop-2-ynyl) Benzamide (7-8):

Nitro acid **6** (5.0 g, 15.15 mmol, 1.0 equiv.) was converted to its acid chloride **7** (5.11 g, 14.68 mmol, 1.0 equiv.) in the presence of $SOCl_2$ (1.64 mL, 13.78 mmol, 1.5

equiv.) and catalytic amount of DMF (2-3 drops) in dry benzene in 97 %. This freshly prepared acid chloride was added drop wise to stirred solution of Propargyl amine (0.96 g, 17.45 mmol, 1.2 equiv.) and Et_3N (2.64 g, 26.08 mmol, 1.5 equiv.) in dry THF at 0 °C. The stirring was continued further at room temperature for a period of 3-4 hours. Solvent THF was removed in vacuo under reduced pressure. The resulting crude solid was extracted with ethyl acetate (3 x 50 mL), washed with a saturated solution of $NaHCO_3$, 1N Hc1 and cold water to remove if any unreacted starting materials were present. The combined organic layers were distilled by vacuo to afford solid compound which was recrystallized from methanol to obtain yellow crystals of **8** (4.03 g) in 75 % yield, m.p. 194-195 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 1H, acetylenic-H), 3.92 (s, 3H, OCH_3), 4.10-4.24 (m, 2H, N-CH_2), 7.07-7.21 (dd, 1H, J_1 = 2.26 Hz, J_2 = 8.87,Hz, Ar-H), 7.39-7.5 (d, 1H, J= 1.70 Hz, Ar-H), 7.66-7.73 (d, 1H, J = 8.12 Hz, Ar-H), 7.92-8.04 (d, 1H, J = 9.06 Hz, Ar-H), 8.24-8.32 (m, 1H, Ar-H), 8.65 (s, 1H, Ar-H), 8.96 (brs, 1H, NH). ^{13}C NMR (75MHz, DMSO-d_6, TMS) δ 28.55, 55.77, 73.55, 80.18, 104.80, 116.67, 121.63, 123.95, 130.29, 131.26, 132.80, 135.00, 136.54, 147.51, 147.68, 158.04, 161.26, 164.47.IR (Neat): Vmax 3280.98, 3070.14, 2935.41, 1651.24, 1611.21, 1540.90, 1466.70, 1426.12, 1350.31, 1267.51, 1219.50, 1164.29, 1062.40, 1027.16, 850, 33, 809.01, 760.10, 672.77 cm^{-1}. ESI-MS: *m/z* 368 $(M+H)^+$. Elemental Anal. Calcd: C, 58.85; H, 3.57; N, 11.44; S, 8.73; found: C, 58.75; H, 3.62; N, 11.47; S, 8.75%.

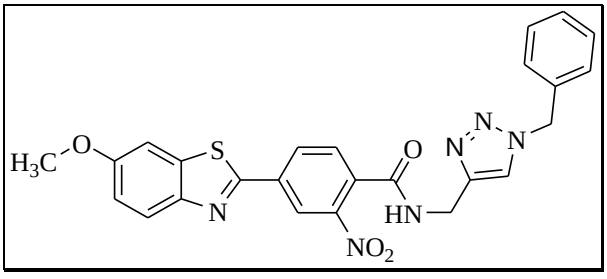
Synthesis of *N*-((1-benzyl-l*H*-l, 2, 3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamide (10a-j):

Water and tertiary alcohol in the ratio (1:1) were added to the round bottom flask containing compounds **8** possessing triple bond and freshly prepared benzyl azide **9a** and stirred for 5-10 minutes. To this reaction mixture were added 0.5 mol % $CuSO_4.5H_2O$ and 10 mole % Sodium ascorbate simultaneously. Reaction was continued for 12 hours till the completion of the reaction (confirmed with TLC). After the completion of the reaction, the reaction mixture was worked up with ethyl acetate, washed with brine and dried over Na_2SO_4. The organic layer was separated and removed in vacuo under reduced pressure. The resulting material was purified by column chromatography by using ethyl acetate and hexanes (8:2) to afford colorless **10a** in 87 % yield.

Table-1: Physical Characterization Data of Compounds 10 a–j:

S. No	Compound. No	molecular formula(10a-j)	Time(hrs)	Yield (%)	M.P (°c)
1.	**10a**	$C_{25}H_{20}N_6O_4S$	12.0	87	205.4-206.6
2.	**10b**	$C_{25}H_{18}N_6O_6S$	11.4	85	210-212
3.	**10c**	$C_{22}H_{20}N_6O_6$ S	12.0	85	196-197
4.	**10d**	$C_{33}H_{28}N_6O_6$ S	11.5	83	181-182
5.	**10e**	$C_{33}H_{28}N_6O_6S$	11.3	83	169.9 -170.8
6.	**10f**	C_{25} $H_{19}ClN_6O_4$ S	11.3	85	187.8-188.7
7.	**10g**	C_{29} $H_{28}N_6O_4S$	12.0	87	184.3-185.6
8.	**10h**	$C_{29}H_{22}N_6O_4S$	12.0	85	193-194
9.	**10i**	$C_{28}H_{26}N_6O_7S$	10.0	84	182.8-184.2
10.	**10j**	$C_{26}H_{19}F_3N_6O_4$ S	11.0	85	196.4-197.5

***N*-((1-benzyl-1*H*-l, 2, 3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamide (10a):** (Protan, Carbon, Mass and IR Spectrums **FIG - 1, 2, 3 & 4)**



Yield (%) : 87

M.P (^oC) : 205.4-206.6

I.R (Neat-cm^{-1}) : 1539 (-NO_2), 1649(-$CONH_2$).

^{1}H NMR (DMSO-d_6 -300 MHz) : δ 3.91 (s, 3H, OCH_3), 4.51-4.65 (d, 2H, *N*-CH_2), 5.58 (s, 2H, CH_2), 7.05-7.20 (d, 1H, Ar-H), 7.25-7.43 (s, 5H, Ar-H), 7.54 (s, 1H, Ar-H), 7.65-7.80 (d, 1H, J= 7.93 Hz), 7.84-8.05 (m, 2H, Ar-H), 8.21-8.36 (d, 1H, J = 7.74 Hz Ar-H), 8.58 (s, 1H, Ar-H), 9.20 (brs, 1H, NH).

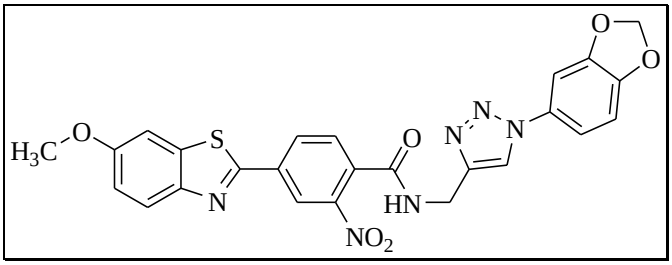
^{13}C NMR (DMSO-d_6 -75 MHz): δ 34.01, 52.23, 54.44, 102.90, 115.20, 120.46, 121.59, 122.73, 126.60, 126.96, 127.47,128.83, 129.69, 132.19, 134.03, 134.20, 135.33,143.42, 146.24, 146.80, 150.99, 159.77, 164.09.

Mass (ESI) : 501 (M^{+}+H).

CHN-Analysis : Anal. Calcd. For $C_{25}H_{20}N_6O_4S$: C, 59.99; H, 4.03; N, 16.79; S, 6.41; found: C, 59.90; H, 4.07; N, 16.83;S, 6.42%.

The same experimental procedure is used for following derivatives (**10b-j**) has been synthesized.

***N*-((l-(benzo[*d*] [l, 3] dioxol-5-yl)-l*H*-l, 2, 3-triazol-5-yl) methyl)-4-(6-methoxybenzo[*d*] thiazol-2-yl)-2-nitrobenzamide (10b)**



Yield (%) : 85

M.P (^{o}C) : 210-212

I.R (Neat-cm^{-1}) : 1545 (-NO_2), 1639(-$CONH_2$).

^{1}H NMR (DMSO-d_6 -300 MHz) : δ 3.91 (s, 3H, OCH_3), 4.64 (s, 2H, *N*-CH_2), 6.18 (s, 2H, O-CH_2-O), 6.67-7.6 (m, 4H, Ar-H),

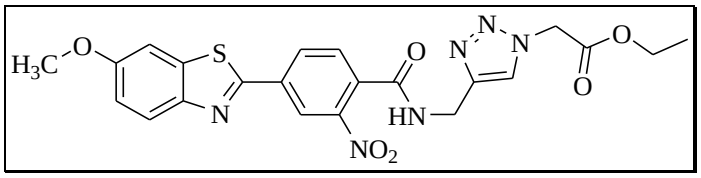
7.64-8.19 (m, 3H, Ar-H), 8.41 (s, 1H, Ar-H), 8.49-8.78 (m, 1H, Ar-H), 9.43 (broad singlet, 1H, NH).

^{13}C NMR (DMSO-d_6-75 MHz): δ 28.86, 55.61, 101.70, 101.92, 104.55, 108.40, 113.48, 116.45, 121.44, 123.79, 130.28, 130.93, 134.96, 144.85, 147.52, 157.94, 161.06, 164.67.

Mass (ESI) : 531 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{25}H_{18}N_6O_6S$: C, 56.60; H, 3.42; N, 15.84; S, 6.04, found: C, 56.70; H, 3.37; N, 12.84; S, 6.02%.

Ethyl-2-(5-((4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamido) methyl)-1*H*-l, 2, 3-triazol-1-yl) acetate (10c): (Protan, Carbon, Mass and IR Spectrums **FIG - 5, 6, 7 & 8)**



Yield (%) : 85

M.P (^{o}C) : 196-197

I.R (Neat-cm^{-1}) : 1535 (-NO_2), 1638(-CONH).

^{1}H NMR (DMSO-d_6-300 MHz): δ 1.23 (t, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.09-4.27 (q, 2H, O-CH_2), 4.47-4.65 (d, 2H, *N*-CH_2), 5.40 (s, 2H, CH_2), 7.06-7.27 (m, 1H, Ar-H), 7.69-7.83 (m, 2H, Ar-H), 7.93-8.14 (m, 2H, Ar-H), 8.28-8.43 (m, 1H, Ar-H), 8.58 (s, 1H, Ar-H), 9.38 (brs, 1H, NH).

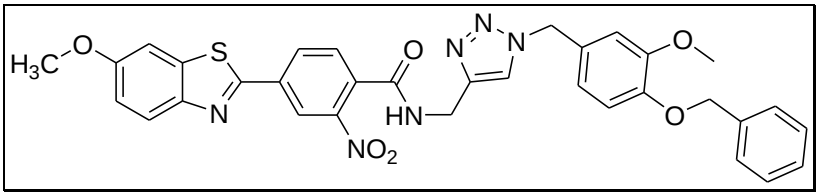
^{13}C NMR (DMSO-d_6-75 MHz): δ 13.90, 34.79, 50.32, 55.77, 61.43, 108.41, 116.64, 121.60, 123.93, 124.38, 130.31, 131.17,

133.11, 134.95, 136.54, 144.14, 147.58, 147.68, 158.04, 161.29, 164.75, 167.15.

Mass (ESI) : 497 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{22}H_{20}N_6O_6S$: C, 53.22; H, 4.06; N, 16.93; S, 6.46, found: C, 53.12; H, 4.11; N, 16.96; S, 6.48 %.

_N_-((1-(4-(benzyloxy)-3-methoxybenzyl)-1_H_-1, 2, 3-triazol-4-yl) methyl)-4-(6-methoxybenzo[_d_] thiazol-2-yl)-2-nitrobenzamide (10d):



Yield (%) : 83

M.P (^oC) : 181-182

I.R (Neat-cm^{-1}) : 1535 (-NO_2), 1638(-CONH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.51 (d, 2H, J= 5.47 Hz, _N_-CH_2), 5.06 (s, 2H, O-CH_2), 5.51 (s, 2H, CH_2), 6.82-6.91 (m, 1H, Ar-H), 6.97-7.08 (m, 2H, Ar-H), 7.15-7.23 (dd, 1H, J_1 = 2.45 Hz, J_2 = 8.87 Hz, Ar-H), 7.27-7.48 (m, 5H, Ar-H), 7.71-7.83 (m, 2H, Ar-H), 8.29-8.45 (dd, 1H, J_1 = 1.51 Hz, J_2 = 7.93 Hz, Ar-H), 8.58 (d, 1H, J = 1.51 Hz, ArH), 9.31 (t, 1H, J= 5.47 Hz, NH) .

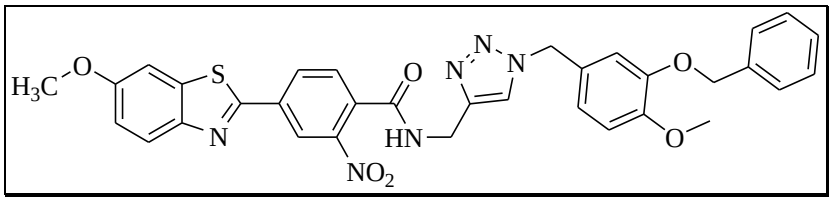
^{13}C NMR (DMSO-d_6-75 MHz) : δ 34.80, 52.57, 55.47, 55.71, 69.80, 104.77, 112.26, 113.55, 116.58, 120.43, 121.54, 122.75, 123.86, 127.58, 127.67, 128.24, 128.56, 130.24, 131.07, 133.06, 134.86, 136.47, 136.90, 144.16,

147.54, 147.57, 147.62, 149.04, 157.97, 161.22, 164.58.

Mass (ESI) : 637 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{33}H_{28}N_6O_6S$: C, 62.25; H, 4.43; N, 13.20; S, 5.04, found C, 62.15; H, 4.48; N, 13.24; S, 5.05 %.

_N_-(1-(3-(benzyloxy)-4-methoxybenzyl)-1_H_-1,2,3-triazol-4-yl) methyl)-4-(6-methoxybenzo [_d_]thiazol-2-yl)-2-nitrobenzamide (10e):



Yield (%) : 83

M.P (^oC) : 169.9-170.8

I.R (Neat-cm^{-1}) : 1538 (-NO_2), 1647(-CONH).

^{1}H NMR (DMSO-d_6 -300 MHz) : δ 3.74 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.52 (d, 2H, J = 4.91 Hz, _N_-CH_2), 5.03 (s, 2H, O-CH_2), 5.50 (s, 2H, CH_2), 6.85-7.03 (m, 2H, Ar-H), 7.08-7.25 (m, 2H, Ar-H), 7.27-7.55 (m, 5H, Ar-H), 7.66-7,87 (m, 2H, Ar-H), 7.92-8.14 (m, 2H, Ar-H), 8.33 (d, 1H, J = 8.30 Hz, Ar-H), 8.56 (s, 1H, Ar-H), 9.33 (t, 1H, J = 5.09 Hz, NH).

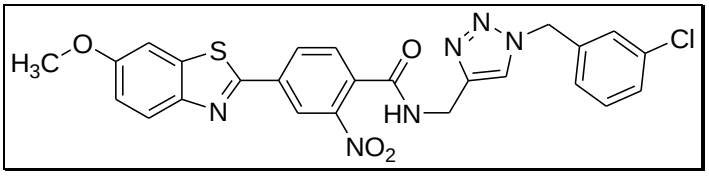
^{13}C NMR (DMSO-d_6 -75 MHz) : δ 34.83, 52.58, 55.50, 55.69, 69.95, 104.72, 112.06, 113.71, 116.55, 121.01, 121.52, 122.75, 123.86, 127.80, 128.06, 128.13, 128.23, 130.24, 131.04, 133.05,134.87, 136.47, 136.72,

144.19,147.53, 147.62, 147.70, 149.01, 157.97, 161.18, 164.61.

Mass (ESI) : 637 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{33}H_{28}N_6O_6S$: C, 62.25; H, 4.43; N, 13.20; S, 5.04, found: C, 62.15; H, 4.48; N, 13.24; S, 5.05 %.

_N_-((1-(3-chlorobenzyl)-l_H_-1,2,3-triazol-4-yl)methyl)-4-(6-fluorobenzo[_d_]thiazol-2-yl)-2-nitrobenzamide (10f):



Yield (%) : 85

M.P (^oC) : 187.8-188.7

I.R (Neat-cm^{-1}) : 1529 (-NO_2), 1636(-CONH).

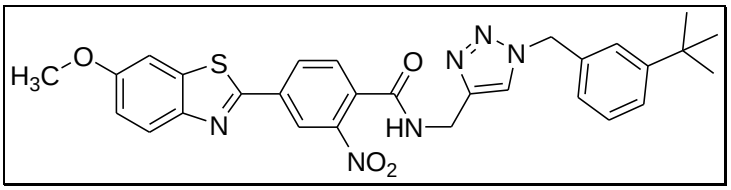
^{1}H NMR (DMSO-d_6-300 MHz) : δ 3.86 (s, 3H, OCH_3), 4.52 (d, 2H, J= 5.47 Hz, N-CH_2), 5.64 (s, 2H, CH_2), 7.14-7.32 (m, 2H, Ar-H), 7.35-7.47 (m, 3H, Ar-H), 7.72-7.83 (m, 2H, Ar-H), 8.01 (d, 1H, J= 8.87 Hz, Ar-H), 8.13 (s, 1H, Ar-H), 8.32-8.42 (dd, 1H, J_1 = 1.70 Hz, J_2 = 7.93 Hz, Ar-H), 8.54 (d, 1H, J= 1.70 Hz, Ar-H), 9.33 (t, 1H, J= 5.47 Hz, NH).

^{13}C NMR (DMSO-d_6-75 MHz) : δ 34.80, 51.90, 55.70, 104.74, 116.53, 121.52, 123.28, 123.85, 126.48, 127.68, 127.96, 130.24, 130.50, 131.06, 133.06, 133.17, 134.87, 136.47, 138.34, 144.32, 147.51, 147.63, 157.96, 161.19, 164.63.

Mass (ESI) : 535 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{25}H_{19}ClN_6O_4S$: C, 56.13; H, 3.58; Cl, 6.63; N, 15.71; S, 5.99, found: C, 56.03; H, 3.63; Cl, 6.66; N, 15.73; S, 6.00 %.

_N_-((1-(3-tert-butylbenzyl)-l_H_-1, 2, 3-triazol-4-yl) methyl)-4-(6-methoxybenzo[_d_]thiazol-2-yl)-2-nitrobenzamide (10g):



Yield (%) : 87

M.P (^oC) : 184.3-185.6

I.R (Neat-cm^{-1}) : 1538 (-NO_2), 1658(-CONH).

^{1}H NMR (DMSO-d_6 -300 MHz): δ 1.24 (s, 9H, CH_3), 3.86 (s, 3H, OCH_3), 4.52 (d, 2H, J= 5.28 Hz, _N_-CH_2), 5.57 (s, 2H, CH_2), 7.15-7.22 I (dd, 1H, J_1 = 2.45 Hz, J_2 = 9.06 Hz, Ar-H), 7.24-7.31 (d, 2H, J= 8.30 Hz, Ar-H), 7.32-7.50 (d, 2H, J= 8.30 Hz, Ar-H), 7.70-7.89 (m, 2H, Ar-H), 8.01 (d, 1H, J= 9.06 Hz, Ar-H), 8.07 (s, 1H, Ar-H), 8.29-8.47 (m, 1H, Ar-H), 8.50-8.69 (d, 1H, .7= 1.32 Hz, Ar-H), 9.32 (t, 1H, J = 5.47 Hz, NH).

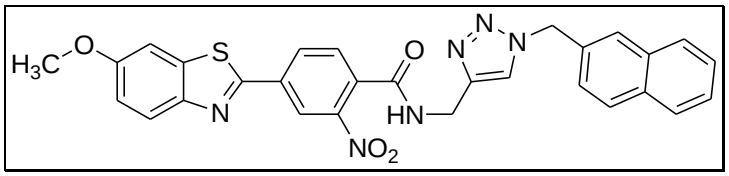
^{13}C NMR (DMSO-d_6 -75 MHz): δ 30.91, 34.15, 52.41, 55.71, 59.63, 104.74, 116.57, 121.52, 122.95, 123.86, 125.35,127.63, 130.27, 131.06, 133.01, 133.06, 134.87, 136.48,

144.21, 147.56, 147.64, 150.46, 157.97, 161.20, 164.61.

Mass (ESI) : 557 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{29}H_{28}N_6O_4S$: C, 62.57; H, 5.07; N, 15.10; S, 5.76, found: C, 62.47; H, 5.10;N,15.12;S, 5.77 %.

_N_-(6-fluorobenzo[_d_]thiazol-2-yl)-_N_-((1-(Naphthalen-2-ylmethyl)-l _H_-1, 2, 3-triazol-4-yl) methyl)-2-nitrobenzamide (10h)



Yield (%) : 85

M.P (^oC) : 193-194

I.R (Neat-cm^{-1}) : 1533 (-NO_2), 1644(-CONH).

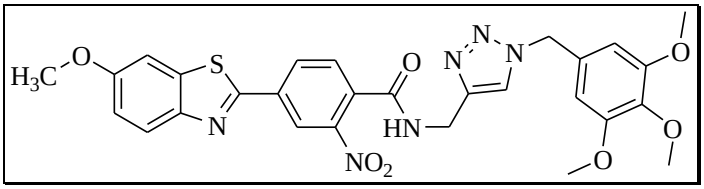
^{1}H NMR (DMSO-d_6-300 MHz): δ 3.86 (s, 3H, OCH_3), 4.50 (d, 2H, J= 5.47 Hz, _N_-CH_2), 6.11 (s, 2H, CH_2), 7.14-7.23 (m, 1H, Ar-H), 7.38-7.66 (m, 4H, Ar-H), 7.69-7.81 (m, 2H, Ar-H), 7.89-8.09 (m, 4H, Ar-H), 8.23 (d, 1H, J= 7.93 Hz, Ar-H), 8.30-8.38 (dd, 1H, J_1 = 1.70 Hz, J_2 = 8.12 Hz, Ar-H), 8.56 (d, 1H, J = 1.70 Hz, Ar-H), 9.30 (t, 1H, J= 5.47 Hz, NH).

^{13}C NMR (DMSO-d_6-75 MHz): δ 34.83, 50.68, 55.71, 104.72, 116.57, 121.52, 123.22, 123.87,125.43, 126.05, 126.67, 127.06, 128.54, 128.90, 130.23,130.55, 131.07, 131.48, 133.06, 133.25, 134.87, 136.48,144.21, 147.52, 147.64, 157.99, 161.19, 164.65.

Mass (ESI) : 551 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{29}H_{22}N_6O_4S$: C, 63.26; H, 4.03; N, 15.26; S, 5.82, found: C, 63.16; H, 4.08; N, 15.29; S, 5.84%.

_N_-(6-methoxybenzo[_d_]thiazol-2-yl)-2-nitro-_N_-((1-(3, 4, 5-trimethoxybenzyl)-1_H_-1, 2, 3-triazol-4-yl) methyl) benzamide (10i)



Yield (%) : 84

M.P (^oC) : 182.8-184.2

I.R (Neat-cm^{-1}) : 1540 (-NO_2), 1647(-CONH).

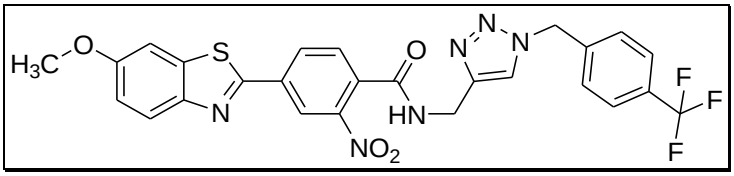
^{1}H NMR (DMSO-d_6-300 MHz): δ 3.63 (s, 3H, OCH_3), 3.75 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 4.52 (d, 2H, J= 5.72 Hz, _N_-CH_2), 5.51 (s, 2H, CH_2), 6.73 (s, 2H, Ar-H), 7.18 (d, 1H, J= 7.74 Hz, Ar-H), 7.77 (s, 2H, Ar-H), 8.00 (d, 1H, J = 8.87 Hz, Ar-H), 8.09 (s, 1H, Ar-H), 8.27-8.43 (m, 1H, Ar-H), 8.57 (s, 1H, Ar-H), 9.33 (brs, 1H, NH).

^{13}C NMR (DMSO-d_6-75 MHz): δ 34.86, 53.01, 55.79, 59.90, 104.75, 105.62, 116.63, 121.60, 122.98, 123.91, 130.28, 131.14, 131.34, 133.11, 134.90, 136.52, 137.18, 144.29, 147.57, 147.65, 152.93, 158.00, 161.24, 164.69.

Mass (ESI) : 591 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{28}H_{26}N_6O_7S$: C, 56.94; H, 4.44; N, 14.23; S, 5.43, found: C, 56.84; H, 4.49; N, 14.26; S, 5.45 %.

***N*-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitro-*N*-((1-(4-(trifluoromethyl) benzyl)-1*H*-1, 2, 3-triazol-4-yl) methyl) benzamide (10j)**



Yield (%) : 85

M.P (^{o}C) : 196.4-197.5

I.R (Neat-cm^{-1}) : 1559 (-NO_2), 1631(-CONH).

^{1}H NMR (DMSO-d_6 -300 MHz): δ 3.87 (s, 3H, OCH_3), 4.54 (d, 2H, J = 5.79 Hz, N-CH_2), 5.74 (s, 2H, CH_2), 7.07-7.24 (m, 1H, Ar-H), 7.51 (d, 2H, J= 8.27 Hz, Ar-H), 7.60-7.84 (m, 4H, Ar-H), 7.89-8.06 (m, 1H, Ar- H), 8.07-8.18 (m, 1H, Ar-H), 8.25-8.42 (m, 1H, Ar-H), 8.47-8.65 (s, 1H, Ar-H), 9.32 (brs, 1H, NH).

^{13}C NMR (DMSO-d_6 -75 MHz): δ 34.74, 52.00, 55.57, 104.51, 116.40, 121.39, 123.33, 123.73, 125.31, 125.35, 128.30, 130.12, 130.91, 133.04, 134.89, 136.38, 140.41, 144.28, 147.42, 147.62, 157.91, 164.60.

Mass (ESI) : 569 (M^{+}+H).

CHN-Analysis : Anal. Calcd. For $C_{26}H_{19}F_3N_6O_4S$: C, 54.93; H, 3.37; F, 10.03; N, 14.78; S, 5.64 found: C, 54.83; H, 3.42; F, 10.06; N, 14.79; S, 5.65 %.

3.5. Biological Activity

3.5.1. Antimicrobial Activity

In view of developing new class of antimicrobial agents, synthesized novel compounds and were screened for their *in vitro* antimicrobial activities to determine zone of inhibition at 100 μg/mL against two Gram-positive bacteria (*Staphylococcus aureus* (MTCC 096), *Bacillus subtilis* (MTCC 441) and two Gram-negative bacteria (*Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 424), as well as two fungi (*Aspergillusniger* (MTCC 282), *Aspergillus fumigates* (MTCC 343), strains using cup plate method. where inoculated Muller-Hilton agar for bacteria and Sabouraud dextrose agar for fungi was poured onto the sterilized petri dishes (25–30 mL each petri dish). The poured material was allowed to set (30 min) and thereafter the 'cups' (6mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution (0.1mL) was added with the help of a micro pipette. The plates were incubated at 37°C for 14h for bacteria and 30 h for fungi and the results were noted. The test solution was prepared by DMSO as solvent. Clinically antimicrobial drugs Ciprofloxacin and Miconazole were used as the positive control and DMSO was used for blank.

The results of antimicrobial screening are summarized in **Table-2,** revealed that all the synthesized compounds, **10a-j** could effectively, to some extent, inhibit the growth of all tested strains *in vitro*. In antibacterial studies, all the compounds tested were found less active towards *Bacillus subtilis,* as compared to other three strains of bacteria. Most of the compounds showed moderate to good activity against *Staphylococcus aureus.* In general, **10a**, **10h** and **10i** have shown good antibacterial activity against *Staphylococcus aureus.* **10b**, **10c** and **10i** have shown moderate activity against *Escherichia coli.* Out of two strains of fungi, these compounds were found to be less active against *Aspergillusniger* where as showed moderate to good activity against *Aspergillusfumigatus*. Compounds, **10a**, **10b, 10c, 10d, 10e, 10f, 10g, 10h, 10i** and **10j** possessed good antifungal activity against *Aspergillus fumigates.* we observed that electron-donating methoxy ($-OCH_3$) and benzoxyl (–OBn) substituted compounds **10d**, **10e**, **10i** and **10j** showed more antibacterial active compared withother

substitute *N*-((l-benzyl-l*H*-l,2,3-triazol-5-yl)methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides (**10a-j**).

Table-2: Antimicrobial activity of title compounds 10a-j

Zones of inhibition in mm						
Compound	**Anti-bacterial activity(100 *µg*/mL)**				**Antifungal activity (100*µg*/mL)**	
	Gram positive bacteria		**Gram negative bacteria**		**Fungi**	
	Staphylococcus aureus	***Bacillus subtilis***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Aspergillus Niger***	***Aspergillus fumigates***
10a	17	14	12	13	10	17
10b	13	12	15	12	10	18
10c	15	11	16	12	11	17
10d	13	11	12	10	12	18
10e	13	10	10	11	11	18
10f	14	11	10	13	13	19
10g	13	11	12	12	13	18
10h	16	10	14	14	14	18
10i	17	13	16	14	14	18
10j	14	11	13	14	13	18
Ciprofloxacin	20	21	22	20	--	--
Miconazole	--	--	--	--	29	22

Standard drug for bacteria: Ciprofloxacin; Standard drug for fungi: Miconazole Zone of Inhibition (Internal diameter: 6mm) All the compounds were screened at **100*μg*/mL** concentration.

3.6. Conclusion

In conclusion, we accomplished the synthesis of the proposed structure of novel *N*-((l-benzyl-l*H*-l, 2, 3-triazol5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides following by in situ intra molecular 1, 3-dipolar cycloaddition reaction between easily affordable azides and alkynes with good yields and high purity. The synthesized compounds were screened for the Antimicrobial activity study by Cup plate method. Some of the compounds shown strong anti-microbial activity at low concentrations and hence further design and synthesis of compounds in this direction is in progress. This study can provide a road map to design and synthesis of Benzothiazole scaffold based anti-microbial active compounds.

3.7. Spectrums:

Compound 10a: ^{1}H NMR

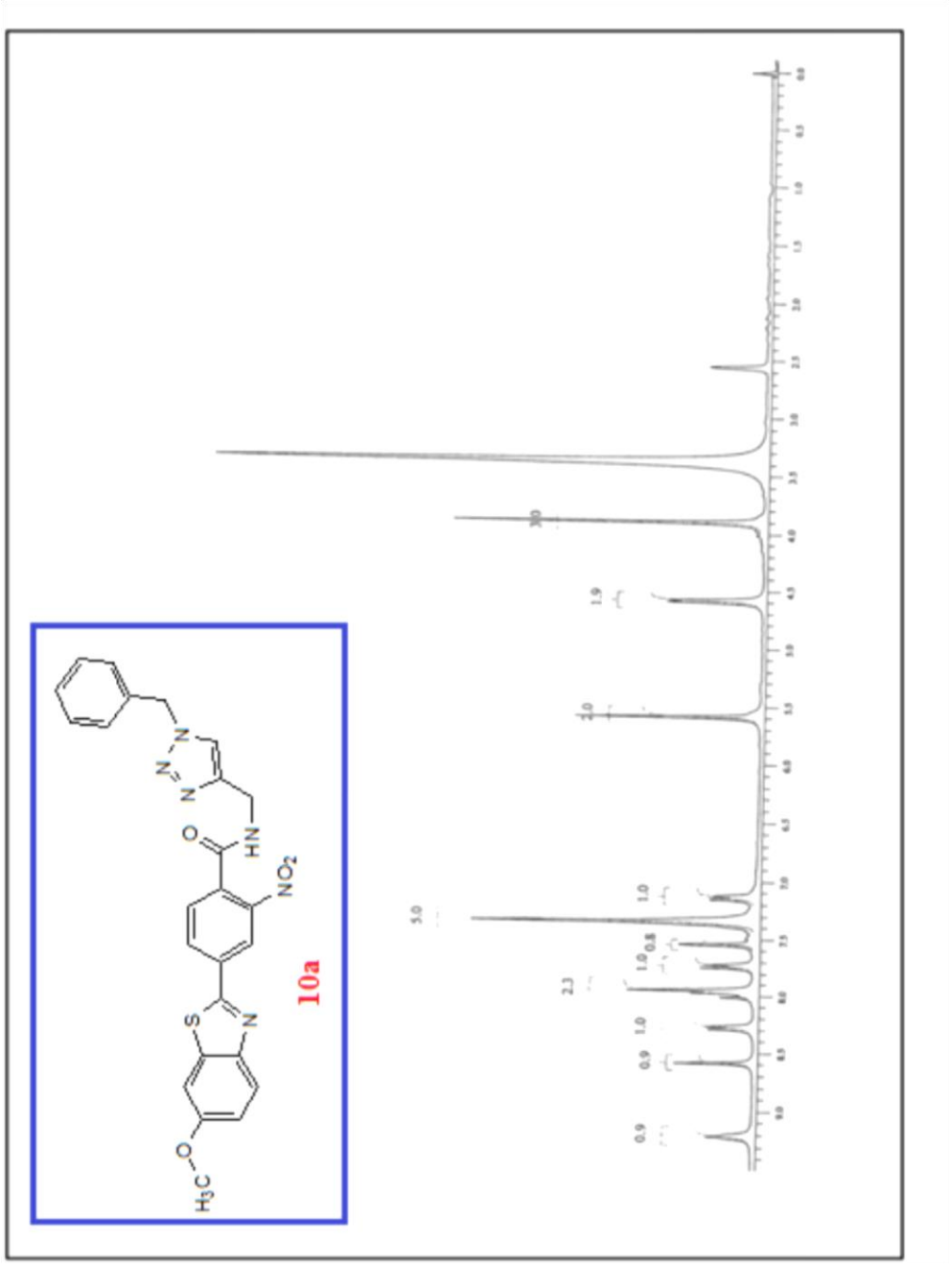


FIG-1: ^{1}H NMR Spectrum of Compound 10a (DMSO-d_6, 300 MHz)

Compound 10: ^{13}C NMR

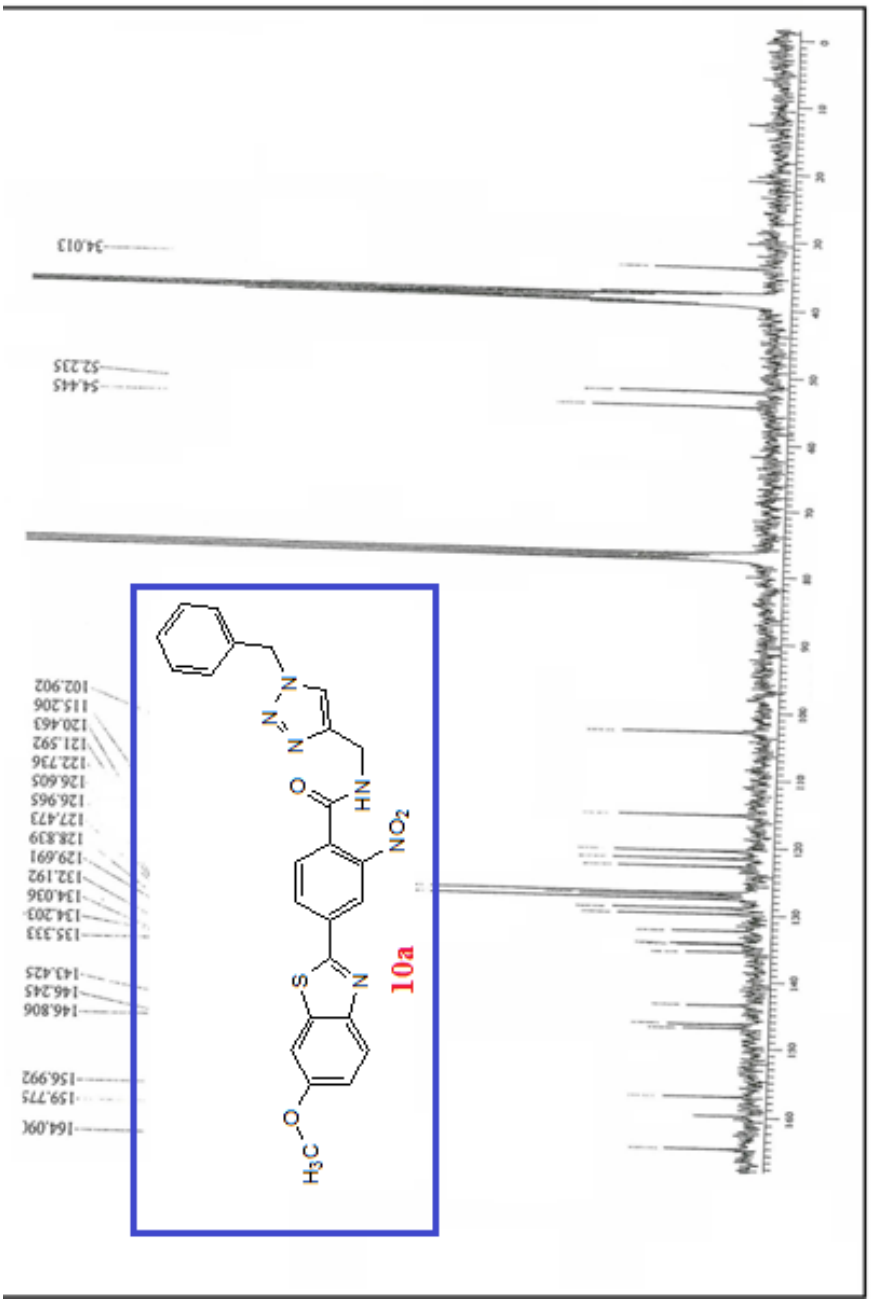


FIG-2: ^{13}C NMR Spectrum of Compound 10a (DMSO-D_6, 75 MHz)

Compound 10a : Mass spectrum and IR spectrum

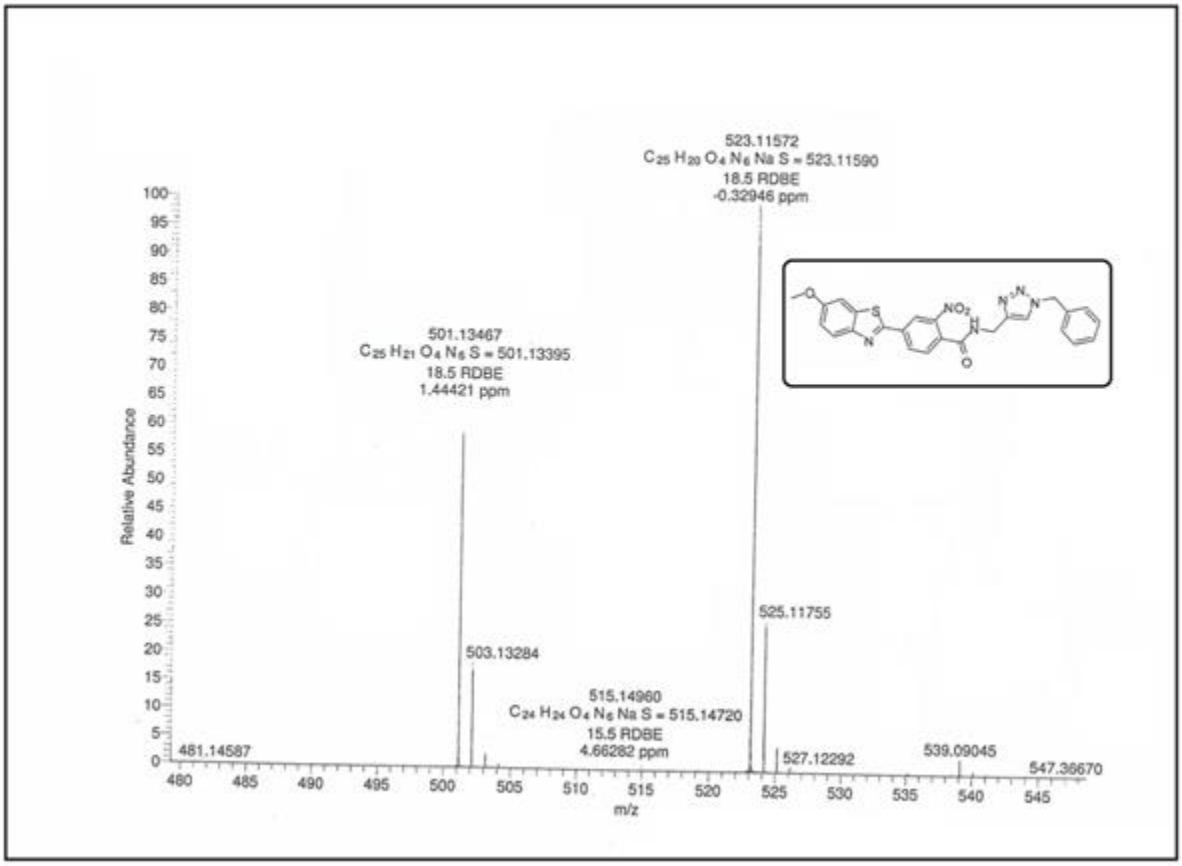


FIG- 3: ESI-MS spectrum of Compound 10a

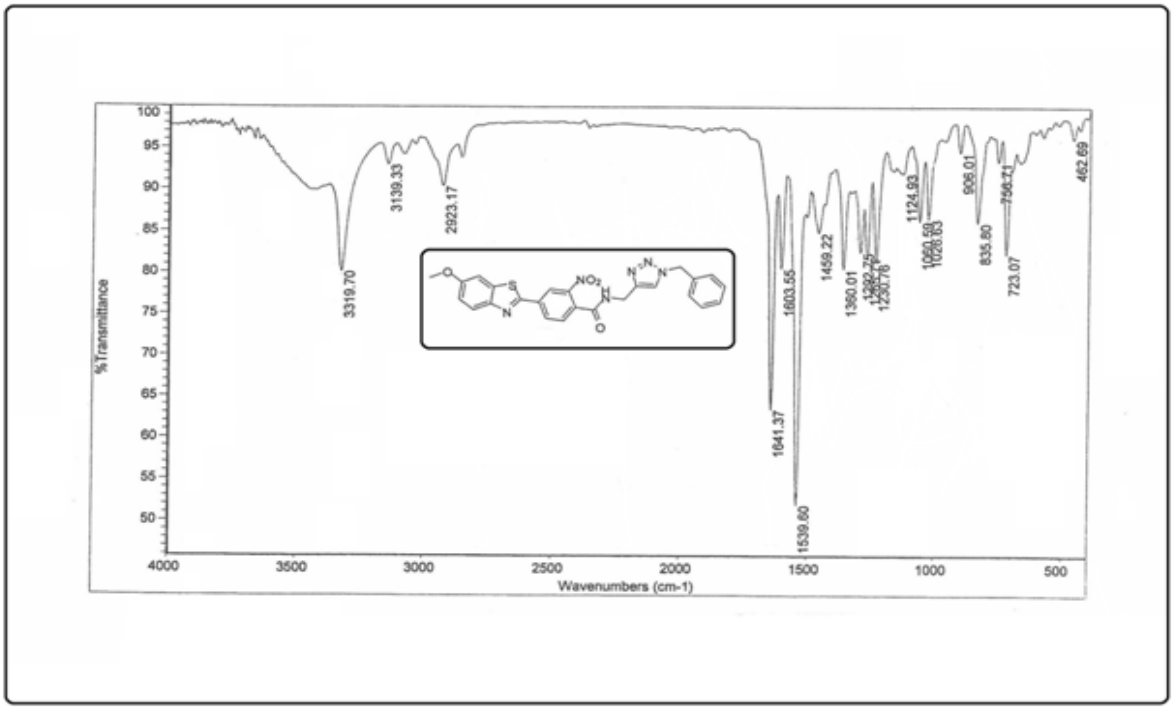


FIG-4: IR Spectrum of Compound 10a

Compound 10c: ^{1}H NMR spectrum

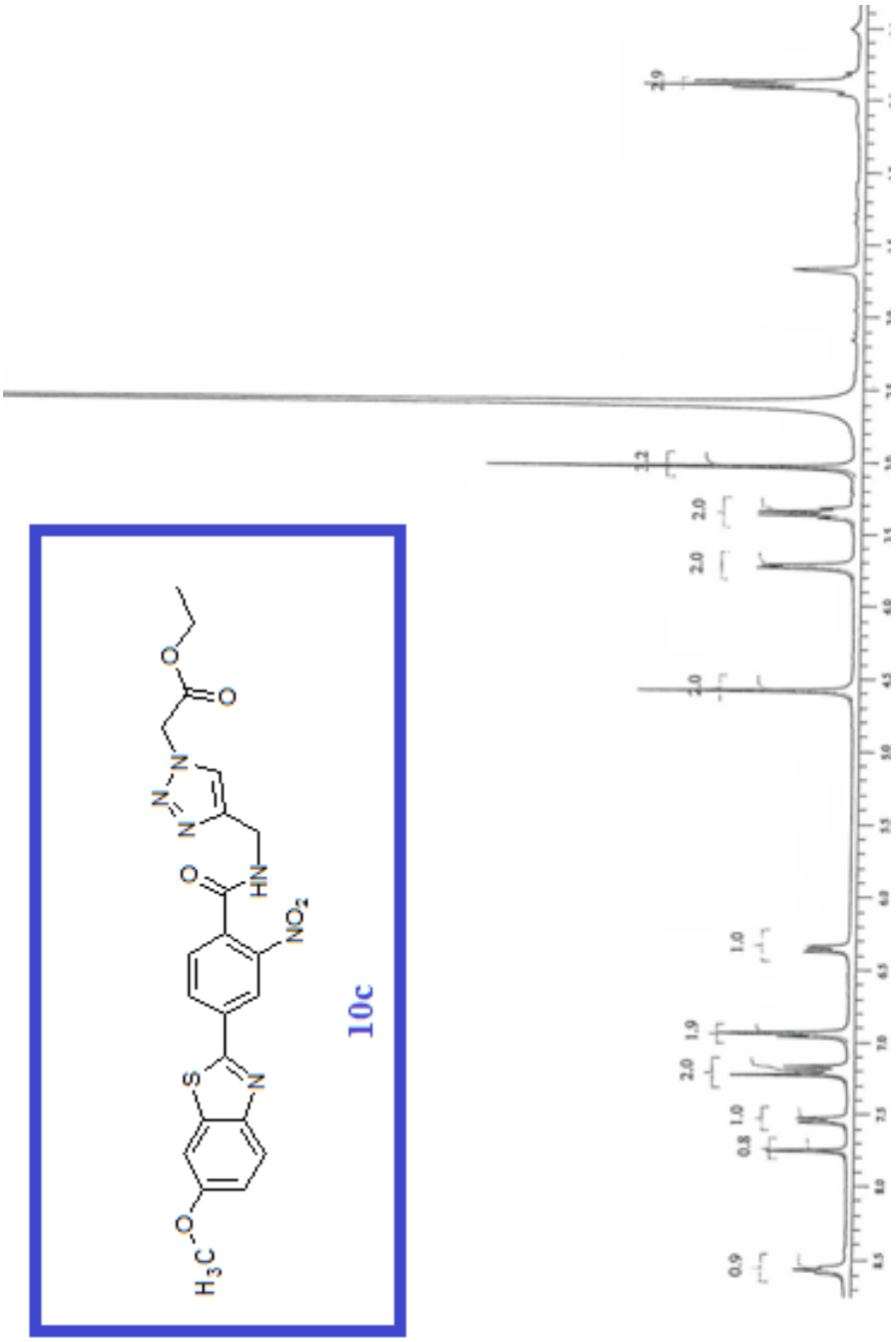


FIG-5: ^{1}H NMR spectrum of compound 10c (DMSO-d_6, 300MHz)

Compound 10c: ^{13}C NMR spectrum

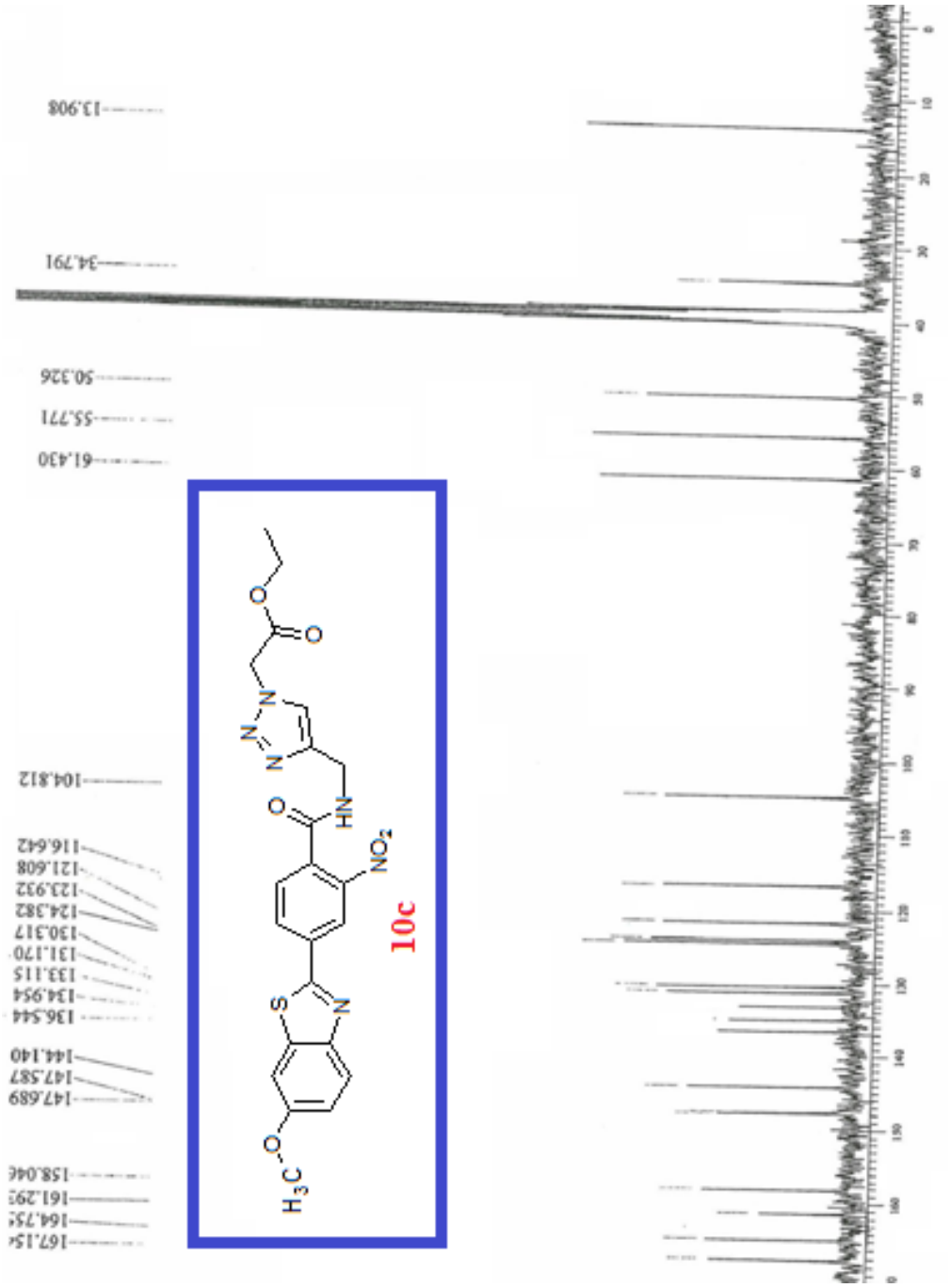


FIG-6: ^{13}C NMR spectrum of compound 10c (DMSO-d_6, 75 MHz)

Compound 10c: Mass spectrum and IR spectrum

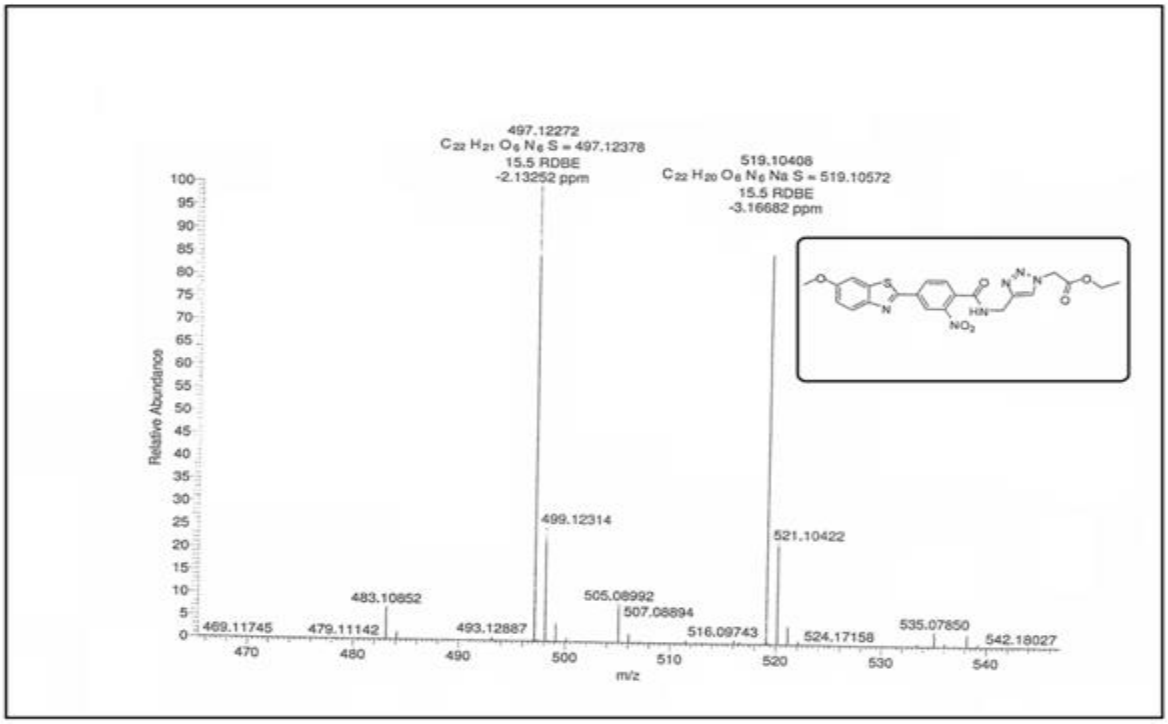


FIG-7: ESI-MS spectrum of compound 10c

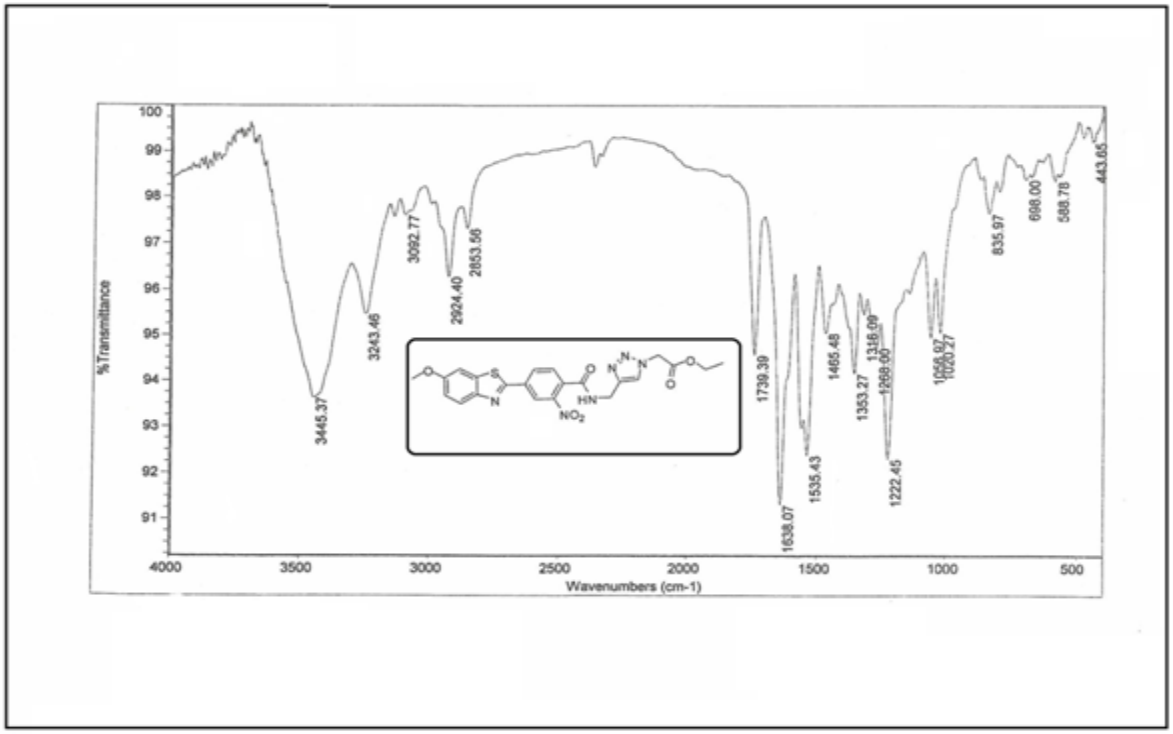


FIG-8: IR spectrum of compound 10c

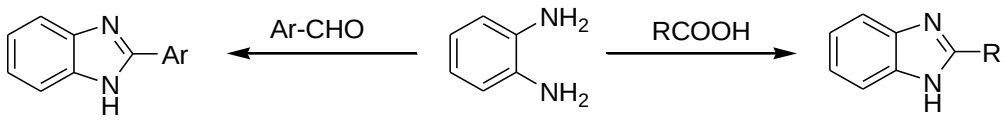
CHAPTER 4

Efficient method Microwave irradiation for synthesis of 2-substituted Benzimidazoles from *1, 2*- phenylenediamine and β-keto esters /1, 3-di ketones Using $Gd(OTf)_3$ as a Catalyst.

4.1. Introduction:

Development of new synthetic methods using cost-effective catalysts, biodegradable solvents and green reactions with atom cost-cutting measure and using non hazardous chemicals and multicomponent reactions have become the up to date interest for organic chemists all over the world. Recovery and recyclic of the solvents and catalysts are the additional advantages of the methods or process.

Benzimadazoles are an important class of potential organic molecules due to their broad range of activity like antiparasitic (Gabriel et al, 2001 and Juan et al, 2002), antiprotozoal (Gabriel et al, 2006 and Fransisco et al, 2010), antibacterial (Nakamura et al, 2005), fungicidal (Keith et al, 1978), antihelmentic (Mavrova et al, 2006), antihypertensive (Kohara et al, 1996) and anticancer agents. The general method for synthesis of 2-substituted benzimadazoles involves the reaction between *1*, *2*-phenylene diamine and a carboxylic acid or an acid chloride or nitrile in the presence of strong acid catalyst (Fairley et al, 1993 and Czarny et al, 1996) or with aldehydes in the presence of oxidants (Patzold et al, 1992, Lombardy et al, 1996 and Beaulieu et al, 2003). However, a variety of these methods have certain drawbacks such as moderate yields, usage of exclusive reagents, a scrupulous oxidation process or lengthened reaction times, tedious work-up procedures and poor selectivity.



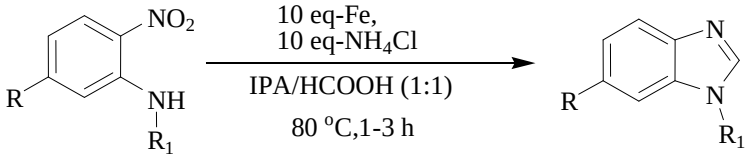
Scheme-1

The combinatorial method also provides on solid-phase synthesis for benzimadazoles (Mazurov et al, 2000 and Tumelty et al, 2001) and *o*-nitro anilines also used for the synthesis of benzimidazoles on solid phase support (Kilburn et al ,2000 and Diao et al, 2009). 2-Halo anilines can be used for the preparation of benzimidazoles under unsympathetic reaction conditions (Saha et al, 2009 and Taniguchi et al, 1993). A Lot of methods were reported for the preparation of a choice of benzimidazoles based on their biological importance (Schulz et al, 1995 and Downing et al, 1995).

4.2. Literature Updates on 2-Substituted Benzimidazoles:

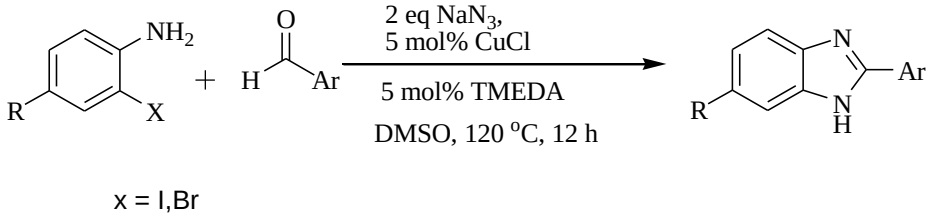
1) Preaparation of 2- substituted benzimidazole by using nitroanilines: (Hanan *et al*, 2010)

Emily J. Hanan et.al have reported synthesis of one-pot procedure for the conversion of aromatic and hetero aromatic 2-nitroamines into bi cyclic 2*H*-benzimidazoles employs formic acid, Iron powder, and NH_4Cl as stabilizer to reduce the nitro group to amine and effect the imidazole cyclisation with high-yielding conversions generally within one to two hours. The compatibility with a wide range of functional groups demonstrates the general utility of this procedure.



2) Preaparation of 2-substituted benzimidazole by using 2- halo anilines. (Guru *et al*, 2011)

Guru et *al* have reported synthesis of Copper-catalyzed, one-pot, three-component reaction of 2-haloanilines, aldehydes, and NaN_3 enabled the synthesis of benzimidazoles in good yields using catalytic amounts of CuCl and TMEDA in DMSO at 120 °C for12 h.

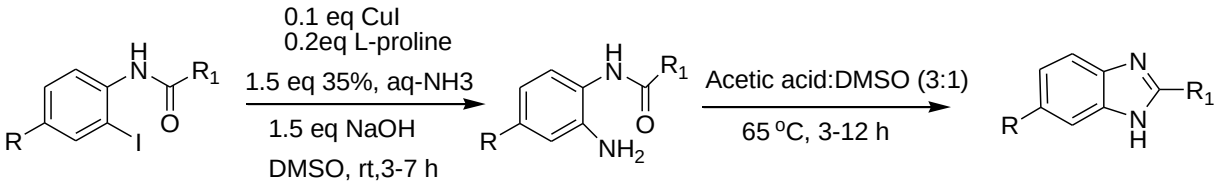


x = I,Br

3) Preparation of 2-subtituted benzimidazoles from 2-iodoacetanilides/2-iodophenyl carbamates: (Diao *et al*, 2009)

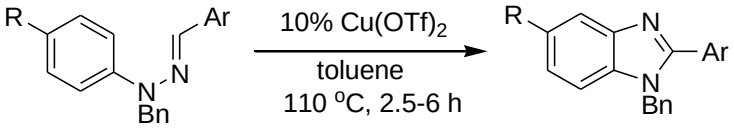
Diao et .al, have reported the synthesis of CuI/L-proline catalyzed coupling of aqueous ammonia with 2-iodoacetanilides and 2-iodophenylcarbamates affords aryl amination products at room temperature, which undergo *in situ* additive cyclisation

under acidic conditions or heating to give substituted 1*H*-Benzimidazoles and 1, 3-dihydrobenzimidazol-2-ones, respectively.



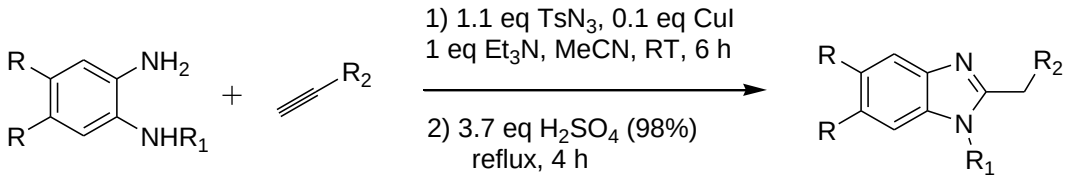
4) Preparation of 2-substituted benzimidazoles from *N*-benzyl bis aryl hydrazones/bis aryl oxime ethers (Guru *et al*, 2011)

***Guru et al* have** reported an efficient method for the transformation of *N*-benzyl bis aryl hydrazones and bis aryl oxime ethers to functionalized 2-aryl-*N*-benzylbenzimidazoles and 2-arylbenzoxazoles involves a copper (II)-mediated cascade C-H functionalization/C-N/C-O bond formation under neutral conditions. Substrates having either electron-donating or withdrawing substituents undergo the cyclization at moderate temperature.



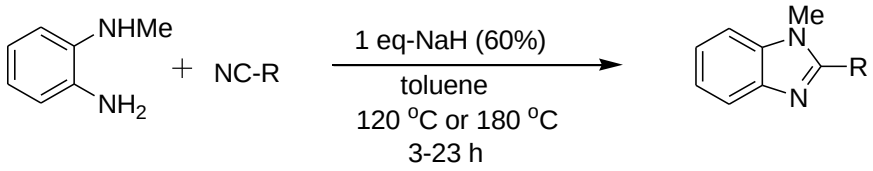
5) Preparation of 2-substituted benzimidazole from o-aminoanilines or naphthalene-1, 8-diamine (Yanguang *et al*, 2009)

Yanguang Wang et.al have reported an Efficient and general reactions of *o*-aminoanilines or naphthalene-1, 8-diamine with terminal alkynes and *p*-tolylsulfonyl azide allow a one-pot synthesis of functionalized benzimidazoles and 1*H*-pyrimidines in good yields.



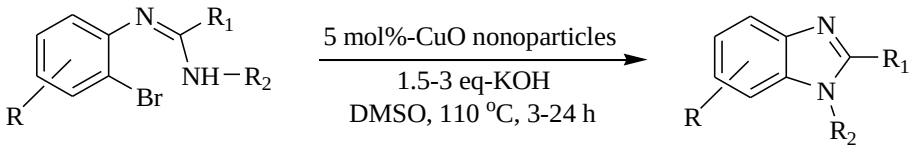
6) Preparation of 2-substituted benzimidazole from *N*-methyl-1, 2-phenylenediamine: (Sluiter *et al*, 2009)

Sluiter et.al have reported a synthesis of NaH-mediated reaction of carbonitriles and *N*-methyl-1, 2-phenylenediamine allows the formation of *N*-methylbenzimidazole and stand for acid-labile acetal protective groups. Products were further converted in Suzuki, Sonogashira, Heck and Buchwald-Hartwig reactions.



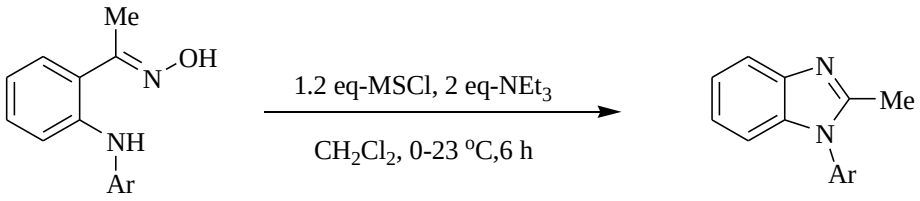
7) Preparation of 2-substituted benzimidazole from *o*-bromoaryl derivatives: (Punniyamurthy *et al*, 2009)

Punniyamurthy et.al have reported An experimentally easy, general, efficient, and ligand-free synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles via intramolecular cyclization of *o*-bromoaryl derivatives is catalyzed by copper (II) oxide nanoparticles in DMSO under air. The heterogeneous catalyst can be recovered and recycled without loss of activity.



8) Preparation of 2- substituted benzimidazole from arylamino oximes: (Stambuli *et al*, 2010)

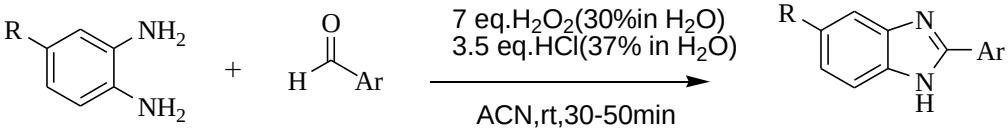
Stambuli et.al have reported an Various *N*-aryl-1*H*-indazoles and benzimidazoles were synthesized from common arylamino oximes in good to excellent yields depending upon the base used in the reaction. Triethylamine promoted the formation of benzimidazoles, where as 2-aminopyridine promoted the formation of *N*-arylindazoles.



The cyclization of *N*-haloamidines with sodium ethoxide forms benzimidazoles through a nitrene intermediate.

9) Preparation of 2-substituted benzimidazole from o-phenylenediamines: (Bahrami *et al*, 2007)

Bahrami *et.al* have reported an efficient one-pot condensation of o-phenylenediamines with aryl aldehydes in the presence of H_2O_2 and HCl in acetonitrile at room temperature features short reaction time, easy and quick isolation of the products, using a simple and efficient method, in result good yields obtained.



Objectives

1) To synthesize nucleus containing benzimidazole.

2) To simple and green synthetic method for the preparation of 2-substituted benzimidazoles

under mild reaction conditions by using Microwave Irradiation.

3) To synthesize targeted compounds.

4) To establish the structure on the basis of melting point, Infrared spectra, NMR spectra and

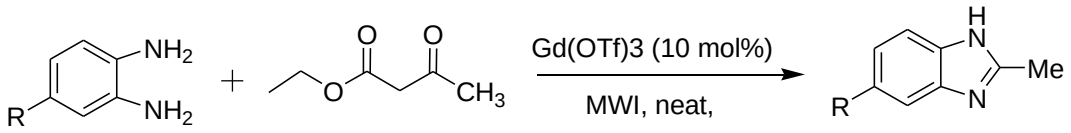
mass spectra.

4.3. Present Work

4.3.1. Chemistry, Results and Discussion:

The objective of this study was to develop one simple and green synthetic method for the preparation of 2-substituted benzimidazoles under mild reaction conditions. It has been observed that benzimidazoles can be synthesized efficiently by treatment of *1,2* phenylenediamines with *β*-keto esters or 1, 3-diketones without any side products.Here we found a Gadalonium triflate is a simple and efficient catalyst .

As a model reaction the condensation of *1, 2*-phenylenediamine and excess ethylacetoacetate in presence of Gadalonium triflate under Microwave irradiation at ambient temperature afforded the corresponding 2-substituted benzimidazole in 80-87% yield.

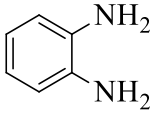
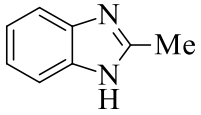
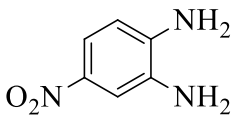
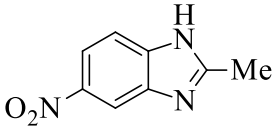


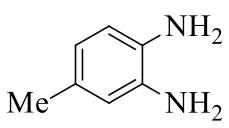
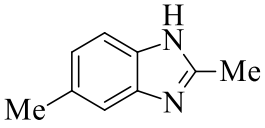
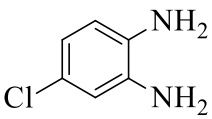
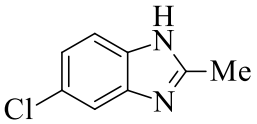
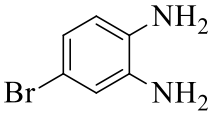
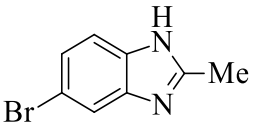
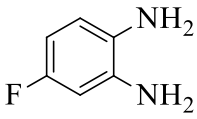
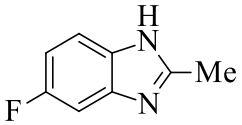
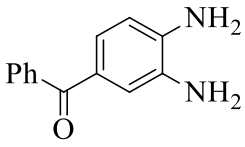
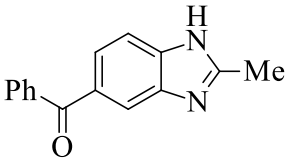
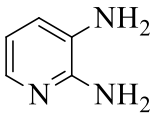
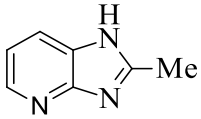
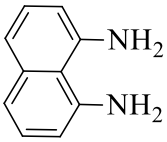
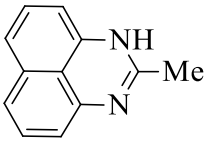
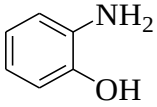
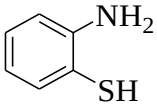
1a-i **2** **3a-i**

Scheme 1

The reaction was broadened to different diamines with *β*-keto esters afforded number of benzimidazoles (**Table 1**). The effect of electron realsing and electron-withdrawing groups on diamines was negligible on the formation of benzimidazoles. Here we made an attempt to prepare benoxazoles and benzthiozoles, by using this method, but unfortunately the reactions were not successful.

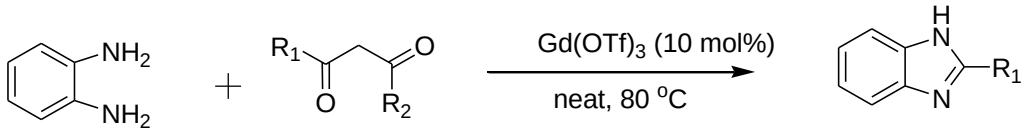
Table 1: Gadalonium (III) triflate catalysed benzimidazoles (3a-i).

Entry	Diamine (1)	Benzimadazoles (3a-i)	Time (mins.)	Yiled[a]
1			10.0	86
2			8.5	80

3			10.5	85
4			8.5	76
5			7.5	71
6			6.5	70
7			8.0	65
8			11.0	70
9			12.5	65
10		No Reaction		
11		No Reaction		

[a] Isolated yields. All products gave agrreble ^{1}H NMR, IR and mass spectral data.

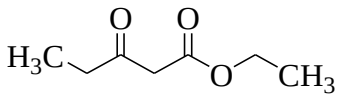
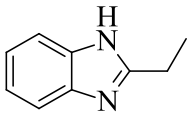
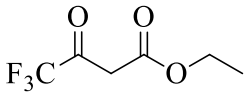
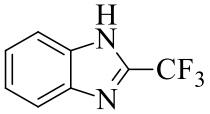
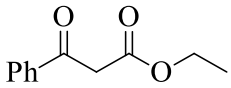
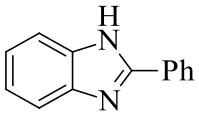
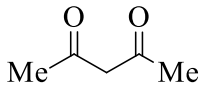
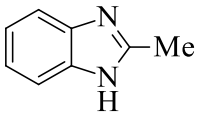
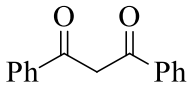
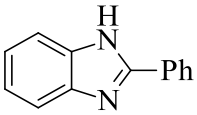
The adaptability of the reaction was confirmed by the condensation of 1, 2 phenylenediamines with 1, 3-diketones in presence of Gadalonium (III) Triflate furnished the related benzimadazoles in excellent yields.



1 **2a-e** **4a-e**

Scheme 2

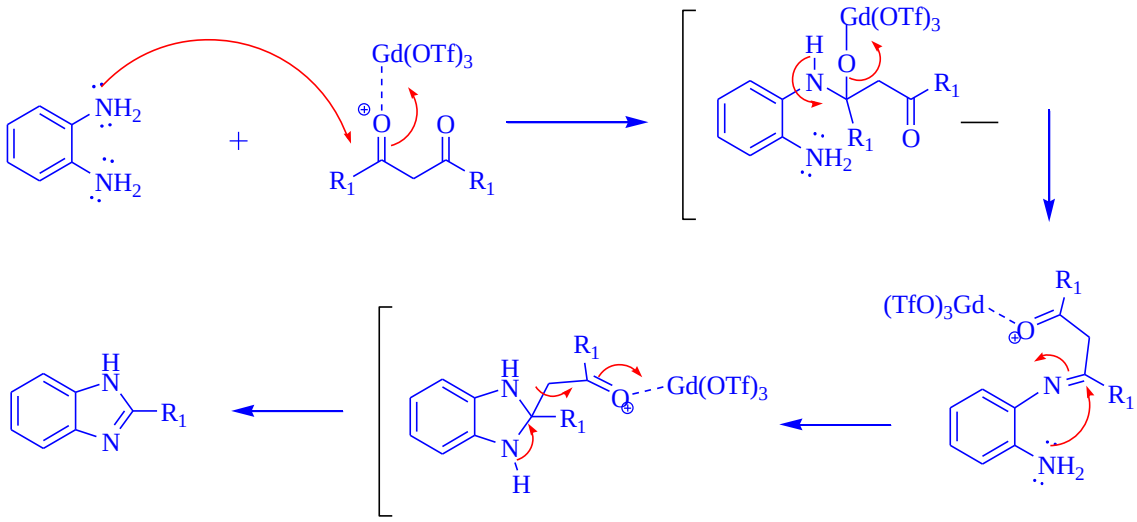
Table 2: Gadalonium (III) Triflate catalysed benzimidazoles (4a-e).

Entry[a]	1,3 –di ketones(**2**)	Benzimdazoles (**4**)	Time (mins)	Yiled
1			7.5	60
2			5.5	65
3			4.5	63
4			4.0	60
5			6.5	63

[a] Isolated yields. All products gave satisfactory ^{1}H NMR, IR and mass spectral data.

4.4. Mechanism:

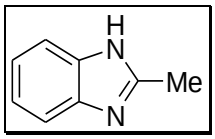
The catalyst Gadolinium triflate may be forming a complex with the carbonyl functional group in *β*-keto esters / 1, 3-diketones resulting the π bond electrons of carbonyl group to shift towards the metal. The nonbonding lone pair of electrons of amine attacks on to carbonyl carbon followed by movement of electrons leading to the imine bond formation. The nonbonding electrons of another amine then attacks on to imine carbon; the π bond electrons of imine group shifted towards the nitrogen atom. The rearrangement takes *via* C-C bond cleavage at *α*-position of the carbonyl group finally yielding the 2-substituted benzimadazoles.



4.5. Experimental Procedure:

Typical procedure for 2-substituted benzimadazoles under Gadalonium (III) Triflate catalysis: 1, 2-phenylenediamine **1** (0.5 g, 4.62 mmol), ethylacetoacetate **2a** (1.805 g, 13.87 mmol) and Gd $(OTf)_3$ (0.050 g) were taken into a 50 ml single neck flask and after mixing them properly with glass rod, the flask was placed under Microwave irradiation at 300W (CEM-discover, model number-908010). The reaction progress was monitored by TLC for every 60 sec by using mobile phase ethyl acetate and hexane (6:4 ratios). After completion of the reaction (TLC), the reaction mixture was poured into ice cold water and extracted with ethyl acetate (2 x15ml). The organic layer was dried over $MgSO_4$ and distilled under reduced pressure afforded the corresponding 2-methyl benzimidazole in 86% yield.

2-Methyl-1*H*-benzo[*d*]imidazole (3a) (Table 1, Entry-1):



Yield (%) : 86

M.P (^oC) : 175-177

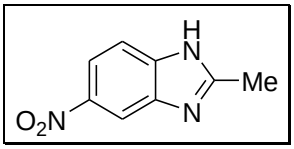
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.47 (s, 3H, -CH_3), 6.32 (br s, 1H, -NH), 7.17-7.28 (m, 1H, Ar-H), 7.62 (d, 1H, Ar-H, *J = 8.6* Hz), 7.78- 7.90 (m, 1H, Ar-H), 8.02 (d, 1H, Ar-H, *J* = 8.1 Hz).

Mass (ESI) : 133 (M^++H).

CHN-Analysis : Anal. Calcd. for $C_8H_8N_2$: C, 72.68; H, 6.13; N, 21.19%. Found: C, 72.66; H, 6.14; N, 21.20%.

2-Methyl-5-nitro-1*H*-benzo[*d*]imidazole (3b) (Table 1, Entry-2): (Protan, Mass and IR spectrum **FIG- 9, 10 & 11**)



Yield (%) : 80

M.P (^{o}C) : 222-224

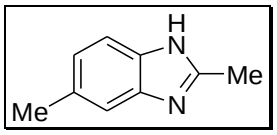
I.R (KBr-cm^{-1}) : 3400-3600 (-NH_2).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.66 (s, 3H, -CH_3), 14.17 (br s, 1H, -NH), 7.54 (d, 1H, Ar-H, *J* = 9.4 Hz), 8.08 (d, 1H, Ar-H, *J* = 9.4 Hz), 8.43 (s, 1H, Ar-H).

Mass (ESI) : 178 (M^++H).

CHN-Analysis : Anal.Calcd. for $C_8H_8N_2$: C, 54.23; H, 3.96; N, 23.73%. Found: C, 54.22; H, 3.97; N, 23.75%.

2,5-Dimethyl-1*H*-benzo[*d*]imidazole (3c) (Table 1, Entry-3):



Yield (%) : 85

M.P (^{o}C) : 204-206

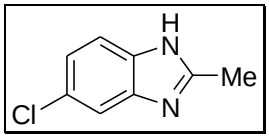
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.43 (s, 3H, -CH_3), 2.55(s, 3H, Ar-H), 6.96 (d, 1H, Ar-H, J = 7.5 Hz),7.26 (s, 1H, Ar-H), 7.36 (d, 1H, Ar-H, J = 7.5 Hz), 7.67 (br s, 1H, -NH).

Mass (ESI) : 148 (M^{+}+H).

CHN-Analysis : Anal.Calcd. for $C_8H_8N_2$: C, 73.96; H, 6.85; N, 19.18%. Found: C, 73.97; H, 6.86; N, 19.16%.

5-Chloro-2-methyl-1H-benzo[*d*]imidazole (3d) (Table 1, Entry-4): (Protan, Mass and IR spectrum **FIG- 12, 13 & 14)**



Yield (%) : 76

M.P (^{o}C) : 210-212

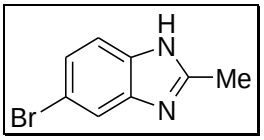
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.58 (s, 3H, -CH_3), 7.10 (d, 1H, Ar-H, J = 7.7 Hz), 7.40 (d, 1H, Ar-H, J = 7.7 Hz), 7.46 (s, 1H, Ar-H), 7.58 (br s, 1H, -NH).

Mass (ESI) : 167 (M^{+}+H).

CHN-Analysis : Anal. Calcd. for $C_8H_7ClN_2$: C, 57.65; H, 4.25; Cl, 21.27; N, 16.83%.Found: C, 57.64; H, 4.23; Cl, 21.29; N, 16.84%.

5-Bromo-2-methyl-1H-benzo[*d*]imidazole (3e) (Table 1, Entry-5):



Yield (%) : 71

M.P (^oC) : 224-226

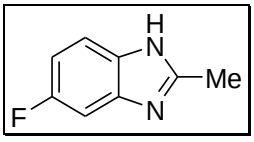
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^1H NMR (DMSO-d_6-300 MHz) : δ 2.59 (s, 3H, -CH_3), 7.25 (d, 1H, Ar-H, *J* = 7.3 Hz), 7.38 (d, 1H, Ar-H, *J* = 7.3 Hz), 7.52 (s, 1H, Ar-H), 7.64 (br s, 1H, -NH).

Mass (ESI) : 210 (M^++H).

CHN-Analysis : Anal. Calcd. for $C_8H_7BrN_2$: C, 45.51; H, 3.36; Br, 37.85; N, 13.28%.Found: C, 45.53; H, 3.33; Br, 37.84; N, 13.29%.

5-Fluoro-2-methyl-1*H*-benzo[*d*]imidazole (3f) (Table 1, Entry-6):



Yield (%) : 70

M.P (^oC) : 178-180

I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

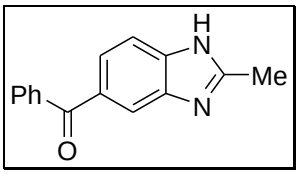
^1H NMR (DMSO-d_6-300 MHz) : δ 2.55 (s, 3H, -CH_3), 6.87 (d, 1H, Ar-H, *J* = 7.3

Hz), 7.15 (d, 1H, Ar-H, *J* = 7.3 Hz), 7.40 (s, 1H, Ar-H), 7.98 (br s, 1H, -NH).

Mass (ESI) : 151 (M^++H).

CHN-Analysis : Anal. Calcd. for $C_8H_7FN_2$: C, 63.97; H, 4.71; F, 12.63; N, 18.69%. Found: C, 63.96; H, 4.73; F, 12.64; N, 18.67%.

(2-Methyl-1*H*-benzo[*d*]imidazol-5-yl)(Phenyl) methanone (3g) (Table 1, Entry-7):



Yield (%) : 65

M.P (^oC) : 210-212

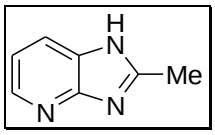
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.51 (s, 3H, -CH_3), 7.57-7.65 (m, 2H, Ar-H), 7.80-7.85(m, 4H, Ar-H), 7.898-7.97 (m, 1H, Ar-H), 8.20 (d, 1H, Ar-H, *J* = 9.0 Hz), 11.91 (broad s, 1H, -NH).

Mass (ESI) : 237 (M^++H).

CHN-Analysis : Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.13; N, 11.82%. Found: C, 76.23; H, 5.15; N, 11.80%.

2-Methyl-1*H*-imidazo [4, 5-*b*] pyridine (3h) (Table 1, Entry-8):



Yield (%) : 70

M.P (^{o}C) : 193-195

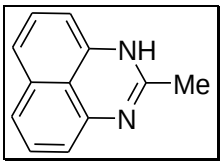
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.70 (s, 3H, -CH_3), 6.88-6.93 (m, 1H, Ar-H), 7.19 (dd, 1H, Ar-H, J = 7.7 Hz, 1.133 Hz), 7.23-7.29 (m, 1H, Ar-H).

Mass (ESI) : 134 (M^{+}+H).

CHN-Analysis : Anal. Calcd. for $C_7H_7N_3$: C, 63.12; H, 5.31; N, 31.51%. Found: C, 63.11; H, 5.33; N, 31.50%.

2-Methyl-1*H*-perimidine (3i) (Table 1, Entry-9):



Yield (%) : 65

M.P (^{o}C) : 211-213

I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

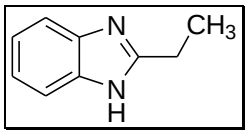
^{1}H NMR (DMSO-d_6-300 MHz) : δ 2.09 (s, 3H,-CH_3), 6.35-6.57 (m, 2H, Ar-H), 6.90-7.26 (m, 4H, Ar-H).

Mass (ESI) : 183 (M^{+}+H).

CHN-Analysis : Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.12; H, 5.52; N,

15.36%. Found: C, 79.10; H, 5.53; N, 15.37%.

2-Ethyl-1*H*-benzo[*d*]imidazole (4a) (Table 2, Entry-1):



Yield (%) : 60

M.P (^{o}C) : 178-180

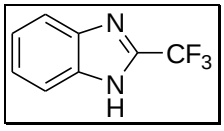
I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 1.31 (t, 3H, -CH_2CH_3, J = 7.1), 2.73 (q, 3H, Ar-CH_2CH_3, J = 7.1), 6.12 (br s, 1H, NH), 7.15-7.23 (m, 1H, Ar-H), 7.61 (d, 1H, Ar-H, J = 6.7 Hz), 7.76-7.87 (m, 1H, Ar-H), 8.04 (d, 1H, Ar-H, J = 6.7 Hz).

Mass (ESI) : 147 (M^{+}+H).

CHN-Analysis : Anal. Calcd. for $C_9H_{10}N_2$: C, 73.92; H, 6.93; N, 19.16%. Found: C, 73.91; H, 6.95; N, 19.15%.

2-(Trifluoromethyl)-1*H*-benzo[*d*]imidazole (4b) (Table 2, Entry-2):



Yield (%) : 65

M.P (^{o}C) : 210-212

I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

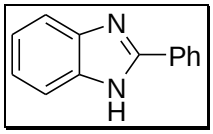
^{1}H NMR (DMSO-d_6-300 MHz) : 7.38-7.58 (m, 2H, -CH_3), 7.67 (t, 1H, Ar-H, J =

7.9 Hz), 7.86 (d, 1H, Ar-H, J = 7.7 Hz).

Mass (ESI) : 187 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_8H_5F_3N_2$: C, 51.64; H, 2.70; F, 30.63, N, 15.03%. Found: C, 51.61; H, 2.72; F, 30.64, N, 15.05%.

2-Phenyl-1*H*-benzo[*d*]imidazole (4c) (Table 2, Entry-c):



Yield (%) : 63

M.P (^oC) : 290-292

I.R (KBr-cm^{-1}) : 3400-3600 (-NH).

^{1}H NMR (DMSO-d_6-300 MHz) : δ 7.19-7.26 (m, 2H, Ar-H), 7.41-7.53 (m, 3H, Ar-H), 7.56-7.64 (m, 2H, Ar-H), 8.18-8.23 (m, 2H, Ar-H).

Mass (ESI) : 195 (M^++H).

CHN-Analysis : Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.36; H, 5.21; N, 14.43%. Found: C, 80.34; H, 5.20; N, 14.46%.

4.6. Conclusion:

In conclusion, we have widened a practical and novel procedure for the selective synthesis of 2-substituted benzimadazoles derivatives by using Microwave irradiation technique and, commercially available Gadolinium triflate as a catalyst under the neat reaction conditions. The present procedure has several advantages; mild reaction conditions, nonhazardous method, experimental easy and simple workup process and less reaction time compared to conventional methods.

4.7. Spectrums:

Compound 3d (Table -1, entry -2): ^{1}H NMR spectrum

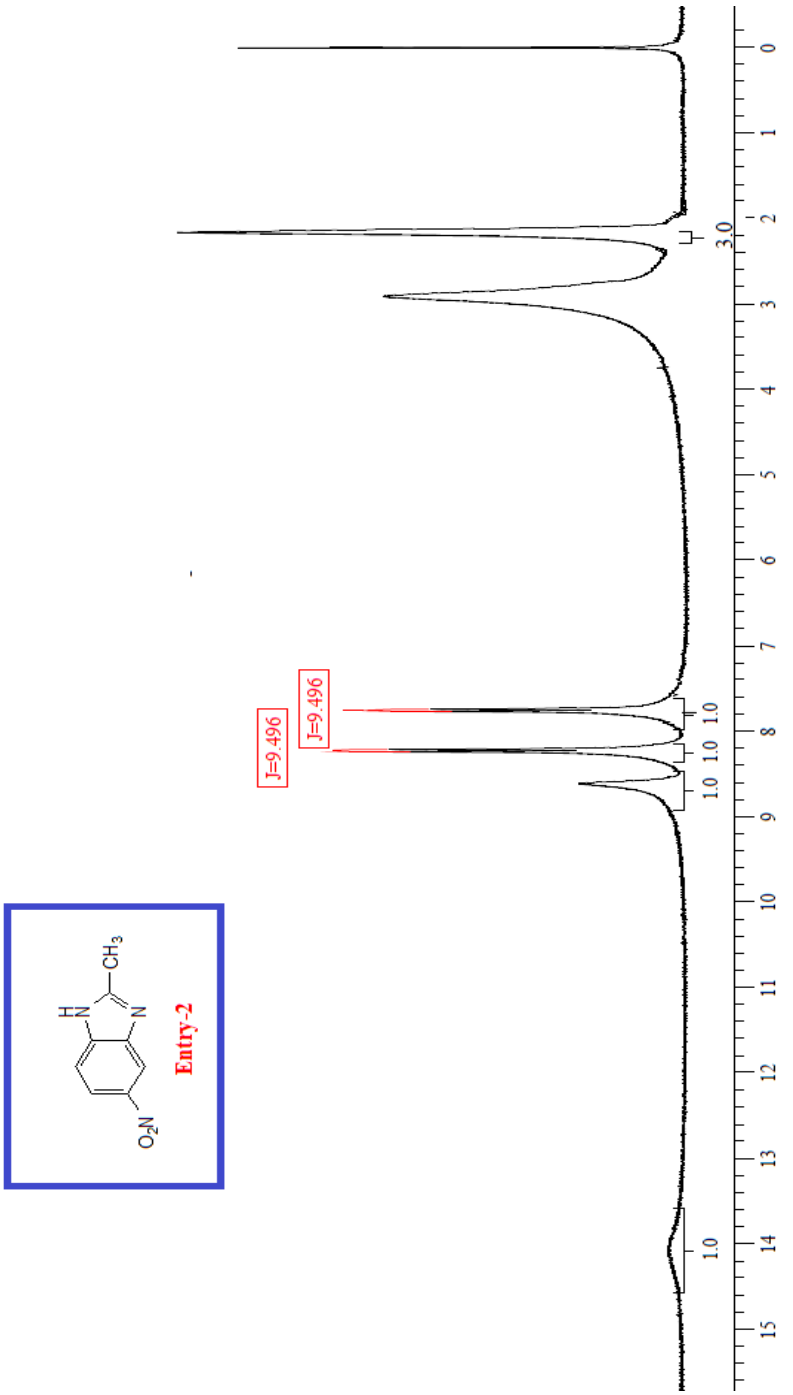


FIG -9: ^{1}H NMR spectrum of compound 3b (DMSO-d_6, 300MHz) (Table -1, entry-2)

Compound 3d (Table-1, entry-4): Mass spectrum

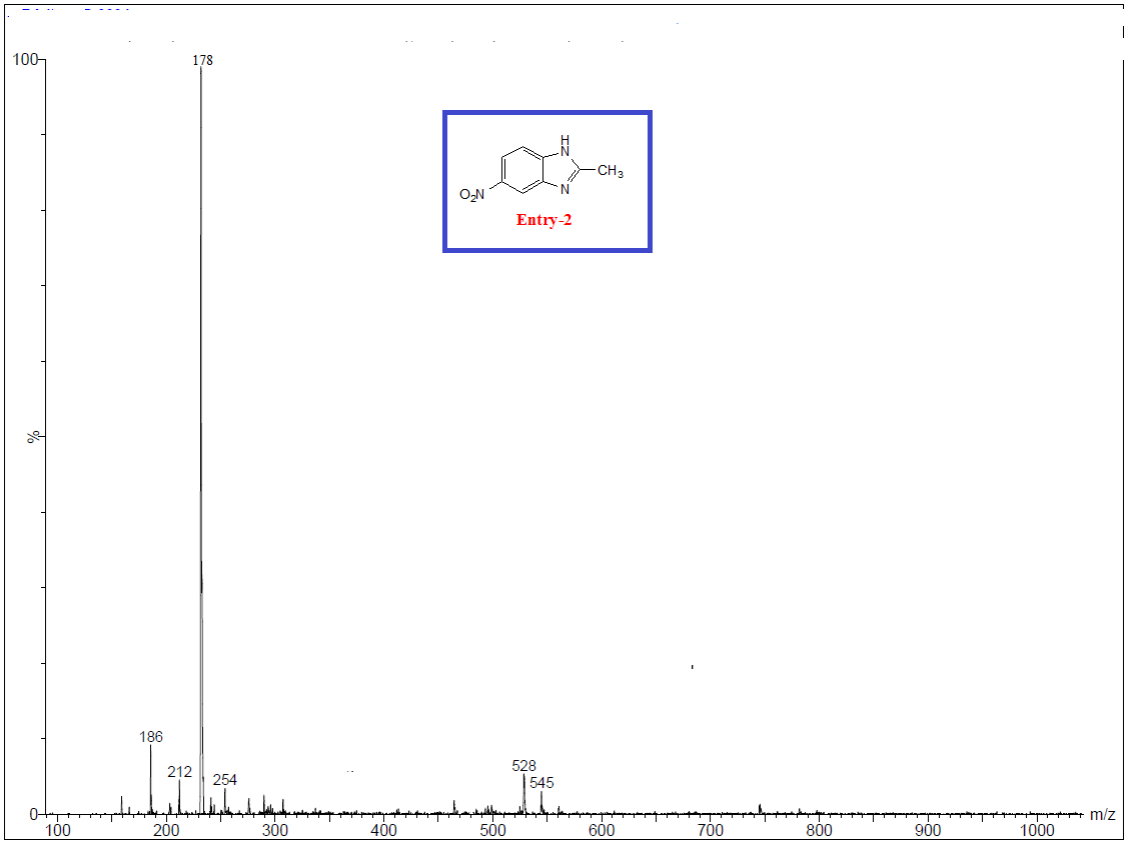


FIG -10: ESI-MS spectrum **of compound 3b (Table -1, entry-2)**

Compound 3d (Table-1, entry-4): IR spectrum

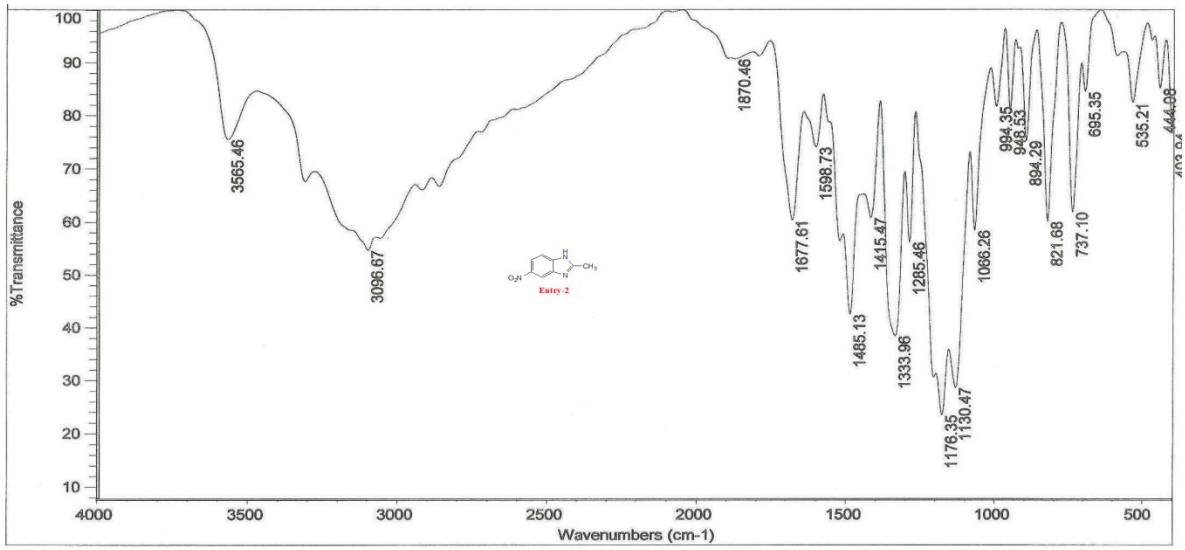


FIG-11: IR spectrum of compound 3b (Table-1, Entry -2)

Compound 3d (Table -1, entry -4): ^{1}H NMR spectrum

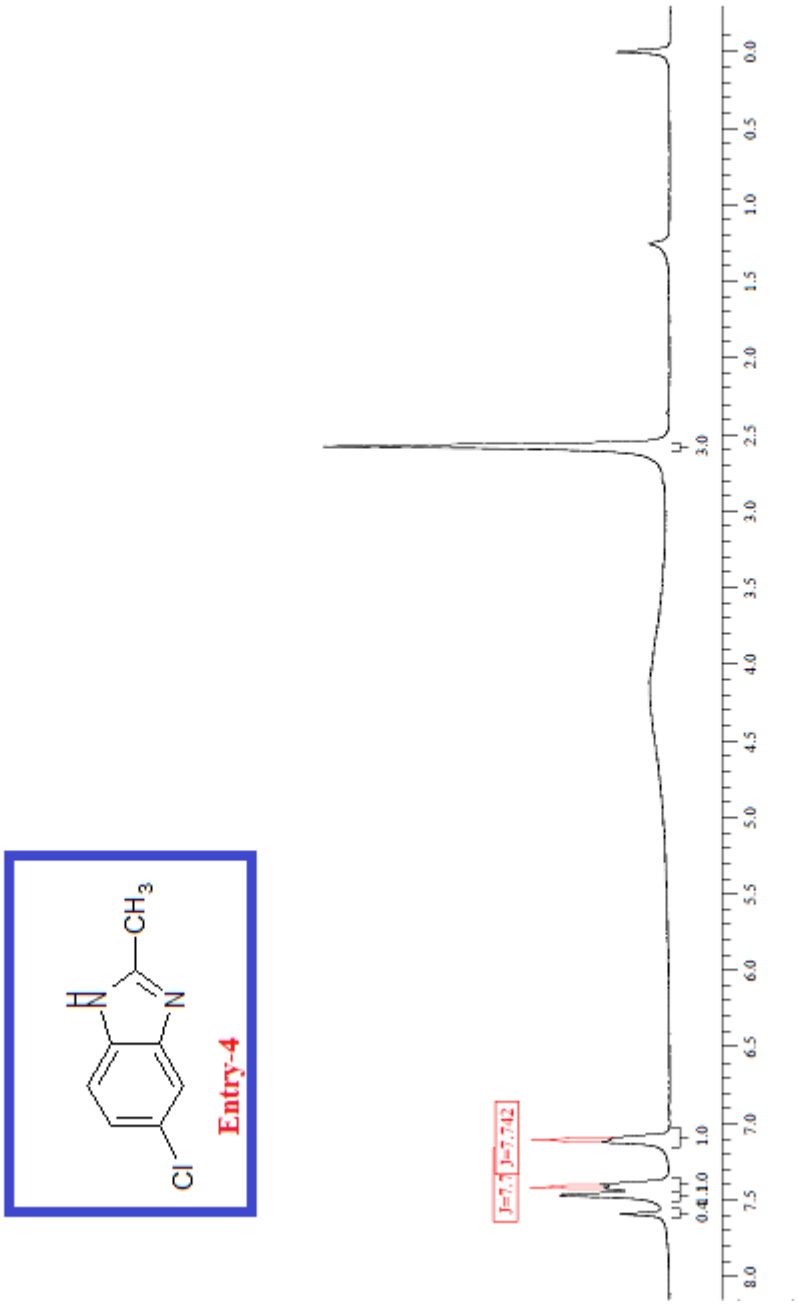


FIG -12:^{1}HNMR spectrum of compound 3d (DMSO-d_6, 300MHz) (Table-1, Entry -4)

Compound 3d (Table-1, entry-4): Mass spectrum

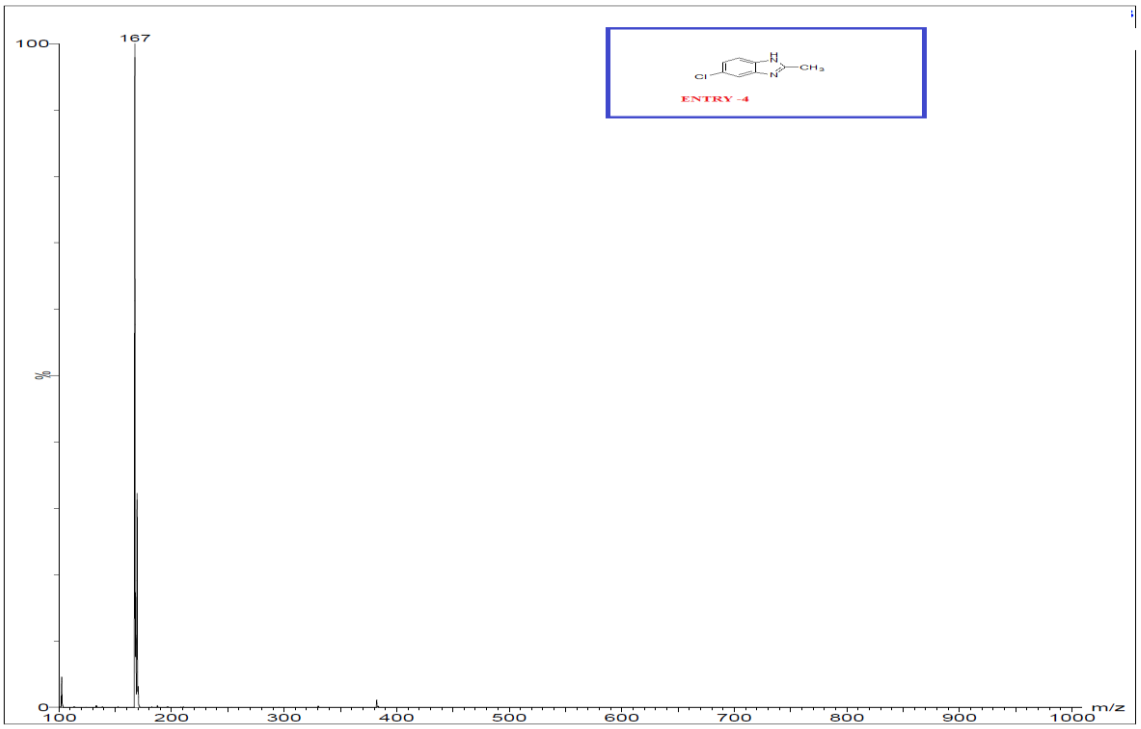


FIG- 13: ESI-MS spectrum of compound 3d (Table-1, entry-4)

Compound 3d (Table-1, entry-4): IR spectrum

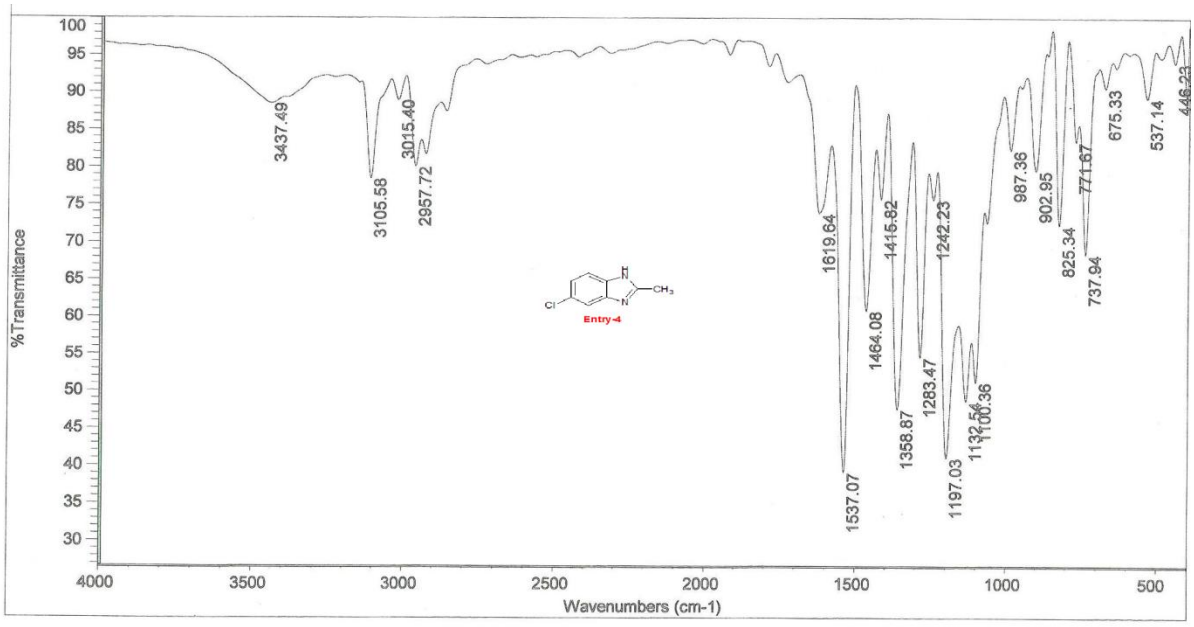


FIG- 14: IR spectrum of compound 3d (Table-1, entry-4)

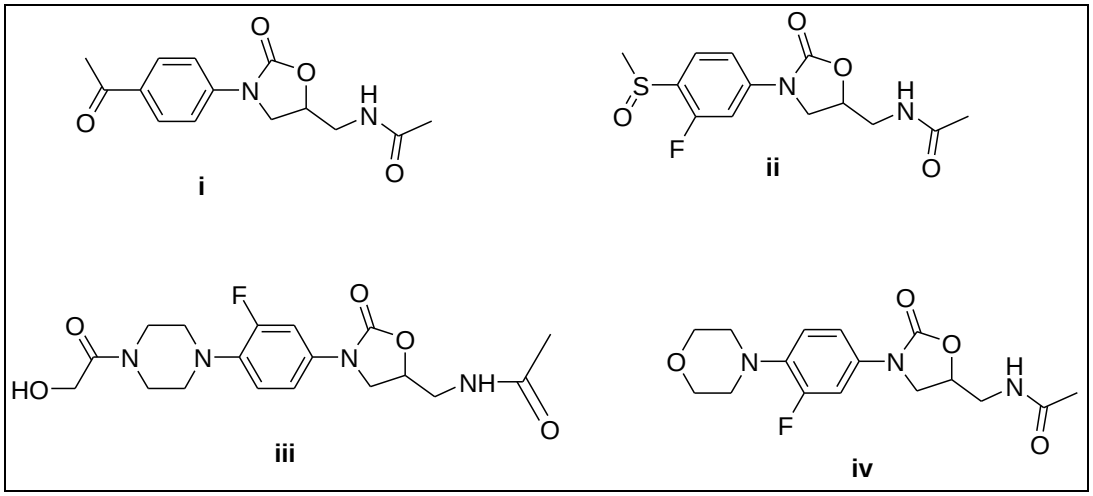
CHAPTER 5

Synthesis of antitubercular and antibacterial activity of new oxazolidino-Amides/sulfonamides conjugates

5.1 Introduction:

Nosocomial infections or Hospital-acquired infections are related with severe complications. Bacterial pathogens which are the causative agents for this infection have resistance to one or more antibiotics (Martone et al, 1998). Patients suffering from these infections do not respond to general antibiotic treatment. The majority of these infections are caused by Gram positive pathogens; among them most problematic are methicillin-resistant *Staphylococcusepidermidis*, vancomycin-resistant *Enterococcus faecium* (VRE), *Staphylococcus aureus* (MRSA), and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Furthermore, certain Gram negative strains like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* also develops drug-resistance towards leading antibiotics (Fridkin et al, 2001 and Whitney et al, 2003). To prevent these alarmingly emerging multidrug-resistance and total drug-resistance strains, there is an urgent requirement for the development of new antibiotics. It must follow a different mode of action to avoid problems of shared cross-resistance between prior therapeutic agents.

The discovery of the novel oxazolidinones [DuP-721 (**i**), DuP-105 (**ii**)] in the 1980's led to the development of a new class of synthetic antibiotics (Hutchinson et al, 2001 and Ford et al, 2001). The eperezolid (**iii**) and linezolid (**iv**) clinical candidates have been developed and discovered by Upjohn Company (Barbachyn et al, 1995). These compounds display excellent activity against Gram-positive bacteria as well as several anaerobes and *Mycobacterium tuberculosis*. Approved by PDA, in 2000, linezolid was introduced into the market for the treatment of community acquired nasocomial infections. Linezolid was the first synthetic antibiotic launched into the market after 40 years (Moise et al, 2002 and Peppard et al, 2006). However, linezolid has been reported to show certain side effects that includes diarrhoea, nausea, headache http://www.pfizer.com/ files/priducts/uspi zyvox.pdf. and the prolonged usage (more than 2 weeks) of it is associated with reversible myelosupperssion (Kuter et al, 2001) , Tactic acidosis (Apodaca et al, 2003) , peripheral and opticalneuropathies (Bressler et al, 2004 , Wigen et al, 2002, Bergeron et al, 2005 and Gillman et al, 2003).



5.1.1. Mode of action

The oxazolidinones appears to have a unique mechanism of action. The oxazolidinones are inhibitors of bacterial ribosomal peptide synthesis, but unlike other antimicrobial agents that target ribosome by interfering in the first step of bacterial ribosomal assembling process (Matassaova et al, 1999). Oxazolidinones bind to the *P* site of 5O'S subunit, where 5O'S sub-unit interface with the 30'S unit and thus prevent the formation of a 70'S initiation complex (Lin et al, 1997) , which includes *N*-formylmethionyl tRNA (fMet-tRNA), messenger RNA (mRNA), and two ribosomal subunits. No other known antimicrobial agents inhibits this process, therefore there is no cross-resistance (Aoki et al, 2002, Bobkova et al, 2003 and Parket al, 1992).

5.1.2. Structure-activity-relationship

The early structure-activity-relationship (SAR) points out significant features of the oxazolidinone pharmacophore that are (i) the optimal activity of a C-5 acetamidomethyl group, (ii) the importance of the *N*-aryl group, (iii) the requirement of *S*-configuration at C-5 position, (iv) additional substitutions at the aryl ortho position or C-4 of oxazolidinone ring for best effect on the antibacterial activity and (v) electron-withdrawing groups in the aryl Para position (Figure-1). On the SAR studies of oxazolidinone several revisions have been made, the most interesting ones are finding the appropriate electron-donating amino substituent on the phenyl ring that can contribute to excellent antibacterial activity. Another important result is the potent

effect of one or two fluorine atoms flanking the morpholine or piperazine ring (Joseph et al, 2008).

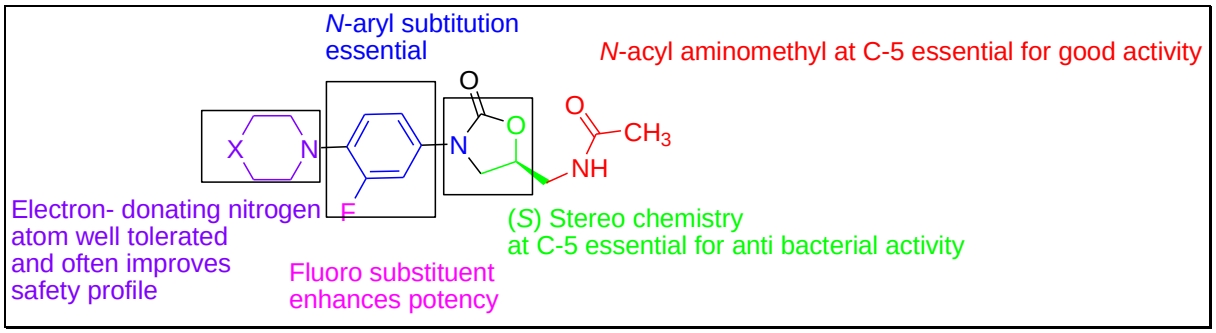


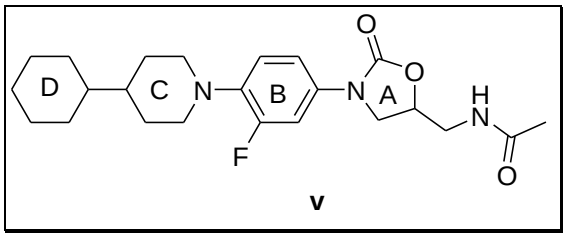
Figure-1

5.1.3. Resistance to oxazolidinone

As oxazolidinones does not belongs to natural product class the microbial community has not been exposed to this chemical scaffold in the past. Therefore, oxazolidinones resistance is far rare and hence, occurrences of ribosomal mutations are rare and the presence of multiple 23's rRNA gene makes homozygocity. But genera of *Enterococcus*, and *Staphylococcus* have shown some resistance towards linezolid (MIC > 8 μg/mL) (Johnson et al, 2002 and Tsiodras et al, 2001). This is due to resistance that occurs because of site mutations in the domain V region of the 23'S rRNA. Linezolid resistance has been associated with G-U mutation at position 2576 of the 23'S rRNA (Quesnella et al, 2005).

5.1.4. EARLIER WORK

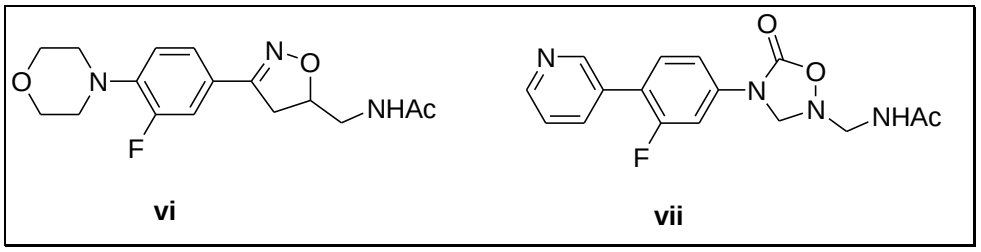
The basic oxazolidinone pharmacophore **(v)** contains A-ring with "*S* "configuration at C-5 side-arm with an acetamide substituent. Ring B can be aromatic or heterocyclic. However, aromatic ring such as phenyl with fluorine as substituent on it's often improving activity. Similarly ring C based can be aliphatic or aromatic or fused aromatic. Extensive works have been done on the modifications at this position of oxazolidinones. Here some of the reports on modification of the different rings and side chain are discussed.



v

(i)A-ring modifications

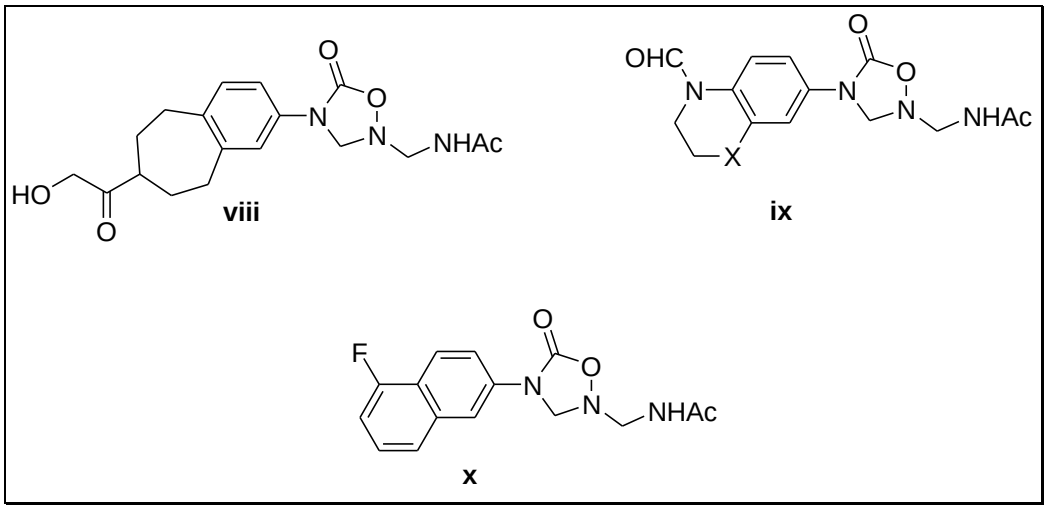
Barbachyn and co-workers have reported isoxazolinones as replacement for the isooxazolidinone A-ring **(VI)**. These analogs have displayed comparative antimicrobial activity with linezolid. All these analogs lack the C-2 carbonyl group. However, Bristol - Myers has reported C-2 carbonyl containing isooxazolinones (**vii**) (Sakoulas et al, 2003) which have shown similar activities of oxazolidinone.



vi **vii**

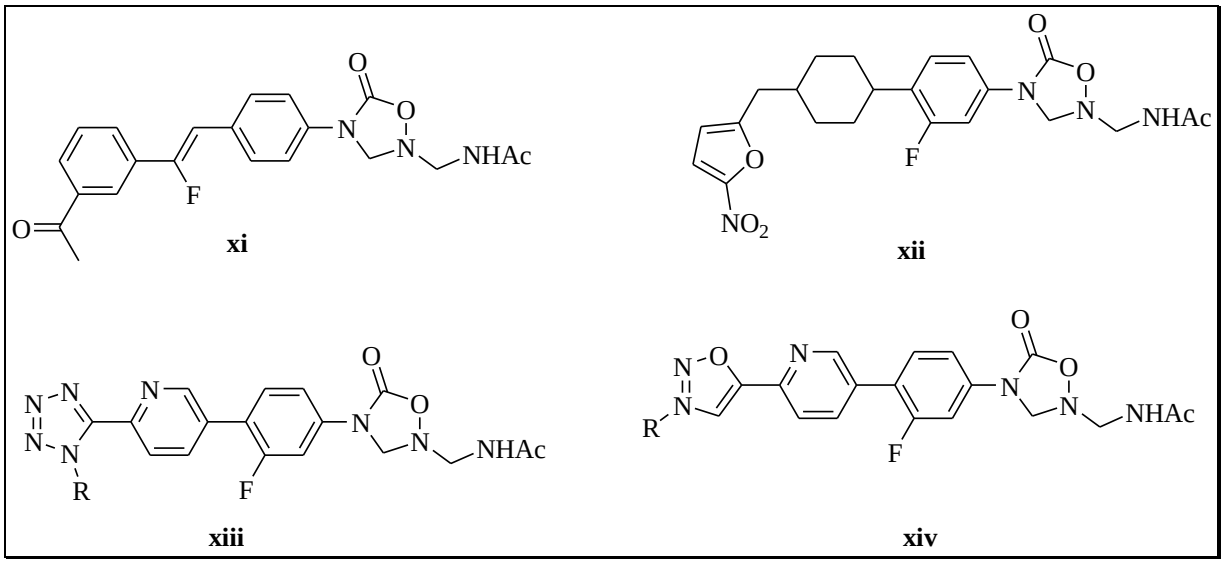
(ii) B-ring modifications

In addition to modifications on ring A, *Barbachyn and coworkers* have separately reported C ring fused B-ring bicyclic oxazolidinones **(viii, ix) (**Sbardeila et al, 2004) that have shown comparable activity with linezolid. A replacement of the B-ring of oxazolidinone with a pyrrole ring **(x)** has been reported by Sbardella and co-workers. However, the synthesized linezolid derivatives congeners were many folds less active then linezolid (Ciske et al, 2003).

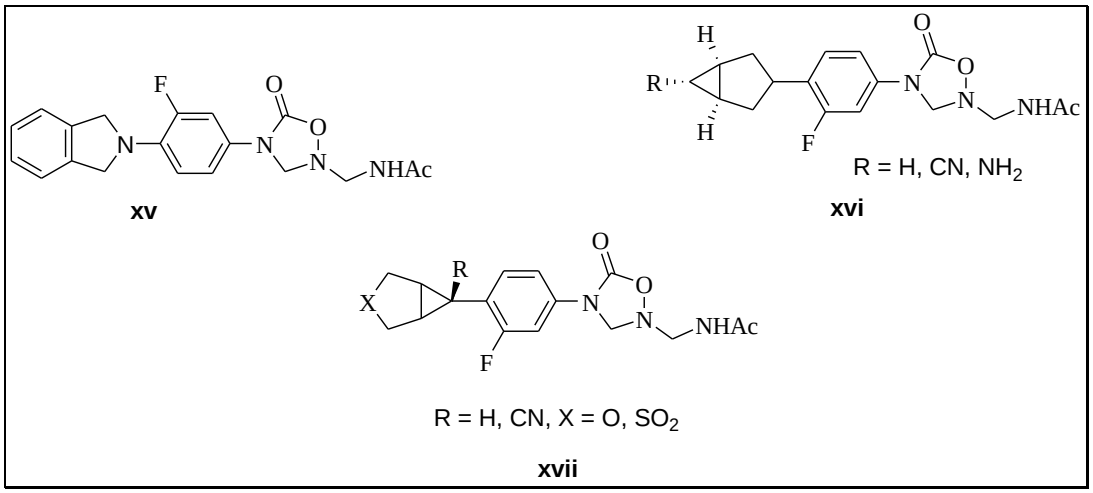


(iii) C-ring modifications

The 40 position (C-ring) of phenyloxazolidinones is the most attractive position for improvising the antimicrobial activity. Extensive works have been done on the modifications at this position of oxazolidinones. Researchers from *Ranbaxy laboratories* have prepared a clinical candidate ranbezolid (**xi**) (Selvakumar et al, 2003) which contains nirofuran ring system. A research group from *Abbot Laboratories* has used less flexible fluoroalkenes spacer between B and C rings (**xii**) (Bush et al, 2004). Potent oxazolidinones which contains incorporation of tetrazoles (**xiii, DA-7867**) and isoxazoles (**xiv**) has been reported separately by researchers at Dong-A and AstraZeneca (Lee et al, 2003).

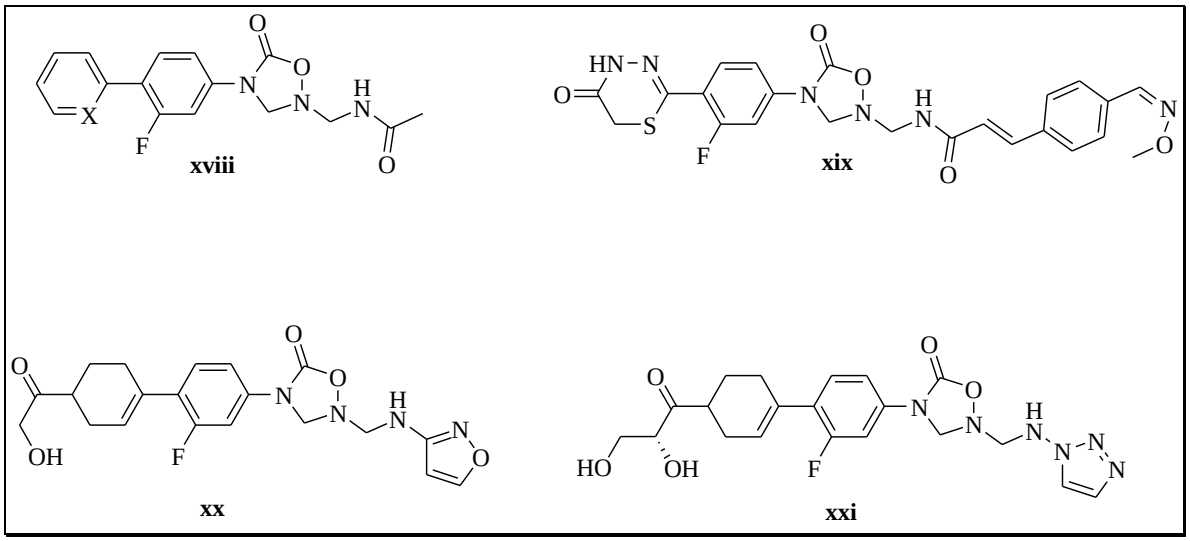


Pagetand and co-workers have reported the preparation of novel pyrroloaryl system (**xv**) (Paget et al, 2003) by modifications at C-ring that have exhibited **8** fold more activity than linezolid. Kyorin/Merck group have reported for the first time the replacement of the piperazine moiety by azabicyclo [3.1.0] hexylphenyl moiety (**xvi**). Researchers from Pfizer and Vicuron have also reported same class of bicycle [3.1.0] hexylphenyl oxazolidinones (**xvii**).



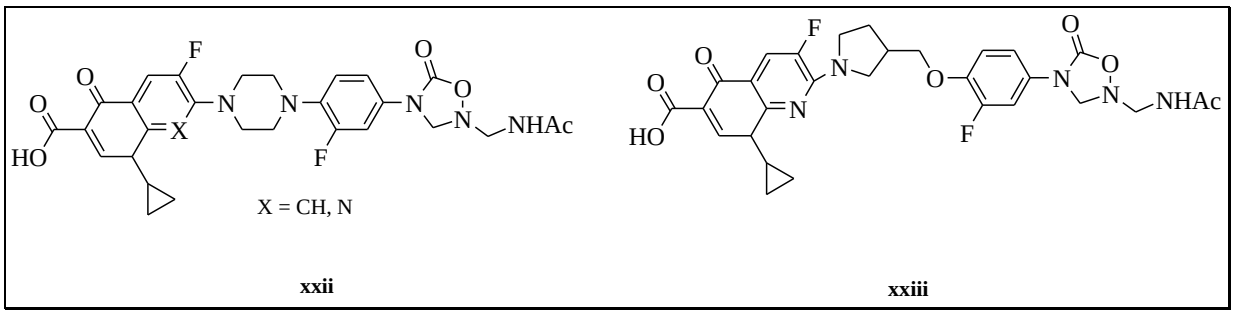
(iv) C-5 side chain modifications

Riedl et al, 1997 *and co-workers* have introduced thioacetamide and thiocarbamate (**xviii**) group at C-5 position of oxazolidinone instead of acyl amine group and these analogs have exhibited improved antimicrobial activity. Researchers at *Vicuron* have synthesized novel C-5 modified, cinnamic acid amide (**xix**) oxazolidinones. *Gravestock and co-workers* have recently reported oxazolidinone **(xx)** with isoxazole heterocyclic incorporated at C-5 side arm (Reck et al, 2005). Researchers in *AstraZeneca* have prepared azoles containing oxazolidinones by using click chemistry (**xxi**) (Gravestock et al, 2004).



(v) Oxazolidinone hybrids

Chemists at *Vicuron and Pfizer* have prepared novel oxazolidinone-ciprofloxacin hybrids, in which piperazine unit joins these two pharmocophores (**xxii-xxiii**) (Hubschwerlen et al, 2003). Analogs of this type exhibit broad spectrum of antibacterial activity, which includes linezolid and fluroquinone-resistant bacteria.



Objectives

i) To synthesize hetrocyclic derivatives containing oxazolidinones nucleus derrivatives.

ii) To synthesize the C-ring modified oxazolidinone targeted compounds.

iii) To synthesize the C-5 substituted oxazolidinone targeted compounds.

iv) To establish the structure on the basis of NMR spectra and Mass spectra.

v) To evaluate biological activity of targetd compounds.

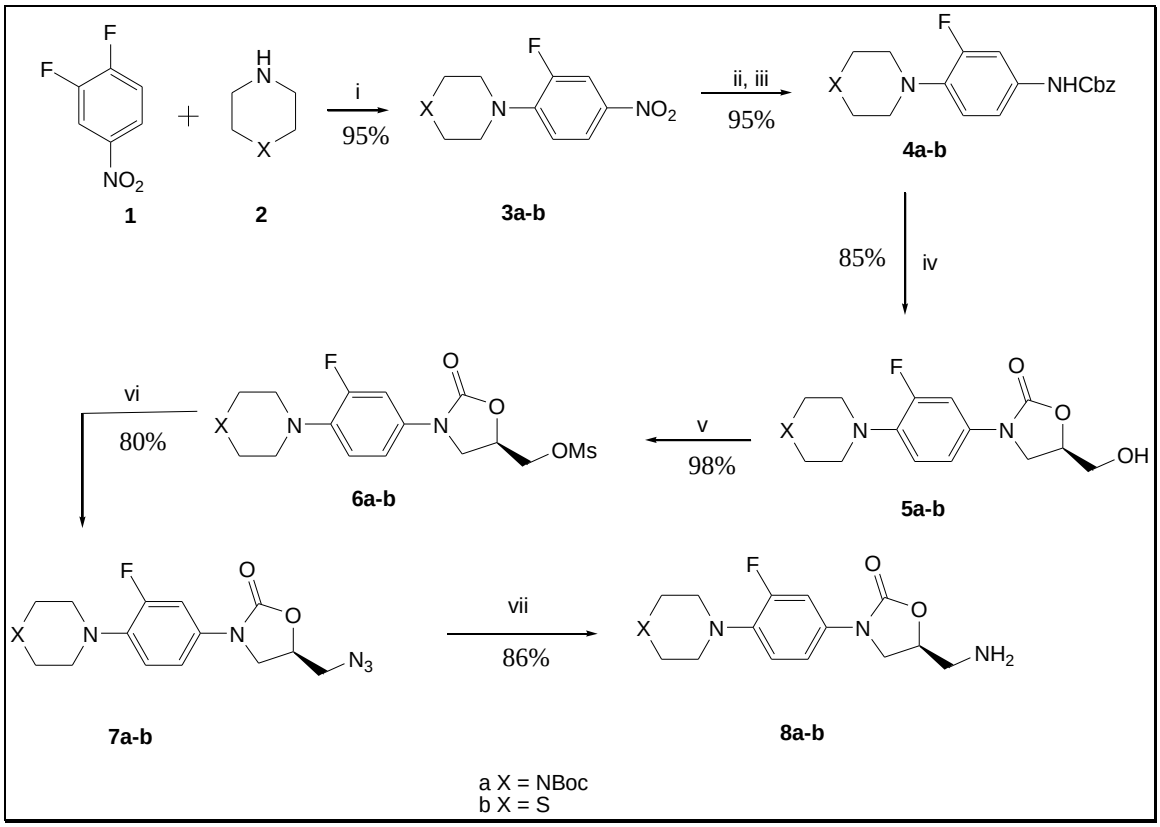
5.2. Present work:

The unique mode of action combined with a high potential of antimicrobial activity of oxazolidinones, has prompted us to investigate new molecules with enhanced activity based on them. In this present investigation an attempt has been made to synthesize a novel series of C-ring modified and C-5 substituted modified oxazolidino-arylamido/sulphonamides analogs. In the present work the main focus has been on improving the activity and limiting the cytotoxicity of oxazolidinone based derivatives. The present work describes the synthesis and evaluation of bacterial and anti-tubercular activity of oxazolidino-aryl amides and sulphonamide conjugates particularly for drug resistance bacteria.

5.2.1. Chemistry, Results and Discussion:

The preparation of intermediates oxazolidinyl methyl amines (**8a** and **8b**) have been carried out by the synthesis sequence illustrated in **Scheme 1**. The treatment of commercially available *tert*-butyl piperazine-1-carboxylate (**2**) with 3, 4-difluoronitrobenzene (**1**) in acetonitrile in the presence of diisopropyl ethyl amine under reflux at 80^{o}C affords the compounds **3a-b**. The nitro compounds in the presence of stannous chloride are reduced to their corresponding amines and protected with chlorobenzoyl format (CBZ) to afford compounds **4a-b**. The benzyloxy *N*-protected compounds (**4a-b**) have been treated with (*R*)-glycidyl butyrate in presence of n-butyl lithium at -78 ^{o}C to gives compounds oxazolidinyl methanol (**5a-b**). The intermediates **5a-b** treated with methyl sulfonyl chloride in the presence of triethyl amine in dichloromethane as solvent affords compounds **6a-b**. The mesylated intermediates further undergoes in SN^2 nucleophilic substitution by azide in presence of sodium azide under reflux in dimethyl formamide to afford oxazolidinone azide **7a-b**. Further, on reduction in presence of hydrogen and palladium in ethyl acetate, azide (**7a-b**) converted to corresponding amines (**8a-b)**.

Synthesis of (*R*)-tert-Butyl-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (8a-b):



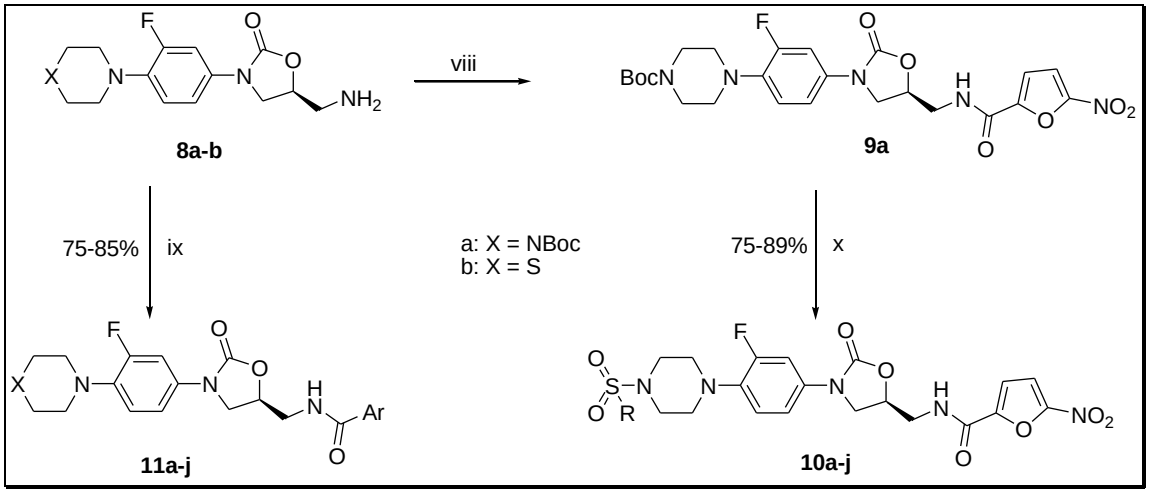
Reagents and conditions: (i) ACN, DIPEA, reflux, 3 h; (ii) $SnCl_2$, methanol, 12 h; (iii) benzylchloroformate, acetone, aq.$NaHCO_3$, 12 h; (iv) (*R*)-glycidyl butyrate, THF, n-BuLi, -78^o C to rt, 12 h; (v) MsCl, DCM, TEA, 5 h; (vi) NaN_3, DMF, reflux, 5 h; (vii) H_2, Pd, methanol, 2 h.

Scheme-1

The sequential reactions as described above were carried out starting from **3b** and the product **8b** was isolated and characterized.

The synthesis of target compounds **10a-j** and **11a-j** have been achieved by the procedure described in **Scheme 2**. The amine intermediates (**8a-b**) on coupling reaction with different acids and sulfonyl chlorides to afford final conjugates. The oxazolidinone amines (**8a-b**) treated with 5-nitro furoic acid in the presence of coupling reagent EDC in dry CH_2Cl_2 afforded the amide coupled compound **9a**. Further the deprotection of intermediate (**9a**) by $BF_3.Et_2O$ in CH_2Cl_2 followed by treatment with different sulfonyl chlorides in dry pyridine at room temperature afforded C-5 substituted modified oxazolo sulphonamides analogs (**10a-j**). Similarly, the intermediate (**8a**) in the presence of amide coupling reagent l-ethyl-3-(3-

dimethylaminopropyl) carbodiimide (EDC) in CH_2Cl_2 treated with various aromatic acids to afford final conjugates **11a-j** in significant yields.



Scheme-2

Reagents and conditions: (viii) 5-nitro furoic acid, EDC, CH_2Cl_2 , rt, 8h; (ix)Aryl / heteroaryl acid , EDC, CH_2Cl_2 , rt, 8h; (x) a) $BF_3.Et_2O$, CH_2Cl_2, rt ; b) sulfonyl chloride, pyridines, rt, 2h.

Table-1: C-ring modified and C-5 substituted modified oxazolidino-arylamido/ Sulfonamides Analogs (10a-j) and (11a-j).

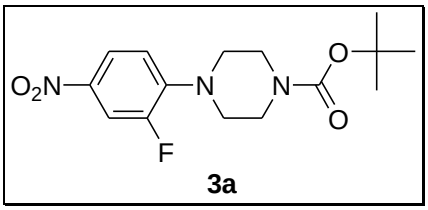
Entry	Comp.No	R or Ar
1	**10a**	(*E*)-2, 3-Diphenylacryloyl
2	**10b**	Benzofuran-3-carbonyl
3	**10c**	Pyrazine-2-carbonyl
4	**10d**	3-chloro-5-Methylbenzo [*b*]thiophene-2-Carbonyl
5	**10e**	(*E*)-3-(5-(4-chlorophenyl)furan-2-yl)acryloyl
6	**10f**	N-Boc piperazinoyl, X =S
7	**10g**	N-Boc piperazinoyl, X =NBoc

8	**10h**	Pyrazine-2-carbonyl, X = NBoc
9	**10i**	5-methyl-1*H*-indole-2-carbonyl
10	**10j**	2-chloronicotinoyl
11	**11a**	Methyl
12	**11b**	4-Methylphenyl
13	**11c**	4-Acetylphenyl
14	**11d**	3-Trifluoromethylphenyl
15	**11e**	4-Methoxyphenyl
16	**11f**	4-Chlorophenyl
17	**11g**	4-Fluorophenyl
18	**11h**	2,4-Difluorophenyl
19	**11i**	3, 4-difluoropheny
20	**11j**	8-Quinolyl

5.3. Experimental procedure:

Preparation of tert-Butyl 4-(2-fluoro-4-nitrophenyl) piperazine-1-carboxylate (3a)

To a solution of 3, 4-difluoronitrobenzene **1** (3.1 gm, 2 mmol) and tert-butyl piperazine-1-carboxylate (**2a**) (5gm, 3 mmol) in dry acetone (30 ml), anhydrous potassium carbonate (1.1gm, 10 mmol) was added under N_2 atmosphere. The reaction mixture was stirred under reflux at 70^{o}C for 12 h. After monitoring the reaction mixture on TLC, the potassium carbonate was filtered over a celite pad and washed with ethyl acetate. The filtrate was distilled under reduced pressure and the residue obtained was re-dissolved in ethyl acetate. The organic layer was washed with brine solution and dried over Na_2SO_4. The solvent reduced under reduced pressure and residue was purified by column chromatography to give 5.8 gm of pure tert-butyl 4-(2-fluoro-4-nitrophenyl) piperazine-1-carboxylate **3a** as yellow solid in quantitative yield (95%).



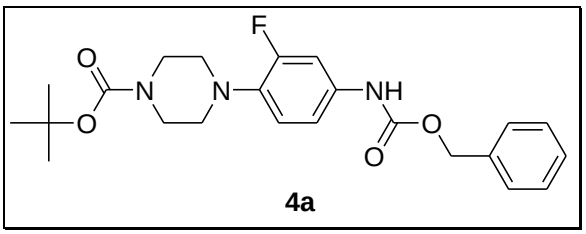
3a

^{1}H NMR and ESI mass of Compound 3a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (9H, s), 3.24(4H; t, *J* = 5.2Hz), 3.6 (4H, t, *J* = 4.5Hz), 6.91 (1H, t, *J* = 8.3Hz, 9.06 Hz), 7.89-7.94 (1H, dd, *J* = 3.02Hz), 7.97-8.0 (1H, dd, *J* = 1.5Hz, 3.02Hz); ESI-MS: m/z = 326 (M^+ + 1).

Preparation of *tert*-Butyl 4-(4-(benzyloxycarbonylamino)-2-fluorophenyl) piperazine-l-carboxylate (4a) (Mass spectrum of **4b FIG –15)**

To a solution of tert-butyl 4-(2-fluoro-4-nitrophenyl) piperazine-1-carboxylate (**3a**) was treated with stannous chloride in the presence of methnol gives *tert*-butyl 4-(4-amino-2-fluorophenyl) piperazine-1-carboxylate (3 gm, 10 mmol),it was taken in acetone (50 mL) and water (25 mL) at 0^{o}C (3.4 g, 40 mmol) of $NaHCO_3$ and then 2.0 ml (14 mmol) of benzyl chloroformate(CBz) were added. The reaction mixture was stirred overnight and then poured onto 50 ml of ice and 120 mL of water and the solid filtered and washed thoroughly with water (3 X 25 mL) to give 4.1 g of **4a** as a solid, which was purified by column chromatography by using ethyl acetate and hexane (3:7) as eluent affords compound **4a** Yields 95%.



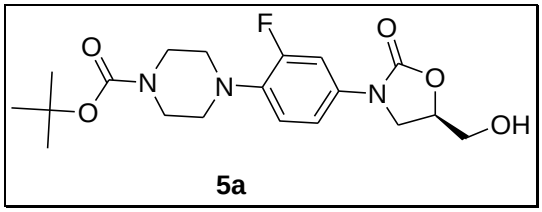
4a

^{1}H NMR of Compound 4a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (9H, s), 2.95 (4H, t, *J* = 4.9Hz, 4.7Hz), 3.57 (4H, t, *J* = 4.9Hz, 4.7Hz), 5.18 (2H, s), 6.67 (1H, s), 6.85 (1H, t, *J* = 8.8Hz, 8.8Hz), 6.95 (1H, d, *J* = 8.49Hz), 7.29-7.39 (6H, m); ESI-MS: *m/z* = 430 (M^+ + 1).

Preparation of (*R*)-*tert*-Butyl 4-(2-fluoro-4-(5-(hydroxymethyl)-2-oxooxazolidin-3-yl) phenyl) piperazine-1-carboxylate (5a)

To a solution of (4.0 g, 1.0 mmol) of **4** in tetrahydrofuran (20 mL) under nitrogen at -78^{o}C was added *n*-butyllithium (7.7 mL, 1.6 M in hexane, 1.0 mmol) over 20 min *via* syringe. The reaction mixture was stirred at -78^{o}C for 35 min, and then a tetrahydrofuran solution (2.5 mL) of (*R*)-glycidyl butyrate (1.8 mL, 1.2 mmol) was added in a drop wise fashion *via* syringe, over 30 min. After stirring at -78^{o}C for 1 h, the bath was removed and the reaction mixture was stirred at room temperature over night. The reaction was then quenched with saturated ammonium chloride (5 mL), ethyl acetate (30 mL), and water (30 mL) was added, the phases were separated, and the aqueous portion was extracted with ethyl acetate (3 X 300 mL). The combined organic portions were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated to give **5a** as a yellow solid. This was purified by column chromatography employing ethylacetate, hexane (1:1) as eluent affords compound **5a** (3.0g) Yield: 85%.



5a

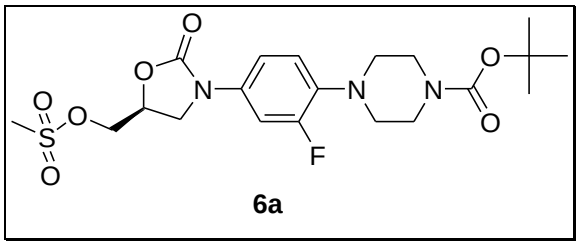
^{1}H NMR and ESI mass of Compound 5a (Mass spectrum of 5b **FIG-16)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (9H, s), 2.98 (4H, t, *J* = 4.53 Hz), 3.57 (4H, t, *J* = 4.53 Hz), 3.72 (1H, dd, *J* = 3.7Hz, 3.02 Hz), 3.9-4.0 (3H, m), 4.73 (1H, m), 6.90 (1H, t, *J* = 9.06Hz), 7.12 (1H, dd, *J* =3.02 Hz), 7.41 (1H, dd, *J* = 3.02 Hz); ESI-MS: *m/z* = 396 (M^+ + 1).

Preparation of (*R*)-*tert*-Butyl-4-(2-fluoro-4-(5-((methylsulfonyloxy) methyl)-2-oxooxazolidin-3-yljphenyl) piperazine-1-carboxylate (6a)

A solution of (*R*)-*tert*-Butyl 4-(2-fluoro-4-(5-(hydroxymethyl)-2-oxooxazolidin-3-yl)phenyl) piperazine-l-carboxylate **(5a)** (3g, 7.5 mmol) in dry CH_2Cl_2 (25 ml) was cooled in an ice bath, and treated with triethyl amine (6.38 ml, 3 mmol) and methanesulfonyl chloride (3.6 g, 2.48 ml). After completion of reaction (2h), the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water,

saturated aqueous $NaHCO_3$, and brine. The organic layer was then dried (Na_2SO_4), concentrated in vacuum at 30±5 °C to afford a white solid **(6a)** Yield 4.4g, 98%.



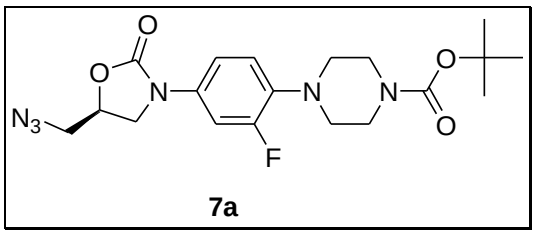
6a

^{1}H NMR and ESI mass of Compound 6a (Mass spectrum **FIG- 17)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 2.98 (4H, t, *J* = 4.5Hz), 3.11 (3H, s), 3.59 (4H, t, *J* = 4.5Hz), 3.9 (1H, dd, *J* = 6.7Hz, 2.26 Hz), 4.12 (1H, t, *J* = 9.06 Hz), 4.39-4.53 (2H, m), 4.90 (1H, m), 6.93 (1H, t, *J* = 9.05Hz), 7.08 (1H, d, *J* = 8.3 Hz), 7.42 (1H, dd, *J* = 3.02 Hz, 2.26 Hz); ESI-MS: *m/z* = 474 (M^+ + 1).

Preparation of (*R*)-*tert*-Butyl-4-(4-(5-(azidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-l-carboxylate (7a)

A mixture of 3.0g (6.3mmol) of ((*R*)-*tert*-Butyl-4-(2-fluoro-4-(5-((methyl sulfonyloxy) methyl)-2- oxooxazolidin-3-yl) phenyl) piperazine-1-carboxylate **(7a)** and 1.6 g (25.36 mmol) of sodium azide in 10 mL of dimethyl formamide was heated at 75^{o}C for 16 h,and reaction mass cooled to 30±5°C , water (50 mL) and ethyl acetate (30 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give 2.3 g of compound **(7a)**, which was not purified.



7a

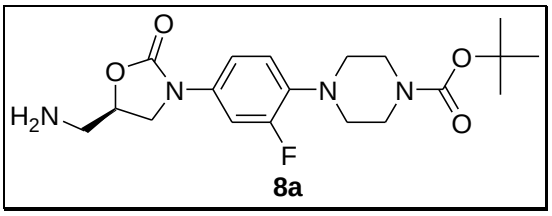
^{1}H NMR and ESI mass of Compound 7a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 2.99 (4H, t, *J* = 5.5, 4.5 Hz), 3.59 (4H, t, *J* = 5.5, 4.5 Hz), 3.69 (1H, dd, *J* = 8.83 Hz), 3.81 (1H, dd, *J* =3.81 hz), 4.04 (1H, dd, *J* = 8.83 Hz), 4.12 (1H, dd, *J* = 6.62 Hz), 4.80- 4.78 (1H, m), 6.92 (1H, t, *J* = 8.8,

9.9Hz), 7.11 (1H, d, *J* = 6.6 Hz), 7.44 (1H, dd, *J* = 11.0, 2.2 Hz) ; ESI-MS: *m/z* = 421(M^+ + 1).

Preparation of (*R*)-*tert*-Butyl-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (8a)

To a stirred solution of **7a** (420 mg, 1 mmol) in methanol (10 ml) was added Pd/C (1.5 mmol), followed by ammonium formate (3 mmol). The resulting mixture was stirred at room temperature until completion of the reaction as indicated by TLC. The reaction mixture was then filtered through a Celite pad and diluted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel using ethyl acetate/hexane (9:1) to afford pure compound **(8a)**. Yield: 80%.



8a

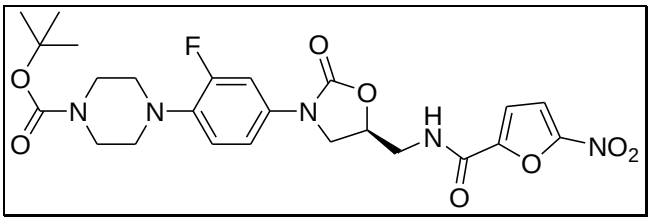
^{1}H NMR and ESI mass of Compound 8a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 2.03 (NH_2, 2H, d, *J* = 10.6 Hz), 2.98 (4H, m), 3.62-3.54 (5H, m), 3.80 (1H, t, *J* = 7.75 Hz), 4.02 (1H, t, *J* = 8.5Hz), 4.69 (1H, m), 6.92 (1H, t, *J* = 9.0 Hz), 7.45 (1H, dd, *J* = 15.7 Hz); ESI-MS: *m/z* = 395 (M^+ + 1).

Preparation of (*R*)-*tert*-Butyl-4-(2-fluoro-4-(5-((2-nitrofuran-5-carboxamido) methyl)-2-oxooxazolidin-3-yl) phenyl) piperazine-l-carboxylate (9a)

To a stirred solution of **8a** (394 mg, 1 mmol) in CH_2Cl_2 (15 mL) was added l-(3-dimethyl aminopropyl)-3-ethyl carbodimide hydrochloride (EDC) (382 mg, 2mmol) in ice bath followed by the addition 5-nitro furoic acid (314 mg, 2 mmol). The resulting mixture was stirred at room temperature until completion of the reaction as indicated by TLC. The reaction mixture was neutralized by 10% sodium bicarbonate solution and separated the CH_2Cl_2 layer, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue

thus obtained was purified by column chromatography on silica gel using hexane /Ethyl acetate (7:3) to afford pure compound **(9a)**. Yield: 88%.



^{1}H NMR and ESI mass of Compound 9a

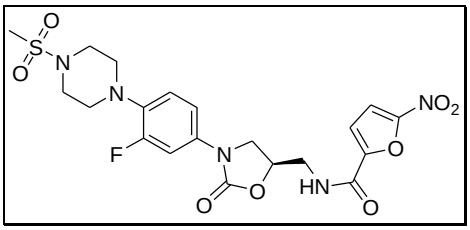
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 2.97 (4H, m), 3.58 (4H, m), 3.74 -3.84 (2H ,m), 3.92 - 4.00 (1H, m), 4.14 (1H, t, *J* = 9.06, 8.87 Hz), 4.92 (1H, m), 6.89 (1H, t, *J* = 9.25, 8.87 Hz), 7.06 (1H, dd, *J* = 6.98, 1.88 Hz), 7.26 (1H, d, *J* = 3.77 Hz), 7.33 (1H, d, *J* = 3.77 Hz), 7.39 (1H, dd, *J* = 12.27, 2.45 Hz), 7.99 (1H, t, *J* = 6.04 Hz); ESI-MS: *m/z* = 534 (M^+ + l).

5.4. General Experimental Procedure for C-ring modified and C-5 arm modified oxazolidino-arylamido/sulfonamides analogs:

5.4.1.1. Preparation of (*S*)-*N*-((3-(3-Fluoro-4-(4-(methyl sulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl) -5-nitrofuran-2-carboxamide (10a):

The target compound **10a** was obtained by treating **9a** (533 mg, 1 mmol) with $BF_3.EtO_2$ (2mL, 1.5 mmol) in CH_2Cl_2 in first step, the crude deprotected compound was directly reacted with methyl sulfonyl chloride (1.2 ml, 1 mmol) in the presence of triethyl amine (3.3 ml, 3mmol) in dry THF (50 ml). After stirring the reaction mixture for 6 hrs,the reaction mixtures was poured on to crushed ice (1.4 g) and the reaction mixture extracted and purified by column chromatography on silica gel using ethyl acetate/hexane (4:6) ,affords the final product **10a.**

(*S*)-*N*-((3-(3-Fluoro-4-(4-(methyl sulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl) -5-nitrofuran-2-carboxamide (10a) (Table-1, Entry 1): (Protan, Carbon and Mass Spectras in **FIG – 18, 19 & 20)**



Yield (%) : 85

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.83 (3H, s), 3.14 (4H, t, *J* = 5.2, 4.5 Hz), 3.41 (4H, t, *J* = 5.2, 4.5 Hz), 3.77 (1H, dd, *J* = 7.5 Hz), 3.90-4.00 (1H, dd, *J* = 11.3, 7.55 Hz), 4.12 (1H, dd, *J* = 9.05, 4.5 Hz), 4.89 (1H, m), 6.93 (1H, t, *J* = 9.0, 8.3 Hz), 7.08 (1H, dd, *J* = 7.5,1.5 Hz), 7.28 (1H, d, *J* = 3.7 Hz), 7.36 (1H, d, *J* = 3.7 Hz), 7.43 -7.51 (1H, dd, *J* = 11.33, 2.26 Hz).

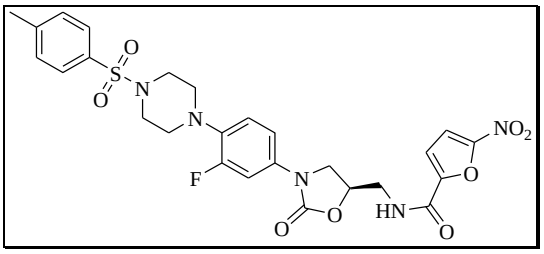
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 28.90, 42.32, 44.33, 48.14, 50.98, 80.26, 114.23, 119.64, 133.47, 136.96, 143.13, 143.92, 144.70, 148.10, 154.21, 155.03, 157.50, 164.30.

Mass (ESI) : 512 (M^{+}+H).

CHN-Analysis : Anal. Calcd. For $C_{20}H_{22}FN_5O_8S$: C, 46.96; H, 4.34; F, 3.71; N, 13.69; O, 25.02; S, 6.27; found: C, 46.98; H, 4.38; F, 3.76; N, 13.83; O, 25.12; S, 6.32. %.

(*S*)-*N*-((3-(3-Fluoro-4-(4-tosylpiperazin-l-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10b): (Table-1, Entry-2)

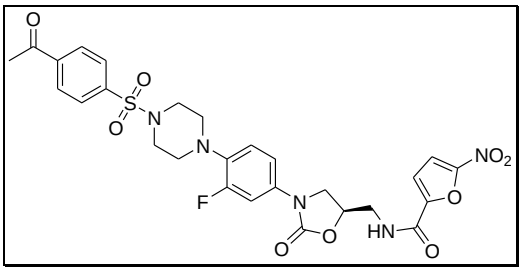
The compound (**10b**) was obtained from **9a** (533mg, 1mmol) and 4-methylbenzene-l-sulfonyl chloride (380mg, 2mmol) according to the procedure as described for **10a**.



Yield (%)	:	85
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 2.46 (3H, s), 3.13 (4H, m), 3.47 (1H, dd, *J* = 6.7 Hz), 3.7 (6H, m), 4.07 (1H, dd, *J* = 9.06, 8.30 Hz), 4.89 (1H, m), 6.91 (1H, dd, *J* = 9.06 Hz), 7.07 (1H, dd, *J* = 8.30 Hz), 7.30-7.51 (5H, m), 7.67 (2H, d, *J* = 7.5 Hz), 8.95 (1H, m) .
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 27.90, 41.32, 45.33, 48.14, 51.98, 80.26, 115.23, 120.64, 133.47, 136.96, 144.13, 145.92, 144.70, 148.10, 155.21, 155.03, 156.50, 164.30.
Mass (ESI)	:	588 (M^++H).
CHN-Analysis	:	Anal. Calcd. For $C_{26}H_{26}FN_5O_8S$: C, 53.15; H, 4.46; F, 3.23; N, 11.92; O, 21.78; S, 5.46; found: C, 53.18; H, 4.48; F, 3.46; N, 11.94; O, 21.82; S, 5.49

(*S*)-*N*-((3-(4-(4-(4-acetylphenylsulfonyl)piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10c) :(Table-1, Entry-3)

The compound (**10c**) was obtained from **9a** (533mg, 1mmol) and 4-acetylbenzene-l-sulfonyl chloride (434mg, 2mmol) according to the procedure as described for **10a**.



Yield (%) : 82

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.46 (3H, s), 3.13 (4H, m), 3.47 (1H, dd, J = 6.7 Hz), 3.7 (6H, m), 4.07 (1H, dd, J = 9.06, 8.30 Hz), 4.89 (1H, m), 6.91 (1H, dd, *J* = 9.06 Hz), 7.07 (1H, dd, *J* = 8.30 Hz), 7.30-7.51 (5H, m), 7.67 (2H, d, *J* = 7.5 Hz), 8.95 (1H, m).

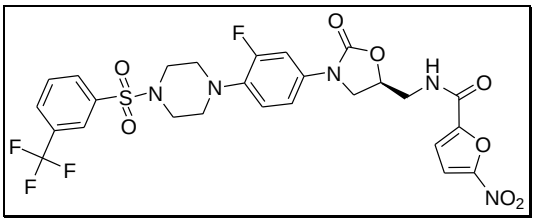
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 27.90, 41.32, 45.33, 48.14, 51.98, 80.26, 115.23, 120.64, 133.47, 136.96, 144.13, 145.92, 144.70, 148.10, 155.21, 155.03, 156.50, 164.30.

Mass (ESI) : 616 (M^++H).

CHN-Analysis : Anal. Calcd. For$C_{27}H_{26}FN_5O_9S$: C, 52.68; H, 4.26; F, 3.09; N, 11.38; O, 23.39; S, 5.21; found: C, 52.71; H, 4.32; F, 3.16; N, 11.44; O, 23.42; S, 5.29 %.

(*S*)-*N*-((3-(3-fluoro-4-(4-(3-(trifluoromethyl) phenyl sulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10d): (Table-1, Entry-4)

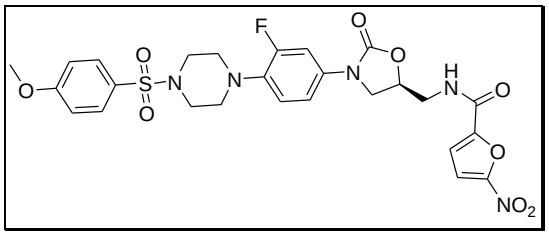
The compound (**10d**) was obtained from **9a** (533mg, 1mmol) and 3-(trifluoromethyl) benzene-l-sulfonyl chloride (366mg, 1.5mmol) according to the procedure as described for **10a**.



Yield (%)	:	75
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 3.11 (4H, m), 3.21 (4H, m), 3.74 (1H, m), 3.95 (1H, dd, *J* = 8.9 , 4.9 Hz), 4.08 (1H, t, *J* = 8.92 Hz), 4.86 (1H, m), 7.1 (1H, d, *J* = 8.6 Hz), 7.3 (1H, d, *J* = 2.87 Hz), 7.54 (1H, t, *J* = 7.65 Hz), 7.69 (1H, d, *J* = 7.65 Hz), 7.84 (1H, dd, *J* = 7.65 Hz), 7.99 (2H, m), 8.08 (1H, d, *J*= 5.74), 8.16 (1H, s), 8.49 (1H, t, *J* = 7.65 Hz).
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 41.33, 44.10, 45.45, 45.62, 47.73, 111.48, 114.11, 118.03, 123.92, 125.45, 125.67, 128.33,128.77, 129.71, 129.96, 130.86, 133.36, 134.91,140.14, 144.47, 146.31, 152.08, 154.88.
Mass (ESI)	:	642 (M^++H).
CHN-Analysis	:	Anal. Calcd. For $C_{26}H_{23}F_4N_5O_8S$: C, 48.68; H, 3.61; F, 11.85; N, 10.92; O, 19.95; S, 5.00; found: C, 48.71; H, 3.62; F, 11.86; N, 10.94; O, 19.95; S, 5.04%.

(*S*)-*N*-((3-(3-Fluoro-4-(4-(4-methoxyphenylsulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10e): (Table-1, Entry-5)

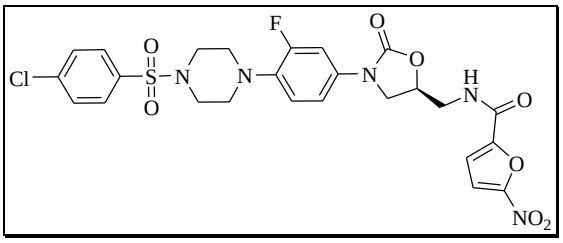
The compound **(10e)** was obtained from **9a** (533mg, 1mmol) and 4-methoxybenzene-l-sulfonyl chloride (307mg, 1.5mmol) according to the procedure as described for **10a**.



Yield (%)	:	80
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 3.10 (4H, m), 3.15 (4H, m), 3.7 (2H, m), 3.8 (3H, s), 3.94 (1H, m), 4.06 (1H, m), 4.83 (1H, m), 6.89 (1H, t, *J* = 9.00 Hz), 7.02 (2H, d, *J* = 9.0 Hz), 7.12 (1H, t, *J* = 6.0 Hz), 7.21 (2H, d, *J* =6.00 Hz), 7.34 (1H, d, *J* = 4.00 Hz), 7.41 (1H, dd, *J* = 12.0. 2.02 Hz), 7.73 (2H, d, *J* = 9.00 Hz) .
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 42.67, 47.61, 46.37, 50.45, 70.72, 105.89, 112.12, 115.38, 115.57, 120.08, 127.50, 127.48, 133.32, 134.71, 138.64, 139.75, 147.60, 150.97, 153.10, 153.69, 157.88.
Mass (ESI)	:	604 (M^++H).
CHN-Analysis	:	Anal. Calcd. For $C_{26}H_{26}FN_5O_9S$: C, 51.74; H, 4.34; F, 3.15; N, 11.60; O, 23.86; S, 5.31; found: C, 51.76; H, 4.38; F, 3.16; N, 11.70; O, 23.86; S, 5.34%.

(*S*)-*N*-((3-(4-(4-(4-Chlorophenylsulfonyl) piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10f): (Table-1, Entry-6)

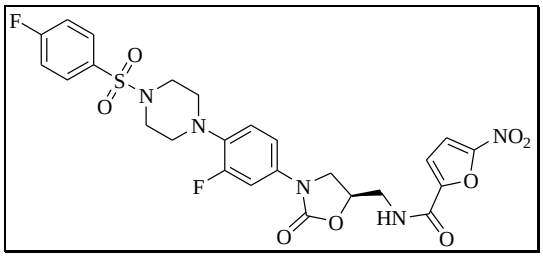
The compound **(10f)** was obtained from **9a** (533mg, 1mmol) and 4-chlorobenzene-l-sulfonyl chloride (313mg, 1.5mmol) according to the procedure as described for **10a.**



Yield (%)	:	84
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 3.09 (4H, m), 3.17 (4H, m), 3.65 (2H, m), 3.89 (1H, m), 4.01 (1H, m), 4.81 (1H, m), 6.96 (2H, d, *J* = 8.70 Hz), 7.02 (1H, t, *J* = 5.17 Hz), 7.13 (2H, d, *J* = 5.17 Hz), 7.36 (1H, d, *J* = 4.37 Hz), 7.49 (1H, dd, *J* = 9.18, 2.26Hz), 7.79 (2H, d, *J* = 8.70 Hz) .
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 41.67, 45.61, 47.37, 49.45, 70.72, 106.89, 112.12, 113.38, 115.57, 119.08, 127.50, 128.48, 133.32, 134.71, 138.64, 139.75, 147.60, 150.97, 153.10, 153.69, 156.88.
Mass (ESI)	:	608 (M^++H).
CHN-Analysis	:	Anal. Calcd. For $C_{25}H_{23}ClFN_5O_8S$: C, 49.39; H, 3.81; Cl, 5.83; F, 3.12; N, 11.52; O, 21.05; S, 5.27; found: C, 49.41; H, 3.85; F, 3.16; N, 11.60; O, 21.06; S, 5.29%.

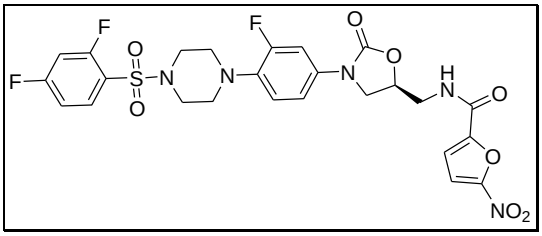
(*S*)-*N*-((3-(3-Fluoro-4-(4-(4-fluorophenylsulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10g): (Table-1, Entry-7)

The compound **(10g)** was obtained from **9a** (533mg, 1 mmol) and 4-fluorobenzene-l-sulfonyl chloride (289mg, 1.5mmol) according to the procedure as described for **10a**.



Yield (%)	:	86
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 3.11-3.13 (4H, m), 3.21-3.24 (4H, m), 3.74-3.78 (2H, m), 3.93-3.97 (2H, m), 4.91 (1H, m), 6.89 (1H, t, *J* = 9.0 Hz), 7.07 (1H, d, *J* = 8.00 Hz), 7.22 (1H, m), 7.35 (1H, d, *J* = 4.00 Hz), 7.42 (1H, dd, *J* = 11.99), 7.90 (2H, d, *J* = 8.00 Hz), 8.12 (2H, d, *J* = 8.00 Hz), 8.95 (1H, m) .
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 41.70, 45.63, 47.47, 49.48, 70.75, 112.18, 115.63, 119.05, 125.37, 127.18, 128.77, 129.19, 132.70, 134.59, 145.30, 145.88, 147.56, 151.03, 153.76, 156.88.
Mass (ESI)	:	592 (M^{+}+H).
CHN-Analysis	:	Anal. Calcd. For $C_{25}H_{23}F_2N_5O_8S$: C, 50.76; H, 3.92; F, 6.42; N, 11.84; O, 21.64; S, 5.42; found: C, 50.79; H, 3.95; F, 6.46; N, 11.88; O, 21.66; S, 5.44%.

(*S*)-*N*-((3-(4-(4-(2, 4-Difluorophenylsulfonyl) piperazin-l-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10h): (Table-1, Entry-8)

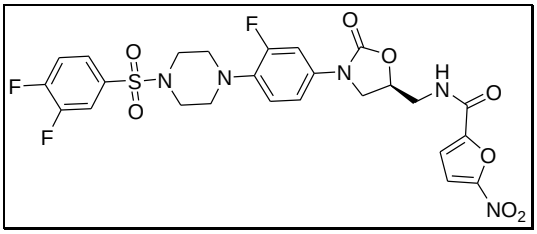


The compound **(10h)** was obtained from **9a** (533mg, 1 mmol) and 2, 4-difluorobenzene-l-sulfonyl chloride (316mg, 1.5mmol) according to the procedure as described for **10a**

Yield (%)	:	86
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 2.94-2.98 (4H, m), 3.07-3.19 (4H, m), 3.73-3.79 (2H, m), 3.85-3.89 (1H, m), 4.02-4.12 (1H, m), 4.88 (1H, m), 6.91 (1H, t, *J* = 8.30), 7.31 (1H, d, *J* = 3.02 Hz), 7.35-7.50 (4H, m), 7.67 (1H, d, *J* = 3.77 Hz), 8.93 (1H, m) .
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 42.78, 45.47, 47.00, 48.50, 67.71, 115.57, 111.93, 115.51, 118.48, 125.74, 128.78, 130.44, 130.10, 130.40, 131.33, 140.59, 145.05, 146.35, 146.68, 150.01, 152.53, 155.45, 156.12.
Mass (ESI)	:	610 (M^{+}+H).
CHN-Analysis	:	Anal. Calcd. For $C_{25}H_{22}F_3N_5O_8S$: C, 49.26; H, 3.64; F, 9.35; N, 11.49; O, 21.00; S, 5.26; found: C, 49.29; H, 3.65; F, 9.36; N, 11.49; O, 21.06; S, 5.27%.

(*S*)-*N*-((3-(4-(4-(3,4-Difluorophenylsulfonyl)piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methyl)-5-nitrofuran-2-carboxamide(10i) (Table-1, Entry-9)

The compound **(10i)** was obtained from **9a** (533mg, 1 mmol) and 2, 4-difluorobenzene-l-sulfonyl chloride (316mg, 1.5 mmol) according to the procedure as described for **10a.**



Yield (%) : 86

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 3.45-3.49 (4H, m), 3.62-3.67 (4H, m), 3.84 (2H, m), 3.95 (1H, m), 4.11 (1H, t, *J* = 4.7 Hz), 4.90-4.94 (1H, m), 7.10 (1H, t, *J* = 8.61 Hz), 7.29-7.34 (1H, m), 7.53 (1H, d, *J* = 7.65, 6.7 Hz), 7.68 (1H ,d *J* = 8.68 Hz), 7.82-7.84 (1H, m), 7.97-8.04 (2H, m), 8.09 (1H, d, *J* = 7.65 Hz), 9.01 (1H, m) .

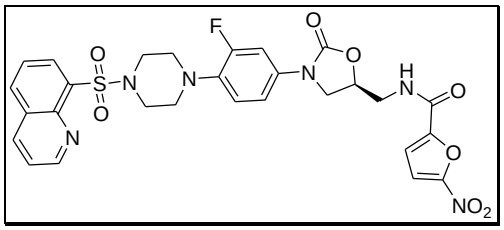
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 41.78, 44.47, 46.00, 48.18, 69.71, 111.57, 111.93, 114.51, 118.48, 127.74, 128.78, 129.44, 130.10, 130.40, 131.33, 140.59, 145.05, 146.35, 146.68, 150.01, 152.53, 155.45, 158.12.

Mass (ESI) : 610 (M^{+}+H).

CHN-Analysis : Anal. Calcd. For $C_{25}H_{22}F_3N_5O_8S$: C, 49.26; H, 3.64; F, 9.35; N, 11.49; O, 21.00; S, 5.26; found: C, 49.29; H, 3.65; F, 9.36; N, 11.49; O, 21.06; S, 5.29%.

(*S*)-*N*-((3-(3-Fluoro-4-(4-(quinolin-8-ylsulfonyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)-5-nitrofuran-2-carboxamide (10j): (Table-1, Entry-10)

The compound **(10j)** was obtained from **9a** (533mg, 1mmol) and quinoline-8-sulfonyl chloride (339mg, 1.5 mmol) according to the procedure as described for **10a**.

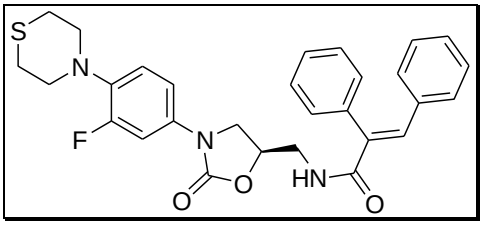


Yield (%)	:	89
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$-300 MHz)	:	δ 3.08-3.12 (4H, m), 3.59-3.63 (4H, m), 3.74-3.80 (2H, m), 4.07-4.14 (2H, m), 4.87 (1H, m), 6.91 (1H, t, *J* = 8.30 Hz), 7.04-7.09 (1H, m), 7.34-7.44 (3H, m), 7.54 (1H, m), 7.62-7.67 (1H, dd, *J* = 8.30, 7.5 Hz), 8.06 (1H, dd, *J* = 6.79, 1.5 Hz), 8.25 (1H, dd, *J* = 6.79, 1.5 Hz), 8.50 (1H, dd, *J* = 7.51, 1.52 Hz), 8.86 (1H, m), 9.09 (1H, d, *J* = 2.26 Hz).
^{13}C NMR ($CDCl_3$-75 MHz)	:	δ 41.78, 44.47, 46.00, 48.18, 69.71, 111.57, 111.93, 114.51, 118.48, 127.74, 128.78, 129.44, 130.10, 130.40, 131.33, 140.59, 145.05, 146.35, 146.68, 150.01, 152.53, 155.45, 158.12.
Mass (ESI)	:	625 (M^++H).
CHN-Analysis	:	Anal. Calcd. For $C_{28}H_{25}FN_6O_8S$: C, 53.84; H, 4.03; F, 3.04; N, 13.46; O, 20.49; S, 5.13; found: C, 53.89; H, 4.05; F, 3.06; N, 13.49; O, 20.49; S, 5.19%.

5.4.1.2 Preparation of (*S*)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2, 3-diphenylacrylamide (11a):

Compound **11a** prepared by amide bond formation between (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**9b**, 155mg, 0.50 mmol) and (*E*)-2, 3-diphenylacrylic acid (156mg, 0.7mmol) in dry CH_2Cl_2. The coupling reagents EDC (1.2 mmol) and HOBt (1.2 mmol) were added, and the reaction mixture was stirred at room temperature for 10 h. After completion of reaction as indicated by TLC, the reaction mixture was quenched with $NaHCO_3$ and extracted in EtOAc (4x25 ml) from the ice-cold aqueous layer and dried over anhydrous Na_2SO_4. The resulting product **11a** was purified by column chromatography to afford 232 mg, a yellow solid.

(S)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-2, 3-diphenylacrylamide (11a): (Table-1, Entry-11)

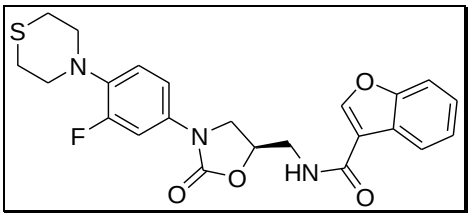


Yield (%)	:	90
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 2.69 (4H, m), 3.59 (4H, m), 3.69-3.79 (3H, m), 3.98 (1H, t, *J* = 8.87 Hz), 4.80 (1H, m), 5.98 (1H, t, *J* = 6.04 Hz), 6.55-6.63 (2H, m), 7.00 (2H, d), 7.13-7.27 (6H, m), 7.43-7.47 (3H, m), 7.87 (1H, s).
^{13}C NMR ($CDCl_3$, 75 MHz)	:	δ 25.55, 28.11, 42.72, 50.78, 72.36, 103.12, 103.43, 111.35, 127.85, 132.70 135.58, 137.89, 139.32, 139.93, 142.90, 143.80, 150.68, 154.17, 156.01, 159.62, 174.97.
Mass (ESI)	:	518 (M^++H).
CHN-Analysis	:	Anal. Calcd. For $C_{29}H_{28}FN_3O_3S$: C, 67.29; H, 5.45; F, 3.67; N, 8.12; O, 9.27; S, 6.19; found:

C, 67.59; H, 5.55; F, 3.68; N, 8.19; O, 9.29; S, 6.20%.

(*S*)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl) benzofuran-3-carboxamide (11b): (Table-1, Entry-12)

The compound **11b** was prepared by the method as described for the preparation of the compound **11a**, employing (*R*)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**9b**, 155mg, 0.50 mmol) and benzofuran-3-carboxylic acid (113mg, 0.7 mmol) to afford pure compound **11b** as a yellow solid in 193 mg.



Yield (%) : 85

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.67 (4H, m), 3.56 (4H, m), 3.77-3.84 (2H, m), 3.96-4.01 (1H, m), 4.07 (1H, t, *J* = 9.00, 8.85 Hz), 4.91 (1H, m), 6.53-6.58 (2H, m), 7.21-7.25 (2H, m), 7.31 (1H, t, *J* = 7.17, 0.76 Hz), 7.44 (1H, t, *J* = 7.17, 1.22 Hz), 7.50 (1H, s), 7.53 (1H, d, *J* = 8.39 Hz), 7.68 (1H, d, *J* = 7.78 Hz) .

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 25.37, 41.49, 49.20, 50.62, 72.23, 102.98, 103.28, 110.42, 111.43, 122.17, 123.21, 126.63, 127.83, 147.38, 150.59, 154.28, 155.63, 158.80, 159.44.

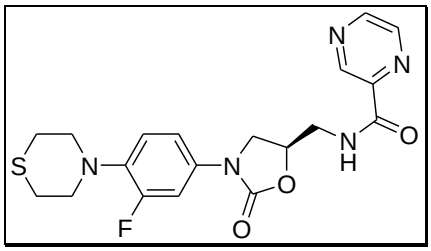
Mass (ESI) : 456 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{23}H_{22}FN_3O_4S$: C, 60.65; H, 4.87; F, 4.17; N, 9.23; O, 14.05; S, 7.04; found:

C, 60.69; H, 4.88; F, 4.18; N, 9.29; O, 14.09; S, 7.08 %.

(*S*)-*N*-((3-(3-Fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl) pyrazine-2-carboxamide (11c): (Table-1, Entry-13)

The compound **11c** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**9b**, 155mg, 0.50 mmol) and pyrazine-2-carboxylic acid (87mg, 0.7 mmol) to afford the pure compound **11c** as a yellow solid in 173mg.



Yield (%) : 82

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.68 (4H,m), 3.58 (4H, m), 3.77-3.80 (1H, dd, *J* = 9.00, 6.25 Hz), 8.82-8.87 (1H, m), 3.94-3.99 (1H, m), 4.06 (1H, t, *J* = 9.00, 8.85 Hz), 4.90 (1H, m), 6.53-6.60 (2H, m), 7.21 (1H, t, *J* = 9.00, 8.85 Hz), 8.29 (1H, t, *J* = 6.25 Hz), 8.57 (1H, dd, *J* = 1.52, 0.91 Hz), 8.79 (1H, d, *J* = 2.44 Hz), 9.41 (1H, s) .

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 25.98, 42.20, 49.58, 51.18, 72.55, 103.60, 111.76, 115.05, 128.47, 142.72, 144.31, 147.64, 151.14, 155.98, 157.31, 159.28, 163.81.

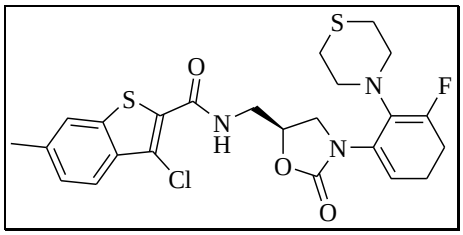
Mass (ESI) : 418 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{19}H_{20}FN_5O_3S$: C, 54.67; H, 4.83; F, 4.55; N, 16.78; O, 11.50; S, 7.68;

found: C, 54.69; H, 4.84; F, 4.56; N, 16.79; O, 11.52; S, 7.69 %.

(*S*)-3-Chloro-*N*-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl)-6-methylbenzo [*b*]thiophene-2-carboxamide (11d): (Table-1, Entry-14)

The compound **11d** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**9b**, 155mg, 0.50 mmol) and 5-methylbenzo[*b*]thiophene-2-carboxylic acid (134mg, 0.7 mmol) to afford the pure compound **11d** as a yellow solid in 194mg.

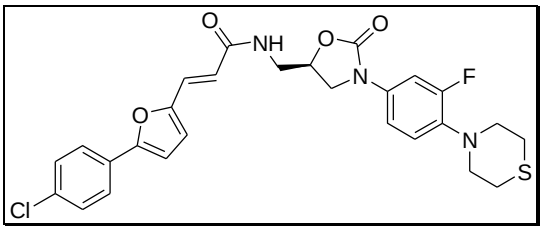


Yield (%)	:	80
Colour	:	yellow solid
^{1}H NMR ($CDCl_3$-300 MHz)	:	δ 2.50 (3H, s), 2.67 (4H, m), 3.56 (4H, m), 3.79 (1H, dd, *J* = 9.00, 6.45 Hz), 3.88-3.99 (2H, m), 4.06 (1H, t, *J* = 9.00, 8.85 Hz), 4.93 (1H, m), 6.53-6.59(2H, m), 7.23 (1H, t, *J* = 9.00, 8.85 Hz), 7.31 (1H, d, *J* = 7.62 Hz), 7.57 (1H, t, *J* =5.95 Hz), 7.62 (1H, s), 7.76 (1H, d, *J* = 8.39 Hz) .
^{13}C NMR ($CDCl_3$-300 MHz)	:	δ 25.80, 32.86, 41.92, 49.63, 51.05, 72.66, 103.71, 103.40, 110.84, 111.62, 114.80, 122.82, 123.64, 127.06, 128.26, 147.81, 150.89, 154.70, 156.06, 156.58, 159.42, 159.87.
Mass (ESI)	:	523 (M^{+}+H).

CHN-Analysis : Anal. Calcd. For $C_{24}H_{25}ClFN_3O_3S_2$: C, 55.22; H, 4.83; Cl, 6.79; F, 3.64; N, 8.05; O, 9.19; S, 12.28; found: C, 55.24; H, 4.84; Cl, 6.80; F, 3.66; N, 8.09; O, 9.19; S, 12.29 %.

(*S*)-3-(5-(4-Chlorophenyl) furan-2-yl)-*N*-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acryl amide (11e): (Table-1, Entry-15) (Protan, Carbon and Mass spectras in **FIG -21, 22 & 23)**

The compound **11e** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholinophenyl) oxazolidin-2-one (**9b**, 155mg, 0.50 mmol) and (*E*)-3-(5-(4-chlorophenyl)furan-2-yl)acrylic acid (173mg, 0.7 mmol) to afford the pure compound **11e** as a yellow solid in 243 mg.



Yield (%) : 80

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.65 (4H, m), 3.54 (4H, m), 3.75-3.84 (3H, m), 4.02 (1H, t, *J* = 8.30 Hz), 4.88 (1H, m), 6.51-6.66 (4H, m), 6.69 (1H, d, *J* = 3.02 Hz), 7.25 (1H, d, *J* = 8.30 Hz), 7.34-7.45 (3H, m), 7.63 (2H, d, *J* = 9.06 Hz) .

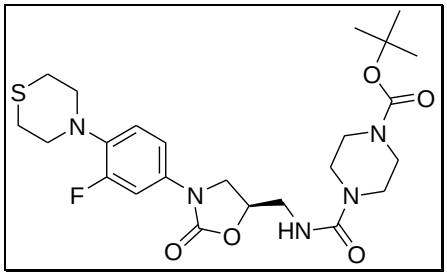
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 25.62, 41.78, 49.31, 50.79, 72.82, 103.23, 107.63, 111.36, 114.74, 116.03, 117.52, 125.01, 127.58, 128.01, 128.64, 133.50, 150.52, 150.65, 153.90, 156.15, 157.00, 158.98, 166.53.

Mass (ESI) : 542 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{27}H_{25}ClFN_3O_4S$: C, 59.83; H, 4.65; Cl, 6.54; F, 3.51; N, 7.75; O, 11.81; S, 5.92; found: C, 59.83; H, 4.66; Cl, 6.58; F, 3.52; N, 7.75; O, 11.89; S, 5.93 %.

(*S*)-*tert*-Butyl 4-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl) methyl carbamoyl) piperazine-1-carboxylate (11f): (Table-1, Entry-16)

The compound **11f** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-5-(amino methyl)-3-(3-fluoro-4-thiomorphormophenyl) oxazolidin-2-one (**9b**, 155mg, 0.50 mmol) and 4-(tert-butoxycarbonyl) piperazin-l-carboxylic acid (161mg, 0.7 mmol) to afford the pure compound **11f** as a yellow solid in 248 mg.



Yield (%) : 95

Colour : yellow solid

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.49 (9H, s), 2.74 (4H, m), 3.01 (4H,m), 3.62 (4H, m), 3.69 (4H, m), 3.77 (1H , dd, *J* = 6.39, 2.44 Hz), 3.98-4.16 (3H, m), 4.79 (1H, m), 6.43 (1H, t, *J* = 6.27, 6.04 Hz), 6.94 (1H, t, *J* = 9.00 Hz), 7.08 (1H, *J* = 6.77, 1.73 Hz), 7.46 (1H, dd, *J* = 9.78, 2.44 Hz).

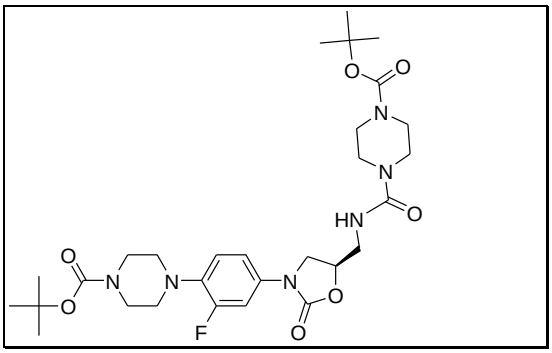
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 25.43, 42.50, 49.10, 72.18, 76.14, 103.41, 111.29, 127.65, 129.33, 134.88, 137.40, 155.50, 156.17, 159.46, 167.45, 103.41.

Mass (ESI) : 524 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{24}H_{34}FN_5O_5S$: C, 55.05; H, 6.54; F, 3.63; N, 13.37; O, 15.28; S, 6.12; found: C, 55.23; H, 6.56; F, 3.74; N, 13.45; O, 15.34; S, 6.19 %.

(*S*)-*tert*-butyl4-((3-(4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)methylcarbamoyl)piperazine-1-carboxylate(11g):(Table-1, Entry-17)

The compound **11g** was prepared by the method as described for the preparation of compound **11a,** employing (*R*)-*tert*-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-l-carboxylate (**9a**, 197mg, 0.50 mmol) and 4-(*tert*-butoxycarbonyl) piperazin-l-carboxylic acid (161mg, 0.7 mmol) to afford the pure compound **11g** as a yellow solid in 260 mg.



Yield (%) : 86

Colour : yellow solid

^{1}H NMR ($CDCl_3$-300 MHz) : δ 1.44 (9H, s), 1.48 (9H, s), 2.72 (4H, m), 2.99 (4H,m), 3.59 (4H,m), 3.69 (4H, m), 3.76 (1H , dd, *J* = 6.41, 2.4 Hz), 3.98-4.16 (3H, m), 4.77 (1H, m), 6.41 (1H, t, *J* = 6.23, 6.04 Hz), 6.91 (1H, t, *J* = 9.06 Hz), 7.04 (1H, *J* = 6.98,1.7 Hz), 7.43 (1H, dd, *J* = 11.7, 2.45 Hz),.

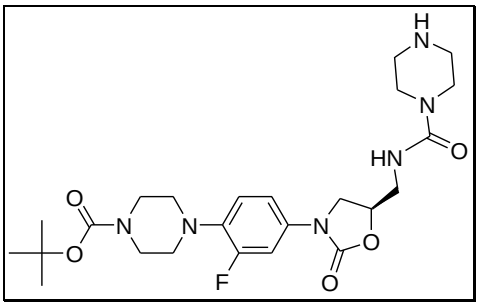
^{13}C NMR ($CDCl_3$-300 MHz) : δ 28.42, 29.47, 41.98, 47.79, 50.46, 71.50, 79.97, 113.83, 119.29, 142.28, 143.59, 144.35, 147.75, 154.03, 154.91, 157.15, 163.95.

Mass (ESI) : 607 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{29}H_{43}FN_6O_7$: C, 57.41; H, 7.14; F, 3.13; N, 13.85; O, 18.46; found: C, 57.75; H, 7.18; F, 3.14; N, 13.99; O, 18.49 %.

(*S*)-*tert*-butyl 4-(2-fluoro-4-(2-oxo-5-((pyrazine-2-carboxamido)methyl)oxazolidin-3-yl)phenyl) piperazine-1-carboxylate(11h): (Table-1, Entry-18)

The compound **11h** was prepared by the method as described for the preparation of compound **11a**, employing (*R)-tert*-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-l-carboxylate (**9a**, 197mg, 0.50 mmol) and pyrazine-2-carboxylic acid (86mg, 0.7 mmol) to afford the pure compound **11h** as a yellow solid in 232 mg .



Yield (%) : 92

Colour : yellow solid

^{1}H NMR ($CDCl_3$-300 MHz) : δ 1.48 (9H, s), 2.97 (4H, m), 3.58 (4H, m), 3.80-3.88 (2H, m), 3.94-3.99 (1H, m), 4.09 (1H, t, *J* = 9.00 Hz), 4.89 (1H, m), 6.90 (1H, t, *J* = 9.00 Hz), 7.06 (1H, dd, *J* = 7.01, 2.59 Hz), 7.42 (1H, dd, *J* = 11.59, 2.59 Hz), 8.27 (1H, t, *J* = 6.40 Hz), 8.55 (1H, dd, *J* = 2.44, 1.52 Hz), 8.78 (1H, d, *J* = 2.44 Hz), 9.38 (1H, s) .

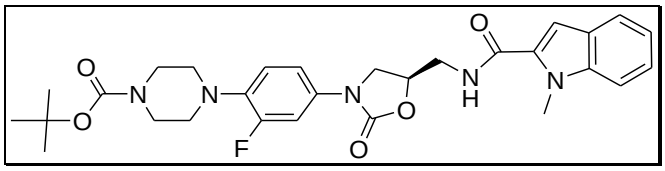
^{13}C NMR ($CDCl_3$-300 MHz) : δ 28.35, 41.89, 47.88, 50.69, 71.59, 79.82, 107.29, 107.55, 113.75, 119.20, 133.08, 136.52, 142.69, 143.51, 144.26, 147.67, 154.06, 154.71, 163.87, 157.06.

Mass (ESI) : 507 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{24}H_{35}FN_6O_5$: C, 56.90; H, 6.96; F, 3.75; N, 16.59; O, 15.79; found: C, 56.91; H, 6.97; F, 3.87; N, 16.79; O, 15.49.

(*S*)-*tert*-Butyl-4-(2-fluoro-4-(5-((5-methyl-*1H*-indole-2-carboxamido)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazine-1-carboxylate (11i) : (Table-1, Entry-19)

The compound **11i** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-*tert*-butyl 4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-l-carboxylate (**9a**, 197mg, 0.50 mmol) and 5-methyl-*1H*-indole-2-carboxylic acid (122mg, 0.7 mmol) to afford the pure compound **11i** as a yellow solid in 250mg.



Yield (%) : 91

Colour : yellow solid

^{1}H NMR ($CDCl_3$-300 MHz) : δ 1.45 (9H, s), 2.59 (3H, s), 2.96 (4H, m), 3.55 (4H, m), 3.78 (2H, m), 3.92 (1H, m), 4.11 (1H, t, *J* = 8.87, 8.68 Hz), 4.91 (1H, m), 6.93 (1H, t, *J* = 9.06 Hz), 7.02-7.22 (4H, m), 7.41-7.62 (2H, m), 7.76 (1H, s) , 11.20 (1H, s).

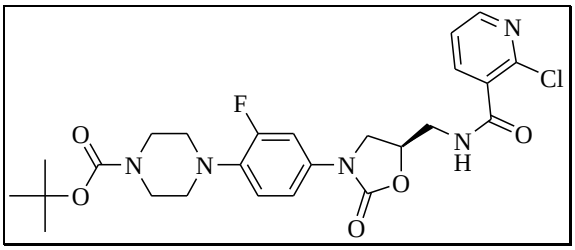
^{13}C NMR ($CDCl_3$-300 MHz) : δ 27.80, 40.25, 47.33, 49.99, 77.56, 78.18, 78.56, 103.21, 106.76, 111.88, 113.44, 118.91, 119.37, 121.08, 123.11, 126.67, 130.64, 132.13, 136.27, 138.43, 151.79, 153.68, 158.16, 161.77.

Mass (ESI) : 552 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{29}H_{34}FN_5O_5$: C, 63.14; H, 6.21; F, 3.44; N, 12.70; O, 14.50; found: C, 63.27; H, 6.27; F, 3.57; N, 12.65; O, 14.89.

(*S*)-*tert*-Butyl-4-(4-(5-((2-chloronicotinamido)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (11j): (Table 1, Entry-20)

The compound **11j** was prepared by the method as described for the preparation of compound **11a**, employing (*R*)-*tert*-butyl 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-l-carboxylate (**9a**, 197mg, 0.50 mmol) and 2-chloronicotinic acid (109mg, 0.7 mmol) to afford the pure compound **11j** as a yellow solid in 234mg .



Yield (%) : 88

Colour : yellow solid

^{1}H NMR ($CDCl_3$-300 MHz) : δ 1.47 (9H, s), 2.99 (4H, m), 3.58 (4H,m), 3.78-3.98 (3H, m), 4.09 (1H, t, *J* = 9.06 Hz), 4.91 (1H, m), 6.90 (1H, t, *J* = 9.06 Hz), 7.04 (1H, d, *J* = 9.06 Hz), 7.28-7.34 (2H, m), 7.39 (1H, dd, *J* = 2.26,12.06 Hz), 7.92 (1H, d, *J* = 6.04 Hz), 8.43 (1H, dd, *J* = 4.5, 3.02 Hz) .

^{13}C NMR ($CDCl_3$-300 MHz) : δ 28.31, 42.03, 43.94, 47.66, 50.50, 71.86, 79.83, 106.99, 107.38, 113.89, 122.72, 119.35, 131.29, 132.92, 136.13, 138.82, 147.15, 150.77, 153.70, 154.57, 156.96, 166.33.

Mass (ESI) : 534 (M^++H).

CHN-Analysis : Anal. Calcd. For $C_{25}H_{29}ClFN_5O_5$: C, 56.23; H, 5.47; Cl, 6.64; F, 3.56; N, 13.12; O, 14.98;

found: C, 56.25; H, 5.49; Cl, 6.65; F, 3.57; N, 13.15; O, 14.99.

5.5. Biological activity

5.5.1. Antibacterial and antifungal activity

The compounds **9a, 10a-j and 11a-j** have been screened for their antibacterial activity against *Staphylococcus aureus (*MTCC 96) , *Bacillus subtillis*(MTCC 121), *E. coll* (MTCC 739), *P. aeruginosa (MTCC2453)* bacteria and the antifungal activity was evaluated against yeast *Candida albicans* (MTCC 3017). The inhibitory zones (in mm) are determined by using agar well method (cup plate method) (Wallace et al, 1986). Neomycin and Flucanozole are used as positive controls against bacteria and fungi, respectively.

The results summarized in **Table 2** shows that all compounds exhibited moderate to good antibacterial activity (MIC=1.1-75.0 μg/mL). All Compounds have shown significant inhibition against all the bacteria tested and were not strain dependent. In the series, the compound **9a** and **10a** are the most active (MIC: **9a** = **10a** = l.1μg/mL) and an exception has been observed with compound **11j**. It is found to be inactive with to all the bacterial strain tested, whereas the remaining all the synthesized compounds showed significant activities.

Table 2: Antibacterial and antifungal activity of oxazolidinones (**9a, 10a-j** and **11a-j**).

	Minimum inhibitory concentration (μg/ml)				
Compounds	*S. aureus* MTCC 96	*Bacillus subtilis* MTCC 121	*E.coli* MTCC 739	*Pseudomonas aeruginosa* MTCC 2453	*Candida albicans* MTCC 3 017
9a	150	1.17	1.17	1.17	2.34
10a	18.75	1.1	4.68	1.1	1.1
10b	37.5	2.34	18.75	4.68	4.68
10c	37.5	37.5	4.6	4.6	4.6

10d	150	18.75	75	75	37.5
10e	4.68	37.5	-	-	-
10f	4.68	9.37	9.37	4.68	9.37
10g	75	75	37.5	75	37.5
10h	37.5	37.5	18.75	18.75	9.37
10i	37.5	37.5	18.75	18.75	18.75
10j	-	2.34	9.37	4.68	9.37
11a	18.75	9.37	75	3.37	18.75
11b	37.5	37.5	18.75	18.75	4.6
11c	18.75	2.34	4.68	4.68	4.68
11d	37.5	2.34	18.75	4.68	4.68
11e	37.5	2.34	4.68	4.68	4.68
11f	37.5	37.5	18.75	18.75	4.6
11g	-	9.37	75	75	37.5
11h	37.5	37.5	18.75	18.75	4.6
11i	37.5	37.5	4.6	4.6	18.75
11j	-	-	-	-	-
Neomycin	18.75	18.75	18.75	18.75	-
Fluconazole	-	-	-	-	75

Antifungal screening of compounds **9a** and **10a** carried out for twelve strains of *Candida albicans*. The investigation of antifungal screening data from **Table 3** reveals that both the compounds showed good fungal inhibition. The oxazolidinones derivatives (**9a** and **10a**) exhibited very good inhibitory activity against fungal strain *C. Albicans* (1.17-2.34 μg/mL).

Table 3: Antimycotic activity of oxazolidinones derivatives (**9a** and **10a**) against twelve different strains of *Candida albicans*.

Minimum inhibitory concentration (MIC, *mg*/mL)			
Test organism	**9a**	**10a**	**Flucanozole**
Candida albicans MTCC 183 (ATCC 2091)	1.17	2.34	37.5
Candida albicans MTCC 227 (ATCC 10231)	2.34	2.34	37.5
Candida albicans MTCC 854	2.34	2.34	37.5
Candida albicans MTCC 1637 (ATCC 18804)	1.17	2.34	75
Candida parapsilosis MTCC 1744	2.34	2.34	18.75
Candida albicans MTCC 3018 (ATCC 24433)	2.34	2.34	75
Candida albicans MTCC 3958	1.17	2.34	37.5
C.albicans MTCC 3017 (ATCC 90028)	2.34	2.34	75
Candida glabrata MTCC 3019 (ATCC 90030)	2.34	2.34	75
Issatchenkia orientalis MTCC 3020 (ATCC 749)	2.34	2.34	150
Issatchenkia hanoiensis MTCC 4755	2.34	2.34	150
Candida aaseri MTCC 1962 (ATCC 18805)	2.34	2.34	75

5.5.2. Antimycobacterial activity

All the synthesized compounds (**9a, 10a-j** and **11a-j**) have been evaluated for the antimycobacterial activity and the results are summarized in **Table 4**. All compounds were initially screened against *M. tuberculosis* H37Rv at the single concentration of 100 (μg/mL). The active compounds from this screening were further tested for Minimum Inhibitory Concentration (MIC) determination using a broth micro dilution assay. Compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentrations by serial dilution against *M. tuberculosis* H37Rv to determine the actual MIC, using the Nitrate Reductase Assay (NRA). The growth in the microtitre plate is indicated by the change in colour to pink detected by the addition of NRA reagent. The MIC is defined as the lowest concentration of the compound showing no change in the color relative to controls. Rifampicin was used as

reference drug. Most of these compounds have shown activity between 1-16 μg/mL among these C-ring modified **9a** and **10a** compound has shown promising *in vivo* antimycobacterial activity (MIC: **9a** = 1**, 10a** = 2 μg/mL). The replacement of alkyl groups with phenyl group has reduced the effectiveness.

Table 4: Antimycobacterial activity of oxazolidinones against ***M.tuberculosis*** (H37Rv) expressed in MIC (μg/mL)

S. No.	Compound	C log P	CMR	MIC (μg/ml)
1	**9a**	3.22	13.06	1
2	**10a**	1.25	11.89	2
3	**10b**	2.92	13.94	8
4	**10c**	3.07	13.95	8
5	**10d**	3.14	13.97	8
6	**10e**	3.21	13.97	8
7	**10f**	3.64	14.43	8
8	**10g**	4.05	14.92	16
9	**10h**	3.09	14.56	16
10	**10i**	2.80	15.17	>16
11	**10j**	2.50	14.90	16
12	**11a**	3.42	14.40	8
13	**11b**	2.92	15.42	>16
14	**11c**	4.10	15.63	>16
15	**11d**	2.40	15.27	>16
16	**11e**	2.67	14.55	8
17	**11f**	4.75	15.79	>16
18	**11g**	3.17	15.01	>16
19	**11h**	3.81	14.45	8
20	**11i**	4.95	14.82	16
21	**11j**	3.08	13.52	>16

22	Linezolid	---	---	1

RMP, Rifampcin; C log P (Hydrophobicity); and CMR (molar refractivity) was calculated using the ChemDraw Ultra, version 10.0

5.6. CONCLUSIONS

In conclusion, we accomplished the synthesis the library of aryl amides and aryl sulfonamide conjugates of oxazolidinone has been designed, synthesized and evaluated against *M. tuberculosis* H37Rv, bacterial strains and fungal strains. Of them compound **9a** and **10a** have shown remarkable anti-mycobacterial activity (*MIC* = 1 and 2 $\mu g/ml$ respectively) equal to linezolid. Further all the compounds have been evaluated against twelve fungal strains. Compounds **9a** and **10a** have displayed significant Antimycotic activities approximately 37 folds more potent than Flucanozole. This study can provide a road map to design and synthesis of oxazolidinone scaffold based anti-microbial active compounds.

5.7. Spectrums:

Compound 4b: ESI-MS spectrum

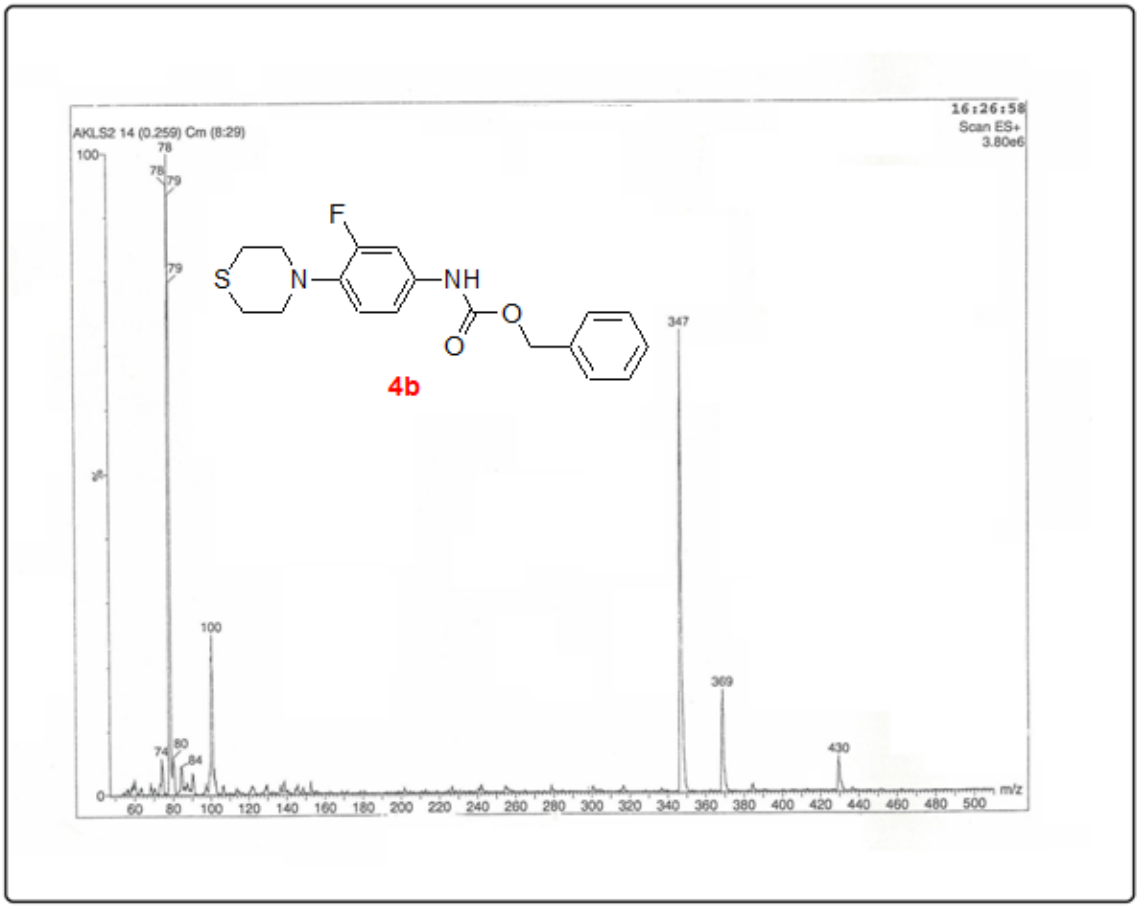


FIG-15: ESI-MS Spectrum of Compound 4b

Compound 5b: ESI-MS spectrum

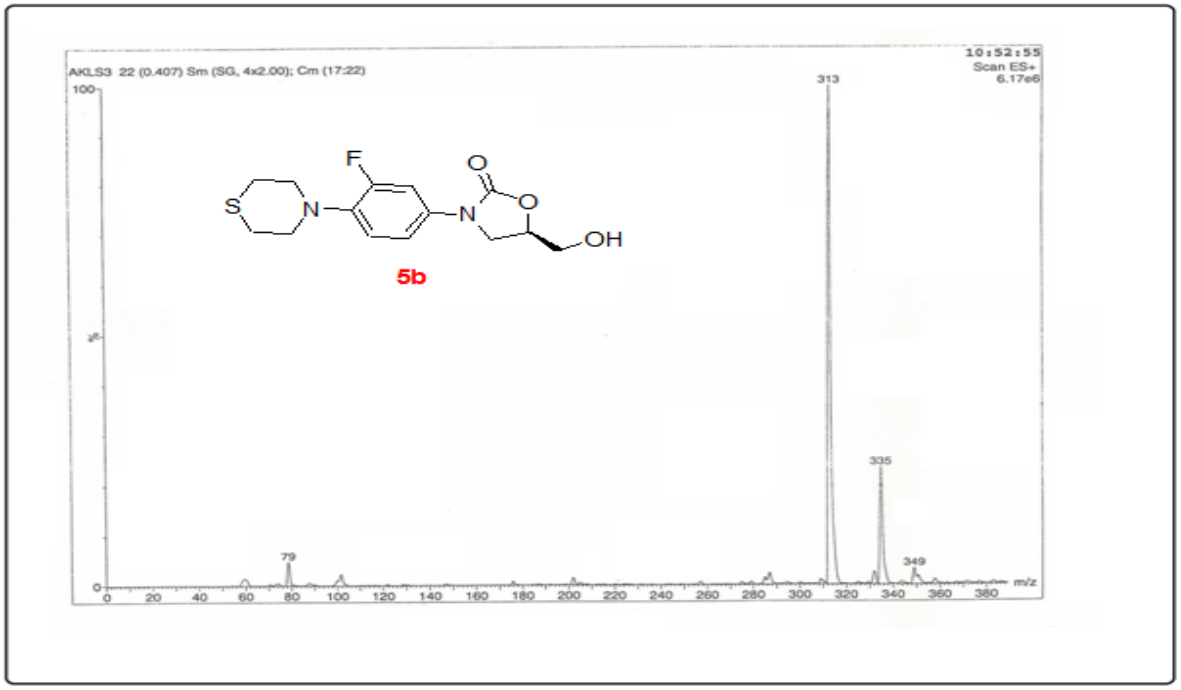


FIG- 16: ESI-MS Spectrum of Compound 5b

Compound 6a: ESI-Ms spectrum

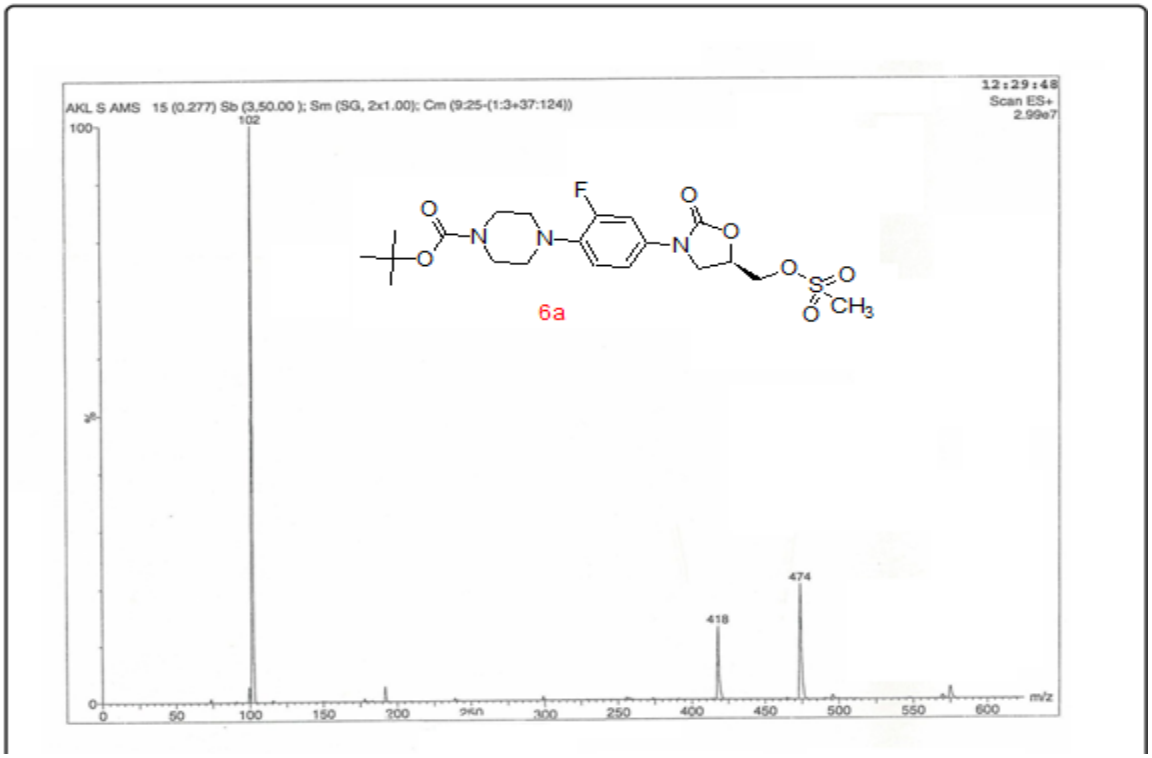


FIG-17: ESI-MS Spectrum of Compound 6a

Compound 10a: ^{1}H NMR specturm

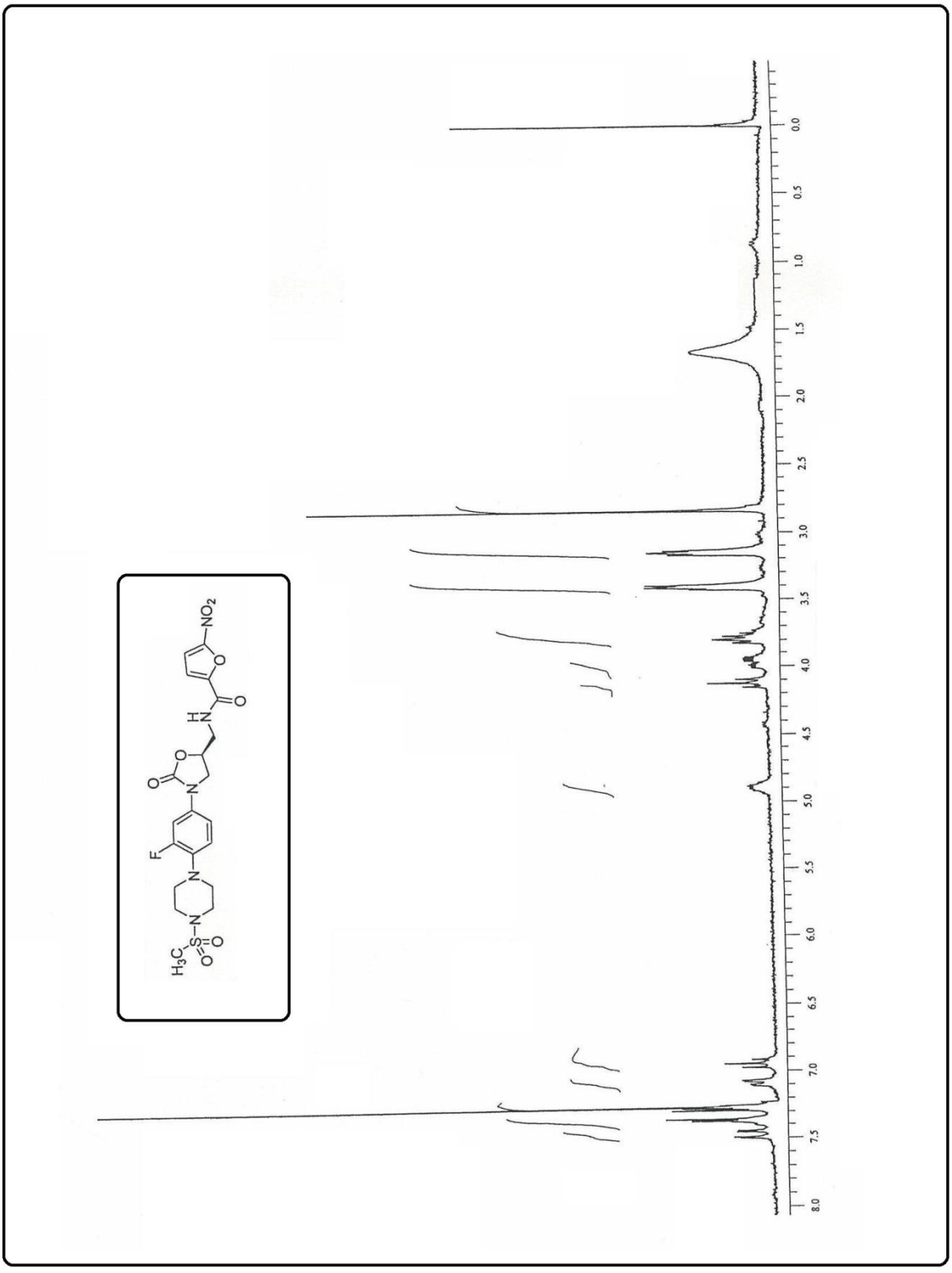


FIG-18: ^{1}H NMR Spectrum of Compound 10a ($CDCl_3$, 300 MHz)

Compound 10a: ^{13}C NMR specturm

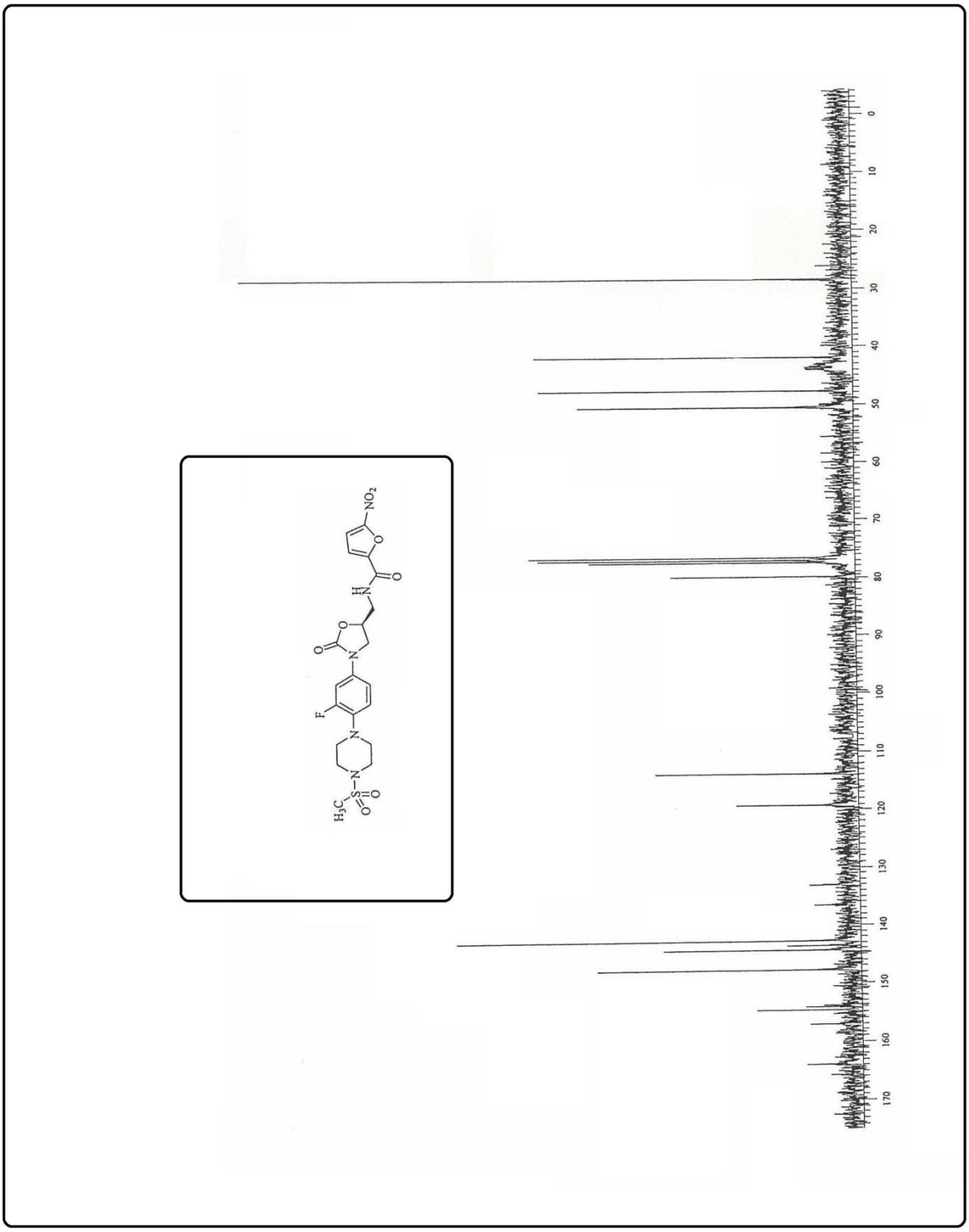


FIG-19: ^{13}C NMR Spectrum of Compound 10a ($CDCl_3$, 75 MHz)

Compound 10a: ESI-MS spectrum

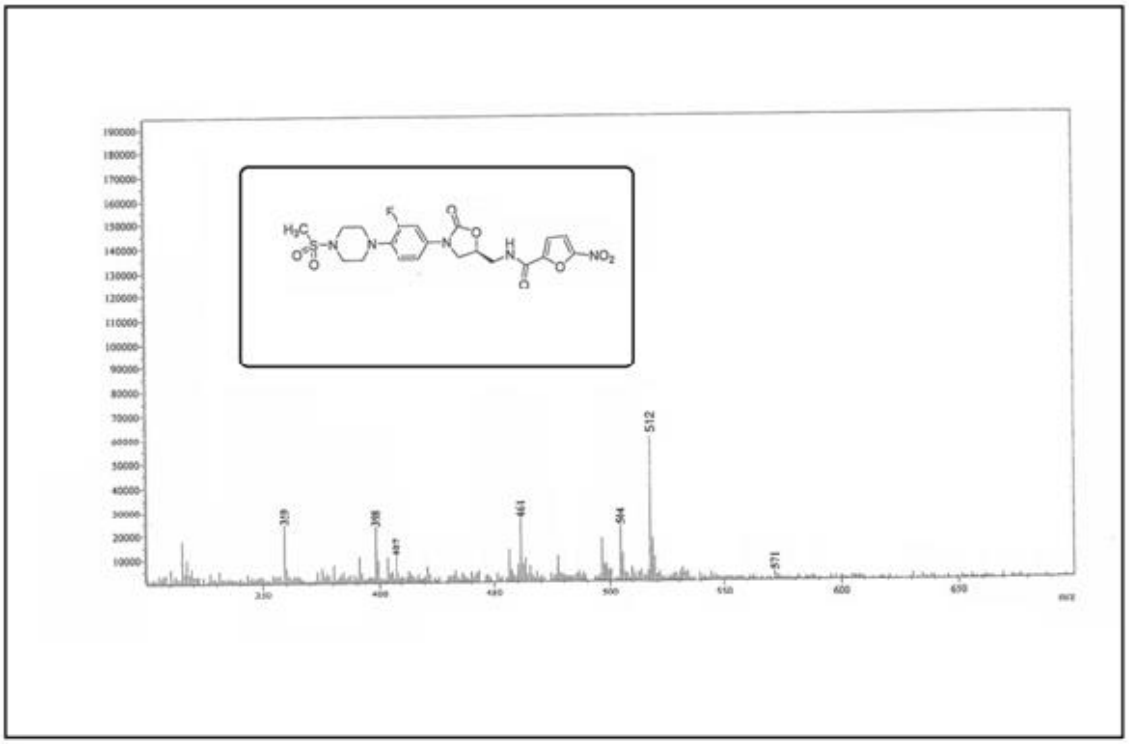


FIG-20: ESI-MS Spectrum of Compound 10a

Compound 11e: ^{1}H NMR specturm

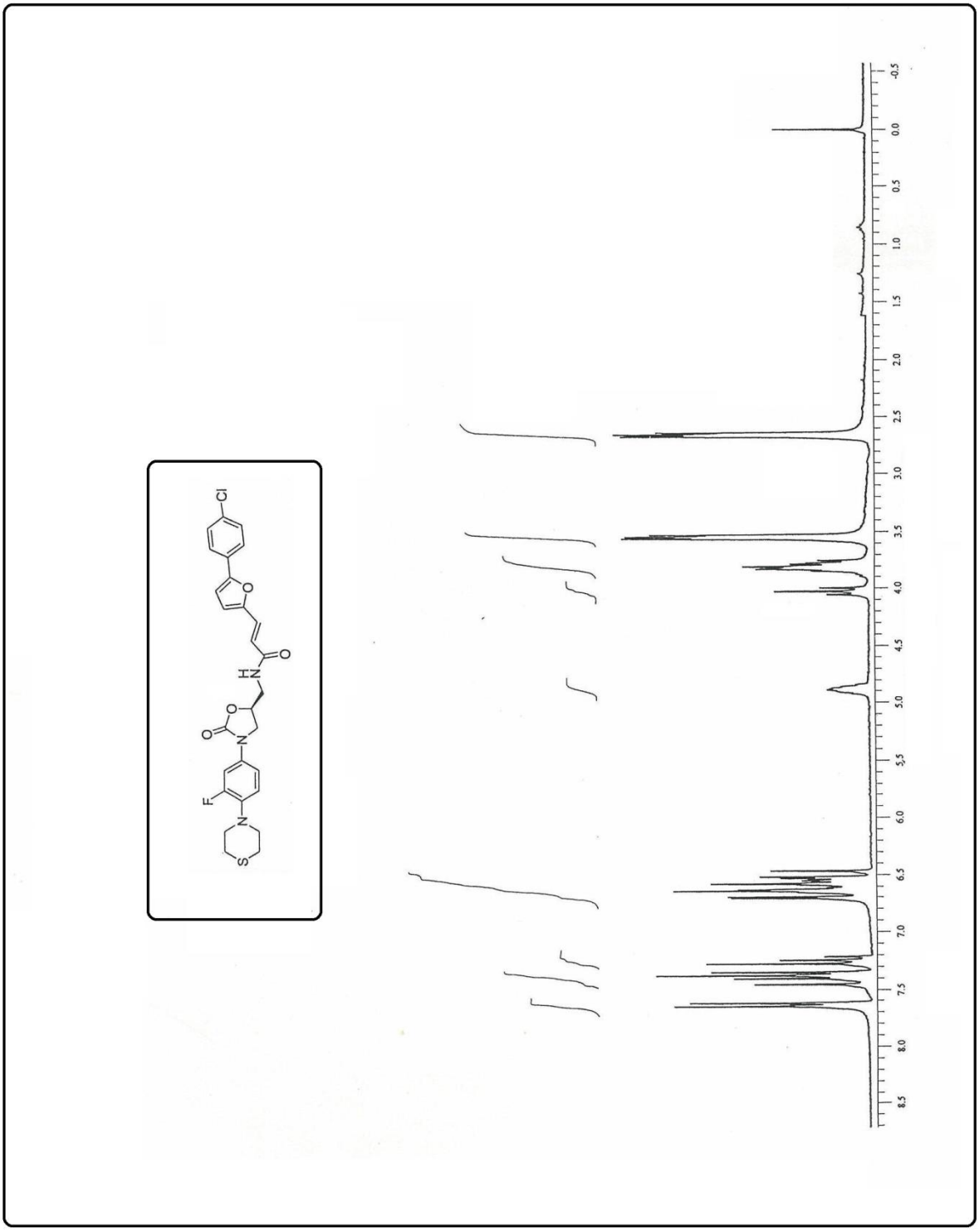


FIG-21: ^{1}H NMR Spectrum of Compound 11e ($CDCl_3$, 300 MHz)

Compound 11e: ^{13} C NMR Spectrum

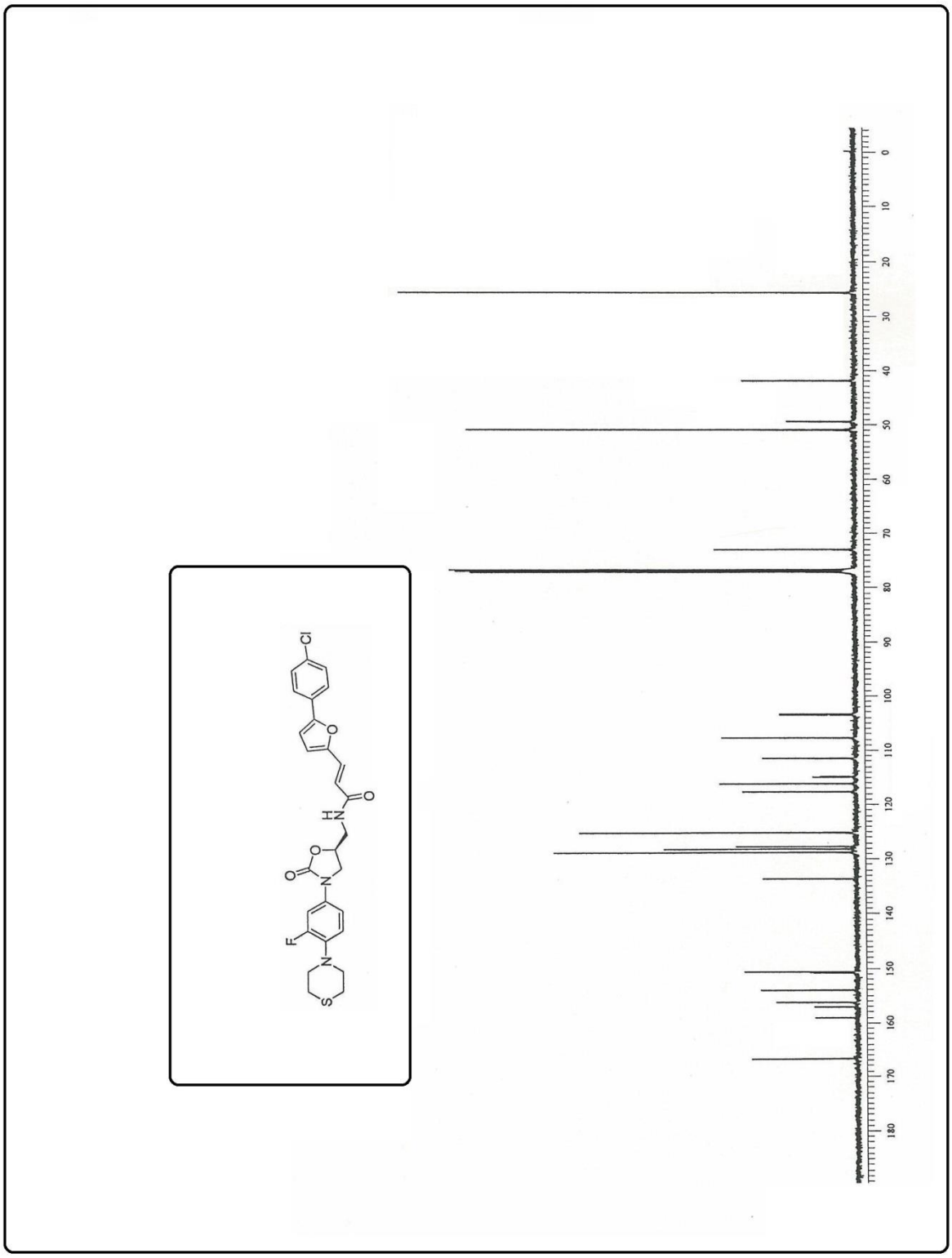


FIG-22: ^{13} C NMR Spectrum of Compound 11e ($CDCl_3$, 75 MHz)

Compound 11e: ESI-MS spectrum

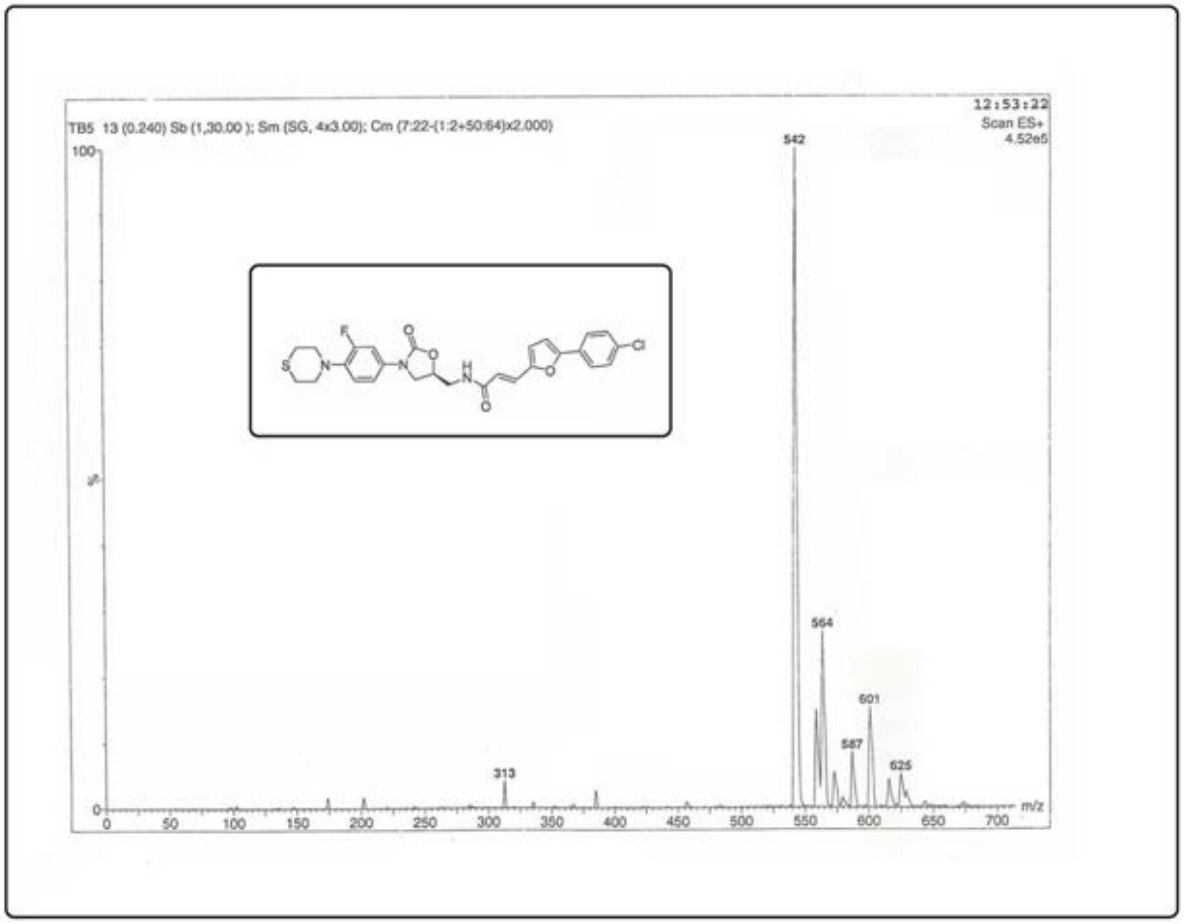


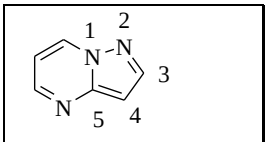
FIG-23: ESI-MS Spectrum of Compound 11e

CHAPTER 6

Synthesis of Ultrasound assisted Synthesis of 2-Alkynyl Pyrazolo [1, 5-*a*] Pyrimidines under Pd/C-Cu Catalysis

6.1. Introduction:

Pyrazolo [1, 5-*a*] pyrimidines are purine analogues (Fig-1) and possesses useful properties as anti-metabolites in purine biochemical reactions. Compounds belong to this class have attracted wide interest in pharmaceutical research because of their pharmalogical properties including anti-trypanosomal activities (Novinson et al, 1976), anti-schistosomal activities (Senga et al, 1981). Derivatives of pyrazolo [1, 5-*a*] pyrimidines are used as HMG-CoA reductase inhibitors (Suzuki et al, 2001), COX-2-selective inhibitors (Al-mansa et al, 2001), AMP phosphodiesterase inhibitors (Fraley et al, 2002), KDR kinase inhibitors (Novinson et al, 1974), selective peripheral benzodiazepine receptor ligands (Selleri et al, 2001), and antianxiety agents (Kirkpatrick et al, 1977). These interesting biological properties prompted medicinal chemist to develop novel, efficient and general procedures for the synthesis of pyrazolo [1, 5-*a*] pyrimidine derivatives including those assisted by Ultrasound sonication.



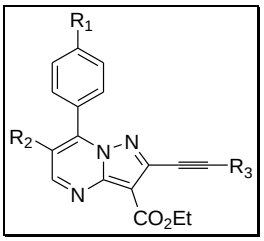
Pyrazolo[1,5-a]pyrimidine

The pyrazolo [1, 5-*a*] pyrimidine frame work (Fig-1) is composed of a pyrimidine ring and a pyrazole ring. The pyrimidine part is π-electron deficient that allows Nucleophilic displacement reaction take place on this ring more readily. The 7-position is more active than the 5-position. The pyrazole part is π-electron excessive, and therefore this moiety can readily participate in electrophilic substitution reactions.

Cancer remains the second leading cause of death (Jemal et al, 2011) worldwide after the cardiovascular diseases, according to WHO. Indeed, leukemia, neuroblastoma [a malignant (cancerous) tumor that develops from nerve tissue] and hepatocarcinoma (a primary malignancy of the liver) along with colon, and breast cancers cause the most cancer deaths worldwide each year. Thus, it is highly desirable to discover and develop suitable agents that are promising for the potential treatment of various types of cancer especially the breast cancer. Since the anti-proliferative and cytotoxic agents play a major role in cancer therapy whether used alone or in combination with other treatment options (e.g. surgery, radiation and biological therapy) discovery and

development of such agents have attracted enormous interest among medicinal chemists over the years.

Alkynes possessing a hetero aryl substituent e.g.uracil (Marrision et al, 2002 and Lee et al, 2002), pyrone (Hocek et al, 2002), purin (Volpini et al, 2001), adenosine (Cristalli et al, 1995), quinolines (Nolan et al, 2003), etc have been explored as potential anticancer agents. Some of them e.g. 5-ethynyl uracil was identified as a potential anti-cancer drug and underwent clinical trials. The pyrazolo [1, 5-*a*] pyrimidine derivatives on the other hand have shown interesting pharmacological properties (Damont et al, 2015). These reports and our continuing interest in identification of potential anti-cancer agents prompted us to build a library of small molecules based on 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine (**A**, Figure 2). Various substituents's such as R^1, R^2 and R^3 were introduced to **A** (Diagram-2) to create diversity around this framework. We envisioned that 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine framework might provide a template for the discovery of novel and potential anticancer agents.



A

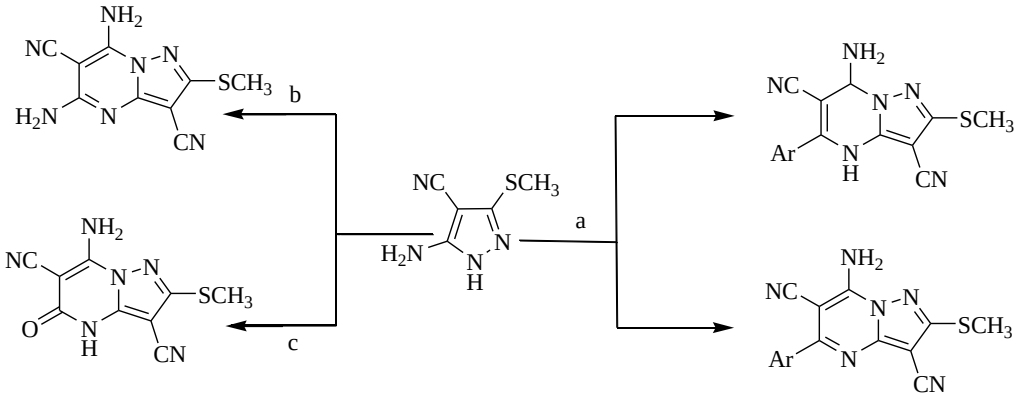
Diagram-2. Design of small molecules based on 2-alkynyl pyrazolo [1,5-*a*] pyrimidine framework.

6.2. Literature update for synthesis of pyrazolopyrimidine derivatives.

1. Synthesis of containing pyrazolo [1, 5- *a*] pyrimidine derivatives, 2-methylsulphanyl,

3-nitrile and 7-amino groups. (Hala Bakr El *et al*, 2011)

Hala Bakr El-Nassan and co-authors have reported synthesis of several pyrazolo [1, 5- *a*] pyrimidine derivatives, containing 2-methylsulphanyl group, 3-nitrile groups and 7-amino group.



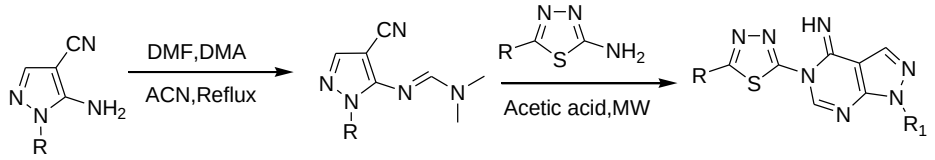
Reagents and conditions:a) ArCH = $CH(CN)_2$,TEA,ETOH, b) $CH_2(CN)_2$,TEA,ETOH,

c)$(CN)CH_2COOC_2H_5$,at 160°c

2. Synthesis of containing pyrazolo [3, 4-*d*] pyrimidine derivatives, containing 1, 3, 4-

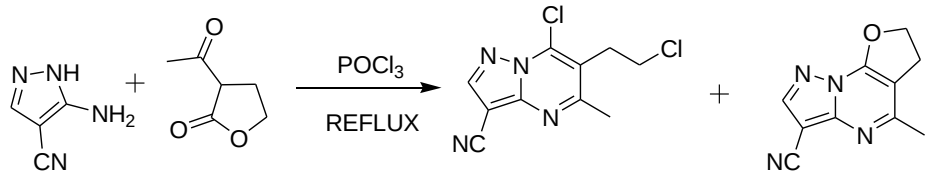
thiadiazole moiety. (Xin Jian *et al*, 2011)

Xin Jian Song and co-authors reported the synthesis of pyrazolo [3,4-*d*] pyrimidine derivatives *containing* 1, 3, 4-thiadiazole as potential antitumor agents. These derivatives were prepared from 5-aminopyrazole starting compound



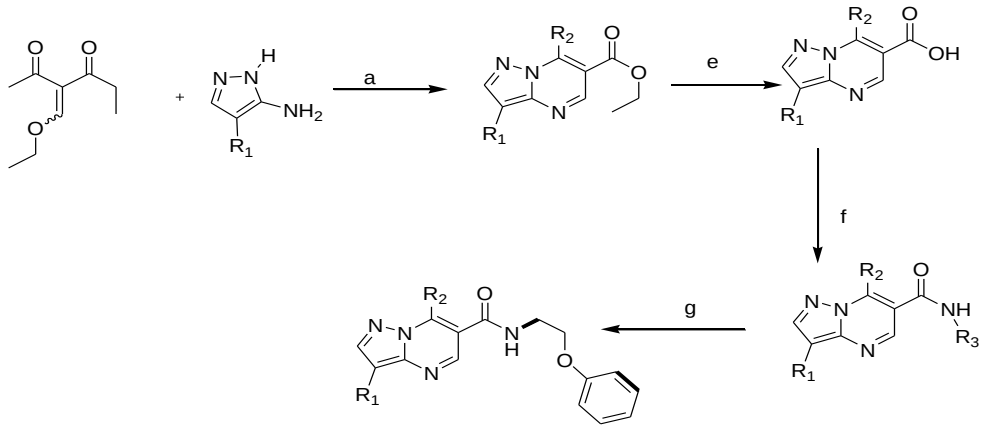
3. Synthesis of pyrazolo [1, 5-*a*] pyrimidine-3-carbonitrile: (Madhukar N. J. *et al*, 2011)

Madhukar N. Jachak et al. have studied the reaction of 5 amino-1*H*-pyrazole-4-carbonitrile with *α*-acetyl-*γ*-butyrolactone that furnished a mixture of pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile and pyrazolo[1 ,5-*a*]pyrimidine-3–carbonitrile .



4. Synthesis of pyrazolopyrimidine and biological activity: (Ijzerman *et al*, 2012)

A number of pyrazolopyrimidine were synthesized and tested for their positive allosteric modulation of the HCA_2 receptor (GPR109A) by *A. P. IJzerman* and co-authors



Reagents and conditions :(a) EtOH, Reflux, 3h (b) $POCl_3$, N,N-dimethylaniline, reflux, 3h

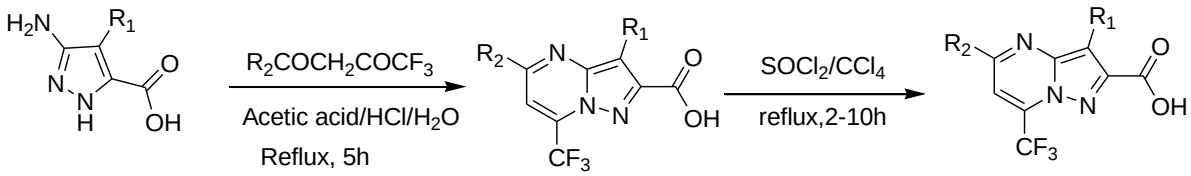
(c) NaOAC, 5 % Pd/C, rt, 1h (d) NBS, DCM, 0 ^{0}C, 1.5 h, rt, 16h

(e) LiOH,H_2O/MeOH/THF, rt, 16h (f)R_3NH_2, EDC.HCl, DCM, rt, 4 h;

(g) $R_1B(OH)_2$ Microwave, 150 ^{0}C, 2 h.

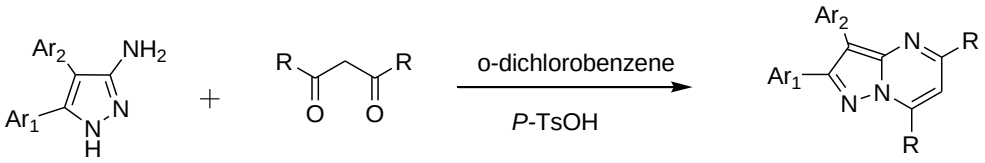
5. **Synthesis of pyrazolopyrimidine from 3-carboxy-5-aminopyrazoles:** (Ivachtchenko Igor *et al*, 2005).

Pyrazolo [1, 5-*a*] pyrimidine Carboxylates and were synthesized from 3-carboxy-5-aminopyrazoles via their acid chloride derivatives as reported by *Alexandre V. Ivachtchenko* and co-authors.



6. Synthesis of pyrazolopyrimidine by condensation of 3-amino-4, 5-diarylpyrazole: (Katzenellenbogen *et al*, 2004)

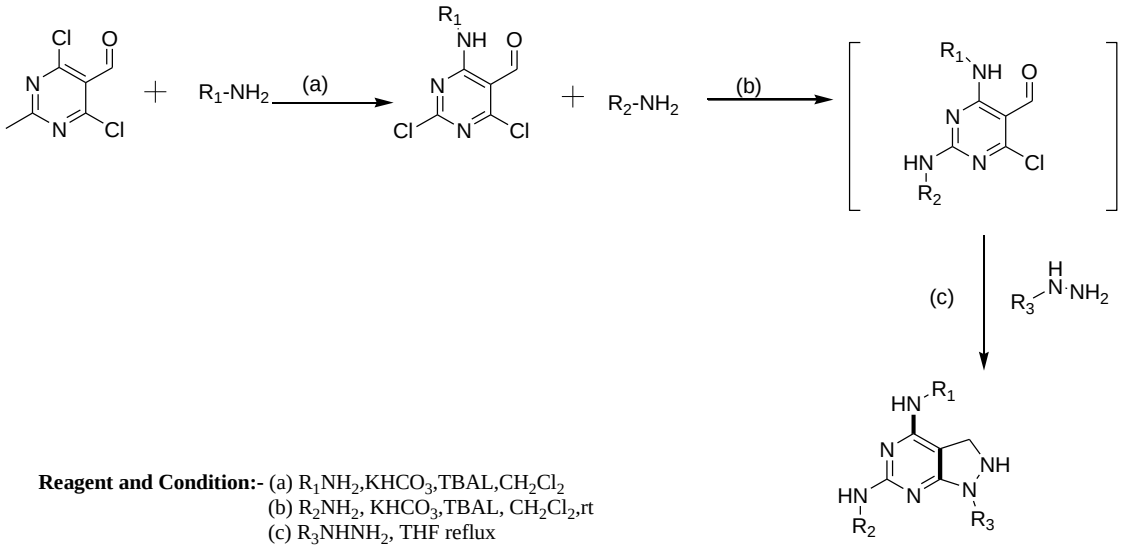
Pyrazolo [1, 5-*a*] pyrimidin can be formed *via* the condensation of 3-amino- 4, 5-diarylpyrazole with a diketone as reported by *John A. Katzenellenbogen* and co-authors



a=R= t-Bu
b=R= Ph

7. syntheis of pyrazolopyrimidine from 2, 4, 6-trichloropyrimidin-5-carbaldehyde: (Thomas *et al*, 2010)

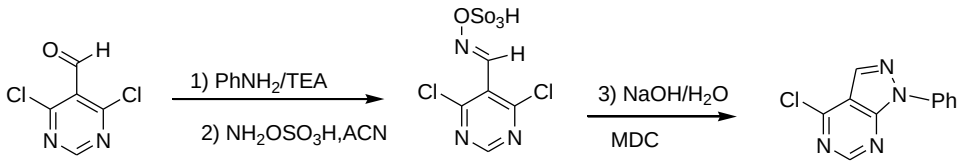
Thomas R. Webb and co-authors was reported the synthesis of pyrazolopyrimidine from 2, 4, 6- trichloropyrimidin-5-carbaldehyde.



Reagent and Condition:- (a) R_1NH_2,$KHCO_3$,TBAL,CH_2Cl_2
(b) R_2NH_2, $KHCO_3$,TBAL, CH_2Cl_2,rt
(c) R_3NHNH_2, THF reflux

8. Synthesis of *N*-aryl [3, 4] pyrazolopyrimidine: (Jones *et al*, 2012)

One pot synthesis of *N* -Aryl [3, 4]-pyrazolopyrimidine via the N-N bond forming cyclization was studied by *Keith Jones* and co-authors.



6.3. Origin of Research Work

The search for new anticancer chemotherapeutic agents continues to be a thrust area of research in many research institutes worldwide (Bridges et al, 2001). During the Last decade pyrazolopyrimidine derivatives have received significant attention due to their wide-range pharmacological properties such as anti-inflammatory, anti-tumor, antimycobacterial, antifungal and anti-viral activities (Rashad et al, 2008). The pyrazolo[4,3-*d*]pyrimidine analogue and pyrazolo[1,5-*a*] pyrimidine derivatives were reported as inhibitors of tyrosine kinase and cyclin dependent kinases (CDK) which involved in mediating the transmission of mitogenic signals and various other cellular events (Kim et al, 2008 and Shenone et al ,2004), including cell proliferation, migration, differentiation, metabolism and immune response. It was also found that many of these derivatives may block propagation of various cancer cell lines (Krystof et al, 2006). All these reports on pharmacological importance of pyrazolopyrimidine promoted us to undertake the synthesis of new functionalized pyrazolopyrimidine derivatives and evaluate their potential for anticancer activities using Hep-G2 cell line.

Objectives

i) To synthesize and purify the 2-alkynyl pyrazolo [1, 5-*a*] pyrimidines derivatives under Pd/C-Cu Catalyst by using ultra sonic assite.

ii) To characterize the compounds using spectral (IR, ^{1}H NMR and Mass) methods and elemental analysis. The data related to structural characterization are given individually.

iii) To screen the synthesized pyrazolo pyrimidines for their toxicity and possible biological- activity anticancer.

iv) To identify the active compounds for further exploitation.

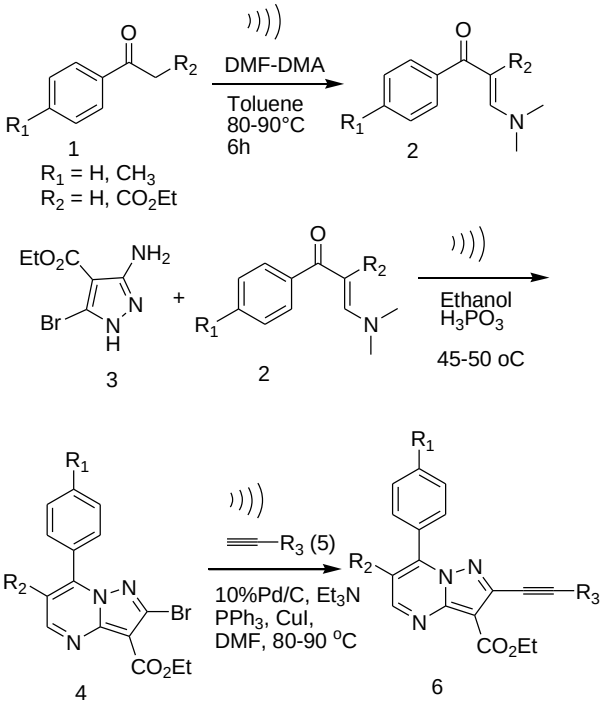
6.4. Present Work:

6.4.1. Chemistry, Results and Discusion

Ultrasound assisted synthesis of 2-alkynyl pyrazolo [1, 5-*a*] pyrimidines (6) under Pd/C-Cu catalysis:

The ultrasound mediated reactions have gained considerable interest in recent time. Compared to the traditional methods the ultrasound mediated reactions offer several advantages such as shorter reaction time, mild conditions, and good yields of products (li et al, 2005 and Ratoarinoro et al, 1992). Thus, the use of ultrasound radiation has emerged as a common strategy in present day organic synthesis. Herein, we report the ultrasound assisted synthesis of a series of 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine derivatives **6(a-j) (**Scheme 1) *via* a 3-step method. While, the ultrasound-assisted synthesis of pyrazolo [1, 5-*a*] pyrimidine derivatives has been reported earlier, the use of ultrasound for the synthesis of compound **6(a-j)** is not known. To the best of our knowledge synthesis of this class of compounds using ultrasound irradiation is not known in the literature.

Thus the ketone **1** was treated with DMF-DMA in toluene at 80-90 ^{o}C for 6h to afford the compound **2**. The compound **2** on reaction with the pyrazole derivative **3** in the presence of H_3PO_3 in ethanol under ultrasound irradiation at 45-50 ^{o}C afforded the bromo compound **4**. On alkynylation of compound **4** using a range of terminal alkynes(**5**) in the presence of 10% Pd/C, CuI and PPh_3 as catalysts and Et_3N as a base in DMF at 80-90 ^{o}C under ultrasound irradiation afforded the desired compound **6**. The details of this work are presented in the following sections.

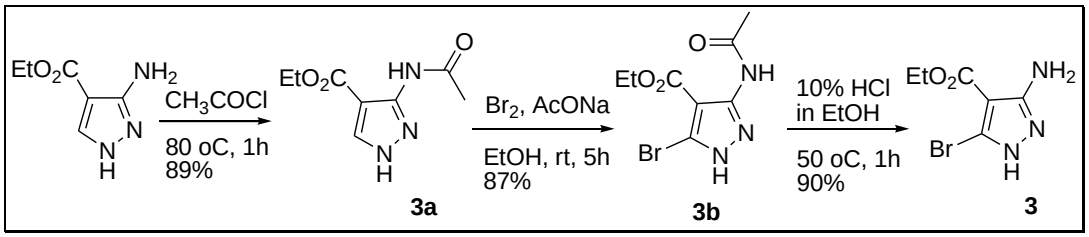


Scheme 1. Ultrasound assisted synthesis of 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine derivatives **6(a-j).**

6.5. Experimental Section:

General methods: Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60-120 mesh) using distilled petroleum ether and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$/DMSO-*d6* solution using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.0) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants *(J)* are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus.

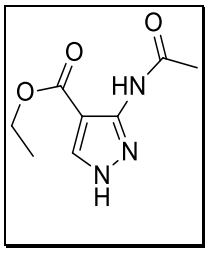
6.5.1 General procedure for the preparation of ethyl 3-amino-5-bromo-1*H*-pyrazole-4-carboxylate (**3**)



Scheme-2

Step 1: Preparation of ethyl 3-acetamido-1*H*-pyrazole-4-carboxylate (3a):

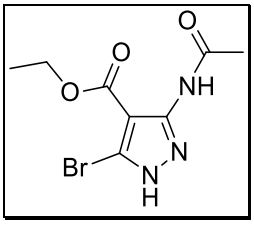
3-Amino-1*H*-pyrazole-4-carboxylic acid ethyl ester (5 g, 32 mmol) was added into acetyl chloride (25 mL) at room temperature. After stirring for 5 min, the mixture was heated to 80 °C for 1.0 h and cooled to 50 °C. The excess of acetyl chloride was evaporated off under reduced pressure, 10% sodium bi carbonate solution (50 mL) was added, and the resulting mixture was stirred for 1.0 h, the white solid precipitate was filtered off and dried to give brownish white solid, ethyl 3-acetamido-1*H*-pyrazole-4-carboxylate (**3a**) (yield 89%); mp 128-130 °C, The IR spectrum of **3a** showed characteristic broad absorption peak in the range 3239 cm^{-1} indicates amide -NH- stretching frequency. The amide carbonyl appeared at 1697 cm^{-1} ,and ^{1}H NMR spectrum shows amide -NH proton of **3a** appeared as broad doublet at δ 11.90 ppm (D_2O exchangeable) and -NHMe protons signal appeared as slightly splitted doublet at 2.29 ppm with equal coupling constant J = 7.3 Hz. One signal appeared at 9.59 ppm for one NH proton and two singlets at 7.77 and quaterlet at 4.31 ppm for OCH_2 protons.



Brownish white solid, mp 128-130 °C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.90 (bs, 1H, NH), 9.59 (bs, 1H, NH), 7.77 (s, 1H, CH), 4.31 (q, J=7.3 Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.38 (t, J=7.3 Hz, 3H, CH_3). ^{13}CNMR (DMSO-d_6, 100MHz): δ 169.2, 163.0, 140.9, 139.0, 99.0, 59.7, 23.1, 14.3. IR (KBr): 3239, 2982, 1697, 1621 cm^{-1}.

Step 2: Preparation of ethyl 3-acetamido-5-bromo-1*H*-pyrazole-4-carboxylate (3b):

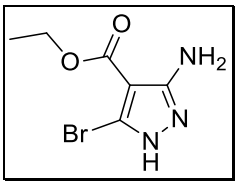
To a mixture of ethyl 3-acetamido-1*H*-pyrazole-4-carboxylate **3a** (1 mmol), sodium acetate (4 mmol) in water (12 vol) and ethanol (12 vol) was added bromine (2 mmol) at room temperature. After stirring for 5.0 h, sodium bi carbonate solution (50 mL) was added, and the resulting mixture was stirred for 1.0 h, the white solid precipitate was filtered off and dried to give ethyl 3-acetamido-5-bromo-1*H*-pyrazole-4-carboxylate **(3b**) (yield 87%).due to electronegative atom bromine NH proton deshielded to δ 13.56 ppm .



Off white solid, mp 195-197 °C.^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.56 (bs, 1H, NH), 9.99 (bs, 1H, NH), 4.27 (q, J=7.0 Hz, 2H, OCH_2), 2.19 (s, 3H, CH_3), 1.30 (t, J= 7.0 Hz, 3H, CH_3). ^{13}CNMR (DMSO-d_6, 50 MHz): δ 169.1, 161.6, 141.9, 126.2, 99.6, 60.1, 23.2, 14.1. IR (KBr): 3220, 2980, 1692, 1605 cm^{-1}

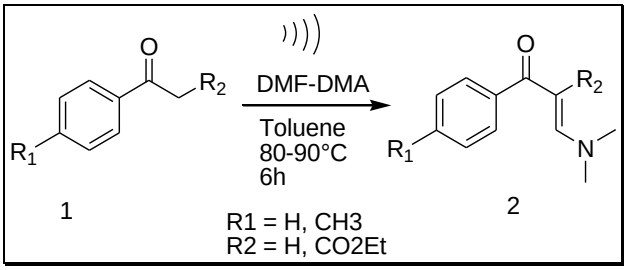
Step 3: Preparation of ethyl 3-amino-5-bromo-1*H*-pyrazole-4-carboxylate (3):

Ethyl 3-acetamido-5-bromo-1*H*-pyrazole-4-carboxylate (**3b**) was added in to 10% ethanol HCl (25 mL) at room temperature. After stirring for 5 min, the mixture was heated at 50 °C for 1.0 h. The excess of ethanol HCl was evaporated off under reduced pressure, di-isopropyl ether(DIPE) was added (25 mL), and the resulting mixture was stirred for 1.0 h, the white solid was filtered off and dried to give ethyl 3-amino-5-bromo-1*H*-pyrazole-4-carboxylate (**3**) (Yield 90%).Acetyl group was deprotected and it was confirmed by IR spectrum as the characteristic broad absorption peak appeared near 3445 cm^{-1} indicating amine -NH_2 stretching frequency .The ^{1}H NMR spectrum reveals that broad peak at δ 6.08 ppm instead of δ 9.99 ppm.



Cream colored solid, mp 141-143 °C.^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.0 (bs, 1H, NH), 6.08 (bs, 1H, NH_2), 4.27 (q, J=7.0 Hz, 2H, OCH_2), 1.26 (t, J=7.0 Hz, 3H, CH_3).^{13}CNMR (DMSO-d_6, 100 MHz): δ 162.7, 152.6, 126.3, 92.7, 59.3, 14.6. IR (KBr): 3445, 2992, 1683, 1510 cm^{-1}.

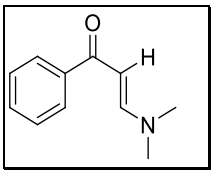
6.5.2. Ultrasound mediated synthesis of 2-benzoyl-3-(dimethylamino) derivatives (2a-c)



Scheme-3

Appropriately substituted acetophenone **1** (1 mmol) was added in to DMF-DMA adduct (10 mL) at room temperature. After stirring for 5 min, the mixture was heated at 80-90 °C under ultrasound irradiation using a laboratory ultrasonic bath SONOREX SUPER RK 510H model producing irradiation of 35 kHz for 6 h. After completion of the reaction (indicated by TLC) the mixture was cooled to 50 °C. The excess of DMF-DMA was evaporated off under reduced pressure. The residue was triturated with diisopropyl ether; the solid precipitate was filtered and washed with diisopropyl ether to give the desired product **2(a-c)**.

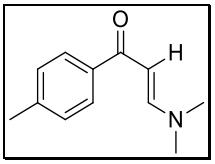
(*E*)-3-(*N*,*N*-Dimethylamino)-1-phenyl-2-propen-1-one (2a)



Off white solid, mp 90-92 °C;^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.88 (m, 2H, arom H), 7.82 (d, J=12.2 Hz, 1H, CH) , 7.47 – 7.38 (m, 3H, arom H), 5.73 (d, J=12.2 Hz, 1H, CH) , 3.13 (bs, 3H, NCH_3), 3.02 (bs, 3H, NCH_3);^{13}CNMR (DMSO-d_6, 100 MHz):

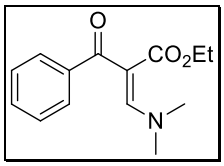
δ 185.7, 154.1, 140.2, 130.7, 128.1, 127.2, 90.9, 44.4, 37.1;IR (KBr):3442, 1638, 1584, 1543 cm^{-1}

(*E*)-3-(*N,N*-Dimethylamino-1-(4-methylphenyl)-2-propen-1-one (2b)



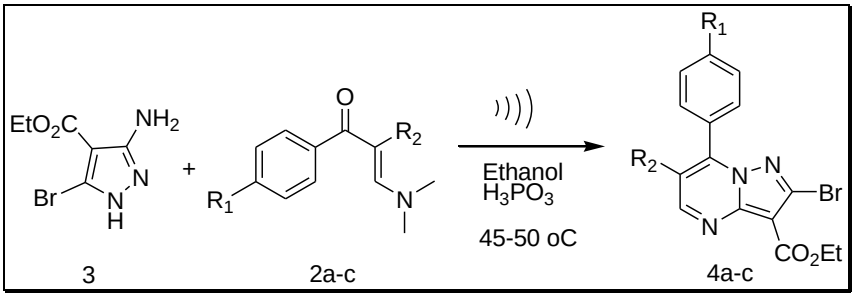
Pale yellow solid, mp 89-91 °C;^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, *J*=8.4 Hz, 2H, arom H), 7.80 (d, *J*=12.2 Hz, 1H, CH) , 7.22 (d, *J*=7.8 Hz, 2H, arom H), 5.73 (d, *J*=12.2 Hz, 1H, CH) , 3.11 (bs, 3H, CH_3), 2.93 (bs, 3H, NCH_3), 2.39 (s, 3H, CH_3).^{13}CNMR ($CDCl_3$, 100 MHz): δ 188.1, 153.9, 141.1, 137.6, 128.6, 127.4, 91.8, 44.5, 36.3, 21.3;IR (KBr):3441, 1645, 1581, 1539 cm^{-1}.

(*E*)-Ethyl 2-(*N,N*-dimethylaminomethyliden) benzoylacetate (2c)



Ash color semi solid;^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.72 (m, 2H, arom H), 7.49-7.37 (m, 3H, arom H), 3.96 (q, *J*=7.2 Hz, 1H, OCH_2), 2.90-3.20 (bs, 6H, NCH_3), 0.88 (t, *J*=7.2 Hz, 3H, CH_3);^{13}CNMR ($CDCl_3$, 100 MHz): δ 193.9, 168.5, 155.7, 140.9, 131.5, 128.9, 128.6, 128.3, 127.8, 99.5, 59.5, 46.1, 41.9, 13.9;IR (KBr):3443, 1640, 1706, 1592cm^{-1}.

6.5.3. Preparation of 2-bromopyrazolo [1, 5-*a*] pyrimidine derivatives (4a-c).[a]



Scheme-4

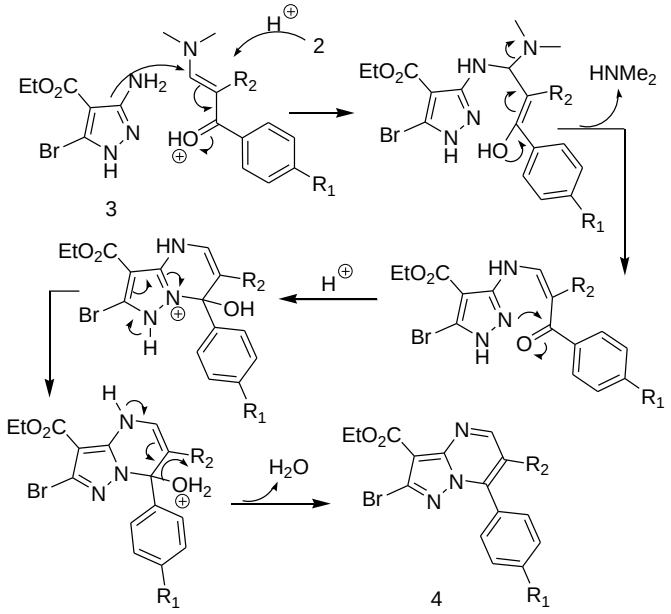
The other starting compound **2a-c** was prepared by treating the appropriate ketone with DMF-DMA in toluene at 80-90 ºC for 6h. The reaction was performed under

ultrasound irradiation using a laboratory ultrasonic bath Sonorex Super RK 510H model producing irradiation of 35 kHz.With both the starting compounds i.e. **3** and **2(a-c)** in hand we then proceeded to synthesize the 2-bromo substituted pyrazolo [1,5-*a*]pyrimidine derivatives **4(a-c)** as shown in **Scheme 4**. Thus the reaction of **3** and **2** in the presence of H_3PO_3 in ethanol under ultrasound irradiation at 45-50 ºC afforded the bromo compound **4**. All together, three compounds were prepared using this methodology in good yields (**Table 1**). The present ultrasound assisted reaction mediated by H_3PO_3 seemed to follow the pathway shown in **Scheme 5**. Thus protonation of **2** followed by the attack of **3** and subsequent intramolecular cyclization of the resulting intermediate via several steps afforded the desired compound **4**.

Table 1: 2-Bromo substituted pyrazolo [1,5-*a*]pyrimidine derivatives(4a-c)

Entry	Ketone (**2a-c**) R^1, R^2	Time (min)	Product (**4a-c**)	%Yield[b]
1.	H, H (**2a)**	30	**4a**	87
2.	CH_3, H **(2b)**	30	**4b**	85
3.	H, CO_2Et (**2c)**	40	**4c**	80

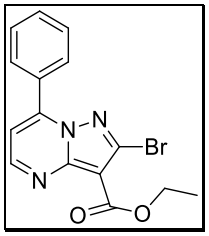
[a]All the reactions were carried out by using compound **3** (1.0 mmol), **2** (1.0 mmol) and H_3PO_3 (1.0 mmol) in ethanol at 45-50 ºC under ultrasound irradiation. [b] Isolated yield.



Scheme 5. Pausible reaction mechanism for the formation of compound **4**

A typical procedure: To a mixture of ethyl 3-amino-5-bromo-1*H*-pyrazole-4-carboxylate (**3**) (1 mmol) and 3-(dimethylamino)-1-phenylprop-2-en-1-one (**2a**) (1 mmol) in ethanol (100 mL) was added H_3PO_3 (1 mmol) at room temperature. After stirring for 5 min, the mixture was heated at 45-50 °C under ultrasound irradiation using a laboratory ultrasonic bath Sonorex Super RK 510H model producing irradiation of 35 kHz. The temperature of the bath was maintained by adding cold water from time to time in case an increase in temperature was observed due to the prolonged irradiation. The reaction continued according to the time mentioned in the above **Table-1** and cooled to 0-5°C. The solid precipitate was filtered and washed with diisopropyl ether to give the desired product.

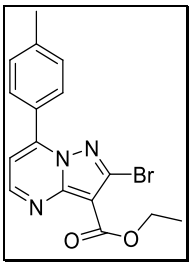
Ethyl 2-bromo-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4a)



Ash colored solid; mp 146-148 °C,; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (d, *J*=4.9 Hz, 1H, arom H), 8.02-8.00 (m, 2H, arom H), 7.62-7.56 (m, 3H, arom H), 7.10 (d, *J*=4.9 Hz, 1H, arom H), 4.52 (q, *J*=6.9 Hz, 2H, OCH_2), 1.47 (t, *J*=6.9 Hz, 3H, CH_3),;

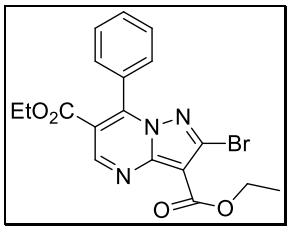
^{13}CNMR ($CDCl_3$, 100 MHz): δ 161.5, 152.6, 149.7, 147.1, 137.5, 131.8, 129.5, 128.8, 109.5, 102.6, 60.7, 14.4,; IR (KBr): 3388, 2983, 1712, 1610, 1543 cm^{-1}.

Ethyl 2-bromo-7-(p-tolyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4b)



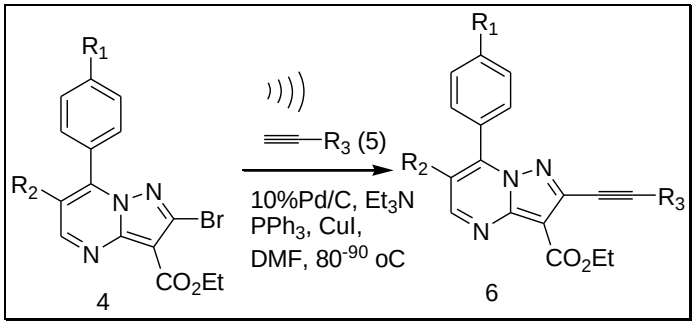
Off white solid, mp 144-146 °C,; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.78 (d, *J*=4.8 Hz, 1H, arom H), 7.94 (d, *J*=7.8 Hz, 2H, arom H), 7.40 (d, *J*=7.8 Hz, 2H, arom H), 7.08 (d, *J*=4.8 Hz, 1H, arom H), 4.49 (q, *J*=6.8 Hz, 2H, OCH_2), 2.47 (s, 3H, CH_3), 1.46 (t, *J*=6.8 Hz, 3H, CH_3),;^{13}CNMR ($CDCl_3$, 100 MHz): δ 161.6, 152.6, 149.8, 147.3, 142.6, 137.5, 129.6, 126.6, 109.1, 102.4, 60.7, 21.6, 14.4,; IR (KBr): 3422, 1707, 1604, 1542 cm^{-1}.

Diethyl 2-bromo-7-phenylpyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (4c)



Off white solid, mp 151-152 °C,; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.23 (s, 1H, arom H), 7.61-7.48 (m, 5H, arom H), 4.51 (q, *J*=6.8 Hz, 2H, OCH_2), 4.17 (q, *J*=6.8 Hz, 2H, OCH_2), 1.46 (t, *J*=6.8 Hz, 3H, CH_3), 1.03 (t, *J*=6.8 Hz, 3H, CH_3),; ^{13}CNMR ($CDCl_3$, 100 MHz): δ 163.7, 161.2, 153.6, 149.4, 139.4, 131.0, 129.2, 128.7, 128.4, 114.1, 103.8, 62.0, 61.0, 14.4, 13.6,;
IR (KBr): 3424, 2981, 1723, 1706, 1592, 1526 cm^{-1}.

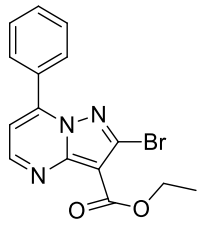
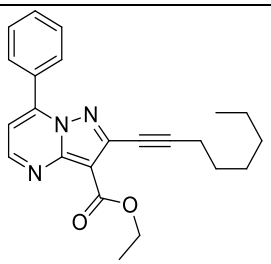
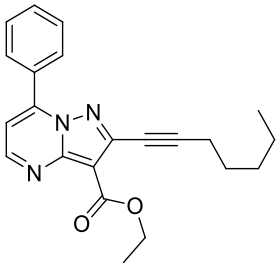
6.5.4. Ultrasound assisted synthesis of 2-alkynyl pyrazolo [1, 5-*a*] pyrimidines (6) under Pd/C-Cu catalysis.[a]

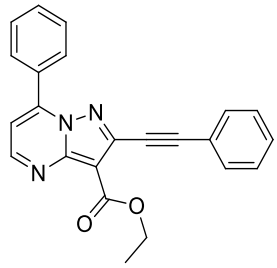
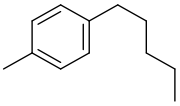
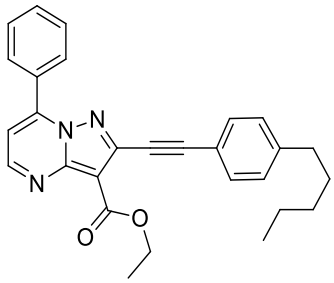
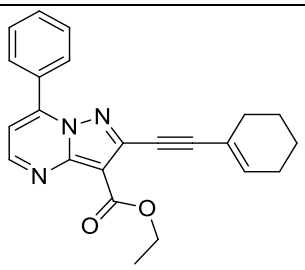
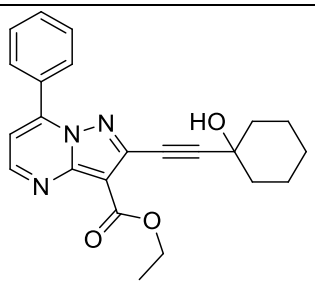
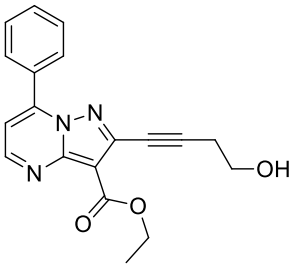


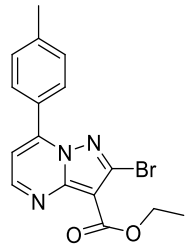
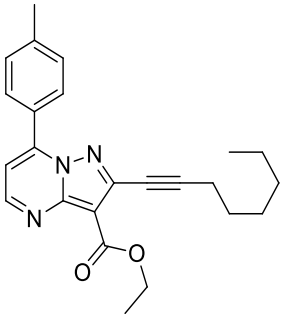
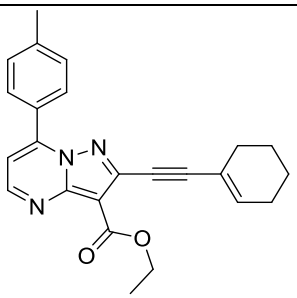
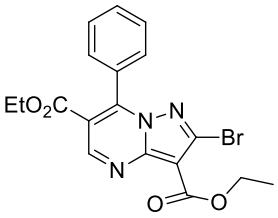
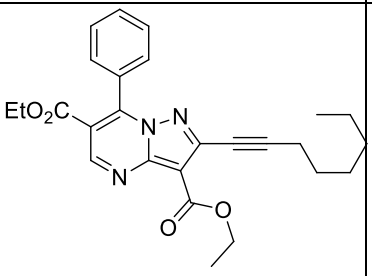
Scheme-5

The compound **4** was then taken for Pd/C-catalyzed alkynylation *via* C-C bond forming reaction under ultrasound irradiation. The coupling reaction of compound **4** was performed using a range of terminal alkynes (**5a-j**) in the presence of 10%Pd/C, CuI and PPh_3 as catalysts and Et_3N as a base in DMF at 80-90 ºC under ultrasound irradiation. The terminal alkynes containing various functional groups such as aryl, alkyl, alkenyl, hydroxylalkyl etc were employed to give a variety of alkynylated product **6(a-j)** in good yields (Table 2).

Table 2: 2-alkynyl pyrazolo [1, 5-*a*] pyrimidines (6a-j)

Entry	Bromo compound (**4**)	Alkyne (**5**; R^3 =)	Time (h)	Product (**6**)	%yield [b]
1.	 **4a**	**5a;** n-Hexyl	5	 **6a**	77
2.	**4a**	**5b**; n-Pentyl	5	 **6b**	71

3.	**4a**	**5c;** 	4	 **6c**	73
4.	**4a**	**5d;** 	6	 **6d**	79
5.	**4a**	**5e;** 	4	 **6e**	70
6.	**4a**	**5f;** 	3	 **6f**	79
7.	**4a**	**5g;** - CH_2CH_2OH	3	 **6g**	78

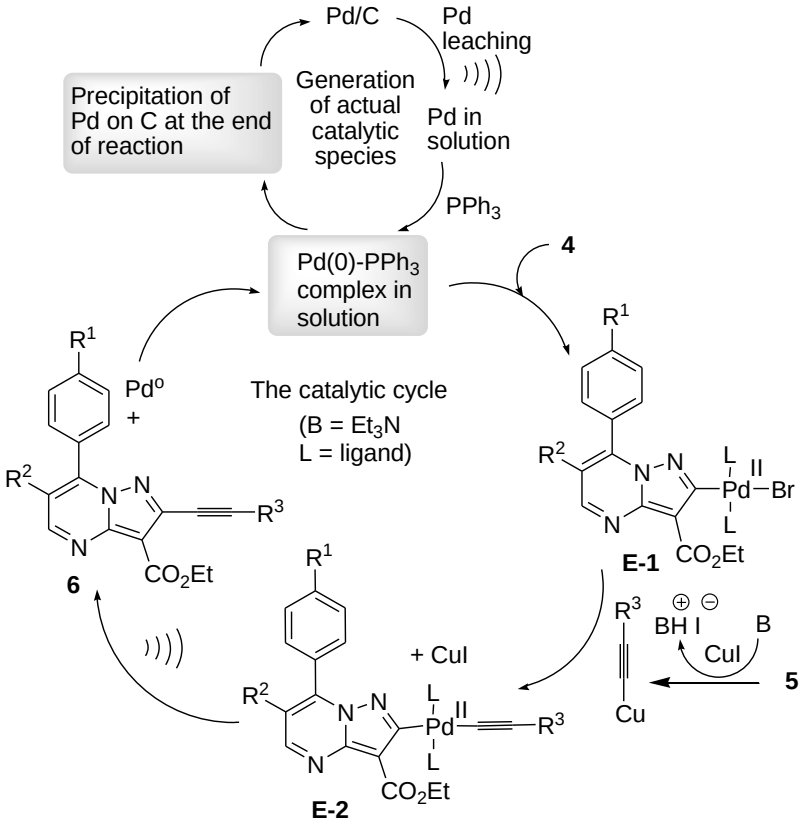
8.	 **4b**	**5a;** n-Hexyl	5	 **6h**	80
9.	**4b**	**5e;** 	4	 **6i**	78
10.	 **4c**	**5a;** n-Hexyl	5	 **6j**	69

[a] All the reactions were carried out by using **4** (1.0 mmol), terminal alkyne **5** (1.5 mmol), 1:4:2 ratio of 10%Pd/C–PPh_3–CuI and Et_3N (4 mmol) in DMF at 80-90 °C under ultrasound irradiation. [b] Isolated yield.

A typical procedure: A mixture of ethyl 2-bromo-7-phenylpyrazolo [1,5-*a*] pyrimidine-3-carboxylate (**4a**) (1 mmol), 10% Pd/C (0.01 mmol), PPh_3 (0.0.04 mmol), CuI (0.0.02 mmol) and triethylamine (4 mmol) in DMF (5 mL) was stirred at 25 °C for 30 min. To this mixture was added an appropriate terminal alkyne **(5a-j)** (1.5 mmol) slowly with stirring. The mixture was then heated to 80-90 °C under ultrasound irradiation using a laboratory ultrasonic bath Sonorex Super RK 510H model producing irradiation of 35 kHz for the time indicated in the above **Table-2**. After completion of the reaction (indicated by TLC) the mixture was cooled to room temperature and poured into ethyl acetate (25 mL). The organic layer was collected, washed with brine solution (3x15 mL), dried over anhydrous Na_2SO_4, filtered and

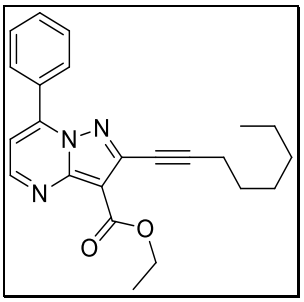
concentrated. The residue was purified by column chromatography using petroleum ether-EtOAc to give the desired product.

A plausible reaction mechanism for the ultrasound assisted Pd/C-catalyzed synthesis of **6** is shown in Scheme **5** (Sonogashira et al, 2002 and Chinchilla et al, 2011). The steps involved in this reaction are (i) generation of Pd(0)-PPh_3 complex, the actual catalytic species, in solution, (ii) oxidative addition of Pd(0) to the bromo compound (**4**) affording the organo-Pd(II) species **E-1** (iii) transmetallation of **E-1** with the copper-acetylide generated from **4** to give **E-2** (iv) reductive elimination of Pd(0) from **E-2** to give the desired product **5**. The generation of Pd (0) species in the initial step involved a Pd leaching process into the solution [from the minor portion of the bound palladium (Pd/C)] followed by interactions with the PPh_3 ligands. The Pd (0)–PPh_3 complex in solution then participated in subsequent steps of the catalytic cycle that seemed to work in solution rather than on the surface. The Pd was re-precipitated on the charcoal surface at the end of the reaction. The role of ultrasound in the present reaction can be explained as follows: The cavitation caused by ultrasound is involved with the growth, oscillation, and collapse of bubbles under the action of an acoustic field (Pal et al, 2009 and Mason et al, 2007). On the other hand the cavitational collapse creates drastic conditions (e.g. the temperature of 2000–5000 K and pressure up to 1800 atmosphere) inside the medium within an extremely short period of time. Thus, these cavitation-induced overall effects are responsible for the facilitation of key steps in the present reaction especially the Pd leaching process and the rapid reductive elimination of Pd(0) leading to **6**.



Scheme 6. Plausible reaction mechanism for the Pd/C-Cu mediated coupling of **4** with **5** leading to the desired product **6**.

Ethyl 2-(oct-1-yn-1-yl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6a) : (Table-2, Entry -1) (Protan and Carbon spectras in **FIG-25 &26**)



Yield (%)	:	77
M.P (^{o}C)	:	120-122 °C
I.R (KBr,cm^{-1})	:	3458, 2975(Acetynyl), 2220, 1704(-$CO_2C_2H_5$), 1610 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 1.47 (t, *J*=7.0 Hz, 3H, CH_3), 4.55 (q, *J*=7.0 Hz, 2H, OCH_2), 7.12 (d, *J*=4.4 Hz, 1H, arom

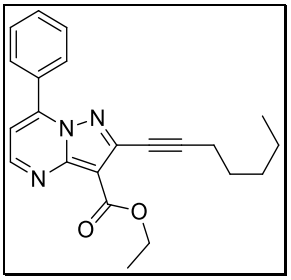
H), 7.40-7.35 (m, 3H, arom H), 7.66-7.60 (m, 5H, arom H), 8.06-8.04 (m, 2H, arom H), 8.83 (d, *J*=4.4 Hz, 1H, arom H),.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 14.6, 60.6, 81.6, 95.9, 104.5, 109.8, 122.2, 128.4, 128.9, 129.2, 129.5, 129.9, 131.7, 132.0, 141.6, 147.2, 149.3, 152.5, 162.0.

Colour : Off white solid

Mass(ESI) : 376.2 (M^++H)

Ethyl 2-(hept-1-yn-1-yl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6b) : (Table-2, Entry -2) (Protan and Carbon spectras in **FIG-27 &28**)



Yield (%) : 71

M.P (^oC) : 80-82 °C

I.R (KBr-cm^{-1}) : 3449, 2955(Acetynyl), 2230, 1713(-$CO_2C_2H_5$), 1612

cm^{-1}.

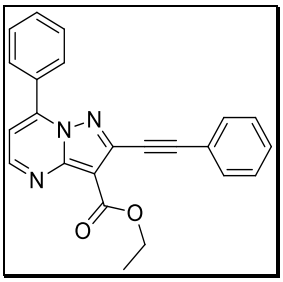
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.92 (t, *J*=7.3 Hz, 3H, CH_3), 1.72-1.35 (m, 9H, CH_2, CH_3), 2.52 (t, *J*=7.4 Hz, 2H, CH_2), 4.49 (q, *J*=7.3 Hz, 2H, OCH_2), 7.08 (d, *J*=4.4 Hz, 1H, arom H), 7.60-7.55 (m, 3H, arom H), 8.02-8.00 (m, 2H, arom H), 8.80 (d, *J*=4.4 Hz, 1H, arom H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 13.9, 14.5, 19.8, 22.1, 27.9, 31.1, 60.4, 72.8, 98.4, 104.1, 109.6, 128.7, 128.8, 129.5, 129.9, 131.5, 142.1, 147.0, 149.2, 152.3, 162.2.

Colour : Ash colored solid .

Mass(ESI) : 362.2 (M^++H)

Ethyl 7-phenyl-2-(phenylethynyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6c): (Table-2, Entry -3) (Protan and Carbon spectras in **FIG-29 &30**)



Yield (%) : 73

M.P (^{o}C) : 120-122

I.R (KBr-cm^{-1}) : 3458, 2975(Acetynyl), 2220, 1704(-$CO_2C_2H_5$), 1610

cm^{-1}.

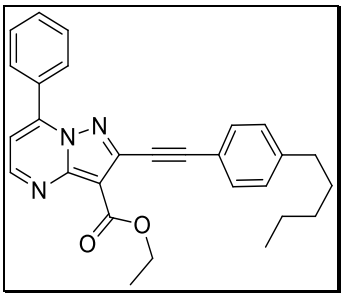
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.47 (t, *J*=7.0 Hz, 3H, CH_3), 4.55 (q, *J*=7.0 Hz, 2H, OCH_2), 7.12 (d, *J*=4.4 Hz, 1H, arom H), 7.40-7.35 (m, 3H, arom H), 7.66-7.60 (m, 5H, arom H), 8.06-8.04 (m, 2H, arom H), 8.83 (d, *J*=4.4 Hz, 1H, arom H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 14.6, 60.6, 81.6, 95.9, 104.5, 109.8, 122.2, 128.4, 128.9, 129.2, 129.5, 129.9, 131.7, 132.0, 141.6, 147.2, 149.3, 152.5, 162.0.

Colour : off white solid .

Mass(ESI) : 368.1 (M^++H)

Ethyl-2-((4-pentylphenyl)ethynyl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6d) : (Table-2, Entry -4)



Yield (%) : 79

M.P (^{o}C) : 118-120

I.R (KBr-cm^{-1}) : 3458, 2934(Acetynyl), 2229, 1705(-$CO_2C_2H_5$), 1608

cm^{-1}.

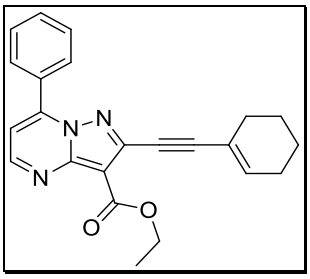
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.89 (t, *J*=6.8 Hz, 3H, CH_3), 1.66-1.30 (m, 9H, CH_2, CH_3), 2.63 (t, *J*=7.9 Hz, 2H, CH_2), 4.53 (q, *J*=6.8 Hz, 2H, OCH_2), 7.09 (d, *J*=4.4 Hz, 1H, arom H), 7.26-7.10 (m, 2H, arom H), 7.61-7.55 (m, 5H, arom H), 8.06-8.03 (m, 2H, arom H), 8.82 (d, *J*=4.4 Hz, 1H, arom H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 162.1, 152.4, 149.3, 147.1, 144.5, 141.7, 132.0, 131.6, 129.9, 129.5, 128.8, 128.5, 119.3, 109.7, 104.4, 96.4, 81.0, 60.5, 35.9, 31.4, 30.8, 22.4, 14.6, 13.9.

Colour : off white solid .

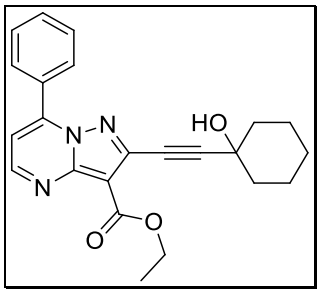
Mass(ESI) : 438.2 (M^{+}+H)

Ethyl-2-(cyclohex-1-en-1-ylethynyl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6e) : (Table-2, Entry -5)



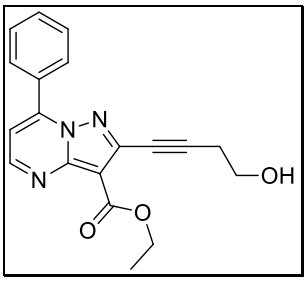
Yield (%)	:	79
M.P (^{o}C)	:	121-123
I.R (KBr-cm^{-1})	:	3423, 2935(Acetynyl), 2229, 1716(-$CO_2C_2H_5$), 1613 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 1.46 (t, *J*=7.00 Hz, 3H, CH_3), 2.30-1.63 (m, 8H, CH_2), 4.50 (q, *J*=7.0 Hz, 2H, OCH_2), 6.41-6.43 (m, 1H, CH), 7.09 (d, *J*=4.4 Hz, 1H, arom H), 7.60-7.57 (m, 3H, arom H), 8.03-8.00 (m, 2H, arom H), 8.80 (d, *J*=4.4 Hz, 1H, arom H).
^{13}C NMR ($CDCl_3$, 100 MHz)	:	δ 16.5, 23.3, 24.1, 27.9, 30.5, 62.4, 80.9, 100.1, 106.1, 111.6, 122.2, 130.8, 130.9, 131.5, 131.9, 133.6, 140.1, 144.0, 149.1, 151.3, 154.3, 164.1.
Colour	:	white solid .
Mass(ESI)	:	372.2 (M^{+}+H)

Ethyl-2-((1-hydroxycyclohexyl)ethynyl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6f) : (Table-2, Entry -6)



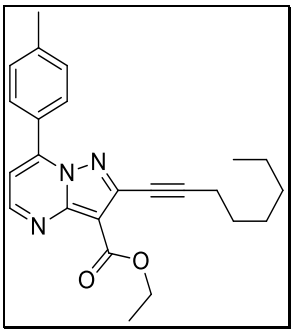
Yield (%)	:	79
M.P (^{o}C)	:	97-99
I.R (KBr-cm^{-1})	:	3449, 2934(Acetynyl), 2230, 1701(-$CO_2C_2H_5$), 1606 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 1.45 (t, *J*=7.0 Hz, 3H, CH_3), 1.49-1.80 (m, 8H, CH_2), 2.08 (t, *J*=7.0 Hz, 2H, CH_2), 2.38 (bs, 1H, OH), 4.49 (q, *J*=7.0 Hz, 2H, OCH_2), 7.10 (d, *J*=4.4 Hz, 1H, arom H), 7.61-7.55 (m, 3H, arom H), 8.04-8.00 (m, 2H, arom H), 8.82 (d, *J*=4.4 Hz, 1H, arom H) .
^{13}C NMR ($CDCl_3$, 100 MHz)	:	δ 14.6, 23.0, 25.2, 39.5, 60.6, 69.1, 100.0, 104.5, 109.8, 128.8, 129.6, 129.8, 131.7, 141.2, 147.2, 149.2, 152.5, 162.0.
Colour	:	Off white solid .
Mass(ESI)	:	390.2 (M^{+}+H).

Ethyl-2-(4-hydroxybut-1-yn-1-yl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6g) : (Table-2, Entry -7)



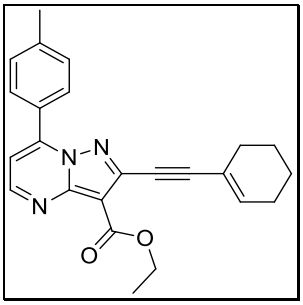
Yield (%)	:	78
M.P (^{o}C)	:	114-116
I.R (KBr-cm^{-1})	:	3440, 2874(Acetynyl), 2235, 1708(-$CO_2C_2H_5$), 1606 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 1.45 (t, *J*=7.0 Hz, 3H, CH_3), 2.78 (t, *J*=5.9 Hz, 2H, OCH_2), 3.38 (bs, 1H, OH), 3.91 (t, *J*=5.9 Hz, 2H, OCH_2), 4.52 (q, *J*=7.0 Hz, 2H, OCH_2), 7.11 (d, *J*=4.4 Hz, 1H, arom H), 7.54-7.61 (m, 3H, arom H), 8.00-7.98 (m, 2H, arom H), 8.81 (d, *J*=4.4 Hz, 1H, arom H).
^{13}C NMR ($CDCl_3$, 100 MHz)	:	δ 14.5, 24.4, 60.6, 60.8, 75.1, 96.3, 104.5, 109.8, 128.8, 129.5, 129.8, 131.6, 142.2, 147.4, 148.8, 152.5, 162.5.
Colour	:	Pale yellow solid .
Mass(ESI)	:	336.1 (M^{+}+H)

Ethyl- 2-(oct-1-yn-1-yl)-7-(*p*-tolyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6h) : (Table-2, Entry -8)



Yield (%)	:	80
M.P (^{o}C)	:	114-116
I.R (KBr-cm^{-1}) 1613	:	3460, 2953(Acetynyl), 2231, 1715(-$CO_2C_2H_5$), cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 0.89 (t, *J*=6.8 Hz, 3H, CH_3), 1.32 (t, *J*=7.4 Hz, 2H, CH_3), 1.30 -1.72(m, 6H, CH_2), 2.46 (s, 3H, CH_3), 2.52 (t, *J*=7.4 Hz, 2H, CH_2), 4.49 (q, *J*=6.4 Hz, 2H, OCH_2), 7.07 (d, *J*=4.4 Hz, 1H, arom H), 7.26-7.40 (m, 2H, arom H), 7.93 (d, *J*=7.9 Hz, 2H, arom H), 8.78 (d, *J*=4.4 Hz, 1H, arom H).
^{13}C NMR ($CDCl_3$, 100 MHz)	:	δ 14.0, 14.4, 19.8, 21.5, 22.5, 28.2, 28.7, 31.3, 60.3, 72.8, 98.3, 104.0, 109.2, 127.0, 129.4, 129.5, 142.2, 147.2, 149.3, 152.2, 152.6, 162.2.
Colour	:	Off white solid .
Mass(ESI)	:	390.4 (M^{+}+H)

Ethyl-2-(cyclohex-1-en-1-ylethynyl)-7-(*p*-tolyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6i) : (Table-2, Entry -9)



Yield (%) : 78

M.P (^{o}C) : 114-116

I.R (KBr-cm^{-1}) : 3461, 2928(Acetynyl), 2213, 1705(-$CO_2C_2H_5$), 1603

cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.44 (t, *J*=6.8 Hz, 3H, CH_3), 1.57-1.70 (m, 4H, CH_2), 2.17-2.31 (m, 4H, CH_2), 2.46 (s, 3H, CH_3), 4.48 (q, *J*=6.8 Hz, 2H, OCH_2), 6.40-6.42 (m, 1H, CH), 7.07 (d, *J*=4.4 Hz, 1H, arom H), 7.26-7.39 (m, 2H, arom H), 7.95 (d, *J*=8.3 Hz, 2H, arom H), 8.77 (d, *J*=4.4 Hz, 1H, arom H).

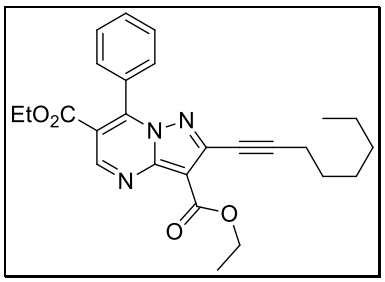
^{13}C NMR ($CDCl_3$, 100 MHz) : δ 14.5, 21.3, 21.5, 22.1, 25.8, 28.6, 60.4, 79.1, 98.0, 103.9, 109.2, 120.2, 127.0, 129.4, 129.5, 137.9, 142.0, 147.1, 149.3, 152.2, 152.6, 162.2.

Colour : white solid .

Mass(ESI) : 386.2 (M^{+}+H)

Diethyl -2-(oct-1-yn-1-yl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (6j) :

(Table-2, Entry -10)



Yield (%)	:	69
M.P (^{o}C)	:	107-109
I.R (KBr-cm^{-1})	:	3440, 2928(Acetynyl), 2249, 1716(-$CO_2C_2H_5$), 1607 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 0.88 (t, *J*=6.8 Hz, 3H, CH_3), 1.02 (t, *J*=6.8 Hz, 2H, CH_3), 1.25-1.68 (m, 8H, CH_2), 2.47 (t, *J*=7.4 Hz, 2H, CH_2), 4.15 (q, *J*=6.8 Hz, 2H, OCH_2), 4.50 (q, *J*=6.8 Hz, 2H, OCH_2), 7.48-7.58 (m, 6H, arom H), 9.21 (s, 1H, arom H).
^{13}C NMR ($CDCl_3$, 100 MHz)	:	δ 13.6, 14.0, 14.4, 19.8, 22.5, 28.1, 28.7, 29.7, 31.2, 60.6, 61.9, 72.5, 99.8, 105.2, 114.1, 128.4, 129.1, 129.2, 130.8, 143.9, 149.0, 149.4, 153.3, 161.8, 164.0.
Colour	:	Pale yellow solid .
Mass(ESI)	:	448.2 (M^{+}+H)

6.6 Biological activity:

Cytotoxicity studies:

MTT Assay: Cell viability was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells (5×10^3 cells/well) were seeded to 96-well culture plate and cultured with or without compounds at 10 μM concentration (five different concentrations i.e., 10, 5, 1, 0.5, 0.1 and 0.01 μM for dose response study) in triplicates for 24 h in a final volume of 200 μl. After treatment, the medium was removed and 20 μl of MTT (5 *mg*/mL in PBS) was added to the fresh medium. After 3 h incubation at 37 °C, 100 μl of DMSO was added to each well and plates were agitated for 1 min. Absorbance was read at 570 nm on a multi-well plate reader (Victor3, Perkin Emler). Percent inhibition of proliferation was calculated as a fraction of DMSO control (without compound).

All the synthesized 2-alkynyl pyrazolo [1,5-*a*]pyrimidines (**6a-j**) were tested for their potential anti-cancer properties *in vitro*. We used human metastatic breast cancer cells i.e. MDA-MB 231, human chronic myeloid leukemia cells i.e. K562, and non-cancerous human embryonic kidney cells i.e. HEK293 for our *in vitro* studies. A colorimetric MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (after 24h of treatment in culture medium containing PBS) was used to evaluate the effect of test compounds on cell viability at a concentration of 10 μM. Doxorubicin was used as a reference compound in this assay (Lown et al, 1992 and Kundu et al, 1990) . While all the compounds showed good to moderate activities (> 50% growth inhibition at 10 µM) against MDA-MB 231 cell lines only few of them were found to be effective against K562 cell lines at 10 µM (Table 3). The compound **6e** and **6i** was found to be most effective among all the compounds tested against both the cell lines used. In a separate study, these compounds showed little or no effects on HEK293 cells indicating their selectivity towards the growth inhibition of cancer cells. For example compound **6e** and **6i** showed 5-8 and 6-7 fold selectivity, respectively. In a dose response study using MDA-MB 231 cell lines the compound **6i** showed IC_{50} = 1.12±0.27 µM comparable to that of doxorubicin (IC_{50} = 0.73±0.16 µM).

The anticancer properties of alkynyl-substituted pyrimidine derivatives have been reported to be because of their ability to inhibit thymidylate synthase (TS), a key enzyme required for the cellular growth (Rao et al, 1992) . A possible explanation for

observed cytotoxic activities of compound **6e** and **6i**, therefore, could be due to its potential inhibition of TS in the presence of a cofactor e.g. methylene terahydrofolate [41]. Thus the binding of TS enzyme through its sulfhydryl (-SH) moiety with the eneyne moiety of compound **6e** and **6i** generates the corresponding drug–enzyme-cofactor ternary complex (**Diagram 3**) thereby inactivating the TS enzyme. Notably, the absence of enyne moiety in rest of the analogues of **6e** and **6i** could be the reason for their inferior activities towards the cancer cell lines used. Nevertheless, it is evident from the present study that 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine can be used as a template for the identification of novel and potential anticancer agents.

Table 3. In vitro activities of compounds 6a-j against cancer cell lines.

Compounds	**% inhibition of growth of cancer cell lines by compounds 5 at 10 µM**		
	MDA-MB 231	**K562**	**HEK293[a]**
6a	55.3±2.1	33.1±1.3	5.3±0.9
6b	51.6±1.8	31.9±2.2	9.2±0.5
6c	57.2±1.1	47.6±2.6	10.9±1.8
6d	47.9±2.3	49.8±1.7	7.6±2.1
6e	72.1±3.1	50.2±1.9	9.1±1.0
6f	43.6±1.5	32.8±2.0	1.8±2.1
6g	67.5±1.7	44.5±1.6	12.4±2.5
6h	52.1±2.0	38.1±1.5	10.8±1.9
6i	75.9±1.9	63.2±2.3	9.8±0.8
6j	56.4±3.0	37.2±2.1	6.3±0.6
Doxorubicin	88.1±1.7	n.d.	n.d.

[a]HEK293 cell line was used as non cancerous cell line.

nd = not done

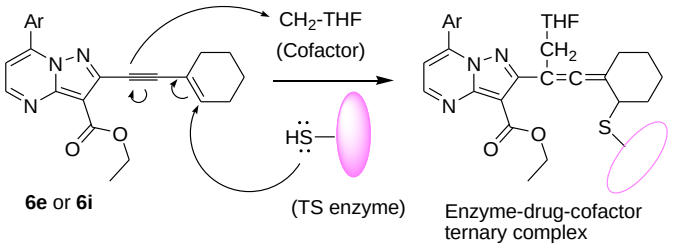


Diagram. (3). Possible interactions of compound 6e and 6i with thymidylate synthase enzyme.

Conclusion:

In conclusion, 2-alkynyl pyrazolo [1, 5-*a*] pyrimidines derivatives have been explored as new and potential anticancer agents. Synthesis of these compounds was carried out by using a multi-step method involving the H_3PO_3 mediated construction of pyrazolo [1, 5-*a*] pyrimidine ring possessing a bromo group at C-2 position followed by Pd/C-Cu catalyzed alkynylation methodology as the key steps. All the steps were performed under ultrasound irradiation. All these compounds were evaluated for their anti-Cytotoxity properties *in vitro* against two cancer cell lines including breast cancer cells i.e. MDA-MB 231 and human chronic myeloid leukemia cells i.e. K562 as well as noncancerous cell line e.g. HEK293. All these compounds showed selective growth inhibition of cancer cells and the compound 5i was found to be most effective among them. Overall, our study suggests that 2-alkynyl pyrazolo[1,5-*a*]pyrimidine framework presented here could be an attractive template for the identification of novel and potential anticancer agents and the corresponding synthetic strategy described could be useful for generating diversity based library of small molecules related to this scaffold.

6.7 Spectrums

Compound 6a: ^{1}H NMR Spectrum

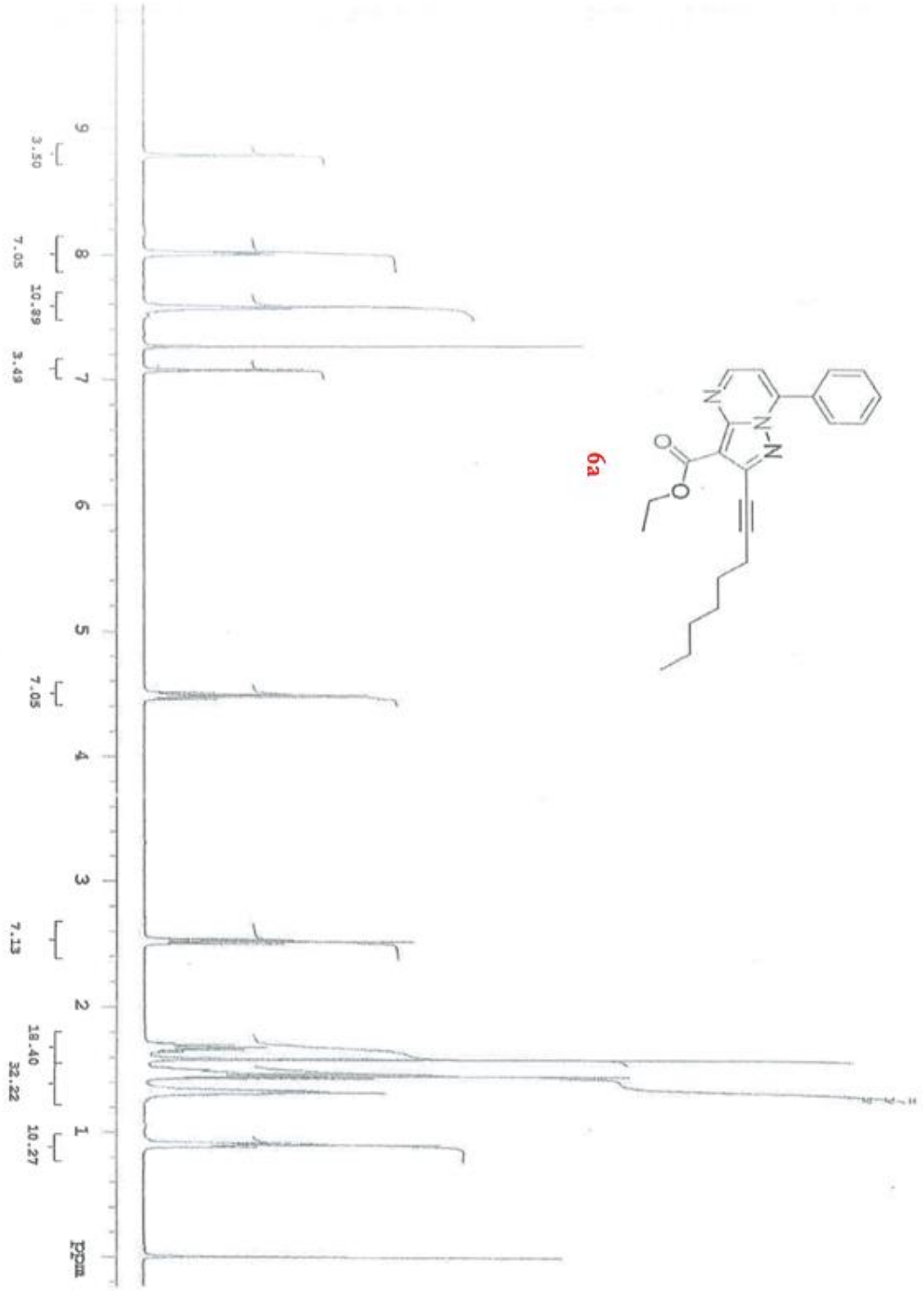


FIG-1: ^{1}H NMR Spectrum of Compound 6a (CDCl3, 400 MHz)

Compound 6a: ^{13}C NMR Spectrum

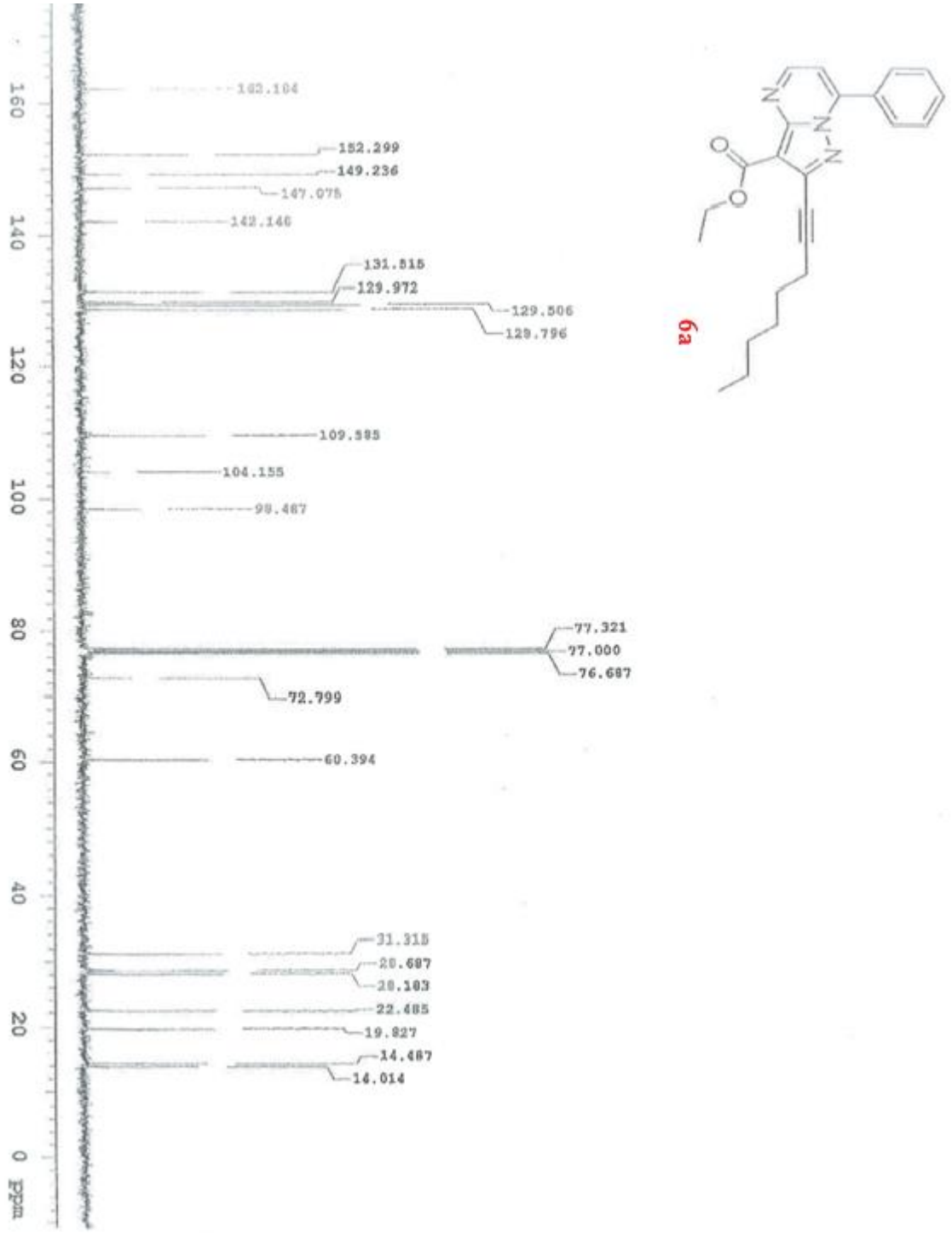


FIG-2: ^{13}CNMR Spectrum of Compound 6a (CDCl3, 100 MHz)

Compound 6b: ^{1}H NMR Spectrum

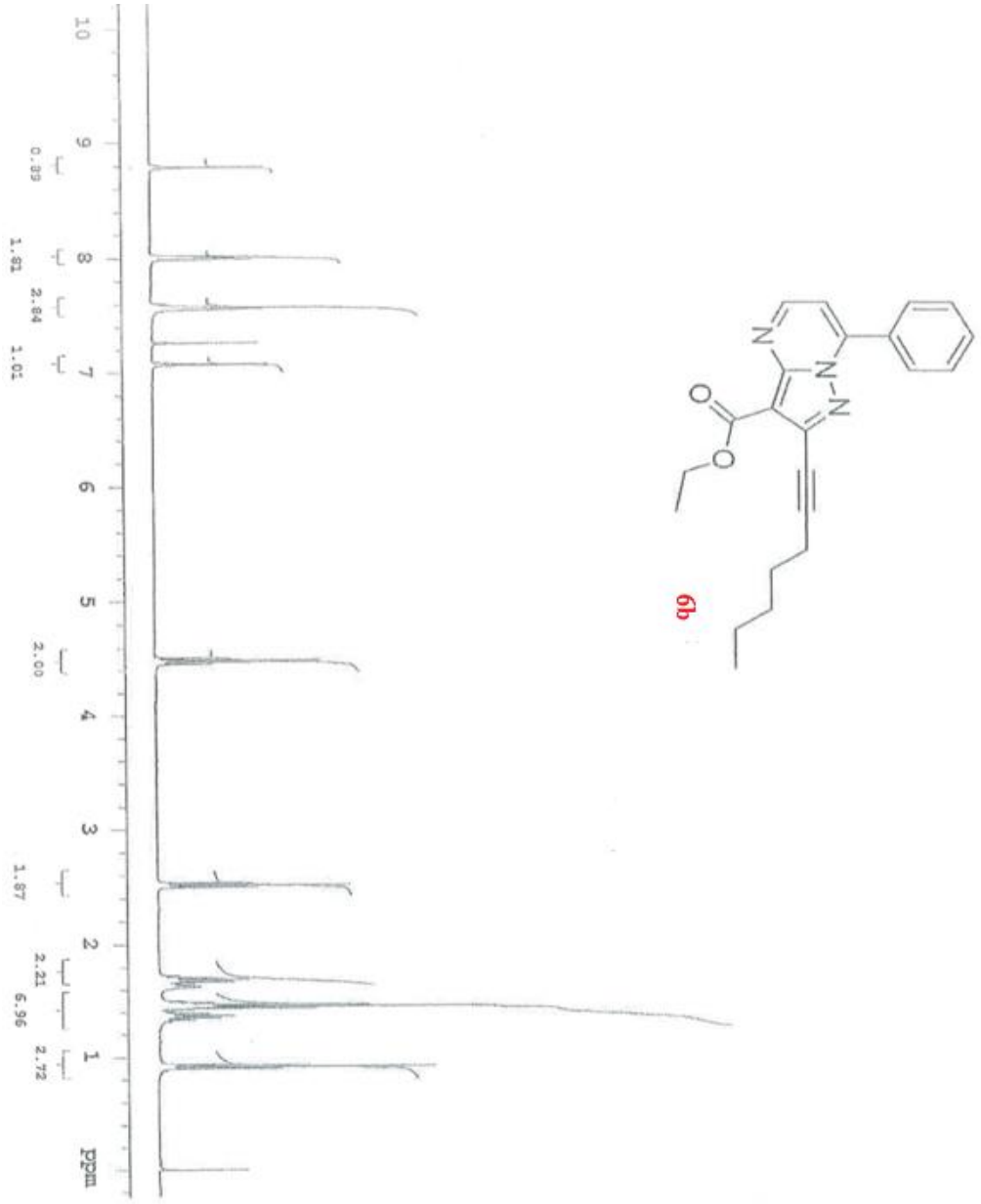


FIG-3: ^{1}HNMR Spectrum of Compound 6b (CDCl3, 400 MHz)

Compound 6b: 13C NMR spectrum

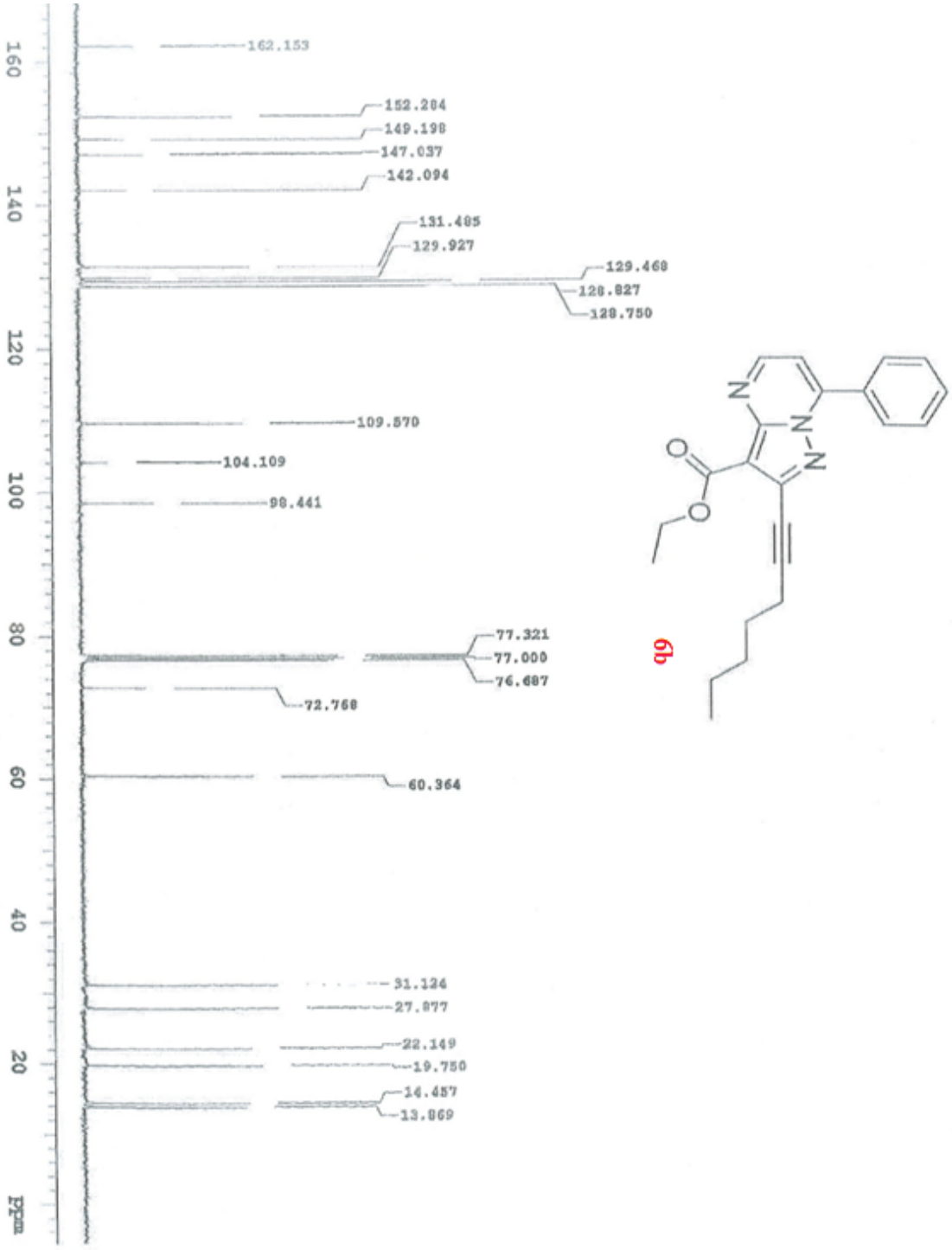


FIG-4: ^{13}C NMR Spectrum of Compound 6b (CDCl3, 100 MHz)

Compound 6c: ^{1}H NMR spectrum

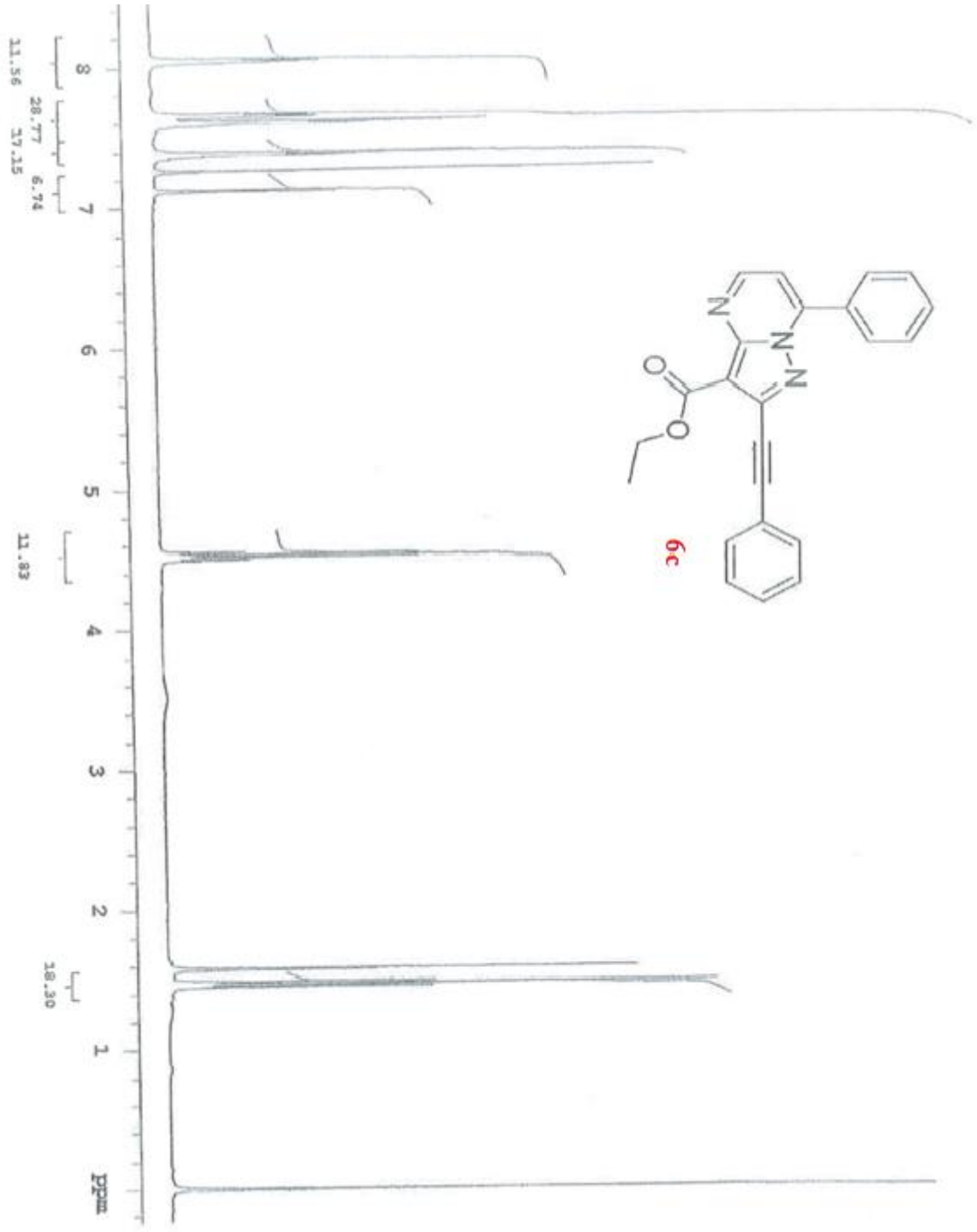


FIG-5: ^{1} H NMR Spectrum of Compound 6c (CDCl3, 400 MHz)

Compound 6c: ^{13}C NMR spectrum

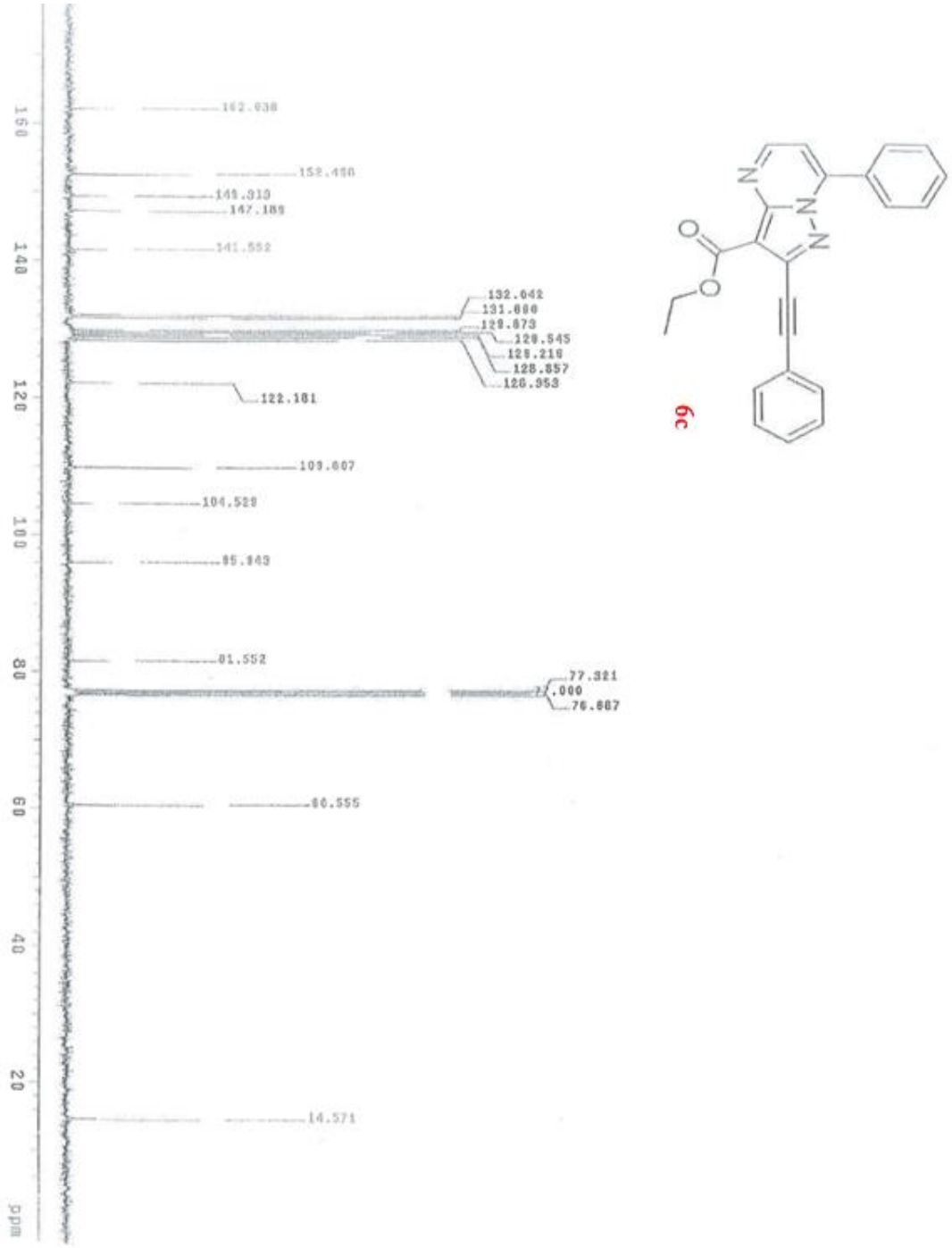


FIG-6: ^{13}C NMR Spectrum of Compound 6c (CDCl3, 100 MHz)

Summary & Scope for Future Work

Chapter 1: General introduction:

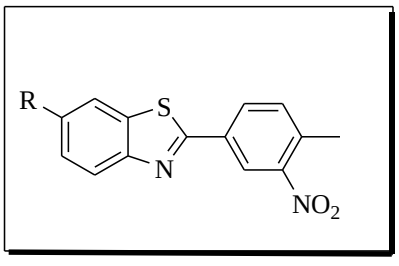
1.0 Introduction:

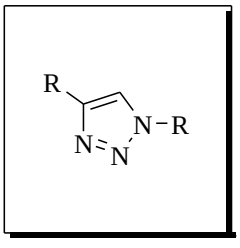
Benzothiazoles, benzimidazoles, oxazolidinones and pyrazolopyrimidine belong to the important class of compounds with antibacterial, antifungal, antimalarial and antihelmintic activity. Though several drugs are available commercially, an comparable activity was in growth to develop and discover new active molecules. Among the major challenges, one of the concerns is that the certain drugs have become resistant towards certain bacterial strains. Therefore the medicinal chemists are engaged to synthesize innovative hybrid molecules or hetero cyclic derivatives to come out with new lead molecules (in association with biologists) with the intention to identify new drugs candidates to meet the resistance problems.

1. 1 Benzothiazole:

Although the demand for new chemical materials and biologically active molecules continues to grow, chemists have hardly begun to discover the enormous pool of potentially active compounds. In the scenario of a persistent request especially from the pharmaceuticals companies for better drugs, it has become a challenging task for medicinal chemists to prepare new patentable molecules that combine high activity and selectivity, drug-likeness, and good pharmacokinetic properties.

As part of our continuing interest in the synthesis of biologically active compounds we have successfully synthesized such derivatives which consist of two distinct pharmacophores; benzothiazoles and trizoles, each certainly, possessing a wide range of biological and pharmacological activities.



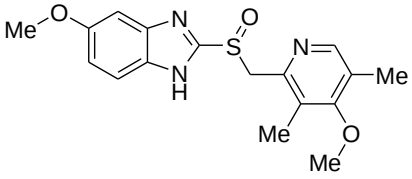


Benzothiazole scaffold derivatives consist of fused bicyclic ring systems. Benzothiazoles are an important class of potential organic molecules in medicinal chemistry due to their extensive range of activity such as neuron protective, anti-convulsive, anti-glutamate, anti-malarial, anthelmintic, anti-tubercular, analgesic, anti-inflammatory, anti-microbial, and anti-

cancer to name a few . In this context, synthetically accessible molecules having new benzothiazole scaffold with promising biological profile have attracted the attention of medicinal organic chemists for their applications in potential chemotherapeutics.

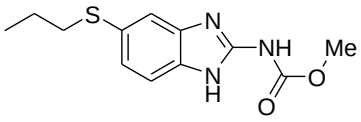
1.2 Benzimidazoles:

Benzimidazole is an important heterocyclic compound which, can be prepared simply from the condensation of *1,2*-phenylenediamine and carbonyl compounds. The benzimidazole derivatives are of broad interest because of their diverse biological activity as anti hypertension drugs, antihelmintic drugs, anti-psychotic agents, anti-ulcer agents, fungicidal drugs and antibacterial agents. They are extremely effective with respect to their inhibitory activity. Benzimidazoles are among the significant heterocyclic compounds found in several natural and non-natural products. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin-B_{12}. Marine alkaloid kealiiquinone and benzimidazole nucleosides etc. can also be included as other examples .Benzimidazoles are active synthons in numerous organic reactions. As far as their medicinal activity is concerned, Some of the benzimidazoles- based drugs are among the most widely-used drugs, some of which are depicted below.



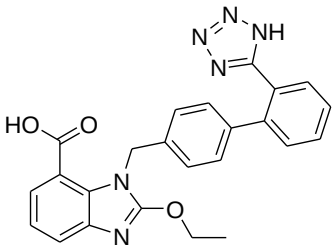
Omeprazole

(antiulcer agent)



Albendazole

(antihelmintic agent)

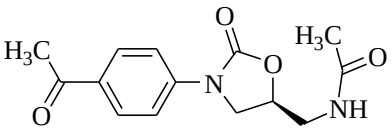


Candesartan

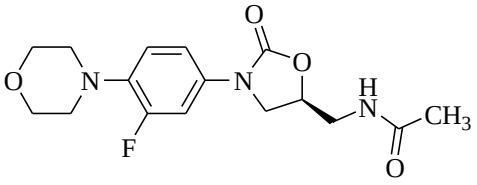
(anti -hypertensive)

1.3 Oxazolidinones

The unique mode of action combined with a high antimicrobial activity of oxazolidinones, has prompted us to investigate newer molecules based on oxazolidinone scaffolds with enhanced activity. In this present investigation an attempt has been made to synthesize a novel series of C-ring modified and C-5 arm modified oxazolidino-arylamido/sulphonamides analogues. In the present work the main focus has been on improving the activity and limiting the Cytotoxicity of oxazolidinone based derivatives. The present work describes the synthesis and evaluation of bacterial and anti-tubercular activity of oxazolidino-aryl amides and sulphonamide conjugates particularly for drug resistance bacteria.



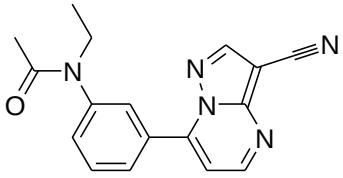
DuP 721



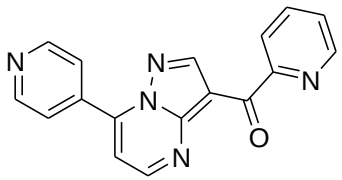
Linezolid

1.4 pyrazolo pyrimidine

Pyrazolo [1,5-*a*] pyrimidines are purine analogues and possess useful properties as anti-metabolites in purine biochemical reactions. Compounds belonging to this class have attracted wide interest in pharmaceutical research because of their pharmacological properties including anti-trypanosomal activities, anti-schistosomal activities. Derivatives of pyrazolo [1,5-*a*] pyrimidines are used as HMG-CoA reductase inhibitors, COX-2-selective inhibitors, AMP phosphodiesterase inhibitors, KDR kinase inhibitors, selective peripheral benzodiazepine receptor ligands, and antianxiety agents. These interesting biological properties prompted medicinal chemist to develop novel, efficient and general procedures for the synthesis of pyrazolo [1, 5-*a*] pyrimidine derivatives including those assisted by microwave irradiation.



Zaleplon
(sedative)



ocinaplon
(anxiolytic)

1.5 Objective:

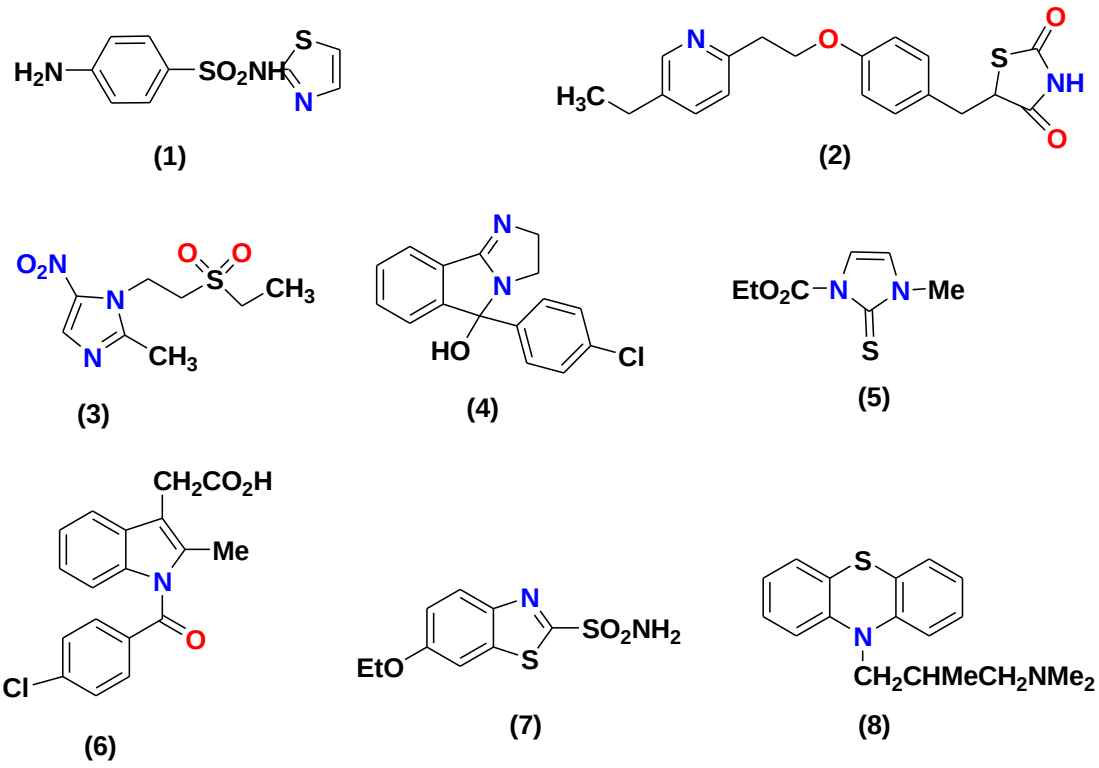
The main objective is to prepare hetero ring fused benzothiazole, benzimadazoles and oxazolidinones and pyrazolo pyrimidines as our target compounds and to evaluate their biological activity. The major problem in the recent times was the resistance of bacterial strains towards certain heterocyclic drugs and other antibacterial agents across the world. In order to meet this problem several strategies were planned to synthesize new class of compounds such as combination of two active pharmocophores to make the hybrid molecules or fusion of two active ring systems to make hetero ring fused bioactive molecules.

Chapter 2: Micro Review on Hetero Cyclic Compounds

Heterocyclic compounds hold a special place among pharmaceutically significant natural products and synthetic compounds. The significant ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmocophores has basically contributed to their unique value as conventional key elements of numerous drugs. Heterocycles afford a large area for new lead molecules and for generation of activity relationship with biological targets. For these reasons, it is not surprising that this structural class has received unique concentration in drug discovery.

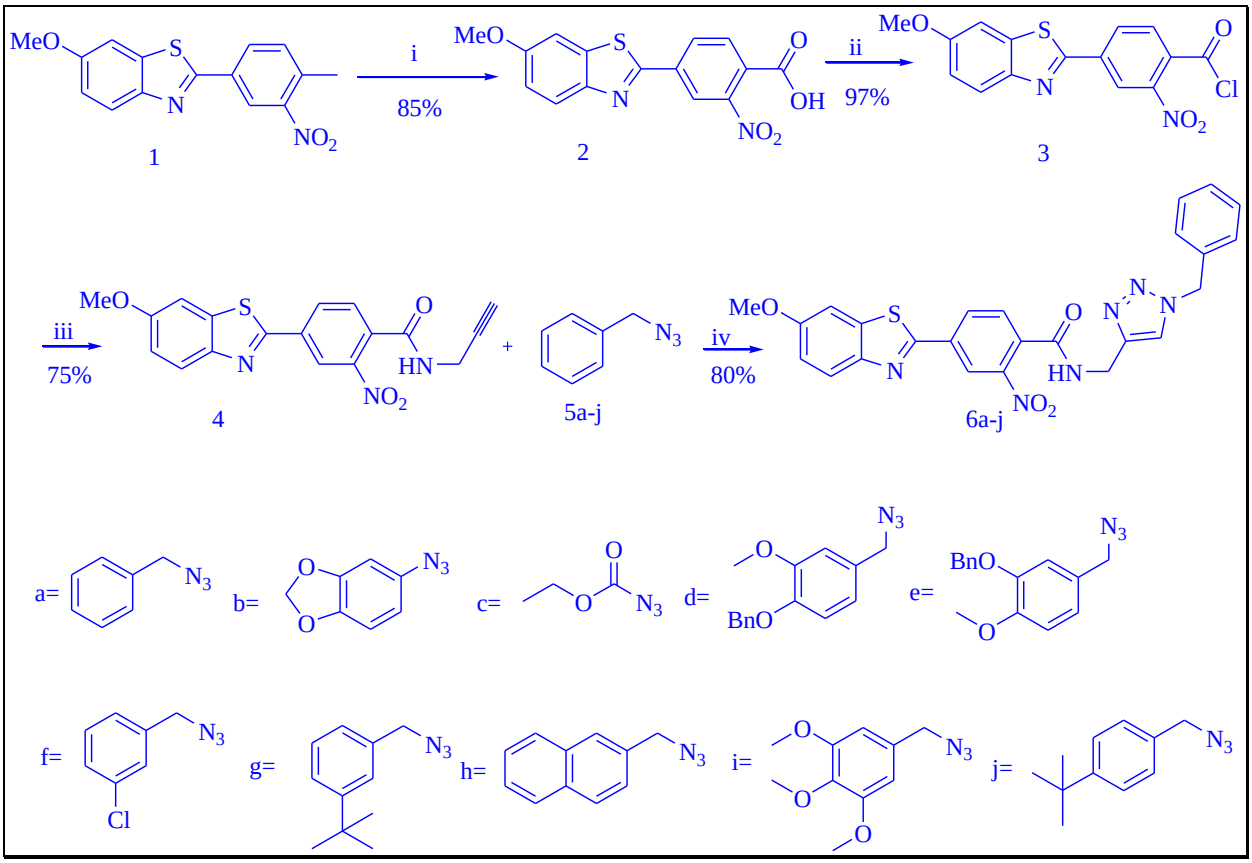
The molecules containing a ring with of two or more different kinds of atoms (commonly carbon [C], nitrogen [N], oxygen [O] and sulfur[S]) - like indole, oxadiazole, chroman, pyran, furan, thiophene, pyrrole and thiazole etc. are called as heterocyclic moieties. Heterocyclic rings can have hydrogen bond donors and acceptors in a semi-rigid scaffold and they can therefore present a diverse range of pharmocophores. The convenience of heterocyclic is due to their combination of compact and robust molecular structures with high degree of molecular diversity that results in properties which can be finally adjusted to the need of complicated applications. Derivatization of heterocyclic pharmocophores with different groups or substituent's represents an adaptable approach to generate chemical diversity for lead identification and optimization of probable drug targets.

Natural products such as antibiotics, penicillin, indolmycin and cephalosporins; alkaloids like vinblastine, ellipticine, morphine, reserpine; cyclopeptides, cyclicdepsipeptides, macrolides, polyketides, steroids, saponins - and glycosides all have heterocyclic moieties. It can be esteemed by looking at the structures of various marketed drugs that are presently in therapeutic use .The drugs like psicofaranine and tubercidin; aminoglycosidal antibiotics such as (streptomycin and kanamycin); sulfa drugs like Sulphathiazole [1] used against a broad range of bacteria; antidiabetic drugs, Pioglitazone [2]; antiprotozoal drug, Tinidazole [3]; CNS stimulant drug, Mazindaol [4]; antithyroid drugs, Carbimazole [5]; anti-inflammatory drug, Indomethacin [6]; diuretics as Ethoxzolamide [7] and antihistamine drug, Trimeprazine [8] all hold different heterocyclic moieties.



Chapter 3: Facile Synthesis of *N*-(Benzyl-1*H*-1, 2, 3-Trizole-5-yl-Methyl)-4-(6-Methoxy benzo [*d*] Thiazol-2-yl) -2-Nitro benzamides *via* Click Chemistry.

In this work, we accomplished the synthesis of the proposed structure of novel *N*-((l-benzyl-l*H*-l,2,3-triazol5-yl) methyl)-4-(6-methoxybenzo[*d*]thiazol-2-yl)-2-nitrobenzamides (Scheme-1) following by *an* situ inter molecular 1, 3-dipolar cyclo-addition reaction between easily affordable azides and alkynes with good yields and high purity. The synthesized compounds were screened for the Antimicrobial activity study using Cup plate method. Some of the compounds showed strong anti-microbial activity at low concentrations and hence the further design and synthesis of compounds in this direction are in progress. This study can provide a road map to design and synthesis of Benzothiazole scaffold based anti-microbial active compounds



Scheme-1: preparation benzothiazole –trizoles derivatives *via click chemistry*

Reagents and conditions: (i) Tetra butyl Ammonium Permanganate (TBAP), dry Pyridine (ii) $SOC1_2$, cat. DMF, CH_2C1_2 (iii) Propargyl amine, Et_3N, dry THF, 0 °C,r.t. (iv) 0.25-2 mol% $CuSO_4.5H_2O$, 5-10 mol% Sodium ascorbate, *t*-BuOH:H_2O, r.t., 30 min.

Here, we describe the final step of the scheme 1 i.e. synthesis of **6a-j** as a model synthesis and corresponding physical data are provided below. Water and tertiary alcohol in the ratio 1:1 (50 ml) were added to the round bottom flask containing compounds **4**, (5 g, 27.2 mmol) possessing triple bond and freshly prepared benzyl azides (4.68 g, 35.1 mmol) (**5a**) and stirred for 5- 10 minutes. To this reaction mixture were added 0.5 mol % $CuSO_4$.$5H_2O$ (0.339 g, 1.36 mmol.) and 10 mol% sodium ascorbate (2.155g, 0.40 mmol) simultaneously. Reaction was continued for 12h at room temperature till the completion of the reaction. After the completion of the reaction (monitored by TLC), tertiary alcohol was removed under pressure and the aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with brine solution and dried over Na_2SO_4. The organic layer was separated and removed in vacuum under reduced pressure. The resulting material was

purified by column chromatography to afford colourless compound **6a** (4.35 g) in 87% as a white solid.

Activity: The screening studies of Benzothiazoles **6a-j** were carried out against bacterial strains and antifungal strains. The activity results are summarised in Table-1

Table: 1 Anti bacterial activity of benzothiazole 6(a-j)

Compound	**Gram positive bacteria**		**Gram negative bacteria**		**Fungi**	
	S. Areas	**B. subtilis**	**E.coli**	**P.Aeruginosa**	**A. Niger**	**A. fumigatus**
6a	17	14	12	13	10	17
6b	13	12	15	12	10	18
6c	15	11	16	12	11	17
6d	13	11	12	10	12	18
6e	13	10	10	11	11	18
6f	14	11	10	13	13	19
6g	13	11	12	12	13	18
6h	16	10	14	14	14	18
6i	17	13	16	14	14	18
6j	14	11	13	14	13	18
std	20	21	22	20	29	22

The standard drug for bacteria: Ciprofloxacin; Standard drug for fungi: Miconazole Zone of Inhibition (Internal diameter: 6mm) All the compounds were screened at 100μg/ml concentration.

Conclusion

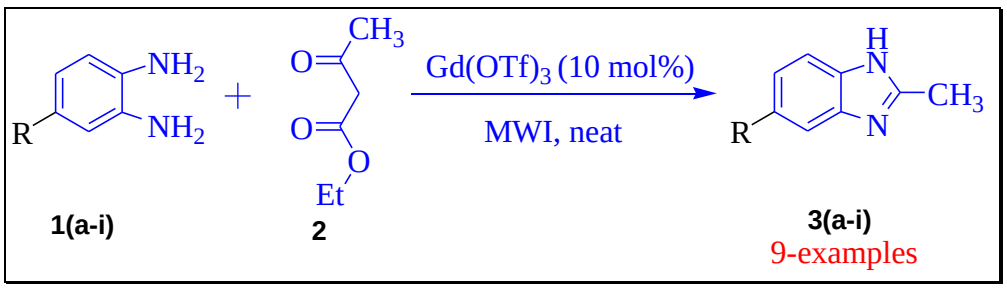
In conclusion, The described method for the synthesis of proposed structure of novel *N*-((l-benzyl-1*H*-l,2,3-triazol5-yl) methyl)-4-(6-methoxybenzo[*d*] thiazol-2-yl)-2-nitrobenzamides following by in situ intra molecular 1, 3-dipolar cyclo-addition reaction between easily affordable azides and alkynes with good yields and high purity. The synthesized compounds were screened for the Antimicrobial activity study by using Cup plate method. Some of the compounds shown strong anti-microbial activity even at low concentrations and hence further design and synthesis of compounds in this direction is in progress. This study can provide a road map to design and synthesis of Benzothiazole scaffold based anti-microbial active compounds.

Chapter 4:

Efficient method Microwave-assisted for synthesis of 2-substituted benzimidazoles from *1, 2*-phenylenediamine and β-keto esters /1, 3-di ketones using Gd (OTf) $_3$ as catalyst

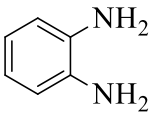
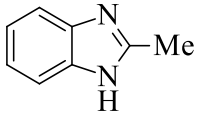
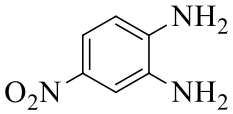
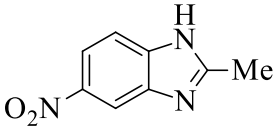
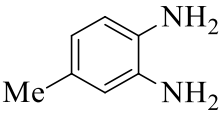
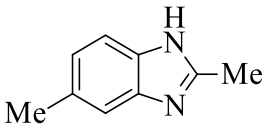
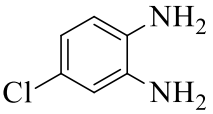
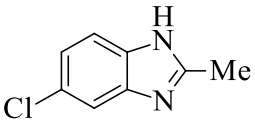
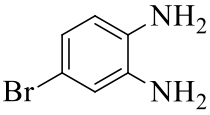
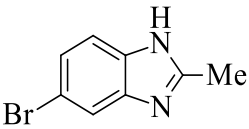
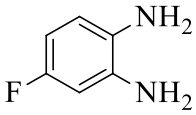
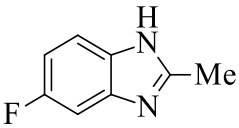
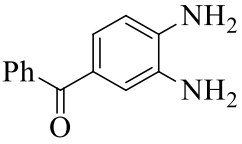
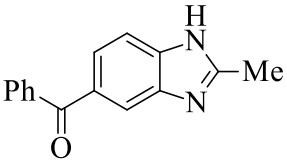
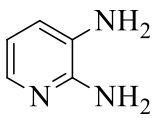
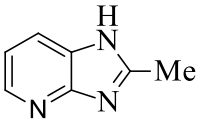
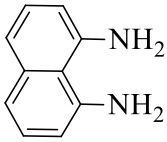
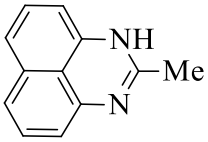
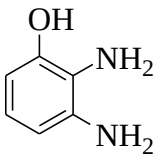
A simple, convenient and green synthetic method was developed for the preparation of 2-substituted benzimidazoles under mild reaction conditions by using Microwave irradiation. The methodology involves the formation of benzimidazoles from 1, 2 phenylenediamines with β-keto esters or 1, 3-di ketones using Gadolinium triflate as catalyst without any side products with lower reaction times and good yields compared to conventional methods.

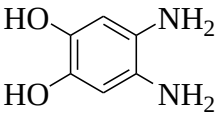
The efficacy of Gadolinium triflate was studied as a model reaction using 1, 2 phenylenediamine and ethylacetoacetate in neat condition under microwave irradiation at ambient temperature to afforded the corresponding 2-substituted benzimidazole in 80-90% yield (Scheme 2). By using this method we also made an attempt with prepare diol substrates, but unfortunatly the reactions were not successful.



Scheme-2 preparation of 2- substituted benzimadazoles from O- phenyl diamines

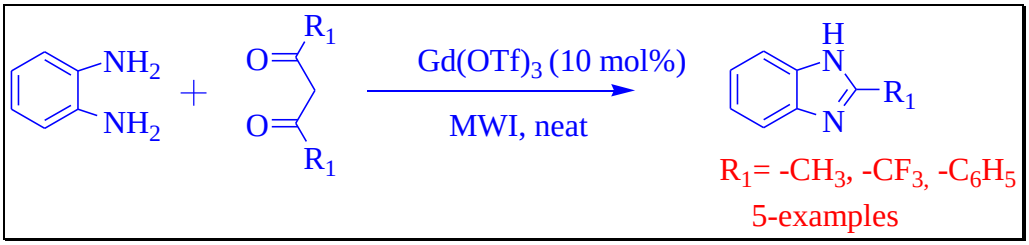
Table 2: Gadolinium (III) triflate catalyzed benzimidazoles

Entry	Diamine (1)	Benzimadazoles (3)	Time (mins.)	Yield [a]
1			10.0	86
2			8.5	80
3			10.5	85
4			8.5	76
5			7.5	71
6			6.5	70
7			8.0	65
8			11.0	70
9			12.5	65
10		No Reaction		

11		No Reaction

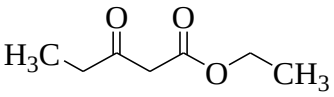
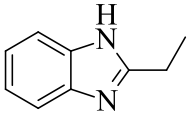
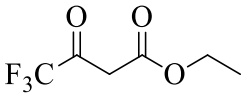
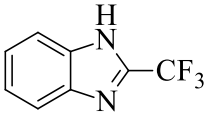
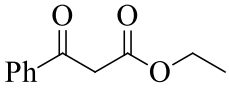
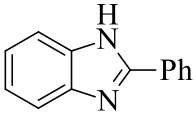
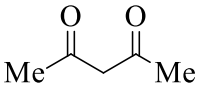
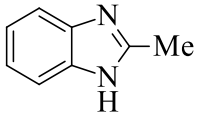
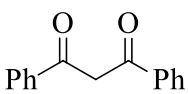
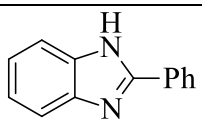
[a] Isolated yields. All products gave agrreble ^{1}H NMR, IR and mass spectral data

The feasibility of the reaction method was confirmed by using the reaction of different β-keto esters and 1, 3-di ketones (aromatic and aliphatic) with 1, 2-phenylenediamine subjected to the above reaction provided to form a series of benzimidazoles. In this process 1, 3-di ketones gave excellent yields compare to the *β*-keto esters. **(Scheme 3).**



Scheme-3: preparation of Benzimidazoles from 1, 3- di ketones

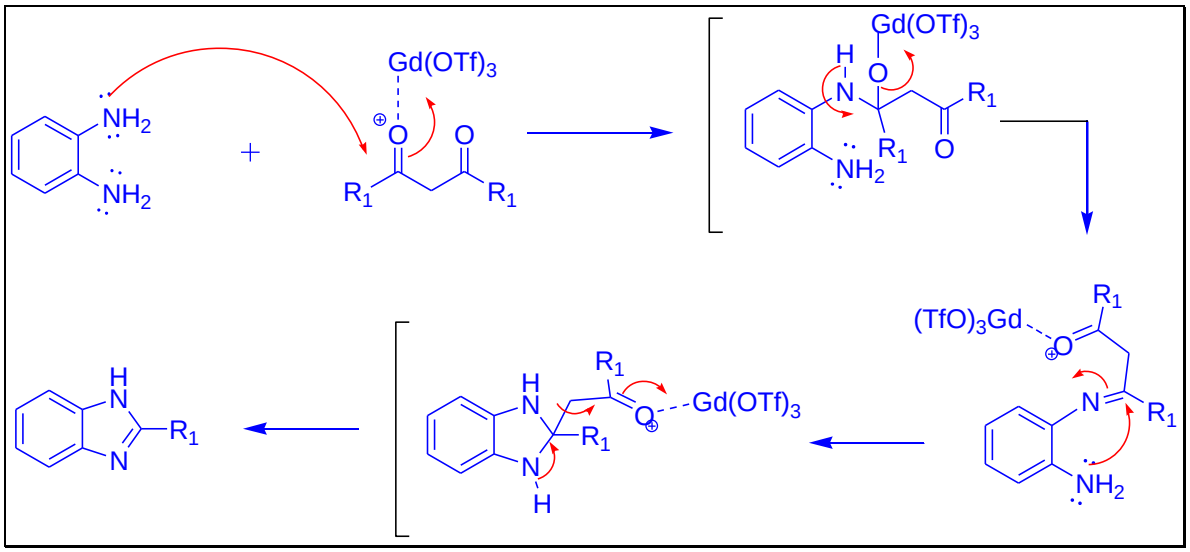
Table 3: Gadolinium (III) Triflate catalysed benzimidazoles.

Entry	1,3 –di ketones(**2**)	Benzimdazoles (**4**)	Time (mins)	Yield [a]
1			7.5	60
2			5.5	65
3			4.5	63
4			4.0	60
5			6.5	63

[a] Isolated yields. All products were characterized by ^{1}H NMR, IR and mass spectral data

Mechanism:

The catalyst Gadolinium triflate may be forming a complex with the carbonyl functional group in *β*-keto esters / 1, 3-diketones resulting the π bond electrons of carbonyl group to shift towards the metal. The nonbonding lone pair of electrons of amine attacks on to carbonyl carbon followed by movement of electrons leading to the imine bond formation. The nonbonding electrons of another amine then attacks on to imine carbon; the π bond electrons of imine group shifted towards the nitrogen atom. The rearrangement takes *via* C-C bond cleavage at α-position of the carbonyl group finally yielding the 2-substituted benzimadazoles.



Typical procedure: 1, 2-phenylenediamine **1** (0.2 g, 1.85 mmol), ethylacetoacetate **2a** (0.722 g, 5.55 mmol) and Gd $(OTf)_3$ (0.050 g, 0.185 mmol) were taken into a 50 ml single neck flask and after mixing them properly , the flask was placed under Microwave irradiation at 300W(CEM-discover , model number-908010). The reaction progress was monitored by TLC by using mobile phase ethyl acetate and hexane (6:4 ratio). After completion of the reaction (TLC), the reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and distilled under reduced pressure afforded the corresponding 2-methyl benzimidazole in 86% yield.

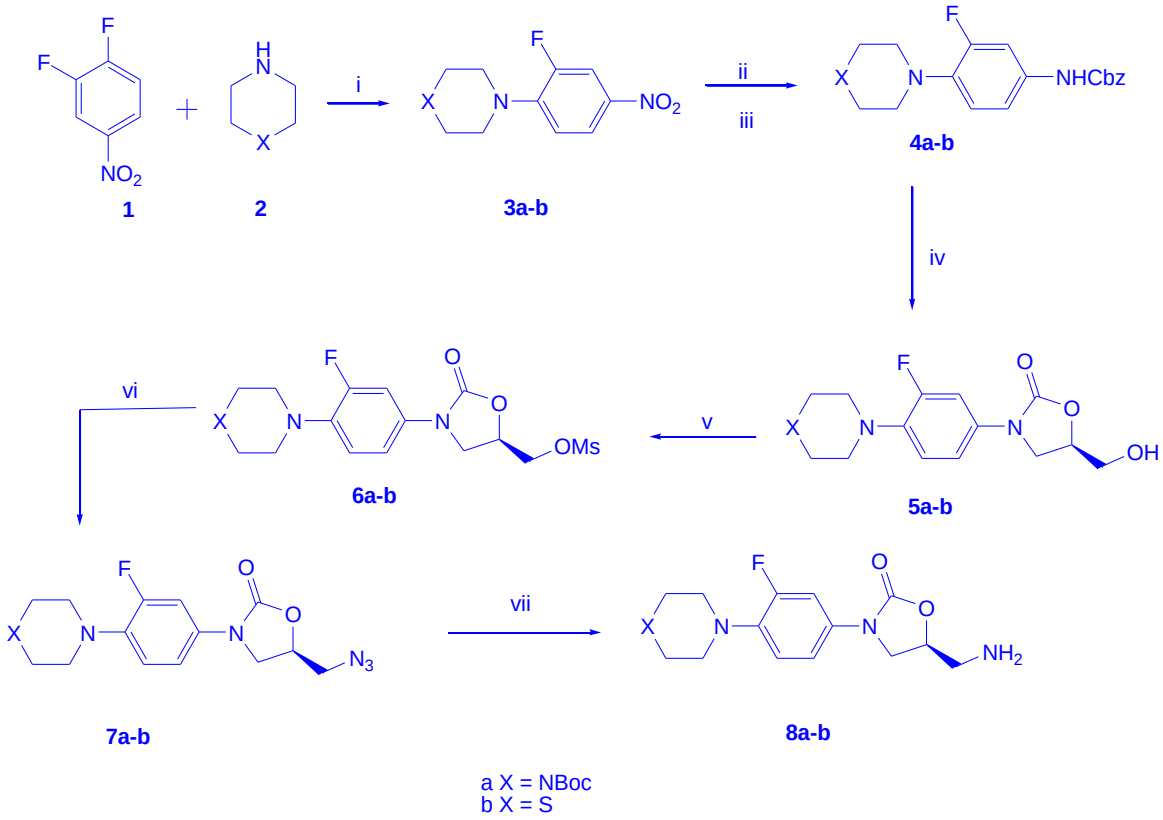
Conclusion:

In conclusion, we have widened a practical and novel procedure for the selective synthesis of 2-substituted benzimadazoles derivatives by using Microwave irradiation technique and,

commercially available Gadolinium triflate as a catalyst under the neat reaction conditions. The present procedure has several advantages; mild reaction conditions, nonhazardous method, experimental easy and simple workup process and less reaction time compared to conventional methods.

Chapter 5: Synthesis of antitubercular and antibacterial activity of new oxazolidino-amides/sulfonamides conjugates

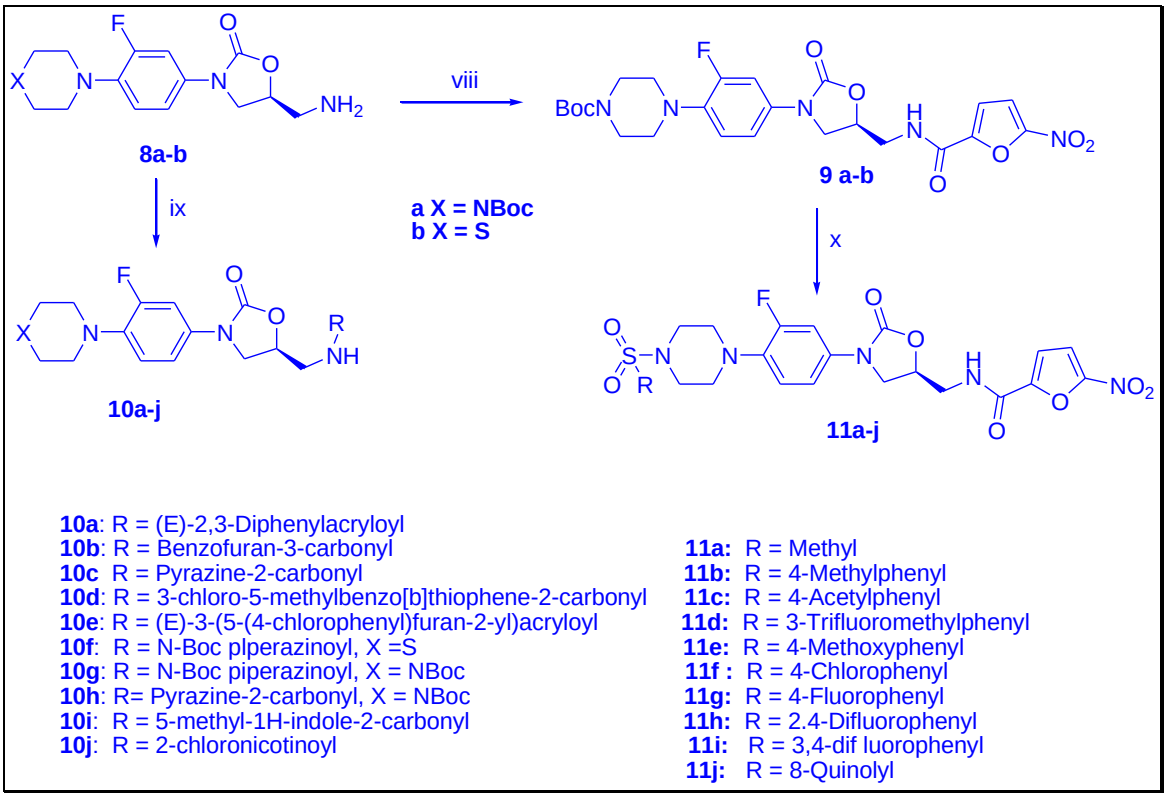
The preparation of intermediates oxazolidinyl methyl amines (**8a** and **8b**) has been carried out by the synthesis sequence illustrated in **Scheme 4**. The treatment of commercially available *tert*-butyl piperazine-1-carboxylate (**2**) with 3, 4-difluoronitrobenzene (**1**) in acetonitrile in presence of diisopropyl ethyl amine under reflux at 80^{o}C affords the compounds **3a (3b** was also synthesized when thiomorpholine was used instead of **2).** The nitro compounds in the presence of stannous chloride are reduced to their corresponding amines and protected with chlorobenzoyl format to afford compounds **4a-b**. The benzyloxy *N*-protected compounds (**4a-b**) have been treated with (*R*)-glycidyl butyrate in presence of n-butyl lithium at -78 ^{o}C to give compounds oxazolidinyl methanol (**5a-b**). The intermediates **5a-b** were treated with methanesulfonyl chloride in the presence of triethyl amine in dichloromethane as solvent to afford compounds **6a-b**. The mesylated intermediates further undergoes in SN^2 nucleophilic substitution by azide in presence of sodium azide under reflux in dimethyl formamide to yield oxazolidinone azide **7a-b**. Further, on reduction in presence of hydrogen and palladium in ethyl acetate, azide (**7a-b**) converted to corresponding amines **8a-b**.



Scheme-4: preparation of oxazolidinone moiety

Reagents and conditions: (i) ACN, DIPEA, reflux, 3 h; (ii) $SnCl_2$, methanol, 12 h; (iii) benzylchloroformate, acetone, aq.$NaHCO_3$, 12 h; (iv) (*R*)-glycidyl butyrate, THF, n-BuLi, -78^o C to rt, 12 h; (v) MsCl, DCM, TEA, 5 h; (vi) NaN_3, DMF, reflux, 5 h; (vii) H_2, Pd, methanol, 2 h.

The synthesis of target compounds **10a-j** and **11a-j** have been achieved by the procedure described in **Scheme 5**. The amine intermediates (**8a-b**) on coupling reaction with different acids and sulfonyl chlorides afford final conjugates. The oxazolidinone amines (**8a-b**) treated with 5-nitro furoic acid in the presence of EDC in dry CH_2Cl_2 afforded the amide coupled compound 9a. Further the deprotection of the intermediate (**9a**) by $BF_3.Et_2O$ in CH_2Cl_2 followed by treatment with different sulfonyl chloride in dry pyridine at room temperature afforded C-5 substituted modified oxazolo sulphonamides analogs (**10a-j**). Similarly, the intermediate (**8a**) in the presence of amide coupling reagent l-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) in CH_2Cl_2 treated with various aromatic acids to afford final conjugates **11a-j** in significant yields.



Scheme-5: C-ring and C-5 substituted oxazolidinones derivatives

Reagents and conditions: (viii) 5-nitro furoic acid, EDCI, DCM, rt, 8h; (ix) Aryl/ hetero aryl chloride, EDCI, DCM, rt, 8h; (x) a) $BF_3.Et_2O$, CH_2Cl_2, rt; b) sulfonyl chloride, pyridines, rt, 2h.

The library of aryl amides and aryl sulfonamide conjugates of oxazolidinone has been designed, synthesized and evaluated against *M. tuberculosis* H37Rv, bacterial strains and fungal strains. Of them compounds **9a** and **10a** have shown remarkable antimycobacterial activity (*MIC* = 1 and 2 *μg/ml* respectively) equal to linezolid. Further all the compounds have also been evaluated against twelve fungal strains. Compounds **9a** and **10a** have displayed significant Antimycotic activities (approximately 37 folds more potent than Flucanozole). This study can provide a road map to design and synthesis of oxazolidinone scaffold based anti-microbial active compounds.

Biological activity

The compounds **9a, 10a-j and 11a-j** have been screened for their antibacterial activity against *Staphylococcus aureus, Bacillus subtillis, E. coll, P. aeruginosa* bacteria and the antifungal activity was evaluated against yeast *Candida albicans* (MTCC 3017). The inhibitory zones (in mm) are determined by using agar well method (cup plate method).

Neomycin and Flucanozole are used as positive controls against bacteria and fungi, respectively.

The results summarized in **Table 1** show that all compounds exhibited moderate to good antibacterial activity (MIC 1.1-75.0 μg/mL). All Compounds have shown significant inhibition against all the bacteria tested and were not strain dependent. In the series, the compound **9a** and **10a** are the most active (MIC: **9a** = **10a** = l.1μg/mL) and an exception has been observed with compound **11j**. It is found to be inactive with respect to all the bacterial strain tested, whereas the remaining all the synthesized compounds showed significant activities.

Table 4: Antibacterial and antifungal activity of oxazolidinones (**9a, 10a-j** and **11a-j**).

Compounds	Minimum inhibitory concentration (μg/ml)				
	S. aureus MTCC 96	Bacillus subtilis MTCC 121	S. aureus MLS16 MTCC 2940	Pseudomonas aeruginosa MTCC 2453	Candida albicans MTCC 3017
9a	150	1.17	1.17	1.17	2.34
10a	18.75	1.1	4.68	1.1	1.1
10b	37.5	2.34	18.75	4.68	4.68
10c	37.5	37.5	4.6	4.6	4.6
10d	150	18.75	75	75	37.5
10e	4.68	37.5	-	-	-
10f	4.68	9.37	9.37	4.68	9.37
10g	75	75	37.5	75	37.5
10h	37.5	37.5	18.75	18.75	9.37
10i	37.5	37.5	18.75	18.75	18.75
10j	-	2.34	9.37	4.68	9.37
11a	18.75	9.37	75	3.37	18.75
11b	37.5	37.5	18.75	18.75	4.6
11c	18.75	2.34	4.68	4.68	4.68

11d	37.5	2.34	18.75	4.68	4.68
11e	37.5	2.34	4.68	4.68	4.68
11f	37.5	37.5	18.75	18.75	4.6
11g	-	9.37	75	75	37.5
11h	37.5	37.5	18.75	18.75	4.6
11i	37.5	37.5	4.6	4.6	18.75
11j	-	-	-	-	-
Neomycin	18.75	18.75	18.75	18.75	-
Fluconazole	-	-	-	-	75

Antimycobacterial activity

All the synthesized compounds (**9a, 10a-j** and **11a-j**) have been evaluated for the antimycobacterial activity and the results are summarized in **Table 5**. All compounds were initially screened against *M. tuberculosis* H37Rv at the single concentration of 100 μg/mL. The active compounds from this screening were further tested for Minimum Inhibitory Concentration (MIC) determination using a broth micro dilution assay. Compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentrations by serial dilution against *M. tuberculosis* H37Rv to determine the actual MIC, using the Nitrate Reductase Assay (NRA). The growth in the microtitre plate is indicated by the change in colour to pink detected by the addition of NRA reagent. The MIC is defined as the lowest concentration of the compound showing no change in the color relative to controls. Rifampicin was used as reference drug. Most of these compounds have shown activity between 1-16 μg/mL but among them C-ring modified **9a** and **10a** compound have shown promising *in vivo* antimycobacterial activity (MIC: **9a =** 1**, 10a =** 2 μg/mL). The replacement of alkyl groups with phenyl group has reduced the effectiveness.

Table 5: Antimycobacterial activity of oxazolidinones against ***M.tuberculosis*** (H37Rv) expressed in MIC (μg/mL)

S. No.	Compound	C log P	CMR	MIC (μg/ml)
1	**9a**	3.22	13.06	1
2	**10a**	1.25	11.89	2

3	**10b**	2.92	13.94	8
4	**10c**	3.07	13.95	8
5	**10d**	3.14	13.97	8
6	**10e**	3.21	13.97	8
7	**10f**	3.64	14.43	8
8	**10g**	4.05	14.92	16
9	**10h**	3.09	14.56	16
10	**10i**	2.80	15.17	>16
11	**10j**	2.50	14.90	16
12	**11a**	3.42	14.40	8
13	**11b**	2.92	15.42	>16
14	**11c**	4.10	15.63	>16
15	**11d**	2.40	15.27	>16
16	**11e**	2.67	14.55	8
17	**11f**	4.75	15.79	>16
18	**11g**	3.17	15.01	>16
19	**11h**	3.81	14.45	8
20	**11i**	4.95	14.82	16
21	**11j**	3.08	13.52	>16
22	**Linezolid**	---	---	1

RMP, Rifampcin; C log P (Hydrophobicity); and CMR (molar refractivity) was calculated using the ChemDraw Ultra, version 10.0

CONCLUSION:

In conclusion, we accomplished the synthesis the library of aryl amides and aryl sulfonamide conjugates of oxazolidinone has been designed, synthesized and evaluated against *M. tuberculosis* H37Rv, bacterial strains and fungal strains. Of them compound **9a** and **10a** have shown remarkable anti-mycobacterial activity (*MIC* = 1 and 2 *μg/ml* respectively) equal to linezolid. Further all the compounds have been evaluated against

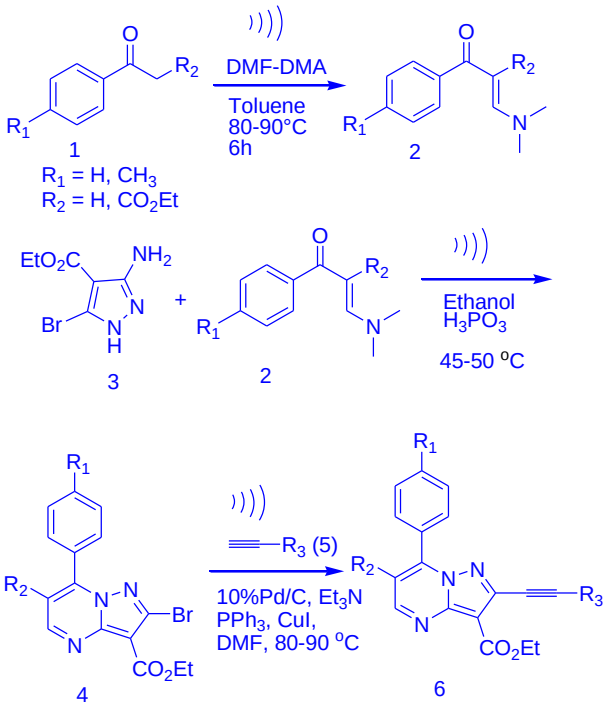
twelve fungal strains. Compounds **9a** and **10a** have displayed significant Antimycotic activities approximately 37 folds more potent than Flucanozole. This study can provide a road map to design and synthesis of oxazolidinone scaffold based anti-microbial active compounds.

Chapter 6:

Ultrasound assisted synthesis of 2-alkynyl pyrazolo [1, 5-*a*] pyrimidines (6) using Pd/C-Cu catalysis

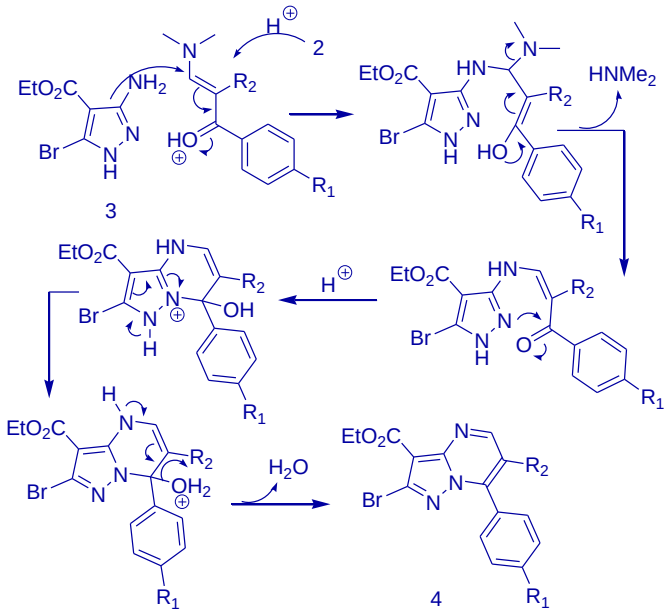
The ultrasound mediated reactions have gained considerable interest in recent time. Compared to the traditional methods the ultrasound mediated reactions offer several advantages such as shorter reaction time, mild conditions, and good yields of products. Thus, the use of ultrasound radiation has emerged as a common strategy in present day organic synthesis. Herein, we report the ultrasound assisted synthesis of a series of 2-alkynyl pyrazolo [1,5-*a*] pyrimidine derivatives **6(a-j) (**Scheme 6) *via* a 3-step method. While, the ultrasound-assisted synthesis of pyrazolo [1,5-*a*]pyrimidine derivatives has been reported earlier, to the best of our knowledge the use of ultrasound for the synthesis of compounds **6(a-j)** or of the similar class is not known. To the best of our knowledge synthesis of this class of compounds using ultrasound irradiation is not known in the literature.

In this process the ketone **1** was treated with DMF-DMA in toluene at 80-90 ^{o}C for 6h to afford the compound **2**. The compound **2** on reaction with the pyrazole derivative **3** in the presence of H_3PO_3 in ethanol under ultrasound irradiation at 45-50 ^{o}C afforded the bromo compound **4**. On alkynylation of compound **4** using a range of terminal alkynes(**5**) in the presence of 10% Pd/C, CuI and PPh_3 as catalysts and Et_3N as a base in DMF at 80-90 ^{o}C under ultrasound irradiation afforded the desired compounds **6(a-j)**. The details of this work are presented in the following sections.



Scheme 6: Ultrasound assisted synthesis of 2-alkynyl pyrazolo [1, 5-*a*] pyrimidine derivatives **6(a-j)**

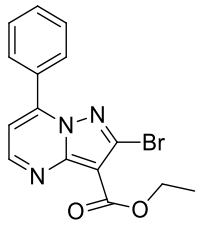
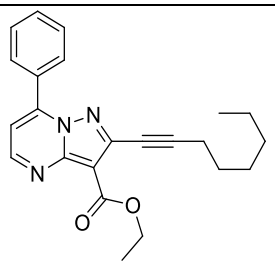
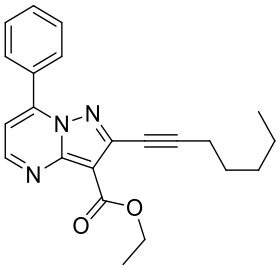
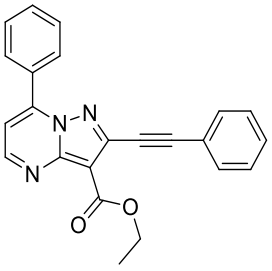
The present ultrasound assisted reaction mediated by H_3PO_3 seemed to follow the pathway shown in **Scheme 7**. Thus protonation of **2** followed by the attack of **3** and subsequent intramolecular cyclization of the resulting intermediate via several steps afforded the desired compound **4**.

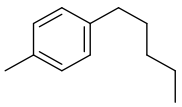
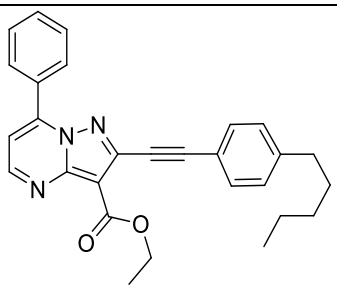
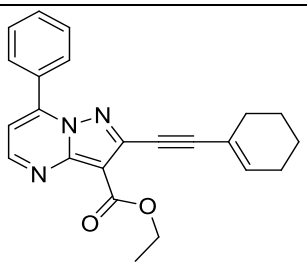
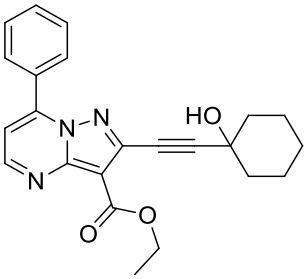
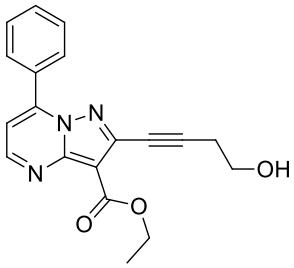
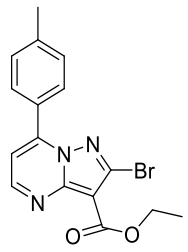
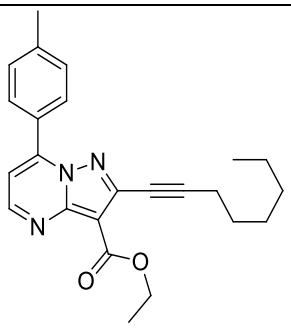


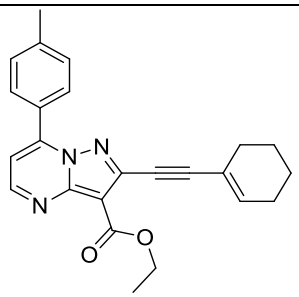
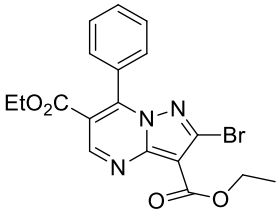
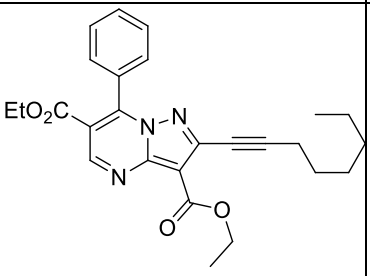
Scheme: 7 Plausible reaction mechanism for the formation of compound **4**

The compound **4** was then taken for Pd/C-catalyzed alkynylation *via* C-C bond forming reaction under ultrasound irradiation. The coupling reaction of compound **4** was performed using a range of terminal alkynes (**5a-j**) in the presence of 10%Pd/C, CuI and PPh_3 as catalysts and Et_3N as a base in DMF at 80-90 ºC under ultrasound irradiation. The terminal alkynes containing various functional groups such as aryl, alkyl, alkenyl, hydroxylalkyl etc were employed to give a variety of alkynylated product **6(a-j)** in good yields (Table 1).

Table 6: Ultrasound assisted synthesis of 2- alkynyl pyrazolo [1,5-*a*]pyrimidines

Entry	Bromo compound (**4**)	Alkyne (**5**; R^3 =)	Time (h)	Product (**6**)	%yield
1.	 **4a**	**5a;** n-Hexyl	5	 **6a**	77
2.	**4a**	**5b**; n-Pentyl	5	 **6b**	71
3.	**4a**	**5c;** 	4	 **6c**	73

4.	**4a**	**5d;** 	6	 **6d**	79
5.	**4a**	**5e;** 	4	 **6e**	70
6.	**4a**	**5f;** 	3	 **6f**	79
7.	**4a**	**5g;** - CH_2CH_2OH	3	 **6g**	78
8.	 **4b**	**5a;** n-Hexyl	5	 **6h**	80

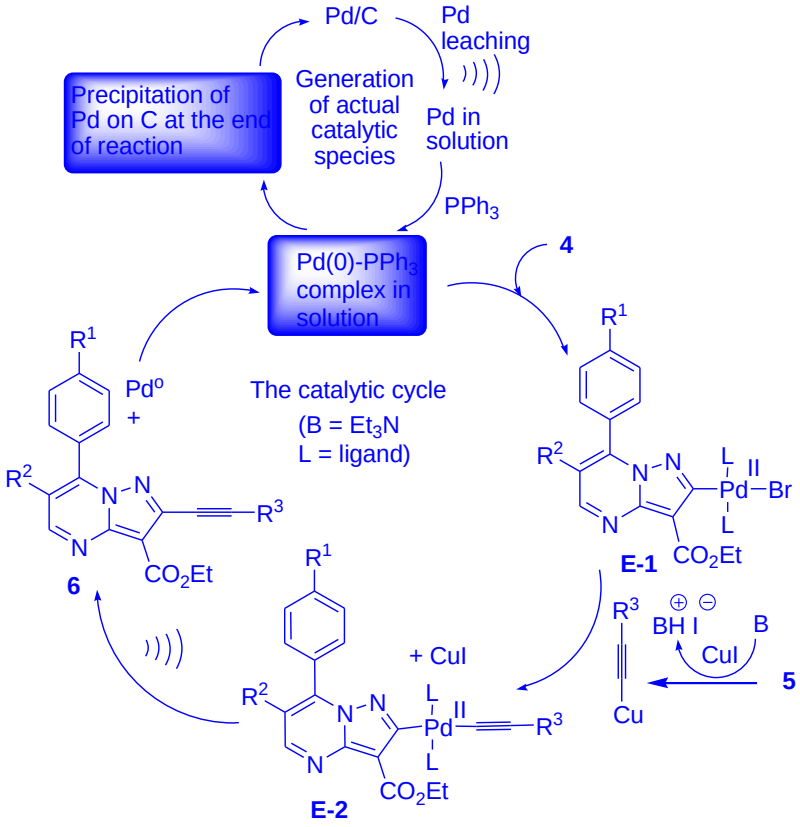
9.	**4b**	**5e;** 	4	 **6i**	78
10.	 **4c**	**5a;** n-Hexyl	5	 **6j**	69

[a] All the reactions were carried out by using **4** (1.0 mmol), terminal alkyne **5** (1.5 mmol), 1:4:2 ratio of 10%Pd/C–PPh_3–CuI and Et_3N (4 mmol) in DMF at 80-90 °C under ultrasound irradiation. [b] Isolated yield.

A mixture of ethyl 2-bromo-7-phenylpyrazolo [1,5-*a*] pyrimidine-3-carboxylate (**4a**) (1 mmol), 10% Pd/C (0.01 mmol), PPh_3 (0.0.04 mmol), CuI (0.0.02 mmol) and triethylamine (4 mmol) in DMF (5 mL) was stirred at 25 °C for 30 min. To this mixture was added an appropriate terminal alkyne (5a-j) (1.5 mmol) slowly with stirring. The mixture was then heated to 80-90 °C under ultrasound irradiation using a laboratory ultrasonic bath Sonorex Super RK 510H model producing irradiation of 35 kHz for the time indicated in Table 6. After completion of the reaction (indicated by TLC) the mixture was cooled to room temperature and poured into ethyl acetate (25 mL). The organic layer was collected, washed with brine solution (3x15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography using petroleum ether-EtOAc to give the desired product.

A plausible reaction mechanism for the ultrasound assisted Pd/C-catalyzed synthesis of **6** is shown in Scheme 8. The steps involved in this reaction are (i) generation of Pd(0)-PPh_3 complex, the actual catalytic species, in solution, (ii) oxidative addition of Pd(0) to the bromo compound (**4**) affording the organo-Pd(II) species **E-1** (iii) transmetallation of **E-1** with the copper-acetylide generated from **4** to give **E-2** (iv) reductive elimination of Pd(0) from **E-2** to give the desired product **5**. The generation of Pd (0) species in the initial step involved a Pd leaching process in to the solution [from the minor portion of the bound palladium (Pd/C)]

followed by interactions with the PPh_3 ligands. The Pd (0)–PPh_3 complex in solution then participated in subsequent steps of the catalytic cycle that seemed to work in solution rather than on the surface. The Pd was re-precipitated on the charcoal surface at the end of the reaction. The role of ultrasound in the present reaction can be explained as follows: The cavitation caused by ultrasound is involved in the growth, oscillation, and collapse of bubbles under the action of an acoustic field. On the other hand the cavitational collapse creates drastic conditions (e.g. the temperature of 2000–5000 K and pressure up to 1800 atmosphere) inside the medium within an extremely short period of time. Thus, these cavitation-induced effects are responsible for the facilitation of key steps in the present reaction especially the Pd leaching process and the rapid reductive elimination of Pd (0) leading to compound **6**.



Scheme 8. Plausible reaction mechanism for the Pd/C-Cu mediated coupling of **4** with **5** leading to the desired product **6**.

2-alkynyl pyrazolo [1, 5-*a*] pyrimidines derivatives have been explored as new and potential anticancer agents. Synthesis of these compounds was carried out using a multi-step method involving the H_3PO_3 mediated construction of pyrazolo [1, 5-*a*] pyrimidine ring possessing a bromo group at C-2 position followed by Pd/C-Cu catalyzed alkynylation methodology as the key steps. All the steps were performed under ultrasound irradiation. All these compounds were evaluated for their anti-proliferative properties *in vitro* against cancer cell lines including breast cancer cells i.e. MDA-MB 231 and human chronic myeloid leukemia cells

i.e. K562 as well as noncancerous cell line e.g. HEK293. All these compounds showed selective growth inhibition of cancer cells and the compound 5i was found to be most effective among them. Overall, our study suggests that 2-alkynyl pyrazolo[1,5-*a*]pyrimidine framework presented here could be an attractive template for the identification of novel and potential anticancer agents and the corresponding synthetic strategy described could be useful for generating diversity based library of small molecules related to this scaffold.

Biological activity

All the synthesized 2-alkynyl pyrazolo [1,5-*a*]pyrimidines (**6a-j**) were tested for their potential anti-cancer properties *in vitro*. The used human metastatic breast cancer cells i.e. MDA-MB 231, human chronic myeloid leukemia cells i.e. K562, and non-cancerous human embryonic kidney cells i.e. HEK293 for our *in vitro* studies. A colorimetric MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (after 24h treatment of the samples in culture medium containing PBS) was used to evaluate the effect of test compounds on cell viability at a concentration of 10 µM. Doxorubicin was used as a reference compound in this assay. [38,39] While all the compounds showed good to moderate activities (> 50% growth inhibition at 10 µM) against MDA-MB 231 cell lines only few of them were found to be effective against K562 cell lines at 10 µM (Table 3). The compound **6e** and **6i** were found to be the most effective among all the compounds tested against both the cell lines used. In a separate study, these compounds showed little or no effects on HEK293 cells indicating their selectivity towards the growth inhibition of cancer cells. For example compounds **6e** and **6i** showed 5-8 and 6-7 fold selectivity, respectively. In a dose response study using MDA-MB 231 cell lines the compound **6i** showed IC_{50} = 1.12±0.27 µM comparable to that of doxorubicin (IC_{50} = 0.73±0.16 µM).

Table 7. In vitro activities of compounds 6a-j against cancer cell lines.

Compounds	**% inhibition of growth of cancer cell lines by compounds 5 at 10 µM**		
	MDA-MB 231	**K562**	**HEK293[a]**
6a	55.3±2.1	33.1±1.3	5.3±0.9
6b	51.6±1.8	31.9±2.2	9.2±0.5

6c	57.2±1.1	47.6±2.6	10.9±1.8
6d	47.9±2.3	49.8±1.7	7.6±2.1
6e	72.1±3.1	50.2±1.9	9.1±1.0
6f	43.6±1.5	32.8±2.0	1.8±2.1
6g	67.5±1.7	44.5±1.6	12.4±2.5
6h	52.1±2.0	38.1±1.5	10.8±1.9
6i	75.9±1.9	63.2±2.3	9.8±0.8
6j	56.4±3.0	37.2±2.1	6.3±0.6
Doxorubicin	88.1±1.7	n.d.	n.d.

[a]HEK293 cell line was used as non cancerous cell line.

nd = not done

Conclusion:

In conclusion, 2-alkynyl pyrazolo [1, 5-*a*] Pyrimidines derivatives has been explored as new and potential anticancer agents. Synthesis of these compounds was carried out by using a multi-step method involving the H_3PO_3 mediated construction of pyrazolo [1,5-*a*] pyrimidine ring possessing a bromo group at C-2 position followed by using Pd/C-Cu catalyzed alkynylation methodology as the key steps. All the steps were performed under ultrasound irradiation. All these compounds were evaluated for their anti-Cytotoxity properties *in vitro* against two cancer cell lines including breast cancer cells *i.e.* MDA-MB 231 and human chronic myeloid leukemia cells i.e. K562 as well as noncancerous cell line e.g. HEK293. All these compounds showed selective growth inhibition of cancer cells and the compound 5i was found to be most effective among them. Overall, our study suggests that 2-alkynyl pyrazolo[1,5-*a*] pyrimidine framework presented here could be an attractive template for the identification of novel and potential anticancer agents and the corresponding synthetic strategy described could be useful for generating diversity based library of small molecules related to this scaffold.

The present research work,

1) Involving design, synthesis, and characterization of new, Benzothiazole, Benzimidazole, Oxazolidinone and Pyrazolopyrimidine derivatives and evaluation of their preliminary antibacterial, antifungal activities, has been aimed at development of new active antimicrobials, which may have future commercial applications.
2) Further, the optimized synthetic methods and purification techniques developed these derivatives would be highly useful for future researchers.

3) The research study is expected to add some more data to the chemistry of new heterocyclic compounds. The utility of above new heterocyclic compounds may be explored in other area of applications also.

List of Publications:

1. **Y .Bharath**, D. Nagaraju, and M.V. Basaveswara Rao,* "Facile Synthesis of *N*-(Benzyl-1*H*-1,2,3-Triazol-5-yl)Methyl)-4-(6-Methoxybenzo[*d*]Thiazol-2-yl)-2-Nitrobenzamides *via* Click Chemistry" (2017). *J. Heterocyclic Chem., 54,864*-870.
2. **Y. Bharath,** M. V. Basaveswara Rao.* "Synthesis of Ultrasound assisted Synthesis of 2-Alkynyl Pyrazolo [1, 5-*a*] Pyrimidines under Pd/C-Cu Catalysis," (2017), (Accepted in Letters In Drug Discovery And Design Letters, Banthem science).
3. **Y. Bharath**, G. Sathaiah , G. lakshmi prasana, M. V.Basaveswara Rao.* " Synthesis and biological evaluation of friedlander annulation approach for the diversity oriented of functionalized quinolines," (2016), *Der pharma chemicia*, *8(13),*165-174.
4. K .Suman , Y.**Bharath**, Ch. S. S. Murthy., D. Nagaraju , " Synthesis and antimicrobial activities of Novel 2-(Benzo [*d*] [1,3] Dioxol-5-yl) -6,7-dimethoxyl Quinazolin-4 (3*H*) – ones," (2015) , *Heterocyclic Letters, Vol. 5*,645-652.
5. G. chendra Shekar.,**Y. Bharath**., A. V. Ramana Reddy , "Synthesis of Novel -2-(benzo [*d*] [1,3] dioxol-5-yl) -5-Fluoro-4-Phenylquinolines as Antibacterial Agents,",(2014), *IJESRT, 3 (3).*

Conference and abstarcts:

1. Yarlagadda.Bharath and Mandava.Venkata Basveswara Rao, (**2016**), Ultrasound Assisted synthesis of 2-Alkynylpyrazolo [1, 5-*a*] Pyrimidines under Pd/C-Cu catalysis. Second AP congress held the P.B. Siddhartha Collegeege of Arts & Science, Vijayawada, India
2. Yarlagadda. Bharath , and Mandava.Venkata Basveswara Rao (**2014**), Synthesis of Novel Benzothiozoles Based [1,2,3] -Trizoles and supramolecular Interactions *via* Click – chemistry DST sponsored National conference on Recent Challenges in Chemical & Biological science, Vignan University, Guntur, India.
3. Yarlagadda. Bharath ,Devunuri. Nagaraju and Mandava. Venkata Basveswara Rao, (**2014**), Facile Synthesis and Biological Evaluation of DNA Interactive Fused Benzothiazoles., DST sponsored national conference on The Role of Natural Product Chemistry in Drug Discovery. Krishna University, Machalipatnam, India.
4. Yarlagadda Bharath , and Mandava. basveswara Rao (**2013**), National poster Symposium on Advances in Organic/medicinal chemistry, conducted by the Royal Chemical Society of chemistry (London) -DS in association with Krishna University, India.

Abbanat. D, Macielag. M. Bush. K, "Novel antibacterial agents for the treatment of serious Gram-Positive infections," (2003), Expert Opin.Investig.Drugs., 12, 379-399.

Adams. J.B, Hockessin. D, Geffken. D, Rayner. D.R, (1993), Fungicidal Oxazolidinones. US Patent 5,223,523.

Albright, J. D.; Reich, M. F.; De los Santos, E. G.; Dusza, J. P.; Sum, F. W.; Venkatesan, A. M.; Coupet, J.; Chan, P. S.; Ru, X.; Mazandarani, H.; Bailey, T, "5-Fluoro-2-methyl-*N*-[4-(5*H*-pyrrolo [2, 1-*c*]-[1, 4] benzodiazepin-10(11*H*)-ylcarbonyl)-3-chlorophenyl] benzamide (VPA-985): an orally active arginine vasopressin antagonist with selectivity for V_2 receptors," (1998), J. Med. Chem., 41, 2442-2444.

Al-mansa.C, Arriba. A. F, Cavalcanti. F. L, Gomez. L. A, Miralles. A, Forn. J, "Synthesis and SAR of a new series of COX-2-selective inhibitors: pyrazolo [1, 5-a] pyrimidines,"(2001), J. Med.Chem., 44, 350-361.

Almerico, A.M.; Diana, P.; Burraja, P, "Glycosidopyrroles.Part 1. Acyclic derivatives: 1-(2-hydroxyethoxy)methylpyrroles as potential anti-viral agents,"(1998), Farmaco 1998, 53, 33-40.

Al-Tel. T.H, Al-Qawasmeh. R.A, Zaarour. R, "Design, synthesis and in vitro antimicrobial evaluation of novel Imidazo[l,2-*a*] pyridine and imidazo[2, l-*b*][l,3]benzothiazole motifs,"(2011),Eur J Med Chem., 46, 1874-1881.

Amino. N, Ideyama. Y, Yamano. M, "an orally active antitumour agent with selective inhibition of vascular endothelial cell proliferation," (2006),Cancer.Lett., 238,119-127.

Amnerkar.N.D, Bhusari.K.P, "Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole," (2010), Eur. J. Med. Chem., 45, 149-159.

Aoki. H, Ke. L J, Poppe. S. M, Poel. T. J, Weaver. E. A, Gadwood. R. C, Thomas. R. C, Shinabarger. D. L, Ganoza. M. C, "Oxazolidinone antibiotics target the P site on Escherichia coli ribosomes," (2002), Antimicrob. Agents Chemother., 46, 1080-1085.

Apodaca.A. A, Rakita. R. M, "Linezolid-Induced Lactic Acidosis," (2003), N. Engl. J. Med., 348, 86-87.

Bae. H.J, Lee. Y.S., Kang.D.W, "Neuroprotective effect of low dose riluzole in gerbil model of transient global ischemia"*Neurosci. Lett.*, (2000), 294, 29-32.

Bahrami. K, M,Kavianinia. I, "A simple and efficient one-pot synthesis of 2-substituted benzimidazoles," (2007), synthesis, 417-427.

Banavara.L.Mylari, Thomas. A. Bayer, Pamela. J. Scott, Charles. E.Aldinger, Michael.F. Dee, Toold. W.Stegel ,William. J. Zembrowaki, "Potent, orally active aldose reductase inhibitors related to zopolrestat: surrogates for benzothiazole side chain," (1992),J. Med. Chem., 35,457-465.

Barbachyn, M. R.; Brickner, S. J.; Hutchinson, D. K. US 5688792, 1997, Chem. Abstr., 1995, 123, 256742.

Barker.H. A, Smyth.R.D, Weissbach.H, Toohey.J. I, Ladd.J. N,Volcani.B. E, "Isolation and properties of crystalline cobamide coenzymes containing benzimidazole or 5, 6-dimethylbenzimidazole," (1960)Journal of Biological Chemistry, 235 (2), 480-488.

Beaulieu. P. L, Hach. B., von Moos. E,"A Practical Oxone ®-Mediated, High-Throughput, Solution-Phase Synthesis of Benzimidazoles from 1,2-Phenylenediamines and Aldehydes and its Application to Preparative Scale Synthesis,"(2003), Synthesis, 11,1683-1692.

Bedos.P, Amblard. M, Subra. G, Dodey. P, Lucarini. J. M, Paquet. J. L, Pruneau. D, Aumelas. A, Martinez. J, "Synthesis and Biological Evaluation of Bradykinin B_1/B_2 and Selective B_1Receptor Antagonists,"(2000), J. Med. Chem., 43, 2382-2386.

Ben-Alloum.A, Bakkas. S, Soufiaoui. M, "Nouvelle voie de synthese des 2- arythiazoles transfert d,electrons active par micro-cndes,"(1997), Tetrahedron Lett. 38, 6395-6396.

Benedi. C, Bravo. F, Uriz. P, Fernandez. E, Claver.C, Castillon. S, "Synthesis of 2-substituted-benzothiazoles by palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas and *o*-bromophenylthioamides," (2003), Tetrahedron Lett., 44, 6073-6077.

Benzoxazoles,"(2009),J. Org. Chem.,74, 8719-8725.

Bergeron.L, Boule.M, Perreeault.S, "Serotonin toxicity associated with concomitant use of linezolid," (2005), S.Ann.Pharmacother., 39, 956-961.

Bermudez. J, Chales.S.F , Joiner. K. A, King. F. D, "5-Hydroxytryptamine (5-HT3) receptor antagonists. 1. Indazole and indolizine-3-carboxylic acid derivatives,"(1990), J. Med. Chem., 33, 1924-1929.

Bobkova.E. V, Van. Y. P, Jordan. D. B, Kurilla. M. G, Pompliano. D. L, "Catalytic properties of mutant 23 S ribosomes resistant to oxazolidinones,"(2003), J. Biol. Chem., 278, 9802-9807.

Bom.A, Booth. S, Bruin. J, Clark. J, Miller. S, Wathey. B, "Parallel solid-phase synthesis of zatebradine analogues as potential I (f) channel blockers," (2001), Bioorg. Med. Chem. Lett., 2001, 11, 2351-2354.

Bradshaw.D, Wrigley.S, Schultz.R.J,PauU.K.D, Stevens.M.F.G, "2-(4-amino phenyl) benzothiazoles: novel agents with selective profiles of in vitro anti-tumour activity," (1998), Br. J. Cancer, 77, 745-752.

Bradshaw.T. D, Bibby. M. C, Double. J. A, Fichtner. I, Cooper. P. A, Alley. M. C, Donohue. S, Stinson. S. F, Tomaszewjski. J. E, Sausville. E. A, Stevens, M. F, "Preclinical evaluation of amino acid prodrugs of novel antitumor 2-(4-amino-3-methylphenyl) benzothiazoles," (2002), Mol. Cancer. Therapeutics, 1, 239-246.

Breen.E.C, Walsh. J.J, "Tubulin-targeting agents in hybrid drugs," (2010),Curr Med Chem., 17,609-639.

Brickner. S.J, "Oxazolidinone antibacterial agents," (1996) Curr Pharm Des., 2, 75-194.

Bridges.A.J, "Chemical inhibitors of protein kinases," (2001) Chem. Rev., 101, 2541-2572.

Brown.H.D, "Antiparasitic drugs. iv. 2-(4'-thiazolyl)-benzimidazole, a new anthelmintic," (1961),j. ame. che. soc.,83, 1764-1765.

Bryson. M, Fulton. B, Benfield. P, "Riluzole. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in amyotrophic lateral sclerosis," (1996), Drugs. 52, 549-563.

Bujdakova. H, Kuchta. T, Sidoova. E, Gvozdjakova. A, "Anti-Candida activity of four antifungal benzothiazoles," (1993), FEMS. Microbiol .Lett., 112, 329-333.

Burger.A, Sawhey.S.N, "Antimalarials.Benzothiazole amino alcohols," (1986), J Med Chem., 11, 270-273.

Bush. K, Macielag. M, Weidner.wells. M, "Taking inventory: antibacterial agents currently at or beyond phase 1,"(2004), Curr. Opin.Microbiol., 7, 466-476.

Caleta.I, Kralj.M, Branimir. B.B, "Novel cyano- and amidinobenzothiazole derivatives: synthesis, antitumour evaluation, and X-ray and quantitative structure-activity relationship (QSAR) analysis," (2009), J. Med. Chem., 52, 1744-1756.

Carcanague. D, Shue. Y. K, Wuonola. M. A, Nickelsen. M. U, Joubran. C, Abedi. J. K, Jones. J, Kuhler. T. C, "Novel Structures Derived from 2-[[(2-Pyridyl) methyl] thio]-1*H*-benzimidazole as Anti-Helicobacter pylori Agents, Part 2," (2002),J. Med. Chem., 45, 4300-4309.

Castro, J. L.; Broughton, H. B.; Russell, M. G.; Rathbone, D.; Watt, A. P.; Ball, R. G.; Chapman, K. L.; Patel, S.; Smith, A. J.; Marshall, G. R.; Matassa, V. G, "5-(Piperidin-2-yl)- and 5-(Homopiperidin-2-yl)-1,4-benzodiazepines: High-Affinity, Basic Ligands for the Cholecystokinin-B Receptor,"(1997), J. Med. Chem., 40, 2491-2501.

Chakraborti. A. K, Rudrawar. S, Kaur. G, Sharma. L, "An Efficient Conversion of Phenolic Esters to Benzothiazoles under Mild and Virtually Neutral Conditions,"(2004) Synlett, 1533-1536.

Chao. Q, Deng. L, Shih. H, Leoni. L. M, Genini. D, Carson. D. A, Cottam. H. B, "Substituted Isoquinolines and Quinazolines as Potential Antiinflammatory Agents. Synthesis and Biological Evaluation of Inhibitors of Tumor Necrosis Factor α," (1999), J. Med. Chem., 42, 3860-3873.

Charrier. J. D, Landreau. C, Deniaud. D, Reliquet. F, Reliquet. A, "From benzil arylimines to 2*H*-benzo-1,4-thiazines, benzothiazoles or indoles,"(2001),Tetrahedron, 57,4195-4202.

Chaudhary. P, Sharma. P. K, Sharma. A, Varshney. J, "Recent advances in pharmacological activity of benzothiazole derivatives," (2010),Int J Curr Pharm Res., 4, 5-11.

Chimenti. F, Bizzarri. B, Bolasco. A, Secci. D, Chimenti. P, Carradori. S, Granese. A, Rivanera. D, Lilli. D, Zicari. A, Scaltrito. M. M, Sisto. F, "A novel class of selective anti-Helicobacter pylori agents 2-oxo-2H-chromene-3-carboxamide derivatives," (2007), Bioorg. Med. Chem. Lett., 17(11), 3065-3071.

Chinchilla. R, Najera. C, "Recent advances in Sonogashira reactions," (2011), Chem. Soc. Rev., 40, 5084-5121.

Chohan. Z. H, Scozzafava. A, Supuran. C.T, "Zinc complexes of benzothiazole-derived Schiff bases with antibacterial activity," (2003), J. Enzyme.Inhib.Med.Chem., 2003, 18, 259-263.

Chopade.R.S, Bahekar.R.H, Khedekar. P.B, "Synthesis and anticonvulsant activity of 3- (6-substituted-enzothiazol-2-yl)-6-phenyl-[1,3]-xazinane-2-hiones,"*Arch.Pharm*., (2002), 335, 381-388.

Chua.M.S,Kashiyama.E, Bradshaw.T.D,Stinson.S.F,Brantley.E,Sausville.E.A, Stevens.M.F.G, "Role of Cyp1A_1 in modulation of antitumor properties of the novel agent 2-(4-amino-3-methylphenyl) benzothiazole (DF 203, NSC 674495) in human breast cancer cells," (2000),Cancer Res, 60, 5196 (2000).

Cicchi.S, Cordero. F. M, Giomi. D, "Five-membered ring systems: With O &N atoms," (2001), Prog. Heterocycl. Chem., 13, 217-237.

Ciske. F. L, Barbanchyn. M. R, Genin. M. J, Grega. K.C, Lee. C. S, Dolak. L A, Seest. E. P, Watt. W, Adams. W. J, Friis. J. M, Ford. C. W, Zurenko. G. E, "The effect of remote chirality on the antibacterial activity of indolinyl, tetrahydroquinolyl and dihydrobenzoxazinyl oxazolidinones,"(2003), Bioorg. Med. Chem., 13, 4235-4239.

Coruzzi. G, Adami. M, Guaita. E, Deesch. I. J, Leurs. R, "Antiinflammatory and antinociceptive effects of the selective histamine H4-receptor antagonists JNJ7777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation," (2007), European, Journal of pharmacology, 563 (1-3), 240-244.

Crecetto, H.; Di Maio, R.; Gonzalez, M.; Risso, M.; Saenz, P.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Olea-Azar, C, "1,2,5-Oxadiazole N-oxide derivatives and related compounds as potential antitrypanosomal drugs: structure-activity relationships,"(1999), J. Med. Chem., 42, 1941-1950.

Cristalli. G, Camaioni. E, Vittori. S, Volpini. R, Borea. P. A, Conti. A, Dionisotti. S, Ongini. E, Monopoli. A, "2-Aralkynyl and 2-heteroalkynyl derivatives of adenosine-5'-N-ethyluronamide as selective A2a adenosine receptor agonists,"(1995), J. Med. Chem., 38, 1462-1472.

Cyrille. L, Dravid. d, Michel. E, Alain. R, Jean-claude. M,"Efficient region selective synthesis of triheterocyclic compounds: imidazole [2,1-*b*] benzothiazoles,pyrimido [2,1-*b*] benzothiazolones and pyrimido[2,1-*b*]benzothiazoles," (2002), J. Chem. Soc, Perkin Trans.,1, 741-747.

Czarny.A, Wilson. W. D, Boykin. D. W, "Synthesis of mono-cationic and dicationic analogs of hoechst 33258,"(1996), J. Heterocycl. Chem., 33, 1393-1397.

D'Ambrosio. M., Guerriero.A, Debitus. C, Pietra. F , "Leucascandrolide A, a New Type of Macrolide: The first powerfully bioactive metabolite of calcareous sponges

(Leucascandra caveolata, a new genus from the coral sea)," (1996), Helv. Chim. Acta, 79, 51-60.

Daidone. G, Maggio. B, Schillari. D, "Salicylanilide and its heterocyclic analogues.A Comparative study of their antimicrobial activity," (1990),*Pharmazie* 1990, 45, 441-442.

Dalla Via.L, Marciani-Mangno.S, "Photochemotherapy in the treatment of cancer," (2001), Curr. Med. Chem., 8, 1405-1418.

Damont.A, Médran-Navarrete. V, Cacheux. F, Kuhnast. B, Pottier .G, Bernards. N, Marguet. F, Puech F, Boisgard R, Dollé F, "Novel Pyrazolo [1, 5-a] pyrimidines as Translocator Protein 18 kDa (TSPO) Ligands: Synthesis, in Vitro Biological Evaluation, [(18) F]-Labeling, and in Vivo Neuroinflammation PET Images,"(2015),*J Med Chem.* 2015, 58, 7449-7464.

Davidson. J.R, "First-line pharmacotherapy approaches for generalized anxiety disorder," (2001),*J. Clin. Psychiatry*, 70(Suppl.), 25-31.

De Leon.C.Y, Ganem.B, "A new approach to porphobilinogen and its analogs," (1997),*Tetrahedron*, 53, 7731-7752.

De Nanteuil. G, Lila-Ambroise. C, Vallez. M. O, Verbeuren. T. J, "New fibrinolytic agents: benzothiophene derivatives as inhibitors of the t-PA-PAI-1 complex formation,"(2003),Bioorg. Med. Chem. Lett., 13, 1705-1708.

Decker M, "Hybrid molecules incorporating natural products: applications in cancer therapy,neurodegenerative disorders and beyond,"(2011),Curr Med Chem.,18, 1464-1475.

Deidda.D, Lampis. G, Fioravanti. R, Biava. M, Porretta. G. C, Zanetti. S, Pompei. R, Bactericidal activities of the pyrrole derivative BM212 against multidrug-resistant and intramacrophagic Mycobacterium tuberculosis strains,"(1998), Antimicrob. Agents Chemother., 42, 3055-3037.

Delbecq.F,Cordonnier. G,Pommery. N,Barbry. D, Henichart.J.P, "New heteroarylbenzenesulphonamides as matrix metalloproteinase inhibitors," (2004), Bioorg. Med. Chem. Lett., 14, 1119-1121.

Deng.X.Q, Song.M.X, Wei. C.X, "Synthesis and anticonvulsant activity of 7-alkoxy-triazolo- [3, 4-*b*] benzo[*d*]Thiazoles," (2010), Med Chem., 6, 313-320.

Diao. X, Wang. Y, Jiang. Y, Ma, D., "Assembly of substituted 1*H*-benzimidazoles and 1, 3-dihydrobenzimidazol-2-ones *via* cuI/l-proline catalyzed coupling of aqueous ammonia with 2-iodoacetanilides and 2 iodophenylcarbamates," (2009),J. Org. Chem.,74, 7974-7977.

Downing, D. M. ; Glase, S. A. ; Johnson, S. J. ; Wise, L. D. ; Wright, J. L. PCT Inst. Appl. **1995**, WO 9530659, (*Chem. Abstr*., 1996, *124*,202263c).

Engler. M. B, Engler. M. M , "The vasculoprotective effects of flavonoid-rich cocoa and chocolate" (2004),*Nutr. Res.*, 24, 695-706.

Eva. S, Katarina.K, Dusan, L, "3-(2-Alkylsulfanyl-6-benzothiazolylaminomethyl)-2-benzoxazo-lethiones - Synthesis and Photosynthesis-Inhibiting Activity in Spinach Chloropasts," (1999),Molecules, 4, 73-80.

Fairley. T. A, Tidwell. R. R, Donkor. I, Naiman. N. A, Ohemeng. K. A, Lombardy. R. J, Bentley. J. A, Cory. M, "Structure, DNA minor groove binding, and base pair specificity of alkyl- and aryl-linked bis(amidinobenzimidazoles) and bis(amidinoindoles),"(1993), J. Med. Chem., 36, 1746-1753.

Fawzi. A. B, Macdonald. D, Benbow. L. L, Smith-Torhan. A, Zhang. H. T, Weig. B. C, Ho. G, Tulshian. D, Linder. M. E, Graziano. M. P , "SCH-202676: An Allosteric Modulator of Both Agonist and Antagonist Binding to G Protein-Coupled Receptors," (2001),*Mol. Pharmacol.*, 59, 30-37.

Ford. C. W, Zurenko. G. E, Barbacyn. M. R , "The Discovery of Linezolid, the First Oxazolidinone Antibacterial Agent," (2001), Cur. Drug.Target, 19,188-199.

Ford.C.W, Hamel.J.C, Stapert. D, Moerman. J.K, Hutchinson.D.K, Barbachyn. M.R, "Oxazolidinones: new antibacterial agents," (1997) Trends Microbiol., 5,196-200.

Ford.C.W, Zurenko.G.E, Barbachyn.M.R, "The discovery of linezolid, the first oxazolidinone antibacterial agent," (2001) Curr Drug Targets Infect Disord., 1,181- 199.

Fraley.M. E, Rubino. R. S, Hoffman. W. F, Hambaugh. S. R, Thomas. K. A, Optimization of a pyrazolo [1,5-a]pyrimidine class of KDR kinase inhibitors: improvements in physical Properties enhance cellular activity and pharmacokinetics,"(2002), Bioorg. Med. Chem. Lett., 12, 3537-3541.

Franchini. C, Muraglia. M, Corbo. F, “Synthesis and biological evaluation of 2-mercapto-1,3-benzothiazole derivatives with potential antimicrobial activity,” (2009), Arch Pharm., (Weinheim), 342,605-613.

Fransisco.H. L, Alicia. H. C, Rafeal. C, Gabriel. N. V, Olivia. S. A, Manuel. H, Libian.G.M,“Synthesis and biological activity of 2-(trifluoromethyl)-1*H*-benzimidazole derivatives against some protozoa and Trichinella spiralis,”(2010), Eur. J. Med. Chem.,45, 3135-3141.

Fridkin.S. K, Edwards. J. R, Courval. J. M, Hill. H, Tenover. F. C, Lawton. R, Gaynes. R. P, McGowan. J. E, “The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units,” (2001), Ann. Intern. Med., 135, 175-183.

Frohlich. L. G, Kotsonis. P, Traub. H, Taghavi-Moghadam.S, Al-Masoudi. N, Hofmann. H, Srobel. H, Matter. H, Pfeiderer. W, Schmidt. H, “Inhibition of Neuronal Nitric Oxide Synthase by 4-Amino Pteridine Derivatives: Structure−Activity Relationship of Antagonists of (6*R*)-5, 6, 7, 8-Tetrahydrobiopterin Cofactor,”(1999),*J. Med. Chem.*, 42, 4108.

Gabriel. N. V, Roberto. C, Aliica. H. C, Cilian. G, Fransisco. K. L, Suan. V, Raual. M, Rafeal. C, Manuel. H, Rafel. C,“Synthesis and antiparasitic activity of 2-(trifluoromethyl)-1*H*-benzimidazole derivatives,” (2001), Bioorg. Med. Chem. Lett., 11, 1879-1883.

Gabriel.N. V, de Maria. M. R. V, Cilian.V, Victor. M, Lucia. G, Alicia. H, Rafeal. C, Fransisco. H. L, “Synthesis and antiprotozoal activity of some 2-(trifluoromethyl)-1*H*-benzimidazole bioisosteres,” (2006), *Eur J. Med. Chem.*,41, 135-141.

Gagos. M, Menestrina. G, Niewiadomy. A, Gruszecki. W.I, J, “Molecular organization of the antifungal and anticancer drug 2-(2,4-dihydroxyphenylo)-5,6-dichlorobenzothiazole in solution and in monolayers: an effect of pH,” (2005),Photochem. Photobiol.B., 80, 101-106.

Gebauer.M, “Synthesis and structure-activity relationships of novel warfarin derivatives,” (2007), Bioorg. Med. Chem., 15, 2414-2420.

Gilani.S.J, Khan.S.A, Siddiqui.N, “Synthesis and in vitro antimicrobial activity of novel *N*-(6-chlorobenzo[d]thiazol-2-yl) hydrazine carboxamide derivatives of benzothiazole class,”(2011), J. Enzyme.Inhib. Med. Chem., 26, 332-340.

Gillman. P. K, “Linezolid and serotonin toxicity,” (2003), Clin. Infect. Dis., 37, 1274-1275.

Glennon. R. A, Isaiel. A. M, Ablordeppy. S, El-Ashmawy. M, Fisher. J. B , “Thioxanthene-derived analogs as σ_1 receptor ligands,”(2004),*Bioorg. Med. Chem. Lett.* , 14, 2217-2220.

Goldfarb; H. Ronald, Ohashi; Masami; Yoshino; Kochichiro, (2000), US Patent, 6013659.

Goldstein. F. W, “Combating resistance in a challenging, changing environment,” (2007),Clin. Microbiol.Infect., 2007, 13, 2-6.

Gomstsyan.A, Didomenico. S, Lee. C, Stewart. A. O, Bhagwat. S. S, Kowaluk. E. A, Jarvis. M. F, “Synthesis and biological evaluation of pteridine and pyrazolopyrimidine based adenosine kinase inhibitors,”(2004), Bioorg. Med. Chem. Lett., 14, 4165-4168.

Gonzalez-Gomez. J. C, Santana. L, Uriarte. E, “A furan ring expansion approach to the synthesis of novel pyridazino-psoralen derivatives,” (2005),*Tetrahedron,* 61, 4805-4810.

Gopkumar.P,Shivakumar. B, Jayachandran. E, Nagappa. A. N, Nargund. L. V. G,Gurupadaiah.B.M, “Some-6-fluoro-7-(substituted) -(2-*N*-*p*-anilinosulfonamido) benzothiazoles were synthesized and studied for their antimicrobial and antifungal activities,”(2001),*Indian J. Heterocyclic. Chem*., 11, 39-42.

Gravestock, M. B, Hales, N. J, Carcanague, D. R, (2004), PCT W02004078753. Guru. M. M, Ali. M. A, Punniyamurthy. T, “Copper-Mediated Synthesis of Substituted 2-Aryl- N-benzylbenzimidazoles and 2-Arylbenzoxazoles via C-H Functionalization/C-N/C-O Bond Formation,” (2011), J. Org. Chem., 76, 5295-5308.

Gu. X. H, Wan. X. Z, Jing. B, “Syntheses and biological activities of bis(3-indolyl)thiazoles, analogues of marine bis(indole)alkaloid nortopsentins,”(1999), Bioorg. Med. Chem. Lett., 9, 569-572.

Gubin.J,Lucchetti. J, Mahaux. J, Nisato. D, Rossels. G, Clinet. M, Polster. P, Chalelain. P, “A novel class of calcium-entry blockers: the 1-[[4-(aminoalkoxy) phenyl] sulfonyl]indolizines,”(1992), J. Med. Chem., 35, 981-988.

Guerrera. F, Salerno. L, Sarva. M. C, Siracusa. M. A, “Synthesis and antifungal activity of pyrido[3',2':4,5]thieno[3,2-d]- 1,2,3-triazine derivatives,”(1993),*Farmaco,* 48, 1725-1733.

Guiraudou. P, Puchu. S. C, Gayraud. R, Gautier. P, Roccon. A, Herbert. J. M, Nisato. D, “Involvement of nitric oxide in amiodarone- and dronedarone-induced coronary vasodilation in guinea pig heart,” (2004), Eur. J. Pharmacology, 496, 119-127.

Gupta. R. R, Dev. P. K, Sharma. M. L, Rajoria. C. M, Gupta. A, Nayati. M, "Anticancer activities of 2, 3-dihydro-1, 4-benzothiazines, and of their 4-(N-alkyl amides) and 4-(N-alkyl N-nitrosoamides)," (1993), Anti-cancer drugs ., 4, 589-592.

Habermann. J, Ley. S.V, Smits. R, "Three-step synthesis of an array of substituted benzofurans using polymer-supported reagents," (1999), J. Chem. Soc. Perkin Trans 1, 2421-2423.

Hafeez M. El-Shaaer, Pavlima. F,Margita.L,Jamila. C, Herrieta. S,"Synthesis, antimicrobial activity and bleaching effect of some reaction products of 4-oxo-4H-benzopyran-3-carboxaldehydes with aminobenzothiazoles and hydrazides,"(1998),Farmaco, 53, 224-232.

Hala Bakr El-Nassan, Mervat Mostafa El-Enany, Mona Monir Kamel, Omneya Mahmoud Khalil ,"Synthesis and antitumor activity of novel pyrazolo[1,5-a]pyrimidine derivatives," (2011),European Journal of Chemistry, 2, 331-336.

Hanan, E. J. ; Chan, B. K. ; Estrada, A. A. ; Shore, D.G. ; Lyssikatos, J. P. , "Mild and General One-Pot Reduction and Cyclization of Aromatic and Heteroaromatic 2-Nitroamines to Bicyclic 2*H*-Imidazoles,"(2010),Synlett., 2759-2764.

Hanley.D. F, Pozo. M, "Treatment of status epilepticus with midazolam in the critical care setting," (2000), Int. J. Clin.Pract., 54, 30-35.

Hartmann.M, Decking .U .K. M, Schrader.J, Naunyn-Schmiedeberg .S, "Cardioprotective actions of KC 12291 II. Delaying Na+ overload in ischemia improves cardiac function and energy status in reperfusion," (1998),*Arch. Pharmacol.*, 358, 554-560.

Hasegawa. E, Yoneoka. A, Suzuki. K, Kato. T, Kitazume. T, Yangi. K, "Reductive transformation of α, β-epoxy ketones and other compounds promoted through photoinduced electron transfer processes with 1,3-dimethyl-2-phenylbenzimidazoline (DMPBI)," (1999), Tetrahedron, 55, 12957-12968.

Havrylyuk. D, Mosula. L, Zimenkovsky. B, "Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety," (2010), Eur. J. Med. Chem., 45, 5012-5021.

Hazeldine. S. T, Polin. L, Kushner. J, Paluch. J, White. K, Edelstein. M, Palomino. E, Corbett. T. H, Horwitz. J. P, "Synthesis and biological evaluation of some bioisosteres and congeners Of the antitumor agent, 2-(4-[(7-chloro-2-quinoxalinyl) oxy]phenoxy)propionic acid (XK469)," (2001), J. Med. Chem. 2001, 44, 3130-3137.

Heinelt.U, Herok. S, Matter. H, Wildgoose. P, "Solid-phase optimisation of achiral amidinobenzyl indoles as potent and selective factor Xa inhibitors," (2001), Bioorg. Med. Chem. Lett., 11, 227-230.

Hiroki.M, Shinji. U, Mitsuhiro. S, Jinichi. H, Masamumi.T, Keiichi.S, Tadayuki.S, Jin.W, "New nonsteroidal antiinflammatory agent. 3. Analogs of 2-substituted 5-benzothiazoleacetic acids and their derivatives," (1974), J. Med. Chem., 17,491-496.

Ho, W.; Kukla, M. J.; Beslin, H. J.; Ludovici, D. W.; Grous, P. P.; Diamond, C. J.; Miranda, M.; Rodgers, J. D.; Ho, C. Y.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A, "Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TlBO) Derivatives,"(1995), J. Med. Chem., 38, 794-802.

Hocek. M, Votruba. I, "Covalent analogues of DNA base-Pairs and triplets. Part Synthesis and cytostatic activity of bis(purin-6-yl)acetylenes,-diacetylenes and related compounds,"(2002),*Bioorg. Med. Chem. Lett.,12,* 1055-1058.

Hoeksema, H.;Caron, E. L.; Hinman, J. W, "novobiocin, the structure of novobiocin,"(1956), J. Am. Chem. Soc. 1956, 78, 2019-2020.

Hori. N, Tsukamoto. G, Imamura. A, "Novel disease-modifying antirheumatic drugs. I. Synthesis andantiarthritic activity of 2-(4-methylphenyl) benzothiazoles," (1992), Chem.pharmaBull., (Tokyo),40,2387-2390.

Hori. N, Tsukamoto. G, Imamura. A,"Novel Disease-Modifying Antirheumatic Drugs. I. Sythesis and Antiarthritic Activity of 2-(4-Methylphenyl)benzothiazoles,"Chem .Pharm Bull (Tokyo).,(1992), 40, 2387-2390.

Houlihan.W. J, Remers. W. A, Brown. R. K, "Indoles part I," Wiley & sons: New York 1992.

Hout.S, Azas. N,Darque. A, Robin. M, Di Giorgio.C, Gasquet.M, Galy.J, Timon-David.P, "Activity of benzothiazoles and chemical derivatives on Plasmodium falciparum," (2004), Parasitology, 129, 525-535.

Huang .S, Liu. Z, Tian. S.S, "Discovery of 2-amino-6-carboxamidobenzothiazoles as potent Lck inhibitors," (2008),Bioorg. Med. Chem. Lett., 18, 2324-2328.

Huang. Q, Mao. J, Wan. B, "Searching for New Cures for Tuberculosis: Design, Synthesis, and Biological Evaluation of 2-Methylbenzothiazoles," J Med. Chem., (2009), 52, 6757-6767.

Huang. Q, Mao. J, Wan. B, "Searching for new cures for tuberculosis: design, synthesis, and biological evaluation of 2-methylbenzothiazoles,"(2009), J Med Chem., 52, 6757-6767.

Hubschwerlen. C, Specklin. J. L, Schroeder. S, Locher. H. H, "Structure-activity relationship in the oxazolidinone-quinolone hybrid series: influence of the central spacer on the antibacterial activity and the mode of action," (2003), Bioorg. Med. Chem. Lett., 13, 4229-4233.

Hurdle. J. G, O'Neill. A. J, Chopra. I, "Prospects for aminoacyl-tRNA synthetase inhibitors as new antimicrobial agents," (2005), Antimicrob. Agents Chemother. 49, 4821-4833.

Hutchinson, D. K, "Oxazolidinone Antibacterial Agents: A Critical Review," (2003), Curr. Top. Med. Chem., 3, 1021-1042.

Hutchinson. I, Jennings. S. A, Vishnuvajjala. B. R, Westwell. A. D, Stevens. M. F. G, "Synthesis and pharmaceutical properties of antitumor 2-(4-aminophenyl) benzothiazole amino acid prodrugs," (2002), *J. Med. Chem.*, 45, 744-747.

Hutchinson. I, Stevens.M.F.G, West well. A.D, "The regiospecific synthesis of 5- and 7-monosubstituted and 5,6-disubstituted 2-arylbenzothiazoles," (2000), Tetrahydran Lett., 41, 425-428.

Hutchinson.I, Tracey D. Bradshaw, Charles S. Mathews, Malcolm F.G. Steven and Andrew D. West well, "3′-Cyano and 3′-Alkynyl-Substituted 2-(4′-Aminophenyl) benzothiazoles as new potent and selective analogues," (2003), Bioorganic and Medicinal Letters,13, 471-474.

Idrees.M, Subhas. D. B, "Hypervalent iodine mediated intramolecular cyclization of thioformanilides: expeditious approach to 2-substituted benzothiazoles," (2006), J. Org. Chem., 71, 8261-8263.

IJzerman.A.P ,Blad. C. C, van Veldhoven, J. P. D , Klopman, C, Wolfram. D. R, Brussee, J, Lane. J. R, "Novel 3, 6, 7-Substituted Pyrazolopyrimidines as Positive Allosteric Modulators for the Hydroxycarboxylic Acid Receptor 2 (GPR109A)," (2012),J. Med. Chem., 55, 3563-3567.

Ingle .V.S, Gorepatil. P. B., Yogesh .D. M, "Samarium (III) Triflate as an Efficient and Reusable Catalyst for Facile Synthesis of Benzoxazoles and Benzothiazoles in Aqueous Medium,"(2013),*Synlett*, 24, 2241-2244.

Ingle. R. G, Magar. D. D, “Heterocycic chemistry of benzimidazole and potential activities of derivatives,” (2011), Int. J. Drug Res. Tech., 1 (1), 26-32.

Ingolfsdotter.K, “Usnic acid,” (2002),*Phytochemistry*, 61, 729-736.

Ishihara. Y, Goto. G, Miyamoto. M, “Central selective acetylcholinesterase inhibitor with neurotrophic activity: structure-activity relationships of TAK-147 and related Compounds,” (2000), Curr. Med. Chem., 7, 341-354.

Ivachtchenko Igor, A. V, Dalinger. L, Vatsadse. I. A, Shevelev. S. A, “Synthesis of 4- diazo-3, 5-dinitropyrazole and characteristic features of its behaviour towards nucleophiles,”(2005), J. Comb. Chem., 7, 236-239.

Jacobsen. E. J, Stelzer. L. S, Ten Brink. R. E, Belonga. K. L, Carter. D. B, Im. H. K, Im. W. B, Sethy. V. H, Tang. A. H, Von Voigtlander. P. F, Petke. J. D, Zhong. W. Z, Mickelson. J. W, “Piperazine imidazo[1,5-a]quinoxaline ureas as high-affinity GABAA ligands of dual functionality,”(1999), J. Med. Chem., 42, 1123-1140.

Jain. N, Kanojia. R. M, Xu. J, Jian-Zhong. G, Pacia. E, Lai. Muh-Tsann, Du. F, Musto. A, Allan. G, Hahn. D, Lundeen. S, Sui. Z, “Novel chromene-derived selective estrogen receptor modulators useful for alleviating hot flushes and vaginal dryness,” (2006), J. Med. Chem., 49, 3059-3059.

Jemal.A, Bray. F, Center. M. M, Ferlay. J, Ward. E, Forman. D, “Global cancer Statistics,” (2011), CA: Cancer J. Clin.,61, 69–90.

Jeyaseeli. L, Gupta. A. D, Kumar. K. A, Mazumdar. K, Dutta. N. K, Dastidar. S. G, “Antimicrobial potentiality of the thioxanthene flupenthixol through extensive in vitro and in vivo experiments,”(2006), *Inter. J. Antimicrob. Agent*, 27, 58-62.

Jimonet. P, Audiau. F, Barreau. M, “Riluzole series.“Synthesis and in vivo "antiglutamate" activity of 6-substituted-2-benzothiazolamines and 3-substituted-2-imino-benzothiazolines,” (1999),*J. Med .Chem.*, 42, 2828-2843.

Jin. G.H, Li. H, An. S, “Design, synthesis and activity of benzothiazole-based inhibitors of NO production in LPS-activated macrophages,” (2010),Bioorg Med Chem Lett., 20, 6199-6202.

Johnson. A. P, Tysall. L,Stockdale. M, Woodford. N, Kanufmann. M. E, Warner. M, Livermore. D. M, Asboth. F, Allerberger. F,“Emerging linezolid-resistant Enterococcus faecalis and

Enterococcus faecium isolated from two Austrian patients in the same intensive care unit," (2002),Eur. J. Clin. Microbiol. Infect. Dis., 21, 751-754.

Jones. K, Evans. L. E, Cheeseman. M. D, "N–N Bond-Forming Cyclization for the One-Pot Synthesis of *N*-Aryl[3,4-d]pyrazolopyrimidines," (2012),Organic Letter, 14, 13, 3546-3549.

Jones.R.N, Biedenbach.D.J, Anderegg. T.R, "In vitro evaluation of AZD2563, a new oxazolidinone, tested against unusual gram-positive species," (2002), DiagMicrInfec Dis., 42,119-122.

Joseph.A. I, Zoltan. F. K, Doping. W, Francosis. J. F, Meter. B. M, Thomas. A. S, Erin. M. D, "Crystal Structure of the Oxazolidinone Antibiotic Linezolid Bound to the 50S Ribosomal Subunit," (2008), J. Med. Chem., 51, 3353-3356.

Juan. V, Roberto. C, Alicia. H. C, Lilian. G, Fransisco. H. L, Gabriel. N. V, Amparo. T, Rafel. C, Manuel. H, Rafel. C,"Synthesis and antiparasitic activity of 1H-benzimidazole derivatives," (2002), Bioorg. Med. Chem. Lett., 12, 2221-2224.

Kaiser. D. G, Glenn. E. M, "Correlation of plasma 4, 5-bis (*p*-methoxyphenyl)-2-phenylpyrrole-3-acetonitrile levels with biological activity," (1972), J. *Pharm. Sci*., 61, 1908-1911.

Kalagutkar. A. S, Naguyen. H. T, Vaz Alfin. D. N, Dalvu. D. K, Mcleod. D. G, Murray. J. C , "In vitro metabolism studies on the isoxazole ring scission in the anti-inflammatory agent leflunomide to its active α-cyanoenol metabolite a771726: mechanistic similarities with the cytochrome p450-catalyzed dehydration of aldoximes," (2003),*drug metabolism and disposition*, 31, 1240-1250.

Kamal.A, Srikanth.Y.W, Khan. M.N.A, "2-Anilinonicotinyl linked 2-aminobenzothiazoles and [l,2,4] triazolo[l,5-*b*] [l,2,4] benzothiadiazineconjugates as potential mitochondrial apoptoticinducers," (2011),Bioorg Med Chem.,23, 7136-7150.

Kamal. A, Srikanth.Y.W, Khan. M.N.A,"2-Anilinonicotinyllinked 2-aminobenzothiazoles and [1, 2, 4]triazolo[1,5-*b*] [1,2,4]benzothiadiazine conjugates as potential mitochondrial apoptotic inducers," (2011), Bioorg. Med. Chem., 23, 7136-7150.

Kamei. K, Maeda. N, Ogino. R, Koyama. M, Nakajima. M, Tatsuoka. T, Ohno. T, Inoue. T, "New 5-HT1A receptor agonists possessing 1,4-benzoxazepine scaffold exhibit highly potent anti-ischemic effects," (2001),*Bioorg. Med. Chem. Lett.*, 11, 595-599.

Kantoci. D, Murray. E. D, Quiggle. D. D, Wechter. W, "Endogenous Natriuretic Factors. 5. Synthesis and Biological Activity of a Natriuretic Metabolite of Diltiazem and Its Derivatives," (1996), J. Med. Chem., 39, 1196-1200.

Karabinis.A, Hill.C,Leclercq.B,Tanciade.C, Baume.D, Andrement.A, "Risk factors for candidemia in cancer patients: a case-control study," (1988), J. Clin. Micobiol, 26, 429-432.

Karatas, F.; Koca, M.; Kara, H.; Servi, S, "Synthesis and oxidant properties of novel (5-bromobenzofuran-2-yl)(3-methyl-3-esitylcyclobutyl)ketonethiosemicarbazone,"(2006), Eur. J. Med. Chem., 41, 664-649.

Katzenellenbogen. J. A ,Compton. D. R, Shubin Sheng, Kathryn E. Carlson, Natalie A. Rebacz, In Young Lee, Katzenellenbogen. B. S , "Pyrazolo[1,5-a]pyrimidines: Estrogen Receptor Ligands Possessing Estrogen Receptor β Antagonist Activity,"2004, J. Med. Chem., 47, 5872-5893.

Kearney. J.A, Barbadora. K, Mason. E.O, Wald.E.R, Green. M, "In vitro activities of the oxazolidinone compounds linezolid (PNU-100766) and eperzolid (PNU-100592) against middle ear isolates of *Streptococcus pneumoniae*," (1999),Int J Antimicrob agents, 12,141-144.

Keith.W. A. M, Allen. C. B, Sharon. H, Richard. E. J, Thomas. R. M,"1-[4-(4-Chloro phenyl)-2-(2,6-dichlorophenylthio)-n-butyl]-1*H*-imidazole nitrate a new point antifungal agent, (1978), J. Med. Chem., *21*, 840-843.

Kelson. A. B, McNamara. J. P, Pandey. A, Ryan. K. J, Dorie. M. J, MaAfee. P. A, Menke. D. R, Brown. J. M, Tracy. M, "Anti-Cancer Drug Design," (1998), Anticancer Drug Des., 13, 575-592.

Khaled. M. A, Morin. R. D, Benington. F, Daughery. J. P, "2,4-Diamino-6-(bis-2-chloroethyl) aminomethyl pteridine,"(1984),*Cancer Chemother. Pharmacol.,* 13, 73-74.

Khedekar.P.B, Bahekar.R.H, Chopade.R.S, Umathe.S.N, Rao. A.R,Bhusari. K.P, "Synthesis and anti-inflammatory activity of alkyl/arylidene-2-aminobenzothiazoles and 1-benzothiazol-2-yl-3-chloro-4-substituted-azetidin-2-ones," (2003),Arznelmittelforshung, 53 (9), 640-647.

Khokra.S.L, Arora. K, Mehta. H, "Common methods to synthesize benzothiazole derivatives and their medicinal significance: a review," (2011),Int J Curr Pharm Res., 2, 1356-1377.

Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M, "Tetrahydrobenzindoles: selective antagonists of the 5-HT7 receptor," (1999),*J. Med. Chem.*, 42, 533-535.

Kilburn.J.P,Lau. J, Jones. R.C.F,"Solid-phase synthesis of substituted 2-aminomethyl benzimidazoles, " (2000), Tetrahedron. Lett., 41, 5419-5421.

Kim. D.C, Lee. Y.R, Yang. B, Shin. K.J, Kim. D.J, Chung. B.Y, Yoo. K.H, "Synthesis and biological evaluations of pyrazolo[3,4-d]pyrimidines as cyclin-dependent kinase 2 inhibitors,"(2008), Eur. J. Med.Chem. 38, 525-532.

Kirkpatrick. W. E, Okabe. T, Hillyard. I. W, Robin. R. K, Dren. A. T, "3-Halo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines, a nonbenzodiazepinoid class of antianxiety agents devoid of potentiation of central nervous system depressant effects of ethanol or barbiturates,"(1977),J. Med. Chem., 20, 386-393.

Kohara.Y, Kubo. K, Imamiya.E, Wada.T, Inada.Y, Naka. T, "Synthesis and angiotensin II receptor antagonistic activities of benzimidazole derivatives bearing acidic heterocycles as novel tetrazolebioisosteres," (1996),J. Med. Chem., 39, 5228-5235.

Konkoy. C. S, Fick. D. B, Cai. S. X, Lam. N. C, Keana. J. F, (2000), W. PCT Int. Appl. WO 0075123,; Chem. Abstr. **2001**, 134, 29313a.

Krajewski. K, Zhang. Y, Parrish. D, Deschamps. J, Roller. P. P, Pathak. V. K , "New HIV-1 reverse transcriptase inhibitors based on a tricyclic benzothiophene scaffold: Synthesis, resolution, and inhibitory activity,"(2006), *Bioorg. Med. Chem. Lett.***2006**, 16, 3034-3038.

Krystof. V, Moravcova. D, Paprskarova. M, Barbier. P, Peyrot. V, Hlobikova. A, Havlicek. L, Stramd. M, "Synthesis and biological activity of 8-azapurine and pyrazolo[4,3-*d*]pyrimidine analogues of myoseverin,"(2006), Eur. J. Med. Chem. 41, 1405-1411.

Kubo.I, Kinst-Hori.I, Chaudhari. S. K, Kubo. Y, Sanchez. Y, Ogura. T, "Flavonols from Heterotheca inuloides: tyrosinase inhibitory activity and structural criteria," (2000),Bioorg.Med. Chem., 8, 1749-1755.

Kumbhare.R.M, Kumar.K.V, Ramaiah. M.J, "Synthesis and biological evaluation of novel Mannich bases of 2-arylimidazo [2, l-*b*] benzothiazoles as potential anti-cancer agents," (2011), Eur J Med Chem.,46, 4258-4266.

Kundu. N. G, Pal. M, Mahanty. J. S, De. M , "Palladium-catalysed heteroannulation with acetylenic compounds: synthesis of benzofurans,"(1997), J. Chem. Soc. Perkin Trans 1, 2815-2820.

Kundu.N.G, Das. B, Spears. C.P, Majumdar.A, Kang. S.I, "Synthesis and biological activities of novel 5-(2-acylethynyl)uracils," (1990), J. Med. Chem., 33, 1975-1979.

Kuter.D. J, Tilloston. G. S, "Hematologic Effects of Antimicrobials: Focus on the Oxazolidinone Linezolid,"(2001), Pharmacotheraphy, 21, 1010-1013.

Lagunin.A, Stepanchikova.A, Filimonov. D, Poroikov. V, "PASS:prediction of activity spectra for biologically active substances,"(2000), Bioinformatics, 16, 747-748.

Latrofa.A, Franco. M, Lopedota. A, "Structural modifications and antimicrobial activity of *N*-cycloalkenyl-2-acylalkylidene-2, 3-dihydro-1, 3-benzothiazoles," (2005),*Farmaco.*,60, 291-297.

Lee. J. S, Cho. Y. S, Chang. M. H, Koh. H. Y, Chung. B. Y, Pae. A. N, "Synthesis and in vitro activity of novel isoxazolyl tetrahydropyridinyl oxazolidinone antibacterial agents," (2003), Bioorg. Med. Chem. Lett., 13, 4117-4120.

Lee. J.H, Park. J.S, Cho, C.G, "Regioselective synthesis of 3-alkynyl-5-bromo-2-pyrones via Pd-catalyzed couplings on 3,5-dibromo-2-pyrone,"(2002), Org. Lett., 4, 1171-1173.

Lee. Y.R, Jin. G.H, Lee. S.M, "Inhibition of TNF-alpha-mediated inflammatory responses by a benzodioxolylacetylamino-linked benzothiazole analog in human fibroblast-like synoviocytes," (2011),BiochemBiophys Res Commun., 408, 625-629.

Lemaire.S, Kosowska-Shick. K, Appelbaum. P.C, Vereen. G, Tulkens. P.M, Van Bambeke. F, "Cellular pharmacokinetics of the novel biaryloxazolidinoneradezolid in phagocytic cells: studies with macrophages and polymorphonuclear neutrophils," (2010), Antimicrob Agents Chemother., 54, 2549- 2559.

Li. J.T, Wang. S.X, Chen.G.F, Li. T.S, "Some applications of ultrasound irradiation in organic synthesis," (2005), Curr. Org. Synth., 2, 415-436.

Lin.A. H, Murray. R. W, Vidmar. T. J, Marotti. K. R, "The oxazolidinone eperezolid binds to the 50S ribosomal subunit and competes with binding of chloramphenicol and lincomycin," (1997), Antimicrob. Agents Chemother., 41, 2127-2131.

Link.A, Kunick. C, "d-Fused [1]Benzazepines with Selective in Vitro Antitumor Activity: Synthesis and Structure−Activity Relationships,"(1998), J. Med. Chem., 41, 1299-1305.

Liu.M, Reiser. O.A, "A Copper(I) Isonitrile Complex as a Heterogeneous Catalyst for Azide-Alkyne Cycloaddition in Water,"(2011), Org .Lett., 13, 1102-1105.

Lombardy.R. L, Tanious. F. A, Ramachandran. K, Tidwell. R. R, Wilson. W. D, "Synthesis and DNA interactions of benzimidazole dications which have activity against opportunistic infections," (1996) J. Med. Chem., 39, 1452-1462.

Lown. J.W, " Anthracycline and anthraquinone anticancer agents: current status and recent developments,"(1993), Pharmacol. Ther., 60, 185-214.

Macchiarulo.A, Constantino. G, Fringuelli. D, Vecchiarelli. A, Fausto. S, Renata. F, "1,4-Benzothiazine and 1,4-Benzoxazine imidazole derivatives with antifungal activity: A docking study," (2002),Bioorg. Med. Chem., 10, 3415-3423.

Madhukar.N.J, Rote. R. V, Shelar. D. P, Patil. S. R, Shinde. S. S, Toche. R. B, "Effect of donor-acceptor chromophores on photophysical properties of newly synthesized pyrazolo-pyrrolo-pyrimidines,"(2011),J. Fluoresc., 21, 453-459.

Mali. R. S, Joshi. P. P, Saudhu. P. K, Manekar-Tilve. A , "Efficient syntheses of 6-prenylcoumarins and linear pyranocoumarins: Total synthesis of suberosin, toddaculin, O-methylapigravin(O-methylbrosiperin), O-methylbalsamiferone, dihydroxanthyletin, xanthyletin and luvangetin,"(2002), J. Chem. Soc. Perkin Trans. 1, 371-376.

Marrision, L. R.; Dickinson, J. M.; Ahmed, R.; Fairlamb, I. J. S, "An efficient synthesis of 4-Alkenyl/alkynyl-6-methyl-2-pyrones via Pd-catalysed coupling on 4-bromo-6-methyl-2-pyrone," (2002), Tetrahedron Lett.,43, 8853-8857.

Martone, W. J.; Jarvis, W. R.; Edwards, J. R.; Culver, D.; Haley, R. W. *Hospital Infections*, 4th ed, 1998, 461.

Masakasu Ban, Hiroki Tagchi, Takeo katsushima, Mitsuru Takashi, Kiyotaka Shimoda, Akihiko Watanabe and TakanariTomianaga, *Bioorganic and Medicinal Chemistry, 6,* 1069 (1998).

Mason. T.J, "Sonochemistry and the environment - providing a "green" link between Chemistry, physics and engineering,"(2007), Ultrason. Sonochem., 14, 476-483.

Matassaova.N. B, Rodnina. M. V, Endermann. R, Kroll. H. P, Pleiss. U, Wild. H, Wintermeyer. W, "Ribosomal RNA is the target for oxazolidinones, a novel class of translational inhibitors,"(1999), RNA., 5, 939-946.

Mavrova.A. T, Anichina. K. K, Vuchev. D. I, Tsenov. J. A, Denkova. P. S, Kondeva. M. S, Micheva. M. K, "Antihelminthic activity of some newly synthesized 5(6)-(un)substituted-

1H-benzimidazol-2-ylthioacetylpiperazine derivatives,"(2006), Eur. J. Med. Chem., 41, 1412-1420.

Mazurov, A.,"Traceless synthesis of benzimidazoles on solid support," (2000), Bioorg. Med. Chem. Lett., 10, 67-70.

McCall. W. V, "A psychiatric perspective on insomnia,"(2001), J. Clin. Psychiatry, 62(Suppl.), 27-32.

McEvoy. M. T, Stern. R. S, "Psoralens and related compounds in the treatment of psoriasis," (1987), Pharmacol. Ther., 34(1), 75-97.

Mehta. G, Singh. V, "Hybrid systems through natural product leads: an approach towards new molecular entities," (2002),ChemSoc Rev., 31, 324-334.

Meseguer.B, Alonso-Diaz. D, Griebenow. N, Herget. T, Waldmann. H, "Natural Product Synthesis on Polymeric Supports-Synthesis and Biological Evaluation of an Indolactam Library," (1999), Angew. Chem. Int. Ed. 1999, 38, 2902-2906.

Middleton. W.J, Wilmington. D, "2,2,5,5 Tetrakis(Polyhalomethyl),4-oxazolidinone Herbicides",(1972), US Patent 3,690,862.

Moghadhan.F.M, Ismaili. H, Bardajee. C.R, "Zirconium (IV) oxide chloride and anhydrous Copper (II) sulfate mediated synthesis of 2-substituted benzothiazoles," (2006), Heteroatom Chem., 17, 136–141.

Moise.P.A, Forrest. A,Birminggham. M. C, Schentag.J.J, "The efficacy and safety of linezolid as treatment for Staphylococcus aureus infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin," (2002), J.Antimicrob. Chemother., 50, 1017-1026.

Momparler. R. L, Bovenzi. V, "DNA methylation and cancer," (2000), J. Cell Physiol., 183, 145-154.

Mourtas. S, Gatos. D, Barlos. K ,"Solid phase synthesis of benzothiazolyl compounds," (2001),Tetrahedron Letters ,42 , 2201–2204.

Muller. G, Napier. J, Balestra. M, DeCory. T, Hale. G, Macor. J, Mack. R, Loch. J, Wu. E,Kover. A, Verhoest. P, Sampognaro. A, Phillips. E, Zhu. Y, Murray. R, Griffith. R, Blosser. J, Gurley. D, Machulskis. A, Zongrone. J, Rosen. A, Gordon. J, "(-)-Spiro [1-azabicyclo [2.2.2] octane-3,5'-oxazolidin-2'-one], a conformationally restricted analogue of

acetylcholine, is a highly selective full agonist at the alpha 7 nicotinic acetylcholine receptor," (2000), J. Med Chem., 43,4045-4050.

Muller. M, Schimz. K.L, "A novel class of antibiotics,"(1999) Cell Mol Life Sci., 56,280-285.

Musser.J. H, Brown. R. E, Love. B, Baily. K, Jones. H, Kahen. R, "Synthesis of 2-(2,3- Dihydro-2-oxo-l,3,4-oxadiazol-5-yl) Benzo Heterocycles. A Novel Series of Orally Active AntiallergicAgents," (1984),J. Med.Chem., *27*, 121-125.

Mylari.B.L, Larson.E.R, Bayer. T.A, Zembrwaki.W J, Aldlinger.C.E, Des.M.F, Siegel, T.W, Singleton.D.H, "Novel, potent aldose reductase inhibitors: 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl] methyl]-1-phthalazineacetic acid (zopolrestat) and congeners," (1991), J. Med. Chem, 34,108-122.

Naemati. N, Mazumdar. A, Sunder. S, Owen. J. M, Tandon. M, Lown. J. W, Pommier. Y, "Highly potent synthetic polyamides, bisdistamycins, and lexitropsins as inhibitors of human immunodeficiency virus type 1 integrase," (1998),*Mol. Pharmacol.* 1998, 54, 280-290.

Nakamura .S, "Structure of Azomycin, a New Antibiotic," (2005), Chem Pharm Bull. 3, 379-383.

Nam. N.H, Dung.P.T, Thuong. P.T, "Synthesis and biological evaluation of a series of 2-(substitutedphenyl)benzothiazoles,"(2011), Med .Chem., 7, 127-134.

Nelson. M. E, Loktionova. N. A, Pegg. A. E, Moschel. R. C, "2-Amino-O^4-benzylpteridine Derivatives: Potent Inactivators of O^6-Alkylguanine-DNA Alkyltransferase,"(2004), J. Med. Chem., 47, 3887-3891.

Niewiadomy.A, Krajewska- Kulak.E,Lukaszuk.C,Matysiak.J,Kostccka.M, "In vitro Antifungal activityofn-3-(1,2,4-dithiazole-5-thione)-beta-resorcylcarbothioamide," (2005), rocznikiakadentiimedycznejbiadymstoka, 50, 31-35.

Nogradi.A, Vrbova. G,"The effect of riluzole treatment in rats on the survival of injuredadult and grafted embryonic motoneurons," (2001),Eur J Neurosci.,13, 113-118.

Nolan. J. M, Comins. D. L, "Regioselective Sonogashira Couplings of 2,4- Dibromoquinolines. A Correction,"(2003),*J. Org. Chem*. 2003, *68*, 3736-3738.

Novinson. T, Bhooshan. B, Okabe. T, Revankar. G. R, Wilson, H. R, "Novel heterocyclic nitrofurfural hydrazones. In vivo antitrypanosomal activity," (1976), J. Med.Chem. 1976, 19, 512-516.

Novinson. T, Hanson. R, Dimmitt. M. K, Simmon. L. N, Robins. R. K, O'Brien. D. E, "3-Substituted 5, 7-dimethylpyrazolo [1, 5-a]pyrimidines, 3',5'-cyclic AMP hosphodiesterase Inhibitors," (1974), J. Med. Chem., 17, 645-648.

Oett. K, Reibnegger. G, "Pteridines as inhibitors of xanthine oxidase: structural requirements," (1999), *Biochim. Biophys. Acta*, 1430, 387-395.

Ogundaini . A, Farah. M, Prera. P, Samuelsson. G, Bohlin. L, "Isolation of two new anti-inflammatory biflavanoids from Sarcophyte piriei,"(1996), J. Nat. Prod., 59, 587-590.

Oparil. S, Bakir. S. E, "Calcium antagonists in cardiovascular disease. Clinical evidence from morbidity and mortality trials," (2000), Drugs 2000, 59, 25-37.

Orjales.A, Mosquera. R, Labeaga. L, Rodes. R, "New 2-piperazinylbenzimidazole derivatives as 5-HT_3 antagonists. Synthesis and pharmacological evaluation,"(1997),J. Med. Chem., 40, 586-593.

Pal. M, "Palladium-Catalyzed Alkynylation of Aryl and Hetaryl Halides: A Journey from Conventional Palladium Complexes or Salts to Palladium/Carbon," (2009), *Synlett* 2896-2912.

Palmer. P.J, Trigg.R.B, Warrington.J.V, "Benzothiazolines as antituberculous agents" J. Med. Chem., 1971, 14, 248-251.

Panek. J. S, Liu. P, "Total Synthesis of the Actin-Depolymerizing Agent (−)-Mycalolide A: Application of Chiral Silane-Based Bond Construction Methodology," (2000), J. Am. Chem. Soc., 122, 11090-11097.

Paola. Vicini, AthinaGeronikaki, Matteo Incerti, BernadeltaBusonera, Graziell Poni, Carla Alba Cabras and Paolo La CoUa, "Synthesis and biological evaluation of benzo[d]isothiazole, benzothiazole and thiazole Schiff bases," (2003), Bioorganic and Medicinal Chemistry, 11**,** 4785-4789.

Paramashivappa. R, Phani. K. P, Subba. R. P.V, Srinivasa, R. A, "Design, synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors, " (2003),Bioorg .Med. Chem.Lett., 13, 657-660.

Paranjape.S.D,Bobade.A.S,KhsLdse.B.G, "Synthesis and evaluation of new triazolobenzothiazole derivatives as potential anti-tubercular agents," (2001), Arzneimittelforschung, 51(11), 916-919.

Park.C. H, Brittelli. D. R, Wang. C. L, Marsh. F. D, Gregory. W. A, Wuonola. M. A, McRipley. R. J, Eberly. V. S, Slee. A. M, Fobes. M, "Antibacterials. synthesis and structure-activity studies of 3-aryl-2-oxooxazolidines. 4. Multiply-substituted aryl derivatives,"(1992), J. Med. Chem., 1992, 35, 1156-1165.

Patel.N.B, Khan. I.H, Rajani, S.D, "Antimycobacterial and antimicrobial study of new 1, 2, 4-triazoles with benzothiazoles," Arch. Pharm (Weinheim)., (2010), 343, 692-699.

Patel.N.B, Khan.I.H, Rajani. S.D. "Antimycobacterial and antimicrobial study of new 1,2,4-triazoles with benzothiazoles," (2010), Arch Pharm (Weinheim), 343, 692-699.

Pattan. S. R, Suresh. C, Pujar. V. D, Reddy. V. V. K, Rasal. V. P, Kotti. B. C, "Synthesis and antidiabetic activity of 2-amino [5′(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole," (2005),*Indian J Chem.*, *4*B, 2404-2408.

Patzold.F, Zeuner. F, Heyer. T. H, Niclas. H.J,"Dehydrogenations Using Benzofuroxan as Oxidant," (1992), Synth. Commun., 22, 281-288.

Paula. M.T, Ferreira.Hernani. L. S, "Synthesis of 2, 3, 5-substituted pyrrole derivatives," (2002), *Tetrahedron Lett.*, 43, 4491-4493.

Peppard.W. J, Weigelt. J. A, "Role of linezolid in the treatment of complicated skin and soft tissue infections," (2006), Expert. Rev. Anti. Infect Ther., 2006, 4, 357-366.

Petrounia.I. P, Goldberg. J, Brush. E, "Transient inactivation of almond mandelonitrile lyase by 3-methyleneoxindole: a photooxidation product of the natural plant hormone indole-3-acetic acid," (1994), J. Biochemistry, 33, 2891-2899.

polyhydroxylated 2-phenylbenzothiazoles and a comparison of their cytotoxicities and pharmacological properties with genistein and quercetin," (1994), J Med Chem., 37, 1689-1695.

Porcari. A. R, Devivar. R. V, Kucera. L. S, Drach. J. C, Townsend. L. B, "Design, synthesis, and antiviral evaluations of 1-(substitutedbenzyl)-2-substituted-5,6-dichlorobenzimidazoles asnonnucleosideanaloguesof2,5,6-trichloro-1-(a-d-ribofuranosyl) benzimidazole," (1998), J. Med. Chem., 41(8), 1252-1262.

Priyanka.N.K, Jha. K.K, "Benzothiazole: the molecule of diverse biological activities,"(2010), Int .J. Curr. Pharm. Res., 2, 1-6.

Punniyamurthy, T, Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; "Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and

Quesnella, C. A.; Gill, P.; Roy, S.; Dodier, M.; Martel, A.; Synder, L. B.; D'Andrea, S. V.; Bronson. J. J.; Frosco, M, "Biaryl isoxazolinone antibacterial agents," (2005) Bioorg. Med. Chem., 15, 2728-2733.

Raboisson.P, Lenz. O, Lin. Tse-I, Surleraux. D, Chakravarty. S, Scholliers. A, Vermeiren. K, Dclouvroy. F, Verbinnen. T, Simmen. K, "Synthesis and biological activity of novel macrocyclic antifungals: modification of the tyrosine moiety of the lipopeptidolactone FR901469," (2007),*Bioorg. Med. Chem. Lett.*, 17, 1843-1849.

Rahback. L, Breinholt. J, " Circumdatins D, E, and F: Further Fungal Benzodiazepine Analogues from Aspergillus ochraceus," (1999), J. Nat. Prod., 62, 904-905.

Rahman, M.; Gray, A. I, "New salicylic acid and isoflavone derivatives from Flemingia paniculata,"(2002), J nat prod., 67, 402-406.

Rao .K.N, Bhattacharya.R.K, Venkatachalam.S.R, "Thymidylate synthase activity in leukocytes from patients with chronic myelocytic leukemia and acute lymphocytic leukemia and its inhibition by phenanthroindolizidine alkaloids pergularinine and tylophorinidine," (1998), Cancer Lett., 128, 183-188.

Rashad.A.E, Hegab.M.I, Abdel-Megeid.R.E, Micky.J.A, Abdel-Megeid.F.M.E, "Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives," (2008), Bioorg.Med. Chem. 16, 7102-7106.

Ratoarinoro. N, Wilhelm. A.M, Berlan. J , Delmas. H, "Effects of ultrasound emitter type and power on a heterogeneous reaction," (1992),*Chem. Eng. J.*, 50, 27-31.

Reck. F, Zhou. F, Girardot. M, Kern. G, Eyermann. C. J, Hales. N. J, Ramsay. R. R, Gravestock. M. B, "Identification of 4-substituted 1,2,3-triazoles as novel oxazolidinone antibacterial agents with reduced activity against monoamine oxidase A,"(2005), J. Med. Chem.,48, 499-506.

Refouvelet. B, Guyon. C, Jacquot. Y, Girard. C, Fein. H, Be'valot. F, Robert. J. F, Heyd. B, Mantion. G, Richert. L, Xiduna. A, "Synthesis of 4-hydroxycoumarin and 2, 4-quinolinediol derivatives and evaluation of their effects on the viability of HepG2 cells and human hepatocytes culture,"(2004),*Eur. J. Med. Chem.*, 39, 931-937.

Reinicke, C. Z, "Nonsteroid antirheumatic agents," (1977), Gesamte *Inn. Med.*, 32, 333-337.

Revesz. L, Di Padova. F. E, Buhl. T,Feifel. R, Gram. H,Hiestand. P, Manning. U, Wolf. R, Zimmerlin. A. G, "SAR of 2,6-diamino-3,5-difluoropyridinyl substituted heterocycles as novel p38MAP kinase inhibitors," (2002),Bioorg. Med. Chem. Lett., 12, 2109-2112.

Reynolds. R. C, Srivastava. S, Ross. L. J, Suling. W. J, White. E. L, "A new 2-carbamoyl pteridine that inhibits mycobacterial FtsZ,"(2004),*Bioorg. Med. Chem. Lett.* 14, 3161-3164.

Riedl, B.; Haebich, D.; Stolle, A.; Ruppelt, M.; Bartel, S.; Guarnieri, W.; Endermann, R.; Kroll, H. P. (1997) German Patent 19604223.

Robert. M, Scarborough. A.M, Laibelman. L. A, Clizbe. L. J, Petto.P. B, Conley. E. E, Reyolds., Sedlock.D. M, Hans-Michael,Jantzen, "Novel Tricyclic Benzothiazolo[2,3-c]thiadiazine Antagonists of the Platelet ADP Receptor ($P2Y_{12}$)," (2001), Bioorganic and Medicinal Letters, 11,1801-1808.

Robinson. R. P, Reiter. L. A, Barth. W. E, Campeta. A. M, Cooper. K, Cronin. B. J, Destito. R, Donahue. K. M, Falkner. F. C, Fiese. E. F, Johnson. D. L, Kuperman. A. V, Liston. T. E, Malloy. D, Rusek. F. W, Shamblin. S. L, Wright. C. F, "Discovery of the hemifumarate and (alpha-L-alanyloxy) methyl ether as prodrugs of an antirheumatic oxindole: prodrugs for the enolic OH group," (1996), J. Med. Chem., 39, 10-18.

Roelens. F, Huvaere. K, Dhooge. W, van Cleemput. M, Comhaire. F, De Keukeleire. D, "Regioselective synthesis and estrogenicity of (+/-)-8-alkyl-5, 7-dihydroxy-4-(4-hydroxyphenyl)-3, 4-dihydrocoumarins," (2005), Eur. J. Med. Chem., 40(10), 1042-1051.

Rosenblatt. J. E, "Antiparasitic agents," (1992), Mayo Clin. Proc., 67, 276-287.

Rosowsky.A, Chen. K. N, Amand. R. S, Modest. E. J, "Chemical and Biological Studies on 1,2-Dihydro-s-triazines XVIII: Synthesis of 1-(5,6- and 5,'7-Dichloro-2-naphthyl) Derivatives and Related Compounds as Candidate Antimalarial and Antitumor Agents," (1973), J. Pharm. Sci., 62, 477-479.

Rudrawar. S, Kondaskar. A, Chakraborti. A. K, "An Efficient Acid- and Metal-Free One-Pot Synthesis of Benzothiazoles from Carboxylic Acids," (2005), Synthesis, 15, 2521-2526.

Saha. P, Ramana. T, Purkait. N, Ali. M. A, Paul. R, Punniyamurthy. T, "Ligand-free copper-catalyzed synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles,"(2009),J. Org. Chem.,74, 8719-8725.

Sakoulas.G, Gold. H. S, Venkataraman. L, Moellering. R. C, Ferraro. M. J, Eliopoulos. G. M, "Introduction of erm(C) into a linezolid- and methicillin-resistant Staphylococcus aureus does not restore linezolid susceptibility," (2003), *J. Antimicrob Chemother.*, 51,1039-1041.

Sanap.M.S, Dighe.N.S, Pattan. S.R, "Benzothiazole its current pharmacological profile and methods of synthesis," (2010),Pharmacology., 1, 238-244.

Sanugul. K, Akao. T, Li. Y, Kakiuchi. N, Nakamura. N, Hattori. M, "Isolation of a human intestinal bacterium that transforms mangiferin to norathyriol and inducibility of the enzyme that cleaves a C-glucosyl bond," (2005), Biol. Pharm. Bull., 28, 1672-1678.

Sarges. R, Howard. H. R, Browne. R. G, Lebel. L.A, Seymour. P. A, Koe. B. K , "4-Amino[1,2,4]triazolo[4,3-a]quinoxalines. A novel class of potent adenosine receptor antagonists and potential rapid-onset antidepressants," (1990), J. Med. Chem., 33, 2240-2254.

Sbardeila. G, Mai. A, Artico. M, Loddo. R, Setzu. M. G, La Colla. P, "Synthesis and in vitro antimycobacterial activity of novel 3-(1H-pyrrol-1-yl)-2-oxazolidinone analogues of PNU-100480," (2004), Bioorg. Med. Chem. Lett., 14, 1537-1541.

Schaefer.E. J, McNamara. J. R, Tayler. T, Daly. J. A, Gleason. L, Seman. L. J, Ferrari. A, Rubenstein. J. J, "Comparisons of effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects," (2004)*Am. J. Cardiol.* 2004, 93, 31-35.

Schulz. W. G, Islam. E, Skibo. E. B, "Pyrrolo[1,2-*a*]benzimidazole-based quinones and iminoquinones. The role of the 3-substituent on Cytotoxicity," (1995), J. Med. Chem., 38, 109-118.

Selleri . S, Bruni . F, Costagli. C, Costanzo. A, Guerrini. G, Ciciani. G, Costa. B,Martini. C, "Synthesis and Structure-Activity Relationships of 5, 6,7-substitute prazolopyrimidines: Discovery of a novel TSPO PET Ligand for Cancer Imaging," (2001), Bioorg. Med. Chem., 9, 2661-2671.

Selnick, H. G.; Liverton, N. J.; Baldwin, J. J.; Butcher, J. W.; Clareman, D. A.; Elliott, J. M.; Freidinger, R. M.; King, S. A.; Libby, B. E.; McIntyre, C. J.; Pribush, D. A.; Remy, D. C.; Smith, G. R.; Tebben, A. J.; Jurkiewicz,N. K.; Lynch, J. J.; Salata, J. J.; Sanguinetti, M. C.; Siegl, P. K.; Slaughter, D. E.; Vyas, K, "Class III Antiarrhythmic Activity in Vivo

by Selective Blockade of the Slowly Activating Cardiac Delayed Rectifier Potassium Current I_{Ks} by (R)-2-(2,4- Trifluoromethyl)-N-[2-oxo-5-phenyl- 1-(2,2,2-trifluoroethyl)-2,3-dihydro- 1H-benzo[e][1,4]diazepin-3-yl]acetamide,"(1997), J. Med. Chem., 40, 3865-3868.

Selvakumar. N, Raheem. M. A, Khera. M. K, Rajale. T. V, Kumar. M. S, Kandepu. S, Das. J, Rajagopalan. R, Iqbal. J, Trehan. S,"Influence of ethylene-oxy spacer group on the activity of linezolid: synthesis of potent antibacterials possessing a thiocarbonyl group," (2003), Bioorg. Med. Chem. Lett., 13, 4169-4172.

Senga. K, Novinson. T, Wilson. H. R, "Synthesis and antischistosomal activity of certain Pyrazolo [1,5-a]pyrimidines,"(1981), J. Med. Chem., 24, 610-613.

Shenone. S, Bruno. O, Ranise. A, Bondavalli. F, Fossa. P, Mosti. L, Menozzi. G, Carraro. F, Naldini. A, Bernini. C, Manetti. F, Botta. M, "New pyrazolo[3,4-d]pyrimidines endowed with A431 antiproliferative activity and inhibitory properties of Src phosphorylation,"(2004), Bioorg. Med. Chem. Lett. 14, 2511-2517.

Shi,D. F, Bradshaw.T. D, Wrigley.S,McCall.C. J, Lelieved. P,Pichtner. I, Stevens.M. F. G, "Antitumor benzothiazoles. 3. Synthesis of 2-(4-aminophenyl) benzothiazoles and evaluation of their activities against breast cancer cell lines in vitro and in vivo," (1996),J.Med.Chem.,39, 3375-3384.

Shi.D.F, Bradshaw.T.D, Wrigley.S, "Antirumour benzothiazoles.3. Synthesis of 2-(4-aminophenyl) benzothiazoles and evaluation of their activities against breast cancer cell lines in vitro and in vivo," (1996), J Med Chem., 39, 3375-3384.

Shoichi. K, Ryutaro. N, Kanako. T, Jun. T, Junko. O, Tsuneaki. O, Makoto. Y, Kazushi.A, Jum.O "Potent Antidiabetic Effects of Rivoglitazone, a Novel Peroxisome Proliferator-Activated Receptor-γ Agonist, in Obese Diabetic Rodent Models," (2009), Journal of Pharmacological Sciences, 111,155-166.

Siddiqui. N, Ahsan. W, "Benzothiazole Incorporated Barbituric Acid Derivatives: Synthesis and Anticonvulsant Screening,"*Arch .Pharm (Weinheim).,* (2009), 342(8), 462-468.

Singh. S.P,Seghal. S, "Studyoffungicidal activities of somebenzothiazoles, (1988), *Indian J Chem*., *27* B, 941-943.

Singh.T,Srivastava. V.K, Saxena. K. K, "Synthesis of new thiazolyl thiazolidinylbenzothiazoles and thiazolyl azetidinyl benzothiazoles as potential insecticidal, antifungal, and antibacterial agents," (2006), Arch. Pharm (Weinheim)., 339, 466-472.

Slade. J, Stanton. J. L, Ben- David. D, Mazzenga. G. C, "Angiotensin converting enzyme inhibitors: 1,5 benzothiazepine derivatives,"(1985), J. Med. Chem., 28, 1517-1521.

Slee. A.M, Wuonola. M.A, McRipley.R.J, Zajac.I, Zawada. M.J, Bartholomew. P.T, "Oxazolidinones, a new class of synthetic antibacterial agents: in vitro and in vivo activities of DuP 105 and DuP 721," (1987) Antimicrob Agents Chemother., 31,1791-1797.

Sluiter.J,Christoffers. J,"Synthesis of 1-methylbenzimidazoles from carbonitriles,"(2009),synlett., 63-66.

Smith. R. D, Li. J, Noguchi. C. T, Schechter. A. N, "Quantitative PCR analysis of HbF inducers in primary human adult erythroid cells,"(2000), Blood, 95, 863-869.

Sonogashira. K, "Development of Pd-Cu catalyzed cross coupling of terminal acetylenes with sp2-carbon halides," (2002), J. Organomet. Chem., 653, 46-49.

Sparatore.A, Novelli. F, Sparatore. F, "Synthesis and biological investigations of 1-(tetrahydropyran-2'-yl) and 1-(tetrahydrofuran-2'-yl)benzimidazoles and 1/2-(tetrahydropyran-2'-yl) and 1/2-(tetrahydrofuran-2'-yl) benzotriazoles," (1997),*Farmaco*, 52, 509-521.

Spencer. C. M, Brogolen. R. N, "Anagrelide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of thrombocythaemia," (1994), Drugs, 47, 809-822.

Sreenivasa, M. V, Nagappa. A. N, Nargund. L. V. G, "Various benzothiazolo triazole derivatives possess good antimicrobial activity,"(1998),Indian J. Heterocyclic. Chem. 1998, 8, 23-32.

Srinivasan. R. Nagarajan. Gary A. De Crescenzo, Daniel P. Getman, Hwang-FunLu, James A. Sikorski, Jeffrey L. Walker, Joseph J. McDonald, Kathryn P. Kocan, Nandini Kishore, Pramod P. Mehtha, Christie L. Funkes-Shippy and LisaBlystone, "Discovery of novel benzothiazolesulfonamides as potent inhibitors of HIV-1 protease," (2003), Bioorganic and Medicinal Chemistry, 11, 4769-4777.

Stambuli. J. P, Wray.B. C, "synthesis of *N*-arylindazoles and benzimidazoles from a common intermediate brenda c. wray and james p. stambuli," (2010), Org. Lett.,12, 4576-4579.

Steen. F. H, Koten. G. V,"Syntheses of 3-amino-2-azetidinones: A literature survey," (1991), Tetrahedron, 47, 7503-7524.

Stefani. S, Bongiorno. D, Mongelli. G, Campanile. F, "Linezolid resistance in staphylococci,"(2010), Pharmaceuticals., 7,1988-2006.

Stella. A, Segers. K, De Jonghe. S, "Synthesis and antibacterial evaluation of a novel series of 2-(l,2-dihydro-3-oxo-3H-pyrazol-2-yl) benzothiazoles," (2011),Chem Biodiverse., 8, 253-265.

Stevens. D.L, Dotter. B, Madaras. Kelly. K, "A review of linezolid: the first oxazolidinone antibiotic," (2004) Expert Rev Anti Infect Ther., 2,51-59.

Stevens. M.F, McCall.C.J, Lelieveld.P, "Structural studies on bioactive compounds.23. Synthesis of polyhydroxylated 2-phenylbenzothiazoles and a comparison of their cytotoxicities and pharmacological properties with genistein and quercetin," (1994),J Med. Chem., 37, 1689-1695.

Stevenson. P. C, Veitch. N. C , "A 2-arylbenzofuran from the roots of Cicer bijugum associated with Fusarium wilt resistance,"(1998), Phytochemistry, 48, 947-951.

Suzuki. M, Iwasaki. H, Fujikawa. Y, Sakashita. M, Kitahara. M, Sakoda. R, "Synthesis and biological evaluations of condensed pyridine and condensed pyrimidine-based HMG-CoA reductase inhibitors," (2001), Bioorg. Med. Chem. Lett., 11, 1285-1288.

Swaney.S. M, Aoki. H, Ganoza. M. C, Shinabarger. D. L, "The Oxazolidinone Linezolid Inhibits Initiation of Protein Synthesis in Bacteria,"(1998), Antimicrob. Agents Chemother. , 42, 3251-3255.

Syed. S, Mohammad. M. A, Naveen. M, Chaitanya. M, Reddanna. P, "Synthesis of novel 2-mercapto benzothiazole and 1,2,3-triazole based bis-heterocycles: Their anti-inflammatory and anti-nociceptive activities,"(2012), European Journal of Medicinal Chemistry, 49, 324-333.

Takahashi.S, Matsunga. T, Hasegawa. C, Saito. H, Fujita. D, Kiuchi. F, Tsuda. Y, "Martefragin A, a novel indole alkaloid isolated from red alga, inhibits lipid peroxidation,"(1998), Chem. Pharm. Bull., 46, 1527-1529.

Tale. R.H, "Novel synthesis of 2-arylbenzothiaozles mediated by ceric ammonium nitrate (CAN)," (2002), Organic Letters, 4(10), 1641-1642.

Taniguchi.K, Shigenaga. S, Ogahara. T, Fujitsu. T, Matsuo. M, "Synthesis and antiinflammatory and analgesic properties of 2-amino-1H-benzimidazole and 1,2-dihydro-2-iminocycloheptimidazole derivatives,"(1993),Chem. Pharm. Bull., 1993, 41, 301-309.

The Merck Index, 13th Edition, Ed. M. J. O'Neil, M. Smith, P. E Heckelman, Merck &Co.Inc., NJ. P-1785, Monograph Number: 10074, 2001.

Thomas. R. Webb, Slavish. P. J, Price. J. E, Hanumesh. P,Thomas. R. Webb, "Efficient Synthesis of Pyrazolopyrimidine Libraries," (2010), J. Comb. Chem. 12, 807-809.

Tilford, C. H.; Hudak, W. J.; Lewis, R, "Antihypertensive agents.Substituted 3-pyrrolemethylamines," (1971),*J. Med. Chem.*, 14, 328-331.

Trapani. G, Franco .M, Latrofa. A, "Synthesis, in vitro and in vivo cytotoxicity, and prediction of the intestinal absorption of substituted 2-ethoxycarbonyl-imidazo [2, l-*b*] benzothiazoles," (2001),Eur J Pharm Sci.,14, 209-216.

Trapani.V, Patel. V, Leong. C. O, Ciolino. H. P, Yeh. G. C, Hose. C, Trepel. J. B,Steven. M. F. G,Stausvill. E. A, Loaiza-Perez. A. I, "DNA damage and cell cycle arrest induced by 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F 203, NSC 703786) is attenuated in aryl hydrocarbon receptor deficient MCF-7 cells," (2003),Brit. J. Cancer, 88, 599-605.

Tsiodras. S, Gold. H. S, Sakoulas. G, Eliopouls. G. M, Wennersten. C, Venkataraman. L, Mollering. R. C, Ferraro. M, "Linezolid resistance in a clinical isolate of Staphylococcus aureus," (2001), Lancet, 358, 207-208.

Tumelty.D, Cao. K, Holmes. C. P, "Traceless solid-phase synthesis of substituted benzimidazoles via a base-cleavable linker," (2001), Org. Lett., 3, 83-86.

Tuncbilek. M, Kiper. T,Altanlar. N, "Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA," (2009),Eur J. Med Chem., 2009, 44, 1024-1033.

Van Loevezijin. A, Allen. J. D, Schinkel. A. H, Koomen. G. J, "Inhibition of BCRP-mediated drug efflux by fumitremorgin-type indolyl diketopiperazines," (2001), Bioorg. Med. Chem. Lett., 11, 29-32.

van Muijlwyk- Koezen. J. E, Timmerman. H, van der Goot. H, Menge. W. M, Frijtag Von Drabbe Kunzel. J, de Groote. M, Ijzerman. A. P, "Isoquinoline and quinazoline urea analogues as antagonists for the human A_3 adenosine receptor," (2000),*J. Med. Chem.*, 43, 2227-2238.

Van Zandt.M. C, Jones.M. L, Gunn.D. E, Geraci.L. S, Howard.J.J, Sawicki.D. R, Janet S, Jacot.J. L, Thomas.P.A, Andre Mitschler, Alberto D. P, "Discovery of 3- [(4,5,7-Trifluorobenzothiazol-2-yl) methyl] indole-*N*-acetic Acid (Lidorestat) and Congeners as Highly Potent and Selective Inhibitors of Aldose Reductase for Treatment of Chronic diabetic Complications," (2005), J. Med. Chem., 48(9), 3141-3152.

Vaughan, W. R.; Klownowski, R. S., "Synthesis of Potential Anticancer Agents.VI. N-(3-Hydroxypropyl)-benzaldimine and Related Compounds," (1961), J. Org. Chem., 21, 145-148.

Veeresa. G, Viet. N, James.T.D, Duane. D. M, "Efficient Microwave Enhanced Synthesis of 4-Thiazolidinones," (2004), Synlett., 2004, *13*, 2357-2358.

Viegas-Junior. C, Danuello. A, da Silva Bolzani. V, "Molecular hybridization: a useful tool in the design of new drug prototypes," (2007),Curr Med Chem.,14(17), 1829-1852.

Vilar. S, Quezada. E, Santana. L, Uriarte. E, Yanez. M, Frez. N, Alcaide. C, Cano. E, Orallo. F, "Design, Synthesis, and Vasorelaxant and platelet antiaggregatory activities of coumarin-resveratrol hybrids,"(2006),*Bioorg. Med. Chem. Lett.*, 16, 257-261.

Volpini, R.; Costanzi, S.; Lambertucci, C.; Vittori, S.; Klotz, K.N.; Lorenzen, A.; Cristalli, G, "Introduction of alkynyl chains on C-8 of adenosine led to very selective antagonists of the A(3) adenosine receptor,"(2001),*Bioorg. Med. Chem. Lett.* 2001, *11*, 1931-1934.

Waisser. K, Doleza. M, Sidoova. E, "Biological side-effects of potential anti-tubercular agents. XIV. Relation between the chemical structure, antitubercular activity and hepatotoxicity of 2-alkylthio-6-(2-chlorobenzamido) benzothiazoles,"*Ceska .Farm.*, (1988), 37, 437-439.

Wallace. R. J. Jr, Nash. D. R, Steele. L. C, Steingrube. V, "Susceptibility testing of slowly growing mycobacteria by a microdilution MIC method with 7H9 broth," (1986), J. Clin.Microbiol., 24, 976-981.

Wang. C. L, Li. H. Q, Meng. W. D, Qing. F. L, "Trifluoromethylation of flavonoids and anti-tumor activity of the trifluoromethylated flavonoid derivatives,"(2005),*Bioorg. Med. Chem. Lett.*, 15, 4456-4458.

Wigen.C. L, Goetz. M. B, "Serotonin syndrome and linezolid,"(2002), Clin. Infect. Dis., 34, 1651-1652.

Wookey.A,Tuner. J. P, Greenhalgh.J.M,Eastwood.M,Clarke.J,Sefton.C "AZD2563, a novel oxazolidinone: definition of antibacterial spectrum, assessment of bactericidal potential and the impact of miscellaneous factors on activity in vitro," (2004), Clin.Micro.and infec., 10(3),247-254.

Wu. C. P, vanSchalkwyk. D. A, Taylor. D, Smith. P. J, Chibale. K, "Reversal of chloroquine resistance in Plasmodium falciparum by 9H-xanthene derivatives," (2005), Inter. J. Antimicrob. Agents 2005, 26, 170-175.

Xie. L, Zhai. X, Ren. L, "Design, Synthesis and Antitumor Activity of Novel Artemisinin Derivatives Using Hybrid Approach," (2011), Chem Pharm Bull (Tokyo).,59,984-990.

Xin Jian Song, Yu Shao, Xing Gao Dong, "Microwave-assisted synthesis of some novel fluorinated pyrazolo[3,4-d]pyrimidine derivatives containing 1,3,4-thiadiazole as potential antitumor agents,"(2011),*Chinese Chemical Letters, 22,* 1036-1038**.**

Yadav.P.S, Devprakash.Senthilkumar. G.P,"Benzothiazole: different methods of synthesis and diverse biological activities," (2011),Int J Pharm Sci Drug Res.,3, 1-7.

Yamamoto. T, Fujita. K, Asari. S, Cheba. A, Kataba. Y, Ohsumi. K, Ijichi. C, Iwayama. S, Fukuchi. N, Shoji. M, "Synthesis and evaluation of isoxazole derivatives as lysophosphatidic acid (LPA) antagonists,"(2007),*Bioorg. Med. Chem. Lett.*, 17, 3736-3740.

Yanguang.W, She. J, Jiang. Z, , "One-pot synthesis of functionalized benzimidazoles and *1H*-pyrimidines via cascade reactions of *o*-aminoanilines or naphthalene-1,8-diamine with alkynes and p-tolylsulfonyl azide,"(2009), Synlett., 2023-2027.

Yates. P.C, Mccall. C.J, Stevens. M.F.G,"Structural Studies on Benxothiazoles. Crystal and molecular structure of 5,6-Dimethoxy-Z-(4-methoxyphenyl)-benzothiazole and molecular orbital calculations on related compounds," (1991), Tetrahedron, 47, 6493-6502.

Ying-Hung. S, DeCaire. R, "2-Arylbenzothiazoles and 2-Arylbenzoxazoles from α,α,α-Trihalomethyl Aromatic Compounds," (1998),Synthetic Comm., 28, 4123-4135.

Yoshida. M, Hayakawa. I, Hyashi. N, Agatsuma. T, Oda. Y, Tanzawa. F, "Synthesis and biological evaluation of benzothiazole derivatives as potent antitumor agents," (2005),Bioorg Med chem. Lett., 15, 3328-3332.

Youssef. A.M, Noaman. E, “Synthesis and evaluation of some novel benzothiazole derivatives as potential anticancer and antimicrobial agents,” (2007),Arzneimittel-forschung., 57, 547-553.

Zhang. M, Thurmond. R. L, Dunford. P. J, “The histamine H (4) receptor: a novel modulator of Inflammatory and immune disorders,” (2007), Pharmacology and therapeutics, 113 (3), 594-606.

Zhou. Y. S, Hou. A. J, Zhu. G. F, Chen. Y. F, Sun. H. D, Zhao. Q. S, “Cytotoxic isoprenylated xanthones from Cudrania tricuspidata,”(2004), Bioorg. Med. Chem. 2004, 12, 1947-1953.

List of Publications:

1. **Y .Bharath**, D. Nagaraju, and M.V. Basaveswara Rao,* "Facile Synthesis of *N*-(Benzyl-1*H*-1,2,3-Triazol-5-yl)Methyl)-4-(6-Methoxybenzo[*d*]Thiazol-2-yl)-2-Nitrobenzamides *via* Click Chemistry" (2017). *J. Heterocyclic Chem., 54,864*-870.
2. **Y. Bharath,** M. V. Basaveswara Rao.* "Synthesis of Ultrasound assisted Synthesis of 2-Alkynyl Pyrazolo [1, 5-*a*] Pyrimidines under Pd/C-Cu Catalysis," (2017), (Accepted in Letters In Drug Discovery And Design Letters, Banthem science).
3. **Y. Bharath**, G. Sathaiah , G. lakshmi prasana, M. V.Basaveswara Rao.* " Synthesis and biological evaluation of friedlander annulation approach for the diversity oriented of functionalized quinolines," (2016), *Der pharma chemicia*, *8(13),*165-174.
4. K .Suman , Y.**Bharath**, Ch. S. S. Murthy., D. Nagaraju , " Synthesis and antimicrobial activities of Novel 2-(Benzo [*d*] [1,3] Dioxol-5-yl) -6,7-dimethoxyl Quinazolin-4 (3*H*) – ones," (2015) , *Heterocyclic Letters, Vol. 5*,645-652.
5. G. chendra Shekar.,**Y. Bharath**., A. V. Ramana Reddy , "Synthesis of Novel -2-(benzo [*d*] [1,3] dioxol-5-yl) -5-Fluoro-4-Phenylquinolines as Antibacterial Agents,",(2014), *IJESRT, 3 (3).*

Conference and abstarcts:

1. Yarlagadda.Bharath and Mandava.Venkata Basveswara Rao, (**2016**), Ultrasound Assisted synthesis of 2-Alkynylpyrazolo [1, 5-*a*] Pyrimidines under Pd/C-Cu catalysis. Second AP congress held the P.B. Siddhartha Collegeege of Arts & Science, Vijayawada, India
2. Yarlagadda. Bharath , and Mandava.Venkata Basveswara Rao (**2014**), Synthesis of Novel Benzothiozoles Based [1,2,3] -Trizoles and supramolecular Interactions *via* Click – chemistry DST sponsored National conference on Recent Challenges in Chemical & Biological science, Vignan University, Guntur, India.
3. Yarlagadda. Bharath ,Devunuri. Nagaraju and Mandava. Venkata Basveswara Rao, (**2014**), Facile Synthesis and Biological Evaluation of DNA Interactive Fused Benzothiazoles., DST sponsored national conference on The Role of Natural Product Chemistry in Drug Discovery. Krishna University, Machalipatnam, India.
4. Yarlagadda Bharath , and Mandava. basveswara Rao (**2013**), National poster Symposium on Advances in Organic/medicinal chemistry, conducted by the Royal Chemical Society of chemistry (London) -DS in association with Krishna University, India.

CURRICULUM VITAE

YARLAGADDA BHARATH

Email id:
Bharathyarlys55@gmail.com
Contact. No.:
+91-9642703699

Contact Address:
s/o SrinivasaRao.Y,
Jogannavari street,
karamchedu(MD),
Prakasam(dist.),
Pin:- 523168
Andrapradesh

Personal Details:
Date of Birth:

05/08/1986

Age: 30.

Sex: Male.

Marital Status: Married.

Nationality: Indian.

Languages Known:
English, Hindi, Telugu (Mother Tongue), kannada.

Career Objective

I am seeking a challenging position with a company that is rapidly expanding and offer good advancement potential. I would like a position that would help me progress and bring the best in me.

Education

- Master's in Organic Chemistry (68%) from Pragathi College, Vishakhapatnam.AndraUniversity (**2006-2008**), Andrapradesh.
- Bachelor of Science (67%) from V.R.S&Y.R.N College, chirala, Nagarjuna University (**2003-2006**), Andra Pradesh.
- Higher Secondary Exam (10+2), 71.00% From SSC Board and Intermediate board, Andrapradesh.

Work Experience:

1) Current working as **Research Executive** (R&D department) in **Mylan Laborites Ltd at Hyderabad.** From ***MAY-2012*** to **till date.**

Job profile:

- Design and development of new synthetic methods for APIs, NCEs & their key components.
- Well versed with most modern analytical instrumentation and expertise in characterizing organic molecules using NMR, MASS and LCMS
- Scaling up of organic molecules and technology transfer from lab scale to plant scale.
- Well experienced in handling of hygroscopic, air sensitive reagents and reactions
- Capable of collaborative and independent work.
- Well versed in carrying out the work on literature survey.
- Performing micro reaction on milligram & gram scale of complex molecule. (Synthesis)
- Individually handle the complex project of good chemistry.

2) Working as Research Associate (R&D department) in **INTAS PHARMA LTD** at Ahmedabad from *May 2010 to April-2012*.

3) Working experience of 22 months in **DIVIS REASEARCH CENTER**, Vishakhapatnam, Andrapradesh, as a Research Chemist.

Having 8+ experience in API (Chemical Research Synthesis Division)

Current Job Profile and Responsibilities:

Scientific responsibilities:

- Development of APIs in the laboratory. This involves Literature search of products by using effective resources and proposals of new schemes for existing drug on the basis of Retro synthetic chemistry. Route selection, development of Non Infringing process and synthesis of bulk drugs conforming to quality specified by IP, BP, USP.
- Process development and cost improvement process of active pharmaceutical ingredients and intermediates by using innovative ideas to reach the market requirements.
- Identifying the key cost contributing areas in the selected project and describing the possible areas of cost improvement process.
- Planning and delivery the project in time.
- Checking the ruggedness of the designed process by doing the feasibility experiments.
- Conducting the negative experimental study for the designed process.
- Validating the designed process in the laboratory.
- Preparing specifications for the designed process before lab validation.
- Preparation of development reports as per SOP.
- Study the stability data of the lab validated samples.
  Checking the absence studies for the carry over impurities from KSM and all process related Possible genotoxic impurities if any in the cost improvement process.

Research Experience and Capabilities

- Route evaluation and designing non-infringing routes for APIs and its intermediates.
- Synthesis of small molecules especially intermediates for NCEs (New Chemical Entities).
- Skilled in the interpretation of NMR (^{1}H, ^{13}C), MS, IR, UV-VIS spectroscopy data for structure elucidation of unknown compounds such as impurities during development of API projects.
- Expertise in development of scalable process and its demonstration at pilot plant and manufacturing units.
- Purification of organic compounds through implementing crystallization and chromatographic techniques.
- Supporting to DMF filling and regulatory query related works.

Ability in Soft skills

- Computer literacy: MS word, Excel, Power point Presentations, usage of Chemistry related software's such as ISIS, Chem-draw, Reaxys and others.
- Writing skills: Skilled in writing scientific reports such as development reports, lab validation batch repots, project updates to superiors, research manuscripts and others.
- Good communication and presentation skills

STRENGTHS:

- Always try to put my all efforts into work whatever it may be.
- Good leadership and Multi-tasking qualities.
- Calmness & Cheerfulness.
- I am good listener to new things.

Having 8+ experience in API (Chemical Research Synthesis Division)

- I agree with my mistakes and don't repeat them.
- I am punctual, dedicated and confident towards my work.
- I accept challenges.
- Flexibility to work hard for long hours and patient enough until the goal I accomplish.

Safety Awareness:

- Experience in handling different hazardous chemicals with proper safety measures and good lab practices.
- Knowledge of searching MSDS and its proper utilization. Firefighting and first aid training.

Declaration

I hereby solemnly declare that all statements made above are true and correct to the best of my knowledge and belief.

Yours Sincerely,
Y.Bharath