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Synthesis of Newer Indolyl Thiadiazoles and their Thiazolidinones and Formazans as Potential Anticonvulsant Agents

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A series of 2-(substituted arylidenyl imino)-5-(3' indolomethylene)-l,3,4-thiadiazoles have been synthesized via condensation of 2-amino-5-(3'-indolomethylene)-l,3,4-thiadiazole(3) with various aromatic alde-hydes. Cycloaddition of thioglycolic acid to 4-8 yielded 3-[5-(3"indolo-methylene)-l',3',4'-thiadiazol-2'-yl]-2-substitutedaryl-4-thiazolidinones and with diazonium salt solution of 4-8 gave l-[5'-(3"-indolomethylene]-2'-imino-l',3',4'-thiadiazol-2'-yl]-l,3-disubstitutedaryl)-formazans. These compounds were screened for anticonvulsant activity and acute toxicity. Compound 3-(3'-indolomethylene-l',3',4'-thiadiazol-2'-yl)-2-(p-methoxy-phenyl)-4-thiazolidinones showed most potent anticonvulsant activity. The structure of all the synthesized compounds were delineated by element analysis, IR and proton magnetic resonance.

Recent literature describes the anticonvulsant activity of a large number of indoles[1-4] derivatives substituted by different heterocyclic moieties at 3-position of this heterocyclic system. Several of these 3-heterocyclic substituted indoles show a high level of protection against maximal electroshock (MES)-induced convulsions in animal models. Since, thiadiazoles[5-8] thiazolidin-4-ones[9-12] and formazans[13] of different heterocyclic nuclei were also found to possess anticonvulsant activity, so in the on going quest to develop potent anticonvulsant agents for controlling epilepsy, we therefore, propose to synthesize some promising anticonvulsant agents by incorporating thiadiazolyl, thiazolidinyl and formazanyl moieties at the 3-position of the indole nucleus. These compounds were evaluated for anticonvulsant activity and were found to possess highly remarkable protection against convulsions produced by maximal electroshock seizures.

MATERIALS AND METHODS

The melting points are uncorrected. Carbon and hydrogen analysis were performed on CHN analyses. Carlo Erba 1108, Heracus, at the Central Drug Research Institute (Lucknow). Analysis (C,H,N) were within ±0.04% of the theoretical values. The IR spectra were recorded on Backman Acculab-10 spectrophotometer (V_{max} in cm^{-1}). The 'H-NMR spectra were recorded in $CDCl_3$ on a Brucker 400-FT instrument. The homogeniety of all the compounds was checked by using silica gel-G plates (Qualigens Fine Chemicals, Mumbai).

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Synthesis of ethyl-3-indoloacetate (1):

A solution of indole (0.01 mol) (CDH, New Delhi), ethyl chloroacetate (0.01 mol) (Qualigens Fine Chemicals, Mumbai), anhydrous acetone (90 ml) (Merck, Mumbai), anhydrous K_2CO_3 (8 g) (Merck, Mumbai) were refluxed for 24 h. After refluxing, the excess solvent was distilled off. The reaction mixture was cooled, filtered and washed with water and recrystallised from methanol, m.p. 44°, yield 65%, IR: 1735 cm^{-1} (>CO), 2853 cm^{-1} (CH2), 3220 cm^{-1} NH of indole), ^{1}H-NMR ($CDCl_3$) δ 2.20 (t,3H, $COOCH_2\underline{CH_3}$), 4.25 (q,2H,$COO\underline{CH_2}CH_3$), 5.20 (s,2H, $C\underline{H_2}$), 7.10-7.30 (m, 5H, Ar-H), 8.70 (brs, 1H, NH of indole, D_2O exchangeable) (Scheme 1).

Synthesis of 1-(3'-Indoloacetyl)-thiosemicarbazide (2):

A solution of ethyl-3-indoloacetate (0.075 mol) and

thiosemicarbazide (0.075 mol) (CDH, New Delhi) in methanol (dry 50 ml) (Qualigens Fine Chemicals, Mumbai) was refluxed on a steam bath for about 15 h. The excess of the solvent was distilled off and the viscous mass poured into ice-cold water, filtered and recrystallised from methanol/water, m.p. 120°, yield 70%, IR: 1152 cm^{-1} (>CH_2), 1675 cm^{-1} (-CONH), 2840 cm^{-1} (-CH_2), 3190 cm^{-1} (NH of indole), 3340 cm^{-1} (-$NHNH_2$), ^{1}H-NMR ($CDCl_3$): δ 5.30 (s,2H, CH_2), 7.10-7.27 (m, 4H, Ar-H), 8.40 (brs, 4H, NHNHCSNH_2. D_2O exchangeable), 8.65 (brs, 1H, NH of indole, D_2O exchangeable) (Scheme 1).

Synthesis of 2-Amino-5-(3'-indolomethylene)-1,3,4-thiadiazole (3):

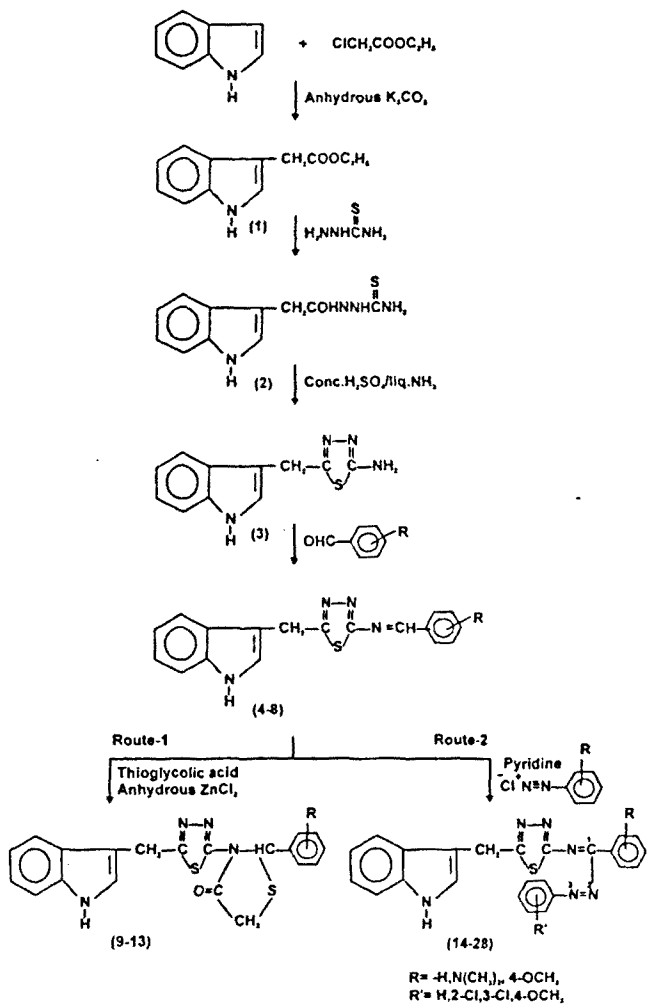
Concentrated H_2SO_4 (15 ml) (Qualigens Fine Chemicals, Mumbai) was added to 1-(3'-indoloacetyl) thiosemicarbazide (0.05 mol) and the reaction mixture was kept overnight at room temperature, poured into ice-cold water, neutrallised with liq. ammonia (CDH, New Delhi) and filtered. The product obtained was washed with petroleum ether (40-60°) (CDH, New Delhi) and recrystallised from ethanol/water, m.p. 175°, yield 70%, IR: 683 cm^{-1} (C-S-C), 1530 cm^{-1} (N-N), 1582 cm^{-1} (C····C of aromatic ring), 1670 cm^{-1} (C=N), 2860 cm^{-1} (CH_2), 3180 cm^{-1} (NH of indole), 3350 cm^{-1} (NH_2), ^{1}H-NMR ($CDCl_3$): δ 5.25 (s,2H, CH_2), 6.10 (ss, 2H, NH_2, D_2O exchangeable), 7.00-7.29 (m, 5H, Ar-H), 8.10 (brs, 1H, NH of indole, D_2O exchangeable) (Scheme 1).

Synthesis of 2-(4"-Methoxyphenyl imino)-5-(3'-indolomethylene)1,3,4-thiadiazoles (5):

A mixture of 2-amino-5-(3'-indolomethylene)-l,3,4-thiadiazole (2.5 mol) was condensed with *p*-anisaldehyde (2.5 mol.) Aldrich Fine Chemicals, Millwaukee, WI, USA), in presence of a few drops of glacial acetic acid in methanol for 8 h. The excess of solvent was distilled off and the viscous mass thus obtained was recrystallised from ethanol/water, (Qualigens Fine Chemicals, Mumbai) m.p. 190°, yield 60%, IR: 680 cm^{-1} (C-S-C), 735 cm^{-1} (monosubstituted benzene ring), 1560 cm^{-1} (C=C of aromatic ring), 1640 cm^{-1} (C=N), 2840 cm^{-1} (-CH_2), 3060 cm^{-1} (C-H aromatic), 3220 cm^{-1} (NH of indole), ^{1}H-NMR ($CDCl_3$): δ 3.48 (s, 3H, Ar-OCH_3), 5.15 (s,2H, CH_2), 7.20-7.80 (m, 9H, Ar-H), 8.15 (brs, 1H, NH of indole, D_2O exchangeable) 8.60 (s,1H,N=CH-Ar) (Scheme 1).

Synthesis of 3-[5'-(3"-Indolomethylene)-1',3',4'-thiadiazol-2'-yl]-2-(4'"-methoxyphenyl) 4-thiazolidinones (10):

To a cooled mixture of compound (5) (0.01 mol) and



Scheme 1

anhydrous $ZnCl_2$ (0.02 mol) (CDH, New Delhi) in DMF (50 ml), (Qualigens Fine Chemicals, Mumbai), thioglycolic acid (0.02 mol) (Qualigens Fine Chemicals, Mumbai), was added dropwise with stirring at ambient temperature and the mixture was kept for 2 days at room temperature and refluxed for 12 h. The reaction mixture was filtered, washed with water and poured into cooled water. The resulting solids were recrystallised from ethanol/water, m.p. 240°, yield 55%, IR: 675 cm^{-1} (C-S-C), 740 cm^{-1} (monosubstituted benzene ring), 1580 cm^{-1} (C····C of aromatic ring), 1635 cm^{-1} (C=N), 1760 cm^{-1} (C=O of β-thialactam ring), 2850 cm^{-1} (CH_2), 3050 cm^{-1} (C-H aromatic), 3240 cm^{-1} (NH of indole), ^{1}H-NMR ($CDCl_3$): δ 3.53 (s, 3H, Ar-OCH_3), 3.95 (s,2H, CH_2 of thiazolidinone ring), 5.25 (s, 2H, CH_2), 6.35 (t, IH, N-CH-Ar), 7.0-7.6 (m, 9H, Ar-H), 8.20 (brs, 1H, NH of indole, D_2O exchangeable) (Scheme 1).

Synthesis of 1-[5'-(3"-Indolomethylene)-2'-imino-l',3',4',-thiadiazol-2'-yl] l-(4'"-methoxyphenyl) 3-phenyl-formazans (15):

Different anilines (0.01 mol) (BDH, Mumbai) were dissolved in 4 ml glacial acetic acid (Indian Drugs and Pharmaceuticals Ltd., Hyderabad) and 3 ml of concentrated. HCl (Merck, Mumbai) was added at 0-5°. A solution of sodium nitrite (1 g $NaNO_2$ in 5 ml of water) (Sarabhai M. Chemicals, Baroda) was then added dropwise. The diazonium salt solution thus prepared were added with stirring to solution of compound (10) in toluene. During the addition the temperature was maintained below 5°. The reaction mixture thus obtained were left at room temperature for 2-3 d[14,15] and then poured into cold water. Dark red solid which separated out was washed, filtered and recrystallised from methanol, m.p. 140°, yield 50%, IR: 750 cm^{-1} (monosubstituted benzene ring), 1260 cm^{-1} (C-N), 1425 cm^{-1} (N=N), 1680 cm^{-1} (C=N), 2860 cm^{-1} (-CH2), 3250 cm^{-1} (NH indole), ^{1}H-NMR ($CDCl_3$): δ 3.50 (s, 3H, Ar-OCH_3), 5.20 (s, 2H, CH_2), 7.20-8.10 (m, 13H, Ar-H), 8.25 (brs, 1H, NH of indole D_2O exchangeable) (Scheme 1).

Compounds (4 and 6-8), compounds (9 and 11-13) and compounds (14 and 16-28) have been prepared by following the methods of preparation of compounds 5, 10 and 15 respectively.

Anticonvulsant activity:

The anticonvulsant activity was performed according to the method of Toman *et al*[16] on Charles Foster rats of either sex weighing, between 80-120 g. Rats were divided into groups of ten animals each. Pregnancy was excluded in female rats. The rats were treated with different doses of test drugs or phenytoin sodium 30 mg/kg i.p. After one hour they were subjected to a shock of 150 mA 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]. The experimental protocol was approved by the Institutional Animals Ethics Committee.

RESULTS AND DISCUSSION

Newly synthesized compounds were evaluated for anticonvulsant activity at a dose of 50 mg/kg i.p. and have shown varying degree (40% to 90%) of anticonvulsant activity. The presence of a five membered thiadiazole ring at the 3-position of indolyl moiety which was further substituted with imino arylidenyl or imino substituted arylidenyl group at the 2-position of five membered thiadiazole ring was the characteristic feature of this series. All these compounds (4-8) exhibited moderate anticonvulsant activity (40-60%). It was observed that compound having phenyl group (compound 4) as substitutent showed the least activity (40%) while compound (5) substituted with 4-methoxyphenyl ring exhibited the maximum percent protection (60%) against seizures. Compounds (6, 7 and 8) substituted with 4-hydroxyphenyl ring (6) N,N-dimethylphenyl ring (7) and 3-methoxy-4-hydroxyphenyl ring (8) exhibited 50% inhibition of seizures.

Further, (route-1) of the series was characterised by the presence of a thiazolidinone ring in addition to thiadiazole ring. Almost all compounds showed potent and statistically significant anticonvulsant activity ranging from (60-90%). However, compound 10 substituted with 4-methoxyphenyl ring have shown more potent activity (90%) than standard drug phenytoin sodium (80%). Considering the potentiality of this compound i.e. 3-[5'-(3"-indolomethylene)-l',3',4'-thiadiazol-2'-yl]-2-(4"-methoxyphenyl)-4-thiazolidinone, it was further studied in detail for its anticonvulsant activity. Table 1 shows the results of compound 10 and standard drug phenytoin sodium. Compound 11 substituted with 4-hydroxyphenyl ring have shown equipotent activity to phenytoin sodium (80%). Compound 9 having phenyl group as substitutent showed 60% activity and compound 12 substituted with 4-N,N-dimethylphenyl ring also exhibited same percent inhibition (60%) of seizures, while compound 13 substituted with 3-methoxy-4-hydroxyphenyl ring exhibited a potent (70%) activity.

The other side of the series (route-2) was characterised by the addition of a substituted formazan chain at the 2-position of thiadiazole ring. These compounds have also shown promising anti-convulsant activity raning from (50-80%). Compound 25 in which both the phenyl moieties at the formazan chain (at position I and 3) were substituted with 4-methoxyphenyl ring was found to be equipotent (80%) to phenytoin sodium and hence it was also studied in detail at three graded doses (25, 50 and 100 mg/kg i.p.) for its anticonvulsant activity. Table 1 shows the results of compound 25 and standard drug phenytoin sodium. Compound 14 showed minimum percent inhibition of seizures (50%). However, compounds 16; 17 and 18 substituted with phenyl ring having 4-hydroxy group, 4-N,N-dimethyl group and 3-methoxy with 4-hydroxy group respectively at l-position of formazan chain and phenyl group at 3-position of

TABLE 1: PHYSICAL AND BIOLOGICAL DATA OF COMPOUNDS SYNTHESISED.

Compd. Number	R.	R'	M.P. (°)	Yield (%)	Molecular## formula	Dose (mg/kg i.p.)	Anticonvulsant activity# (% inhibition)	ALD_{50} (mg/kg) i.p. Maximum dose tested)
4	H	-	150	70	$C_{18}H_{14}N_4S$	50	40	>1000
5	4-OCH_3	-	19	60	$C_{19}H_{16}H_4OS$	50	60	>1000
6	4-OH	-	180	75	$C_{18}H_{14}N_4OS$	50	50	>1000
7	4-$N(CH_3)_2$	-	115	73	$C_{20}H_{19}N_5S$	50	50	>1000
8	3-OCH_3,4-OH	-	190	68	$C_{19}H_{17}N_4O_2S$	50	50	>1000
9	H	-	260	50	$C_{20}H_{16}N_4OS_2$	50	60	>1000
						25	60	
10	4-OCH_3	-	240	55	$C_{21}H_{18}N_4O_2S_2$	50	90*	>2000
						100	90*	
11	4-OH	-	225	54	$C_{20}H_{16}N_4O_2S_2$	50	80*	>1000
12	4-$N(CH_3)_2$	-	250	56	$C_{22}H_{21}N_5OS_2$	50	60	>1000
13	3-OCH_3,4-OH	-	265	50	$C_{21}H_{18}N_4O_3S_2$	50	70	>1000
14	H	H	240	45	$C_{24}H_{18}N_6S$	50	50	>1000
15	4-OCH_3	H	140	50	$C_{25}H_{20}N_6OS$	50	70	>1000
16	4-OH	H	210	48	$C_{24}H_{18}N_6OS$	50	60	>1000
17	4-$H(CH_3)_2$	H	235	40	$C_{26}H_{23}N_7S$	50	60	>1000
18	3-OCH_3,4-OH	H	240	55	$C_{25}H_{20}N_6O_2S$	50	60	>1000
19	H	3-Cl	185	50	$C_{24}H_{17}N_6ClS$	50	60	>1000
20	4-OCH_3	3-Cl	175	45	$C_{25}H_{19}N_6OClS$	50	70	>1000
21	4-OH	3-Cl	160	52	$C_{24}H_{17}N_6OClS$	50	70	>1000
22	4-$N(CH_3)_2$	3-Cl	120	55	$C_{26}H_{22}N_7ClS$	50	70	>1000
23	3-OCH_3,4-OH	3-Cl	140	48	$C_{25}H_{19}N_6O_2ClS$	50	70	>1000
24	H	4-OCH_3	120	56	$C_{25}H_{20}N_6OS$	50	70	>1000
						25	40	
25	4-OCH_3	4-OCH_3	150	55	$C_{26}H_{22}N_6O_2S$	50	80*	>1000
						100	90*	
26	4-OH	4-OCH_3	135	48	$C_{25}H_{20}N_6O_2S$	50	70	>1000
27	4-$N(CH_3)_2$	4-OCH_3	140	45	$C_{27}H_{25}N_7OS$	50	70	>1000
28	3-OCH_3,4-OH	4-OCH_3	155	52	$C_{26}H_{22}N_6O_3S$	50	70	>1000
	Phenytoin sodium**					30	80*	

*p<0.001; ##C,H, and N are within the limit of ±0.04%; # all the compound were tested at a dose of 50 m/kg; compound nos. 10 and 25 were tested at three graded doses of 25, 50 and 100 mg/kg i.p.; **standard drug for anticonvulsant activity.

formazan chain exhibited 60% inhibition of seizures. Compound 19 in which formazan chain was substituted with phenyl group at I-position and 3-chlorophenyl group at 3-position showed protection of 60% against convulsions. Compounds 20, 21, 22, and 23 in which formazan chain substituted with substituted phenyl group at I-position and 3- chlorophenyl group at 3-position exhibited 70% inhibition of seizures. Moreover, compounds 24, 26, 27 and 28 in which formazan chain substituted with phenyl ring at I-position and 4-methoxy phenyl ring at 3-position exhibited 70% inhibition of seizures. In summary, it may be possible to conclude that thiazolidinone analogies could be more potent than formazan analogies in general and that compounds with a p-methoxyphenyl substituents tend to exhibit more potent anticonvulsant activity.

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