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SYNTHESIS AND CHARACTERIZATION OF SOME NEW OXADIAZOLE DERIVATIVES AS ANTICONVULSANT AGENTS

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ABSTRACT

Oxadiazole have often been described as bio-isosters for amide & esters. Due to increased hydrolytic & metabolic stability of oxadiazole ring an improved, pharmacokinetic and *in-vivo* performance is often observed, which makes these heterocyclic ring as an important structural motif for the pharmaceutical Industry. Due to these characteristics oxadiazoles have impacted numerous areas of drug discovery like muscarinic antagonists, benzodiazepines receptor partial agonists, dopamine transporters, antirhinovirals, growth hormone secretagogues, 5-HT antagonists, antispasmodics, nematocidals, fungicidal & microbicides, analgesics, anti- inflammatory, anticonvulsant, antibacterial, immunosuppressants, antiplatelet & antithrombics. In the present work, an attempt was made to synthesize some novel oxadiazole derivatives by converting the Aromatic carboxylic acids into acid esters by conventional esterification. The esters obtained were treated with hydrazine hydrate to give aromatic hydrazides. Those hydrazides on refluxing with carbon di sulfide in presence of potassium hydroxide yielded different oxadiazole derivatives. Then those oxadiazole derivatives were subjected to acetylation and aromatic group attachment. The synthesized compounds were characterized and confirmed by IR and ^{1}HNMR spectroscopy and then screened for anticonvulsant activity. The anticonvulsant activity of newly synthesized oxadiazole derivatives was carried out by maximal electro-shock-induced convulsion method (MES) using ear electrodes in mice. Diazepam was used as positive control and normal saline served as solvent control. The investigation revealed that out of twelve newly synthesized derivatives six were found to possess anticonvulsant activity.

KEYWORDS: Bioisosters, oxadiazoles, anticonvulsants.

INTRODUCTION

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Because of this, anticonvulsants also have proven effective in treating many kinds of dysfunctional anxiety. Failing this, an effect ive anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects. Anticonvulsants are often called antiepileptic drugs (abbreviated "AEDs") or antiseizure drugs (abbreviated "ASDs").

Anticonvulsant drugs are prescribed widely to treat a range of medical conditions like-bipolar disorder, fibromyalgia & neuralgia caused by injuries or diseases that adversely affect the nervous system. It was observed from the literature that five membered heterocyclic compounds like Oxadiazoles possess interesting anticonvulsant activity.[1]

MATERIALS AND METHODS

Materials

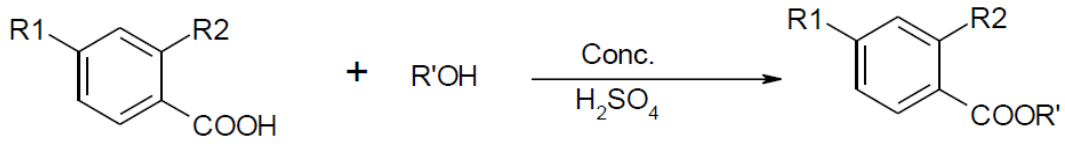
The chemical used in the present project work were of AR grade and LR grade, purchased from Loba Chemie, Qualigens, Sigma, Ranchem and Merck India. The IR spectra of the synthesize compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8400s) in the range of 400-4000 using KBR pellets and the values of Vmax are reported in cm^{-1}. ^{1}H-NMR spectra were recorded in Brookfield 200 MHz-NMR spectrometer (Astra Zeneca Pharma India Ltd) using $CDCl_3$ and chemical shift (s) are reported in parts per million downfield from internal reference Tetramethylsilane (TMS).

Methods

Step I: preparation of aromatic esters[2]

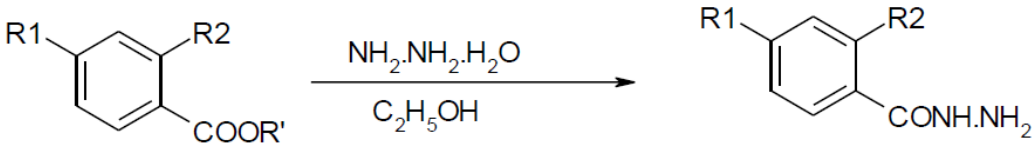
In a round bottom flask 30g (0.246mol) of aromatic acid, 145ml (115g, 2.5mol) of absolute ethanol and 5g (2.7ml) of conc. Sulphuric acid was taken. The mixture was refluxed for 4 hours. Distilled off excess of alcohol on a water bath and allowed to cool. Poured it slowly and with stirring on to 200g of crushed ice. Added sufficient ammonia solution to render the resulting solution

strongly alkaline. Extract the mixture with five 25 ml portion of ether, dry the combined ethereal extracts over $MgSO_4$, removed the ether and distilled the residue under pressure.



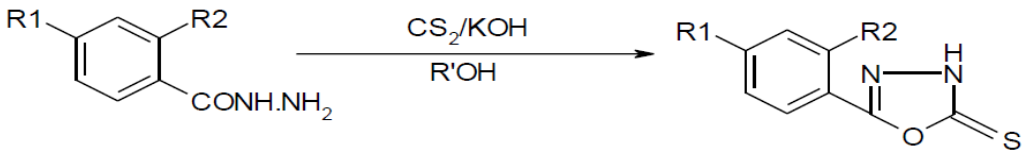
Step II: preparation of Hydrazides[3]

A mixture of 0.1 mol of ester and 0.2 mol of hydrazine hydrate were refluxed in 50ml of 95% ethanol for 5 hours. The resultant mixture was concentrated, cooled and poured onto crushed ice. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol.



Step III: Preparation of 1, 3, 4-oxadiazole derivatives[4]

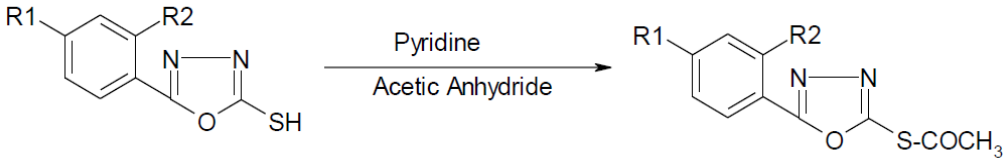
Potassium Hydroxide (0.01 mol) was dissolved in 100ml of alcohol (ethanol) and to this 20 ml carbon disulphide was added in a drop wise fashion for 30 minutes. Then hydrazide (0.01 mol) was added and stirred for 2 hours. After stirring the mixture was refluxed for 4 hours. Later solvent was removed by distillation and the residues was dissolved in crushed ice and acidified with dilute HCl. The solid separated was collected by filtration and dried and recrystallized by ethanol.



IR (KBr) cm^{-1}: 3147 (NH), 1494 (C=N), 1344 (C-N), 1178 (C-O-C), 1060 (C=S), 759 (Ar, C=C).^{1}H-NMR, ppm: 7.26-7.58 (m, aromatic), 7.96 (1H, s, SH).

Step IV: Acetylation of oxadiazole[5]

A mixture of oxadiazole derivatives (0.005mol) and acetic anhydride (10ml) and pyridine (5ml) was refluxed for 4 hours. The excess acetic anhydride was distilled off and residue was poured into ice-cold water, solid was filtered and recrystallised from ethanol - DMF.

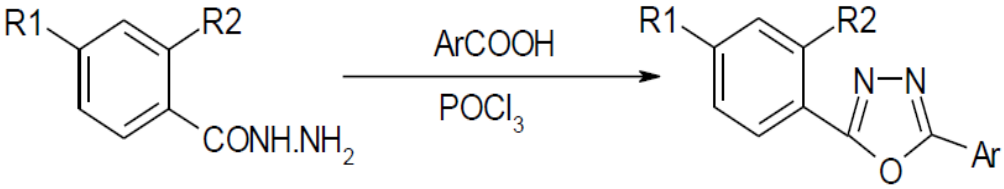


IR (KBr) cm^{-1}: 2946 (C-H), 1755 (C=O), 1612 (C=N), 1182 (C-O-C), 1064 (C=S), 763 (Ar, C=C).

^{1}H-NMR, ppm: 7.2-7.8, (m, aromatic), 2.7 (s, 3H, CH_3).

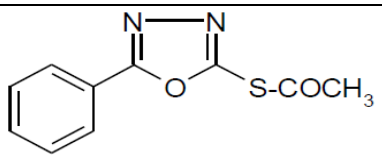
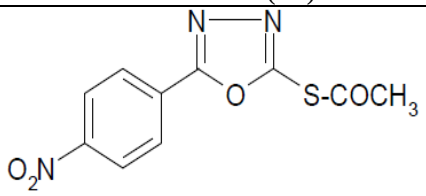
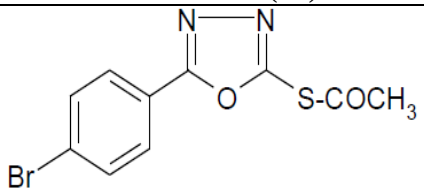
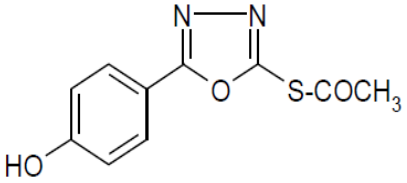
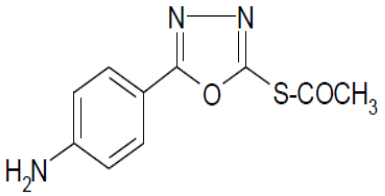
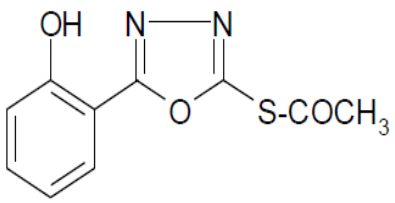
Step 3a: Preparation of 2-phenyl 1, 3, 4-oxadiazole derivatives from hydrazide

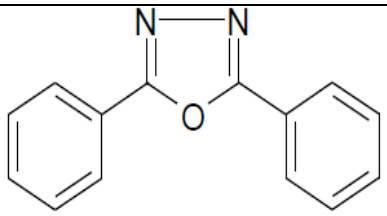
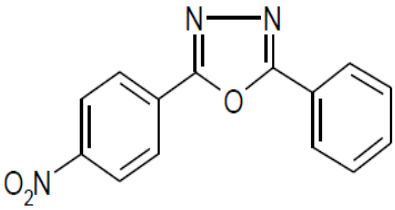
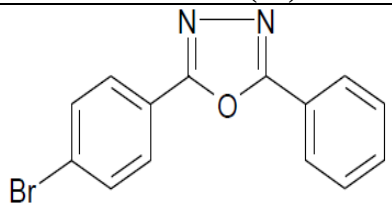
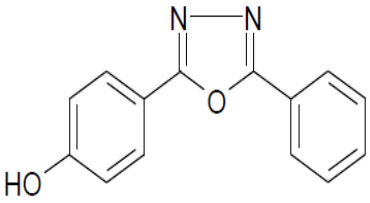
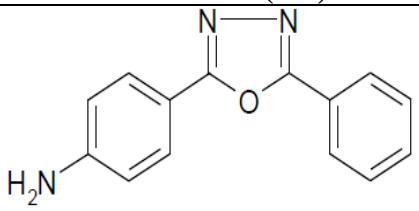
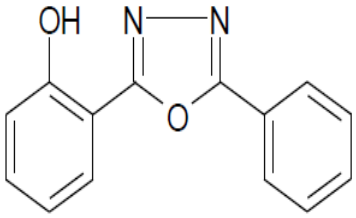
A mixture of 0.01 mol of hydrazide and 0.01mol (1.22g) of benzoic acid was dissolved in phosphorous oxychloride and refluxed for about 14 hours. The reaction mixture was slowly poured in crushed ice and kept overnight. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol.



IR(KBr) cm^{-1}: 1479 (C=N), 1273 (C-O-C), 700 (Ar, C=C).^{1}H-NMR, ppm: 7.2-7.9 (m, aromatic).

Table 1: List of compounds synthesized.

SL N.	Structure & Mol. Formula	IUPAC Name	Mol. Wt.	% yield	M.P. (0C)
1.	 C10H8O2N2S (1R)	S-[5-phenyl-1,3,4- oxadiazol-2-yl] ethanethioate	220	72.72	43-46
2.	 C10H7O4N3S (2R)	S-[5-(4'-nitrophenyl)- 1,3,4-oxadiazol-2-yl] ethanethioate	265	36.11	48-51
3.	 C10H7O2N2SBr (3R)	S-[5-(4'-bromo phenyl)- 1,3,4-oxadiazol-2-yl] ethanethioate	289	68.34	120-22
4.	 C10H8O3N2S (4R)	S-[5-(4'-hydroxy phenyl)-1,3,4-oxadiazol- 2-yl] ethanethioate	236	44.91	52-55
5.	 C10H9O2N2S (5R)	S-[5-(4'-amino phenyl)- 1,3,4-oxadiazol-2-yl] ethanethioate	235	57.26	90-93
6.	 C10H8O3N2S (6R)	S-[5-(2'-hydroxy phenyl)-1,3,4-oxadiazol- 2-yl] ethanethioate	236	94.01	67-70

7.	 C14H10N2O (7R)	2,5-diphenyl-1,3,4- oxadiazole	222	75.90	85-90
8.	 C14H9N3O3 (8R)	5-(4'-nitrophenyl)-2- phenyl-1,3,4-oxadiazole	267	67.41	110-13
9.	 C14H9N2OBr (9R)	5-(4'-bromophenyl)-2- phenyl-1,3,4-oxadiazole	291	76.63	67-69
10	 C14H10N2O2 (10R)	5-(4'-hydroxyphenyl)-2- phenyl-1,3,4-oxadiazole	238	46.21	78-81
11	 C14H11N3O (11R)	5-(4'-aminophenyl)-2- phenyl-1,3,4-oxadiazole	237	80.16	42-44
12	 C14H10N2O2 (12R)	5-(2'-hydroxyphenyl)-2- phenyl-1,3,4-oxadiazole	238	91.59	38-40

Pharmacological Studies

Acute toxicity studies (ID_{50}): The acute toxicity of acetylated Oxadiazole derivatives was determined by using Albino swiss mice (23-25gm). The animals were fasted for 24 hrs prior to the experiment and up and down procedure (OECD guideline no. 425) method of CPCSEA was adopted for acute toxicity studies. A maximum dose up to 700 mg/kg has been tested for any mortality. From that one dose is selected, 70 mg/kg which is $1/10^{th}$ of the LD_{50} value.

Anticonvulsant activity of 1, 3, 4-oxadiazole derivatives

In the present study, maximal electroshock method (MES) is selected. In MES-convulsions, electroshock is applied through the ear electrodes. Through otic stimulation, cortial excitation is produced. The MES-convulsions are divided into five phases such as (a) tonic

flexion, (b) tonic extensor, (c) clonic convulsions, (d) stupor and, (e) recovery or death. A substance is known to possess anticonvulsant property, if it reduces or abolish the extensor phase of MES convulsions. This procedure may be used to produce convulsions both in rats and mice.

Procedure

1. The animals were Divided into fourteen groups each consisting of 6 mice. One group is used as control, one group for Diazepam and other groups are for test compounds.
2. A suspension of the test compound was made by taking 70mg in 1% acacia solution (10ml) so as to get the dose of 7mg/ml.
3. The normal response of the test animals in the control group was recorded by placing ear electrode on the ears of the animal and an electric current of 42 mA was applied for 0.2 sec.
4. Diazepam was injected intraperitoneally to the standard group. The test compounds were administered in the similar manner to the other groups by oral route. As the drugs are insoluble in water, suspension of test compounds in acacia was employed. At the end of 1hr, the animals were subjected to electro convulsions. The time for different responses was noted. The readings are tabulated in Table No 2.

Table No. 2: Effect of 1, 3, 4-oxadiazole derivatives by maximal electric shock induced convulsions in mice.

SL. No.	Compounds	Body weight	Dose (mg/kg)	Extensor phase (Mean±SEM)
1.	Control	25	Saline Solution 0.25ml	21.33±0.667
2.	Diazepam	25	4	5.666±2.33***
3.	1R	25	70	22.33 ± 0.8819^{ns}
4.	2R	25	70	11.66±0.333***
5.	3R	25	70	19.66 ± 0.8819^{ns}
6.	4R	24	70	21.33 ± 0.6667^{ns}
7.	5R	24	70	14±2.082**
8.	6R	26	70	10±1***
9.	7R	26	70	8.333±0.333***
10.	8R	25	70	24±0.000ns
11.	9R	27	70	10±0.5774***
12.	10R	25	70	15±2.000*
13.	11R	25	70	17.33 ± 0.667^{ns}
14.	12R	25	70	17.66 ± 0.6667^{ns}

Values are expressed as Mean ± SEM, [number of animal (n) = 6]
Values were analysed one way ANOVA followed by Tukey-Kramer's test.
* represents mild significant at P<0.05, ** represents moderate significant at P<0.01, *** represents highly significant at P<0.001, ns represents non significant at P>0.05 Vs control.

RESULTS AND DISCUSSION

The titled compounds were synthesized according to the procedures as given in the methodology. The reactions were monitored by TLC. The physical constants like melting point and solubility were determined for all the intermediate and final products. The compounds were further characterized by IR and ^{1}HNMR. All the titled compounds were evaluated for their anticonvulsant activities. All the test compounds were screened for anticonvulsant activity by maximal electro-shock induced convulsions using ear electrode in mice. The Diazepam was used as positive control of dose 4mg/kg and normal saline as solvent control. Out of 12 derivatives, compounds 4'-nitro phenyl S-acetylated oxadiazole, 2'-hydroxy derivatives, 2,5-Diphenyl oxadiazole, 4'-bromo phenyl-2-phenyl derivative were found to show highly significant activity with p<0.001 value, 4'-amino phenyl S-acetylated compound was found as moderate significant with p<0.01, 4'-hydroxy-2-phenyl oxadiazole compound was evaluated as mild significant with p<0.05 and compounds phenyl S-acetylated oxadiazole, 4'-Bromo derivative, 4'-hydroxy derivative, 4'-nitrophenyl-2-phenyl oxadiazole derivative, 4'-aminophenyl-2-phenyl, 2'- hydroxyphenyl - 2-phenyl derivative were found non significant with p>0.05.

CONCLUSION

The main focus of this work was to synthesize, purify, characterize and evaluate anticonvulsant activities of novel 1, 3, 4-Oxadiazole derivatives. A series of titled compounds, i.e. [1-12] have been synthesized using appropriate synthetic procedure, as per the scheme given in the methodology. The yields of the synthesized compounds were found to be in the range from 36%-94%. Structures of synthesized compounds were characterized and confirmed with the help of analytical data such as IR and ^{1}HNMR. Anticonvulsant activities was carried out using Maximal electro-shock (MES) induced convulsion in mice. Among the 12 synthesized compounds four compounds were found to show highly significant activity with p<0.001 value. Hence it is concluded that newly synthesized 1, 3, 4-Oxadiazle derivatives do possess considerable anticonvulsant

activity and further lead optimization could be carried out for the better-expected Anticonvulsant activity.

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