ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Issue 4, 2014

ISSN - 0974-2441

Review Article

BIOLOGICAL ASPECTS OF 1,3,4-OXADIAZOLE DERIVATIVES

KAVITHA S, GNANAVEL S, KANNAN K

Department of Chemistry, Government College of Engineering, Salem, Tamil Nadu, India. Email: kavisundar06@gmail.com

Received: 14 July 2014, Revised and Accepted: 08 August 2014

ABSTRACT

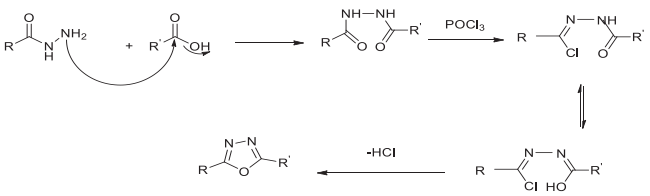
Heterocyclic compounds analog have attracted wide attention due to their useful biological properties. Among them, 1,3,4-oxadiazoles have exhibited a wide range of biological properties including anti-bacterial, anti-viral, anti-fungal, anti-cancer, anti-tumor, anti-inflammatory, anti-hypertensive, anti-convulsant and anti-diabetic properties. The purpose of this review is to collect the literature work reported by researchers on oxadiazole derivatives for their various pharmacological activities and also efforts made on this moiety. This review covers the work reported on various biological activities of oxadiazole derivatives from 2010 to 2014.

Keywords: Anti-cancer, Anti-microbial, 1,3,4-Oxadiazole.

INTRODUCTION

Oxadiazole is a versatile heterocyclic nucleus, which has attracted a wide attention of the medicinal chemists for development of new drugs. Oxadiazole is a cyclic compound containing one oxygen and two nitrogen atoms in a five member ring having general formula $C_2H_2ON_2$. There are four isomers of oxadiazoles. 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-oxadiazole ARE known, but 1,2,3 is unbalanced and reverse to the diazoketone tautomers. Oxadiazole is derived from furan by substitution of two methylene groups with two pyridine type nitrogen. The 1,3,4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical reactions.

The common synthetic method for these compounds is cyclodehydration of diacylhydrazines and their derivatives with dehydrants such as phosphorous oxychloride, trifluoroacetic anhydride, thionyl chloride polyphosphoric acid and also reaction between the properly substituted acid hydrazide, carbon disulfide and potassium hydroxide.



Mechanism of formation of oxadiazole

Derivatives of oxadiazole are used in the market such as Raltegravir, Nosapidil, Furamizole, etc. During recent years, there have been some interesting developments in the biological activities of oxadiazole derivatives. Literature survey reveals that the various derivatives of oxadiazole have been synthesized for their pharmacological activities.

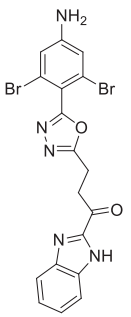
BIOLOGICAL ASPECTS

Oxadiazole nucleus is found to possess a number of biological activities such as anti-cancer, anti-microbial, anti-tuberculosis, anti-inflammatory, anti-oxidant, anti-convulsant, and anti-HIV.

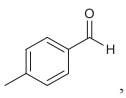
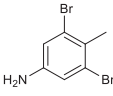
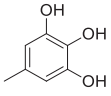
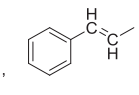
Anti-cancer activity

Cancer is a group of various diseases characterized by uncontrolled growth of cells, leading to the invasion of surrounding tissue and often spreading to other parts of the body, and there are more than 100 different types of cancer. It is a serious worldwide health problem, almost killing 7 million people/year and poses great challenges to medical science. Cancer is a major health problem in developing as well as undeveloped countries. In worldwide increases the search for new, safer and efficient anti-cancer agents to aiming the prevention or the cure of this illness. Research laboratories are still trying to develop, synthesize new anti-cancer drug. Literature survey revealed that, the various substituted derivatives of 1,3,4-oxadiazole derivatives showed remarkable biological activity as anti-tumor/anti-proliferative/anti-cancer activity.

A novel series of benzimidazole bearing oxadiazole and triazolo-thiadiazoles have been synthesized using 4(1H-benzo(d)imidazol-2-yl)-4-oxabutane hydrazide. Synthesised compounds were screened at the National Cancer Institute (NCI), USA, according to their protocol against full NCI 60 cell line panel. These exhibit good anti-cancer activity. Among them, the compound, namely 3-(5-4 amino-2, 6-dibromophyneyl)-1, 3, 4-oxadiazol-2-yl)1-(1H-benzo(d)imidozole-2-yl) propan-1one emerged as lead compound with good anti-cancer activity on tumor cell lines-MG-MID 12.62 of GI_{50} and −5.13, −4.23, −4.02 value of $Log_{10}GI_{50,}$ $Log_{10}TGI$, $Log_{10}LC_{50}$, respectively [1].

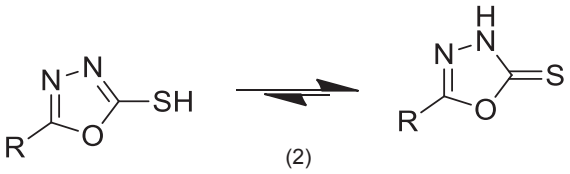


(1)

R= –CH_2CN,  ,  ,  ,  ,

Ahmad *et al.* [2] synthesized novel series of long chain alkenyl substituted 1,3,4-oxadiazol-2-thiones derivatives were tested for anti-cancer activity against a panel of three different cell lines namely; human hepatocellular carcinoma (Hep3B), human breast adeno carcinoma (MCF7) and human cervical carcinoma (HELA) and peripheral blood mononucleated cells (normal human cells) by 2,5-diphenyltetrazolium

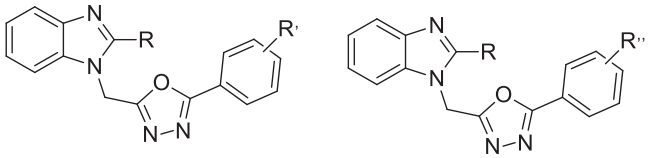
bromide (MTT) assay. It showed that among the three human cancer cell lines, Hep3B were found to be sensitive to all synthesized compounds. Some of the compounds showed remarkable inhibitory activities against different human cancer cell lines, while comparable to the standard drugs due to the nature of the fatty acid chain and heterocyclic ring system. Doxorubicin and 5-fluorouracil were used as standard drugs.



(2)

R=Substituted long chain alkenyl

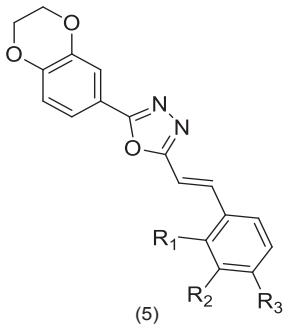
Novel series of 2-Naphthalen-1-ylmethyl-1-(5-substituted phenyl-[1,3,4] oxadiazol-2-ylmethyl)-1*H*-benzimidazole(3) and 2-(Naphthalen-2-yl oxymethyl)-1-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimida zole(4) have been synthesized by using Chloramin-T from Schiff base and phosphorus oxychloride from hydrazides. Anti-cancer evaluation was carried out by NCI 60 cell screen at a single high dose (10^{-5} M) on various panel/cell lines on leukemia, melanoma, lung, colon, central nervous system (CNS), ovarian, renal, prostate and breast cancer cell lines, nearly 60 in number. One compound 2-Naphthalen-1-ylmethyl-1-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-1H-benzimidazole was found to be the most active on breast cancer cell line MDA-MB-468 and SK-MEL-28 (Melanoma) (GP=36.23 and 47.56, respectively) probably because of more electron withdrawing power of the other substituent. While the other compounds showed moderate activity against selected cancer cell line [3].



(3) (4)

R'=H,4-Cl,4-NO_2,4-OCH_3 4-$(CH3)_2$N,2-OH R"=H,2-Cl,4-NH_2,4-NO_2, 3,5-diNO_2

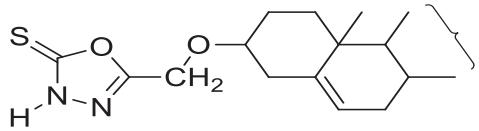
Sun *et al.* [4] have designed and synthesized a series of 1,3,4-oxadiazole derivatives containing 1,4-benzodioxan and screened their anti-tumor activity. Most of the titled compounds have potent anti-tumor activity and low toxicity. Among them, (E)-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-(2-fluorostyryl)-1, 3,4-oxadiazole compound showed the most potent biological activity against human umbilical vein endothelial cells with IC_{50} of 1.16 μM and inhibited activity of MetAP2 with IC_{50} of 2.08 μM, which was comparable to the positive controTNP-470. The results of apoptosis and flow cytometry demonstrated that the compound 7a induce cell apoptosis by the inhibition of MetAP2 pathway. SAR indicated that compounds with electron-with drawing group showed stronger activity than that with electron-donating group, with all the IC_{50} values below 50 μM.



(5)

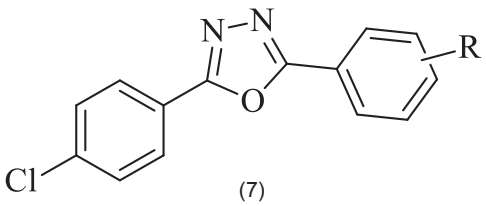
(a) R_1=F, R_2=H, R_3=H, (b) R_1=H, R_2=F, R_3=H, (c) R_1=H, R_2=H, R_3=F, (d) R_1=Cl, R_2=H, R_3=H, (e) R_1=H, R_2=H, R_3=Cl, (f) R_1=Br, R_2=H, R_3=H, (g) R_1=H, R_2=Br, R_3=H, (h) R_1=H, R_2=H, R_3=Br, (i) R_1=CH_3, R_2=H, R_3=H, (j) R_1=H, R_2=CH_3, R_3=H, (k) R_1=H, R_2=H, R_3=CH_3, (l) R_1=NO_2, R_2=H, R_2=H, (m) R_1=H, R_2=NO_2, R_3=H, (n) R_1=H, R_2=H, R_3=NO_2, (o) R_1=H, R_2=H, R_3=H, (p) R_1=H, R_2=CH_3O, R_3=H, (q) R_1=H, R_2=H, R_3=CH_3O

3β-[5'-mercapto-1',3',4'-oxadiazole-2-yl] methoxycholest-5-ene have been synthesized from cholest-5-en-3b-*O*-acetyl hydrazide using CS_2/KOH and also evaluated for anti-cancer activity against human leukemia cell line (HL-60) by MTT (3-(4,5-dimethylthiazol-2-yl)-MTT) assay. Compound showed moderate anti-cancer activity by showing IC_{50}=17.33 and 18.57, respectively [5].



(6)

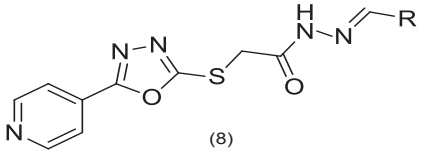
Ashan *et al.* [6] synthesized series of 10 oxadiazole analogue. 2-(4-chlorophenyl)-5-(4-fluorophenyl)-1, 3,4-oxadiazole and 2- (4-chlorophenyl)-5-(4-methoxyphenyl)-1, 3,4-oxadiazole submitted to the NCI 60 cell line screen were evaluated initially at single high dose (10^{-5} M) on leukemia. Melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancer cell lines nearly 60 in number. Compound 2-(4-chlorophenyl)-5-(4-fluorophenyl)-1, 3,4-oxadiazole with methoxy phenyl at the fifth position of the oxadiazole ring showed more anti-cancer activity (leukemia, prostate) than compound 2-(4-chlorophenyl)-5-(-(4-methoxyphenyl)-1, 3,4-oxadiazole with fluoro phenyl group at fifth positon of oxadiazole nucleus. Remaining oxadiazole analog showed moderate anti-cancer activity on various cell lines.



(7)

R=Substituted aryl

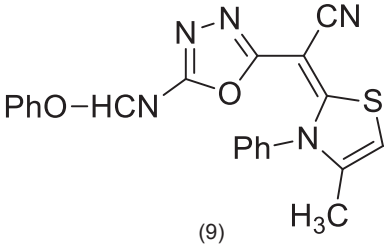
Zhang *et al.* [7] reported a series of new 1, 3,4-oxadiazole derivatives containing pyridine and acylhydrazone moieties were synthesized and developed as potential telomerase inhibitors. Synthesized compounds were evaluated for their anti-proliferative activity against the HEPG2 (Human liver cancer cell), MCF (human breast cancer cell), SW1116 (human colorectal carcinoma cell) and BGC823 (human gastric cancer) by MTT assay. Most of the compounds exhibited significant anti-tumor activity. Among them, compound (E)-N'-(3,4-Dihydroxybenzylidene)-2-((5-(pyridine-4-yl)-1, 3,4-oxadiazol-2-yl) thio)acetohydrazide showed the most potent anti-cancer activity with IC_{50} of 0.76±1.54 μM against four different original cancer cells (HEPG2, MCF7, SW1116 and BGC823) and exhibit telomerase inhibitory activity with IC_{50} of 1.18±0.14 μM using telomeric repeat amplification protocol-polymerase chain reaction-enzyme-linked immunosorbent (TRAP-PCR-ELSIA) assay.



(8)

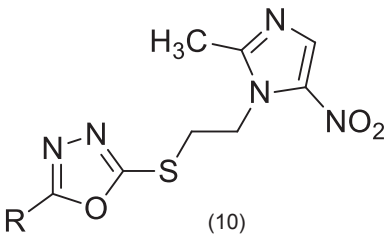
(a) R=ph-, (b) R=4-F-C_6H_4-, (c) R=4-Cl-C_6H_4-, (d) R=4-Br-C_6H_4-, (e) R=4-O_2N-C_6H_4-, (f) R=4-HO-C_6H_4-, (g) R=4-MeO-C_6H_4-, (h) R=4-H_3C-C_6H_4-, (i) R=3-F-C_6H_4-, (j) R=3-FC-C_6H_4-, (k) R=3-MeO-C_6H_4-, (l) R=2-F-C_6H_4-, (m) R=2-O_2N-C_6H_4-, (n) R=2-HO-C_6H_4-, (o) R=2HO-5-Cl-C_6H_3-, (p) R=2HO-5-Br-C_6H_3-, (q) R=2HO-3,5-2Cl-C_6H_2-, (r) R=2HO-3,5-2Br-C_6H_2-, (s) R=3,4-2OH-C_6H_3-, (t) R=3-MeO-4-HO-C_6H_3-, (u) R=2,4-2Cl-C_6H_3-, (v) R=2-Furan-, (w) R=2-Thiophene-, (x) R=(E)-styryl-

Novel 1,3,4-oxadiazole derivatives were synthesized by Bondock *et al.* [8] and their anti-cancer activity evaluated according to the protocol of the NCI *in vitro* disease-oriented human cells screening panel assay. The results revealed that five compounds were found to exhibit variable degrees of anti-cancer activities against the four used cell lines heptacelluar carcinoma HEPG2, lung fibroblasts WI 38, kidney of a normal adult African green monkey VERO, and breast cancer MCF-7 by MTT method. Particularly, N-(5-(Cyano (4-methyl-3-phenylthiazol-2(3H)-ylidene) methyl)-1, 3,4-oxadiazol-2-yl) benzamide compound showed a considerable broad spectrum of anti-cancer activity against the four tested human tumor cell lines. Five fluorouracil was used as a standard anti-cancer drug.



(9)

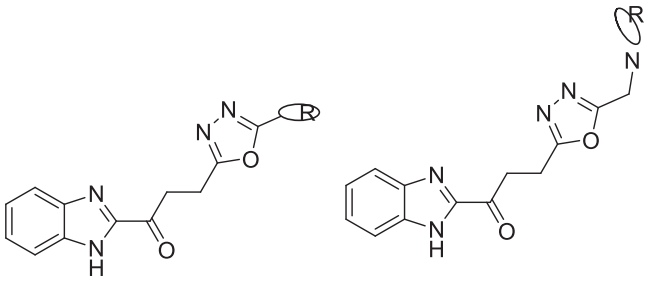
All newly synthesized compounds were screened for their *in vitro* anti-cancer activities against HEPG2 (human hepatomacells), SGC-7901 (human gastric cancer cells), and MCF-7 (human breast cancer cells) cell lines by the MTT method. A number of 1,3,4-oxadiazole thioether derivatives showed remarkable effects on anti-cancer activities. Among all the designed compounds, compound bearing a nitro substituent exhibited more potent *in vitro* anti-cancer activities with IC_{50} values of 0.7±0.2, 30.0±1.2, 18.3±1.4l M, respectively, which was superior to the positive control [9].



(10)

R=Aryl substituted groups

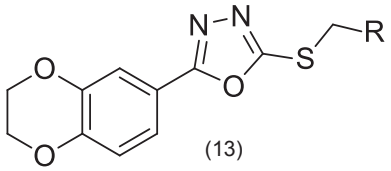
Twenty-five new benzimidazoles bearing 1,3,4-oxadiazole nucleus were successfully synthesized from 4-(1H-benzo[d]imidazol-2-yl)-4-oxobutanehydrazide under microwave irradiation by Rashid *et al.* [10]. The synthesized compounds were evaluated for their *in vitro* anti-cancer activity toward full NCI 60 cell lines panel representing full nine human systems as leukemia, melanoma and cancer of lung, colon, brain, ovary, kidney and prostate at single dose (10 μM) and showed significant to good anti-cancer activity. The selected compounds are evaluated against all the 60 cell lines at five-dose [0.01-100 μM]). Among tested compounds, 1-(1H-benzo[d]imidazol-2-yl)-3-(5-(2, 4-dichlorophenyl)-1, 3,4-oxadiazol-2-yl) propan-1-one showed maximum growth inhibition and found to be the most active compound of the series.



(11) (12)

R=Alkyl and aryl substituted groups

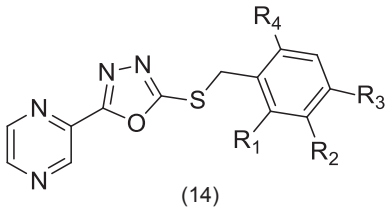
Zhang *et al.* [11] synthesized a series of new 1,3,4-oxadiazole containing 1,4-benzodioxan moiety from 5-(2,3-dihydrobenzo[b] [1,4]dioxin-6-yl)-1, 3,4-oxadiazo-le-2-thiol. All synthesized 1,3,4,-oxadiazole derivatives were screened for their anti-proliferative activity against the HEPG2 (human liver cancer cell), HELA (human cervical cancer cell), SW1116 (human colorectal carcinoma cell) and BGC823 (human gastric cancer). Some of the compounds exhibited broad spectrum of anti-tumor activity with IC_{50} concentration range from 7.21 to 25.87 μM against the four cancer cell lines compared with the five-fluorouracil that was widely used in the treatment of cancer in clinical. Among these, compound 2-(2,3-Dihydrobenzo[b] [1,4]dioxin-6-yl)-5-(2-iodobenzylthio)-1, 3,4-oxadiazole displayed the most potent anti-tumor activity (IC_{50}=7.21 μM). All the title compounds were assayed for telomerase inhibition using the TRAP-PCR-ELISA assay.



(13)

R=Ph-, 3-Me-C_6H_4, 4-NO_2-C_6H_4, 2-F-C_6H_4, 2-NO_2-C_6H_4, Me-C_6H_4, 4-F-C_6H_4, 3-NO_2-C_6H_4, Cl-C_6H_4, 4-I-C_6H_4, 2-Me-C_6H_4, 2-Br-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 2-Cl-C6H4, 3-Cl-C_6H_4, 2,6-2F-C_6H_4, 2,4-2F-C_6H_4, 2-I-C_6H_4-

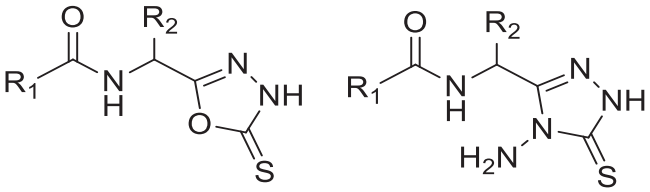
All the synthesized heterocyclic azoles derivatives were evaluated for their anti-proliferative activity against the HEPG2 (human liver cancer cell), SW1116 (human colorectal carcinoma cell), HELA (human cervical cancer cell) and BGC823 (human gastric cancer). Most of the compounds showed better activities against cell lines HEPG2 and SW1116 than HELA and BGC823 with lower IC_{50} values. Especially; these compounds showed effectiveness against cell line human hepato cellular liver carcinoma HEPG2 with IC_{50} values range of 0.78-22.57 μM comparative to staurosporine (1.30 μM). Among these compounds, 2-([2-Bromobenzyl] oxy)-5-(pyrazin-2-yl)-1, 3,4-oxadiazole showed the most potent inhibitory activity in tumor (IC_{50}=0.78 μM [12].



(14)

(a) R_1=F, R_2=R_3=R_4=H, (b) R_1=Cl, R_2=R_3=R_4=H, (c) R_1=Br, R_2=R_3=R_4=H, (d) R_2=Cl, R_1=R_3=R_4=H, (e) R_2=Br, R_1=R_3=R_4=H, (f): R_3=F, R_1=R_2=R_4=H, (g) R_3=Cl, R_1=R_2=R_4=H, (h) R_3=Br, R_1=R_2=R_4=H, (i) R_1=R_3=F, R_2=R_4=H, (j) R_1=R_4=F, R_2=R_3=H, (k) R_1=R_2=R_3=R_4=H

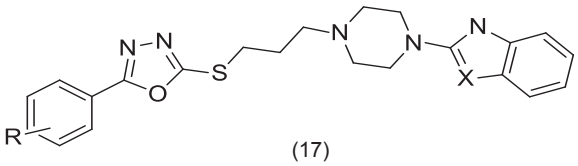
The anti-cancer activity of all synthesized 1,3,4-oxadiazole-2(3H)-thiones and 1,2,4-triazole-5(1H)-thiones derivatives was evaluated *in vitro* against human tumor cell line: Leukemia (K-562) by measuring cell viability by the MTT method using Hydroxyurea (HU) as a positive control. A fair number of compounds were found to have significant anti-tumor activity [13].



(15) (16)

(15a and 16a) R_1=C_6H_5, R_2=CH_3, (15b and 16b) R_1=4-ClC_6H_4, R_2=CH_3, (15c and 16c) R_1=$C_6H_5R_2$=$CH(CH_3)_2$, (15d) R_1=4-$NO_2C_6H_4$, R_2=$CH(CH_3)_2$, (15e) R_1=3-pyridine, R_2=CH_3, (15f) R_1=$C_6H_5CH_2R_2$=CH_3, (15g) R_1=Trans-4-$CH_3OC_6H_4CH$=CH, R_2=CH_3, (15h) R_1=Trans-C_6H_4CH=CH, R_2=CH_2OH

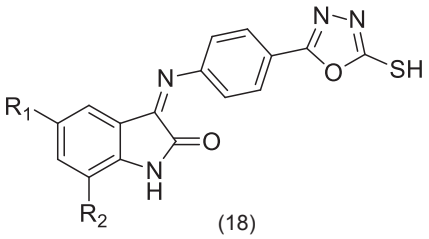
The synthesis of a series of substituted 2-(piperazin-1-yl) benzothiazole/benzoxazole coupled with 1,3,4-oxadiazole-2-thiolpharmacophore. All the synthesized compounds have been evaluated for their cytotoxicity towards five human cancer cell lines of different origins (MCF-7 (breast), HELA (cervical), HEPG2 (liver), A431 (skin) and A549 (lung), and IC_{50} values). Among the compounds tested, 2-(5-[3-(4-[Benzo(d)oxazol-2-yl]piperazin-1-yl)propylthio]-1, 3,4-oxadiazol-2-yl)-N-phenylacetamide and 2-(5-[3-(4-[Benzo(d)thiazol-2-yl]piperazin-1-yl)propylthio]-1, 3,4-oxadiazol-2-yl)-N-phenylacetamide displayed maximum cytotoxic activity. A431 was the most sensitive cell line against tested compounds followed by MCF7, A549, HEPG2 and HELA [14].



(17)

R=Substituted aryl

A series of 5- or 7-substituted 3-(4-[5-mercapto-1, 3,4-oxadiazol-2-yl] phenylimino)-indolin-2-one derivatives were synthesized by treating 5-(4-aminophenyl)-1, 3,4-oxadiazole-2-thiol with different isatin derivatives. All the synthesized derivatives were screened for anti-cancer activity against HELA, IMR-32 and MCF-7 cancer cell lines using MTT assay. All the synthetic compounds produced a dose-dependent inhibition of growth of the cells. The IC_{50} values of all the synthetic test compounds were found between 10.64 and 33.62 µM. Among synthesized compounds, 3-(4-[5-mercapto-1, 3,4-oxadiazol-2-yl] phenylimino)-5 or 7-substituted indolin-2-one derivatives possessing halogen atom (electron withdrawing groups) at C5 position showed the most potent activity. These results indicate that C5 substituted derivatives may be useful leads for anti-cancer drug development in the future [15].



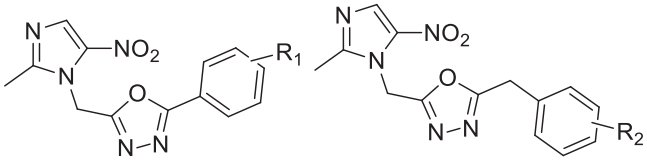
(18)

(a) R_1=H, R_2=H, (b) R_1=F, R_2=H, (c) R_1=Cl, R_2=H, (d) R_1=Br, R_2=H, (e) R_1=CH_3, R_2=H, (f) R_1=NO_2, R_2=H, (h) R_1=COOH, R_2=H, (i) R_1=H, R_2=Cl, (j) R_1=H, R_2=NO_2, (k) R_1=H, R_2=COOH, (l) R_1=H, R_2=$COOCH_3$

Anti-bacterial activity

The treatment of infectional diseases still remains a challenging factor because of the increase in a number of multi-drug-resistant microbial pathogens and new infectious diseases such as severe acute respiratory syndrome and avain influenza. 1,3,4-oxadiazole have shown sigificant anti-microbial activity against a wide variety of micro-organism like fungi, Gram-positive, Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtillis* and *Staphylococus aureus* etc.

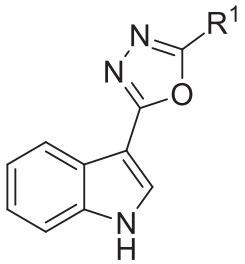
Li *et al.* [16] synthesized a two serious of secnidazole analog based on oxadiazole scaffold. Synthesized compounds were screened for anti-bacterial activities against *E. coli, P. aeruginosa, B. subtillis and S. aureus and E.coli* FabH inhibitory activities. Particularly, Compounds 2-(2-methoxy phenyl)-5-((2-methyl-5-nitro-1Himidozol -1-yl)-1, 3,4-oxadiazole and 2-(2-methyl-5-nitro-1H-imidazol-1-yl)-5-(2-methylbenzyl)-1, 3,4-oxadiazole were proved to be most potent inhibitors of *E. coli* FabH.



(19) (20)

R_1=R_2=4-F, 4-Cl, 3-F, 3-Br, 4-NO_2, 3-OCH_3, 2-OCH_3, 2-CH_3

Three series of novel 2-(1-ethyl-indolyl)-5-substituted-1, 3,4-oxadiazoles, 2-indolyl-5-substituted-1, 3,4-oxadiazoles and 2-(3-indolyl)-methyl-5-substituted-1, 3,4-oxadiazoles designed as analogues of the anti-fungal natural product pimprinine, and evaluated their anti-fungal activities against *Phytophthora infestans*, *Septoria tritici*, *Uromyces-viciae-fabae*, *Pythium dissimile*, *Alternaria solani*, *Botryotinia fuckeliana*, *Gibberella zeae*. Several of the synthesized compounds exhibit higher anti-fungal activity than pimprinine, the natural product, which inspired this synthesis. In most cases, two main structural alterations were found to broaden the spectrum of biological activity. Pimprinine and streptochlorin are used as standard drugs [17].

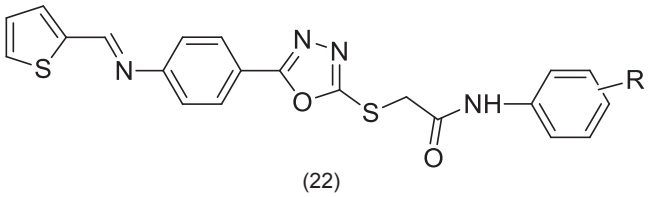


(21)

R^1=CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $(CH_2)_3CCH_2$, $CH_3CH_2(CH_2)_2C$, $(CH_3)_3CCH_2(CH_3)CHCH_2$, CF_3, CH_2Cl, 2-F-C_6H_4, 2-I-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Me-C_6H_4.

Desai *et al.* [18] design and prepared, a series of 2-(5-[4-(1-aza-2-[2-thienyl] vinyl) phenyl] (1,3,4-oxadiazol-2-ylthio])-N-aryl acetamides and tested for their anti-microbial activity. Twelve synthesized compounds were screened for their anti-bacterial activity against Gram-positive bacteria *S. aureus* (MTCC96), *Staphylococcus pyogenes* (MTCC 442) and Gram-negative bacteria *E. coli* (MTCC 443), *P. aeruginosa* (MTCC 1688) by serial broth dilution method and the above same compounds tested for anti-fungal activity). The synthesized bio-active

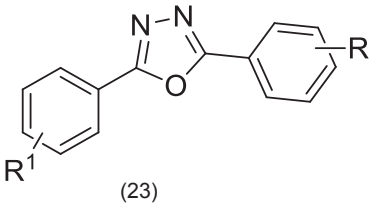
compounds showed excellently to moderate anti-microbial activity. 4-$(CH_3)_2$, 3-OCH_3 and 3,4-$(Cl)_2$ substituted synthesized compounds possess excellent anti-bacterial activity, whereas 3-OCH_3, C1 and 4-NO_2 substituted compounds showed excellent anti-fungal activity.



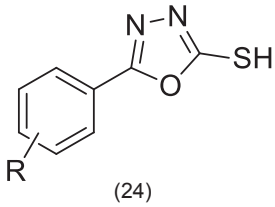
(22)

R=H, 2-Cl, 2-NO_2, 2-CH_3, 2,4-$(CH_3)_2$, 3-OCH_3, 3,4-$(Cl)_2$, 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OCH_3

2,5-Subtituted oxadiazole derivatives were synthesized by ring closure reaction of various acylhydrazides with carbon disulfide and with aromatic acids in $POCl_3$. All synthesized compounds. The newly prepared compounds were screened for their anti-bacterial activity against *E. coli* (MTCC 443), *Staphylococcus epidermidis* (ATCC12228) and *S. aureus* (ATCC25923) bacterial strains by disc method. The compounds 2-(5-sulfonyl-1, 3,4-oxadiazol-2-yl) phenyl-acetate, 5-(pydridin-3-yl)-1, 3,4-oxadiazole-2-thiol and 3-(phenyl-1, 3,4-oxadiazol-2-yl) pyridine showed significance inhibition comparable to ciprofloxacin as standard [18].

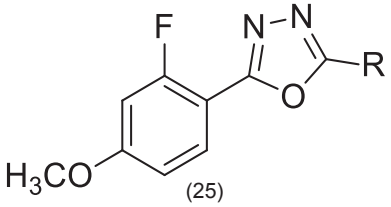


(23)



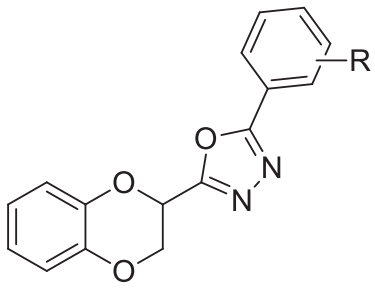
(24)

Fluorine containing compounds molecules showed wide spectrum anti-microbial and biological properties. Keeping in view of that, novel 2(2-fluoro-4-methoxyphenyl)-5-susbtituted-1, 3,4-oxadiazoles were synthesized and evaluated for anti-bacterial and anti-fungal activity against *S. aureus, B. subtilis, E. coli and P. aeruginosa* (anti-bacterial) and *Candida albican* (anti-fungal). Both microbial studies were assessed by minimum inhibitory concentration (MIC) by serial dilution method. Anti-microbial studies revealed that compounds 2-(3-Bromo-2-methylphenyl)-1,3,4-oxadiazole and 2-(2-fluoro-4-methyoxy)-5-2,3,4-trifluorophenyl)-1, 3,4-oxadiazole showed excellent anti-bacterial activity against *E. coli* and *P. aeruginosa*. Particularly, compound 2-(2-fluoro-4-methoxyphenyl)-5-(3-fluoro-4-nitro phenyl)-1, 3,4-oxadiazole exhibited significant anti-fungal activity against *C. albicans* [19].



(25)

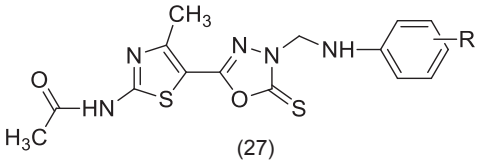
Khalilullah *et al.* [20] have been synthesized a series of 1,3,4-oxadiazole derivatives containing 1,4-benzodioxane ring system and synthesized compounds were screened for anti-bacterial activity against *S. aureus* (NCIM 2079) and *B. subtilis* (NCIM 2439) as Gram-positive bacteria, *E. coli* (NCIM 5051) as Gram-negative bacteria as well as anti-fungal activities against *Aspergillus niger* (ATCC 1034), *Aspergillus flavus* (MTCC 2799), *C. albicans* (ATCC 753) by two fold dilution technique at concentration of 0.25-512 µg/mL. Synthesized compounds exhibited moderate to excellent activities than reference drugs norfloxacin, chloramphenicol and fluconazole against all tested strains. Anti-microbial activity data revealed that the presence of electron withdrawing group in aromatic ring of 1,3,4-oxadiazole ring improved the activity; however, more lipophilic group at the same position greatly enhanced the anti-fungal activities of the synthesized azole derivatives.



(26)

R=H, 2-Br, 3-Br, 4-Br, 2-Cl, 3-Cl, 4-Cl, 2,4-(Cl), 2-CH_3, 3-CH_3, 4-CH_3, 4-OH,3,4-$(OH)_2$, 4-OCH_3, 3,4-$(OCH_3)_2$, 4-NH_2

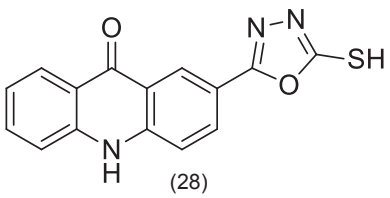
A novel series of thiazole clubbed 1,3,4-oxadiazole derivatives have been synthesized and characterized by Desai *et al.* [21]. Synthesized compounds carried out by broth micro dilution method against the standard bacterial strains *S. aureus* MTCC 96, *S. pyogenes* MTCC 442, *E. coli* MTCC 443 and *P. aeruginosa* MTCC 1688 and anti-fungal activity against the standard fungal strains *C. albicans* MTCC 227, *A. niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 were evaluated for their anti-microbial activities. The results indicated that, compounds N-(5-[4-([(4-fluorophenyl)amino]methyl)-5-thioxo-4,5-dihydro-1, 3,4-oxadiazol-2-yl]-4-methylthiazol-2-yl) acetamide and N-(4-methyl-5-[05-thioxo-4-([p-tolylamino] methyl)-4,5-dihydro-1, 3,4-oxadiazol-2-yl] thiazol-2-yl) acetamide showed the most potent anti-bacterial activity. Whereas, Compound N-(5-[4-([(4-methoxyphenyl) amino] methyl)-5-thioxo-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl]-4-methylthiazol-2-yl) acetamide with electron releasing group at para position was found to be the most potent anti-fungal agent. SAR revealed that the presence of electron withdrawing groups at para position of phenyl ring remarkably enhanced the anti-bacterial activity of synthesized compounds.



(27)

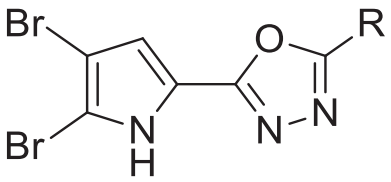
Where R=-2-F,-3-F,-4-F,-2-OCH_3,-3-OCH_3,-4-OCH_3,-2-NO_2,-3-NO_2,-4-NO_2,-2-CH_3,-3-CH_3,-4-CH_3

Salimon *et al.* [22] have synthesized new acridone derivatives. All newly synthesized compounds were screened for their anti-bacterial (*S. aureus, Streptococcus viridans* and *E. coli*) and anti-fungal (*Gibberela*, *Cercospora arachidicola, Physolosporapiricola* and *Fusarium oxysporum*) studies. Ampicillin trihydrate (anti-bacterial) and Fluconazole (anti-fungal) were used as reference drugs. Both anti-microbials studies were assessed by MIC and show that all compounds showed certain activity against the tested microorganisms.



(28)

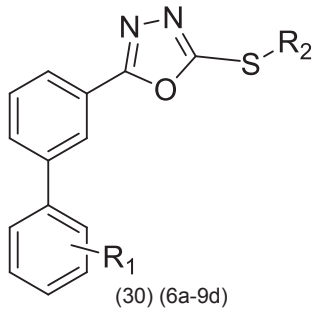
Twenty 2-(4, 5-dibromopyrrol-2-yl)-5-substituted-1, 3,4-oxadiazoles were designed based on molecular hybridization technique and synthesized by Rane *et al.* [23]. The newly prepared compounds were screened for their anti-bacterial activity against *E. coli* (ATCC-25922), *S. aureus* (ATCC-25923), *P. aeruginosa* (ATCC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains and anti-fungal activity toward *K. pneumonia*, *C. abilcans*. MICs were determined by broth dilution technique (anti-bacterial) and agar dilution method (anti-fungal). Some of the compounds exhibited equivalent anti-bacterial activity (MIC of 1.56 lg/mL) compared with standard drug ciprofloxacin against *S. aureus* and *E. coli*. Equal anti-fungal activity (MIC of 1.56 lg/mL) was shown by some of the hybrids compared with standard amphotericin-B.



(29)

R=2-hydroxyphenyl, phenyl acetic, 4-aminophenyl, 4-chlorophenyl, 4-methoxyphenyl, 2,4-dichlorophenyl, 2-phenylethenyl, 4-hydroxyphenyl, 5-fluoro-2-chlorophenyl, 4-nitrophenyl, 4,5-dibromo-1H-pyrrol-2-yl,4H-chromen-3-yl-vinyl.

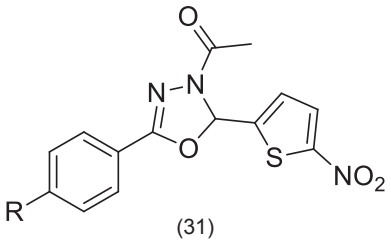
A series of biphenyl 1, 3, 4-oxadiazoles namely 5-[substituted-(1,1'-biphenyl)3-yl]-1, 3, 4-oxadiazole-2(3H)-thiones and its-Alkyl derivatives prepared by Ramprasad *et al.* [24] Synthesized compounds were screened for anti-bacterial activity against four bacterial strains namely *P. aeruginosa*, *E. coli*, *B. subtilis* by cup-plate method. Among the tested compounds, the fluoro substituted compound exhibited the highest activity against all tested microorganism.



(30) (6a-9d)

R_1	R_2	R_1	R_2
6a: 5'-F, 2'-OMe-$(CH_2)_3COOMe$	-$(CH_2)_3COOMe$	8a: 5'-F, 2'-OMe	-$(CH_2)_3CN$
6b: 2'-OMe		8b: 2'-OMe-$(CH_2)_3CN$	
6c: 2'-F-$(CH_2)_3COOMe$		8c: 2'-F-$(CH_2)_3CN$	
6d: 3'-Cl-$(CH_2)_3COOMe$		8d: 3'-Cl-$(CH_2)_3CN$	
7a: 5'-F, 2'-OMe-$(CH_2)_4F$		9a: 5'-F, 2'-OMe-C_2H_5	
7b: 2'-OMe-$(CH_2)_4F$		9b: 2'-OMe-C_2H_5	
7c: 2'-F-$(CH_2)_4F$		9 c: 2'-F-C_2H_5	
7d: 3'-Cl-$(CH_2)_4F$		9d: 3'-Cl-C_2H_5	

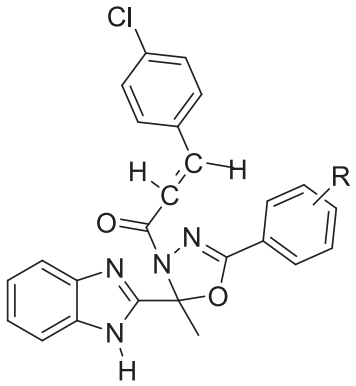
Ishii *et al.* [25] reported 3-acetyl-2, 5-disubstitued-2, 3-dihydro-1, 3,4-oxadiazole derivatives of anti-microbial activities against *S. aureus*, *Trypanosoma cruzi and C. albians*.



(31)

R=H, Cl, Br, I, CF_3, CH_3, C_2H_5, C_3H_7, OCH_3, OC_2H_5, C_3H_7, OC_4H_9, NO_2, CN, $C_2H_3O_2$

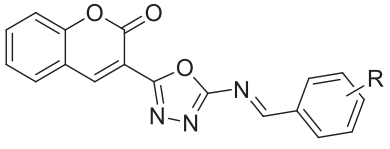
Desai *et al.* [26] reported novel series of 1-(2-[1H-benzo(d)imidazol-2-yl]-2-methyl-5-aryl-1, 3,4-oxadiazol-3(2H)-yl)-3-(4-chlorophenyl)prop-2-en-1-ones under microwave irradiation technique. Synthesized compounds were tested for their *in vitro* anti-microbial activity against gram-positive, gram-negative strains of bacteria as well as fungal strains. Out of them, substituted derivatives with fluoro and nitro groups at para position displayed highest anti-bacterial activity, while 1-(2-(1H-benzo[d]imidazol-2-yl)-2-methyl-5-(4-nitrophenyl)-1, 3,4-oxadiazol-3(2H)-yl)-3-(4-chlorophenyl)prop-2-en-1-one also showed highest anti-fungal potency with four-fold higher MIC than standard griseofulvin.



(32)

R=H,3-Cl,4-Cl,4-F,3-CH_3,4-CH_3,3-NO_2,4-NO_2,3-OH,4-OH,3-OCH_3,4-OCH_3,3-Br,4-Br

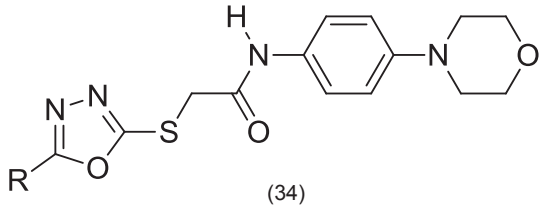
A series of 3-{5-[(E)-(substituted benzylidene) amino]-1, 3,4-oxadiazol-2-yl}-2H-chromen-2-ones have been synthesized from 3-(5-amino]-1, 3,4-oxadiazol-2-yl}-2H-chromen-2-one with different substituted benzaldehydes to form Schiff bases of coumarin-incorporated1, 3,4-oxadiazole derivatives. The compounds were screened against bacterial strains *S. aureus* NCTC (10418), *E. coli* NCTC (6571), and fungal strain *C. albicans* ATCC (10231) by cup plate method (agar diffusion method). Ciprofloxacin and Ketoconazole were used as a reference. The test compounds and standards were evaluated at 100 lg/ml concentration. Most of the synthesized compounds possess significant anti-microbial activity. Compound (4 m) without any substitution of the phenyl ring, which is attached to 1,3,4-oxadiazole moiety showed highly significant *in vitro* growth inhibition against *S. aureus* and *E. coli*, whereas compound (4 g) with para N(CH3)2 showed highly significant *in vitro* growth inhibition against *C. albicans* [27].



(33)

R=3-NO_2, 3,4-$(OCH_3)_2$ 4-OH 2-OH, 2-NO_2,3-OH, 4-$N(CH_3)_2$, 4-F, 4-OCH_3, 2-Cl3-Cl, 4-Cl,4H, 4-NO_2, 3-F,2-F, 2-$OCH_3$3-OCH_3

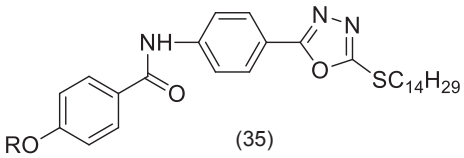
Gul *et al.* [28] reported new series of 2-([5-alkyl/aralkyl-1, 3, 4-oxadiazol-2-yl]thio)-N-(4-[4-morpholinyl]phenyl)acetamides were the synthesized by stirring 5-aryl/aralkyl-1, 3, 4-oxadiazol-2-thiols with 2-bromo-N-(4-[4-morpholinyl]phenyl)acetamide. The synthesized compounds were tested against microorganisms, including gram-positive bacteria: *B. subtilis* and *S. aureus* and gram-negative bacteria: *Pasteurella multocida* (*P. multocida*) and *E. coli*; and four pathogenic fungi, *A. flavus*, *A. niger*, *Alternaria alternate* (*A. alternate*) and *Ganoderma lucidum* (*G. lucidum*) by disc diffusion method. It revealed that compound2-([5-(4-Chlorophenyl)-1, 3,4-oxadiazol-2-yl]thio)-N-(4-[4-morpholinyl]phenyl) acetamide possessed better anti-fungal and bacterial activities against all strains, and that might be because of 4-chlorophenyl group present in the molecule. While, Compound, 2-([5-(3-Aminophenyl)-1, 3,4-oxadiazol-2-yl]thio)-N-(4-[4-morpholinyl]phenyl)acetamide exhibited good activity against three bacterial and fungal strains. Some of the derivatives possess good cytotoxic potential.



(34)

R=Different 5-substituted aryl/aralkyl groups

The synthesis of novel achiral and chiral amides incorporating 1,3,4-oxadiazole ring are reported by Visal and Prabha [29] All the synthesized compounds of the series were screened for the microbial activity against *E. coli*, *S. aureus*, *Aspergillus oryzae* and *A. niger* by cup-plate agar diffusion method. In the newly synthesized oxadiazole derivatives have well to moderate anti-bacterial and anti-fungal activities, Activity increases as the number of carbon increases in the alkyl chain. All the compounds were found to possess cytotoxic activity.

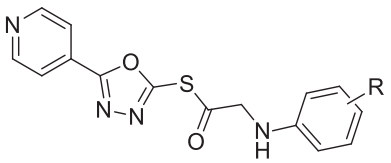


(35)

R=C_nH_{2n+1} Where n= 4, 5, 6, 7, 8, 10 (I a-f), Chiral alkoxyacid chloride (I g, h).

Anti-tuberclosis

Raval *et al.* [30] prepared a series of 2(4-pydridyl)5[(aryl/heteroarylamino)-1-oxoethyl]thio-1, 3,4-oxadiazole were synthesized using isonicotino hydrazide and substituted aryl/heteroamine using pyridine as solvent. All newly synthesized derivatives were tested for their anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system and isoniazid used as standard drugs. Especially, some of the compounds exhibited better potency than the standard drugs.

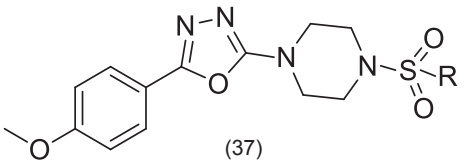


(36)

Where, R=4a, 5a=H 4b, 5b=2-Cl 4c, 5c=3-Cl 4d, 5c=4-Cl4e, 5d=2-NO_2, 5e=3-$NO_2$4g, 5g=4-$NO_2$4h, 5h=2-$CH_3$4i, 5i=3-$CH_3$4j, 5j=4-CH_3 4k, 5k=2-C_5H_5N 4l, 5l=2-OH

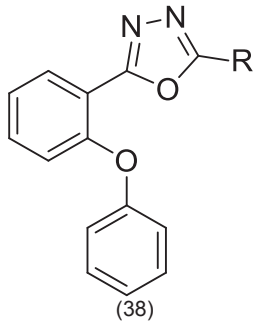
Anti-convulsant activity

The anti-convulsant activity of the fifteen new synthesized 1-[5-4-methoxy-phenyl)[1,3,4]oxadiazol-2-yl]-piperazine derivatives was evaluated by maximal electroshock seizure (MES) model in male Wistar rats at the dose of 100 mg/kg and compared with the standard drug phenytoin. Some of the substituted sulfonamide derivatives showed significant activity and electron withdrawing groups, and heteroaryl derivatives showed excellent anti-convulsant activity on MES model. The nature of groups in sulfonyl moiety is important for anti-convulsant activity in MES model [31].



(37)

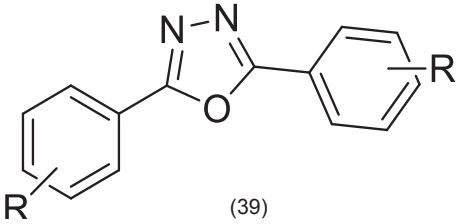
Tabatabai *et al.* [32] prepared2-(2-Phenoxy) phenyl-1, 3,4-oxadiazole derivatives. Anti-convulsant activities of the synthesized compounds were determined by pentylene tetrazole-induced lethal convulsion test. Diazepam was considered as a standard benzodiazepine agonist. It showed that the introduction of an amino substituent in position 5 of 1,3,4-oxadiazole ring generates compound namely, 2-Amino-5-(2-phenoxy) phenyl-1, 3,4-oxadiazole, which has a respectable effect. Since the elimination of electronegative substituent in position 2 of phenoxy ring or position 4 of phenyl ring reduces the anti-convulsant activity.



(38)

R=SH, SCH_3, OH, NH_2, H

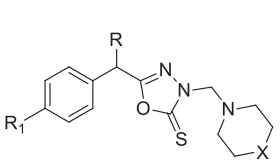
Ponamsingh *et al.* [33] have been synthesized substituted diphenyl-1, 3,4-oxadiazole derivatives. The synthesized compounds were screened for their anti-convulsant activity using MES method. Two compounds 5-(4-nitrophenyl)-2-(4-chlorophenyl)-1, 3,4-oxadiazole and 5-(4-nitrophenyl)-2-(4-nitrophenyl)-1, 3,4-oxadiazole were found to be the most promising compounds of the series in anti-depressant, anti-convulsant with no neurotoxicity when compared with standard drug phenytoin.



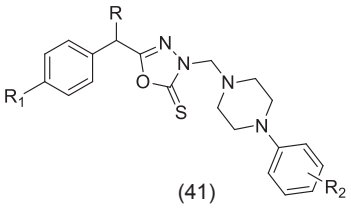
(39)

Anti-inflammatory activity

Manjunatha *et al.* [34] reported various oxadiazole mannich bases and evaluated for mainly their anti-inflammatory activity. Some of the derivatives were found to have anti-inflammatory activity greater than standard drug as diclofenac sodium at 10 mg/kg.



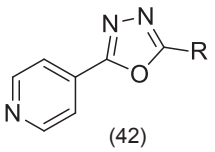
(40)



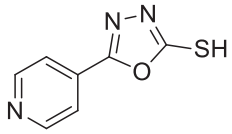
(41)

R=CH_3, H; R_1=$CH_2CH(CH_3)_2$, SCH_3; X=CH-COO_2EtO, NH, N-CH_3, CH_2; R_2=4-OCH_3, 4-Cl, 3-Cl, 4-NO_2, 4-F, 2-OC_2H_5

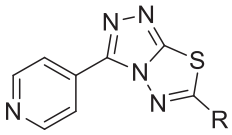
Gilani *et al.* [35] reported a series of 6-substituted-1, 2,4-triazolo-[3,4-b]-1, 3,4-thiadiazole and 1, 3, 4-oxadiazole derivatives of isoniazid were synthesized and pharmacologically evaluated for their anti-inflammatory activity. Compound namely, 2-(2,4-dichlorophenyl-5-(pyridin-4-yl)-1, 3, 4-oxadiazole showed maximum anti-inflammatory. It revealed was revealed that triazolo thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid might afford a safer alternative to isoniazid for the treatment of inflammatory disease.



(42)



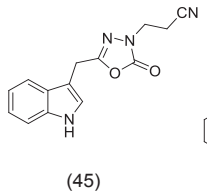
(43)



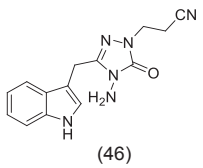
(44)

Where R=C_6H_5, 2-C_6H_4Cl, 2,4-C_6H_3Cl, 2-$C_6H_4CH_3$, 2-$C_6H_4OCOCH_3$, OC_6H_5 (phenoxy), 4-CH_4NO_2.

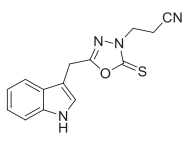
A series of novel 3-[5-(1H-indol-3-yl-methyl)-2-oxo-[1,3,4]oxadiazol-3-yl]propionitrile, 3-[4-amino-3-(1H-indol-3-yl-methyl)-5-oxo-4, 5-dihydro-[1,2,4]triazol-1-yl]propionitrile, 3-[5-(1Hindol-3-yl-methyl)-2-thioxo-[1,3,4]oxadiazol-3-yl]propionitrile and 3-[4-amino-3-(1H-indol-3-ylmethyl)-5-thioxo-4, 5-dihydro-[1,2,4]triazol-1-yl] propionitrile were synthesized in good yields from the intermediate (1H-indol-3-yl)-acetic acid N0-(2-cyanoethyl) hydrazide and also tested toward anti-inflammatory activity (at a dose of 10 mg/kg body weight) was determined *in vivo* by the acute carrageen an-induced paw edema standard. The anti-inflammatory properties were recorded at successive time intervals 0.5, 1, 2, 3, and 4 h and compared with that of Indomethacin (at a dose of 10 mg/kg body weight), which was used as a reference standard. It was noticed that after 1 hr, all the tested compounds exhibit considerable anti-inflammatory properties [36].



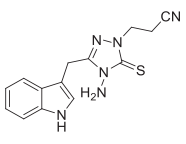
(45)



(46)



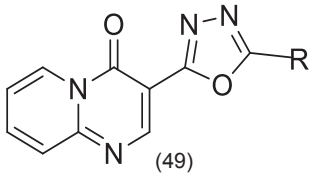
(47)



(48)

Anti-HIV activity

Hajimahdi *et al.* [37] designed and synthesized a new series of 4-oxo-4H-pyrido(1,2-a) pyrimidine derivatives containing 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives and evaluated for their *in vitro* anti-HIV-1 activity. Most of the compounds exhibited moderate inhibitory properties against HIV-1 virus (NL4-3) in Hela cell cultures. When introduce para-substituted phenyl at C-5 position of the 1,3,4-oxadiazole ring led to increased anti-HIV-1 activity. However, Compounds namely 3 -(5-[4-Fluorophenyl]-1, 3,4-thiadiazol-2-yl)-4Hpyrido(1,2-a)pyrimidin-4-one and 3-(5-p-Tolyl-1, 3,4-thiadiazol-2-yl)-4H-pyrido(1,2-a)pyrimidin-4-one displayed the highest activity among the synthesized compounds with inhibition rate of 51 and 48% at concentration of 100 μM.

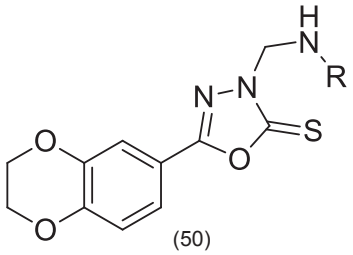


(49)

X=O, SR=NH_2, SH, Phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-Methylphenyl

Anti-oxidant activity

A new series of Mannich base of 1, 3, 4-oxadiazole derivatives possessing 1, 4-benzodioxan were synthesized by Ma *et al.* [38] All these novel compounds were screened for their *in vitro* anti-oxidant activity employing 2, 2'-diphenyl-1-picrylhydrazyl radical (DPPH), 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonate) cationic radical and ferric reducing anti-oxidant power scavenging assays. Most of them exhibited good anti-oxidant activities due to the combination of 1,4-benzodioxan, 1,3,4-oxadiazoles and substituted phenyl ring. Particularly, compounds 3-([[2, 6-Difluorophenyl)amino]methyl)-5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1, 3, 4-oxadiazole-2(3H)-thione and 5-(2, 3-Dihydrobenzo[b][1,4]dioxin-6-yl)-3-([[3,4,5-trifluorophenyl)amino]methyl)-1, 3,4-oxadiazole-2(3H)-thione showed significant radical scavenging ability comparable to the commonly used anti-oxidants, butylated hydroxytoluene (BHT) and Trolox. Most of the compounds with substituted phenyl exhibited better anti-oxidant activity than the standard anti-oxidant agents Trolox and BHT.

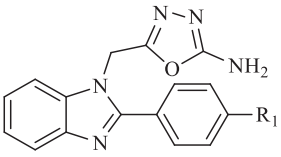


(50)

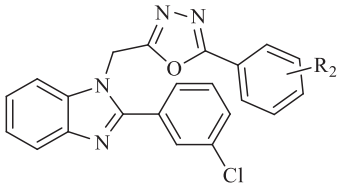
(a) C_6H_5-, (b) 2-F-C_6H_4-, (c) 3-F-C_6H_4-, (d) 4-F-C_6H_4-, (e) 2,6-2F-C_6H_3-, (f) 3,4,5-3F-C_6H_2-, (g) 2-CF_3-C_6H_4-, (h) 3-CF_3-C_6H_4-,(i) 3,5-2CF_3-C_6H_3-, (j) 2-Cl-C_6H_4-, (k) 3-Cl-C_6H_4-, (l) 4-Cl-C_6H_4-, (m) 2,4-2Cl-C_6H_3-, (n) 2,5-2Cl-C_6H_3-, (o) 3,4-2Cl-C_6H_3-, (p) 2-Br-C_6H_4-, (q) 3-Br-C_6H_4-, (r) 4-Br-C_6H_4-, (s) 2,4-2Br-C_6H_3-, (t) 2-NO_2-C_6H_4-, (u) 3-NO_2-C_6H_4-, (v) 4-NO_2-C_6H_4-, (w) 2-Cl-4-NO_2-C_6H_3-, (x) 2-CH_3-C_6H_4-, (y) 4-CH_3-C_6H_4-, (z) 2-OCH_3-C_6H_4-, (ab) 4-OCH_3-C_6H_4-, (ac) 2-OCH_2CH_3-C_6H_4-, (ad) -cyclohexane, (ae) -hexadecyl

Kerimov *et al.* [39] reported two new series of 2-amino-1, 3,4-oxadiazoles and 5-aryl-1, 3,4-oxadiazoles carrying benzimidazole moiety were synthesized. The anti-oxidant properties of these compounds were investigated *in vitro* by the determination of the microsomal NADPH-dependent inhibition of lipid peroxidation levels, the microsomal ethoxyresorufin O-deethylase activity, and

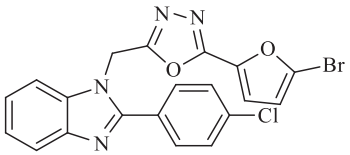
DPPH radical scavenger effects. Among the tested compounds, 2-([2-(4-chlorophenyl)-1H-benzo(d)imidazole-1-yl] methyl)-5-(4-fluorophenyl)-1, 3,4-oxadiazole was found to be the most active compound in all three *in vitro* systems.



(51)



(52)

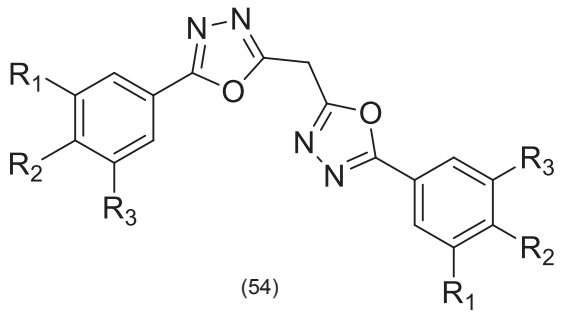


(53)

R1=H, Cl, OCH_3, $OCH_2C_6H_5$

R_2=4-C_2H_5, 4-CH_3, 3-CH_3, 2-CH_3, 4-F, 4-OCH_3, 4-Br, 4-CF_3, 3-CN, 3-Cl, 2-Cl, 2,4-diCl, 4-NO_3, 3-NO_2, 3,5-diNO_2, 3-NO_2, 4-OCH_3, 3-NO_3, 4-Cl, 2-F, 5-NO_2

Two series of five-membered heterocyclic bis (1,3,4-oxadiazole) derivatives and 3,5-bis(substituted) pyrazoles, isoxazoleswere synthesized by oxidative cyclization of some diaroyl hydrazones using chloramine-T and cyclo condensation reaction with hydrazine hydrate and hydroxylamine hydrochloride, respectively. The newly synthesized compounds were screened for anti-oxidant activity. Among oxadiazole derivatives, compound 4,4′-(5,5′-methylenebis(1,3,4-oxadiazole-5, 2-diaryl)bis(N,N-dimethylaniline) showed higher anti-oxidant activity at 10 µg/ml. The presence of either electron-donating or electron-withdrawing groups on the phenyl ring mostly favor the activity. Particularly, with a strong electron donating group such as-$N(CH_3)_2$ or a strong electron-withdrawing group (NO_2). These are related with their electron or hydrogen radical donating ability to DPPH radical, it may be reason for the higher anti-oxidant activity of the second series of compounds [40].



(54)

(a) R_1=H, R_2=$N(CH_3)_2$, R_3=H (b) R_1=H, R_2=OH, R_3=H (c) R_1=H, R_2=H, R_3=OH (d) R_1=H, R_2=Cl, R_3=H (e) R_1=R_2= R_3=H (f) R_1=H, R_2=$O(CH_3)$, R_3=H (g) R_1=H, R_2=R_3=$O(CH_3)$, (h) R_1=H, R_2=R_3=$O(CH_3)$, (i) R_1=H, R_2=NO_2, R_3=H

CONCLUSION

The present review highlights that the oxadiazole moiety as a template for the development of newer therapeutic agents. Modified oxadiazole moiety displayed the valuable biological activities. The 1,3,4-oxadiazole derivatives showed significant anti-cancer and anti-microbial activities while compared with other activities. They may be used for the development of new drugs for the treatment of cancer, bacterial and fungal diseases by researcher for developing new, innovative drugs.

REFERENCES

1. Husain A, Rashid M, Mishra R, Parveen S, Shin DS, Kumar D. Benzimidazole bearing oxadiazole and triazolo-thiadiazoles nucleus: Design and synthesis as anticancer agents. Bioorg Med Chem Lett 2012;22(17):5438-44.
2. Ahmad A, Varshney H, Rauf A, Sherwani A, Owais M. Synthesis and anti-cancer activity of long chain subtituted 1,3,4-oxadiazol-2-thione.1,2,4 trizol-3-thione and 1,2,4 –triazolo(3,4-b)-1,3,4-thiadiazine derivatives**.** Arabian J Chem 2014.
3. Salahuddin, Shaharyar M, Mazumder A, Ashan MJ. Synthesis, characterisation and anticancer evaluation of 2-(naphthalen-1-yl methyl/ naphthalen-2-yloxymethyl)-1-(5-substituted phenyl)-(1,3,4)oxadiazol-2-ylmethyl)-1H-benzimidazole. Arabian J Chem 2013;7(4):419-24.
4. Sun J, Li MH, Qian SS, Guo FJ, Dang XF, Wang XM, *et al.* Synthesis and antitumor activity of 1,3,4-oxadiazole possessing 1,4-benzodioxan moiety as a novel class of potent methionine aminopeptidase type II inhibitors. Bioorg Med Chem Lett 2013;23(10):2876-9.
5. Shamsuzzaman, Siddiqui T, Alam MG, Dar AM. Synthesis, chacterization and anticancer studies of new steroidal oxadiazole, pyrrole and pyrazole derivatives. J Saudi Chem Soc 2012.
6. Ashan MJ, Rathod VP, Singh M, Sharma R, Jadav SS, Yasmin S, *et al*. Synthesis, Anticancer and molecular docking studies of 2-(4-chloro phenyl)-5-aryl-1, 3, 4-oxadiazole analogues. Med Chem 2013;3:3-4.
7. Zhang F, Wang XL, Shi J, Wang SF, Yin Y, Yang YS, *et al.* Synthesis, molecular modeling and biological evaluation of N-benzylidene-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide derivatives as potential anticancer agents. Bioorg Med Chem 2014;22(1):468-77.
8. Bondock S, Adel S, Etman HA, Badria FA. Synthesis and antitumor evaluation of some new 1,3,4-oxadiazole-based heterocycles. Eur J Med Chem 2012;48:192-9.
9. Du QR, Li DD, Pi YZ, Li JR, Sun J, Fang F, *et al.* Novel 1,3,4-oxadiazole thioether derivatives targeting thymidylate synthase as dual anticancer/ antimicrobial agents. Bioorg Med Chem 2013;21(8):2286-97.
10. Rashid M, Husain A, Mishra R. Synthesis of benzimidazoles bearing oxadiazole nucleus as anticancer agents. Eur J Med Chem 2012;54:855-66.
11. Zhang XM, Qiu M, Sun J, Zhang YB, Yang YS, Wang XL, *et al.* Synthesis, biological evaluation, and molecular docking studies of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan moiety as potential anticancer agents. Bioorg Med Chem 2011;19(21):6518-24.
12. Zhang YB, Wang XL, Liu W, Yang YS, Tang JF, Zhu HL. Design, synthesis and biological evaluation of heterocyclic azoles derivatives containing pyrazine moiety as potential telomerase inhibitors. Bioorg Med Chem 2012;20(21):6356-65.
13. Feng CT, Wang LD, Yan YJ, Liu J, Li SH. Synthesis and antitumor evaluation of some 1, 3, 4-oxadiazole-2(3H)-thione and 1, 2, 4-triazole-5(1H)-thione derivatives. Med Chem Res 2012;2:315-20.
14. Murty MS, Ramalingeswara Rao B, Katiki MR, Nath LR, Anto RJ. Synthesis of piperazinyl benzothiazole/benzoxazole derivatives coupled with 1,3,4-oxadiazole-2-thiol: Novel hybrid heterocycles as anticancer agents. Med Chem Res 2013;22:4980-91.
15. Gudipati R, Anreddy RN, Manda S. Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives. Saudi Pharm J 2011;19(3):153-8.
16. Li Y, Luo Y, Hu Y, Zhu DD, Zhang S, Liu ZJ, *et al.* Design, synthesis and antimicrobial activities of nitroimidazole derivatives containing 1,3,4-oxadiazole scaffold as FabH inhibitors. Bioorg Med Chem 2012;20(14):4316-22.
17. Zhang MZ, Mulholland N, Beattie D, Irwin D, Gu YC, Chen Q, *et al.* Synthesis and antifungal activity of 3-(1,3,4-oxadiazol-5-yl)-indoles and 3-(1,3,4-oxadiazol-5-yl)methyl-indoles. Eur J Med Chem 2013;63:22-32.
18. Desai NC, Dodiya AM, Rajpara KM, Rupala YM. Synthesis and antimicrobial screening of 1,3,4-oxadiazole and clubbed thiophene derivatives. J Saudi Chem Soc 2011.
19. Jha KK, Samad A, Kumar Y, Shaharyar M, Khosa RL, Jain J, *et al.* Design, synthesis and biological evaluation of 1,3,4-oxadiazole derivatives. Eur J Med Chem 2010;45(11):4963-7.
20. Chandrakantha B, Shetty P, Nambiyar V, Isloor N, Isloor AM. Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety. Eur J Med Chem 2010;45(3):1206-10.
21. Khalilullah H, Khan S, Nomani S, Ahmed B. Synthesis, characterization and antimicrobial activity of benzodioxane ring 1,3,4-oxadiazole derivatives. Arabian J Chem 2011.

22. Desai NC, Bhatt N, Somani H, Trivedi A. Synthesis, antimicrobial and cytotoxic activities of some novel thiazole clubbed 1,3,4-oxadiazoles. Eur J Med Chem 2013;67:54-9.
23. Salimon J, Salih N, Yousif E, Hameed A, Kreem A. Synthesis and pharmacological evaluation of 9(10H)-acridone bearing 1,3,4-oxadiazole derivatives as antimicrobial agents. Arabian J Chem 2010;3:205-10.
24. Rane RA, Gutte SD, Sahu NU. Synthesis and evaluation of novel 1,3,4-oxadiazole derivatives of marine bromopyrrole alkaloids as antimicrobial agent. Bioorg Med Chem Lett 2012 15;22:6429-32.
25. Ramaprasad GC, Kalluraya B, Kumar BS, Hunnur RK. Synthesis and biological property of some novel 1,3,4-oxadiazoles. Eur J Med Chem 2010;45(10):4587-93.
26. Ishii M, Jorge SD, de Oliveira AA, Palace-Berl F, Sonehara IY, Pasqualoto KF, *et al.* Synthesis, molecular modeling and preliminary biological evaluation of a set of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole as potential antibacterial, anti-Trypanosoma cruzi and antifungal agents. Bioorg Med Chem 2011;19(21):6292-301.
27. Desai NC. Kotadiya GM. Microwave-assisted synthesis of benzimidazole bearing 1,3, 4-oxadiazole derivatives: Screening for their *in vitro* antimicrobial activity. Med Chem Res 2014;23:4021-4033.
28. Mashooq Ahmad Bhat, Mohamed A. Al-Omar, Nadeem Siddiqui. Antimicrobial activity of Schiff bases of coumarin-incorporated 1,3,4-oxadiazole derivatives: An *in vitro* evaluation. Med Chem Res 2013;22:4455-8.
29. Gul S, Aziz-ur-Rehman, Abbasi MA, Khan KM, Nafeesa K, Siddiqa A, *et al.* Synthesis, antimicrobial evaluation and hemolytic activity of 2-[[5-alkyl/aralkylsubstituted-1,3,4-Oxadiazol-2-yl]thio]-*N*-[4-(4-morpholinyl) phenyl]acetamide derivatives. J Saudi Chem Soc 2014.
30. Modi V, Modi P. Oxadiazole: Synthesis, characterization and biological activities. J Saudi Chem Soc 2012;16(3):327-32.
31. Manjunatha K, Poojary B, Lobo PL, Fernandes J, Kumari NS. Synthesis and biological evaluation of some 1,3,4-oxadiazole derivatives. Eur J Med Chem 2010;45(11):5225-33.
32. Hemalatha G, Manda S. Synthesis and screening of some novel substituted indoles contained 1,3,4-oxadiazole and 1,2,4-triazole moiety. Chin Chem Lett 2013;24(2):127-30.
33. Gilani SJ, Khan SA, Siddiqui N. Synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid. Bioorg Med Chem Lett 2010;20(16):4762-5.
34. Raval JP, Akhaja TN, Jaspara DM, Myangar KN, Patel NH. Synthesis and *in vitro* antibacterial activity of new oxaethylthio-1,3,4-oxadiazole derivatives. J Saudi Chem Soc 2014;18:101-6.
35. Harish KP, Mohana KN, Mallesha L, Prasanna Kumar BN. Synthesis of novel 1-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-piperazine derivatives and evaluation of their *in vivo* anticonvulsant activity. Eur J Med Chem 2013;65:276-83.
36. Tabatabai SA, Barghi Lashkari S, Zarrindast MR, Gholibeikian M, Shafiee A. Design, Synthesis and Anticonvulsant Activity of 2-(2-Phenoxy) phenyl- 1,3,4-oxadiazole Derivatives. Iran J Pharm Res 2013;12 Suppl:105-11.
37. Singh P, Sharma PK, Sharma JK, Upadhyay A, Kumar N. Synthesis and evaluation of substituted diphenyl-1,3,4-oxadiazole derivatives for central nervous system depressant activity. Org Med Chem Lett 2012;2(1):8.
38. Hajimahdi Z, Zarghi A, Zabihollahi R, Aghasadeghi MR. Synthesis, biological evaluation, and molecular modeling studies of new 1,3,4-oxadiazole and 1,3,4-thiadiazole-substituted 4-oxo-4H-pyrido[1,2-a] pyrimidines as anti-HIV-1 agents. Med Chem Res 2013;22(5):2467-75.
39. Kerimov I, Ayhan-Kilcigil G, Özdamar ED, Can-Eke B, Çoban T, Özbey S, *et al.* Design and one-pot and microwave-assisted synthesis of 2-amino/5-aryl-1,3,4-oxadiazoles bearing a benzimidazole moiety as antioxidants. Arch Pharm (Weinheim) 2012;345(7):549-56.
40. Abdu Musad E, Mohamed R, Saeed BA, Vishwanath BS, Rai KM. Synthesis and evaluation of antioxidant and antibacterial activities of new substituted bis(1,3,4-oxadiazoles), 3,5-bis(substituted) pyrazoles and isoxazoles. Bioorg Med Chem Lett 2011;21(12):3536-40.