1,3,4-Oxadiazole: A Biologically Active Scaffold

H. Khalilullah*[,1,2], M.J. Ahsan[2,3], Md. Hedaitullah[4], S. Khan[5] and B. Ahmed[1]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110 062, India;* [2]*Department of Pharmaceutical Chemistry, Alwar Pharmacy College, Alwar 301 030, Rajasthan, India;* [3]*Department of Pharmaceutical Sciences, Nims University, Jaipur 303 121, Rajasthan, India;* [4]*Department of Pharmaceutical Chemistry, HIMT College of Pharmacy, Greater Noida 201 301, U. P., India;* [5]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Qassim University, Buraidah, Kingdom of Saudi Arabia*

Abstract: There has been considerable interest in the development of novel compounds with anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiallergic, antipsychotic, antimicrobial, antimycobecterial, antitumour, antiviral and antitubercular activities. 1,3,4-oxadiazoles constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations led to the development of new 1,3,4-oxadiazole derivatives. This review article describes the various biological activities associated with 1,3,4-oxadiazole ring system and is useful in guiding the researchers across the world working on this moiety and consequently have been instrumental in the advancement of 1,3,4-oxadiazole chemistry.

Keywords: 1,3,4-Oxadiazole, oxadiazole, azole.

INTRODUCTION

1,3,4-oxadiazoles represent a series of synthetic compounds of considerable medicinal importance. The focus of this article will be on recent pharmacological results in the area of 1,3,4-oxadiazoles. 1,3,4-oxadiazole is an important moiety and has been the focus of other recent review articles [1-4], This article describes the various biological activities associated with 1,3,4-oxadiazole ring system.

No trivial name for the 1,3,4-oxadiazole ring, such as "azoxime" (for 1,2,4-oxadiazole) or "furazan" (for 1,2,5-oxadiazole) has gained acceptance and as a consequence, the literature is cursed with a multiplicity of names for this nucleus. Among these are "oxbiazole", "oxadiazole", "diazoxole", "furo[bb$_1$]diazole" and "biazole" the systematic name 1,3,4-oxadiazole has gradually become prevalent, and is used exclusively here. Oxadiazoles are the compounds having five membered ring with two nitrogen atoms and one oxygen atom.

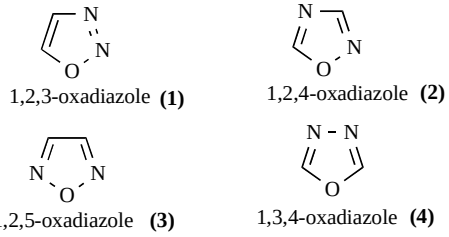

Fig. (1). Molecular Scaffold of oxadiazole.

*Address correspondence to this author at the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110 062, India; Tel: (+91)-0144-5121027; Mobile: +91-8058790282; E-mail: shabib79@yahoo.co.in

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two –CH═ groups in furan by two pyridine type nitrogen (–N═) reduces aromaticity of the resulting oxadiazole ring to such an extent that the oxadiazole ring exhibits the character of conjugated diene. Due to relatively low electron density on the carbon atom, the oxadiazole ring is extremely resistant towards electrophillic substitutions at carbon atom; however the attack of electrophile occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Nucleophilic attack is quite difficult in oxadiazole ring; however, halogen-substituted oxadiazoles can undergo nucleophilic substitution with replacement of halogen atom by nucleophiles.

Although 1,3,4-oxadiazoles have been known for about 80 years[5,6], its biological investigations have been intensified only in the last decade. Moreover, ring cleavage reactions of the 1,3,4-oxadiazoles have also excited great interest in various fields, since they lead to new aliphatic nitrogen- containing compounds and to other ring system. Generally, the 1,3,4-oxadiazole ring is very stable towards heat but somewhat less to the chemical reagents.

POTASSIUM CHANNEL OPENER

Romine *et al*. [7] synthesized and demonstrated the efficacy of 3-[(5-chloro-2- hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazole-2(3*H*)-one **(5)** as an opener of large-conductance Ca^{2+}-activated potassium channel which led to its nomination as a candidate for clinical evaluation.

SELECTIVE PROTEASOME INHIBITORS

A series of vinyl sulfones (VS) were synthesized [8] for evaluation as inhibitors of the chymotrypsin-like activity of

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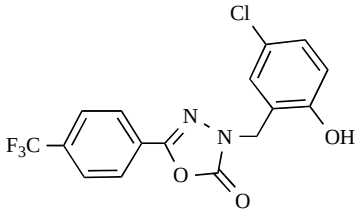
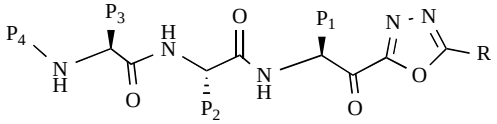


(5)

Fig. (2). Chemical structure of 1,3,4-oxadiazole studied for potassium channel opener.

the 20S proteasome. The resulting optimized P4-P3-P2 sequence was grafted onto a novel proteasome inhibitor warhead, 2-keto-1,3,4-oxadiazoles **(6)** (KOD), to produce reversible, subnanomolar proteasome inhibitors that were 1000-fold selective versus cathepsin B (CatB), cathepsin S (CatS), and trypsin-like as well as PGPH-like proteasome activity. A number of compounds in both the VS and the KOD series exhibited growth inhibitory effects against the human prostate cancer cell line PC3 at submicromolar concentrations.

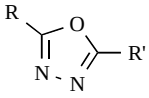


(6)

Fig. (3). Chemical structure of 1,3,4-oxadiazole as Proteasome Inhibitors.

MUSCLE RELAXANT

Yale *et al.* [9] synthesized a series of 2-amino-5-substituted-1,3,4-oxadiazoles **(7)** by the reaction of 1-acyl-3-thiosemcarbazide with Pb_3O_4. Several of these oxadiazoles were found highly potent in producing a profound flaccid paralysis in laboratory animals.



(7)

R = H, *o*-chloro-phenyl, *m*-chlorophenyl, *p*-chlorophenyl, phenyl

R' = NH, $NHCOCH_3$

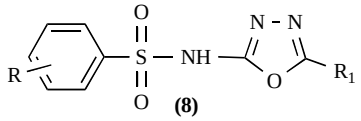
Fig. (4). Chemical structure of 1,3,4-oxadiazole derivatives studied as muscle relaxant.

HYPOGLYCEMIC ACTIVITY

A number of 5-alkyl-2-arylsulfonamido-l,3,4-oxadiazoles **(8)** [10] and 2(*p*-substituted-sulfonamido)-5-substituted-1,3,4-oxadiazoles **(9)** [11] have been prepared. Several of them exerted a powerful hypoglycemic activity.

ANTIALLERGIC ACTIVITY

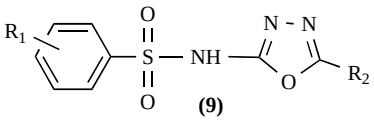
A series of new 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-y1) benzo heterocycles **(10)** have been prepared [12]. These compounds were tested as inhibitors of antigen-induced



(8)

R_1 = alkyl

R = *p*-F, *p*-OCH_3,Cl, *o*-Br



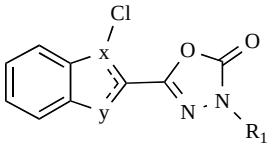
(9)

R_1 = *p*-Cl, *p*-CH_3

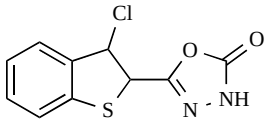
R_2 = cyclohexyl, $(CH_3)_2CHCH_3$

Fig. (5). Chemical structure of 1,3,4-oxadiazole derivatives studied for hypoglycemic activity.

release of histamine (AIR) *in vitro* from rat peritoneal mast cells (RMC) and as inhibitors of IgE-mediated rat passive cutaneous anaphylaxis (PCA) in the rat. Most of this new class of antiallergic agents showed good activity in the RMC assay. The most potent compound, 3-chloro-2-(2,3-dihydro-2-oxo-l,3,4-oxadiazol-5-yl)benzo[b]thiophene **(10a),** with an **IC_{50}** value of **0.2** μM, is 15 times more potent than disodium cromoglycate (DSCG) in the RMC assay. Many compounds were orally active in the PCA test, and several of these compounds showed higher potency as compared to DSCG when given intraperitoneally.



(10)



(10a)

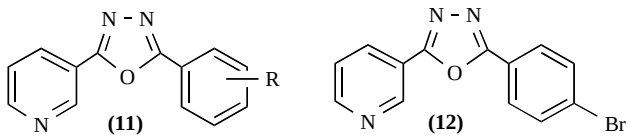
X = O, S, N-Me, CH; Y = N, S, O, CH_2, NH

R_1 = H , Ac, CO_2Et, Me, H ; R_2 = H, 5-Cl, 4-Me, 5-Me, 6-Me

Fig. (6). Chemical structure of 1,3,4-oxadiazole derivatives studied for antiallergic activity.

TYROSINASE INHIBITORY

A series of 2,5-disubstituted-1,3,4-oxadiazoles **(11)** were prepared [13] and studied to explain their inhibition patterns and structure–activity relationship (SAR) against the enzyme tyrosinase, which is a multifunctional copper-containing enzyme, widely distributed in plants and animals and catalyses the *o*-hydroxylation of monophenols and also the oxidation of *o*-diphenols to *o*-quinones. It was concluded that for a better inhibition of tyrosinase, electronegative substitution is essential, as most probably the active site of the enzyme contain some hydrophobic site and position is also very important for the inhibition purposes due to the conformational space. The compound 3′-[5-(4′-bromo-phenyl)-1,3,4-oxadiazol-2-yl] pyridine **(12)** exhibited most potent (IC_{50} = 2.18 μM) inhibition against the enzyme tyrosinase which is more potent than the standard potent inhibitor L-mimosine (IC_{50} = 3.68 μM).



R= NO_2, Br, CH_3

Fig. (7). Chemical structure of 1,3,4-oxadiazole derivatives studied as tyrosinase inhibitors.

ANTICANCER ACTIVITY

Aboraia *et al.* [14] synthesized a series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione **(13)** derivatives and evaluated them for their *in-vitro* anticancer activity. Seven of the investigated compounds displayed high anticancer activity in the primary assay. These compounds were selected for a full anticancer screening against a 60-cell panel assay where they showed non-selective broad spectrum and promising activity against all cancer cell lines. Some compounds in this study were found to be highly active as compared to 5-fluorouracil and cyclophosphamide as reference drugs, respectively.

5-(6,7,8,9-Tetrahydro-5*H*-[1,2,4]-triazolo[1,5-a]-azepine-2-ylmethylene)-1,3,4-oxadiazole-2-thione **(14)** and related derivatives **15** and **15a** were synthesized [15] and evaluated in a series of human cancer cell line cultures. None of the oxadiazole derivatives showed prominent anticancer activity.

Lee *et al*. [16] designed and synthesized a series of novel 2,5-diaryl-1,3,4-oxadiazoline analogs of combretastatin and evaluated them for anticancer activity. Biological evaluation demonstrated that multiple structural features control the biological potency. Four of the compounds **16a-16d** has shown potent antiproliferative activities against multiple cancer cell lines.

Zhang *et al.* [17] synthesized a series of novel 1,3,4-oxadiazole derivatives containing 1,4-benzodioxane moiety **(17)** and screened them for antitumor activity. The antiproliferative activity was determined against four different original cancer cells (HEPG2, HELA, SW1116 and BGC823). The results indicated that the some compounds exhibited excellent antitumor activity as compared to 5-fluorouracil which is widely used in treatment of cancer. They further analyzed their inhibitory effects on telomerase expressed in cancer cells.

A series of 2-anilinonicotinyl linked 1,3,4-oxadiazoles were synthesized [18] and evaluated for their antitumor activity against various cancer cell lines, inhibition of tubulin polymerization and cell cycle effects. Some of these compounds showed good antiproliferative activity with GI_{50} values ranging from 4.57 to 97.09 μM in the human cancer cell lines and one of the compounds **18** showed potent antitumour activity in all the cell lines tested. This compound also inhibited tubulin polymerization under both *in vitro* and *in vivo* conditions. Analysis of tubulin by Western blot experiments demonstrated that this compound depolymerizes microtubules by causing disturbances in the ratio of soluble *versus* polymerized tubulin in cells, leading to the cell cycle arrest at G_2/M phase of the cell cycle followed by activation of caspase-3 activity and apoptotic cell death.

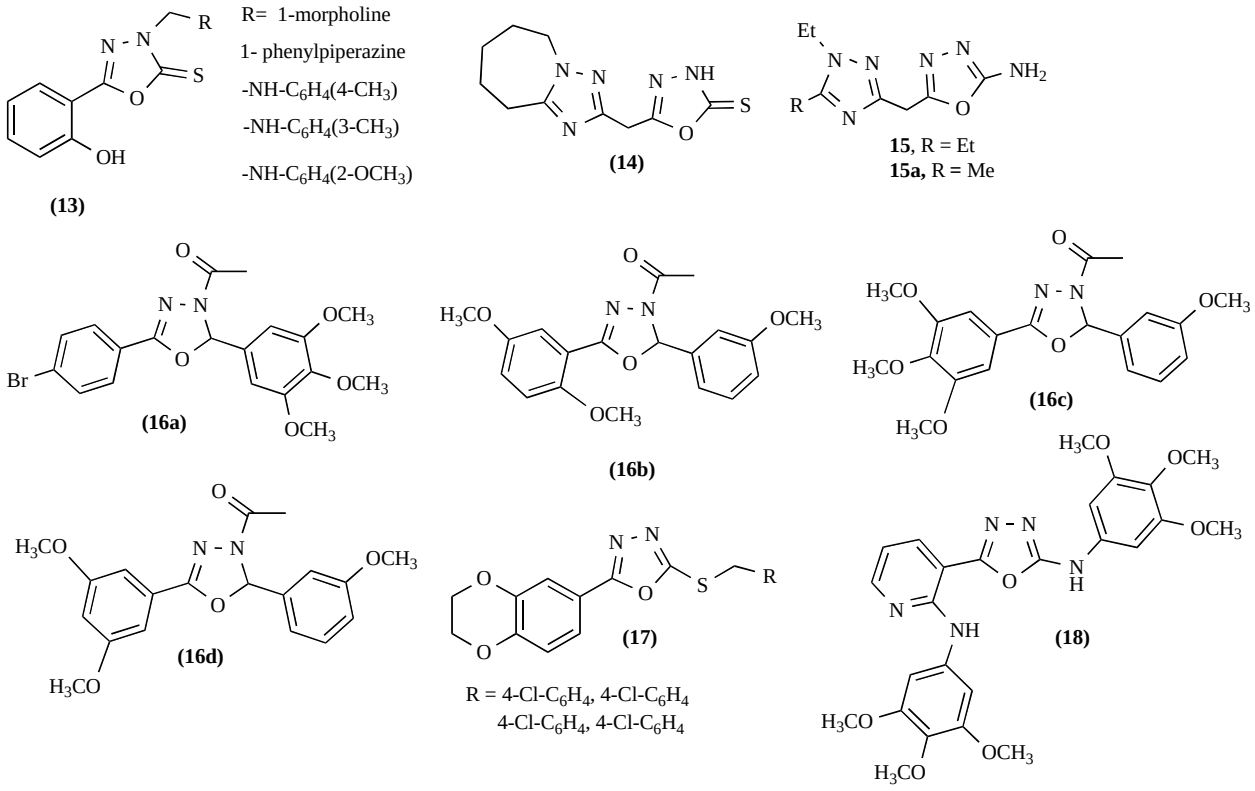
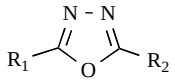
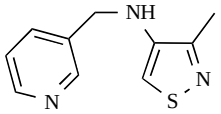
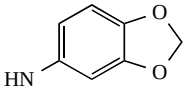
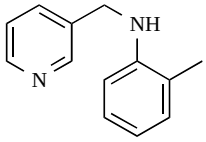
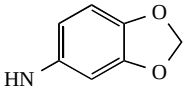
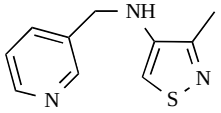
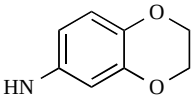
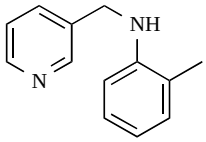
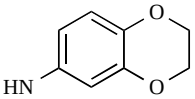
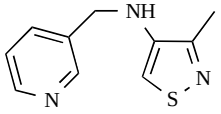
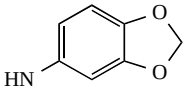
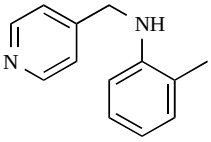
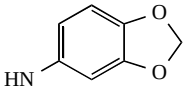
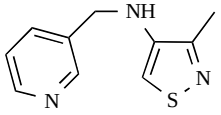
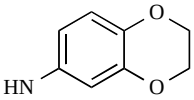
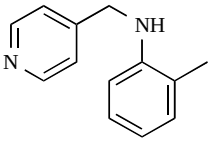
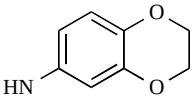


Fig. (8). Chemical structure of 1,3,4-oxadiazole derivatives studied for anticancer activity.

Table 1. Anticancer Activity of 1,3,4-Oxadiazole Derivatives Synthesized by Kiselyov *et al.* [19]



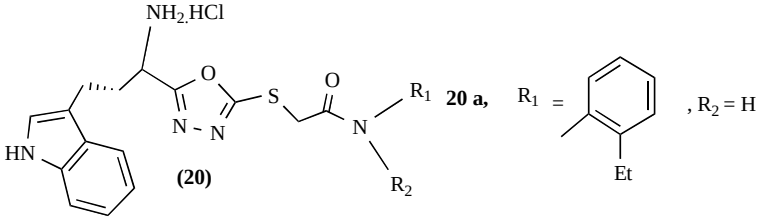
(19)

No.	R_1	R_2	No	R_1	R_2
19a			**19e**		
19b			**19f**		
19c			**19g**		
19d			**19h**		

A series [19] of novel 1,3,4-oxadiazole derivatives (Table **1**) based on structural and electronic overlap with combretastatins have been designed and synthesized. All the new compounds were tested initially *in vivo* using the phenotypic sea urchin embryo assay to yield a number of agents with anti-proliferative, anti-mitotic, and microtubule destabilizing activities. The experimental data led to identification of 1,3,4-oxadiazole derivatives with isothiazole **(19a-19d)** and phenyl **(19e-19h)** pharmacophores featuring activity profiles comparable to that of combretastatins, podophyllotoxin and nocodazole. Cytotoxic effects of the two lead molecules, namely **19b** and **19h**, were further confirmed and evaluated by conventional assays with the A549 human cancer cell line including cell proliferation, cell cycle arrest at the G_2/M phase, cellular microtubule distribution, and finally *in vitro* microtubule assembly with purified tubulin. The modeling results using 3D similarity (ROCS) and docking (FRED) correlated well with the observed activity of the molecules. Docking data suggested that the most potent molecules are likely to target the colchicine binding site.

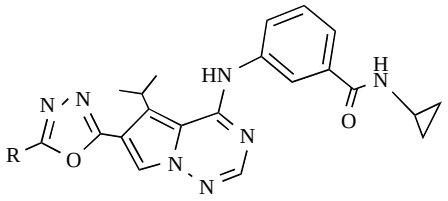
THIOCARBAZATE CATHEPSIN L INHIBITOR

The cathepsins comprise a family of lysosomal protease enzymes whose primary function (i.e., protein degradation) plays a critical role in normal cellular homeostasis [20]. Over expression of cathepsin L and/or abnormal activity has been implicated in a number of disease states like osteo- and rheumatoid arthritis [21]. Myers *et al.* [22] identified 2,5-disubstituted oxadiazoles derivatives **(20)** as potent hits in a high throughput screen (HTS). However, when synthesized in pure form, the putative actives were found to be devoid of biological activity. Initial HTS results of cathepsin L screen indicated that several structurally related oxadiazoles exhibited potent inhibitory activity. The most potent hit, cataloged in the NIH Molecular Libraries Small Molecule



(20) **20 a,** R_1 = , R_2 = H

Fig. (9). Chemical structure of 1,3,4-oxadiazole derivatives studied for thiocarbazate cathepsin L inhibitory activity.



R=NHMe, $NHMe_2$, NHipr, $NHCH_2CH_2OH$, $NHCH_2CH_2CH_2NH_2$, $NHCH_2CH_2CH_2CH_2NHMe$, $NHCH_2CH_2CH_2CH_2NHMe$, $NHCH_2CH_2NHMe_2$, $NHnBuNH_2$

(21)

Fig. (10). Chemical structure of 1,3,4-oxadiazole derivatives studied for VEGFR-2 kinase inhibitory activity.

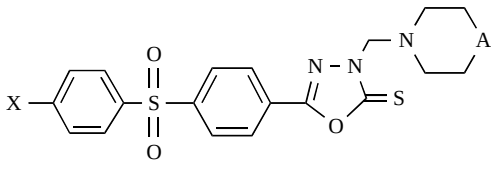
Repository (MLSMR) as disubstituted oxadiazole **(20 a)** exhibited an IC_{50} of 0.13 μM.

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR-2 KINASE) INHIBITORS

Vascular endothelial growth factor receptor-2 (VEGFR-2) is a protein tyrosine kinase that drives angiogenesis, a process critical for tumor growth and metastasis [23]. Cai [24] and co-workers synthesized the N- and O-tethered oxadiazole **(21)** compounds and screened for the inhibition of VEGFR-2 activity and human cytochrome CYP P450 isozyme activity.

CARBONIC ANHYDRASE INHIBITORS

The carbonic anhydrases are ubiquitous metallo-enzymes, present in prokaryotes and eukaryotes [25]**.** These enzymes catalyze a very simple physiological reaction, the interconversion between carbon dioxide and the bicarbonate ion, and are thus involved in crucial physiological processes connected with respiration and transport of CO_2/bicarbonate between metabolizing tissues and lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues/ organs, biosynthetic reactions (such as gluconeogenesis, lipogenesis and ureagenesis), bone resorption, calcification, tumorigenicity, and many other physiological or pathological processes.[25] Almajan *et al.* [26] synthesized a series of mercapto-1,3,4-oxadiazole **(22)** derivatives. Heterocyclic mercaptans prepared in this way were assayed as inhibitors of three physiologically relevant isoforms of the zinc enzyme carbonic anhydrase (CA), i.e., the cytosolic CA I and II, and the tumor-associated, transmembrane isozyme CA IX. The compounds have shown good to moderate activity.



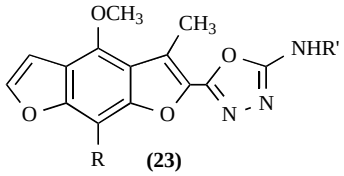
(22)

X = H, Cl, Br A = CH_2, O

Fig. (11). Chemical structure of 1,3,4-oxadiazole derivatives as carbonic anhydrase inhibitors.

ABILITY TO BIND TO DNA

A series of new benzo[1,2-b:5,4-b′]difuranyl-1,3,4-oxadiazoles **(23)** derivatives were synthesized [27] and biologically evaluated for their ability to bind to DNA using a colorimetric assay. Some of these derivatives showed moderate activity.



R	R'
H	Ph
H	CH_2Ph
H	C_2H_5
H	C_6H_{11}
OCH_3	Ph

(23)

Fig. (12). Chemical structure of 1,3,4-oxadiazole derivatives.

COMPETITIVE MONOAMINE OXIDASE INHIBITORS

Mazouz *et al.* [28] prepared a series of new 5-aryl-1,3,4-oxadiazol-2(*3H*)-one derivatives **(24)** and their sulfur analogues **(25)** and evaluated *in vitro* for their inhibitory properties on monoamine oxidase (MAO) types A and B. The most active compounds in this series acted preferentially against MAO B with IC_{50} values in the range of 1.8-0.056 μM. The 5-(4-biphenyl)-3-(2-cyanoethyl)-1,3,4-oxadiazol-2(*3H*)-one and its oxadiazole thione analogue (**26, 27)** were found to act as potent, selective and competitive MAO B inhibitors with a slight slow-binding character. Both compounds inhibited MAO A in a classical competitive manner and found to be most active and selective competitive MAO B inhibitors in this series.

A series of 5- [4-(benzyloxy) phenyl]-3-(2-cyanoethyl)-l,3,4-oxadiazol-2(*3H*)-one **(26)** and 5-[4-(benzyloxy) phenyl]-1,3,4-oxadiazol-2(*3H*)-one **(27)** derivatives were synthesized [29] and investigated *in vitro* and *ex vivo* MAO B inhibitory activity. The most active compounds have their IC_{50}(MAO B**)** values in the range of 1.4-4.6 nM and their selectivity, estimated by the ratio of IC_{50} values (A/B), are from 3200 to >71400. Compound **26a** exhibited the highest activity against MAO B.

CALCIUM- AND CALMODULIN-ANTAGONISTS

Manhold *et al*. [30] synthesized a series of compounds **(28, 29, 30)** in which 5-position of dihydropyridine (elnadipine) is substituted with 1,3,4-oxadiazole ring system. Lipophilic substituents of the oxadiazole in 5-position of the dihydropyridine (DHP) ring resulted in increased calmodulin (CaM) antagonistic properties and decreased Ca^{2+}-antagonistic potency; correspondingly the unsubstituted compound have shown the strongest Ca^{2+}- and the weakest CaM-antagonistic activity. 1,3,4-oxadiazole substitution is

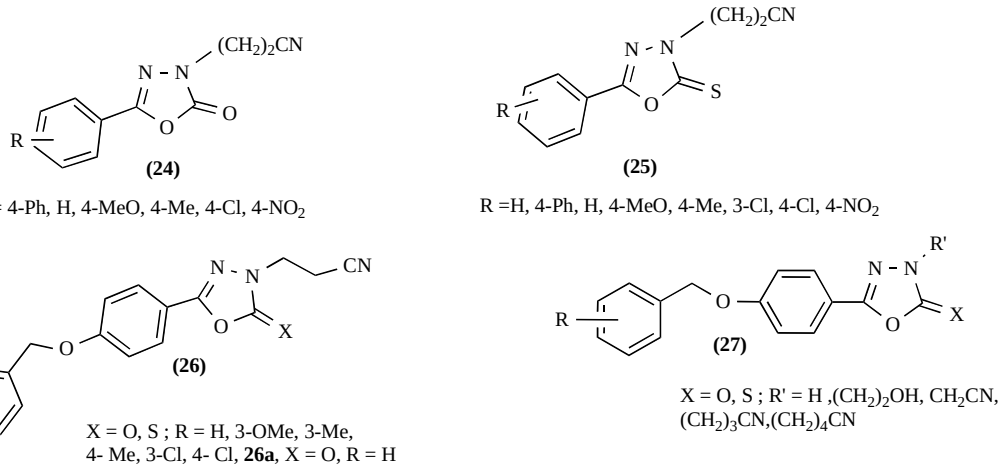


Fig. (13). Chemical structure of 1,3,4-oxadiazole derivatives as monoamine oxidase inhibitors.

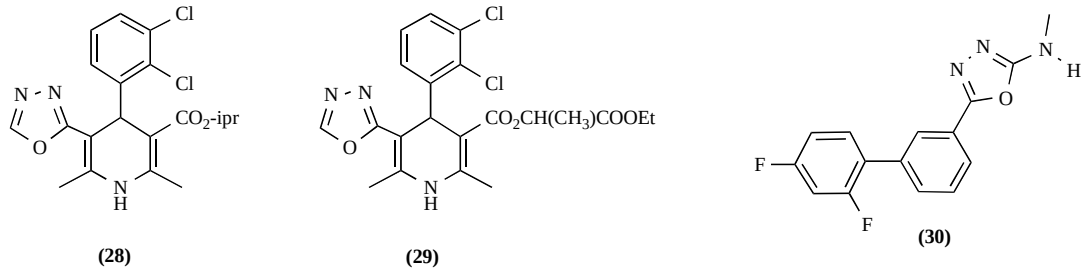


Fig. (14). Chemical structure of 1,3,4-oxadiazole derivatives studied as Calcium- and Calmodulin-Antagonist.

found to be superior in comparison with 1,2,4-oxadiazole as regards Ca^{2+}- and CaM-antagonistic potency.

DUAL INHIBITORS OF CYCLOOXYGENASE AND 5-LIPOXYGENASE

Boschelli *et al.* [31] reported that the replacement of the carboxylic acid functionality with 1,3,4-oxadiazole **(31)** heterocycles resulted in the conversion of NSAIDs into balanced dual inhibitors of cyclooxygenase and 5-lipoxygenase.

Mullican [32] and co-workers reasoned that a dual inhibitor of cyclooxygenase and 5-lipoxygenase would provide an anti-inflammatory agent with not only improved efficacy, but with fewer side effects and hence designed, synthesized and evaluated anti-inflammatory activity of a series of 5-[3,5-bis (l,l-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxadiazoles derivatives **(32**, **33)**

Boschelli *et al.* [33] replaced the carboxylic acid group of several fenamates with 1,3,4-oxadiazoles **(34)**, in hope of obtaining dual inhibition of cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) and further evaluated their potential to inhibit COX and 5-LOX enzyme activities.

ANTI-INFLAMMATORY

A number of 3-heterocyclyl-1,2-benoisothiazoles **(35)**, having 1,3,4-oxadiazole ring system attached to the position-3 of 1,2-benzisothiazole nucleus were prepared and evaluated for anti-inflammatory activity [34]. Some of the synthesized compounds showed potent anti-inflammatory activity as compared to standard drug Ibuprofen.

Palaska *et al.* [35] prepared 2-(2-naphthyloxymethyl)-5-substituted-amino-1,3,4-oxadiazole derivatives **(36)** and found them to be orally active anti-inflammatory agents with reduced side-effects.

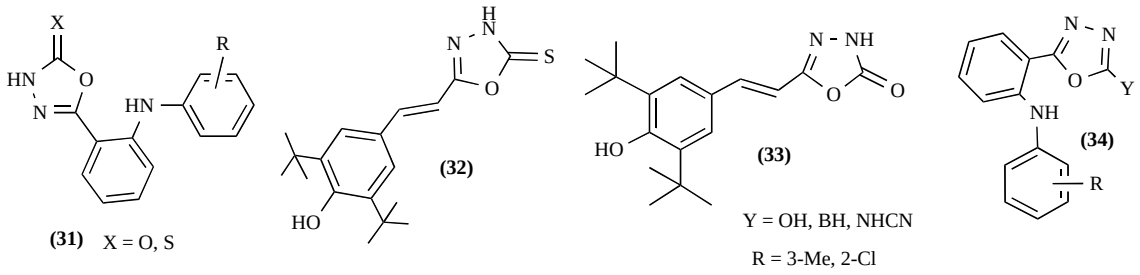


Fig. (15). Chemical structure of 1,3,4-oxadiazole derivatives studied as dual inhibitors of cyclooxygenase and 5-lipoxygenase.

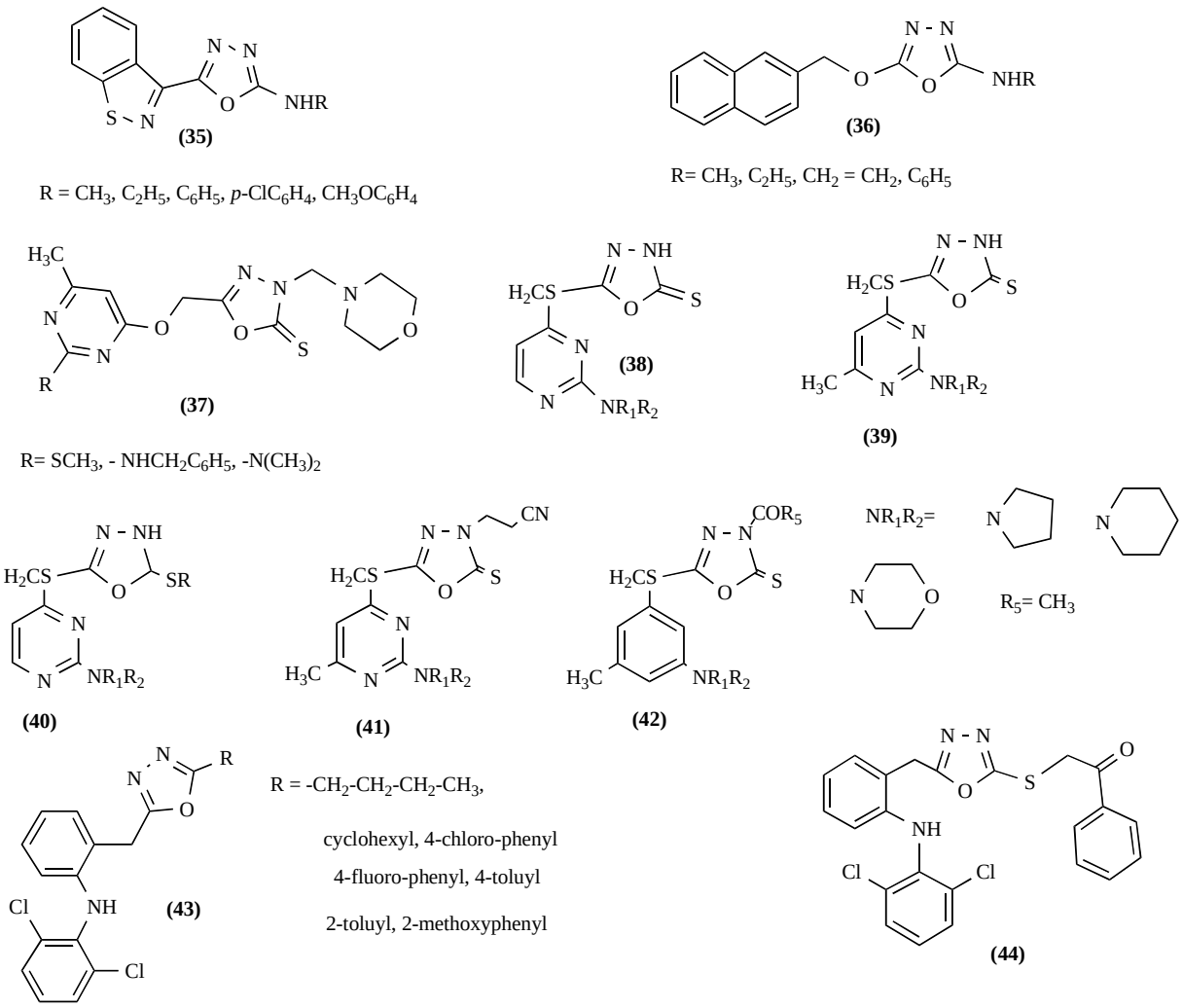


Fig. (16). Chemical structure of 1,3,4-oxadiazole derivatives studied as anti-inflammatory agents.

Methods for synthesis and *in-vivo* anti-inflammatory activity of 5-(6-methyl-2-substituted-4-pyrimidinyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones and their 3-morpholino methyl and 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3*H*-1,3,4-oxadiazole-2-thiones and their *S*-alkyl-, N_3-acyl- and N_3-aminomethyl derivatives [36] **(37-42)** were described. Most of the tested compounds exhibited anti-inflammatory activity and some of them were more active than acetylsalicylic acid.

Amir *et al.* [37] prepared oxadiazole **(43)** derivatives of 2-[(2,6-dichloroanilino) phenyl] acetic acid with the objective of developing better anti-inflammatory molecules with minimum ulcerogenic activity. It was noted that the compounds bearing *o*-methoxy phenyl amino, *p*-methyl phenyl amino, *p*-fluoro phenyl amino and *n*-butyl amino group at second position in the oxadiazole have shown better anti-inflammatory activity whereas presence of cyclohexyl amino and *o*-methyl phenyl amino group have reduced the anti-inflammatory activity.

Bhandari and co-workers [38] reported the anti-inflammatory and analgesic activity of a series of S-substituted phenacyl 1,3,4-oxadiazole **(44)** derivatives.

ANTIBACTERIAL, ANTIMYCOBECTERIAL AND ANTIFUNGAL ACTIVITIES

Mamolo *et al.* [39] synthesized a series of 5-(pyridin-4-yl)-3*H*-1,3,4-oxadiazol-2-thione and 5-(pyridin-4-yl)-3*H*-1,3,4-oxadiazol-2-one derivatives **(45)**, in which the nitrogen at the 3- position is linked through a methylene bridge to a cyclic amine. The *in-vitro* antimycobacterial activities of these derivatives were performed against *M. tuberculosis* H_{37}Rv strain and the results were compared with isoniazid and ofloxacin. Molecular modeling investigations showed that the active compounds may interact at the active site of the mycobacterial cytochrome P450-dependent sterol 14α-demethylase in the sterol biosynthesis pathway and their binding free energy values were in agreement with their MIC values.

El-Azab *et al.* [40] synthesized a series of 2-[(1,3,4-oxadiazol-2-yl)methylthio]-3-(4-chlorophenyl)-4-oxo-6-iodo-3*H*-quinazoline **(46)** derivatives and screened them for antimicrobial activity. The compounds showed remarkable activity against *E. coli* and moderate activity against *S. aureus.*

A series of new 2-[(4-alkylthio/alkylsulfonyl-phenoxy) methyl]-5-substituted-1,3,4-oxadiazoles [41] **(47, 48, 49)** have been reported to possess moderate to good antimicrobial and antifungal activities against pathogenic strains.

Saleh *et al.* [42] reported the synthesis and antimicrobial activity of 3-phenylamino-2-(5-thioxo-4,5-dihydro [1,3,4] oxadiazol-2-ylmethylthio)-3H-quinazolin-4-one **(50)**.

El-Emam *et al.* [43] reported the alkylation pattern of 2 (1-adamantyl)- 1,3,4-oxadiazole-5-thiol **(51, 52)**. The synthesized compounds were tested for their activity against certain strains of bacteria and pathogenic fungi. Some of the derivatives were found to be highly active.

5-aryl-2-[(*N,N*-disubstitutedthiocarbamoylthio)acylamino]-1,3,4-oxadiazole **(53)** [44] derivatives were synthesized and evaluated for antimicrobial activities against *S. aureus and S. epidermidis.*

5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-thione **(54)**, 2-amino-5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole **(55)** and 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one **(56)** derivatives [45] were synthesized. The antimicrobial properties of the compounds were investigated against *S. aureus, E. coli, P. aeruginosa, C. albicans, C. krusei* and *C. parapsilosis.* 2-Amino-5-(2-naphthyloxymethyl)-1,3,4-oxadiazole and 5-(2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one have shown significant activity whereas, 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-thione,2-amino-5-(1-naphthyloxymethyl)-1,3,4-oxadiazole and 5-(1-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one were found to possess moderate activity against *C. krusei.* All the compounds were active against *S. aureus, E. coli, P. aeruginosa, C. albicans*, and *C. parapsilosis* at 64–256 μg/ml concentration.

El-masry *et al.* [46] synthesized 5-[2-(2-methylbenzimidazol-1-yl)ethyl]-3-diethyl amino methyl (or 3-*N*-morpholinylmethyl, or 3-*N*-piprazinylmethyl)[1,3,4]oxadiazole-2(3H)-thione derivatives **(57)** and evaluated them for antimicrobial activity against *B. cereus, E. coli, S. cerevisae* and *A. niger*. Compounds were found slightly effective only against *B. cereus* and inactive against *E. coli, S. cerevisae* and *A. niger*.

Kuckguzel *et al.* [47] synthesized a series of 2-[4-(4-methoxybenzoylamino)phenyl]-5-(substituted-phenyl)amino-1,3,4-oxadiazoles **(58)** derivatives and evaluated them for antimicrobial activity. None of the oxadiazole derivatives showed antimicrobial activity at 6.25 μg mL^{-1}

5-(4-pyrrol-1-yl phenyl)-1,3,4-oxadiazole-2-thiol **(59)** and other oxadiazole derivatives **(60)** were synthesized by Joshi *et al.* [48] and their antibacterial activity was carried out on Gram-positive (*S. aureus, S. faecalis, B. subtilis*) and Gram-negative bacteria. Furthermore the compounds were also tested for their antitubercular activity.

5-{[(4-phenyl-5-pyridin-4-yl-*4H*-1,2,4-triazol-3-yl)thio]-methyl}-1,3,4-oxadiazole-2-thiol **(61)** [49] caused slight antimicrobial activities against *S. aureus* and *B. cereus* and 5-{[(4-Phenyl-5-pyridin-4-yl-*4H*-1,2,4-triazol-3-yl)thio]methyl}-3-{[(2-morpholin-4-ylethyl) amino]methyl}-1,3,4-oxadiazole-2(*3H*)-thione **(62)** which is the Mannich base derivative of compound **62** demonstrated slight activity only towards *E. coli.*

A series of 2,4-dichloro-5-fluorophenyl containing 1,3,4-oxadiazoles **(63, 64)** [50] were prepared by $POCl_3$ cyclization of 2,4-dichloro-5-fluorobenzoyl hydrazide and 2-(2,4-dichloro-5-fluorophenyl)cinchoninyl hydrazide with aryloxyacetic acids. All the compounds were screened for their antibacterial and antifungal activities. Some compounds showed very good antimicrobial activity.

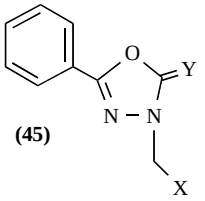
Chen *et al.* [51] prepared a series of new 1,2,4-triazolo[1,5-a]pyrimidine derivatives **(65)** bearing 1,3,4-oxadiazole moieties and evaluated their antifungal activities against *Rhizoctonia solani.* Based on the quantitative structure activity relationships analyses, 2-(1-(5-(*sec*-butylthio)-1,3,4-oxadiazol-2-yl)-ethylthio)-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine **(65a)** was found to display potent antifungal activity (EC_{50} = 3.34 $mgmL^{-1}$)

Macaev *et al.* [52] designed and synthesized a series of 2,5-disubstituted-1,3,4-oxadiazoles **(66, 67, 68)** and screened them for anti-tuberculosis activity against *M. tuberculosis* H37Rv. A systematic SAR study was performed through application of the ETM (electronic-topological method) approach to the series of compounds relative to their experimentally measured anti-tuberculosis activity. Data obtained from conformation and quantum-chemistry calculations were used to form electronic-topological matrices. These matrices were effectively used in the search for a system of pharmacophores and anti-pharmacophores capable of effective separation of compounds from the examination set into groups of active and inactive compounds. Low activity molecules are badly responsive to the activity prognostication, because they form a buffer zone consisting of compounds that can include both pharmacophores and anti-pharmacophores.

Recently we have synthesized and reported a series of 1,3,4-oxadizole derivatives containing 1,4-benzodioxane ring [53] **(69)** system for antibacterial activity against *Staphylococcus aureus, Escherichia coli and Bacillus subtilis* and antifungal activity against *Aspergillus niger, Aspergillus flavus* and *Candida albicans* by two fold serial dilution technique. Some of the synthesized compounds displayed comparable or even better antibacterial and antifungal activities than reference drugs norfloxacin, chloramphenicol and fluconazole, against tested strains.

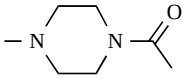
In search of potential therapeutics for tuberculosis, Ahsan *et al.* [54] has synthesized a series of 1,5-dimethyl-2-phenyl-4-([5-(arylamino)-1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-3*H*-pyrazol-3-one analogues. Among the synthesized compounds, 4-[(5-[(4-fluorophenylamino]-1,3,4-oxadiazol-2-yl)methylamino]-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (**70**) was found to be the most promising compound active against *Mycobacterium tuberculosis* H_{37}Rv and isoniazid resistant *M. tuberculosis* with minimum inhibitory concentrations, 0.78 and 3.12 μg/mL respectively and free from any cytotoxicity (>62.5 μg/mL).

Ahsan *et al.* [55] synthesized a series of 1,5-dimethyl-2-phenyl-4-{[(5-aryl-1,3,4-oxadiazol-2-yl)methyl]amino}-1,2-



(45)

X =



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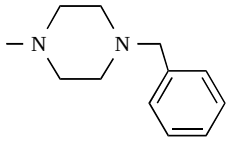
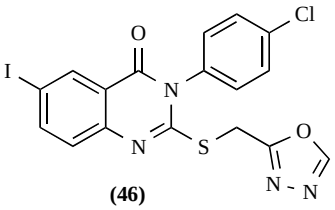
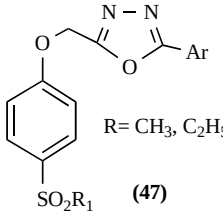


Y = O, S

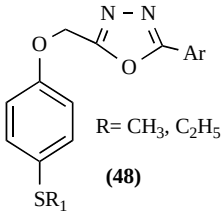


(46)



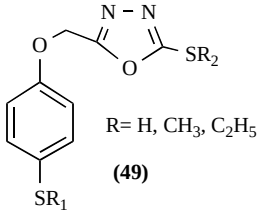
R= CH_3, C_2H_5

(47)



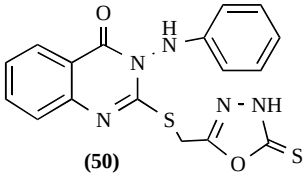
R= CH_3, C_2H_5

(48)

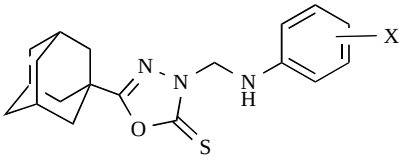


R= H, CH_3, C_2H_5

(49)

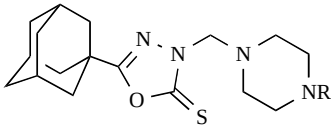


(50)



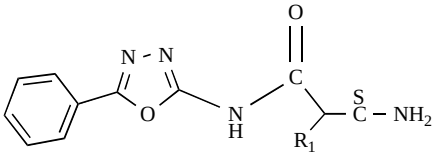
(51)

X = Cl, F, Br, I



(52)

R= CH_3, C_2H_5, isopropyl



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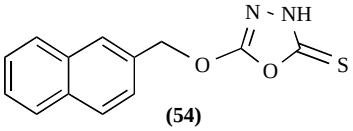

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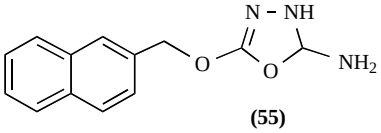

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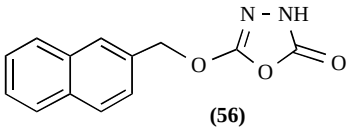

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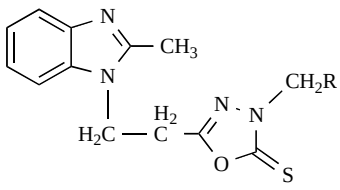

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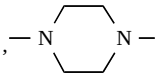

R= $N(C_2H_5)_2$

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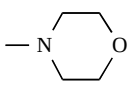
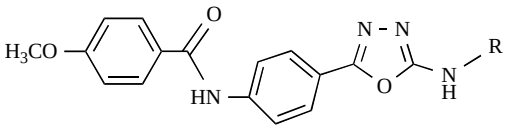




(58)

R= C_6H_5, CH_3-C_6H_4, OCH_3-C_6H_4

(Fig. 17). Contd…..

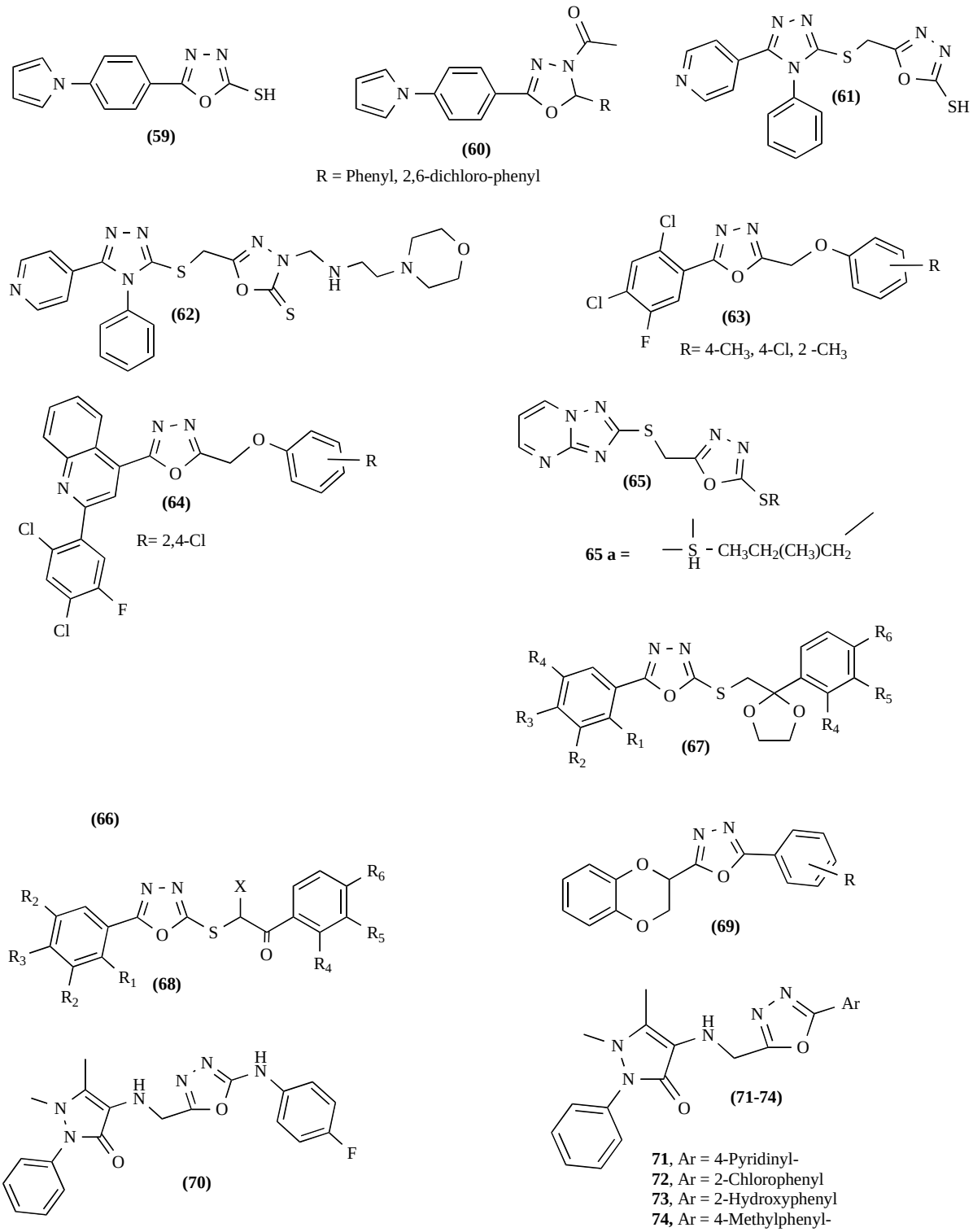
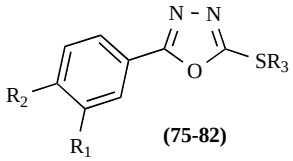


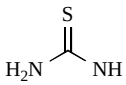
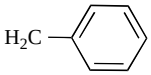
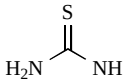
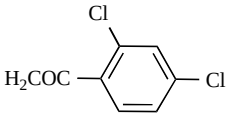
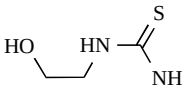
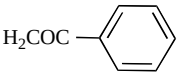
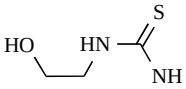
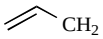
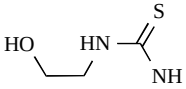
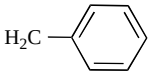
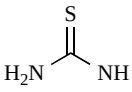
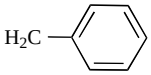
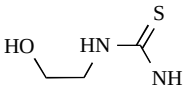
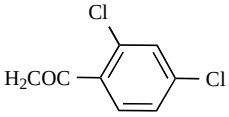
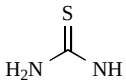
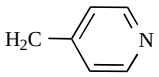
Fig. (17). Chemical structure of 1,3,4-oxadiazole derivatives studied for antibacterial, antimycobecterial and antifungal activity.

dihydro-3*H*-pyrazol-3-one analogues after molecular properties prediction, drug-likeness, lipophilicity and solubility parameters using. The compound **71** showed pronounced activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and isoniazid resistant *M. tuberculosis* (INHR-TB) with minimum inhibitory concentrations (MICs) 0.78 μM and 1.52 μM respectively. The compound **72** showed maximum activity against all bacterial strains with MIC 4-8 μg/mL comparable to standard drug ciprofloxacin, while the compounds **73** and **74** showed maximum antifungal activity with MIC 8-16 μg/mL less active than standard drug fluconazole.

Table 2. Compounds Synthesized by Macaev *et al.* Against M. Tuberculosis H37Rv (*In Vitro*)



(75-82)

No.	R_1	R_2	R_3	Inh (%)
75		H		91
76		H		93
77		H		96
78		H		96
79		H		97
80		H		98
81		H		98
82		H		97

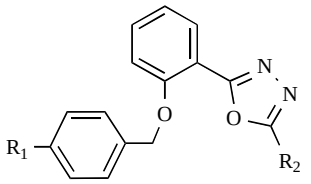
Macaev *et al.* [56] synthesized a series of 82, 5-aryl-2-thio-1,3,4-oxadiazole derivatives (Table **2**) and screened them for their anti-mycobacterial activities against *Mycobacterium tuberculosis* H37Rv. They further studied structure–activity relationships of the given series by using the electronic topological method combined with neural networks (ETM–NN). The synthesized compounds **(75-82)** appeared to be the most active derivatives exhibiting more than 90% inhibition of mycobacterial growth at 12.5 kg/mL. Structure–activity relationships study was performed for the given series by using the electronic topological method combined with neural networks (ETM–NN). A system for the anti-mycobacterial activity prediction was developed as the result of training associative neural network (ASNN) with weights calculated from projections of a compound and each pharmacophoric fragment found on the elements of the Kohonen's self-organizing maps (SOMs). From the detailed analysis of all compounds under study, the necessary requirements for a compound to possess antituberculosis activity have been formulated. The analysis has shown that any requirement's violation for a molecule implies a considerable decrease or even complete loss of its activity. Molecular docking studies of the compounds allowed shedding light on the binding mode of these novel anti-mycobacterial inhibitors.

ANTICONVULSANT ACTIVITY

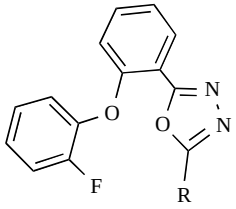
Zarghi *et al.* [57] reported the synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyl-oxyphenyl)-1,3,4-oxadiazoles **(83)** Almasirad *et al.* [58] reported the synthesis and anticonvulsant activity of 2-subsituted- 5-[2-(2- fluoro-phenoxy) phenyl]-1,3,4-oxadiazoles **(84)**.

SPASMOLYTIC AND HYPOTENSIVE ACTIVITY

Mishra *et al.* [59] reported the spasmolytic and hypotensive activity of 2-(substituted acetyl) amino-5-alkyl-1,3,4-oxadiazoles **(85)**.



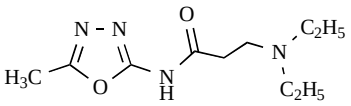
(83)



R = NH_2, SH, CH_3

(84)

Fig. (18). Chemical structure of 1,3,4-oxadiazole derivatives studied for anticonvulsant activity.



(85)

Fig. (19). Chemical structure of 1,3,4-oxadiazoles as spasmolytic and hypotensive agents.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENT

None declared.

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