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Synthesis and Anticonvulsant Studies of Thiazolidinone and Azetidinone Derivatives from Indole Moiety

Authors
Archana[1], Sachin Saini[2]

Affiliations
1 Assistant Professor, Medicinal Chemistry Laboratory, Department of Chemistry, Meerut College, Meerut, U.P., India
2 Research Scholar, Department of Chemistry, Mewar University, Rajasthan, India

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Correspondence
Dr. Archana Archana
Medicinal Chemistry Laboratory
Department of Chemistry
Meerut College
250001 Meerut
U.P.
India
Tel.: + 91/941/2208 444
archanachemistrymcm@gmail.com

ABSTRACT

2-Amino-5-(3'-indolomethylene)-1, 3 , 4 - oxadiazole **(3)** undergoes facile condensation with various aromatic aldehydes to gave 2-substitiuted arylidenylamino-5-(3'- indolomethylene) – 1, 3 , 4 – oxadiazole **(4–8)**. Cyclocondensation of **(4–8)** with thioglycolic acid and triethylamine yielded 3-[5'-(3"- indolomethylene)- 1', 3', 4'- oxadiazol-2'-yl]- 2- (substituted aryl)-4- thiazolidinones **(9–13)** and 1-[5'-(3"- indolomethylene) -1', 3', 4'- oxadiazol - 2'- yl] -4-(substituted aryl) -2- azetidinones **(14–18)**. The structures of these compounds were established on the basis of analytical and spectral data. The newly synthesised compounds were evaluated for their anticonvulsant activity and acute toxicity.

Introduction

The term epilepsy is a collective term that includes disorders of the brain function characterized by the periodic and unpredictable occurrence of seizures . The usage of most anticonvulsant agents is limited, not only by rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of epilepsy and drug side-effects. Indoles and their derivatives constitute an important class of heterocyclic compounds. In addition the chemistry and pharmacology of indole have been of great interest to medicinal chemists because indole derivatives possessed various biological activities, such as anti-inflammatory [1–3], antibacterial [4, 5], antimicrobial [6, 7],antifungal [8], antihypertensive [9] , anticonvulsant [10–16] activities. It is interesting to note from chemical literature that various new pharmacophores like oxadiazoles [17–19], thiazolidinones [20–25] and azetidinones [26–29] were also found to possess wide spectrum of anticonvulsant activity in various experimental models. However, these compounds have not been in clinical use as they possess either less activity or more side effects.

Incorporating these moieties in 3rd position of indole nucleus might be thought to yield more potent anticonvulsant compound as substituted moieties are themselves anticonvulsant and substitution at 3rd position further results in protection against convulsions. Thus, the substitution by these moieties may be synergistic. The present project is therefore, aimed at synthesizing such compounds with better anticonvulsant activity and lesser toxicity

Materials and Methods

Chemistry

Melting points were determined in open capillary tubes and are uncorrected. The homogeneity of all the compounds was checked by using silica gel-G plates. Carbon, hydrogen and nitrogen analysis were performed on CHN analysis , Carlo Erba 1108, Heracus. Analysis (C, H, N) were within ± 0.4 % of the theoretical values. The IR spectra were recorded on Backman Acculab-10 spectrophotometer (υ_{max} in cm^{-1} ; KBr). The ^{1}H-NMR spetra were recorded in $CDCl_3$ on Brucker 400-FT instrument.

Synthesis

Compounds **(1–33)** were synthesized according to the synthetic pathway shown in ▶ **Fig. 1**.

Synthesis of ethyl-3-indoloacetate (1)

Indole (0.01 mole), ethylchloroacetate (0.01 mole), in anhydrous acetone (80 ml) and anhydrous K_2CO_3 (8.0 g) were heated under reflux for 24 h. The excess of solvent was distilled off and after cooling, it was filtered, washed with water. The compound thus obtained was recrystallised from methanol to give compound **1**. The physical and analytical data of compound **1** is given in ▶ **Table 1**. Compound **1** : IR (cm^{-1}, KBr): 3180 (NH of indole), 3050 (aromatic CH), 2860 (CH_2), 1740 (C = O), 1580 (C-C of aromatic ring). ^{1}H-NMR $CDCl_3$ δ : 9.85 (brs, 1 H, NH of indole), 7.69–7.00 (m, 5 H, Ar-H), 4.30 (s, 2 H, CH_2), 3.75 (q, 2 H, $COOCH_2CH_3$) (ppm).

Synthesis of 1-(3'- indoloacetyl) semicarbazide (2)

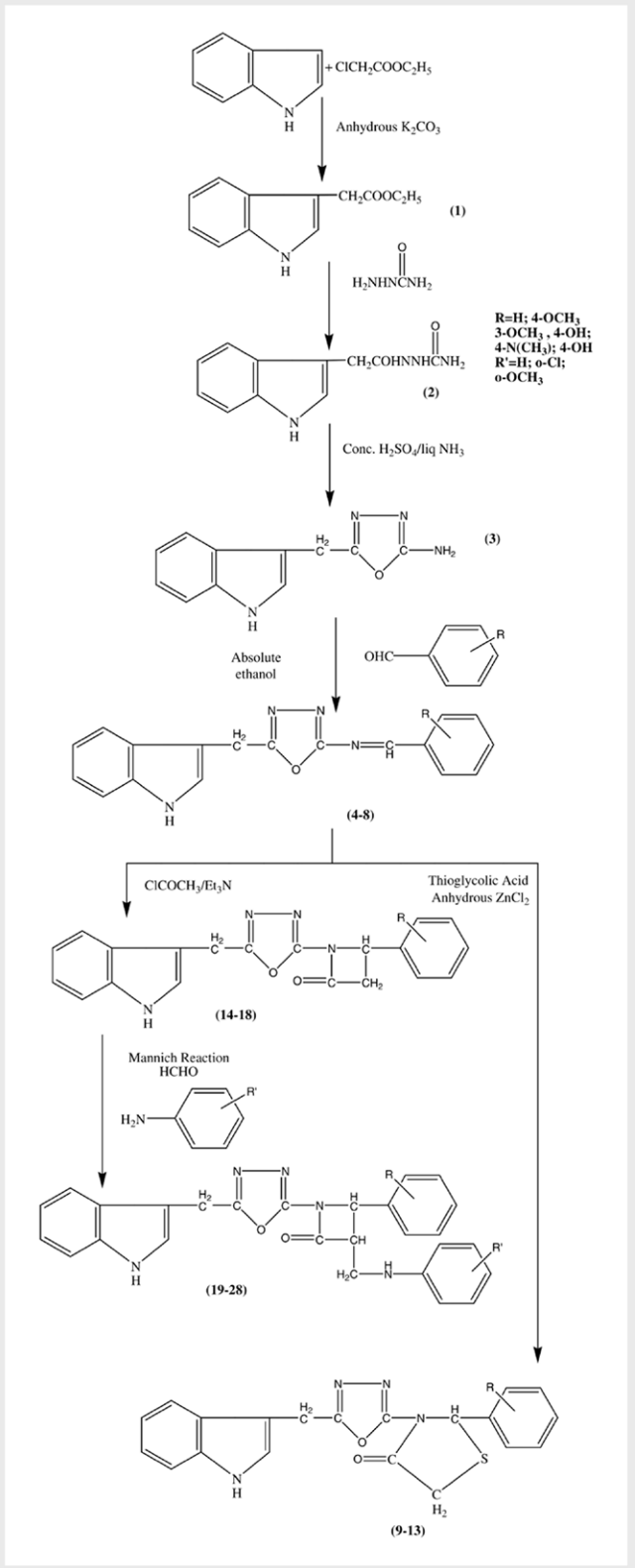
Semicarbazide (0.075 mole) and ethyl-3-indoloacetate (0.075 mole) in methanol (70 ml) were refluxed on a steam bath for 16 h. The excess of the solvent was distilled off and the viscous mass was poured into ice cold water, filtered and recrystallised from ethanol to give compound **2**. The physical and analytical data of compound **2** is given in ▶ **Table 1**. Compound **2** : IR (cm^{-1}, KBr): 3350 ($NHNH_2$), 3160 (NH of indole), 3040 (aromatic C-H), 2853 (CH_2), 1720 (C = O), 1560 (C-C of aromatic ring). ^{1}H-NMR $CDCl_3$ δ : 9.74 (brs, 1 H, NH of indole), 8.30 (brs, 4 H, $NHNHCONH_2$), 7.15–6.60 (m, 5 H, Ar-H), 4.25 (s, 2 H, CH_2) (ppm).

Synthesis of 2- amino-5-(3'-indolomethylene) – 1, 3, 4 – oxadiazole (3)

A mixture of 1- (3'- indoloacetyl) semicarnazide (0.05 mole) and concentrated H_2SO_4 (15 ml) was kept overnight at room temperature, poured into ice cold water, neutrallised with liquid ammonia and the solid thus obtained was filtered and recrystallised from methanol to get compound **3**. The physical and analytical data of compound **3** is given in ▶ **Table 1**. Compound **3** : IR (cm^{-1}, KBr): 3340 (NH_2), 3140 (NH of indole), 3060 (aromatic C-H), 2840 (CH_2), 1680 (C = N), 1560 (C-C ^{of} aromatic ring), 1093 (C-O-C). ^{1}H-NMR $CDCl_3$ δ : 9.10 (brs, 1 H, NH of indole), 8.30 (brs, 1 H, 1 H of indole), 7.67–7.10 (m, 5 H, Ar-H), 4.10 (s, 2 H, CH_2) (ppm).

Synthesis of 2-substitiuted arylidenylamino-5-(3'- indolomethylene) – 1, 3 , 4 – oxadiazoles (4–8)

To a solution of compound **3** (0.01 mole) in absolute ethanol (80 ml) and a few drops of glacial acetic acid were added various aromatic aldehyde (0.01 mole) and the mixtures were refluxed for 8 h. The excess of solvent was distilled off and the viscous masses were washed with a mixture of water and petroleum ether. The solids



▶ **Fig. 1** Scheme route depicting synthetic pathway of compounds.

▶ **Table 1** Physical and analytical data of compounds 1–33.

Comp. No.	R	R'	M.P. ^{0}C	Recryst. Solvent	Yield (%)	Molecular Formula	Calcd. (Found) %		
							C	H	N
1	-	-	44	methanol	44	$C_{12}H_{13}NO_2$	70.93 (70.90)	6.40 (6.44)	16.89 (16.92)
2	-	-	125	ethanol	65	$C_{11}H_{12}N_4O_2$	56.89 (56.92)	5.17 (5.20)	24.13 (24.17)
3	-	-	185	methanol	60	$C_{11}H_{10}N_4O$	61.68 (61.70)	4.67 (4.65)	26.16 (26.14)
4	4-OCH_3	-	240	ethanol	58	$C_{19}H_{16}N_4O_2$	68.67 (68.65)	4.81 (4.85)	16.86 (16.90)
5	H	-	268	methanol	55	$C_{18}H_{14}N_4O$	71.52 (71.56)	4.63 (4.68)	18.54 (15.56)
6	3-OCH_3, 4-OH	-	300	DMF	45	$C_{19}H_{16}N_4O_3$	65.51 (65.49)	4.59 (4.63)	16.09 (16.06)
7	4-$N(CH_3)_2$	-	230	ethanol	48	$C_{20}H_{19}N_5O$	69.56 (69.60)	5.50 (5.54)	20.28 (20.30)
8	4-OH	-	200	ethanol	40	$C_{18}H_{14}N_4O_2$	67.92 (67.90)	4.40 (4.42)	17.61 (17.64)
9	4-OCH_3	-	200	ethanol	50	$C_{21}H_{18}N_4O_2S$	62.06 (62.10)	4.43 (4.47)	13.79 (13.82)
10	H	-	220	ethanol	45	$C_{20}H_{16}N_4O_2S$	63.92 (63.80)	4.25 (4.27)	14.89 (14.91)
11	3-OCH_3, 4-OH	-	250	ethanol	42	$C_{21}H_{18}N_4O_4S$	59.71 (59.75)	4.26 (4.24)	13.27 (13.30)
12	4-$N(CH_3)_2$	-	310	ethanol	40	$C_{22}H_{21}N_5O_2S$	63.00 (63.04)	5.01 (5.04)	16.70 (16.72)
13	4-OH	-	210	ethanol	38	$C_{20}H_{16}N_4O_3S$	61.22 (61.25)	4.08 (4.12)	14.28 (14.25)
14	4-OCH_3	-	256	benzene	55	$C_{21}H_{18}N_4O_3$	67.37 (67.40)	4.81 (4.84)	14.97 (14.95)
15	H	-	180	methanol	50	$C_{20}H_{16}N_4O_2$	69.76 (69.74)	4.65 (4.62)	16.27 (16.22)
16	3-OCH_3, 4-OH	-	115	methanol	40	$C_{21}H_{18}N_4O_4$	64.61 (64.63)	4.61 (4.58)	14.35 (14.38)
17	4-$N(CH_3)_2$	-	100	methanol	45	$C_{22}H_{21}N_5O_2$	68.21 (68.23)	5.42 (5.45)	18.08 (18.06)
18	4-OH	-	210	methanol	35	$C_{20}H_{16}N_4O_3$	66.66 (66.66)	4.44 (4.40)	15.55 (15.58)
19	4-OCH_3	H	200	methanol	35	$C_{28}H_{25}N_5O_3$	70.14 (70.11)	5.21 (5.19)	14.61 (14.58)
20	H	H	270	DMF	33	$C_{27}H_{23}N_5O_2$	72.16 (72.18)	5.12 (5.14)	14.14 (14.18)
21	3-OCH_3, 4-OH	H	120	DMF	32	$C_{28}H_{25}N_5O_4$	67.87 (67.90)	5.05 (5.09)	14.14 (14.18)
22	4-$N(CH_3)_2$	H	150	ethanol	38	$C_{29}H_{28}N_6O_2$	70.73 (70.75)	5.69 (5.71)	17.07 (17.10)
23	4-OH	H	240	acetone/pet. ether	30	$C_{27}H_{23}N_5O_3$	69.67 (69.70)	4.94 (4.96)	15.05 (15.08)
24	4-OCH_3	o-Cl	280	toluene/pet. ether	30	$C_{28}H_{24}N_5O_3Cl$	65.43 (65.40)	4.67 (4.63)	13.63 (13.61)
25	H	o-Cl	260	DMF	30	$C_{27}H_{22}N_5O_2Cl$	67.01 (67.04)	4.55 (4.58)	14.47 (14.50)
26	3-OCH_3, 4-OH	o-Cl	165	pet. ether	35	$C_{28}H_{24}N_5O_4Cl$	63.45 (63.46)	4.53 (4.50)	13.22 (13.25)
27	4-$N(CH_3)_2$	o-Cl	180	ethanol/water	32	$C_{29}H_{27}N_6O_2Cl$	66.09 (66.13)	5.12 (5.14)	15.95 (15.92)

▶ **Table 1** Continued

Comp. No.	R	R'	M.P. ^{0}C	Recryst. Solvent	Yield (%)	Molecular Formula	Calcd. (Found) %		
							C	H	N
28	4-OH	o-Cl	250	DMF/ water	30	$C_{27}H_{22}N_5O_3Cl$	64.86 (64.82)	4.40 (4.44)	14.01 (14.05)
29	4-OCH_3	o-OCH_3	210	toluene/ pet.ether	30	$C_{29}H_{27}N_5O_4$	68.36 (68.40)	5.30 (5.32)	13.75 (13.72)
30	H	o-OCH_3	250	acetone/ pet. ether	32	$C_{28}H_{25}N_5O_3$	70.14 (70.11)	5.21 (5.19)	19.61 (19.58)
31	3-OCH_3, 4-OH	o-OCH_3	220	Pet. ether	30	$C_{29}H_{27}N_5O_5$	66.28 (66.32)	5.14 (5.16)	13.33 (13.30)
32	4-$N(CH_3)_2$	o-OCH_3	130	ethanol/ water	30	$C_{30}H_{30}N_6O_3$	68.96 (68.92)	5.74 (5.78)	16.09 (16.12)
33	4-OH	o-OCH_3	180	methanol/ water	38	$C_{28}H_{25}N_5O_4$	67.87 (67.84)	5.05 (5.08)	14.14 (14.17)
C, H, N were found within ± 0.4 %									

thus obtained were recrystallised from various solvents to give compounds **(4–8)**. The physical and analytical data of compounds **(4–8)** is given in ▶ **Table 1**. Compound **4** : IR (cm^{-1}, KBr): 3120 (NH of indole), 3050 (aromatic C-H), 2860 (CH_2), 1635 (C = N), 1582 (C-C of aromatic ring), 1080 (C-O-C). ^{1}H-NMR $CDCl_3$ δ : 8.40 (ss, 1 H, N = CH-Ar), 8.21 (brs, 1 H, 1 H of indole), 7.90–6.55 (m, 9 H, Ar-H), 4.30 (s, 2 H, CH_2), 3.40 (s, 3 H, Ar-OCH_3) (ppm).

Synthesis of 3-[5'-(3"- indolomethylene)-1', 3', 4'- oxadiazol-2'-yl]- 2- (substituted aryl)-4- thiazolidinones (9–13)

Stirred solutions of compounds **(4–8)** (0.01 mole) were refluxed in dry DMF (80 ml) containing a small amount of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mole) for 18 h. The reaction mixtures were cooled and poured into ice cold water. The separated solids were filtered, washed and recrystallised with appropriate solvents to yield compounds **(9–13)**. The physical and analytical data of compounds **(9–13)** is given in ▶ **Table 1**. Compound **9** : IR (cm^{-1}, KBr): 3170 (NH of indole), 3060 (aromatic C-H), 2853 (CH_2), 1670 (C = N), 1560 (C-C of aromatic ring), 1086 (C-O-C), 1740 (C = O of β-thialactam ring). ^{1}H-NMR $CDCl_3$ δ : 6.75 (s, 1 H, N = CH-Ar), 8.10 (brs, 1 H, 1 H of indole), 7.90–7.10 (m, 9 H, Ar-H), 4.25 (s, 2 H, CH_2 adjacent to indole nucleus), 3.90 (s, 2 H, CH_2 of thiazolidinone ring), 3.45 (s, 3 H, Ar-OCH_3) (ppm).

Synthesis of 1-[5'-(3"- indolomethylene)-1', 3', 4'-oxadiazol-2-yl]-4-(substituted aryl)-2-azetidinones (14–18)

To well stirred solutions of compounds **(14–18)** (0.01 mole) and triethylamine (0.02 mole) in dioxane (40 ml), acetyl chloride (0.02 mole) was added dropwise at 0–5 °C. The reaction mixtures were stirred for about 5 h and precipitated amine hydrochloride was filtered off. The filterate was concentrated under reduced pressure and poured into ice cold water. The products so obtained were recrystallised from appropriate solvents to give compounds **(14–18).** The physical and analytical data of compounds **(14–18)** is given in ▶ **Table 1**. Compound 1**4** : IR (cm^{-1}, KBr): 3180 (NH of indole), 3060 (aromatic C-H), 2860 (CH_2), 1760 (C = O of β-lactam ring),1640 (C = N), 1580 (C-C of aromatic ring). ^{1}H-NMR $CDCl_3$ δ : 8.40 (ss, 1 H, N = CH-Ar), 8.12 (brs, 1 H, 1 H of indole), 7.80–6.90 (m, 9 H, Ar-H),6.65 (t, 1 H, J-7Hz, CH-C_6H_5),5.20 (d, 2 H, J = 9 Hz, CH_2 of azetidinone ring), 4.25 (s, 2 H, CH_2), 3.39 (s, 3 H, Ar-OCH_3) (ppm).

Synthesis of 1-[5'-(3''-indolomethylene)-1',3',4'-oxadiazol-2'-yl]-4-(substitutedaryl)-3-(aminomethylene substitutedphenyl)-2-azetidinones (19–33)

To solutions of compounds **(14–18)** (0.01 mole) in ethanol (50 ml), formaldehyde (0.02 mole) and various substituted anilines (0.02 mole) were added dropwise and the reaction mixtures were refluxed for 4 h. The excess of the solvents were distilled off and the solids thus obtained were washed with petroleum ether (40–60 °C) and recrystallised from appropriate solvents to give compounds **(19–33)**. The physical and analytical data of compounds **(19–33)** is given in ▶ **Table 1**. Compound 2**4** : IR (cm^{-1}, KBr): 3140 (NH of indole), 3055 (aromatic C-H), 2845 (CH_2), 1740 (C = O of β-lactam ring),1670 (C = N), 1560 (C-C of aromatic ring), 1040 (C-O-C), 615 (C-Cl). ^{1}H-NMR $CDCl_3$ δ : 8.15 (brs, 1 H, 1 H of indole), 8.56–7.00–6.90 (m, 13 H, Ar-H),6.45 (d, 1 H, J-9Hz, CH-C_6H_5), 5.54 (brs, 1 H, NH-Ar),3.75 (m, 3 H, J = 9 Hz, $CHCH_2$), 5.25 (d, 2 H, J = 9 Hz, CH_2 of azetidinone ring), 4.30 (s, 2 H, CH_2 adjacent to indole nucleus), 3.40 (s, 3 H, Ar-OCH_3) (ppm).

Pharmacology

Acute toxicity in mice

All the compounds were investigated for their acute toxicity (ALD_{50}) in mice by following the procedure of Smith [30].

Anticonvulsant activity- Supra maximal electroshock seizure pattern test (SMES)

This activity was performed by following the method of Toman et al.[31]. In albino rats. Rats of either sex weighing 90–120 g were divided into groups of 10 animals each. The test drugs and reference drug (phenytoin sodium) were administered intraperitoneally in rats. After 1 h they were subjected to a shock of 150 MA by ear electrodes for 0.2 s and the presence or absence of extensor re-

sponse was noted. Animals in which extensor response was abolished were taken as protected rats.

Results

Acute toxicity

All the compounds of the present series showed ALD_{50} > 1000 mg/kg i.p., thus indicating a good safety margin. However, compounds **9** and **29** exhibited ALD_{50} > 2000 mg/kg i.p.

Anticonvulsant activity in rats

In the maximal electroshock induced seizure test (MES), out of 30 compounds tested, compounds **9** abd **29** exhibited most potent activity with 80 and 90 % inhibition of seizures respectively. The results are shown in ▶ **Table 2**.

Discussion

Newly synthesised compounds were evaluated for anticonvulsant activity at a dose of 30 mg/kg i.p. and have shown varying degree (40–90 %) of anticonvulsant activity. The results are depicted in ▶ **Table 2**.

The characteristic feature of this series is the presence of a 5 membered oxadiazole ring at the 3rd position of indolyl moiety which was further substituted with imino arylidenyl or imino substituted arylidenyl group at the 2nd position of 5 membered oxadiazole ring. All the compounds **(4–8)** exhibited moderate activity (▶ **Table 2**). It was observed that compound having phenyl group (compound **5**) as substituent showed the least activity (40 %) while compound **4** substituted with 4-methoxyphenyl ring exhibited the maximum percent protection (60 %) against seizures. Compounds (**6,7** and **8**) substituted with 3-methoxy-4-hydroxy phenyl ring (**6**), N,N-dimethylphenyl ring (**7**) and 4-hydroxyphenyl ring (**8**) exhibited 50 % inhibition of seizures.

Further, (route-1) of the series was characterized by the addition of a substituted azetidinone at the 2nd position of oxadiazole ring. These compounds have shown promising anticonvulsant activity. Compound **29** in which both the phenyl moieties at the azetidinone (at position 3 and 4) were substituted with 4-methoxy was found to be equipotent (80 %) to phenytoin sodium and hence, it was studied in detail at 3 graded doses (7.5, 15 and 30 mg/kg i.p.) for its anticonvulsant activity. Result of compound **29** and standard drug phenytoin sodium is depicted in ▶ **Table 2**. Compound **20** in which the azetidinone was substituted with 2 phenyl rings (at position 3 and 4) showed minimum percent inhibition of seizures (50 %).

However, compounds **21,22** and **23** substituted with phenyl ring having 3-methoxy-4-hydroxy group, 4-N,N-dimethyl group and 4-hydroxy group respectively at 4th position of azetidinone exhibited 60 % inhibition of seizures. Compound **25** in which azetidinone was substituted with phenyl group at 3rd position of azetidinone showed protection of 60 % against convulsions. Compounds **24, 26, 27** and **28** in which azetidinone is substituted with substituted phenyl group at 4th position and o-chlorophenyl group at 3rd position exhibited 70 % inhibition of seizures. Moreover, compounds **30, 31, 32** and **33** in which azetidinone is substituted with substituted phenyl ring at 4th position and o-methoxy phenyl ring at 3rd position exhibited 70 % inhibition of seizures.

Other side of the series (route 2) was characterised by the presence of a thiazolidinone ring in addition to oxadiazole ring. Almost all compounds showed potent and statistically significant anticonvulsant activity. However, compound **9** substituted with 4-methoxy phenyl ring have shown more potent activity (90 %) than phenytoin sodium (80 %) standard drug. Considering the potentiality of this compound **9** i. e., 3-[5'-(3''-indolomethylene)-1',3',4'-oxadiazol-2'-yl]-2-(p-methoxyphenyl)-4-thiazolidinone, it was studied in detail at 3 graded doses. Results of compound **9** and standard

▶ **Table 2** Pharmacological data of compounds (4–33).

Compound	Acute toxicity	Anticonvulsant activity	
	ALD_{50} (mg/kg i.p.)	Dose (mg/kg i.p.)	% inhibition of seizures
4	>1000	30	60**
5	>1000	30	40*
6	>1000	30	50*
7	>1000	30	50*
8	>1000	30	50*
9	>1000	7.5	60**
		15	90***
		30	90***
10	>1000	30	60**
11	>1000	30	70**
12	>1000	30	60**
13	>1000	30	80***
14	>1000	30	70**
15	>1000	30	50*
16	>1000	30	60**
17	>1000	30	60**
18	>1000	30	60**
19	>1000	30	70**
20	>1000	30	50*
21	>1000	30	60**
22	>1000	30	60**
23	>1000	30	60**
24	>1000	30	70**
25	>1000	30	60**
26	>1000	30	70**
27	>1000	30	70**
28	>1000	30	70**
29	>1000	7.5	40*
		15	80***
		30	80***
30	>1000	30	70**
31	>1000	30	70**
32	>1000	30	70**
33	>1000	30	70**
Phenytoin sodium		30	80***
Propylene glycol		2.0 ml	0

*p < 0.05, **p < 0.01, ***p < 0.001

drug phenytoin sodium are depicted in ▶ **Table 2**. Compound **13** substituted with 4-hydroxyphenyl ring have shown equipotent activity to phenytoin sodium (80 %). Compound **10** having phenyl group as substituent showed 60 % activity and compound **12** substituted with 4-N,N-dimethyl phenyl ring also exhibited same percent inhibition (60 %) of seizures, while compound **11** substituted with 3-methoxy-4-hydroxyphenyl ring exhibited a potent (70 %) activity.

Conflict of Interest

There is no conflict of interest among the authors of this manuscript.

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