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EVALUATION OF ANTICONVULSANT ACTIVITY OF NOVEL INDOLE DERIVATIVES

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ABSTRACT

Epilepsy affects 0.5-1% of the population. Often, there is no recognizable cause, although it may develop after brain damage, such as trauma, infection or tumor growth or other kinds of neurological disease. Epilepsy is a very common neurological disorder, characterized by seizures, which take various forms and results from episodic neuronal discharges, the form of the seizure depending on the part of the brain affected. Current antiepileptic drugs are effective in controlling seizures in about 70% of patients, but their use is often limited by side effects.

Novel mannich bases of indole were synthesized by using a series of aldehydes and secondary amines in presence of ethanol with magnetic stirring for 4-6 hours in cold condition. The structures of these compounds were established on the basis of spectral data. The synthesized compounds were evaluated for anticonvulsant activity by maximum electroshock induced convulsions method on Wister albino mice of either sex (25-30 gm). Phenytoin was used as standard drug. Some of these synthesized compounds shown significant anticonvulsant activity.

Key words: Indole, Aldehydes, Secondary amines, Methanol, Anticonvulsant activity

INTRODUCTION

Epilepsy is a very common neurological disorder, characterized by seizures, which take various forms and results from episodic neuronal discharges, the form of the seizure depending on the part of the brain affected. Epilepsy affects 0.5-1% of the population. Often there is no recognizable cause, although it may develop after brain damage, such as trauma, infection or tumor growth or other kinds of neurological disease.[1]

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Indole nucleus is a versatile lead molecule and has wide range of biological activities such as anti-inflammatory[2], analgesics, anticonvulsant, antipsychotic, antimicrobial and antitubercular and also found to show anticancer activity[3].

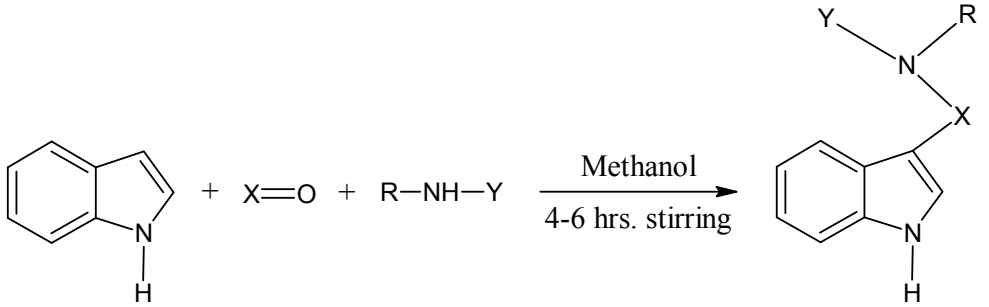
Mannich bases of indole were not found in the literature. Mannich bases of indole have shown pharmacological profile such as antiepileptic, analgesics[4] and biological profile such as antimicrobial[5]. Based on the above reports, we have synthesized various indole derivatives and evaluated them for anticonvulsant activity.

EXPERIMENTAL

Materials and methods

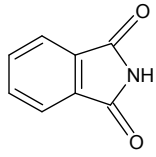
Synthesis of Mannich bases of indole[6]

Equimolar quantities (0.01 mol) of indole and amino compounds and series of aldehyde derivatives (such as formaldehyde, p-dimethyl amino benzaldehyde, respectively) were dissolved in ethanol and stirred for 4-6 hrs. in cold condition. The content was kept over night in the freezer. The product obtained was recrystallised from alcohol **(Scheme 1)**.

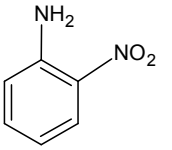
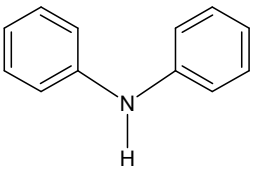
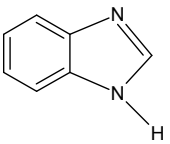
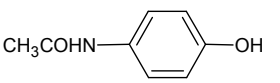
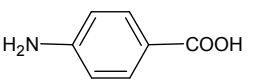
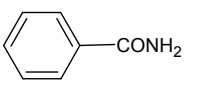
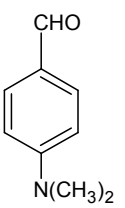
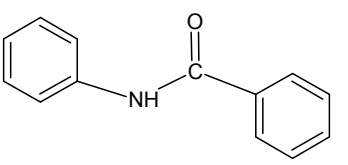
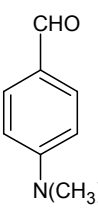
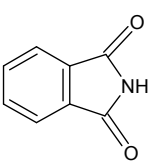
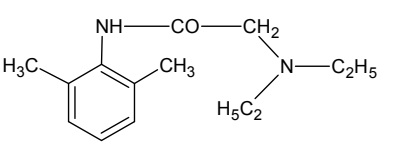


Scheme 1

Table 1[7]

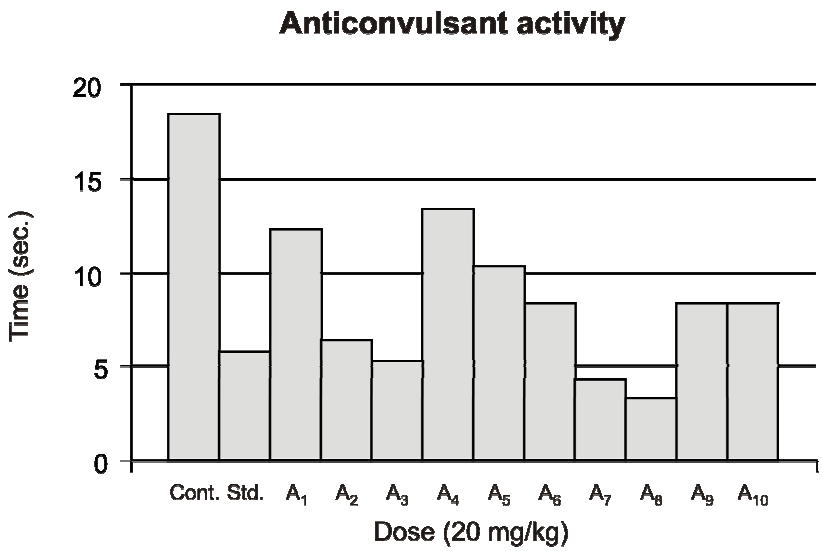
Compound	X=O	R-NH-Y
A_1	CH_2O	

Cont…

Compound	X=O	R-NH-Y
A_2	CH_2O	
A_3	CH_2O	
A_4	CH2O	
A_5	CH_2O	
A_6	CH_2O	
A_7	CH_2O	
A_8		
A_9		
A_{10}	CH_2O	

Evaluation of anticonvulsant activity of novel indole derivatives[8]

Anticonvulsant activity was observed out by using maximum electroshock induced convulsions method. Albino mice of either sex (25-30 g) were used for the study and divided into 19 groups of 5 mice each. They were given electrical shock through ear electrodes of 150 mA. For 0.2 sec by Electro Convulsiometer. Group I was treated with 0.5% Tween 80 suspension and served as control. Group II were treated with phenytoin (20 mg/kg) and served as standard. Groups III – XIX were treated with newly synthesized compounds (20 mg/kg), respectively. 30 min before seizure induction onset time of tonic flexion, extension and clonic, phases were noted.



Spectral studies[9]

Melting points were determined by open capillary method. Purity of compounds was checked on silica Gel TLC plates. IR spectra were recorded on Shimadzu 4000 FTIR spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on BRUKER amx-4000 using DMSO-d6 as an internal standard.

Statistical analysis[10]

The protective index was observed as reduction time of tonic extensor phase and all the data (Mean + SEM) were analyzed statistically by students “t” test and tabulated in Table 2.

Data table and observations

Table 2.

Comp.	Mol. formula	Mol. wt.	M. P. (°C)	Yield (%)	R_f Value	Anticonvulsant activity Extensor (sec) Mean ± SEM
A_1	$C_{17}H_{12}N_2O_2$	276	89-92	65	0.49	12.33 ± 0.33
A_2	$C_{14}H_{13}N_2$	255	68-72	72	0.39	6.33 ± 0.35
A_3	$C_{21}H_{28}N_2$	308	95-102	75	0.6	5.01 ± 0.36
A_4	$C_{16}H_{13}N_3$	247	80-82	74	0.54	13.12 ± 0.35
A_5	$C_{17}H_{16}N_2O_2$	280	75-80	73	0.53	10.19 ± 0.33
A_6	$C_{16}H_{14}N_3O_2$		102-104	62	0.55	8.41 ± 0.34
A_7	$C_{16}H_{14}N_2O_2$	266	104-106	65	0.75	4.25 ± 0.35
A_8	$C_{30}H_{27}N_2O$	431	121-123	73	0.65	4.44 ± 0.33
A_9	$C_{25}H_{21}N_3O_2$	395	83-85	64	0.67	8.40 ± 0.36
A_{10}	$C_{23}H_{29}N_3O$	363	69-71	68	0.45	9.76 ± 0.34
Control	-	-	-	-	-	18.46 ± 0.82
Standard	$C_{15}H_{12}N_2O_2$	252	293-295	99	0.89	5.75 ± 1.04
$p \geq 0.05$						

RESULTS AND DISCUSSION

Novel Mannich bases were synthesized by Mannich reaction and spectral data were analyzed by ^{1}H NMR and FT-IR. The title compounds synthesized were evaluated for anticonvulsant activity by maximum electroshock induced convulsion method. Most of the compounds have shown significant anticonvulsant activity. Compounds A_3, A_7 and A_8 have showed maximum anticonvulsant activity Compounds A_2, A_4, A_5 and A_{10} have shown less significant anticonvulsant activity. Phenytoin was used as a standard drug.

Spectral data

A_1 : IR (KB r) cm^{-1} : 3447 (NH str.), 2980 (Ar-CH), 1604 (C = O str.), ^{1}H NMR (δ ppm) :

7.12-7.89 (Ar.m,8H), 5.25 (1H, s,NH), 6.95 (1H,s,CH), 4.25 (2H, t,CH_2)

A_2: IR (KB r) $cm^{-1:}$ 3374 (NH str.), 1444 (CH_2 str.), 2980 (Ar. CH str.), 1343 (Ar. 2^0 amine (C-N), 1574 (Ar. NO_2 str.), ^1H NMR (δ ppm): 7.02-8.42 (8H, m, Ar.H) 5.64 (1H, t, NH), 6.76 (2H, t, CH_2), 6.89 (1H, s, CH)

A_3: IR (KBr) $cm^{-1:}$ 3400 (NH str.), 3059 (Ar.CH str.), 1468 (CH_2 str.), 1374 (Ar. t^0 amine str.), 715 (Ar. m substituted C-N).

A_4: IR (KBr) $cm^{-1:}$ 3252 (NH str.), 1457 (CH_2 str.), 3050 (Ar.CH str.), 740 (.Ar disubstituted str.)

A_5: IR (KBr) $cm^{-1:}$ 3327 (NH str.), 1440 (CH_2 str.), 1653 (C=O), 1227 (Phenol OH str.)

A_6: IR (KBr) cm^{-1}: 3396 (NH str.), 3099 (Ar.CH str.), 1475 (CH_2 str.), 1339 (C-N str.), 758 (Ar.Disubstituted str.)

A_7: IR (KB r) cm^{-1}: 3370 (NH str.), 3031 (Ar.CH str.), 1487(CH_2 str.), 1661(C=O), 3308 (Ar. Sec. Amide N-H str.), ^1H NMR (δ ppm): 7.08-7.83(10H,s NH), 5.06 (1H,t,NH of amide), 3.77(2H, q, CH_2)

A_8: IR (KB r) cm^{-1}: 3247 (NH str.), 3050(Ar.CH str.), 2949 (Methine C-H str.) 1699 (C=O str.), 692 (Ar.m.substituted)

A_9: IR (KB r) cm^{-1}: 3367 (NH str.), 3064 (Ar.CH str.), 1652 (C=O str.), 2900 (Methine C-H str.)

A_{10}: IR (KB r) cm^{-1}: 3329 (NH str.), 3029 (Ar.CH str.), 1647 (C=O str.), 1457 (CH_3 str.), 1309 (Ar. 3º amine str.)

REFERENCES

1. Textbook of Pharmacology, V^{th} Edition H. P. Rang, M. M. Dale, J. M. Ritter and P. K. Moore, Antiepileptic Drugs, p. 550.
2. A. Rajasekaran, R. Mahesh and P. Parimoo, Synthesis and Antinflammatory Activity of 1, 3 – Disubstituted Indolinones, Indian J. Hetro. Chem., **8**, 151, (1998).
3. Anshu Dandia, Harshita Taneja and C. S. Sharma, Microwave Induced Synthesis of Spiro [indole – pyrazole/ isoxazole, pyrimidine] Derivatives, Indian J. Hetero. Chem., **9**, 223 (2000).

4. V. Rajamanickam, K. Anandarajagopal and R. Kalirajan, Evaluation of Antinociceptive and Anti-Epiliptic Activity of N-Mannnich Bases of Some Substituted Benztriazoles, Inter. J. Chem. Sci., **4**, 1048 (2006).

5. Pramila Sah and S. Rajpurohit, Synthesis and Antimicrobial Activity of Some 2-(4', 5'- Disubstituted Thiazolo) -1H- Isoindole-1, 3 (2H) – Diones/Succinimides Asian J. Chem., **17**, 2251 (2005).

6. V. Rajamanickam et al., Project Wor, A. H. Stead, Clearks Isolation & Identification of Drugs II Ed. (2005) pp. 1106-1109.

7. Cambridge Software of Structure, Chem Office, Chem Draw Ultra-8. 0

8. S. K. Kulkarni, Arch. Int. Pharmacodyn., **252**, 124 (1981).

9. Robert M. Silverstein and Francis X, Webster Spectrometric Identification of Organic Compounds, John Wiley Sons, Sixth Edition (1998).

10. N. B. Eddy and D. J. Leimbech, I. Pharmact. Expt. Ther., **107**, 353 (1953).

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