SYNTHESIS OF NEW *N,N*-DISUBSTITUTED ARYL- AND ALKYLARYL SULPHONAMIDES AND THEIR ANTIMICROBIAL PROPERTIES

BY

AJANI, OLAYINKA OYEWALE

(CUGP050127)

MAY, 2012

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A THESIS SUBMITTED

TO

THE DEPARTMENT OF CHEMISTRY, SCHOOL OF NATURAL AND APPLIED SCIENCES, COLLEGE OF SCIENCE & TECHNOLOGY

COVENANT UNIVERSITY, OTA

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF DOCTOR OF PHILOSOPHY (Ph.D) IN CHEMISTRY

MAY, 2012

CERTIFICATION

We certify that the thesis titled "Synthesis of New *N,N*-Disubstituted Aryl- and Alkylaryl Sulphonamides and Their Antimicrobial Properties" is an original work carried out by Mr. Ajani Olayinka Oyewale (CUGP050127) in the Department of Chemistry, Covenant University, Ota, Ogun State under the supervision of Prof. O. B. Familoni and Prof. J. O. Echeme. We have examined and found the work acceptable for the award of a degree of Doctor of Philosophy in Chemistry.

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DEDICATION

This research work is dedicated to my Lord Jesus Christ, in whom dwells the fullness of the Godhead bodily. May His Name be praised forever for the Grace and mighty revelation birthed by the Light in the evening time.

.

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Olayinka Oyewale Ajani

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LIST OF ABBREVIATIONS

BzCl	Benzenesulphonyl chloride
BuLi	Butyl Lithium
CA	Carbonic Anhydrase
COX-2	Cyclooxygenase-2
DEA	Diethyl amine
DCM	Dichloromethane
DMB	2,4-Dimethoxybenzyl amine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl Sulphoxide
FT-IR	Fourier Transform-InfraRed
HDAC	Histone Deacetylase
HIV	Human Immunodeficiency Virus
Ki	Kinase Inhibition
LDA	Lithium Diisopropylamide
LOX	Lipoxygenase
MIC	Minimum Inhibitory Concentration
NMR	Nuclear Magnetic Resonance
PABA	*p*-Amino Benzoic Acid
RT	Room Temperature
S.I.	Selectivity Index
TCT	2,4,6-Trichloro-[1,3,5]-triazine
TEA	Triethyl amine

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
α-TsCl	α-Toluenesulphonyl chloride
p-TsCl	*p*-Toluenesulphonyl chloride
USHMM	United State Holocaust Memorial Museum
UV	Ultraviolent
WHO	World Health Organization
Z.O.I.	Zones of Inhibition

Chemical Symbols

cm	centimeter
^{o}C	degree celsius
g	gramme
g/cm^2	gramme per centimetre square
g/mol	gramme per mole
μg/mL	microgramme per millilitre
mL	milliliter
mmHg	millimetre mercury
mmol	millimole
MHz	megahertz
ppm	part per million

ABSTRACT

The reaction of α–toluenesulphonyl chloride with various readily available amino acids in basic medium afforded α–toluenesulphonamides **(1a-k)** which had their acid function subsequently amidated with diethyl amine to obtain their corresponding new *N*,*N*-diethylalkanamido substituted α–toluenesulphonamide derivatives **(2a-k)**. The electrophilic addition of *p*-toluenesulphonyl chloride with various amino acids' nitrogen gave *p*-tolylsulphonamide derivatives **(4a-k)** which upon further reaction of the corresponding acid chloride with diethylamine afforded *N*, *N*-diethylamido substituted moieties **(5a-k).** Sulphonylation of the amino acids with benzenesulphonyl chloride yielded benzenesulphonamides derivatives, **(7a-k)** which were used as the intermediate for the synthesis of the *N′, N′*-diethylated alkanamido benzenesulphonamide derivatives, **(8a-k).** The chemical structures of synthesized compounds were confirmed using elemental analysis and spectroscopic tools which include Fourier Transform-Infrared (FT-IR), Mass Spectra, proton and carbon-13 Nuclear Magnetic Resonance (^{1}H- and ^{13}C-NMR). The antimicrobial properties of the synthesized sulphonamides (fifty five compounds) were determined on *Staphylococcus aureus* and *Escherichia coli* using agar diffusion method where 1-(benzylsulphonyl)pyrrolidine-2-carboxylic acid**, (1a)** was the most active compound against *Staphylococcus aureus* at MIC value of 1.8 µg/mL while 4-(3-(diethylamino)-3-oxo-2-(phenylmethylsulphonamido)propyl)phenyl phenyl methane sulphonate **(2k)** and *N*,*N*-diethyl-2-(4-methylphenylsulphonamido)-3-phenyl propanamide **(5j)** were the most active on *Escherichia coli* at MIC of 12.5 µg/mL.

CHAPTER ONE

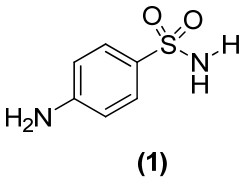
INTRODUCTION

1.1. Background of the Study

Sulphonamide is a very important class of compounds in the pharmaceutical industry that has been attracting a lot of attention (Behmadi *et al.,* 2009; Hopper *et al.,* 2009). Sulphonamide is one of the most widely used classes of antibiotics in the world (Connor, 1998). They contain the functional group ($-SO_2NH_2$) which are the amides of sulphonic acids. They are obtained by chemical conversion of hydroxyl of sulphonic acid into amino group (Connor, 1998). They have been in clinical use since 1968 (Connor, 1998) and are known to represent a class of medicinally important compounds which are extensively used as antibacterial agents (Chohan *et al.,* 2010*a*). Domagk's discovery of antibacterial activity for the azo dye, prontosil led to the first effective chemotherapeutic agent, sulphanilamide (Anand and Remer, 2010). The development of sulphonamides is a fascinating and informative area in medicinal chemistry, highlighting the role of skillful planning and serendipity in drug research (Gadad *et al.,* 2000).

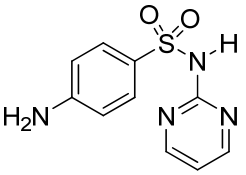
In primary care medicine, sulphonamides are widely used in various conditions including gastrointestinal (Gadad *et al.,* 2000) and urinary tract infections (Giguere *et al.,* 2006; Chambers and Jawetz, 1998). Sulphonamide is the organic framework of main focus in this research and it belongs to the family of sulphur-containing compounds (LaMarche *et al.,* 2011), which are earlier referred to as the sulpha drugs. Some of these sulpha drugs that have performed ‘’healing magic’’ in the world of chemotherapy include; sulphanilamide **(1)**, sulphadiazine **(2)**, sulphacetamide **(3)**, sulphamonomethoxine **(4)**, sulphasalazine **(5)**, sulphadoxin **(6)** among others. Sulphonamides have long been the

subject of pharmaceutical interest as a result of their potent biological activities (Purushottamachar *et al.,* 2008; Stranix *et al.,* 2006; Harter *et al.,* 2004; Reddy *et al.,* 2004).



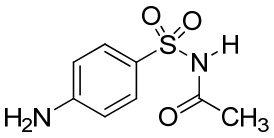
(1)

Sulphanilamide
(Antibacterial Drug)



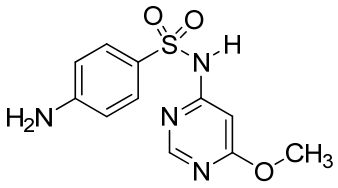
(2)

Sulphadiazine (Treatment of meningitis)



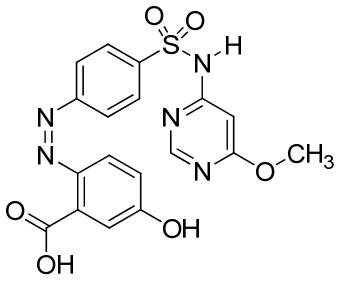
(3)

Sulphacetamide (Analgesic)



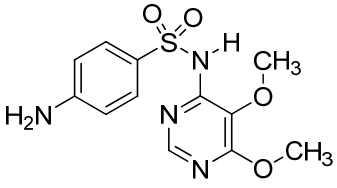
(4)

Sulphamonomethoxine
(Diuretic drug)



(5)

Sulphasalazine
(Antihypertensive drug)

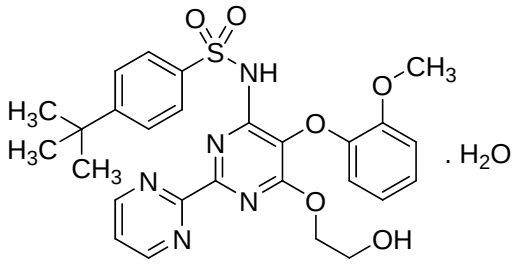


(6)

Sulphadoxin
(Antimalarial)

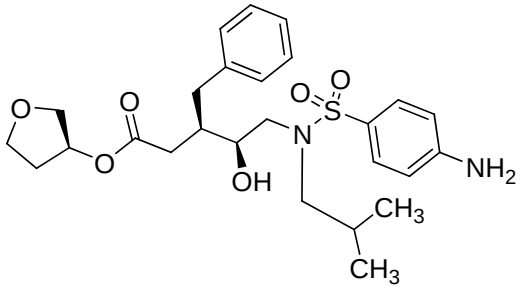
Furthermore, the sulphonamide group has been proven to have remarkable utility in medicinal chemistry and features in the structure of a number of clinically relevant small molecules (Njardarson, 2008; Supuran, 2008). For instance, some currently approved drugs with sulphonamide structural skeletons include; the antihypertensive agent *bosentan* **(7)** (Ueda *et al.,* 2011; Wu *et al.,* 2001), the antiviral HIV protease inhibitor *amprenavir* **(8)** (Shen *et al.,* 2010; De Clercq, 2001), the phophodiesterase-5 inhibitor *sildenafil* **(9)** (Masson *et al.,* 2005; Setter *et al.,* 2005; Rotella, 2002), antidiabetic drug *glibenclamide* **(10)** (Gianotto *et al.,* 2007; Gribble and Reimann, 2003),

antidiabetic nonantibiotic *glimepiride* **(11)** and the diuretic drug *torasemide* **(12)** (Lopez *et al.*, 2009; Knauf and Mutschler, 1998).



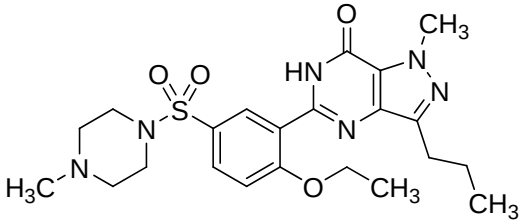
(7)

Bosentan (antihypertensive drug)



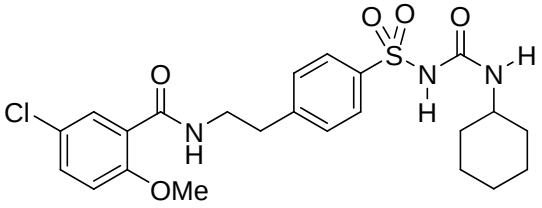
(8)

Amprenavir (anti-HIV)



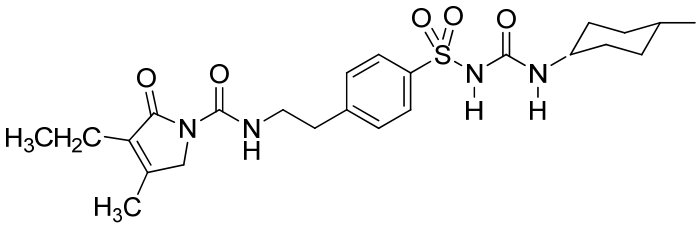
(9)

Sildenafil (phophodiesterase inhibitor)
(treament of erectile dysfunction)



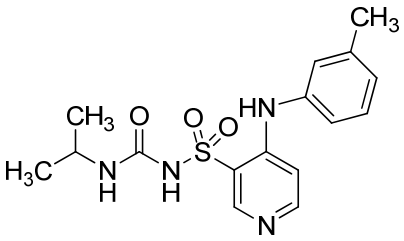
(10)

Glibenclamide (antidiabetic drug)



(11)

Glimepiride (antidiabetic nonantibiotic drug)



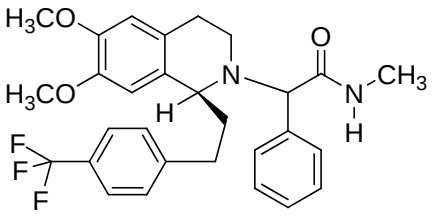
(12)

Torasemide (diuretic drug)

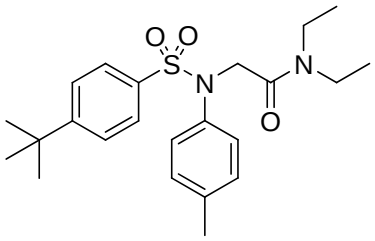
In addition, sulphonamides are also highly relevant both in the animal world and the plant life cycle. In fact, the breakdown of cyclic guanosine monophosphate is retarded by sildenafil, a substituted guanine analog, which indeed keeps cut flowers fresh for

another week and also strengthens plant stem to stand straight even in the midst of storm and wind (Bergmann, 2010). A preserving effect on fruit and vegetables was also found, making sildenafil **(9),** a promising agent (Bergmann, 2010). Today, it is marketed under the trade name Viagra (Bergmann, 2010; Siegel-Itzkovich, 1999) which is a potent drug used in the treatment of erectile dysfunction in man (Blonde, 2006; Fink *et al.,* 2002), an illness that affects 34 million men in the United States (Seftel *et al.,* 2004) and more than 150 million men worldwide (Hellstrom *et al.,* 2003). In another discovery, sulphonamide has been documented as highly efficient candidate with high HDAC inhibitory activity (Oh *et al.,* 2007).

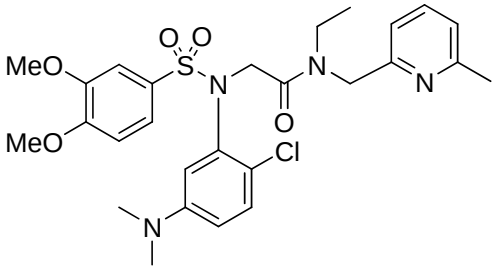
Similarly, some sulphonamides have been established as potent drugs in treatment of insomnia and other sleepless challenges in man by antagonizing orexin neural activity. Activation of orexin neurons contributes to the promotion and maintenance of wakefulness (Brisbare-Roch *et al.,* 2007). Conversely, relative inactivity of orexin neurons allows the onset of sleep (Lee *et al.,* 2005; Estrabrooke *et al.,* 2001). Consequently, blocking orexin signaling with receptor antagonists may provide a new mechanism for decreasing wakefulness. Thus, a novel therapeutic opportunity for the treatment of insomnia was reported using a dual OX_1R and OX_2R receptor antagonist almorexant **(13)** (Brisbare-Roch *et al.,* 2007). Also, low molecular weight aryl containing *N*-glycine-sulphonamide (2-[(4-*tert*-butyl-benzenesulphonyl)-*p*-tolyl-amino]-*N*,*N*-diethyl-acetamide) **(14)** was discovered as a potent and selective OX_2R antagonist with very poor oral bioavailability (F = 1%) in Wistar rats while recently discovered optimized orexin antagonist but with good oral bioavailabilty is compound **(15)** which was prepared based on *N*-glycine-sulphonamide core (Aissaoui *et al.,* 2008).



(13)
Almorexant or
2-((*S*)-1-(4-(trifluoromethyl)phenethyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-methyl-2-phenylacetamide



(14)
2-(4-*tert*-butyl-*N*-*p*-tolylphenyl sulfonamido)-*N*,*N*-diethylacetamide



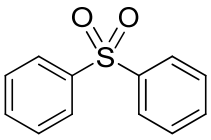
(15)
2-(*N*-(2-chloro-5-(dimethylamino)phenyl)-3,4-dimethoxyphenyl sulfonamido)-*N*-ethyl-*N*-((6-methylpyridin-2-yl)methyl)acetamide

The mode of action of sulphonamide is by mimicking *p*-aminobenzoic acid (PABA) (Evanthia *et al.,* 2010). Their molecular structures are similar to *p*-aminobenzoic acid (PABA), which is needed in bacteria as a substrate of the enzyme dihydropteroate synthetase for the synthesis of tetrahydrofolic acid which is a basic growth factor essential for the metabolic process of bacteria (Evanthia *et al.,* 2010). They are preferred due to the ease of administration (Fehintola *et al.,* 2004), wide spectrum of antimicrobial activity (Moylett *et al.,* 2003), noninterference with the host defense mechanism and relative freedom from problems of super-infection (Gadad *et al.,* 2000). Sulphonamide function is the basis of several groups of drugs (More, 2010). The original antibacterial sulphonamides (sometimes called sulpha drugs) are synthetic antimicrobial agents that contain the sulphonamide functional group (More, 2010).

Moreover, sulphonamides have been classified using various parameters. For instance, by using the antibiotic properties, it can be classified into antibiotic or antimicrobial sulphonamide and nonantibiotic or nonantimicrobial sulphonamides (Ponka, 2006). Although, almost all therapeutically useful sulphonamides are aromatic linked Ar-SO_2NH_2 or Ar-SO_2NHR (Supuran, 2008; Anand, 1996), yet, there are important distinctions between sulphonylarylamines (antimicrobial/sulphonamides), nonarylamine (nonantimicrobial) sulphonamides, and sulphones, with regard to allergic and other adverse drug reactions (Dibbern and Montanaro, 2008). Sulphone **(16)**, unlike the sulphonamide, has its SO_2 unit incorporated between two carbon systems which may be from either aliphatic or aromatic moieties (Dibbern and Montanaro, 2008).

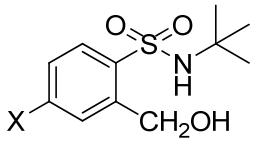
Most reactions to sulphonylarylamines probably result from multifactorial immunologic and toxic metabolic mechanisms, whereas less is known about the precise mechanisms of reactions to other sulphur-containing drugs. Some sulphonamides such as the anticonvulsant, sultiames are also devoid of antibacterial activity. The sulphonylurea and thiazide diuretics are newer drug groups based on the antibacterial sulphonamides (Kourlas and Morey, 2007). One of the sulphonamides of paramount importance in this study is benzenesulphonamide derivatives. Benzenesulphonamide moiety is an integral part of many drugs and drug-like scaffolds (Bhat *et al.,* 2005; Supuran *et al.,* 2004). Many derivatives of benzenesulphonamide have been explored as important starting materials and reactive intermediates in various organic syntheses. For example, 2-hydroxyalkylbenzene sulphonamides **(17)** and **(18)** have been reported as the important starting materials produced in large quantities (Singh *et al.,* 2007), for the structure-activity relationship (SAR) study during the search of cyclooxygenase-2 (COX-2)

inhibitors as analgesic (Zebardast *et al.,* 2009) and anti-inflammatory agents (Singh *et al.,* 2005; Singh *et al.,* 2004*a*, Singh *et al.,* 2004*b*).



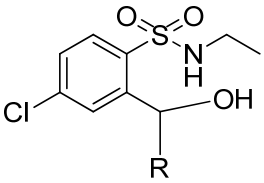
(16)

Sulphone or
1-(phenylsulphonyl)benzene



(17)

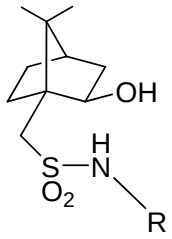
N-tert-butyl-4-halo-2-(hydroxy methyl)benzenesulphonamide



(18)

4-chloro-*N*-ethyl-2-(1-hydroxy alkyl)benzenesulphonamide

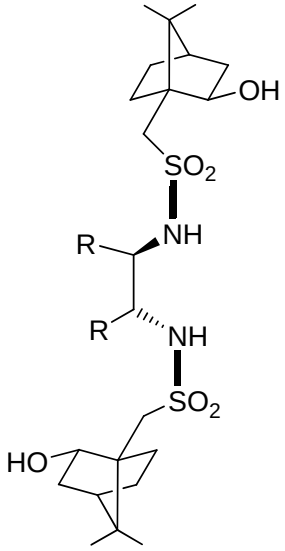
The chemistry of sulphonamides has recently shown them to be highly efficient synthons in the preparation of various valuable biologically active compounds (Bahrami *et al.,* 2009; Yuan *et al.,* 2001). In view of the versatile chemistry of sulphonamides as ligands, various researchers have attempted and embarked upon designing and synthesizing various novel metal based sulphonamides (Chohan *et al.,* 2006*a*; Puccetti *et al.,* 2005; Bregman *et al.,* 2004; Hassan *et al.,* 2002). The chiral ligands with an isoborneol-10-sulphonamide structure has been discovered as 10 years odyssey, designed as first **(19)**, second **(20)** and third generation **(21)** ligands for catalyzing and stereoselective synthesis of highly relevant asymmetric compounds (Ramon and Yus, 2007). In a similar manner, a new series of sulphonamide derived Schiff bases has been synthesized by a condensation reaction of various sulphonamides with aromatic aldehydes (Chohan *et al.,* 2010*b*). The sulphonamides obtained were further investigated for their metal complexes potential in terms of chelation (Aoki *et al.,* 2009) and biological properties (Chohan *et al.,* 2010*b*).



(19)

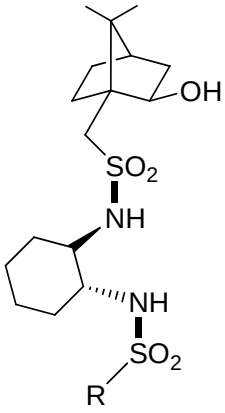
(2-hydroxy-7,7-dimethylbicyclo [2.2.1]heptan-1-yl)-*N*-alkylmethanesulfonamide

first generation



(20)

second generation



(21)

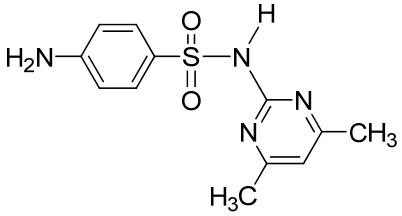
third generation

Ramon and Yus, 2007

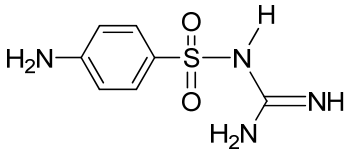
Based on the side effect factor, it is important to make a distinction between sulpha drugs and other sulphur-containing drugs and additives, such as sulphates and sulphites, which are chemically unrelated to the sulphonamide group, and do not cause the same hypersensitivity reactions seen in the sulphonamides. Although, there are reported cases of allergy to sulphonamide drug, but the term *sulpha allergy* is imprecise and misleading and therefore, should be discouraged (Dibbern and Montanaro, 2008). Sulpha allergies are commonly reported as the side effect of sulphonamide drugs (More, 2010); hence, medications containing sulphonamides are prescribed carefully. In fact, issues in understanding the clinical evidence and drug market dynamics as they relate to individuals and populations have been explored (Mamdani, 2005). Statistics have shown that approximately 3% of the general population show sulpha drugs allergy, when treated with sulphonamide and other similar antibiotics (Srivastava, 2011).

Furthermore, the potential utilization of sulpha drug compounds as corrosion inhibitors has been established (El-Naggar, 2007). The inhibitory effect of four sulpha

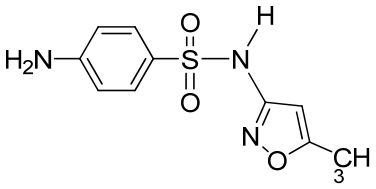
drugs compounds namely: sulphamethazine **(22)**, sulphaguanidine **(23)**, sulphamethoxazole **(24)** and sulphadiazine **(2)**, on mild steel corrosion in 1.0 M HCl solutions was evaluated using both galvanostatic polarization and weight loss techniques (El-Naggar, 2007). All the examined sulpha drug compounds were reported to reduce the corrosion of mild steel indicating their high potency as anti-corrosion agents. Among the compounds studied, sulphadiazine **(2)** was claimed to have the best inhibition efficiency (El-Naggar, 2007). Sulphonamide derivatives of azo dyes achieve improved light stability, water solubility and fixation to fiber (Hansch *et al.,* 1990).



(22)
Sulphamethazine



(23)
Sulphaguanidine



(24)
Sulphamethoxazole

Some quantum mechanical studies have successfully linked the corrosion inhibition efficiency with molecular properties for different kinds of organic compounds (Khalil, 2003; Bereket *et al.,* 2001). In fact, quantum chemical calculations using the density functional theory (DFT) and some semi-empirical methods (Arslan *et al.,* 2009) were performed on four sulphonamides in order to determine the relationship between molecular structure and their inhibition efficiencies (Arslan *et al.,* 2009). The sulphonamide dyes, especially secondary sulphonamide dyes, exhibited superior dye exhaustion and color fastnesses to washing, sublimation, and rubbing on fine denier PP fabrics (Cui *et al.,* 2009). They have been used as protecting groups of hydroxyl, OH or amino, NH functionalities for easy removal under mild conditions (Chandrasekhar and Mohapatra, 1998; O'Connell and Rapoport, 1992).

Even though many synthetic methods have been reported for the preparation of sulphonamides (Wright and Hallstrom, 2006; Katritzky *et al.,* 2005; Caddick *et al.,* 2004), the sulphonylation of ammonia (Behmadi *et al.,* 2009) or primary and secondary amines with sulphonyl chlorides in the presence of a base is still being used as the method of choice because of high efficiency and simplicity of the reaction (Meshram and Patil, 2009). Nevertheless, various acceptable techniques involve the need to reduce the amount of toxic waste and by-product arising from chemical processes required thereby increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods (Li, 2005). One of the most promising approaches is using water as the reaction media (Shi *et al.,* 2010) while others include microwave irradiation technique, heterogeneous catalytic approach, solvent free media usage, nontoxic solid support resin etc. Sulphonamides, ionizable, polar antimicrobial compounds, may reach the environment in substantial amounts by the spreading of manure (Kahle and Stamm, 2007) or other means.

Adsorption of three sulphonamide antimicrobials to clay minerals was investigated as a function of pH, ionic strength, and type of exchangeable cation. Sulphonamide antimicrobial adsorption exhibited pronounced pH dependence consistent with sorbate speciation and clay properties (Gao and Pedersen, 2005). In a similar manner, amide formation is a fundamental reaction of great interest in organic chemistry (Naik *et al.,* 2004; Katritzky *et al.,* 2000). The development of efficient methods for the synthesis of amides remains a great challenge because of their importance in chemistry and biology, with a wide range of industrial and pharmaceutical applications and as valuable intermediates in organic synthesis (Theodorou *et al.,* 2009; Katritzky *et al.,*

2006). Hence, it is conceivable to design the synthetic route in such a way to have amide functionality, being incorporated within the framework of the synthesized sulphonamides. This will help in the comparative study of the antimicrobial activity of the ordinary sulphonamide with amide bearing sulphonamide derivatives.

Despite the various hazardous effects posed by deadly microbes (Zabransky, 2002), it is highly pathetic to know that no new antimicrobial drug has been discovered in the last few years. Therefore, there is a continuous need for the design and synthetic formulation of new class of antimicrobial drugs in order to control rapid spread of harmful microbes. Biofilm effect is the mechanism responsible for the frequent failure of antibiotic treatment to cure infections of medical devices and other prosthetic materials (Ceri *et al.,* 2001). In the biofilm stage, a phenotypic change occurs in which the bacteria require generally much higher concentrations of antibiotics to inhibit their growth. In fact, it has been recently discovered that the comparative study of the minimum inhibitory concentration (MIC) and minimum biofilm eliminating concentration (MBEC) is a potential factor for determining the changes in the pattern of antibiotic sensitivity of Gram negative bacilli from planktonic to the biofilm stage of growth (Sepandj *et al.,* 2004). In addition, the rapid emergence of drug resistance has become the most urgent concern because it renders current treatments ineffective and therefore compels the scientific community to continue efforts in the design of inhibitory agents that can efficiently combat drug resistance (Ghosh *et al.,* 2008).

1.2. Objectives of the Study

The specific objectives of the study are:

- to synthesize aryl sulphonamides and alkylaryl sulphonamides as reactive intermediates and subsequently use them to synthesize various novel *N*,*N*-diethyl alkanamide substituted sulphonamides and characterize using elemental analysis and spectroscopic means, especially FT-IR, Mass Spectra, ^{1}H- and ^{13}C-NMR.
- to investigate the antimicrobial activities of the series of new sulphonamide compounds on *Escherichia coli* and *Staphylococcus aureus* by comparing their inhibitory activity and antimicrobial efficiency with streptomycin clinical reference.

REFERENCES

Hossein Behmadi, Seyed M. Saadatia, *et al.,* 2009, Synthesis of new disulphonamides from different substituted diamino pyridines. *Eclética Química, 34(3),* pp 27-31.

Darrin, W. Hopper, Matthew D. Vera, *et al.,* 2009, Synthesis and biological evaluation of ((4-keto)-phenoxy)methyl biphenyl-4-sulphonamides: A class of potent aggrecanase-1 inhibitors. *Bioorganic and Medicinal Chemistry Letters, 19,* pp 2487-2491.

Erin E. Connor, 1998, Sulphonamide antibiotics. *Primary Care Update for OB/GYN, 5(1),* pp 32-35.

Zahid H. Chohan, Moulay H. Youssoufi, *et al.,* 2010a, Identification of antibacterial and antifungal pharmacophore sites for potent bacteria and fungi inhibition: Indolenyl sulphonamide derivatives. *European Journal of Medicinal Chemistry, 45,* pp 1189-1199.

Nitya Anand and William A. Remer, 2010, Synthetic antibacterial agents. *Burger's Medicinal Chemistry, Drug Discovery and Development,* John Wiley and Sons, New York, pp 1-80.

Andanappa K. Gadad, Chanabasappa S. Mahajanshetti, *et al.,* 2000, Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulphonamide derivatives. *European Journal of Medicinal Chemistry, 35,* pp 853-857.

Steeve Giguere, John F. Prescott, *et al.,* 2006, Sulphonamides, diaminopyrimidines and their combinations, in: *Antimicrobial Therapy in Veterinary Medicine,* pp 249-250.

Hans F. Chambers and Eric Jawetz, 1998, Sulphonamides, trimethoprim, and quinolones, in *Basic and Clinical Pharmacology*, Katzung, B.G. (Ed.) Appleton-Lange, pp. 761-763.

Matthew J. LaMarche, Jennifer A. Leeds, *et al.,* 2011, 4-Amino-thiazolyl analogues of GE2270 A: Antibacterial lead finding. *Journal of Medicinal Chemistry, 54(7),* pp 2517–2521.

Puranik Purushottamachar, Aakanksha Khandelwal, *et al.,* 2008, Potent anti-prostate cancer agents derived from a novel androgen receptor down-regulating agent. *Bioorganic and Medicinal Chemistry, 16(7),* pp 3519-3529.

Brent R. Stranix, Jean-François Lavallee, *et al.,* 2006, Lysine sulphonamides as novel HIV-protease inhibitors: Nepsilon-acyl aromatic alpha amino acids. *Bioorganic and Medicinal Chemistry Letters, 16(13),* pp 3459-3462.

William G. Harter, Hans Albrect, *et al.,* 2004, The design and synthesis of sulphonamides as caspase-1 inhibitors. *Bioorganic and Medicinal Chemistry Letters, 14(3),* 809-812.

Natala S. Reddy, Muralidhar R. Mallireddigari, *et al.,* 2004, Synthesis of new coumarin 3-(*N*-aryl) sulphonamides and their anticancer activity. *Bioorganic and Medicinal Chemistry Letters, 14(15),* pp 4093-4097.

Jón T. Njardarson, 2008, Cornell University; Outreach Web Page. Available online at http://www.chem.cornell.edu/jn96/outreach.html (accessed November, 2008).

Claudiu T. Supuran, 2008, Carbonic anhydrases: Novel therapeutic applications for inhibitors and activators. *Nature Re*views *Drug Discovery, 7(2)*, pp 168-182.

Yutaka Ueda, Yasuhiro Takahashi, *et al.,* 2011, Successful bosentan therapy in a case of pulmonary arterial hypertension developed during immunosuppressive therapy for lupus nephritis. *Nihon Rinsho Meneki Gakkai Kaishi, 34(2),* pp 99-104.

Chengde Wu, Radford E. Decker, *et al.,* 2001, Nonpeptide endothelin antagonists in clinical development. *Drugs of Today, 37(7),* pp 441-443.

Chen H. Shen, Yuan F. Wang, *et al.,* 2010, Amprenavir complexes with HIV-1 protease and its drug-resistant mutants altering hydrophobic clusters. *FEBS Journal, 277(18),* pp 3699-3714.

Erik De Clercq, 2001, New developments in anti-HIV chemotherapy. *Current Medicinal Chemistry, 8(13),* pp 1543-1572.

Puneet Masson, Sarah M. Lambert, *et al.,* 2005, PDE-5 inhibitors: Current status and future trends. *Urologic Clinics of North America, 32(4),* pp 511-525.

Stephen M. Setter, Jason L. Iltz, *et al.,* 2005, Phosphodiesterase 5 inhibitors for erectile dysfunction. *The Annals of Pharmacotherapy, 39(7-8),* pp 1286-1295.

David P. Rotella, 2002, Phosphodiesterase 5 inhibitor: Current status and potential applications. *Nature Reviews Drug Discovery, 1(9),* pp 674-682.

Elisabeth Aparecida S. Gianotto, Renata P. Arantes, *et al.,* 2007, Dissolution test for glibenclamide tablets. *Quimica Nova, 30(5),* pp 1218-1221.

Fiona M. Gribble, and Frank Reimann, 2003, Differential selectivity of insulin secretagogues: Mechanisms, clinical implications, and drug interactions. *Journal Diabetes and its Complications*, *2*, pp 11–15.

Marie Lopez, Nicolas Drillaud, *et al.,* 2009, Synthesis of s-glycosyl primary sulphonamides. *Journal of Organic Chemistry, 74(7),* pp 2811-2816.

H. Knauf, and E. Mutschler, 1998, Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clinical Pharmacokinetics, 34*, pp 1–24.

Ralph Bergmann, 2010, Prolongation of the shelf life of fruits and flowers. Material from Biocenter Klein Flottbek, University of Hamburg, Accessed online on 4th December, 2010 at: http://www.biologie.uni-hamburg.de/lehre/bza/molnews/sildenafil/sildenafil.htm

Judy Siegel-Itzkovich, 1999, Viagra makes flowers stand up straight. *British Medical Journal, 319,* p 274.

Blonde L., 2006, Sildenafil citrate for erectile dysfunction in men with diabetes and cardiovascular risk factors: A retrospective analysis of pooled data from placebo-controlled trials. *Current Medical Research and Opinion, 22(11),* pp 2111-2120.

H.A. Fink, R. Mac Donald, *et al.,* 2002, Sildenafil for male erectile dysfunction: A systematic review and meta-analysis. *Archives of Internal Medicine, 162(12),* pp 1349-1360.

Allen D. Seftel, Prairie Sun, *et al.,* 2004, The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *The Journal of Urology, 171(6),* pp 2341-2345.

Wayne J.G. Hellstrom, Gittelman, M., *et al.,* 2003, Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: Results of a randomized, double-bind, 26-week placebo-controlled pivotal trial. *Urology, 61(4),* pp 8-14.

Seikwan Oh, Hyung-In Moon, *et al.,* 2007, Synthesis of sulphonamides and evaluation of their histone deacetylase (HDAC) activity. *Molecules, 12,* pp 1125-1135.

C. Brisbare-Roch, J. Dingemanse, *et al.,* 2007, Promotion of sleep by targeting orexin system in rats, dogs and humans. *Nature Medicine, 13(2),* pp 150-155.

M.G. Lee, O.K. Hassani, *et al.,* 2005, Discharge of identified orexin/ hypocretin neurons across the sleep-waking cycle. *Journal of Neuroscience, 25(28),* pp 6716-6720.

I.V. Estabrooke, M.T. McCarthy, *et al.,* 2001, Fos expression in orexin neurons varies with behavioral state. *Journal of Neuroscience, 21(5),* pp 1656-1662.

Hamed Aissaoui, Ralf Koberstein, *et al.,* 2008, *N*-Glycine-sulphonamides as potent dual orexin 1/orexin 2 receptor antagonists. *Bioorganic and Medicinal Chemistry Letters, 18(21),* pp 5729-5733.

P.T. Evanthia, F.S. Victoria, *et al.,* 2010, An overview of chromatographic analysis of sulphonamides in pharmaceutical preparations and biological fluids. *Current Pharmaceutical Analysis, 6(3),* pp 198-212.

F.A. Fehintola, A.A. Adedeji, *et al.,* 2004, Cotrimoxazole in the treatment of acute uncomplicated falciparum malaria in Nigerian children: A controlled clinical trial. *Clinical Drug Investigation, 24(3),* pp 149-155.

Edina H. Moylett, Susan E. Pacheco, *et al.,* 2003, Clinical experience with linezolid for the treatment of *Nocardia* infection. *Clinical Infectious Diseases, 36(3),* pp 313-318.

D. More, 2010, Sulpha Medication Allergies in: Sulpha Drug Allergy, updated on 1st of June, 2010. Accessed online on 5th December, 2010 at: http://allergies.about.com/od/medicationallergies/a/sulfa.htm.

David Ponka, 2006, Approach to managing patients with sulfa allergy: Use of antibiotic and nonantibiotic sulphonamides. *Canadian Family Physician, 52(11),* pp 1434-1438.

N. Anand, 1996, *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wollf, M.E., Ed.; John Wiley & Sons: New York, Vol. 2, p 527.

D.A. Dibbern and A. Montanaro, 2008, Allergies to sulphonamide antibiotics and sulphur-containing drugs. *Annals of Allergy, Asthma and Immunology, 100(2),* pp 91-101.

H. Kourlas and S. Morey, 2007, Sulphonamide allergies and possible cross-reactivity. *Journal of Pharmacy Practice, 20(5),* pp 399-402.

M.A. Bhat, M. Imran, *et al.,* 2005, Biological activities of sulphonamides. *Indian Journal of Pharmaceutical Sciences, 67(2),* pp 151-159.

Claudiu T. Supuran, Andrea Casini, *et al.,* 2004, COX-2 selective inhibitors, carbonic anhydrase inhibition and anticancer properties of sulphonamides belonging to this class of pharmacological agents. *Mini-Reviews in Medicinal Chemistry, 4,* pp 625-632.

Sunil K. Singh, Saibaba V. Shivaramakrishna, *et al.,* 2007, Pharmacophoric 2-hydroxyalkyl benzenesulphonamide: A single-step synthesis from benzenesulphonamide via hemiaminal. *European Journal of Medicinal Chemistry, 42(4),* pp 456-462.

Tannaz Zebardast, Afshin Zarghi, *et al.,* 2009, Design and synthesis of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorganic and Medicinal Chemistry Letters, 19(12),* pp 3162-3165.

Sunil K. Singh, Saibaba, V. Shivaramakrishna, *et al.,* 2005, Synthesis and SAR/3D-QSAR studies on the COX-2 inhibitory activity of 1,5-diarylpyrazoles to validate the modified pharmacophore. *European Journal of Medicinal Chemistry, 40(10),* pp 977-990.

Sunil K. Singh, P. Ganapati Reddy, *et al.,* 2004a, Polar substitutions in the benzenesulphonamide ring of celecoxib afford a potent 1,5-diarylpyrazole class of COX-2 inhibitors. *Bioorganic and Medicinal Chemistry Letters, 14(2),* pp 499-504.

Sunil K. Singh, Saibaba V. Shivaramakrishna, *et al.,* 2004b, 2-Hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-1-pyrazolyl]-1-benzene sulphonamide (DRF-4367): An orally active COX-2 inhibitor identified through pharmacophoric modulation. *Organic and Biomolecular Chemistry, 2(17)*, pp 2442-2450.

Kiumars Bahrami, Mohammad M. Khodaei, *et al.,* 2009, Direct conversion of thiols to sulphonyl chlorides and sulphonamides. *Journal of Organic Chemistry, 74(24),* pp 9287-9291.

R.X. Yuan, R.G. Xiong, *et al.,* 2001, Crystal structure of zinc(ii) 2-sulphanilamido pyrimidine: A widely used topical burn drug. *Journal of Chemical Society Dalton Transaction, 6,* pp 774-776.

Zahid H. Chohan, A.U. Shaikh, *et al.,* 2006a, *In-vitro* antibacterial, antifungal and cytotoxicity properties of metal-based furanyl derived sulphonamides. *Journal of Enzyme Inhibition and Medicinal Chemistry, 21(6),* pp 771-781.

Luca Puccetti, Giuseppe Fasolis, *et al.,* 2005, Carbonic anhydrase inhibitors. Inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, IX, and XII with Schiff's bases incorporating chromone and aromatic sulphonamide moieties, and their zinc complexes. *Bioorganic and Medicinal Chemistry Letters, 15(12),* pp 3096-3101.

H. Bregman, D.S. Williams, *et al.,* 2004, An organometallic inhibitor for glycogen synthase kinase 3. *Journal of American Chemical Society, 126(42),* pp 13594-13595.

Mohammad U. Hassan, Zahid H. Chohan, *et al.,* 2002, Antibacterial Zn (II) compounds of Schiff bases derived from some benzothiazoles. *Main Group Metal Chemistry, 25(5),* pp 291-296.

Diego J. Ramon and Miguel Yus, 2007, Chiral ligands with an isoborneol-10-sulphonamide structure: A ten-year odyssey. *Synlett*, *No 15,* pp 2309-2320.

Zahid H. Chohan, Hazoor A. Shad, *et al.,* 2010b, Some new biologically active metal-based sulphonamides. *European Journal of Medicinal Chemistry, 45(7)*, pp 2893-2901.

S. Aoki, Y. Tomiyama, *et al.,* 2009, Photolysis of the sulphonamide bond of metal complexes of *N*-dansyl-1,4,7,10-tetraazacyclododecane in aqueous solution: A mechanistic study and application to the photorepair of *cis, syn*-cyclobutane thymine photodimer. *Chemistry, An Asian Journal, 4(4),* pp 561-573.

Mahmood Mamdani, 2005, Are rates of gastrointestinal bleeding higher following the introduction of COX-2 inhibitors? *Expert Opinion on Drug Safety, 4(3),* pp 591-598.
Sanjay Srivastava, 2011, Sulpha drug allergy. Buzzle Article: life on the web 2011. Accessed online on 3rd March, 2011 at: http://www.buzzle.com/articles/sulfa-drugs-allergy.html

Mohammed M. El-Naggar, 2007, Corrosion inhibition of mild steel in acidic medium by some sulpha drug compounds. *Corrosion Science, 49(5),* pp 2226-2236.

Corvin Hansch, Peter G. Sammes, e*t al.,* 1990, *Comprehensive Medicinal Chemistry*, Pergamon Press, Oxford, Vol. 2, Chapter 7.1, p. 212.

N. Khalil, 2003, Quantum chemical approach of corrosion inhibition. *Electrochimica Acta, 48,* pp 2635-2640.

G. Bereket, C. Ogretir, *et al.,* 2001, Quantum mechanical calculations on some 4-methyl-5-substituted imidazole derivatives as acidic corrosion inhibitor for zinc. *Journal of Molecular Structure (Theochem.), 571*, pp 139–145.

T. Arslan, F. Kandemirli, *et al.,* 2009, Quantum chemical studies on the corrosion inhibition of some sulphonamides on mild steel in acidic medium. *Corrosion Science, 51(1),* pp 35-47.

Z. Cui, J. Yang, *et al.,* 2009, Dyeing fine denier polypropylene fibers with phenylazo-β-naphthol-containing sulphonamide disperse dyes. *Frontiers of Chemical Engineering in China, 4(3),* pp 328-335.

S. Chandrasekhar, and S. Mohapatra, 1998, Neighbouring group assisted sulphonamide cleavage of sharpless aminols under acetonation conditions. *Tetrahedron Letters, 39(7),* pp 695-698.

J.F. O'Connell, and H. Rapoport, 1992, 1-Benzenesulphonyl- and 1-*p*-toluenesulphonyl-3-methyl imidazolium triflates: Efficient reagents for the preparation of arylsulphonamides and arylsulphonates. *Journal of Organic Chemistry, 57(17),* pp 4775-4777.

Stephen W. Wright and Kelly N. Hallstrom, 2006, A convenient preparation of heteroaryl sulphonamides and sulphonyl fluorides from heteroaryl thiols. *Journal of Organic Chemistry, 71(3),* pp 1080-1084.

Alan R. Katritzky, A.A.A. Adbel-Fattah, *et al.,* 2005, *N*-Sulphonyl benzotriazoles as advantageous reagents for C-sulphonylation. *Journal of Organic Chemistry, 70(23),* pp 9191-9197.

S. Caddick, J.D. Wilden, *et al.,* 2004, Direct synthesis of sulphonamides and activated sulphonate esters from sulphonic acids. *Journal of American Chemical Society, 126(4),* pp 1024-1025.

G.A. Meshram, and Vishvanath D. Patil, 2009, A simple and efficient method for sulphonylation of amines, alcohols and phenols with cupric oxide under mild conditions. *Tetrahedron Letters, 50(10),* pp 1117-1121.

Chao-Jun Li, 2005, Organic reactions in aqueous media with a focus on carbon-carbon bond formations: A decade update. *Chemical Reviews, 105(8)*, pp 3095-3165.

D. Shi, J. Shi, *et al.,* 2010, A facile and clean synthesis of pyrimidine derivatives via three-component reaction in aqueous media. *Chinese Journal of Chemistry, 28,* pp 791-796.

M. Kahle, and C. Stamm, 2007, Sorption of the veterinary antimicrobial sulphathiazole to organic materials of different origin. *Environmental Science and Technology, 41(1),* pp 132-138.

Jiali Gao and Joel A. Pedersen, 2009, Sorption of sulphonamide antimicrobial agents to humic acid-clay complexes. *Journal of Environmental Quality, 39(1),* pp 228-235.

Naik, S., Bhattacharjya, G., *et al.,* 2004, Chemoselective acylation of amines in aqueous media. *European Journal of Organic Chemistry, 6,* pp, 1254-1260.

Alan R. Katritzky, He, H.Y. *et al.,* 2000, *N*-Acylbenzotriazoles: Neutral acylating reagents for the preparation of primary, secondary and tertiary amides. *Journal of Organic Chemistry, 65(24),* pp 8210-8213.

Vassiliki Theodorou, Aris Karkatsoulis, *et al.,* 2009, Tritylamine as an ammonia synthetic equivalent: Preparation of primary amides. *Arkivoc, (xi),* pp 277-287.

Alan R. Katritzky, Cai, C., *et al.,* 2006, Efficient microwave access to polysubstituted amidines from imidoylbenzotriazoles. *Journal of Organic Chemistry, 71(9),* pp 3375-3380.

Zabransky, R.J., 2002, Linezolid: The first of a new class of antimicrobial agents. *Clinical Microbiology Newsletters, 24(4),* pp 25-30.

H. Ceri, M.E. Olson, *et al*., 2001, The MBEC Assay System: Multiple equivalent biofilms for antibiotic and biocide susceptibility testing. In Doyle (Eds.), *Methods in Enzymology, 337,* pp 377–385.

F. Sepandj, H. Ceri, *et al.,* 2004, Minimum inhibitory concentration (MIC) versus biofilm eliminating concentration (MBEC) in evaluation of antibiotic sensitivity of gram-negative bacilli causing peritonitis. *Peritoneal Dialysis International, 24,* pp 65-67.

Arun K. Ghosh, Bruno D. Chapsal, *et al.,* 2008, Design of HIV protease inhibitors targeting protein backbone: An effective strategy for combating drug resistance. *Account of Chemical Research, 41(1),* pp 78-86.

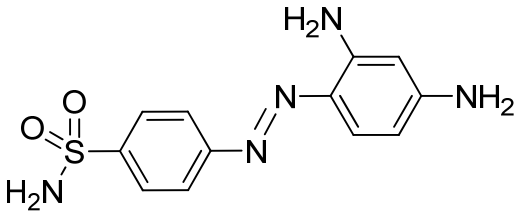
CHAPTER TWO

LITERATURE REVIEW

2.1. History of Sulphonamide Drug Discovery

Sulphonamide drugs were the first antimicrobial drugs which paved way for the unprecedented revolution in the world of antibiotics in medicine (Domagk, 1986). The first of such sulphonamide was actually a prodrug with the trade name Prontosil **(25)** (Domagk, 1986). Experiments with Prontosil **(25)** began in 1932 in the laboratories of Bayer AG where the Bayer team believed that coal-tar dyes' ability to preferentially bind to bacteria and parasites might be used to target harmful organisms in the body. After years of fruitless efforts, a team led by Gerhard Domagk finally found one that worked. It was a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice (Domagk, 1986).

The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch. Later, at the Pasteur Institute, it was accidentally discovered by a French research team, led by Ernest Fourneau, who also established that the drug was metabolized into two pieces inside the body, releasing from the inactive dye portion a smaller, colourless, active compound called sulphanilamide.



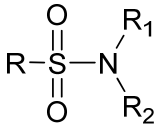
(25)
Prontosil

For several years in the late 1930s, hundreds of manufacturers produced tens of thousands of tons of myriad forms of sulpha. This phenomenon coupled with a nonexistent testing requirement led to the Elixir Sulphanilamide disaster in the fall of 1937, during which at least 100 people were poisoned with diethylene glycol (Kent, 2011). This led to the passage of the Federal Food, Drug, and Cosmetic Act in United State (US) in 1938. However, as the first and only effective antibiotic available in the years before penicillin, sulpha drugs continued to thrive through the early years of World War II (Kent, 2011). They are credited with saving the lives of tens of thousands of patients including Franklin Delano Roosevelt, Jr. (son of President Franklin Delano Roosevelt) in 1936 and Winston Churchill (Hager, 2010). Sulpha had a central role in preventing wound infections during the war. American soldiers were issued a first-aid kit containing sulpha pills and powder and were told to sprinkle it on any open wound. During the years 1942 to 1943, Nazi doctors conducted sulphanilamide experiments on prisoners in concentration camps (USHMM, 2011; Tyson, 2011). Many thousands of molecules containing the sulphanilamide structure have been created since its discovery (by one account, over 5,400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity. Sulpha drugs are still widely used for conditions such as acne and urinary tract infections. They are also receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics (Kent, 2011).

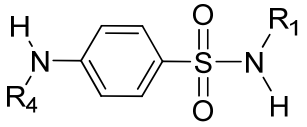
2.2. Structure of Sulphonamide

Sulphonamides or sulpha drugs have the following general structure represented by **(26)**. In this structure **(26)**, R may be alkyl, aromatic or heteroaromatic and R_1, R_2 may be hydrogen, alkyl aromatic or heteroaromatic group. However, sulphanilamide which

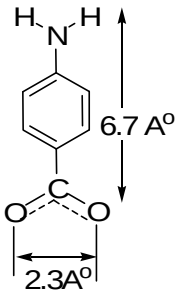
was the first compound used of this type has the sulphonamide base structure **(27)** in which R_1 and R_4 are hydrogen (Ophardt, 2003). To date about 15,000 sulphonamide derivatives, analogues and related compounds have been synthesized (Ophardt, 2003). This has led to the discovery of many useful drugs which are effective as diuretics **(28)**, antimalarial **(29)**, antileprosy agents **(30)**, antithyroid agents and so on (Ophardt, 2003).



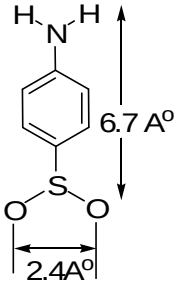
(26)



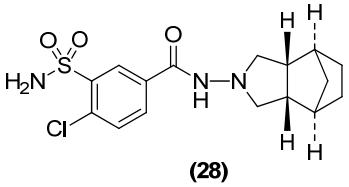
(27)
Sulphonamide base structure



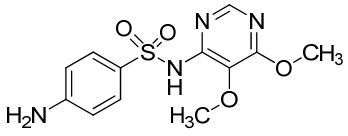
PABA



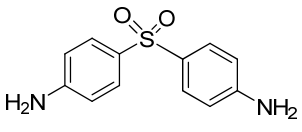
Sulphanilamide



(28)
6-chloro-3-(*N*-substitutedamido)benzenesulphonamide (Diuretic Drug)



(29)
4-amino-*N*-(5,6-dimethoxypyrimidin-4-yl) benzenesulphonamide (Antimalarial Drug)



(30)
4-(4-aminophenylsulphonyl) benzenamine or dapsone (Antileprosy Agent)

The basic structure of sulphonamide cannot be modified if it is to be an effective competitive "mimic" for *p*-aminobenzoic acid (Levin *et al.,* 2007). Essential structural features are the benzene ring with two substituents para to each other; an amino group in the fourth position; and the singly substituted 1-sulphonamido group. The chemical

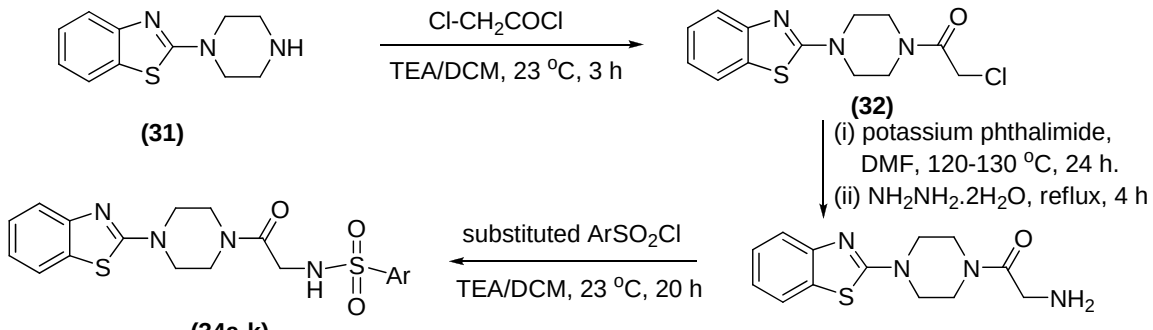
structure of sulphonamide antibiotics and sulphonamide nonantibiotics can affect the potential for adverse drug reactions (Verdel *et al.,* 2006).

2.3. Synthesis of Sulphonamide Derivatives

Sulphonamide is widely used in medicine and has been tagged an essential functional group in drug design (Kalgutkar *et al.,* 2010). Hence, due to its versatility, numerous derivatives have been synthesized in order to obtain biologically active scaffolds. Some of the synthtetic approaches for the formation of sulphonamides were discussed below:

2.3.1. Sulphonylation of 2-Amino-1-(4-(benzo[*d*]thiazol-2-yl)piperazin-1-yl)ethanone

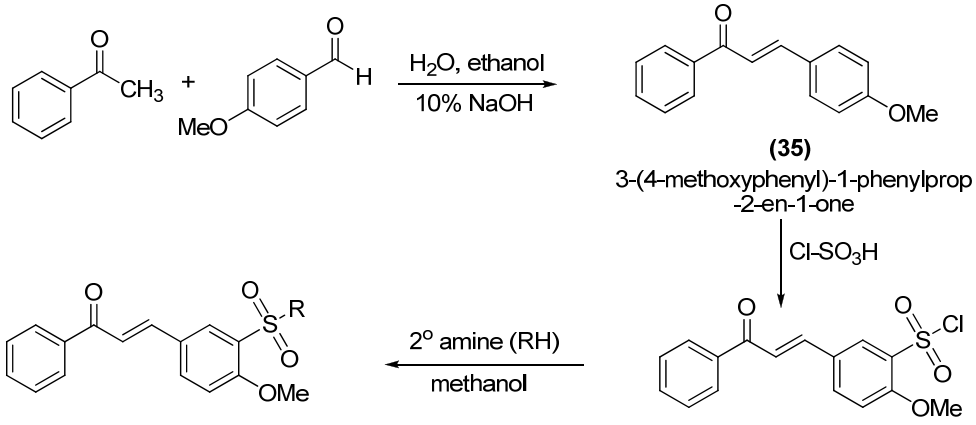
The 2-amino-1-(4-(benzo[*d*]thiazol-2-yl)piperazin-1-yl)ethanone **(33)** (Al-Soud *et al.,* 2008*a*) which was prepared by transformation of 2-(piperazin-1-yl)benzo[*d*]thiazole **(31)** via the chloro derivative **(32)**, has been recently utilized in the synthesis of some sulphonamide derivatives **(34a-k)**. This was achieved by the reaction of the amino end of compound **(33)** with various substituted arylsulphonyl chlorides in triethylamine base for 20 h at room temperature in the presence of dichloromethane (Al-Soud *et al.,* 2008*b*).



Ar is (a) Ph; (b) 4-Me-Ph; (c) 4-Cl-Ph; (d) 2,5-Cl-Ph; (e) 4-NO_2-Ph; (f) 3-CF_3-Ph;(g) 4-MeO-Ph; (h) quinolin-8-yl; (i) thiophen-2-yl; (j) 2,5-dichloro thiophen-3-yl; (k) 3-bromo-5-chlorothiophen-2-yl

2.3.2. Synthesis from Amination of Chalcones

Treatment of 4-methoxychalcone **(35)** with chlorosulphonic acid at room temperature for one week afforded the sulphonyl chloride derivative **(36)** which was subsequently reacted with secondary amines in the presence of methanol to afford sulphonamide derivatives **(37a-i)** (Andrighetti-Fröhner *et al.,* 2009). The 4-methoxychalcone used as the versatile precursor in the synthetic pathway to obtain the sulphonamide, was itself prepared by a standard procedure (Bhattacharya *et al.,* 2002).

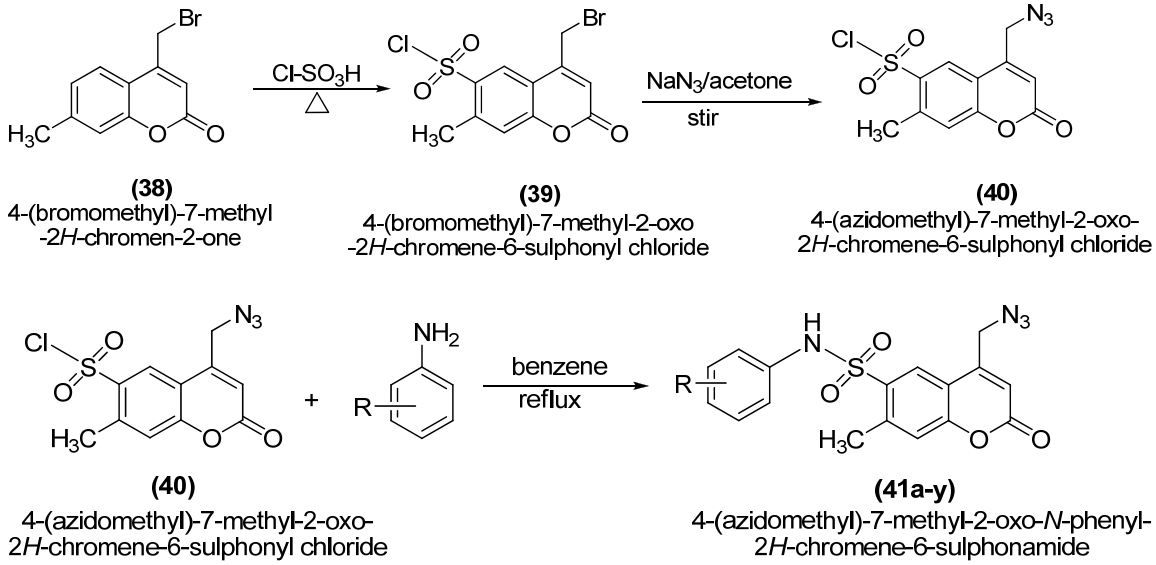


R => **(37a)** = $N(CH_3)_2$; **(37b)** = $N(CH_2CH_3)_2$; (**37c)** = pyrrolidin-1-yl; **(37d)** = morpholin-4-yl; (**37e)** = phenylamino; (**37f)** = 4-chlorophenyl amino; (**37g)** = 3,4-dichlorophenylamino; (**37h)** = 4-methoxyphenyl amino; **(37i)** = benzylamino

2.3.3. Synthesis from 4-Azidomethyl Coumarin

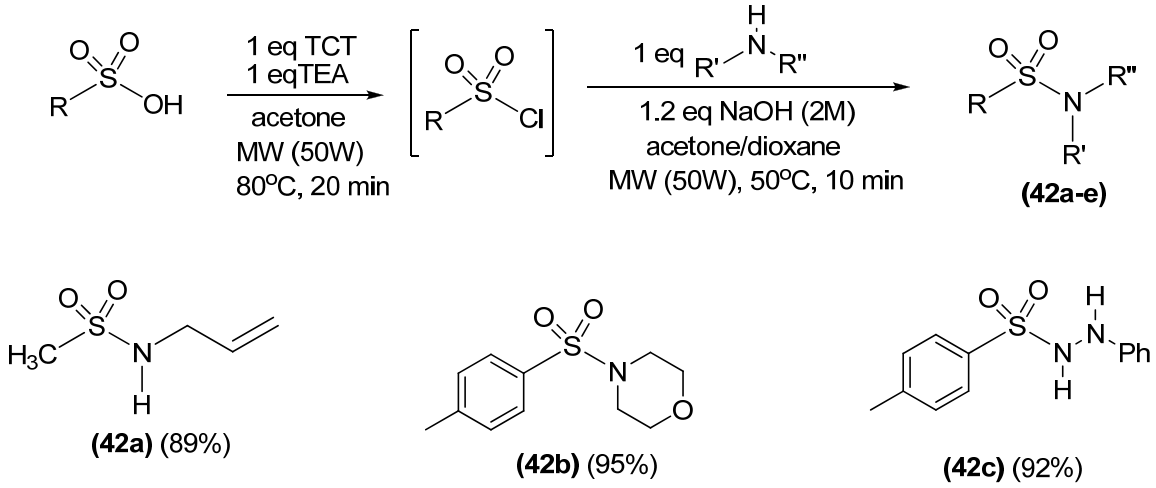
A series of new and novel coumarin-6-sulphonamides with a free C4-azidomethyl group **(41a-y)** have been synthesized as antimicrobials in three steps starting from 7-methyl-4-bromomethylcoumarin **(38)** (Basanagouda *et al.,* 2010). The reaction of **(38)** with chlorosulphonic acid was found to yield the corresponding 6-sulphonylchloride **(39)**, which when treated with sodium azide led to intermediate **(40).** The titled sulphonamides **(401a–y)** were finally obtained from the reaction of **(40)** with aromatic amines in

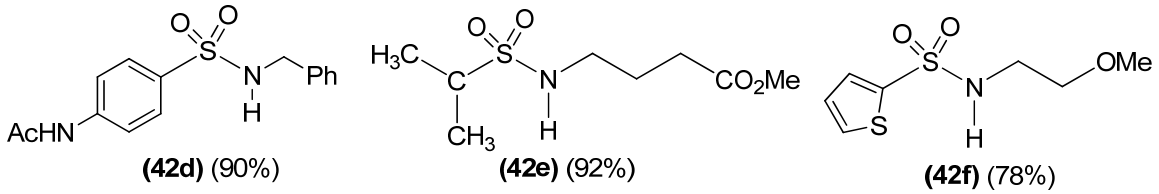
refluxing benzene.



2.3.4. Microwave-Assisted Synthesis for Sulphonamide

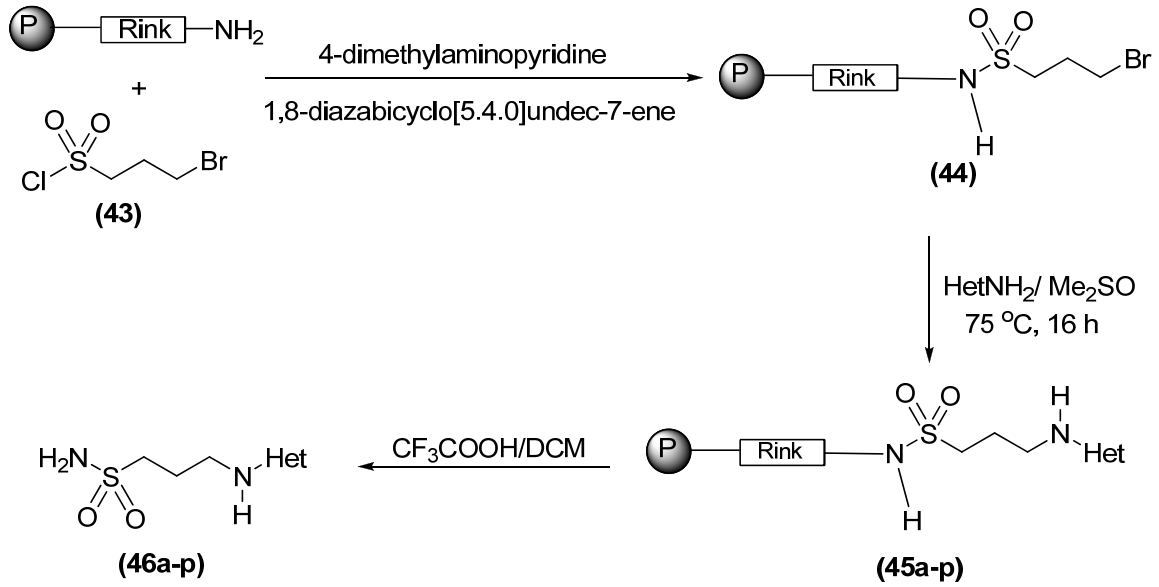
An easy and handy synthesis of sulphonamides **(42a-e)** directly from sulphonic acids or its sodium salts is performed under microwave irradiation. This approach was reported to show a good functional group tolerance and the products were formed in excellent yield (Luca and Giacomelli, 2008).

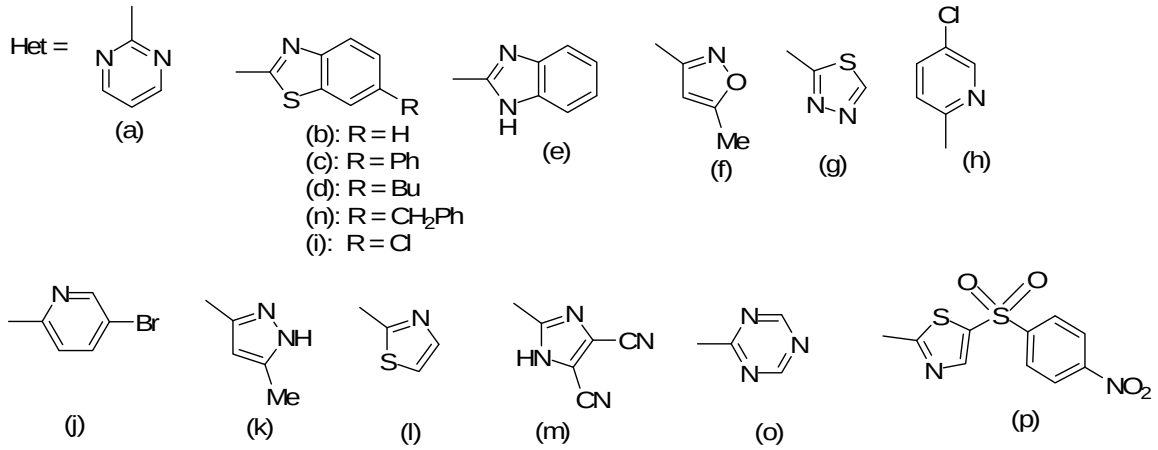




2.3.5. Synthesis from Solid Phase Combinatorial Technique

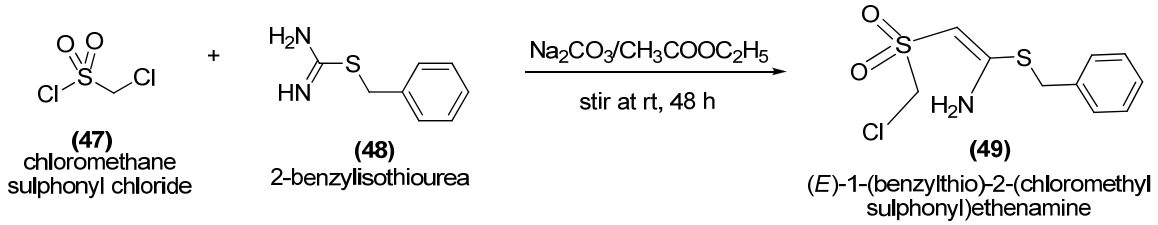
Solid phase technique, with the aid of different resin linker, has been utilized to synthesize series of potentially active sulphonamides (Maclean *et al.,* 2001; Wagman *et al.,* 2000; Yan *et al.,* 2000). In fact, the resin-bound sulphonamide **(44)** which was synthesized by reaction of the 3-bromopropylsulphonyl chloride **(43)** with the rink amide resin, was reported to react with a 2 M solution of the amino heterocycle ($HetNH_2$) or other amine in dimethyl sulphoxide at 75° C for 16 h to form **(45)** (Millan and Prager, 2000). Finally, the desired hetero-aminopropyl sulphonamide **(46)** was achieved by cleaving away the resin from **(45)** with the help of equimolar mixture of trifluoroacetic acid/dichloromethane (Millan and Prager, 2000).





2.3.6. Chloromethylsulphonylation of S-Benzylisothiourea

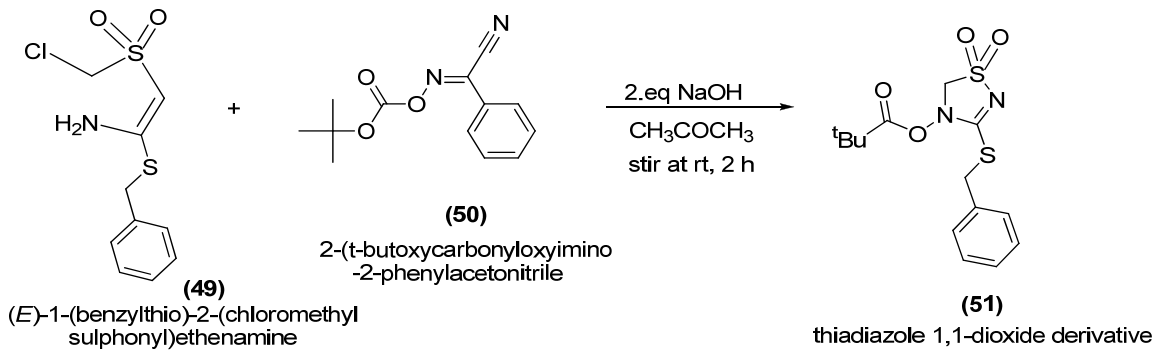
Sulphonamide analogues of creatinine have been conveniently synthesized by chloromethylsulphonylation of substituted benzylisothiourea as reported by Fares and co-workers (1997). The treatment of a mixture of chloromethylsuphonyl chloride **(47)** and benzylisothiourea **(48)** in the presence of anhydrous sodium carbonate and anhydrous ethyl acetate at room temperature for 2 days gave the sulphonamide *(E)*-1-(benzylthio)-2-(chloromethylsulphonyl)ethenamine **(49)** in good yield. They also demonstrated the effectiveness of base-induced cyclization of **(49)** with 2 molar equivalent of sodium hydroxide in the presence of 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile **(50)** in sodium hydroxide to afford thiadiazole 1,1-dioxide derivative **(51)** in 61% yield (Fares *et al.,* 1997).



(47)
chloromethane sulphonyl chloride

(48)
2-benzylisothiourea

(49)
(*E*)-1-(benzylthio)-2-(chloromethyl sulphonyl)ethenamine



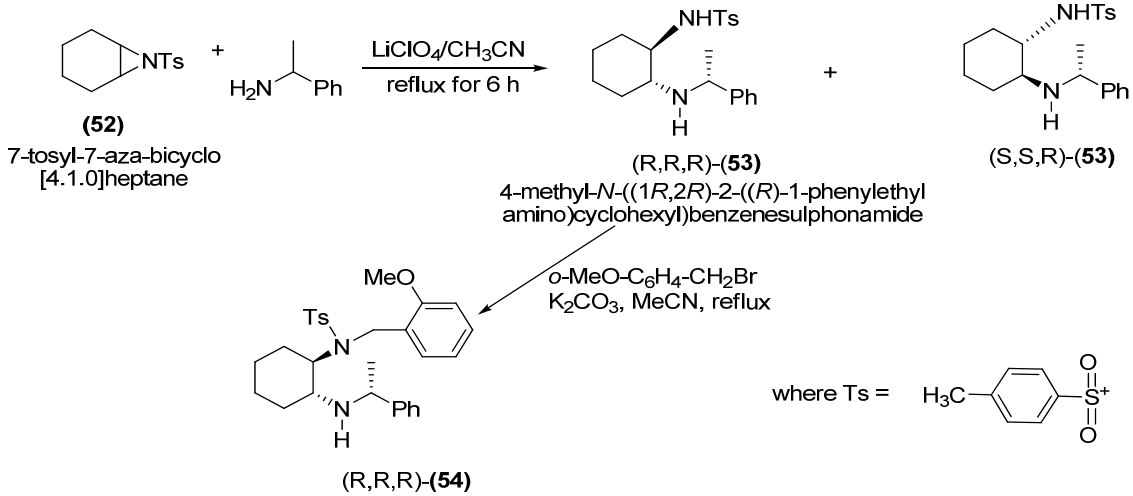
(49)
(*E*)-1-(benzylthio)-2-(chloromethyl sulphonyl)ethenamine

(50)
2-(t-butoxycarbonyloxyimino -2-phenylacetonitrile

(51)
thiadiazole 1,1-dioxide derivative

2.3.7. Synthesis via Ring Opening Aminolysis of *N*-Tosylaziridines

Bisai and co-workers reported that the ring-opening of *N*-tosylaziridines **(52)** with chiral benzylamine derivative can be efficiently catalyzed by lithium perchlorate to provide derivatives of the *trans*-1,2-diamine and (S,S,R)-**(53)** in high yields. Alkylation of (R,R,R)-**(53)** intermediate with 2-methoxybenzyl bromide gave sulphonamide (R,R,R)-**(54)** in 72% yield. The reaction was used in desymmetrization of several cyclic *N*-tosylaziridines using chiral amines. Using this strategy, an efficient synthesis was developed of chiral vicinal *C*2 symmetric *bis*-(sulphonamides), unsymmetrical bis(sulphonamides) and other symmetric and unsymmetric ligands based on *trans*- 1,2-cyclohexanediamine (Bisai *et al.*, 2007).



(52)
7-tosyl-7-aza-bicyclo [4.1.0]heptane

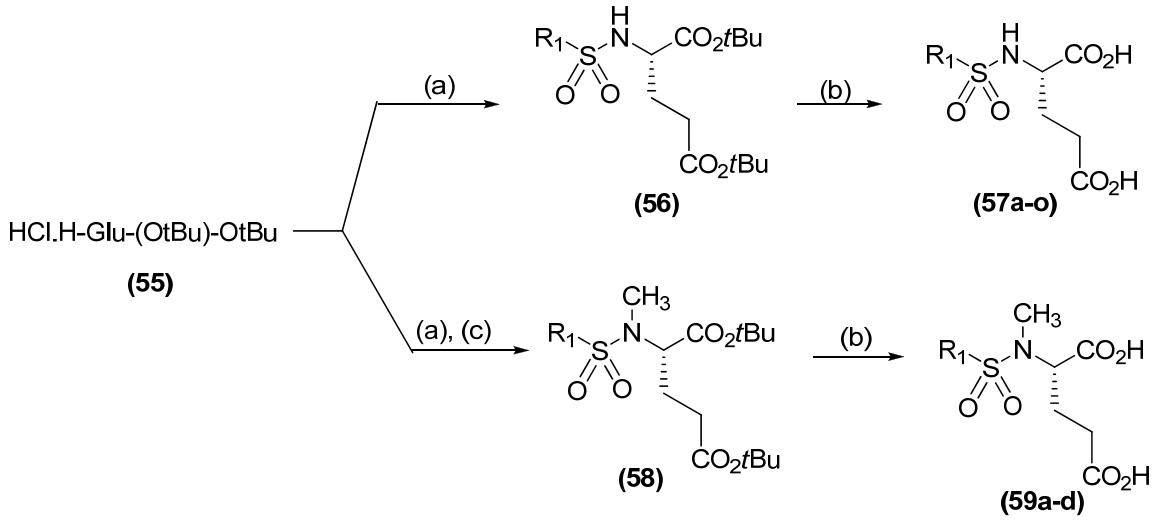
(R,R,R)-**(53)**
4-methyl-*N*-((1*R*,2*R*)-2-((*R*)-1-phenylethyl amino)cyclohexyl)benzenesulphonamide

(S,S,R)-**(53)**

(R,R,R)-**(54)**
N-(2-methoxybenzyl)-4-methyl-*N*-((1*R*,2*R*)-2-((*R*)-1-phenylethylamino)cyclohexyl)benzenesulphonamide

2.3.8. Synthesis from Diprotected Glutamic Acid

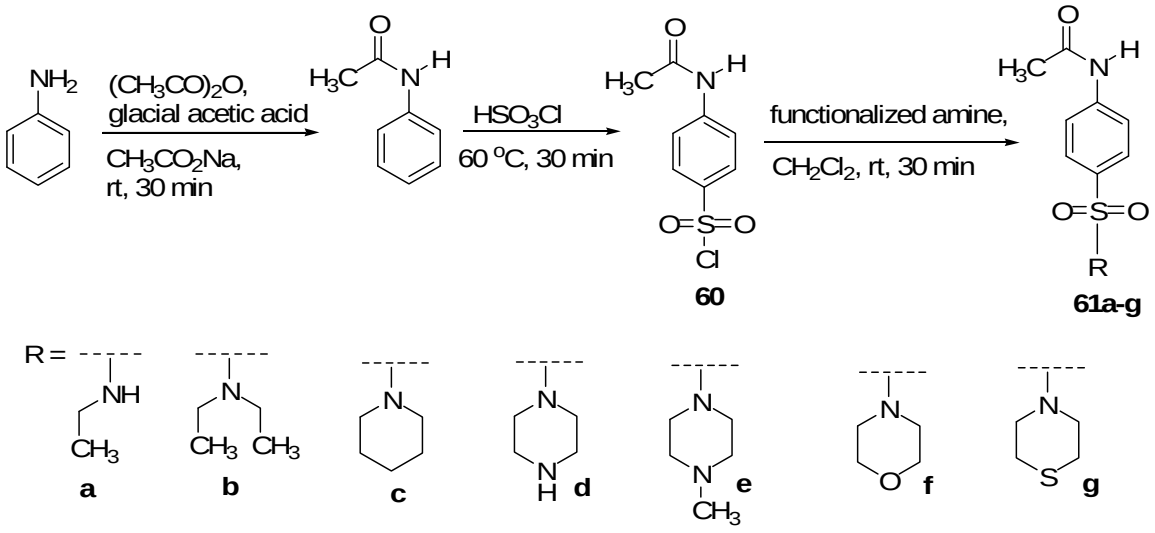
Diprotected glutamic acid **(55)** was directly conjugated with commercially available sulphonyl chlorides to obtain sulphonamides **(56)** which were then deprotected with TFA to produce the library of sulphonamide inhibitors **(57a-o)**. Alternatively, compound **(55)** was conjugated with sulphonyl chlorides and then treated with iodomethane to afford *N*-methylsulphonamide analogs **(58)**, which thereafter, were deprotected to give the final *N*-methylsulphonamide inhibitor library **(59a-d)** (Blank *et al.,* 2011).



Reagents and conditions: (a) sulphonyl chloride or triflic anhydride (1.05 eq), Et_3N (3.0 eq), 1h; (b) TFA (20 eq), DCM; (c) CH_3I (4.0 eq), K_2CO_3 (4.0 eq), 16-crown-6 (1.0 eq).

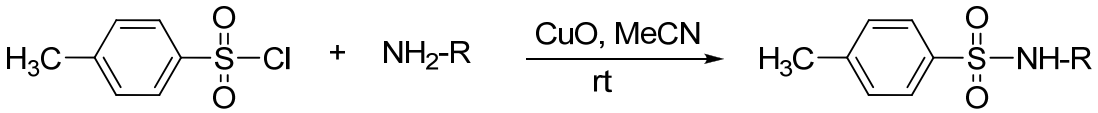
2.3.9. Synthesis from Structural Modification of Paracetamol Derivative

The 4-(acetylamine)benzenesulphonyl chloride **(60)**, a derivative of paracetamol earlier prepared by several interconversion of functional group of aniline (Bastos *et al.,* 2008) was condensed with functionalized amines in DCM to give the desired *N*-phenyl-acetamide sulphonamide derivatives **(61a-g)** in 50 – 70% yield (Barbosa *et al.,* 2009).

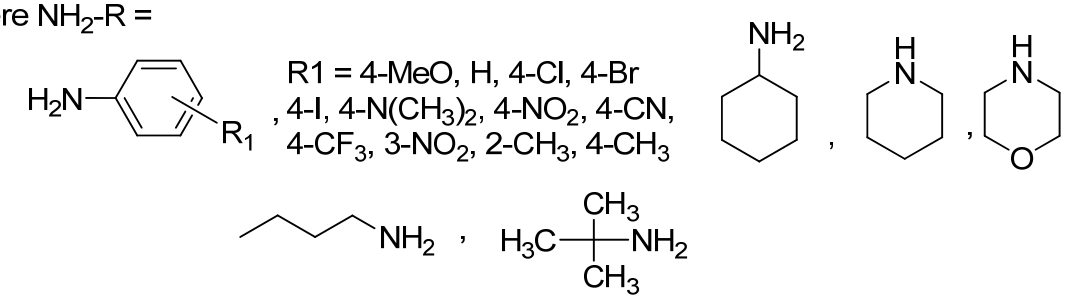


2.3.10. Copper II Oxide Catalytic Sulphonylation Method

The catalytic activity of cupric oxide for the sulphonylation of *p*-anisidine (2 mmol), other aromatic amines as well as some aliphatic amines with *p*-toluene sulphonyl chloride (2 mmol) at room temperature were studied (Meshram and Patil, 2009). It was found that the application of less than 0.1 mmol of cupric oxide in acetonitrile (5 ml) gave a moderate yield of the corresponding sulphonamide **(62)**, whereas the use of more than 0.1 mmol of cupric oxide gave an excellent yield (Meshram and Patil, 2009).

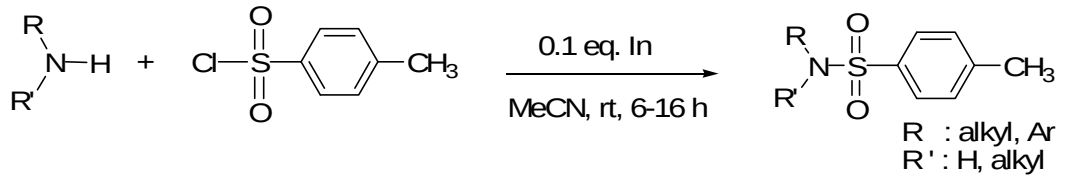


where NH_2-R =



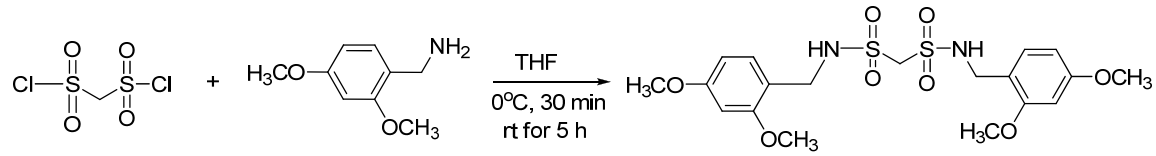
2.3.11. Indium Catalyzed Sulphonylation

A facile and efficient indium-catalyzed sulphonylation of amines with *p*-toluenesulphonyl chloride allows the synthesis of a wide range of sulphonamides in excellent yields. The method showed a generality for substrates including less nucleophilic and sterically hindered anilines, and it is also applicable for preparing sulphonic esters from sulphonyl chlorides and alcohols (Kim and Jang, 2007).



2.3.12. Sequential Mitsunobu Condensation Reaction

Chen and co-workers reported recently that bis(sulphonamide) analogues could be assembled by two sequential Mitsunobu reactions which linked protected mycophenolic and adenosine derivative through a properly protected methylene bis(sulphonamide) **(65)** linker intermediate. The intermediate was prepared by treating methanedisulphonyl dichloride **(63)** with 2,4-dimethoxybenzyl amine (DMB) **(64)** in THF at 0^{o}C for 30 min and later stirred at room temperature for 5 h (Chen *et al.,* 2008).



(63)
methanedisulphonyl dichloride

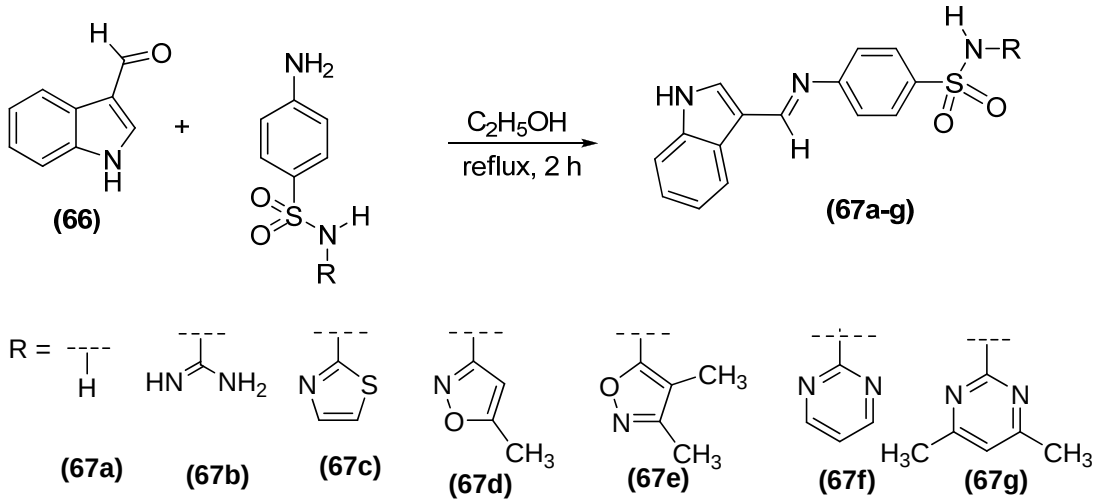
(64)
(2,4-dimethoxyphenyl) methanamine

(65)
N',*N*-bis(2,4-dimethoxy benzyl)methanedisulphonamide

2.3.13. Synthesis from Condensation Reaction of Indole-3-Carbaldehyde

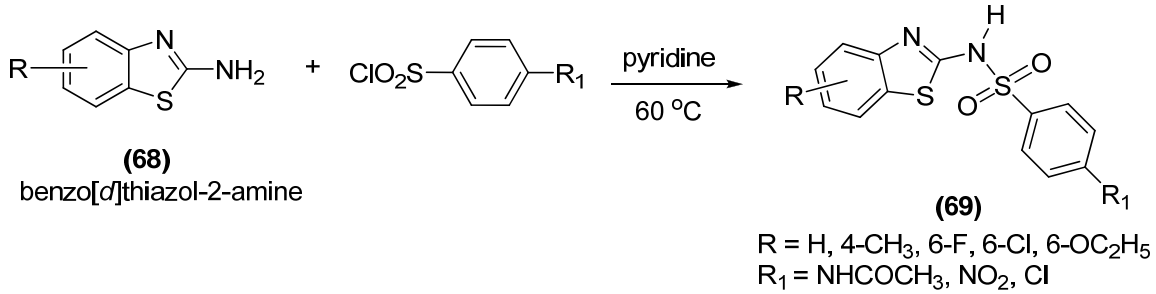
A rapid condensation of indole-3-carbaldehyde **(66)** with various existing sulphonamides under reflux has successfully led to a new series of sulphonamides,

containing indole moiety **(67a-g)** in good yield (80–86%). These synthesized compounds were used as potential ligands for complexation with some selected divalent transition metals ions (Chohan *et al.*, 2010*a*).



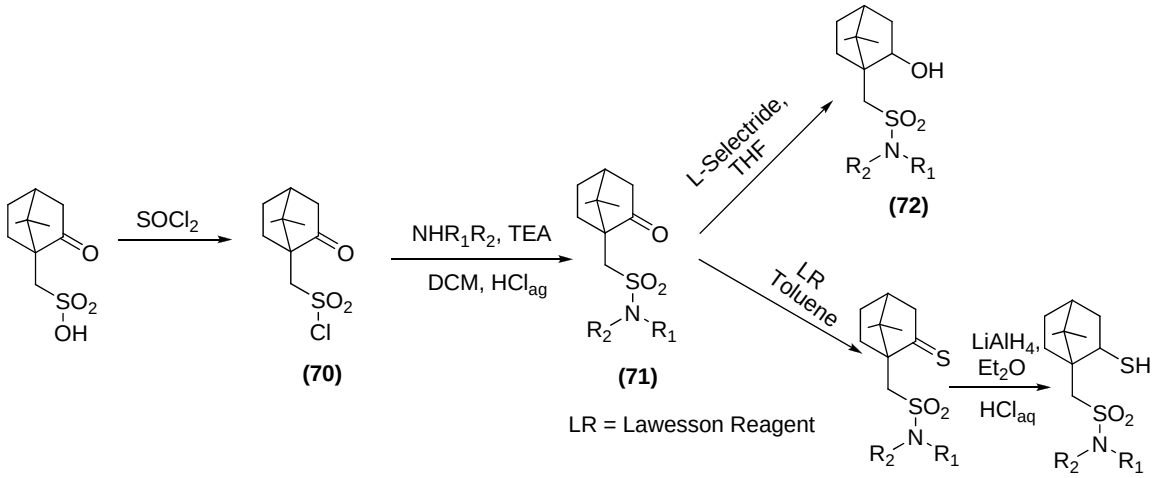
2.3.14. Synthesis from Sulphonylation of Benzo[*d*]thiazol-2-amine

Subsituted *N*-(benzo[*d*]thiazol-2-yl)benzenesulphonamides **(69)** were prepared by heating the appropriate heteroarylamine (benzo[*d*]thiazol-2-amine) **(68)** with the selected benzenesulphonyl chlorides in pyridine for several hours. Nucleophilic addition of the NH_2 group to the sulphonyl function of the benzenesulphonyl chlorides takes place at 60 ^{o}C (Argyropoulou *et al.*, 2009).



2.3.15. Amination of (+)-10-Camphorsulphonic Acid Chloride

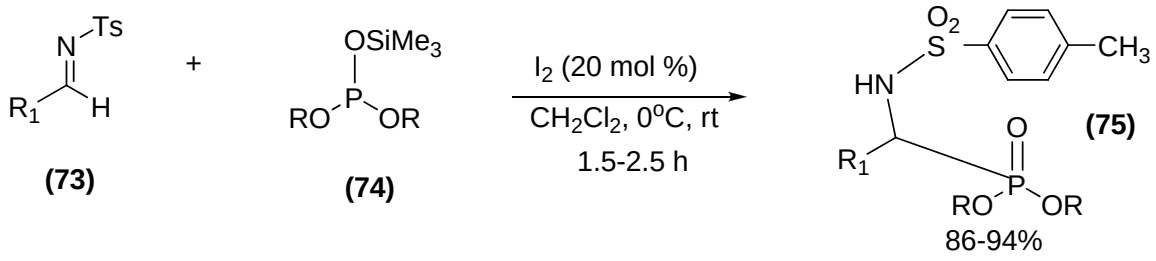
New chiral sulphonamides from (+)-camphor derivative **(72)**, with different substituents on camphor *C2* and sulphonamide *N*, were synthesized (Kozakiewicz *et al.,* 2010). This was achieved by first stirring a DCM solution of (+)-10-camphorsulphonic acid chloride **(70)** in cooled solution of various amines for 2.5 h to form ketosulphonamide **(71)**, which consecutively underwent L-selectride reduction to produce hydroxysulphonamide **(72)**. The catalytic activity of these new chiral sulphonamides was also investigated by Kozakiewicz and coworkers in 2010.



In recent years, a large variety of amino-alcohols starting from camphor (Parrott and Hitchcock, 2008; Martinez *et al.,* 2002; Chen *et al.,* 2001; Dimitrov *et al.,* 2001), camphor-10-sulphonamides (Hui *et al.,* 2008; Hui *et al.,* 2006; Ramon and Yus, 2007; Forrat *et al.,* 2006) and similar chiral compounds (Binder *et al.,* 2009; Szakonyi *et al.,* 2008; Tanyeli *et al.,* 2007; Martins *et al.,* 2006; Soki *et al.,* 2005) were prepared and used as catalysts. The commercially available (+)-camphor-10-sulphonyl chloride was also reported to be easily transformed into the dimethylsulphonamide through a reaction almost similar to the one above but using diethyl ether as the solvent (Kamenova-Nacheva *et al.,* 2009).

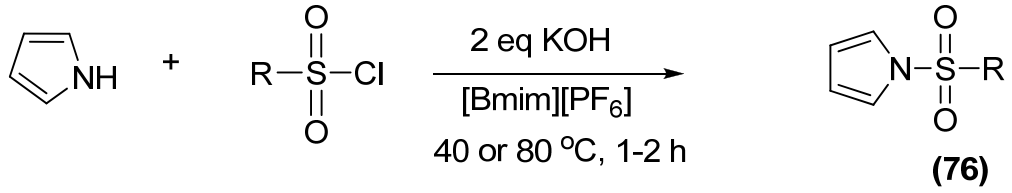
2.3.16. Iodine-Catalyzed Hydrophosphonylation Method

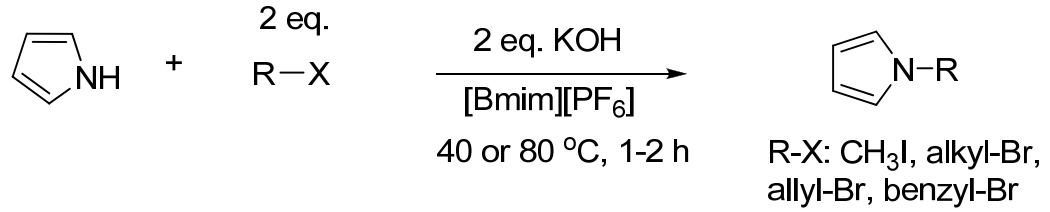
Treatment of *N*-tosyl aldimines **(73)** with dialkyl trimethylsilyl phosphites **(74)** at 0 °C in the presence of iodine as a catalyst afforded the corresponding sulphonamide phosphonates **(75)** in excellent yields within 1.5 to 2.5 h (Das *et al.,* 2009).



2.3.17. Synthesis from Ionic Liquid Mediated Approach

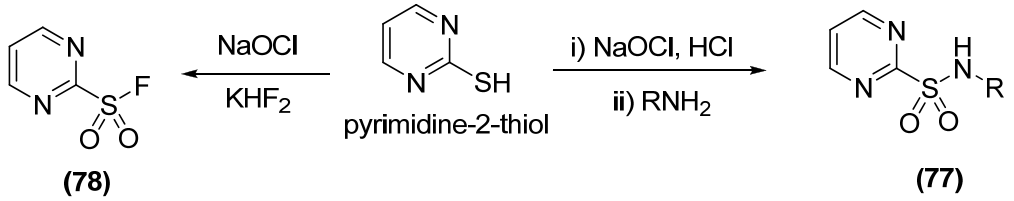
The coupling of pyrrole with aryl- or alkylsulphonyl chloride in 2 h by reflux in the presence of KOH and ionic liquid gave the corresponding heteroaromatic sulphonamide **(76)** in excellent yield. Generally speaking, in ionic liquids [Bmim][PF_6] or [Bmim][BF_4], a highly regioselective *N*-substitution of pyrrole with alkyl halides, sulphonyl chlorides, and benzoyl chloride gave substituted pyrrole in excellent yields. Michael addition of pyrrole with electrophilic olefins was completed in a highly regioselective manner to afford *N*-alkylpyrroles (Lea *et al.,* 2004).

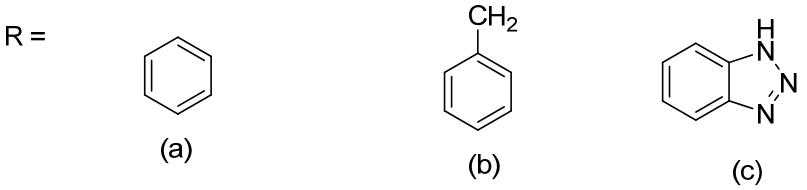




2.3.18. Synthesis from Heteroaryl Thiols

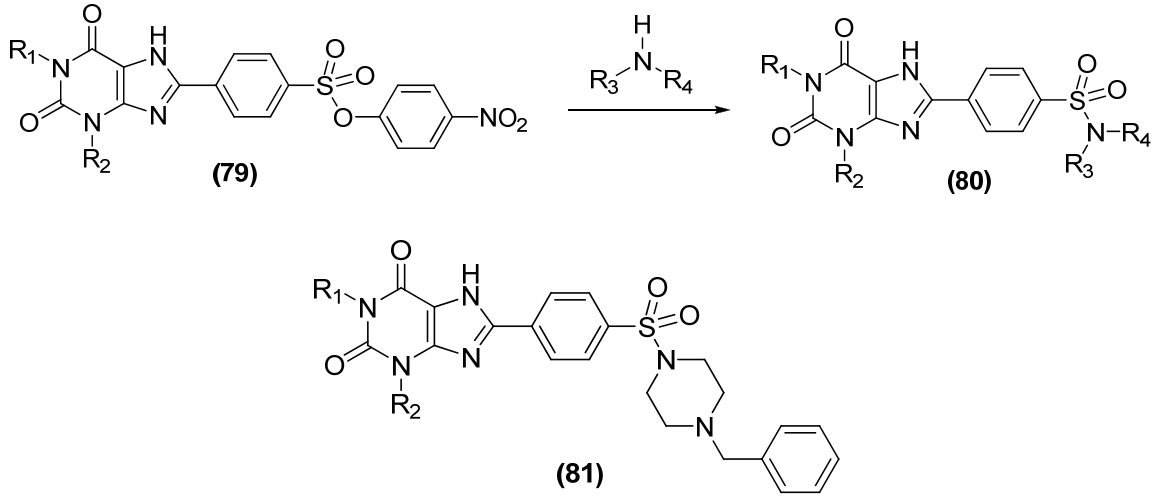
Since direct oxidative conversion of thiols (Bahrami *et al.,* 2009) and disulphide to sulphonamide was achieved by Prakash and co-workers (2007), pyrimidine-2-thiol was conveniently converted to sulphonyl chloride at low temperature (-25 ^{o}C) by using 3.3 equiv. of aqueous sodium hypochlorite. The treatment of such sulphonyl chloride with amine afforded corresponding sulphonamide **(77)** (Wright and Hallstrom, 2006). In addition, the method allowed the preparation of sulphonyl fluorides **(78)**, which are stable enough to be purified and stored, making them to be potentially useful monomers in parallel chemistry efforts (Wright and Hallstrom, 2006).





2.3.19. Aminolysis of *p*-Nitrophenoxysulphonylphenylxanthine

A large variety of amines, including aniline, benzylamine, phenethylamine, propylamine, butylamine, 2-hydroxyethylamine, aminoacetic acid and *N*-benzylpiperazine reacted with *p*-nitrophenoxysulphonylphenylxanthine derivative **(79)** to yield the desired sulphonamide products **(80)** in satisfying to very good yields (Yan *et al.,* 2006). It was also reported that the resulting sulphonamides were much more potent at A_{2B} receptor than the parent sulphonates.



The most active compound of the series was 8-[4-(4-benzylpiperazide-1-sulphonyl) phenyl]-1-propylxanthine **(81)** with kinase inhibition (ki) value of 3.6 nM for the human A_{2B} receptor combined with high selectivity versus the other human adenosine receptor subtypes (575-fold versus A_1, 134-fold versus A_{2A}, and > 278-fold versus A_3).

2.4. Pharmacokinetic Properties of Sulphonamides

Pharmacokinetic was first introduced to describe the characteristics of drug after the application. It is the study of time course of the administered drug and xenobiotic concentration in the body. The sulphonamides were reported to constitute a series of weak organic acids with pK_a values ranging from 10.4 for sulphanilamides to 5.0 for sulphisoxazole (Giguere *et al.*, 2006). The result of an investigation indicated that the moieties corresponding to specific pK_a's were identified based on chemical structures of antibiotics (Qiang and Adams, 2004) and the co-solvent effect (Ebead, 2010).

Sulphonamides exist predominantly in nonionized form in biologic fluids of pH lower than their pKa. It is the nonionized moiety that diffuses through cell membranes and penetrates cellular barriers. Sulphonamides are eliminated by a combination of renal

excretion and biotransformation (Dwight *et al.,* 2004). This combination contributes to species variations in the half-life of individual drug which also play a major role in the classification of sulphonamides (Giguere *et al.,* 2006). Sulphadimethoxine, for example, has half-life of 12.5 hours in cattle (Giguere *et al.,* 2006), 8.6 hours in goats, 11.3 hours in horses (Oukessou and Alsouss, 1998), 15.5 hours in swines, 13.2 hours in dogs and 10.2 hours in cats (Giguere *et al.,* 2006). A quantitative method was developed and validated to measure the concentration of sulphadimethoxine (SDM) and its major metabolite (Li *et al.,* 2009).

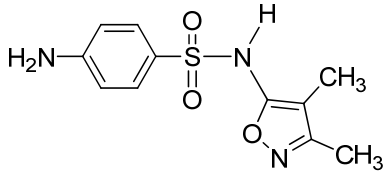
2.5. Classification of Sulphonamides

Sulphonamides have been classified based on several parameters. These parameters include; chemical structure, duration of action, spectrum of activity and therapeutic application (Aschenbrenner and Venable, 2008). The commonest one is based on therapeutic usage in term of the duration of action. This has to do with observation according to plasma concentration and time profile which is essentially the rapidity with which compounds are absorbed and excreted (Paige and Tollefson, 2003). There are three groups of sulphonamide based on their duration of action. They are short acting, intermediate acting and long acting (Wiholm, 2001).

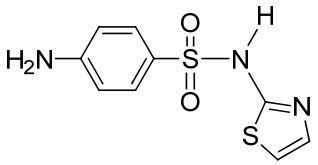
2.5.1. Short Acting Sulphonamide

The sulphonamides are considered short acting if the blood concentration levels remain higher than 50 g/mL for less than 12 h after a single therapeutic dose (Paige and Tollefson, 2003). They have been preferred for systemic infections as they are rapidly absorbed and rapidly excreted (Yasuda, 2005). Some examples of sulphonamides with

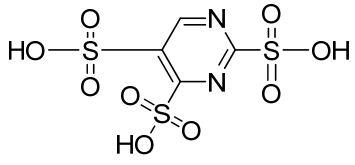
short acting character are sulphisoxazole **(82)**, sulphathiazole **(83)**, trisulphapyrimidine **(84),** sulphadimidine **(85)** and sulphisomidine also unknown as sulphaisodimidine **(86)**. For instance, sulphamethoxazole is classified as a short acting sulphonamide because its half-life is estimated at 11 h (Derouin *et al.*, 2000) and sulphamethazine has been used effectively and conveniently for the treatment of urinary tract infections.



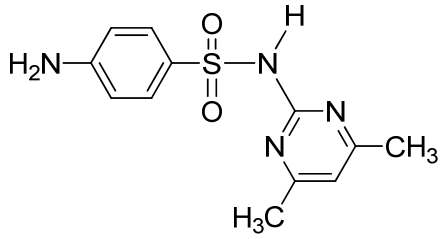
(82)
Sulphisoxazole



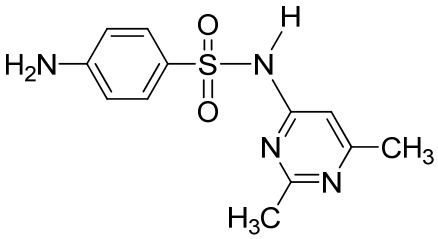
(83)
Sulphathiazole



(84)
Trisulphopyrimidine



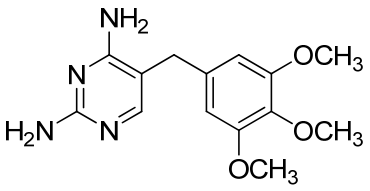
(85)
Sulphadimidine



(86)
Sulphaisodimidine

2.5.2. Intermediate Acting Sulphonamide

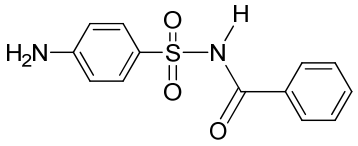
The sulphonamides are considered intermediate acting if the blood plasma levels concentration of higher than 50 g/ml are obtained between 12 and 24 h (Paige and Tollefson, 2003). They have been used for infections requiring prolonged treatment. For instance, sulphamethoxazole **(24)** in combination with trimethoprim **(87)** commonly known as septran (Korolkovas, 1998*a*) has been used for various infections such as recurrent urinary tract infections and especially active against invasive aspergillosis in AIDS patients. Other examples are sulphamimethoxine and sulphamethazine **(22)**.



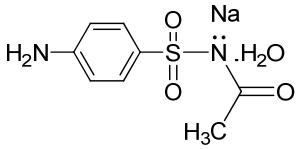
(87)
Trimethoprim

2.5.3. Long Acting Sulphonamide

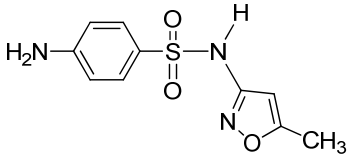
The sulphonamides are considered long acting if the blood plasma levels concentration of higher than 50 g/ml are obtained 24 h after dosing (Paige and Tollefson, 2003). They are rapidly absorbed and slowly excreted. Sulphasalazine **(5)**, which has been used as antihypertensive agent, is an example of this category. In addition, there are different types of sulphonamide which have been used in various types of infections (Kovolkovas, 1998*b*) such as mucous membranes sulphabenzamide **(88)**; superficial ocular infection *sulphacetamide sodium* **(89)**; urinary infections *sulphadiazine* **(2)** and anticancer *sulphamethizole* **(90)**. Other examples are sulphadoxine **(6)**, sulphamethoxy-pyridazine **(91)**, sulphaphenazole **(92)** and veterinary product sulphadimethoxine **(93)**. It is noteworthy that long acting sulphonamides are not available for use in the United States because of their ability to cause Stevens-Johnson syndrome (Aschenbrenner and Venable, 2008).



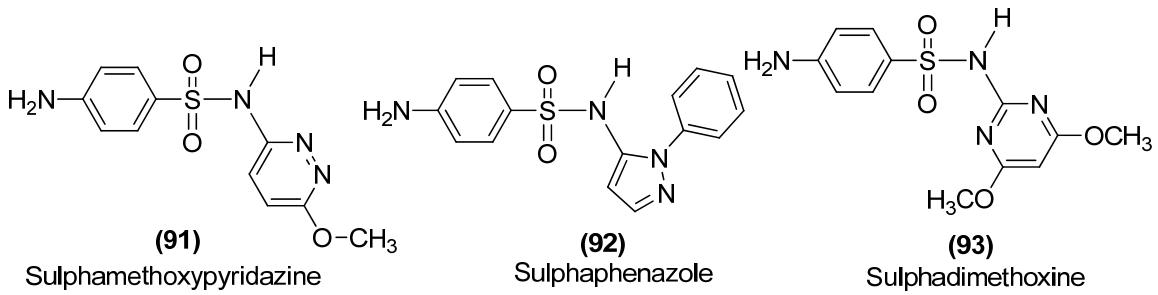
(88)
Sulphabenzamide



(89)
Sulphacetamide sodium



(90)
Sulphamethizole



(91) Sulphamethoxypyridazine

(92) Sulphaphenazole

(93) Sulphadimethoxine

2.6. Sulphonamide as Antimicrobial Agents

The sulphonamides are synthetic antimicrobial agents with a wide spectrum encompassing most gram-positive and many gram-negative organisms (Shei, 2010). These drugs are bacteriostatic in action and were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections (Vicente and Pérez-Trallero, 2010). Their use introduced and substantiated the concept of metabolic antagonism. Sulphonamides, as antimetabolites, compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The substrate similarity resulted in site competition. The action of sulphonamides illustrates the principle of selective toxicity where some differences between mammalian cells and bacterial cells are exploited. All cells require folic acid for growth. Folic acid (as a vitamin is in food) diffuses or is transported into human cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason, bacteria must synthesize folic acid from *p*-aminobenzoic acid. In order to have a greater insight into the world of antimicrobial efficacy of sulphonamide (Shoji *et al.,* 2009), it is expedient to look into the mechanism of action of such drugs and the mechanism of resistance of microbes to them.

2.6.1. Mechanism of Action of Sulphonamides

Sulphonamides are synthetic, broad-spectrum bacteriostatic antibiotics. They were the first effective systemic antimicrobial agents. Their mode of action is based on

the inhibition of DNA synthesis (Pérez-Trallero and Iglesias, 2003). Sulphonamides interfere with the biosynthesis of folic acid in bacterial cells by competitively preventing *para*-aminobenzoic acid (PABA) incorporation into the folic (pteroylglutamic) acid molecule (Fig. 2.1). Specifically, sulphonamides compete with PABA for the enzyme dihydropteroate synthetase (Levin *et al.,* 2007). Their selective bacteriostatic action depends on the difference between bacterial and mammalian cells in the source of folic acid. Susceptible microorganisms must synthesize folic acid, whereas mammalian cells use preformed folic acid. The bacteriostatic action can be reversed by an excess of PABA, so that tissue exudates and necrotic tissue should be removed if animals are to be treated with sulphonamides (Giguere *et al.,* 2006).

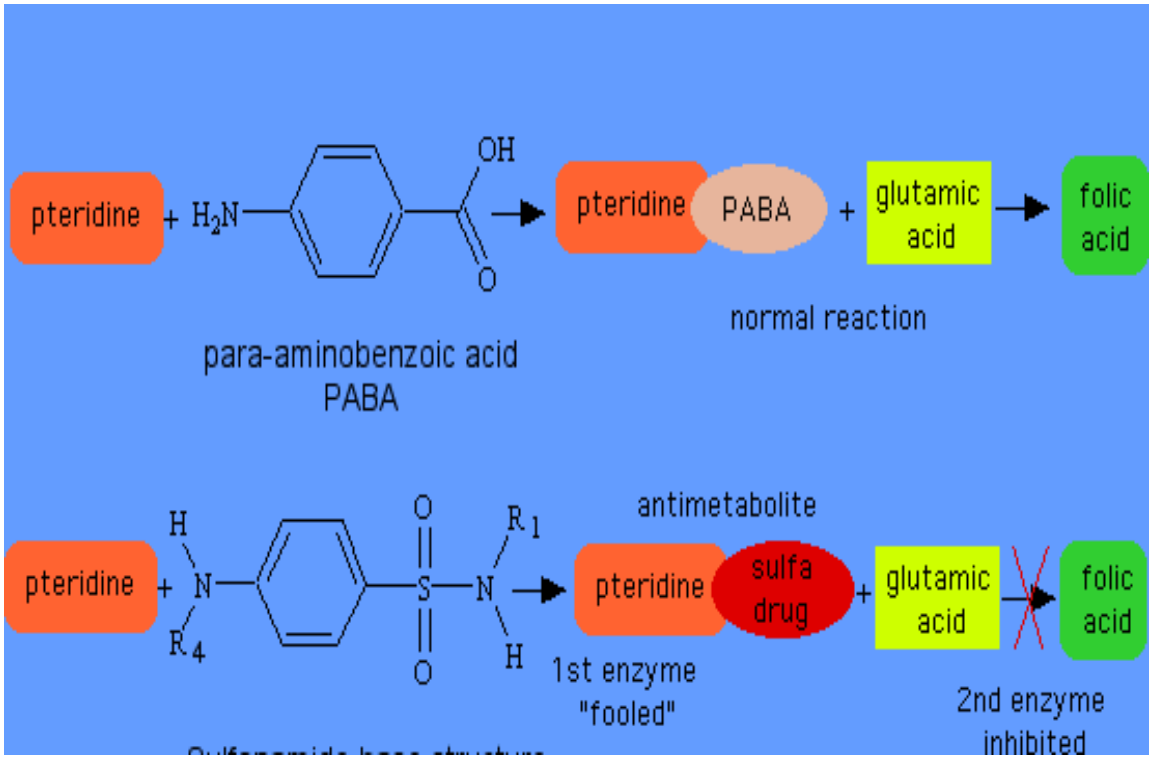


Fig. 2.1: Antimetabolite Action of Sulpha Drug

Source: Ophardt, 2003.

In detail, normally folic acid is synthesized in two steps in bacteria by the top reaction on the left. If a sulpha drug is used, the first enzyme is not too specific and can use the sulphonamide in the first reaction. This reaction produces the product containing pteridine and the sulpha drug. The next and final step is the reaction of PABA with glutamic acid to make folic acid. If the sulpha drug has been substituted for the PABA, then the final enzyme is inhibited and no folic acid is produced as shown in the Fig. 2.1 above (Ophardt, 2003). Recent studies indicate that substituents on the N(1) nitrogen may play the role of competing for a site on the enzyme surface reserved for the glutamate residue in *p*-aminobenzoic acid-glutamate through one of the following two ways: (a) Direct competition in the linking of PABA-glutamate with the pteridine derivative (b) Indirect interference with the coupling of glutamate to dihydropteroic acid (Shei, 2010).

2.6.2. Mechanism of Metabolic Resistance in Sulphonamide

Widespread resistance has been reported and there is complete cross-resistance among sulphonamides (Greenwood, 2003). Bacteria either have preexisting resistance to drugs, or they develop resistance. Human activity has contributed greatly to the increase in resistant strains of bacteria. Often, when bacteria acquire resistance to a certain drug from a particular class (e.g., the penicillins), the bacteria also acquire resistance to all other drugs in that class. There are various types of mechanisms of resistance that have been established for different type of antibiotic usage. Some of these mechanisms include efflux of antibiotics from the cell (Wright, 2005), ribosomal modifications (Yan *et al.,* 2010; Triinu *et al.,* 2009; Weisblum, 1995), protein modifications (Smith and Mankin, 2008; Wright, 2005), enzyme-based resistance (Yin, 2010), metabolic resistance (Li *et al.,* 2007; Claudianos *et al.,* 2002). However, the mechanism of resistance that is prevalent in

sulphonamide is metabolic resistance. Sulphonamide resistance is due to the metabolic bypass they acquired (Greenwood, 2003).

In the case of sulphonamides, which operate by mimicking *p*-aminobenzoic acid (PABA) and competing for an enzyme that synthesizes folic acid, an increase in the amount of PABA can out-compete the sulphonamide and render it ineffective. In addition, an alteration in the code for the enzyme itself can prevent its sulphonamide binding thereby resulting in resistance. For example, multiple levels of sulphonamide resistance have been reported in pneumococci (Wolstenholme *et al.,* 2008). In the recent time, it has been documented that resistance is found in 20-45% of strains of *Escherichia coli* and enterobacteria infecting the urinary tracts (Aschenbrenner and Venable, 2008). In fact, plasmid-mediated resistance is common among the enterobacteria (Gosh *et al.,* 2008; Greenwood, 2003; Claudianos *et al.,* 2002; Dyatkina *et al.,* 2002).

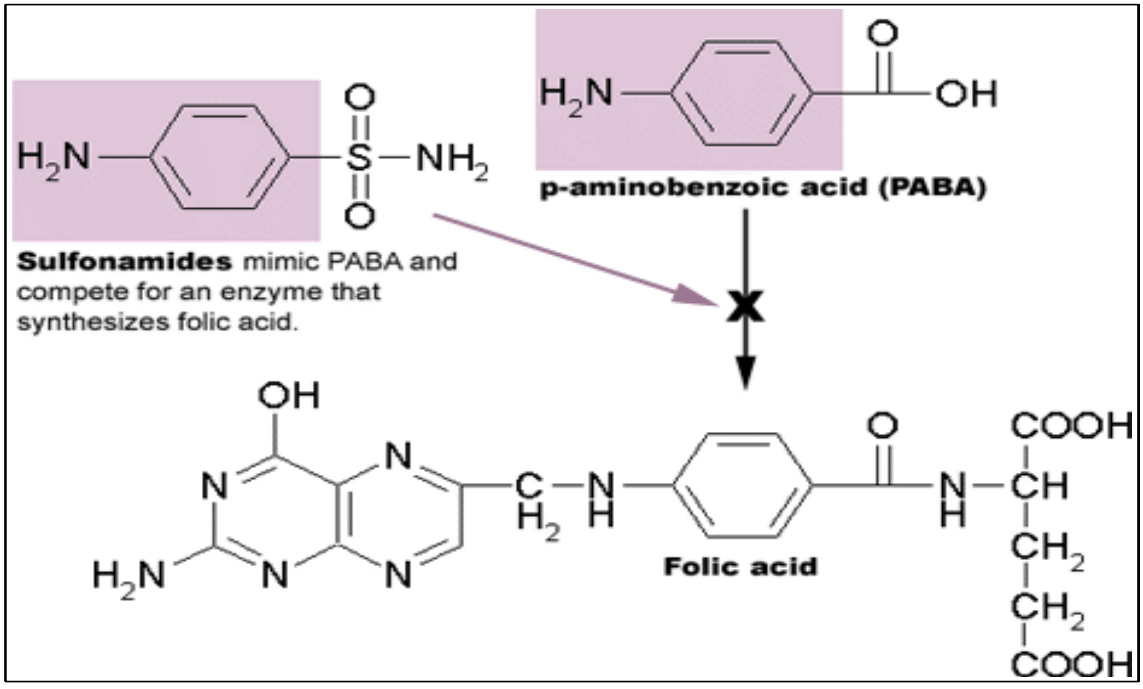


Fig. 2.2: Metabolic Bypass Experienced in Folic Acid Synthesis

Source: Greenwood, 2003

2.7. Sulphonamide Ligand in Metal Complexes Preparation

Transition metals have an important place within medicinal biochemistry (Rafique *et al.,* 2010). The rational design and synthesis of metal–organic frameworks, also known as coordination polymers, has attracted considerable attention because of their interesting supramolecular architectures (Fang *et al.,* 2011). Various sulphonamide ligands are highly versatile precursors in the synthesis of numerous metal complexes of great medicinal properties (Mondelli *et al.,* 2008; Borras *et al.,* 2004). In order to find better compounds, some metal sulphonamides have attracted much attention due to the fact that complexes showed more activities than both free ligands and the corresponding metallic salts (Chohan *et al.,* 2006*b*). It is well documented that toxicological (Chohan and Supuran, 2008; Torre *et al.,* 2003) and pharmacological properties are enhanced when sulphonamides are administered in the form of their metal complexes (Chohan, 2008; Cejudo-Marin *et al.,* 2004).

In particular, Ag-sulphadiazine has proved to be an effective topical antimicrobial agent, of significance in burn therapy, better than the free ligand or than $AgNO_3$ (Reynolds, 1996). Moreover, several Cu(II), Ce(III), Bi(III), Cd(II) and Hg(II) sulphonamide complexes have shown antibacterial activity (Chohan *et al.,* 2006*c*; Bellu *et al.,* 2003). Specially, a series of copper complexes with heterocyclic sulphonamides was studied and a plausible explanation of their activities was presented (Kremer *et al.,* 2006). However, Nickel-sulphonamide complexes have not been well studied and only a few complexes are described in the literature. Some of them presented lower antimicrobial activity than the free ligands (Yang *et al.,* 2003) and others higher activity (Chohan *et al.,* 2005). Similarly, complexes of sulphamethoxydiazine with Cu(II), Zn(II),

Ni(II), Cd(II), Cr(III) and Fe(III) have been synthesized and showed that sulphamethoxydiazine behaved as a bidentate ligand, binding the metal ion through the sulphonyl oxygen and sulphonamide nitrogen (Yang *et al.,* 2003).

2.8. Classification of Immune Responses to Sulphonamide Antibiotics

In the recent time, issues about cross-allergenicity between sulphonamide antibiotics and nonantibiotic sulphonamide-containing drugs continue to complicate pharmacotherapy (Brackett, 2007). There is an association between hypersensitivity after the receipt of sulphonamide antibiotics and a subsequent allergic reaction after the receipt of a sulphonamide nonantibiotic, but this association appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulphonamide-based drugs (Strom *et al.,* 2003). In fact, several elegant investigations have demonstrated unequivocal lack of interaction between the sulphonamide group and either cellular or humoral immunity.

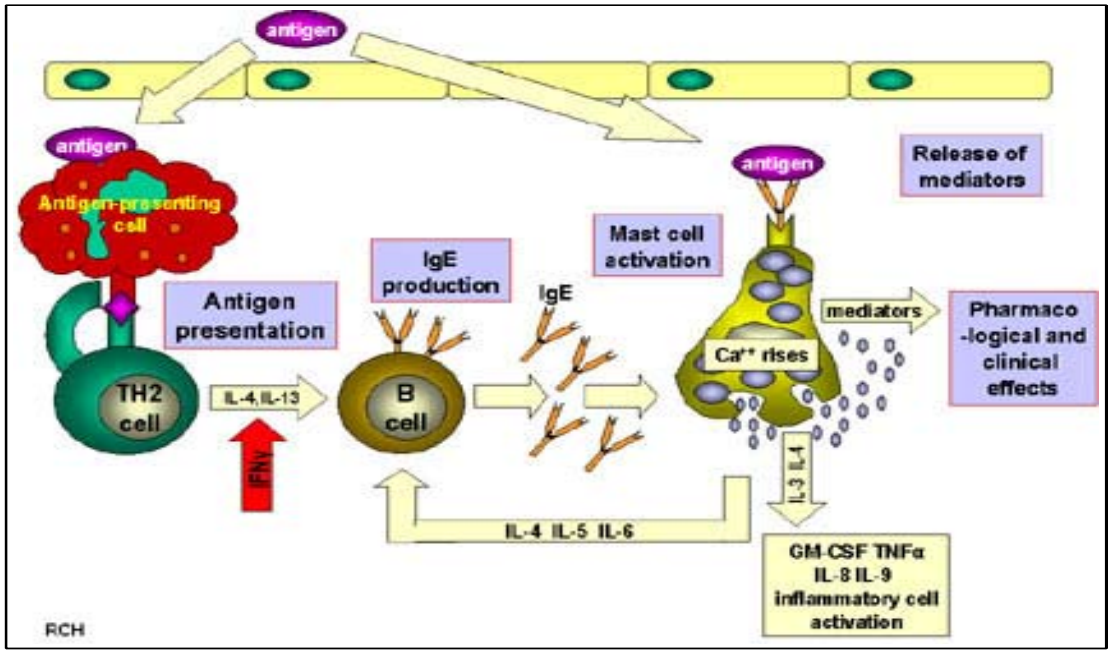


Fig. 2.3: The Role and Effect of Antigen and Hypersensitivity
Source: Moore, 2008

In hypersensitivity, the immune system is ineffective, erratically targeting innocent proteins. Hypersensitivity is caused by a defect in the immune system's functional properties similar to the defect seen in acquired and other immune deficiency syndromes (Turgeon, 2003). However, in hypersensitivity reactions, the immune system overreacts while in immune deficiency syndromes, the immune system under-reacts (Moore, 2008). Nevertheless, the immunologically mediated reactions caused by sulphonamide antibiotics encompass the entire Gell-Coombs spectrum (Cribb *et al.,* 1996). These reactions can be classified into four major categories which are: type I, type II, type III and type IV hypersensitive immune response or reactions.

2.8.1. The Type I Reactions:

The type I reactions are also known as the antibody-mediated anaphylactic or immediate hypersensitivity reactions. These are the most feared types which underlie immunoglobulin E-mediated reactions such as anaphylaxis (Ben-Shoshan and Clarke, 2011), urticaria, angioedema and hypotension with attendant cardiovascular collapse (Butani, 2002). Type I reactions usually occur within 30 minutes of drug administration and are more common with parenteral than with oral administration. The immunologic determinant of type I immunologic response to sulphonamide antibiotics is the N1 heterocyclic ring, and nonantibiotic sulphonamides lack this structural feature (Brackett, 2007).

2.8.2. The Type II (Cytolytic) Hypersensitivity Reactions

These involve antibody-mediated destruction of cells. Both IgG and IgM antibodies may participate in these reactions. Type II hypersensitivity reactions are responsible for immune-mediated hemolytic anemias, neutropenias, thrombocytopenias,

and vasculitis caused by sulphonamide antibiotics. In these reactions, mature circulating or marrow progenitor cells are affected either directly or as "innocent bystanders" as antigenic drug or drug-antibody complexes adhere to them (Bergfeld and DeClerck, 2010; Brackett *et al.,* 2004). Activated complement subsequently lyses the immunologically marked cells, resulting in drug-induced cytopenias. The cytopenias generally become evident within 7-14 days and are often dose dependent (Klinker *et al.,* 2002).

2.8.3. Type III (Immune Complex) Reactions

These also involve IgG and IgM antibodies, but they differ from type II reactions in that antibodies are directed against widely distributed soluble antigens in serum. Thus, whereas damage caused by type II reactions tends to be localized to a tissue or cell type, type III reactions affect entire organs in which antigen-antibody complexes are deposited. Skin, joints, and kidneys are commonly involved (Silbernagl and Lang, 2009). Clinical manifestations of these reactions result from complement activation by immune complexes. Complement split products are anaphylatoxins that can cause localized mast cell degranulation with subsequent localized histamine release and urticaria. In addition, deposition of large immune complexes in joint spaces and in the basement membranes of blood vessels or glomeruli is responsible for vasculitis, glomerulonephritis, and arthritis. These reactions underlie development of classic serum sickness syndromes that occur several days to a few weeks after exposure to an offending drug. Symptoms of serum sickness usually include constellations of fever, vasculitis, lymphadenopathy, and rashes or urticaria.

2.8.4. The Type IV (Cell-Mediated Immunity) Reactions

Type IV (cell-mediated immunity or delayed hypersensitivity) reactions are mediated by cytokines released by sensitized T cells. Cytokines attract and activate macrophages that subsequently elaborate lytic enzymes. The tissue damage caused by type IV reactions typically requires 48-72 hours to develop and may be responsible for such cutaneous reactions as maculopapular rashes, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Fritsch and Sidoroff, 2000; Leyva *et al.,* 2000). An example is the delayed rash that can occur 2 days after receiving an inoculation of tuberculin in the tuberculosis skin test (Moore, 2008).

2.9. Biological Activities of Sulphonamide Derivatives

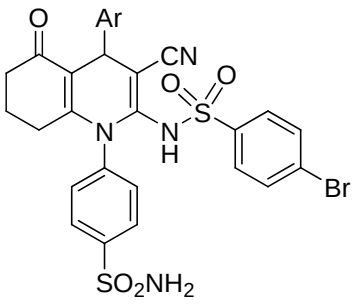
In the past few years, considerable evidence has been accumulated concerning the efficiency of sulphonamide in antibacterial, antimalarial, anticonvulsant, antitubercular, antifungal, antiviral (Chen *et al.,* 2010), antihypertensive, analgesic among others.

2.9.1. Anticancer and Antitumor

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected. Cancers happen when cells that are not normal, grow and spread very fast. Normal body cells grow and divide and know to stop growing. Over time, they also die. Unlike these normal cells, cancer cells just continue to grow and divide out of control and don't die when they're supposed to.

According to the National Cancer Institute, smoking causes 30% of all cancer deaths in the U.S. and is responsible for 87% of cases of lung cancer. Not only does it affect the lungs, it can cause kidney, pancreatic, cervical and stomach cancers and acute

myeloid leukemia (Fayed, 2010). Sulphonamides have attracted great attention, as many sulphonamide derivatives were reported to have interesting antitumor activity (Rostom, 2006; Ghorab *et al.,* 2004).



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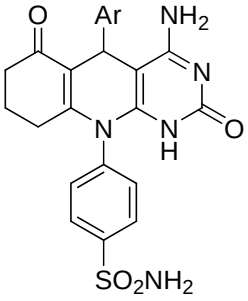

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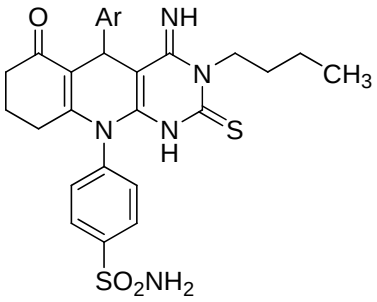


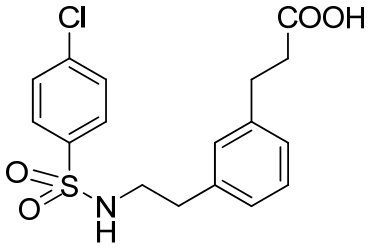
(96)

Several mechanisms have been reported for the anticancer activity of the sulphonamide compounds. It has been known that aryl/heteroaryl sulphonamides may act as antitumor agents through a variety of mechanisms such as cell cycle perturbation in the G1 phase, disruption of microtubule assembly, angiogenesis inhibition, and functional suppression of the transcriptional activator NF-Y (Ghorab *et al.,* 2010). However, the most prominent of mechanism was through the inhibition of the carbonic anhydrase isozymes (Bertucci *et al.,* 2009; Supuran and Scozzafava, 2007; Kivela *et al.,* 2005). Some novel quinolines and pyrimido[4,5-*b*]quinolines bearing sulphonamide moieties have been synthesized and evaluated for antitumoral activity. Out of them all, compounds **(94), (95),** and **(96)** were reported to have higher activity with IC_{50} value of 5.5, 6.9 and 7 µg/mL respectively (Alqasoumi *et al.,* 2010).

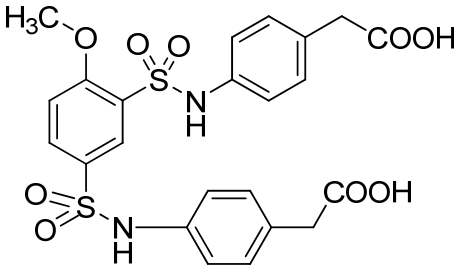
2.9.2. Antiplatelet Aggregation Inhibitory Activity

It is accepted that platelets play a vital role in the progress and development of thrombotic disorder such as cerebral vascular diseases (Maguire *et al.,* 2008; Sonoda *et al.,* 2000). Thromboxane A2 (TXA2) is known to exhibit the activity of stimulation of

platelet function and smooth muscle contraction, including platelet aggregation (Joachim *et al.*, 2001), vasoconstriction, and bronchoconstriction. It has been reported that arylsulphonamide and arylamide derivatives have the activity of thromboxane synthase inhibitor and thromboxane receptor antagonist. There are examples from using compound **(97)**, HN-11 500, DT-TX30, EK112, (Jose *et al.*, 2000; Wang *et al.*, 2003). Centrally constrained thieno[2,3-*b*]thiophene sulphonamides have provided a potent, selective, orally active series of platelet aggregation inhibitors. Compound **(98)** showed excellent activity in the dog after a single oral dose of 200 μg/Kg (Prugh *et al.*, 1997).



(97)



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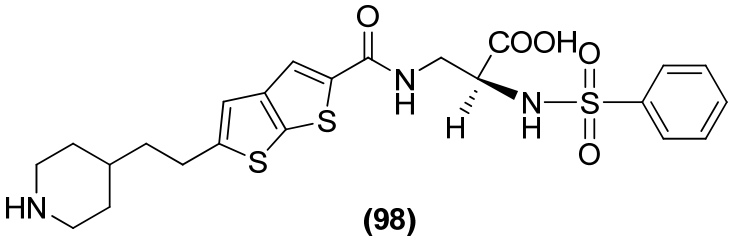


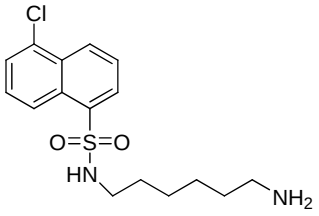
(98)

In addition, a series of arylsulphonamide and arylamide derivatives have been prepared and evaluated for platelet aggregation inhibition with **(99)** having the highest activity with % inhibition of 79.16 (Wang *et al.*, 2003).

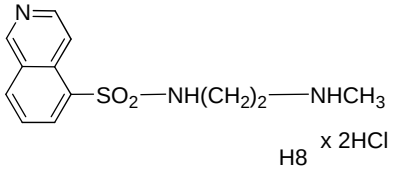
2.9.3. Calmodulin (CaM) Antagonist

Calmodulin (CaM) is an 18-kd multifunctional protein and is the major intracellular Ca^{2+}-binding protein. The molecule consists of two globular lobes connected

by a long exposed α-helix. Two calcium ions bind to each lobe through helix-loop-helix domains similar to those of other calcium-binding proteins. CaM is a Ca^{2+} binding protein that is a key component of the Ca^{2+} second-messenger system and is involved in controlling many of the biochemical processes of cells (Ahn *et al.,* 2003). *N*-(6-aminohexyl)-5-chloro-1-naphthalene-sulphonamide **(100)** (Bariwal *et al.,* 2008) and *N*-(5-aminopentyl)-5-chloro-1-naphthalene-sulphonamide hydrochloride **(101)** have been reported as calmodulin antagonist sulphonamide which showed dose dependant inhibitory action with the potencies comparable to that of calmodulin antagonist.

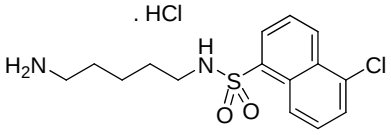


(100)
N-(6-aminohexyl)-5-chloro-1-naphthalene sulphonamide

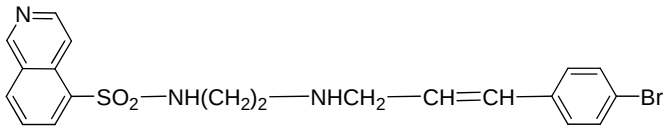


H8 x 2HCl

(102)
N-(2-(methylamino)ethyl)isoquinoline-1-sulphonamide hydrochloride



(101)
N-(5-aminopentyl)-5-chloro-1-naphthalene sulphonamide hydrochloride



H89

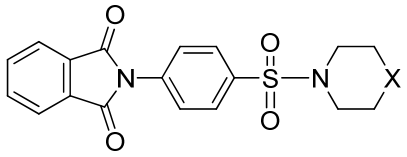
(103)
N-(2-(4-bromocinnamylamino)ethyl) isoquinoline-1-sulphonamide

Furthermore, *N*-(2-methylaminoethyl)-5-isoquinolinesulphonamide H8 **(102)** selectively inhibits several cAMP-dependent protein kinases while a newly synthesized isoquinoline sulphonamide, designated H89 **(103)** is even more potent than H8 in inhibiting cAMP-dependent protein kinases (Cope, 2011). In many instances, calcium exerts its regulatory role by activation of a family of related, high-affinity calcium binding proteins (i.e., calmodulin, troponin C, and parvalbumin) which are present in

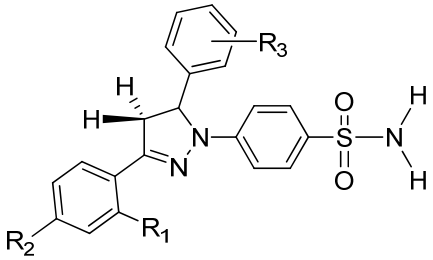
eukaryotes (Veigl *et al.,* 1984). Within this class of regulatory proteins, calmodulin appears to be the major intracellular receptor for Ca^{2+} (Veigl *et al.,* 1986).

2.9.4. Anti-inflammatory Activity

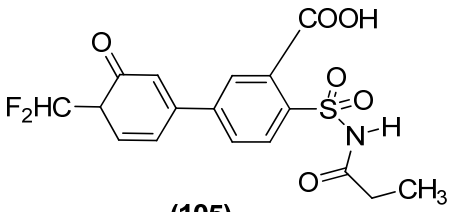
Non-steroidal anti-inflammatory drugs (NSAIDs) are very widely used to treat a variety of acute and chronic inflammatory diseases. Today these drugs are being increasingly used for the treatment of postoperative pain (Ong *et al.,* 2005). Since COX-2 is involved in inflammation and pain, molecules that inhibit it's enzymatic activity would be of therapeutic value. Many non-steroidal anti-inflammatory drugs (NSAIDs) were found to interact with these enzymes and inhibit their enzymatic activity (Ratish *et al.,* 2009). The synthesis and anti-inflammatory activity of new *N*-phenyl-phthalimide sulphonamides **(104a–e)** has been reported (Lima *et al.,* 2002). Compound **(104e)** (LASSBio-468), having a sulphonyl-thiomorpholine unit, showed potent inhibitory activity on neutrophil recruitment with ED_{50} 2.5 mg kg^{-1}, which was correlated with its inhibitory effect on TNF-α level. Out of 19 new pyrazoline bearing sulphonamide synthesized by Ratish and coworkers, **(104k)** and **(104i)** were found to be more active than celecoxib (Ratish *et al.,* 2009).



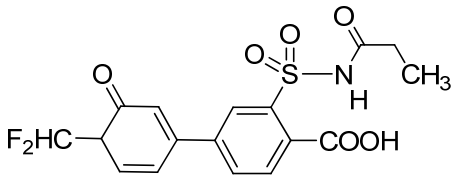
(104e): X = S



(104i): $R_1 = R_2 = OCH_3$, R_3 = 4-Cl
(104k): $R_1 = R_2 = OCH_3$, R_3 = 3,4,5-$(OCH_3)_3$



(105)



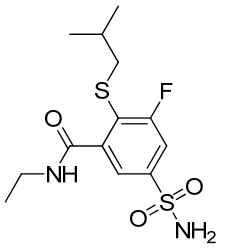
(106)

In another study, *N*-acetyl-2-carboxylbenzenesulphonamide regioisomers possessing a *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety (i.e. *N*-acetyl 4- **(105)** and 5-(*N*-difluoro methyl-1,2-dihydropyrid-2-one-4-yl)carboxybenzenesulphonamides **(106)** were reported to exhibit weak to moderate *in vitro* COX-2 isozyme inhibitory potency and good COX-2 selectivity in conjunction with potent inhibition of the 5-LOX enzyme (Chowdhury *et al.,* 2009).

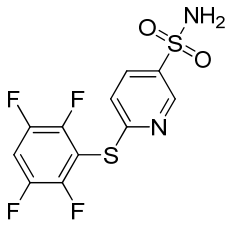
2.9.5. Carbonic Anhydrase Inhibitory Activity

The carbonic anhydrase program started in the Legacy Pharmacia Company with a screening effort of proprietary compounds that identified pyrazole benzenesulphonamides as inhibitors of CAII (Vernier *et al.,* 2010). There was also collaboration at Pharmacia with C. Supuran that identified celecoxib as an inhibitor of CAII (Weber *et al.,* 2004). For existing assays, esterase activity for the CAIV isozyme was much weaker than for the CAII isozyme (Landolfi *et al.,* 1997). To improve sensitivity as well as throughput, a new assay for CAIV was developed (Maren *et al.,* 1983). Glaucoma is a disease characterized by increased intraocular pressure (IOP) (Libby *et al.,* 2005). Carbonic anhydrase (CA) inhibition has been demonstrated to reduce fluid flow into the eye and alleviate high IOP (Supuran, 2008; Maren *et al.,* 1983). For over 40 years, CA inhibitors (CAIs) were available only as pills, and these were intended for other therapies. A novel series of potent thioether benzenesulphonamide

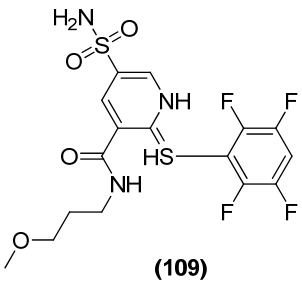
inhibitors of carbonic anhydrases II and IV was discovered using structure-based drug design.



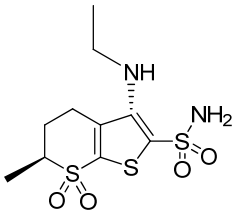
(107)



(108)



(109)



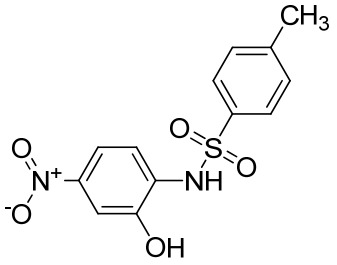
(110)

It was reported that 5-(aminosulphonyl)-*N*-ethyl-3-fluoro-2-(isobutylthio)-benzamide **(107)**, 6-[(2,3,5,6-tetrafluorophenyl)thio]pyridine-3-sulphonamide **(108)**, 5-(aminosulphonyl)-*N*-(3-methoxypropyl)-2-[(2,3,5,6-tetrafluorophenyl)thio]nicotinamide **(109)** exhibited very high CAII inhibition with IC_{50} of 2.79, 8.29 and 10.6 nM respectively. However, they are not as high as that of clinical reference dorzolamine **(110)** (IC_{50} < 2 nM). Synthesis, structure–activity relationship, and optimization of physicochemical properties of such templates are also described. Low nanomolar potency was achieved (Vernier *et al.,* 2010).

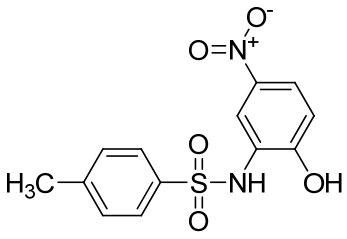
2.9.6. Antimicrobial Activity

Sulphonamides are a class of broad-spectrum synthetic bacteriostatic antibiotics. They inhibit multiplication of bacterial but do not actively kill bacteria. Although the sulphonamide therapy has been reduced, owing to development of more effective antimicrobial agents and to the gradual increase in the resistance of bacterial species, clinical treatment with sulphonamides has undergone a revival by the combination of sulphamethoxazole and trimethoprim (Genç *et al.,* 2008). Antimicrobial activity of some sulphonamides against clinical isolates of *Staphylococcus aureus* has been investigated (Genç *et al.,* 2008). The strongest inhibition was observed in the screening of [*N*-(2-

hydroxy-4-nitrophenyl)-4-methylbenzenesulphonamide] **(111)** and [*N*-(2-hydroxy-5-nitro-phenyl)-4-methylbenzene sulphonamide] **(112)** against *S. aureus.* In fact, compound **(111)** showed higher effect on twenty one *S. aureus* MRSA isolates than oxacillin antibiotic. Introduction of an electron withdrawing group on the ring increased the antimicrobial activity remarkably.



(111)
N-(2-hydroxy-4-nitrophenyl)-4-methylbenzenesulphonamide



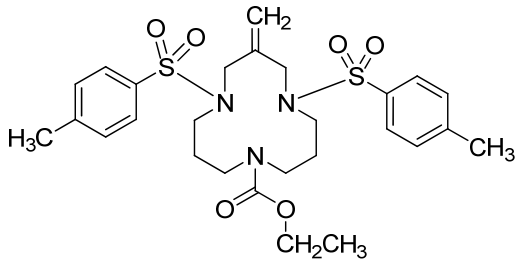
(112)
N-(2-hydroxy-5-nitrophenyl)-4-methylbenzenesulphonamide

2.9.7. Anti-Human Immunodeficiency Virus (Anti-HIV)

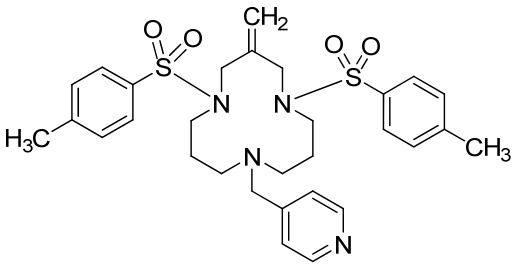
Acquired immunodeficiency syndrome (AIDS) is a clinical syndrome caused by the infection with human immunodeficiency virus-1 (HIV-1), which results in profound immunosuppression (Chauthe *et al.,* 2010). The present line of research focuses on the presumption that an inhibitor that can maximize interactions in the HIV-1 protease active site, particularly with the enzyme backbone atoms, will likely retain these interactions with mutant enzymes (Ghosh *et al.,* 2008). Human immunodeficiency virus type 1 (HIV-1) infection remains a major global health problem due to the emergence of drug-resistant strains (Sorbera *et al.,* 2005). It has been a serious, life-threatening health problem which has claimed 25 million lives world wide in the last 25 years (Chauthe *et al.,* 2010).

Human immunodeficiency virus type 1 (HIV-1) integrase (IN) is not only a key molecule for HIV genomic integration but also is important in other steps of HIV-1 replication, including reverse transcription, nuclear import, chromatin targeting, virus

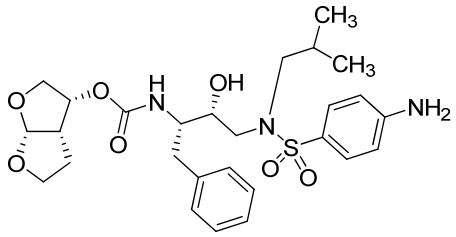
release and maturation (Ao *et al.,* 2010). Recently, a series of cyclotriazadisulphonamide analogues **(113)** and **(114)** derived from computer-aided prediction (Pinheiro *et al*., 2008) as well as sulphonamide marketed as darunavir **(115)** were reported as potent anti-HIV agent (Temesgen, 2007; Koh *et al*., 2003). Sulphonamide derivative amprenavir, **(116)** has also been designed and identified as a novel nonpeptidic human immunodeficiency virus type I (Ray *et al*., 2005).



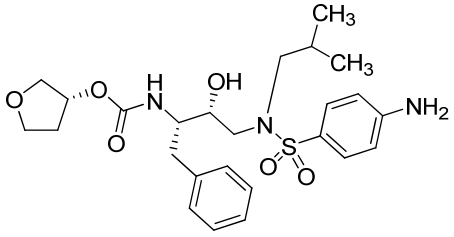
(113)



(114)



(115)
Darunavir

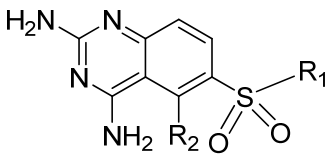


(116)
Amprenavir

2.9.8. Antimalarial Activity

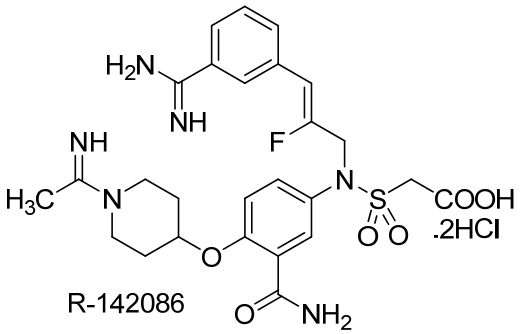
Malarial is a tropical infectious disease which poses serious problem to man's health (Lee *et al.,* 2010; Hay *et al.,* 2005). It is caused primarily by a protozoan *Plasmodium falciparum*, which is responsible for the death of over 1 million individuals every year with more than 40% of the global population at risk (WHO, 2005). During the past 10 years, real progress has been made in scaling up malaria control and prevention

efforts. Since resistance to currently used antimalarials is spreading rapidly, there is a great need for new drugs. Thus, there is a compelling and urgent necessity for new antimalarials, with mechanisms of action different from the existing ones and to identify new drug targets (Miller *et al.,* 2002). An array of sixteen 2,4-diamino-6-quinazoline sulphonamide derivatives **(117a-p)** were evaluated for antimalarial activity and were shown to have promising activity (Agrawal *et al*., 2001). In like manner, sulphonamide **(118)**, was identified as an important compound with potent antimalarial activity (Miller *et al.,* 2002).



(117a-p)

R_2 = H for all except **(117b)** where R_2 = Cl. However R_1 was never the same for any two compounds



R-142086

(118)

2.10 Justification for the Study

Multi-drug resistance is one of the major immediate threats to human health today (Dyatkina *et al.,* 2002). This is because the upsurge of the antibiotic resistant bacteria in the recent years has contributed much towards the increased mortality and morbidity associated with systemic infectious diseases like pneumonia, tuberculosis and meningitis (Kanamaru *et al.,* 2001). For instance, methicillin is a good antibacterial agent, yet, methicillin resistance among *Staphylococcus aureus* (Kaatz *et al.,* 2005) and *Staphylococcus epidermidis* (Nayak *et al.,* 2007; Masunari *et al.,* 2007) had been

identified to be of great concern in public health, especially if the control of the spread is not quickly initiated. Likewise, ampicillin and fluoroquinolone derivatives (e.g. norfloxacin and ciprofloxacin) have been commonly prescribed for the treatment of bacteria caused infection because of their broad spectrum activities (Pecoul *et al.,* 1991; Smolyakov *et al.,* 2001). Nevertheless, the loss of potency of these antibiotics has occurred due to issues of drug resistance. The expression for the loss of potency as a result of development of resistance by the bacterial organism is as shown in Fig. 2.4

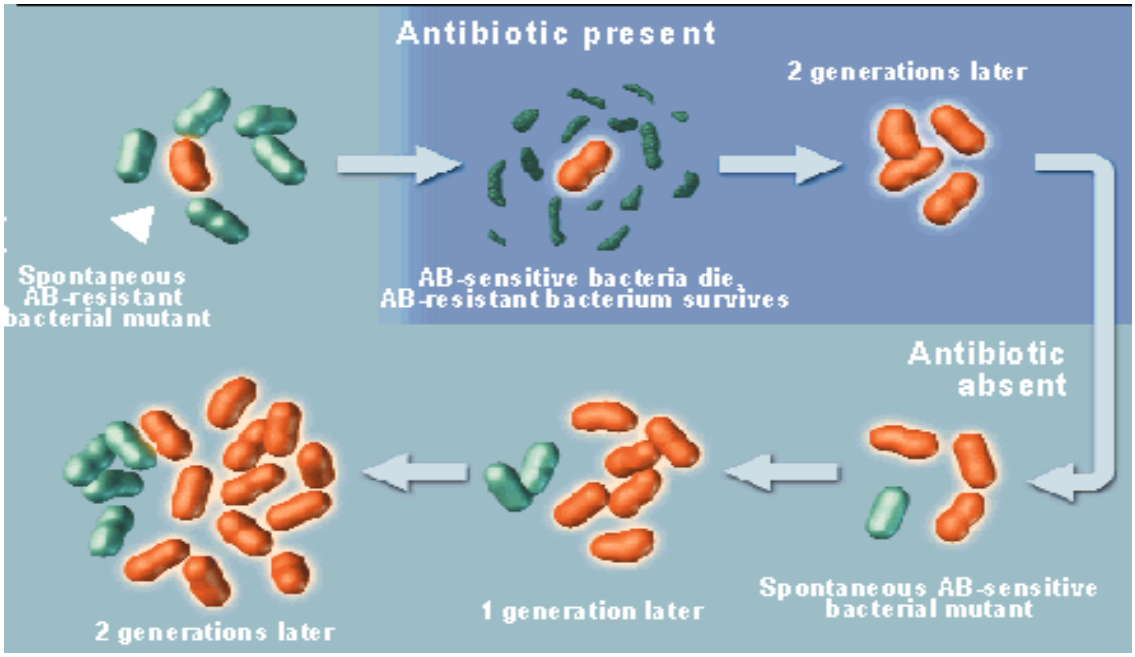


Fig. 2.4: Selection of Resistant Bacteria

Source: Clatworthy *et al.,* 2007; Wright, 2005

However, the intensive use of these antibiotics has led to emergence of multidrug-resistant strains of *Pseudomonas aeruginosa* (Jensen *et al.,* 2001; Wong and Hancock, 2000). In these cases, the cells which were originally susceptible to a particular drug, over the time may acquire a tolerance (resistance) to that drug (Clatworthy *et al.,* 2007). In other cases, it was found that the drug actually reversed its original action by stimulating instead of inhibiting the microorganisms activity (Finar, 1986).

Epidemiological studies have also revealed that emergence of new diseases is at the alarming rates in the recent time (WHO, 2005), while occurrence of side effects during the administration of some of these antimicrobial agents cannot be overemphasized. Phlebitis occurs consistently with the intravenous administration of vancomycin, erythromycin and amphotericin B (Lamb *et al.,* 2002).

Furthermore, other side effects include itching of the body, gut irritation among others. This is why some of those drugs have to be constantly replaced by synthetic drugs with less toxicity for animal tissues. Sulphonamides are a very important class of compounds in the pharmaceutical industry, being widely used as antimicrobial (Eshghi *et al.,* 2011; Santosh *et al.,* 2010; Gao and Pedersen, 2009), anticancer, anti-inflammatory and antiviral agents (Supuran *et al.,* 2003; Scozzafava *et al.,* 2003). Over 30 drugs containing this functionality are in clinical use (Behmadi *et al.,* 2009), including, anti-bacterials, diuretics, anticonvulsants, hypoglycemic and HIV protease inhibitors (Hansch *et al.,* 1990). As a class; the sulpha drugs have a veritable history of application for the treatment of bacterial infection (Korbila *et al.,* 2009; Hughes *et al.,* 2005). Sulphonamides are among the most widely used antibacterial agents in the world, chiefly because of their low cost, low toxicity and excellent activity against common bacterial diseases (Özbek *et al.,* 2007).

New diseases of humans, animals and plants emerge regularly (Sekkides, 2010; Friesen *et al.,* 2006). As at 2008, mankind is confronted by 346 generic infectious diseases, distributed in a seemingly haphazard fashion across 220 countries. An average of three new diseases is described every two years and a new infecting organism is published every week! Over 1,600 human pathogens have been reported, each with a

specific set of phenotypic, genomic and susceptibility characteristics which must be confronted by diagnostic laboratories and clinicians. The pathogens are in turn confronted by 276 generic anti-infective agents and 67 vaccines – marketed under 10,493 proprietary names (Gideon, 2008). The examples of some emerging pathogens and major infectious diseases reported since 1972 are presented in Table 1.1 (Gideon, 2008).

Table 2.1: Major Infectious Diseases Reported Since 1972

Year	Agent	Disease
1973	Rotavirus	Rotavirus disease
1975	Parvovirus B19	Fifth disease
1976	*Cryptosporidium parvum*	Cryptosporidiosis
1977	Ebola virus	Ebola
1977	*Legionella pneumophila*	Legionellosis
1977	Hantavirus	Hemorrhagic fevers
1977	*Campylobacter jejuni*	Campylobacteriosis
1980	T-lymphotrophic virus	T-cell leukemia
1981	Toxigenic *S. aureus*	Toxic shock syndrome
1982	*E. coli* O157:H7	Hemorrhagic colitis, HUS
1982	HTLV-II	Hairy cell leukemia
1982	*Borrelia burgdorferi*	Lyme disease
1983	HIV	AIDS
1983	*Helicobacter pylori*	Peptic ulcer disease
1985	*Enterocytozoon bieneusi*	Microsporidiosis
1986	*Cyclospora cayatenensis*	Cyclosporidiosis
1988	Human Herpes 6	Roseola infantum
1988	*Hepatitis E* virus	Hepatitis E
1989	*Ehrlichia chaffeensis*	Ehrlichiosis
1989	*Hepatitis C* virus	Hepatitis C
1989	Guanarito virus	Venezuelan hemorrhagic fever
1992	*Bartonella henselae*	Cat scratch disease
1993	*Sin nombre* virus	Hantavirus pulmonary syndrome
1994	Sabia virus	Brazilian hemorrhagic fever
1995	Human herpesvirus 8	Kaposi sarcoma
1999	Nipah virus	Nipah virus disease
2003	SARS Coronavirus	SARS

Source: Gideon, 2008

Furthermore, sulphonamides are clinically important drugs (sulphamethazine, sulphanilamide, sulphaguanidine and sulphadoxin) in treating various gastrointestinal

diseases and other forms of infections (Bornholdt *et al.,* 2009). Starting with the antibacterial sulpha drugs and later incorporated into launched drugs such as argatroban (Thrombin inhibitor), udenafil (PDE5 inhibitor), sumatriptan (5-HT agonist) and tipranavir (HIV protease inhibitor) with a variety of different pharmacological effects (Bornholdt *et al.,* 2009). The mode of action of sulphonamide drug is based on the inhibition of DNA synthesis (Pérez-Trallero and Iglesias, 2003) by interfering with *para*-aminobenzoic acid (PABA) in biosynthesis of folic acid which is essential for growth of bacterial cells (Levin *et al.,* 2007).

Sulphonamides were reported to be less toxic when compared with other antibiotics such as atovaquone and azithromycin (Chohan, 2008; Hughes *et al.,* 2005). In fact, sulphonamide-based compound E7070 successfully underwent phase II clinical trials because of its tolerable toxicity profile (Owa *et al.,* 2002). Methicillin-resistant staphylococci are resistant to many antibiotics such as penicillin, carbapenems, cephems and beta-lactam, quinolone, amino glycosides and tetracycline (Jain *et al.,* 2004; Knauer *et al.,* 2004; Huang *et al.,* 2003), whereas sulphonamides and their combination therapies are gaining more attention by the day in antimicrobial drug research (Genç *et al.,* 2008). Based on the various challenges mentioned above, there is a continuous need for the synthesis of new organic sulphonamide compounds as potential antimicrobial agents for the replacement of the old existing ones currently available in the market or to enhance the potency of the former ones. Thus, it is conceivable to develop a series of functionalized sulphonamides and benzothiazepine compounds with different substituents on their fused phenyl framework (for structure-activity relationship purpose).

REFERENCES

Gerahard Domagk, 1986, A contribution to chemotherapy of bacterial infections. *Clinical Infectious Diseases, 8(1),* pp 163-166.

Micheal Kent, 2011, Sulphonamide (Medicine). Accessed online on 17th March, 2011 at: http://en.wikipedia.org/wiki/Sulfonamide_(medicine).

Thomas Hager, 2010, Demon under the microscope. Tantor Exclusive. Accessed online on 20th November, 2010 at: https://www.tantor.com/SellSheets/0306_DemonMicro.pdf.

USHMM, (United State Holocaust Memorial Museum), 2011, Nazi medical experiment. Retrieved from United State Holocaust Memorial Museum, Washington DC, Accessed online on 6th January, 2011 at: http://www.ushmm.org/wlc/en/article. php?ModuleId =10005168

Peter Tyson, 2011, The experiment: Holocaust on trial. Nova Online 2000. Accessed online on 8th February, 2011 at: http://www.pbs.org/wgbh/nova/holocaust/experiside.html

Charles E. Ophardt, 2003, Antibacterial agent – sulpha drug. Virtual Chembook, Elmhurst College. Accessed online on 25th January, 2011 at: http://www.elmhurst.edu/~chm/ vchem book/653sulfa.html

Irvin Levin, M. Mevarech, *et al.,* 2007, Characterization of a novel bifunctional dihydropteroate synthase/dihydropteroate reductase enzyme from Helicobacter pylori. *Journal of Bacteriology, 189(11),* pp 4062-4069.

B.M. Verdel, P.C. Souverein, *et al.,* 2006, Difference in risks of allergic reaction to sulphonamide drugs based on chemical structure. *The Annals of Pharmacotherapy, 40(6),* pp 1040-1046.

A.S. Kalgutkar, R. Jones, *et al.,* 2010, Sulphonamide as an essential functional group in drug design, in: *Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of Chemical Building Blocks on ADMET*, pp 210-274.

Yaseen A. Al-Soud, Haitham H. Al-Sa'doni, *et al.,* 2008*a*, Synthesis, characterization and anti-HIV and antitumor activities of new coumarin derivatives. *Zeitschrift fuer Naturforschung, 63b,* p 83.

Yaseen A. Al-Soud, Haitham H. Al-Sa'doni, *et al.,* 2008*b*, Synthesis and *in vitro* antiproliferative activity of new benzothiazole derivatives. *Arkivoc, xv,* pp 225-238.

Carla R. Andrighetti-Fröhner, Kelly N. De Oliveira, *et al.,* 2009, Synthesis, biological evaluation and SAR of sulphonamide 4-methoxychalcone derivatives with potential antileishmanial activity. *European Journal of Medicinal Chemistry, 44,* pp 755-763.

Bhattacharya, G., Salem, M.M. *et al.,* 2002, Antileishmanial dinitroaniline sulphonamides with activity against parasite tubulin. *Bioorganic and Medicinal Chemistry Letters, 12(17),* pp 2395-2398.

Mahantesha Basanagouda, K. Shivashankar, K., *et al.,* 2010, Synthesis and antimicrobial studies on novel sulphonamides containing 4-azidomethyl coumarin. *European Journal of Medicinal Chemistry, 45,* pp 1151-1157.

Lidia D. Luca and Giampaolo Giacomelli, 2008, An easy microwave-assisted synthesis of sulphonamides directly from sulphonic acid. *Journal of Organic Chemistry, 73,* pp 3967-3969.

D. Maclean, R. Hale, *et al.,* 2001, The reversed kenner linker: A new safety-catch linker for the preparation of *N*-alkyl sulphonamides. *Organic Letters, 3(19),* pp 2977-2980.

Allan S. Wagman, Liang Wang, *et al.,* 2000, Simple and efficient synthesis of 3,4-dihydro-2-pyridones via novel solid-supported aza-annulation. *Journal of Organic Chemistry, 65(26),* pp 9103-9113.

B. Yan, N. Nguyen, *et al.,* 2000, Kinetic comparison of trifluoroacetic acid cleavage reactions of resin-bound carbamates, ureas, secondary amides and sulphonamides from benzyl-, benhydryl-, and indole-based linkers. *Journal of Combinatorial Chemistry, 2(1),* pp 66-74.

David S. Millan, and Rolf H. Prager, 2000, Potential $GABA_B$ receptor antagonists. XI Synthesis of a small library of sulphonamide analogues. *Australian Journal of Chemistry, 53,* pp 615-618.

Fares A. Fares, Damon D. Ridley, *et al.,* 1997, Sulphonamide analogues of creatinine. The synthesis of 3-amino-4,5-dihydro-1,2,4-thiadiazole 1,1-dioxides from base-induced cyclization reactions. *Australian Journal of Chemistry, 50,* pp 1027-1029.

Alakesh Bisai, Bhanu A.B. Prasad, *et al.,* 2007, Aminolysis of *N*-tosylaziridines: An approach to asymmetric synthesis of symmetric and unsymmetric chiral sulphonamide ligands. *Arkivoc, v,* pp 20-37.

Brain R. Blank, Pinar Alayoglu, *et al.,* 2011, *N*-Substituted glutamyl sulphonamides as inhibitors of glutamate carboxypeptidase II (GCP2). *Chemical Biology and Drug Design, 77,* pp 241-247.

R.S. Bastos, A.S. Cunha, *et al.,* 2008, Preparation of *para*-chloroaniline: A simple, fast and inexpensive experiment. *Quimica Nova, 31(1),* pp 172–173.

Maria Leticia C. Barbosa, Gabriela Muniz A. Melo, *et al.,* 2009, Synthesis and pharmacological evaluation of *N*-phenylacetamide sulphonamides. *European Journal of Medicinal Chemistry, 44,* pp 3612-3620.

Meshram, G.A. and Vishvanath D. Patil, 2009, A simple and efficient method for sulphonylation of amines, alcohols and phenols with cupric oxide under mild conditions. *Tetrahedron Letters, 50(10),* pp 1117-1121.

J-G. Kim and D.O. Jang, 2007, Mild and efficient indium metal catalyzed synthesis of sulphonamides and sulphonic esters. *Synlett, 16,* pp 2501-2504.

Liqiang Chen, Riccardo Petrelli, *et al.,* 2008, Bis(sulphonamide) isosters of mycophenolic adenine dinucleotide analogues: Inhibition of inosine monophosphate dehydrogenase. *Bioorganic and Medicinal Chemistry, 16,* pp 7462-7469.

Zahid H. Chohan, Mohammad H. Youssoufi, *et al.,* 2010a, Identification of antibacterial and antifungal pharmacophore sites for potent bacteria and fungi inhibition: Indolenyl sulphonamide derivatives. *European Journal of Medicinal Chemistry, 45,* pp 1189-1199.

Iro Argyropoulou, Athina Geronikaki, *et al.,* 2009, Synthesis and biological evaluation of sulphonamide thiazole and benzothiazole derivatives as antimicrobial agents. *Arkivoc, vi,* pp 89-102.

Anna Kozakiewicz, Małgorzata Ullrich, *et al.,* 2010, Synthesis, structure and activity of sulphonamides derived from (+)-camphor in the enantioselective addition of diethylzinc to benzaldehyde. *Journal of Molecular Catalysis A: Chemical, 326,* pp 128-140.

Raleigh W. Parrott II and Shawn R. Hitchcock, 2008, β-Amino alcohols derived from (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine as catalysts in the asymmetric addition of diethylzinc to aldehydes. *Tetrahedron: Asymmetry, 19(1)*, pp 19-26.

Antonio G. Martinez, Enrique T. Vilar, *et al.,* 2002, Bridgehead-norbornane-derived β-amino alcohol catalysts: Structural factors influencing the chirality transfer. *Tetrahedron: Asymmetry, 13(1)*, pp 1-4.

Y.K. Chen, A.M. Costa, *et al.,* 2001, Substrate dependence of nonlinear effects: Mechanistic probe and practical applications. *Journal of American Chemical Society, 123(22)*, pp 5378-5379.

Vladimir Dimitrov, Goergi Dobrikov, *et al.,* 2001, Chiral β- and γ-aminoalcohols derived from (+)-camphor and (−)-fenchone as catalysts for the enantioselective addition of diethylzinc to benzaldehyde. *Tetrahedron: Asymmetry, 12(9)*, pp 1323-1329.

Ailing Hui, Jintang Zhang, *et al.,* 2008, Efficient asymmetric addition of diethylzinc to ketones using tartaric acid derivative as chiral ligand. *Arkivoc, (ii)*, pp 25-32.

Ailing Hui, Jintang Zhang, *et al.,* 2006, A new chiral sulphonamide ligand based on tartaric acid: Synthesis and application in the enantioselective addition of diethylzinc to aldehydes and ketones. *Tetrahedron: Asymmetry 17(14)*, pp 2101-2107.

Diego J. Ramon and Miguel Yus, 2007, Chiral ligands with an isoborneol-10-sulphonamide structure: A ten-year odyssey. *Synlett*, *No 15,* pp 2309-2320.

Vicente J. Forrat, Diego J. Ramon, *et al.,* 2006, Polymer supported *trans*-1-phenylsulphonyl amino-2-isoborneolsulfonylaminocyclohexane ligand for the titanium catalyzed organozinc addition to ketones. *Tetrahedron: Asymmetry, 17(14)*, pp 2054-2058.

C.M. Binder, A. Bautista, *et al.,* 2009, Dual stereoselectivity in the dialkylzinc reaction using (−)-β-pinene derived amino alcohol chiral auxiliaries. *Journal of Organic Chemistry, 74(6)*, pp 2337-2343.

Z. Szakonyi, A. Hetényi, *et al.,* 2008, Synthesis and application of monoterpene-based chiral aminodiols. *Tetrahedron, 64(6)*, pp 1034-1039.

Cihangir Tanyeli, Serhat Odabaş, *et al.,* 2007, Asymmetric synthesis of novel 1,4-aminoalcohol ligands with norbornene and norbornane backbone: Use in the asymmetric diethylzinc addition to benzaldehyde. *Tetrahedron: Asymmetry, 18(19)*, pp 2349-2357.

E.D. Jose Martins, Clarissa M. Mehlecke, *et al.,* 2006, Synthesis of chiral norbornane derivatives as γ-amino alcohol catalysts: The effect of the functional group positions on the chirality transfer. *Tetrahedron: Asymmetry, 17(12)*, pp 1817-1823.

F. Soki, J.M. Neudörfl, *et al.,* 2005, Surprising fenchone induced cyclization: Synthesis of the new chiral diol biphenyl-2,2′-sulphone-3,3′-bisfenchol (BISFOL). *Tetrahedron, 61(44)*, pp 10449-10453.

Mariana Kamenova-Nacheva, Georgi Dobrikov, *et al.,* 2009, Preparation of –amino-alcohol analogs by the addition of N-, O- and S-containing substituents to ferrocenylcamphor sulphonamide-ligands for enantioselective addition of diethylzinc to benzaldehyde. *Arkivoc, xii,* pp 141-152.

B. Das, P. Balasubramanyam, *et al.,* 2009, Iodine-catalyzed efficient hydrophosphonylation of *N*-tosyl aldimines. *Journal of Organic Chemistry,* 74*(11),* pp 4393–4395.

Z-G. Lea, Z-C. Chen, *et al.,* 2004, Organic Reactions in Ionic Liquids. A simple and highly regioselective *N*-substitution of pyrrole. *Synthesis, 12,* pp 1951-1954.

K. Bahrami, M.M. Khodaei, *et al.,* 2009, Direct conversion of thiols to sulphonyl chlorides and sulphonamides. *Journal of Organic Chemistry, 74(24),* pp 9287-9291.

S.W. Wright, and K.N. Hallstrom, 2006, A convenient preparation of heteroaryl sulphonamides and sulphonyl fluorides from heteroaryl thiols. *Journal of Organic Chemistry, 71(3),* pp 1080-1084.

L. Yan, D.C.G. Bertarelli, *et al.,* 2006, A new synthesis of sulphonamides by aminolysis of *p*-nitrophenylsulphonates yielding potent and selective adenosine A_{2B} receptor antagonists. *Journal of Medicinal Chemistry, 49(14),* pp 4384-4391.

Stephen, Giguere, John F. Prescott, *et al.,* 2006, Sulphonamides, diaminopyrimidines and their combinations, in: *Antimicrobial Therapy in Veterinary Medicine,* pp 249-250.

Z. Qiang, and C. Adams, 2004, Potentiometric determination of acid dissociation constants (pK_a) for human and veterinary antibiotics. *Water Research, 38(12),* pp 2874-2890.

Y.H. Ebead, 2010, The role of medium on acid dissociation constants of some azo dyes in view of experimental and theoretical data. *Journal of Molecular Structure, 982(1-3),* pp 100-106.

C.H. Dwight, J.M. Nigel, *et al.,* 2004, Antimicrobial chemotherapy: Sulphonamide and trimethoprim, in: *Veterinary Microbiology;* John Wiley and Sons Inc, USA, Chapter 4, pp 31-33.

M. Oukessou, and L. Alsouss, 1998, Pharmacokinetics of sulphonamides and trimethoprim in the donkey (*Equus asinus*). *Journal of Veterinary Medicine Series A, 45(1-10),* 191-198.

H. Li, M.L. Smith, *et al.,* 2009, Determination of sulphadimethoxine and ^{4}*N*-acetylsulphadimethoxine in bovine plasma, urine, oral fluid, and kidney and liver biopsy samples obtained surgically from standing animals by LC/MS/MS. *Journal of Chromatography B, 877(3),* 237-246.

D.S. Aschenbrenner, and S.J. Venable, 2008, Drugs treating urinary tract infections, in: *Drug Therapy in Nursing*; Lippincott Williams & Wilkins Publishing USA, Chapter 42, pp 817-827.

J.C. Paige, and L. Tollefson, 2003, Veterinary products: Residues and resistant pathogens, in: *Food Safety: Contaminants and Toxins;* 3Rd Edition, D'Mello, J.P.F. (Ed.), CABI Publishing Wallingford, UK, Chapter 13, pp 293-306.

B-E. Wiholm, 2001, Identification of sulphonamide-like adverse drug reactions to celecoxib in the world health organization database. *Current Medical Research and Opinion, 17(3),* pp 210-216.

M.A.S. Yasuda, 2005, Pharmacological management of paracoccidioidomycosis. *Expert Opinion on Pharmacotherapy, 6(3),* pp 385-397.

F. Derouin, E. Jacqz-Aigrain, *et al.,* 2000, Cotrimoxazole for prenatal treatment of congenital toxoplasmosis? *Parasitology Today, 16(6),* pp 254-256.

A. Korolkovas, 1998, *Essentials of Medicinal Chemistry;* 2nd Edition, John Wiley and Sons, Inc., USA, (a) pp 699-719; (b) p 140 and p 157.

D. Shei, 2010, Antibiotics as enzymes in: Biochemistry, Toxic Medicine. Posted on 19th June, 2010. Accessed online on 15th November, 2010 at: http://littledoctors.word press. com /2010/06/19/antibiotics-as-enzymes/

D. Vicente, and E. Pérez-Trallero, 2010, Tetracyclines, sulphonamides and metronidazole. *Enfermedades Infecciosas y Microbiología Clínica, 28(2),* pp 122-130.

Yoshimichi Shoji, Kenji Takahashi, *et al.,* 2009, Novel indoline-based acyl-CoA: cholesterol acyltransferase inhibitor: Effects of introducing a methanesulphonamide group on physicochemical properties and biological activities. *Bioorganic and Medicinal Chemistry, 17,* pp 6020-6031.

E. Pérez-Trallero, and L. Iglesias, 2003, Tetracyclines, sulphonamides and metronidazole. *Enfermedades Infecciosas y Microbiología Clínica, 21(9),* pp 529-533.

D. Greenwood, 2003, Sulphonamide, in *Antibiotic and Chemotherapy: Anti-infective Agents and Their Use in Therapy;* Finch, R.G. (Ed.), Elsevier Publisher, UK, Chapter 32, pp 385-392.

Gerard D. Wright, 2005, Bacterial resistance to antibiotics: Enzymatic degradation and modification. *Advanced Drug Delivery Reviews, 57(10),* pp 1451-1470.

F. Yan, J.M. LaMarre, *et al.,* 2010, RlmN and Cfr are radical SAM enzymes involved in methylation of ribosomal RNA. *Journal of American Chemical Society, 132(11),* pp 3953-3964.

Siibak Triinu, Peil Lauri, *et al.,* 2009, Erythromycin- and chloramphenicol-induced ribosomal assembly defects are secondary effects of protein synthesis inhibition. *Antimicrobial Agents and Chemotherapy, 53(2),* pp 563-571.

B. Weisblum, 1995, Erythromycin resistance by ribosome modification. *Antimicrobial Agents and Chemotherapy, 39(3),* pp 577-585.

Lisa K. Smith and Alexander S. Mankin, 2008, Transcriptional and translational control of mlr operon, which confers resistance to seven classes of protein synthesis inhibitors. *Antimicrobial Agents and Chemotherapy, 52(5),* pp 1703-1712.

Shao-Ma Yin, 2010, Insecticide resistance. *Pest Control Newsletters Issue No 20,* p. 1

X. Li, M.A. Schuler, *et al.,* 2007, Molecular mechanism of metabolic resistance to synthetic and natural xenobiotics. *Annual Review of Entomology, 52,* pp 231-253.

C. Claudianos, E. Crone, *et al.,* 2002, A genomic perspective on mutant aliesterases and metabolic resistance to organophosphate in: *ACS Symposium Series, 808,* Chapter 5, pp 90-101.

G.E.W. Wolstenholme, C.M. O'Connor, *et al.,* 2008, Genetic and metabolic mechanisms underlying multiple levels of sulphonamide resistance in Pneumococci, in: *Ciba Foundation Symposium–Drug Resistance in microorganisms of Development,* John Wiley, USA, Chapter 10. DOI: 10.1002 /9780470719053.ch10

Arun K. Ghosh, Bruno D. Chapsal, *et al.,* 2008, Design of HIV protease inhibitors targeting protein backbone: An effective strategy for combating drug resistance. *Account of Chemical Research, 41(1),* pp 78-86.

Natalia B. Dyatkina, Christopher D. Roberts, *et al.,* 2002, Minor groove DNA binders as antimicrobial agents, i, pyrazoles tetraamides are potential antibacteria against vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* agents. *Journal of Medicinal Chemistry, 45*, pp 805-817.

S. Rafique, M. Idrees, *et al.,* 2010, Transition metal complexes as potential therapeutic agents. *Biotechnology and Molecular Biology Reviews, 5(2),* pp 38-45.

Shao-Ming Fang, E. Carolina Saňudo, *et al.,* 2011, Copper(ii) complex with *cis*-epoxysuccinate ligand: Syntheses, crystal structures, and magnetic properties. *Australian Journal of Chemistry, 64,* pp 217-226.

Melina Mondelli, Veronica Brune, *et al.,* 2008, New Ni(II)-sulphonamide complexes: Synthesis, structural characterization and antibacterial properties. X-ray diffraction of $[Ni(sulphisoxazole)_2(H_2O)_4].2H_2O$ and $[Ni(sulphapyridine)_2]$. *Journal of Inorganic Biochemistry, 102,* pp 285-292.

Joaquin Borrás, Ferrer, A.S. *et al.,* 2004, *Carbonic anhydrase: Its Inhibitors and Activators, Metal Complexes of Heterocyclic Sulphonamides as Carbonic Anhydrase Inhibitors***,** Supuran, C.T.; Scozzafava, A.; Conway, J. (Eds.), CSC Press, Boca Raton, USA, pp. 14-19.

Zahid H. Chohan, A.U. Shaikh, *et al.,* 2006*b*, Metal-based isatin-bearing sulphonamides: Their synthesis, characterization and biological properties. *Applied Organometallic Chemistry, 20(11),* pp 729-739.

Zahid H. Chohan and Claudiu T. Supuran, 2008, Structure and biological properties of first row d-transition metal complexes with *N*-substituted sulphonamides. *Journal of Enzyme Inhibition and Medicinal Chemistry, 23(2),* pp 240–251.

Maria H. Torre, G. Facchin *et al.,* 2003, Characterization of a copper (II) complex of sulphadimethoxine. *Journal of Inorganic Biochemistry, 94(1-2),* pp 200–204.

Zahid H. Chohan, 2008, Metal-based sulphonamides: Their preparation, characterization, in vitro antibacterial, antifungal and cytotoxicity properties. X-ray structure of 4-[(2-hydroxybenzylidene)amino]benzenesulphonamide. *Journal of Enzyme Inhibition and Medicinal Chemistry, 23(1),* pp 120–130.

R. Cejudo-Marin, G. Alzuet, *et al.,* 2004, Copper (II) complexes with 4-amino-*N*-[4,6-dimethyl-2-pyrimidinyl] benzene sulphonamide. Synthesis, crystal structure, magnetic properties, EPR and theoretical studies of a novel mixed μ-carboxylato, NCN-bridged dinuclear copper compound. *Inorganic Chemistry, 43(21),* pp 6805–6814.

J.E.F. Reynolds, (Ed.), 1996, Martindale. The Extra Pharmacopoeia, Royal Pharmaceutical Society, London.

Zahid H. Chohan, H. Pervez, *et al.,* 2006*c*, Antibacterial cobalt (II), copper (II), nickel (II) and zinc (II) complexes of mercaptothiadiazole-derived furanyl, thienyl, pyrrolyl, salicylyl and pyridinyl Schiff bases. *Journal of Enzyme Inhibition and Medicinal Chemistry, 21(2),* pp 193–201.

Sebastian Bellú, Estela Hure, *et al.,* 2003, The interaction between mercury(II) and sulphathiazole. *Quimica Nova, 26(2),* pp 188-192.

E. Kremer, G. Facchin, *et al.,* 2006, Copper complexes with heterocyclic sulphonamides: Synthesis, spectroscopic characterization, microbiological and SOD-like activities: Crystal structure of $[Cu(sulphisoxazole)_2(H_2O)_4]\cdot 2H_2O$. *Journal of Inorganic Biochemistry, 100(7),* pp 1167–1175.

L. Yang, X. Yang, *et al.,* 2003, Synthesis, characterization and susceptibility of bacteria against sulphamethoxydiazine complexes of copper(II), zinc(II), nickel(II), cadmium(II), chromium(II) and iron(II). *Journal of Coordination Chemistry, 56(13),* pp 1131–1139.

Zahid H. Chohan, K. Mahmood-Ul-Hassan, *et al.,* 2005, *In-vitro* antibacterial, antifungal and cytotoxic properties of sulphonamide-derived Schiff's bases and their metal complexes. *Journal of Enzyme Inhibition and Medicinal Chemistry, 20(2),* pp 183–188.

Carolyn C. Brackett, 2007, Sulphonamide allergy and cross-reactivity. *Current Allergy and Asthma Reports, 7(1),* pp 41-48.

Brain L. Strom, R. Schinnar, *et al.,* 2003, Absence of cross-reactivity between sulphonamide antibiotics and sulphonamide nonantibiotics. *New England Journal of Medicine, 349(17),* pp 1628-1635.

Mary L. Turgeon, 2003, Basic immunologic Mechanism - an overview of immunology in: Immunology and Serology in Laboratory Medicine 4th Edition, Mosby Inc. Publishers, pp 104-116.

Elaine Moore, 2008, Hypersensitivity reactions: An exaggerated immune response to autoimmune disease. General Medicine. Posted on 16th of September 2008. Accessed online on 2nd December, 2008 at: http://www.suite101.com/content/hypersensitivity-reactions-a69024.

A.E. Cribb, B. Lee, *et al.,* 1996, Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: Clinical syndromes and pathogenesis. *Adverse Drug Reaction Toxicology Review, 15,* pp 9-10.

Moshe Ben-Shoshan, Anna E. Clarke, 2011, Anaphylaxis: Past, present and future. *Allergy, 66,* pp 1-14. DOI:10.1111/j.1398-9995.2010.02422.x

Lavjay Butani, 2002, Corticosteroid-induced hypersensitivity reactions. *Annals of Allergy, Asthma and Immunology, 89(5),* pp 439-445.

Scott A. Bergfeld, and Yves A. DeClerck, 2010, Bone marrow-derived mesenchymal stem cells and the tumor microenvironment. *Cancer Metastasis Review, 29,* pp 249-261.

Carolyn C. Brackett, Harbhajan Singh, *et al.,* 2004, Likelihood and mechanisms of cross-allergenicity between sulphonamide antibiotics and other drugs containing a sulphonamide functional group. *Pharmacotherapy, 24(7),* pp 856-870.

K.P. Klinker, J.W. Harbilas, *et al.,* 2002, Drug-induced hematologic disorders. In: DiPiro, J.; Talbert, R.; Yee, G.; Matzke, G.; Wells, B.; Posey, L.M. eds. Pharmacotherapy: A pathophysiologic approach, 5th ed. New York, McGraw-Hill, pp 1783-1795.

S. Silbernagl, and F. Lang, 2009, Color Atlas of Pathophysiology 2nd Edition, Thieme Medical Publishers, pp 58-60.

P.O. Fritsch, and A. Sidoroff, 2000, Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *American Journal of Clinical Dermatology, 1(6),* pp 349-360.

Laura Leyva, Maria J. Torres, *et al.,* 2000, Anticonvulsant-induced toxic epidermal necrolysis: Monitoring the immunologic response. *Journal of Allergy and Clinical Immunology, 105,* pp 157-165.

Zhou Chen, Weiming Xu, *et al.,* 2010, Synthesis and antiviral activity of 5-(4-chlorophenyl)-1,3,4-thiadiazole sulphonamides. *Molecules, 15,* pp 9046-9056.

Lisa Fayed, 2010, The causes and risk factors of cancer. Accessed online 10th August, 2010 at: http://cancer.about.com/od/causes/a/causesrisks.htm.

Sherif A. Rostom, 2006, Synthesis and *in vitro* antitumor evaluation of some indeno[1,2-*c*] pyrazol(in)es substituted with sulphonamide, sulphonylurea(-thiourea)pharmacophores, and some derived thiazole ring systems. *Bioorganic and Medicinal Chemistry, 14(19),* pp 6475–6485.

Mostafa M. Ghorab, Zahid H. Ismail, *et al.,* 2004, Antimicrobial activity of amino acid, imidazole and sulphonamide derivatives of pyrazolo[3,4-*d*] pyrimidine. *Heteroatom Chemistry, 15(1),* pp 57–62.

Mostafa M. Ghorab, Fatma A. Ragab, *et al.,* 2010, In vitro anticancer screening and radiosensitizing evaluation of some new quinolines and pyrimido[4,5-*b*]quinolines bearing a sulphonamide moiety. *European Journal of Medicinal Chemistry, 45,* pp 3677-3684.

Anthony Bertucci, Alessio Innocenti, *et al.,* 2009, Carbonic anhydrase inhibitors. Inhibition studies of a coral secretory isoform by sulphonamides. *Bioorganic and Medicinal Chemistry, 17(14),* pp 5054-5058.

Claudiu T. Supuran, and Andrea Scozzafava, 2007, Carbonic anhydrases as targets for medicinal chemistry. *Bioorganic and Medicinal Chemistry, 15(13),* pp 4336–4350.

A.J. Kivela, J. Kivela, *et al.,* 2005, Carbonic anhydrases in normal gastrointestinal tract and gastrointestinal tumours. *World Journal of Gastroenterology, 11(2),* pp 155–163.

Saleh I. Alqasoumi, Areej M. Al-Taweel, *et al.,* 2010, Novel quinolines and primido[4,5-*b*] quinolines bearing biologically active sulphonamide moiety as a new class of Antitumor agents. *European Journal of Medicinal Chemistry, 45,* pp 738-744.

J.M. Maguire, A. Thakkinstain, *et al.,* 2008, Polymorphisms in platelet glycoprotein Ib{alpha} and factor vii and risk of ischemic stroke: A meta-analysis. *Stroke, 39(6),* pp 1710-1716.

A. Sonoda, M. Murata, *et al.,* 2000, Association between platelet glycoprotein Ibα genotype and ischemic cerebrovascular disease. *Stroke, 31(2),* pp 493-497.

F.S. Joachim, R. Piotr, *et al.,* 2001, Antiplatelet and anticoagulant effects of "HN-11 500," a selective thromboxane receptor antagonist. *Thrombosis Research, 103(2)*, pp 79-91.

P.D.L.C. José, M. Antonio, *et al.,* 2000, Effect of DT-TX 30, a combined thromboxane synthase inhibitor and thromboxane receptor antagonist, on retinal vascularity in experimental diabetes mellitus. *Thrombosis Research, 97(3)*, pp 125-131.

S.Q. Wang, X.J. Liu, *et al.,* 2003, Design and synthesis of new arylsulphonamdie and arylamide derivatives for the platelet aggregation inhibitor. *Chinese Chemical Letters, 14(6),* pp 581-584.

J.D. Prugh, R.J. Gould, *et al.,* 1997, Nonpeptide GPIIB/IIIA inhibitors. 16. Thieno[2,3-*b*]thiophene α-sulphonamides are potent inhibitors of platelet aggregation. *Bioorganic and Medicinal Chemistry, 7(7),* pp 865-870.

E-Y. Ahn, G. Pan, *et al.,* 2003, The combination of calmodulin antagonists and interferon-γ induces apoptosis through caspase-dependent and –independent pathways in cholangiocarcinoma cells. *American Journal of Pathology, 163(5),* pp 2053-2054.

Jitender B. Bariwal, Kuldip D. Upadhyay, *et al.,* 2008, 1,5-Benzothiazepine, a versatile pharmacophore: A review. *European Journal of Medicinal Chemistry, 43,* pp 2279-2290.

Cope, 2011, Cytokine Cells Online Pathfinder Encyclopedia. Available online at: www.copewithcytokines.de/cope.cgi?key=H8 (Accessed on 15th June, 2011).

M.L. Veigl, T.C. Vanaman, *et al.,* 1984, Calcium and calmodulin in cell growth and transformation. *Biochimica and Biophysica Acta, 738,* pp 21-48.

M.L. Veigl, W.D. Sedwick, *et al.,* 1986, Induction of myeloid differentiation of HL-60 cells with naphthalene sulphonamide calmodulin antagonist. *Cancer Research, 46,* pp 2300-2305.

C.K-S. Ong, P. Lirk, *et al.,* 2005, The efficacy of preemptive analgesia for acute postoperative pain management: A metal-analysis. *Anesthesia and Analgesia, 100(3),* pp 757-773.

I.G. Ratish, Kalim Javed, *et al.,* 2009, Synthesis ans anti-inflammatory activity of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulphonamide. *Bioorganic and Medicinal Chemistry, 19(1),* pp 225-258.

Lidia M. Lima, Paulo Castro, *et al.,* 2002, Synthesis and anti-inflammatory activity of phthalimide derivatives, designed as new thalidomide analogues. *Bioorganic and Medicinal Chemistry, 10(9),* pp 3067-3073.

Morshed A. Chowdhury, Khaled R.A. Abdellatif, *et al.,* 2009, Synthesis and biological evaluation of salicylic acid and *N*-acetyl-2-carboxybenzenesulphonamide regioisomers possessing a *N*-difluoro methyl-1,2-dihydropyrid-2-one pharmacophore: Dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. *Bioorganic and Medicinal Chemistry Letters, 19,* pp 6855-6861.

William Vernier, Wesley Chong, *et al.,* 2010, Thioether benzene sulphonamide inhibitors of carbonic anhydrases II and IV: Structure-based drug design, synthesis and biological evaluation. *Bioorganic and Medicinal Chemistry, 18,* pp 3307-3319.

Weber, A., Casini, A., *et al.,* 2004, Unexpected nanomolar inhibition of carbonic anhydrase by COX-2-selective celecobix: New pharmacological opportunities due to related binding site recognition. *Journal of Medicinal Chemistry, 47(3),* pp 550-557.

Carla Landolfi, Marcello Marchetti, *et al.,* 1997, Development and pharmacological characterization of a modified procedure for the measurement of carbonic anhydrase activity. *Journal of Pharmacological and Toxicological Methods, 38(3),* pp 169-172.

Thomas H. Maren, Lidia Jankowska, *et al.,* 1983, The transcorneal permeability of sulphonamide carbonic anhydrase inhibitors and their effect on aqueous humor secretion. *Experimental Eye Research, 36(4),* pp 457-480.

Richard T. Libby, Douglas B. Gould, *et al.,* 2005, Complex genetics of glaucoma susceptibility. *Annual Reviews of Genomics and Human Genetics, 6,* pp 15-44.

Claudiu T. Supuran, 2008, Carbonic anhydrases: Novel therapeutic applications for inhibitors and activators. *Nature Re*views *Drug Discovery, 7(2)*, pp 168-182.

Yeliz Genç, Reşit Özkanca, *et al.,* 2008, Antimicrobial activity of some sulphonamide derivatives on clinical isolates of *Staphylococcus aureus. Annals of Clinical Microbiology and Antimicrobials, 7(17),* 6 pp. DOI:10.1186/1476-0711-7-17

Siddheshwar K. Chauthe, Sandip B. Bharate *et al.,* 2010, Biomimetic synthesis and anti-HIV activity of dimeric phloroglucinols. *Bioorganic and Medicinal Chemistry, 18(5),* pp 2029-2036.

L.A. Sorbera, J. Castaner, *et al.,* 2005, Darunavir. Anti-HIV agents, HIV protease inhibitor. *Drugs of the Future, 30(5),* pp 441-449.

Zhujun Ao, Kallesh D. Jayappa, *et al.,* 2010, Characterization of anti-HIV activity mediated by HIV-1 integrase c-terminal domain polypeptides expressed in susceptible cells. *Journal of Antivirals and Antiretrovirals, 2(1),* pp 20-28.

Julia R. Pinheiro, Michelle Bitencourt, *et al.,* 2008, Novel anti-HIV cyclotriazadisulphonamide derivatives as modeled by ligand- and receptor-based approaches. *Bioorganic and Medicinal Chemistry, 16(4),* pp 1683-1690.

Z. Temesgen, 2007, Antiretroviral drugs in development: A report from HIV DART 2006. *Drugs of the Future, 32(1),* pp 83-84.

Yasuhiro Koh, Hirotomi Nakata, *et al.,* 2003, Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC 114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro. *Antimicrobial Agents Chemotherapy, 47(10),* pp 3123-3129.

S. Ray, S.R. Pathak, *et al.,* 2005, Organic carbamates in drug development. Part II. Antimicrobial agents – Recent report. *Drugs of the Future, 30(2),* pp 161-162.

P-W. Lee, C-T. Liu, *et al.,* 2010, Pre-elimination of malaria on the island of Príncipe. *Malaria Journal, 9,* pp 26-27.

S.I. Hay, C.A. Guerra, *et al.,* 2005, Tropical infectious diseases: Urbanization, malaria transmission and disease burden in Africa. *Nature Reviews Microbiology, 3,* pp 81-90.

WHO (World Health Organisation), 2005, World Malaria Report. Accessed online on 7th January, 2011 at: http://rbm.who.int/wmr2005.

L.H. Miller, D.I. Baruch, *et al.,* 2002, The pathogenic basis of malaria. *Nature, 415(6872),* pp 673-679. DOI: 10.1038/415673a.

V.K. Agrawal, S. Sinha, *et al.,* 2001, QSAR studies on antimalarial 2,4-diamino-6-quinazoline sulphonamides. *Acta Microbiologica et Immunologica Hungarica, 48(1),* pp 17-26.

Tsuneo Kanamaru, Yoshitaka Nakano, *et al.,* 2001, *In vitro* and *in vivo* antibacterial activities of TAK-083, an agent for treatment of *Helicobacter pylori* infection. *Antimicrobial Agents and Chemotherapy, 45(9),* pp 2455-2459.

Glenn W. Kaatz, Fionnuala McAleese, *et al.,* 2005, Multidrug resistance in *Staphylococcus aureus* due to over expression of a novel Multidrug and Toxin Extrusion (MATE) transport protein. *Antimicrobial Agents and Chemotherapy, 49(5),* pp 1857-1864.

N. Nayak, T.C. Nag, *et al.,* 2007, Ultrastructural analysis of slime positive and slime negative of *Staphylococcus epidermidis* isolates in infectious keratitis. *Indian Journal of Medical Research, 125*, pp 767-771.

Andrea Masunari, and Leoberto C. Tavares, 2007, A new class of nifuroxazide analogues: synthesis of 5-nitrophene derivatives with antimicrobial activity against multidrug-resistant *Staphylococcus aureus. Bioorganic and Medicinal Chemistry, 15(12)*, pp 4229-4236.

B. Pecoul, F. Varaine, *et al.,* 1991, Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. *Lancet, 338*, pp 862-866.

R. Smolyakov, F. Schlaeffer, *et al.,* 2001, Ampicillin-Sulbactam treatment of nosocomial multi-resistant acinetobacter baumanii bacteremia. *Interscience Conference on Antimicrobial Agents and Chemotherapy, 41*, K-1188.

Lars Bogø Jensen, Suraj Baloda, *et al.,* 2001, Antimicrobial resistance among *Pseudomonas spp*. and the *Bacillus cereus* group isolated from Danish agricultural soil. *Environment International*, *26(7-8),* pp 581-587.

Kendy K.Y. Wong, and Robert E.W. Hancock, 2000, Insertion mutagenesis and membrane topology model of the *Pseudomonas aeruginosa* outer membrane protein OprM. *Journal of Bacteriology, 182(9),* pp 2402-2410.

Anne E. Clatworthy, Emily Pierson, *et al.,* 2007, Targeting virulence: A new paradigm for antimicrobial therapy. *Nature Chemical Biology, 3(9),* pp 541-548.

I.L. Finar, 1986, Chemotherapy in: Organic Chemistry, vol 2: Stereochemistry and the Chemistry of Natural Product, 5th edition, Longman Group Limited, Longman House, England, pp 861-880.

Harriet M. Lamb, Douglas Ormrod, *et al.,* 2002, Ceftriaxone: An update of its use in the management of community-acquired and nosocomial infections. *Drugs, 62(7),* pp 1041-1089.

Hossein Eshghi, Mohammad Rahimizadeh, *et al.,* 2011, Synthesis and antimicrobial activity of some new macrocyclic *bis*-sulphonamide and disulphides. *European Journal of Chemistry, 2(1),* pp 47-50.

Kumar Santosh, M.S. Niranjan, *et al.,* 2010, Synthesis and antimicrobial study of some schiff bases of sulphonamides. *Journal of Current Pharmaceutical Research, 1,* pp 39-42.

Juan Gao, and Joel A. Pedersen, 2009, Sorption of sulphonamide antimicrobial agents to humic acid-clay complexes. *Journal of Environmental Quality, 39(1),* pp 228-235.

Claudiu T. Supuran, A. Casini, *et al.,* 2003, Protease inhibitors of the sulphonamide type: Anticancer, anti-inflammatory, and antiviral agents. *Medicinal Research Review, 23(5),* pp 535-558.

Andrea Scozzafava, Takashi Owa, *et al.,* 2003, Anticancer and antiviral sulphonamide. *Current Medicinal Chemistry, 10,* pp 925-953.

Hossein Behmadi, Seyed M. Saadatia, *et al.,* 2009, Synthesis of new disulphonamides from different substituted diamino pyridines. *Eclética Química, 34(3),* pp 27-31.

Corwin Hansch, Peter G. Sammes, *et al.,* 1990, *Comprehensive Medicinal Chemistry*, Pergamon Press, Oxford, Vol. 2, Chapter 7.1, p. 212.

Ioanna P. Korbila, Katerina G. Manta, *et al.,* 2009, Penicillins vs trimethoprim-based regimens for acute bacterial exacerbations of chronic bronchitis meta-analysis of randomized controlled trials. *Canadian Family Physician, 55(1),* pp 60-67.

Walter T. Hughes, Wayne M. Dankner, *et al.,* 2005, Comparison of atovaquone and azithromycin with trimethoprim-sulphamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clinical Infectious Diseases, 40(1),* pp 136-145.

Neslihan Özbek, Hikmet Katircioğlu, *et al.,* 2007, Synthesis, characterization and antimicrobial activity of new aliphatic sulphonamide. *Bioorganic and Medicinal Chemistry, 15,* pp 5105-5109.

Onisillos Sekkides, 2010, Infectious disease surveillance update. *The Lancet 10(9),* p 589.

Timothy L Friesen, Eva H. Stukenbrock, *et al.,* 2006, Emergence of a new disease as a result of interspecific virulence gene transfer. *Nature Genetics, 38(8),* pp 953-956.

Gideon, 2008, Emergence of infectious diseases in the 21st century. Accessed online on 5th May, 2010 at: http://www.gideononline.com/2008/03/05/emergence-of-infectious-diseases-in-the-21st-century/

Jan Bornholdt, Karianne W. Fjære, *et al.,* 2009, Heterocyclic pentafluorophenyl sulphonate esters as shelf stable alternatives to sulphonyl chlorides. *Tetrahedron, 65,* pp 9280-9284.

Takashi Owa, Hiroshi Yoshino, *et al.,* 2002, Synthesis and biological evaluation of *N*-(7-indolyl) -3-pyridinesulphonamide derivatives as potent antitumor agents. *Bioorganic and Medicinal Chemistry Letters, 12(16),* pp 2097-2100.

Amita Jain, Jyotsna Agarwal, *et al.,* 2004, Prevelance of methicillin-resistant, coagulase-neagative staphylococci in neonatal intensive care units; finding from a tertiary care hospital in India. *Journal of Medical Microbiology, 53(9),* pp 941-944.

Ariane Knauer, Petra Fladerer, *et al.,* 2004, Effect of hospitalization and antimicrobial therapy an antimicrobial resistance of colonizing Staphylococcus epidermidis. *Wien Klin Wochenschr, 116(14),* pp 489-494.

Shi-Ying Huang, Ren-Bin Tang, *et al.,* 2003, Coagulase-negative staphylococcal bacteremia in critically ill children: risk factors and antimicrobial susceptibility. *Journal of Microbiology and Immunological Infections, 36(1),* pp 51-56.

CHAPTER THREE

MATERIALS AND METHODS

3.1. General Conditions

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6, unless otherwise stated, on NMR Bruker DPX 400 spectrometer operating at 400 MHz and 100 MHz respectively. TMS was used as internal standard with the deuterium signal of the solvent as the lock and chemical shifts δ recorded in ppm. The melting points were determined on X-4 Digital Microscopic melting point apparatus manufactured by Beijing Technical Instrument Co. Ltd. and were uncorrected. IR spectra were run on Varian Excalibur HE 3100 FT-IR Spectrometer while the Mass Spectra were obtained using Waters GCT Premier Spectrometer. The elemental analysis (C, H, N) of the compounds were performed at the Institute of Chemistry, Chinese Academy of Sciences, Beijing, using Flash EA 1112 Elemental Analyzer. Lyophilization was carried out with the FD-1 Freeze Drier while the concentration and removal of solvents was achieved with the RE-2000B Rotary Evaporator.

In addition, the pH was monitored and confirmed during acidification with a Portable pH Meter Model PHB4. All drying were conducted at reduced pressure with DHG-9023A Vacuum Oven. The reaction progress was monitored with TLC using $CHCl_3/CH_3OH$ solvent system; developed plates were visualized under UV lamp where necessary and the retention factor (R_f) values were duly calculated. Column chromatographic purifications were carried out on Merck silica gel F (Mesh 200-300). Organic solutions were dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated with a Buchi rotary evaporator at reduced pressure. At all stage of the experiments, the

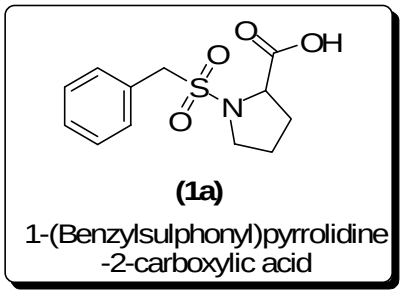
synthetic protocols were effected in bone dried solvents under nitrogen atmosphere in dried glassware which were flushed with stream flow of nitrogen gas prior to use and thionyl chloride ($SOCl_2$) was freshly distilled prior to use. *p*-Toluenesulphonyl chloride (*p*-TsCl) was purified by recrystallization from chloroform/pet ether before use while other reagents were used directly after ascertaining the purity condition. All the amino acids used as well as anthranilic acid, *n*-butyllithium (2.2M in hexane), carbon tetrachloride and potassium phthalate were obtained from Aladdin Chemical Co. Ltd., Shanghai. The benzenesulphonyl chloride and *p*-toluenesulphonyl chloride were supplied by Huaxueshiji China while oxalyl chloride and α–toluenesulphonyl chloride were obtained from Zur Synthese and Alfa Aesar Chemicals respectively. All other chemicals were obtained from Beijing Chemical Works, China.

3.2. General Procedure for Synthesis of α-Toluenesulphonamides (1a-k)

Sodium caebonate (Na_2CO_3) (1.113 g, 10.5 mmol) was added to a solution of the amino acid (5 mmol) in H_2O (6 mL) with continuous stirring until all the solutes had dissolved. The clear solution was cooled to -10 ^oC and α-toluenesulphonyl chloride (α-TsCl) (1.144 g, 6 mmol) was added in three batches over a period of 1 h. It was warmed up to 0 ^oC and stirred at the same temperature for 1 h. Finally, the reacting mixture was then warmed up to room temperature and allowed to stir for 48 h. The reaction mixture was transferred into a separatory funnel where the excess of α-TsCl was removed by extraction with DCM. The aqueous layer was then worked up by addition of 2M HCl until pH 2.2 was attained. The clear liquid was then lyophilized at -52 ^oC under reduced pressure (1pa, 0.00750 mmHg) for 12 h to obtain the crude solid product which was

purified by column chromatography ($CHCl_3/CH_3OH$, 3:1) to afford α-toluenesulphonamides **(1a-k)** in excellent yields (87.7 - 98.8%).

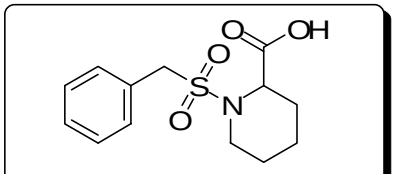
3.2.1. 1-(Benzylsulphonyl)pyrrolidine-2-carboxylic acid (1a). The amino acid was L-proline; yield 1.24 g (92.0%); mp 161 ^oC; R_f = 0.84 ($CHCl_3/CH_3OH$, 3:1, at RT). ^1H-NMR (D_2O) δ: 7.47 (s, 5H, Ar-H), 4.46-4.43 (dd, J_1 = 7.20 Hz, J_2 = 15.76 Hz, 1H, HOOC-CH-CH_2(a,b)), 4.24 (s, 2H, CH_2-SO_2), 3.48-3.45 (t, J = 7.28 Hz, 2H, N-CH_2-CH_2), 2.46-2.45 (m, 1H, CHa of CH_2), 2.22-2.21 (m, 1H, CHb of CH_2), 2.15-2.09 (quintet, J = 6.80 Hz, 2H, CH_2-CH_2-CH_2(a,b)) ppm. ^{13}C-NMR (Dioxane) δ: 173.1 (CO), 132.6, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 60.6, 57.7, 47.1, 29.2, 24.3 ppm. IR (KBr) cm^{-1}: 3441 (OH of acid), 2980 (CH aromatic), 2828 (CH aliphatic), 1728 (C=O of COOH), 1620 (C=C), 1219, 1151 (SO_2 two bands), 700 (Ar-H). MS: in m/z [rel. %]: 270.1 [MH^+, 6.5%], 269.1 [M^+, 9%], 179.1 [18.4%], 178.1 [M^+ - $PhCH_2^{\cdot}$, 100%], 176.1 [32.4%], 122.0 [49%], 105.0 [32%]. Anal. calcd. for $C_{12}H_{15}NO_4S$ (269.32): C, 53.52; H, 5.61; N, 5.20. Found: C, 53.77; H, 5.49; N, 5.34.



(1a)
1-(Benzylsulphonyl)pyrrolidine
-2-carboxylic acid

3.2.2. 1-(Benzylsulphonyl)piperidine-2-carboxylic acid (1b). The amino acid was pipecolic acid; yield 1.38 g (98.0%); mp 248 ^oC (dec); R_f = 0.87 ($CHCl_3/CH_3OH$, 3:1, at RT). ^1H-NMR (D_2O) δ: 7.52 (s, 5H, Ar-H), 4.28 (s, 2H, CH_2-SO_2), 4.08-4.03 (dd, J_1 = 3.44 Hz, J_2 = 15.12 Hz, 1H, HOOC-CH-CH_2), 3.57-3.53 (m, 1H, CHa of CH_2-N), 3.16-3.10 (m, 1H, CHb of CH_2-N), 2.40-2.36 (m, 1H, CH), 2.01-1.92 (m, 2H, 2 × CH), 1.81-

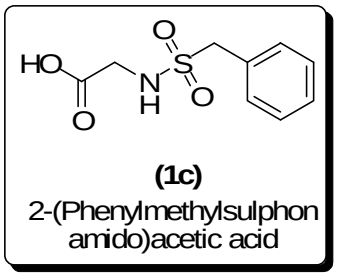
1.68 (m, 3H, CH & CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 172.5 (CO), 132.5, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 57.7, 57.6, 44.8, 26.5, 22.1 (2 × CH_2) ppm. IR (KBr) cm^{-1}: 3422 (OH of acid), 2974 (CH aromatic), 2822 (CH aliphatic), 1736 (C=O of COOH), 1603 (C=C), 1238, 1159 (SO_2 two bands), 700 (Ar-H). MS: in m/z [rel. %]: 269.1 [M^+ - $CH_2^{\cdot}$, 3.2%], 180.1 [55%], 179.1 [65%], 178.1 [M^+ - $PhCH_2$, 100%], 165.1 [30%], 121.0 [42%], 77.0 [Ph^+, 13%], 64.0 [SO_2^+, 31.7%]. Anal. calcd. for $C_{13}H_{17}NO_4S$ (283.35): C, 55.11; H, 6.05; N, 4.94. Found: C, 55.29; H, 5.94; N, 4.86.



(1b)

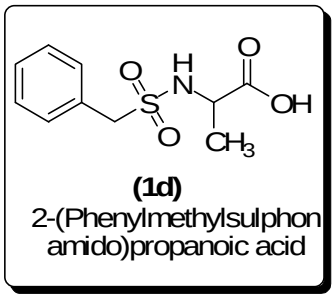
1-(Benzylsulphonyl)piperidine -2-carboxylic acid

3.2.3. 2-(Phenylmethylsulphonamido)acetic acid (1c). The amino acid was glycine; yield 1.08 g (94.0%); mp 142-143 ^oC; R_f = 0.51 ($CHCl_3$/CH_3OH, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.45 (s, 5H, Ar-H), 4.19 (s, 2H, $\underline{CH_2}$-SO_2), 3.76 (s, 2H, $\underline{CH_2}$-COOH) ppm. ^{13}C-NMR (Dioxane) δ: 170.6 (CO), 132.7, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 57.7, 40.8 ppm. IR (KBr) cm^{-1}: 3433 (OH of acid), 3030 (N-H), 2990 (CH aromatic), 2832 (CH aliphatic), 1736 (C=O of COOH), 1616 (C=C), 1215, 1171 (SO_2 two bands), 702 (Ar-H). MS: in m/z [rel. %]: 212.1 [M^+ - OH, 7.9%], 180.1 [73%], 179.1 [88%], 178.1 [M^+ - $PhCH_2$, 100%], 91.1 [$PhCH_2^+$, 48%], 64 [26%] 45 [$^+$COOH, 2.4%]. Anal. calcd. for $C_9H_{11}NO_4S$ (229.26): C, 47.15; H, 4.84; N, 6.11. Found: C, 46.90; H, 5.01; N, 5.97.



(1c)
2-(Phenylmethylsulphonamido)acetic acid

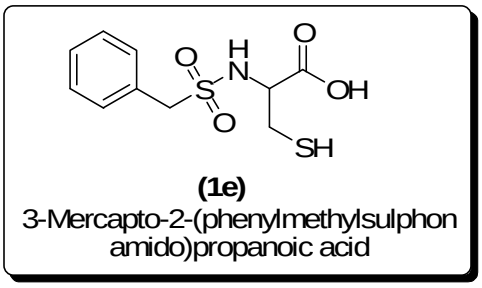
3.2.4. 2-(Phenylmethylsulphonamido)propanoic acid (1d). The amino acid was alanine; yield 1.18 g (97.0%); mp 220-224 ^{o}C; R_f = 0.81 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.47 (s, 5H, Ar-H), 4.22 (s, 2H, $\underline{CH_2}$-SO_2), 4.14-4.08 (q, J = 7.28 Hz, 1H, $\underline{CH}$-CH_3), 1.60-1.58 (d, J = 7.28 Hz, 3H, $\underline{CH_3}$-CH) ppm. ^{13}C-NMR (Dioxane) δ: 176.8 (CO), 131.0, 130.6 (2 × CH aromatic), 129.3 (2 × CH aromatic), 129.1, 60.4, 52.1, 19.6 ppm. IR (KBr) cm^{-1}: 3424 (OH of acid), 2974 (CH aromatic), 2822 (CH aliphatic), 1751 (C=O of COOH), 1599 (C=C), 1213, 1169 (SO_2 two bands), 698 (Ar-H). MS: in m/z [rel. %]: 212.1 [22%], 180.1 [81.5%], 179.1 [91%], 178.1 [85%], 165.1 [M^+ – $PhCH_3$, 55%], 122.0 [80%], 121.0 [100%], 77.0 [Ph^+, 71.4%], 64.0 [SO_2^+, 54.6%], 51.0 [28%]. Anal. calcd. for $C_{10}H_{13}NO_4S$ (243.28): C, 49.37; H, 5.39; N, 5.76. Found: C, 49.29; H, 5.28; N, 5.94.



(1d)
2-(Phenylmethylsulphonamido)propanoic acid

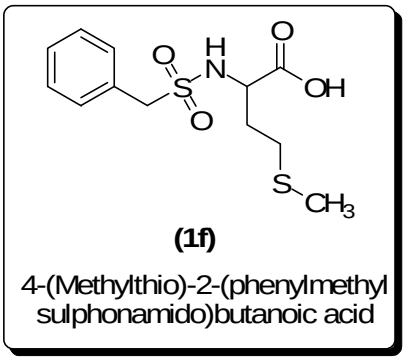
3.2.5. 3-Mercapto-2-(phenylmethylsulphonamido)propanoic acid (1e). The amino acid was cysteine; yield 1.22 g (89.0%); mp 183-186 ^{o}C; R_f = 0.49 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.49 (s, 5H, Ar-H), 4.50-4.47 (dd, J_1 = 4.24 Hz, J_2 = 7.92 Hz,

1H, CH_2-<u>CH</u>-COOH), 4.24 (s, 2H, <u>CH_2</u>-SO_2), 3.55-3.50 (dd, J_1 = 4.24 Hz, J_2 = 20.00 Hz, 1H, CHa of <u>CH_2</u>-CH), 3.39-3.33 (dd, J_1 = 7.92 Hz, J_2 = 20 Hz, 1H, CHb of <u>CH_2</u>-CH) ppm. ^{13}C-NMR (Dioxane) δ: 171.5 (CO), 132.6, 131.3 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.7, 57.8, 52.7, 37.2 ppm. IR (KBr) cm^{-1}: 3439 (OH of acid), 2978 (CH aromatic), 2832 (CH aliphatic), 1728 (C=O of COOH), 1618 (C=C), 1207, 1159 (SO_2 two bands), 810 (Ar-H). MS: in m/z [rel. %]: 214.1 [31.7%], 123.0 [100%], 122.0 [90%], 92.1 [$PhCH_3^+$, 33%], 91.0 [$PhCH_2^+$, 88%], 77.0 [Ph^+, 8%], 65.0 [HSO_2^+, 34%], 45.0 [$^+$COOH, 28%], 36.0 [34%]. Anal. calcd. for $C_{10}H_{13}NO_4S_2$ (275.35): C, 43.62; H, 4.76; N, 5.09. Found: C, 43.45; H, 4.94; N, 5.07.



(1e)
3-Mercapto-2-(phenylmethylsulphon amido)propanoic acid

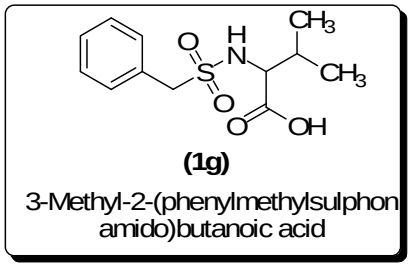
3.2.6. 4-(Methylthio)-2-(phenylmethylsulphonamido)butanoic acid (1f). The amino acid was methionine; yield 1.33 g (87.7%); mp 138-140 ^oC; R_f = 0.68 ($CHCl_3$/CH_3OH, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.47 (s, 5H, Ar-H), 4.23 (s, 2H, <u>CH_2</u>-SO_2), 4.01-3.97 (t, J = 8.84 Hz, 1H, <u>CH</u>-CH_2), 2.76-2.72 (t, J = 7.40 Hz, 2H, CH_2-<u>CH_2</u>-S), 2.33-2.29 (m, 1H, CH), 2.28-2.21 (m, 1H, CH), 2.19 (s, 3H, <u>CH_3</u>-S) ppm. ^{13}C-NMR (Dioxane) δ: 172.9 (CO), 132.6, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.7, 57.9, 52.8, 29.8, 29.4, 14.7 ppm. IR (KBr) cm^{-1}: 3442 (OH of acid), 2974 (CH aromatic), 2833 (CH aliphatic), 2774 (CH aliphatic), 1742 (C=O of COOH), 1590 (C=C), 1211, 1161 (SO_2 two bands), 698 (Ar-H). Anal. calcd. for $C_{12}H_{17}NO_4S_2$ (303.40): C, 47.51; H, 5.65; N, 4.62. Found: C, 47.49; H, 5.64; N, 4.66.



(1f)

4-(Methylthio)-2-(phenylmethyl sulphonamido)butanoic acid

3.2.7. 3-Methyl-2-(phenylmethylsulphonamido)butanoic acid (1g). The amino acid was valine; yield 1.34 g (98.7%); mp 197-200 ^{o}C; R_f = 0.83 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.49 (s, 5H, Ar-H), 4.25 (s, 2H, $\underline{CH_2}$-SO_2), 4.04-4.03 (d, *J* = 4.40 Hz, 1H, CH-$\underline{CH}$-COOH), 2.47-2.38 (m, 1H, CH-$\underline{CH}$-$(CH_3)_2$), 1.15-1.13 (d, *J* = 7.04 Hz, 3H, $\underline{CH_3}$-CH), 1.13-1.11 (d, *J* = 7.08 Hz, 3H, $\underline{CH_3}$-CH) ppm. ^{13}C-NMR (Dioxane) δ: 172.4 (CO), 132.5, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 59.2, 57.7, 29.8, 18.1, 17.8 ppm. IR (KBr) cm^{-1}: 3447 (OH of acid), 2974 (CH aromatic), 2833 (CH aliphatic), 2783 (CH aliphatic), 1730 (C=O of COOH), 1618 (C=C), 1225, 1165 (SO_2 two bands), 700 (Ar-H). MS: in m/z [rel. %]: 271.1 [M^+, 14%], 91.0 [$PhCH_2^+$, 30%], 75.0 [65%], 72.1 [100%], 55.0 [79%], 29.0 [50%]. Anal. calcd. for $C_{12}H_{17}NO_4S$ (271.34): C, 53.12; H, 6.32; N, 5.16. Found: C, 53.31; H, 6.50; N, 5.20.

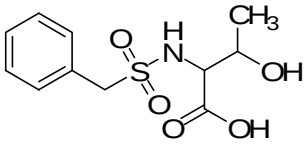


(1g)

3-Methyl-2-(phenylmethylsulphon amido)butanoic acid

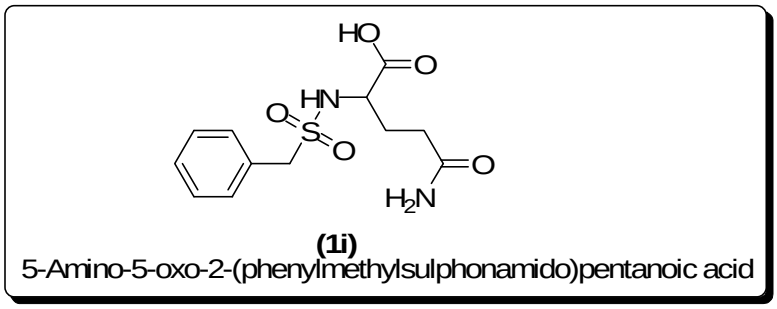
3.2.8. 3-Hydroxy-2-(phenylmethylsulphonamido)butanoic acid (1h). The amino acid was threonine; yield 1.25 g (91.5%); mp 194-195 ^{o}C; R_f = 0.48 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.49 (s, 5H, Ar-H), 4.48-4.46 (m, 1H, CH), 4.24 (s, 2H, $\underline{CH_2}$-

SO_2), 4.05-4.04 (d, J = 4.40 Hz, 1H, CH-<u>CH</u>-COOH), 1.42-1.41 (d, J = 6.64 Hz, 3H, <u>CH_3</u>-CH) ppm. ^{13}C-NMR (Dioxane) δ: 171.5 (CO), 132.5, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 66.1, 59.4, 57.7, 19.8 ppm. IR (KBr) cm^{-1}: 3404 (OH of acid), 2976 (CH aromatic), 2824 (CH aliphatic), 1740 (C=O of COOH), 1601 (C=C), 1219, 1157 (SO_2 two bands), 700 (Ar-H). Anal. calcd. for $C_{11}H_{15}NO_5S$ (273.31): C, 48.34; H, 5.53; N, 5.12. Found: C, 48.29; H, 5.61; N, 4.98.



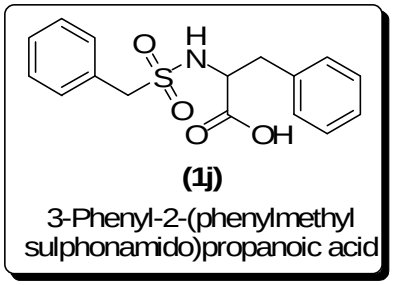
(1h)
3-Hydroxy-2-(phenylmethylsulphonamido)butanoic acid

3.2.9. 5-Amino-5-oxo-2-(phenylmethylsulphonamido)pentanoic acid (1i). The amino acid was glutamine; yield 1.41 g (94.1%); mp 211-214 ^{o}C; R_f = 0.38 ($CHCl_3$/CH_3OH, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.48 (s, 5H, Ar-H), 4.47-4.43 (dd, J_1 = 5.04 Hz, J_2 = 14.32 Hz, 1H, HOOC-<u>CH</u>-CH_2), 4.23 (s, 2H, <u>CH_2</u>-SO_2), 2.62-2.55 (m, 1H, CH), 2.49-2.44 (dd, J_1 = 9.20 Hz, J_2 = 18.72 Hz, 2H, CH_2-<u>CH_2</u>-CON), 2.27-2.20 (m, 1H, CH) ppm. ^{13}C-NMR (Dioxane) δ: 181.1 (CO of acid), 163.2 (CO of amide), 132.5, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 59.2, 57.7, 30.5, 26.2 ppm. IR (KBr) cm^{-1}: 3246 (OH of acid), 3075, 3053 (NH two bands), 2983 (CH aromatic), 2951 (CH aliphatic), 1703 (C=O of COOH), 1659 (C=O amide), 1412 (OH bending in-plane), 1221, 1193 (SO_2 two bands), 696 (Ar-H), 631 (N-H bending with wagging). Anal. calcd. for $C_{12}H_{16}N_2O_5S$ (300.34): C, 47.99; H, 5.37; N, 9.33. Found: C, 48.03; H, 5.56; N, 9.41.



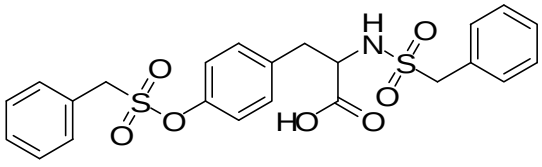
(1i)
5-Amino-5-oxo-2-(phenylmethylsulphonamido)pentanoic acid

3.2.10. 3-Phenyl-2-(phenylmethylsulphonamido)propanoic acid (1j). The amino acid was phenylalanine; yield 1.58 g (98.8%); mp 218 ^{o}C (dec); R_f = 0.84 ($CHCl_3$/CH_3OH, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.46 (s, 10H, 2 × Ar-H), 4.34-4.31 (dd, J_1 = 5.60 Hz, J_2 = 13.28 Hz, 1H, $PhCH_2$-CH-COOH), 4.22 (s, 2H, CH_2-SO_2), 3.41-3.36 (dd, J_1 = 5.60 Hz, J_2 = 20.00 Hz, CHa of CH_2-Ph), 3.28-3.22 (dd, J_1 = 7.60 Hz, J_2 = 20.00 Hz, 1H, CHb of CH_2-Ph) ppm. ^{13}C-NMR (Dioxane) δ: 172.3 (CO of acid), 134.8, 132.6, 131.2 (2 × CH aromatic), 130.3 (2 × CH aromatic), 130.1 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9 (2 × CH aromatic), 57.7, 55.0, 36.4 ppm. IR (KBr) cm^{-1}: 3441 (OH of acid), 2974 (NH), 2822 (CH aromatic), 2776 (CH aliphatic), 1740 (C=O of COOH), 1609 (C=C), 1221, 1171 (SO_2 two bands), 702 (Ar-H), 623 (N-H bending). MS: in m/z [rel. %]: 270.1 [4%], 212.1 [12%], 180.1 [90%], 179.1 [95%], 178.1 [100%], 165.1 [60%], 122.0 [34%], 121.0 [67%], 64 [SO_2^+, 70%]. Anal. calcd. for $C_{16}H_{17}NO_4S$ (319.38): C, 60.17; H, 5.37; N, 4.39. Found: C, 59.98; H, 5.21; N, 4.42.



(1j)
3-Phenyl-2-(phenylmethyl sulphonamido)propanoic acid

3.2.11. 3-(4-(Benzylsulphonyloxy)phenyl)-2-(phenylmethylsulphonamido)propanoic acid (1k). The amino acid was tyrosine; yield 2.19 g (89.6%); mp 258-260 ^{o}C; R_f = 0.82 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.43 (s, 10H, 2 × Ar-H), 7.22-7.20 (d, *J* = 8.40 Hz, 2H, OTs-H), 6.93-6.91 (d, *J* = 8.40 Hz, 2H, OTs-H), 4.31-4.28 (dd, J_1 = 5.60 Hz, J_2 = 13.08 Hz, 1H, $PhCH_2$-CH-COOH), 4.19 (s, 4H, 2 × CH_2-SO_2), 3.31-3.26 (dd, J_1 = 5.60 Hz, J_2 = 20.00 Hz, CHa of CH_2-Ph), 3.19-3.14 (dd, J_1 7.52 Hz, J_2 = 20.00 Hz, 1H, CHb of CH_2-Ph) ppm. ^{13}C-NMR (Dioxane) δ: 172.8 (CO of acid), 156.5, 140.9, 132.0, 131.8 (2CH aromatic), 131.3 (2 × CH aromatic), 129.6 (2 × CH aromatic), 129.0 (2 × CH aromatic), 126.6, 123.6 (2 × CH aromatic), 117.1 (2 × CH aromatic), 111.8 (2 × CH aromatic), 58.4, 55.4, 36.1 ppm. IR (KBr) cm^{-1}: 3435 (OH of acid), 3167 (NH), 3028 (CH aromatic), 2949 (CH aliphatic), 1724 (C=O of COOH), 1597 (C=C), 1194, 1148 (SO_2 two bands), 789 (S-OR ester), 694 (Ar-H), 631 (N-H bending). MS: in m/z [rel. %]: 180.1 [74%], 179.1 [90%], 178.1 [100%], 165.1 [30%], 122.0 [10%], 91.1 [$PhCH_2^+$, 47%], 64 [SO_2^+, 24%]. Anal. calcd. for $C_{23}H_{23}NO_7S_2$ (489.57): C, 56.43; H, 4.76; N, 2.86. Found: C, 56.38; H, 4.79; N, 2.69.



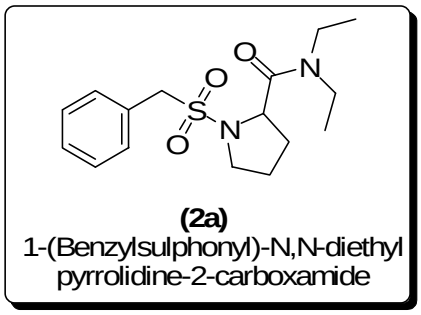
(1k)
3-(4-(benzylsulphonyloxy)phenyl)-2-(phenylmethyl sulphonamido)propanoic acid

3.3. General Procedure for *N,N*-Diethylalkanamide of α-Toluenesulphonamide (2a-k)

Oxalyl chloride (0.34 mL, 3.85 mmol, 1.30 equiv.) was added via dropping pipette to a solution of α-toluenesulphonamides **1a-k** (2.96 mmol) in H_2O (10 mL) in a streaming

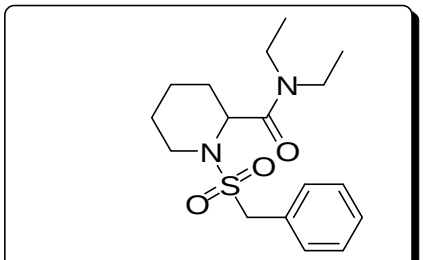
flow of nitrogen gas, followed by addition of 1 drop of DMF. The resulting mixture was stirred at room temperature for 2 h to obtain the crude acid chloride which was kept air-tighted prior to use. In a separate 250 mL three-necked round bottom flask, equipped with a magnetic stirring bar, was added Na_2CO_3 (0.628 g, 5.92 mmol, 2 equiv.) and H_2O (10 mL) followed by diethyl amine DEA (0.4 mL, 3.85 mmol, 1.3 equiv.) in continuous stirring and cooled to -15 ^oC. Then, earlier kept acid chloride was added in such a way to maintain the internal temperature of the reaction mixture at around -10 ^oC. The reacting mixture was then stirred at -10 ^oC for 1 h; at 0 ^oC for 1 h and finally at room temperature for 1 h. The reaction was terminated, worked up by acidifying with 2M HCl and concentrated in rotary evaporator. The clear solution obtained was freeze-dried to obtain the crude solid product which was purified by column chromatography ($CHCl_3$ / CH_3OH, 3:1) to afford *N,N*-diethylalkanamide of α-toluenesulphonamide derivatives **(2a-k)**.

3.3.1. 1-(Benzylsulphonyl)-*N,N*-diethylpyrrolidine-2-carboxamide (2a). Yield 0.94 g (97.9%); mp 185-187 ^oC; R_f = 0.71 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.53 (s, 5H, Ar-H), 4.54-4.50 (m, 1H, <u>CH</u>-CON), 4.28 (s, 2H, <u>CH_2</u>-SO_2), 3.56-3.54 (m, 2H, CH_2-N), 3.19-3.14 (q, *J* = 7.28 Hz, 4H, 2 × <u>CH_2</u>-CH_3), 2.54-2.51 (m, 1H, CH), 2.28-2.24 (m, 1H, CH), 2.16-2.14 (m, 2H, CH_2), 1.39-1.35 (t, *J* = 7.28 Hz, 6H, 2 × <u>CH_3</u>-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 173.2 (C=O), 132.6, 131.1 (2 × CH aromatic), 129.4 (2 × CH aromatic), 128.8, 60.8, 57.7, 47.1, 43.3 (2 × CH_2), 29.2, 24.2, 11.4 (2 × CH_3) ppm. Anal. calcd. for $C_{16}H_{24}N_2O_3S$ (324.45): C, 59.23; H, 7.46; N, 8.63. Found: C, 59.09; H, 7.46; N, 8.48.



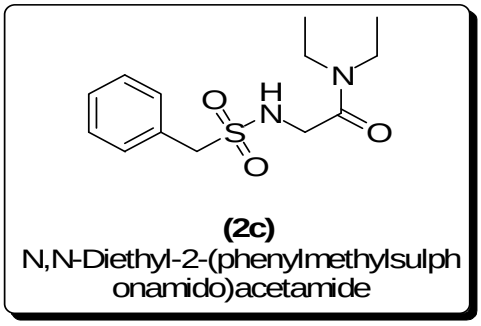
(2a)
1-(Benzylsulphonyl)-N,N-diethyl pyrrolidine-2-carboxamide

3.3.2. 1-(Benzylsulphonyl)-*N,N*-diethylpiperidine-2-carboxamide (2b). Yield 0.99 g (99.0%); mp 210-211 ^{o}C; R_f = 0.72 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.54 (s, 5H, Ar-H), 4.30 (s, 2H, $\underline{CH_2}$-SO_2), 4.08-4.04 (dd, J_1 = 3.52 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2-N), 3.60-3.57 (m, 1H, $\underline{CH}$-CON), 3.21-3.16 (q, J = 7.20 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 2.42-2.38 (dd, J_1 = 3.32 Hz, J_2 = 20.00 Hz, 1H, CH of CH_2-N), 2.03-1.99 (m, 2H, CH_2), 1.86-1.73 (m, 3H, CH & CH_2), 1.40-1.37 (t, J = 7.20 Hz, 6H, 2 × $\underline{CH_3}$-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 173.5 (C=O), 132.9, 131.1 (2 × CH aromatic), 129.8 (2 × CH aromatic), 128.6, 60.6, 57.8, 47.4, 43.4 (CH_2), 29.4, 24.2, 18.1, 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 3028 (CH aromatic), 2951 (CH aliphatic), 1720 (C=O), 1593 (C=C), 1188, 1148 (SO_2 two bands), 696 (Ar-H). Anal. calcd. for $C_{17}H_{26}N_2O_3S$ (338.47): C, 60.33; H, 7.74; N, 8.28. Found: C, 60.29; H, 6.94; N, 7.98.



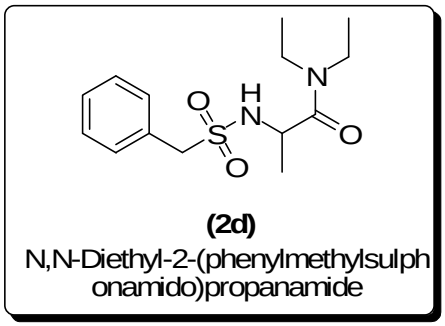
(2b)
1-(Benzylsulphonyl)-N,N-diethylpiperidine-2-carboxamide

3.3.3. *N,N*-Diethyl-2-(phenylmethylsulphonamido)acetamide (2c). Yield 0.78 g (92.6%); mp 213-215 ^{o}C; R_f = 0.51 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.53 (s, 5H, Ar-H), 4.29 (s, 2H, $\underline{CH_2}$-SO_2), 4.01 (s, 2H, $\underline{CH_2}$-CON), 3.20-3.14 (q, *J* = 7.30 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 1.39-1.36 (t, *J* = 7.30 Hz, 6H, 2 × $\underline{CH_3}$-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 174.1 (C=O), 133.4, 131.6 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.6, 57.7, 49.8, 43.1 (CH_2), 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 3217 (N-H), 3036 (CH aromatic), 2947 (CH aliphatic), 1712 (C=O), 1601 (C=C), 1219, 1194, (SO_2 two bands), 694 (Ar-H). Anal. calcd. for $C_{13}H_{20}N_2O_3S$ (284.38): C, 54.91; H, 7.09; N, 9.85. Found: C, 55.13; H, 6.94; N, 10.08.



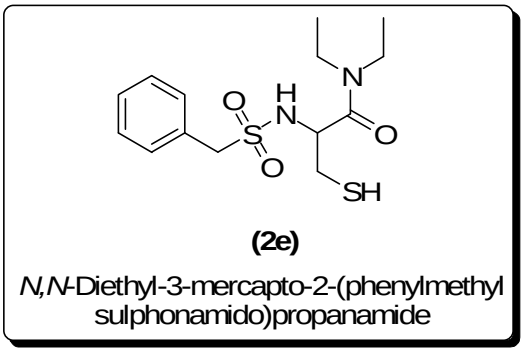
(2c)
N,N-Diethyl-2-(phenylmethylsulph onamido)acetamide

3.3.4. *N,N*-Diethyl-2-(phenylmethylsulphonamido)propanamide (2d). Yield 0.87 g (98.5%); mp 238-240 ^{o}C; R_f = 0.56 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.50 (s, 5H, Ar-H), 4.26 (s, 2H, $\underline{CH_2}$-SO_2), 4.22-4.16 (q, *J* = 7.28 Hz, 1H, $\underline{CH}$-CH_3), 3.18-3.12 (q, *J* = 7.32 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 1.65-1.63 (d, *J* = 7.28 Hz, 3H, $\underline{CH_3}$-CH), 1.37-1.33 (t, *J* = 7.32 Hz, 6H, 2 × $\underline{CH_3}$-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 173.8 (C=O), 132.7, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 57.7, 49.8, 43.1 (CH_2), 16.2, 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 3058 (N-H), 3036 (CH aromatic), 2951 (CH aliphatic), 1719 (C=O), 1601 (C=C), 1219, 1196, 1148 (SO_2 two bands), 696 (Ar-H). Anal. calcd. for $C_{14}H_{22}N_2O_3S$ (298.41): C, 56.35; H, 7.43; N, 9.39. Found: C, 56.11; H, 7.33; N, 9.28.



(2d)
N,N-Diethyl-2-(phenylmethylsulphonamido)propanamide

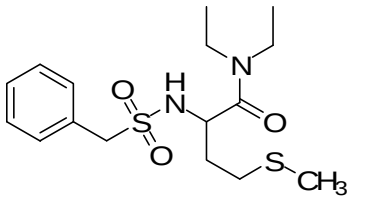
3.3.5. *N,N*-Diethyl-3-mercapto-2-(phenylmethylsulphonamido)propanamide (2e). Yield 0.87 g (89.0%); mp 198-200 ^{o}C; R_f = 0.71 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.46 (s, 5H, Ar-H), 4.54-4.51 (dd, J_1 = 4.24 Hz, J_2 = 7.92 Hz, 1H, CH_2-CH-COOH), 4.21 (s, 2H, CH_2-SO_2), 3.57-3.52 (dd, J_1 = 4.24 Hz, J_2 = 20.00 Hz, 1H, CHa of CH_2-CH), 3.41-3.36 (dd, J_1 = 7.92 Hz, J_2 = 20.00 Hz, 1H, CHb of CH_2-CH), 3.18-3.12 (q, J = 7.35 Hz, 4H, 2 × CH_2-CH_3), 1.37-1.33 (t, J = 7.35 Hz, 6H, 2 × CH_3-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 173.5 (C=O), 132.7, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 57.4, 49.5, 43.1 (CH_2), 35.5, 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 2997 (CH aromatic), 2911 (CH aliphatic), 1719 (C=O), 1591 (C=C), 1194, 1144 (SO_2 two bands), 696 (Ar-H). Anal. calcd. for $C_{14}H_{22}N_2O_3S_2$ (330.47): C, 50.88; H, 6.71; N, 8.48. Found: C, 50.71; H, 6.99; N, 7.97.



(2e)
N,N-Diethyl-3-mercapto-2-(phenylmethylsulphonamido)propanamide

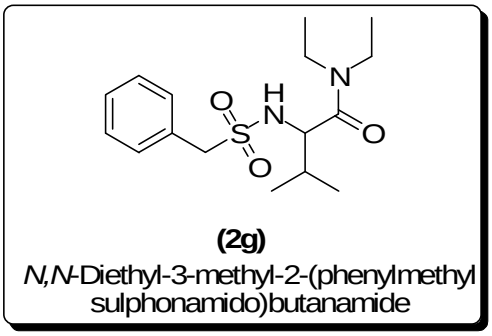
3.3.6. *N,N*-Diethyl-4-(methylthio)-2-(phenylmethylsulphonamido)butanamide (2f). Yield 0.96 g (90.6%); mp 170-172 ^{o}C; R_f = 0.65 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR

(D_2O) δ: 7.49 (s, 5H, Ar-H), 4.24 (s, 2H, $\underline{CH_2}$-SO_2), 4.23-4.20 (t, *J* = 6.72 Hz, 1H, $\underline{CH}$-CH_2), 3.16-3.10 (q, *J* = 7.32 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 2.77-2.73 (t, *J* = 7.40 Hz, 2H, S-$\underline{CH_2}$-CH_2), 2.34-2.24 (m, 2H, CH-$\underline{CH_2}$-CH_2-S), 2.19 (s, 3H, $\underline{CH_3}$-S), 1.35-1.31 (t, *J* = 7.32 Hz, 6H, 2 × $\underline{CH_3}$-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 173.8, 132.7, 131.2 (2 × CH aromatic), 129.5, (2 × CH aromatic), 57.7, 49.8, 43.1 (CH_2), 30.8, 29.5, 16.2, 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 3028 (CH aromatic), 2945 (CH aliphatic), 1722 (C=O), 1620 (C=C), 1200, 1126 (SO_2 two bands) 698 (Ar-H). Anal. calcd. for $C_{16}H_{26}N_2O_3S_2$ (358.53): C, 53.60; H, 7.31; N, 7.81. Found: C, 53.55; H, 7.22; N, 7.69.



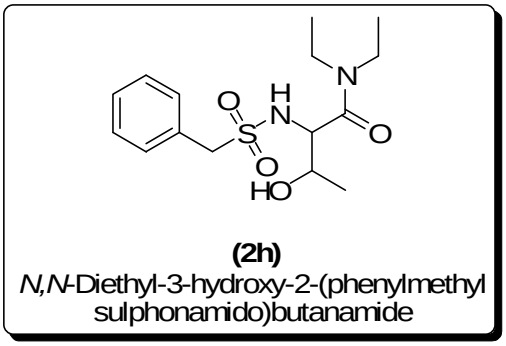
(2f)
N,N-Diethyl-4-(methylthio)-2-(phenylmethyl sulphonamido)butanamide

3.3.7. *N,N*-Diethyl-3-methyl-2-(phenylmethylsulphonamido)butanamide (2g). Yield 0.94 g (97.3%); mp 226-230 ^oC; R_f = 0.69 ($CHCl_3$/CH_3OH, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.50 (s, 5H, Ar-H), 4.25 (s, 2H, $\underline{CH_2}$-SO_2), 4.00-3.97 (d, *J* = 2.84 Hz, 1H, CH-$\underline{CH}$-CON), 3.17-3.11 (q, *J* = 7.32 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 2.45-2.38 (m, 1H, CH), 1.36-1.32 (t, *J* = 7.32 Hz, 6H, 2 × $\underline{CH_3}$-CH_2), 1.15-1.13 (d, *J* = 7.00 Hz, 3H, $\underline{CH_3}$-CH), 1.12-1.10 (d, *J* = 7.00 Hz, 3H, $\underline{CH_3}$-CH) ppm. ^{13}C-NMR (Dioxane) δ: 173.8 (C=O), 132.7, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 60.8, 57.7, 49.8, 43.1 (CH_2), 16.2, 15.5, 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 3053 (CH aromatic), 2945 (CH aliphatic), 1718 (C=O), 1611 (C=C), 1219, 1194 (SO_2 two bands), 696 (Ar-H). Anal. calcd. for $C_{16}H_{26}N_2O_3S$ (326.46): C, 58.87; H, 8.03; N, 8.58. Found: C, 59.01; H, 7.96; N, 8.61.



(2g)
N,N-Diethyl-3-methyl-2-(phenylmethyl sulphonamido)butanamide

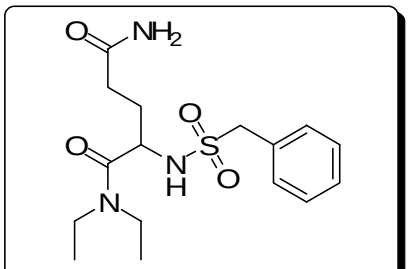
3.3.8. *N,N*-Diethyl-3-hydroxy-2-(phenylmethylsulphonamido)butanamide (2h). Yield 0.78 g (80.2%); mp 245 ^{o}C (dec); R_f = 0.53 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.55 (s, 5H, Ar-H), 4.54-4.52 (m, 1H, CH-<u>CH</u>-CH_3), 4.31 (s, 2H, <u>CH_2</u>-SO_2), 4.09-4.08 (d, *J* = 3.96 Hz, 1H, CH-<u>CH</u>-CON), 3.22-3.17 (q, *J* = 7.32 Hz, 4H, 2 × <u>CH_2</u>-CH_3), 2.85 (s, 1H, OH), 1.49-1.47 (d, *J* = 6.60 Hz, 3H, CH_3-CH), 1.41-1.37 (t, *J* = 7.32 Hz, 6H, 2 × <u>CH_3</u>-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 173.5 (C=O), 132.9, 131.3 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 61.2, 58.1, 49.5, 42.5 (CH_2), 16.6, 11.1 (CH_3) ppm. IR (KBr) cm^{-1}: 3396 (OH), 3030 (CH aromatic), 2945 (CH aliphatic), 1720 (C=O), 1601 (C=C), 1221, 1194 (SO_2 two bands), 694 (Ar-H). Anal. calcd. for $C_{15}H_{24}N_2O_4S$ (328.43): C, 54.86; H, 7.37; N, 8.53. Found: C, 54.71; H, 7.26; N, 8.65.



(2h)
N,N-Diethyl-3-hydroxy-2-(phenylmethyl sulphonamido)butanamide

3.3.9. *N^1,N^1*-Diethyl-2-(phenylmethylsulphonamido)pentanediamide (2i). Yield 0.98 g (93.2%); mp 251-253 ^{o}C; R_f = 0.58 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.51 (s, 5H, Ar-H), 4.52-4.48 (dd, J_1 = 5 Hz, J_2 = 14.32 Hz, 1H, NOC-<u>CH</u>-$CH_{2a,b}$), 4.26

(s, 2H, $\underline{CH_2}$-SO_2), 3.17-3.12 (q, J = 7.32 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 2.67-2.60 (m, 1H, CH_a of CH_2), 2.53-2.48 (t, J = 8 Hz, 2H, CO-$\underline{CH_2}$-CH_2), 2.30-2.24 (m, 1H, CH_b of CH_2), 1.37-1.33 (t, J = 7.32 Hz, 6H, 2 × $\underline{CH_3}$-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 182.7 (C=O), 177.1 (C=O), 132.6, 131.2 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9, 57.7, 53.3, 43.1 (CH_2), 30.1, 25.2, 11.4 (CH_3) ppm. IR (KBr) cm^{-1}: 3075 (NH), 3053 (CH aromatic), 2951 (CH aliphatic), 1703 (C=O), 1659 (C=O of CON), 1601 (C=C), 1221, 1193 (SO_2 two bands), 696 (Ar-H) ppm. Anal. calcd. for $C_{16}H_{25}N_3O_4S$ (355.46): C, 54.06; H, 7.09; N, 11.82. Found: C, 53.95; H, 6.88; N, 12.01.

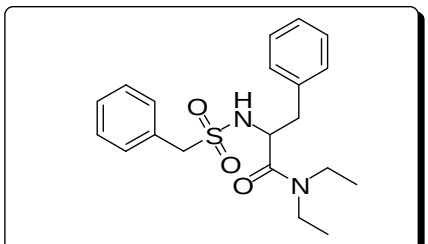


(2i)

N^1,N^1-Diethyl-2-(phenylmethyl sulphonamido)pentanediamide

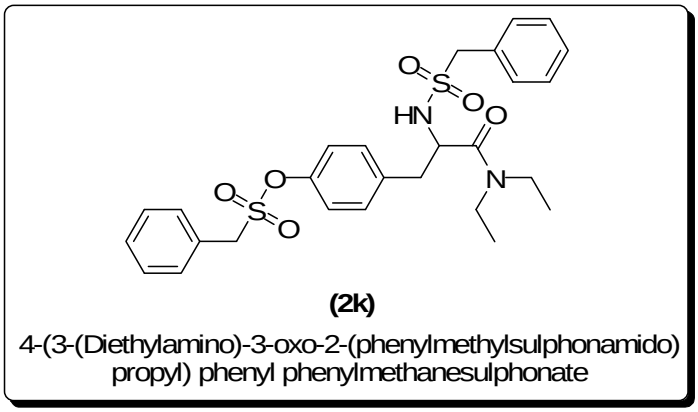
3.3.10. *N,N*-Diethyl-3-phenyl-2-(phenylmethylsulphonamido)propanamide (2j). Yield 1.00 g (90.2%); mp 227-229 ^{o}C; R_f = 0.70 ($CHCl_3$/CH_3OH, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.49 (s, 10H, 2 × Ar-H), 4.39-4.36 (dd, J_1 = 5.60 Hz, J_2 = 7.60 Hz, 1H, NOC-$\underline{CH}$-$CH_{2a,b}$), 4.24 (s, 2H, $\underline{CH_2}$-SO_2), 3.44-3.39 (dd, J_1 = 5.60 Hz, J_2 = 20.00 Hz, 1H, CH_a of $CH_{2a,b}$), 3.31-3.26 (dd, J_1 = 7.60 Hz, J_2 = 20.00 Hz, 1H, CH_b of $CH_{2a,b}$), 3.16-3.10 (q, J = 7.32 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 2.78 (s, 2H, CH_2), 1.35-1.31 (t, J = 7.32 Hz, 6H, 2 × $\underline{CH_3}$-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 172.4 (C=O), 135.1, 132.7, 131.2 (2 × CH aromatic), 130.3 (2 × CH aromatic), 130.1 (2 × CH aromatic), 129.5 (2 × CH aromatic), 128.9 (2 × CH aromatic), 57.8, 55.2, 43.1 (CH_2), 36.5, 11.5 (CH_3) ppm. IR (KBr) cm^{-1}: 2976 (NH),

2828 (CH aromatic), 2774 (CH aliphatic), 1736 (C=O), 1620 (C=C), 1206, 1153, 1148 (SO_2 two bands), 698 (Ar-H). Anal. calcd. for $C_{20}H_{26}N_2O_3S$ (374.51): C, 64.14; H, 7.00; N, 7.48. Found: C, 64.00; H, 6.84; N, 7.29.



(2j)
N,N-Diethyl-3-phenyl-2-(phenylmethyl sulphonamido)propanamide

3.3.11. 4-(3-(Diethylamino)-3-oxo-2-(phenylmethylsulphonamido)propyl)phenyl phenylmethanesulphonate (2k). Yield 1.44 g (89.3%); mp 265 ^oC (dec); R_f = 0.69 ($CHCl_3/CH_3OH$, 3:1, at RT). ^{1}H-NMR (D_2O) δ: 7.50 (s, 10H, 2 × Ar-H), 7.29-7.27 (d, J = 8.00 Hz, 2H, Ar-H), 6.99-6.97 (d, J = 8.00 Hz, 2H, Ar-H), 4.37-4.33 (dd, J_1 = 5.60 Hz, J_2 = 7.60 Hz, 1H, NOC-CH-$CH_{2a,b}$), 4.26 (s, 2H, CH_2-SO_2), 3.37-3.32 (dd, J_1 = 5.60 Hz, J_2 = 20.00 Hz, 1H, CH_a of $CH_{2a,b}$), 3.26-3.21 (dd, J_1 = 7.60 Hz, J_2 = 20.00 Hz, 1H, CH_b of $CH_{2a,b}$), 3.17-3.12 (q, J = 7.32 Hz, 4H, 2 × CH_2-CH_3), 1.37-1.33 (t, J = 7.32 Hz, 6H, 2 × CH_3-CH_2) ppm. ^{13}C-NMR (Dioxane) δ: 172.4 (C=O), 155.9, 141.3, 131.8 (2 × CH aromatic), 131.3 (2 × CH aromatic), 129.6 (2 × CH aromatic), 129.0 (2 × CH aromatic), 126.6, 123.0 (2 × CH aromatic), 116.9 (2 × CH aromatic), 111.6 (2 × CH aromatic), 57.8, 55.2, 43.2 (CH_2), 35.6, 11.6 (CH_3) ppm. IR (KBr) cm^{-1}: 3058 (NH), 3036 (CH aromatic), 2951 (CH aliphatic), 1719 (C=O), 1601 (C=C), 1219, 1196, 1148 (SO_2 two bands), 696 (Ar-H). Anal. calcd. for $C_{27}H_{32}N_2O_6S_2$ (544.69): C, 59.54; H, 5.92; N, 5.14. Found: C, 59.43; H, 5.99; N, 4.98.



(2k)

4-(3-(Diethylamino)-3-oxo-2-(phenylmethylsulphonamido) propyl) phenyl phenylmethanesulphonate

3.3.12. General Procedure for Attempted Synthesis of Benzothiazepine (3a)

Method A: A solution of 1-(benzylsulphonyl)-*N*,*N*-diethylpyrrolidine-2-carboxamide **2a** (0.324 g, 1.0 mmol) in THF (5 mL) was added to a solution of Lithium diisopropylamide (LDA) (freshly prepared from diisopropyl amine [(0.57 mL, 4 mmol) and *n*-BuLi (1.82 mL of 2.2 M, 4.0 mmol)] in THF (20 mL) at 0 ^{o}C in stream of N_2 gas. The ice bath was immediately removed, the solution was stirred at room temperature until the reaction was completed (TLC monitored for ca 1 h) and quenched with saturated aq. NH_4Cl (5 mL). The reaction mixture was evaporated to dryness, H_2O (30 mL) was added and the whole was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Since, the starting material did not dissolve throughout the reaction it was observed that the bulky of the product was in aqueous layer. Hence, the aqueous layer was worked up to obtain a solid which was not the expected benzothiazepine. However, both organic layer and aqueous layers product were not benzothiazepine according to the ^{1}H-NMR spectrum of the product which showed the same spectral data with the starting material **(2a)**.

Method B: $AlCl_3$-SiO_2 (0.0232 g, 0.12 mmol) was added to a solution of 1-(benzylsulphonyl)-*N*,*N*-diethylpyrrolidine-2-carboxamide **(2a)** (0.324 g, 1.0 mmol) in

DCM (20 mL). The reaction mixture was magnetically stirred at 80 ^{o}C until the reaction was completed 2 h. The catalyst was filtered off, washed with DCM and the filterate was concentrated on rotary evaporator to afford the solid expected to be benzothiazepine **(3a)**. Nevertheless, there was no evidence of cyclization as the product gave the same ^{1}H-NMR spectrum similar to that of the starting material **(2a).**

Preparation of SiO_2-$AlCl_3$

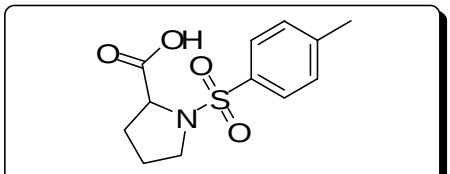
Anhydrous $AlCl_3$ (5.1 g) was added to silica gel (Merck, grade 60, 230-400, washed with 1 M HCl and dried under vacuum at 80 ^{o}C for 72 h, 10.2 g) in carbon tetrachloride (30 mL). The mixture was stirred using a magnetic stirrer under reflux conditions for 2 days under N_2 atmosphere, filtered and washed with 50 mL of dry CCl_4, and then dried under vacuum at 60 ^{o}C for 3 h according to Boroujeni (2010).

3.4. General Procedure for Synthesis of *p*-Toluenesulphonamides (4a-k)

Na_2CO_3 (2.785 g, 26.25 mmol) was added to a solution of amino acid (12.5 mmol) in H_2O (15 mL) at 0 ^{o}C followed by addition of *p*-toluenesulphonyl chloride, *p*-TsCl (2.86 g, 15 mmol) in three portions over a period of 1 h. The slurry was then warmed to room temperature and allowed to stir for 4 h. Upon completion of the reaction which was TLC monitored using $CHCl_3$/CH_3OH solvent system (9:1), the reaction mixture was acidified with 20 % concentrated aqueous HCl solution to pH 2, after which crystallization occurred and the product was obtained via suction filtration. The filtered crude product was washed with pH 2.2 buffer and dried in a vacuum oven at 60 ^{o}C for 12 h to afford *p*-toluenesulphonamides **(4a-k)** in good to excellent yields (60.5 – 99.0%).

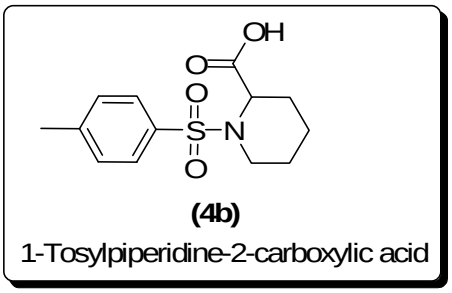
3.4.1. 1-Tosylpyrrolidine-2-carboxylic acid (4a). The amino acid was L-proline, yield 3.23 g (95.9%), mp 41-43 ^{o}C, {Literature mp 42-44 ^{o}C (Zhang *et al.*, 2005)}, R_f = 0.82

($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 7.72-7.70 (d, J = 8 Hz, 2H, Ar-H), 7.43-7.41 (d, J = 8 Hz, 2H, Ar-H), 4.08-4.05 (m, 1H, CH-COOH), 3.36-3.30 (m, 1H, CHb of CH_2-N), 3.16-3.10 (m, 1H, CHa of CH_2-N), 2.39 (s, 3H, CH_3), 1.89-1.77 (m, 3H, CH & CH_2), 1.56-1.50 (m, 1H, CH). ^{13}C-NMR (DMSO-d_6) δ: 173.2 (CO), 143.5, 134.7, 129.9, 127.2, 67.1, 60.5, 48.5, 30.5, 25.2, 24.3, 21.1. IR (KBr) cm^{-1}: 3217 (OH), 2939 (CH aromatic), 2860 (CH aliphatic), 1734 (C=O of COOH), 1601 (C=C aromatic), 1184, 1151 (SO_2 two bands), 662 (Ar-H).



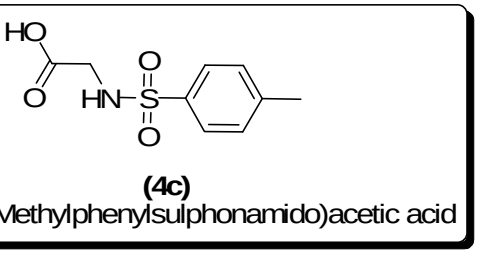
(4a)
1-tosylpyrrolidine-2-carboxylic acid

3.4.2. 1-Tosylpiperidine-2-carboxylic acid (4b). The amino acid was pipecolic acid, yield 3.36 g (95%), R_f = 0.89 ($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 7.71-7.63 (d, J = 8 Hz, 2H, Ar-H), 7.29-7.24 (d, J = 8 Hz, 2H, Ar-H), 4.74-4.73 (m, 1H, CH-COOH), 3.72-3.69 (dd, J_1 = 10.4 Hz, J_2 = 20 Hz, 1H), 3.23-3.18 (dd, J_1 = 12 Hz, J_2 = 20 Hz, 1H), 2.41 (s, 3H, CH_3), 2.18-2.15 (dd, J_1 = 3.7 Hz, J_2 = 12.7 Hz, 1H), 1.74-1.55 (m, 4H), 1.48-1.35 (m, 3H, CH_2 & CH). ^{13}C-NMR (DMSO-d_6) δ: 171.8 (CO), 142.9, 137.4, 129.6, 129.4, 126.9, 126.8, 54.6 (CH-CO), 42.1 (CH_2-N), 27.0, 23.9, 19.7 (CH_2), 21.0 (CH_3-Ph). MS: in m/z [rel. %]: 239.1 [M^+ - CO_2, 10%], 238.1 [M^+ - COOH, 74%], 220.1 [37%], 191.1 [M^+ - $PhCH_2$, 28%], 91.1 [$PhCH_2^+$, 100%]. Anal. calcd. for $C_{13}H_{17}NO_4S$ (283.35): C, 55.11; H, 6.05; N, 4.94. Found: C, 54.10; H, 6.08; N, 5.02.



(4b)
1-Tosylpiperidine-2-carboxylic acid

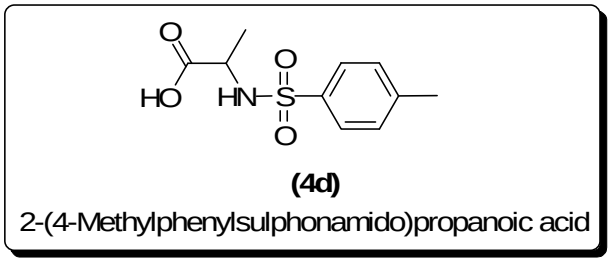
3.4.3. 2-(4-Methylphenylsulphonamido)acetic acid (4c). The amino acid was glycine, yield 2.75 g (95.8%), mp 120-122 ^{o}C, R_f = 0.47 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.63 (s-br, 1H, OH of -COOH), 7.95-7.92 (t, *J* = 6 Hz, 1H, NH-CH_2), 7.68-7.66 (d, *J* = 8 Hz, 2H, Ar-H), 7.38-7.36 (d, *J* = 8 Hz, 2H, Ar-H), 3.55-3.53 (d, *J* = 6 Hz, 2H, CH_2-NH), 2.37 (s, 3H, CH_3). IR (KBr) cm^{-1}: 3279 (N-H), 3102 (CH aromatic), 2980 (CH aliphatic), 1726 (C=O of COOH), 1595 (C=C aromatic), 1234, 1161 (SO_2 two bands), 669 (Ar-H). MS: in m/z [rel. %]: 238.1 [41%], 184.0 [55%], 155.0 [$PhCH_2SO_2^+$, 100%], 91.1 [$PhCH_2^+$, 65%], 65.0 [63%].



(4c)
2-(4-Methylphenylsulphonamido)acetic acid

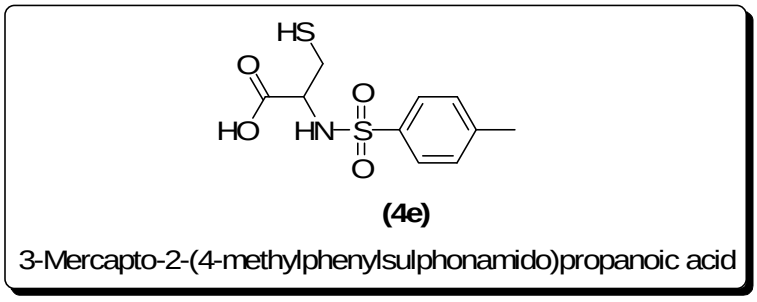
3.4.4. 2-(4-Methylphenylsulphonamido)propanoic acid (4d). The amino acid was alanine, yield 2.51 g (82.6%), mp 116-118 ^{o}C, R_f = 0.78 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 8.05-8.03 (d, *J* = 8.3 Hz, 1H, NH), 7.68-7.65 (d, *J* = 8 Hz, 2H, Ar-H), 7.37-7.35 (d, *J* = 8 Hz, 2H, Ar-H), 3.74-3.71 (m, 1H, CH), 2.37 (s, 3H, CH_3-Ph), 1.13-1.12 (d, *J* = 7.2 Hz, 3H, CH_3-CH). IR (KBr) cm^{-1}: 3277 (N-H), 3084 (OH), 2934 (CH aliphatic), 1715 (C=O of COOH), 1595 (C=C aromatic), 1233, 1150 (SO_2 two bands), 677 (Ar-H). MS: in m/z [rel. %]: 199.1 [M^+ - CO_2, 12%], 198.0 [M^+ - CO_2H,

89%], 156.0 [$CH_3PhSO_2^+$, 21%], 155.0 [$PhCH_2SO_2^+$, 97%], 91.1 [$PhCH_2^+$, 100%], 65.0 [47%], 44.1 [27%].



(4d)
2-(4-Methylphenylsulphonamido)propanoic acid

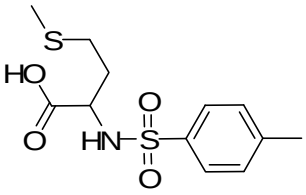
3.4.5. 3-Mercapto-2-(4-methylphenylsulphonamido)propanoic acid (4e). The amino acid was cysteine, yield 3.03 g (88.1%), mp 161-164 ^oC, R_f = 0.39 ($CHCl_3/CH_3OH$, 9:1, at RT). ^1H-NMR (DMSO-d_6) δ: 8.59-8.53 (s-br, 1H, SH), 8.29-8.27 (d, *J* = 8.4 Hz, 1H, NH-CH), 7.71-7.69 (m, 1H, CH_2-CH-NH), 7.65-7.58 (d, *J* = 8 Hz, 2H, Ar-H), 7.48-7.46 (d, *J* = 7.6 Hz, 1H, CH_b of CH_2), 7.35-7.33 (d, *J* = 8 Hz, 2H, Ar-H), 7.12-7.10 (d, *J* = 7.6 Hz, 1H, CH_a of CH_2), 2.37 (s, 3H, CH_3-Ph). IR (KBr) cm^{-1}: 3445 (N-H), 3003 (CH aromatic), 2907 (CH aliphatic), 1736 (C=O of COOH), 1596 (C=C aromatic), 1221, 1152 (SO_2 two bands), 679 (Ar-H).



(4e)
3-Mercapto-2-(4-methylphenylsulphonamido)propanoic acid

3.4.6. 2-(4-Methylphenylsulphonamido)-4-(methylthio)butanoic acid (4f). The amino acid was methionine, yield 2.62 g (69.1%), R_f = 0.80 ($CHCl_3/CH_3OH$, 9:1, at RT). ^1H-NMR ($CDCl_3$) δ: 7.75-7.73 (d, *J* = 8 Hz, 2H, Ar-H), 7.29-7.27 (d, *J* = 8 Hz, 2H, Ar-H), 4.07 (s-br, 1H, NH), 2.50-2.48 (m, 1H, CH-NH), 2.45-2.33 (m, 2H, CH_2-S), 2.40 (s, 3H, CH_3-Ph), 2.10-2.03 (m, 1H, CH of CH_2), 1.99 (s, 3H, CH_3-S), 1.94-1.87 (m, 1H, CH of

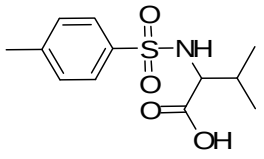
CH_2). IR (KBr) cm^{-1}: 2997 (CH aromatic), 2911 (CH aliphatic), 1726 (C=O of COOH), 1591 (C=C aromatic), 1220, 1144 (SO_2 two bands), 696 (Ar-H).



(4f)

2-(4-Methylphenylsulphonamido)-4-(methylthio)butanoic acid

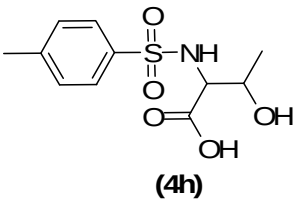
3.4.7. 3-Methyl-2-(4-methylphenylsulphonamido)butanoic acid (4g). The amino acid was valine, yield 3.21 g (94.7%), mp 125-126 ^oC, R_f = 0.81 ($CHCl_3/CH_3OH$, 9:1, at RT). ^1H-NMR ($CDCl_3$) δ: 7.73-7.71 (d, *J* = 8 Hz, 2H, Ar-H), 7.29-7.27 (d, *J* = 8 Hz, 2H, Ar-H), 5.07-5.04 (d, *J* = 9.9 Hz, 1H, NH), 3.82-3.78 (dd, J_1 = 4.6 Hz, J_2 = 9.9 Hz, 1H, CH-CH-NH), 2.41 (s, 3H, CH_3-Ph), 2.13-2.08 (m, 1H, CH), 0.97-0.96 (d, *J* = 6.8 Hz, 3H, CH_3), 0.88-0.86 (d, *J* = 6.8 Hz, 3H, CH_3). IR (KBr) cm^{-1}: 3289 (N-H), 2967 (CH aromatic), 2876 (CH aliphatic), 1711 (C=O of COOH), 1595 (C=C aromatic), 1335, 1163 (SO_2 two bands), 687 (Ar-H). MS: in m/z [rel. %]: 227.1 [M^+ - CO_2, 11%], 226.1 [M^+ - CO_2H, 100%], 155.0 [$PhCH_2SO_2^+$, 98%], 92.1 [$PhCH_3^+$, 33%], 91.1 [$PhCH_2^+$, 92%], 65.0 [48%]. Anal. calcd. for $C_{12}H_{17}NO_4S$ (271.34): C, 53.12; H, 6.32; N, 5.16. Found: C, 52.91; H, 6.33; N, 5.08.



(4g)

3-Methyl-2-(4-methylphenylsulphonamido) butanoic acid

3.4.8. 3-Hydroxy-2-(4-methylphenylsulphonamido)butanoic acid (4h). The amino acid was threonine, yield 3.22 g (94.4%), mp 90-92 ^{o}C, R_f = 0.62 ($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 7.68-7.66 (d, J = 8 Hz, 2H, Ar-H), 7.52-7.50 (d, J = 9.2 Hz, 1H, NH-CH), 7.34-7.32 (d, J = 8 Hz, 2H, Ar-H), 3.95-3.91 (m, 1H, CH), 3.64-3.61 (dd, J_1 = 3.6 Hz, J_2 = 9.2 Hz, 1H, CH-CH-NH), 2.36 (s, 3H, CH_3-Ph), 2.08 (s, 1H, -OH), 1.01-0.99 (d, J = 6.36 Hz, 3H, CH_3-CH). IR (KBr) cm^{-1}: 3501 (OH free), 3435 (N-H), 3360 (OH of COOH), 3262 (N-H), 2976 (CH aliphatic), 1697 (C=O), 1595 (C=C aromatic), 1167 (SO_2), 673 (Ar-H).

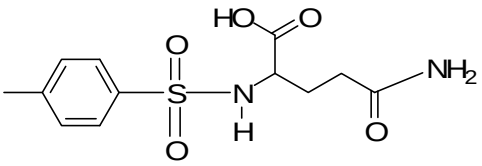


(4h)

3-Hydroxy-2-(4-methylphenylsulphonamido) butanoic acid

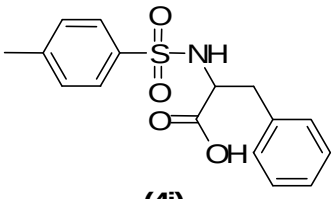
3.4.9. 5-Amino-2-(4-methylphenylsulphonamido)-5-oxopentanoic acid (4i). The amino acid was glutamine, yield 3.10 g (82.7%), mp 145-146 ^{o}C, R_f = 0.14 ($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 8.06-8.04 (d, J = 8.76 Hz, 1H, NH-CH), 7.65-7.63 (d, J = 8 Hz, 2H, Ar-H), 7.36-7.34 (d, J = 8 Hz, 2H, Ar-H), 7.24 (s, 1H, NH of NH_2), 6.73 (s, 1H, NH of NH_2), 3.69-3.65 (dd, J_1 = 8.76 Hz, J_2 = 17.24 Hz, 1H, CH-COOH), 2.37 (s, 3H, CH_3-Ph), 2.08-2.04 (t, J = 7.68 Hz, 2H, CH_2), 1.83-1.80 (t, J = 4 Hz, 1H, CH), 1.67-1.61 (q, J_1 = 4 Hz, J_2 = 7.6 Hz, CH). IR (KBr) cm^{-1}: 3456 (N-H), 3331 (OH of COOH), 3246 (N-H), 2955 (CH aliphatic), 1678 (C=O), 1640 (C=O), 1570 (C=C aromatic), 1321, 1167 (SO_2 two bands), 685 (Ar-H). MS: in m/z [rel. %]: 246.0 [97%], 238.1 [16%], 171.0 [$CH_3PhSO_2NH_2^+$, 49%], 156.0 [$CH_3PhSO_2^+$, 84%], 139.0

[52%], 123.0 [100%], 92.1 [$PhCH_3^+$, 38%], 44.0 [$CONH_2^+$, 32%]. Anal. calcd. for $C_{12}H_{16}N_2O_5S$ (300.34): C, 47.99; H, 5.37; N, 9.33. Found: C, 47.77; H, 5.39; N, 9.04.



(4i)
5-Amino-2-(4-methylphenylsulphonamido)-5-oxopentanoic acid

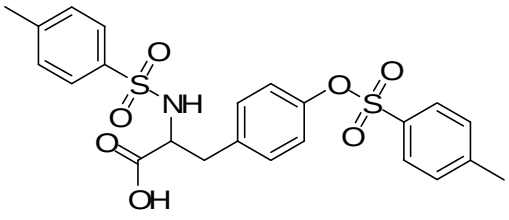
3.4.10. 2-(4-Methylphenylsulphonamido)-3-phenylpropanoic acid (4j). The amino acid was phenylalanine, yield 3.95 g (99.0%), 139-140 ^oC, R_f = 0.76 ($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 7.61-7.59 (d, *J* = 8 Hz, 2H, Ar-H), 7.24-7.21 (m, 5H, Ar-H), 7.10-7.08 (d, *J* = 8 Hz, 2H, Ar-H), 5.16-5.14 (d, *J* = 8.64 Hz, 1H, NH), 4.22-4.17 (ddd, J_1 = 5.6 Hz, J_2 = 6.4 Hz, J_3 = 8.64 Hz, 1H, CH-COOH), 3.12-3.08 (dd, J_1 = 5.6 Hz, J_2 = 20 Hz, 1H), 3.03-2.98 (dd, J_1 = 6.4 Hz, J_2 = 20 Hz, 1H), 2.40 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 175 (CO), 143.9, 136.6, 134.9, 129.8 (2CH aromatic), 129.6 (2CH aromatic), 128.8 (2CH aromatic), 127.5, 127.2 (2CH aromatic), 56.5, 39.0 (CH_2), 21.7 (CH_3). IR (KBr) cm^{-1}: 3350 (N-H), 3188 (OH), 3057 (CH aromatic), 2961 (CH aliphatic), 1736 (C=O of COOH), 1350, 1171 (SO_2 two bands), 675 (Ar-H).



(4j)
2-(4-Methylphenylsulphonamido)-3-phenylpropanoic acid

3.4.11. 2-(4-Methylphenylsulphonamido)-3-(4-(tosyloxy)phenyl)propanoic acid (4k). The amino acid was tyrosine, yield 3.70 g (60.5%), mp 101-103 ^oC, R_f = 0.76

($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 7.69-7.67 (d, *J* = 8.26 Hz, 2H, Ar-H of OTs), 7.59-7.57 (d, *J* = 8.26 Hz, 2H, Ar-H of OTs), 7.32-7.30 (d, *J* = 8 Hz, 2H, Ar-H), 7.24-7.22 (d, *J* = 8 Hz, 2H, Ar-H), 7.03-7.01 (d, *J* = 8.4 Hz, 2H, Ar-H of benzyl), 6.85-6.83 (d, *J* = 8.4 Hz, 2H, Ar-H of benzyl), 5.14-5.12 (d, *J* = 8.5 Hz, 1H, NH-CH), 4.17-4.12 (q, *J* = 6.8 Hz, 1H, NH-CH-CH_2), 3.11-3.06 (dd, J_1 = 5.2 Hz, J_2 = 20 Hz, 1H, CH of CH_2-Ar), 2.97-2.92 (dd, J_1 = 6.8 Hz, J_2 = 20 Hz, 1H, CH of CH_2-Ar), 2.45 (s, 3H, CH_3-OTs), 2.41 (s, 3H, CH_3-Ph). ^{13}C-NMR ($CDCl_3$) δ: 173.9 (CO), 148.9, 145.7, 144.2, 136.4, 134.3, 132.4 (six benzylic aromatic carbon atoms), 130.9, 130.9, 130.0, 130.0, 129.9, 129.9, 128.6, 128.6, 127.2, 127.2, 122.6, 122.6 (twelve sulphonyl aromatic carbon atoms), 56.4 (CH), 38.3 (benzylic CH_2), 21.9 (CH_3 linked to SO_3-Ar), 21.7 (CH_3 linked to SO_2-Ar). IR (KBr) cm^{-1}: 3561 (N-H), 3339 (OH of COOH), 2924 (CH aliphatic), 1717 (C=O), 1559 (C=C aromatic), 1150, 1092 (SO_2 two bands), 669 (Ar-H). MS: in m/z [rel. %]: 443.1 [M^+ - COOH, 23%], 171.0 [$CH_3PhSO_2NH_2^+$, 35%], 156.0 [$CH_3PhSO_2^+$, 58%], 155.0 [$PhCH_2SO_2^+$, 90%], 134.1 [90%], 92.1 [$PhCH_3^+$, 64%], 65.0 [100%]. Anal. calcd. for $C_{23}H_{23}NO_7S_2$ (489.57): C, 56.43; H, 4.74; N, 2.86. Found: C, 54.16; H, 4.79; N, 5.31.



(4k)
2-(4-Methylphenylsulphonamido)-3-(4-(tosyloxy)phenyl) propanoic acid

3.5. General Procedure for *N,N*-Diethylalkanamide of *p*-Toluenesulphonamide (5a-k)

A three-necked 250 mL flask equipped with magnetic stirring bar was charged with appropriate *p*-toluenesulphonamide **(4a-k)** (2.96 mmol) and dichloromethane (DCM)

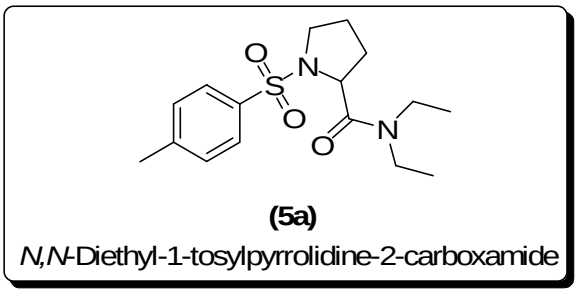
(10 mL). The flask was stoppered, cooled to 0 ^{o}C and N_2 was bubbled into it continuously. Oxalyl chloride (0.34 mL, 3.85 mmol, 1.3 equiv.) was added via dropping pipette to maintain the temperature below 10 ^{o}C followed by the addition of 2 drops of dimethyl formamide (DMF). The resulting mixture was stirred at room temperature until the conversion to acid chloride was completed (i.e. for about 1.5 h) and then concentrated to dryness with rotary evaporator (23 ^{o}C, 40 mmHg). Dichloromethane (DCM) (20 mL) was added to the resulting crude acid chloride and the solution was concentrated again.

In a separate 250 mL three-necked round bottom flask, equipped with a magnetic stirring bar, a N_2 inlet, a rubber septum, 125-mL pressure equalizing addition funnel and a temperature probe was charged with dichloromethane (DCM) (10 mL), triethylamine (0.62 mL, 4.44 mmol, 1.5 equiv.) and diethylamine (0.4 mL, 3.85 mmol, 1.3 equiv.) and the mixture was cooled to -10 ^{o}C (acetone/ice bath). The crude acid chloride was dissolved in dichloromethane (DCM) (10 mL) and this solution was transferred to the addition funnel. The acid chloride was then added dropwisely to the stirred diethylamine solution at such a rate that the internal temperature was maintained below 10 ^{o}C. Upon completion of the addition of the acid chloride solution (ca 30 min), the mixture was stirred at -10 to 0 ^{o}C for 1 h and at room temperarure for 1 h.

The mixture was then diluted with 2M HCl (6 mL) and was transferred into a 250 mL separatory funnel and the layers separated. The organic layer was washed with brine (6 mL) and was then concentrated under reduced pressure (23 ^{o}C, 40 mmHg), diluted with methanol (6 mL) and re-concentrated to give a crude solid. The solid was slurried in methanol (7.5 mL) and water (15 mL) was added dropwise with continuous stirring for 10 min. The slurry was stirred at room temperature for 1 h and allowed to crystallize

according to Kuethe and Beutner, (2009). It was filtered by suction and dried under vacuum/N_2 sweep for 8 h to afford *N,N*-diethyl substituted *p*-tolylsulphonamides **(5a-k).**

3.5.1. *N,N*-Diethyl-1-tosylpyrrolidine-2-carboxamide (5a). Yield 0.89 g (92.3%), mp 114-116 ^{o}C, ^{1}H-NMR ($CDCl_3$) δ: 7.76-7.73 (m, 2H, Ar-H), 7.33-7.31 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.28-7.26 (d, *J* = 8.0 Hz, 1H, Ar-H), 4.73-4.70 (m, 1H, CHa of CH_2-N), 4.26-4.24 (m, 1H, CHb of CH_2-N), 3.50-3.41 (m, 2H, $\underline{CH_2}$-CH_3), 3.34-3.29 (m, 2H, $\underline{CH_2}$-CH_3), 2.42-2.39 (d, *J* = 12.12 Hz, 3H, CH_3), 2.11-2.09 (m, 2H, CH_2 of pyrrolo), 1.94-1.71 (m, 3H, CH_2 & CH of pyrrolo), 1.27-1.23 (t, *J* = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2), 1.09-1.06 (t, *J* = 7.12 Hz, 3H, $\underline{CH_3}$-CH_2). IR (KBr) cm^{-1}: 2974 (aromatic), 2866 (CH aliphatic), 1657 (C=O), 1609 (C=C aromatic), 1149, 1107 (SO_2 two bands), 673 (Ar-H). MS: in m/z [rel. %]: 225.0 [MH^+ - $CON(CH_2CH_3)_2$, 62%], 224.0 [M^+ - $CON(CH_2CH_3)_2$, 100%], 169.1 [89%], 155.0 [$PhCH_2SO_2^+$, 93%], 100.1 [$^+CON(CH_2CH_3)_2$, 17%], 91.0 [$PhCH_2^+$, 82%], 72.0 [45%], 65.0 [42%]. Anal. calcd. for $C_{16}H_{24}N_2O_3S$ (324.45): C, 59.23; H, 7.46; N, 8.63. Found: C, 57.97; H, 7.20; N, 7.92.

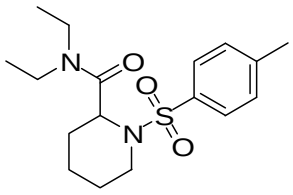


(5a)

N,N-Diethyl-1-tosylpyrrolidine-2-carboxamide

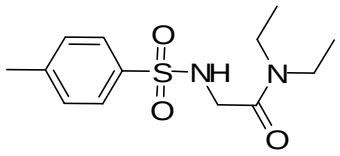
3.5.2. *N,N*-Diethyl-1-tosylpiperidine-2-carboxamide (5b). Yield 0.94 g (94.1%), mp 127-129 ^{o}C, ^{1}H-NMR ($CDCl_3$) δ: 7.58-7.56 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.21-7.19 (d, *J* = 8.0 Hz, 2H, Ar-H), 4.86-4.85 (m, 1H, $\underline{CH}$-COOH), 3.73-3.70 (q, *J* = 7.2 Hz, 2H, $\underline{CH_2}$-CH_3), 3.31-3.26 (q, *J* = 7.08 Hz, 2H, $\underline{CH_2}$-CH_3), 3.15-3.14 (m, 1H, CHa of CH_2-N), 3.09-3.08 (m, 1H, CHb of CH_2-N), 2.36 (s, 3H, CH_3), 1.75-1.66 (m, 3H, CH & CH_2 of

piperidine), 1.59-1.50 (m, 3H, CH & CH_2 of piperidine), 1.26-1.23 (t, *J* = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2), 0.96-0.93 (t, *J* = 7.02 Hz, 3H, $\underline{CH_3}$-CH_2). Anal. calcd. for $C_{17}H_{26}N_2O_3S$ (338.47): C, 60.33; H, 7.74; N, 8.28. Found: C, 60.27; H, 7.60; N, 8.32.



(5b)
N,N-Diethyl-1-tosylpiperidine-2-carboxamide

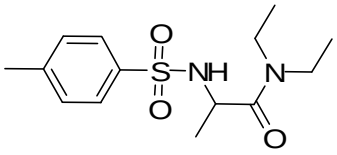
3.5.3. *N,N*-Diethyl-2-(4-methylphenylsulphonamido)acetamide (5c). Yield 0.69 g (82.7%), mp 109-111 ^oC, ^1H-NMR ($CDCl_3$) δ: 7.75-7.73 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.29-7.27 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.80 (s-br, 1H, NH), 3.73-3.72 (d, *J* = 4.12 Hz, 2H, $\underline{CH_2}$-NH), 3.31-3.26 (q, *J* = 7.14 Hz, 2H, $\underline{CH_2}$-CH_3), 3.17-3.11 (q, *J* = 7.18 Hz, 2H, $\underline{CH_2}$-CH_3), 2.40 (s, 3H, CH_3-Ar), 1.12-1.08 (t, *J* = 7.18 Hz, 3H, $\underline{CH_3}$-CH_2), 1.02-0.99 (t, *J* = 7.14 Hz, 3H, $\underline{CH_3}$-CH_2). IR (KBr) cm^{-1}: 3034 (CH aromatic), 2946 (CH aliphatic), 1707 (C=O), 1601 (C=C aromatic), 1191, 1145 (SO_2 two bands), 694 (Ar-H). Anal. calcd. for $C_{13}H_{20}N_2O_3S$ (284.38): C, 54.91; H, 7.09; N, 9.85. Found: C, 55.03; H, 7.13; N, 9.92.



(5c)
N,N-Diethyl-2-(4-methylphenylsulphonamido)acetamide

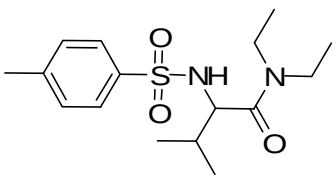
3.5.4. *N,N*-Diethyl-2-(4-methylphenylsulphonamido)propanamide (5d). Yield 0.68 g (77.9%), mp 121-124 ^oC, ^1H-NMR ($CDCl_3$) δ: 7.74-7.66 (m, 2H, Ar-H), 7.28-7.22 (m, 2H, Ar-H), 5.46-5.44 (d, *J* = 8.48 Hz, 1H, $\underline{NH}$-CH), 4.25-4.15 (m, 1H, NH-$\underline{CH}$-CH_3), 3.99-3.92 (q, *J* = 7.12 Hz, 4H, 2 × $\underline{CH_2}$-CH_3), 2.38 (s, 3H, CH_3-Ar), 1.39-1.37 (d, *J* =

7.16 Hz, 3H, $\underline{CH_3}$-CH), 1.13-1.09 (t, J = 7.12 Hz, 6H, 2 × $\underline{CH_3}$-CH_2). IR (KBr) cm^{-1}: 3279 (N-H), 3107 (CH aromatic), 1711 (C=O), 1620 (C=C aromatic), 1225, 1152 (SO_2 two bands), 677 (Ar-H). Anal. calcd. for $C_{14}H_{22}N_2O_3S$ (298.41): C, 56.35; H, 7.43; N, 9.39. Found: C, 56.42; H, 7.35; N, 9.44.



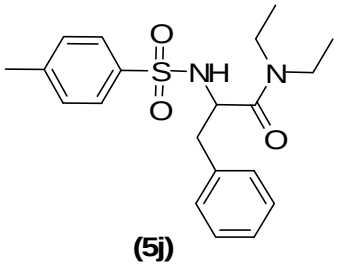
(5d)
N,N-Diethyl-2-(4-methylphenylsulphonamido)propanamide

3.5.5. *N,N*-Diethyl-3-methyl-2-(4-methylphenylsulphonamido)butanamide (5g). Yield 0.86 g (89.1%), mp 164-166 ^oC, ^1H-NMR ($CDCl_3$) δ: 7.68-7.66 (d, J = 8.0 Hz, 2H, Ar-H), 7.23-7.21 (d, J = 8.0 Hz, 2H, Ar-H), 5.78-5.75 (d, J = 9.24 Hz, 1H, $\underline{NH}$-CH), 3.81-3.78 (dd, J_1 = 4.22 Hz, J_2 = 9.24 Hz, 1H, NH-$\underline{CH}$-CH), 3.15-3.02 (m, 4H, 2x$\underline{CH_2}$-CH_3), 2.37 (s, 3H, CH_3-Ar), 1.83-1.78 (m, 1H, CH-$\underline{CH}(CH_3)_2$), 1.03-1.01 (d, J = 6.8 Hz, 3H, $\underline{CH_3}$-CH), 0.92-0.88 (t, J = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2), 0.84-0.82 (d, J = 6.0 Hz, 3H, $\underline{CH_3}$-CH), 0.84-0.81 (t, J = 6.48 Hz, 3H, $\underline{CH_3}$-CH_2). IR (KBr) cm^{-1}: 3260 (N-H), 2974 (CH aliphatic), 1668 (C=O), 1167, 1090 (SO_2 two bands), 689 (Ar-H). Anal. calcd. for $C_{16}H_{26}N_2O_3S$ (326.46): C, 58.87; H, 8.03; N, 8.58. Found: C, 58.79; H, 7.98; N, 8.59.



(5g)
N,N-diethyl-3-methyl-2-(4-methylphenylsulphonamido)butanamide

3.5.6. *N,N*-Diethyl-2-(4-methylphenylsulphonamido)-3-phenylpropanamide (5j). Yield 0.99 g (89.4%), mp 164-166 ^{o}C, ^{1}H-NMR ($CDCl_3$) δ: 7.67-7.65 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.24-7.19 (m, 5H, Ar-H), 7.13-7.09 (m, 2H, Ar-H), 5.88-5.86 (d, *J* = 9.48 Hz, 1H, NH-CH), 4.31-4.25 (m, 1H, CH), 3.21-3.15 (m, 1H, CHa of CH_2-Ph), 2.99-2.96 (m, 1H, CHb of CH_2-Ph), 2.94-2.90 (m, 2H, CH_2-CH_3), 2.80-2.74 (q, *J* = 7.2 Hz, 2H, CH_2-CH_3), 2.37 (s, 3H, CH_3-Ar), 0.88-0.84 (t, *J* = 7.14 Hz, 3H, CH_3-CH_2), 0.84-0.81 (t, *J* = 7.2 Hz, 3H, CH_3-CH_2). IR (KBr) cm^{-1}: 3306 (N-H), 2947 (CH aliphatic), 1710 (C=O), 1601 (C=C aromatic), 1213, 1171 (SO_2 two bands), 685 (Ar-H). Anal. calcd. for $C_{20}H_{26}N_2O_3S$ (374.51): C, 64.14; H, 7.00; N, 7.48. Found: C, 64.07; H, 6.91; N, 7.63.

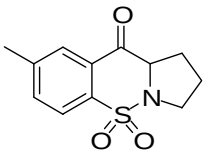


(5j)

N,N-Diethyl-2-(4-methylphenylsulphonamido)-3-phenylpropanamide

3.5.7. 8-Methyl-1a,1,2,3-tetrahydropyrrolo[1,2-*b*][1,2]benzothiazin-10-one-5,5-dioxide (6a). A solution of *N,N*-Diethyl-1-tosylpyrrolidine-2-carboxamide **(5a)** (0.324 g, 1.0 mmol) in tetrahydrofuran (THF) (5 mL) was added to a solution of lithium diisopropylamide (LDA) (freshly prepared from diisopropyl amine [(0.57 mL, 4 mmol) and *n*-BuLi (1.82 mL of 2.2 M, 4.0 mmol)] in THF (20 mL) at 0 ^{o}C in stream of N_2 gas. The ice bath was immediately removed, the solution was stirred at room temperature until the reaction was completed (TLC monitored for ca 1 h) and quenched with saturated aq. NH_4Cl (5 mL). The reaction mixture was evaporated to dryness, H_2O (30 mL) was added and the whole was extracted with DCM (3 x 15 mL). The combined organic extracts were

washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was chromatographed (SiO_2: EtOAc/hexane 3:7 eluent, at RT) to afford 24% of 8-methyl-1a,1,2,3-tetrahydropyrrolo[1,2-*b*][1,2]benzothiazin-10-one 5,5-dioxide **(6a)**. An analytically pure sample was obtained by recrystallization from *i*-Pr_2O. Yield 0.06 g (24.0%), mp 88-89 ^oC, ^1H-NMR ($CDCl_3$) δ: 7.9-7.7 (m, 3H, Ar-H), 5.01 (t, J = 3.7 Hz, 1H, NCHCO), 3.72 (dt, J_1 = 11.7 Hz, J_2 = 3.6 Hz, 1H, NCH_2), 2.8-2.5 (m, 2H, CH_2), 1.9-1.6 (m, 2H, CH_2), 2.37 (s, 3H, CH_3-Ar). ^1C-NMR ($CDCl_3$) δ: 192.9 (C=O), 138.2, 135.2, 132.9, 129.1, 128.1, 125.1, 63.9, 46.1, 24.3, 24.1, 21.1 (CH_3). IR (KBr) cm^{-1}: 2928, 2842, 1694, 1588, 1449, 1342, 1192, 1171, 1126, 1042, 1006, 927, 833, 770, 749. The melting point, other physical and spectroscopic data were identical with that of the authentic sample earlier reported (Bakker *et al.,* 1997).



(6a)

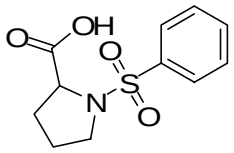
8-Methyl-1a,1,2,3-tetrahydropyrrolo[1,2-b][1,2] benzothiazin-10-one 5,5-dioxide

3.6. General Procedure for Synthesis of Benzenesulphonamides (7a-k)

Na_2CO_3 (5.565 g, 52.5 mmol) was added to a solution of amino acid (25 mmol) in H_2O (30 mL) at 0 ^oC, cooled to -5 ^oC followed by addition of benzenesulphonyl chloride, BzCl (5.299 g, 3.84 mL, 30 mmol) in three portions over a period of 1 h. The reacting mixture was then warmed to room temperature and allowed to stir for 4 h. Upon completion of the reaction, 20 % concentrated aqueous HCl solution was added with continuous stirring to avoid foaming on the surface until the pH 2 was attained. The solid separated out and was allowed to settle down over night and the product isolated via

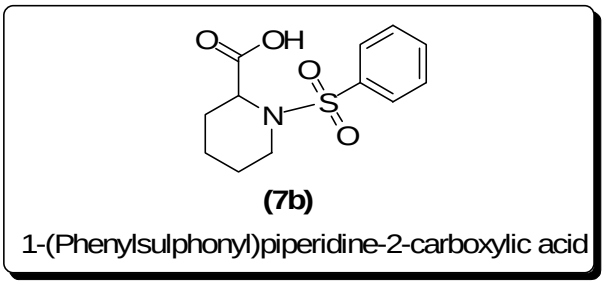
suction filtration. The filtered crude product was washed with pH 2.2 buffer and dried in a vacuum oven at 60 ^{o}C for 12 h to afford benzenesulphonamides **(7a-k)** in good to excellent yields (73.2 – 96.6%).

3.6.1. 1-(Phenylsulphonyl)pyrrolidine-2-carboxylic acid (7a). The amino acid was L-proline, yield 6.11 g (95.7%), mp 75-77 ^{o}C, R_f = 0.77 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 7.92-7.90 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.68-7.60 (m, 3H, Ar-H), 4.32-4.30 (dd, J_1 = 3.2 Hz, J_2 = 12 Hz, 1H, CH-COOH), 3.56-3.54 (m, 1H, CHa of CH_2-N), 3.33-3.27 (m, 1H, CHb of CH_2-N), 2.18-2.15 (m, 1H, CH), 1.97-1.95 (m, 2H, CH_2), 1.83-1.79 (m, 1H, CH). IR (KBr) cm^{-1}: 3065 (CH aromatic), 2957 (CH aliphatic), 1728 (C=O of COOH), 1157, 1094 (SO_2 two bands), 689 (Ar-H). Anal. calcd. for $C_{11}H_{13}NO_4S$ (255.29): C, 51.75; H, 5.13; N, 5.49. Found: C, 51.72; H, 4.92; N, 5.35.



(7a)
1-(Phenylsulphonyl)pyrrolidine-2-carboxylic acid

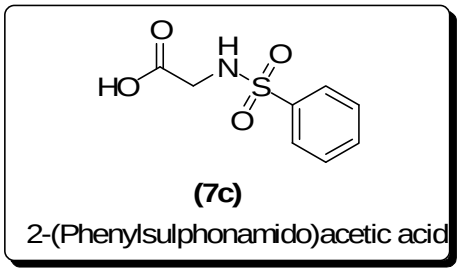
3.6.2. 1-(Phenylsulphonyl)piperidine-2-carboxylic acid (7b). The amino acid was pipecolic acid, yield 6.50 g (96.6%), mp 81-82 ^{o}C, R_f = 0.79 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 10.06-9.95 (s-br, 1H, OH of COOH), 7.81-7.78 (d, *J* = 8.76 Hz, 2H, Ar-H), 7.55-7.46 (m, 3H, Ar-H), 4.78-4.77 (d, *J* = 5 Hz, 1H, CH-COOH), 3.77-3.74 (d, *J* = 10 Hz, 1H, CHa of CH_2-N), 3.23-3.16 (dt, J_1 = 2.8 Hz, J_2 = 10 Hz, 1H, CHb of CH_2-N), 2.17-2.13 (m, 1H, CH), 1.71-1.66 (m, 3H, CH_2 & CH), 1.46-1.41 (m, 1H, CH), 1.32-1.23 (m, 1H, CH). Anal. calcd. for $C_{12}H_{15}NO_4S$ (269.32): C, 53.52; H, 5.61; N, 5.20. Found: C, 53.71; H, 5.59; N, 5.31.



(7b)

1-(Phenylsulphonyl)piperidine-2-carboxylic acid

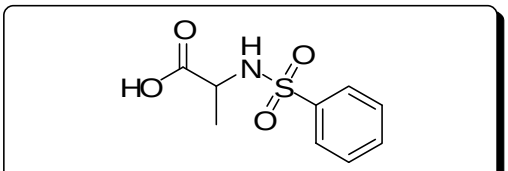
3.6.3. 2-(Phenylsulphonamido)acetic acid (7c). The amino acid was glycine, yield 3.94 g (73.2%), mp 160-161 ^{o}C, R_f = 0.45 ($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.68 (s-br, 1H, OH of COOH), 8.07-8.04 (t, J = 6 Hz, 1H, NH-CH_2), 7.80-7.78 (d, J = 8 Hz, 2H, Ar-H), 7.65-7.55 (m, 3H, Ar-H), 3.58-3.57 (d, J = 6 Hz, 2H, CH_2-NH). IR (KBr) cm^{-1}: 3314 (N-H), 3088 (C-H aromatic), 2974 (CH aliphatic), 1726 (C=O of COOH), 1157, 1128 (SO_2 two bands), 691 (Ar-H). Anal. calcd. for $C_8H_9NO_4S$ (215.23): C, 44.65; H, 4.21; N, 6.51. Found: C, 44.45; H, 4.32; N, 6.49.



(7c)

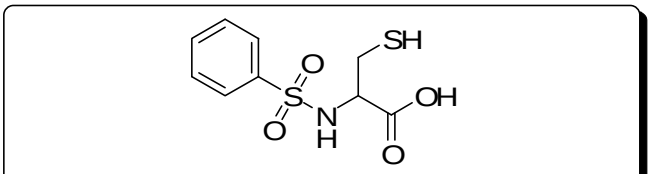
2-(Phenylsulphonamido)acetic acid

3.6.4. 2-(Phenylsulphonamido)propanoic acid (7d). The amino acid was alanine, yield 4.72 g (82.4%), mp 118-119 ^{o}C, R_f = 0.70 ($CHCl_3/CH_3OH$, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.62 (s-br, 1H, OH of COOH), 8.16-8.14 (d, J = 8.36 Hz, 1H, NH-CH), 7.80-7.78 (d, J = 8.52 Hz, 2H, Ar-H), 7.64-7.54 (m, 3H, Ar-H), 3.78-3.73 (dt, J_1 = 7.20 Hz, J_2 = 8.36 Hz, 1H, NH-CH-CH_3), 1.14-1.12 (d, J = 7.20 Hz, 3H, CH_3-CH). IR (KBr) cm^{-1}: 3327, 3267 (N-H), 3065 (C-H aromatic), 2990 (CH aliphatic), 1721 (C=O of COOH), 1153, 1086 (SO_2 two bands), 725 (Ar-H). Anal. calcd. for $C_9H_{11}NO_4S$ (229.26): C, 47.15; H, 4.84; N, 6.11. Found: C, 46.98; H, 4.82; N, 6.06.



(7d)
2-(Phenylsulphonamido)propanoic acid

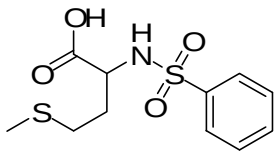
3.6.5. 3-Mercapto-2-(phenylsulphonamido)propanoic acid (7e). The amino acid was cysteine, yield 2.75 g (84.1%), 176-177 ^{o}C, R_f = 0.35 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.95 (s-br, 1H, OH of COOH), 8.35-8.32 (d, J = 8.40 Hz, 1H, NH-CH), 7.77-7.75 (d, J = 8.64 Hz, 2H, Ar-H), 7.64-7.53 (m, 3H, Ar-H), 3.93-3.88 (dd, J_1 = 8.40 Hz, J_2 = 20.00 Hz, 1H, NH-CH-CHa), 2.92-2.87 (dd, J_1 = 5.60 Hz, J_2 = 20.00 Hz, 1H, CHa of CH_2-S), 2.62-2.56 (dd, J_1 = 8.22 Hz, J_2 = 20.00 Hz, 1H, CHb of CH_2-SH). IR (KBr) cm^{-1}: 3294 (N-H), 3057 (CH aromatic), 2922 (CH aliphatic), 1736 (C=O of COOH), 1582 (C=C), 1148, 1088 (SO_2 two bands), 689 (Ar-H). Anal. calcd. for $C_9H_{11}NO_4S_2$ (261.32): C, 41.37; H, 4.24; N, 5.36. Found: C, 41.34; H, 4.06; N, 5.29.



(7e)
3-Mercapto-2-(phenylsulphonamido)propanoic acid

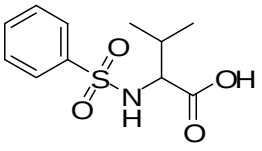
3.6.6. 4-(Methylthio)-2-(phenylsulphonamido)butanoic acid (7f). The amino acid was methionine, yield 2.98 g (82.3%), mp 128-130 ^{o}C, R_f = 0.77 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.73 (s-br, 1H, OH of COOH), 8.21-8.19 (d, J = 8.8 Hz, 1H, NH-CH), 7.78-7.76 (d, J = 8.52 Hz, 2H, Ar-H), 7.63-7.54 (m, 3H, Ar-H), 3.87-3.84 (dt, J_1 = 4.00 Hz, J_2 = 8.80 Hz, 1H, NH-CH-CH_2), 2.36-2.25 (m, 2H, CH_2S), 1.91 (s, 3H, CH_3), 1.82-1.73 (m, 2H, CH_2-CH_2-S). IR (KBr) cm^{-1}: 3254 (N-H), 3001 (CH aromatic),

2914 (CH aliphatic), 1724 (C=O of COOH), 1159, 1094 (SO_2 two bands), 691 (Ar-H). Anal. calcd. for $C_{11}H_{15}NO_4S_2$ (289.37): C, 45.66; H, 5.22; N, 4.84. Found: C, 45.54; H, 5.19; N, 4.67.



(7f)
4-(Methylthio)-2-(phenylsulphonamido)butanoic acid

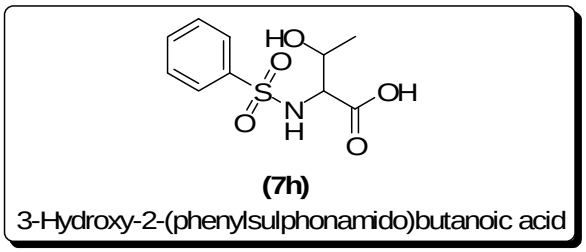
3.6.7. 3-Methyl-2-(phenylsulphonamido)butanoic acid (7g). The amino acid was valine, yield 5.08 g (79.0%), mp 143-144 ^oC, R_f = 0.76 ($CHCl_3/CH_3OH$, 9:1, at RT). ^1H-NMR ($CDCl_3$) δ: 7.85-7.83 (d, *J* = 8.68 Hz, 2H, Ar-H), 7.58-7.54 (m, 1H, Ar-H), 7.51-7.47 (m, 2H, Ar-H), 5.15-5.13 (d, *J* = 12.00 Hz, 1H, NH-CH), 3.82-3.79 (dd, J_1 = 4.80 Hz, J_2 = 12.00 Hz, 1H, NH-CH-CH), 2.12-2.07 (m, 1H, CH), 0.97-0.95 (d, *J* = 6.80 Hz, 3H, CH_3-CH), 0.88-0.86 (d, *J* = 6.88 Hz, 3H, CH_3-CH). IR (KBr) cm^{-1}: 3294 (N-H), 3090 (CH aromatic), 2972 (CH aliphatic), 1715 (C=O of COOH), 1173, 1094 (SO_2 two bands), 687 (Ar-H). Anal. calcd. for $C_{11}H_{15}NO_4S$ (257.31): C, 51.35; H, 5.88; N, 5.44. Found: C, 49.77; H, 5.70; N, 5.18.



(7g)
3-Methyl-2-(phenylsulphonamido)butanoic acid

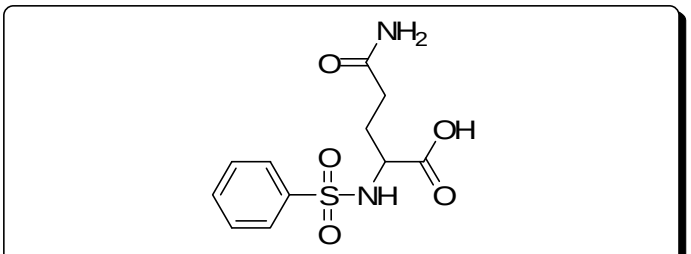
3.6.8. 3-Hydroxy-2-(phenylsulphonamido)butanoic acid (7h). The amino acid was threonine, yield 2.88 g (88.9%), 144-146 ^oC, R_f = 0.55 ($CHCl_3/CH_3OH$, 9:1, at RT). ^1H-NMR (DMSO-d_6) δ: 12.55 (s-br, 1H, OH of COOH), 7.81-7.79 (d, *J* = 8.6 Hz, 2H, Ar-H),

7.68-7.65 (d, J = 9.2 Hz, 1H, NH-CH), 7.59-7.51 (m, 3H, Ar-H), 3.98-3.96 (dq, J_1 = 3.60 Hz, J_2 = 6.40 Hz, 1H, CH-CH-CH_3), 3.68-3.65 (dd, J_1 = 3.60 Hz, J_2 = 9.20 Hz, 1H, NH-CH-CH), 2.08 (s, 1H, OH), 1.00-0.99 (d, J = 6.40 Hz, 3H, CH_3-CH). IR (KBr) cm^{-1}: 3445 (OH free), 3296 (N-H), 3017 (CH aromatic), 2945 (CH aliphatic), 1726 (C=O of COOH), 1167, 1078 (SO_2 two bands), 669 (Ar-H). Anal. calcd. for $C_{10}H_{13}NO_5S$ (259.28): C, 46.32; H, 5.05; N, 5.40. Found: C, 46.47; H, 4.99; N, 5.59.



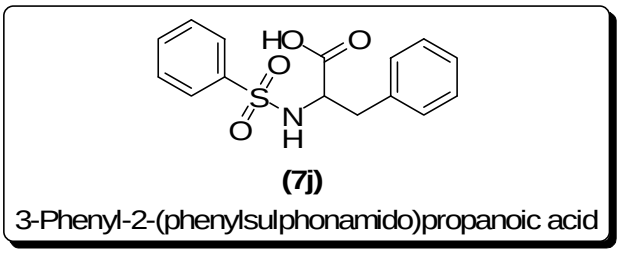
(7h)
3-Hydroxy-2-(phenylsulphonamido)butanoic acid

3.6.9. 5-Amino-5-oxo-2-(phenylsulphonamido)pentanoic acid (7i). The amino acid was glutamine, yield 3.25 g (90.8%), mp 173-174 ^oC, R_f = 0.34 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.61 (s-br, 1H, OH of COOH), 8.17-8.15 (d, J = 8.8 Hz, 1H, NH-CH), 7.77-7.75 (d, J = 8.64 Hz, 2H, Ar-H), 7.61-7.53 (m, 3H, Ar-H), 7.25 (s, 1H, NHa of CO-NH_2), 6.74 (s, 1H, NHb of CO-NH_2), 3.74-3.68 (dt, J_1 = 5.60 Hz, J_2 = 8.80 Hz, 1H, NH-CH-CH_2), 2.08-2.04 (t, J = 7.6 Hz, CO-CH_2-CH_2), 1.84-1.82 (m, 1H, CHa of CH_2-CH_2CO), 1.65-1.63 (m, 1H, CHb of CH_2-CH_2CO). IR (KBr) cm^{-1}: 3429, 3227 (N-H), 2978 (CH aliphatic), 1740 (C=O of COOH), 1684 (CO of amide), 1541 (C=C), 1171, 1092 (SO_2 two bands), 604 (Ar-H). Anal. calcd. for $C_{11}H_{14}N_2O_5S$ (286.31): C, 46.15; H, 4.93; N, 9.78. Found: C, 46.03; H, 4.95; N, 9.84.



(7i)
5-Amino-5-oxo-2-(phenylsulphonamido)pentanoic acid

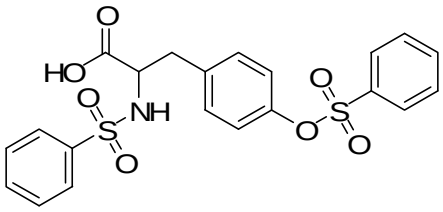
3.6.10. 3-Phenyl-2-(phenylsulphonamido)propanoic acid (7j). The amino acid was phenylalanine, yield 3.03 g (79.3%), mp 124-125 ^{o}C, R_f = 0.63 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 12.71 (s-br, 1H, OH of COOH), 8.30-8.28 (d, J = 9.00 Hz, 1H, NH-CH), 7.57-7.53 (m, 3H, Ar-H), 7.45-7.41 (m, 2H, Ar-H), 7.23-7.13 (m, 3H, Ar-H), 7.12-7.11 (m, 2H, Ar-H), 3.88-3.84 (ddd, J_1 = 5.76 Hz, J_2 = 8.96 Hz, J_3 = 9.00 Hz, 1H, NH-CH-CH_2-Ar), 2.96-2.91 (dd, J_1 = 5.76 Hz, J_2 = 20.00 Hz, 1H, CHa of CH_2-Ar), 2.73-2.68 (dd, J_1 = 8.96 Hz, J_2 = 20.00 Hz, 1H, CHb of CH_2-Ar). IR (KBr) cm^{-1}: 3341 (N-H), 3173 (OH), 3059 (CH aromatic), 2964 (CH aliphatic), 1736 (C=O of COOH), 1169, 1092 (SO_2 two bands), 689 (Ar-H). Anal. calcd. for $C_{15}H_{15}NO_4S$ (305.36): C, 59.00; H, 4.95; N, 4.59. Found: C, 58.88; H, 4.83; N, 4.47.



(7j)
3-Phenyl-2-(phenylsulphonamido)propanoic acid

3.6.11. 2-(Phenylsulphonamido)-3-(4-(phenylsulphonyloxy)phenyl)propanoic acid (7k). The amino acid was tyrosine, yield 4.23 g (73.3%), mp 109-110 ^{o}C, R_f = 0.61 ($CHCl_3$/CH_3OH, 9:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 7.82-7.82 (d, J = 8.60 Hz, 2H, Ar-H), 7.74-7.72 (d, J = 8.52 Hz, 2H, Ar-H), 7.70-7.68 (m, 1H, Ar-H), 7.56-7.53 (m, 3H, Ar-H),

7.48-7.46 (m, 2H, Ar-H), 7.05-7.03 (d, *J* = 8.40 Hz, 2H, Ar-H), 6.87-6.85 (d, *J* = 8.40 Hz, 2H, Ar-H), 5.10-5.08 (d, *J* = 8.80 Hz, 1H, NH-CH), 4.19-4.18 (m, 1H, CH), 3.13-3.08 (dd, J_1 = 5.20 Hz, J_2 = 20.00 Hz, 1H, CHa of CH_2-Ar), 2.99-2.94 (dd, J_1 = 6.60 Hz, J_2 = 20.00 Hz, 1H, CHb of CH_2-Ar). IR (KBr) cm^{-1}: 3225 (N-H), 3071 (CH aromatic), 2932 (CH aliphatic), 1755 (C=O of COOH), 1625 (C=C), 1161, 1092 (SO_2 two bands), 687 (Ar-H). Anal. calcd. for $C_{21}H_{19}NO_7S_2$ (461.52): C, 54.65; H, 4.15; N, 3.03. Found: C, 54.74; H, 4.25; N, 2.85.



(7k)

2-(Phenylsulphonamido)-3-(4-(phenylsulphonyloxy)phenyl) propanoic acid

3.7. General Procedure for *N,N*-Diethylalkanamide of Benzenesulphonamide (8a-k)

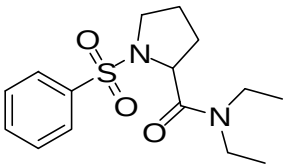
A three-necked 250 mL flask equipped with magnetic stirring bar was charged with **(7a-k)** (9.35 mmol) and DCM (30 mL). The flask was closed and N_2 was bubbled into it continuously. Oxalyl chloride (1.0 mL, 12.16 mmol, 1.3 equiv.) was added via dropping pipette followed by the addition of 2 drops of DMF. The mixture was stirred at room temperature for 2 h and then concentrated to dryness with rotary evaporator (23 ^oC, 40 mmHg). Dichloromethane (DCM) (40 mL) was added to the resulting crude acid chloride and the solution was concentrated again. In a separate 250 mL three-necked round bottom flask, equipped with a magnetic stirring bar, a N_2 inlet, a rubber septum, 125-mL pressure equalizing addition funnel and a temperature probe was charged with DCM (20 mL), triethylamine (2.0 mL, 14.03 mmol, 1.5 equiv.) and diethylamine (1.3 mL,

12.16 mmol, 1.3 equiv.) and the mixture was cooled to -15 ^{o}C. The crude acid chloride was dissolved in DCM (20 mL) and this solution was transferred to the addition funnel. The acid chloride was then added dropwisely to the stirred diethylamine solution at such a rate that the internal temperature was maintained below 10 ^{o}C.

Upon completion of the addition of the acid chloride solution (ca 30 min), the mixture was stirred at -10 to 0 ^{o}C for 1 h and at room temperarure for 1 h. The mixture was then diluted with 2M HCl (18 mL) and was transferred into a 250 mL separatory funnel and the layers separated. The organic layer was washed with brine (18 mL) and was then concentrated under reduced pressure (23 ^{o}C, 40 mmHg), diluted with methanol (18 mL) and re-concentrated to give a crude solid. The solid was slurried in methanol (20 mL) and water (30 mL) was added dropwisely with continuous stirring for 10 min. The slurry was stirred at room temperature for 1 h and methanol was removed by rotary evaporator. The resulting solution was transferred into separatory funnel and extracted with DCM. The organic layer was and dried under vacuum/N_2 sweep for 12 h to afford *N,N*-diethyl alkanamide substituted benzenesulphonamides **(8a-k)** in 71.5% - 95.8%.

3.7.1. *N,N*-Diethyl-1-(phenylsulphonyl)pyrrolidine-2-carboxamide (8a). Yield 2.20g (75.9%), mp 84-85 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ: 7.92-7.90 (d, J = 7.12 Hz, 2H, Ar-H), 7.56-7.48 (m, 3H, Ar-H), 4.81-4.78 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, 1H, CH-CON), 3.58-3.50 (m, 2H, N-CH_2-CH_3), 3.48-3.41 (m, 2H, CH_2-N of pyrrolo), 3.37-3.30 (m, 2H, N-CH_2-CH_3), 2.15-2.07 (m, 2H, CH_2 of pyrrolo), 1.92-1.85 (m, 2H, CH_2 of pyrrolo), 1.29-1.26 (t, J = 7.08 Hz, 3H, CH_3-CH_2N), 1.11-1.07 (t, J = 7.08 Hz, 3H, CH_3-CH_2N). IR (KBr) cm^{-1}: 2982 (CH aromatic), 2926 (CH aliphatic), 2860 (CH aliphatic), 1649 (C=O of amide),

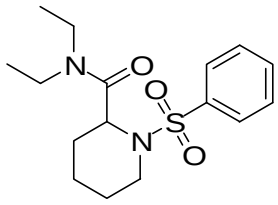
1152, 1086 (SO_2 two bands), 687 (Ar-H). Anal. calcd. for $C_{15}H_{22}N_2O_3S$ (310.42): C, 58.04; H, 7.14; N, 9.02. Found: C, 57.98; H, 7.25; N, 9.02.



(8a)

N,N-Diethyl-1-(phenylsulphonyl)pyrrolidine-2-carboxamide

3.7.2. *N,N*-Diethyl-1-(phenylsulphonyl)piperidine-2-carboxamide (8b). Yield 2.90 g (95.8%), mp 128-129 ^oC. ^1H-NMR ($CDCl_3$) δ: 7.73-7.71 (d, J = 8.6 Hz, 2H, Ar-H), 7.54-7.42 (m, 3H, Ar-H), 4.90-4.88 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H, CH-CON), 3.79-3.76 (m, 2H, N-CH_2-CH_3), 3.33-3.28 (m, 2H, N-CH_2-CH_3), 3.18-3.15 (m, 1H, CHa of CH_2-N piperidine), 3.10-3.07 (m, 1H, CHb of CH_2-N piperidine), 1.78-1.65 (m, 3H, CH & CH_2 of piperidine), 1.61-1.47 (m, 3H, CH & CH_2 of piperidine), 1.29-1.26 (t, J = 7.16 Hz, 3H, CH_3-CH_2N), 0.98-0.94 (t, J = 7.12 Hz, 3H, CH_3-CH_2N). Anal. calcd. for $C_{16}H_{24}N_2O_3S$ (324.45): C, 59.23; H, 7.46; N, 8.63. Found: C, 59.17; H, 7.29; N, 8.55.

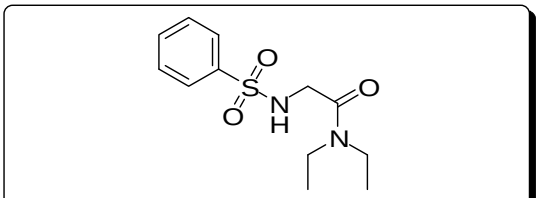


(8b)

N,N-Diethyl-1-(phenylsulphonyl)piperidine-2-carboxamide

3.7.3. *N,N*-Diethyl-2-(phenylsulphonamido)acetamide (8c). Yield 2.23 g (88.2%), mp 201-202 ^oC. ^1H-NMR ($CDCl_3$) δ: 7.89-7.85 (m, 2H, Ar-H), 7.64-7.48 (m, 3H, Ar-H), 5.92 (s-br, 1H, NH), 3.76-3.75 (d, J = 5.08 Hz, 2H, CH_2-NH), 3.31-3.25 (q, J = 7.12 Hz, 2H, N-CH_2CH_3), 3.18-3.12 (q, J = 7.16 Hz, 2H, N-CH_2CH_3), 1.12-1.09 (t, J = 7.16 Hz,

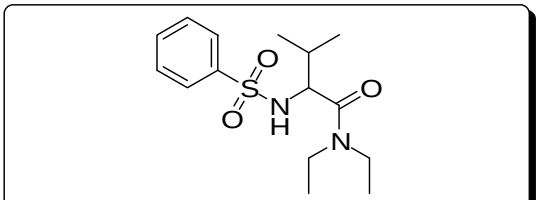
3H, $\underline{CH_3}$-CH_2), 1.03-0.99 (t, J = 7.12 Hz, 3H, $\underline{CH_3}$-CH_2). IR (KBr) cm^{-1}: 3294 (N-H), 3057 (CH aromatic), 2986 (CH aliphatic), 1726 (C=O of amide), 1625 (C=C), 1167, 1092 (SO_2 two bands), 689 (Ar-H). Anal. calcd. for $C_{12}H_{18}N_2O_3S$ (270.35): C, 53.31; H, 6.71; N, 10.36. Found: C, 53.19; H, 6.84; N, 10.51.



(8c)

N,N-Diethyl-2-(phenylsulphonamido)acetamide

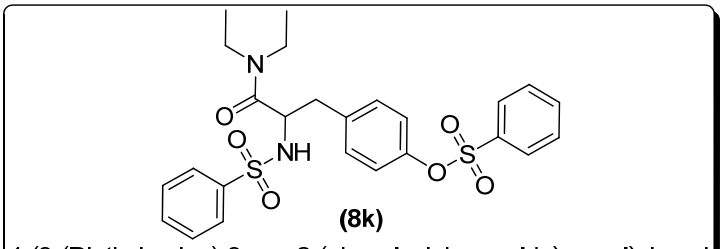
3.7.4. *N,N*-Diethyl-3-methyl-2-(phenylsulphonamido)butanamide (8g). Yield 2.11 g (72.3%), mp 89-90 ^oC. ^1H-NMR ($CDCl_3$) δ: 7.82-7.79 (d, J = 8.72 Hz, 2H, Ar-H), 7.54-7.43 (m, 3H, Ar-H), 5.83-5.81 (d, J = 9.16 Hz, 1H, $\underline{NH}$-CH), 3.84-3.81 (dd, J_1 = 4.16 Hz, J_2 = 9.16 Hz, 1H, NH-$\underline{CH}$-CH), 3.17-2.99 (m, 4H, 2 × $\underline{CH_2}$-CH_3), 1.83-1.81 (m, 1H, CH), 1.05-1.01 (d, J = 15.88 Hz, 3H, $\underline{CH_3}$-CH), 0.93-0.89 (t, J = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2), 0.87-0.83 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 0.87-0.83 (d, J = 14.2 Hz, 3H, $\underline{CH_3}$-CH). IR (KBr) cm^{-1}: 3258 (N-H), 2967 (CH aliphatic), 1640 (C=O of amide), 1625 (C=C), 1165, 1092 (SO_2 two bands), 606 (Ar-H). Anal. calcd. for $C_{15}H_{24}N_2O_3S$ (312.43): C, 57.67; H, 7.74; N, 8.97. Found: C, 57.44; H, 7.83; N, 9.09.



(8g)

N,N-Diethyl-3-methyl-2-(phenylsulphonamido) butanamide

3.7.5. 4-(3-(Diethylamino)-3-oxo-2-(phenylsulphonamido)propyl)phenyl benzene sulphonate (8k). Yield 3.46 g (71.5%), mp 72-73 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ: 7.81-7.79 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.75-7.74 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.68-7.64 (m, 1H, Ar-H), 7.54-7.50 (m, 3H, Ar-H), 7.45-7.41 (m, 2H, Ar-H), 7.06-7.03 (d, *J* = 8.44 Hz, 2H, Ar-H), 6.88-6.85 (d, *J* = 8.44 Hz, 2H, Ar-H), 4.23-4.21 (d, *J* = 9.2 Hz, 1H, NH-CH), 4.24-4.21 (dd, J_1 = 9.2 Hz, J_2 = 13.6 Hz, 1H, NH-CH-CH), 3.17-3.14 (m, 1H, CHa of CH_2-Ar), 2.98-2.95 (m, 1H, CHb of CH_2-Ar), 2.88-2.80 (m, 4H, 2 × CH_2-CH_3), 0.86-0.82 (t, *J* = 7.1 Hz, 3H, CH_3-CH_2), 0.78-0.75 (t, *J* = 7.16 Hz, 3H, CH_3-CH_2). IR (KBr) cm^{-1}: 3248 (N-H), 3073 (CH aromatic), 2974 (CH aliphatic), 1690 (C=O of amide), 1625 (C=C), 1161, 1088 (SO_2 two bands), 687 (Ar-H). Anal. calcd. for $C_{25}H_{28}N_2O_6S_2$ (516.64): C, 58.12; H, 5.46; N, 5.42. Found: C, 57.97; H, 5.39; N, 5.31.



(8k)

4-(3-(Diethylamino)-3-oxo-2-(phenylsulphonamido)propyl)phenyl benzenesulphonate

3.8. Antimicrobial Activity

The antimicrobial properties of the sulphonamides were investigated in form of the general sensitivity testing and MIC with respect to freshly cultured targeted organisms. The two organisms used in this present study are one Gram positive (*Staphylococcus aureus* ATCC 6538) and one Gram negative (*Escherichia coli* ATCC 25922) which are

associated with the gastrointestinal tract infections in man and animal (Nwinyi *et al.*, 2008).

3.8.1. Preparation of the Inoculum

The standard strains of *S. aureus and E. coli* used were obtained from Center for Antimicrobial Test, TIPC, Beijing. No clinically isolated organism was used based on in-availablilty in this laboratory as at the time of this study. The strains were propagated on nutrient agar plates and maintained on the plate at 4 ^{o}C. The isolates were sub-cultured in nutrient broth at 37^{o}C for 8 h prior to antibacterial testing.

3.8.2. Antibacterial Sensitivity Testing of Compounds

Agar well diffusion technique as described by Adeniyi *et al.*, (1996) was used to determine the antibacterial activity of the synthesized compounds. Sensitivity test agar plates were seeded with 0.1 ml of an overnight culture of each bacterial strain (equivalent to $10^{7} – 10^{8}$ CFU mL^{-1}). The seeded plates were allowed to set and a standard cork borer of 8 mm diameter was used to cut uniform wells on the surface of the agar. The wells were then filled with 0.3 mL of each sulphonamide solution in appropriate solvent at a concentration of 1000 μg/mL (0.02 g of sulphonamide dissolved in 20 mL of solvent). It should be noted that the solubilizing solvent for α-tolylsulphonamides was distilled water while the required solvent for *p*-tolylsulphonamides and benzenesulphonamides categories was DMSO). All the plates were incubated at 37 ^{o}C for 24 h. The assay was conducted at regular intervals of 24 h until marked decline in the potency of the sulphonamide solution to inhibit the growth of the test organisms was noticed. Zones of clearance round each well means inhibition and the diameter of such zones were measured. The procedure was repeated for the streptomycin (standard).

3.8.3. Minimum Inhibitory Concentration (MIC) Testing

Agar well dilution method as described by Russell and Furr (1977) was used to determine the minimum inhibitory concentration (MIC) of the sulphonamides and streptomycin. Different dilutions of the sulphonamides were prepared first at ≤ 100 µg/mL to give final concentrations in the range of 100, 50, 25, 12.5, 6.25, and 1.8 µg/mL. The different dilution of sulphonamide derivatives that could not inhibit the microbial growth at ≤ 100 µg/mL were later prepared at ≤ 1000 µg/mL to give final concentrations in the range of 1000, 500, 250, 125, 62.5 µg/mL. Two milliliter (2 ml) of each dilution was mixed with Mueller Hinton agar (18 mL) (MHA, Difco, France) and poured into Petri-dishes and allowed to set. The agar was streaked with an overnight broth culture of the bacterial strains and incubated overnight. The plates were then examined for the presence or absence of growth. The minimum concentration that completely inhibited macroscopic growth was regarded as the minimum inhibitory concentration (MIC) of the respective sulphonamide. The procedure was repeated for streptomycin (standard).

REFERENCES

Kaveh P. Boroujeni, 2010, Friedel-Crafts acylation of arenes with carboxylic acids using silical gel supported $AlCl_3$. *Turkish Journal of Chemistry, 34,* pp 621-630.

Weifeng Zhang, Yuancheng Qin, *et al.,* 2005, Synthesis of novel N-heterocyclic carbene-Rh complexes derived from L-proline and their catalysis in the addition of arylboronic acids to aldehyde. *Arkivoc 14,* pp 39-48.

Jeffrey T. Kuethe and Gregory L. Beutner, 2009, Synthesis of 2-arylindole-4-carboxylic amides: [2-(4-Fluorophenyl)-1*H*-indol-4-yl]-1-pyrrolidinylmethanone. *Organic Synthesis, 86,* pp 92-104.

Wouter I. Iwema Bakker, Oluwole B. Familoni *et al.,* 1997, Intramolecular anionic Friedel-Crafts equivalents. An expeditious synthesis of 4*H*-1,2-benzothiazin-4-one 1,1-dioxide from *N*-arylsulphonylated amino acid. *Synlett, 1532,* pp 1079-1080.

Obinna C. Nwinyi, Shalom N. Chinedu *et al.,* 2008, Evaluation of antibacterial activity of pisidium guajava and Gongronema latifolium. *Journal of Medicinal Plant Research, 2(8),* pp 189-192.

B.A. Adeniyi, H.A. Odelola, *et al.,* 1996, Antimicrobial potentials of *Diospyros mespiliformis* (Ebenaceae). *African Journal of Medicinal Science***,** *255,* pp 221-224.

Alan D. Russell and John R. Furr, 1977, Antibacterial activity of a new chloroxylenol preparation containing ethylenediamine tetraacetic acid. *Journal of Applied Bacteriology UK, 43*, pp 253-260.

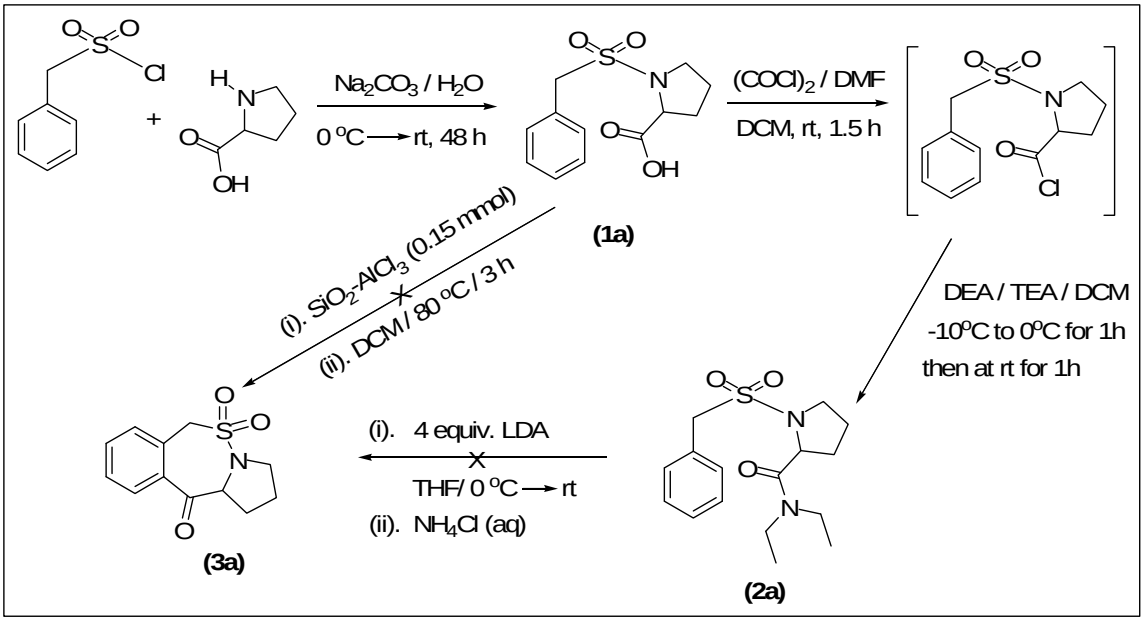
CHAPTER FOUR

RESULTS AND DISCUSSION

4.1. Derivatives of α-Toluenesulphonamide

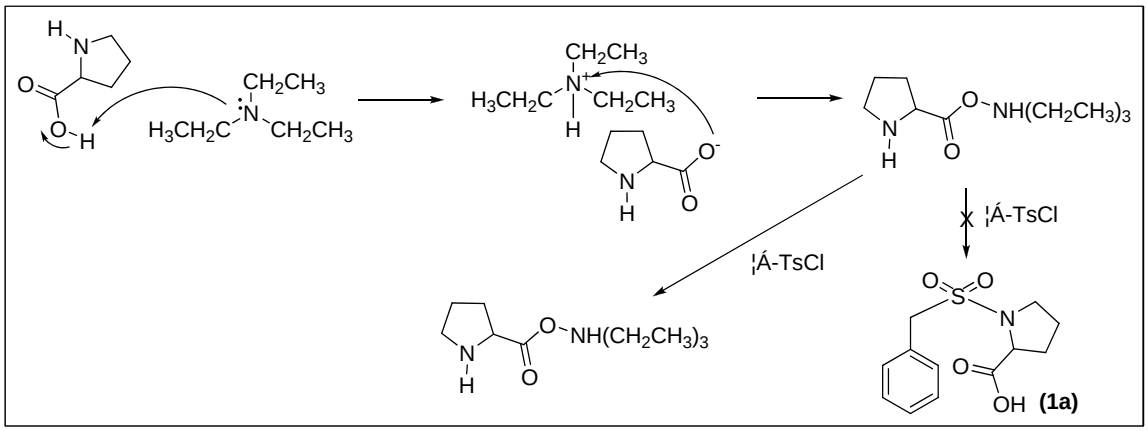
Synthesis of various functionalized α-toluenesulphonamides and synthetic modification of the derivatives were carried out towards achieving novel *N*,*N*-diethylamide of α-tolylsulphonamide which was the targeted key intermediate for the synthesis of benzothiazepinone. In detail, for the first time, a successful approach to the synthesis of α-toluenesulphonamides from the reaction of α-toluenesulphonyl chloride (α-TsCl) with some readily available amino acids was here-in described. Using L-proline as the representative amino acid, which upon effective coupling with α-TsCl in basic medium afforded α-toluenesulphonamide, 1-(benzylsulphonyl)pyrrolidine-2-carboxylic acid **(1a)** which was converted to the acid chloride intermediate and subsequently amidated to obtain 1-(benzylsulphonyl)-*N*,*N*-diethylpyrrolidine-2-carboxamide **(2a)**.

The intramolecular cyclization of **(2a)** via either direct ortho metalation or heterogeneous catalytic approach was also attempted to see the possibility of achieving the corresponding benzothiazepinone **(3a)** (Scheme 4.1). This was based on the earlier report of direct ortho metalated conversion of some *N*,*N*-diethylamide of *p*-tolyl sulphonamide to benzothiazinone heterocyclic templates (Bakker *et al.,* 1997). It was very crucial to explore various reaction conditions for effective optimization study as regard reaction of α-TsCl with L-proline, since the present work has never been embarked upon to the best of our knowledge.



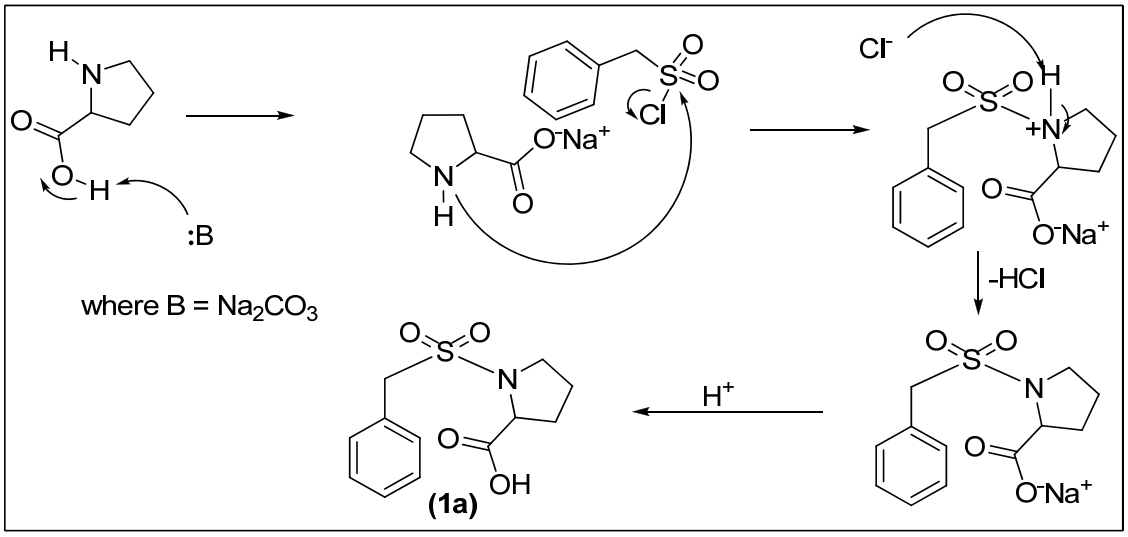
Scheme 4.1: Overall Pathway for Representative Derivative of α-Toluenesulphonamide

Hence, preliminary optimization of reaction conditions for α-toluenesulphonamide was carried out by comparing the sulphonylation of L-proline as the representative of amino acid for the synthesis of **(1a)** under two different cases namely: in the presence of (i) triethylamine base using THF solvent and (ii) Na_2CO_3 base using water as the solvent. It was discovered that although, in case i, proline was effectively converted to its ammonium salt as a way of protecting the carboxyl functionality by triethylamine nucleophilic attack on its acidic proton, but it failed to couple with α-TsCl as envisaged (Scheme 4.2). This was established through the ^{1}H-NMR spectrum of the product from case i which had no aromatic protons in the region around 6.0 to 8.0 ppm showing that there was no effective coupling with α-TsCl. The failure of the case (i) reaction condition may be as a result of poor solubility of L-proline in THF and possibility of steric hinderance exerted by the alkylated ammonium side chain. Therefore, the case (i) approach was discarded due to this disappointment.



Scheme 4.2: Mechanism for Formation of Sulphonamide (1a) using Case i

On the other hand, case (ii) condition using aqueous Na_2CO_3 gave the expected α-toluenesulphonamide product named 1-**(**benzylsulphonyl)pyrrolidine-2-carboxylic acid **(1a)** via the modified procedure according to Zhang and co-workers (2005). Basifying of L-proline with Na_2CO_3 aqueous turned the carboxyl end to the sodium salt which did not only act as protecting group but also increased the solubility of the amino acid in aqueous medium. The amino group then attacked the sulphonyl chloride at the highly electrophilic sulphur site. After all, the sodium salt side chain of the sulphonamide was re-converted to the carboxylic functional group by acidifying with 2M HCl until pH 2.2 was attained (Scheme 4.3). It is important to note at this stage that the solid product could not crystallize out, even after being kept in refrigerator for several days. However, the TLC spotting indicated that the coupling was successful; hence, the clear liquid obtained was freeze-dried to obtain a bulky solid which upon purification with column chromatography afforded **(1a)**. Difficulty connected with the poor reactivity of some starting materials especially the α-tolylsulphonyl chloride was overcome by increasing the duration of stirring at room temperature to 48 h.



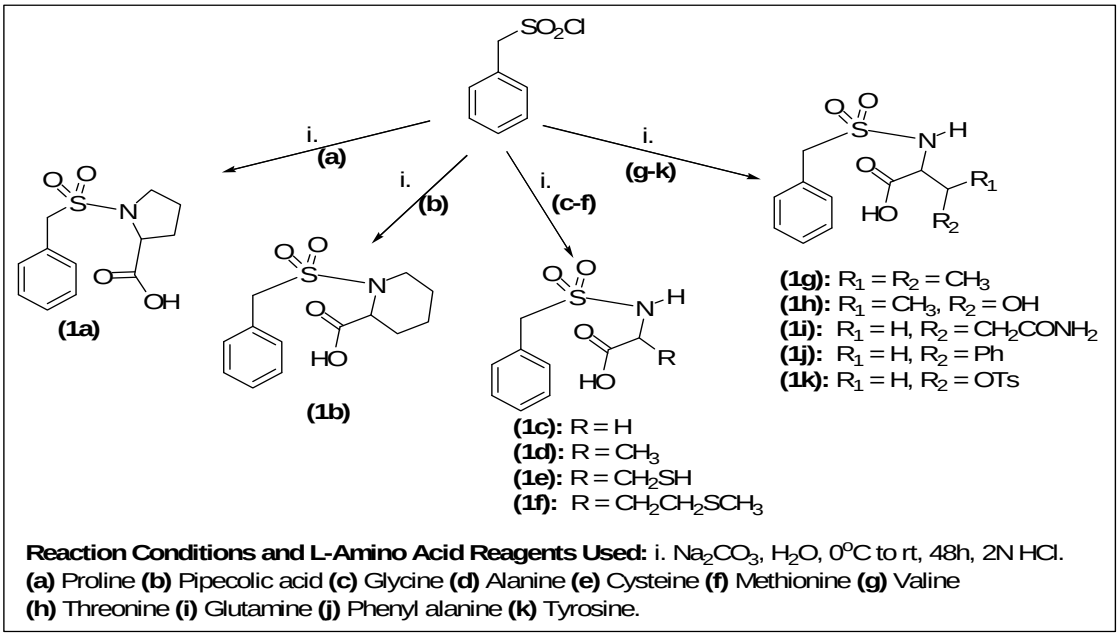
Scheme 4.3: **Mechanism for Formation α-Toluenesulphonamide using aq. Na_2CO_3**

Meanwhile, after establishing case (ii) as the more acceptable working procedure, it is thoughtful to explore the thermodynamic potential in order to validate the best reaction temperature to afford maximum yield. Hence, the effect of variation in temperature was carefully studied by carrying out the coupling of proline with α-TsCl in aqueous Na_2CO_3 at carefully controlled temperature of 0^{o}C to room temperature, at 60 ^{o}C to 80 ^{o}C and at 120 ^{o}C to 140 ^{o}C as shown in entries 1, 2 and 3 respectively (Table 4.1). It was observed that the synthesis at 0 ^{o}C followed by stirring at room temperature afforded **(1a)** at excellent yield 92%, while at an elevated temperature of 60 ^{o}C to 80 ^{o}C, majority of the reacting species reverted back to the starting material thereby resulting in poor **(1a)** yield of 37%.

Table 4.1: Synthesis of 1-(Benzylsulphonyl)pyrrolidine-2-carboxylic acid (1a) at Different Temperatures for Optimization Study

Entry	Reagent/Solvent	Temperature ^{o}C	Time h	Yield %
1	Na_2CO_3 / H_2O	0 to rt	48	92
2	Na_2CO_3 / H_2O	60 - 80	48	37
3	Na_2CO_3 / H_2O	120 - 140	48	-

At extremely high temperature (120 ^{o}C to 140 ^{o}C) as shown in entry 3, no isolable product was obtained. This was because of thermal decomposition of the proline precursor at this elevated reaction temperature. Based on this result, it could be seen that the best optimization condition was to couple proline with α-TsCl in aqueous Na_2CO_3 at 0^{o}C to room temperature. Hence, this protocol was repeated using ten other amino acids and it was established as an efficient procedure for accessing diverse highly functionalized α-toluenesulphonamide **(1a-k)** in excellent yield (87.7% - 98.8%) (Scheme 4.4). The structures of all these new compounds **(1a-k)** were confirmed using FT-IR, ^{1}H- and ^{13}C-NMR, Mass spectral and elemental analytical data. Generally, IR spectra of compounds **(1a-k)** showed absorption bands due to the stretching vibrations of O-H of acid, CH aromatic, CH aliphatic, C=O and C=C at 3447-3404 cm^{-1}, 2990-2974 cm^{-1}, 2878-2774 cm^{-1}, 1751-1728 cm^{-1} and 1620-1590 cm^{-1} respectively. They all experienced stretching vibrational frequency of SO_2 units as two bands near 1238-1206 cm^{-1} and 1171-1151 cm^{-1} whereas Ar-H bands were noticed at 810-698 cm^{-1} as expected.



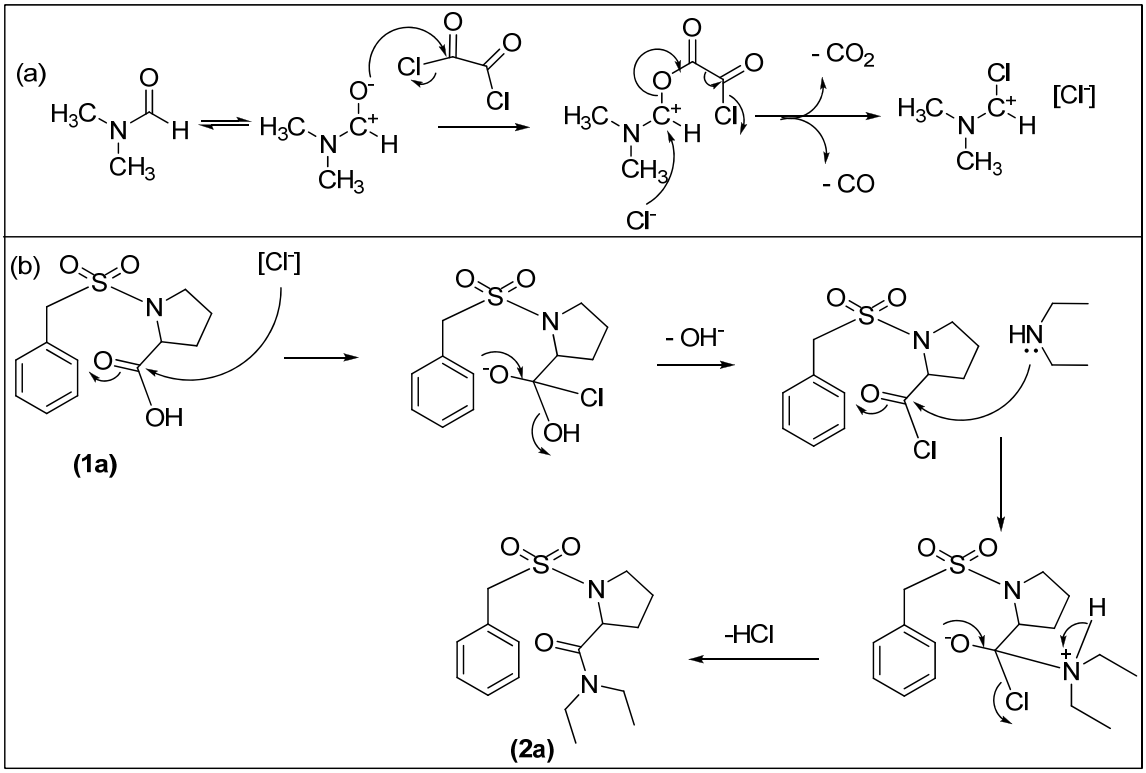
Scheme 4.4: Synthesis of Novel α-Toluenesulphonamide Derivatives (1a-k)

In particular, the IR spectrum of **(1a)** as a representative of this group, exhibited the absorption band at 3441 cm^{-1} due to the presence of O-H of carboxylic acid while bands for the CH of both aromatic and aliphatic were noticed at 2980 cm^{-1} and 2828 cm^{-1} respectively. The stretching vibrations at 1728 cm^{-1} and 1620 cm^{-1} depicted C=O of acid and C=C of aromatic ring respectively while the two bands at 1219 cm^{-1} and 1151 cm^{-1} were as a result of the presence of SO_2 functionality. The mass spectral data of **(1a)** showed the molecular ion peak at m/z 269.1 which correlated well with the molecular mass of the compound (269.32) while the base peak found at m/z 178.1 was as a result of loss of benzylic radical ($PhCH_2^{\cdot}$). Other daughter peaks produced by some fragmentation patterns of **(1a)**, were observed at m/z 179.1, 176.1, 122.0 and 105.0 with relative intensities of 18.4%, 32.4%, 49% and 32% respectively.

In addition, the chemical shifts and the multiplicity patterns of ^{1}H- and ^{13}C-NMR were consistent with that of the proposed structure for **(1a)**. So, the ^{1}H NMR spectrum of **(1a)** in D_2O exhibited a five aromatic protons singlet at δ 7.47 and two protons singlet of benzylic methylene (i.e. Ph-$\underline{CH_2}$-SO_2) at δ 4.24. All other signals observed upfield of TMS from δ 3.48-3.45 to δ 2.15-2.09 were due to the presence of six pyrrolo protons while that of the seventh pyrrolo proton ($\underline{CH}$-COO) resonated as a doublet-doublet at δ 4.46-4.43 (J_1 = 7.20 Hz, J_2 = 15.76 Hz). The ^{13}C-NMR spectrum of **(1a)** showed the presence of twelve different carbon atoms with the signals ranging from 173.1 (C=O) to 24.3 (CH_2) ppm. The six aromatic carbon of phenyl resonated downfield between 132.6 and 128.9 ppm while benzylic CH_2 linked to SO_2 was observed at 57.7 ppm. The three sp^3 hybridized CH_2 of proline nucleus appeared between 47.1 and 24.3 ppm while its CH linked to –COOH resonated at 67.4 ppm. The mass spectrum of **(1a)** showed the

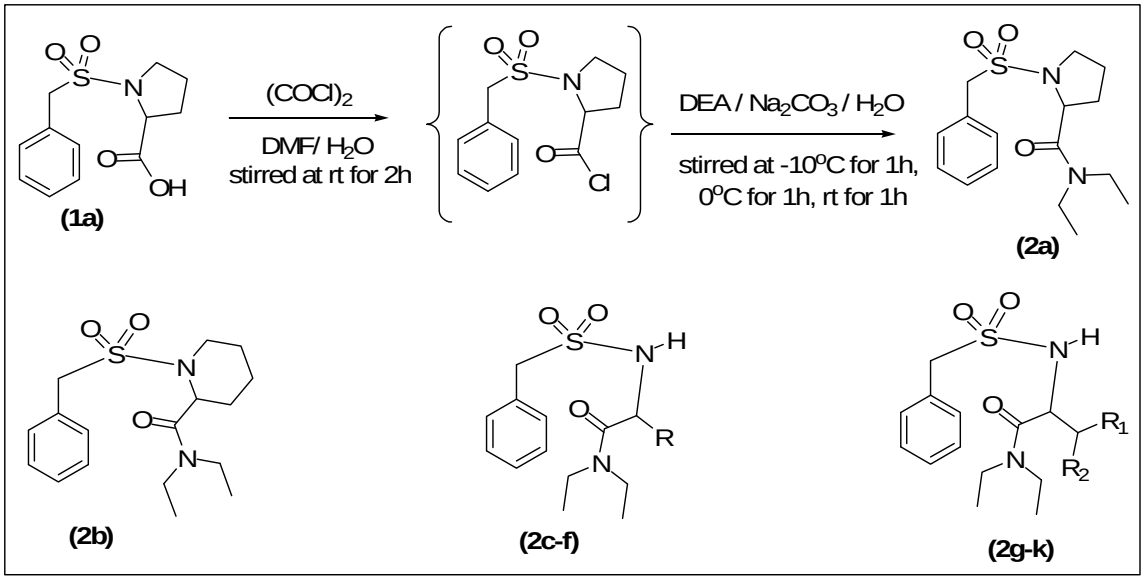
molecular ion peak at m/z 269.1 which correlated well with molecular mass of the compound within precision limit of $\pm$0.2 while the base peak experienced at m/z 178.1 was as a result of loss of benzylic radical. Other fragmentation patterns resulted in some other prominent daughter fragments at m/z of 179.1, 176.1, 122.0, and 105.0 with the intensities of 18.4%, 32.4%, 49% and 32% respectively.

Furthermore, the conversion of α-toluenesulphonamide **(1a)** (i.e. 1-(benzyl sulphonyl)pyrrolidine-2-carboxylic acid) to the target novel corresponding *N*,*N*-diethyl alkanamide of α-tolylsulphonamide **(2a)** (i.e. 1-(benzylsulphonyl)-*N*,*N*-diethyl pyrrolidine-2-carboxamide) was achieved via one pot two steps amidation technique (Kuethe and Beutner, 2009). This involved treatment of **(1a)** with oxalyl chloride in one drop of DMF. The chloride ion which was the reaction initiator and precedential species for the formation of acid chlorides, was generated by molecular interaction between oxalyl chloride and DMF via a proposed mechanism (Scheme 4.5a) similar to that of Swern oxidation (Kawaguchi *et al.,* 2005). The nucleophilic attack of the –COOH by the chloride ion generated above led to the conversion of **(1a)** to the acid chloride reactive intermediate which upon further treatment with diethylamine in basic medium between controlled temperature of -10 ^{o}C and room temperature afforded the amide bearing sulphonamide **(2a)** according to a well established mechanism (Scheme 4.5).



Scheme 4.5: Mechanism for the Formation of Amide (2a)

In more elaborate terms, the protocol for the conversion of **(1a)** to the amide **(2a)** also worked successfully for other α-toluenesulphonamide derivatives. Thus, the treatment of α-toluenesulphonamides **(1a-k)** with oxalyl chloride in DMF generated the intermediate acid chloride which when subsequently treated with diethylamine in the presence of Na_2CO_3 in aqueous medium afforded *N*,*N*-diethyl alkanamide of α-tolyl sulphonamides **(2a-k)** in excellent yields (Scheme 4.6). This medium was used as a result of high hydrophilic nature of the sulphonamides that were to be amidated which made them practically insoluble in every other solvent except water.



Scheme 4.6: Synthesis of *N,N*-Diethylalkanamide Substituted α-Tolylsulphonamides (2a-k)

Table 4.2: Physical Data of *N,N*-Diethyl Substituted α-Tolylsulphonamides (2a-k)

Sample Code	R	R_1	R_2	Molecular Weight	Mp °C	R_f[a]	Yield
(2a)	-	-	-	324.45	185-187	0.71	97.9
(2b)	-	-	-	338.47	210-211	0.72	99.0
(2c)	H	-	-	284.38	213-215	0.51	92.6
(2d)	CH_3	-	-	298.41	238-240	0.56	98.5
(2e)	CH_2SH	-	-	330.47	198-200	0.71	89.0
(2f)	$(CH_2)_2SCH_3$	-	-	358.53	170-172	0.65	90.6
(2g)	-	CH_3	CH_3	326.46	226-230	0.69	97.3
(2h)	-	CH_3	OH	328.43	240 (dec)	0.53	80.2
(2i)	-	H	CH_2CONH_2	355.46	251-253	0.58	93.2
(2j)	-	H	Ph	374.51	227-229	0.70	90.2
(2k)	-	H	$PhCH_2OSO_2$-	544.69	265 (dec)	0.69	89.3

[a] Solvent system. Chloroform: Methanol (3:1)

The result of the physical parameters in terms of the molecular weights, melting points, R_f values as well as the percentage yields of the synthesized *N,N*-diethyl alkanamide substituted α-tolylsulphonamides **(2a-k)** is as shown in Table 4.2. Hence, the molecular weights of **(2a-k)** ranged from 284.38 to 544.69 while the melting points ranged from 170 - 172 °C to 251 - 253 °C except that of **(2h)** and **(2k)** which decomposed at 240 °C and 265 °C respectively. The inability of **(2h)** and **(2k)** to melt even at high

temperature might be as a result of intermolecular hydrogen bonding occurrence in the molecule. It was also observed that upon TLC spotting, each reaction gave one spot each in chloroform: methanol (3:1) solvent system with the R_f values varying between 0.51 and 0.72. It should be noted that the R_f values were reported at 23^oC and 1 atm.

Moreover, from the high polar nature of the eluting solvent system and the R_f values obtained, it could be easily seen that these compounds were very polar. This may be responsible for the complete solubility in water and failure to crystallize from water even after several days. Hence, this may explain why the only method by which the solid **(2a-k)** were obtained from the solution was lyophilization technique. It was worthy of note that the entire solid **(2a-k)** were obtained in excellent yields ranging between a minimum of 80.2% for **(2h)** to a maximum of 99.0% for **(2b)** according to Table 4. The spectroscopic properties of the synthesized *N*,*N*-diethyl substituted α-tolylsulphonamides **(2a-k)** were studied and the structural characterization using FT-IR, ^{1}H-, ^{13}C-NMR, mass sprectra data as well as elemental analyses were carried out. It was discovered that all the spectroscopic parameters were consistent with the proposed structures for **(2a-k)**.

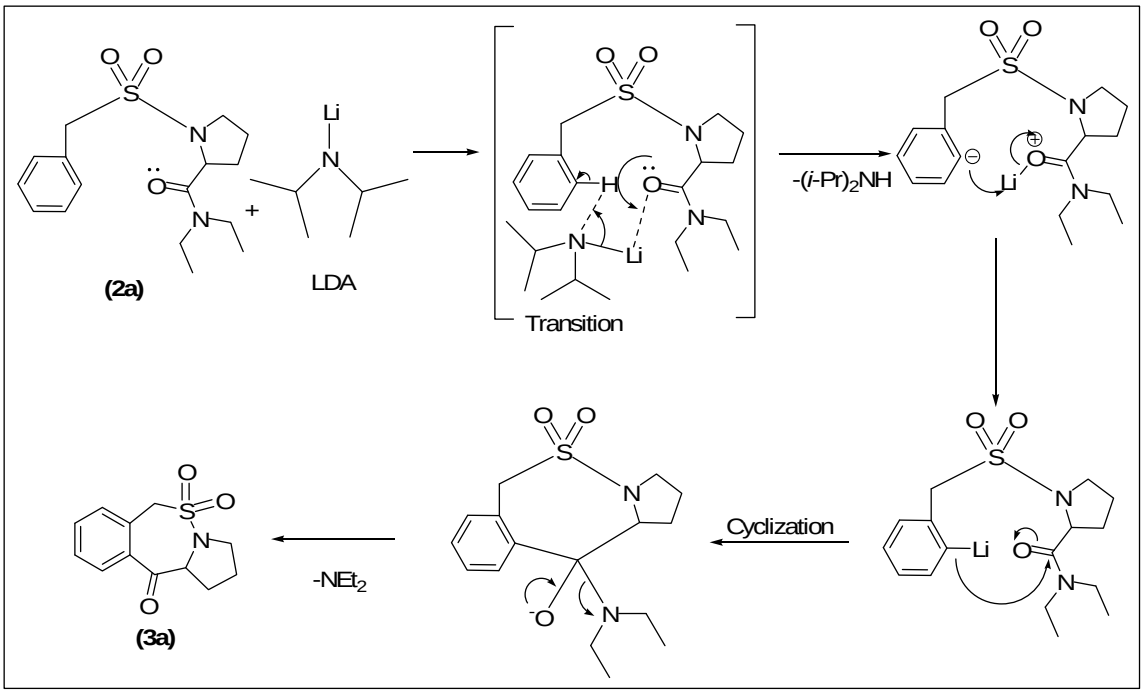
Attempted Cyclization of the Amide (2a)

Intramolecular cyclization of *N*,*N*-diethylalkanamide of α-tolylsulphonamide **(2a)** to the corresponding benzothiazepinone **(3a)** was attempted with (a) ortho-metalation procedure via lithiation technique and (b) heterogeneous catalytic approach with silica-mediated aluminium chloride as solid acid catalyst.

(a) Using Ortho-Metalation Technique:

Lithium dialkylamides are generally used as bases to generate lithio species due to their strength and low nucleophilicity, especially when they are derived from sterically hindered amines (Parra *et al.,* 2003; Familoni *et al.,* 1997). Based on this discovery, the reaction of *n*-butyllithium (*n*-BuLi) with diisopropylamine in THF at -78 ^{o}C afforded lithium diisopropylamide (LDA) which was subsequently used in attempting the intramolecular cyclization of amide **(2a)** to obtain the benzothiazepinone **(3a)**. This was attempted by taking clue from the lithiation technique earlier reported in literature as a successful tool for the conversion of benzenesulphonamide counterpart to the benzothiazinone equivalent (Bakker *et al.,* 1997). The excess LDA-promoted cyclization of α-tolylsulphonamide amide **(2a)** to benzothiazepinone **(3a)** and relative ease of lithiation was attributed to a prelithiation phenomenon called Complex Induced Proximity Effect (CIPE) which occurred in the transition state before deprotonation.

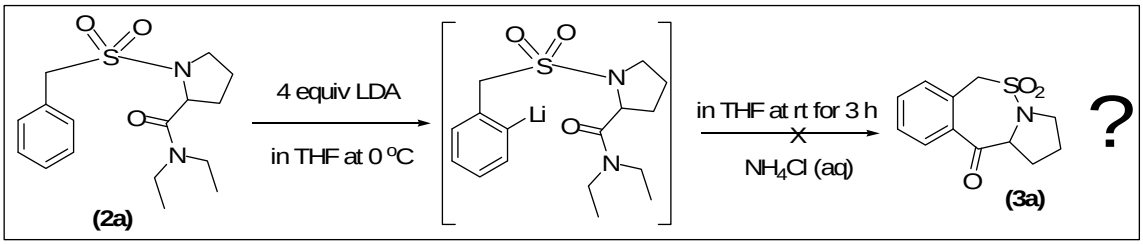
Mechanistically, the comparable intramolecular information transfer was effected by formation of a prelithiation complex which brought reactive groups into proximity for directed deprotonation (Scheme 4.7). This process utilized the shape of one part of a molecule to control the stereoselectivity of reactions occurring some distance away (Clayden *et al.,* 2004). The mechanism of this reaction involved a complexing between LDA and the amide of interest **(2a)** in the prelithiation process which facilitated the deprotonation of hydrogen in the ortho position of the ring to achieve the lithio species. The carbanion generated from the lithio species exerted a nucleophilic attack on the sp^2 hybridized carbon center of C=O for effective cyclization. The driving force for the ring closure was the loss of a stable molecule of NEt_2 as a good leaving group (Scheme 7).



Scheme 4.7: Mechanism for Attempted Cyclization to (3a) using Ortho-Metalation

The representative equation for this reaction involved lithation of the ortho position with 4 equivalent of LDA in THF to form an intermediate at 0 ^{o}C which upon stirring at room temperature and quenching with NH_4Cl (aq), was expected to afford the fused benzothiazepinone **(3a)** (Scheme 4.8). In contrast to the observation made in successful synthesis of benzothiazinone (Bakker *et al.,* 1997), a directed metalation group did not dictate the expected regiochemistry even in the presence of excess LDA, hence, the effort of the intramolecular cyclization towards obtaining **(3a)** here-in proved abortive. The failure observed in using metalation as means of intramolecular cyclization here might be as a result of high polar nature of the *N*,*N*-diethyl substituted α-tolyl sulphonamide **(2a)** precursor which made it practically difficult for it to dissolve in either THF or DCM or any other solvent except water alone. However, water that was the only friendly solvent for solubilizing the amide **(2a)** was not acceptable solvent in ortho-

metelation approach as it destroyed the *n*-BuLi used to generate the LDA that was required as the metalating agent. It could be deduced that methylene insertion has led to decrease in lipophilicity of the sulphonamide and also increase hydrophilicity thereof (Shoji *et al.*, 2009).

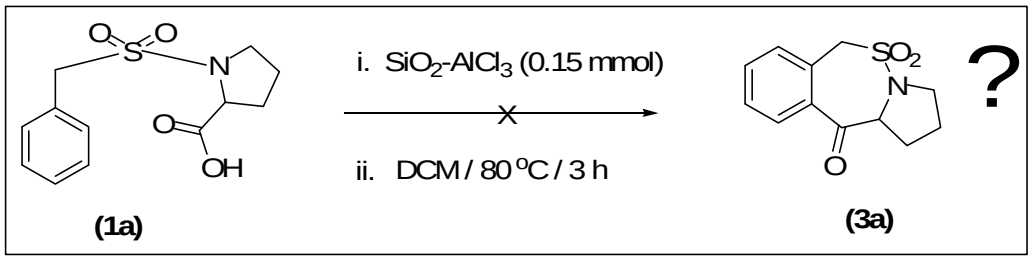


Scheme 4.8: Attempted Synthesis of Benzothiazepinone (3a) using Ortho-Metalation

(b) Using Heterogenous Catalytic Approach:

An attempt to carry out the intramolecular cyclization of **(1a)** toward formation of benzothiazepinone **(3a)** via heterogeneous catalytic approach with the aid of silica mediated aluminium chloride was also examined. This was carried out by refluxing **(1a)** in catalytic amount of SiO_2-$AlCl_3$ at 80 ^oC for 3 h using DCM solvent (Scheme 4.9). This was based on the earlier literature finding that reported SiO_2-$AlCl_3$ as heterogeneous catalyst of choice for intramolecular cyclization of the -COOH side chain of 4-phenylbutanoic acid to achieving the cyclic ketone product, tetralone (Boroujeni, 2010). Thus, it was envisaged that the –COOH side chain of the **(1a)** might cyclized at the ortho-position of benzene as a result of intermediate Friedel-Craft anionic equivalent generated by the effect of the solid acid catalyst. The significant advantages of this methodology are mild reaction conditions, high to excellent yields, short reaction times, solvent-free conditions, low cost, simple reaction work-up, easy preparation and handling of the catalyst. In addition, the use of SiO_2-$AlCl_3$ resulted in a reduction of the unwanted and

hazardous waste that is produced during conventional homogeneous processes. Despite all the merits and wide acceptability of this approach, it was not successful in the intramolecular cyclization of **(1a)** in this study. The failure observed, just like in the case of ortho-metalation technique, may be as a result of high hydrophilic character of α-toluenesulphonamide **(1a)** precursor which made it insoluble in DCM through the course of reaction. The only good solvent that dissolved **(1a)** was water which was indeed not compatible with $AlCl_3$ used in preparing the solid acid catalyst (SiO_2-$AlCl_3$).

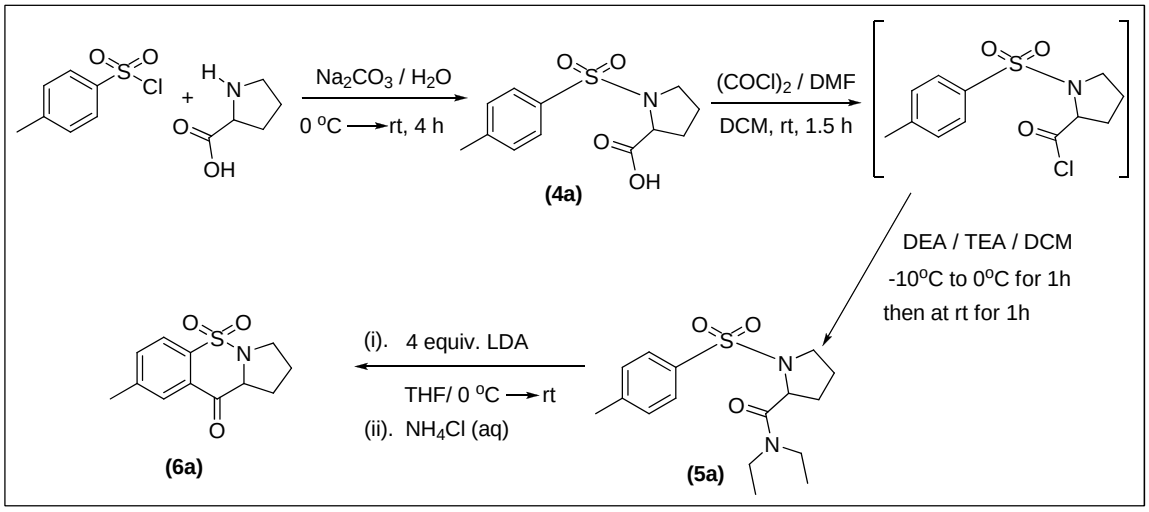


Scheme 4.9: Attempted Synthesis of Benzothiazepinone (3a) using SiO_2-$AlCl_3$

4.2. Derivatives of *p*-Toluenesulphonamide

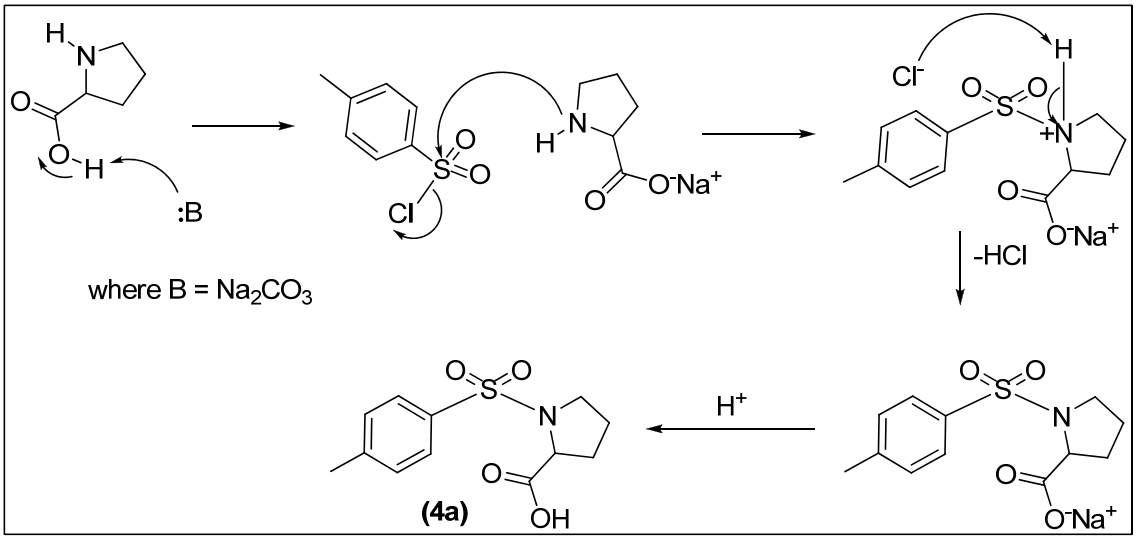
p-Toluenesulphonyl chloride (*p*-TsCl) and various amino acids were readily available; they were found as convenient starting materials in this present work. The reaction started with arylsulphonylation of various amino acids to afford the *p*-toluenesulphonamide **(4a-k)** in good to excellent yields (60.5 – 99.0%) using a known procedure (Zhang *et al.,* 2005). To show the overall reaction under this class, it was conceivable to use proline as the representative amino acid. Hence, the coupling of L-proline with *p*-toluenesulphonyl chloride, *p*-TsCl in basic medium within 4 h at room temperature gave arylsulphonamide, **(4a)** which was subsequently amidated by Kuethe and Beutner methodology (2009) to obtain *N,N*-diethylsubstituted amide of *p*-

tolylsulphonamide **(5a)** in excellent yield (92.3%). Metalation of the amide **(5a)** using excess LDA-promoted cyclization gave the benzothiazinone **(6a)** (Scheme 4.10), although in a low yield (24%). This result authenticated the synthesis earlier reported by Bakker and co-workers in (1997).

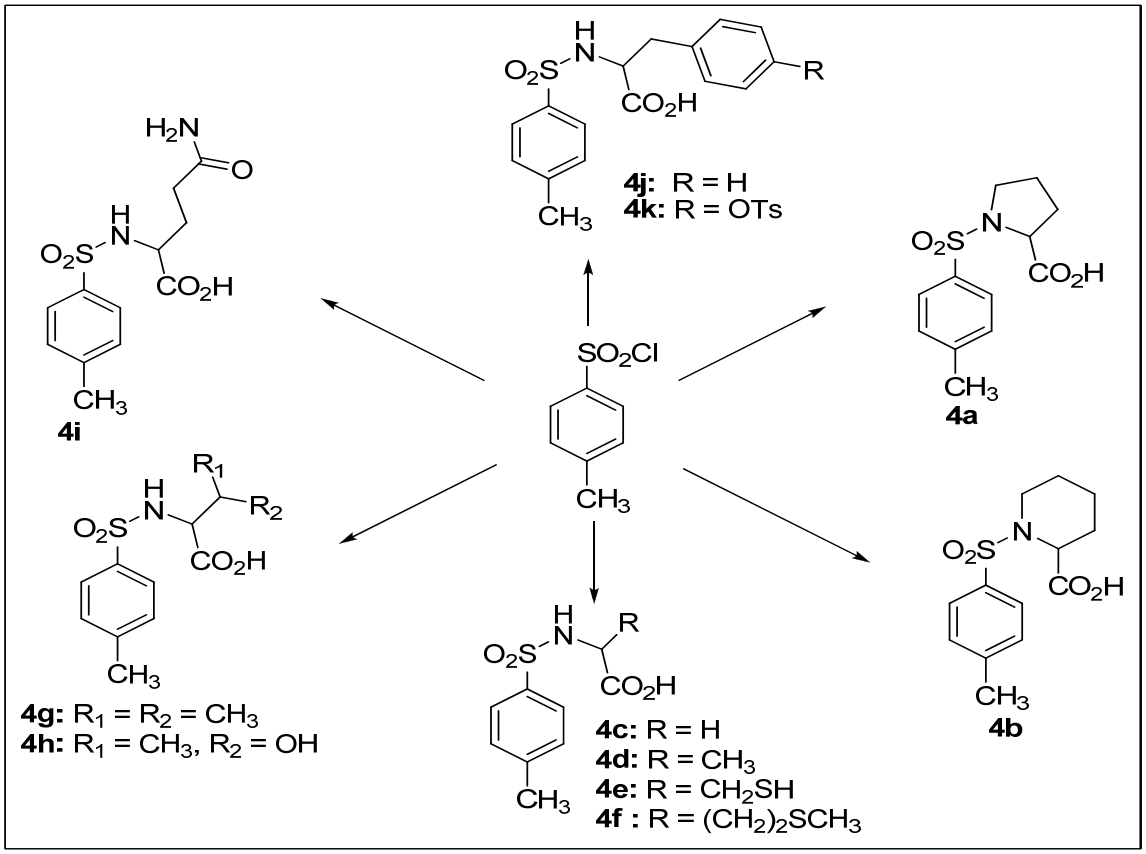


Scheme 4.10: Overall Pathway for Representative Derivative of *p*-Toluenesulphonamide

The mechanism of the reaction started with conversion of –COOH end of proline to the sodium salt of the acid through electrophilic substitution of H^+ with Na^+ released from the base. This served as a protection for –COOH functionality and enhanced the solubility of proline better in aqueous medium. The cross coupling with *p*-TsCl occurred by nucleophilic attack of the electrophilic sulphur by the amino group of proline to from ammonium ion where chloride ion was the leaving group. The abstraction of the ammonium proton by the chloride ion led to the formation of sodium salt of the amide which subsequently underwent acidification with 2M HCl to afford the expected *p*-toluenesulphonamide **(4a)** as shown in Scheme 4.11. This procedure was repeated with sulphonylation of ten other amino acids apart from L-proline to obtain corresponding *p*-toluenesulphonamide derivatives **(4b-k)** (Scheme 4.12).

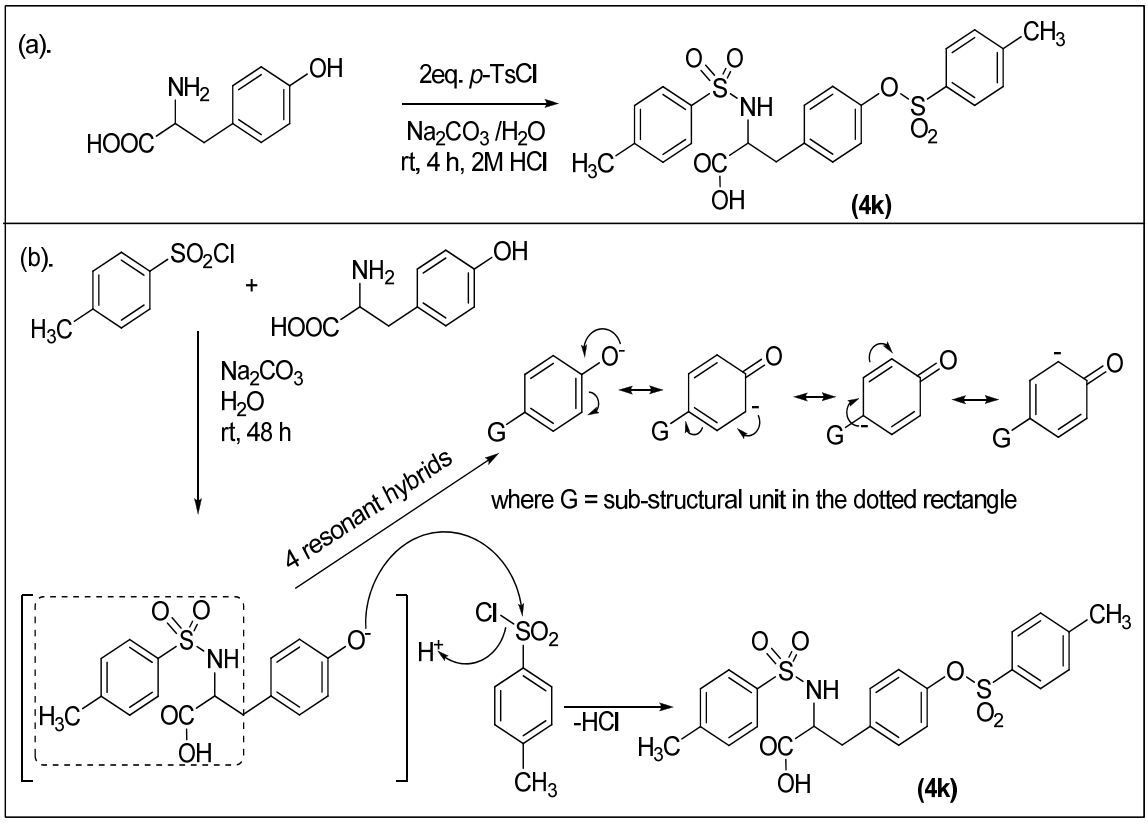


Scheme 4.11: Mechanism for Formation *p*-Toluenesulphonamide using aq. Na_2CO_3



Scheme 4.12: Synthesis of a Series of *p*-Toluenesulphonamides (4a-k)

However, tyrosine required double molar proportion of *p*-TsCl for complete reaction to give **(4k)** in 80.5% yield (Scheme 4.13a). This is due to the fact that in addition to the sulphonylation, tyrosine also underwent tosylation on the phenolic hydroxyl group at the *para* position of the phenyl ring to give **(4k)** whose structure was consistent with the assigned ^{1}H- and ^{13}C-NMR spectra (Experimental). This double sulphonylation in **(4k)** was as a result of the resonant stabilization of the phenolate anion conjugate base as shown by the reaction path in Scheme 4.13b. This resonant stabilization caused the equilibrium to shift forward; hence, tosylation is highly favoured. The spectroscopic study was investigated for the structural elucidation using IR, ^{1}H- and ^{13}C-NMR, mass spectral and elemental analytical data. The data correlated well with the proposed structures for the synthesized *p*-toluenesulphonamide derivatives **(4a-k)**.



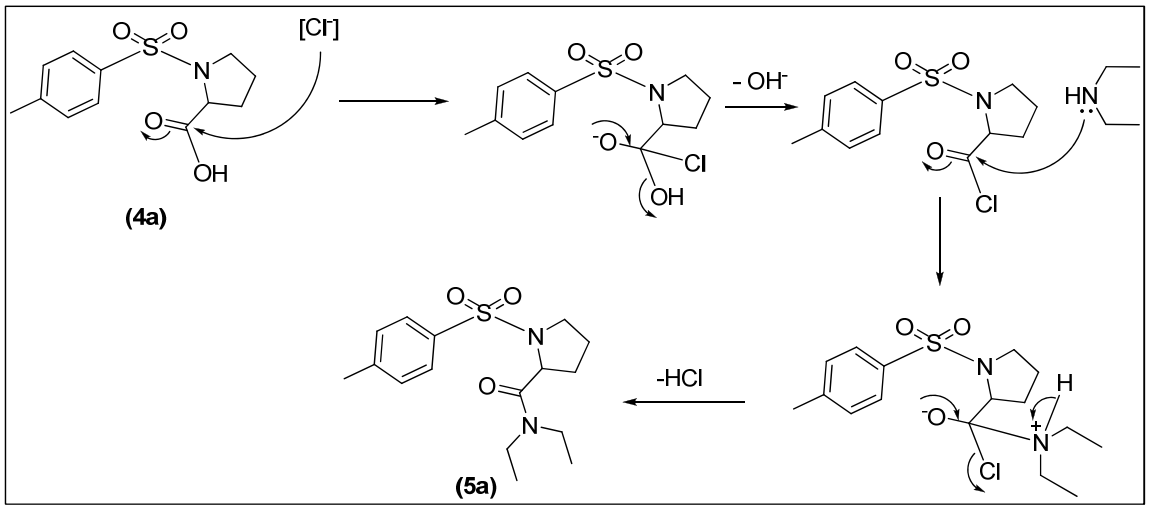
Scheme 4.13: Mechanistic Justification for the Chain End Tosylation of (4k)

Meanwhile, **(4k)** was used as representative compound for the spectroscopic explanation for this group. The ^{1}H-NMR spectrum of **(4k)** in deuterated chloroform showed -CH_3 attached to phenyl and tosylate as singlet at 2.41 and 2.45 ppm respectively while the two benzylic protons (-CH_2-Ar) resonated upfield of TMS as two separate doublet of doublet at δ 2.97-2.92 (J_1 = 6.8 Hz, J_2 = 20 Hz) and 3.11-3.06 (J_1 = 5.2 Hz, J_2 = 20 Hz) ppm. This was as a result of shield effect in the sp^3 hybridized carbon atoms which required higher external magnetic field to bring it to resonance. The -NH and its neighboring –CH, resonated as a doublet and a quartet at δ 5.14-5.12 (J = 8.5 Hz) and 4.17-4.12 (J = 6.8 Hz) ppm respectively. All the twelve aromatic protons were found as expected between δ 6.85-6.83 ppm and 7.69-7.67 ppm. ^{13}C-NMR spectrum confirmed **(4k)** to have twenty three carbon atoms ranging from δ 21.7 ppm (CH_3) to 173.9 ppm (C=O) as envisaged. All the eighteen aromatic carbons resonated between δ 122.6 ppm and 148.9 ppm while the three remaining signals which depicted -CH_3 linked to tosylate, -CH_2 linked to phenyl and -CH linked to -NH were observed at δ 21.9, 38.3 and 56.4 ppm respectively.

The IR spectrum of **(4k)** exhibited the absorption bands at 1717 cm^{-1} and 1559 cm^{-1} due to the presence of C=O (acid) and C=C respectively while SO_2 functionality was observed as two bands at 1150 and 1092 cm^{-1}. In addition, -NH vibrational mode was responsible for the absorption band noticed at 3339 cm^{-1}. Mass spectrum of **(4k)** showed the base peak at m/z 65.0. Although, molecular ion peak was not observed, however; there was an appearance of a fragment m/z 443.1 which was as a result of loss of -COOH. Other fragmentation patterns resulted in some other prominent daughter fragments at m/z of 171.0, 156.0, 155.0, 134.1 and 92.1 with the intensities of 35%, 58%, 90%, 90% and

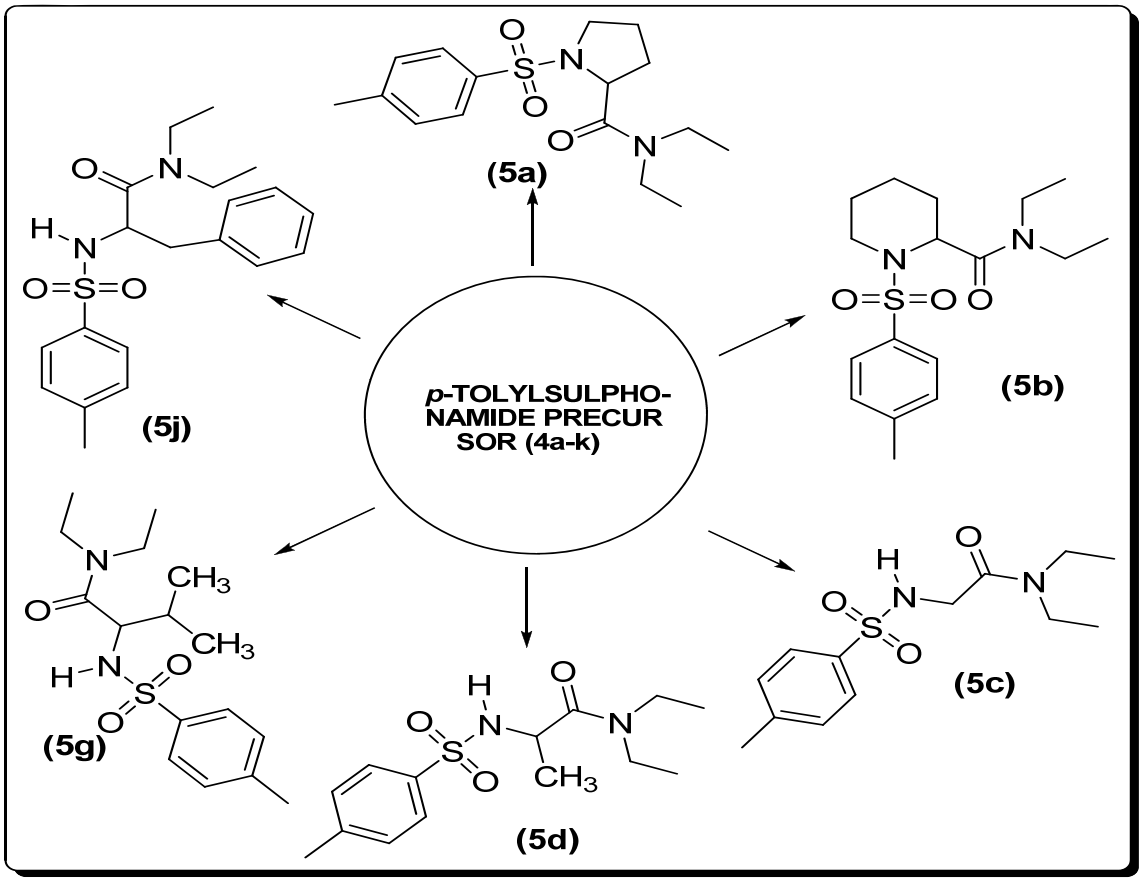
64% respectively. The result of elemental analysis was consistent with that of the proposed structure, showing not more than a maximum different of ±0.30 between % calculated and % found for the carbon, hydrogen and nitrogen of the prepared sulphonamides.

Secondly, the intermediate arylsulphonamides **(4a-k)** subsequently underwent one pot two steps amination procedure to afford *N,N*-diethylsubstituted amide **(5a-k).** The mechanism behind this amidation was given by using amidation of **(4a)** to produce *N,N*-diethyl-1-tosylpyrrolidine-2-carboxamide **(5a)** as a representative for this group. It entailed initial conversion of **(4a)** to its acid chloride with the aid of $(COCl)_2$/DMF earlier discussed (Scheme 4.5a). The acid chloride intermediate was then treated with diethylamine in the presence of TEA base to obtain *N,N*-diethyl-1-tosylpyrrolidine-2-carboxamide **(5a)** where hydrogen chloride gas was eliminated as the byproduct (Scheme 4.14). In order to compare the stereochemical assignment and yield improvement of *N,N*-disubstituted amide, we deviated from conventional method of using thionyl chloride for the conversion of –COOH functionality to acid chloride before subsequent amination.



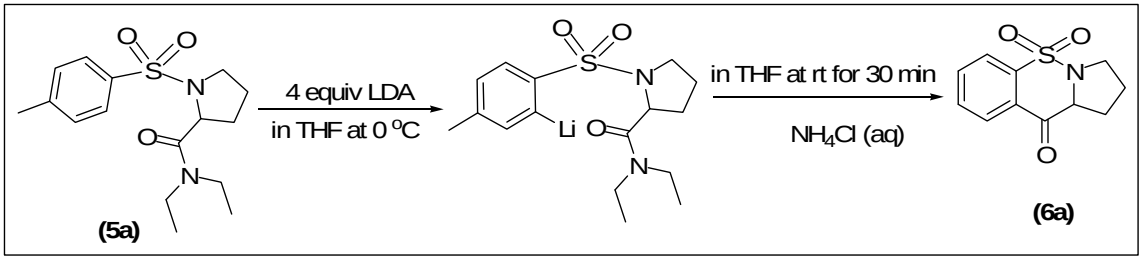
Scheme 4.14: Mechanism for *N,N*-Diethyl-1-tosylpyrrolidine-2-carboxamide (5a).

In a nutshell, *N*,*N*-diethylsubstituted amide **(5a-k)** was obtained from **(4a-k)** by one pot two steps amination protocol according to a recently used procedure (Kuethe and Beutner, 2009) (Scheme 4.15). Although, some of the *N*,*N*-diethylsubstituted amides **(5a), (5b), (5d)** had been reported by using conventional method of thionyl chloride for conversion to acid chloride (Bakker *et al.,* 1997), but it is interesting to note that the procedural route used here-in afforded *N*,*N*-diethylsubstituted amides which showed improvement over the previous method. These include higher yields, easy work up, shorter synthetic route because each of the crude intermediates required no purification before further usage of such intermediate; thus, providing a quick and efficient synthetic route. In addition, although some of *p*-toluenesulphonamide group had been synthesized, the antimicrobial activities of those compounds have not been evaluated to the best of our knowledge. Hence, there was need for repeating the synthesis of such categories, even in this work, in order to investigate their antimicrobial potential.

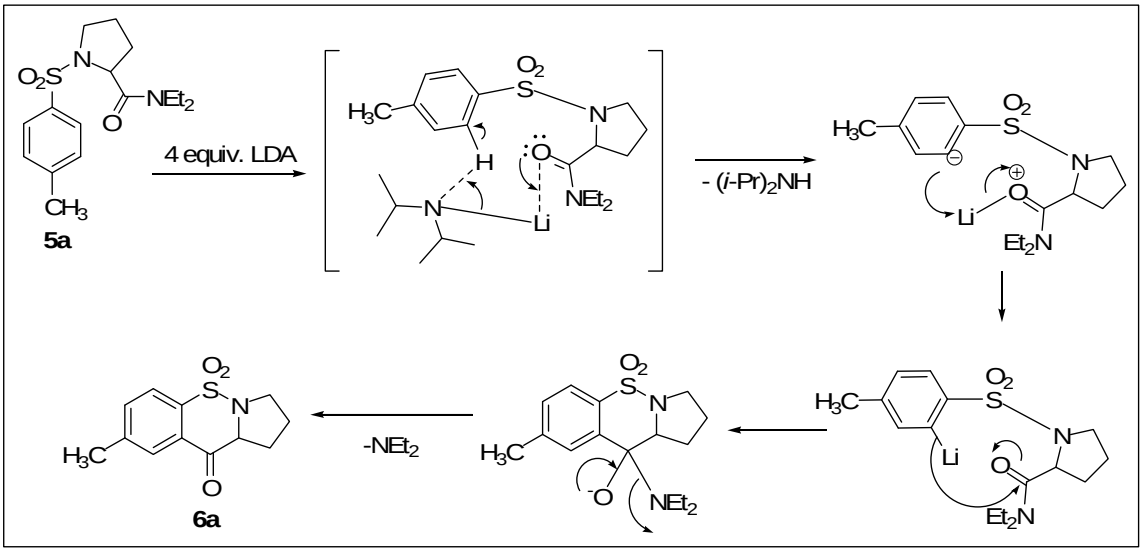


Scheme 4.15: Conversion of *p*-Tolylsulphonamides to *N,N*-Diethylsulphonamides

Thirdly, further synthetic utility of *N,N*-diethylalkanamide substituted *p*-tolylsulphonamide **(5a)** was attempted, by direct metalating approach with lithium diisopropylamide (LDA), to evaluate the possibility of getting benzothiazinone **(6a).** The preparation of **(6a)** was successfully achieved by first lithiating the THF solution of amide **(5a)** in 4 eqivalent of LDA at 0 ^{o}C, which was followed by stirring at room temperature for 30 mins. The reaction was quenched by addition of aqueous ammonium chloride and worked up accordingly (Scheme 4.16). The product **(6a)** was in comformity with the benzothiazinone of an earlier report (Bakker *et al.,* 1997). The mechanism is shown in Scheme 4.17.



Scheme 4.16: **Synthesis of Benzothiazinone (6a)**

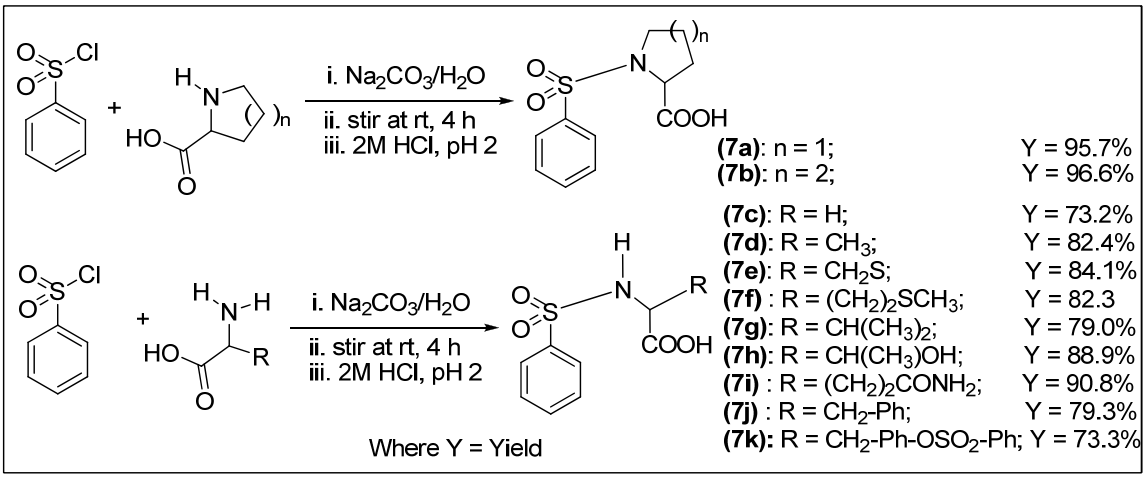


Scheme 4.17: Mechanism for Intramolecular Cyclization of (5a) to afford (6a)

The mechanism for the regiospecific construction of the targeted benzothiazinone framework **(6a)** was preceded by a prelithiation complex formation via the Complex Induced Proximity Effect (CIPE) and followed by subsequent deprotonation by electronic effect to generate Friedel-Craft anionic equivalent. The nucleophilic attack of the ortho carbanion of benzene ring on sp^2 hybridized carbonyl of amide resulted in the effective intramolecular cyclization which was driven by the departure of a good leaving group, NEt_2 (Scheme 4.17).

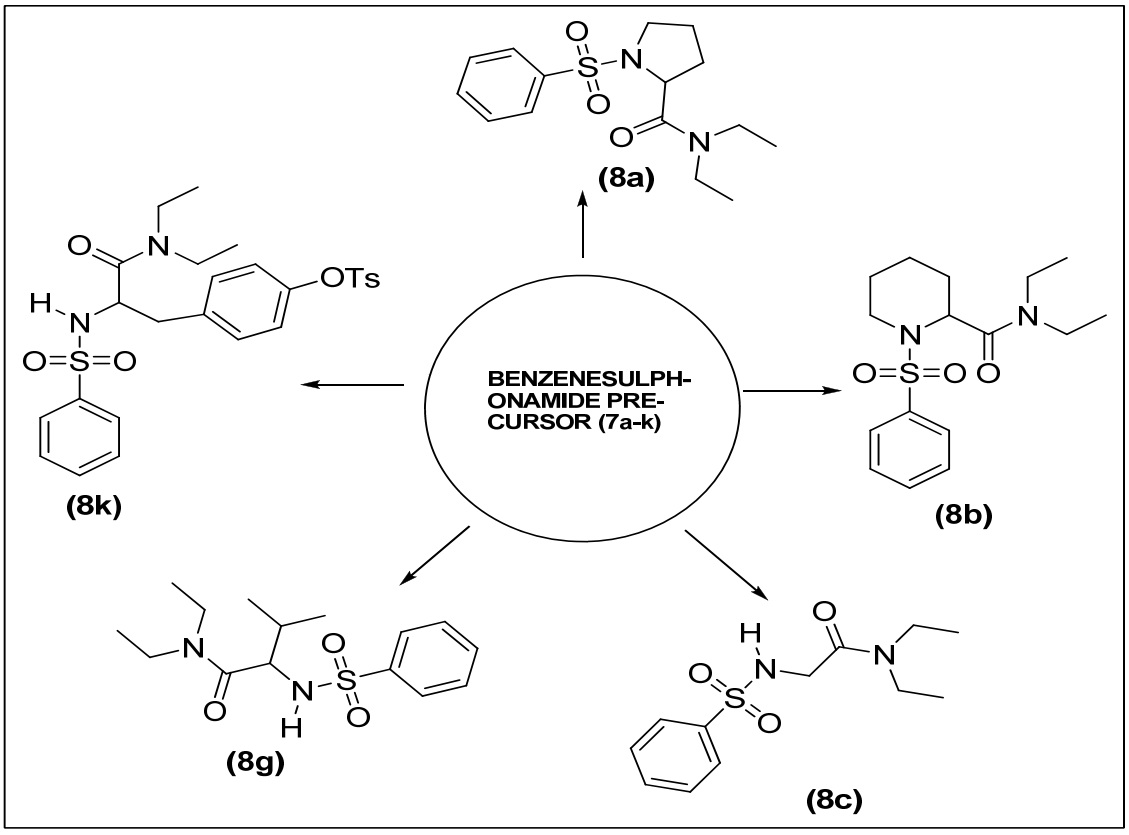
4.3. Derivatives of Benzenesulphonamide

Benzenesulphonyl chloride and its para-substituted counterparts were earlier used in the protection of amino functional group, identification of amino acid and distinguishing between three classes of amine. However, we have here-in successfully used benzenesulphonyl chloride as the cost effective and highly efficient main precursor in order to synthesize our targeted substituted benzenesulphonamide derivatives **(7a-k)** in this present work. Benzenesulphonyl chloride underwent condensation reaction with secondary amine of two different amino acids to afford *N,N*-disubstituted benzenesulphonamides **(7a)** and **(7b),** while its treatment with primary amine functionality of nine other amino acids in alkaline medium generated *N*-substituted benzenesulphonamide **(7c-k)** according to Scheme 4.18. It is important to note that amide formation is a fundamental reaction of great interest in organic chemistry (Naik *et al.,* 2004; Katritzky *et al.,* 2000). The development of efficient methods for the synthesis of amides remains good tools because of their importance in chemistry and biology, with a wide range of industrial and pharmaceutical applications and as valuable intermediates in organic synthesis (Theodorou *et al.,* 2009; Katritzky *et al.,* 2006).



Scheme 4.18: Synthesis of Benzenesulphonamide Derivatives (7a-k)

The carboxylic acid end of the benzenesulphonamide **(7a-k)** prepared was converted to the corresponding diethylsubstituted alkanamide of benzenesulphonamide **(8a-k).** Thus, some selected benzenesulphonamides containing free carboxyl side chain was further treated via two steps one pot mechanism to produce some selected new and known series of *N*,*N*-diethylated alkanamido benzene sulphonamides **(8a), (8b), (8c), (8g)** and (**8k)** in good to excellent yield (Scheme 4.19). This involved, first reacting the arylsulphonamide with oxalyl chloride in presence of one drop of DMF catalyst to produce the acid chloride. This acid chloride was then converted to *N*,*N*-diethyl substituted arylsulphonamide by treating it with diethylamine in the presence of triethylamine base using dichloromethane (DCM) solvent.



Scheme 4.19: Conversion of Benzenesulphonamides to *N*,*N*-Diethylamides

4.4. Antimicrobial Activity

The antibacterial general sensitivity testing (inhibition zone, mm) of all the series of fifty five synthesized sulphonamides (twenty two α-tolylsulphonamides, seventeen *p*-tolylsulphonamides and sixteen benzenesulphonamides) along side with that of streptomycin clinical standard were assayed on test organisms (*Escherichia coli* and *Staphylococcus aureus*) using agar diffusion technique (Adeniyi *et al.,* 1996). The choice of *E. coli* as the Gram –ve organism is because it is easily transmissible through food, water, soil, animal and man (Nwinyi *et al.,* 2008). *E. coli* is a normal flora of human body which causes a lot of vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* (MRSA) (Dyatkina *et al.,* 2002).

Based on our previous report (Ajani *et al*., 2010), the choice of streptomycin as clinical standards is due to the fact that at low concentrations, streptomycin only inhibits growth of the bacteria through induction of prokaryotic ribosomes to misread *m*RNA (Voet and Voet, 2004) and it also possesses broad spectrum of antibacterial activity. There were reported cases of *E. coli* and *Staphylococcus aureus* being susceptible to streptomycin (Eshghi *et al.,* 2011; Ajani and Nwinyi, 2009). The biological relevance of the synthesized sulphonamides here-in was authenticated by screening them *in vitro* against *Staphylococcus aureus* ATCC 6538 (*S. aureus*) and *Escherichia coli* ATCC 25922 (*E. coli*) with the reported selectivity index (S.I.) duly calculated by comparing zones of inhibition (Z.O.I) of compound to that of streptomycin (i.e. ZO.I of compound/Z.O.I. of streptomycin standard

(a) Antimicrobial Activity of α-Tolylsulphonamides: The result of sensitivity testing revealed that the probable activities of α-tolylsulphonamide family on the test organisms were categorized based on the size of zone of inhibition (Table 4.3). Interestingly, it was observed that some of the compounds exhibited probable significant activities based on the large zone of inhibition reported. For instance, compounds **(1f)**, **(1g)**, **(2b)**, **(2c)** and **(2k)** were highly active on *E. coli* while compounds **(1a)**, **(1b)**, **(1d)**, **(1e)**, **(1j)**, **(1k)**, **(2e)** and **(2i)** exhibited moderate activities on the same organism. All other compounds showed low activities on *E. coli* except **(1c)** and **(2e)** which were inactive on the *E. coli* even at 1000 μg/mL. The scenario of comparative study of effect of the sulphonamides and streptomycin on *E. coli* could be vividly understood by observing the selectivity index (S.I.). All the sulphonamides have selectivity indices ranging from 0.29 for compound **(2g)** to 0.96 for compound **(2k)** (i.e. less than 1). This implies that streptomycin (S.I. = 1) was probably more active than any of the sulphonamide scaffolds as regarding the inhibition of *E. coli* growth. In the same vein, looking through the effect on *S. aureus*, compounds **(1a)**, **(1e)**, **(2f)**, **(2j)** and **(2k)** were highly active; **(1d)**, **(1f), (1h)**, **(1j)**, **(1k)**, **(2b)**, **(2c)** and **(2h)** were moderately active; **(1b)**, **(1c)**, **(1g)**, **(1i)**, **(2a)**, **(2d)**, **(2g)** and **(2i)** exhibited low activity while **(2e)** was inactive on *S. aureus* (Table 4.3).

The comparative study of α-toluenesulphonamides to streptomycin on *S. aureus* growth inhibition is worthy of commendation. The S.I. values indicated that compounds (**1i)**, (**2b)**, (**2g)** and (**2i)** competed favourably with streptomycin while **(1a)**, **(1d)**, **(1e)**, **(1f)**, **(1h)**, **(2a)**, **(2c)**, **(2f)**, **(2h)**, **(2j)** and **(2k)** (S.I. = 1.08 - 2.31) showed even a better activity than streptomycin on *S. aureus*. All other compounds exhibited lesser activity than streptomycin (S.I. = 0.46 - 0.92) on *S. aureus* except **(2e)** which was inactive.

Table 4.3: **General Sensitivity Testing with of Organisms with Zones of Inhibition**

Organisms → / Compd. No ↓	*In vitro* antibacterial activity			
	E. coli		*S. aureus*	
	Z.O.I (mm)	S.I.	Z.O.I. (mm)	S.I.
(1a)	++	0.54	+++	2.31
(1b)	++	0.61	+	0.92
(1c)	-	-	+	0.69
(1d)	++	0.57	++	1.08
(1e)	++	0.57	+++	2.15
(1f)	+++	0.86	++	1.15
(1g)	+++	0.89	+	0.46
(1h)	+	0.46	++	1.15
(1i)	+	0.36	+	1.00
(1j)	++	0.57	++	0.92
(1k)	++	0.75	++	0.92
(2a)	+	0.43	+	1.08
(2b)	+++	0.84	++	1.00
(2c)	+++	0.82	++	1.38
(2d)	+	0.36	+	0.92
(2e)	-	-	-	-
(2f)	++	0.57	+++	2.23
(2g)	+	0.29	+	1.00
(2h)	+	0.43	++	1.08
(2i)	++	0.54	+	1.00
(2j)	+	0.39	+++	2.00
(2k)	+++	0.96	+++	2.00
Str.	+++	1.00	++	1.00

+ = Less active 5-12mm; ++ = moderately active 13-19mm; +++ = highly active 20-31mm; - = resistance; str. = streptomycin clinical reference; Z.O.I. = zone of inhibition; S.I. = selective index obtained by comparing inhibition zone of compound to that of streptomycin standard; *E. coli* = *Escherichia coli* (ATCC 25922)$^{G-}$; *S. aureus* = *Staphylococcus aureus* (ATCC 6538)$^{G+}$; G- = Gram negative; G+ = Gram positive.

Due to high zones of inhibition obtained during general sensitivity testing, the Minimum Inhibitory Concentration was conducted, first at 100 μg/mL using Russell and Furr method (Russell and Furr, 1977). However, those compounds that could not effect the inhibition of microbial growth at this concentration were further repeated for MIC test at 1000 μg/mL. The result of the MIC of this class of compounds on *E. coli* and *S. aureus* was as shown in Table 4.4.

Interestingly all the sulphonamides tested showed a concentration-dependent inhibitory effect on the *in vitro* microbial growth assays (Andrighetti-Fröhner *et al.,* 2009).

Considering the MIC testing on the gram negative organism (*E. coli*), it was observed that compounds **(1b), (1f), (1g), (1k), (2b), (2c)** and **(2k)** inhibited the microbial growth at varying values less than or equal to 100 μg/mL; whereas, all other compounds were active on *E. coli* at higher concentration (between 125 and 1000 μg/mL) except **(1c)** and **(2e)** which had no activity even at 1000 μg/mL. Specifically speaking, MIC values of the synthesized compounds on *E. coli* was reported to be 50 μg/mL for **(2b)** and **(2c)**; 100 μg/mL for (**1b)** and (**1k)**; 125 μg/mL for **(1a)**, **(1d)**, **(1e)**, **(1j)**, **(2f)** and **(2i)**; 250 μg/mL for **(1h)**, **(1i)**, **(2a)**, **(2d)**, **(2h)** and **(2j)**.

Although the most active sulphonamide on *E. coli* were **(1f)**, **(1g)** and **(2k)** with MIC values of 25, 25 and 12.5 μg/mL respectively, but none of them could compete with streptomycin (with MIC value of 6.25 μg/mL) in term of activity. The two rings presenct in 2k and their π-character might be resposible for the high for it being the most active as deduced from the finding of Aissaoui *et al.* (2008). To face the stark reality, eight sulphonamides **(1a)**, **(1e)**, **(1f)**, **(1h)**, **(2c)**, **(2f)**, **(2j)** and **(2k**) inhibited the *S. aureus* growth at concentration ranging from 1.8 and 100 μg/mL. All others compounds were

able to effect the expected inhibition from 125 μg/mL to 1000 μg/mL except **(2e)** which was inactive even at 1000 μg/mL. The significant antibacterial activity of the synthesized compounds may be explained as earlier documented in literatures (Shei, 2010; Levin *et al.,* 2007), by the ability of its sulphonamide binding site to mimic *p*-aminobenzoic acid (PABA) which is an essential growth factor in the targeted organisms.

Table 4.4: MIC Test of α-Tolylsulphonamides on Targeted Organisms (μg/mL)

Organisms → / Compd. No ↓	Minimum Inhibitory Concentration (μg/mL)			
	E. coli ATCC 25922		*S. aureus* ATCC 6538	
	@100μg/mL	@1000μg/mL	@100μg/mL	@1000μg/mL
(1a)	>100	125	1.8	<1000
(1b)	100	<1000	>100	250
(1c)	>100	-	>100	250
(1d)	>100	125	>100	125
(1e)	>100	125	50	<1000
(1f)	25	<1000	100	<1000
(1g)	25	<1000	>100	500
(1h)	>100	250	100	<1000
(1i)	>100	1000	>100	250
(1j)	>100	125	>100	125
(1k)	100	<1000	>100	125
(2a)	>100	250	>100	250
(2b)	50	<1000	>100	125
(2c)	50	<1000	62.5	<1000
(2d)	>100	200	>100	1000
(2e)	>100	-	>100	-
(2f)	>100	125	25	<1000
(2g)	>100	500	>100	1000
(2h)	>100	250	>100	125
(2i)	>100	125	>100	250
(2j)	>100	200	25	<1000

(2k)	12.5	<1000	25	<1000
Str.	6.25	<1000	>100	125

>100 means that if there was no growth inhibition at 100 μg/mL, it was repeated at 1000 μg/mL , <1000 μg/mL means that growth inhibition has already been experienced at lower concentration less than or equal to 100 μg/mL; hence, there is no need to repeat the test at 1000 μg/mL. – means no activity was observed even at 1000 μg/mL. Str. means Streptomycin clinical reference.

(b) Antimicrobial Activity of *p*-Tolylsulphonamides: For the sake of brevity and better understanding, the selectivity index of the synthesized *p*-tolylsulphonamide derivatives on *E. coli* is as shown in Fig. 4.1. The selectivity index, which was evaluated by comparing the zone of inhibition (mm) obtained from each of the synthesized compounds with that of clinical standard (streptomycin), gave a clearer picture of the antibacterial activity of this group of sulphonamide on the targeted organisms. Although majority of the *p*-tolylsuphonamides have moderate to high activity, but none of them could compete with the streptomycin in *E. coli* growth inhibition efficacy. It was observable that the S.I. of *p*-tolylsulphonamide varied from 0.5 for **(4c)** to 0.98 for **(5j)**. Unequivocally speaking, streptomycin, with S.I. value of 1, demonstrated high level of superiority to all the synthesized *p*-tolylsulphonamide on the inhibition of *E. coli* growth. The highest activity was observed in **(5j)** with S.I. of 0.98. This improved activity might be as a result of additional conjugation which occurred in **(5j)**, other compounds that showed high activity include **(4d)**, **(4e)**, **(4k)**, **(5a)**, **(5b)**, **(5c)**, **(5d)** and **(5g)** (S.I. > 0.8). Within the class, it was noticeable that only seven compounds showed moderate activity, in a decreasing order **(4f)** ≈ **(4g)** > **(4h)** > **(4j)** > **(4a)** ≈ **(4i)** > **(4b)** (0.6 < S.I. < 0.8) while the least activity which was categorized by S.I. < 0.6, was experienced in one compound **(4c)** with S.I. value of 0.5 to be precised.

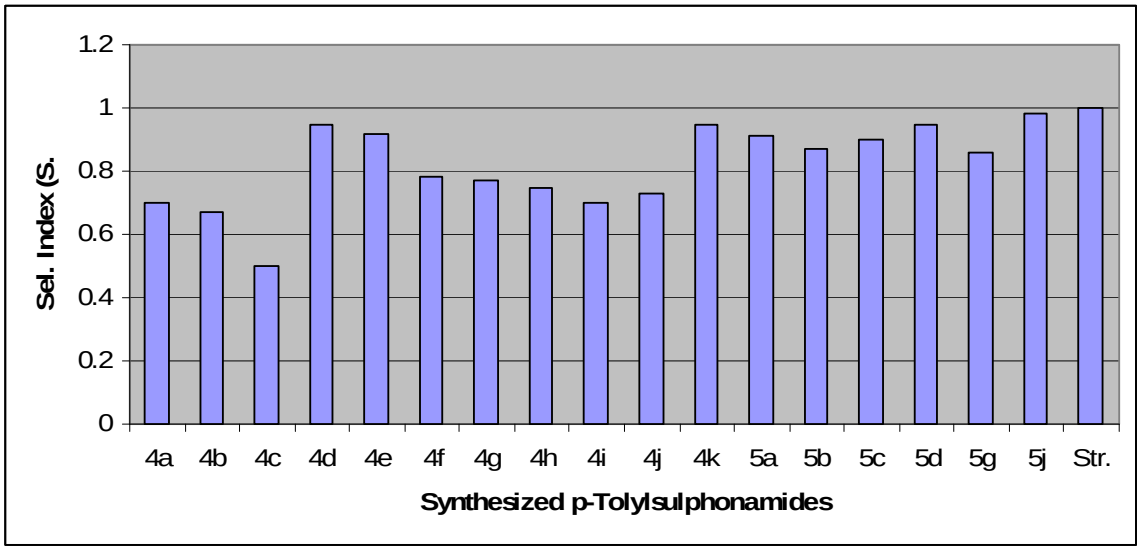


Fig. 4.1: Antibacterial Activity of *p*-Tolylsulphonamides against *Escherichia coli*

In like manner, the antibacterial activity of *p*-tolylsulphonamides with respect to streptomycin antibiotic on the *S. aureus* clinical isolate was also evaluated and pictorially presented as shown in Fig. 4.2. Based on the intensity of the selectivity index, **(5j)** could be considered as the most active (S.I. value = 1.6) while **(4a)** and **(5g)** were the least active having S.I. value of 0.47. It is worthy to note that two compounds **(4f)** and **(5j)** were more active than the streptomycin as far as *S. aureus* screening was concerned. All other *p*-tolylsulphonamides were less active than streptomycin except **(4i),** which in this case, competed favourably with the streptomycin standard. Hence, ten *p*-tolylsulphonamides exhibited moderate activity on *S. aureus* in a decreasing order as **(4k)** > **(4g)** > **(4d)** ≈ **(4e)** ≈ **(4h)** ≈ **(5a)** > **(4j)** > **(5c)** ≈ **(5b)** > **(5d)** (0.5 < S.I. < 0.8) whereas lesser activity was exhibited by compounds **(4c)** > **(4b)** > **(4a)** ≈ **(5g)** (S.I. < 0.5).

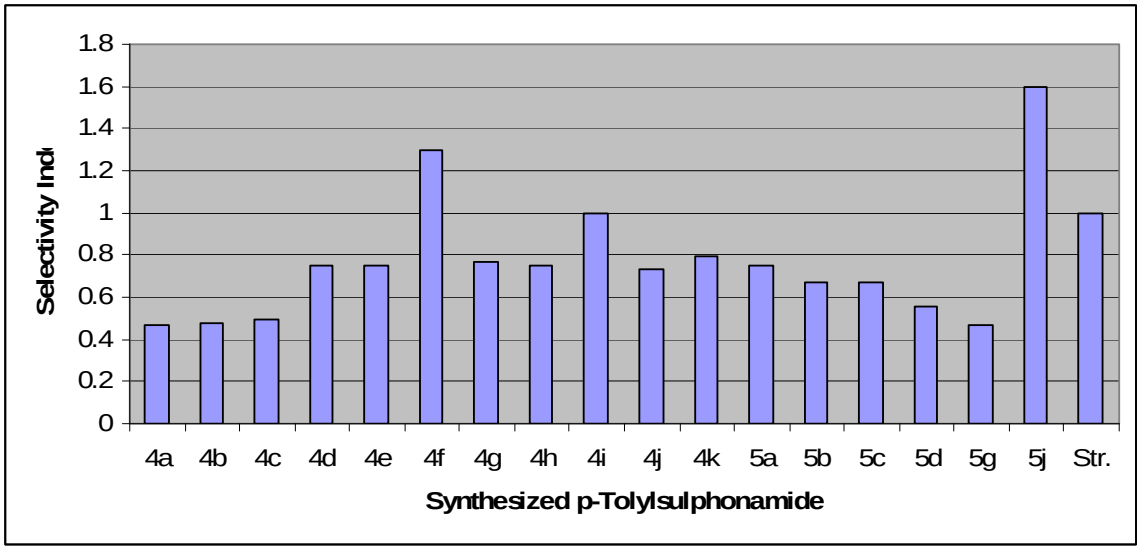


Fig. 4.2: Antibacterial Activity of *p*-Tolylsulphonamides against *Staphylococcus aureus*

Furthermore, in order to establish the lowest concentration at which the growth of *E. coli* and *S. aureus* was inhibited by *p*-tolylsulphonamide scaffolds, the MIC test was carried out and the result is as shown in Table 4.5. From the point of view of *E. coli,* the MIC values ranged from 12.5 µg/mL **(5j)** to 1000 µg/mL **(4c)** while the MIC value for streptomycin under similar condition was 6.25 µg/mL. Although, streptomycin was more active than any of the *p*-tolylsulphonamides, it was apparent that different *p*-tolylsulphonamides exhibited varying MIC values against the strain of *E. coli.* Thus, the MIC values ranging from 12.5 µg/mL to 50 µg/mL was observable among **(5j)**, (**5d)**, (**4k)**, (**4d)**, (**4e)**, (**5a)** and (**5c)**; between 62.5 µg/mL and 100 µg/mL for (**5b)**, (**5g)**, (**4f)** and (**4g)**; between 125 µg/mL and 500 µg/mL for **(4a), (4b), (4i), (4h)** and **(4j)** and the least activity was observed in compound **(4c)** with an MIC value of 1000 µg/mL.

In addition, the MIC test for the series of *p*-tolylsulphonamides was carried out on *S. aureus* (Table 4.5) and it should be noted that the lowest MIC value culminated into highest potency (Sepandj *et al.,* 2004). It is therefore paramount to note that the highest potency was observed in **(5j)** (MIC = 25 µg/mL) while compound **(5g)** exhibited the least

potency (MIC = 1000 μg/mL) on *S. aureus*. This is higher activity than one reported by Ghorab *et al.,* (2004). From comparative study, many members of this group such as **(4d), (4e), (4f), (4g), (4h), (4i), (4j), (4k), (5a)** and **(5j)** (MIC = 25 μg/mL – 100 μg/mL) were more active than streptomycin (MIC = 125 μg/mL) using the MIC test involving *S. aureus*. Under the same condition, **(5b)** (MIC = 125 μg/mL) competed favorably with streptomycin in its inhibitory potential on *S. aureus*. Seven compounds **(4d)**, **(4e)**, **(4g)**, **(4h)**, **(4j)**, **(4k)** and **(5a**) had MIC value 100 μg/mL and other seven *p*-tolylsulphonamides **(5b)**, **(5c)**, **(5d)**, **(4a)**, **(4b)**, **(4c)** and **(5g**) had MIC values between 125 μg/mL and 1000 μg/mL.

Table 4.5: MIC Test of *p*-Tolylsulphonamides on Targeted Organisms (μg/mL)

Organisms → / Compd. No ↓	Minimum Inhibitory Concentration (μg/mL)			
	E. coli ATCC 25922		*S. aureus* ATCC 6538	
	@100μg/mL	@1000μg/mL	@100μg/mL	@1000μg/mL
(4a)	> 100	125	> 100	250
(4b)	> 100	250	> 100	250
(4c)	> 100	1000	> 100	500
(4d)	25	< 1000	100	< 1000
(4e)	50	< 1000	100	< 1000
(4f)	100	< 1000	50	< 1000
(4g)	100	< 1000	100	< 1000
(4h)	> 100	500	100	< 1000
(4i)	> 100	250	62.5	< 1000
(4j)	> 100	500	100	< 1000
(4k)	25	< 1000	100	< 1000
(5a)	50	< 1000	100	< 1000

(5b)	62.5	< 1000	> 100	125
(5c)	50	< 1000	> 100	250
(5d)	25	< 1000	> 100	250
(5g)	62.5	< 1000	> 100	1000
(5j)	12.5	< 1000	25	< 1000
Str.	6.25	< 1000	> 100	125

>100 means that if there was no growth inhibition at 100 μg/mL, it was repeated at 1000 μg/mL , <1000 μg/mL means that growth inhibition has already been experienced at lower concentration less than or equal to 100 μg/mL; hence, there is no need to repeat the test at 1000 μg/mL. – means no activity was observed even at 1000 μg/mL. Str. means Streptomycin clinical reference.

(c) Antimicrobial Activity of Benzenesulphonamides: The comparative study of activity of the benzenesulphonamides with that of streptomycin standard was commensurated using selectivity index on both *E. coli* and *S. aureus*. The selectivity index of benzenesulphonamide derivatives along side with that of streptomycin was evaluated on *E. coli* (Fig. 4.3). The selectivity index of this series of sulphonamide varied from 0.97 to 0.31; hence, streptomycin is more active than all the benzenesulphonamide. Since increasing intensity of selectivity index connotes improved antibacterial activity; thus, the most active compound of this class was **(7b)** (S.I. = 0.97) while the least active was **(8c)** (S.I. = 0.31). The activities of other benzenesulphonamides were between the two extremists as shown in Fig. 4.3. They were categorized into most active (S.I. > 0.8), moderately active (0.6 < S.I. < 0.8) and least active (S.I. < 0.6). Bearing this classification in mind, it was noticeable that the occurrence of the most active scaffolds in a decreasing order of activity was **(7b)** ≈ **(7k)** > **(7d)** > **(8a)** ≈ **(8g)** > (**8k)** > **7i** ≈ **8b** > **7j**; that of moderate activity was **(7c)** ≈ **(7e)** ≈ **(7f)** > **(7g)** whereas the least activity was in order of **(7a)** ≈ **(7h)** > **(8c)**.

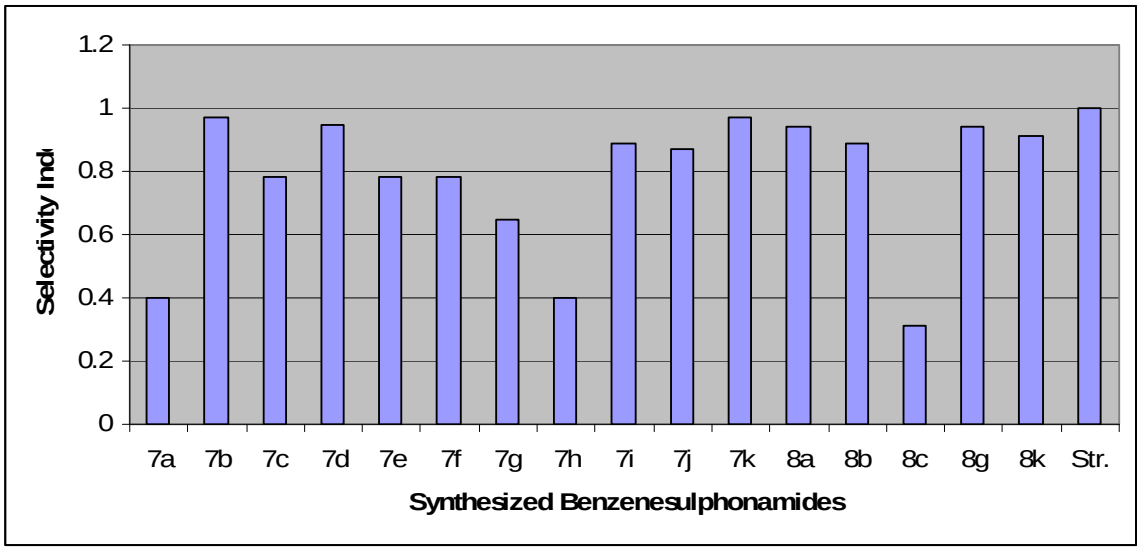


Fig. 4.3: Antibacterial Activity of Benzenesulphonamides against *Escherichia coli*

Furthermore, the selectivity index of benzenesulphonamides was also investigated on *S. aureus* and the values varied from 1.6 to 0.28 (Fig. 4.4). In comparing with the activity of streptomycin, five compounds **(7b)**, **(7j)**, **(7k)**, **(8b)** and **(8k)** were more active; one compound **(7a)** had invariably similar activity with the standard while all other compounds were less potent than streptomycin. Nevertheless, by comparing the trend of activity within the series, the highly active compounds in order of priority of potency were **(7k)** ≈ **(8b)** ≈ **(8k)** > **(7b)** ≈ **(7j)** > **(7a)** > **(7f)** > **(7g)** (0.95 < S.I. < 1.6); the moderate activity was found in **(8a)** ≈ **(8c)** ≈ **(8g)** (S.I. = 0.62) while the remaining five benzenesulphonamides **(7e)** > **(7d)** > **(7c)** ≈ **(7i)** > **(7h)** (0.28 < S.I. < 0.48) were the series with least activity.

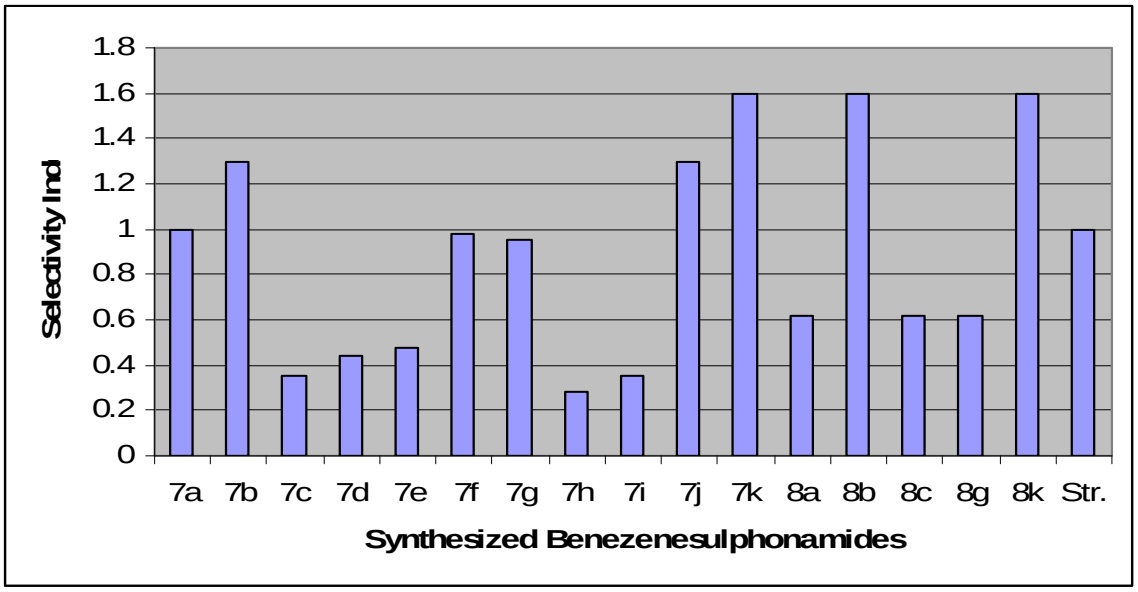


Fig. 4.4: Antibacterial Activity of Benzenesulphonamides against *Staphylococcus aureus*

The minimum inhibitory concentration was determined in order to authenticate the actual concentration responsible for the benzenesulphonamide activity observed on both *E. coli* and *S. aureus* (Masunari *et al.,* 2007). The result was as shown in Table 4.6. Thus, to start with, the lowest concentration of these sulphonamides that inhibited the growth of *E. coli* varied from 25 µg/mL to 1000 µg/mL. Hence, the compound that had highest potency was **(8b)** with MIC value of 25 µg/mL while the least active ones were **(7e)** and **(7h)** with MIC of 1000 µg/mL. Other sulphonamides exhibited the potency at diverse ranges. They were compounds **(7b)**, **(7d)**, **(8a)**, **(8g), (8k)** and **(7i)** with MIC value between 50 µg/mL and 100 µg/mL; **(7a), (7f), (7g), (8c)** and **(7c).** This class of sulphonamide followed a peculiar trend in activity, as it was noticed that all the *N,N*-disubstituted sulphonamides **(8a)**, **(8b)**, **(8c)**, **(8g)** and **(8k**) showed better activity than their corresponding non-subsituted sulphonamides **(7a)**, **(7b)**, **(7c)**, **(7g)** and **(7k**) according to Table 4.6. This was in line with earlier work of Dobek *et al.,* (1980) which

reported that *N,N*-disubstituted thiosemicarbazone were more active than the non- and mono-substituted analogs.

Considering the MIC test of benzenesulphonamides on the gram positive organism (*S. aureus*), it was observed that compounds **(8k), (8b), (7j), (7k), (7f)** and **(7b)** inhibited the microbial growth at varying MIC values ≤ 100 μg/mL; whereas, all other compounds were active on *S. aureus* at higher concentrations (between 125 μg/mL and 1000 μg/mL). Specifically speaking, MIC value of the most potent in this series **(8b)** and **(8k)** on *S. aureus* was reported to be 25 μg/mL which were two fold more active than **(7j)**, with MIC value of 50 μg/mL and four times more active than **(7b)** (100 μg/mL). The MIC value **(7j)** was reported to be 50 μg/mL which established it to be ten times more active than **(7d), (7h)** and **(7i)** with MIC value of 500 μg/mL. The compound with least activity was **(7c)** (1000 μg/mL).

Table 4.6: MIC Test of Benzenesulphonamides on Targeted Organisms (μg/mL)

Organisms → / Compd. No ↓	Minimum Inhibitory Concentration (μg/mL)			
	E. coli ATCC 25922		*S. aureus* ATCC 6538	
	@100μg/mL	@1000μg/mL	@100μg/mL	@1000μg/mL
(7a)	>100	125	>100	125
(7b)	50	< 1000	100	< 1000
(7c)	>100	500	>100	1000
(7d)	50	< 1000	>100	500
(7e)	>100	1000	>100	250
(7f)	>100	125	62.5	< 1000
(7g)	>100	250	>100	250
(7h)	>100	1000	>100	500

(7i)	100	< 1000	>100	500
(7j)	250	< 1000	50	< 1000
(7k)	125	< 1000	62.5	< 1000
(8a)	50	< 1000	>100	125
(8b)	25	< 1000	25	< 1000
(8c)	>100	250	>100	250
(8g)	50	< 1000	>100	125
(8k)	62.5	< 1000	25	< 1000
Str.	12.5	< 1000	>100	125

>100 means that if there was no growth inhibition at 100 μg/mL, it was repeated at 1000 μg/mL , <1000 μg/mL means that growth inhibition has already been experienced at lower concentration less than or equal to 100 μg/mL; hence, there is no need to repeat the test at 1000 μg/mL. – means no activity was observed even at 1000 μg/mL. Str. means Streptomycin clinical reference.

REFERENCES

Wouter I. Iwema Bakker, Oluwole B. Familoni *et al.,* 1997, Intramolecular anionic Friedel-Crafts equivalents. An expeditious synthesis of 4*H*-1,2-benzothiazin-4-one 1,1-dioxide from *N*-arylsulphonylated amino acid. *Synlett, 1532,* pp 1079-1080.

Weifeng Zhang, Yuancheng Qin, *et al.,* 2005, Synthesis of novel N-heterocyclic carbene-Rh complexes derived from L-proline and their catalysis in the addition of arylboronic acids to aldehyde. *Arkivoc 14,* pp 39-48.

Jeffrey T. Kuethe and Gregory L. Beutner, 2009, Synthesis of 2-arylindole-4-carboxylic amides: [2-(4-Fluorophenyl)-1*H*-indol-4-yl]-1-pyrrolidinylmethanone. *Organic Synthesis, 86,* pp 92-104.

T. Kawaguchi, H. Miyata, *et al.,* 2005, Room-Temperature Swern oxidations by using a microscale flow system. *Angewandte Chemie International Edition, 44(16),* pp 2413-2416.

Margarita Parra, Enrique Sotoca, *et al.,* 2003, A convenient generation of acetic acid dianion. *European Journal of Organic Chemistry, Issue 8,* 1386-1388.

Oluwole B. Familoni, Ileana Ionica, *et al.,* 1997, Intramolecular anionic friedel-crafts equivalents. A general regiospecific route to substituted and naturally occurring xanthen-9-ones. *Synlett, 1533,* pp 1081-1083.

Jonathan Clayden, Arve Lund, *et al.,* 2004, Ultra-remote stereocontrol by conformational communication of information along a carbon chain. *Nature, 431,* pp 966-971.

Yoshimichi Shoji, Kenji Takahashi, *et al.,* 2009, Novel indoline-based acyl-CoA: cholesterol acyltransferase inhibitor: Effects of introducing a methanesulphonamide group on physicochemical properties and biological activities. *Bioorganic and Medicinal Chemistry, 17,* pp 6020-6031.

Kaveh P. Boroujeni, 2010, Friedel-Crafts acylation of arenes with carboxylic acids using silical gel supported $AlCl_3$. *Turkish Journal of Chemistry, 34,* pp 621-630.

S. Naik, G. Bhattacharjya, *et al.,* 2004, Chemoselective acylation of amines in aqueous media. *European Journal of Organic Chemistry, 6,* pp 1254-1260.

Alan R. Katritzky, H.Y. He, *et al.,* 2000, *N*-Acylbenzotriazoles: Neutral acylating reagents for the preparation of primary, secondary and tertiary amides. *Journal of Organic Chemistry, 65(24),* pp 8210-8213.

Vasilliki. Theodorou, Aris Karkatsoulis, *et al.,* 2009, Tritylamine as an ammonia synthetic equivalent: Preparation of primary amides. *Arkivoc, (xi),* pp 277-287.

Alan R. Katritzky, C. Cai, *et al.,* 2006, Efficient microwave access to polysubstituted amidines from imidoylbenzotriazoles. *Journal of Organic Chemistry, 71(9),* pp 3375-3380.

B.A. Adeniyi, H.A. Odelola, *et al.,* 1996, Antimicrobial potentials of *Diospyros mespiliformis* (Ebenaceae). *African Journal of Medicinal Science***,** *255,* pp 221-224.

Obinna C. Nwinyi, Shalom N. Chinedu, *et al.,* 2008, Evaluation of antibacterial activity of pisidium guajava and Gongronema latifolium. *Journal of Medicinal Plant Research, 2(8),* pp 189-192.

Natalia B. Dyatkina, Christopher D. Roberts, *et al.,* 2002, Minor groove DNA binders as antimicrobial agents, i, pyrazoles tetraamides are potential antibacteria against vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* agents. *Journal of Medicinal Chemistry, 45*, pp 805-817.

Olayinka O. Ajani, Craig A. Obafemi, *et al.,* 2010, Microwave assisted synthesis and antimicrobial activity of 2-quinoxalinone-3-hydrazone derivatives. *Bioorganic and Medicinal Chemistry, 18,* pp 214-221.

Donald Voet and J.D. Voet, 2004, In *Biochemistry* 3rd Edition, pp 1341-1342. ISBN 0-471-19250-x (cloth).

Hossein Eshghi, Mohammad Rahimizadeh, *et al.,* 2011, Synthesis and antimicrobial activity of some new macrocyclic *bis*-sulphonamide and disulphides. *European Journal of Chemistry, 2(1),* pp 47-50.

Olayinka O. Ajani and Obinna C. Nwinyi, 2009, Synthesis and evaluation of antimicrobial activity of phenyl and furan-2-yl[1,2,4]triazolo[4,3-*a*]quinoxalin-4(5*H*)-one and their hydrazone precursors. *Canadian Journal of Pure and Applied Sciences, 3(3),* pp 983-992.

Alan D. Russell and John R. Furr, 1977, Antibacterial activity of a new chloroxylenol preparation containing ethylenediamine tetraacetic acid. *Journal of Applied Bacteriology UK, 43*, pp 253-260.

Carla A. Andrighetti-Fröhner, Kelly N. De Oliveira, *et al.,* 2009, Synthesis, biological evaluation and SAR of sulphonamide 4-methoxychalcone derivatives with potential antileishmanial activity. *European Journal of Medicinal Chemistry, 44,* pp 755-763.

Hamed Aissaoui, Ralf Koberstein, *et al.,* 2008, *N*-Glycine-sulphonamides as potent dual orexin 1/orexin 2 receptor antagonists. *Bioorganic and Medicinal Chemistry Letters, 18,* pp 5729-5733.

Darlene Shei, 2010, Antibiotics as enzymes in: Biochemistry, Toxic Medicine. Posted on 19th June, 2010. Accessed online on 15th November, 2010 at: http://littledoctors.wordpress.com /2010/06/19/antibiotics-as-enzymes/

I. Levin, M. Mevarech, *et al.,* 2007, Characterization of a novel bifunctional dihydropteroate synthase/dihydropteroate reductase enzyme from Helicobacter pylori. *Journal of Bacteriology, 189(11),* pp 4062-4069.

F. Sepandj, H. Ceri, *et al.,* 2004, Minimum inhibitory concentration (MIC) versus biofilm eliminating concentration (MBEC) in evaluation of antibiotic sensitivity of gram-negative bacilli causing peritonitis. *Peritoneal Dialysis International, 24,* pp 65-67.

M.M. Ghorab, Ragab, *et al.,* 2010, *In vitro* anticancer screening and radiosensitizing evaluation of some new quinolines and pyrimido[4,5-*b*]quinolines bearing a sulphonamide moiety. *European Journal of Medicinal Chemistry, 45,* pp 3677-3684.

A. Masunari, and L.C. Tavares, 2007, A new class of nifuroxazide analogues: synthesis of 5-nitrophene derivatives with antimicrobial activity against multidrug-resistant *Staphylococcus aureus. Bioorganic and Medicinal Chemistry, 15*, pp 4229-4236.

A.S. Dobek, D.L. Klayman, *et al.,* 1980, Inhibition of clinically significant bacterial organisms *in vitro* by 2-acetylpyridine thiosemicarbazones. *Antimicrobial Agents and Chemotherapy 18(1),* pp 27-36.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1. Conclusions

In summary, it was discovered that α-toluenesulphonamide derivatives had a reverse order of behaviour in terms of solubility properties as compared with *p*-toluenesulphonamide and benzenesulphonamide derivatives. The α-toluenesulphonamide derivatives were perfectly soluble in water thereby making it difficult to isolate. This was an abnormal behaviour as it contradicted the long standing hydrophobic pattern of normal sulphonamides which made them crystallizable from water by acidifying to low pH (2.2). Hence, of all the sulphonamides, the one that involves α-toluenesulphonamide framework has always been a great challenge to synthetic Chemists.

However, the synthesis of this targeted novel α-toluenesulphonamide derivatives **(1a-k)** in excellent yields was obtained for the first time to the best of our knowledge, by introducing freeze drying at the work-up stage in order to obtain the α-toluenesulphonamide crystals since the acidification resulted in water-soluble sulphonamides. The proferred solution in this present work made the α-toluenesulphonamide derivatives available in crystalline form for further work. The reaction of *N*,*N*-diethyl amine with α-toluenesulphonamides in the preparation of *N*,*N*-diethylalkanamide substituted sulphonamides **(2a-k)** was carried out successfully. Furthermore, a convenient synthesis of *p*-toluenesulphonamide derivatives **(4a-k)** via simple and cheap sulphonylation technique was developed. In this research work, the design and development of *p*-toluenesulphonamide pharmacophores bearing amide that

has been disubstituted with ethyl group (*N*,*N*-diethylamido substituted sulphonamide) **(5a-k)** has been obtained in improved yields using variation of the amidation approach.

The synthesis of benzenesulphonamide derivatives **(7a-k)** was obtained from benzenesulphonyl chloride as the sulphonylation agent. Some of the benzenesulphonamide derivatives were already known, but the protocol used in this work gave better yields and simplified the procedure. The subsequent amidation of some benzenesulphonamide intermediates using diethyl amine, afforded the diethyl substituted amide bearing benzenesulphonamide scaffolds **(8a), (8b), (8c), (8g)**and **(8k)** as envisaged. The purification of the synthesized compounds was carried out using recrystallization and column chromatography, while characterization was carried out using elemental analysis and spectroscopic means, especially FT-IR, Mass Spectra, ^{1}H- and ^{13}C-NMR.

The compounds that were prepared were tested for their antimicrobial activity. The result of the antimicrobial activity of the series of sulphonamides revealed that they were very active on *E. coli* and *S. aureus* as the targeted organisms and some of them also competed favourable with a standard antibiotic (streptomycin) which was used as the clinical reference. The general sensitivity testing was evaluated using selectivity index which was obtainable from the zone of inhibition (Z O I) while the actual lowest concentration at which the inhibition took place was determined using MIC test. The results indicated the series of sulphonamide has broad spectrum of antimicrobial activity (against both gram positive and negative bacteria) with majority having moderate activity. The most active of all sulphonamides on *S. aureus* was **(1a)** (MIC = 1.8 (μg/mL) while the most active sulphonamide on *E. coli* was **(2k) and (5j)** (12.5 μg/mL). Interestingly, both compounds were from the α-toluenesulphonamide series. It is also interesting to

note that compound **(1a)** reported above was more active than streptomycin standard as far as potency against *S. aureus* was concerned.

5.2. Recommendations

It is hereby recommended that further study should be carried out in order to establish and identify a new and facile approach toward achieving the benzofused heterocycle such as benzothiazepinone from intramolecular cyclization of the amide of various α-toluene sulphonamide. Due to abnormally high hydrophilicity of the α-toluenesulphonamide derivatives, it is recommended that the work-up stage should be effected via lyophilization.

The quest to getting the desired approach to obtain the cyclized compounds is a worthwhile adventure because it will lead to achieving new functionalized benzothiazepinone which are heterocyclic framework of great interest in drug discovery and therapeutic agents design. This is so because it is known that cyclized compounds most time are more active that the acyclic ones. The new α-toluenesulphonamide derivatives are also good candidates for further study in terms of toxicological and other pharmacological screening.

A work of this magnitude could not have been achieved without the help of latest spectroscopic method for structural characterization which were not available in the home University. Hence, it is recommended that the University Management should help the Central instrumentation laboratory to purchase some of these instruments such as NMR and mass spectrometer in order to take α-toluenesulphonamide research and other scientific research to the next level.

BIBLOGRAPHY

Adeniyi, B.A., Odelola, H.A. and Oso, B.A., 1996, Antimicrobial potentials of *Diospyros mespiliformis* (Ebenaceae). *African Journal of Medicinal Science*, *255,* 221-224.

Agrawal V.K., Sinha, S., Bano, S. and Khadikar, P.V., 2001, QSAR studies on antimalarial 2,4-diamino-6-quinazoline sulphonamides. *Acta Microbiologica et Immunologica Hungarica, 48(1),* 17-26.

Ahn, E-Y., Pan, G., Oh, J.H., Tytler, E.M. and McDonald, J.M., 2003, The combination of calmodulin antagonists and interferon-γ induces apoptosis through caspase-dependent and –independent pathways in cholangiocarcinoma cells. *American Journal of Pathology, 163(5),* 2053-2054.

Aissaoui, H., Koberstein, R., Zumbrunn, C., Gatfield, J., Brisbare-Roch, C., Jenck, F., Trieber, A. and Boss, C., 2008, *N*-Glycine-sulphonamides as potent dual orexin 1/orexin 2 receptor antagonists. *Bioorganic and Medicinal Chemistry Letters, 18,* 5729-5733.

Ajani, O.O. and Nwinyi, O.C., 2009, Synthesis and evaluation of antimicrobial activity of phenyl and furan-2-yl[1,2,4]triazolo[4,3-a]quinoxalin-4(5*H*)-one and their hydrazone precursors. *Canadian Journal of Pure and Applied Sciences, 3(3),* 983-992.

Ajani, O.O., Obafemi, C.A., Nwinyi, O.C. and Akinpelu, D.A., 2010, Microwave assisted synthesis and antimicrobial activity of 2-quinoxalinone-3-hydrazone derivatives. *Bioorganic and Medicinal Chemistry, 18,* 214-221.

Alqasoumi, S.I., Al-Taweel, A.M., Alafeefy, A.M., Noaman, E. and Ghorab, M.M., 2010, Novel quinolines and primido[4,5-*b*]quinolines bearing biologically active sulphonamide moiety as a new class of Antitumor agents. *European Journal of Medicinal Chemistry, 45,* 738-744.

Al-Soud, Y.A., Al-Sa'doni, H.H., Amjaour, H.A.S., Salih, K.S.M., Mubarak, M.S., Al-Masoudi, N.A. and Jaber, I.H., 2008*a*, Synthesis, characterization and anti-HIV and antitumor activities of new coumarin derivatives. *Zeitschrift fuer Naturforschung, 63b,* 83.

Al-Soud, Y.A., Al-Sa′doni, H.H., Saheed, B., Jaber, I.H., Beni-Khalid, M.O., Al-Masoudi, N.A., Abdul-Kadir, T., Colla, P.L., Busonera, B., Sanna, T. and Loddo, R., 2008*b*, Synthesis and *in vitro* antiproliferative activity of new benzothiazole derivatives. *Arkivoc, xv,* 225-238.

Anand, N., 1996, *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Wollf, M.E., Ed.; John Wiley & Sons: New York, Vol. 2, p 527.

Anand, N. and Remer, W.A., 2010, Synthetic antibacterial agents. *Burger's Medicinal Chemistry, Drug Discovery and Development,* John Wiley and Sons, New York, pp 1-80.

Andrighetti-Fröhner, C.A., De Oliveira, K.N., Gaspar-Silva, D., Pacheco, L.K., Joussef, A.C., Steindel, M., Simões, C.M.O., De Souza, A.M.T., Magalhaes, U.O., Afonso, I.F., Rodrigues, C.R., Nunes, R.J. and Castro, H.C., 2009, Synthesis, biological evaluation and SAR of sulphonamide 4-methoxychalcone derivatives with potential antileishmanial activity. *European Journal of Medicinal Chemistry, 44,* 755-763.

Ao, Z., Jayappa, K.D., Labine, M., Zheng, Y., Matthews, C., Kobinger, G. and Yao, X., 2010, Characterization of anti-HIV activity mediated by HIV-1 integrase c-terminal domain polypeptides expressed in susceptible cells. *Journal of Antivirals and Antiretrovirals, 2(1),* 20-28.

Aoki, S., Tomiyama, Y., Kageyama, Y., Yamada, Y., Shiro, M. and Kimura, E., 2009, Photolysis of the sulphonamide bond of metal complexes of *N*-dansyl-1,4,7,10-tetraazacyclododecane in aqueous solution: A mechanistic study and application to the photorepair of *cis, syn*-cyclobutane thymine photodimer. *Chemistry, An Asian Journal, 4(4),* 561-573.

Argyropoulou, I., Geronikaki, A., Vicini, P. and Zanib, F., 2009, Synthesis and biological evaluation of sulphonamide thiazole and benzothiazole derivatives as antimicrobial agents. *Arkivoc, vi,* 89-102.

Arslan, T., Kandemirli, F., Ebenso, E.E., Love, I. and Alemu, H., 2009, Quantum chemical studies on the corrosion inhibition of some sulphonamides on mild steel in acidic medium. *Corrosion Science, 51(1),* 35-47.

Aschenbrenner, D.S. and Venable, S.J., 2008, Drugs treating urinary tract infections, in: *Drug Therapy in Nursing*; Lippincott Williams & Wilkins Publishing USA, Chapter 42, pp 817-827.

Bahrami, K., Khodaei, M.M. and Soheilizad, M., 2009, Direct conversion of thiols to sulphonyl chlorides and sulphonamides. *Journal of Organic Chemistry, 74(24),* 9287-9291.

Bakker, W.I.I., Familoni, O.B., Padfield, J. and Snieckus, V., 1997, Intramolecular anionic Friedel-Crafts equivalents. An expeditious synthesis of 4*H*-1,2-benzothiazin-4-one 1,1-dioxide from *N*-arylsulphonylated amino acid. *Synlett, 1532,* 1079-1080.

Barbosa, M.L.C., Melo, G.M.A., Da Silva, Y.K.C., Lopes, R.O., De Souza, E.T., De Queiroz, A.C., Smaniotto, S., Alexandre-Moreira, M.S., Barreiro, E.J. and Lima, L.M., 2009, Synthesis and pharmacological evaluation of *N*-phenylacetamide sulphonamides. *European Journal of Medicinal Chemistry, 44,* 3612-3620.

Bariwal, J.B., Upadhyay, K.D., Manvar, A.T., Trivedi, J.C., Singh, J.S., Jain, K.S. and Shah, A.K., 2008, 1,5-Benzothiazepine, a versatile pharmacophore: A review. *European Journal of Medicinal Chemistry, 43,* 2279-2290.

Basanagouda, M., Shivashankar, K., Kulkarni, M.V., Rasal, V.P., Patel, H., Mutha, S.S. and Mohite, A.A., 2010, Synthesis and antimicrobial studies on novel sulphonamides containing 4-azidomethyl coumarin. *European Journal of Medicinal Chemistry, 45,* 1151-1157.

Bastos, R.S., Cunha, A.S., Da Silva, L.C., Oliveira, C.C.P., Rezende, C.M. and Pinto, A.C., 2008, Preparation of *para*-chloroaniline: A simple, fast and inexpensive experiment. *Quimica Nova, 31(1),* 172–173.

Behmadi, H., Saadatia, S.M., Roshania, M. and Ghaemy, M., 2009, Synthesis of new disulphonamides from different substituted diamino pyridines. *Eclética Química, 34(3),* 27-31.

Bellú, S., Hure, E., Trape, M. and Rizzotto, M., 2003, The interaction between mercury(II) and sulphathiazole. *Quimica Nova, 26(2),* 188-192.

Ben-Shoshan, M and Clarke, A.E., 2011, Anaphylaxis: Past, present and future. *Allergy, 66,* 1-14. DOI:10.1111/j.1398-9995.2010.02422.x

Bereket, G., Ogretir, C. and Yurt, A., 2001, Quantum mechanical calculations on some 4-methyl-5-substituted imidazole derivatives as acidic corrosion inhibitor for zinc. *Journal of Molecular Structure (Theochem.), 571*, 139–145.

Bergfeld, S.A. and DeClerck, Y.A., 2010, Bone marrow-derived mesenchymal stem cells and the tumor microenvironment. *Cancer Metastasis Review, 29,* 249-261.

Bergmann, R., 2010, Prolongation of the shelf life of fruits and flowers. Material from Biocenter Klein Flottbek, University of Hamburg, Accessed online on 4th December, 2010 at: http://www.biologie.uni-hamburg.de/lehre/bza/molnews/sildenafil/sildenafil.htm

Bertucci, A., Innocenti, A., Zoccola, D., Scozzafava, A., Tambutte′, S. and Supuran, C.T., 2009, Carbonic anhydrase inhibitors. Inhibition studies of a coral secretory isoform by sulphonamides. *Bioorganic and Medicinal Chemistry, 17(14),* 5054-5058.

Bhat, M.A., Imran, M., Khan, S.A. and Siddiqui, N., 2005, Biological activities of sulphonamides. *Indian Journal of Pharmaceutical Sciences, 67(2),* 151-159.

Bhattacharya, G., Salem, M.M. and Werbovetz, K.A., 2002, Antileishmanial dinitro-aniline sulphonamides with activity against parasite tubulin. *Bioorganic and Medicinal Chemistry Letters, 12(17),* 2395-2398.

Binder, C.M., Bautista, A., Zaidlewicz, M., Krzeminski, M.P., Oliver, A. and Singaram, B., 2009, Dual stereoselectivity in the dialkylzinc reaction using (−)-β-pinene derived amino alcohol chiral auxiliaries. *Journal of Organic Chemistry,74(6)*, 2337-2343.

Bisai, A., Prasad, B.A.B. and Singh, V.K., 2007, Aminolysis of *N*-tosylaziridines: An approach to asymmetric synthesis of symmetric and unsymmetric chiral sulfonamide ligands. *Arkivoc, v,* 20-37.

Blank, B.R., Alayoglu, P., Engen, W., Choi, J.K., Berkman, C.E., Anderson, M.O., 2011, *N*-Substituted glutamyl sulphonamides as inhibitors of glutamate carboxypeptidase II (GCP2). *Chemical Biology and Drug Design, 77,* 241-247.

Blonde L., 2006, Sildenafil citrate for erectile dysfunction in men with diabetes and cardiovasc- ular risk factors: A retrospective analysis of pooled data from placebo-controlled trials. *Current Medical Research and Opinion, 22(11),* 2111-2120.

Bornholdt, J., Fjære, K.W., Felding, J. and Kristensen, J.L., 2009, Heterocyclic penta-fluorophenyl sulphonate esters as shelf stable alternatives to sulphonyl chlorides. *Tetrahedron, 65,* 9280-9284.

Boroujeni, K.P., 2010, Friedel-Crafts acylation of arenes with carboxylic acids using silical gel supported $AlCl_3$. *Turkish Journal of Chemistry, 34,* 621-630.

Borrás, J., Ferrer, A.S. and Supuran, C.T., 2004, *Carbonic anhydrase: Its Inhibitors and Activators, Metal Complexes of Heterocyclic Sulphonamides as Carbonic Anhydrase Inhibitors***,** Supuran, C.T.; Scozzafava, A.; Conway, J. (Eds.), CSC Press, Boca Raton, USA, pp. 14-19.

Brackett, C.C., 2007, Sulphonamide allergy and cross-reactivity. *Current Allergy and Asthma Reports, 7(1),* 41-48.

Brackett, C.C, Singh, H. and Block, J.H., 2004, Likelihood and mechanisms of cross-allergenicity between sulphonamide antibiotics and other drugs containing a sulphonamide functional group. *Pharmacotherapy, 24(7),* 856-870.

Bregman, H., Williams, D.S., Atilla, G.E., Carroll, P.J. and Meggers, E., 2004, An organometallic inhibitor for glycogen synthase kinase 3. *Journal of American Chemical Society, 126(42),* 13594-13595.

Brisbare-Roch, C., Dingemanse, J., Koberstein, R., Hoever, P., Aissaoui, H., Flores, S., Mueller, C., Nayler, O., van Gerven, J., de Haas, S. L., Hess, P., Qiu, C., Buchmann, S., Schertz, M., Weller, T., Fischli, W., Clozel, M. and Jenck, F., 2007, Promotion of sleep by targeting orexin system in rats, dogs and humans. *Nature Medicine, 13(2),* 150-155.

Butani, L., 2002, Corticosteroid-induced hypersensitivity reactions. *Annals of Allergy, Asthma and Immunology, 89(5),* 439-445.

Caddick, S., Wilden, J.D. and Judd, D.B., 2004, Direct synthesis of sulphonamides and activated sulphonate esters from sulphonic acids. *Journal of American Chemical Society, 126(4),* 1024-1025.

Cejudo-Marin, R., Alzuet, G., Ferrer, S., Borras, J., Castineiras, A., Monzani, E. and Casella, L., 2004, Copper (II) complexes with 4-amino-*N*-[4,6-dimethyl-2-pyrimidinyl] benzene sulphonamide. Synthesis, crystal structure, magnetic properties, EPR and theoretical studies of a novel mixed μ-carboxylato, NCN-bridged dinuclear copper compound. *Inorganic Chemistry, 43(21),* 6805–6814.

Ceri, H., Olson, M.E., Morck, D.W., Storey, D., Read, R.R., Buret, A.G., *et al*., 2001, The MBEC Assay System: Multiple equivalent biofilms for antibiotic and biocide susceptibility testing. In Doyle (Eds.), *Methods in Enzymology, 337,* 377–385.

Chambers, H.F. and Jawetz, E., 1998, Sulphonamides, trimethoprim, and quinolones, in *Basic and Clinical Pharmacology*, Katzung, B.G. (Ed.) Appleton-Lange, pp. 761-763.

Chandrasekhar, S. and Mohapatra, S., 1998, Neighbouring group assisted sulphonamide cleavage of sharpless aminols under acetonation conditions. *Tetrahedron Letters, 39(7),* 695-698.

Chauthe, S.K., Bharate, S.B., Sabde, S., Mitra, D., Bhutani, K.K. and Singh, I.P., 2010, Biomimetic synthesis and anti-HIV activity of dimeric phloroglucinols. *Bioorganic and Medicinal Chemistry, 18(5),* 2029-2036.

Chen, L., Petrelli, R., Olesiak, M., Wilson, D.J., Labello, N.P. and Pankiewicz, K.W., 2008, Bis(sulphonamide) isosters of mycophenolic adenine dinucleotide analogues: Inhibition of inosine monophosphate dehydrogenase. *Bioorganic and Medicinal Chemistry, 16,* 7462-7469.

Chen, Y.K., Costa, A.M. and Walsh, P.J., 2001, Substrate dependence of nonlinear effects: Mechanistic probe and practical applications. *Journal of American Chemical Society, 123(22)*, 5378-5379.

Chen, Z., Xu, W., Liu, K., Yang, S., Fan, H., Bhadury, P.S., Hu, D-Y. and Zhang, Y., 2010, Synthesis and antiviral activity of 5-(4-chlorophenyl)-1,3,4-thiadiazole sulphonamides. *Molecules, 15,* 9046-9056.

Chohan, Z.H., 2008, Metal-based sulphonamides: Their preparation, characterization, in vitro antibacterial, antifungal and cytotoxicity properties. X-ray structure of 4-[(2-hydroxybenzylidene)amino]benzenesulphonamide. *Journal of Enzyme Inhibition and Medicinal Chemistry, 23(1),* 120–130.

Chohan, Z.H., Mahmood-Ul-Hassan, K., Khan, M. and Supuran, C.T., 2005, *In-vitro* antibacterial, antifungal and cytotoxic properties of sulphonamide-derived Schiff's bases

and their metal complexes. *Journal of Enzyme Inhibition and Medicinal Chemistry, 20(2),* 183–188.

Chohan, Z.H., Pervez, H., Rauf, A., Khalid, K.M. and Supuran, C.T., 2006c, Antibacterial cobalt (II), copper (II), nickel (II) and zinc (II) complexes of mercaptothiadiazole-derived furanyl, thienyl, pyrrolyl, salicylyl and pyridinyl Schiff bases. *Journal of Enzyme Inhibition and Medicinal Chemistry, 21(2),* 193–201.

Chohan, Z.H., Shad, H.A., Youssoufi, M.H. and Hadda, T.B., 2010b, Some new biologically active metal-based sulphonamides. *European Journal of Medicinal Chemistry, 45,* 2893-2901.

Chohan, Z.H., Shaikh, A.U. and Naseer, M.M., 2006b, Metal-based isatin-bearing sulphonamides: Their synthesis, characterization and biological properties. *Applied Organometallic Chemistry, 20(11),* 729-739.

Chohan, Z.H., Shaikh, A.U., Naseer, M.M. and Supuran, C.T., 2006a, *In-vitro* antibacterial, antifungal and cytotoxicity properties of metal-based furanyl derived sulphonamides. *Journal of Enzyme Inhibition and Medicinal Chemistry, 21(6),* 771-781.

Chohan, Z.H. and Supuran, C.T., 2008, Structure and biological properties of first row d-transition metal complexes with *N*-substituted sulphonamides. *Journal of Enzyme Inhibition and Medicinal Chemistry, 23(2),* 240–251.

Chohan, Z.H., Youssoufi, M.H., Jarrahpour, A. and Hadda, T.B., 2010a, Identification of antibacterial and antifungal pharmacophore sites for potent bacteria and fungi inhibition: Indolenyl sulphonamide derivatives. *European Journal of Medicinal Chemistry, 45,* 1189-1199.

Chowdhury, M.A., Abdellatif, K.R.A., Dong, Y., Das, G., Yu, G., Velózquez, C.A., Sursh, M.R. and Knaus, E.E., 2009, Synthesis and biological evaluation of salicylic acid and *N*-acetyl-2-carboxybenzenesulphonamide regioisomers possessing a *N*-difluoro methyl-1,2-dihydropyrid-2-one pharmacophore: Dual inhibitors of cyclooxygenases and 5-lipoxygenase with anti-inflammatory activity. *Bioorganic and Medicinal Chemistry Letters, 19,* 6855-6861.

Clatworthy, A.E., Pierson, E. and Hung, D.T., 2007, Targeting virulence: A new paradigm for antimicrobial therapy. *Nature Chemical Biology, 3,* 541-548.

Clayden, J., Lund, A., Vallverdú, L. and Helliwell, M., 2004, Ultra-remote stereocontrol by conformational communication of information along a carbon chain. *Nature, 431,* 966-971.

Claudianos, C., Crone, E., Coppin, C., Russell, R. and Oakeshott, J., 2002, A genomic perspective on mutant aliesterases and metabolic resistance to organophosphate in: *ACS Symposium Series, 808,* Chapter 5, pp 90-101.

Cribb, A.E., Lee, B., Trepanier, L. and Spielberg, S.P., 1996, Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: Clinical syndromes and pathogenesis. *Adverse Drug Reaction Toxicology Review, 15,* 9-10.

Connor, E.E., 1998, Sulphonamide antibiotics. *Primary Care Update for OB/GYN, 5(1),* 32-35.

Cope, 2011, Cytokine Cells Online Pathfinder Encyclopedia. Available online at: www.copewithcytokines.de/cope.cgi?key=H8 (Accessed on 15th June, 2011)

Cui, Z., Yang, J., Chen, W. and Zhang, S., 2009, Dyeing fine denier polypropylene fibers with phenylazo-β-naphthol-containing sulphonamide disperse dyes. *Frontiers of Chemical Engineering in China, 4(3),* 328-335.

Das, B., Balasubramanyam, P., Krishnaiah, M., Veeranjaneyulu, B. and Reddy, G.C., 2009, Iodine-catalyzed efficient hydrophosphonylation of *N*-tosyl aldimines. *Journal of Organic Chemistry*, 74*(11),* 4393–4395.

De Clercq, E., 2001, New developments in anti-HIV chemotherapy. *Current Medicinal Chemistry, 8(13),* 1543-1572.

Derouin, F., Jacqz-Aigrain, E., Thulliez, P., Couvreur, J. and Leport, C., 2000, Cotrimoxazole for prenatal treatment of congenital toxoplasmosis? *Parasitology Today, 16(6),* 254-256.

Dibbern, D.A. and Montanaro, A., 2008, Allergies to sulphonamide antibiotics and sulphur-containing drugs. *Annals of Allergy, Asthma and Immunology, 100(2),* 91-101.

Dimitrov, V., Dobrikov, G. and Genov, M., 2001, Chiral β- and γ-aminoalcohols derived from (+)-camphor and (−)-fenchone as catalysts for the enantioselective addition of diethylzinc to benzaldehyde. *Tetrahedron: Asymmetry, 12(9)*, 1323-1329.

Dobek, A.S., Klayman, D.L., Dickson, E.T., Scovill, J.P. and Tramonts, E.D., 1980, Inhibition of clinically significant bacterial organisms *in vitro* by 2-acetylpyridine thiosemicarbazones. *Antimicrobial Agents and Chemotherapy 18(1),* 27-36.

Domagk, G. 1986, A contribution to chemotherapy of bacterial infections. *Clinical Infectious Diseases, 8(1),* 163-166.

Dwight, C.H., Nigel, J.M. and Richard, L.W., 2004, Antimicrobial chemotherapy: Sulphonamide and trimethoprim, in: *Veterinary Microbiology;* John Wiley and Sons Inc, USA, Chapter 4, pp 31-33.

Dyatkina, N.B., Roberts, C.D., Keicher, J.D., Dai, Y., Nadherny, J.P., Zhang, W., Schmitz, U., Kongpachith, A., Fung, K., Novikov, A.A., Lou, L., Velligan, M., Khorlin, A.A. and Chen, M.S., 2002, Minor groove DNA binders as antimicrobial agents, i,

pyrazoles tetraamides are potential antibacteria against vancomycin-resistant *Enterococci* and methicillin-resistant *Staphylococcus aureus* agents. *Journal of Medicinal Chemistry, 45*, 805-817.

Ebead, Y.H., 2010, The role of medium on acid dissociation constants of some azo dyes in view of experimental and theoretical data. *Journal of Molecular Structure, 982(1-3),* 100-106.

El-Naggar, M.M., 2007, Corrosion inhibition of mild steel in acidic medium by some sulpha drug compounds. *Corrosion Science, 49(5),* 2226-2236.

Eshghi, H., Rahimizadeh, M., Zokaei, M., Eshghi, S., Eshghi, S., Faghihi, Z., Tabasi, E. and Kihanyan, M., 2011, Synthesis and antimicrobial activity of some new macrocyclic *bis*-sulphonamide and disulphides. *European Journal of Chemistry, 2(1),* 47-50.

Estabrooke, I.V., McCarthy, M.T., Ko, E., Chou, T.C., Chemelli, R.M., Yanagisawa, M., Saper, C.B. and Scammell, T.E., 2001, Fos expression in orexin neurons varies with behavioral state. *Journal of Neuroscience, 21(5),* 1656-1662.

Evanthia, P.T., Victoria, F.S. and Ioannis, N.P., 2010, An overview of chromatographic analysis of sulphonamides in pharmaceutical preparations and biological fluids. *Current Pharmaceutical Analysis, 6(3),* 198-212.

Familoni, O.B., Ionica, I., Bower, J.F. and Snieckus, V., 1997, Intramolecular anionic friedel-crafts equivalents. A general regiospecific route to substituted and naturally occurring xanthen-9-ones. *Synlett, 1533,* 1081-1083.

Fang, S-M., Saňudo, E.C., Hu, M., Zhang, Q., Zhou, L-M. and Liu, C-S., 2011, Copper(ii) complex with *cis*-epoxysuccinate ligand: Syntheses, crystal structures, and magnetic properties. *Australian Journal of Chemistry, 64,* 217-226.

Fares, F.A., Ridley, D.D. and Yin, P., 1997, Sulphonamide analogues of creatinine. The synthesis of 3-amino-4,5-dihydro-1,2,4-thiadiazole 1,1-dioxides from base-induced cyclization reactions. *Australian Journal of Chemistry, 50,* 1027-1029.

Fayed, L., 2010, The causes and risk factors of cancer. Accessed online 10th August, 2010 at: http://cancer.about.com/od/causes/a/causesrisks.htm.

Fehintola, F.A., Adedeji, A.A., Tambo, E. Fateye, B.B., Happi, T.C. and Sowunmi, A., 2004, Cotrimoxazole in the treatment of acute uncomplicated falciparum malaria in Nigerian children: A controlled clinical trial. *Clinical Drug Investigation, 24(3),* 149-155.

Finar, I.L., 1986, Chemotherapy in: Organic Chemistry, vol 2: Stereochemistry and the Chemistry of Natural Product, 5th edition, Longman Group Limited, Longman House, England, 1986, pp 861-880.

Fink, H.A., Mac Donald, R., Rutks, I.R., Nelson, D.B. and Wilt, T.J., 2002, Sildenafil for male erectile dysfunction: A systematic review and meta-analysis. *Archives of Internal Medicine, 162(12),* 1349-1360.

Forrat, V.J., Ramon, D.J. and Yus, M., 2006, Polymer supported *trans*-1-phenylsulphonyl amino-2-isoborneolsulfonylaminocyclohexane ligand for the titanium catalyzed organozinc addition to ketones. *Tetrahedron: Asymmetry, 17(14)*, 2054-2058.

Friesen, T.L., Stukenbrock, E.H., Liu, Z., Meinhardt, S., Ling, H., Faris, J.D., Rasmussen, J.B., Solomon, P.S., McDonald, B.A. and Oliver, R.P., 2006, Emergence of a new disease as a result of interspecific virulence gene transfer. *Nature Genetics, 38(8),* 953-956.

Fritsch, P.O. and Sidoroff, A., 2000, Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *American Journal of Clinical Dermatology, 1(6),* 349-360.

Gadad, A.K., Mahajanshetti, C.S., Nimbalkar, S. and Raichurkar, A., 2000, Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulphonamide derivatives. *European Journal of Medicinal Chemistry, 35,* 853-857.

Gao, J. and Pedersen, J.A., 2009, Sorption of sulphonamide antimicrobial agents to humic acid-clay complexes. *Journal of Environmental Quality, 39(1),* 228-235.

Gao, J. and Pedersen, J.A., 2005, Adsorption of sulphonamide antimicrobial agents to clay minerals. *Environmental Science and Technology, 39(24),* 9505-9516.

Genç, Y., Özkanca, R. and Bekdemir, Y., 2008, Antimicrobial activity of some sulphonamide derivatives on clinical isolates of *Staphylococcus aureus. Annals of Clinical Microbiology and Antimicrobials, 7(17),* 6 pp. DOI:10.1186/1476-0711-7-17

Ghorab, M.M., Ismail, Z.H., Abdel-Gawad, S.M. and Abdel-Aziem, A., 2004, Antimicrobial activity of amino acid, imidazole and sulphonamide derivatives of pyrazolo[3,4-*d*] pyrimidine. *Heteroatom Chemistry, 15(1),* 57–62.

Ghorab, M.M., Ragab, F.A., Heiba, H.I., Arafa, R.K. and El-Hossary, E.M., 2010, In vitro anticancer screening and radiosensitizing evaluation of some new quinolines and pyrimido[4,5-*b*]quinolines bearing a sulphonamide moiety. *European Journal of Medicinal Chemistry, 45,* 3677-3684.

Ghosh, A.K., Chapsal, B.D., Weber, I.T. and Mitsuya, H., 2008, Design of HIV protease inhibitors targeting protein backbone: An effective strategy for combating drug resistance. *Account of Chemical Research, 41(1),* 78-86.

Gianotto, E.A.S., Arantes, R.P., Lara-Filho, M.J., Filho, A.C.S.C. and Fregonezi-Nery, M.M., 2007, Dissolution test for glibenclamide tablets. *Quimica Nova, 30(5),* 1218-1221.

Gideon, 2008, Emergence of infectious diseases in the 21st century. Accessed online on 5th May, 2010 at: http://www.gideononline.com/2008/03/05/emergence-of-infectious-diseases-in-the-21st-century/

Giguere, S., Prescott, J.F. and Baggot, J.D., 2006, Sulphonamides, diaminopyrimidines and their combinations, in: *Antimicrobial Therapy in Veterinary Medicine,* pp 249-250.

Greenwood, D., 2003, Sulphonamide, in *Antibiotic and Chemotherapy: Anti-infective Agents and Their Use in Therapy;* Finch, R.G. (Ed.), Elsevier Publisher, UK, Chapter 32, 385-392.

Gribble, F.M. and Reimann, F., 2003, Differential selectivity of insulin secretagogues: Mechanisms, clinical implications, and drug interactions. *Journal Diabetes and its Complications*, *2*, 11–15.

Hager, T., 2010, Demon under the microscope. Tantor Exclusive. Accessed online on 20th November, 2010 at: https://www.tantor.com/SellSheets/0306_DemonMicro.pdf.

Hanko, V.P., Lacourse, W.R., Dasenbrock, C.O. and Rohrer, J.S., 2001, Determination of sulphur-containing antibiotics using high-performance liquid chromatography with integrated pulsed amperometric detection. *Drug Development Research, 53(4),* 268-280.

Hansch, C., Sammes, P.G. and Taylor, J.B., 1990, *Comprehensive Medicinal Chemistry*, Pergamon Press, Oxford, Vol. 2, Chapter 7.1, p. 212.

Harter, W.G., Albrect, H., Brady, K., Caprathe, B., Dunbar, J., Gilmore, J., Hays, S., Kostlan, C.R., Lunney, B. and Walker, N., 2004, The design and synthesis of sulphonamides as caspase-1 inhibitors. *Bioorganic and Medicinal Chemistry Letters, 14(3),* 809-812.

Hassan, M.U., Chohan, Z.H. and Supuran, C.T., 2002, Antibacterial Zn (II) compounds of Schiff bases derived from some benzothiazoles. *Main Group Metal Chemistry, 25(5),* 291-296.

Hay, S.I., Guerra, C.A., Tatem, A.J., Atkinson, P.M. and Snow, R.W., 2005, Tropical infectious diseases: Urbanization, malaria transmission and disease burden in Africa. *Nature Reviews Microbiology, 3,* 81-90.

Hellstrom, W.J.G., Gittelman, M., Karlin, G., Segerson, T., Thibonnier, M., Taylor, T. and Padma-Nathan, H., 2003, Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: Results of a randomized, double-bind, 26-week placebo-controlled pivotal trial. *Urology, 61(4),* 8-14.

Hopper, D.W. Vera, M.D., How, D., Sabatini, J., Xiang, J.S., Ipek, M., Thomason, J., Hu, Y., Feyfant, E., Wang, Q., Georgiadis, K.E., Reifenberg, E., Sheldon, R.T., Keohan, C.C.,

Majumdar, M.K., Morris, E.A., Skotnicki, J. and Sum, P-E., 2009, Synthesis and biological evaluation of ((4-keto)-phenoxy)methyl biphenyl-4-sulphonamides: A class of potent aggrecanase-1 inhibitors. *Bioorganic and Medicinal Chemistry Letters, 19,* 2487-2491.

Huang, S.Y., Tang, R.B., Chen, S.T. and Chung, R.L., 2003, Coagulase-negative staphylococcal bacteremia in critically ill children: risk factors and antimicrobial susceptibility. *Journal of Microbiology and Immunological Infections, 36,* 51-56.

Hughes, W.T., Dankner, W.M., Yogev, R., Huang, S., Paul, M.E., Flores, M.A., Kline, M.W. and Wei, L-J., 2005, Comparison of atovaquone and azithromycin with trimethoprim-sulphamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clinical Infectious Diseases, 40(1),* 136-145.

Hui, A., Zhang, J., Fan, J. and Wang, Z., 2006, A new chiral sulphonamide ligand based on tartaric acid: Synthesis and application in the enantioselective addition of diethylzinc to aldehydes and ketones. *Tetrahedron: Asymmetry 17(14)*, 2101-2107.

Hui, A., Zhang, J., Sun, H. and Wang, Z., 2008, Efficient asymmetric addition of diethylzinc to ketones using tartaric acid derivative as chiral ligand. *Arkivoc, (ii)*, 25-32.

Jain, A., Agarwal, J. and Bansal, S., 2004, Prevelance of methicillin-resistant, coagulase-neagative staphylococci in neonatal intensive care units; finding from a tertiary care hospital in India*. Journal of Medical Microbiology, 53*, 941-944.

Jensen, L.B., Baloda, S., Boye, M. and Aerestrup, F.M., 2001, Antimicrobial resistance among *Pseudomonas spp*. and the *Bacillus cereus* group isolated from Danish agricultural soil. *Environment International*, *26(7-8),* 581-587.

Joachim, F.S., Piotr, R., Harald, F. and Hans, K.B., 2001, Antiplatelet and anticoagulant effects of "HN-11 500," a selective thromboxane receptor antagonist. *Thrombosis Research, 103(2)*, 79-91.

José, P.D.L.C, Antonio, M., María, I.R-R. and Felipe, S.D.L.C., 2000, Effect of DT-TX 30, a combined thromboxane synthase inhibitor and thromboxane receptor antagonist, on retinal vascularity in experimental diabetes mellitus. *Thrombosis Research, 97(3)*, 125-131.

Kaatz, G.W., McAleese, F. and Seo, S.M., 2005, Multidrug resistance in *Staphylococcus aureus* due to over expression of a novel Multidrug and Toxin Extrusion (MATE) transport protein. *Antimicrobial Agents and Chemotherapy, 49(5),* 1857-1864.

Kahle, M. and Stamm, C., 2007, Sorption of the veterinary antimicrobial sulphathiazole to organic materials of different origin. *Environmental Science and Technology, 41(1),* 132-138.

Kalgutkar, A.S., Jones, R. and Sawant, A., 2010, Sulphonamide as an essential functional group in drug design, in: *Metabolism, Pharmacokinetics and Toxicity of Functional Groups: Impact of Chemical Building Blocks on ADMET*, pp 210-274.

Kamenova-Nacheva, M., Dobrikov, G. and Dimitrov, V., 2009, Preparation of –amino-alcohol analogs by the addition of N-, O- and S-containing substituents to ferrocenylcamphor sulphonamide-ligands for enantioselective addition of diethylzinc to benzaldehyde. *Arkivoc, xii,* 141-152.

Kanamaru, T., Nakano, Y., Toyoda, Y., Miyagawa, K.I., Tada, M., Kaisho, T. and Nakao, M., 2001, *In vitro* and *in vivo* antibacterial activities of TAK-083, an agent for treatment of *Helicobacter pylori* infection. *Antimicrobial Agents and Chemotherapy, 45,* 2455-2459.

Katritzky, A.R., Adbel-Fattah, A.A.A., Vakulenko, A.V. and Tao, H., 2005, *N*-Sulphonyl benzotriazoles as advantageous reagents for C-sulphonylation. *Journal of Organic Chemistry, 70(23),* 9191-9197.

Katritzky, A.R., Cai, C. and Singh, S.K., 2006, Efficient microwave access to polysubstituted amidines from imidoylbenzotriazoles. *Journal of Organic Chemistry, 71(9),* 3375-3380.

Katritzky, A.R., He, H.Y. and Suzuki, K., 2000, *N*-Acylbenzotriazoles: Neutral acylating reagents for the preparation of primary, secondary and tertiary amides. *Journal of Organic Chemistry, 65(24),* 8210-8213.

Kawaguchi, T., Miyata, H., Ataka, K., Mae, K. and Yoshida, J., 2005, Room-Temperature Swern oxidations by using a microscale flow system. *Angewandte Chemie International Edition, 44(16),* 2413-2416.

Kent, M., 2011, Sulphonamide (Medicine). Accessed online on 17th March, 2011 at: http://en. wikipedia.org/wiki/Sulfonamide_(medicine).

Khalil, N., 2003, Quantum chemical approach of corrosion inhibition. *Electrochimica Acta, 48,* 2635-2640.

Kim, J-G. and Jang, D.O., 2007, Mild and efficient indium metal catalyzed synthesis of sulphonamides and sulphonic esters. *Synlett, 16,* 2501-2504.

Kivela, A.J., Kivela, J., Saarnio, J. and Parkkila, S., 2005, Carbonic anhydrases in normal gastrointestinal tract and gastrointestinal tumours. *World Journal of Gastroenterology, 11(2),* 155–163.

Klinker, K.P., Harbilas, J.W. and Johns, T.E., 2002, Drug-induced hematologic disorders. In: DiPiro, J.; Talbert, R.; Yee, G.; Matzke, G.; Wells, B.; Posey, L.M. eds. Pharmacotherapy: A pathophysiologic approach, 5th ed. New York, McGraw-Hill, 1783-1795.

Knauer, A., Fladerer, P., Strempfl, C., Krause, R. and Wenisch, C., 2004, Effect of hospitalization and antimicrobial therapy an antimicrobial resistance of colonizing Staphylococcus epidermidis. *Wien Klin Wochenschr, 116(14),* 489-494.

Knauf, H. and Mutschler, E., 1998, Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clinical Pharmacokinetics, 34*, 1–24.

Koh, Y., Nakata, H., Maeda, K., Ogata, H., Bilcer, G., Devasamudram, T., Kincaid, J.F., Boross, P., Wang, Y.F., Tie, Y., Volarath, P., Gaddis, L., Harrison, R.W., Weber, I.T., Ghosh, A.K. and Mitsuya, H., 2003, Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC 114) with potent activity against multi-PI-resistant human immunodeficiency virus in vitro. *Antimicrobial Agents Chemotherapy, 47(10),* 3123-3129.

Korbila, I.P., Manta, K.G. and Siempos, I.I., 2009, Penicillins vs trimethoprim-based regimens for acute bacterial exacerbations of chronic bronchitis meta-analysis of randomized controlled trials. *Canadian Family Physician, 55(1),* 60-67.

Korolkovas, A., 1998, *Essentials of Medicinal Chemistry;* 2nd Edition, John Wiley and Sons, Inc., USA, (a) pp 699-719; (b) p 140 and 157.

Kourlas, H. and Morey, S., 2007, Sulphonamide allergies and possible cross-reactivity. *Journal of Pharmacy Practice, 20(5),* 399-402.

Kozakiewicz, A., Ullrich, M., Welniak, M., Wojtczak, A., 2010, Synthesis, structure and activity of sulphonamides derived from (+)-camphor in the enantioselective addition of diethylzinc to benzaldehyde. *Journal of Molecular Catalysis A: Chemical, 326,* 128-140.

Kremer, E., Facchin, G., Este′vez, E., Albore′s, P., Baran, E.J., Ellena, J. and Torre, M.H., 2006, Copper complexes with heterocyclic sulphonamides: Synthesis, spectroscopic characterization, microbiological and SOD-like activities: Crystal structure of $[Cu(sulphisoxazole)_2(H_2O)_4]\cdot 2H_2O$. *Journal of Inorganic Biochemistry, 100(7),* 1167–1175.

Kuethe, J.T. and Beutner, G.L., 2009, Synthesis of 2-arylindole-4-carboxylic amides: [2-(4-Fluorophenyl)-1*H*-indol-4-yl]-1-pyrrolidinylmethanone. *Organic Synthesis, 86,* 92-104.

LaMarche, M.J., Leeds, J.A., Dzink-Fox, J.A., Gunderson, K., Krastel, P., Memmert, K., Patane, M.A., Rann, M.E., Schmitt, E., Tiamfook, S. and Wang, B., 2011, 4-Aminothiazolyl analogues of GE2270 A: Antibacterial lead finding. *Journal of Medicinal Chemistry, 54(7),* 2517–2521.

Lamb, H.M., Ormrod, D., Scott, L.J. and Figgitt, D.P., 2002, Ceftriaxone: An update of its use in the management of community-acquired and nosocomial infections. *Drugs, 62(7),* 1041-1089.

Landolfi, C., Marchetti, M., Ciocci, G. and Milanese, C., 1997, Development and pharmacological characterization of a modified procedure for the measurement of carbonic anhydrase activity. *Journal of Pharmacological and Toxicological Methods, 38(3),* 169-172.

Lea, Z-G., Chen, Z-C., Hu, Y. and Zheng, Q-G., 2004, Organic Reactions in Ionic Liquids. A simple and highly regioselective *N*-substitution of pyrrole. *Synthesis, 12,* 1951-1954.

Lee, M.G., Hassani, O.K. and Jones, B.E., 2005, Discharge of identified orexin/ hypocretin neurons across the sleep-waking cycle. *Journal of Neuroscience, 25(28),* 6716-6720.

Lee, P-W., Liu, C-T., Rampao, H.S., Rosario, V.E. and Shaio, M-F., 2010, Pre-elimination of malaria on the island of Príncipe. *Malaria Journal, 9,* 26-27.

Levin, I., Mevarech, M. and Palfey, B.A., 2007, Characterization of a novel bifunctional dihydropteroate synthase/dihydropteroate reductase enzyme from Helicobacter pylori. *Journal of Bacteriology, 189(11),* 4062-4069.

Leyva, L., Torres, M.J., Posadas, S., Blanca, M., Besso, G., O'Valle, F., Del Moral, R.G., Santamaria, L.E. and Juárez, C., 2000, Anticonvulsant-induced toxic epidermal necrolysis: Monitoring the immunologic response. *Journal of Allergy and Clinical Immunology, 105,* 157-165.

Li, C.J., 2005, Organic reactions in aqueous media with a focus on carbon-carbon bond formations: A decade update. *Chemical Reviews, 105(8),* 3095-3165.

Li, H., Smith, M.L., Chiesa, O.A. and Kijak, P.J., 2009, Determination of sulphadimethoxine and ^{4}*N*-acetylsulphadimethoxine in bovine plasma, urine, oral fluid, and kidney and liver biopsy samples obtained surgically from standing animals by LC/MS/MS. *Journal of Chromatography B, 877(3),* 237-246.

Li, X., Schuler, M.A. and Berenbaum, M.R., 2007, Molecular mechanism of metabolic resistance to synthetic and natural xenobiotics. *Annual Review of Entomology, 52,* 231-253.

Libby, R.T., Gould, D.B., Anderson, M.G. and John, S.W.M., 2005, Complex genetics of glaucoma susceptibility. *Annual Reviews of Genomics and Human Genetics, 6,* 15-44.

Lima, L.M., Castro, P., Machado, A.L., Fraga, C.A.M., Lugnier, C., De Moraes, V.L.G. and Barreiro, E.J., 2002, Synthesis and anti-inflammatory activity of phthalimide derivatives, designed as new thalidomide analogues. *Bioorganic and Medicinal Chemistry, 10(9),* 3067-3073.

Lopez, M., Drillaud, N., Bornaghi, L.F. and Poulsen, S-A., 2009, Synthesis of s-glycosyl primary sulphonamides. *Journal of Organic Chemistry, 74(7),* 2811-2816.

Luca, L.D. and Giacomelli, G., 2008, An easy microwave-assisted synthesis of sulphonamides directly from sulphonic acid. *Journal of Organic Chemistry, 73,* 3967-3969.

Maclean, D., Hale, R. and Chen, M., 2001, The reversed kenner linker: A new safety-catch linker for the preparation of *N*-alkyl sulphonamides. *Organic Letters, 3(19),* 2977-2980.

Maguire, J.M., Thakkinstain, A., Sturm, J., Levi, C., Lincz, L., Parsons, M., Whyte, S. and Attia, J., 2008, Polymorphisms in platelet glycoprotein Ib{alpha} and factor vii and risk of ischemic stroke: A meta-analysis. *Stroke, 39(6),* 1710-1716.

Mamdani, M., 2005, Are rates of gastrointestinal bleeding higher following the introduction of COX-2 inhibitors? *Expert Opinion on Drug Safety, 4(3),* 591-598.

Maren, T.H., Jankowska, L., Sanyal, G. and Edelhauser, H.F., 1983, The transcorneal permeability of sulphonamide carbonic anhydrase inhibitors and their effect on aqueous humor secretion. *Experimental Eye Research, 36(4),* 457-480.

Martinez, A.G., Vilar, E.T., Fraile, A.G., Cerero, S.D.M, Martinez-Ruiz, P. and Villas, P.C., 2002, Bridgehead-norbornane-derived β-amino alcohol catalysts: Structural factors influencing the chirality transfer. *Tetrahedron: Asymmetry, 13(1)*, 1-4.

Martins, J.E.D., Mehlecke, C.M., Gamba, M. and Costa, V.E.U., 2006, Synthesis of chiral norbornane derivatives as γ-amino alcohol catalysts: The effect of the functional group positions on the chirality transfer. *Tetrahedron: Asymmetry, 17(12)*, 1817-1823.

Masson, P., Lambert, S.M., Brown, M. and Shabsigh, R., 2005, PDE-5 inhibitors: Current status and future trends. *Urologic Clinics of North America, 32(4),* 511-525.

Masunari, A. and Tavares, L.C., 2007, A new class of nifuroxazide analogues: synthesis of 5-nitrophene derivatives with antimicrobial activity against multidrug-resistant *Staphylococcus aureus. Bioorganic and Medicinal Chemistry, 15*, 4229-4236.

Meshram, G.A. and Patil, V.D., 2009, A simple and efficient method for sulphonylation of amines, alcohols and phenols with cupric oxide under mild conditions. *Tetrahedron Letters, 50(10),* 1117-1121.

Millan, D.S. and Prager, R.H., 2000, Potential $GABA_B$ receptor antagonists. XI Synthesis of a small library of sulphonamide analogues. *Australian Journal of Chemistry, 53,* 615-618.

Miller, L.H., Baruch, D.I., Marsh, K. and Doumbo, O.K., 2002, The pathogenic basis of malaria. *Nature, 415(6872),* 673-679. DOI: 10.1038/415673a.

Mondelli, M., Brune, V., Borthagaray, G., Ellena, J., Nascimento, O.R., Leite, C.Q., Batista, A.A. and Torre, M.H., 2008, New Ni(II)-sulphonamide complexes: Synthesis, structural characterization and antibacterial properties. X-ray diffraction of $[Ni(sulphisoxazole)_2(H_2O)_4].2H_2O$ and $[Ni(sulphapyridine)_2]$. *Journal of Inorganic Biochemistry, 102,* 285-292.

Moore, E., 2008, Hypersensitivity reactions: An exaggerated immune response to autoimmune disease. General Medicine. Posted on 16th of September 2008. Accessed online on 2nd December, 2008 at: http://www.suite101.com/content/hypersensitivity-reactions-a69024.

More, D., 2010, Sulpha Medication Allergies in: Sulpha Drug Allergy, updated on 1st of June, 2010. Accessed online on 5th December, 2010 at: http://allergies.about.com/od/medicationallergies/a/sulfa.htm.

Moylett, E.H., Pacheco, S.E., Brown-Elliot, B.A., Perry, T.R., Buescher, E.S., Birmingham, M.C., Schentag, J.J., Gimbel, J.F., Apodaca, A., Schwartz, M.A., Rakita, R.M. and Wallace, R.J., 2003, Clinical experience with linezolid for the treatment of *Nocardia* infection. *Clinical Infectious Diseases, 36(3),* 313-318.

Naik, S., Bhattacharjya, G., Talukdar, B. and Patel, B.K., 2004, Chemoselective acylation of amines in aqueous media. *European Journal of Organic Chemistry, 6,* 1254-1260.

Nayak, N., Nag, T.C., Satpathy, G. and Ray, S.B., 2007, Ultrastructural analysis of slime positive and slime negative of *Staphylococcus epidermidis* isolates in infectious keratitis. *Indian Journal of Medical Research, 125*, 767-771.

Njardarson, J.T., 2008, Cornell University; Outreach Web Page. Available online at http://www.chem.cornell.edu/jn96/outreach.html (accessed November, 2008).

Nwinyi, O.C., Chinedu, N.S. and Ajani, O.O., 2008, Evaluation of antibacterial activity of pisidium guajava and Gongronema latifolium. *Journal of Medicinal Plant Research, 2(8),* 189-192.

O'Connell, J.F. and Rapoport, H., 1992, 1-Benzenesulphonyl- and 1-*p*-toluenesulphonyl-3-methyl imidazolium triflates: Efficient reagents for the preparation of arylsulphonamides and arylsulphonates. *Journal of Organic Chemistry, 57(17),* 4775-4777.

Oh, S., Moon, H-I., Son, I-H. and Jung, J-C., 2007, Synthesis of sulphonamides and evaluation of their histone deacetylase (HDAC) activity. *Molecules, 12,* 1125-1135.

Ong, C.K-S., Lirk, P., Seymour, R.A. and Jenkins, B.J., 2005, The efficacy of preemptive analgesia for acute postoperative pain management: A metal-analysis. *Anesthesia and Analgesia, 100(3),* 757-773.

Ophardt, C.E., 2003, Antibacterial agent – sulpha drug. Virtual Chembook, Elmhurst College. Accessed online on 25th January, 2011 at: http://www.elmhurst.edu/~chm/vchem book/653sulfa.html

Oukessou, M. and Alsouss, L., 1998, Pharmacokinetics of sulphonamides and trimethoprim in the donkey (*Equus asinus*). *Journal of Veterinary Medicine Series A, 45(1-10),* 191-198.

Owa. T., Yoshino, H., Okauchi, T., Okabe, T., Ozawa, Y., Sugi, N.H., Yoshimatsu, K., Nagasu, T., Koyanagi, N. and Kitoh, K., 2002, Synthesis and biological evaluation of *N*-(7-indolyl) -3-pyridinesulphonamide derivatives as potent antitumor agents. *Bioorganic and Medicinal Chemistry Letters, 12,* 2097-2100.

Özbek, N., Katircioğlu, H., Karacan, N. and Baykal, T., 2007, Synthesis, characterization and antimicrobial activity of new aliphatic sulphonamide. *Bioorganic and Medicinal Chemistry, 15,* 5105-5109.

Paige, J.C. and Tollefson, L., 2003, Veterinary products: Residues and resistant pathogens, in: *Food Safety: Contaminants and Toxins;* 3Rd Edition, D'Mello, J.P.F. (Ed.), CABI Publishing Wallingford, UK, Chapter 13, pp 293-306.

Parra, M., Sotoca, E. and Gil, S., 2003, A convenient generation of acetic acid dianion. *European Journal of Organic Chemistry, Issue 8,* 1386-1388.

Parrott, I.R.W. and Hitchcock, S.R., 2008, β-Amino alcohols derived from (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine as catalysts in the asymmetric addition of diethylzinc to aldehydes. *Tetrahedron: Asymmetry, 19(1)*, 19-26.

Pecoul, B., Varaine, F., Keita, M., Soga, G., Djibo, A., Soula, G., Abdou, A., Etienne, J. and Rey, M., 1991, Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. *Lancet, 338*, 862-866.

Pérez-Trallero, E. and Iglesias, L., 2003, Tetracyclines, sulphonamides and metronidazole. *Enfermedades Infecciosas y Microbiología Clínica, 21(9),* 529-533.

Pinheiro, J.R., Bitencourt, M., Da Cunha, E.F., Ramalho, T.C. and Freitas, M.P., 2008, Novel anti-HIV cyclotriazadisulphonamide derivatives as modeled by ligand- and receptor-based approaches. *Bioorganic and Medicinal Chemistry, 16(4),* 1683-1690.

Ponka, D., 2006, Approach to managing patients with sulfa allergy: Use of antibiotic and nonantibiotic sulphonamides. *Canadian Family Physician, 52(11),* 1434-1438.

Prakash, G.K.S., Matthew, T., Panja, C. and Olah, G.A. 2007, Chlorotrimethylsilane-nitrate salts as oxidants: Direct oxidative conversion of thiols and disulphides to sulphonyl chlorides. *Journal of Organic Chemistry, 72(15),* 5847-5850.

Prugh, J.D., Gould, R.J., Lynch, R.J., Zhang, G., Cook, J.J, Holahan, M.A., Stranieri, M.T., Sitko, G.R., Gaul, L., Bednar, R.A., Bednar, B. and Hartman, G.D., 1997, Nonpeptide GPIIB/IIIA inhibitors. 16. Thieno[2,3-*b*]thiophene α-sulphonamides are potent inhibitors of platelet aggregation. *Bioorganic and Medicinal Chemistry, 7(7),* 865-870.

Puccetti, L., Fosolis, G., Daniela, V., Chohan, Z.H., Andrea, S. and Supuran, C.T., 2005, Carbonic anhydrase inhibitors. Inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes I, II, IX, and XII with Schiff's bases incorporating chromone and aromatic sulphonamide moieties, and their zinc complexes. *Bioorganic and Medicinal Chemistry Letters, 15(12),* 3096-3101.

Purushottamachar, P., Khandelwal, A., Vasaitis, T.S., Bruno, R.D., Gediya, L.K. and Njar, V.C.O., 2008, Potent anti-prostate cancer agents derived from a novel androgen receptor down-regulating agent. *Bioorganic and Medicinal Chemistry, 16(7),* 3519-3529.

Qiang, Z. and Adams, C., 2004, Potentiometric determination of acid dissociation constants (pK_a) for human and veterinary antibiotics. *Water Research, 38(12),* 2874-2890.

Rafique, S., Idrees, M., Nasim, A., Akbar, H. and Athar, A., 2010, Transition metal complexes as potential therapeutic agents. *Biotechnology and Molecular Biology Reviews, 5(2),* 38-45.

Ramon, D.J. and Yus, M., 2007, Chiral ligands with an isoborneol-10-sulphonamide structure: A ten-year odyssey. *Synlett*, *No 15,* 2309-2320.

Ratish, I.G., Javed, K., Ahmad, S., Bano, S., Alam, M.S., Pillai, K.K., Singh, S. and Bagchi, V., 2009, Synthesis ans anti-inflammatory activity of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulphonamide. *Bioorganic and Medicinal Chemistry, 19(1),* 225-258.

Ray, S., Pathak, S.R. and Chaturvedi, D., 2005, Organic carbamates in drug development. Part II. Antimicrobial agents – Recent report. *Drugs of the Future, 30(2),* 161-162.

Reddy, N.S., Mallireddigari, M.R., Cosenza, S., Gumireddy, K., Bell, S.C., Reddy, E.P. and Reddy, M.V., 2004, Synthesis of new coumarin 3-(*N*-aryl) sulphonamides and their anticancer activity. *Bioorganic and Medicinal Chemistry Letters, 14(15),* 4093-4097.

Reynolds, J.E.F. (Ed.), 1996, Martindale. The Extra Pharmacopoeia, Royal Pharmaceutical Society, London.

Rostom, S.A., 2006, Synthesis and in vitro antitumor evaluation of some indeno[1,2-*c*] pyrazol(in)es substituted with sulphonamide, sulphonylurea(-thiourea)pharmacophores, and some derived thiazole ring systems. *Bioorganic and Medicinal Chemistry, 14(19),* 6475–6485.

Rotella, D.P., 2002, Phosphodiesterase 5 inhibitor: Current status and potential applications. *Nature Reviews Drug Discovery, 1(9),* 674-682.

Russell. A.D. and Furr, J.R., 1977, Antibacterial activity of a new chloroxylenol preparation containing ethylenediamine tetraacetic acid. *Journal of Applied Bacteriology UK, 43*, 253-260.

Santosh, K., Niranjan, M.S., Chaluvaraju, K.C., Jamakhandi, C.M. and Kadadevar, D., 2010, Synthesis and antimicrobial study of some schiff bases of sulphonamides. *Journal of Current Pharmaceutical Research, 1,* 39-42.

Scozzafava, A., Owa, T., Mastrolorenzo, A. and Supuran, C.T., 2003, Anticancer and antiviral sulphonamide. *Current Medicinal Chemistry, 10,* 925-953.

Seftel, A.D., Sun, P. and Swindle, R., 2004, The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *The Journal of Urology, 171(6),* 2341-2345.

Sekkides, O., 2010, Infectious disease surveillance update. *The Lancet 10(9),* 589.

Sepandj, F., Ceri, H., Gibb, A., Read, R. and Olson, M., 2004, Minimum inhibitory concentration (MIC) versus biofilm eliminating concentration (MBEC) in evaluation of antibiotic sensitivity of gram-negative bacilli causing peritonitis. *Peritoneal Dialysis International, 24,* 65-67.

Setter, S.M., Iltz, J.L., Fincham, J.E., Campbell, R.K. and Baker, D.E., 2005, Phosphodiesterase 5 inhibitors for erectile dysfunction. *The Annals of Pharmacotherapy, 39(7-8),* 1286-1295.

Shei, D., 2010, Antibiotics as enzymes in: Biochemistry, Toxic Medicine. Posted on 19th June, 2010. Accessed online on 15th November, 2010 at: http://littledoctors.wordpress.com /2010/06/19/antibiotics-as-enzymes/

Shen, C.H., Wang, Y.F., Kovalevsky, A.Y., Harrison, R.W. and Weber, I.T., 2010, Amprenavir complexes with HIV-1 protease and its drug-resistant mutants altering hydrophobic clusters. *FEBS Journal, 277(18),* 3699-3714.

Shi, D., Shi, J. and Rong, S., 2010, A facile and clean synthesis of pyrimidine derivatives via three-component reaction in aqueous media. *Chinese Journal of Chemistry, 28,* 791-796.

Shoji, Y., Takahashi, K., Ohta, M., Kasai, M., Kunishiro, K., Kanda, M., Ogai, S., Takeuchi, Y. and Shirahase, H., 2009, Novel indoline-based acyl-CoA: cholesterol acyltransferase inhibitor: Effects of introducing a methanesulphonamide group on physicochemical properties and biological activities. *Bioorganic and Medicinal Chemistry, 17,* 6020-6031.

Siegel-Itzkovich, J., 1999, Viagra makes flowers stand up straight. *British Medical Journal, 319,* 274.

Silbernagl, S. and Lang, F., 2009, Color Atlas of Pathophysiology 2nd Edition, Thieme Medical Publishers, pp 58-60.

Singh, S.K., Reddy, P.G., Rao, K.S., Lohray, B.B., Misra, P., Rajjak, S.A., Rao, Y.K. and Venkateswarlu, A., 2004a, Polar substitutions in the benzenesulphonamide ring of celecoxib afford a potent 1,5-diarylpyrazole class of COX-2 inhibitors. *Bioorganic and Medicinal Chemistry Letters, 14(2),* 499-504.

Singh, S.K., Saibaba, V., Rao, K.S., Rajjak, S.A., Casturi, S.R., Datla, S.R., Mamidi, N.V.S.R., Ramesh, M., Ravikanth, B., Rajagopalan, R., Venkateswarlu, A. and Rao, Y.K., 2004b, 2-Hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethyl-1*H*-1-pyrazolyl]-1-benzene sulphonamide (DRF-4367): An orally active COX-2 inhibitor identified through pharmacophoric modulation. *Organic and Biomolecular Chemistry, 2(17)*, 2442-2450.

Singh, S.K., Saibaba, V., Rao, K.S., Reddy, P.G., Daga, P.R., Rajjak, S.A., Misra, P. and Rao, Y.K., 2005, Synthesis and SAR/3D-QSAR studies on the COX-2 inhibitory activity of 1,5-diarylpyrazoles to validate the modified pharmacophore. *European Journal of Medicinal Chemistry, 40(10),* 977-990.

Singh, S.K., Shivaramakrishna, S., Saibaba, V., Rao, K.S., Ganesh, K.R., Vasudev, R., Kumar, P.P., Babu, J.M., Vyas, K., Rao, Y.K. and Iqbal, J., 2007, Pharmacophoric 2-hydroxyalkyl benzenesulphonamide: A single-step synthesis from benzenesulphonamide via hemiaminal. *European Journal of Medicinal Chemistry, 42,* 456-462.

Smith, L.K. and Mankin, A.S., 2008, Transcriptional and translational control of mlr operon, which confers resistance to seven classes of protein synthesis inhibitors. *Antimicrobial Agents and Chemotherapy, 52(5),* 1703-1712.

Smolyakov, R., Schlaeffer, F., Alkan, M., Porat, A., Rimar, D., Borer, A., Almog, Y. and Riesenberg, K., 2001, Ampicillin-Sulbactam treatment of nosocomial multi-resistant acinetobacter baumanii bacteremia. *Interscience Conference on Antimicrobial Agents and Chemotherapy, 41*, K-1188.

Soki, F., Neudörfl, J.M. and Goldfuss, B., 2005, Surprising fenchone induced cyclization: Synthesis of the new chiral diol biphenyl-2,2′-sulphone-3,3′-bisfenchol (BISFOL). *Tetrahedron, 61(44)*, 10449-10453.

Sonoda, A., Murata, M., Ito, D., Tanahashi, N., Ohta, A., Tada, Y., Takeshita, E., Yoshida, T., Saito, I., Yamamoto, M., Ikeda, Y., Fukuuchi, Y. and Watanabe, K., 2000, Association between platelet glycoprotein Ibα genotype and ischemic cerebrovascular disease. *Stroke, 31(2),* 493-497.

Sorbera, L.A., Castaner, J. and Bayes, M., 2005, Darunavir. Anti-HIV agents, HIV protease inhibitor. *Drugs of the Future, 30(5),* 441-449.

Srivastava, S., 2011, Sulpha drug allergy. Buzzle Article: life on the web 2011. Accessed online on 3rd March, 2011 at: http://www.buzzle.com/articles/sulfa-drugs-allergy.html

Stranix, B.R., Lavallee, J.-F., Sevigny, G., Yelle, J., Perron, V., LeBerre, N., Herbart, D. and Wu, J.J., 2006, Lysine sulphonamides as novel HIV-protease inhibitors: Nepsilon-acyl aromatic alpha amino acids. *Bioorganic and Medicinal Chemistry Letters, 16(13),* 3459-3462.

Strom, B.L., Schinnar, R., Apter, A.J., Margolis, D.J., Lautenbach, E., Hennessy, S., Bilker, W.B. and Pettitt, D., 2003, Absence of cross-reactivity between sulphonamide antibiotics and sulphonamide nonantibiotics. *New England Journal of Medicine, 349(17),* 1628-1635.

Supuran, C.T., 2008, Carbonic anhydrases: Novel therapeutic applications for inhibitors and activators. *Nature Re*views *Drug Discovery, 7(2)*, 168-182.

Supuran, C.T., Casini, A., Mastrolorenzo, A. and Scozzafava, A., 2004, COX-2 selective inhibitors, carbonic anhydrase inhibition and anticancer properties of sulphonamides belonging to this class of pharmacological agents. *Mini-Reviews in Medicinal Chemistry, 4,* 625-632.

Supuran, C.T., Casini, A. and Scozzafava, A., 2003, Protease inhibitors of the sulphonamide type: Anticancer, anti-inflammatory, and antiviral agents. *Medicinal Research Review, 23(5),* 535-558.

Supuran, C.T. and Scozzafava, A., 2007, Carbonic anhydrases as targets for medicinal chemistry. *Bioorganic and Medicinal Chemistry, 15(13),* 4336–4350.

Szakonyi, Z., Hetényi, A. and Fülöp, F., 2008, Synthesis and application of monoterpene-based chiral aminodiols. *Tetrahedron, 64(6)*, 1034-1039.

Tanyeli, C., Odabaş, S., Erdem, M., Çakir, E. and Keskin, E., 2007, Asymmetric synthesis of novel 1,4-aminoalcohol ligands with norbornene and norbornane backbone: Use in the asymmetric diethylzinc addition to benzaldehyde. *Tetrahedron: Asymmetry, 18(19)*, 2349-2357.

Temesgen, Z., 2007, Antiretroviral drugs in development: A report from HIV DART 2006. *Drugs of the Future, 32(1),* 83-84.

Theodorou, V., Karkatsoulis, A., Kinigopoupou, M., Ragoussis, V. and Skobridis, K., 2009, Tritylamine as an ammonia synthetic equivalent: Preparation of primary amides. *Arkivoc, (xi),* 277-287.

Torre, M.H., Facchin, G., Kremer, E., Castellanos, E.E., Piro, O.E. and Baran, E.J., 2003, Characterization of a copper (II) complex of sulphadimethoxine. *Journal of Inorganic Biochemistry, 94(1-2),* 200–204.

Triinu, S., Lauri, P., Liqun, X., Alexander, M., Jannus, R. and Tanel, T., 2009, Erythromycin- and chloramphenicol-induced ribosomal assembly defects are secondary effects of protein synthesis inhibition. *Antimicrobial Agents and Chemotherapy, 53(2),* 563-571.

Turgeon, M.L., 2003, Basic immunologic Mechanism - an overview of immunology in: Immunology and Serology in Laboratory Medicine 4th Edition, Mosby Inc. Publishers, pp 104-116.

Tyson, P., 2011, The experiment: Holocaust on trial. Nova Online 2000. Accessed online on 8th February, 2011 at: http://www.pbs.org/wgbh/nova/holocaust/experiside.html

Ueda, Y., Takahashi, Y., Yamashita, H., Kaneko, H. and Mimori, A., 2011, Successful bosentan therapy in a case of pulmonary arterial hypertention developed during immunosuppressive therapy for lupus nephritis. *Nihon Rinsho Meneki Gakkai Kaishi, 34(2),* 99-104.

USHMM, (United State Holocaust Memorial Museum), 2011, Nazi medical experiment. Retrieved from United State Holocaust Memorial Museum, Washington DC, Accessed online on 6th January, 2011 at: http://www.ushmm.org/wlc/en/article. php?ModuleId =10005168

Veigl, M.L., Sedwick, W.D., Niedel, J. and Branch, M.E., 1986, Induction of myeloid differentiation of HL-60 cells with naphthalene sulphonamide calmodulin antagonist. *Cancer Research, 46,* 2300-2305.

Veigl, M.L., Vanaman, T.C. and Sedwick, W.D., 1984, Calcium and calmodulin in cell growth and transformation. *Biochimica and Biophysica Acta, 738,* 21-48.

Verdel, B.M., Souverein, P.C., Egberts, A.C. and Leufkens, H.G., 2006, Difference in risks of allergic reaction to sulphonamide drugs based on chemical structure. *The Annals of Pharmacotherapy, 40(6),* 1040-1046.

Vernier, W., Chong, W., Rewolinski, D., Greasley, S., Pauly, T., Shaw, M., Dingh, D., Ferre, R.A., Nukui, S., Ornelas, M. and Reyner, E., 2010, Thioether benzene sulphonamide inhibitors of carbonic anhydrases II and IV: Structure-based drug design, synthesis and biological evaluation. *Bioorganic and Medicinal Chemistry, 18,* 3307-3319.

Vicente, D. and Pérez-Trallero, E., 2010, Tetracyclines, sulphonamides and metronidazole. *Enfermedades Infecciosas y Microbiología Clínica, 28(2),* 122-130.

Voet, D. and Voet, J.D., 2004, In *Biochemistry* 3rd Edition, pp 1341-1342. ISBN 0-471-19250-x (cloth).

Wagman, A.S., Wang, L. and Nuss, J.M., 2000, Simple and efficient synthesis of 3,4-dihydro-2-pyridones via novel solid-supported aza-annulation. *Journal of Organic Chemistry, 65(26),* 9103-9113.

Wang, S.Q., Liu, X.J., Yi, Z.M. and Zhao, K., 2003, Design and synthesis of new arylsulphonamdie and arylamide derivatives for the platelet aggregation inhibitor. *Chinese Chemical Letters, 14(6),* 581-584.

Weber, A., Casini, A., Heine, A., Kuhn, D., Supuran, C.T., Scozzafava, A. and Klebe, G., 2004, Unexpected nanomolar inhibition of carbonic anhydrase by COX-2-selective celecobix: New pharmacological opportunities due to related binding site recognition. *Journal of Medicinal Chemistry, 47(3),* 550-557.

Weisblum, B. 1995, Erythromycin resistance by ribosome modification. *Antimicrobial Agents and Chemotherapy, 39(3),* 577-585.

Wiholm, B-E. 2001, Identification of sulphonamide-like adverse drug reactions to celecoxib in the world health organization database. *Current Medical Research and Opinion, 17(3),* 210-216.

Wolstenholme, G.E.W., O'Connor, C.M., Hotchkiss, R.D. and Evans, A.H., 2008, Genetic and metabolic mechanisms underlying multiple levels of sulphonamide resistance in Pneumococci, in: *Ciba Foundation Symposium–Drug Resistance in microorganisms of Development,* John Wiley, USA, Chapter 10. DOI: 10.1002 /9780470719053.ch10

Wong, K.K.Y. and Hancock, R.E.W., 2000, Insertion mutagenesis and membrane topology model of the *Pseudomonas aeruginosa* outer membrane protein OprM. *Journal of Bacteriology, 182(9),* 2402-2410.

WHO (World Health Organisation), 2005, World Malaria Report. Accessed online on 7th January, 2011 at: http://rbm.who.int/wmr2005.

Wright, G.D., 2005, Bacterial resistance to antibiotics: Enzymatic degradation and modification. *Advanced Drug Delivery Reviews, 57(10),* 1451-1470.

Wright, S.W. and Hallstrom, K.N., 2006, A convenient preparation of heteroaryl sulphonamides and sulphonyl fluorides from heteroaryl thiols. *Journal of Organic Chemistry, 71(3),* 1080-1084.

Wu, C., Decker, E.R., Holland, G.W., Brown, P.M., Stavros, F.D., Brock, T.A. and Dixon, R.A.F., 2001, Nonpeptide endothelin antagonists in clinical development. *Drugs of Today, 37(7),* 441-443.

Yan, B., Nguyen, N., Liu, L., Holland, G. and Raju, B., 2000, Kinetic comparison of trifluoroacetic acid cleavage reactions of resin-bound carbamates, ureas, secondary amides and sulphonamides from benzyl-, benhydryl-, and indole-based linkers. *Journal of Combinatorial Chemistry, 2(1),* 66-74.

Yan, F., LaMarre, J.M., Röhrich, R., Wiesner, J., Jomaa, H., Mankin, A.S. and Fujimori, D.G., 2010, RlmN and Cfr are radical SAM enzymes involved in methylation of ribosomal RNA. *Journal of American Chemical Society, 132(11),* 3953-3964.

Yan, L., Bertarelli, D.C.G., Hayallah, A.M., Meyer, H., Klotz, K-N. and Müller, C.E., 2006, A new synthesis of sulphonamides by aminolysis of *p*-nitrophenylsulphonates yielding potent and selective adenosine A_{2B} receptor antagonists. *Journal of Medicinal Chemistry, 49(14),* 4384-4391.

Yang, L., Yang, X., Liu, L., Li, Y., Lou, Q. and Liu, Q., 2003, Synthesis, characterization and susceptibility of bacteria against sulphamethoxydiazine complexes of copper(II), zinc(II), nickel(II), cadmium(II), chromium(II) and iron(II). *Journal of Coordination Chemistry, 56(13),* 1131–1139.

Yasuda, M.A.S., 2005, Pharmacological management of paracoccidioidomycosis. *Expert Opinion on Pharmacotherapy, 6(3),* 385-397.

Yin, S.M., 2010, Insecticide resistance. *Pest Control Newsletters Issue No 20,* p. 1

Yuan, R.X., Xiong, R.G., Chen, Z.F., Zhang, P., Ju, H.X., Dai, Z., Guo, Z.J., Fun, H.K. and You, X.Z., 2001, Crystal structure of zinc(ii) 2-sulphanilamidopyrimidine: A widely used topical burn drug. *Journal of Chemical Society Dalton Transaction, 6,* 774-776.

Zabransky, R.J., 2002, Linezolid: The first of a new class of antimicrobial agents. *Clinical Microbiology Newsletters, 24(4),* 25-30.

Zareef, M., 2006, Synthesis, characterization and antimicrobial activity of some novel sulphonamide bearing 1,3,4-oxadiazole. A Ph.D Thesis Submitted to Department of Chemistry, Quaid-i-Azam, Islamabad.

Zebardast, T., Zarghi, A., Daraie, B., Hedayati, M. and Dadrass, O.G., 2009, Design and synthesis of 3-alkyl-2-aryl-1,3-thiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. *Bioorganic and Medicinal Chemistry Letters, 19(12),* 3162-3165.

Zhang, W., Qin, Y., Zhang, S. and Luo, M., 2005, Synthesis of novel N-heterocyclic carbene-Rh complexes derived from L-proline and their catalysis in the addition of arylboronic acids to aldehyde. *Arkivoc 14,* 39-48.

APPENDICES

^{1}H-NMR Spectral Data of α-Tolylsulphonamide Derivatives

Fig. 5.1: ^{1}H-NMR Spectrum of 1a

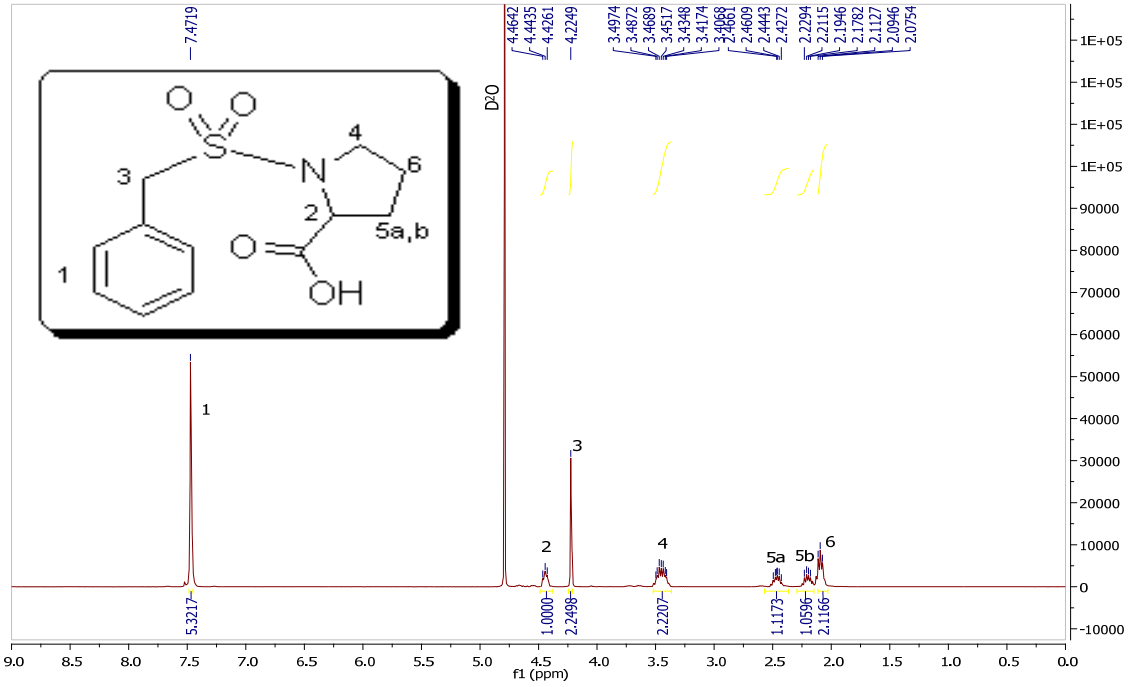


Fig. 5.2: ^{1}H-NMR Spectrum of 1b

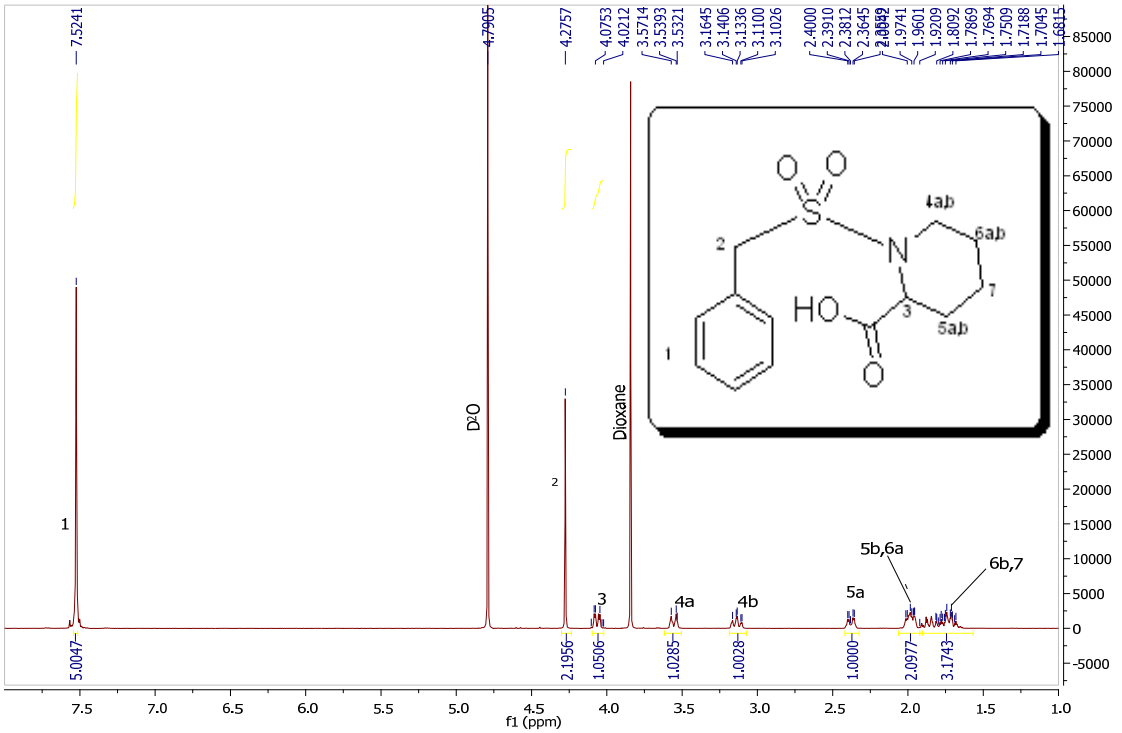


Fig. 5.3: ^{1}H-NMR Spectrum of 1c

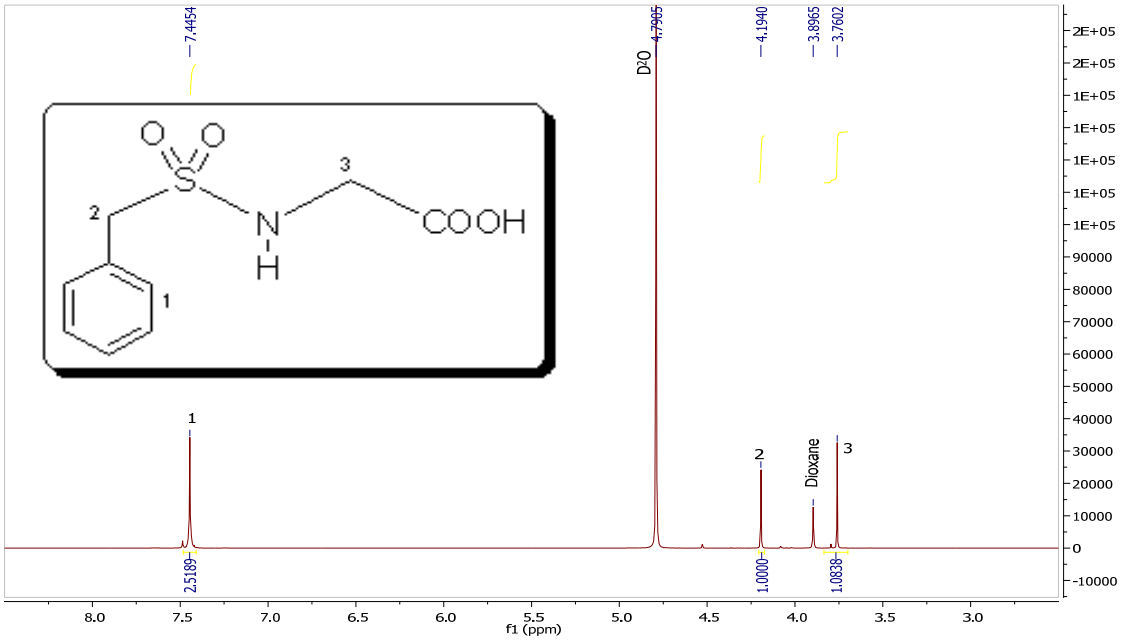


Fig. 5.4: ^{1}H-NMR Spectrum of 1d

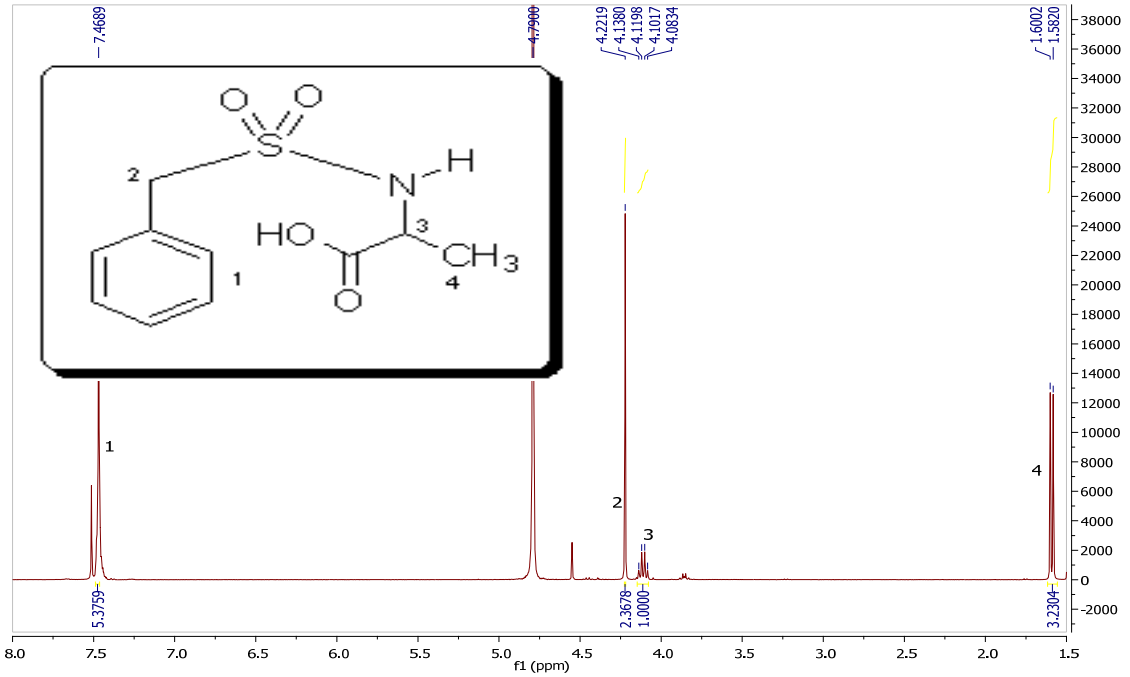


Fig. 5.5: ^{1}H-NMR Spectrum of 1e

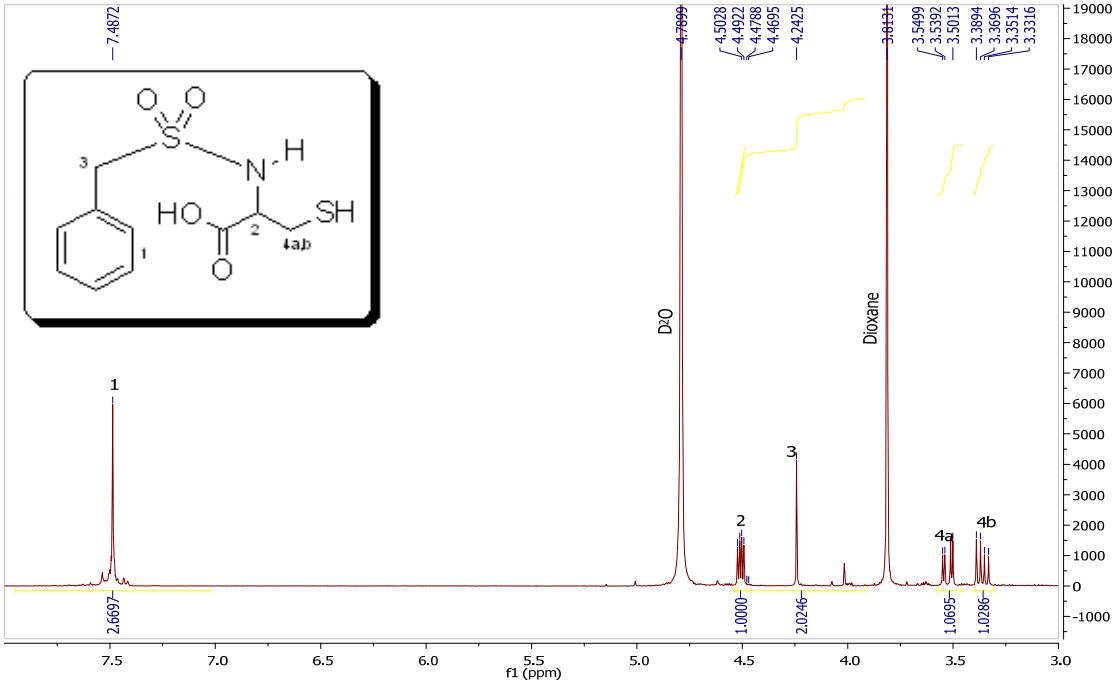


Fig. 5.6: ^{1}H-NMR Spectrum of 1f

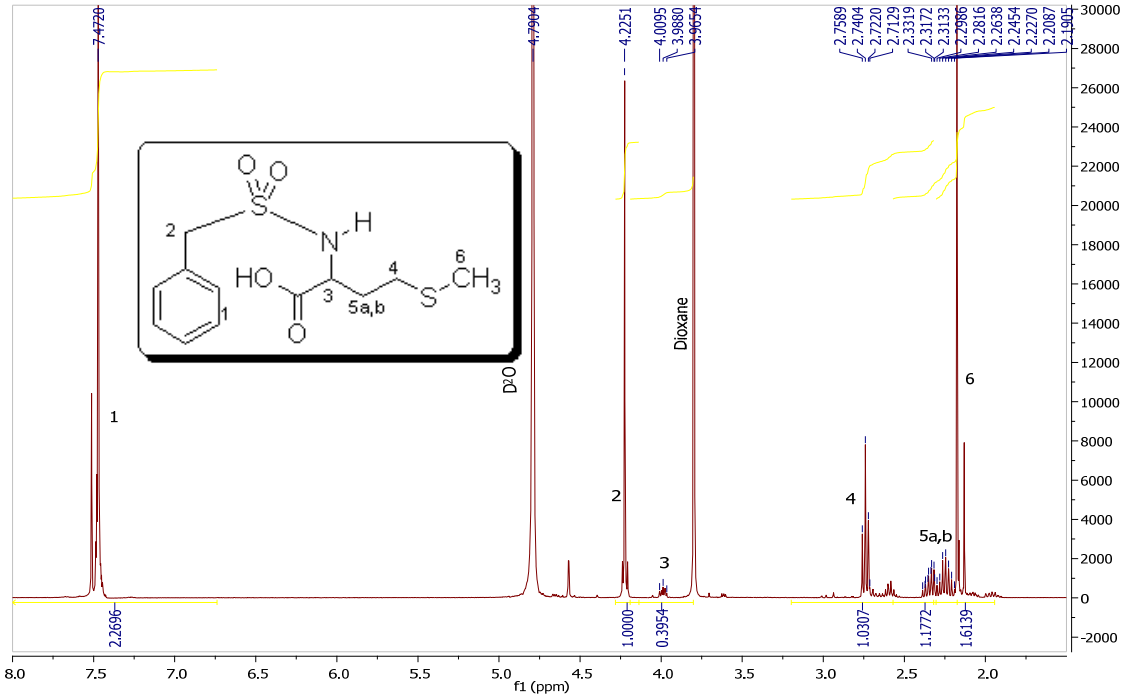


Fig. 5.7: ^{1}H-NMR Spectrum of 1g

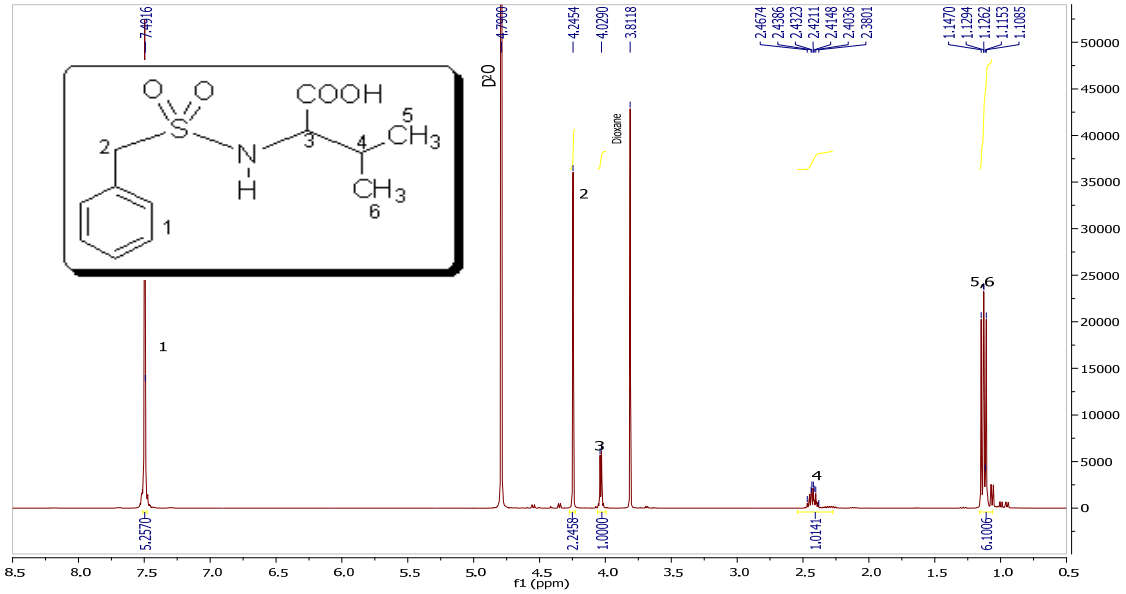


Fig. 5.8: ^{1}H-NMR Spectrum of 1h

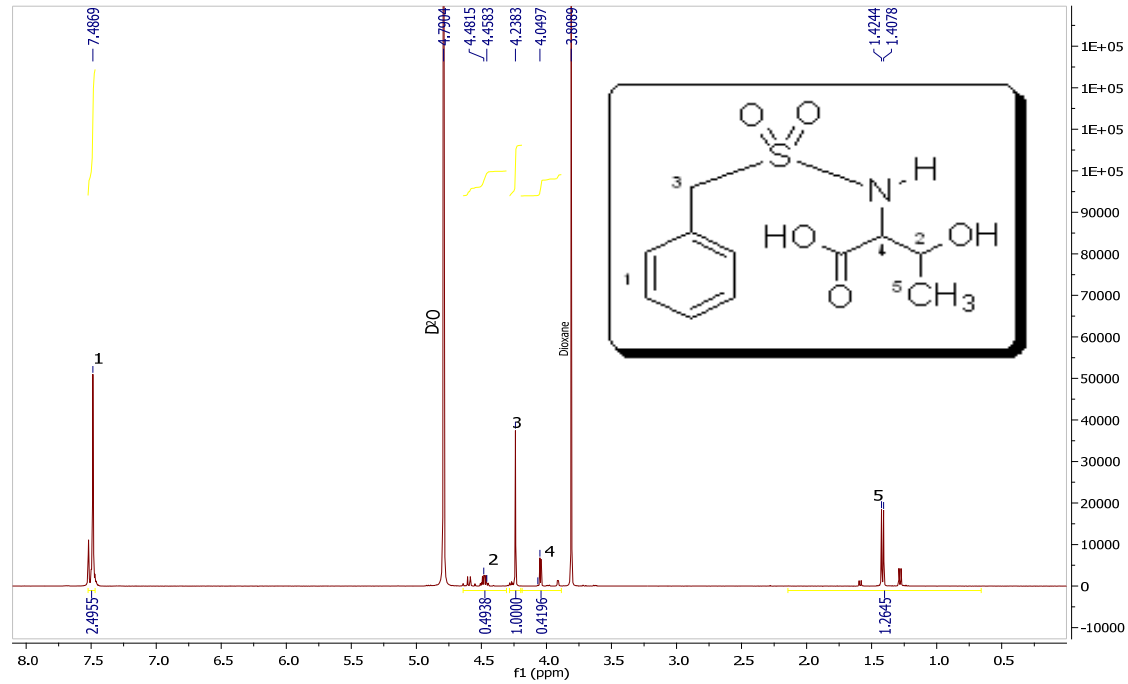


Fig. 5.9: ^{1}H-NMR Spectrum of 1i

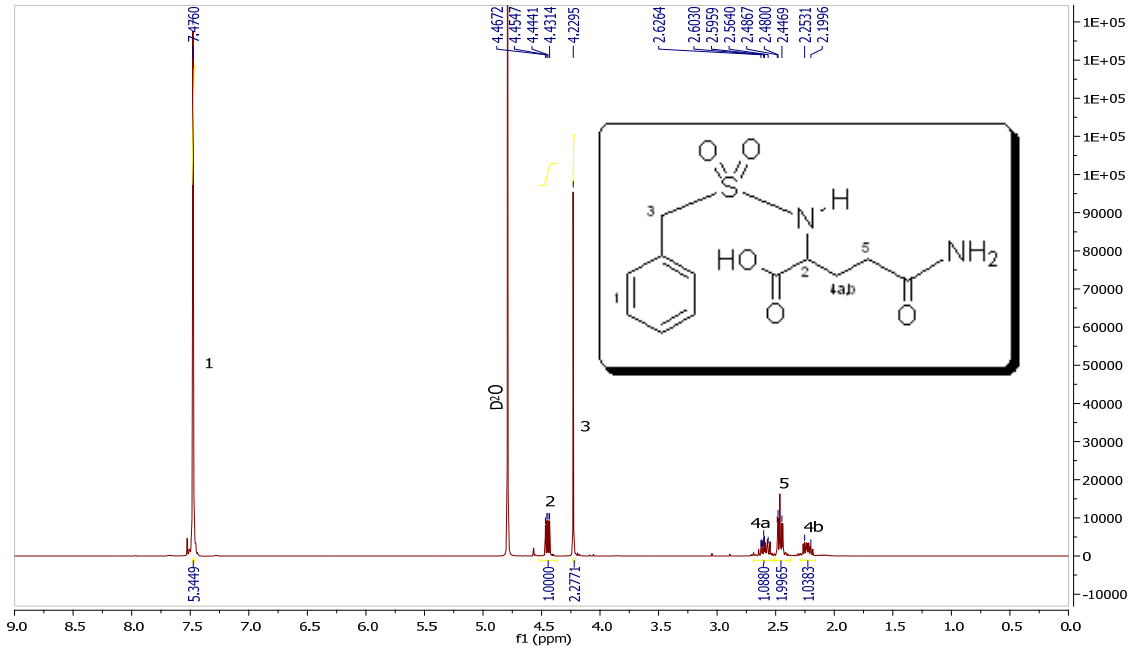


Fig. 5.10: ^{1}H-NMR Spectrum of 1j

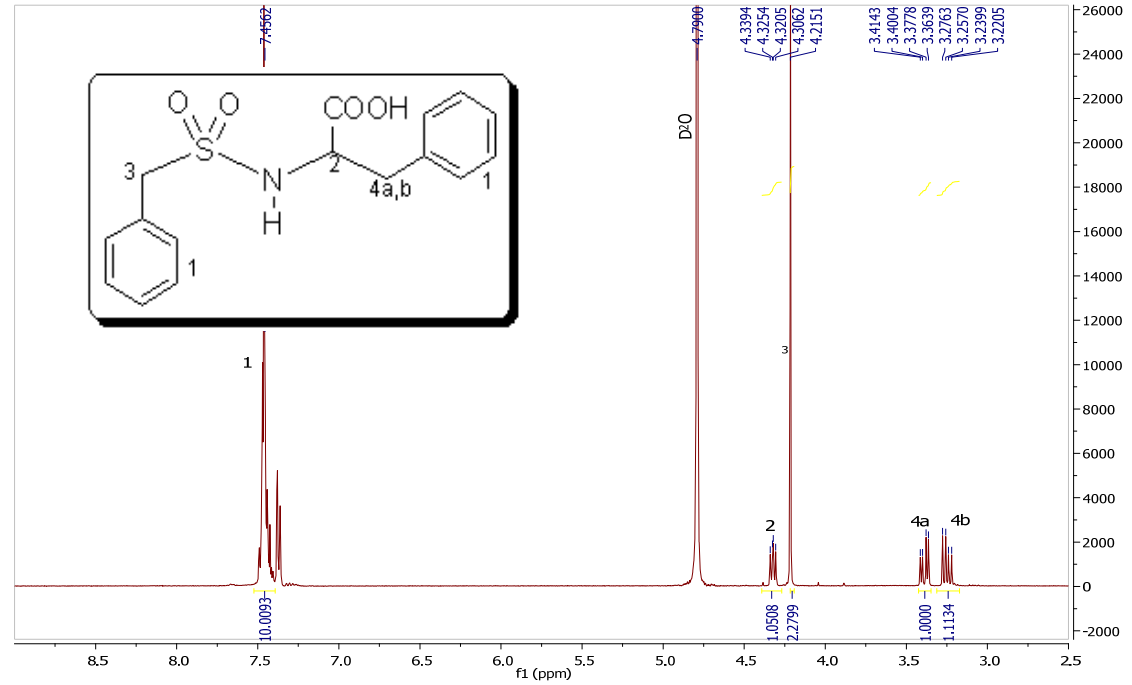


Fig. 5.11: ^{1}H-NMR Spectrum of 1k

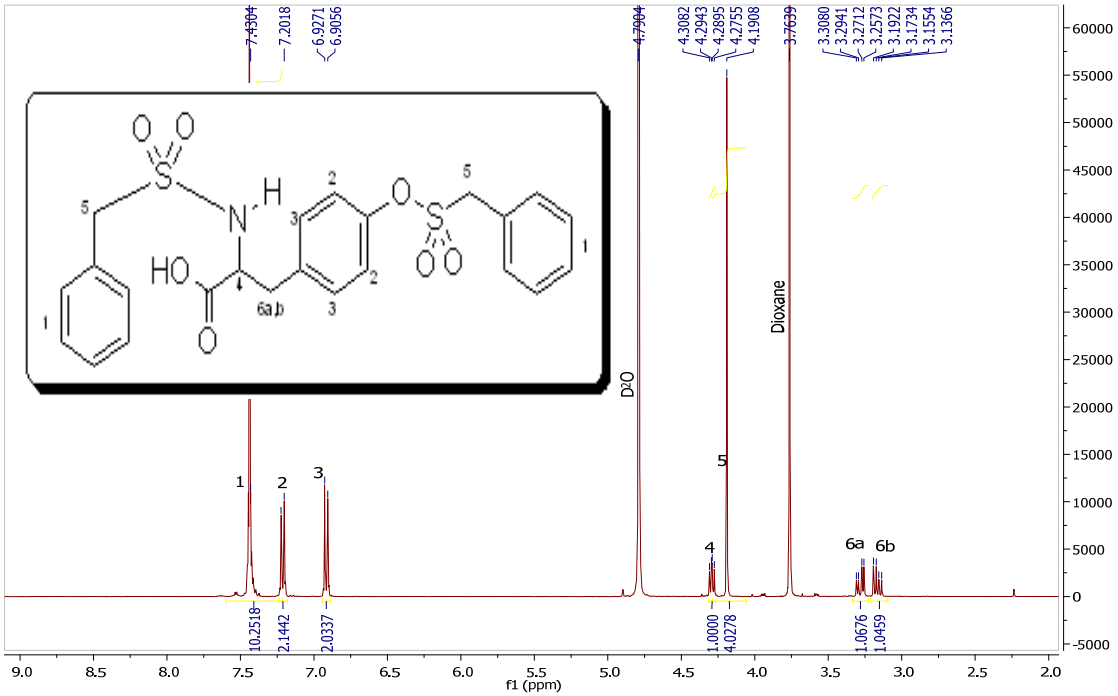


Fig. 5.12: ^{1}H-NMR Spectrum of 2a

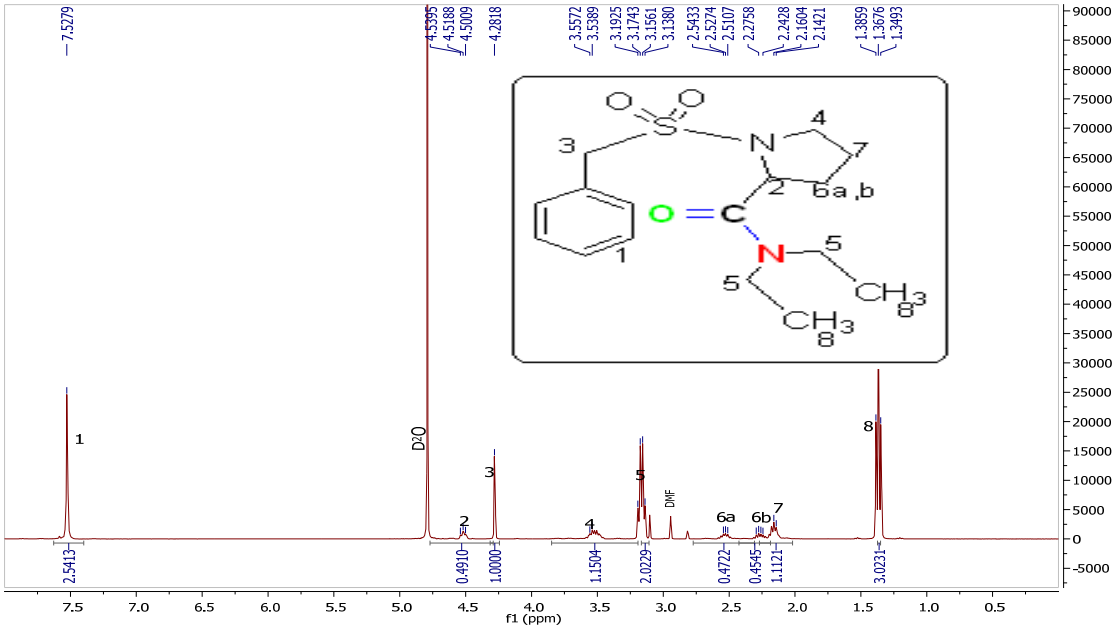


Fig. 5.13: ^{1}H-NMR Spectrum of 2b

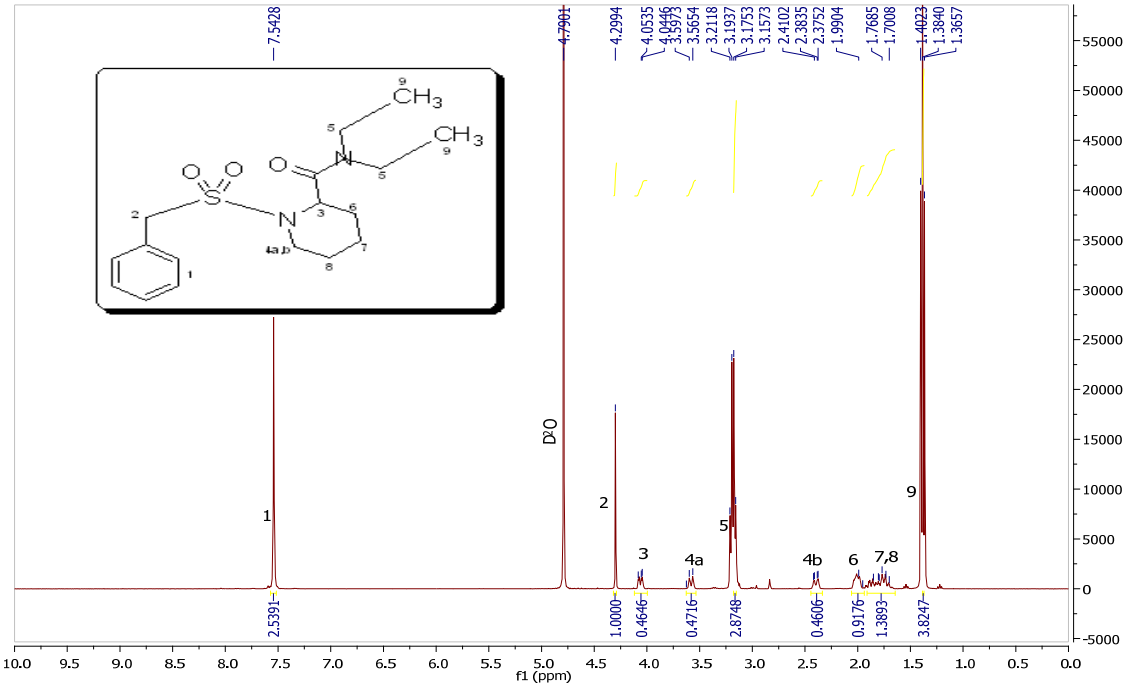


Fig. 5.14: ^{1}H-NMR Spectrum of 2c

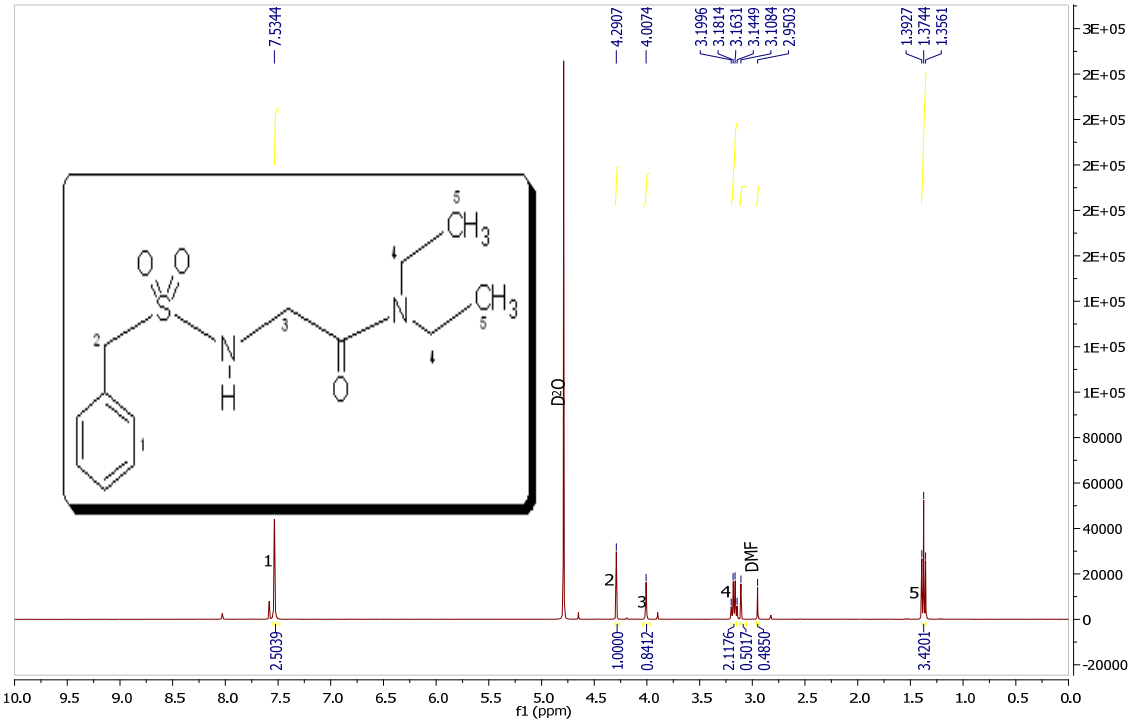


Fig. 5.15: ^{1}H-NMR Spectrum of 2d

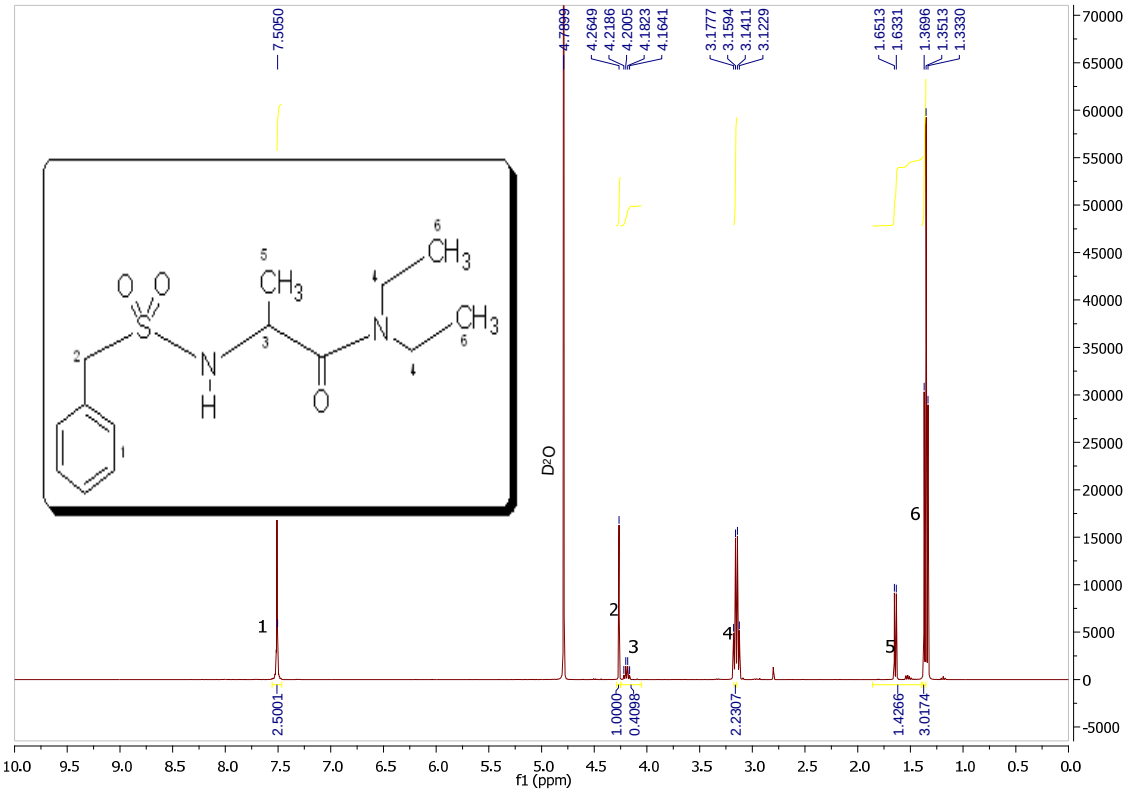


Fig. 5.16: ^{1}H-NMR Spectrum of 2e

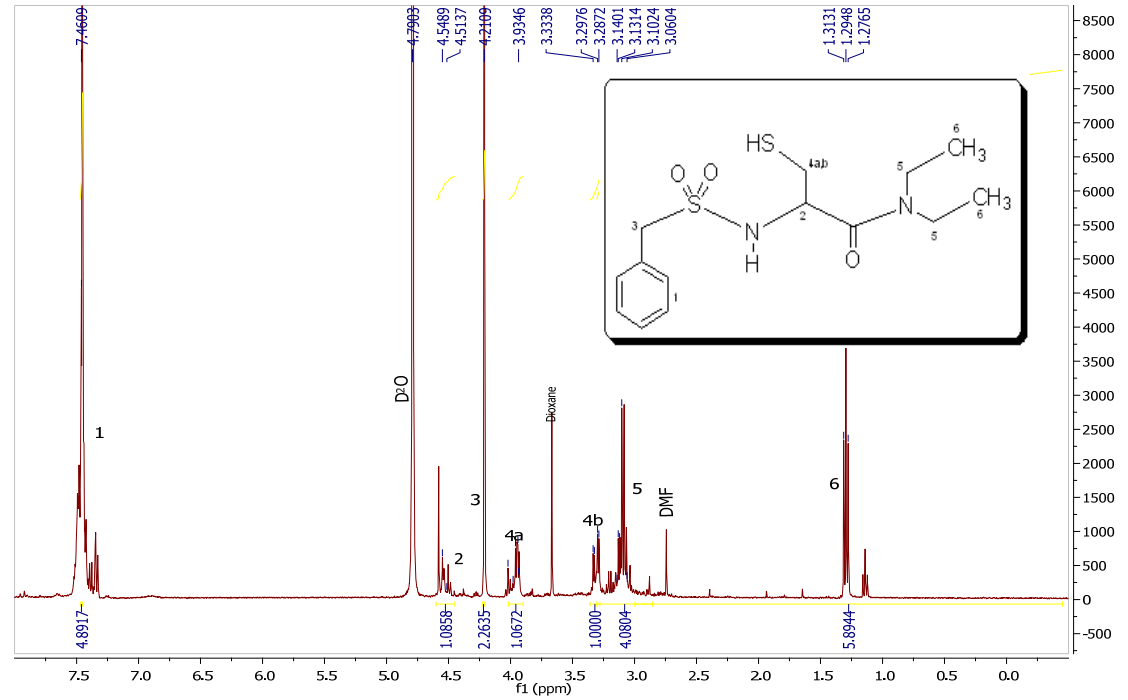


Fig. 5.17: ^{1}H-NMR Spectrum of 2f

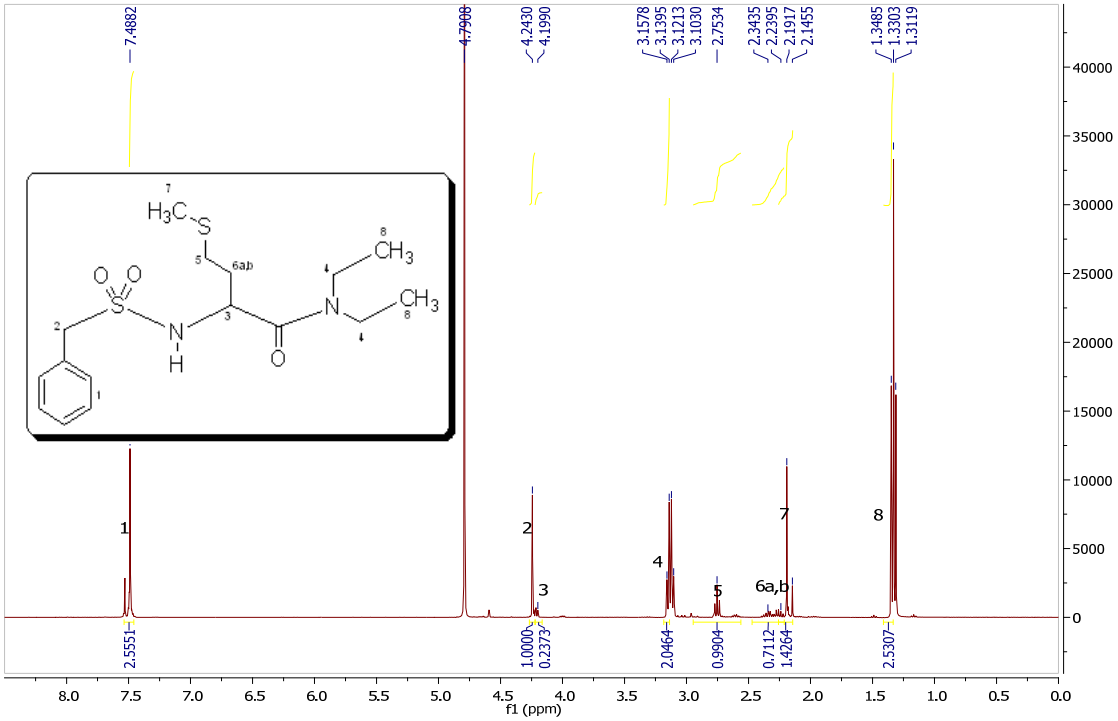


Fig. 5.18: ^{1}H-NMR Spectrum of 2g

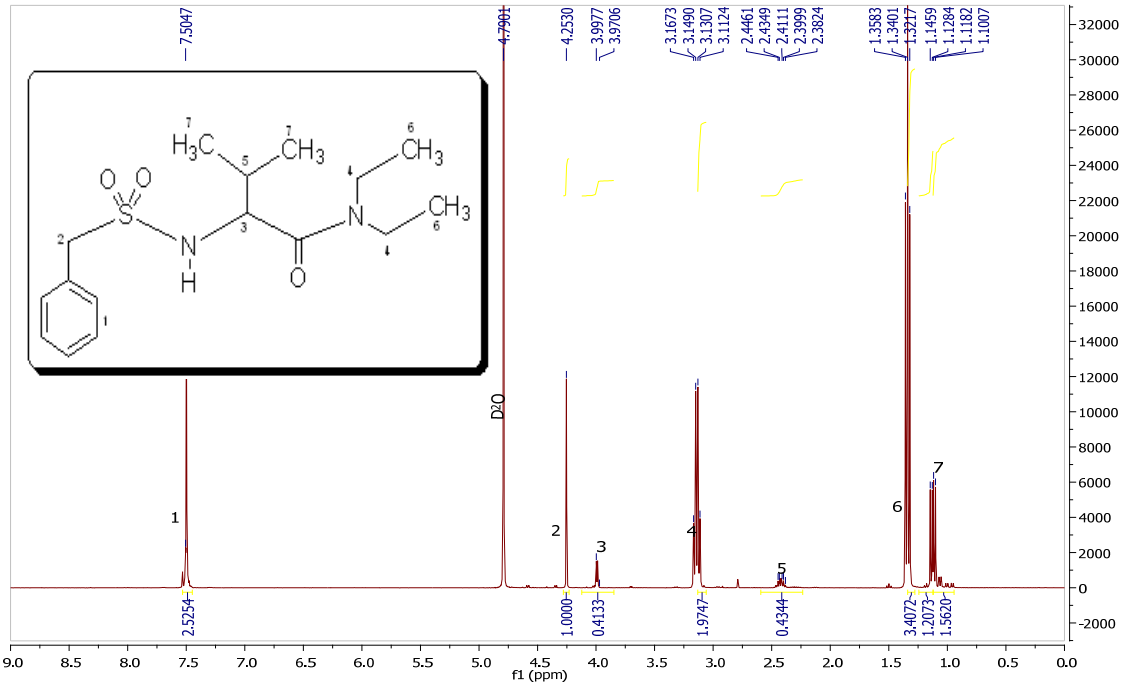


Fig. 5.19: ^{1}H-NMR Spectrum of 2h

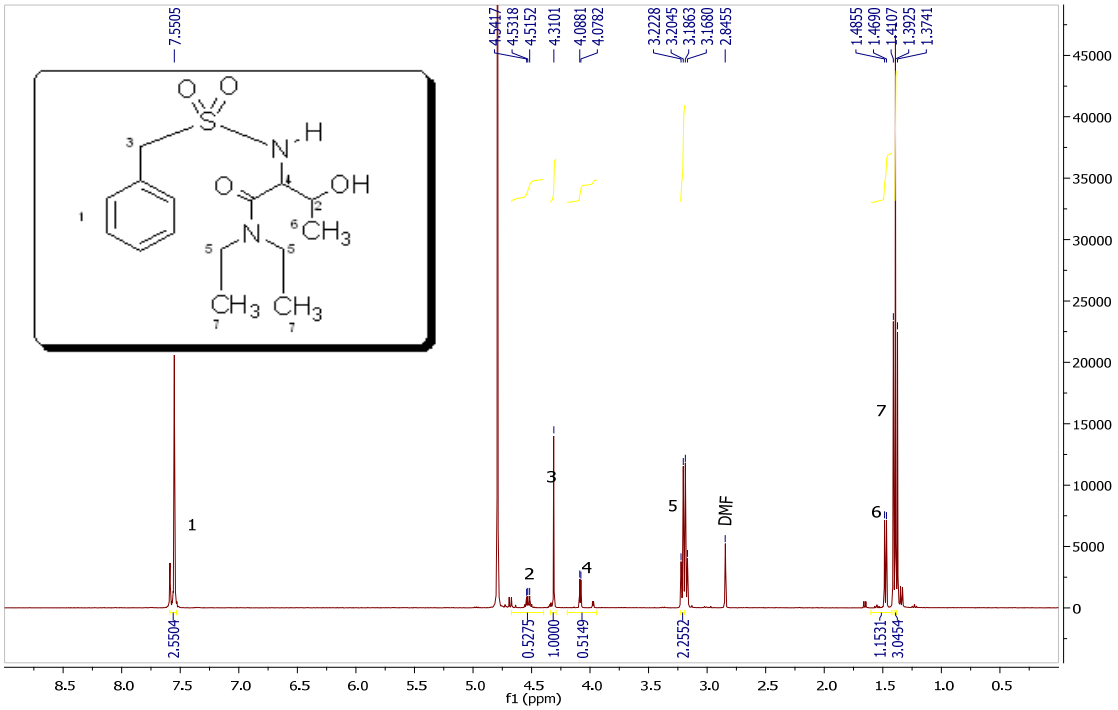


Fig. 5.20: ^{1}H-NMR Spectrum of 2i

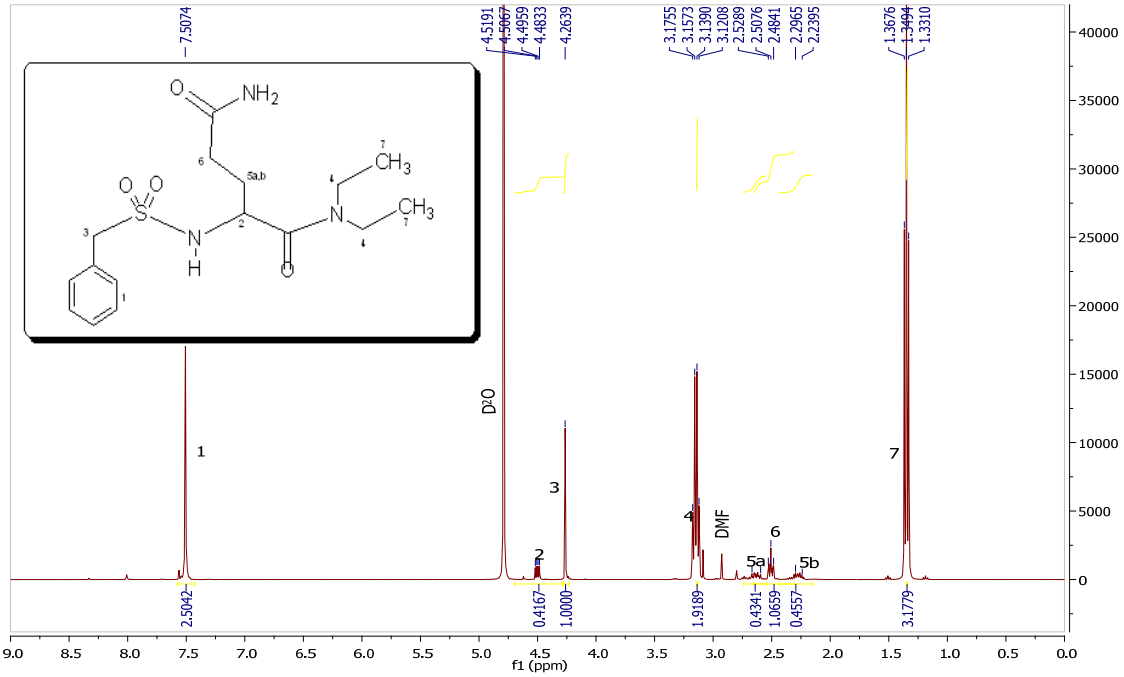


Fig. 5.21: ^{1}H-NMR Spectrum of 2j

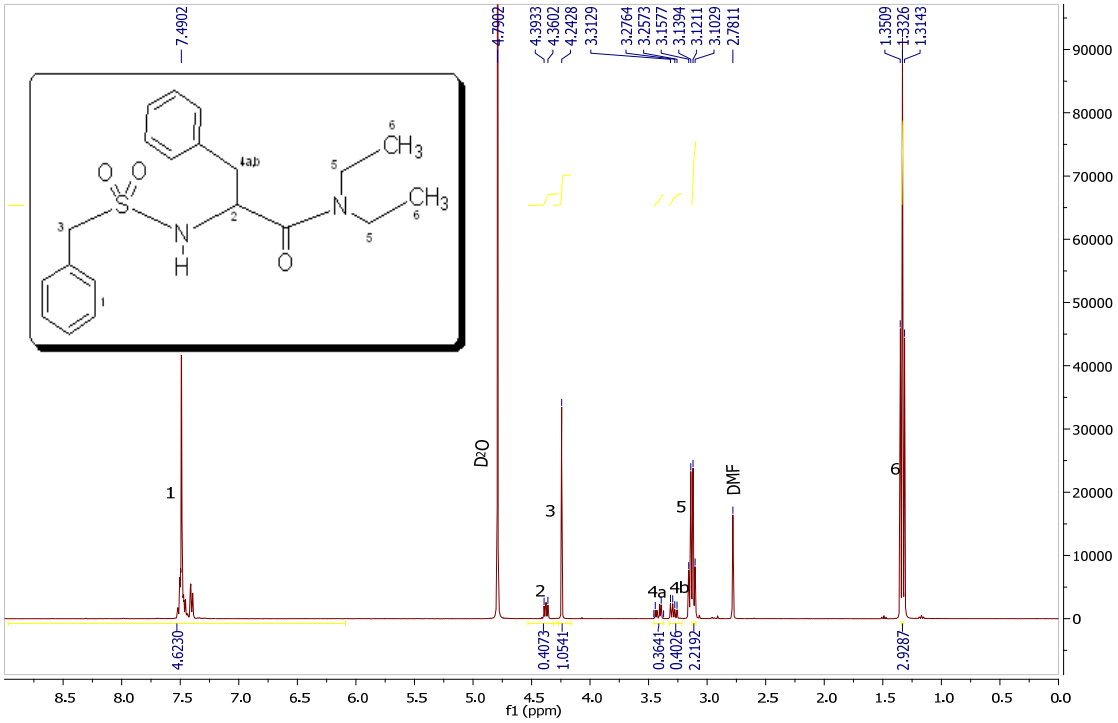
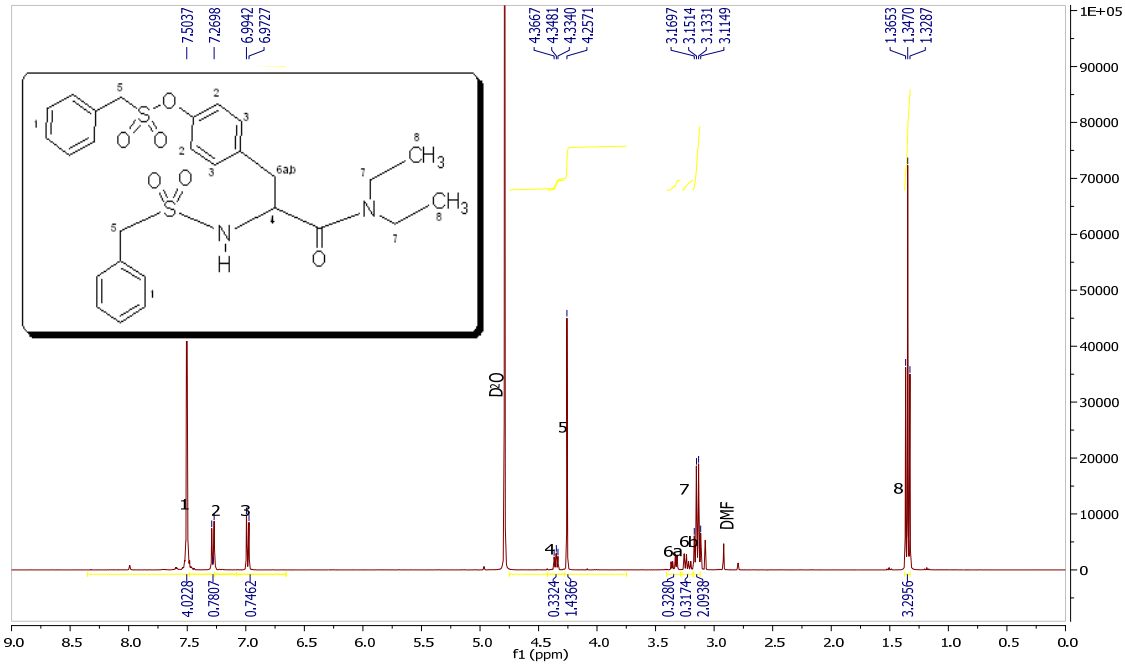


Fig. 5.22: ^{1}H-NMR Spectrum of 2k



^{13}C-NMR Spectral Data of α-Tolylsulphonamide Derivatives

Fig. 5.23: ^{13}C-NMR Spectrum of 1a

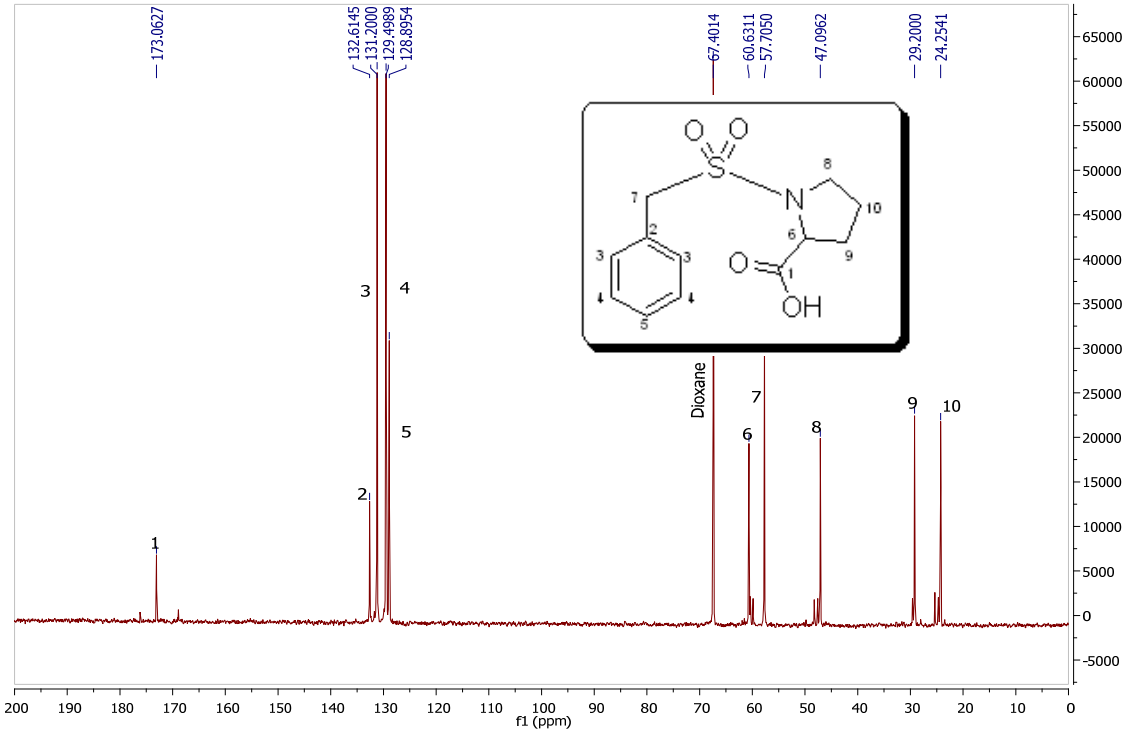


Fig. 5.24: ^{13}C-NMR Spectrum of 1b

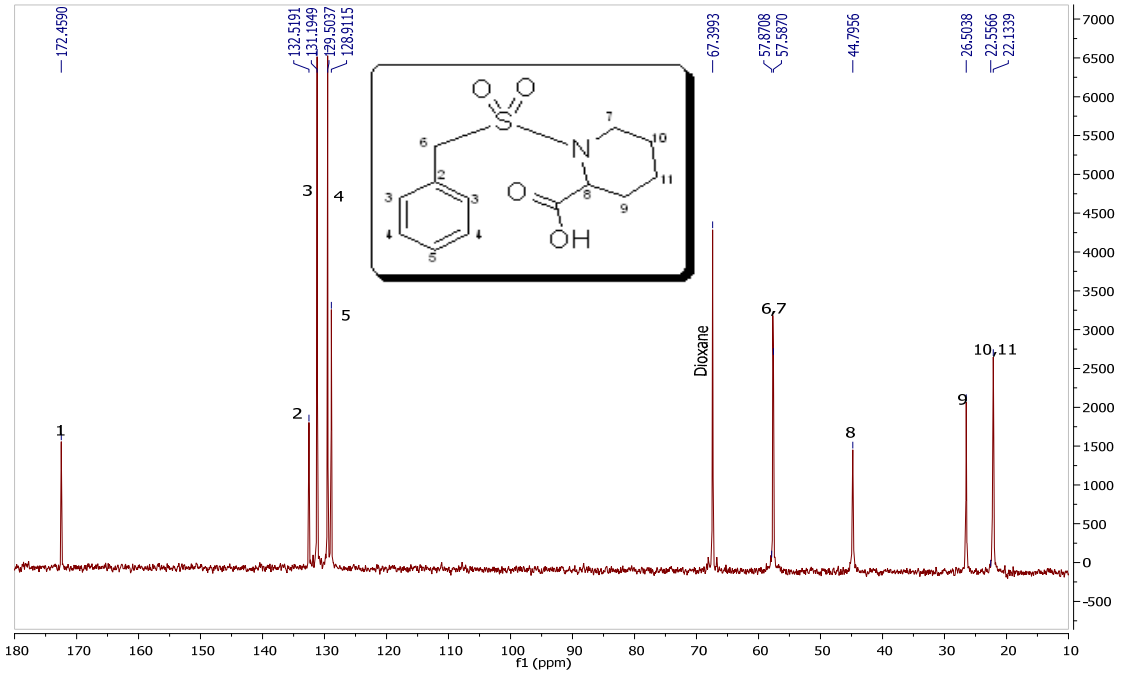


Fig. 5.25: ^{13}C-NMR Spectrum of 1c

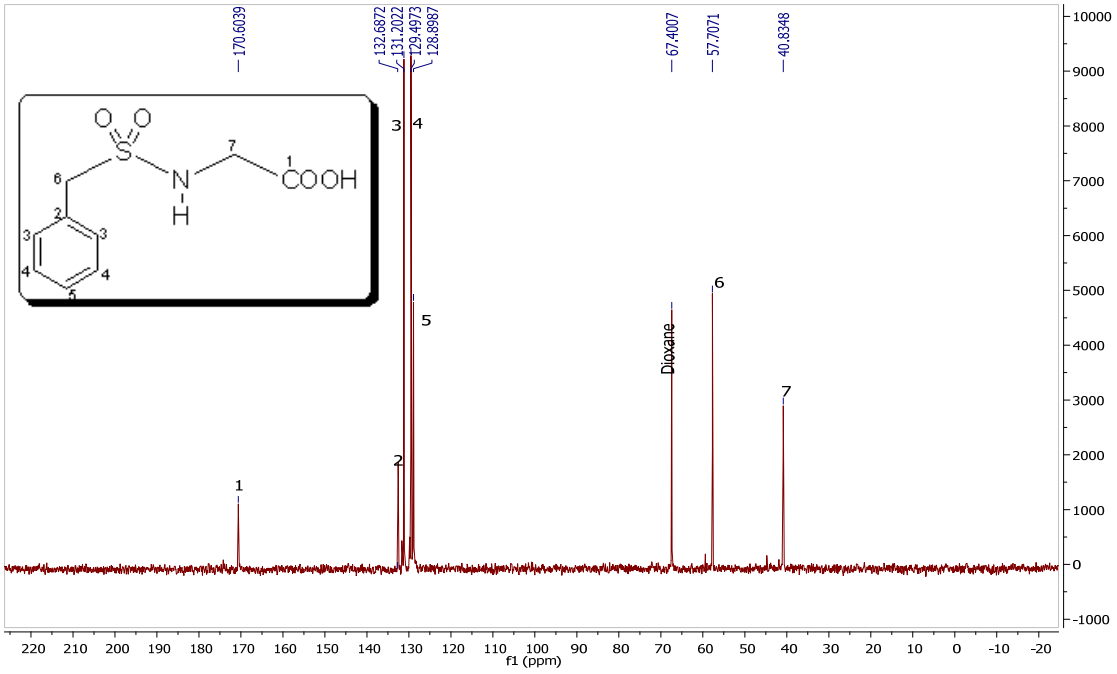


Fig. 5.26: ^{13}C-NMR Spectrum of 1d

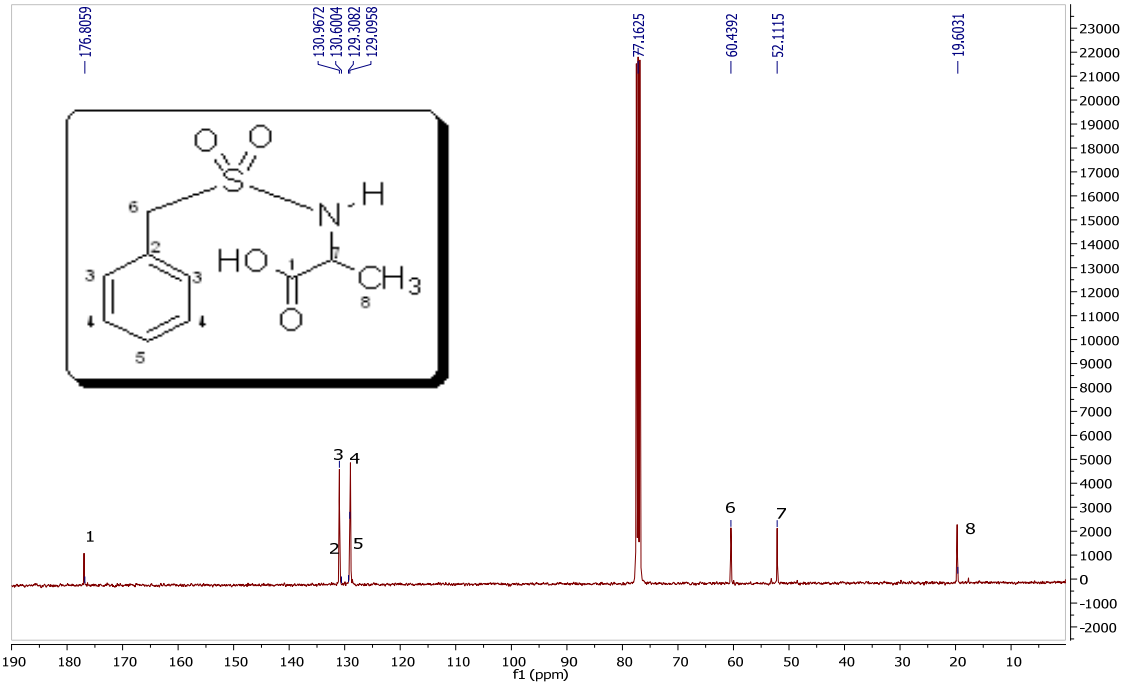


Fig. 5.27: ^{13}C-NMR Spectrum of 1e

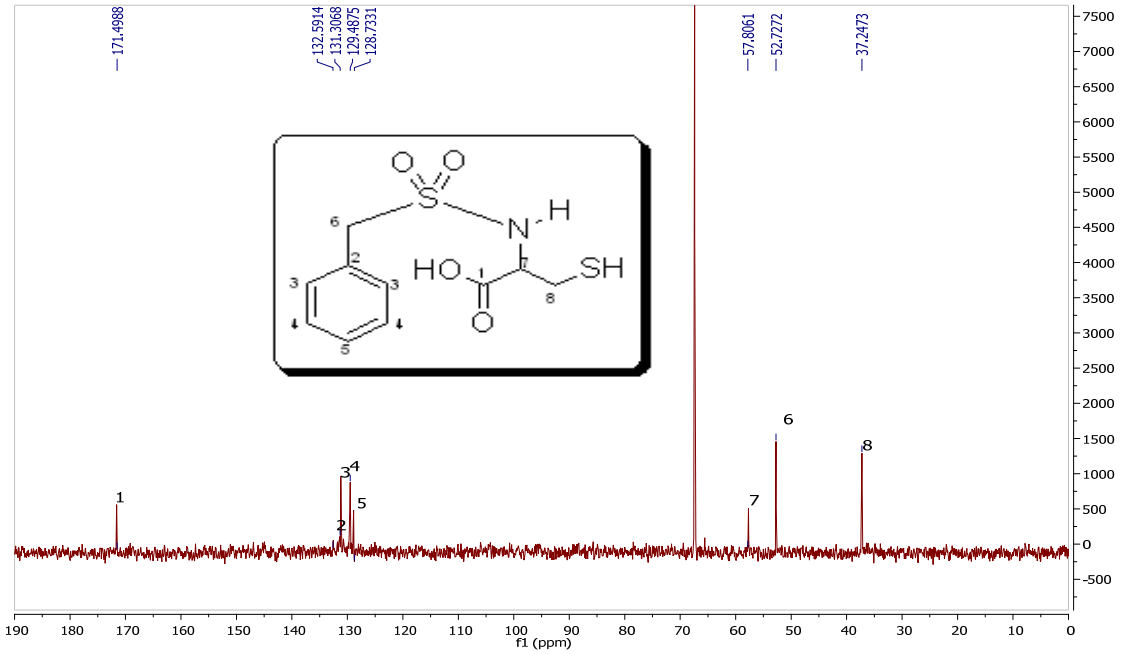


Fig. 5.28: ^{13}C-NMR Spectrum of 1f

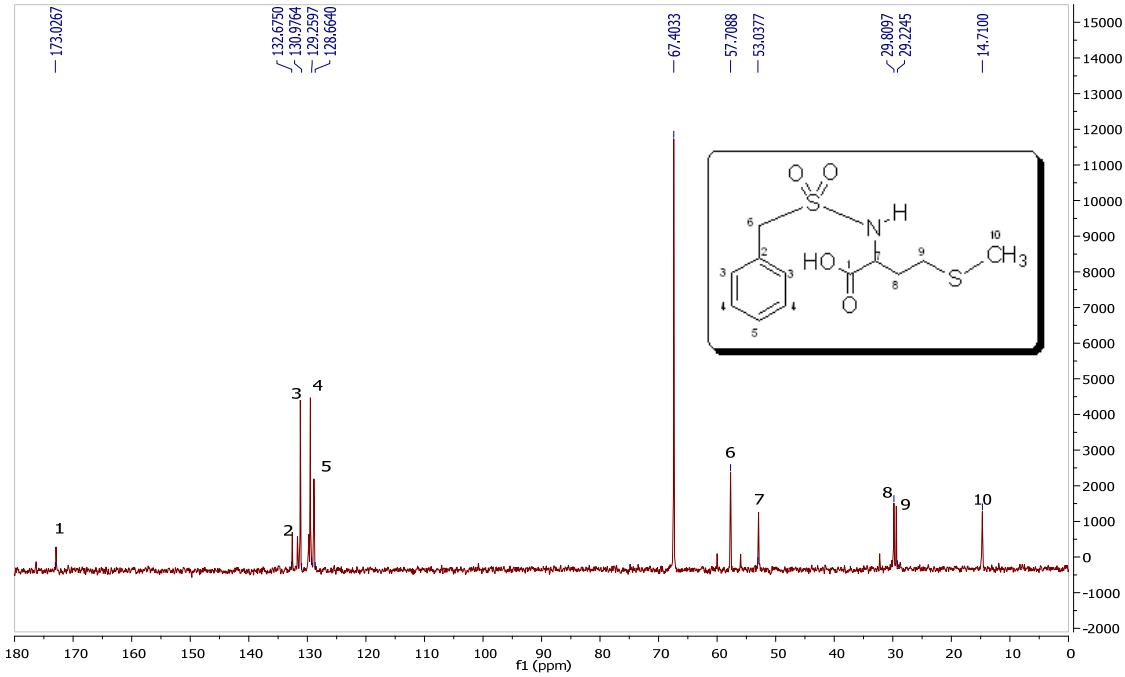


Fig. 5.29: ^{13}C-NMR Spectrum of 1g

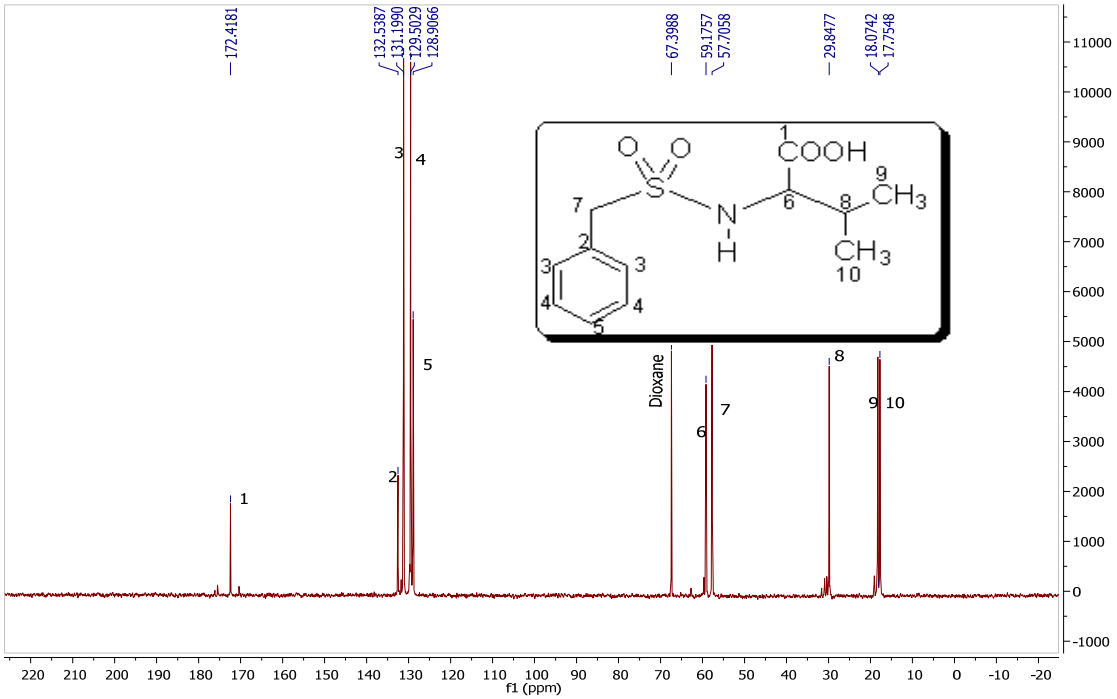


Fig. 5.30: ^{13}C-NMR Spectrum of 1h

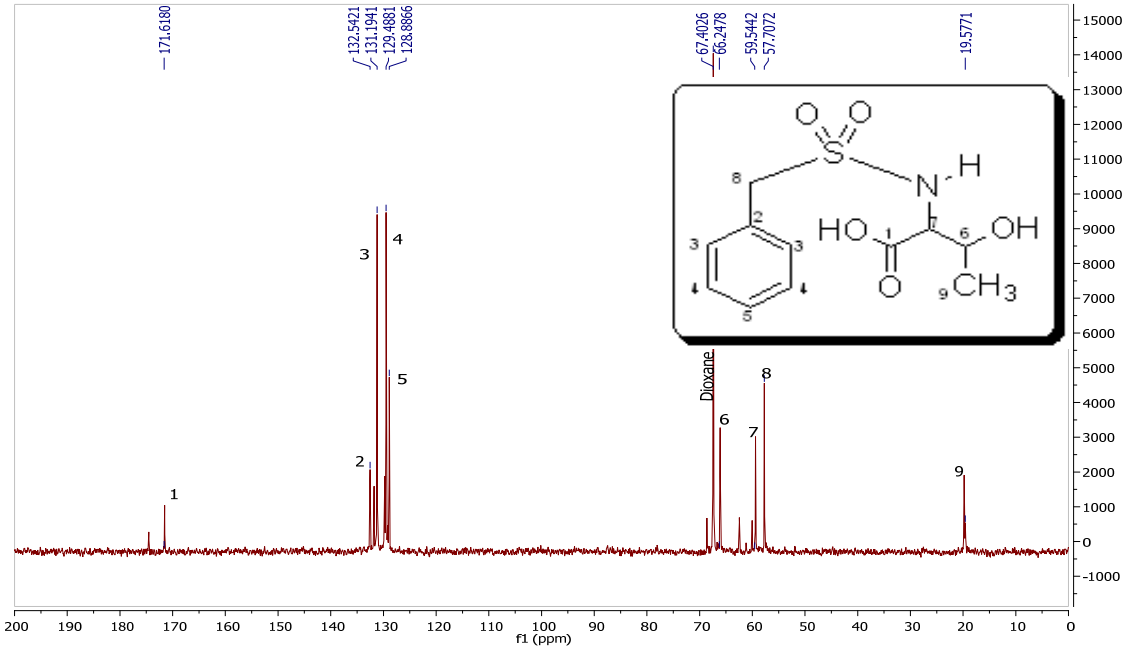


Fig. 5.31: ^{13}C-NMR Spectrum of 1i

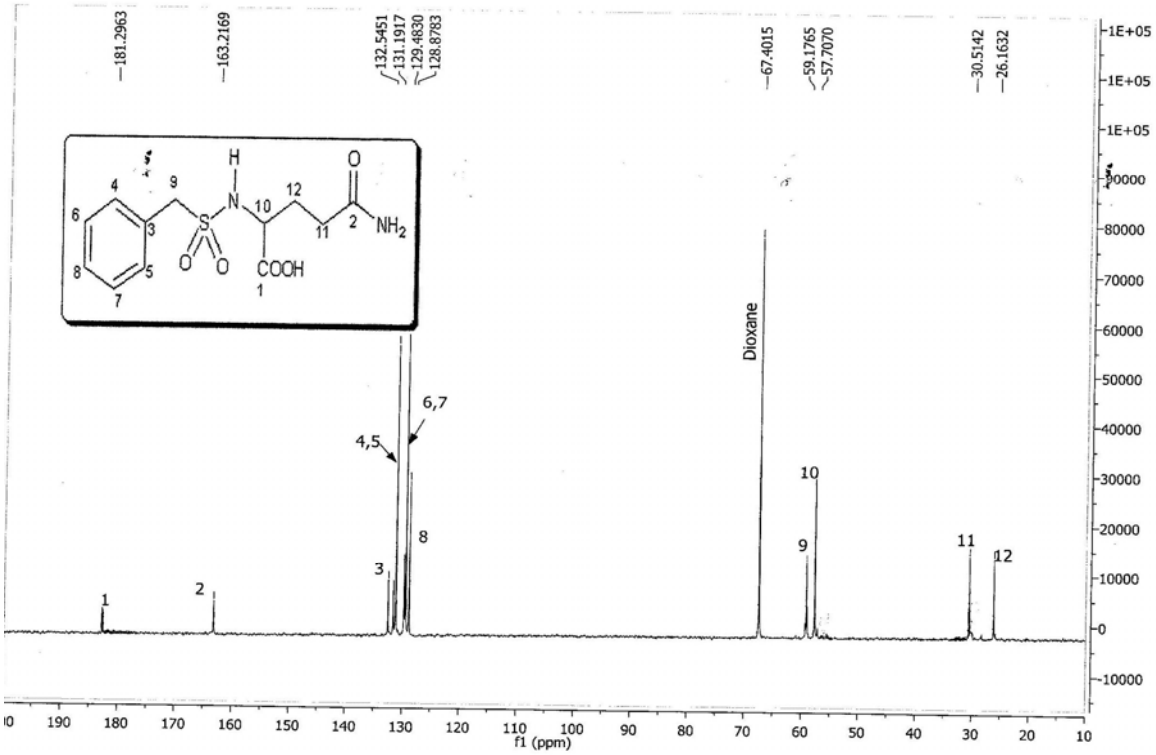


Fig. 5.32: ^{13}C-NMR Spectrum of 1j

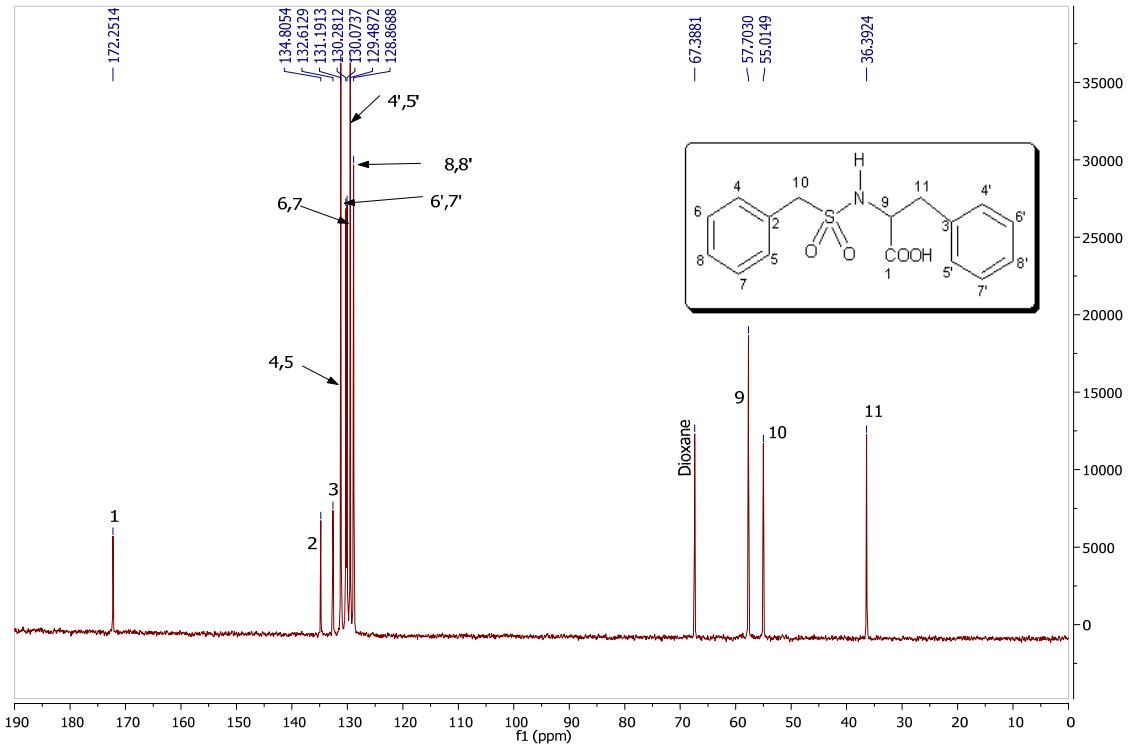


Fig. 5.33: ^{13}C-NMR Spectrum of 1j (Expanded in Aromatic Region)

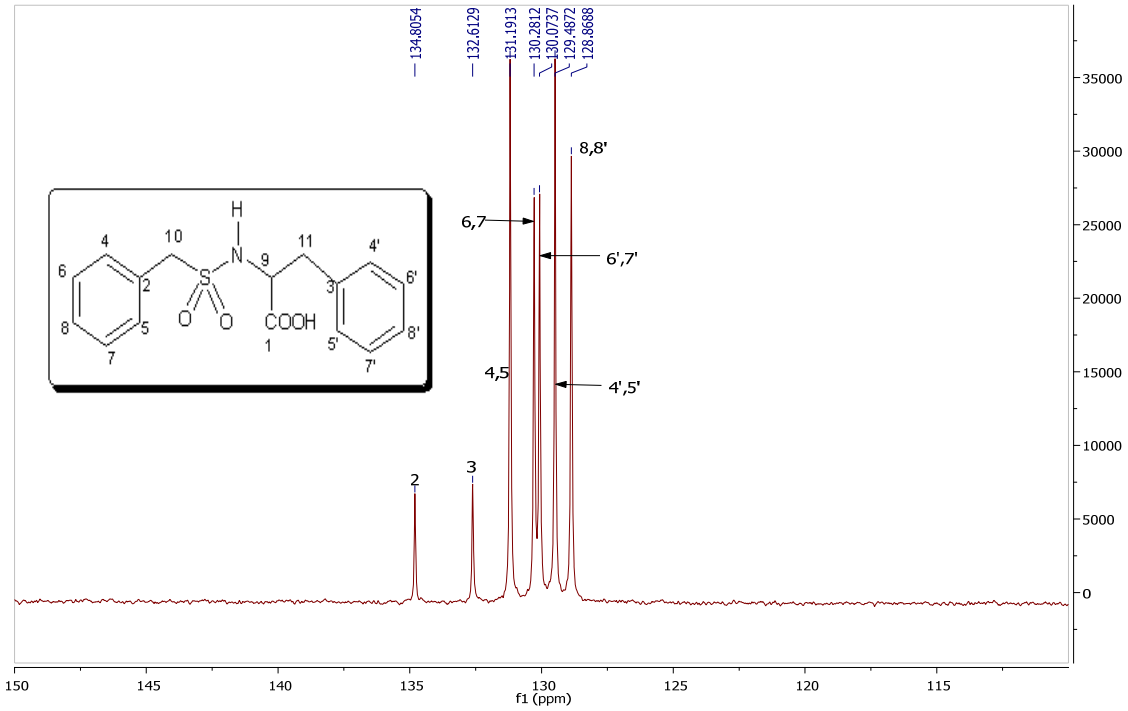


Fig. 5.34: ^{13}C-NMR Spectrum of 1k

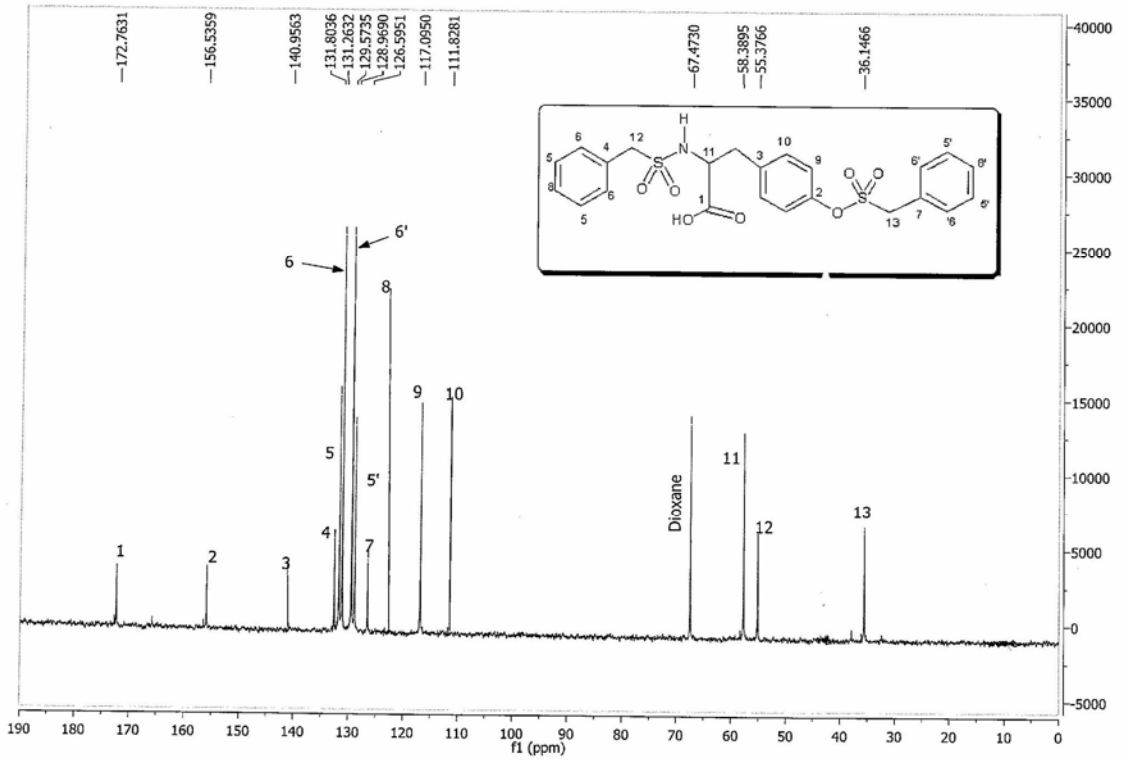


Fig. 5.35: ^{13}C-NMR Spectrum of 2a

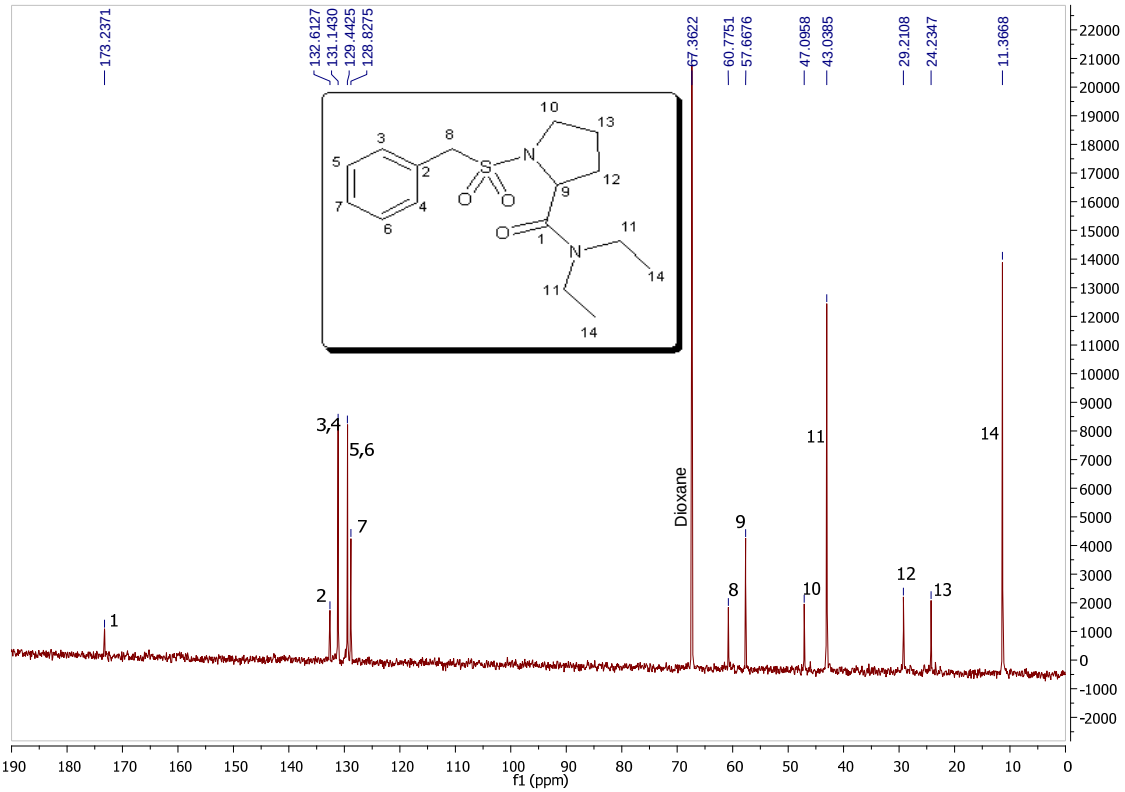


Fig. 5.36: ^{13}C-NMR Spectrum of 2b

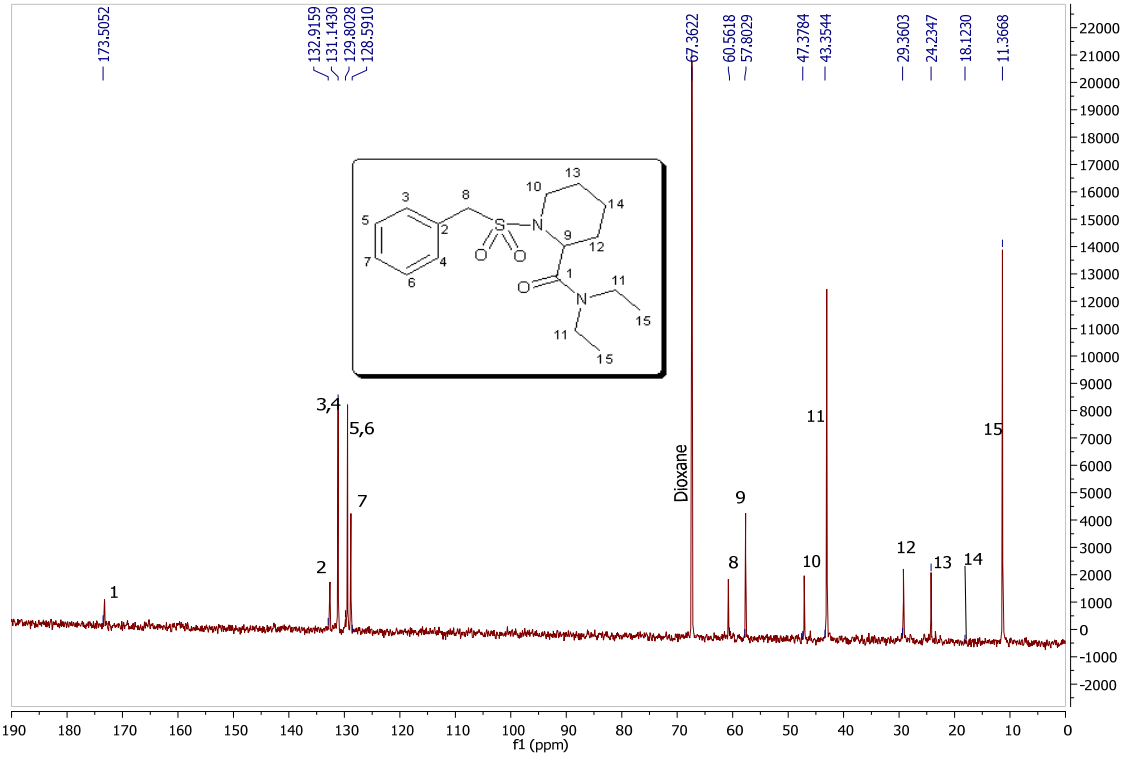


Fig. 5.37: ^{13}C-NMR Spectrum of 2c

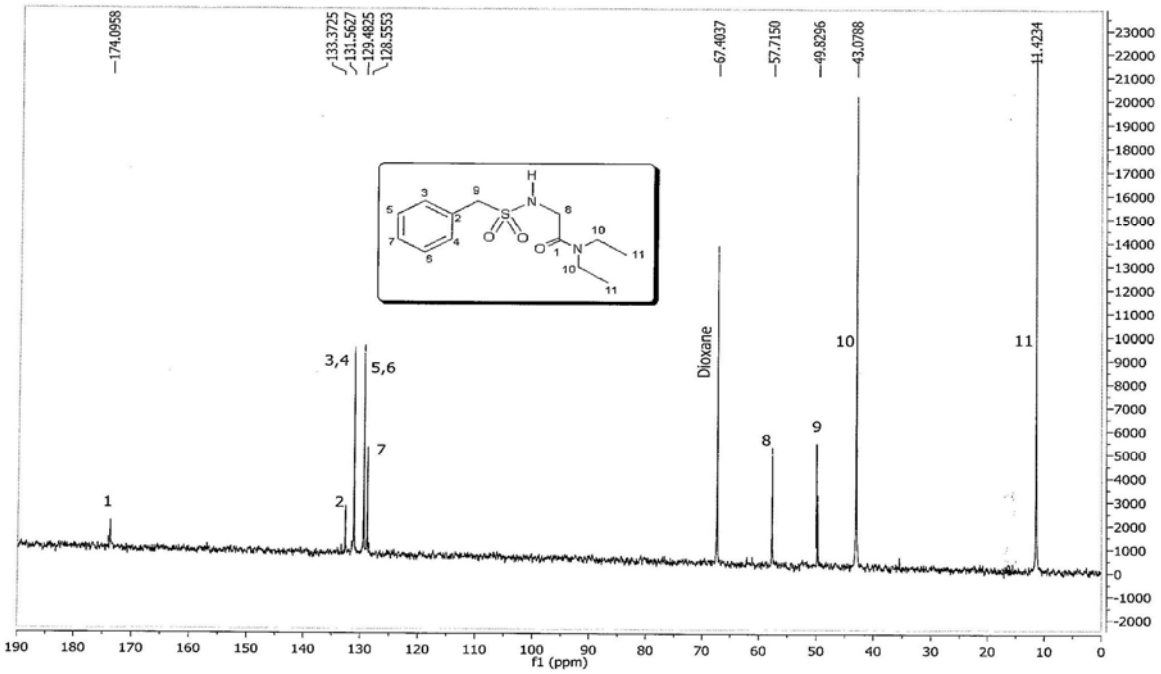


Fig. 5.38: ^{13}C-NMR Spectrum of 2d

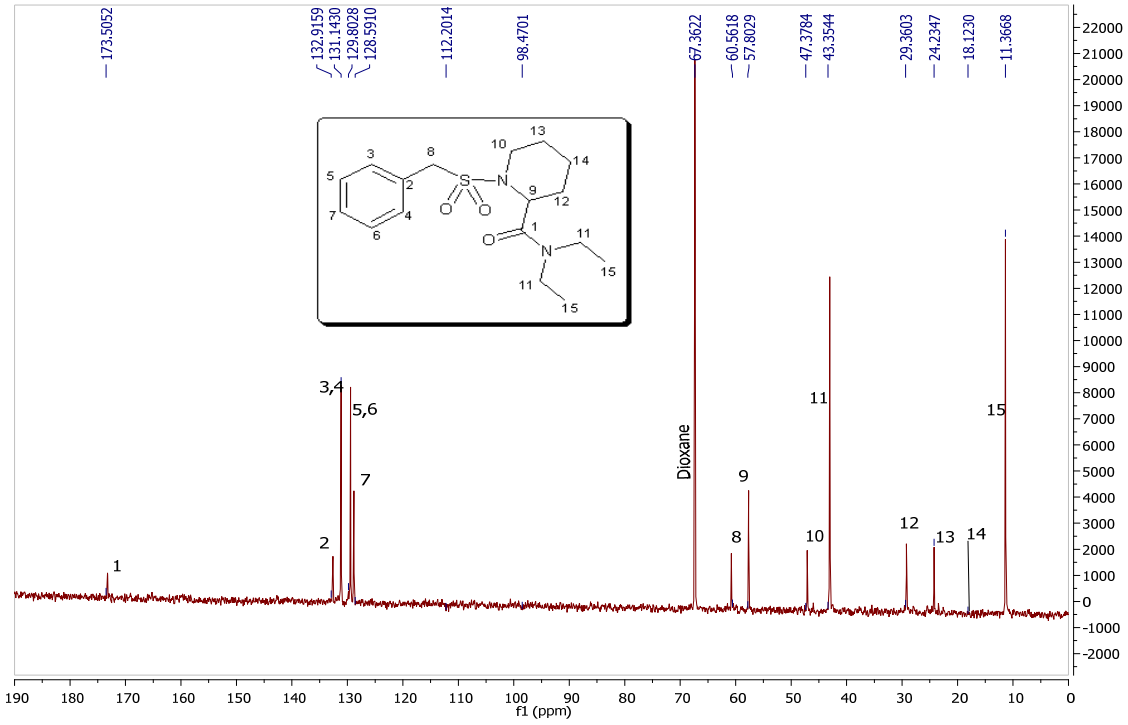


Fig. 5.39: ^{13}C-NMR Spectrum of 2e

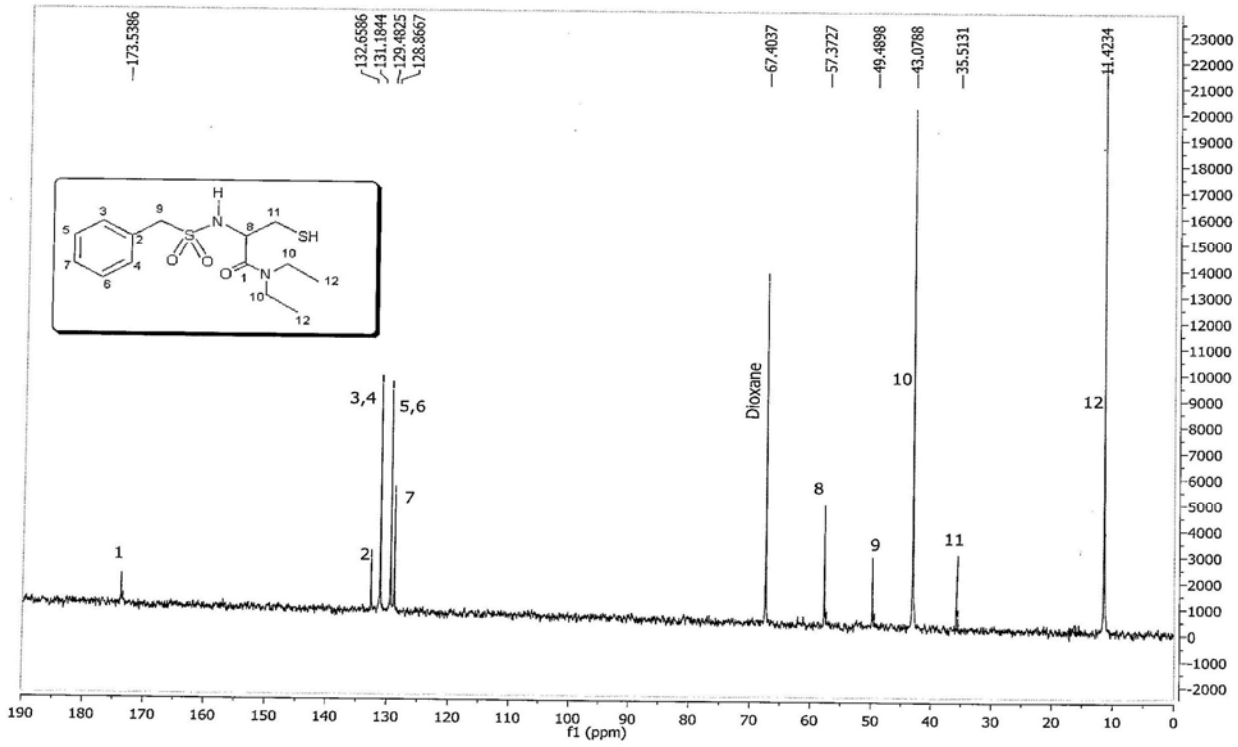


Fig. 5.40: ^{13}C-NMR Spectrum of 2f

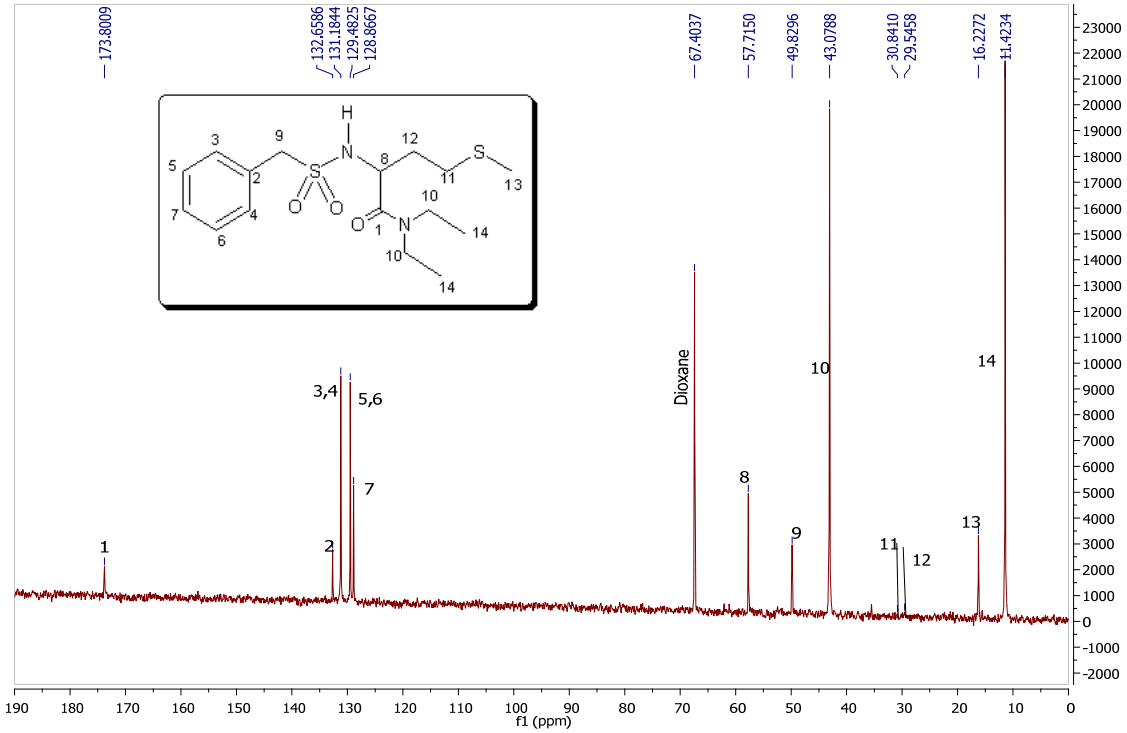


Fig. 5.41: ^{13}C-NMR Spectrum of 2g

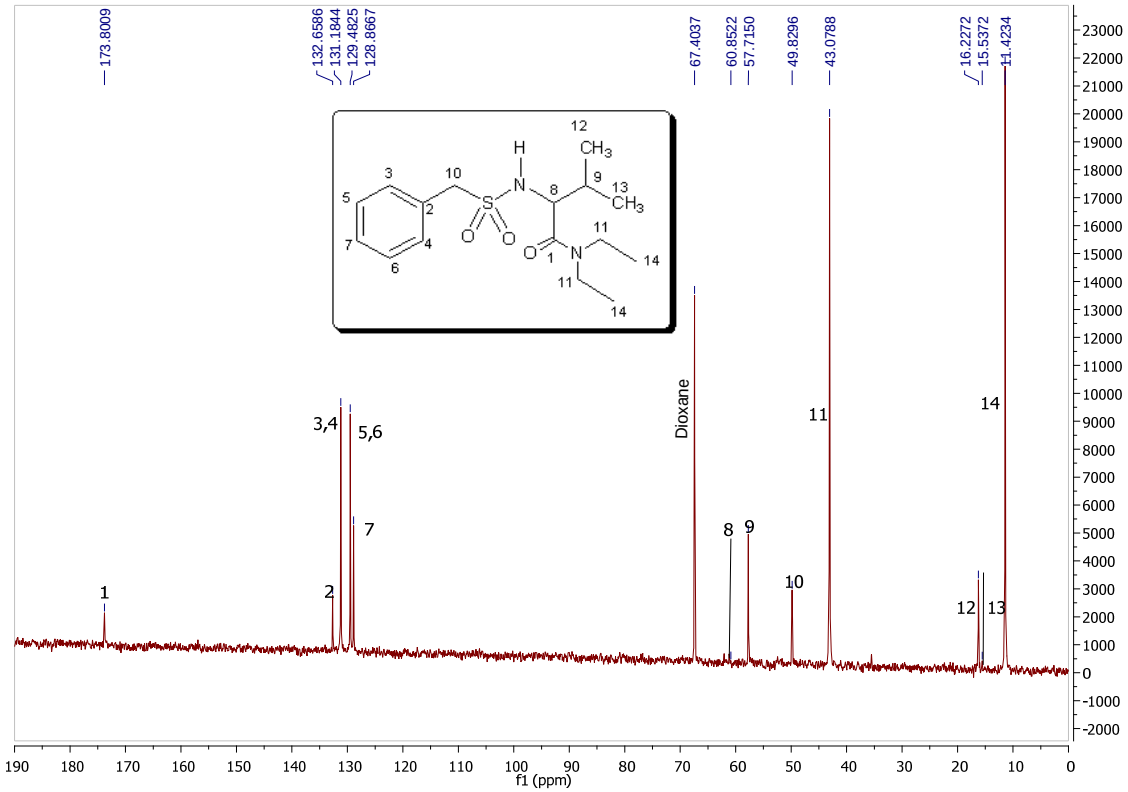


Fig. 5.42: ^{13}C-NMR Spectrum of 2h

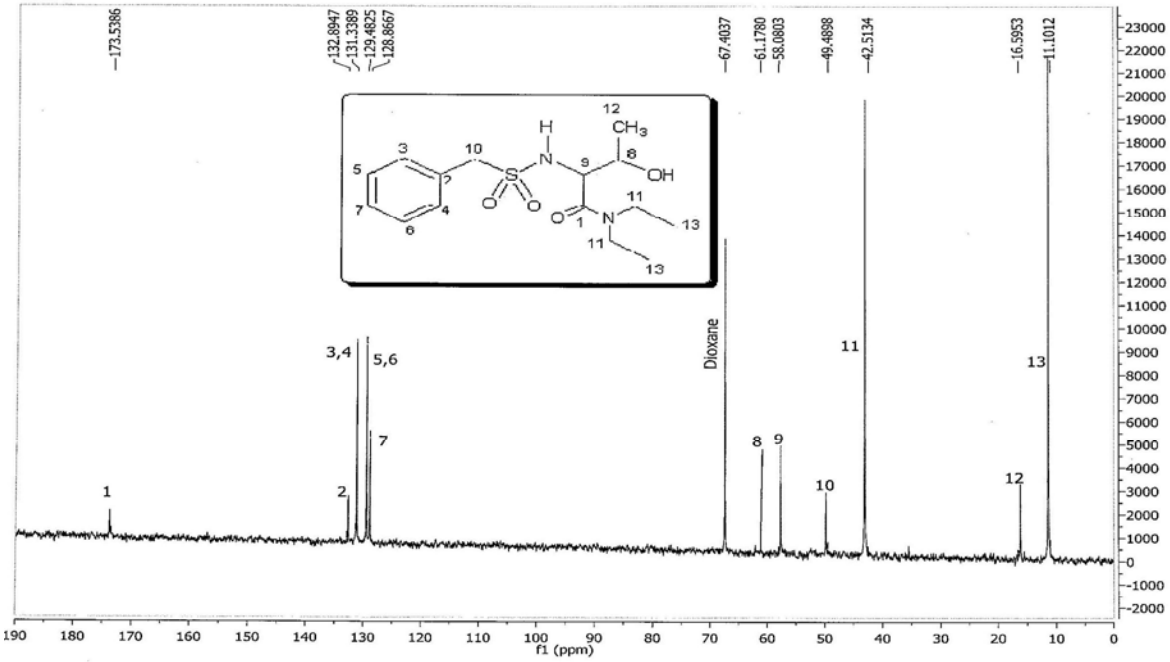


Fig. 5.43: ^{13}C-NMR Spectrum of 2i

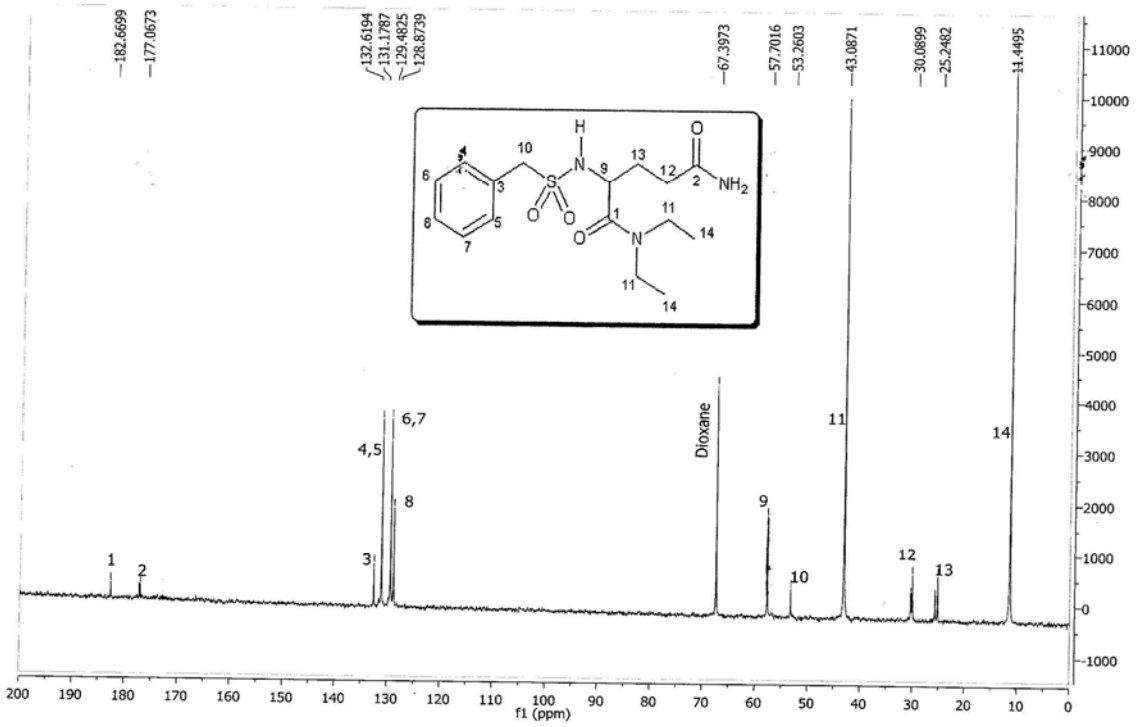


Fig. 5.44: ^{13}C-NMR Spectrum of 2j

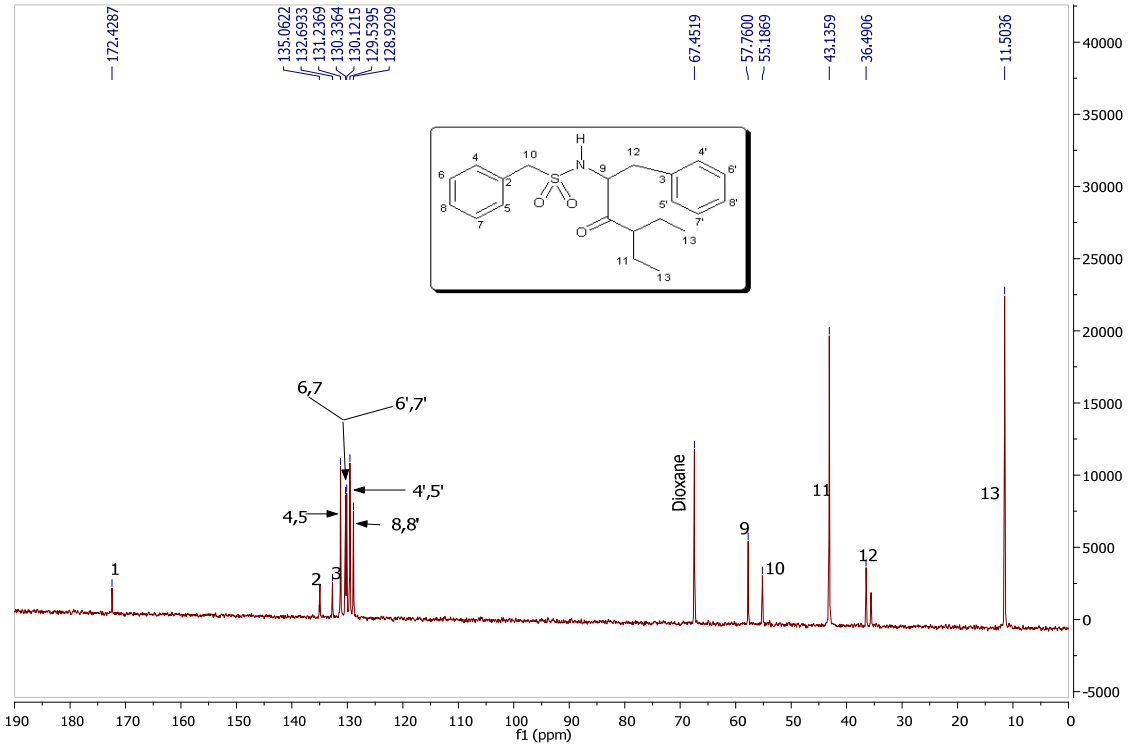


Fig. 5.45: ^{13}C-NMR Spectrum of 2j (Expanded in Aromatic Region)

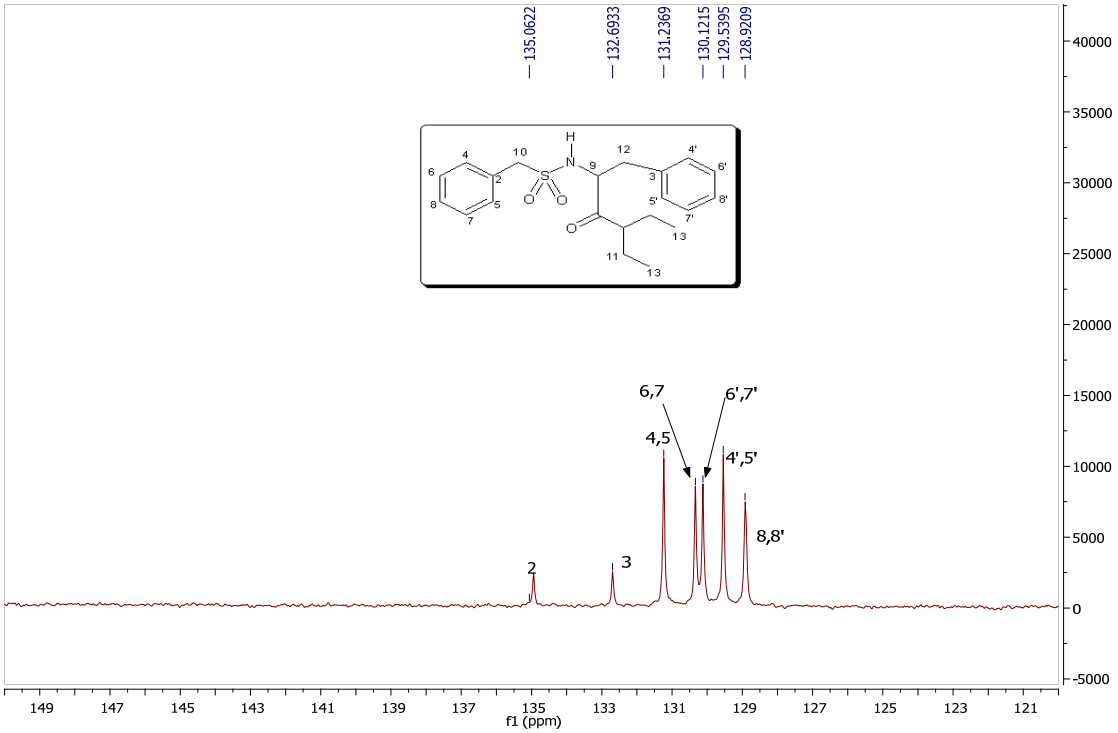
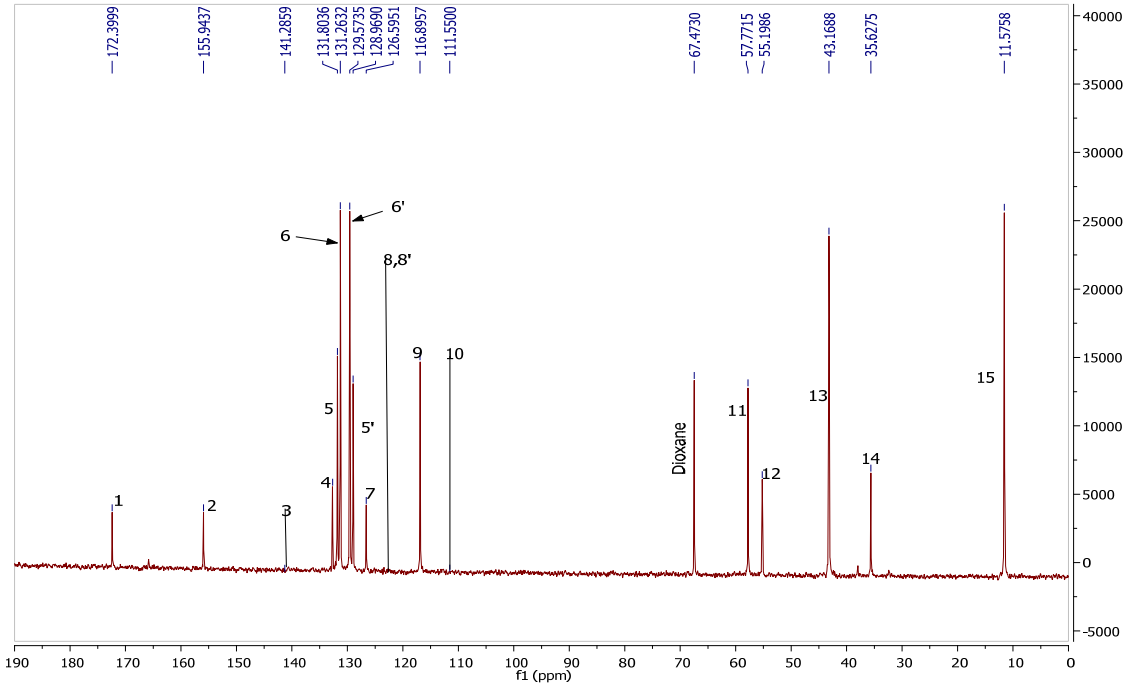


Fig. 5.46: ^{13}C-NMR Spectrum of 2k



Infrared Spectral Data of α-Tolylsulphonamide Derivatives

Fig. 5.47: IR Spectrum of 1a

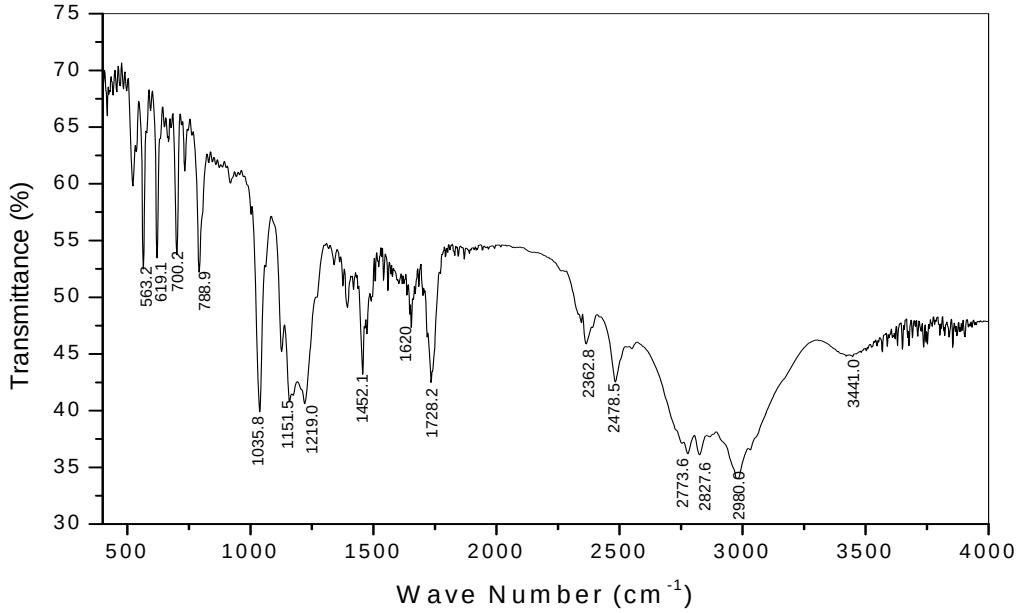


Fig. 5.48: IR Spectrum of 1b

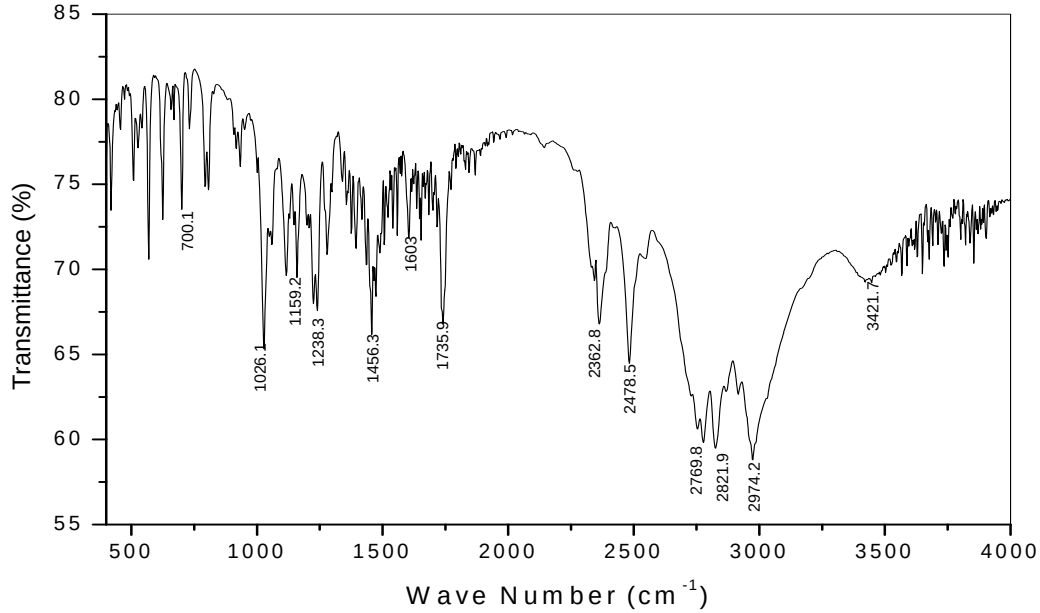


Fig. 5.49: IR Spectrum of 1c

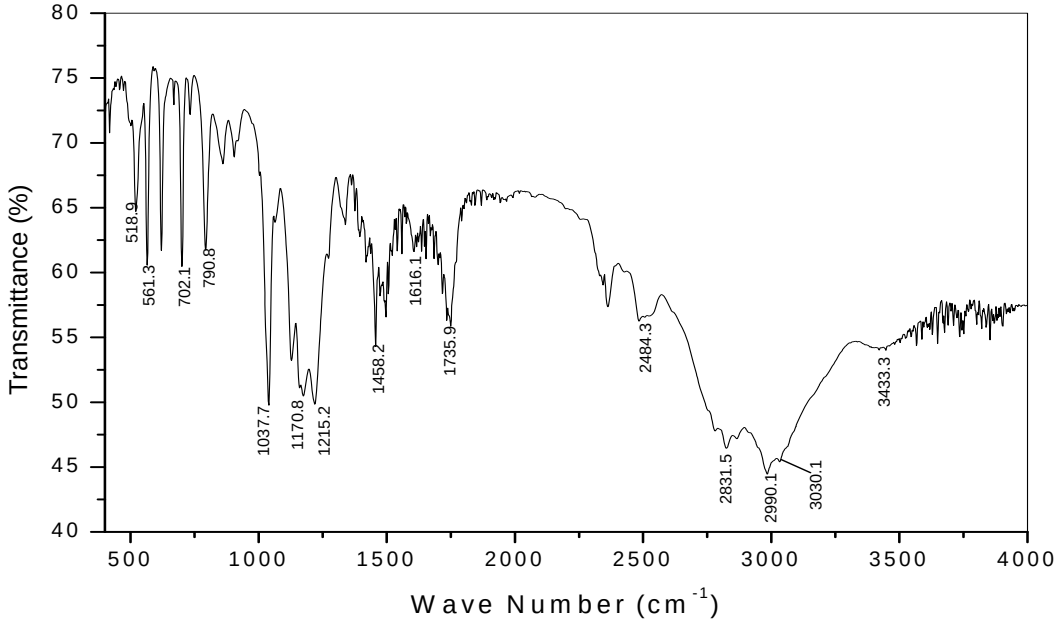


Fig. 5.50: IR Spectrum of 1d

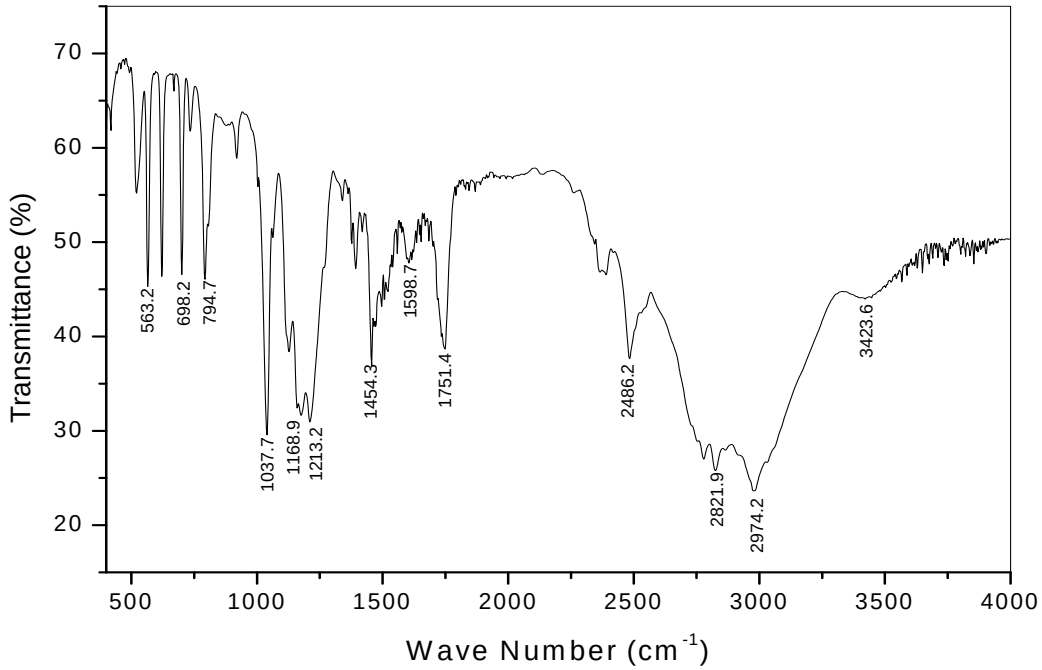


Fig. 5.51: IR Spectrum of 1e

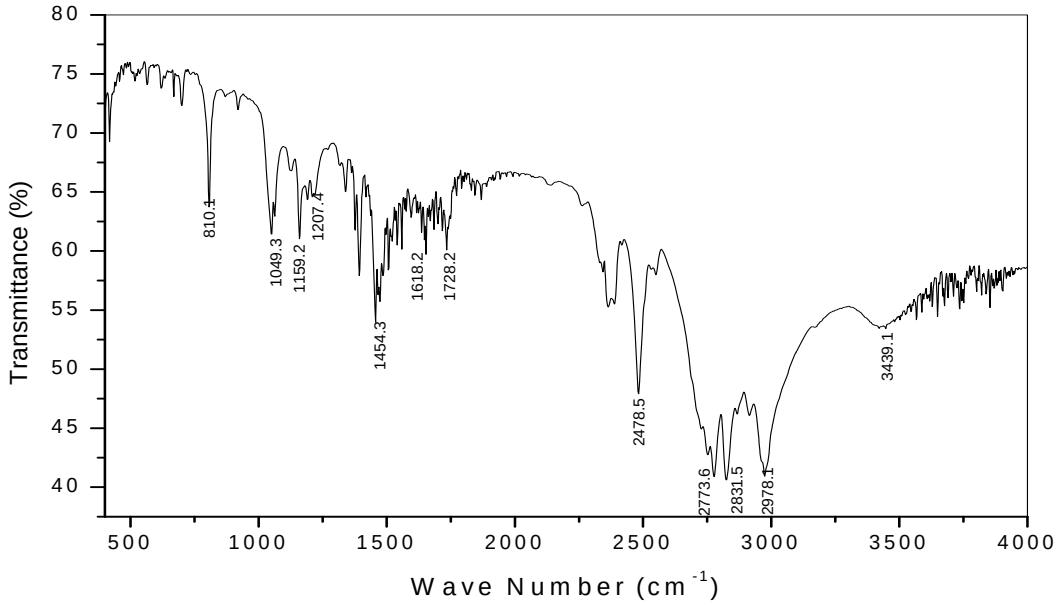


Fig. 5.52: IR Spectrum of 1f

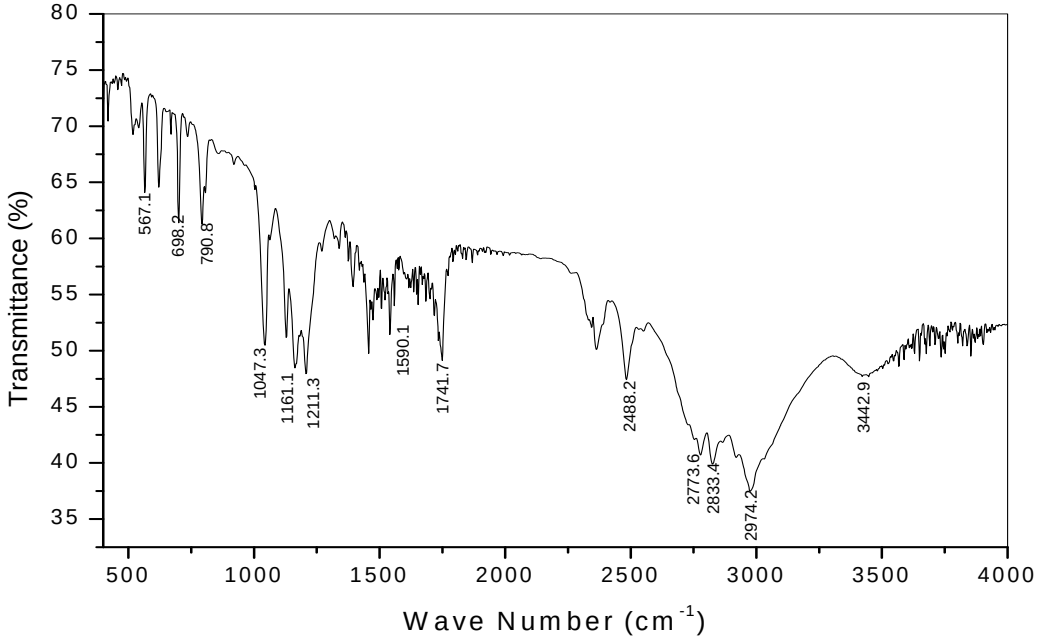


Fig. 5.53: IR Spectrum of 1g

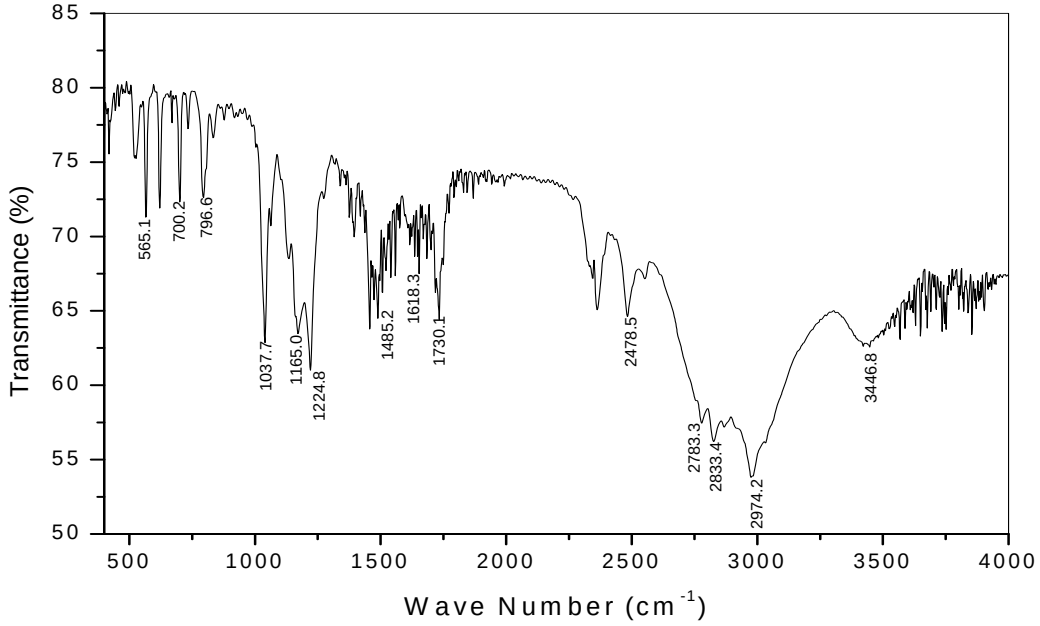


Fig. 5.54: IR Spectrum of 1h

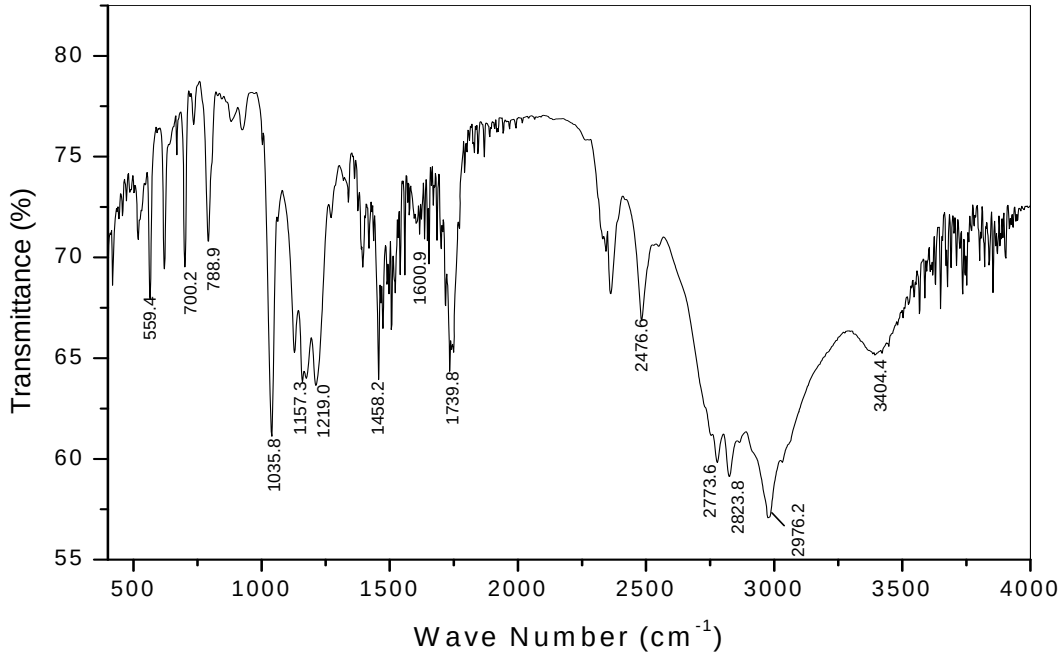


Fig. 5.55: IR Spectrum of 1i

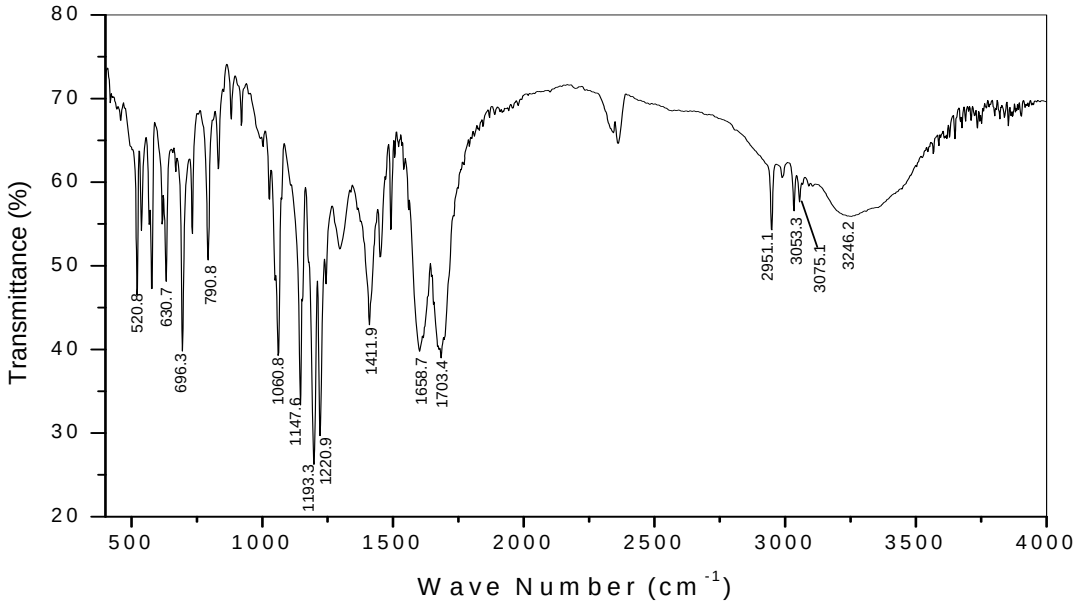


Fig. 5.56: IR Spectrum of 1j

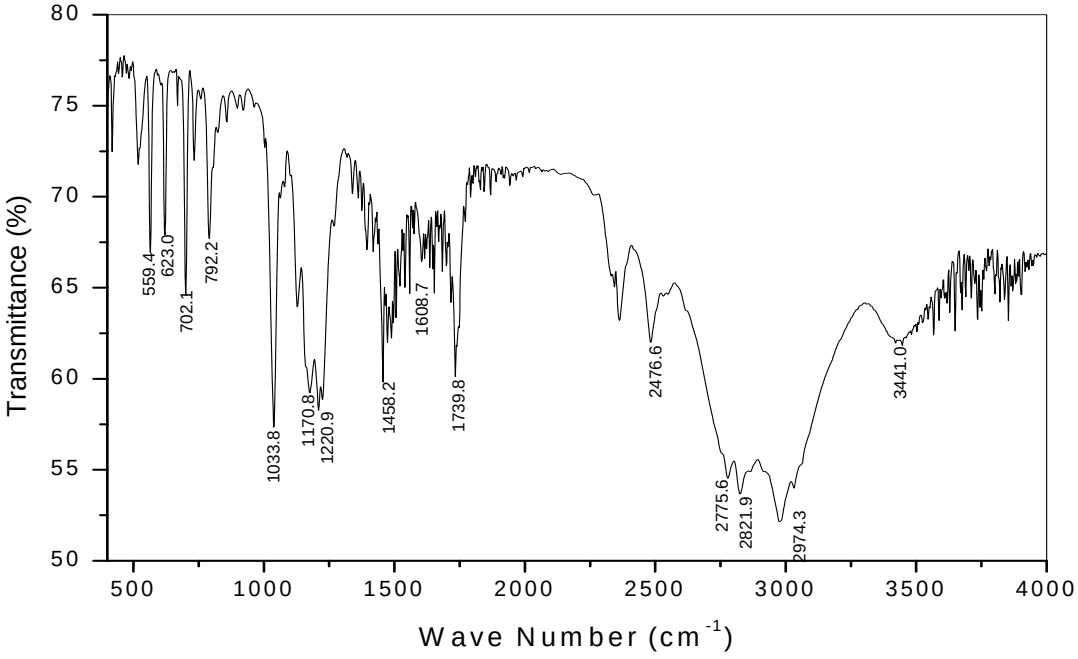


Fig. 5.57: IR Spectrum of 1k

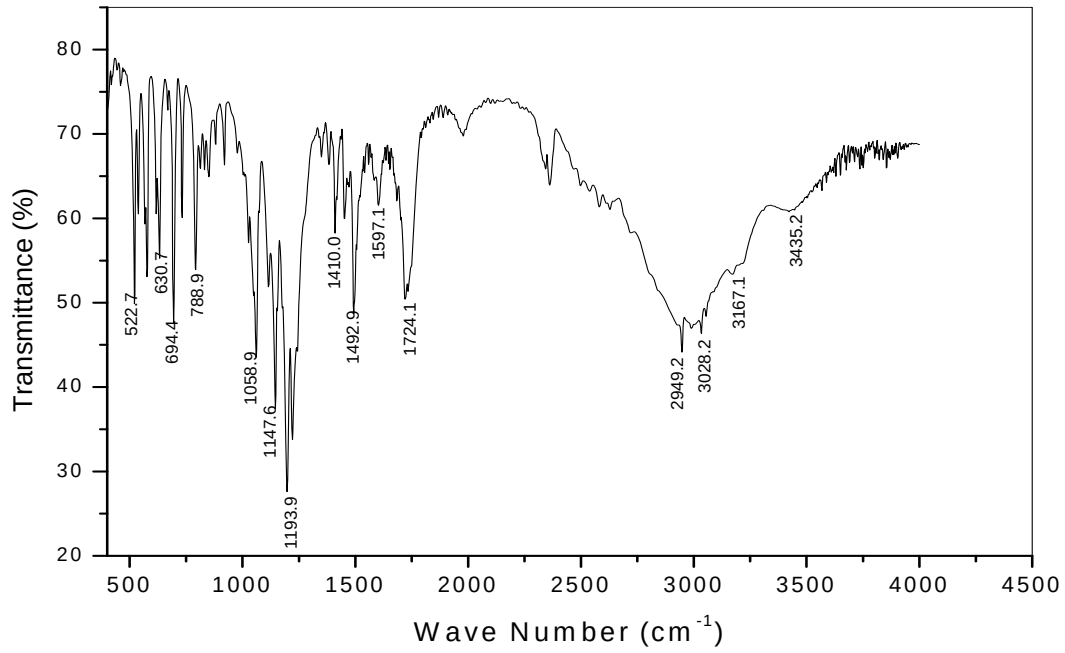


Fig. 5.58: IR Spectrum of 2b

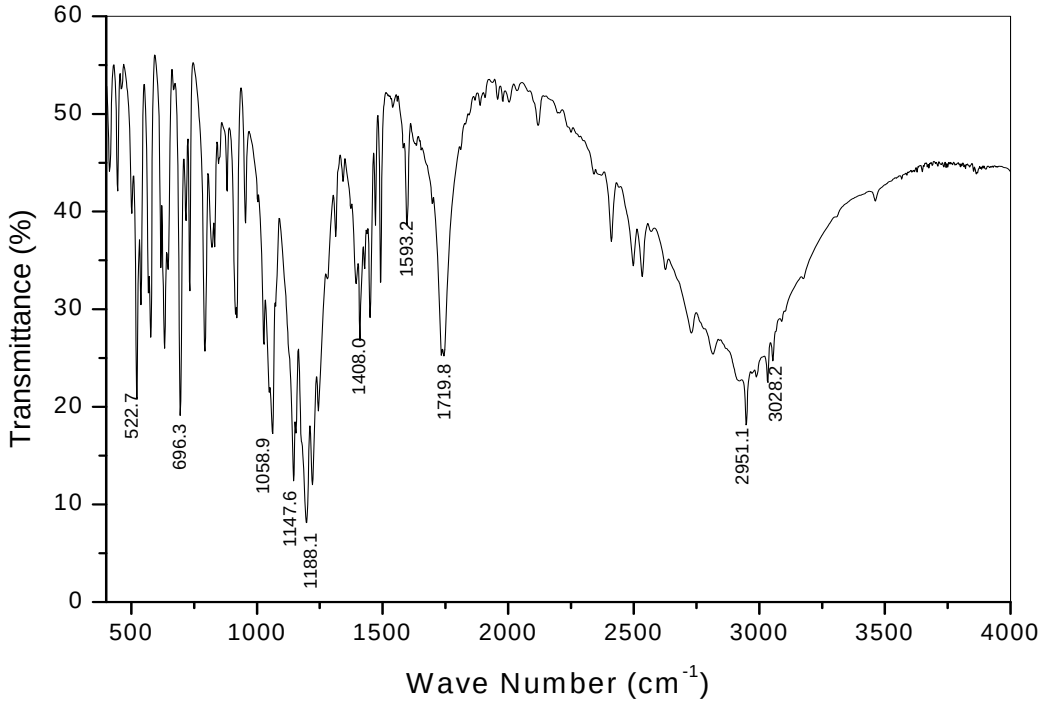


Fig. 5.59: IR Spectrum of 2c

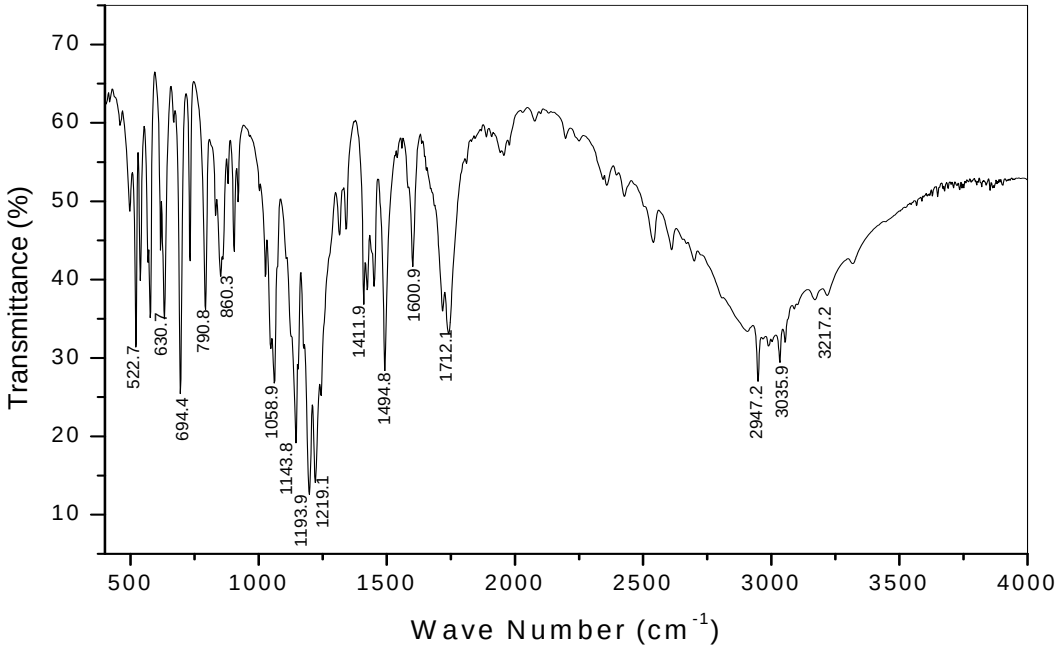


Fig. 5.60: IR Spectrum of 2d

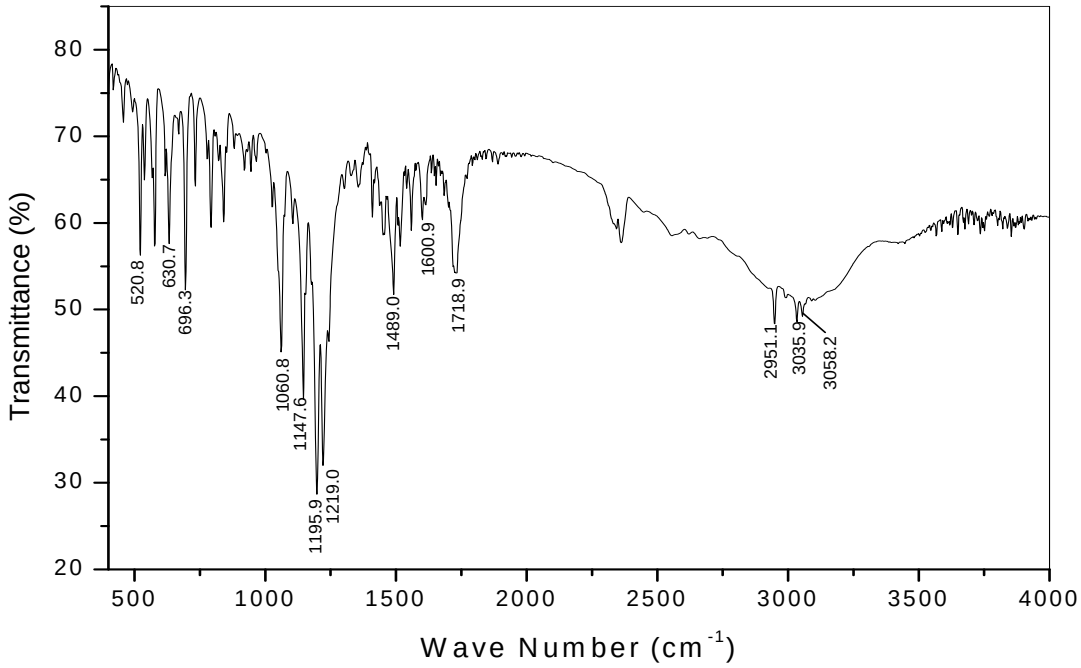


Fig. 5.61: IR Spectrum of 2e

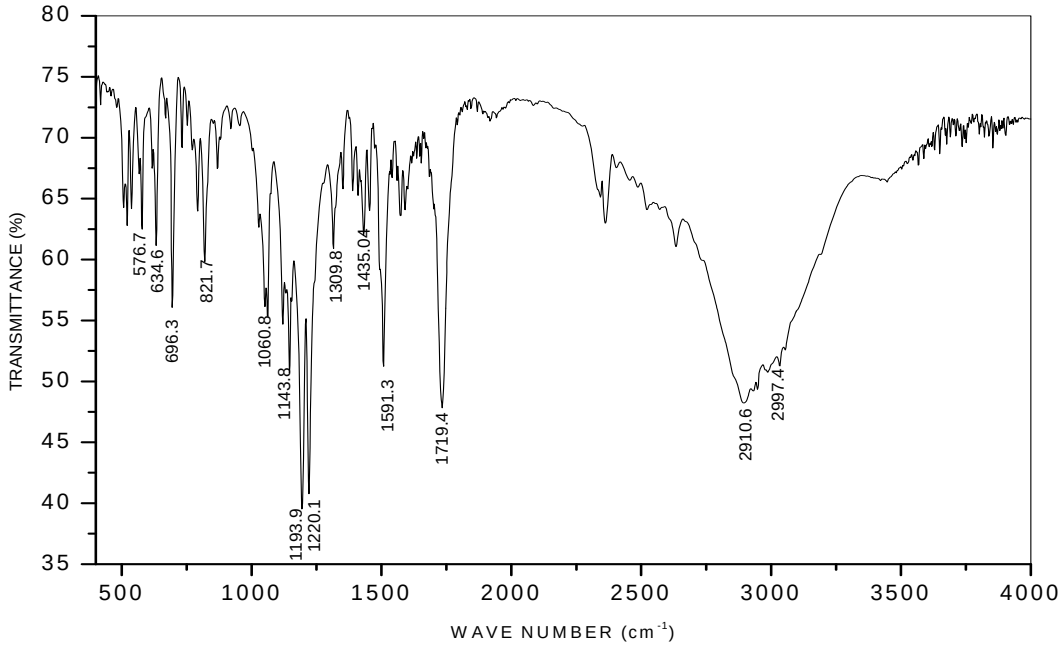


Fig. 5.62: IR Spectrum of 2f

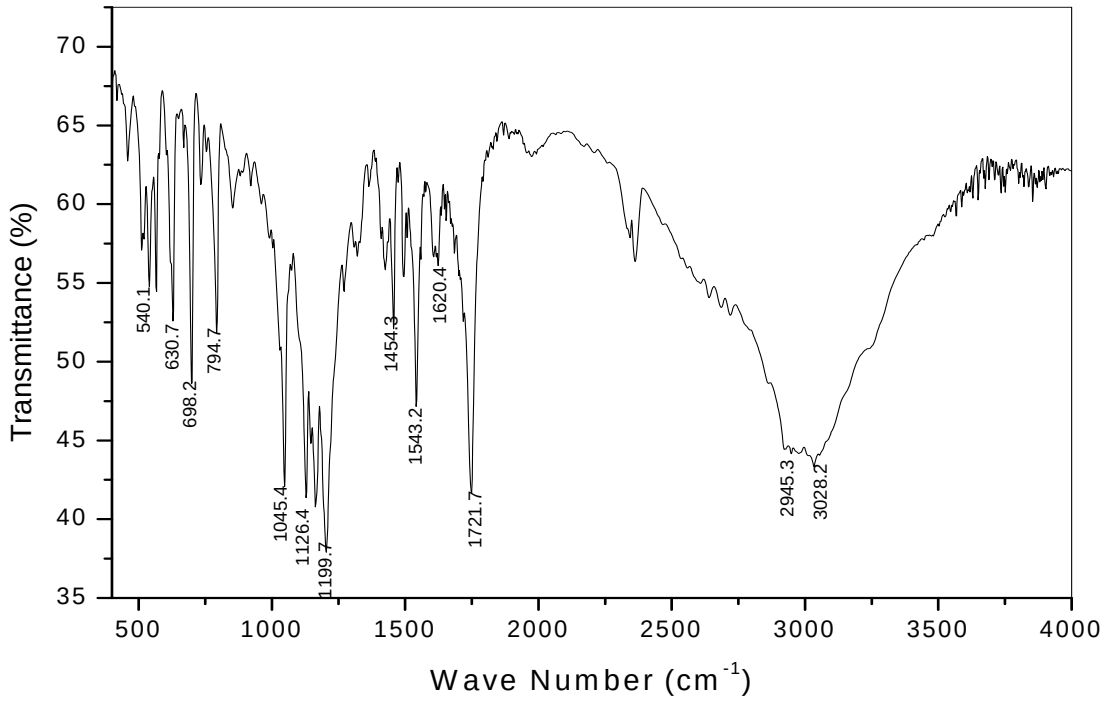


Fig. 5.63: IR Spectrum of 2g

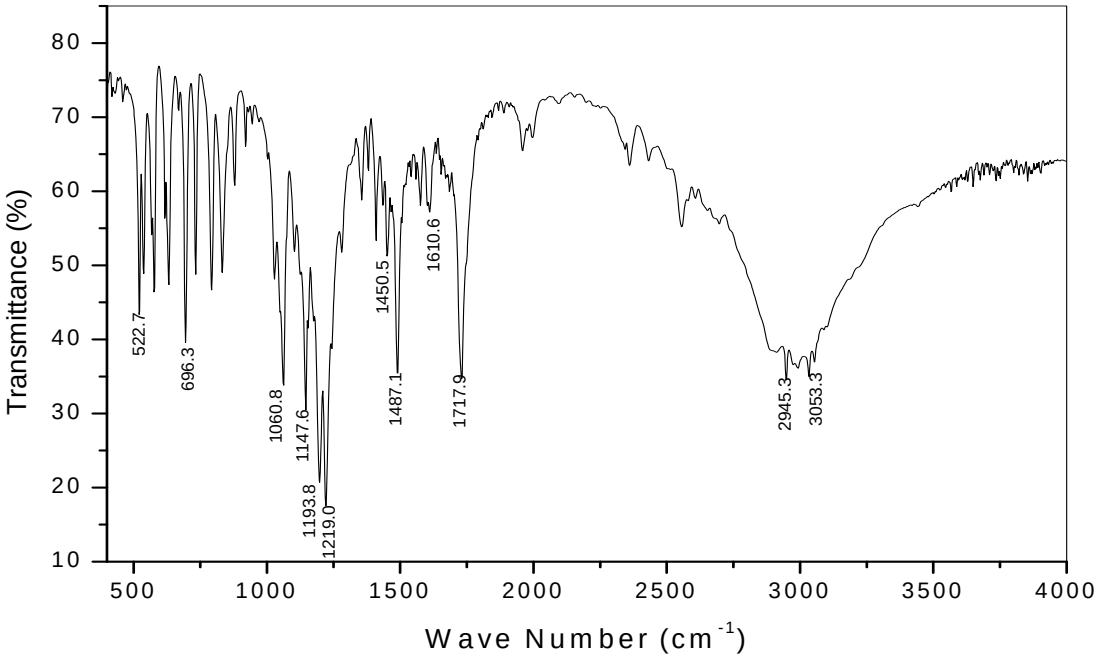


Fig. 5.64: IR Spectrum of 2h

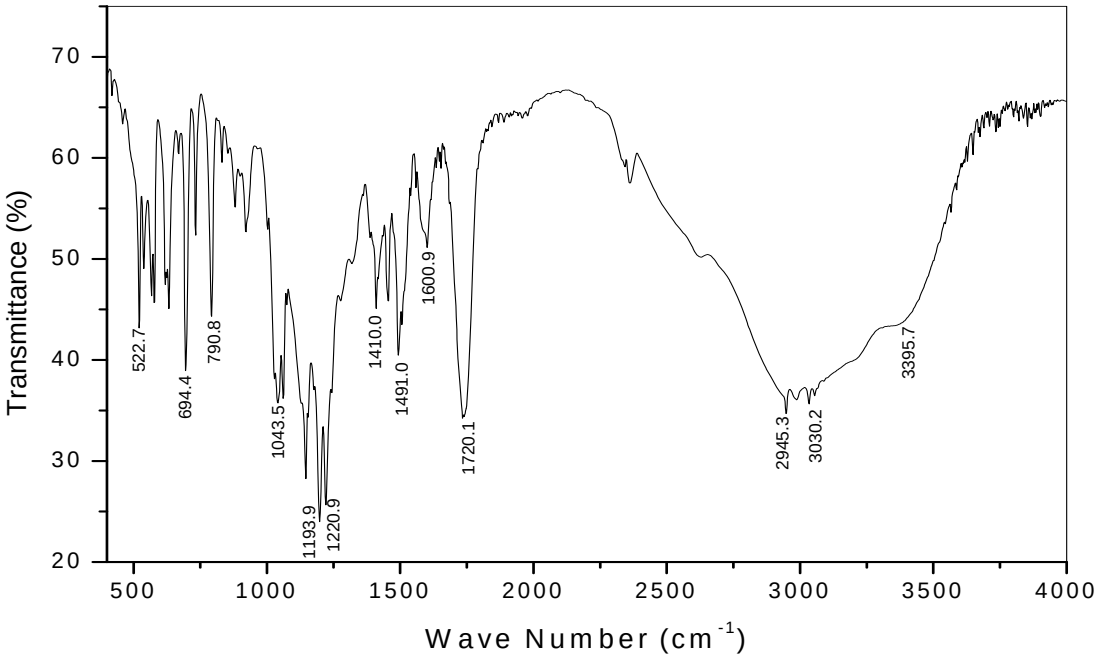


Fig. 5.65: IR Spectrum of 2i

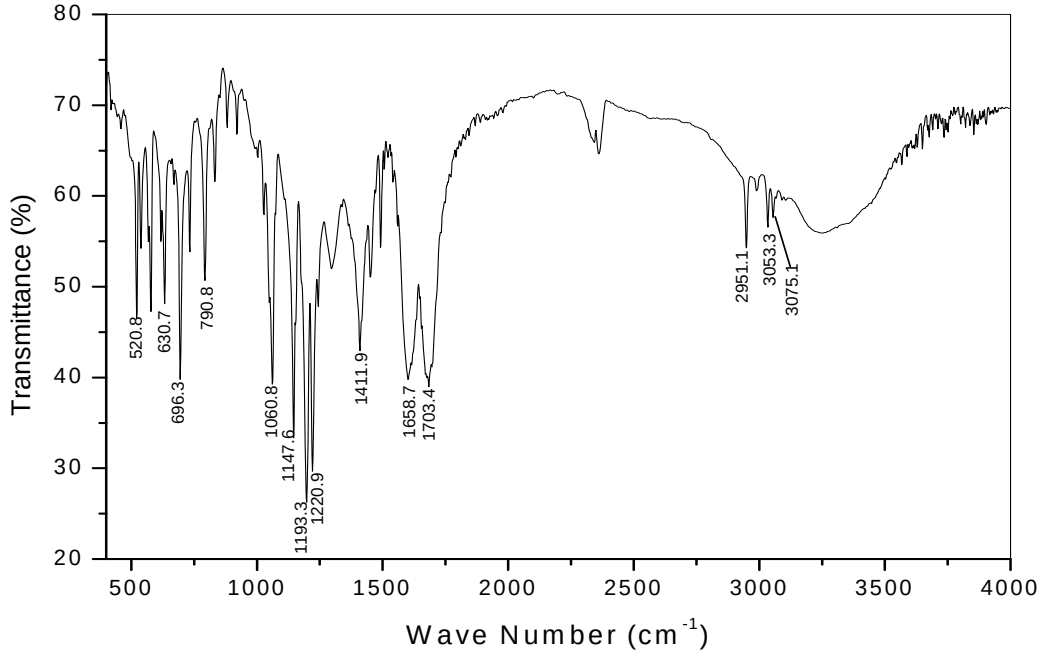


Fig. 5.66: IR Spectrum of 2j

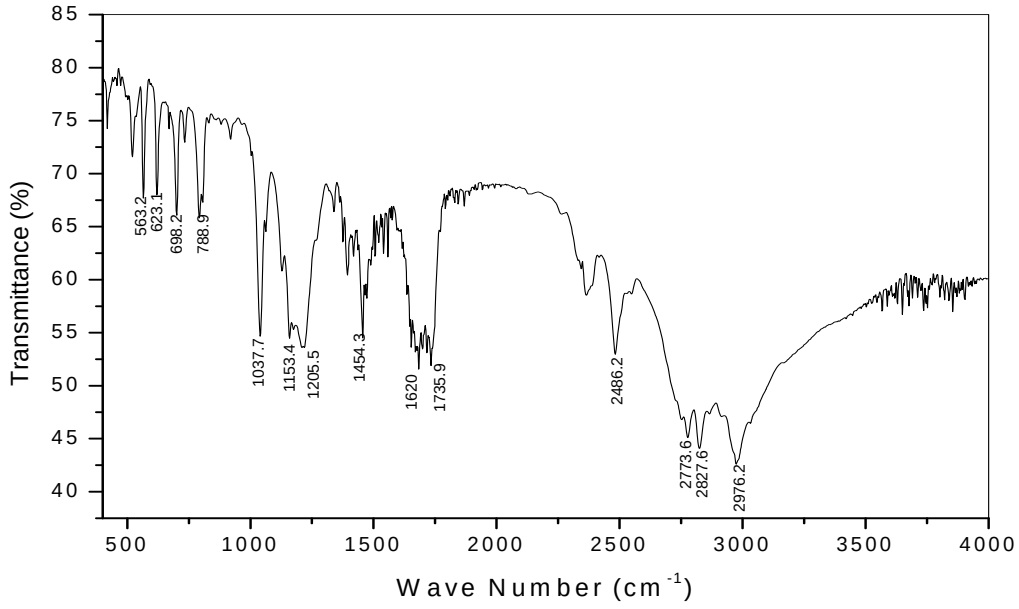
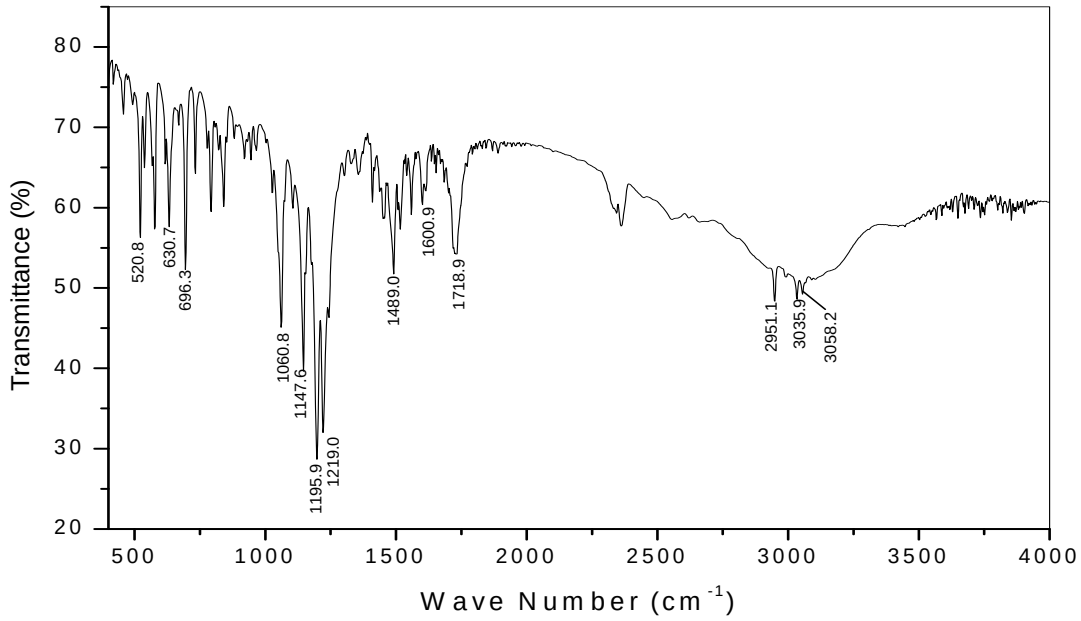


Fig. 5.67: IR Spectrum of 2k



Mass Spectral Data of α-Tolylsulphonamide Derivatives

Fig. 5.68: Mass Spectrum of 1a

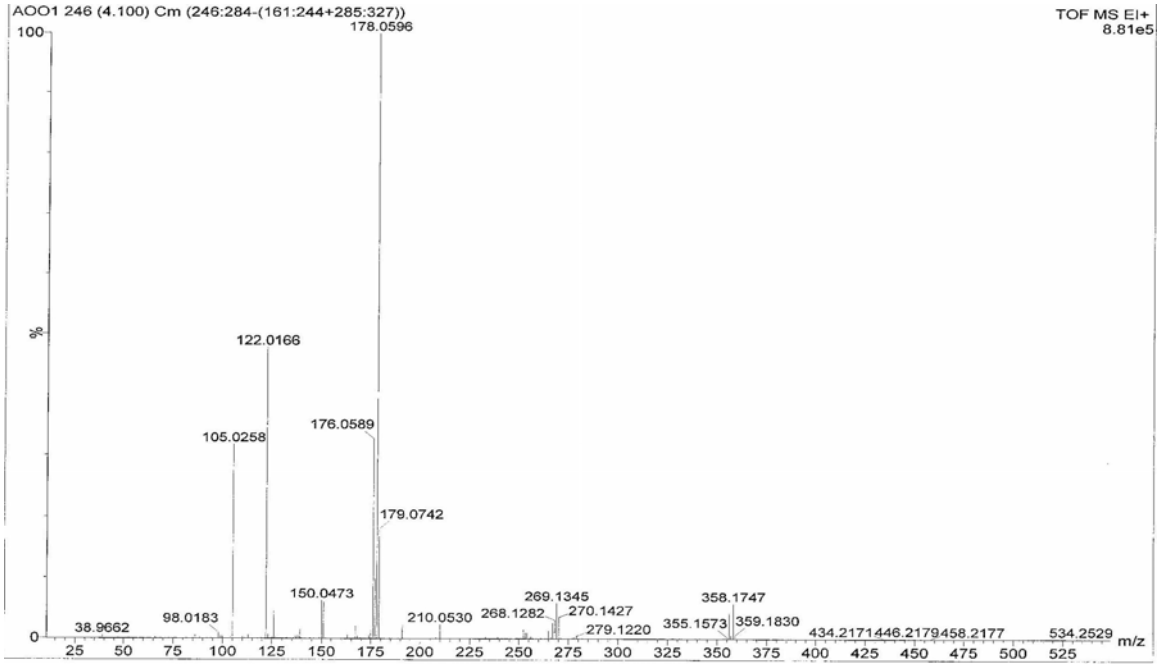


Fig. 5.69: Mass Spectrum of 1b

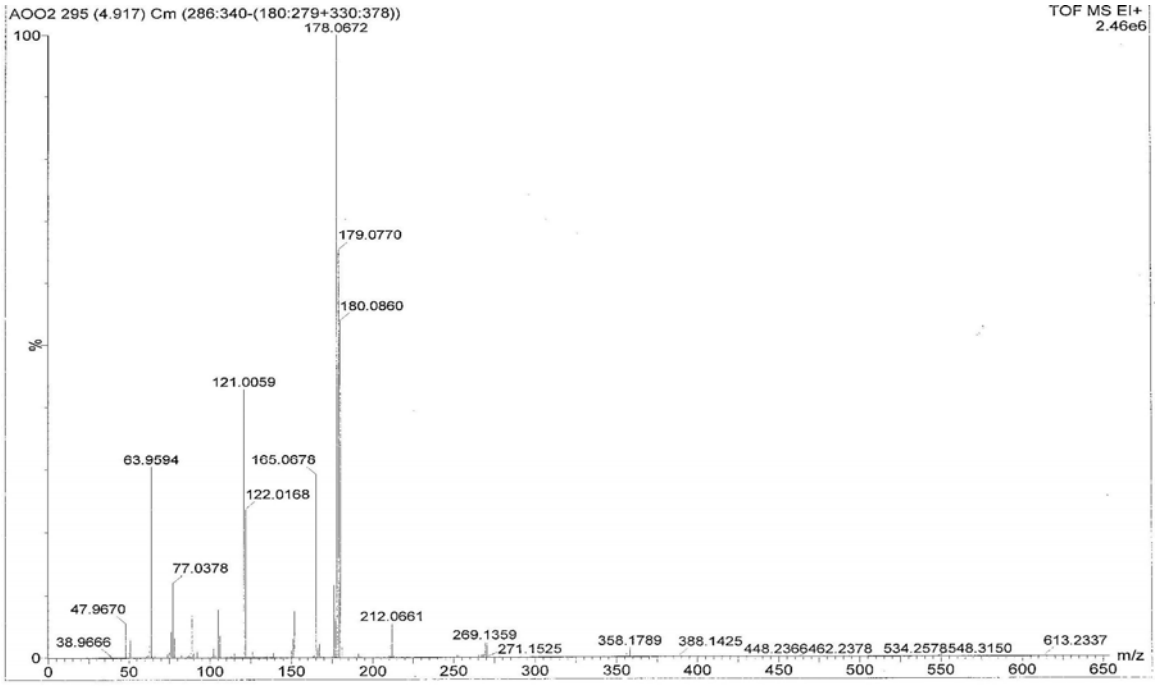


Fig. 5.70: Mass Spectrum of 1c

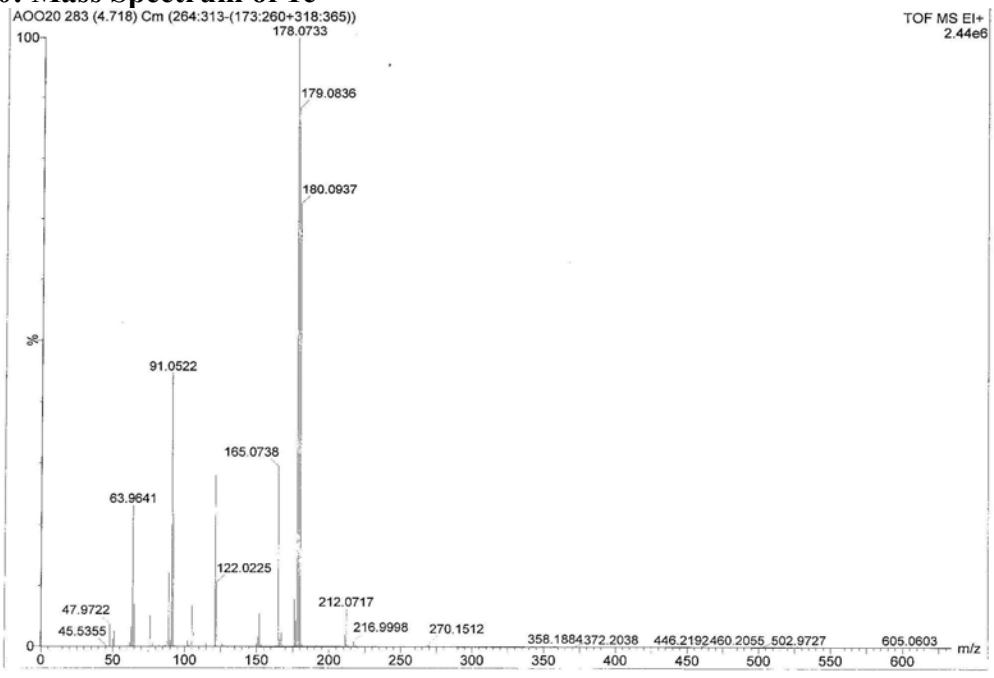


Fig. 5.71: Mass Spectrum of 1e

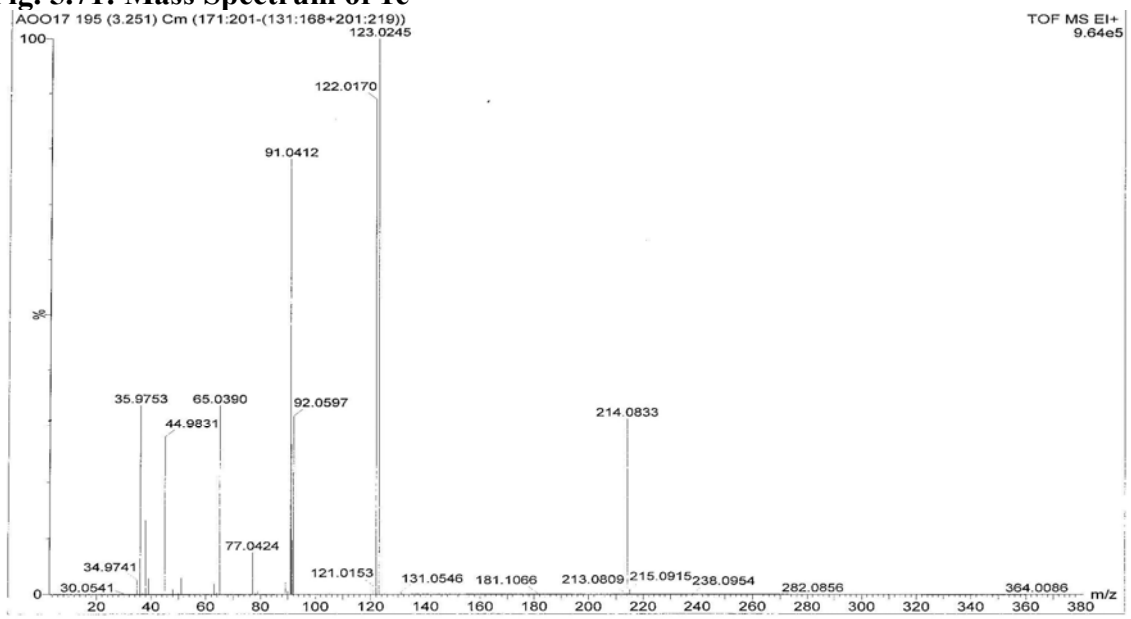


Fig. 5.72: Mass Spectrum of 1g

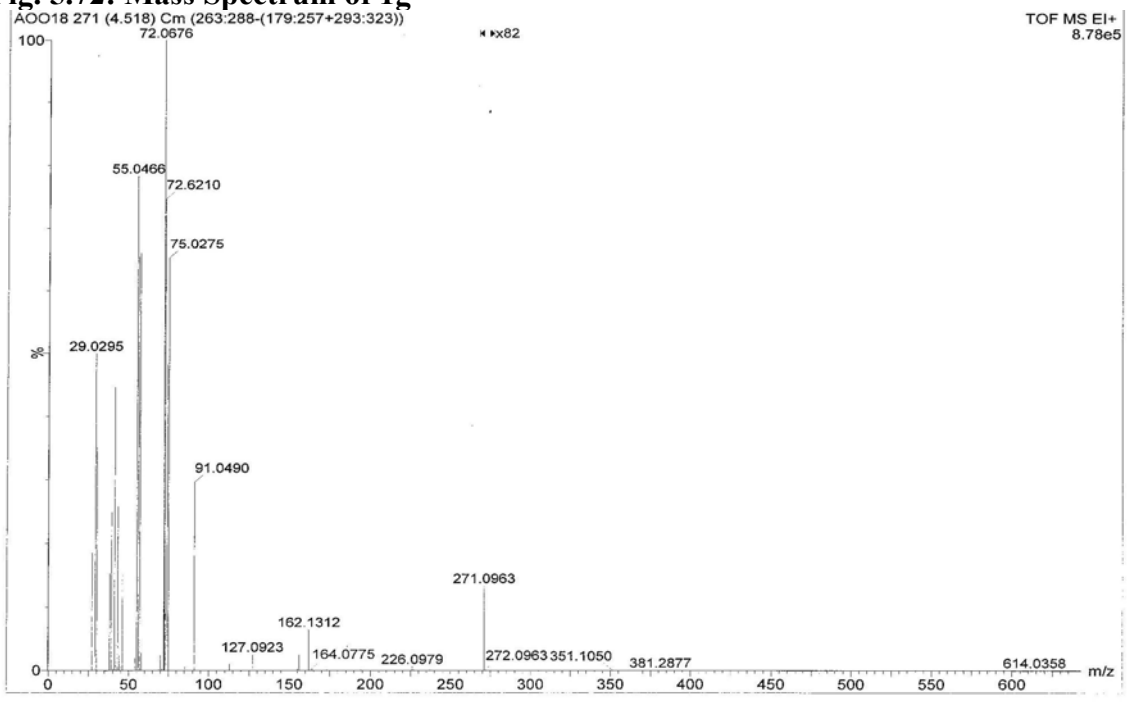


Fig. 5.73: Mass Spectrum of 1j

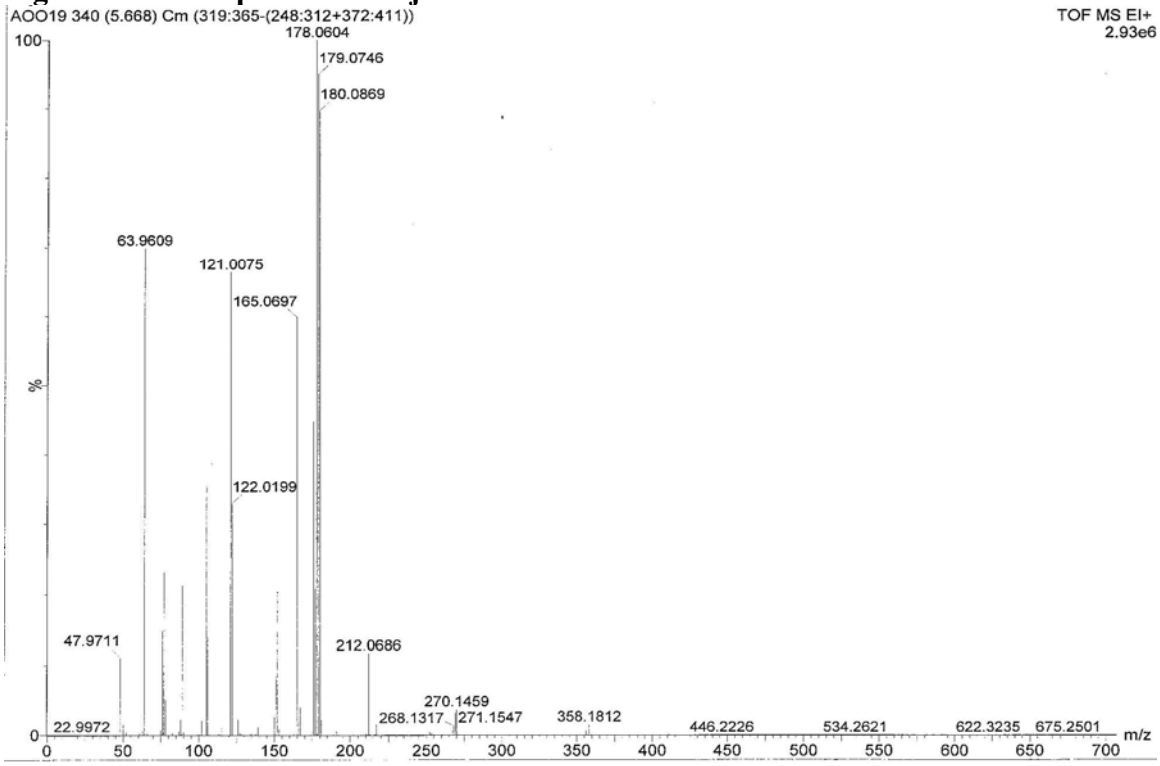
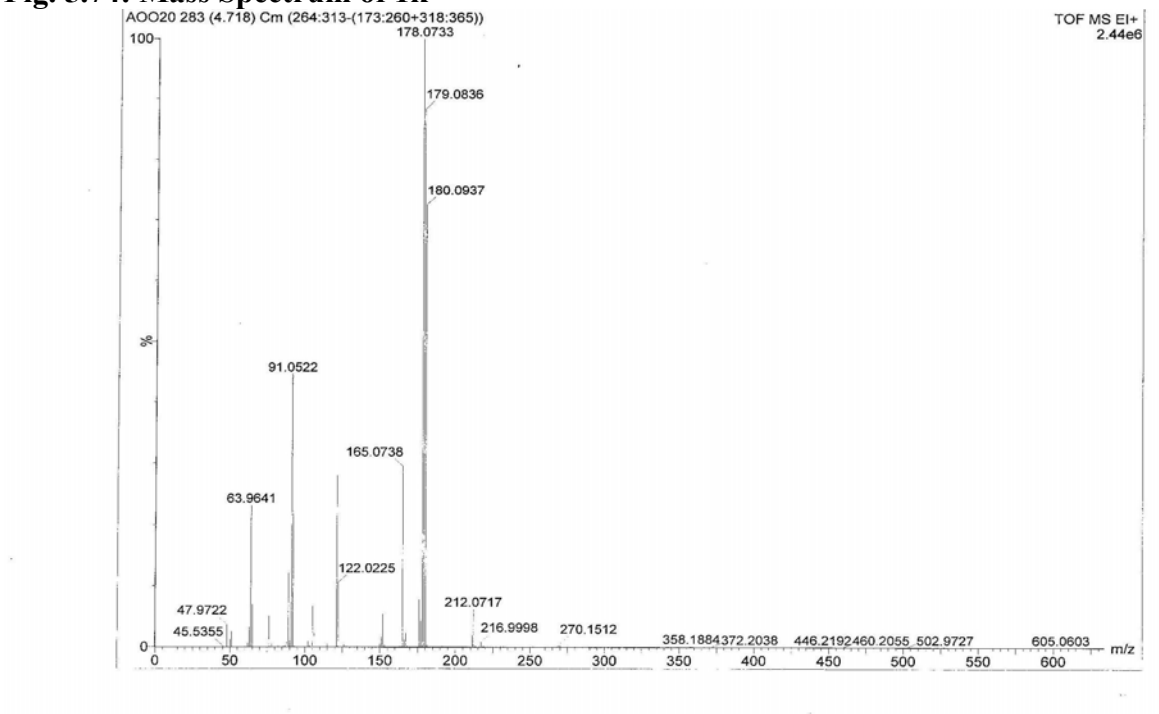


Fig. 5.74: Mass Spectrum of 1k



^{1}H-NMR Spectral Data of *p*-Tolylsulphonamide Derivatives

Fig. 5.75: ^{1}H-NMR Spectrum of 4a

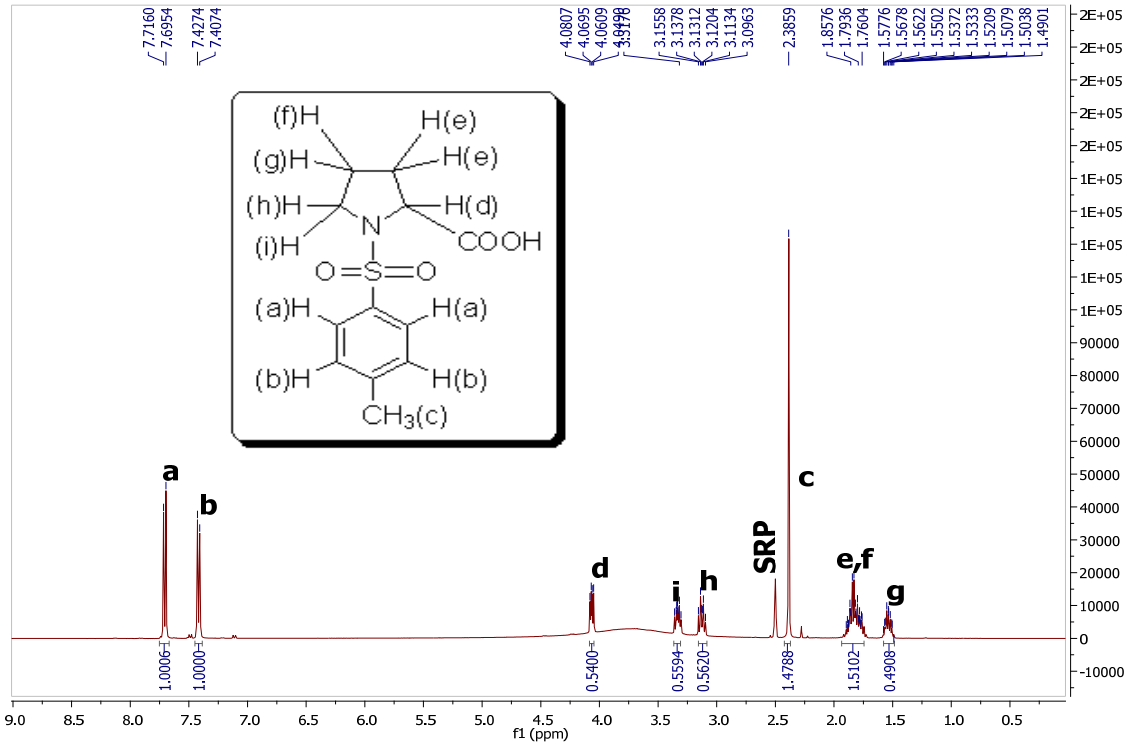


Fig. 5.76: ^{1}H-NMR Spectrum of 4b

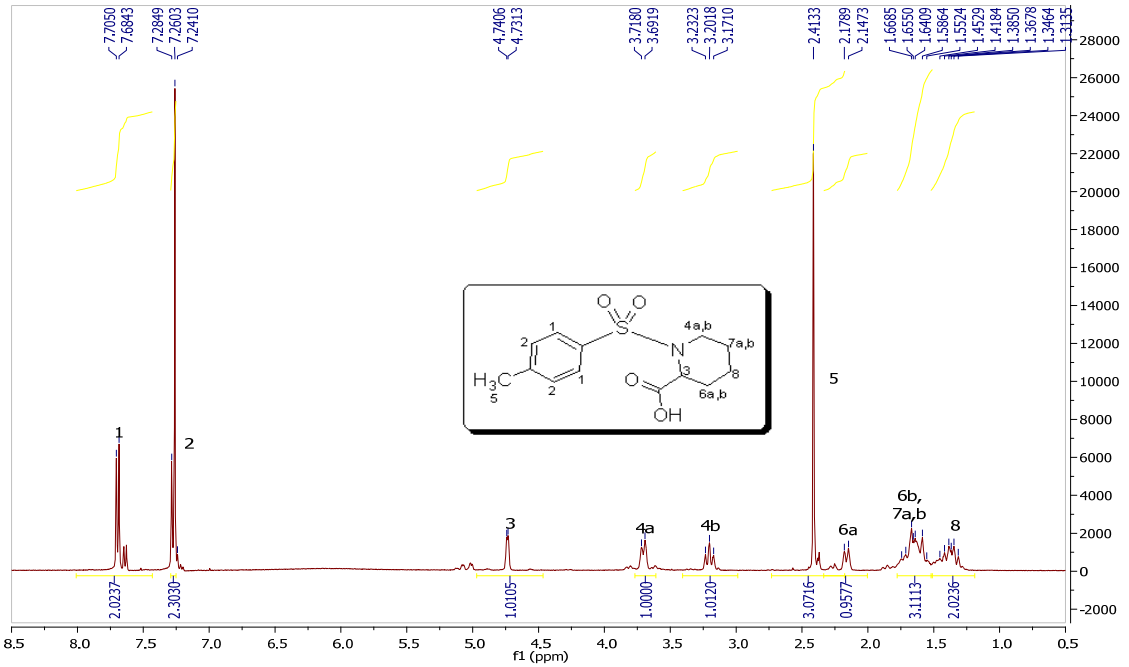


Fig. 5.77: ^{1}H-NMR Spectrum of 4c

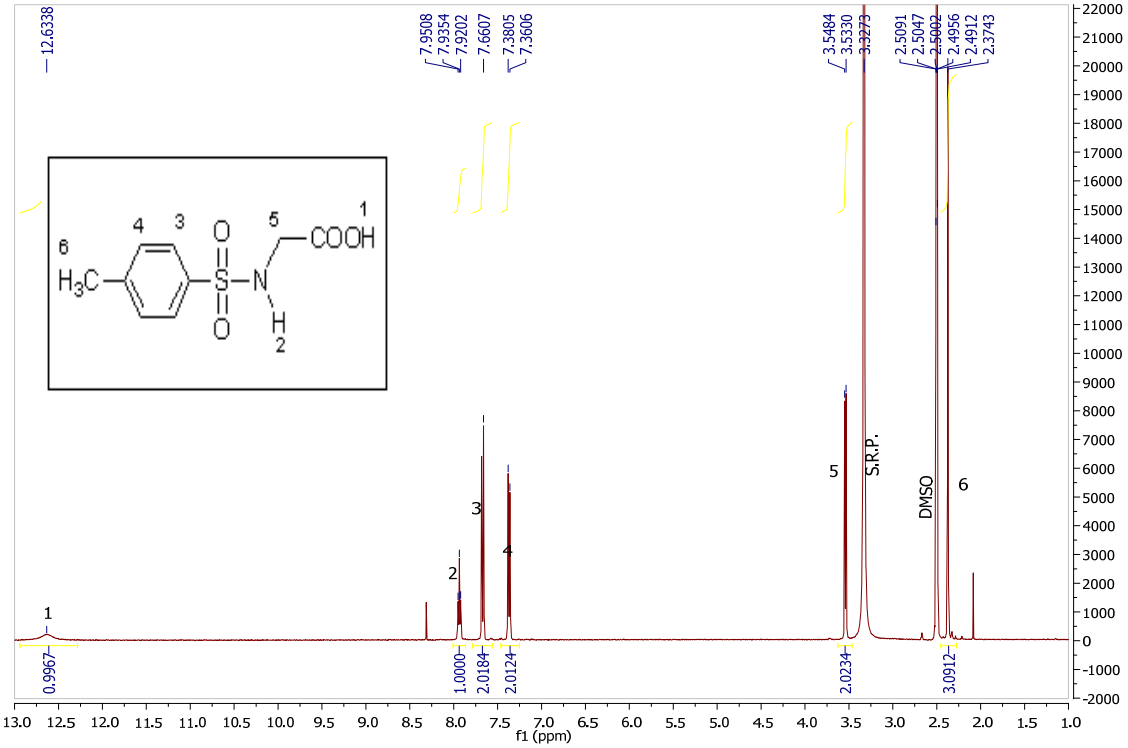


Fig. 5.78: ^{1}H-NMR Spectrum of 4d

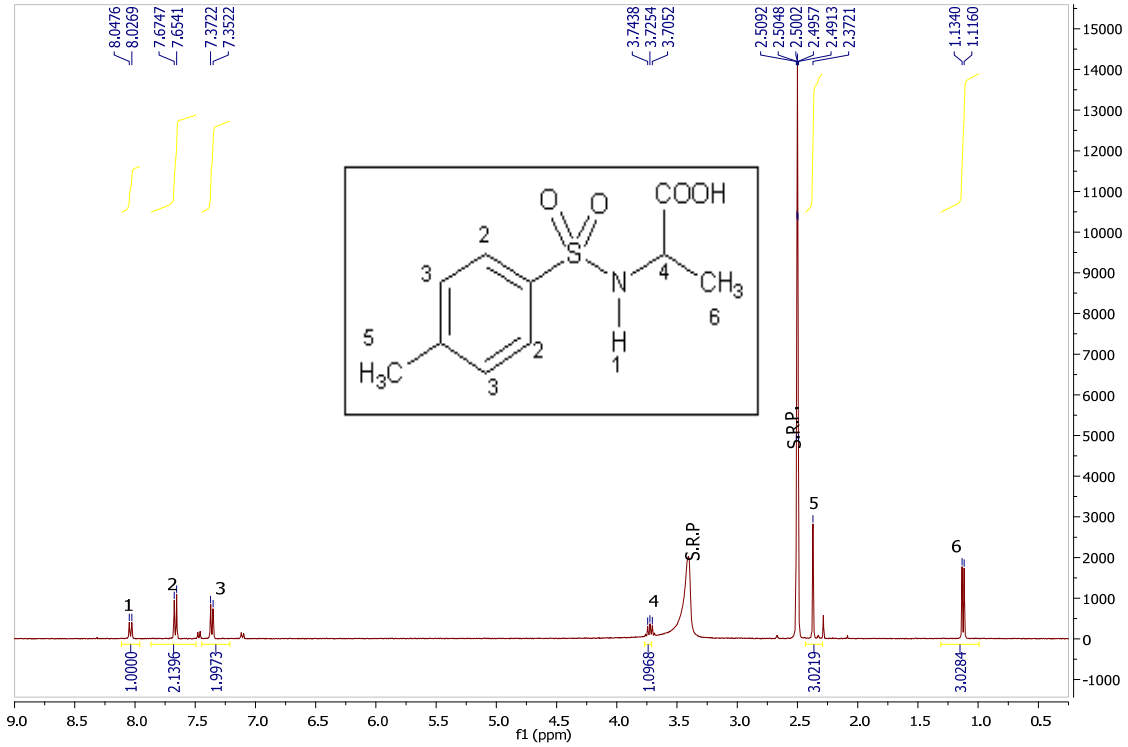


Fig. 5.79: ^{1}H-NMR Spectrum of 4f

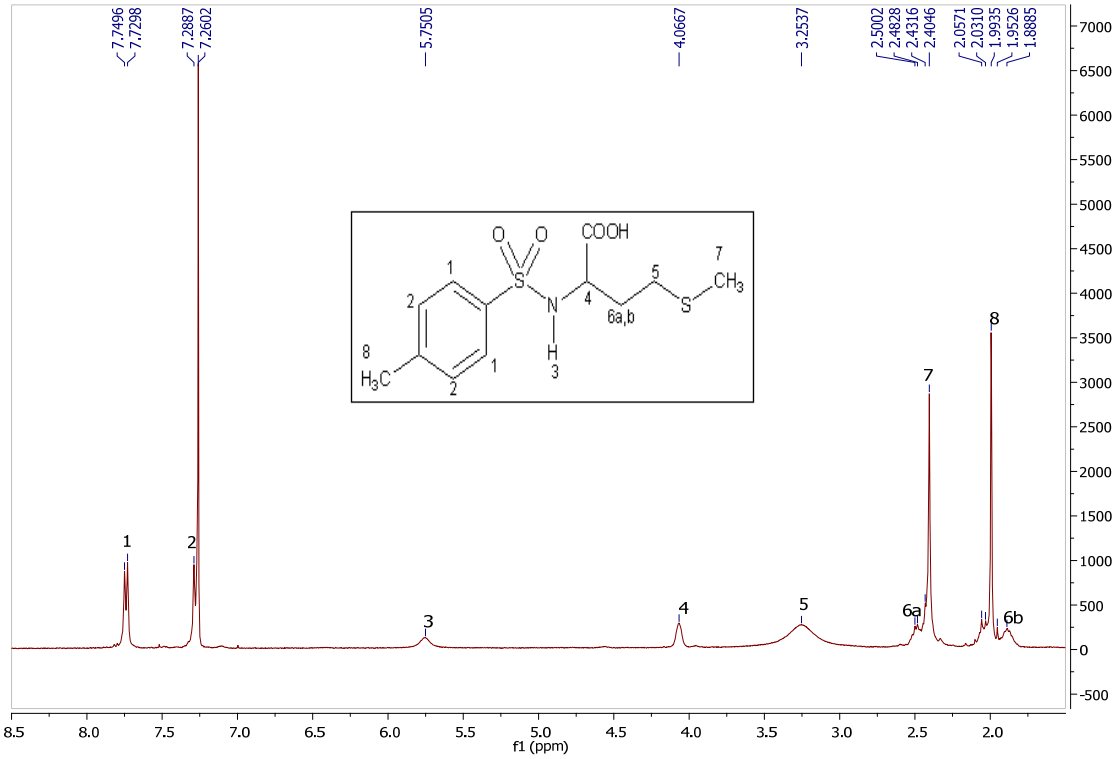


Fig. 5.80: ^{1}H-NMR Spectrum of 4g

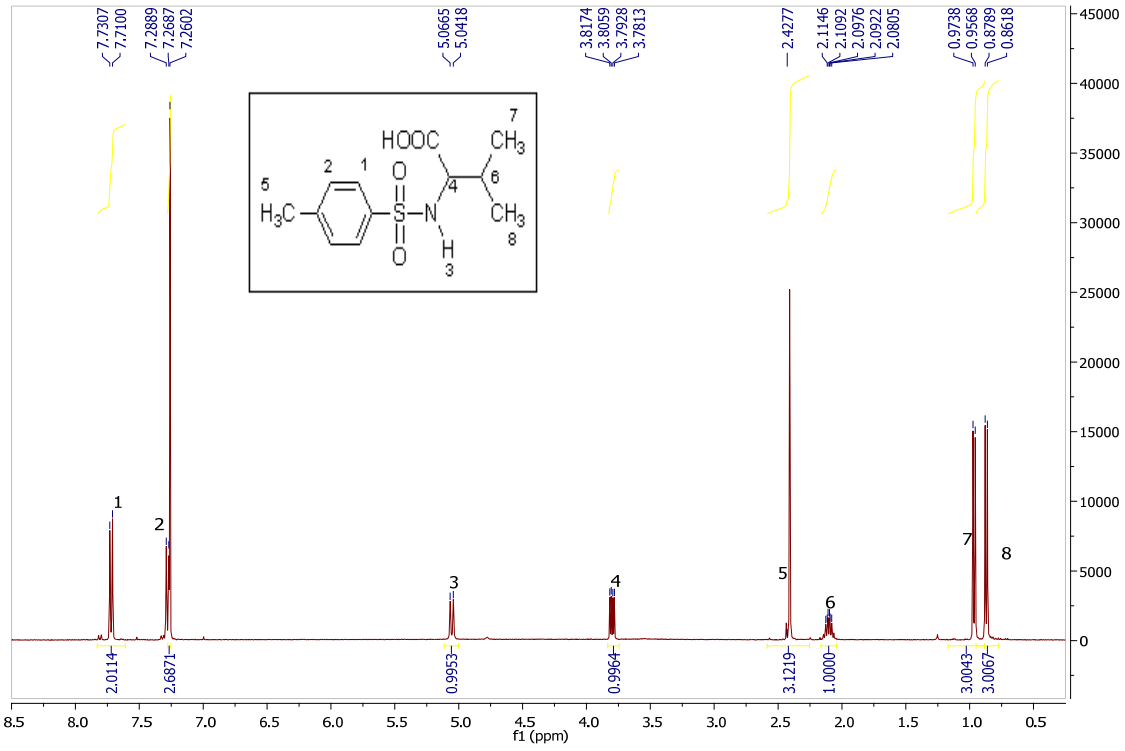


Fig. 5.81: ^{1}H-NMR Spectrum of 4h

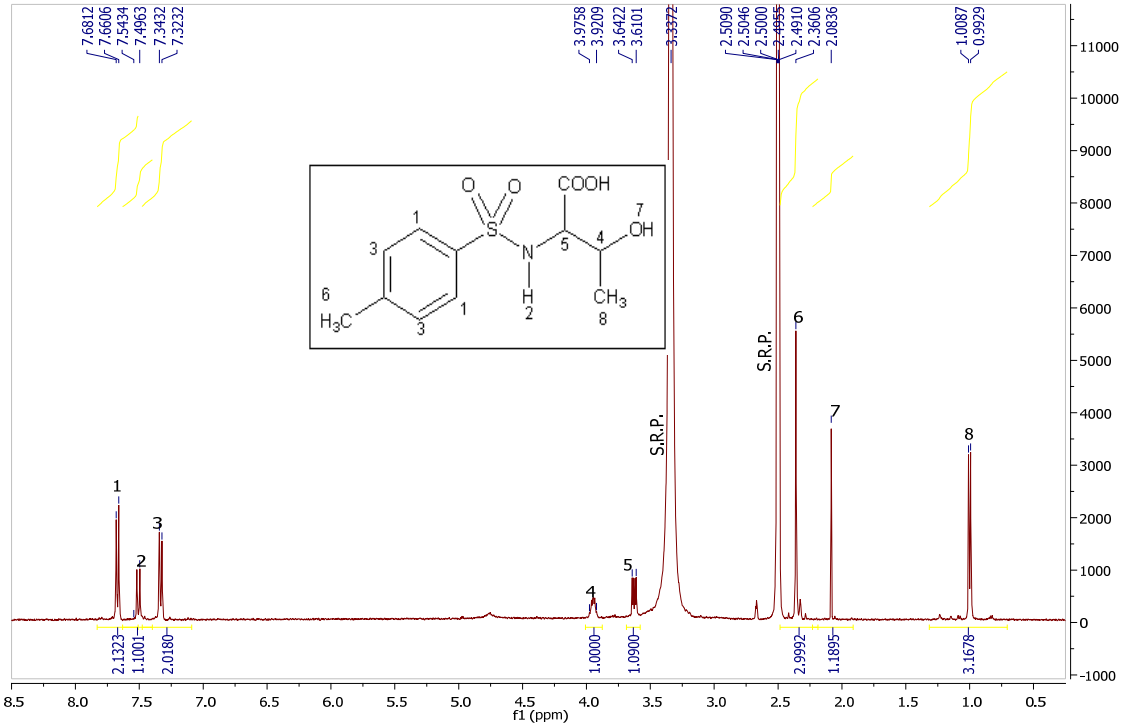


Fig. 5.82: ^{1}H-NMR Spectrum of 4i

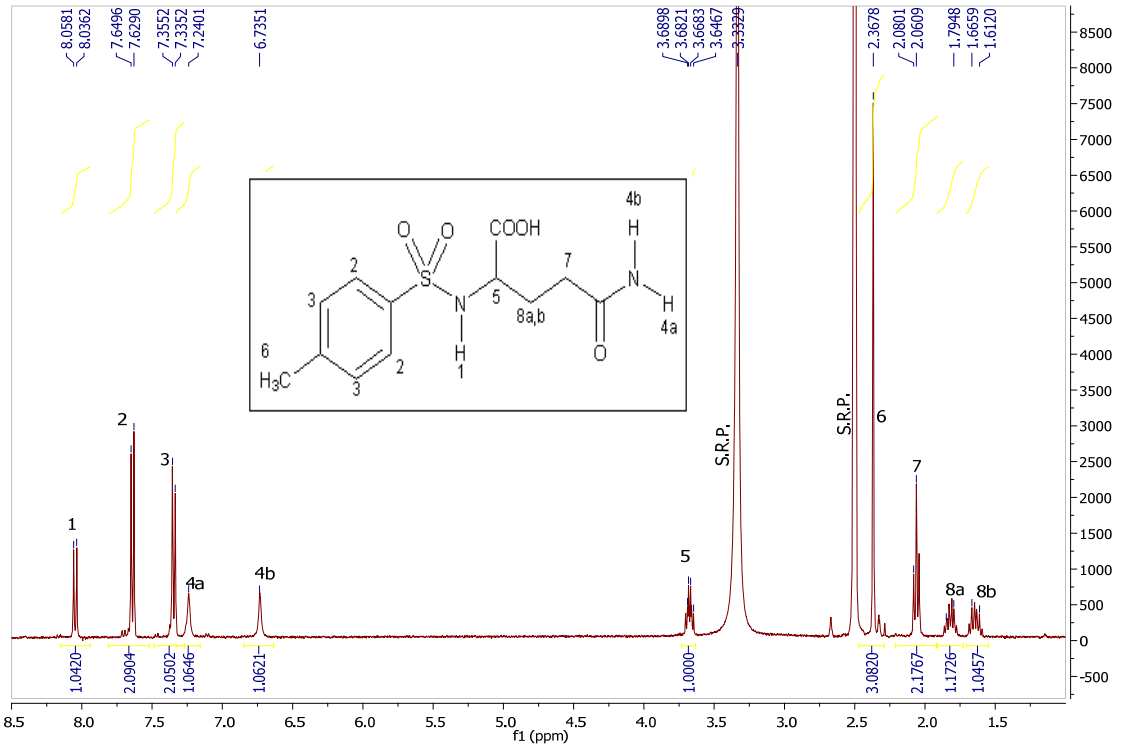


Fig. 5.83: ^{1}H-NMR Spectrum of 4j

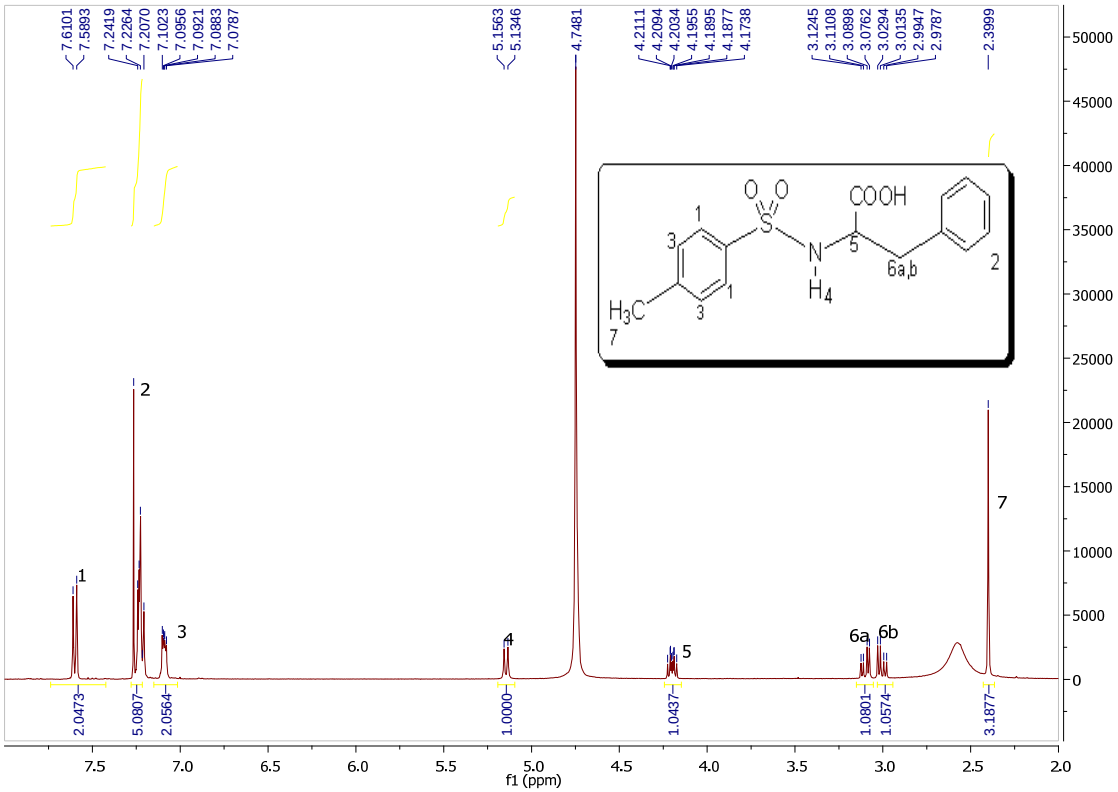


Fig. 5.84: ^{1}H-NMR Spectrum of 4k

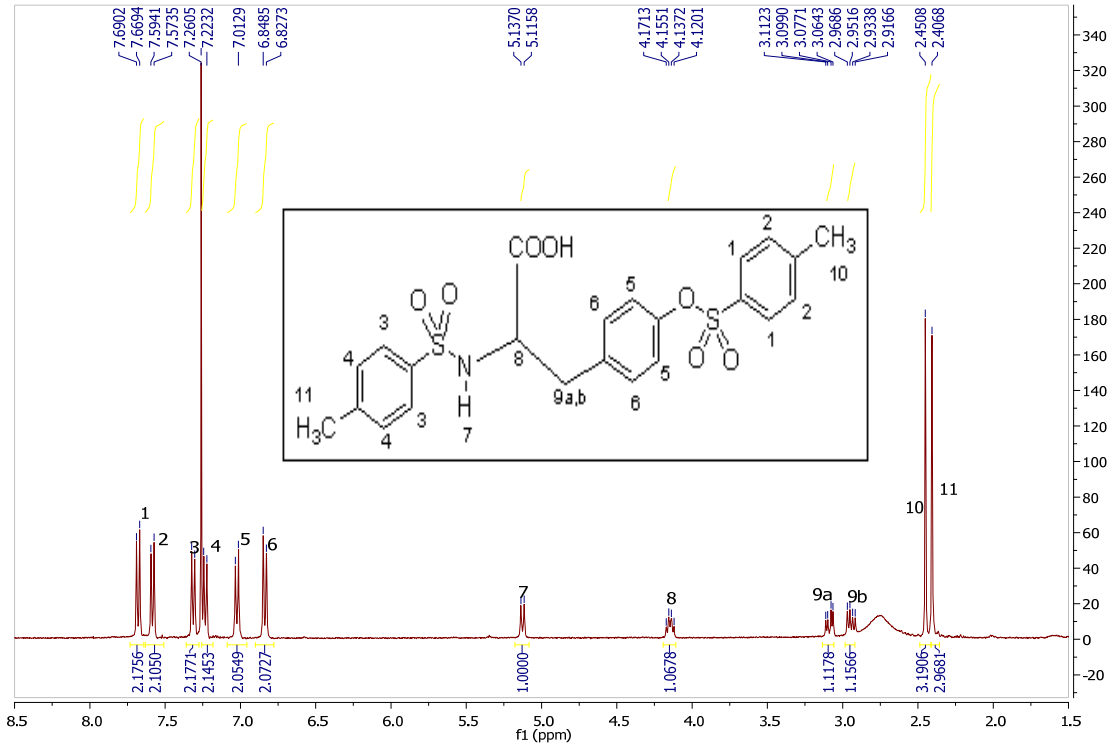


Fig. 5.85: ^{1}H-NMR Spectrum of 5a

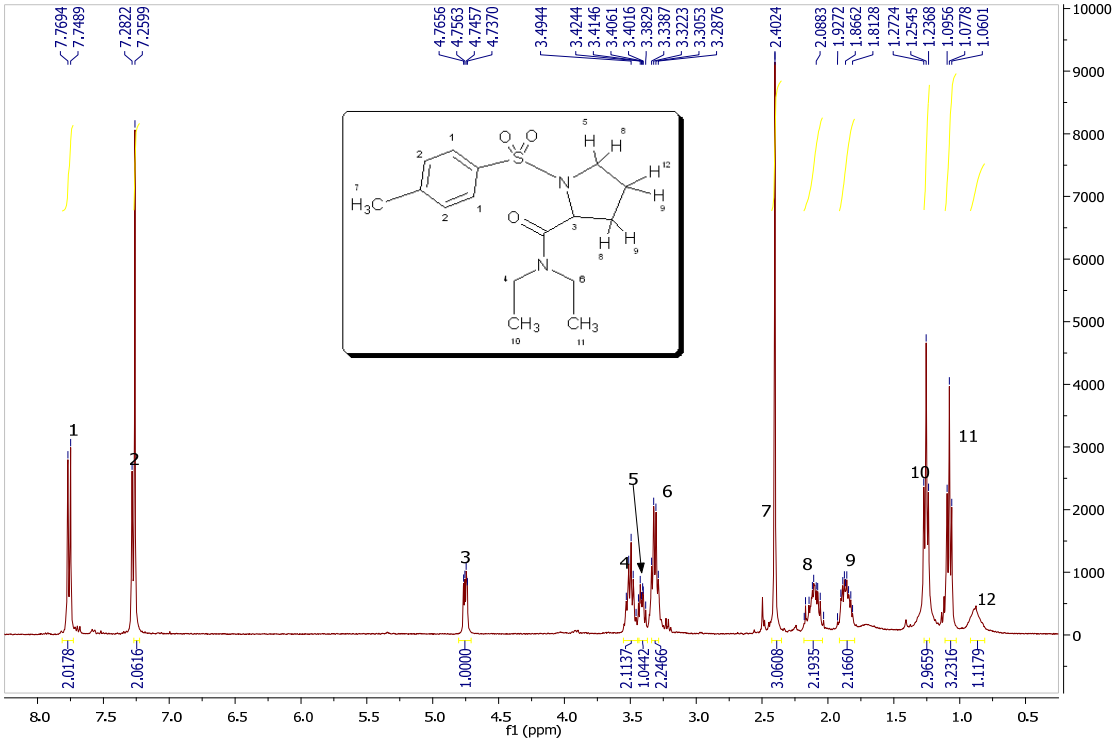


Fig. 5.86: ^{1}H-NMR Spectrum of 5b

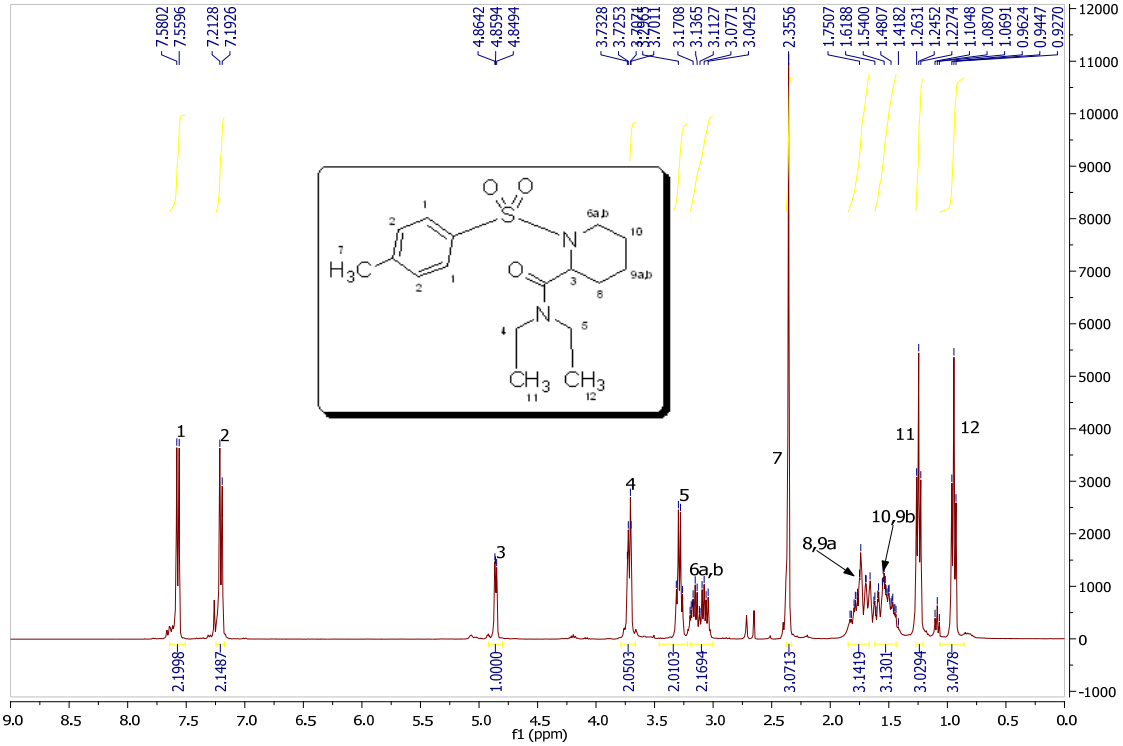


Fig. 5.87: ^{1}H-NMR Spectrum of 5c

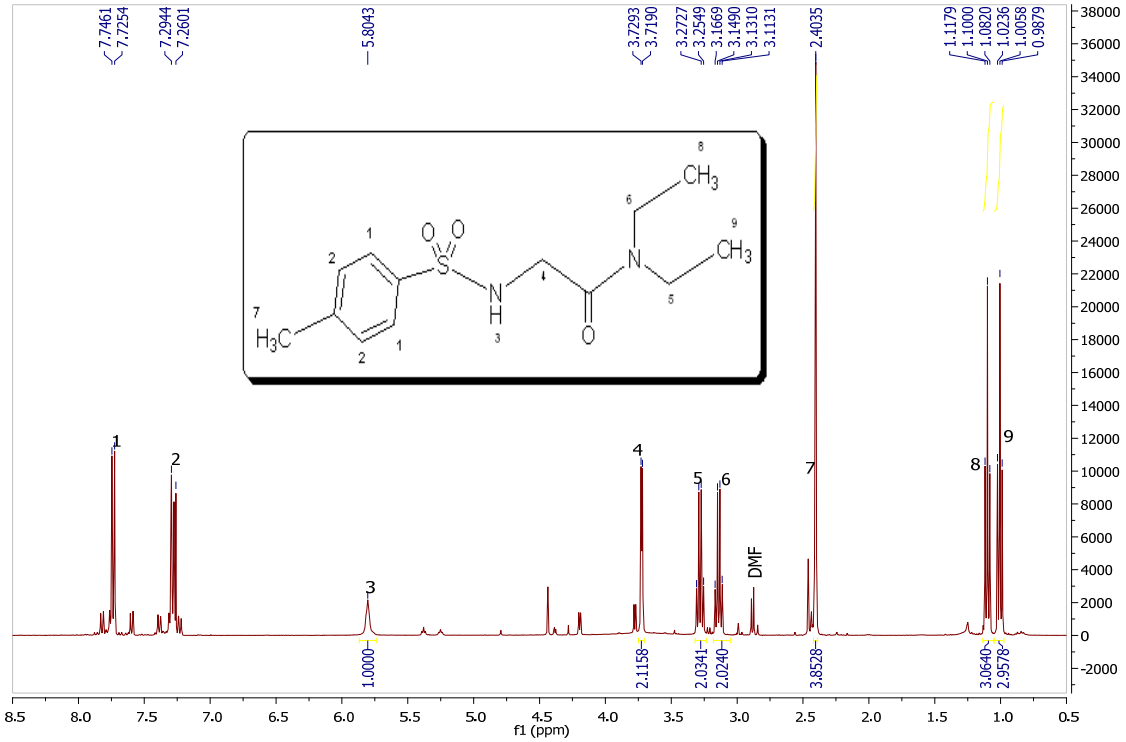


Fig. 5.88: ^{1}H-NMR Spectrum of 5d

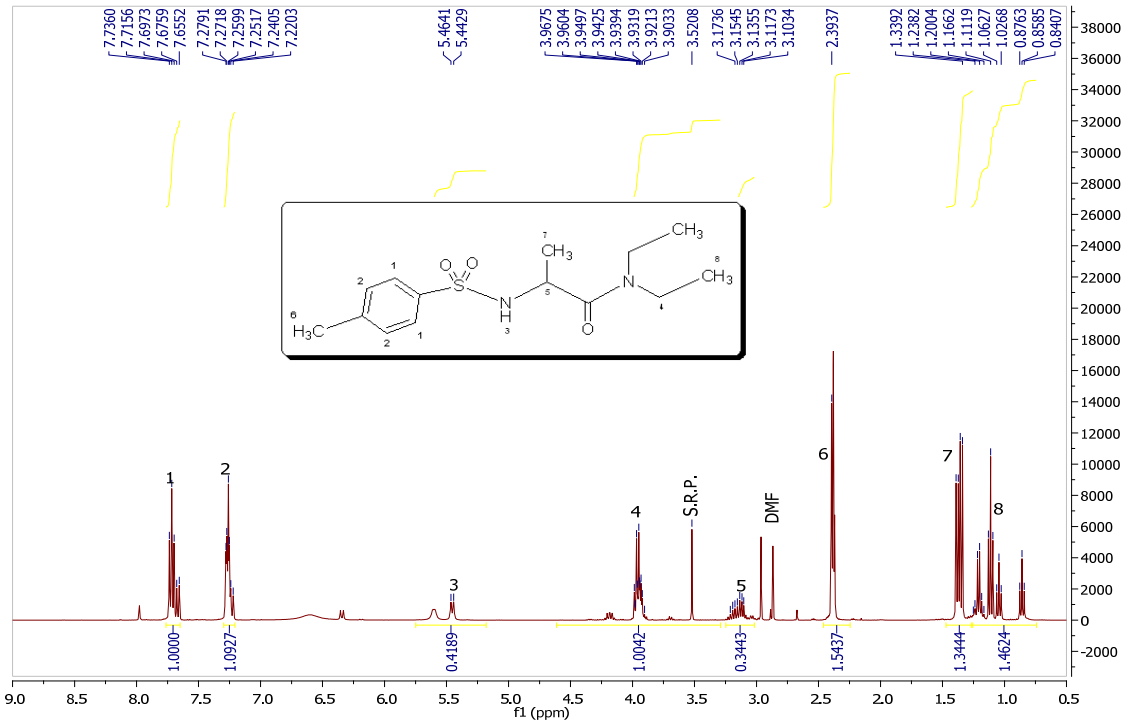


Fig. 5.89: ^{1}H-NMR Spectrum of 5g

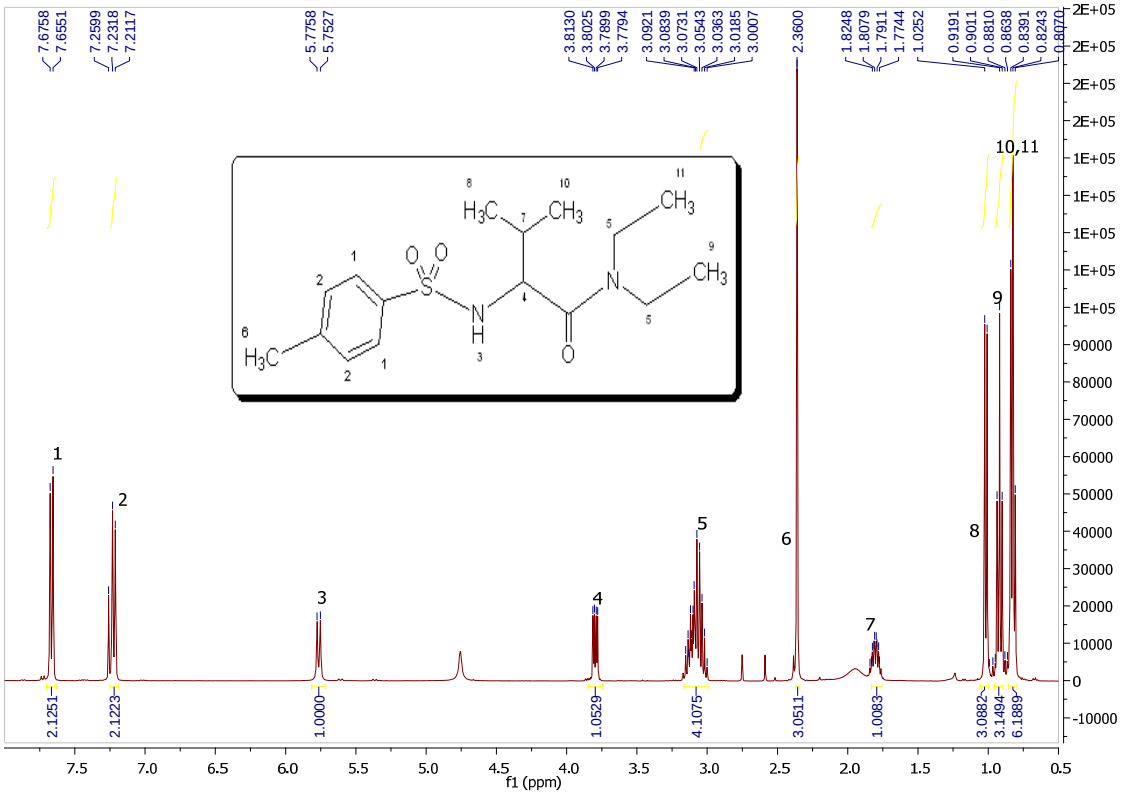


Fig. 5.90: ^{1}H-NMR Spectrum of 5j

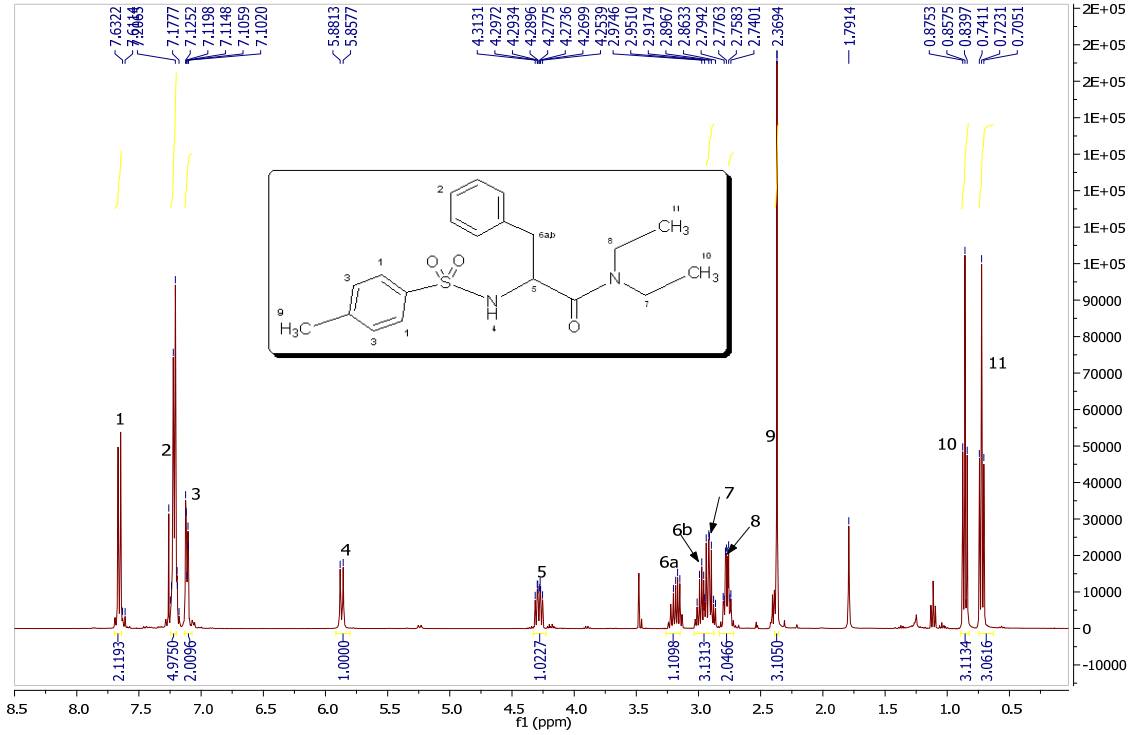


Fig. 5.91: ^{13}C-NMR Spectrum of 4b

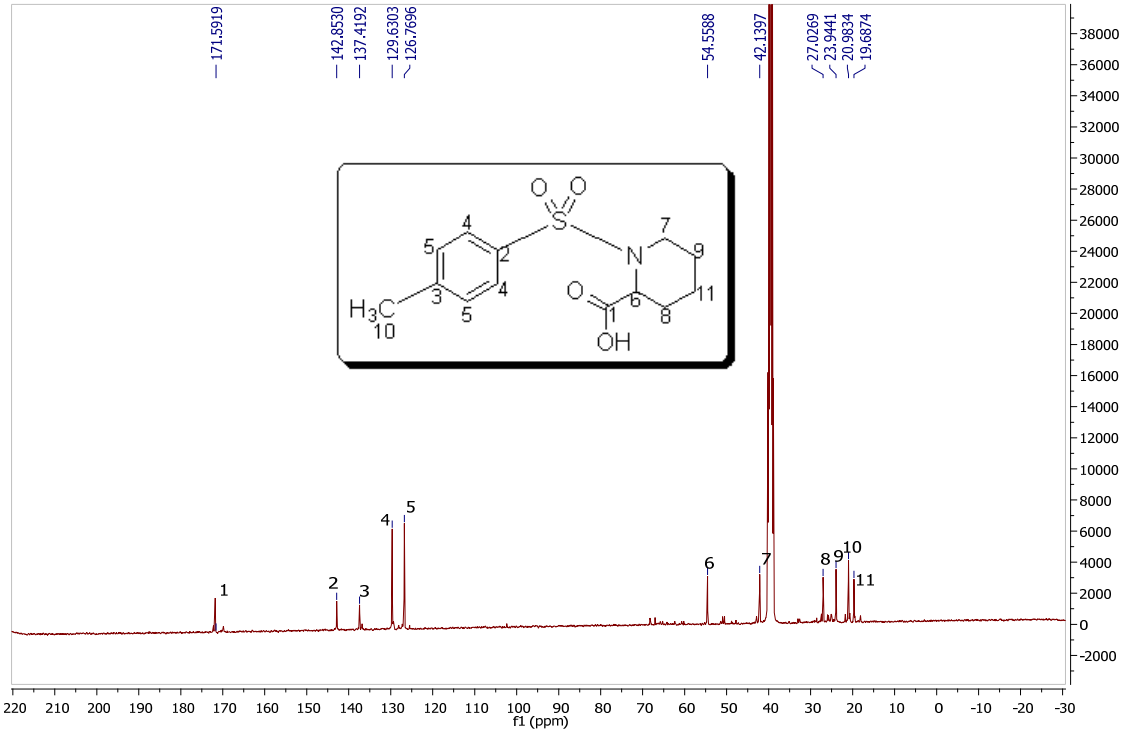


Fig. 5.92: ^{13}C-NMR Spectrum of 4j

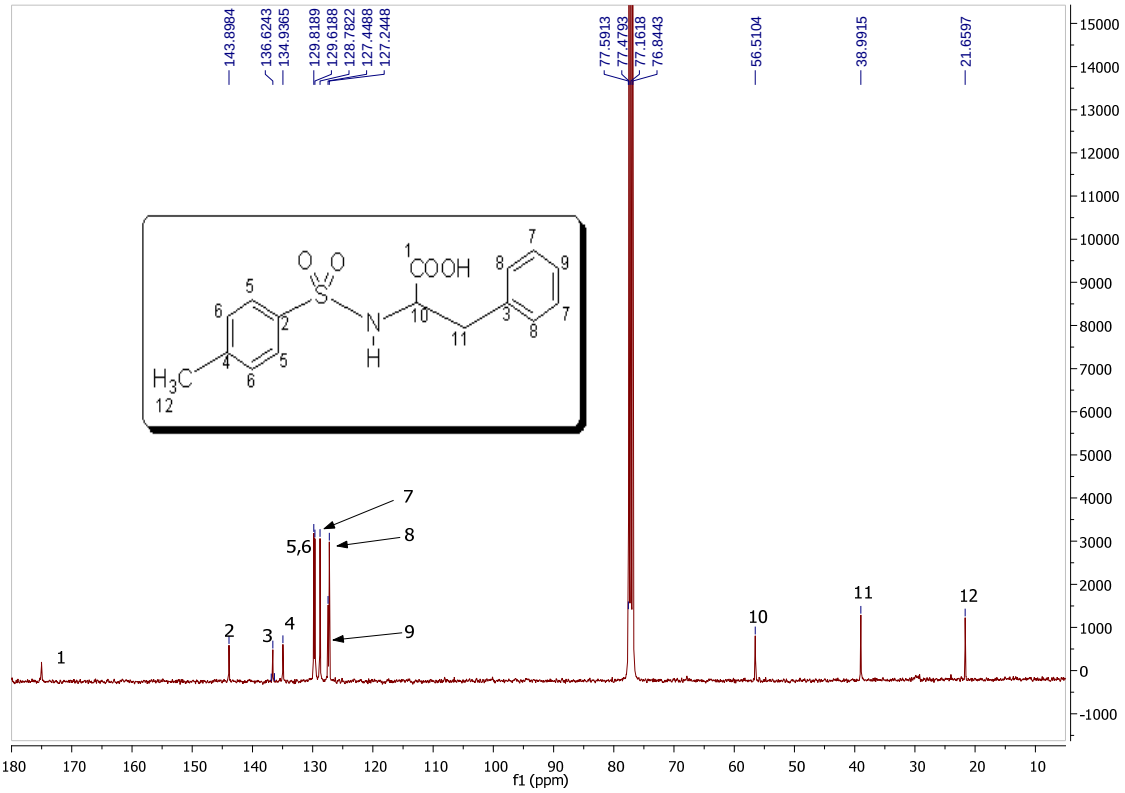
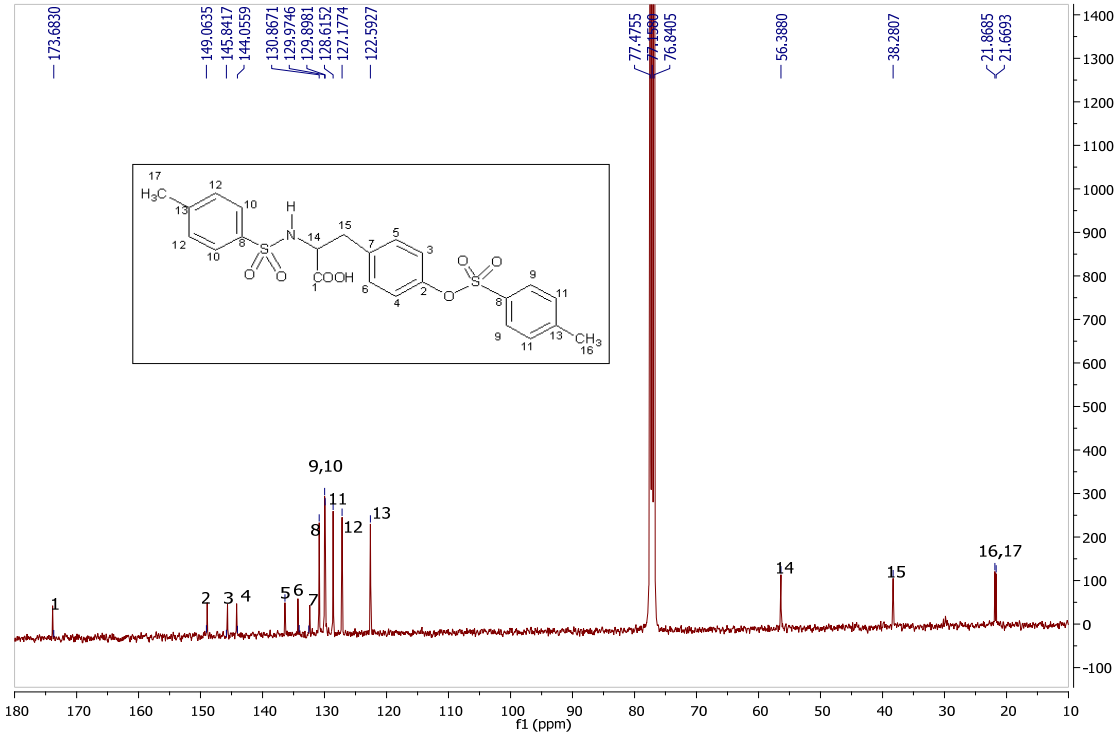


Fig. 5.93: ^{13}C-NMR Spectrum of 4k



Infrared Spectral Data of *p*-Tolylsulphonamide Derivatives

Fig. 5.94: IR Spectrum of 4a

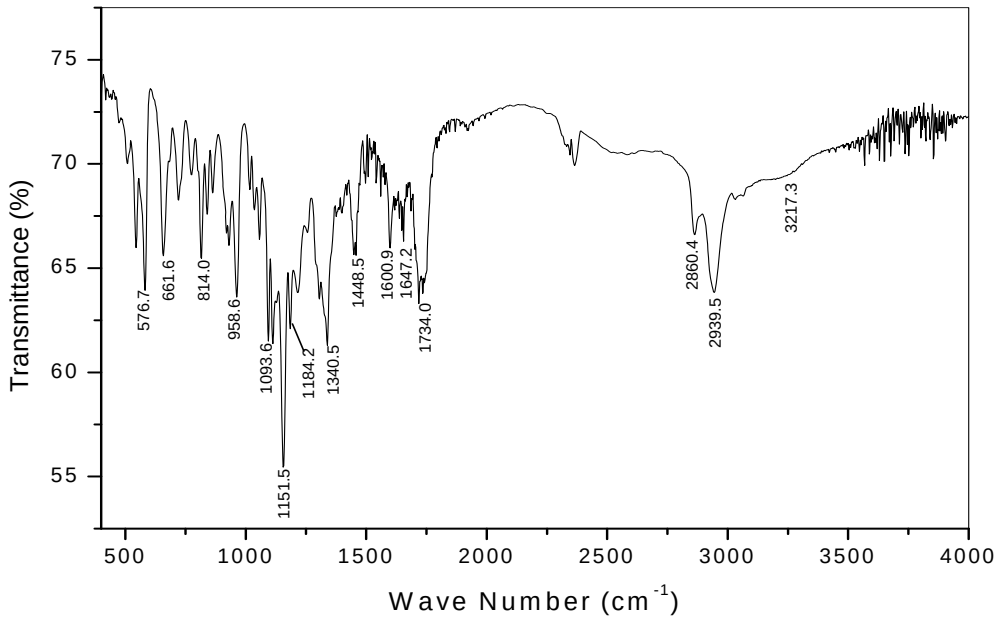


Fig. 5.95: IR Spectrum of 4c

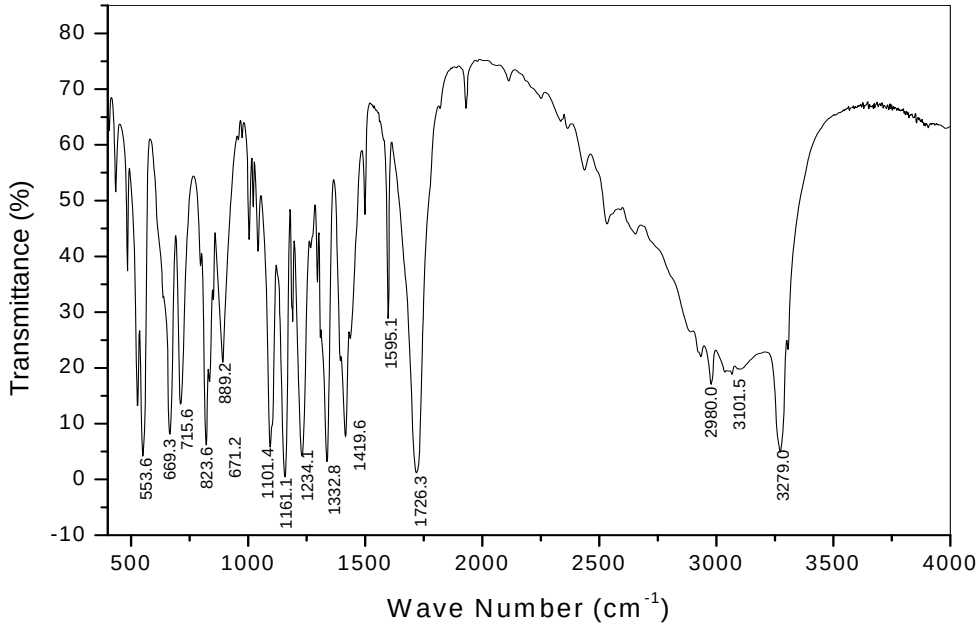


Fig. 5.96: IR Spectrum of 4d

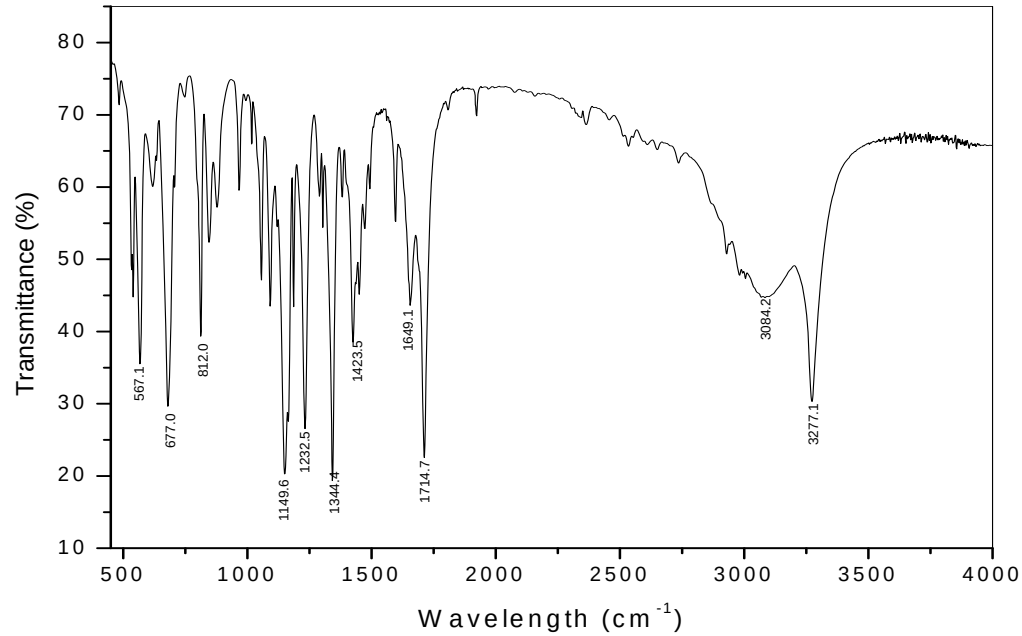


Fig. 5.97: IR Spectrum of 4e

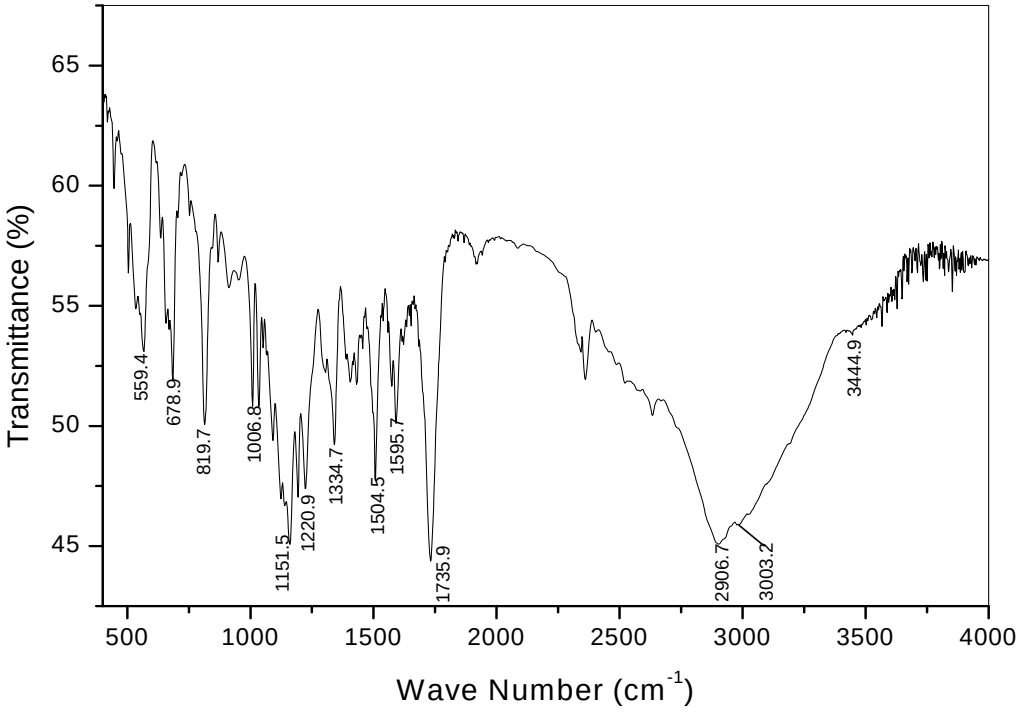


Fig. 5.98: IR Spectrum of 4f

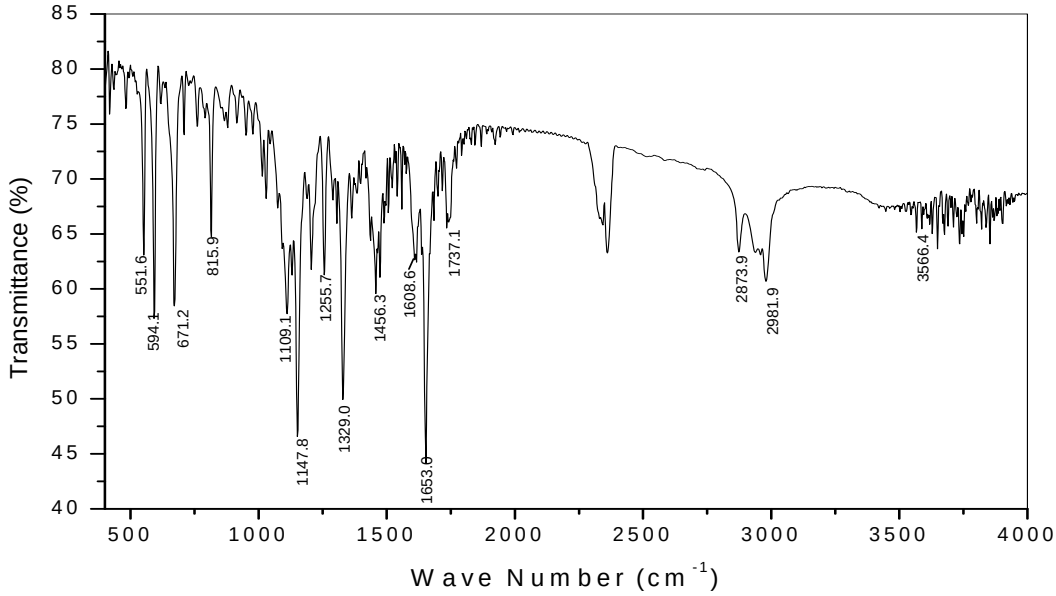


Fig. 5.99: IR Spectrum of 4g

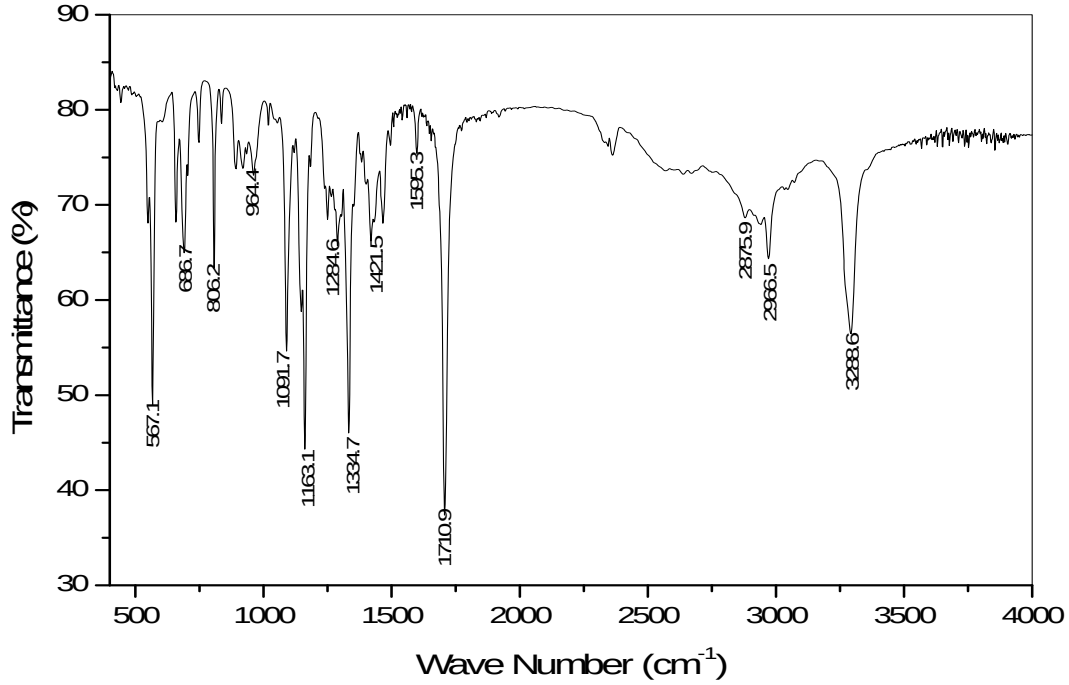


Fig. 5.100: IR Spectrum of 4h

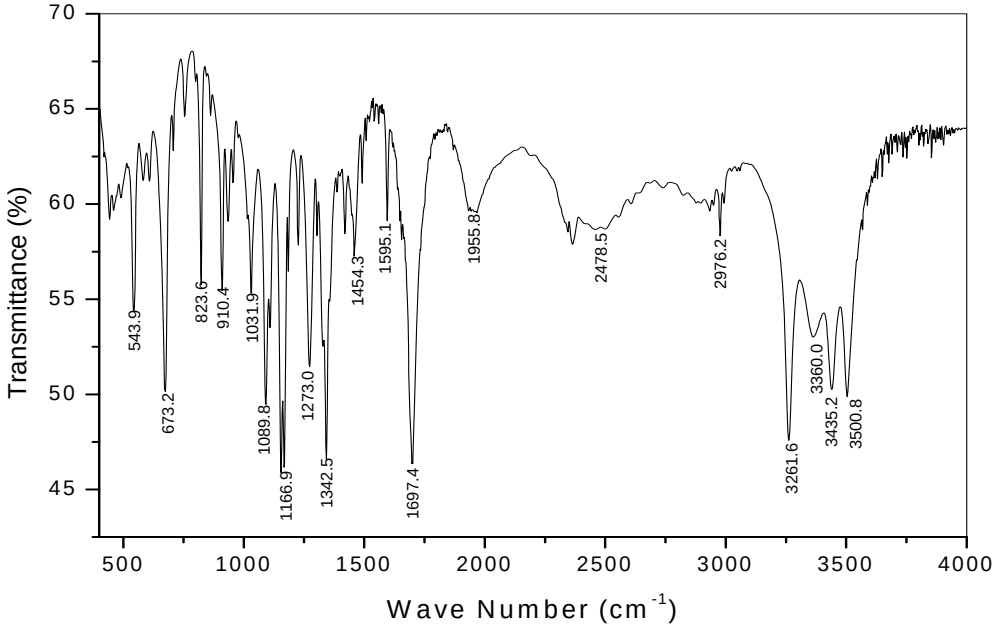


Fig. 5.101: IR Spectrum of 4i

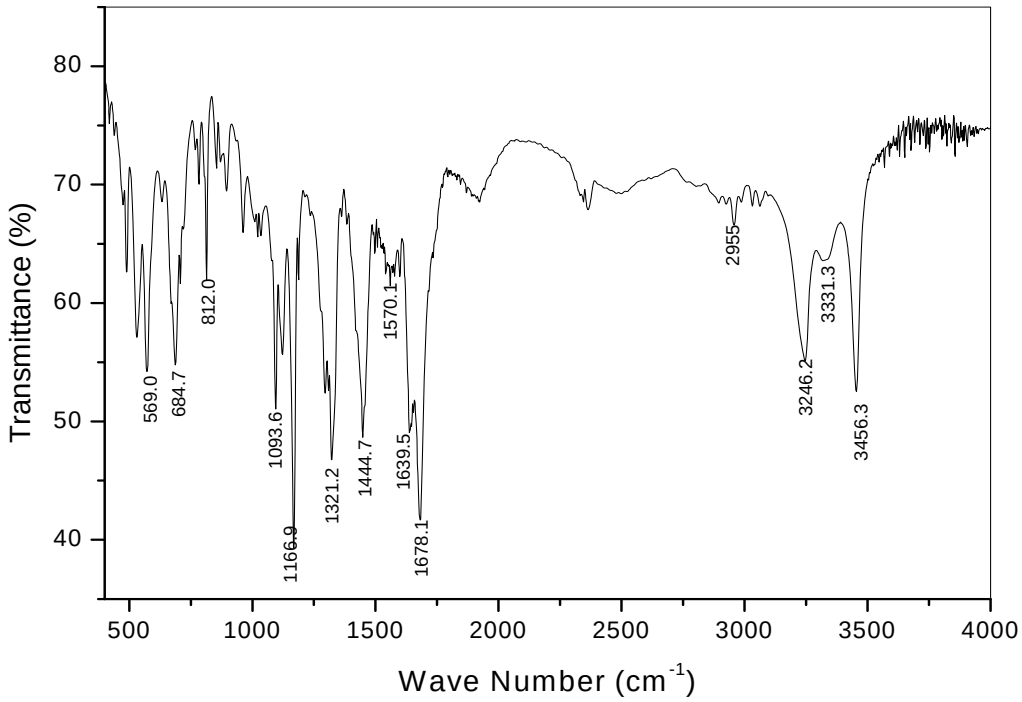


Fig. 5.102: IR Spectrum of 4j

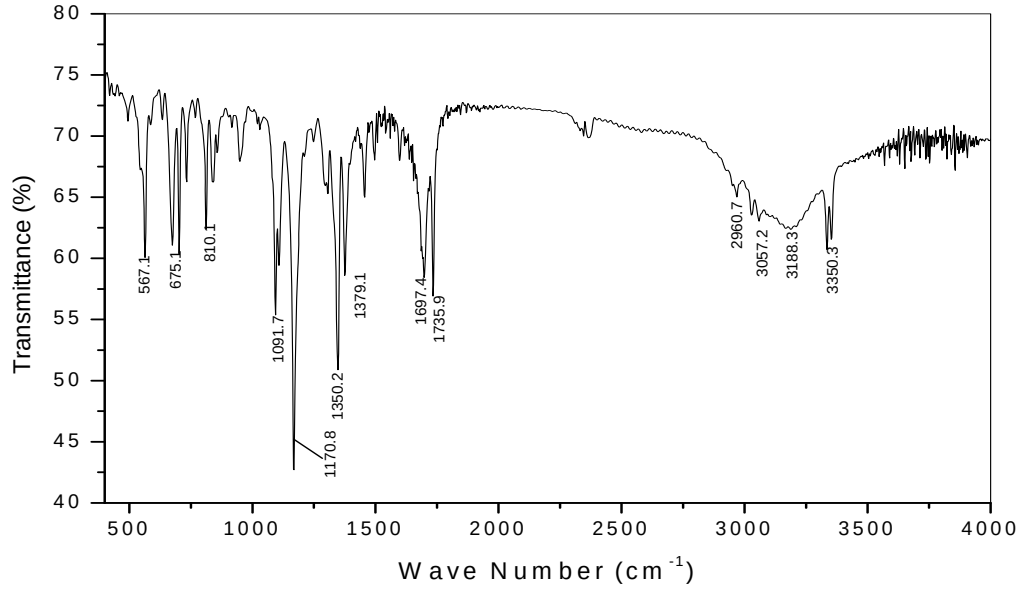


Fig. 5.103: IR Spectrum of 4k

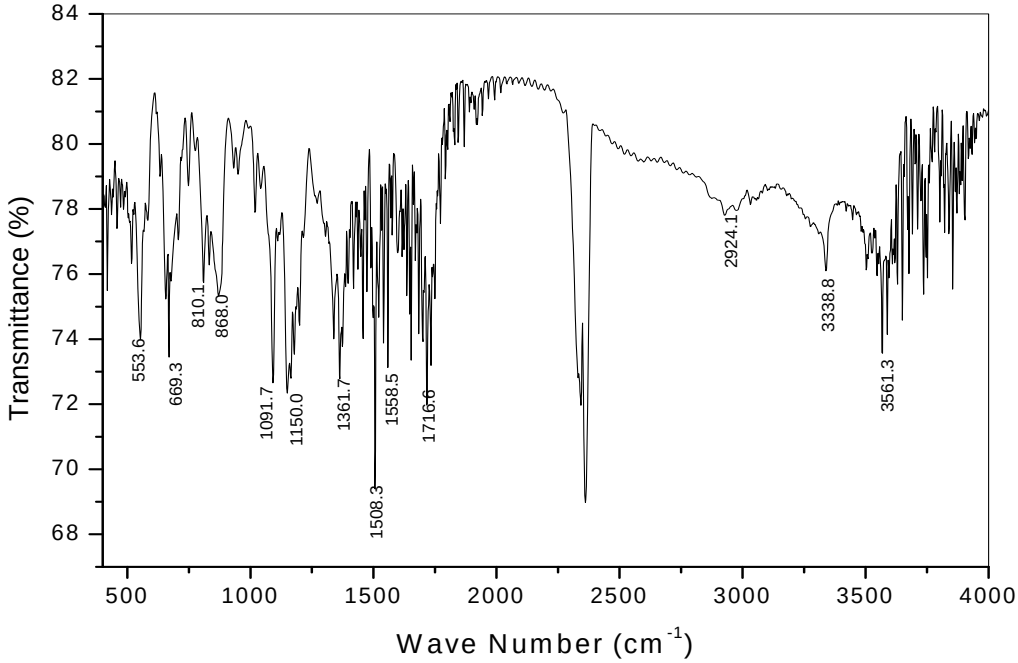


Fig. 5.104: IR Spectrum of 5a

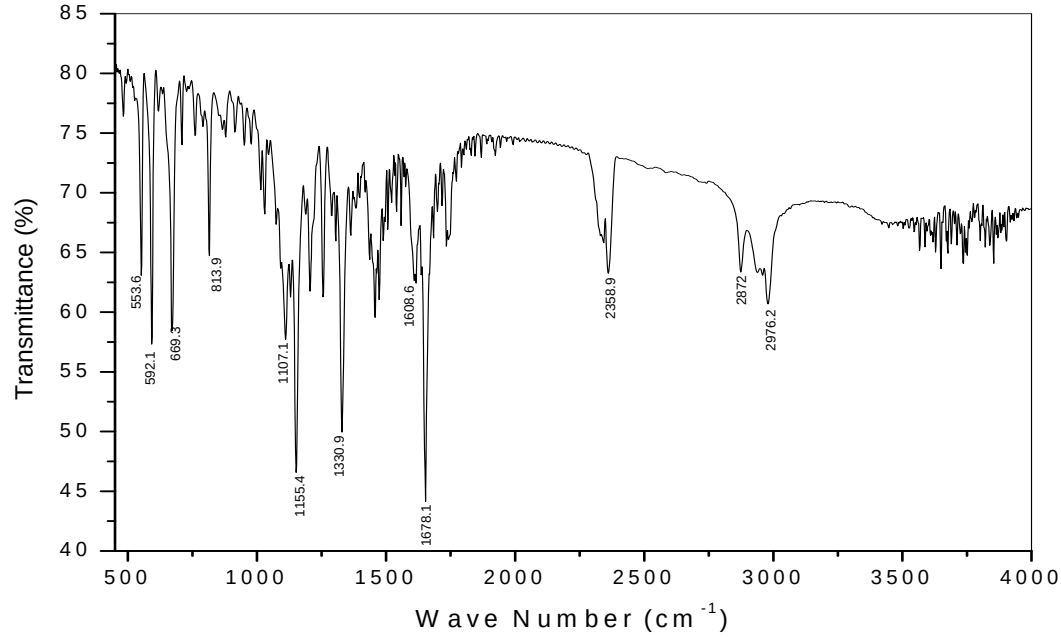


Fig. 5.105: IR Spectrum of 5c

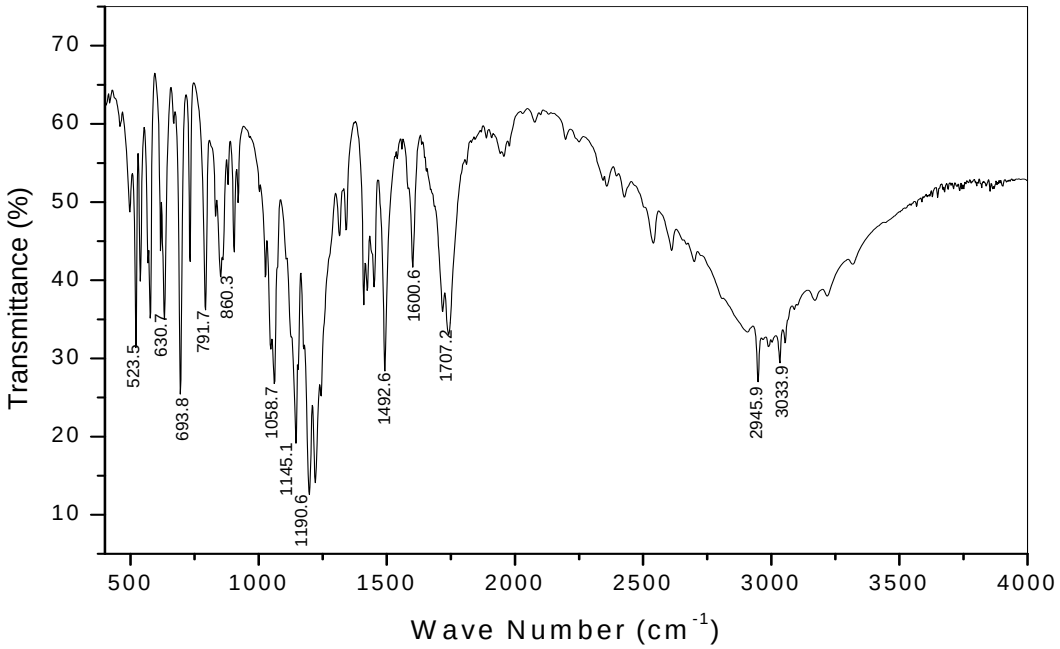


Fig. 5.106: IR Spectrum of 5d

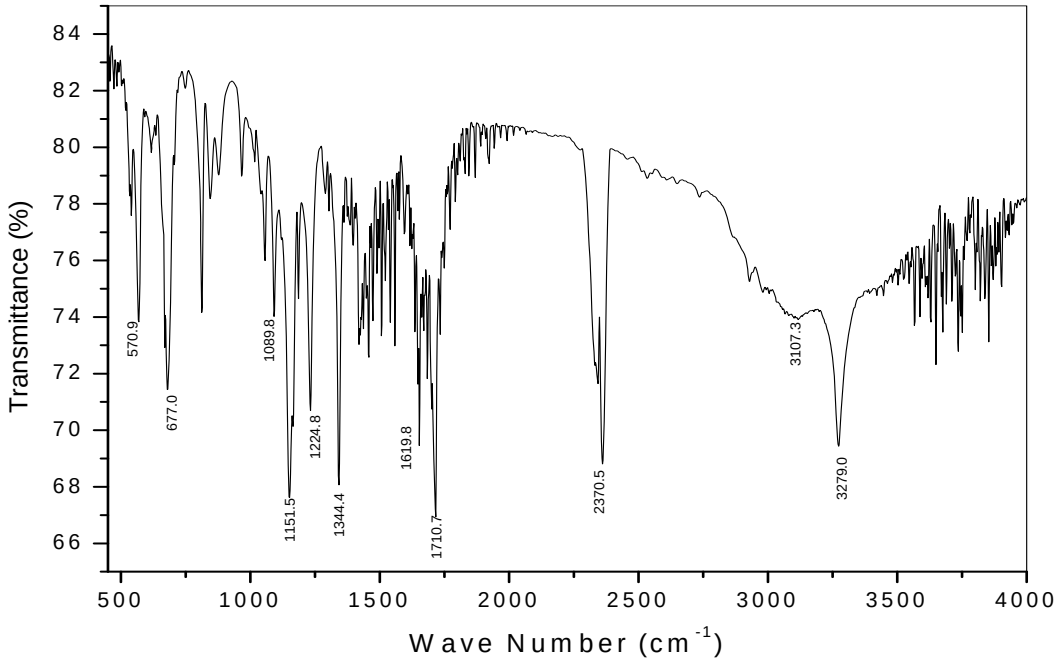
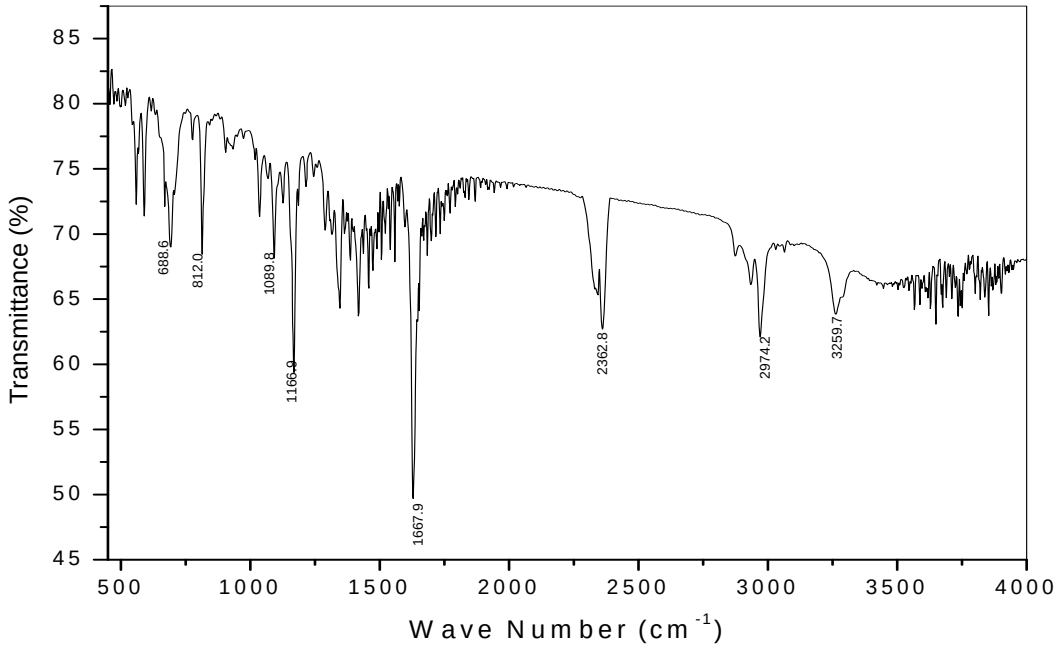


Fig. 5.107: IR Spectrum of 5j



(a) Calculation of Selectivity Index

$$S.I. = \frac{\text{Zones of inhibition of the compound}}{\text{Zones of inhibition of the streptomycin}}$$

(b) Preparation of 20% HCl (v/v)

20 mL of conc. HCl was added to small amount of distilled water and made up to mark in 100 mL standard flask with distlled water.

(c) Preparation of Buffer Solution (pH 2.2)

25 mL of 0.2 M potassium hydrogen phthalate (KHP) was mixed with 20.35 mL of 0.2 M HCl and the mixture was made up to mark in 100 mL standard flask with distilled water.

(d) Preparation of Lithium Diisopropylamide (LDA)

Disopropyl amine, *i*-Pr_2NH (0.57 mL, 4 mmol) was added to dry THF (20 mL) in an air-tighted quick fit flask with continuous stirring at room temperature. It was allowed to cool to -78^oC and *n*-BuLi (1.82 mL of a 2.2 M solution, 4 mmol) was added with the aid of cannula and stirred at same temperature for 20 mins. prior to use.