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Microwave assisted synthesis, characterization & biological evaluation of Benzimidazole substituted 1,3,4-oxadiazole

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Abstract: In an effort to develop novel 1,3,4-oxadiazoles, with various substituents characterizing and biologically screening them for anticonvulsant and antibacterial activities, a series of benzimidazole containing 1,3,4- oxadiazoles were synthesized by microwave assisted methods from presynthesized acetohydrazide by refluxing them with substituted aromatic acids at appropriate temperature in the suitably designed experimental conditions. The synthesized compounds were characterized by means of their IR, HNMR data, Mass spectrophotometry and elemental analysis. All compounds were tested for their anticonvulsant (using MES method) and antibacterial (against E. coli, S. aureus etc) activities.

Key words: - Microwave, Benzimidazole, Oxadiazole, Anticonvulsant, Antimicrobial.

Introduction

Benzimidazole & oxadiazole both are heterocyclic compounds which have been reported to possess anticonvulsant[1-5] and antimicrobial activities. Since long (400 BC) medicinal chemists are in search of single drug for the treatment of epilepsy in all of its seizure types. With such prime assumptions, the research work was aimed to incorporate both the heterocyclic systems in the single molecule for some better outcomes from these combinations. The earlier combinations have shown various biological activities such as antimicrobial[6], antifungal[7], antitubercular[8] etc.

In the present communication we report the synthesis of various benzimidazole containing 1,3,4-oxadiazoles (IVa-r) by the reaction of 2- [2-(phenoxymethyl) – 3H-inole – 3yl] acetohydrazide with differently substituted aromatic acids.

Experimental

General

Melting points were determined in open glass capillary melting point apparatus and are uncorrected. The ^{1}HNMR was recorded in DMSO-d_6 using TMS as internal standard. The IR spectrum was recorded on Schimadzu 8400S model FTIR spectrophotometer using KBr pellets. The elemental analysis was performed on Carlo Erba 1108 elemental analyzer. The molecular masses were confirmed by EI-MS studies. The purity of the compounds were checked by TLC using Silica Gel- G (Merk) with two solvent systems Benzene: Acetone (9:1) and (8;2) & Toluene: ethyl acetate: formic acid (5:4:1). Ash less Whatmann no. 1 filter paper was used for vacuum filtration. Column chromatography was performed on Silica Gel (Merk, 60-120 mesh).

General procedure for the preparation of benzimidazole containing 1,3,4- oxadiazoles(Iva-r) as represented in scheme – I.

Preparation of benzimidazole containing 1,3,4-oxadiazoles

(a) Synthesis of 2-(phenoxymethyl)-1H–benz imidazol (I):- A mixture of o- phenylene diamine (0.05 ml, 5.40gm) and phenoxyacetic acid (0.05 mole, 7.60g) was refluxed in 4NHCl for 30 min. in a microwave at 80^0 C. After completion of the reaction, solution was poured in to the crushed ice. Ammonia solution was added drop wise to neutralize the reaction mixture and the resulting solid was filtered, washed with cold water, dried and recrystallized in ethanol. TLC examination in TEF (5: 4: 1) the compound gave single spot.

(b) Synthesis of ethyl[2-(phenoxymethyl) –1H-benzimidazol-1-yl]-acetate (II):- To a suspension of compound-(I) (0.01 mole, 2.24g) & anhydrous K_2CO_3 (2g) in dry acetone, ethyl chloroacetate (0.01 mole, 1.2 ml) was added drop wise for 20-30 minutes at room temperature. The reaction mixture was stirred for 6 hrs with the help of magnetic stirrer at the temperature not exceeding 30-35^0 C. The inorganic solid thus obtained was filtered off and the filtrate was concentrated under reduced pressure, to produce a solid product (compound-II).

(c) Synthesis of 2-[2-(phenoxymethyl)-3H- indol-3yl]acetohydrazide (III):- An ethanolic solution of compound II (0.01mole, 3.10g) was added with hydrazine hydrate (0.01 mole, 0.49 ml) and the mixture was refluxed in a round bottom flask in the microwave apparatus for 15 minutes at 30-40^0C. After completion of the reaction, the mixture was cooled and the solid thus obtained was filtered, washed with cold water and re crystallized from methanol.

(d) Synthesis of 2-(phenoxymethyl)-1-[(5-aryl-1,3,4-oxadiazol-2-yl)methyl]-1H- benz imidazole (IVa) :- A mixture of presyntesized compound (III) (0.0025 mole, 0.738g) and benzoic acid (0.0025mole, 0.305g) was refluxed in the presence of $POCl_3$ (5ml) for 45 minutes in a microwave at a temperature of 80-85^0 C.

(e) Synthesis of 2-(phenoxymethyl)-1-[{5-(2-methyl phenyl)-1,3,4-oxadiazol-2-yl}me- thyl]-1H-benzimidazole (IVb):- The mixture of compound III (0.0025mole, 0.738g) and 2-methyl benzoic acid (0.0025mole, 0.340g) was refluxed in the presence of $POCl_3$ (5ml) for 30 minutes at 85^0C in a microwave apparatus till the reaction completed.

(f) Synthesis of 2-(phenoxymethyl)-1-[{5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl} met hyl]-1H-benzimidazole (IVc):- A mixture of 3-methylbenzoic acid (0.0025mole, 0.340g) and compound (III) (0.0025 mole, 0.738g) was added with $POCl_3$ (5ml) and refluxed for 35 minutes at a temperature of 85^0C in a microwave apparatus till the reaction completed.

(g) Synthesis of 2-(phenoxymethyl)-1-[{5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl}me thyl]-1H-benzimidazole (IVd):- The equimolar quantity (0.0025moles) of compound III (0.738g) and 4-methyl benzoic acid (0.34g) was refluxed with $POCl_3$ (5 ml) for 30 minutes in a microwave apparatus at the temperature of 80-85^0C and completion of the reaction was judged.

(h) Synthesis of 1-[{5-(2-chlorophenyl)-1,3,4-oxadiazole-2yl}methyl]-2-(phenolxymet hyl)-1H-benzimidazole (IVe):- An equimolar quantity (0.0025moles) of compound III (0.738g) and 1-chlorobenzoic acid (0.391g) were mixed with $POCl_3$ (5 ml), refluxed for 30 minutes in a microwave oven at the temperature of 90^0C and completion of the reaction was judged.

(i) Synthesis of 1-[{5-(4-chlorophenyl)-1,3,4-oxa diazole-2yl}methyl]-2-(phenoxymet hyl)-1H-benz imidazole (IVf):- Compound (IVf) was synthesized by the method as described for compound (IVe) except the reagents in this case were compound (III) (0.738g) and 4-cholorobenzoic acid (0.0391g) in equimolar quantities (0.0025 moles each) and reflux duration was 30 minutes at 85-90^0 C till the reaction completed.

(j) Synthesis of 1-[{5-(2-bromophenyl)-1,3,4-oxa diazol-2yl}methyl]-2-(phenoxymeth yl)-1H-benz imidazole (IVg):- The equimolar quantity (0.0025moles) of compound III (0.738g) and 2-bromobenzoic acid (0.502g) were refluxed in 5 ml $POCl_3$ at 80-85^0C for 40 minutes until the reaction completed.

(k) Synthesis of 1-[{5-(4-bromophenyl)-1,3,4-oxa diazol-2yl}methyl]-2-(phenoxymet hyl)-1H-benz imidazole (IVh):- 0.0025 moles each of compound(III) (0.738g) 4- bromobenzoic acid (0.502g) were mixed, added with 5ml $POCl_3$ and refluxed in a microwave oven at 75-80^0 C for 45 minutes until the reaction was complete.

(l) Synthesis of 1-[{5-(2-nitrophenyl)-1,3,4-oxa diazol-2yl}methyl]-2-(phenoxymeth yl)-1H-benzimidazole (IVi):- 2-nitrobenzoic acid (0.417g) was added with compound III (0.738g) in equimolar quantities (0.0025 moles)and the mixture was refluxed with 5 ml $POCl_3$ at the temperature of 90-95^0 C in a microwave apparatus till the reaction was complete.

(m) Synthesis of 1-[{5-(4-nitrophenyl)-1,3,4-oxa diazol-2yl}methyl]-2-(phenoxymeth yl)-1H-benz imidazole (IV j):- The equimolar quantities (0.0025 mole) of compound III (0.738g) and 4-nitrobenzoic acid (0.417g) were mixed in dried powder form and added with 5 ml of $POCl_3$. The mixture was refluxed in a microwave apparatus at the temperature of 85-90^0 C for 30 minutes untill the reaction was complete.

(n) Synthesis of 2-(phenoxymethyl)-1-[{5-(4-methoxyphenyl)-1,3,4-oxadiazol-2yl}me thyl]- 1H-benzimidazole (IV k):- 4-methoxybenzoic acid (0.380g) and compound III (0.738g)were mixed together in equimolar quantities (0.0025 moles) and mixture was added with 5 ml $POCl_3$. The produced reaction mixture was refluxed in a microwave oven at the temperature of 90-92^0 C for 40 minutes until the reaction was complete.

(o) Synthesis of 2-(phenoxymethyl)1-[{5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2yl} methyl]-1H-benzimidazole (IVl):- In 5 ml of $POCl_3$, equimolar amounts (0.0025 moles) each of compound III (0.738g) and 3,4-dimethoxybenzoic acid (0.455g) were mixed together and refluxed in a microwave apparatus at the temperature of 80-85^{0}C for 25-30 minutes.

(q) Synthesis of 1-[(5-benzyl-1,3,4-oxadiazol-2yl} methyl]-2-(phenoxymethyl)-1H-ben zimidazole (IV m):- An equimolar amounts (0.0025 moles) of compound III (0.738g) and phenylacetic acid (0.340g) was refluxed in 5 ml $POCl_3$ at the temperature of 95-100^{0}C for 25-30 minutes in a microwave apparatus.

(r) Synthesis of 1-[(5- phenoxymethyl -1,3,4-oxadiazol-2yl}methyl]-2-(phenoxymeth yl)-1H-benz imidazole (IV n):- A mixture containing equimolar quantities (0.0025 moles) of compound III (0.738g) and phenoxyacetic acid (0.380g) was refluxed with 5 ml $POCl_3$ in a microwave apparatus at the temperature of 90-95^{0}C for 25-30 minutes. The completion of reaction was judged markably.

(s) Synthesis of 1-[(5- naphthylmethyl -1,3,4-oxadiazol-2yl}methyl]-2-(phenoxymet hyl)-1H-benz imidazole (IV o):- A mixture of compound III n(0.0025 mole, 0.738g) and α- naphthylacetic acid (0.0025mole, 0.315g) was refluxed in the presence of $POCl_3$ (5 ml) in a microwave oven at the temperature of 85-90^0 C for 30-35 minutes till the completion of reaction .

(t) Synthesis of 1-[(5- diphenyl -1,3,4-oxadiazol-2yl}methyl]-2-(phenoxymethyl)-1H-benzimidazole (IV p):- A mixture of compound III (0.0025 mole, 0.738g) and biphenylacetic acid (0.0025 mole, 0.538g) was refluxed with $POCl_3$ (5ml) in a microwave apparatus at the temperature of 80-85^{0}C for 45 minutes until the reaction completed.

(t) Synthesis of 2-[5{2- phenoxymethyl)-1H-benzimidazol-1-yl)methyl}-1,3,4-oxad iazole-2yl}aniline (IV q):- Compound III(0.738g) and anthranilic acid (0.342g) in equimolar quantities (0.0025 moles) were mixed in dried powder form and added with 5 ml $POCl_3$ (dried). The reaction mixture was refluxed at the temperature of 88-92^{0}C for 35-37 minutes in a microwave apparatus until the reaction completed.

(u) Synthesis of 2-[(phenoxymethyl)-1-[(5-pyridine-4yl-1,3,4-oxadiazole-2yl}methyl] -1H-benzimidazole (IV r):- The equimolar quantities (0.0025 mole) of compound III (0.738g) and nicotinic acid (0.307g) were refluxed 5ml $POCl_3$ at the temperature of 90^0-95^{0}C for 35-40 minutes in a microwave apparatus until the reaction completed.

After completion of the reaction, the mixture was cooled at the room temperature, poured in crushed ice, and it was basified with 5 % (w/v) solution of sodium bicarbonate. The solid mass obtained in each case was separated out, washed with water and recrystallized from alcohols or suitable solvents.

Compound IVa, IVc, IVd, IVf, IVg, IVh, IVi, IVj, IVk, IVl, IVn, IVo, IVp were recrystallized from methanol and rest others from ethanol except IVr from petroleum ether.

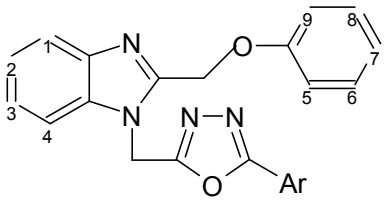
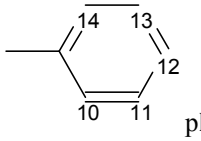
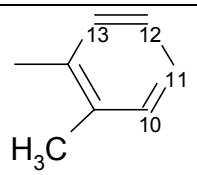
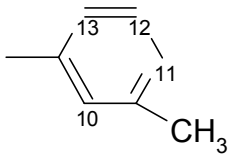
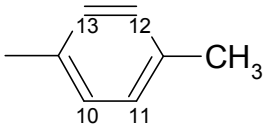
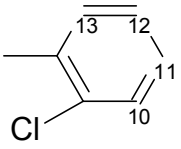
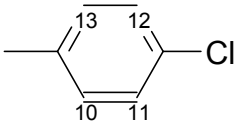
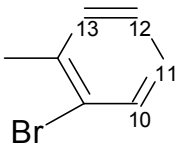
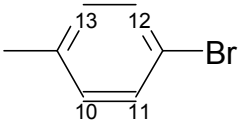
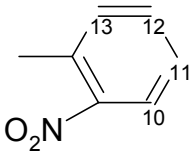
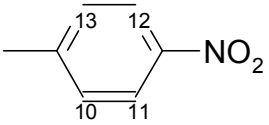
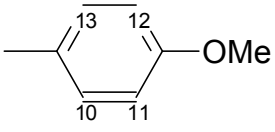
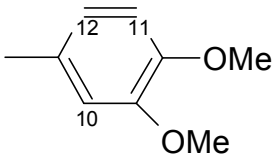
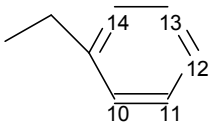
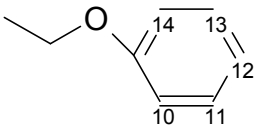
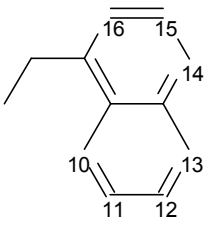
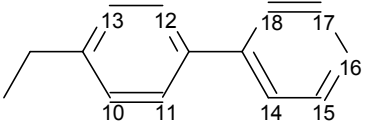
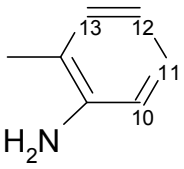
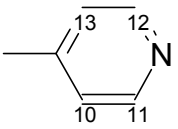
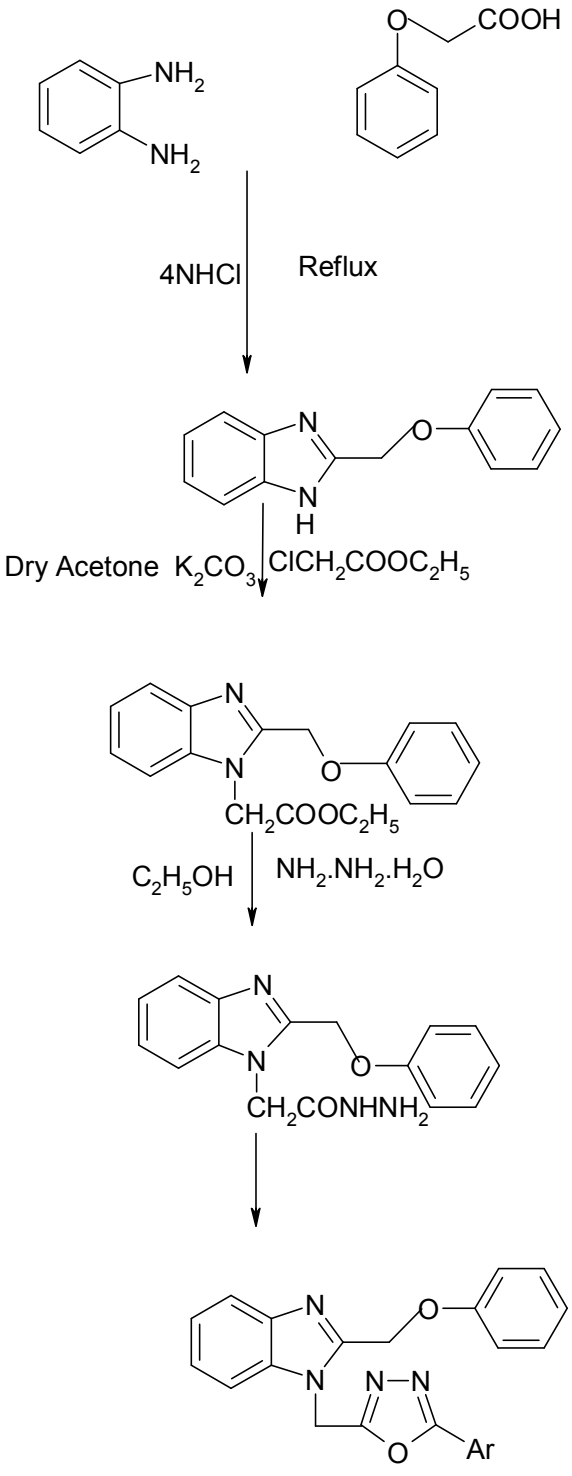


Table 1 :

S.No.	Compounds Name	Structure of Ar
1.	IV a	 phenyl

2.	**IV b**	 **2- methylphenyl**
3.	**IV c**	 **3- methylphenyl**
4.	**IV d**	 **4- methylphenyl**
5.	**IV e**	 **2- chlorophenyl**
6.	**IV f**	 **4- chlorophenyl**
7.	**IV g**	 **2- bromophenyl**
8.	**IV h**	 **4 - bromophenyl**
9.	**IV i**	 **2- nitrophenyl**
10.	**IV j**	 **4- nitrophenyl**
11.	**IV k**	 **4- methoxyphenyl**

12.	**IV l**	 **3,4- dimethoxyphenyl**
13.	**IV m**	 **benzyl**
14.	**IV n**	 **phenoxymethyl**
15.	**IV o**	 **nephthylmethyl**
16.	**IV p**	 **biphenylmethyl**
17.	**IV q**	 **2- aminophenyl**
18	**IV r**	 **4- pyridinyl**



(VIa-r)

Scheme - 1

Spectral Analysis:

Almost eighteen new 2-Benzimidazole substituted 1,3,4 – Oxadiazoles were synthesized .IR, ^{1}HNMR & Mass spectra were recorded and all of them found in full agreement with structural consignments.

Compound IVa (Ar = Phenyl): Yield: 78%; m.pt: 148°-152°C. IR(KBR, Cm^{-1}): 1034(N-N); 1241(C-O); 1602(C=N). ^{1}HNMR(DMSO-d_6, δ ppm): 5.52(s, 2H, CH_2); 6.04(s, 2H, OCH_2); 7.00(s, 3H, H 5, 7, 9); 7.25(s, 4H, H 6, 8, 11, 13); 7.56(s, 3H, H 2, 3, 4); 7.73-7.81(d, 4H, 1, 10, 12, 14). m/z (M^+382). Anal calcd for $C_{23}H_{18}N_4O_2$: C, 72.25; H, 4.71; N, 14.65; O, 8.38. Found: C, 73.82; H, 4.96; N, 14.38; O, 8.40.

Compound IVb (Ar = 2-methyl phenyl): Yield: 60%; m.pt: 138°-140°C. IR(KBR, Cm^{-1}): 1034(N-N); 1239(C-O); 1593(C=N); 3056(CH-Ar). ^{1}HNMR (DMSO-d_6, δ ppm): 2.48(s, 3H, CH_3); 5.45(s, 2H, CH_2); 5.93(s, 2H, OCH_2); 6.83 – 6.87(m, 2H, H 7, 11); 6.92 – 6.94(d, 2H, H 5, 9); 7.14-7.36(m, 6H, H 2, 3, 6, 8, 10, 12); 7.57-7.59(m, 3H, H 1, 4, 13). m/z (M^+396). Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.72; H, 5.05; N, 14.14; O, 8.08. Found: C, 72.14; H, 5.25; N, 14.30; O, 8.10.

Compound IVc (Ar = 3-methyl phenyl): Yield: 60%; m.pt: 170°-172°C. IR(KBR, Cm^{-1}): 1031(N-N); 1238(C-O); 1600(C=N); 3032(CH-Ar). ^{1}HNMR (DMSO- d_6, δ ppm): 3.21-3.38(δ, 3H, CH_3 merged with H_2O in DMSO); 5.50(s, 2H, CH_2); 6.03(s, 2H, OCH_2); 6.99(s, 3H, H 5, 7, 9); 7.23(s, 4H, H 2, 3, 12, 13); 7.43(s, 2H, H 6, 8,); 7.64(s, 2H, H 10, 11); 7.72(s, 2H, H 1, 4). m/z (M^+395). Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.72; H, 5.05; N, 14.14; O, 8.08. Found: C, 71.96; H, 5.24; N, 14.60; O, 8.16.

Compound IVd (Ar = 4-methyl phenyl): Yield: 66%; m.pt: 164°-166°C. IR(KBR, Cm^{-1}): 1237(N-N); 1277(C-O); 1654(C=N). ^{1}HNMR(DMSO-d_6, δ ppm): 2.37(s, 3H, CH_3); 5.50(s, 2H, CH_2); 6.02(s, 2H, OCH_2); 6.91–7.00(m, 3H, H 5, 7, 9); 7.22-7.37(m, 6H, 1, 2, 3, 4, 6, 8); 7.69-7.71(d, 4H, H 10, 11, 12, 13). m/z (M^+397). Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.72; H, 5.05; N, 14.14; O, 8.08. Found: C, 72.80; H, 5.20; N, 14.56; O, 8.38.

Compound IVe (Ar = 2- chlorophenyl): Yield: 72%; m.pt: 170°- 173°C. IR(KBR, Cm^{-1}): 737(C-Cl); 1239(C-O); 1600(C=N); 2982(CH-Ar). ^{1}HNMR (DMSO-d_6, δ ppm): 5.50(s, 2H, CH_2); 6.07(s, 2H, OCH_2); 6.91-6.96(t, 3H, H 5, 7, 9); 7.15-7.34(m, 5H, H 6, 8, 11, 12, 13); 7.59-7.65(t, 2H, H 2, 3); 7.70-7.78(m, 3H, H 1, 4, 10). m/z (M^+416). Anal calcd for $C_{23}H_{17}ClN_4O_2$: C, 66.18; H, 4.07; N, 13.43; O, 7.67. Found: C, 66.24; H, 4.14; N, 13.62; O, 7.22.

Compound IVf (Ar = 4- chlorophenyl): Yield: 69%; m.pt: 236°- 238°C. IR(KBR, Cm^{-1}): 740(C-Cl); 1092(N-N); 1238(C-O); 1608(C=N). 3155(CH-Ar). ^{1}HNMR(DMSO-d_6, δ ppm): 5.47(s, 2H, CH_2); 6.01(s, 2H, OCH_2); 6.87-6.94(m, 3H, H 5, 7, 9); 7.18-7.32(m, 4H, H 2, 3, 6, 8); 7.60(d, 2H, H 10, 13); 7.70-7.71(d, 2H, H 11, 12); 7.76-7.78(d, 2H, H 1, 4). m/z (M^+417). Anal calcd for $C_{23}H_{17}ClN_4O_2$: C, 66.18; H, 4.07; N, 13.43; O, 7.67. Found: C, 66.08; H, 3.97; N, 13.35; O, 7.46.

Compound IVg (Ar = 2- bromophenyl): Yield: 80%; m.pt: 160°- 162°C. IR(KBR, Cm^{-1}): 738(C-Br); 1082(N-N); 1240(C-O); 1592(C=N); 3062(CH-Ar). ^{1}HNMR(DMSO-d_6, δ ppm): 5.50(s, 2H, CH_2); 6.08(s, 2H, OCH_2); 6.88-6.97(m, 3H, H 7, 11, 12); 7.29-7.37(m, 4H, H 2, 3, 6, 8); 7.52-7.55(t, 2H, H 5, 9); 7.70-7.75(t, 3H, H 1, 4, 13); 7.81-7.83(d,1H, 10). m/z (M^+462). Anal calcd for $C_{23}H_{17}BrN_4O_2$: C, 59.87; H, 3.69; N, 12.15; O, 6.94. Found : C, 59.68; H, 3.56; N, 12.22; O, 6.68.

Compound IVh (Ar = 4- bromophenyl): Yield: 76%; m.pt: 204°- 206°C. IR(KBR, Cm^{-1}): 738(C-Br); 1083(N-N); 1241(C-O); 1604(C=N). 2917(CH-Ar). ^{1}HNMR(DMSO-d_6, δ ppm): 5.57(s, 2H, CH_2); 5.85(s, 2H, OCH_2); 6.99-7.03(t, 1H, H 7); 7.08-7.10(d, 2H, H 5, 9); 7.26-7.36(m, 4H, H 2, 3, 6, 8); 7.52-7.57(m, 5H, H 4, 10, 11, 12 13); 7.80-7.82(m,1H, H 1). m/z (M^+460). Anal calcd for $C_{23}H_{17}BrN_4O_2$: C, 59.87; H, 3.69; N, 12.15; O, 6.94. Found: C, 59.36; H, 3.72; N, 12.32; O, 6.74.

Compound IVi (Ar = 2- nitrophenyl): Yield: 58.10%; m.pt: 226°- 228°C. IR(KBR, Cm^{-1}): 1035(N-N); 1239(C-O); 1566 and 1350(NO_2); 1685(C=N); 3063(CH-Ar). ^{1}HNMR (DMSO-d_6, δ ppm): 5.38(s, 2H, CH_2); 5.61(s, 2H, OCH_2); 6.88-6.93(t, 1H, H 7); 7.04-7.06(d, 2H, H 5, 9); 7.23-7.27(t, 4H, H 2, 3, 11, 12); 7.58-7.61(d, 1H, H 6); 7.68(t, 2H, H 10, 13); 7.76-7.81(t, 1H, H 8); 8.01-8.09(t, 2H, H 1, 4). m/z (M^+427). Anal calcd for $C_{23}H_{17}N_5O_4$: C, 64.64; H, 1.64; N, 16.39; O, 14.98. Found: C, 64.80; H, 1.52; N, 16.98; O, 14.96.

Compound IVj (Ar = 4- nitrophenyl): Yield: 70 %; m.pt: 232°- 234°C. IR (KBR Cm^{-1}): 1036(N-N); 1237(C-O); 1287 and 1349(NO_2); 1598(C=C); 1630(C=N). ^{1}HNMR (DMSO- d6, δ ppm): 5.50(s, 2H, CH_2); 6.04(s, 2H, OCH_2); 6.96-6.98(m, 3H, H 5, 7, 9); 7.26-7.40(m, 6H, H 2, 3, 6, 8, 11, 12); 7.71-7.76(m, 4H, H 1, 4, 10, 13). m/z (M^+426). Anal calcd for $C_{23}H_{17}N_5O_4$: C, 64.64; H, 1.64; N, 16.39; O, 14.98. Found: C, 64.76; H, 1.49; N, 16.17; O, 14.68.

Compound IV k (Ar = 4- methoxyphenyl): Yield: 80%; m.pt: 168°- 170°C. IR(KBR, Cm^{-1}): 1028 (N-N); 1256(C-O); 1610 (C=N);. ^{1}HNMR(DMSO-d_6, δ ppm): 3.82(s, 3H, OCH_3); 5.51(s, 2H, CH_2); 6.01(s, 2H, OCH_2); 6.94-7.01(t, 3H, H 5,7, 9); 7.07-7.10(d, 2H, H 6, 8); 7.25-7.35(m, 4H, H 2, 4, 11, 12); 7.73(s, 4H, H 1, 3, 10, 13). m/z (M^+413). Anal calcd for $C_4H_{20}N_4O_3$: C, 69.90; H, 4.85; N, 13.59; O, 11.65. Found: C, 69.38; H, 4.90; N, 13.20; O, 11.76.

Compound IVl (Ar = 2- dimethoxy phenyl): Yield: 85 %; m.pt: 182°- 184°C. IR(KBR, Cm^{-1}): 1025(N-N); 1240(C-O); 1600(C=N); 3025(CH-Ar). ^{1}HNMR (DMSO-d_6, δ ppm): 3.83(s, 6H, OCH_3); 5.50(s, 2H, CH_2); 6.00(s, 2H, OCH_2); 6.92-6.99(m, 3H, H 5, 7, 9); 7.02(d, 1H, H 12); 7.23-7.36(m, 6H, H 2, 3, 6, 8, 10, 11); 7.70-7.75(s, 2H, H 1, 4). m/z (M^+441). Anal calcd for $C_{25}H_{22}N_4O_4$: C, 67.87; H, 4.98; N, 12.66; O, 14.48. Found: C, 67.93; H, 4.90; N, 12.39; O, 14.26.

Compound IVm (Ar = 2- benzyl): Yield: 75 %; m.pt: 234°- 236°C. IR(KBR, Cm^{-1}): 1034(N-N); 1239(C-O); 1610(C=N); 3178(CH-Ar). ^{1}HNMR(DMSO-d_6, ppm): 4.17(s, 2H, CH_2-benzylic); 4.96(s, 2H, CH_2); 5.29(s, 2H, OCH_2.); 6.96-7.03(t, 1H, H 7); 7.09-7.12(d, 2H, H 5, 9); 7.24-7.28(Broad peak ,9H, H 2, 3, 6, 8, 10, 11, 12, 13, 14); 7.51-7.54(d,1H, H 4); 7.64-7.66(d,1H, H 1). m/z (M^+396). Anal calcd for $C_{24}H_{20}N_4O_2$: C, 72.72; H, 5.05; N, 14.14; O, 8.08. Found: C, 72.98; H, 4.98; N, 13.89; O, 08.30.

Compound IVn (Ar = 2- phenoxymethyl): Yield: 73 %; m.pt: 224°-226°C. IR (KBR, Cm^{-1}): 1079(N-N); 1220(C-O); 1623(C=N); 3055(CH-Ar). ^{1}HNMR (DMSO-d_6, δppm): 4.61(s, 2H, OCH_2-phenoxy); 5.12(s, 2H, CH_2); 5.39(s, 2H, OCH_2.); 6.97(s ,4H,H 5, 7, 9, 12); 7.11-7.13(d, 2H, H 10, 14); 7.29(s,6H, H 2, 3, 6, 8, 11, 13); 7.53-7.56(d, 1H, H 4); 7.65-7.67(d,1H, H 1). m/z (M^+411). Anal calcd for $C_{24}H_{20}N_4O_3$: C, 69.90; H, 4.85; N, 13.59; O, 11.65. Found: C, 69.89; H, 4.68; N, 13.87; O, 11.46.

Compound IVo (Ar = α - methylnapthyl): Yield: 65 %; m.pt: 138°- 140°C. IR(KBR, Cm^{-1}): 1036(N-N); 1201(C-O); 1711(C=N); 3158(CH-Ar). ^{1}HNMR (DMSO-d_6, δppm): 3.99(S, 2H, CH_2-Napthyl); 5.24(s, 2H, CH_2); 5.51(s, 2H, OCH_2.); 7.00(s,1H, H 7); 7.11-7.14(d, 2H, H 5,9); 7.30-7.51(m , 7H, H 2,4,6,8,11,12,15); 7.73-7.78(m, 4H, H 1,3,13,16); 7.92-8.10(s, 2H, H 10,14). m/z (M^+445). Anal calcd for $C_{28}H_{22}N_4O_2$: C, 75.33; H, 4.93; N, 12.56; O, 7.17. Found : C, 75.03; H, 4.86; N, 12.74; O, 7.34.

Compound IVp (Ar = 2- biphenylmethyl): Yield: 62%; m.pt: 152°- 154°C. IR(KBR, Cm^{-1}): 1036(N-N); 1240(C-O); 1613(C=N); 3142(CH-Ar). ^{1}HNMR (DMSO-d_6, δppm): 5.16(s, 2H, CH_2-biphenyl); 5.42(s, 2H, CH_2); 5.96(s, 2H, OCH_2.); 6.82-6.85 (d ,2H,H 7,10); 6.91-6.95(t, 2H, H 5,9); 7.18-7.27(broad multiplet,14H, H 2,3,6,7,8,10,11,12,13,14,15,16,17,18); 7.63-7.71(m, 2H, H 1,4). m/z (M^+471). Anal calcd for $C_{30}H_{24}N_4O_2$: C, 76.27; H, 5.08; N, 1.18; O, 6.78. Found: C, 76.46; H, 5.40; N, 1.26; O, 6.46.

Compound IVq (Ar = 2-aminophenyl): Field:56%; m.pt:170^0 -172°C. IR(KBr, Cm^{-1}): 1036(N-N); 1238(C-O); 1626(C=N); 3392(N-H). ^{1}HNMR(DMSO-d_6, δppm): 5.51(s, 2H, CH_2); 6.02(S, 2H, OCH_2); 6.55-6.60(t, 2H, H5,7); 6.66(S ,1H, H11);6.84-7.01(m, 4H, H2,3,5,9); 7.23-7.33(m ,5H,H1,4,6,8,12);7.70-7.72(d, 2H, H10,13). m/z (M^+398). Anal calcd for $C_{23}H_{19}N_5O_2$: C, 69.52; H, 4.78; N, 4.79; O, 8.06. Found : C, 69.70; H, 4.64; N, 4.37; O, 8.28.

Compound IVr (Ar = 2-pyridinyl):
Field: 60%; mpt:210^0 -212°C. IR(KBr, Cm^{-1}):1083(N-N); 1237(C-O); 1731(C=N); 3107(CH-Ar). ^{1}HNMR (DMSO-d_6, δppm): 5.25(s, 2H, CH_2); 5.47(S, 2H, OCH_2); 6.97-7.02(t, 1H, H 7); 7.07-7.35(d, 2H, H 5,9); 7.30-7.35(m, 4H, H 2,3,6,8); 7.68-7.73(t, 2H, H 1,4); missing peak(d_{each}, 2x2H, H 10,11,12,13). m/z (M^+384). Anal calcd for $C_{22}H_{17}N_5O_2$: C, 68.93; H, 4.44; N, 1.83; O, 8.35. Found: C, 68.72; H, 5.02; N, 1.38; O, 8.18.

Biological Evaluations : The compounds were evaluated for anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsiometer in albino mice using phenytoin (25 mg/kg body weight) as the reference drug. Antimicrobial screening of the synthesized compounds were performed for their activity against S. aureus and E. Coli by agar diffusion techemiques using ofloxacin (50mg/ml) as the reference drug. All experiments were approved by the Animal Ethical Committee of the Institute.

Anticonvulsant Activity : The investigations were conducted on albino mice of either sex (25-30)g which were kept under standard condition at an ambient temperature of 25 ± 2^{0}c. Food and water were withdrawn prior to the experimentation. The compounds were screened for their anticonvulsant activity by Maximal Electro shok seizere (MES) method as reported by (Krall et al[9]) Supramaximal electroshock of current intensity of 50mA, 60 Hz for 0.2 sec duration was given to mice administered with the equimolar dose of standard (phenytion : 25mg/kg body weight) and the test (31.77-46.72 mg/kg body wt). The abolition of the hind tonic extensor spasm was recorded as an increased anticonvulsant activity. The results have been shown in table :

Antimicrobial Activity : The principle[10], involved in the antimicrobial evaluation, is the inhibition of microbial growth under standard condition utilized for demonstrating the therapeutic efficacy of any subtle change in any antimicrobial molecule. The present work revealed the efficacy of eighteen compounds (IVa-r) determined against S.aureus (gram (+)ve) and E. Coli (gram (–) ve) microbes.

The nutrient agar medium was prepared and autoclaved at 15.1 lbs pressure for 20 mins. The medium was poured into Petri plate and allowed to solidity. On the surface of medium, the microbial suspention was spread with the help of sterilized cotton swab. Five cups were made in each Petri plate. Afterwards, the concentrations (50 mcg/ml, 100 mcg/ml and 200 mcg/ml) of test compounds were added into first three cups. The fourth was filled with standard and finally fifth one was filled with control (DMSO). The plates were kept in cold for one hour to allow the diffusion of test compds and then after incubated for 24 hrs. at a temperature of 37 + 0.5^{0}C. The zone of inhibition was measured and % inhibition of each test compd was calculated.

Table 2: Anticonvulsant activity of compounds (Iv_a-IV_r)

S.No.	Compound No.	Ar	Anticonvulsant Activity MES (60 min) % Protection
1	IV_a	C_6H_5	66.66*
2	IV_b	2-$CH_3C_6H_5$	66.66*
3	IV_c	3-$CH_3C_6H_5$	50.00
4	IV_d	4-$CH_3C_6H_5$	66.66*
5	IV_e	2-ClC_6H_5	83.33**
6	IV_f	4-ClC_6H_5	66.66*
7	IV_g	2-BrC_6H_5	100***
8	IV_h	4-BrC_6H_5	83.33**
9	IV_i	2-$NO_2C_6H_5$	66.66*
10	IV_j	4-$NO_2C_6H_5$	33.33
11	IV_k	4-$OCH_3C_6H_5$	66.66*
12	IV_l	3,4-di$OCH_3C_6H_5$	83.33**
13	IV_m	$C_6H_5CH_2$	66.66*
14	IV_n	$C_6H_5OCH_2$	66.66*
15	IV_o	$C_{10}H_7CH_2$	50.00
16	IV_p	$C_{12}H_9CH_2$	50.00
17	IV_q	2-$NH_2C_6H_5$	66.66*
18	IV_r	C_5H_4N	66.66*
19	Phenytoin		100***

*P<0.05, **P,0.01, ***P,0.001

Table 3 : Antibacterial activity of compounds (Iv_a-IV_r) against E. Coli

The reference drug **Ofloxacin** showed the zone of inhibition **(32 mm)** at 50 µg/ml concentration.

Compounds	Zone of Inhibition (mm)			% Inhibition		
	50 µg/ml	100 µg/ml	200 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml
IV_a	12	15	17	-	+	+
IV_b	13	15	16	+	+	+
IV_c	12	13	16	-	+	+
IV_d	22	24	27	++	++	+++
IV_e	13	14	17	+	+	+
IV_f	23	25	29	++	++	+++
IV_g	14	16	18	+	+	+
IV_h	15	17	19	+	+	++
IV_i	11	14	16	-	+	+
IV_j	13	15	18	+	+	+
IV_k	10	14	17	-	+	+
IV_l	12	15	19	-	+	+
IV_m	13	14	16	+	+	+
IV_n	10	12	14	-	-	+
IV_o	15	17	18	+	+	+
IV_p	16	18	20	+	+	++
IV_q	11	13	15	-	+	+
IV_r	21	24	28	++	++	+++

% inhibition of ofloxacin -++++ (100%)

+++ (80%-99%), ++ (60%-79%), + (40%-59%), - (<39% or no activity)

Table 4: Antibacterial activity of compounds (Iv_a-IV_r) against S. aureus

The reference drug **Ofloxacin** showed the zone of inhibition **(32 mm)** at 50 µg/ml concentration.

Compounds	Zone of Inhibition (mm)			% Inhibition		
	50 µg/ml	100 µg/ml	200 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml
IV_a	10	13	17	-	+	+
IV_b	12	16	19	+	+	++
IV_c	13	15	18	+	+	+
IV_d	23	25	28	++	++	+++
IV_e	14	17	20	+	+	++
IV_f	21	25	27	++	++	+++
IV_g	09	13	15	-	+	+
IV_h	12	13	16	+	+	+
IV_i	14	16	19	+	+	++
IV_j	13	17	20	+	+	++
IV_k	11	14	16	-	+	+
IV_l	11	14	17	-	+	+
IV_m	13	17	19	+	+	++
IV_n	15	18	19	+	+	++
IV_o	16	18	20	+	+	++
IV_p	10	14	17	-	+	+
IV_q	13	14	17	+	+	+
IV_r	23	25	29	++	++	+++

% inhibition of ofloxacin -++++ (100%)

+++ (80%-99%), ++ (60%-79%), + (40%-59%), - (<39% or no activity)

Result & Disscussion

Anticonvulsant studies of these compounds revealed that compd IV_g was equipotent with that of the standard (i.e. 100% protection) at equiimolar dose. Compds IV_e, IV_h & IV_l showed equal protection of 83.33% and rest other compds of the series exhibited anticonvulsant activity between 50.0% - 66.66% at equimolar dose to phenytoin.

The antimicrobial studies revealed that compds IV_d, IV_f & IV_r showed more than 80% inhibition against E.Coli (NCTE 6571) at the concentration of 200 mcg/ml Rest other compds exhibited inhibition between 40% - 79% against E.Coli.

The screening against S.aureus (NCTE 7447) described that compds IV_d, IV_f & IV_r produced 80% inhibition at the concentration of 200mcg/ml. Rest other compds elicited % inhibition raging between 40% - 79% against S.aureus.

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