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Synthesis of Newer Substituted Azetidinone and Thiazolidinone derivatives as potent Anticonvulsant Agents

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Abstract : Various 2-N-(2-Phenyl -1H-indol-3yl)-imino benzene/thiophenol (3a – 3e) , 3-Chloro-1-(benzyl/thiophenyl)-4-(2-1H-indol-3yl) azetidin-2-ones (4a-4e) and 3-Substituted benzyl/thiophenyl -4-(2-phenyl 1H-indol-3-yl) thiazolidin-4-ones (5a-5e) have been synthesised . The structures of these compounds have been established by elemental (C,H,N) and spectral (IR, H-NMR, and Mass) analysis. The synthesised compounds were screened in vivo ,for their acute toxicity and anticonvulsant activity in MES and PTZ models. Almost all compounds have shown promising anticonvulsant activity. Compound 5d was the most potent compound of this series.

Key words : Substituted Indolyl azetidinones, Substituted Indolyl thiazolidinones, anticonvulsant activity, acute toxicity.

Introduction

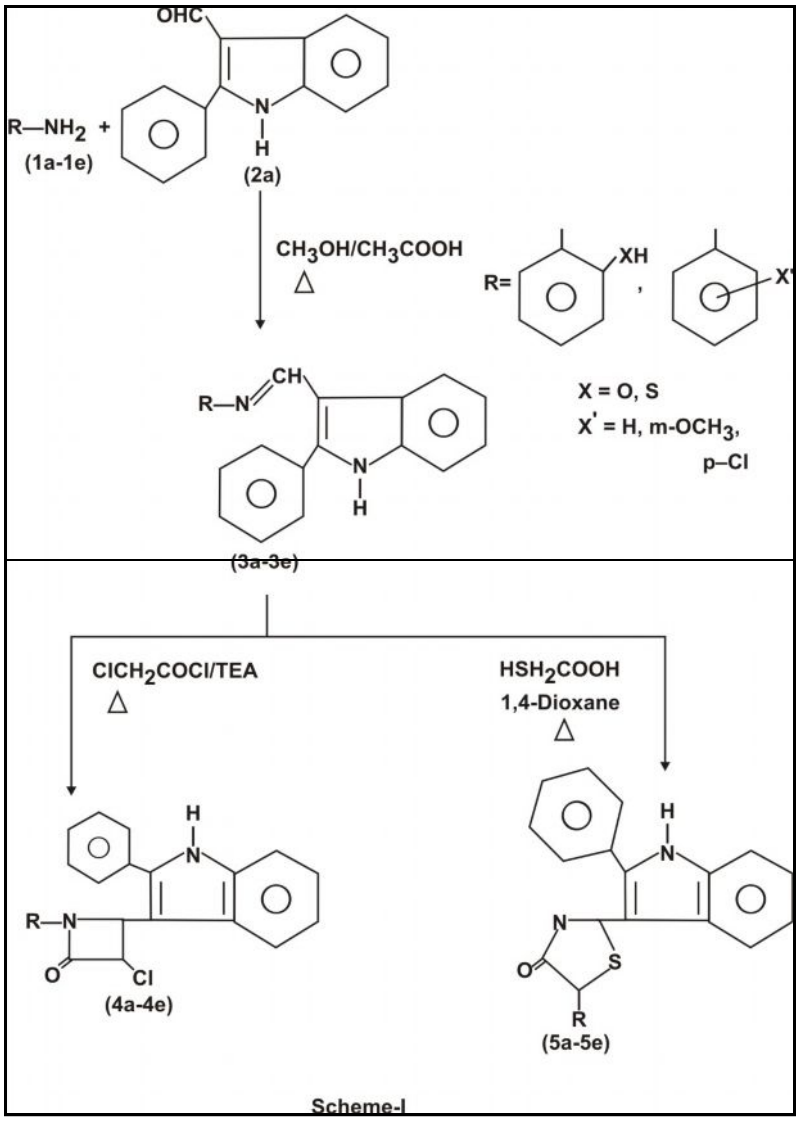
Literature survey reveals that anticonvulsant activity is present in a number of heterocyclic nuclei like phenothiazine (1), barbituric/thiobarbituric acids (2) along with Indole derivatives (3) etc. Indole derivatives have documented consistent advances in the design of novel anticonvulsant agents (4-7). Moreover, compounds containing azetidinones (8-9) and thiazolidinones (10-14) nucleus make up a broad class that attracted attention in the past few years owing to its wide range of activities especially anticonvulsant and CNS depressant activities. Incorporating , these moieties (azetidinones and thiazolidinones) in indole nucleus might be thought to yield potent anticonvulsant agents.

Chemistry

The synthetic route of compounds are outlined in Scheme-1. 2-N-(2-Phenyl-1H-indol-3yl)-imino benzene/thiophenol (3a-3e) were prepared by reacting substituted anilines/2-amino thiophenol (1a-1e) with 2-phenyl-1H-indol-3-carboxaldehyde (2a) in presence of glacial acetic acid. Compounds (3a-3e) on reaction with chloroacetyl chloride and triethyl amine in dry benzene yielded 3-chloro-1-(benzyl/thiophenyl)-4-(2-phenl-1H-indol-3yl) azetidin-2-ones (4a-4e) .When compounds (3a-3e) were reacted with thioglycolic acid , in presence of anhydrous zinc chloride indry 1,4-dioxane yielded 3-benzyl/thiophenyl 4-(2-phenyl-1H-indol-3-yl)-thiazolidin-4-ones (5a-5e)

Table 1: Physical and analytical data of compounds (3a-3e), (4a-4e) and (5a-5e)

Compd.	R	X	X'	M.P. (^{0}C)	Yield (%)	Recryst. solvent	Mol.For. (MolWt)	Elemental Analysis (%)		
								C (calcd ; found)	H (calcd; Found)	N (calcd; found)
3a	XC_6H_4-	H	-	127	67	methanol	$C_{21}H_{18}N_2$ (298)	84.56 ; 84.52	6.04 ; 6.06	9.39 ; 9.36
3b	XC_6H_4-	p-Cl	-	130	62	methanol	$C_{21}H_{17}N_2CI$ (332.5)	75.78 ; 75.79	5.11 ; 5.09	8.42 ; 8.40
3c	XC_6H_4-	m-OCH_3	–	125	65	ethanol	$C_{22}H_{20}N_2O$ (328)	80.84 ; 80.86	6.08 ; 6.10	8.53 ; 8.55
3d	X'C_6H_5-	-	S	140	60	benzene	$C_{21}H_{18}N_2S$ (330)	76.36 ; 76.34	5.45 ; 5.42	8.48 ; 8.47
3e	X'C_6H_5-	-	O	132	65	methanol	$C_{21}H_{18}N_2O$ (314)	80.25 ; 80.23	5.73 ; 5.75	8.91 ; 8.94
4a	XC_6H_4-	H	-	110	57	ethanol	$C_{23}H_{19}N_2$ (374.5)	73.69 ; 73.67	5.07 ; 5.05	7.47 ; 7.43
4b	XC_6H_4-	p-CI	-	120	55	methanol	$C_{23}H_{18}N_2OCI_2$ (408)	67.64 ; 67.66	4.41 ; 4.45	6.86 ; 6.82
4c	XC_6H_4-	m-OCH_3	-	105	54	benzene	$C_{23}H_{21}N_2O_2CI_2$(439)	65.60 ; 65.64	4.78 ; 4.76	6.37 ; 6.39
4d	X'C_6H_5-	_	S	130	56	methanol	$C_{23}H_{19}N_2OCIS$(406.5)	67.89 ; 67.86	4.67 ; 4.62	6.88 ; 6.90
4e	X'C_6H_5-	_	O	120	52	ethanol	$C_{23}H_{19}N_2OCIS_2$(438.5	62.94 ; 62.95	4.33 ; 4.30	6.38 ; 6.41
5a	XC_6H_4-	H	-	114	60	ethanol	$C_{23}H_{18}N_2OS$ (370)	74.59 ; 74.62	4.86 ; 4.83	7.56 ; 7.60
5b	XC_6H_4-	p-CI	-	118	56	ethanol	$C_{23}H_{17}N_{2O}SC$ (404.5)	68.23 ; 68.19	4.20 ; 4.18	6.92 ; 6.89
5c	XC_6H_4-	m-OCH_3	-	120	62	ethanol	$C_{24}H_{20}N_2O_2SCI$(435.5	66.13 ; 66.16	4.59 ; 4.62	6.42 ; 6.39
5d	X'C_6H_5-	-	S	135	58	methanol	$C_{23}H_{18}N_2OS_2$ (402)	68.65 ; 68.68	4.47 ; 4.51	6.96 ; 6.92
5e	X'C_6H_5-	-	O	130	63	methanol	$C_{23}H_{18}N_2O_2S$ (386)	71.50 ; 71.47	4.66 ; 4.70	7.25 ; 7.23S



Scheme-I

Pharmacological Activities

Anticonvulsant activity

Maximum electroshock seizure (MES) test

This test was performed according to the method of Tomen et al (15). The group of ten rats were treated with test drugs (50mg/kg i.p.) / phenytoin sodium (30mg/kg i.p.). After 1h they were subjected to a shock of 150 mA by convulsiometer through ear electrodes for 0.2s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

Pentylenetetrazole (PTZ) induced test

This test was performed by following the method oh Fischer (16) .The rats were injectewd with pentylenetetrazole in dose of 70mg/kg subcutaneously in scruff of neck. After 2-4 min. Of PTZ injection animals developed sequence of excitement, myclonic jerks, clonic seizures, one or more maximum tonic seizures. Animals exihibiting these seizure pattern were selected. Standard drug used in this model was sodium valproate (80mg/kg i.p.) and was injected 60 min. prior to PTZ challenge.

All the newly synthesised compounds were studied for their anticonvulsant activity at a dose of 50mg/kg i.p. in maximal electroshock and pentylenetetrazole induced seizures respectively. All the newly synthesised compounds have shown anticonvulsant activity in both the models (ranging from 50-90% and 40-80% in MES and PTZ models respectively). The anticonvulsant activity of all the compounds are reported in

Table 2. Compound 5d was found to possess potent anticonvulsant activity it was studied three graded doses (12.5, 25and50mg/kg i. P.).

Table 2: Pharmacological data of compounds (3a- 3e), (4a-4e) and (5a-5e)

Compounds	Acute toxicity ALD_{50} (mg/kg i.p.)	Anticonvusant activity		
		Dose (mg/kg i.p.)	MES	PTZ
3a	>1000	50	50**	40
3b	>1000	50	60**	50**
3c	>1000	50	40	40
3d	>1000	50	60**	60**
3e	>1000	50	50**	50**
4a	>1000	50	60**	50**
4b	>1000	50	60***	60***
4c	>1000	50	50**	60**
4d	>1000	50	70***	70***
4e	>1000	50	60**	60**
5a	>1000	50	60**	50**
5b	>1000	50	70***	60**
5c	>1000	50	80***	70***
5d	>1000	50 25 12.5	90*** 50** 25	80*** 40 20
5e	>1000	50	80***	70***
Phenytoin sodium		30	80***	
Sodium Valproate	>1000	80		80***
Propylene glycol		20ml	0	0

*p < 0.05, **p < 0.01, ***p < o.001.

Acute toxicity study

The compounds were investigated for their ALD_{50} which was estimated by following the method of Smith (17).

Experimental

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H. N, were within + 0.05 % of the theoretical value. IR spectra (KBr) are recorded on Bachmann Acculab-spectrophotometer.[1] H NMR spectra were recorded by Bruker WM 400 FT instrument using $CDCI_3$ as solvent and tetramethylsilicane (TMS) as internal reference standard . All chemical shift (d) are in ppm. The purities of the compounds were checked by thin layer chromatography (TLC) on silica gel-G plates of 0.5 mm thickness. The elemental analysis of the compounds were performed on Heracus Carlo Erba 1108 analyser.

Preparation of 2-N-(2-Phenyl-1H-indol-3yl)-imino –benzene/thiophenol (3a-3e) : A mixture of (1a-1b) i.e. various substituted anilines/2-amino thiophenols (0.01 mol) and 2-phenyl-1H-indol-3-carboxaldehyde (2a) (0.01 mol) containing 4-5 drops of glacial acetic acid was refluxed in methanol (35 ml) on a water bath for 6h. The reaction contents were cooled and poured into ice-cold water. The resulting solid was filtered, washed with sodium bisulphite solution followed by cold water, dried and recrystallised from appropriate solvent to get pure (3a-3e).

2-N-(2-Phenyl-1H-indol-3-yl)imino benzene (3a) : Yield 67% ; mp 127^0 C ; IR (KBr ;cm^{-1}) : 1559 (C=C of aromatic ring), 3250 (NH), 1655 (N=CH) ; ^{1} H NMR ($CDCI_3$) : d 7.90- 7.25 (M, 13H, Ar-H) , 12.43 (s,1H,N-H of indole), 8.14 (s, 1H, N=CH) (ppm) ; MS: $[M]^+$ m/z 298.

Preparation of 3-Chloro-1-(benzyl/thiophenyl) -4-(2 -phenyl-1H- indol-3-yl) azetidin – 2 –ones (4a-4e) : To compounds (3a-3e) (0.02 mol) few drops of triethylamine and Chloroacetyl Chloride (0.02 mol) was added with stirring at room temperature during 15 min. The mixture was then refluxed for 1h. Triethylamine hydrochloride formed was filtered off and washed several times with benzene. The filtrate and washing were combined and concentrated under reduced pressure and the residue obtained was washed with petroleum ether (40:60) to remove unreacted Schiff's base. The product was dried and crystallised from 1,4-dioxane and appropriate solvent to get pure (4a-4e) .

3-Chloro-1-benzyl-4-(2-phenyl-1H-indol-3-yl)-azetidin-2-one (4a): Yield 57% ; mp 110^0 ; IR (KBr, cm^{-2}) : 3101 (NH), 1744 (CO), 772 (C-CI) ; ^{1} H-NMR ($CDCI_3$) : d 12.44 (s, 1H, indole NH), 6.73 – 7.83 (m, 13H, Ar-H), 4.55 (d, 1H, CHCi), 3.18 (d, 1H , NCH)(ppm) ; MS : $[M]^+$ m/z 374.5

Preparation of 3-(substituted benzyl/thiophenyl) -4- (2-phenyl-1H-indol-3-yl)-thiazolidin-4-ones (5a-5e) : A mixture of compounds (3a-3e) (0.01 mol), thioglycolic acid (0.01mol) and a pinch of anhydrous zinc Chloride in dry 1,4-dioxane was refluxed for 12-14h. The reaction mixture was then cooled and neutralised with sodium bicarbonate (10%) . The product thus separated was filtered, washed with water, dried and recrystallised from appropriate solvent to get pure (5a-5e).

3-Benzyl 4-(2-phenyl-1H-indol-yl)-thiazolidin-4-ones (5a) : Yield 60% ; mp 114^0C ; IR (KBr, cm^{-1}) : 3131 (NH), 1712 (C=), 700 (C-S-C) ; ^{1} H- NMR ($CDCl_3$) : d 12.49 (s, 1H, indole NH), 6.88-7.90 (m, 13H, Ar-H), 5.01 (s, 1H, NCH), 4.12 (s,2H, SCH_2) ; MS : $[M]^+$ m/z 370

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