ABSTRACT

The thesis includes the synthesis of some novel heterocyclic compounds derived from benzimidazole, benzotriazole and imidazole along with their various biological properties. The thesis has been divided into five chapters -

CHAPTER - 1

The first chapter is introductory. It deals with the scope, development and significance of heterocyclic chemistry with particular emphasis on the chemistry of benzimidazole, benzotriazole, imidazole compounds and their uses in various industries and in other ways. Some important heterocyclic compounds containing these moieties along with their biological importance have also been described.

CHAPTER - 2

This chapter has been divided into two sections-I and II respectively.

Section - I: This section deals with the general experimental procedure regarding the synthesis of the compounds. A brief description of the synthesis of compounds and their pathway of synthesis are mentioned herein:

Phenoxy acetic acid and its various derivatives
as well as benzimidazole, benzotriazole and imidazole have been reported to possess wide spectrum of biological activity. These results stimulated me to undertake the synthesis of some phenoxy, bromophenoxy, chlorophenoxy, nitrophenoxy, methylphenoxy-acetic acids, propionic acids and naphthoxy acetic acids with benzimidazole, benzotriazole and imidazole moieties.

Phenoxy acetic acid and their various bromo, chloro, nitro and methyl derivatives; phenoxy propionic acid, their tribromo, trichloro and trinitro derivatives; 1-naphthoxy and 2-naphthoxy acetic acids were synthesised by condensing the sodium salt of the appropriate phenols - (0.07 - 0.1 mole) with the sodium salt of monochloroacetic acid and α-monochloropropionic acid (0.07 - 0.1 mole). To a solution of above phenoxy acetic acids and propionic acids (0.046 mole in 20-30 ml EtOAc/MeOH/EtOH) were added thionyl chloride (0.056 mole) and the mixture were refluxed on a water bath about 7 hours. The acid chlorides thus obtained were added dropwise to an ice-cooled solutions of benzimidazole, benzotriazole and imidazole (0.036 mole in 20-30 ml MeOH/EtOH) respectively and 5 ml of 4N NaOH solution with constant stirring (40 to 90 minutes). The amides were separated by ether. The ethereal solution was washed with sodium bicarbonate solution followed by
distilled water (4x30 ml) and on concentration yielded
the product which were purified over the column of
neutral alumina/silica gel using appropriate organic
solvent(s) as an eluant. Finally, the eluate (110-190
ml) were concentrated and the products were crystallised
from appropriate solvent(s). Then they were proceeded
further for their structural assignments by IR spectra
and elemental analyses. The purity were monitored by
TLC. The names of all the compounds are given herein:

(i) \( \text{N-[2-(phenoxy, bromo, chloro, nitro, methyl-}
\text{phenoxy) acetyl] benzimidazoles and}
\text{benzotriazoles.} \)

(ii) \( \text{N-[2-(phenoxy, tribromo, trichloro and trinitro-}
\text{phenoxy) propionyl] benzimidazoles, benzotriazoles}
\text{and imidazoles.} \)

(iii) \( \text{N-[2-(chloro, methyl-phenoxy) acetyl] imidazoles.} \)

(iv) \( \text{N-[2-(1-naphthoxy, 2-naphthoxy) acetyl] benzimi-}
\text{dazoles, benzotriazoles and imidazoles.} \)

Section - II: This section deals with general
description of the activity performed, techniques of the
evaluation of antimicrobial (antibacterial and antifi-
gungal), anti-inflammatory and analgesic activities.

Antibacterial activity of all the compounds were
tested by adopting standardized single disk method on
the following pathogenic bacteria using streptomycin as a standard.

(A) Escherichia coli, gram (-)
(B) Proteus vulgaris, gram (-)
(C) Staphylococcus aureus, gram (+)
(D) Bacillus anthracis, gram (+)

The few compounds of benzotriazoles were only tested against the following gram (-) bacteria: E.coli, Salmonella typhimurium, Vibrio cholerae and Klebsiella pneumoniae with the same standard.

Antifungal activity of all the compounds were screened by the filter paper disc method on the following fungi using mycostatin as a standard.

(A) Aspergillus fumigatus
(B) Fusarium oxysporium
(C) Candida albicans

The few compounds of benzotriazoles were only tested against A.fumigatus, C.albicans, Microsporum gypseum and Trychophyton mentagrophytes with the same standard.

Anti-inflammatory activity of all the compounds was tested by adopting the carrageenan induced rat paw oedema method using acetyl salicylic acid (ASA) as a standard.
Analgesic activity of all the compounds were tested by hot plate method on the albino rats using ASA as a standard.

CHAPTER - 3

This chapter has been divided into two sections- I and II respectively.

Section - I : This section deals with the synthesis of twenty one new compounds of the following series-

(i) $N\{2-(\text{phenoxy, bromo, chloro, nitro, methyl-phenoxy}) \text{ acetyl}\}'\text{benzimidazoles.}$

(ii) $N\{2-(\text{phenoxy, tribromo, trichloro, trinitro-phenoxy}) \text{ propionyl}\}'\text{benzimidazoles.}$

(iii) $N\{2-(1-\text{naphthoxy, 2-naphthoxy}) \text{ acetyl}\}'\text{benzimidazoles.}$

A brief description of the synthesis of the compounds are given herein:

Phenoxy acetic acid and their various bromo, chloro, nitro and methyl derivatives; phenoxy propionic acid and their tribromo, trichloro and trinitro derivatives; 1- and 2- naphthoxy acetic acids were synthesised by condensing the equimolecular quantities (0.07 - 0.1 mole) of sodium salt of appropriate phenol
with sodium salt of monochloroacetic acid and \( \alpha \)-monochloropropionic acid, followed by the excess of thionyl chloride (0.056 mole) and the mixture were separately refluxed (7 hours) on a water bath and worked up further by the same method as given on page II using benzimidazole (0.036 mole in 20-30 ml MeOH) to get the desired product.

The synthesised compounds have represented by the following structures -

![Structure Diagram](image)

<table>
<thead>
<tr>
<th>Compounds Number</th>
<th>Groups Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>( R_1, R_2, R_3, R_4, R_5, R=H )</td>
</tr>
<tr>
<td>II</td>
<td>( R_1, R_2, R_3, R_4, R_5=H; R=CH_3 )</td>
</tr>
<tr>
<td>III</td>
<td>( R_1, R_3, R_5=Br; R_2, R_4, R=H )</td>
</tr>
<tr>
<td>IV</td>
<td>( R_1, R_3, R_5=Br; R_2, R_4=H; R=CH_3 )</td>
</tr>
<tr>
<td>V</td>
<td>( R_1, R_3=Br; R_2, R_4, R_5, R=H )</td>
</tr>
<tr>
<td>VI</td>
<td>( R_1, R_3, R_5=Cl; R_2, R_4, R=H )</td>
</tr>
<tr>
<td>VII</td>
<td>( R_1, R_3, R_5=Cl; R_2, R_4=H; R=CH_3 )</td>
</tr>
<tr>
<td>VIII</td>
<td>( R_1, R_3=Cl; R_2, R_4, R_5, R=H )</td>
</tr>
<tr>
<td>IX</td>
<td>( R_1, R_4=Cl; R_2, R_3, R_5, R=H )</td>
</tr>
<tr>
<td>X</td>
<td>( R_1=Cl; R_2, R_3, R_4, R_5, R=H )</td>
</tr>
<tr>
<td>XI</td>
<td>( R_3=Cl; R_1, R_2, R_4, R_5, R=H )</td>
</tr>
<tr>
<td>XII</td>
<td>( R_1, R_3, R_5=NO_2; R_2, R_4, R=H )</td>
</tr>
</tbody>
</table>
XIII : \( R_1, R_3, R_5 = NO_2; R_2, R_4 = H; R = CH_3 \)
XIV : \( R_1 = NO_2; R_2, R_3, R_4, R_5 = H \)
XV : \( R_2 = NO_2; R_1, R_3, R_4, R_5 = H \)
XVI : \( R_3 = NO_2; R_1, R_2, R_4, R_5 = H \)
XVII : \( R_1 = CH_3; R_2, R_3, R_4, R_5 = H \)
XVIII : \( R_2 = CH_3; R_1, R_3, R_4, R_5 = H \)
XIX : \( R_3 = CH_3; R_1, R_2, R_4, R_5 = H \)

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**Section - II**: This section deals with the results and conclusions of the screening of antibacterial, antifungal, anti-inflammatory and analgesic activities of the synthesised compounds.

Most of the synthesised compounds exhibited mild to moderately and better antimicrobial activity. The compounds-III to VII showed good antimicrobial activity while the compound-VI exhibited promising antifungal activity.

The compounds - III to V and VI to VII showed good anti-inflammatory activity. All the compounds produce symptoms of depression, ataxia and fast
respiration in animals at the dose level of > 200 mg/kg b.w.

The compounds IV displayed good analgesic activity. The compounds III, V, VII, XII, XIII and XVIII showed moderately better analgesic activity.

CHAPTER - 4

This chapter has been divided into two sections I and II respectively.

Section - I : This section deals with the synthesis of twenty one new compounds of the following series -

(i) \( N-[2-(\text{phenoxy, bromo, chloro, nitro, methyl-phenoxy}) \text{ acetyl}] \text{ benzotriazoles}. \)

(ii) \( N-[2-(\text{phenoxy, tribromo, trichloro, trinitro-phenoxy}) \text{ propionyl}] \text{ benzotriazoles}. \)

(iii) \( N-[2-(1-naphthoxy, 2-naphthoxy) \text{ acetyl}] \text{ benzotriazoles}. \)

A brief description of the synthesis of the compounds are given herein :

Phenoxy acetic acid and their various bromo, chloro, nitro and methyl derivatives; phenoxy propionic acid and their tribromo, trichloro and trinitro derivatives; 1- and 2-naphthoxy acetic acids were
synthesised by condensing the equimolecular quantities (0.07 - 0.1 mole) of sodium salt of appropriate phenol with sodium salt of monochloroacetic acid and α-mono-
chloropropionic acid, followed by the excess of thionyl chloride (0.056 mole) and the mixture were separately refluxed (7 hours) on a water bath and worked up further by the same method as given on page 11 using benzo-
trizole (0.036 mole in 20-30 ml EtOH) to get the desired product.

The synthesised compounds have represented by

the following structures -

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Compounds</th>
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<tbody>
<tr>
<td>I</td>
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</tr>
<tr>
<td>VIII</td>
<td>$R_1, R_3=Cl; R_2, R_4, R_5, R=H$</td>
</tr>
<tr>
<td>IX</td>
<td>$R_1, R_4=Cl; R_2, R_3, R_5, R=H$</td>
</tr>
</tbody>
</table>
$X$ : $R_1=Cl; R_2, R_3, R_4, R_5, R=H

$XI$ : $R_3=Cl; R_1, R_2, R_4, R_5, R=H

$XII$ : $R_1, R_3, R_5=NO_2; R_2, R_4, R=H

$XIII$ : $R_1, R_3, R_5=NO_2; R_2, R_4=H; R=CH_3

$XIV$ : $R_1=NO_2; R_2, R_3, R_4, R_5, R=H

$XV$ : $R_2=NO_2; R_1, R_3, R_4, R_5, R=H

$XVI$ : $R_3=NO_2; R_1, R_2, R_4, R_5, R=H

$XVII$ : $R_1=CH_3; R_2, R_3, R_4, R_5, R=H

$XVIII$ : $R_2=CH_3; R_1, R_3, R_4, R_5, R=H

$XIX$ : $R_3=CH_3; R_1, R_2, R_4, R_5, R=H

\[ \text{XX} \]

\[ \text{XXI} \]

**Section - II**: This section deals with the results and conclusions of the screening of antibacterial, antifungal, anti-inflammatory and analgesic activities of the synthesised compounds.

The compounds I to V and XII to XIX were screened only against the bacteria: *E. coli*, *V. cholerae*, *K. pneumoniae* and *S. typhimurium* and fungi: *A. fumigatus*, *C. albicans*, *M. gypseum* and *T. mentagrophytes* whereas remaining compounds - VI to XI and XX to XXI were tested against bacteria: *E. coli*, *P. vulgaris*, *S. aureus* and

The compound - III was found to be effective against all the bacteria except S. typhimurium, the compound - IV was only inactive against V. cholerae and compound-V showed activity against E. coli, and V. cholerae only. The compounds VI, VII and IX were found to be active against all the tested bacteria and fungi. The compounds-VIII and XI showed activity against B. anthracis while the compound - X showed activity against E. coli. The compounds-III to V showed better activity against C. albicans, M. gypseum and A. fumigatus respectively. The compound - XVI showed promising antifungal activity against all the fungi tested except T. mentagrophytes.

The compound-VI was found to be highly active against inflammation. The compounds-III, IV, VII and IX showed good anti-inflammatory activity.

The compounds-III & IV exhibited good analgesic activity whereas the compounds-XVII showed moderate analgesic activity. The compound-VI was found to be CNS stimulant at a dose level to > 200 mg/kg b.w. while others were CNS depressant.

CHAPTER - 5

This chapter has been divided into two sections I and II respectively.
Section - 1: This section deals with the synthesis of fourteen new compounds of the following series -

(i) $N\{2-(\text{chloro, methyl-phenoxy\text{) acetyl\}}}$ imidazoles.

(ii) $N\{2-(\text{phenoxy, tribromo, trinitro, trichloro\}}$ propionyl\} imidazoles.

(iii) $N\{2-(1\text{-naphthoxy, 2-naphthoxy\}}$ acetyl\} imidazoles.

A brief description of the synthesis of the compounds are given herein:

Phenoxy acetic acid derivatives, chloro and methyl; phenoxy propionic acid and its derivatives tribromo, trichloro and trinitro; 1- and 2-naphthoxy acetic acids were synthesised by condensing the equimolecular quantities (0.07 - 0.1 mole) of sodium salt of appropriate phenol with sodium salt of monochloroacetic acid and $\alpha$-monochloropropionic acid, followed by the excess of thionyl chloride (0.056 mole) and the mixture were separately refluxed (7 hours) on a water bath and worked up further by the same method as given on page ii using imidazole (0.036 mole in 20-30 ml $\text{EtOH}$) to get the desired product.

The synthesised compounds have represented by the following structures -
Section - II: This section deals with the results and conclusions of the screening of antibacterial, antifungal, anti-inflammatory and analgesic activities of the synthesised compounds.
All the synthesised compounds did not show any antifungal activity. The compounds-III to VI and X showed significant antibacterial activity.

The compounds - IV and X exhibited good anti-inflammatory activity than the other compounds of this series.

The compounds - II, IV and X showed very effective analgesic activity with respect to ASA.