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Synthesis, Characterization and Anti-Convulsant Activity of Novel Substituted Oxadiazole Derivatives

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Abstract

Seizures are sudden, transitory, and uncontrolled episodes of brain dysfunction resulting from abnormal discharge of neuronal cells with associated motor, sensory or behavioral changes. Anticonvulsants (also commonly known as antiepileptic drugs or as ant seizure drugs) 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, and for the treatment of neuropathic pain. Anticonvulsants suppress the rapid and excessive firing of neurons during seizures. Anticonvulsants also prevent the spread of the seizure within the brain. Synthesis of starting material by reacting with KOH resulting substituted benzoate obtained then (2.58gm, 10 m mol) DMF (10 ml), hydrazine hydrate (50 m mol) was added give substituted hydrazide product then take methanolic solution of hydrazide product (5.1 m mol), cyanogens bromide (7.5 m mol) was added give oxadiazole derivatives, The purity of all compounds have been checked by the TLC monitoring and the conformation of structure will be checked by different spectra like IR, Mass and NMR, and then evaluated for anti-convulsant activity.

Keywords: Oxadiazole, Oxadiazole derivatives, Convulsion, Anti-convulsant activity.

INTRODUCTION:

Anticonvulsants (also commonly known as antiepileptic drugs or as antiseizure drugs) 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, and for the treatment of neuropathic pain. Anticonvulsants suppress the rapid and excessive firing of neurons during seizures. Anticonvulsants also prevent the spread of the seizure within the brain. Some investigators have observed that anticonvulsants themselves may cause reduced IQ in children.[2] However these adverse effects must be balanced against the significant risk epileptic seizures pose to children and the distinct possibility of death and devastating neurological sequel a secondary to seizures. Anticonvulsants are more accurately called antiepileptic drugs (abbreviated "AEDs"), and are often referred to as antiseizure drugs because they provide symptomatic treatment only and have not been demonstrated to alter the course of epilepsy[2]

Conventional antiepileptic drugs may block sodium channels or enhance γ-aminobutyric acid (GABA) function. Several antiepileptic drugs have multiple or uncertain mechanisms of action.[3] Next to the voltage-gated sodium channels and components of the GABA system, their targets include $GABA_A$ receptors, the GAT-1 GABA transporter, and GABA transaminase.[4] Additional targets include voltage-gated calcium channels, SV_2A, and $\alpha_2\delta$.[5][6] By blocking sodium or calcium channels, antiepileptic drugs reduce the release of excitatory glutamate, whose release is considered to be elevated in epilepsy, but also that of GABA. This is probably a side effect or even the actual mechanism of action for some antiepileptic drugs, since GABA can itself, directly or indirectly, act proconvulsively.[7] The drug class was the US's 5th-best-selling in 2007.[8]

Anticonvulsants are agents which selectively depress the CNS. The term epilepsy (seize) is characterized by abnormal & excessive electroencephalographic discharge & a disturbance or loss of consciousness. These agents are used in the prevention & control of epileptic seizures.[9] anticonvulsant activity provides protection against convulsion induced by electro convulsiometer. The newly synthesized compounds 2-(4-chlorophenyl) ami no-5-(4-pyridyl)-1,3,4-oxadiazole were tested for their anticonvulsant activity by MES (maximal electroshock) method, the range of all compounds showed activity in33-100%. Compound (a) showed maximal activity & compound (b) showed good activity.

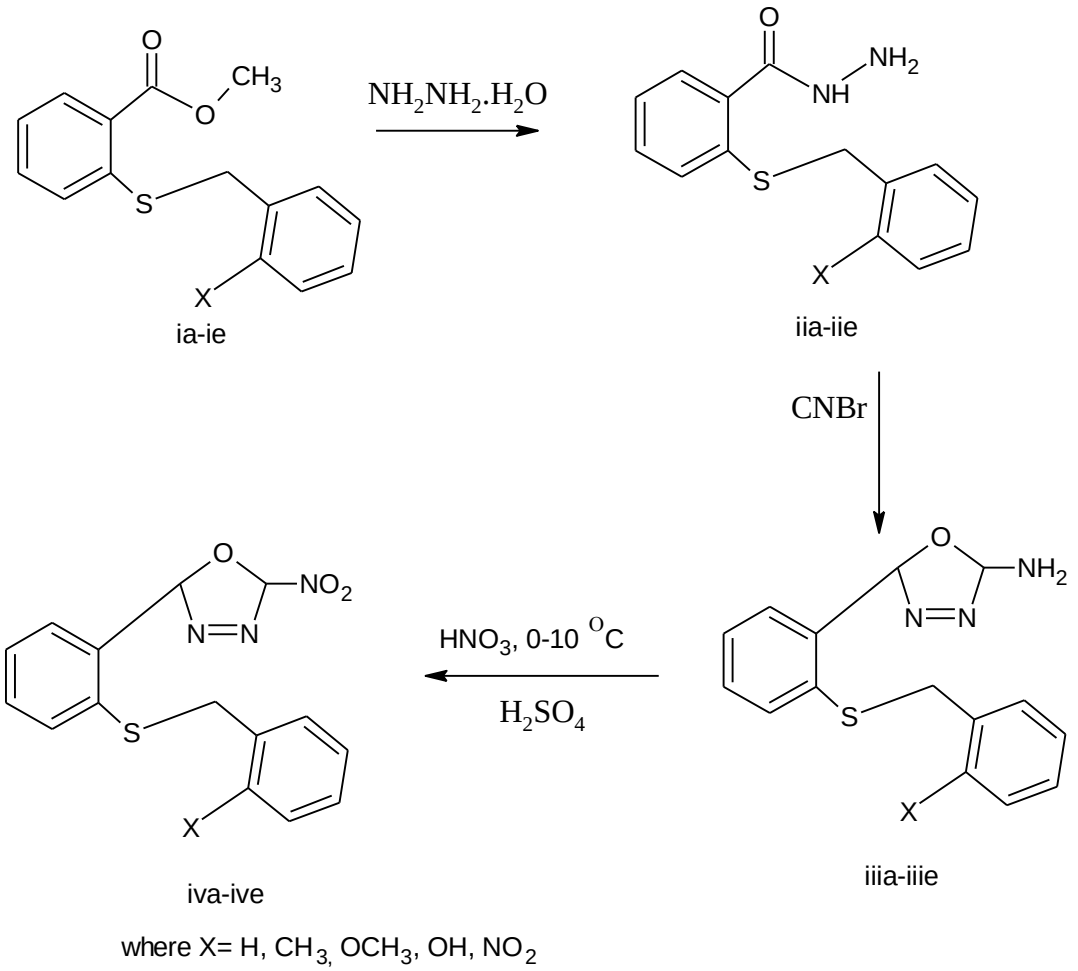
MATERIALS AND METHODS:

Chemical and reagents:

All chemicals were provided from our college. All solvents were redistilled before use. Reactions were routinely

monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour or UV light. All the synthesized compounds were purified by recrystallization. Melting points were determined by using open capillary method. Fourier Transform Infra-Red spectra (FTIR) were recorded on Shimadzu FTIR-8400S spectrophotometer using potassium bromide pellets and sodium chloride cell. Nuclear Magnetic Resonance spectra (^{1}H-NMR) were recorded on JEOL-300 MHz spectrophotometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm). Mass spectra were recorded on HEWLETT 180017, PACKARD GCD System mass spectrophotometer using electron ionization detector and anticonvulsant activity checked by Electroconvulsometer (LABTECH).

Synthetic Scheme:



Synthetic Procedure:

Synthesis of starting material:

Step 1:-Synthesis of 2-substituted 2-(benzyl)sulfanyl)benzohdrazide:-

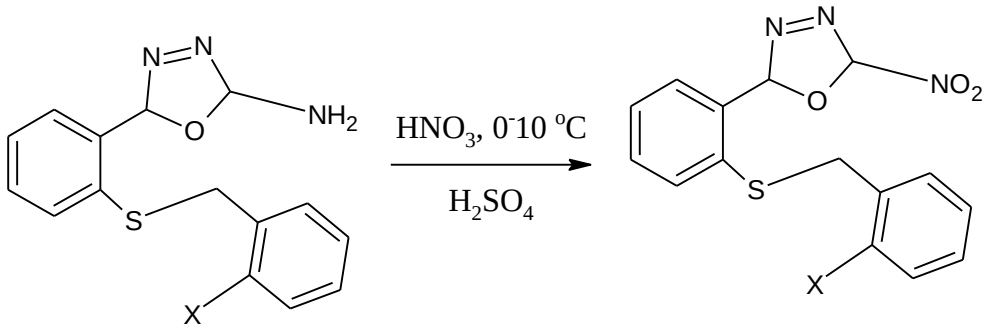
To a solution of 2-substituted 2-(benzyl)sulfanyl) benzohdrazide (ia-e) (2.58gm, 10 m mol) DMF (10 ml), hydrazine hydrate (50 m mol) was added and stirred at room temperature for 10 hours. After this time, 100 ml water was added and the solid thus separated was filtered, dried and recrystallised from ethanol [9-12] gave compounds (ii a-e).

Step-2:- General procedure for preparation of 5-{2-[(2-substituted benzyl)thio] phenyl}-1,3,4-oxadiazole-2-nitro (iii a-e)

To a methanolic solution of (ii a-e) (5.1 m mol), cyanogens bromide (7.5 m mol) was added. The reaction mixture was stirred at room temperature for 3 hours. The resulting solution was neutralized with sodium bicarbonate solution[13]. The solid thus separated out was filtered, washed with water, dried and recrystallised from ethanol.

Step 3: General procedure for preparation of 2-{2-[(2-substitutedbenzyl)thio] phenyl}-5-nitro-2,5-dihydro-1,3,4-oxadiazole (iva-e)

Place 17.5 ml (25gm, 0.5mol) of concentrated nitric acid in 250ml round bottom flask, and add in portions with shaking 20ml (37gm) of concentrated sulphuric acid. Keep the mixture cool during the addition by immersing the flask in cold water. Stir for 10min, then add compound **(iii a-e)** in reaction mixture in small portions with continuous stirring in ice bath. Stir for 1 hr and then add crushed ice in that solution[14-19]. Filter off the precipitates and recrystallised from ethanol give compound (iv **a-e**). Solvent system for TLC- Ethanol: n-hexane (65:35)



(iiia-e) **(iva-e)**

Where X=H, CH_3, OCH_3, OH, NO_2

Anti-convulsion activity:

All antiepileptic drugs (AEDs) are rigorously study in animals, particularly rodents, before they are given to patients. Understanding how drugs are screened in animals is useful to the clinician, since the screening process is valuable in predicting the type of seizure in which the drug would be efficacious, as well as determining the mechanism of the drug's anti-seizure action. Indeed, the dramatic discovery of the anti-seizure properties of phenytoin was identified by Merritt and Putnam in 1938 using the electroshock-induced seizure model.

Experimental design and procedure:

Animals were weighed and numbered. Mice were divided into 7 groups of six animals each. Group 1 served as control which was treated with vehicle (2% v/v Tween 80), group 2 was treated with standard drug phenytoin (25 mg/kg, i.p.) and groups 3– 7 were treated with newly synthesized oxadiazole derivatives (25 mg/kg, i. p.). One hour after injection, the animals were subjected to electro shock through ear electrodes of 80 mA for 0.2 sec by electroconvulsiometer[20] and the duration of time for extensor response was noted and the activity was expressed in terms of % protection. All the results are expressed as mean ± SEM. The % inhibition of epileptic seizures was calculated by using the formula, Percent (%) protection = VC – VT/VC X 100, Where, VT- Mean time in test group, VC- Mean time in control group.

RESULT AND DISCUSSION:

Table 1: Data for Analysis of synthesize compound

S. No.	Compound	% yield	Rf value	Mol. formula
1	iia	73.64	0.65	$C_{14}H_{14}N_2OS$
2	iib	61.27	0.71	$C_{15}H_{16}N_2OS$
3	iic	89.33	0.69	$C_{15}H_{16}N_2O_2S$
4	iid	71.01	0.81	$C_{14}H_{14}N_2O_2S$
5	iie	49.82	0.76	$C_{14}H_{13}N_3O_3S$
6	iiia	72.64	0.68	$C_{15}H_{15}N_3OS$
7	iiib	63.27	0.72	$C_{16}H_{17}N_3OS$
8	iiic	79.33	0.64	$C_{16}H_{17}N_3O_2S$
9	iiid	71.01	0.73	$C_{15}H_{15}N_3O_2S$
10	iiie	59.82	0.66	$C_{15}H_{14}N_4O_3S$
11	Iv a	63.64	0.63	$C_{15}H_{13}N_3O_3S$
12	Iv b	73.27	0.82	$C_{16}H_{15}N_3O_3S$
13	Iv c	77.33	0.74	$C_{16}H_{15}N_3O_4S$
14	Iv d	61.01	0.79	$C_{15}H_{13}N_3O_4S$
15	Iv e	69.82	0.62	$C_{15}H_{12}N_4O_5S$

Table 2: Spectral Characteristics of synthesized compounds

Compound	IVa	
^{1}H-NMR		**Mass value**
5.036 Singlet 1H, NO_2 6.591-6.647 Multiplet 4H, Ar-H 7.061-8.020 Multiplet 5H, Ar-H 2.401 Singlet 2H, CH_2		315.3 m/e it shows that the m+ peak.
IVb		
5.0176Singlet 0H, NO_2 6.5614-6.6470 Multiplet 4H, Ar-H 7.0670-8.0204 Multiplet 4H, Ar-H 3.0045 Singlet 2H, CH_2 1.897 Singlet 3H, CH_3		330.3 m/e it shows that the M+ 1peak
IVc		
5.0516 Singlet 0H, NO_2 6.3074-6.7032 Multiplet 4H, Ar-H 7.0704-8.0214 Multiplet 4H, Ar-H 3.555 Singlet 2H, CH_2 3.013Singlet 3H, OCH_3		334.0 m/e it shows that the m+ peak.
IVd		
5.0175 Singlet 1H, OH 6.6814-6.6842 Multiplet 4H, Ar-H 7.0670-8.0204 Multiplet 4H, Ar-H 3.876 Singlet 2H, CH_2 5.4566 Singlet 0H, NO_2		332.1 m/e it shows that the M+1 peak.
IVe		
2853.78,2923.22, 2956.11 4.0065, Singlet 0H, NO_2 6.623-7.04Multiplet 4H, Ar-H 7.874-8.204 Multiplet 4H, Ar-H		360.02 m/e and 361.02 it shows M+ peak and M+1 respectively.

Screening of anti-convulsant activity:

Table 3: Screening of Anti-convulsant activity in Albino Mice (By Maximal electro shock method)

Compound Code	Duration (Mean±SEM,Sec, sec)					% Protection
	Flexion	Extension	Clonus	Stupor	Recovery	
Control	12.75±0.3	15.85±0.23	27.50±0.19	96.0±0.09	Recovered	
Standard (Phenytoin)	9.80±0.08	11.83±0.19	3.07±0.05	1.91±0.03	Recovered	83.95 %
Comp-iv a	10.5±0.12	12.5±0.13	6.5±0.07	22.5±0.02	Recovered	65.8%
Comp-iv b	10.0±0.09	12.0±0.15	5.0±0.14	33.7±0.01	Recovered	60.0%
Comp-ivc	11.2±0.11	15.5±0.25	15.0±0.15	20.5±0.11	Recovered	59.23%
Comp-ivd	10.1±0.09	13.2±0.15	6.1±0.14	32.7±0.01	Recovered	59.90%
Comp-ive	11.1±0.09	14.2±0.15	6.5±0.14	33.9±0.01	Recovered	58.90%

DISCUSSION:

The pharmacological screening of the synthesized compounds showed anti-convulsion activity ranging from 59.23 % to 65.8 % inhibition of epileptic seizures in mice, where as the standard drug Phenytoin showed 83.95 % inhibition of epileptic seizures in mice. The compounds iva, ivb, ivd were found to be nearly potent to Phenytoin which was used as standard drug. Compounds ivc, ive shown less % of inhibition of epileptic seizures in mice than Phenytoin (standard drug).

CONCULSION:

The present work, which has undertaken is bonafied, and novel for the synthesis of oxadiazole derivatives. In this view we have made an attempt in reviewing the literature on substituted indole for their medicinal significance with help of chemical abstract, journals and internet sites. All synthesize compounds were tested for the preliminary tests, physical constants and TLC. All structures of final compound were confirmed by IR and ^{1}HNMR spectra as well as Mass spectra. The pharmacological screening of the synthesized compounds showed anti convulsion activity ranging from 59.23 % to 65.8 % inhibition of epileptic seizures in mice, where as the standard drug Phenytoin showed 83.95 % inhibition of epileptic seizures in mice. The compounds iva, ivb and ivd were found to be nearly potent to Phenytoin which was used as standard drug. Compounds ivc shown less % of inhibition of epileptic seizures in mice than Phenytoin (standard drug).

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