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SYNTHESIS AND INVIVO ANTICONVULSANT EVALVATION OF 1-{5-[4-(MORPHOLIN-4-YL) PHENYL]-1,3,4-OXADIAZOL-3(2H)-YL} ETHANONE DRRIVATIVES

Somashekhar M.[1]* and R.B. Kotnal[1]

[1]Department of Pharmaceutical Chemistry, BLDEA's SSM College of Pharmacy and Research Centre Vijaypur-586103, Karnataka.

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***Corresponding Author**
Dr. Somashekhar M.
Department of Pharmaceutical Chemistry, BLDEA's SSM College of Pharmacy and Research Centre Vijaypur-586103, Karnataka.

ABSTRACT

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Various heterocyclic compounds along their derivatives were evaluated for their biological activities**.** The widespread use of 1,3, 4 –oxadiazole as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocyclic compounds. These compounds have biological properties like antipyretic, antimitotic, antitubercular, antimicrobial, antiviral, antitumor, anticonvulsant, antibacterial, antifungal, antituberculosis, analgesic, anti-inflammatory, antidiabetic, antihistamine and other biological activities. The parent tetrahydro-1,4-oxazine, commonly called morpholine, is produced on a large scale for use as a solvent, corrosion inhibitor, and fungicide. The morpholine ring is also present in the sedative-hypnotic drug trimetozine and in some fungicides such as tridemorph and fenpropimorph. The novel derivatives of 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl} ethanone has been biologically screened for in-vivo and in-vitro anticonvulsant activity and reported. This research work can be helpful to develop various more new compounds possessing 1,3,4-oxadiazoles and Morpholine moiety that could be better in terms of efficacy and lesser toxicity.

KEYWORDS: 1,3,4-Oxadiazole, Morpholine and Anticonvulsant.

INTRODUCTION

Epilepsy is one of the most common neurological disorders responsible for substantial morbidity and mortality. It is a chronic neurological disorder characterized by paroxysmal, excessive, and hyper-synchronous neuronal activity in the brain affecting around 1-2% of the world population. 75-80% of the epileptic patients may be provided with adequate seizure control with the help of conventional antiepileptic drugs. Despite the development of several new anticonvulsants, the treatments of epilepsy still remain inadequate. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Most people with epilepsy have a normal emotional and cognitive life, however neurobehavioral problems can be found in a large number of patients. Higher rates of psychopathology have been reported in people with epilepsy compared with the general population and in people with chronic non-neurological disorders. Depression and anxiety are the most frequent types of psychiatric disorders identified in patients with epilepsy. The novel derivatives of 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl} ethanone has been biologically screened for in-vivo anticonvulsant activity and reported. This research work can be helpful to develop various more new compounds possessing 1,3,4-oxadiazoles and Morpholine moiety that could be better in terms of efficacy and lesser toxicity.

MATERIAL AND METHODS

Method of preparation of 4-Morpholin-4-yl-benzonitrile (SMRB3-1)

To a mixture of morpholine (4gm, 0.14 mol) in ethanol (25ml) and 4-chloro-benzonitrile (3.2gm, 0.05 mol) in 250ml round bottom flask, added anhydrous potassium carbonate (3gm). Then the reaction mixture was heated at 120^{o}C for 12 h. Water (25ml) was added onto the reaction mixture. The precipitate was filtered off, washed with water and dried under vacuum (30^{o} C) to obtain title compound. The crude product was recrystalized from 50% aqueous ethanol.

Method of preparation of Synthesis of 4-morpholin-4-yl-benzoicacid (SMRB3-2)

To a solution of sodium hydroxide (6gm, 0.3mol) in water (120ml), 4-morpholin–4ylbenzonitrile (SMRB3-1) (3gm, 0.01mol) was added. Small amount of methanol was added to increase the rate of the reaction. The reaction mixture was refluxed on water bath for 5 hrs. It was cooled to room temperature and make acidic by the addition of HCl (10%) with efficient stirring. The precipitate was filtered off, washed with water and dried under vacuum (60^{o} C) to obtain the title compound. Crude product was recrystallized from ethanol.

Method of Preparation of Synthesis of 4-Morpholin-4-yl-Benzoylchloride (SMRB3-3)

A mixture of 4-morpholin– 4yl-benzoic acid (SMRB3-2) (6gm, 1 mol) in ethanol (25ml) and thionyl chloride (SOCl2) (3.3ml, 0.5 mol) was refluxed on water bath for 6 hrs. Excess of thionyl chloride was removed by distillation under reduced pressure or by adding formic acid dropwise as required and the residue so collected was used for the next step.

Method of Preparation of Synthesis of (4-morpholin-4-yl) benzohydrazide (SMRB3-4)

To the solution of 4-morpholin– 4ylbenzoyl chloride (SMRB3-3) (6gm, 0.01 mol) in 15ml of methanol, 99% hydrazine hydrate (1.94ml, 0.03 mol) was added and the mixture was refluxed with on water bath for 4hrs. After cooling the precipitate was filtered off, washed with water and dried under vacuum (60°C) to obtain title compound. The crude product was recrystalized from 50% aqueous ethanol.

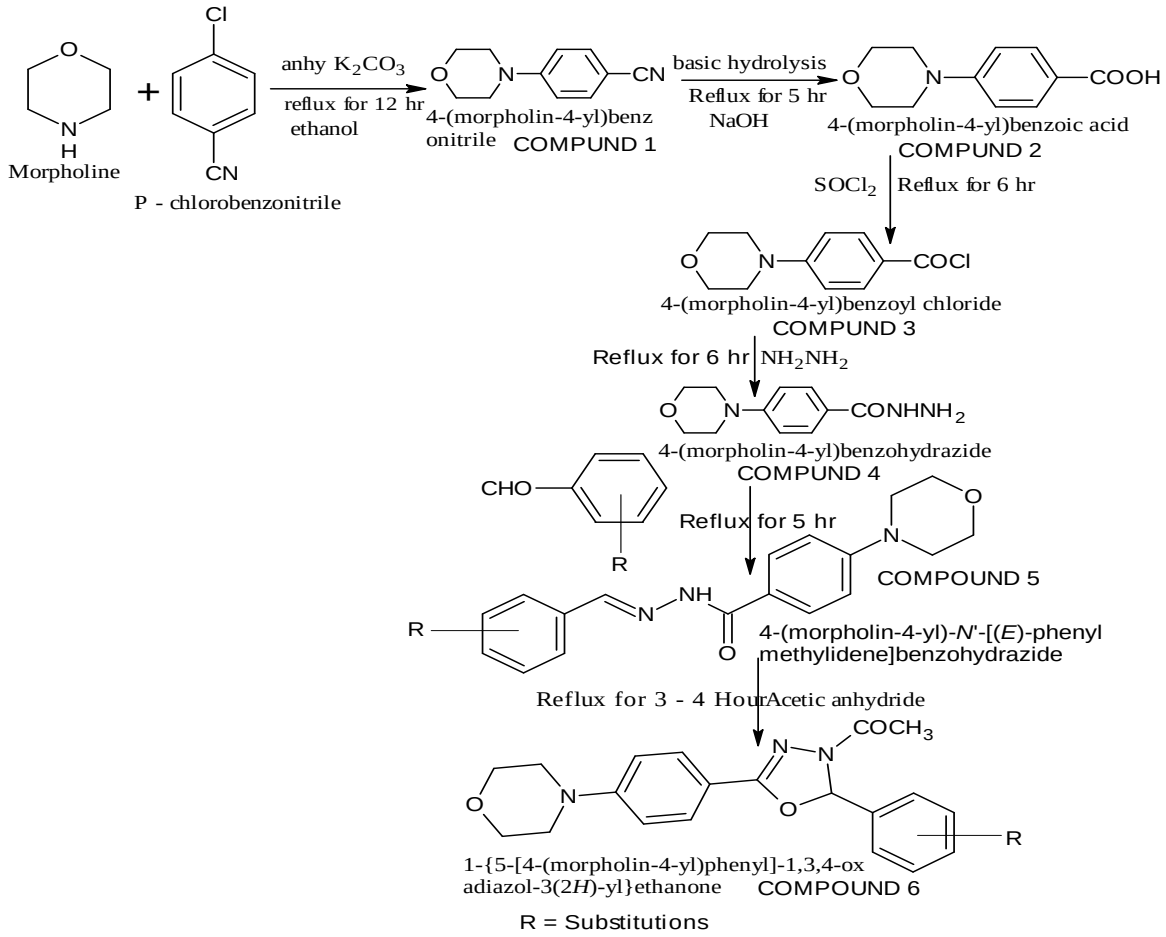
Method of Preparation of Synthesis of 4-(morpholin-4-yl)-*N*'-[(*E*)-phenyl methylidene] benzohydrazide (SMRB3-5)

A mixture of compound 4 (2.13 g, 0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in dioxane (50 mL) was refluxed for 4-8 h. The reaction mixture was concentrated under reduced pressure, cooled and the obtained solid was filtered, washed with water and cold ethanol. The crude product was purified by crystallization from dioxane.

Method of Preparation of Derivatives of 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl} ethanone (SMRB3-6A-6M)

A mixture of Compound 5 (0.01 mol) and an excess of acetic anhydride (10 mL) was refluxed for 3-4 h. The acetic anhydride was distilled off and the residue was poured onto crushed ice. The solid thus obtained was collected by filtration, washed with water and recrystallized from ethanol. The purity of the product **(SMRB3-6A-6M)** was confirmed by a single spot on TLC plate using methanol: carbon tetrachloride (8: 2, v/v) as solvent system.

SCHEME



Scheme: 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl}ethanone.

Table No.1: Derivatives of 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl} ethanone (SMRB3-6).

Sl. No	Product Code	Name of -ArCHO	Name of Derivatives of SMRB3-6
1	SMRB3-6A	Benzaldehyde	1-{5-[4-(morpholin-4-yl)phenyl]-2-phenyl-1,3,4-oxadiazol-3(2*H*)-yl}ethanone
2	SMRB3-6B	4- Fluorobenzaldehyde	1-[2-(4-fluorophenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
3	SMRB3-6C	3- Methoxy Benzaldehyde	1-[2-(3-methoxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
4	SMRB3-6D	2- Chlorobenzaldehyde	1-[2-(2-chlorophenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
5	SMRB3-6E	4- Methoxy Benzaldehyde	1-[2-(4-methoxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
6	SMRB3-6F	3- Nitrobenzaldehyde	1-[2-(3-nitrophenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
7	SMRB3-6G	4- Chlorobenzaldehyde	1-[2-(4-chlorophenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
8	SMRB3-6H	3-Methoxy 4-Hydoxy Benzaldehyde	1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-

			3(2*H*)-yl]ethanone
9	SMRB3-6I	4- Hydroxy Benzaldehyde	1-[2-(4-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
10	SMRB3-6J	3-Hydroxy 4-Methoxy Benzaldehyde	1-[2-(4-methoxy 3-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
11	SMRB3-6K	4- Bromobenzaldehyde	1-[2-(4-bromophenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
12	SMRB3-6L	2- Hydroxy Benzaldehyde	1-[2-(2-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone
13	SMRB3-6M	4- Nitrobenzaldehyde	1-[2-(4-nitrophenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone

FTIR spectrum of Derivatives of 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl}ethanone(SMRB3-6). Shown in below figure along with spectral data. Infrared spectra's (v-cm-1) were recorded on a Shimadzu IRAffinity-1(Miracle-10) auto sampler.

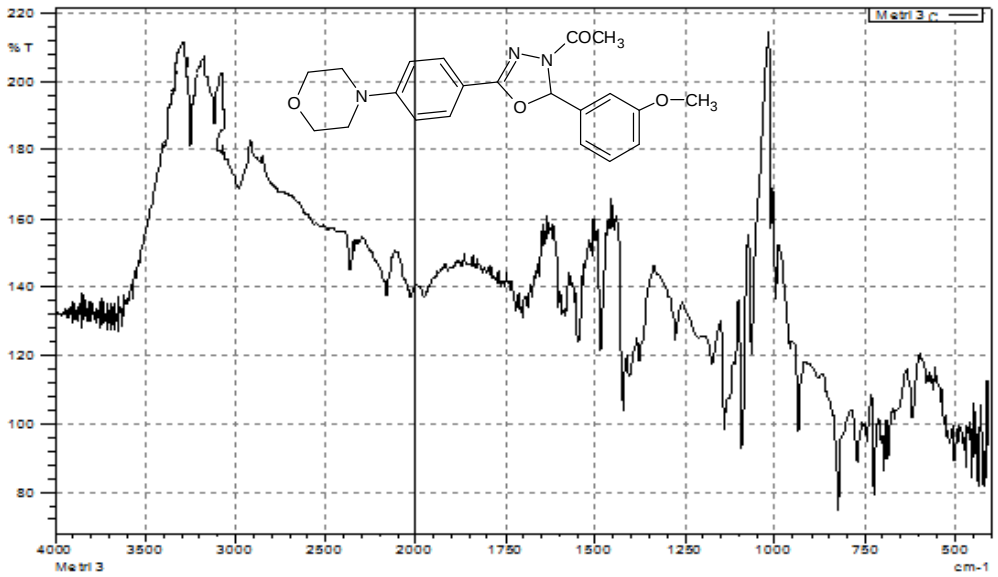


Fig No 1: FTIR spectrum of compound 1-[2-(3-methoxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone(SMRB3-6C): 3300 cm^{-1} N-H stretch of 2^{o} amine, 3120 cm^{-1} aromatic C-H stretch, 3030 cm^{-1} aliphatic C-H stretch, 2830 cm^{-1} - OCH_3 stretch, 1690 cm^{-1} C = O stretch, 1610 cm^{-1} C = N stretch, 1390 cm^{-1} $–CH_3$ Bending Vibrations.

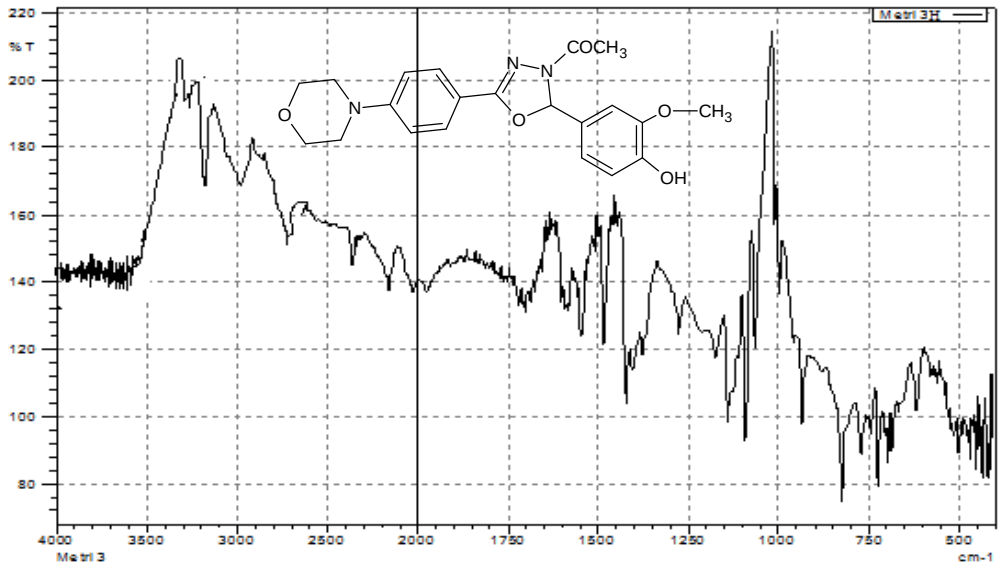


Fig No 2: FTIR spectrum of compound 1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H): 3295 cm^{-1} N-H stretch of 2^{o} amine, 3190 cm^{-1} -OH stretch, 3000 cm^{-1} aromatic C-H stretch, 2790 cm^{-1} aliphatic C-H stretch, 2823 cm^{-1} -OCH_3 stretch, 1650 cm^{-1} C = O stretch, 1630 cm^{-1} C = N stretch, 1370 cm^{-1} –CH_3 Bending Vibrations.

H^1 NMR spectrum of synthesized compounds shown in below figure along with spectral data. Derivatives of 1-{5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl}ethanone(SMRB3-6).1-[2-(3-methoxy phenyl)-5 -[4- (morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (SMRB3-6C).

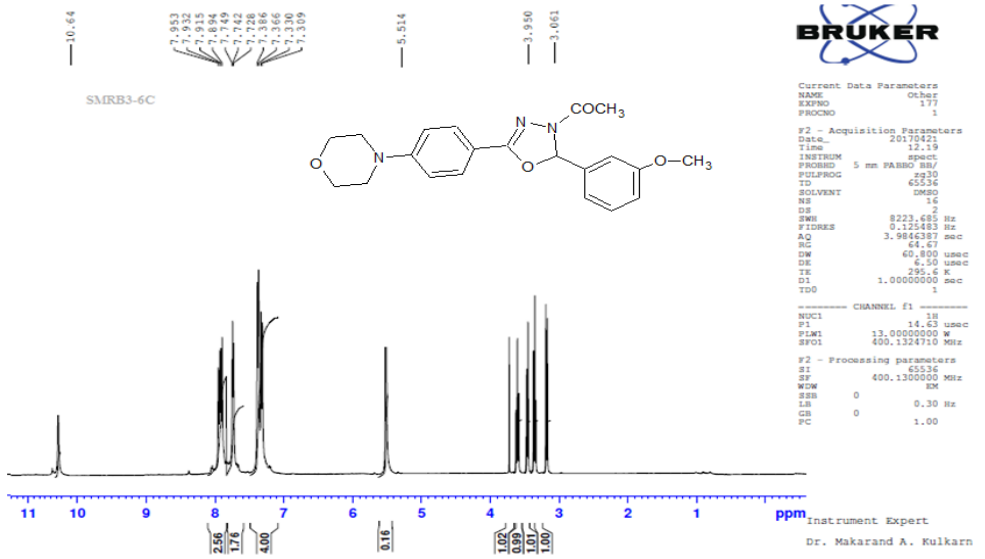


Fig No 3: H^1 NMR spectrum of compound 1-[2-(3-methoxy phenyl)-5 -[4- (morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (SMRB3-6C).

Table No 2: H^1 NMR spectrum data of 1-[2-(3-methoxy phenyl)-5 -[4- (morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (SMRB3-6C).

Sl. No	δ Value (ppm)	Observed δ Value (ppm)	Peak assigned
1	3.5-2.90	3.061	3H, -CH_3 (s)
2	4.1-3.1	3.950	8H, -$N(CH_2)_2$ Morpholine(d)
3	6.0-5.3	5.51	H, -CH (s)
4	8.3-7.1	7.30-7.90	8H, Ar-H (m)
5	11.0-10.2	10.64	3H, -C=O (s)

Mass spectrum of synthesized compounds shown in below figure along with spectral data 1-[2-(3-methoxy phenyl)-5 -[4- (morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (SMRB3-6C).

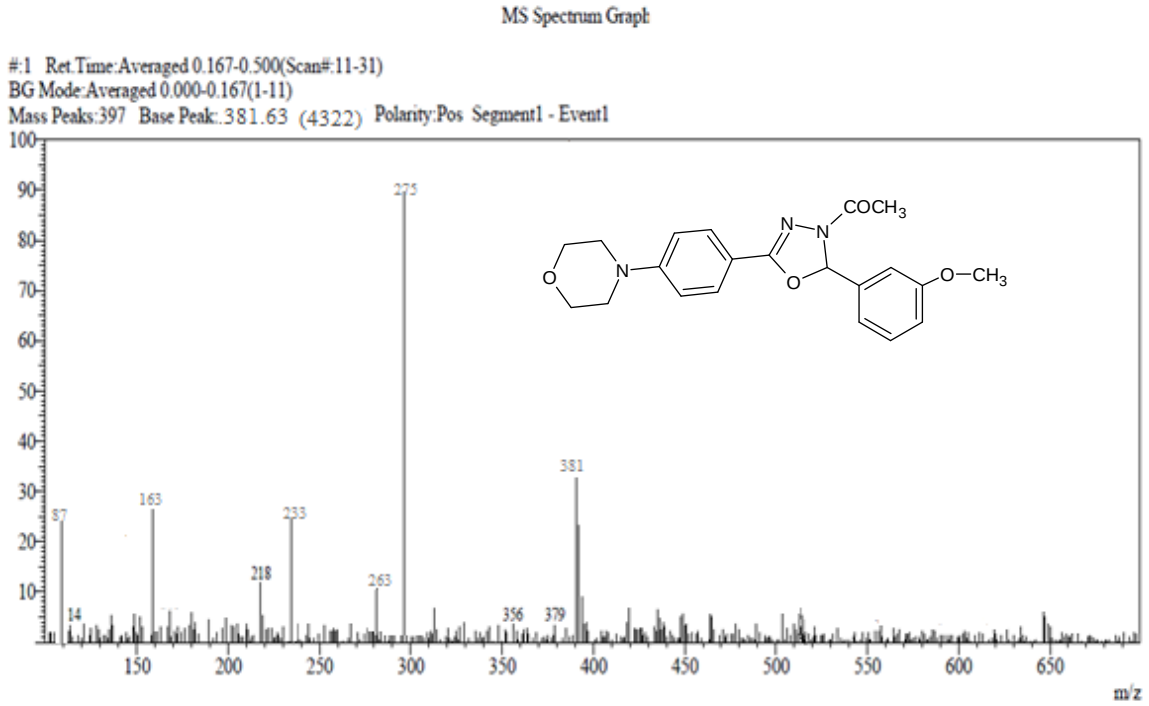


Fig No 4: - Mass spectrum of compound 1-[2-(3-methoxy phenyl)-5 -[4- (morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (SMRB3-6C).

- **M^+ Peaks (Mass Peak)at m/z 381 and Base Peak is 275**
- Molecular weight of compound 1-[2-(3-methoxy phenyl)-5 - [4- (morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (SMRB3-6C) is 381.

H^1 NMR spectrum of compound 1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H).

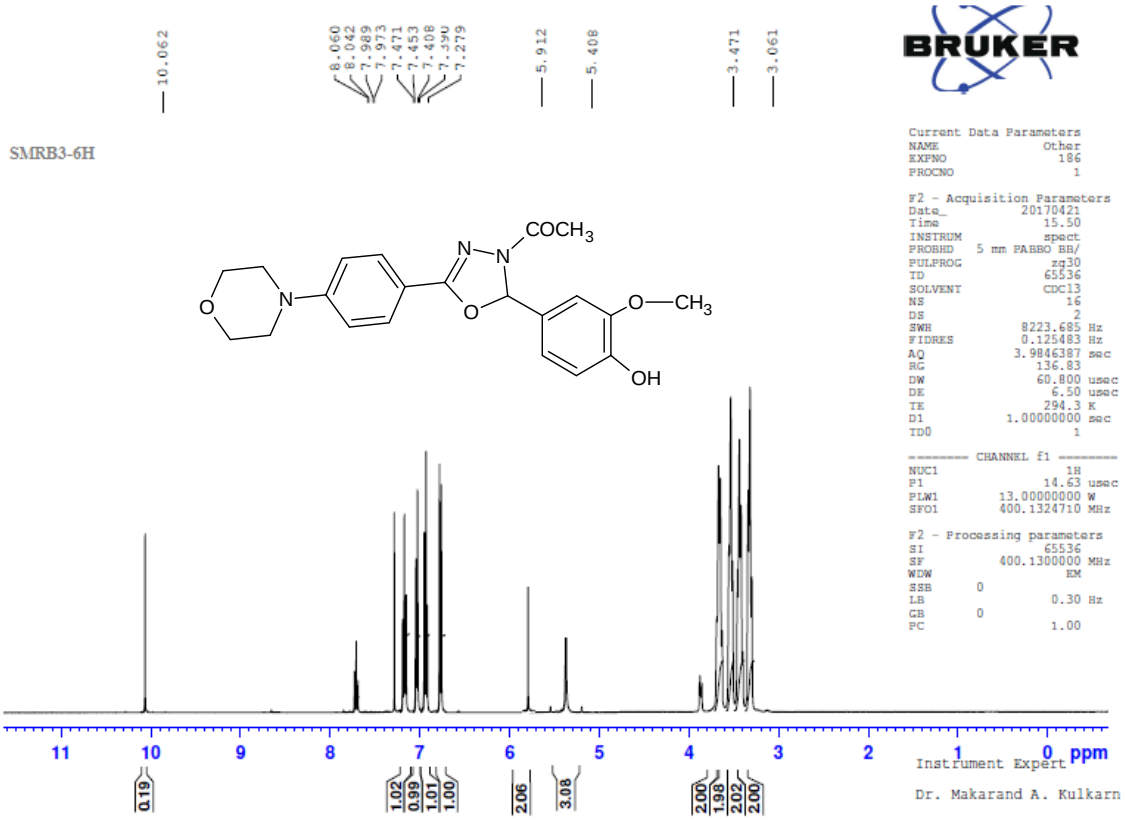


Fig No 5: H^1 NMR spectrum of compound 1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H).

Table No 3: H^1 NMR spectrum data of 1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H).

Sl. No	δ Value (ppm)	Observed δ Value (ppm)	Peak assigned
1	3.2-2.80	3.061	3H, -CH_3 (s)
2	4.0-3.2	3.47	8H, -$N(CH_2)_2$ Morpholine(d)
3	5.5-5.0	5.40	H, -CH (s)
4	6.0-5.5	5.91	H, -OH (s)
5	8.1-6.9	7.29-8.10	8H, Ar-H (m)
6	11.0-10.1	10.062	3H, -C=O (s)

Mass spectrum of 1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl)phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H).

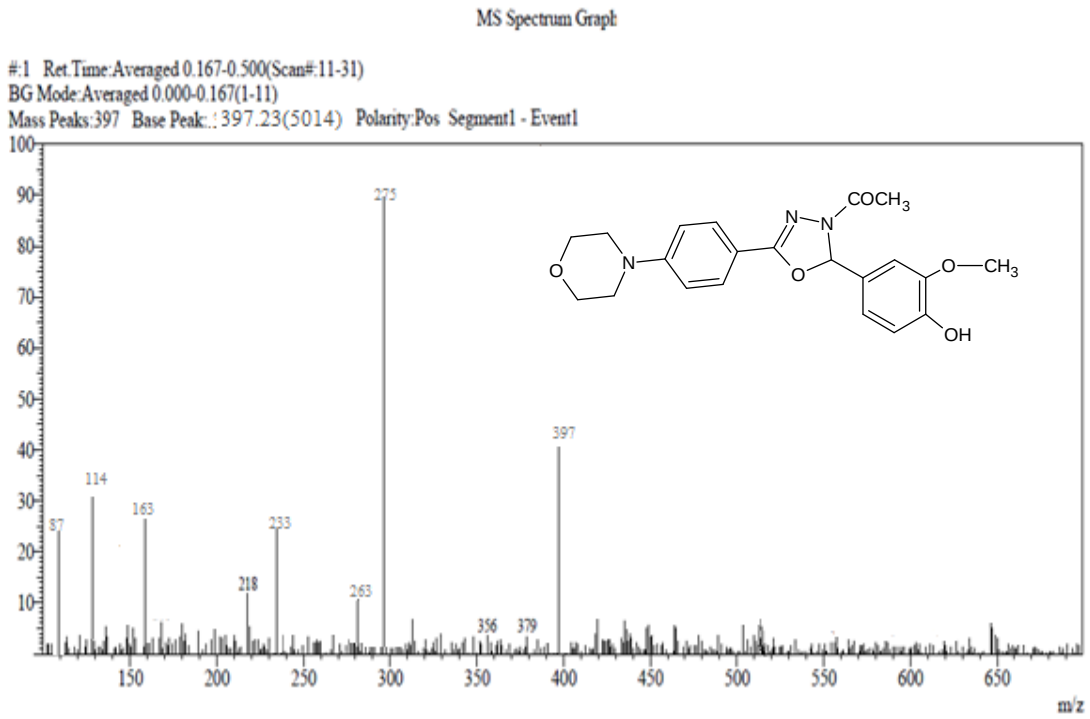


Fig No 6: - Mass spectrum of compound **1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4-yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H).**

- **M^+ Peaks (Mass Peak) at m/z 397 and Base Peak is 275**
- Molecular weight of compound 1-[2-(3-methoxy 4-hydroxyphenyl)-5-[4-(morpholin-4 yl) phenyl]-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (SMRB3-6H) is 397.

ANTICONVULSANT ACTIVITY

Maximal Electro Shock Model: For the assessment of anticonvulsant activity, the Swiss albino mice (25 – 30gm) of either sex were used. The animals were obtained from animal house animals were divided into five groups of five animals each Swiss albino mice.

Group I received Normal saline

Group II received Phenytoin

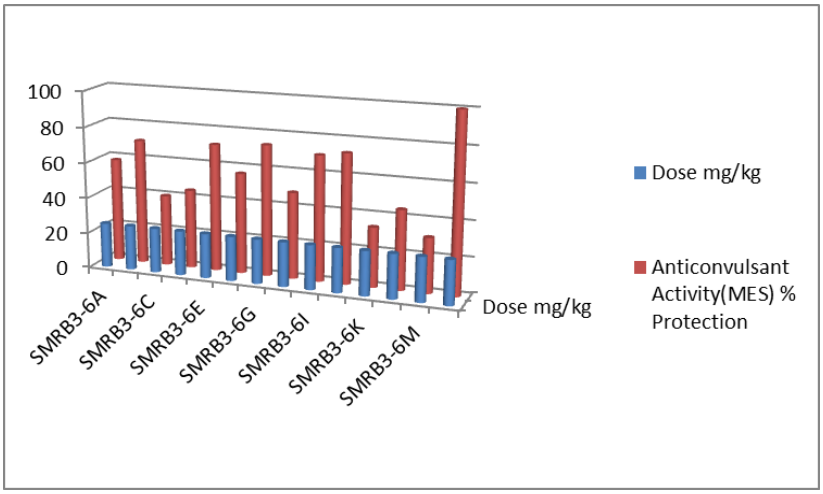
Group III received 25 mg/kg of 1,3,4-oxadiazole derivatives (SMRB3-6A-SMRB3-6M).

Corneal electrodes were used for bilateral delivery of electrical stimulus. Electroconvulsive shock (50 mA for 0.2 sec) was delivered through corneal electrode to induce Hind Limb Tonic Extensor (HLTE) phase in mice. There are five phases observed in mice after giving maximal electroshock. The five phases are (i) Flexor (ii) Extensor (iii) Convulsion (iv) Stupor and (v) Recovery or Death are noted and also the time spent by mice in each phase. Prior to delivery, the current output was checked by using multimeter. The orientation for the

anticonvulsant affect was abolition of HLTE within 10 sec after delivery of the electroshock statical analysis shown in table no 4 and Graph 1.

Table No 4: Anticonvulsant Activity (MES) % Protection.

Comp code	Dose mg/kg	Anticonvulsant Activity(MES) % Protection
SMRB3-6A	25	58.20
SMRB3-6B	25	70.34
SMRB3-6C	25	39.87
SMRB3-6D	25	44.33
SMRB3-6E	25	71.48
SMRB3-6F	25	56.45
SMRB3-6G	25	73.56
SMRB3-6H	25	48.44
SMRB3-6I	25	70.34
SMRB3-6J	25	72.66
SMRB3-6K	25	33.48
SMRB3-6L	25	44.56
SMRB3-6M	25	30.82
Phenytoin Sodium	25	100



Graph 1: In-vivo Anticonvulsant Activity (MES).

Statical Analysis

All the newly synthesized compounds were evaluated for their anticonvulsant activity by MES method. All the compounds showed activity in the range of 30-74% in comparison to Phenytoin which completely inhibited the convulsions produced by electroconvulsometer in albino mice. Compounds, SMRB3-6G, and SMRB3-6J showed maximal activity whereas compounds SMRB3-6B, SMRB3-6E and SMRB3-6I showed good activity shown in table no 4 and Graph 1.

CONCLUSION

Compounds reported were derivatives of reaction scheme-SMRB3; they were obtained in high purity with good yield. The FTIR studies show peeks at 2800-2850 cm^{-1} -OCH_3 stretch proves formation of derivatives of corresponding structure **(SMRB3-6)** and H^1 NMR spectrum data and mass spectra of synthesized derivatives compounds of Scheme SMRB3-6 analysis proves that resultant compound tested for their biological activities.

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