ORIGINAL RESEARCH ARTICLES

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF NEWER BENZOTHIAZINYL / BENZOXAZINYL INDOLES

Archana[a]* and Sakshi Chaudhary[b]

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ABSTRACT

3-Acetyl-2-methyl-indole (1) was synthesized by acetylation of 2-methyl indole with acetyl chloride. Facile condensation of compound (1) with various aromatic aldehydes yielded 1-(2'-methylindolyl) arylidenyl chalcones (2-7), which on treating with 2-aminothiophenol and 2-aminophenol afforded 2-substitutedphenyl-2,3-dihydro-4-(2'-methylindolyl)-1,5-benzthiazepines (8-13) and 2-substitutedphenyl-2,3-dihydro-4-(2'-methylindolyl)-1,5-benzoxazepines (14-19), respectively. The structures of all the compounds were delineated by elemental analysis, IR and proton magnetic resonance. The newly synthesized compounds were evaluated for their anticonvulsant activity and were compared with standard drug phenytoin sodium. These compounds were also tested for acute toxicity. Compound 12 was found to be the most potent compound of the series, exhibiting activity of 90 % more potent than standard drug. Compounds 13 and 18 also showed promising activity of 80 %, equipotent to standard drug.

Keywords: Benzothiazinyl indoles, benzoxazinyl indoles, synthesis, anticonvulsant activity, acute toxicity

INTRODUCTION

Epilepsy or seizure disorder is a disorder in which nerve cell activity in the brain is distributed, causing seizure. Epilepsy may occur as a result of a genetic disorder or an acquired brain injury, such as a trauma or stroke. Anticonvulsants are a diverse group of pharmacological agents used in the treatment of epileptic seizures.

The usage of most anticonvulsant agents is limited not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of convulsions and drug side effects – which includes sedation, hypnosis, etc, thereby hampering day time work.

Indoles and their derivatives constitute an important class of heterocyclic compounds. They gained prominence in medicinal chemistry due to their diverse biological activities such as antiviral[1-4], anticancer[5-8], antioxidant[9-12], antibacterial[13-16], anti-inflammatory[17-20] and anticonvulsant[21-24]. Chemical literature reveals that several organic compounds containing fused seven membered heterocyclic ring, that is, benzoxazepines[25-27] and benzothiazepines[26-28], have been reported to possess anticonvulsant activity. Hence, it was thought of interest to synthesize some newer indole derivatives by merging benzoxazepine and benzothiazepine moieties at 3rd-position of indole nucleus, with the hope to synthesize better anticonvulsant agents.

MATERIALS AND METHODS

Chemistry

The melting points are uncorrected. Carbon, hydrogen and nitrogen analysis were performed on CHN analysis, Carlo Erba 1108. Analyses (C,H,N) were within ± 0.04 % of the theoretical values. The purity of the compounds was checked by TLC on silica gel-G. The plates and spots were located by iodine. IR spectra were recorded on Beckman-Acculab-10-spectrophotometer (ν_{max} in cm^{-1}). 1H-NMR spectra were recorded in $CDCl_3$ on a Bruker 300-FT instrument.

The synthetic routes for the synthesis of compounds 1-19 is depicted in Scheme-1. The analytical data of compounds 1-19 is given in Table I. The compounds 1-19 were tested for their anticonvulsant activity as well as for their acute toxicity. Phenytoin sodium was used

[a] Medicinal Chemistry Laboratory, Department of Chemistry, Meerut College, Meerut-250 002, Uttar Pradesh, India
[b] Department of Chemistry, D.N.P.G. College, Meerut-250 002, Uttar Pradesh, India
*For Correspondence: E-mail: archanachemistrymcm@gmail.com

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Table I: Physical and analytical data of compounds 1-19

Compd. No.	R	M.P. (°C)	Yield	Recrystallization solvent	Molecular Formula	Calculated % (Found %)		
						C	H	N
1.	-	135	70	Methanol	$C_{11}H_{11}NO$	76.30 (76.27)	6.35 (6.37)	8.09 (8.11)
2.	H	152	60	Methanol	$C_{18}H_{15}NO$	82.75 (82.72)	5.74 (5.77)	5.36 (5.33)
3.	p-OCH_3	181	55	Ethanol	$C_{19}H_{17}NO_2$	78.35 (78.36)	5.84 (5.82)	4.81 (4.79)
4.	m-OCH_3	165	62	Benzene	$C_{19}H_{17}NO_2$	79.36 (79.37)	5.84 (5.86)	4.81 (4.79)
5.	p-OH	178	58	Petroleum ether	$C_{18}H_{15}NO_2$	77.97 (78.00)	5.41 (5.38)	5.05 (5.08)
6.	p-$N(CH_3)_2$	170	56	Acetone	$C_{20}H_{20}N_2O$	78.94 (78.91)	6.57 (6.60)	9.21 (9.19)
7.	m-OCH_3, p-OH	188	62	Ethanol	$C_{19}H_{17}NO_3$	74.26 (74.28)	5.53 (5.56)	4.56 (4.53)
8.	H	120	64	Acetone	$C_{24}H_{20}N_2S$	78.26 (78.24)	5.43 (5.45)	7.60 (7.58)
9.	p-OCH_3	155	55	Methanol	$C_{25}H_{22}N_2OS$	75.37 (75.39)	5.52 (5.49)	7.03 (7.00)
10.	m-OCH_3	148	68	Methanol	$C_{25}H_{22}N_2OS$	75.37 (75.40)	5.52 (5.49)	7.03 (7.00)
11.	p-OH	162	65	Ethanol	$C_{24}H_{20}N_2OS$	75.00 (74.98)	5.20 (5.18)	7.29 (7.32)
12.	p-$N(CH_3)_2$	134	55	Petroleum ether	$C_{26}H_{25}N_3S$	78.98 (79.00)	6.32 (6.29)	10.63 (10.60)
13.	m-OCH_3, p-OH	138	50	DMF	$C_{25}H_{22}N_2O_2S$	72.46 (72.47)	5.31 (5.28)	6.76 (6.79)
14.	H	135	52	Benzene	$C_{24}H_{20}N_2O$	81.81 (81.79)	5.68 (5.70)	7.95 (7.92)
15.	p-OCH_3	162	50	Acetone	$C_{25}H_{22}N_2O_2$	78.53 (78.50)	5.75 (5.77)	7.32 (7.29)
16.	m-OCH_3	125	55	Acetone	$C_{25}H_{22}N_2O_2$	78.53 (78.55)	5.75 (5.77)	7.32 (7.29)
17.	p-OH	148	60	Ethanol	$C_{24}H_{20}N_2O_2$	78.26 (78.24)	5.43 (5.45)	7.60 (7.58)
18.	p-$N(CH_3)_2$	156	62	Methanol	$C_{26}H_{25}N_3O$	78.98 (79.00)	6.32 (6.29)	10.63 (10.65)
19.	m-OCH_3, p-OH	170	65	Ethanol	$C_{25}H_{22}N_2O_3$	75.37 (75.35)	5.52 (5.49)	7.03 (7.00)

C, H, N were found within ± 0.04%

as reference drug for anticonvulsant activity. The results of biological activity given in Table II.

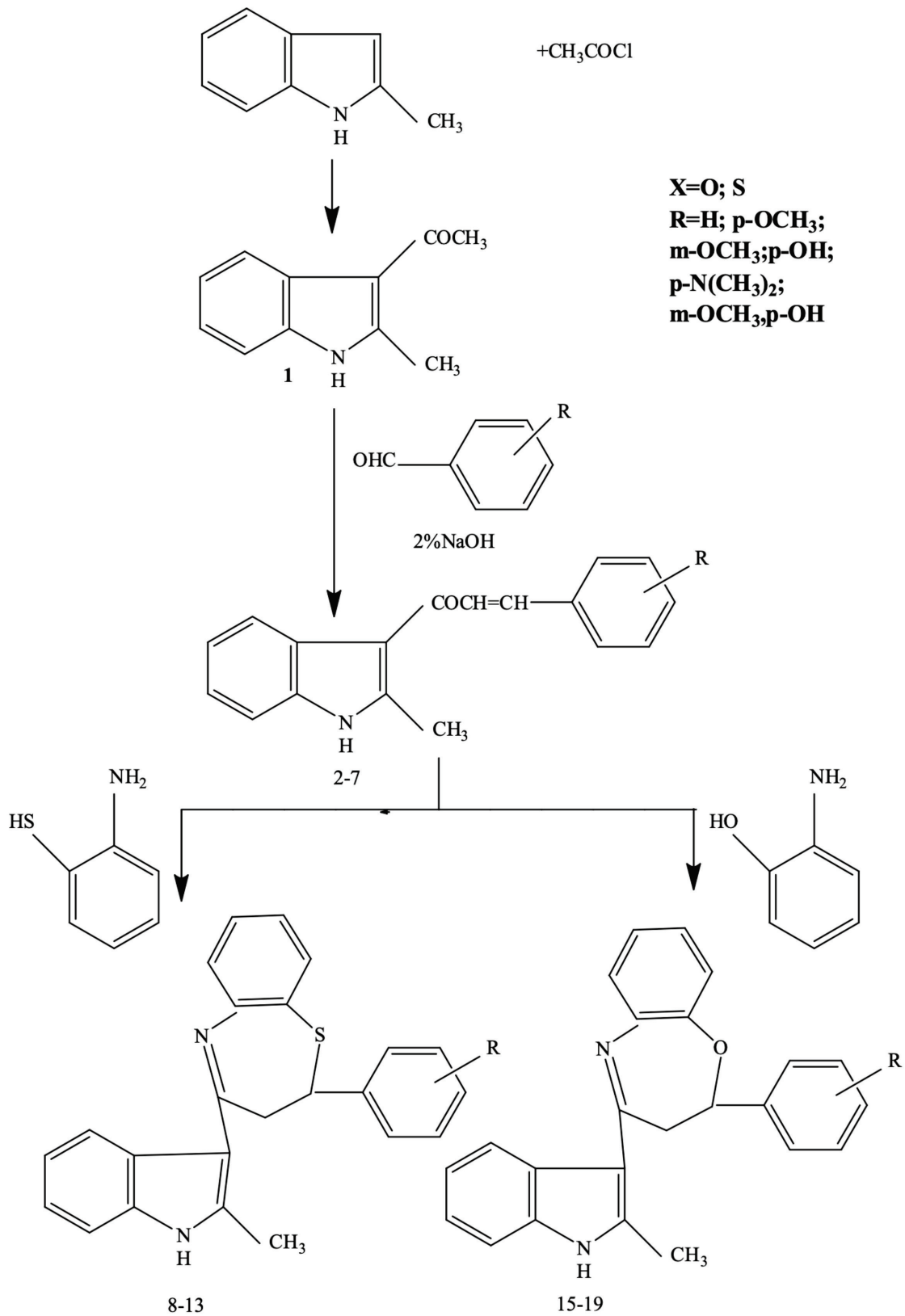
Synthesis

Synthesis of 3-acetyl-2-methyl-indole (1)

Acetyl chloride (50 mL) was added to 2-methyl indole (20 g) drop by drop with stirring at 0-5 ^{0}C. The reaction mixture was further stirred for 10 h using a magnetic stirrer and kept overnight. The excess of acetyl chloride was distilled off with the help of a distillation assembly. The residue thus obtained was washed with petroleum ether (40-60 ^{0}C) a number of times and then poured onto ice. The solid thus obtained was filtered with the help of a filtration pump. The solid thus obtained was recrystallized from appropriate solvents. The physical and analytical data of compound 1 is given in Table I. Compound 1: ^{1}H-NMR $CDCl_3$ δ: 9. 80 (brs, 1H, NH of indole), 7.10 - 7.70

Table II: Pharmacological data of compounds 1-19

Compound Number	Anticonvulsant activity		Acute toxicity (ALD_{50}) mg kg^{-1} i.p.
	Dose (mg kg^{-1} i.p.)	% inhibition of seizures	
1.	30	40*	>1000
2.	30	40**	>1000
3.	30	50**	>1000
4.	30	50**	>1000
5.	30	50**	>1000
6.	30	70***	>1000
7.	30	60***	>1000
8.	30	60**	>1000
9.	30	70**	>1000
10.	30	70**	>1000
11.	30	70***	>1000
12.	7.5 15 30	70** 80*** 90***	>2000
13.	7.5 15 30	40 50 80***	>1000
14.	30	60**	>1000
15.	30	70**	>1000
16.	30	70**	>1000
17.	30	60**	>1000
18.	7.5 15 30	50** 60** 80***	>2000
19.	30	70***	>1000
Phenytoin sodium	30	80***	
Propylene glycol	2.0 mL	0	
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$*			


+CH3COCl
X=O; S
R=H; p-OCH3;
m-OCH3;p-OH;
p-N(CH3)2;
m-OCH3,p-OH
1
2%NaOH
2-7
8-13
15-19

SCHEME-1

(m, 4H, Ar-H), 1. 30 (s, 3H, CH_3), 2.47 (s, 3H, $COCH_3$). IR (cm^{-1}, KBr): 3184 (NH of indole), 3048 (aromatic CH), 1710 (C=O).

Synthesis of 1-(2'-methylindolyl) arylidenyl chalcones (2-7)

To the solution of compound 1 (0.01 mol) in absolute ethanol (50 mL), various aromatic aldehydes (0. 01 mol) were refluxed for 12 h in presence of 2 % NaOH. The resulting mixtures were concentrated, cooled and poured onto ice. The solids thus obtained were filtered with the help of a filtration pump. After filtration the solid obtained was washed with petroleum ether (40-60 ^{0}C), and recrystallized from appropriate solvents. The physical and analytical data of compounds 2-7 are given in Table I. Compound 3: ^{1}H-NMR $CDCl_3$ δ: 9.85 (brs, 1H, NH of indole), 7.00 - 7.85 (m, 4H, Ar-H), 1. 55 (s, 3H, CH_3), 3.50 (s, 3H, Ar-OCH_3), 5.75 (m, 1H, C H CO), 6.60 (d, 1H, -COCH=), 7.27-7.75 (m, 4H, Ar-H), 8.35 (d, 1H, =CH-Ar). IR (cm^{-1}, KBr): 3182 (NH of indole), 3048 (aromatic CH), 1715 (C=O), 1620 (CH=CH), 1580 (C-C of aromatic ring).

Synthesis of 2-substitutedphenyl-2,3-dihydro-4-(2'-methylindolyl)-1,5-benzthiazepines (8-13)

An equimolar mixture (0.01 mol) of ethanolic solution of compounds 2-7, i.e. 1-(2'-methylindolyl) arylidenyl chalcones, and 2-aminothiophenol were refluxed for 3-4 h in the presence of few drops of glacial acetic acid (1 mL). The completion of reactions was determined by TLC. The solvents were distilled off under reduced pressure. The solids thus obtained were recrystallized by suitable solvents to give compounds 8-13. The physical and analytical data of compounds 8-13 are given in Table I. Compound 9: ^{1}H-NMR $CDCl_3$ δ: 9.88 (brs, 1H, NH of indole), 7.05 - 7.68 (m, 12H, Ar-H), 1. 59 (s, 3H, CH_3), 3.25 (d, 2H, CH_2 of thiazepine ring), 4.25 (t, 1H of thiazepine ring), 3.65 (s, 3H, OCH_3). IR (cm^{-1}, KBr): 3188 (NH of indole), 3045 (aromatic CH), 1585 (C-C of aromatic ring), 1668 (C=N), 1485 (C-N), 690 (C-S-C).

Synthesis of 2-substitutedphenyl-2,3-dihydro-4-(2'-methylindolyl)-1,5-benzoxazepines (14-19)

An equimolar mixture (0.01 mol) of ethanolic solution of compounds 2-7, i.e. 1-(2'-methylindolyl) arylidenyl chalcones, and 2-aminophenol were refluxed for 3-4 h in the presence of few drops of glacial acetic acid (1 mL). The completion of reactions was determined by TLC. The solvents were distilled off under reduced pressure. The solids thus obtained were recrystallized by suitable solvents to give compounds 14-19. The physical and analytical data of compounds 14-19 are given in Table I. Compound 15: ^{1}H-NMR $CDCl_3$ δ: 9.80 (brs, 1H, NH of indole), 7.15 - 7.88 (m, 12H, Ar-H), 1. 62 (s, 3H, CH_3), 3.28 (d, 2H, CH_2 of thiazepine ring), 4.30 (t, 1H of thiazepine ring), 3.68 (s, 3H, OCH_3). IR (cm^{-1}, KBr): 3200 (NH of indole), 304+2 (aromatic CH), 158+2 (C-C of aromatic ring), 166+5 (C=N), 1480 (C-N), 1070 (C-O-C).

PHARMACOLOGY

Anticonvulsant activity

Anticonvulsant activity was performed using supra maximal electroshock seizure pattern test (SMES) model. For this model, method of Tomen et al[29] was used. Albino rats of either sex weighing between 90-120 g were used and were divided into groups such that each group contains ten animals. Phenytoin sodium – reference drug and test drugs were administered intraperitoneally in rats. The rats were subjected to a shock of 150MA through ear electrodes for 0.2 s after 1 h of drug administration. The presence or absence of extensor response was noted. Animals in which extensor response was eliminated were taken as protected rats.

Acute toxicity (ALD_{50})

The acute toxicity studies were performed in mice. All the compounds synthesized were investigated for acute toxicity (ALD_{50}) in mice. This activity was performed by following the procedure of Smith[30].

RESULTS AND DISCUSSION

Anticonvulsant activity in rats

In the supra maximal electroshock induced seizure test (SMES), out of 19 compounds tested, compounds 12, 13 and 18 were found to be most potent with 90%, 80% and 80% inhibition of seizures, respectively. The results of anticonvulsant activity are depicted in Table II.

Acute toxicity in mice

All the compounds of the series were evaluated for acute toxicity (ALD_{50}). All the 19 compounds tested showed ALD_{50} >1000 mg kg^{-1} i.p., thereby indicating a good safety margin. However, compounds 12 and 18 exhibited ALD_{50} > 2000 mg kg^{-1} i.p. The results of acute toxicity studies are given in Table II.

Discussion

All the newly synthesized compounds (1-19) were evaluated for anticonvulsant activity at a dose of 30 mg kg^{-1} i.p. and were compared with the standard drug – phenytoin sodium, given at a same dose. Compounds (1 to 19) have shown varying degree

of anticonvulsant activity ranging from 40 % to 90 % (Table II).

Introduction of chalconyl moiety at 3rd position of indole nucleus, which was further substituted with benzothiazinyl/ benzoxazinyl moiety, was the characteristic feature of this series. The series started with the introduction of acetyl group at 3rd position of indole nucleus. This compound 1, exhibited though less, an activity of 40 %, when tested. The compounds synthesized in the next step i.e. compounds (2 to 7) showed moderate anticonvulsant activity ranging from 40 % to 70 %. It was noted that compound having phenyl group (compound 2) as substituent showed least activity (40 %) while compound 6 substituted with *p-N,N*-dimethyl ring elicited the maximum percent protection (70 %) against seizures. Compounds 3, 4 and 5 substituted with *p*-methoxy ring, *m*-methoxy ring and *p*-hydroxy ring exhibited 50 % inhibition of seizures. Compound 7, substituted with *m*-methoxy-*p*-hydroxy rings, was found to possess 60 % anticonvulsant activity.

Further, route-1 of the series was characterized by the presence of a substituted benzothiazinyl moiety at 3rd position of indole nucleus. Almost all compounds (8-13) showed potent and statistically significant anticonvulsant activity ranging from 60 % to 90 %. However compound 12 containing benzothiazepinyl moiety substituted with *p-N,N*-dimethyl ring was found to be the most potent compound of the series. This compound showed 90% inhibition of seizures and was reported to be more potent than the standard drug- phenytoin sodium, which provides 80 % protection against seizures. Compound 13, substituted with *m*-methoxy-*p*-hydroxy rings on benzothiazepinyl moiety, also shown activity equipotent to standard drug (80 %). Compounds 9, 10 and 11 having *p*-methoxy ring, *m*-methoxy ring and *p*-hydroxy ring on benzothiazepinyl moiety, exhibited good anticonvulsant activity providing 70 % protection, whereas compound 8, substituted with phenyl ring on benzothiazepinyl moiety, showed moderate activity of 60%.

The other aspect of the series that is route-2 was characterized by the presence of a substituted benzoxazepinyl moiety at 3rd position of indole nucleus. These compounds 14-19 have also shown promising anticonvulsant activity ranging from 60 % to 80 %. Compound 18, having benzoxazepinyl moiety substituted with *p-N,N*-dimethyl ring, was found to be equipotent to standard drug providing 80 % anticonvulsant activity. Compounds 14 and 17, containing benzoxazepinyl moiety substituted with phenyl group and *p*-hydroxy phenyl group, were found to possess 60 % protection. Compounds 15, 16 and 17 showed 70 % activity, which were substituted with *p*-methoxy, *m*-methoxy and *m*-methoxy-*p*-hydroxy, respectively.

Despite promising anticonvulsant activity reported in compounds 12 (90 % activity) and 18 (80 % activity), these two compounds have shown a very high value of ALD_{50} > 2000 mg kg^{-1} i.p. Considering the potentiality and good safety margin of these compounds, they were further studied in detail at three graded doses of 7.5, 15 and 30 mg kg^{-1} i.p. for their anticonvulsant activity. Result of this detailed study are given in Table II.

CONCLUSION

On the basis of above discussion, it can be concluded that:

Benzothiazepines **8-13** and benzoxazepines **14-19** possess more activity than their corresponding chalcones **2-7**. Benzothiazepine **8-13** containing compounds showed more potent activity than their corresponding benzoxazepine **14-19** containing compounds. Compounds having *p-N,N*-dimethyl group **6**, **12** and **18** as substituent elicited most potent anticonvulsant activity at each step of the series.

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