MOLECULAR DESIGN, SYNTHESIS, CHARACTERIZATION &

IN-VITRO BIOLOGICAL EVALUATION OF SOME SUBSTITUTED QUINOXALINE-2(1H) ONE DERIVATIVES

Dissertation submitted to

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MASTER OF PHARMACY

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COLLEGE OF PHARMACY
MADURAI MEDICAL COLLEGE
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Madurai-20

CERTIFICATE

This is to certify that the dissertation entitled "***MOLECULAR DESIGN, SYNTHESIS, CHARACTERIZATION & IN-VITRO BIOLOGICAL EVALUATION OF SOME SUBSTITUTED QUINOXALINE-2(1H) ONE DERIVATIVES"*** was done by **Miss. R. Parvathi Devi, (Reg. No: 26108632)** 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.

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

Station: Madurai **DR. (Mrs.) Ajithadas Aruna, M.pharm.,Ph.D.,**

Date:

Evaluation Certificate

Internal Examiner

External Examiner

DEDICATED TO

MY BELOVED PARENTS,

GUIDE,

ALMIGHTY

&

MY WELL WISHERS……✍

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CONTENTS

LIST OF ABBREVATIONS

^{0}C	:	Degree Centigrade
µg	:	Microgram
%	:	Percentage
gm	:	Gram
mg	:	Milligram
ml	:	Milliliter
m.p	:	Melting point
pH	:	Hydrogen ion concentration
^{1}H-NMR	:	Proton Nuclear Magnetic Resonance
IR	:	Infra Red
h	:	Hour
mts	:	Minutes
M	:	Mole
DMF	:	Dimethyl formamide
TLC	:	Thin Layer Chromatography
Ar	:	Aromatic
o, m. p	:	Ortho, Meta, Para
δ	:	Delta
ppm	:	Parts per million
m/z	:	Mass / charge
R_f	:	Retention factor
m.f	:	molecular formula
m.w	:	molecular weight
DMSO	:	Dimethyl sulfoxide
Comp.code	:	compound code
C	:	carbon
H	:	hydrogen
N	:	nitrogen

O	:	oxygen
S	:	sulphur
Cl	:	chlorine
mm	:	millimeter
E.coli	:	Escherichia coli
S.aureus	:	Staphylococcus aureus
P.aeruginosa	:	Pseudomonas aueroginosa
K.pneumoniae	:	Klebsiella pneumoniae
MTT assay	:	Microculture tetrazolium assay
HCT116	:	Human colorectal carcinoma cell line
R^2	:	Regression coefficient
IC 50	:	Inhibition concentration (50%)

Introduction

1. GENERAL INTRODUCTION

Medicinal Chemistry is a science whose roots lie in all branches of Chemistry and Biology. The practice of Medicinal Chemistry is devoted to the discovery and development of new agents for treating diseases. Medicinal Chemistry occupies a strategic position at the interface of Chemistry and Biology.

The earliest drug discoveries were made by the presumably random sampling of higher plants. However in recent year the introduction of new synthetic pharmaceuticals has out placed that of natural products.

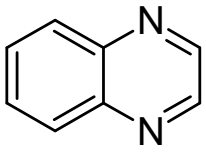
Hundreds of thousands of new organic chemicals are prepared annually throughout the world, and many of them are entered into pharmacologic screens to determine if they have useful biologic activity. This process of random screening is inefficient, but it has resulted in the identification of new lead compounds not produced naturally or imagined by chemists.

Once of new pharmaceutical lead compound has been discovered, extensive and costly efforts usually are made to prepare a series of analogue in the hope that even better activity will be found such programs included the branching, lengthening or shortening of chain structure, the variation of the kinds and positions of substituents, the replacement of rings by similar cyclic structures and other empirical molecular modifications within the framework of reasonably close analogy.

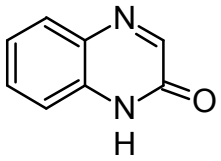
Quinoxalinones –an outlook

Quinoxalinone is well known for its broad coverage in the field of medicine as well as for its application in the pharmaceuticals. Quinoxalinone and its derivative have shown wide range of biological properties such as antimicrobial, antitubercular, antiprotozoal, anticandida, anti-AIDS activities. Quinoxalin-2-ones display interesting biological properties, including the inhibition of the Aldose reductase enzyme, partial

agonists for complex receptors γ-aminobutyricacid(GABA)/benzodiazepine2, potent antithrombotic



quinoxaline



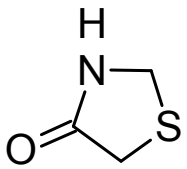
quinoxaline-2(1H) one

Quinoxaline, also called a benzopyrazine, in organic chemistry, is a heterocyclic compound containing a ring complex made up of benzene ring and pyrazine ring and they are isomeric with cinnolenes, phthalazines and quinazolines. Synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin, levomycin and actinomycin.

Quinoxaline and its derivatives have shown wide range of biological properties such as Antimicrobial, Antibacterial, Antitubercular, Antiprotozoal, Anti-candida, Anticancer, Anti- AIDS, and Antiinflammatory

4-Thiazolidinones-An outlook

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. antimicrobial, anticonvulsant , analgesic, anti-inflammatory, anticancer, Follicle stimulating hormone (FSH) receptor agonist activity and CFTR inhibitor The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated chloride channel,which when mutated can produce the hereditary disease cystic fibrosis. CFTR inhibition is a potential strategy for therapy of secretory diarrhoeas



Hydrazone –An outlook

Hydrazone constitute an important class of compounds for new drug development. Hydrazones containing an azometine -NHN=CH- proton are synthesized by heating the appropriate substituted hydrazines/hydrazides with aldehydes and ketone in solvent.

.Hydrazones have been reported to possess, antimicrobial, antitubercular ,anticonvulsant ,analgesic, anti-inflammatory antiplatelet ,anticancer ,antifungal, antiviral , ,antibacterial and antimalarial activities

Cancer

Cancer (medical term: malignant neoplasm) is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from bengin tumours, which are self-limited, and do not invade or metastasize.

What causes cancer?

- Cancer arises from the mutation of a normal gene.
- Mutated genes that cause cancer are called oncogenes.
- It is thought that several mutations need to occur to give rise to cancer

- Cells that are old or not functioning properly normally self destruct and are replaced by new cells.
- However, cancerous cells do not self destruct and continue to divide rapidly producing millions of new cancerous cells.
- A factor which brings about a mutation is called a **mutagen**. A mutagen is **mutagenic.** Any agent that causes cancer is called a carcinogen and is described as **carcinogenic**. So some mutagens are carcinogenic.

carcinogens:

- Ionising radiation – X Rays, UV light
- Chemicals – tar from cigarettes
- Virus infection – papilloma virus can be responsible for cervical cancer.
- Hereditary predisposition – Some families are more susceptible to getting certain cancers, it cannot be inherited just that more susceptible to getting it.

Classification

Cancer are classified by the type of cell that resembles the tumor and, therefore, the tissue presumed to be the origin of the tumor. These are the histology and the location, respectively. Example of general categories includes:

- **Carcinoma:** Malignant tumors derived from epithelial cells. This group represents the most common cancers, including the common forms of breast, prostate, lung and colon cancer.
- **Sarcoma:** Malignant tumors derived from connective tissue, or mesenchymal cells.
- **Lymphoma and leukaemia:** Malignancies derived from hematopoietic (blood-forming) cells.

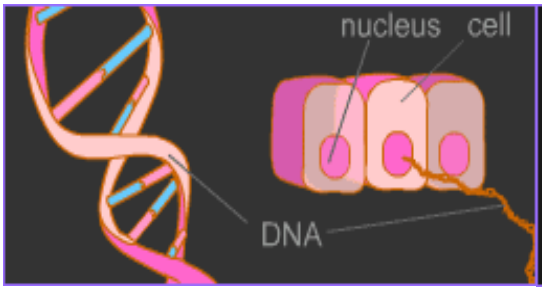
- **Germ cell tumor**: Tumor derived from totipotent cells. In adults most often found in the testicle and ovary; in foetuses, babies and young children most often found on the body midline, particularly at the tip of the tailbone; in horses most often found at the poll(base of the skull).
- **Blastic tumor or blastoma:** A tumor (usually malignant) which resembles an immature or embryonic tissue. Many of these tumors are most common in children.

Malignant tumors (cancers) are usually named using **–carcinoma**, **-sarcoma** or **–blastoma** as a suffix, with the Latin or Greek word for the organ of origin as the root. For instance, a cancer of the liver is called *hepatocarcinoma;* a cancer of the fat cells is called *liposarcoma.* For common cancers, the English organ name is used. For instance, the most common type of breast cancer is called *ductal carcinoma* of the breast or *mammary ductal carcinoma*. Here, the adjective ductal refers to the appearance of the cancer under the microscope, resembling normal breast ducts.

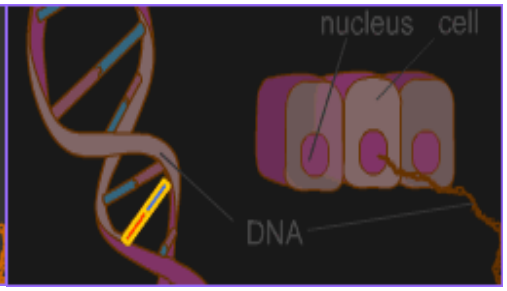
Benign tumors (which are not cancers) are named using **–oma** as a suffix with the organ name as the root. For instance, a benign tumor of the smooth muscles of the uterus is called leiomyoma (fibroid).

STAGES INVOLVED IN THE DEVELOPMENT OF CANCER

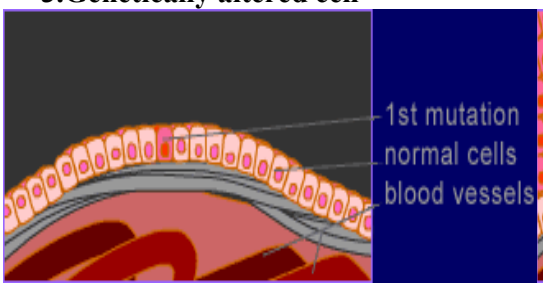
1. Normal cell



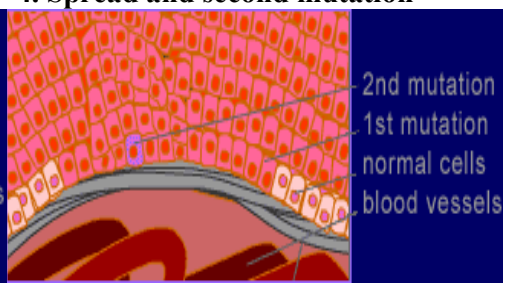
2. Mutation of DNA



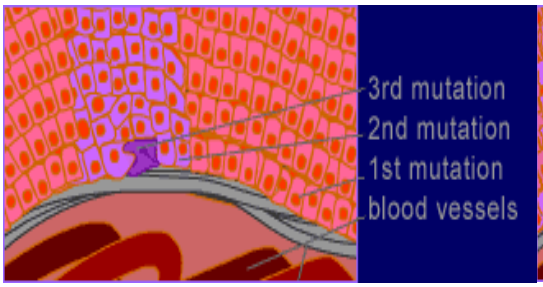
3.Genetically altered cell



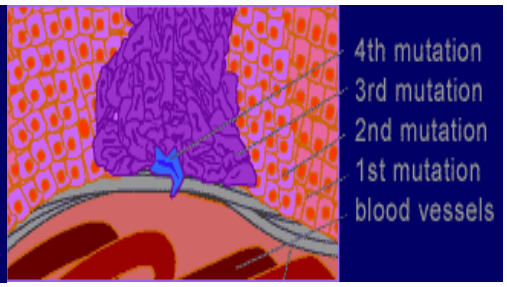
4. Spread and second mutation



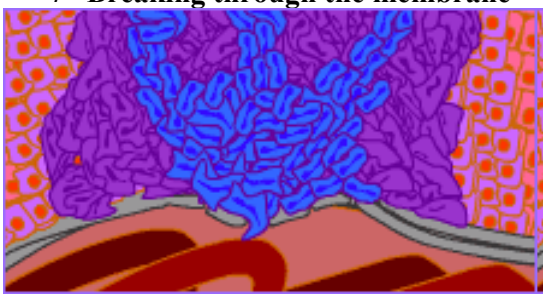
5. Third mutation



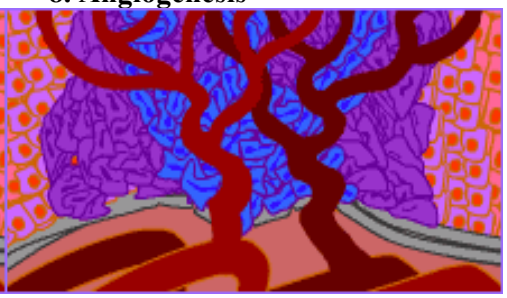
6. Fourth mutation



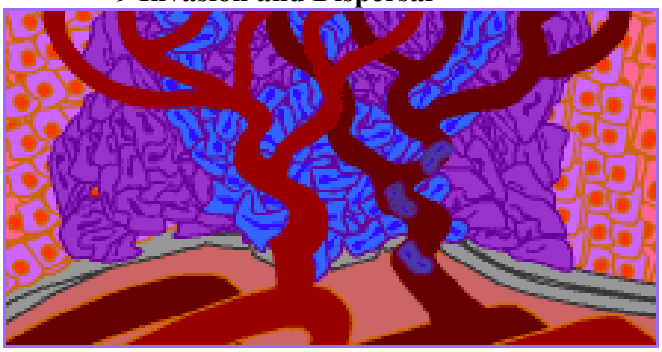
7 Breaking through the membrane



8. Angiogenesis



9 Invasion and Dispersal



1. DNA of a normal cell

This piece of DNA is an exact copy of the DNA from which it came. When the parent cell divided to create two cells, the cell's DNA also divided, creating two identical copies of the original DNA.

2. Mutation of DNA

With this section of DNA, one of the base pairs is different from the original. This DNA has suffered a mutation, either through mis-copying (when its parent cell divided), or through the damaging effects of exposure to radiation or a chemical carcinogen.

3. Genetically altered cell

Body cells replicate through mitosis. The DNA of the cell highlighted above has a mutation that causes the cell to replicate even though this tissue doesn't need replacement cells at this time or at this place.

4. Spread and second mutation

The genetically altered cells (look like normal cell and carry two mutant gene) have, overtime, reproduced unchecked, crowding out the surrounding normal cells. The growth may contain one million cells.

5. Third mutation

A mutation may simply cause a cell to keep from self-destructing. All normal cells have surveillance mechanisms that look for damage or for problems with their own control systems. If such problems are found, the cell destroys itself. Over time and after many cell divisions, a third mutation may arise.

6. Fourth mutation

At this point the next mutation paves the way for the development of an even more aggressive cancer

7. Breaking through the membrane

The newer, wilder cells created by another mutation are able to push their way through the epithelial tissue's basement membrane. At this point the cancer is still too small to be detected

8. Angiogenesis

The tumour has broken through the basement membrane (as pictured above), angiogenesis takes place.Angiogenesis is the recruitment of blood vessels from the network of neighbouring vessels.

9. Invasion and Dispersal

Individual cells from the tumour enter into the network of newly formed blood vessels, using these vessels as highways by which they can move to other parts of the body.

10**. Metastasis**

To form a secondary tumour, a tumour cell needs to leave the vessel system and invade tissue. The cell must attach itself to a vessel's wall. Once this is done, it can work its way through the vessel and enter the tissue. Although perhaps less than one in 10,000 tumour cells will survive long enough to establish a new tumour site, a few survivors can escape and initiate new colonies of the cancer.

Signs and Symptoms

Symptoms of cancer metastasis depend on the location of the tumor.

Roughly, cancer symptoms can be divided into three groups:

- Local symptoms: Unusual lumps or swelling (tumor), hemorrhage (bleeding), pain and/or ulceration. Compression of surrounding tissues may cause symptoms such as jaundice (yellowing the eyes and skin).

- Symptoms of metastasis (Spreading): Enlarged lymph nodes, cough and hemoptysis, hepatomegaly (enlarged liver), bone pain, fracture of affected bones and neurological symptoms. Although advanced cancer may cause pain, it is often not the first symptom.
- Systemic symptoms: Weight loss, poor appetite, fatigue and cachexia (wasting), excessive sweating (night sweats), anaemia and specific paraneoplastic phenomena, i.e. specific conditions that are due to an active cancer, such as thrombosis or hormonal changes.

Every symptom in the above list can be caused by a variety of conditions (a list of which is referred to as the differential diagnosis). Cancer may be a common or uncommon cause of each item.

Anti-microbial drugs

The control of microorganism is critical for the prevention and treatment of disease. Microorganisms also grow on and within other organism, and microbial colonization can lead to disease, disability, and death. Thus the control or destruction of microorganisms residing within the bodies of humans and other animals is great importance.

Antibiotics are chemical substances excreted by some microorganism which inhibit the growth and development of other microbes. Some of these drugs that were obtained naturally were put to chemical modifications in attempts to enhance beneficial effects while minimizing the toxic effects. The resultant modified product is termed as semi synthetic antibiotics. Most antibiotic currently used are semi synthetic. The chemist has synthesized many drugs that have got the antibacterial property and less toxicity. These drugs are called synthetic antibiotic drugs. Naturally occurring antibiotics, their semi synthetic derivatives and

synthetic antibiotics have got the same target. i.e., antimicrobial action. Hence all these drugs were put together to be called antimicrobial agents.

General Characteristics of Antimicrobial Drugs:

A successful chemotherapeutic agent must have selective toxicity. It must kill or inhibit the microbial pathogen while damaging the host as little as possible. The degree of selective toxicity may be expressed in following terms.

a) The therapeutic dose, the drug level required for clinical treatment of a particular infection.
b) The toxic dose, the drug level at which the agent becomes too toxic for the host.

The therapeutic index is the ratio of the toxic dose to the therapeutic dose. The larger the therapeutic index, the better the chemotherapeutic agent

Thus anti-microbial are divided in to

1. Antibacterial drugs
2. Antiviral drugs
3. Antifungal drugs
4. Antiprotozoal drugs
5. Anthelmintic drugs.

Chemotherapeutic agents can be either bactericidal or bacteriostatic.

Introduction to anti-inflammatory drugs

In order to screen new potential anti-inflammatory-anti-arthritic compounds, one must have clear understanding about the prime cause of inflammation, the nature of inflammation, target organ involved, various stages of inflammation, biochemical and other systemic changes due to inflammation.

Inflammation may broadly classify into three categories:

(1) **Acute inflammation**.

When a tissue injury is caused by a single event such as mechanical trauma, a thermal or chemical burn or a single exposure to non-replicating antigen the protective phenomena results in inflammation and repairative process proceeds smoothly from injury to recovery.

(2) **Chronic inflammation**.

There are many diseases which are distinguished by signs and symptoms characteristic of response to chronic inflammatory process of unknown etiology ss Ex: rheumatic fever, rheumatoid arthritis, ankylosing spondylitis and osteoarthritis,

(3) **Miscellaneous kinds of inflammation**.

This category may include allergic and dermatological disorders.

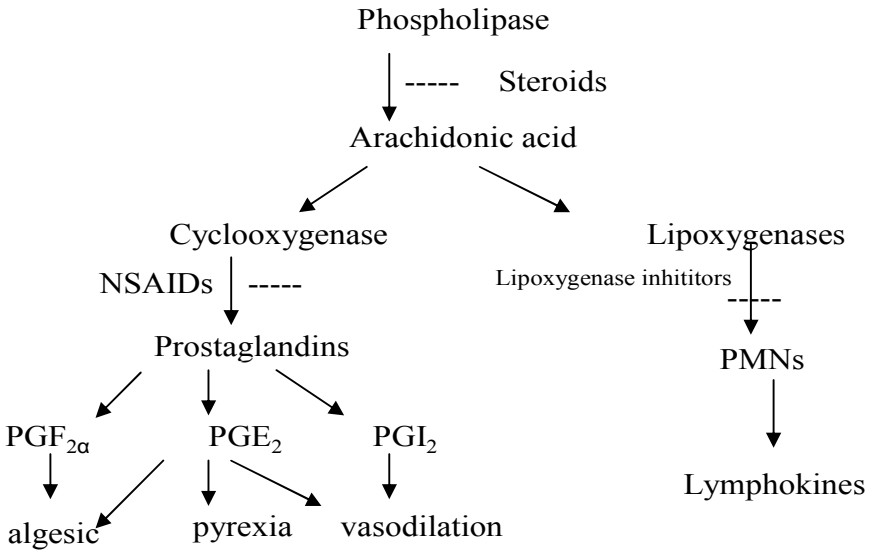
NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps Aspirin (also an NSAID) is used to inhibit the clotting of blood and prevent strokes and heartattacks in individuals at high risk. NSAIDs also are included in many cold and allergy preparations.

Mechanism of NSAIDS

Prostaglandins are produced within the body's cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach. Nonsteroidal antiinflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and

blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

The events of the inflammtory response and mechanisms of anti-flammatory

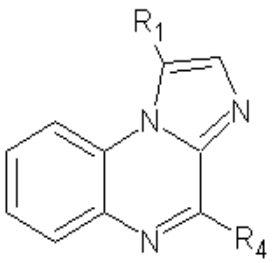


Thus attempt is made to review the inflammation, various factors involved in the inflammatory process, available methods for screening potential anti-inflammatory agents which would come near enough to steroids without any deleterious effects. and finally future trend of research in the field of inflammation or connective tissue dis-orders.

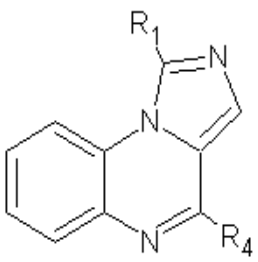
2. Literature Review

Anti cancer activity

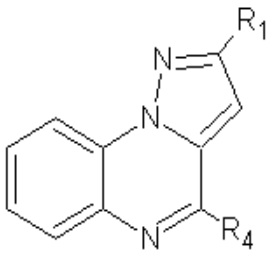
1) Moarbess G., *et al.*, were assessed In-vitro cytotoxicity studies against melanoma (A375, M4Be, and RPMI-7591), colon (LS174T), breast (MCF7), and lymphoma (Raji) human cancer cell lines. In vivo studies were carried out in M4Be xenografted athymic mice. EAPB (I), EAPB (II), EAPB (III), showed significant in vitro activities against A375 compared to fotemustine and imiquimod used as references.



EAPB (I)



EAPB (II)

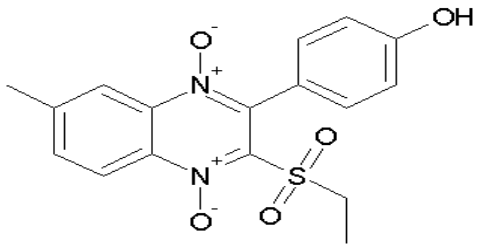


EAPB (III)

Substituted pyrazolo[1,5-*a*]quinoxaline

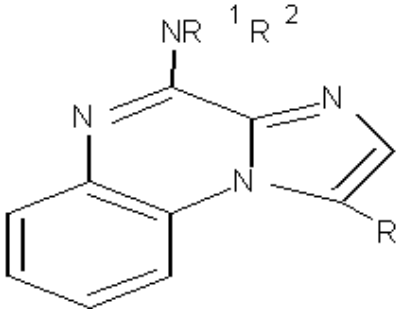
Where, R_1=$(CH3)_2$–CH–CH_2–,C_6H_5–$(CH_2)_2$–andR_4=CH_3–NH–NH_2

2) Weng Q., *et al.,* Synthesized compounds a and showed that 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline 1,4-dioxide (Q39), derived from Quinoxaline 1,4-Di-N-oxide, possessed high anti-cancer activity in hypoxia. Cytotoxicity assay demonstrated that Q39 is a potential and high efficient anti-cancer compound in all tested cell. In their work showing the mechanism of Q39 in hypoxia.



Chemical structure of Q39

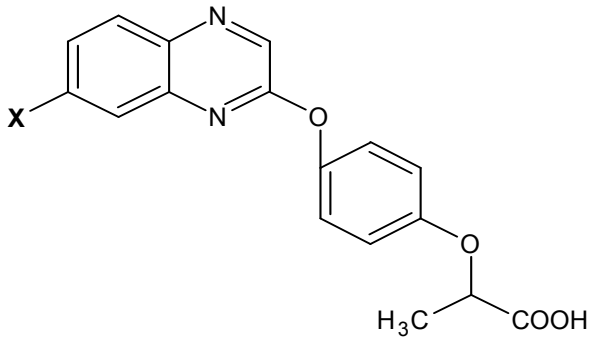
3) Masquefa C., *et al* .,were synthesized New series of imidazo[1,2-a]quinoxaline analogues have been in good yields via a bimolecular condensation of 2-imidazole carboxylic acid, followed by a coupling with ortho-fluoroaniline and subsequent substitution on the imidazole ring by Suzuki Cross-coupling reaction using microwave assistance. Antitumor activities of these derivatives were evaluated by growth inhibition of A375 cells in vitro. It was proposed that all compounds exhibited high activities compared to imiquimod and fotemustine used as reference.



Where, R= $(CH_3)_2CHCH$, R= $C_6H_5\,(CH_2)_2$

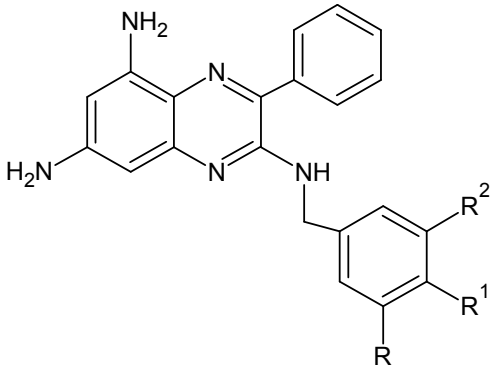
Iimidazo [1, 2-a]quinoxaline analogues

4) Stuart T. Hazeldine., *et al.,* carried out Synthetic modification of the 2-oxypropionic acid moietyin 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469).All halogenated derivatives of above showed to be active antitumor activity of colon cancer cells



X= Cl,F,Br,I

5) Paloa Caronoa., et al., synthesized 5,7-diamino-3- phenyl-2-benzylamino, 2-phenoxy and 2-phenylthio substituted quinoxalines. The compound 1b-6b exhibited better anticancer activity for lung, breast cancer cells.



1b: R = R2 = H; R1 = OCH3

2b: R = R2 = OCH3; R1 = H

3b: R = R1 = OCH3; R2 = H

4b: R = R1 = R2 = OCH3

5b: R = R1 = Cl; R2 = H

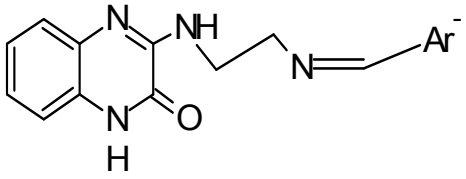
6b: R = R2 = H; R1 = F

7b: R = R2 = H; R1 = CO-Glu-Et

Anticonvulsant activity

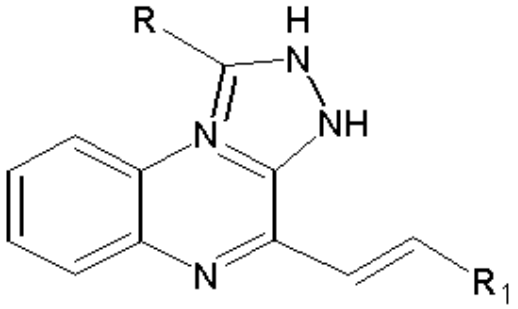
6) Rantnadee v.ghadge .,*et al*., Synthesized Schiff's bases of 3-{[2-({(E)

- [(substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1H)-one were evaluated for anticonvulsant activity screening showed a generally good activity with 2- nitro group substituted derivative



Ar =C_6H_5CHO, $2NO_2C_6H_5CHO$, $3NO_2C_6H_5CHO$, $OHC_{12}H_8CHO$, $4OCH_3C_6H_5CHO$

7)Wagle S., *et al.,* synthesized N-arylidenehydrazino quinoxalines. Further, the oxidative cyclizations of hydrazones by nitrobenzene yielded the synthesized compounds were showed anti-convulsant activity.

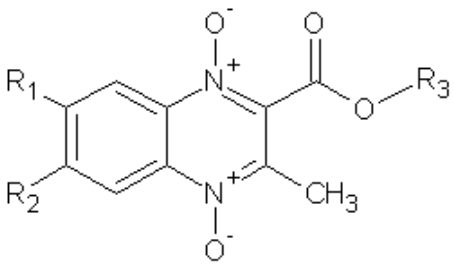


Where, R=H, CH_3, CF_3, (Un) substituted phenyl, R_1= (UN) substituted phenyl

1-aryl-4-methyl [1,2,4] triazolo[4,3-a]quinoxalines.

Anti-tubercular activity:

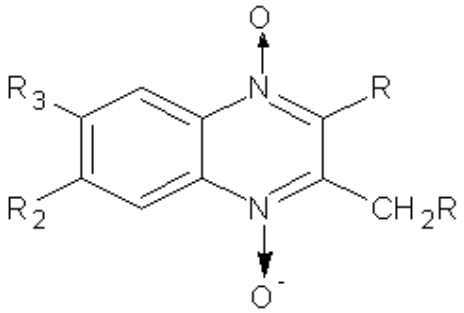
8) Vicente E., *et al*., evaluated for in vitro efficacies of the 1,4-di-N-oxide quinoxaline derivatives against Mycobacterium tuberculosis and has lead to the discovery of a derivative with in vivo efficacy in the mouse model of tuberculosis



Where, **R1/R2= H/CH3,H/OCH3, H/H, H/Cl, F/F, Cl/Cl,CH3/CH3, H/F, H/CF3**

R3= CH2CH3, CH2Ph, CH3

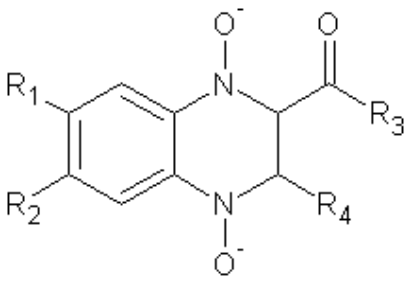
9) Carta A., *et al*., synthesized 6-(7)-substituted-3-methyl- or 3-halogenomethyl-2 phenylthio–phenylsulphonyl–chloro-quinoxaline 1,4-dioxides derivatives were evaluated for in vitro antimycobacterial and Antitubercular screening showed a generally good activity of 3-methyl-2-phenylthioquinoxaline 1,4-dioxides against Mycobacterium tuberculosis



Where, R=Cl,S-Ph,SO2Ph, R1=H,Br and R2/R3=H, Cl,F,,CF3,CH3

3-halogenomethyl-2phenylthio–phenylsulphonyl–chloro-quinoxaline 1, 4-dioxides

10) Jaso A., *et al*., synthesized A series of 2-acetyl and 2-benzoyl-6(7)-substituted quinoxaline 1, 4-di-N-oxide derivatives were evaluated for in vitro antituberculosis activity. The results show that 2-acetyl-3-methylquinoxaline 1,4-di-N-oxide derivatives with chlorine, methyl or methoxy group in position 7 of the benzene moiety and unsubstituted have good antitubercular activity.

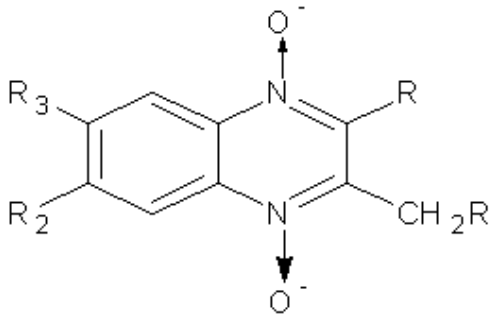


Where, R1=Cl, CH3, R2=Cl, H, R3 andR4=CH3

2-acetyl and 2-benzoyl-6(7)-substituted quinoxaline 1, 4-di-N-oxide derivatives

Antifungal activity

11)Carta A. ,*et al*., synthesized (7)-substituted-3-methyl- or 3-halogenomethyl-2 phenylthio–phenylsulphonyl–chloro-quinoxaline 1, 4-dioxides.this derivatives were found to be good antimycobacterial and anticandida activity

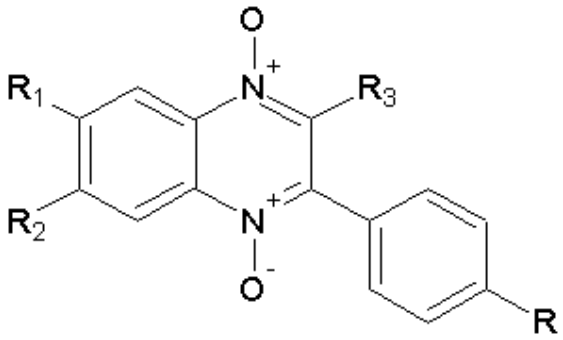


Where, **R= Cl,S-Ph,SO2Ph, R1= H, Br and R2/R3= H, Cl,F,,CF3,CH3**

(7)-substituted-3-methyl- or 3-halogenomethyl-2 phenylthio–phenylsulphonyl - quinoxaline 1, 4-dioxides

Anti-malarial activity

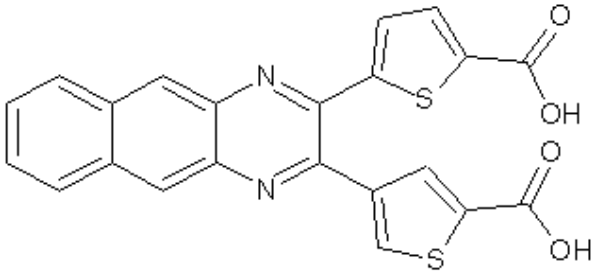
12)Vicente E. ,*et al* .,reported 3-phenylquinoxaline 1,4-di-N-oxide derivatives have been Antiplasmodial activity vitro against Plasmodium falciparum by the incorporation of [3H]-hypoxanthine. Some of them were shown to be more active than chloroquine in the resistant strain



3-phenylquinoxaline 1,4-di-N-oxide derivatives

SRPK-1 kinase inhibitor

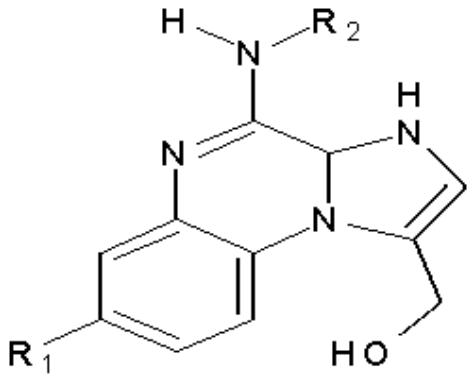
13)Szekelyhidi Z.,*et al*., synthesized novel tricycle quinoxaline derivatives and synthesized as potential kinase inhibitory antiviral agents and were found to be active and selective for SRPK-1 kinase.



Tricyclic quinoxaline derivatives

Adenosine A1 receptor inhibitory activity

14)Liu C., *et al*., Synthesized 4-alkylamino-1-hydroxymethylimidazo [1,2-a]quinoxalines have been synthesized and evaluated for their adenosine A1 receptor inhibitory activity in the radioligand binding assays. The compounds were tested for the inhibition percent (IP) and the affinity toward A1AR (Ki) that IP were more than 90% in the nanomolar ranges.

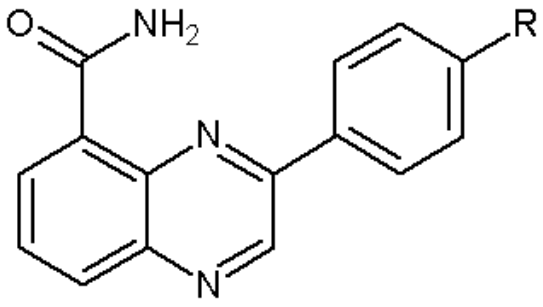


Where**, R1=H and R2= (CH3)2CH2CH2-**

4 -alkylamino-1-hydroxymethylimidazo [1,2-a]quinoxalines

Poly- (ADP-ribose) polymerase-1,2 inhibitor:

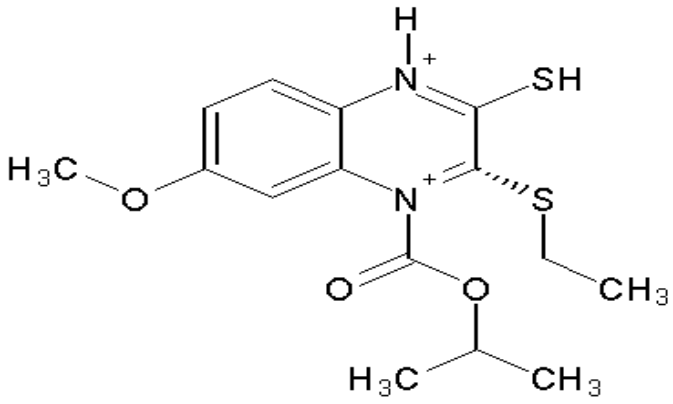
15)Iwashita A., *et al* .,were identified as potent and selective poly- (ADP-ribose) polymerase-1 and 2 (PARP-1) and (PARP-2) inhibitors, respectively. In PARP enzyme assays using recombinant PARP-1 and PARP-2, quinazolinone derivatives displayed relatively high selectivity for PARP-1 and quinoxaline derivatives showed superior selectivity for PARP-2. SBDD analysis via a combination of X-ray structural study and homology modeling suggested distinct interactions of inhibitors with PARP-1 and PARP-2. These findings provide a new structural framework for the design of selective inhibitors for PARP-1 and PARP-2.



Where **R= H, NH_2, Cl, OMe**

HIV-1 inhibitor

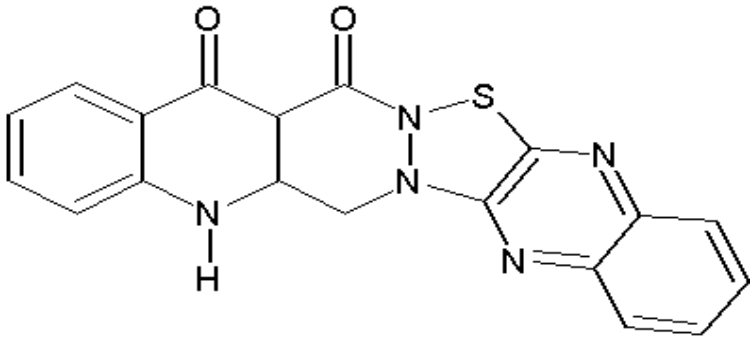
16) (S) - 4 - isopropoxycarbonyl- 6 - methoxy-3- (methylthiomethyl)-3,4dihydroquinoxaline-2(1H)-thione (HBY 097) was used to select for drug-resistant HIV-1 variants in vitro. The viruses first developed mutations affecting the NNRTI binding pocket, and five of six strains displayed the RT G190-E substitution, which is characteristic for HIV-1 resistance against quinoxalines.



Structure of (HBY 097)

Analgesic and anti-inflammatory activities:

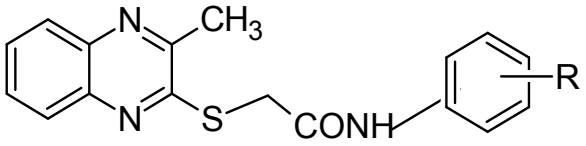
17)Hashem A., *et al*., demonstrated analgesic and anti-inflammatory activities of 2-aminopyrimido [thiazolo[4,5-b]quinoxaline-4-one. Some of these compounds exhibited promising activities.



Where, **R= F, H, CH_3O**

2-aminopyrimido [thiazolo[4,5-b]quinoxaline-4-one.

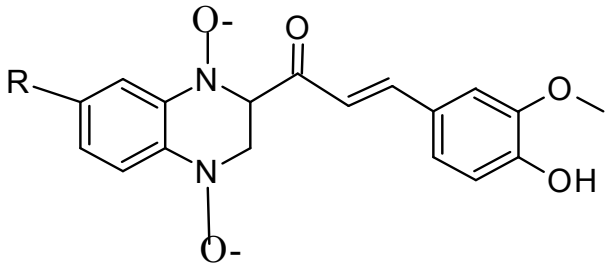
18)Singh,DharmchandPrasad., *et al.,* Some New Thio-Ether Derivatives of Quinoxaline and evaluated for anti-inflammatory activity. The compound substituted with cl showed good anti inflammatory



2-(2-methylquinoxalin-3-ylthio)-N-substitutedphenyl)acetamides

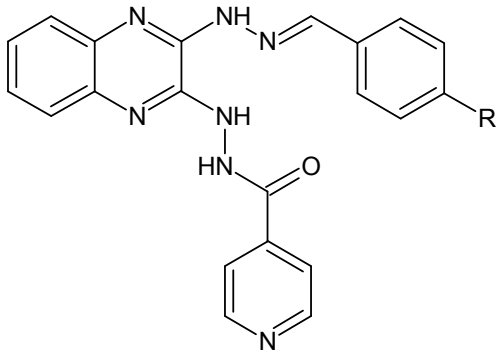
R=2-Cl;3-Cl;4-Cl;4-Br;4-CH3 4-OCH3 ;3-Cl 4-F;2-CH3 3-CH3 2-COOCH3

19) Asuncio ´n Burguete., *et al.,* Synthesized somenew ring substituted 3-phenyl-1-(1,4-di-N-oxide quinoxalin-2-yl)-2-propen-1-one derivatives and evaluated for anti-inflammatory activity. The result showed compound of R=H exhibited good anti -inflammatory activity



where **R=H R=F R=CH3O**

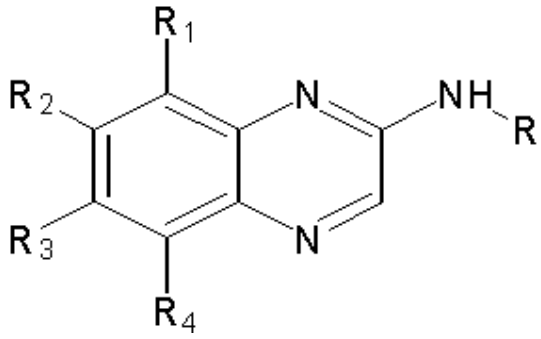
20) SMD Noorulla.,*et al.,* synthesized some novel substituted quinoxaline heterocycle nucleus .The antiinflammatory activity were conducted . the presence of OCH3 on phenyl nucleus attached to second position of the quinoxaline nucleus may be responsible for marked anti-inflammatory activity.



R= O-OCH_3, p- OH, m-NO_2, m-OH, P-OCH_3

PDGF-R inhibitor

21)Myers M., *et al*., Demonstrated activity novel substituted 2-anilino- and 2-cycloalkylaminoquinoxalines as inhibitors of PDGF-R autophosphorylation. The found that Replacement of an anilino-substituent with substituted cyclohexylamino- or norbornylamino substituents lead to significant improvements in the pharmacokinetic profile of these analogues.

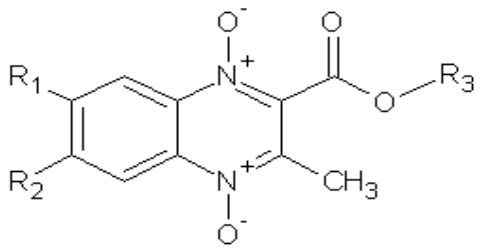


Where, R_1=H, Me, R_2= H, Me, R_3 and R_4= H, Me, MeO

Antimicrobial activity

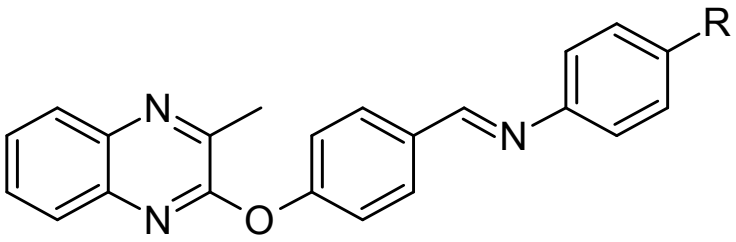
22) Refaat H., *et al*., were synthesized series of 2-[4-N-2-acylhydrazinocarbonyl) aniline]-3-methyl quinoxalines, as well as their cyclized oxadiazolyl derivatives were also prepared. Some of these derivatives were evaluated for antimicrobial activity in

vitro. It was found that all the selected compounds exhibit antimicrobial activity and some of these compounds had a broad spectrum of activity.

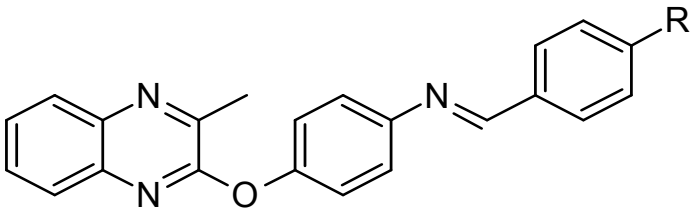


Where, Ar – 3-Br-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4

23) Dharmchand Prasad Singh.,*et al*., synthesized 2-[4-(substituted-benziminomethyl)-phenoxy]-3-methyl quinoxalines and 4-(2-methylquinoxalin-3-yloxy)- *N*-substituted benzylidine benzamines and evaluated for antimicrobial activity . The compound with 3-OCH_3 showed high active against E.coli

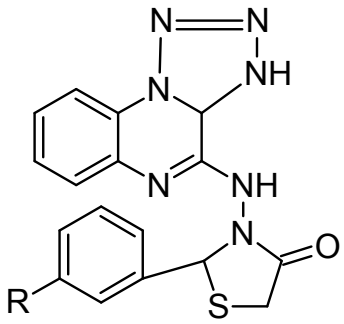


R= H; Cl; CH3; 4-COOH; 2- CH3 6- CH3



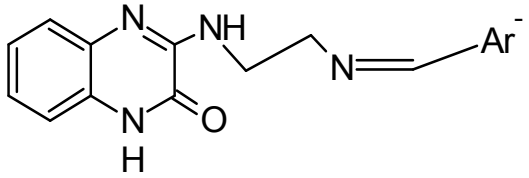
R= 4-OH; 2-NO2 ; 4-N(CH3)2 ; 2-OH,3-OCH3 ; 2-OCH3 ,3-OCH3 ,4OCH3

24) Shiv Kumar., *et al*., Synthesized Tetrazolo[1,5-a]quinoxaline based Azetidinones & Thiazolidinones . Some of these derivatives were evaluated for antimicrobial activity in vitro. It was found that all the selected compounds exhibit antimicrobial activity and some of these compounds had a broad spectrum of activity.



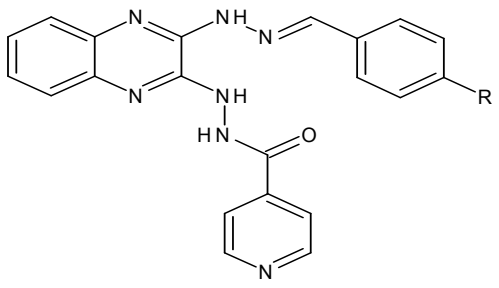
R=C_6H_5, 0-Cl C_6H_4,O-F C_6H_4,O-NO_2 C_6H_4,P-ClC_6H_4,P-F C_6H_4 ,P-NO_2 C_6H_4

25) Rantnadee v.ghadge. *et al*., Synthesized Schiff's bases of 3-{[2-({(E) -[(substituted) phenyl] methylidene} amino) ethyl] amino}quinoxalin-2(1H)-one were evaluated for antimicrobial activity screening showed a generally all compound are more active against p.aerogenosa



Ar=3-Cl-C_6H_5CHO, 3,4,CLC_6H_3CHO, (CH3)2N-C_6H_5CHO, $OHC_{12}H_8CHO$

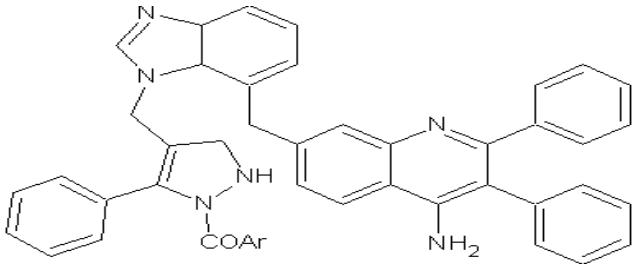
26) SMD Noorulla.,et al., synthesized some novel substituted quinoxaline heterocycle nucleus .The antibacterial tests were conducted on four common microorganisms such as *Bacillus subtilis*, *Staphylococcus aureus* , *Escherichia coli* and *Klebsiella pneumoniae* .The synthesized compound found to be active against *Bacillus subtilis.*



R=p-OCH_3, P- OH, m-NO_2,m-OH

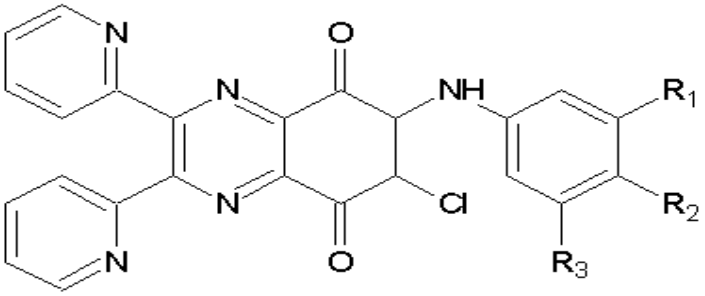
Antihistaminic activity

27) Sridevi C.*, et al*., synthesized phenyl pyrazolo benzimidazole quinoxaline. All the synthesized compounds were screened for their antihistaminic activity.Some were shown good % protection of anti-histamic activity.



Anti-proliferativeactivity:

28) Chung H., *et al*., were synthesized a series of 6-arylamino-2,3-bis(pyridin-2-yl)-7-chloro-quinoxaline-5,8-diones and evaluated for their inhibitory activity on rat aortic smooth muscle cell proliferation. They were observed that The quinoxaline-5,8-diones exhibited a potent anti-proliferative activity.

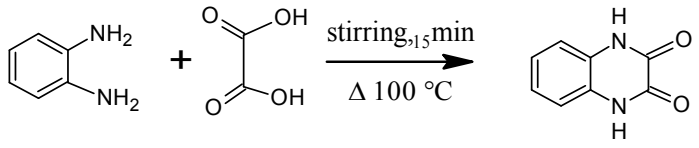


6-arylamino-2, 3-bis(pyridin-2-yl)-7-substituted -quinoxaline-5,8-diones

Review of reaction

The various method of preparation of some substituted quinoxaline-2(1H)-one derivative by phillip's condensation mechanism

I)Condensation of oxalic acid with o-phenylenediamine

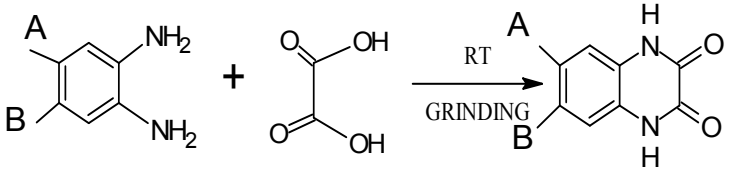


o-phenylene diamine

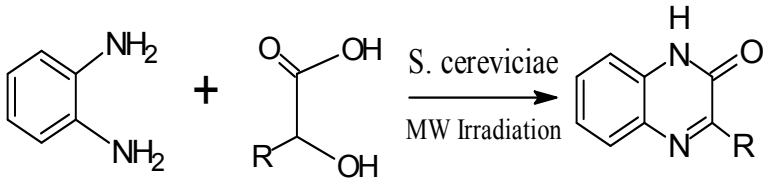
oxalic acid

1,4-dihydroquinoxaline-2,3-dione

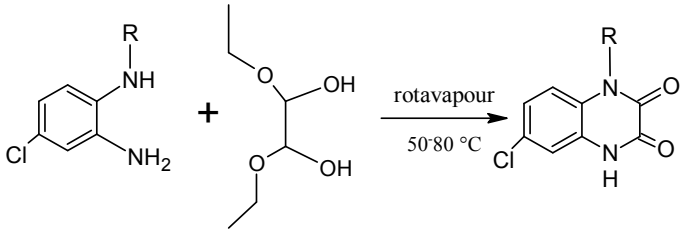
2)One-pot efficientgreen synthesis of 1,4-dihydro-quinoxaline-2,3-dione



3)Gris J et al29 has carried out the microwave-assisted Hinsberg reaction of quinoxalinone derivatives



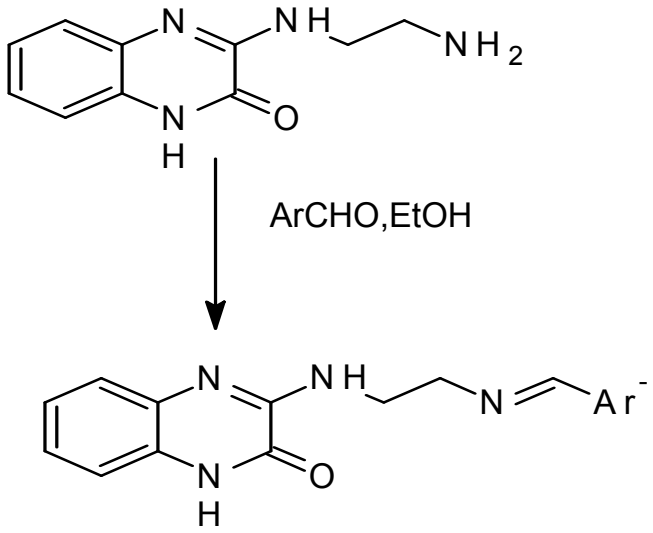
4) **Various quinoxaline-2,3-diones32 were synthesized by rotatory evaporation of 1,2-diamino aromaticcompounds in diethyl oxalate .**



One of the most features in quinoxaline-2(1H)-one chemistry is their use as key starting materials for further transformation. The reaction of ethylene diamine with quinoxaline-2(1H)-one results in the formation of 3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one

3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one could be used as versatile building blocks in the synthesis of new heterocyclic systems

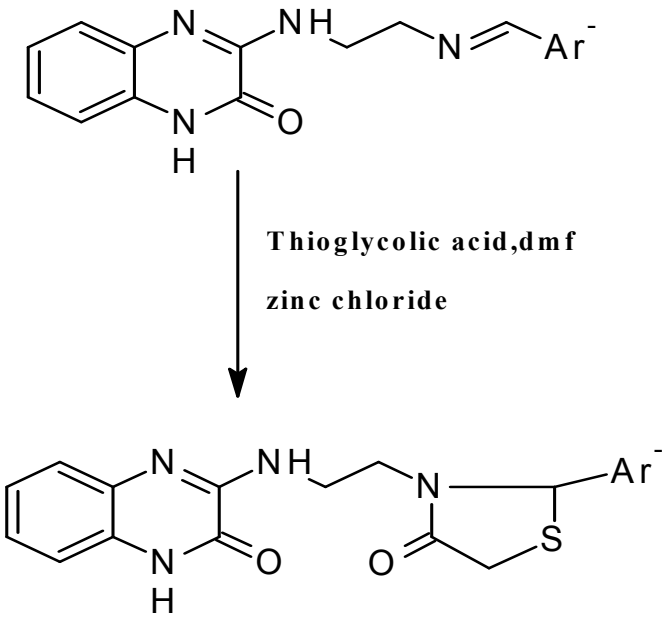
Thus the present work is in conjuction with the reaction of the amino functionality of 3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one with carbon electrophiles namely substituted aromatic aldehydes



The nucleophilic attack of the amino group on the electronically deficient carbonyl carbon atom of the aldehyde , followed by dehydration results in the formation of Schiff bases

As mentioned earlier , 4-Thiazolidinones are reported to possess a variety of therapeutic activities.

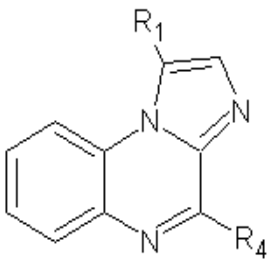
Taking in to this consideration .,Cyclocondensation of Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives,



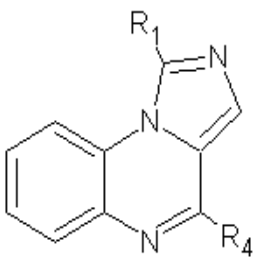
2. Literature Review

Anti cancer activity

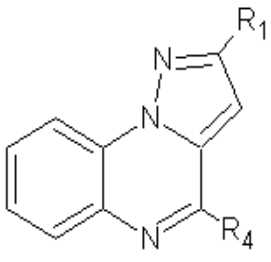
1) Moarbess G., *et al.*, were assessed In-vitro cytotoxicity studies against melanoma (A375, M4Be, and RPMI-7591), colon (LS174T), breast (MCF7), and lymphoma (Raji) human cancer cell lines. In vivo studies were carried out in M4Be xenografted athymic mice. EAPB (I), EAPB (II), EAPB (III), showed significant in vitro activities against A375 compared to fotemustine and imiquimod used as references.



EAPB (I)



EAPB (II)

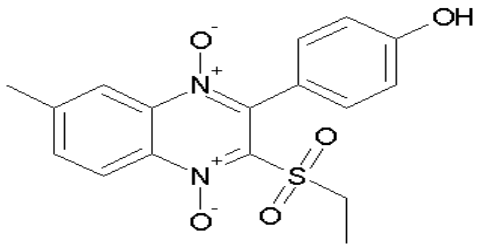


EAPB (III)

Substituted pyrazolo[1,5-*a*]quinoxaline

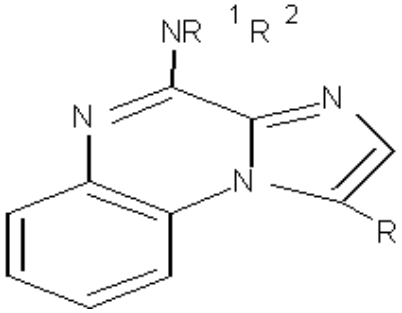
Where, R_1=$(CH3)_2$–CH–CH_2–,C_6H_5–$(CH_2)_2$–andR_4=CH_3–NH–NH_2

2) Weng Q., *et al.,* Synthesized compounds a and showed that 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline 1,4-dioxide (Q39), derived from Quinoxaline 1,4-Di-N-oxide, possessed high anti-cancer activity in hypoxia. Cytotoxicity assay demonstrated that Q39 is a potential and high efficient anti-cancer compound in all tested cell. In their work showing the mechanism of Q39 in hypoxia.



Chemical structure of Q39

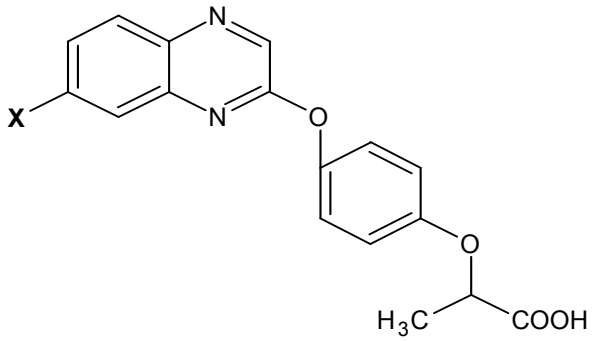
3) Masquefa C., *et al* .,were synthesized New series of imidazo[1,2-a]quinoxaline analogues have been in good yields via a bimolecular condensation of 2-imidazole carboxylic acid, followed by a coupling with ortho-fluoroaniline and subsequent substitution on the imidazole ring by Suzuki Cross-coupling reaction using microwave assistance. Antitumor activities of these derivatives were evaluated by growth inhibition of A375 cells in vitro. It was proposed that all compounds exhibited high activities compared to imiquimod and fotemustine used as reference.



Where, R= $(CH_3)_2CHCH$, R= $C_6H_5\,(CH_2)_2$

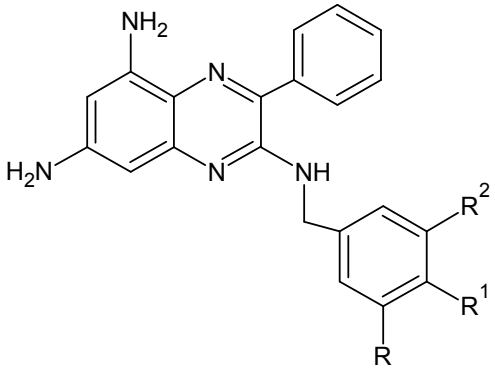
Iimidazo [1, 2-a]quinoxaline analogues

4) Stuart T. Hazeldine., *et al.,* carried out Synthetic modification of the 2-oxypropionic acid moietyin 2-{4-[(7-chloro-2-quinoxalinyl)oxy]phenoxy}propionic acid (XK469).All halogenated derivatives of above showed to be active antitumor activity of colon cancer cells



X= Cl,F,Br,I

5) Paloa Caronoa., et al., synthesized 5,7-diamino-3- phenyl-2-benzylamino, 2-phenoxy and 2-phenylthio substituted quinoxalines. The compound 1b-6b exhibited better anticancer activity for lung, breast cancer cells.



1b: R = R2 = H; R1 = OCH3

2b: R = R2 = OCH3; R1 = H

3b: R = R1 = OCH3; R2 = H

4b: R = R1 = R2 = OCH3

5b: R = R1 = Cl; R2 = H

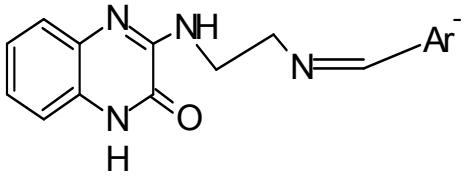
6b: R = R2 = H; R1 = F

7b: R = R2 = H; R1 = CO-Glu-Et

Anticonvulsant activity

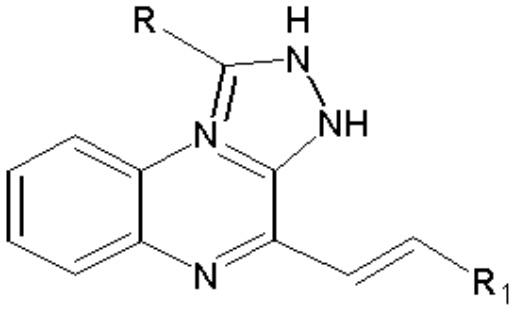
6) Rantnadee v.ghadge .,*et al*., Synthesized Schiff's bases of 3-{[2-({(E)

- [(substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1H)-one were evaluated for anticonvulsant activity screening showed a generally good activity with 2- nitro group substituted derivative



Ar =C_6H_5CHO, $2NO_2C_6H_5CHO$, $3NO_2C_6H_5CHO$, $OHC_{12}H_8CHO$, $4OCH_3C_6H_5CHO$

7)Wagle S., *et al.,* synthesized N-arylidenehydrazino quinoxalines. Further, the oxidative cyclizations of hydrazones by nitrobenzene yielded the synthesized compounds were showed anti-convulsant activity.

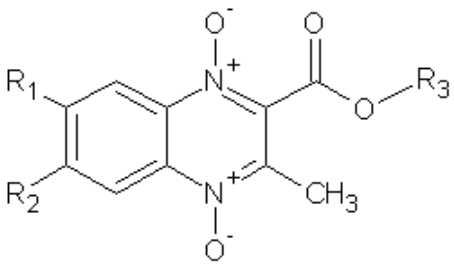


Where, R=H, CH_3, CF_3, (Un) substituted phenyl, R_1= (UN) substituted phenyl

1-aryl-4-methyl [1,2,4] triazolo[4,3-a]quinoxalines.

Anti-tubercular activity:

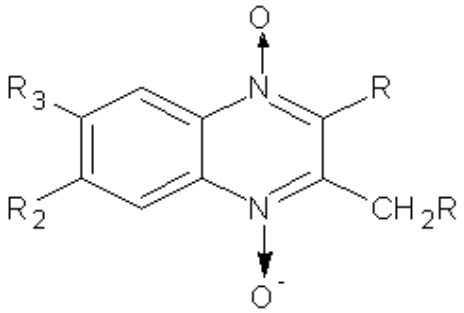
8) Vicente E., *et al*., evaluated for in vitro efficacies of the 1,4-di-N-oxide quinoxaline derivatives against Mycobacterium tuberculosis and has lead to the discovery of a derivative with in vivo efficacy in the mouse model of tuberculosis



Where, **R1/R2= H/CH3,H/OCH3, H/H, H/Cl, F/F, Cl/Cl,CH3/CH3, H/F, H/CF3**

R3= CH2CH3, CH2Ph, CH3

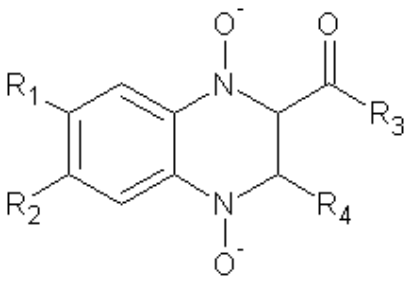
9) Carta A., *et al*., synthesized 6-(7)-substituted-3-methyl- or 3-halogenomethyl-2 phenylthio–phenylsulphonyl–chloro-quinoxaline 1,4-dioxides derivatives were evaluated for in vitro antimycobacterial and Antitubercular screening showed a generally good activity of 3-methyl-2-phenylthioquinoxaline 1,4-dioxides against Mycobacterium tuberculosis



Where, R=Cl,S-Ph,SO2Ph, R1=H,Br and R2/R3=H, Cl,F,,CF3,CH3

3-halogenomethyl-2phenylthio–phenylsulphonyl–chloro-quinoxaline 1, 4-dioxides

10) Jaso A., *et al*., synthesized A series of 2-acetyl and 2-benzoyl-6(7)-substituted quinoxaline 1, 4-di-N-oxide derivatives were evaluated for in vitro antituberculosis activity. The results show that 2-acetyl-3-methylquinoxaline 1,4-di-N-oxide derivatives with chlorine, methyl or methoxy group in position 7 of the benzene moiety and unsubstituted have good antitubercular activity.

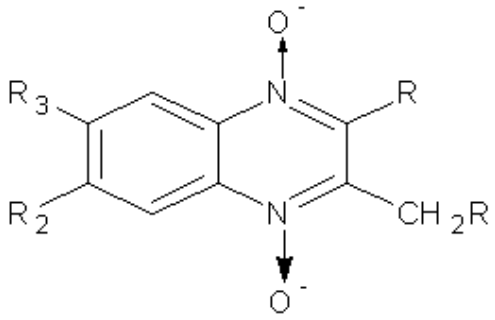


Where, R1=Cl, CH3, R2=Cl, H, R3 andR4=CH3

2-acetyl and 2-benzoyl-6(7)-substituted quinoxaline 1, 4-di-N-oxide derivatives

Antifungal activity

11)Carta A. ,*et al*., synthesized (7)-substituted-3-methyl- or 3-halogenomethyl-2 phenylthio–phenylsulphonyl–chloro-quinoxaline 1, 4-dioxides.this derivatives were found to be good antimycobacterial and anticandida activity

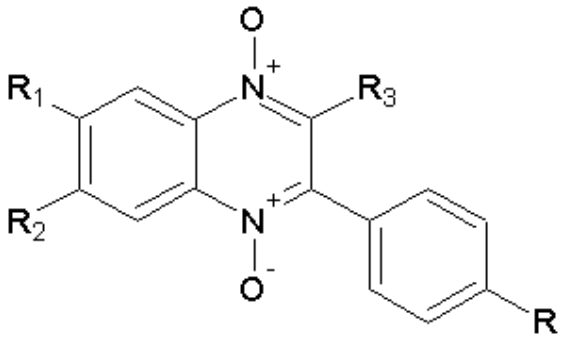


Where, **R= Cl,S-Ph,SO2Ph, R1= H, Br and R2/R3= H, Cl,F,,CF3,CH3**

(7)-substituted-3-methyl- or 3-halogenomethyl-2 phenylthio–phenylsulphonyl - quinoxaline 1, 4-dioxides

Anti-malarial activity

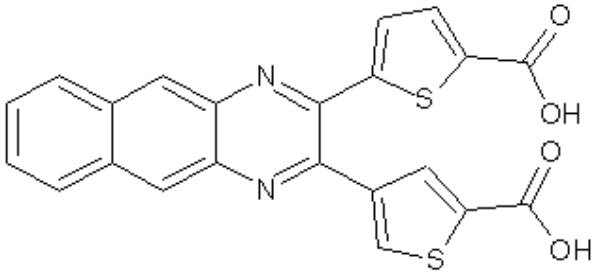
12)Vicente E. ,*et al* .,reported 3-phenylquinoxaline 1,4-di-N-oxide derivatives have been Antiplasmodial activity vitro against Plasmodium falciparum by the incorporation of [3H]-hypoxanthine. Some of them were shown to be more active than chloroquine in the resistant strain



3-phenylquinoxaline 1,4-di-N-oxide derivatives

SRPK-1 kinase inhibitor

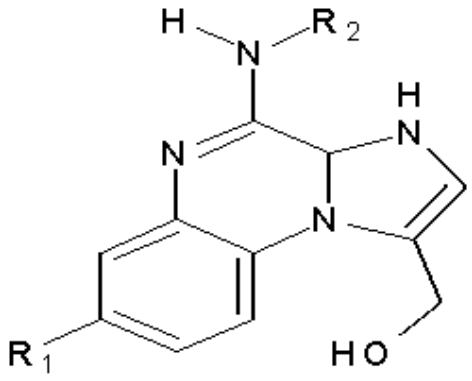
13)Szekelyhidi Z.,*et al*., synthesized novel tricycle quinoxaline derivatives and synthesized as potential kinase inhibitory antiviral agents and were found to be active and selective for SRPK-1 kinase.



Tricyclic quinoxaline derivatives

Adenosine A1 receptor inhibitory activity

14)Liu C., *et al*., Synthesized 4-alkylamino-1-hydroxymethylimidazo [1,2-a]quinoxalines have been synthesized and evaluated for their adenosine A1 receptor inhibitory activity in the radioligand binding assays. The compounds were tested for the inhibition percent (IP) and the affinity toward A1AR (Ki) that IP were more than 90% in the nanomolar ranges.

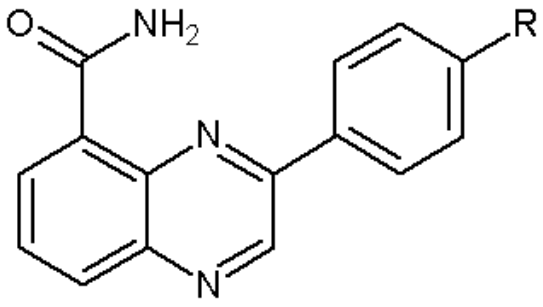


Where**, R1=H and R2= (CH3)2CH2CH2-**

4 -alkylamino-1-hydroxymethylimidazo [1,2-a]quinoxalines

Poly- (ADP-ribose) polymerase-1,2 inhibitor:

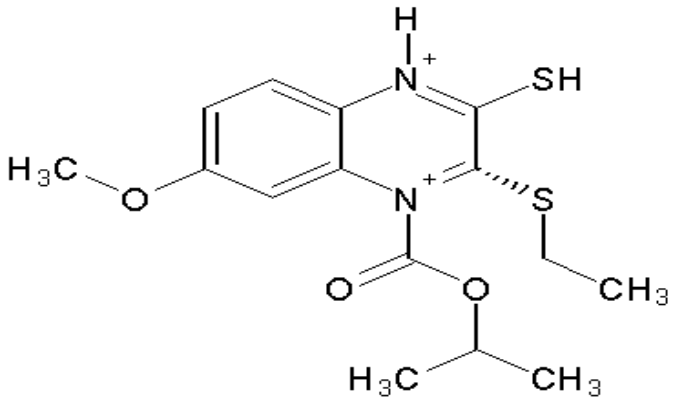
15)Iwashita A., *et al* .,were identified as potent and selective poly- (ADP-ribose) polymerase-1 and 2 (PARP-1) and (PARP-2) inhibitors, respectively. In PARP enzyme assays using recombinant PARP-1 and PARP-2, quinazolinone derivatives displayed relatively high selectivity for PARP-1 and quinoxaline derivatives showed superior selectivity for PARP-2. SBDD analysis via a combination of X-ray structural study and homology modeling suggested distinct interactions of inhibitors with PARP-1 and PARP-2. These findings provide a new structural framework for the design of selective inhibitors for PARP-1 and PARP-2.



Where **R= H, NH_2, Cl, OMe**

HIV-1 inhibitor

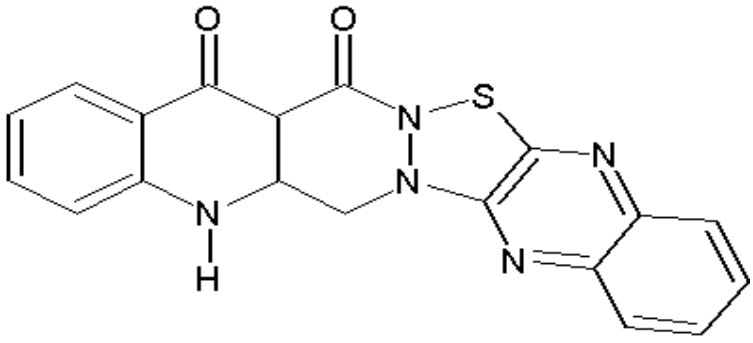
16) (S) - 4 - isopropoxycarbonyl- 6 - methoxy-3- (methylthiomethyl)-3,4dihydroquinoxaline-2(1H)-thione (HBY 097) was used to select for drug-resistant HIV-1 variants in vitro. The viruses first developed mutations affecting the NNRTI binding pocket, and five of six strains displayed the RT G190-E substitution, which is characteristic for HIV-1 resistance against quinoxalines.



Structure of (HBY 097)

Analgesic and anti-inflammatory activities:

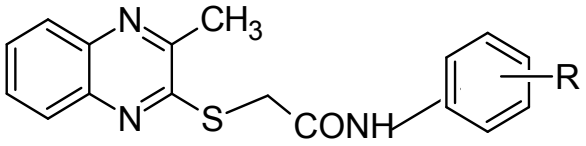
17)Hashem A., *et al*., demonstrated analgesic and anti-inflammatory activities of 2-aminopyrimido [thiazolo[4,5-b]quinoxaline-4-one. Some of these compounds exhibited promising activities.



Where, **R= F, H, CH_3O**

2-aminopyrimido [thiazolo[4,5-b]quinoxaline-4-one.

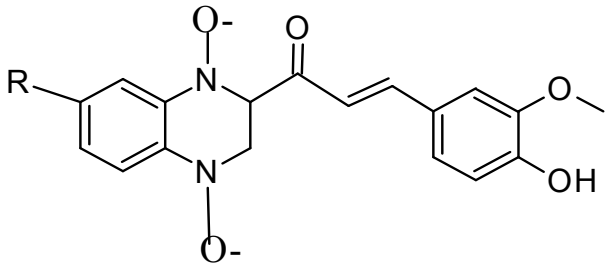
18)Singh,DharmchandPrasad., *et al.,* Some New Thio-Ether Derivatives of Quinoxaline and evaluated for anti-inflammatory activity. The compound substituted with cl showed good anti inflammatory



2-(2-methylquinoxalin-3-ylthio)-N-substitutedphenyl)acetamides

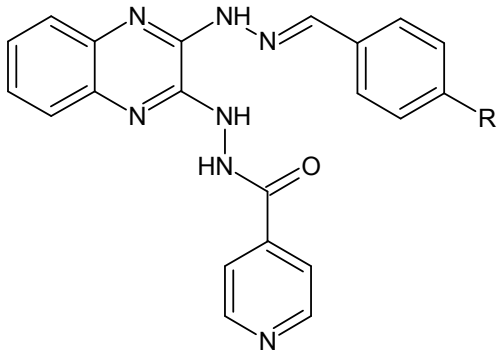
R=2-Cl;3-Cl;4-Cl;4-Br;4-CH3 4-OCH3 ;3-Cl 4-F;2-CH3 3-CH3 2-COOCH3

19) Asuncio ´n Burguete., *et al.,* Synthesized somenew ring substituted 3-phenyl-1-(1,4-di-N-oxide quinoxalin-2-yl)-2-propen-1-one derivatives and evaluated for anti-inflammatory activity. The result showed compound of R=H exhibited good anti -inflammatory activity



where **R=H R=F R=CH3O**

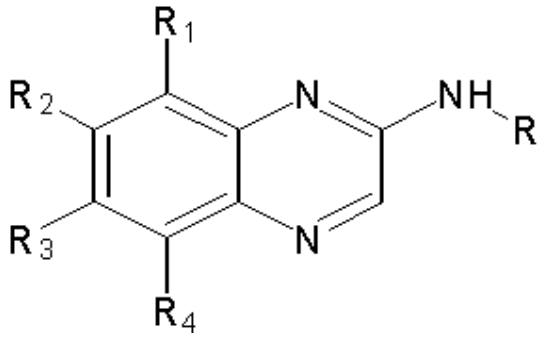
20) SMD Noorulla.,*et al.,* synthesized some novel substituted quinoxaline heterocycle nucleus .The antiinflammatory activity were conducted . the presence of OCH3 on phenyl nucleus attached to second position of the quinoxaline nucleus may be responsible for marked anti-inflammatory activity.



R= O-OCH_3, p- OH, m-NO_2, m-OH, P-OCH_3

PDGF-R inhibitor

21)Myers M., *et al*., Demonstrated activity novel substituted 2-anilino- and 2-cycloalkylaminoquinoxalines as inhibitors of PDGF-R autophosphorylation. The found that Replacement of an anilino-substituent with substituted cyclohexylamino- or norbornylamino substituents lead to significant improvements in the pharmacokinetic profile of these analogues.

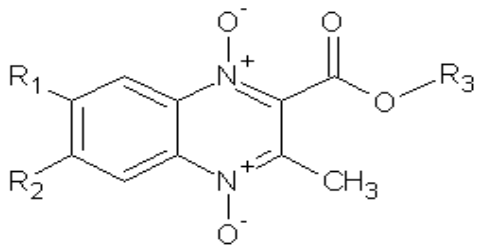


Where, R_1=H, Me, R_2= H, Me, R_3 and R_4= H, Me, MeO

Antimicrobial activity

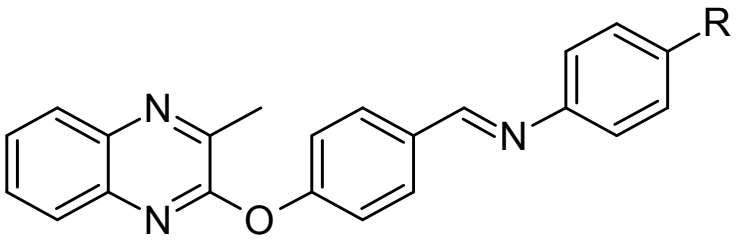
22) Refaat H., *et al*., were synthesized series of 2-[4-N-2-acylhydrazinocarbonyl) aniline]-3-methyl quinoxalines, as well as their cyclized oxadiazolyl derivatives were also prepared. Some of these derivatives were evaluated for antimicrobial activity in

vitro. It was found that all the selected compounds exhibit antimicrobial activity and some of these compounds had a broad spectrum of activity.

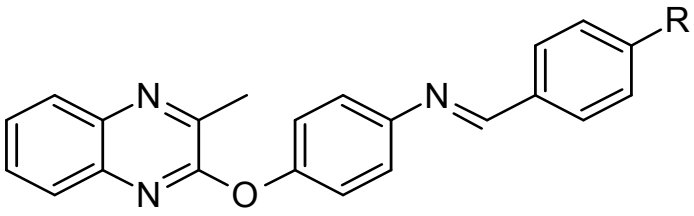


Where, Ar – 3-Br-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4

23) Dharmchand Prasad Singh.,*et al*., synthesized 2-[4-(substituted-benziminomethyl)-phenoxy]-3-methyl quinoxalines and 4-(2-methylquinoxalin-3-yloxy)- *N*-substituted benzylidine benzamines and evaluated for antimicrobial activity . The compound with 3-OCH_3 showed high active against E.coli

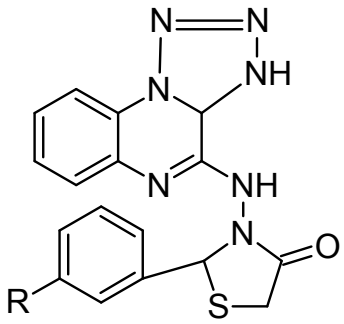


R= H; Cl; CH3; 4-COOH; 2- CH3 6- CH3



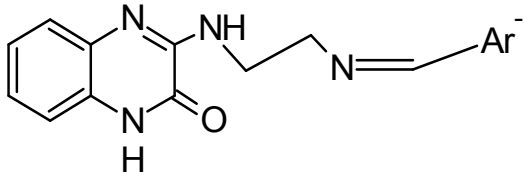
R= 4-OH; 2-NO2 ; 4-N(CH3)2 ; 2-OH,3-OCH3 ; 2-OCH3 ,3-OCH3 ,4OCH3

24) Shiv Kumar., *et al*., Synthesized Tetrazolo[1,5-a]quinoxaline based Azetidinones & Thiazolidinones . Some of these derivatives were evaluated for antimicrobial activity in vitro. It was found that all the selected compounds exhibit antimicrobial activity and some of these compounds had a broad spectrum of activity.



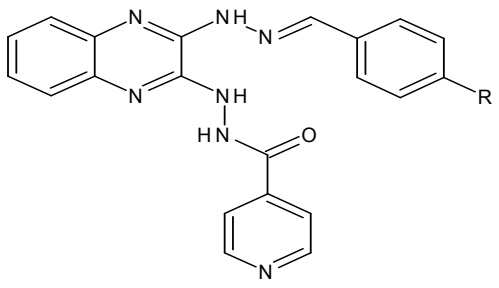
R=C_6H_5, 0-Cl C_6H_4,O-F C_6H_4,O-NO_2 C_6H_4,P-ClC_6H_4,P-F C_6H_4 ,P-NO_2 C_6H_4

25) Rantnadee v.ghadge. *et al*., Synthesized Schiff's bases of 3-{[2-({(E) -[(substituted) phenyl] methylidene} amino) ethyl] amino}quinoxalin-2(1H)-one were evaluated for antimicrobial activity screening showed a generally all compound are more active against p.aerogenosa



Ar=3-Cl-C_6H_5CHO, 3,4,CLC_6H_3CHO, (CH3)2N-C_6H_5CHO, $OHC_{12}H_8CHO$

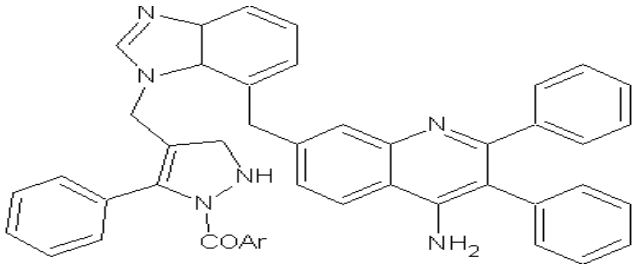
26) SMD Noorulla.,et al., synthesized some novel substituted quinoxaline heterocycle nucleus .The antibacterial tests were conducted on four common microorganisms such as *Bacillus subtilis*, *Staphylococcus aureus* , *Escherichia coli* and *Klebsiella pneumoniae* .The synthesized compound found to be active against *Bacillus subtilis.*



R=p-OCH_3, P- OH, m-NO_2,m-OH

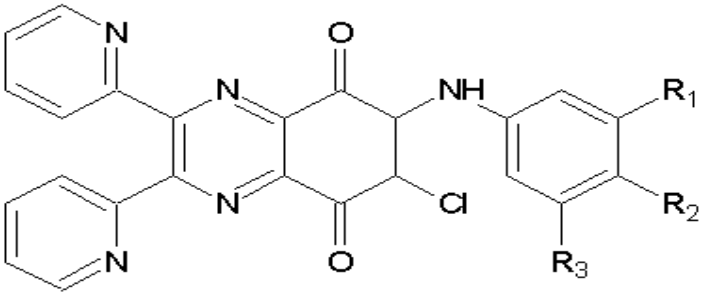
Antihistaminic activity

27) Sridevi C.*, et al*., synthesized phenyl pyrazolo benzimidazole quinoxaline. All the synthesized compounds were screened for their antihistaminic activity.Some were shown good % protection of anti-histamic activity.



Anti-proliferativeactivity:

28) Chung H., *et al*., were synthesized a series of 6-arylamino-2,3-bis(pyridin-2-yl)-7-chloro-quinoxaline-5,8-diones and evaluated for their inhibitory activity on rat aortic smooth muscle cell proliferation. They were observed that The quinoxaline-5,8-diones exhibited a potent anti-proliferative activity.

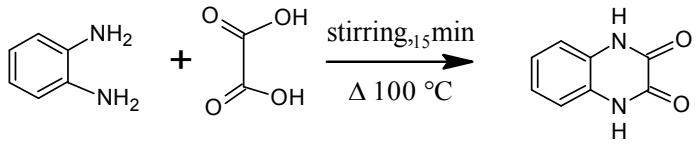


6-arylamino-2, 3-bis(pyridin-2-yl)-7-substituted -quinoxaline-5,8-diones

Review of reaction

The various method of preparation of some substituted quinoxaline-2(1H)-one derivative by phillip's condensation mechanism

I)Condensation of oxalic acid with o-phenylenediamine

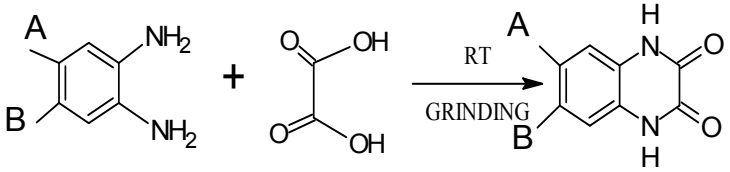


o-phenylene diamine

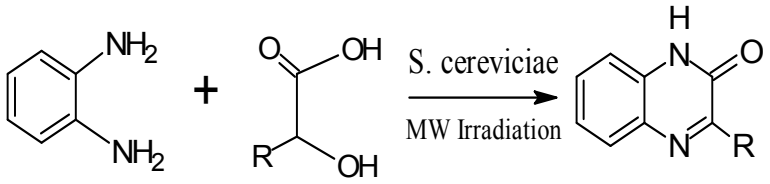
oxalic acid

1,4-dihydroquinoxaline-2,3-dione

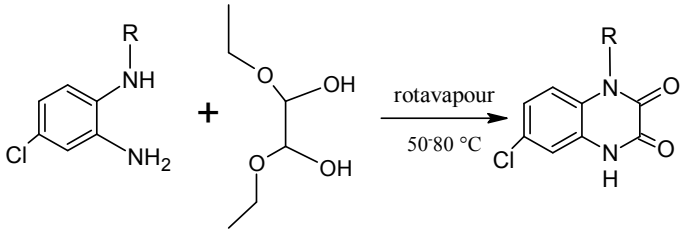
2)One-pot efficientgreen synthesis of 1,4-dihydro-quinoxaline-2,3-dione



3)Gris J et al29 has carried out the microwave-assisted Hinsberg reaction of quinoxalinone derivatives



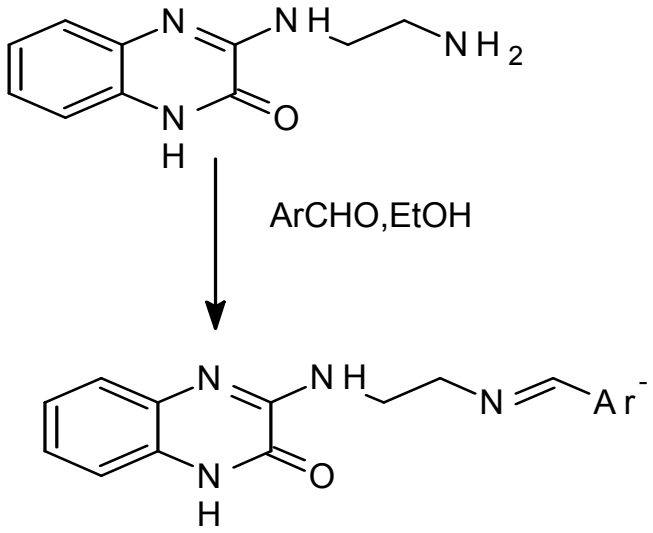
4) **Various quinoxaline-2,3-diones32 were synthesized by rotatory evaporation of 1,2-diamino aromaticcompounds in diethyl oxalate .**



One of the most features in quinoxaline-2(1H)-one chemistry is their use as key starting materials for further transformation. The reaction of ethylene diamine with quinoxaline-2(1H)-one results in the formation of 3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one

3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one could be used as versatile building blocks in the synthesis of new heterocyclic systems

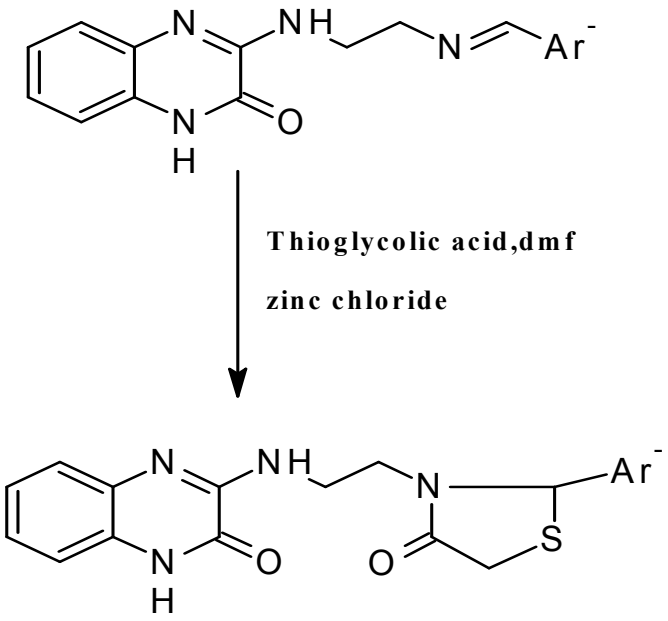
Thus the present work is in conjuction with the reaction of the amino functionality of 3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one with carbon electrophiles namely substituted aromatic aldehydes



The nucleophilic attack of the amino group on the electronically deficient carbonyl carbon atom of the aldehyde , followed by dehydration results in the formation of Schiff bases

As mentioned earlier , 4-Thiazolidinones are reported to possess a variety of therapeutic activities.

Taking in to this consideration .,Cyclocondensation of Schiff's bases with 2-mercaptopropionic acid afforded 4-thiazolidinone derivatives,



Scope
&
Plan of Work

3. SCOPE OF STUDY

The aim of the present study was to obtain "Schiff bases quinoxaline incorporated with 4-thiazolidinone as biologically effective agent with good therapeutic values and minimum toxic levels.

From the literature point of view, quinoxaline derivatives display a broad spectrum of biological activities. For the development of new therapeutic agents it was thought worthwhile to do some chemical modification in quinoxaline moieties. In this present study the effort were made to synthesize.

a) Schiff bases of quinoxalinedione derivative

b) Introducing 4-thiazolidinone nucleus to the Schiff bases

Our aim in this review is to focus on quinoxaline structure and to analyze how slight modification in quinoxaline nucleus can act as a precursor for assembly of large number of quinoxaline derivatives and providing a tremendous number of pharmacologically active molecules having a wide variety of biological activity and also their therapeutic applications and to highlight the importance of quinoxaline moiety as a novel drug template for the discovery of new agents in various areas of medicines

PLAN OF WORK

- To design lead molecule of Quinoxaline-2(1H)-one and to assess ADMET property.
- To establish the method of synthesis for the proposed compounds
- To synthesize the title compounds by appropriate methods
- To carry out the preliminary tests such as physical constant determination, solubility, TLC.
- To confirm the structures of the synthesized compounds by IR, ^{1}H NMR and Mass spectra
- To evaluate the proposed compounds for their ***in-vitro*** -anticancer activity , Anti-inflammatory activity and antibacterial activity

Experimental Work

4. EXPERIMENTAL WORK

4.1 Molecular design

A) OSIRIS PROPERTY EXPLORER

It is a software tool in calculating drug relevant property such as

Toxicity Risk Assessment

Mutagenicity ,irritating effect, reproductive effect, tumorigenicity are predicted. The prediction process relies on a precomputed set of structural fragment that give rise to toxicity alerts in case they are encountered in the structure currently drawn.

cLogP Prediction:

1. The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water $\log(c_{octanol}/c_{water})$,
2. It measure of the compound's hydrophilicity. Low hydrophilicities and therefore high logP values cause poor absorption or permeation. The value must not be greater than 5.0.

Solubility Prediction:

1. poor soluble drugs affect absorption and distribution.It is calculated interms of logS value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter. logS value greater than -4.
2. **Molecular Weights**

Most of the trade drug shows molecular weight below 500

Drug- Likeness Prediction:

The druglikeness is calculated with the following equation summing up score values of those fragments that are present in the molecule under investigation .The value should be positive indicating the fragments predominately present in commercial drugs

Overall Drug- Likeness Score:

The drug score combines all above parameters to judge the compound's potency. The values are 1.0, 0.8 and 0.6 for no risk, medium risk and high risk, respectively

B) LIPINSKI'S RULE BY CHEMDOODLE

Lipinski's Rule of Five is a refinement of drug-likeness and is used to predict whether a chemical compound will have pharmacological or biological activity as an orally active drug in humans. This rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small, lipophilic molecules.

Lipinski's Rule of Five states that, in general, an orally active drug has:

1. Not more than 5 hydrogen bond donors (OH and NH groups);

2. Not more than 10 hydrogen bond acceptors (notably N and O);

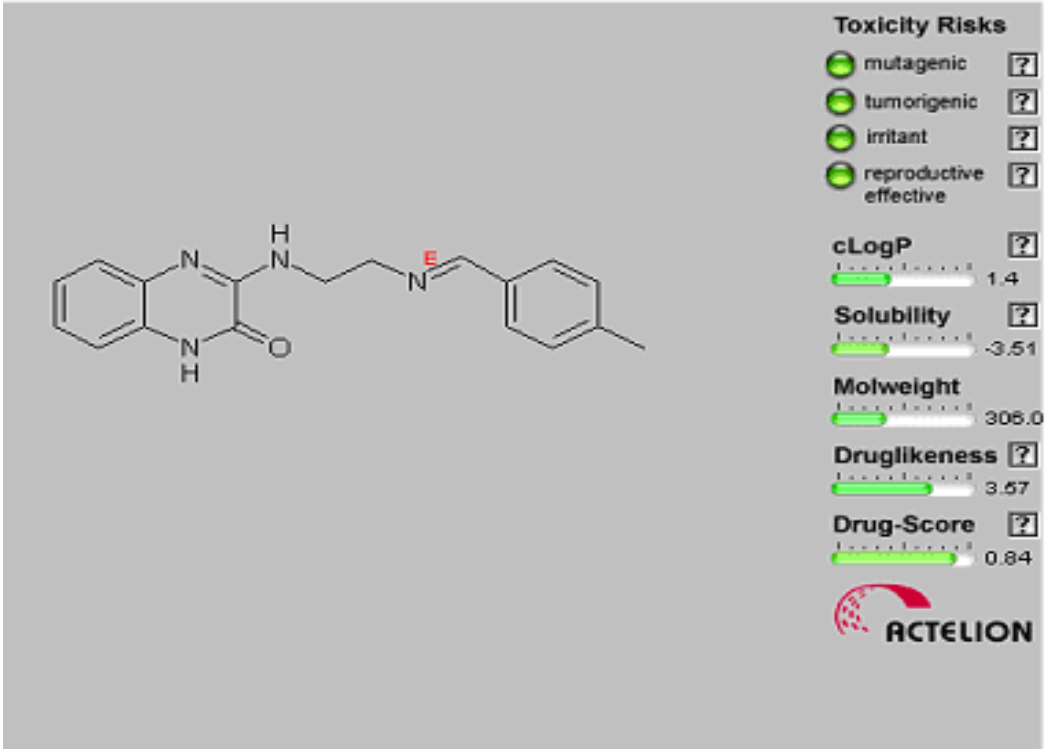
3.A molecular weight under 500 g/mol; and

4. A partition coefficient log P less than 5

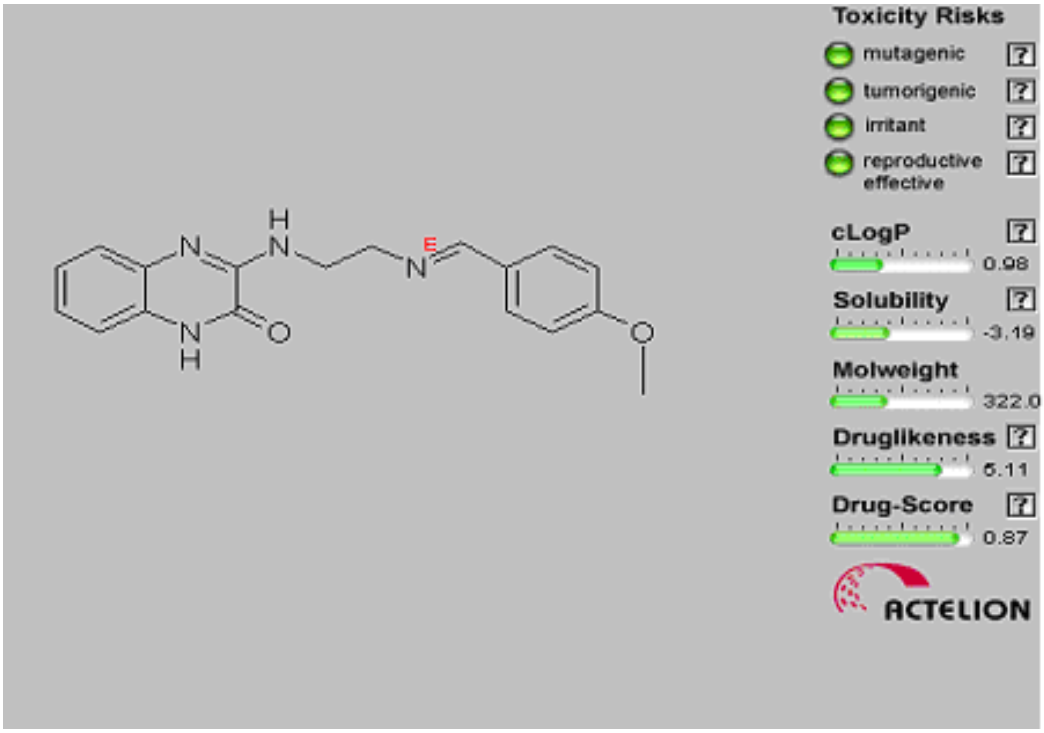
Note that all numbers are multiples of five, which is the origin of the rule's name.

Synthetic compound were screened by using osiris property explorer.

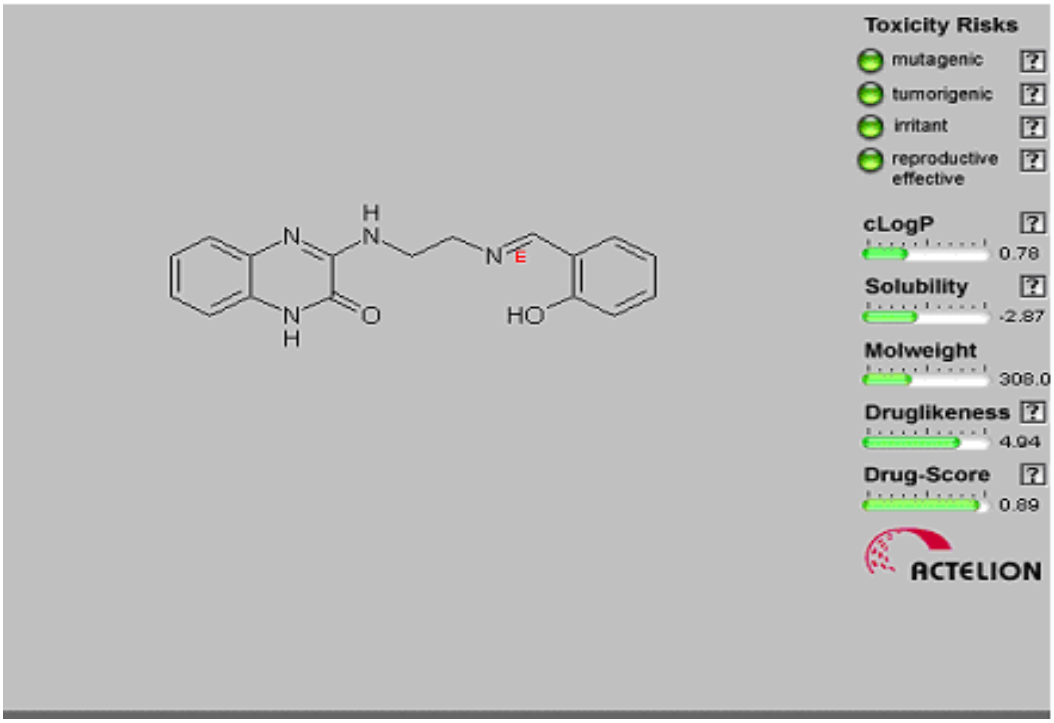
Compound1



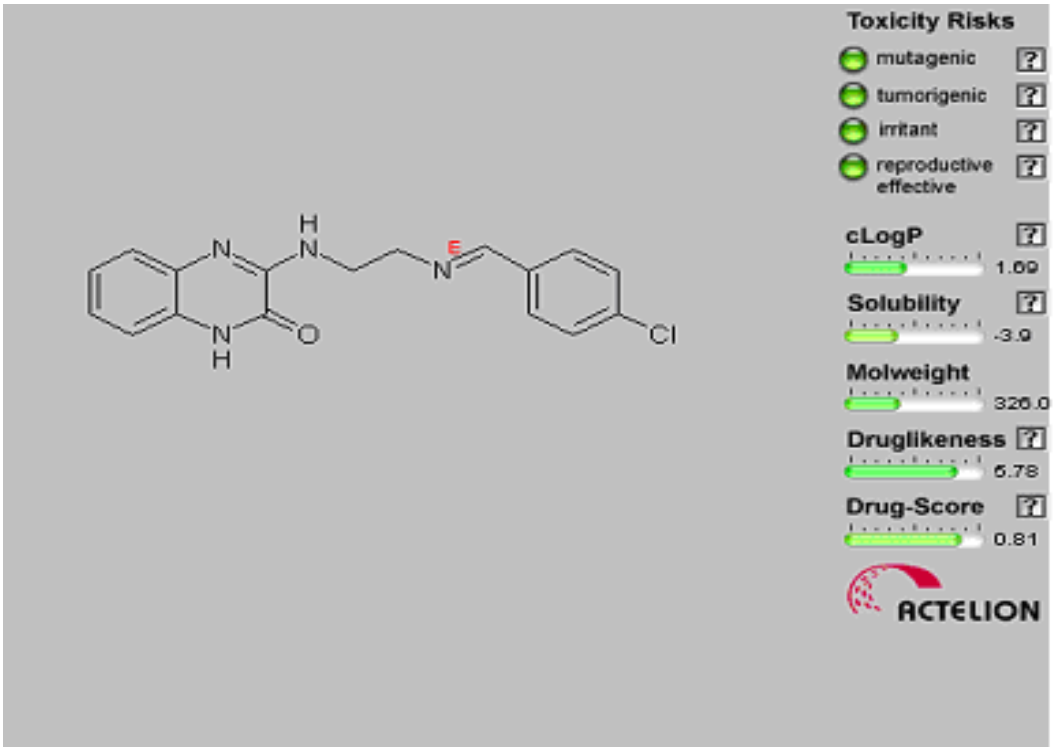
Compound2



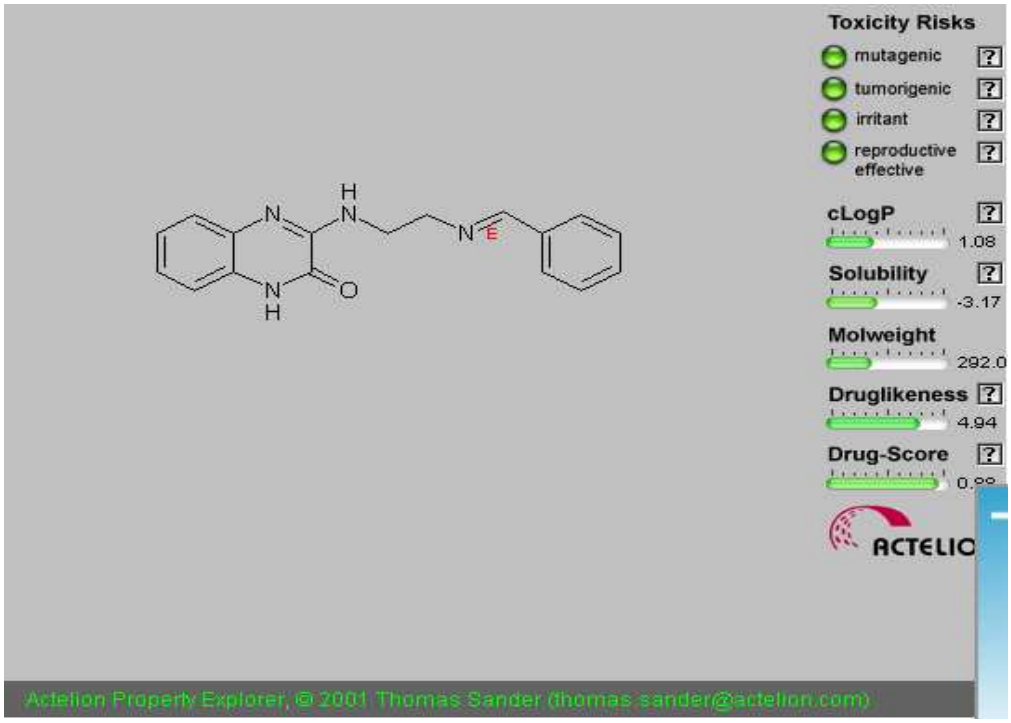
Compound3



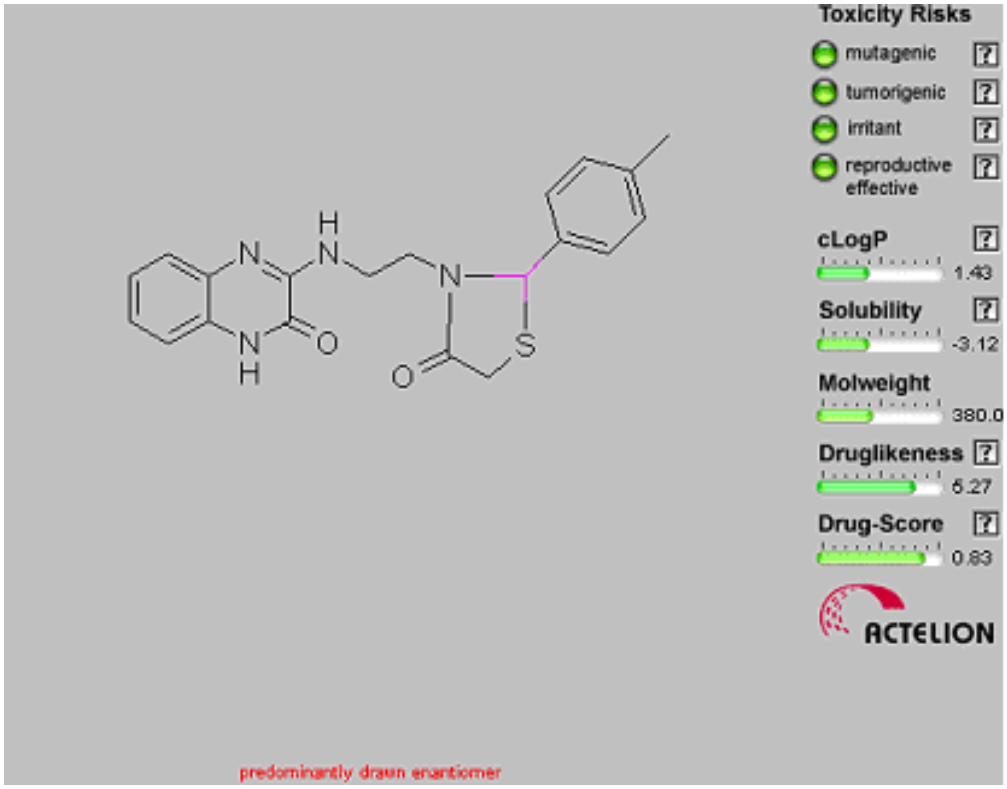
Compound4



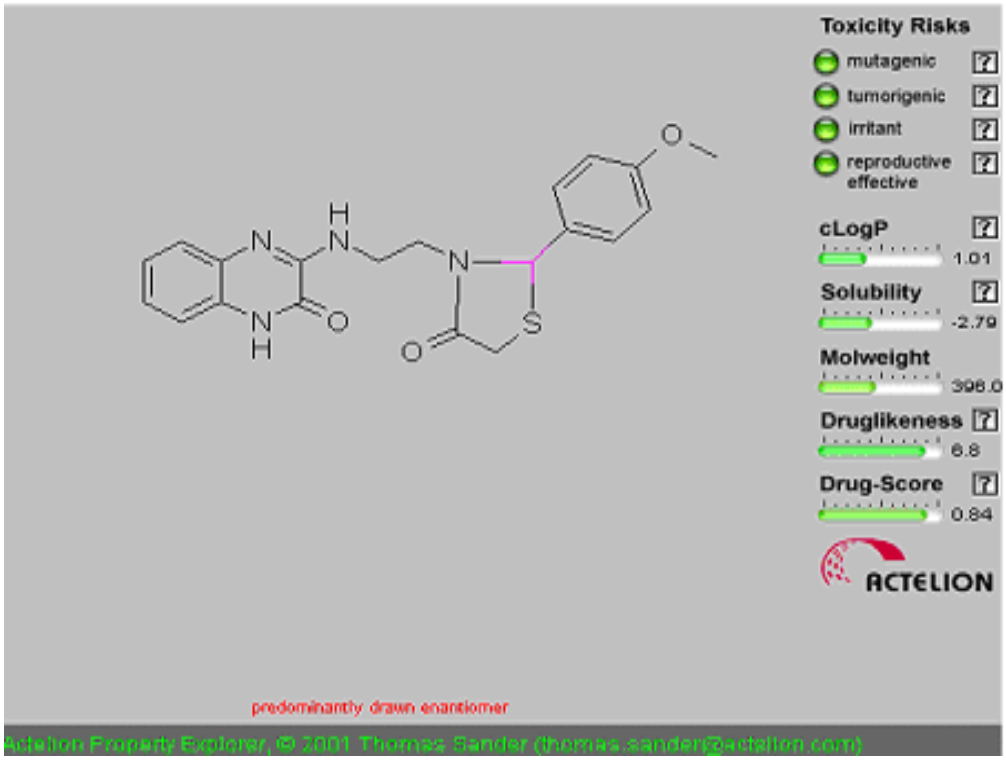
compound5



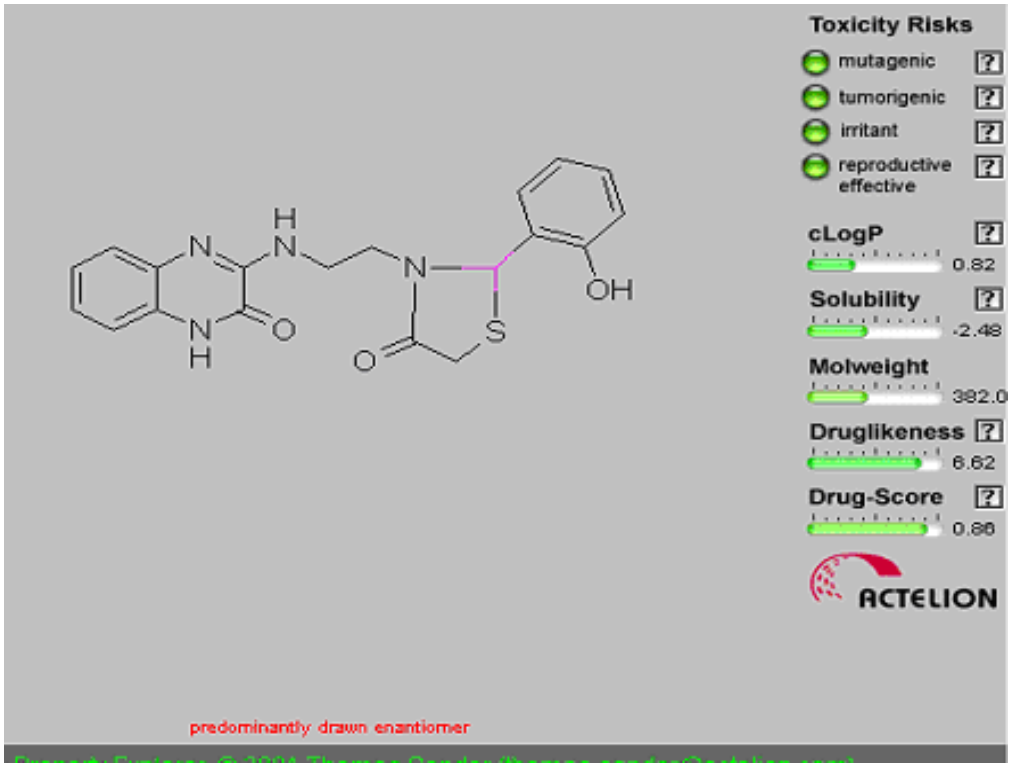
Compound6



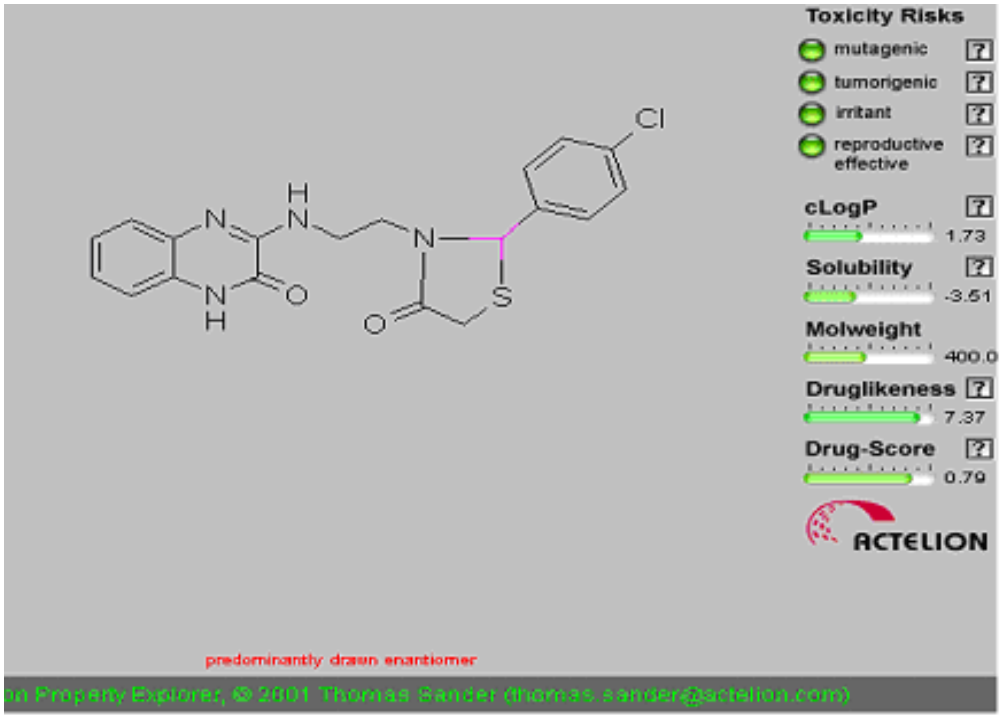
Compound7



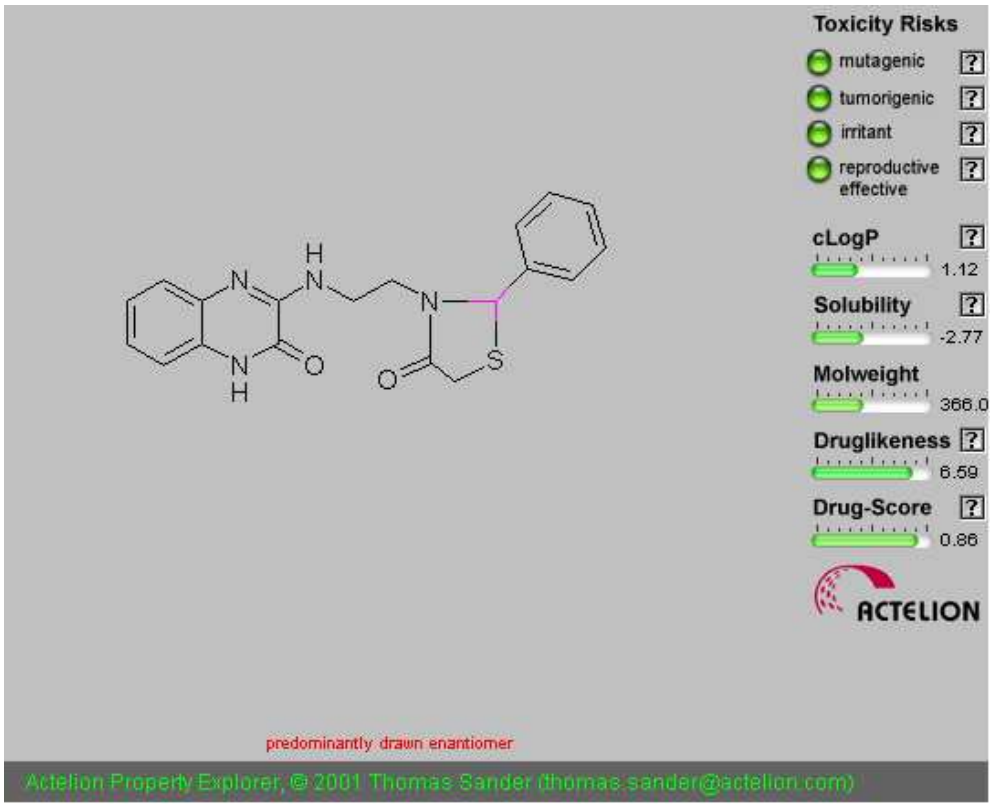
compound8



Compound9

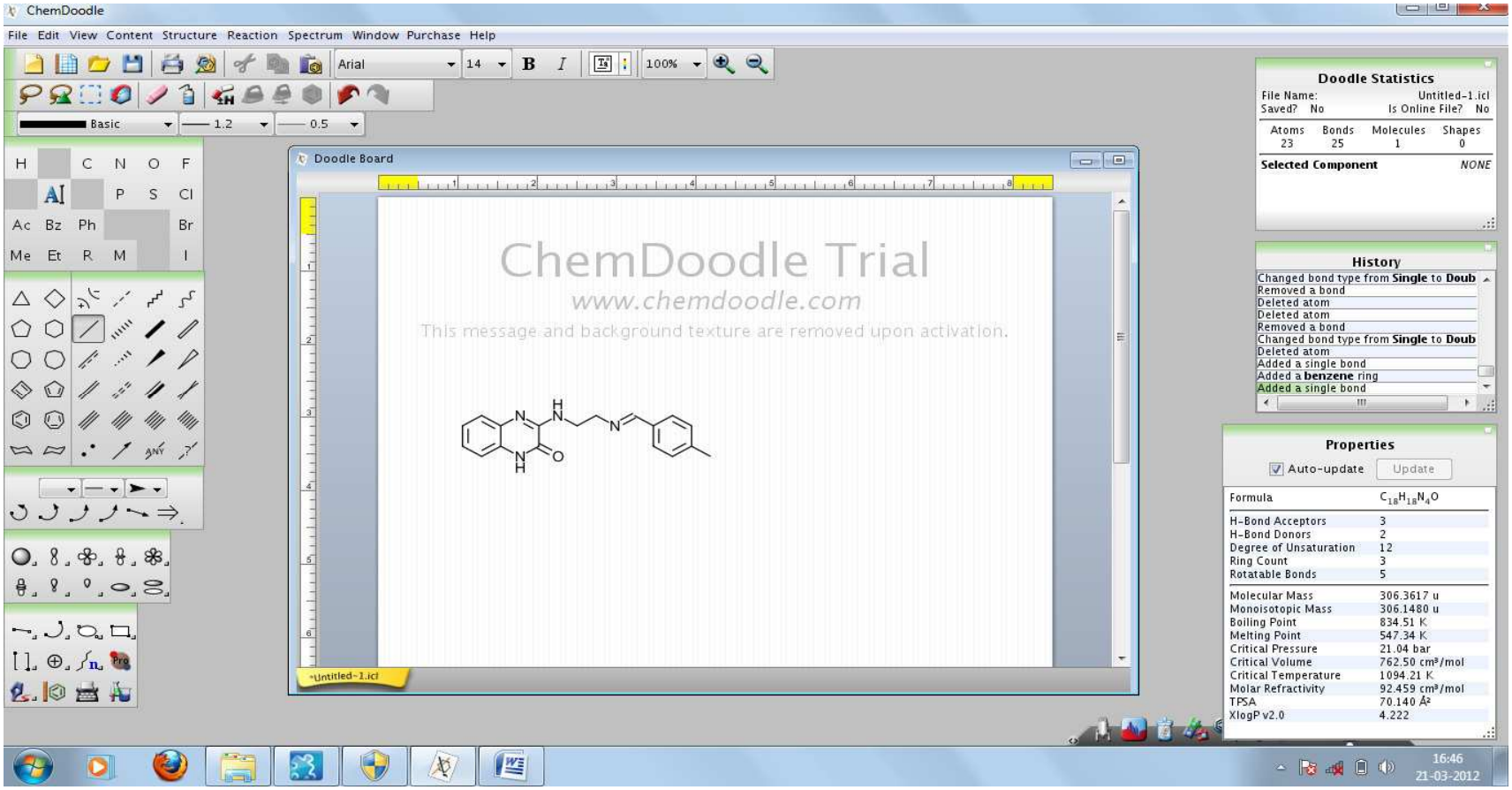


compound 10



(LIPINSKI'S RULE)ADME property is predicted by Chem.-Doodle software

Compound 1



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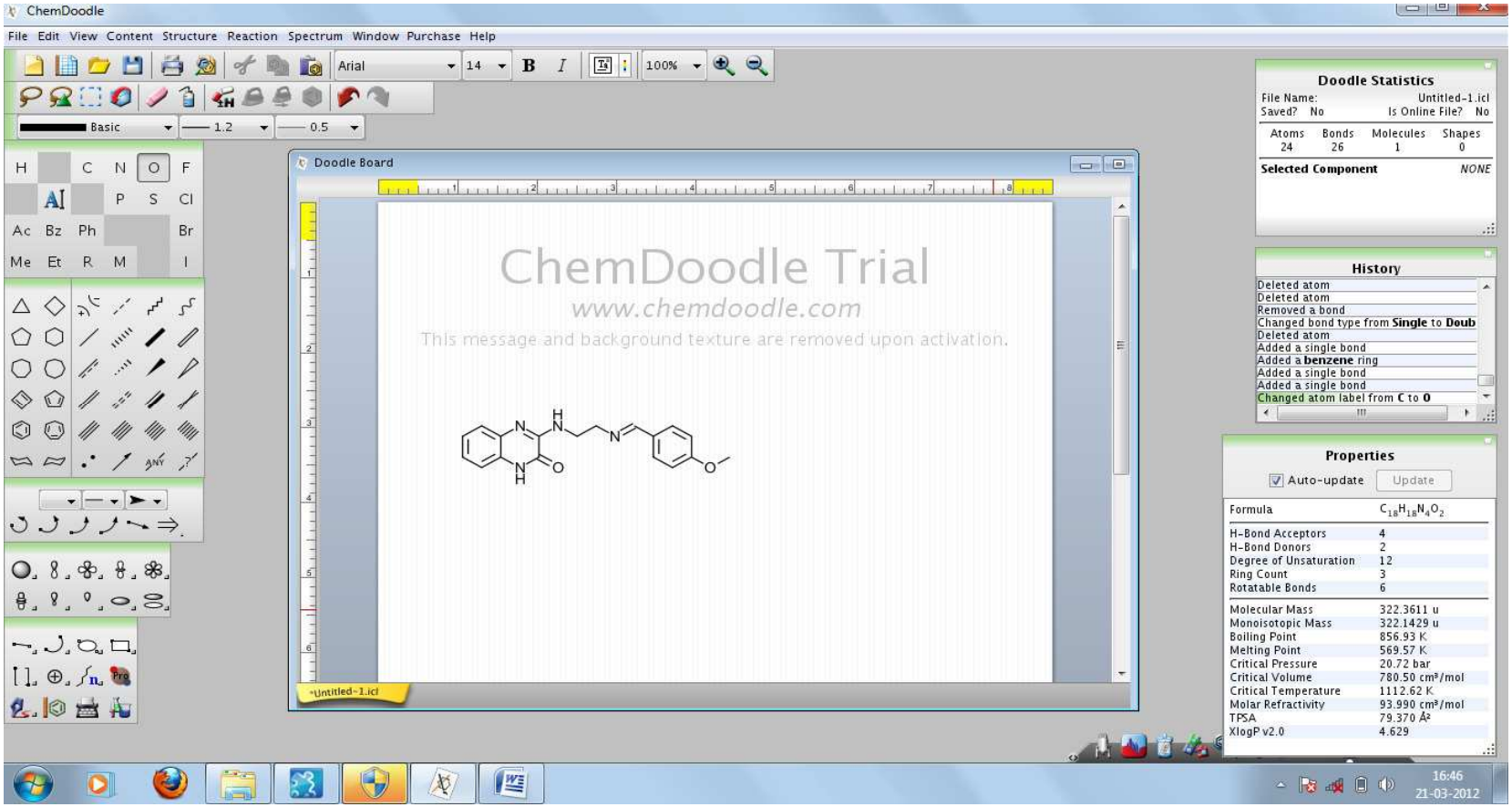
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Doodle Board
ChemDoodle Trial
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Deleted atom
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Added a single bond
Added a single bond
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Properties
Auto-update
Update
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H-Bond Donors 2
Degree of Unsaturation 12
Ring Count 3
Rotatable Bonds 6
Molecular Mass 322.3611 u
Monoisotopic Mass 322.1429 u
Boiling Point 856.93 K
Melting Point 569.57 K
Critical Pressure 20.72 bar
Critical Volume 780.50 cm³/mol
Critical Temperature 1112.62 K
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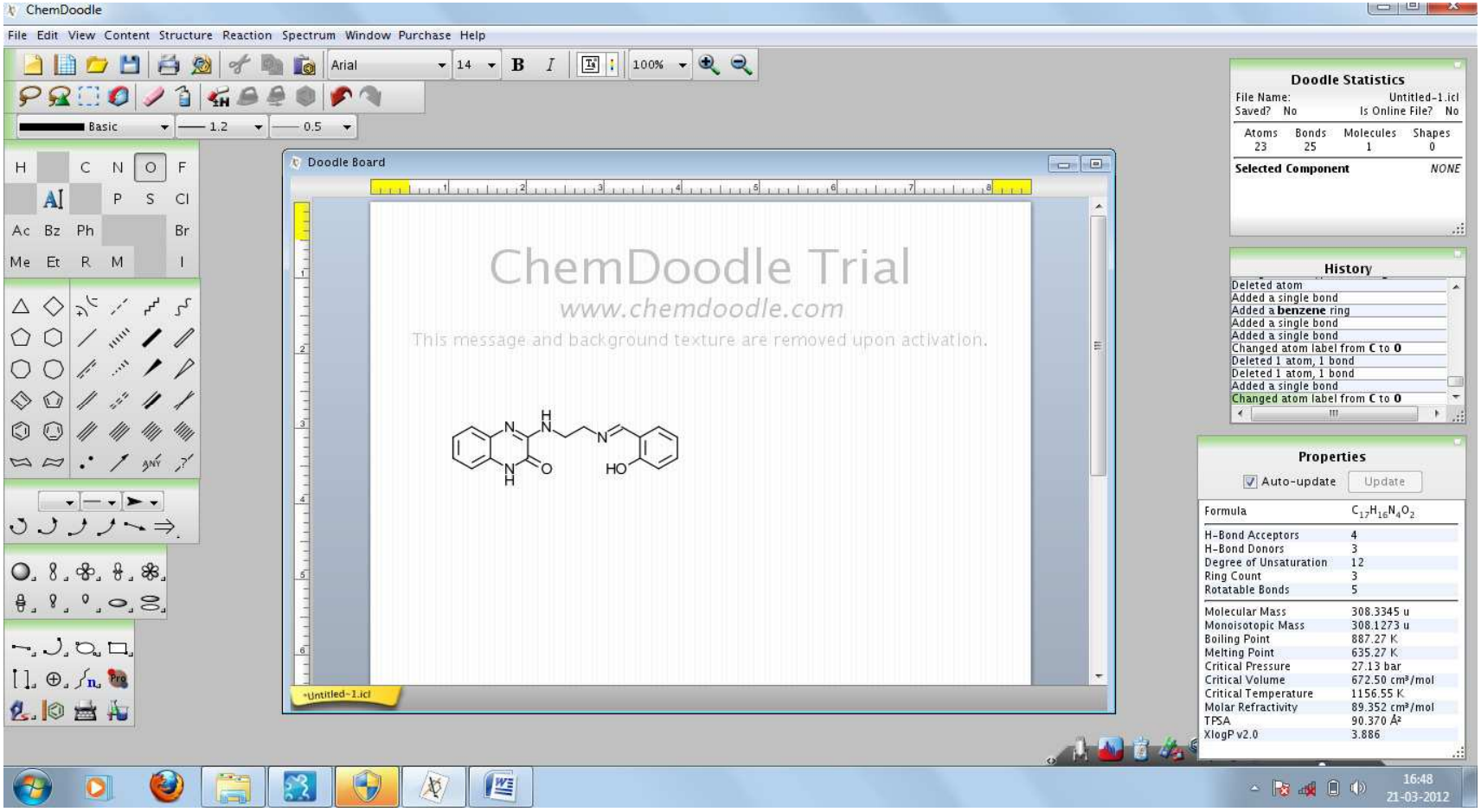
16:46
21-03-2012

Compound 3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Added a single bond
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Deleted 1 atom, 1 bond
Added a single bond
Changed atom label from C to O
Properties
Auto-update
Update
Formula C17H16N4O2
H-Bond Acceptors 4
H-Bond Donors 3
Degree of Unsaturation 12
Ring Count 3
Rotatable Bonds 5
Molecular Mass 308.3345 u
Monoisotopic Mass 308.1273 u
Boiling Point 887.27 K
Melting Point 635.27 K
Critical Pressure 27.13 bar
Critical Volume 672.50 cm³/mol
Critical Temperature 1156.55 K
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TPSA 90.370 Å²
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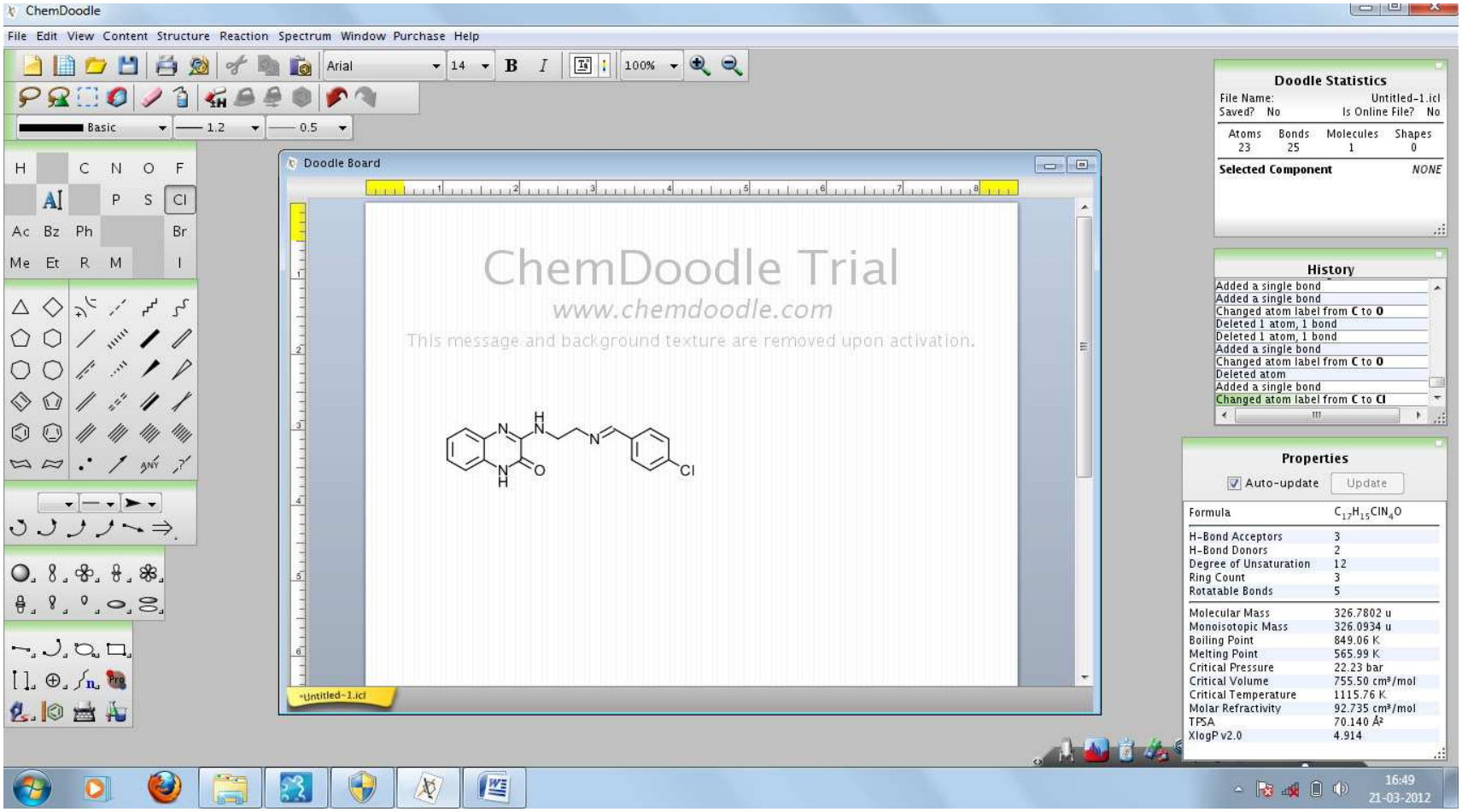
21-03-2012

Compound 4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Added a single bond
Changed atom label from C to O
Deleted atom
Added a single bond
Changed atom label from C to Cl
Properties
Auto-update
Update
Formula C17H15ClN4O
H-Bond Acceptors 3
H-Bond Donors 2
Degree of Unsaturation 12
Ring Count 3
Rotatable Bonds 5
Molecular Mass 326.7802 u
Monoisotopic Mass 326.0934 u
Boiling Point 849.06 K
Melting Point 565.99 K
Critical Pressure 22.23 bar
Critical Volume 755.50 cm³/mol
Critical Temperature 1115.76 K
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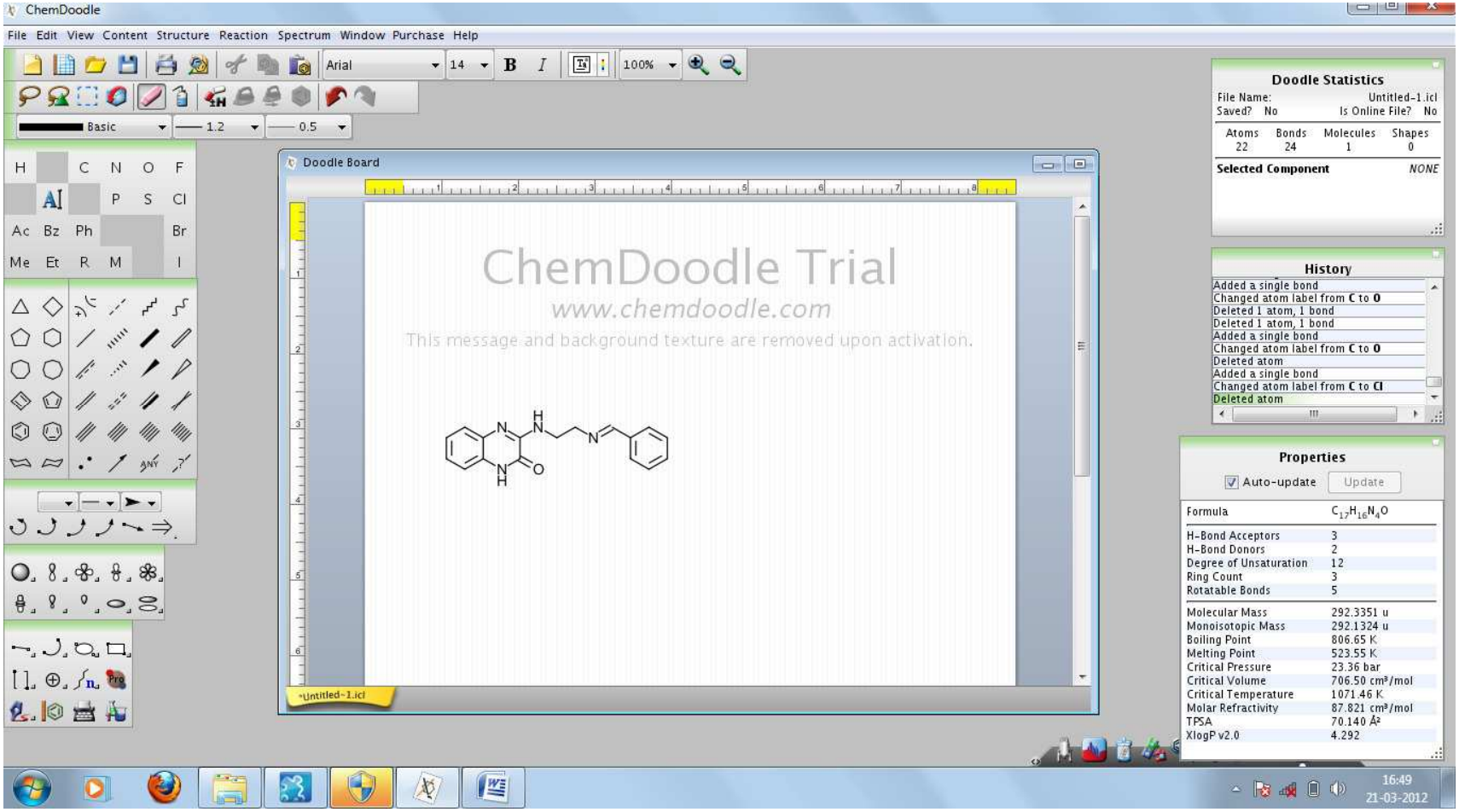
21-03-2012

Compound 5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Deleted atom
Added a single bond
Changed atom label from C to Cl
Deleted atom
Properties
Auto-update
Update
Formula C17H16N4O
H-Bond Acceptors 3
H-Bond Donors 2
Degree of Unsaturation 12
Ring Count 3
Rotatable Bonds 5
Molecular Mass 292.3351 u
Monoisotopic Mass 292.1324 u
Boiling Point 806.65 K
Melting Point 523.55 K
Critical Pressure 23.36 bar
Critical Volume 706.50 cm³/mol
Critical Temperature 1071.46 K
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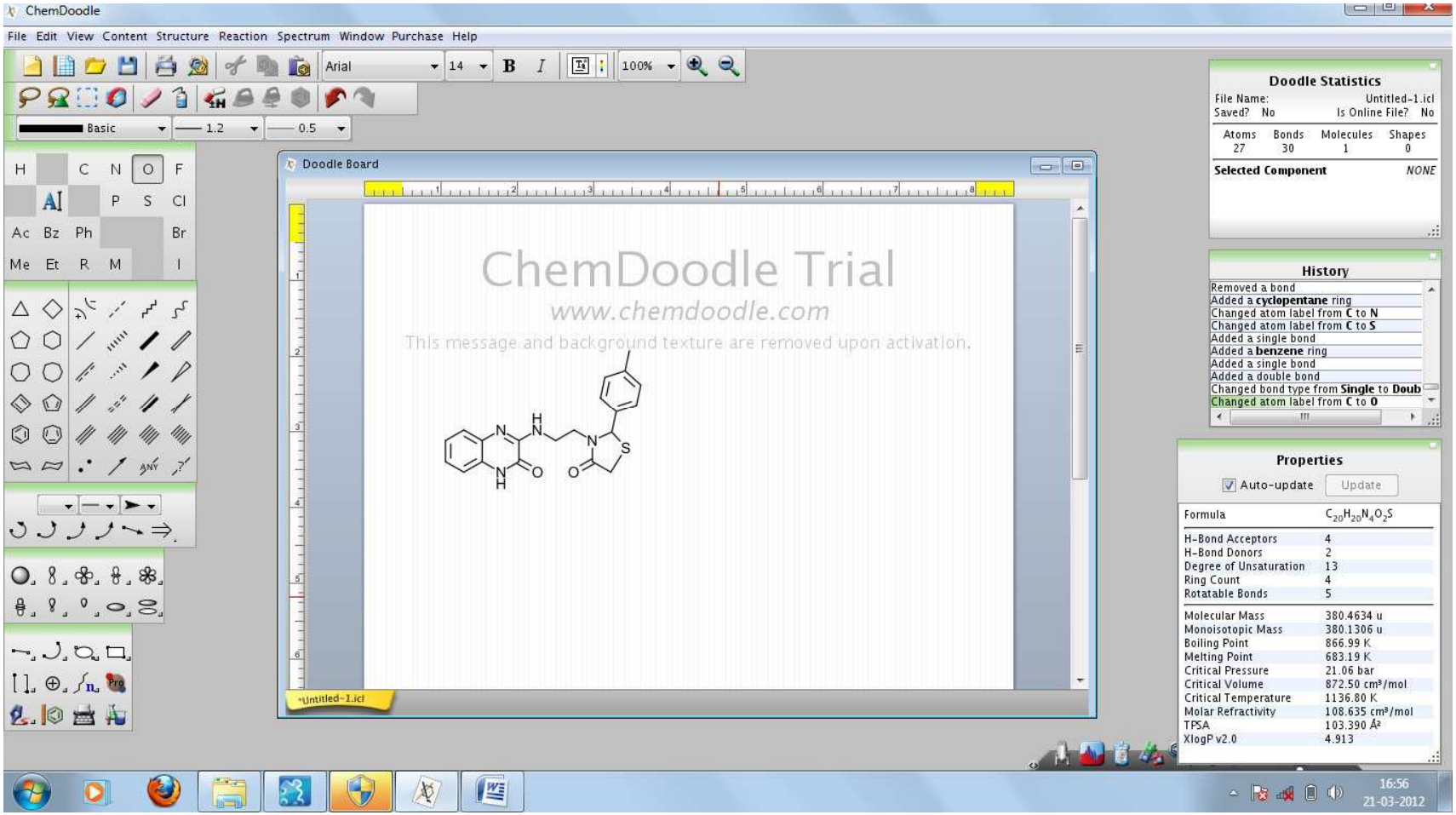
21-03-2012

Compound 6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Molecules 1
Shapes 0
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Changed atom label from C to S
Added a single bond
Added a benzene ring
Added a single bond
Added a double bond
Changed bond type from Single to Doub
Changed atom label from C to O
Properties
Auto-update
Update
Formula C20H20N4O2S
H-Bond Acceptors 4
H-Bond Donors 2
Degree of Unsaturation 13
Ring Count 4
Rotatable Bonds 5
Molecular Mass 380.4634 u
Monoisotopic Mass 380.1306 u
Boiling Point 866.99 K
Melting Point 683.19 K
Critical Pressure 21.06 bar
Critical Volume 872.50 cm³/mol
Critical Temperature 1136.80 K
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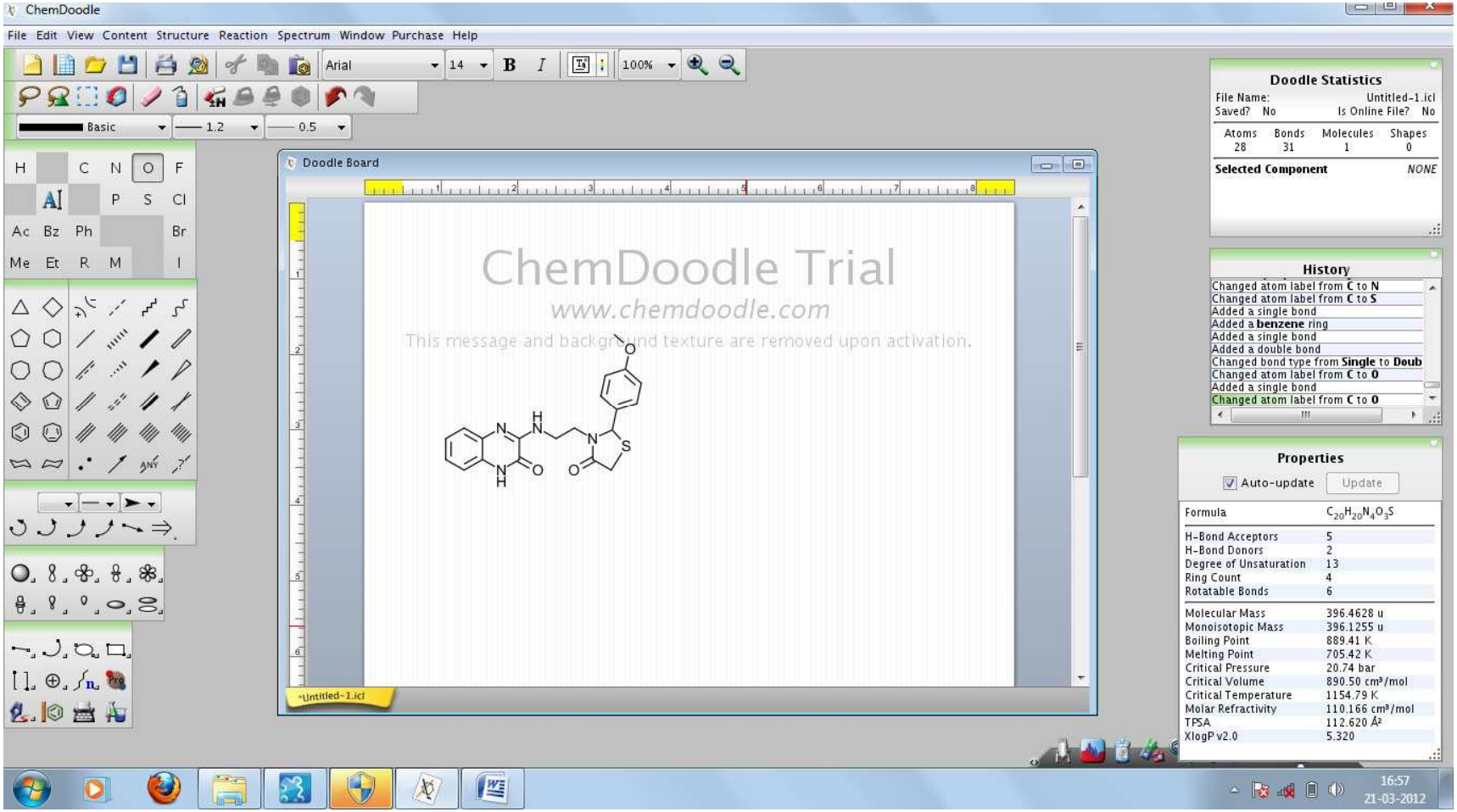
16:56
21-03-2012

Compound 7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Bonds 31
Molecules 1
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Changed atom label from C to S
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Added a benzene ring
Added a single bond
Added a double bond
Changed bond type from Single to Doub
Changed atom label from C to O
Added a single bond
Changed atom label from C to O
Properties
Auto-update
Update
Formula C20H20N4O3S
H-Bond Acceptors 5
H-Bond Donors 2
Degree of Unsaturation 13
Ring Count 4
Rotatable Bonds 6
Molecular Mass 396.4628 u
Monoisotopic Mass 396.1255 u
Boiling Point 889.41 K
Melting Point 705.42 K
Critical Pressure 20.74 bar
Critical Volume 890.50 cm³/mol
Critical Temperature 1154.79 K
Molar Refractivity 110.166 cm³/mol
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XlogP v2.0 5.320
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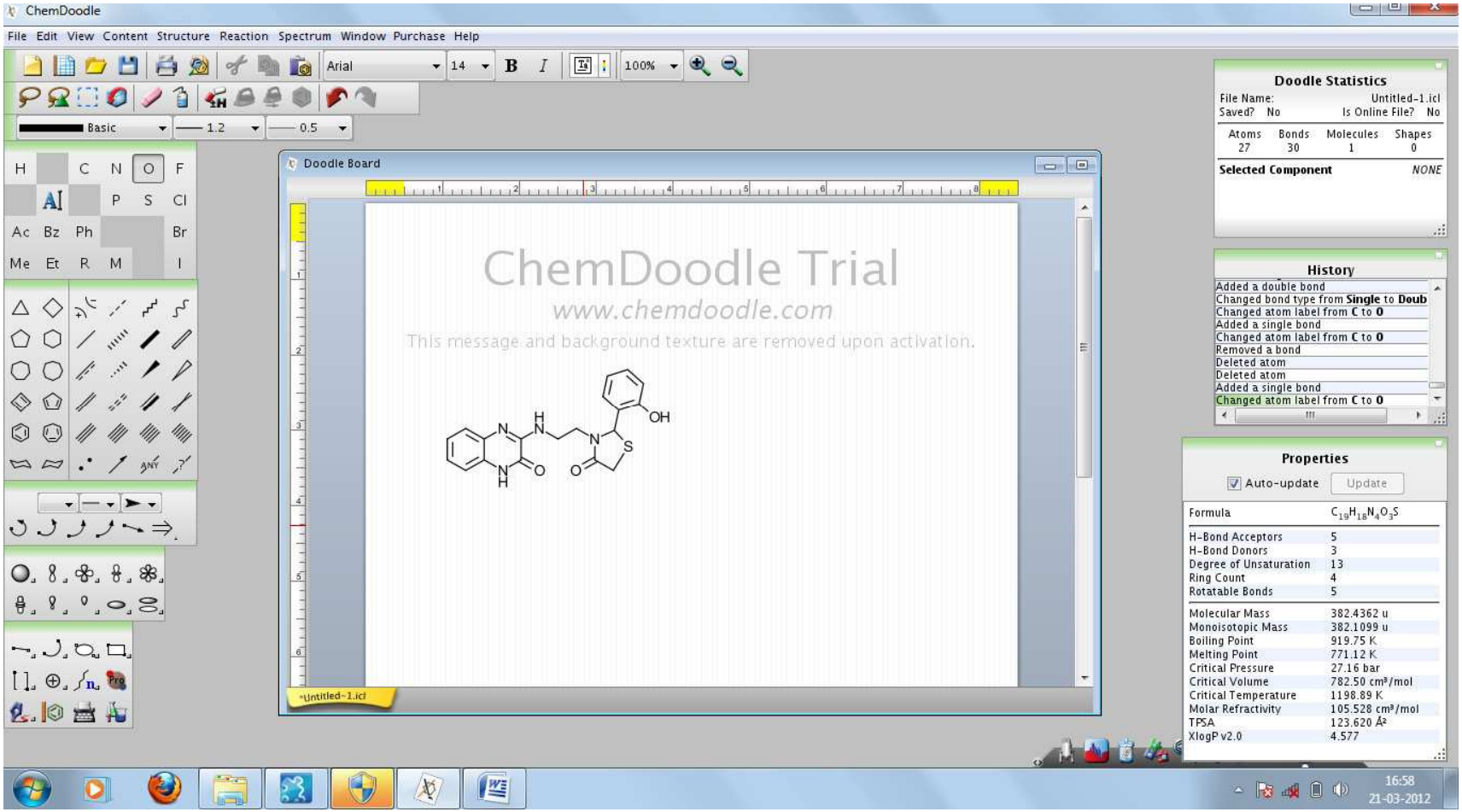
21-03-2012

Compound 8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Is Online File? No
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Bonds 30
Molecules 1
Shapes 0
Selected Component NONE
History
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Changed atom label from C to O
Added a single bond
Changed atom label from C to O
Removed a bond
Deleted atom
Deleted atom
Added a single bond
Changed atom label from C to O
Properties
Auto-update
Update
Formula C19H18N4O3S
H-Bond Acceptors 5
H-Bond Donors 3
Degree of Unsaturation 13
Ring Count 4
Rotatable Bonds 5
Molecular Mass 382.4362 u
Monoisotopic Mass 382.1099 u
Boiling Point 919.75 K
Melting Point 771.12 K
Critical Pressure 27.16 bar
Critical Volume 782.50 cm³/mol
Critical Temperature 1198.89 K
Molar Refractivity 105.528 cm³/mol
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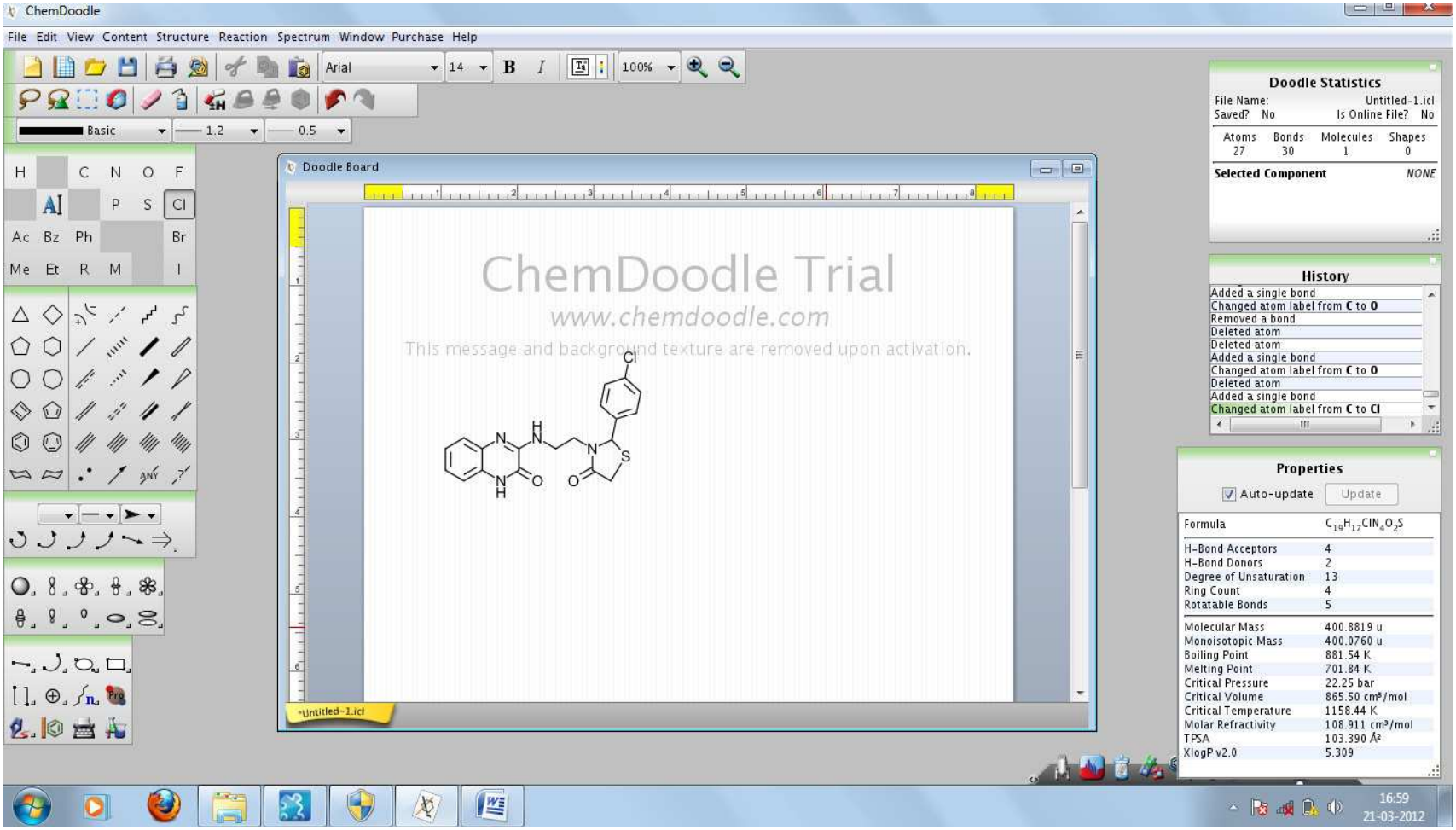
16:58
21-03-2012

Compound 9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Bonds 30
Molecules 1
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Removed a bond
Deleted atom
Deleted atom
Added a single bond
Changed atom label from C to O
Deleted atom
Added a single bond
Changed atom label from C to Cl
Properties
Auto-update
Update
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H-Bond Acceptors 4
H-Bond Donors 2
Degree of Unsaturation 13
Ring Count 4
Rotatable Bonds 5
Molecular Mass 400.8819 u
Monoisotopic Mass 400.0760 u
Boiling Point 881.54 K
Melting Point 701.84 K
Critical Pressure 22.25 bar
Critical Volume 865.50 cm³/mol
Critical Temperature 1158.44 K
Molar Refractivity 108.911 cm³/mol
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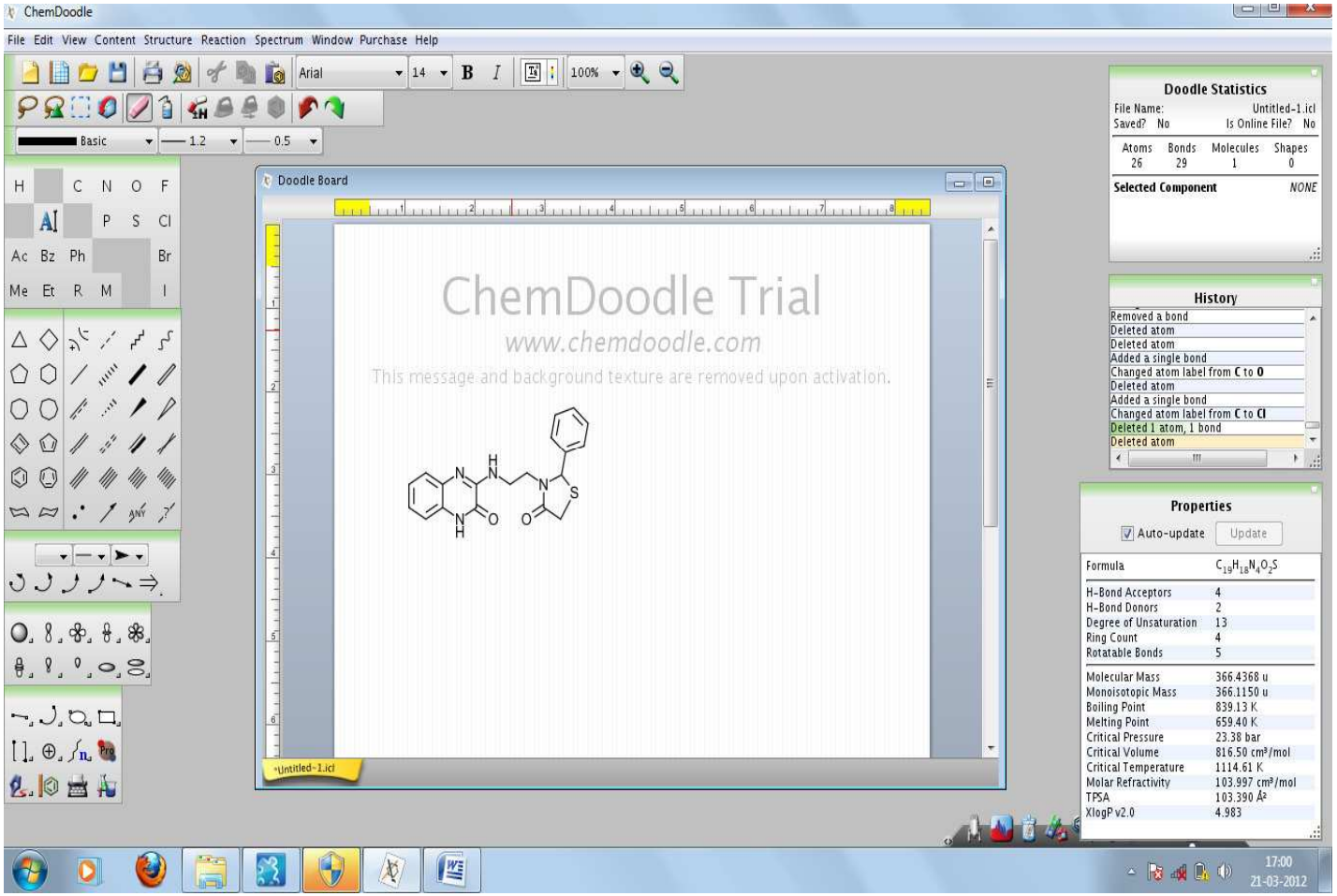
21-03-2012

Compound 10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Is Online File? No
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Bonds 29
Molecules 1
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Deleted atom
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Deleted atom
Added a single bond
Changed atom label from C to Cl
Deleted 1 atom, 1 bond
Deleted atom
Properties
Auto-update
Update
Formula C19H18N4O2S
H-Bond Acceptors 4
H-Bond Donors 2
Degree of Unsaturation 13
Ring Count 4
Rotatable Bonds 5
Molecular Mass 366.4368 u
Monoisotopic Mass 366.1150 u
Boiling Point 839.13 K
Melting Point 659.40 K
Critical Pressure 23.38 bar
Critical Volume 816.50 cm³/mol
Critical Temperature 1114.61 K
Molar Refractivity 103.997 cm³/mol
TPSA 103.390 Å²
XlogP v2.0 4.983
17:00
21-03-2012

4.2, SYNTHETIC METHODS

Scheme of synthesis

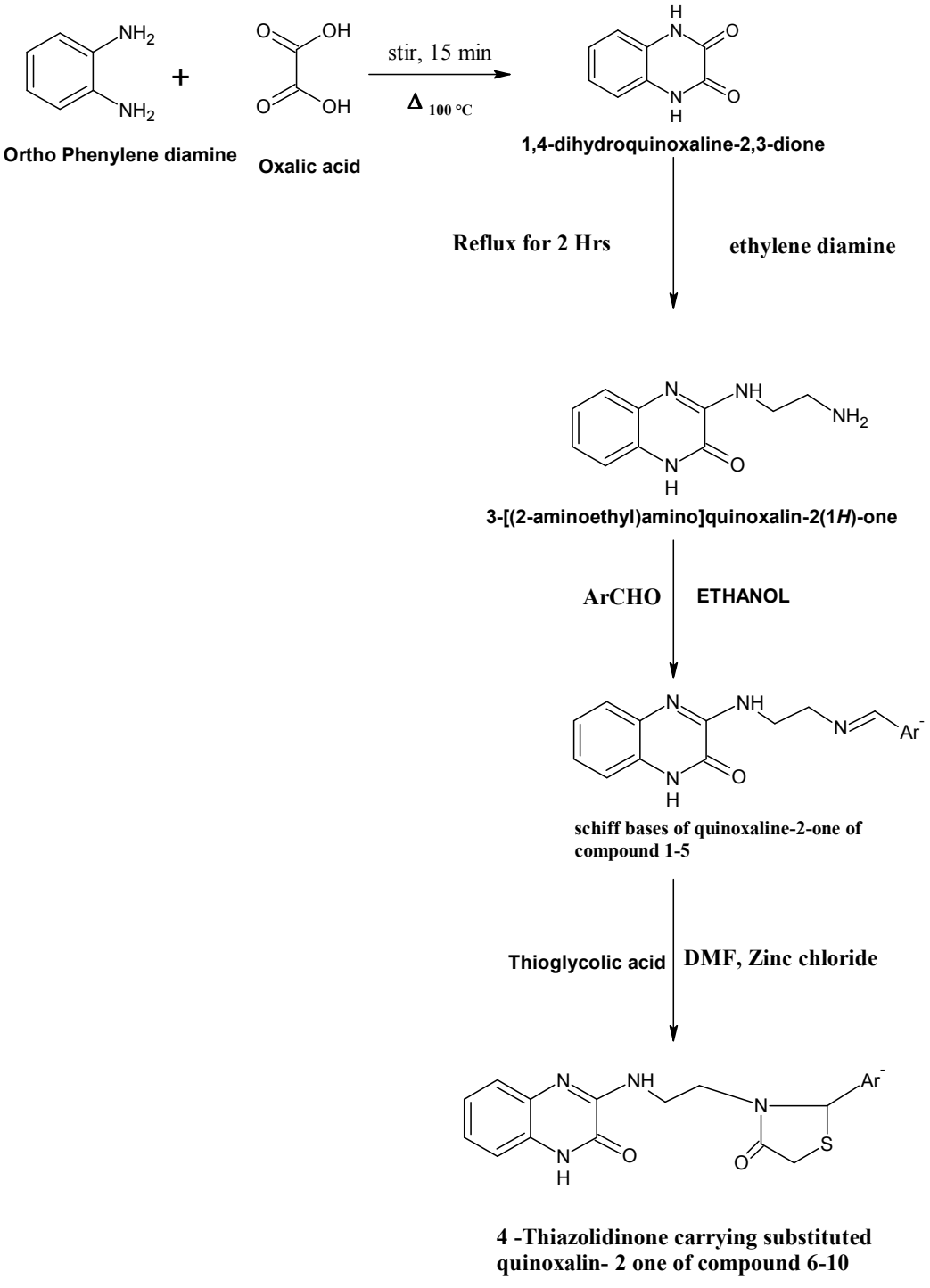


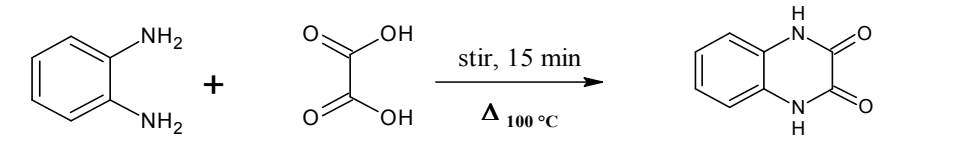
Table1-List of aromatic aldehydes used

Comp.code	aldehydes	Ar
1,6	**Para methyl benzaldehyde** 4 -$CH_3C_6H_4CHO$	4 -$CH_3C_6H_4$
2,7	**Para methoxy benzaldehyde** 4 -$OCH_3C_6H_4CHO$	4 -OCH_3 C_6H_4
3,8	**Salicylaldehyde** 2 -OHC_6H_4CHO	2 -OHC_6H_4
4,9	**Para chloro benzaldehyde** 4 -Cl C_6H_4CHO	4 -Cl C_6H_4
5,10	**Benzaldehyde** C_6H_5CHO	C_6H_5

GENERAL PROCEDURE

STEP1:

Synthesis of 1,4-dihydroquinoxaline-2,3-dione

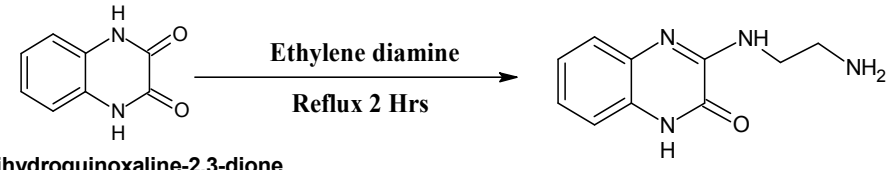


Ortho Phenylene diamine **Oxalic acid** **1,4-dihydroquinoxaline-2,3-dione**

A solution of oxalic acid dehydrate (0.238mole, 30g) in water (100ml) was heated to 100 °C and conc. HCl 45ml was added, followed by O-phenylendiamine (0.204 mole, 22g) with stirring, temperature was maintained at 100 °C for 20 min. The mixture cooled by addition of ice. The precipitate was formed and washed with water. Product was recrystallized form ethanol.

STEP 2:

Synthesis of 3-[(2-aminoethyl)amino]-3,4- dihydroquinoxalin-2(1H)-one



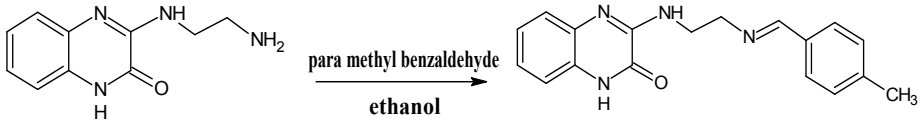
1,4-dihydroquinoxaline-2,3-dione

3-[(2-aminoethyl)amino]quinoxalin-2(1*H*)-one

A mixture of the quinoxalindione (l) (0.062 mole, 10.04g), ethylene diamine (1mole, 50ml,) and water (50ml) was heated under reflux for 2hrs, then cooled to room temperature, the precipitate was filtered, washed with water and crystallized from 2-butanol.

PREPARATION OF SCHIFF'S BASES OF QUINOXALINES OF COMPOUND 1 TO COMPOUND5:

Synthesis of compound 1:

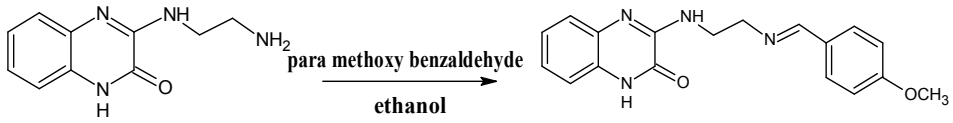


3-[(2-aminoethyl)amino]quinoxalin -2(1H)-one

3-({2-[(E)-(4-methylbenzylidene)amin o]ethyl}amino)quinoxalin-2(1H)-one

In this step, compound 3-[(2 amino ethyl) amino] quinoxalin-2(1H) – one and para methyl benzadehyde (0.01mole of each) in ethanol as solvent (20ml) was refluxed for 5hr. Upon cooling the precipitate was obtained, filtered, dried and crystallized from ethanol.

Synthesis of compound 2:

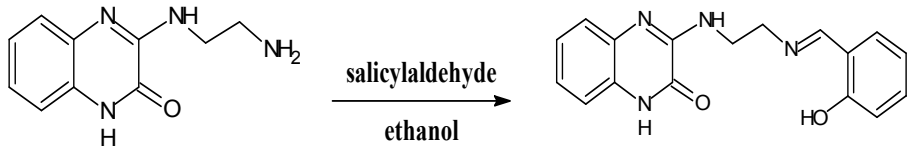


3-[(2-aminoethyl)amino]quinoxalin -2(1H)-one

3-({2-[(E)-(4-methoxybenzylidene)amino] ethyl}amino)quinoxalin-2(1H)-one

In this step, compound 3-[(2 amino ethyl) amino] quinoxalin-2(1H) – one and para methoxy benzadehyde (0.01mole of each) in ethanol as solvent (20ml) was refluxed for 5hr. Upon cooling the precipitate was obtained, filtered, dried and crystallized from ethanol.

Synthesis of compound 3:

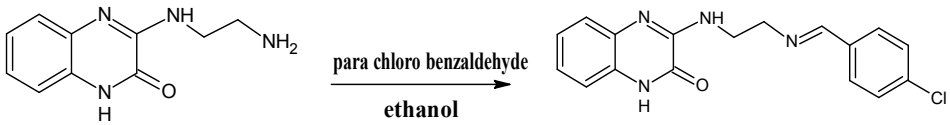


3-[(2-aminoethyl)amino]quinoxalin -2(1H)-one

3-({2-[(E)-(2-hydroxybenzylidene)amino] ethyl}amino)quinoxalin-2(1H)-one

In this step, compound 3-[(2 amino ethyl) amino] quinoxalin-2(1H) – one and 2-hydroxy benzadehyde (0.01mole of each) in ethanol as solvent (20ml) was refluxed for 5hr. Upon cooling the precipitate was obtained, filtered, dried and crystallized from ethanol.

Synthesis of compound 4:

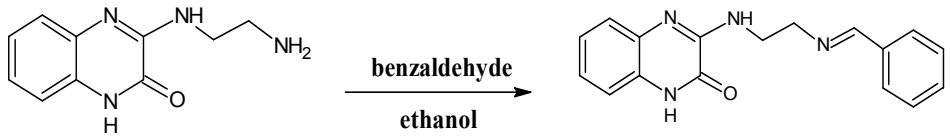


3-[(2-aminoethyl)amino]quinoxalin -2(1H)-one

3-({2-[(E)-(4-chlorobenzylidene)amino]ethyl}amino)quinoxalin-2(1H)-one

In this step, compound 3-[(2 amino ethyl) amino] quinoxalin-2(1H) – one and para chloro benzadehyde (0.01mole of each) in ethanol as solvent (20ml) was refluxed for 5hr. Upon cooling the precipitate was obtained, filtered, dried and crystallized from ethanol.

synthesis of compound 5:



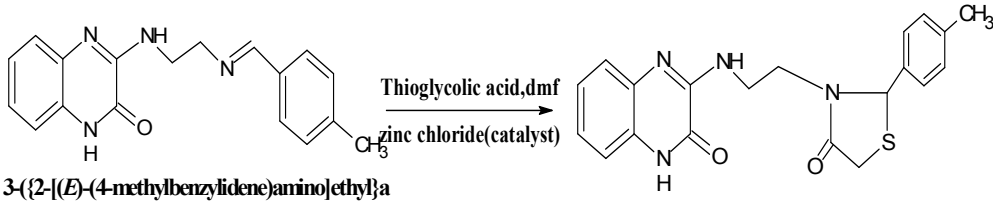
3-[(2-aminoethyl)amino]quinoxalin-2(1H)-one

3-({2-[(E)-benzylideneamino]ethyl}amino)quinoxalin-2(1H)-one

In this step, compound 3-[(2 amino ethyl) amino] quinoxalin-2(1H) – one and benzadehyde (0.01mole of each) in ethanol as solvent (20ml) was refluxed for 5hr. Upon cooling the precipitate was obtained, filtered, dried and crystallized from ethanol.

Synthesis of quinoxaline based 4-thiazolidinone(compound6-compound10) from Schiff bases of compound(1-5)

Synthesis of compound6:

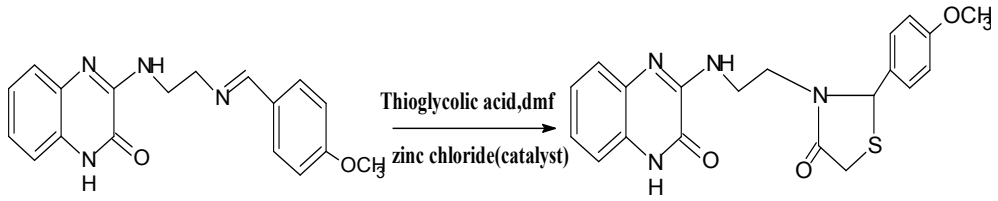


3-({2-[(*E*)-(4-methylbenzylidene)amino]ethyl}amino)quinoxalin-2(1*H*)-one

3-({2-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl}amino)quinoxalin-2(1H)-one

A mixture of 3-(p-methyl benzylidene ethylenediamino) quinoxaline-2-(1H)-one(compound 1, 0.01mol) and thioglycolic acid (0.01mol) in 30ml of DMF in the presence of catalytic amount of anhydrous zinc chloride and was refluxed in sand bath for about 10hrs. The residue was washed with sodium bicarbonate solution and the product was washed with water thoroughly and crystallized from alcohol to get solid crystals.

Synthesis of compound 7:

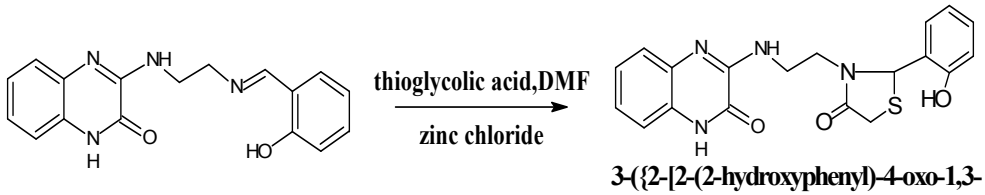


3-({2-[(E)-(4-methoxybenzylidene)amino]ethyl}amino)quinoxalin-2(1H)-one

3-({2-[2-(4-methoxyphenyl)-4-oxo-1, 3-thiazolidin-3-yl]ethyl}amino)quin oxalin-2(1H)-one

A mixture of 3-(p-methoxyy benzylidene ethylenediamino) quinoxaline-2-(1H)- one (compound 2, 0.01mol) and thioglycolic acid (0.01mol) in 30ml of DMF in the presence of catalytic amount of anhydrous zinc chloride and was refluxed in sand bath for about 10hrs. The residue was washed with sodium bicarbonate solution and the product was washed with water thoroughly and crystallized from alcohol to get solid crystals.

Synthesis of compound 8:

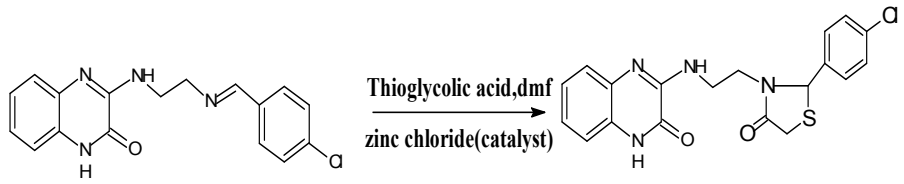


3-({2-[(E)-(2-hydroxybenzylidene)amino] ethyl}amino)quinoxalin-2(1H)-one

3-({2-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl}amino)quinoxal in-2(1H)-one

A mixture of 3-(2-OH benzylidene ethylenediamino) quinoxaline-2-(1H)-one(compound 3, 0.01mol) and thioglycolic acid (0.01mol) in 30ml of DMF in the presence of catalytic amount of anhydrous zinc chloride and was refluxed in sand bath for about 10hrs. The residue was washed with sodium bicarbonate solution and the product was washed with water thoroughly and crystallized from alcohol to get solid crystals.

Synthesis of compound 9:

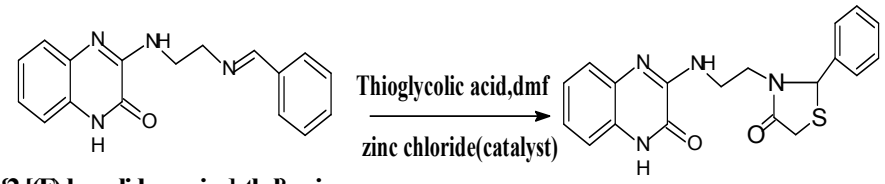


3-({2-[(E)-(4-chlorobenzylidene)amino]ethyl}amino)quinoxalin-2(1H)-one

3-({2-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl}amino)quinoxalin-2(1H)-one

A mixture of 3-(p-cl benzylidene ethylenediamino)quinoxaline-2-(1H)-one(compound 4, 0.01mol) and thioglycolic acid (0.01mol) in 30ml of DMF in the presence of catalytic amount of anhydrous zinc chloride and was refluxed in sand bath for about 10hrs. The residue was washed with sodium bicarbonate solution and the product was washed with water thoroughly and crystallized from alcohol to get solid crystals.

Synthesis of compound 10:



3-({2-[(E)-benzylideneamino]ethyl}amin o)quinoxalin-2(1H)-one

3-{[2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)ethyl] amino}quinoxalin-2(1H)-one

A mixture of 3-(benzylidene ethylenediamino) quinoxaline-2-(1H)- one (compound 5, 0.01mol) and thioglycolic acid (0.01mol) in 30ml of DMF in the presence of catalytic amount of anhydrous zinc chloride and was refluxed in sand bath for about 10hrs. The residue was washed with sodium bicarbonate solution and the product was washed with water thoroughly and crystallized from alcohol to get solid crystals.

4.3 ANALYTICAL TECHNIQUES

Physical Data:

Melting point was found in an open end capillary tube method by electrically heating melting point apparatus.

Thin Layer Chromatography (TLC):

Thin layer chromatographic analysis was carried out by using silica gel (0.5mm thickness) coated over glass plate (12x20cm)as stationary phase. Ethyl acetate: n-Hexane(1:1) as mobile phase, the spots were visualized by iodine vapours.

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 DMSO and chemical shifts were reported in parts per million (δ ppm)

Mass spectroscopy:

Mass spectra were recorded on Mass Spectroscopy JEOL GC mate and molecular ion peak are recorded in m/z ratio.

4.4 Evaluation of biological activity

a) *IN -VITRO* ANTICANCER ACTIVITY

Introduction

The cytotoxicity of Quinoxaline 2-one derivative was evaluated by MTT assay (Microculture tetrazolium assay). The percentage growth inhibition was calculated by measuring the absorbance using microplate reader at a wavelength of 570nm.

Principle

MTT is a yellow water soluble substrate 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. Therefore, the amount of formazan produced is directly proportional to the number of viable cells.

Materials and method

Cell line used

The human colorectal carcinoma cell line (HCT116) was obtained from National Centre for Cell Science (NCCS), Pune,

Media

Dulbeccos Modified Eagles Medium (DMEM) containing 10% fetal bovine serum (FBS).

Equipments

96-well micro titre plate,tissue culture flask,co_2 incubator

Cell treatment procedure

All cells were grown in DMEM and maintained at 37^0C, 5% CO2, 95% air and 100% relative humidity. Maintenance cultures were passaged weekly, and the culture medium was changed twice a week. The monolayer cells were detached with trypsin-ethylenediaminetetraacetic acid (EDTA) to make single cell suspensions and viable

cells were counted using a hemocytometer and diluted with medium with 5% FBS to give final density of $1x10^5$ cells/ml. one hundred microlitres per well of cell suspension were seeded into 96-well plates at plating density of 10,000 cells/well and incubated to allow for cell attachment at 37^0C, 5% CO_2, 95% air and 100% relative humidity. After 24 h the cells were treated with serial concentrations of the extracts and fractions. They were initially dissolved in neat dimethylsulfoxide (DMSO) and further diluted in serum free medium to produce five concentrations. One hundred microlitres per well of each concentration was added to plates to obtain final concentrations of 100, 10, 1.0 and 0.1 µM. The final volume in each well was 200 µl and the plates were incubated at 37^0C, 5% CO_2, 95% air and 100% relative humidity for 48h. The medium containing without samples were served as control. Triplicate was maintained for all concentrations.

After 48h of incubation, 15µl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37^0C for 4h. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100µl of DMSO and then measured the absorbance at 570 nm using micro plate reader. The % cell inhibition was determined using the following formula.

% cell Inhibition = 100- Abs (sample)/Abs (control) x100.

Nonlinear regression graph was plotted between % Cell inhibition and Log_{10} concentration and IC50 was determined using Graph Pad Prism software.

B) *IN-VITRO* ANTI-INFLAMMATORY ACTIVITY

Introduction

A number of anti-inflammatory drugs are known to inhibit the denaturation of proteins as an invitro screening model for anti-inflammatory compounds. The synthesized compounds were screened for anti-inflammatory activity by using inhibition of albumin denaturation technique.

Materials and method

Equipment

BOD incubator,uv spectrophotometer and thermostatically controlled water bath

Media

Bovine serum albumin

Reagent

Phosphate buffer -0.2M, pH7.4

Drugs

Standard drug : different concentration of Ibuprofen

Test drug : different concentration of compound1-10

Procedure

The standard drug and test compounds were dissolved in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different concentrations of drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 27°±1°C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60°±1°C in water bath for 10 min. After cooling the turbidity was measured at 660 nm (UV-Visible

Spectrophotometer.). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken

% Inhibition of denaturation= [(Vt/Vc)-1] × 100

Where, Vt = mean absorption of test compound,

Vc = mean absorption of control

C). In-vitro evaluation of antibacterial activity

Introduction

The invitro antibacterial activity can be evaluated by a) Agar streak dilution method b) Serial dilution method c) Agar diffusion method(Cup plate method, Cylinder method, Paper disc method)d) Turbidimetry method .Among this diffusion techniques are widely used to carry out sensitivity test for pathogenic microorganism .It was evaluated by measuring the zone of inhibition in mm

Materials and method

Equipments

Sterile petriplates ,sterile forceps and loop, whatmannno.1 filter paper

medium

muller hinton agar medium

***Organisms Used*:**

Gram Positive Organisam:

Staphylococcus aureus

Gram Negative Organisam

Escherichia coli

Klebsiella pneumonae

Pseudomonas aureginosa

Proteus mirabilis

The antibacterial activities of the synthesized compounds were studied by disc diffusion method. All the compounds were used in the concentration of 150 μg/ disc using a solvent DMSO. Ciprofloxacin 30 μg/ disc was used as standard

Preparation of Muller Hinton Agar

Composition of muller Hinton agar

- Beef Extract -10gms
- Casein acid hydrosylate - 17.5gms
- Starch -1.5gms
- Agar - 20gms
- Distilled water -1000ml

Procedure:

The above mentioned ingredients were dissolved with help of heat. It was filtered and sterilized by maintaining at 121^{o}C for 20 minutes in autoclave and adjusted the pH to 7.3 ± 0.1

Method:

Disc diffusion Method:

A suspension of the organism was added to sterile nutrient agar medium at 45^{o}C. The mixture was transferred to sterile petridishes and allowed to solidify. Sterile disc 5 mm in diameter (made from Whatmann filter paper which is previously sterilized in UV lamp now commercially also available) was dipped in solution of different concentrations of compound for around 1 h, standard and a blank were placed on the surface of agar plates.

Left the plates to stand for 1 h at room temperature as a period of preincubation to minimize the effects of variation in time between the applications of the different solutions. Then the plate were incubated for 24 h at 37 ± 1^{o}C and observed for antibacterial activity. The diameter of zone of inhibition was observed

In this method

a) The inoculums was adjusted to give uniform dense

b) A standard sensitivity medium was used

c) Disc containing suitable known amounts of drug should be stable on storage and reproducible results were obtained between batches

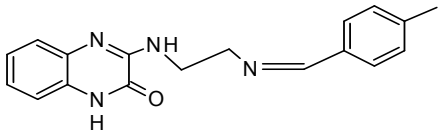
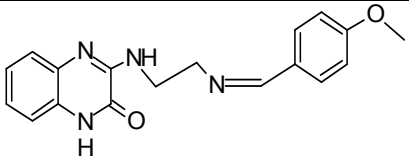
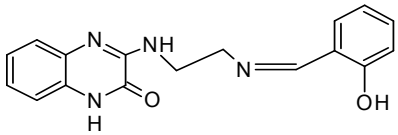
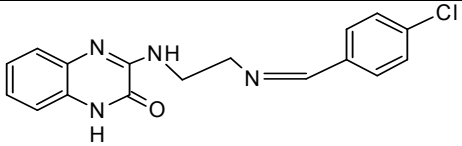
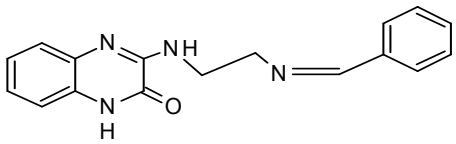
d) The conditions of incubation and other factors also must be standardized as well as the method of interpreting the inhibition zone around discs.

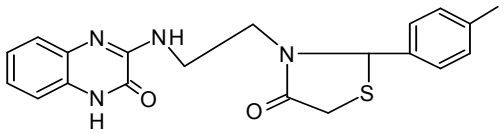
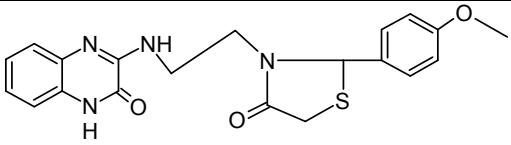
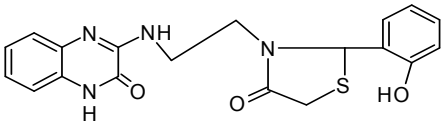
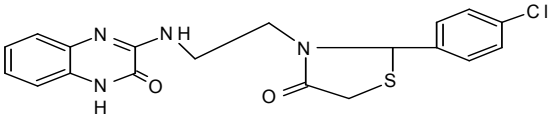
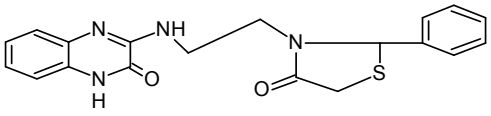
Results
&
Discussion

5. Results & Discussion

Characterization of synthezised compound

Table2-Structure and IUPAC name of the newly synthesized compounds

Comp code	structure and chemical name
1	 3-({2-[(4-methylbenzylidene)amino]ethyl}amino)quinoxalin-2(1*H*)-one
2	 3-({2-[(4-methoxybenzylidene)amino]ethyl}amino)quinoxalin-2(1*H*)-one
3	 3-({2-[(2-hydroxybenzylidene)amino]ethyl}amino)quinoxalin-2(1*H*)-one
4	 3-({2-[(4-chlorobenzylidene)amino]ethyl}amino)quinoxalin-2(1*H*)-one
5	 3-({2-[benzylideneamino]ethyl}amino)quinoxalin-2(1*H*)-one

6	 3-({2-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl] ethyl}amino)quinoxalin-2(1*H*)-one
7	 3-({2-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl} amino)quinoxalin-2(1*H*)-one
8	 3-({2-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl}amino) quinoxalin-2(1*H*)-one
9	 3-({2-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl}amino) quinoxalin-2(1*H*)-one
10	 3-{[2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)ethyl]amino}quinoxalin-2(1*H*)-one

5.1 PHYSICAL CHARACTERIZATION

Table3-Physical Data of the Synthesized Compounds

comp code	m.f	m.w	m.p (°c)	Rf	% yield	solubility	Appearance/color
1	$C_{18}H_{18}N_4O$	306.3	212	0.76	58	DMSO	Solid/white
2	$C_{18}H_{18}N_4O_2$	322.3	190	0.82	61	DMSO	Solid/white
3	$C_{17}H_{16}N_4O_2$	308.3	222	0.76	60	DMSO	Solid/yellow
4	$C_{17}H_{15}ON_4Cl$	326.7	300	0.85	62	DMSO	Solid/white
5	$C_{17}H_{16}N_4O$	292.3	230	0.82	71	DMSO	Solid/white
6	$C_{20}H_{20}N_4O_2S$	380.4	157	0.66	58	DMSO	Solid/buff
7	$C_{20}H_{20}N_4O_3S$	396.4	177	0.78	60	DMSO	Solid/yellow
8	$C_{19}H_{18}N_4O_3S$	382.4	182	0.82	62	DMSO	Solid/pale yellow
9	$C_{19}H_{17}N_4O_2SCl$	400.8	122	0.71	56	DMSO	Solid/pale yellow
10	$C_{19}H_{18}N_4O_2S$	366.4	156	0.8	77	DMSO	Solid/yellow

Table4-- Elemental analysis of synthesized compound

Elemental analysis						
comp code	**%C**	**%H**	**%N**	**%O**	**%S**	**%Cl**
1	70.57	5.92	18.29	5.22	-	-
2	67.07	5.63	17..38	9.93	-	-
3	66.22	5.23	18.17	10.38	-	-
4	62.48	4.63	17.15	4.9	-	10.85
5	69.85	5.52	19.17	5.47	-	-
6	63.14	5.3	14.73	8.41	8.43	-
7	60.59	5.08	14.13	12.11	8.09	-
8	59.67	4.74	14.65	12.55	8.38	-
9	56.93	4.27	13.98	7.98	8	8.84
10	62.28	4.95	15.29	8.73	8.75	-

5.2 RESULTS OF MOLECULAR DESIGN

Table5 – Drug relevant property by using OSIRIS property Explorer

The toxicity of synthesized compound are under safety margin ,which shows green in *Osiris* property explorer

Comp Code	Drug-likeness	Drug score
1	3.57	0.84
2	5.11	0.87
3	4.94	0.89
4	5.78	0.81
5	4.94	0.88
6	5.27	0.83
7	6.8	0.84
8	6.62	0.80
9	7.37	0.70
10	6.59	0.86

Table6--Lipinski rule of synthesized compound using Chemdoodle software

Comp	M. W	Log P	H bond donor	H bond acceptor	Mol. refractivity	Number of criteria met
rule	***< 500***	***<5***	***<5***	***<10***	***40-130***	***At least 3***
1	306.3	1.4	2	3	92.459	All
2	322.3	0.08	2	4	93.990	All
3	308.3	0.78	3	4	89.352	All
4	326.7	1.00	2	3	92.735	All
5	292.3	1.08	2	3	87.821	All
6	380.4	1.43	2	4	108.635	All
7	396.5	1.01	2	5	110.166	All
8	382.4	0.82	3	5	105.528	All
9	400.8	1.73	2	4	108.911	All
10	366.4	1.12	2	4	103.997	All

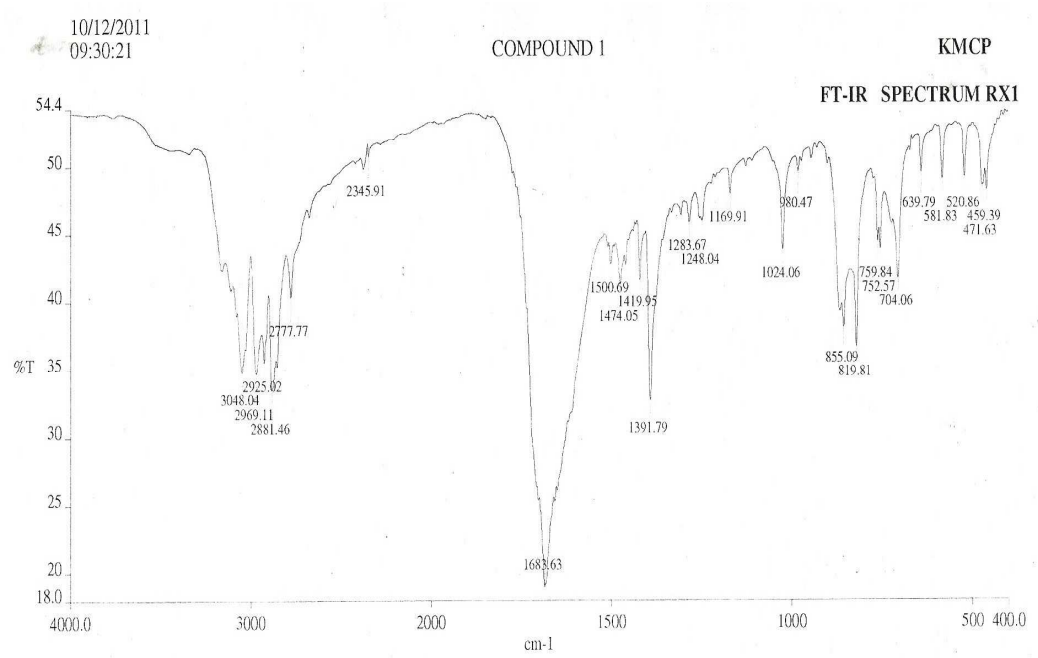
5.3 SPECTRAL ANALYSIS

Table 7-IR studies of synthesized compound

Compound code	Spectral peaks(cm-1)	Molecular nature
1	3048.04	Ar. C – H Stretching
	1683.63	C=0 Stretching
	1500.69	C=C Stretching(aromatics)
	1474.05	CH=N Stretching
	1419.05	C-H def (in CH_3)
	819.81	P- substituted Benzene
2	3317.91	N – H Stretching
	3016.12	Ar. C – H Stretching
	1677.58	C=0 Stretching
	1511.97	C=C Stretching(aromatics)
	1465.55	CH=N Stretching
	1312.20	C-O stretching (phenol)
	1021.65	C-O-C Stretching
3	3317.91	N – H Stretching
	2920.61	OH Stretching
	1677.58	C=O Stretching
	1511.97	C=CStretching(aromatics)
	1465.55	CH=N Stretching
	1248.13	C-N Stretching
4	3049.73	Ar. C – H Stretching
	1681.75	C=O Stretching
	1419.77	CH=N Stretching
	1500.92	C=CStretching(aromatics)
	1248.32	C-NStretching
	759.40	C-Cl
5	3317.70	N – H Stretching
	3015.93	Ar. C – H Stretching
	1677.01	C=0 Stretching
	1464.28	CH=N Stretching
	1512.23	C=CStretching(aromatics)
	1247.79	C-NStretching

Compound code	Spectral peaks(cm-1)	Molecular nature
6	3048.23 2968.95 1683.97 1500.87 1473.56 1419.81 1247.69	Ar. C – H Stretching CH Stretching OF CH3 C=0 Stretching C=CStretching(aromatics) CH=N Stretching CH2-S- C-N Stretching
7	3395.94 3048.51 2968.34 1683.35 1510.58 1419.90 1249.44 1030.71 854.81	N – H Stretching CAr. C – H Stretching CH Stretching OF CH3 C=0 Stretching C=CStretching(aromatics CH2-S- C-N Stretching C-O-C Stretching P- substituted Benzenes
8	3159.92 3049.30 1683.42 1501.12 1419.88 1473.71 1248.07	OH Stretching Ar. C – H Stretching C=0 Stretching C=CStretching(aromatics CH2-S- CH=N Stretching C-N Stretching
9	3411.44 3022.06 1685.31 1488.77 1264.79 743.58	N – H Stretching Ar. C – H Stretching C=0 Stretching CH2-S- C-N Stretching C-Cl
10	3421.79 3050.74 1683.36 1501.73 1474.20 1420.09 1248.48	N – H Stretching Ar. C – H Stretching C=0 Stretching C=CStretching(aromatics CH=N Stretching CH2-S- C-N Stretching

Compound 1



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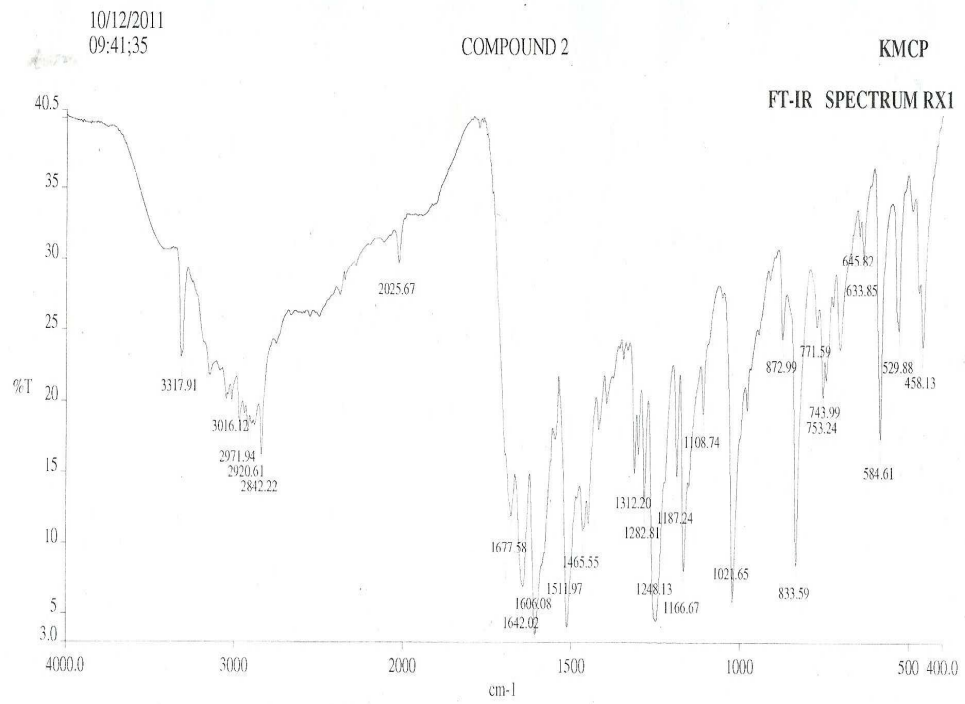

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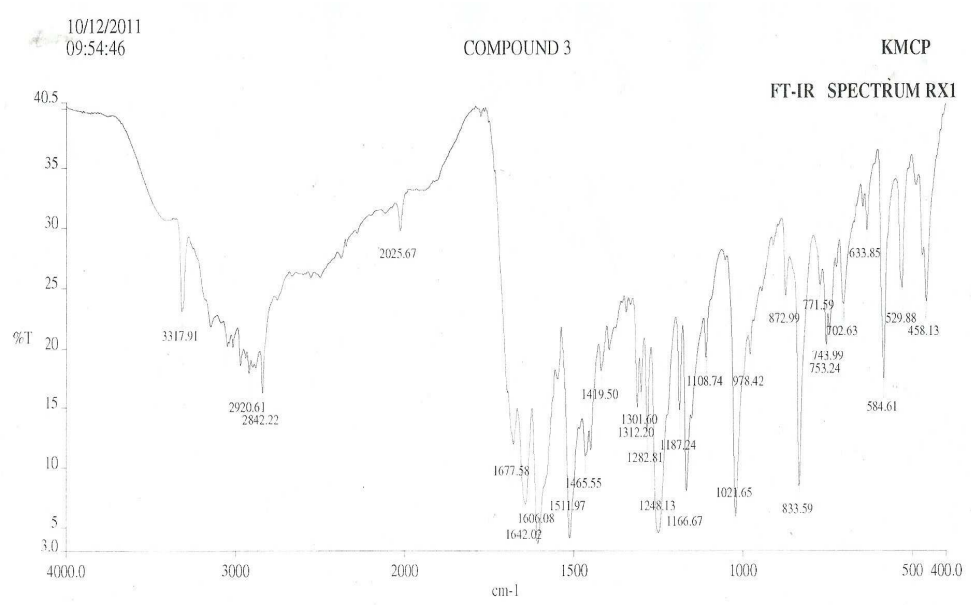

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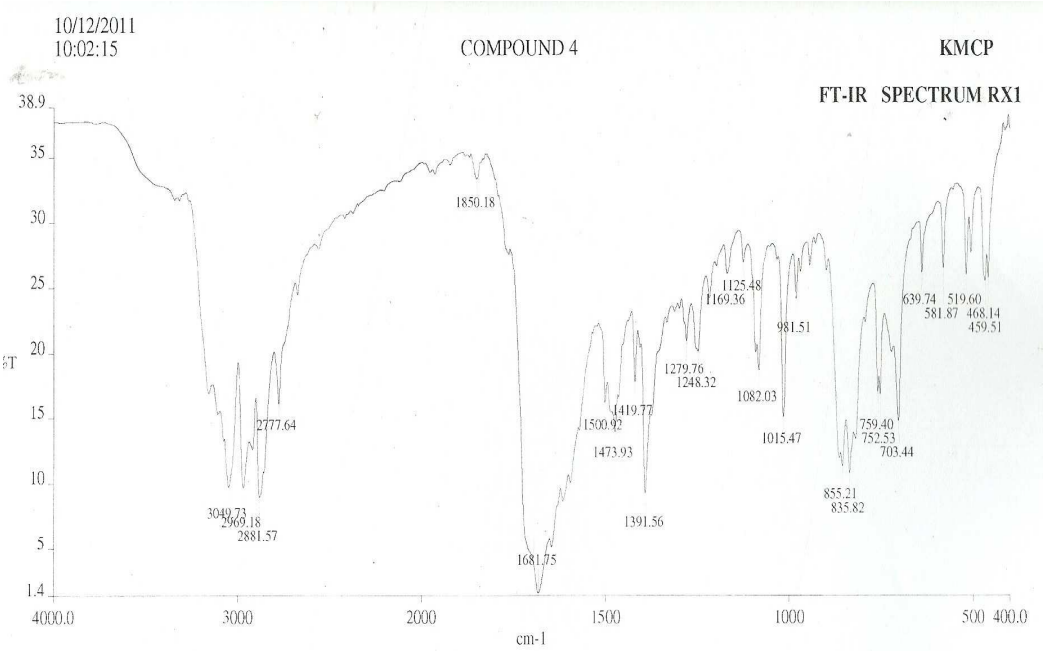
Compound4



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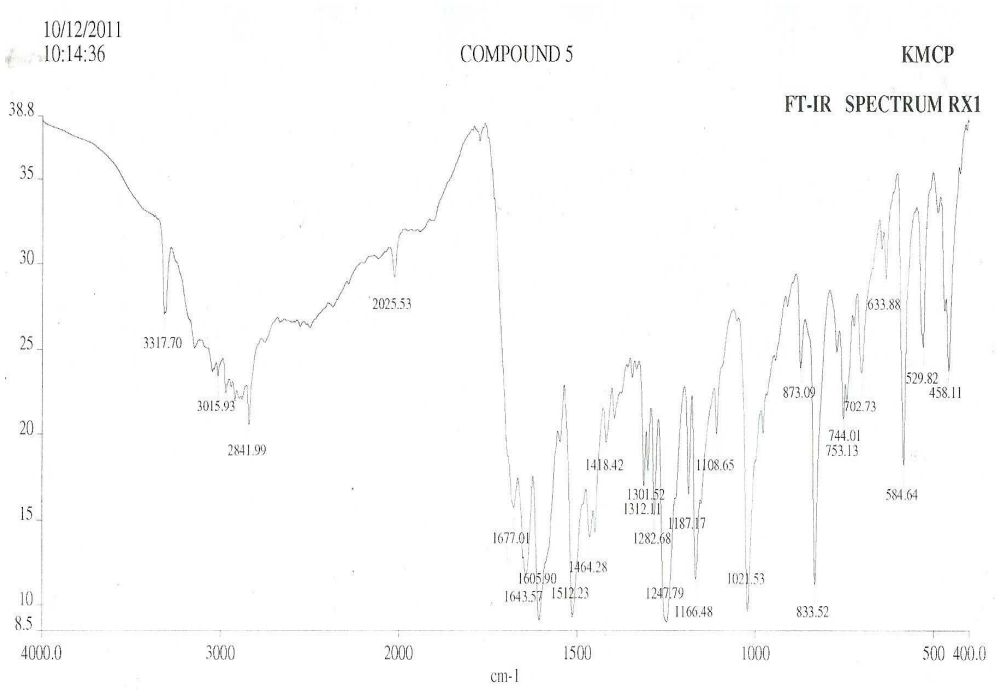

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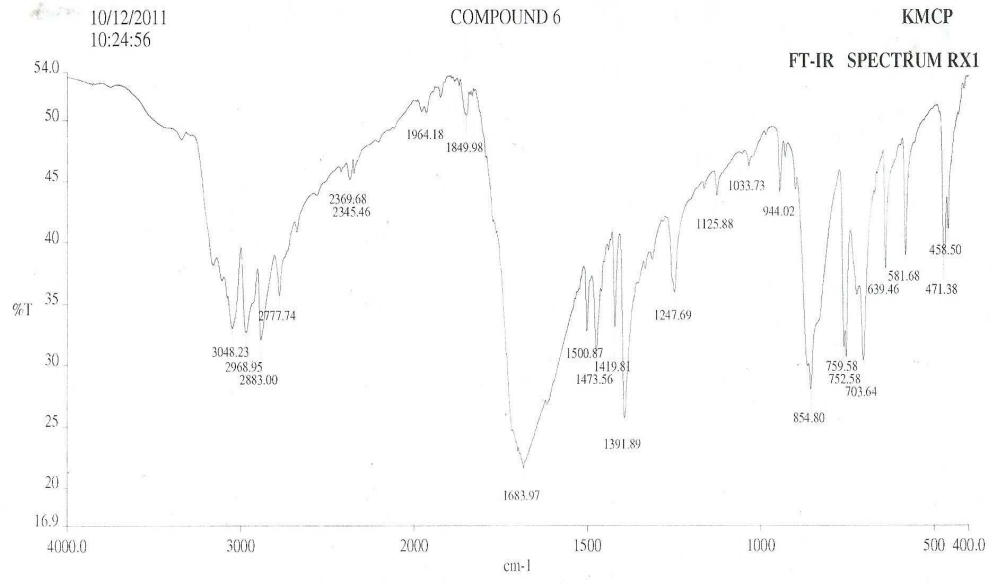

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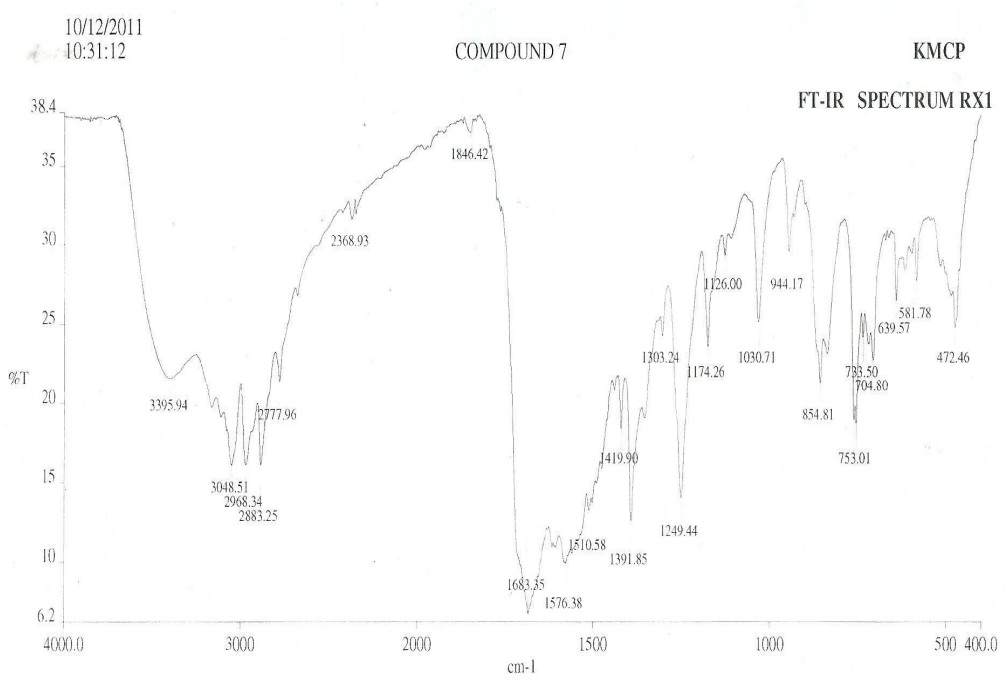

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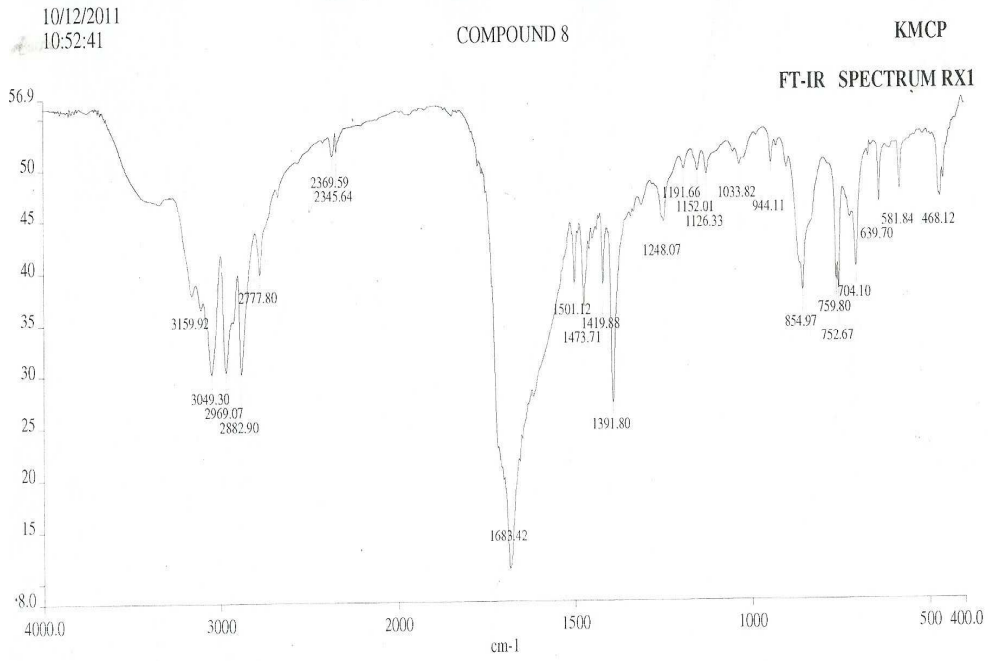
Compound 8



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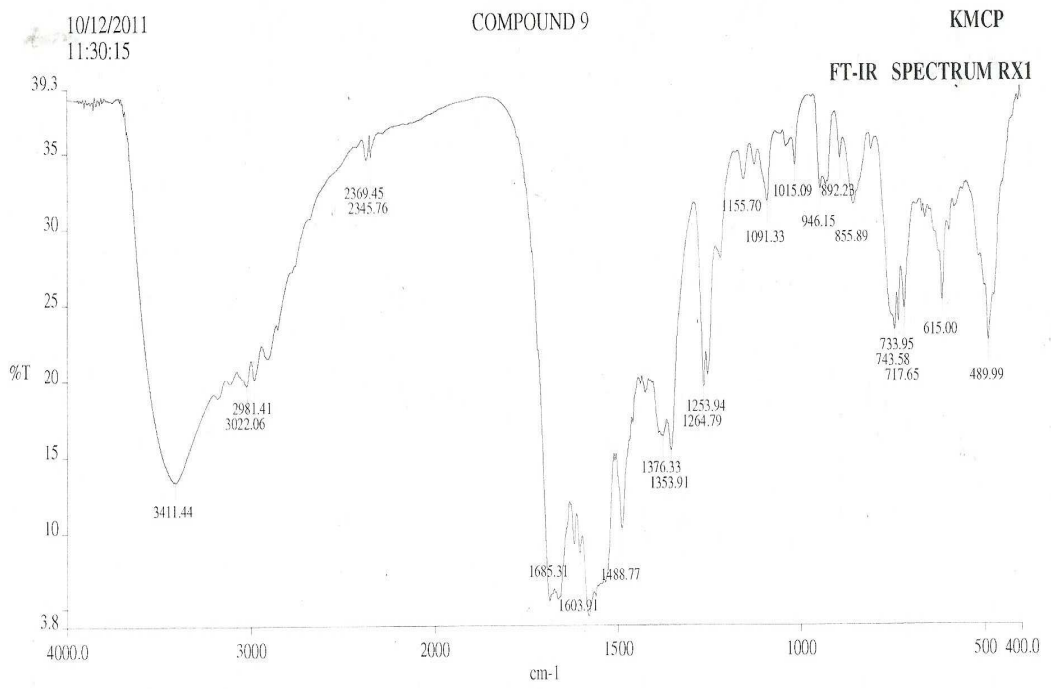

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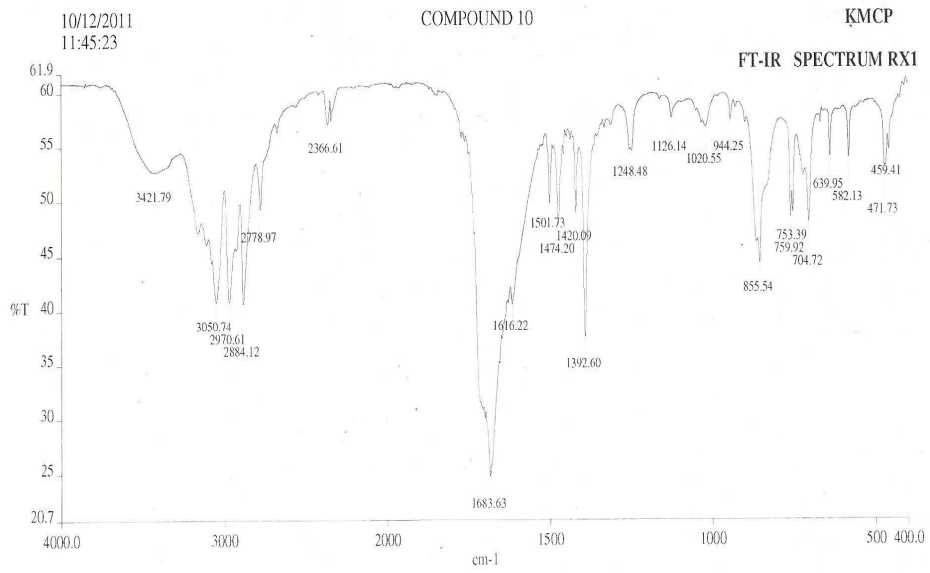
Compound 10



Spectrum Pathname: C:\PEL_DATA\SPECTRA\pdq10.001

Table8- NMR studies of synthesized compound

Compound code	Chemical shift	Proton nature
1	7.9678	t,2H,Ar-H
	7.2963	d,2H,Ar-H
	6.8103	d,5H,Ar-H
	9.9735	s,1H,CH=N
	3.7332	s,1H,NH
	8.5615	s,1H,NHCO
	2.6825	t,2H,CH_2
2	7.9225	t,2H,Ar-H
	7.2035	d,2H,Ar-H
	4.05097	s,1H,NH
	7.2891	s,1H,NHCO
	2.6276	t,2H,CH_2
	2.3235	s,3H,OCH_3
3	7.9427	t,2H,Ar-H
	7.2964	d,2H,Ar-H
	6.8693	d,5H,Ar-H
	3.7933	s,1H,NH
	9.0258	s,1H,CH=N
	8.1497	s,1H,NHCO
	2.5907	t,2H,CH_2
4	7.2474	d,2H,Ar-H
	6.9905	d,5H,Ar-H
	4.0812	s,1H,NH
	7.5861	s,1H,NHCO
	2.6754	t,2H,CH_2
5	7.2679	d,2H,Ar-H
	6.7634	d,5H,Ar-H
	4.1300	s,1H,NH
	7.1783	s,1H,NHCO
	3.8403	t,2H,CH_2

Compound code	Chemical shift	Proton nature
6	7.4731	t,2H,Ar-H
	7.2181	d,2H,Ar-H
	6.2307	d,5H,Ar-H
	9.0745	s,1H,CH=N
	3.5515	s,1H,NH
	8.0772	s,1H,NHCO
	2.6012	t,2H,CH_2
7	7.5473	t,2H,Ar-H
	7.2132	d,2H,Ar-H
	3.9650	s,1H,NH
	2.5103	t,2H,CH_2
	2.3652	s,3H,OCH_3
8	7.5473	t,2H,Ar-H
	7.2676	d,2H,Ar-H
	6.7663	d,5H,Ar-H
	9.1853	s,1H,CH=N
	3.9803	s,1H,NH
	8.0099	s,1H,NHCO
	2.5959	t,2H,CH_2
9	7.2656	d,2H,Ar-H
	6.7543	d,5H,Ar-H
	3.9324	s,1H,NH
	8.4251	s,1H,NHCO
	2.5995	t,2H,CH_2
10	7.5363	t,2H,Ar-H
	7.2723	d,2H,Ar-H
	6.8350	d,5H,Ar-H
	3.9353	s,1H,NH
	8.6903	s,1H,NHCO
	2.5984	t,2H,CH_2

Compound1

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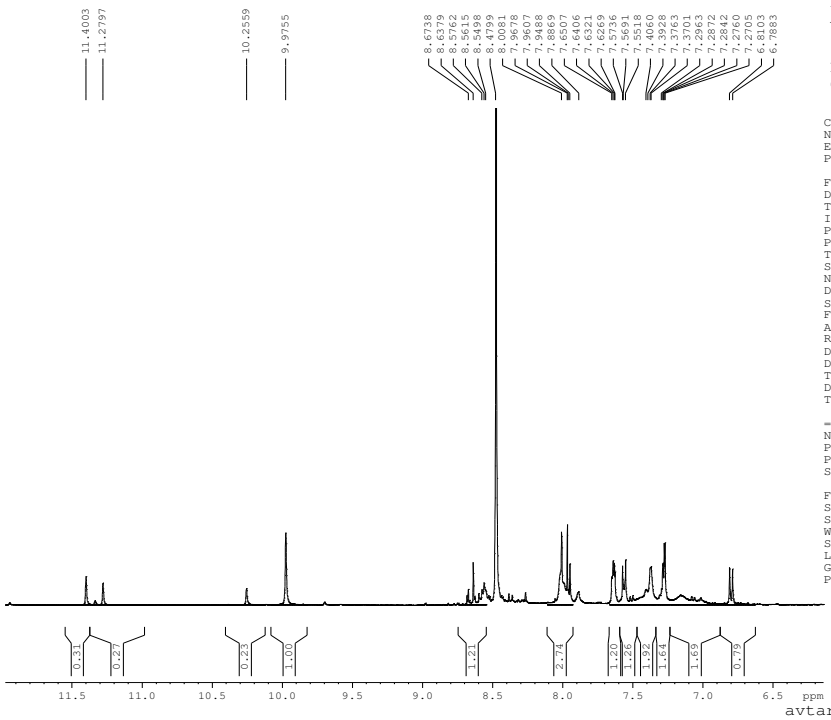

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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PROCNO                 1

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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                    36
DW               41.600 usec
DE                6.00 usec
TE               292.6 K
D1           1.00000000 sec
TD0                    1

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P1                10.90 usec
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
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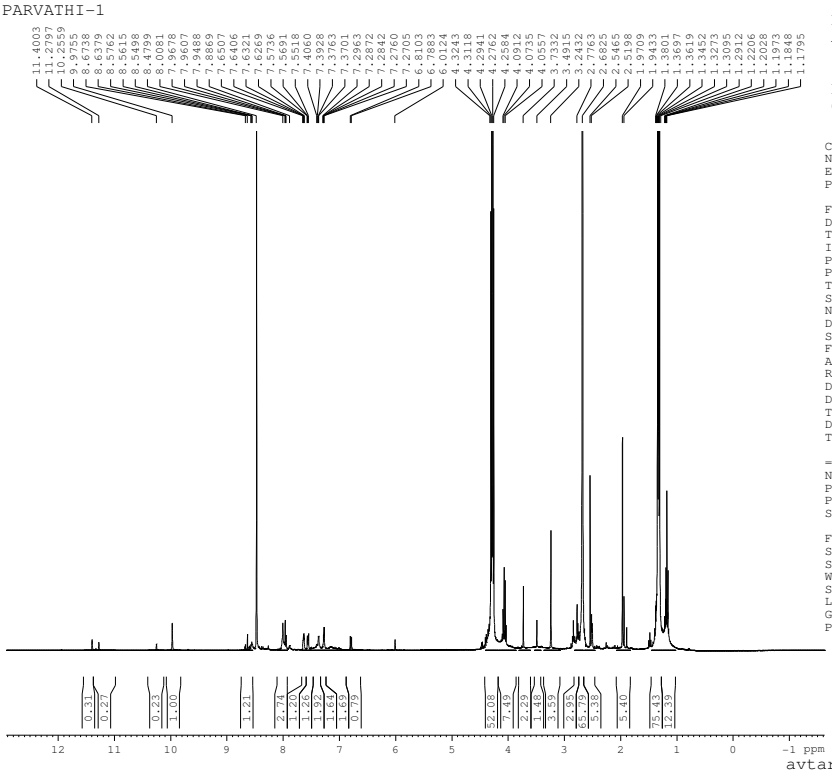
avtar_saifpu@yahoo.co.in

PARVATHI-1



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
Current Data Parameters
NAME          Jan13-2012
EXPNO                110
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               14.07
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                    36
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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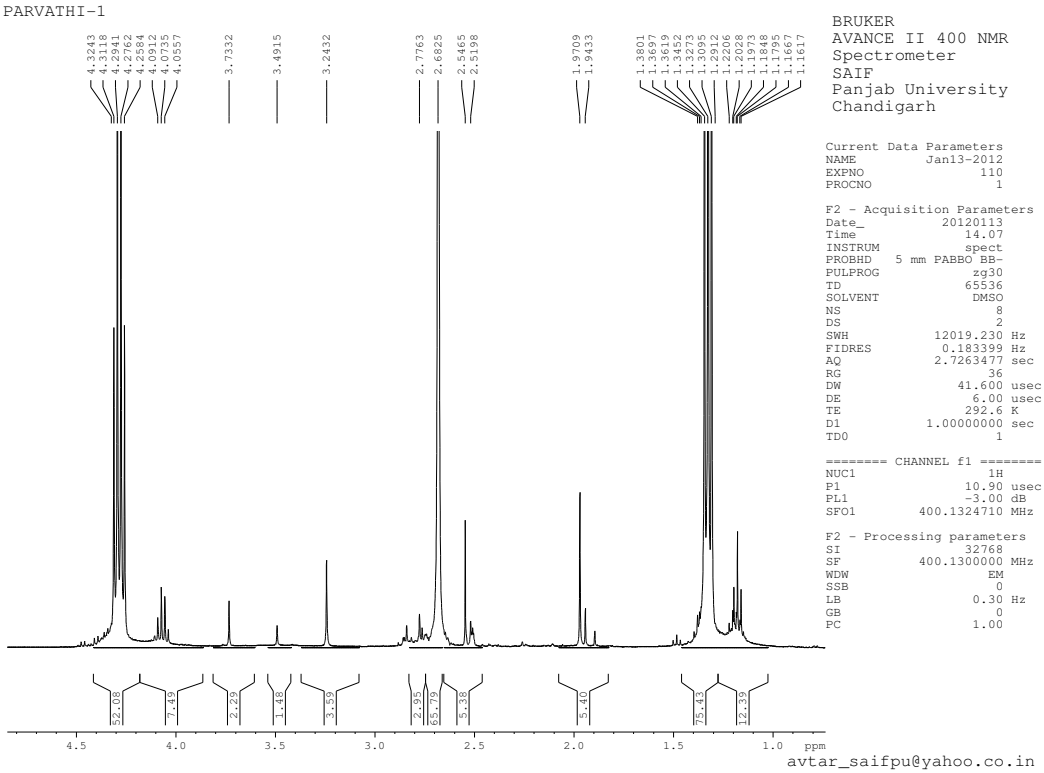

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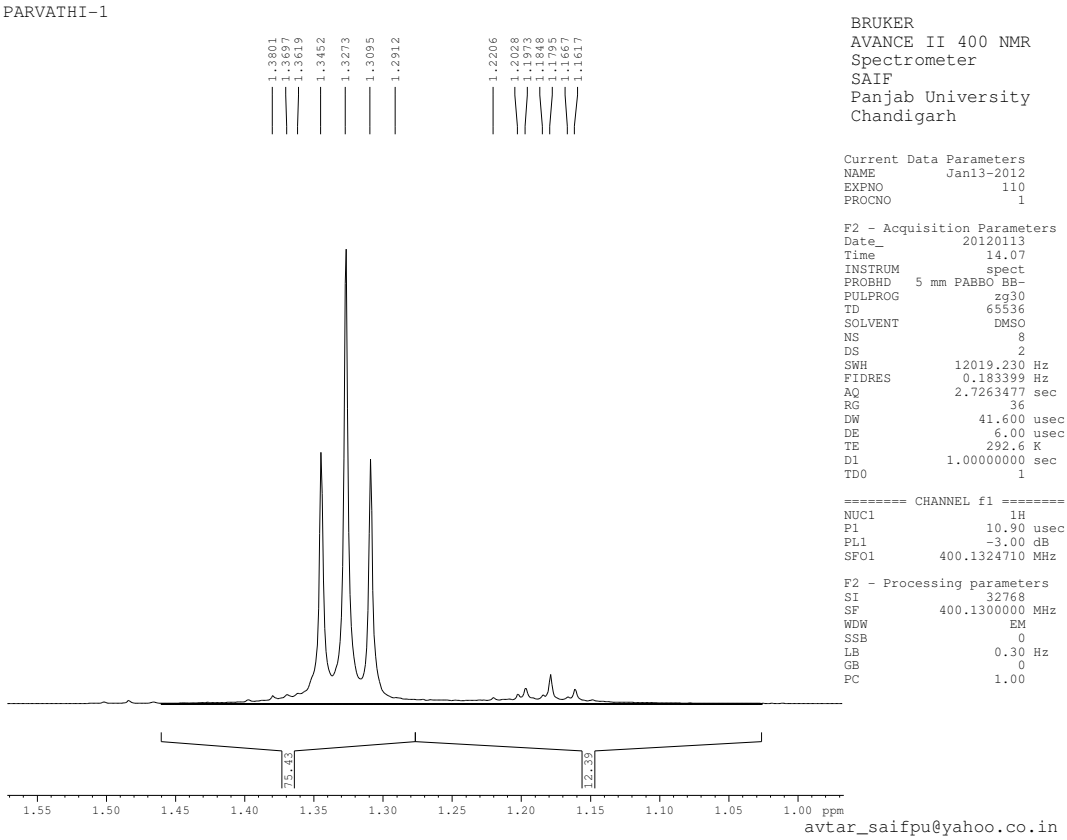

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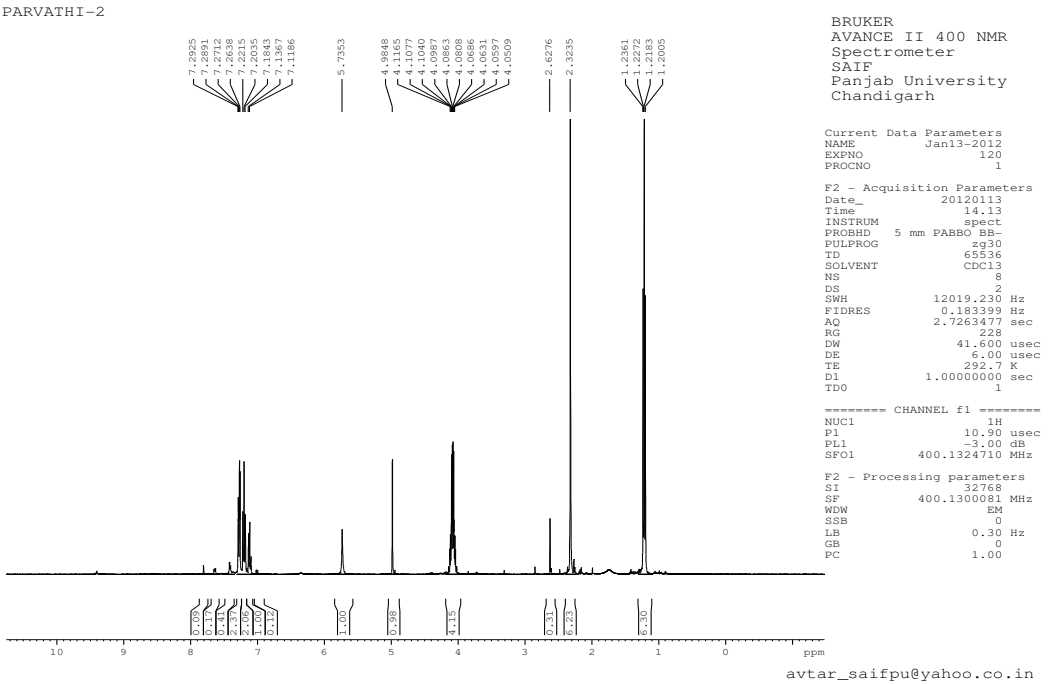
Compound 2



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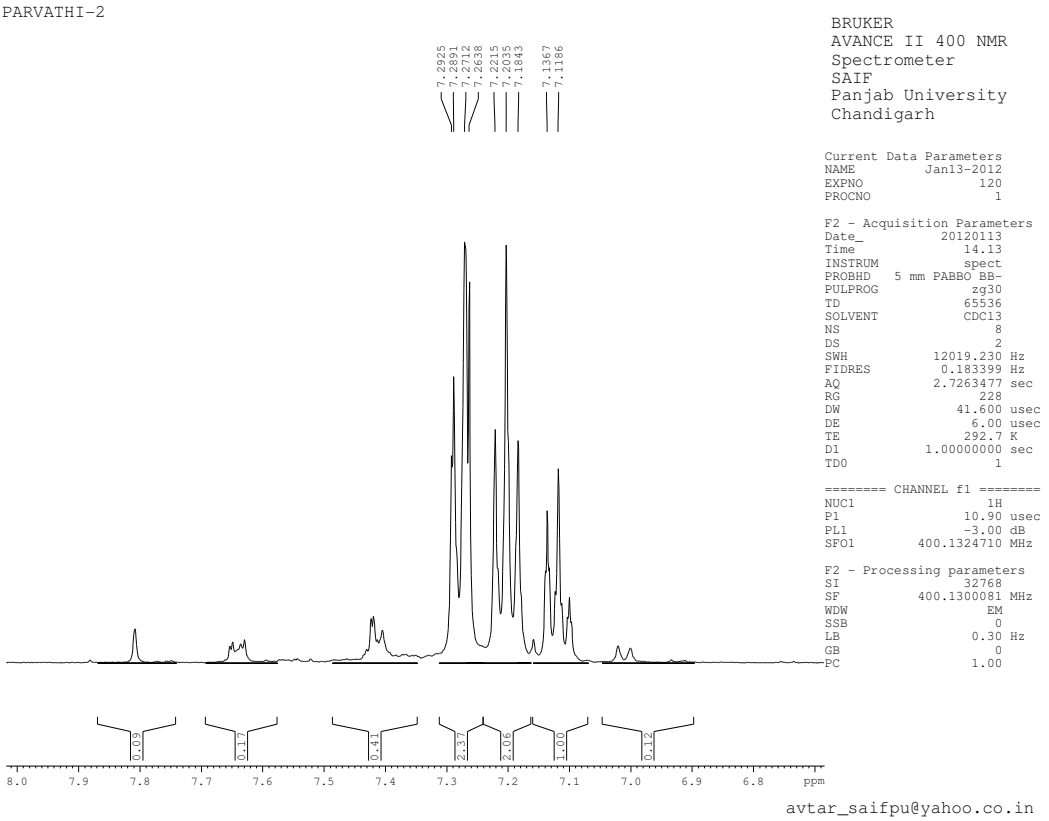

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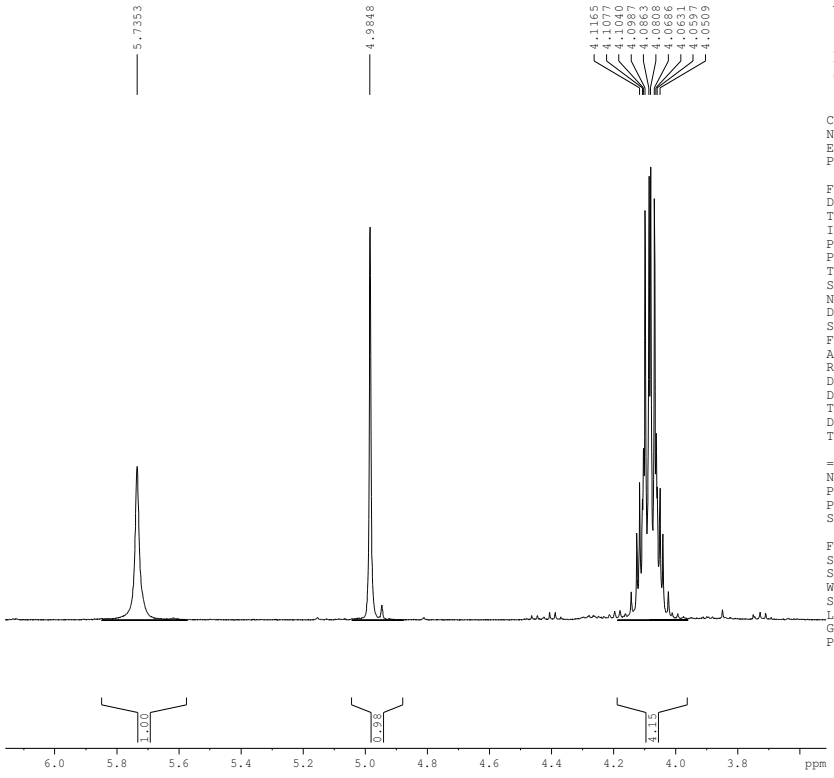

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 228
DW 41.600 usec
DE 6.00 usec
TE 292.7 K
D1 1.00000000 sec
TD0 1

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P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

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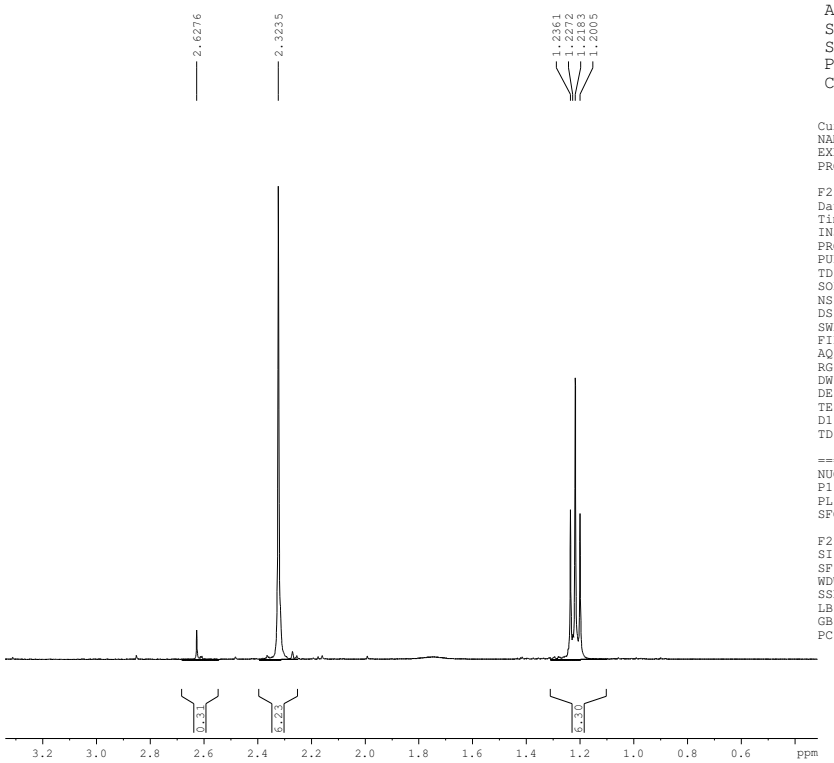
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

PARVATHI-2



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EXPNO 120
PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDC13
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 228
DW 41.600 usec
DE 6.00 usec
TE 292.7 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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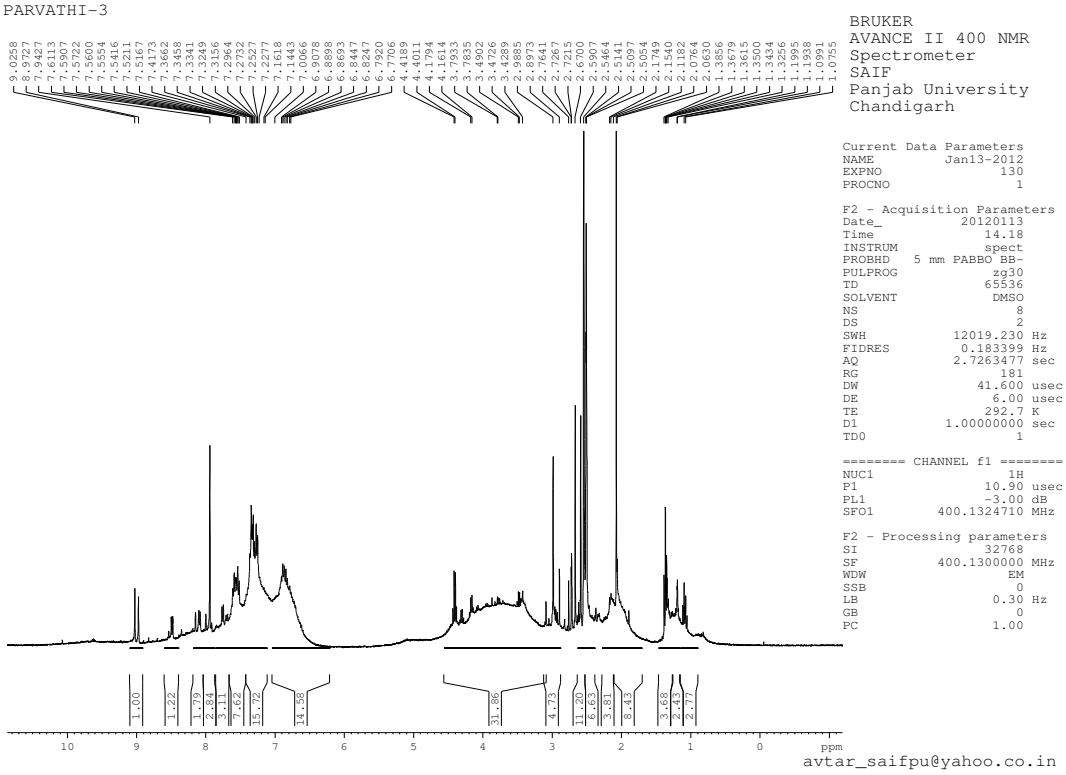
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

Compound 3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BRUKER
AVANCE II 400 NMR
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
NS 8
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SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 181
DW 41.600 usec
DE 6.00 usec
TE 292.7 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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WDW EM
SSB 0
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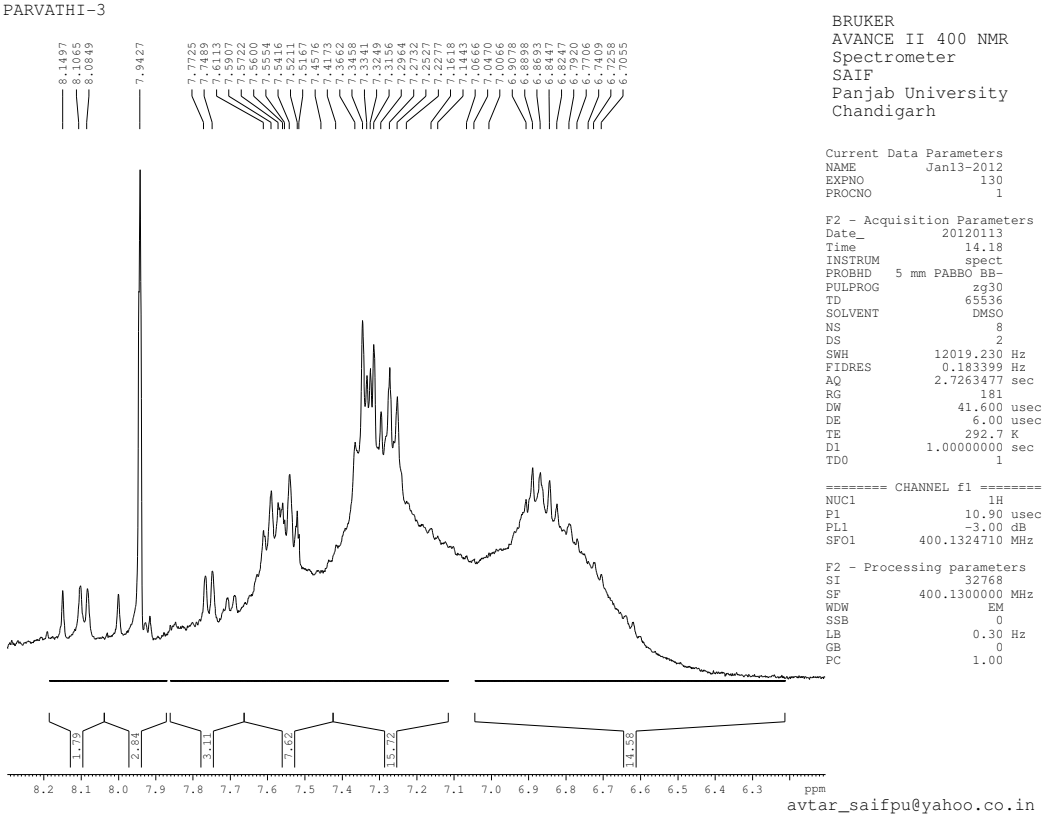
PC 1.00
avtar_saifpu@yahoo.co.in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BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh
Current Data Parameters
NAME Jan13-2012
EXPNO 130
PROCNO 1
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Time 14.18
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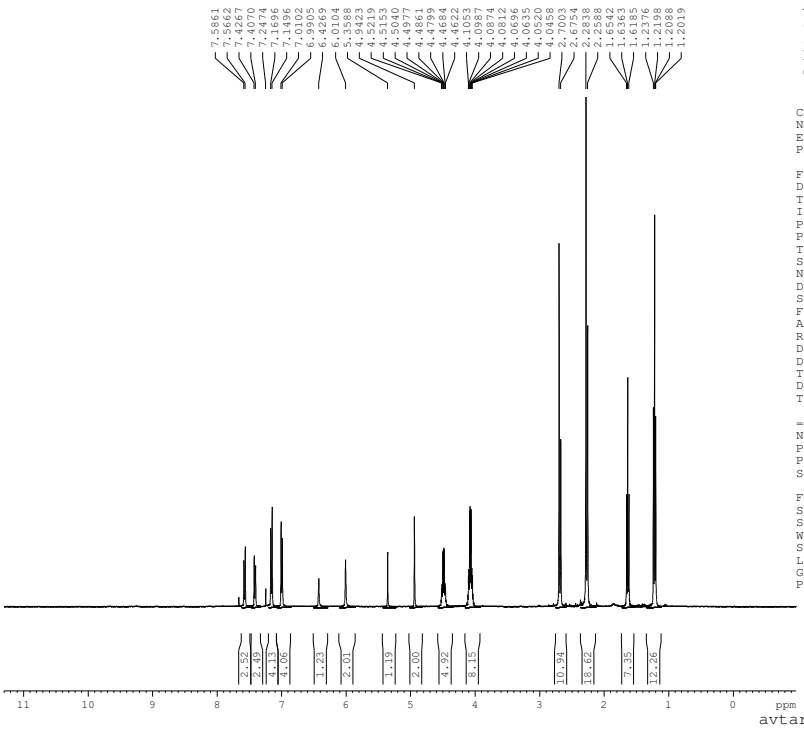
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 181
DW 41.600 usec
DE 6.00 usec
TE 292.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
avtar_saifpu@yahoo.co.in

Compound 4

PARVATHI-4



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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Current Data Parameters
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PROCNO                 1

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Time               14.23
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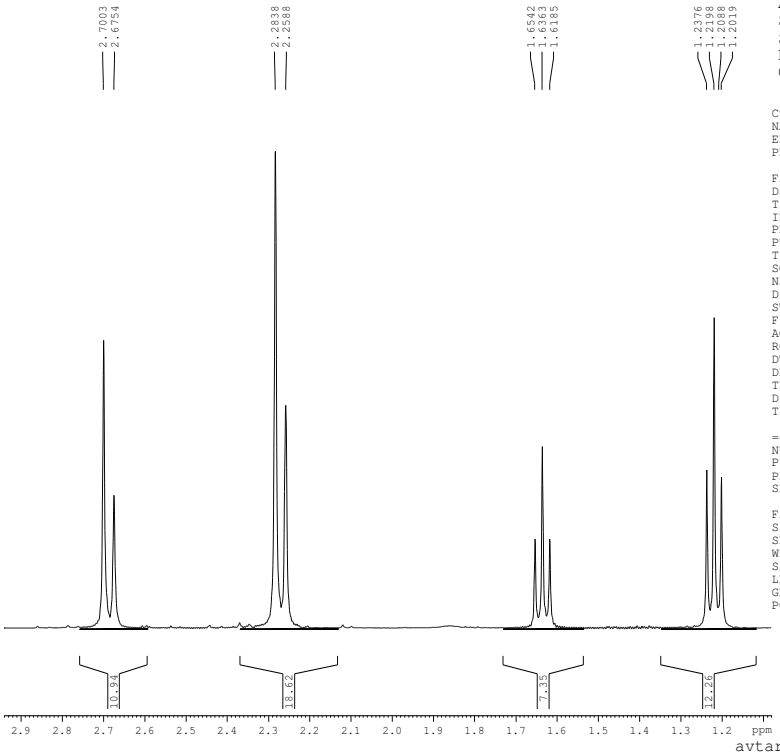
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     2
SWH           12019.230 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 sec
RG                    57
DW               41.600 usec
DE                6.00 usec
TE               292.8 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          400.1281138 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

avtar_saifpu@yahoo.co.in

PARVATHI-4



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
Current Data Parameters
NAME          Jan13-2012
EXPNO                140
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               14.23
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                    57
DW               41.600 usec
DE                6.00 usec
TE               292.8 K
D1           1.00000000 sec
TD0                    1

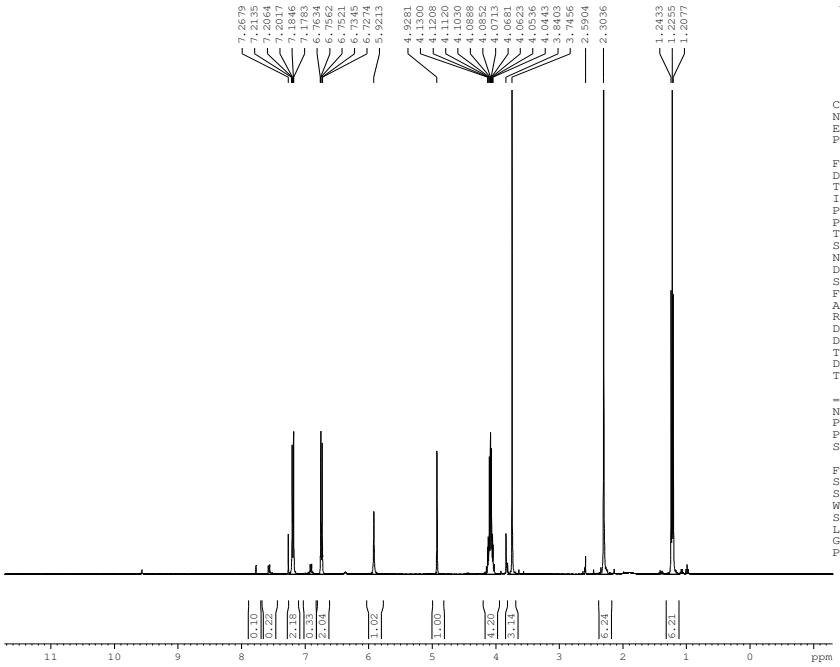
======== CHANNEL f1 ========
NUC1                  1H
P1                10.90 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1281138 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

avtar_saifpu@yahoo.co.in

Compound 5

PARVATHI-5

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BRUKER
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Current Data Parameters
NAME          Jan13-2012
EXPNO                150
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               14.29
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
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                292.8 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          400.1300063 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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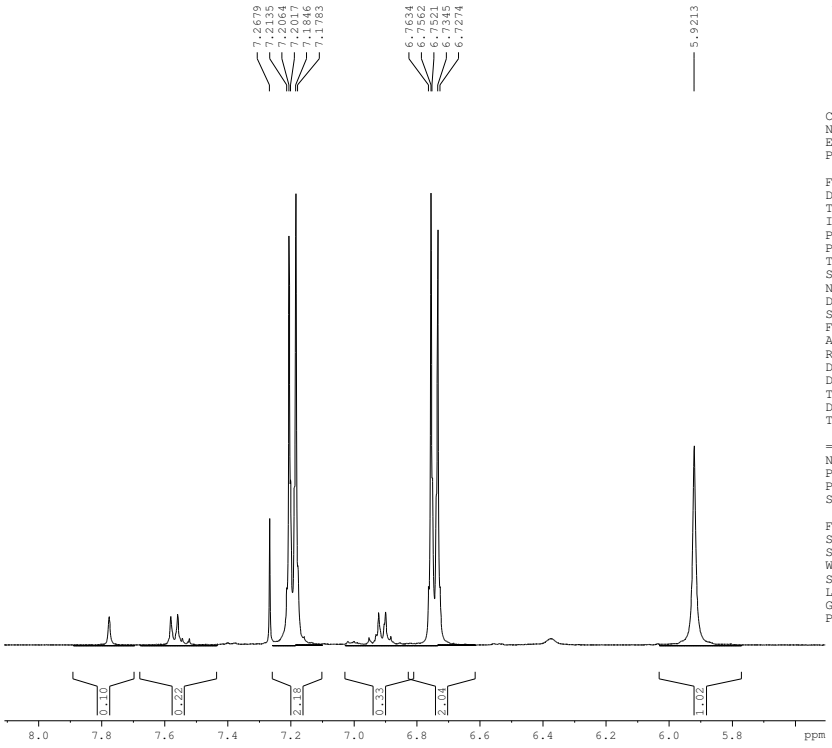
avtar_saifpu@yahoo.co.in

PARVATHI-5

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BRUKER
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Current Data Parameters
NAME          Jan13-2012
EXPNO                150
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               14.29
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
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                292.8 K
D1            1.00000000 sec
TD0                    1

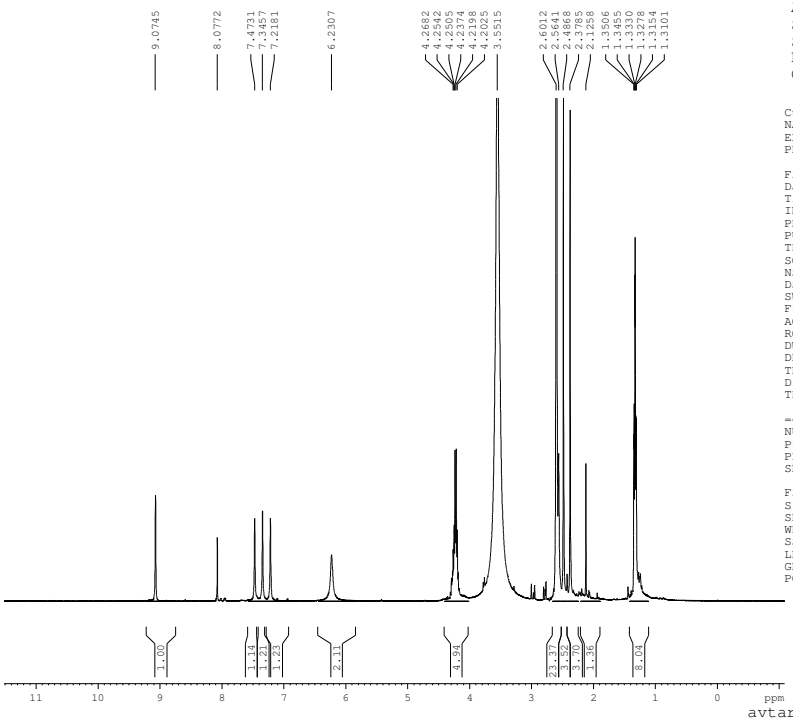
======== CHANNEL f1 ========
NUC1                  1H
P1                 10.90 usec
PL1                -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300063 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

avtar_saifpu@yahoo.co.in

Compound 6

PARVATHI-6



BRUKER
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Current Data Parameters
NAME Jan13-2012
EXPNO 160
PROCNO 1

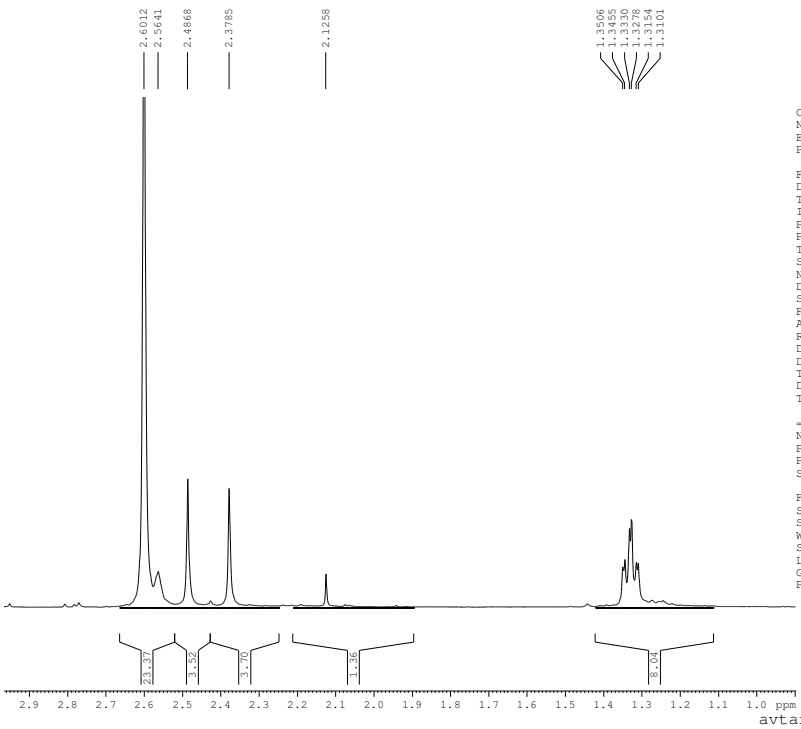
F2 - Acquisition Parameters
Date_ 20120113
Time 14.35
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 114
DW 41.600 usec
DE 6.00 usec
TE 292.8 K
D1 1.00000000 sec
TD0 1

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

F2 - Processing parameters
SI 32768
SF 400.1299779 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

PARVATHI-6



BRUKER
AVANCE II 400 NMR
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Current Data Parameters
NAME Jan13-2012
EXPNO 160
PROCNO 1

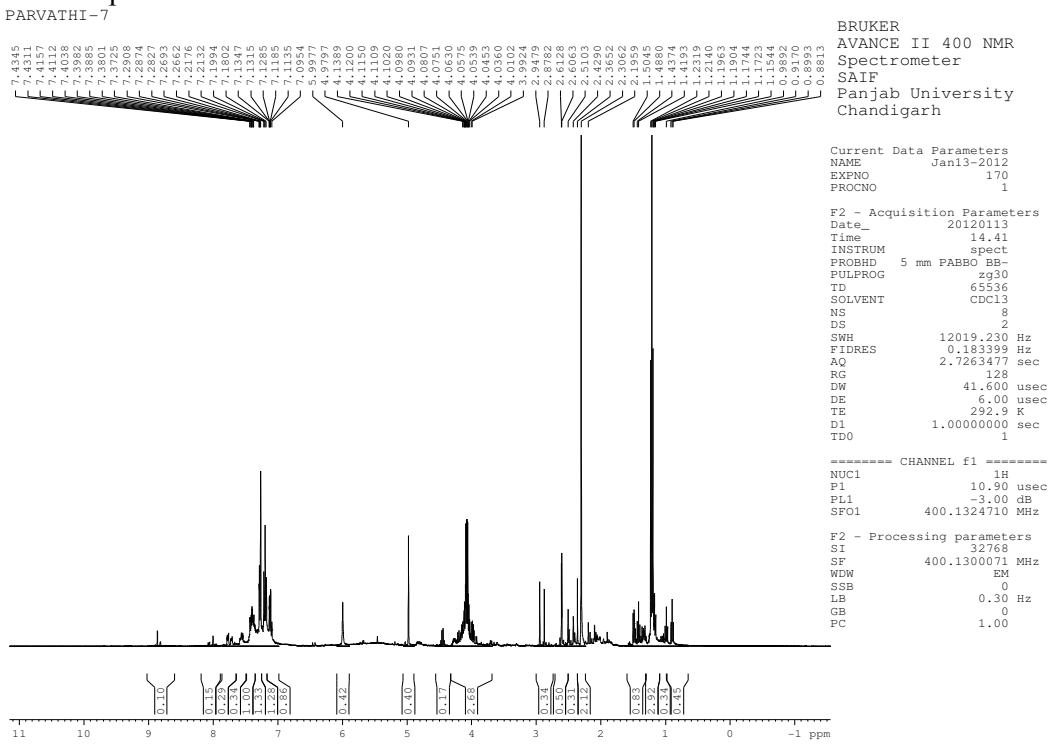
F2 - Acquisition Parameters
Date_ 20120113
Time 14.35
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 114
DW 41.600 usec
DE 6.00 usec
TE 292.8 K
D1 1.00000000 sec
TD0 1

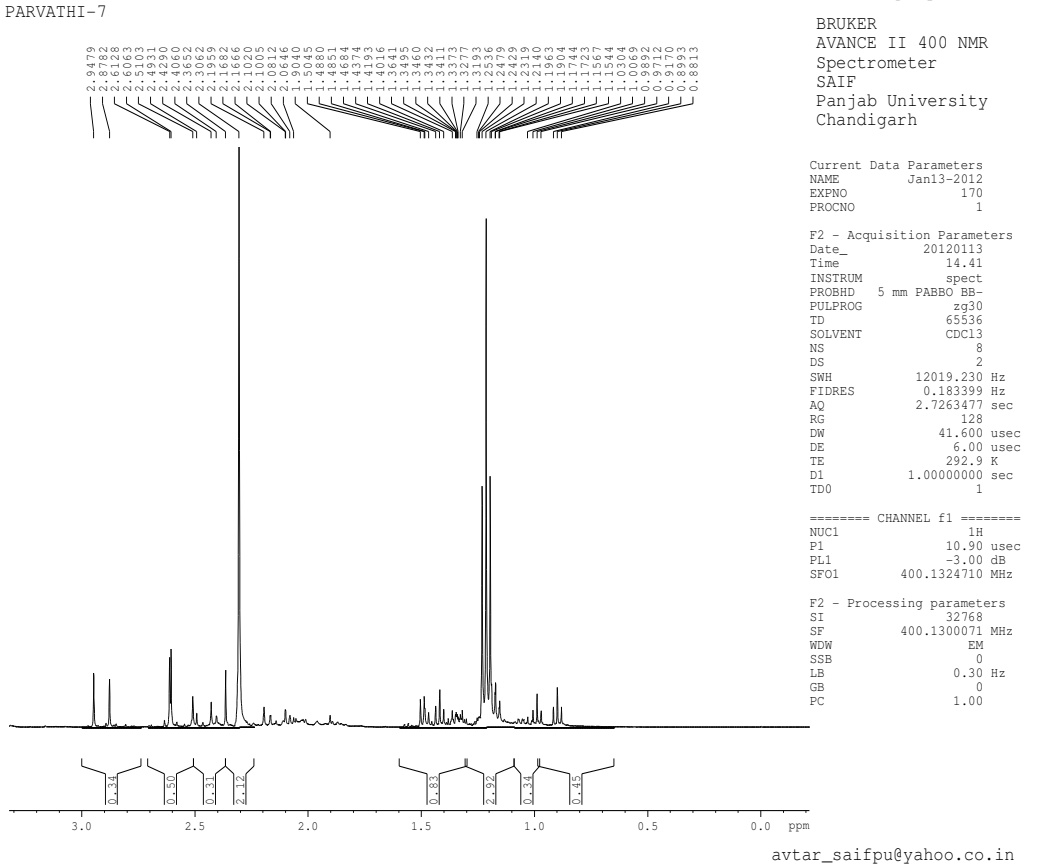
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1299779 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

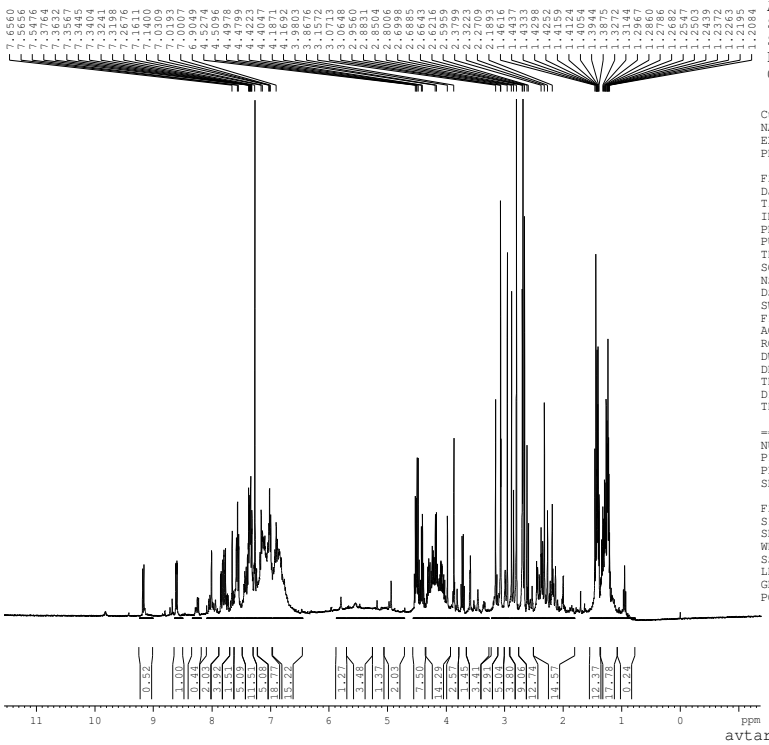
Compound 7


PARVATHI-7
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh
Current Data Parameters
NAME Jan13-2012
EXPNO 170
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120113
Time 14.41
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 128
DW 41.600 usec
DE 6.00 usec
TE 292.9 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 400.1300071 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
avtar_saifpu@yahoo.co.in


PARVATHI-7
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh
Current Data Parameters
NAME Jan13-2012
EXPNO 170
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120113
Time 14.41
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 128
DW 41.600 usec
DE 6.00 usec
TE 292.9 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 400.1300071 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
avtar_saifpu@yahoo.co.in

Compound 8

PARVATHI-8



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Current Data Parameters	
NAME	Jan13-2012
EXPNO	180
PROCNO	1
F2 - Acquisition Parameters	
Date_	20120113
Time	14.46
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	203
DW	41.600 usec
DE	6.00 usec
TE	292.9 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	400.1300065 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

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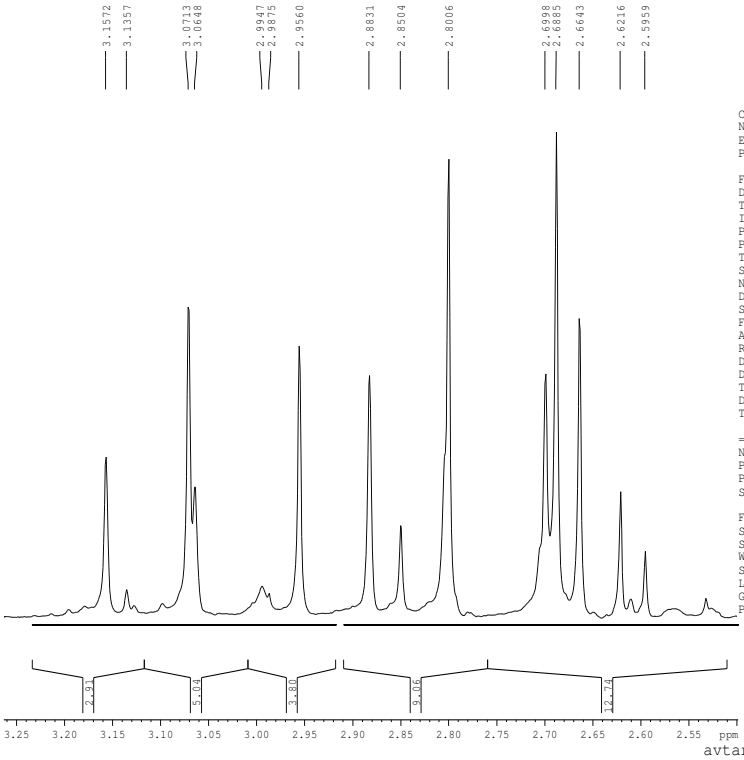
PARVATHI-8



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Current Data Parameters	
NAME	Jan13-2012
EXPNO	180
PROCNO	1
F2 - Acquisition Parameters	
Date_	20120113
Time	14.46
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	203
DW	41.600 usec
DE	6.00 usec
TE	292.9 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	400.1300065 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

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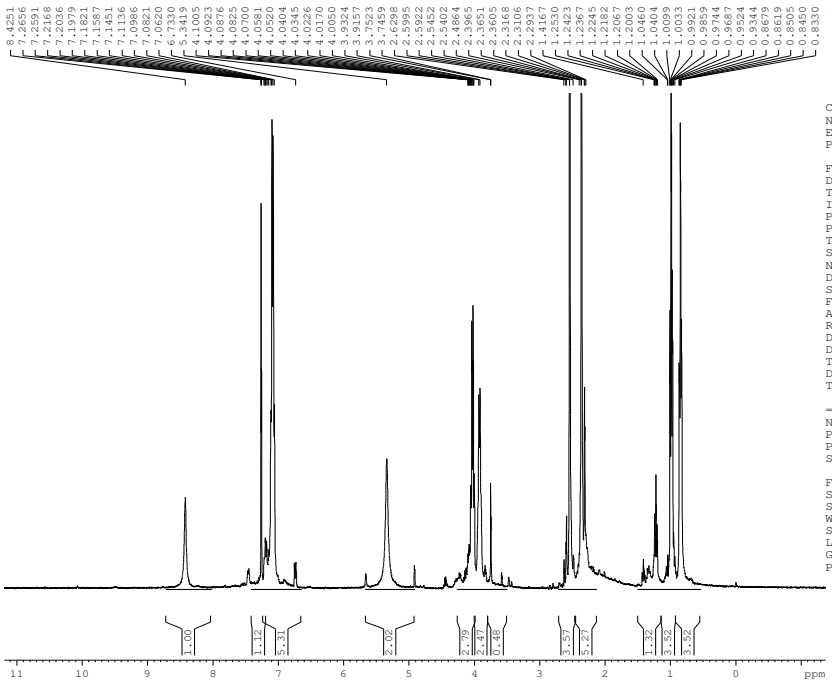
Compound 9

PARVATHI-9



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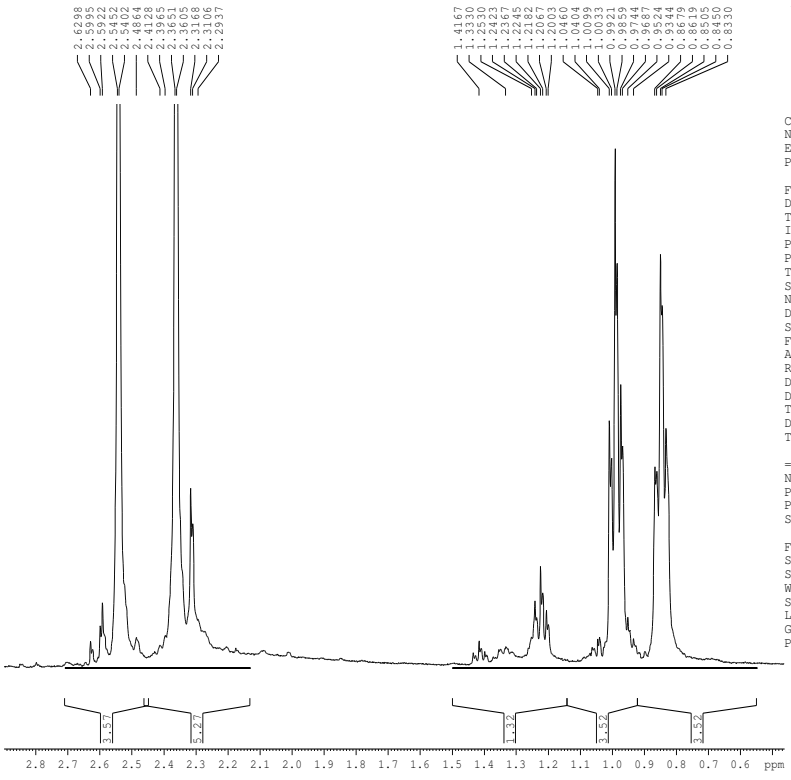
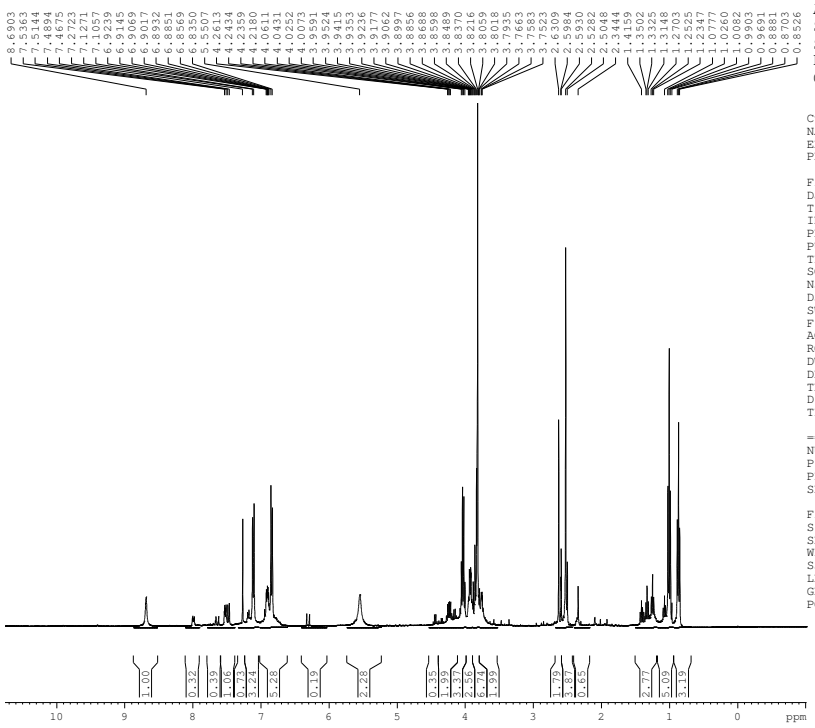
PARVATHI-9



avtar_saifpu@yahoo.co.in

Compound 10

PARVATHI-10



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```
Current Data Parameters
NAME          Jan13-2012
EXPNO                200
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               14.57
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           12019.230 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 sec
RG                  161
DW               41.600 usec
DE                6.00 usec
TE               292.9 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          400.1300046 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                 1.00
```

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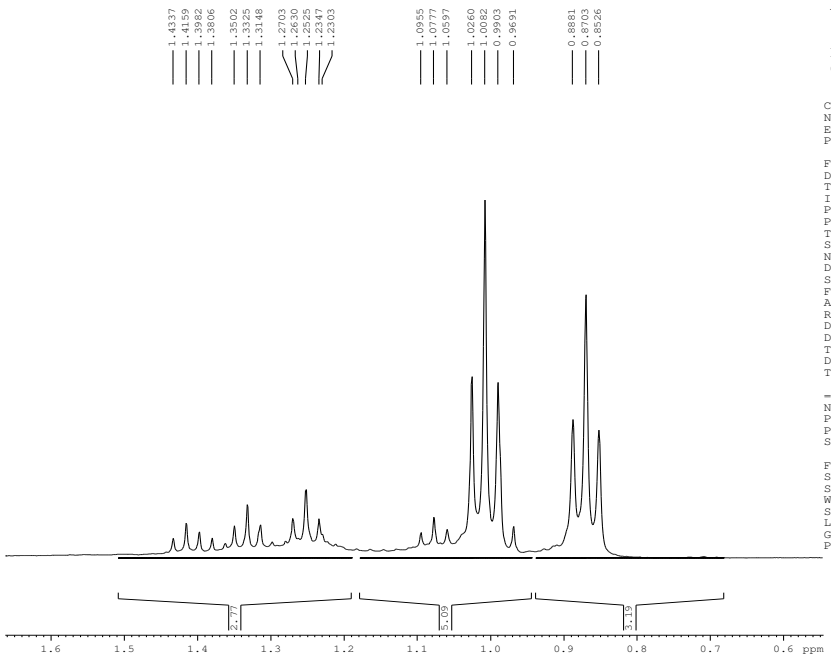
PARVATHI-10



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```
Current Data Parameters
NAME          Jan13-2012
EXPNO                200
PROCNO                 1

F2 - Acquisition Parameters
Date_           20120113
Time               14.57
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           12019.230 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 sec
RG                  161
DW               41.600 usec
DE                6.00 usec
TE               292.9 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          400.1300046 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                 1.00
```

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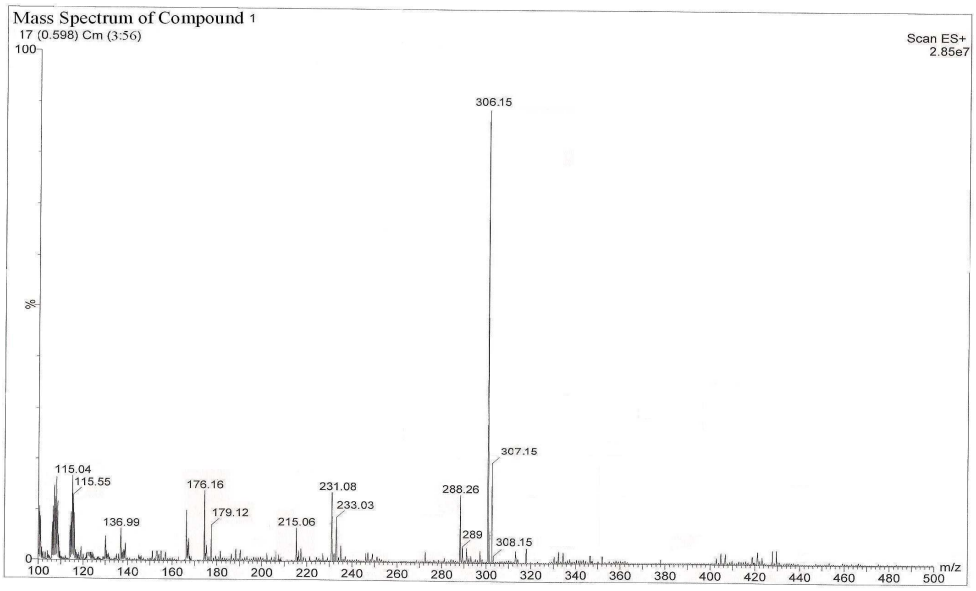
Table: 9

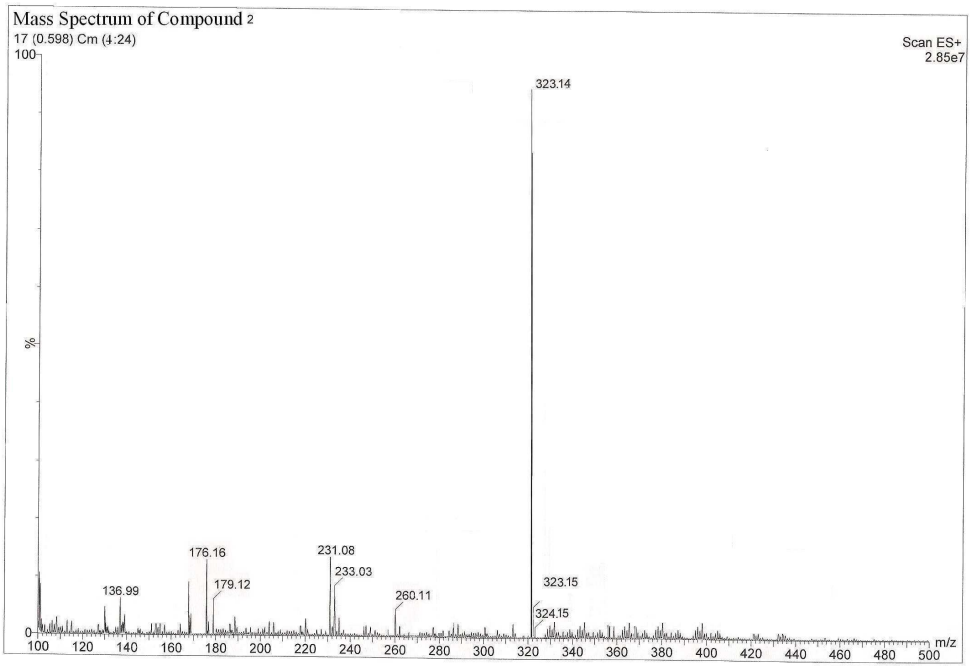
MASS spectral study of the compounds synthesized

Compound Code	Molecular ions
1	306.15(306)
2	323.14(322)
3	308.13(308)
4	326.09(326.5)
5	292.13(292)
6	380.13(380.1)
7	396.13(396.1)
8	382.11(382.4)
9	400.08(400.6)
10	366.08(366.4)

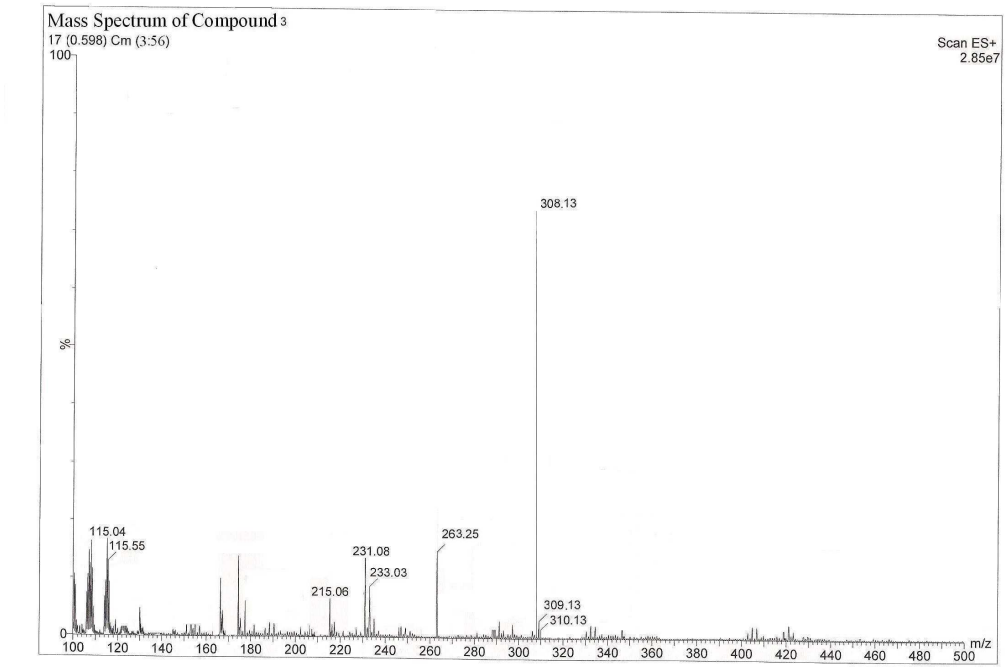
Compound- 1



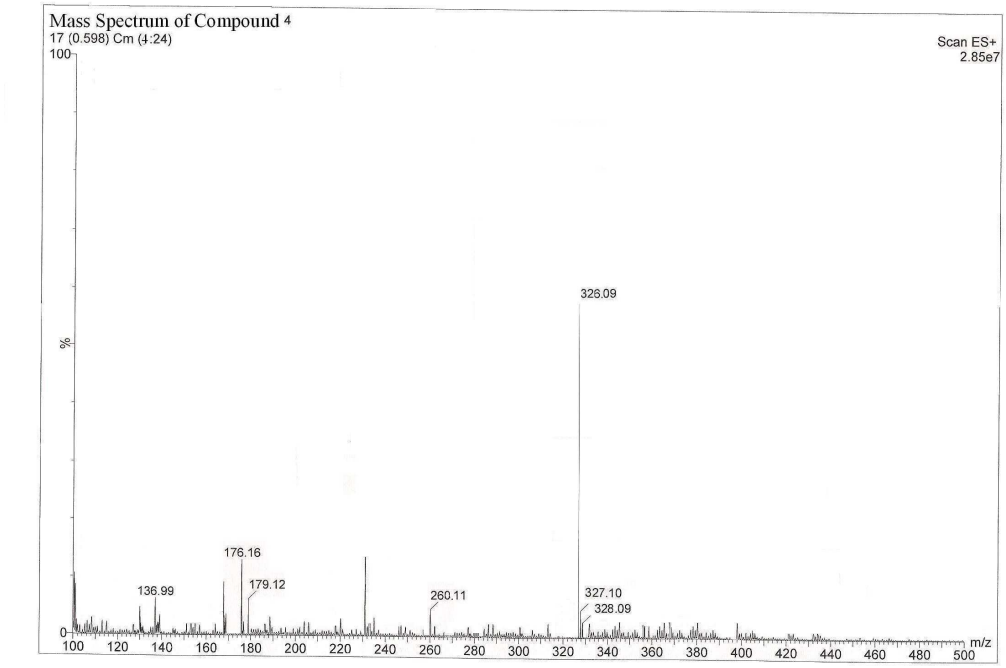
Compound-2



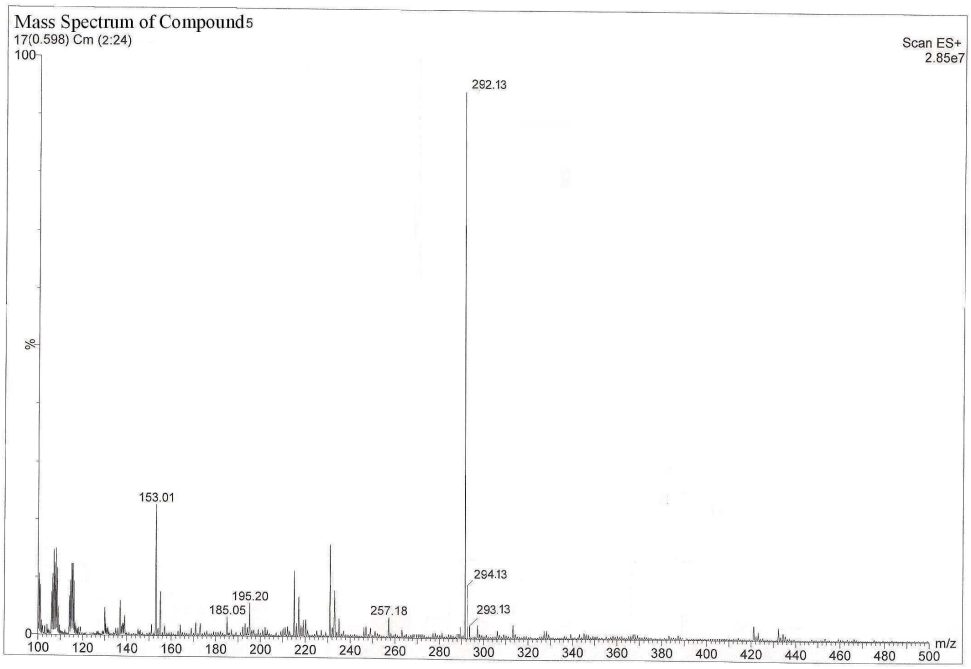
Compound-3



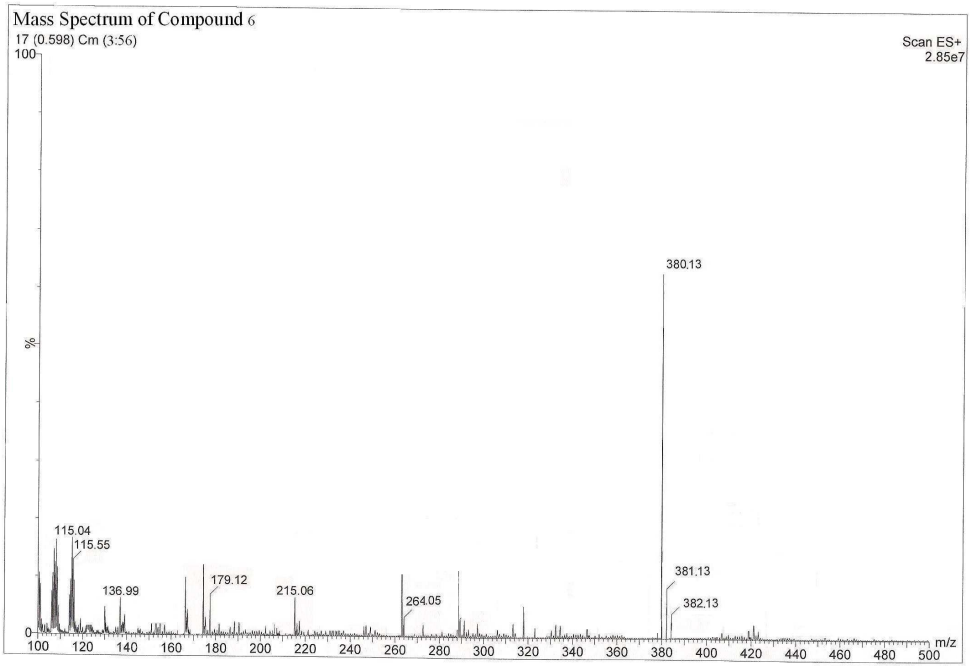
Compound -4



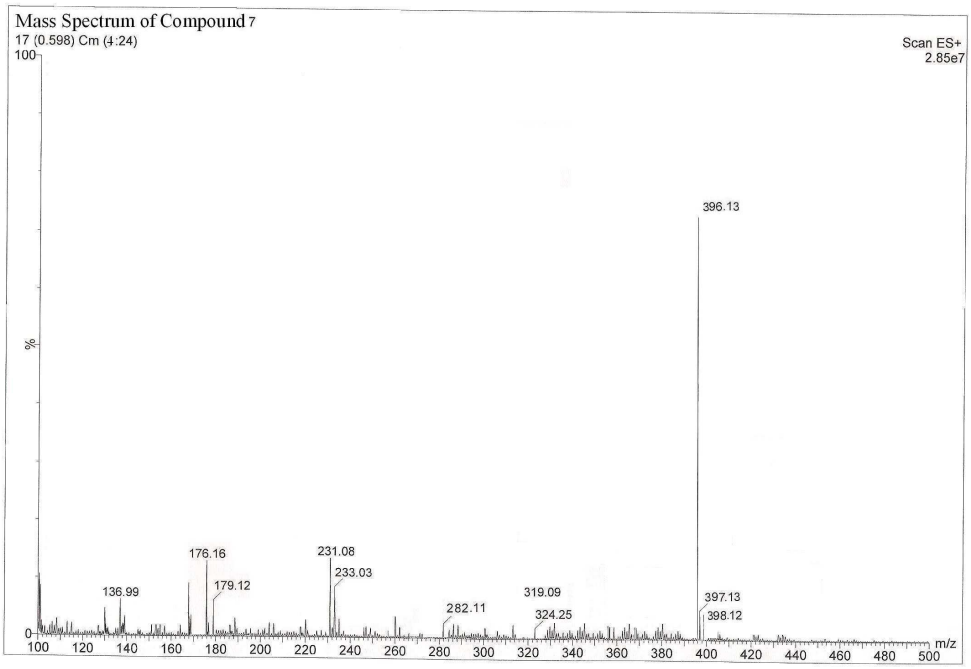
Compound-5



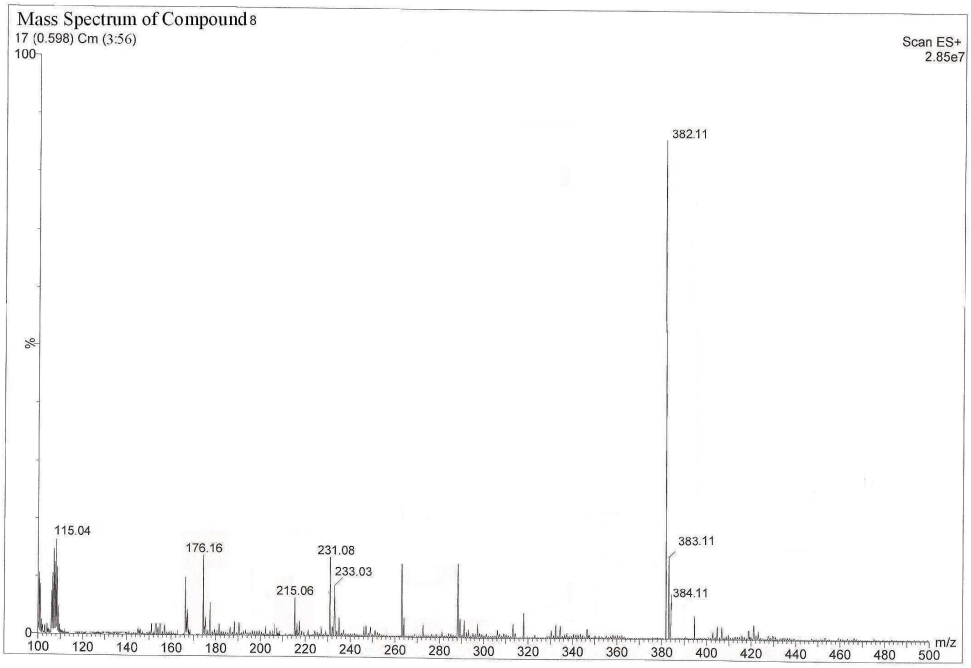
Compound-6



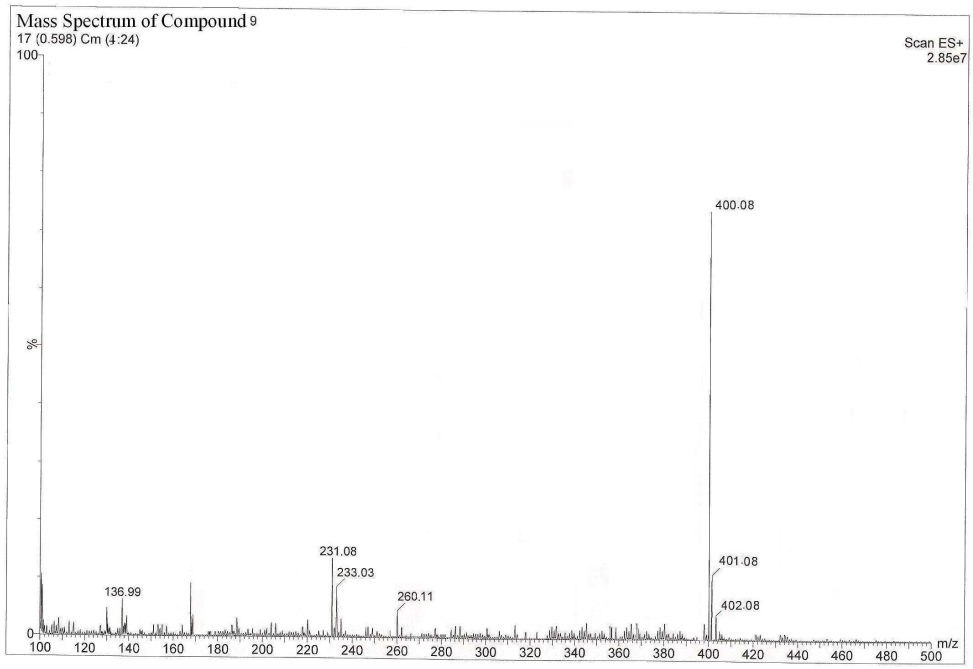
Compound-7



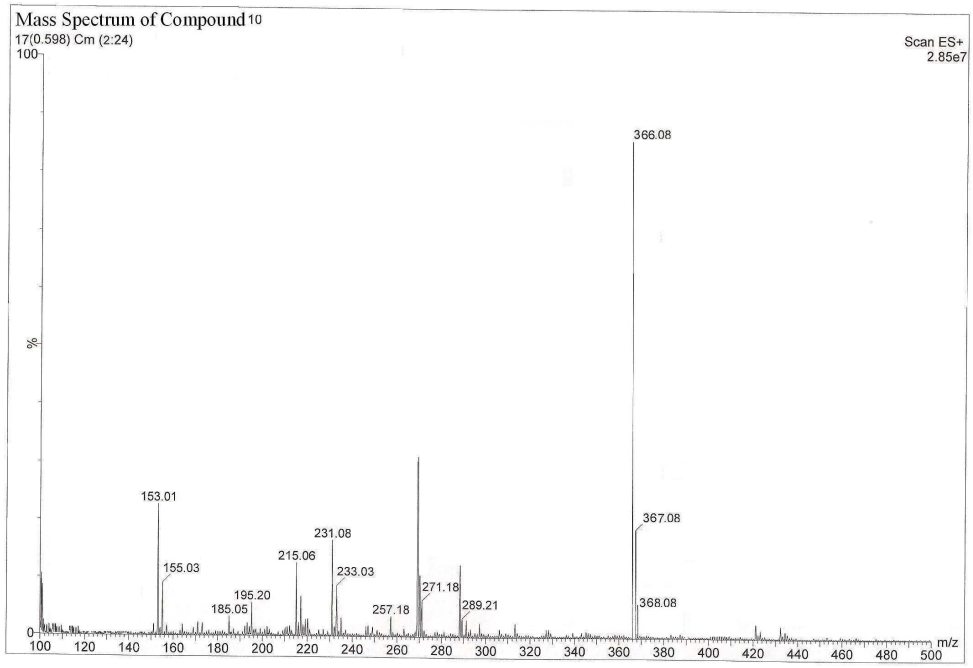
Compound-8



Compound-9



Compound-10



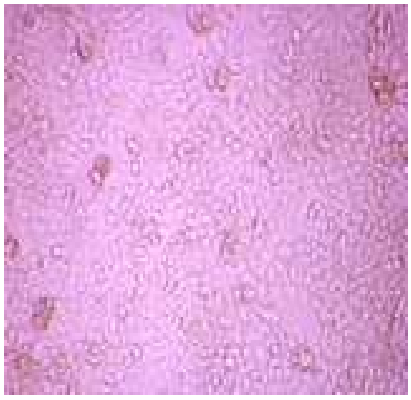
5.4 Results of *In-vitro* biological activity

A) *In-vitro* cytotoxicity by MTT assay

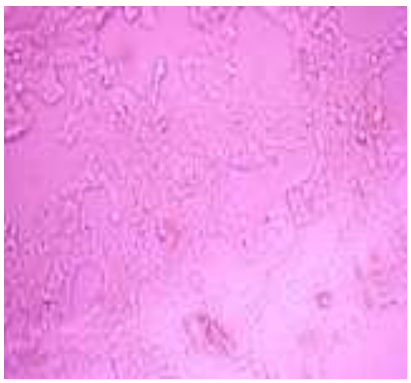
Figure:1

In-vitro Cytotoxicity of compounds 7

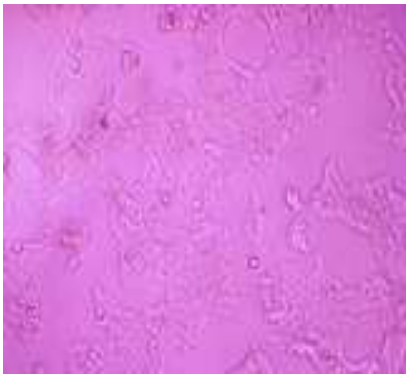
Control



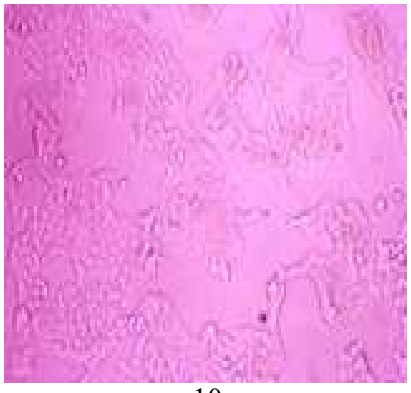
Compound-7



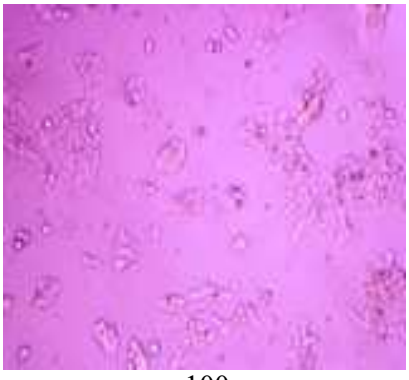
0.1µm



1.0 µm



10 µm

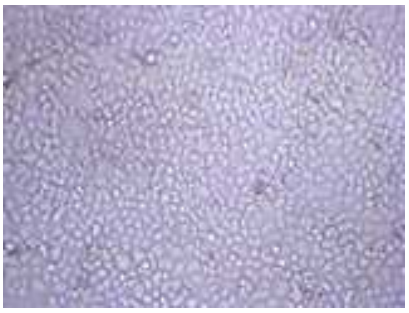


100 µm

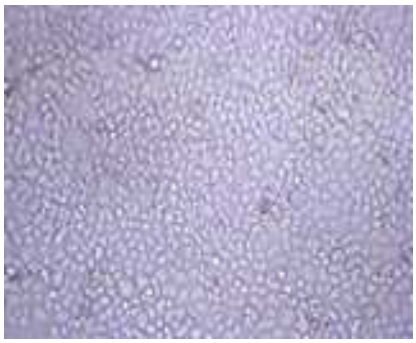
Figure:2

In-vitro Cytotoxicity of compounds 10

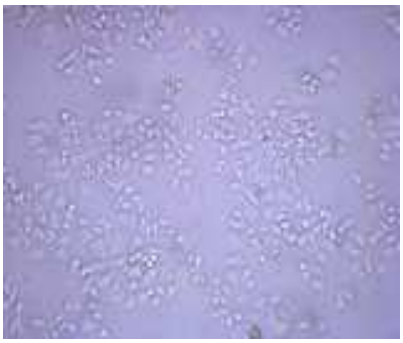
Control



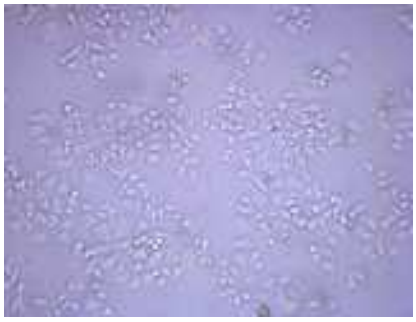
Compound-10



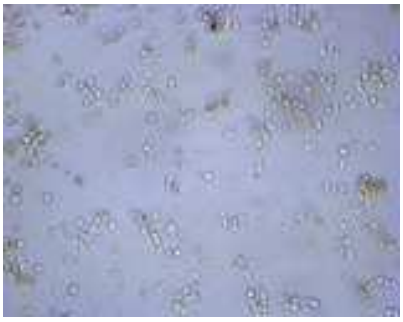
0.1 µm



1.0 µm



10 µm



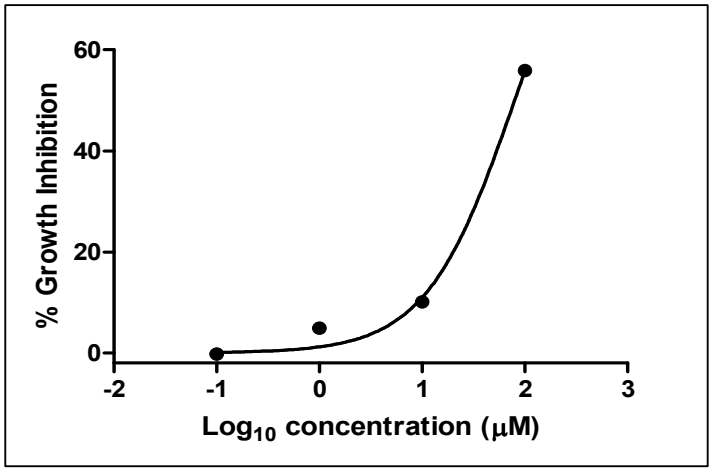
100 µm

Table10 – ***Invitro*** *c*ytotoxicity compound against The human colorectal carcinoma cell line (HCT116) data

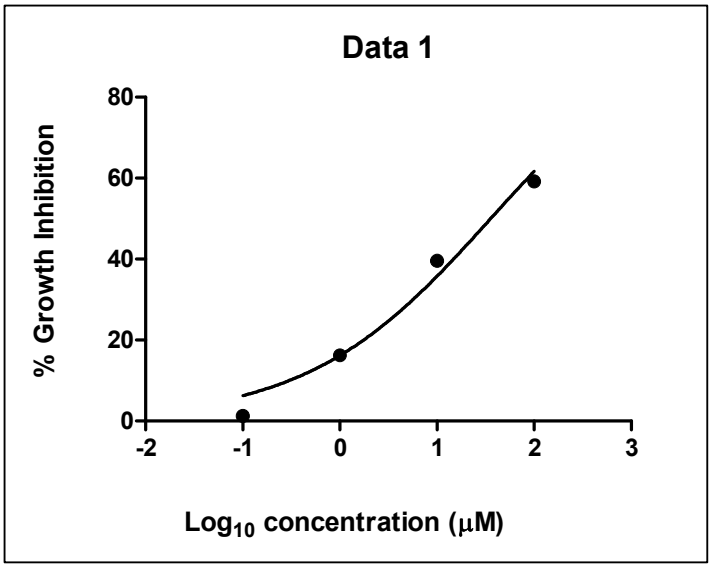
comp code	Conc (µM)	absorbance	% inhibition	IC_{50}	R^2
1	0.1	0.442333	0	>100 µM	-
	1.0	0.419667	5.124341		
	10	0.405333	8.364732		
	100	0.367333	16.95554		
2	0.1	0.442	0.075358	>100 µM	-
	1.0	0.435	1.657875		
	10	0.412	6.857573		
	100	0.322333	27.12886		
3	0.1	0.437	1.205727	>100 µM	-
	1.0	0.400333	9.495102		
	10	0.370667	16.20196		
	100	0.267333	39.56292		
4	0.1	0.440667	0.37679	>100 µM	-
	1.0	0.432333	2.260739		
	10	0.421	4.822909		
	100	0.334333	24.41598		
5	0.1	0.457	-3.31575	>100 µM	-
	1.0	0.441	0.301432		
	10	0.417667	5.576488		
	100	0.342	22.68274		
6	0.1	0.462333	-4.52148	>100 µM	-
	1.0	0.418333	5.425772		
	10	0.380333	14.01658		
	100	0.266	39.86436		
7	0.1	0.437	1.205727	35.72 µM	0.9764
	1.0	0.370667	16.20573		
	10	0.267333	39.56292		
	100	0.180666	59.15611		
8	0.1	0.806333	-2.71762	>100 µM	-
	1.0	0.769333	1.995754		
	10	0.738667	5.902335		
	100	0.633333	19.32059		
9	0.1	0.794333	-1.18896	>100 µM	-
	1.0	0.779667	0.679406		
	10	0.724	7.770701		
	100	0.610667	22.20807		
10	0.1	0.443333	-0.22607	79.56 µM	0.9927
	1.0	0.420667	4.898267		
	10	0.397667	10.09797		
	100	0.195	55.9156		

Determination of cyto-toxicity by MTT assay on HCT116

Compound10



Compound 7



B) Results for *In-vitro* anti-inflammatory of synthesized compound

Table-11

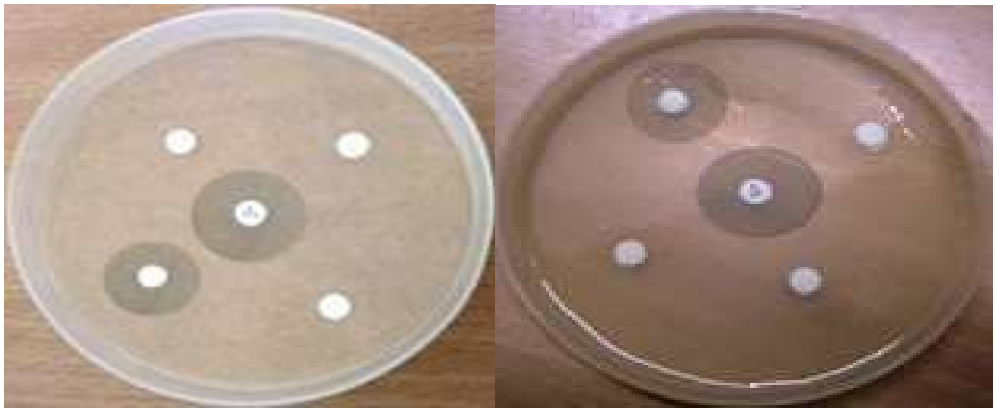
comp. Code	Absorbance value (Mean ± SEM)	Inhibition of denaturation (in %)
Control	0.070±0.002	-
1	0.096±0.002	37.14
2	0.118±0.002	68.57
3	0.081±0.002	15.71
4	0.114±0.002	62.7
5	0.097±0.0050	38
6	0.086±0.003	22.85
7	**0.125±0.003**	**78.57**
8	0.091±0.003	30
9	**0.121±0.004**	**72.8**
10	**0.123±0.003**	**75.71**
Ibuprofen	0.130±0.002	85.71

N=3, Inhibition of de-naturation (in %) is represented by Mean ± SEM

C) Zone of Inhibition of Antibacterial activity

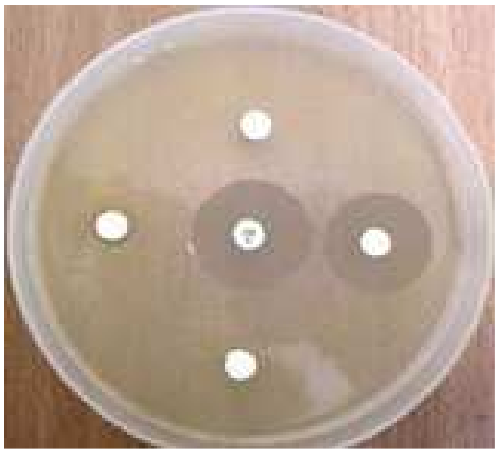
Figure 3

compound 10 showing inhibition at 150mcg/ml



Escherichia coli *Klebsiella pneumoniae*

Proteus mirabilis *Pseudomonas aureoginosa*



Staphylococcus. aureus

Table-12, Anti- Microbial Activity data

Comp. code	conc (µg/mL)	Zone of inhibition in mm				
		E. coli	***S. aureus***	***P. aeruginosa***	***K. pneumoniae***	***proteus mirabilis***
6	150	8	9	10	7	7
7	150	9	9	11	12	8
8	150	10	9	8	8	9
9	150	9	8	11	9	10
10	150	22	20	24	23	8
standard	30	25	22	26	24	23
control	00	00	00	00	00	00

Standard ------- ciprofloxacin
Control -------- DMSO

DISCUSSION

The molecular design of synthesized compound were done by using osrisis property explorer. The toxicity assessment, drug score and drug likeness were predicted by *osiris* reveals that all synthesized compounds are under safety margin.The results are shown in table**-.5**

The Lipinski rule was predicted for all synthesized compound using "*Chemdoodle*". It shows no violation in basic properties. It's proves that the synthesized molecule has ability to reach the target site for the action. It conclude that the molecules have positive nature on ADME character. The results were shown in table-**6**

Based on the literature review some novel derivatives of quinoxaline -2-one were synthesized. All the synthesized compounds were purified by re-crystallization. The structures of the synthesized compounds were confirmed by IR spectra, ^{1}H-NMR spectra and Mass spectra. The results were shown in table-**7 , 8 & 9**.

Melting Point

All synthesized compound's melting point and its reactants melting point were recorded by open capillary tube method. All the reactant and obtained products were differ in their melting point. It clearly indicates that the formation of a new chemical entities. The melting point values are given in table **-3.**

Thin Layer Chromatography

Thin layer chromatography techniques were performed for all synthesized compound as well as the parent compounds, all synthesized compounds gave a single spot whose R_f values are different from their reactants. It ultimately shows that the compound's identity and completion of the reaction. The R_f value are given in table-**3**

Infra Red Spectra

Infra red spectroscopy was taken for all the synthesized compounds .The characteristics absorption peaks were observed for all relevant groups. The absorption peak around 1600-1500 cm-1 indicates the formation of CH=N Schiff bases. C=O stretching vibration around 1670 cm-1 ,N-H stretching was observed at 3300-3500 cm-1,CH_2-S stretching was observed at 1410-1490 cm-1, aromatic spectra was found near 3040 cm-1,759 cm-1 for C-Cl , C-N stretching at 1247 cm-1 and all other relevant groups absorption were observed for all the synthesized compounds.

^{1}H Nuclear Magnetic Resonance

^{1}H Nuclear Magnetic Spectra were taken for all the synthesized compounds .Aromatic protons were observed at 6.68-8.138 ppm and CH=N proton was observed at 9.90-9.97ppm, for all the synthesized compounds. It further established the structure of compounds.

Mass Spectra

The mass spectra of these compounds are showed molecular ion peaks corresponding to their molecular formula.

Anticancer activity

All the synthesized compounds were tested for invitro anticancer activity by MTTassay .Among the synthetic derivatives compound 7 and compound 10 possess cytotoxicity against the Human Colorectal Carcinoma cell line (HCT116). IC50 and R^2 for compound 7 and compound10 shows 35.72µm, 0.9764 and 79.56 µm, 0.9927 .The other compound show more than 100µm. The results were shown in table-10.

Anti inflammatory activity

All of the newly obtained compounds were tested for in vitro anti-inflammatory activity by protein denaturation technique. From the results of anti-inflammatory activity it has been found that compound 7, compound 9,compound 10 showed maximum activity when compared to Ibuprofen. It was also observed that compound 2 & compound4 exhibit better activity. The remaining compound showed weaker activity. The results were shown in table-11.

Antibacterial activity

The synthesized compounds of 6-10 were screened for anti bacterial activity at the concentration of 150 mcg/ml using DMSO as a solvent against the organism's ***Staphylococcus aureus, Pseudomonas aureginosa, Proteus mirabilis, Klebsiella pneumonia & Escherichia coli*** by using disc diffusion technique .The result shows that compound10 showed displayed maximum activity against all the organism. The results were shown in table-12.

Summary
&
Conclusion

Summary and Conclusion

1. Preliminary screening of novel quinoxaline 2-one was done by using Osiris property explorer and Chemdoodle software.
2. The present work describes the synthesis of series of some 3-{[2-({(E)-[substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1H)-one derivatives and 3-({2-[2-(substituted phenyl)-4-oxo-1,3-thiazolidin-3-yl]ethyl}amino)quinoxalin-2(1H)-one using 0-phenylene diamine and oxalic acid as starting material.
3. All the synthesized compounds were purified and characterized by the IR, NMR and MASS spectral datas.
4. The synthesized compounds were found to be identified by TLC.
5. The spectral datas were coinciding with the structure of synthesized compounds.
6. All the relevant peaks were identified in all the spectras.
7. The synthesized compounds were screened for *Invitro* anticancer, anti-inflammatory and antimicrobial activity.
8. The result obtained showed that synthesized compound 7 and compound 10 possesses cytotoxicity against cancer cells. It proves that suitable structural modification will have to be carried out to get novel compound having potent anticancer activity with least effect on normal cells.
9. As per invitro anti inflammatory assay (protein denaturation). The synthesized compound (7,9,10) shows significant anti inflammatory activity.The result from present study shows that introducing thiazolidinone nucleus to the quinoxaline-2-one and aromatic ring having methoxy group increases the activity . A further study (Toxicological study and in *vivo* Pharmacological

screening) on this compounds suggests attractive starting point to find new lead compounds with potential improvements, ultimate use as pain reliever.

10. The synthesized compounds were screened to obtain **Zone of inhibition**.
11. The antimicrobial activities of the compounds were compared with standard drug **Ciprofloxacin.**
12. Among the synthesized derivatives compound 10 were found to be good in antimicrobial activity. Thus based on the above observations we can conclude that only at high concentrations, the compound(6,7,8,9) may act as antibacterial activity as compared to the standard drug.
13. The entire study reveals that the compounds will be modified structurally based on substitution and the difference in activity can also determined.By incorporating many more ring system to the quinoxaline nucleus could lead to more potent and highly active compound.

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