MOLECULAR DESIGN, SYNTHESIS, CHARACTERIZATION & BIOLOGICAL EVALUATION OF NEW SERIES OF SUBSTITUTED 1, 4 DIHYDRO PYRIDINE DERIVATIVES

Dissertation submitted to

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In partial fulfillment of the requirements
for the award of the degree of

MASTER OF PHARMACY

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DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

COLLEGE OF PHARMACY
MADURAI MEDICAL COLLEGE
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CERTIFICATE

This is to certify that the dissertation entitled "***MOLECULAR DESIGN, SYNTHESIS, CHARACTRIZATION & BIOLOGICAL EVALUATION OF NEW SERIES OF SUBSTITUTED 1, 4 DIHYDRO PYRIDINE DERIVATIVES*****"** was done by **Mr. M. Srinivasan, (Reg. No: 26108634)** in the department of pharmaceutical chemistry, College of Pharmacy, Madurai Medical College, Madurai-625020, in partial fulfillment of the requirement for the Degree of Master of pharmacy in pharmaceutical chemistry under my guidance and supervision for academic year 2011-2012.

This dissertation is forwarded to the Controller of Examination, The Tamil Nadu Dr. M. G. R. Medical University, Chennai.

Station: Madurai **Prof. (Mrs.) R. THARABAI, M.Pharm.,**
Date:

DR. (Mrs.) R. Ajithadas Aruna, M.Pharm, Ph. D.,
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Head of the Department of Pharmacognosy,
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Date:

Evaluation Certificate

Internal Examiner

External Examiner

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Ref. No. 14024 / E1/4 /2011

ETHICAL CLEARANCE CERTIFICATE

DR. A. Edwin Joe M.D, Dean& Chairman, Animal Ethical committee, Madurai Medical College, Madurai, hereby endorse ethical clearance to the proposal.

"Molecular Design, Synthesis, Characterization &Anti Diabetic action of new series of 1, 4 Di hydro pyridine derivatives"

Submitted by

Mr.M.Srinivasan
Post Graduate Student,
Department of Pharmaceutical Chemistry,
Madurai Medical College, Madurai.

The study did not violate the regulations and guidelines prescribed by ICMR and are within the permitted norms of animal experimentation in this country. The out come of the study may be beneficial to the human and animals.

Date: .01.2012
Place: Madurai

DEAN, MADURAI MEDICAL COLLEGE
MADURAI-20.

Dean& Chairman

CONTENTS

LIST OF ABBREVATIONS

^{0}C	:	Degree Centigrade
mcg	:	Microgram
%	:	Percentage
gm	:	Gram
mg	:	Milligram
ml	:	Milliliter
m.p	:	Melting point
pH	:	Hydrogen ion concentration
DHPs	:	Di-Hydro Pyridine
^{1}H-NMR	:	Proton Nuclear Magnetic Resonance
IR	:	Infra Red
H	:	Hour
mts	:	Minutes
M	:	Mole
DMSO	:	Dimethyl Sulfoxide
QSAR	:	Quantitative Structural Activity
Relationship		
TLC	:	Thin Layer Chromatography
Ar	:	Aromatic
Alip.	:	Aliphatic
KBr	:	Potassium bromide
Me	:	Methyl
Et	:	Ethyl

o, m. p	:	Ortho, Meta, Para
δ	:	Delta
ppm	:	Parts per million
m/e	:	Mass / charge
R_f	:	Retention factor
Str.	:	Stretching
E.coli	:	*Escherichia coli*
C. albus	:	*Candida albicans*
MeOH	:	Methanol
EtOH	:	Ethanol
Ph	:	Phenyl

Introduction

Introduction

Medicinal chemistry is branch of pharmaceutical chemistry, which deals with design, chemical synthesis & development for market of pharmaceutical agents (drugs).

Drug design is a repeat process which begins when a chemist identifies a compound that displays an interesting biological profile and ends when both the activity profile and the chemical synthesis of the new chemical entity are optimized. Traditional methods to drug discovery rely on a step-wise synthesis and screening program for large numbers of compounds to optimize activity profiles. Past few decades, scientists have used computer models of new chemical entities to help define activity at molecular level.

Dihydropyridines (DHPs) represent a group of small organic compounds consist of pyridine core. Theoretically, five isomeric DHPs can exist, among that the recognized DHPs have either the 1,2-dihydro or the 1,4-dihydro structure. DHPs have a wide range of pharmacological actions as agents in vasodilation, bronchodilation, hepatoprotection and geroprotection and as antiatherosclerosis, antidiabetes, antitumor, antimutagenic, antioxidant, anticonvulsant and antiradical agents . Dexniguldipine is a chemosensitizer with low hypotensive properties. It is clear that the new generation of DHP derivatives are a potential source of valuable drug candidates with remarkable potential and ongoing interest.

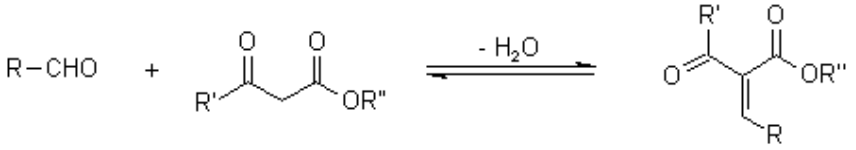
General Method of synthesis of 1,4 DHP Synthesis

The *Hantzsch* pyridine synthesis or *Hantzsch* dihydropyridine synthesis is a multi-component organic reaction between an aldehyde such as formaldehyde, 2

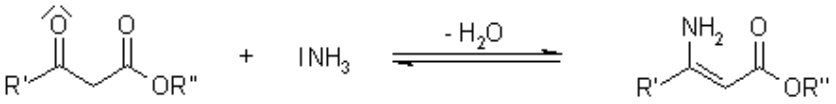
equivalents of a β-keto ester such as ethyl acetoacetate and a nitrogen donor such as ammonium acetate or ammonia.

Mechanism of the *Hantzsch* Dihydropyridine Synthesis

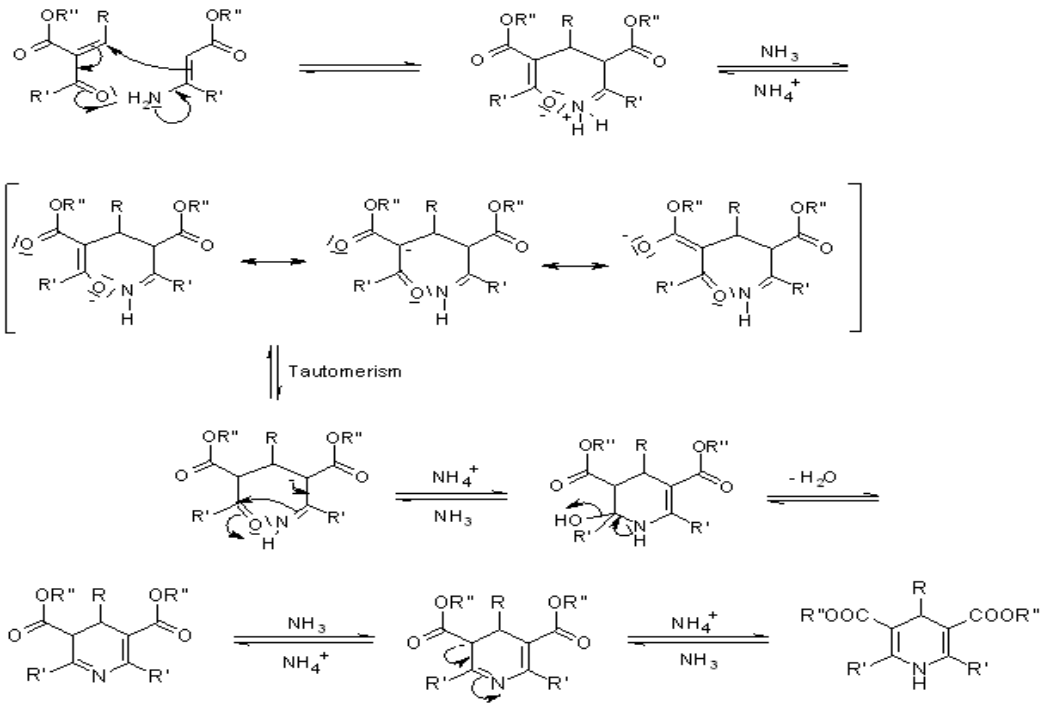
The reaction can be visualized as proceeding through a Knoevenagel Condensation product as a key intermediate:



A second key intermediate is an ester enamine, which is produced by condensation of the second equivalent of the β-ketoester with ammonia:



Further condensation between these two fragments gives the dihydropyridine derivative:



Molecular Modeling

One of the basic tenets of medicinal chemistry is that biological activity is dependent on the three-dimensional placement of specific functional groups (the pharmacophore). Over the past few years, advances in the development of new mathematical models which describe new molecules and development of more intuitive program interfaces coupled with the availability of faster, smaller and affordable computer hardware have provided experimental scientists with a new set of computational tools. These tools are being successfully used, in conjunction with traditional research techniques, to examine the structural properties of existing compounds, develop and quantify a hypothesis which relates these properties to observed activity and utilize these "rules" to predict properties and activities for new chemical entities. The development of molecular modeling programs and their application in pharmaceutical research has been formalized as a field of study known as computer assisted drug design (CADD) or computer assisted molecular design (CAMD).

Computational chemistry molecular modeling is the science (or) art of representing molecular structures numerically and simulating their behavior with the equations of quantum and classical physics. Computational chemistry programs allow scientists to generate and present molecular data including geometries (bond lengths, bond angles, torsion angles), energies (heat of formation, activation energy, etc.), electronic properties (moments, charges, ionization potential, electron affinity), spectroscopic properties (vibrational modes, chemical shifts) and bulk properties (volumes, surface areas, diffusion, viscosity, etc.). As with all models however, the chemist's intuition and training is necessary to interpret the results appropriately.

Comparison to experimental data, where available, is also important to guide both laboratory and computational work.

Hit to Lead, and Lead Optimization

Further chemistry and analysis is necessary, first to identify and sorting compounds that do not provide series displaying suitable SAR and chemical characteristics associated with long-term potential for development, then to improve remaining hit series with regard to the desired primary activity, as well as secondary activities and physiochemical properties such that the agent will be useful when administered in real patients. In this regard, chemical modifications can improve the recognition and binding geometries (pharmacophores) of the candidate compounds, and so their affinities for their targets, as well as improving the physicochemical properties of the molecule that underlie necessary pharmacokinetic/pharmacodynamic (PK/PD), and toxicology profiles (stability toward metabolic degradation, lack of geno, hepatic, and cardiac toxicities, etc.) such that the chemical compound or biologic is suitable for introduction into animal and human studies.

Drug design parameter

Lipinski's Rule of Five is a set of principles that to evaluate drug likeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small and lipophilic molecules.

This rule describes molecular properties important for a drugs pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active.

The rule is important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski's rule.

Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria:

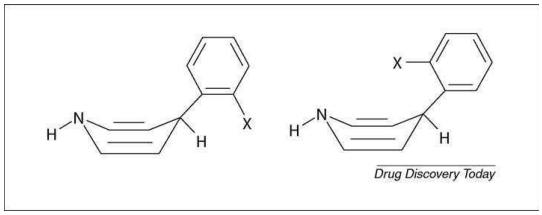
- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass not greater than 500 daltons.
- An octanol-water partition coefficient log *P* not greater than 5.

QSAR of 1, 4 DHP

The DHPs a group of compounds has been the aim of many quantitative structure–activity relationship (QSAR) studies to find the most important quantitative parameter for optimal activity of these compounds. The Hansch analysis method to a series of 4-phenyl-substituted DHPs. They concluded that the biological activity of DHPs is dependent on the lipophilic, as well as the electronic and steric properties, of the substituent on 4-phenyl DHP analogs of nifedipine. *Hansch* analysis on a small number of the same DHPs and found that bulky and lipophilic groups at the ortho-position and bulky groups with high Hammet electronic constant (s) at the meta-

position of the 4-phenyl ring increase the DHPs' activity. They also concluded that the potency of DHPs decreases with the increase in minimum width or length of substituents at the para-position, and optimal values were found to be those for hydrogen. They found that the activity of meta-substituted compounds is affected by both steric and electronic parameters, whereas the hydrophobic and electronic parameters of the para-substituted DHPs affect the drug's activity. Hansch analysis for those nifedipine analogs containing nitroimidazolyl, phenylimidazolyl and methylsulphonylimidazolyl groups at the C-4 position and different ester substituents at C-3 and C-5 positions of DHP ring and showed that Hammett's electronic and hydrophobic properties are highly correlated with the biological activity. Different linear and nonlinear methods have been used in QSAR studies (Non-3D, also known as classical QSAR) of DHP analogs to get additional and more precise parameters that are important for the biological activity of these compounds. Partial least squares and principal component artificial neural network were employed, using theoretically derived descriptors for different DHP analogs. In addition, the quantum chemical QSAR study of these compounds indicated the importance of electronic features of the DHP derivatives for receptor binding. Compared with classical QSAR investigations, 3D QSAR approaches yield better results for the correlation of the internal dataset and prediction of test set DHP derivatives. Different 3D QSAR approaches have been conducted to simplify the design of optimized DHP derivatives with increased calcium antagonist activity. 3D QSAR study-COMFA of 4-phenyl-substituted DHPs indicates unfavuorable steric interactions for bulky moieties in the para-position of the phenyl ring and that bulky substituents are favorable in ortho- and meta-positions. The best combination is obtained when the bulky substituent at ortho or meta produce negatively charged electrostatic potential. In addition, this study

indicated that repulsive electronic interaction with binding-site residue or to the potential of electron-deficient 4-aryl moieties behave as electron acceptors in charge transfer mechanism.



Diabetes

Diabetes is not a disease but a disorder, affecting 10% of the human population where the body does not produce insulin or does not properly use insulin due to which the glucose concentration remains high in the blood stream.

Glucose, Insulin and Diabetes

Glucose is derived from all kind of foods that we consume. Pancreas, a small gland below the stomach secretes a hormone called insulin. The insulin released carries the blood glucose present in the blood stream to cells that need extra energy. The cells do not and can not use glucose without the help of insulin. Once inside the cells, the glucose produces heat and energy. But if the insulin is not helping, then the glucose is not of use to body and in fact it is bad for body to have too much of unused glucose. In a normal individual, body manages to maintain a ideal level of glucose concentration. But in diabetes insulin is either not produced or not utilized properly, and hence the glucose remains in the blood causing the condition “Diabetes”.

Types of Diabetes

Diabetes due to absence of insulin

This is frequently seen in childhood and hence called, Juvenile Onset or Childhood Diabetes. In this diabetes which is called Type 1, the patient has failed to produce insulin and the only remedy to overcome this is to go in for Insulin injections. The problem can happen in any age of the individual, though majority are from childhood. The injected insulin, the frequency and dose is decided by the medical expert. The synthesized insulin is injected and it mimics the natural insulin and the individual can lead a normal life.

Diabetes due to ineffective insulin

This is commonly seen in adults and called as Type 2. Though the body produces insulin it has trouble using it, that is body is resistant to its own insulin. High blood sugar is found in the blood without being transported to the cells. Routine checkups with dietary restrictions and healthy life style along with regular affordable physical and mental activities are the only solution. There are medicines available which make insulin more effective in such individuals and a combination of medicines and calorie control can help the patients a lot in keeping the disorder under control.

Diabetes Management

Both types of diabetes have different treatment options and in general population the Type 2 diabetes is more prevalent than Type 1. More than 80% of the patients have Type 2 which means it is a problem of ineffective insulin.

In case of Type 1, the objective of treatment is to give adequate insulin, in right intervals so that the patient will not have “Hypo” or “Hyper” sugar levels. This

requires frequent monitoring for sugar levels and require higher frequency of medical supervision and intervention.

In case of Type 2, the objective of treatment is to make insulin more effective and reduce the consumption of unwanted food materials. This is achieved by reduction in quantity of food or modifications in type of food, increase in physical exercises or avoid sedentary life styles and also take such medicines which improve the action of insulin. This requires less often blood sugar monitoring, compared to Type 1, but requires constant and periodic medical monitoring and supervision.

Diabetes is a manageable disease if one knows how to control the sugar levels. But uncontrolled diabetes can give rise to so many health complications such as Heart Disease, Kidney Disease, Blindness, Brain Failure and Amputations of legs or Limbs.

Treatment of diabetes mellitus

Modalities of treatment

- Diet
- Physical exercise
- Insulin
- Oral anti-diabetic agents

Oral anti-diabetic agents

Oral anti-diabetic agents are of use in type-2 Diabetes Mellitus when it is not controlled by diet and exercise. These drugs can bring the blood glucose level back to normal in mild diseases.

Drugs

Sulfonyl ureas

First Generation

- ✍ Tolbutamide
- ✍ Chlorpropamide
- ✍ Tolazamide
- ✍ Acetohexamide

Second Generation

- ✍ Glibenclamide (Glyburide)
- ✍ Glipizide
- ✍ Gliclazide
- ✍ Glimepride

Biguanides

- ✓ Metformin
- ✓ Phenformin

Meglitinides

- Repaglinide
- Nateglinide

Thiazolidinediones

- ▪ Pioglitazone
- ▪ Rosiglitazone

Alpha glucosidase inhibitors

- ❖ Acarbose
- ❖ Miglitol

Newer drugs

- ➢ Pramlintide
- ➢ Exenatide
- ➢ Sitagliptin
- ➢ Mosapride
- ➢ Diapep 277
- ➢ Vildagliptin

Antimicrobial Agents

The control of pathogens place important role in chemotherapy. The existing molecule had been resisted due to mutational changes; this lead to severity of disease is increased. In-order to avoid resistance the selection of target protein place prominent role in chemotherapeutic agents.

These are the agents which kill or inhibit the growth of micro-organisms such as bacteria, protozoan, fungi & Viruses. It produce both bacteriostatic & bactericidal action based on the concentration.

Drugs:

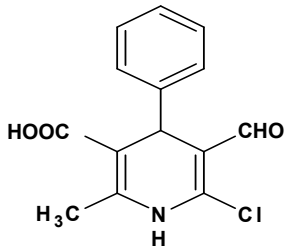
There are the two main classes of anti-microbial agents

1. ***From natural source***
    a. Beta-lactam antibiotics- Penicillin & Cephalosporin
    b. Protease inhibitors
2. ***Synthetic agents***
    a. Sulphonamides, Cotrimazole, Quinalones
    b. Anti-fungal
    c. Anti-viral
    d. Anti-malarial
    e. Anti-protozoval
    f. Anti-tubercular
    g. Anti-leprotic

Literature Review

Literature Review

Enrique Ruiz.*, et al., (2012)* A facile, efficient and environment-friendly protocol for the synthesis of 6-chloro-5-formyl-1,4-dihydropyridine derivatives has been developed by the convenient ultrasound-mediated reaction of 2(1H)pyridine derivatives with the Vilsmeier–Haack reagent.

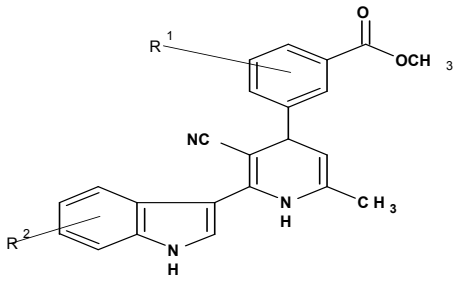


Product	X
2a	H
2b	-NO2
2c	3-NO2
2d	4-NO2

Chunchi Lin and Ching-Fa Yao.*, et al.,* (2005) 4-substituted-1,4-dihydropyridines from the reaction of different aryl or alkyl aldehydes, 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate in the presence of catalytic amount of iodine at room temperature. The advantages such as shorter reaction times, milder conditions, simplicity of the reaction, excellent product yields.

Tao Chen, Xiao-Ping Xu.*, et al.,* (2011) 1,4-dihydropyridine scaffold, indol-3-yl-5-oxo-1,4,5,6,7,8- hexahydroquinoline, and indol-3-yl-1,4-dihydropyridine derivatives were facilely synthesized through three-component reactions of aromatic aldehydes, 3-cyanoacetyl indoles with 3-amino-2-enones in the presence of ammonium acetate. The 1,4-dihydropyridine core structure can be efficiently aromatized in the presence of stoichiometric 2,3-dichloro-5,6-dicyano-1,4-

benzoquinone (DDQ). The advantages of the present protocol are atom-economy, simple work-up and easy purification of products by non-chromatographic methods.

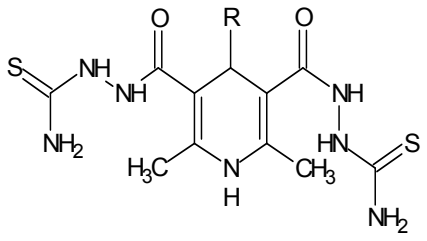


R1= Br, NO_2, Cl_2, CH_3, OCH_3

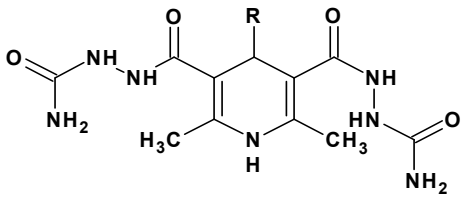
R2= CH_3, OCH_3

Neeloo Singh.*, et al.*, (2011) Glycosyl 1,4-dihydropyridine analogue (2,6-dimethyl-4-(3-O-benzyl-1,2-O-isopropylidene-b-L-threo pentofuranos-4-yl)-1-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester) synthesized , inhibited Leishmania donovani infection in vitro and in hamsters (Mesocricetus auratus) when administered orally. This analogue is nontoxic, cell-permeable and orally effective. This glycosyl dihydropyridine analogue functioned through arrest of cells in sub-G0/G1-phase, triggering mitochondrial membrane depolarization-mediated programmed cell death of the intracellular amastigotes.

J. Jasmal Abdul Nasser.*, et al.*, (2011), a series of 1,4 DHP derivatives have been prepared by Hantzsch method. The structure of synthesized compounds were conformed by FTIR, 1H NMR, 13NMR, Mass spectroscopy & elemental analysis. The compounds have been screened for preliminary anticancer activity against HepaG2(Liver), Hela (Cervical) & MCF-7 (Breast) cancer cells. The compounds 2a is highly active against HepaG2, MCF-7 and 3a is highly active against Hela.



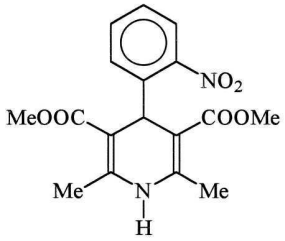
2a: R- 4-OH-3-OCH3-Ph



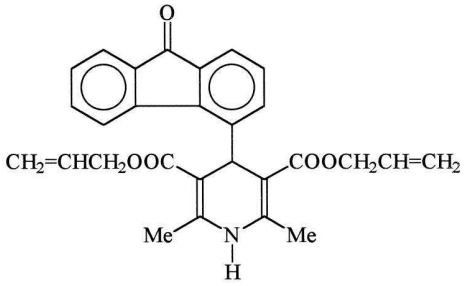
3a: R- 4-OH-3-OCH_3-Ph

Devanand B. Shinde.*, et al.,* (2006) A novel method, which is eco friendly, cost effective, solvent free, was developed for the synthesis of 1,4dihydropyridines from ethyl acetoacetate, aldehyde and ammonium acetate under domestic microwave oven. The yield of 1,4DHP enhanced while the reaction time was reduced.

Roberta Budriesi.*, et al.,* (1998) The effect of the dihydropyridine derivative, 1,4-dihydro-2,6-dimethyl-4- fluorenon-4-yl.pyridine-3,5-dicarboxylic acid diallyl ester fluodipine was studied in vitro in different rabbit, rat and guinea pig preparations and in vivo in the rabbit in order to characterize its pharmacological profile at cardiac and at vascular sites. The highest tissue selectivity was observed in guinea pig preparations: fluodipine (B) was about 2–3 times more effective than nifedipine (A) on chronotropism and inotropism in isolated atria, and about 150 times less effective on aortic strip contraction.

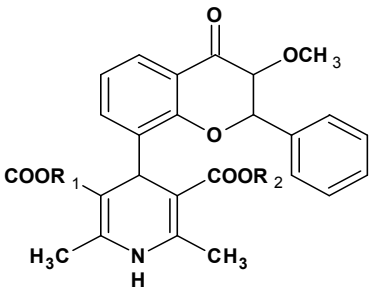


A



B

Pierfranco Ioan.*, et al.,* (2005) Novel substituted 1,4-dihydropyridines with a 3-methoxy-flavone moiety were synthesized and structural modifications of the substituent's in the dihydropyridine ring of nifedipine were carried out in order to find tissue specific compounds. The negative inotropic, chronotropic and vasorelaxant effects were investigated on guinea-pig left, right atria and aortic strips. The different residues in the 1,4-dihydropyridine ring could modulate the chronotropic versus inotropic activity.

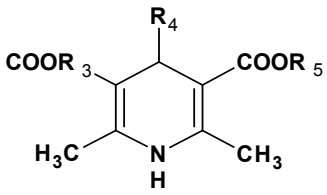


3a $R_1 = R_2 = CH_3$

3b $R_1 = R_2 = CH_2\text{-}CH_3$

3b $R_1 = R_2 = CH_2\text{-}CH{=}CH_2$

Jonna Rzeszowska- wolny., ***et al.,*** **(2005)** Compounds of the 1,4-dihydropyridine (1,4-DHP) series have been shown to reduce spontaneous, alkylation- and radiation induced mutation rates in animal test systems. Here we report studies using AV-153, the 1,4-DHP derivative that showed the highest antimutagenic activity in those tests, to examine if it modulates DNA repair in human peripheral blood lymphocytes and in two human lymphoblastoid cell lines, Raji and HL-60. This compound's structure to that of dihydronicotinamide, a substrate for poly(ADP-rybose)polymerase, the modulation of DNA repair by AV-153 could involve an influence on poly(ADP) ribosylation.



AV-153

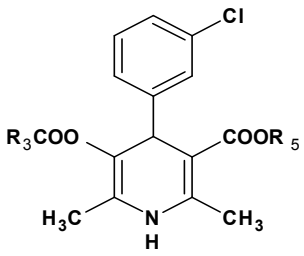
R_4- COONa

$R_3 = R_5 = OC_2H_5$

Nadezhda I. Ryabokon., ***et al., (2009)*** a compound of the carbonyl-1,4-dihydropyridine series (AV-153 or sodium 3,5-bis-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate), which has high efficiency in stimulating DNA repair, can simultaneously modulate apoptosis in human cells. Peripheral blood lymphocytes of healthy donors were used in this study. DNA strand-break rejoining was assessed with the alkaline comet assay after a 3-h incubation of lymphocytes in the presence of

a wide range of concentrations of AV-153 (10−10–10−5 M).It reveals that maximal efficiency of 67% was found for reduction of DNA strand breaks, while for MN cells and apoptotic cells the efficiencies were, respectively, 47% and 44%.

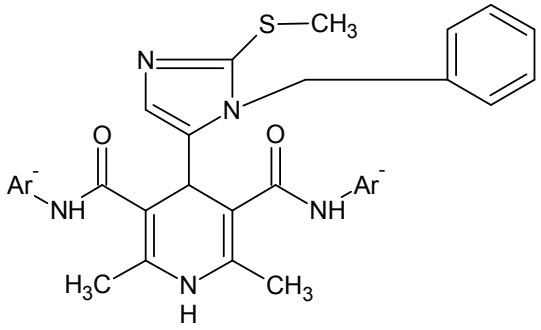
Antonio Morello., ***et al.,*****(2000)** A series of 3-chloro-phenyl-1,4-dihydropyridine derivatives produced different degrees of inhibition of parasite growth and respiration on clone Brener, LQ and Tulahuen strains of *Trypanosome cruzi* epimastigotes. Respiratory chain inhibition appears to be a possible determinant of the trypanosomicidal activity of this compounds. The presence of a fused ring on the dihydropyridine moiety significantly diminished the inhibitory effects.



1a $R_3=R_5=CH_3$

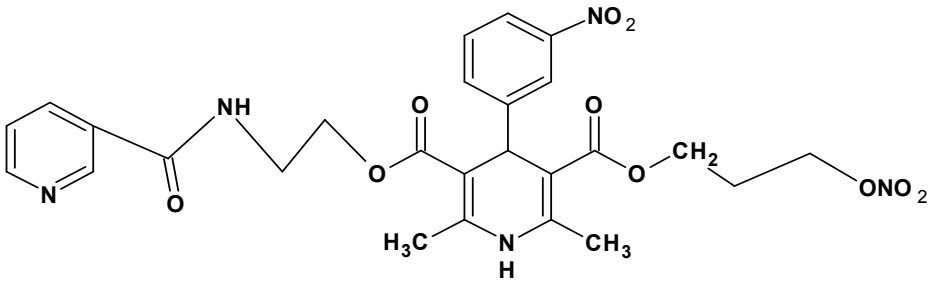
1b $R_3= CH_3$; $R_5=C_2H_5$

Afshin Fassihi., ***et al.,*****(2009)** A series of 4-substituted imidazolyl-2,6-dimethyl-N3,N5 bisaryl-1,4-dihydropyridine-3,5-dicarboxamides were prepared. They were screened as anti-tubercular agents against Mycobacterium tuberculosis H37Rv. Minimum inhibitory concentrations (MICs) were determined using agar proportion method. Compound 3i with 1-benzyl-2-methylthio-1H-imidazole-5-yl substituent at C-4 position and 40-chloromophenyl group at C-3 and C-5 positions of the 1,4-dihydropyridine ring was the most potent one among the tested compounds. It was as potent as rifampicin against M. tuberculosis H37RV. Compound 3l also was an active anti-tubercular agent with the same substituent as compound 3i at the C-4 position and 30-pyridyl group at C-3 and C-5 positions of the 1,4-dihydropyridine ring.

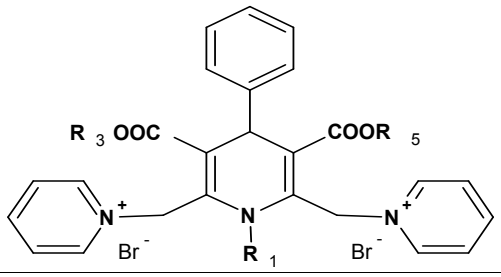


3i: Ar=4-Cl- Pheneyl, 3j: Ar= 3 Pyridyl

Takashi Adachi., ***et al.,*****(1997)** (4R)-(-)-2-(Nicotinoylamino)ethyl3-nitrooxypropyl 2,6-dimethyl-4-(3_nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate **,** a new calcium antagonist, was synthesized via both enantioselective hydrolysis and transesterification of prochiral bis[2-(nicotinoylamino)ethyl]ester 2HCl by using enzymes. Enzymatic transesterification of 5 with 3-nitrooxypropanol gave **1** in more than 99.5% directly.

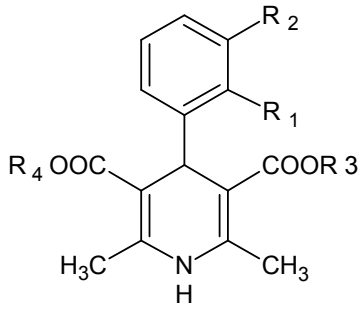


Zanna Hyvonen., ***et al.,*** **(2002)** Double-charged 1,4-dihydropyridine (1,4-DHP) amphiphiles have been shown to condense DNA and efficiently transfect it into cells invitro. In this study examined how those chemical modifications of amphiphile–DNA complexes (amphiplexes) affect their interactions with extracellular polyanions (glycosaminoglycans, albumin) and lipid bilayers, their cellular uptake and intracellular distribution. To evaluate cellular uptake, CV1-P cells were incubated with labeled DNA–amphiphile complexes and analyzed by flow cytometry. The results showed that biophysical properties of compounds can be changed by slight structural modifications.



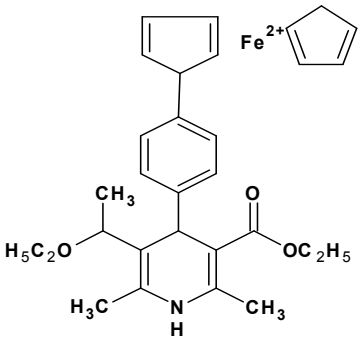
R1	R3=R5	Compound
H	**$C_{10}H_{21}$**	**I**
H	**$C^{12}H^{25}$**	**II**
H	**$C^{14}H^{29}$**	**III**
H	**$C^{16}H^{33}$**	**IV**
CH3	**$C^{12}H^{25}$**	**V**

Antonio Morello., *et al.*, (1997) A series of nitro aryl 1,4-dihydropyridine derivatives produced inhibition of both cell growth and oxygen consumption on Tulahuen and LQ strains, and clone Dm 28c of epimastigotes of *Trypanosoma cruzi*. Nicardipine was found to be the most potent derivative in both growth cell (I50 5 70 mM) and oxygen uptake (I50 5 26 mM in intact parasites, I50 5 325 mM *in situ* mitochondria). Thus, nicardipine, the most potent derivative, exhibited the highest apparent rate constant, ku, (0.043 min21). On the other hand, no susceptibility differences by strains and clone Dm 28c to the action of these drugs were found.

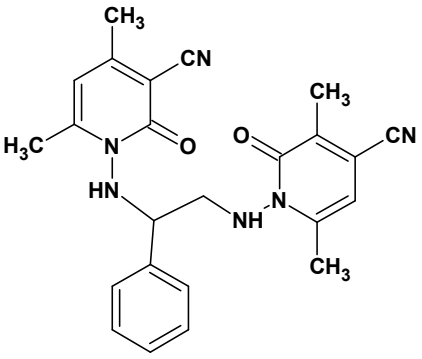


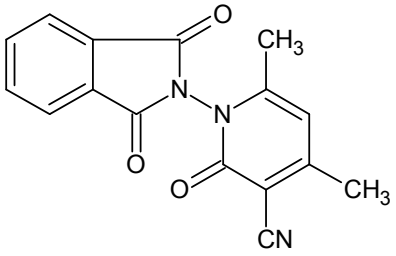
1, 4 DHPs	R1	R2	R3	R4
Nifidepine	-NO2	-H	$-CH_3$	$-CH_3$
Nitrandepine	-H	-NO2	$-CH_3$	$-CH_2 - CH_3$

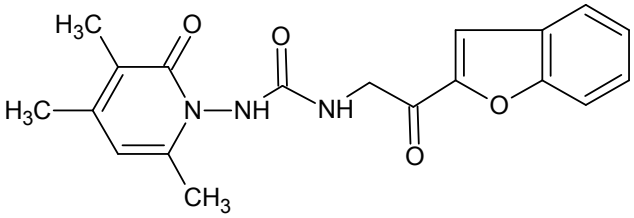
Jose Marco-Contelles., ***et al.,*****(2004)** Synthesis, electrochemical and biological studies on polyfunctionalized 4 ferrocenyl -4H-pyran and 4-ferrocenyl- 1,4 dihydropyridine derivatives. The first synthesis of polyfunctionalized 4-ferrocenyl-4H-pyran and 4-ferrocenyl-1,4-dihydropyridine derivatives, as well as some of their relevant properties, including an electrochemical study and some aspects of their biological profile have been described.



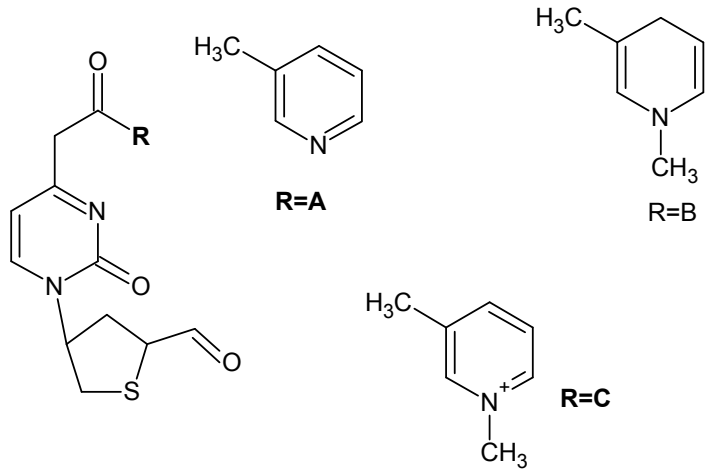
Ameen A. Abu-Hashem b,c., *et al.,*(2007) Synthesis and anti-microbial activity of some 1- substituted amino-4,6-dimethyl-2-oxo-pyridine-3-carbonitrile derivatives.The antibacterial and antifungal activities of the synthesized compounds were evaluated. The obtained data indicated that the majority of the tested compounds exhibited both antibacterial and antifungal activities, comparable effect to a well known antibacterial and antifungal agent.



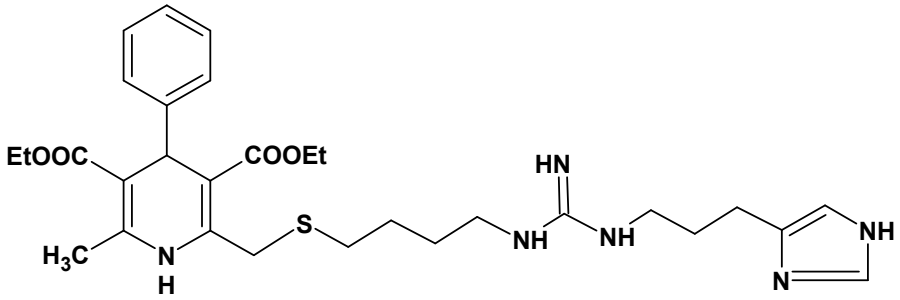


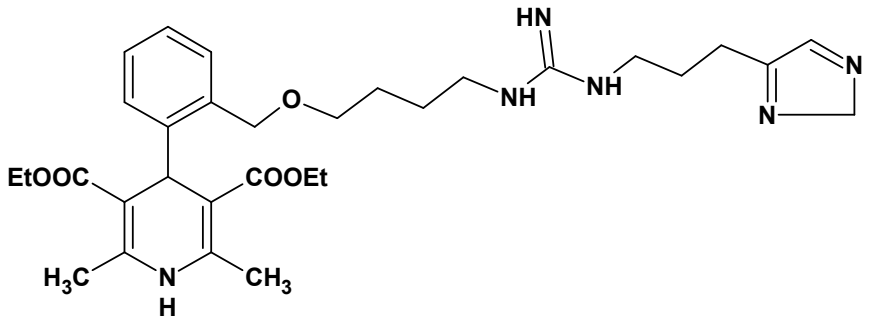


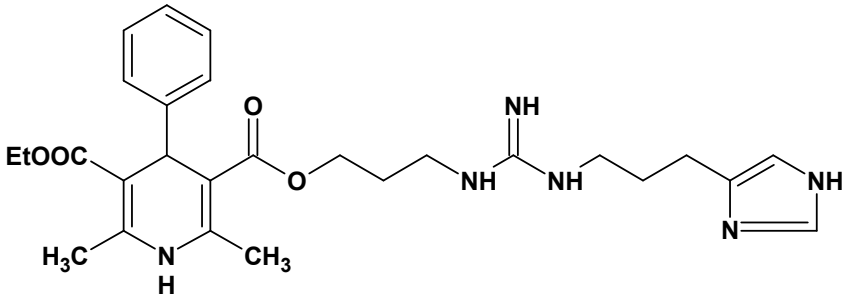
JC Cherrnannz, JL Krausl., et al., Synthesis and antiviral activity of N-4'-dihydropyridinyl and dihydroquinolinylcarbonyl- 2-hydroxymethyl-5-[cytosin-l'-yl]-1,3-oxathiolane derivatives against human immunodeficiency virus and duck hepatitis B virus.



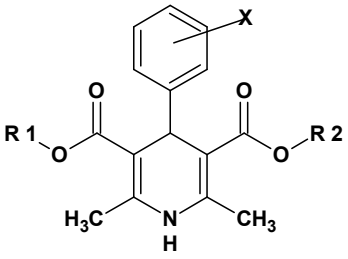
JAM Christiaans., *et al*., (1994) Synthesis and in vitro pharmacology of a series of hybrid molecules possessing 1,4-dihydropyridine calcium-channel blocking activity and histamine H,-agonistic properties.

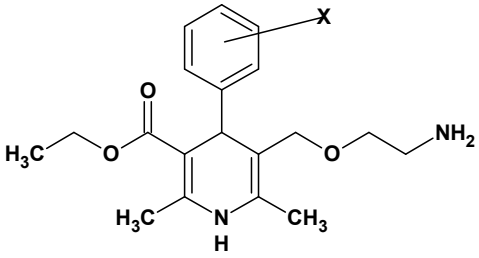


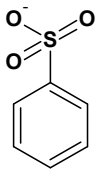




Marija Bester-Rogac., et al., Molecular interactions of 1,4-dihydropyridine derivatives with selected organic solvents: A volumetric, spectroscopic and computational study.

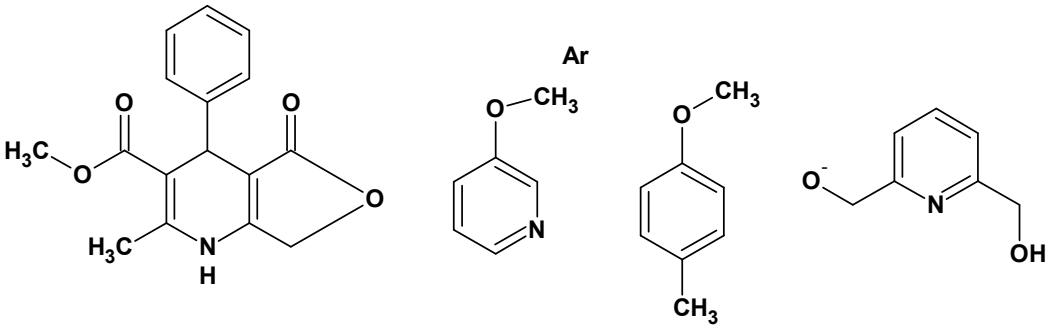




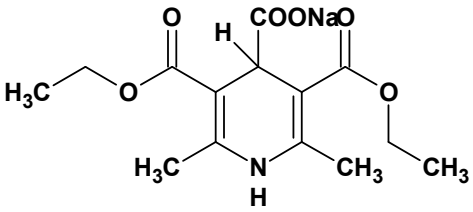


Compound	R_1	R_2	X
Nifidipine	CH_3	CH_3	$2NO_2$
Nitredipine	CH_3	CH_3	$3NO_2$
Nimodepine	C_2H_4OCH3	$CH(CH3)_2$	$3NO_2$

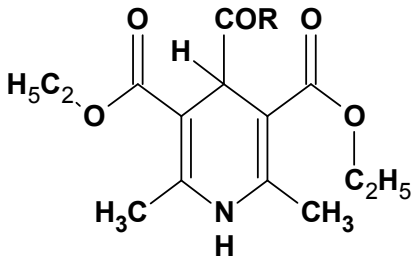
. Alkefl and A.G. Swanson, (1990) formation, synthetic utility and structure elucidation of a 2-bromomethyl 1,4-dihydropyridine



M. Wojewodzka., ***et al.,*** Dihydropyridines decrease X-ray-induced DNA base damage in mammalian cells.



Neven Zarkovic., *et al*., (2006) Bioactive 1,4-dihydroisonicotinic acid derivatives prevent oxidative damage of liver cells.

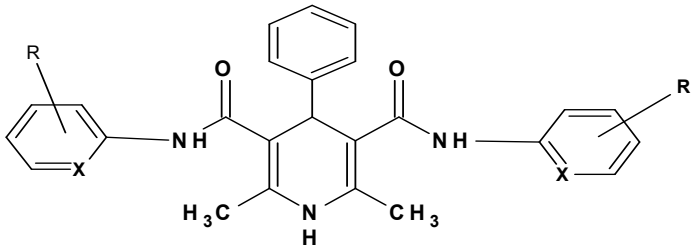


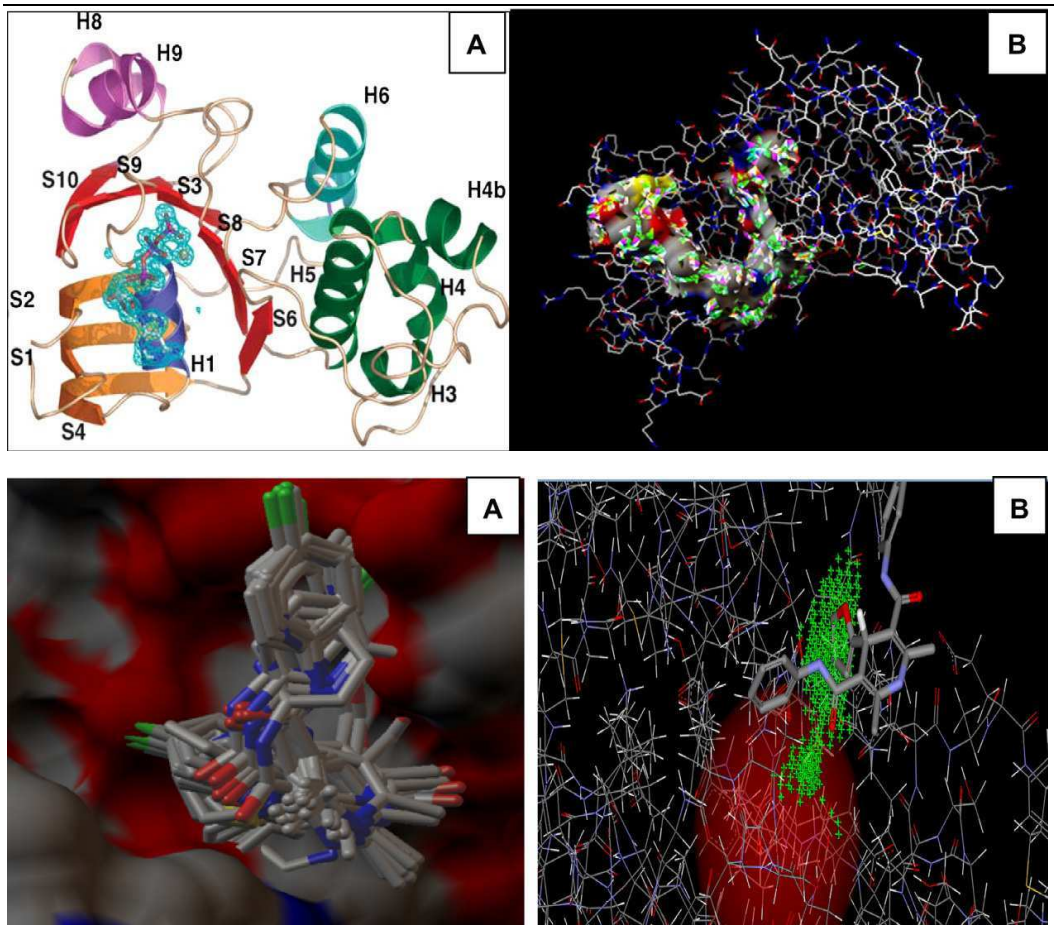
1a, R=ONa

1b, R= HNCH(CooNa) CH_2 -CH_2

1c, R=$HNCH_2$ - CH_2 - SO_3Na

Vanga Malla Reddy., *et al*., (2011) Molecular docking studies and in vitro screening of new dihydropyridine derivatives as human MRP1 inhibitors.





Yuji Takahataa., *et al*., (1997) A comparative study of principal component and linear multiple regression analysis in SAR and QSAR applied to 1,4-dihydropyridine calcium channel antagonists (nifedipine analogues)

Yuichi Hattori., *et al*., Invitro assessment for vascular selectivity of a new dihydro pyridine derivatives.

Aim
&
Objective

Aim and Objective of the Work

The chemistry and pharmacology of new serious of 1, 4 DHP derivatives have been great interest, because of various biological action.

In search for new bioactive molecule, it was thought worthwhile to incorporate some additional semicarbazide & thio-semicarbazide moiety in the 1,4 DHP nucleolus and study their biological activity, the review of literature reveal prompted us to synthesis of substituted 1, 4 DHP derivatives with semicarbazide & thiosemicarbazide side chain and those will screened for anti-diabetic & anti-microbial action.

Plan of Work

Plan of work

- To design the molecule with help of software tools.
- To establish the methods of synthesis for the proposed compounds.
- To carry out the preliminary test such as physical constant determination, solubility….etc.
- To confirm the structure of the synthesized compounds by using FTIR, ^{1}H NMR, Mass spectra.
- To evaluate the proposed compounds for their antimicrobial, anti-.diabetic action.

Scheme

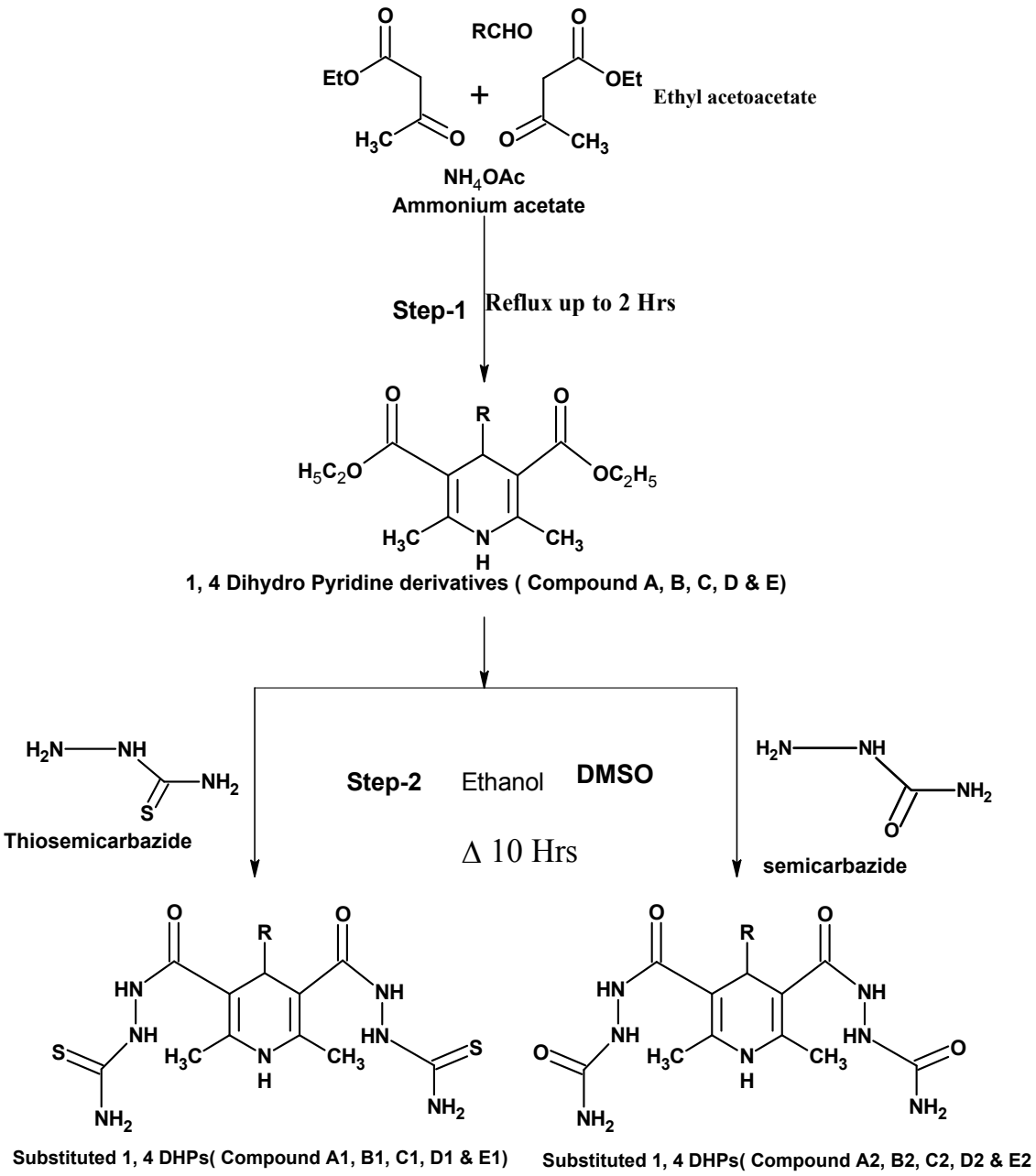
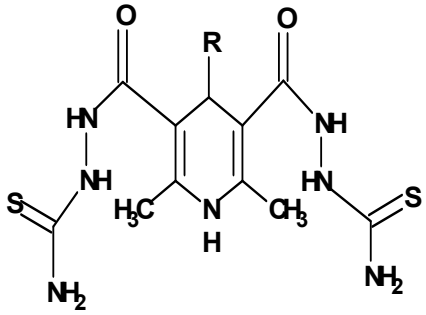
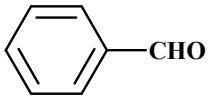
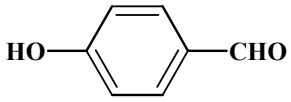
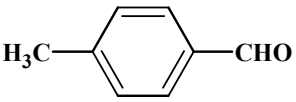
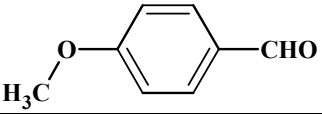
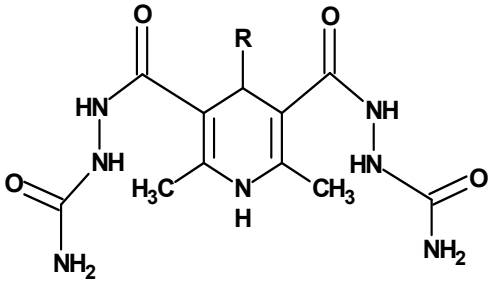
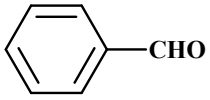
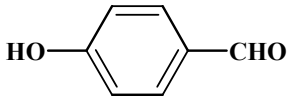
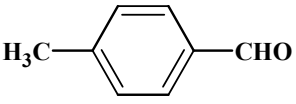
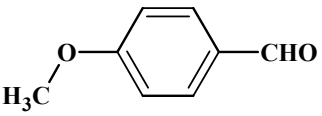

RCHO
EtO
OEt
Ethyl acetoacetate
NH_4OAc
Ammonium acetate
Step-1
Reflux up to 2 Hrs
1, 4 Dihydro Pyridine derivatives (Compound A, B, C, D & E)
Thiosemicarbazide
Step-2
Ethanol
DMSO
Δ 10 Hrs
semicarbazide
Substituted 1, 4 DHPs(Compound A1, B1, C1, D1 & E1)
Substituted 1, 4 DHPs(Compound A2, B2, C2, D2 & E2

Table – 1

Different substitution in compounds

Compound No.	Structure	R
A1		CH_3CHO
B1		
C1		
D1		
E1		
A2		CH_3CHO
B2		
C2		
D2		
E2		

Experimental Work

Experimental work

Table-2

List of Software used

Name of the software	Version	URL Link
Acetelion Property Exlorer	2001	www.oranicwebportal.com
Molinspiration	On-line	www.molinspiration.com
Graph pad prisam	3.05	-

Table-3

List of Chemicals/ Reagents used

S. No	Name of the Chemical/ Reagent	Manufacturer
1	Ethylacetoacetate	Sigma aldrich
2	Ammonium acetate	Spectrochem
3	Formaldehyde	Sigma aldrich
4	Benzaldehyde	Fisher scientific
5	P- OH Benzaldehyde	Sigma aldrich
6	P- CH_3 Benzaldehyde	Sigma aldrich
7	P- OCH_3 Benzaldehyde	Sigma aldrich
8	DMSO	Spectrochem
9	Ethanol	Qualigens
10	Ethyl acetate	Fisher scientific
11	Chloroform	Sigma aldrich
12	Glacial Acetic Acid	Sigma aldrich
13	Isopropyl alcohol	Fisher scientific
14	Xylinol	Fisher scientific

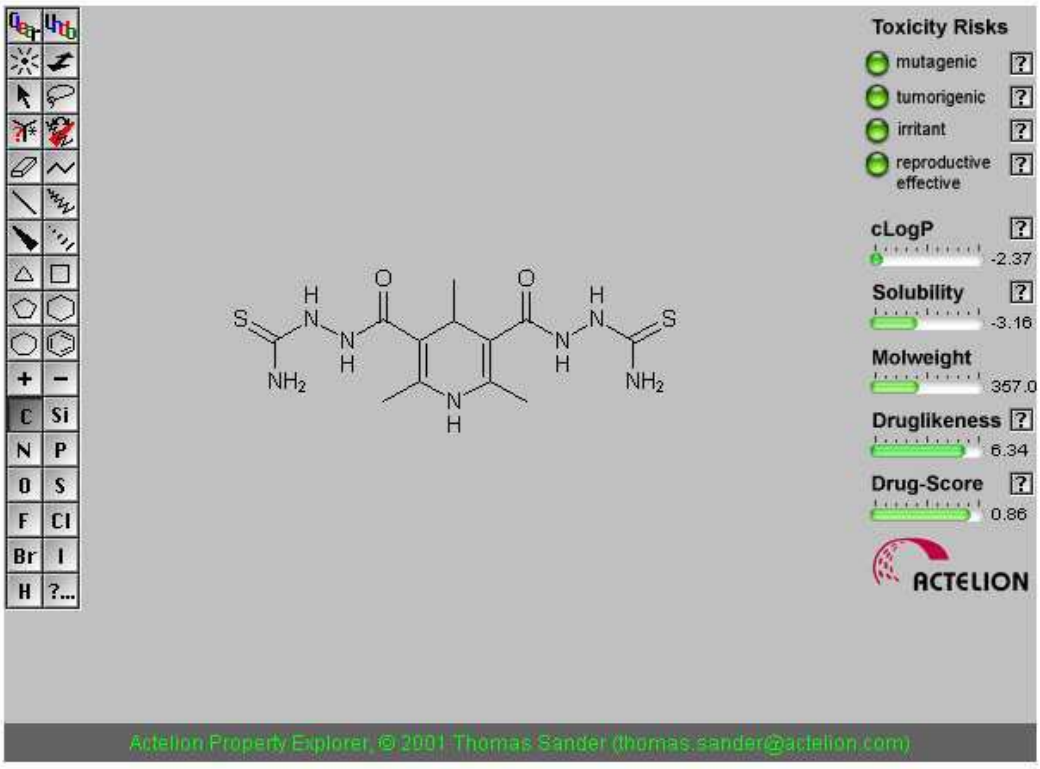
Table-4

List of Equipments used

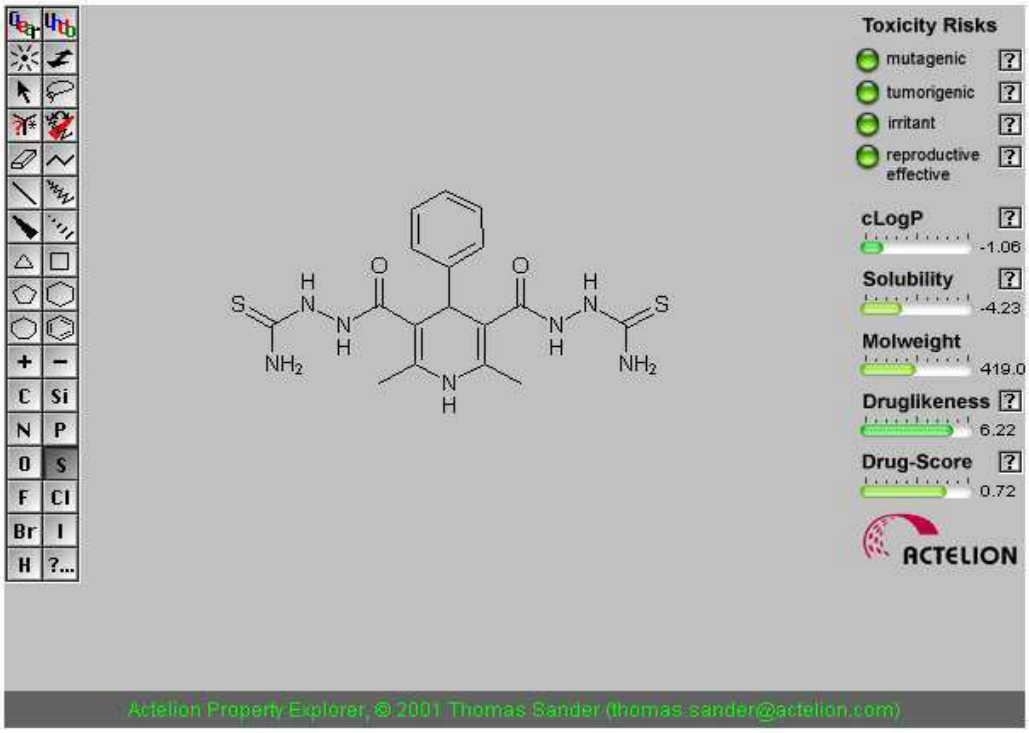
S. No	Instrument	Manufactures
1	Digital electronic balance	Shimadzu Ax - 200
2	Magnetic stirrer	Remi Equipments, Chennai
3	Melting point apparatus	Sunbim, Guna Enterprises
4	FT-IR Spectroscopy	Perkin Elmer-I
5	^{1}H-NMR Spectroscopy	Bruker – NMR 400 MHz
6	Mass Spectroscopy	JEOL GC mate
7	Hot air oven	Picses
8	Microwave oven	ONIDA electronics

Figure-1; Molecular design by using Osiris's property explorer

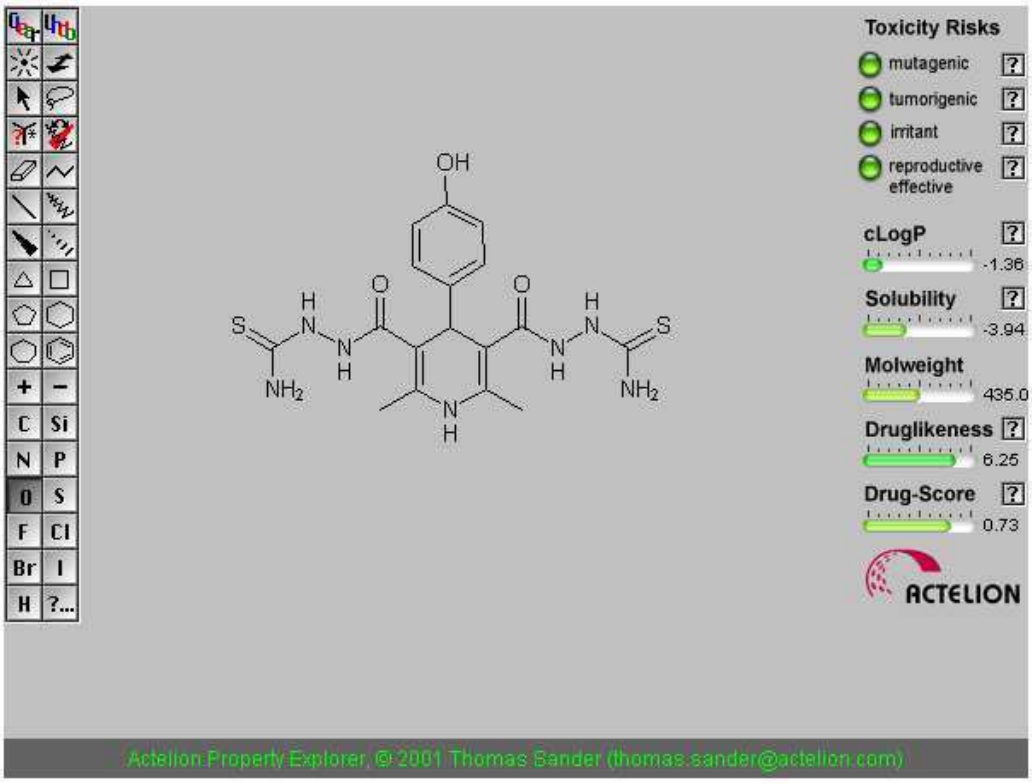
Compound-A1



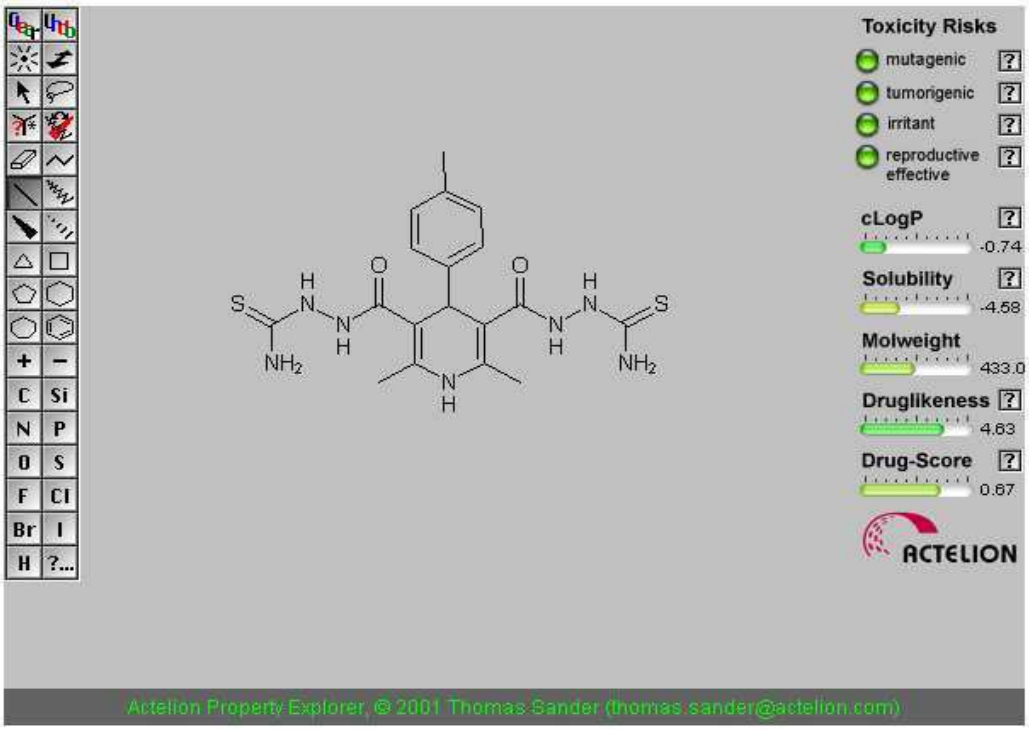
Compound-B1



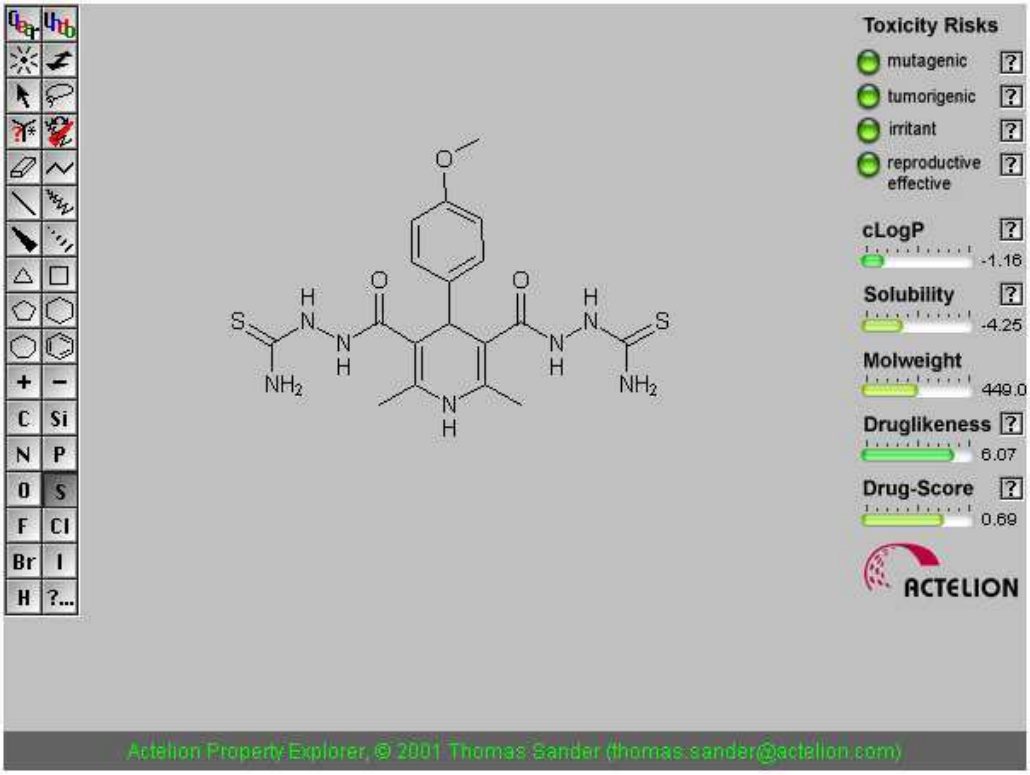
Compound-C1



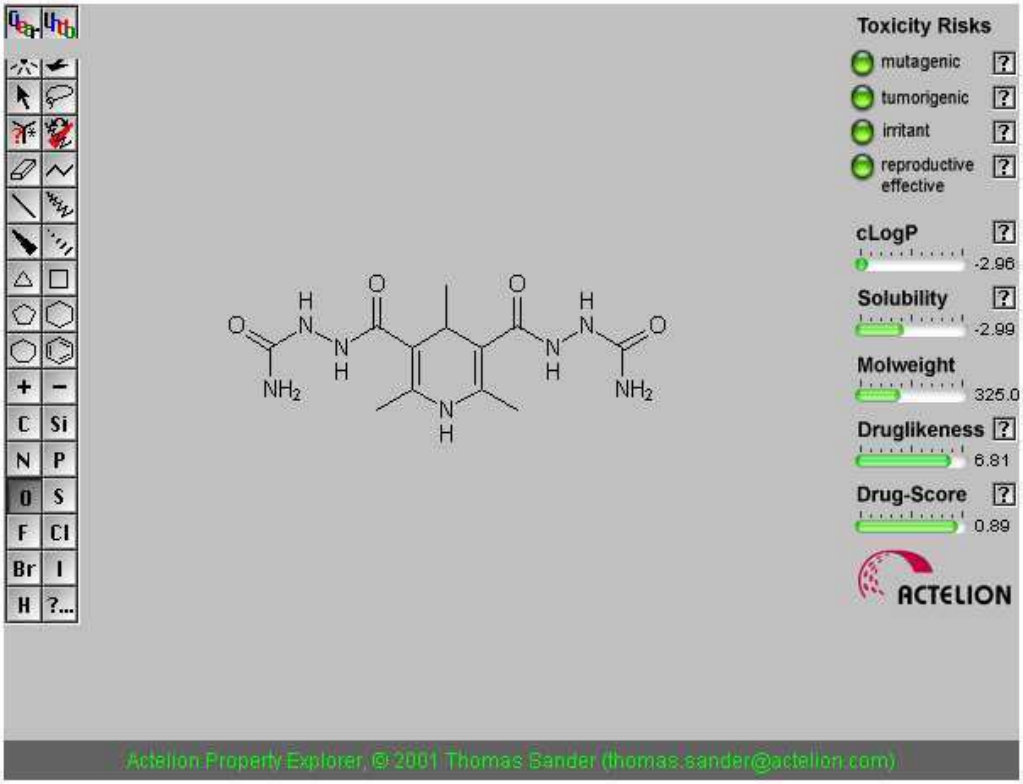
Compound-D1



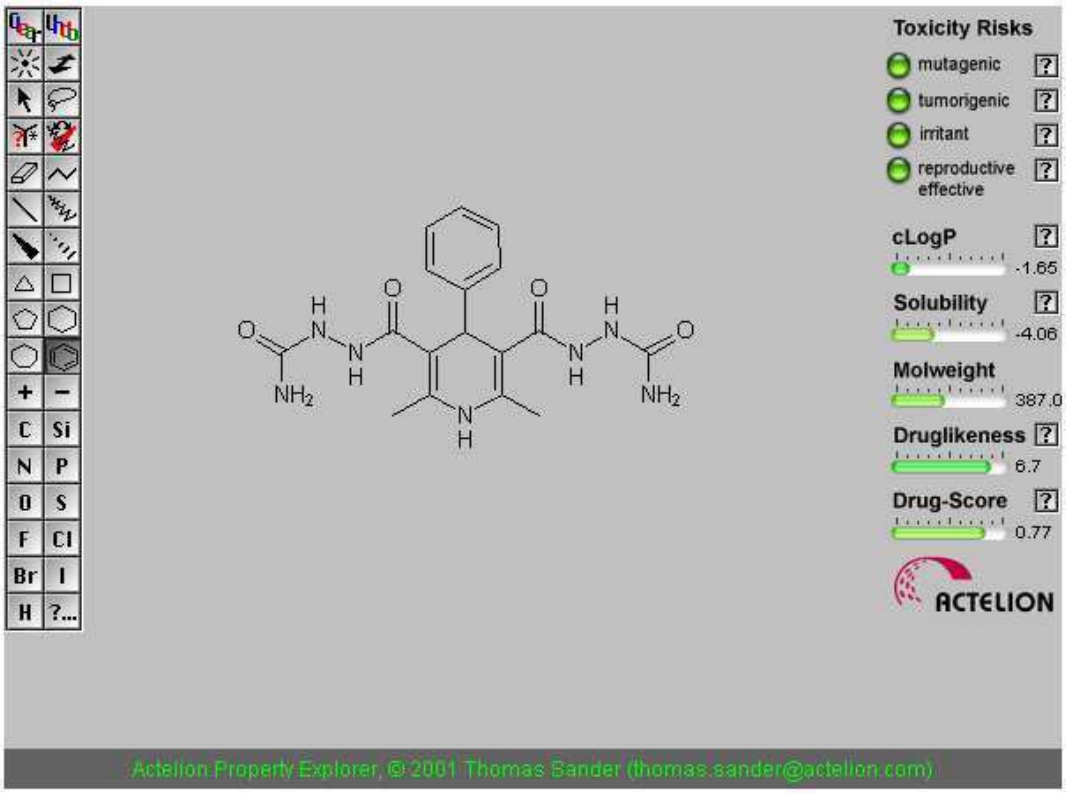
Compound-E1



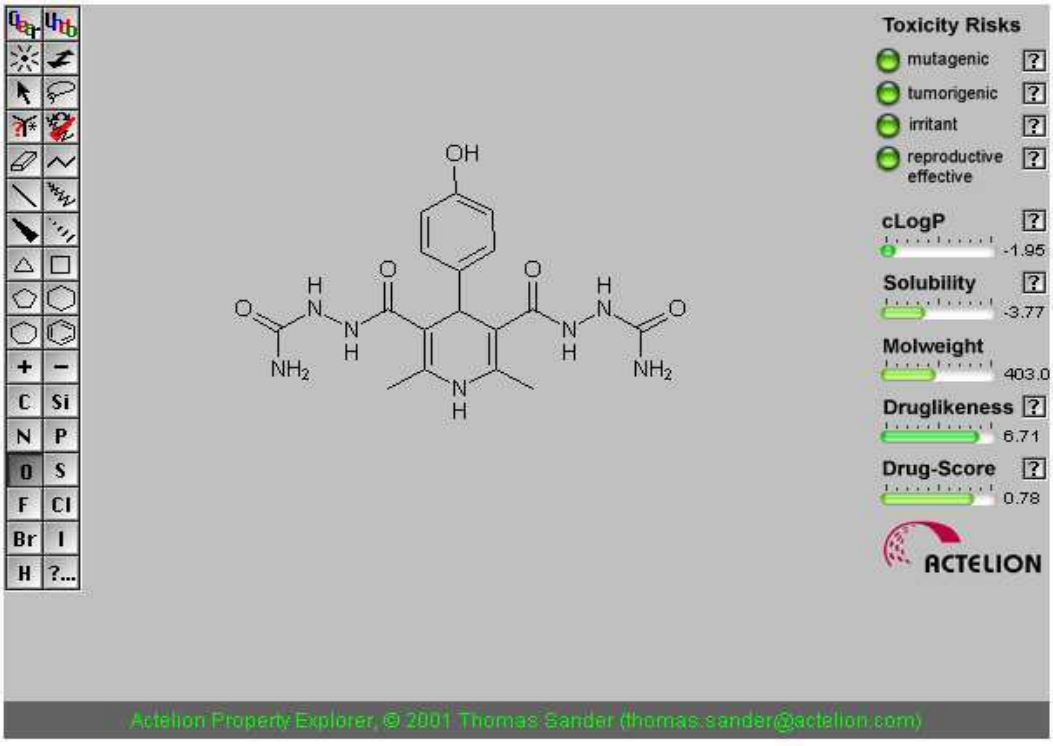
Compound-A2



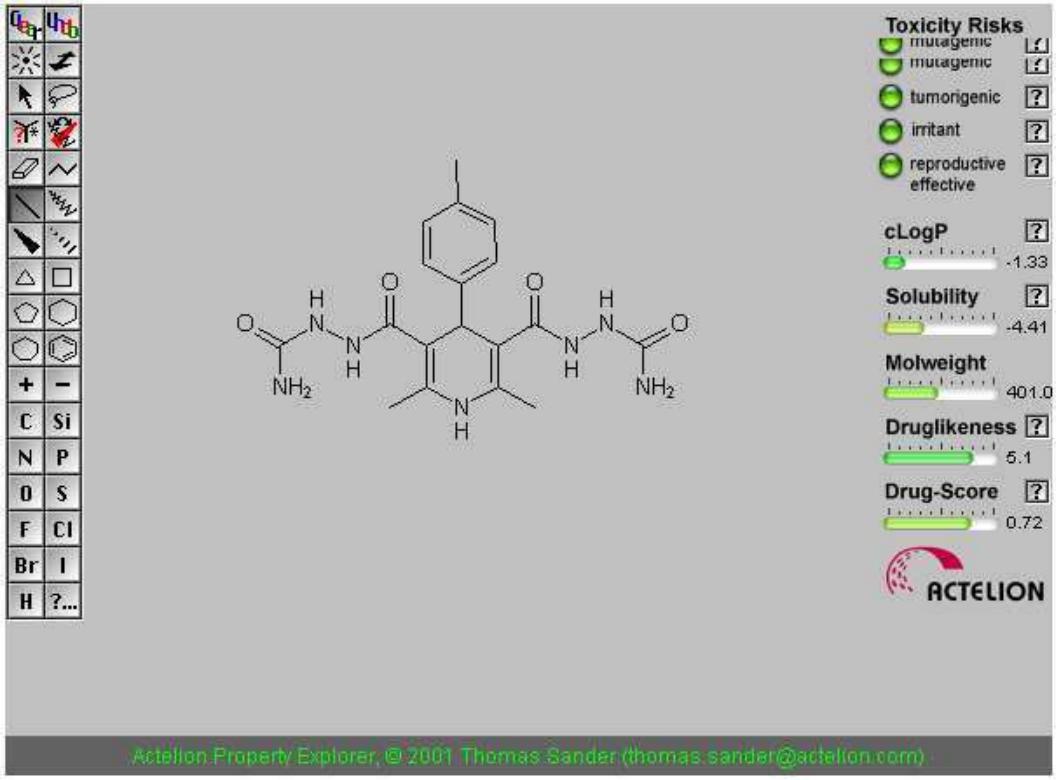
Compound-B2



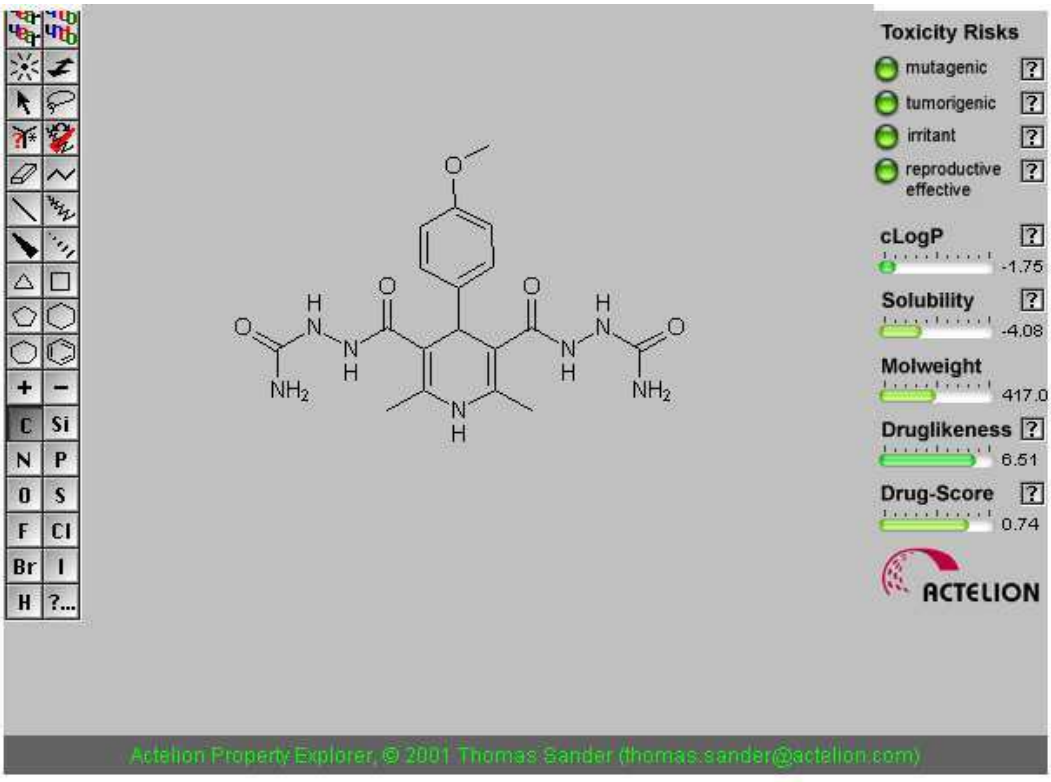
Compound-C2



Compound-D2



Compound-E2



Mol-inspiration

Virtual screening or ***in silico screening*** is the use of computational chemistry techniques to analyze large chemical databases in order to identify possible new drug candidates. Virtual screening techniques range from simple ones, based on the presence or absence of specific substructures, or match in calculated molecular properties, up to sophisticated virtual docking methods aimed at fitting putative ligand molecules into the target receptor site.
Miscreen - a Molinspiration virtual screening engine offers very good balance between screening speed, requirements on information needed to start a new virtual screening project and screening performance.

The miscreen engine first analysis a training set of active structures (in extreme case even single active molecule is sufficient to built a usable model) and compares it with inactive molecules by using sophisticated Bayesian statistics. Only SMILES or SDfile structures of active molecules are sufficient for the training, no information about the active site or binding mode is necessary. This is particularly useful in projects where structure-based approach cannot be applied because information about 3D receptor structure is not available, for example in screens aiming to find ligands modulating G-protein coupled receptors. Based on this analysis a fragment-based model is developed, where for each substructure fragment a bioactivity contribution is calculated. Once a model is build the bioactivity of screened molecules may be then calculated as a sum of activity contributions of fragments in these molecules. This provides a molecule activity score (a number, typically between -3 and 3). Molecules with the highest activity score have the highest

probability to be active. Such *in silico* screening is very fast, large collections of molecules (more than 100'000 molecules) may be screened in an hour.

Molecular property

LogP (octanol/water partition coefficient)

LogP is calculated by the methodology developed by Mol-inspiration as a sum of fragment-based contributions and correction factors. Method is very robust and is able to process practically all organic, and most organometallic molecules.

Molecular Polar Surface Area TPSA

It is calculated based on the methodology as a sum of fragment contributions. O- and N- centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration.

Molecular Volume

Method for calculation of molecule volume developed at Mol-inspiration is based on group contributions. These have been obtained by fitting sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semi-empirical AM1 method.

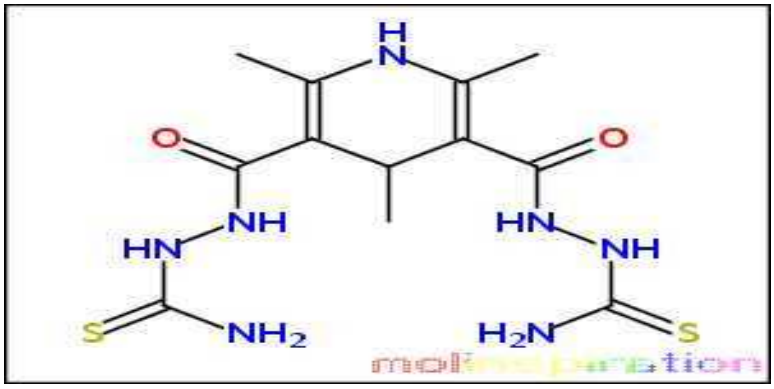
"Rule of 5" Properties

It is set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5" . The rule states, that most "drug-like" molecules have log P <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5",

Number of Rotatable Bonds – nrotb

This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to non terminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

Figure-2: **Compound A1**



miSMILES CC1C(C(=O)NNC(N)=S)=C(C)NC(C)=C1C(=O)NNC(N)=S

Properties

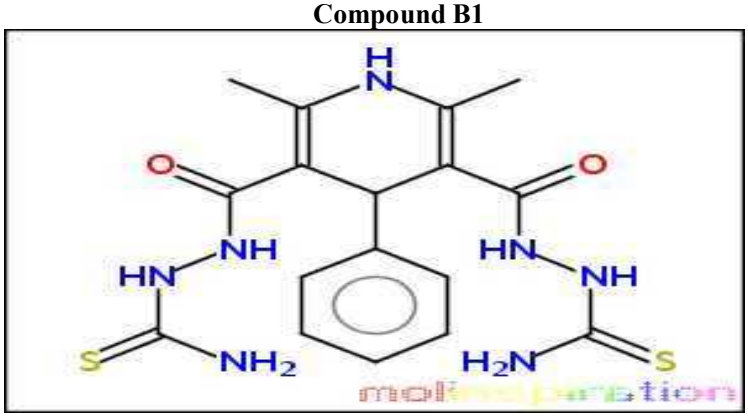
miLogP	-0.047
TPSA	146.323
natoms	23.0
MW	357.465
nON	9
nOHNH	9
nviolations	1
nrotb	6
volume	301.417

Bioactivity score

GPCR ligand	-0.63
Ion channel modulator	-0.62
Kinase inhibitor	-0.86
Nuclear receptor ligand	-0.90
Protease inhibitor	-0.37
Enzyme inhibitor	-0.51

Molecular Formula	= $C_{12}H_{19}N_7O_2S_2$
Formula Weight	= 357.45496
Composition	= C (40.32%) H (5.36%) N (27.43%) O (8.95%) S (17.94%)
Molar Refractivity	= 94.16 ± 0.3 cm^3
Molar Volume	= 256.1 ± 3.0 cm^3
Parachor	= 743.7 ± 6.0 cm^3
Index of Refraction	= 1.656 ± 0.02
Surface Tension	= 71.1 ± 3.0 dyne/cm
Density	= 1.395 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 37.32 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 357.104163 Da
Nominal Mass	= 357 Da
Average Mass	= 357.455 Da
M+	= 357.103614 Da
M-	= 357.104711 Da
[M+H]+	= 358.111439 Da
[M+H]-	= 358.112537 Da
[M-H]+	= 356.095789 Da
[M-H]-	= 356.096886 Da

Compound B1



miSMILES CC2=C(C(=O)NNC(N)=S)C(c1ccccc1)C(C(=O)NNC(N)=S)=C(C)N2

Properties

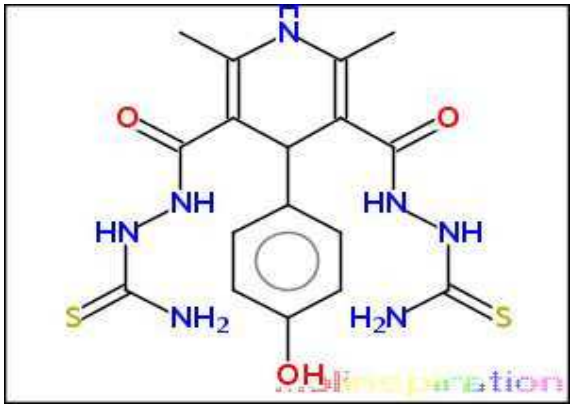
miLogP	1.275
TPSA	146.323
natoms	28.0
MW	419.536
nON	9
nOHNH	9
nviolations	1
nrotb	7
volume	356.264

Bio activity score

GPCR ligand	-0.59
Ion channel modulator	-0.54
Kinase inhibitor	-0.81
Nuclear receptor ligand	-0.81
Protease inhibitor	-0.56
Enzyme inhibitor	-0.47

Molecular Formula	= $C_{17}H_{21}N_7O_2S_2$
Formula Weight	= 419.52434
Composition	= C(48.67%) H(5.05%) N(23.37%) O(7.63%) S(15.29%)
Molar Refractivity	= 113.89 ± 0.3 cm^3
Molar Volume	= 300.3 ± 3.0 cm^3
Parachor	= 877.5 ± 6.0 cm^3
Index of Refraction	= 1.683 ± 0.02
Surface Tension	= 72.9 ± 3.0 dyne/cm
Density	= 1.396 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 45.15 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 419.119813 Da
Nominal Mass	= 419 Da
Average Mass	= 419.5243 Da
M+	= 419.119264 Da
M-	= 419.120362 Da
[M+H]+	= 420.127089 Da
[M+H]-	= 420.128187 Da
[M-H]+	= 418.111439 Da
[M-H]-	= 418.112537 Da

Compound C1



miSMILES CC2=C(C(=O)NNC(N)=S)C(c1ccc(O)cc1)C(C(=O)NNC(N)=S)=C(C)N2

Properties

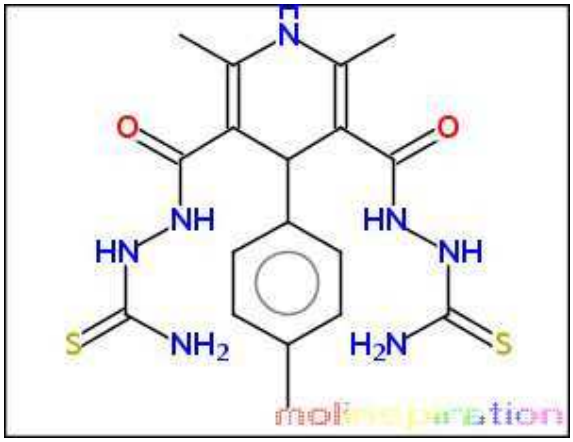
miLogP	0.796
TPSA	166.551
natoms	29.0
MW	435.535
nON	10
nOHNH	10
nviolations	1
nrotb	7
volume	364.282

Bio activity score

GPCR ligand	-0.59
Ion channel modulator	-0.54
Kinase inhibitor	-0.81
Nuclear receptor ligand	-0.81
Protease inhibitor	-0.56
Enzyme inhibitor	-0.47

Molecular Formula	= $C_{17}H_{21}N_7O_3S_2$
Formula Weight	= 435.52374
Composition	= C(46.88%) H(4.86%) N(22.51%) O(11.02%) S(14.72%)
Molar Refractivity	= 115.77 ± 0.3 cm^3
Molar Volume	= 298.7 ± 3.0 cm^3
Parachor	= 892.7 ± 6.0 cm^3
Index of Refraction	= 1.702 ± 0.02
Surface Tension	= 79.7 ± 3.0 dyne/cm
Density	= 1.457 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 45.89 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 435.114728 Da
Nominal Mass	= 435 Da
Average Mass	= 435.5237 Da
M+	= 435.114179 Da
M-	= 435.115276 Da
[M+H]+	= 436.122004 Da
[M+H]-	= 436.123101 Da
[M-H]+	= 434.106354 Da
[M-H]-	= 434.107451 Da

Compound D1



miSMILES CC2=C(C(=O)NNC(N)=S)C(c1ccc(C)cc1)C(C(=O)NNC(N)=S)=C(C)N2

Properties

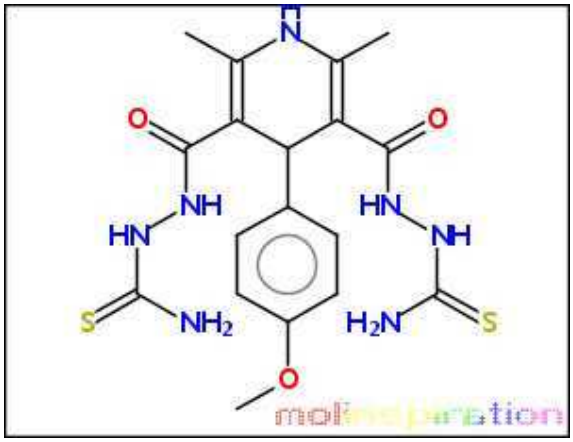
miLogP	1.723
TPSA	146.323
natoms	29.0
MW	433.563
nON	9
nOHNH	9
nviolations	1
nrotb	7
volume	372.825

Bio activity score

GPCR ligand	-0.60
Ion channel modulator	-0.58
Kinase inhibitor	-0.81
Nuclear receptor ligand	-0.81
Protease inhibitor	-0.60
Enzyme inhibitor	-0.50

Molecular Formula	= $C_{18}H_{23}N_7O_2S_2$
Formula Weight	= 433.55092
Composition	= C(49.87%) H(5.35%) N(22.61%) O(7.38%) S(14.79%)
Molar Refractivity	= 118.72 ± 0.3 cm^3
Molar Volume	= 316.5 ± 3.0 cm^3
Parachor	= 915.8 ± 6.0 cm^3
Index of Refraction	= 1.673 ± 0.02
Surface Tension	= 70.0 ± 3.0 dyne/cm
Density	= 1.369 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 47.06 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 433.135463 Da
Nominal Mass	= 433 Da
Average Mass	= 433.5509 Da
M+	= 433.134914 Da
M-	= 433.136012 Da
[M+H]+	= 434.142739 Da
[M+H]-	= 434.143837 Da
[M-H]+	= 432.127089 Da
[M-H]-	= 432.128187 Da

Compound E1



miSMILES COc2ccc(C1C(C(=O)NNC(N)=S)=C(C)NC(C)=C1C(=O)NNC(N)=S)cc2

Properties

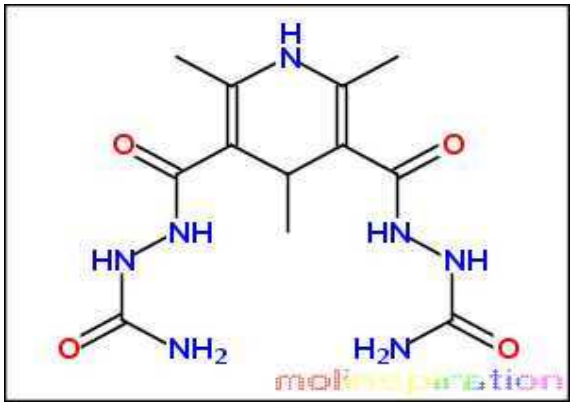
miLogP	1.331
TPSA	155.557
natoms	30.0
MW	449.562
nON	10
nOHNH	9
nviolations	1
nrotb	8
volume	381.81

Bio activity score

GPCR ligand	-0.59
Ion channel modulator	-0.57
Kinase inhibitor	-0.79
Nuclear receptor ligand	-0.77
Protease inhibitor	-0.58
Enzyme inhibitor	-0.48

Molecular Formula	= $C_{18}H_{23}N_7O_3S_2$
Formula Weight	= 449.55032
Composition	= C(48.09%) H(5.16%) N(21.81%) O(10.68%) S(14.27%)
Molar Refractivity	= 120.57 ± 0.3 cm^3
Molar Volume	= 324.3 ± 3.0 cm^3
Parachor	= 936.1 ± 6.0 cm^3
Index of Refraction	= 1.665 ± 0.02
Surface Tension	= 69.4 ± 3.0 dyne/cm
Density	= 1.386 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 47.80 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 449.130378 Da
Nominal Mass	= 449 Da
Average Mass	= 449.5503 Da
M+	= 449.129829 Da
M-	= 449.130926 Da
[M+H]+	= 450.137654 Da
[M+H]-	= 450.138751 Da
[M-H]+	= 448.122004 Da
[M-H]-	= 448.123101 Da

Compound A2



miSMILES CC1C(C(=O)NNC(N)=O)=C(C)NC(C)=C1C(=O)NNC(N)=O

Properties

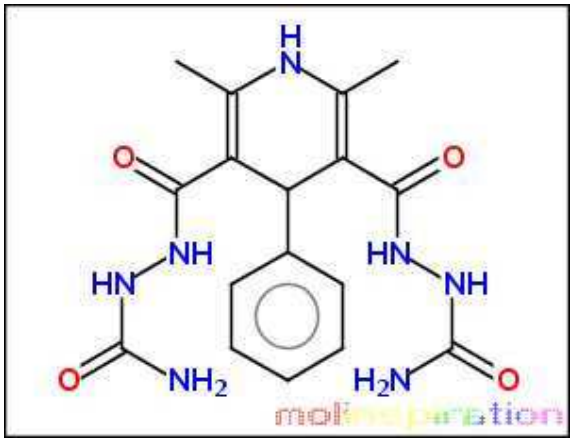
miLogP	-1.129
TPSA	180.465
natoms	23.0
MW	325.329
nON	11
nOHNH	9
nviolations	2
nrotb	4
volume	283.661

Bio activity score

GPCR ligand	-0.22
Ion channel modulator	-0.34
Kinase inhibitor	-0.49
Nuclear receptor ligand	-0.71
Protease inhibitor	-0.23
Enzyme inhibitor	-0.37

Molecular Formula	= $C_{12}H_{19}N_7O_4$
Formula Weight	= 325.32376
Composition	= C(44.30%) H(5.89%) N(30.14%) O(19.67%)
Molar Refractivity	= 79.64 ± 0.3 cm^3
Molar Volume	= 240.3 ± 3.0 cm^3
Parachor	= 660.8 ± 6.0 cm^3
Index of Refraction	= 1.576 ± 0.02
Surface Tension	= 57.1 ± 3.0 dyne/cm
Density	= 1.353 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 31.57 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 325.149852 Da
Nominal Mass	= 325 Da
Average Mass	= 325.3238 Da
M+	= 325.149304 Da
M-	= 325.150401 Da
[M+H]+	= 326.157129 Da
[M+H]-	= 326.158226 Da
[M-H]+	= 324.141478 Da
[M-H]-	= 324.142576 Da

Compound B2



miSMILES CC2=C(C(=O)NNC(N)=O)C(c1ccccc1)C(C(=O)NNC(N)=O)=C(C)N2

Properties

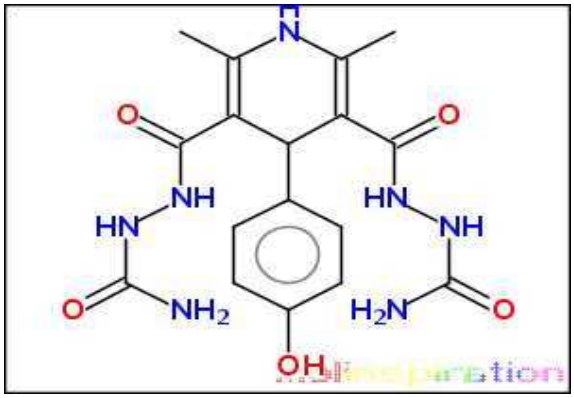
miLogP	0.193
TPSA	180.465
natoms	28.0
MW	387.4
nON	11
nOHNH	9
nviolations	2
nrotb	5
volume	338.508

Bio activity score

GPCR ligand	-0.25
Ion channel modulator	-0.31
Kinase inhibitor	-0.50
Nuclear receptor ligand	-0.65
Protease inhibitor	-0.45
Enzyme inhibitor	-0.35

Molecular Formula	= $C_{17}H_{21}N_7O_4$
Formula Weight	= 387.39314
Composition	= C(52.71%) H(5.46%) N(25.31%) O(16.52%)
Molar Refractivity	= 99.37 ± 0.3 cm^3
Molar Volume	= 284.5 ± 3.0 cm^3
Parachor	= 794.6 ± 6.0 cm^3
Index of Refraction	= 1.615 ± 0.02
Surface Tension	= 60.7 ± 3.0 dyne/cm
Density	= 1.361 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 39.39 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 387.165502 Da
Nominal Mass	= 387 Da
Average Mass	= 387.3931 Da
M+	= 387.164954 Da
M-	= 387.166051 Da
[M+H]+	= 388.172779 Da
[M+H]-	= 388.173876 Da
[M-H]+	= 386.157129 Da
[M-H]-	= 386.158226 Da

Compound C2



miSMILES CC2=C(C(=O)NNC(N)=O)C(c1ccc(O)cc1)C(C(=O)NNC(N)=O)=C(C)N2

Properties

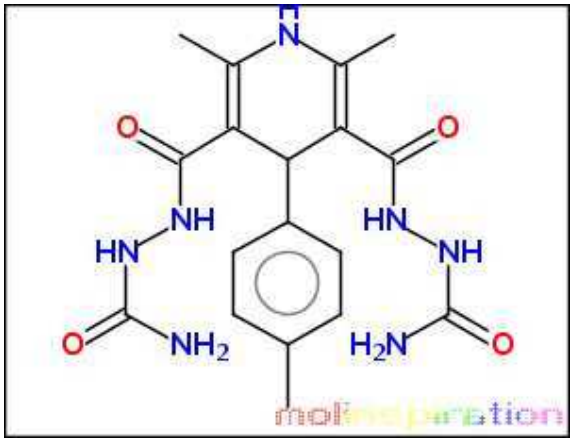
miLogP	-0.286
TPSA	200.693
natoms	29.0
MW	403.399
nON	12
nOHNH	10
nviolations	2
nrotb	5
volume	346.526

Bio activity score

GPCR ligand	-0.21
Ion channel modulator	-0.26
Kinase inhibitor	-0.45
Nuclear receptor ligand	-0.51
Protease inhibitor	-0.43
Enzyme inhibitor	-0.30

Molecular Formula	= $C_{17}H_{21}N_7O_5$
Formula Weight	= 403.39254
Composition	= C(50.62%) H(5.25%) N(24.31%) O(19.83%)
Molar Refractivity	= 101.26 ± 0.3 cm^3
Molar Volume	= 282.9 ± 3.0 cm^3
Parachor	= 809.8 ± 6.0 cm^3
Index of Refraction	= 1.634 ± 0.02
Surface Tension	= 67.0 ± 3.0 dyne/cm
Density	= 1.425 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 40.14 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 403.160417 Da
Nominal Mass	= 403 Da
Average Mass	= 403.3925 Da
M+	= 403.159868 Da
M-	= 403.160965 Da
[M+H]+	= 404.167693 Da
[M+H]-	= 404.16879 Da
[M-H]+	= 402.152043 Da
[M-H]-	= 402.15314 Da

Compound D2



miSMILES CC2=C(C(=O)NNC(N)=O)C(c1ccc(C)cc1)C(C(=O)NNC(N)=O)=C(C)N2

Properties

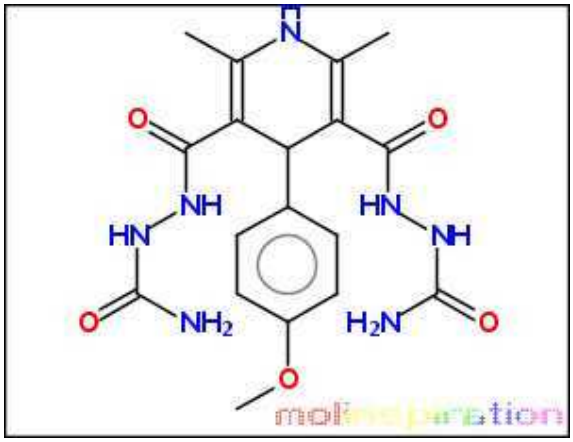
miLogP	0.642
TPSA	180.465
natoms	29.0
MW	401.427
nON	11
nOHNH	9
nviolations	2
nrotb	5
volume	355.069

Bio activity score

GPCR ligand	-0.28
Ion channel modulator	-0.36
Kinase inhibitor	-0.52
Nuclear receptor ligand	-0.65
Protease inhibitor	-0.49
Enzyme inhibitor	-0.39

Molecular Formula	= $C_{18}H_{23}N_7O_4$
Formula Weight	= 401.41972
Composition	= C(53.86%) H(5.78%) N(24.43%) O(15.94%)
Molar Refractivity	= 104.20 ± 0.3 cm^3
Molar Volume	= 300.8 ± 3.0 cm^3
Parachor	= 832.8 ± 6.0 cm^3
Index of Refraction	= 1.609 ± 0.02
Surface Tension	= 58.7 ± 3.0 dyne/cm
Density	= 1.334 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 41.30 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 401.181152 Da
Nominal Mass	= 401 Da
Average Mass	= 401.4197 Da
M+	= 401.180604 Da
M-	= 401.181701 Da
[M+H]+	= 402.188429 Da
[M+H]-	= 402.189526 Da
[M-H]+	= 400.172779 Da
[M-H]-	= 400.173876 Da

Compound E2



miSMILES COc2ccc(C1C(C(=O)NNC(N)=O)=C(C)NC(C)=C1C(=O)NNC(N)=O)cc2

Properties

miLogP	0.25
TPSA	189.699
natoms	30.0
MW	417.426
nON	12
nOHNH	9
nviolations	2
nrotb	6
volume	364.054

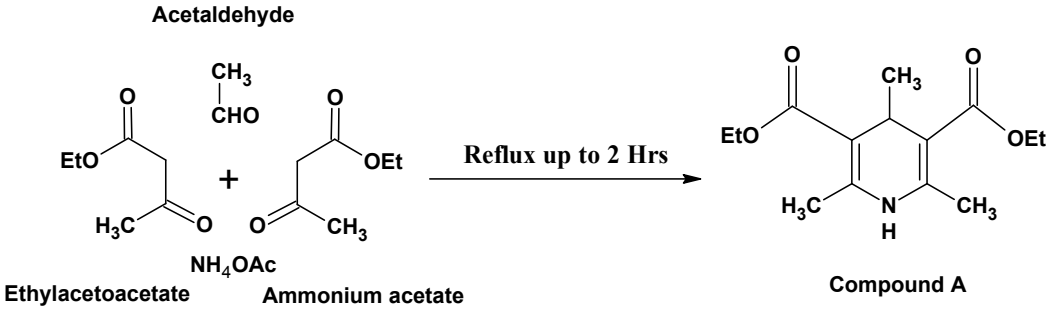
Bio activity score

GPCR ligand	-0.27
Ion channel modulator	-0.35
Kinase inhibitor	-0.50
Nuclear receptor ligand	-0.62
Protease inhibitor	-0.47
Enzyme inhibitor	-0.37

Molecular Formula	= $C_{18}H_{23}N_7O_5$
Formula Weight	= 417.41912
Composition	= C(51.79%) H(5.55%) N(23.49%) O(19.16%)
Molar Refractivity	= 106.05 ± 0.3 cm^3
Molar Volume	= 308.5 ± 3.0 cm^3
Parachor	= 853.2 ± 6.0 cm^3
Index of Refraction	= 1.603 ± 0.02
Surface Tension	= 58.4 ± 3.0 dyne/cm
Density	= 1.352 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 42.04 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 417.176067 Da
Nominal Mass	= 417 Da
Average Mass	= 417.4191 Da
M+	= 417.175518 Da
M-	= 417.176615 Da
[M+H]+	= 418.183343 Da
[M+H]-	= 418.184441 Da
[M-H]+	= 416.167693 Da
[M-H]-	= 416.16879 Da

Molecular synthesis

Synthesis of Compound A



Chemicals Required

Ethylacetoacetate -0.2 mole

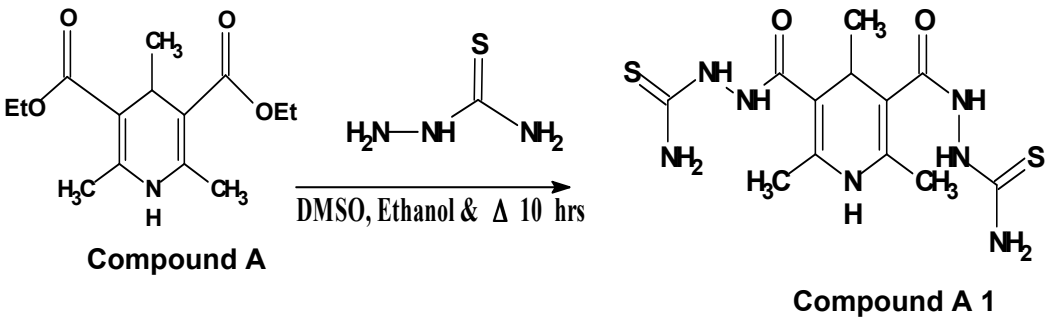
Ammonium acetate -0.1 mole

Acetaldehyde -0.1 mole

Procedure

A reaction mixture was made up of ethylacetoacetate (0.2 mol), Ammonium acetate(0.1 mol) acetaldehyde(0.1 mol) in ethanol. It was then heated refluxed for 2 hr. The obtained solid was filter off, and washed with water and purified by recrystalisation from absolute ethanol.

Synthesis of Compound A1



Chemicals Required

Compound A - 0.1 mole

Thiosemicarbazide - 0.1 mole

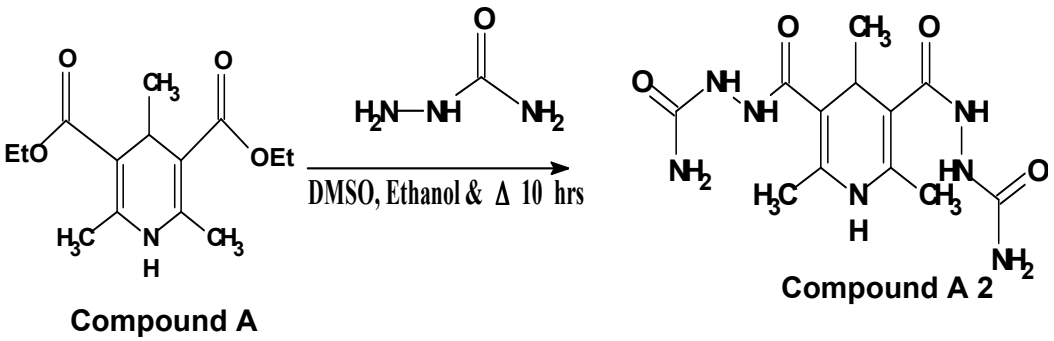
DMSO - 5 ml

Ethanol - 10ml

Procedure

Equal molar weight of compound A and thiosemicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound A2



Compound A

Compound A 2

Chemicals Required

Compound A - 0.1 mole

Semicarbazide - 0.1 mole

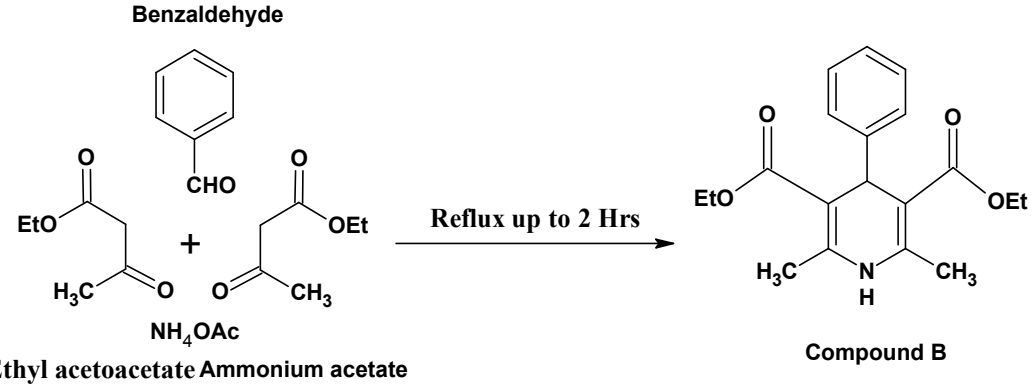
DMSO - 5 ml

Ethanol - 10ml

Procedure

Equal molar weight of compound A and semicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound B



Chemicals Required

Ethylacetoacetate -0.2 mole

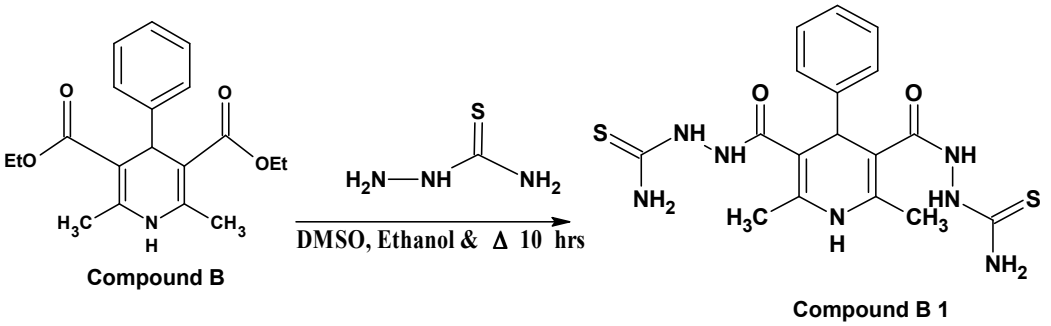
Ammonium acetate -0.1 mole

Benzaldehyde -0.1 mole

Procedure

A reaction mixture was made up of ethylacetoacetate (0.2 mol), Ammonium acetate(0.1 mol) benzaldehyde (0.1 mol) in ethanol. It was then heated refluxed for 2 hr. The obtained solid was filter off, and washed with water and purified by recrystalisation from absolute ethanol.

Synthesis of Compound B1



Chemicals Required

Compound B - 0.1 mole

Thiosemicarbazide - 0.1 mole

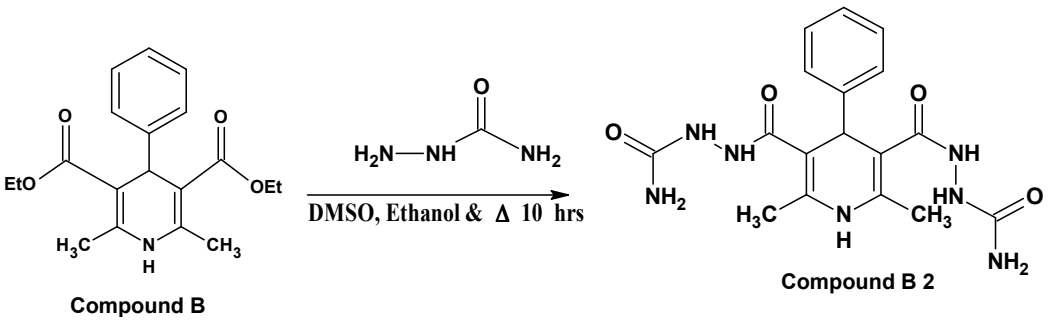
DMSO - 5 ml

Ethanol - 10ml

Procedure

Equal molar weight of compound A and thiosemicarbaside dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound B2



Chemicals Required

Compound B - 0.1 mole

Semicarbazide - 0.1 mole

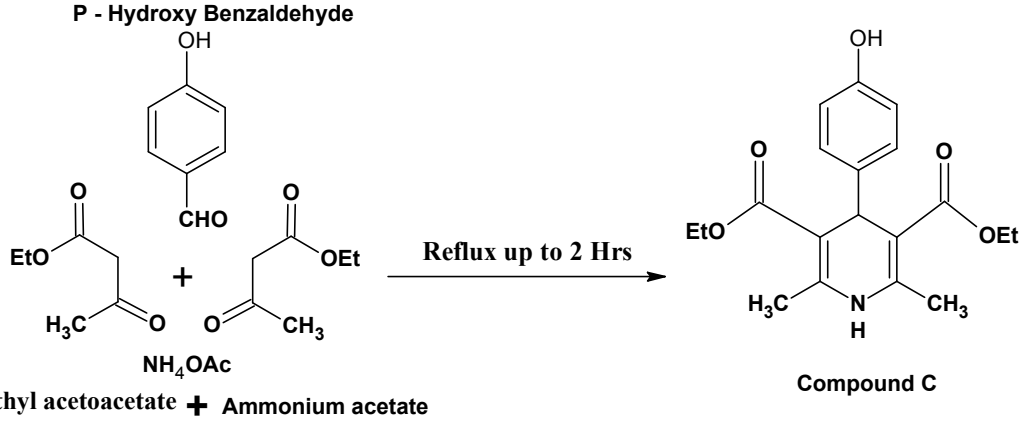
DMSO - 5 ml

Ethanol - 10ml

Procedure

Equal molar weight of compound B and semicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound C



Chemicals Required

Ethylacetoacetate -0.2 mole

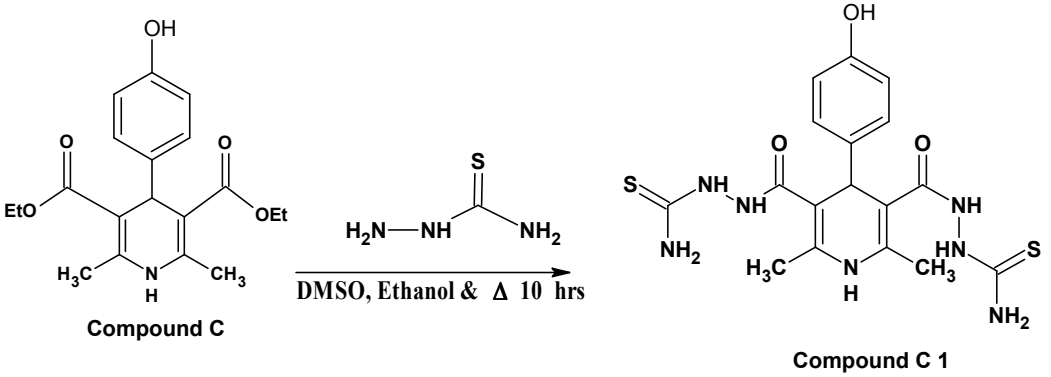
Ammonium acetate -0.1 mole

Para- Hydroxy Benzaldehyde -0.1 mole

Procedure

A reaction mixture was made up of ethylacetoacetate (0.2 mol), Ammonium acetate(0.1 mol) Para hydroxyl benzaldehyde (0.1 mol) in ethanol. It was then heated refluxed for 2 hr. The obtained solid was filter off, and washed with water and purified by recrystalisation from absolute ethanol.

Synthesis of Compound C1



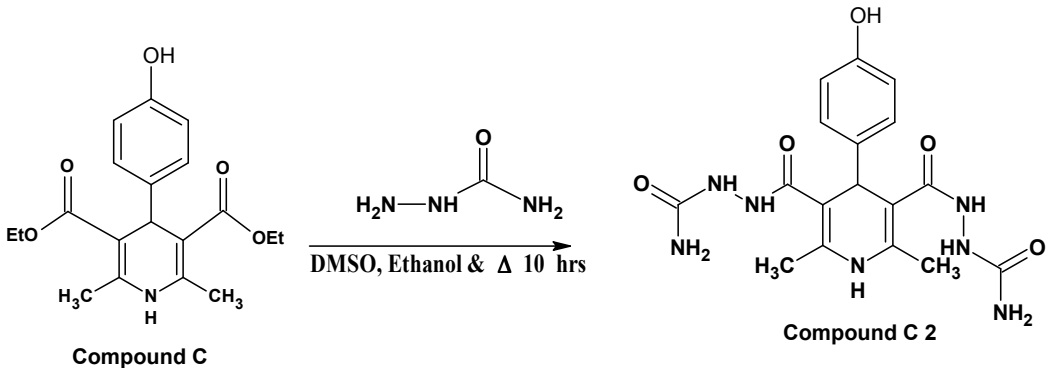
Chemicals Required

Compound C	- 0.1 mole
Thiosemicarbazide	- 0.1 mole
DMSO	- 5 ml
Ethanol	- 10ml

Procedure

Equal molar weight of compound C and thiosemicarbaside dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound C2



Chemicals Required

Compound C - 0.1 mole

Semicarbazide - 0.1 mole

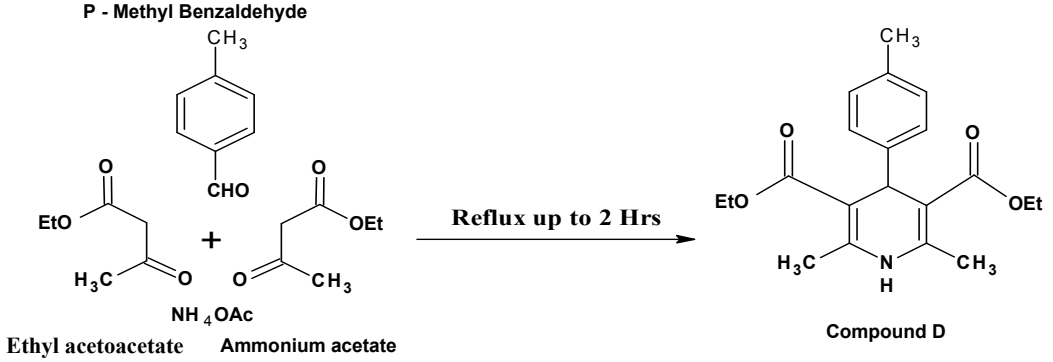
DMSO - 5 ml

Ethanol - 10ml

Procedure

Equal molar weight of compound C and semicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound D



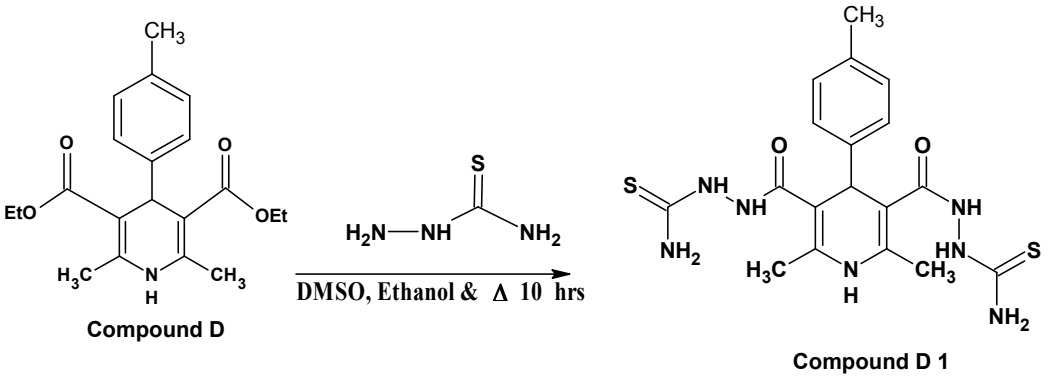
Chemicals Required

Ethylacetoacetate	-0.2 mole
Ammonium acetate	-0.1 mole
Para- Methyl Benzaldehyde	-0.1 mole

Procedure

A reaction mixture was made up of ethylacetoacetate (0.2 mol), Ammonium acetate(0.1 mol) paramethyl benzaldehyde (0.1 mol) in ethanol. It was then heated refluxed for 2 hr. The obtained solid was filter off, and washed with water and purified by recrystalisation from absolute ethanol.

Synthesis of Compound D1



Compound D

Compound D 1

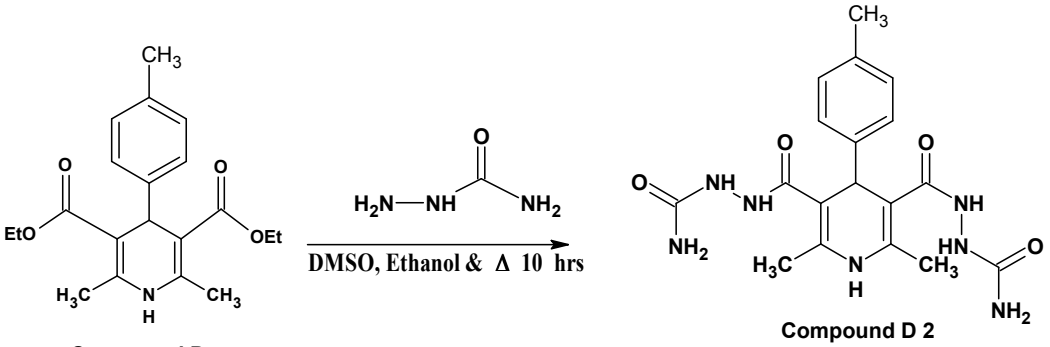
Chemicals Required

Compound D	- 0.1 mole
Thiosemicarbazide	- 0.1 mole
DMSO	- 5 ml
Ethanol	- 10ml

Procedure

Equal molar weight of compound D and thiosemicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound D2



Compound D

Compound D 2

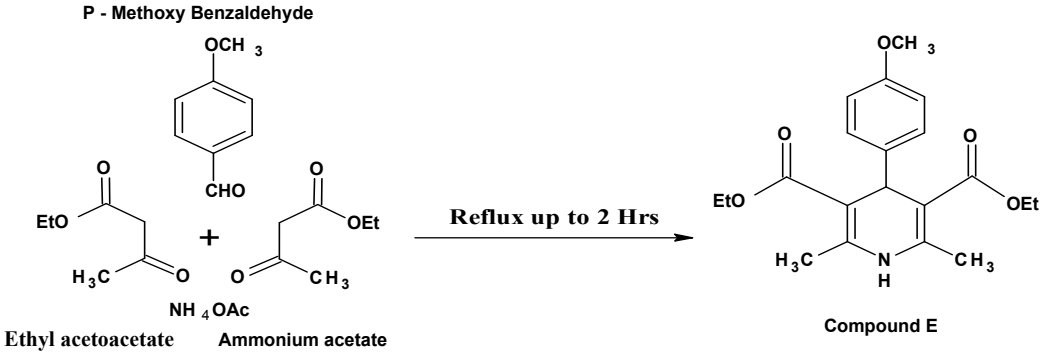
Chemicals Required

Compound D	- 0.1 mole
Semicarbazide	- 0.1 mole
DMSO	- 5 ml
Ethanol	- 10ml

Procedure

Equal molar weight of compound A and semicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound E



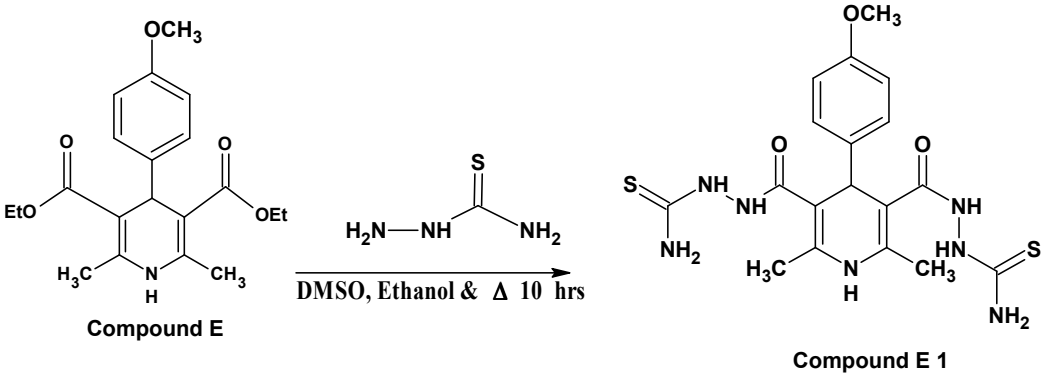
Chemicals Required

Ethylacetoacetate	-0.2 mole
Ammonium acetate	-0.1 mole
Para- Methoxy Benzaldehyde	-0.1 mole

Procedure

A reaction mixture was made up of ethylacetoacetate (0.2 mol), Ammonium acetate(0.1 mol) para-methoxy benzaldehyde (0.1 mol) in ethanol. It was then heated refluxed for 2 hr. The obtained solid was filter off, and washed with water and purified by recrystalisation from absolute ethanol.

Synthesis of Compound E1



Chemicals Required

Compound E - 0.1 mole

Thiosemicarbazide - 0.1 mole

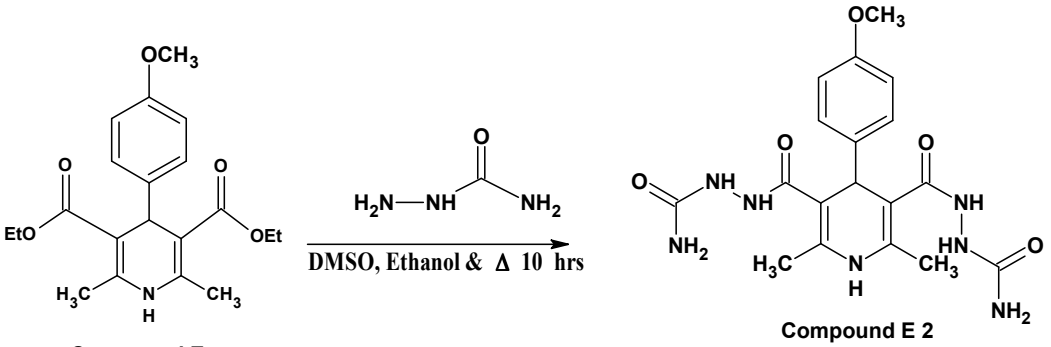
DMSO - 5 ml

Ethanol - 10ml

Synthesis

Equal molar weight of compound E and thiosemicarbaside dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Synthesis of Compound E2



Chemicals Required

Compound E - 0.1 mole

Semicarbazide - 0.1 mole

DMSO - 5 ml

Ethanol - 10ml

Procedure:

Equal molar weight of compound E and semicarbazide dissolved in ethanol then add 5 ml of DMSO. It was the heated under reflux for 10 hr. The solid was obtained, after cool and pour it into crushed ice. The solid was collected by filtration, washed with water and purified by re-crystallization with ethanol.

Thin layer Chromatography

Purity of the compounds was checked by thin layer chromatography using silica gel G as stationary phase and various combinations of ethyl acetate and chloroform (2:1) mobile phase. The spots resolved were visualized in UV chamber or Iodine vapour.

Instrumentation:

The techniques employed for the characterization of the synthesized compounds were IR spectra, ^{1}H-NMR spectra, Mass spectra.

Infrared Spectra:

The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (Perkin-Elmer) in the range of 4000 – 450 cm^{-1} Nujol mull technique and the values are reported.

Nuclear Magnetic Resonance Spectra (^{1}H-NMR):

^{1}H-NMR spectra were recorded on Bruker – NMR 400 MHz using $(CD_3)_2SO$ and chemical shifts were reported in parts per million (δ ppm).

Mass Spectra- m/e peak.

Biological Evaluation

Biological Evaluation

Anti-Diabetic action

The study was done in the Central animal house , Madurai Medical College, Madurai after getting approval by Institutional Animal Ethical Committee of Madurai Medical College, Madurai, for a period of 3 months.

Animals

Inbred *male albino rats* from central animal house Madurai Medical College were utilized in this study. Each weighing 200 to 250 grams were included in the study. Animals were allowed standard diet and tap water *ad libitum*.

Each group of animals were housed separately with a distinct identity for each animal throughout the study. The diabetic rats were given special care. The floor of cages were filled with thick layer of sawdust and it was changed daily. The diabetic rats were given adequate food pellets and plenty of water by providing two water bottles as the diabetic rats will have polyphagia, polyuria and polydipsia. The bottles were filled with fresh tap water every morning.

Oral acute toxicity studies

Acute toxicity study is generally carried out for the determination of LD50 value in experimental animals. The LD50 determination was done in mice by OECD guidelines 423. The aim of performing acute toxicity study is for establishing the therapeutic index of a particular drug and to ensure the safety *in vivo*.

Table-5: Compound : C1

S. No	Number of animals	Dose	No. of death of animals
1	3	5 mg/kg	0
2	3	50 mg/kg	0
3	3	300 mg/kg	0
4	3	1000 mg/kg	2*

*Dose is repeated to confirm LD_{50}

Table-6: Compound : D1

S. No	Number of animals	Dose	No. of death of animals
1	3	300 mg/kg	0
2	3	1000 mg/kg	2*

*Dose is repeated to confirm LD_{50}

Table-7 Physiology of animals

Parameter			
	Animal No:1	Animal No:2	Animal No:3
Eye ball movement	+	+	+
Salivation	-	-	-
Muscle strength	+	+	+
Diarrhea	-	-	-
Frequent urination	-	-	-
Farness	-	-	-
Body temperature	Optimum	Optimum	Optimum
Respiration	Normal	Normal	Normal
vagueness	-	-	-
hyperactive	+	-	+
Insomnia	-	-	-
Nasal discharge	+	-	-

Hypoglycemic activity:

Materials used for the study

1. Male Albino Rats
2. Alloxan Monohydrate
3. Glibenclamide (Sonafi- Aventis)
4. Synthetic drug (1,4 DHP derivatives)
5. Carboxy Methyl Cellulose (CMC 1% solution)
6. Blood glucometer and glucostrips (Acu-Check Active)
7. Oral feeding tube with syringe.

Experimental Design

Each group consisting of six rats.

Group I - Control rats received vehicle solution (1% CMC)

Group II - Diabetic control rats received vehicle solution (1%CMC)

Group III & IV- Diabetic rats treated with Compound-C1, 50 & 100mg/kg body weight in (1% CMC), respectively

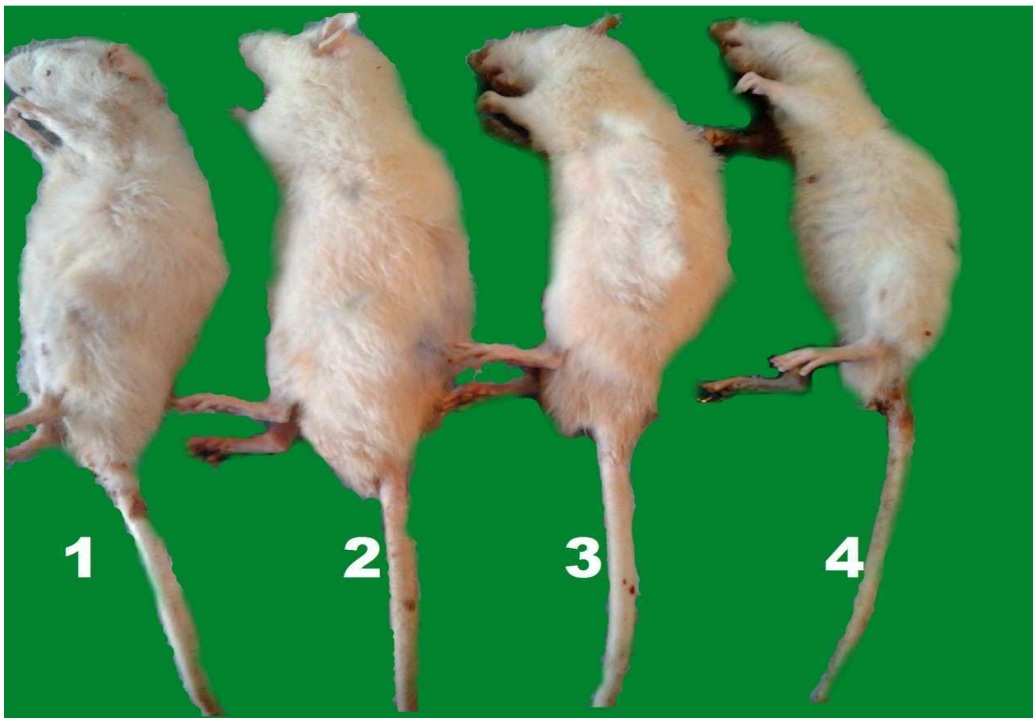
Group V & VI- Diabetic rats treated with Compound-D1, 50 & 100mg/kg body weight in (1% CMC), respectively

Group VII - Diabetic rats treated with standard drug Glibenclamide 0.25 mg/kg body weight in aqueous solution.

The vehicles and the drugs were administered orally using oral intubation tube daily for three weeks. Blood samples were collected for the measurement of blood glucose level from the tail vein on 0 day, 2^{nd} , 5^{th} and 7^{th} day. The blood glucose level was determined by glucometer (one touch). The values of sample treated were compared with that of the standard group which was treated with Glibenclamide. Then the animals were sacrificed by cervical dislocation.

The collected blood samples were immediately centrifuged at 2500 rpm for 15 min. The serum separated and analyzed by using auto analyzer.

Diabetic Induced Rat



S. No	Groups
1	Drug C1
2	Drug D1
3	Standard
4	Positive control

***In vitro* Evaluation of Antibacterial Activity of Synthesized Compounds:**

Preliminary Antibacterial & Antifungal Activity:

Evaluation Methods:

The antibacterial activity can be evaluated by the following techniques.

a) Agar streak dilution method

b) Serial dilution method

c) Agar diffusion method

(i) Cup plate method

(ii) Cylinder method

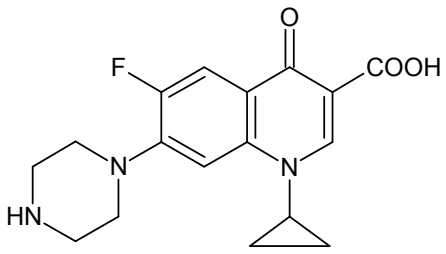
(iii) Paper disc method

d) Turbidimetry method

Diffusion technique is widely used to carry out sensitivity test for pathogenic microorganism. Literature reviews reveals that substituted 1, 4 DHPs exhibited pronounced antimicrobial activity. The antimicrobial activity was evaluated by measuring the zone of inhibition in mm.

This test shows an idea about the usefulness of different antimicrobial agents when used at the usual therapeutic doses. It gave a very approximate measure of the degree of sensitivity, when compared to the standard.

Bacteria- Standard Drug Selection:



Ciprofloxacin

Ciprofloxacin:

Chemically it is 1-cyclopropyl-6-fluro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid.

- ✓ It is used as a prototype drug against wide range of microorganism
- ✓ It is a broad spectrum antibiotic

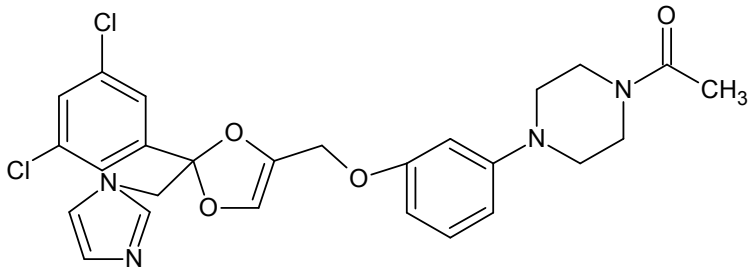
Mechanism:

The fluroquinolines are rapidly bactericidal as a consequence of inhibition of DNA gyrase and Topoisomerase IV. It is important for gram positive and DNA gyrase is important for gram negative bacteria.

Advantages:

- ❖ Rapid bactericidal activity and high potency
- ❖ Long post antibiotic effect on entrobacteriaceae
- ❖ Low frequency of mutation
- ❖ Active against many β-lactam and aminogycoside resistant bacteria.

Fungal - Standard Drug Used:



Ketaconazole

Ketoconazole (KTZ):

1. It is an imidazole derivative
2. It is a broad spectrum anti fungal agent (or) antibiotic

Mechanism:

They inhibit the fungal cytochrome P450 enzyme lanosterol 14-demethylase and thus impair ergosterol synthesis leading to a cascade of membrane abnormalities in the fungus.

Advantages

- ∇ Both orally and topically used
- ∇ Less toxicity
- ∇ Greater efficacy
- ∇ Alternative to griseofulvin

Organisms Used:

Gram Positive Organism:

- *Staphylococcus epidermidis*
- *Streptococcus aurus*
- *Streptococcus albus*

Gram Negative Organism:

- *Escherichia coli*
- *Proteus*
- *Salmonellatyphi*
- *Shigella*
- *Chromobacterium violaceum*
- *Xanthomonas*

Fungai:

- *Candida albicans*

Solvent- DMSO

Bacterial Medium- Nutrient Agar Medium (pH: 7.6 ± 0.2)

Composition:

1. Beef extract - 10 gm
2. Peptone - 10 gm
3. Sodium chloride - 5 gm
4. Agar - 1-2 %
5. Water - 100 ml

Procedure

All the ingredients mixed together and dissolve with 100 ml of distilled water in conical flask. The PH was adjusted 7.6 ± 0.2 and sterilized in an autoclave at 120ºC for 15 min.

Fungal medium- Sabouraud dextrose agar media (pH: 5.6±0.2)

1. Dextrose - 4 gm
2. Mixture of equal part of (Digest animal tissue + Pancreatic digest of casein) - 1 gm
3. Agar - 1.5 gm
4. Water - 100 ml

Procedure

All the ingredients mixed together and dissolve with 100 ml of distilled water in conical flask. The PH was adjusted 5.6±0.2 and sterilized in an autoclave at 120ºC for 15 min.

Experimental Procedure

A suspension of the micro-organism was added to sterile nutrient agar medium at 45^{o}C. The mixture was transferred to sterile petri dishes and allowed to solidify. Sterile disc 5 mm in diameter made from Whatmann No.1 filter paper which is previously sterilized in UV lamp was dipped in solution of different concentrations of compound, standard and a blank were placed on the surface of agar plates.

The plates to keep for 1 h at room temperature as a period of pre-incubation to minimize the effects of variation in time between the applications of the different solutions. Then the plate were incubated for 24 h (for *Candida albicans* 48 h) at 37 ± 1^{o}C and observed for antibacterial activity. The diameter of zone of inhibition was observed and recorded.

Results
&
Discussion

Results & Discussion

Table:8

Comp	Molecular weight	Log P	Drug Likeness	Drug Score
A1	357.465	-0.047	6.34	0.86
B1	419.536	1.275	6.22	0.72
C1	435.53	0.796	6.25	0.73
D1	433.56	1.723	4.63	0.67
E1	449.56	1.331	6.07	0.69
A2	325.32	-1.129	6.81	0.89
B2	387.40	0.193	6.70	0.77
C2	403.39	-0.286	6.71	0.78
D2	401.42	0.642	5.1	0.72
E2	417.41	0.25	6.51	0.74

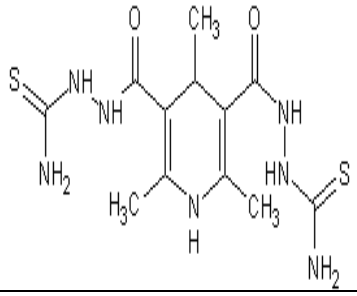
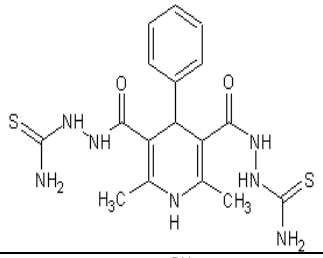
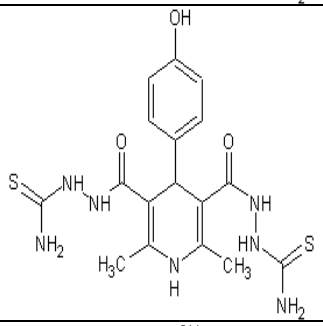
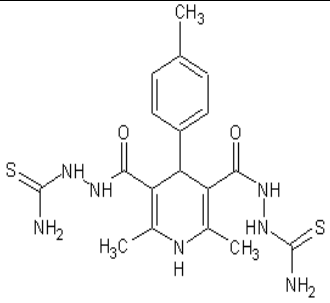
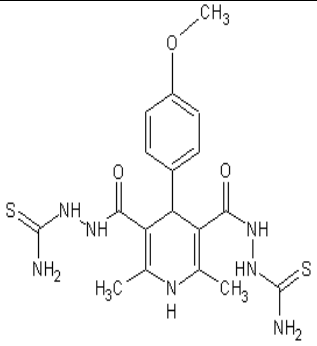
Table 9: Lipinski properties of the synthesized compounds

Comp	Molecular weight	Log P	H bond donor	H bond acceptor	Molar refractivity	Number of criteria met
rule	***< 500***	***<5***	***<5***	***<10***	***40-130***	***At least 3***
A1	357.465	-0.047	9	9	94.16	4
B1	419.536	1.275	9	9	113.89	4
C1	435.53	0.796	10	10	115.77	4
D1	433.56	1.723	9	9	118.72	4
E1	449.56	1.331	9	10	120.57	4
A2	325.32	-1.129	9	11	79.64	3
B2	387.40	0.193	9	11	99.37	3
C2	403.39	-0.286	10	12	101.26	3
D2	401.42	0.642	9	11	104.20	3
E2	417.41	0.25	9	12	106.05	3

Table-10: Analytical Data for compounds

Compound	Nature of the crystals	% yield	Melting Point(^{0}C)	Soluble in	Molecular Formula	Molecular weight
A1	White solid	73	210	DMSO	$C_{12}H_{19}N_7O_2S_2$	357.45
B1	White solid	78	220	DMSO	$C_{17}H_{21}N_7O_2S_2$	419.52
C1	White solid	74	211	DMSO	$C_{17}H_{21}N_7O_3S_2$	435.52
D1	White solid	62	240	DMSO	$C_{18}H_{23}N_7O_2S_2$	433.55
E1	White solid	59	201	DMSO	$C_{18}H_{23}N_7O_3S_2$	449.55
A2	Yellowish Gummy solid	65	190	DMSO	$C_{12}H_{19}N_7O_4$	325.32
B2	Yellowish Gummy solid	61	197	DMSO	$C_{17}H_{21}N_7O_4$	387.39
C2	Yellowish Gummy solid	69	191	DMSO	$C_{17}H_{21}N_7O_5$	403.39
D2	Yellowish Gummy solid	66	187	DMSO	$C_{18}H_{23}N_7O_4$	401.41
E2	Brown solid	67	220	DMSO	$C_{18}H_{23}N_7O_5$	417.44

Table:11 List of synthesized Compounds its IUPAC Name

S. NO	Compounds	IUPAC Name
A1		2,2'-[(2,4,6-trimethyl-1,4-dihydropyridine-3,5diyl) dicarbonyl] dihydrazine carbothioamide
B1		2,2'-[(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5 diyl) dicarbonyl] dihydrazine carbothioamide
C1		2,2'-{[4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazine carbothioamide
D1		2,2'-{[4-(4-methyl phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl] dicarbonyl} dihydrazinecarbothioamide
E1		2,2'-{[4-(4-methoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5diyl]dicarbonyl} dihydrazine carbothioamide

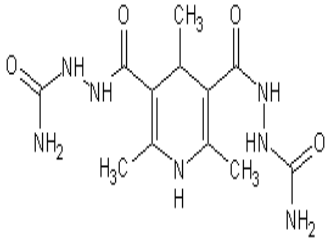
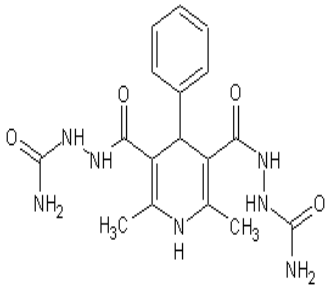
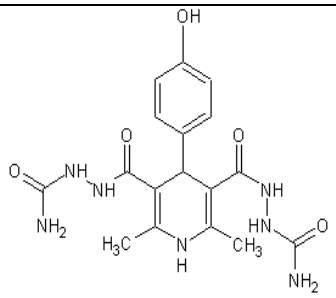
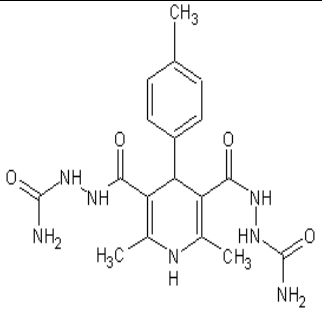
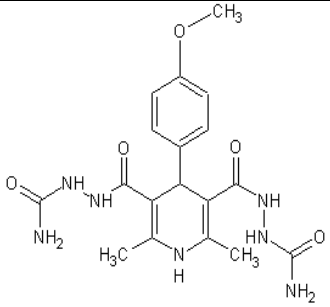
S.No	Compounds	IUPAC Name
A2		2,2'-[(2,4,6-trimethyl-1,4-dihydropyridine-3,5-diyl)dicarbonyl]dihydrazinecarboxamide
B2		2,2'-[(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)dicarbonyl]dihydrazinecarboxamide
C2		2,2'-{[4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl}dihydrazinecarboxamide
D2		2,2'-{[4-(4-methyl phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl}dihydrazinecarboxamide
E2		2,2'-{[4-(4-methoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarboxamide

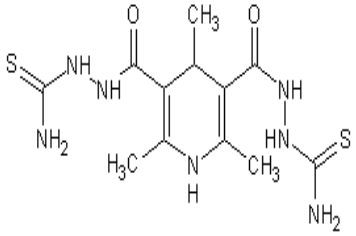
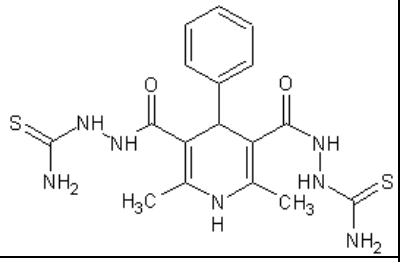
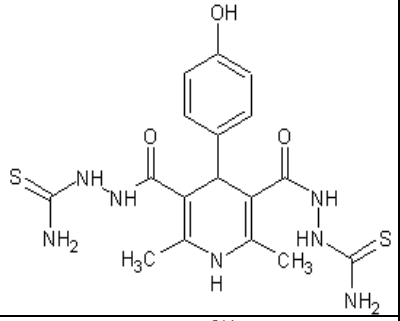
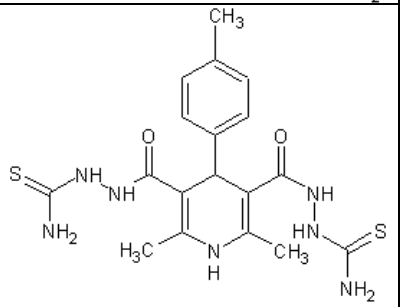
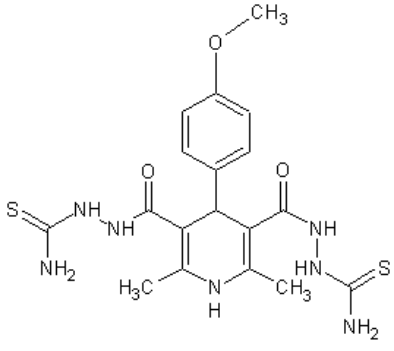
Table-12: Elemental Composition of synthesized compounds

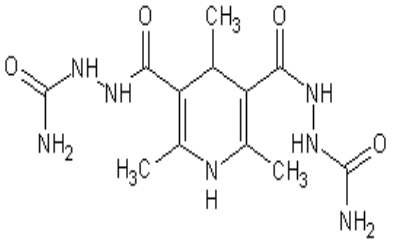
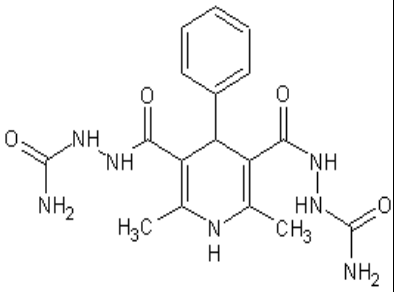
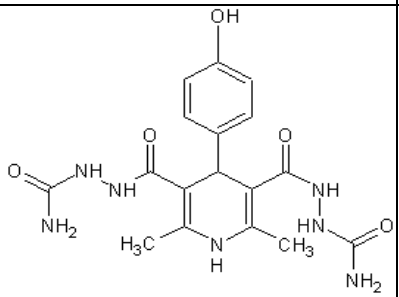
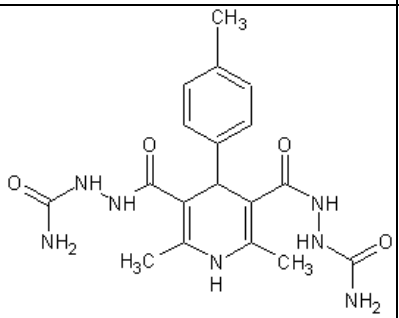
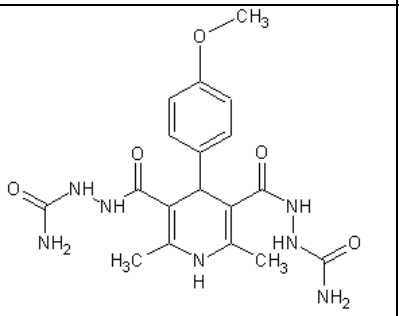
Compounds	Elemental Composition in Percentage (%)				
	C	H	N	O	S
A1	40.32	5.36	27.43	8.95	19.94
B1	48.67	5.05	23.37	7.63	15.29
C1	46.88	4.86	22.51	11.02	14.72
D1	49.87	5.35	22.61	7.38	14.79
E1	48.09	5.16	21.81	10.68	14.27
A2	44.30	5.89	30.14	19.67	-
B2	52.71	5.46	25.31	16.52	-
C2	50.26	5.25	24.31	19.83	-
D2	53.68	5.78	24.43	15.94	-
E2	51.79	5.55	23.49	19.16	-

Table-13 R_f Value of synthesized compounds

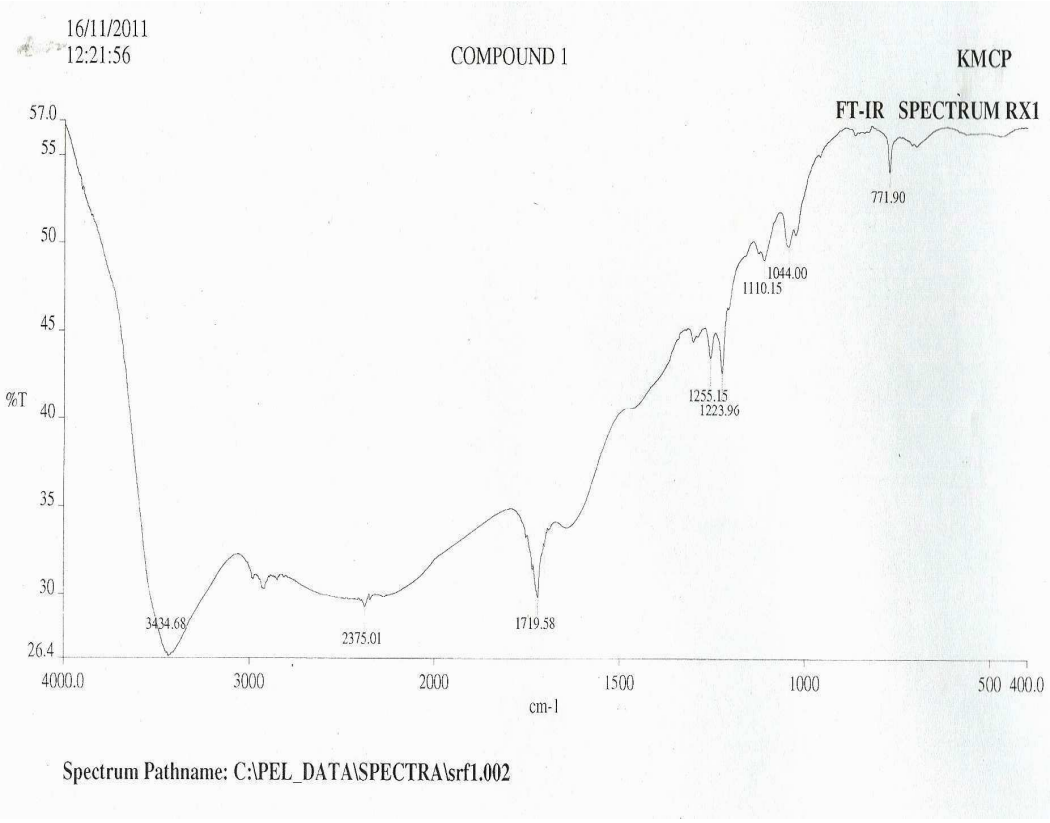
Compounds	Rf Value
A1	0.83
B1	0.72
C1	0.78
D1	0.65
E1	0.81
A2	0.80
B2	0.75
C2	0.72
D2	0.70
E2	0.84

Table-14: Infra Red spectral study of the complexes synthesized Compound

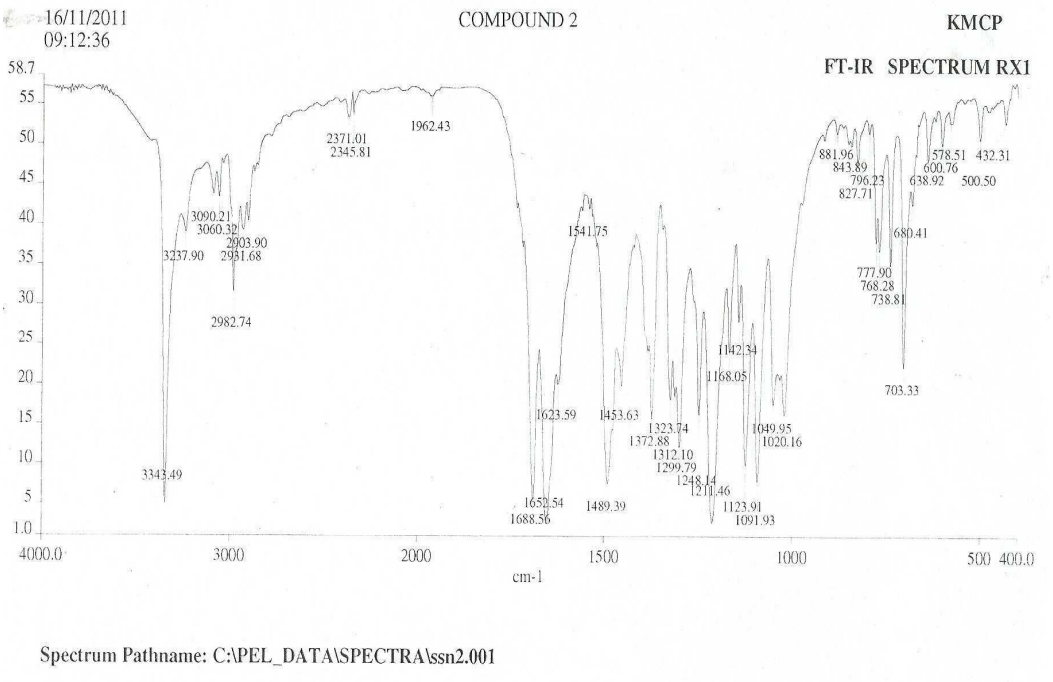
Compounds		Spectral peaks(cm^{-1})	Molecular nature
A1		3334 1719 1233 1044 771	-NH stretching -C=O stretching (ketone) -C=S stretching -C-N vibrational -C-H (bending atomatic)
B1		3343 3237 3060 2982 1688 1248	-NH stretching -NH-C=O streching -CH-CH stre. (aromatic) -C-H stret. (methyl) -C=O stretching (ketone) -C=S stretching
C1		3342 3184 1579 1248 1093	-O-H stretching -NH-C=O stretching -C=C stre. (aromatic) -C=S stretching -N-C-N bending
D1		3359 2986 1696 1653 1093	-NH stretching -CH-CH- stret. Aromatic -C=O stret. (ketone) -C=S stretching -N-C-N bending
E1		3241 3097 1690 1651 1609	-NH stretching -CH-CH- stret. (Aromatic) -C=O stret. (ketone) -C=S stretching -N=N- bending

Compounds		Spectral peaks(cm-1)	Molecular nature
A2		3432 2923 1721 1654 1224	-NH2 stretching -CH stretching(methyl) -C=O stretching (ketone) -C=O stretching (ester) -N-C-N bending
B2		3342 3090 1689 1651 1091	-NH stretching -CH-CH stre. (aromatic) -C=O stretching -N=N- stretching -N-C-N bending
C2		3321 2936 1718 1597 1097	>C=O—H(bonded) stret. -CH-CH stre. (aromatic) -C=0 stretching (ester) -N=N stretching -N-C-N bending
D2		3214 2986 1689 1076	NH-C=O stretching -CH-CH stre. (aromatic) -C=0 stretching (ester) -N-C-N bending
E2		3342 2980 1689 1118 834	-NH stretching -CH-CH stret. (aromatic) -C=0 stretching (ketone) -N-C-N bending -C-H bending (aromatic)

Compound-A1



Compound-B1



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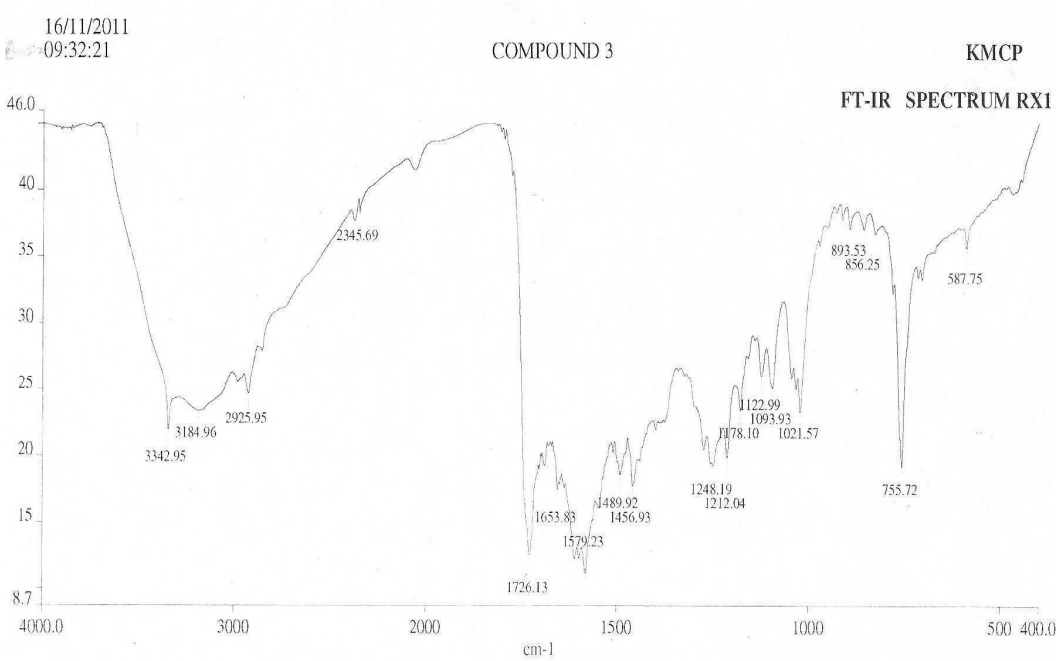

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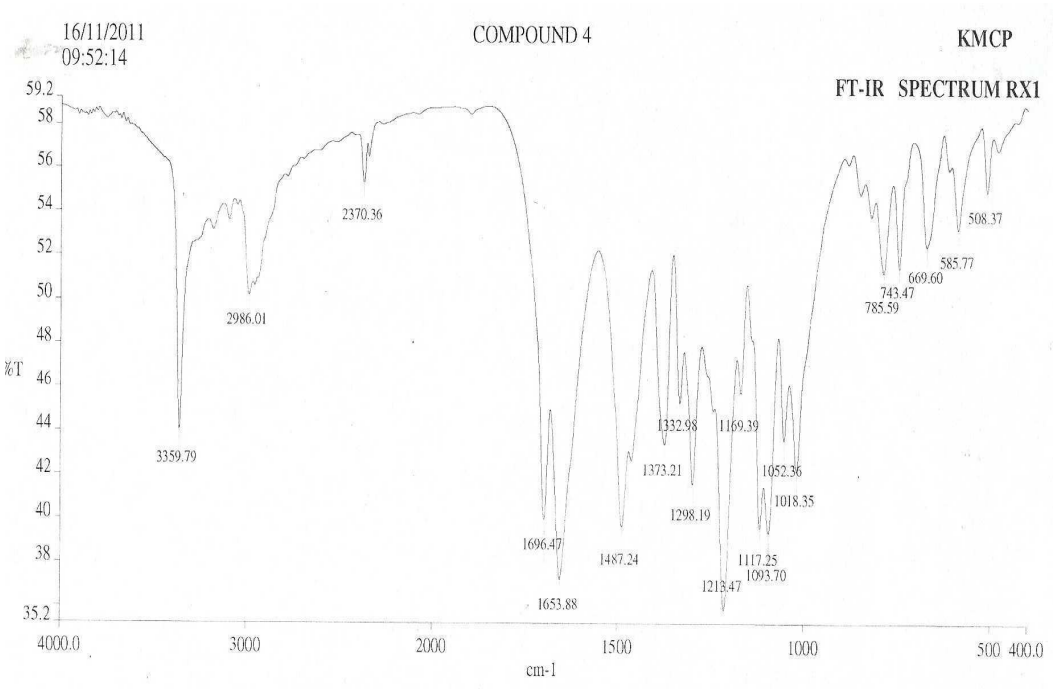

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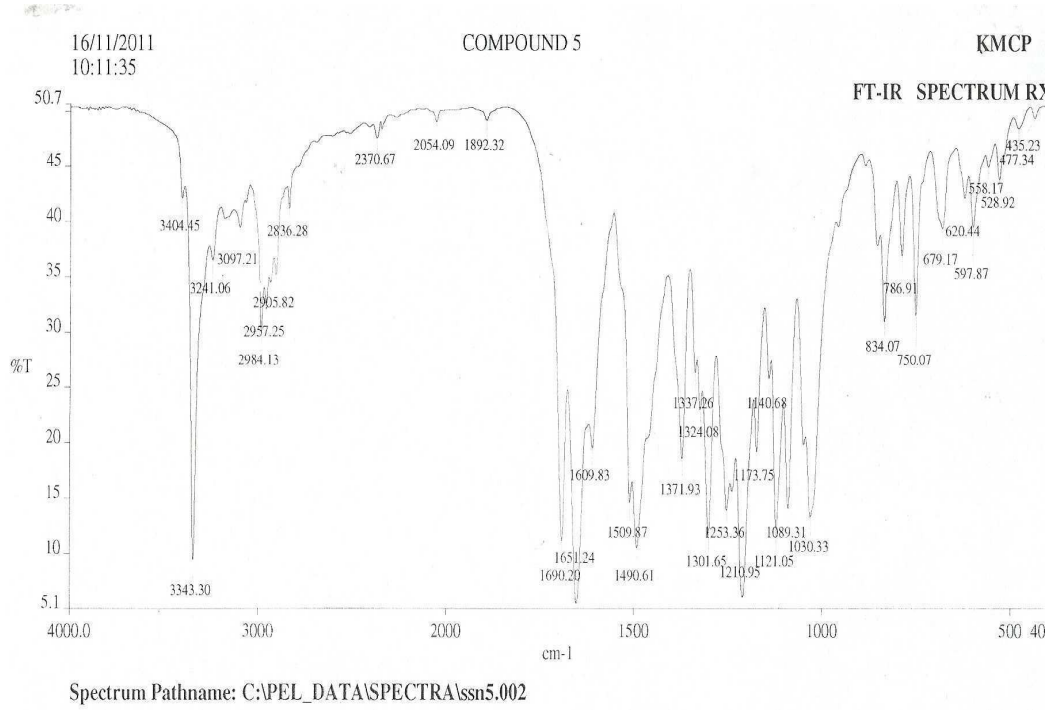

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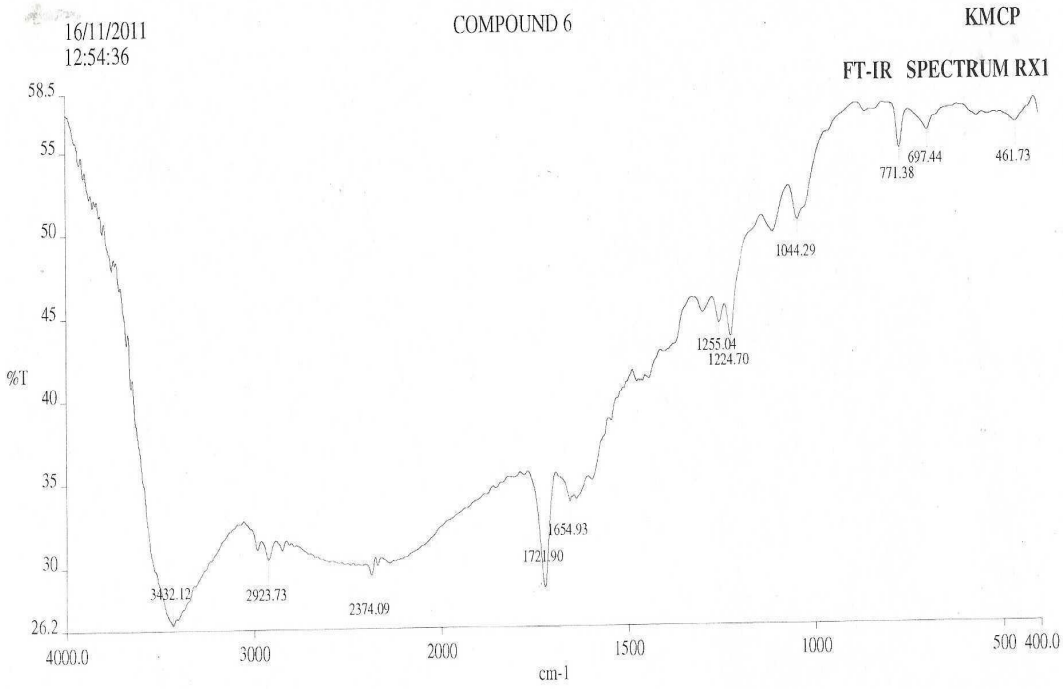

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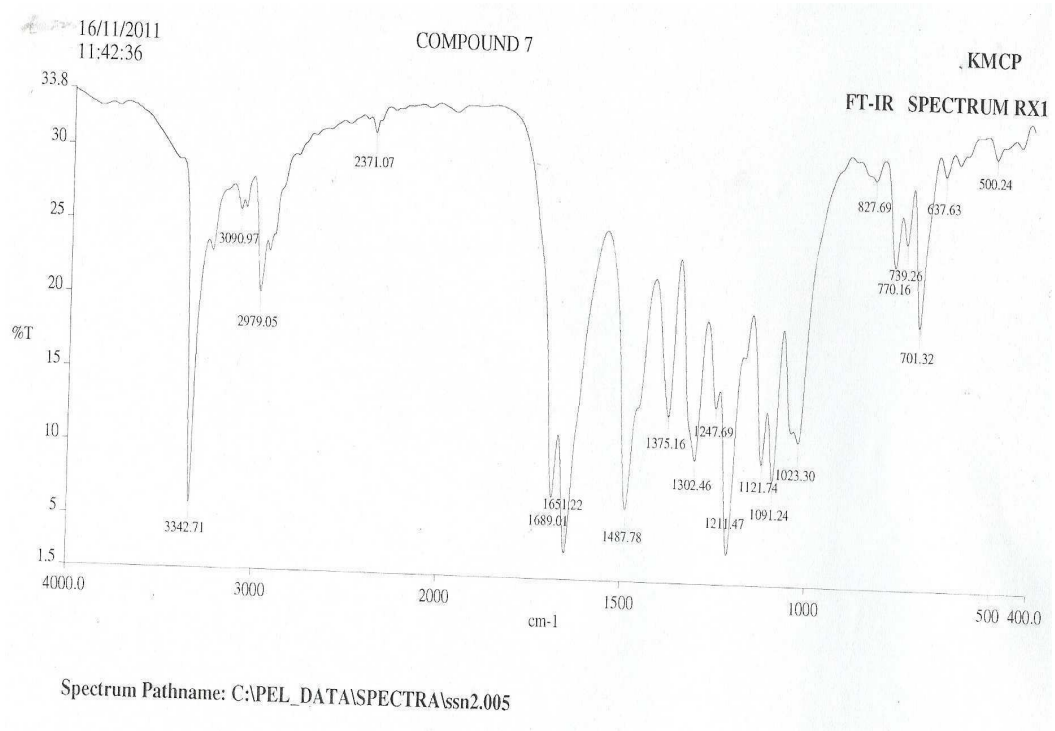

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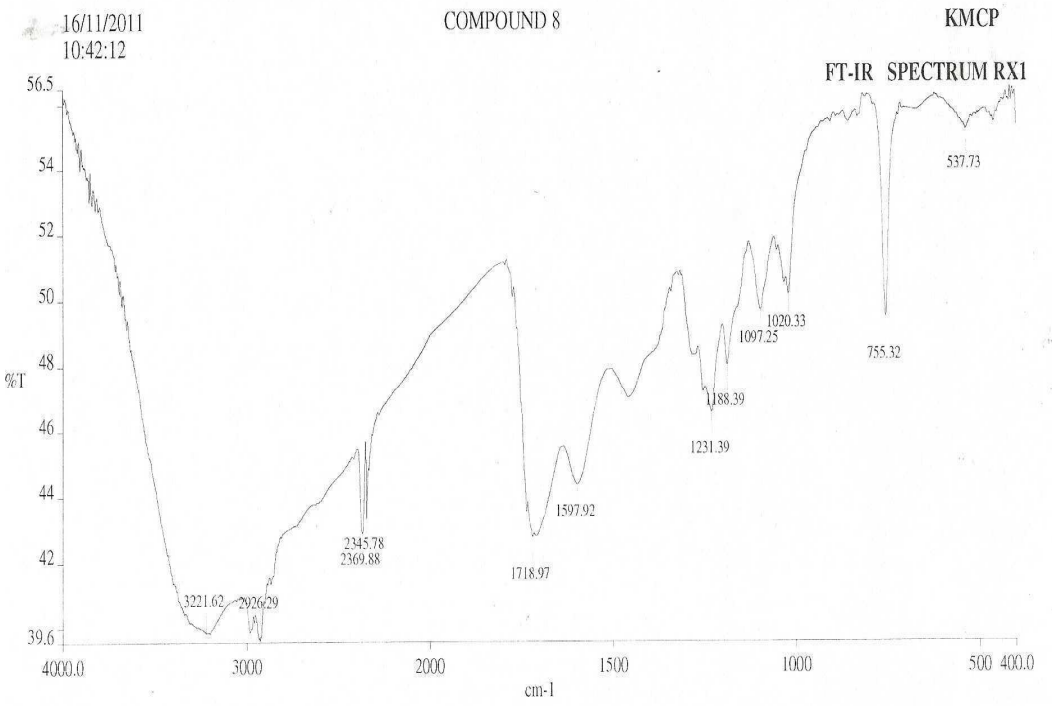
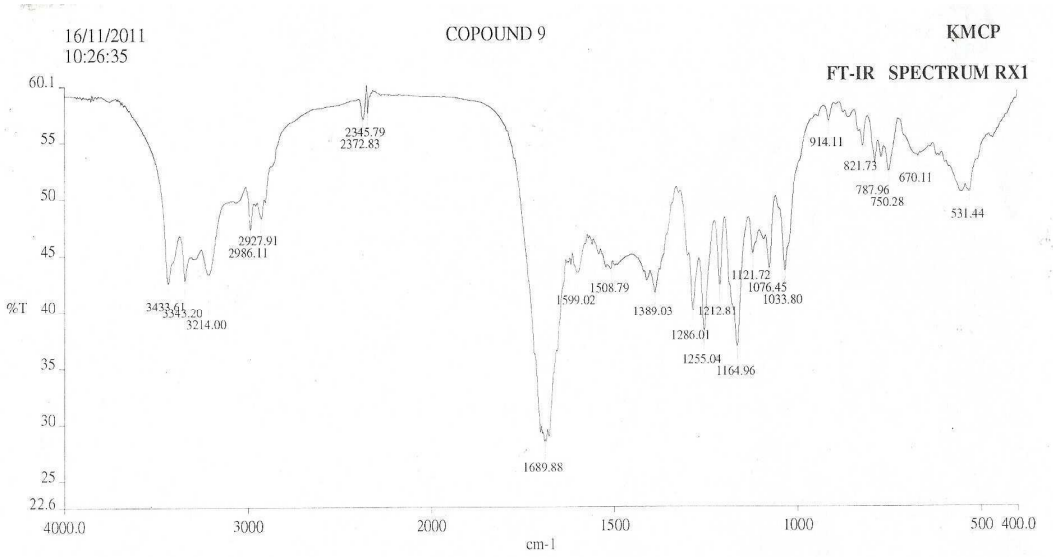
Compound-C2



Spectrum Pathname: C:\PEL_DATA\SPECTRA\srf 8.002

Compound-D2



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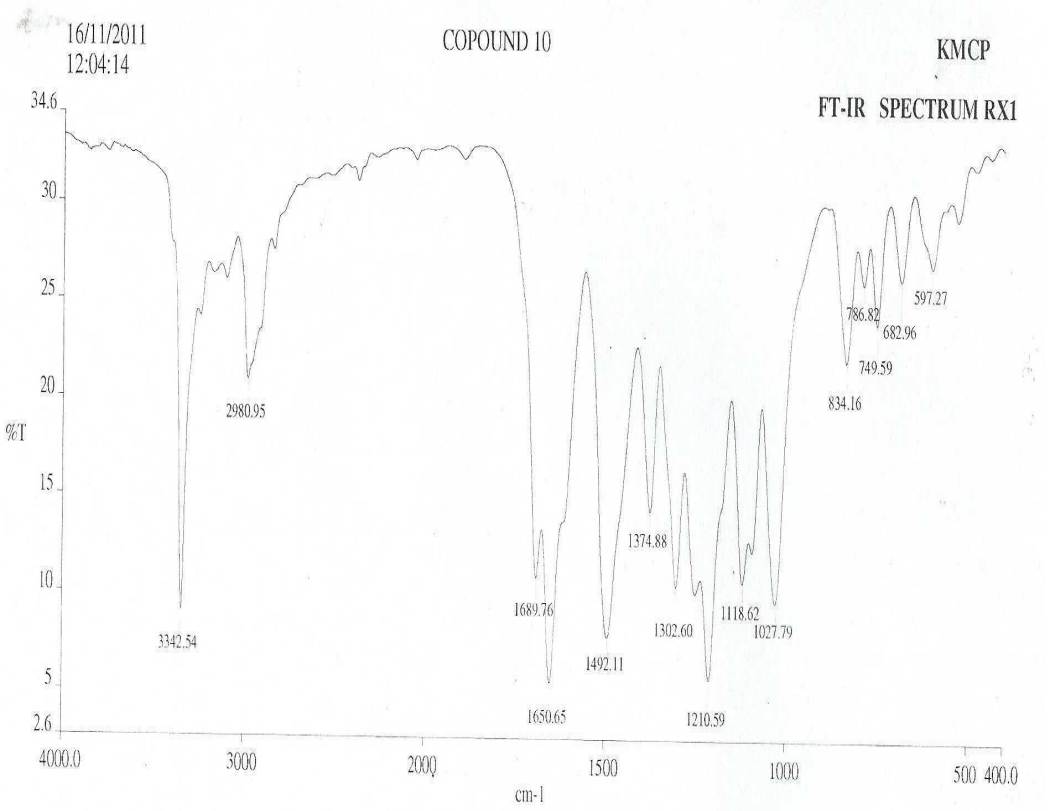
Compound-E2



Spectrum Pathname: C:\PEL_DATA\SPECTRA\ssn5.004

Table-15

^{1}H NMR Spectral data

Compound	Chemical Shift value	Proton nature
A1	11.53	s, H, -NH
	8.17	s, 1H, NH of Pyridine ring
	7.09	m, 5H, Ar-H
	3.83	s, 2H, N-CH2
	2.28	s, 6H, C2-CH3 & C6-CH3
B1	11.58	s, H, -NH
	8.14	s, 1H, NH of Pyridine ring
	6.83	m, 5H, Ar-H
	3.83	s, 2H, N-CH2
	2.28	s, 6H, C2-CH3 & C6-CH3
C1	13.25	s, H, -NH
	8.40	s, 1H, NH of Pyridine ring
	7.27	m, 5H, Ar-H
	3.88	s, 2H, N-CH2
	2.28	s, 6H, C2-CH3 & C6-CH3
D1	11.73	s, H, -NH
	8.27	s, 1H, NH of Pyridine ring
	7.17	m, 5H, Ar-H
	3.90	s, 2H, N-CH2
	2.18	s, 6H, C2-CH3 & C6-CH3

^{1}H NMR Spectral data

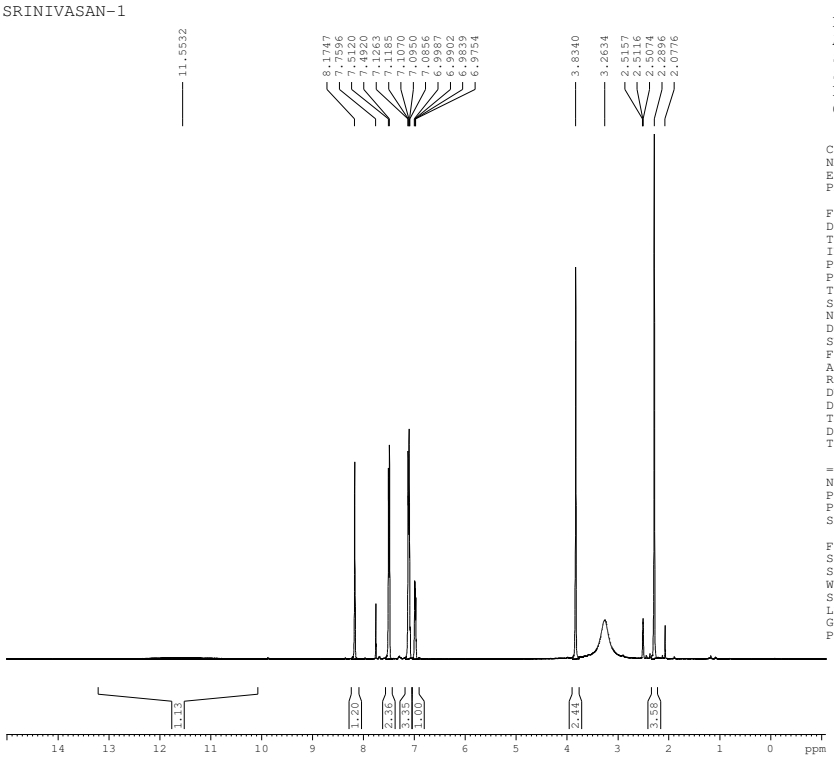
Compound	Chemical Shift value	Proton nature
E1	11.52	s, H, -NH
	8.30	s, 1H, NH of Pyridine ring
	7.18	m, 5H, Ar-H
	3.83	s, 2H, N-CH2
	2.28	s, 6H, C2-CH3 & C6-CH3
A2	11.98	s, H, -NH
	8.14	s, 1H, NH of Pyridine ring
	7.13	m, 5H, Ar-H
	3.63	s, 2H, N-CH2
	2.30	s, 6H, C2-CH3 & C6-CH3
B2	11.91	s, H, -NH
	8.07	s, 1H, NH of Pyridine ring
	7.17	m, 5H, Ar-H
	3.70	s, 2H, N-CH2
	2.95	s, 6H, C2-CH3 & C6-CH3
C2	11.90	s, H, -NH
	8.13	s, 1H, NH of Pyridine ring
	7.10	m, 5H, Ar-H
	3.73	s, 2H, N-CH2
	2.74	s, 6H, C2-CH3 & C6-CH3

^{1}H NMR Spectral data

Compound	Chemical Shift value	Proton nature
D2	11.42	s, H, -NH
	8.09	s, 1H, NH of Pyridine ring
	7.26	m, 5H, Ar-H
	3.28	s, 2H, N-CH2
	2.58	s, 6H, C2-CH3 & C6-CH3
E2	11.97	s, H, -NH
	8.14	s, 1H, NH of Pyridine ring
	7.13	m, 5H, Ar-H
	3.39	s, 2H, N-CH2
	2.54	s, 6H, C2-CH3 & C6-CH3

NMR Spectra

Compound A1



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
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PROCNO 1

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FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 203
DW 41.600 usec
DE 6.00 usec
TE 292.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
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PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
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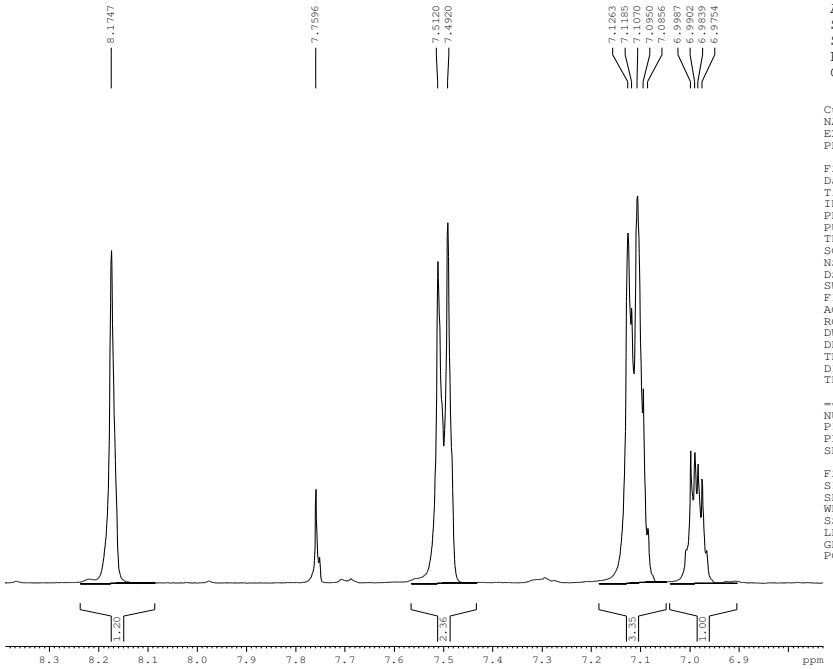
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in



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AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Jan13-2012
EXPNO 10
PROCNO 1

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Date_ 20120113
Time 13.17
INSTRUM spect
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
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AQ 2.7263477 sec
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DW 41.600 usec
DE 6.00 usec
TE 292.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
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P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

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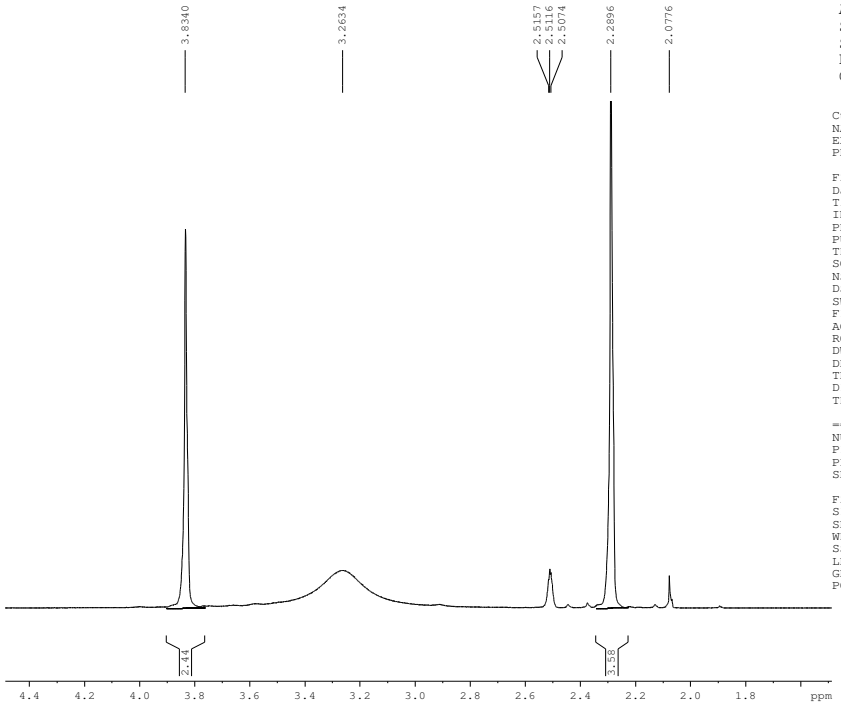

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Current Data Parameters
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PROCNO                 1

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INSTRUM            spect
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TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
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FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                   203
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.90 usec
PL1                -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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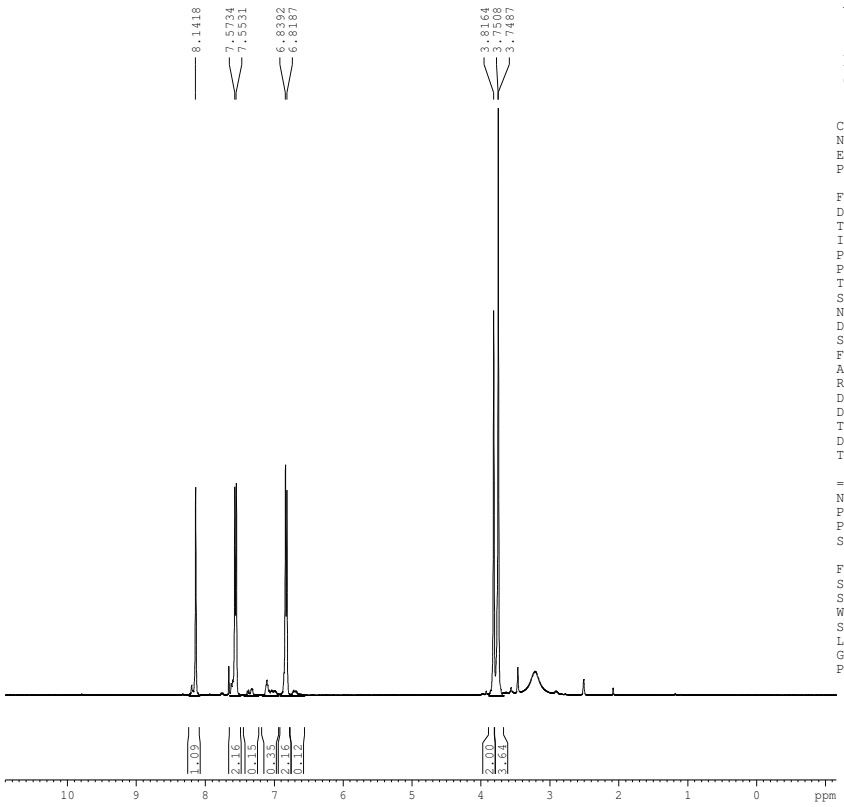
Compound B1

SRINIVASAN-2



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AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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Current Data Parameters
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EXPNO                 20
PROCNO                 1

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INSTRUM            spect
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PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                   144
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.90 usec
PL1                -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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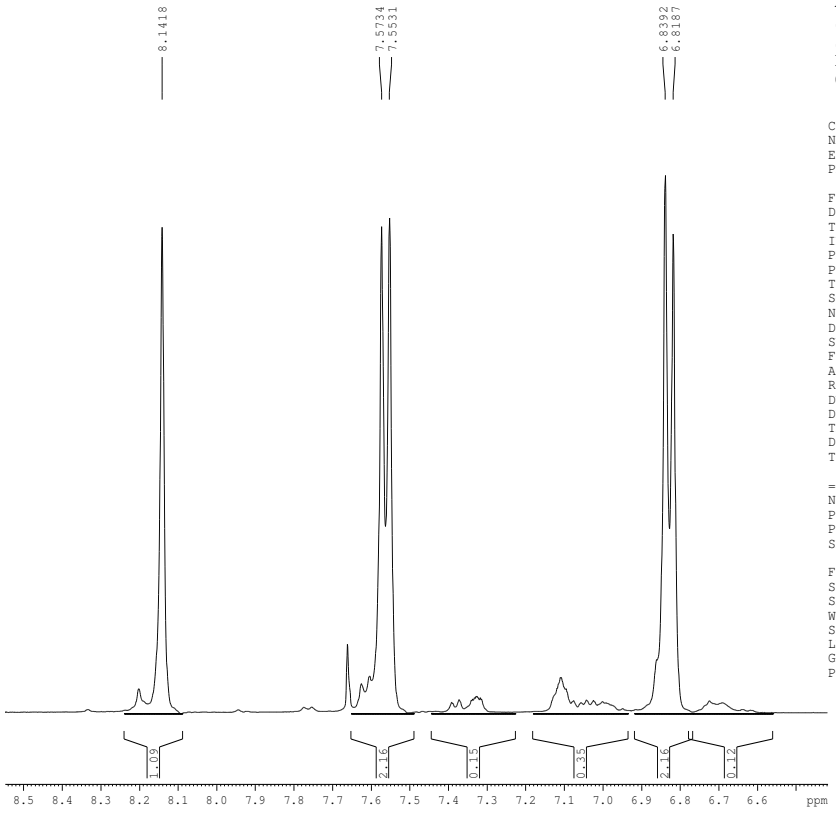
SRINIVASAN-2



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AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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Current Data Parameters
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PROCNO                1

F2 - Acquisition Parameters
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Time              13.22
INSTRUM           spect
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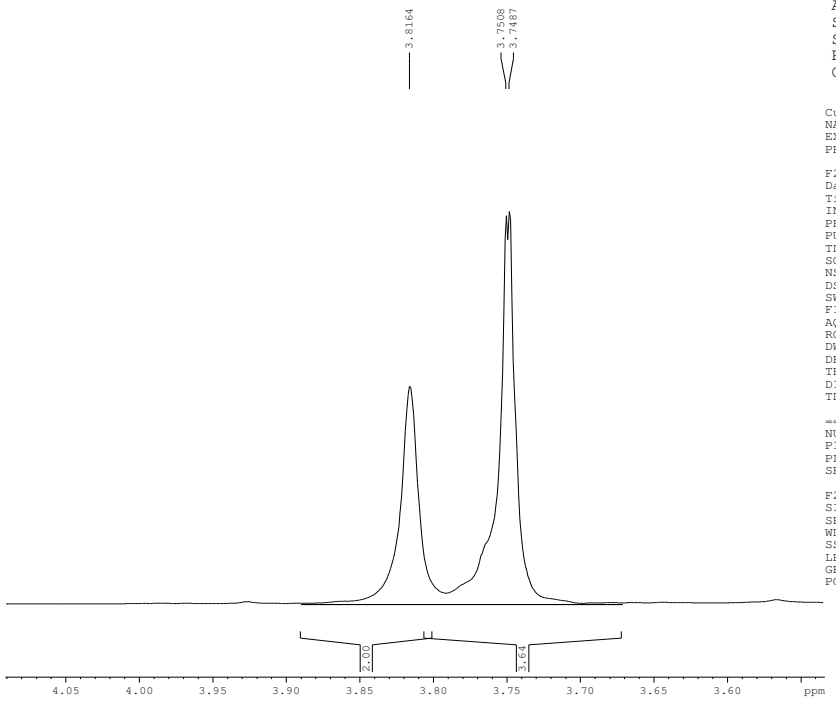
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                   144
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.90 usec
PL1                -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF            400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

avtar_saifpu@yahoo.co.in

SRINIVASAN-2



BRUKER
AVANCE II 400 NMR
Spectrometer
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```
Current Data Parameters
NAME         Jan13-2012
EXPNO                20
PROCNO                1

F2 - Acquisition Parameters
Date_          20120113
Time              13.22
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                   144
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.90 usec
PL1                -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF            400.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

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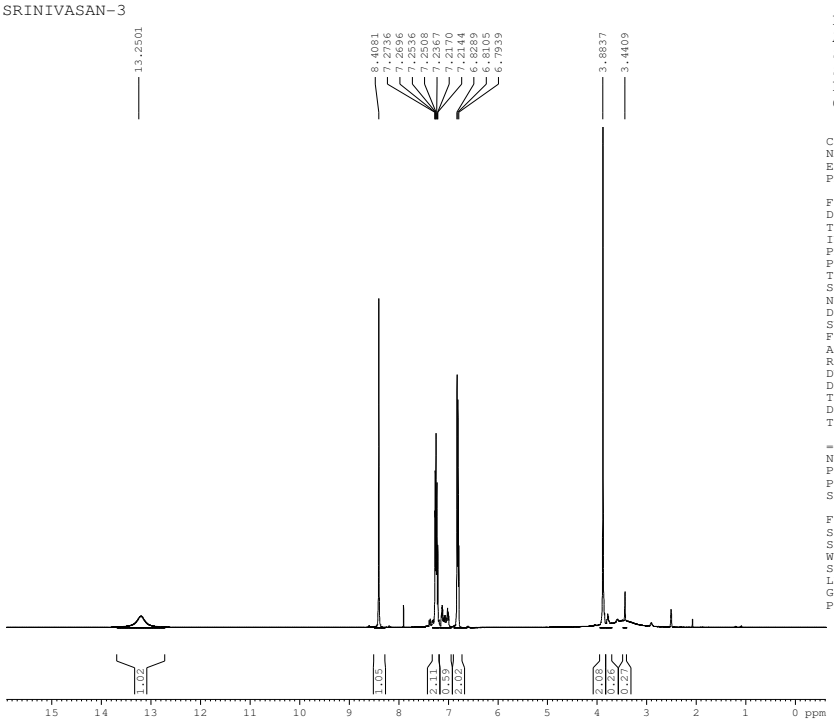
Compound C1



BRUKER
AVANCE II 400 NMR
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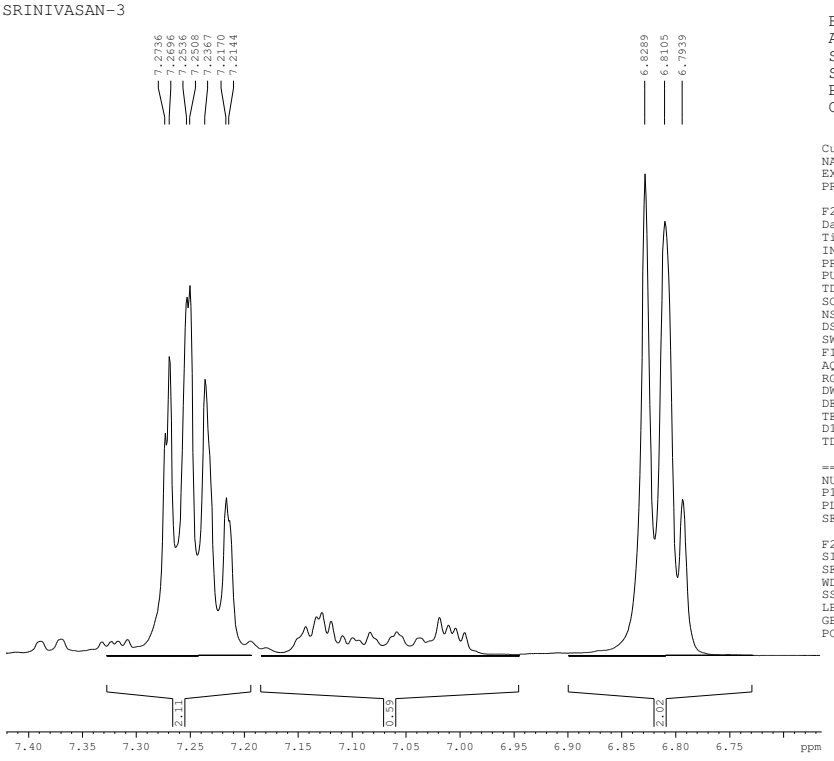
```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 30
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               13.27
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                  71.8
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                  1.00
```

avtar_saifpu@yahoo.co.in



BRUKER
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```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 30
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               13.27
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                  71.8
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300000 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                  1.00
```

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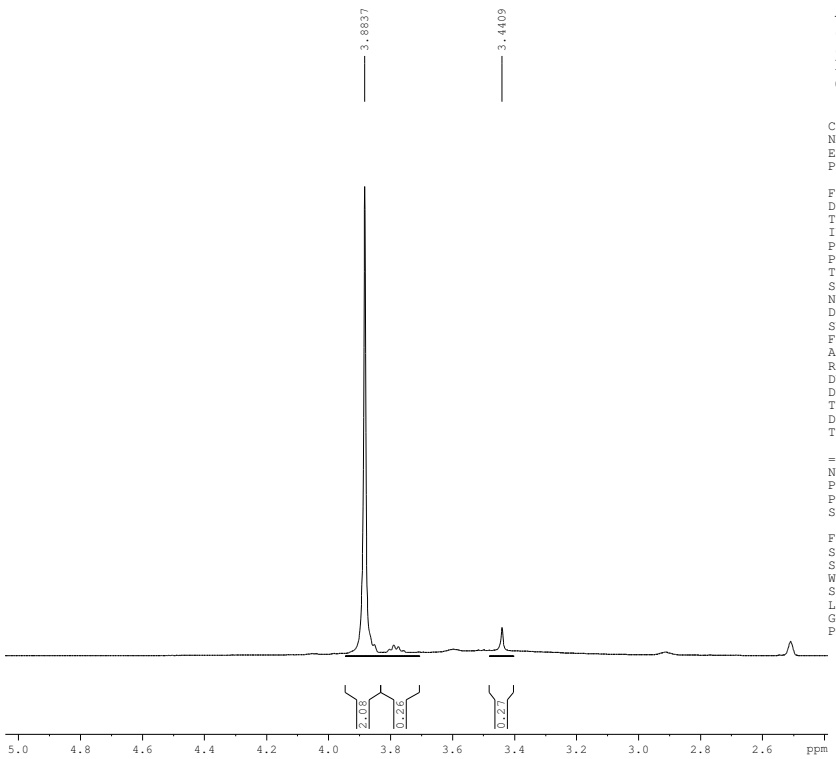
SRINIVASAN-3



BRUKER
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Current Data Parameters
NAME Jan13-2012
EXPNO 30
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120113
Time 13.27
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 71.8
DW 41.600 usec
DE 6.00 usec
TE 292.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

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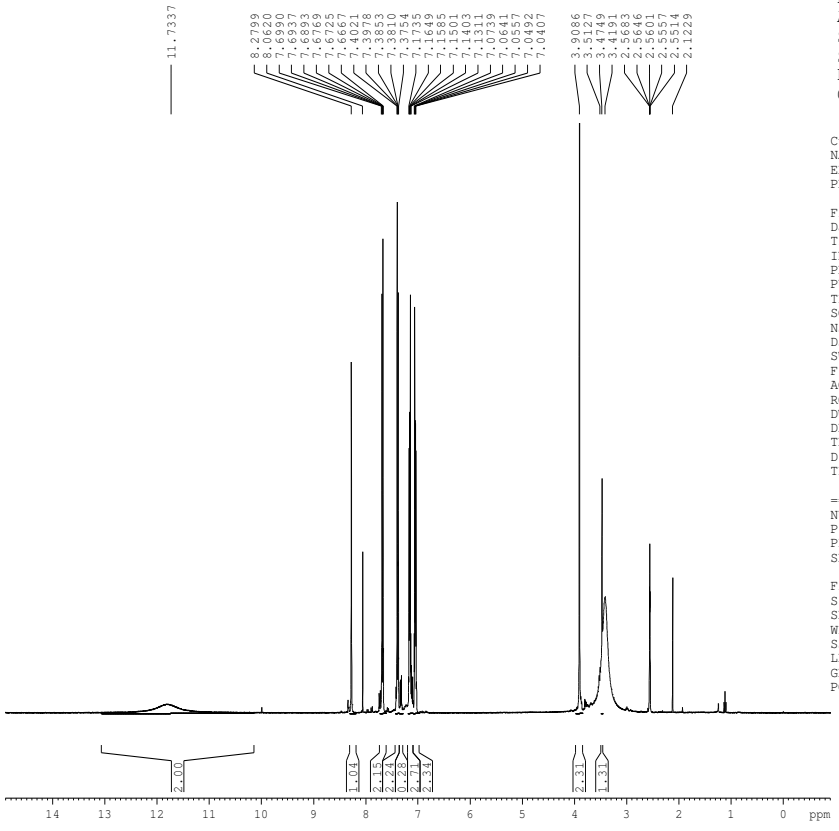
Compound D1

SRINIVASAN-4



BRUKER
AVANCE II 400 NMR
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Current Data Parameters
NAME Jan13-2012
EXPNO 40
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120113
Time 13.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 256
DW 41.600 usec
DE 6.00 usec
TE 292.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1299797 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

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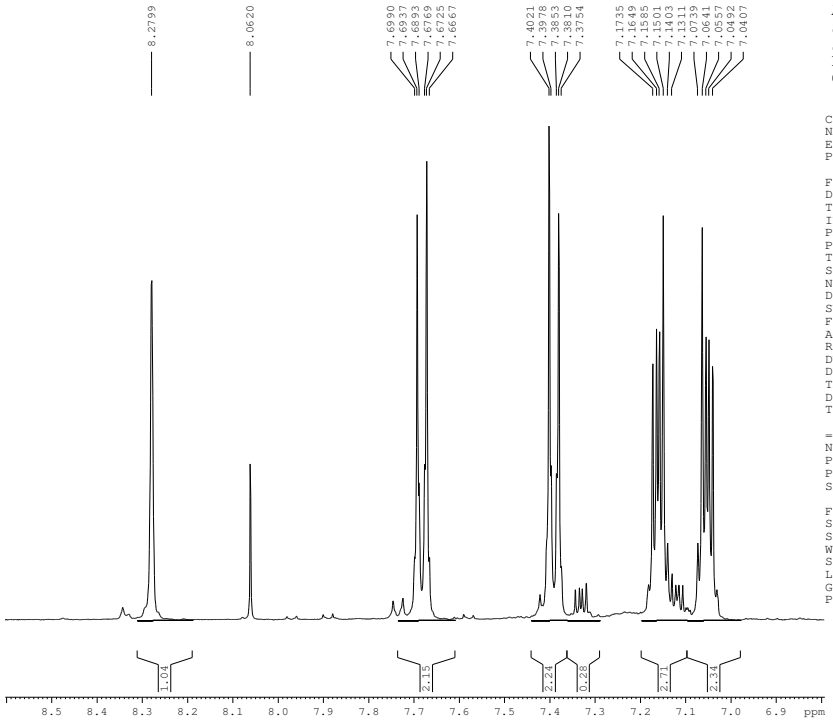
SRINIVASAN-4



BRUKER
AVANCE II 400 NMR
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Chandigarh

```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 40
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               13.32
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                   256
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1299797 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                  1.00
```

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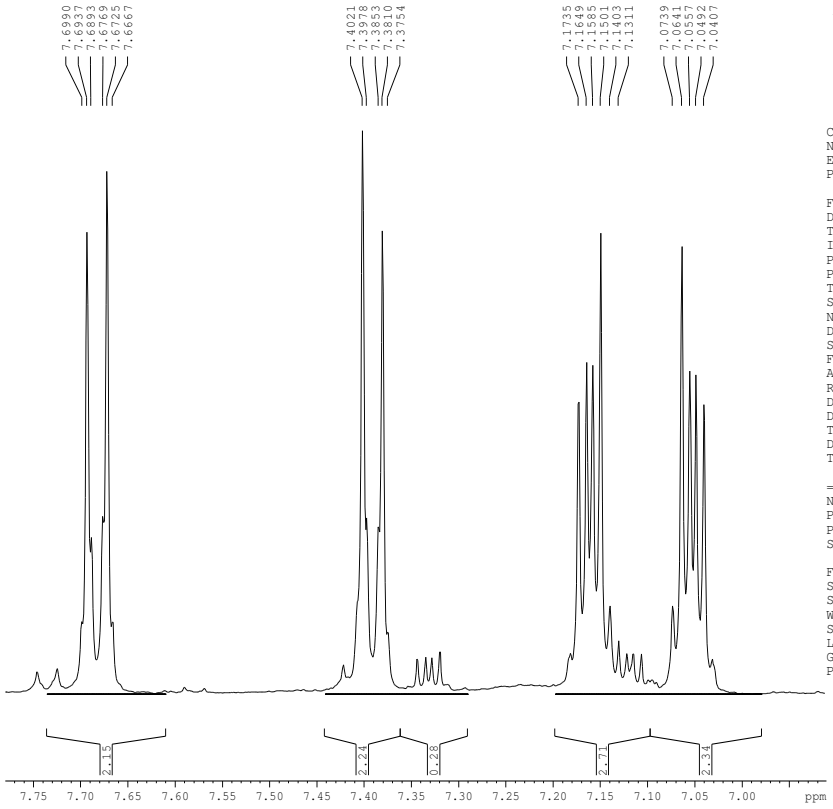
SRINIVASAN-4



BRUKER
AVANCE II 400 NMR
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```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 40
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               13.32
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                   256
DW                41.600 usec
DE                 6.00 usec
TE                292.4 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1299797 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                  1.00
```

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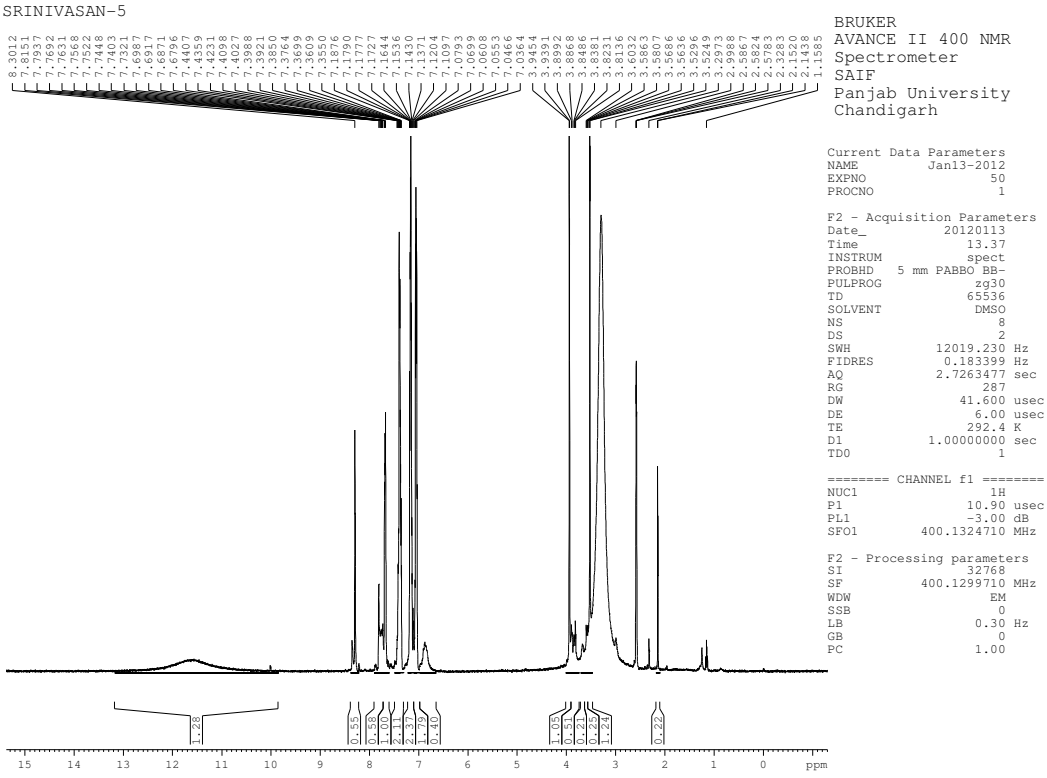
Compound E1



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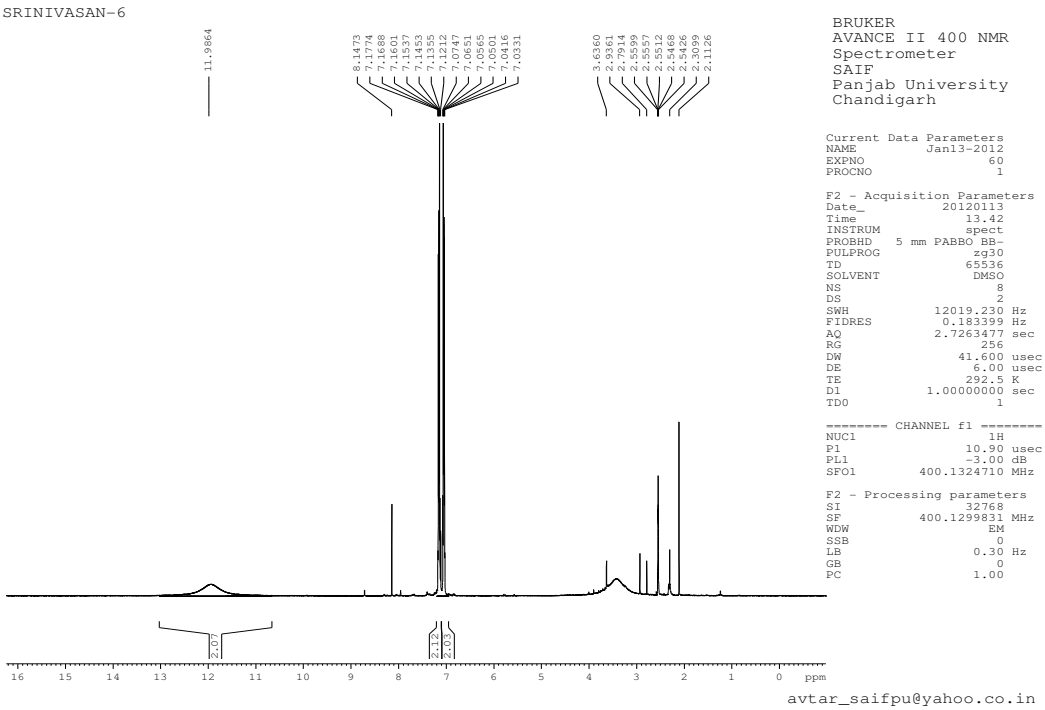
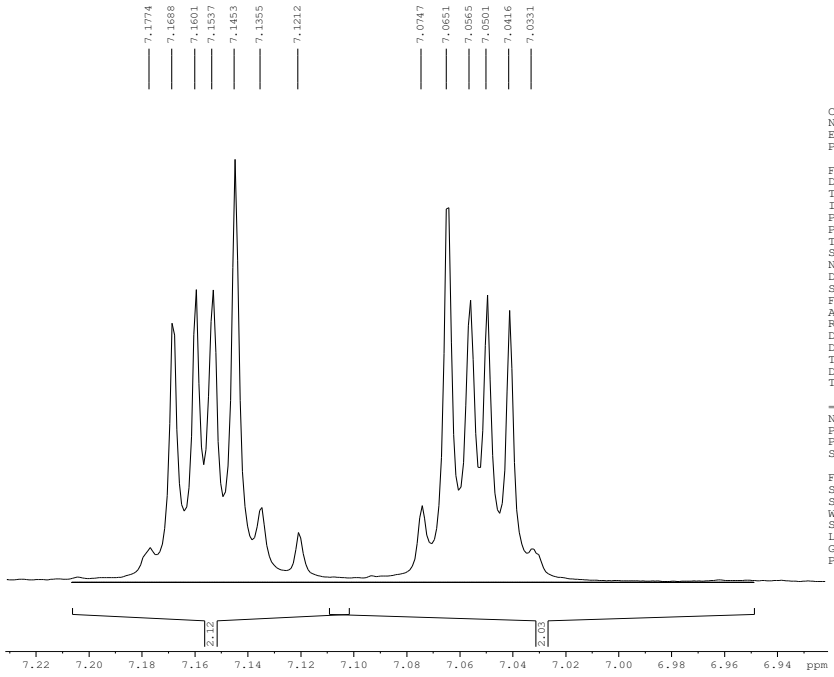
Compound A2



avtar_saifpu@yahoo.co.in

SRINIVASAN-6



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Current Data Parameters
NAME Jan13-2012
EXPNO 60
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120113
Time 13.42
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 256
DW 41.600 usec
DE 6.00 usec
TE 292.5 K
D1 1.00000000 sec
TD0 1

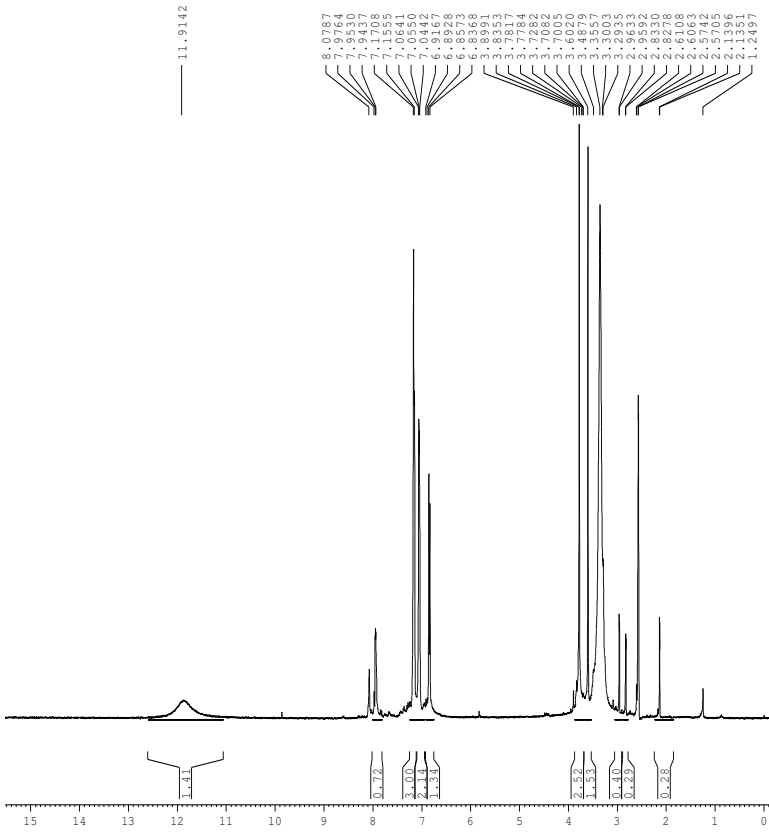
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1299831 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

Compound B2

SRINIVASAN-7



BRUKER
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Current Data Parameters
NAME Jan13-2012
EXPNO 70
PROCNO 1

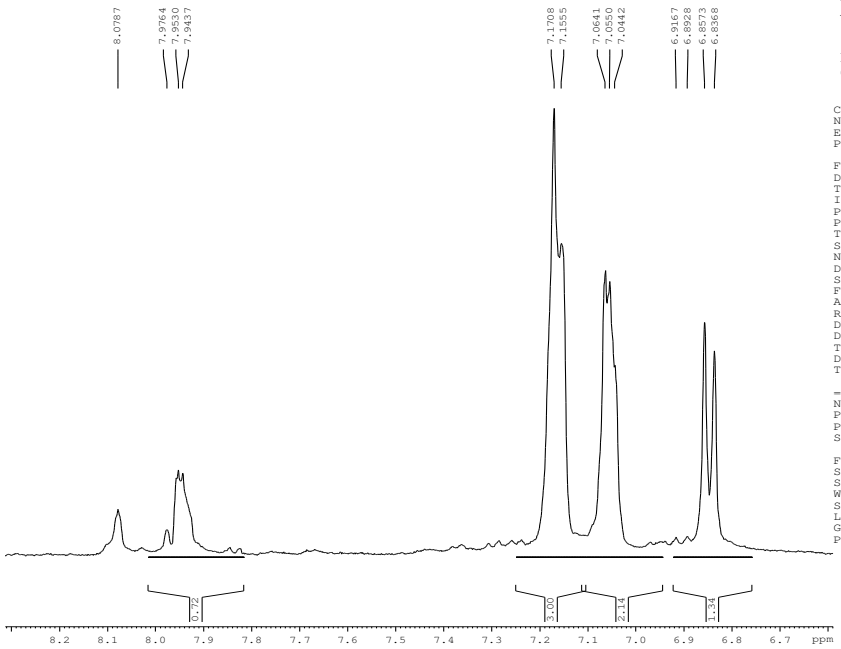
F2 - Acquisition Parameters
Date_ 20120113
Time 13.47
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 362
DW 41.600 usec
DE 6.00 usec
TE 292.5 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1299749 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

SRINIVASAN-7



BRUKER
AVANCE II 400 NMR
Spectrometer
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Chandigarh

Current Data Parameters	
NAME	Jan13-2012
EXPNO	70
PROCNO	1
F2 - Acquisition Parameters	
Date_	20120113
Time	13.47
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	292.5 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324710 MHz
F2 - Processing parameters	
SI	32768
SF	400.1299749 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

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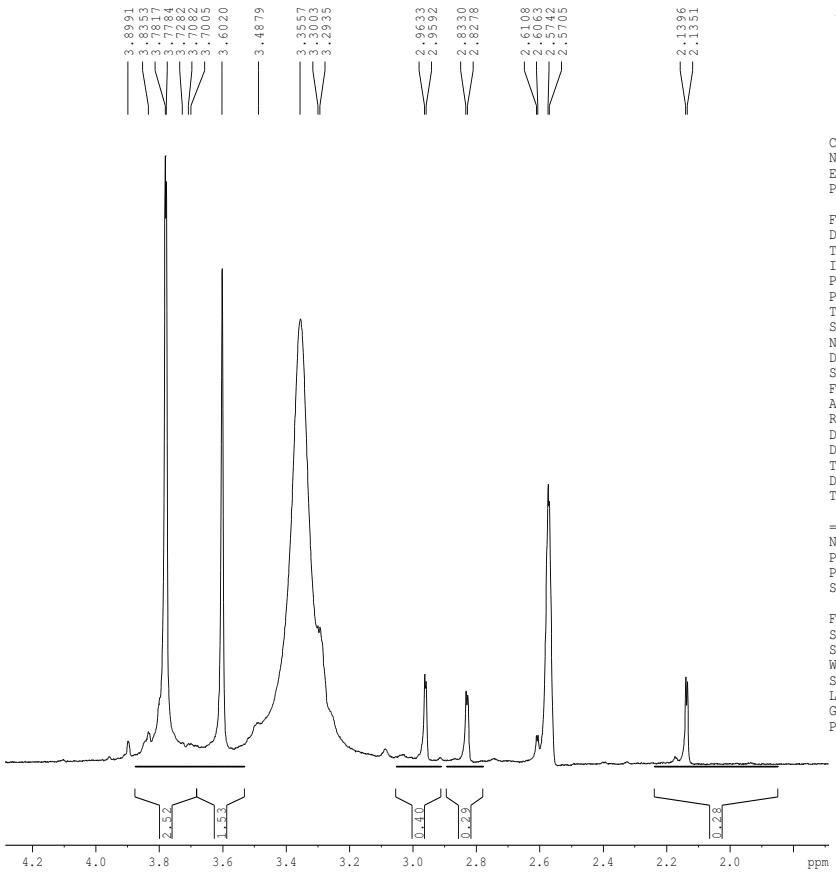
SRINIVASAN-7



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
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Chandigarh

Current Data Parameters	
NAME	Jan13-2012
EXPNO	70
PROCNO	1
F2 - Acquisition Parameters	
Date_	20120113
Time	13.47
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	292.5 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324710 MHz
F2 - Processing parameters	
SI	32768
SF	400.1299749 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

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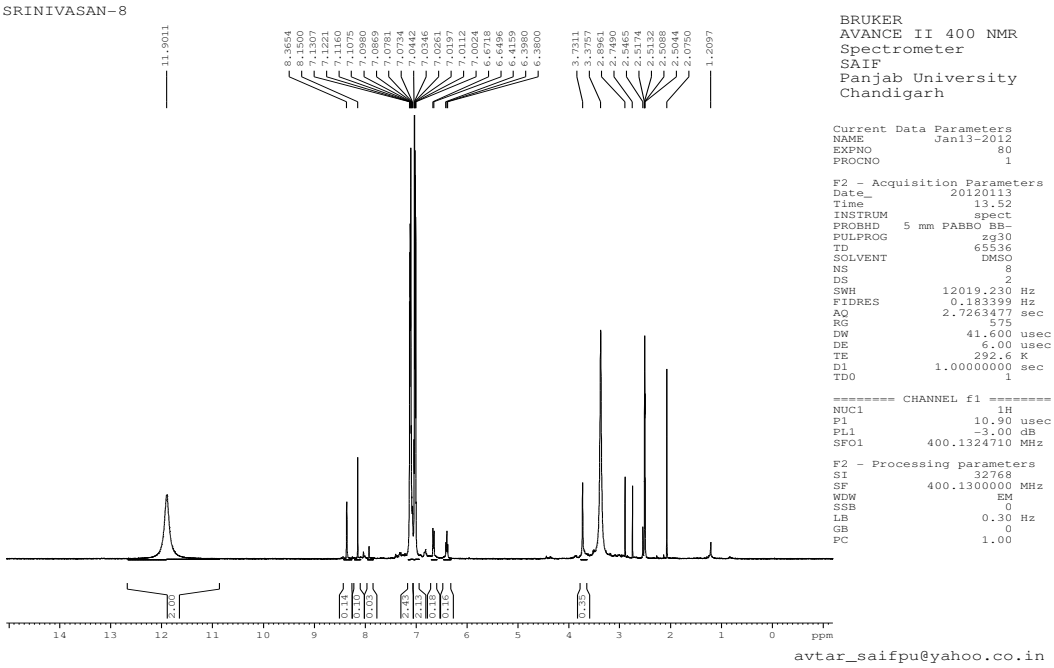
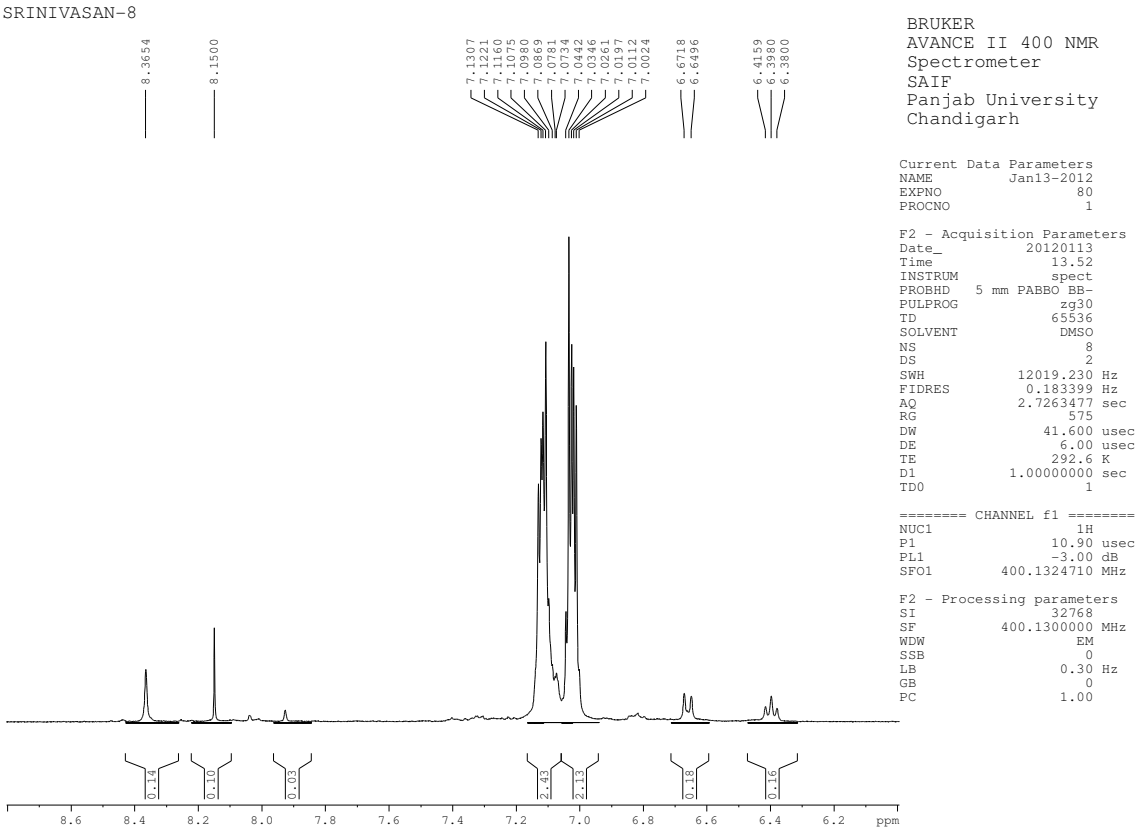
Compound C2

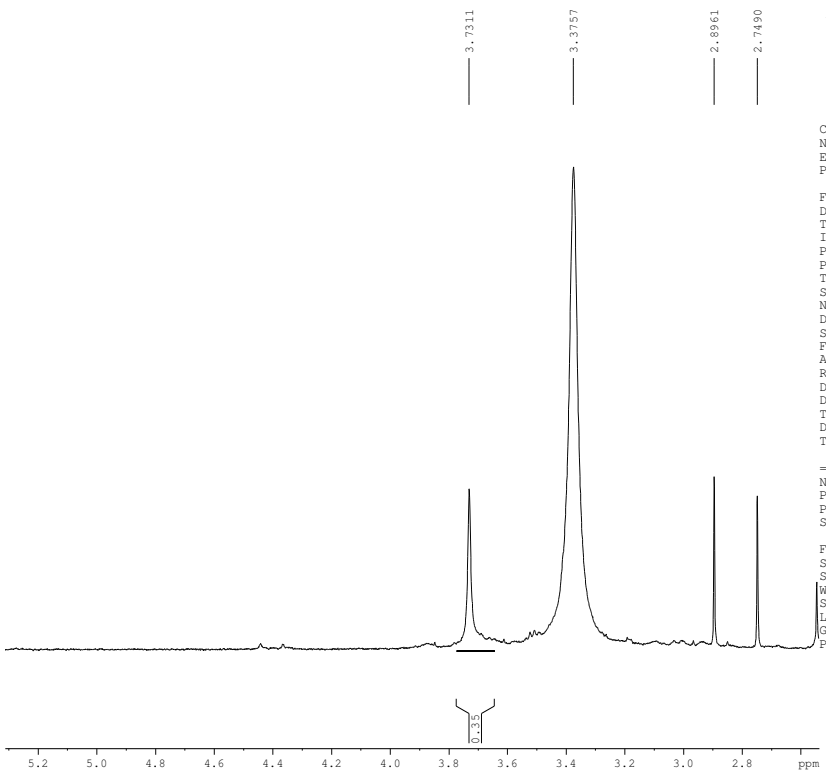


avtar_saifpu@yahoo.co.in



avtar_saifpu@yahoo.co.in

SRINIVASAN-8



BRUKER
AVANCE II 400 NMR
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Panjab University
Chandigarh

```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 80
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               13.52
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                   575
DW               41.600 usec
DE                6.00 usec
TE                292.6 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300000 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                1.00
```

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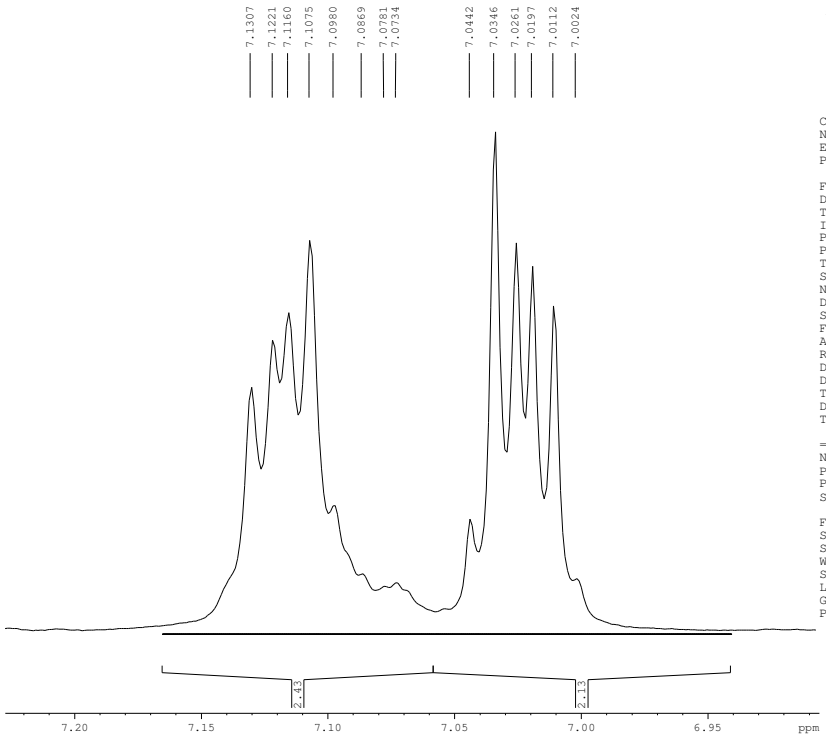
SRINIVASAN-8



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```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 80
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               13.52
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                   575
DW               41.600 usec
DE                6.00 usec
TE                292.6 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300000 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                1.00
```

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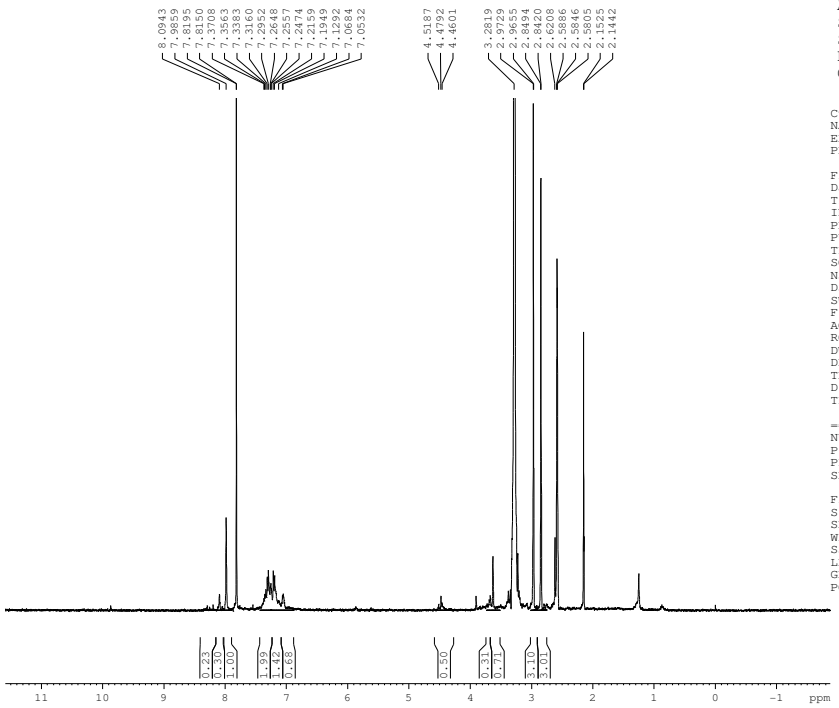
Compound D2

SRINIVASAN-9



BRUKER
AVANCE II 400 NMR
Spectrometer
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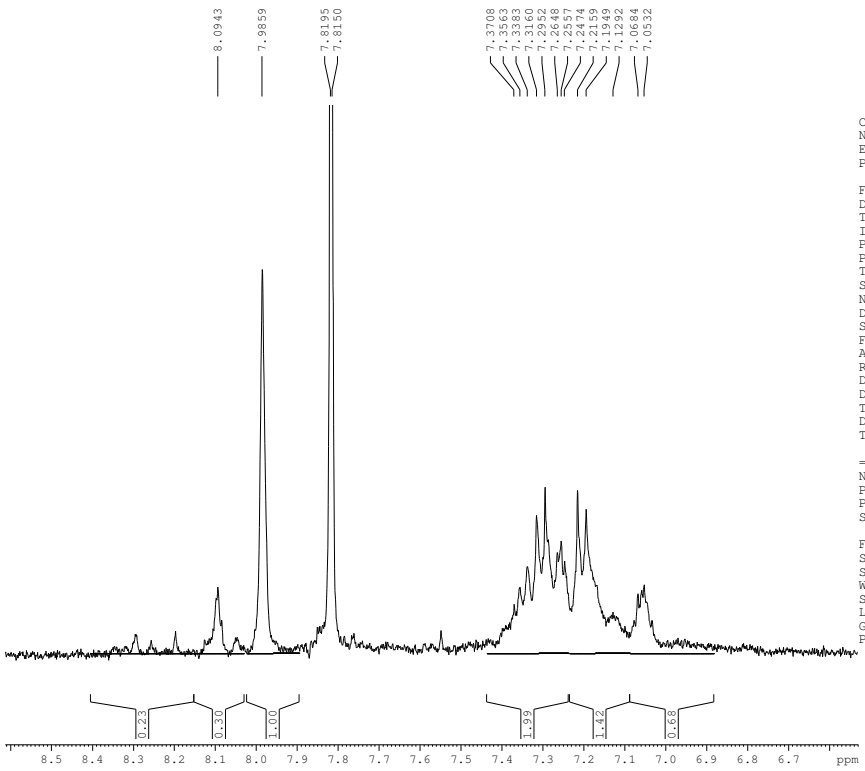
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jan13-2012
EXPNO	90
PROCNO	1
F2 - Acquisition Parameters	
Date_	20120113
Time	13.57
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	406
DW	41.600 usec
DE	6.00 usec
TE	292.6 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324710 MHz
F2 - Processing parameters	
SI	32768
SF	400.1299709 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

SRINIVASAN-9



BRUKER
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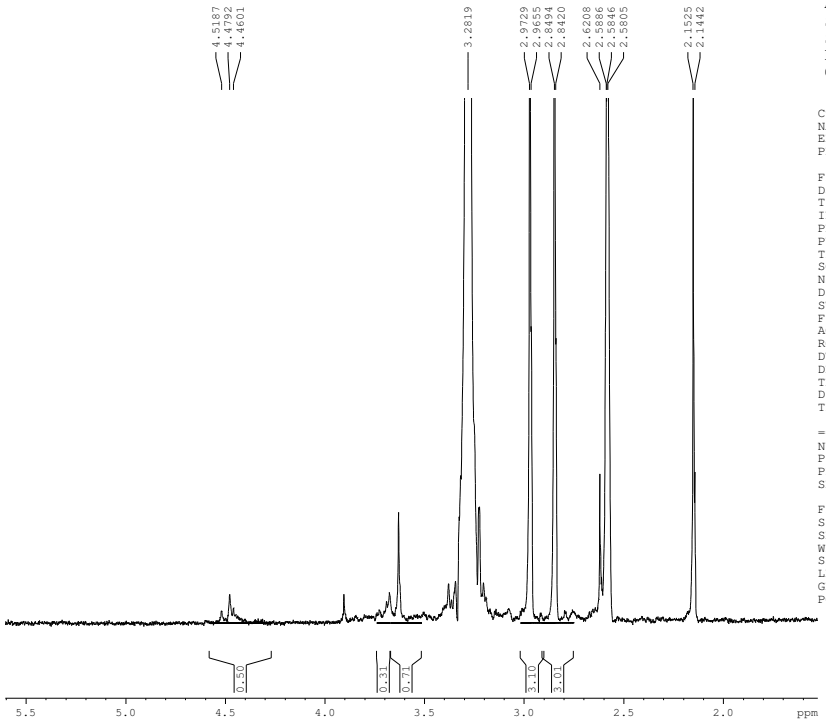
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jan13-2012
EXPNO	90
PROCNO	1
F2 - Acquisition Parameters	
Date_	20120113
Time	13.57
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	406
DW	41.600 usec
DE	6.00 usec
TE	292.6 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324710 MHz
F2 - Processing parameters	
SI	32768
SF	400.1299709 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

SRINIVASAN-9



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
Current Data Parameters
NAME          Jan13-2012
EXPNO                 90
PROCNO                 1

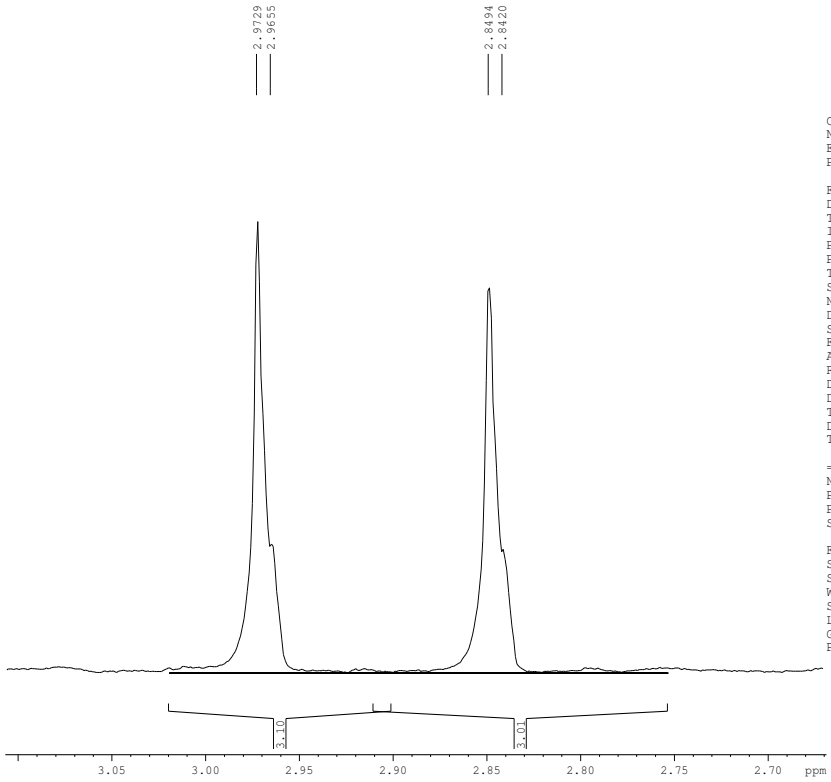
F2 - Acquisition Parameters
Date_           20120113
Time               13.57
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                   406
DW                41.600 usec
DE                 6.00 usec
TE                292.6 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1299709 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

avtar_saifpu@yahoo.co.in

SRINIVASAN-9



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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Current Data Parameters
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EXPNO                 90
PROCNO                 1

F2 - Acquisition Parameters
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PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH            12019.230 Hz
FIDRES          0.183399 Hz
AQ             2.7263477 sec
RG                   406
DW                41.600 usec
DE                 6.00 usec
TE                292.6 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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P1                10.90 usec
PL1               -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
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WDW                   EM
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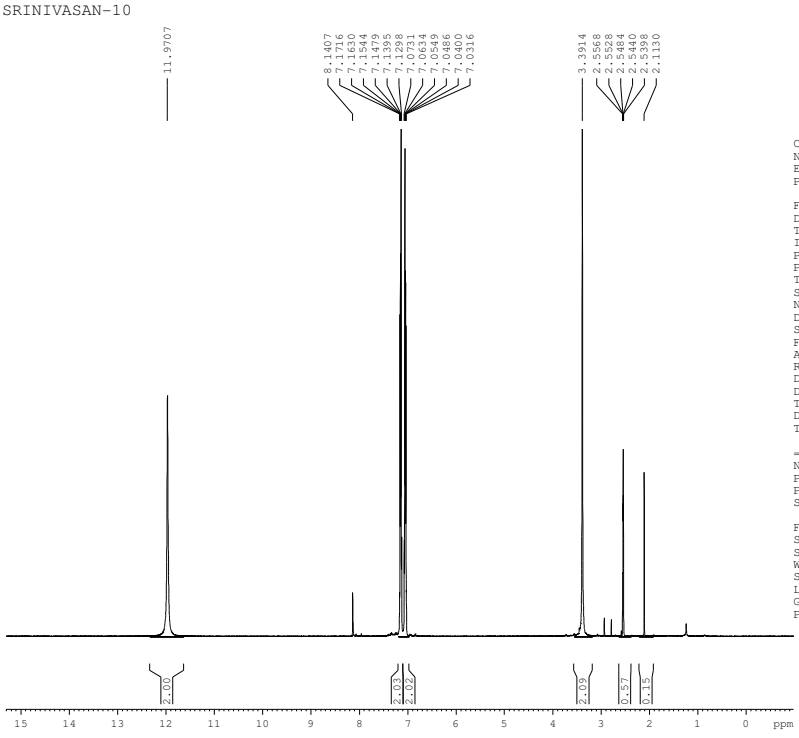
Compound E2



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Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Jan13-2012
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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT DMSO
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DS 2
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FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 362
DW 41.600 usec
DE 6.00 usec
TE 292.6 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
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PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
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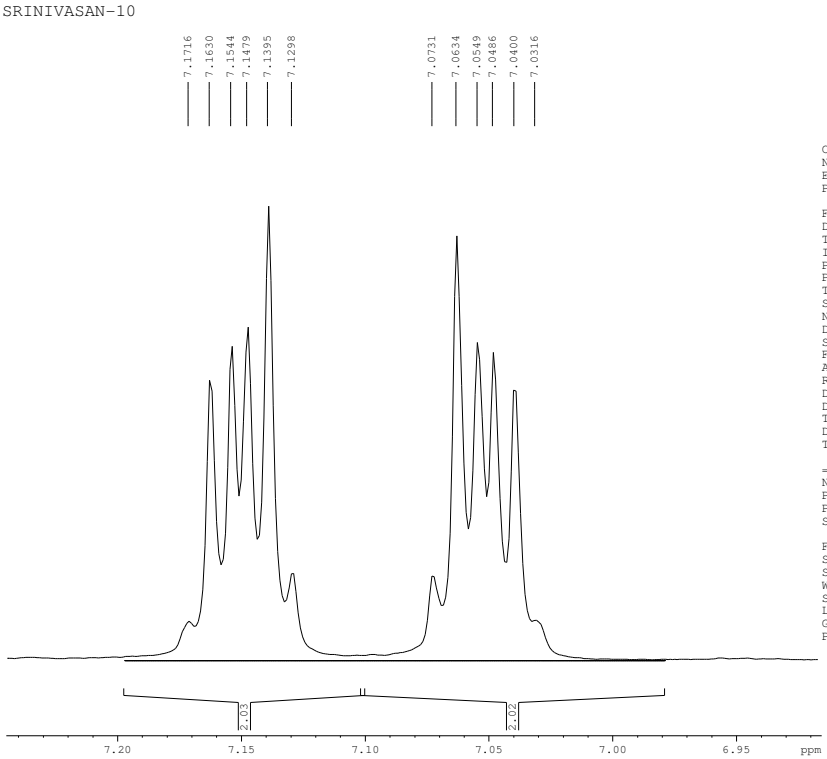
avtar_saifpu@yahoo.co.in



BRUKER
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Spectrometer
SAIF
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Chandigarh

Current Data Parameters
NAME Jan13-2012
EXPNO 100
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120113
Time 14.02
INSTRUM spect
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 362
DW 41.600 usec
DE 6.00 usec
TE 292.6 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
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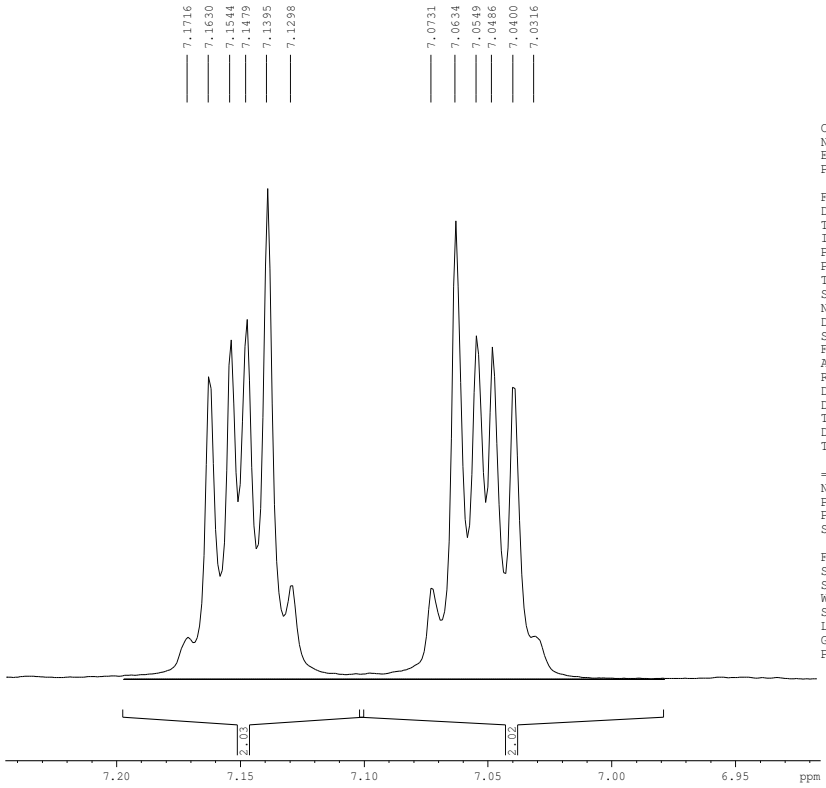
avtar_saifpu@yahoo.co.in

SRINIVASAN-10



BRUKER
AVANCE II 400 NMR
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SAIF
Panjab University
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Current Data Parameters
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EXPNO               100
PROCNO                1

F2 - Acquisition Parameters
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Time              14.02
INSTRUM           spect
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PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                  362
DW               41.600 usec
DE                6.00 usec
TE               292.6 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
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SF          400.1299843 MHz
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GB                    0
PC                 1.00
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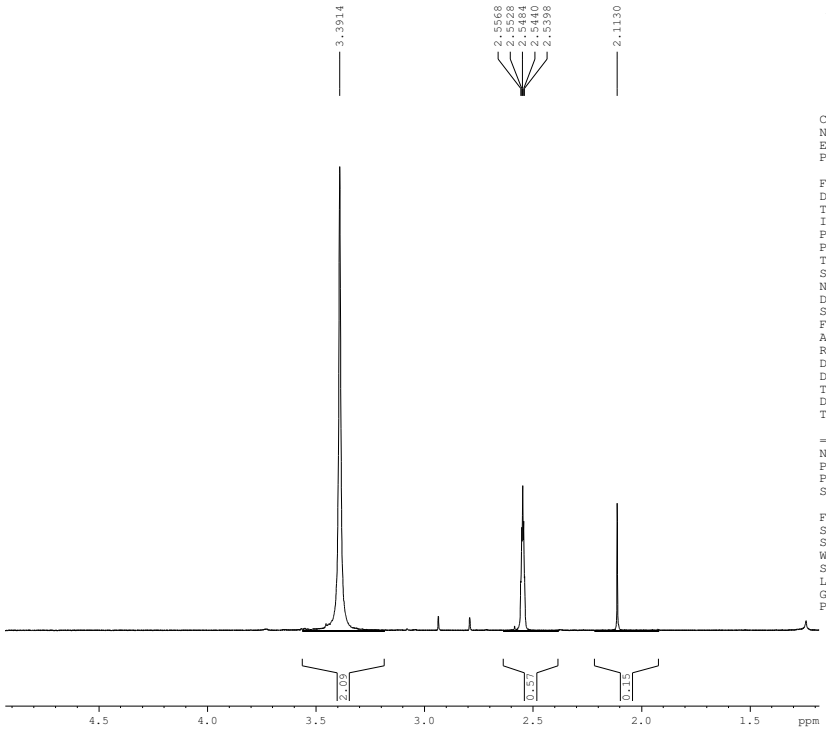
avtar_saifpu@yahoo.co.in

SRINIVASAN-10



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
Current Data Parameters
NAME         Jan13-2012
EXPNO               100
PROCNO                1

F2 - Acquisition Parameters
Date_          20120113
Time              14.02
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    2
SWH           12019.230 Hz
FIDRES         0.183399 Hz
AQ            2.7263477 sec
RG                  362
DW               41.600 usec
DE                6.00 usec
TE               292.6 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                32768
SF          400.1299843 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```

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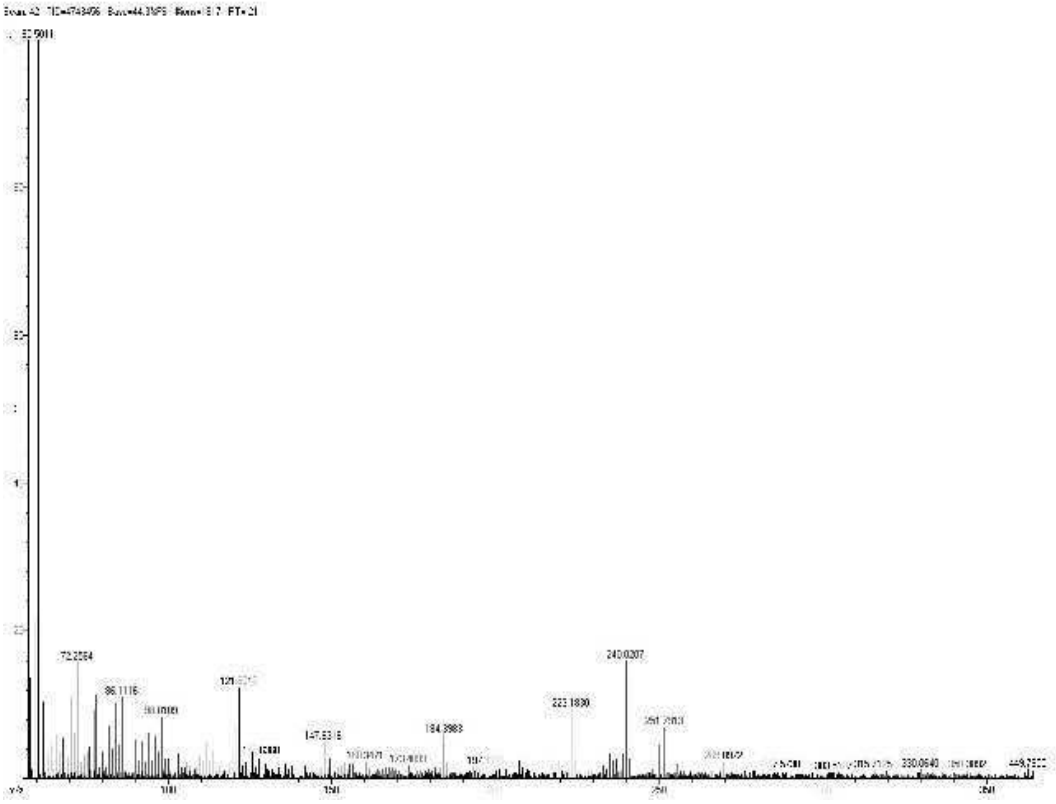
Table: 16

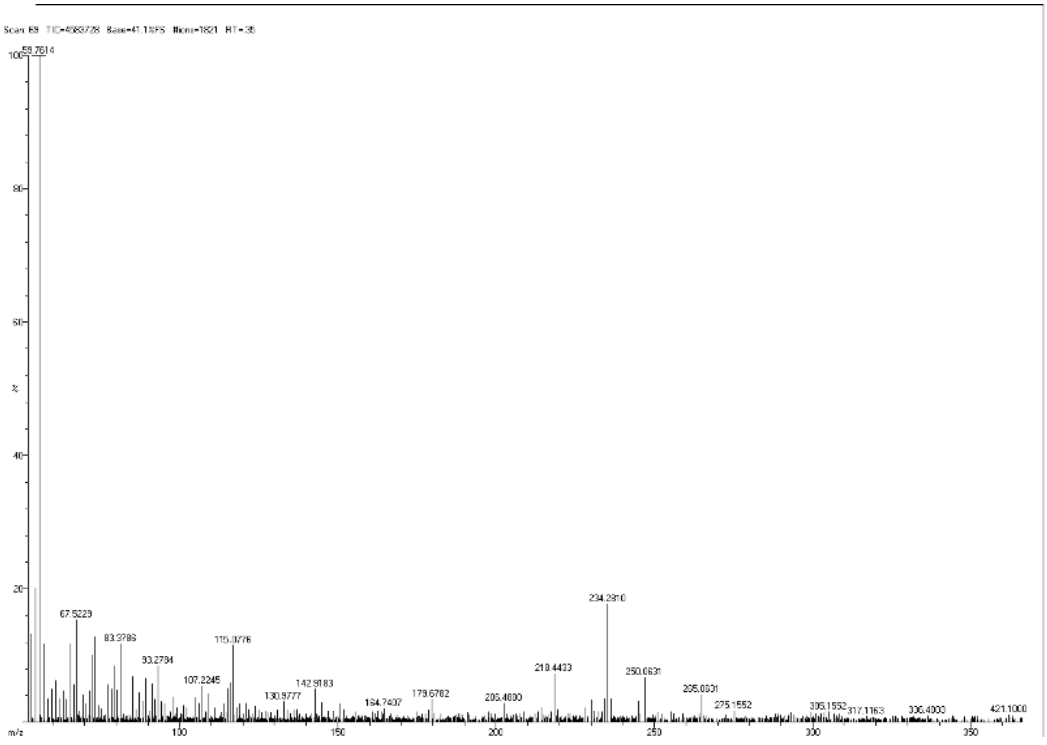
MASS Spectral study of the compounds synthesized:

Compound	Molecular ion peak
S-1	357.45(358)
S-2	419.52(421)
S-3	435.52(437)
S-4	433.55(435)
S-5	449.55(451)
S-6	325.32(329)
S-7	387.39(389)
S-8	403.39(407)
S-9	401.41(411)
S-10	417.44(424)

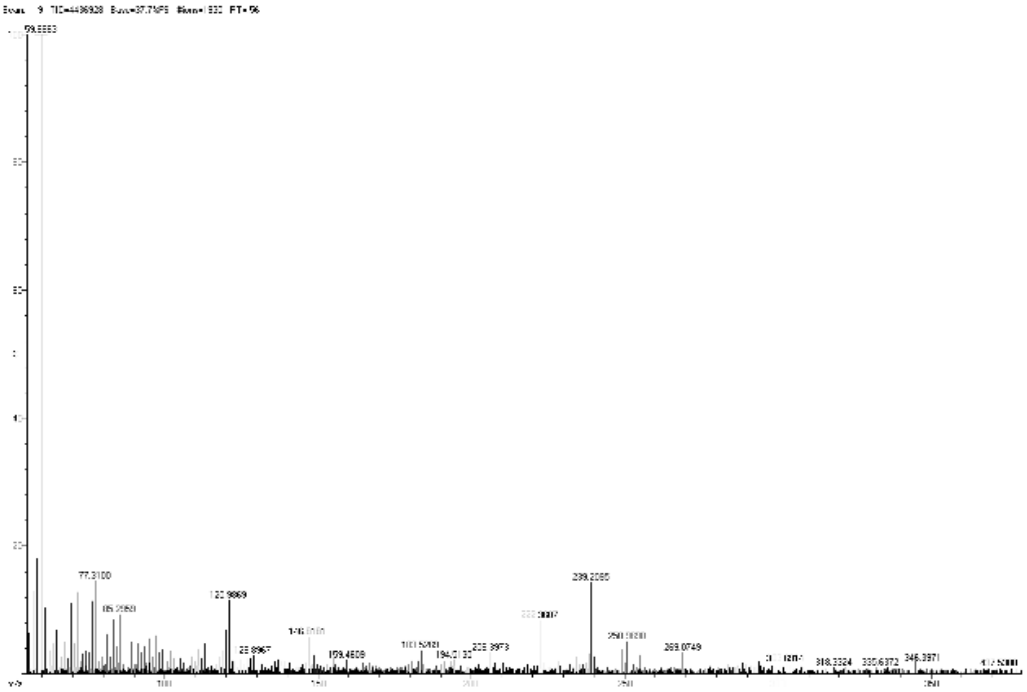
Compound-A1



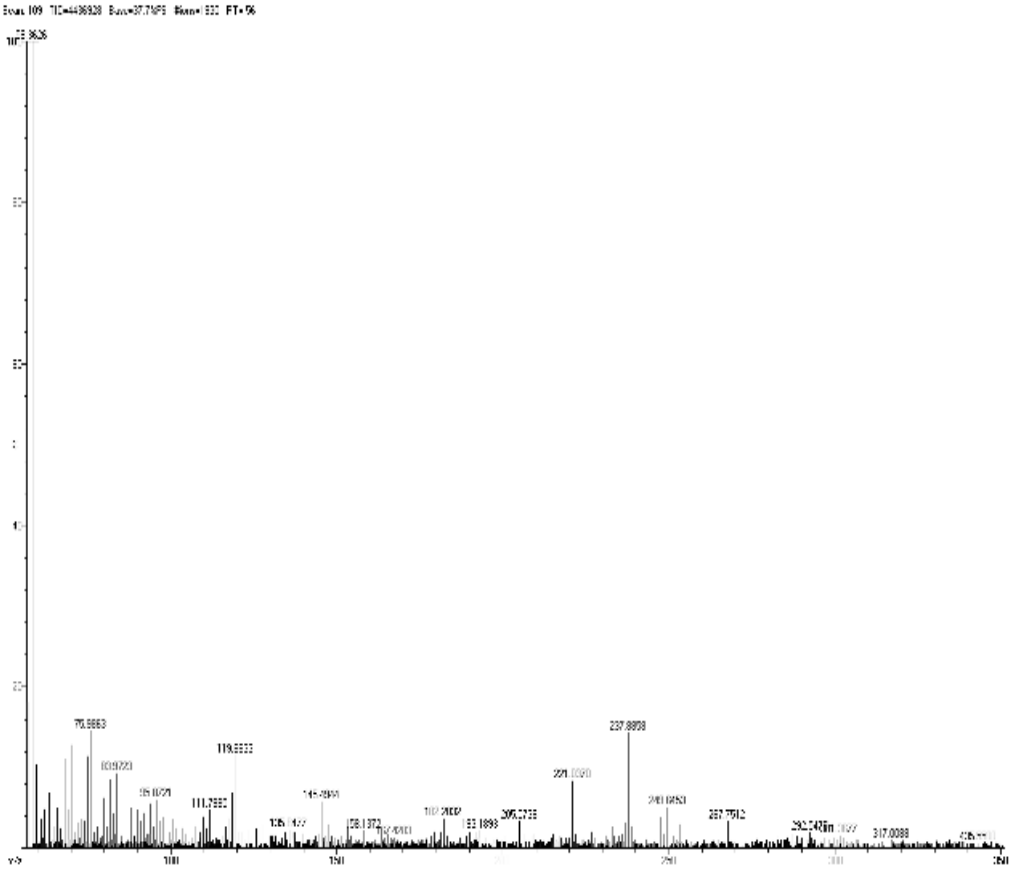
Compound-B1



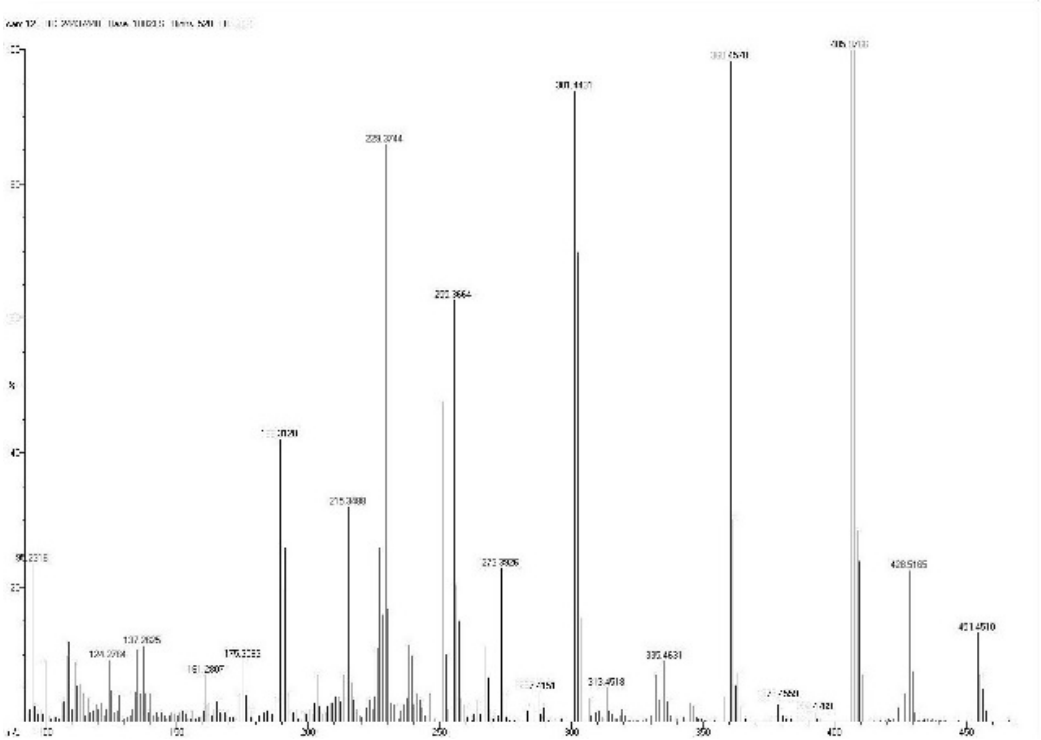
Compound-C1



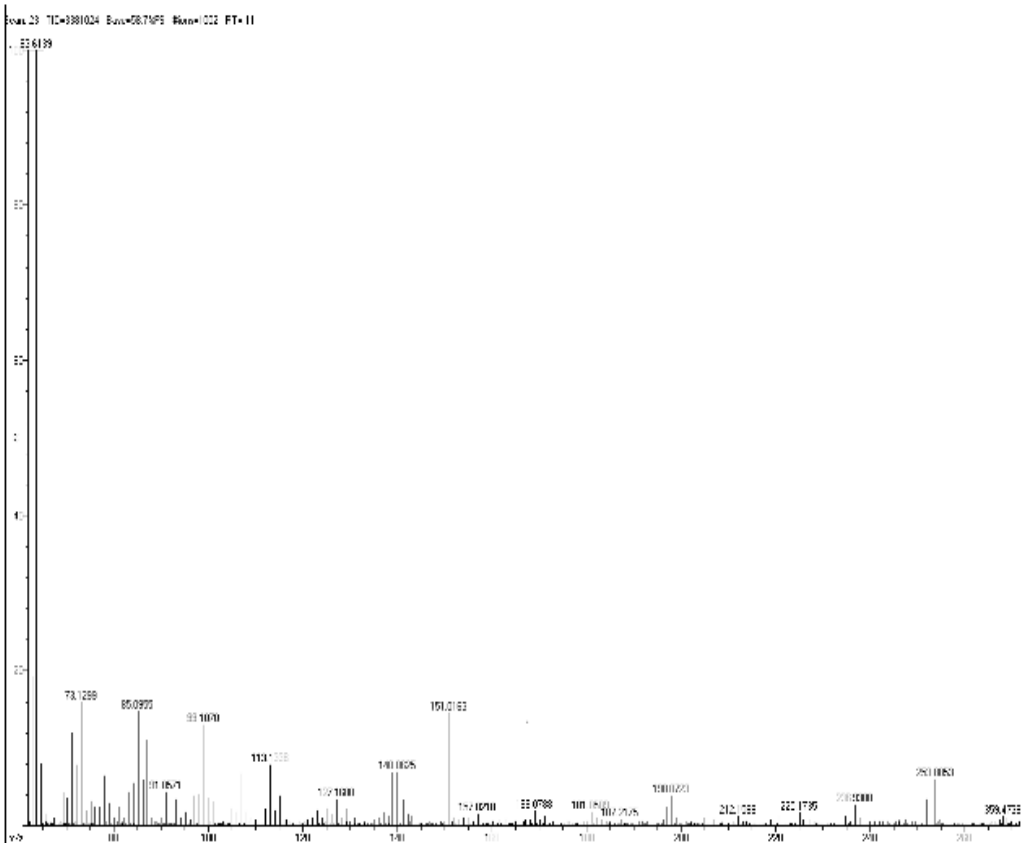
Compound-D1



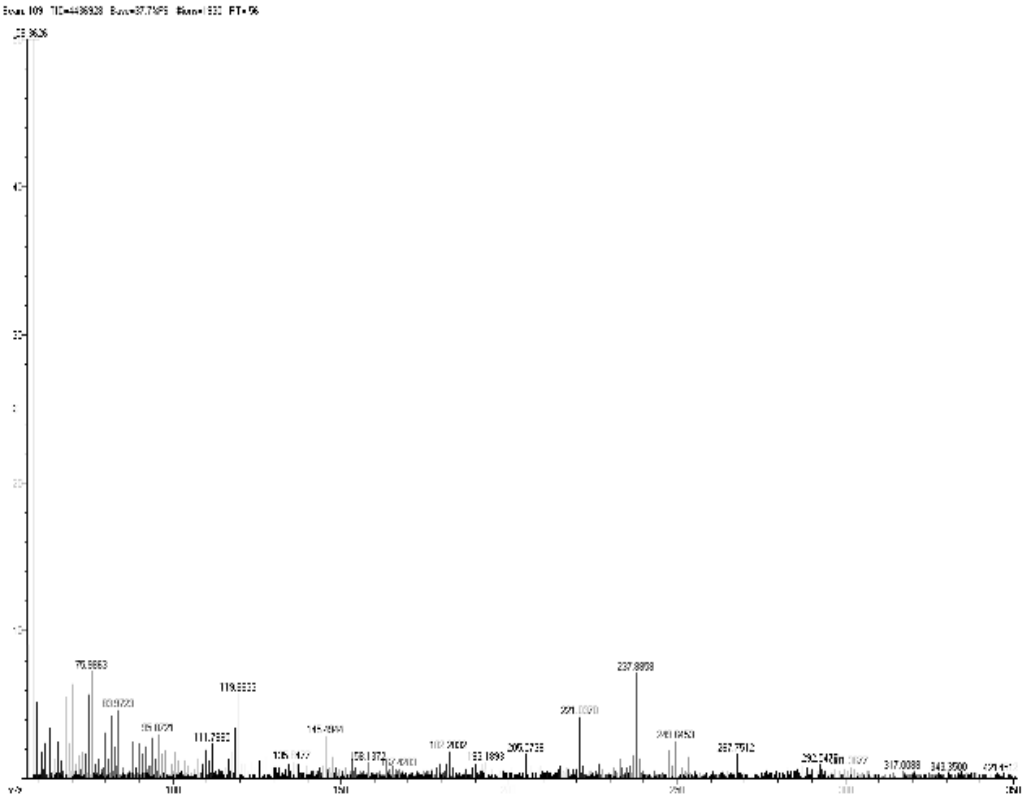
Compound-E1



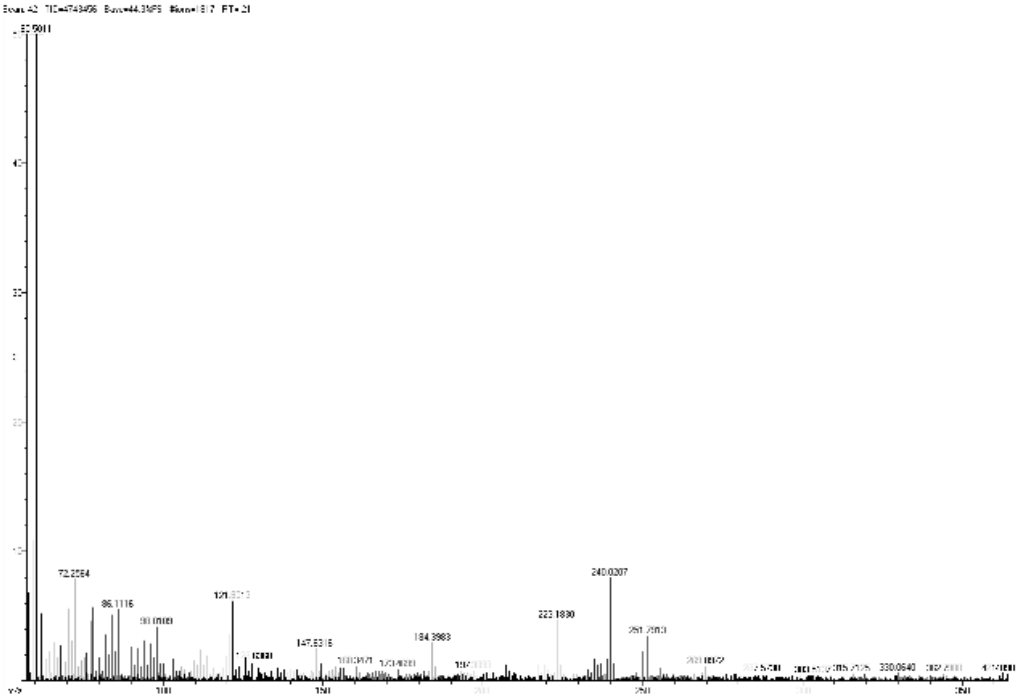
Compound-A2



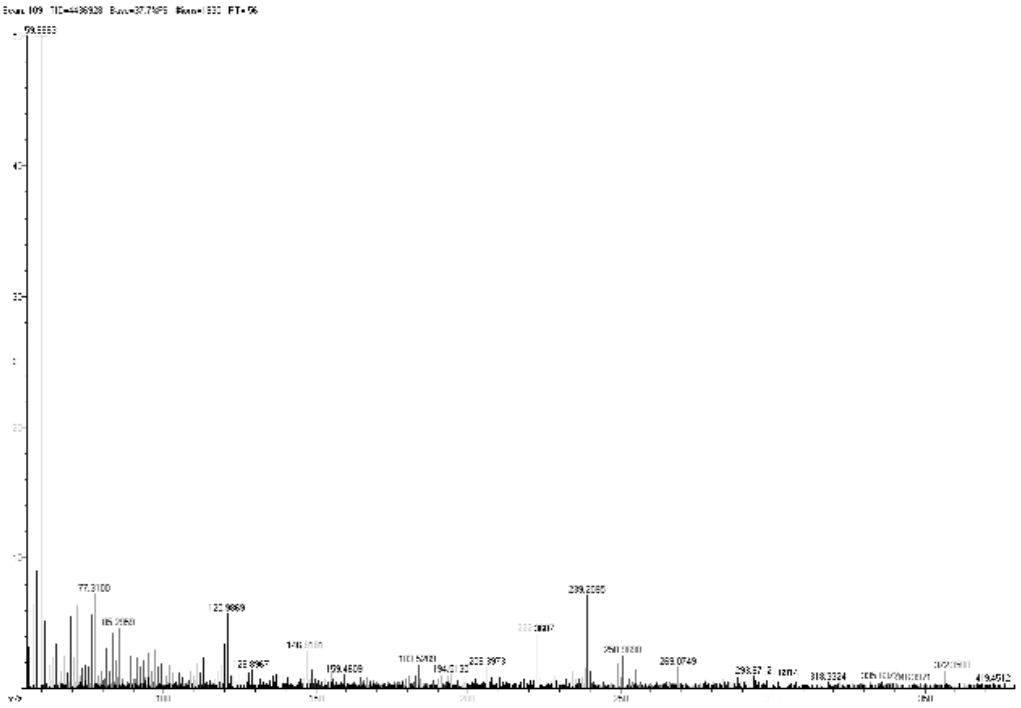
Compound-B2



Compound-C2



Compound-D2



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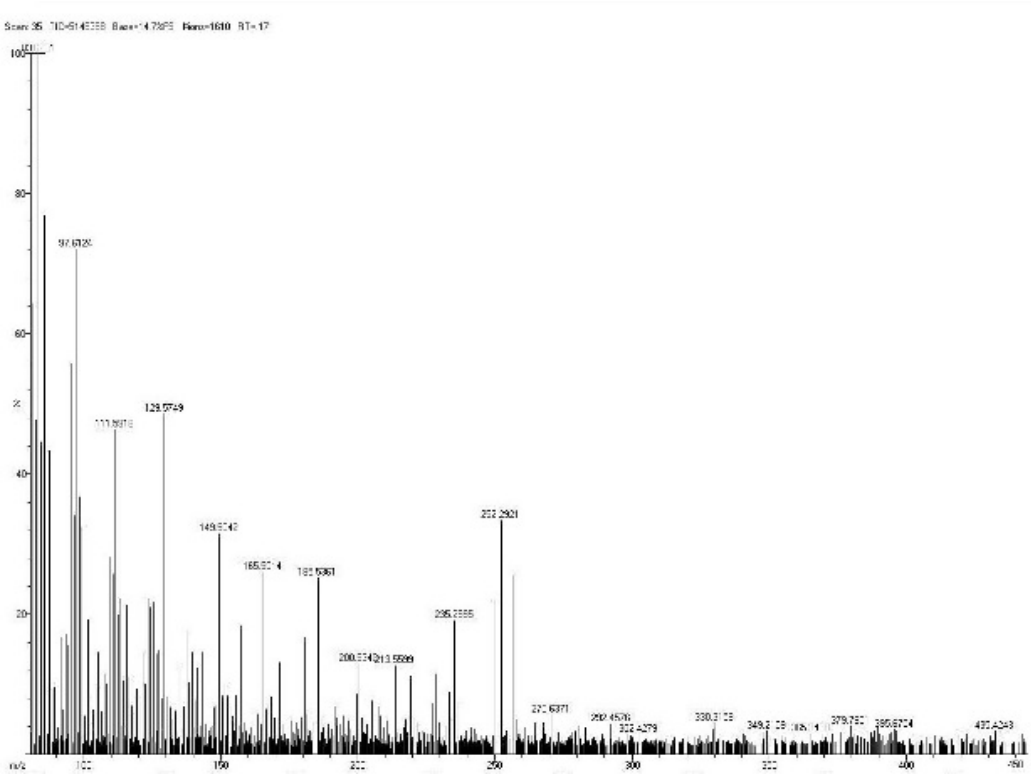


Table-17: % Reduction of Blood Glucose Level

Groups	Treatment/Dose	Blood glucose level (mg/dcl)					% Reduction in glucose level on 7th day
		Normal	0 day	2nd day	5th day	7th day	
Normal Control	1% CMC, 10 ml/kg	96.66±3.87	96.66±3.71	96.66±3.35	93.66±3.41	99.33±5.98	0
Positive Control	1% CMC, 10 ml/kg	100.66±1.85	204±4.86	215±3.08	230.16±5.19	247.16±6.21	0
Standard	Glybenclamide 0.25 mg/kg	107.33±4.02	264.16±11.51	133.5±2.72	127.83±5.7	113.66±3.42	56.97**
Compound-C1	50 mg/kg B.W	105.66±3.32	298.83±2.83	223.5±11.30	208.33±9.21	193.5±10.44	34.37**
Compound-C1	100 mg/kg B.W	106±2.35	297.33±6.51	282.16±6.23	264.5±6.04	257.16±7.76	13.5***
Compound-D1	50 mg/kg B.W	112.33±4.33	303.66±6.59	286.83±9.53	279.5±9.82	272.5±11.11	10.24***
Compound-D1	100 mg/kg B.W	107.83±4.15	293.66±7.43	280±6.26	271.66±6.18	260.66±4.17	11.24***

n=6, Results were presented as mean ± standard error of mean (SEM) and the statistical analysis was done using one way analysis of variance (ANOVA). A p-value of $p < 0.01$ was considered to be statistically significant.

** P<0.01; *** P<0.1

Figure-2

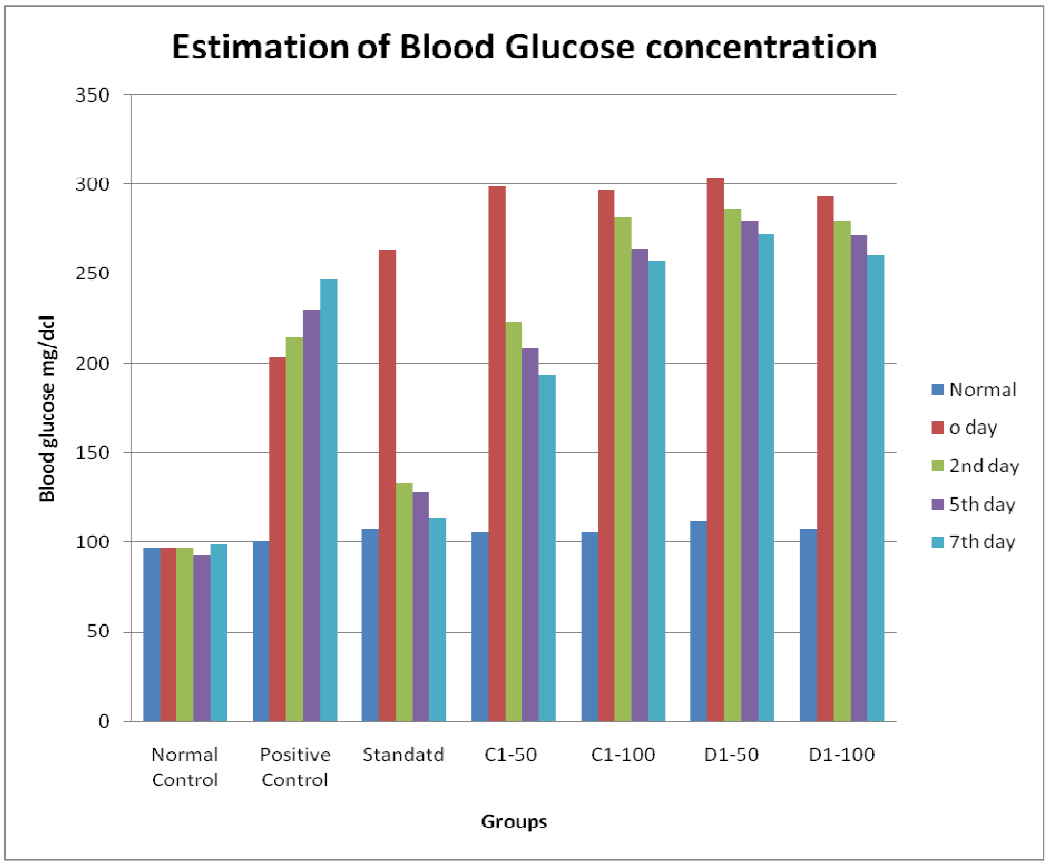


Figure-3

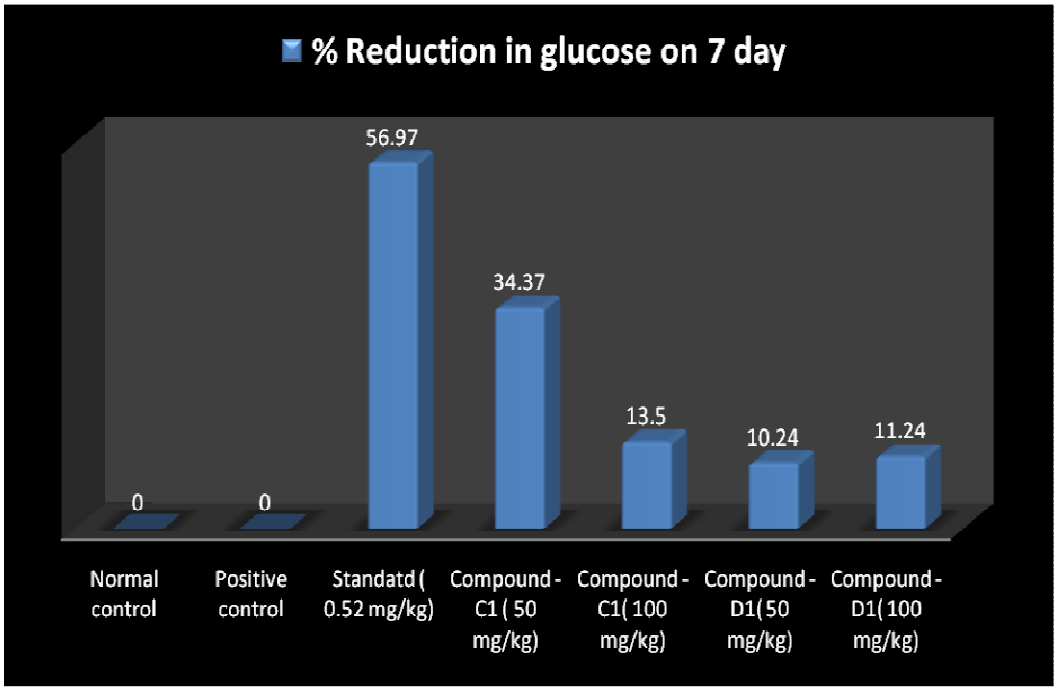


Table-18: Serum profile of experimental animals

Groups	Treatment/Dose	Biochemical parameters			
		Serum Urea (mg/dl)	Serum Creatinine (mg/dl)	Serum Cholesterol (mg/dl)	Serum protein (g/dl)
Normal Control	1% CMC, 10 ml/kg	30.09±1.09	0.52±0.02	104.60±2.02	6.17±0.16
Positive Control	1% CMC, 10 ml/kg	60.42±1.02	1.47±0.04	178.80±1.36	4.71±0.92
Standard	Glybenclimide 0.25 mg/kg	32.18±1.24	0.64±0.02	127.9±2.15	6.20±0.22
Com-C1	50 mg/kg B.W	37.33±0.64*	0.72±0.02*	132±2.64*	5.56±0.02
Com-C1	100 mg/kg B.W	59.24±1.48	1.29±0.02	170.4±6.26	4.57±0.13
Com-D1	50 mg/kg B.W	52.47±1.64	0.94±0.02	161±2.20	5.86±0.20
Com-D1	100 mg/kg B.W	44.21±1.82	0.91±0.02	147.00±2.68	5.72±0.15

Results were presented as mean ± standard error of mean (SEM), n=6, P<0.01
*Test is significant with standard
Figure-

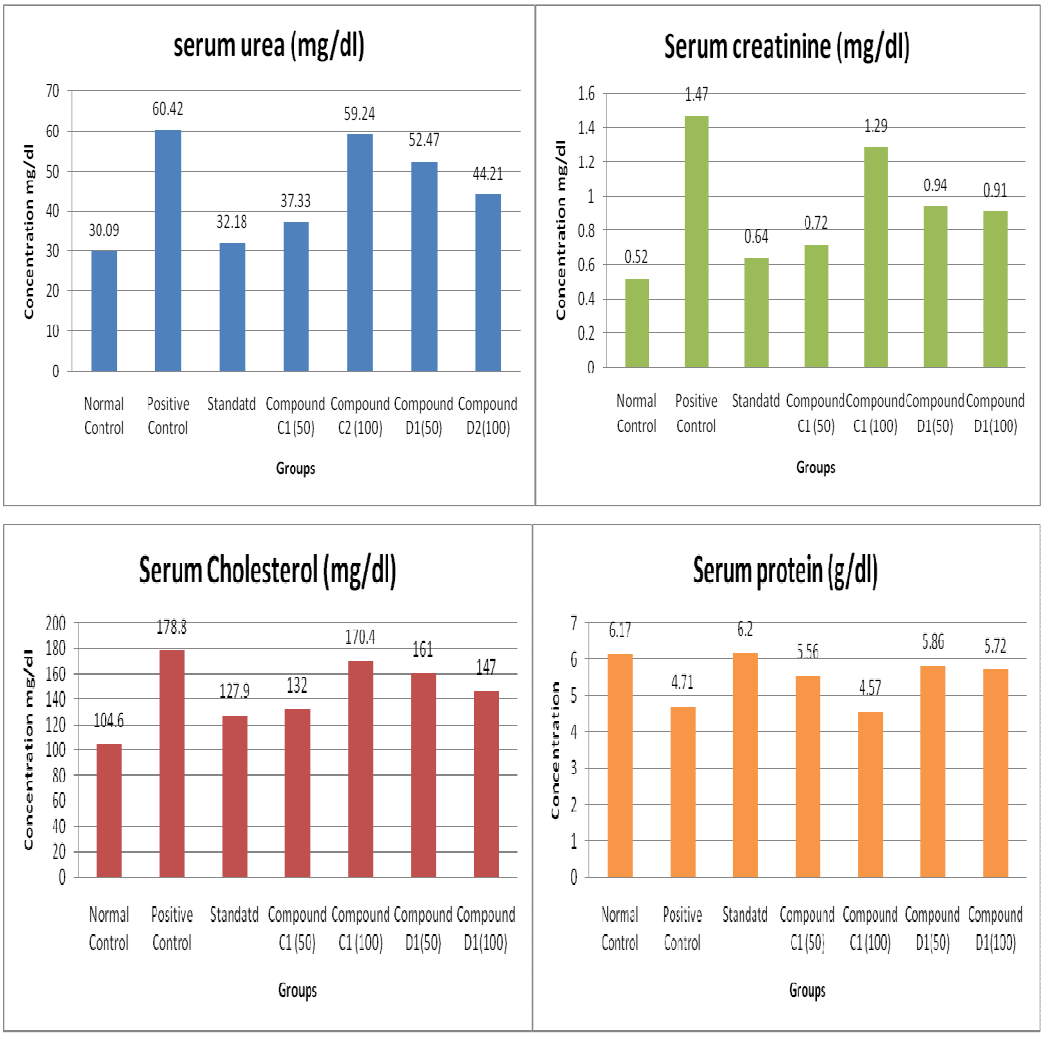


Table:19 Anti-Microbial activity(Zone of inhibition)

		Gram Postive			Gram Negative						Fungal
Compound	**Dose**	***S. epi***	***S. aurus***	***S. albus***	***E. coli***	***Proteus***	***S. thphi***	***Shigella***	***A. violaceum***	***X. monas***	***C. albicans***
A1	Control	6	8	5	10	7	6	6	7	9	6
	Standard	18	14	12	30**	18	25	18	16	18	17
	500 mcg	12	13	8	17	10	8	12	10	12	14
	1000 mcg	15	13	10	23**	12	14	14	11	15	14
	1500 mcg	14	12	9	20	15	14	12	14	15	15
	2000 mcg	15	12	10	20	17	15	10	14	14	15
B1	Control	6	7	9	6	10	6	8	9	6	7
	Standard	22	18**	16	24	19	21	15	19	26	12
	500 mcg	11	14	9	12	12	6	12	10	17	8
	1000 mcg	14	17**	13	15	12	9	16	14	19	7
	1500 mcg	15	15	15	15	13	7	17	16	20	9
	2000 mcg	15	15	12	16	14	8	15	16	20	10
C1	Control	8	6	7	9	6	7	6	11	8	12
	Standard	28	31	22	29**	24	27	29	23	20	24
	500 mcg	15	16	19	22	18	12	14	13	12	15
	1000 mcg	24	8	15	25**	16	12	17	17	12	16
	1500 mcg	22	12	19	19	19	14	14	19	14	13
	2000 mcg	22	12	20	22	20	16	12	20	17	13

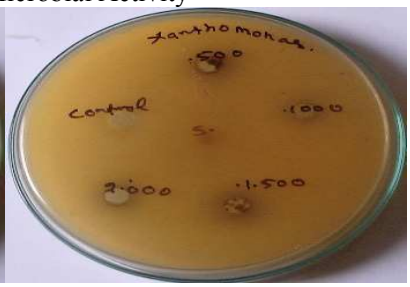
		Gram Postive			Gram Negative						Fungal
Compound	Dose	*S. epi*	*S. aurus*	*S. albus*	*E. coli*	*Proteus*	*S. thphi*	*Shigella*	*A. violaceum*	*X. monas*	*C. albicans*
D1	Control	8	7	10	6	9	8	6	10	11	10
	Standard	32	24	27	30	27**	29	28	30	25	29
	500 mcg	16	12	16	17	14	11	16	18	15	16
	1000 mcg	19	15	17	19	16	14	19	14	19	20
	1500 mcg	22	17	20	18	17	15	20	14	22	23
	2000 mcg	20	18	20	18	24**	17	23	15	22	25
E1	Control	9	7	11	8	10	6	9	6	10	8
	Standard	26	29	22	19	24	24	26	24	25	27**
	500 mcg	13	17	14	15	16	12	11	10	11	23**
	1000 mcg	19	19	16	15	15	16	19	14	16	21
	1500 mcg	19	17	17	18	17	14	21	17	19	22
	2000 mcg	21	18	19	17	19	16	20	16	20	23
A2	Control	8	9	7	10	7	11	6	8	7	8
	Standard	22	18	20	21	17	19	22	20	17	23
	500 mcg	11	14	13	12	10	11	14	15	10	11
	1000 mcg	14	15	13	13	10	10	16	16	12	13
	1500 mcg	15	14	15	15	12	12	17	18	14	15
	2000 mcg	17	14	17	16	14	12	19	18	13	17
B2	Control	7	6	7	9	10	6	6	10	6	8
	Standard	22	20	26	19	21	23	18	16	20	17
	500 mcg	11	12	14	9	13	10	9	11	10	10
	1000 mcg	13	13	16	12	15	12	11	14	13	13
	1500 mcg	12	11	13	10	14	12	15	10	13	14
	2000 mcg	13	11	15	10	14	10	13	11	16	14

		Gram Postive			Gram Negative						Fungal
Compound	Dose	*S. epi*	*S. aurus*	*S. albus*	*E. coli*	*Proteus*	*S. thphi*	*Shigella*	*A. violaceum*	*X. monas*	*C. albicans*
C2	Control	6	8	9	8	10	7	9	10	9	8
	Standard	20	19	22	25	26	29	30	24	22	20
	500 mcg	9	11	10	12	13	14	11	12	13	9
	1000 mcg	13	13	13	10	16	15	13	14	11	12
	1500 mcg	15	16	14	12	15	17	15	16	10	11
	2000 mcg	14	15	13	11	14	19	19	13	14	14
D2	Control	7	9	6	9	10	6	8	9	9	8
	Standard	26	26	23	28	21	20	19	24	22	20
	500 mcg	13	12	10	9	13	11	13	12	10	11
	1000 mcg	15	14	12	13	15	14	15	16	15	13
	1500 mcg	14	17	17	15	17	10	15	15	14	10
	2000 mcg	14	19	17	14	15	16	14	14	12	14
E2	Control	7	8	10	9	8	10	9	8	10	8
	Standard	24	20	21	19	26	17	22	20	19	18
	500 mcg	11	10	11	12	10	13	10	11	11	10
	1000 mcg	13	14	15	14	13	15	12	10	13	13
	1500 mcg	15	14	18	16	15	15	11	13	16	13
	2000 mcg	17	16	13	18	15	17	15	13	14	16

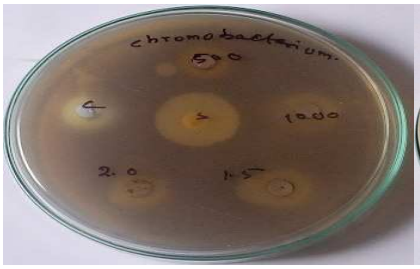
Note: ** Test is siginificant with Standard

Figure-4: Anti-Microbial Activity

E. coli

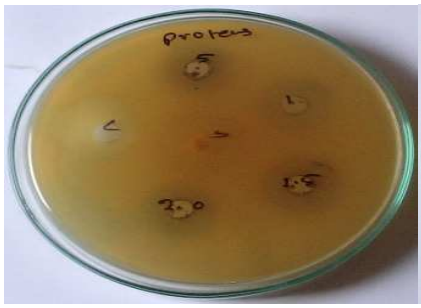


Xanthomonas

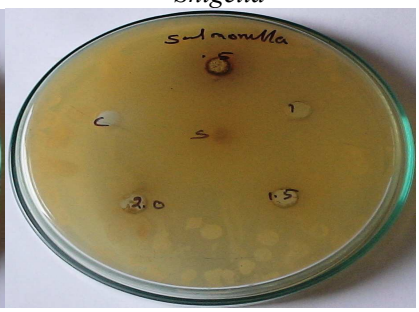


Chromobacterium

Shigella

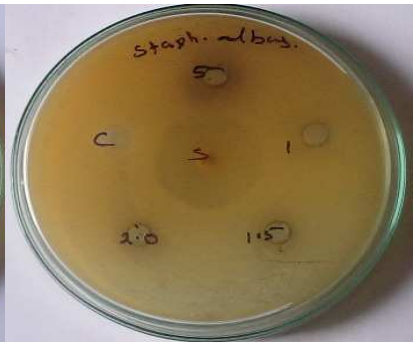


Proteus



Salmonella

Strepto cocci



Staph. albus

Step. Aurus

Candida albicans

Discussion

The molecular design shows that the synthesised compounds were accessed for the toxicity prediction and safety marigin by using "osrisis property explorer". It shows the drug likeness and drug score. The results were shown in the figure No.1 & Table-8.

The ADME property of synthesised compounds were predicted by using software tool "Molinspiration".

Lipinski Rule 5 were predicted for the synthesised compounds, compound A1, B1, C1, D1& E1 shows only one violation in basic properties. Compound A2, B2, C2, D2 & E2 shows two violation in basic properties. The results were shown in the table No-9.

The new series of 1,4 DHPs have been prepared from aldehydes, ethylacetoacetate & ammonium acetate by Hantzsch method. From the intermediate compounds A, B, C, D & E were reacted with thiosemicarbazide to give compound A1, B1, C, D1, E1 and react with semicarbazide to give compounds A2, B2, C2, D2 & E2. The physical data of synthesised were determined and results were shown in the table-10. The strucuture of synthesised compounds were confirmed by FTIR, 1 H NMR & Mass spectra. The results were shown in the table No-14,15 &16.

According to literature review and SAR of 1, 4 DHPs reveals that, substituted aromatic group at 4^{th} position significant for biological action. Based on that compound C1 & D1 were selected for anti-diabetic action.

LD50 of the synthesised compounds (C1&D1) were determined according to OECD guideliness 423, the lethality were found at dose 1000 mg/kg b.w. From lethal

dose, 1/10 & 1/20 consider as a effective dose. The results were shown in the table No- 5 &6.

Pancreas is the primary organ involved in sensing the organism's dietary and energetic states via glucose concentration in the blood and in response to elevated blood glucose, insulin is secreted. However, alloxan causes diabetes through its ability to destroy the insulin-producing -cells of the pancreas. When there are not enough available beta-cells to supply sufficient insulin to meet the needs of the body, insulin-dependent diabetes results .The cytotoxic action of alloxan is mediated by reactive oxygen species with simultaneous massive increase in cytosolic calcium concentration leading to rapid destruction of -cells. This results in a decrease in endogenous insulin secretion.

In the present study substituted 1, 4 DHPs (C1 & D1) were evaluated anti-hyperglycemic effect. In the normal fasted rats there was no siginificant hypoglycemic effect.

In alloxan induced diabetic rats revealed that compound C1-100, D1- 50 & 100 mg/kg b.w., has no siginificant antihyperglycemic effect ($P<0.1$) compare with standard. But the compound C1 at 50 mg/kg b.w., produced siginificant reduction in blood glucose level in compare with standard drug (glibenclamide) $P<0.01$. The results were shown in the table-17, figure- 2&3.

Serum profile shows the elevated level in control, test group (C1-100, D1 -50 & 100. But it decreases elevated level in test group C1-50 is significant with standard group & normal control. The results were shown in the table No-18, Figure-4.

Antibacterial activity:

1, 4 DHPs containing aromatic hydroxyl are well known for their anti-microbial properties. All 1,4 DHP derivatives were subjected to anti-microbial assay by Disc-diffusion method. The area of zone of inhibition was recorded in mm. All the 10 derivatives were evaluated for anti-bacterial activity against both gram positive and gram negative bacteria.

In the antibacterial screening of the synthesized compounds most of them showed moderate antibacterial activity at various concentrations as compared to the standard (Ciprofloxacin). It is seen that these compounds showed some activity against gram negative as compared to gram positive microorganisms.

Gram positive - Compound B1 significant with standard at 500 mcg/ml for *S. aureus*.

Gram negative - Within the series, C1>A1 *(E. coli),* D1 *(Proteus)* significant with standard.

Anti-fungal activity

The synthesized compounds were subjected to antifungal activity by the disc diffusion method. The antifungal activity was evaluated against *Candida albicans* and their zone of inhibition in mm were recorded and compared with the standard Ketoconazole. Within the series, the compound E1 shown significant with standard. The results were shown in the table No.19 & Figure No-5.

Summary
&
Conclusion

Summary & Conclusion

The main focus of this research work was to synthesize new series of 1,4 DHPs and look for their better antibacterial and antifungal activity. The yield of the newly synthesized DHP series were found to be in the range from 36 to 42%. The identification of the structures was ascertained by melting point and TLC. Structure of the synthesized compounds were confirmed and characterized with the help of IR, ^{1}H-NMR and mass spectra.

The IR data of synthesized new series of 1, 4 DHPs clearly showed the presence of functional groups C-S, C=N, N-H, and aromatic rings. The ^{1}H-NMR data also showed characteristic peaks of NH and Ar H have been confirmed.

The current study provides some useful insight into the anti-hyperglycemic potency of new series of 1,4 DHPs in alloxan induced diabetes and antimicrobial activity of wide range of bacteria and fungi.

The antibacterial activity of 1,4 DHP derivatives were produced $+^{ve}$ results. In the series of synthesized compounds B1 significant with standard (G $^{+ve}$) and compounds A1&C1 were shown greater activity against *E. Coli*, D1 against *proteus*. The antifungal activity E1 compound showed superior activity.

However, we suggest that further work should be carried out at molecular level to find out the absolute mechanism of action of 1,4 DHPs in experimental diabetes and wide range of micro-organisms.

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