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ORIGINAL RESEARCH ARTICLE

Synthesis And Evaluation Of Some Newer Indole Derivatives As Anticonvulsant Agents

Anil Kumar, Deepak Kumar#, Mohd.Akram and H. Kaur

Department of Chemistry, NAS College, Meerut-250002 (U.P.) India.
#Department of Chemistry D.N.(P.G.)College,Meerut-250002

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ABSTRACT

A new series of 3-(4-substituted phenyl)-3-(substituted phenyl aminomethylene)-2,3-dihydrobenzoxazepin/benzothiazepin-2-yl)-2,5-disubstituted indoles **(13-36)** were synthesized for anticonvulsant activity. Compound **(30)** found to be most potent compound of this series. All compounds were screened in vivo for their anticonvulsant activity and acute toxicity studies. The structural assignment of these compounds has been made on the basis of elemental analysis, IR and ^{1}H-NMR data.

Key Words: Indole, Benzothiazepines; benzoxazepines; anticonvulsant activity; toxicity studies

INTRODUCTION

Indole is the most beneficial heterocyclic nucleus which has gained prominence in medicinal chemistry due to its diverse biological activities such as anticonvulsant [1-6], anti-inflammatory [7], antipsychotic [8] activities. It is interesting to note from chemical literature that triazole[9-13] and azetidinone[14-15] exhibit spectrum of biological activities in different heterocyclic nuclei. It is therefore thought worthwhile to synthesize some new indole derivatives by incorporating triazolyl and azetidinonyl moieties in single molecular frame work with the hope to possess better anticonvulsant agents.

CHEMISTRY

The synthetic routes of compounds are outlined in scheme-1.substituted phenyl chalconyl-2,5-di substituted indoles were synthesized by the reaction of 4-chloro acetophenone and substituted indole-3-carboxyldehyde i.e. compounds(1-4). To the ethanolic solution of compound(1) amino benzophenol was added in the presence of glacial acetic acid to obtain compounds(5-12).compound(5) further reacted with aniline and formaldehyde in the presence of methanol yielded substituted phenylaminomethylene -(2,3-dihydrobenzoxazepin/benzothiazepin-2-yl)-disubstituted indoles i.e. compounds(13-36). The structures of newly synthesized compounds were confirmed on the basis of their physical and elemental analysis as illustrated in (Table 1, 2, 3).

PHARMACOLOGICAL EVOLUTION

The anticonvulsant activity was performed according the method of Toman et al[16] on Charles foster rats of either sex weighing, between in 90-150 g. Rats were divided into groups of ten animal each. The rats were treated with different doses of test drugs or phenytoin sodium 30 mg/kg i.p. After 1 h they were subjected to a shock of 150 m.A by convulsiometer through ear electrodes for 0.2 s and the presence or absence of extensor response was noted . Animals in which extensor response was abolished were taken as protected rats. The compounds were also investigated for their acute toxicity (ALD_{50}) in mice by following the method of smith [17].

EXPERIMENTAL

The melting points of compounds were determined in open capillaries and thin layer chromatography was done on Silica gel-G plates. The eluent was a mixture of different polarity in different proportion and spots were located by iodine. Elemental analysis (C, H, N) of these newly synthesized compounds were done on Carlo Erba-1108 elemental analyzer. The IR spectra were recorded on Bruker IFS-66 V FI-IR

***Corresponding Author:** Anil Kumar, **Email:** anilshivalik@yahoo.in, **Contact No:** +91-9897204028

(ν max in cm^{-1}). The ^1H NMR spectra were recorded by Bruker DRX-400 FT-NMR instrument using $CDCl_3$ as solvent, tetramethyl silane (TMS) as internal reference standard Chemical shift (δ) value recorded in ppm.

3-(4-Chloro Phenyl Chalconyl)-2-methyl indole (1)

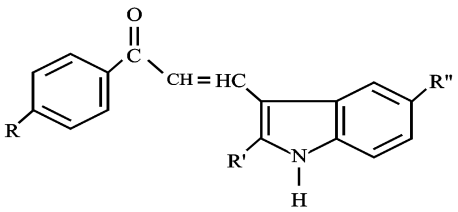
To the ethanolic solution of 4-chloro acetophenone (0.01 mole) was added 2-methyl indole-3- carboxyldehyde (0.01 mol.) and 2% NaOH solution. (2 ml.) and the mixture was refluxed for 10-14 h. Completion of the reaction was monitored by TLC and after completion of the reaction, the reaction mixture was conc. to half of its volume and poured onto crushed ice. The resultant solution was then mixed with benzene and separated by separating funnel. Benzene from the organic layer was distilled off and the residue thus obtained was washed several times with water and finally recrystallized from methanol/water to obtained compound (1) melting point 122ºC; yield 75%;

Spectral Analysis:

IR (KBr) ν_{max} in cm^{-1} : 3415 (N-H), 3025 (aromatic C-H), 2856, 2966 (aliphatic C-H), 1705 (C=O), 1672 (CH=CH-), 1550 (C⋯C of aromatic ring), 1225 (C-N) .^1H NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: 9.78 (s,1H,NH of indolic exchangeable), 8.65 (d, 1H, COCH = CH-), 7.82-6.80 (m, 8H, Ar-H), 6.65 (d, 1H, COCH=), 2.20 (s, 3H, Methyl indole). Anal. Calcd $C_{18}H_{14}ClNO$. for : C, 70.10 ; H, 4.77 ;N, 4.74.; Found C, 73.23; H,4.42 ;N, 4.58 %. MS: $[M]^+$ at *m/z* 295.7.

Other 3-(4-substituted phenyl chalconyl)-2, 5-di substituted indoles. Compound (2-4) was also prepared by the same procedure and their physical and analytical data are given in (**Table 1**).

Table-I: Physical and analytical data of 3-(4 substituted phenyl chalconyl)- 2, 5-di substituted Indoles (1-4).



Comp	R	R'	R"	M.P ºC	Yield %	Recrystalizing Solvent	Mol. formula	Mol. wt	Element Analysis					
									% C		% H		% N	
									Calcd	Found	Calcd	Found	Calcd	Found
1	4-Cl	2-CH_3	-H	122	75	Methanol	$C_{18}H_{14}ClNO$	295.7	73.10	73.23	4.77	4.42	4.74	4.58
2	4-Cl	2-CH_3	5-CH_3	136	72	Ethanol	$C_{19}H_{16}ClNO$	309.7	73.66	73.74	5.21	4.54	4.52	3.49
3	4-Br	2-CH_3	-H	144	80	Methanol	$C_{18}H_{14}BrNO$	340.2	63.55	63.28	4.15	4.32	4.12	4.46
4	4-Br	2-CH_3	5-CH_3	154	85	Ethanol	$C_{19}H_{16}BrNO$	354.2	64.42	64.45	4.55	4.66	3.95	3.46

3-(4-chloro phenyl-2, 3-dihydro benzoxazepin-2-yl)-2-methyl indole (5)

To the ethanolic solution of compound 1 (0.01 mole) was added 2-amino benzophenol with few drops of glacial acetic acid was refluxed for 3-5 h after refluxing, solvent was distilled off under reduced pressure and the solid thus obtained was recrystallized with ethanol to afford compound (5). Compound (5) melting point 138ºC yield 65%;

Spectral Analysis:

IR (KBr) ν_{max} in cm^{-1} : 3426 (N-H), 3029 (aromatic C-H), 2864, 2974 (aliphatic C-H), 1544 (C⋯C of aromatic ring), 1232 (C-N), 1048 (C-O-C), 1461(C=N), 860 (C-Cl).

^1H-NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: 9.84(s,1H,NH of indolic exchangeable), 8.40 (t, 1H, ring of benzoxazepine), 7.78-6.76 (m, 12H, Ar-H), 5.82 (d, 2H, ring of benzoxazepine), 2.35 (s, 3H methyl indole). Anal. Calcd $C_{24}H_{19}ClN_2O$. for : C, 74.51 ; H, 4.95 ;N, 7.24.; Found C, 74.73; H,4.72 ;N, 7.43 %. MS: $[M]^+$ at *m/z* 386.5.

Other 3-(4-substituted phenyl (2,3-dihydro benzoxazepin/benzothiazepin-2-yl)-2,5-di substituted indoles (6-12) were prepared by the same method as described for compound(5) and their physical and analytical data are given in (**Table 2**).

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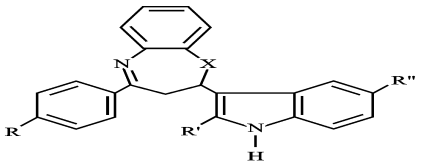
Table-2: Physical and analytical data of 3-(4-substituted phenyl-2, 3-di hydro benzoxazepin/ benzothiazepin-2-yl)- 2, 5-di substituted indoles (5-12).



Comp	R	R'	R"	X	M.P °C	Yield %	Recrystalizing Solvent	Mol. formula	Mol. wt	Element Analysis					
										% C		% H		% N	
										Calcd	Found	Calcd	Found	Calcd	Found
5	4-	2-	-H	O	138	65	Ethanol	$C_{24}H_{19}ClN_2$	386.8	74.51	74.73	4.95	4.72	7.24	7.43
6	4-	2-	-H	O	152	77	Acetic acid/water	$C_{24}H_{19}BrN_2$	430.5	66.83	66.53	4.44	4.11	6.49	6.23
7	4-	2-	5-	O	168	68	Ethanol	$C_{30}H_{23}ClN_2$	426.5	77.83	77.54	4.97	4.69	6.05	6.36
8	4-	2-	5-	O	172	79	Acetic acid/water	$C_{30}H_{23}BrN_2$	506.9	71.01	71.32	4.53	4.27	5.52	5.28
9	4-	2-	-H	S	142	63	Benzene Pt	$C_{24}H_{19}ClN_2$	402.9	71.54	71.68	4.75	4.89	6.95	6.64
10	4-	2-	-H	S	162	75	DMF/Water	$C_{24}H_{19}BrN_2$	447.3	64.43	64.67	4.28	4.46	6.26	6.54
11	4-	2-	5-	S	163	65	Benzene/ benzene	$C_{30}H_{23}ClN_2$	478.5	75.23	75.52	4.80	4.96	5.85	5.63
12	4-	2-	5-	S	178	72	DMF/Water	$C_{30}H_{23}BrN_2$	506.9	71.01	71.37	4.53	4.73	5.52	5.79

3-(4-chloro phenyl, 2, 3-di hydro benzothiazepin-2-yl)-2-methyl indole (9).

Compound (9) m. point 142ºC; yield 63%.

Spectral Analysis:

IR (KBr) ν_{max} in cm^{-1} : 3430 (N-H), 3010 (aromatic C-H),2853,2960 (aliphatic C-H), 1540 (C⎓C of aromatic ring), 1225 (C-N), 754 (C-S-C), 1460 (C=N), 846 (C-Cl).

^{1}H-NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: 9.86(s,1H,NH of indolic exchangeable), 8.42 (t, 1H, ring of benzoxazepine), 7.82-6.79 (m, 12H, Ar-H), 5.86 (d, 2H, ring of benzoxazepine), 2.44 (s, 3H, methyl indole). Anal. Calcd $C_{24}H_{19}ClN_2S$. for : C, 71.54 ; H, 4.75 ;N, 6.95.; Found C, 71.68; H, 4.89 ; N, 6.64 %. MS : $[M]^+$ at *m/z* 402.5.

3-(4-chloro phenyl-3-(phenyl aminomethylene), 2,3 dihydro benzoxazepin-2-yl)-2-methyl indole (13)

The mixture of compound (5) (0.001 mol.), aniline (0.001 mol.) and formaldehyde (0.001 mol.) in methanol (30 ml.) was refluxed for 4-6 h the resultant reaction mixture was concentrated cooled and poured onto ice. The separated solids were filtered and recrystallised from Methanol to yield compound 13.

Compound 13 : m. point 144ºC; yield 58%.

Spectral Analysis:

IR (KBr) ν_{max} in cm^{-1} : 3437 (N-H), 3012 (aromatic C-H), 2865, 2968 (aliphatic C-H), 1535 (C⎓C of aromatic ring), 1229 (C-N), 1085 (C-O-C), 1470 (C=N), 810 (C-Cl)

^{1}H-NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: (s,1H,NH of indolic exchangeable), 9.10 (S, 1H, NH-CH_2), 8.35 (d, 1H, ring of benzoxazepine), 7.74-6.76 (m, 17H, Ar-H), 6.42 (d, 2H, CH-CH_2-NH), 5.75 (d, 1H, ring of benzoxazepine), 2.65 (s, 3H, methyl IInd position of indole ring). Anal. Calcd $C_{31}H_{26}ClN_3O$. for : C, 75.68 ; H, 5.28 ;N, 8.54.; Found C, 75.95; H, 5.50 ; N, 8.35 %. MS : $[M]^+$ at *m/z* 492.0.

Other 3-(4-substituted phenyl 3-(substituted phenyl amino methylene) (2,3- di hydro benzothiazepin/ benzoxazepin-2-yl)-2,5-di substituted indoles (14-36) were prepared by the same method as described for compound (13) and their physical and analytical data are given in (**Table 3**).

3-(4-Bromo phenyl)-3-(di phenyl amino methylene), 2,3 di hydro benzothiazepin-2-yl)-5-chloro-2methyl indole (36)

Compound (36): m. point 211ºC; yield 56%

Spectral Analysis:

IR (KBr) ν_{max} in cm^{-1} : 3433 (N-H), 3005 (aromatic C-H), 2860, 2958 (aliphatic C-H), 1530 (C⎓C of aromatic ring), 1220 (C-N), 765 (C-S-C), 1440 (C=N), 790 (C-Br).

^{1}H NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: 9.84 (s, 1H of indolic exchangeable), 9.12 (S, 1H, NH-CH_2), 8.35 (d, 1H, ring of benzothiazepine), 7.76-6.82 (m, 20H, Ar-H), 6.42 (d, 2H, CH-CH_2-NH), 5.75 (d, 1H, ring of benzothiazepine), 3.15 (s, 3H methyl IInd position of indole ring). Anal. Calcd $C_{37}H_{29}BrClN_3S$. for : C, 67.02 ; H, 4.41 ;N, 6.34.; Found C, 67.22; H, 4.67 ; N, 6.52 %. MS: $[M]^+$ at *m/z* 663.0.

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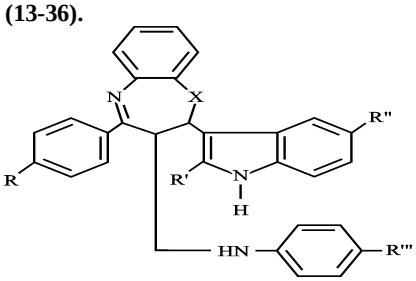
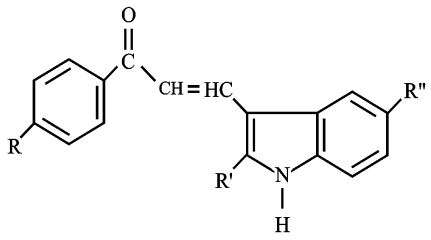
Table 3: Physical and analytical data of 3-(4-substituted phenyl)-3-(substituted phenyl aminomethylene)-2, 3-dihydrobenzoxazepin/ benzothiazepin-2-yl)-2,5-disubstituted indoles. (13-36).



Comp	R	R'	R"	R"'	X	M.P °C	Yield %	Recrystalizing Solvent	Mol. formula	Mol. wt	Element Analysis % C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
13	Cl	CH_3	H	H	O	144	58	Methanol	$C_{31}H_{26}N_3OCl$	492.0	75.68	75.72	5.33	5.82	8.54	8.62
14	Cl	CH_3	H	CH	O	176	55	Methanol	$C_{32}H_{28}N_3OCl$	506.0	75.95	75.80	5.58	5.38	8.30	8.52
15	Cl	CH_3	H	Cl	O	182	45	Methanol	$C_{31}H_{25}N_3OCl_2$	526.4	70.72	70.94	4.79	4.93	7.98	7.65
16	Br	CH_3	H	H	O	156	55	Methanol	$C_{31}H_{26}N_3OBr$	536.4	69.41	69.32	4.89	4.71	7.83	7.58
17	Br	CH_3	H	CH	O	168	41	Methanol	$C_{32}H_{28}N_3OBr$	549.1	69.82	69.68	5.13	5.42	7.63	7.34
18	Br	CH_3	H	Cl	O	178	48	Methanol	$C_{31}H_{25}N_3OBrC$	570.9	65.22	65.38	4.41	4.72	7.36	7.58
19	Cl	C_6H_5	CH_3	H	O	179	43	Methanol	$C_{37}H_{30}N_3OCl$	568.1	78.22	78.54	5.32	5.06	7.40	4.68
20	Cl	C_6H_5	CH_3	CH	O	181	48	Methanol	$C_{38}H_{32}N_3OCl$	582.1	78.40	78.19	5.54	5.73	7.22	7.44
21	Cl	C_6H_5	CH_3	Cl	O	184	42	Methanol	$C_{38}H_{29}N_3OCl_2$	602.5	73.75	73.52	4.85	4.67	6.97	6.71
22	Br	C_6H_5	CH_3	H	O	172	44	Methanol	$C_{37}H_{30}N_3OBr$	612.5	72.55	72.34	4.94	4.71	6.86	6.54
23	Br	C_6H_5	CH_3	CH	O	179	49	Methanol	$C_{38}H_{32}N_3OBr$	626.5	72.84	72.61	5.15	5.34	6.71	6.51
24	Br	C_6H_5	CH_3	Cl	O	188	51	Methanol	$C_{37}H_{29}N_3OBrC$	647.0	68.69	68.44	4.52	4.28	6.49	6.21
25	Cl	CH_3	H	H	S	182	54	Ethanol	$C_{31}H_{26}N_3SCl$	508.0	73.28	73.52	5.16	5.38	8.27	8.54
26	Cl	CH_3	H	CH	S	190	42	Ethanol	$C_{32}H_{28}N_3SCl$	522.1	73.61	73.34	5.41	4.72	8.05	8.29
27	Cl	CH_3	H	Cl	S	198	40	Ethanol	$C_{31}H_{25}N_3SCl_2$	542.5	68.63	68.42	4.64	4.87	7.75	7.53
28	Br	CH_3	H	H	S	163	52	Ethanol	$C_{31}H_{26}N_3SBr$	552.5	67.39	67.66	4.74	4.51	7.61	7.84
29	Br	CH_3	H	CH	S	176	54	Ethanol	$C_{32}H_{28}N_3SBr$	566.5	67.84	67.62	4.98	4.68	7.42	7.23
30	Br	CH_3	H	Cl	S	204	51	Ethanol	$C_{31}H_{25}N_3SBrCl$	586.9	63.43	63.64	4.29	4.54	7.16	7.38
31	Cl	C_6H_5	CH_3	H	S	173	43	Ethanol	$C_{37}H_{30}N_3SCl$	584.1	76.07	76.32	5.18	5.44	7.19	7.42
32	Cl	C_6H_5	CH_3	CH	S	182	50	Ethanol	$C_{38}H_{32}N_3SCl$	598.2	76.30	76.58	5.39	5.67	7.02	7.18
33	Cl	C_6H_5	CH_3	Cl	S	192	46	Ethanol	$C_{38}H_{29}N_3SCl_2$	617.1	71.84	71.56	4.73	4.52	6.79	7.49
34	Br	C_6H_5	CH_3	H	S	194	48	Ethanol	$C_{37}H_{30}N_3SBr$	628.6	70.69	70.41	4.81	4.48	6.68	6.41
35	Br	C_6H_5	CH_3	CH	S	206	53	Ethanol	$C_{38}H_{32}N_3SBr$	642.6	71.02	71.18	5.02	5.28	6.54	6.78
36	Br	C_6H_5	CH_3	Cl	S	211	56	Ethanol	$C_{37}H_{29}N_3SBrCl$	663.0	67.02	67.22	4.41	4.67	6.34	6.52

Table-4: Anticonvulsant activity of 3-(4 substituted phenyl chalconyl)- 2, 5-di substituted Indoles (1-4).



Comp.	R	R'	R''	Dose (mg/kg i.p.)	Anticonvulsant activity (SMESC) No. of animals exhibiting convulsion	Anticonvulsant activity (SMESC) % seizure protection	ALD_{50} (mg/kg i.p.)
		P.G.[a]		2 ml.	10	0	
		phenytoin sodium[b]		30	2	80***	
1.	4-Cl	2-CH_3	5-H	30	6	40*	> 1000
2.	4-Cl	2-C_6H_5	5-CH_3	30	7	30	> 1000
3.	4-Cl	2-CH_3	5-H	30	7	30	> 1000
4.	4-Cl	2-C_6H_5	5-CH_3	30	6	40*	> 1000

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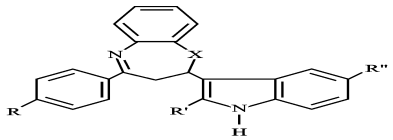
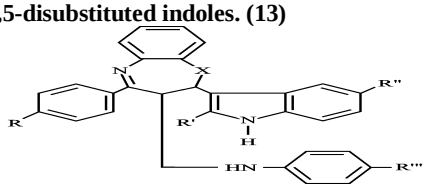
Table 5: Anticonvulsant activity of 3-(4-substituted phenyl-2, 3-di hydro benzoxazepin/benzothiazepin-2-yl)- 2, 5-di substituted indoles (5-12).



Comp.	X	R	R'	R''	Dose (Mg/kg i.p.)	Anticonvulsant activity (SMESC)		ALD_{50} (mg/kg i.p.)
						No. of animals exhibiting convulsion	% seizure protection	
			P.G.[a]		2 ml.	10	0	
			phenytoin sodium[b]		30	2	80***	
5.	O	-Cl	$-CH_3$	-H	30	4	60**	> 1000
6.	O	-Br	$-CH_3$	-H	30	5	50**	> 1000
7.	O	-Cl	$-C_6H_5$	$-CH_3$	30	5	50**	> 1000
8.	O	-Br	$-C_6H_5$	$-CH_3$	30	6	40*	> 1000
9.	S	-Cl	$-CH_3$	-H	30	4	60**	> 1000
					7.5	8	20	
10.	S	-Br	$-CH_3$	-H	15	6	40*	>2000
					30	2	80***	
11.	S	-Cl	$-C_6H_5$	$-CH_3$	30	4	60**	> 1000
12.	S	-Br	$-C_6H_5$	$-CH_3$	30	3	70**	> 1000

Table 6: Anticonvulsant activity of 3-(4-substituted phenyl)-3-(substituted phenyl-aminomethylene)-2, 3-dihydrobenzoxazepin/benzo-thiazepin-2-yl)-2,5-disubstituted indoles. (13)



Comp.	X	R	R'	R''	R'''	Dose (mg/kg i.p.)	Anticonvulsant activity (SMESC)		ALD_{50} (mg/kg i.p.)
							No. of animals exhibiting convulsion	% seizure protection	
			P.G.[a]			2 ml.	10	0	
			phenytoin sodium			30	2	80***	
13.	O	Cl	$-CH_3$	-H	-H	30	4	60**	> 1000
14.	O	Cl	$-CH_3$	-H	$-CH_3$	30	4	60**	> 1000
15.	O	Cl	$-CH_3$	-H	-Cl	30	3	70**	> 1000
16.	O	Br	$-CH_3$	-H	-H	30	4	60**	> 1000
17.	O	Br	$-CH_3$	-H	$-CH_3$	30	4	60**	> 1000
18.	O	Br	$-CH_3$	-H	-Cl	30	2	80**	> 1000
19.	O	Cl	$-C_6H_5$	$-CH_3$	-H	30	3	70**	> 1000
20.	O	Cl	$-C_6H_5$	$-CH_3$	$-CH_3$	30	3	70**	> 1000
21.	O	Cl	$-C_6H_5$	$-CH_3$	-Cl	30	3	70**	> 1000
22.	O	Br	$-C_6H_5$	$-CH_3$	-H	30	2	80**	> 1000
23.	O	Br	$-C_6H_5$	$-CH_3$	$-CH_3$	30	3	70**	> 1000
24.	O	Br	$-C_6H_5$	$-CH_3$	-Cl	30	2	80**	> 1000
25.	S	Cl	$-CH_3$	-H	-H	30	3	70**	> 1000
26.	S	Cl	$-CH_3$	-H	$-CH_3$	30	3	70**	> 1000
27.	S	Cl	$-CH_3$	-H	-Cl	30	3	70**	> 1000
28.	S	Br	$-CH_3$	-H	-H	30	2	70**	> 1000
29.	S	Br	$-CH_3$	-H	$-CH_3$	30	3	70**	> 1000
						7.5	8	20	
30.	S	Br	$-CH_3$	-H	-Cl	15.0	5	50*	> 2000
						30.0	1	90***	
31.	S	Cl	$-C_6H_5$	$-CH_3$	-H	30	3	70**	> 1000
32.	S	Cl	$-C_6H_5$	$-CH_3$	$-CH_3$	30	3	70**	> 1000
33.	S	Cl	$-C_6H_5$	$-CH_3$	-Cl	30	4	60**	> 1000
34.	S	Br	$-C_6H_5$	$-CH_3$	-H	30	2	80***	> 1000
35.	S	Br	$-C_6H_5$	$-CH_3$	$-CH_3$	30	3	70**	> 1000
						7.5	7	30***	
36.	S	Br	$-C_6H_5$	$-CH_3$	-Cl	15.0	5	50**	> 1000
						30.0	2	80***	

* P < 0.05; ** P < 0.01; *** P < 0.001

a. P.G. = Propylene glycol standard for control group.

b. Phenytoin Sodium = reference standard for anticonvulsant activity.

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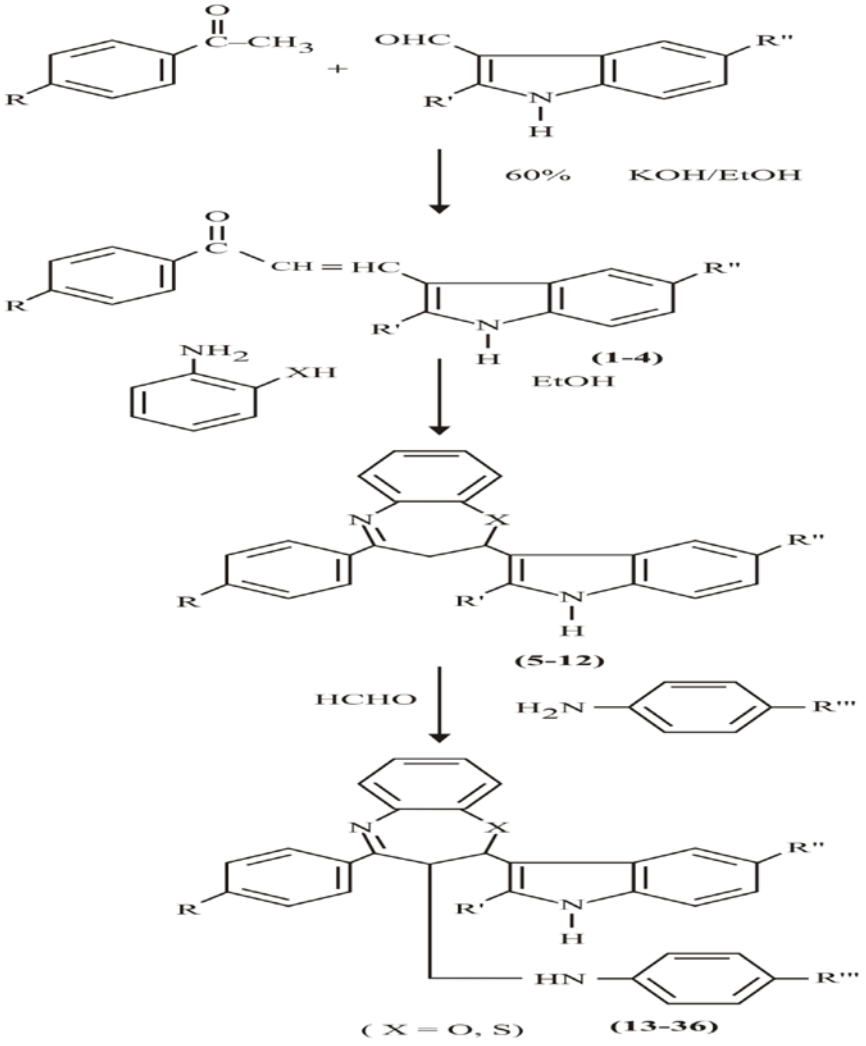
c. Subramaximal Electroshock seizure pattern test.

RESULTS AND DISCUSSION

All the newly synthesized compounds were tested in vivo in order to screen them for their anticonvulsant activity the pharmacological data of all the compounds of this series have been reported in table IV, V & VI. These compounds were tested for their anticonvulsant activity against maximal electroshock induced seizures tested at 30 mg/kg i.p. exhibited anticonvulsant activity.

Out of the compounds screened, compound 30 was found most potent than standard drug phenytoin sodium at a dose of 30 mg/kg i.p. compound 10, 18, 22, 24, 34 & 36 were found to possess activity equipotent to that of reference drugs shows the anticonvulsant activity of compounds 10, 30 & 36 were found to possess activity equipotent to that of reference drugs. fig. no. (1) shows the anticonvulsant activity of compounds 10, 30 & 36 at three graded doses (7.5, 15 & 30 mg/kg i.p.), the reference drug phenytoin sodium (30 mg/kg i.p.) and propylene glycol (2 ml). Compound 30 should more potent activity at a dose of 30 mg/kg i.p. and less potent at a dose of 7.5 and 15 mg/kg i.p. the compound no. 10 exhibited equipotent activity to the reference drug at a dose of 30 mg/kg i.p. in comparison to the compound 30.

However, the compounds of this series showed good anticonvulsant activity, the compounds having benzoxazepine moiety revealed less percentage inhibition (ranging between 50-80%) of seizures in Albino rats while the compounds having benzothiazepine moiety exhibited comparatively greater percentage inhibition of seizure ranging between 60-90%. Out of four newly synthesized halo substituted acetophenyl 2, 3, 5-tri substituted indolidinones the two compounds (1 & 4) have shown equal percentage of inhibition of seizures. Furthermore compounds having 4-chloro and 2-methyl group as a substituent on the phenyl ring & indole ring respectively exhibited 40% inhibition of seizures, compound (1) and compound having 4-bromo and 2-phenyl substituent at phenyl ring & indolering respectively exhibited 40% inhibition of seizures.



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CONCLUSION

It was found that the presence of electonegative atom Cl, as a substituents at 4-position of phenyl rings in compound no. (30) showed better anticonvulsant activities hence following conclusions were drawn:

1. Presences of benzothiazepine moiety have shown better anticonvulsant activity than the compound having benzoxazepine moiety.
2. p-chloro methylene amino phenyl substitution at IVth position of benzothiazepine ring showed more potent activity than other substituted benzoxazepine.
3. The presence of electronegative substituents (Cl) plays a pivotal role to increase the anticonvulsant activity.

All the compounds showed ALD_{50} values > 1000 mg/kg i.p. suggesting a good safety margin. However the most potent compounds 10 & 30 exhibited an ALD_{50} > 2000 mg/kg i.p. maximum dose tested.

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