DRUG DESIGN, MOLECULAR DOCKING STUDIES, MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF NOVEL SCHIFF'S BASES OF DIBENZOSUBERENONE DERIVATIVES AS ANTI-HISTAMINE AND ANTI-DEPRESSANT

A Dissertation submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600 032

In partial fulfillment of the requirements for the award of the degree of
MASTER OF PHARMACY
IN
BRANCH II-PHARMACEUTICAL CHEMISTRY

Submitted by
A.SATHISHKUMAR
261915753

Under the guidance of
Mrs.G.TAMILARASI., M.Pharm.,
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

COLLEGE OF PHARMACY
MADURAI MEDICAL COLLEGE
MADURAI – 625 020

OCTOBER 2021

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CERTIFICATE

This is to certify that the dissertation entitled **'DRUG DESIGN, MOLECULAR DOCKING STUDIES, MICROWAVE ASSISTED SYNTHESIS, AND CHARACTERIZATION OF NOVEL SCHIFF'S BASE OF DIBENZOSUBERENONE DERIVATIVES AS ANTIHISTAMINE AND ANTIDEPRESSANT"** is a bonafide work done by **SATHISHKUMAR.A(Reg.No:261915753)** DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, COLLEGE OF PHARMACY, MADURAI MEDICAL COLLEGE, MADURAI-625020 in partial fulfillment of the TamilNadu Dr.M.G.R. Medical University rules and regulations for award of MASTER OF PHARMACY IN PHARMACEUTICAL CHEMISTRY under my guidance and supervision during the academic year 2019-2021.

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"Parents are the only ones who love you without any expectations"

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CHAPTER I

INTRODUCTION

INTRODUCTION

GREEN SYNTHESIS

The term Green Chemistry is becoming the worldwide term used to describe the design of chemical products and processes that reduce or eliminate the use or generation of substances hazardous to human health. The term was coined by the US Environmental Protection Agency and has been defined as the utilization of a set of principles that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and application of chemical products.

Green chemistry is defined as environmentally benign chemical synthesis. Any synthesis, whether performed in teaching laboratories or industries should create none or minimum by products which pollute the atmosphere. According to the work carried out by Paul T.Anastas, the following basic principles of green chemistry have been formulated.

Green synthesis is an environmentally friendly method presenting a different way of thinking in chemistry intended to eliminate toxic waste, reduce energy consumption, and to use ecological solvents water, ethanol, ethyl acetate. Polar solvents such as

- Ethanol,
- 1-propanol,
- Acetone,
- Acetonitrile,
- 2-propanol, and
- Methanol are listed as environmentally safe in the industrial SSGs and are at the top of the list of green chemicals

12 BASIC PRINCIPLES OF GREEN SYNTHESIS

Green chemistry is generally based on the 12 principles proposed by Anastas and Warner. Nowadays, these 12 principles of green chemistry are considered the fundaments to contribute to sustainable development.

The principles comprise instructions to implement

- New chemical products,
- New synthesis and
- New process

1. Prevention of waste/by-products.

2. Maximum incorporation of the reactants (starting materials and reagents) into the final product.

3. Prevention or minimization of hazardous products.

4. Designing of safer chemicals.

5. Energy requirement for any synthesis should be minimum.

6. Selecting the most appropriate solvent.

7. Selecting the appropriate starting materials.

8. Use of the protecting group should be avoided whenever possible.

9. Use of catalysts should be preferred wherever possible.

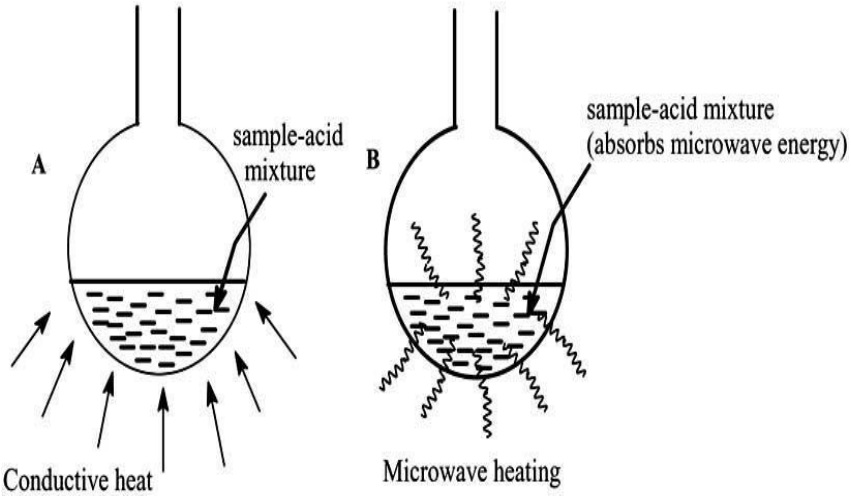
10. Products obtained should be biodegradable.

11. The manufacturing plants should be so designed as to eliminate the possibility of accidents during operation.

12. Strengthening of analytical techniques to control hazardous compounds.

MICROWAVE SYNTHESIS

The interest in the microwave assisted organic synthesis has been growing during the recent years. It results from an increasing knowledge of fundamentals of the dielectric heating theory, availability of equipment designed especially for the laboratory use as well as the discovery of the special techniques of the microwave synthesis. The efficiency of microwave flash-heating chemistry in dramatically reducing reaction times (reduced from days and hours to minutes and seconds) has recently been proven in several different fields of organic chemistry and this aspect is of great importance in high speed combinatorial and medicinal chemistry. In this contribution, the current state of the art is summarized providing examples of the most recent applications in the field of microwave assisted synthesis of biologically active compounds both in heterocyclic and in peptide and peptide mimetic optimization.



MECHANISM OF MICROWAVE HEATING

All the materials are not susceptible to microwave heating as response of various materials to microwave radiation is diverse. Based on their response to microwaves, materials can be broadly classified as follows

(1) Materials that are transparent to microwaves, e.g. sulphur

(2) Materials that reflect microwaves, e.g. copper

(3) Materials that absorb microwaves, e.g. water

Microwave absorbing materials are of utmost important for microwave chemistry and three main different mechanisms are involved for their heating namely

- Dipolar polarization,
- Conduction mechanism,
- Interfacial polarization.

Microwave heating is proving to be a transformational technique in preparative chemistry. Using modern scientific microwave apparatus, it is possible to access elevated temperatures in an easy, safe, and reproducible way. By using microwave heating, reaction times can often be decreased, product yields increased, and purity enhanced as compared with conventional heating methods. The origins of the rate enhancements observed have been a topic of considerable debate over the years. It is now accepted, however, that microwave heating is just that – heating. In this chapter the key tenets of microwave-assisted organic chemistry are explored in the context of particular classes of reaction. The chapter discusses topics such as metal catalysis, reactions involving gases as reagents, combinatorial chemistry, monitoring reactions in real-time, and reaction scale-up, as well as giving an overview of the concepts behind microwave heating.

VARIOUS TECHNIQUES OF MICROWAVE SYSTEM

1. Domestic house hold ovens – 'solvent-free' open vessel reactions:

Most of published chemistry has been performed using domestic microwave ovens. The key reasons for using a device intended for heating items to perform synthesis are that they are readily available and inexpensive. The use of domestic ovens might be one of the main reasons why microwave assisted organic synthesis has not increased greatly in popularity, due to factors outlined earlier, and conducting synthesis in domestic microwave ovens is clearly not the intended application, as stipulated by the CE code for electro thermal appliances.

2. Reflux system:

A number of reflux system have been developed in an effort to use solvents in microwave assisted organic synthesis without the risk of explosion. Some systems are modified domestic ovens, while other have been designed with a single mode cavities. There is a little risk of explosion with reflux systems, since the systems are at atmospheric pressure and flammable vapors cannot be released into the microwave cavity. The temperature however cannot be increased by more than 13-26^{o}C above the normal boiling point of the solvent and only for a limited time.

3. Pressurized systems:

Reactions performed under pressure in a microwave cavity also benefit from the rapid heating rates and remote heating of microwave dielectric heating this type of experiments lead to the one of very earlier development using microwave assisted organic synthesis.

4. Continuous flow system:

If the outcome of a reaction is strongly dependent on the heating profile of the reaction mixture, it is crucial to maintain that heating profile when scaling up the reaction. If for example, 3 ml of a solvent is heated to 150^{o}C in 20s using microwave irradiation at 300 W, it will be necessary to use at least 15 kW power to heat 150 ml of same solvent, in order to maintain the same heating profile.

THERE ARE SOME REACTIONS THAT ARE EASILY PROCEED BY MICROWAVE SYNTHESIS

Microwave synthesis for Nanomaterials:

Amongst the several methods that exist for synthesizing of nanoparticles, the use of microwave assisted synthesis has shown promise. Synthesis of silver nanoparticles from silver nitrate employing starch as the reductant stabilizing agent has been carried out under direct heating, controlled heating and microwave irradiation. The microwave irradiation was considered as better for reduction of silver ions to silver nanoparticles. It also afforded smaller particle sizes and particle size distribution. Compared to conventional methods, microwave assisted synthesis was faster and provided particles with an average particle size of 12 nm.

Microwave-Assisted Peptide Synthesis:

A microwave-assisted, rapid solid phase peptide synthesis procedure has been reported. The application of microwave heating to solid-phase peptide synthesis is particularly advantageous as the acceleration of coupling and deportation reactions should lead to shorter cycle times, higher repetitive yields, and ultimately purer peptides. The protocols for the synthesis of cystine rich peptides in the presence of microwave radiation with solid phase peptide synthesis.

Polymer Chain Reactions:

Polymerase chain reactions with focused microwave irradiation as the source of heat were demonstrated and the results indicated the possibility to shorten the total reaction time as well as the possibility to perform PCR reactions in millilitre scale. Scientists focused on the microwave technology for advance to the various chemical and biological reactions and the microwave irradiatation to rooling circle amplification reaction on controlling the temperature. The extract and detection of anthrax DNA from spores and vegetative cells in two steps within 1 min has been reported.

SOME COMMON REACTIONS OCCUR IN MICROWAVE SYNTHESIS

Cycloaddition Reaction:

Conventional cycloaddition reactions require, in many cases, the use of harsh conditions such as high temperatures and long reaction times, but they can be performed with great success with the aid of microwave heating. Diels–Alder cycloadditions performed by microwave dielectric heating. In both cases the diene and dienophile were reacted neat without the addition of solvent. For the transformation described by Trost and Crawley, irradiation for 20 minutes at 165^0 C gave the cycloadduct which is in near quantitative yield. In the above reaction 4_{n+2}cycloaddition reaction occurs.

Asymmetric Allylic Alkylations:

A frequent criticism of microwave synthesis has been that the typically high reaction temperatures will invariably lead to reduced selectivity's. This is perhaps the reason why comparatively few enantio selective processes driven by microwave heating have been reported in the literature. For a reactions to occur with high enantio selectivity there must be a large enough difference in the activation energy for the processes leading to the two enantiomers. The higher there action temperature, the larger the difference in energy required to achieve high selectivity. The research groups of Moberg, Hallberg, and Larhed reported on microwave-mediated palladium and molybdenum- catalyzed asymmetric allylic alkylation reactions involving neutral carbon, nitrogen, and oxygen.

Glycosylation Reaction:

Glycosylation reactions involving oxazoline donors are generally rather slow and require prolonged reaction times because of the low reactivity of the donors. Oscarson and co-workers have reported the preparation of dimers of N-acetyl lactosamine linked by alkyl spacers by microwave assisted glycosylations with oxazoline donors in the presence of pyridinium triflate as a promoter. Rapid and efficient coupling was achieved in dichloromethane with four different diols using 2.2 equivalents each of the oxazoline donor and pyridinium triflate as a promoter.

Neucleophillic Aromatic Subsitution:

An alternative to the palladium-catalyzed Buchwald– Hartwig reactions and the related copper-catalyzed methods for C(aryl)- N, C(aryl) -O, and C(aryl)- S bond formations are nucleophilic aromatic substitution reactions. Eg. Benzene and amines

Oxidations:

The osmium-catalyzed dihydroxylation reaction, the addition of osmium tetroxide to olefins to produce a vicinal diol, is one of the most selective and reliable organic transformations. Recent work by Sharpless, Fokin, and coworkers has uncovered that electron-deficient olefins can be converted into the corresponding diols much more efficiently when the reaction medium is kept acidic. Which in combination with 4-methylmorpholine N-oxide (NMO) as the reoxidant for $K_2OsO_2(OH)_4$ (0.2 mol%) as a stable, nonvolatile substitute for OsO_4, allows the conversion of many olefinic substrates into their corresponding diols at ambient temperatures.

Buchwald-Hartwig Reaction:

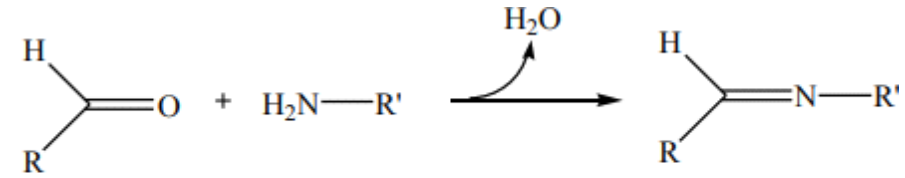
The research groups of Buchwald and Hartwig have developed a large variety of useful palladium-mediated methods for C-O and C-N bond formation. These arylations have been enormously popular in recent years. A vast amount of published material is available describing a wide range of palladium-catalyzed methods, ligands, solvents, temperatures, and substrates which has led to a broad spectrum of tuneable reaction conditions that allows access to most target molecules that incorporate an aryl amine.

Ullmann Condensation Reactions:-

Copper-mediated C-N, C-O and C-S bond forming protocols. Examples of microwave assisted Ullmann-type condensations from researchers at Bristol–Myers Squibb. In the first example, (S)-1-(3- bromophenyl) ethylamine was coupled with eleven heteroarenes containing N-H groups in the presence of 10 mol% CuI and 2.0 equivalents of K_2CO_3 base. The comparatively high reaction temperature (195^0C) and For the coupling of 3,5-dimethylpyrazole, for example, microwave heating for 22 h was required to afford a 49 % yield of the isolated product.

SCHIFF BASE

Generally, Schiff bases (imines) occur from primary amines and carbonyl compounds. Hugo Schiff, a German chemist, isolated the first condensed product of amines with carbonyl compounds, which he referred to as Schiff base. Thus the Schiff bases are the organic compounds containing azomethine –R-C=N- group and are usually formed by the condensation of a primary amine with an active carbonyl compound.



Aldehyde or ketone Primary amine Schiff base

$R_1R_2C=NR_3$,

where R is an organic side chain. In this definition, Schiff base is synonymous with azomethines. Some restrict the term to the secondary aldimines (azomethines where the carbon is connected to a hydrogen atom), thus with the general formula, RCH=NR,

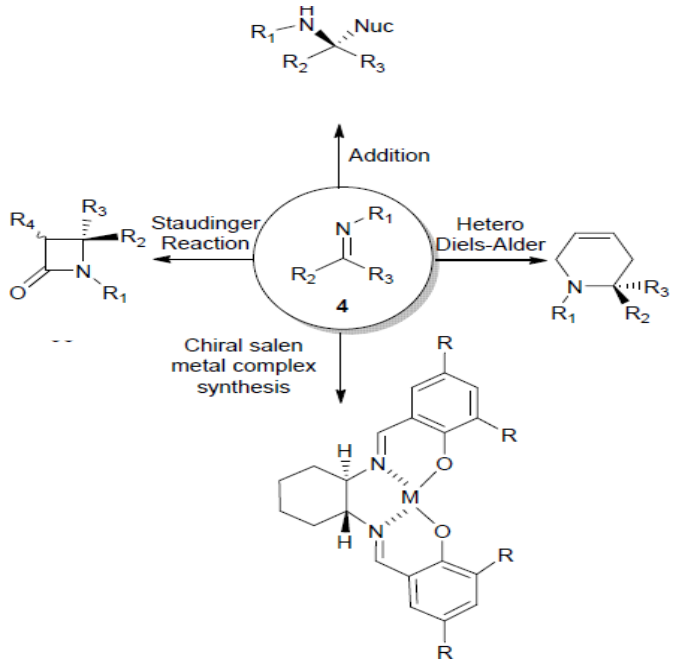
The chain on the nitrogen makes the Schiff base stable imines. A Schiff base derived from aniline, where R_3 is a phenyl or a substituted phenyl. Imines can also be represented by the general formula RCH = NR′, wherein R and R′ are alkyl or alkyl substituents . Many imines have been worked due to their very varying structural properties and used as chelating ligands in coordination Chemistry. This interest in Schiff bases can be explained due to their availability in many areas, such as biological systems, medicine, and also in new technologies. In addition these, imines are important intermediates and multipurpose starting materials for the synthesis of many reaction such as Mannich bases, indoles, betalactam, pyrimidine derivatives.Compounds obtained from these reactions accompanied by Schiff bases have been used in the treatment of various diseases due to their biological activity. Many reagents have been used for the synthesis of imines such as Lewis acids, metal complex, metal-free conditions, promoted by microwave irradiation and ultrasound radiation.

IMPORTANCE OF SCHIFF BASES IN ORGANIC SYNTHESIS, BIO-PROCESSES AND PHARMACEUTICAL CHEMISTRY

As a versatile precursor for organic syntheses, we can identify, in an oversimplification, four different types of reactions in which Schiff bases have been found extremely important applications.

Addition of organometallic reagents or hydride to C=N bond to afford compounds of structure hetero Diels-Alder reaction to furnish six membered nitrogen containing heterocyclic compounds of general formula skeletons for the building-up scaffolds, as the very famous salen scaffold, to be used as "privileged ligand" for the formation of the corresponding chiral salen metal complexes staudinger reaction with ketene to furnish biologically important β-lactam ring. It must be underlined for point that we are reporting only the applications of chiral salen complexes. For different complex catalysts, as salophen, or for theuse of Schiff bases, different from salen backbone, we refer the interested reader to the following up-to-date survey of extremely good and dedicated reviews on the subject authored by specialists inthe field.

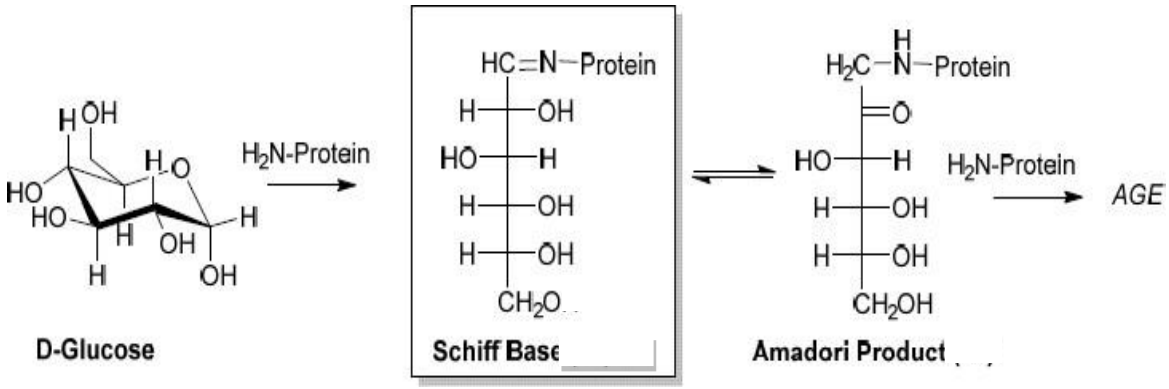
APPLICATIONS OF SCHIFF BASES IN ORGANIC SYNTHESIS



Reduction of C=N bond, focused on asymmetric formation of carbon-carbon bond, Hetero Diels-Alder reactions with the formation ofheterocyclic compounds, Use of chiral salen metal complexes in the asymmetric synthesis, Staudinger reactions for the preparation of β-lactams. In the following paragraphs we will emphasize the importance of imines, first discovered by theUgo Schiff, providing the reader with relevant information highlighting the importance of Schiff bases and their applications in a wide range of organic and pharmaceutical chemistry fields.

SCHIFF BASES AS INTERMEDIATE OF BIO-PROCESSES

The importance of Schiff bases as intermediates in bio-processes is very well established. Other important bio-processes, that lately are attracting the interest of chemists and biologists, are related to the glycation of albumin that leads to the formation of important biomarkers, which are predictive of type II diabetes or to the reaction between sugars and biologically relevant amines with the formation of Schiff bases.



AGEs are involved in many pathological conditions such as cardiovascular disease, Alzheimer.

APPLICATION OF SCHIFF BASES IN PHARMACEUTICAL RESEARCH

There are numerous publications covering the use of Schiff bases in therapeutic or biological applications either as potential drug candidates or diagnostic probes and analytical tools. The activity of Schiff bases as anticancer compounds including radioactive nuclide complexes,

- Antidepressant,
- Antibacterial ,
- Antifungal ,
- Antiviral agents, has been extensively studied.

Moreover, Schiff bases are present in various

- Natural,
- Semi-synthetic, and
- Synthetic compounds.

"Schiff bases" in any chemistry database a countless number of records appears as proof of the importance of such derivatives in chemistry. They are present as reactants in synthetic organic processes, as important scaffolds in organo metallic chemistry, as backbones of precious catalysts and as pharmaceutical presidiums against a series of different diseases and pathological states.

APPLICATION OF SCHIFF BASE IN BIO-CHEMISTRY

Schiff bases have been investigated in relation to a wide range of contexts, including antimicrobial, antiviral and anticancer activity. They have also been considered for the inhibition of amyloid-β aggregation.

Schiff bases are common enzymatic intermediates where an amine, such as the terminal group of a lysine residue, reversibly reacts with an aldehyde or ketone of a cofactor or substrate. The common enzyme cofactor PLP forms a Schiff base with a lysine residue and is transaldiminated to the substrate(s). Similarly, the cofactor retinal forms a Schiff base in rhodopsins, including human rhodopsin via Lysine , which is key in the photoreception mechanism.

DIBENZOSUBERENONE

OTHER NAMES:

5H-Dibenzo[a,d]cyclohepten-5-one,

10,11-dihydro-; Dibenzosuberan-5-one;

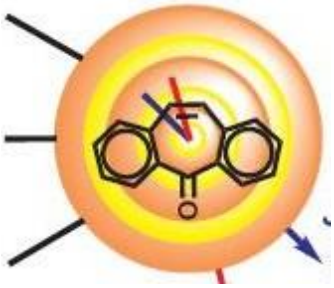
Dibenzo[a,d]cycloheptadien-5-one;

Dibenzo[a,d]cyclohepta[1,4]dien-5-one;

10,11-Dihydrodibenzo[a,d]cyclohepten-5-one;

2,3:6,7-Dibenzosuberone;

The tricyclic structure of 5-dibenzosuberenone is a useful scaffold for a wide range of synthetic, mechanistic, theoretical, and medicinal applications. This core skeleton exists in the structure of drugs marketed as antidepressants. This class of molecules has attracted noticeable attention from both synthetic and biological communities due to their interesting chemical structures and potential biological activities.



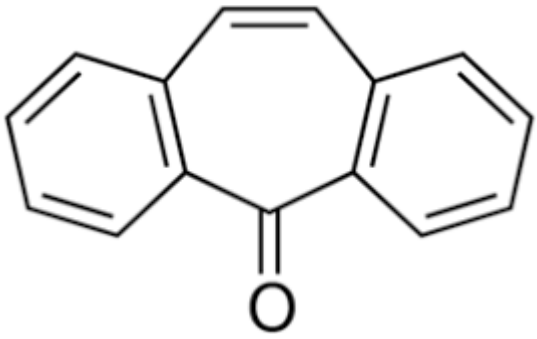
DIBENZOSUBERENONE

Preparation of dibenzosuberenone analogues initiated in 1950s, based on synthetic interest and the same in the present could widely be seen in literature as synthetic intermediates. The use of these intermediates drastically increased with the advent of invention of the dibenzosuberenone analogues as psychotropic by Davis and co-workers .

A class named as tricyclic antidepressants (TCAs) gained utmost popularity. For example, drugs of this class such as

- Amitriptyline ,
- Imipramine and
- Noxiptiline

continue as first line agents to treat depressive disorders. Likewise, several dibenzosuberenone based analogues have been synthesized and tested for wide array of applications and the moiety continues to be of interest to synthetic and medicinal chemists.



Dibenzosuberenone analogues were previously prepared starting from simple or substituted compounds which, in turn, were accessed through multi-step synthetic routes. But currently, compounds 1-3 and a few related analogues are widely available from various commercial sources making the analogue synthesis of dibenzosuberenone more accessible easily. Preparation of the analogues based on dibenzosuberenone skeleton was approached by chemists through different modes of which functionalization of the seven-membered ring is the key mode which led to majority compounds. In other words, most of the dibenzosuberenone analogues were prepared by modifications of either “double bond” or carbonyl group present on the central “seven-membered ring” or both. Though most of these synthetic details appeared in respective research articles, the comprehensive information dealt with chemistry of dibenzosuberenone is not found in literature.

REACTIONS OF DIBENZOSUBERENONE

The structural modifications of the dibenzosuberenone performed limit to the chemistry on suberyl ring. In particular, dibenzosuberenone has two important sites for functionalization, by virtue of its structure, namely, the "double bond" and the "carbonyl group". In the following section, preparation of various analogues of DBS synthesized by modification of the parent skeleton based on reactions of the carbonyl group and the "double bond" and both(miscellaneous reactions) will be addressed.

FUNCTIONALAISATION OF CORBONAYL GROUP

George and co-workers have synthesized new series of benzo [4,5]cyclohept [1,2,3]isoquinolines by condensation reaction of compound 3 with aminoacetaldehyde diethylacetal followed by treatment of the corresponding imines 35 with PPA to afford the tetracyclic compound.

In another work, Coppola and co-workers reported transformations in Dibenzo[a,d]cycloheptene series through two routes. Authors designed these compounds by integrating norepinephrine and dibenzosuberene skeletons resulting in series of 5-aminomethyl-5-hydroxy-5H-dibenzo[a,d]cycloheptene derivatives.

The compound was converted to an epoxide intermediate in the presence of dimethylsulfonium methylide (Corey's reagent) followed by ring opening of epoxide with various amines resulting in the desired analogs of compound. Alternatively, compound were prepared from series of steps starting from Reformatsky reaction of compound with ethyl bromoacetate to affording initially ethyl ester .

Treatment of compound followed by treatment of the hydrazide with nitrous acid resulted in spirooxazolidone derivative . Finally, N-alkylation followed by alkali hydrolysis of compound resulted in required aminoalcohols of general structure.synthesis of N-alkylidenearenesulfenamides using dibenzosuberenone in their investigations on tertiary carbinamines, which are useful precursor to several imino-bridged heterocycles.

FUNCTIONALIZATION OF DOUBLE BOND AND CARBONYL GROUP

In this section reactions starting from dibenzosuberenone involving both functionalities, i.e., "carbonyl group" and "double bond" of the 7-membered ring which led to analogues based on dibenzosuberenone skeleton will be discussed. Majority of the active dibenzosuberenone analogues prepared so far belong to the class of tricyclic antidepressants (TCAs). Their syntheses initiated with addition of Grignard reagent to carbonyl group at position '5' leading to tertiary carbinol . Further, addition of α-effect nucleophile NH2OH to compound yielded the intermediate , which was subjected to trans-annular ring closure in presence of potassium tert-butoxide in dimethyl sulfoxide to afford compound. Finally, hydrogenolysis of hydroxylamine yielded dizocilpine . Recently, different approach for synthesis of dizocilpine which starts with conversion of dibenzosuberenone to aziridine in presence of chloramine-T.

IMPORTANCE OF DIBENZOSUBERENONE ANALOGUES

Applications of the tricyclic framework of the 5H-dibenzo [a,d] cycloheptene system in synthesis of novel derivatives. Additionally, the dibenzosuberenone skeleton is known to undergo photochemical reactions and chemists have exploited photochemical properties of the dibenzosuberenone analogues for preparing novel complex molecules of synthetic interest. Besides, several researchers explored dibenzosuberenone skeleton for preparation of novel analogues that were tested for varied biological activities e.g., Nicholas and co-workers for purinoceptor 7-transmembrane G-protein coupled receptor antagonist activity, acetylcholine binding protein and α7 nicotinic receptor ligand binding affinities, for antihistamine properties, steroid hormone nuclear receptor modulation, farnesyl protein transferase inhibition, Arya and co-workers for anti-inflammation, N-methyl- D-aspartate antagonist activity, cytokine biosynthesis inhibition, anti-convulsant activity.

Since the introduction of amitriptyline for the treatment of depression, DBS skeleton has been varied almost infinitely in the search for improved biological activity which led to many second generation potent compounds such as protriptyline and cyproheptadine. Additionally, dibenzosuberenone shares a structural resemblance with a key dibenzazepine intermediate which has been exploited in synthesis of several compounds with anti-depressant properties. Clozapine is a tricyclic dibenzodiazepine derivative which interferes with the binding of

dopamine molecules at the D1, D2, D3, D4 and D5 dopamine receptors . Carbamazepine is an anti-epileptic drug used to control grandma and focal seizures besides being a specific analgesic for trigeminal neuralgia.

DBS analogues are known to possess other interesting pharmacological activities. Especially, ability of some DBS analogues to reverse the multi drug resistance which prompted researchers to investigate their application in cancer chemotherapy. series of compounds based on dibenzosuberenone skeleton were found to be selective inhibitors of p38 mitogen-activated protein kinase (p38 MAP kinase) with Skepinone-L being known as potent inhibitor of p38 mitogen-activated kinase.

TRICYCLIC ANTIDEPRESSANTS

The majority of the tricyclic antidepressants (TCAs) act primarily as serotonin–norepinephrine reuptake inhibitors (SNRIs) by blocking the serotonin transporter (SERT) and the norepinephrine transporter (NET), respectively, which results in an elevation of the synaptic concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. Notably, with the sole exception of amineptine, the TCAs have weak affinity for the dopamine transporter (DAT), and therefore have low efficacy as dopamine reuptake inhibitors (DRIs). Although TCAs are sometimes prescribed for depressive disorders, they have been largely replaced in clinical use in most parts of the world by newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NRIs). Adverse effects have been found to be of a similar level between TCAs and SSRIs.

AN ATTEMPT HAS BEEN MADE IN THIS STUDY TO DRUG DESIGN, MOLECULAR DOCKING STUDIES, MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF NOVEL SCHIFF'S BASE OF DIBENZOSUBRENONE DERIVATIVES AS ANTI-HISTAMINE AND ANTI-DEPRESSANT. THIS STUDY IS NOT REPORTED TILL DATE.

CHAPTER II

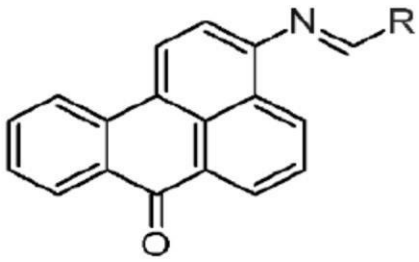
LITERATURE REVIEW

LITERATURE REVIEW

1.Ramazan Koçak.*et.al*.,(2021).,

Dihydropyridazine dyes were synthesized by inverse electron demand Diels–Alder cycloaddition reactions between a dibenzosuberenone and tetrazines that bear various substituents. The pyridazines were synthesized in high yields by oxidation of dihydropyridazine-appended dibenzosuberenone. p-Quinone derivatives of pyridazines were alsoobtained by H-shift isomerization following the inverse electron-demand Diels–Alder reaction oftetrazines with p-quinone dibenzosuberenone. Then these pyridazines were converted to the corresponding pyrroles by reductive treatment with zinc.

2.Natalja Orlova.*et.al*.,(2021).,

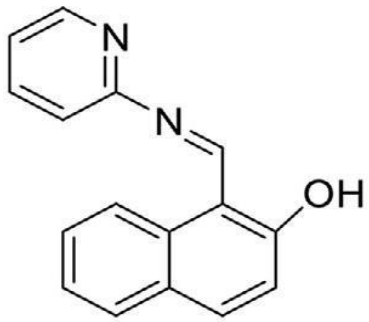


Synthesis of new substituted azomethines of benzanthrone with heterocyclic substituents were synthesized by condensation reaction of 3-aminobenzo[de]anthracen-7-one with appropriate aromatic aldehydes. The resulting imines were reduced with sodium borohydride to the corresponding amines, the luminescence of which is more pronounced in comparison with the initial azomethines. The novel benzanthrone derivatives were characterized by NMR, IR, MS, UV/Vis, and fluorescence spectroscopy. The structure of three dyes was studied by the X-ray single crystal structure analysis. The solvent effect on photophysical behaviors of synthesized imines and amines was investigated. The obtained compounds absorb at 420–525 nm, have relatively large Stokes shifts (up to 150 nm in ethanol), and emit at 500–660 nm. The results testify that emission of the studied compounds is sensitive to the solvent polarity, exhibiting negative fluorosolvatochromism for the synthesized azomethines and positive fluorosolvatochromism for the obtained amines.

3. Nayana Adhikari.*et.al*., (2020).,

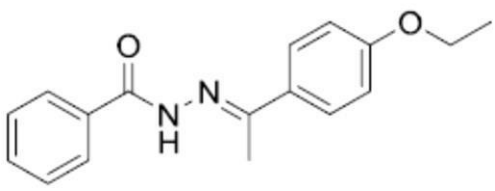
Reported a series of novel PABA-substituted 1,3,5-triazine derivatives were developed via microwave assisted synthesis and subsequently tested for antimalarial activity against chloroquine sensitive 3D7 strain of Plasmodium falciparum using chloroquine as standard. Antimalarial screening result showed that synthesized compounds exhibited IC50 in the range of 4.46 to 79.72 μg mL−1.

4.Maria Sadia.*et.,al.,(*2020).,



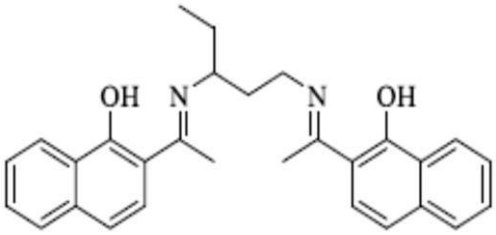
were developed the synthesis of Schiff base ligand L [1(pyridine-2-ylimino) methyl) naphthalene-2-ol], and its applications as anticancer agent against human lung (H-460) and breast (MCF-7) cell lines, and as antidepressant agent. The Schiff base ligand L was synthesized by aldol condensation reaction by reacting commercially available 2-hydroxy-1-napthaldehyde with 2-amino-pyridine. The synthesized ligand was characterized by different spectroscopic techniques and evaluated for its anticancer potential against H-460 and MCF-7 cell lines. The antidepressant activity was evaluated by means of elevated plus maze model using Diazepam as reference drug.

5.Zhi Xiang Zhao.*et.,al.,(*2019).,



Synthesized the Schiff-bases have important applications in the field of analysis, biomedicine, as well as material sciences. Hydrazones and acylhydrazones are two representative types of Schiff-bases. In this study, a green synthesis of aromatic hydrazones and acylhydrazones via Schiff-base reaction of aryl ketones and aromatic acylhydrazines/hydrazines had been reported. In the synthesis, water was used as solvent and AlCl3 •6H2O was used as catalyst. The reaction is simple, highly efficient, and eco-friendly.

6. B.T. Vhanale,*et.al.,(*2019).,



Reported The four Schiff bases (I - IV) were synthesized by the condensation reaction of 1(1-hydroxynaphthalen-2-yl)ethanone, 1-(4-chloro-1hydroxynaphthalen-2-yl)ethanone and 1- (4-bromo-1-hydroxynaphthalen-2-yl)ethanone with propane-1,3-diamine and pentane-1,3- diamine. The structural analysis is done by UVvis., FT-IR, 1H NMR, 13C NMR, LC-MS and elemental analyses. These compounds were assayed for antibacterial (Escherichia coli and Salmonella Typhi) activity and antioxidant (2,2-Diphenyl-1-Picryl Hydrazyl(DPPH) and Hydroxyl radical scavenging method) activity. The antibacterial and antioxidant activities of synthesized Schiff bases exhibited better degrees of inhibitory effects. Among these, Schiff base 2,2'-((propane-1,3-diylbis(azanylylidene))bis(ethan-1-yl-1-ylidene))
bis(4-chloronaphthalen-1-ol) (II) exhibited excellent antibacterial activity with MICs of 0.12, 0.25, 0.5 and 1 mg/ml against E. coli and Salmonella Typhi.

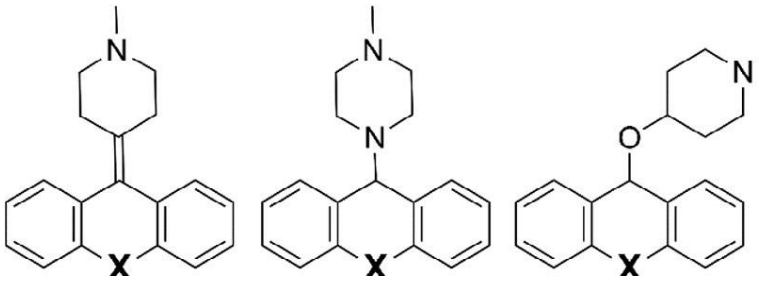
7.Gabriel Marc1, *et.al.,(*2018)., synthesized series of 12 new thiazolidine-2,4-dione derivatives were obtained by microwave-assisted synthesis. All compounds were physicochemically characterized by quantitative elemental C, H, N, S analysis and spectral data (mass spectrometry [MS], infrared [IR], and nuclear magnetic resonance [NMR]), with the results being in agreement with the expected data. An in vitro screening performed on Candida albicans ATCC

10231 showed their moderate antifungal activity, which was further investigated by determining the minimum inhibitory concentration and minimum fungicidal concentration values for the most active compounds on four strains of Candida. The molecular docking studies, performed against a fungal lanosterol 14α-demethylase, emphasized the importance of different molecular fragments in the compounds' structures for their antifungal activity. The synthesized compounds were subjected to in silico screening for the prediction of their absorption, distribution, metabolism, excretion, and toxicity (ADMET) and molecular properties.

8. Ambatkar MP.*et.al*.,(2018).,

Reported Some common molecules like antipyrine and toluene-p-sulphonamide have been synthesized by Microwave Assisted method i.e. "Green Synthesis". The reaction yields were compared with reported conventional method. The purpose of this study was increasing practical yield, lowering the reaction time and reducing pollution. The products were characterized by various techniques like melting point, Thin Layer Chromatography (TLC), partition coefficients, dissociation constants, % ionization, Fourier Transform Infrared (FTIR) spectroscopy, Mass and Proton Nuclear Magnetic Resonance (1H-NMR) spectroscopy.

9. Takashi Fujiwara, *et.al.,(*2016),

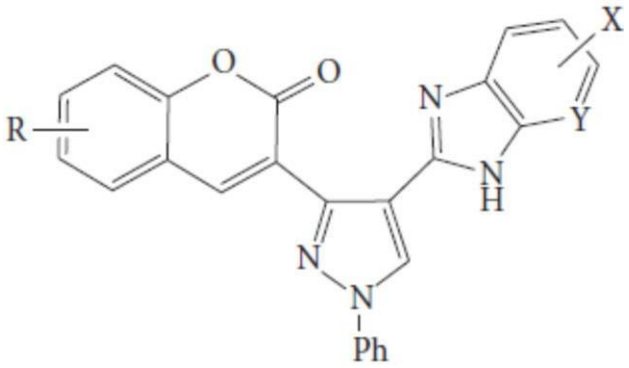


Synthesized several derivatives in order to examine the steric structure–inhibitory activity relationship. We found that even a small change of molecular shape due to reduction or replacement of the 10,11-olefinic bond of the tricyclic ring generally resulted in a drastic decrease of the inhibitory activity.

10.Jin-Xia Mu.*et.al*.,(2016).,

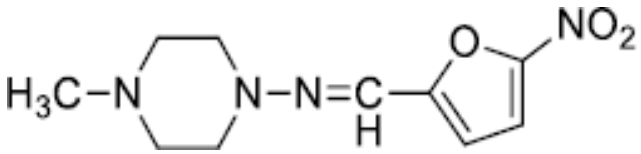
Synthesized series of novel 1,2,4-triazolo[4,3-a]pyridine derivatives containing hydrazone moiety were designed and synthesized from 2,3-dichloropyridine, hydrazine hydrate by multi-step reactions under microwave irradiation condition, and their structures were characterized by FT IR, 1H NMR, 13C NMR, 19F NMR, MS and elemental analysis. The antifungal activities of title compounds were determined. A practical synthetic route to obtain 1,2,4-triazolo[4,3-a]pyridine derivatives is presented. This study suggests that the 1,2,4-triazolo[4,3-a]pyridine derivatives exhibited good antifungal activity. we have reported efficient and environmentally benign methodologies for the synthesis of 3-[4-(1H-benzo[d]imidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl]-2H-chromen- 2-one derivatives by using thermal and by microwave irradiation under neat conditions in presence of ethanol. The reactions carried out under microwave irradiation afforded benzimidazoles in short period of time with excellent yields.

11.Mahadev N.Kumbar.*et.al*.,*(*2016).,



Reported efficient and environmentally benignmethodologies for the synthesis of 3-[4-(1H-benzo[d]imidazol-2-yl)-1-phenyl-1H-pyrazol-3-yl]-2H-chromen- 2-one derivatives by using thermal and by microwave irradiation under neat conditions in presence of ethanol. The reactions carried out under microwave irradiation afforded benzimidazoles in short period of time with excellent yields. Hence, this methodology would make an interesting strategy for the synthesis of various substituted coumarin pyrazole benzimidazoles.

12.Emriye .*et.al.,(*2016),

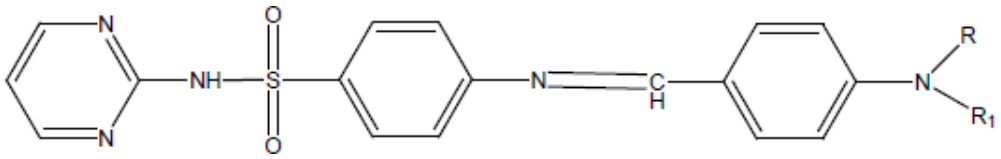


Reported potentially biological active new Schiff bases were synthesized in good yield from 1-amino-4- methylpiperazine and aromatic aldehydes as a 3-nitro-benzaldehyde, 4-fluoro-benzaldehyde,3,4,5-trimethoxybenzaldehyde,3,4dichlorobenzaldehyde,4-diethylamino benzaldehyde, 2,5-dimethoxybenzaldehyde and 5-nitro-2-furaldehyde and structure of the synthesized compounds were elucidated by FTIR, LC-MS, 1H-NMR and 13C-NMR techniques.

13. Joydeb Acharjee,*et.al.,(*2015).,

Developed to explore and establish the utility and opportunities of microwave technology in carrying out common organic reactions like esterification, hydrolysis, benzoin condensation, benzilic acid rearrangement, Wolf-Kishner reduction and Cannizzaro reaction. Our aim was to use an environment-friendly green chemistry approach in carrying out the reactions, thus causing less exposure to hazardous chemicals.

14. K.Hariprasath,*et.al*.,(2014).,



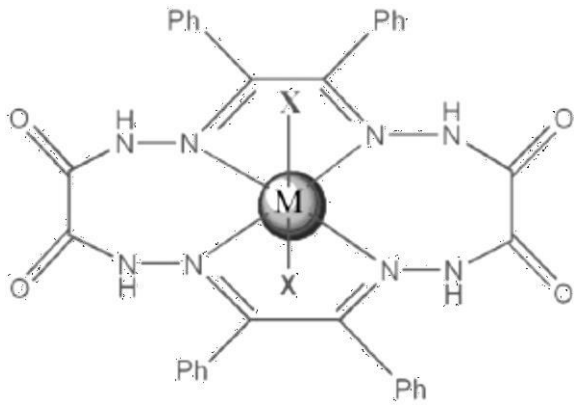
Synthesized schiff' base of sulphadiazine on treating with aromatic aldehydes like para diethyl amino benzyldehyde and paradimethyl amino benzyldehyde. The synthesized schiff's bases were converted to its cationic amphiphilic bases by treating with methyl iodide.

The cationic schiff bases were converted to metal complexes by treating with metals like copper

chloride (CuCl2), zinc chloride (ZnCl2) and cadmium chloride (CdCl2).

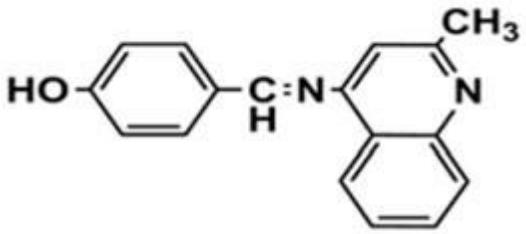
All the synthesized compounds were characterized by elemental analysis, IR and H1 NMR. Synthesized compounds were screened for anti-inflammatory and antidepressant activity.

15. Hina Zafarey.*et.al.*,(2014).,



Reported condensation reaction between 1,2-diphenylethane-1,2-dione dihydrazone (DPEDDH) and dimethyl or diethyloxalate in methanol resulted in a novel Schiff base octaazamacrocyclic ligand, (L): (6,7,14, 15-tetraoxa-2,3,10,11-tetraphenyl-1,4,5,8,9,12,13,16-octaazacyclohexadecane-1,3,9,11-tetraene). Subsequently metal complexes of the type [MLX2] and [CuL]X2; (M = Mn(II), Co(II), Ni(II) and Zn(II); X = Cl or NO3) were synthesized by the reaction of the free macrocyclic ligand (L) with the corresponding metal salts in 1:1 molar ratio. These complexes were characterized on the basis of analytical data, molar conductivity and magnetic susceptibility measurements, ESI-mass, IR, NMR (1H and 13C), EPR and electronic spectral studies. The thermal stability of the complexes was also studied by TGA and DTA analyses. These studies show that all the complexes have octahedral arrangement around the metal ions except copper complexes which are square planar. The ligand and its complexes were screened for their antibacterial activity in vitro against Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria and were also studied for their anticancer activity against the human cancer cells lines: HeLa (Human cervical carcinoma), MCF7 (Human breast adenocarcinoma) and Hep3B (Human Hepatocellular carcinoma). The recorded IC50 values for the tested compounds show moderate to good cytotoxicity against these cancer cell lines.

16. Ismet Kaya.,*et.al.,(*2014).,

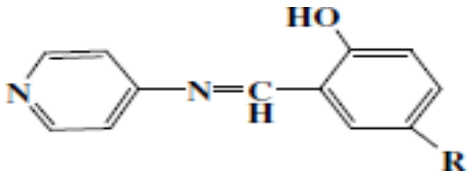


A series of imine polymers from 4-amino-2-methylquinoline (4-aminoquinaldine) were synthesized by a chemical oxidative polycondensation in aqueous alkaline medium with aldehydes, such as 4-hydroxy benzaldehyde, salicylaldehyde and o-vanillin by NaOCl as oxidants at optimum reaction temperature of 90 °C. The findings about polymerization of 4-amino-2-methylquinoline are reported. The molecular structures of synthesized compounds were characterized by the FT-IR, UV–vis, 1H NMR and 13C NMR analyses. Using thermogravimetric analysis-differential thermal analysis, size exclusion chromatography and the solubility tests, the characterization of all compounds could be identified. The initial degradation temperatures of the polymers were found in the range of 140–203 °C. UV–vis measurements give information about the optical band (Eg) gaps. Fluorescence measurements were carried out to obtain the maximum Photoluminescence (PL) intensities. PL properties of the synthesized materials were determined in solution forms. The spectral analysis outcomes signified a multicolor emission behavior when irradiated at different wavelengths.Cyclic voltammetry is an effective method to estimate the HOMO and LUMO energy levels and electrochemical (E0g)band gaps of the polymers. Optical and electrochemical band gaps of the polymers were lower than those of the monomers, indicating the more conjugated structures of the polymers.

17. Tushar Datta apsunde.*et.al.*, (2013).,

Reported Various functionalized nicotine and anabasine analogues are synthesized via a three-step sequence that exploits a microwave assisted iridium-catalyzed N-heterocyclization of 1,4- and 1,5-diols for the construction of the pyrrolidine and piperidine ring systems. The microwave-assisted N-heterocyclization furnishes derivatives of nicotine and anabasine.

18. Cordelia.u.*et.al*.,(2013).,



Synthesized Six Schiff bases, namely, N-(2-hydroxylbenzylidene)pyridine-4- amine,N-(2-hydroxylbenzylidene)pyridine-2-amine, N-(5- nitro-2-hydroxylbenzylidene)pyridin-4-amine,N-(5-nitro-2-hydroxylbenzylidene) pyridin-2-amine, N-(5-bromo2hydroxylbenzylidene)pyridin-4-amine,N-(5-bromo-2hydroxylbenzylidene) pyridin-2-amine derived from condensation reactions of 4-aminopyridine or 2-aminopyridine with salicylaldehye, 5-nitrosalicylaldehye and 5-bromosalicylaldehye were synthesized and characterized using elemental analysis, IR, NMR and Raman spectroscopic techniques. The effect of solvent on the electronic absorption spectra was examined in five solvents of different polarities, namely, 1,4-dioxane, chloroform, ethanol, acetonitrile and N,Ndimethyl formamide. The bands involving different electronic transitions were interpreted and regression coefficients calculated for the absorption band involving intermolecular charge transfer transition within the whole Schiff base molecule using an equation that relates the absorption maxima to empirical solvent parameters that depend on the dielectric constant, refractive index and hydrogen bonding ability of the solvents.

19. Solveigh C. Koeberle. *et.al*., (2012).,

Reported Hydrophilic moieties were introduced at the 7-, 8-,and 9-position of the 2-phenylamino-dibenzosuberones, improving physicochemical properties as well as potency. Extremely potent inhibitors were obtained, with half-maximal inhibitory concentration (IC50) values in the low nM range in a whole blood assay measuring the inhibition of cytokine release.

20. Faramarz Rostami-Charati.*et.al*.,*(*2012).,

One-pot synthesis of cyclopentanone derivatives from phosphorus ylide under lab-type microwave assisted methodology was described. The phosphorus ylides were obtained via the reaction of activated acetylenic compounds, ethyl 4-chloroacetoacetate and triphenylphosphine. The structure of phosphorus ylides was assigned by 1H, 13C and 31PNMR.

21.A.S.P.Azzouz*. et.al*.,(2012).,

Synthesized the fifteen imines derived from 2-acetyl pyridine ,3 or 4 –hydroxy benzaldehyde and m-anisaldehyde with aromatic primary amines by standard method . These imines include namely ,hydroxylamine hydrochloride,o,m,p-amino phenols ,4-amino naphthol ,bromo or chloro aniline and p-anisidine . This seems important from chemistry point of view as in the elucidation of tautomerism reactions happen in some oximes and phenolic oximes .

22. Theivendren Panneer Selvam.*et.al.,(*2011).,

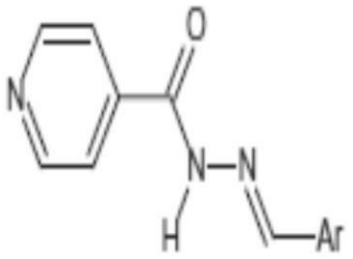
A series of 1-(4-substitutedphenyl)-3-phenyl-1H-pyrazole-4-carbaldehydes 4a–l have been synthesized and tested for their biological activities. Formation of the pyrazole derivatives was achieved by treating with Vilsmeier-Haack reagent.

23. Lokman H. Choudhury.*et.,al*.,(2011).,

Developed various applications of imines in multicomponent reactions. Imines represent a challenging array of functionalities that can be employed to explore chemical space efficiently and identify small molecular probes for biology. We believe that we have painted an accurate picture of the advances made by imines in the field of MCR chemistry, and this review may be a convincing case for the need todevelop new MCR processes involving the versatile reactivity of imines towards many other substrates to enlarge the scope of this field, allowing the facile and selective construction of highly functionalised small organic molecules of high synthetic and biological value.

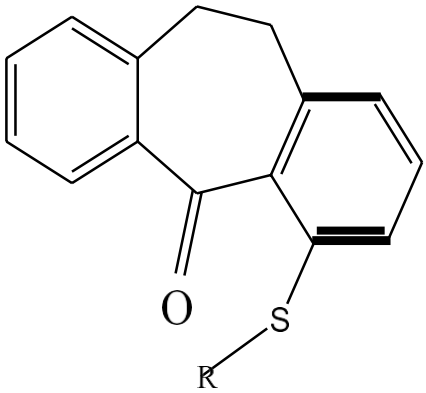
24. Asha B. Thomas.*et.,al.,(*2011).,

Reported the synthesis and pharmacological activity of N0-[(1Z)-(substituted aromatic) methylidene] pyridine-4-carbohydrazides and N-[3-chloro-2-(substituted aromatic)-4-oxoazetidin-1- yl]pyridine-4-carboxamides. Synthesis of 2-azetidinones was performed by novel methods of stirring and sonication involving the cyclocondensation of the appropriate Schiff's bases with chloroacetyl chloride, followed by the addition of triethyl amine in the presence of molecular sieves



The compounds were investigated for their antidepressant activity,compoundsN0-[(1Z)-(2,5dimethoxyphenyl) methylidene] pyridine-4-carbohydrazide and N-[3-chloro-2- (2,5-dimethoxyphenyl)-4-oxoazetidin-1-yl]pyridine-4-carboxamide with 2,5-dimethoxy substitution on the aryl ring exhibited the highest antidepressant activity. In the elevated plus maze test and passive avoidance test in mice for the evaluation of nootropic activity.

25. Paulo R.C. Martins *et.al.,(*2010).,

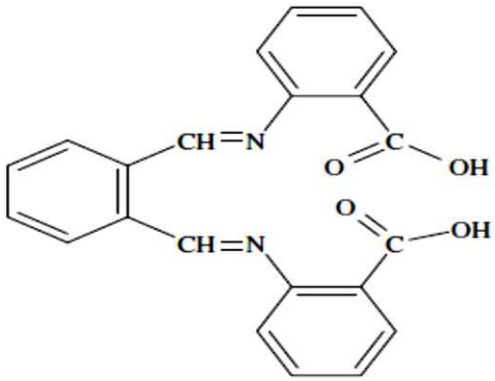


Synthesized the series of nine 4-thio dibenzosuberone derivatives (10,11-dihydro-5Hdibenzo a,d cycloheptane-5-one derivatives). Ullmann´s reaction was used to synthesize six 4-thio dibenzosuberone derivatives from 4-iodo dibenzosuberone . Compound was synthesized from dibenzosuberone through the use of TTFA [thallium (III) trifluoroacetate] and KI. Hydrolysis of yielded derivative.

26. Renata Wietecha-Posłuszny *et.al.*, (2010).,

Developed, optimize, and validate a modern, rapid method of preparation of human hair samples, using microwave irradiation, for analysis of eight tricyclic antidepressants (TCADs): nordoxepin, nortriptyline, imipramine, amitriptyline, doxepin, desipramine, clomipramine, and norclomipramine. It was based on simultaneous alkaline hair microwave-assisted hydrolysis and microwave-assisted extraction (MAH–MAE). Extracts were analyzed by high-performance liquid chromatography with diode-array detection (HPLC–DAD). A mixture of n-hexane and isoamyl alcohol (99:1, v/v) was used as extraction solvent and the process was performed at 60°C.

27. Sayed M. *et.al.,(*2010).,

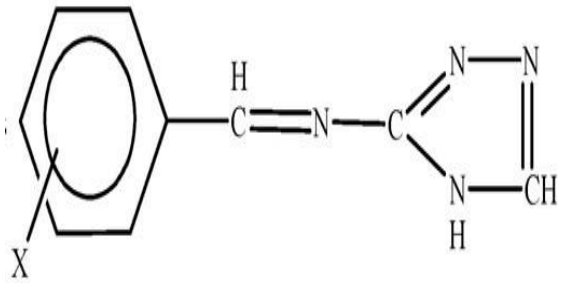


Synthesized new Schiff base (H2L) ligand is prepared via condensation of o-phthaldehyde and 2-aminobenzoic acid in 1:2 ratio. Metal complexes are prepared and characterized using elemental analyses, IR, solid reflectance, magnetic moment, molar conductance, 1H NMR, ESR and thermal analysis (TGA). From the elemental analyses data, the complexes were proposed to have the general formulae [MCl(L)(H2O)]Æ2H2O (where M =Cr(III) and Fe(III)); [M(L)]ÆyH2O (where M= Mn(II), Ni(II), Cu(II) and Zn(II), y=1–2) and [M(L)(H2O)n]ÆyH2O (where M =Co(II) (n = y =2), Co(II) (n= y= 1), Ni(II) (n= 2, y= 1). The molar conductance data reveal that all the metal chelates were non-electrolytes. IR spectra show that H2L is coordinated to the metal ions in a bi-negative tetradentate manner with NOON donor sites of the azomethine-N and carboxylate- O. The 1H NMR spectral data indicate that the two carboxylate protons are also displaced during complexation.

28.Sham M.*et.al.,*(2009).,

A number of N-substituted cyclic imides have been synthesized in very high yields, by condensation of various diacids 2, 4, 6, and 8 with different amines under microwave irradiation. These compounds were screened for anticancer and anti-inflammatory activities, and compounds exhibited anticancer activity against colon (COLO 205) cancer better than 5-fluorouracil and mitomycin-C.

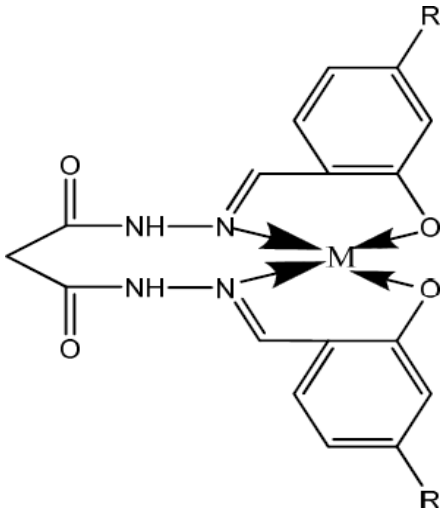
29.Y.M. Issa.*et.al.,*(2009).,



Reported heterocyclic Schiff bases derived from 3-amino-1,2,4-triazole and different substituted aromatic aldehydes are prepared and subjected to 1H NMR, 13C NMR and mass spectral analyses. 1H NMR spectra in DMSO exhibit a sharp singlet within the 9.35–8.90ppm region which corresponds to the azomethine proton. The position of this signal is largely dependent on the nature of the substituents on the benzal moiety. It is observed that the shape, position and the integration value of the signal of the aromatic proton of the triazole ring are clearly affected by the rate of exchange, relaxation time, concentration of solution as well as the solvent used. 13C NMR is taken as substantial support for the results reached from1H NMR studies. The mass spectral results are taken as a tool to confirm the structure of the investigated compounds.

30. SEEMA RAJENDRA SAPALE.*et.al.,*(2009).,

Synthesized novel Schiff base from substituted 2-hydroxy benzaldehydes and dihydrazide. These Schiff bases were used to prepare metal complexes. The complexes were distinctly coloured and stable to atmospheric conditions.



The Schiff bases were shown to behave as a tetadentate ligand. The metal complexes were proposed to square planar geometry and 1:1 metals to ligands ratio was suggested, Some of these Schiff bases and their metal complexes were screened for their biological activities (Antibacterial and antifungal) One of the ligand was studied for spectrophotometric determination of Cu (Extractive spectrophotometry), The stability constants of their complexes with Copper ions and Nickel ions, have been studied. Ion-selective electrode for Ni was developed.

31. Laak AMT *et al.,(*2003).,

Reported on QSAR and molecular modelling studies which have been performed on both classical and non-classical histamine H1- antagonists were evaluated. It is concluded that cyproheptadine with the piperidylene ring in a boat conformation can be used as a template for further modelling studies.

32.P.O. PATIL *et.al*.,(2008).,

A series of 1,3,5-triphenyl-2-pyrazoline derivatives were synthesized through microwave assisted condensation of 1,3-diphenyl-2-propene-1-one (chalcones) with phenylhydrazine using dry acetic acid as cyclizing agent and evaluated for antidepressant activity. The chemical structures of the compounds were confirmed by means of their IR, GC-MS and 1H NMR spectroscopic data. All synthesized 2-pyrazoline derivatives were found to possess ssignificant antidepressant activity.

33.Wang L *et.al,.(*2007).,

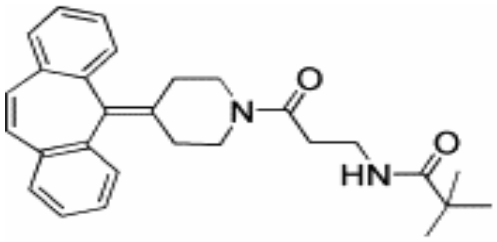
Reported on the design, synthesis and biological activity of 5,10- dihydro-dibenzo[b,e][1,4]diazepin-11-one-based potent and selective Chk-1 inhibitors.

34. Stone CA *et.al.,(*2006).,

Reported on the antihistaminic-antiserotonin actions of 1- methyl-4-(5 -dibenzo[a,e] cycloheptatrien ylidine)-piperidine hydrochloride (cyproheptadine) have been demonstrated in several different experimental situations. The anti-serotonin actions of cyproheptadine included an ability to block the vasopressor actions of serotonin in the anesthetized, ganglionic blocking agent treated dog, a capacity to block the spasmogenic effect of serotonin on the isolated rat uterus and an inhibitory effect ofthe swelling and edema produced by the local injection of serotonin in the hind feet of rats.

The antihistaminic and antiserotonin actions of cyproheptadine were compared with similar properties of a variety of other agents, including lysergic acid diethylamide and other simple indole derivatives, chlorpromazine, chlorpheniramine, pyrilamine, thenalidine, promethazine, trimeprazine, thenylpyramine and diphenhydramine.

35.Yamamoto T.*et.al.,(*2006).,



Reported on antiallergic drug cyproheptadine is known to have inhibitory activities for L-type calcium channels in addition to histamine and serotonin receptors. Since they found that cyproheptadine had an inhibitory activity against N-type calcium channel, cyproheptadine was optimized to obtain more selective N-type calcium channel blocker with analgesic action. As a consequence of the optimization, they found N-[3-(4-dibenzo[a,d]cyclohepten-5-ylidene-piperidin-1-yl)-3-oxo-propyl]-2,2-dimethyl-propion- amide with potent N-type calcium channel

inhibitory activity which had lower inhibitory activities against L-type calcium channel, histamine (H1), and serotonin (5- HT2A) receptors than those of Cyproheptadine.N-[3-(4-dibenzo[a,d]cyclohepten-5-ylidene-piperidin-1-yl)-3-oxo-propyl]-2,2-dimethyl-propionamide showed an oral analgesic activity in rat formalin-induced pain model.The synthesis, structure–activity relationship study, and biological testings of novel series of cyproheptadine derivatives with N-type calcium channel inhibitory activity were described.

36.Shou-Yuan Lin.*et.al.*, (2006).,

One-pot synthesis of benzimidazoles from diamines and carboxylic acids was developed under microwave irradiation condition, which provided a practical and efficient method for high-throughput synthesis of this important class of heterocyclic compounds.

37.Bhatt PV*et.al*,.(2005).,

The synthesis of 5H-dibenzo(b,f) azepine-5- carboxylic acid [3-chloro-2-(sustituted phenyl)-4-oxoazetidin-1-yl]amide from 5H-dibenzo(b,f) azepine-5-carbonyl chloride. 5H-dibenzo(b,f)azepine-5- carbonyl chloride was prepared from 5H-dibenzo(b,f)azepine by phosgenation and further treated with hydrazine hydrate. Final synthesis was achieved in presence of triethylamine.

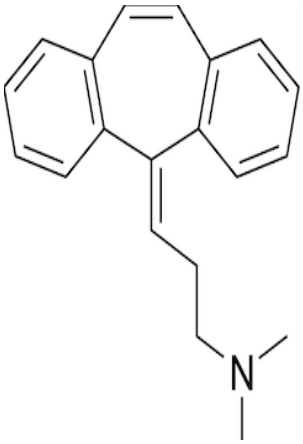
38. Padmavathi V *et.al*.,(2005).,

Study on the reactivity of 1,3-dimethyl-2,6- diphenyl-4-piperidone.The reactive functionalities,keto and keto methylene were explored to obtain important heterocycles furanylmetylene piperidone, pyridoindole by using microwave, ultrasound and conventional methods.

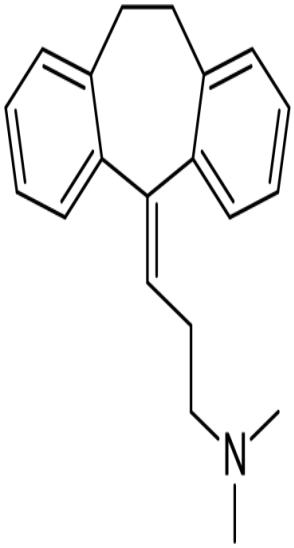
40.LOZA Mi,*et.al*.,(2003).,

Reported on a series of cyproheptadine related compounds which was synthesized and tested pharmacologically. Structure activity relationships were studied by Mulliken net charges, molecular electrostatic potentials, and conformational analysis; activities are better correlated with electrostatic potentials than with net charges.

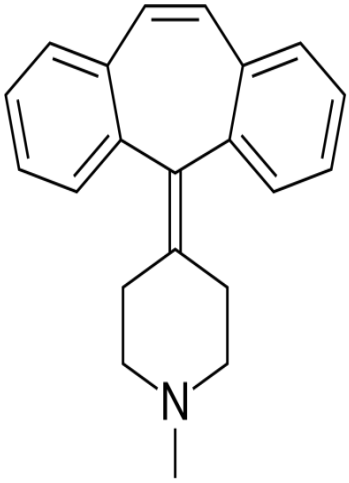
39.Honda M,*et al.,(*2003),



CYPROHEPTADINE



AMITRIPTYLINE



CYCLOBENZAPRINE

Reported that the structure of cyclobenzaprine is similar to those of amitriptyline (a tricyclic antidepressant) and cyproheptadine (5-HT receptor antagonist). In the present study, an attempt was made to elucidate the relationship between 5-HT2 receptor antagonistic and inhibitory effects of cyclobenzaprine,amitriptyline, cyproheptadine and ketanserin (a 5-HT2 receptor antagonist) on the spinal reflexes. To evaluate the antagonistic effects on 5-HT2 receptors of these drugs invivo, they studied the effects on the facilitatory actions of 1-(2,5-dimethoxy-4-iodophenyl)- 2-aminopropane (DOI), a selective 5-HT2 receptor agonist, on flexor reflexes and spinal mono- and polysynaptic reflex potentials in spinalized rats. The involvement of serotonergic nervous system in the inhibitory effects of these drugs on spinal reflex potentials was studied in 5-HT depleted intact (nonspinalized) rats.

41. Groot MJ *et.al.,(*1999).,

Reported a novel approach to predicting P450 mediated drug metabolism.CYP2D6 catalyzed N-dealkylation reactions and qualitative metabolite predictions using combined protein an pharmacophore model for CYP2D6.

42. Zhang MQ *et.al.,(*1997).,

Reported on a novel series of cyproheptadine derivatives, in which an amino acid or a dipeptide moiety was introduced at the piperidine nitrogen, have been synthesized. The amino acid and dipeptide moieties were taken as part of leukotriene D4 (LTD4) pharmacophore. One compound, (S)-2- benzyloxycarbonyl-amino-3-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5-yloxy) piperidin-1-yl]propionic acid was tested in an invitro guinea-pig asthma model and does not readily pass the blood-brain barrier, and therefore is unlikely to cause sedating side-effects at a therapeutic dose.

43. Nakagami Y,*et.al*.,(1986).,

Reported on the effects of serotonin, cyproheptadine and reserpine on corticotropin-releasing factor (CRF) release from the rat hypothalamus, and the effect of cyproheptadine on CRF-induced adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary (AP) invitro using a perifusion system for rat hypothalami and AP, and a rat CRF radioimmunoassay. In addition an anti-serotonergic mechanism is involved in the inhibitory action of cyproheptadine.

44. Remy DC,*et.al*.,(1977).,

Reported on a series of cyproheptadine derivatives having furan nuclei fused to the 10,11-vinylene bridge has been prepared. None of the compounds retain the potent antiserotonin and antihistaminic actions of cyproheptadine. 1-Methyl-4-(1-methyl-8H-dibenzo[a,e]furo[3,4-c]cyclohepten-8-ylidene)piperidine(7),1-methyl-4-(1,3-dihydro-1-oxo-8H-[3,4,6,7]cyclohepta[1,2-c]furan-8ylidene)piperidine retained the peripheral anticholinergic activity of cyproheptadine.

CHAPTER III

AIM AND OBJECTIVE

AIM AND OBJECTIVE

An extensive literature review revealed that dibenzosuberenone and Schiff's bases exist a wide range of biological activity. Based on the above observations, an attempt has been made to develop novel schiff's base of dibenzosuberenone moiety by microwave assisted synthesis.

AIM:

- Drug design, molecular docking studies, microwave assisted synthesis and characterization of novel Schiff's base of Dibenzosuberenone derivative as antihistamine and anti-Depressant is proposed.

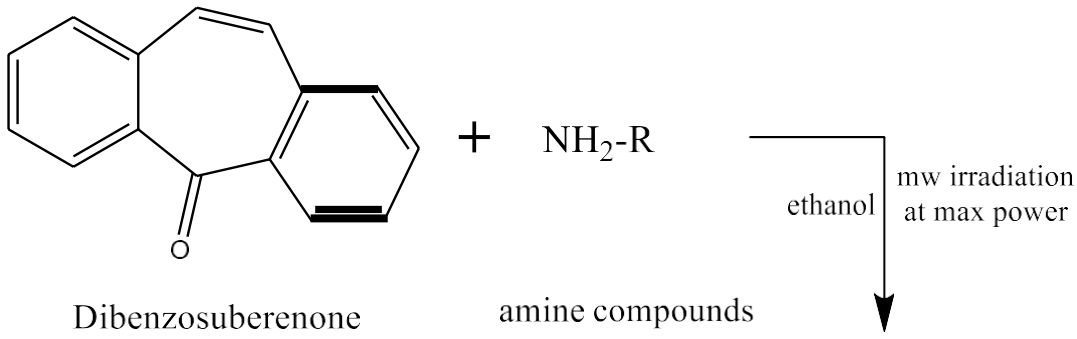
OBJECTIVE OF STUDY:

- To design the molecules based on the selected nucleus and perform the molecular docking studies.
- To synthesize a series of novel Schiff's bases of dibenzosuberenone derivatives by using microwave irradiation technique.
- To characterization of the synthesized compounds by following methods
    - Thin layer chromatography.
    - Ultra-violet spectroscopy.
    - FT-IR.
    - Nuclear Magnetic Resonance Spectroscopy.
    - MASS spectroscopy.

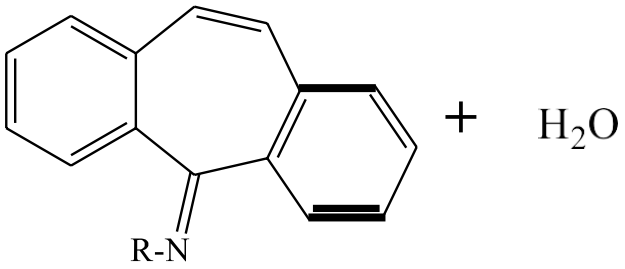
CHAPTER VI

SCHEME OF REACTION

SCHEME OF REACTION



Dibenzosuberenone amine compounds



Schiff base of dibenzosuberenone derivatives

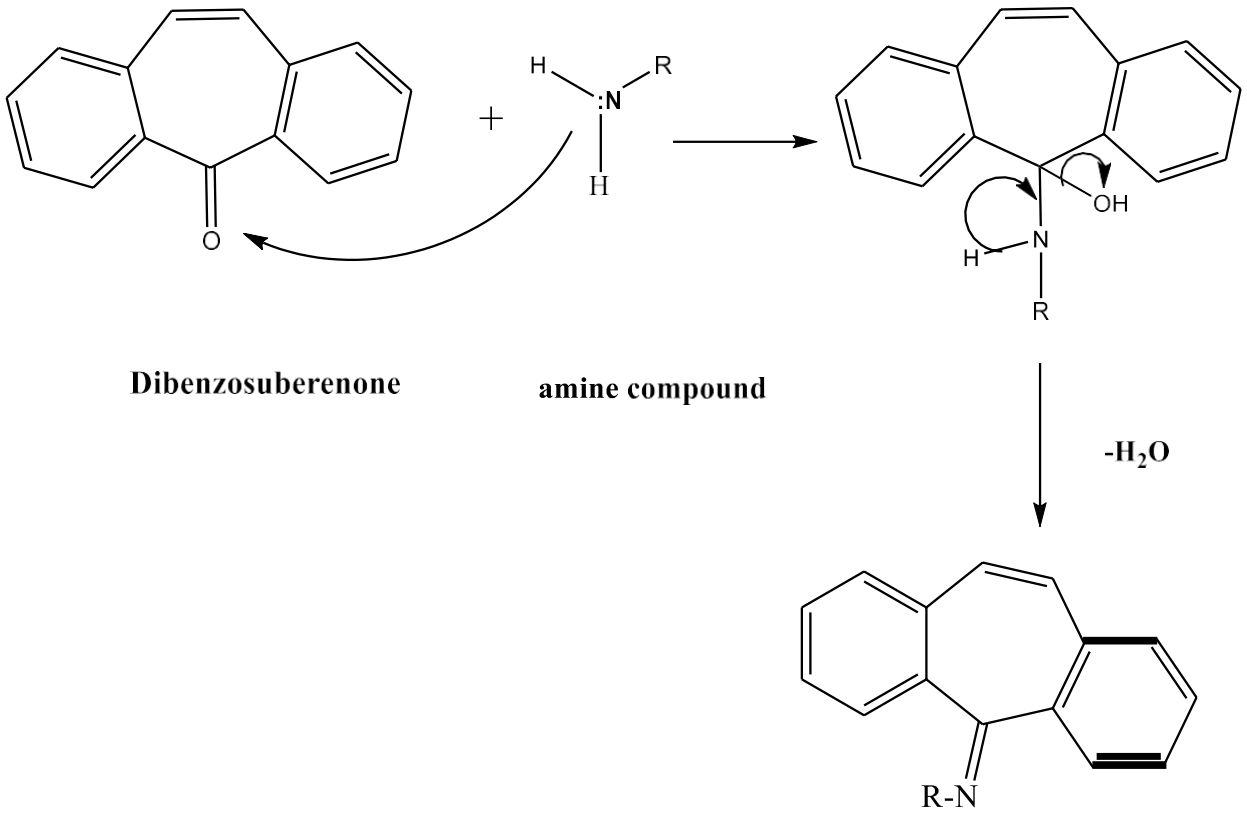
$R_1 = C_6H_5NHNH_2$

$R_2 = C_6H_3(NO_2)NHNH_2$

$R_3 = NH_2OH$

$R_4 = H_2NNHCONH_2$

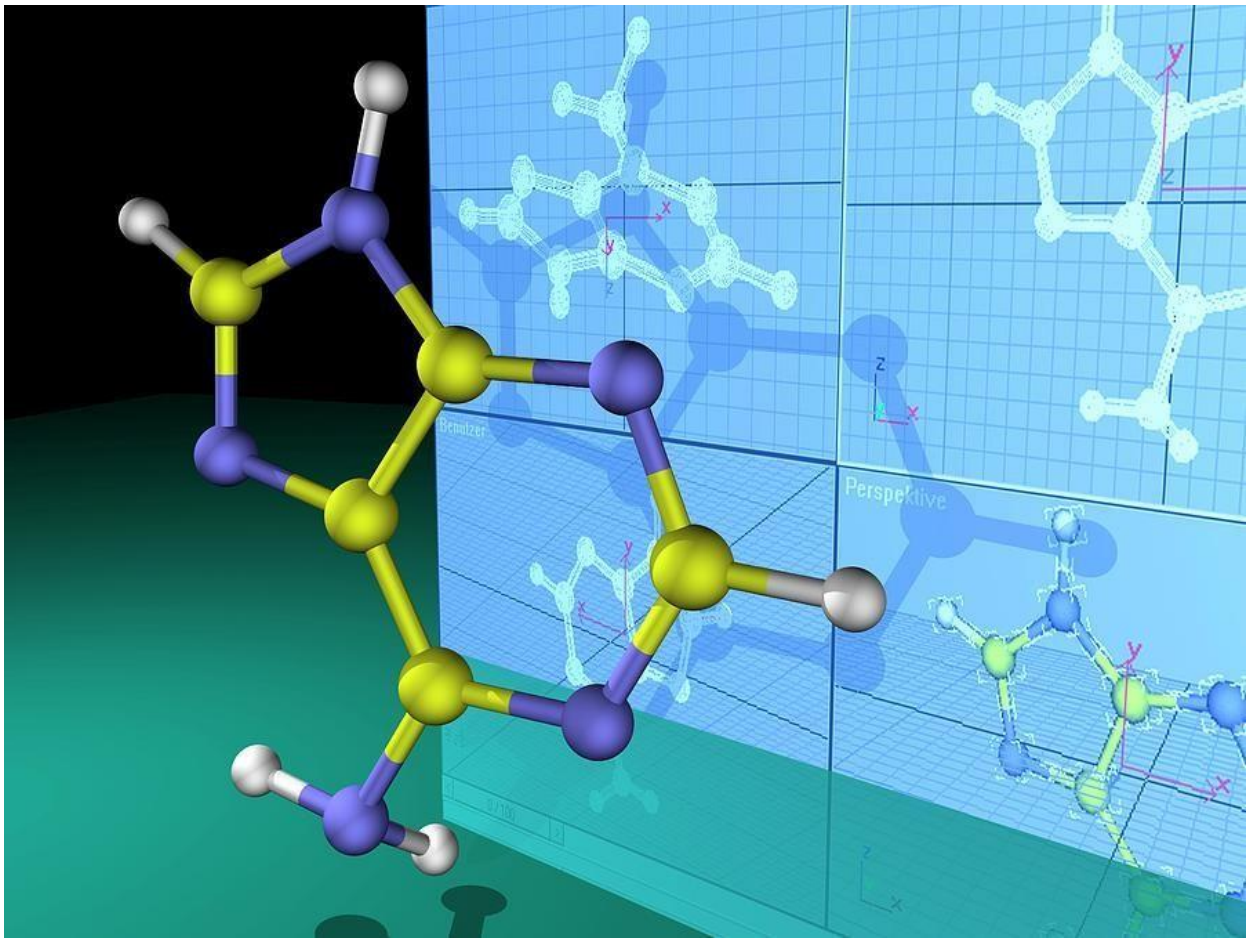
MECHANISM OF REACTION



Dibenzosuberenone **amine compound**

schiff base of dibenzosuberenone derivatives

CHAPTER V



MOLECULAR DESIGN

MOLECULAR DESIGN

Molecular design is the process of finding new medicines based on the knowledge of biological target, it enabled the chemist to predict the structure and it also allows the medicinal chemist to evaluate the interaction between a compound and its target site before synthesizing a compound so as to increase the ability by reducing the side effects.

VARIOUS SOFTWARES USED:

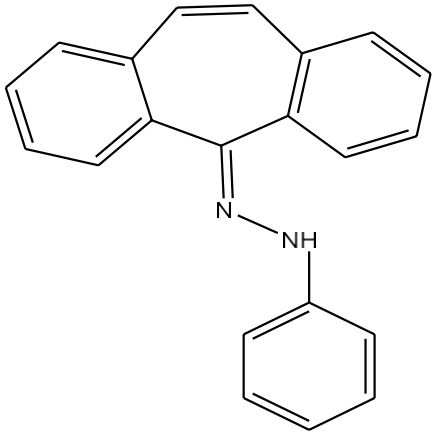
- ChemSketch
- Mol inspiration
- Swiss ADME

Chemsketch

This software is used to predict the following properties:

- Molecular weight
- Molecular formula
- Composition
- Molar volume
- Parachor
- Index of refraction
- Surface tension
- Density
- Dielectric constant
- Polarizability
- Monoisotopic mass
- Nominal mass
- Average mass

COMPOUND 1



Molecular Formula: $C_{21}H_{16}N_2$

Formula Weight: 296.36514

Composition: C(85.11%) H(5.44%) N(9.45%)

Molar Refractivity: 95.24 ± 0.5 cm^3

Molar Volume: 265.9 ± 7.0 cm^3

Parachor: 685.4 ± 8.0 cm^3

Index of Refraction: 1.635 ± 0.05

Surface Tension: 44.1 ± 7.0 dyne/cm

Density: 1.11 ± 0.1 g/cm^3

Dielectric Constant: Not available

Polarizability: 37.75 ± 0.5 $10^{-24}cm^3$

Monoisotopic Mass: 296.131349 Da

Nominal Mass: 296 Da

Average Mass: 296.3651 Da

M+: 296.1308 Da

M-: 296.131897 Da

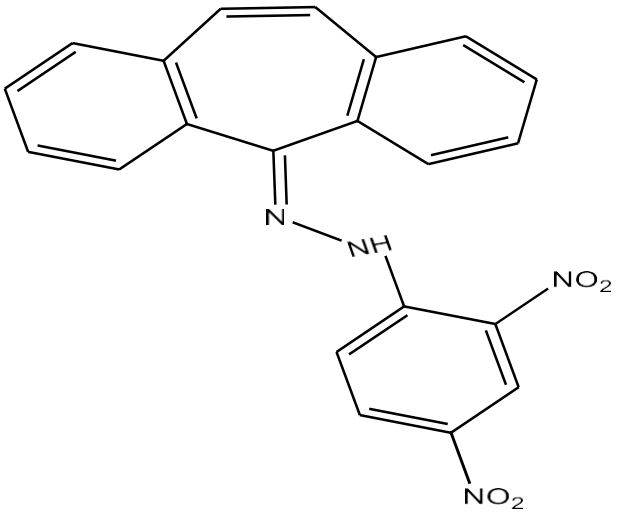
[M+H]+: 297.138625 Da

[M+H]-: 297.139722 Da

[M-H]+: 295.122975 Da

[M-H]-: 295.124072 Da

COMPOUND 2



Molecular Formula: $C_{21}H_{14}N_4O_4$

Formula Weight: 386.36026

Composition: C(65.28%) H(3.65%) N(14.50%) O(16.56%)

Molar Refractivity: 106.56 ± 0.5 cm^3

Molar Volume: 276.5 ± 7.0 cm^3

Parachor: 776.4 ± 8.0 cm^3

Index of Refraction: 1.697 ± 0.05

Surface Tension: 62.1 ± 7.0 dyne/cm

Density: 1.39 ± 0.1 g/cm^3

Dielectric Constant: Not available

Polarizability: 42.24 ± 0.5 $10^{-24}cm^3$

Monoisotopic Mass: 386.101505 Da

Nominal Mass: 386 Da

Average Mass: 386.3603 Da

M+: 386.100956 Da

M-: 386.102054 Da

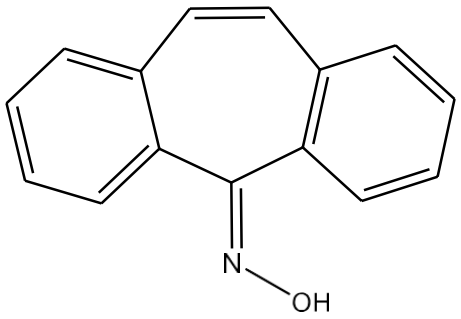
[M+H]+: 387.108781 Da

[M+H]-: 387.109879 Da

[M-H]+: 385.093131 Da

[M-H]-: 385.094229 Da

COMPOUND 3



Molecular Formula: $C_{15}H_{11}NO$

Formula Weight: 221.25394

Composition: C(81.43%) H(5.01%) N(6.33%) O(7.23%)

Molar Refractivity: 67.93 ± 0.5 cm^3

Molar Volume: 190.5 ± 7.0 cm^3

Parachor: 494.5 ± 8.0 cm^3

Index of Refraction: 1.631 ± 0.05

Surface Tension: 45.3 ± 7.0 dyne/cm

Density: 1.16 ± 0.1 g/cm^3

Dielectric Constant: Not available

Polarizability: 26.93 ± 0.5 $10^{-24}cm^3$

Monoisotopic Mass: 221.084064 Da

Nominal Mass: 221 Da

Average Mass: 221.2539 Da

M+: 221.083515 Da

M-: 221.084613 Da

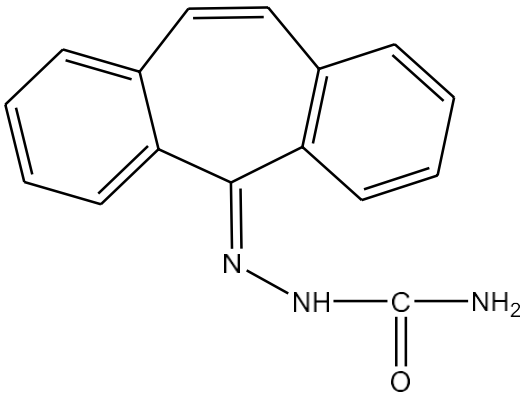
[M+H]+: 222.09134 Da

[M+H]-: 222.092438 Da

[M-H]+: 220.07569 Da

[M-H]-: 220.076788 Da

COMPOUND 4



Molecular Formula: $C_{16}H_{13}N_3O$

Formula Weight: 263.29392

Composition: C(72.99%) H(4.98%) N(15.96%) O(6.08%)

Molar Refractivity: 77.51 ± 0.5 cm^3

Molar Volume: 208.1 ± 7.0 cm^3

Parachor: 560.0 ± 8.0 cm^3

Index of Refraction: 1.667 ± 0.05

Surface Tension: 52.4 ± 7.0 dyne/cm

Density: 1.26 ± 0.1 g/cm^3

Dielectric Constant: Not available

Polarizability: 30.72 ± 0.5 $10^{-24}cm^3$

Monoisotopic Mass: 263.105862 Da

Nominal Mass: 263 Da

Average Mass: 263.2939 Da

M+: 263.105313 Da

M-: 263.106411 Da

[M+H]+: 264.113138 Da

[M+H]-: 264.114236 Da

[M-H]+: 262.097488 Da

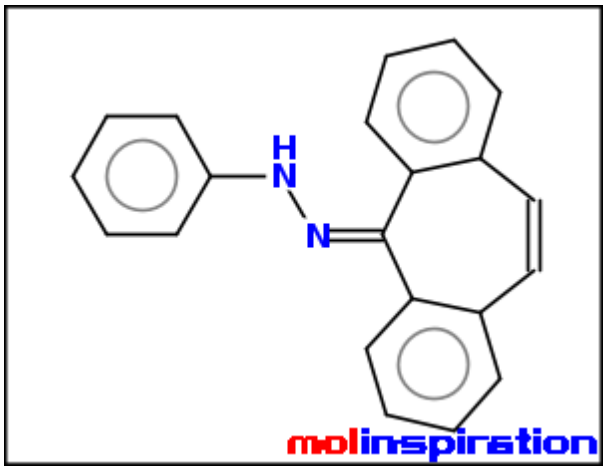
[M-H]-: 262.098586 Da

MOLINSPIRATION

Molinspiration software is used to calculate the following properties:

- Log P
- Molecular weight
- Number of H- bond donor
- Number of H- bond acceptor
- Number of rotatable bonds

Compound 1

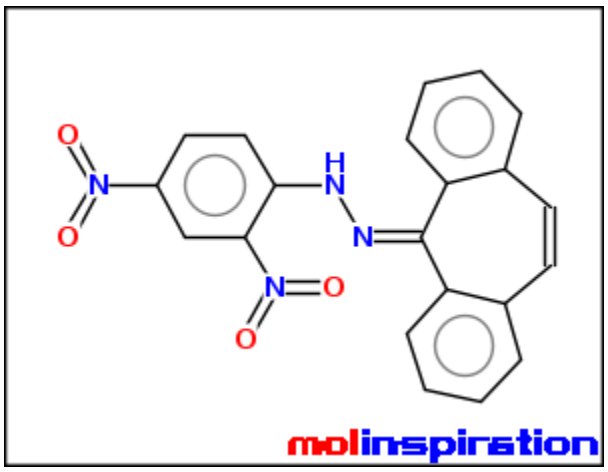


miLogP	4.78
TPSA	24.39
natoms	23
MW	296.37
nON	2
nOHNH	1
nviolations	0
nrotb	2
volume	279.10

Molinspiration bioactivity score v2021.03

GPCR ligand	-0.30
Ion channel modulator	-0.43
Kinase inhibitor	-0.01
Nuclear receptor ligand	-0.75
Protease inhibitor	-0.51
Enzyme inhibitor	-0.13

Compound 2



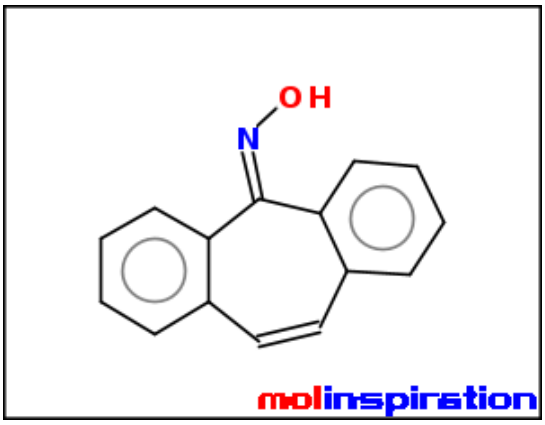
Molinspiration property engine v2021.10

miLogP	4.45
TPSA	116.04
natoms	29
MW	386.37
nON	8
nOHNH	1
nviolations	0
nrotb	4
volume	325.77

Molinspiration bioactivity score v2021.03

GPCR ligand	-0.36
Ion channel modulator	-0.50
Kinase inhibitor	-0.22
Nuclear receptor ligand	-0.81
Protease inhibitor	-0.58
Enzyme inhibitor	-0.23

Compound 3

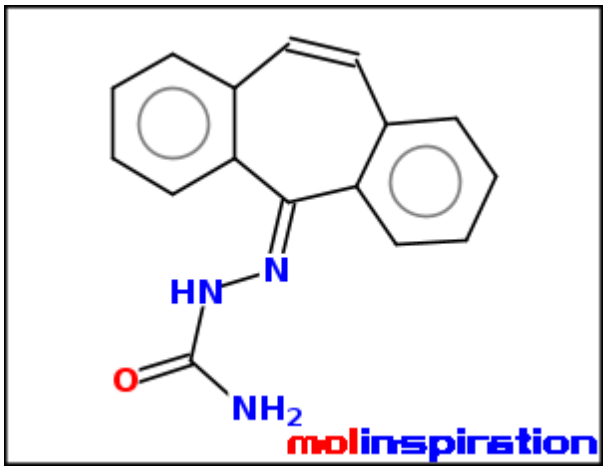


Molinspiration property engine v2021.10

miLogP	4.25
TPSA	32.59
natoms	17
MW	221.26
nON	2
nOHNH	1
nviolations	0
nrotb	0
volume	203.31

Molinspiration bioactivity score v2021.03
GPCR ligand -0.23
Ion channel modulator 0.02
Kinase inhibitor -0.09
Nuclear receptor ligand -0.51
Protease inhibitor -0.69
Enzyme inhibitor 0.02

Compound 4



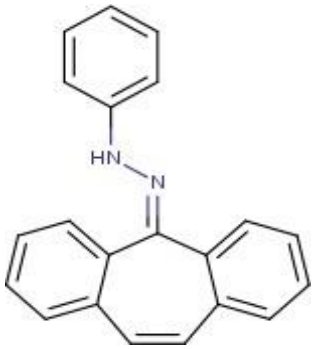
Molinspiration property engine v2021.10

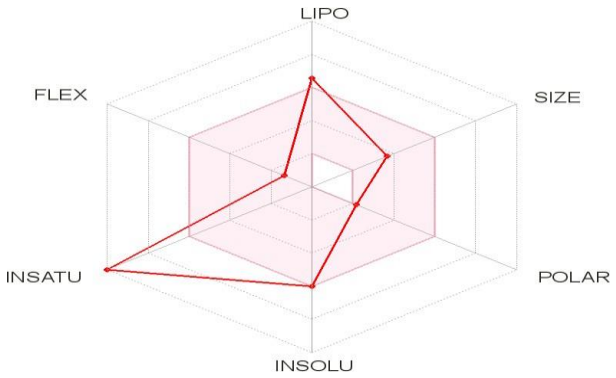
miLogP 3.61
TPSA 67.48
natoms 20
MW 263.30
nON 4
nOHNH 3
nviolations 0
nrotb 1
volume 237.96

Molinspiration bioactivity score v2021.03
GPCR ligand -0.30
Ion channel modulator -0.43
Kinase inhibitor -0.31
Nuclear receptor ligand -0.83
Protease inhibitor -0.46
Enzyme inhibitor -0.07

SwissADME

Compound 1



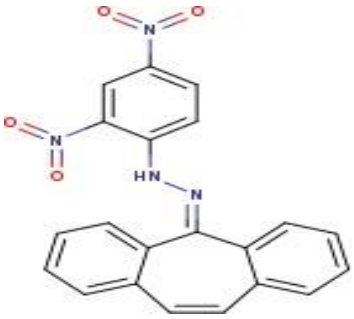


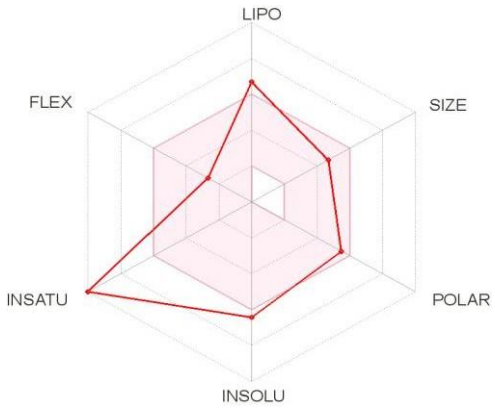
SMILES c1ccc(cc1)NN=c1c2ccccc2ccc2c1cccc2

Physicochemical Properties	
Formula	C21H16N2
Molecular weight	296.37 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	21
Fraction Csp3	0.00
Num. rotatable bonds	2
Num. H-bond acceptors	1
Num. H-bond donors	1
Molar Refractivity	96.90
TPSA	24.39 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.26
Log $P_{o/w}$ (XLOGP3)	6.00
Log $P_{o/w}$ (WLOGP)	4.73
Log $P_{o/w}$ (MLOGP)	4.28
Log $P_{o/w}$ (SILICOS-IT)	5.02
Consensus Log $P_{o/w}$	4.66
Water Solubility	
Log *S* (ESOL)	-6.00
Solubility	2.96e-04 mg/ml ; 9.97e-07 mol/l

Class	Poorly soluble
Log *S* (Ali)	-6.29
Solubility	1.52e-04 mg/ml ; 5.13e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.78
Solubility	4.95e-07 mg/ml ; 1.67e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.85 cm/s
Druglikeness	
Lipinski	Yes; 0 violation:
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	3.24

COMPOUND 2:



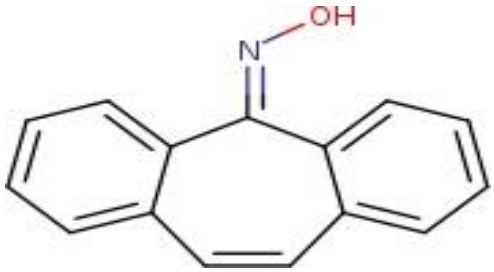


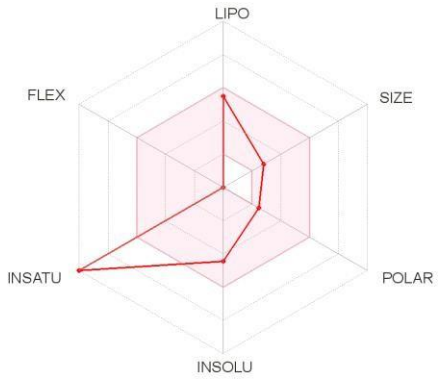
SMILES O=N(=O)c1cc(ccc1NN=c1c2ccccc2ccc2c1cccc2)N(=O)=O

Physicochemical Properties	
Formula	C21H14N4O4
Molecular weight	386.36 g/mol
Num. heavy atoms	29
Num. arom. heavy atoms	21
Fraction Csp3	0.00
Num. rotatable bonds	4
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	114.54
TPSA	116.03 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.73
Log $P_{o/w}$ (XLOGP3)	6.21
Log $P_{o/w}$ (WLOGP)	5.59
Log $P_{o/w}$ (MLOGP)	2.97
Log $P_{o/w}$ (SILICOS-IT)	1.42
Consensus Log $P_{o/w}$	3.78
Water Solubility	
Log *S* (ESOL)	-6.42
Solubility	1.47e-04 mg/ml ; 3.81e-07 mol/l
Class	Poorly soluble

Log *S* (Ali)	-8.43
Solubility	1.43e-06 mg/ml ; 3.70e-09 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.44
Solubility	1.41e-06 mg/ml ; 3.65e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.25 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: nitro_group
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.8

compound 3

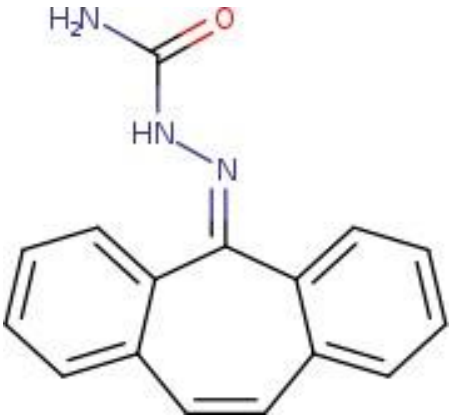


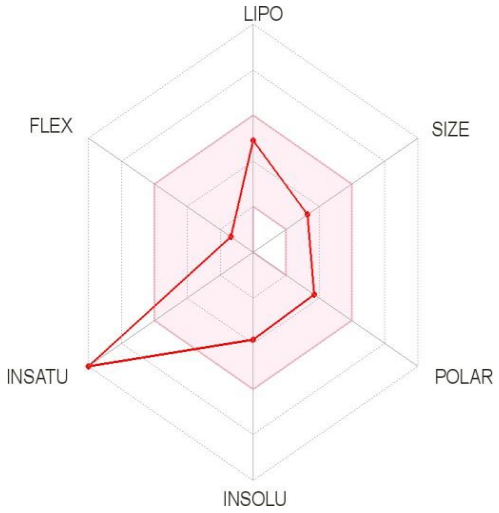


SMILES	ON=c1c2ccccc2ccc2c1cccc2
Physicochemical Properties	
Formula	C15H11NO
Molecular weight	221.25 g/mol
Num. heavy atoms	17
Num. arom. heavy atoms	15
Fraction Csp3	0.00
Num. rotatable bonds	0
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	68.80
TPSA	32.59 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.95
Log $P_{o/w}$ (XLOGP3)	4.11
Log $P_{o/w}$ (WLOGP)	3.28
Log $P_{o/w}$ (MLOGP)	2.82
Log $P_{o/w}$ (SILICOS-IT)	3.76
Consensus Log $P_{o/w}$	3.19
Water Solubility	
Log *S* (ESOL)	-4.45
Solubility	7.78e-03 mg/ml ; 3.52e-05 mol/l

Class	Moderately soluble
Log *S* (Ali)	-4.50
Solubility	6.99e-03 mg/ml ; 3.16e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-5.65
Solubility	4.95e-04 mg/ml ; 2.24e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-4.73 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: oxime_1, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW<250, XLOGP3>3.5
Synthetic accessibility	2.59

COMPOUND 4:





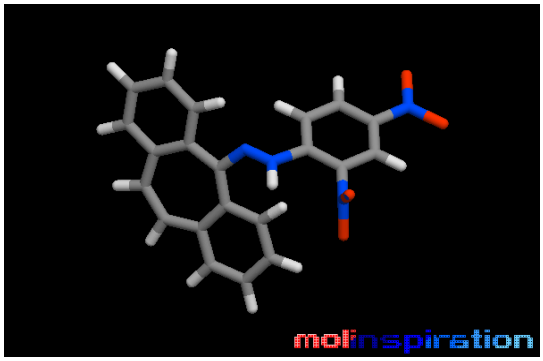
SMILES NC(=O)NN=c1c2ccccc2ccc2c1cccc2

Physicochemical Properties	
Formula	C16H13N3O
Molecular weight	263.29 g/mol
Num. heavy atoms	20
Num. arom. heavy atoms	15
Fraction Csp3	0.00
Num. rotatable bonds	2
Num. H-bond acceptors	2
Num. H-bond donors	2
Molar Refractivity	78.98
TPSA	67.48 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.76
Log $P_{o/w}$ (XLOGP3)	3.07
Log $P_{o/w}$ (WLOGP)	2.48
Log $P_{o/w}$ (MLOGP)	2.48
Log $P_{o/w}$ (SILICOS-IT)	2.60
Consensus Log $P_{o/w}$	2.48

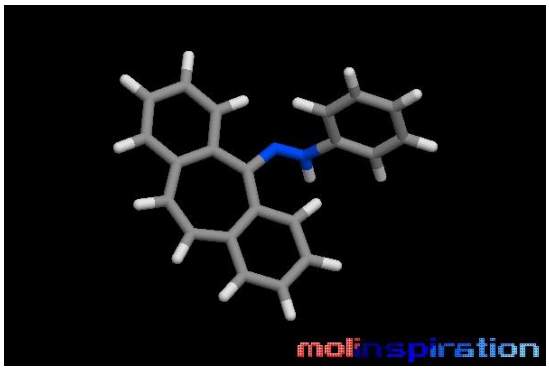
Water Solubility	
Log *S* (ESOL)	-3.83
Solubility	3.90e-02 mg/ml ; 1.48e-04 mol/l
Class	Soluble
Log *S* (Ali)	-4.15
Solubility	1.85e-02 mg/ml ; 7.01e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-5.86
Solubility	3.63e-04 mg/ml ; 1.38e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.73 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	Yes
Synthetic accessibility	3.14

3D VIEW OF DESIGNED COMPOUNDS

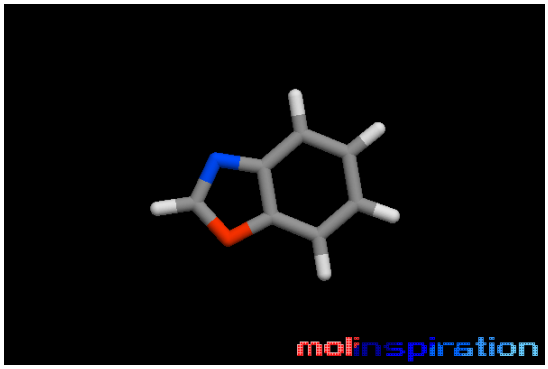
Compound 1:



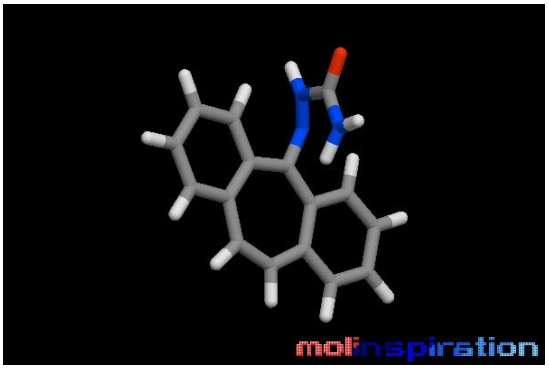
compound 2:



Compound 3:



compound 4:



CHAPTER VI

MATERIALS AND METHODS

LIST OF CHEMICALS

Table :1

S.NO	CHEMICALS	MANUFACTURER/ SUPPLIERS
1	Dibenzosuberenone	TCI chemicals
2	Phenylhydrazine	Central drug house
3	2,4 dinitro phenylhydrazine	Central drug house
4	Hydroxylamine	Central drug house
5	Semicarbazide	Central drug house
6	Ethanol	Central drug house
7	Ethylacetate	Central drug house
8	Petroleum ether	Central drug house
9	Methanol	Central drug house

MOLECULAR DOCKING STUDIES

DRUG DESIGN

Drug design is carried out using an automated docking program like GLIDE (grid based ligand docking with energetics) maestro 9.0 Schrodinger suites, MGL TOOLS. It helps search molecules (ligands) having maximum favorable interactions with a receptor (target) usually a protein. Ligand is a single molecule whereas receptor may include proteins, metals and cofactors. It runs on rigid and flexible docking modes. The later which one generates conformations automatically for the input of each ligand and gives out the best fit pose of the molecule been docked on the receptor.

TYPES

There are two major types of drug design.

- ligand based drug design,
- structure based drug design.

1.Ligand based

Ligand based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics. A molecule must possess in order to bind to the target. In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively a quantitative structure activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs.

2.Structure based

Structure based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as X-ray Crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively various automated computational procedures may be used to suggest new drug candidates.

DOCKING

Docking involves the fitting of a molecule into the target structure in a variety of positions, conformations and orientations. Molecular docking is used to predict the structure of intermolecular complex formed between two molecules. The small molecule called ligand usually interacts with protein's binding sites.Binding sites are areas of protein known to be active in forming of compounds. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes. It also predicts the strength of the binding, the energy of the complex, the types of signal produced and calculate the binding affinity between two molecules using scoring functions.

TYPES OF DOCKING

- Lock and key or rigid docking- In lock and key docking, both the internal geometry of the receptor and ligand is kept fixed and docking was performed.
- Induced fit or flexible docking- An enumeration on the rotations of one of the molecules (usually smaller one) is performed. For every rotation the surface cell occupancy and energy is calculated; later the most optimum pose is selected.

MOLECULAR DOCKING BY AUTODOCK

Autodock1.5.6 is an automated procedure for predicting the interaction of ligands with bio macromolecular targets. Progress in biomolecular x-ray crystallography continues to provide important protein and nucleic acid structures. These structures could be targets for bioactive agents in the control of animal and plant diseases, or simply key to the understanding of fundamental aspects of biology. In any docking scheme, two conflicting requirements must be balanced, the desire for a robust and accurate procedure, and the desire to keep the computational demands at a reasonable level. The ideal procedure would find the global minimum in the interaction energy between the substrate and the target protein and exploring all available degrees of freedom (DOF) for the system.

AutoDock combines two methods to achieve these goals: rapid grid-based energy evaluation and efficient search of torsional freedom. The current version of AutoDock® using the Lamarckian Genetic Algorithm and empirical free energy scoring function typically will provide reproducible docking results for ligands with approximately 10 flexible bonds. The quality of any docking results depends on the starting structure of both the protein and the potential ligand. The protein and ligand structure need to be prepared to achieve the best docking results.

DOCKING PROCEDURE

- Required Softwares And Servers
- Chem sketch or chem Draw – for strawing a structure and generate the smiles
- Online smile translator – to convert ligand to .pdb file
- Supporting softwares – pymol

Mgl tools (auto dock & auto grid).

Step: 1 Refining The Protein Download the required protein complex with the ligand from RCSB

Step:2 Download The Enzyme In Pdb Format Show in folder (downloads) – right click open with –pymol.

View – delete chains (unwanted) – delete ligand and water - Save as .pdb – saved in (bin) location

PREPARATION OF LIGAND

→ Draw the structure in chem. Sketch or chem. Draw and generate smiles

→ Online smile translator in google - enter smiles - pdb – 3D – click translate – open – rename from folder – copy to bin as .pdb file.

→ Saving and refining the enzyme:

→ Open autodock-file-read molecules-open from saved location (bin)-click on enzyme – open.

→ Select –select from string –atom-type HOH-add no charges-ok-dismiss.

→ Edit – hydrogrns – add – polar only – ok

→ Edit – charges – add kollman charges – ok

→ File – save – write PDB – browse – save in location (bin) – replace old enzyme – ok – overwrite – ok

→ Edit – delete – delete all molecules – continue

→ Saving and Refining the Ligand

→ Click ligand – input – open (from bin) – add gaster charges – ok

Ligand – torsion tree – detect root

Ligand – torsion tree – show root expansion

Ligand – torsion tree – choose torsions – done

Ligand – torsion tree – set no/ of torsions – dismiss

Ligand – torsion tree – hide root expansion

Ligand – torsion tree – show/hide root markers

Ligand – output – save as .pdbqt – saved in location (bin)

Edit – delete – delete all molecules – done

Grid –macromolecules (enzyme)-poen from location (bin)-ok-save as.pdbt file in location (bin).

Grid – set map types – open ligand – open from location (bin)

Grid – grid box – X- 60, Y-60 , Z-60 – file – close saving current

Grid – output – save as .gpf file – in location (bin)

Edit – delete - delete all molecules - continue

Docking – macromolecule – set rigid file name – open from location – click enzyme – (nothing will be seen on screen full blank only)

Docking – ligand – open from location (bin) – accept (default)

Docking – search parameters – genetic algorithm – accept (default)

Docking – docking parameters – accept (default)

Docking – output – lamarchin GA – file name .dpf – save in location (bin)

Commends

autogrid4.exe -p filename.gpf -l filename.glg - enter

check the bin for glg file

autodock4.exe -p filename.dpf -l file name.dlg - enter it takes long time so check bin and cygwin at interval of time after successful completion of .dlg file

autodock – edit – delete – delete all molecules- continue

ANALYSE THE RESULT

Analyse – docking – open - .dlg file from bin

Analyse – confirmations – play (don't close place at side)

Analyse – confirmations – load – click the first one

Analyse – docking – show interaction

Analyse – macro molecule – open from bin (enzyme)

Anallyse – docking – show interaction – don't close place at side – unclick display msms

On atoms unclick close contact

Set backgrounds

Ligand colouring

File – save – save as image – saved in a location (bin) – ok

LIPINSKI'S RULE

In an attempt to improve the predictions of druglikeness, the rules have spawned many extensions,

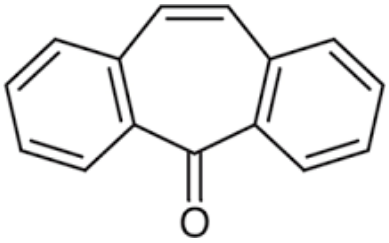
- Partition coefficient log P in −0.4 to +5.6 range
- Molar refractivity from 40 to 130
- Molecular weight from 180 to 500
- Number of atoms from 20 to 70 (includes H-bond donors [e.g. OHs and NHs] and H-bond acceptors [e.g. Ns and Os])
- Also the 500 molecular weight cutoff has been questioned. Polar surface area and the number of rotatable bonds has been found to better discriminate between compounds that are orally active and those that are not for a large data set of compounds in the rat.

  In particular, compounds which meet only the two criteria

  - 10 or fewer rotatable bonds and
  - Polar surface area no greater than 140 A2 are predicted to have good oral bioavailability.

REACTANT PROFILE

DIBENZOSUBERENONE:



Molecular formula: $C_{15}H_{10}O$
Molecular weight: 206.24

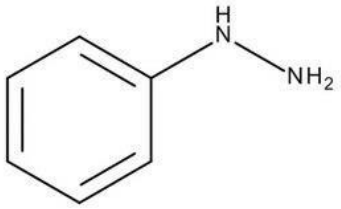
Appearance: white to pale yellow liquid or solid

Solubility: chloroform

Melting point: 88.5^0C

Boiling point: 210^0C

PHENYLHYDRAZINE:



Molecular formula: C_6H_8N
Molecular weight: 108.14

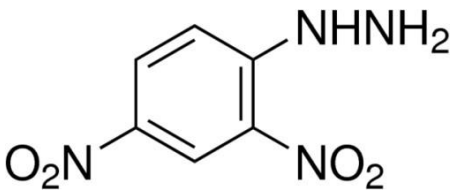
Appearance: white to slight blue powder

Solubility: dilute acid

Melting point: 21^0C

Boiling point: 240^0C

2,4 DINITROPHENYL HYDRAZINE:



Molecular formula: $C_6H_6N_4O_4$
Molecular weight: 198.14

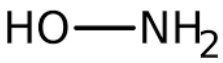
Appearance: red colour powder

Solubility: sulfuric acid

Melting point: 198^0C

Boiling point: 335^0C

HYDROXYLAMINE:



Molecular formula: H_3NO
Molecular weight: 33.03

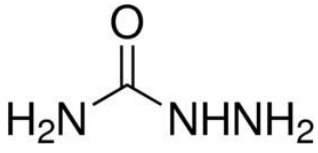
Appearance: white colour powder

Solubility: methanol

Melting point: 7^0C

Boiling point: 100^0C

SEMICARBAZIDE:



Molecular formula: CH_5N_3O
Molecular weight: 75.07

Appearance: white colour powder

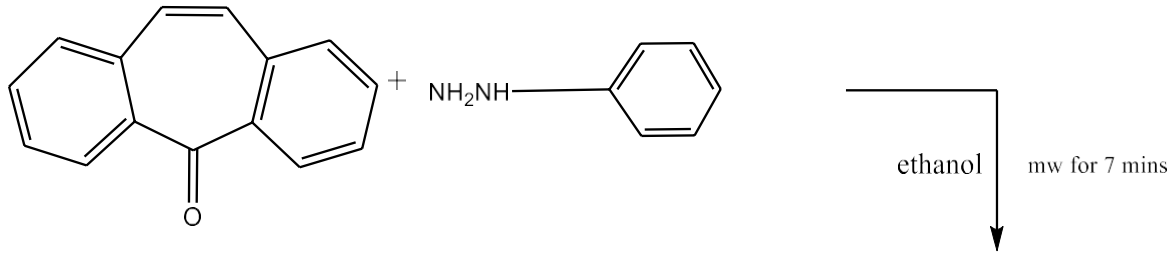
Solubility: water

Melting point: 96^0C

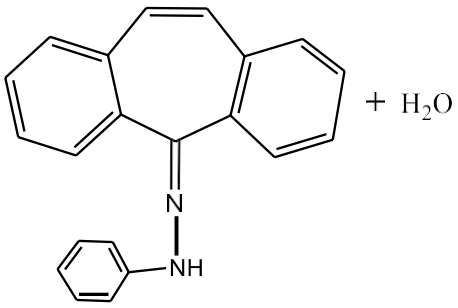
Boiling point: 133.7^0C

SYNTHETIC PROCEDURE

COMPOUND 1



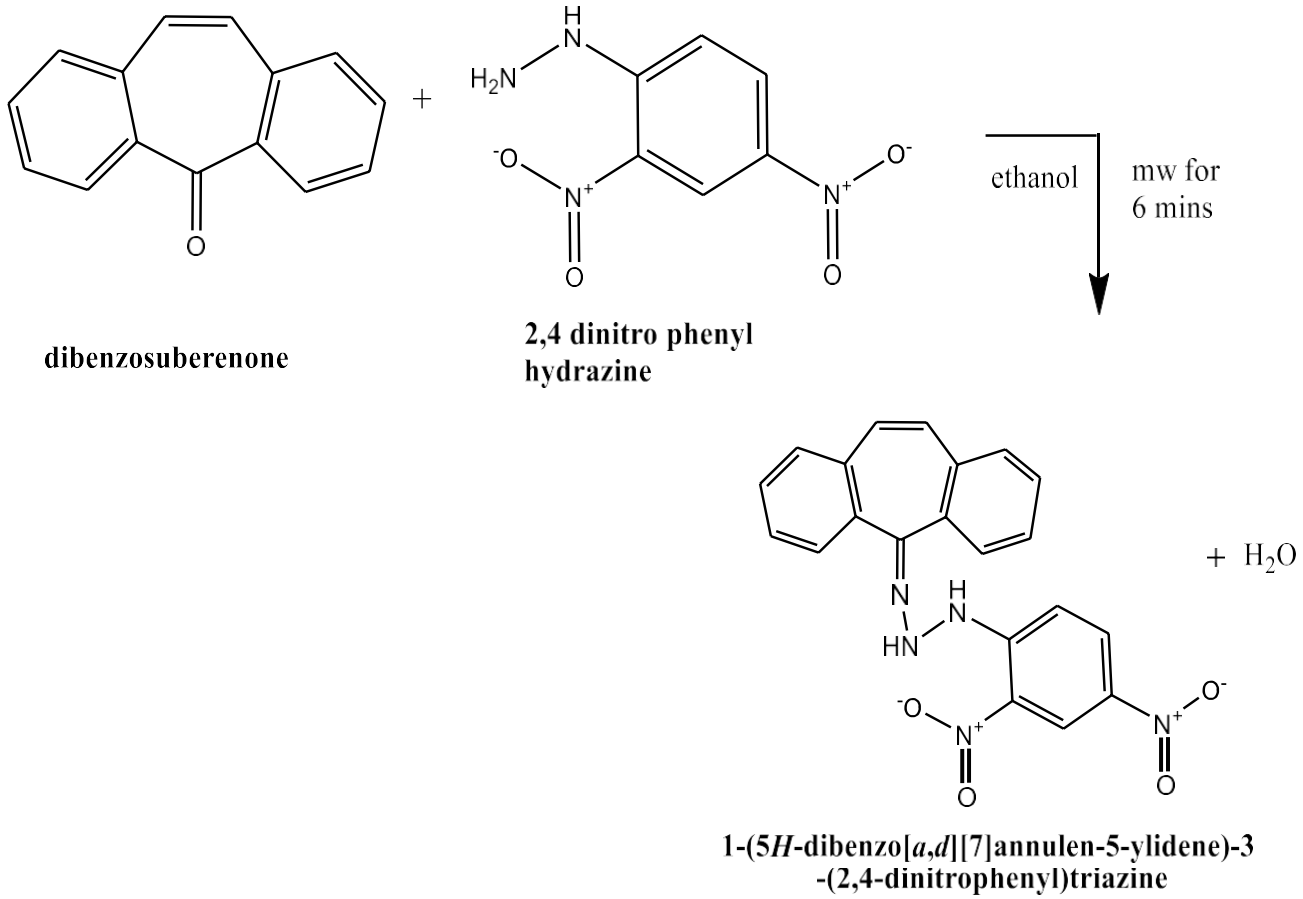
dibenzosuberenone **phenyl hydrazine**



1-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-2 -phenylhydrazine

Dibenzosubrenone (0.01m) and phenyl hydrazine (0.01m) was taken in a beaker and then added 10 ml of ethanol to continuous stirring. The reaction mixture was heated in a microwave oven at maximum power for 7 mins. After completion of the reaction, the reaction mixture poured into ice Water. The crude product was filtered, purified, dried and recrystallized by using methanol.

COMPOUND



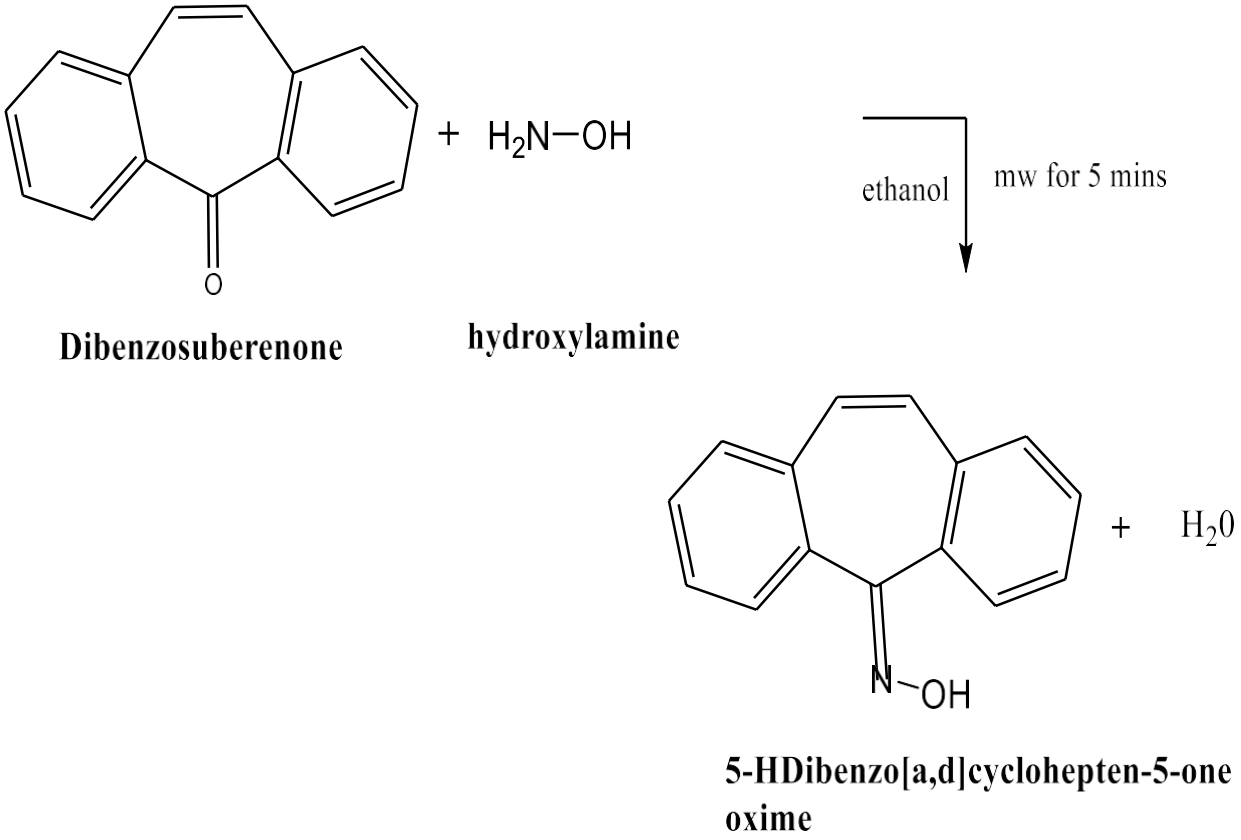
dibenzosuberenone

2,4 dinitro phenyl hydrazine

1-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-3 -(2,4-dinitrophenyl)triazine

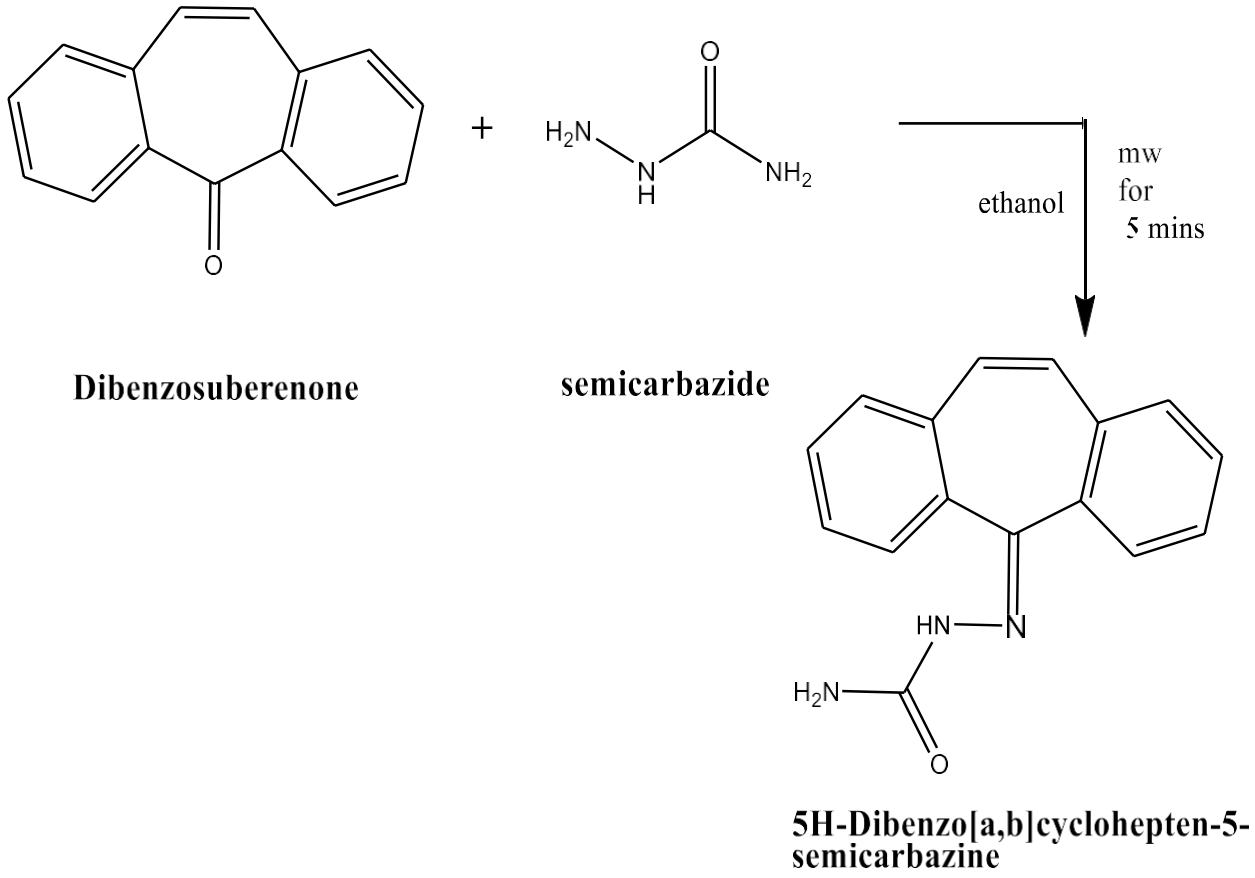
Dibenzosubrenone (0.01m) and 24 dinitrophenyl hydrazine (0.01m) was taken in a beaker and then added 10 ml of ethanol to continuous stirring. The reaction mixture was heated in a microwave oven at maximum power for 6 mins. After completion of the reaction,the reaction mixture poured into ice Water.The crude product was filtered, purified, dried and recrystallized by using methanol.

COMPOUND



Dibenzosubrenone (0.01m) and hydroxylamine (0.01m) was taken in a beaker and then added 10 ml of ethanol to continuous stirring. The reaction mixture was heated in a microwave oven at maximum power for 5 mins. After completion of the reaction, the reaction mixture poured into ice Water. The crude product was filtered, purified, dried and recrystallized by using methanol.

COMPOUND 4



Dibenzosuberenone **semicarbazide**

5H-Dibenzo[a,b]cyclohepten-5-semicarbazine

Dibenzosubrenone (0.01m) and semicarbazide (0.01m) was taken in a beaker and then added 10 ml of ethanol to continuous stirring. The reaction mixture was heated in a microwave oven at maximum power for 5 mins. After completion of the reaction, the reaction mixture poured into ice Water. The crude product was filtered, purified, dried and recrystallized by using methanol.

CHARACTERIZATION

MELTING POINT

The melting point of the synthesized compound to be determined by one end open capillary tube method. The temperature at which the compound starts losing its crystallinity and changes from solid to liquid form to be recorded.

TLC:

Thin layer chromatography used to determine the purity of the compounds using readymade silica gel plate and spots were visualized using iodine chamber. The solvent system used ethylacetate : petroleum ether (9 :1).

ULTRAVIOLET SPECTROSCOPY

Ultraviolet spectroscopy is concerned with the study of absorption of UV radiation which ranges from 200nm to 400 nm. In uv spectroscopy,the valence electrons absorb the energy, thereby the molecules undergoes transition from ground state to excited state.

IR SPECTROSCOPY

IR spectroscopy helps to ascertain the presence and absence of the functional group. The synthesized compound made into a pellet with potassium bromide by pressed pellet technique using pellet press (Model No: M15). The pellet mounted on the pellet disc and percentage transmittance recorded in ABB IR Spectrophotometer (Model No: 3000). IR Spectroscopy is an important tool for structure elucidation and compound identification.

NMR SPECTROSCOPY

Proton NMR Spectroscopy helps us to study the number of equivalent protons and their environment thereby we can ascertain the structure of the molecule. The NMR spectra to be recorded on 400 MHz BRUKER Advance III NMR Spectrometer CDCL3 used as a solvent.

MASS SPECTROSCOPY

Mass Spectra to be recorded on Shimadzu HPLC-MS using Electron Spray Ionization Technique and quantified using Lab Solutions Software 7.0, Samples prepared by dissolving a minute quantity of pure compounds in ethanol. The fragmentation patterns reported in m/z values.

CHAPTER VII

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

MOLECULAR DESIGN:

The molecular designing of the compounds were carried out by using different software's.

Lipinski's rule:

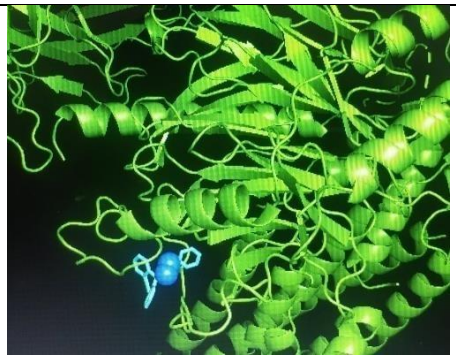
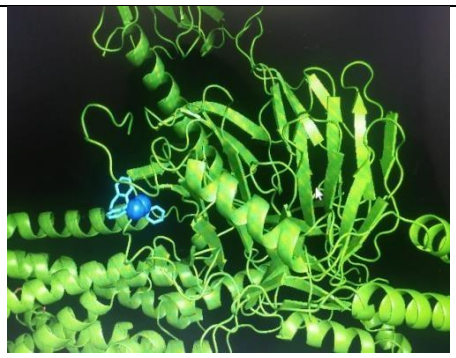
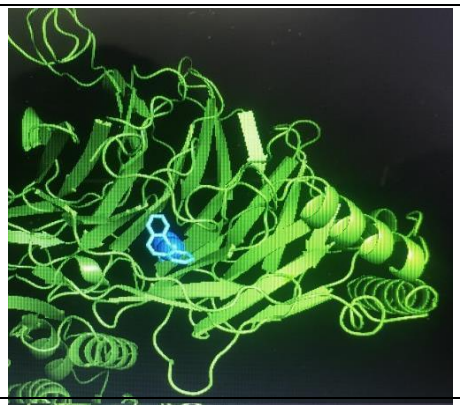
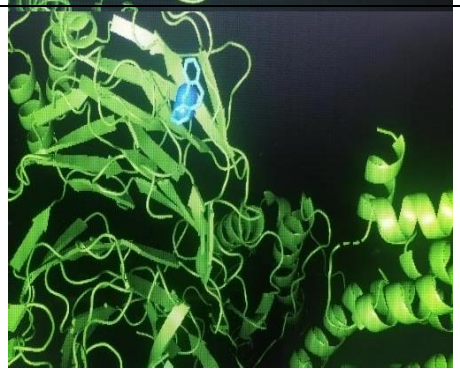
Lipinski's rule of five is a rule to evaluate drug likeness, or to determine if a chemical compound either a certain pharmacological or biological activity has properties that would make it a likely Orally active drug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME).

Table: 2

Code	**M.W**	**H-bond acceptor**	**H-bond donor**	**Log P**	**M.R (Cm^3/mol)**	**No. of criteria**
Rule	**< 500**	**< 10**	**< 5**	**< 5**	**< 150**	**Atleast-3**
compound-1	296.37	1	1	3.26	96.90	ALL
compound-2	386.36	5	1	2.71	114.54	ALL
compound-3	221.25	2	1	1.95	68.80	ALL
compound-4	263.29	2	2	1.76	78.98	ALL

MOLECULAR DOCKING STUDIES

Table: 3

Compound name	Dibenzosubrenone With various Schiff base	Binding energy	Image of the docked compounds
Compound-1	1-(5H-dibenzo [a,d][7]annulen-5-ylidene)-2-phenylhydrazone	-7.5	
Compound-2	1-(5H-dibenzo [a,d][7]annulen-5-ylidene)-2-(2,4-dinitrophenyl)hydrazone.	-7.2	
Compound-3	5H-dibenzo [a,d][7]annulen-5-one oxime	-6.9	
Compound- 4	5H-dibenzo [a,d][7]annulen-5-semicarbazone.	-7.9	

PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

The designed compounds synthesized by the various schiff base react with the dibenzosubrenone to formed the imine compounds .The molecular formula, IUPAC name, physical appearance, percentage yield, melting point, and solubility of the compound are determined. This details are given as following data.

TABLE NO: 4

Code	**Molecular Formula**	**IUPAC Name**
Compound- 1	$C_{21}H_{16}N_2$	1-(5H-dibenzo[a,d][7]annulen-5-ylidene)-2-phenylhydrazine
Compound-2	$C_{21}H_{14}N_4O_4$	1-(5H-dibenzo[a,d][7]annulen-5-ylidene)-2-(2,4-dinitrophenyl)hydrazine
Compound-3	$C_{15}H_{11}NO$	5H-dibenzo[a,d][7]annulen-5-one oxime
Compound- 4	$C_{16}H_{13}N_3O$	5H-dibenzo[a,d][7]annulen-5-semicarbazine

TABLE NO :5

Code	Appearance	Yield (%)	Melting point	Solubility
DSD 1	Light yellow colour	81.7%	175.2°	Ethanol, chloroform
DSD 2	reddish brown colour	80.5%	170.4°	Ethanol, chloroform
DSD 3	White colour	79.4%	168.3°	Ethanol, chloroform
DSD 4	Light yellow colour	78.1%	184.2°	Ethanol, chloroform

THINLAYER CHROMATOGRAPHY:

- The purity of the compound were checked by the TLC by using solvent system ethyl acetate and petroleum ether ratio (9: 1).

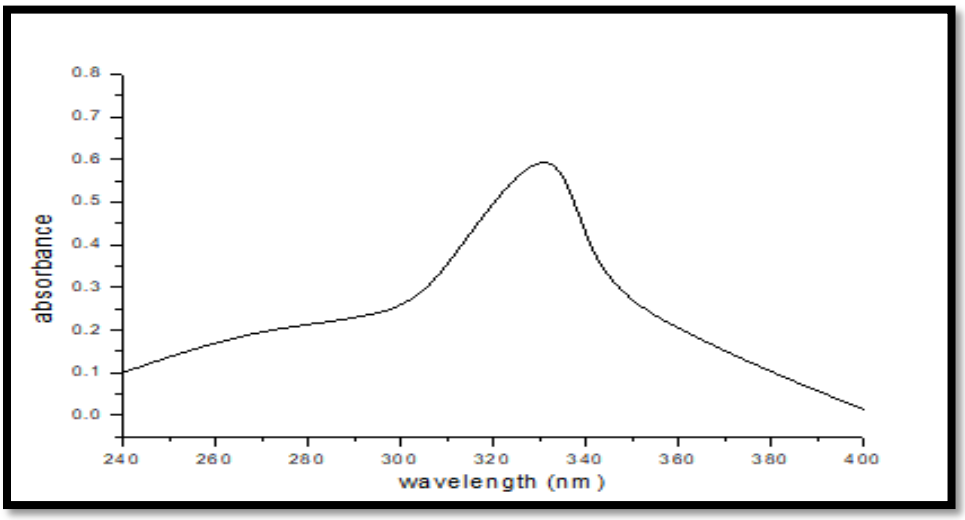
TABLE .NO : 6

S.No	Compound Code	Rf-valuve
1.	Compound-1	0.75
2.	Compound-2	0.76
3.	Compound-3	0.45
4.	Compound- 4	0.62

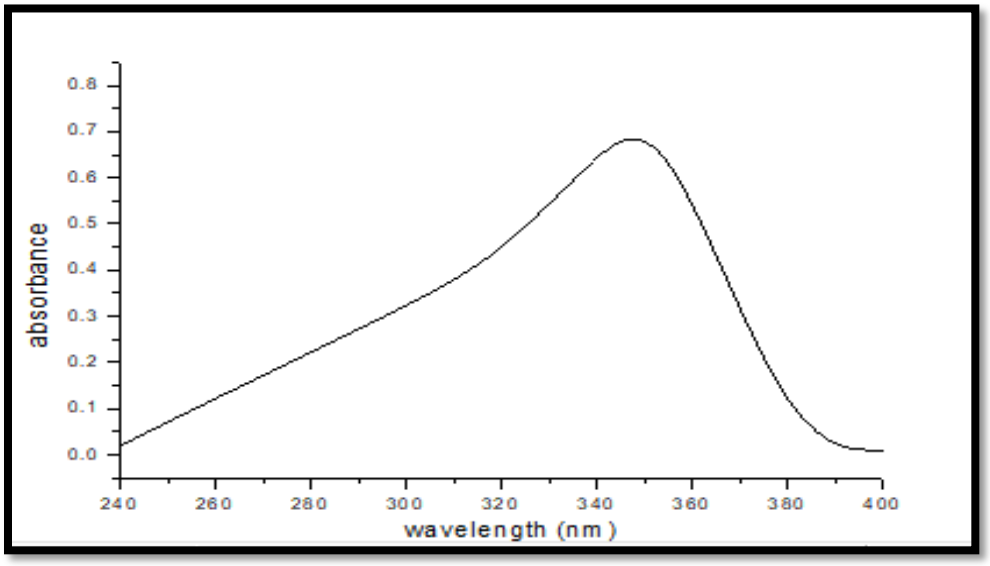
SPECTRAL DATA

UV SPECTRAL STUDIES:

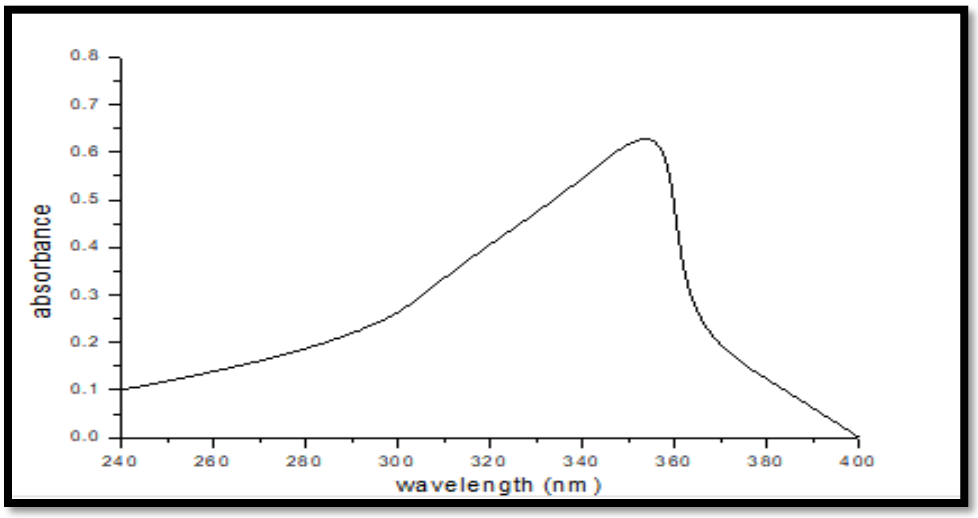
Uv spectrum of compound 1



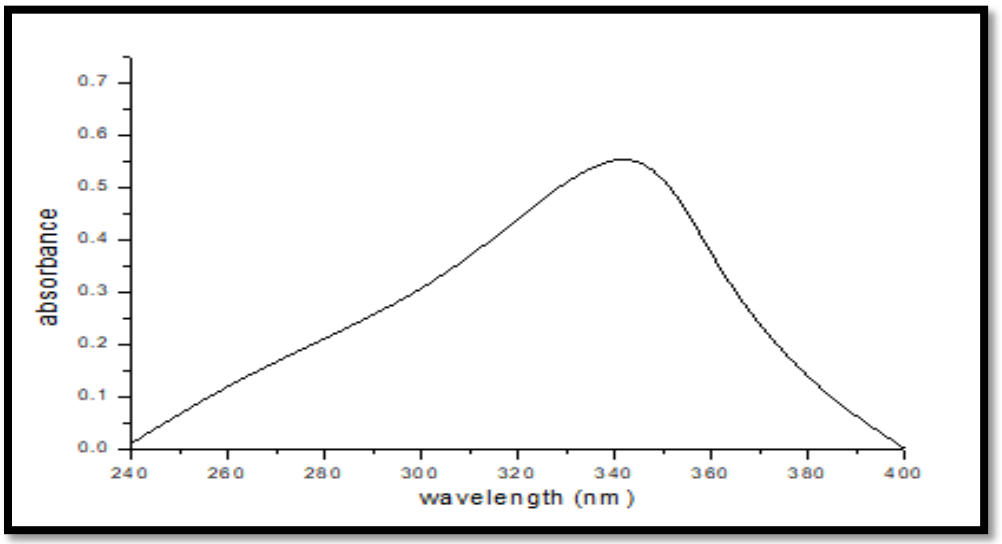
Uv spectrum of compound- 2:



Uv spectrum of compound -3:



Uv spectrum of compound-4:



Uv spectral data

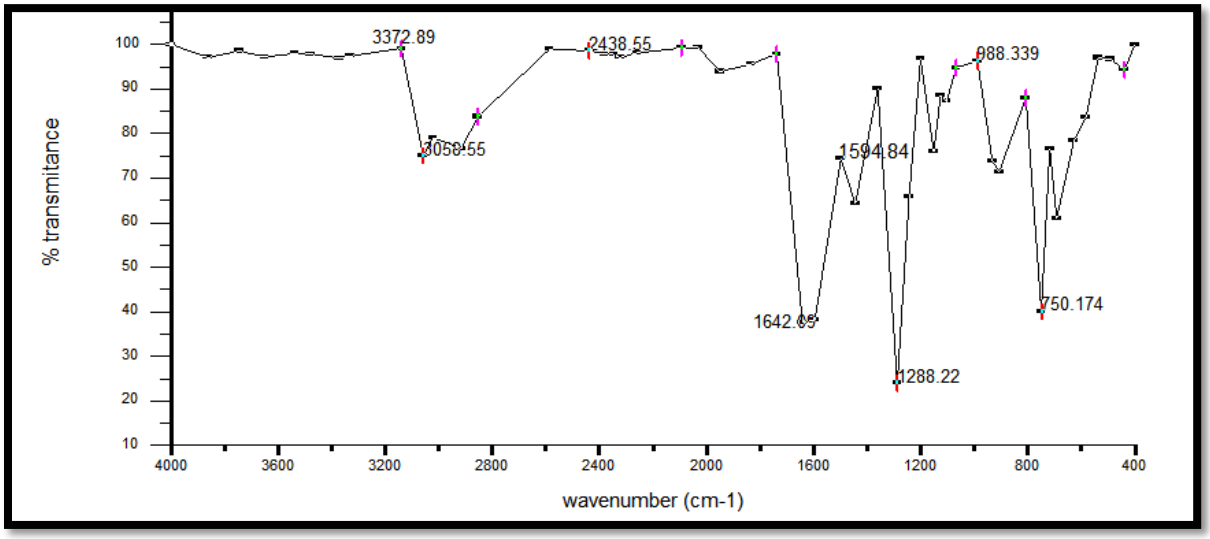
S.NO	COMPOUND NAME	ABSORPTION MAXIMA(λ_{max})
1	Compound 1	335nm
2	Compound 2	350nm
3	Compound 3	357nm
4	Compound4	340nm

IR SPECTRAL STUDIES

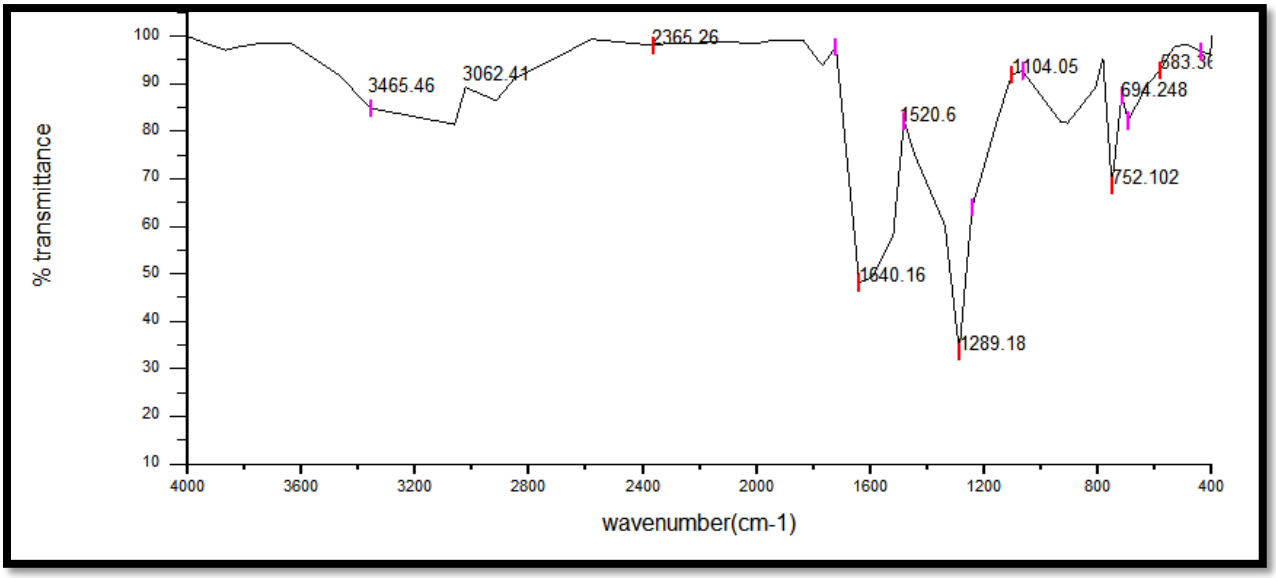
FT-IR

The IR spectrum was determined by using KBr pellet technique.

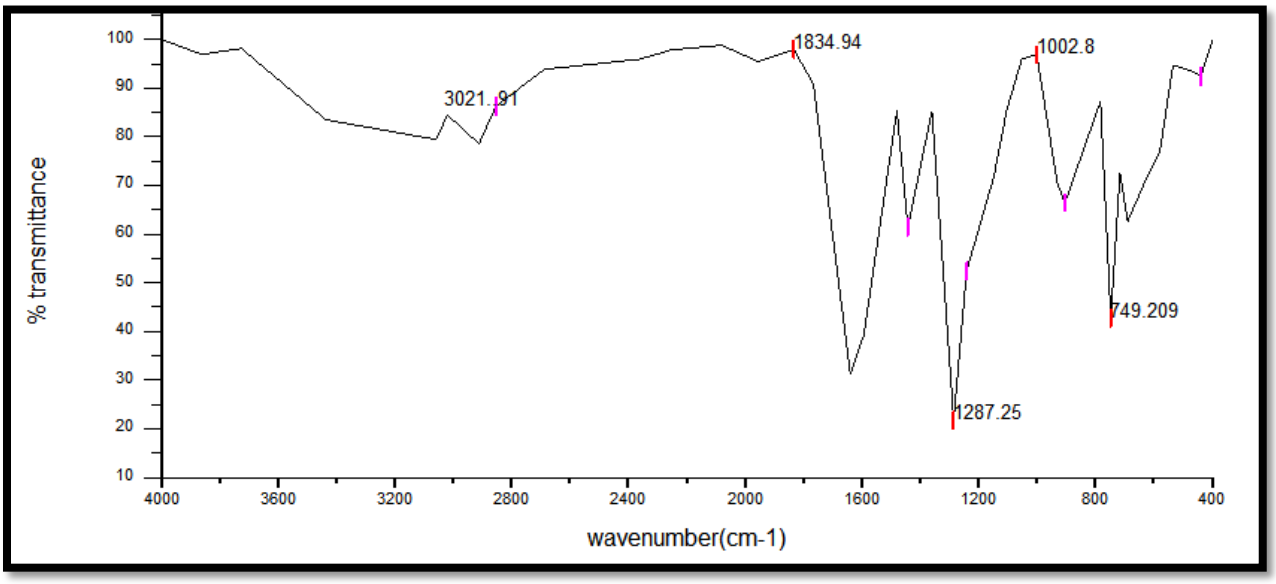
Ir spectrum of compound 1



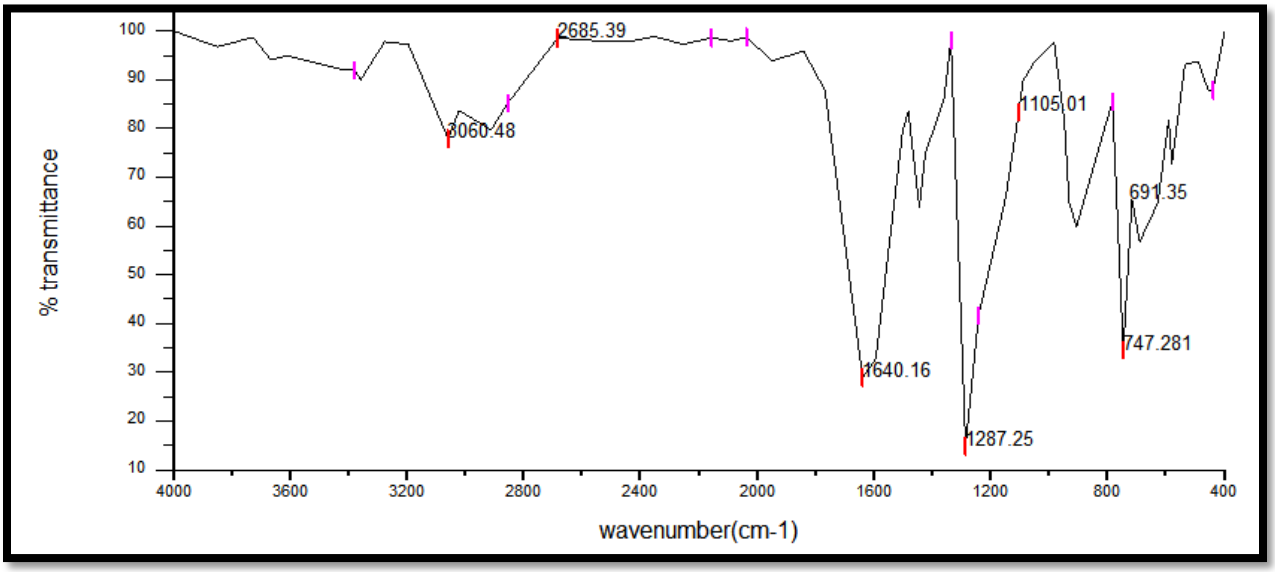
Ir spectrum of compound 2



Ir spectrum of compound 3



IR SPECTRUM OF COMPOUND 4

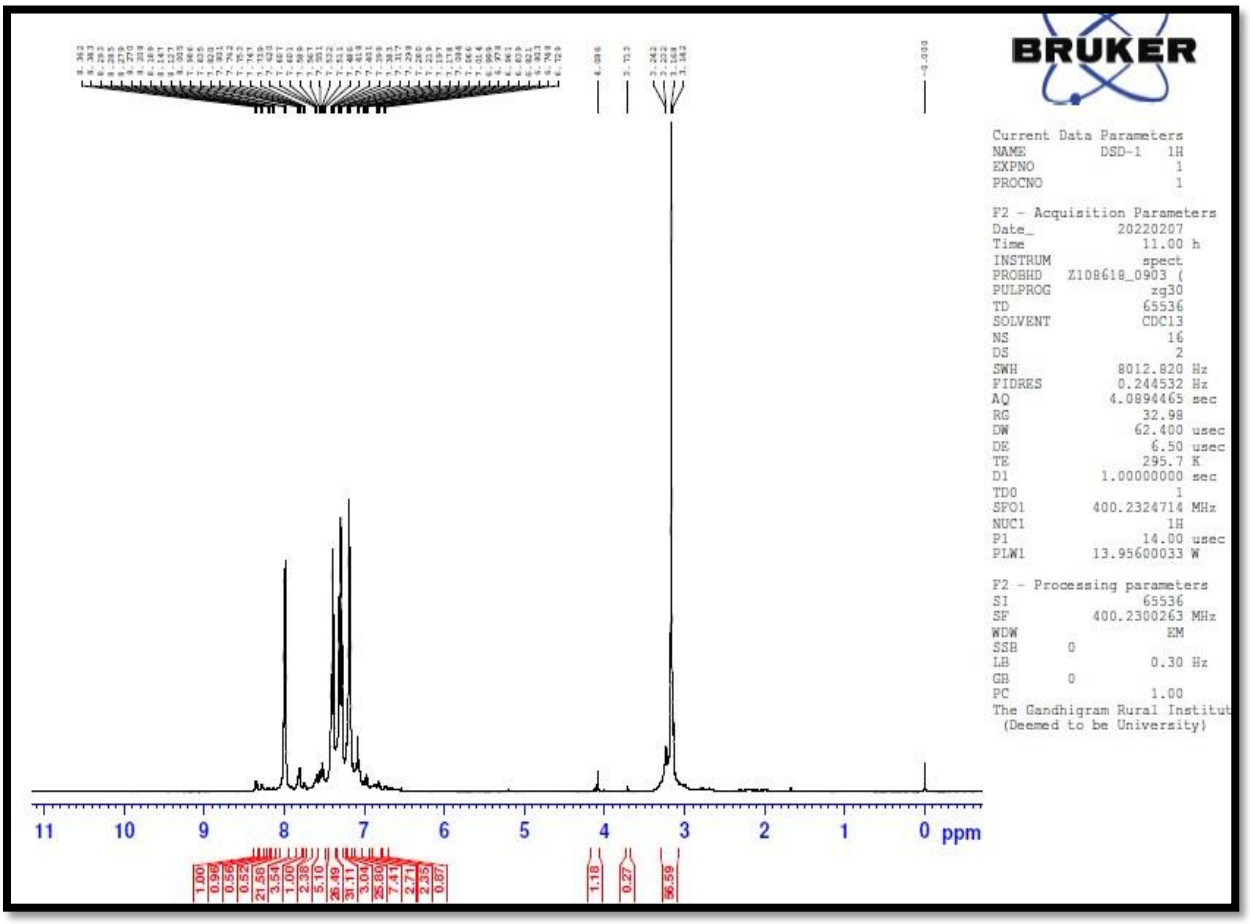


Ir spectral data

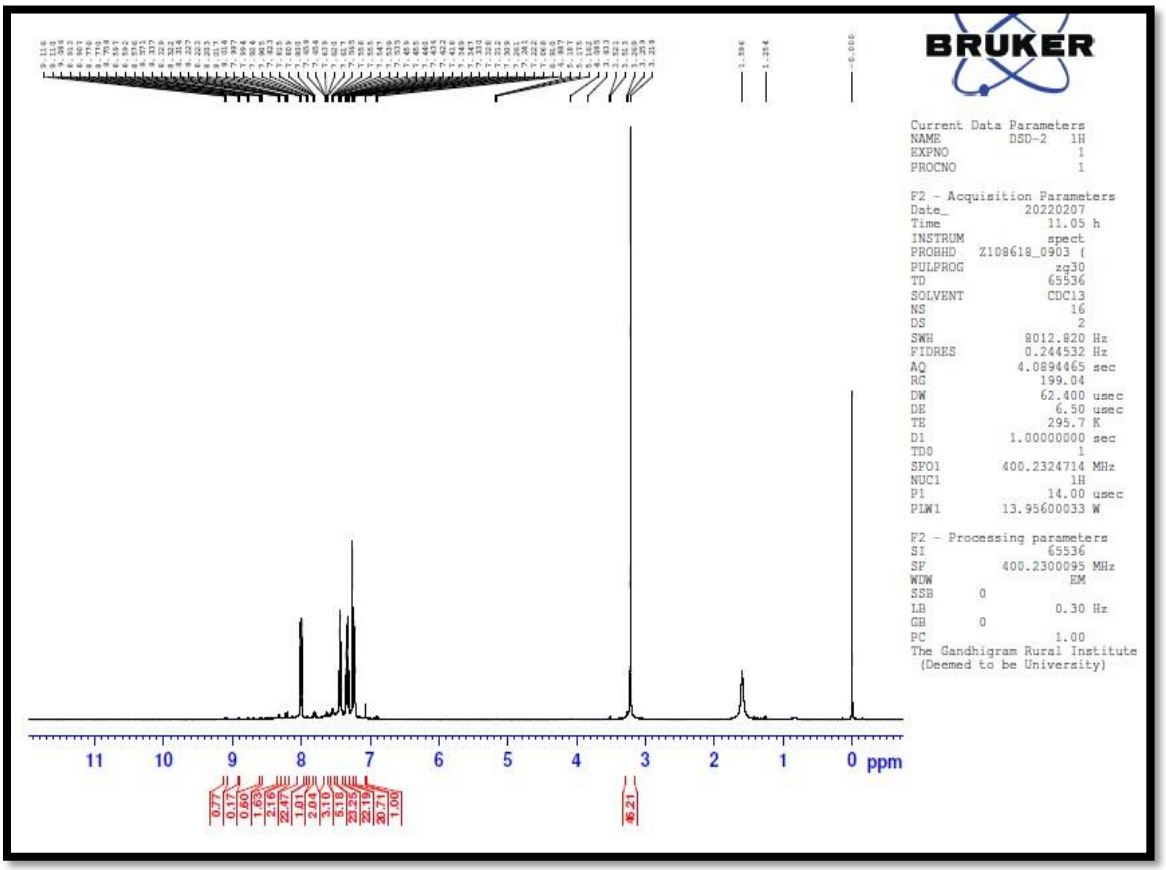
Compound name	**Functional group**	**Observed value in wavenumber (cm^{-1})**
compound 1	CH Str, in aromatic	3058
	C=C Str	1594
	C=N Str	1642
	N-H Str	3372
compound 2	CH Str, in aromatic	3465
	C=C Str	1593
	C=N Str	1640
	N=O Str	1520
compound 3	CH Str, in aromatic	3021
	C=C Str	1482
	C=N Str	1641
	N=O Str	1594
compound 4	CH Str, in aromatic	3022
	C=C Str	1594
	C=N Str	1769
	C=O Str	1640

NMR SPECTRAL STUDIES:

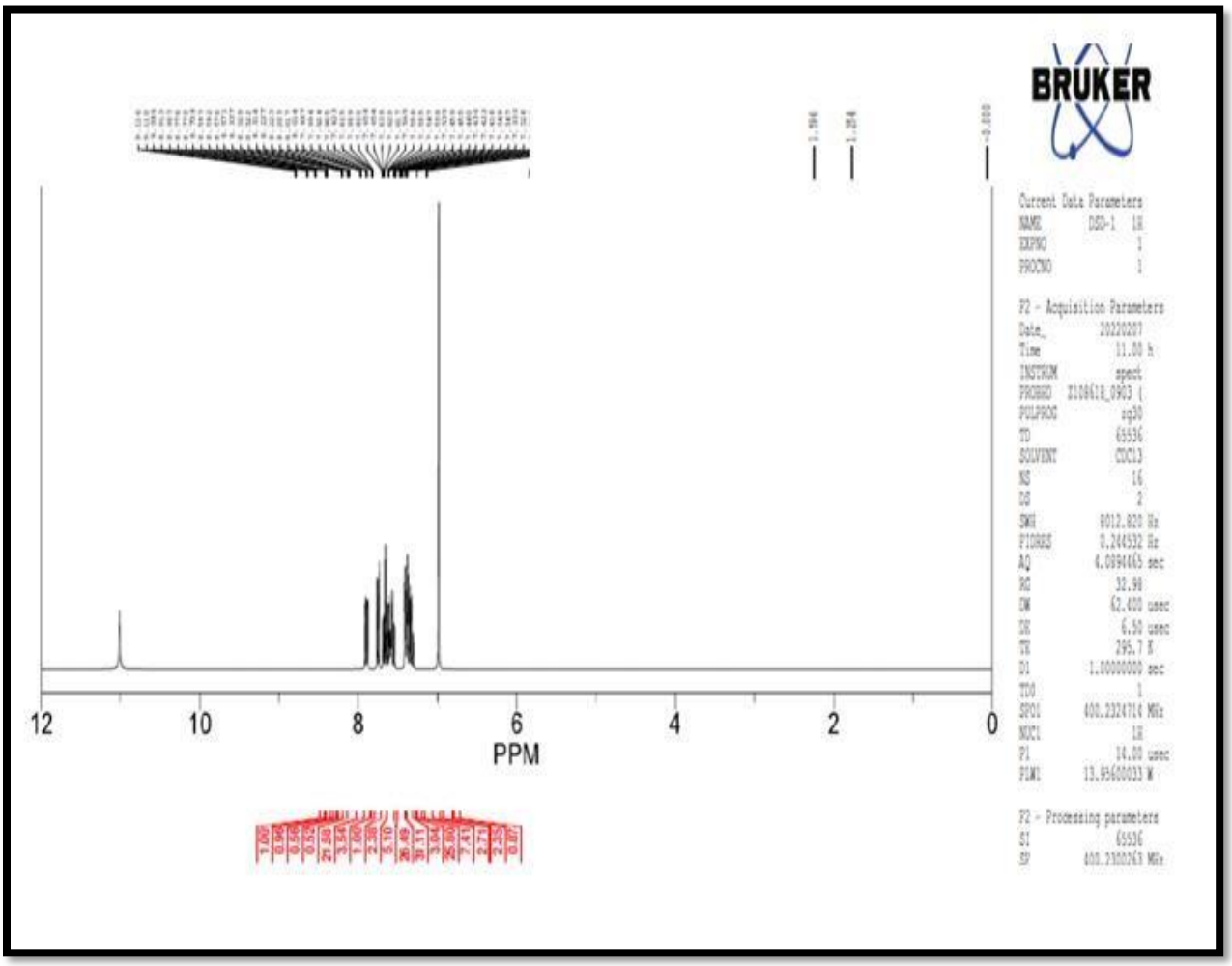
^{1}H NMR spectrum of compound 1



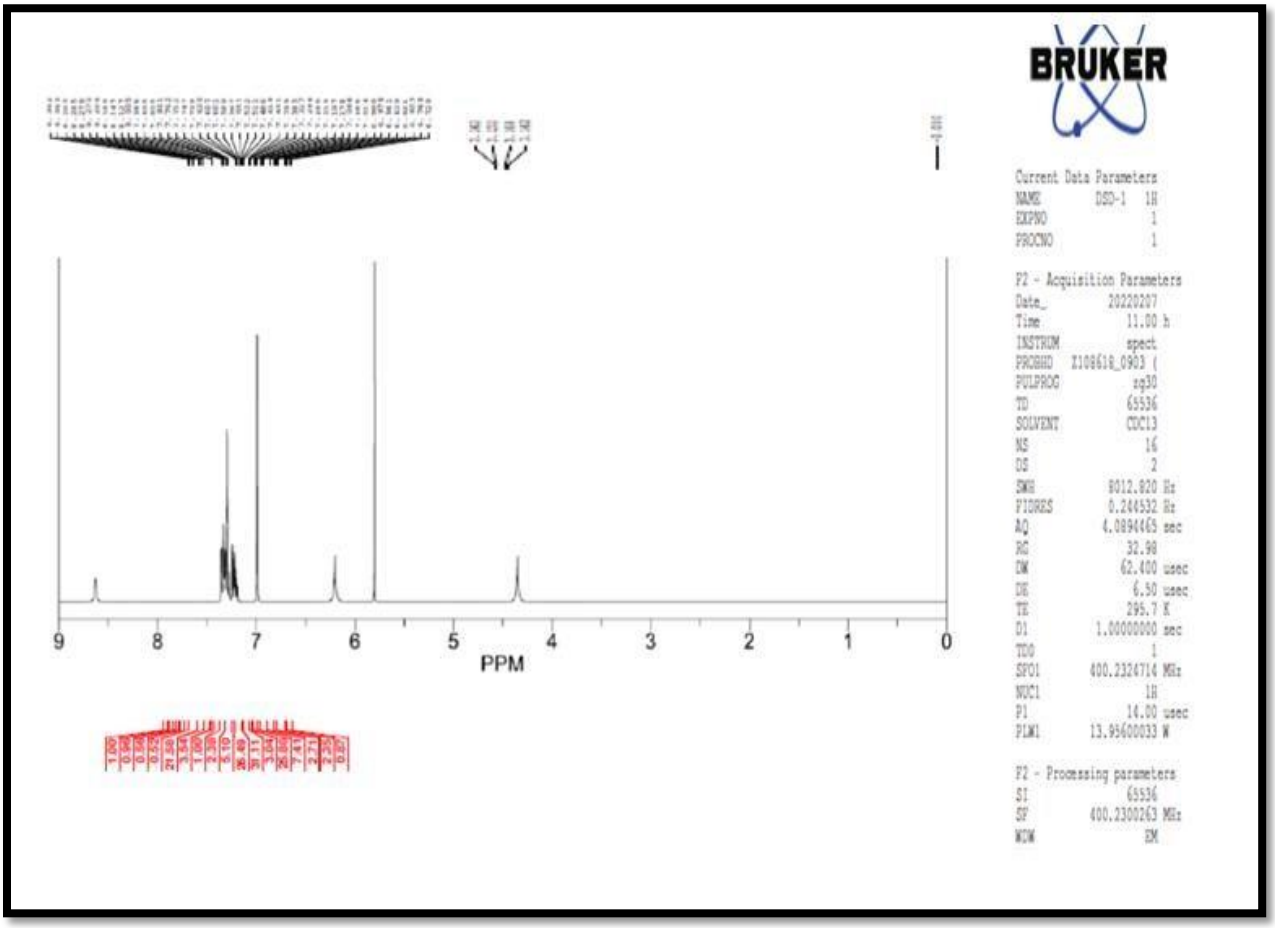
^{1}H NMR spectrum of compound 2



^{1}H NMR SPECTRUM OF COMPOUND 3



[1]HNMR spectrum of compound 4

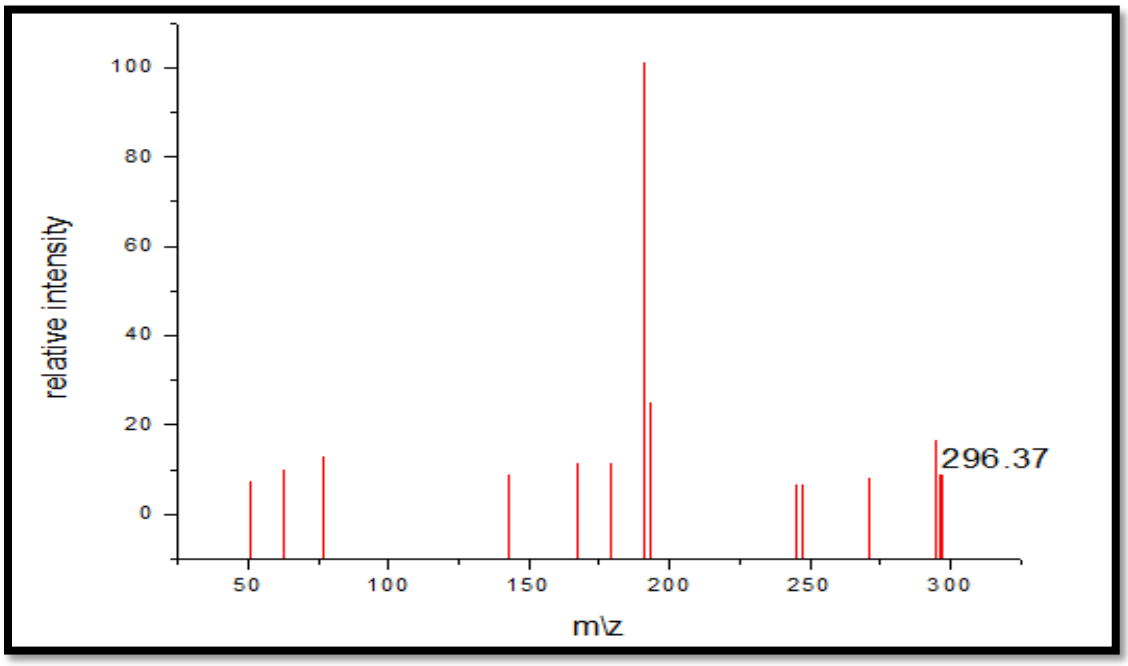


^{1}HNMR SPECTRAL DATA

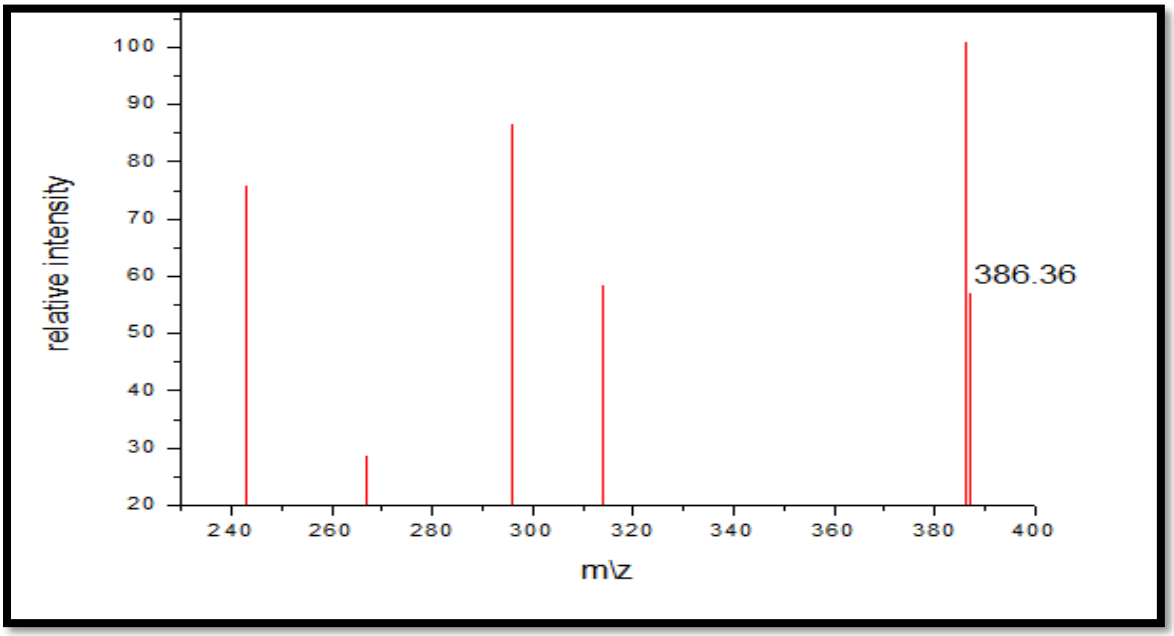
COMPOUND NAME	TYPES OF PROTON	OBSERVED VALUE IN ppm
Compound 1	M-8H, 6H	7.2-8.1, 3.4
COMPOUND2	1H, 6H, M-8H	1.5,3.4, 7.1-8.2
COMPOUND 3	M-8H, N-1H	7.3- 8.0, 11.6
COMPOUND 4	M-8H, N-H,O-H	7.4-8.0,1.5,8.5

MASS SPECTRAL STUDIES:

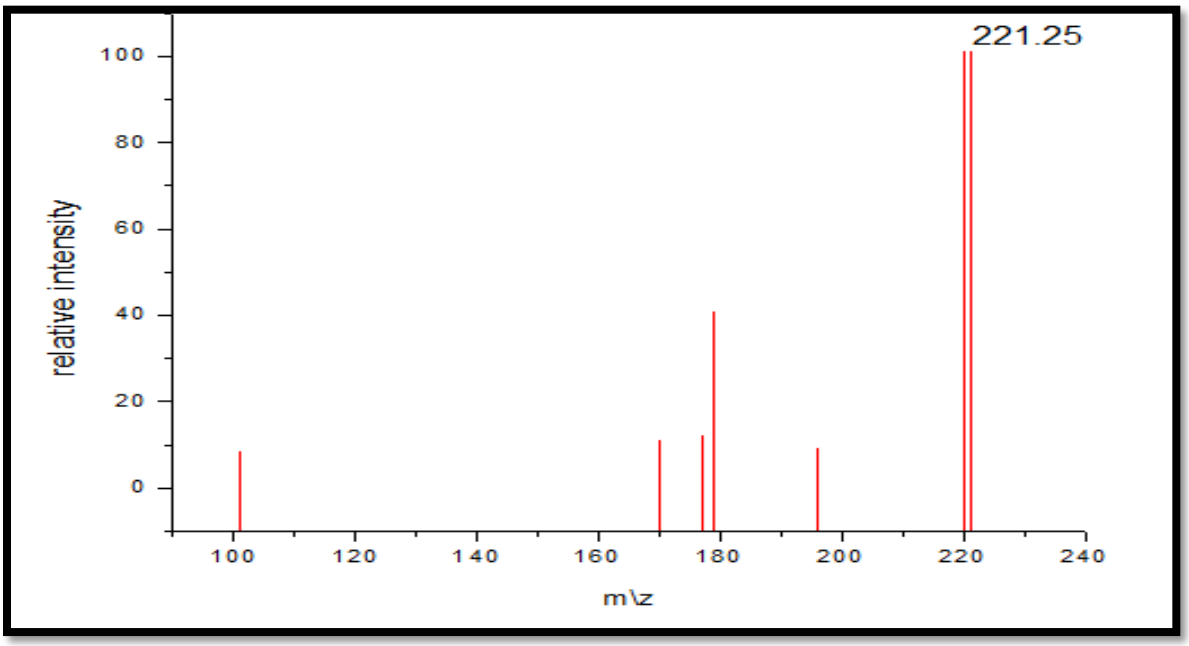
Mass spectrum of compound 1



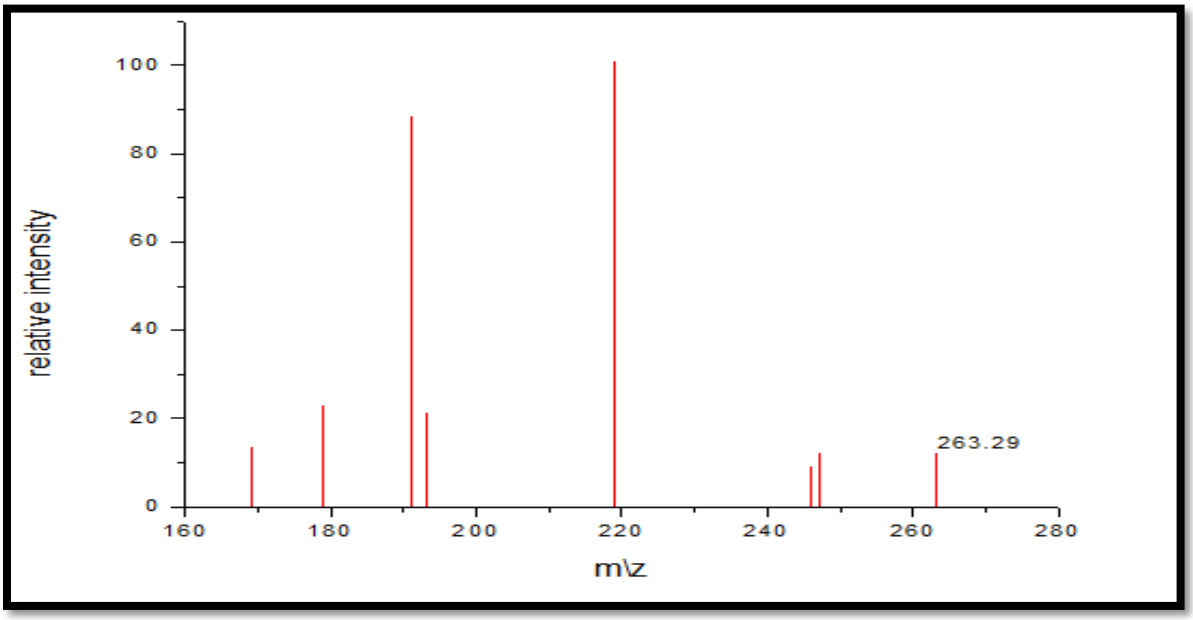
Mass spectrum of compound 2



Mass spectrum of compound 3



Mass spectrum of compound 4

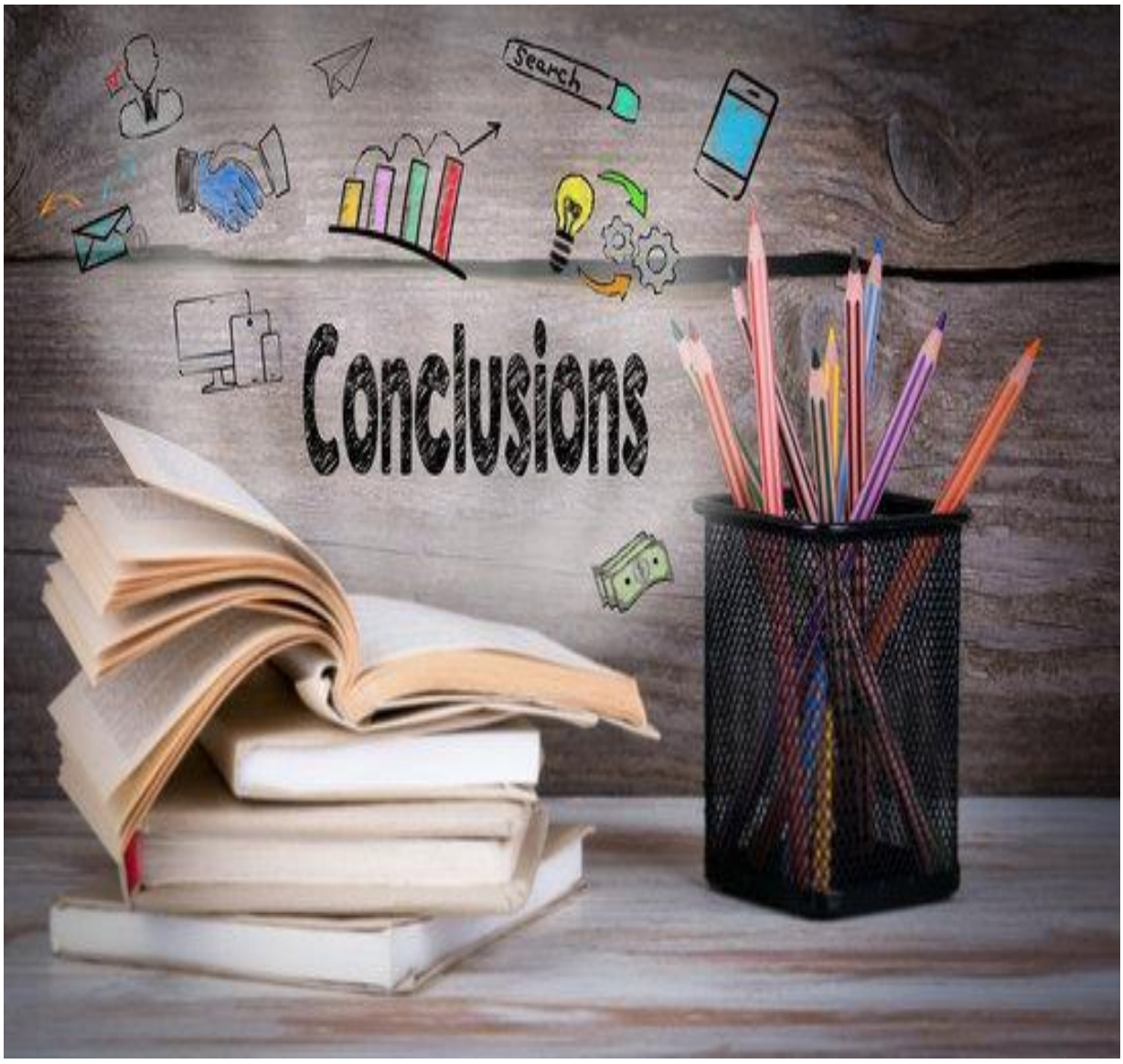


MASS SPECTRAL DATA

TABLE NO:

S.NO	COMPOUND NAME	MOLECULAR ION PEAK
1	COMPOUND 1	296.3
2	COMPOUND 2	386.3
3	COMPOUND 3	221.2
4	COMPOUND 4	263.2

CHAPTER VIII



SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

The project work entitled **"Drug Design, Molecular docking studies, Microwave assisted synthesis and Characterization of novel Schiff's base of Dibenzosuberenone derivatives as antihistamine and anti-Depressant**".

The methods proposed have not been reported till date.

The above study comprises of the following steps:

- Designed the Schiff 's base of dibenzosuberenone and assessed ADME property by chemsketch, molinspiration, and swissADME software.
- molecular docking studies were performed on the designed compounds
- Optimized the method of synthesis for the proposed compounds.
- Synthesized the dibenzosuberenone derivatives by using microwave irradiation technique.
- The synthesized compounds were purified by recrystallization and identified by TLC.
- Determined the physical properties such as solubility, melting point and R_f value.
- Characterized the structure of synthesized compounds by
  - ✓ UV SPECTROSCOPY
  - ✓ IR SPECTROSCOPY
  - ✓ ^{1}H NMR
  - ✓ MASS
- The IR spectra showed the relevant functional group for all synthesized compounds.
- The ^{1}H NMR showed the relevant proton signals for all synthesized compounds.
- The molecular mass was determined by MASS spectroscopy.

A new series of novel Schiff base of Dibenzosuberenone derivatives have been prepared and characterized by spectral data.

CONCLUSION

Efficient and environmentally benign methodologies for the synthesis of novel schiff's base of Dibenzosuberenone derivatives using microwave irradiation has been reported. several advantages including percentage yield, reduced time and reduced pollution.

So further development of the novel schiff's base of dibenzosuberenone derivatives may be used to achieve the antihistamine and antidepressant activity in future.

CHAPTER IX

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BIBLIOGRAPHY

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SEMINARS AND CONFERENCES

71st Indian Pharmaceutical Congress

Theme: Healthcare System - Role of Regulators

Chennai, TamilNadu.

Certificate of Participation

This is to certify that Prof. /Dr. /Mr. /Ms. **SATHISHKUMAR.A**

of **MADURAI MEDICAL COLLEGE** *has presented in the Scientific session of 71st Indian Pharmaceutical Congress 2019 held at Sri Ramachandra Institute of Higher Education and Research (DU) during 20th to 22nd December 2019, Chennai, TamilNadu.*

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09th April 2021

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Department of Pharmaceutical Chemistry
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(An ISO 9001:2015 certified Institution)

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CERTIFICATE OF PARTICIPATION

Operant Pharmacy Federation

This is to Certify that **SATHISHKUMAR.A** of **College of pharmacy,madurai Medical College,madurai.** has participated as Delegate in **PharmaNEST'21** International Virtual E-tech Fest on **"Data Science, Computational Tools, Artificial Intelligence and more Novel Technologies: Evolution and Contribution in the Pharmaceutical Research"** held From May 26, 2021 to June 12, 2021, Organized by **Operant Pharmacy Federation.**

Certificate ID: OPF-PHP59395

Dr. Zareen Delawar Hussain
(Chief Patron)
PharmaNEST'21

Mr. Vikram Choudhary
(Patron)
PharmaNEST'21

Mei nee Chiu
(Convener)
PharmaNEST'21