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ANALGESIC AND ANTI–EPILEPTIC ACTIVITY OF N–MANNICH BASES OF SOME SUBSTITUTED BENZTRIAZOLES

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ABSTRACT

N–Mannich bases of benztriazole were synthesized by reacting benztriazole, formaldehyde and various secondary amines. Synthesized compounds were characterized by IR spectra. Synthesized compounds were evaluated for analgesic and anti–epileptic activity by Eddy's hot plate and maximal electrical shock induced convulsion method, respectively. The statistical analysis was done by student's t–test and the values were expressed as Mean ± SEM.

Key words : Mannich bases, Benztriazole, Analgesic, Anti–epileptic.

INTRODUCTION

A reaction between a compound containing a reactive hydrogen atom, formaldehyde and a secondary amine[1] became a general reaction by the name of Mannich[2]. This reaction is useful in adding one carbon atom in a reaction in making N–methyl derivatives and many drug molecules. The drugs with benztriazole moiety were found to possess analgesic[3], anti–inflammatory[4], gastro–prokinetic[5], anti–ulcer[6], potassium channel activation[7], antitubercular[8], anti-platelet aggregation[9], diuretic[10], 5-HT receptor antagonist[11], anti-muscarinic[12], and anti-hypertensive[13] activity. All these observations and essential role of the substituted benztriazole compounds prompted us to synthesize various N–substituted benztriazole derivatives. Further, the structure of the synthesized compounds was deduced on the basis of thin layer chromatographic and IR data.

EXPERIMENTAL

Melting points were determined in open capillaries in the electrical melting point apparatus and are uncorrected. Purity of the compounds was checked on silica gel coated Merck–TLC plates using water, chloroform, acetone and benzene as irrigant. Visualization of spots was carried out in an iodine chamber. IR spectra (KBr) were recorded with Perkin–Elmer 1800 spectrophotometer and reported in Table 1.

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Table 1. Physical data of synthesized compounds

Compound	Molecular Formula	Melting Point (°C)	% Yield	R_f Value	IR spectra (cm^{-1})
(a)	$C_{11}H_{16}N_4$	100–104	63.70	0.576	1616, 1208, 2863
(b)	$C_{19}H_{16}N_4$	>360	59.00	0.738	1616, 1208, 2863
(c)	$C_{11}H_{15}N_5$	170–172	64.50	0.125	1616, 1208, 2863, 3380
(d)	$C_{11}H_{14}N_4O$	80–84	57.30	0.189	1616, 1208, 1111, 2863, 749
(e)	$C_{15}H_{12}N_4$	110–114	68.50	0.910	1616, 1208, 2863
(f)	$C_{15}H_{14}N_4O$	80–82	64.80	0.785	1616, 1208, 2863, 1725
(g)	$C_{20}H_{16}N_4O$	165–168	58.30	0.889	1616, 1208, 2863, 1720
(h)	$C_{15}H_{14}N_4O_2$	80–84	60.20	0.625	1616, 1208, 1111, 2863, 3480, 2960, 749
(i)	$C_{21}H_{15}N_4O_2Cl_2$	220–224	50.58	0.418	1616, 1208, 1111, 2863, 715, 667, 1739

Preparation of N–Mannich bases of benztriazoles

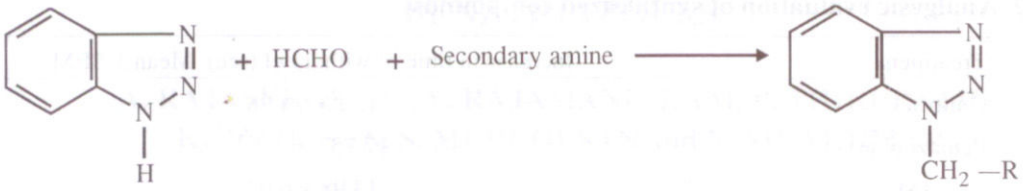
Benztriazole (0.02 mole) was dissolved in methanol (25 mL) under ice–cold condition. To this, formaldehyde (0.02 mole) and morpholine (0.02 mole) was added slowly with constant stirring. Stirring was continued in ice–cold condition for 4 hr. The content of the beaker was kept overnight in the freezer. Crystallized product was recrystallized from methanol and dried. The same procedure was adopted for the synthesis of other Mannich bases using diethylamine, diphenylamine, piperazine, morphine, indole, acetamide, benzamide, paracetamol, and diclofenac sodium. (Scheme-1)

Analgesic activity

The synthesized compounds were screened for their analgesic activity by Eddy's hot plate method[14(a)]. Adult albino mice in the weight of 20–30 g were used for the study. Animals were divided into nine groups each containing six animals. The mice were treated with synthesized compounds (50 mg/kg i.p.) and pentazocine (50 mg/kg, i.p.) was used as standard drug for comparison. The percentage increase in the basal reaction time was measured at 15, 30, 60 and 120 minutes after administration of synthesized compounds and results are tabulated in Table 2.

Anti–epileptic activity

The synthesized compounds were screened for their anti–epileptic activity by maximal electrical shock induced convulsion method[14(b)]. Adult albino mice in the weight of 20–30 g were used for the study. Mice were treated with synthesized compounds (30 mg/kg, i.p) and Gaba pentin (30 mg/kg, i.p.) was used as standard drug for the comparison. After 30 min, the animals were subjected to a shock of 150 mA by convulsiometer through ear electrodes for 0.2



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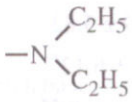
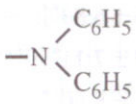
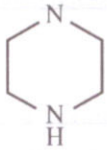
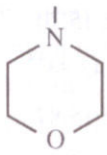
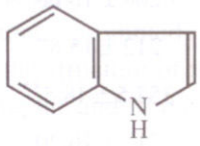
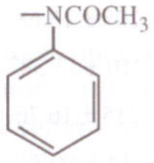
(a) 

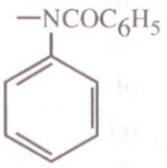
(b) 

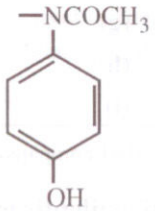
(c) 

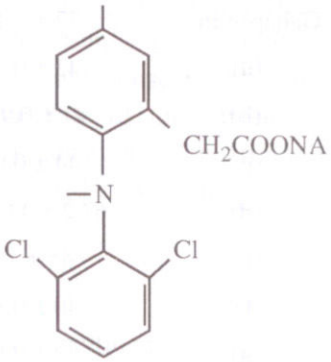
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

Scheme-1

sec and the presence or absence of extensor response was noted. Duration of extensor phase was measured and results are tabulated in Table 3.

Table 2. Analgesic evaluation of synthesized compounds

S.No.	Treatment	Increase in time of withdrawl (sec). Mean ± SEM
1.	Control	13.25 ± 5.98
2.	Pentazocine	17.75 ± 6.60**
3.	**(a)**	13.98 ± 6.02
4.	**(b)**	12.88 ± 5.47*
5.	**(c)**	13.89 ± 5.82
6.	**(d)**	15.73 ± 6.12**
7.	**(e)**	14.75 ± 6.40**
8.	**(f)**	13.25 ± 6.83**
9.	**(g)**	15.84 ± 7.11**
10.	**(h)**	16.82 ± 8.60**
11.	**(i)**	14.28 ± 6.87*

*$p < 0.05$, ** $p < 0.01$ compared with control.

Table 3. Anti–epileptic evaluation of synthesized compounds

Treatment	Duration (sec) Mean ± SEM			Recovery/Death
Control	42 ± 0.92	70 ± 15.70	210 ± 15.70	Recovered
Gabapentin	52 ± 4.19	95 ± 16.20	370 ± 42.83**	Recovered
(a)	43 ± 0.96	71 ± 5.20	211 ± 15.87	Recovered
(b)	41 ± 0.90*	70 ± 4.98	209 ± 15.68	Recovered
(c)	44 ± 0.99	72 ± 4.96*	212 ± 15.82	Recovered
(d)	67.2 ± 42.99**	210.5 ± 48.28*	357.5 ± 48.5**	Recovered
(e)	45 ± 1.1	73 ± 4.99+*	213 ± 16.20	Recovered
(f)	40 ± 0.88	68 ± 4.85	208 ± 15.68	Recovered
(g)	42 ± 0.89	70 ± 5.60	210 ± 15.38*	Recovered
(h)	46 ± 1.20**	75 ± 5.80*	215 ± 16.76	Recovered
(i)	45 ± 1.23	74 ± 5.00	214 ± 16.79*	Recovered

*$p < 0.05$, ** $p < 0.01$ compared with control

RESULTS AND DISCUSSION

Among the compounds, **(a)**, **(e)**, **(f)**, **(g)**, and **(i)** showed significant analgesic activity. The compound N–acetyl–p–hydroxyanilo–N–methyl benztriazole **(h)** showed synergesic analgesic activity. This may be due to inhibition of prostaglandin synthesis. The synthesized compounds N–methyl morpholinyl benztriazole **(d)** exhibits moderate antiepileptic activity, when compared with control. The other compounds were devoid of antiepileptic activity.

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