CHAPTER-4

Synthesis and biological activities of Isoxazoles and Pyrazoles
3.1 Introduction

Aryl ketones and aromatic aldehydes were condensed in presence of base resulted Chalcones.

Isoxazole is an azole with an oxygen atom next to nitrogen. Isoxazole rings are found in natural products like ibotonic acid. Isoxazoles are the basic for a number of drugs like cox-2 inhibitor, nitric oxide donor–furaxan etc. A highly appreciable number of five membered heterocycles containing nitrogen atom and oxygen atoms obtained by laboratory synthesis. Which are having potential therapeutic and pharmaco therapeutic activities. Some of useful synthetic analogues with improved therapeutic activity can be obtained from single lead compound by structural modifications. A lot of modifications have been done during the last few years on Isoxazole nucleous.

Chalcone derivatives have different activities\(^1\)\(^-\)\(^9\). Therefore new compounds are synthesized.

Synthesis of heterocyclic molecules inventive advance methods are available, this subject is ever innovative area for the world of chemistry. Pyrazoles and isoxazoles nucleus blocks have used widely for pharma world. Their derivatives are brilliantly used with high pharmacology properties. Like Hypoglycemic, Analgesic, Anti-inflammatory, Anti-bacterial, Anti-HIV and Anti-cancer activity\(^1\(^0\)\), with other hand use in schizophrenia, Hypertension and alzheimer disease\(^1\(^1\). They are also used in Insecticides\(^1\(^2\)\) and Pesticides. Pyrazoles are used in recently Anti-parasites activity\(^1\(^3\)\) and kinase inhibitor.

Pyrazoles and isoxazoles are well known five member heterocyclic compounds and several procedures for its synthesis have been extensively studied.
Henry Feuer and Sheldon Markofsky\cite{14,15} using the Michael-type addition between sodium 1-alkane nitronates and α-nitro olefins, which were generated \textit{in situ} from 2-nitroalkyl acetates leads largely to the formation of 3,5-dialkyl isoxazoles. The latter also are obtained by the demethylation of 2-alkyl-2,4-dinitro 1-alkanols and by the rearrangement of secondary 8-dinitroalkanes in weakly basic media. The Michael-type addition between 2-alkane nitronates and α-nitro olefins can really proceeds in reasonably good yields\cite{16-20}. In contrast, 1-alkane nitronates give the desired Michael adducts, secondary α-dinitro alkanes, only in poor yields. No explanations have been given to account for the poor yields in this reaction. however, reports in the literature in which attempts to prepare phenyl-substituted α-dinitro alkenes gave rise largely to isoxazoles and isoxaoline N-oxides\cite{21-23} For example, Heim obtained in the mbase-catalyzed reaction between phenyl nitro methane and benzaldehyde, in addition to 1,2,3-triphenyl-1,3-dinitropropane and nitrostilbene, 3,4,5-triphenylisoxazole. Heim and other workers\cite{22,24-26} were able to show that phenyl-substituted α-dinitro compounds were unstable in the presence of base and eliminated nitrous acid to form isoxazoline N-oxides and isoxazoles

\begin{align*}
\text{R} \quad \text{NO}_2^- & \quad \text{R}_1 \quad \text{NO}_2^- \quad H^+ \quad \text{O}_2\text{N} \quad \text{R} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{NO}_2^- \quad \text{R} \quad \text{R}_1 \quad \text{H} \quad \text{O}_2\text{N} \quad \text{R}\quad \text{R}_1 \quad \text{HNO}_2
\end{align*}

Fig-3.2

Tweedie S. R. et al.\cite{27} have synthesized heteraryl amines couples with aryl halides catalysed by palladium & base.
Yavari I. et al\textsuperscript{28} were synthesized isoxazole derivatives in the presence of triphenylphosphine by the reaction of acetylenes and alkyl 2-nitroethanoates.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3.4.png}
\caption{Fig-3.4}
\end{figure}

\section*{3.2 Biological activity:-}

Oxazolidine-2-one, benzo[d]isoxazole are made in Cushman M. et al\textsuperscript{29}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3.5.png}
\caption{Fig-3.5}
\end{figure}

New isoxazole and pyrazole series found by D. Thomas\textsuperscript{30}. Some compounds are having effective properties which is made from glutarate.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3.6.png}
\caption{Fig-3.6}
\end{figure}

Liljefors T. et al\textsuperscript{31} have synthesized a series of Aryl piperidyl isoxazololes and evaluated for GABAA antagonists. 2 & 4-substituted compounds having good activities.
The strength of binding on receptors of indazole derivatives and isoxazole derivatives have described by Barceló\textsuperscript{32}.

Amgad G. Habeeb et al.\textsuperscript{33} also reported a isoxazolines belonging various substitutes at 3\textsuperscript{rd} position of the aromatic ring, which made for analysis as analgesic inhibitory, anti-inflammatory agents.

When isoxazolines have not Carbon-3 Me substituent, shown potency analgesic and AI activities.

Chih Y. Ho et al.\textsuperscript{34} have reeport a series of pyrazol-phenylamines derivatives have developed to keep potency against the angiogenesis task, the receptor tyrosine enzyme obtained moving factor and to develop the broad tumor cell antiproliferative activity of these derivatives. These work finds in (JNJ-10198409).

Giovannoni M. P. et al.\textsuperscript{35} have synthesized a number of arylpiperazinyl alkylpyridazinones and checked for painkiller activity. They were observed that they checked compounds at the appropriate dose, shown high pain remover activity, in specific compounds,
substitute molecules leading in which was able to reduce huge abdominal methods by more than half in test. In the investigation of the compound’s action it seen analgesic effect.

![Fig-3.9](image)

Christian Peifer et al.\(^{36}\) have reported the discovery of isoxazoleas a potent biphasic inhibitors. In the designed of isoxazoles, some molecules have 76 enzymes and tested of their cellular effects shown 18 (CKP138) to be a high dual inhibitors of CK1\(\delta\) and p38ba. And In 2006, Johnson & Johnson Pharmaceutical Research & Development\(^{37}\), has been reported the synthesis of a series of Amino dihydrobenzopyranoo isoxazole derivatives using substituted salicylaldehydes and ethyl 4-bromocrotonate. Among the synthesized isoxazoles, few have proven that most potency blockers with potent serotonin (5-HT) reuptake inhibiting activity. Serotonin is one of the important monoamine for human body and the deficit of 5-HT mainly lead to the depression.

![Fig-3.10](image)
Carr J. B. et. al. have been synthesized a series of highly substituted isoxazoles and screened for helminthic activity checked by dose range of 17 to 499 mg/kg to the mouse roundworm, Nippostrongylus Eratikensis. They were found that the newly synthesized isoxazole derivatives have potent anthelmintic activity.

![Fig-3.11](image)

Biological evaluate of potency HAD-C3 and HAD-C8 isoxazoles and pyrazoles based diazide suitable for bind profile by photo labeling experiment in cell is shown. In isoxazoles and pyrazoles based compounds showed less nanomolar activity against HAD-C3 and HAD-C8. The pyrazoles base the active HAD-C8 inhibitor reports in the literatures with IC-50 of 18 nm.

In studies suggestions the unlike the isoxazoles base ligand the pyrazole base ligand having flexible to the another binding site as HAD-C8. Some molecules shown the different activities at minimum concentration, indicates they are cells holey and the azides or diazides group doesn’t obstruct with the neuro-protection property, cellular cyto-toxicity, or influence cell permeability.

Anti oxidant antimicrobial activities of P.Manoj kumar et.al. synthesized some new series of 1-isonicotinyl 3,5 dimethyl-4-arylazo isoxazoles which shows Antioxidant Antibacterial and Antimicrobial activities against staphylococcus aurous and antibacterial against albican. The antioxidant activity is compared with standard drug ascorbic acid.

![Fig-3.12](image)
Immunological activities of Stanislaw ryng and Michael zimeki synthesized some new derivatives of isoxazoles including isoxazole triazoline derivatives which shown immune modulator activity. The compounds were tested for their ability to affect the proliferative response of moule splelenocytes to conconavalin (A) and secondary humoral immune response of splelenocytes to sheep red blood cells measured as the number of antibody forming cells and Cyclosporine A served as a reference compound.

![Fig-3.13](image)

K.Karthikeyan, T.veenuseelan et.al.\textsuperscript{44-46} was developed a systematic procedure for the synthesis of pyrazolyl isoxazole and they performed the activity of anti nociceptive action by using various animal tissues. The lead molecule was synthesized by using 1, 3 dipolar cyclo addition of pyrazole derived nitric oxide with various dipolarophiles suchmas N-substituted maleimide, diethyl acetylene dicarboxylate and phenyl acetylene. The given structure of synthesized pyrazolyl isoxazoles shows maximum anti nociceptive activity.

Five member N\textsubscript{2} contained heterocyclic compound possess wide spectrum of activity\textsuperscript{47}. Isoxazole\textsuperscript{48-50} and Pyrazole\textsuperscript{51-52} have proven record of biological activities, which contains two nitrogen atoms. In view of the pharmacological profiles of these two chemical moieties as described above, we considered it interesting to synthesized two chemically different but pharmacologically compatible molecules with the aim of obtaining some novel heterocyclic systems with potentially improved biological properties. In the present investigation a new series of novel 3-[bis-3,5(methyltrifluoro)phenyl]-5-phenyloxazole / 3-[bis-
3.5(methyltrifluoro)phenyl]-5-(4-chlorophenyl)-1H-pyrazole [TV-116 TO 145] were synthesized and evaluated for in vitro microbial activity.

### 3.3 Current work

With the biodynamic activities of chalcones and as a fine synthon for different fluorinated compounds, the awareness has been paying attention on the creation of new chalcones. With an observation to obtained compounds having good biological activity, two new synthesized 3-[bis-3,5(methyltrifluoro)phenyl]-5-phenylisoxazole and 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-chlorophenyl)-1H-pyrazole by the cyclization of different (E)-1-[bis-3,5(methyltrifluoro)phenyl]-3-phenylprop-2-en-1-one by hydroxyl amine/sodium acetate and hydrazine hydride.

We have synthesized two new series of 3-[bis-3,5(methyltrifluoro)phenyl]-5-phenylisoxazole and 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-chlorophenyl)-1H-pyrazole (TV-116 to 145). The structures of all the synthesized compounds were elucidated by FT-IR, mass spectra, $^1$H NMR and elemental analyses. The newly synthesized compounds were subjected to antimicrobial activity.
3.4 Reaction Scheme

![Reaction Scheme](image)

**Fig-3.14**

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<th>Code</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M.F.</th>
<th>M.W.</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>R&lt;sub&gt;f1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;f2&lt;/sub&gt;</th>
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<td>391</td>
<td>168</td>
<td>57</td>
<td>0.49</td>
<td>0.60</td>
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<td>169</td>
<td>72</td>
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</tbody>
</table>
Table-3.1

TLC Solvent system $R_{f1}$: Hexane: Ethyl acetate – 7:3;

$R_{f2}$: Chloroform: Methanol - 9:1.

3.5 Plausible Reaction Mechanism

Fig-3.15
3.6 Experimental

3.6.1 Materials and Methods

Open capillary tubes are used for melting points. TLC has been checked for formation of compounds regularly and spots were seen by iodine. FT-IR-8400 instrument is using for IR spectra. Shimadzu GC-MS-QP-2010 model used for Mass spectra. Brucker Ac 400 MHz spectrometer was used for $^1$H NMR.

3.6.2 General procedure for the synthesis of 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-substitutedphenyl)isoxazole (TV- 116 to 130)

A mixture of (E)-1-[bis-3,5(methyltrifluoro)phenyl]-3-(4-substitutedphenyl)propenone (0.021 Mole), hydroxylamine hydrochloride (0.021 Mole) and Sodium acetate in ethyl alcohol (25 ML) was refluxed for 6.5 hrs. The solvent was distilled out under vacuum and added into chilled water. The solid was filtered, washed and crystallized. TLC was used for completion of the reaction.

3.6.2.1 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-chlorphenyl)isoxazole (TV116)

Yield: 77%; mp 203°C; Analytical Calculation for C$_{17}$H$_8$ClF$_6$NO: Carbon, 51.13; Hydrogen, 2.06; Chlorine, 9.05; Fluorine, 29.10; Nitrogen, 3.58; Oxygen, 4.08; Found: Carbon, 52.02; Hydrogen, 2.02; Chlorine, 9.01; Fluorine, 29.04; Nitrogen, 3.49; Oxygen, 4.01; IR (cm$^{-1}$): 3049 (C-H stretching of aromatic ring), 1703 (C=O stretching ), 1681, 1585 and 1531 (C=C stretching of aromatic ring), 1240 (N-O stretching ), 1084 (C-H in plane deformation of aromatic ring), 1012 (C-F stretching), 829 (C-H out of plane bending of 1,4-disubstitution); MS: m/z 391; $^1$H NMR (DMSO-$d_6$) δ ppm: 5.27-5.28 (s, 1H ,H$_a$), 7.06-7.08 (d, 1H, H$_b$), 7.10-7.14 (m, 1H, H$_c$), 7.27-7.29 (d, 2H, H$_{dd'}$), 7.46-7.48 (m, 2H, H$_{ee'}$), 7.82-7.83 (m, 1H, H$_f$).
3.6.2.2 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-fluorophenyl)isoxazole (TV-117).

Yield: 58%; mp 201°C; Analytical Calculation for C$_{17}$H$_8$F$_7$NO: Carbon, 54.41; Hydrogen, 2.15; Fluorine, 35.44; Nitrogen, 3.73; Oxygen, 4.26; Found: Carbon, 54.31; Hydrogen, 2.06; Fluorine, 30.37; Nitrogen, 3.63; Oxygen, 4.15%; MS: $m/z$ 375.

3.6.2.3 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-bromophenyl)isoxazole (TV-118).

Yield: 67%; mp 189°C; Analytical Calculation for C$_{17}$H$_8$BrF$_6$NO: Carbon, 46.82; Hydrogen, 1.85; Bromine, 18.32; Fluorine, 26.14; Nitrogen, 3.21; Oxygen, 3.67; Found: Carbon, 46.71; Hydrogen, 1.67; Bromine, 18.21; Fluorine, 26.05; Nitrogen, 3.11; Oxygen, 3.54%; MS: $m/z$ 436.

3.6.2.4 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-methylphenyl)isoxazole (TV-119).
Yield: 68%; mp 186ºC; Analytical Calculation for C\textsubscript{17}H\textsubscript{9}F\textsubscript{7}O: Carbon, 58.23; Hydrogen, 2.99; Fluorine, 30.70; Nitrogen, 3.77; Oxygen, 4.31; Found: Carbon, 58.03; Hydrogen, 2.75; Fluorine, 30.40; Nitrogen, 3.57; Oxygen, 4.11%; MS: \(m/z\) 371.

3.6.2.5 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-methoxyphenyl)isoxazole (TV-120)

Yield: 74%; mp 221ºC; Analytical Calculation for C\textsubscript{17}H\textsubscript{9}BrF\textsubscript{6}O: Carbon, 55.82; Hydrogen, 2.86; Fluorine, 29.43; Nitrogen, 3.62; Oxygen, 8.26; Found: Carbon, 55.52; Hydrogen, 2.76; Fluorine, 29.13; Nitrogen, 3.22; Oxygen, 8.06%; MS: \(m/z\) 387.

3.6.2.6 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-chlorophenyl)isoxazole (TV-121).
Yield: 56%; mp 204°C; Analytical Calculation for C_{19}H_{14}F_6O_3: Carbon, 52.13; Hydrogen, 2.06; Chlorine, 9.05; Fluorine, 29.10; Nitrogen, 3.58; Oxygen, 4.08; Found: Carbon, 52.02; Hydrogen, 2.02; Chlorine, 9.01; Fluorine, 29.04; Nitrogen, 3.49; Oxygen, 4.01%; MS: m/z 391.

3.6.2.7 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-fluorophenyl)isoxazole (TV-122).

Yield: 76%; mp 224°C; Analytical Calculation for C_{17}H_{8}Cl_2F_6O: Carbon, 54.41; Hydrogen, 2.15; Fluorine, 35.44; Nitrogen, 3.73; Oxygen, 4.26; Found: Carbon, 54.21; Hydrogen, 2.01; Fluorine, 35.11; Nitrogen, 3.53; Oxygen, 4.11%; MS: m/z 375.

3.6.2.8 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-bromophenyl)isoxazole (TV-123).

Yield: 71%; mp 212°C; Analytical Calculation for C_{18}H_{12}F_6O_2: Carbon, 46.82; Hydrogen, 1.85; Bromine, 18.32; Fluorine, 26.14; Nitrogen, 3.21; Oxygen, 3.67; Found: Carbon, 46.62; Hydrogen, 1.65; Bromine, 18.02; Fluorine, 16.14; Nitrogen, 3.11; Oxygen, 3.27%; MS: m/z 436.

3.6.2.9 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-methoxyphenyl)isoxazole (TV-124)
Yield: 80%; mp 195ºC; Analytical Calculation for C_{17}H_{9}ClF_{6}O: Carbon, 55.82; Hydrogen, 2.86; Fluorine, 29.43; Nitrogen, 3.62; Oxygen, 8.26; Found: Carbon, 55.76; Hydrogen, 2.72; Fluorine, 29.32; Nitrogen, 3.54; Oxygen, 8.12% MS: m/z 387.

3.6.2.10 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3,4-dimethoxyphenyl)isoxazole (TV-125)

Yield: 77%; mp 182ºC; Analytical Calculation for C_{17}H_{9}BrF_{6}O: Carbon, 54.69; Hydrogen, 3.14; Fluorine, 27.32; Nitrogen, 3.36; Oxygen, 11.50; Found: Carbon, 54.52; Hydrogen, 3.07; Fluorine, 27.23; Nitrogen, 3.24; Oxygen, 11.43%; MS: m/z 417.

3.6.2.11 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-chlorophenyl)isoxazole (TV-126)
Yield: 58%; mp 242°C; Analytical Calculation for C_{17}H_{9}ClF_{6}O: Carbon, 52.13; Hydrogen, 2.06; Chlorine, 9.05; Fluorine, 29.10; Nitrogen, 3.58; Oxygen, 4.08; Found: Carbon, 52.08; Hydrogen, 2.04; Chlorine, 9.01; Fluorine, 29.01; Nitrogen, 3.43; Oxygen, 4.01% MS: m/z 391.

3.6.2.12 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-fluorophenyl)isoxazole (TV-127)

Yield: 60%; mp 212°C; Analytical Calculation for C_{17}H_{9}F_{7}O: Carbon, 54.41; Hydrogen, 2.15; Fluorine, 35.44; Nitrogen, 3.73; Oxygen, 4.26; Found: Carbon, 54.31; Hydrogen, 2.06; Fluorine, 35.37; Nitrogen, 3.63; Oxygen, 4.15% MS: m/z 375.

3.6.2.13 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-bromophenyl)isoxazole (TV-128)

Yield: 62%; mp 224°C; Analytical Calculation for C_{19}H_{14}F_{6}O: Carbon, 46.82; Hydrogen, 1.85; Bromine, 18.32; Fluorine, 26.14; Nitrogen, 3.21; Oxygen, 3.67; Found: Carbon, 46.71; Hydrogen, 1.67; Bromine, 18.21; Fluorine, 26.05; Nitrogen, 3.11; Oxygen, 3.54%; MS: m/z 436.

3.6.2.14 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-methoxyphenyl)isoxazole (TV-129).
Yield: 66%; mp 209ºC; Analytical Calculation for C\textsubscript{18}H\textsubscript{12}F\textsubscript{6}O\textsubscript{2}: Carbon, 55.82; Hydrogen, 2.86; Fluorine, 29.43; Nitrogen, 3.62; Oxygen, 8.26; Found: Carbon, 55.76; Hydrogen, 2.73; Fluorine, 29.39; Nitrogen, 3.57; Oxygen, 8.22%; MS: m/z 387.

3.6.2.15 3-[bis-3,5(methyltrifluoro)phenyl]-5-phenylisoxazole (TV-130)

Yield: 76%; mp 200ºC; Analytical Calculation for C\textsubscript{17}H\textsubscript{10}F\textsubscript{6}O: Carbon, 59.31; Hydrogen, 2.93; Fluorine, 33.11; Oxygen, 4.65; Found: Carbon, 59.31; Hydrogen, 2.93; Fluorine, 33.11; Oxygen, 4.65%; MS: m/z 344.
3.7 Reaction Scheme

![Reaction Scheme](image)

Fig-3.16

Table 3.2 Physical Data Table of Series-3

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<th>MP</th>
<th>Yield %</th>
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<td>0.69</td>
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</table>

_Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives_
Table-3.2

TLC Solvent system $R_f$1: Hexane: Ethyl acetate – 8:2;

$R_f$2: Chloroform: Methanol - 7:3.

3.8 Plausible Reaction Mechanism

![Plausible Reaction Mechanism](image-url)
3.9 Experimental

3.9.1 Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using potassium bromide pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct injection probe technique. $^1$H NMR was determined in DMSO-$d_6$ solution on a bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on elemental vario EL III carlo erba 1108 model and the results are in agreements with the structures assigned.

3.9.2 General procedure for the synthesis of 3-[bis-3,5(methyltrifluoro)phenyl]-5-(substitutedphenyl)-1H-pyrazole (TV-131 to 145)

A mixture of (E)-1-[bis-3,5(methyltrifluoro)phenyl]-3-(4-substitutedphenyl)prop-2-en-1-one (0.02 mol), hydrazine hydrate (0.02 mol) and sodium acetate in ethanol (30 ml) was refluxed for 4 hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized. The completion of the reaction was monitored by TLC.

3.9.2.1 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-chlorophenyl)-1H-pyrazole (TV-131)

Yield: 77%; mp 203°C; Analytical Calculation for C$_{17}$H$_9$ClF$_6$N$_2$: Carbon, 52.26; Hydrogen, 2.32; Chlorine, 9.07; Fluorine, 29.18; Nitrogen, 7.17; Found: Carbon, 52.16; Hydrogen, 2.14;
Chlorine, 8.94; Fluorine, 29.02; Nitrogen, 7.01%; IR (cm$^{-1}$): 3363/3271 (Carbon-H stretch of aromatic ring), 1703 (Carbon=O stretch), 1662, 1597 and 1523 (Carbon=Carbon stretch of aromatic ring), 1070 (C-H in plane deformation of aromatic ring), 1014 (C-F stretching), 833 (C-H out of plane bending of 1,4-disubstituion), 1012 (C-F stretching); MS: m/z 390; $^1$H NMR (DMSO-d$_6$) $\delta$ ppm: 7.09-7.11 (s, 1H, H$_a$), 7.27-7.29 (d, 2H, H$_{bb'}$), 7.44-7.46 (d, 2H, H$_{cc'}$), 7.61-7.65 (m, 1H, H$_{dd'}$), 7.88 (s, 1H, H$_e$), 12.50 (s, 1H, H$_f$).

3.9.2.2 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-fluorophenyl)-1H-pyrazole (TV-132)

![Chemical Structure of TV-132](image)

Yield: 58%; mp 201ºC; Analytical Calculation for C$_{17}$H$_9$F$_7$N$_2$: Carbon, 54.56; Hydrogen, 2.42; Fluorine, 35.53; Nitrogen, 7.49; Found: Carbon, 54.46; Hydrogen, 2.12; Fluorine, 35.23; Nitrogen, 7.33%; MS: m/z 374.

3.9.2.3 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-bromophenyl)-1H-pyrazole (TV-133)

![Chemical Structure of TV-133](image)

Yield: 67%; mp 189ºC; Analytical Calculation for C$_{17}$H$_9$BrF$_6$N$_2$: Chlorine, 46.92; Hydrogen, 2.08; Bromine, 18.36; Fluorine, 26.19; Nitrogen, 6.44; Found: Carbon, 46.52; Hydrogen, 2.01; Bromine, 18.21; Fluorine, 26.01; Nitrogen, 6.44%; MS: m/z 435.
3.9.2.4 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-methylphenyl)-1H-pyrazole (TV-134).

Yield: 68%; mp 186ºC; Analytical Calculation for C_{17}H_{10}F_{6}N_{2}: Carbon, 58.38; Hydrogen, 3.27; Fluorine, 30.78; Nitrogen, 7.57; Found: Carbon, 58.10; Hydrogen, 3.16; Fluorine, 30.58; Nitrogen, 7.23 %; MS: m/z 370.

3.9.2.5 3-[bis-3,5(methyltrifluoro)phenyl]-5-(4-methoxyphenyl)-1H-pyrazole (TV-135).

Yield: 74%; mp 221ºC; Analytical Calculation for C_{18}H_{13}F_{6}ON_{2}: Carbon, 55.97; Hydrogen, 3.13; Fluorine, 29.51; Nitrogen, 7.25; Oxygen, 4.14; Found: Carbon, 55.77; Hydrogen, 3.03; Fluorine, 29.21; Nitrogen, 7.25; Oxygen, 4.04%; MS: m/z 386.

3.9.2.6 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-chlorophenyl)-1H-pyrazole (TV-136).
Yield: 56%; mp 204°C; Analytical Calculation for C$_{17}$H$_9$ClF$_6$N$_2$: Carbon, 52.26; Hydrogen, 2.32; Chlorine, 9.07; Fluorine, 29.18; Nitrogen, 7.17; Found: Carbon, 52.06; Hydrogen, 2.04; Chlorine, 8.74; Fluorine, 29.12; Nitrogen, 7.10%; MS: $m/z$ 390.

3.9.2.7 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-fluorophenyl)-1H-pyrazole (TV-137)

Yield: 76%; mp 224°C; Analytical Calculation for C$_{17}$H$_9$F$_7$N$_2$: Carbon, 54.56; Hydrogen, 2.42; Fluorine, 35.53; Nitrogen, 7.49; Found: Chlorine, 54.36; Hydrogen, 2.14; Fluorine, 35.13; Nitrogen, 7.33%; MS: $m/z$ 374.

3.9.2.8 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-bromophenyl)-1H-pyrazole (TV-138).
Yield: 71%; mp 212°C; Analytical Calculation for C_{17}H_9BrF_6N_2: Carbon, 46.92; Hydrogen, 2.08; Bromine, 18.36; Fluorine, 26.19; Nitrogen, 6.44; Found: Carbon, 46.82; Hydrogen, 2.01; Bromine, 18.30; Fluorine, 26.10; Nitrogen, 6.40%; MS: m/z 435.

3.9.2.9 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3-methoxyphenyl)-1H-pyrazole (TV-139)

Yield: 80%; mp 195°C; Analytical Calculation for C_{18}H_{13}F_6ON_2: Carbon, 55.97; Hydrogen, 3.13; Fluorine, 29.51; Nitrogen, 7.25; Oxygen, 4.14; Found: Carbon, 55.47; Hydrogen, 3.12; Fluorine, 29.34; Nitrogen, 7.15; Oxygen, 4.04%; MS: m/z 386.

3.9.2.10 3-[bis-3,5(methyltrifluoro)phenyl]-5-(3,4 dimethoxyphenyl)-1H-pyrazole (TV-140).
Yield: 77%; mp 182°C; Analytical Calculation for C_{19}H_{14}F_{6}N_{2}O_{2}: Carbon, 54.81; Hydrogen, 3.39; Fluorine, 27.38; Nitrogen, 6.73; Oxygen, 7.69; Found: Carbon, 54.51; Hydrogen, 3.29; Fluorine, 27.18; Nitrogen, 6.43; Oxygen, 7.49%; MS: m/z 416.

3.9.2.11 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-chlorophenyl)-1H-pyrazole (TV-141).

Yield: 58%; mp 242°C; Analytical Calculation for C_{17}H_{9}ClF_{6}N_{2}: Carbon, 52.26; Hydrogen, 2.32; Chlorine, 9.07; Fluorine, 29.18; Nitrogen, 7.17; Found: Carbon, 52.06; Hydrogen, 2.02; Chlorine, 8.82; Fluorine, 28.85; Nitrogen, 6.95%; MS: m/z 379.

3.9.2.12 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-fluorophenyl)-1H-pyrazole (TV-142)

Yield: 60%; mp 212°C; Analytical Calculation for C_{17}H_{9}F_{7}N_{2}: Carbon, 54.56; Hydrogen, 2.42; Fluorine, 35.53; Nitrogen, 7.49; Found: Carbon, 54.37; Hydrogen, 2.27; Fluorine, 35.18; Nitrogen, 7.16%; MS: m/z 374.

3.9.2.13 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-bromophenyl)-1H-pyrazole (TV-143)
Yield: 62%; mp 224°C; Analytical Calculation for C_{17}H_{9}BrF_{6}N_{2}: Carbon, 46.92; Hydrogen, 2.08; Bromine, 18.36; Fluorine, 26.19; Nitrogen, 6.44; Found: Carbon, 46.72; Hydrogen, 1.95; Bromine, 18.16; Fluorine, 16.19; Nitrogen, 6.14%; MS: m/z 435.

3.9.2.14 3-[bis-3,5(methyltrifluoro)phenyl]-5-(2-methoxyphenyl)-1H-pyrazole (TV-144).

Yield: 66%; mp 209°C; Analytical Calculation for C_{18}H_{13}F_{6}ON_{2}: Carbon, 55.97; Hydrogen, 3.13; Fluorine, 29.51; Nitrogen, 7.25; Oxygen, 4.14; Found: Carbon, 55.97; Hydrogen, 3.13; Fluorine, 29.51; Nitrogen, 7.25; Oxygen, 4.14%; MS: m/z 386.
3.9.2.15 3-[bis-3,5(methyltrifluoro)phenyl]-5-(phenyl)-1H-pyrazole (TV-145).

Yield: 76%; mp 200ºC; Analytical Calculation for $\text{C}_{17}\text{H}_{10}\text{F}_{6}\text{N}_{2}$: Carbon, 57.31; Hydrogen, 2.83; Fluorine, 32.00; Nitrogen, 7.86; Found: Carbon, 57.21; Hydrogen, 2.53; Fluorine, 31.34; Nitrogen, 7.66%; MS: $m/z$ 356.

3.10 Spectral discussion

3.10.1 Mass spectral study

Shimadzu GC-MS-QP-2010 model was using for mass spectra. Proper fragmentation came in spectral studies. Molecular weight peaks came of respective compounds. It has given below.
Mass fragmentation pattern for TV-116

Fig-3.18
Mass fragmentation pattern for TV-131

![Diagram showing mass fragmentation pattern for TV-131](image)

Fig-3.19
3.10.2 IR spectral study

Shimadzu FT-IR-8400 model records IR spectra using KBr pellet method. Various functional groups here in molecule were identified by characteristic frequency obtained for them. For Chalcones TV-116 to 145, assenting bands for secondary amine were observed at 3450-3200 cm\(^{-1}\) correspondingly. -N-H stretching bands at 3250-3390 cm\(^{-1}\) observed. Aromatic ring skeleton (C=C starching) groups were observed at 1600-1400 cm\(^{-1}\). C-N stretching aromatic of isoxazole ring were observed at 1180-1200 cm\(^{-1}\) and 1300-1360 cm\(^{-1}\). C-Cl stretching were observed at 700-850 cm\(^{-1}\). Another characteristic C-F (stretching vibration) was observed at 1000-1100 cm\(^{-1}\), which suggested formation of desired products TV-116 to 145.

3.10.3 \(^1\)H NMR spectral study

In \(^1\)H NMR DMSO-d\(_6\) used as a solvent with Brucker 400 MHz spectrometer & TMS used as a standard. Synthesis compounds structures were proven by all protons and their chemical shifts.

\(^1\)H NMR spectra confirmed the structures of Chalcones TV-116 to 145 on the basis of following signals: Aromatic fluoro-ring protons observed at 7.4-7.8 \(\delta\) ppm and aromatic other ring protons observed around 7.0-7.2 \(\delta\) ppm. A singlet for the (C-H) proton of five member ring at 5.0-6.0 \(\delta\) ppm, and singlets for N-H of pyrazole at 8.80-12.60 \(\delta\) ppm and correspondingly.
Mass spectrum of TV – 116

![Mass spectrum of TV – 116](image)

Fig-3.20

IR spectrum of TV – 116

![IR spectrum of TV – 116](image)

Fig-3.21

Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives
$^1$H NMR spectrum of TV – 116

Fig-3.22

Expanded $^1$NMR spectrum of TV – 116

Fig-3.23

Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives
Mass spectrum of TV – 131

Fig-3.24

IR spectrum of TV – 131

Fig-3.25

Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives
Synthesis and biological activities of Isoxazole & Pyrazole

$^1$H NMR spectrum of TV – 131

Expanded 1NMR spectrum of TV – 131

Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives
3.11 Biological evaluation

3.11.1 Antimicrobial evaluation

Antibacterial and antifungal activity was tested for all compounds. Staphyl-ococcus (Aureus) Mtcc-96, Strept-ococcus (Pyogenes) Mtcc-443 as gram positive, e-coli mtcc (442), pseudomonas (aeruginosa) mtcc (441) as gram negative, candida (albicans) mtcc (227), aspergillus (niger) mtcc (282), aspergillus (clavatus) mtcc (1323) was taken with different drugs. microbial type culture collection (mtcc) strains was used. Compounds growth at lowest concentration was prevented. For MIC broth dilution method is more appropriate.

1. For both primary and secondary screening serial dilutions were prepared.

2. In absence of antibiotic in control tube is subculture immediately.

3. Drug concentration is check by control of MIC.

4. MIC records the lowest concentration growth of organism.

5. Amount of growth is tested.

**Used methods for 1<sup>st</sup> and 2<sup>nd</sup> screening: -**

In stock solution synthesis drugs concentration was 2000 (µg mL<sup>-1</sup>)

**First screening: -** In 1<sup>st</sup> screening (250 µg mL<sup>-1</sup>), (500 µg mL<sup>-1</sup>), (1000 µg mL<sup>-1</sup>) concentration was taken of all compounds. Only Active drug will go in 2<sup>nd</sup> screening.

**Second screening: -** In second screening concentration of all drugs were taken even less then first screening.

**Reading Result: -** As MIC 99.2% inhibited zone was taken showing highest dilution.

Results are given below.
### 3.12 Table-1: Screening Result of antimicrobial activity for TV-116 to 130.

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<th>Gram Positive</th>
<th>Gram Negative</th>
<th>Fungal species</th>
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Table-3.3
Antimicrobial Screening Results for TV-131 to 145

<table>
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<tr>
<th>Code</th>
<th>Concentration of minimum inhibition µg mL⁻¹</th>
<th>Gram Positive</th>
<th>Gram Negative</th>
<th>Fungal species</th>
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Table-3.4
3.12 References


*Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives*
Chapter: -4  

Synthesis and biological activities of Isoxazole & Pyrazole


*Synthesis, Characterization and Biological Evaluation of some Chalcones and their Derivatives*


