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Anticonvulsant Study of Thiadiazoles and Phenothiazines

PAYAL SINGH†, PANKAJ KUMAR†, YESHOWARDHAN†,
JAI SINGH† and ASHOK KUMAR*
Department of Pharmocology, L.L.R.M. Medical College, Meerut-250 006, India

Ethyl-3-heteroarylacetates, 1-(3'-heteroarylacetyl)-semicarbazides/thiosemicarbazides, 2-amino-5-(3'-hetero-arylmethylene)-1,3,4-oxadiazoles/thiadiazoles, 5-(2'-heteroaryl methylene-1',3',4'-oxadiazol-2'-yl/thiadiazol-2'-yl)-2-oxo/thiobarbituric acid, have been prepared. Their structures have been confirmed by TLC, elemental analysis, infrared spectra, NMR spectra and mass spectra. They have been screened for their anticonvulsant activity and ALD_{50}.

Key Words: Anticonvulsant, Thiadiazoles, Phenothiazines.

INTRODUCTION

Several heterocyclic compounds have gained the medicinal importance in the recent years. Among these, thiadiazole[1-8] have been the most potent. Substitution by different heterocyclic moieties at position 2- and 4- either imparts biological activity or enhances it. Some more effective compounds were prepared and screened for anticonvulsant activity.

EXPERIMENTAL

Ethyl-3-indoloacetate: A solution of indole (0.01 mol), ethylchloro-acetate (0.01 mol), anhydrous acetone (90 mL), anhydrous K_2CO_3 (8.0 g) were refluxed for 24 h. After refluxing, the excess of solvent was distilled off. The reaction mixture was cooled, filtered and washed with water and recrystallized from ethanol to give ethyl-3-indoleacetate. Compound **1** melting point 42 ºC, yield 60 %.

Compound **1**, IR (KBr, ν_{max}, cm^{-1}): 3310 (NH of indole), 2843 (CH_2), 1720 (>C=O). ^1H NMR ($CDCl_3$): 8.60 (brs, 1H, NH of indole), 7.40-7.15 (m, 5H, Ar-H), 5.25 (s, 2H, CH_2), 4.35 (q, 2H, $COOCH_2$ CH_3), 2.35 (t, 3H, $COOCH_2CH_3$) (ppm). MS: $[M]^+$ m/z = 203.

Compound **2** was prepared in the similar manner.

1-(3'-Indoloacetyl) semicarbazide: A solution of ethyl-3-indoloacetate (0.075 mol) and semicarbazide (0.075 mol) in methanol (dry 50 mL) was

†Department of Chemistry, D.N. College, Meerut-250 002, India.

refluxed on a steam bath for *ca.* 15 h. The excess of the solvent was distilled off and the viscous mass poured into ice cold water, filtered and recrystallized from ethanol to give the desired compound. Compound **3** melting point 132 ºC yield 73 %.

Compound **3**, IR (KBr, ν_{max}, cm^{-1}): 3335 (NH, NH_2), 3175 (NH of indole), 2845 (CH_2), 1670 (-CONH), 1630 (>C=O). ^1H NMR ($CDCl_3$): 8.66 (brs, 1H, NH of indole), 8.25 (m, 4H, $NHNHCONH_2$), 7.35-7.25 (m, 5H, Ar-H), 5.30 (s, 2H, CH_2) (ppm). MS: $[M]^+$ m/z = 232.

Various other compounds of this series have been synthesized by the same procedure.

2-Amino-5-(3'-indolomethylene)-1, 3, 4-oxadiazole: Conc. H_2SO_4 (15 mL) was added to compound **3** (0.05 mol) and the reaction mixture was kept overnight at room temperature poured into ice cold water, neutrallized with liquid ammonia and filtered. The product obtained was washed with petroleum ether (40-60 ºC) and recrystallized from methanol/water to give the desired compound. Compound **7** melting point 187 ºC yield 70 %.

Compound **7**, IR (KBr, ν_{max}, cm^{-1}): 3330 (NH_2), 3150 (NH of indole), 2850 (CH_2), 1590 (C=N), 1586 (C=C of aromatic ring), 1540 (N-N), 1060 (C-O-C). ^1H NMR ($CDCl_3$): 8.90 (brs, 1H, NH of indole), 7.60-7.10 (m, 5H, Ar-H), 6.65 (s, 2H, NH_2), 5.20 (s, 2H, CH_2) (ppm). MS: $[M]^+$ m/z = 214.

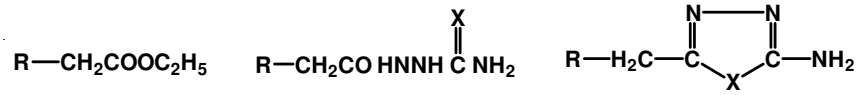
Other compounds of this series were prepared by the same procedure.

5-(2'-Indolomethylene-5'-aminomethylene-1',3',4'-oxadiazole-2'-yl)-2-barbituric acid: To a solution of barbituric acid (0.01 mol) in ethanol (70 mL), formaldehyde (0.02 mol) and compound **7** (0.02 mol) were added dropwise and the reaction mixture was refluxed for 4 h. The excess of solvent was distilled off. The solid thus obtained was washed with petroleum ether (40-60 ºC) and recrystallized from acetone to furnish 5-(2'-indolomethylene-5'-aminomethylene-1', 3', 4'-oxadiazole-2'-yl)-2-barbituric acid. Compound **11** melting point 207 ºC, yield 65 %.

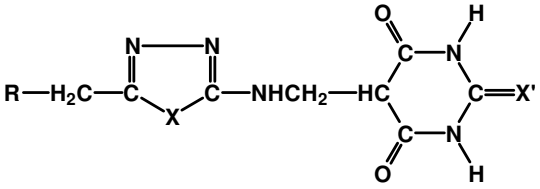
Compound **11**, IR (KBr, ν_{max}, cm^{-1}): 3225 (NH of indole), 1710, 1720, 1670 (amidic C=O), 1580 (C=N), 1555 (C=C of aromatic ring), 1500 (N-N), 1070 (C-O-C). ^1H NMR ($CDCl_3$): 8.95 (ss, 2H, 2XNH CO), 8.10 (brs, 1H, NH of indole), 7.40-7.05 (m, 5H, Ar-H), 5.75 (brs, 1H, $NHCH_2$), 5.35 (s, 2H, CH_2), 4.00 (dd, 2H, NH CH_2), 3.10 (s, 1H, CH of barbituric acid) (ppm). MS: $[M]^+$ m/z = 354.

The other compounds of this series were prepared by the same procedure.

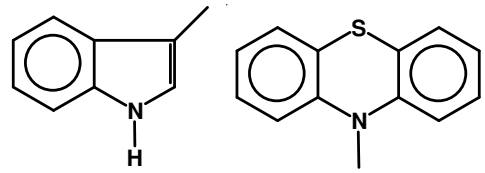
Mass spectral studies of compound 11: The general mass spectral fragmentation pattern of this compound is outlined in **Scheme-II**. The relative intensities of molecular ion peak, base peak and some other major peaks are depicted in Table-1. A mass spectrum of compound **11** is given in Fig. 1.



(Compound **1-2**) (Compound **3-6**) (Compound **7-10**)



(Compound **11-18**)



(R) (R′)

Scheme

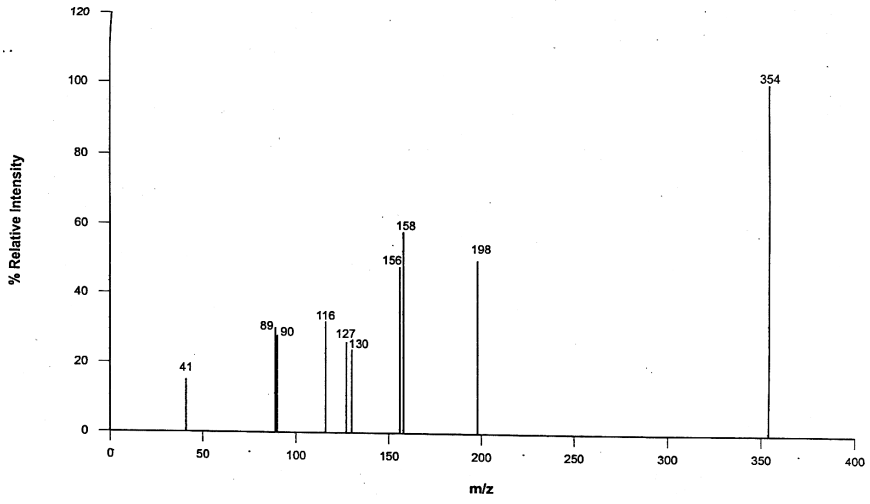


Fig. 1. Mass spectrum of compound **11** *i.e.*, 5-[2′-Indomethylene-5′-aminomethylene-1′,3′,4′-oxadiazol-2′-yl)-2-barbituric acid

TABLE-1

Major fragments	m/z	Relative intensity (%)
$[M]^+$	354	100
$[a]^+$	158	58
$[b]^+$	130	24
$[c]^+$	116	32
$[d]^+$	90	28
$[e]^+$	89	30
$[f]^+$	89	30
$[g]^+$	354	100
$[h]^+$	156	48
$[i]^+$	198	50
$[j]^+$	156	48
$[k]^+$	127	26
$[l]^+$	41	15

The molecular ion peak $[M]^+$ forms a base peak which was observed at m/z = 354. Molecular ion peak on fission of C=N and C-O linkages yielded ion $[a]^+$ at m/z = 158. Molecular ion peak also underwent fission of C-O bond producing an open molecular cation $[g]^+$ at m/z = 354 resulted in the formation of ion $[h]^+$ at m/z = 156 and $[i]^+$ at m/z = 198. The mass spectral fragmentation of this compound has analogy with the fragmentation pattern described by Selva *et al.*[9].

Expulsion of -CO radical from $[a]^+$ gives ion $[b]^+$ at m/z = 130. Further, on loss of CH_2 radical from ion $[b]^+$ indolyl moiety $[c]^+$ at m/z = 116 as intense peak was formed. Loss of cyanide radical from ion $[c]^+$ leads to the formation of ion $[d]^+$ at m/z = 90, ion $[d]^+$ loses H radical and resulted in the formation of ion $[f]^+$ at m/z = 89, which get rearranged into $[e]^+$ at m/z = 89. Fragmentation pattern of indole has analogies with the fragmentation pattern observed by Kumar *et al.*[10]. Expulsion of NCO radical from ion $[i]^+$ gave ion $[j]^+$ at m/z = 156. Ion $[j]^+$ further loses $NHCH_2$ radical to afford barbiturinyl moiety $[k]^+$ at m/z = 127. Barbiturinyl moiety ion $[k]^+$ loses 2 NHCO radicals to give ion $[l]^+$ at m/z = 41. This type of loss of NHCO has also been reported by Bourgeois *et al.*[11] in different barbituric acid derivatives.

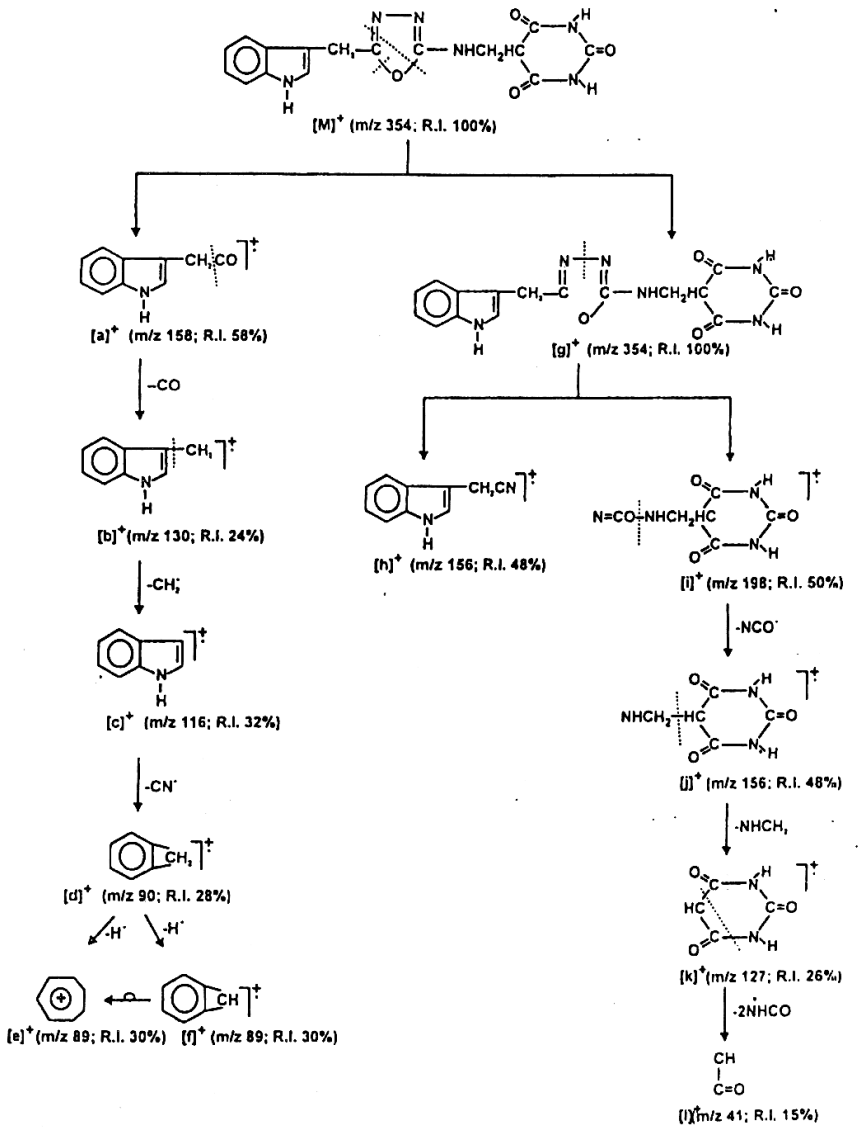
RESULTS AND DISCUSSION

All the newly synthesized compounds were screened for anticonvulsant activity and were compared with the standard drug phenytoin sodium. The results are given in Table-2.

TABLE-2
PHYSICAL DATA AND ANTICONVULSANT ACTIVITY OF COMPOUNDS (**1-18**)

Compd.	R/R'	X	X'	m.p. (ºC)	Yield (%)	Recrystallization solvent	m.f.[d]	Dose mg/kg i.p.	Seizure protection[c] (%)	ALD_{50} (mg/kg i.p.)
1	R	–	–	52	66	Ethanol	$C_{12}H_{13}NO_2$	–	–	–
2	R'	–	–	204	78	Ethanol	$C_{16}H_{15}NO_2S$	–	–	–
3	R	O	–	132	73	Ethanol/Water	$C_{11}H_{12}N_4O_2$	100	40**	>1500
4	R	S	–	122	65	Ethanol/Water	$C_{11}H_{12}N_4OS$	100	40**	>1500
5	R'	O	–	146	75	Methanol	$C_{11}H_{12}N_3OS$	100	40**	>1500
6	R'	S	–	166	70	Methanol	$C_{16}H_{15}N_4OS_2$	100	40**	>1500
7	R	O	–	187	70	Methanol/Water	$C_{11}H_{10}N_4O$	100	50**	>1500
8	R	S	–	176	75	Methanol/Water	$C_{11}H_{10}N_4S$	100	60**	>1500
9	R'	O	–	201	62	Ethanol	$C_{15}H_{12}N_4OS$	100	70**	>1500
10	R'	S	–	140	65	Ethanol	$C_{15}H_{12}N_4S_2$	30	10*	>1500
								60	30**	
								120	70***	
11	R	O	O	207	65	Benzene	$C_{16}H_{14}N_6O_4$	100	60**	>1500
12	R	O	S	224	75	Methanol/Water	$C_{16}H_{14}N_6O_3S$	100	70**	>1500
13	R	S	O	256	60	Ethanol	$C_{16}H_{14}N_6O_3S$	100	60**	>1500
14	R	S	S	236	60	Methanol	$C_{16}H_{14}N_6O_2S_2$	100	70***	>1500
15	R'	O	O	162	65	Benzene/Pet. ether	$C_{20}H_{16}N_6O_4S$	100	60**	>1500
16	R'	O	S	184	60	Ethanol	$C_{20}H_{16}N_6O_3S_2$	100	70***	>1500
17	R'	S	O	215	63	Benzene	$C_{20}H_{16}N_6O_3S_2$	100	70**	>1500
18	R'	S	S	246	65	Acetic acid/water	$C_{20}H_{16}N_6O_2S_3$	30	10*	>2500
								60	30**	
								120	80***	
	P.G.[a]							2.0 mL		
	Phenytoin sodium[b]							30		

*$p < 0.05$; **$p < 0.01$; ***$p < 0.01$; [a]P.G. = Propylene glycol standard for control group; [b]Phenytoin sodium = Reference standard for anticonvulsant activity; [c]Supra maximal electroshock seizure pattern test; [d]The Elemental analysis was found to be within ± 0.4 %.



Scheme-II

Out of compounds tested compound **18** was found to possess potential anticonvulsant activity. Compounds **10**, **12**, **14** and **16** were found to possess activity equipotent to reference drug. Fig. 2 shows the bar diagram showing anticonvulsant activity of compound **10** and **18** at three graded doses (30, 60 and 120 mg/kg i.p.) and its comparison with the reference drug phenytoin sodium (30 mg/kg i.p.) and propylene glycol (2.0 mL). However almost all the compounds have shown promising anticonvulsant activity. Compounds

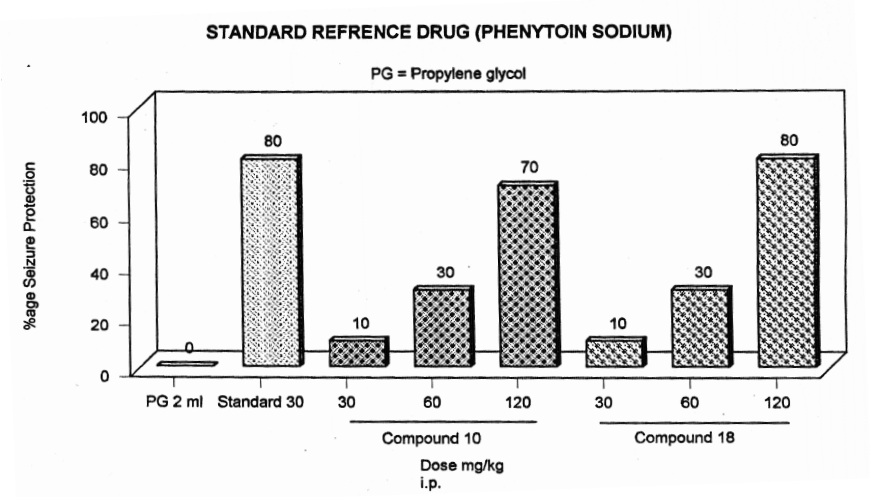


Fig. 2. Bar diagram showing anticonvulsant activity (percentage seizure protection) of compound **10** and **18** their comparison with phenytoin sodium in supra maximal electroshock pattern test

having indolyl moiety as substituent **3**, **4**, **7**, **8**, **11**, **12**, **13**, **14** revealed less percentage inhibition (ranging between 40-70 %) of seizures in rats, while compounds having phenothiazinyl moiety as substituent **5**, **6**, **9**, **10**, **15**, **16**, **17**, **18** exhibited comparatively more percentage inhibition of seizures (ranging between 40-80 %). Further, compounds having oxadiazolyl group **7**, **9**, **11**, **12**, **15**, **16** were found to be less potent exhibiting protection ranging from 50-70 % than their corresponding compounds containing thiadiazolyl group **8**, **10**, **13**, **14**, **17**, **18** (60-80 % protection). Furthermore thiobarbituric acid derivatives **12**, **14**, **16**, **18** showed more potent activity as compared to their corresponding barbituric acid derivatives **11**, **13**, **15**, **17**. Hence it can be concluded that: (i) Presence of phenothiazinyl moiety as substituent was found to increase the anticonvulsant activity. (ii) Oxadiazoles were found to be less potent in comparison to their corresponding thiadiazoles. (iii) Thiobarbituric acid containing compounds showed more potent activity than their corresponding barbituric acid containing compounds.

All the compounds showed ALD_{50} > 1500 mg/kg i.p., suggesting a good safety margin. However, the most potent compound **18** showed ALD_{50} > 2500 mg/kg i.p.

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