Chapter - 3

Rapid Synthesis and Characterization of Novel Tri-substituted Pyrazoles/Isoxazoles Library Using Ketene Dithioacetals
3.1 Introduction

The development of new methods for the synthesis of five-member heterocyclic compound libraries, both in solution and on solid phase, is an ever-expanding area in combinatorial chemistry. Specifically, those containing the pyrazole and isoxazole nucleus have been widely used as key building blocks for pharmaceutical agents. Its derivatives are endowed with high pharmacological properties, for example, hypoglycemic, analgesic, anti-inflammatory, antibacterial, anti-HIV, and anticancer activity, as well as useful activities in conditions like schizophrenia, hypertension, and Alzheimer’s disease. In addition, they also have agrochemical properties including herbicidal and soil fungicidal activity, thus they have been used as pesticides and insecticides. Recently, pyrazoles containing aryl substituted emerged as p38 Kinase inhibitors, antiparasitic activities.

Pyrazoles and isoxazoles are well known five member heterocyclic compounds and several procedures for its synthesis have been extensively studied. The pyrazole ring system consists of a doubly unsaturated five-member ring containing two adjacent nitrogen atoms. Isoxazole ring system consist two hetero atoms oxygen at position 1 and nitrogen at position 2 (Figure-1).

![Figure-1](image)

Pyrazoles and isoxazoles bearing sulfone and carboxamide moieties demonstrated to have significant pharmacological applications. For examples, cyclooxygenase-2 (COX-2) selective inhibitors, celecoxib, rofecoxib and valdecoxib are currently prescribed for the treatment of arthritis and inflammatory diseases. These COX-2 inhibitors exhibited anti-inflammatory activity with reduced gastrointestinal side effects. Oxacillin and its derivatives are useful compounds due to their narrow spectrum antibiotic properties. Recently, pyrrolyl aryl sulfones have been reported by Silvestri et al. and Artico et al. as a new class of human immunodeficiency virus type 1 (HIV-1) RT inhibitors acting at the non-nucleoside binding site of this enzyme. Haruna et al. have been synthesized the propargylic sulfones with various planar molecules and evaluated for their DNA binding properties and DNA cleavage activity.
Moreover, the 1-(4-methylsulfonyl)benzene and 4-(4-methylsulfonyl)benzene substituted pyrazole compound containing a nitric oxide donating group at the 3-position of the pyrazole ring, respectively, have been synthesized and evaluated for its ability to inhibit COX isoenzymes in human whole blood. Pyrazoles containing sulfone group at N position have been exhibited promising antimicrobial activity. Furthermore, amide group linked with isoxazole derivatives found to have combined α2-adrenoceptor antagonistic and serotoni ne reuptake inhibiting activities. The Isoxazoles containing aryl and carboxamide were also shown to have potent in vivo antithrombotic efficacy.

3.2 Biological activity associated with pyrazoles and isoxazoles

As mentioned above, pyrazoles and isoxazoles nucleus have been widely used as key building blocks for pharmaceutical agents. Its derivatives are endowed with high pharmacological properties, for example, hypoglycemic, GABA_{A} antagonist’s analgesic, anti-inflammatory, anti-HIV, and anticancer activity as well as useful activities in conditions like schizophrenia, hypertension, and Alzheimer’s disease.

Thomas D. Penning et al. has described a series of pyrazole and isoxazole analogs (Figure-2) as antagonists of the α_{v}β_{3} receptor. These compounds showed low to sub-nanomolar potency against α_{v}β_{3}, as well as good selectivity against α_{IIb}β_{3}. In HT29 cells, most analogs also demonstrated significant selectivity against α_{v}β_{6}. Several compounds showed good pharmacokinetic properties in rats, in addition to anti-angiogenic activity in a mouse corneal micro pocket model. Compounds were synthesized in a straightforward manner from readily available glutarate precursors.

![Figure-2](image)

Ebraheem Abdu Musad et al. has synthesized pyrazoles and isoxazoles (Figure-3) were screened for antioxidant and anti-microbial activities. Among that some of compounds showed higher antioxidant activity at 10μg/ml and some compounds exhibited better anti-microbial activity at 100μg/ml compared with standard vitamin C and ciprofloxacin, respectively.
Annamaria Lilienkampf et al.\textsuperscript{18} has developed isoxazole-based anti-TB compounds by applying rational drug design approach (Figure-4). The biological activity and the structure-activity relationships (SAR) for a designed series of 5-phenyl-3-isoxazolecarboxylic acid ethyl ester derived anti-TB compounds were investigated. Several compounds were found to exhibit nanomolar activity against the replicating bacteria (R-TB) and low micromolar activity against the non replicating bacteria (NRP-TB). The series showed excellent selectivity toward Mtb, and in general, no cytotoxicity was observed in Vero cells (IC\textsubscript{50}>128 μM). Notably, selected compounds also retained their activity against isoniazid (INH), rifampin (RMP), and streptomycin (SM) resistant Mtb strains. Hence, benzyloxy, benzylamino, and phenoxy derivatives of 5-phenyl-3-isoxazolecarboxylic acid ethyl esters represent a highly potent, selective, and versatile series of anti-TB compounds and as such present attractive lead compounds for further TB drug development.

Recently, biological evaluation of novel potent HDAC3 and HDAC8 isoxazole and pyrazole-based diazide probes (Figure-5) suitable for binding ensemble profiling with photo affinity labeling (BEProFL) experiments in cells is described. Both the isoxazole and pyrazole-based probes exhibit low nanomolar inhibitory activity against HDAC3 and HDAC8, respectively. The pyrazole-based one of the most active HDAC8 inhibitors reported in the literature with an IC\textsubscript{50} of 17 nM.
Docking studies suggest that unlike the isoxazole-based ligands the pyrazole-based ligands are flexible enough to occupy the second binding site of HDAC8. Probes/inhibitors some compounds exerted the antiproliferative and neuroprotective activities at micromolar concentrations through inhibition of nuclear HDACs, indicating that they are cell permeable and the presence of an azide or a diazide group does not interfere with the neuroprotection properties, enhance cellular cytotoxicity, or affect cell permeability.\textsuperscript{19}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Figure-5}
\end{figure}

Maria Barceló et al.\textsuperscript{20} has described synthesis of binding affinities on D₂, 5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} receptors of 6-aminomethyl-6,7-dihydro-1\textsubscript{H}-indazol-4(5\textsubscript{H})-ones and 6-aminomethyl-6,7-dihydro-3-methyl-benzo[d]isoxazol-4(5\textsubscript{H})-ones, as conformationally constrained butyrophenone analogues. One of the new compounds (Figure-6) showed good in vitro binding features, and a Meltzer’s ratio characteristic of an atypical antipsychotic profile.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Figure-6}
\end{figure}

Celecoxib and rofecoxib analogues (Figure-7), in which the respective SO\textsubscript{2}NH\textsubscript{2} and SO\textsubscript{2}Me hydrogen-bonding pharmacophores were replaced by dipolar azido bioisosteric substituents, were investigated. Molecular modeling (docking) studies showed that the azido substituent of these two analogues was inserted deep into the secondary pocket of the human COX-2 binding site where it undergoes electrostatic interaction with Arg513. The azido analogue of rofecoxib is the most potent and selective inhibitor of COX-2 (COX-1 IC\textsubscript{50}= 159.7 µM; COX-2 IC\textsubscript{50}= 0.196 µM; COX-2 selectivity index = 812), exhibited good oral anti-inflammatory and analgesic activity.
Amgad G. Habeeb et al.\textsuperscript{21} also reported a 4,5-diphenyl-4-isoxazolines (Figure-8) possessing a variety of substituents (H, F, MeS, MeSO\textsubscript{2}) at the para position of one of the phenyl rings were synthesized for evaluation as analgesic and selective cyclooxygenase-2 (COX-2) inhibitory anti-inflammatory (AI) agents. Although the 4,5-phenyl-4-isoxazolines (Figure-8), which do not have a C-3 Me substituent, exhibited potent analgesic and AI activities, those compounds evaluated were not selective inhibitors of COX-2. In contrast, 2,3-dimethyl-5-(4-methylsulfonylphenyl)-4-phenyl-4-isoxazoline exhibited excellent analgesic and AI activities, and it was a potent and selective COX-2 inhibitor (COX-1, IC\textsubscript{50} 258 μM; COX-2, IC\textsubscript{50} 0.004 μM).

A related compound (Figure-8) having a F substituent at the para position of the 4-phenyl ring was also a selective (SI = 3162) but less potent (IC\textsubscript{50} = 0.0316 μM) inhibitor of COX-2 than 2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenyl isoxazole. A molecular modeling (docking study) for 4-(4-fluorophenyl)-2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole showed that the S atom of the MeSO\textsubscript{2} substituent is positioned about 6.46 Å inside the entrance to the COX-2 secondary pocket (Val\textsuperscript{523}) and that a C-3 Me (2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole, 4-(4-fluorophenyl)-2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole) central isoxazoline ring substituent is crucial to selective inhibition of COX-2 for this class of compounds. 
Chih Y. Ho et al.\textsuperscript{22} have reported a series of (6,7-dimethoxy-2,4-dihydroindeno[1,2-c]pyrazol-3-yl)phenylamines (Figure-9) has been optimized to preserve both potent kinase inhibition activity against the angiogenesis target, the receptor tyrosine kinase of Platelet-Derived Growth Factor-BB (PDGF-BB), and to improve the broad tumor cell antiproliferative activity of these compounds. This series culminates in the discovery of (JNJ-10198409), a compound with anti-PDGFR-\(\alpha\) kinase activity (IC\textsubscript{50} = 0.0042 \(\mu\)M) and potent antiproliferative activity in six of eight human tumor cell lines (IC\textsubscript{50} = 0.033 \(\mu\)M).

![Figure-9](image)

Chih Y. Ho has developed antiangiogenic compounds with an additional antiproliferative activity capable of inhibiting tumor progression by controlling both the vascularization and proliferation of the tumor mass. Tumors may be regarded as a two-compartment system consisting of the vasculature supporting tumor growth composed of ‘normal’ homogeneous vascular endothelial cells, smooth muscle cells, and pericytes that are surrounded by colonies of neoplastic cancer cells. To find molecules that would affect both the vascular and transformed compartments, we identified several compounds with the potential to inhibit the PDGFR-\(\beta\) kinase-mediated angiogenic effect and then assayed them for collateral antiproliferative activity against a panel of human tumor cell lines.

Christian Peifer et al.\textsuperscript{23} have been reported on the discovery of isoxazole (Figure-10) as a potent dual inhibitor of p38\(\alpha\) (IC\textsubscript{50} = 0.45 \(\mu\)M) and CK1\(\delta\) (IC\textsubscript{50} = 0.23 \(\mu\)M). Because only a few effective small molecule inhibitors of CK1 have been described so far, we aimed to develop this structural class toward specific agents. Molecular modeling studies comparing p38\(\alpha\)/CK1\(\delta\) suggested an optimization strategy leading to design, synthesis, biological characterization, and SAR of highly potent compounds including possessing differentiated specificity. Selected compounds were profiled over 76 kinases and evaluation of their cellular efficacy showed 18 (CKP138) to be a highly potent and dual-specific inhibitor of CK1\(\delta\) and p38\(\alpha\).
Small molecule inhibitors of various protein kinases are utilized extensively in research and drug development. The human kinome consists of more than 500 protein kinases, and kinase inhibitors typically bind in the highly conserved ATP pocket of these enzymes. Thus the specificity of ATP competitive kinase inhibitors is of significant interest and represents a crucial factor for their use in, e.g., signal transduction research or therapeutic applications.

A series of 4-aryl-5-(4-piperidyl)-3-isoxazolol GABA\textsubscript{A} antagonists have been synthesized and pharmacologically characterized. The meta-phenyl-substituted compounds and the para-phenoxy-substituted compound (Figure 11) all display high affinities ($K_i = 10-70$ nM) and antagonist potencies in the low nanomolar range ($K_i = 9-10$ nM). These potencies are significantly higher than those of previously reported 4-PIOL antagonists and considerably higher than that of the standard GABA\textsubscript{A} antagonist SR 95531.

In contrast to the all osteric modulatory sites, the GABA binding site has very distinct and specific structural requirements for recognition and activation. Thus, very few different classes of structures have been reported. Within the series of compounds showing agonist activity at the GABA\textsubscript{A} receptor site are the selective GABA\textsubscript{A} agonists muscimol\textsuperscript{26} and 4,5,6,7-tetrahydroisoxazolo[5,4-\textit{c}]pyridin-3-ol,\textsuperscript{26-27}which have been used for the characterization of the GABA\textsubscript{A} receptors (Figure 11).\textsuperscript{28}

Recently, 4,5,6,7-tetrahydroisoxazolo[5,4-\textit{c}]pyridin-3-ol has been shown to be functionally selective for a subpopulation of GABA\textsubscript{A} receptors and is currently in clinical trials as a therapeutic for the regulation of sleep.
3.3 Synthetic methods for the pyrazole and isoxazole derivatives

There are several methods reported in the literature for the preparation of pyrazoles and isoxazoles described as under.

Pranab K. Mahata et al.\textsuperscript{29} has synthesized 3-dimethoxymethyl-5-(methylthio) pyrazole/isoxazole derivative (Figure 12) shown to be useful three carbon synthon for efficient regiospecific synthesis of a variety of five (pyrazole/isoxazole) with mask or unmask aldehyde functionality by cyclocondensation with bifunctional nucleophiles such as hydrazine and hydroxylamine respectively.

![Figure 12](image)

Sabine Kuettel et al.\textsuperscript{30} has synthesized 4-(3-phenylpyrazole/isoxazol-5-yl)morpholine derivatives (Figure 13) by two synthetic routes, in which substituted acetophenones were reacted with carbon disulfide and methyl iodide in the presence of sodium hydride to give 4-phenoxyphenyl-2,2-bis(methylthio)vinylketones, followed by \textit{in situ} cyclization of the resulting \textit{N,S}-acetals with hydrazine hydrate/hydroxylamine.

![Figure 13](image)

Scott R. Tweedie et al.\textsuperscript{31} has synthesized a pyrazole and isoxazole derivatives \textit{via} palladium-catalyzed couplings of heteroaryl amines with aryl halides using sodium phenolate as the stoichiometric base (Figure 14).

![Figure 14](image)
Kewei Wang et al.\textsuperscript{32} has reported an efficient and divergent one-pot synthesis of fully substituted 1$H$-pyrazoles and isoxazole derivatives. Substituted 1$H$-pyrazoles were synthesized from 1-carbamoyl, 1-oximyl cyclopropanes via sequential ring-opening, chlorovinylation, and intramolecular aza-cyclization under Vilsmeier conditions (POCl$_3$/DMF). Isoxazoles were synthesized from the cyclopropyl oximes via ring-opening and intramolecular nucleophilic vinylic substitution (SN$_V$) reactions in the presence of POCl$_3$/CH$_2$Cl$_2$ (Figure-15).

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure15.png}
\caption{Figure-15}
\end{figure}

Ebraheem Abdu Musad et al.\textsuperscript{33} has prepared a new 3,5-(substituted) pyrazoles and isoxazoles by reaction of (N'\textsuperscript{\textprime}, N'\textsuperscript{\textprime}$'$)-N'\textsuperscript{\textprime}, N'\textsuperscript{\textprime}$'$-bis(3,4,5-substituted-benzylidene)malonohydrazide with hydrazine hydrate and hydroxylamine hydrochloride respectively under solvothermal conditions involving an ecofriendly method without any environmental pollution (Figure-16).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure16.png}
\caption{Figure-16}
\end{figure}

Ch brajakishor singh et al.\textsuperscript{34} have been synthesized a steroidal pyrazole and isoxazole derivatives form 2-ethoxymethene-4-androsten-3-one and 2-bis(methylthio)methene-4-androsten-3-one (Figure-17).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17.png}
\caption{Figure-17}
Alex F. C. Flores et al.\textsuperscript{35} have been synthesized a new series of hydroxyl pyrazoles and 2-methyl-3-isoxazolones from the cyclocondensation reaction of trichloromethyl-substituted 1,3-dielectrophiles with dry hydrazine and N-methyl hydroxylamine respectively (Figure-18).

\begin{equation}
\begin{array}{c}
\text{NH}((\text{Me})\text{OH}, \text{MeOH} \\
25-35 ^\circ\text{C}, 2-3 \text{hrs} \\
90-95 \%
\end{array}
\end{equation}

\begin{array}{c}
\text{R}_{1} = \text{R}_{2} = \text{-(CH}_{2}\text{)}_{n} \text{-(CH}\text{)}_{m} \text{-(CH})_{n} \text{H, Ph, Me}
\end{array}

\text{Figure-18}

Sarvesh Kumar et al.\textsuperscript{36} has synthesized pyrazole and isoxazole derivatives \textit{via} hetero annulations of 10,11-Dihydro-11-[bis(methylthio)methylene]dibenzoepin-10-one (α-oxoketene dithioacetal) (Figure-19).

\begin{equation}
\begin{array}{c}
\text{NH}_{3}\text{H}_{2}\text{H}_{2} \text{O} \\
\text{EtOH/Δ}\text{8hr}
\end{array}
\end{equation}

\text{Figure-19}

Valentina Molteni et al.\textsuperscript{37} have been developed an extremely simple one pot reaction for transforming diketones into the corresponding pyrazoles and isoxazoles promoted by microwave irradiation (Figure-20).

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{R-NHNH}_{2} \text{MW H}_{2}\text{O}
\end{array}
\end{equation}

\text{Figure-20}

Thomas Kurz et al.\textsuperscript{38} has synthesized novel fluorinated ketene \textit{N},\textit{S}-acetals were readily prepared by the reaction of fluorosubstituted cyanoacetamide derivatives with arylisothiocyanate in the presence of potassium hydroxide, followed by the alkylation of the produced salts with methyl iodide. The reaction of fluorinated ketene \textit{N},\textit{S}-acetals with hydrazine afforded different fluorosubstituted pyrazole (Figure-21).
Galal H. Elgemeie et al.\textsuperscript{39} have been synthesized a variety of novel $\alpha$-cyanoketene $S,S$-acetals, readily prepared by the reaction of cyanoacetanilides or cyanothioacetamide with carbon disulfide, followed by alkylation, react smoothly with nucleophile to afford variously substituted methylthio derivatives of pyrazole (\textbf{Figure-22}).

\begin{center}
\textbf{Figure-21}
\end{center}

\begin{center}
\textbf{Figure-22}
\end{center}

Jesse P. Waldo et al.\textsuperscript{40} have been synthesized of isoxazoles (\textbf{Figure-23}) via electrophilic cyclization under mild reaction conditions by the reaction of 2-alkyn-1-one $O$-methyl oximes with ICl, I$_2$, Br$_2$, or PhSeBr.

\begin{center}
\textbf{Figure-23}
\end{center}

David J. Burkhart et al.\textsuperscript{41} have been synthesized ethyl 4-acetyl-5-methyl-3-isoxazoyl carboxylate (\textbf{Figure-24}) was smoothly lithiated at the 5-methyl position. The anion was quenched with a variety of electrophiles such as alkyl halides, aldehyde, TMSCl and Me$_3$SnCl in good to excellent yields.

\begin{center}
\textbf{Figure-24}
\end{center}
V. P. Kislyi et al.\textsuperscript{42} were prepared 4-amino-5-benzoyl (acetyl) isoxazole-3-carboxamides (Figure 25) by cyclization of $\alpha$-hydroxyimino nitriles O-alkylated with bromoacetophenones (bromoacetone). The purity of the target 4-aminoisoxazoles can be substantially increased by treating O-alkylated oximes with LiClO$_4$ before cyclization.

![Figure 25]

Wenli Ma et al.\textsuperscript{43} have been developed an efficient three-component, two-step “catch and release” solid-phase synthesis of 3,4,5-trisubstituted pyrazoles and isoxazoles (Figure-26). The first step involves a base-promoted condensation of a 2-sulfonyl- or a 2-carbonyl-acetonitrile derivative (1 or 7) with an isothiocyanate 2 and in situ immobilization of the resulting thiolate anion on Merrifield resin. Reaction of the resin-bound sulfonyl intermediate 4 with hydrazine or hydroxylamine, followed by release from the resin and intramolecular cyclization, affords 3,5-diamino-4-(arylsulfonyl)-1H-pyrazoles 5 or isoxazoles 6, respectively. Reaction of the resin-bound carbonyl intermediate 9 with hydrazine, on the other hand, leads to 3-(arylamino)-5-aryl-1H-pyrazole-4-carbonitriles 10.

![Figure-26]
3.4 Some pharmaceutical molecules related to pyrazoles and isoxazoles

Pyrazole and isoxazole nucleus have been widely used as key building blocks for pharmaceutical agents. Its derivatives are endowed with high pharmacological properties, for example, hypoglycemic, analgesic, anti-inflammatory, antibacterial, anti-HIV, and anticancer activity, as well as useful activities in conditions like schizophrenia, hypertension, and Alzheimer’s disease.
3.5 Current research work

α-Oxoketene dithioacetals especially the dimethylthioacetals have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic compounds.\textsuperscript{44,45} Ketene dithioacetals, in the presence of various regents, undergo different types of reactions to yield other heterocyclic compounds, e.g., isoxazole, pyrazole, thiophenes, pyrimidines, pyridines, etc. Consequently we were interested in surveying the synthetic utility of ketene dithioacetals.

Recently, we have reported solution-phase library of pyrazoles and isoxazoles functionalized with methyl, sulfone and carboxamide moieties in two steps with excellent yield and chemical purity for medicinally interesting molecules. Water was emerged as an efficient and green solvent in the condensation reaction of various ketene dithioacetals with hydrazine hydrate or hydroxyl amine hydrochloride.\textsuperscript{46}

![Figure-27](image)

In an extension to this work, we describe here a novel synthesis of solvent free library of trisubstituted pyrazoles (B) and isoxazoles (C) (Figure-27) by the reaction of ketene dithioacetals with hydrazine hydrate and hydroxylamine hydrochloride under microwave irradiations Thus, it has been found that reaction of substituted acetoacetonilide derivatives with carbon disulfide in the presence of potassium carbonate followed by the alkylation with methyl iodide gives the novel ketene dithioacetals (A) (Figure 27), the structures of which have been established on the basis of their elemental analysis and spectral data.
### 3.6 Results and discussion

Scheme: Synthesis of novel trisubstituted pyrazoles and isoxazoles from ketene dithioacetals

#### Scheme-1

![Scheme 1](image)

### Scheme-2

![Scheme 2](image)

### Scheme-3

![Scheme 3](image)

Where R=CH₃, OCH₃, F, NO₂, Cl

Various substituted 3-cyclopropyl-3-oxo-N-arylpropanamide (3a-o) were prepared by reacting substituted amines (1a-h) and methyl 3-cyclopropyl-3-oxopropanoate (2) in toluene with a catalytic amount of NaOH or KOH (Scheme 1). The reaction mixture was refluxed for 15-20 h. Fifteen different acetoacetanilide were synthesized bearing various electron donating and electron withdrawing groups such as 2,3-diCH₃; 3,4-diCH₃; 4-CH₃; H; 2,5-diCH₃; 2,4-diCH₃; 3-Cl-4-F; 4-F; 4-Cl; 2-Cl; 2-F; 4-OCH₃; 2,5-diCl and 3-NO₂ on the phenyl ring. The reaction of substituted acetoacetanilide 3a-o derivatives with carbon disulfide in the presence of potassium carbonate followed by the alkylation with methyl iodide (Scheme 2) gave the novel ketene dithioacetals 4a-o. Further treatment of 4a-o with hydrazine hydrate or hydroxyl amine hydrochloride in the presence of potassium hydroxide (Scheme-3) to furnish pyrazoles 5a-o and isoxazoles 6a-o in excellent yield. As a part of ‘green chemistry’ approaches, we have done all reaction in solvent free reaction condition and under microwave irradiation. Comparative study of reaction time and yield in conventional and microwave irradiation methods are summarized in Table-1.
Chapter 3  Synthesis of trisubstituted pyrazoles/isoxazoles

Table-1: 3-cyclopropyl, 5-methylthio, 4-carboxamide substituted pyrazoles and isoxazoles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reaction time</th>
<th>Conventional (hrs)</th>
<th>Yield (%)</th>
<th>MW (min.)</th>
<th>Yield (%)</th>
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<td>4-CH₃Ph</td>
<td></td>
<td>2.0</td>
<td>85</td>
<td>13.0</td>
<td>88</td>
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<tr>
<td>5b</td>
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<td>88</td>
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<td>90</td>
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<tr>
<td>5c</td>
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<td>1.5</td>
<td>87</td>
<td>10.0</td>
<td>92</td>
</tr>
<tr>
<td>5d</td>
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<td></td>
<td>2.0</td>
<td>83</td>
<td>12.0</td>
<td>90</td>
</tr>
<tr>
<td>5e</td>
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The structures of 4a-o were established on the basis of their elemental analysis and spectral data (MS, IR, and ¹H NMR). The analytical data for 4b revealed a molecular formula C₁₅H₁₆ClNO₂S₂ (m/z 342). The ¹H NMR spectrum revealed a two multiplet at δ = 1.02-1.06 and 1.21-1.24 ppm assigned two –CH₂ groups in cyclopropane ring, a multiplet at δ = 2.37-2.43 ppm assigned to the –CH protons,
a singlet at $\delta = 2.47$ ppm assigned to $(2 \times \text{SCH}_3)$, a multiplet at $\delta = 7.26-7.59$ ppm assigned to the aromatic protons, and one broad singlet at $\delta = 8.69$ ppm assigned to $-\text{CONH}$ groups.

The structures of $5a-o$ were established on the basis of their elemental analysis and spectral data (MS, IR, $^1$H NMR and $^{13}$C NMR). Structure $5a$ was supported by its mass ($m/z$ 287), which agrees with its molecular formula C$_{15}$H$_{17}$N$_3$OS; its $^1$H NMR spectrum had signals at $\delta = 0.81-0.82$ and 0.96-0.99 (m, 2x CH$_2$) in cyclopropane ring, a multiplet at $\delta = 2.24$ ppm assigned to the cyclopropyl-CH protons, a singlet at $\delta = 2.40$ assigned to -CH$_3$ protons, a singlet at $\delta = 2.48$ ppm assigned to (SCH$_3$), a multiplet signal at $\delta = 7.09-7.53$ ppm related to the aromatic protons, 9.36 (broad, $-\text{CONH}$) and 12.84 (broad, pyrazole NH).

The structures of $6a-o$ were established on the basis of their elemental analysis and spectral data (MS, IR, $^1$H NMR and $^{13}$C NMR). The analytical data for $6b$ revealed a molecular formula C$_{15}$H$_{16}$ClNO$_2$S$_2$ ($m/z$ 342). The $^1$H NMR spectrum revealed a two multiplets at $\delta = 1.14-1.06$ and 1.21-1.16 ppm assigned two –CH$_2$ groups in cyclopropane ring, a multiplet at $\delta = 2.16-2.20$ ppm assigned to the –CH protons, a singlet at $\delta = 2.68$ ppm assigned to (SCH$_3$), a multiplet at $\delta = 7.26-7.56$ ppm assigned to the aromatic protons, and one broad singlet at $\delta = 8.19$ ppm assigned to $-\text{CONH}$ groups.

The proposed mechanism for the formation of $5a-o$ and isoxazoles $6a-o$ from the corresponding 3-cyclopropyl-3-oxo-N-arylpropanamide ($3a-o$) is shown in Figure 28 & 29. In the ketene dithioacetal system the carbonyl carbon and $\beta$-carbon atoms regarded as hard and soft electrophilic centers, since the carbonyl carbon is adjacent to the hard-base oxygen while the $\beta$-carbon is flanked by the soft-base methylthio groups. Thus, the nucleophile hydrazine hydrate or hydroxyl amine hydrochloride may attack on $\beta$-carbon of systems and formed heterocyclic product by removal of methylthio and group as good leaving group and water molecule.
Mechanism

Figure 28: Proposed mechanism for the formation of pyrazole

Figure 29: Proposed mechanism for the formation of isoxazole
3.7 Conclusion

In summary, we have synthesized a library of pyrazoles and isoxazoles functionalized with cyclopropyl, thiomethyl and carboxamide moieties in single steps with excellent yield under microwave irradiation. As a part of ‘green chemistry’ approach condensation reaction of various ketene dithioacetals with hydrazine hydrate or hydroxyl amine hydrochloride in solvent free condition under microwave irradiation. The present procedure is significant over the existing methods to develop this class of molecules with excellent yield, purity and simple isolation of products.
3.8 Experimental section

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. $^1$H (300 MHz), $^1$H (400 MHz), $^{13}$C (75 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl₃ and DMSO. Chemical shifts are expressed in $\delta$ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

General synthesis of 3-cyclopropyl-3-oxo-N-arylpropanamide (3a-o).

A mixture containing the primary amine (1a-h, 10 mmol), methyl 3-cyclopropyl-3-oxopropanoate (2, 10 mmol), and catalytic amount of sodium or potassium hydroxide (10 %) in toluene (50 mL) was reflux at 110 °C for the approximately 12-15 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under $\text{vaccuo}$ and the solid or oil was crystallized from methanol which afforded pure products.

General synthesis of ketene dithioacetals (4a-o).

A 100mL conical flask equipped with magnetic stirrer and septum was charged with a solution of 3-cyclopropyl-3-oxo-N-arylpropanamide (3a-o, 10 mmol) in DMF (10 mL). Dried K₂CO₃ (20 mmol) was added and the mixture was stirred for 2 h at room temperature. CS₂ (10 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Methyl iodide (20 mmol) was added at 0-5 °C and the mixture was stirred for 4 h at room temperature. The reaction was monitored by TLC. After completion, the mixture poured into water (40 mL). The precipitated crude product was purified by filtration followed by crystallization from EtOH. When the product was oil, the organic phase was extracted with Et₂O (3 \times 10 mL). The combined organic extracts were washed with H₂O (2 \times 10 mL), dried (MgSO₄), and concentrated in $\text{vaccuo}$ to afford ketene dithioacetals directly used for the next step.
General procedure for the synthesis of trisubstituted pyrazoles 5a-o.

Conventional method:
A 25mL conical flask equipped with magnetic stirrer and septum was charged with hydrazine hydrate (15 mmol) and various ketene dithioacetals (3a-o, 10 mmol) and heated up to 75-85 °C for appropriate times (Table-1). After completion of the reaction, the reaction mixture was allowed to come to room temperature and add cold water (50 mL). The separated suspension was filtered, washed with water, dried and crystallized from methanol to afford analytically pure products with 80-90% yield.

Microwave assisted method:
A one neck flat bottom flask charged with the hydrazine hydrate (15 mmol), and various ketene dithioacetals 3a-o (10 mmol), was heated at 90 °C under microwave irradiation for appropriate time (Table-1). After completion of the reaction, the reaction mixture was allowed to attain room temperature and added cold water (50 mL). The suspension was filtered, washed with water, dried and crystallized from methanol to afford analytically pure products with 85-95% yield.

General procedure for the synthesis of trisubstituted isoxazoles 6a-o.

Conventional method:
A 25mL conical flask equipped with magnetic stirrer and septum was charged with hydroxyl amine hydrochloride (15 mmol), potassium hydroxide (15 mmol) and various ketene dithioacetals (3a-o, 10 mmol) and heated up to 75-85 °C for appropriate times (Table-1). After completion of the reaction, the reaction mixtures were cooled to room temperature and add cold water (50 mL). The separated solid was filtered, washed with water, dried and crystallized from methanol to afford analytically pure products with 80-90% yield.

Microwave assisted method:
A one neck flat bottom flask charged with hydroxyl amine hydrochloride (15 mmol), potassium hydroxide (15 mmol) and various ketene dithioacetals 3a-o (10 mmol) and reaction mixture heated at 90 °C under microwave irradiation for appropriate time (Table-1). After completion of the reaction, the reaction mixture was allowed to come to room temperature and add cold water (50 mL). The separated solid was filtered, washed with water, dried and crystallized from methanol to afford analytically pure products with 85-95% yield.
Spectral data of the synthesized compounds

3-Cyclopropyl-N-(4-fluorophenyl)-3-oxopropanamide 3c. White solid; \( R_f \) 0.42 (8:2 hexane-EtOAc); IR (KBr): 3364, 2927, 1674, 1533, 1462, 1281, 1112, 873 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 1.07-1.13 (q, 2H, CH\(_2\)), 1.14-1.20 (q, 2H, CH\(_2\)), 2.00-2.06 (m, 1H, CH), 3.71 (s, 2H, CH\(_2\)), 6.97-7.03 (m, 2H, Ar-H), 7.48-7.53 (m, 2H, Ar-H), 9.43 (s, 1H, NH); MS (m/z): 221 (M\(^+\)); Anal. Calcd for C\(_{12}\)H\(_{12}\)FNO\(_2\): C, 65.15; H, 5.47; N, 6.33; Found: C, 65.17; H, 5.45; N, 6.34.

N-(4-chlorophenyl)-2-(cyclopropylcarbonyl)-3,3-bis(methylsulfanyl)prop-2-enamide 4b. Yellow solid; \( R_f \) 0.48 (8:2 hexane-EtOAc); IR (KBr): 3033, 2927, 1674, 1533, 1462, 1281, 1112, 873 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.02-1.06 (m, 2H, CH\(_2\)), 1.21-1.24 (m, 2H, CH\(_2\)), 2.37-2.43 (m, 1H, CH), 2.47 (s, 6H, 2xSCH\(_3\)), 7.26-7.29 (d, 2H, \( j=9.6\) Hz, Ar-H), 7.53-7.59 (d, 2H, \( j=8.7\) Hz, Ar-H), 8.69 (s, 1H, NH); MS (m/z): 342 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_{16}\)ClNO\(_2\)S\(_2\): C, 52.70; H, 4.72; N, 4.10; Found: C, 52.72; H, 4.75; N, 4.12.

2-(Cyclopropylcarbonyl)-N-(4-methoxyphenyl)-3,3-bis(methylsulfanyl)prop-2-enamide 4d. Yellow solid; \( R_f \) 0.42 (9:1 Chloroform: Methanol); IR (KBr): 3364, 2927, 1674, 1533, 1462, 1281, 1112, 873 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 0.81-0.82 (m, 2H, CH\(_2\)), 0.96-0.99 (m, 2H, CH\(_2\)), 2.24 (m, 1H, CH), 2.40 (s, 3H, CH\(_3\)), 2.48 (s, 3H, SCH\(_3\)), 7.09-7.11 (d, 2H, \( j=8.1\) Hz, Ar-H), 7.51-7.53 (d, 2H, \( j=8.1\) Hz, Ar-H), 9.36 (s, 1H, NH); MS (m/z): 337 (M\(^+\)); Anal. Calcd for C\(_{16}\)H\(_{19}\)NO\(_3\)S\(_2\): C, 56.95; H, 5.68; N, 4.15; Found: C, 56.92; H, 5.65; N, 4.12.

3-Cyclopropyl-5-(methylthio)-N-p-tolyl-1H-pyrazole-4-carboxamide 5a. White solid; \( R_f \) 0.71 (9:1 Chloroform: Methanol); mp 155-157 °C; IR (KBr): 3284, 3151, 3083, 3031, 2968, 2841, 1628, 1586, 1408, 1238, 1037, 887, 834 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 0.81-0.82 (m, 2H, CH\(_2\)), 0.96-0.99 (m, 2H, CH\(_2\)), 2.24 (m, 1H, CH), 2.40 (s, 3H, CH\(_3\)), 2.48 (s, 3H, SCH\(_3\)), 7.09-7.11 (d, 2H, \( j=8.1\) Hz, Ar-H), 7.51-7.53 (d, 2H, \( j=8.1\) Hz, Ar-H), 9.36 (s, 1H, NH), 12.84 (s, 1H, NH); MS (m/z): 287 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_{15}\)N\(_3\)OS: C, 62.69; H, 5.96; N, 14.62; Found: C, 62.68; H, 5.95; N, 14.62.
N-(4-chlorophenyl)-3-cyclopropyl-5-(methylthio)-1H-pyrazole-4-carboxamide
5b. White solid; Rf 0.68 (9:1 Chloroform: Methanol); mp 133-135 °C; IR (KBr): 3294, 3259, 3153, 3020, 2953, 2895, 1681, 1589, 1485, 1251, 1006, 898, 821, 759, 732, 690 cm⁻¹; ¹³C NMR (100 MHz, CDCl₃): 7.52, 120.82, 127.03, 128.23, 137.74, 161.69; MS (m/z): 307 (M⁺); Anal. Calcd for C₁₄H₁₄ClN₃OS: C, 54.63; H, 4.58; N, 13.65; Found: C, 54.62; H, 4.55; N, 13.62.

3-Cyclopropyl-N-(4-fluorophenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide
5c. White solid; Rf 0.71 (9:1 Chloroform: Methanol); mp 122-124 °C; IR (KBr): 3287, 3136, 3081, 2968, 2833, 1641, 1584, 1251, 1024, 882, 832 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.82-0.83 (m, 2H, CH₂), 0.96-1.03 (m, 2H, CH₂), 2.26 (m, 1H, CH), 2.40 (s, 3H, SCH₃), 7.11-7.17 (m, 2H, Ar-H), 7.63-7.67 (d, 2H, j=13.2 Hz, Ar-H), 9.53 (s, 1H, NH), 12.88 (s, 1H, NH); MS (m/z): 291 (M⁺); Anal. Calcd for C₁₄H₁₄ClN₃OS: C, 57.72; H, 4.84; N, 14.42; Found: C, 57.74; H, 4.85; N, 14.46.

3-Cyclopropyl-N-(4-methoxyphenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide
5d. White solid; Rf 0.42 (9:1 Chloroform: Methanol); mp 141-143 °C; IR (KBr): 3298, 3142, 3086, 3001, 2956, 2829, 1631, 1415, 1245, 1023, 828, 782 cm⁻¹; MS (m/z): 303 (M⁺); Anal. Calcd for C₁₅H₁₇N₃O₂S: C, 59.38; H, 5.65; N, 13.85; Found: C, 59.36; H, 5.65; N, 13.82.

N-(3,4-dichlorophenyl)-3-cyclopropyl-5-(methylthio)-1H-pyrazole-4-carboxamide
5e. White solid; Rf 0.69 (9:1 Chloroform: Methanol); mp 179-181 °C; IR (KBr): 3298, 3142, 3086, 3001, 2956, 2829, 1631, 1415, 1245, 1023, 828, 782 cm⁻¹; MS (m/z): 342 (M⁺); Anal. Calcd for C₁₄H₁₃Cl₂N₃OS: C, 49.13; H, 3.83; N, 12.28; Found: C, 49.15; H, 3.85; N, 12.26.

N-(3-chloro-4-fluorophenyl)-3-cyclopropyl-5-(methylthio)-1H-pyrazole-4-carboxamide
5f. White solid; Rf 0.65 (9:1 Chloroform: Methanol); mp 179-181 °C; IR (KBr): 3287, 3082, 2961, 1628, 1041, 835, 789 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.80-0.82 (m, 2H, CH₂), 0.95-1.03 (m, 2H, CH₂), 2.24 (m, 1H, CH), 2.41 (s, 3H, SCH₃), 7.33-7.39 (m, 1H, Ar-H), 7.55-7.58 (d, 1H, j=4.2 Hz, Ar-H), 7.93-7.96 (d, 1H, j=6.9 Hz, Ar-H), 9.71 (s, 1H, NH), 12.90 (s, 1H, NH); MS (m/z): 325 (M⁺); Anal. Calcd for C₁₄H₁₃ClFN₃OS: C, 51.61; H, 4.02; N, 12.90; Found: C, 51.64; H, 4.05; N, 12.96.
3-Cyclopropyl-N-(2,3-dimethylphenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide 5g. White solid; \( R_f \) 0.81 (9:1 Chloroform: Methanol); mp 183-185 °C; IR (KBr): 3289, 3136, 3094, 3013, 2958, 2826, 1638, 1587, 1418, 1239, 1028, 758, 785 cm\(^{-1}\); MS (m/z): 301 (M\(^+\)); Anal. Calcd for C\(_{16}\)H\(_{19}\)N\(_3\)O\(_2\)S: C, 63.76; H, 6.35; N, 13.94; Found: C, 63.76; H, 6.35; N, 13.93.

3-Cyclopropyl-5-(methylthio)-N-(4-nitrophenyl)-1H-pyrazole-4-carboxamide 5h. White solid; \( R_f \) 0.86 (9:1 Chloroform: Methanol); mp 212-215 °C; IR (KBr): 3278, 3145, 3097, 3015, 2947, 2832, 1641, 1584, 1408, 1233, 1021, 834 cm\(^{-1}\); MS (m/z): 318 (M\(^+\)); Anal. Calcd for C\(_{14}\)H\(_{14}\)N\(_4\)O\(_3\)S: C, 52.82; H, 4.43; N, 17.60; Found: C, 52.86; H, 4.45; N, 17.63.

3-Cyclopropyl-N-(2-methoxyphenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide 5i. White solid; \( R_f \) 0.76 (9:1 Chloroform: Methanol); mp 111-113 °C; IR (KBr): 3287, 3139, 3085, 3011, 2955, 2824, 1631, 1587, 1417, 1241, 1026, 744 cm\(^{-1}\); MS (m/z): 303 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_{17}\)N\(_3\)O\(_2\)S: C, 59.38; H, 5.65; N, 13.85; Found: C, 59.36; H, 5.65; N, 13.82.

3-Cyclopropyl-5-(methylthio)-N-o-tolyl-1H-pyrazole-4-carboxamide 5j. White solid; \( R_f \) 0.63 (9:1 Chloroform: Methanol); mp 142-144 °C; IR (KBr): 3283, 3141, 3088, 3016, 2967, 2836, 1641, 1593, 1412, 1231, 1037, 755 cm\(^{-1}\); MS (m/z): 287 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_{17}\)N\(_3\)O\(_2\)S: C, 62.69; H, 5.96; N, 14.62; Found: C, 62.68; H, 5.95; N, 14.62.

3-Cyclopropyl-N-(4-ethylphenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide 5k. White solid; \( R_f \) 0.71 (9:1 Chloroform: Methanol); mp 187-189 °C; IR (KBr): 3287, 3147, 3091, 3008, 2958, 2828, 1638, 1584, 1410, 1248, 1028, 837 cm\(^{-1}\); MS (m/z): 301 (M\(^+\)); Anal. Calcd for C\(_{16}\)H\(_{19}\)N\(_3\)O\(_2\)S: C, 63.76; H, 6.35; N, 13.94; Found: C, 63.76; H, 6.35; N, 13.93.

\( N-(5\text{-Chloro-2-methoxyphenyl})\)-3-cyclopropyl-5-(methylthio)-1H-pyrazole-4-carboxamide 5l. White solid; \( R_f \) 0.69 (9:1 Chloroform: Methanol); mp 205-207 °C; IR (KBr): 3285, 3141, 3088, 3013, 2964, 2838, 1634, 1587, 1415, 1238, 1034, 878, 748 cm\(^{-1}\); MS (m/z): 338 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_{16}\)ClN\(_3\)O\(_2\)S: C, 53.33; H, 4.77; N, 12.44; Found: C, 53.36; H, 4.75; N, 12.43
**N-(2,5-dichlorophenyl)-3-cyclopropyl-5-(methylthio)-1H-pyrazole-4-carboxamide 5m.** White solid; \( R_f 0.62 \) (9:1 Chloroform: Methanol); mp 188-187 °C; IR (KBr): 3279, 3136, 3079, 3021, 2959, 2831, 1628, 1581, 1422, 1242, 1039, 892, 761 cm\(^{-1}\); MS \((m/z)\): 342 \((M^+)\); Anal. Calcd for C\(_{14}H_{13}Cl_2N_3OS\): C, 49.13; H, 3.83; N, 12.28; Found: C, 49.15; H, 3.85; N, 12.26.

**3-Cyclopropyl-N-(2,5-dimethylphenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide 5n.** White solid; \( R_f 0.78 \) (9:1 Chloroform: Methanol); mp 177-178 °C; IR (KBr): 3281, 3087, 2955, 2841, 1631, 1591, 886, 748 cm\(^{-1}\); MS \((m/z)\): 301 \((M^+)\); Anal. Calcd for C\(_{16}H_{19}N_3O_2S\): C, 63.76; H, 6.35; N, 13.94; Found: C, 63.76; H, 6.35; N, 13.93.

**3-Cyclopropyl-N-(3,4-difluorophenyl)-5-(methylthio)-1H-pyrazole-4-carboxamide 5o.** White solid; \( R_f 0.63 \) (9:1 Chloroform: Methanol); mp 202-204 °C; IR (KBr): 3287, 3142, 3093, 3014, 2969, 2838, 1628, 1587, 1410, 1248, 1034, 833, 786 cm\(^{-1}\); MS \((m/z)\): 309 \((M^+)\); Anal. Calcd for C\(_{14}H_{13}F_2N_3OS\): C, 54.36; H, 4.24; N, 13.58; Found: C, 54.36; H, 4.25; N, 13.59.

**3-Cyclopropyl-5-(methylthio)-N-p-tolylisoxazole-4-carboxamide 6a.** White solid; \( R_f 0.61 \) (8:2 hexane-EtOAc); mp 144-146 °C; IR (KBr): 3282, 3149, 3081, 3033, 2978, 2839, 1630, 1584, 1410, 1236, 1039, 883, 837 cm\(^{-1}\); MS \((m/z)\): 288 \((M^+)\); Anal. Calcd for C\(_{14}H_{13}F_2N_2OS\): C, 62.48; H, 5.59; N, 9.71; Found: C, 62.49; H, 5.57; N, 9.72.

**N-(4-Chlorophenyl)-3-cyclopropyl-5-(methylthio)isoxazole-4-carboxamide 6b.** White solid; \( R_f 0.70 \) (8:2 hexane-EtOAc); mp 125-127 °C; IR (KBr): 3294, 3149, 3018, 2895, 1695, 1591, 1496, 1253, 1058, 810, 759, 715, 690 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta 1.14-1.16 \) (m, 2H, CH\(_2\)), 1.25 (m, 2H, CH\(_2\)), 2.16-2.20 (m, 1H, CH), 2.68 (s, 3H, SCH\(_3\)), 7.26-7.33 (m, 1H, Ar-H), 7.53-7.56 (d, 1H, \( j=8.7\) Hz, Ar-H), 8.19 (broad, 1H, CONH); \(^13\)C NMR (100 MHz, CDCl\(_3\)): 6.85, 13.66, 22.72, 29.18, 110.84, 121.05, 129.13, 136.09, 159.32, 162.66, 172.03; MS \((m/z)\): 308 \((M^+)\); Anal. Calcd for C\(_{14}H_{13}ClF_2N_2OS\): C, 57.52; H, 4.48; N, 9.58; Found: C, 57.49; H, 4.47; N, 9.52.

**3-Cyclopropyl-N-(4-fluorophenyl)-5-(methylthio)isoxazole-4-carboxamide 6c.** White solid; \( R_f 0.59 \) (8:2 hexane-EtOAc); mp 133-138 °C; IR (KBr): 3289, 3139, 3083, 3017, 2966, 1643, 1410, 1249, 885, 836 cm\(^{-1}\); MS \((m/z)\): 292 \((M^+)\); Anal. Calcd for C\(_{14}H_{13}F_2N_2OS\): C, 57.52; H, 4.48; N, 9.58; Found: C, 57.49; H, 4.47; N, 9.52.
3-Cyclopropyl-N-(4-methoxyphenyl)-5-(methylthio)isoxazole-4-carboxamide 6d. White solid; \(R_f\) 0.67 (8:2 hexane-EtOAc); mp 120-123 °C; IR (KBr): 3288, 3147, 3095, 3031, 2965, 2837, 1637, 1592, 1409, 1247, 1036, 891, 833 cm\(^{-1}\); MS (m/z): 304 (M\(^+\)); Anal. Calcd for \(C_{15}H_{16}N_2O_3S\): C, 59.19; H, 5.30; N, 9.20; Found: C, 59.19; H, 5.31; N, 9.22.

N-(3,4-dichlorophenyl)-3-cyclopropyl-5-(methylthio)isoxazole-4-carboxamide 6e. White solid; \(R_f\) 0.62 (8:2 hexane-EtOAc); mp 180-182 °C; IR (KBr): 3295, 3148, 3091, 3011, 2951, 2831, 1625, 1587, 1418, 1241, 1029, 832, 779 cm\(^{-1}\); MS (m/z): 343 (M\(^+\)); Anal. Calcd for \(C_{14}H_{12}Cl_2N_2O_2S\): C, 48.99; H, 3.52; N, 8.16; Found: C, 48.97; H, 3.53; N, 8.12.

N-(3-chloro-4-fluorophenyl)-3-cyclopropyl-5-(methylthio)isoxazole-4-carboxamide 6f. White solid; \(R_f\) 0.69 (8:2 hexane-EtOAc); mp 197-199 °C; IR (KBr): 3288, 3139, 3072, 3017, 2969, 2834, 1631, 1587, 1417, 1237, 1046, 839, 791 cm\(^{-1}\); MS (m/z): 327 (M\(^+\)); Anal. Calcd for \(C_{14}H_{12}ClIFN_2O_2S\): C, 51.46; H, 3.70; N, 8.57; Found: C, 51.47; H, 3.73; N, 8.54.

3-Cyclopropyl-N-(2,3-dimethylphenyl)-5-(methylthio)isoxazole-4-carboxamide 6g. White solid \(R_f\) 0.72 (8:2 hexane-EtOAc); mp 181-183 °C; IR (KBr): 3297, 3138, 3089, 3015, 2952, 2823, 1631, 1591, 1421, 1237, 1025, 754, 787; MS (m/z): 302 (M\(^+\)); Anal. Calcd for \(C_{16}H_{18}N_2O_2S\): C, 63.55; H, 6.00; N, 9.26; Found: C, 63.57; H, 6.03; N, 9.24.

3-Cyclopropyl-5-(methylthio)-N-(4-nitrophenyl)isoxazole-4-carboxamide 6h. White solid \(R_f\) 0.58 (8:2 hexane-EtOAc); IR mp 177-179 °C; IR (KBr): 3277, 3148, 3091, 3004, 2942, 2839, 1636, 1591, 1419, 1241, 1033, 837 cm\(^{-1}\); MS (m/z): 319 (M\(^+\)); Anal. Calcd for \(C_{14}H_{13}N_3O_4S\): C, 52.66; H, 4.10; N, 13.16; Found: C, 52.65; H, 4.13; N, 13.14.

3-Cyclopropyl-N-(2-methoxyphenyl)-5-(methylthio)isoxazole-4-carboxamide 6i. White solid \(R_f\) 0.63 (8:2 hexane-EtOAc); mp 131-133 °C; IR (KBr): 3285, 3142, 3083, 3013, 2964, 2833, 1637, 1591, 1414, 1246, 1028, 746 cm\(^{-1}\); MS (m/z): 304 (M\(^+\)); Anal. Calcd for \(C_{13}H_{16}N_2O_3S\): C, 59.19; H, 5.30; N, 9.20; Found: C, 59.19; H, 5.31; N, 9.22.
3-Cyclopropyl-5-(methylthio)-N-o-tolylisoxazole-4-carboxamide 6j. White solid; $R_f$ 0.67 (8:2 hexane-EtOAc); mp 155-157 °C; IR (KBr): 3285, 3145, 3091, 3003, 2964, 2831, 1639, 1589, 1413, 1237, 1029, 761 cm$^{-1}$; MS ($m/z$): 288 (M$^+$); Anal. Calcd for C$_{14}$H$_{13}$F$_2$N$_3$OS: C, 62.48; H, 5.59; N, 9.71; Found: C, 62.49; H, 5.57; N, 9.72.

3-Cyclopropyl-N-(4-ethylphenyl)-5-(methylthio)isoxazole-4-carboxamide 6k. White solid; $R_f$ 0.72 (8:2 hexane-EtOAc); mp 160-162 °C; IR (KBr): 3282, 3143, 3093, 3013, 2952, 2822, 1631, 1586, 1418, 1241, 1031, 839 cm$^{-1}$; MS ($m/z$): 302 (M$^+$); Anal. Calcd for C$_{16}$H$_{18}$N$_2$O$_2$S: C, 63.55; H, 6.00; N, 9.26; Found: C, 63.57; H, 6.03; N, 9.24.

N-(5-chloro-2-methoxyphenyl)-3-cyclopropyl-5-(methylthio)isoxazole-4-carboxamide 6l. White solid; $R_f$ 0.65 (8:2 hexane-EtOAc); mp 220-222 °C; IR (KBr): 3291, 3139, 3092, 2968, 2842, 1639, 1582, 1425, 1231, 1029, 872, 739 cm$^{-1}$; MS ($m/z$): 338 (M$^+$); Anal. Calcd for C$_{15}$H$_{15}$ClN$_2$O$_3$S: C, 53.17; H, 4.46; N, 8.27; Found: C, 53.19; H, 4.43; N, 8.29.

N-(2,5-dichlorophenyl)-3-cyclopropyl-5-(methylthio)isoxazole-4-carboxamide 6m. White solid; $R_f$ 0.73 (8:2 hexane-EtOAc); mp 202-204 °C; IR (KBr): 3281, 3139, 3081, 3019, 2951, 2829, 1632, 1584, 1426, 1238, 1037, 894, 763 cm$^{-1}$; MS ($m/z$): 343 (M$^+$); Anal. Calcd for C$_{14}$H$_{12}$Cl$_2$N$_2$O$_2$S: C, 48.99; H, 3.52; N, 8.16; Found: C, 48.97; H, 3.53; N, 8.12.

3-Cyclopropyl-N-(2,5-dimethylphenyl)-5-(methylthio)isoxazole-4-carboxamide 6n. White solid; $R_f$ 0.58 (8:2 hexane-EtOAc); mp 208-210 °C; IR (KBr): 3287, 3139, 3091, 3007, 2959, 2839, 1634, 1594, 1419, 1243, 1029, 882, 742 cm$^{-1}$; MS ($m/z$): 302 (M$^+$); Anal. Calcd for C$_{16}$H$_{18}$N$_2$O$_2$S: C, 63.55; H, 6.00; N, 9.26; Found: C, 63.57; H, 6.03; N, 9.24.

3-Cyclopropyl-N-(3,4-difluorophenyl)-5-(methylthio)isoxazole-4-carboxamide 6o. White solid; $R_f$ 0.67 (8:2 hexane-EtOAc); mp 223-225 °C; IR (KBr): 3292, 3139, 3089, 3008, 2964, 2842, 1632, 1591, 1417, 1239, 1041, 839, 779 cm$^{-1}$; MS ($m/z$): 310 (M$^+$); Anal. Calcd for C$_{14}$H$_{12}$Cl$_2$N$_2$O$_2$S: C, 54.19; H, 3.90; N, 9.03; Found: C, 54.17; H, 3.93; N, 9.02.
$^1$H NMR spectrum of compound 4b

$^1$H NMR spectrum of compound 4d
\(^1\)H NMR spectrum of compound 5b

Expanded \(^1\)H NMR spectrum of compound 5b
$^1\text{H} \text{ NMR spectrum of compound 5e}$

![NMR spectrum of compound 5e](image)

$\text{Expanded }^1\text{H} \text{ NMR spectrum of compound 5e}$

![Expanded NMR spectrum of compound 5e](image)
Chapter 3

Synthesis of trisubstituted pyrazoles/isoxazoles

1H NMR spectrum of compound 5c

1H NMR spectrum of compound 6b
$^{13}$C NMR spectrum of compound 5b

Expanded $^{13}$C NMR spectrum of compound 5b
$^{13}$C NMR spectrum of compound 6b

Expanded $^{13}$C NMR spectrum of compound 6b
MASS spectrum of compound 5a

MASS spectrum of compound 5d
MASS spectrum of compound 6c

MASS spectrum of compound 6d
IR spectrum of compound 5b

![IR spectrum of compound 5b](image)

IR spectrum of compound 6b

![IR spectrum of compound 6b](image)
3.9 References


Chapter 3

Synthesis of trisubstituted pyrazoles/isoxazoles


