Chapter 1

Synthesis and antimicrobial screening
of 3, 5-disubstituted triazole/oxadiazole
derivatives

1.1 Introduction

Triazole

Triazole, a heterocyclic nucleus has attracted a wide attention of the medicinal chemist in search for the new therapeutic molecules. Now a day’s research is concentrated towards the introduction of new and safe therapeutic agents of clinical importance. The heterocycles are gaining their importance as being the center of activity. The nitrogen containing heterocycles are found in abundance in most of the medicinal compounds. The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade. Triazoles are well known five membered heterocyclic compounds belong to one of the most widely used class of antifungal drugs known as azoles. Several procedures for their synthesis have been extensively studied.

Two structural isomeric triazoles are known, 1, 2, 3-triazole and 1, 2, 4-triazole. Each exists in two dissimilar tautomeric forms. The different isomers are characterized by the position of the nascent hydrogen. Thus 1, 2, 4-triazoles are exist in two forms i.e. $1H$ and $4H$. 

![Triazoles Diagram]
1,2,4-triazoles are very interesting targets for medicinal and pharmaceutical applications. 1,2,4-triazole derivatives investigated due to their wide range of biological activities such as antifungal\(^1\), antitubercular\(^2\), anticonvulsants,\(^3,4\) 5-lipoxygenase inhibitors\(^5\) and as anticancer drugs.\(^6\) Platinum(II) complexes comprising 1,2,4-triazoles as ligands show antitumor activity similar to cis-platin.\(^7-9\)

Z. M. Hao\(^10\) and S. T. Steven\(^11\) have been studied briefly with the chemistry of 1,2,4-triazoles. Bladin\(^12,13\) is a pioneer scientist in the field of triazole, who had synthesized the first derivative of 1,2,4-triazole in 1885. 1,2,4-Triazole derivatives not only known for their medicinal applications, but they are also used as analytical reagents\(^14\), dyes and photographic chemicals\(^15\) corrosion inhibitors\(^16,17\) and in the preparation of polymers.\(^18\)

**Oxadiazole**

Oxadiazoles are five member heterocyclic compounds and show various type of biological activities. In the field of medicinal chemistry 2, 5- disubstituted 1, 3, 4- Oxadiazole moieties are important because of their versatile biological actions. During the last few decades, biological activities, synthesis and transformations of five membered heterocyclic compounds have received considerable attention and importance due to their remarkable and wide variety of applications. 2, 5- Disubstituted-1, 3, 4-oxadiazole and its derivatives constitute an important family of heterocyclic compounds. Due to their remarkable unique properties and have been frequently employed in drug synthesis.

Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring. There are three known isomers: 1, 3, 4-oxadiazole (1), 1, 2, 4-oxadiazole (2), 1, 2, 3-oxadiazole (3) and 1, 2, 5-oxadiazole (4). However, 1, 3, 4-oxadiazole and 1, 2, 4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties.
Oxadiazoles have various commercial and industrial applications, various biological activities like antibacterial\textsuperscript{19}, antifungal\textsuperscript{20}, anti-inflammatory\textsuperscript{21}, analgesic\textsuperscript{22}, anticancer\textsuperscript{23}, antihypertensive\textsuperscript{24}, anticonvulsant\textsuperscript{25}, antiproliferative\textsuperscript{26}, cardiovascular\textsuperscript{27}, hypoglycemic\textsuperscript{28}, hypnotic and sedative\textsuperscript{29} and insecticidal\textsuperscript{30}.1, 3, 4-oxadiazoles showed antibacterial properties similar to those of well known sulfonamide drugs.

\subsection{1.2 Pharmacological Profile of triazole derivatives}

Literature survey reveals that various 1, 2, 4-triazole derivatives display significant biological activities such as Bactericidal,\textsuperscript{31} Diuretic,\textsuperscript{32} Fungicidal,\textsuperscript{33} Herbicidal,\textsuperscript{34} Insecticidal and acaricidal,\textsuperscript{35} Plantgrowthregulator,\textsuperscript{36} Anticancer and Anti-HIV,\textsuperscript{37} Antileshmanial,\textsuperscript{38} Antitumor\textsuperscript{39} activities. The clinically useful derivatives of 1, 2, 4-triazole nucleus with their activity are listed as under.

![Figure-1.1](image)

1, 2, 4-triazoles show high levels of biological activity as herbicides and fungicides.\textsuperscript{40}-\textsuperscript{42} 1, 2, 4-Triazoles such as Propiconazol are highly efficient fungicides and are in use as broad-spectrum fungicides in agriculture. The biological effect of 1, 2, 4-triazole fungicides originate from the inhibition of the biosynthesis of ergosterol in fungi.\textsuperscript{43} Examples of pesticides containing a 1, 2, 4-triazole fragment are given as under.
Takahiro Sato et al.\textsuperscript{44} synthesized a series of 3,5-disubstituted-1,2,4-triazole derivatives and, in particular, examined them in vivo activity in lowering the serum uric acid levels in rats. As a result, identified 3-(3-cyano-4-pyridyl)-5-(4-pyridyl)-1,2,4-triazole to be one of the most potent XOR inhibitors; it exhibited an extremely potent in vivo activity as a safe and potent xanthine oxidoreductase (XOR) inhibitor for the treatment of hyperuricemia (Figure 1.3).

Yaseen A. et al.\textsuperscript{45} have prepared 1,5-dialkyl-3-(5-marcepto-4-aryl-1H-1,2,4-triazolo-3-yl-methylene)-1H-1,2,4-triazole which exhibited remarkable activity against nine type of cancer and also anti viral activity. Bozena et al.\textsuperscript{46} have synthesized triazole derivatives and tested for their anticonvulsant and antinonciceptive activity. Sylvie larrat et al.\textsuperscript{47} investigated that ribavarin in combination with alpha-2-interferon is the consensus treatment for chronic hepatitis C. and E. De Clercq et al\textsuperscript{48} screened ribavarin (Figure 1.4) for their antiviral and antimetabolic activities.
Shao-Lin Zhang et al. have synthesized series of novel berberine triazoles. All target compounds and their precursors were screened for in vitro antimicrobial activities. Most of the prepared compounds exhibited good antibacterial and antifungal activities with low MIC values ranging from 2 to 64 µg/mL. Dan Ji et al. have reported a series of 3-S-β-D-glucosides-4-arylideneamino-5-aryl-1, 2, 4-triazoles by the combination of 1, 2, 4-triazole, Schiff base and glucosides and have been evaluated for their antimicrobial activities in vitro against Staphylococcus aureus, Escherichia coli as well as Monilia albican. All the target compounds exhibited better antifungal activity than antibacterial activity (Figure-1.5).

S. Botros Hybrid et al. carried out pharmacophore approach relies on the use of two or more pharmacophores, each with potential pharmacological activity to be combined in one molecule, aiming that this hybridization could produce compounds with better pharmacological profile. Phenytoin, a well-established antiepileptic drug, Hybrids between Phenytoin and 1, 3, 4-oxadiazole or 1, 2, 4-triazole were synthesized and tested for anticonvulsant activity. Whereas the compounds displayed promising anticonvulsant effect in the standard maximal electroshock (MES) model (Figure-1.6).
Figure-1.6

Paolo Polucci et al.\textsuperscript{52} have reported antiproliferative activity and structure activity relationships of Alkyl sulfanyl-1, 2, 4-triazoles. Which inhibits VCP ATPase with an IC\textsubscript{50} of 24 nM and possesses antiproliferative activity in the submicromolar range (Figure-1.7).

Figure-1.7

Daniele Binchi et al.\textsuperscript{53} have screened pure stereoisomer of two new triazole derivatives (Figure 1.8) for their antifungal activity against variety of fungi showing an activity ratio R-form and S-form up to 400.

Figure-1.8

Krzysztof W. et al.\textsuperscript{54} have discovered 1, 2, 4-triazole (Figure 1.9) and reported their antimicrobial activity. Dae-Kee Kim et al have been synthesized 1, 2, 4-triazole derivatives to study their pesticidal and herbicidal activity.
Sherin M. El-Feky et al.\textsuperscript{55} have reported a new series of 3,5-disubstituted triazoles (Figure 1.10) were synthesized and evaluated for \textit{in vitro} antifungal and antibacterial activity. All compounds tested showed significant antifungal activity against micromycetes compared to the commercial fungicide clotrimazole.

Hakan Bekats et al.\textsuperscript{56} have synthesized some novel 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-one (Figure 11) and all newly synthesized compounds were screened for their antimicrobial activities and some of which were found to possess good or moderate activities against the test microorganisms (Figure-1.11).
1.3 Pharmacological Profile of Oxadiazole derivatives

1, 3, 4-oxadiazole has become an important construction motif for the development of new drugs. Two examples of compounds containing the 1, 3, 4-oxadiazole unit currently used in clinical medicine are: Raltegravir an antiretroviral drug, and Zibotentan an anticancer agent (Figure 1.12).

Sangshetti et al.\(^{57}\) investigated the antifungal activity of a number of disubstituted oxadiazoles. Oliveira et al.\(^{58}\) reported synthesis and anti staphylococcal activity of 1,3,4-oxadiazolines against strains of Staphylococcus aureus, compounds showed efficient anti staphylococcal activity at 4 to 32 \(\mu\)g/mL, making all the compounds 2–8 times more active than the standard drug chloramphenicol (Figure-1.13).

Yoshida et al.\(^{59}\) described the synthesis and optimization of anti-Helicobacter pylori activity for a new series of cephem derivatives. Compounds exhibited anti Helicobacter pylori activity at a MIC value of 0.1 \(\mu\)g/mL. Bakal et al.\(^{60}\) investigated anti-tubercular activity for a series of 2, 5-disubstituted oxadiazoles against M. tuberculosis. Compound show MIC\(_{50} = 0.04 \pm 0.01\) \(\mu\)M which was comparable with Isoniazid (Figure-1.14).
Song Cao et al.\textsuperscript{61} have investigated some Oxadiazoles possessing insecticidal activity. Suresh Kumar G. V. et al.\textsuperscript{62} have discovered oxadiazole derivatives and reported their antimycobacterial activity. Ali Almasired et al.\textsuperscript{63} have prepared 1,3,4-oxadiazoles of type as anticonvulsant agent. Meria Grazia Mamolo et al.\textsuperscript{64} have synthesized 3-substituted-5-(pyridine-4-yl)-3H-1,3,4-oxadiazole-2-one of type and studied their antimycobacterial activity. Bhandari S. V. et al.\textsuperscript{65} have reported 1,3,4-oxadiazoles for their anti-inflammatory Activity (Figure 1.15).

T. P. Mohan et al.\textsuperscript{66} have synthesized 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives and screened for their insecticidal activity. Krishna K. J. et al.\textsuperscript{67} have reported antimicrobial activity of oxadiazole derivatives. J.A. Christopher. et al.\textsuperscript{68} have documented anti HIV activity of 1,3,4-oxadiazole derivatives. Gilani S. J. et al.\textsuperscript{69} have synthesized some oxadiazoles as anti-inflammatory and analgesic agents. K. Subrahmanya Bhat et al.\textsuperscript{70} have prepared new fluorine containing 1, 3, 4-oxadiazoles and reported them as potential antibacterial and anticancer agents (Figure 1.16).
Ronald Kim et al.\textsuperscript{71} have discovered oxadiazole derivatives useful as protease inhibitors. Mohd Amir and Kumar Shikha et al.\textsuperscript{72} have documented anti-inflammatory, analgesic and ulcerogenic activity of some newly synthesized oxadiazoles. Ali A. et al.\textsuperscript{73} have investigated some oxadiazole derivatives possessing antimicrobial and anti-HIV-1 activity. Sherif A. et al.\textsuperscript{74} have reported oxadiazoles as potential antitumor and anti-HIV agents. Afshin Zarghi et al.\textsuperscript{75} have synthesized R-substituted-5-(2-benzyl oxy phenyl)-1,3,4-oxadiazoles possessing anticonvulsant activity. Mahamud Tareq et al.\textsuperscript{76} have synthesized 2,5-disubstituted-1,3,4-oxadiazoles useful as tyrosinase inhibitors (Figure 1.17).

\textbf{Figure-1.17}

Qian-Ru Du et al.\textsuperscript{77} were designed and synthesized a series of novel 1, 3, 4-oxadiazole thioether derivatives as potential inhibitors of thymidylate synthase (TS) and as anticancer agents. Compounds show good in vitro anticancer activities with IC50 values of 0.7 ± 0.2. Nimavat B. et al.\textsuperscript{78} have synthesized derivatives of 1, 3, 4-oxadiazoles and evaluated for their in vitro antioxidanr activity (Figure-1.18).

\textbf{Figure-1.18}
1.4 Synthetic strategies for the Triazoles

Odd R. Gautun et al. have synthesized a series of triazoles using unsymmetric bis(α-alkyl aminobenzylidene)-hydrazines via reacting with 40% aqueous methylamine solution or saturated NH$_3$ in 2-propanol in 70-80% yield (Figure-1.19).

H. J. Carlsen et al. have been reported sterically hindered 4-alkyl-3,5-diphenyl-4$H$-1, 2, 4-triazoles by heating bis(α-chlorobenzylidene)hydrazine with alkylamines either neat or in a variety of solvents, were transformed into the corresponding triazoles in high yields (Figure-1.20).

Satoshi Ueda et al. examine the synthesis of 1$H$-1, 2, 4-triazoles from amidines and nitriles via copper-catalyzed oxidative coupling process from. The reactions of benzamidine and benzonitriles in presence of copper bromide as a catalyst and Cs$_2$CO$_3$ as a base afforded triazoles in good yields. The reactions of primary, secondary, and tertiary alkyl amidines provided the corresponding 5-alkyl triazoles in moderate to good yield (Figure-1.21).
Shahnaz Rostamizadeh et al.\textsuperscript{82} have synthesized 3,5-disubstituted-1,2,4-triazoles via three-component condensation reaction of acid hydrazides, S-methyl isothioamide hydroiodides, and ammonium acetate on the surface of silica gel under microwave irradiation in 80-90\% yield (Figure-1.22).

![Figure-1.22](image)

Kap-Sun Yeung et al.\textsuperscript{83} carried out synthesis of 3, 5-disubstituted 1, 2, 4-triazoles that proceeds by the direct reaction of a nitrile and a hydrazide in the presence of catalytic amount of K\textsubscript{2}CO\textsubscript{3} in nBuOH with good yield (Figure-1.23).

![Figure-1.23](image)

Makhluf J. Haddadin et al.\textsuperscript{84} have synthesized 3,5-diaryl-(NH)-1,2,4-triazoles from the reaction of 3,6-diaryl-1,2,4,5-tetrazines and 2-aryl substituted acetonitriles, under basic conditions in moderate yields (Figure-1.24).

![Figure-1.24](image)

Georgette M. Castanedo et al.\textsuperscript{85} have been developed the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from reaction of carboxylic acids, primary amidines and monosubstituted hydrazines using HATU as a coupling reagent (Figure-1.25).
Atli Thorarensen et al. have been synthesized 3,5-disubstituted-1,2,4-triazole from aryl hydrazide and methyl benzimidate via reflux in xylene. 3, 5-disubstituted-1,3,4-oxadiazole were formed by using anion exchange resin Dowex-OH (Figure 1.26).

K. Paulvannam et al. have developed an improved synthesis of 1,3,5-trisubstituted 1,2,4-triazoles via Ag₂CO₃ mediated cyclization of triazenes. The reaction was complete within 3h and the products were isolated in moderate to high yields (Figure 1.27).

Reid and Heindel et al. reported that the reaction of aryl acid hydrazide with CS₂/KOH and hydrazine hydrate yielded triazoles (Figure 1.28).
A.K. Mishra et al. have reported synthesis and antimicrobial activity of some newer oxadiazole/triazole derivatives starting from 2-substituted-1Hbenzimidazole (Figure 1.29).

Shokoofeh Maghari et al. have synthesized 2,5-disubstituted 1,3,4-oxadiazoles from isothiocyanates and hydrazides through cyclodesulfurization in the presence of (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) TBTU as an uronium coupling reagent in good yield (Figure 1.30).

Srimanta Guin et al. have synthesized 2,5-disubstituted 1,3,4-oxadiazoles through an imine C-H functionalization of N-arylidenearylhydrazide using a catalytic quantity of Cu(OTf) (Figure 1.31).
Anil N. Mayekar et al.\textsuperscript{92} reported a series of new 1,3,4 oxadiazole derivatives having 6-bromonaphthalene moiety are synthesized a hydrazide was treated with various substituted aromatic acids in presence of POCl\textsubscript{3} to give 2-\{[(6- bromo-2-naphthyl)oxy]methyl\}-5-aryl-1,3,4-oxadiazole (Figure-1.32).

Chandrakantha, B. et al.\textsuperscript{93} have synthesized Oxadiazoles by the reaction of hydrazide and aromatic acid in presence of POCl\textsubscript{3} (Figure-1.33).

D. Ramesh and B. Sreenivasan et al.\textsuperscript{94} have synthesized 1,3,4-oxadiazoles from semicarbazide in presence of POCl\textsubscript{3} (Figure-1.34).

K. Mogilaiah and B. Sakram et al.\textsuperscript{95} have prepared 1,3,4-oxadiazole from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride (Figure-1.35).
Yu Yuve et al.\textsuperscript{96} have reported microwave assisted synthesis protocol with 91% of the yield (Figure-1.36).
1.6 Current research work

The 1,2,4-triazoles and 1,3,5-oxadiazoles have considerable chemical and pharmaceutical importance because of broad range of biological activities. As we described in most of the reported synthesis of triazoles and oxadiazoles in which acyl hydrazide was used as a synthon.

In present work we have synthesized 1,2,4-triazoles using acyl hydrazide and S-methyl thioamide by heating in dimethylformamide using potassium carbonate as a base. An interesting phenomenon occurs when simply heating in DMF at 120°C without using any base. A reaction of acyl hydrazide and s-methyl thioamide carried out in presence of base only one product 1,2,4-triazole was obtained in high yield, while the reaction was carried out without any base with same reaction condition than the mixture of 1,2,4-triazole and 1,3,5-oxadiazole was obtained in around (60:40) ratio, which was never reported before. Such synthetic aspect for oxadiazole was absent in literature survey.
1.7 Result and discussion

Scheme-1.1 Synthesis of 3,5-disubstituted triazoles/oxadiazoles.

Scheme-1.2

Studies on heterocyclic analogues
A series of 3,5-disubstituted triazoles and oxadiazole was prepared from nitrile derivatives. Initially thioamide derivatives (Int-2 & Int-5) were prepared from corresponding nitriles by simply stirring with sodium hydrogen sulphide and magnesium chloride in DMF, which followed by methylation to S-methyl thioamide derivatives (Int-3 & Int-6).

The condensation of S-methyl thioamide derivative and acyl hydrazide (Int-4) was carried out at 150°C in DMF using potassium carbonate as a base to generate 3,5-disubstituted triazoles (SPG-1Aa-t) in high yield and purity while the reaction was carried out without using any base with same reaction condition than the mixture of 3,5-disubstituted triazoles (SPG-1Aa-t) and oxadiazoles (SPG-1Ba-t) were obtained. The purification was carried out by hydrochloride salt formation of triazole which was
filtered in salt form and filtrate contains oxadiazole in good purity. The synthesis of 1,3,5-oxadiazoles by this method was not reported before.

The structure of triazoles and oxadiazoles was identified by Mass, IR and NMR spectroscopy. In Mass there was only one m/z value difference between corresponding triazole and oxadiazole while in $^1$H NMR spectrum of triazole shows singlet at above 14 δppm which indicate NH of triazole ring, this signal is absent in $^1$H NMR spectrum of oxadiazole and other signals are same as triazoles which prove that the formation of oxadiazoles. Which further support by IR spectrum of triazoles shows a broad peak at around 3200-3400 cm$^{-1}$ for N-H stretching vibration which is absent in IR spectrum of oxadiazoles.

**Table-1.1: Synthesis of 3,5-disubstituted triazoles/oxadiazoles.**

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<th>Time h</th>
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Studies on heterocyclic analogues
The mechanism for the formation of triazole and oxadiazole is depicted in (Figure-1.37). In the mechanism it was proposed that formation of triazole ring is occur by removal of water molecule while oxadiazole ring is form by removing ammonia molecule.

Figure-1.37 Proposed mechanism for the formation of triazole and oxadiazole.
1.8 Antimicrobial sensitivity testing


In vitro effectivity of antimicrobial agents can be demonstrated by observing their capacity to inhibit bacterial growth on suitable media. The production of a zone depends on two factors namely bacterial growth and concentration of antimicrobial agent. The hole/well punch method was first used by Bennett. This diffusion method has proved more effective then many other methods. According to Lt. General Raghunath the well technique is 5-6 times more sensitive than using disk method.

Principle

When antimicrobial substance is added in agar cup (made in a medium previously inoculated with test organism) the redial diffusion of an antimicrobial agent through the agar, produces a concentration gradient. The test organism is inhibited at the minimum inhibitory concentration (MIC), giving rise to a clear zone of inhibition.

Requirements

1. Young broth culture of a standard test organism
2. Sterile Mueller Hinton Agar plate
3. Solution of antimicrobial substance
4. Cup borer
5. Alcohol etc.

Inoculum preparation

Inoculum was prepared by selecting 4-5 colonies from slope of stock culture of the indicator organism and emulsifying them in a suitable broth. The inoculated broth was incubated at 37°C till it equals turbidity of a 0.5 McFarland standard. This happens in 2-8 h.
Procedure

1. Inoculate test organism on the top of Mueller Hinton Agar plate with help of sterile swab. (it can be inoculated in melted agar also )
2. The swab was dipped in the Inoculum and surface of plate was streaked with swab.
3. Streaking was repeated for 3 times and each time the plate was rotated at angle of 60°.
4. Sterilize the cup-borer make four cups of the diameter of 8-10 mm. at equal distance in the plate previously inoculated with seed culture.
5. The depth of well was 2.5-5.0 mm.
6. The wells have been clearly punched so the surrounding medium is not lifted when the plug was removed out.
7. The plates were incubated at 37°C for 24 h. Then the zone of inhibition measured and the size of zone cited in table.
### Antimicrobial Sensitivity Assay

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<th>antifungal activity</th>
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1.9 Conclusion

We have developed a novel simple method for the synthesis of 3,5-disubstituted-1,2,4-triazole and 3,5-disubstituted-oxadiazole in an only single reaction with simple isolation of both product in high yield and purity. The reaction of imidothioate and various acyl hydrazides was carried out by simply heating in DMF. The formation of oxadiazole by this method was first developed by us. All the synthesized compounds were evaluated for their antimicrobial activity. The investigation of antibacterial and antifungal screening data revealed that, the compounds SPG-1Bl, Bp and int2.2 shows very good activity against bacterial stain, SPG-1Bl, Bp, Ac and Af shows comparatively good activity against fungal stain.
1.10 Experimental section

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. \(^1\)H (400 MHz), \(^13\)C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl\(_3\) and DMSO. Chemical shifts are expressed in \(\delta\) ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

- **General synthesis of \(N\)-(3-cyano-4-fluorophenyl)-4-fluorobenzamide (Int-1).**

Thionyl chloride (5.34 mL, 0.0734 mol) was added to a solution of 4-fluoro benzoic acid (5.15 g, 0.0367 mol) in dry DCM (50 mL). Upon the addition of 1-2 drop of DMF a mixture was heated at reflux for 1 h. The resultant solution than cooled to 25°C, to this solution a mixture of 5-amino-2-fluorobenzonitrile (5 g, 0.0367 mol) in DCM (30 mL) was added drop wise with stirring. The reaction mixture was refluxed for 2 h. After the completion of reaction a mixture was washed with water followed by saturated NaHCO\(_3\) solution. The organic phase was dried over anhydrous Na\(_2\)SO\(_4\) and solvent was removed under reduced pressure to afford analytically pure product (9 g, 95% yield).

- **General synthesis of \(N\)-(3-carbamothioyl-4-fluorophenyl)-4-fluorobenzamide (Int-2).**

To the stirred solution of \(N\)-(3-cyano-4-fluorophenyl)-4-fluorobenzamide 1 (2 g, 7.745 mmol) in DMF (20 mL), MgCl\(_2\)-6H\(_2\)O (3.93 g, 19.363 mmol) was added at 0-5°C. The resultant solution stirred for 10 min, than sodium hydrogensulphide (0.868 g, 15.490 mmol) was added portion wise in cooling. A mixture was stirred at room temperature for 1 h. After the completion of reaction, mixture was washed with water followed by saturated NaHCO\(_3\) solution. The organic phase was dried over anhydrous Na\(_2\)SO\(_4\) and solvent was removed under reduced pressure to afford analytically pure product (2.2 g, 97%).
General synthesis of methyl -2-fluoro-5-(4-fluorobenzamido) benzimidothioate (Int-3).

To a solution of N-(3-carbamothioyl-4-fluorophenyl)-4-fluorobenzamide 2 (2 g, 6.842 mmol) in diethyl ether (20 mL) was added methyl iodide (0.51 mL, 8.210 mmol) while stirring at 0°C. this solution was stirred for 30 min at 0°C then warmed to room temperature for 10 h. the solid obtained was filtered and washed with diethyl ether (20 mL), pure product obtained (1.9 g, 90%).

General synthesis of 3,5-disubstituted-1,2,4-triazoles (SPG-1Aa-t).

To a mixture of methyl -2-fluoro-5-(4-fluorobenzamido) benzimidothioate (3.26 mmol) and hydrazides (3.26 mmol) in 10 mL DMF was added K₂CO₃ (9.8 mmol) at room temperature. The resulting reaction mixture was further stirred at rt for 30 min, then heated up to 120°C for 3-4 h. After completion of the reaction, the mixture was poured in ice cold water. The obtained solid was filtered, wash with water and dried it in oven.

General synthesis of 3,5-disubstituted-1,3,5-oxadiazoles (SPG-1Ba-t).

A mixture of methyl -2-fluoro-5-(4-fluorobenzamido) benzimidothioate (3.26 mmol) and hydrazides (3.26 mmol) in 10 mL DMF was heated at 120°C for 3-4 h. After completion of the reaction, the mixture was poured in to ice cold water. The solid mixture of 1,3,5-oxadiazole and 1,2,4-triazole was obtained which was filtered and dried. Now obtained solid was dissolved in diethyl ether and dry HCl gas was pursed with stirring at 5-10°C. The hydrochloride salt of 1,2,4-triazole was precipitated which filtered. The filtrate was washed with water (2 x 100 mL) and organic layer was separated, dried over anhydrous sodium sulfate and evaporated under reduce pressure to afford analytically pure products.
Spectral data of the synthesized compounds

N-(3-cyano-4-fluorophenyl)-4-fluorobenzamide (Int-1): white solid; $R_f$ 0.45 (4:6 hexane-EtOAc); mp 126-128 °C; IR (KBr): 3298, 3144, 3082, 2233, 1654, 1602, 1502, 1408, 1327, 1226, 1163, 1014, 823, 773, 675, 545, 493 cm$^{-1}$; $^1$H NMR: $\delta$ 7.385-7.474 (m, 2H, Ar-H), 7.537-7.583 (t, 1H, Ar-H), 8.028-8.081 (m, 3H, Ar-H), 8.263-8.284 (dd, 1H, Ar-H, $j=2.4,5.6$ Hz), 10.611 (s, 1H, -NH amide); MS ($m/z$): 250 (M$^+$); Anal. Calcd for: C$_{14}$H$_8$F$_2$N$_2$O: C, 65.12; H, 3.12; N, 10.85; Found: C, 65.32; H, 3.18; N, 10.77.

N-(3-carbamothioyl-4-fluorophenyl)-4-fluorobenzamide (Int-2): Pale yellow solid; $R_f$ 0.4 (4:6 hexane-EtOAc); mp 156-158 °C; IR (KBr): 3504, 3450, 3358, 3281, 3174, 1658, 1568, 1431, 1377, 1215, 1169, 1093, 835, 740, 605, 522 cm$^{-1}$; $^1$H NMR: $\delta$ 7.221-7.268 (t, 1H, Ar-H), 7.361-7.405 (t, 2H, Ar-H), 7.849-7.878 (dd, 3H, Ar-H), 8.011-10.8.072 (dd, 1H, Ar-H), 9.644 (s, 1H, -NH$_2$), 10.208 (s, 1H, -NH$_2$), 10.422 (s, 1H, -NH amide); MS ($m/z$): 292 (M$^+$); Anal. Calcd for: C$_{14}$H$_8$F$_2$N$_2$O: C, 65.12; H, 3.12; N, 10.85; Found: C, 65.21; H, 3.20; N, 10.91.

Methyl 2-fluoro-5-(4-fluorobenzamido)benzimidithioate (Int-3): Brown solid; $R_f$ 0.3 (4:6 hexane-EtOAc); mp 168-170 °C; IR (KBr): 3369, 3269, 3076, 1649, 1604, 1531, 1423, 1352, 1246, 1161, 1095, 889, 759, 685, 551 cm$^{-1}$; $^1$H NMR: $\delta$ 2.860 (s, 3H, S-Me), 7.395-7.439 (t, 2H, Ar-H), 7.527-7.574 (t, 1H, Ar-H), 7.910-8.075 (m, 3H, Ar-H), 8.270-8.291 (dd, 1H, Ar-H), 11.978 (s, 1H, =NH), 10.681 (s, 1H, -NH amide); MS ($m/z$): 306 (M$^+$); Anal. Calcd for: C$_{15}$H$_{12}$F$_2$N$_2$O: C, 58.81; H, 3.95; N, 9.14; Found: C, 58.97; H, 3.79; N, 9.21.

4-fluoro-N-(4-fluoro-3-(5-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazol-3-yl)phenyl) benzamide (SPG-1Aa): White solid; $R_f$ 0.38 (4:6 hexane-EtOAc); mp 228-230 °C; IR (KBr, cm$^{-1}$): 3173, 3082, 2943, 1921, 1737, 1656, 1543, 1367, 1219, 1168, 1066, 848, 763, 682, 588 cm$^{-1}$; $^1$H NMR: $\delta$ 7.387-7.431 (t, 3H, Ar-H), 7.923-7.997 (m, 2H, Ar-H), 8.059-8.178 (m, 3H, Ar-H), 8.301-8.321 (d, 2H, Ar-H, $j=8$ Hz), 8.570-8.580 (d, 1H, Ar-H, $j=4$ Hz), 10.553 (s, 1H, -NH amide), 14.684 (s, 1H, -NH triazole); $^{13}$C NMR (100 MHz, DMSO): 115.22, 115.44, 116.44, 116.66, 121.12, 123.77, 125.92, 126.54, 128.34, 130.35, 130.44, 130.82, 135.81, 162.88, 163.44, 164.37, 165.35; MS ($m/z$): 444 (M$^+$); Anal. Calcd for C$_{22}$H$_{13}$F$_5$N$_4$O: C, 59.46; H, 2.95; N, 12.61; Found: C, 59.52; H, 2.87; N, 12.68.
N-(3-(5-(4-bromophenyl)-1H-1,2,4-triazol-3-yl)-4-fluorophenyl)-4-fluorobenzamide (SPG-1Ab): White solid; Rf 0.35 (4:6 hexane-EtOAc); mp 204-206°C; IR (KBr, cm^{-1}): 3163, 3082, 2942, 1941, 1751, 1658, 1526, 1381, 1214, 1167, 1061, 862, 764, 687, 585 cm^{-1}; MS (m/z): 455 (M^+); Anal. Calcd for C_{21}H_{13}BrF_{2}N_{4}O: C, 55.40; H, 2.88; N, 12.31; Found: C, 55.37; H, 2.94; N, 12.35.

4-fluoro-N-(4-fluoro-3-(5-(4-fluorophenyl)-1H-1,2,4-triazol-3-yl)phenyl)benzamide (SPG-1Ac): White solid; Rf 0.4 (4:6 hexane-EtOAc); mp 190-192°C; IR (KBr, cm^{-1}): 3156, 3078, 2952, 1934, 1740, 1661, 1532, 1375, 1208, 1173, 1052, 851, 773, 693, 579 cm^{-1}; 1H NMR: δ 7.377-7.438 (m, 5H, Ar-H), 7.970 (dd, 1H, Ar-H, j=3.6, 8.6 Hz), 8.079-8.146 (m, 4H, Ar-H), 8.535 (dd, 1H, Ar-H, j=2.8, 6.4 Hz), 10.517 (s, 1H, -NH amide), 14.542 (s, 1H, -NH triazole); MS (m/z): 394 (M^+); Anal. Calcd for C_{21}H_{13}F_{3}N_{4}O: C, 63.96; H, 3.32; N, 14.21; Found: C, 63.83; H, 3.41; N, 14.27.

N-(3-(5-(2-chlorobenzyl)-1H-1,2,4-triazol-3-yl)-4-fluorophenyl)-4-fluorobenzamide (SPG-1Ad): Pale yellow solid; Rf 0.42 (4:6 hexane-EtOAc); mp 182-184°C; IR (KBr, cm^{-1}): 3261, 3174, 3066, 2918, 1645, 1545, 1498, 1373, 1230, 1157, 1093, 848, 750, 680, 561 cm^{-1}; 1H NMR: δ 4.262 (s, 2H, -CH2), 7.482 (d, 1H, Ar-H, j=5.6 Hz), 7.949 (s, 1H, Ar-H), 8.071 (s, 1H, Ar-H), 8.366 (s, 1H, Ar-H), 10.451 (s, 1H, -NH amide); MS (m/z): 424 (M^+); Anal. Calcd C_{22}H_{15}ClF_{2}N_{4}O: C, 62.20; H, 3.56; N, 13.19; Found: C, 62.31; H, 3.51; N, 13.21.

N-(3-(5-(3-chlorobenzyl)-1H-1,2,4-triazol-3-yl)-4-fluorophenyl)-4-fluorobenzamide (SPG-1Ae): Pale yellow solid; Rf 0.43 (4:6 hexane-EtOAc); mp 188-190°C; IR (KBr, cm^{-1}): 3251, 3192, 3070, 2941, 1901, 1734, 1660, 1500, 1371, 1271, 1163, 1093, 840, 769, 682, 511 cm^{-1}; 1H NMR: δ 4.262 (s, 2H, -CH2), 7.482 (d, 1H, Ar-H, j=5.6 Hz), 7.949 (s, 1H, Ar-H), 8.071 (s, 1H, Ar-H), 8.366 (s, 1H, Ar-H), 10.451 (s, 1H, -NH amide); MS (m/z): 424 (M^+); Anal. Calcd C_{22}H_{15}ClF_{2}N_{4}O: C, 62.20; H, 3.56; N, 13.19; Found: C, 62.33; H, 3.54; N, 13.22.

N-(3-(5-(3,4-dichlorobenzyl)-1H-1,2,4-triazol-3-yl)-4-fluorophenyl)-4-fluorobenzamide (SPG-1Af): Pale yellow solid; Rf 0.42 (4:6 hexane-EtOAc); mp 194-196°C; IR (KBr, cm^{-1}): 3250, 3173, 3059, 2910, 1651, 1602, 1543, 1379, 1238, 1135, 1043, 889, 771, 675, 555; 1H NMR: δ 4.183 (s, 2H, -CH2), 7.232-7.407 (m, 4H, Ar-
H), 7.481-7.631 (m, 2H, Ar-H), 7.930 (s, 1H, Ar-H), 8.073 (dd, 2H, Ar-H, j=5.6, 8.8 Hz), 8.411 (d, 1H, Ar-H, j=4 Hz), 10.450 (s, 1H, -NH amide); MS (m/z): 459 (M⁺); Anal. Calcd C22H14Cl2F2N4O: C, 57.53; H, 3.07; N, 12.20; Found: C, 57.48; H, 3.10; N, 12.18.

**N-(3-(5-(2,4-dichlorophenyl)-1H-1,2,4-triazol-3-yl)-4-fluorophenyl)-4-fluoro benzamide (SPG-1Ag):** white solid; Rf 0.37 (4:6 hexane-EtOAc); mp 236-238 °C; IR (KBr, cm⁻¹): 3272, 3164, 3072, 2924, 1651, 1539, 1484, 1367, 1237, 1162, 1079, 854, 761, 686, 587 cm⁻¹; ¹H NMR: δ 7.399 (t, 2H, Ar-H), 7.489 (t, 1H, Ar-H), 7.613 (t, 1H, Ar-H), 7.802 (s, 1H, Ar-H), 7.909 (s, 1H, Ar-H), 8.025 (d, 1H, Ar-H), 8.089 (dd, 2H, Ar-H, j=5.6, 8 Hz), 8.538 (s, 1H, Ar-H), 10.555 (s, 1H, -NH amide), 14.622 (s, 1H, -NH triazole); MS (m/z): 445 (M⁺); Anal. Calcd C21H12Cl2F2N4O: C, 56.65; H, 2.72; N, 12.58; Found: C, 56.49; H, 2.89; N, 12.26.

**N-(3-(5-(2,6-dichlorophenyl)-1H-1,2,4-triazol-3-yl)-4-fluorophenyl)-4-fluoro benzamide (SPG-1Ah):** White solid; Rf 0.38 (4:6 hexane-EtOAc); mp 230-232 °C; IR (KBr, cm⁻¹): 3276, 3154, 3040, 2943, 1675, 1580, 1490, 1323, 1297, 1122, 1026, 850, 765, 685, 580 cm⁻¹; MS (m/z): 445 (M⁺); Anal. Calcd C21H12Cl2F2N4O: C, 56.65; H, 2.72; N, 12.58; Found: C, 56.36; H, 2.92; N, 12.38.

**4-fluoro-N-(4-fluoro-3-(5-(5-methylisoxazol-4-yl)-1H-1,2,4-triazol-3-yl)phenyl)benzamide (SPG-1Ai):** Brown solid; Rf 0.31 (4:6 hexane-EtOAc); mp 236-238 °C; IR (KBr, cm⁻¹): 3259, 3181, 3067, 2925, 1643, 1609, 1538, 1383, 1242, 1141, 1052, 877, 763, 681, 562 cm⁻¹; ¹H NMR: δ 2.892 (s, 3H, -CH₃), 7.418- 7.431 (m, 2H, Ar-H), 7.554 (t, 1H, Ar-H), 7.957 (s, 1H, Ar-H), 8.063-8.100 (m, 2H, Ar-H), 8.265-8.287 (dd, 1H, Ar-H, j=2.8, 6 Hz), 8.447-8.471 (dd, 1H, Ar-H, j=2.8, 6.8 Hz), 10.616 (s, 1H, -NH amide); MS (m/z): 381 (M⁺); Anal. Calcd C19H13F2N5O2: C, 59.84; H, 3.44; N, 18.37; Found: C, 59.91; H, 3.38; N, 18.41.

**4-fluoro-N-(4-fluoro-3-(5-(4-nitrophenyl)-1H-1,2,4-triazol-3-yl)phenyl)benzamide (SPG-1Aj):** Yellow solid; Rf 0.28 (4:6 hexane-EtOAc); mp 232-234 °C; IR (KBr, cm⁻¹): 3262, 3187, 3062, 2937, 1922, 1746, 1674, 1512, 1368, 1269, 1174, 1087, 853, 776, 691, 523 cm⁻¹; ¹H NMR: δ 7.428 (t, 3H, Ar-H), 7.856 (m, 2H, Ar-H), 8.124 (m, 3H, Ar-H), 8.265-8.287 (d, 2H, Ar-H, j=8.8 Hz), 7.909 (s, 1H, Ar-H), 8.025 (d, 1H, Ar-H), 8.089 (d, 2H, Ar-H, j=5.6, 8 Hz), 8.538 (s, 1H, Ar-H), 10.555 (s, 1H, -NH
3-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-methoxyphenyl)-1H-1,2,4-triazole (SPG-1Ak): White solid; \( R_f \) 0.35 (5:5 hexane-EtOAc); mp 190-192 °C; IR (KBr, cm\(^{-1}\)): 3252, 3082, 2968, 2843, 1747, 1612, 1500, 1440, 1379, 1311, 1257, 1122, 920, 837, 754, 698, 632 cm\(^{-1}\); 1H NMR: \( \delta \) 3.844 (s, 3H, O-CH\(_3\)), 7.125 (d, 2H, Ar-H, \( j = 8.8 \text{ Hz} \)), 7.804 (d, 1H, Ar-H, \( j = 8 \text{ Hz} \)), 8.032 (dt, 2H, Ar-H, \( j = 2.8, 11.6 \text{ Hz} \)), 8.107 (d, 1H, Ar-H, \( j = 9.2 \text{ Hz} \)), 8.192 (s, 1H, Ar-H); MS (m/z): 337 (M\(^+\)); Anal. Calcd for C\(_{16}\)H\(_{11}\)F\(_4\)N\(_3\)O: C, 56.98; H, 3.29; N, 12.46; Found: C, 56.45; H, 3.56; N, 12.86.

5-(4-chlorophenyl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole (SPG-1Al): White solid; \( R_f \) 0.32 (5:5 hexane-EtOAc); mp 216-218°C; IR (KBr, cm\(^{-1}\)): 3076, 2823, 2658, 1780, 1681, 1616, 1444, 1350, 1139, 839, 742, 696, 505 cm\(^{-1}\); 1H NMR: \( \delta \) 7.615-7.637 (d, 2H, Ar-H, \( j = 8.8 \text{ Hz} \)), 7.809-7.830 (d, 1H, Ar-H, \( j = 8.4 \text{ Hz} \)), 8.129-8.150 (d, 3H, Ar-H, \( j = 8.4 \text{ Hz} \)), 8.267 (s, 1H, Ar-H); MS (m/z): 341 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_8\)ClF\(_4\)N\(_3\): C, 52.73, H, 2.36, N, 12.30; Found: C, 52.42; H, 2.65; N, 12.72.

3-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-nitrophenyl)-1H-1,2,4-triazole (SPG-1Am): Yellow solid; \( R_f \) 0.27 (5:5 hexane-EtOAc); mp 206-208 °C; IR (KBr, cm\(^{-1}\)): 3225, 3144, 3014, 2926, 2858, 1606, 1525, 1334, 1132, 922, 877, 734, 696 cm\(^{-1}\); 1H NMR: \( \delta \) 7.628-7.657 (m, 1H, Ar-H), 8.105-8.127 (d, 1H, Ar-H, \( j = 8.8 \text{ Hz} \)), 8.192-8.211 (d, 1H, Ar-H, \( j = 7.6 \text{ Hz} \)), 8.298-8.320 (d, 2H, Ar-H, \( j = 8.8 \text{ Hz} \)), 8.362-8.385 (d, 2H, Ar-H, \( j = 9.2 \text{ Hz} \)); \( ^{13}\)C NMR (100 MHz, DMSO): 108.93, 113.40, 116.58, 118.93, 124.23, 126.96, 128.24, 131.87, 134.63, 147.82, 152.71, 161.02, 163.48, 165.46; MS (m/z): 352 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_8\)F\(_4\)N\(_4\)O\(_2\): C, 51.15, H, 2.29, N, 15.91; Found: C, 51.36; H, 2.45; N, 15.53.

5-(3-chlorobenzyl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole (SPG-1An): White solid; \( R_f \) 0.38 (5:5 hexane-EtOAc); mp 186-188 °C; IR (KBr, cm\(^{-1}\)): 3225, 3144, 3014, 2926, 2858, 1606, 1525, 1334, 1132, 922, 877, 734, 696 cm\(^{-1}\); 1H NMR: \( \delta \) 7.628-7.657 (m, 1H, Ar-H), 8.105-8.127 (d, 1H, Ar-H, \( j = 8.8 \text{ Hz} \)), 8.192-8.211 (d, 1H, Ar-H, \( j = 7.6 \text{ Hz} \)), 8.298-8.320 (d, 2H, Ar-H, \( j = 8.8 \text{ Hz} \)), 8.362-8.385 (d, 2H, Ar-H, \( j = 9.2 \text{ Hz} \)); \( ^{13}\)C NMR (100 MHz, DMSO): 108.93, 113.40, 116.58, 118.93, 124.23, 126.96, 128.24, 131.87, 134.63, 147.82, 152.71, 161.02, 163.48, 165.46; MS (m/z): 352 (M\(^+\)); Anal. Calcd for C\(_{15}\)H\(_8\)ClF\(_4\)N\(_3\): C, 54.02, H, 2.83, N, 11.81; Found: C, 54.62; H, 2.36; N, 11.45.
3-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-fluorophenyl)-1H-1,2,4-triazole (SPG-1Ao): White solid; Rf 0.32 (5:5 hexane-EtOAc); mp 208-210°C; IR (KBr, cm-1): 3149, 3095, 3036, 2931, 2850, 1608, 1504, 1437, 1325, 1172, 923, 846, 759, 696 cm-1; 1H NMR: δ 7.389-7.433 (t, 2H, Ar-H), 7.803-7.824 (d, 1H, Ar-H, J=8.4 Hz), 8.097 (s, 1H, Ar-H), 8.118-8.153 (m, 2H, Ar-H), 8.199 (s, 1H, Ar-H) 14.817 (s, 1H, -NH triazole); 13C NMR (100 MHz, DMSO): 113.38, 116.18, 116.59, 118.31, 121.73, 124.44, 128.47, 131.52, 131.85, 161.05, 161.86, 163.51, 164.33, 128.56; MS (m/z): 325 (M+); Anal. Calcd for C15H8F5N3: C, 55.39, H, 2.48, N, 12.92; Found: C, 55.23; H, 2.45; N, 11.89.

3-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(p-tolyl)-1H-1,2,4-triazole (SPG-1Ap): White solid; Rf 0.4 (5:5 hexane-EtOAc); mp 142-144°C; IR (KBr, cm-1): 3212, 3105, 3050, 2968, 2856, 1650, 1608, 1544, 1356, 1310, 1102, 950, 856, 754, 690 cm-1; MS (m/z): 321 (M+); Anal. Calcd for C16H11F4N3: C, 59.82, H, 3.45, N, 13.08; Found: C, 59.65; H, 2.65; N, 11.72.

5-(2,4-dichlorophenyl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole (SPG-1Aq): White solid; Rf 0.34 (5:5 hexane-EtOAc); mp 228-230°C; IR (KBr, cm-1): 3265, 3126, 3056, 2950, 2864, 1632, 1545, 1423, 1345, 1268, 1146, 986, 759, 698 cm-1; MS (m/z): 376 (M+); Anal. Calcd for C15H7Cl2F4N3: C, 47.90, H, 1.88, N, 11; Found: C, 47.93; H, 1.56; N, 11.38.

5-(2,4-dimethoxyphenyl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole (SPG-1Ar): Pale yellow solid; Rf 0.36 (5:5 hexane-EtOAc); mp 180-182°C; IR (KBr, cm-1): 3212, 3165, 3023, 2941, 2863, 1653, 1548, 1426, 1385, 1246, 1150, 964, 874, 752, 675 cm-1; MS (m/z): 367 (M+); Anal. Calcd for C17H13F4N3O2: C, 55.59, H, 3.57, N, 11.44; Found: C, 55.13; H, 3.32; N, 11.89.

5-(2-chlorophenyl)-3-(3-fluoro-5-(trifluoromethyl)phenyl)-1H-1,2,4-triazole (SPG-1As): White solid; Rf 0.31 (5:5 hexane-EtOAc); mp 208-210°C; IR (KBr, cm-1): 3072, 2835, 2656, 1788, 1656, 1613, 1465, 1347, 1160, 854, 740, 698, 515 cm-1; MS (m/z): 341 (M+); Anal. Calcd for C15H6ClF4N3: C, 52.73, H, 2.36, N, 12.30; Found: C, 52.42; H, 2.65; N, 12.72.

3-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazole (SPG-1At): White solid; Rf 0.30 (5:5 hexane-EtOAc); mp 180-182°C; IR
(KBr, cm⁻¹): 3052, 2968, 2862, 1752, 1631, 1546, 1493, 1323, 1195, 968, 856, 798, 654 cm⁻¹; MS (m/z): 375 (M⁺); Anal. Calcd for C_{16}H_{8}F_{7}N_{3}: C, 51.21, H, 2.15, N, 11.20; Found: C, 52.45; H, 2.98; N, 11.96.

4-fluoro-N-(4-fluoro-3-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide (SPG-1Ba): White solid; R_f 0.47 (4:6 hexane-EtOAc); mp 156-158°C; IR (KBr, cm⁻¹): 3075, 2956, 2869, 1745, 1635, 1545, 1395, 1244, 1115, 997, 856, 764, 678, 589 cm⁻¹; ¹H NMR: δ 7.395-7.438 (t, 2H, Ar-H), 7.530-7.578 (t, 1H, Ar-H), 8.037-8.113 (m, 5H, Ar-H), 8.291-8.310 (d, 2H, Ar-H, j=7.6 Hz), 8.641-8.651 (d, 1H, Ar-H, j=4 Hz), 10.616 (s, 1H, -NH amide); MS (m/z): 445 (M⁺); Anal. Calcd for C_{22}H_{12}F_{5}N_{3}O_{2}: C, 59.33, H, 2.72, N, 9.44; Found: C, 59.42; H, 2.45; N, 9.54.

N-(3-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)-4-fluorobenzamide (SPG-1Bb): White solid; R_f 0.46 (4:6 hexane-EtOAc); mp 142-144°C; IR (KBr, cm⁻¹): 3045, 2952, 2844, 1763, 1664, 1512, 1344, 1265, 1175, 968, 863, 764, 697, 587 cm⁻¹; MS (m/z): 456 (M⁺); Anal. Calcd for C_{21}H_{12}BrF_{2}N_{3}O_{2}: C, 55.28, H, 2.65, N, 9.21; Found: C, 55.44; H, 2.72; N, 9.56.

4-fluoro-N-(4-fluoro-3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)benzamide (SPG-1Bc): White solid; R_f 0.52 (4:6 hexane-EtOAc); mp 138-140°C; IR (KBr, cm⁻¹): 3044, 2967, 2856, 1775, 1653, 1542, 1344, 1265, 1154, 997, 854, 778, 698, 568 cm⁻¹; ¹H NMR: δ 7.391-7.435 (t, 2H, Ar-H), 7.497-7.562 (m, 3H, Ar-H), 8.076-8.167 (m, 5H, Ar-H), 8.607-8.628 (dd, 1H, Ar-H, j=2.4, 6 Hz), 10.597 (s, 1H, -NH amide); MS (m/z): 395 (M⁺); Anal. Calcd for C_{21}H_{12}F_{3}N_{3}O_{2}: C, 63.80, H, 3.06, N, 10.63; Found: C, 63.65; H, 3.13; N, 10.84.

4-fluoro-N-(4-fluoro-3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)phenyl)benzamide (SPG-1Bd): Yellow solid; R_f 0.56 (4:6 hexane-EtOAc); mp 126-128°C; IR (KBr, cm⁻¹): 3165, 3039, 2950, 2867, 1664, 1554, 1476, 1364, 1282, 1160, 1007, 852, 753, 682, 566 cm⁻¹; MS (m/z): 425 (M⁺); Anal. Calcd C_{22}H_{14}ClF_{2}N_{3}O_{2}: C, 62.05, H, 3.31, N, 9.87; Found: C, 62.61; H, 3.35; N, 13.54.

N-(3-(5-(2-chlorobenzyl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)-4-fluorobenzamide (SPG-1Be): Yellow solid; R_f 0.57 (4:6 hexane-EtOAc); mp 132-
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134°C; IR (KBr, cm⁻¹): 3062, 1632, 1564, 1422, 1368, 1254, 1163, 896, 864, 754, 654, 534 cm⁻¹; MS (m/z): 425 (M⁺); Anal. Calcd C₂₂H₁₄ClF₂N₃O₂: C, 62.05, H, 3.31, N, 9.87; Found: C, 62.45; H, 3.32; N, 9.31.

N-(3-(5-(3,4-dichlorobenzyl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)-4-fluoro benzamide (SPG-1Bf): White solid; Rf 0.53 (4:6 hexane-EtOAc); mp 134-136°C; IR (KBr, cm⁻¹): 3072, 1602, 1527, 1417, 1356, 1245, 1159, 895, 845, 756, 654, 534 cm⁻¹; MS (m/z): 460 (M⁺); Anal. Calcd C₂₂H₁₃Cl₂F₂N₃O₂: C, 57.41, H, 2.85, N, 9.13; Found: C, 57.54; H, 2.98; N, 9.12.

N-(3-(5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)-4-fluoro benzamide (SPG-1Bg): white solid; Rf 0.48 (4:6 hexane-EtOAc); mp 146-148°C; IR (KBr, cm⁻¹): 3065, 1653, 1545, 1487, 1365, 1245, 1158, 898, 845, 756, 654, 563 cm⁻¹; MS (m/z): 446 (M⁺); Anal. Calcd C₂₁H₁₁Cl₂F₂N₃O₂: C, 56.52, H, 2.48, N, 9.42; Found: C, 56.12; H, 2.36; N, 9.68.

N-(3-(5-(2,6-dichlorophenyl)-1,3,4-oxadiazol-2-yl)-4-fluorophenyl)-4-fluoro benzamide (SPG-1Bh): White solid; Rf 0.45 (4:6 hexane-EtOAc); mp 142-144°C; IR (KBr, cm⁻¹): 3073, 1632, 1539, 1454, 1335, 1264, 1139, 865, 798, 752, 652, 552 cm⁻¹; MS (m/z): 446 (M⁺); Anal. Calcd C₂₁H₁₁Cl₂F₂N₃O₂: C, 56.52, H, 2.48, N, 9.42; Found: C, 56.32; H, 2.54; N, 9.65.

4-fluoro-N-(4-fluoro-3-(5-(5-methylisoxazol-4-yl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide (SPG-1Bi): Brown solid; Rf 0.42 (4:6 hexane-EtOAc); mp 138-140°C; IR (KBr, cm⁻¹): 3152, 3054, 2962, 1623, 1602, 1556, 1344, 1265, 1123, 1065, 875, 762, 686, 560 cm⁻¹; MS (m/z): 382 (M⁺); Anal. Calcd C₁₉H₁₂F₂N₄O₃: C, 59.69, H, 3.16, N, 14.65; Found: C, 59.32; H, 3.18; N, 14.54.

4-fluoro-N-(4-fluoro-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)benzamide (SPG-1Bj): Yellow solid; Rf 0.35 (4:6 hexane-EtOAc); mp 232-234°C; IR (KBr, cm⁻¹): 3152, 3039, 2950, 1917, 1752, 1635, 1504, 1336, 1257, 1165, 1035, 848, 775, 697, 523 cm⁻¹; MS (m/z): 422 (M⁺); Anal. Calcd for C₂₁H₁₂F₂N₄O₄: C, 59.7, H, 2.86; N, 13.27; Found: C, 59.45; H, 3.02; N, 13.68.

2-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (SPG-1Bk): Light pink solid; Rf 0.48 (5:5 hexane-EtOAc); mp 132-134°C; IR (KBr, cm⁻¹): 7032, 2945, 2850, 1901, 1784, 1608, 1550, 1487, 1448, 1484, 1448, 1373,
1321, 1261, 1132, 1024, 916, 891, 837, 698, 623, 522 cm$^{-1}$; 1H NMR: δ 3.878 (s, 3H, O-CH$_3$), 7.159-7.195 (dt, 2H, Ar-H, $j$=2.8, 11.6 Hz), 8.025-8.047 (d, 1H, Ar-H, $j$=8.8 Hz), 8.129-8.165 (dt, 2H, Ar-H, $j$=2.4, 11.6 Hz), 8.306 (s, 1H, Ar-H), 8.260 (s, 1H, Ar-H), 8.280-8.306 (d, 1H, Ar-H, $j$=1.6, 10.4 Hz); MS (m/z): 338 (M$^+$); Anal. Calcd for C$_{16}$H$_{10}$F$_4$N$_2$O$_2$: C, 56.81, H, 2.98, N, 8.28; Found: C, 56.35; H, 2.54; N, 8.13.

2-(4-chlorophenyl)-5-(3-fluoro-5-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (SPG-1Bl): White solid; $R_f$ 0.45 (5:5 hexane-EtOAc); mp 146-148°C; IR (KBr, cm$^{-1}$): 3082, 2991, 1778, 1604, 1546, 1479, 1373, 1330, 1259, 1147, 1095, 922, 887, 738, 696, 509 cm$^{-1}$; 1H NMR: δ 7.462-7.494 (m, 3H, Ar-H), 7.971-7.991 (d, 1H, Ar-H, $j$=8 Hz), 8.028-8.046 (d, 2H, Ar-H, $j$=7.2 Hz), 8.050 (s, 1H, Ar-H)$^1$; $^1$C NMR (100 MHz, DMSO): 115.99, 117.20, 119.59, 121.33, 124.04, 126.62, 128.11, 129.68, 133.78, 138.68, 161.41, 162.58, 163.91, 164.54; MS (m/z): 342 (M$^+$); Anal. Calcd for C$_{15}$H$_7$ClF$_4$N$_2$O: C, 52.57, H, 2.06, N, 8.17; Found: C, 52.86; H, 1.98; N, 8.47.

2-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (SPG-1Bm): Yellow solid; $R_f$ 0.35 (5:5 hexane-EtOAc); mp 198-200°C; IR (KBr, cm$^{-1}$): 3088, 3014, 2854, 1796, 1604, 1523, 1435, 1348, 1261, 1012, 970, 873, 698 cm$^{-1}$; 1H NMR: δ 8.097-8.118 (d, 1H, Ar-H, $j$=8.4 Hz), 8.350 (s, 1H, Ar-H), 8.381-8.403 (d, 1H, Ar-H, $j$=8.8 Hz), 8.460-8.510 (m, 1H, Ar-H); MS (m/z): 353 (M$^+$); Anal. Calcd for C$_{15}$H$_7$F$_4$N$_3$O$_3$: C, 51.00, H, 2.00, N, 11.90; Found: C, 51.45; H, 1.97; N, 11.67.

2-(3-chlorobenzyl)-5-(3-fluoro-5-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (SPG-1Bn): White solid; $R_f$ 0.5 (5:5 hexane-EtOAc); mp 178-180°C; IR (KBr, cm$^{-1}$): 3073, 2869, 1790, 1615, 1536, 1438, 1687, 1354, 1278, 1092, 978, 856, 198, 654 cm$^{-1}$; MS (m/z): 356 (M$^+$); Anal. Calcd for C$_{15}$H$_9$ClF$_4$N$_2$O: C, 53.87, H, 2.54, N, 7.85; Found: C, 53.92; H, 2.68; N, 7.94.

2-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (SPG-1Bo): White solid; $R_f$ 0.43 (5:5 hexane-EtOAc); mp 164-166°C; IR (KBr, cm$^{-1}$): 3095, 3024, 2939, 1782, 1602, 1550, 1492, 1375, 1253, 1130, 970, 922, 848, 746, 698, 615 cm$^{-1}$; 1H NMR: δ 7.497-7.541 (m, 2H, Ar-H), 8.068-8.089 (d, 1H, Ar-H, $j$=8.4 Hz), 8.289-8.362 (m, 4H, Ar-H); MS (m/z): 326 (M$^+$); Anal. Calcd for C$_{15}$H$_7$F$_4$N$_2$O: C, 55.23, H, 2.16, N, 8.59; Found: C, 55.34; H, 2.44; N, 9.02.
2-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(p-tolyl)-1,3,4-oxadiazole (SPG-1Bp):

White solid; $R_f 0.52$ (5:5 hexane-EtOAc); mp 128-130°C; IR (KBr, cm$^{-1}$): 3092, 3039, 2950, 1785, 1635, 1554, 1486, 1368, 1286, 1136, 965, 854, 748, 687, 623 cm$^{-1}$; 1H NMR: $\delta$ 2.396 (s, 3H, -CH$_3$), 7.289-7.309 (d, 2H, Ar-H, $j=8.0$ Hz), 7.444-7.464 (d, 1H, Ar-H, $j=8.0$ Hz), 7.971-7.991 (d, 3H, Ar-H, $j=8.0$ Hz), 8.130 (s, 1H, Ar-H); $^{13}$C NMR (100 MHz, DMSO): 21.76, 115.69, 117.71, 119.52, 120.47, 121.39, 124.10, 127.02, 129.97, 133.66, 143.02, 161.39, 162.20, 163.88, 165.49; MS (m/z): 322 (M$^+$); Anal. Calcd for C$_{16}$H$_{10}$F$_4$N$_2$O: C, 59.63, H, 3.13, N, 8.69; Found: C, 59.41; H, 3.25; N, 8.92.

2-(2,4-dichlorophenyl)-5-(3-fluoro-5-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (SPG-1Bq):

White solid; $R_f 0.45$ (5:5 hexane-EtOAc); mp 136-138°C; IR (KBr, cm$^{-1}$): 3156, 3040, 2940, 2865, 1605, 1550, 1468, 1365, 1248, 1135, 990, 752, 693 cm$^{-1}$; $^{13}$C NMR (100 MHz, DMSO): 116.39, 119.22, 121.06, 123.99, 126.47, 127.87, 130.44, 131.77, 134.10, 137.16, 138.75, 161.41, 163.09, 163.91; MS (m/z): 377 (M$^+$); Anal. Calcd for C$_{15}$H$_6$Cl$_2$F$_4$N$_2$O: C, 47.77, H, 1.60, N, 7.43; Found: C, 47.42; H, 1.44; N, 7.46.

2-(2,4-dimethoxyphenyl)-5-(3-fluoro-5-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (SPG-1Br):

White solid; Rf 0.49 (5:5 hexane-EtOAc); mp 206-208°C; IR (KBr, cm$^{-1}$): 3132, 3045, 2950, 2867, 1630, 1545, 1465, 1320, 1213, 1164, 950, 864, 755, 674 cm$^{-1}$; MS (m/z): 368 (M$^+$); Anal. Calcd for C$_{17}$H$_{12}$F$_4$N$_2$O$_3$: C, 55.44, H, 3.28, N, 7.61; Found: C, 55.22; H, 3.65; N, 7.68.

2-(2-chlorophenyl)-5-(3-fluoro-5-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (SPG-1Bs):

White solid; Rf 0.43 (5:5 hexane-EtOAc); mp 202-204°C; IR (KBr, cm$^{-1}$): 3046, 2944, 2886, 1789, 1634, 1602, 1432, 1354, 1148, 852, 749, 697, 505 cm$^{-1}$; MS (m/z): 342 (M$^+$); Anal. Calcd for C$_{15}$H$_7$ClF$_4$N$_2$O: C, 52.57, H, 2.06, N, 8.17; Found: C, 52.45; H, 2.32; N, 8.44.

2-(3-fluoro-5-(trifluoromethyl)phenyl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (SPG-1Bt):

White solid; $R_f 0.43$ (5:5 hexane-EtOAc); mp 176-178°C; IR (KBr, cm$^{-1}$): 3072, 2950, 2832, 1798, 1624, 1535, 1445, 1361, 1117, 965, 851, 799, 652 cm$^{-1}$; MS (m/z): 376 (M$^+$); Anal. Calcd for C$_{16}$H$_7$F$_7$N$_2$O: C, 51.08, H, 1.88, N, 7.45; Found: C, 51.36; H, 1.44; N, 7.63.
$^1$H NMR Spectrum of Int-1

$^1$H NMR spectrum of Int-2
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Expanded $^1$H NMR spectrum of Int-2

D$_2$O exchange spectrum of Int-2
$^1$H NMR spectrum of Int-3

Expanded $^1$H NMR spectrum of Int-3
$^1$H NMR spectrum of SPG-1Aa

$^1$H NMR spectrum of SPG-1Ba
\textbf{1H NMR spectrum of SPG-1Ac}

\textbf{Expanded 1H NMR spectrum of SPG-1Ac}
$^1$H NMR spectrum of SPG-1Bc

Expanded $^1$H NMR spectrum of SPG-1Bc

$\text{dd, } \rho=2.4,6 \text{ Hz}$
$^1$H NMR spectrum of SPG-1Ak

Expanded $^1$H NMR spectrum of SPG-1Ak
$^1$H NMR spectrum of SPG-1Bk

Expanded $^1$H NMR spectrum of SPG-1Bk
1H NMR spectrum of SPG-1Ao

Expanded 1H NMR spectrum of SPG-1Bo
$^{13}$C NMR spectrum of 1-Aa

$^{13}$C NMR spectrum of 1-Ao
$^{13}$C NMR spectrum of 1-Al

$^{13}$C NMR spectrum of 1-Bl
$^{13}$C NMR spectrum of 1-Bp

$^{13}$C NMR spectrum of 1-Bq
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Studies on Triazoles/Oxadiazoles

Mass spectrum of Int-1

Mass spectrum of Int-3
Mass spectrum of SPG1Aa

Mass spectrum of SPG1Ba
Mass spectrum of SPG1Ag

Mass spectrum of SPG1Bg
Mass spectrum of SPG-1Ak

Mass spectrum of SPG-1Bk
Mass spectrum of SPG-1Ao

![Mass spectrum of SPG-1Ao](image1)

Mass spectrum of SPG-1Bo

![Mass spectrum of SPG-1Bo](image2)
IR spectrum of Int-1

IR spectrum of Int-2
IR spectrum of Int-3

IR spectrum of SPG-1Aa
IR spectrum of SPG-1Af

IR spectrum of SPG-1Bf
IR spectrum of SPG-1Ak

IR spectrum of SPG-1Bk
1.11 References


