Chapter - 2

Synthesis of Pyrazoles and Triazoles
linked to Benzoxazoles
2.1 Introduction

Foregoing discussion reveal the importance of benzoxazole moiety as significant pharmacophore. Hence in the present work, it was contemplated to combine benzoxazole nucleus with other heterocycles such as,

- Pyrazole
- Triazole
- Oxadiazole
- Thiazolidine and
- Quinoline

to study synergic effect due to the combination of benzoxazole with pyrazole and triazole derivatives have been discussed in this chapter. Whereas, combining with oxadiazole and thiazolidine is dealt with, in chapter-3 and with that of quinoline is described in chapter-4. In this connection, it was thought appropriate and necessary to give brief introduction about pyrazoles and triazoles in this chapter. Even though plenty of literature is available regarding synthesis and biological activity of these systems, keeping in view the limitations of this thesis, only important and relevant references are discussed in the following pages.

2.1.1 Introduction to Pyrazoles

Pyrazoles and their reduced forms, pyrazolines, are well known nitrogen-containing heterocyclic compounds. Pyrazoles have occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anticancer activities¹. In fact, pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the broad range of biological activities they possess, antibacterial², antifungal³, antiparkinsonian⁴, antidepressant⁵, antiviral⁶, antitubercular⁷, antiparasitic⁸ and antitumor⁹ properties.

Substituted pyrazoles are important synthetic targets in the pharmaceutical industry as the pyrazole structure forms part of numerous biologically active compounds¹⁰, including blockbuster drug such as Viagra¹¹.
Since the introduction of antipyrine; the first pyrazolone derivative used in the management of pain, inflammation and fever into clinical use in 1884, great attention has been focused on pyrazole derivatives as potent anti-inflammatory, analgesic and antipyretic agents. As a result, a large number of pyrazoles have been obtained and some have gained application on the clinical level. Among the already marketed COX-2 inhibitors that comprise the pyrazole nucleus, celecoxib; 4-[5-(4-methylphenyl)-3-(trifluorophenyl)-1H-pyrazol-1-yl]benzene sulfonamide 1; proved to be a potent and GI safe anti-inflammatory and analgesic agent.

Interest in this field has been intensified after the discovery of the natural pyrazole C-glycoside pyrazofurin; 4-hydroxy-3-β-D-ribofuranosyl-1H-pyrazole-5-carboxamide 2. This antibiotic was reported to possess a broad spectrum of antimicrobial and antiviral activities in addition to being active against several tumor cell lines. Consequently, several pyrazole derivatives that exhibited antimicrobial activity were reported by Tanitame et al.

Ramagnoli et al. have been evaluated antifungal activity of synthetic compounds comprising pyrazole moiety against dermatophytes, i.e. *Epidermophyton floccosum* and *Trichophyton rubrum*. Among the tested compounds, 5-amino-3-methyl-1-phenylpyrazole-4-thiocyanate and 5-amino-1-[1,2,6-dichloro-4-(trifluoromethyl)phenyl]-3-methylpyrazole-4-thiocyanates exhibited promising activity on both fungi.

Pancic et al. tested antiviral activity of Win 412528-3, a pyrazole compound against herpes simplex virus in mouse genital infection and guinea pig skin infection. It was effective against herpes simplex virus types 1 and 2 in mouse genital infection and guinea pig skin infection produced by herpes simplex virus type 1.
2.1.2 Introduction to Triazoles

Numerous 1,2,4-triazoles have been designed and screened, revealing their important biological activities. The following 1,2,4-triazole derivatives found application in medicine: alprazolam (tranquilizer), estazolam (hypnotic, sedative, tranquilizer), rilmazafon (hypnotic, anxiolytic, used in the case of neurotic insomnia), benatradin (diuretic), trapidil (hypotensive), trazodon (antidepressant, anxiolytic), etoperidone (antidepressant), nefazodone (antidepressant, 5-HT₂ A-antagonist), anastrozole, letrozole, vorozole (antineoplastics, non-steroidal aromatase inhibitors), ribavirin (the potent antiviral N-nucleoside), fluconazole, itraconazole and terconazole (powerful azole antifungal agents).^18

During the last few decades, a considerable attention has been devoted to the synthesis of 1,2,4-triazole derivatives possessing diverse pharmacological properties as antimicrobial^19, anti-inflammatory^20, analgesic^21, antitumor^22, antihypertensive^23, anticonvulsant^24, antidepressants^25, fungicidal^26, insecticidal^27 and plant growth regulator anticoagulants^28.

Moreover, synthesis of triazoles fused to another heterocyclic ring has attracted widespread attention due to their diverse applications as antibacterial^29, local anesthetic^30, anticonvulsant^31, antineoplastic^32, antimalarial^33, antiviral agents^34 and some of them exhibited antiproliferative^35 and anticancer activities^36.

Over the past two decades, the incidences of systemic fungal infections have been increasing due to an increase in the number of immunocompromised hosts. Patients undergoing organ transplants, anticancer chemotherapy or long-term treatment with antimicrobial agents and patients with AIDS are immunosuppressed and susceptible to
life threatening systemic fungal infections such as candidiasis, cryptococcosis and aspergillosis. Orally active antifungal azoles, fluconazole and itraconazole, which are strong inhibitors of lanosterol 14-a-demethylase (cytochrome P45014DM), have been widely used in antifungal chemotherapy. However, the development of resistance to currently available antifungal azoles in Candida spp. as well as clinical failures in the treatment of fungal infections have been reported in recent years. Furthermore, invasive aspergillosis still remains resistant to antifungal chemotherapy, although injectable amphotericin B has been used for this purpose.

Therefore, there is still the medical need for new and more effective antifungal agents with a broad antifungal spectrum.

Encouraged by these biological and pharmacological activities associated with these structures, our laboratory has reported results regarding synthesis and biological activities of triazoles are as follows:

Ravindra et al. have reported the synthesis of substituted biheterocycles of triazole, thiadiazole and oxadiazole involving naphtho[2,1-b]furan and their antimicrobial activity. Synthesis, characterization and pharmacological studies on some triazolothiadiazines and triazolothiadiazoles containing naphtho[2,1-b]furan have been studied.

Synthesis of new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: A novel class of potential antibacterial and antitubercular agents have been reported. Synthesis, antibacterial and antitubercular activities of some new 3-substituted phenyl-5-(4-Pyrrol-1ylphenyl)-4H-1,2,4-triazoles have been published by Joshi et al.

Prompted by the biological properties of pyrazoles, 1,2,4-triazoles and as a part of our general search concerning chemotherapeutically importantazole heterocycles, we decided to study new pyrazole, triazoles derivatives of 2-substituted benzoxazoles.

In view of these observations, we synthesized new benzoxazole derivatives encompassing pyrazoles, 1,2,4-triazoles and tested for antibacterial activity against, Staphylococcus aureus, Staphylococcus epidermidis and antifungal activity against dermatophytes i.e. Trichophyton rubrum and Microsporum gypseum.
2.2 Present work

The various biological activities associated with compounds formed by the combination of pyrazole/triazole with various heterocyclic systems prompted us to synthesize and investigate biological activities of pyrazole/triazole derivatives involving 1,3-benzoxazole-thiols.

It was contemplated to explore newer methods for linking two heterocycles viz. 1,3-benzoxazole-thiol and pyrazole via amide (-S–CH₂–CO-) linkage. Such amide (-CH₂–CO-) linked heterocycles gathered enormous interest because of their wide spectrum of pharmacological activities. By referring to various synthetic approaches to achieve the desired goal, it was thought of synthesize 2-(1,3-benzoxazol-2-ylthio)acetohydrizes 4(a-b), which could serve as important starting materials to accomplish the construction of benzoxazole with pyrazole and triazole.

Therefore, the present work, necessitated the synthesis of 2-(1,3-benzoxazol-2-ylthio)acetohydrizes 4(a-b) which has been carried out systematically in following steps.

The synthetic strategy involved the following steps:

1. Synthesis of 1,3-benzoxazole-2-thiols 2(a-b) from 2-Aminophenols 1(a-b)
2. Conversion of 1,3-benzoxazole-2-thiols 2(a-b) into ethyl[(1,3-benzoxazol-2-yl)thio] acetates 3(a-b)
3. Conversion of ethyl[(1,3-benzoxazol-2-yl)thio] acetates 3(a-b) into 2-(1,3-benzoxazol-2-ylthio)acetohydrizes 4(a-b)

The schematic representation of the synthesized molecules are given in the Scheme-I
Scheme-I

1(a-b) undergoes a reaction with CS2/KOH in MeOH to form 2(a-b).

K2CO3/Acetone in CICH2COOC2H5 converts 2(a-b) into 3(a-b).

NH2NH2, 2H2O reduces 3(a-b) to 4(a-b).

Acetone reacts with 4(a-b) to form 5(a-t) and 6(a-j).

DMF/POCl3 further modifies 6(a-j) into 7(a-j).
\[
\begin{array}{cccc}
R & R' & R^2 & \text{R} & R' & R^2 \\
5a & -H & -H & -4F & 5k & -CH_3 & -H & -4F \\
5b & -H & -H & -4Cl & 5l & -CH_3 & -H & -4Cl \\
5c & -H & -H & -3NO_2 & 5m & -CH_3 & -H & -3NO_2 \\
5d & -H & -H & -4OCH_3 & 5n & -CH_3 & -H & -4OCH_3 \\
5e & -H & -OH & -4Cl & 5o & -CH_3 & -OH & -4Cl \\
5f & -H & -OH & -3NO_2 & 5p & -CH_3 & -OH & -3NO_2 \\
5g & -H & -OCH_3 & -4F & 5q & -CH_3 & -OCH_3 & -4F \\
5h & -H & -OCH_3 & -4Cl & 5r & -CH_3 & -OCH_3 & -4Cl \\
5i & -H & -OCH_3 & -3NO_2 & 5s & -CH_3 & -OCH_3 & -3NO_2 \\
5j & -H & -OCH_3 & -4OCH_3 & 5t & -CH_3 & -OCH_3 & -4OCH_3 \\
6a & -H & -Cl & 7a & -H & -Cl \\
6b & -H & -Br & 7b & -H & -Br \\
6c & -H & -NH_2 & 7c & -H & -NH_2 \\
6d & -H & -OCH_3 & 7d & -H & -OCH_3 \\
6e & -H & -OH & 7e & -H & -OH \\
6f & -CH_3 & -Cl & 7f & -CH_3 & -Cl \\
6g & -CH_3 & -Br & 7g & -CH_3 & -Br \\
6h & -CH_3 & -NH_2 & 7h & -CH_3 & -NH_2 \\
6i & -CH_3 & -OCH_3 & 7i & -CH_3 & -OCH_3 \\
6j & -CH_3 & -OH & 7j & -CH_3 & -OH \\
8a & -H & -4Cl & 8e & -CH_3 & -4Cl \\
8b & -H & -3NO_2 & 8f & -CH_3 & -3NO_2 \\
8c & -H & -4OCH_3 & 8g & -CH_3 & -4OCH_3 \\
8d & -H & -4OH & 8h & -CH_3 & -4OH \\
\end{array}
\]
2.2.1 Synthesis of 1,3-benzoxazole-2-thiols 2(a-b)

To build amide bridge, thiols are constructed first by the reaction of substituted 2-aminophenol with carbon disulphide and potassium hydroxide. Sulfur containing compounds exhibit wide spectrum of fungicidal activity hence it was contemplated to construct -S-CH$_2$-CO- bridge using thiols.

The required 1,3-benzoxazole-2-thiols 2(a-b) were prepared from 2-aminophenols 1(a-b) by reacting with carbon disulphide in presence of potassium hydroxide in methanol.

\[
\begin{align*}
R^-\text{O}H & \xrightarrow{\text{CS$_2$/KOH, MeOH}}^\text{R} \text{N}^{-}\text{SH} \\
1(a-b) & \rightarrow 2(a-b)
\end{align*}
\]

\(R=\text{-H, -CH$_3$}\)

The structure of 2(a-b) were established by IR, $^1$HNMR and mass spectral studies. The IR spectrum of 2b (Fig. 2.1) exhibited absorption band at 3333 cm$^{-1}$ for -SH stretching frequency. In the $^1$H NMR spectrum of the same molecule (Fig. 2.2), the appearance of singlet at $\delta$ 2.36 is due to three protons of methyl group, multiplet between $\delta$ 7.05-7.38 corresponding to three protons of aromatic ring and a singlet at $\delta$ 13.9 is due to -SH proton.

The mass spectrum of 2b (Fig. 2.3) displayed a molecular ion peak at m/z 165, which confirms its molecular weight.

2.2.2 Synthesis of ethyl[(1,3-benzoxazol-2-yl)thio]acetates 3(a-b)

Esters are the highly reactive functionality in organic synthesis. Hence, we adopted easiest way of synthesizing -CO-NH-NH$_2$ functionality through ester from thiol. The yield obtained was good, with less interval of time.

The compounds ethyl[(1,3-benzoxazol-2-yl)thio]acetates 3(a-b) were obtained by the reaction of ethyl chloroacetate in presence of anhydrous potassium carbonate in dry
acetone at reflux temperature and condensation occurred in a single step and gave 3(a-b) in good yield.

IR spectrum of 3b (Fig.2.4) showed characteristic absorption band at 1738 cm⁻¹ due to stretching frequency of ester carbonyl group. ¹H NMR spectrum of 3b (Fig.2.5) was consistent with the assigned structure. It showed a triplet at δ 1.28 due three protons of –CH₃ group of ester, a singlet at δ 2.42 due to three protons of –CH₃ group attached to aromatic ring, a singlet at δ 4.10 due to two protons of –S-CH₂ group, quartet at δ 4.25 due to two protons of –CH₂ ester group and multiplets ranging from δ 7.30 to δ 7.40 for three aromatic protons.

2.2.3 Synthesis of 2-[(1,3-benzoxazol-2-yl)thiolacetohydrazides 4(a-b)]

The target molecules were pyrazole, pyrazoline and triazoles. These nuclei were easily constructed from hydrazides. Hence, esters 3(a-b) were converted to hydrazides 4(a-b) by reacting with hydrazine hydrate.

The IR spectrum of 4b (Fig.2.6) exhibited broad absorption bands at 3307 cm⁻¹ due to NH₂ and a sharp band at 1639 cm⁻¹ due to carbonyl group. Further evidence for the structure assigned to 4b was obtained by recording ¹H NMR spectra. The ¹H NMR spectrum of 4b (Fig.2.7) showed a singlet at δ 2.38 for three protons of –CH₃ group, singlet at 4.05 due to two protons of –S-CH₂ group and two D₂O exchangeable singlets at δ 4.33 and δ 9.40 due to -NH₂, –NH functional groups respectively. The three aromatic protons appeared as multiplets between δ 7.10- δ 7.50.
The additional support for the structure was obtained by recording its mass spectrum. The mass spectrum of 4b (Fig.2.8) showed a molecular ion peak at m/z 237, which corresponds to its molecular weight.

### Table 2.1. IR and $^1$H NMR and Mass spectral data of 2a, 3a and 4a

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>IR (KBr) cm$^{-1}$</th>
<th>$^1$H NMR δ ppm</th>
<th>Molecular ion (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-H</td>
<td>3400 (-SH)</td>
<td>δ 7.16-7.50 (m, 4H, ArH) &amp; δ 14.00 (s, 1H, -SH)</td>
<td>151</td>
</tr>
<tr>
<td>3a</td>
<td>-H</td>
<td>1723 (C=O)</td>
<td>δ 1.28 (t, 3H, -CH$_3$), δ 4.12 (s, 2H, -S-CH$_2$), δ 4.26 (q, 2H, -CH$_2$) &amp; δ 7.22-7.62 (m, 4H, ArH)</td>
<td>237</td>
</tr>
<tr>
<td>4a</td>
<td>-H</td>
<td>1643 (C=O) 3307(NH$_2$)</td>
<td>δ 4.08 (s, 2H, -S-CH$_2$), δ 4.34 (s, 2H, -NH$_2$), δ 7.29-7.66 (m, 4H, ArH) &amp; δ 9.42 (s, 1H, -NH)</td>
<td>223</td>
</tr>
</tbody>
</table>
Fig. 2.1.

Fig. 2.2.
Fig. 2.3.

Fig. 2.4.
Fig. 2.5.

Fig. 2.6.
Fig. 2.7a.

Fig. 2.7b.
Fig. 2.8.
2.2.4 Synthesis of 2-[(2-(3,5-diphenylsubstituted-2,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl]thio]-1,3-benzoxazoles 5(a-t)

Pyrazole moiety is the biologically active scaffold. There are several methods available for the construction of pyrazole ring system. Out of these, the following two methods have been adopted in the present work.

Method-A: This method involved the reaction between 2-(1,3-benzoxazol-2-ylthio)acetohydrazides 4(a-b) and chalcones, i.e., 1,3-disubstitutedphenyl-2-en-1-ones i-x by acid catalyzed reaction to give pyrazoles.

Method-B: In this method 2-(1,3-benzoxazol-2-ylthio)acetohydrazides 4(a-b) were reacted with substituted acetophenones followed by cyclization with dimethylformamide and phosphorus oxychloride to give pyrazolecarbaldehydes.

Method-A involved two steps.

2.2.5 Synthesis of 1,3-disubstituted phenyl-2-en-1-ones i-x

The synthesis of title compounds required other reactants i.e., chalcones i-x were synthesized by Claisen condensation employing substituted acetophenones and different aromatic aldehydes.

Following substituted acetophenones and aromatic aldehydes were used in the synthesis of chalcones. Due care was taken in selecting the substituted acetophenones and aldehydes. Electron donating and withdrawing groups present on appropriate position of the aromatic ring were selected. This helped in the prediction of biological activity.

a. 4-Flurobenzaldehyde  
b. 4-Chlorobenzaldehyde  
c. 3-Nitrobenzaldehyde  
d. 4-Methoxybenzaldehyde  
a. Acetophenone  
b. 4-Hydroxyacetophenone  
c. 4-Methoxyacetophenone
2.2.6 Synthesis of 2-{(2-(3,5-diphenylsubstituted-2,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl[thio]-1,3-benzoxazoles 5(a-t)

The reaction of hydrazides 4(a-b) with chalcones i-x to obtain the title compounds 5(a-t) was attempted by employing various reagents and reaction conditions. However the desired condensation was successful only when the reaction was carried out by using acetic acid as catalyst and acetone as a solvent at reflux temperature.
<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R'</th>
<th>R²</th>
<th></th>
<th>R</th>
<th>R'</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>-H</td>
<td>-H</td>
<td>-4F</td>
<td>5k</td>
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<td>-H</td>
<td>-4F</td>
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<td>-H</td>
<td>-4Cl</td>
<td>5l</td>
<td>-CH₃</td>
<td>-H</td>
<td>-4Cl</td>
</tr>
<tr>
<td>5c</td>
<td>-H</td>
<td>-H</td>
<td>-3NO₂</td>
<td>5m</td>
<td>-CH₃</td>
<td>-H</td>
<td>-3NO₂</td>
</tr>
<tr>
<td>5d</td>
<td>-H</td>
<td>-H</td>
<td>-4OCH₃</td>
<td>5n</td>
<td>-CH₃</td>
<td>-H</td>
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<td>5g</td>
<td>-H</td>
<td>-4OCH₃</td>
<td>-4F</td>
<td>5q</td>
<td>-CH₃</td>
<td>-4OCH₃</td>
<td>-4F</td>
</tr>
<tr>
<td>5h</td>
<td>-H</td>
<td>-4OCH₃</td>
<td>-4Cl</td>
<td>5r</td>
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<td>-4Cl</td>
</tr>
<tr>
<td>5i</td>
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<td>-4OCH₃</td>
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<td>-4OCH₃</td>
<td>-4OCH₃</td>
<td>5t</td>
<td>-CH₃</td>
<td>-4OCH₃</td>
<td>-4OCH₃</td>
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</table>

The IR spectrum of 5a (Fig.2.9) exhibited the absorption band at 1671cm⁻¹ due to carbonyl stretching frequency. The ¹H NMR spectrum of 5a (Fig.2.10) recorded in CDCl₃ exhibited a singlet at δ 2.17 due to methylene protons of pyrazole, another singlet at δ 4.43 due to -S-CH₂- group and multiplets ranging from δ 7.09- 8.58 due to thirteen aromatic protons and -CH proton of pyrazole ring.

The additional support for the structure was obtained by recording its mass spectrum. The mass spectrum of 5a (Fig.2.11) showed a molecular ion peak at m/z 431, which corresponding to its molecular weight.

The formation of pyrazole occurs probably via 1,2-addition of hydrazide to the carbonyl carbon of chalcones, followed by dehydrative cyclization and rearrangement.

The plausible mechanism of the reaction is depicted in [Scheme-II].
Mechanism

Scheme-II

Intramolecular nucleophile attack

Het = \[
\begin{array}{c}
\text{Het} \\
\text{Het} \\
\text{Het} \\
\end{array}
\]

Het -^ N^2 H transfer

Het = \[
\begin{array}{c}
\text{Het} \\
\text{Het} \\
\text{Het} \\
\end{array}
\]

Het -NH, H transfer

Het -NH

Het -NH
Table 2.2. IR and $^1$H NMR spectral data of 2-[(2-(3,5-diphenylsubstituted-2,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl]thio]-1,3-benzoxazoles 5(a-t)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>IR (KBr) cm$^{-1}$</th>
<th>$^1$H NMR δ ppm</th>
<th>Molecular ion (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
<td>-H</td>
<td>-H</td>
<td>-4Cl</td>
<td>1658(CO)</td>
<td>δ 2.17 (s, 2H, -CH$_2$), δ 4.43 (s, 2H, -S-CH$_2$) and δ 7.39-8.02 (m, 14H, ArH &amp; CH=C)</td>
<td>447</td>
</tr>
<tr>
<td>5e</td>
<td>-H</td>
<td>-4OH</td>
<td>-4Cl</td>
<td>1669(CO), 3197(OH)</td>
<td>δ 2.17 (s, 2H, -CH$_2$), δ 4.43 (s, 2H, -S-CH$_2$) and δ 6.92-8.00 (m, 13H, ArH &amp; CH=C), δ 8.67 (s, 1H, -OH)</td>
<td>463</td>
</tr>
<tr>
<td>5g</td>
<td>-H</td>
<td>-4OCH$_3$</td>
<td>-4F</td>
<td>1672(CO)</td>
<td>δ 2.17 (s, 2H, -CH$_2$), δ 3.89 (s, 3H, -OCH$_3$), δ 4.43 (s, 2H, -S-CH$_2$) and δ 6.98-8.05 (m, 13H, ArH &amp; CH=C)</td>
<td>444</td>
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<tr>
<td>5i</td>
<td>-H</td>
<td>-4OCH$_3$</td>
<td>-3NO$_2$</td>
<td>1665(CO), 1598(NO$_2$)</td>
<td>δ 2.17 (s, 2H, -CH$_2$), δ 3.91 (s, 3H, -OCH$_3$), δ 4.41 (s, 2H, -S-CH$_2$) and δ 6.93-8.08 (m, 13H, ArH &amp; CH=C)</td>
<td>_</td>
</tr>
<tr>
<td>5k</td>
<td>-CH$_3$</td>
<td>-H</td>
<td>-4F</td>
<td>1662(CO)</td>
<td>δ 2.17 (s, 3H, -CH$_3$), δ 2.45 (s, 2H, -CH$_2$), δ 4.42 (s, 2H, -S-CH$_2$) and δ 7.09-8.52 (m, 13H, ArH &amp; CH=C)</td>
<td>445</td>
</tr>
<tr>
<td>5l</td>
<td>-CH$_3$</td>
<td>-H</td>
<td>-4Cl</td>
<td>1660(CO)</td>
<td>δ 2.17 (s, 3H, -CH$_3$), δ 2.45 (s, 2H, -CH$_2$), δ 4.41 (s, 2H, -S-CH$_2$) and δ 7.10-8.02 (m, 13H, ArH &amp; CH=C)</td>
<td>461</td>
</tr>
<tr>
<td>5o</td>
<td>-CH$_3$</td>
<td>-4OH</td>
<td>-4Cl</td>
<td>1663(CO), 3093(OH)</td>
<td>δ 2.17 (s, 3H, -CH$_3$), δ 2.45 (s, 2H, -CH$_2$), δ 4.42 (s, 2H, -S-CH$_2$) and δ 6.93-8.00 (m, 12H, ArH &amp; CH=C), δ 8.72 (s, 1H, -OH)</td>
<td>477</td>
</tr>
<tr>
<td>5q</td>
<td>-CH$_3$</td>
<td>-4OCH$_3$</td>
<td>-4F</td>
<td>1655(CO)</td>
<td>δ 2.01 (s, 3H, -CH$_3$), δ 2.45 (s, 2H, -CH$_2$), δ 3.90 (s, 3H, -OCH$_3$), δ 4.42 (s, 2H, -S-CH$_2$) and δ 6.98-8.05 (m, 13H, ArH &amp; CH=C)</td>
<td>475</td>
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<td>5r</td>
<td>-CH$_3$</td>
<td>-4OCH$_3$</td>
<td>-4Cl</td>
<td>1665(CO)</td>
<td>δ 1.87 (s, 3H, -CH$_3$), δ 2.17 (s, 2H, -CH$_2$), δ 3.82 (s, 3H, -OCH$_3$), δ 4.42 (s, 2H, -S-CH$_2$) and δ 6.92-7.50 (m, 12H, ArH &amp; CH=C)</td>
<td>492 (M+1)</td>
</tr>
<tr>
<td>5s</td>
<td>-CH$_3$</td>
<td>-4OCH$_3$</td>
<td>-3NO$_2$</td>
<td>1671(C=O), 1598(NO$_2$)</td>
<td>δ 2.17 (s, 2H, -CH$_2$), δ 3.91 (s, 3H, -OCH$_3$), δ 4.43 (s, 2H, -S-CH$_2$) and δ 6.93-8.08 (m, 12H, ArH &amp; CH=C)</td>
<td>_</td>
</tr>
</tbody>
</table>
Fig. 2.9

Fig. 2.10.
Fig. 2.11.
2.2.7 Synthesis of 1-[(1,3-benzoxazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbaldehydes 7(a-j)

Among the methods used to construct the pyrazole moiety, Method-B was used to construct pyrazolecarbaldehydes and explained in the following paragraphs.

The Method-B consists of conversion of hydrazide into acetohydrazides by the reaction with substituted acetophenones. These acetohydrazides upon cyclization by using dimethylformamide and phosphorus oxychloride gave pyrazoles.

Method-B involved two steps.

2.2.8a 2-(1,3-Benzoxazol-2-ylthio)-N'-[1-phenylethylidene]acetohydrazides 6(a-j)

To study the pharmacological variation, carbaldehydesubstituted pyrazole derivatives have been synthesized. These title compounds were synthesized by the intermediate formation of acetohydrazides. The 2-substituted benzoxazole carbohydrazides have been reacted with following substituted aromatic ketones to obtain acetohydrazides.

a. 4-Chloroacetophenone
b. 4-Bromoacetophenone
c. 4-Aminoacetophenone
d. 4-Methoxyacetophenone
e. 4-Hydroxyacetophenone

The compounds 6(a-j) were synthesized by making use of the same starting materials i.e., 2-(1,3-benzoxazol-2-ylthio)acetohydrazides 4(a-b). The compounds 4(a-b) on reaction with various substituted acetophenones in presence of sulfuric acid gave corresponding 2-(1,3-benzoxazol-2-ylthio)-N'-[1-phenylethylidene]acetohydrazides 6(a-j) in good yield.
The IR spectrum of 6a (Fig. 2.12) showed amide carbonyl stretching band at 1667 cm⁻¹ and absorption band at 3170 cm⁻¹ due to amine group.

¹H NMR spectrum of compound 6a (Fig. 2.13) exhibited a singlet at δ 2.27 due to three protons of methyl group, another singlet at δ 4.70 due to –S-CH₂ group, multiplets ranging from δ 7.30-7.86 due to eight aromatic protons and singlet at δ 11.06 due to –NH proton (D₂O exchangeable).

The mass spectrum of 6a (Fig. 2.14) showed a molecular ion peak (M+1) at m/z 360, which corresponding to its molecular weight.

2.2.8b Synthesis of 1-[(1,3-benzoxazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbaldehydes 7(a-j)

The title compounds 1-[(1,3-benzoxazol-2-ylthio)acetyl]-3-substitutedphenyl-1H-pyrazole-4-carbaldehydes 7(a-j) were obtained by stirring 2-(1,3-benzoxazol-2-ylthio)-N-[1-phenylethylidene]acetohydrazides 6(a-j) with Vilsmeir-Haak reagent, prepared by mixing dimethyl formamide and phosphorus oxychloride at 5-10°C.

IR spectrum of 7a (Fig. 2.15) exhibited absorption bands at 1737 cm⁻¹ and 1599 cm⁻¹ due to aldehydic carbonyl group and ketonic carbonyl group respectively.

The ¹H NMR spectrum of 7a (Fig. 2.16) displayed a singlet at δ 4.34 due to two protons of –S-CH₂ group, multiplet at δ 6.83-7.75 due to eight aromatic protons and a singlet at δ 9.89 due to aldehydic proton. The ¹H NMR spectrum conspicuously showed the absence of signal due to methyl group.

The plausible mechanism of the reaction is depicted in Scheme-III.
Further evidence for the formation of 7a was obtained by recording its mass spectrum. The mass spectrum of compound 7a (Fig. 2.17) showed molecular ion peak at m/z 397 which is consistent with its molecular weight.

The plausible mechanism is depicted in Scheme-III.

Table 2.3 IR, NMR and Mass spectral data of 2-(1,3-benzoxazol-2-ythio)-N'-[1-phenylethylidene]acetohydrazides 6(a-j) and 1-[(1,3-benzoxazol-2-ythio)acetyl]-3-phenyl-1H-pyrazole-4-carbaldehydes 7(a-j)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>R'</th>
<th>IR (KBr) cm⁻¹</th>
<th>¹H NMR δ ppm</th>
<th>Molecular ion (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6b</td>
<td>-H</td>
<td>-Br</td>
<td>1667 (-C=O), 3168 (NH)</td>
<td>δ 2.22 (s, 3H, -CH₃), δ 4.58 (s, 2H, -S-CH₂), δ 7.17-7.68 (m, 9H, ArH &amp; CH=C), δ 10.75 (s, 1H, NH)</td>
<td>404</td>
</tr>
<tr>
<td>6d</td>
<td>-H</td>
<td>-OCH₃</td>
<td>1667 (-C=O), 3188 (NH)</td>
<td>δ 2.24 (s, 3H, -CH₃), δ 3.78 (s, 3H, -OCH₃), δ 4.68 (s, 2H, -S-CH₂), δ 6.94-7.77 (m, 9H, ArH &amp; CH=C), δ 10.87 (s, 1H, NH)</td>
<td>355</td>
</tr>
<tr>
<td>6i</td>
<td>-CH₃</td>
<td>-OCH₃</td>
<td>1688 (-C=O), 3189 (NH)</td>
<td>δ 2.24 (s, 3H, N=C-CH₃), δ 2.27 (s, 3H, CH₃), δ 3.78 (s, 3H, -OCH₃), δ 4.65 (s, 2H, -S-CH₂), δ 6.94-7.77 (m, 8H, ArH &amp; CH=C), δ 10.87 (s, 1H, NH)</td>
<td>-</td>
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<tr>
<td>7c</td>
<td>-H</td>
<td>-NH₂</td>
<td>1670 (C=O), 1737 (-C=O), 3214 (NH₂)</td>
<td>δ 4.32 (s, 2H, -S-CH₂), δ 5.21 (s, 2H, NH₂), δ 6.82-7.94 (m, 9H, ArH &amp; CH=C), δ 9.93 (s, 1H, CHO)</td>
<td>-</td>
</tr>
<tr>
<td>7b</td>
<td>-H</td>
<td>-Br</td>
<td>-</td>
<td>δ 4.33 (s, 2H, -S-CH₂), δ 6.95-7.76 (m, 9H, ArH &amp; CH=C), δ 9.97 (s, 1H, CHO)</td>
<td>441</td>
</tr>
<tr>
<td>7i</td>
<td>-CH₃</td>
<td>-OCH₃</td>
<td>-</td>
<td>δ 2.19 (s, 3H, -CH₃), δ 3.81 (s, 3H, -OCH₃), δ 4.31 (s, 2H, -S-CH₂), δ 6.82-7.93 (m, 9H, ArH &amp; CH=C), δ 10.87 (s, 1H, CHO)</td>
<td>-</td>
</tr>
</tbody>
</table>
Mechanism

Scheme-III
Fig. 2.12.

Fig. 2.13.
Fig. 2.14.

Fig. 2.15.
Fig. 2.16.

Fig. 2.17.
2.2.9 Synthesis of 2-[(5-substitutedphenyl-4H-1,2,4-triazol-3-yl)methyl]thio]-1,3-benzoxazoles 8(a-h)

In view of wide spectrum of biological activities associated with 1,2,4-triazoles and also in continuation of our studies, we thought of linking 1,2,4-triazoles to second position of biologically active benzoxazole moiety through phenyl –S-CH$_2$- bridge. One of the easiest ways of constructing 1,2,4-triazoles is the reaction of hydrazides with following aromatic aldehydes in presence of glacial acetic acid, ammonium acetate and liquid ammonia.

The hydrazides 4(a-b) on reaction with different aromatic aldehydes in presence of glacial acetic acid, ammonium acetate and liquid ammonia gave 2-[(5-substitutedphenyl-4H-1,2,4-triazol-3-yl)methyl]thio]-1,3-benzoxazoles 8(a-h).

IR spectrum of 8g (Fig. 2.18) exhibited the absorption bands at 3099 cm$^{-1}$ and 2977 cm$^{-1}$ due to the presence of –OH and –NH groups.

$^1$H NMR spectrum of 8g (Fig. 2.19) showed a peak at $\delta$ 2.5 due to methyl group, another singlet at $\delta$ 4.6 due to two protons of –S-CH$_2$ group, multiplets ranging from $\delta$ 6.8-8.1 ascribed to nine aromatic protons and peaks at $\delta$ 9.9 and $\delta$ 11.5 were assigned for –OH and –NH protons (D$_2$O exchangeable).

The plausible mechanism of the reaction is depicted in Scheme-IV.
Mechanism

Scheme-IV
Table 2.4. IR and $^1$H NMR spectral data of triazoles 8(a-h)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>R'</th>
<th>IR (KBr) cm$^{-1}$</th>
<th>$^1$H NMR δ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>-H</td>
<td>-4Cl</td>
<td>3135(-NH)</td>
<td>δ 4.69 (s, 2H, -S-CH$_2$), δ 7.31-8.05 (m, 8H, ArH) &amp; δ 11.86 (s, 1H, NH)</td>
</tr>
<tr>
<td>8b</td>
<td>-H</td>
<td>-3NO$_2$</td>
<td>2928(-NH)</td>
<td>δ 4.75 (s, 2H, -S-CH$_2$), δ 7.30-8.19 (m, 8H, ArH) &amp; δ 12.07 (s, 1H, NH)</td>
</tr>
<tr>
<td>8c</td>
<td>-H</td>
<td>-4OH</td>
<td>2977(-NH) 3099(-OH)</td>
<td>δ 4.66 (s, 2H, -S-CH$_2$), δ 6.82-7.95 (m, 8H, ArH), δ 9.96 (s, 1H, -OH) &amp; δ 11.60 (s, 1H, NH)</td>
</tr>
<tr>
<td>8d</td>
<td>-H</td>
<td>-4OCH$_3$</td>
<td>2961(-NH)</td>
<td>δ 3.81 (s, 3H, -OCH$_3$), δ 4.67 (s, 2H, -S-CH$_2$), δ 7.06-8.00 (m, 8H, ArH), &amp; δ 11.67 (s, 1H, NH)</td>
</tr>
<tr>
<td>8e</td>
<td>-CH$_3$</td>
<td>-4Cl</td>
<td>2961(-NH)</td>
<td>δ 2.40 (s, 3H, -CH$_3$), δ 4.67 (s, 2H, -S-CH$_2$), δ 7.12-8.05 (m, 7H, ArH), &amp; δ 11.85 (s, 1H, NH)</td>
</tr>
<tr>
<td>8f</td>
<td>-CH$_3$</td>
<td>-3NO$_2$</td>
<td>2927(-NH)</td>
<td>δ 2.39 (s, 3H, -CH$_3$), δ 4.72 (s, 2H, -S-CH$_2$), δ 7.11-8.20 (m, 7H, ArH), &amp; δ 12.02 (s, 1H, NH)</td>
</tr>
<tr>
<td>8h</td>
<td>-CH$_3$</td>
<td>-4OCH$_3$</td>
<td>2964(NH)</td>
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</tr>
</tbody>
</table>
Fig. 2.18.

![Infrared spectrum of compound 8g](image)

Fig. 2.19.

![NMR spectrum of compound 8g](image)
Experimental

1. Synthesis of 1,3-benzoxazole-2-thiols 2(a-b)

A mixture of 2-amino phenols 1(a-b) (0.1 mol), potassium hydroxide (0.1 mol) and methanol (100 ml) was taken in a round bottomed flask and carbon disulphide (0.1 mol) was added drop wise to the mixture with constant stirring in ice cold condition. Then the reaction mixture was refluxed for about 8 hr. and was poured onto crushed ice and acidified with acetic acid (pH 6). The separated product was filtered, dried and recrystallised from ethanol.

2. Synthesis of ethyl[(1,3-benzoxazol-2-yl)thio]acetates 3(a-b)

Equimolar quantity of 1,3-benzoxazole-2-thiols 2(a-b) (0.1 mol) and ethyl chloroacetate (0.1 mol) in dry acetone (40 ml) in presence of anhydrous potassium carbonate (5 g) was refluxed on water bath for about 16 hr. Then the reaction mixture was poured onto crushed ice, solid product thus obtained was filtered, dried and recrystallised from ethanol.

3. Synthesis of 2-[(1,3-benzoxazol-2-yl)thio]acetoxydrazides 4(a-b)

A mixture of ethyl[(1,3-benzoxazol-2-yl)thio]acetates 3(a-b) (0.1 mol) and hydrazine hydrate (0.1 mol) in methanol (30 ml) was stirred for about half an hr. The obtained solid was filtered, dried and recrystallised from dimethyl formamide.

4. Synthesis of 1,3-diphenylprop-2-en-l-ones i-x

Freshly distilled aromatic ketones (0.02 mol) were added to a cooled mixture of sodium hydroxide (0.0275), water (10 ml) and ethanol (6 ml). To this mixture substituted aromatic aldehydes (0.02 mol) were added in ice cold condition. After the addition was over the reaction mixture was stirred vigorously until the reaction mixture becomes thick liquid. It was cooled in ice chest for overnight. The solid obtained was filtered and washed with cold water and rectified spirit. The crude chalcone was dried and recrystallised from rectified spirit.
5. Synthesis of 2-[(2-(3,5-diphenylsubstituted-2,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)thio]-1,3-benzoxazole derivatives 5(a-t)

A mixture of chalcones i-x (0.005 mol), 2-[(1,3-benzoxazol-2-yl)thio]acetohydrazides 4(a-b) (0.005 mol) in acetone (20 ml) were refluxed in presence of acetic acid (0.5 ml) for 6 hr. Then the reaction mixture was poured onto crushed ice. Then the solid was separated, the separated solid was filtered, dried and recrystallised from ethanol.


To a solution of 2-(1,3-benzoxazol-2-ylthio)acetohydrazides 4(a-b) in hot methanol (30 ml), substituted acetophenones (0.01 mol) and a drop of concentrated sulfuric acid were added. The reaction mixture was refluxed for 3-4 hr. and cooled. The solid separated was filtered and recrystallised from DMF.

7. Synthesis of 1-[(1,3-benzoxazol-2-ylthio)acetyl]-3-phenyl-1H-pyrazole-4-carbaldehydes 7(a-j)

To the Vilsmeier-Haak reagent, prepared from dimethyl formamide (10 ml) and phosphorous oxychloride (1.1 ml), hydrazones 6(a-j) (0.01 mol) were added and the reaction mixture was stirred at room temperature for 3 hr. and poured onto crushed ice. The solid thus separated was filtered and recrystallised from DMF.

8. Synthesis of 2-[(5-phenyl-4H-1,2,4-triazol-3-yl)methyl]thio]-1,3-benzoxazoles 8(a-h)

To a solution of 4(a-b) (0.003 mol) in acetic acid (10 ml), a pinch of ammonium acetate was added followed by the addition of appropriate aromatic aldehydes (0.003 mol) and the mixture was stirred for 4 hr. at room temperature. The solution was then neutralized with liquid ammonia and the product obtained was filtered, washed with water. The crude product was recrystallised from alcohol.

Physical data of the newly synthesized compounds are reported in Table 2.5 and Table 2.6.
Table 2.5. Physical data of the synthesized compounds 2(a-b), 3(a-b) and 4(a-b)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Molecular formula</th>
</tr>
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<tbody>
<tr>
<td>2a</td>
<td>-H</td>
<td>192-94</td>
<td>90</td>
<td>C\textsubscript{7}H\textsubscript{5}NOS</td>
</tr>
<tr>
<td>2b</td>
<td>-CH\textsubscript{3}</td>
<td>208-09</td>
<td>84</td>
<td>C\textsubscript{8}H\textsubscript{7}NOS</td>
</tr>
<tr>
<td>3a</td>
<td>-H</td>
<td>52-54</td>
<td>78</td>
<td>C\textsubscript{11}H\textsubscript{11}NO\textsubscript{3}S</td>
</tr>
<tr>
<td>3b</td>
<td>-CH\textsubscript{3}</td>
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<td>76</td>
<td>C\textsubscript{12}H\textsubscript{13}NO\textsubscript{3}S</td>
</tr>
<tr>
<td>4a</td>
<td>-H</td>
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<td>80</td>
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<tr>
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<td>-CH\textsubscript{3}</td>
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<td>86</td>
<td>C\textsubscript{10}H\textsubscript{11}N\textsubscript{3}O\textsubscript{2}S</td>
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Table 2.6. Physical data of synthesized compounds 5(a-t), 6(a-j), 7(a-j) and 8(a-h)

<table>
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<tr>
<th>Comp.</th>
<th>R</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Molecular formula</th>
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<tbody>
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<td>-H</td>
<td>-4F</td>
<td>86-88</td>
<td>81</td>
<td>C\textsubscript{24}H\textsubscript{28}FN\textsubscript{3}O\textsubscript{2}S</td>
</tr>
<tr>
<td>5b</td>
<td>-H</td>
<td>-H</td>
<td>-4Cl</td>
<td>102-04</td>
<td>63</td>
<td>C\textsubscript{24}H\textsubscript{28}ClN\textsubscript{3}O\textsubscript{2}S</td>
</tr>
<tr>
<td>5c</td>
<td>-H</td>
<td>-H</td>
<td>-3NO\textsubscript{2}</td>
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<td>60</td>
<td>C\textsubscript{24}H\textsubscript{28}N\textsubscript{4}O\textsubscript{4}S</td>
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<tr>
<td>5d</td>
<td>-H</td>
<td>-H</td>
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<td>63</td>
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<td>C\textsubscript{27}H\textsubscript{23}N\textsubscript{3}O\textsubscript{4}S</td>
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