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SCHIFF'S BASES PHENAZINAMINES AND ITS ANTIMICROBIAL ACTIVITY

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Abstract
Pharmaceutical chemistry is a science that makes use of the general laws of chemistry to study drugs, viz., their preparation, chemical nature, composition, structure, influence on an organism and studies of the physical and chemical properties of drugs, the methods of quality control, and the conditions of their storage. Heterocycles are an important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals.

Keyword
Phenazinamines, Antimicrobial, Schiff's bases, Docking, Heterocyclic

Introduction
Medicinal chemistry and pharmaceutical chemistry are disciplines at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, where they are involved with design, chemical synthesis and development for market of pharmaceutical agents, or bio-active molecules (Drugs).

Pharmaceutical chemistry involves cures and remedies for disease, analytical techniques,pharmacology, metabolism, quality assurance, and drug chemistry. Chemistry is the science of the composition, structure, properties, and reactions of matter, especially of atomic and molecular systems. At the biological interface, medicinal chemistry combines to form a set of highly interdisciplinary sciences, setting its organic, physical and computational emphases alongside biological areas such as biochemistry, molecular biology, pharmacognosy and pharmacology, toxicology and veterinary and human medicine; these, with project management statistics and pharmaceutical business practices, systematically oversee altering identified chemical agents such that after pharmaceutical formulation, they are safe and efficacious, and therefore suitable for use in treatment of disease.[1]

A number of potent compounds derived either from synthetic or natural origins are commonly in use as medicinal agents. Many pharmaceutical chemists believe that the natural world contains an almost endless supply of yet-to-be-discovered chemicals that will significantly augment the world's supply of drugs. However the true era of medicinal chemistry began in the 1930s with the preparation and use of antibacterial sulfonamide drugs. With the development of the pharmaceutical industries towards the end of the 19th century, drug discovery become a highly focused and managed process. Discovering a new drug moved from the domain of inventive doctors to that of scientist hired for the purpose. Now a day, the bulk of the modern therapeutics and of modern pharmacology is based on a drug that comes from laboratories of pharmaceutical company.[2]

Heterocyclic chemistry

Heterocyclic compounds are of very much interest in our daily life. Heterocyclic compounds have one or more hetero atoms in their structure (Fig1). They may be cyclic or non cyclic in nature. Heterocyclic compunds have a wide range of application. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products. Chemistry of heterocyclic compounds is one of the leading lines of investigations in the organic chemistry. Heterocyclic compounds are widely distributed in nature and are essential for life. They play a vital role in the metabolism of all living cells.[3]

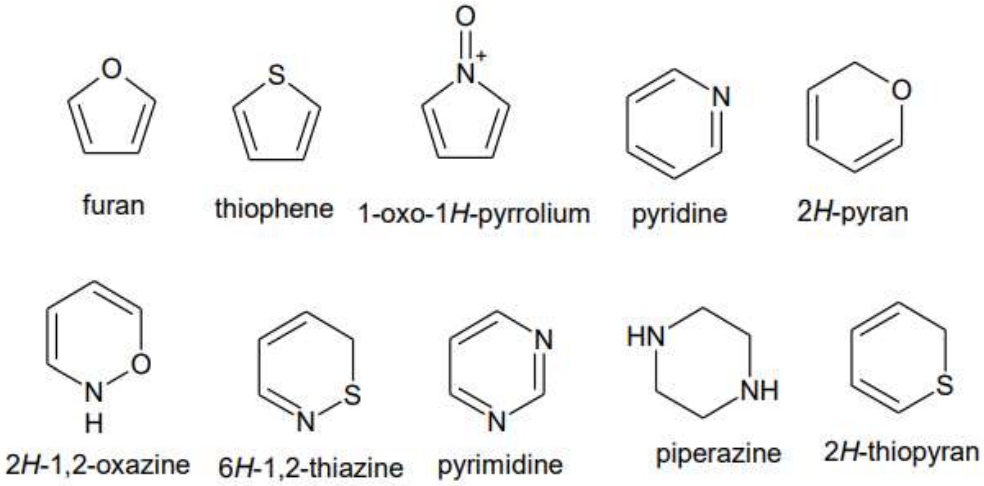


Fig. 1 Various Heterocycles

Heterocycles also play an important role in the design and discovery of new physiological/pharmacologically active compounds. Five membered aromatic systems having three heteroatoms at the symmetrical positions have been studied because of their interesting physiological properties. Heterocycles are routinely used as bioisosteres for a variety of functional groups in drug candidates.[4]

DIAZINES

Any of three heterocyclic aromatic compounds $C_4H_4N_2$ that consist of a six-membered ring and differ in the proximity of the nitrogen atoms to each other or A group of heterocyclic compound normally derived from benzene/naphthalene by replacement of two carbon atoms of a six-membered ring by nitrogen is known as diazines/benzfused diazines. [5]

The three Diazines: Pyridazine, Pyrimidine and Pyrazine

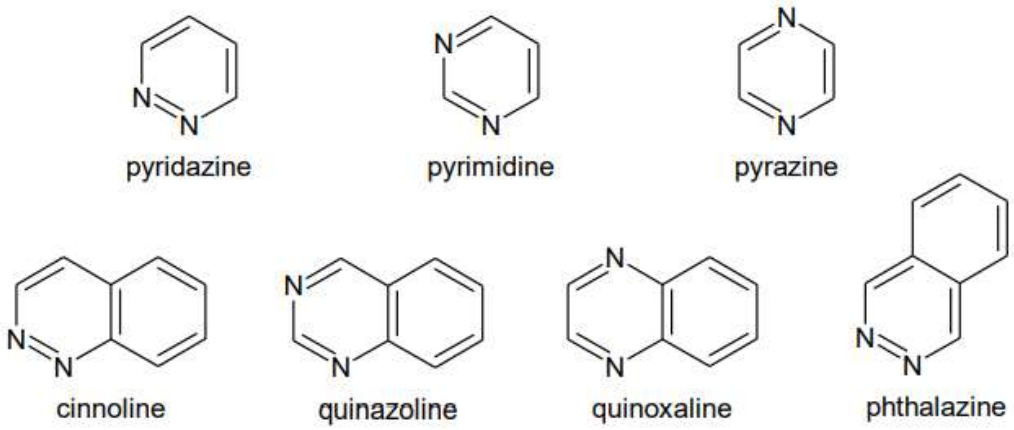
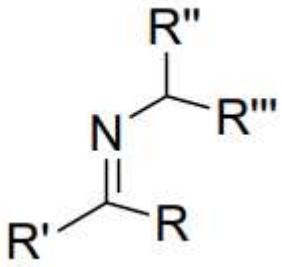


Fig. 2 Diazines

SCHIFF'S BASES



The history of Schiff's bases can be traced back to the early work done by Rassi et al who reported certain aromatic amines that give rise to compounds known as schiffs bases.

A schiff's base (or azomethine), named after Hugo Schiff is a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group but not hydrogen. Schiff's bases are of the general formula R1R2C =N-R3, where R3 is an aryl or alkyl group that makes the Schiff's base a stable imine. A schiff's base derived from aniline, where R3 is a phenyl or substituted phenyl can be called an anil. Schiff's bases play an important role in inorganic chemistry as they easily form stable complexes with most transition metal ions.[6]

TUBERCULOSIS

Tuberculosis (abbreviated as TB for tubercle bacillus) is a common and often deadly communicable disease caused by Mycobacterium tuberculosis, in humans. Tuberculosis usually attacks the lungs (as pulmonary TB) but can also affect central nervous system, lymphatic system, circulatory system, genitourinary system, gastrointestinal system, bones, joints and even skin (as

extra-pulmonary TB). Other mycobacteria such as M. bovis, M. africanum, M. canetti, and M. microti also cause tuberculosis, but these species are less common in humans. The classic symptoms of tuberculosis are a chronic cough with blood-tinged sputum, fever, night sweats and weight loss. Infection of other organs causes a wide range of symptoms. The diagnosis relies on radiology (chest X-rays), tuberculin skin test, blood tests as well as microscopic examination and microbiological culture of body fluids. [7]Tuberculosis is difficult to treat and requires long courses of multiple antibiotics. Antibiotic resistance is a growing problem in multi-drug-resistant tuberculosis. Prevention relies on screening programs and vaccination, usually with Bacillus Calmette-Guérin (BCG vaccine). BCG provides some protection against severe forms of pediatric TB, but has been shown to be unreliable against adult pulmonary TB, which accounts for most of the disease burden worldwide. The factors contributing to higher incidences of tuberculosis are malnutrition, inadequate medical care, poverty, crowding, ill ventilation and chronic debilitating conditions like uncontrolled diabetes, alcoholism and immune-compromised states like AIDS.

TYPES OF TUBERCULOSIS

Tuberculosis is generally divided into pulmonary tuberculosis and extra-pulmonary tuberculosis.Pulmonary tuberculosis is further divided into five different types:

I) Primary tuberculosis pneumonia:
   1. It is an uncommon form of tuberculosis, which mostly occurs in patients with lower immunity like children and the elderly. It presents
   2. itself in the form of pneumonia and is highly contagious.

II) Laryngeal tuberculosis: This form of tuberculosis affect throat in the vocal chord area.

III) Cavitary tuberculosis: It is a highly contagious form of tuberculosis. It tends to form large cavities in the lungs.

IV) Miliary tuberculosis: This form of tuberculosis now commonly known as disseminated TB tends to affect the young, elderly and anyone else who has a weak immune system. It is characterized by the appearance of small granules in the lungs which are visible through the chest in X-ray. This is also called as Koch's disease.

V) Tuberculosis Pleurisy: It can develop shortly after catching the infection. This type of tuberculosis is characterized by shortness of breath, chest pain and accumulation of fluid in the lungs.[8]

Extra pulmonary tuberculosis is further divided into seven different types:

I) Adrenal tuberculosis: This form affects the adrenal gland, hormone production and patient experiences fainting or weakness.

II) Lymph node tuberculosis: It is characterized by the enlargement of the lymph nodes.

III) Osteal tuberculosis: This form of tuberculosis affects the bones. The bone tissues of affected area weaken, and it could cause the fracture of affected area.

IV) Tuberculosis Peritonitis: It usually affects the outer lining of the intestine. Fluid gets collected in the outer lining of the intestine, causing the affected area to experience pain in the abdomen.

V) Renal tuberculosis: It is characterized by pyuria (presence of white blood cells in the urine). It could end up affecting the reproductive organs and cause epididymitis in men.

VI) Tuberculosis Meningitis: The symptoms for these types of tuberculosis include the patient displaying signs of being affected by a stroke or a brain tumor. It is extremely dangerous and could even prove to be fatal.

VII) Tuberculosis Pericarditis: This form of tuberculosis is characterized by an increase in the amount of fluid around the heart and could also hamper its function

ANTIMICROBIAL AGENTS

Any infection is a parasitic colonization of the host by a foreign species of microbes. The infecting organism seeks to utilize the host's resources for multiplication. It interferes with the normal functioning of the host cells and can lead to a chronic condition, which may culminate into gangrene, loss of tissue or organ and finally even death. The host's initial response to infection is inflammation. Inflammation is a complex phenomenon, comprising of biochemical as well as immunological factors. It is recognised by the symptoms: Calor (heat), Rubor (redness), Tumour (swelling) and Dolor (pain). Antimicrobial drugs are the greatest contribution of the 20th century to therapeutics. [9]

Their advent changed the outlook of the physician about the power drugs can have on diseases. They are one of the few curative drugs. Their importance is magnified in the developing countries, where infective diseases predominate. As a class, they are one of the most frequently used as well as misused drugs. Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient[10]

MOLECULAR DOCKING

Molecular docking technique is the famous in structural bioinformatics to solve the problems in protein and ligand interaction studies. A molecule is characterized by a pair (A; B), in which A represents a collection of atoms, and B represents a collection of bonds between pairs of atoms. Information used for kinematic and energy computations is associated with each of the atoms and bonds. Each atom carries standard information, such as its varder Waals radius. Three pieces of information are associated with each bond: (i) the bond length is the distance between atom centers; (ii) the bond angle, is the angle between two consecutive bonds; (iii) whether the bond is rotatable or not. Since bond lengths and angles do not affect significantly the shape of a molecule, it is common practice to consider them fixed. Thus the degrees of freedom of the molecule arise from the rotatable bonds. The three dimensional embedding of a molecule defined when we assign values to its rotatable bonds is called the conformation of the molecule.

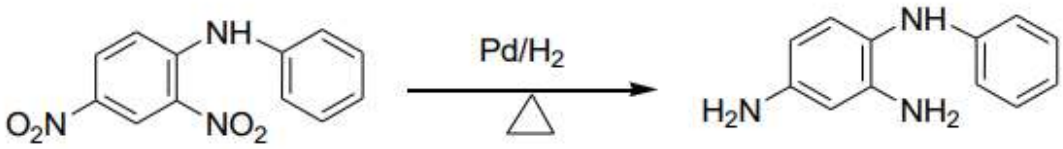
AUTODOCK

AutoDock is an automated procedure for predicting the interaction of ligands with biomacromolecular targets. The motivation for this work arises from problems in the design of bioactive compounds, and in particular the field of computer-aided drug design. 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. The precise

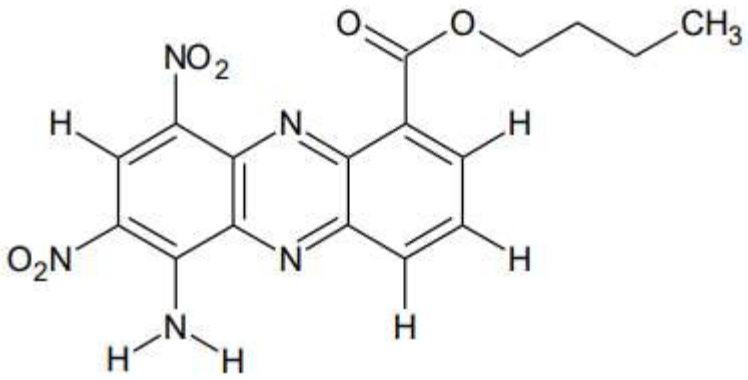
interaction of such agents or candidate molecules with their targets is important in the development process. Our goal has been to provide a computational tool to assist researchers in the determination of biomolecular complexes.In any docking scheme, two conflicting requirements must be balanced: the desire for a robust and accurate procedure, and the desire to keep the computational demands at a reasonable level. [11]The ideal procedure would find the global minimum in the interaction energy between the substrate and the target protein, exploring all available degrees of freedom (DOF) for the system

Review of Literature

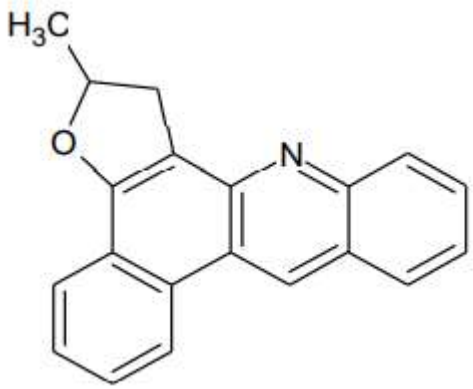
Shaohua G. et al (2002)[12] have reported the new method for the synthesis of N-(2,4 dinitrophenyl) benzeneamine was dissolved in ethyl acetate, then catalytically reduced in a Parr apparatus for 24 h using a 5% Pd/C catalyst under hydrogen atmosphere. After reduction, the reaction mixture was filtered into ethyl acetate. The solvent was removed in vacuo, giving the desired N1-phenylbenzene-1,2,4-triamine A, which was used without further purification



Zheng Ming Li et al (2010)[13] have found A series of novel 6-aminophenazine-1-, 7-aminophenazine-1- and 8-aminophenazine-1-carboxylate derivatives were synthesized by a facile method, and their structures were characterized by 1H NMR, 13C NMR and high-resolution mass spectrometry. Some unexpected byproducts V-7b-V-8d were noticed and isolated, and their structures were identified by 2D NMR spectra including heteronuclear multiple-quantum coherence (HMQC), heteronuclear multiple-bond correlation (Hmbc) and H-H correlation spectrometry (H-H COSY) approach. Their fungicidal activities against five fungi were evaluated, which indicated that most of the title compounds showed low fungicidal activities in vitro against Alternaria solani, Cercospora arachidicola, Fusarium omysporum, Gibberella zeae, and Physalospora piricola at a dosage of 50 μg mL-1, while compounds IV-6a and IV-6b exhibited excellent activities against P. piricola at that dosage. Compound IV-6a could be considered as a leading structure for further design of fungicides.

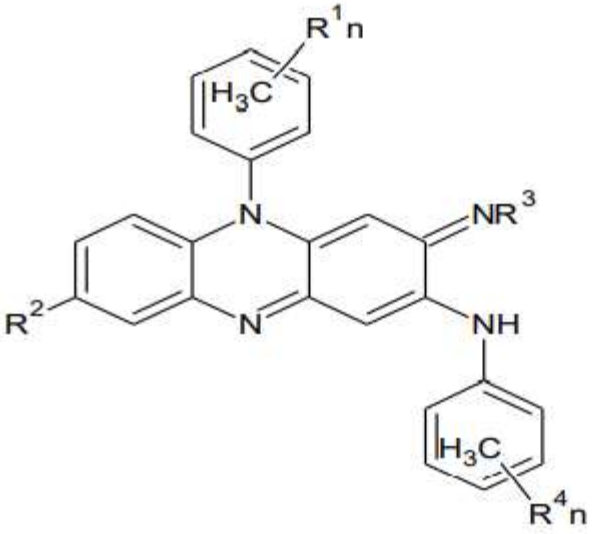


N.S. Hari Narayana Moorthy1,* et al (2014)[14] Fused aryl phenazine derivatives (benzo[a]phenazine, pyrido[a]phenazine, benzo[a]phenazine diones, tetrahydropyrido[a]phenazine (dermacozines), etc) are important heterocyclic compounds, which exhibit various pharmacological activities, prominently in cancer cell lines. These compounds significantly intercalate between DNA base pairs and inhibit the activities of topoisomerase I and II enzymes (Topo I and II). XR11576, XR5944, NC-190 and NC-182 belong to phenazine/fused aryl phenazine category and are under clinical studies. Several fused aryl phenazine dione compounds such as pyridazino[4,5-b]phenazine-5,12-diones, 6,11-dihydro-pyrido[2,3-b]phenazine-6,11-diones, 6,11-dihydrobenzo[2,3-b]phenazine-6,11-diones, tetrahydropyrido[a]phenazine, etc possessed anticancer activities on various cancer cell lines. Benzo[a]phenazine diimine and various other fused aryl phenazine compounds form coordination complex with the metal ions (Ru, Rh, Zn and Pt) that intercalate with the DNA and are used for the treatment of cancer. These molecules have influence on MDR cancer cells and serve as anticancer agents in MDR cancer cells. The structure activity relationship of the fused aryl phenazine derivatives revealed that the occurrence of four or more nitrogen atoms in the compounds has better anticancer activity than those molecules with less number of nitrogen atoms. Phenazine antibiotics derived from marine microbes are used for the treatment of microbial and worm diseases. Recent patents on these scaffolds showed that the benzo[a]phenazine derivatives have inhibitory activity on topoisomerase enzymes (Topo I and II) and that act as anticancer agents.

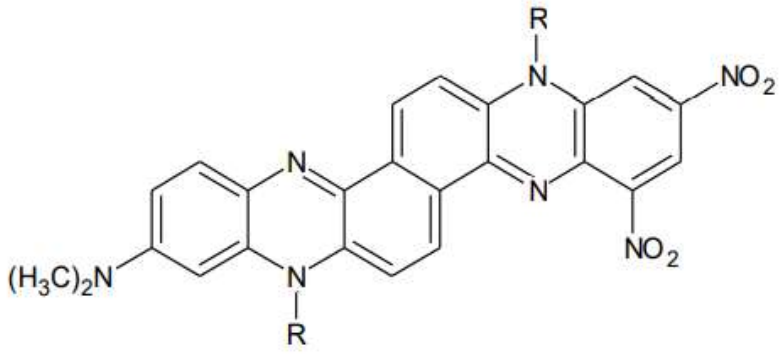


Furan-benzo[a]phenazine

Medlen, et al (1998) [15] have found the invention concerns the new use of riminophenazines in the treatment of a patient who has built up, or could build up, resistance to a therapeutically active substance. Such as a patient requiring treatment for cancer. The riminophenazine conveniently may be of the general formula (I) R1 is a hydrogen atom, a halogen atom or a (C1-C3) alkyl, (C1-C3) alkoxy, fluoromethoxy or trifluoromethyl radical. R2 is a hydrogen or halogen atom. R3 is selected from hydrogen. (C1-C4) alkyl, N,N-dialkylamino alkyl, (Cs-C12) cycloalkyl, methylcyclohexyl, hydroxycyclohexyl, cycloalkylmethyl, piperidyl, alkyl substituted piperidyl or N-benzyl-substituted piperidyl. R4 is a hydrogen or halogen atom or a (Cl-C3) alkyl. (C 1-C3) alkoxy, fluoromethoxy or trifluoromethyl radical and n is 1, 2 or 3. The invention also provides novel rirninophenazines of general formula (1). Their preparation and compositions containing them



Goetz, et al (2011)[16] present invention relates to NLO chromophores for the production of First-, second, third- and/ or higher order polariZabilities of the form of Formula I:



wherein each R represents a spacer system or substituent moiety as disclosed herein.

Objectives

2-Phenazinamine is becoming the novel attractive target molecules for extensive research due to its independent exhibit of a wide spectrum of activities. 2-Phenazinamine linked with various groups is physiologically and pharmacologically active and finds applications in the treatment of several diseases. It is an important pharmacophore and privileged structure in medicinal chemistry encompassing a diverse range of biological activities including anti-bacterial, anti-inflammatory, analgesic, anti-cancer, anti-ulcerative, anti-tumor, anti-HIV and antinociceptive ones.

Research Methodology

Research Methodology refers the discussion regarding the specific methods chosen and used in a research paper. This discussion also encompasses the theoretical concepts that further provide information about the methods selection and application. In order to apply the analytical and descriptive methods to the research a close reading and detailed analysis of secondary sources available.It is significant to get other perceptions to elaborate the textual analysis and this would need close reading analysis of few secondary materials.

Result and Discussion

2,4-Diamino diphenylamine was immediately refluxed for 24 h in nitrobenzene (100 mL) containing $MgSO_4$ in a flask. After nitrobenzene removal in vacuo, and the residue was quenched with water, extracted with dichloromethane and dried over anhydrous Na_2SO_4[17]

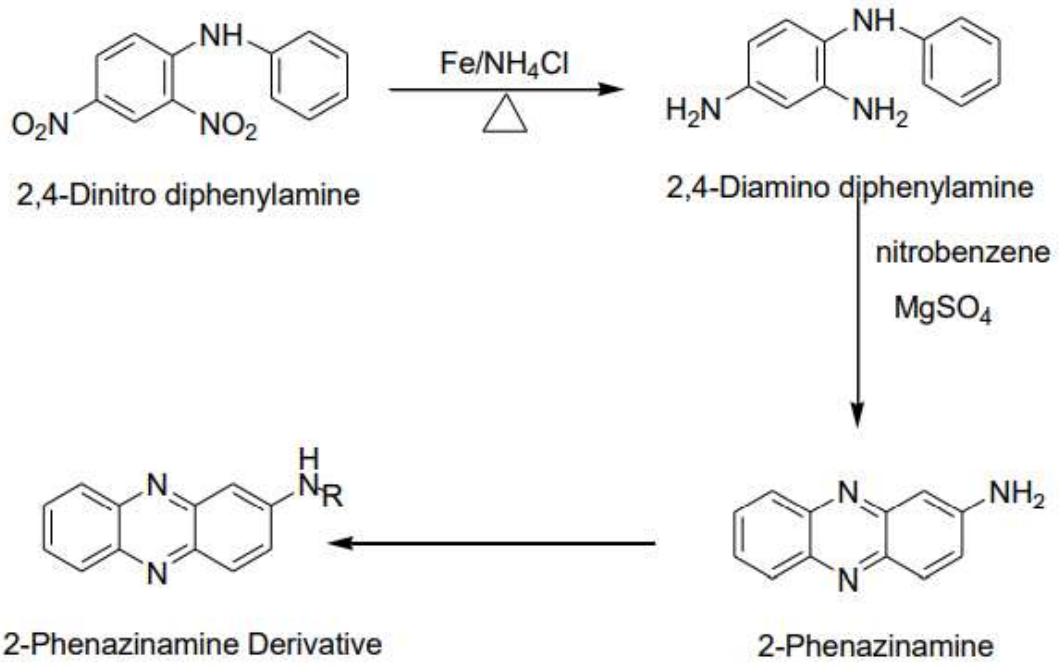


Fig. 3 Synthesis of parent compound 2-phenazinamine

All the synthesized derivatives were characterized by infra red spectroscopy in the range of 400-4000 cm-1 by FTIR. The IR spectra of synthesized derivatives were as follows[18]

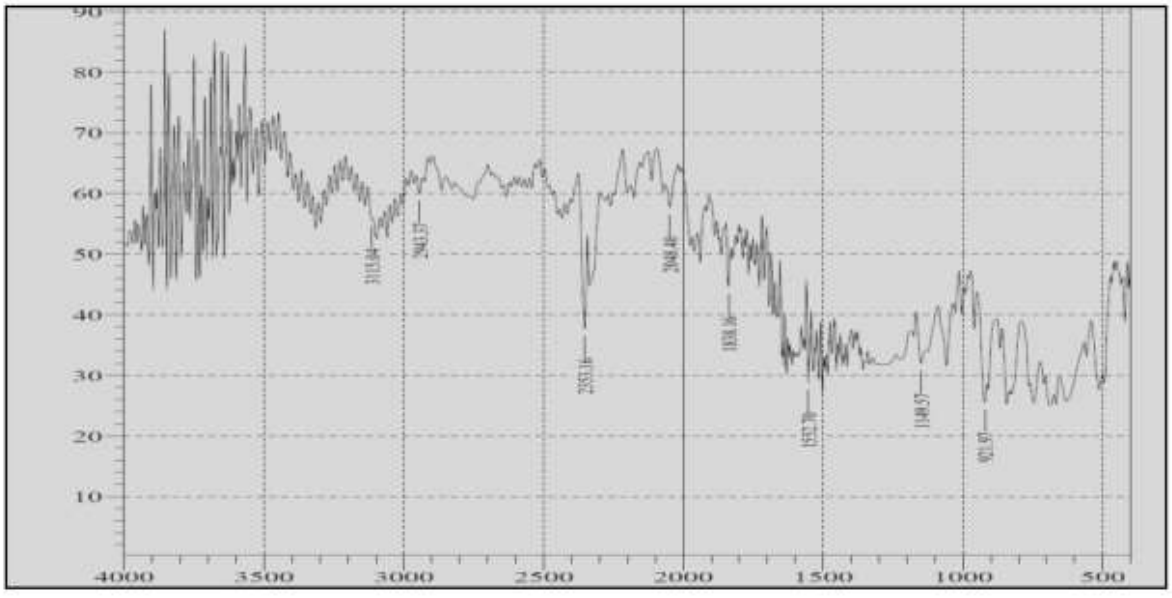


Fig. 4 IR spectra for 2,4-Dinitrodiphenylamine

Mass spectrometry determines the molecular weight of the compound by ionizing it by different techniques and producing different fragment ions peaks. Each ion peak has got its own applications in the determination of molecular weight and identification of the structure of compound.Mass spectral characterization confirms the formation of tetrazole derivatives indicated by molecular ion peaks in the mass spectrum at molecular weight. [19]Mass spectrum of phenazinamine and its derivatives is as depicted below:

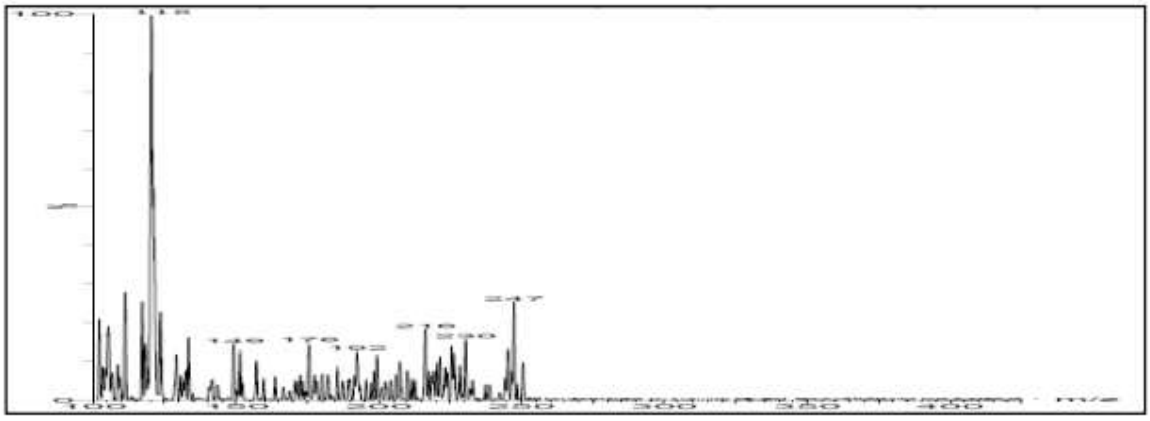


Fig. 5 Mass spectrum of 2-Phenazinamine

Table.1 Standard drugs used for Antibacterial Activity

Standard drug	*E.coli* MTCC 442	*P.aeruginosa* MTCC 441	S.aureus MTCC 96	S.pyogenus MTCC 443
	(MIC µg/ml)			
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	-	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

The results reported in Table indicate that the synthesized compounds are able to inhibit in vitro growth of screened microorganisms showing MIC values between 100-250 µg/ ml[20]

Table 2. Antimicrobial activity of synthesized compounds

	(MIC µg/ml)			
S1	100	50	62.5	100
S2	125	200	150	125
S3	200	100	200	250
S4	100	125	250	125
S5	125	250	100	200
S6	200	125	100	125

Table 2 reveals that the synthesized compounds S1-S6 provided antibacterial activity against Escherichia coli (MTCC 44), P. aeruginosa (MTCC 441), S. aureus (MTCC 96), S. pyogenus (MTCC 443) possessing MIC value between 50-250 µg/ ml, except the derivative S1 which was found active at a MIC value of 100 µg/ ml, 62.5 µg/ ml against S. aureus, S. pyogenus respectively (more potent than Ampicillin). And S1 which was found active at a MIC value of 62.5 µg/ ml (compared with Ampicillin more potent) against S. aureus. However, all the synthesized compounds exhibited lower antibacterial potencies than control drug.

Table 3. Antifungal activity of synthesized compounds

Compound	***C. albicans*** **MTCC 227**	***A. niger*** **MTCC 282**	***A.* clavatus** **MTCC 1323**
	(MIC µg/ml)		
S1	500	1000	>1000
S2	1000	>1000	>1000
S3	250	500	500
S4	500	1000	>1000
S5	500	>1000	1000
S6	1000	1000	>1000

From above table we can view the all compounds with their antifungal activity of synthesized compounds.

Table 4. Standard drugs used for Antifungal Activity

Standard drug	C.ALBICANS MTCC 227	A.NIGER MTCC 282	A.CLAVATUS MTCC 1323
	(MIC µg/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

For Antifungal Activity there are some drugs are available which are Nystain and Greseofulvin which are listed above.

Conclusion

2-Phenazinamine derivatives were synthesized after the prediction of their activities by Vlife MDS 4.3 version software and as per the planned route of synthesis. Reactions were monitored routinely till completion thin layer chromatography.The Infrared spectra of compounds were obtained using FT-IR Spectrophotometer 2000,through KBr pellet method and peaks are expressed in terms of wavenumber (cm-1). The FTIR interpretation is satisfactory and the entire compounds confirm to their anticipated structures.All the derivatives were subjected to antimicrobial susceptibility testing to determine minimum inhibitory concentration (MIC) against gram positive (S. Aureus, S.Ppyogenes) and gram negative bacteria (E. Coli, P aeruginosa).

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