1.1 Introduction:

The drug design by molecular manipulation is a productive source of new drugs. Molecular manipulation, combinations of biologically active moieties into one molecule and synthesis of totally newer moieties have been the methods of research. This observation was a guiding thought in the present work in exploring the synthesis of some new compounds with a desired and highly potent, more specific and less toxic drugs.

Drug discovery and development has a long history and dates back to the early days of human civilization. Religious leaders were often the administrators of drugs. The early drugs or folk medicines were derived mainly from plant products and supplemented by animal materials and minerals. These drugs were probably discovered through a combination of trial and error experimentation and observation of human and animal reactions as a result of ingesting such products. Although these folk medicines probably originated independently in different civilizations, there are a number of similarities, for example, in the use of the same herbs for treating similar diseases. This is likely to be a contribution by ancient traders, who in their travels might have assisted the spread of medical knowledge.

Drug discovery and development started to follow scientific techniques in late 1800s. From then, more and more drugs were discovered, tested, and synthesized in large scale manufacturing plants, as opposed to the extraction of drug products from natural sources in relatively small batch quantities. After the First World War, the modern pharmaceutical industry came into being, and drug discovery and development following scientific principles were firmly established. In the early days, until the late 1800s, most drugs were based on herbs or extraction of ingredients from botanical sources.

Pharmaceutical drugs are now widely used worldwide. The Renaissance period laid the foundation for scientific thoughts in medicinal preparations and medical treatments. There were many advances made in anatomy, physiology, surgery, and medical treatments, including public health care, hygiene, and sanitation. Despite the advances made in the 1800s, there were few drugs available for treating diseases at the
beginning of the 1900 s, More systematic research was being performed to discover new drugs from the early 1900 s.

The synthetic drugs using chemical methods were heralded at the beginning of the 1900 s, and the pharmaceutical industry was founded. Many drugs were investigated and manufactured, but mostly they were used for therapeutic purposes rather than completely curing the diseases. From the early 1930s, drug discovery concentrated on screening natural products and isolating the active ingredients for treating diseases. The active ingredients are normally the synthetic version of the natural products. These synthetic versions, called new chemical entities (NCEs), have to go through many iterations and tests to ensure they are safe, potent, and effective.

The literature survey reveals that most of active drug contain amino moiety.

The following amino moiety drugs are used for synthesis of Schiff base and their derivatives.

a) Sulphadoxine  
b) Pyrazinamide  
c) Zonisamide  
d) Ethionamide  
e) pyrimethamine  
f) Metochlopramide  
g) Tyramine etc.

1.2 Sulphadoxine:

Sulfadoxine is an ultra-long-lasting sulfonamide often used in combination with other drugs used for respiratory, urinary tract, malarial infections and to treat or prevent various infections in livestock. Sulfadoxine competitively inhibits dihydropteroate synthase, interfering with folate synthesis. It acts by increasing oxygen in blood.

Sulfadoxine is a sulfa drug, often used in combination with pyrimethamine to treat malaria. This medicine may also be used to prevent malaria in people who are living in, or will be traveling in an area where there is a chance of getting malaria.
Sulfadoxine targets plasmodium dihydropteroate synthetase and dihydrofolate reductase. Sulfa drugs or Sulfonamides are antimetabolites. They compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides exploits the difference between mammal cells and other kinds of cells in their folic acid metabolism. All cells require folic acid for growth. Folic acid (as a vitamin) diffuses or is transported into human cells. However, folic acid cannot cross bacterial (and certain protozoan) cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from aminobenzoic acid.

Sulphadoxine-pyrimethamine (SP) is still useful as the first-line antimalarial drug in Malawi or it must be quickly withdrawn from the antimalarial repertoire. In-vivo parasitological response to sulfadoxine-pyrimethamine in pregnant women in southern Malawi³.

1.3 Pyrazinamide:

Pyrazinamide is a small molecule quite stable having basic amino functions in aromatic ring. Amide group can be hydrolysed under strong conditions to pyrazinoic acid & ammonia. It forms slight pink metal complexes and sublimes when heated. It is optically active, stable in anhydrous solid state, degrades in solution or when solid is exposed to moisture. Pyrazinamide is a very effective antimycobacterial agent, used in tuberculosis treatment⁴⁻⁵. Pyrazinamide is unusual among anti-tuberculous agents in its ability to promote a durable cure and shorten the duration of therapy⁶.

Pyrazinamide kills or stops the growth of certain bacteria that cause tuberculosis (TB). It is used with other drugs to treat tuberculosis. It is a highly specific agent and is active only against Mycobacterium tuberculosis. Pyrazinamide is an important sterilizing prodrug that shortens tuberculosis (TB) therapy⁷⁻⁹.

Pyrazinamide is well absorbed orally and is an essential part of the treatment of tuberculous meningitis. It is metabolised by the liver and the metabolic products are excreted by the kidneys. Pyrazinamide is a potent antiuricosuric drug¹⁰ and consequently has an off-label use in the diagnosis of causes of hyperuricemia and hyperuricosuria.¹¹
1.4 Zonisamide:

Zonisamide is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents; blocks repetitive firing of voltage sensitive sodium channels and reduces voltage-sensitive T-type calcium currents. Heterocyclic methanesulfonamide with anticonvulsant properties. It is moderately soluble in water and in 0.1N hydrochloric acid. It is used in anticonvulsant and epilepsy, indicated for adjunctive therapeutic used in the treatment of partial seizures in adults. Although zonisamide is only approved for use in epilepsy, it may be helpful in patients suffering from pain syndromes and depression. Zonisamide exerts its anticonvulsant effect in vitro studies suggest a blockade of sodium channels, with consequent stabilization of neuronal membranes and suppression of neuronal hypersynchronization. Whereas other in vitro studies shown zonisamide suppress synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses.

Zonisamide does not potentiate the synaptic activity of GABA. Zonisamide also serves as a weak inhibitor of carbonic anhydrase. Patients with hypersensitivity reactions to sulfonamide antibiotics may also be allergic to zonisamide. Zonisamide increased mutation frequency in Chinese hamster lung cells in the absence of metabolic activation.

Zonisamide has been studied and used as a migraine preventative medication, and has also been shown to be effective in some cases of neuropathic pain. Most people who take zonisamide tolerate it without unwanted side effects. Those who experience undesirable effects most often complain is sleepiness or fatigue, dizziness, loss of appetite/weight, upset stomach, headache, agitation or irritability etc. This drug may make you dizzy or drowsy. Do not drive, use machinery, or do any activity that requires alertness until you are sure you can perform such activities safely.
1.5 Ethionamide:

Ethionamide or 2-ethylthioisonicotinamide was discovered in 1956 which is an antibiotic used in the treatment of tuberculosis. Ethionamide is activated by EthA, a mono-oxygenase in Mycobacterium tuberculosis, and binds NAD to form an adduct which inhibits InhA in the same way as isoniazid. It is a prodrug and as a thioamide, it is used in regimens to treat multi-drug-resistant and extensively drug-resistant tuberculosis. It has been used for treatment of multibacillary leprosy in conjunction with other antimycobacterials. Previously recommended as an alternative agent for use in multiple-drug regimens in leprosy patients who would not accept or could not tolerate clofazimine.

Ethionamide is bactericidal or bacteriostatic in action. It is a highly specific agent; active only against Mycobacterium and acquired resistance to ethionamide demonstrated in vitro and in vivo in strains of M. tuberculosis.

Ethionamide, a prodrug that undergo metabolic activation to exert its cytotoxic effects, is a second line drug against tuberculosis, a disease that infects more than a third of the world's population. Resistance to frontline therapeutics, most notably INH and rifampicin, results in treatment of patients with “second-line” agents that are less effective and/or more toxic. Among these second tier drugs for the treatment of multidrug-resistant tuberculosis, one of the most effective is ethionamide.

1.6 Pyrimethamine:

Pyrimethamine is an anti-microbial drug further classified as anti-parasitic drug more particularly anti-protozoal agent. It is used for the treatment of malerial infection for the treatment of toxoplasmosis and acute malaria and the prevention of malaria in areas non-resistant to pyrimethamine.
Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are essential for DNA synthesis and cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.

Pyrimethamine is a medication used for protozoal infections. It is commonly used as an antimalarial drug for both treatment and prevention of malaria. It is also used in combined with sulfadiazine in the treatment of toxoplasma gondii infections in immunocompromised patients, such as HIV-positive individuals. Pyrimethamine interferes with tetrahydrofolic acid synthesis from folic acid by inhibiting the enzyme dihydrofolate reductase (DHFR). Tetrahydrofolic acid is needed for DNA and RNA synthesis in many species, including protozoa.

Resistance to pyrimethamine is widespread. Mutations in the malarial gene for dihydrofolate reductase may reduce the effectiveness of pyrimethamine. These mutations decrease the binding affinity between pyrimethamine and dihydrofolate reductase via loss of hydrogen bonds and steric interactions. Pyrimethamine has been extensively used as monotherapy in mass drug administrations in Asia and South America, which is likely to have contributed to the emergence and spread of pyrimethamine-resistant Plasmodium falciparum strains.

1.7 Metoclopramide:

Metoclopramide mostly used for stomach and esophageal problems. It belongs to the group of drug known as dopamine-receptor antagonist. It is commonly used to treat nausea and vomiting, to help with emptying of the stomach in people with delayed stomach emptying due to either diabetes or following surgery, and to help with gastro esophageal reflux disease. It is also used to treat migraine headaches. By inhibiting the action of dopamine, it has been used to stimulate lactation. Metoclopramide is also commonly used to prevent vomiting in cats and dogs. It is also used as a gut stimulant in rabbits. Metoclopramide used in all stages of pregnancy with no evidence of harm to the mother or unborn baby.

Metoclopramide can be given for severe and long-lasting vomiting if the cause is known, to stop vomiting caused by cancer treatment such as radiotherapy and chemotherapy, to help in passing a tube into the stomach and intestine and to help stop feeling and being sick before having an operation.
Metoclopramide is contraindicated in case of epilepsy, if a stomach operation has been performed in the previous three or four days, if the patient has ever had bleeding, perforation or blockage of the stomach, in cases of pheochromocytoma, and in newborn babies. It is the most important medication needed in a basic health system by the World Health Organization's List of Essential Medicines.

1.8 Tyramine:

Tyramine is a naturally occurring monoamine compound\textsuperscript{34}. Tyramine acts as a catecholamine releasing agent. Notably, however, it is unable to cross the blood-brain barrier, resulting in only nonpsychoactive peripheral sympathomimetic effects. A hypertensive crisis can result from ingestion of tyramine-rich foods in conjunction with monoamine oxidase inhibitors (MAOIs)\textsuperscript{35,36}.

Tyramine is a natural substance formed from the breakdown of protein as food are aged, fermented, salted, smoked, aged cheese, pickled or spoiled foods for vegetable. Food high in tyramine include aged cheeses: blue, boursault, boursin, brick (natural), brie, Camembert, cheddar, Colby, Emmenthaler, Gruyere, mozzarella, Parmesan, Provolone, Romano, Requefort, and swiss. It can also be found in american cheese, gouda, processed cheese, sour cream etc.

Tyramine is also known as: 4-(2-Aminoethyl)phenol, p-Tyramine, Uteramine, 4-Hydroxyphenethylamine, Tocosine, Systogene, Tyrosamine, Tyramin. Tyramine does not directly activate adrenergic receptors, but it can serve as a substrate for adrenergic uptake systems and monoamine oxidase so it prolongs the actions of adrenergic transmitters. It also provokes transmitter release from adrenergic terminals. Tyramine may be a neurotransmitter in some invertebrate nervous systems.

The longer a high-protein food ages the greater the tyramine content. Alcoholic beverages should be avoided during a tyramine cleanse. Tyramine induced damage occurs as result of use of MAO. Tyramine can increase blood pressure\textsuperscript{37} (increasing the risk of hypertension) by causing the release of catecholamines, especially in the presence of MAO inhibitor drugs\textsuperscript{38-39}. Tyramine can cause anxiety, mood swing, depression, migraines\textsuperscript{40} or headaches\textsuperscript{41} by overstimulating the adrenal gland, resulting
in the depleting of the body's norepinephrine reserves. Tyramine can cause overstimulating of autonomic nervous system as well.

Organic Chemists and researcher have paid more attention to green synthesis, due to the operational simplicity, lesser time, high yields, easy handling procedure and less hazardous to environment. It is worth noting that the methods that have been established for the preparation of imines and their derivatives are associated with one or more of the following drawbacks; long reaction time, unsatisfactory yields, formation of toxic byproducts, and the use of expensive and hazardous reagents. Furthermore, some other procedures need cumbersome experimental and multi-step procedure. Therefore, it seems highly desirable to find a one step, and inexpensive protocol for the synthesis amino moiety drug derivatives.

We also report a simple protocol that makes these valuable building blocks readily available. In this sense, organic reactions can be done such as ease of handling, low corrosion, minimum execution time, environmentally safe disposal and waste minimization by developing cleaner synthesis routes as green chemistry concern by the elimination of volatile organic solvents.

Considering the above subjects on green organic synthesis, the aim and objective of the proposed work is to synthesize amino moiety drug derivatives via an efficient, green and simple method. In present investigations salicylaldehyde or halo-substituted salicylaldehyde or vanillin was condensed with amino moiety drugs to form respective Schiff base. Synthesized Schiff bases were again converted in to different derivatives like 4-thiazolidinones, 2-azetidinones, α-aminophosphonate etc. All the synthesized derivatives were characterized and confirmed from melting point and spectral data analysis like IR, $^1$H NMR and Mass spectra etc. Synthesized derivatives were further screened for antibacterial and antimicrobial activity.

The aim of this work is to synthesize new compounds using amino moiety drug derivatives which are already potent with newer methods. This helps to increases activity of targeted compounds. The literature survey reveals that there is an increase in activity due to different halogen substitution on ring in compounds. It is also shown that less or more different functional moiety in same compound act as more potent respective activity.
1.9 References:


Ph. D. Thesis: S. K. Wasm-atkar, 2015; SRTMU. Nanded