



# ANTI-NOCICEPTIVE AND ANTI-EPILEPTIC EVALUATION OF N-MANNICH BASES OF SOME SUBSTITUTED CARBAZOLES

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## ABSTRACT

N-Mannich bases of newly synthesized carbazole compounds were synthesized from carbazole by reacting with series of aldehyde like formaldehyde and acetaldehyde and the various secondary amines. Synthesized compounds were characterized by spectral studies and evaluated for anti-nociceptive and anti-epileptic activities by Eddy's Hot plate method and maximum electrical shock induced convulsion method respectively. The statistical analysis was done by students "t" test and the values were expressed as mean  $\pm$  SEM.

**Key words:** Mannich bases, Carbazole, Anti-nociceptive, Anti-epileptic.

## INTRODUCTION

A reaction between a compound having a reactive hydrogen atom, an aldehyde and a secondary amine<sup>1</sup> became a general reaction by the name of Mannich.<sup>2</sup> This reaction is useful in making N-methyl derivatives and many drug molecules. The drugs with carbazole moiety were found to possess anti-convulsant<sup>3</sup>, anti-estrogenic<sup>4</sup>, anti-microbial<sup>5</sup>, anti-HIV<sup>6</sup> and anti-tumour<sup>7</sup> activities. All these observations and essential role of the substituted carbazole derivatives prompted us to synthesize various N-substituted carbazoles and to evaluate their anti-nociceptive and anti-epileptic activities.

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## EXPERIMENTAL

Melting points were determined by open-ended capillary tube in the electrical melting point apparatus and are uncorrected and the purity of the compounds were checked by TLC usings silica gel as stationary phase and the spots were visually detected in an iodine chamber. The structure of the synthesized compounds was elucidated by FT-IR (Shizamadu-8400 series) in KBr disc and FT-<sup>1</sup>H NMR (Brucker 400 MHz) in DMSO-d<sub>6</sub>.

### Preparation of N-Mannich bases of carbazoles

Equimolar quantities (0.01mole) of carbazole and secondary amine were dissolved in methanol (30 mL) in a beaker under perfect ice cold condition and stirred constantly and then 0.01 moles of series of aldehyde (such as formaldehyde and acetaldehyde) was added slowly and heated to reflux for 3 hrs. The content was kept overnight in the freezer. Crystallized product obtained was recrystallized from alcohol. The % yield, R<sub>f</sub> value, melting point and spectral data were reported in Table 1.

**Table 1: Physical data of newly synthesized carbazole derivatives**

Compd. code	Melting point (°C)	R <sub>f</sub> value	Log P	IR spectra (cm <sup>-1</sup> )	<sup>1</sup> H NMR spectra
<b>1a</b>	198-203	0.822	4.131	750, 1205, 1394, 1450, 1492, 1602, 1624	6.86 – 7.84(m, Ar-H), 2.32 (s, CH <sub>3</sub> ), 6.02(s, CH <sub>2</sub> ), 5.12(S, OH)
<b>1b</b>	201-205	0.786	7.791	778, 1328, 1378, 1450, 1509, 1650	6.661 – 7.951(m, Ar-H), 5.8(s, OH), 2.02(s, CH <sub>3</sub> )
<b>1c</b>	209-211	0.904	3.443	723, 1315, 1452, 1482, 2938	7.12 – 7.42 (m, Ar-H), 2.32 (s, CH <sub>3</sub> ), 2.48(s, CH <sub>2</sub> ), 4.98(s, CH <sub>2</sub> )
<b>1d</b>	175-182	0.914	4.869	726, 751, 1335, 1449, 1492, 1694	6.78 – 7.66 (m, Ar-H), 3.52 (s, CH <sub>2</sub> ), 5.64(s, CH <sub>2</sub> ), 10.8(d, OH)
<b>2a</b>	216-218	0.618	4.494	750, 1205, 1335, 1450, 1492, 1697	6.562 – 7.888(m, Ar-H)2.499(s, CH <sub>3</sub> ), 2.096(s, CH <sub>3</sub> )

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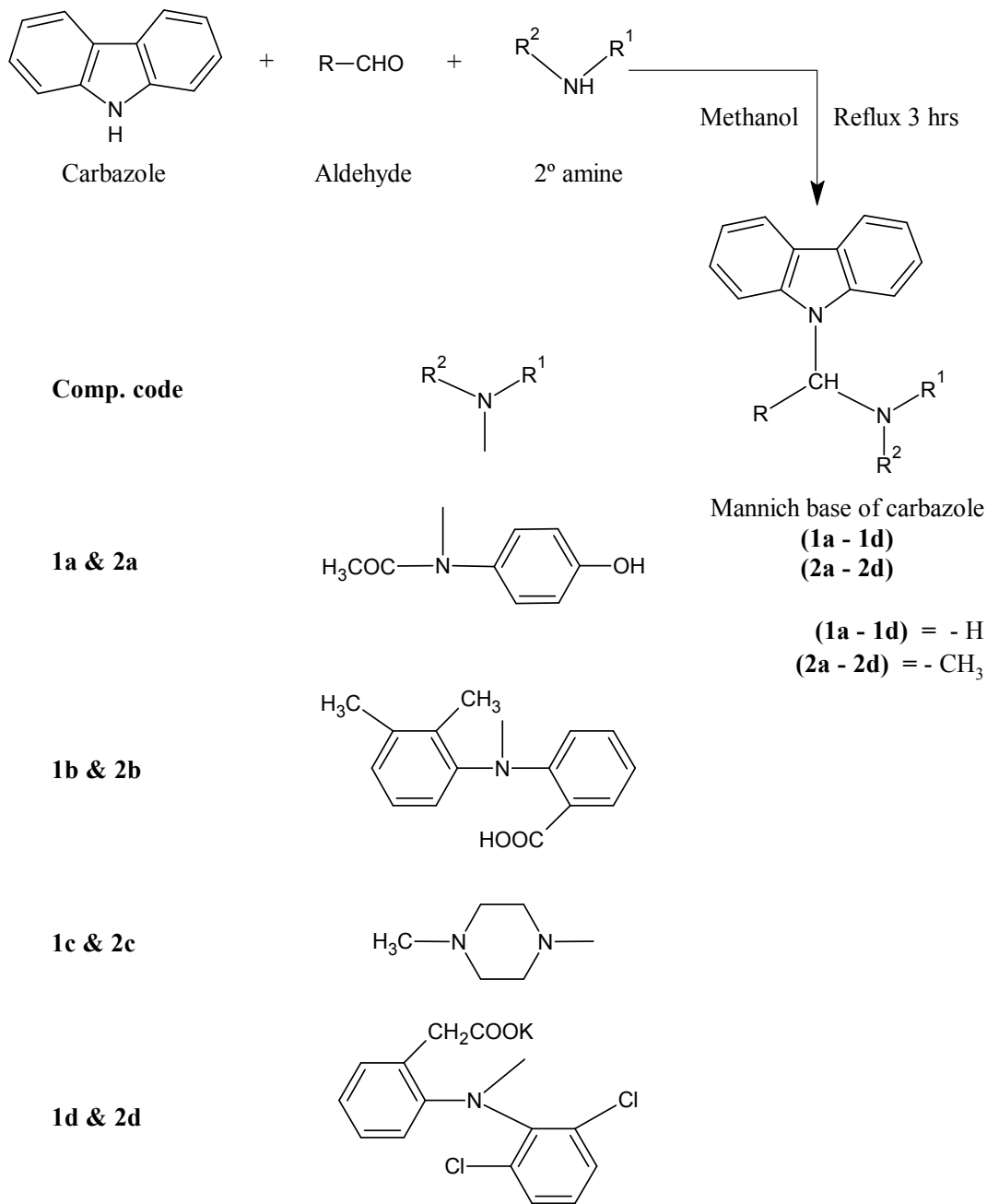
Compd. code	Melting point (°C)	R <sub>f</sub> value	Log P	IR spectra (cm <sup>-1</sup> )	<sup>1</sup> H NMR spectra
<b>2b</b>	190-195	0.762	8.154	777, 1335, 1450, 1785, 2360, 3054	6.653 – 7.341(m, Ar-H), 1.973(s, CH <sub>3</sub> ), 3.312(s, CH <sub>3</sub> )
<b>2c</b>	221-223	0.784	3.806	749, 1335, 1450, 3049	7.08 – 7.46(m, Ar-H), 2.22 (s, CH <sub>3</sub> ), 2.46(s, CH <sub>2</sub> ), 5.02(d, CH), 1.68(d, CH <sub>3</sub> )
<b>2d</b>	268-271	0.622	5.232	666, 752, 1330, 1454, 1648, 2975	7.4 – 8.6(m, Ar-H), 6.11(s, CH), 2.506(d, CH <sub>2</sub> )

### Anti-nociceptive activity

All newly synthesized Mannich bases of carbazole were screened for anti-nociceptive activity<sup>8</sup> by Eddy's hot plate method. Adult albino mice of either sex weighing 20 – 30 g were used for this study. The animals were divided into 10 groups of 6 mice each. Mice were treated with standard drug, pentazocine (5 mg/kg, ip) and newly synthesized series of carbazoles (20 mg/kg, ip). The percentage increase in the basal reaction time was noted on Eddy's hot plate before and after treatment of standard drug and synthesized compounds at 15, 30, 60 and 120 min. All the data were analyzed statistically by students " *t* " test<sup>9</sup> and expressed in mean ± SEM and tabulated in Table 2.

### Anti-epileptic activity (MES method)

The anti-epileptic activity was carried out by maximal electrical shock induced convulsion method<sup>10</sup>. Adult albino mice of either sex weighing of 20 – 30 g were used for the study. Mice were treated with newly synthesized carbazoles (20 mg/kg, ip) and standard drug, phenobarbitone (20 mg/kg, ip). After 30 min, the animals were subjected to electro shock through ear electrodes of 150 mA for 0.2 sec by electro convulsimeter and the presence and absence of extensor response was noted and duration of time was analyzed statistically by students " *t* " test<sup>9</sup> and expressed in mean ± SEM and tabulated in Table 3.



Scheme

Table 2. Anti-nociceptive evaluation of newly synthesized compounds

Treatment	Basel reaction time (sec) before treatment (Mean $\pm$ SEM)	Reaction time (in sec) after administration Mean $\pm$ SEM			
		15 min	30 min	60 min	120 min
<b>Control</b>	4.1232 $\pm$ 0.2342	4.0228 $\pm$ 0.2322	4.1244 $\pm$ 0.2478	4.3244 $\pm$ 0.2286	4.3646 $\pm$ 0.2672
<b>Pentazocine standard</b>	4.5120 $\pm$ 0.9012	8.800 $\pm$ 0.9031**	10.22 $\pm$ 0.2642**	11.48 $\pm$ 0.3476**	13.22 $\pm$ 0.2974**
<b>1a</b>	4.9400 $\pm$ 0.6274	5.560 $\pm$ 0.6325*	6.48 $\pm$ 0.2224*	8.66 $\pm$ 0.2462**	10.34 $\pm$ 0.2874**
<b>1b</b>	4.8819 $\pm$ 0.4654	5.042 $\pm$ 0.4761*	6.58 $\pm$ 0.2978*	8.44 $\pm$ 0.2536**	10.48 $\pm$ 0.3576**
<b>1c</b>	4.5276 $\pm$ 0.4123	4.686 $\pm$ 0.3055	5.66 $\pm$ 0.2732*	6.78 $\pm$ 0.2626*	7.88 $\pm$ 0.2674**
<b>1d</b>	4.7258 $\pm$ 0.4839	5.702 $\pm$ 0.4830*	7.46 $\pm$ 0.2564**	9.26 $\pm$ 0.2978**	11.22 $\pm$ 0.6428**
<b>2a</b>	4.5276 $\pm$ 0.5432	5.226 $\pm$ 0.5428**	7.62 $\pm$ 0.2464**	8.70 $\pm$ 0.3260**	9.86 $\pm$ 0.2642**
<b>2b</b>	4.5276 $\pm$ 0.5324	5.406 $\pm$ 0.5428*	7.44 $\pm$ 0.4242**	9.66 $\pm$ 0.2484**	10.26 $\pm$ 0.2564**
<b>2c</b>	4.0332 $\pm$ 0.7654	4.715 $\pm$ 0.3332	5.26 $\pm$ 0.3678*	5.42 $\pm$ 0.2564*	6.38 $\pm$ 0.5478**
<b>2d</b>	4.6863 $\pm$ 0.4912	5.863 $\pm$ 0.3726*	7.54 $\pm$ 0.4264**	9.02 $\pm$ 0.2478**	10.68 $\pm$ 0.2346**

\*\* p &lt; 0.001 vs. control indicates highly significant.

\* p &lt; 0.01 vs. control indicates significant

**Table 3. Anti-epileptic evaluation of newly synthesized carbazole derivatives**

Treatment	Duration (sec) (Mean $\pm$ SEM)			Recovery/ Death
	Extensor	Clonus	Stupor	
<b>Control</b>	31.50 $\pm$ 0.9220	22.66 $\pm$ 1.7638	69.33 $\pm$ 3.2830	Recovery
<b>Phenytoin Standard</b>	16.667 $\pm$ 1.0541**	9.50 $\pm$ 0.9574**	24.66 $\pm$ 2.1551**	Recovery
<b>1a</b>	29.66 $\pm$ 0.8819	20.33 $\pm$ 0.9819	42.83 $\pm$ 1.9221	Recovery
<b>1b</b>	22.66 $\pm$ 1.1738*	15.33 $\pm$ 1.1293*	28.00 $\pm$ 2.7203*	Recovery
<b>1c</b>	26.83 $\pm$ 0.8724*	15.00 $\pm$ 0.7746*	34.66 $\pm$ 2.5517*	Recovery
<b>1d</b>	37.00 $\pm$ 1.2383	21.33 $\pm$ 0.8028	38.00 $\pm$ 2.4631	Recovery
<b>2a</b>	31.50 $\pm$ 0.7188	22.83 $\pm$ 1.4701	41.33 $\pm$ 2.8597	Recovery
<b>2b</b>	17.00 $\pm$ 2.4766**	17.16 $\pm$ 1.1377**	35.00 $\pm$ 2.3523**	Recovery
<b>2c</b>	25.00 $\pm$ 2.3094*	12.00 $\pm$ 1.0646*	23.50 $\pm$ 2.9183*	Recovery
<b>2d</b>	29.83 $\pm$ 0.8333	21.83 $\pm$ 1.7208	63.16 $\pm$ 1.4926	Recovery

## RESULTS AND DISCUSSION

Totally a series of eight novel carbazoles derivatives were synthesized and elucidated by spectral data and their anti-nociceptive and anti-epileptic activities evaluated. All the compounds except **1c** and **2c** shows highly significant analgesic activity. Compounds **1c** & **2c**, with substitution of n-methyl piperazine shows mild anti-nociceptive activity. All the compounds shows anti-nociceptive activity on set of action at 15 min. after its administration and the activity extends upto 120 min. Compound **2b** shows highly significant anti-epileptic activity due to the substitution with 2-(2,3-dimethylphenylamino)

benzoic acid. Compounds **1a**, **1d**, **2a** and **2d** are devoid from anti-epileptic activity. The maximum anti-nociceptive and anti-epileptic activities were observed in the animals administered with 20 mg/kg body weight of the synthesized compounds as well as in those animals, which received pentazocine (5 mg/kg) and phenytoin (20 mg/kg), respectively.

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