INTERNATIONAL JOURNAL OF ADVANCED BIOLOGICAL RESEARCH

www.scienceandnature.org

Review Article

BIOLOGICAL IMPORTANCE OF 1, 3, 4-OXADIAZOLE DERIVATIVES

[a]Rakesh Singh & [b]Anuja Chauhan
[a]Department of chemistry Govt Degree College for women Kathua, 184101
[b]Department of Chemistry Arni University Indora (Kathgarh) Himachal Pardesh

ABSTRACT
Heterocyclic compounds possess wide range of biological properties. One of these compounds is Oxadiazole. 1,3,4-Oxadiazole is highly privileged structure. Its derivatives exhibit wide range of biological activities which include antibacterial, antitubercular, antifungal, analgesic, anti-inflammatory, vasodilatory, hypolipidemic, cytotoxic, ulcerogenic and anticancer activities. This review attempts to summarize basic information about 1, 3, 4-oxadizole and its biological activity for further development in the field.

KEY WORDS: 1, 3,4-Oxadiazole, Anti-inflammatory activity, Antitubercular activity ,Analgesic activity ,Anticonvulsant Activity ,Antimicrobial Activity, Anticancer Activity.

INTRODUCTION

Oxadiazole is a five membered heterocyclic aromatic compound having molecular formula $C_2H_2ON_2$. Out of its four possible isomers, 1,3,4-oxadiazole is widely being exploited for various biological applications. Literature survey reveals that 1,3,4-oxadiazole is a highly privileged structure. Its 2,5-disubstituted derivatives

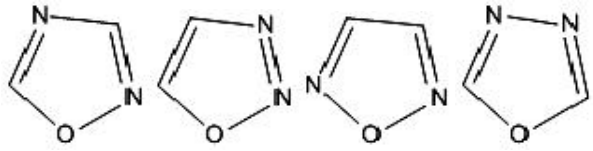


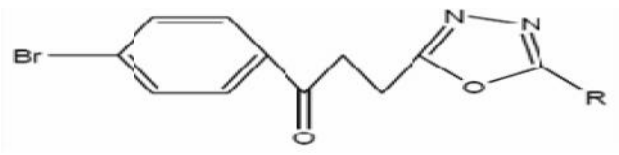
exhibit diverse biological activities[1] like antibacterial[2], antitubercular[3], vasodialatory[4], antifungal[5], anti-inflammatory[6], anticonvulsant[7], cytotoxic[8], anaesthetic[9], analgesic[10],hypolipidemic[11], anticancer[12] and ulcerogenic[13] activities. Moreover 1,3,4-oxadiazole is widely being exploited for its various applications. A number of therapeutic agents such as HIV – integrase inhibitor raltegravir, antibacterial furamizole, a potent PDF inhibitor BB-83698, and nesapidil are based on 1,3,4-oxadiazole moity[14]. Oxadiazole derivatives have been found to possess broad-spectrum antimicrobial activity and useful sub structures for further molecular exploration[15].

BIOLOGICAL IMPORTANCE

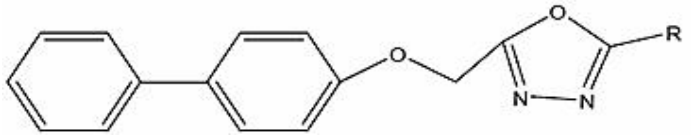
Anti-inflammatory activity

Nonsteroidal anti-inflammatory drugs are widely used in treatment of inflammation and painful conditions including rheumatic arthritis, osteoarthritis *etc*.

a. Asif Husain *et al*., 2009 synthesized a novel series of 2-[3-(4-bromophenyl)propan-3-one]-5(substituted phenyl)-1,3,4-oxadiazoles from 3-(4-bromobenzoyl) propionic acid with the aim to get better anti-inflammatory and analgesic drugs with minimum side effects (ulcerogenicity). Two compounds, 2-[3-(4-bromophenyl)- propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole and 2-[3-(4-bromophenyl) propan-3-one]-5-(3,4-dimethoxy phenyl)-1,3,4-oxadiazole with anti-inflammatory activity of 59.5 and 61.9 %, respectively, were found to have comparable activity with that of indomethacin which showed 64.3 % activity at the same dose[16].

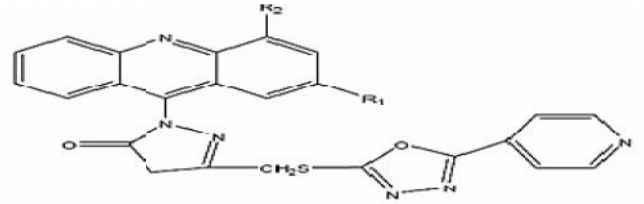


b. Kumar Harish *et al*., 2008 synthesized another series of 1,3,4-oxadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid & screened them for their potent anti-inflammatory activity by using carrageenan induced rat paw edema method. The compounds were found to possess much more anti-inflammatory activity (81.81%) than the reference drug flurbiprofen (79.54%)[17]. More it was found to possess low ulcerogenic effect.

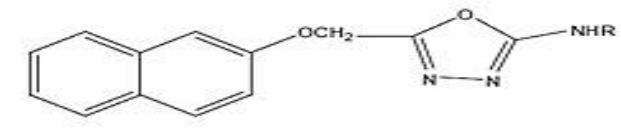


c. Akhtermymoona*et al*., 2009 reported synthesis of 2, 5-disubstituted – 1,3,4-oxadiazole derivatives based on Aroylpropionicacid. These synthesized compounds were studied for their anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation. Some of synthesized compounds showed anti-inflammatory activity 81.46% and 812.48% respectively against standard drug ibruprofen[18].

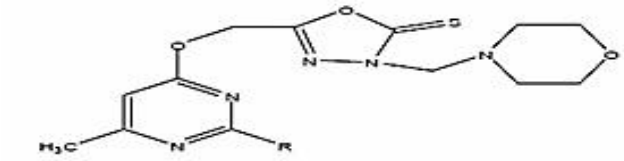
d. Trilok Chandra *et al.,* 2010 synthesized a series of oxadiazole derivatives. These compounds were screened for their anti-inflammatory and analgesic activity. These compounds were found to possess anti-inflammatory activity ranging from 10.8 to 40.8% at a dose of 50mg/kg i.p.[19].In addition these compounds also exhibited analgesic activity.



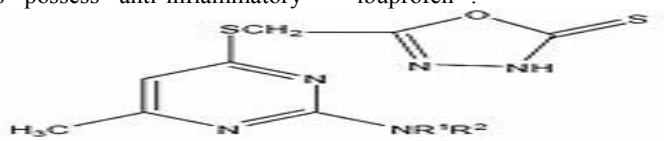
f. Erhan Palaska *et al*., 2002 synthesized a series of 1-(2-nephthyloxyacetyl)-4-substituted-3-thiosemicarbazide, 2-(2-naphthyloxymethyl)-5-substitutedamino-1,3,4-oxadiazole, 2- (2-naphthyloxymethyl)-5-substitutedamino-1,3,4-thiadiazole and 5-(2-naphthyloxymethyl)-4-substituted-1,2,4-triazole-3-thione derivatives and evaluated them for their anti-inflammatory activity with reduced side effects[20].



g. Viriginija Jakubkiene *et al*., 2010 synthesized 5-(6-methyl – 2 –substituted – 4-pyrimidinyloxymethyl)-2, 3-dihydro-1,3,4-oxadiazole-2-thiones and screened them for their anti-inflammatory activity. Most of tested compounds exhibited anti-inflammatory activity with some showing even more activity than acetylsalicylic acid[21].

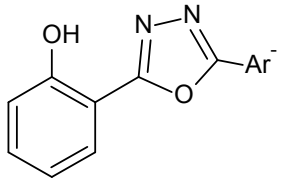


h. Milda Malvina Burbuliene *et al.,* 2004 synthesised a series of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones and their *S*-alkyl-, *N*3-acyl- and *N*3-aminomethyl derivatives. All the tested compounds possess anti-inflammatory activity comparable to that of acetylsalicylic acid and some derivatives of 5-[(6-methyl-2-piperidin-1-yl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1, 3, 4- oxadiazole-2-thione were found to be much more active than ibuprofen[22].

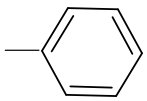


Antitubercular activity

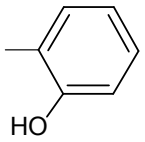
Tuberculosis is a chronic disease and is major health problem in developing countries. It is caused by various strains of mycobacteria usually mycobacterium tuberculosis. Tuberculosis usually affects the lungs but can also affect other parts of body.

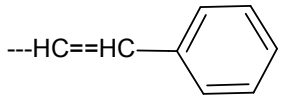


(1a) (1b)



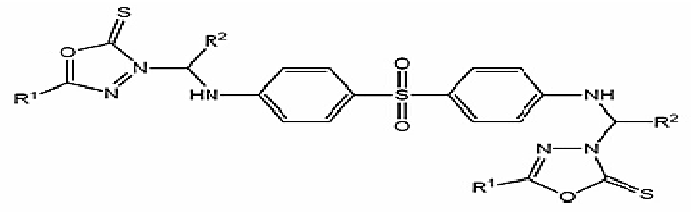
(1c)



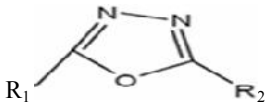


b. Mohamed Ashraf *et al*., 2007 have synthesized a series of oxadiazolemannich base derivatives, by condensation of synthesized oxadiazole with dapsone and appropriate aromatic aldehyde i.p.o methanol. The synthesized compounds were tested for their antimycobacterial activity. They reported that eleven compounds exhibited excellent antimycobectrial activity.

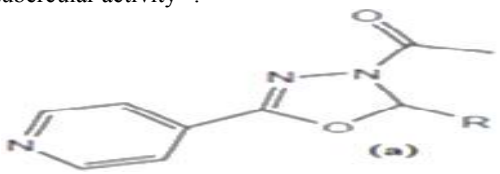
Among various compounds synthesized 3-{ -furyl-[4-(4-{-2-furyl[5-(2-nephthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4- oxadiazole-3yl] methylamino} phenylsulfonyl) aniline] methyl}-5-(2- nephthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione was found to be most potent compound against both *M. tuberculosis* H37Rv and INH resistant tuberculosis[24].



c. Dewangan Dhansay *et al*., 2010 reported in vitro antitubercular activity of series of 2, 5-disubstituted-1,3,4-oxadiazole derivatives. These compounds exhibited better activity against a strain of mycobacterium tuberculosis H37Rv[25].



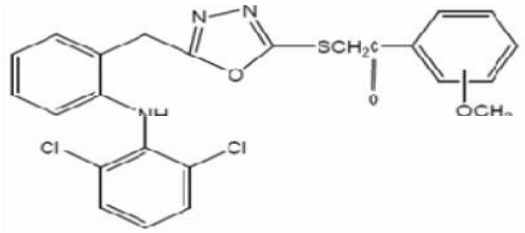
d. Yar Shaharm, *et al*., 2007synthesized a series of 2,5-disubstituted 1,3,4-oxadiazoles and reported their good antitubercular activity[26].



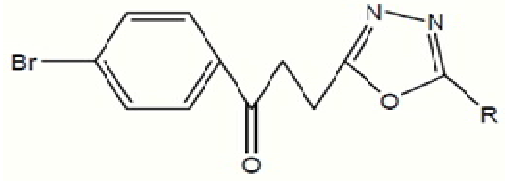
Analgesic activity

Analgesic is any member of group of drugs which relieves body from pain. These include paracetamol, aspirin, morphine, opium etc. The Choice of analgesic is determined from type of pain.

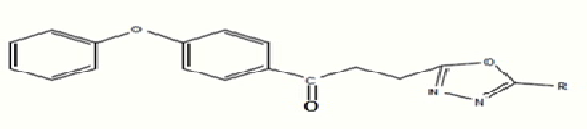
a. Shashikant, V., Bhandari *et al*., 2008 synthesized a series of S-substituted phenacryl -1,3,4-oxadiazole and schiffs bases derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid) Out of 18 compounds synthesized, eight were found to possess significant analgesic activity in acetic acid induced writhing tests with no ulcerogenic activity. *e.g*. following compounds have most prominent analgesic activity[27].



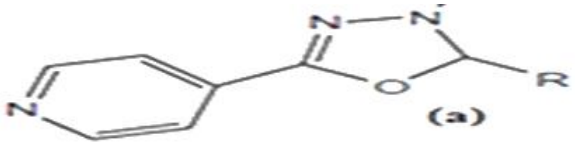
b. Hussain Asif *et al.,* 2008 reported synthesis of some 2-[3-(4-bromo phenyl) propane-3-ones]-5-(substituted phenyl)-1,3,4-oxadiazoles with analgesic activity[28].



c. Husain *et al*., 2009 synthesized aeries of novel 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl] propane-1—ones and screened for analgesic activity. The 2-acetoxy phenyl derivatives of this series have shown 76% analgesic activity which is higher than standard drug indomethacin[29].



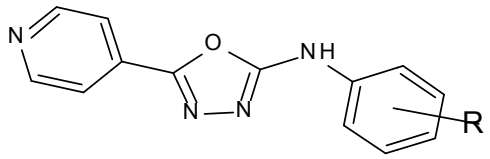
d. Dewangon Dhansay *et al.,* 2010 reported synthesis of some novel 2,5-disubstituted-1,3,4-oxadiazoles (a)and their synthetic analogs and confirmed their analgesic activity by using acetic acid induced writhing method as compared to standard drug diclofenac. Potent analgesic activity have been found in bis (heterocycle) substituted-1,3,4-oxadizole[30].



Anticonvulsant Activity

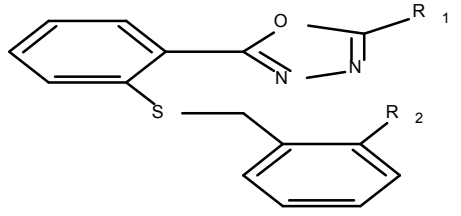
Anticonvulsants are those drugs which selectively depress the central nervous system. These drugs are used in the prevention and control of epileptic seizers.

a. YarShahar Mohammad *et al*., 2007 synthesized a series of 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-thiadiazoles and 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-oxadiazoles. All the compounds showed activity in the range of 33-99% in comparison to phenytoin which completely inhibited the convulsions. Compound (a) showed maximum activity and compound (b) [p-chloro substituted] showed good activity[31].

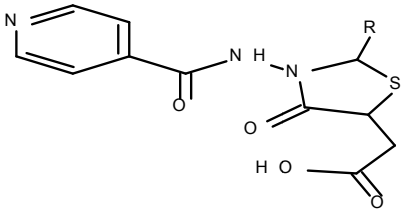


(a) R = H and (b) R = p-Cl

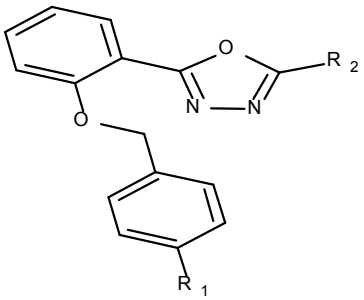
b.Zarghi Afshin *et al*., 2005 synthesizeda new series of 2-substituted-5-{2-[(2-halobenzyl)thio)phenyl}-1,3,4-oxadiazoles and investigated for anticonvulsant activities. Maximal Electroshock and pentylenetetrazole- induced lethal convulsion tests showed that some of the synthesized compounds had significant anticonvulsant activity[32].



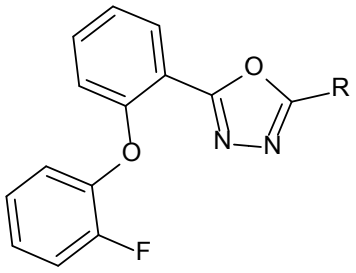
c Sadaf Jamal Gilanil *et al.,* 2009 synthesized a series of Isoninicotinic acid hydrazide (INH) incorporated derivatives of thiazolidin-4-one azetidin-2-one and 1,3,4-oxadiazole. The anticonvulsant activity of all the synthesized compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. All the compounds were active in MES and a majority of compounds were active inscPTZ test. All compounds were less neurotoxin than the standard drug phenytoin[33].



d. Zarghi Afshin *et al.,*2008 synthesized a series of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles and evaluated as anticonvulsant agents.. Some Compounds showed considerable anticonvulsant activity both in PTZ and MES models[34].



e. Almasirad *et al.,* 2004 synthesized a series of 2-substituted-5-[-2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles and found to possess considerable anticonvulsant activity in PTZ and MES models[35]

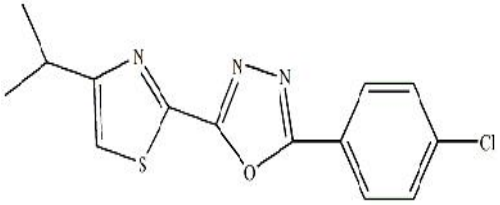


Antimicrobial Activity

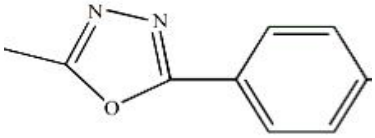
Antimicrobials kill or inhibit the growth of microorganisms such as bacteria, fungi and protozoan's. Antimicrobial drugs are selective and kill microbes (microbiocidal) or prevent their growth (microbiostatic). The 1,3,4- oxadiazole derivatives have shown significant antimicrobial activity against wide range of microorganisms like fungi, gram +ve and gram –ve bacteria.

a. Kumar *et al.,* 2010 synthesised some novel 2-substituted-5-[isopropylthiazole]clubbed1,3,4-Oxadiazoles

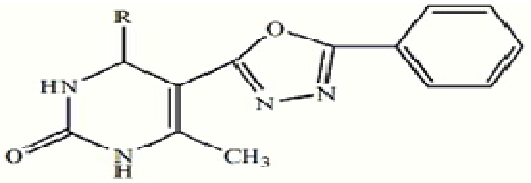
(Compound a and b) and tested for antimicrobial activity by brothmicrodilution method. Among the various synthesized compounds (a) showed improved antibacterial activity against Gram-positive bacteria i.e*Staphylococcus aureus*, *Staphylococcus faecalis, Bacillus subtillis* and compound (b) having *p*-methoxy substitution showed



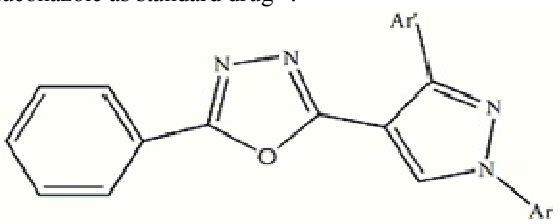
b. Patel Navin *et al*., 2010 synthesized a series 3-(1,3,4-oxdiazole-2-yl) quinoazoline-4-(3H)-ones and tested there in vitro antimicrobial activity. The antimicrobial activity was examined against gram +ve bacteria *S. aureus* and gram –ve bacteria *A. niger* using the broth micro-dilution method.[37]



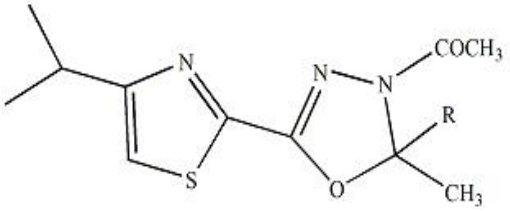
c. Mishra *et al.,* 2010synthesized a series of Oxadiazoles and then final compounds were tested for their antimicrobial activity by cup and plate method. Among the tested compound (a) showed promising antibacterial activity against Gram +ve bacteria *i.e Streptococcus pneumonia* and compound (b) showed promising antibacterial activity against Gram –ve bacteria i.e*Escherichia coli* as compared to standard drugs Ofloxacin and Levofloxacin[38].



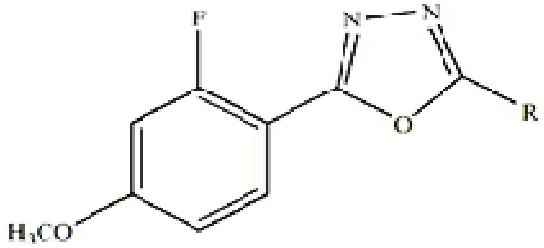
d.Prakash *et al*., 2010 synthesized a series of novel unsymmetrical 2, 5-disubstituted 1, 3, 4-Oxadiazoles and then the final compounds were tested for their antibacterial and antifungal activities. Among the tested compounds, compound a, b showed maximum antibacterial activity against *Staphylococcus aureus* and was compared with ciprofloxacin as standard drug. Compound c, d showed maximum inhibition against both of the fungi *Aspergillus niger* and *Aspergillus flavus* and was compared with Fluconazole as standard drug[39].



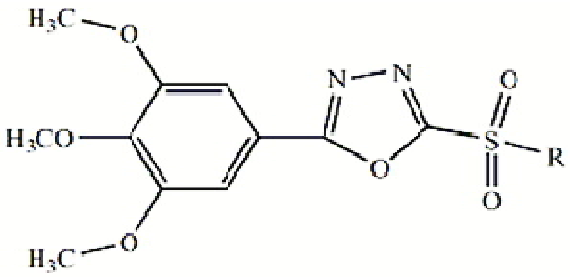
excellent antifungal activity against *Saccharomyces cerevisiae*, *Candida tropicalis*, *Aspergillus niger*. Compound (c) exhibited good inhibition against Gram-positive bacteria. These tested compounds were compared with standard drugs i.e. Ciprofloxacin, Norfloxacin, Flucanozole[36]



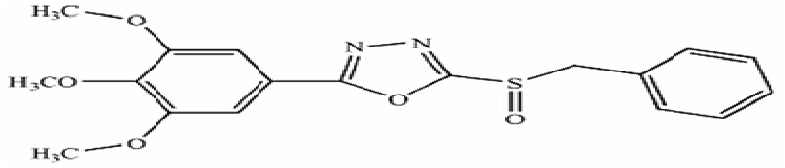
e. Chandrakantha *et al.,* 2010 synthesized some novel 2-flouro-4-methoxyphenyl substituted 1,3,4-Oxadiazole derivatives and screened them for antimicrobial activity by serial dilution method. Among the various synthesized compounds, (a), (b) showed excellent antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* and (c), (d) showed excellent antifungal activity against *Candida albicans.* Compounds tested for antibacterial activity was compared with standard drug Furacin and for antifungal activity standard drug was Flucanazol[40].



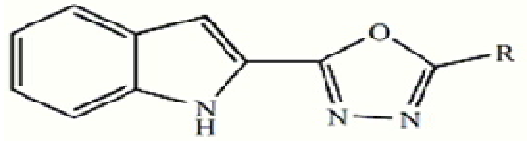
f. Chen *et al*., 2007 synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives and tested for their antifungal activity against *Gibberellazeae, Botrytis cinerea, Sclerotinia sclerotiorum*. Among the tested compounds 15a and 15b exhibiting promising antifungal activities even better than that of the commercial fungicide Hymexazol[41]



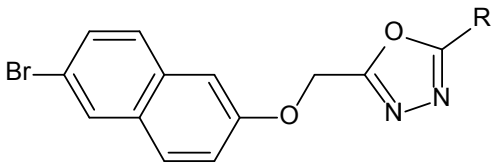
g. Liu *et al*., 2008 synthesized sulfoxide derivatives containing tri-methoxyphenyl substituted 1,3,4-Oxadiazole moiety and tested for their antifungal activity Among the tested compounds, compound (a) was found to be more active against *Gibberellazeae*, *F. oxysporum* and *C. mandshurica* than other ones. Hymexazol was used as standard drug[42].



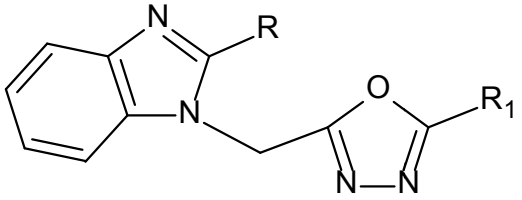
h. Bhardwaj *et al*., 2009 synthesized 1,3,4-Oxadiazoles and tested for their antimicrobial activity on different strains. A total of four compounds were synthesized, out of those only three found to be active against bacterial strains *i.e Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa* and none of the compound were found to be effective against fungal strains. Standard Drug used wereNorfloxacin and Fluconazole[43].



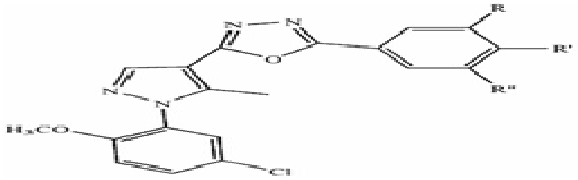
i.Anil N. Mayekar *et al*., 2010synthesized a series of new 1,3,4-oxadiazole derivatives having 6-bromonaphthalene moiety.A series of. 2-{[(6-bromo-2-naphthyl) oxy]methyl} -5-aryl-1,3,4-oxadiazoles and 2-{[(6-bromo-2naphthyl) oxy] methyl} -5-[(alkyl/aryl) thio]-1,3,4-oxadiazoles were synthesized. The newly synthesized compounds were characterized by analytical and spectral data. Antimicrobial activities of these compounds were carried out and some of them have exhibited good antimicrobial activity[44].



j K.F. Ansari *et al*., 2009 synthesized 2-substituted-1-[{(5- Substituted alkyl/aryl)-1,3,4-oxadiazol-2-yl} methyl]-1H-benzimidazole. The structures of the synthesized compounds were evaluated by spectral and elemental methods of analyses. All the synthesized compounds were screened for their antimicrobial activities. All of the derivatives showed good activity towards Gram-positive bacteria and negligible activity towards Gram-negative bacteria. Some of the synthesized compounds showed moderate activity against tested fungi[45].



k Rai*et al*., 2009 synthesized 2-[1-(5-chloro-2-methoxyphenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substituted phenyl)- [1,3,4-oxadiazoles] and tested for their antibacterial activity.From the tested compounds, compound (a) which is unsubstituted showed significant activity against *Bacillus subtilis* and moderate activity against *Escherichia coli, Staphylococcus aureus Klebsiella pneumonia*. Flourine incorporated in phenyl ring (b,c) of 1,3,4-oxadiazole showed improved activity against both Gram +ve bacteria *i.e Bacillus subtilis, Staphylococcus aureus* and Gram – ve bacteria *i.e* against *Escherichia coli, Klebsiella pneumonia*. These compounds were compared with Ampicillin as standard drug[46]

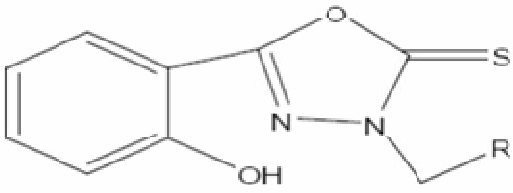


a: R = R' = R"= H, b: R = R" = H , R' = F, c: R = F , R' = R" = H

Antitumor/Anticancer Activity

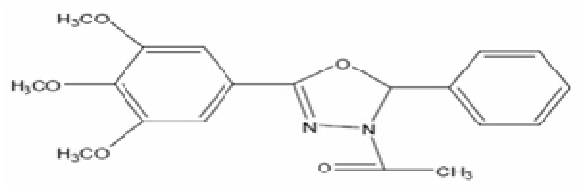
Tumors occur when cells division becomes uncontrolled in the body. Typically, cell division is strictly controlled. New cells are created to replace older ones or to perform new functions. Cells that are damaged or nolonger needed die to make room for healthy replacements. If this balance is disturbed, a tumour may form. Problems with the body's immune system can lead to tumours. Treatment varies based on: the type of tumour, whether it is noncancerous or cancerous, and its location.A variety of antitumoral drugs are currently in clinical use. The search for antitumoral drugs led to the discovery of several 1,3,4-oxadiazol derivatives having antitumoral activity

a Ahmed S. Aboraia *et al.,* 2006 synthesized series of 5-(2-hydroxyphenyl) -3-substituted-2,3- dihydro-1,3,4-oxadiazole-2-thione derivatives and evaluated for their in vitro anticancer activity. These compounds have been selected for a full anticancer screening against a 60-cell panel assay where they showed non-selective broad spectrum and promising activity against all cancer cell lines. The active members in this study compared to 5- fluorouracil and cyclophosphamide as reference drugs, respectively[47].

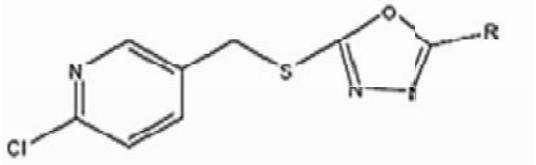


b Linhong Jin *et al*., 2006 synthesised some3-acetyl-2-substituted-phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazolederivatives and studied their antiproliferative activities against some cancer cells in vitro by MTT method. Among them, 2a, 2b, 2c, 2f, 3l, and

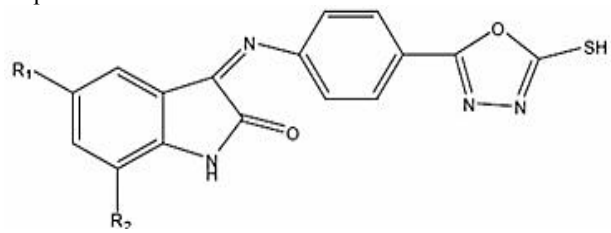
3m were highly effective against PC3 cells and 2a, 2c, and 2fshowed moderate activities against Bcap37 andBGC823 cells. The IC50 values of high active compounds 2a, 2b, 2c, 2f, 3l, and 3m against PC3 cells were 0.2, 1.8, 0.2, 1.2, 1.7, and 0.3 lM, respectively[48].



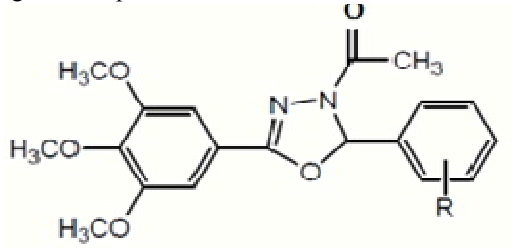
c. Qing-Zhong Zheng *et al.,* 2010 synthesized a series of new 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety . Antiproliferative assay results indicated that compounds exhibited the most potent activity against gastric cancer cell SGC-7901, which was more potent than the positive control ethidium bromide[49].



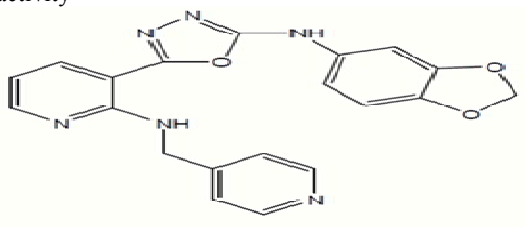
d. Rajyalakshmi Gudipati *et al*., 2011 synthesised a series of 5-or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin–2–one derivatives by treating 5-(4- aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives.. All the synthesized derivatives were screened for anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependant inhibition of growth of the cells. The IC50 values of all the synthetic test compounds were found between 10.64 and 33.62_M. The potency (IC50 values) of anticancer activity of compounds was comparable with that of known anticancer agent, Cisplatin[50].



e.Baoan Song*et al.,* 2006 synthesized some 3-acetyl-2-substituted phenyl-5-(3,4,5trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives. Most of the synthesized compounds were found highly active against PC3 cancercells and some were found moderately active against Bcap37 and BGC823 cells[51].



f. Xiaohu Ouyang *et al.,* 2006 synthesized some oxadiazoles derivatives and evaluated them for their ability to inhibit tubulin polymerization and to arrest mitotic division of tumour cells. Among the synthesized compounds, compound (a) showed potent activity[52]



Compound (a)

REFERENCES

[1]. Asif Hussain, Mohammed Ajmal (2009) Synthesis of novel 1,3,4- oxadiazoles derivatives and their biological properties. Acta Pharm. 59: 223-233.

[2]. Adnan A. Kadi, Nasser R. El-Brollosy, Omar A. Al-Deeb, Elsayed E. Habib, Tarek M. Ibrahim, Ali A. El-Emam (2007) 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, *European Journal of Medicinal Chemistry*, *Volume 42, Issue 2,Pages 235-242*

[3]. Kumar,G.V.S.,Rajendraprasad,Y.,Mallikarjuna,B.P.,Chandrashekar,S.M.,Kistayya,C. (2010) Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents*Eur. J. Med. Chem.*, 45: 2063-2074.

[4]. Girish R. Bankar ,Gopalan Kutty Nampurath, Pawan G. Nayak, Shoumyo Bhattacharya (2010)A possible correlation between the correction of endothelial dysfunction and normalization of high blood pressure levels by 1,3,4-oxadiazole derivative. *Chemico-Biological Interactions*, *Volume 183, Issue 2*, *27 Pages 327-331*

[5]. Parkash,O., Kumar, M., Sharma, C., Aneja, K.R. (2010) Hypervalent iodine(III) mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles as antibacterial and antifungal agents*Eur. J. Med. Chem.*, 2010 Sep; 45(9):4252-7. doi: 10.1016/j.ejmech.2010.06.023.

[6]. Milda Malvina Burbuliene, Virginija Jakubkiene, Giedrute Mekuskiene, Emilija Udrenaite, Romualdas Smicius, PovilasVainilavicius (2004) Synthesis and anti-infammatory activity of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidine)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones.IL Farmaco 59:767-774.

[7]. Yar Shahar mohammad, Akhter Wasim Mohd. (2007) Acta Poloniae Pharmaceutica Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives Vol. 66 No. 4, 393-397.

[8]. Padmavathi,V., Reddy, G. S., Padmaja, A., Kondaiah, P., Ali-Shazia (2009) Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles*Eur. J. Med. Chem.*, 2009, 44, 2106-2112.

[9]. Harish Kumar, Sadique A. Javed , Suroor A. Khan , MohammadAmir (2008) 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid . Synthesis and preliminary evaluation of biological properties. European Journal of Medicinal Chemistry 43(12): 2688-2698.

[10]. Akhter, M. Husain, A., Azad, B., Ajmal, M. (2009) Aroylpropionic acid based 2,5-disubstituted-1,3,4-oxadiazoles: Synthesis and their anti-inflammatory and analgesic activities*Eur. J. Med. Chem.*, 44: 2372-2378.

[11]. Idrees, G.A., Aly, O.M., Abuo-Rahma, Gel-D, Radwan, M.F. (2009) Design, synthesis and hypolipidemic activity of novel 2-(naphthalen-2-yloxy)propionic acid derivatives as desmethyl fibrate analogs. *Eur. J. Med. Chem*. 44:3973-3980.

[12]. Kumar, D. Sundaree, S., Johnson, E.O., Shah, K. (2009) An efficient synthesis and biological study of novel indolyl-1,3,4-oxdiazoles as potent anticancer agents, *Bioorg. Med. Chem. Lett.*, , 19, 4492-4494.

[13]. Shashikant V. Bhandari, Kailash G Bothara, Mayuresh K Raut, Ajit A Patil, Aniket P Sarkate, Vinod J Mokale (2008) Design, Synthesis and Evaluation of Anti-inflammatory, Analgesic and Ulcerogenicity studies of Novel S-Substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of Diclofenac acid as Nonulcerogenic Derivatives *Bioorg. Med. Chem. Lett.*, , 16, 1822-1831

[14]. Nagaraj, Chaluvaraju, K.C., Niranjan Kiran S. (2011) 1,3,4-oxadiazole, a potent drug candidate with various pharmacological activities. *Int J Pharm Sci*., 3(3):9-16.

[15]. Bhatia Shivi, Gupta Monika (2011) 1,3,4-oxdiazole as antimicrobial agents. An Overview. *J.Chem Pharm. Res.,*3(3); 137-147.

[16]. Asif Husain, Mohammed Ajmal (2009) Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. Acta Pharm. 59, 223-233.

[17]. Kumar Harish, Javed A. sadique, Khan A. Suroor (2008) 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid; Synthesis and preliminary evaluation of biological properties. European journal of Medicinal Chemistry 2688-2698.

[18]. Akhtermymoona, Husain Asif, Azad Bismillah, (2009) Aroylpropionic acid based 2,5-disubstituted-1,3,4-oxadiazole: Synthesis and their anti-inflammatory and analgesic activities. *European Journal of Medicinal Chemistry,* 44, 2372-2378.

[19]. Trilok Chandra, Neha Garg, Suman Lata, K.K. Saxsena, Ashok Kumar (2010) Synthesis of substituted acridinylpyrazoline derivatives and their evaluation for anti-inflammatory activity.European Journal of Medicinal Chemistry. 1772-1776.

[20]. Erhan Palaska ,Gulay Sahin, Pelin Kelicen, N. Tug ba Durlu, Gulcin Altinok (2002) Synthesis and anti-inflammatory activity of 1- acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4- thiadiazoles and 1,2,4-triazole-3-thiones. IL Farmaco ; 57,101 107.

[21]. Virginija Jakubkiene , Milda Malvina Burbuliene , Giedrute Mekuskiene, Emilija Udrenaite , Povilas Gaidelis, Povilas Vainilavicius (2010) Synthesis and anti-inflammatory activity of 5 -(6-methyl-2 – substituted4-pyrimidinyloxymethyl)-1,3,4-oxadiazole-2- thiones and their 3 -morpholinomethyl derivatives. Il Farmaco; 45, 1683 1697.58,323-328.

[22]. Milda Malvina Burbuliene, Virginija Jakubkiene, Giedrute Mekuskiene, Emilija Udrenaite, Romualdas Smicius, PovilasVainilavicius (2004) Synthesis and anti-inflammatory activity of derivatives of 5-[(2-disubstitutedamino-6-methylpyrimidin-4-yl)-sulfanyl methyl] -3 H-1,3,4- oxadiazole-2-thiones. IL Farmaco ; 59, 767 774.

[23]. Pallon, R. Shashikant, Rabara, P. A., pattan, S. jayashri (2009) Synthesis and evaluation of some novel substituted 1,3,4-oxadiazole derivatives for their anti-tubercular activity. Indian journal of chemistry vol 48B: 1453-1456.

[24]. Mohamed Ashraf Ali, Mohammad Shaharyr, Oxadiazole Mannich bases (2007) Synthesis and antimycobacterial activity. Bioorganic and Medicinal Chemistry Letters, 17 ; 3314-3316.

[25]. Dewangan Dhansay, Pandey Alok (2010) Synthesis of some Novel 2,5-disubstituted-1,3,4-oxadiazole and its analgesic, anti-inflammatory, antibacterial and anti-tubercular activity, International journal of chemistry vol.2; 1397-1412.

[26]. Yarshahar M, siddiqui ahmed A, aliashraf M. (2007) "Synthesis and Anti-Tuberculostatic activity of Novel 1,3,4-Oxadiazole Derivatives."*Journal of the Chinese Chemical Society*, vol.54,5-8.

[27]. Shashkant, V. Bhandari, Kailash G. Bothara, Mayuresh, K. Raut, Ajit, A. Patil, Ankit P. Sarkate and vinod J. Mokale (2008) Bioorganic and Medicinal Chemistry, 16, 1822-1831.

[28]. Husain Asif, Ajmal Mohammed, *Acta Pharm.* 59 (2009), Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties ,223-233.

[29]. Husain, A. Ahmed, F. J. Ajmal, and M Ahuja, P. (2008) Synthesis of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl] propane-1—ones as safer anti-inflammatory and analgesic agents, J. Serb. Chem. Soc. 73, 781-791.

[30]. Dewangan Dhansay, Pandey Alok (2010) *International journal of chemistry*, Synthesis of some Novel 2, 5- Disubstituted 1, 3, 4-Oxadiazole and its Analgesic, Anti-Inflammatory, Anti-Bacterial and Anti-Tubercular Activity.vol.2, page no.1397-1412.

[31]. Yar Shahar mohammad, Akhter Wasim Mohd. (2007) Acta Poloniae Pharmaceutica Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives Vol. 66 No. 4, 393-397.

[32]. Zarghi Afshin, Hamedi Samaneh, Tootoonifatemeh (2008) "Synthesis and Pharmacological Evaluation of New 2-Substituted-5-{2-[(2- halobenzyl) thio) phenyl}- 1,3,4-oxadiazoles as Anticonvulsant Agents.", 185-201.

[33]. Sadaf Jamal Gilani1, Ozair Alam1, Suroor Ahmad Khan, Nadeem Siddiqui, Harish Kumar. (2009) Synthesis of some derived thiazolidin-4-one, azetidin-2-one and 1,3,4-oxadiazole ring systems from Isoninicotinic acid hydrazide: A novel class of potential anticonvulsant agents. Der PharmaciaLetter, , 1 (2) 1-8.

[34]. Zarghi, A., Tabatabai, S.A., faizi, ahadian A. (2005) synthesis and anticonvulsant activity of new 2-substituted benzyloxyphenyl -1,3,4-oxadiazoles, *bioorglett*. 15: 1863-1865.

[35]. Almasirad, A., Tabatabai, S. A., faizi, M. (2004) synthesis & anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy) phenyl]-1,3,4-oxadiazole & 1,2,4-triazoles, *Bioorg med. Chem. Lett.* 14 : 6057-6059.

[36]. G. V. S. Kumar; Y. Rajendraprasad; B. P. Mallikarjuna; S.M. Chandrashekar; C. Kistayya. (2010) Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercularagents.*Eur. J. Med. Chem.*, 45, 2063-2074.

[37]. Patel Navin B., Patel Jaymin C. (2010) Synthesis and Antimicrobial Activity of 3-(1,3,4-Oxadiazol-2-yl)quinazolin-4(3H)-ones., 173-193.

[38]. . Mishra, M.K., Gupta, A.K., Negi, S., Bhatt M. (2010) Antibacterial activity of synthesized 6 – Methyl – 4 – aryl – 5 - (5- phenyl -1, 3, 4 – oxadiazol -2- yl) -1, 2, 3, 4-tetrahydropyrimidine-2(1*H*)-one*Int. J. Pharma Sciences and Reserch*,1(3), 172-177.

[39]. O. Parkash, M. Kumar, C. Sharma, K.R. Aneja. (2010) Hypervalentiodine (III) mediated synthesis of novel unsymmetrical 2, 5-disubstituted 1,3,4-oxadiazoles as antibacterial and antifungal agents. *Eur. J. Med. Chem.*,Volume 45, Issue 9, Pages 4252–4257

[40]. B. Chandrakantha, P. Shetty; V. Nambiyar; N. Isloor; A.M. (2010) Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety European Journal of Medicinal Chemistry Volume: 45 Issue: 3 Pages: 1206-1210 .*Eur. J. Med. Chem.*, 45, 1206-1210.

[41]. C. Chen; B. Song; S. Yang; G. Xu; P.S. Bhadury; L. Jin; D. Hu; Q. Li; F. Liu; W. Xue; P.Lu and Z. Chen.(2007) Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. *Bioorg. Med. Chem.*,vol 15, 3981-3989.

[42]. F. Liu; X. Luo; B. Song; P.S. Bhadury; S. Yang; L. Jin; W. Xue and D. Hu. (2008) Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole moiety**.** *Bioorg. Med. Chem.*, 16, 3632-3640.

[43]. Bhardwaj, N., Saraf, S. K., Sharma, P., Kumar P. (2009) synthesis of1,3,4-Oxadiazoles and their antimicrobial activity *E-J. Chem.*, 6(4), 1133-1138.

[44]. Anil N. Mayekar, H. S. Yathirajan, B. Narayana, B. K. Sarojini, N. Suchetha Kumari (2010) Synthesis and Antimicrobial Activity of 3-(1,3,4-Oxadiazol-2-yl)quinazolin-4(3H)-ones. Sci Pharm.; 78: 171–193.

[45]. Ansari, K. F., Lal, C. (2009) Synthesis, physicochemical properties and antimicrobial activity of some newbenzimidazole derivatives. European Journal of Medicinal Chemistry .44 4028–4033.

[46]. Rai, N.P., Narayanaswamy, V.K., Shashikanth, S., Arunachalam, P.N. (2009) Synthesis, characterization and antibacterial activity of 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substituted -phenyl) -[1,3,4]oxadiazoles..*Eur. J. Med. Chem.*2009, 44, 4522-4527.

[47]. Ahmed S. Aboraia, Hamdy M. Abdel-Rahman, Nadia M. Mahfouz and Mahmoud A. EL-Gendy. (2006) Novel 5-(2-hydroxyphenyl) -3-substituted -2,3-dihydro- 1, 3,4-oxadiazole-2-thione derivatives: Promising anticancer agents. Bioorganic &Medicinal Chemistry;14, 1236 1246.

[48]. Linhong Jin, Jiang Chen, Baoan Song, Zhuo Chen, Song Yang, QianzhuLi,Deyu Hu and RuiqingXu (2006). Synthesis, structure, and bioactivity of N0-substituted benzylidene-3,4,5 trimethoxy benzohydrazide and 3-acetyl-2 - substituted pheny l-5 - (3 ,4 ,5 -trimethoxyphenyl)- 2,3-dihydro-1 ,3 ,4 -

oxadiazole derivatives. Bioorganic & Medicinal Chemistry Letters; 16, 5036 5040.

[49]. Qing-ZhongZheng, Xiao-Min Zhang, Ying Xu, Kui Cheng, Qing-Cai Jiao, Hai-Liang Zhu. (2010) Synthesis, biological evaluation, and molecular docking studies of 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety as potential antitumor and analgesic activities. Bioorganic and medicinal chemistry ; 18, 7836-7841.

[50]. Rajya Lakshmi Gudipati, Rama Narsimha Reddy Anreddy, Narsimha Reddy Yellu and Sarangapani Manda (2011) Synthesis, characterization and anticancer activity of certain3-{4- (5 - mercapto-1,3,4- oxadiazole-2-yl) phenylimino}indolin 2 one derivatives. Saudi Pharmaceutical Journal; 1319-0164(11)00024-7.

[51]. Linhong Jin, Jiang Chen, Baoan Song, Zhuo Chen, Song Yang, Qianzhu Li, Deyu Hu and RuiqingXu (2006) Bioorganic & Medicinal Chemistry Letters ; 16,5036- 5040.

[52]. Xiaohu Ouyang, Evgueni, L. Piatnitski, Vatee Pattaropong, Xiaoling Chen, Hai- Ying He, Alexander, S. Kiselyov, Avdhoot Velankar, Joel Kawakami, Marc Labelle, Leon Smith, II, Julia Lohman, Sui Ping Lee, AsraMalikzay, James Fleming, Jason Gerlak, Ying Wang, Robin L. Rosler, Kai Zhou, Stan Mitelman, Margarita Camara, David Surguladze, Jacqueline F. Doody and M. Carolina Tuma (2006) Bioorganic & Medicinal Chemistry Letters; 16 1191-1196.