Chapter 6

Synthesis of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole and 3,6-diphenyl[1,2,4]triazole[3,4-b][1,3,4]thiadiazole derivatives
6.1. Introduction

Nitrogen and oxygen containing five membered heterocycles are important bioactive agents, due to its vast pharmacological and industrial applications. Syntheses of such heterocyclic compounds are of pharmaceutical importance and foremost task for chemists. 1,3,4-Oxadiazole and 1,3,4-thiadiazole derivatives are heterocyclic compounds which exhibit remarkable pharmacological activities. It has been known that the activity of azo linkage increases with the incorporation of suitable heterocyclic moiety. Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 2,5-Substituted diphenyl-1,3,4- oxadiazoles are associated with diverse biological activities by the virtue of -N = C-O- grouping. Tetrazole, thiadiazole, quinoline and indole derivatives are well known for their significant biological activities. A large number of 1,2,4--triazolo[3,4-b]-1,3,4-thiadiazoles has been reported to exhibit various biological activities. Examples of such compounds bearing the 1,2,4-triazole moieties are fluconazole, a powerfulazole antifungal agents well as the potent antiviral N-nucleoside ribavarin. 1,3,4-Thiadiazole analogs are associated with diverse biological activities probably by virtue of toxophoric –N=C-S- group.

Heterocyclic azo compounds are well known for their medicinal importance and are recognized for their use as antineoplastics [1], antidiabetics [2], antiseptics [3], anti-inflammatory, antibacterial [4,5] and other useful chemotherapeutic agents [6,7]. Azo dyes are used as hypnotic drugs for the nervous system in detecting cancer as chemotherapeutic agents and are involved in the structure of nucleic acids in living cells. Azo dyes are known to be involved in a number of biological reactions such as inhibition of DNA, RNA, protein synthesis, carcinogenesis and nitrogen fixation [3, 8]. Evans blue and congo red are being studied as HIV inhibitors. This effect is believed to be caused by binding of azo dyes to both protease and reverse transcriptase
of this virus [9]. 1,2,3-Oxadiazoles can also act as HIV integrase inhibitors [10]. 1,3,4-
Oxadiazoles are five membered heterocyclic compounds having significant position in
synthetic and medicinal chemistry due to their wide array of biological activities such as antifungal [11] antimicrobial [12], anti-inflammatory, analgesic [13-15],
hypolipidemic [16] anti tubercular [17,18], anticonvulsant [19,20] , cytotoxicity [21],
prostaglandin receptor antagonists [22] and antioxidant agent [23,24]. The ability of
1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has
made them important for molecule planning because of their privileged structure,
which has an enormous biological potential. Two examples of compounds containing
the 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir, an
antiretroviral drug [25] and Zibotentan an anticancer agent [26].

\[
\begin{align*}
\text{Raltegravir} & \\
\text{Zibotentan} & 
\end{align*}
\]

Research on 1,3,4-oxadiazole skeleton derivatives has attracted sizeable interest
because of their assorted biological activity, including anti-HIV [27], antibacterial
[28-30], antifungal, analgesic and anti-inflammatory activities [31-34] and as smooth
muscle relaxant [35,36]. Moreover, they are also effective in conjunction with imines
and nitric oxide and display diverse potent physiological actions [37-41]. With regard
to the cardiovascular system, it helps to maintain micro- and macro-vascular
homeostasis through several mechanisms including vasodilatation, inhibition of
platelet aggregation, and modulation of platelet and leukocyte adhesion to the
endothelium [42, 43]. Based on the fact, it is envisioned that the attachment of imines
to the 1,3,4-oxadiazole can enhance the pulmonary vein relaxation which may contribute to maintain the homeostasis.

The compounds containing 1,2,4-triazole nucleus, represent an important class of heterocyclic compounds and their derivatives are characterized with a broad spectrum of biological activity. Structurally, triazole nucleus forms a part of a wide variety of therapeutically active drug candidates, including H1/H2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety and sedative agents [44]. Many 1,2,4-triazole and 1,3,4-thiadiazole derivatives have been used as ‘privileged’ scaffolds to produce active pharmaceutical ingredients. Some of the modern-day drugs like Ribavirin (antiviral agent), Alprazolam (anxiolytic agent), Fluconazole, Itraconazole (antifungal agents) and Rizatriptan (antimigrane agent) are having triazole nucleus in their structure. The ambient nucleophilic centers present in 3-substituted-4-amino-5-mercapto-1,2,4-triazoles render them useful synthons for the synthesis of various N-bridged heterocycles. 1,2,4-Triazole, 1,3,4-thiadiazole and thiadiazine are explored to the maximum extent owing to their wide spectrum of pharmacological activities such as antibacterial, anti-fungal [45,46], antitubercular [47], anticancer [48], anticonvulsant [49], anti-inflammatory [50,51], analgesic [52,53], antitumor [54], molluscicidal [55] and antiviral [56] activities. Among the pharmacological profiles of 1,2,4-triazoles, their antimicrobial, anticonvulsant, and antidepressant properties have been best documented. Recently, some benzoxazoline, trisubstituted triazoles, and 4-benzylidenamino derivatives containing triazole and thiadiazole units have been found to be endowed with excellent free radical scavenging activities [57-59]. Timolol and Tizanidine contain thiadiazole nucleus.
The stable oxadiazoles appear in a variety of pharmaceutical drugs including Raltegravir (anti-HIV), Butalamine (4) (vasodilator), Fasiplon (anxiolytic), Oxolamine (5) (cough suppressant), and Pleconaril (6) (antiviral- asthma, common cold).

Anil Rathavi et al [60] synthesized a series of 2-(4-flourophenyl-1,3,4-oxadiazolyl)-5-thio-4-(morpholino)-6-(arylamino)-s-triazine(7) and subjected them for antimicrobial activities.
Poonam Singh et al [61] synthesized and evaluated substituted diphenyl-1,3,4-oxadiazole derivatives for central nervous system depressant activity. Wael A. et al synthesized new substituted 1,3,4-oxadiazole derivatives (8) and evaluated them for Anti-HIV activity [62].

![Image 8]

Jignesh P. Raval et al [63] synthesized and evaluated antibacterial activity of new oxoethylthio-1,3,4-oxadiazole derivatives (9).

![Image 9]

Jain et al [64] synthesized series of 2-(3,4,5-trihydroxyphenyl)-5-aryl-1,3,4-oxadiazoles (10) and the synthesized compounds were subjected to antimicrobial activity.
Weiming Xu et al [65] reported the synthesis novel sulfone derivatives containing 1,3,4-oxadiazole moieties and evaluated for antifungal activity.

\[
\begin{align*}
\text{HS} & \xrightarrow{\text{Dimethyl sulphate oxidation}} \text{SO}_2 \text{O} \\
\end{align*}
\]

Sohail Anjum Shahzada [66] synthesized 5-substituted 1,3,4-oxadiazole-2(3H)-thiones (12) using microwave from hydrazides and carbon disulfide.

\[
\begin{align*}
\text{R} - \text{O} & \xrightarrow{\text{KOH/Al}_2\text{O}_3} \text{N} = \text{N} \\
\end{align*}
\]

Asif Husain [67] reported the synthesis of 3,6-disubstituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives (13) and evaluated for their anticonvulsant activity and neurotoxicity.

\[
\begin{align*}
\end{align*}
\]

Ram J. Singha [68] synthesised series of novel 3-pyridyl-6-aryl-s-triazolo[3,4-b]-[1,3,4]-thiadiazoles (14) and screened for antibacterial activity.
Recently Kokila Parmar [69] synthesized new 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole derivatives (15) and these compounds showed significant anti bacterial activities.

Mohammad A [70] reported the synthesis and pharmacological evaluation of condensed heterocyclic 6- substituted-1,2,4-triazolo[3,4-b]-1,3,4- thiadiazole derivatives (16).
6.2. Present work

In view of biological importance of substituted 1,3,4-oxadiazole and thiadiazole derivatives, it was contemplated to synthesize and characterize substituted 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole derivatives (19a-c) and 3,6-diphenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives (22a-g) with a view to explore their potency as better chemotherapeutic agents. The newly synthesized compounds were screened for their antimicrobial activity. The synthetic strategy for the synthesis of these series of compounds has been described in the scheme 7.

<table>
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<tr>
<th>Compd</th>
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<th>R²</th>
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<tbody>
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</tr>
<tr>
<td>19b</td>
<td>4-Cl,2-CH₃</td>
<td>4-NO₂</td>
</tr>
<tr>
<td>19c</td>
<td>4-Cl,2-CH₃</td>
<td>5-F,2-CF₃</td>
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</tr>
<tr>
<td>22c</td>
<td>2-CH₃</td>
<td>3-Br,5-1</td>
</tr>
<tr>
<td>22d</td>
<td>2-CH₃</td>
<td>5-F,2-CF₃</td>
</tr>
<tr>
<td>22e</td>
<td>4-Cl,2-CH₃</td>
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<tr>
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<td>4-Cl,2-CH₃</td>
<td>3-Br,5-1</td>
</tr>
<tr>
<td>22g</td>
<td>4-Cl,2-CH₃</td>
<td>3-Br</td>
</tr>
</tbody>
</table>
6.2.1. Synthesis of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazoles

2,5-Diphenyl-1,3,4-oxadiazoles (19a-c) were obtained from 2-methylbenzohydrazide (18) or 5-chloro-2-methylbenzohydrazide (18a) on treatment with different benzoic acids in the presence of phosphorous oxychloride. The synthetic strategy for the synthesis of these series of compounds has been described in the following scheme.

The synthesis of substituted 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole derivatives (19a-c) involves the following steps;

1. Synthesis of 2-methylbenzohydrazide (18)/ 5-chloro-2-methylbenzohydrazide (18a)
2. Reaction of 2-methylbenzohydrazide (18)/ 5-chloro-2-methylbenzohydrazide (18a) with appropriate benzoic acid in the presence of phosphorous oxychloride.

6.2.1.1. Synthesis of 2-Methylbenzohydrazide (18)/ 5-chloro-2-methylbenzohydrazide (18a) from methyl-2-methyl benzoate (17)/ 5-chloro-2-methylphenyl benzoate (17a)

The hydrazide 2-methylbenzohydrazide (18) / 5-chloro-2-methylbenzohydrazide (18a) were prepared from their methyl ester, methyl-2-methyl benzoate (17) / 5-chloro-2-methylphenyl benzoate (17a) by reacting with hydrazine hydrate in the presence of ethanol under reflux conditions for about 8 hr.
The formation of methyl ester 17/17a was confirmed by TLC and mass spectral analysis. Methyl-2-methyl benzoate was obtained as pale yellow oil with 82% yield and 5-chloro-2-methylphenyl benzoate with 75% yield. The formation of hydride 18 or 18a was confirmed by mass spectral analysis and melting point. 2-methylbenzohydrazide (18) was obtained as white solid and 5-chloro-2-methylbenzohydrazide (18a) as off-white solid.

6.2.1.2. Synthesis of 1,3,4-oxadiazole derivatives (19a-c)

2,5-Diphenyl-1,3,4-oxadiazole (19a-c) were obtained from 2-methylbenzohydrazide (18)/5-chloro-2-methylbenzohydrazide (18a) on treatment with different benzoic acids in the presence of phosphorous oxychloride.

<table>
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<tr>
<th>Compd</th>
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<th>R^2</th>
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<td>4-Cl,2-CH₃</td>
<td>2-CH₂</td>
</tr>
<tr>
<td>19b</td>
<td>4-Cl,2-CH₃</td>
<td>4-NO₂</td>
</tr>
<tr>
<td>19c</td>
<td>4-Cl,2-CH₃</td>
<td>5-F,2-CF₃</td>
</tr>
</tbody>
</table>
The synthesized compounds were characterized by IR, $^1$H-NMR and $^{13}$C-NMR, and mass spectral analysis. The IR spectrum of compounds 2-(4-chloro-2-methylphenyl)-5-(2-methylphenyl)-1,3,4-oxadiazole (19a) exhibited a band at 1040 cm$^{-1}$ corresponding to C-F stretching, 1606 cm$^{-1}$ corresponding to C=N stretching and frequency at 2923 cm$^{-1}$ is due to aromatic C-H stretching. $^1$H-NMR displayed multiplet between 7.2-8.0 ppm corresponding to seven aromatic protons and a singlet at 2.7 ppm corresponding to six methyl protons.
IR spectrum of compound 19a
1H NMR spectrum of compound 19a
1H NMR spectrum of compound 19a

Current Data Parameters
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EXPNO 2
PROCNO 1

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Time 16:24
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SOLVENT CDCl3
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FRES 0.356518 Hz
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F2 - Processing parameters
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INSTRUMENT CODE:BIL/LAB/RND/221
6.2.2. Synthesis of 3,6-Diphenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole

The synthesis of 3,6-diphenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives (22a-g) involves the following steps:

1. Synthesis of potassium dithiocarbazate 20 / 20a from 2-methylbenzohydrazide (18) 5-chloro-2-methylbenzohydrazide (18a)

2. Synthesis of 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21) / 4-amino-5-(5-chloro-2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21a) from 20 or 20a.

3. Synthesis of 22a-g, by treating compound 21 or 21a with appropriate benzoic acid derivatives

For the synthesis of title compounds 22a-g, 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21) / 4-amino-5-(5-chloro-2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21a) required as starting material was prepared according to a method which involves the condensation of 2-methylbenzohydrazide (18) / 5-chloro-2-methylbenzohydrazide (18a) with carbon disulfide and potassium hydroxide to yield potassium dithiocarbazate 20 / 20a, which underwent ring closure with excess of hydrazine hydrate to produce aminothiol 21 / 21a in good yield (79-87%). Cyclocondensation of the -SH and -NH₂ groups of compound 21 or 21a with appropriate benzoic acid derivatives in presence of phosphoryl chloride gave 3,6-
diphenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives (22a-g). The structure of synthesized compounds was confirmed through $^1$H-NMR and $^{13}$C-NMR. The $^{13}$C-NMR spectra data were consistent with the assigned structure; triazole -C=N- carbon of 22a-g was observed at around 150.1 ppm; thiadiazole -N=C=N-S carbon was observed at 164.9 ppm.

6.2.2.1. Synthesis of 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21)/4-amino-5-(5-chloro-2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21a)

Aminothiols, 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21) or 4-amino-5-(5-chloro-2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21a) were obtained from their corresponding potassium salts of 2-(2-methylbenzoyl)hydrazinecarbodithiol (20)/2-(5-chloro-2-methylbenzoyl)hydrazinecarbodithiol(20a) by reacting with hydrazine hydrate. Compound 20/20a were obtained by reaction of 2-methylbenzohydrazide (18)/5-chloro-2-methylbenzohydrazide (18a) with carbon disulphide in the presence of potassium hydroxide and ethanol.

The aminothiol compound 21 or 21a were characterised by $^1$H-NMR and mass spectral analysis. $^1$H-NMR of 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21) displayed multiplet between 7.18-7.37 ppm corresponding to four aromatic protons; a singlet at 14.25 ppm corresponding to SH proton, a broad singlet of two protons at 5.29 ppm corresponding to two amine protons and a singlet of three protons at 2.27 ppm corresponding to three methyl protons. Further, the mass spectrum of compound 21 showed a molecular ion peak M$^+$ at m/z 270.4.
6.2.2.2. Synthesis of [1,2,4]triazolo[3,4,b][1,3,4]thiadiazole derivatives (22a-g)

Cyclo-condensation of the SH and NH₂ groups of compound 21/21a with appropriate benzoic acid derivatives in presence of phosphoryl chloride gave 3,6-diphenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives (22a-g). The newly synthesized compounds were characterized by spectroscopic methods like IR, ¹H-NMR, ¹³C-NMR and mass. Synthetic strategy for these compounds is described in the scheme.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R¹</th>
<th>R²</th>
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<tbody>
<tr>
<td>22a</td>
<td>2-CH₃</td>
<td>4-NO₂</td>
</tr>
<tr>
<td>22b</td>
<td>2-CH₃</td>
<td>2,6-CH₃</td>
</tr>
<tr>
<td>22c</td>
<td>2-CH₃</td>
<td>3-Br,5-I</td>
</tr>
<tr>
<td>22d</td>
<td>2-CH₃</td>
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<td>22f</td>
<td>4-Cl,2-CH₃</td>
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</tr>
<tr>
<td>22g</td>
<td>4-Cl,2-CH₃</td>
<td>3-Br</td>
</tr>
</tbody>
</table>

The IR spectrum of compound 6-(3-bromo-5-iodophenyl)-3-(2-methylphenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (22c) exhibited absorption band at 546 cm⁻¹ corresponding to C-Br stretching, 1021 cm⁻¹ corresponding to C-I stretching, 1595 cm⁻¹ corresponding to C=N stretching and frequency at 2925 cm⁻¹ is due to aromatic C-H stretching. ¹H-NMR exhibited multiplet between 7.4-8.2 ppm corresponding to seven aromatic protons and a singlet at 2.67 ppm corresponding to three methyl protons. The ¹³C-NMR spectra data were consistent with the assigned structure; triazole -C=N- carbon of 22c was observed at 154.79 ppm; thiadiazole -N=C=N-S carbon was observed at 165.16 ppm. Further, the mass spectrum of compound 22c showed a molecular ion peak M⁺ at m/z 497.
IR spectrum for compound 22c
$^{1}$HNMR spectrum for the compound 22c
13CNMR of compound 22c
3: UV Detector: TIC Smooth (Mn, 2x3)

Peak no | R.T | Area | %Area |
---|---|---|---|
1 | 1.88 | 249.0390 | 100.00 |

Peak ID | Time  
---|---|
1 | 1.88 |

Mass spectrum of compound 22c
6.3. Experimental protocol

6.3.1. Synthesis of Methyl-2-methyl benzoate (17) or 5-chloro-2-methylphenyl benzoate (17a)

To a stirred solution of 2-methyl benzoic acid 16 (73.45 mmol) in dry methanol (100 mL), was added 3-4 drops of con.\(\text{H}_2\text{SO}_4\). The reaction mixture was refluxed for 8-10 h under nitrogen atmosphere. Methanol was distilled off and the residue was dissolved in ethyl acetate (200 mL). The organic layer was washed with 10% sodium bicarbonate solution (50 mL) and water (50 mL) followed by saturated sodium chloride solution. The organic layer was treated with anhydrous sodium sulphate, filtered and concentrated under vacuum to afford title compound, methyl-2-methyl benzoate. Pale yellow oil, Yield: 81.74%, Mol.formula: C\(_9\)H\(_{10}\)O\(_2\), MW: 150.17; 5-chloro-2-methylphenyl benzoate was prepared using similar procedure, Yield: 76.2%.

6.3.2. Synthesis of 2-methylbenzohydrazide (18) or 5-chloro-2-methylbenzohydrazide (18a)

To a stirred solution of methyl 2-methyl benzoate (17) or 5-chloro-2-methylphenyl benzoate (17a) (59.93 mmol) in absolute ethanol (90 mL) was added hydrazine hydrate (269.68 mmol). The reaction mixture was refluxed for about 8 h. The reaction was monitored by TLC. After the reaction completion (checked by TLC), the solvent was distilled under vacuum, added ice-water (50 mL) and stirred for 15 min. The solid obtained was filtered and dried under vacuum to obtain 2-methylbenzohydrazide (18) as white solid/5-chloro-2-methylbenzohydrazide (18a) as off-white solid. Compound 18: Yield: 86.3%. m.p: 152-154.5°C; m/z: [M+] 151.2.

6.3.3. Synthesis of 1,3,4-oxadiazole derivatives (19a-c)

To a mixture of equimolar 18 or 18a and substituted benzoic acid, was added phosphorous oxychloride (10 vol) at 0°C. The contents were slowly heated to 115°C and maintained at that temperature for 16 h under nitrogen. The reaction completion
was monitored by TLC. After completion, the reaction mass was cooled to room
temperature and poured into ice-cold water (250 ml). The product was extracted with
ethyl acetate; the organic layer was washed with 10% sodium bicarbonate solution
followed by water wash and saturated sodium chloride solution. The organic layer was
dried over sodium sulphate and concentrated under vacuum to residue. The crude
compounds were purified by flash chromatography using ethylacetate and hexane as
eluent.

**2-(4-chloro-2-methylphenyl)-5-(2-methylphenyl)-1,3,4-oxadiazole (19a):**
Off white solid, Yield- 61%; m.p. 255-258.5°C; \(^1\)H-NMR (400 MHz, DMSO-d6, \(\delta\)
ppm): 2.71 (s, 6H), 7.28-7.97 (m, 7H, Ar-H); \(^13\)C-NMR (400 MHz, DMSO-d6, \(\delta\) ppm):
164.49, 163.66, 140.34, 138.56, 137.18, 131.88, 131.34, 131.20, 130.15, 128.98,
126.54, 122.85, 121.57, 22.7, 22.2; MS (LCMS) 285.6 [M+]: Mol. formula; C\(_{16}\)H\(_{13}\)ClN\(_2\)O.

**2-(4-chloro-2-methylphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (19b):**
Yellow solid, Yield-64%, m.p.: 229-232°C; \(^1\)H-NMR (400 MHz, DMSO-d6, \(\delta\)
ppm): 2.69 (s, 3H), 7.42-8.76 (m, 7H, Ar-H); \(^13\)C-NMR (400 MHz, DMSO-d6, \(\delta\) ppm):
165.49, 164.74, 137.33, 134.12, 132.22, 131.56, 130.69, 130.67, 130.34, 125.34,
125.22, 124.88, 123.18, 122.67, 22.29; MS(LCMS) ;m/z 316.6[M+]: Mol. formula
C\(_{17}\)H\(_{10}\)ClN\(_2\)O\(_3\).

**2-(4-chloro-2-methylphenyl)-5-[2-fluoro-5-(trifluoromethyl)phenyl]-1,3,4-
oxadiazole (19c):**
Light Brown solid, Yield-67%; m.p.: 262-266.5°C; \(^1\)H-NMR (400 MHz, DMSO-d6, \(\delta\)
ppm): 2.67 (s, 3H), 7.43-8.09 (m, 6H, Ar-H); \(^13\)C-NMR (400 MHz, DMSO-d6, \(\delta\) ppm):
163.49, 160.74, 137.33, 133.12, 132.22, 131.55, 130.99, 130.77, 130.34,
125.34, 125.22, 124.88, 123.88, 122.67, 121.98, 22.21; MS(LCMS) ; m/z: 357.6[M+]. Mol. formula: C\(_{18}\)H\(_9\)ClF\(_3\)N\(_2\)O.
6.3.4. Synthesis of 2-(2-methylbenzoyl)hydrazinecarbodithiol acid potassium salt (20) / 2-(5-chloro-2-methylbenzoyl)hydrazinecarbodithiol acid potassium salt (20a)

Potassium hydroxide pellets (106.54 mmol) were dissolved in 40 mL absolute ethanol. To this solution, added 2-methylbenzohydrazide (18) or 5-chloro-2-methylbenzohydrazide (18a) (53.27 mmol) followed by carbon disulfide (117.19 mmol) and contents were stirred at room temperature for 5 h. The reaction was monitored by TLC. After the reaction completion, added di-ethylether (100 mL) and stirred for 10 min. The solid formed was filtered and dried under vacuum to obtain 2-(2-Methylbenzoyl)hydrazinecarbodithiol acid potassium salt (19) as white solid or 2-(5-chloro-2-methylbenzoyl)hydrazinecarbodithiol acid potassium salt (19a) as off-white solid. Compound 19: Yield: 85.10%; m.p: 167-170°C; Mol formula: C$_9$H$_9$KN$_2$OS$_2$; MW: 264.42; [m/z]$^+$: 265.3.

6.3.5. Synthesis of 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21) or 4-amino-5-(5-chloro-2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (21a)

Hydrazine hydrate (45.38 mmol) was added to compound 19 or 19a (45.38 mmol) and the contents were refluxed for 2 h. After the reaction completion (checked by TLC), the reaction mixture was acidified with con. HCl. The precipitate was filtered and dried under vacuum to obtain compound 20 or 20a. 4-amino-5-(2-methyl phenyl)-4H-1,2,4-triazole-3-thiol (20). White solid, Yield: 87.7%, m.p.: 167-170°C; $^1$H-NMR: 2.27 (s, 3H), 5.49 (bs, 2H), 7.18-7.37 (m, 4H, Ar-H), 14.25 (s, 1H); Mol formula: C$_9$H$_9$N$_4$S; MW: 206.3, [m/z]$^+$: 207.4.

6.3.6. Synthesis of Thiadiazole derivatives (22a-g)

To a stirred solution of 1,2,4-triazole-3-thiol 21/21a (4.84 mmol) in phosphoryl chloride (10 mL), was added benzoic acid (1 eq.) and the reaction mixture was refluxed about 10 h. The reaction was monitored by TLC, after the reaction
completion, the mass was quenched with ice-water, and the product was extracted with ethyl acetate (2×75 mL). The organic layer was washed 10% sodium bicarbonate solution (50 mL) followed by water and saturated sodium chloride solution. The organic layer was treated with anhydrous sodium sulphate and concentrated under vacuum to afford title compounds. These compounds were purified by column chromatography using ethyl acetate and petroleum ether.

3-(2-Methylphenyl)-6-(4-nitrophenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (22a):
Off white solid, Yield-83%; m.p. 126-129°C; IR (KBr, ν max, cm⁻¹): 2925 (Ar-CH), 1595 (C=N); 1H NMR (400 MHz, DMSO-d₆, δ ppm): 2.49 (s, 3H), 7.28-7.99 (m, 7H, Ar-H); 13C NMR (400 MHz, DMSO-d₆, δ ppm): 165.16, 164.30, 162.63, 154.79, 146.58, 137.81, 134.75, 134.66, 131.61, 130.86, 130.78, 129.85, 126.79, 121.97, 116.38, 21.1; MS (LCMS): m/z 338.3[M⁺]: Mol. formula; C₁₆H₁₁N₅O₂S.

6-(2,6-Dimethylphenyl)-3-(2-methylphenyl)[1,2,4]triazole[3,4-b][1,3,4]thiadiazole (22b)
White solid, Yield-73%, m.p 152-154.5°C; 1H NMR (400 MHz, DMSO-d₆, δ ppm) 2.26 (s, 6H), 2.41 (s, 3H), 7.26 -8.16 (m, 7H, Ar-H); 13C NMR (400 MHz, DMSO-d₆, δ ppm), 168.0, 148.0, 143.3, 138.7, 138.2, 136.6, 134.2, 132.6, 130.9, 129.3, 126.3, 126.1, 21.8, 21.2; MS (LCMS): m/z 320.3[M⁺]: Mol. formula; C₁₈H₁₆N₄S.

6-(3-Bromo-5-iodophenyl)-3-(2-methylphenyl)[1,2,4]triazole[3,4-b][1,3,4]thiadiazole (22c)
Yellow solid, Yield-76%; m.p 141-142°C; 1H NMR (400 MHz, DMSO-d₆, δ ppm) 2.48 (s, 3H), 7.29-8.17 (m, 7H, Ar-H); 13C NMR (400 MHz, DMSO-d₆, δ ppm) 165.16, 164.3, 162.6, 154.79, 146.5, 137.8, 134.7, 131.6, 129.8, 126.8, 125.07, 121.9, 121.7, 116.6, 116.38, 21.2. MS (LCMS), m/z 497.0[M⁺]: Mol. formula: C₁₆H₁₀BrIN₄S.
6-[2-Fluoro-5-(trifluoromethyl)phenyl]-3-(2-methylphenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (22d)
Light brown solid, Yield-89%; m.p. 126-129°C; $^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 2.41 (s, 3H), 7.67-8.20 (m, 6H, Ar-H), 8.24 (s, 1H); $^{13}$C-NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm): 165.16, 164.30, 162.63, 154.79, 146.58, 137.81, 134.75, 134.66, 131.61, 130.86, 130.78, 129.85, 126.79, 121.97, 116.38, 21.10; MS(LCMS) m/z 379.2 [M]: Mol.formula: C$_{17}$H$_{10}$F$_4$N$_4$S.

6-(2,6-dimethylphenyl)-3-(4-chloro-2-methylphenyl)[1,2,4]triazolo[3,4,b][1,3,4]thiadiazole (22e)
White solid, Yield-75%, m.p.: 152-154.5°C; $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm) 2.26 (s, 6H), 2.41 (s, 3H), 7.26-8.16 (m, 6H, Ar-H); $^{13}$C NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm), 168.0, 148.0, 143.3, 138.7, 138.2, 136.6, 134.2, 132.6, 130.9, 129.3, 126.3, 126.1, 21.8, 21.2; MS (LCMS) m/z354.07[M+]: Mol.formula: C$_{18}$H$_{15}$ClN$_4$S.

6-(3-bromo-5-iodophenyl)-3-(4-chloro-2-methylphenyl)[1,2,4]triazolo[3,4,b][1,3,4]thiadiazole (22f)
Brown solid, Yield-70%; m.p 141-142°C; $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm), 2.48 (s, 3H), 7.65-8.36 (m, 6H, Ar-H); $^{13}$C NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm), 168.0, 148.0, 143.3, 143.0, 138.2, 136.6, 135.6, 134.5, 134.2, 131.6, 129.3, 128.8, 126.3, 124.8, 96.6, 21.2; MS (LCMS): m/z 531.6[M+], Mol.formula: C$_{18}$H$_{16}$BrClIN$_4$S.

6-(3-bromophenyl)-3-(4-chloro-2-methylphenyl)[1,2,4]triazolo[3,4,b][1,3,4]thiadiazole (22g)
White solid, Yield- 72%, m.p. 149-153°C; $^1$H NMR (400 MHz, DMSO- $\delta$ ppm), 2.45 (s, 3H), 7.61-8.25 (m, 7H, Ar-H): $^{13}$ CNMR (400 MHz, DMSO- $d_6$, $\delta$ ppm) 165.16, 164.3, 162.6, 154.79, 146.5, 137.8, 134.7, 131.6, 129.8, 126.8, 125.07, 121.9, 121.7, 116.6, 116.38, 21.2, MS (LCMS) 405.7, [m/z] = 406[M+]. Mol.formula: C$_{16}$H$_{10}$BrClIN$_4$S.
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CHAPTER 6

1,3,4-oxadiazole and thiadiazole derivatives


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