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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 **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. Substituted Oxadiazole derivatives synthesized by Hydrazination, formation, Cyclization process, Nitration and then evaluated for anti-convulsant activity.

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 evaluated for antimicrobial activity by calculate zone of inhibition. In conclusion, we have found some of the compounds prepared in course of this investigation are effective than the standard drug and some of them are found to be as active as the standard drug.

Key Words:- 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 [1]. 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

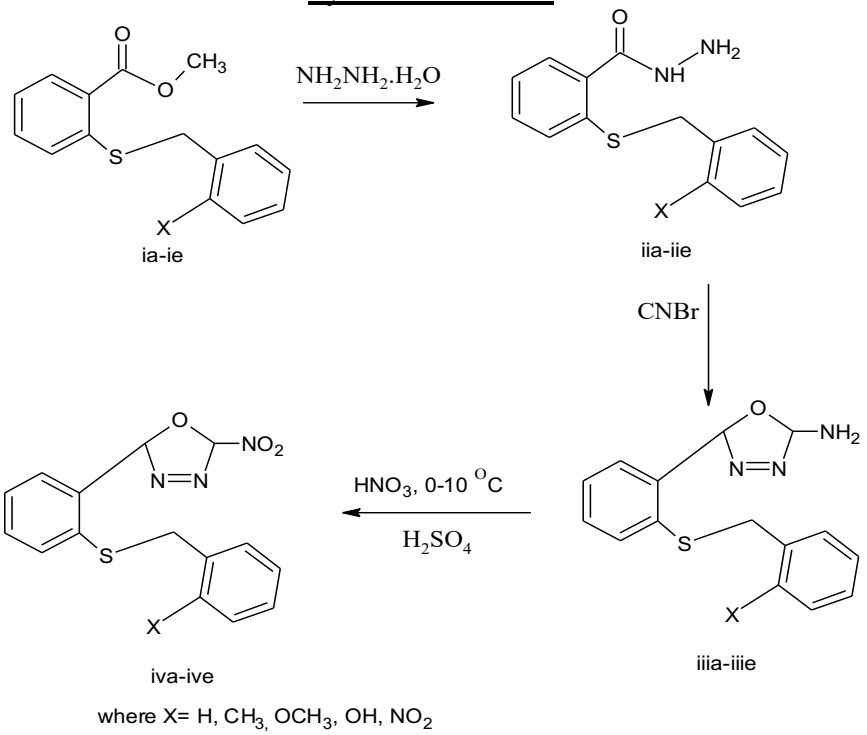
to as antiseizure drugs because they provide symptomatic treatment only and have not been demonstrated to alter the course of epilepsy[2]

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, affecting millions of people worldwide. The development of new anticonvulsant drugs is essential due to the limited efficacy and side effects of existing therapies. Heterocyclic compounds, particularly oxadiazoles [3], have emerged as promising candidates in the search for novel antiepileptic agents. Oxadiazoles are five-membered heterocyclic compounds containing two nitrogen atoms and one oxygen atom. They exist in several isomeric forms, including 1,2,4-oxadiazole and 1,3,4-oxadiazole, which have shown significant pharmacological potential [4]. These compounds are known for their broad biological activities, including antimicrobial, anti-inflammatory, anticancer, and notably, anticonvulsant properties. Recent studies have demonstrated that oxadiazole derivatives can modulate various neurotransmitter systems and ion channels involved in seizure activity [5]. Structural modifications of oxadiazole rings have led to enhanced anticonvulsant efficacy and reduced toxicity, making them attractive scaffolds for drug development. In summary, oxadiazole derivatives represent a valuable class of compounds with significant potential in the treatment of epilepsy, warranting further investigation and optimization in medicinal chemistry research [6].

MATERIALS AND METHODS:

All chemicals were provided from our college. All solvents were redistilled and dried before use. Reactions were routinely monitored by thin layer chromatography and spots were visualized by exposure to iodine vapour. All the synthesized compounds were purified by recrystallization. Melting points were determined by using open capillary method.

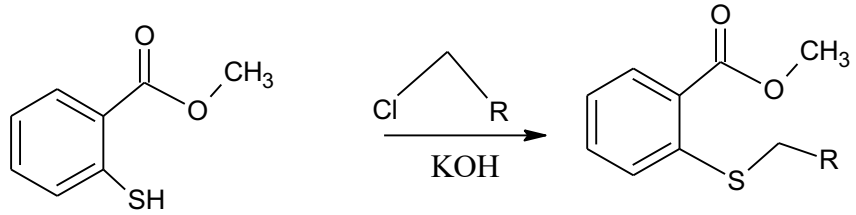
Synthetic scheme:



SYNTHETIC PROCEDURE:

SYNTHETIC PROCEDURE:

STEP 1. SYNTHESIS OF STARTING MATERIAL:-

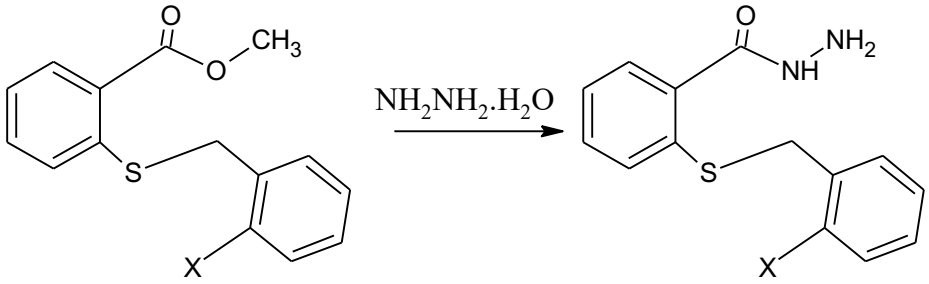


methyl 2-sulfanylbenzoate methyl-2 substituted -2-sulfanylbenzoate (ia-e)

WHERE R=A=C_6H_5, B=$C_6H_5CH_3$, C=$C_6H_5OCH_3$, D=C_6H_5OH, E=$C_6H_5NO_2$

STEP 2:-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 [7-9], DRIED AND RECRYSTALLISED FROM ETHANOL GAVE COMPOUNDS. (II A-E).

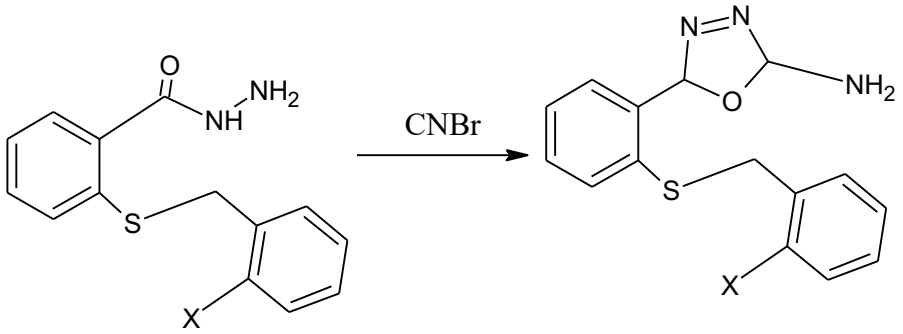


(I A-E) (II A-E)

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

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 [10-12]. THE SOLID THUS SEPARATED OUT WAS FILTERED, WASHED WITH WATER, DRIED AND RECRYSTALLISED FROM ETHANOL.



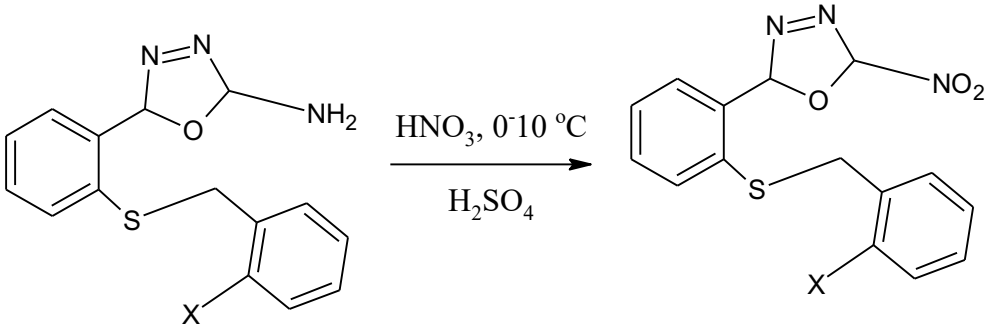
(IIA-E)

(IIIA-E)

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

STEP 4: NITRATION -

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 [13-15]. FILTER OFF THE PRECIPITATES AND RECRYSTALLISED FROM ETHANOL GIVE COMPOUND (IV A-E).



(III A-E) (IV A-E)

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

PHARMACOLOGICAL SCREENING:

Anti-convulsant activity has been performed by Aakar biotechnology laboratory Lucknow (U.P.). 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 [16].

Animals: Animals Albino mice, weighing 18-30 g, were used for experiments. The animals were kept in colony cages (6 mice each), maintained on a standard pellet diet with water, and left for 2 days for acclimatization before the experimental

session. The food was withdrawn on the day before the experiment, but free access to water was allowed. All experiments were carried out according to the suggested ethical guidelines for the care of laboratory animals [17].

Selection of experimental animals:

Healthy Albino wistar male rats weighing between 18-30 g were used for the evaluation of anti-convulsant activity.

Laboratory conditions: The rats were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its top. Environmental room should be 22°C (± 3°C) relative humidity was kept at least 30 % and preferably not exceed 70 % other than during room cleaning the aim was maintained between 50-60%. Lighting was artificial, the sequence being 12 hours light and 12 hours.

Food and water: All animals were allowed free access to water and standard palletized laboratory animal diet.

Bedding: In the present study animals were provided with clean paddy husk bedding. Bedding was changed every alternate day to maintain proper hygienic conditions.

The anticonvulsant activity was carried out by maximal electrical shock induced convulsion method in albino mice.

Animals to be use: - Albino mice

No. of animals used per group:-6 mice

Dose of test compound:-0.5ml/100g

Dose of standard drug:-0.5ml/100 (Phenytoin)

Route of administration:-Intra peritoneal (suspended in 1% tween-80 solution)

Requirements:-

Instruments: - Electroconvulsiometer

Chemicals:-Tween-80

Standard drug: - Phenytoin (25 mg/kg) aqueous suspension was prepared using solution of tween-80 as a suspending agent.

Test compounds:-suspension of compounds were prepared and administered intra peritoneal similar to that of standard drug.

Apparatus: -Syringes (1 ml, 2 ml), sample tubes.

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 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:

Physical and Spectral Characteristics

All the synthesized compounds were light creamish to brown coloured crystalline solids. Most of the compounds are freely soluble in chloroform and other solvents like methanol, ethanol. The melting point of the compounds was in the range of 152ºC to 251ºC.

IR spectra: IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr. All the synthesized compounds have shown characteristic stretching and bending in desired range.

Mass spectra: Mass spectra were obtained using. All the spectra were taken by direct infusion mass with ESI and APCI in positive and negative mode ionization ranging from 500-2000 m/e. All the compounds possess a molecular ion M^+, M+1 peak.

^{1}H- NMR spectra: The ^{1}H-NMR spectra of some of the compounds were studied in d6-DMSO on a Bruker II Avance 400 MHz NMR spectrometer. All the compounds show characteristic chemical shift from TMS in terms of δ ppm. δ value obtained in the desired range which signifies the presence of aromatic ring.

Physical and Spectral Characteristics of substituted benzoate:

Table no. 1: Physical Characteristics

Compound	Mol. formula	Mol. Wt. gm/mole	Melting point range (°C)	% Yield (w/w)	Rf value
Comp-Ia	$C_{15}H_{14}O_2S$	258.35	180-82	84.80	0.71

Table 2: Physical characteristics of compound (iia-e)

Compound	X	Mol.formula	Mol. Wt. gm/mole	Melting point (°C)	% Yield (w/w)	Rf value
Comp-ii a	H	$C_{14}H_{14}N_2OS$	258.33	112-113	73.64	0.65
Comp-ii b	CH_3	$C_{15}H_{16}N_2OS$	272.62	123-124	61.27	0.71
Comp-iic	OCH_3	$C_{15}H_{16}N_2O_2S$	288.36	145-146	89.33	0.69
Comp-ii d	OH	$C_{14}H_{14}N_2O_2S$	274.33	153-54	71.01	0.81
Comp-ii e	NO_2	$C_{14}H_{13}N_3O_3S$	303.33	167-68	49.82	0.76

Table 3 Physical characteristics of compound (iiia-e)

Compound	X	Mol.formula	Mol. Wt. gm/mole	Melting point (°C)	% Yield (w/w)	Rf value
Comp-IIIa	H	$C_{15}H_{15}N_3OS$	285.36		72.64	0.68
Comp-IIIb	CH_3	$C_{16}H_{17}N_3OS$	299.39		63.27	0.72
Comp-III c	OCH_3	$C_{16}H_{17}N_3O_2S$	315.39		79.33	0.64
Comp-III d	OH	$C_{15}H_{15}N_3O_2S$	301.33		71.01	0.73
Comp-III e	NO_2	$C_{15}H_{14}N_4O_3S$	330.36		59.82	0.66

Table 4: IR spectral data of (iva)

Fun. group assigned	Group frequency in Wave number (cm^{-1})
Aromatic C-H (stretching)	2985.90, 2885.10
Aliphatic C-H (stretching)	2673.67
Cyclic Ether C-O-C (stretching)	1638.53
Nitrile N=N (stretching)	1558.60
C=C (stretching)	1487.53
C-S-C	743.10
NO_2	1543.10
C-N	1558.66

Table 5: IR spectral data of (ivb)

Fun. group assigned	Group frequency in Wave number (cm^{-1})
Aromatic C-H stretching	2968.55, 2962.76
Aliphatic C-H	2983.12, 2924.18, 2852.81
C-O-C	1656.91
N=N	1543.10
NO_2	1462.91
C-S-C	629.81

Table 6: IR spectral data of (ivd)

Fun. group assigned	Group frequency in Wave number (cm^{-1})
Aromatic C-H stretching	2958.01
Aliphatic C-H stretching	2923.22, 2863.78
N=N	1553.71
Ether C-O-C	1663.66
NO_2	1472.10
OH	3372.70
C-S-C	747.44

Table 7: IR spectral data of (ive)

Fun. group assigned	Group frequency in Wave number (cm^{-1})
Aromatic C-H stretching	2968.73, 2973.13
Aliphatic C-H stretching	2950.12, 2929.18
N=N	1573.73
Ether C-O-C	1662.13
NO_2	1527.67, 1573.75
C-S-C	732.21
C=C	1481.38

Mass Data: The molecular weight of the compound is 315 and the mass spectral data matching the same as 315.3 m/e it shows that the m+ peak (iva). The molecular weight of the compound is 329 and the mass spectral data matching the same as 330.3 m/e it shows that the M+ 1peak(ivb). The molecular weight of the compound is 334and the mass spectral data matching the same as 334.0 m/e it shows that the m+ peak (ivc). The molecular weight of the compound is 331 and the mass spectral data matching the same as 332.1 m/e it shows that the M+1 peak (ivd). The molecular weight of the compound is 360 and the mass spectral data matching the same as 360.02 m/e and 361.02 it shows M+ peak and M+1 respectively(ive).

Table 7: NMR spectral data of (iva)

Sl. No	Value (δ)	Nature of segment	Type
1	5.036	**Singlet**	**1H, NO_2**
2	6.591-6.647	**Multiplet**	**4H, Ar-H**
3	7.061-8.020	**Multiplet**	**5H, Ar-H**
4	2.401	**Singlet**	**2H, CH_2**

Table 8: NMR spectral data of (ivb)

Sl. No	Value (δ)	Nature of segment	Type
1	5.0176	**Singlet**	**0H, NO_2**
2	6.5614-6.6470	**Multiplet**	**4H, Ar-H**
3	7.0670-8.0204	**Multiplet**	**4H, Ar-H**
4	3.0045	**Singlet**	**2H, CH_2**
5	1.897	**Singlet**	**3H, CH_3**

Table 9: NMR spectral data of (ivc)

Sl. No	Value (δ)	Nature of segment	Type
1	5.0516	**Singlet**	**0H, NO_2**
2	6.3074-6.7032	**Multiplet**	**4H, Ar-H**
3	7.0704-8.0214	**Multiplet**	**4H, Ar-H**
4	3.5557	**Singlet**	**2H, CH_2**
5	3.013	**Singlet**	**3H, OCH_3**

Table 10: NMR spectral data of (ivd)

Sl. No	Value (δ)	Nature of segment	Type
1	5.0175	**Singlet**	**1H, OH**
2	6.6814-6.6842	**Multiplet**	**4H, Ar-H**
3	7.0670-8.0204	**Multiplet**	**4H, Ar-H**
4	3.876	**Singlet**	**2H, CH_2**
5	5.4566	**Singlet**	**0H, NO_2**

Table 11: NMR spectral data of (ive)

Sl. No	Value (δ)	Nature of segment	Type
1	4.0065	**Singlet**	**0H, NO_2**
2	6.623-7.040	**Multiplet**	**4H, Ar-H**
3	7.874-8.204	**Multiplet**	**4H, Ar-H**
4	1.8974	**Singlet**	**2H, CH_2**
5	5.0176	**Singlet**	**0H, NO_2**

SCREENING OF ANTI-CONVULSANT ACTIVITY

Table 12 :-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-iva	10.5±0.12	12.5±0.13	6.5±0.07	22.5±0.02	Recovered	65.8%
Comp-ivb	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	12.6±0.10	17.2±0.03	17.0±0.12	21.2±0.08	Recovered	49.06%
Comp ive	12.2±0.10	18.1±0.22	19.1±0.10	21.9±0.14	Recovered	46.32%

CONCLUSION

The pharmacological screening of the synthesized compounds showed anti convulsant 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 seizure in mice. The compound IVa, IVb was found to be nearly potent to Phenytoin which is used as standard drug. Compounds IVc, IVd, IVe shown less % of inhibition of epileptic seizures in mice than Phenytoin (standard drug).

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