THESIS ABSTRACT

Heterocyclic compounds have wide range of applications: they are predominant among the types of compounds used as pharmaceuticals, as agrochemicals and as veterinary products. They are used as optical brightening agents, as antioxidants, as corrosion inhibitors and as additives with a variety of other functions. Many dyestuffs and pigments have heterocyclic structures.

Benzimidazoles are very useful intermediates for the development of pharmaceutical molecules with biological interest. Substituted benzimidazole derivatives have found applications as diverse therapeutic agents including antiulcer, antihelmintic, antihypertensive, anticoagulant, antiallergic, analgesic, anti-inflammatory, antipyretic, antibacterial, antifungal, antiviral, antiparasitic, antioxidant, anticancer and antianxiolytic.

On the other hand, Benzisoxazole is an aromatic organic compound with a molecular formula C$_7$H$_5$NO containing a benzene-fused isoxazole ring structure. Benzisoxazole has no household use. It is used primarily in industry and research. Being a heterocyclic compound, benzisoxazole finds use in research as a starting material for the synthesis of large number of bioactive structures. It is found within the chemical structures of pharmaceutical drugs such as antipsychotic risperidone and anticonvulsant zonisamide. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization.

In the present thesis, a series of pyridine conjugated benzimidazole and piperidine conjugated benzisoxazole derivatives were synthesized and evaluated for their antibacterial, anti-oxidant and anti-inflammatory activities.
**Chapter – 1** presents a brief introduction to biological importance of benzimidazole and benzisoxazole derivatives along with a brief introduction to present work.

**Chapter – 2** describes the synthesis and characterization of novel pyridine conjugated N-alkyl/aralkyl benzimidazole derivatives according to Scheme - 1. The synthesized compounds were evaluated for their antibacterial, anti-oxidant and anti-inflammatory activities. The results showed that most of the tested compounds exhibited moderate to good antimicrobial activity against some strains of Gram negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, Shigella flexineri*) and Gram positive bacteria *Bacillus subtilis*. Further, the molecules were evaluated for antioxidant assays such as DPPH, superoxide radical and hydroxyl radical scavenging assays.

![Scheme 1](attachment:image.png)

**Reagents and condition:** i) NaOCH$_2$CF$_3$ ii) NaNO$_2$, H$_2$SO$_4$ iii) H$_2$SO$_4$, CH$_3$OH iv) NaBH$_4$, Methanol v) SOCl$_2$, DCM vi) Mercaptobenzimidazole, Methanol vii) R-X, (8a-l) Toluene, 30% NaOH, TBAB.

**Scheme 1**
Most of the compounds showed potent antioxidant activities. Also, the synthesized compounds were screened for anti-inflammatory activities by using lipoxygenase inhibition and indirect haemolytic assays, where compounds revealed good activity.

**Chapter – 3**, a library of novel N-arylsulfonylbenzimidazole derivatives were synthesized according to Scheme – 2, and evaluated for their antibacterial, antioxidant and anti-inflammatory activities. The results showed that most of the tested compounds exhibited potent to moderate antimicrobial activities against some strains of Gram negative bacteria (*Escherichia coli, Klebsiella pneumonia, Salmonella typhi, Shigella flexneri*).

![Scheme 2](image)

**Reagents and reaction conditions**: I) NaOCH₂CF₃. II) NaNO₂, H₂SO₄. III) H₂SO₄, CH₃OH. IV) NaBH₄, Methanol. V) SOCl₂, DCM. VI) Mercaptobenzimidazole, Methanol. VII) R-SO₂-Cl, (8a-g) Toluene, 50% KOH, TBAB.

**Scheme 2**
The compounds synthesized were more vivid particularly towards the Gram negative bacterial strain *Salmonella typhi* as they displayed prominent zone of inhibition and with low minimum inhibitory concentrations compared to the standard.

In addition, the molecules were evaluated for antioxidant assays such as DPPH scavenging, super oxide radical scavenging and hydroxyl radical scavenging assays. Most of the tested compounds showed potent antioxidant activities. Furthermore, the synthesized novel benzimidazole compounds were also screened for anti-inflammatory activities such as lipoxygenase inhibition and indirect haemolytic assays, where compounds revealed good activity.

**Chapter – 4,** a series of piperidine conjugated benzisoxazole derivatives were synthesized according to Scheme - 3 and evaluated for their antibacterial, anti-oxidant and anti-inflammatory activities.

![Scheme 3](image-url)

**Reagents and reaction conditions:** (a) MeONa/THF, 0°C-RT, 8 h. (b) LiOH/MeOH/H₂O, 0°C-RT, 3 h. (c) 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride 5, EDC·HCl/HOBt/DIPEA/CH₂Cl₂, 0 °C-RT, 8h. (d) HCl/ether, 0 °C-RT, 1h. (e) RCOCl 8, TEA/EDC, 0 °C-RT, 3-4 h.

**Scheme 3**
The results showed that most of the tested compounds exhibited moderate to good antimicrobial activity against some strains of Gram negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, Shigella flexineri*) and Gram positive bacteria (*Bacillus subtilis*). In further, the molecules were evaluated for antioxidant assays such as DPPH scavenging, super oxide radical scavenging and hydroxyl radical scavenging assays. Most of the compounds showed potent antioxidant activities. Also, the synthesized compounds were screened for anti-inflammatory activities such as lipooxygenase inhibition and indirect haemolytic assays, where these compounds revealed good activity.

**Chapter – 5**, a series of benzisoxazole derivatives were synthesized according to Scheme - 4 and evaluated for their antibacterial, antioxidant and anti-inflammatory activities.

![Scheme 4](image)

**Reagents and reaction conditions:** (a) MeONa/THF, 0 °C-RT, 8 h. (b) LiOH/MeOH/H₂O, 0°C-RT, 3h. (c) 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride 5, EDC/HCl/HOBT/DIPEA/CH₂Cl₂, 0 °C-RT, 8h. (d) HCl/ether, 0 °C-RT, 1h. (e) RSO₂Cl 8, TEA/EDC, 0 °C-RT, 3-4 h.

**Scheme 4**
The results indicated that most of the compounds exhibited moderate antimicrobial activity against Gram negative (*Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, Shigella flexneri*) and Gram positive (*Bacillus subtilis*) bacterial cultures. The molecules were evaluated for antioxidant activities using 2,2-diphenyl-1-picrylhydrazyl, super oxide radical and hydroxyl radical scavenging assays and most of them showed good antioxidant activities. Also, the synthesized compounds were screened for anti-inflammatory activities using lipoxygenase inhibition and indirect haemolytic assays.

In summary, synthesized several biologically significant pyridine conjugated benzimidazole and piperidine conjugated benzisoxazole derivatives, were evaluated for their antimicrobial, antioxidant and anti-inflammatory activities. The results indicated that, some of the compounds were promising biological agents.