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Oxadiazoles: A novel class of anti-convulsant agents

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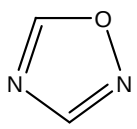
ABSTRACT

Oxadiazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. The derivatives of oxadiazole nuclei showed diverse biological activities such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, anticancer, anti-HIV, hypogycemic and genotoxic. In the present study, we have discussed about the oxadiazoles possessing anticonvulsant activity and the effect of different substituents on the oxadiazole ring on its anticonvulsant activity. These derivatives of oxadiazole are analysed in present article.

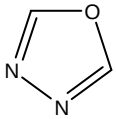
Keywords: Oxadiazole, anticonvulsant activity.

INTRODUCTION

Five membered heterocyclic compounds show various types of biological activities, among them substituted oxadiazoles display wide spectrum of activities such as antibacterial [1], antimalarial [2], anti-inflammatory [3], antifungal [4] and anticonvulsant [5]. The therapeutic importance of these rings prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities.



1,2,4 Oxadiazole



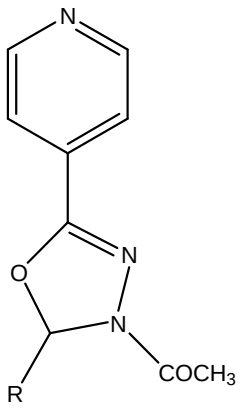
1,3,4 Oxadiazole

Oxadiazole is any five-membered heterocycle having two carbon, two nitrogen, one oxygen atoms and two double bonds having general formula $C_2H_2ON_2$. Oxadiazole (Oxazole) is the

parent compound for a vast class of heterocyclic compounds. These are azoles with oxygen and nitrogen.

Anticonvulsant Activity of Oxadiazoles

A new series of Isoninicotinic acid hydrazide (INH) incorporated derivatives of 1,3,4-oxadiazole (5a-h) has been synthesized by Sadaf Jamal Gilani *et al.* [6]. The anti-convulsant activity of all the synthesized compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (sc PTZ) induced seizure models in mice. All compounds were shown to be less neurotoxic than the standard drug phenytoin. Various 1-(2-(2-substituted phenyl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone (5a-h) has been prepared by reaction between (E)-N'-(substitutedbenzylidene) isonicotinohydrazide with acetic anhydride.

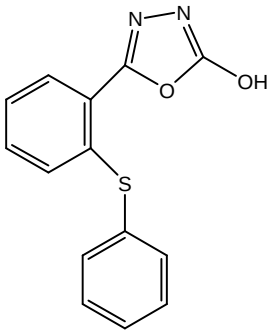


Compound	R
5a	o-C_6H_5
5b	p-C_6H_5
5c	o-C_6H_5OH
5d	m-C_6H_5OH
5e	p-$C_6H_5OCH_3$
5f	p-C_6H_5F
5g	o-$C_6H_5NO_2$
5h	p-$C_6H_5N(CH_3)_2$

Among the synthesized compounds (5a-h), compounds 5a, 5c, 5f & 5g showed protection after 0.5h and 4h time interval at a dose of 30mg/kg, compounds 5b, 5d & 5e showed protection at a dose of 100mg/kg after 0.5h and 4h time interval Compound 5h showed protection in MES test at 300mg/kg both after 0.5h and 4h duration. In the scPTZ screen, compounds 5a, 5c & 5g had shown activity at 30 mg/kg dose level after 0.5h time interval and 100 mg/kg dose level after 4h time interval but compound 5f had shown activity at the dose level of 100 mg/kg after 0.5h time interval.

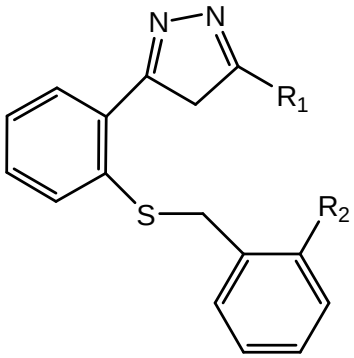
Ali Almasirad *et al.* [7] synthesized a series of 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole derivatives and evaluated *in vivo* for their anticonvulsant using PTZ and rotarod tests, respectively. However, most of the compounds were active in rotarod test and the most effective compound was the one with hydroxy, thiole and methylthio groups on position 3 of 1,3,4-oxadiazole ring i.e 5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole-2(3*H*)-one (compound 13) which showed comparable activity with diazepam being used as a reference drug.

A new series of 2-substituted-5-{2-[(2 halobenzyl)thio)phenyl}-1,3,4-oxadiazoles were synthesized and investigated for anticonvulsant activity by Afshin Zarghi *et al.* [8]. The designed compounds contain the main essential pharmacophore for binding to the benzodiazepine receptors. Electroshock and pentylenetetrazole-induced lethal convulsion tests showed that some of the synthesized compounds had significant anticonvulsant activity.



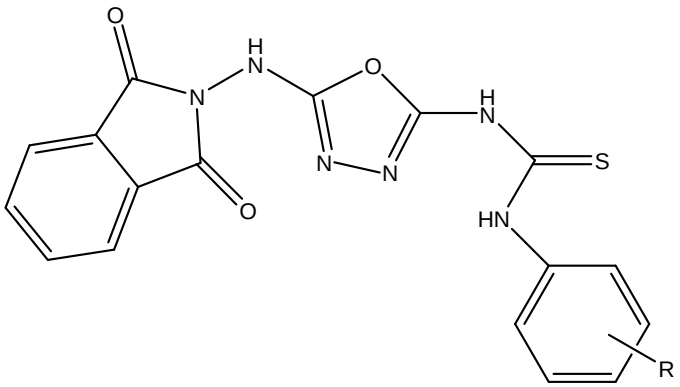
Compound 13

The structure-activity relationship study of these compounds indicate that the introduction of an amino group at position 2 of 1,3,4-oxadiazole ring and a fluoro substituent at the ortho position of the benzylthio moiety showed the best anticonvulsant activity. Compounds 5a and 5b possessing a small alkylthio group at C-2 of the 1,3,4-oxadiazole ring had good anticonvulsant activity in the MES model but showed mild activity against PTZ induced convulsion. Increasing the size of the alkyl group (5c and 5f) significantly decreases the anticonvulsant activity in both PTZ and MES models. Accordingly, compounds 5e and 5f with a bulky benzylthio group did not show any anticonvulsant effects. Therefore, the size and nature of groups at C-2 position of 1,3,4-oxadiazole ring are very important for anticonvulsant activity in both PTZ and MES models. In addition, the size of electron withdrawing substituents at ortho position of the benzylthio moiety is also important for their anticonvulsant effects. Anticonvulsant effects of active compounds were antagonized by flumazenil, a benzodiazepine antagonist, which establishes the involvement of benzodiazepine receptors in these effects.



Compound	R_1	R_2
5a	SCH_3	F
5b	SCH_3	Cl
5c	SC_2H_5	F
5e	SBz	F
5f	SBz	Cl

Mashooq A. Bhat *et al.* [9] has synthesized a series of novel 1,3,4-oxadiazole derivatives of phthalimide (4a-j) and evaluated for their anticonvulsant and neurotoxicity studies. Oxadiazole derivatives were synthesized by reacting phthalic anhydride with semicarbazide and hydrazine hydrate in presence of sodium hydroxide. Among the compounds synthesized by him 4(a-j) compound 4j with para methoxy substituent demonstrated that distal hydrophobic center could be made more lipophilic than phenyl ring thus displaying the highest anticonvulsant activity.



Compound 4j: R= 4-OCH_3

Pandeya has proposed the identifiable features for anticonvulsant activity like (i) hydrophobic aryl ring (ii) a hydrogen bonding domain (iii) an electron-donor group, and (iv) another distal hydrophobic site [10]. Basic structure of the compound that fulfilled all the pharmacophoric structural requirements (Fig-1).

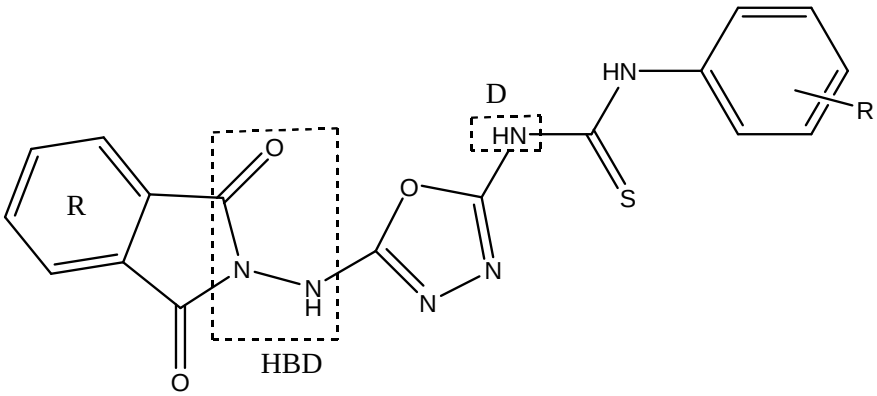
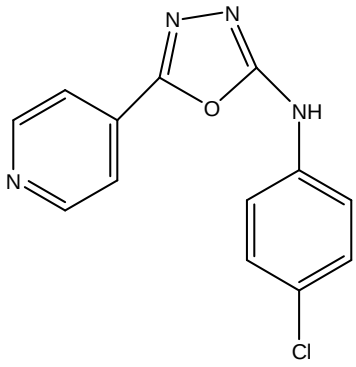


Fig-1 Pharmacophoric model of compounds (4a-j)

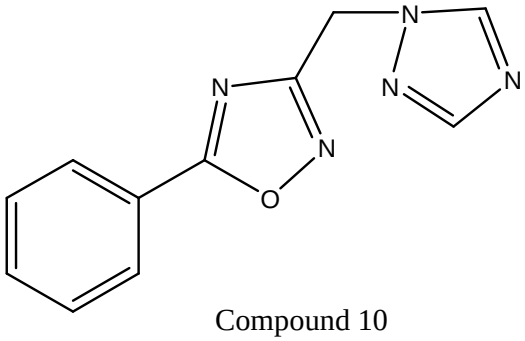
Presence of constituent like OCH_3 at distant phenyl ring especially at para position, showed highly potent activity in anti-MES screen. Presence of alkyl groups (CH_3) at distal aryl ring (ring B) has potent activity. It has already been established that there are at least four parameters for anticonvulsant drugs (i) lipophilic domain (ii) distal aryl ring (hydrophobic centre) whose size effects pharmacokinetic properties (iii) (CONH) acts as hydrogen donar (iv) an electron donar (C=N) system is also present. Hydrophobic size appears to govern the MES activity. If there is larger hydrophobic moiety, the MES activity is favored.

A series of five membered heterocyclics were synthesized by reaction between isoniazid and various substituted isothiocyanates by Mohammad Shahar Yar *et al.* [11] and were tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer. Among the synthesized compounds (IIIa-f), all the compounds showed activity in the range of 33-100 % in comparison to phenytoin which completely inhibited the convulsions produced by electro-convulsometer, but compound 2-(4 chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4-oxadiazole (IIIf) having electron withdrawing groups showed excellent anticonvulsant activity whereas compounds with unsubstituted phenyl ring (IIIa) showed good activity.



Compound III_f

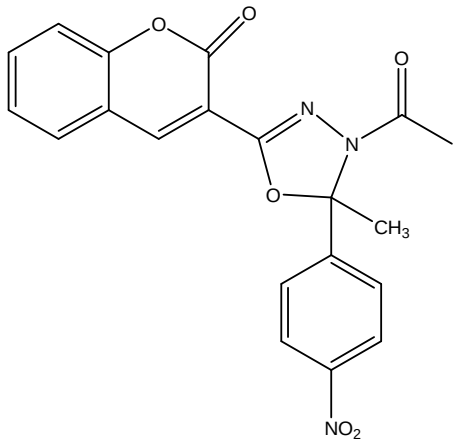
Hans-Joachim Lankau *et al.* [12] synthesized a series of 3- and 5-aryl-1,2,4-oxadiazole derivatives and tested for anticonvulsant activity in a variety of models. These 1,2,4-oxadiazoles derivatives exhibit considerable activity in both pentylenetetrazole (PTZ) and maximal electroshock seizure (MES) models. Compound 10 was protective in the PTZ model with an oral ED_{50} of 25.5 mg/kg and in the MES model with an oral ED_{50} of 14.6 mg/kg. Several oxadiazoles were synthesized that act as a selective GABA potentiating compounds with no interaction to the benzodiazepine binding site.



Compound 10

Key intermediates for the synthesis of 5-aryl[1,2,4]oxadiazole derivatives are 5-aryl 3-chloromethyl[1,2,4]oxadiazoles, respectively. New 3- and 5-aryl-1,2,4-oxadiazole derivatives were described to act as selective GABA potentiating compounds with no interaction to the benzodiazepine binding site. Both the GABA potentiation and the sodium channel blocking are mechanisms known to result in anticonvulsant activity.

Mashooq A. Bhat *et al.* [13] synthesized a series of 3-(4-acetyl-5*H*/methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*chromene-2-ones (6a-j) and evaluated for anticonvulsant activity and neurotoxicity. Compound (6e) was found to be potent and had activity at lower dose of 30 mg/kg in MES-test. All the compounds were less toxic as compared with the standard drug phenytoin. The synthesized compounds (6a-j) were initially screened at 30, 100 and 300 mg/kg intraperitoneally Compound (6e) with *p*-nitrophenyl substitution at position 5 of oxadiazole ring was active at lower dose of 30 mg/kg after 4 h. Thus compound (6e) showing activity at lower dose of 30 mg/kg seems to be potent in anticonvulsant MES screening.



Compound 6e

CONCLUSION

Oxadiazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions, which have already been discussed in previous articles. This article mainly focused on the various derivatives of oxadiazole that showed potent anticonvulsant activity, like compound with hydroxy, thiole and methylthio groups and various other electron withdrawing groups at ortho and para position of oxadiazole nuclei. Thus by studying all the derivatives showing anticonvulsant activity we can say that oxadiazole ring have been explored in past years and is still be used for future development of new drugs to be used against epilepsy.

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