

**CHAPTER - I**  
**INTRODUCTION**

## **CHAPTER 1**

### **INTRODUCTION**

A large proportion of modern pharmaceutical chemistry involves aromatic and non-aromatic heterocyclic compounds. Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophors has largely contributed to their unique value as traditional key elements of numerous drugs for example; the antibiotic penicillin and streptomycin, the sedative Phenobarbital, and the nonnutritive sweetener saccharin all have heterocyclic rings. Many natural pigments such as indigo, hemoglobin and phthalocyanin are heterocycles.

Heterocyclic compounds have great biological significance because:

- a. They have a specific chemical reactivity.
- b. They resemble essential metabolism and can also provide false synthons in biosynthetic process.
- c. They fit receptors and block their normal working.
- d. They provide convenient building blockers to which biologically active substituents can be attached.

The ability to vary the properties of heterocycles by manipulating their structures makes such systems highly amenable to drug discovery and accounts for the widespread occurrence of active compounds

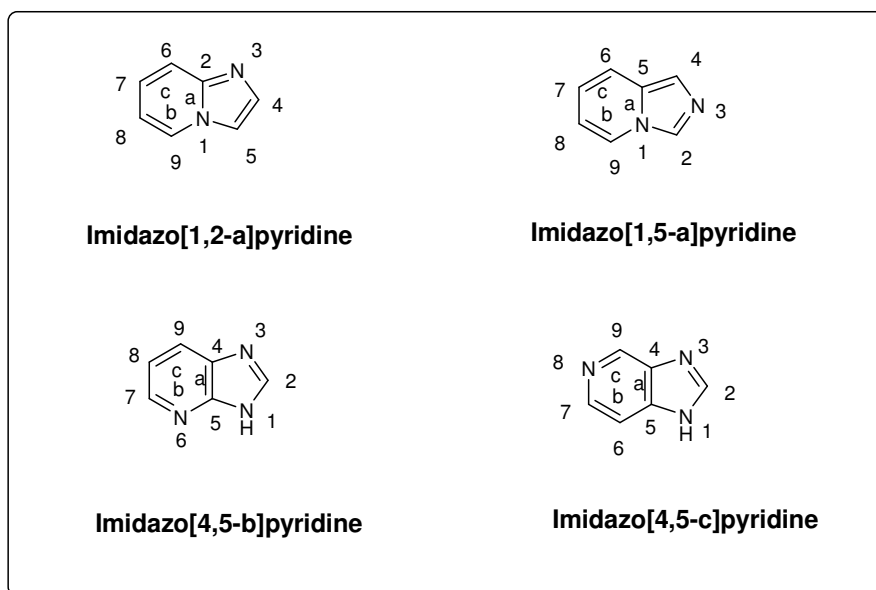
containing a heterocyclic core. However, the elaboration of heterocycles is often difficult due to their sometimes low reactivity and selectivity. There are various approaches that have been adopted, often in combination with one another, to circumvent these inherent disadvantages such as multicomponent,<sup>1</sup> metal-catalysed coupling<sup>2</sup> and cycloaddition reactions, annulation of alkynes and their equivalents,<sup>3,4</sup> and sequential nucleophilic aromatic substitution.<sup>5,6</sup>

The [5,6] fused-ring motif has been shown to be in the top eight most frequently occurring frameworks in drugs.<sup>7</sup> This is, of course, largely due to the relatively commonly employed pharmacophores indole, benzimidazole and purine. However, the ability to vary the hetero atoms present in these scaffolds gives systems with differing electronic properties and, potentially, improved activities. The pyridine ring-fused heterocycles are an important source of biologically relevant compounds and have been made through various methods, often involving building the fused ring by attaching functionality around pyridine, a compound that is difficult to functionalise selective in a quick and flexible manner.<sup>8</sup>

Imidazopyridine is one of the important fused bicyclic 5–6 heterocycles. These are important class of biologically active nitrogen containing heterocyclic compounds. The imidazole moiety fused with the pyridine ring to form a bicyclic imidazoheterocyclic scaffold is recognized as a privileged structure. Nitrogen bridgehead-fused heterocycles containing an imidazole ring are common structural

motifs in pharmacologically important molecule with activities spanning a diverse range of targets. It represents a promising area due to its wide applications in medicinal chemistry. This moiety is also useful in material science because of its structural character.

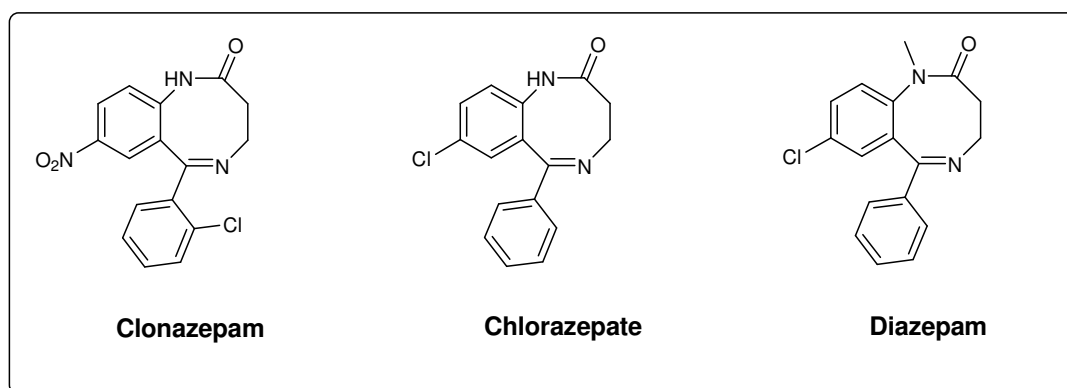
Imidazopyridine derivatives are of great importance because of their remarkable biological properties. They are of chemical and pharmacological interest due to their isosterism with indoles and azaindoles, two important heterocycles involved in many alkaloids. Some of them have been used as herbicides, fungicides, pesticides, medicines and dyes. The imidazopyridines comprise four important isomers: imidazo[1,2-a]-pyridine, imidazo[1,5-a]pyridine, imidazo[4,5-b]pyridine, and imidazo[4,5-c]pyridine.



**Fig 1.1: Isomers of midazopyridines**

The imidazopyridines are a class of drugs defined by their chemical structure. These derivatives found to have good potency for various diseases. In general, they are gamma amino butyric acid (GABA) receptor agonists, proton pump inhibitors, aromatase inhibitors, Non steroidal anti-inflammatory drugs (NSAIDs) and other classes of drugs. Despite usually being similar to them in effect, they are not chemically related to benzodiazepines. As such, GABA agonizing imidazopyridines, pyrazolopyrimidines and cyclopyrrones are sometimes grouped together and referred to as “nonbenzodiazepines.”

**Benzodiazepine** – Benzodiazepine is a class of drugs has properties of hypnotic, anxiolytic, anticonvulsive, amnestic (memory disturbance), anticonvulsant and muscle relaxant. Benzodiazepines are used as a central nervous system depressant. At long-term use can be problematic because of the reduction of anticonvulsant effects and make addiction.



**Fig 1.2: Benzodiazepine drugs**

### ***Non benzodiazepine***

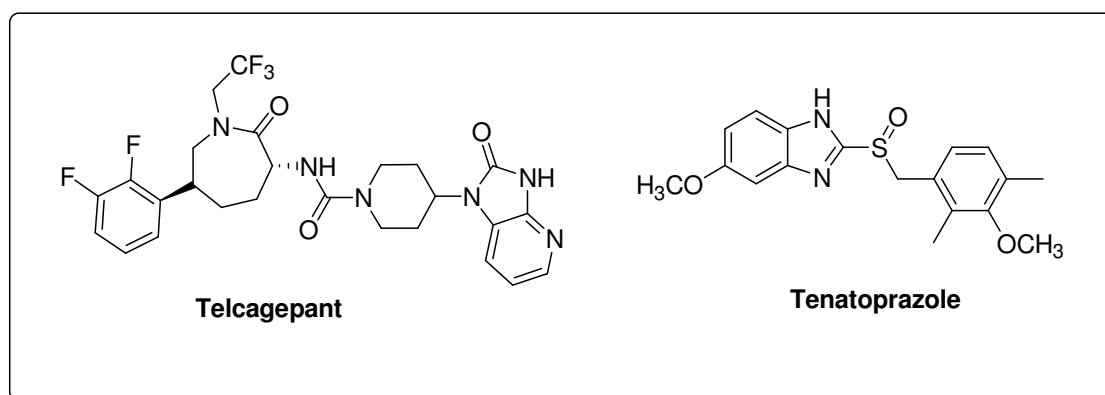
Nonbenzodiazepines are also called benzodiazepine-like drugs. The nonbenzodiazepine class of psychoactive drugs, although completely different or mismatches chemical structures, has pharmacologically similar benefits and risks of side effects. Nonbenzodiazepines have shorter duration of action than benzodiazepines and have fewer side effects. Both benzodiazepines and nonbenzodiazepines as sedative hypnotics, effect GABA receptor sites in the brain but non benzodiazepines are more specific to the target sub-units. The nonbenzodiazepines are generally used as sedatives, anticonvulsants, hypnotics, anxiolytics and muscle relaxants as they show less adverse effects compared to classical benzodiazepines.<sup>9</sup>

There are three main classes of chemical non-benzodiazepines. These are a) imidazopyridines (ex: zolpidem) b) cyclopyrrolones (ex: zopiclone) and c) pyrazolopyrimidines (ex: zaleplon). All three classes of these drugs are approved for the use in the US and are classified as Control Substances Schedule IV by FDA. Zolpidem, eszopiclone and zaleplon have strong sedative properties without anxiolytic, myorelaxant or anticonvulsant effects. They all bind to GABA receptor complex.

Imidazopyridines are one of the most important non benzodiazepine drugs and commonly biologically active compounds. Especially imidazo [1,2-a] pyridines are an essential part of pharmacologically

important molecules. In particular, imidazo[1,2-a]pyridine moiety is a vital fragment present in biologically active molecules, which include several anxiolytic drugs and other potent molecules which have properties as antivirals, anticancer, anti-inflammatory effects. By looking at the work done for Imidazo[1,2-a]pyridines that has the potential in various fields such as cancer, neurology, virology, endocrinology therapeutic applications. Other imidazopyridines also had shown interesting therapeutic activities.

**Imidazo[4,5-b]pyridine related biologically active molecules:**



**Fig 1.3: Imidazo[4,5-b]pyridine related drugs**

**Telcagepant:**

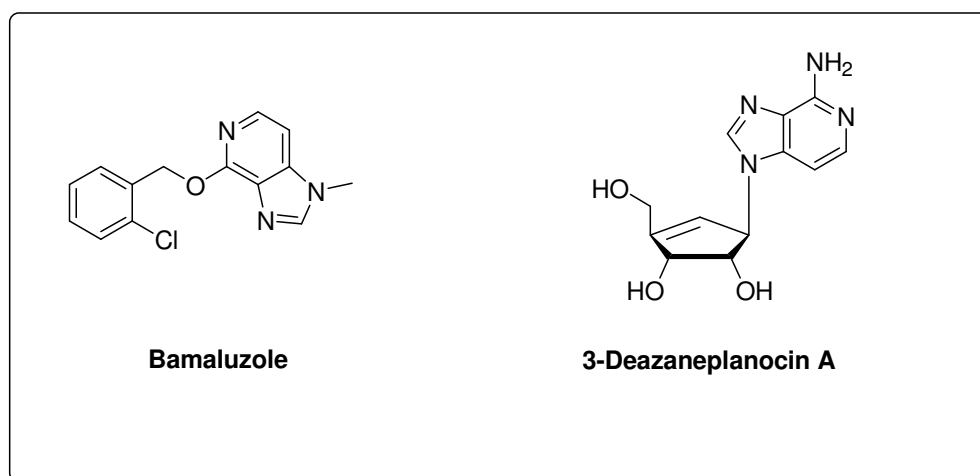
Telcagepant is an oral calcitonin gene related peptide (CGRP) receptor antagonist that is being developed by Merck&Co. This drug is potentially very exciting for migraine patients because it works by a totally new mechanism.<sup>10</sup> Telcagepant works by blocking the dilation of blood vessels surrounding the brain during a migraine. This means that this drug may be particularly helpful for people who haven't done

well with the currently available drugs that target serotonin receptors, like the triptans.

### **Tenatoprazole:**

Tenatoprazole is a proton pump inhibitor drug candidate. It blocks the gastric proton pump leading to decline of gastric acid production.<sup>11</sup> The compound was invented by Mitsubishi Tanabe Pharma. Tenatoprazole has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors and has a half-life about seven times longer than other proton pump inhibitors.

### **Imidazo[4,5-c]pyridine related biologically active molecules:**



**Fig 1.4: Imidazo[4,5-c]pyridine related drugs**

### **Bamaluzole:**

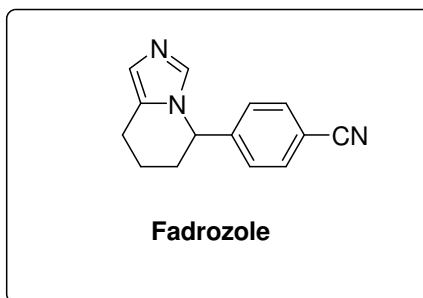
Bamaluzole is a gamma amino butyric acid (GABA) receptor agonizing anticonvulsant. It was patented as an anticonvulsant by Merck Co but this drug not in the market due to side effects in the biological activity.



### 3-Deazaneplanocin A:

3-Deazaneplanocin A is a cyclopentenyl analog of 3-deazaadenosine, originally synthesized as an inhibitor of S-adenosyl-L-homocysteine hydrolase.<sup>12</sup> It acts as both a S-adenosylhomocysteine synthesis inhibitor and also a histone methyltransferase EZH2 inhibitor. Studies have shown that it has *in vitro* against a variety of different tumor cell lines.<sup>13</sup> It was also found to be effective for the treatment of Ebola virus disease,<sup>14</sup> apparently interfering with the Ebola viruses ability to block interferon production which usually allows it to evade immune responses.

### Imidazo[1,5-a]pyridine related biologically active molecules:



**Fig 1.5: Imidazo[1,5-a]pyridine related drug**

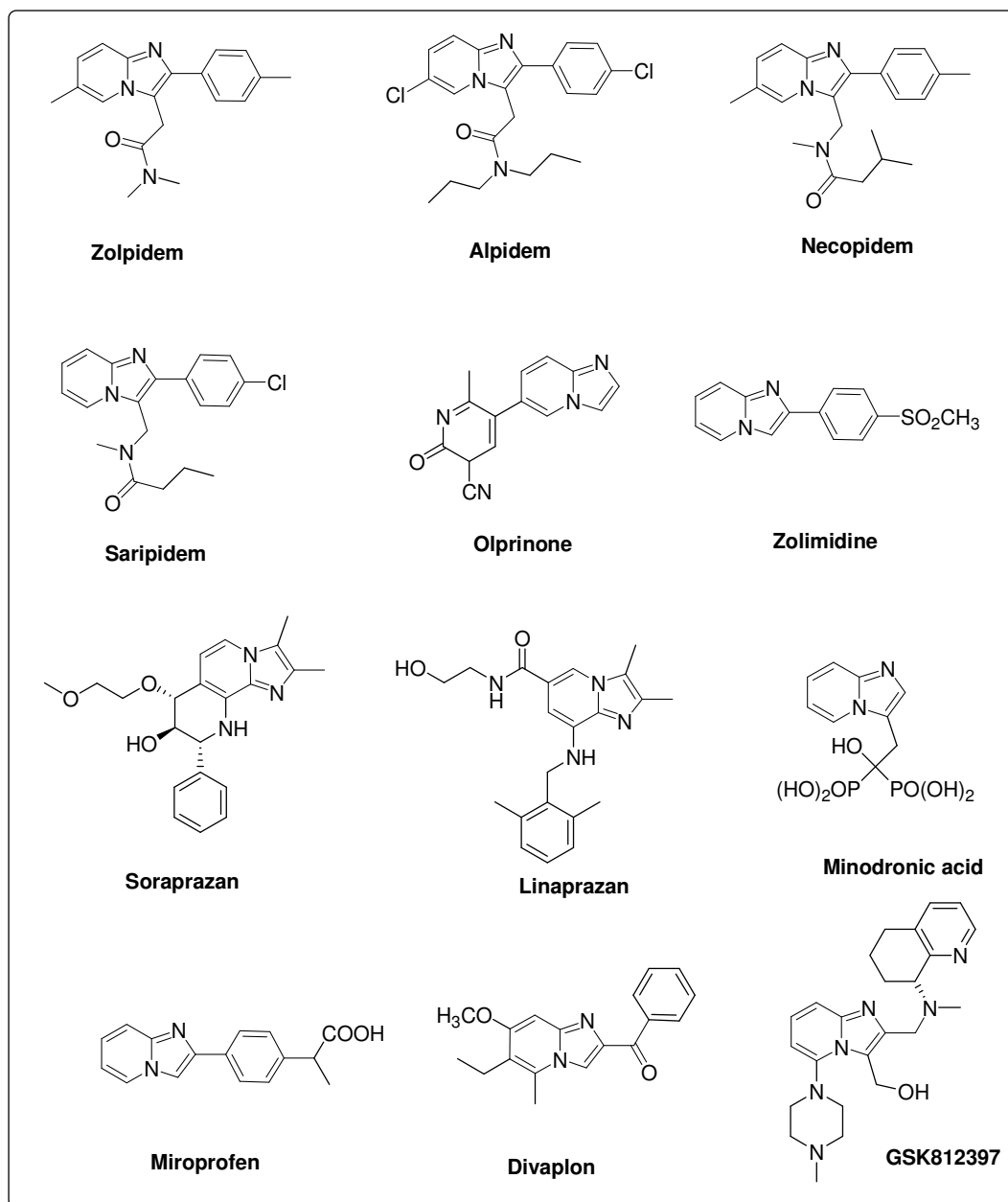
#### **Fadrozole:**

Fadrozole is a potent, selective nonsteroidal aromatase inhibitor. Its chemical name is 4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzotrile. It has ability to selectively inhibit aromatase over other cytochrome P-450 enzymes and suppress estrogen production when administered orally make it a suitable candidate to test the potential

of an aromatase inhibitor in estrogen-dependent diseases<sup>15</sup> including breast cancer.

**Imidazo[1,2-*a*]pyridine related biologically active molecules:**

Imidazo[1,2-*a*]pyridines are a class of *N*-bridged fused bicyclic compounds, which attracted significant attention in recent years due to the broad spectrum of pharmacological profiles displayed. Among the various imidazopyridine derivatives, imidazo[1,2-*a*]pyridine moiety is the most important in the area of natural products and pharmaceuticals. These derivatives show a wide range of biological activities such as antifungal, antiinflammatory, antitumor, antiviral, antibacterial, antiprotozoal, antipyretic, analgesic, antiapoptotic, hypnoselective and anxioselective activities.<sup>16-26</sup> They also act as  $\beta$ -amyloid formation inhibitors, GABA and benzodiazepine receptor agonists, and cardiotoxic agents.<sup>27-30</sup> There are several drugs available in the market which contain imidazo[1,2-*a*]pyridine moiety and many research groups are working to explore towards the development new derivatives of this moiety . In general, these profiles are shown to be strongly dependent on the nature of substituent at 2 and 3 positions of imidazo[1,2-*a*]pyridine functional group.



**Fig 1.6: Imidazo[1,2-a]pyridine related drugs**

**Zolpidem:**

zolpidem is more popular drug of imidazo[1,2-a]pyridine related drugs and widely used for short-term treatment of insomnia. It addresses sleep-initiation problems. Zolpidem has slight muscle relaxant and anticonvulsant properties, but has not been approved for use in

muscle relaxation or seizure prevention. It is developed by Synthe labo.<sup>31</sup>

**Alpidem:**

Alpidem is an anxiolytic drug from the imidazo[1,2-a]pyridine family and developed by Synthe labo.<sup>32,33</sup> This is used specifically for the treatment of anxiety and does not produce sedative effects at normal doses.

**Necopidem:**

Necopidem is a drug related to imidazo[1,2-a]pyridine family and considered to have sedative and anxiolytic effects.<sup>34</sup>

**Saripidem:**

Saripidem is a sedative and anxiolytic<sup>34</sup> drug and has similar pharmacological profile to the benzodiazepine related drugs.

**Olprinone:**

Olprinone is cardio tonic agent. It is a phosphodiesterase III inhibitor,<sup>35</sup> augments cerebral blood flow by a direct vasodilator effect on cerebral arteries.

**Zolimidine:**

Zolimidine is a useful drug for the treatment of peptic ulcer.<sup>36</sup> It is a gastroprotective drug used for gastroesophageal reflux disease.

**Soraprazan:**

Soraprazan is useful for the treatment of Stargardt's disease,<sup>37</sup> which is genetic disorder of the eye that leads to progressive loss of sight. It shown positive results for inhibition of acid secretion in in-vitro models. It is also used for the treatment of gastro esophageal reflux disease (GERD).

**Linaprazan:**

Linaprazan is a potassium competitive acid blocker, used in the treatment of gastro esophageal reflux disease (GERD).<sup>38</sup>

**Minodronic acid:**

Minodronic acid is a third-generation bisphosphonate drug.<sup>39</sup> It is approved for use in Japan for the treatment of osteoporosis. Its mechanism of action involves inhibition of farnesyl pyrophosphate synthase activity.

**Miroprofen:**

Miroprofen is an analgesic and non-steroidal anti inflammatory drug.<sup>40,41</sup> It has activity for anti inflammatory, antipyretic and antiplatelete aggregation. Chemically it is a carbocyclic acid and phenylpropionate.

**Divaplon:**

Divaplon is a nonbenzodiazepine, anxiolytic and anticonvulsant drug from the pyrazolopyrimidine family of drugs.<sup>42</sup> It acts as a partial agonist at the "benzodiazepine site" of the GABA receptor in the brain.

**GSK812397:**

Developed by GSK for the treatment of HIV as antiviral agent.<sup>43</sup>

**Mycobacterium tuberculosis**

*Mycobacterium tuberculosis* is a pathogenic bacteria and the causative agent of most cases of tuberculosis (TB). TB is one of the most prevalent diseases and is responsible for the deaths of about one billion people during the last two centuries.<sup>44,45</sup> The statistics shows that around 32% of the world's population is infected by *M. tuberculosis*, the main causal agent of TB and today more people die from tuberculosis than ever before.<sup>46</sup> According to estimates of the World Health Organization (WHO), TB is a frequently fatal infectious disease that causes more than 1.4 million deaths annually and there were an estimated 8.7 million new cases of TB every year.<sup>47</sup> Globally, there were an estimated 48% of the TB patients known to be living with HIV in 2011. TB is an airborne infectious disease that often remains in its latent form, it is very different from that for other bacterial infections. The organism has a long generation time and a capacity for dormancy, when its low metabolic activity makes it a difficult therapeutic target.<sup>48,49</sup> In addition, *M. tuberculosis* may be located in pulmonary cavities, empyemaps, or solid caseous material, where penetration of antibiotics is difficult or the pH is sufficiently low to inhibit the activity of most antibiotics.<sup>50</sup> Despite the fact that the present chemotherapy has a cure rate of up to 95%, because of poor patient compliance arising from prolonged therapy,

the disease has been spreading at a steady rate. This leads to the evolution of multi-drug resistant (MDR-TB) and extensively drug resistant TB causing a major impediment in treating the disease.<sup>51</sup> The resurgence in TB is alarming due to the development of pathogenic synergy with HIV.<sup>52</sup> The currently employed first-line drugs, isoniazid, rifampin, ethambutol and pyrazinamide for the initial 2 months and rifampin and isoniazid for an additional 4 months. The need for such lengthy treatment is largely because the drugs are relatively ineffective against the persistent form of the disease<sup>53</sup> and second-line agents such as kanamycin, p-aminosalicylic acid, ciprofloxacin or cycloserine<sup>54</sup> also suffer from associated side-effects and poor efficacy in eradicating dormant pathogens. In the last 50 years, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB, which reflects the inherent difficulties in the discovery and clinical testing of new agents.<sup>55</sup> Hence, the discovery of fast-acting effective newer drugs to effectively cure TB, including multidrug resistant tuberculosis, is imperative.

To date, several anti-tubercular agents in different combinations are in clinical application for the treatment. However, patients often develop resistance to commonly used regimen. The expansion of multidrug-resistant TB (MDR-TB) and the emergence of drug-resistant TB (XDR-TB) cause new tackle for the prevention, cure and manage of this lethal disease.<sup>56</sup> Therefore, the development of new drugs with

enhanced activity against MDR-TB and XDR-TB is highly appreciated for the prevention of disease.

Current approaches to drug discovery tends to involve the rapid analogue synthesis and testing of small, focused libraries of low molecular weight, structurally similar "druglike" molecules, often based around heterocyclic core scaffolds. If some desired activity is shown by a compound, elaboration can give higher activity and more favorable pharmacokinetic properties. As this "lead generation" stage of drug development has been identified as a major bottleneck in the drug pipeline process, there is a great demand for methodology detailing the synthesis of highly functionalised heterocyclic compounds.

Many researchers in the area of drug discovery are now working to identify inhibitors of *M.tuberculosis*. Diarylquinoline TMC207 was identified as a potent inhibitor of the *M. tuberculosis* ATP synthase in Phase II clinical trials places TMC207 as a future front-line anti-tubercular agent.<sup>57</sup> Similarly, the *M. tuberculosis* inhibitors SQ109,<sup>58-60</sup> adamantly ureas,<sup>61,62</sup> and benzimidazole<sup>63</sup> were identified. Another inhibitor series found to have anti-TB activity are the imidazo[1,2-a]pyridine-3-nitroso compounds, but they exhibit undesirable toxicity in a VERO cell line.<sup>64</sup> A similar family of compounds, the imidazo[1,2-a]pyridine-3-hydrazones, have been synthesized but are all inactive against *M. tuberculosis* H37Rv.<sup>65</sup> More recently, 3-amino-imidazo[1,2-a]pyridines were shown as *M. tuberculosis* glutamine synthetase



inhibitors.<sup>66</sup> The anti-TB properties of the 2,7-dimethylimidazo [1,2-a]pyridine-3-carboxamides have also been investigated.<sup>67</sup> Abrahams *et al.* also identified <sup>68</sup> and tested four imidazo[1,2-a]pyridine compounds which showed good MIC against various strains of *M. tuberculosis* and low toxicity against the HepG2 cell line. Schorey *et al.* also determined the pharmacokinetics and *in vivo* activity<sup>69</sup> of N-(4-(4-chlorophenoxy)benzyl)-2,7-dimethylimidazo[1,2-a]pyridine-3-carboxamide (ND-09759), which showed a low MIC against various strains of *M. tuberculosis*.

Imidazo[1,2-a]pyridines have been identified as potent inhibitors of *M. tuberculosis* and *M. bovis* BCG. These compounds are synthetically tractable, possess druggable properties, and have excellent selective potency against MDR- and XDR-TB. Accordingly, there is continuous effort towards the development of new methods for the synthesis of imidazo[1,2-a]pyridine derivatives with variety of substituents at the 2 and 3-positions of this moiety.

In this thesis we presented a series imidazo[1,2-a]pyridine derivatives containing benzothiazole moiety at the 2 position and various acetamide substituents at the 3 position and depicted in Chapter 2. Various Bis imidazo[1,2-a]pyridine derivatives synthesized and presented in chapter 3. Novel synthesis of key intermediate of zolpidem, 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetonitrile, presented . By using this approach a simplified process for the preparation of zolpidem depicted in chapter 4. A new series of

thiomethyl derivatives at the 3 position of imidazo[1,2-a]pyridines presented in chapter 5. All the compounds structures confirmed by its analytical data using NMR analysis, Mass and X-ray studies.

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