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Review on substituted 1,3,4-oxadiazole derivatives

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Abstract
1,3,4-Oxadiazole is a five membered heterocyclic nucleus and is considered to be derived from furan by replacement of two methane (-CH=) group by pyridine type nitrogen. 1,3,4-Oxadiazole is a versatile lead compound for scheming potent bioactive agents. The derivative of oxadiazole nucleus (1,3,4-oxadiazole) showed various biological activities such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, anticancer, anti-HIV, hypoglycemic and genotoxic activities. In this article, an attempt is made to compile some of the major researches carried out for the compound 1,3,4- oxadiazole. 1,3,4-oxadiadole have produced interest in synthetic organic and medicinal chemistry as surrogates of carboxylic acid.

Keywords: oxadiazole, antimicrobial, anti-inflammatory, anticancer

Introduction
1,3,4-Oxadiazole are the heterocyclic compounds containing one oxygen and two nitrogen atoms in a five-membered ring possessing a diversity of useful biological effects. 1,3,4-Oxadiazole derivatives are recognized for their pharmacological importance and are reported to possess a wide spectrum of activities such as antibacterial [1], antifungal [2], anti-inflammatory [3], analgesic, anticonvulsant [4], hypoglycemic and anticancer [5] properties. Researchers have already reported that Gram positive bacteria are much more susceptible to antimicrobial agents compared to Gram-negative bacteria [6]. These differences may be attributed to the fact that the cell wall in Gram-positive bacteria is of single layer whereas the Gram-negative bacteria have a multilayered cell wall. Gram-negative bacteria possess a outer membrane and a unique periplasmic space which is not found in Gram-positive bacteria [7]. Several methods have been reported for the synthesis of 1,3,4-oxadiazoles.

a) Chemistry of oxadiazole ring
Oxadiazoles having a five membered ring containing one oxygen and two nitrogen atoms and the molecular formula of oxadiazole $C_2H_2N_2O$. Four isomers of oxadiazole: 1,2,3-oxadiazole. 1,2,4-oxadiazole, 1,2,5- oxadiazole and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unbalanced and reverts to the diazoketone tautomer. Name for oxadiazole ring are given as 'Azoxime' [8].
Literature survey reveals that the oxadiazoles undergo the number of reactions such as electrophilic substitution, nucleophilic substitution, thermal and photochemical reaction [9]. The substituted aromatic acids are used as a versatile starting material for the synthesis of 1,3,4-oxadiazoles derivatives involving the formation of corresponding esters and hydrazides. 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers for the reason that these oxadiazoles have many important chemical and biological properties. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important building moiety for the development of new drugs [10].

b) Physical properties
1,3,4-Oxadiazole is a five member heterocyclic compound having two carbon, two nitrogen, one oxygen and two double bonds. The percentage of C, H, N, and bond angle present in 1,3,4-oxadiazole are given in Table A & B [11].

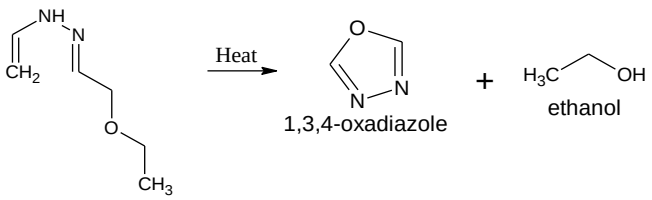
Table A: Percentage of C, H, N present in 1,3,4-oxadiazole.

Component	Calculated %	Found %
C	34.29	34.56
H	2.88	3.19
N	40.00	39.71

Table B: Bond angle.

Bond/Angle	Bond angle (°)	Bond length (pm)
A	105.6	139.7
B	113.4	129.9
C	102.0	134.8
D	113.4	134.8
E	105.6	19.7

c) Preparation of 1,3,4-oxadiazole ring
1, 3, 4-Oxadiazole is considered as a liquid, which boils at 150°C. Ainsworth first prepared it in 1965 by the thermolysis of ethyl formate formula hydrazone at atmospheric pressure as given below [12].



d) Reactivity of 1, 3, 4-oxadiazole
1,3,4-Oxadiazole have a relatively low electron density at carbon (positions 2 and 5) and a relatively high electron density at nitrogen (positions 3 and 4), the major reactions are the nucleophilic attack at carbon, usually followed by ring cleavage and electrophilic attack at nitrogen.
The oxadiazole exists in different isomeric forms such as

1,3,4- (fig a), 1,2,5-(fig b), 1,2,4-(fig c), and 1,2,3-(fig. d) oxadiazole, out of which thermally stable 1,3,4-oxadiazole is the only isomer not containing a nitrogen-oxygen bond [12].

Fig a **Fig b** **Fig c** **Fig d**

1,3,4-Oxadiazole is a thermally stable neutral aromatic molecule [13] and its estimated resonance energy is 167.4 kJ/mol. Mostly, aryl group at position 2 increases the thermal stability of 1,3,4-oxadiazole. Ring is stable to heat, a property which has been exploited in the production of heat-resistant poly-1,3,4-oxadiazoles. UV spectra of substituted 1,3,4-oxadiazoles are identical to those of substituted benzenes, particularly in the case of 2-phenyl-1,3,4-oxadiazoles (λmax in ethanol = 247.5 nm, log ε 4.26). Studies on 1,3,4-oxadiazoles and its cation indicate a maximum positive charge on the second position. Alkyl and aryl-1,3,4-oxadiazoles are neutral compounds and 2-amino-1,3,4- oxadiazoles are weakly basic.

The relatively low electron density at carbon, coupled with the possibility of protonation at nitrogen, make electrophilic substitution at carbon difficult. No examples of nitration or sulfonation of the oxadiazole ring have been reported and attempted bromination reactions were unsuccessful. 1,3,4-Oxadiazole is associated with potent pharmacological activity due to the presence of toxophoric –N=C-O- linkage [15].

The derivative of 1,3,4-oxadiazole with suitable substitution at 2, 5-position are becoming an important member in the heterocyclic family not only because of their wide range usages as photosensitive & electrical materials but also for the reason that of their broad spectrum in biological activities [16].

Biological Activities

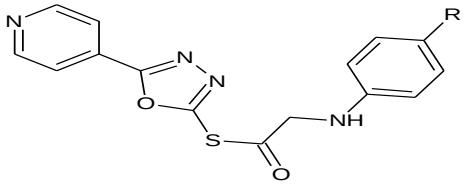
It is an important challenging task for medicinal chemists to develop new anti-microbial, anti-inflammatory, analgesic, antitumor, anti-convulsant, antidiabetic, antiosteoporotic activity, activity on skin, activity against snake venom, mao inhibitor and anti alzheimer activity.

There are two basic approaches for development of new drugs: (a) Synthesis of analogous and their modifications as well as derivatization gives novel substituted compounds for better and improved treatment and (b) Searching and synthesis of novel compounds, that the bacterias and diseases has never been presented before [17].

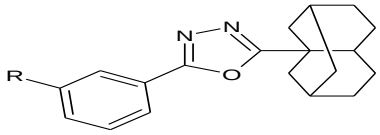
Antimicrobial activity

Researches on 1,3,4-oxadiazole and their derivatives have shown that they are having very prominent antimicrobial activity against a wide range of microbes. Specially 2, 5-disubstituted 1,3,4-oxadiazole has gained the attention of the medicinal chemists [18].

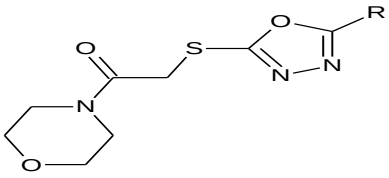
Jignesh P Raval *et al.,* reported a series of 2(4-pyridyl)-5[(aryl/heteroarylamino)-1-oxoethyl]thio-1,3,4-oxadiazole were tested for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis H37Rv* using the BACTEC 460 radiometric system. All the new compounds were pharmacologically evaluated for their *in vitro* antimicrobial activity and synthesized oxoethylthio-1,3,4-oxadiazole derivatives provide valuable leads for developing new antibacterial agents [19].



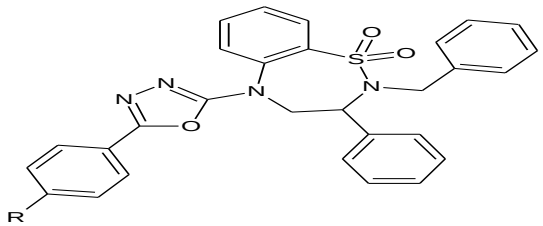
Mahmood-ul-Hassan Khanv *et al.,* reported in the synthesis of 2- Adamantyl/adamantylmethyl-5-aryl-1,3,4-oxadiazoles. All the compounds were screened for antibacterial, antifungal, where compounds exhibit moderate activity *in vitro* against both virus types, suggesting for further structural modification as a new lead in the development of an antiviral agent [20].



M Somashekhar *et al.,* reported all the synthesised compounds of 1-(morpholin-4-yl)-2- (1,3,4-oxadiazol-2 ylsulfanyl) ethanone were screened *in vitro* antibacterial and antifungal activities. The minimum inhibitory concentration (MIC) was determined by the cup plate method [21].

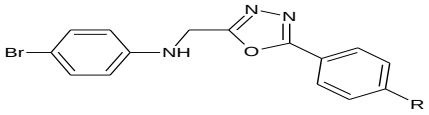


S. Harikrishna *et al.,* reported 1,3,4-Oxadiazole derivatives of Sultams namely 2- benzyl-5-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)-3-phenyl 2,3,4,5-tetrahydrobenzo[f][1,2,4]thiadiazepine 1,1-dioxides. Antimicrobial studies revealed that the pharmacological properties of 1,3,4-oxadiazoles were enhanced by introducing alkoxy and halogen substituents. Novel 1, 3, 4-oxadiazole derivatives of sultams have been synthesized and evaluated for antimicrobial activities. From the antimicrobial studies of newly synthesized compounds it revealed that the compounds possessed significant antibacterial and moderate antifungal activities. Compounds with methoxy substitution were found to be most potent compounds of the series with antibacterial activity higher than that of standard drug *i.e,* ciprofloxacin against *S. aureus* and *B. subtilis* [22].

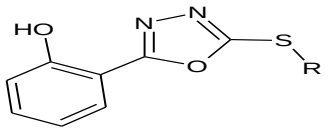


KI Bhat *et al.,* reported structures of all the synthesized 1,3,4-oxadiazole analogs and were confirmed by

IR, ^{1}HNMR and Mass spectroscopic analysis. The newly synthesized compounds were screened for antibacterial, antifungal and anti-inflammatory activities [23].



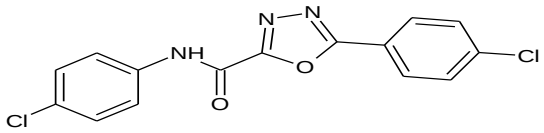
Palak K Parikh *et al.*, reported the *in-vitro* antibacterial activity of synthesized compound was tested against Gram-positive and Gram-negative microorganisms (*Staphylococcus aureus* ATCC 9144, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* MTCC 1688 the Gram negative: *Escherichia coli* ATCC 25922) by filter paper disc method. The *in-vitro* antifungal activity was tested against *Candida albicans* by filter paper disc method [24].



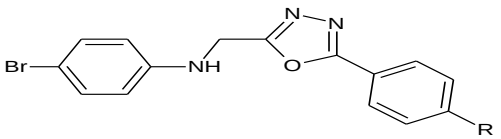
Analgesic and Anti-inflammatory activity

The novel mercapto substituted 1,3,4-oxadiazole bears good anti-inflammatory activity and if secondary amines are added to this scaffold then the activity increases [25].

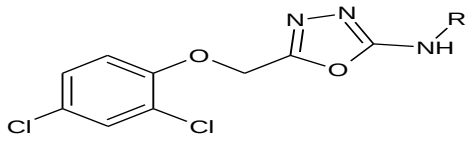
Arvind Kumar Singh *et al.*, reported all the 1,3,4 Oxadiazole derivaties were determined by the carrageenin-induced rat-paw-oedema model for anti-inflammatory activity. The entire compound gives good response for the anti-inflammatory activity [26].



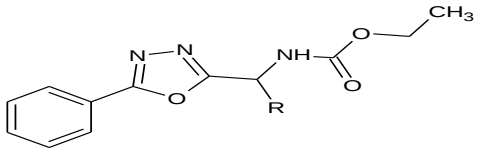
KI Bhat *et al.*, reported structures of all the synthesized 1,3,4-oxadiazole analogs were confirmed by IR, ^{1}HNMR and MASS spectroscopic analysis. The newly synthesized compounds were screened for antibacterial, antifungal and anti-inflammatory activities [23].



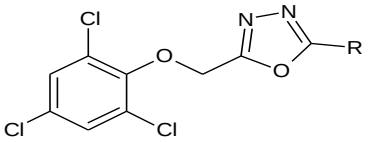
Mohammad Asif *et al*., reported 2,5-di-substituted 1,3,4-oxadiazoIe derivatives show anti-intlammatory activity. The presence of n-butyl amino group at 2nd position of 1,3,4-oxadiazole nucleus showed maximum activity, where as the presence of cyclohexyil amino group showed minimum activity [27].



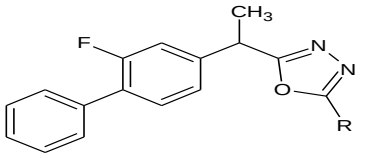
Luciano Dornelles *et al.*, reported two methodologies studied for the synthesis of 1,3,4-oxadiazoles use a small amount of the dehydrating agent $POCl_3$ [28].



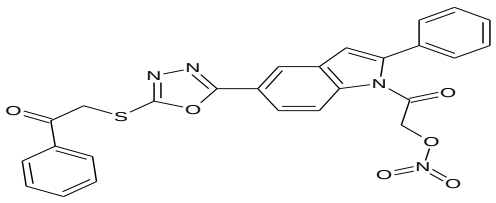
Mhmd. Amir *et al.*, reported the synthesis of various derivatives of 1,3,4-oxadiazole are proposed to be synthesized by treating 2,4-dihydro-3H-pyrazole-3-one with ethylchloroacetate and hydrazine, the products then treated with $POCl_3$ and different carboxylic acids. All the derivatives have been tested *in vivo* for their anti-inflammatory activity by carrageenin-induced rat paw edema method. The compounds, which show good anti-inflammatory activity, have been screened for their ulcerogenic and lipid peroxidation activities [29].



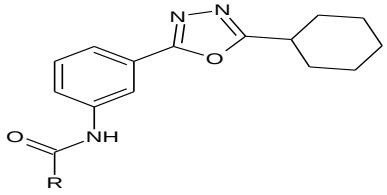
Omar F *et al.*, reported series of substituted 1,3,4-oxadiazole derivatives were synthesized as anti-inflammatory agents [30].



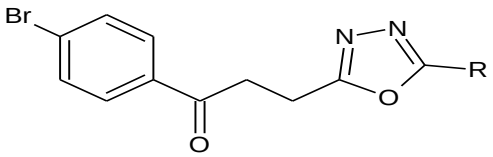
Shashikant V *et al.*, reported the analgesic activity of a series of hybrid molecules 2-(5-(5-(substituted phenyl)-2-oxo-ethylthio)-1,3,4-oxadiazole-2-yl)-2-phenyl-1H-indol-1-yl)-2-oxoethyl nitrate were evaluated using the acetic acid induced writhing method [31].



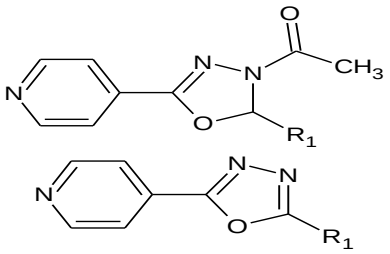
Kavitha Selvaraj *et al.*, reported 2,5 substituted-1,3,4 oxadiazole derivatives are characterized and confirmed by FT-IR, ^{1} H and ^{13}C NMR and mass spectral studies with the intention of developing the novel biologically active compounds. All synthetic compounds were screened for their antidiabetic, antiinflammatory and anticancer activities [32].



Asif Husain *et al.,* reported the synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties the to develop better anti-inflammatory and analgesic molecules with or without ulcerogenic activity [33].



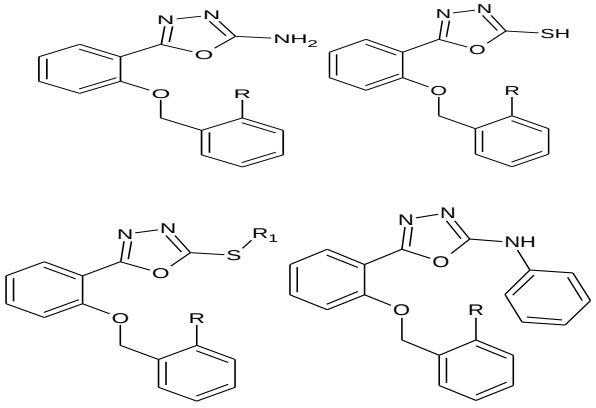
Dhansay Dewangan *et al*., reported synthesized 2, 5-Disubstituted 1, 3, 4-Oxadiazole derivatives newly synthesized compounds were investigated for their analgesic activity by acetic acid induced writhing method using swiss albino mice and anti-inflammatory activity by carrageenan induced rat paw edema and were determined according to mercury displacement method by using plethysmograph on adult albino rats. So compounds were shown significant analgesic activity where as compounds were shows good anti- inflammatory activity [34].



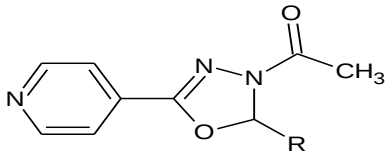
Anti-Convulsant Activity

1,3,4-oxadiazole when substituted with an amino group at 5th position have good anti-convulsant activity [35].

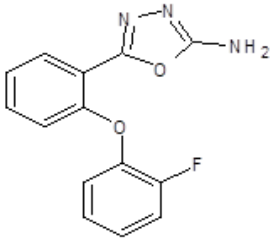
Afshin Zarghi *et al.,* synthesized 2-Amino-5-(2-halo-2-benzyloxyphenyl)- 1,3,4-oxadiazoles, 5-(2-Halo-2benzyloxyphenyl)- 2-mercapto-1,3,4-oxadiazole, 2-Alkylthio-5-(2-halo-2-benzyloxyphenyl)- 1,3,4-oxadiazole and 2-Anilino-5-(2-halo-2-benzyloxyphenyl)- 1,3,4-oxadiazole, newly synthesized compounds were investigated for anticonvulsant evaluations by qualitative assays using MES (maximal electroshock) and PTZ (pentylenetetrazole) tests [36].



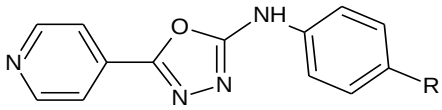
Sadaf Jamal Gilani *et al.,* reported that 1-(2-(2-substitutedphenyl)-5-(pyridine-4-yl)-1,3,4- oxadiazol-3(2H)- yl)ethanone synthesized compounds were investigated for anti-convulsant evaluations by qualitative assays using MES (maximal electroshock) and scPTZ (subcutaneous pentylenetetrazole) tests using adult male albino mice [37].



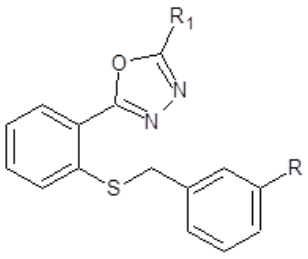
Ali Almasirad *et al.,* synthesized new 2-substituted-5- [2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles newly synthesized compounds were screened for the anti-convulsant activity by PTZ and MES models, and the compound found to have good anti-convulsant activity [38].



Girish R *et al.,* reported a series of 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-oxadiazole was prepared from ionized and substituted phenyl isothiocyanates derived thiosemicarbazides All the compounds showed activity in the range of 33-100 % in comparison to phenytoin which completely inhibited the convulsions produced by electro convulsometer in albino mice [39].

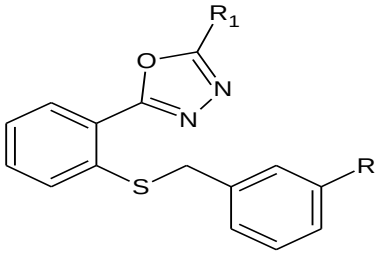


Mohammead Sahar Yar *et al.,* reported a new series of 2-substituted-5-{2-(2- halobenzyl)thio phenyl}-1,3,4-oxadiazoles were designed, synthesized and investigated for anticonvulsant activities. Electroshock and pentylene tetrazole-induced lethal convulsion tests showed that some of the synthesized compounds had significant anticonvulsant activity [40].



Afsohin Zarghi *et al.,* reported a series of Isonicotinic acid hydrazide (INH) incorporated derivatives of 1,3,4-oxadiazole azetidin- 2-one and has been synthesized. Maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice were used to evaluate the anticonvulsant activity of all the synthesized compounds. All the compounds were active in MES and a majority of compounds were active in scPTZ test. All compounds were

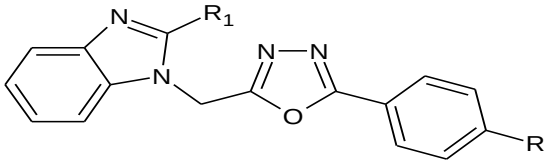
less neurotoxin than the standard drug phenytoin [41].



Anti-Tumor Activity

There is a wide scope of novel substituted 1,3,4-oxadiazole as chemotherapeutic agents against breast cancers, [42] leukemia, lung cancers etc.

Salahuddin *et al.,* synthesized 2-(Naphthalen-2-yloxymethyl)-1-(5-substituted phenyl [1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazole, newly synthesized compounds were properly examined for anticancer activity in melanoma, leukemia, lung, colon, breast, ovarian, prostate cancer cell lines in vitro. In this the anti-cancer screening was carried out according to the NCI US protocol. Compound substituted with 4-NO2 showed moderate to good activity against selected cell line [43].



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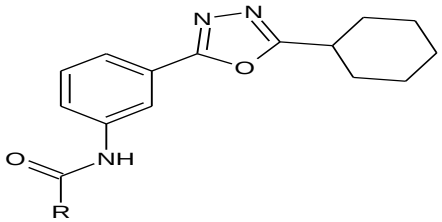
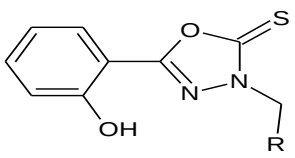
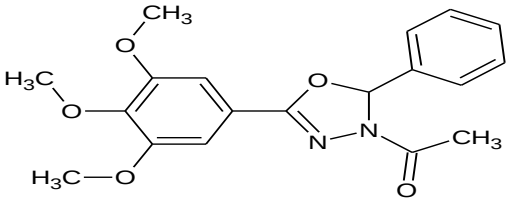


Anticancer-activity

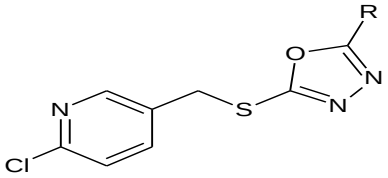
Ahmed S Aboraia *et al.,* reported a series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives was synthesized and evaluated for their *in vitro* anticancer activity. The derivatives displayed high anticancer activity in the primary assay. Compounds were proved to be the active members in this study compared to 5- fluorouracil and cyclophosphamide as reference drugs, respectively [44].



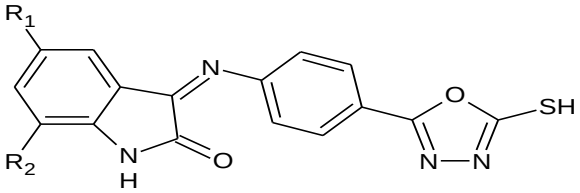
Linhong Jin *et al.,* reorted the synthesis of 3-acetyl-2-substituted-phenyl-5-(3,4,5- trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole by cyclization reaction of nitro-substituted benzylidene-3,4,5-trimethoxybenzo hydrazide in acetic anhydride. Their anti proliferative activities against some cancer cells *in vitro* tests done by MTT method [45].



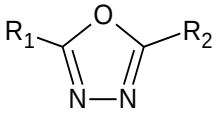
Qing-Zhong Zheng, *et al.,* reported a series of new 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety were synthesized. Antiproliferative assay results indicated that compounds exhibited the most potent activity against gastric cancer cell SGC-7901, which was more potent than the positive control. Docking simulation was performed to position compounds into the active site of telomerase to determine the probable binding model [46].



Rajyalakshmi Gudipati *et al.,* reported the synthesis of 5- or 7-substituted 3-{4-(5-mercapto- 1,3,4-oxadiazol-2-yl)phenylimino} indolin–2–one derivatives by treating 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives.. All the synthesized derivatives were screened for anticancer activity against HeLa cancer cell lines using MTT assay [47].



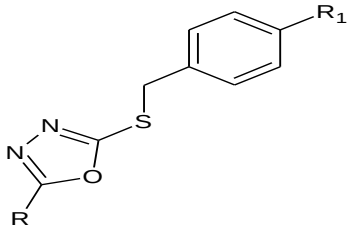
Alex S. Kiselyov *et al.,* reported a series of novel 1,3,4-oxadiazole derivatives based on structural and electronic overlap with combretastatin A-2 have been designed, synthesized and tested *in vivo* using the sea urchin embryo development assay. The effects of these agents on two specific developmental stages of the embryo, were monitered namely i) fertilized egg to assess antimitotic activity; ii) free swimming blastulae to detect behavioral changes in the embryo swimming pattern [48].



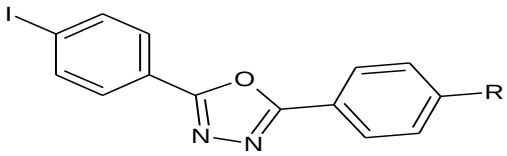
Anti Alzimer Activity

Afshin Zarghi *et al.,* reported glycogen syntheses kinase-3b (GSK-3b) is implicated in abnormal hyper phosphorylation

of tau protein and its inhibitors are expected to be promising therapeutic agents for the treatment of Alzheimer's disease. In this design, synthesis and structure–activity relationships of a novel series of oxadiazole derivatives as GSK-3b inhibitors [49].



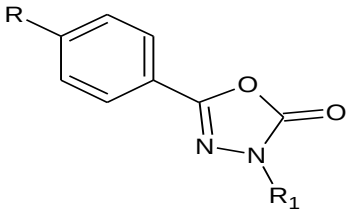
Morihisa Saitoh *et al.,* reported a series of 2,5-diphenyl-1,3,4-oxadiazole derivatives for detecting b-amyloid plaques in Alzheimer's brains. The affinity for amyloidal plaques was assessed by an *in vitro* binding assay using preformed synthetic Ab42 aggregates. Compared to 3,5-diphenyl-1,2,4-oxadiazole (1,2,4- DPOD) derivatives, They have good penetration of and fast washout from the brain in bio distribution experiments using normal mice when compared to 3,5-diphenyl-1,2,4-oxadiazole (1,2,4- DPOD) derivatives. The novel radio iodinated 1,3,4-DPOD derivatives may be useful probes for detecting b-amyloid plaques in the Alzheimer's brain [50].



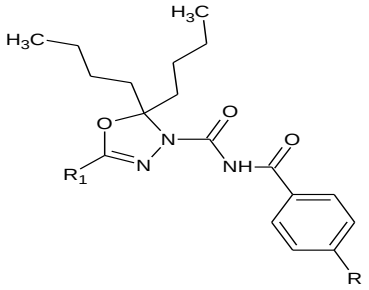
R= NH_2, C_6H_5 NH_2

MAO Inhibitor

Hiroyuki Watanabe *et al*., reported the synthesis of 5-aryl-1,3,4-oxadiazol-2(3H)-one derivatives and sulfur analogues and evaluated *in vitro* for their inhibitory properties on monoamine oxidase (MAO) types A and B. The most active compounds were found to act as potent, selective and competitive MAO B inhibitors with a slight slow-binding character [51].

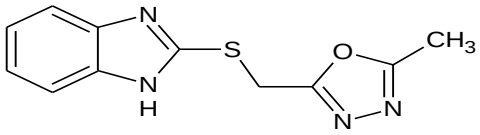


F Mazouzl *et al.,* reported 1,3,4-oxadiazole-3(2H)-carboxamide derivatives were prepared by direct heterocyclization reaction of substituted benzoylisocyanate with various arylhydrazones as novel monoamine oxidize inhibitors (MAOIs) [52].



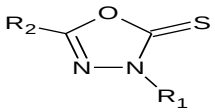
Antidiabetic

Shaoyong Ke *et al.,* reported 1,3,4-oxadiazoles containing 2-mercapto benzimidazole moiety was synthesized and screened for *in vivo* anticonvulsant activity by Maximal Electroshock (MES) model and antidiabetic activity using Oral Glucose Tolerance Test (OGTT) [53].



Activity against Snake Venom

Ramya V Shingalapur *et al.,* reported the synthesis of derivatives of 1,3,4-oxadiazole-2 (3H)-thiones and evaluated for their inhibitory activities against the two nucleotide pyrophosphates phosphodiesterase 1 enzymes [4-(t-butyldimethylsilyloxy)-phenyl]-1,3,4- oxadiazole-2 (3*H*)-thione was found to be the most active compounds with IC50 values [54].



Activity on Skin

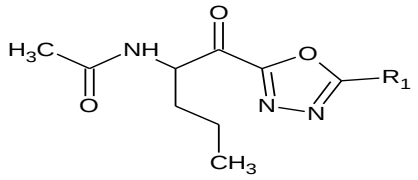
Khalid M. Khan *et al.,* reported the tyrosinase inhibition studies of library of 2,5- disubstituted-1,3,4-oxadiazoles and their structure–activity relationship (SAR). This molecule can be the best candidate as a lead compound for further development of drug for the treatments of several skin disorders [55].

Mahmud Tareq Hassan Khan *et al.,* reported a series of 1,3,4-oxadiazole-2(3H)-thiones and substituted hydrazides were tailored and synthesized as new potent inhibitors of tyrosinase [56].

Antiosteoporotic Activity

Usman Ghani *et al.,* reported the synthesis of cathepsin K inhibitors bearing the keto-1,3,4-oxadiazole were capable of forming a hemithioketal complex with the target enzyme. By modifying binding moieties at the P1, P2, and prime side positions of the inhibitors, achieved selectivity over cathepsins B, L, and S, and have achieved sub-nanomolar potency against cathepsin K. This series thus represents a

promising chemotype that could be used in diseases implicated by imbalances in cathepsin K activity such as osteoporosis [57].



Conclusion

The key therapeutic activities of the 1,3,4-oxadiazole has been concluded in this review. This compound has shown a wide range of therapeutic importance. In this paper comprises of all the major pharmacological activities of 1,3,4-oxadiazole and it can be used for further researches. The major activities of 1,3,4-oxadiazole are antimicrobial, anti-inflammatory, analgesic, antitumour, anticonvulsant, antidiabetic, antiosteoporotic activity, activity on skin, activity against snake venom, mao inhibitor and antialzimer activity.

Reference

1. Padmavathi V, Reddy G, Padmaja A, Kondaiah P, Shazia A. Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. Eur J Med Chem. 2002; 44(5):2106-2112.
2. Kadi AA, El-Brollosy NR, Al-Deeb OA, Habib EE, Ibrahim TM, El-Emam AA. Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. Eur J Med Chem. 2008; 42(2):235-242.
3. Sahin G, Palaska E, Ekizoglu M, Ozalp M. Synthesis and antimicrobial activity of some 1,3,4-oxadiazole derivatives. Farmaco II. 2002; 57(7):539-542.
4. Almasirad A, Tabatabai SA, Faizi M, Kebriaceezadeh A, Mehrabi N, Dalvandi A, *et al*. Synthesis and anticonvulsant activity of new 2-substituted-5- [2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles. Bioorg Med Chem Lett. 2004; 14(20):6057-6059.
5. Sengupta P, Dash DK, Yeligar CV, Murugesh K, Rajalingam D, Singh J, *et al*. Evaluation of anticancer activity of some 1,3,4-oxadiazole derivatives. Indian J Chem. 2008; 147(2):460-462.
6. Franski R. Biological activities of the compounds bearing1,3,4-oxa(thia)diazole ring. Arabian J Chem. 2005; 17(4):2063-2075.
7. Gomes D, Borges CP, Pinto JC. Study of the synthesis of poly(4,4,'-diphenyl ether-1,3,4-oxadiazole). In solution of poly(phosphoric acid), polymer. Arabian J Chem. 2001; 42(3):851-865.
8. Omar F, Mahfouz NM, Rahman M. Design, synthesis and anti-inflammatory activity of some 1,3,4-oxadiazole derivatives. Eur J Chem. 1996; 31(10):819-825.
9. Kumar H, Javed SA, Khan SA, Amir M. 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-aryloxy acetic acid: Synthesis and preliminary evaluation of biological properties. Eur J Chem. 2008; 43(12):2688-2698.
10. Tan TMC, Chem Y, Kong KH, Bai J, Li Y, Lim SG, *et al*. Synthesis and the biological evalution of 2-benzene sulfonylalkyl-5-substitutedsulfanyl-[1,3,4]-oxadiazoles as potential antihepatitis B virus agents. Eur J Chem. 2006; 71(2):7-14.
11. Ainsworth C. 1,3,4-Oxadiazole. American J Med Chem. 1965; 12(3):18795800-187958001.
12. Rigo B, Couturier D. Synthesis of 5-(5-oxo-2-pyrrolidinyl)-1, 3, 5-oxadiazole- 2-thione derivatives. J Hetro Chem. 1985; 22(3):287-288.
13. Banday MR, Mattoo RH, Rauf A. Synthesis, characterization and anti-bacterial activity of 5-(alkenyl)-2-amino- and 2-(alkenyl)-5-phenyl-1,3,4-oxadiazoles. J Chem Science. 2010; 122(2):177-182.
14. Borg S, Estenne-Bouhtou G, Luthman K, Csöregh I, Hesselink W, Hacksell U. Synthesis of 1,2,4-Oxadiazole-, 1,3,4-Oxadiazole-, and 1,2,4-Triazole-Derived Dipeptidomimetics. J Org Chem. 1995; 60(10):3112-20.
15. Patel KD, Prajapati SM, Panchal SN, Patel HD. Review of synthesis of 1,3,4-oxadiazole derivatives. Synth Commun. 2014; 44(13):1859-75.
16. CR BKI, Prathap MKR. Design and microwave-assisted synthesis of 1,3,4-oxadiazole derivatives for analgesic and anti-inflammatory activity. J Young Pharm. 2012; 4(1):33-7.
17. Vachharajani PR, Solanki MJ, Dubal GG, Shah VH. Synthesis of some novel 1, 3, 4-oxadiazole and its antibacterial and anti-fungal activity. Der Pharm Chem. 2011; 3(1):280-285.
18. Arvind Kumar Singh, Parthasarathy R, Lohani M. Synthesis, Characterization and Anti-Inflammatory Activity of Some 1, 3,4 -Oxadiazole Derivatives. Indian J Med Chem. 2013; 12(2):319-323.
19. Jignesh P Raval, Tarunkumar N Akhaja, Dhaval M Jaspara, Kruti N Myangar, Nilesh H Patel. Synthesis and *in vitro* antibacterial activity of new oxoethylthio-1,3,4-oxadiazole derivatives. Indian J Med Chem. 2014; 18(5):101-106.
20. Mahmood-ul-Hassan Khan, Tashfeen Akhtar, Najim A Al-Masoudi, Helen Stoeckli-Evans, Shahid Hameed. Synthesis, Crystal Structure and Anti-HIV Activity of 2- Adamantyl/adamantylmethyl-5-aryl-1,3,4-oxadiazoles. Indian J Med Chem. 2012; 8(2):1190-1197
21. Somashekhar M, Kotnal RB, Kalyane NV. Synthesis, characterisation and antimicrobial activity of 1-(morpholin-4-yl)-2- (1,3,4-oxadiazol-2 ylsulfanyl) ethanone derivatives. Indian J Med Chem. 2015; 3(2):891-895.
22. Harikrishna S, Ravindranath LK. Synthesis, characterization and biological studies of 1, 3, 4-oxadiazole derivatives of sultams. Der Pharm Chem. 2014; 4(1):1284-1293.
23. Bhat KI, Sufeera K, Sunil Kumar P Chaitanya. Synthesis, characterization and biological activity studies of 1,3,4-oxadiazole analogs. Indian J Med Chem. 2011; 3(4):310-314.
24. Palak K Parikh, Hiren M Marvaniya, Prof Dr Dhrubo Jyoti Sen. Synthesis and biological evaluation of 1,3,4-oxadiazole derivatives as potential antibacterial and antifungal agents. Indian J Med Chem. 2011; 3(2):248-253.
25. Sahoo BM, Kumar RBVV, Kumari BUBP. Synthesis, characterisation and biological evaluation of novel

oxadiazole derivatives. Inter J Pharma Sci and Res. 2011; 2(2):344-350.
26. Arvind Kumar Singh, Parthasarathy R, Lohani M. Synthesis, characterization and anti-inflammatory activity of some 1, 3,4 -oxadiazole derivatives. Indian J Med Chem. 2013; 12(2):319-323.
27. Mohammad Asif. biological potentials of biological active triazole Derivatives. Org Chem Curr Res. 2016; 5(4), DOI:10.4172/2161-0401.1000173
28. Luciano Dornelles, Oscar ED Rodrigues, Elisiane F Heck, Caroline R Bender, Mariane B Cansian, Ricardo S Schwab, Wolmar A Severo Filhoc. Synthesis of 1,3,4-oxadiazole derivatives from α-amino acid and acyl hydrazides under thermal heating or microwave irradiation conditions. Arkivoc. 2015; 7(1)131-144.
29. Amir M, Javed SA, Kumar H. Synthesis of some 1,3,4-oxadiazole derivatives as potential anti-inflammatory agents. Indian J Med Chem. 2007; 46(6):1014-1019.
30. Omar F, Mahfouz NM, Rahman M. Design, synthesis and anti-inflammatory activity of some 1,3,4-oxadiazole derivatives. Eur J Chem. 1996; 31(10):819-828.
31. Shashikant V Bhandari, Jignesh K Parikh, Kailash G Bothara, Trupti S Chitre, Deepak K Lokwani, Titiksh L Devale, *et al*. Design, synthesis, and evaluation of anti-inflammatory, analgesic, ulcerogenicity, and nitric oxide releasing studies of novel indomethacin analogs as non-ulcerogenic derivatives. Bioorg Med Chem. 2010; 25(4):520-530.
32. Kavitha Selvaraj, Kannan Kulanthai, Gnanavel Sadhasivam. Synthesis, characterization and biological evaluation of novel 2,5 substituted-1,3,4 oxadiazole derivatives. Saudi Pharma J. 2017; 25(12):337-345.
33. Asif Husain, Mohammed Ajmal. Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. Arabian J Pharma. 2009; 59(2):223-233.
34. Dewangan D, Pandey A, Sivakumar T, Rajavel R, Dubey RD. Synthesis of some novel 2, 5- disubstituted 1, 3, 4- oxadiazole and its analgesic, anti-inflammatory, antibacterial and anti-tubercular activity. Indian J Chem. 2010; 2(3):1397-1412.
35. Tabatabai SA, Lashkari SB, 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):105-111.
36. Zarghi A, Hajimahdi Z, Mohebbi S, Rashidi H, Mozaffari S, Sarraf S. Design and synthesis of new 2-substituted-5-[2-(2 halobenzyloxy) phenyl]- 1,3,4-oxadiazoles. Inter Res J Pharm. 2016; 7(2):7-18.
37. Gilani SJ, Alam O, Khan SA, Siddiqui N, Kumar H. Synthesis of some derived thiazolidin-4-one, azetidin-2-one and 1,3,4-oxadiazole ring systems from Isoninicotinic acid hydrazide. Der Pharmacia Lett. 2009; 1(2):1-8.
38. Ali Almasirad, Sayyed A. Tabatabai, Mehrdad Faizi, Abbas Kebriaeezadeh, Nazila Mehrabi, Afshin Dalvandi and Abbas Shafiee. Synthesis and anticonvulsant activity of new 2- substituted-5- [2-(2-fluorophenoxy)phenyl]-1,3,4- oxadiazoles and 1,2,4-triazoles. Bioorg Med Chem. 2004; 14(24):6057-6059.
39. Girish R Bankar, Nandakumar K, Pawan G Nayak, Anjali Thakur, Mallikarjuna Rao Chamallamudi, Gopalan Kutty Nampurath. A preliminary *in vitro* assessment of a 1,3,4-oxadiazole derivative; vaso relaxant effect in rat aortic rings through calcium channel blockage. Chem Biolo Inter. 2009; 181(9):377-382.
40. Mohammead Sahar Yar and Mohammad Wasim Akhter. Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives. Acta Polo Pharm Drug Res. 2009; 66(4):393-397.
41. Afsohin Zarghi, Samaneh Hamedi, Fatemeh Tootooni, Behzad Amini, Behrang Sharifi, Mehrdad Faizi, *et al*. Synthesis and pharmacological evaluation of new 2-substituted-5-{2-[(2- halobenzyl)thio)phenyl}- 1,3,4-oxadiazoles as anticonvulsant agents. Sci Pharm. 2008; 76(23)00:185-201.
42. El-Hamouly WS, Amin KM, El-Assaly SA, Eman A, El-Meguid A. Synthesis and antitumor activity of some new 1,3,4-oxadiazole, pyrazole and pyrazolo[3,4-d]pyrimidine derivatives attached to 4-benzothiazol-2-yl phenyl moiety. Der Pharma Chemica. 2011; 3(6):282-292.
43. Salahuddin, Shaharyar M, Mazumder A, Ahsan MJ. Synthesis, characterization and anticancer evaluation of 2- (naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1- [5- (substituted phenyl)-[1,3,4] oxadiazol-2-ylmethyl]- 1Hbenzimidazole. Arabian J Chem. 2014; 7(2):418-424.
44. Ahmed S Aboraia, Hamdy M Abdel-Rahman, Nadia M Mahfouz, Mahmoud A EL-Gendy. Novel 5-(2-hydroxyphenyl)-3-substituted-2,3- dihydro-1,3,4-oxadiazole-2-thione derivatives: Promising anticancer agents. Bio org & Med Chem. 2006; 14(8):1236-1246.
45. Linhong Jin, Jiang Chen, Baoan Song, Zhuo Chen, Song Yang, Qianzhu Li, *et al*. Synthesis, structure, and bioactivity of Nitro-substituted benzylidene- 3,4,5-trimethoxybenzohydrazide and 3-acetyl-2- substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives. Bio org & Med Chem Let. 2006; 16(2):5036-5040.
46. Qing-Zhong Zheng, Xiao-Min Zhang, Ying Xu, Kui Cheng, Qing-Cai Jiao, Hai-Liang Zhu. Synthesis, biological evaluation, and molecular docking studies of 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety as potential antitumor agents. Bio org & Med Chem. 2010; 18(6):7836-7841.
47. Rajyalakshmi Gudipati, Rama Narsimha Reddy Anreddy, Narsimha Reddy Yellu, Sarangapani Manda. Synthesis, characterization and anticancer activity of certain 3-{4-(5- mercapto-1,3,4- oxadiazole-2-yl)phenylimino}indolin–2–one derivatives. Saudi Pharma J. 2011; 11(3):1319-1420.
48. Alex S Kiselyov, Marina N Semenova, Natalya B Chernyshova, Andrei Leitao, Alexandr V Samet, Konstantine A Kislyi, *et al*. Novel derivatives of 1,3,4-oxadiazoles are potent mitostatic agents featuring strong microtubule depolymerizing activity in the sea urchin embryo and cell culture assays. Euro J Med Chem. 2010; 45(5);1683-1697.
49. Afshin Zarghi, Sayyed A. Tabatabai, Mehrdad Faizi, Avideh Ahadian, Parisa Navabi, Vahideh Zanganehb and Abbas Shafieec. Synthesis and anticonvulsant activity of new 2-substituted-5-(2- benzyloxyphenyl)-1,3,4-oxadiazoles. Bio org & Med Chem Let. 2005; 15(2):1863-1865.
50. Morihisa Saitoh, Jun Kunitomo, Eiji Kimura, Yoji

Hayase, Hiromi Kobayashi, Noriko Uchiyama, Tomohiro Kawamoto, *et al*. Textor, Gyorgy P Snell, Fumio Itoh. Design, synthesis and structure–activity relationships of 1,3,4-oxadiazole derivatives as novel inhibitors of glycogen synthase kinase. Bio org & Med Chem. 2009; 17(9):2017-2029.

51. Hiroyuki Watanabe, Masahiro Ono, Ryoichi Ikeoka, Mamoru Haratake, Hideo Saji, Morio Nakayama. Synthesis and biological evaluation of radioiodinated 2,5-diphenyl-1,3,4-oxadiazoles for detecting b-amyloid plaques in the brain. Bio org & Med Chem. 2009; 17(11):6402-6406.
52. Mazouzl F, Lebretonl L, Milcentl R, Bursteid C. 5Aryl-1,3,4-oxadiazoL2(3H)-one derivatives and sulfur analogues as new selective and competitive monoamine oxidase type B inhibitors. Euro J Med Chem. 1999; 25(6):659-671.
53. Shaoyong Ke, Zhong Li, Xuhong Qian. 1,3,4-Oxadiazole-3(2H)-carboxamide derivatives as potential novel class of monoamine oxidase (MAO) inhibitors: synthesis, evaluation, and role of urea moiety. Bio org & Med Chem. 2008; 16(7):7565-7572.
54. Ramya V Shingalapur, Kallappa M Hosamani, Rangappa S Keri, Mallinath H Hugar. Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Euro J Med Chem. 2010; 45(10):1753-1759.
55. Khalid M Khan, Naheed Fatima, Maimona Rasheed, Saima Jalil, Nida Ambreen, Shahnaz Perveen, M Iqbal Choudhary. 1,3,4-Oxadiazole- 2(3H)-thione and its analogues: a new class of non-competitive nucleotide pyrophosphatases/phosphodiesterases 1 inhibitors. Bio organic & Med Chem. 2009; 17(9):7816-7822.
56. Mahmud Tareq Hassan Khan, Muhammad Iqbal Choudhary, Khalid Mohammed Khan, Mubeen Ranib and Atta-ur-Rahmanb. Structure–activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4- oxadiazole analogues. Bio org & Med Chem. 2005; 13(5):3385-3395.
57. Usman Ghani, Nisar Ullah. New potent inhibitors of tyrosinase: novel clues to binding of 1,3,4- thiadiazole-2(3H)-thiones, 1,3,4-oxadiazole- 2(3H)-thiones,4-amino-1,2,4-triazole-5(4H)- thiones, and substituted hydrazides to the dicopper active site. Bio org & Med Chem. 2010; 18(9):4042-4048.