CHAPTER 3

Novel Polyfluorinated Pyrazoles: Synthesis And Attachment Of Amino Acids As Well As N-Aryl Acetamide Linkers And Evaluation Of Antimicrobial Activity

3.1 INTRODUCTION

Pyrazoles have been widely described as pharmaceutical therapeutic agents, including anti-inflammatory and anti-diabetic agents. Formation of halogenated 1-arylbutane-1,3-diones has been described [1-3]. In addition the preparation of pyrazoles by the condensation of diketones and hydrazines has also reported [4-6]. Poly and perfluoroalkyl derivatives of aromatic and heteroaromatic compounds are intensively studied [7-11]. The 1,3,5-trisubstituted pyrazole structural motif is found in numerous drug targets. A common approach into these systems including commercial process is to react substituted hydrazine with diketone [12]. The π-excessive five membered nitrogen heterocycles such as pyrazole, have been extensively used in transition metal chemistry because pyrazoles are poorer π-acceptor and behaves as π-donor sites [13-14]. Pyrazole derivatives posses anti-inflammatory and antitumor activity. Pyrazoles also are of particular interest to the chemical community because they exhibit pesticide properties and increasing interest on biological model system containing pyrazole chelates [15-28]. The synthesis of pyrazoles remains of great interest due to the wide application of such heterocycles in the pharmaceutical and agrochemical industry. The most important methods for preparing this

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A class of heterocycles are of reaction between hydrazines with β-difunctional compounds [29-32]. The Polyfluoro 1,3-diketones function as metal chelating agents and have been shown to act as hydrogen ionophores, disrupting intercellular pH gradients. This results in an uncoupling of mitochondrial oxidative phosphorylation, thus disrupting energy production. Various members of this class of compounds have been shown to exhibit antibacterial, antiviral, antihelmintic, fungicide and/or herbicidal activity [33-45].

**Literature update for polyfuorinated pyrazoles:**

1. **Synthesis of pyrazoles and their derivatives from β-enaminoketones and substituted hydrazines:**

   a) A new simple and effective route for various pyrazoles from β-enaminoketones with N-substituted hydrazines were well demonstrated by Touzot A and Coworkers [46].

   ![Chemical Structure](image)

   They observed effect of the substituent during condensation and found that depending on the N-substituent on hydrazine 1a-c single pyrazole 4a or mixture of pyrazoles 3/4b-c were obtained.
b) Liu, N. et al demonstrated that the formation of 3-trifluoromethyl-4-pyrazole carboxylate 6 proceeds regioselectively with only one isomer in 82% yield. The starting enamino ketone 5

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{F}_3\text{C} \\
\text{CH}_3\text{NHNH}_2 & \quad \text{CH}_3\text{NHNH}_2 \\
\text{EtOH} & \quad \text{EtOH}
\end{align*}
\]

was prepared from ethyl trifluoroacetate and dimethylformamide-dimethyl acetal [47].

c) The reactivity of the enamino ketone 7 was studied by Pashkevich, K. I and Coworkers [48] with hydrazine hydrate which gave 52% pyrazole product 8 whereas reaction with phenyl hydrazine produced mixture of 3,5-dihydropyrazole 10 and pyrazole 9 in 26% and 17% respectively.

d) Singh, S. P. and Kumar D. [49] carried out the reactions of various N-substituted hydrazines with $\beta$-ethoxy-trifluoromethyl-enone 11 containing an acetyl group in the $\alpha$-position which showed that the heterocyclisation is directed to the acetyl group 12 for
aryl substituted hydrazine and to the trifluoroacetyl carbonyl 13 for N-methyl hydrazine to furnish the corresponding pyrazoles in moderate yield.

e) For the synthesis of aminopyrazoles 17, The O,N-acetal-aminals of trifluoromethyl ketene is utilized by Martin M.A.P. and coworkers [50]. The trifluoromethyl ketene is obtained from corresponding diethoxy enone 14 in 54-98% yield. The target trifluoromethyl containing pyrazoles were prepared in 58-86% yield by reaction with various hydrazines.
f) Martin M.A.P. and coworkers synthesised various N,N'-dimethyl pyrazolium salts 19 from the enone containing trifluoromethyl group with N,N'-dimethyl hydrazine·2HCl. The furnished compounds are very attractive because of having very high herbicidal activity [51].

\[
\begin{align*}
R' & \quad \text{MeNHNHMe. 2HCl} \\
\text{EtOH, H }^+ , 20^\circ \text{C, 5 Hr} & \quad \rightarrow \\
\text{RO} & \quad \text{MeNHNHMe. 2HCl} \\
\text{CF}_3 & \quad \text{EtOH, H }^+ , 20^\circ \text{C, 5 Hr} \\
\end{align*}
\]

18

19

18

19

\[ R' \quad \text{MeNHNHMe. 2HCl} \]

\[ \text{EtOH, H }^+ , 20^\circ \text{C, 5 Hr} \]

\[ \text{RO} \quad \text{MeNHNHMe. 2HCl} \]

\[ \text{CF}_3 \quad \text{EtOH, H }^+ , 20^\circ \text{C, 5 Hr} \]


g) Levskovskaya, G. et al. [52] obtained 5-halo-3-trifluoromethyl pyrazole 21 which could be accessed from β,β-dihalogen substituted trifluoromethyl ketones 20 and N,N'-disubstituted hydrazine in 45-70% yield. Similarly Bozhenkov et al utilized monosubstituted hydrazine and furnished the pyrazoles in 75-88% yield [53].

\[ \begin{align*}
\text{Hal} & \quad \text{O} \\
\text{CF}_3 & \quad \text{Hal} \\
\end{align*} \]

\[ \begin{align*}
\text{RNHNH}_2 & \quad \text{Or H}_2\text{N-NR}_2 \\
\text{Hal} = \text{Chloro(75%)} & \quad \text{Hal} = \text{Bromo(88%)} \\
\end{align*} \]

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h) Another study conducted by Flores A.F. et. al. regarding the reaction of phenyl hydrazine with β-ethoxy trifluoromethyl enones showed that a short reaction time and lower temperature with pure phenyl hydrazine furnished dihydropyrazole 23 whereas
reaction at elevated temperature or using the hydrochloride salt of phenyl hydrazine gave pyrazoles 24 and 25 in 80-82% yield [54].

2) Synthesis of pyrazole from trifluoroacetyl pyrroline:

The new synthesis of pyrazoles well demonstrated by Kawase, M and coworkers [55]. The starting enaminoketone 27 obtained by acetylation of N-substituted proline 26 with TFAA. It was found that this compound is a new 1,3-ambidentate electrophile reacting with bifunctional N-nucleophiles such as hydrazine and amidines to give trifluoromethyl substituted pyrazoles 28,29 containing side chain with β-amino ethyl moiety.
Heterocycles bearing both amino ethyl side chain and the trifluoromethyl appendage is a very attractive method of transformation via ring-chain transfer mechanism.

3) Synthesis of pyrazoles from ketene dithioactals at β-position of trifluoromethyl enone:

Reaction of trifluoromethyl enones 30 containing a dithioacetal fragment in the β-position with various bifunctional nucleophiles like hydrazine are investigated for pyrazole formation by Mellor, J. M. et al [56]. By this method, pyrazoles 32 containing a 1,3-dithiopropyl substituent were prepared.
4) Synthesis of pyrazole from acetylenic trifluoromethyl ketone:

*Lantzsch, R. and coworkers* [57] developed another method for the preparation of trifluoromethyl containing pyrazole 34 by reacting acetylenic trifluoromethyl ketone 33 with hydrazine in toluene at reflux temperature. Similarly *Reddy, M. and Bell, S.* utilized aryl substituted hydrazine 36 in ethanol at reflux temperature to obtain the pyrazole 37 having the aryl sulfone or sulfonamide moiety [58-59].
5) The work reported by Nenajdenko, V. G. et al [60] is devoted to [2+3]-dipolar cycloaddition of various diazo-compounds 39 to α, β-unsaturated trifluromethyl ketones 38. The ketones react with diazoalkanes forming pyrazolines with 100% regioselectivity and with high stereo selectivity.
6) Seigo Ishibuchi et al [61] synthesized a series of 1-phenyl pyrazoles and evaluated for inhibitory activity against Xanthine Oxidase (XO) in vitro. Among all the compounds the 1-(3-cyano-4-neopentyloxyphenyl) pyrazole-4-carboxylic acid had the potent enzyme inhibition and displayed longer lasting hypouricemic action than allopurinol in a rat model of hyperuricemia induced by the uricase inhibitor potassium oxonate.

\[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{NC} \quad \text{O} \quad \text{EtO} \\
\text{EtO} & \quad \text{42} \quad \text{43} \\
\text{HO} & \quad \text{AlCl}_3 \quad \text{ClCH}_2\text{CH}_2\text{Cl} \\
\text{45} & \quad \text{44} \\
\text{HO} & \quad \text{HNO}_3, \text{AcOH} \\
\text{O}_2\text{N} & \quad \text{R-X, K}_2\text{CO}_3 \quad \text{1N NaOH} \quad \text{EtOH} \\
\text{46} & \quad \text{47}
\end{align*}
\]

7) Lynette M. Oh [62] developed totally new synthesis of Celecoxib a widely used COX-2 inhibitor via 1,3-dipolar cycloaddition reaction between a nitrile imine and an enamine. The nitrile imines are generated in situ from the corresponding hydrazonoyl benzene sulfonates.
8) The utilization of pyrazole containing chelating ligands in co-ordination chemistry encounters problem of low solubility of ligands and complexes in organic solvents due to $\pi-\pi$ stacking interactions. The incorporation of alkyl group at N-1 position of pyrazole, the solubility can be increased. Recently three interesting reviews on biological model systems containing pyrazole chelates have been published [63-65]. The computational study of the alkylation of 3,5-pyrazole is done theoretically by Josefina and coworkers [66] and correlated with the experimental results. They found that presence of pyridyl group directs the regioselectivity of pyrazole formation by forming initial Na$^+$ chelates. The synthetic path involves an intermolecular nucleophilic reaction ($SN^2$) at a carbon center of alkyl
halide. The ratio of regioisomers has been calculated through $^1H$ NMR experiments, especially from the integration of the pyrazolic proton.

9) Waldrep, T. W. and Coworkers [67] prepared a series of 1-aryl-5-halo and 1-aryl-5-trifluoromethyl -1H-pyrazole-4-carboxamides exhibit moderate to strong herbicidal activity in preemergence and post mergerence tests. They examined the SAR of different substituents towards the activity.

10) MAP Martins [68] synthesized regiospecifically polyfluorinated heterocycles from the reaction of 1,1,1-trfluoro-4,4-diethoxy-3-buten-2-one and 1,1,1,2,2-pentafluoro-4,4-diethoxy-3-penten-2-one with different dinucleophiles like hydrazine, methyl hydrazine, hydroxylamine and sodium cyanide in moderate to good yield under mild conditions.

11) Jimenez-Cruz F and coworkers [69] synthesized novel monohydrated 3-p-niophenyl pyrazole derived from 1,3-diketone malonate. The molecular structure has been studied by using NMR, single crystal X-ray diffraction and ab initio calculations.
The results of the structural investigation of the monohydrated pyrazole with the particular N-H...OH$_2$ hydrogen bond is reported. The hydration is preferentially occurred with 3-tautomer over the 5-tautomer [69].

In this chapter we have used polyfluoro 1,3-diketone as bifunctional compound which is condensed with hydrazine/substituted hydrazines to furnish pyrazoles having substitution at 1,3,5-position. The regioselectivity of pyrazole formation either in the condensation reaction or during the N-alkylation of pyrazole formed is studied.
3.2 PRESENT WORK

The plan for the synthesis of polyfluorinated pyrazole derivatives is presented in the following scheme. The N-aminoacid ester linked pyrazole derivatives 82 could be prepared by multistep reaction with pyrazole 72. Similarly N-linked N-arylacetamide derivatives 77 could be accessed by reaction of pyrazole 72 with 2-bromo arylacetamides under basic condition. The isomeric pyrazoles 74 and 75 could result from diketone 71 on condensation with monosubstituted hydrazines whereas the open chain hydrazones 74 are possible when diketone is reacted with acylhydrazides under acidic condition.
The claisen condensation of 3,5-bis trifluoromethyl acetophenone 69 with ethyl trifluoroacetate 70 would lead to the formation of diketone 71.

### 3.3 RESULTS AND DISCUSSION

There are many methods as described in the introduction part to prepare the pyrazole ring, the condensation of the 1,3-dicarbonyl compounds with hydrazines and its variations remains the most common and an efficient method to construct these five membered heterocyclic system i.e. Knorr pyrazole synthesis. The brief discussion of which is given below.

The Knorr pyrazole synthesis is the reaction of hydrazine or substituted hydrazines with 1,3-dicarbonyl compounds to furnish five membered ring system containing two heteroatoms [70-73]. Knorr introduced the name pyrazole for these compounds to denote that the nucleus was derived from the pyrrole by replacement of a carbon with nitrogen [74].

The mechanism of Knorr reaction has been studied by many researchers using low temperature NMR methods [75-78]. Salivanov and coworkers studied the formation of pyrazole ring system using low temperature flow NMR and found that it proceeds through complex combination of consecutive reactions with at least three transient intermediates at $-70^\circ\text{C}$ [78]. In case of unsymmetrical 1,3-diketones the 3,5-dihydroxypyrazolidine and hydrazone intermediates have been isolated in some cases [79].

The regioisomers of pyrazole formation depends on enolisation of dione. Recently Singh et. al summarized the mechanism of pyrazole formation via Knorr reaction between 1,1,1-trifluoropentane-2,4-dione with monosubstituted hydrazines [80]. The study of $^{19}\text{F}$ NMR
showed greater enolization of trifluoromethyl ketone versus the methyl ketone. Thus free \( \text{NH}_2 \) of hydrazine reacts with ketone rather than enol as revealed by NMR studies and have shown that the carbonyl group reacts faster than enol form [76-78, 81-83].

The rates of dehydration of 3,5-dihydroxy pyrazolidine intermediates of the two isomers of unsymmetrical diketone decides the product distribution ratio. The computational studies were done to show the affect of hydrazine substituent on the dehydration in conjunction with the semi-empirical calculations [80].

In case of unsymmetrical diketone, definitely there is potential of producing regioisomers as well as the effect of hydrazine substituent on the rate of dehydration. Many efforts have been done and reported in literature to mitigate the difficulty to isolate the single pure regioisomer by enhancing the selectivity of product formation. The methods like masking of either counterpart i.e. hydrazine or diketone and made available in situ during the course of reaction by releasing from the masked derivative directs the Knorr pyrazole synthesis to the formation of major product. Another method which enhance the selectivity is the green
solvent less process of getting the pyrazole derivative by mixing the equimolar amounts of
1,3-dicarboxyl compound with the hydrazine with a drop of sulfuric acid [84].

Although these methods increased the selectivity of product formation up to 85-95 %, still
could not guarantee to furnish either regioisomer as a single exclusive product.
The increasing demand of many pharmaceutical active ingredients, dyes, chelates insists on
single exclusive regioisomer because of the total bioactivity that resides in a required
isomer and another may have toxicity. Hence there is need to optimize the parameters
which may vary with the substrates are like water associated with them, solvent of the
reaction, the strength of acid responsible for the dehydration step as well as competitive
reactivities of the diketone carbonyls and the secondary and primary amino group of the
hydrazine counterpart. We have tried to investigate these parameters in detail in our
product as discussed below.

**Synthesis of 1-(3, 5-bis(trifluoromethyl)phenyl)-4,4,4-trifluorobutane-1,3-dione 71**

The starting material unsymmetrical 1,3-diketone bearing trifluoromethyl substituents was
prepared from 3,5-bis trifluoromethyl acetophenone upon Claisen condensation with ethyl
trifluoroacetate using sodium methoxide as base in a methyl tert-butyl ether. Thus, 3,5-bis
trifluoromethyl acetophenone was dissolved in tert-butyl methyl ether and treated with
ethyl trifluoroacetate at room temperature for 14 hrs. Acidification to pH 4-5 with 4N HCl,
extraction of the compound in tert-butyl methyl ether and evaporation of the solvent
produced oil which was purified by column chromatography eluting with dichloromethane.
The pure fractions were collected and evaporated under reduced pressure to obtain light
yellow oil in 89.4% yield (Experiment No.1, page No. 173). The oil was characterized by
spectral and analytical methods. The IR spectrum of this oil showed presence of two broad
bands at 1823 and 1745 cm\(^{-1}\) corresponding to the carbonyls of aryl and trifluoromethyl substituted ketones. The broad bands at 3345 cm\(^{-1}\) indicates that enol form was also present in this compound. The \(^1\)H NMR(Spectrum No-1) showed tautomeric signals at 8.63\(\delta\) and 8.42 \(\delta\) ppm in the downfield region for aromatic protons. It was interesting to note that the compound showed sharp singlet at 7.23 \(\delta\) ppm for olefinic proton (in case of enolised form) and singlet at 2.70 \(\delta\) ppm for methylene protons which was flanked by two carbonyls indicated that compound exist in keto-enol form. The structure was also supported by \(^{13}\)C NMR (Spectrum No-2) which showed two signals in the downfield at 196 \(\delta\) 194 \(\delta\) and 182 \(\delta\) ppm for two carbonyl carbons and one for its tautomer. The signals for quaternary carbons, methylene carbons and CH carbons were identified by DEPT experiment(Spectrum No-3). The compound showed signal at 94.6 \(\delta\) ppm for CH carbon of the enol form whereas the reverse signal for CH\(_2\) group appeared at 53.1 \(\delta\) ppm indicates the presence of keto form. The mass spectral analysis showed molecular ion peak at [M]\(^{+}\)352. The elemental analysis was in well agreement with the molecular formula \(\text{C}_{12}\text{H}_{5}\text{F}_{9}\text{O}_{2}\). Based on the above structural investigation the assignment was done to structure 71 as 1-(3,5-bis(trifluoromethyl)phenyl)-4,4,4-trifluorobutane-1,3-dione.
**Scheme 1**

3,5-Bis-Trifluoromethyl Acetophenone

\[ \text{NaOMe, methyl tert-butyl ether} \]

\[ \begin{align*}
   \text{F}_3\text{C} & \quad \text{O} \\
   \text{CF}_3 & \quad \text{CH}_3 \\
   \text{69} &
\end{align*} \]

\[ \begin{align*}
   \text{F}_3\text{C} & \quad \text{O} \\
   \text{F}_3 & \quad \text{C} \\
   \text{70} &
\end{align*} \]

\[ \text{71} \]

\[ \begin{align*}
   \text{F}_3\text{C} & \quad \text{O} \\
   \text{CF}_3 & \quad \text{CH}_3 \\
   \text{71} &
\end{align*} \]

\[ \text{NH}_2\text{-NH}_2\text{H}_2\text{O} \quad \text{Ethanol, AcOH} \]

\[ \begin{align*}
   \text{F}_3\text{C} & \quad \text{O} \\
   \text{CF}_3 & \quad \text{NH}_2\text{-NH}_2\text{H}_2\text{O} \\
   \text{72} &
\end{align*} \]

**Spectrum No. 3:** $^1\text{H}$ NMR Spectrum of $1-(3,5$-bis(trifluoromethyl)phenyl)-4,4,4-trifluorobutane-1,3-dione 71 in DMSO-$d_6$
Spectrum No. 1: $^{13}$C NMR Spectrum of Spectrum of 1-(3, 5-bis(trifluoromethyl)phenyl)-4,4,4-trifluorobutane-1,3-dione 71 in DMSO-$d_6$
Synthesis of 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole 72

The analytically confirmed 1,3-diketone 71 having two electrophilic centers was reacted with bidentate nucleophiles like hydrazine hydrate or substituted hydrazines to construct a electron rich five membered heterocycles. Thus, compound 71 was reacted with hydrazine hydrate in ethanol in presence of catalytic amount of acetic acid at reflux temperature for 20 hrs. The residue obtained after evaporation of the solvent was purified by column chromatography eluting with dichloromethane. The pure fractions were collected and evaporated under reduced pressure to furnish colorless needles in 92% yield (Experiment No.2, Page No.174). The obtained needles were characterized by spectral and analytical methods.
Spectrum No. 4: $^1$H NMR Spectrum of 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole 72 in DMSO-d$_6$

Spectrum No. 5: $^{13}$C NMR Spectrum of 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole 72 in DMSO-d$_6$
The IR spectrum showed weak signal for C-H (pyrazole proton) at 3272 cm\(^{-1}\) and another very strong signal at 1566 cm\(^{-1}\) for C=N of the pyrazole ring. The very strong signal for C-F at 1376 cm\(^{-1}\) and disappearance of two carbonyl frequencies clearly indicates that heterocyclisation was occurred. Further absence of broad signal at around 3300-3200 cm\(^{-1}\) for O-H indicates the complete dehydration leading to the formation of pyrazole ring. The \(^1\)H NMR (Spectrum No-4) showed signals at 8.526 ppm for two protons and at 8.085 ppm for one protons from the 3,5-bis trifluoromethyl phenyl ring. The presence of signal at 7.608 ppm for one proton correspond to the pyrazolic proton. The broad and flat signal at 12.62 δ ppm disappeared on D\(_2\)O exchange indicated the presence of replaceable proton attached to pyrazolic nitrogen. The \(^13\)C NMR (Spectrum No-4) showed absence of signals for two carbonyl carbons and presence of signal at 103.2 δ ppm for pyrazole carbon indicates the formation of pyrazole ring. The two signals as quartet at 131.5 and 121.8 δ ppm with two bond coupling constant for the carbons bearing the CF\(_3\) group of \(^2J_{\text{CF}} = 33.7 \text{ and } 36 \text{ Hz}\) indicates the presence of trifluoromethyl substituent on aryl as well as on pyrazole ring. The rest of the six signals corresponded to aromatic carbons appeared in between 141.5 δ and 123.2 δ ppm. The mass spectral analysis showed molecular ion peak at 348[M]\(^{+}\) and elemental analysis was in well agreement with the molecular formula C\(_{12}\)H\(_{5}\)F\(_9\)N\(_2\). On the basis of above spectral analytical data the structure was assigned to the compound 72 i.e. 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole.

**Synthesis of N-substituted pyrazoles 74 and 75 ; Study of regioisomer formation:**

We extended this methodology to a series of substituted pyrazoles using monosubstituted hydrazines 73a-g. Thus, solution of 71 in ethanol was treated with 73a in presence of catalytic amount of acetic acid at reflux temperature for 20 hrs. As revealed by TLC two
products formed in this reaction were separated by column chromatography eluting with dichloromethane. The pure fractions were collected and evaporated completely to obtain two compounds as major and minor derivatives in 80% and 6.4% yield respectively (Experiment No.3, Page No.175). The major and minor compounds were characterised by spectral and analytical methods.

Scheme 2

Spectrum No. 6: $^1$H NMR Spectrum of 2-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-N-methyl ethane sulfonamide 74a in DMSO-d$_6$
Spectrum No. 7: $^{13}$C NMR Spectrum of 2-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)phenyl)-N-methyl ethane sulfonamide 74a in DMSO-$d_6$

Spectrum No. 8: $^1$H NMR Spectrum of 2-(4-(3-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1yl)phenyl)-N-methyl ethane sulfonamide 75a in DMSO-$d_6$
The IR spectrum of major compound showed weak signal for C-H (pyrazole proton) at 3263 cm\(^{-1}\) and another very strong signal at 1571 cm\(^{-1}\) for C=N of the pyrazole ring. The very strong signal for C-F at 1367 cm\(^{-1}\) and disappearance of two carbonyl frequencies and absence of broad signal at around 3300-3200 cm\(^{-1}\) for O-H clearly indicates the complete dehydration during heterocyclisation leading to the formation of pyrazole ring. The \(^1\)H NMR (Spectrum No.6, page No. 150) showed quartet at 7.03 δ ppm \(J = 6.0\) Hz for NH of the methyl sulfonamide whereas signals at 8.128 ppm for two protons and at 7.89 δ ppm for one proton from the 3,5-bis trifluoromethyl phenyl ring. The presence of signal at 7.55 δ ppm for one proton correspond to the pyrazolic proton. The two doublets at 7.4 δ and 7.35 δ ppm with \(J = 9.0\) Hz represents the para disubstituted pattern of phenyl ring. Two triplates at 3.24 δ and 3.02 δ ppm \(J = 6.0\) Hz corresponded to two CH\(_2\) group and the doublet at 2.6 δ ppm \(J = 6.0\) Hz for three protons represent the presence of methyl group attached to nitrogen. The \(^13\)C NMR (Spectrum No.7, page No. 151) showed absence of signals for two carbonyl carbons and presence of signal at 106.9 δ ppm for pyrazole carbon indicates the formation of pyrazole ring. The two signals as quartet at 130.5 and 122.4 δ ppm with two bond coupling constant for the carbons bearing the CF\(_3\) group of 21.0 and 40.0 Hz indicates the presence of trifluoromethyl substituent on aryl as well as on pyrazole ring. The rest of the signals corresponded to aromatic carbons appeared between 141.7 δ and 117.4 δ ppm. In the upfield region three distinct signal were observed at 50.2 δ, 28.8 δ and 28.6 δ ppm for two methylene carbon and one methyl carbon. The mass spectral analysis showed molecular ion peak at 545[M]\(^+\) and elemental analysis is in well agreement with the molecular formula C\(_{21}\)H\(_{16}\)F\(_6\)N\(_3\)O\(_2\)S. On the basis of above spectral analytical data the structure was assigned to the compound 74a i.e.2-(4-(5-(3,5-
bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)phenyl)-N-methyl ethane sulfonamide. Similarly, the minor compound was characterized by spectral and analytical methods. The IR spectrum of minor compound showed weak signal for C-H (pyrazole proton) at 3276 cm\(^{-1}\) and another very strong signal at 1549 cm\(^{-1}\) for C-N of the pyrazole ring. The very strong signal for C-F at 1389 cm\(^{-1}\) and disappearance of two carbonyl frequencies and absence of broad signal at around 3300-3200 cm\(^{-1}\) for O-H clearly indicates the complete dehydration during heterocyclisation leading to the formation of pyrazole ring. The \(^1\)H NMR (Spectrum No.8, page No. 151) showed quartet at 7.03 \(\delta\) ppm \(J = 6.0\) Hz for NH of the methyl sulfonamide whereas signals at 8.55 \(\delta\) ppm for two protons and at 8.12 \(\delta\) ppm for one proton from the 3,5-bis trifluoromethyl phenyl ring. The presence of signal at 8.08 \(\delta\) ppm for one proton correspond to the pyrazolic proton. Instead of the two doublets at 7.4 \(\delta\) and 7.35 \(\delta\) ppm with \(J = 9.0\) Hz represents the para disubstituted pattern of phenyl ring the singlet at 7.53 \(\delta\) ppm was observed. Two triplets at 3.34 \(\delta\) and 3.07 \(\delta\) ppm \(J = 6.0\) Hz corresponded to two CH\(_2\) group and the doublet at 2.62 \(\delta\) ppm \(J = 6.0\) Hz for three protons represent the presence of methyl group attached to nitrogen were clearly seen. The \(^{13}\)C NMR showed absence of signals for two carbonyl carbons and presence of signal at 107.2 \(\delta\) ppm for pyrazole carbon indicates the formation of pyrazole ring. The two signals as quartet at 132.8 and 123.8 \(\delta\) ppm with two bond coupling constant for the carbons bearing the CF\(_3\) group of 21.0 and 40.0 Hz indicates the presence of trifluoromethyl substituent on aryl as well as on pyrazole ring. The rest of the signals corresponded to aromatic carbons appeared between 142.7 \(\delta\) and 118.2 \(\delta\) ppm. In the upfield region three distinct signal were observed at 51.4 \(\delta\), 27.5 \(\delta\) and 25.9 \(\delta\) ppm for two methylene carbon and one methyl carbon. The mass spectral analysis showed molecular
ion peak at $545[M]^+$ and elemental analysis is in well agreement with the molecular formula $C_{21}H_{16}F_9N_3O_2S$. On the basis of above spectral analytical data the structure was assigned to the compound 75a i.e.2-(4-(3-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1yl)phenyl)-N-methyl ethane sulfonamide.

Analoguously compound 71 was reacted with 73b-g and the obtained pyrazole derivatives were characterised by spectral and analytical methods. The data of which is given in the experimental section (Experiment No.3, page No. 175). It was observed that reacton of 73b produced two compounds in 76.6 % and 8% yield respectively. However, only single major products 74c-g were obtained from the reactions of 71 with 73c-g.

The condensation of 71 with substituted hydrazides 73h-i in a analogous way produced the compounds as uncyclised derivatives (Scheme 3). The structures of these compounds were deduced from spectral and analytical methods which is given in the experimental section (Experiment No.4, Page No.175).

![Scheme 3](image)

Following Substituted hydrazines 73a-i were used for the formation of pyrazole 74 and 75:
It is known from the literature that regioisomer formation lies in the reactivity of the carbonyls of asymmetrical diketone and the nucleophilicity of the two nitrogens of hydrazine. It is obvious to note that in compound 71 the carbonyl bearing the more electronegative trifluoromethyl group is more reactive or the carbonyl bearing aryl substituent having two trifluoromethyl groups meta to the reaction centre i.e. the enolisation in cross conjugation with the aryl ring. In case of hydrazines the presence of substituent plays important role to decide the reactivity of two nitrogens. We have used aryl substituted hydrazines and hence due to the electron withdrawing nature of phenyl ring the primary NH$_2$ nitrogen is more reactive than the secondary NH nitrogen. Under these circumstances the formation of 74a or 74b is kinetically favored over the regioisomers 75a or 75b. Other factors for the formation of regioisomers could be due to the presence of water associated with either hydrazine or diketone and secondly may be due to the strength
of acid used as well as the solvent used in the reaction. Hence we carried out the reactions of 71 with substituted hydrazine 73a in various conditions to understand the regioselectivity of pyrazole formation of 74a and 75a. Without being bound by any particular theory and based on evidence to date, it appears that the diketone can potentially exist in three different tautomeric species, designated below as 76a, 76b and 76c. It further appears that water reacts with one of the carbons containing an oxygen group (carbonyl or hydroxyl) of the species 76a, 76b or 76c depicted below to form diketone hydrate species.

In compound 71, the trifluoromethyl group being the more electronegative the water reacts almost exclusively at the carbon bearing the trifluoromethyl group to produce hydrate species as depicted in the following reaction:
The hydrate then acts as blocking group against the reaction of hydrazine at the carbonyl center bearing the more electronegative trifluoromethyl group which in turn allows the hydrazine to react at the more electropositive group bearing carbonyl resulting in the formation of regioisomers. We have studied the effect of water present in the reaction system responsible for the formation of regioisomer 74a and 75a as hydrazine and water reacts competitively with the diketone clearly indicates that the reaction kinetics favoring pyrazole formation over diketone hydration. The results are given in table 1.

**Table 1a**: Effect of added water on the formation of regioisomers 74a and 75a. 5 parts of water is added per part of the diketone. The hydrazine 73a is used as its hydrochloride salt. Reaction is carried out at 80 °C. Aliquots were taken periodically and analyzed on RP-HPLC.

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Diketone (%)</th>
<th>Isomer 74a (%)</th>
<th>Isomer 75a (%)</th>
<th>Ratio of % 74a / % 75a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83.3</td>
<td>8.2</td>
<td>1.79</td>
<td>4.58</td>
</tr>
<tr>
<td>5</td>
<td>62.1</td>
<td>25.7</td>
<td>2.24</td>
<td>11.47</td>
</tr>
<tr>
<td>10</td>
<td>35.8</td>
<td>56.4</td>
<td>3.67</td>
<td>15.37</td>
</tr>
<tr>
<td>15</td>
<td>10.4</td>
<td>85.7</td>
<td>4.82</td>
<td>17.78</td>
</tr>
<tr>
<td>20</td>
<td>N. D.</td>
<td>93.3</td>
<td>4.86</td>
<td>19.20</td>
</tr>
</tbody>
</table>

**Table 1b**: Formation of regioisomers 74a and 75a under anhydrous condition. Reaction is carried out at 80 °C. Aliquots were taken periodically and analyzed on RP-HPLC.

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Diketone (%)</th>
<th>Isomer 74a (%)</th>
<th>Isomer 75a (%)</th>
<th>Ratio of % 74a / % 75a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73.5</td>
<td>18.2</td>
<td>0.24</td>
<td>75.83</td>
</tr>
<tr>
<td>5</td>
<td>53.1</td>
<td>36.8</td>
<td>0.15</td>
<td>245.33</td>
</tr>
<tr>
<td>10</td>
<td>22.5</td>
<td>68.4</td>
<td>0.09</td>
<td>760.00</td>
</tr>
<tr>
<td>15</td>
<td>5.6</td>
<td>93.1</td>
<td>0.07</td>
<td>1330.00</td>
</tr>
<tr>
<td>20</td>
<td>N. D.</td>
<td>97.8</td>
<td>0.08</td>
<td>1222.50</td>
</tr>
</tbody>
</table>
We further studied the effect of pKa of the acid used in the reaction mixture for the formation of regioisomers. It was observed that the formation of regioisomer was decreased by increasing the acid strength. Thus the formation of regioisomer 75a was drastically reduced when the strong acid is used. The preferred reaction condition comprising the acid having a pKa less than 2 could be recommended. The results are given in table 2.

Table 2: Effect of pKa on the formation of regioisomers 74a and 75a. The hydrazine 73a is used as its hydrochloride salt. Reaction is carried out at 80 °C. Analysis is done on RP-HPLC of the isolated materials.

<table>
<thead>
<tr>
<th>Acid</th>
<th>pKa</th>
<th>Isomer 74a(%)</th>
<th>Isomer 75a (%)</th>
<th>Ratio of % 74a / % 75a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifluoroacetic</td>
<td>0</td>
<td>99.52</td>
<td>0.07</td>
<td>1421.71</td>
</tr>
<tr>
<td>Trichloroacetic</td>
<td>0.65</td>
<td>99.12</td>
<td>0.14</td>
<td>708.00</td>
</tr>
<tr>
<td>Dichloroacetic</td>
<td>1.29</td>
<td>98.24</td>
<td>0.62</td>
<td>158.45</td>
</tr>
<tr>
<td>Chloroacetic</td>
<td>2.86</td>
<td>97.89</td>
<td>2.84</td>
<td>34.47</td>
</tr>
<tr>
<td>Acetic</td>
<td>4.76</td>
<td>93.37</td>
<td>3.92</td>
<td>23.82</td>
</tr>
</tbody>
</table>

It was further investigated that the solvents used for the reaction has also responsible for the formation of regioisomers. Generally, polar solvents lacking a group reactive with hydrazine such as alcohols, in combination with an acid of low pKa, have been found to reduce the formation of 75a. It was observed that the alcohols such as methanol and ethanol which can easily form the diketone hemi-ketal species at the carbonyl bearing the trifluoromethyl group diverting the hydrazine to react with the carbonyl bearing the aryl group, resulting in the formation of 75a. The alcohols having three or four carbons gave superior purity of 74a and the results are given in table 3.
Table 3: Effect of solvent on the formation of regioisomers 74a and 75a. The hydrazine 73a is used as its hydrochloride salt. Reaction is carried out at reflux temperature of the solvent. Analysis is done on RP-HPLC of the isolated materials.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature(°C)</th>
<th>Time(Hour)</th>
<th>% of 74a</th>
<th>% of 75a</th>
<th>Ratio of %74a/%75a</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>65</td>
<td>24</td>
<td>93.56</td>
<td>3.62</td>
<td>25.85</td>
</tr>
<tr>
<td>EtOH</td>
<td>80</td>
<td>18</td>
<td>95.69</td>
<td>2.89</td>
<td>33.11</td>
</tr>
<tr>
<td>n-PrOH</td>
<td>95</td>
<td>20</td>
<td>96.28</td>
<td>0.32</td>
<td>300.08</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>80</td>
<td>20</td>
<td>98.24</td>
<td>0.26</td>
<td>377.85</td>
</tr>
<tr>
<td>CF₃CH₂OH</td>
<td>80</td>
<td>20</td>
<td>98.32</td>
<td>0.22</td>
<td>446.9</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>110</td>
<td>14</td>
<td>98.45</td>
<td>0.19</td>
<td>518.16</td>
</tr>
</tbody>
</table>

The pyrazoles 74c-g were obtained as single isomer however compounds 74h-i were not cyclised further under similar reaction conditions and isolated as hydrazone intermediates.

Alkylation of 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole 72:

Synthesis of 77a-g:

We elaborated this methodology of obtaining N-substituted pyrazoles by introducing carbamoyl functionality to the unsubstituted (at Nitrogen) pyrazole 72 to obtain the N-linked N-aryl acetamide derivatives. The N-aryl acetamides 76a-g were prepared from the ring substituted anilines with the 2-bromoacetyl bromide by Schotten Baumann procedure in a biphasic media. Thus, compound 72 which was in our hand reacted with 2-bromo-N-aryl acetamide compound 76d in DMF at room temperature under basic condition of potassium carbonate for 3 hrs. The colorless solid obtained after quenching the reaction mass in ice cold water was isolated and crystallized from ethanol to furnish colorless solid
in 80.8% yield (Experiment No.5, Page No. 181). The obtained solid was characterized by spectral and analytical methods.

![Chemical Structure](image)

**Scheme 4**

<table>
<thead>
<tr>
<th>76,77</th>
<th>Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-Chloro-6-Fluoro</td>
</tr>
<tr>
<td>b</td>
<td>2,4-dichloro</td>
</tr>
<tr>
<td>c</td>
<td>4-Methyl</td>
</tr>
<tr>
<td>d</td>
<td>4-Chloro</td>
</tr>
<tr>
<td>e</td>
<td>4-Chloro-3-trifluoromethyl</td>
</tr>
<tr>
<td>f</td>
<td>4-Fluoro</td>
</tr>
<tr>
<td>g</td>
<td>2,5-Bis trifluoromethyl</td>
</tr>
</tbody>
</table>

The IR spectrum of colorless solid showed weak signal for NH (pyrazole proton) at 3283 cm⁻¹ and another very strong signal at 1596 cm⁻¹ for C=N of the pyrazole ring. The very strong signal for C-F at 1387 cm⁻¹. The $^1$H NMR(Spectrum No-9) showed singlet at 8.506 ppm for two protons and at 7.92 δ ppm for one proton from the 3,5-bis trifluoromethyl phenyl ring. The presence of signal at 7.57δ ppm for one proton correspond to the pyrazolic proton. The two doublets at 7.55 δ and 7.35 δ ppm represents the para disubstituted pattern of phenyl ring. The singlet at 5.30 δ ppm corresponded to methylene protons. The $^{13}$C NMR
(Spectrum No-10) showed presence of signal at 164.1 δ ppm for amide carbonyl and 107.0 δ ppm for pyrazole carbon indicates the aromatic carbon of pyrazole ring. The two signals as quartet at 131.6 and 121.8 δ ppm for the carbons bearing the CF₃ group indicates the presence of trifluoromethyl substituent on aryl as well as on pyrazole ring. The rest of the signals corresponded to aromatic carbons appeared between 147.2 and 117.8 δ ppm. The mass spectral analysis showed molecular ion peak at 515[M]⁺ as well as 517[M]⁺² for presence of isotopic chlorine and elemental analysis was in well agreement with the molecular formula C₂₀H₁₁ClF₉N₂O. On the basis of above spectral analytical data the structure was assigned to this compound as 77d i.e.2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)-N-(4-chlorophenyl)acetamide. In the similar way compounds all the alkylated pyrazole 77 a-c, e-g derivatives were synthesised and characterised by spectral and analytical methods and the data is given in the experimental section (Experiment No.5, Page No.181).

Spectrum No. 9: ¹H NMR Spectrum of 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)-N-(4-chlorophenyl)acetamide 77d in DMSO-d₆
We planned the third protocol to obtain the pyrazole derivatives using aprotic nonpolar solvent. It is interesting to observe that using aprotic polar solvent and lower temperature for alkylation of 3,5-disubstituted pyrazole 72 the only one isomer is obtained exclusively as 1,3,5-trisubstituted derivatives 77a-g in good yield. All the reactions were carried out at room temperature in dimethyl formamide and using potassium carbonate as base.

**Attachment of amino acid linkers to 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)-N-(4-chlorophenyl)acetamide 77d in DMSO-d₆**

The polyfluorinated pyrazole 72 was utilized further for hooking the amino acids with a similar methodology adopted for uracils in chapter 2. In this protocol the pyrazole 72 was
linked to amino acid esters through multistep process. The pyrazole was first reacted with ethyl 2-bromo acetate to obtain the N-linked acetate in 96.3% yield after crystallization from ethanol as colorless needles (Expt-6, Page No. 163). The colourless needles were characterized by $^1$H NMR and Mass analysis. The signals in $^1$H NMR (Spectrum No. 11, Page No. 163) at 8.3 $\delta$ ppm for one aromatic proton and another signal at 8.23 $\delta$ ppm for two aromatic protons were clearly present. The signal corresponding to pyrazolic proton appeared at 7.28 $\delta$ ppm. A distinct singlet was observed at 5.34 $\delta$ ppm for methylene protons. The quartet at 4.06 $\delta$ and triplet at 1.06 $\delta$ ppm in the upfield region clearly indicated the presence of ethyl ester group. The mass spectral analysis showed molecular ion peak at [M]$^+$ 434. Based on the above analysis structure 79 was assigned to this compound i.e. Ethyl 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)acetate.

![Spectrum No. 11: $^1$H NMR Spectrum of Ethyl 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)acetate 79 in DMSO-d$_6$]
Hydrolysis of pure 79 is carried out in tetrahydrofuran in presence of 2N NaOH. Thus, compound 79 was dissolved in tetrahydrofuran and treated with 2N NaOH for 5 hrs at 50°C. Colorless material was isolated on acidification of the reaction mass in 90% yield (Experiment No.7, Page No.186). The obtained colorless solid was characterized by proton NMR and Mass analysis. The 1H NMR (Spectrum No. 12, Page No. 164) showed disappearance of quartet triplet of the ethyl ester group present in compound 79 and a broad signal at 13.57 δ ppm appeared in the downfield indicates the presence of carboxylic acid. The three aromatic protons appeared at 8.52 δ and 8.24 δ ppm whereas the singlet at 7.94 δ ppm corresponded to pyrazolic proton. The sharp singlet for methylene protons appeared at 5.32 δ ppm. The mass spectral analysis showed molecular ion peak at [M]+406. Based on the analysis the structure 80 was assigned to this compound i.e. 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)acetic acid.

![Chemical Structure](image)

**Spectrum No. 12: 1H NMR Spectrum of 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)acetic acid 80 in DMSO-d6**
\[
\begin{align*}
72 & \xrightarrow{\text{K2CO3 / Acetonitrile Reflux}} 79 \\
\text{H}_3\text{C} & \xrightarrow{\text{78}} \text{H}_3\text{C} \\
& \xrightarrow{1. \text{2N NaOH} \ \text{THF}} \xrightarrow{2. \text{2N HCl}} \\
82a-d & \xleftarrow{\text{TBTU / Hunig Base}} 80
\end{align*}
\]

**Scheme 4**

<table>
<thead>
<tr>
<th>81,82</th>
<th>Amino Acid ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>L-Phenyl alanine ethyl ester</td>
</tr>
<tr>
<td>b</td>
<td>L-Proline ethyl ester</td>
</tr>
<tr>
<td>c</td>
<td>L-Tyrosine ethyl ester</td>
</tr>
<tr>
<td>d</td>
<td>L-Norvaline ethyl ester</td>
</tr>
</tbody>
</table>
This acid 80 was then coupled with the amino acid esters 81a-d of the L-series using TBTU as peptide coupling reagent to furnish colorless solids in 78-88% yield. Thus, compound 80 was reacted with 81d in presence of peptide coupling reagent and diisopropyl ethylamine. After stirring at room temperature for 2 hrs the solid was isolated by concentrating the reaction mass and purified by column chromatography eluting with dichloromethane. The desired fractions were collected and evaporated completely to furnish colourless solid in 78% yield (Experiment No. 8, Page No.187). The colorless solid was characterized by spectral and analytical methods. The IR spectrum of 82d showed sharp peaks at 1729 and 1685 cm\(^{-1}\) for two carbonyl carbons and the band appeared at 3258 cm\(^{-1}\) for NH stretching. The \(^1\)H NMR spectrum (DMSO-d\(_6\)) of this compound showed peaks at 5.12 \(\delta\) (singlet) ppm for one methylene protons and the singlet at 7.90 \(\delta\) ppm for \(=\text{CH}\) proton of pyrazole. The doublet for NH proton was appeared downfield at 8.78 \(\delta\) ppm. The methylene protons attached to the chiral centre appeared as double doublet at \(\delta\) 4.24 \((J = 8.2\) and 8.3 Hz) ppm. The ester group showed quartet triplet pattern of the ethyl group and the signals for quartet appeared upfield at \(\delta\) 4.08 and triplet at \(\delta\) 1.25 \((J = 7.0\) Hz). The proton attached to chiral carbon showed double doublet at 4.74 \((J = 8.4\) and 8.0 Hz). The multiplet at 1.4 \(\delta\) and doublet for three protons for methyl group at 0.97 \(\delta\) ppm represent propyl chain of norvalin (Spectrum No 13, Page No. 167). The \(^{13}\)C NMR spectrum of 82d in DMSO-d\(_6\) showed the peaks at \(\delta\) 61.3, 59.7, 49.6, 33.4 and 18.8 ppm for four methylene carbons and at \(\delta\) 55.9 ppm for CH and as well as \(\delta\) 14.1 and 13.8 ppm for two methyl carbons of the ester and propyl group of norvaline. Two distinct peaks at \(\delta\) 171.5 and 166.5 ppm corresponded to ester and amide carbonyl carbons. The aromatic carbons were appeared between \(\delta\) 113.8-164.2 ppm and olefinic carbon showed the peak at
δ 105.3. (Spectrum No. 13, Page No. 167). The mass spectrum of 82d revealed a molecular ion peak at 533[M]$^+$. Further, the elemental analysis was in agreement with molecular formula C$_{21}$H$_{20}$F$_3$N$_3$O$_3$. On the basis of this analysis structure 82d was assigned to this compound i.e. Ethyl 2-(2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)acetamido)pentanoate. Similarly, the derivatives 82a-c were synthesized and structures were confirmed by spectral and analytical data which is given in experimental part (Experiment No.8, Page No. 187).

![Spectrum No. 13: $^1$H NMR Spectrum of Ethyl 2-(2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1yl)acetamido)pentanoate 82d in DMSO-d$_6$](image-url)
The amino acid esters were used as their hydrochlorides hence the base like N,N'-diisopropyl ethyl amine is used during the coupling reaction. The byproduct urea and the unreacted starting material contamination is removed by giving the acidic and basic washings. All the N-linked products 82a-d were isolated and crystallized from hexane as colorless solids.
3.4 ANTIMICROBIAL ACTIVITY:

A] Cultures used:

<table>
<thead>
<tr>
<th>Culture code</th>
<th>Culture name</th>
<th>Name of Culture Collection Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli 2109</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa 2036</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Bacillus subtilis 2250</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus 2079</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans 3471</td>
<td>NICM, Pune</td>
<td></td>
</tr>
<tr>
<td>Aspergillus niger 545</td>
<td>NICM, Pune</td>
<td></td>
</tr>
</tbody>
</table>

B] Media Used:

For Bacteria : Muller Hinton agar (Hi-media)
For Fungi : Potato Dextrose agar (Hi-media)

C] Inoculum Size:

Bacteria : 1 X 10^8 bacteria per ml
Fungi : 1 X 10^6 spore per ml

D] Concentration of Compound: 100μg/ml. (Prepared in DMSO)

E] Method used: Agar diffusion assay (disc method, disc size 6mm)

F] Dilution of Drug: Stock prepared 1000μg/ml prepared in DMSO [100μg per disc]
Antimicrobial activity of compounds 71, 72, 74, 77 and 82

<table>
<thead>
<tr>
<th>Compd</th>
<th>Inhibition zone (in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td>71</td>
<td>11.11</td>
</tr>
<tr>
<td>72</td>
<td>12.11</td>
</tr>
<tr>
<td>74a</td>
<td>7.23</td>
</tr>
<tr>
<td>74b</td>
<td>-</td>
</tr>
<tr>
<td>74c</td>
<td>8.92</td>
</tr>
<tr>
<td>74e</td>
<td>7.34</td>
</tr>
<tr>
<td>74f</td>
<td>7.33</td>
</tr>
<tr>
<td>77a</td>
<td>-</td>
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<tr>
<td>77b</td>
<td>-</td>
</tr>
<tr>
<td>77c</td>
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</tr>
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<td>77d</td>
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<tr>
<td>77e</td>
<td>7.25</td>
</tr>
<tr>
<td>77f</td>
<td>-</td>
</tr>
</tbody>
</table>
### Results of antimicrobial activity:

All the synthesized compounds 71, 72, 74a-c, e-f, 77a-g and 82a,c-d were tested against microorganism species at 1000 ppm concentration.

The observed results of antibacterial screening reported in above table indicate that pyrazole compounds 71, 72, 74e and 74f are active against *S.aureus*, *E.coli*, *B. subtilis* and *P.aeruginosa* bacterial species. Whereas Compounds 74a, 74f showed activity against *B.substilis* and *S.aureus* and *E.coli* species. 74b, 77a and 77b are active against *E.coli* and *P.aeruginosa*. Compounds 77c-e, 82d-c are active against *S.aureus* and *B. subtilis*. as well as fungal species. However compounds 74f, 77a-b, 74a-c, 71 and 72 are totally inactive against fungal species.
From the antifungal assay it has been also observed that compound \textbf{77a and 82c} are found to be active against \textit{A. niger species} only. Compound \textbf{74e, 77c and 77e} are active against the bacterial as well as fungal species.

From the above observation it is clear that the pyrazole containing aryl functionality bearing trifluoromethyl substituent \textbf{71, 72, and 77g} showed significant antibacterial activity.

### 3.5 CONCLUSION

A series of 1,3,5-trisubstituted pyrazole derivatives were prepared from asymmetrical polyfluorinated 1,3-diketone \textbf{71}. The reactivity of substituted hydrazines towards the dioxo compound is studied leading to the formation of regioisomers \textbf{74} and \textbf{75}. We have studied the effect of water present in the reaction system responsible for the formation of regioisomer \textbf{74a} and \textbf{75a} as hydrazine and water reacts competitively with the diketone clearly indicates that the reaction kinetics favoring pyrazole formation over diketone hydration. It was further investigated that the solvents used for the reaction has also responsible for the formation of regioisomers. Generally, polar solvents lacking a group reactive with hydrazine such as alcohols, in combination with an acid of low pKa, have been found to reduce the formation of \textbf{75a}. It was observed that the alcohols such as methanol and ethanol which can easily form the diketone hemi-ketal species at the carbonyl bearing the trifluoromethyl group diverting the hydrazine to react with the carbonyl bearing the aryl group, resulting in the formation of \textbf{75a}. The alcohols having three or four carbons gave superior purity of \textbf{74a} and the results are given in table 3.
The pyrazole unsubstituted at nitrogen were linked to N-arylacetamides 77. It is interesting to observe that using aprotic polar solvent and lower temperature for alkylation of 3,5-disubstituted pyrazole 72 the only one isomer is obtained exclusively as 1,3,5-trisubstituted derivatives 77a-g in good yield. All the reactions were carried out at room temperature in dimethyl formamide and using potassium carbonate as base. As well as amino acids to furnish the peptide linked pyrazoles 82. The amino acid esters were used as their hydrochlorides hence the base like N,N'-diisopropyl ethyl amine is used during the coupling reaction. The byproduct urea and the unreacted starting material contamination is removed by giving the acidic and basic washings. All the N-linked products 82a-d were isolated and crystallized from hexane as colorless solids.

3.6 EXPERIMENTAL

Experiment No 1: Procedure for the synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-4,4,4-trifluorobutane-1,3-dione (71)

\[ \text{NaOMe, methyl tert-butyl ether} \]

Ethyl trifluoroacetate (22.7gm, 160.0 mmol) was dissolved in methyl tert-butyl ether (70 ml) and cooled to 0-5°C. 25% Sodium methoxide (36.2 ml, 168.0 mmol) is then charged to it with stirring. 3,5-bis(trifluoromethyl)acetophenone (38.5gm, 160.0 mmol) diluted in
methyl tert-butyl ether (20.0 ml) and added drop wise into the reaction mass over a period of 30 minute at 0-5°C. The reaction mass is then stirred at 25-30°C for 14 hrs. Reaction is monitored by TLC (CHCl₃:MeOH 9:5:0.5). After completion of reaction 4N Hydrochloric acid (40.0 ml, 160.0 mmol) is added to adjust the pH to 4-5. Water is added and the layers were separated. The organic layer was dried over sodium sulfate and evaporated completely under reduced pressure to obtain the brown oil. The oil is purified by column chromatography eluting with dichloromethane. The pure fractions were collected and evaporated under reduced pressure to obtain a light yellow oil. Yield 50 g (89.4 %); IR (Nujol): 3345, 1823, 1745, 1546, 1485, 1356 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.25(s, 2H, Ar-H), 7.91 (s, 1H, Ar-H), 7.23(s, 1H, =CH), 2.70(s, 2H, CH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ 206.0(C=O), 201.1(C=O), 137.3, 131.2, 128.4, 127.5, 124.4(q, 2 Ar-CF₃, ²JCF = 32.6Hz), 117.2(q, C-CF₃, ²JCF = 36.6Hz), 35.1(CH₂); MS: 352 [M⁺], 333, 283, 241, 213, 187, 75, 69; Anal. Calcd. For C₁₂H₅F₉O₂: C, 40.93; H, 1.43; Found: C, 41.09; H, 1.82%.

**Experiment No 2: Procedure for the synthesis of 5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole (72)**

![Chemical structure](image)

To a solution of compound 71 (1.0 gm, 2.84 mmol) in ethanol (20.0 ml), hydrazine hydrate (2.90 mmol) was added along with catalytic amount of acetic acid. The resulting solution was refluxed at 80°C for 20 hrs. Reaction was monitored by TLC (CHCl₃:MeOH,9:1). After completion of reaction the solvent was removed under reduced pressure and the
compound was purified by column chromatography eluting with dichloromethane. The pure fractions were collected and evaporated under reduced pressure to obtain NH-pyrazole 72 as colorless needles. Yield 0.9 g (92 %), mp 128-130 °C (Hexane); IR (KBr): 3272, 1566, 1455, 1376 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 12.62 (bs, 1H, NH), 8.52 (s, 2H, Ar-H), 8.08 (s, 1H, Ar-H), 7.60 (s, 1H, Pyrazole-CH); ¹³C NMR (75 MHz, DMSO-d₆): δ 141.5, 131.5 (q, 3,5- di-C-CF₃, ²J CF = 33 Hz), 128.6, 126.1, 124.9, 123.2, 121.8 (q, pyrazole C₃-CF₃, ²J CF = 36 Hz), 103.2 (Pyrazole-CH); MS : 348[M⁺], 329, 279, 250, 144, 69, 44; Anal. Calcd. For C₁₂H₅F₉N₂ C, 41.40; H, 1.45; N, 8.05; Found: C, 41.59; H, 1.32; N, 7.91%.

Experiment No 3: The synthesis of compounds 74 and 75

![Chemical structure](image)

General procedure

To a solution of compound 71 (1.0 gm, 2.84 mmol) in ethanol (20.0 ml), hydrazines 73a-i (2.90 mmol) were added along with catalytic amount of acetic acid. The resulting solution was refluxed at 80°C for 20 hrs. Reaction was monitored by TLC (CHCl₃:MeOH,9:1). After completion of reaction the solvent was removed under reduced pressure and the compounds were purified by column chromatography eluting with dichloromethane. The pure fractions were collected and evaporated under reduced pressure to obtain 1,3,5-
substituted pyrazoles 74a-g as white solids (70-85%) along with the regioisomers 775a-b (4-10%) and the uncyclised hydrazone derivatives 74h-i in (65-75%) yield.

2-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-N-methyl ethane sulfonamide (74a)

Yield 1.2 g (80 %), mp 143-145 °C (Ethanol); IR (KBr): 3263, 1571, 1472, 1367 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.12 (s, 1H, Ar-H), 7.89 (s, 2H, Ar-H), 7.55 (s, 1H, Pyrazole-CH), 7.40 (d, 2H, Ar-H, J = 9.0Hz), 7.35 (d, 2H, Ar-H, J = 9.0Hz), 7.03 (q, 1H, NH, J = 6.0 Hz), 3.24 (t, 2H, SO₂-CH₂, J = 6.0Hz), 3.02 (t, 2H, CH₂, J = 6.0Hz), 2.59 (d, 3H, N-CH₃, J = 6.0Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 141.7, 141.2, 140.3, 136.5, 130.5 (q, 2 Ar C-CF₃, ²J CF = 21Hz), 129.4, 128.2, 126.2, 124.6, 122.4 (q, Pyrazole-C-CF₃, ²J CF = 40Hz), 120.9, 119.4, 117.4, 106.9 (Pyrazole-CH), 50.2 (SO₂-CH₂), 28.8 (N-CH₃), 28.6 (Ar-CH₂); MS : 545 [M⁺] 526, 450, 429, 103, 77, 65; Anal. Calcd. For C₂₁H₁₆F₉N₃O₂S C, 46.24; H, 2.96; N, 7.70; Found: C, 46.58; H, 2.69; N, 7.56%.

2-(4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-N-methyl methane sulfonamide (74b)

Yield 1.15 g (76.6 %), mp 115-117 °C (Ethanol); IR (KBr): 3276, 1549, 1482, 1375 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.13 (s, 1H, Ar-H), 7.96 (s, 2H, Ar-H), 7.52 (s, 1H, Pyrazole-CH), 7.45 (m, 4H, Ar-H), 6.95 (q, 1H, NH, J = 6.0 Hz), 4.40 (s, 2H, SO₂-CH₂), 2.70 (d, 3H, N-CH₃, J = 6.0Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 141.9, 141.7, 141.4, 137.7, 131.6 (q, 2 Ar C-CF₃, ²J CF = 23.25Hz), 129.7, 128.2, 126.5, 125.8, 124.5, 122.6 (q, Pyrazole-C-CF₃, ²J CF = 25.5Hz), 120.9, 119.4, 117.4, 107.3 (Pyrazole-CH), 55.5 (SO₂-CH₂), 28.9 (N-CH₃); MS : 531 [M⁺] 512, 415, 367, 129, 89, 44; Anal. Calcd. For C₂₀H₁₄F₉N₃O₂S C, 45.2; H, 2.65; N, 7.91; Found : C, 45.45; H, 2.51; N, 7.58%.
4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoic acid (74c)

Yield 1.1 g (84.6 %), mp 213-215 °C (Acetone); IR (KBr): 3279, 1561, 1469, 1387 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 12.8 (s, 1H, COOH), 8.15 (s, 1H, Ar-H), 8.00 (d, 2H, Ar-H, J = 7.5), 7.94 (s, 2H, Ar-H), 7.55 (s, 1H, Pyrazole-CH), 7.52 (d, 2H, Ar-H, J = 7.5 Hz); ¹³C NMR (75 MHz, DMSO-d₆):  δ 166.2 (COOH), 153.6 (C-F₃), 142.4 (Ar-C-N), 141.2 (Ar-C-N-Pyrazole), 131.1 (Ar-C-Pyrazole), 130.5 (q, Ar-C-F₃, ²JCF = 12 Hz), 130.2, 129.6, 128.2 (Ar-C-F₃), 125.9 (2 Ar-C-F₃), 124.5, 122.8 (q, Pyrazole-C-F₃, ²JCF = 9.75 Hz), 120.9, 119.3, 107.6 (Pyrazole-CH); MS: 468 [M⁺]^+, 447, 207, 134, 106, 65, 44; Anal. Calcd. For C₁₉H₉F₉N₂O₂ C, 48.73; H, 1.94; N, 5.98; Found: C, 48.51; H, 2.10; N, 5.66%.

Ethyl 4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoate (74d)

Yield 0.85 g (60.7 %), mp 105-107 °C (Ethanol); IR (KBr): 3286, 1551, 1476, 1391 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 8.17 (s, 1H, Ar-H), 8.03 (s, 2H, Ar-H), 8.00 (d, 2H, Ar-H, J = 7.5 Hz), 7.56 (d, 2H, Ar-H, J = 7.5 Hz), 7.53 (s, 1H, Pyrazole-CH), 4.34 (q, 2H, J = 6.0 Hz, Ester CH₂), 1.30 (t, 3H, J = 6.0 Hz, Ester CH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ 164.6 (Ester C=O), 142.4 (Ar-C-N), 141.5 (Ar-C-N-Pyrazole), 131.0 (Ar-C-Pyrazole), 130.2, 130.0 (C-F₃), 129.7, 126.0 (Ar-C-F₃), 124.5 (2 Ar-C-F₃), 122.8, 119.3 (Pyrazole-C-F₃), 107.5 (Pyrazole-CH), 61.3 (ester CH₂), 14.1 (Ester CH₃); MS: 496 [M⁺]^+; Anal. Calcd. For C₂₁H₁₃F₉N₂O₂ C, 50.82; H, 2.64; N, 5.64; Found: C, 50.57; H, 2.38; N, 5.89%.

4-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzene sulfonamide (74e)

Yield 1.2 g (84.5 %), mp 148-150 °C (Ethanol); IR (KBr): 3276, 1561, 1472, 1394 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.18 (s, 1H, Ar-H), 8.01 (s, 2H, Ar-H), 7.87 (d, 2H, Ar-H, J = 7.8 Hz).
= 9.0Hz), 7.62(d,2H, Ar-H, J = 9.0Hz), 7.59(s, 1H, Pyrazole-CH) 7.55(bs,2H, NH2); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 144.5, 142.9, 142.4, 141.4, 140.3, 130.6, (C-CF$_3$), 129.8, 128.2, 126.7(2Ar-CF$_3$,$^2$J$_{CF}$=36Hz), 124.6, 122.9(Pyrazole-CF$_3$), 120.9, 119.3, 117.3, 115.7, 107.8(Pyrazole-CH); MS: 503[M]$^+$,484, 439, 423, 403, 329, 309, 75, 63; Anal. Calcd. For C$_{18}$H$_{10}$F$_9$N$_2$O$_2$S, 42.95; H, 2.00; N, 8.35; Found: C, 42.68; H, 2.37; N, 8.17%.

5-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazole(74f)
Yield 0.95 g (79.1 %), mp 160-162 °C(Ethyl acetate); IR (KBr): 3291, 1548, 1469, 1388 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 8.43 (s, 1H, Ar-H), 8.31 (s, 2H, Ar-H), 8.10(s, 1H, Pyrazole-CH), 7.50(d, 2H, Ar-H, J = 9.0Hz), 7.33(t, 2H, Ar-H, J= 9.0Hz),7.07(t, 1H, Ar-H, J=9.0Hz) $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 144.4, 141.7, 133.9, 130.9, 130.5, 130.1, 128.4, 125.7, 124.9(2Ar-CF$_3$), 122.8, 121.8(Pyrazole-CF$_3$), 121.3, 119.3, (Pyrazole-CH), 94.1, 93.6; MS : 424[M]$^+$; Anal. Calcd. For C$_{18}$H$_{9}$F$_9$N$_2$ C, 50.96; H, 2.14; N, 6.60; Found: C, 50.74; H, 2.37; N, 6.83%.

5-(3,5-bis(trifluoromethyl)phenyl)-1-(2,4-dichlorophenyl)-3-(trifluoromethyl)-1H-pyrazole(74g)
Yield 1.3 g (93.5 %), mp 130-132 °C(Acetone); IR (KBr): 3281, 1555, 1476, 1395 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 8.13 (s, 1H, Ar-H), 7.88 (s, 2H, Ar-H), 7.69(s, 1H, Ar-H), 7.50(d,1H, Ar-H, J = 7.5Hz), 7.41(s, 1H, Pyrazole-CH),7.37(d,1H, Ar-H, J = 7.5Hz); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 143.5, 141.7, 134.9, 133.6, 133.2(C-Cl), 131.8(C-CF$_3$), 129.8, 127.5. 124.7(2Ar-CF$_3$), 123.1, 122.7, 117.3(Pyrazole-CF$_3$), 107.5(Pyrazole-CH); MS: 493[M]+2, 491[M]$^+$; Anal. Calcd. For C$_{18}$H$_7$Cl$_2$F$_9$N$_2$ C, 43.84; H, 1.43; N, 5.68; Found: C, 43.61; H, 1.72; N, 5.42%.
Experiment No: 4 N’-(4-(3,5-bis(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-oxobutane-2-vidine)acetohydrazide (74h).

General procedure

To a solution of compound 71 (1.0 gm, 2.84 mmol) in ethanol (20.0 ml), hydrazines 73h-i (2.90 mmol) were added along with catalytic amount of acetic acid. The resulting solution was refluxed at 80°C for 20 hrs. Reaction was monitored by TLC (CHCl₃:MeOH,9:1). After completion of reaction the solvent was removed under reduced pressure and the compounds were purified by column chromatography eluting with dichloromethane. The pure fractions were collected and evaporated under reduced pressure to obtain 1,3,5-substituted pyrazoles 74h-i as white solids(75-83%). Yield 0.87 g (75.6 %), mp 113-115°C(Ethanol); IR (KBr): 3278, 1698, 1554, 1471, 1398 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 10.48(bs, 1H, NH), 8.23 (s, 1H, Ar-H), 7.98 (s, 2H, Ar-H), 4.21(s, 2H, CH₂), 2.29(s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ 187.1(C=O),153.6(C-CF₃),145.9(Ar-C-N),143.5,137.5,131.8(C-CF₃),130.5,129.8, 127.7(Ar-C-CF₃), 124.7(2Ar-CF₃), 123.1, 64.1(CH₂), 13.8(CH₃); MS : 408[M]+355, 328, 249, 151, 89, 59, 44; Anal. Calcd. For C₁₄H₉F₉N₂O₂ C, 41.19; H, 2.22; N, 6.86. Found: C, 41.67; H, 2.34; N, 6.61%. 
Synthesis of N’-(4-(3,5-bis(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-oxobutane-2-vlidine)benzohydrazide (74i).

Yield 1.1 g (82.7 %), mp 189-191 °C(Ethanol); IR (KBr): 3282, 1667, 1556, 1475, 1396 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 11.03(bs, 1H, NH), 8.41 (s, 1H, Ar-H), 8.14 (s, 2H, Ar-H), 7.86(d, 2H, Ar-H, J = 9.0Hz), 7.56-7.50(m, 3H, Ar-H), 4.30(s, 2H, -CH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ 165.0(C=O), 140.6, 137.5, 134.5, 133.6, 131.6, 131.1, 130.6, 129.8, 128.3( C-CF₃), 126.7(2Ar-CF₃), 125.1, 122.5, 121.4, 64.1(CH₂); MS: 470[M]⁺, 374, 359, 249, 151, 105, 77, 51; Anal. Calcd. For C₁₉H₁₁F₉N₂O₂ C, 48.52; H, 2.36; N, 5.96; Found: C, 48.71; H, 2.13; N, 5.64%.

2-(4-(3-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-N-methyl ethane sulfonamide(75a)

Yield 0.1 g (6.4%), mp 150-152 °C(Ethanol); IR (KBr): 3276, 1549, 1468, 1389 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.55 (s, 2H, Ar-H), 8.12 (s, 1H, Ar-H), 8.08(s, 1H, Pyrazole-CH), 7.53(s, 4H, Ar-H), 7.03(q, 1H, NH, J = 6.0 Hz), 3.34(t, 2H, SO₂-CH₂, J = 6.0Hz), 3.07(t, 2H, CH₂, J = 6.0Hz), 2.62(d, 3H, N-CH₃, J = 6.0Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 141.7, 141.2, 140.3, 136.5, 136.4, 136.3, 2(JCF = 21Hz), 129.4,128.2, 126.2, 124.6, 123.8(q, Pyrazole-C-CF₃, ²JCF = 40Hz), 120.9,119.4, 118.2, 107.2(Pyrazole-CH), 51.4(SO₂-CH₂), 27.5(N-CH₃), 25.9(Ar-CH₂); MS: 545[M]⁺ 526, 450, 429, 142, 77, 44.; Anal. Calcd. For C₂₁H₁₆F₉N₃O₂S C, 46.24; H, 2.96; N, 7.70; Found: C, 46.58; H, 2.69; N, 7.56%.

2-(4-(3-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-N-methyl methane sulfonamide (75b)

Yield 0.12 g (8 %), mp 132-135 °C(Ethanol); IR (KBr): 3291, 1563, 1482, 1399 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 8.43 (s, 1H, Ar-H), 8.18 (s, 2H, Ar-H), 7.74(q, 1H, NH, J =
9.2 Hz), 7.50 (d, 2H, Ar-H, J = 8.5 Hz), 7.23 (d, 2H, Ar-H, J = 8.5 Hz), 6.51 (s, 1H, Pyrazole-CH), 4.32 (s, 2H, SO2-CH2), 2.47 (d, 3H, N-CH3, J = 9.2 Hz); 13C NMR (75 MHz, DMSO-d6): δ 153.6 (Pyrazole-C-CF3), 143.5, 141.7, 136.7, 133.6, 131.8 (C-CF3), 130.7, 129.8, 129.6, 125.1, 124.7 (2Ar-CF3), 123.1, 117.3 (Pyrazole-CF3), 107.5 (Pyrazole-CH), 65.7 (SO2-CH2), 25.4 (N-CH3); MS: 531 [M]+, 512, 437, 415, 367, 129, 89, 44; Anal. Calcd. For C20H14F9N3O2S C, 45.2; H, 2.66; N, 7.91; Found: C, 45.45; H, 2.51; N, 7.58%.

**Experiment No 5: The synthesis of N-alkylated N-arylacetamide derivatives 77a-g**

![Chemical structure](image)

**General procedure**

To a suspension of 72 (0.5 gm, 1.42 mmol), K2CO3 (0.25 g, 1.86 mmol) and DMF (10 ml) at room temperature was added 76 (1.42 mmol). The reaction mass was then stirred at the same temperature for 3 hrs (TLC Check, CHCl3:MeOH 9:1). Reaction mass was then quenched in ice-cold water and solid obtained was filtered, washed with water, dried and was recrystallized from ethanol to give 77 as a white solids in 70-95 % yields.

2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl)-N-(2-chloro-6-fluorophenyl)acetamide(77a)

Yield 0.58 g (76 %), mp 202-204 °C; IR (KBr): 3118, 1654, 1540 cm⁻¹; 1H NMR (300 MHz, DMSO-d6): δ 10.24 (bs, 1H, NH), 8.53 (s, 1H, Ar-H), 8.08 (s, 2H, Ar-H), 7.46 (m, 3H, Ar-H), 7.37 (s, 1H, Pyrazole-CH), 4.94 (s, 2H, N-CH2); 13C NMR (75 MHz, DMSO-d6): δ 165.2 (C=O), 160.2 (C-F), 142.6, 140.6 (Pyrazole-C-CF3), 133.2, 132.9 (C-Cl), 131.3 (Ar-C-
CF3), 128.8, 128.1, 126.2, 125.4, 123.7(2Ar-CF3), 123.2, 120.7(Pyrazole-CF3), 113.8, 107.2(Pyrazole-CH), 54.3(N-CH2); MS (ESI): 535[M]+, 533[M]+; Anal. Calcd. For C20H10ClF10N3O C, 45.00; H, 1.89; N, 7.87; Found: C, 45.27; H, 1.58; N, 7.53%.

2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(2,4-dichlorophenyl)acetamide(77b)

Yield 0.59 g (74 %), mp 198-200 °C; IR (KBr): 3285, 1687, 1576, 1495, 1399 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 10.24(bs, 1H, NH), 8.51 (s, 1H, Ar-H), 8.28 (s, 2H, Ar-H), 7.57(m, 2H, Ar-H), 7.35(d, 1H, Ar-H, J = 8.4), 7.27(s, 1H, Pyrazole-CH), 4.85(s, 2H, N-CH2); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.2(C=O), 144.6, 142.3(Pyrazole-C-CF3), 134.6, 133.5, 131.2(Ar-C-CF3), 130.2(Cl), 130.1, 129.4, 127.8(Cl), 126.7, 123.9(2Ar-CF3), 123.1, 120.7(Pyrazole-CF3), 121.0, 107.5(Pyrazole-CH), 51.8(N-CH2); MS: 552[M]⁺, 550[M]+; Anal. Calcd. For C20H10Cl2F9N3O C, 43.66; H, 1.83; N, 7.64; Found: C, 43.84; H, 1.98; N, 7.85%.

2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(4-methylphenyl)acetamide(77c)

Yield 0.51 g (71.8 %), mp 235-237 °C; IR (KBr): 3272, 1687, 1566, 1386 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25(bs, 1H, NH), 8.48 (s, 1H, Ar-H), 7.97 (s, 2H, Ar-H), 7.26(d, 2H, Ar-H, J = 5.5Hz), 7.11(d, 1H, Ar-H, J = 8.5Hz), 6.87(s, 1H, Pyrazole-CH), 4.85(s, 2H, N-CH2), 2.45(s, 3H, Ar-CH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ 165.2(C=O), 164.2(C-F), 144.6, 142.3(Pyrazole-C-CF3), 135.8, 134.5, 133.4, 132.7, 131.2(Ar-C-CF3), 129.5, 128.8, 127.3, 125.6, 123.7(2Ar-CF3), 123.2, 121.7(Pyrazole-CF3), 121.2, 112.9, 107.1(Pyrazole-CH), 51.8(N-CH2), 21.5(CH₃); MS (ESI): 495[M]+; Anal. Calcd. For C21H14F9N3O C, 50.92; H, 2.85; N, 8.48; Found: C, 50.68; H, 2.57; N, 8.74%.
2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(4-
chlorophenyl)acetamide(77d)

Yield 0.59 g (80.8 %), mp 193-195 °C; IR (KBr): 3283, 1687, 1596, 1387 cm⁻¹; ¹H NMR
(300 MHz, DMSO-d₆): δ 10.6(bs,1H, NH), 8.50 (s, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 7.57(s, 1H, Pyrazole-CH), 7.55(d, 2H, Ar-H, J = 8.2 Hz), 7.35(d,2H, Ar-H, J = 8.5Hz), 5.30(s, 2H, N-CH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ 164.1(C=O), 147.2, 137.2, 133.8(C-Cl), 131.6(Ar-C-Cl), 128.8, 128.5, 127.3, 125.5, 124.9(2Ar-CF₃), 121.8(Pyrazole-CF₃), 120.7, 117.8, 107.0(Pyrazole-CH), 54.3(N-CH₂); MS: 517[M]+², 515[M]+, 361, 154, 126, 99, 75, 63, 44; Anal. Calcd. For C₂₀H₁₈ClF₉N₃O C, 46.57; H, 2.15; N, 8.15; Found: C, 46.82; H, 2.39; N, 8.51%.

2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(4-
chloro-3-trifluoromethylphenyl)acetamide(77e)

Yield 0.64 g (77.1 %), mp 158-160°C; IR (KBr): 3262, 1687, 1586, 1376 cm⁻¹; ¹H NMR
(300 MHz, DMSO-d₆): δ 10.73(bs,1H, NH), 8.52 (s, 1H, Ar-H), 8.49 (s, 2H, Ar-H),
8.06(s, 1H, Ar-H), 8.11(d, 1H, Ar-H, J = 8.2Hz), 8.05(d,1H, Ar-H, J = 8.2Hz), 7.93 (s, 1H, Ar-H), 7.68(s, 1H, Pyrazole-CH), 5.36(s, 2H, N-CH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.2(C=O), 144.6, 142.6(Pyrazole-C-Cl), 135.2, 133.6, 129.5, 129.3, 129.1(Ar-C-Cl), 128.5(C-Cl), 127.2, 125.7, 123.3(2Ar-CF₃), 123.1, 121.7(Pyrazole-CF₃), 118.8, 113.8, 107.3(Pyrazole-CH), 55.3(N-CH₂); MS : 585[M]+², 583[M]+; Anal. Calcd. For C₂₁H₁₉ClF₁₂N₃O C, 43.21; H, 1.73; N, 7.20; Found: C, 43.56; H, 1.98; N, 7.51%.

2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(4-
fluorophenyl)acetamide(77f)

Yield 0.62 g (87.3 %), mp 243-245 °C; IR (KBr): 3272, 1677, 1546, 1384 cm⁻¹; ¹H NMR
(300 MHz, DMSO-d₆): δ 10.42(bs,1H, NH), 8.48 (s, 1H, Ar-H), 7.98 (s, 2H, Ar-H),
7.54 (m, 2H, Ar-H), 7.28 (m,2H, Ar-H), 7.25 (s, 1H, Pyrazole-CH), 4.75 (s, 2H, N-CH2); 13C NMR (75 MHz, DMSO-d6): δ 164.7(C=O), 162.7(C-F), 144.6, 142.5(Pyrazole-C-CF3), 133.1, 132.5(C-Cl), 131.5(Ar-C-CF3), 129.7, 128.1, 126.8, 125.5, 124.6(2Ar-CF3), 123.2, 121.4(Pyrazole-CF3), 120.3, 114.4, 107.5(Pyrazole-CH), 53.3(O-CH2); MS: 499[M]+; Anal. Calcd. For C20H1I,F10N3O C, 48.11; H, 2.22; N, 8.42; Found: C, 48.42; H, 2.57; N, 8.81%.

N-(2,5-bis(trifluoromethyl)phenyl)-2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide(77g)

Yield 0.75 g (85.2 %), mp 184-186 °C; IR (KBr): 3285, 1679, 1586, 1379 cm−1; 1H NMR (300 MHz, DMSO-d6): δ 10.95 (bs, 1H, NH), 8.50 (s, 2H, Ar-H), 8.12 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 7.94 (s, 1H, Pyrazole-CH), 7.78 (d, 1H, Ar-H, J = 8.5Hz), 7.69(d,1H, Ar-H, J = 8.4Hz), 5.35 (s, 2H, N-CH2); 13C NMR (75 MHz, DMSO-d6): δ 164.7(C=O), 147.3, 137.5, 133.7, 132.3(C-CF3), 131.1(Ar-C-CF3), 130.7, 126.9, 125.6, 124.9(CF3), 124.4(2Ar-CF3), 123.9(CF3), 121.8(Pyrazole-CF3), 117.6, 107.0(Pyrazole-CH), 54.1(O-CH2); MS: 617[M]+; Anal. Calcd. For C22H1I,F15N3O C, 48.20; H, 1.63; N, 6.81; Found: C, 42.57; H, 1.91; N, 6.54%.

Experiment No 6: Procedure for the synthesis of Ethyl 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetate(79)

\[
\begin{align*}
\text{K₂CO₃ / Acetonitrile} & \quad \text{Reflex} \\
\text{H₃C-O-Br} & \quad \text{78} \\
\begin{array}{c}
\text{72} \\
\text{CF₃} \\
\text{F₃C} \\
\text{HN-N} \\
\text{CF₃}
\end{array} & \quad \text{\rightarrow} \\
\begin{array}{c}
\text{CF₃} \\
\text{N-CF₃} \\
\text{F₃C} \\
\text{H₃C-O-} \\
\text{79}
\end{array}
\end{align*}
\]
To a magnetically stirred suspension of 72 (5 gm, 14.3 mmol), K$_2$CO$_3$ (3.3 g, 23.9 mmol) and DMF (100 ml) at room temperature was added 2-bromo ethyl acetate (2.5 g, 15.0 mmol). The reaction mass was then stirred at the same temperature for 3 hrs (TLC Check, CHCl$_3$: MeOH, 9:1). Reaction mass was then quenched in ice-cold water and extracted with 50.0 ml ethyl acetate. The ethyl acetate layer is then washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent is removed under reduced pressure to obtain viscous oil which on trituration with ethanol yielded white needles. Yield 6.0 g (96.3 %), mp 35-38 °C(Ethanol); IR (KBr): 1731, 1557, 1481, 1386 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.30 (s, 1H, Ar-H), 8.23 (s, 2H, Ar-H), 7.28(s, 1H, Pyrazole-CH), 5.34(s, 2H, N-CH$_2$), 4.06(q, 2H, J = 3.0Hz, Ester CH$_2$), 1.06(t, 3H, J = 3.0Hz, Ester CH$_3$); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 168.1(Ester C=O), 154.5(C-CF$_3$), 145.3(Ar-C-N), 143.6(Ar-C-N-Pyrazole), 136.5, 132.4(Ar-C-Pyrazole), 130.7(C-CF$_3$), 130.2, 128.5, 127.8(Ar-C-CF$_3$), 124.8(2Ar-CF$_3$), 122.8, 121.9(Pyrazole-CF$_3$), 107.4(Pyrazole-CH), 64.4(Ester CH$_2$), 53.7(N-CH$_2$), 15.4(Ester CH$_3$); MS: 434[M]$^+$,415, 361, 341, 213, 69,43; Anal. Calcd. For C$_{16}$H$_{11}$F$_9$N$_2$O$_2$ C, 44.25; H, 2.55; N, 6.45; Found: C, 44.57; H, 2.87; N, 6.77%.

**Experiment No 7: Procedure for the synthesis of 2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid(80).**

![Chemical Structures](image_url)
The above obtained compound 79 (6.0 gm, 13.82 mmol) was dissolved in tetrahydrofuran (65 ml) at room temperature and NaOH solution (2N, 7.5 ml, 15.2 mmol) added to it. The reaction mass was heated to 50 °C for 5 hours (TLC check, CHCl₃:MeOH, 9:1). The reaction mass was evaporated completely to obtain residue. The residue was dissolved in water (25 ml) and acidified with 2N HCl to pH 1-2. The product was extracted with ethyl acetate (25 ml), washed with saturated sodium chloride solution. The ethyl acetate extracts were dried over sodium sulfate and evaporated completely to obtain white solid.

Yield: 90.0%; mp 35-38 °C(Ethanol); IR (KBr): 3552, 1725, 1524 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 13.57(bs, 1H, COOH), 8.52 (s, 2H, Ar-H), 8.24 (s, 2H, Ar-H), 7.94(s, 1H, Pyrazole-CH), 5.23(s, 2H, N-CH₂); ¹³C NMR (75 MHz, DMSO-d₆): δ 178.3(Acid C=O), 155.4(C-CF₃), 147.6(Ar-C-N), 144.7(Ar-C-N-Pyrazole), 136.8, 134.9(Ar-C-Pyrazole), 131.7(C-CF₃), 130.6, 128.5, 127.1(Ar-C-CF₃), 123.9(2Ar-CF₃), 123.2, 122.3(Pyrazole-CF₃), 106.8(Pyrazole-CH), 55.2(N-CH₂); MS:406[M]+, 387, 361, 341, 213, 144, 75, 69, 45; Anal. Calcd. For C₁₄H₇F₉N₂O₂ C, 41.40; H, 1.74; N, 6.90; Found: C, 41.76; H, 1.53; N, 6.61%.
Experiment No 8: The synthesis of Amino acid linked pyrazole derivatives 82a-d

![Chemical structures](image)

**General procedure**

To a magnetically stirred suspension of 80 (0.5 g, 1.6 mmol) and dichloromethane (20 ml) at room temperature was added 81 (1.6 mmol) and TBTU (0.64 g, 2.0 mmol). To this was added a solution N,N-diisopropyl ethyl amine (0.774 g, 6.0 mmol) in dichloromethane (10 ml) drop wise at room temperature. The reaction mass was then stirred further for 2 hours (TLC Check, CHCl₃:MeOH, 8:2). Reaction mass was then washed twice with water (20 ml) followed by phosphoric acid (20 ml, 1% ) then with saturated sodium bicarbonate solution (20 ml) and finally with saturated sodium chloride solution(20 ml). The dichloromethane layer was then dried over sodium sulfate and evaporated completely and crystallized from hexane to obtain 82a-d in 78-88 % yield as white solid.

**Ethyl2-(2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-3-phenyl propionate (82a)**

Yield: 83%; mp. 50-53°C (n-Hexane); IR (KBr): 3266, 1736, 1697, 1666, 1622, 1605, 1548 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.86 (d, 1H, NH), 8.50 (s, 2H, Ar-H), 8.12 (s, 1H, Ar-H), 7.89 (s, 1H, Pyrazole-CH), 7.29-7.21 (m, 5H, Ar-H), 5.07 (s, 2H, N-CH₂), 5.01 (dd,
1H, J = 8.4 and 8.0 Hz), 4.51(q, 2H, ester O-CH₂, J = 8.0 Hz), 4.06 (dd, 1H, J = 5.5 and 5.5 Hz, ½ Ph-CH₂), 3.07 (dd, 1H, J = 8.2 and 8.3 Hz, ½ Ph-CH₂), 1.10(t, 3H, J = 7.1 Hz ester CH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ 172.7(Amide C=O), 171.5(Ester C=O), 164.2(C-F), 145.6, 142.6(Pyrazole-C-CF₃), 136.6, 135.5, 133.6, 132.1, 131.8(Ar-C-CF₃), 129.2, 128.6, 127.7, 125.9, 124.7(2Ar-CF₃), 123.1, 121.7(Pyrazole-CF₃), 121.5, 113.8, 105.3(Pyrazole-CH), 61.0(Ester CH₂), 59.3(N-CH₂), 56.7(CH), 36.8(CH₂), 14.1(Ester CH₃); MS: 581[M⁺], 508, 488, 361, 341, 213, 176, 148, 120, 83, 65, 43; Anal. Calcd. For C₂₅H₂₀F₉N₃O₃ C, 51.64; H, 3.47; N, 7.23; Found: C, 51.95; H, 3.58; N, 7.61%.

Ethyl-(2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)pyrrolidine-2-carboxylate(82b)

Yield: 84.3%; mp 35-38 °C(n-Hexane); IR (KBr): 3263, 1726, 1687, 1652, 1612, 1595, 1542 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.23 (s, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 7.83(s, 1H, Pyrazole-CH), 5.02 (s, 2H, N-CH₂), 4.29(dd, 1H, J = 8.4 Hz, 8.0 Hz), 4.21 (q, 2H, J =7.1 Hz ester O-CH₂), 3.51-3.41 (m, 2H, N-CH₂), 2.44-2.19 (m, 2H, ring CH₂), 2.02-1.92(m, 2H, ring CH₂), 1.24 (t, 3H, J =7.1 Hz ester CH₃); ¹³C NMR (75 MHz, DMSO-d₆): 172.7(Amide C=O), 171.5(Ester C=O), 164.2(C-F), 145.6, 142.6(Pyrazole-C-CF₃), 136.6, 135.5, 133.6, 132.1, 131.8(Ar-C-CF₃), 129.2, 128.6, 127.7, 125.9, 124.7(2Ar-CF₃), 123.1, 121.7(Pyrazole-CF₃), 121.5, 113.8, 105.3(Pyrazole-CH), 65.7(CH), 61.0(Ester CH₂), 57.5(N-CH₂), 49.6(N-CH₂), 28.9(CH₂), 24.5(CH₂), 14.1(Ester CH₃); MS: 531[M⁺], 512, 361, 341, 183, 142, 70, 41; Anal. Calcd. For C₂₁H₁₈F₉N₃O₃ C, 47.47; H, 3.41; N, 7.91; Found: C, 47.86; H, 3.82; N, 7.61%.
Ethyl 2-(2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-3-(4-hydroxyphenyl) propionate (82c)

Yield: 88%; mp 43-45 °C (n-Hexane); IR (KBr): 3263, 1746, 1685, 1667, 1632, 1602, 1538 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 9.27 (bs, 1H, OH), 8.80 (d, 1H, NH), 8.51 (s, 2H, Ar-H), 8.29 (s, 1H, Ar-H), 7.89 (s, 1H, Pyrazole-CH), 7.00 (d, 2H, J = 7.5 Hz, Ar-H), 6.67 (d, 2H, J = 7.5 Hz, Ar-H), 5.08 (s, 2H, N-CH₂), 4.43 (dd, 1H, J = 8.4 Hz, 8.0 Hz), 4.21 (q, 2H, ester O-CH₂), 3.23 (dd, 1H, J = 5.5 Hz, 5.5 Hz, Ph-CH₂), 2.85 (dd, 1H, J = 8.2 Hz, 8.3 Hz, ½ Ph-CH₂), 1.29 (t, 3H, J = 7.0 Hz ester CH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ 172.7 (Amide C=O), 171.5 (Ester C=O), 155.7 (Ar-C-OH), 145.6, 142.6 (Pyrazole-C-CF₃), 136.6, 135.5, 133.6, 132.1, 131.8 (Ar-C-F), 130.2, 129.2, 127.7, 125.9, 124.7 (2Ar-C-F), 123.1, 121.7 (Pyrazole-C-CF₃), 121.5, 115.8, 105.3 (Pyrazole-CH), 61.0 (Ester CH₂), 59.3 (N-CH₂), 56.7 (CH), 36.8 (CH₂), 14.1 (Ester CH₃); MS: 597[M⁺]⁺, 470, 438, 419, 244, 216, 188, 145, 117, 77, 63, 51; Anal. Calcd. For C₂₅H₂₀F₉N₃O₄ C, 50.26; H, 3.37; N, 7.03; Found: C, 50.47; H, 3.71; N, 7.24%.

Ethyl 2-(2-(5-(3,5-bis(trifluoromethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-pentanoate (82d)

Yield: 78%; mp 63-65 °C (n-Hexane); IR (KBr): 3258, 1729, 1685, 1654, 1624, 1615, 1541 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 8.78 (d, 1H, NH), 8.51 (s, 2H, Ar-H), 8.28 (s, 1H, Ar-H), 7.90 (s, 1H, Pyrazole-CH), 5.12 (s, 2H, N-CH₂), 4.24 (dd, 1H, CH, J = 8.4 Hz, 8.0 Hz), 4.08 (q, 2H, J = 7.1 Hz ester O-CH₂, J = 8.0 Hz), 1.64 (q, 2H, CH₂, J = 8.4 Hz), 1.33 (m, 2H, CH₂), 1.17 (t, 3H, J = 7.1 Hz ester CH₃, J = 8.4 Hz), 0.88 (t, 3H, CH₃, J = 8.4 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 171.5 (Ester C=O), 166.5 (Amide C=O), 164.2 (C-F), 145.6, 142.6 (Pyrazole-C-CF₃), 136.6, 135.5, 133.6, 132.1, 131.8 (Ar-C-CF₃), 129.2, 128.6, 127.7, 125.9, 124.7 (2Ar-C-F), 123.1, 121.7 (Pyrazole-C-CF₃), 121.5, 113.8,
105.3(Pyrazole-CH), 55.9(CH), 61.3(Ester CH₂), 59.7(N-CH₂), 33.4(CH₂), 18.8(CH₂),
14.1(Ester CH₃), 13.8(Terminal CH₃). MS : 533[M]+, 514, 491, 361, 341, 213, 144, 116,
84, 55, 41; Anal. Calcd. For C₂₁H₂₀F₉N₃O₃ C, 47.29; H, 3.78; N, 7.88; Found: C, 47.16; H,
3.54; N, 7.49%.

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