Summary

The thesis entitled “Syntheses and Screening of nitrogen and sulfur containing new heterocyclic analogues as potential antimicrobial and antitubercular agents” exclusively devoted to the study of the heterocyclic compounds. The work presented in this thesis focuses on the synthetic, structural and biological studies of heterocyclic molecules including Schiff bases and β–lactam. This investigation forms a part of comprehensive programme to design and synthesize various bioactive molecules in presence of heterogenous catalyst via conventional and microwave assisted synthesis.

The thesis has been divided into five chapters. Each chapter has its own significance with regards to the characterization and explanation of the subject concern.

**CHAPTER- I**

This chapter devoted to introduction and literature survey of N and S containing heterocycles and their various derivatives. This chapter also describe the various routes of synthesis via conventional or non-conventional methods. This chapter has been divided into six sections- **1.1, 1.2, 1.3 1.4, 1.5 and 1.6** respectively.

**Sections 1.1:** This section is devoted to general introduction of N ans S containing heterocycles and several aspects related to these compounds such as scope, development and importance etc.

**Section 1.2:** This section deals with an elaborate study of the benzothiazole nucleus with a special emphasis to their uses in industry, agriculture and pharmaceutical fields.

**Section 1.3:** This section describes the importance and applications of isoniazid and its derivatives. This nuclei serve as building block for many drugs and particularly associated with antitubercular activity.

**Section 1.4:** This section describes the importance of Schiff bases and 2-azetidinone derivatives. The therapeutic properties of these N and S containing heterocyclic compounds and azomethine moieties have elicited interest in this area and prompted us to design and synthesize new series of 2-azetidinone derivatives and assess their efficacy as potential bioactive drugs.

**Section-1.5:** This section is related to use of environmentally benign method such as microwave irradiation, ultrasonication, grinding, and catalyst for synthesis of
heterocyclic compounds. This section includes synthesis of heterocycles with energy efficient, minimize formation of waste and avoid the use of toxic reagent strategies.

**Section-1.6:** The all above discussed aspects and with successful implementation of silica based heterogenous catalyst in Schiff base synthesis and they further cyclized to azetidinone derivatives both are important pharmacophore unit.

The objective of the research work has been divided into four parts.

**Part I:** To prepared heterogenous catalyst (Scheme-I) and conform their structure by different characterization techniques.

**Part II:** To synthesized the novel class of N and S containing biologically active important analogues of Schiff bases (step-1 in Scheme-II and Scheme-III) via using heterogenous catalyst and 2-azetidinone derivatives (step-2 in Scheme-II and Scheme-III)

**Part III:** These newly synthesized compounds are identified and characterized by chemical methods, microanalytical data and spectral techniques.

**Part IV:** Evaluation of the biological activity of the newly synthesized compounds.

(a) Antibacterial

(b) Antifungal activity and

(c) Antitubercular activity

**CHAPTER- II**

The second chapter describes the design and synthesis of heterogenous catalyst from supported metal oxides for green and efficient synthesis of Schiff bases. In this chapter we prepared silica supported Lewis acid catalyst, its scope was very well reported. It is showing the excellent yield of synthesis of Schiff bases via green protocol. It has been divided into five main sections - **2.1, 2.2, 2.3, 2.4** and **2.5** respectively.

**Section 2.1:** This section includes a brief description of the literature survey of heterogenous catalyst. The synthesis and applications of heterogenous catalyst in various organic transformations also describes in this section.

**Section 2.2:** This section deals with the activity, selectivity and stability of heterogeneous catalyst in chemical reactions.

**Section 2.3:** This section includes the experimental part of heterogeneous catalyst synthesis. This section has further divided into two sub-sections – **2.3.1, 2.3.2.** includes brief experimental synthesis of heterogenous catalyst (P2Os /SiO2) (Scheme-I)
**Summary**

**SCHEME-I**

*Supporting material + Oxidants*

- Stirring & heating at higher temp.
- Cool
- Grinding

Free flow homogeneous mixture of catalyst

**Section 2.4:** This section related to the formation of silica supported heterogenous catalyst which was confirmed by various spectral analysis. This section has further divided into four sub-sections – 2.4.1, 2.4.2, 2.4.3 and 2.4.4 each sections is devoted own type of characterization techniques.

(i) IR

(ii) XRD

(iii) SEM-EDX

(iv) TGA/DTA

**Section 2.5:** This section concluded the SiO₂ supported heterogeneous catalyst was successfully synthesized by simple facile and environmental benign solid state synthesis. This protocol provides wide range of access to compounds that are useful in synthetic medicinal and heterocyclic chemistry.

**CHAPTER- III**

This chapter has been divided into seven sections -3.1, 3.2, 3.3, 3.4, 3.5, 3.6 and 3.7 respectively.

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Section 3.1: This section describes the aim and work plan of the research work derived from 2-amino-6-nitro-benzothiazole nuclei. This section has further divided into three sub-sections – 3.1.1, 3.1.2 and 3.1.3 each sections is devoted to experimental and characterization part of Scheme-II derived compounds.

There are two main objectives of the research plan.

1. To synthesize the P$_2$O$_5$/SiO$_2$ catalyzed Schiff bases and their 2-azetidinone derivatives derived from 2-amino-6-nitro-benzothiazole nuclei via conventional and microwave synthesis.

Two series of the compounds have been synthesized by following Scheme-II in step-1 and 2 respectively.

The compounds of series-1 have been synthesized from following methods:

**Series-01**: Synthesis of Schiff bases in presence of heterogeneous catalyst via conventional and microwave assisted synthesis of step-1 of Scheme-II.

The compounds of series-1 have been synthesized from following methods:

**Step-1**: P$_2$O$_5$/SiO$_2$ catalyzed synthesis of Schiff bases of series-01 (KA-01 to KA-08)

**Table-3.1**

**Conventional method**: Equimolar mixture of 2-amino-6-nitro-benzothiazole, and 2,4-dichloro benzaldehyde and P$_2$O$_5$/SiO$_2$ catalyst refluxed on a water bath in ethanol to give compound KA-01.

**Microwave method**: Equimolar mixture of 2-amino-6-nitro-benzothiazole and 2,4-dichloro benzaldehyde and P$_2$O$_5$/SiO$_2$ in ethanol were performed at 800W power, on microwave irradiation to give compound KA-01.

Other compounds KA-02 to KA-08 were prepared similarly by treating 1 with various aromatic aldehydes.

**SCHEME-III-(Step-1)**

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**Table-3.1**

<table>
<thead>
<tr>
<th>Series-01 Compounds</th>
<th>Reactant aromatic aldehydes</th>
<th>Quantity (in gms)</th>
<th>Rf Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA-01</td>
<td>2,4-Dichloro benzaldehyde</td>
<td>1.75</td>
<td>0.82</td>
</tr>
<tr>
<td>KA-02</td>
<td>2-Bromo benzaldehyde</td>
<td>1.15</td>
<td>0.76</td>
</tr>
<tr>
<td>KA-03</td>
<td>3-Bromo benzaldehyde</td>
<td>1.17</td>
<td>0.72</td>
</tr>
<tr>
<td>KA-04</td>
<td>3-Methyl benzaldehyde</td>
<td>1.18</td>
<td>0.62</td>
</tr>
<tr>
<td>KA-05</td>
<td>4-Methyl benzaldehyde</td>
<td>1.17</td>
<td>0.68</td>
</tr>
<tr>
<td>KA-06</td>
<td>2-Methoxy benzaldehyde</td>
<td>1.73</td>
<td>0.62</td>
</tr>
<tr>
<td>KA-07</td>
<td>4-Methoxy benzaldehyde</td>
<td>1.74</td>
<td>0.68</td>
</tr>
<tr>
<td>KA-08</td>
<td>3,4,5-Tri-methoxy benzaldehyde</td>
<td>1.96</td>
<td>0.72</td>
</tr>
</tbody>
</table>

**Series-02:** Synthesis of 2-azetidinone derivatives via conventional and microwave synthesis in step-2 of Scheme-II.

**Step-2:** Synthesis of 2-azetidinone compounds of series-02 (KA-09 to KA-16)

**Table-3.2.**

**Conventional method:** An equimolar mixture of compound KA-01 and triethylamine in ethanol was added chloroacetylchloride drop wise in ice bath, then refluxed on a steam bath to give furnish, compound KA-09.

**Microwave method:** An equimolar mixture of compound KA-01 and triethylamine, was added chloroacetylchloride drop wise in ice bath, then transferred in ethanol to an open glass vessel and reaction was performed at 800W power in microwave irradiation to give furnish, compound KA-09.

Other compounds Series-02, KA-10 to KA-16 were prepared similarly using the compounds KA-02 to KA-08 as precursor of series-01 in the place of compound KA-01.

**SCHEME-II (Step-2)**

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Table-3.2

<table>
<thead>
<tr>
<th>Series-02 Compounds</th>
<th>Quantity of Schiff bases</th>
<th>Quantity (in grms)</th>
<th>R_f value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA-09</td>
<td>N-(2,4-dichloro-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>3.50</td>
<td>0.76</td>
</tr>
<tr>
<td>KA-10</td>
<td>N-(2-bromo-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>3.61</td>
<td>0.72</td>
</tr>
<tr>
<td>KA-11</td>
<td>N-(3-bromo-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>3.61</td>
<td>0.70</td>
</tr>
<tr>
<td>KA-12</td>
<td>N-(4-methyl-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>2.97</td>
<td>0.68</td>
</tr>
<tr>
<td>KA-13</td>
<td>N-(3-methyl-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>2.97</td>
<td>0.65</td>
</tr>
<tr>
<td>KA-14</td>
<td>N-(2-methoxy-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>3.13</td>
<td>0.70</td>
</tr>
<tr>
<td>KA-15</td>
<td>N-(4-methoxy-benzylidene)-6-nitrobenzothiazole-2-amine</td>
<td>3.13</td>
<td>0.72</td>
</tr>
<tr>
<td>KA-16</td>
<td>N-(3,4,5-trimethoxy-benzylidene)-nitrobenzothiazole-2-amine</td>
<td>3.73</td>
<td>0.78</td>
</tr>
</tbody>
</table>

2. The synthesized compounds **KA-01 to KA-16** were characterized by using various methods such as thin layer chromatography, elemental analysis and spectral data. The melting points of the compounds were determined by open capillary tube method. IR spectra were recorded in KBr disc on Shimadzu 8300 spectrophotometer and $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL RESONANCE spectrometer in DMSO-$d_6$ at 300 MHz and 100 MHz using TMS as an internal standard a chemical shifts reported on δ scales.

**Section 3.2:** The description of proposed mechanism of overall reactions is given in this sections.

**Section 3.3:** This section includes a comparative study of time and yield via conventional and microwave assisted synthesis.

**Section 3.4:** This section described recyclability of the catalyst.

**Section 3.5:** This section studied about the selection of suitable solvent in Schiff bases synthesis.

**Section 3.6:** This section focused on the conformation of synthesis of series-01 and 02 compounds according to their spectral data.

**Section 3.7:** This section describes overall conclusions of newly synthesized compounds.
CHAPTER- IV

This chapter has been divided into seven sections-4.1, 4.2, 4.3, 4.4, 4.5 and 4.6, 4.7 respectively.

Section 4.1: This section describe the aim and work plan of the research work derived from isoniazid nuclei. There are two main objectives of the research plan. This section has further divided into three sub sections – 4.1.1, 4.1.2 and 4.1.3 each section is devoted to experimental and characterization part of Scheme-III derived compounds. There are two main objectives of the research plan.

1. To synthesize the P_2O_5/SiO_2 catalyzed Schiff bases and their 2-azetidinone derivatives derived from isoniazid nuclei via conventional and microwave synthesis.

Two series of the compounds have been synthesized by following Scheme-III in step-1 and 2 respectively.

Series-3: Synthesis of Schiff bases in presence of heterogeneous catalyst via conventional and microwave assisted synthesis of step-1 from Scheme-III. The compounds of series-3 have been synthesized from following method

Step-1: P_2O_5/SiO_2 catalyzed synthesis of Schiff bases of series-03 (KA-17 to KA-27) Table-4.1

Conventional method: Equimolar mixture of isoniazid and 2,4-dichloro benzaldehyde and P_2O_5/SiO_2 catalyst refluxed on a water bath in ethanol to give compound KA-17.

Microwave method: Equimolar mixture of isoniazid and 2,4-dichloro benzaldehyde and P_2O_5/SiO_2 in ethanol were performed at 800W power, on microwave irradiation to give compound KA-17.

Other compounds KA-18 to KA-27 were prepared similarly by treating 1 with various aromatic aldehydes.

SCHEME-III (Step-1)
Table-4.1

<table>
<thead>
<tr>
<th>Serie-03 Compound No</th>
<th>Reactant aromatic aldehydes</th>
<th>Quantity(in gms)</th>
<th>Rf Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA-17</td>
<td>2,4-Dichloro benzaldehyde</td>
<td>3.50</td>
<td>0.76</td>
</tr>
<tr>
<td>KA-18</td>
<td>3- Bromo benzaldehyde</td>
<td>2.30</td>
<td>0.71</td>
</tr>
<tr>
<td>KA-19</td>
<td>4- Bromo benzaldehyde</td>
<td>3.70</td>
<td>0.70</td>
</tr>
<tr>
<td>KA-20</td>
<td>3-Methyl benzaldehyde</td>
<td>2.37</td>
<td>0.74</td>
</tr>
<tr>
<td>KA-21</td>
<td>4-Methyl benzaldehyde</td>
<td>2.35</td>
<td>0.75</td>
</tr>
<tr>
<td>KA-22</td>
<td>2-Methoxy benzaldehyde</td>
<td>2.41</td>
<td>0.62</td>
</tr>
<tr>
<td>KA-23</td>
<td>4-Methoxy benzaldehyde</td>
<td>2.42</td>
<td>0.65</td>
</tr>
<tr>
<td>KA-24</td>
<td>3-Methoxy benzaldehyde</td>
<td>2.43</td>
<td>0.70</td>
</tr>
<tr>
<td>KA-25</td>
<td>3,4,5- Trimethoxy benzaldehyde</td>
<td>3.92</td>
<td>0.76</td>
</tr>
<tr>
<td>KA-26</td>
<td>Furfuraldehyde</td>
<td>1.65</td>
<td>0.78</td>
</tr>
<tr>
<td>KA-27</td>
<td>2-Nitro benzaldehyde</td>
<td>3.02</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Series-4: Synthesis of 2-azetidinone derivatives via conventional and microwave synthesis in step-2 of SCHEME-III


Conventional method: An equimolar mixture of compound KA-17 and triethylamine in ethanol was added chloroacetylchloride drop wise in ice bath, then refluxed on a steam bath to give furnish, compound KA-28.

Microwave method: An equimolar mixture of compound KA-17 and triethylamine was added chloroacetylchloride drop wise in ice bath, then transferred in ethanol to an open glass vessel and reaction was performed at 800W power in microwave irradiation to give furnish, compound KA-28.

Other compounds Series-04, KA-29 to KA-38 were prepared similarly using the compounds KA-18 to KA-27 as precursor of series-03 in the place of compound KA-28.

SCHEME-III (Step-2)
Table 4.2

<table>
<thead>
<tr>
<th>Series-03 Compounds</th>
<th>Quantity of Schiff bases</th>
<th>Quantity (in grms)</th>
<th>Rf value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KA-28</td>
<td>N(^{\text{N}})-(2,4-dichlorobenzylidene)-isonicotinohydrazide</td>
<td>2.94</td>
<td>0.79</td>
</tr>
<tr>
<td>KA-29</td>
<td>N(^{\text{N}})-(3-bromobenzylidene)-isonicotino- hydrazide</td>
<td>3.01</td>
<td>0.75</td>
</tr>
<tr>
<td>KA-30</td>
<td>N(^{\text{N}})-(4-bromobenzylidene)-isonicotinohydrazide</td>
<td>3.03</td>
<td>0.74</td>
</tr>
<tr>
<td>KA-31</td>
<td>N(^{\text{N}})-(3-methylbenzylidene)-isonicotinohydrazide</td>
<td>2.39</td>
<td>0.69</td>
</tr>
<tr>
<td>KA-32</td>
<td>N(^{\text{N}})-(4-methylbenzylidene)-isonicotinohydrazide</td>
<td>2.39</td>
<td>0.71</td>
</tr>
<tr>
<td>KA-33</td>
<td>N(^{\text{N}})-(2-methoxybenzylidene)-isonicotinohydrazide</td>
<td>2.55</td>
<td>0.73</td>
</tr>
<tr>
<td>KA-34</td>
<td>N(^{\text{N}})-(4-methoxybenzylidene)-isonicotinohydrazide</td>
<td>2.55</td>
<td>0.75</td>
</tr>
<tr>
<td>KA-35</td>
<td>N(^{\text{N}})-(3-methoxybenzylidene)-isonicotinohydrazide</td>
<td>2.55</td>
<td>0.76</td>
</tr>
<tr>
<td>KA-36</td>
<td>N(^{\text{N}})-(3,4,5-trimethoxybenzylidene)-isonicotinohydrazide</td>
<td>3.15</td>
<td>0.74</td>
</tr>
<tr>
<td>KA-37</td>
<td>N(^{\text{N}})-(furfurylidene)-isonicotinohydrazide</td>
<td>2.15</td>
<td>0.76</td>
</tr>
<tr>
<td>KA-38</td>
<td>N(^{\text{N}})-(2-nitrobenzylidene)-isonicotinohydrazide</td>
<td>2.70</td>
<td>0.78</td>
</tr>
</tbody>
</table>

2. The synthesized compounds KA-17 to KA-38 were characterized by using various methods such as thin layer chromatography, elemental analysis and spectral data. The melting points of the compounds were determined by open capillary tube method. IR spectra were recorded in KBr disc on Shimadzu 8300 spectrophotometer and 1H NMR and 13C NMR spectra were recorded on a JEOL RESONANCE spectrometer in DMSO-d6 at 300 MHz and 100 MHz using TMS as an internal standard a chemical shifts reported on δ scales.

Section 4.2: This section includes proposed mechanism of overall reactions.

Section 4.3: This section includes a comparative study of time and yield via conventional and microwave assisted synthesis.

Section 4.4: This section described catalyst recyclability.

Section 4.5: This section studied about the selection of suitable solvent in Schiff bases synthesis.

Section 4.6: This section focused on the conformation of synthesis of series-03 and 04 compounds according to their spectral data.

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Section 4.7: This section describes overall conclusions of newly synthesized compounds.

CHAPTER- V

This chapter is fully devoted to the fourth aim of the research work the pharmacological activities such as antibacterial, antifungal and antitubercular activity of the synthesized compounds KA-01 to KA-38. This chapter has been divided into three sections—5.1, 5.2, and 5.3 respectively.

Section 5.1: This section deals with general description of the pharmacological and biological activities.

Section 5.2: This section describe the methods employed during the screening of various types of biological activities. This section has further divided into three sub-sections – 5.2.1, 5.2.2, and 5.2.3 each section is devoted one type of activity.

Sub-section 5.2.1: Antibacterial activity:

The antibacterial activity of the synthesized compounds KA-01 to KA-38 were screened by filter paper disc techniques at 50 to 100 ppm concentrations against the following bacteria:

✓ *Bacillus subtilis*

✓ *Escherichia coli* and

✓ *Pseudomonas alkaligenes*

Norfloxacin was used as a standard drug at the same concentrations for comparison.

Sub-section 5.2.2: Antifungal activity:

The antifungal activity of the synthesized compounds KA-01 to KA-38 were screened by filter paper disc method at 50 and 100 ppm concentration against the following selected fungi:

✓ *Candida albicans*

✓ *Aspergillus flavus*

✓ *Penicillium citrinum*

Ketoconazole was used as a standard drug at the same concentrations for comparison.
Sub-section 5.2.3: Antitubercular activity:

The Antitubercular of the synthesized compounds **KA-17 to KA-38** were tested at single dose of 100 mg/mL by using the Microplate Alamar Blue Assay (MABA) technique. Pyrazinamide was used as a standard drug for comparison. Synthesized compounds were preliminarily assayed against these following freshly isolate clinical strains:

✓ *Mycobacterium tuberculosis CIP*

✓ *Mycobacterium tuberculosis H37Rv*

**Section 5.3:** This section included results and discussion of the screening of antibacterial, antifungal and antitubercular activity of the newly synthesized compounds. This section has further divided into three subsections **5.3.1, 5.3.2 and 5.3.3** each section is devoted to results of one type of activity. Some of the synthetic products derived from 2-amino-6-nitro- benzothiazole and isoniazid nucleus exhibited pronounced biological activity.