CHAPTER-4
SYNTHESIS OF NOVEL TRIAZOLE COMPOUNDS
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4. [A]. INTRODUCTION:

Triazole moiety which exhibit a broad spectrum of pharmacological activity such as antifungal, antibacterial, anti-inflammatory and anticancer etc. Triazoles have increased our ability to treat many fungal infections, for example, candidiasis, cryptococcal meningitis, aspergillosis etc. However, mortality due to these infections even with antifungal therapy is still unacceptably high. Therefore, the development of new antifungal agents targeting specific fungal structures or functions is being actively pursued.

4. [B] PHARMACOLOGICAL APPLICATION OF TRIAZOLE DERIVATIVES:

Triazole as Antibacterial agents

Day by day medicinal chemistry is towards its advancement, Many antibiotics are now chemically modified from original compounds present naturally e.g. Beta lactams\(^1\). Many of them are still obtained naturally named as amino glycosides and a lot more are synthetically derived as sulfonamides\(^2\), the quinolones and the oxazolidinones. Moreover they are classified in two types based on their mode of action as bactericidal agents and bacteriostatic agent\(^3\). Among various triazole derivatives, base and sugar modified nucleoside derivatives reflect a potent antimicrobial activity resulting in its application in the chemotherapy of cancer and viral infection. The inhibitory effect of N-glucosides (1), 3a, 3b and those of S-glucosides 2a, 2b are manipulated by changing the position of substituent on aromatic ring. The compound resulted higher inhibitory activity against Aspergillus fumigatus, Penicillium italicum, Syncephalastrum racemosum Staphylococcus aureus, Pseudomonas aeruginosa, and Bacillus subtilis\(^4\).
The sequential one pot synthesis assisted in cyclisation of resulting active compound named 1-[1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl] methanamine (4) which was a potent antimicrobial compound against all pathogenic strains. Active piperazine nucleus in this compound is responsive for this activity\(^5\).
3-(4-Chlorobenzylsulfonylmethyl)-5-(2-chlorophenyl)-4H-1,2,4-triazol-4-amine (5) was synthesized and potent antimicrobial activity was evaluated. The compound also exhibited cytotoxic activity\(^6\).

![Image](5)

Condensation product 1-Arylimidazolidine-2-thiones directed the synthesis of 7-(4-methylphenyl)-3-methylthio-5H,6,7-dihydroimidazo[2,1-c][1,2,4]triazole (6) by a series of intermediate steps which showed a profound antimicrobial activity. The activity was superior to reference drug ampicillin in-vitro\(^7\).

![Image](6)

Novel 2-substituted-5-[isopropylthiazole] clubbed1,2,4-triazole (7), (8) were synthesized as potent antimicrobial agent. The activity was shown by the compound named 4-(4-Dimethylaminebenzylideneamino)-5-(4-isopropylthiazol-2-yl)-4H-1, 2, 4-triazole-3-thiol\(^8\).

![Image](7)

![Image](8)
Antimicrobial activity of some newly synthesized compounds were evaluated and resulted in potent activity against many microorganisms. The compounds (9), (10), 11a, 11b, 11c prepared belongs to 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo-[1,2,4]triazole derivatives.\(^9\)

![Chemical structure of compound 9](image)

Compounds from series of 5-[2-(substituted sulfamoyl)-4,5-dimethoxy-benzyl]-4-aryl-S-triazole-3-thiones 13a, 13b were prepared and resulted in antimicrobial activity equipotent to streptomycin, giving an exception against Enterobacter cloacae and Salmonella species. The synthesized compounds were better than chloramphenicol. Moreover Gram-ve strains were sensitive rather than Gram +ve, against the activity.\(^10\)

![Chemical structures of compounds 10 and 11](image)

![Chemical structure of compound 13](image)
In the synthesis of new compounds containing diphenylsulfone moiety 14a, 14b, the results revealed that incorporation of NH$_2$ functional group in azomethine function made a rise in antibacterial activity against B.subtilis, P.aeruginosa in comparison to chloramphenicol$^{11}$.

![Image](image1)

Another series of compounds bearing 5-(4-methyl-1,2,3-triazole)methyl group at C$_5$ of oxazolidine ring were evaluated, compound containing substitution of isopropyl carbonyl group at C$_4$ position of piperazine resulted in most active compound (15) striking gram +ve strains. Taking linezolid and vancomycin as standard compounds, evaluation of this new series of were performed and the compounds showed a potent antimicrobial activity. The variance of the activity depended upon the presence of 4-methyl-1,2,3-triazole moiety within the acyl-piperazine having analogues resulted in raised protein binding efficiency and lowered antimicrobial activity against Streptococcus pneumonia strains$^{12}$.

![Image](image2)

Microwave assisted reaction, involved in nucleophilic substitution reaction, resulted in reduced reaction time and improved yield. Quinoline derivatives synthesized by this technique and were evaluated for antimicrobial activity. SAR of 16a, 16b reveals that presence of CF$_3$, active amine at 8 and 4 position of quinoline respectively, also other bioactive moieties as e.g.-SH, -CH$_2$CH$_2$OCH$_3$ and Ph moieties at triazole ring were shown responsible for the potent antimicrobial activity$^{13}$. 

92
Precursor isonicotinic hydrazide resulted in 4-amino-5-pyridin-4-yl-4H-1, 2,4-triazole-3-thiol through number of steps which was further treated, synthesize and the resulted compound 17a, 17b, 17c were evaluated for antimicrobial property\textsuperscript{14}.

**Triazole as Antiviral agents**

HIV (retrovirus) is a virus resulting in the slow depletion of immune system of the affected human beings resulting in opportunistic infections\textsuperscript{15}. Contrasting from other retroviruses it is different, its single stranded RNA is attached to tightly bound proteins and enzymes for the development of the virion namely reverse transcriptase, proteases, ribonucleases and integrases. The treatment of HIV regimen HAART\textsuperscript{16} (Highly Active Antiretroviral Therapy) is not at the best mainly due to rebound phenomenon of virus at the withdrawal of the treatment resulting in increment of CD4+ T-cells which results in AIDS\textsuperscript{17}. The weak results of present drug regimen against HIVinfection has stressed for refocusing on the bio-mechanism for latency regarding HIV. Some new compounds were synthesized and evaluated for the anti-HIV activity 4-[(1,2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-N (4, 6-dimethyl-2-pyrimidinyl)-benzene sulphonamide and its derivatives 18a, 18b, 18c, 18d were prepared and they were found active against replication of HIV-1 and HIV-2 in MT-4 cells\textsuperscript{18}. 
Synthesis of new 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl) semicarbazide derivatives were prepared and they were found potentially active against T4-lymphocytes infected. The compounds 19a, 19b, 19c were successfully changed to triazoles and it also helpful in finding out SAR\textsuperscript{19}. A new pharmacophore named 8-hydroxy-1,6-naphthyridine core and a triazole is identified. The two metal co-ordination pharmacophore patterns were selected for designing of key structural component 20a, 20b. In potency against enzyme system the benzyl and fluoro-benzyl showed equivalent activity but if the substituent was made smaller in size the activity depleted\textsuperscript{20}.

Various derivatives of trisubstituted triazoles (21) were prepared as inhibitors of reverse transcriptase and the two derivatives with difference in thio group position were found out to be most active compounds which were also analysed with crystallographic analysis\textsuperscript{21}.
Another important compound that were active against HIV reverse transcriptase, 1-benzyl-1H-1,2,3-triazole derivatives linked to carbohydrate moiety, were prepared\textsuperscript{22}. The two new synthesized classes of compounds 22a, 22b consisted of carbohydrate protected and non-protected moieties.

A newly derived 4-triazole modified zanamivir (23) was synthesized via click reaction and the inhibitory activities were found near to that of zanamivir. It was evaluated against Avian Influenza Virus (AIV, H5N1). Binding agreement between the inhibitors and the neuraminidase were provided by molecular modelling\textsuperscript{23}.

The under shown compound (24) were prepared as the novel thiourea derivatives obtained from 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3H-1,2,4triazole-3-thiones which proved to be having a good activity against coxsackie virus B4, also active against the thymidine kinase positive Varicella zoster virus\textsuperscript{24}.
Antiviral activity against cantalago virus was derived from the compound i.e. N-amino-1,2,3-triazole is (25) shown. The structural position 4 at triazole is being further experimented for increasing potential of activities. A series of triazoles and pentafluorophenoxy-substituted pyrimidine nucleoside (26) were synthesized by one pot reaction. The synthesized compounds provided nominal potency as anti-viral compounds as compared to AZT.

**Triazole as Anti-convulsant agents**

Seizures initiate by the rapid and excessive firing of neurons and is controlled by the class of drugs called Anticonvulsant Drugs. They act by the mechanism of mood stabilizing mainly by treatment of bipolar disorder. They are also called antiepileptic drugs (AED’s). The other type of convulsive non-epileptic seizures are not responding to this class of drugs. In epileptic condition area of cortex is hyperirritable and this irritability is being decreased by this class of drugs.

The main targets molecules of the drugs are voltage gated Na channels, GABA receptors, and GABA transaminase, voltage-gated calcium channels, SV2A and α2δ. However antiepileptogenic treatment is under human trials. Here is the review of the newly synthesized compounds showing anticonvulsant activity and they proved to be effective for further research as lead compounds.
The various substituted compounds 27a, 27b, 27c, 27d, 27e, 27f showed the anticonvulsant activity\(^3^3\).

Novel series of 3-\{[(substituted phenyl)methyl]thio\}-4-alkyl/aryl- 5-(4-amoino phenyl)-4H-1,2,4-triazoles 28a, 28b, 28c were synthesized which were similarly evaluated by the above said technique and the two active compounds were evaluated and was concluded that the alkyl substitution or primary amino group were essential for the compound to show an activity\(^3^4\).

Condensation reaction of the N3-substituted amidrazones and with malice anhydrides provided with newer derivatives (29) of 3-(3, 4-diaryl-1,2,4-triazole-5-yl)propenoic acid which were evaluated for the anticonvulsant activity\(^3^5\).

A series of novel 10-alkoxy-5,6-dihydro-triazolo[4,3-d]benzo[f][1,4]oxazepine derivatives were synthesized and evaluated by the maximal electro shock (MES) test and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). The compound (30) was found to have better anticonvulsant activity than marketed drugs namely carbamazepine, phenytoin and it was also shown that the activity was mediated by GABA-mediated mechanism\(^3^6\).
A new class of drug 31a, 31b incorporating triazoles to thiazoles 3-[4-(substitutedphenyl)-1,3-thiazol-2-ylamino]-4-(substitutedphenyl)-4,5-dihydro -1H-1,2,4-triazole -5-thiones were synthesized and found to have anticonvulsant activity which was designed as keeping in view the structural requirement of pharmacophore model. Median Hypnotic Dose (HD50), and Median lethal dose were higher than the standard drugs\(^{37}\).

The same evaluation was also done for the other compounds 32a, 32b named 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole derivatives which exhibited much greater PI value than of prototype drug phenytoin. It concluded that it might have effect on GABA neurotransmission and activate glutamate decarboxylase or inhibit (GABA)a-oxoglutarate amino transferase (GABA-T) in the brain\(^{38}\).

5-hexyloxy-[1,2,4] triazolo [4,3-a] quinoline (33) was synthesized and evaluated, found potent anticonvulsive in nature with low level of neurotoxicity\(^{39}\). All
the possible mechanism of anticonvulsive activity was done in pentylenetetrazole test, isoniazid test, thiosemicarbazide test, 3-mercaptopyruvic acid and strychnine test.

**Triazole as Antifungal agents**

Antifungal are the class of drugs that are used to eradicate fungal infections from the human body. They work by exploiting differences between mammalian and fungal cells to eradicate fungal organism without harming the host cells. As both the cells are eukaryotic in nature so it is more difficult to design the drugs of anti-fungal activity with fine selections of the cells without causing any side effects

Drugs of fungal origin include griseofulvin from Penicillium griseofulvum, used to treat fungal infections, Inhibitions of Sharma et al. IntJCurrPharm Resvol3, Issue2, 105-118 cholesterol synthesis by statins (HMG-CoA reductase inhibitors. E.g devastating from Penicillium citrinum, lovastatin from Aspergillus terreus and the oyster mushroom. So further here we are emphasizing on the newly synthesized compounds including triazole moiety showing better antifungal property.

Candida fungal pathogens were impinged by the new triazole derivatives (34), analogous to the fluconazole both by in vivo and in vitro. The easily accessible molecules, 1,4-disubstituted-1,2,3-triazole compounds with long alkyl chains displayed a good antifungal activity. It was more potent than the standard drugs namely ketoconazole, amphoterecin B and fluconazole. The enantiomers are still under process as they are supposed to have more potent activity than the racemic compounds

Ferrocene is known to have a strange record for a dramatic change in the activity of compounds, was also utilized to incorporate the compound, synthesized by
Mannich type reaction, sequential condensation and cyclisation reaction, resulting in ferrocenyl containing 1H-1,2,4-triazole derivatives 35a, 35b, 35c, 35d. It was also proved that addition of methyl group along ferrocene and aryl linkage resulted in flexible compounds.

![Chemical Structure](image)

The use of Computer docking to produce a series of 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols, analogues to fluconazole, resulted in the screening against 8 human pathogens. A fumigatus was impinged by nearly all type of synthesized compounds and showed broad spectrum activity. The compound (36) showed 128 times more activity against Candida albicans. Also it showed the positive approach to introduce a side chains consisting allyl group and benzyl bromides to interact with hydrophobic pockets and also to generate p-p stacking interaction with Tyr 118.

Another series of compound 37a, 37, 37c were prepared as inhibitors of cytochrome demethylase resulting in activity better than clotrimazole and fluconazole and also a correlation between docking energy and growth inhibition between them.

![Chemical Structure](image)

Series of CYP51 inhibitors were found, synthesized and resulted in novel 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted benzylamino-2-propanols which showed comparable activity to voriconazole. Moreover again substituted benzyl chain showed part in producing an active pharmacophore and an amine side resulted in a higher activity when shortened.
Novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole were synthesized as potent antifungal agent. The activity was shown by the compound (38) named 3-(4-Isopropylthiazol-2-yl)-6-(4-nitrophenyl)-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazole\(^*\).

**4. [C]. REACTIVITY OF TRIAZOLE:**

Deactivation against electrophilic attack accounts for the difficulty or failure of nitration, sulfonation and N-oxidation of 1,2,4-triazoles. However, triazolate anions react readily with electrophilic reagents; alkylation and acylation have received much attention but halogenation and addition reactions less. Systematic study of the formation and reactions of salts and metallic complexes is of recent origin.

Reactivity of the ring towards nucleophiles is enhanced in triazolium cations and mesoionic triazole derivatives. Tautomerism of compounds with formal substituents such as OH, SH and NHR allows their classification not only as aromatic but also as reduced triazoles.

**4. [C]. 1. Oxidation reactions of Triazole:**

Triazolines such as are readily oxidized to acyclic compounds.
4. [C]. 2. Alkylation of Triazole:

Products are obtained in ratios that vary with the alkylating agent; a theoretically unexplained thumb-rule suggests preference for methylation on the nitrogen adjacent to C-phenyl when diazomethane is employed.

\[
\begin{align*}
\text{R}^3 \quad \text{R}^5 \\
\text{N} \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \quad \text{NaOH} \\
(\text{or}) \quad \text{CH}_2\text{N}_2
\end{align*}
\]

N – Alkylation of 3-halotriazoles gives N-1, N-2 and N-4 isomers. Alkylation of triazolinones is rare. If either N-1 or N-4 is substituted, alkylation affords 1,4-disubstituted triazolinones.

4. [C]. 3. Reduction reactions of Triazole:

Triazolidinone are more sensitive to reduction than aromatic triazoles. Paradoxically, reduction of the triazolinone with lithium aluminum hydride affords the more unsatured triazole

\[
\begin{align*}
\text{NH} \\
\text{CH}_3
\end{align*}
\]

4. [D]. DIFFERENT METHODS FOR THE SYNTHESIS OF TRIAZOLE:

4. [D]. 1. By reaction of imides with alkyl hydrazines:

Einhorn-Brunner reported synthesis of a mixture of isomeric 1, 2, 4-triazoles from the reaction of imides with alkyl hydrazines in presence of acyl hydroxide²⁸-⁵⁰.

\[
\begin{align*}
\text{O} \quad \text{O} \\
\text{R}_1 \quad \text{R}_2
\end{align*}
\]

\[
\begin{align*}
\text{R}_3 \quad \text{NH}_2 \\
\text{AcOH}
\end{align*}
\]
4. [D]. 2. Pellizzari’s synthesis:

Pellizzari reported synthesis of substituted 1, 2, 4-triazole by the reaction of an amide and a hydrazide\textsuperscript{51}.

\[
\begin{array}{c}
\text{R} \overset{\text{O}}{\text{N}} \text{H}_{2} + \text{R} \overset{\text{O}}{\text{N}} \text{H}_{2} \rightarrow \text{R} \overset{\text{N}}{\text{N}} \text{R}' \end{array}
\]

4. [D]. 3. G.M. Castanedo’s synthesis:

G.M. Castanedo et al\textsuperscript{52} have synthesized a highly regioselective one-pot process provides rapid access to highly diverse 1, 3, 5-trisubstituted 1, 2, 4-triazoles from reaction of carboxylic acids, primary amidines, and monosubstituted hydrazines.

\[
\begin{array}{c}
\text{O} \overset{\text{H}_{2} \text{NNH-R}''}{\text{N}} \overset{1.5 \text{eq.}}{\text{H}_{2} \text{NNH-R}''} \overset{1.1 \text{eq. HATU}}{\text{N}} \overset{3-4 \text{eq. DIPEA}}{\text{N}} \overset{25^\circ \text{C}, 2-18h}{\text{N}} \overset{10 \text{ eq. AcOH}}{\text{N}} \overset{80 \text{ C}, 1-3h}{\text{N}} \overset{\text{R', R'', alkyl Ar}}{\text{N}} \overset{\text{R'}}{\text{N}} \overset{\text{R'}}{\text{N}} \overset{\text{R'}}{\text{N}}
\end{array}
\]

4. [D]. 4. L.Y. Wang’s synthesis:

L.Y. Wang et al\textsuperscript{53} have synthesized an effective 1, 3-dipolar cycloaddition for the synthesis of 1, 3, 5-trisubstituted 1, 2, 4-triazole derivatives by reaction of oximes with hydrazonoyl hydrochlorides using triethylamine as a base gave the desired 1, 3, 5-trisubstituted 1, 2, 4-triazoles in good yields. The reaction was applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic oxime substrates.

\[
\begin{array}{c}
\text{NOH.HCl} \overset{\text{H}}{\text{O}} \overset{\text{R, alkyl Ar}}{\text{N}} \overset{\text{ArHN}}{\text{N}} \overset{\text{NHCl}}{\text{N}} \overset{\text{Cl}}{\text{CO}_{2}\text{Me}} \overset{2 \text{ eq. NEt}_{3}}{\text{N}} \overset{\text{toluene reflux, 1-2h}}{\text{N}} \overset{9}{\text{R}} \overset{\text{Ar}}{\text{CO}_{2}\text{Me}}
\end{array}
\]
This chapter described the experimental method of synthesis of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4] triazolo [4,3-a] pyrazine hydrochloride. Hydrazine hydrate reacts with ethyl trifluoroacetate to give Trifluoroacetyl hydrazide. It reacts with chloro acetyl chloride to give Trifluoroacetyl acid piperazin-2-ylidene-hydrazide. Take this compound react with phosphorus oxychloride give intramolecular cyclization then added ethylene diamine and then finally treated with Con.Hcl to give 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4] triazolo[4,3-a] pyrazine hydrochloride.

Various Triazole derivatives are reported to possess promising biological activities including antibacterial, antifungal, antiviral and more over some hydrazide, hydrazones\(^2\) and Mannich bases are well known as antibacterial, antifungal and antiviral agents. In view of these findings, it was considered worthwhile to synthesize some triazole derivatives.

4. [E]. MATERIALS:

All the chemicals used in the present study were of A.R.grade Methanol, Hydrazine hydrate, Concentrated HCl, Ethyltrifluoro acetate, Phosphorous oxychloride, acetonitrile, Sodium hydroxide, Toluene, Cyclohexane, Dichloromethane, ethylene diamine, Dioxane, Sodium sulphate [SD’s fine chemical Ltd., Mumbai] were used without further purification.
4. [F].EXPERIMENTAL:

3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride prepared and confirmed by NMR, FT-IR, Mass spectral studies.

- Melting points were taken in one side open capillaries on a Melting point apparatus having model number VMP-D of a make VEERO.
- The Mass spectra of all 48 compounds were recorded on the instrument named LCMS-2010A of make Shimadzu (Oxygen Healthcare Ltd, Ahmadabad, India).
- Carbon, hydrogen and nitrogen were estimated on a Thermo fisher (Thermo electron corporation Limited), Flash Elemental Analyzer-1112.
- The $^1$H NMR and $^{13}$C NMR spectra in deuterated Chloroform-DMSO-MeOD of all novel compounds were recorded on a AVANCE II 300 of make BRUKER spectrophotometer using TMS [(CH$_3$)$_4$Si] as internal standard.
- This series compounds $^1$H NMR, $^{13}$C NMR was recorded on AVANCE II 300 of make BRUKER, IR, Mass are recorded at (Zydus Research Centre, Ahmedabad, India).
- The infrared spectra of the twenty four studied in the present work were recorded on the model FT-IR-PRESTIGE of Shimadzu in KBr (Zydus Research Center, Ahmedabad, India)..
4. [G]. PREPARATION OF 3-TRIFLUOROMETHYL-5,6,7,8-TETRAHYDRO-[1,2,4]TRIAZOLO[4,3-a]PYRAZINE HYDROCHLORIDE:

The 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4] triazolo[4,3-a]pyrazine hydrochloride used in the present study were prepared as follow.

**Reaction Scheme**

1. **NH₂NH₂, H₂O**
   - N₂H₄O
   - Mol. Wt.: 50

2. **CF₃COEt, Acetonitrile 15-20°C**
   - CF₃N₂O
   - Mol. Wt.: 128.05

3. **Cl₂, Acetonitrile NaOH**
   - F₃C
   - Mol. Wt.: 204.54

4. **HCl, Aq HCl**
   - N₂H₆O
   - Mol. Wt.: 50

5. **H₂SO₄, Acetonitrile 10°C**
   - Trifluoro-acetic acid
   - Piperazin-2-ylidene-
     - Hydrazide (d)
   - CF₃
   - Mol. Wt.: 210.16

6. **N₂H₆O, Acetonitrile 10°C**
   - N₂H₆O
   - Mol. Wt.: 50

**Process:**

1. (I) Preparation of Trifluoroacetyl hydrazide:

   1-(2-Nitro-phenyl)-ethanone (0.1 mol) were take in Methanol (50ml) and add tin (II) chloride dihydarte (4 mol) and stir for 30 min at 25-35°C temperature. Then drop wise addition of Con.HCl (10ml) in reaction mass within 20-30min at 25 to 35°C temperature. And heat the reaction mass up to 55-65°C temperature for 6-7 hrs. Stirring continue up to clear and then cool it to 25-35°C and stir for overnight on mechanical stirrer. Then check TLC, it complies. Poured the reaction mass into
crushed ice and stirred it for 30 min, then add 40% sodium hydroxide (30ml) at 25-35°C temperature. Check pH, it’s around 11-12. Then add Dichloromethane (50ml) and stir for 15 min and separate lower organic layer and charge aqueous layer and given another dichloromethane (25ml) and then separate lower organic layer, combine both organic layer and give a water wash (25ml) then separate organic layer. Dried organic layer on sodium sulphate (5gm). Then distill out solvent completely then get oily residue. Add cyclohexana (10ml) and stir for 2-3 hrs at 20-25°C temperature. Product precipitate, then filter the product and was with cyclohexana (5ml). Dry the product at 50-60°C. Recrystalised in Cyclohexane and Isopropyl alcohol to get compound (I).

(II) Preparation of Trifluoroacetyl acid piperazin-2-ylidene-hydrazide:

Process:
Take 1-(2-Amino-phenyl)-ethanone (0.3 mol) in Dioxane (50ml) and cool down the reaction mass up to 5-10°C. Then HCl gas purging in reaction mass for 3-4 hrs below 10°C temperature (0.5 mol). It was used for further step without any isolation and purification.

(III) Preparation of 2-Chloromethyl-5-trifluoromethyl-[1, 3, 4] oxadiazole:

Process:
Take 1-(2-Amino-phenyl)-ethanone Hydrochloride (0.3 mol) and cool down the reaction mass up to 0-5°C temperature. Then slowly drop wise addition of Chloro acetonitrile (0.35 mol) then stir for 3-4 hrs. Then check TLC. It complies. Then added chill water (50 ml) in reaction mass and added sodium hydroxide solution to bring pH 11-12. And stir for 30 min. then added Con HCl (15 ml) in reaction mass to bring pH 4-5 and stir for 30 min. then added Toluene (25 ml) and stir for 15 min and separate the toluene and dried over sodium sulphate. Then distil out completely get oily residue.

(IV) Preparation of Trifluoroacetyl acid piperazin-2-ylidene-hydrazide:

Process:
Charge above 2-Chloromethyl-5-trifluoromethyl-[1,3,4] oxadiazole(0.3mol) and Methanol (40ml) stir the reaction mass at 25-35°C. Then cool down the reaction mass up to 0-5°C temperature. Then add ethylene diamine (0.35mol) in reaction mass
and stir for 5-6 hrs. Then filter it and wash with ethanol (15ml). Dry the product at 50-60°C Purifying in Methanol to obtain pure crystalline Trifluoroacetyl acid piperazin-2-ylidene-hydrazide compound (IV).

(IV) Preparation of Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4] triazolo [4,3-a]pyrazine:

Process:
Charge Methanol (30 ml) in round bottom flask then added Trifluoroacetyl acid piperazin-2-ylidene-hydrazide (0.25 mol) stir the reaction mass for 40-50 min. then added drop wise addition of 35% HCl (25 ml) in reaction mass remove heating and stir the reaction mass up to 15-20°C then stir for 1 hour. then filter the reaction mass and wash with tert-butyl methyl ether to yield corresponding 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4] triazolo[4,3-a] pyrazine hydrochloride.

4.[H]. INTERPRETATION OF 3-TRIFLUOROMETHYL-5,6,7,8-TETRAHYDRO-[1,2,4] TRIAZOLO[4,3-A] PYRAZINE HYDROCHLORIDE BY SPECTROSCOPY:

(1) 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4] triazolo[4,3-a] pyrazine hydrochloride:

- Structural Formula : 

\[ \text{HCl} \cdot \text{HN} \begin{array}{c} \text{N} \\ \text{N} \\ \text{CF}_3 \end{array} \text{N} \]

<table>
<thead>
<tr>
<th>Observed</th>
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<tr>
<td>Color</td>
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</tr>
<tr>
<td>Molecular Formula</td>
<td>C₆H₈ClF₃N₄</td>
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<tr>
<td>Molecular Weight</td>
<td>228.60</td>
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<td>Melting Point</td>
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- **Yield** : 32% - 38%

- **Elemental Analysis** :

<table>
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<th>%H</th>
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<td>24.51</td>
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<tr>
<td>Found</td>
<td>31.25</td>
<td>3.08</td>
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</tbody>
</table>

- **IR Spectra** : Fig. 1.1
  Interpretation from the recorded IR spectrum, the wave numbers of corresponding groups are shown in table given below.

<table>
<thead>
<tr>
<th>Wave number (cm⁻¹)</th>
<th>Assignment</th>
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<tbody>
<tr>
<td>3433.41</td>
<td>N-H stretching of secondary amine</td>
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<tr>
<td>2945.40</td>
<td>C-H stretching of Alkane</td>
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<tr>
<td>1716.70</td>
<td>–C=N Stretching</td>
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<tr>
<td>1180.47</td>
<td>–C-F Stretching</td>
</tr>
<tr>
<td>1024.24</td>
<td>–C-N Stretching of amine</td>
</tr>
</tbody>
</table>

- **Mass Spectral data** : Fig. 1.2
  The Positive ion mass spectral analysis of A1 observes at 192.8 m/z (M⁺), Confirms the theoretical molecular weight i.e. 192.1

- **¹H NMR Spectra** : Fig. 1.3
  **Interpretation:** From the recorded ¹H-NMR spectrum, chemical shifts and the multiplicity of the corresponding protons are shown in table given below.

<table>
<thead>
<tr>
<th>Chemical Shift (δ value in ppm)</th>
<th>Multiplicity</th>
<th>Assigned Proton</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.63-3.67</td>
<td>Triplet</td>
<td>(1)</td>
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</table>
### 13C NMR Spectra: Fig. 1.4

**Interpretation:** From the recorded $^{13}$C-NMR spectrum, chemical shifts and the multiplicity of the corresponding protons are shown in table given below.

<table>
<thead>
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<th>Chemical Shift (δ value in ppm)</th>
<th>Nature of Carbon</th>
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<tr>
<td>38.87</td>
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<tr>
<td>40.13</td>
<td>Secondary</td>
<td>(2)</td>
</tr>
<tr>
<td>40.62</td>
<td>Secondary</td>
<td>(3)</td>
</tr>
<tr>
<td>119.02</td>
<td>Quaternary</td>
<td>(4)</td>
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<tr>
<td>142.39</td>
<td>Quaternary</td>
<td>(5)</td>
</tr>
<tr>
<td>148.48</td>
<td>Quaternary</td>
<td>(6)</td>
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</tbody>
</table>
Fig. 1.1
Fig. 1.3
Chapter 4

4.1 Preparation of substituted 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine derivatives (General Reaction Scheme)

Where

R= Different aliphatic and aromatic acid substituent.

TBTU=2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

DIPEA=N,N-Diisopropyl ethyl amine.

DMF=N,N-Dimethyl formamide.

(1) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-dodecan-1-one (DJP/D156):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and Dodecanoic acid (0.01 mol) in 20 ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then dried over sodium sulphate. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D156) and dry the material at 50-55°C.

Colour: Pale yellow, M.F: C_{18}H_{29}F_{3}N_{4}O, M.W: 374.44, MP: 252-255° C, Yield: 62%
(2) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-nonan-1-one (DJP/D157):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and Nonanoic acid (0.01 mol) in 20 ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20 min. then drop wise addition of DIPEA (0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80 ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25 ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then dried over sodium sulphate. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D157) and dry the material at 50-55°C.

Colour: Pale yellow, M.F: C_{15}H_{23}F_{3}N_{4}O, M.W: 332.36, MP: 241-244°C, Yield: 53%

(3) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-pentane-1,4-dione (DJP/D158):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and 4-Oxo pentanoic acid (0.01 mol) in 20 ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20 min. then drop wise addition of DIPEA (0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80 ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25 ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then dried over sodium sulphate. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C
temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D158) and dry the material at 50-55°C.

Colour: Pale yellow, M.F: C_{11}H_{13}F_{3}N_{4}O_{2}, M.W: 290.24, MP: 70-75°C, Yield: 32%

(4) Preparation of 2-Bromo-3-Methyl-1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-butan-1-one (DJP/D159):

Process:
A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and 2-Bromo-3-Methyl butyric acid (0.01 mol) in 20 ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then dried over sodium sulphate. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D159) and dry the material at 50-55°C.

Colour: Pale yellow, M.F: C_{11}H_{14}BrF_{3}N_{4}O, M.W: 355.15, MP: 110-114°C, Yield: 55%

(5) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazine-7-yl)-2-(2,4,5-trifluoro phenyl)ethanone (DJP/D160):

Process:
A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and Trifluoro phenyl acetic acid (0.01 mol) in 20ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-
Chapter 4

20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then dried over sodium sulphate. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D160) and dry the material at 50-55°C.

Colour: yellow, M.F: C_{19}H_{10}F_{6}N_{4}O, M.W: 364.25, MP: 265-269°C, Yield: 58%

(6) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4] triazolo [4,3-a]pyrazine-7-yl)-butan-1-one (DJP/D161):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a] pyrazine hydrochloride (0.01 mol) and 4-Methyl pentanoic acid (0.01 mol) in 20ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D161) and dry the material at 50-55°C.

Colour: yellow, M.F: C_{12}H_{17}F_{3}N_{4}O, M.W: 290.28, MP: 55-59°C, Yield: 43%

(7) Preparation of 2-Phenyl-1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4] triazolo [4,3-a]pyrazine-7-yl)-ethanone (DJP/D162):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a] pyrazine hydrochloride (0.01 mol) and Phenyl acetic acid (0.01 mol) in 20ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then
Chapter 4

charge 2-((1H-benzo[1,3]thiadiazole-1-y1)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D162) and dry the material at 50-55°C.

Colour: Yellow, M.F: C_{14}H_{13}F_{3}N_{4}O, M.W: 310.27, MP: 178-181°C, Yield: 67%

(8) Preparation of 2-Chloro-1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4] triazolo [4,3-a]pyrazine-7-yl)-ethanone (DJP/D163):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a] pyrazine hydrochloride (0.01 mol) and Chloro acetic acid (0.01 mol) in 20ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-((1H-benzo[1,3]thiadiazole-1-y1)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D163) and dry the material at 50-55°C.

Colour: Pale yellow, M.F: C_{8}H_{8}ClF_{3}N_{4}O, M.W: 268.62, MP: 44-48°C, Yield: 71%

(9) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4] triazolo [4,3-a] pyrazine-7-yl)-pentan-1-one (DJP/D164):
Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and Pentanoic acid (0.01 mol) in 20ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20 min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D164) and dry the material at 50-55°C.

Colour: Yellow, M.F: C_{11}H_{15}F_{3}N_{4}O, M.W: 276.26, MP: 75-79°C, Yield: 64%

(10) Preparation of 1-(3-Trifluoromethyl-5,6-dihydro-8H-[1,2,4] triazolo [4,3-a] pyrazine-7-yl)-propan-1-one (DJP/D165):

Process:

A mixture of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride (0.01 mol) and Propionic acid (0.01 mol) in 20ml of N,N-Dimethyl formamide and Cool the reaction mass up to 10-15°C temperature. Then charge 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (0.015 mol) and stir the reaction mass for 15-20 min. then drop wise addition of DIPEA(0.03 mol) in reaction mass at 10-15°C temperature. Stir the reaction mass for 3-4 hrs. Then add water (80ml) and stir the reaction mass for 15-20 min. then add dichloromethane (25ml) and stir it. Then separate the lower organic layer, and then give 20% sodium carbonate wash of organic layer. Then distil out completely to get crude residue. This crude product was charge in round bottom flask and charges 10ml Isopropyl alcohol (IPA) and heat the reaction mass up to 45-50°C temperature. Then cool the reaction mass up to 10-15°C temperature. Then stir for 30-40 min. then filter the solid product and wash with 5 ml IPA to get (DJP/D165) and dry the material at 50-55°C.

Colour: Yellow, M.F: C_{9}H_{11}F_{3}N_{4}O, M.W: 248.21, MP: 40-43°C, Yield: 74%
4.[J] Table: Physical property of 3-Trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine derivatives (DJP/D156 to DJP/D165):

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
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<th>M.F</th>
<th>M.W</th>
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<td>DJP/D157</td>
<td>CH₃(CH₂)₇</td>
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<td>C₁₅H₂₃F₃N₄O</td>
<td>332.36</td>
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<td>C₁₁H₁₃F₃N₄O₂</td>
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REFERENCES:


36. Xian-Qing Deng , Cheng-Xi Wei, Fu-Nan Li, Zhi-Gang Sun ,Zhe-Shan Quan:. European Journal of Medicinal Chemistry 2010; 45: 3080-3086
44. Xiaoyun Chai, Jun Zhang, Honggang Hu, Shichong Yu, Qingyan Sun, Zhigang Dan, Yuanying Jiang, Qiuye Wu. European Journal of Medicinal Chemistry 2009; 24:1913–1920.

