1,2,4-oxadiazole nucleus with versatile biological applications

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ABSTRACT:

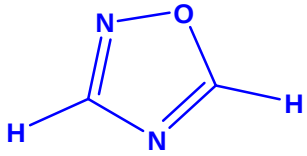
Azoles are the five-membered heterocyclic compounds with two or three nitrogen atoms, constitute a large group of organic substances and have been long targeted for their use as therapeutic agents. 1,2,4-oxadiazoles is a member of azole family containing two nitrogen atoms, two carbon and one oxygen atom in the ring.1,2,4-oxadiazoles have been found to possess variety of biological activities such as human tryptase inhibitory activity, antitrypanosomal activity, β-amyloid imaging agents in Alzheimer's disease, genotoxic activity, peptide inhibitory activity, antihyperglycemic activity, potential combretastatin A-4 (CA-4) analogs and oxadiazole mannich bases show antimyco-bacterial activity. Here in this review article we have reported the recent development in the pharmacological activity of some newly synthesized 1,2,4-oxadiazole derivatives.

Key words: 1,2,4-oxadiazole, synthesis, biological activity

INTRODUCTION:

Compounds containing heterocyclic ring systems are of great importance both medicinally and industrially. As an example, five-membered ring heterocycles containing two carbon

atoms, two nitrogen atoms, and one oxygen atom known as oxadiazoles [**Figure-1a**] are of considerable interest in different areas of medicinal and pesticide chemistry and also polymer and material science.[1]



1,2,4-oxadiazole

Figure-1a

There are three known isomers: 1,2,4-oxadiazole (**1**), 1,3,4-oxadiazole (**2**)1,2,3-oxadiazole (**3**) and 1,2,5-oxadiazole (**4**) **(Figure-1b).** 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.

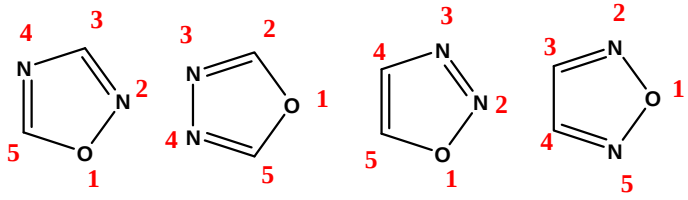


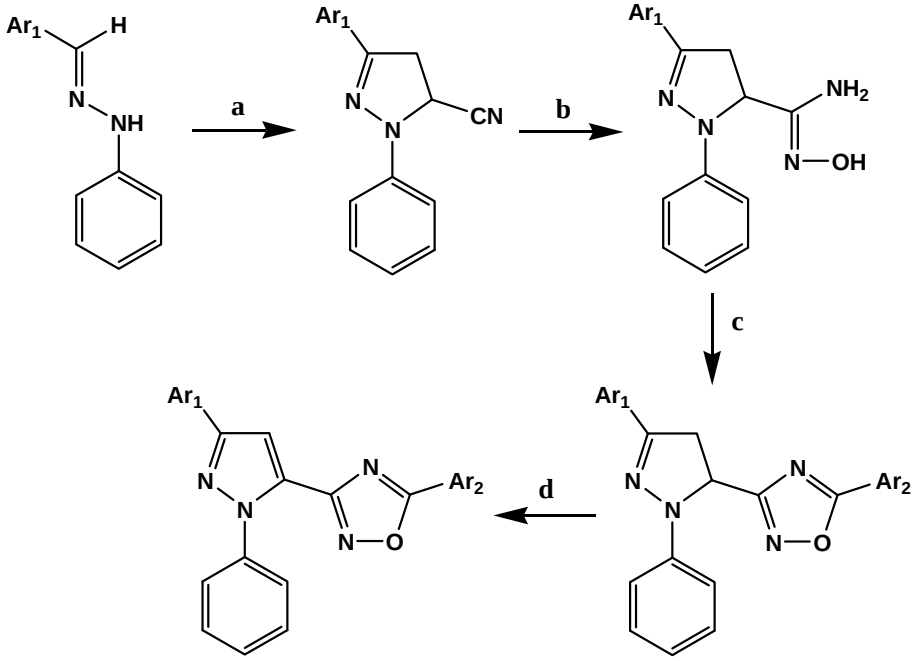
Figure-1b

The 1,2,4-oxadiazole, known as an ester isostere, is present in various biologically active compounds, such as benzodiazepine receptor ligands, muscarinic receptor agonists and 5-HT3 receptor antagonists.[2] 1,2,4-oxadiazole derivatives possess human tryptase inhibitory activity,[3] antitrypanosomal activity,[4] b-amyloid imaging agents in Alzheimer's disease,[5] genotoxic activity,[6] peptide inhibitory activity,[7] antihyperglycemic activity,[8] potential Combretastatin A-4 (CA-4) analogs[9] and oxadiazole mannich bases show antimyco-bacterial activity.[10] Aryl and heteroaryl substituted 1,2,4-oxadiazole-5-carboxamides represent a relatively little explored class of heterocyclic structures with promising physiological activities. Thus, they were recently reported as antiplatelet, antithrombotic agents and partial serotonin antagonists.[11] Several 1,2,4-oxadiazole- and 1,3,4-

oxadiazolecarboxamides containing different lipophilic moieties (i.e., 4-biphenyl-, 1-naphthyl, phenylpropyl-, and n-hexyl substituents) and additional basic groups which are mainly alkyl- and aminoalkyl residues have been recently described as antiplatelet and antithrombotic combounds as well as serotonin antagonists.[11]

Synthesis and pharmacological activity:

S. Ningaiah et al.[12] reported the synthesis of a novel series of pyrazoline amidoxime and pyrazoly-1,2,4-oxadiazole and evaluated for their pharmacological significance. Structures of newly synthesised compounds were characterized by spectral studies. All the compounds were screened for their in vitro antioxidant, antimicrobial and antiinflammatory activities. Among the synthesized compounds, some compounds were found to be active antimicrobial agents in addition to having potent antioxidant activity, while some of them showed promising antiinflammatory activity in comparison with standard drug **[Figure-2].**



Reagents and conditions:
(a) acrylonitrile, chloramine-T, EtOH, reflux 3 h;
(b) NH2OH, HCl, Na2CO3, aq. EtOH, reflux 5–6 h;
(c)i Ar2-COOH, EDC, HCl, CH2Cl, rt for 6 h;
(c)ii heating 110 0C, 12 h;
(d) Br2, CH2Cl2, reflux 1 h.

Figure-2

Y. Wang et al.[13] have described the discovery and optimization of 5-(2-((1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazoles as novel agonists of GPR119. The author also correlated the results with previously described aniline having suboptimal efficacy in signalling assays using cynomolgus monkey (cyno) GPR119 making evaluation of the target in preclinical models difficult. The author observed that replacement of the aniline ring with a tetrahydroquinoline ring constrained the rotation of the aniline C–N bond and gave compounds with increased efficacy on human and cyno receptors **[Figure-3]**.

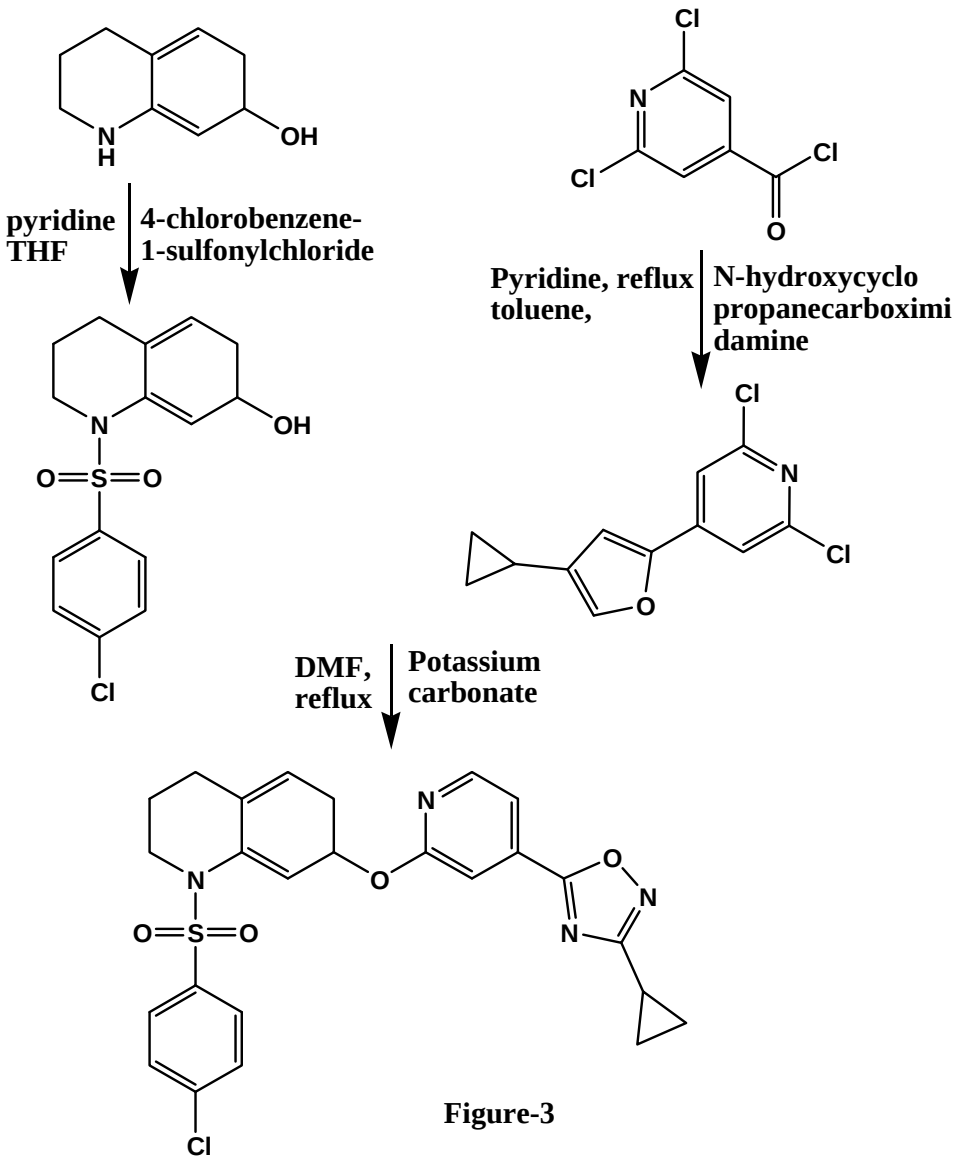


Figure-3

E. Muraglia et al.[14] reported a novel series of 4-[3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl]piperazinylurea as smoothened antagonists was recently described, herein the series has been further optimized through the incorporation of a basic amine into the urea. This development resulted in identification of some exceptionally potent smoothened antagonists with low serum shifts, however, reductive ring opening on the 1,2,4-oxadiazole in rats limits the applicability of these compounds for in vivo studies **[Figure-4]**.

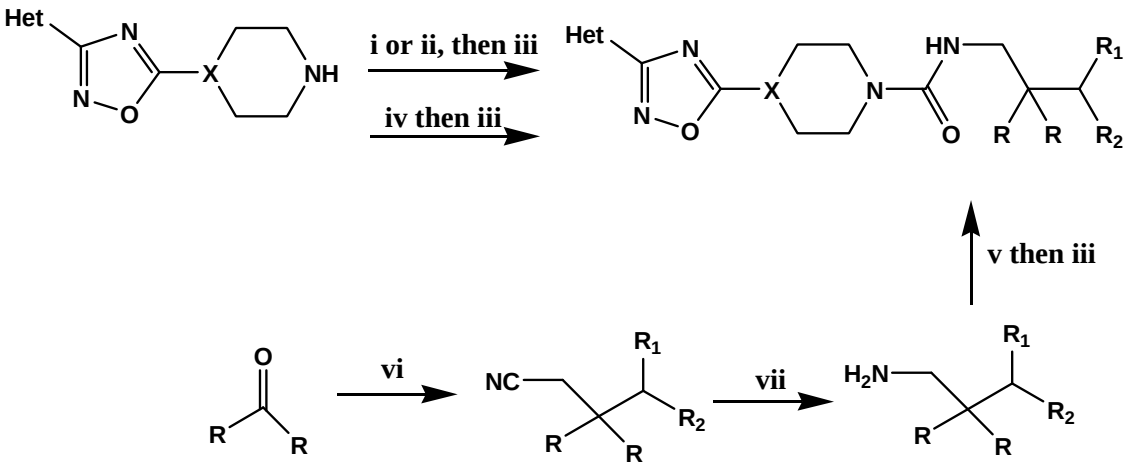


Figure-4

Reagents and conditions:

(i) CDI, Et_3N, MeCN, 1.5 h then MeOTf, DCM, ^oC to RT; (ii) CDI, Et3N, THF, lW, 130 ^0C, 10 min, then MeI, MeCN; (iii) $R00NH_2$, Et_3N, DCM, 12 h; (iv) triphosgene, DIPEA, _20 ^oC, DCM, 20 min; (v) CDI, Et_3N, 5 ^oC, THF; (vi) R0R00NH, HCl, NaCN, H2O, ^0C to RT; (vii) AlH3, THF, 0–45 ^oC.

J. Xu et al.[15] reported a novel series of oxadiazole based amides which have been shown to be potent DPP-4 inhibitors. The optimized compound exhibited excellent selectivity over a variety of DPP-4 homologs **[Figure-5].**

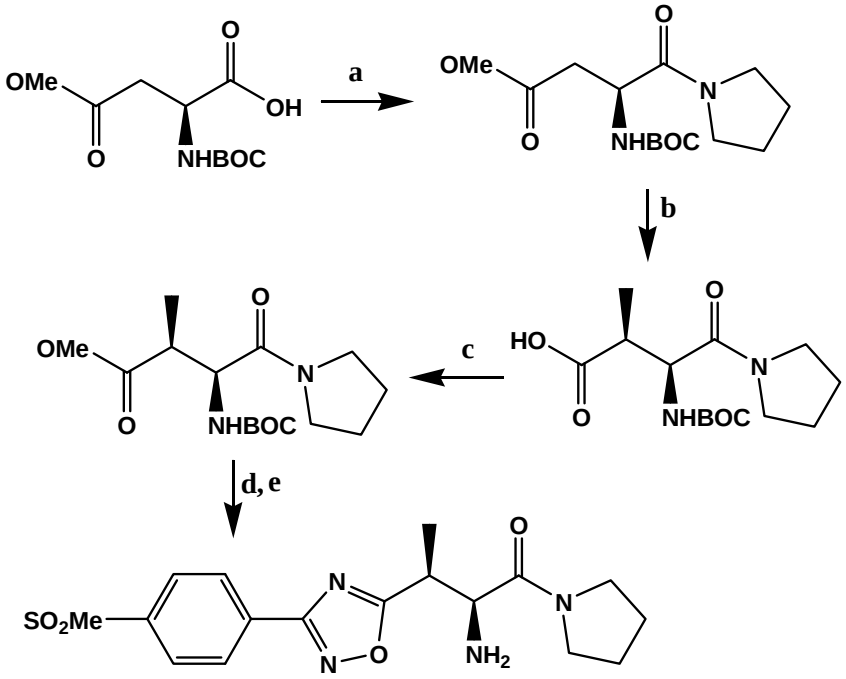


Figure-5

Reagents and conditions: (a) EDC, HOBT, DIEA, pyrrolidine, DMF; (b) KHMDS, MeI, 78 ^oC; (c) LiOH, THF, H_2O; (d) CDI, 4-methanesulfonylbenzamidoxime, rt, 1 h, then 110 ^oC, 12 h; (e) TFA/CH_2Cl_2, 1 h.

K-S Yeung et al.[16] reported the effect of C7-heteroaryl substitution on the potency, in vitro and in vivo profiles of indole-based inhibitors indole-oxoacetic piperazinyl benzamide class of HIV-1 attachment inhibitors. The author explored substitution at the C7 position of the lead 4-fluoroindole 2 with various 5- and 6-membered heteroaryl moieties **[Figure-6]**.

Highly potent (picomolar) inhibitors of pseudotyped HIV-1 in a primary, cell-based assay were identified and selected examples were shown to possess nanomolar inhibitory activity against M- and T-tropic viruses in cell culture. These C7-heteroaryl-indole analogs maintained the ligand efficiency (LE) of selected compounds and

were also lipophilic efficient as measured by LLE and LELP. Pharmacokinetic studies of this class of inhibitor in rats showed that several possessed substantially improved IV clearance and half-lives compared to selected one. Oral exposure in the rat correlated with membrane permeability as measured in a Caco-2 assay where the highly permeable 1,2,4-oxadiazole analogue exhibited the highest exposure.

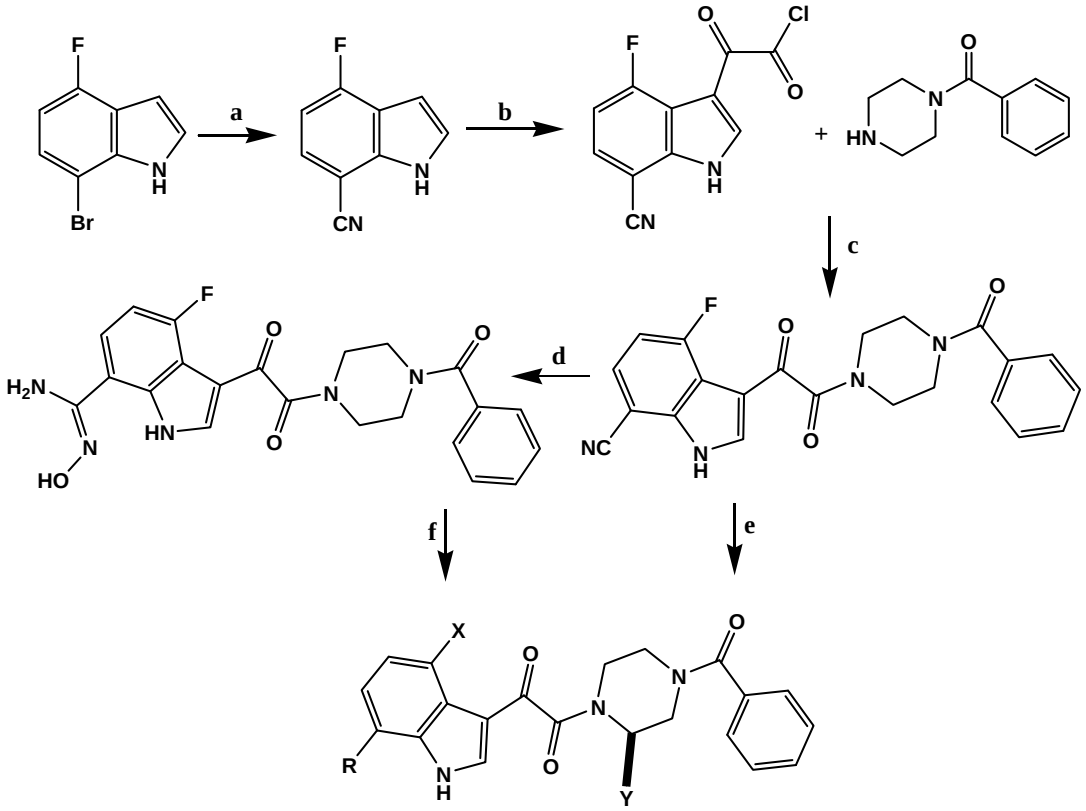


Figure-6

Reagents and conditions: (a) CuCN, DMF, 145 ^{o}C, 17 h; (b) $(ClCO)_2$, CH_2Cl_2, reflux, 3 days; (c) i-Pr_2EtN, THF, rt, 16 h; (d) $HONH_2$, HCl, Et_3N, EtOH, rt, 36 h; (e) $HC(OEt)_3$ 105 ^{o}C, 16 h; (f) NaN_3, NH_4Cl, DMF, 85 ^{o}C; 12 h.

K. D. Rice et al.[17] reported the synthesis of 1,2,4-oxadiazoles on solid support and it was observed that mild reaction conditions applied here and the methodology have a broad scope for variation on oxadiazole at 5-position **[Figure-7]**.

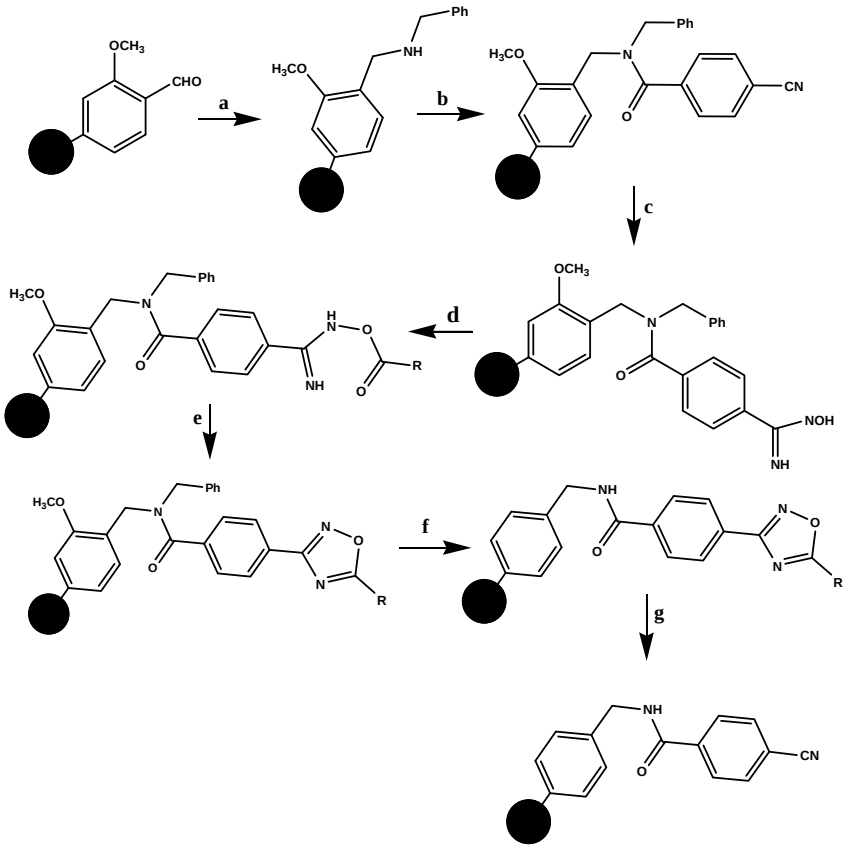


Figure-7

V. Santagada et al.[18] reported one pot microwave-assisted synthesis of substituted 1,2,4-oxadiazoles in solvent and under solvent free condition exploring the importance of some coupling reagents. Good yields and short reaction times were the main aspects of the methods **[Figure-8]**.

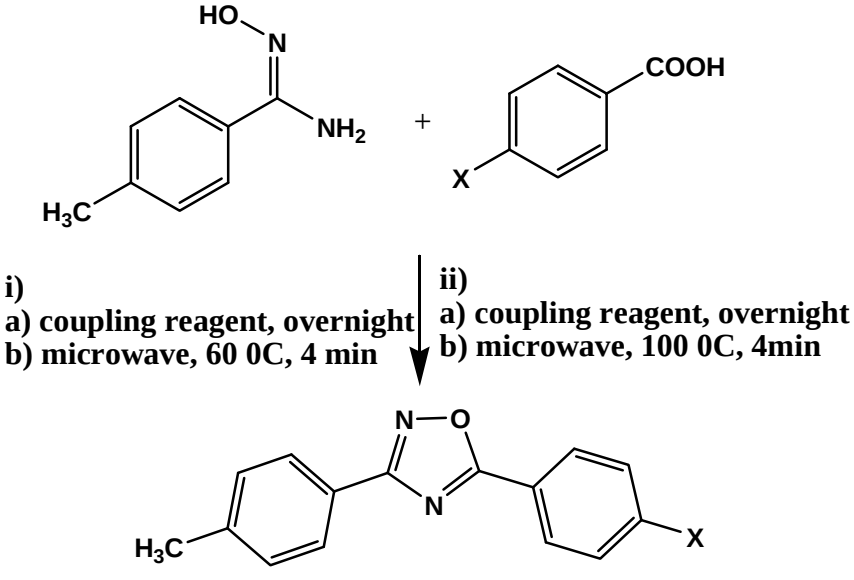


Figure-8

M. A. Weidner-Wells et al.[19] have reported a novel series of 3,5-diarylisoxazole and 3,5-diaryl-1,2,4-oxadiazole IL-8 antagonists has been identified. These compounds exhibit activity in an IL-8 binding assay as well as in a functional assay of IL-8 induced elastase release from neutrophils. In addition, one of the compounds exhibits oral activity in a rat adjuvant arthritis model **[Figure-9]**.

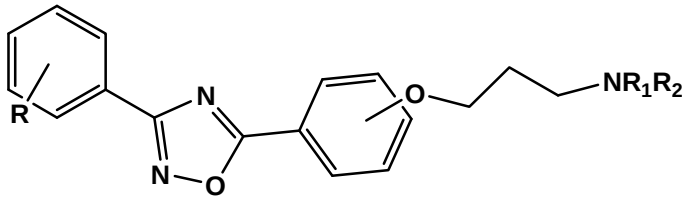


Figure-9

J. T. Palmer et al.[20] have prepared a series of potent keto-1,2,4-oxadiazoles designed to explore the P2 binding pocket of human mast cell tryptase, while building in a high degree of selectivity over human trypsin and other serine proteases **[Figure-10]**.

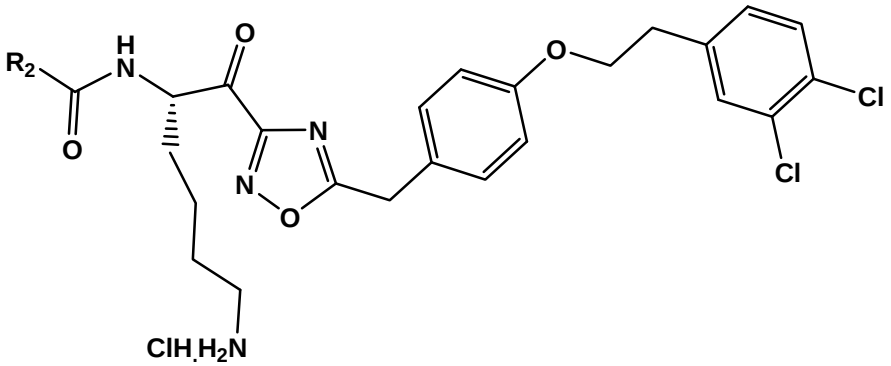
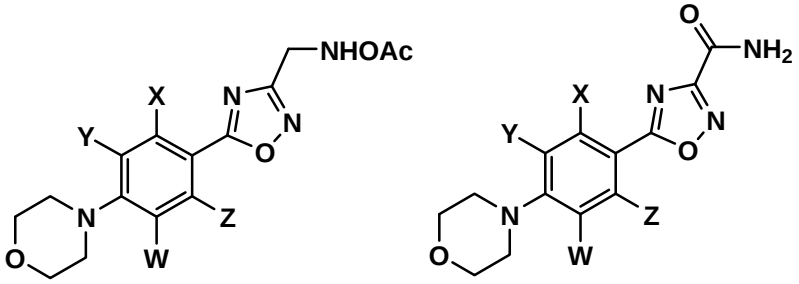


Figure-10

A. P. Piccionello et al.[21] reported the synthesis and preliminary antibacterial evaluation of linezolid-like 1,2,4-oxadiazole derivatives. All the synthesized compounds were tested to evaluate their antibacterial activity against a series of standard and clinical isolates. The antibacterial assay was done using Gram-positive and Gram-negative bacterial pathogens such as S. pyogenes, S. pneumoniae, S. aureus, E. coli and S. marcescens **[Figure-11]**.



X,Y,W,Z=H
X,Y,Z=H;W=F
X,Y,W=H,W=F
X,Y,W=F,Z=H
X,Y,W,Z=F

Figure-11

G. Xi et al.[22] have designed and elaborated a series of piperidyl-oxadiazole derivatives as human 11β-HSD1 inhibitors. On the basis of docking, pharmacokinetic and primary SAR studies, it was found that some compounds were potent and selective human 11β-HSD1 inhibitors with better pharmacokinetic properties than those of the original piperidine-3- carboxamide **[Figure-12]**.

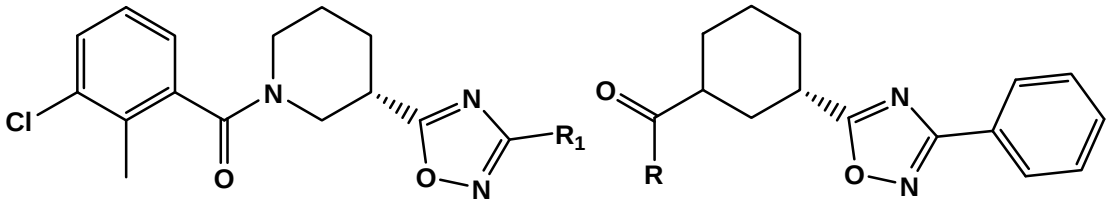


Figure-12

H-J Lankau et al.[23] reported the synthesis of a novel series of 3- and 5-aryl-1,2,4-oxadiazole derivatives and tested for anticonvulsant activity in a variety of models. These 1,2,4-oxadiazoles exhibit considerable activity in both pentylenetetrazole (PTZ) and maximal electroshock seizure (MES) models. The authors found several oxadiazoles that acted as selective GABA potentiating compounds with no interaction to the benzodiazepine binding site **[Figure-13]**.

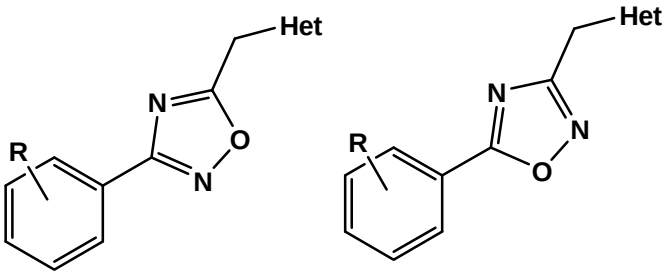


Figure-13

D. J. Ravindra et al.[24] reported the synthesis of some oxadiazole derivatives containing heteroaryl analogs of biaryl ureas and evaluated their biological activity as DGAT1 inhibitors **[Figure-14]**.

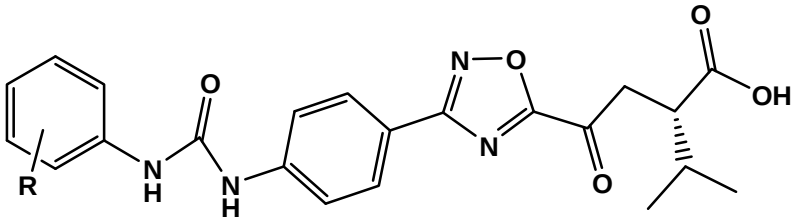


Figure-14

I. Maria et al.[25] reported a convenient straightforward synthesis of 5-amino-substituted 1,2,4-oxadiazoles, upon the reactions of amidoximes with carbodiimides, as well as their further derivatization to acetamides, in good yields. Most of the compounds exhibited in general low interaction with the stable radical 1,1-diphenyl-2-picryl-hydrazyl. Selected compounds were screened for their in vivo anti-inflammatory activity using the carrageenin paw edema model and showed significant anti-inflammatory activity. The ability of the compounds to release NO in the presence of a thiol factor was also investigated **[Figure-15]**.

A convergent strategy was followed to modify systematically carbazole based CB_2 receptor ligands. The length of the *N*-(fluoroalkyl) group (*n* in **7**), the length of the alkanamide (*m* in **7**) and the substitution pattern of the phenyl moiety (X and Y in **7**) were varied systematically. The highest CB_2 affinity was found for the 2-fluoroethyl substituted carbazole derivative (K_i = 5.8 nM) containing the propionamide and the 2-bromo-4-fluorophenyl moiety. According to docking studies fits nicely into the binding pocket of the CB_2 receptor, but elongation of the fluoroethyl side chain leads to a different binding mode of the ligands. The high CB_2 affinity together with the high selectivity over the CB_2 subtype qualifies the fluoroethyl derivative to be developed as a PET tracer.

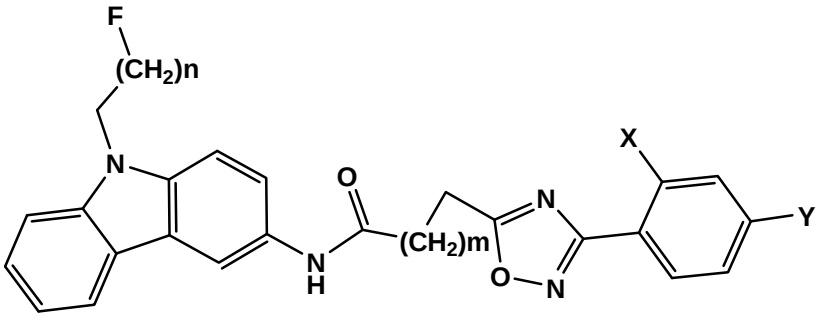


Figure-15

C. Lueg et al.[26] reported that DGAT-1 is an enzyme that catalyzes the final step in triglyceride synthesis mRNA knockout experiments in rodent models suggest that inhibitors of this enzyme could be of value in the treatment of obesity and type II diabetes. The carboxylic acid-based DGAT-1 inhibitor 1 was advanced to clinical trials for the treatment of type-II, diabetes, despite of the low passive permeability of DGAT-1 inhibitor **[Figure-16].**

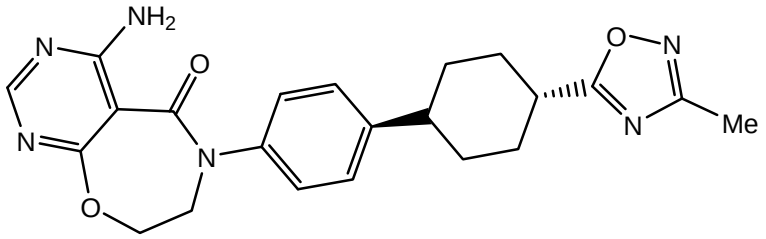


Figure-16

The mosquito *Aedes aegypti* is the vector agent responsible for the transmission of yellow fever and dengue fever viruses to over 80 million people in tropical and subtropical regions of the world. Exhaustive efforts have lead to a vaccine candidate with only 30% effectiveness against the dengue virus and failure to protect patients against the serotype 2. Hence, vector control remains the most viable route to dengue fever control programs.[27] V. S. Oliveira et al.[28] have synthesized a class of 1,2,4-oxadiazole derivatives whose most biologically active compounds exhibit potent activity against *Aedes aegypti* larvae (ca. of 15 ppm) and low toxicity in mammals. Exposure to these larvicides results in larvae pigmentation in a manner correlated with the LC_{50} measurements. Structural comparisons of the 1,2,4-oxadiazole nucleus against known inhibitors of insect enzymes allowed the identification of 3-hydroxykynurenine transaminase as a potential target for these synthetic larvicides. Molecular docking calculations indicate that 1,2,4-oxadiazole compounds can bind to 3-hydroxykynurenine transaminase with similar conformation and binding energies as its crystallographic inhibitor 4-(2-aminophenyl)-4-oxobutanoic acid **[Figure-17].**

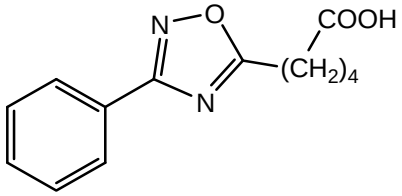


Figure-17

D. Cottrell et al.[29] have reported the synthesis of a series of 5-thiocyanatomethyl and 5-alkyl-3-aryl-[1,2,4]-oxadiazoles derivatives and evaluated them all for their activity against kinetoplastid parasites such as Leishmania donovani and Trypanosoma brucei. Some compound among the entire series displayed promising activity **[Figure-18].**

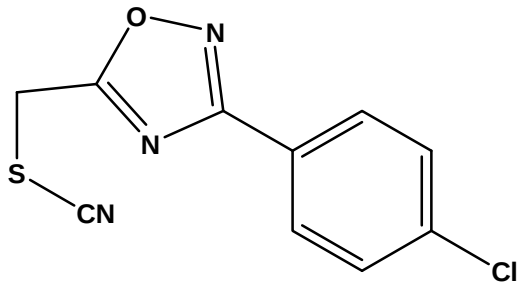


Figure-18

M. A. Weidner-Wells et al.[30] have reported the synthesis of a novel series of 3,5-diaryl-[1,2,4]-oxadiazole and tested them all as IL-8 antagonists. Interleukin-8 (IL-8), a 72-amino acid peptide is a member of C-X-C family of chemokines found in abundant quantities on neutrophils. It is actively involved in the process of inflammation therefore; IL-8 receptor antagonism may lead to unique anti-inflammatory agents **[Figure-19].**

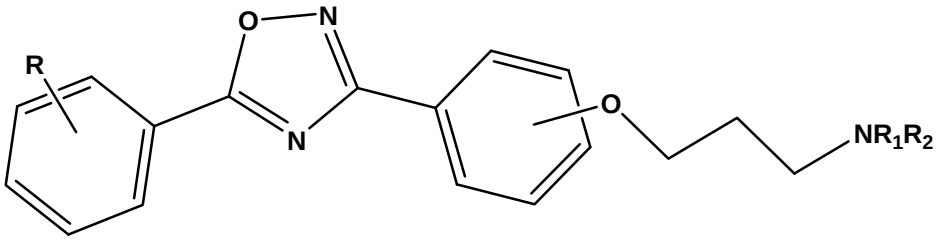


Figure-19

Z. Han-Zhong et al.[31] have synthesized 3, 5-diaryl-[1,2,4]-oxadiazoles as a new series of apoptosis Inducers and potential anticancer agents. 5-(3-chlorothiophen-2-yl)-3-(4-trifluoro-methylphenyl)-[1,2,4]oxadiazole, has been found to show good activity against several breast and colorectal cancer cell lines **[Figure-20].**

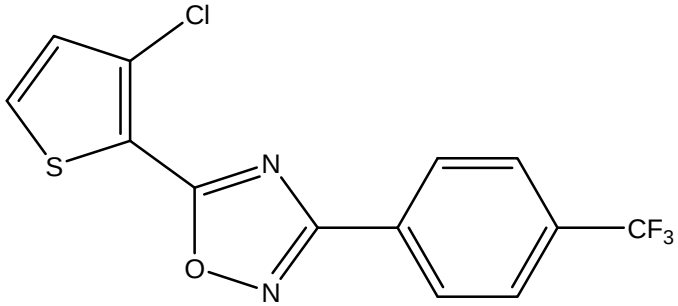


Figure-20

J. T. Palmer et al.[32] have reported the synthesis of a new series of keto-[1,2,4]-oxadiazoles, some compounds have been found to be highly potent and selective human tryptase inhibitors. These compounds could be helpful in the therapy of allergic disease including asthma **[Figure-21].**

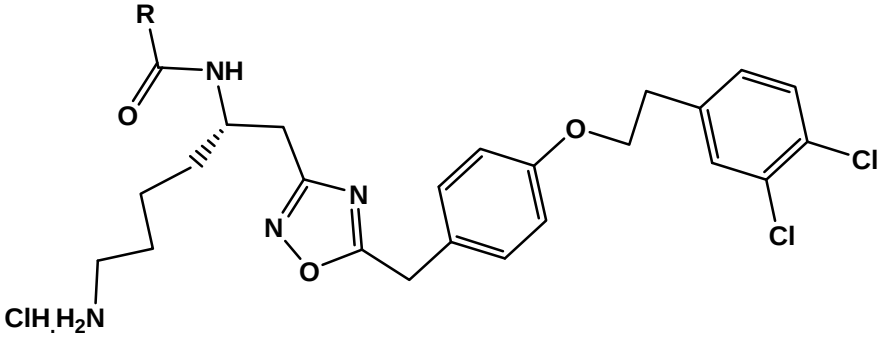


Figure-21

J. V. dos Anjos et al.[33] reported the convergent synthesis of an unusual (but simple) class of compounds has been achieved by the copper-catalyzed [3 + 2] cycloaddition reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide with propynyl 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionates**.** All the compounds were evaluated for their cytotoxicity studies and exhibited weak cytotoxicity but some compounds had somewhat better behaviour showing 22–25% cell growth inhibition against two cell strains: NCI-H_{292} (lung carcinoma) and HEp-2 (larynx carcinoma) **[Figure-22].**

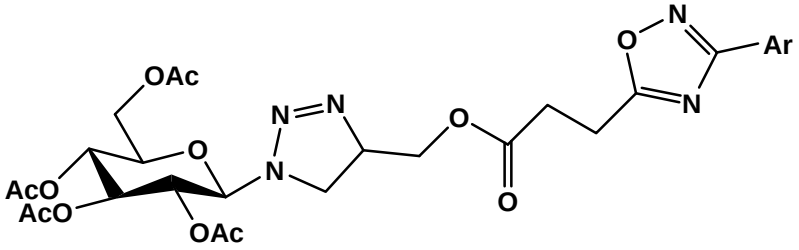


Figure-22

D. Kumar et al.[34] synthesized a library of 3,5-disubstituted-1,2,4-oxadiazoles and their bioisosters, 1,3,4-oxadiazole and 1,3,4-thiadiazole, and evaluated them all for *in vitro* anticancer potential against a panel of six human cancer cell lines. The key step in the synthesis of oxadiazoles involve coupling of amidoxime with an appropriate carboxylic acid followed by thermal cyclization. The bioisosteres, 1,3,4-oxadiazole and 1,3,4-thiadiazole were prepared from the reaction of a common precursor diacylhydrazine with thionyl chloride and Lawesson′s reagent, respectively. The anticancer studies on the synthesized compounds revealed that presence of a cyclopentyloxy or *n*-butyloxy on the C-3 aryl ring and piperdin-4-yl or trichloromethyl at the C-5 position of 1,2,4-oxadiazole is essential for good activity. In particular, 1,2,4-oxadiazole and analogue 1,3,4-thiadiazole exhibited significant activity against DU145 (IC_{50}: 9.3 μM) and MDA-MB-231 (IC_{50}: 9.2 μM) cell lines, respectively **[Figure-23].**

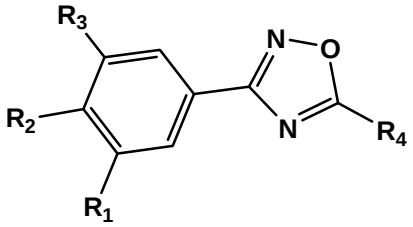


Figure-23

J. N. Sangshetti et al.[35] reported that a novel series of 3-(1-(1-substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-5-substituted phenyl-1,2,4-oxadiazoles bearing 1,2,3-triazole and piperidine ring have been synthesized in one step from amidoxime using Carbonyl diimidazole (CDI) and K_2CO_3 **[Figure-24].** All the synthesized compounds are novel and evaluated for their in vitro antifungal activities. SAR for the series has been developed by comparing their MIC values with miconazole and fluconazole. Some of the compounds from the series like was equipotent with miconazole against *Cryptococcus neoformans* whereas activities of compound against *Aspergillus niger* and *Aspergillus flavus* were comparable to miconazole. Also compound shows activity comparable to miconazole against *Candida albicans*, *A. niger* and *A. flavus*.

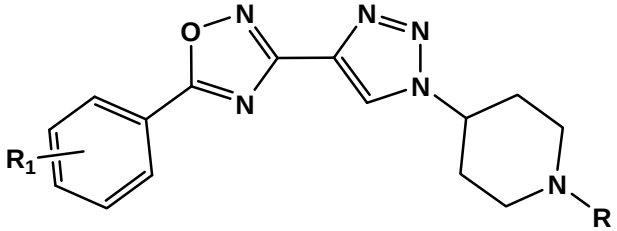


Figure-24

Modulators of sphingosine phosphate receptor-1 ($S1P_1$) have recently been focused as a suppressant of autoimmunity. T. Nakamura et al.[36] reported the synthesis of CS-2100 and pharmacological effects such as $S1P_1$ and $S1P_3$ agonist activity *in vitro*, peripheral blood lymphocyte lowering effects and the suppressive effects on adjuvant-induced arthritis and experimental autoimmune encephalomyelitis (EAE) in animal models. The pharmacokinetic data were also reported. CS-2100 had >5000-fold greater agonist activity for human $S1P_1$

(EC_{50}; 4.0 nM) relative to $S1P_3$ (EC_{50}; >20000 nM). Following administration of single oral doses of 0.1 and 1 mg/kg of CS-2100 in rats, lymphocyte counts decreased significantly, with a nadir at 8 and/or 12 h post-dose and recovery to vehicle control levels by 24–48 h post-dose. CS-2100 is efficacious in the adjuvant-induced arthritis model in rats (ID_{50}; 0.44 mg/kg). In the EAE model compared to the vehicle-treated group, significant decreases in the cumulative EAE scores were observed for 0.3 and 1 mg/kg CS-2100 groups in mice. While CS-2100 showed potent efficacy in various animal disease models, it was also revealed that the central 1,2,4-oxadiazole ring of CS-2100 was decomposed by enterobacteria in intestine of rats and monkeys, implicating the latent concern about an external susceptibility in its metabolic process in the upcoming clinical studies **[Figure-25].**

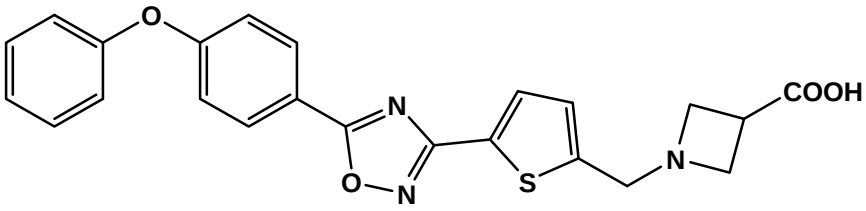


Figure-25

A. G. Koryakova et al.[37] reported the synthesis, biological evaluation, and SAR dependencies for a series of novel aryl and heteroaryl substituted N-[3-(4-phenylpiperazin-

1-yl)propyl]-1,2,4-oxadiazole-5-carboxamide as inhibitors of GSK-3b kinase. It was observed that the inhibitory activity of the synthesized compounds was highly dependent on the type of substituent in the phenyl ring and the nature of terminal heterocyclic fragment of the core molecular scaffold. The most potent compounds from this series contain 3,4-di methyl or 2-methoxy substituent within the phenyl ring and 3-pyridine fragment connected to the 1,2,4-oxadiazole heterocycle **[Figure-26].**

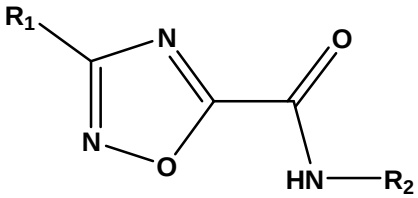


Figure-26

W. Kemnitzer et al.[38] reported the discovery of 3-aryl-5-aryl-1,2,4-oxadiazoles as a new series of apoptosis inducers. 2. Identification of more aqueous soluble analogs as potential anticancer agents. The author explored the substitutions at the 2- and 3-positions of the 3-aryl group to improve the aqueous solubility properties and identify development candidates. A small substitution such as methyl or hydroxymethyl at the 2-position was well tolerated. The modification in combination with a 3-substituted furan ring as the 5-aryl group, have improved solubility properties. Some compounds were found to have good in vivo efficacy in animal studies via intravenous administration **[Figure-26].**

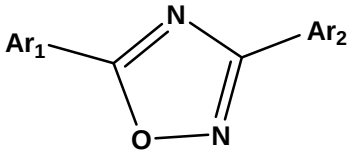


Figure-26

S1P1 receptor driven lymphopenia has proven utility in the treatment of an array of autoimmune disease states. D. Buzard et al.[39] reported a novel chemical series of 4-oxo-4-(5-(5-phenyl-1,2,4-oxadiazol-3-yl)indolin-1-yl)butanoic acid S1P1 receptor agonists **[Figure-27].**

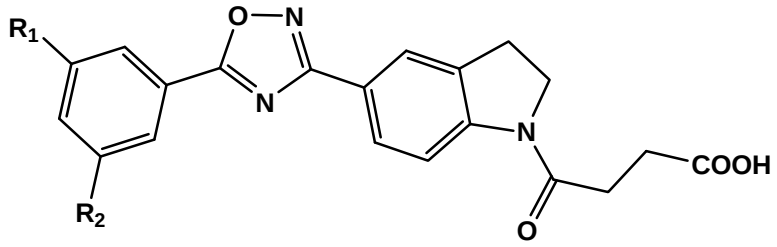


Figure-27

C-S Lee et al.[40] have synthesized a series of novel a-keto-[1,2,4]-oxadiazoles has been and tested as human tryptase inhibitors for evaluation as a new class of anti-asthmatic agent. The inhibitor design was focused on using a prime-side hydrophobic pocket and the S2 pocket of β-tryptase to achieve inhibition potency and selectivity over other serine proteases **[Figure-28].**

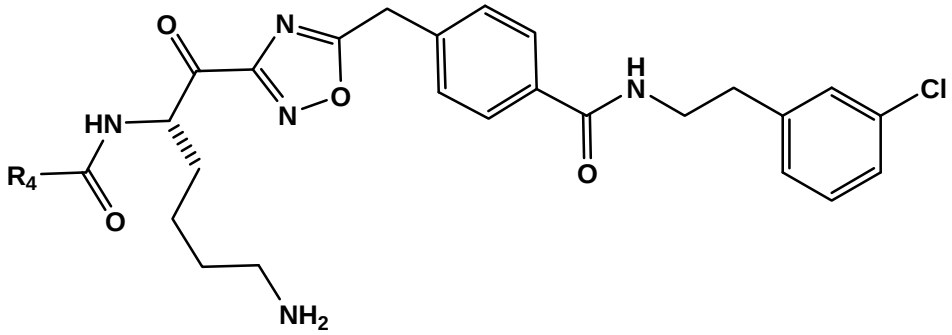


Figure-28

3. CONCLUSION:

The pharmacological potential of 1,2,4-oxadiazole nucleus is cleared from the literature and clinically used drugs. The literature revealed that 1,2,4-oxadiazole possess diverse biological potential, easy synthetic routes for the synthesis and attracted researchers for development of new chemotherapeutic agents and it also revealed the importance of the nucleus.

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