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Synthesis of some new 1,2,5- substituted benzimidazole derivatives and their pharmacological activity

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ABSTRACT

Reaction of ortho phenylenediamine 1 with various organic acids yielded 2-substituted benzimidazole derivatives 2 which were further treated with nitric acid and sulphuric acid to afford 5-nitro-2-substituted benzimdazoles 3. Coupling of this compound with halogenated beta picoline 5 yielded the title compounds. The structures of synthesized compounds were elucidated mainly by spectral evidence. All the compounds were screened for their anti-inflammatory and anti-convulsant potential. The compounds exhibited moderate to significant activities.

Key words: Synthesis, benzimidazoles, anti-inflammatory activity, anti-convulasant activity.

INTRODUCTION

Substituted imidazoles possess various pharmacological activities including analgesic[1], antiviral[2-4], antihistaminic[5], antihelmintic[6], gout curing properties[7], anti-hypertensive[8,9] anti ulcer[10] and anti inflammatory[11] activities. Moreover there is an escalating demand for new anti-inflammatory and anticonvulsant drugs with high potency and fewer side effects. So, in continuation of our efforts for synthesis and evaluation of novel imidazole derivatieves[12, 13], it was felt worthwhile to synthesize some analogues of imidazole by coupling them with beta picoline derivatives and screen them for anti-inflammatory and anti-convulsant activity.

EXPERIMENTAL

The purity of synthesized compounds was ascertained by thin layer chromatography on silica gel G in various solvent systems using iodine vapours as detecting agents. All the melting points reported were determined in open capillaries using Veego VMP-1 melting point apparatus expressed in °C and are uncorrected. The IR spectra of the compounds were recorded on Perkin-Elmer Infra Red-283 FTIR spectrometer in KBr phase and are expressed in cm^{-1}. ^1H NMR spectra were recorded on Brucker 300 MHz NMR spectrometer (chemical shift in d ppm) using TMS as internal standard.

2-substituted Benzimidazoles (2a -2e)

Equimolar solutions of *ortho* phenylene diamine 1 (0.25 M) and appropriately substituted organic acids were refluxed for 6-13 h on a heating mantle. The reaction mixture was cooled and made alkaline with sodium carbonate. The crude product so obtained 2 was dissolved in 95% ethanol and was suitably digested with activated charcoal. The solution was made clear by adding a few drops of ethanol and was kept for recrystallization. Needle shaped off white crystals were obtained.

2a(R=H): yield: (81%), m.p. 170 °C, IR (cm^{-1}, KBr) : 3415(broad N-H stretching); 3062(C-H stretching aromatic); 1500 (N-H bending); 1410

(C=C and C=N ring stretching); 1240 (C-N stretching); 880 (N-H wagging); 700 (C=C, Out of plane).

Other compounds 2b-2e were synthesized in similar manner.

5-nitro-2-substituted Benzimidazoles (3a-3e)

Concentrated nitric acid (7.5 ml) was taken in a 3-necked round bottom flask fitted with a mechanical stirrer and immersed in ice-cold water. Concentrated sulphuric acid (7.5 ml) was added to it slowly down the condensor with slow stirring. Afterwards, 2-substituted benzimidazole derivative 2a-2e was added in portions over a period of 1h at such a rate that the temperature did not exceed 35°C. After continuous stirring for 10-13 h, the reaction mixture was poured slowly over crushed ice with vigorous stirring. The product 3a-3e was filtered and washed with cold water. 3a(R=H): Yield (90%), m.p. 210°C, IR (cm^{-1}, KBr): 3425 (broad N-H stretching); 3080 (C-H stretching aromatic); 1480 (N-H bending); 1640, 1461 (C=C and C=N ring stretching); 1520 ($NO-_2$ sym and asym).

Other compounds 3b-3e were synthesized in similar manner.

Bromo methyl pyridine (5)

A mixture of 2-methyl pyridine 4 (0.25 M), N-bromo succinamide (NBS) (0.25 M) and benzolyl peroxide (0.25 M) in CCl_4 was refluxed for 8.3 h. The solvent was removed and the product thus obtained 5 was filtered and cooled overnight at room temperature.

Title compounds (6a-e & 7a-e)

A suspension of appropriately substituted benzimidazole 2 and 3 (0.1 M) in dimethyl formamide (DMF) and 2.5 g potassium carbonate were stirred vigorously at room temperature on a mechanical stirrer for 1 h. To the reaction mixture, a suspension of bromomethyl pyridine 5 (0.1M) in DMF was added dropwise with stirring for 1h. The reaction was allowed to proceed further for 17-23 h and the excess solvent was removed under vacuum. The product so obtained, was extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous sodium sulphate. The product thus obtained 6&7 was a brownish amorphous solid. 6a: Yield (57%), m.p. 130°, IR (cm^{-1}, KBr): 3162 (C-H stretching aromatic); 2892 (C-H stretching aliphatic); 1470 (N-H bending); 1410 (C=C and C=N ring stretching). Other compounds 6b-6e were synthesized in similar manner.

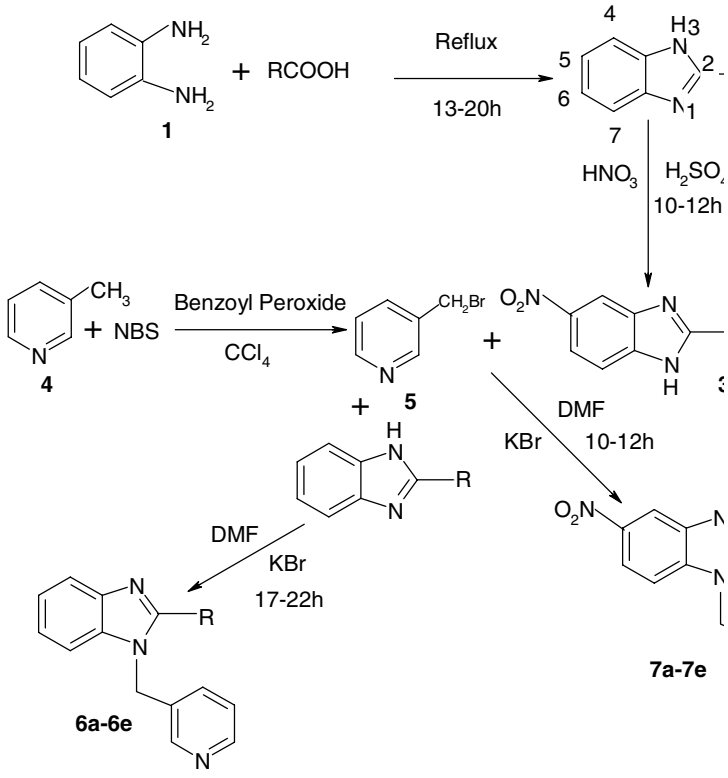
Table 1: Anti-inflammatory and Anticonvulsant activity of synthesized compounds

Compound No.	Anticonvulsant activity (onset of action)	Anti-inflammatory activity Percent Inhibition After 3 h	After 24 h
6a	53.2±10.6	5.62±2.32	2.62±2.01
6b	61.2±12.72	7.88±3.05	10.95±3.98
6c	54.2±13.2	9.79±1.76	25.82±6.75
6d	52.6±12.76	17.49±6.77	28.42±2.98
6e	61.4±10.9	6.38±3.95	16.91±5.53
7a	66.8±13.4	14.6±5.78	17.03±3.27
7b	57.6±11.63	11.09±4.27	18.02±4.8
7c	55.4±12.0	7.17±0.98	12.72±1.62
7d	51.4±7.43	15.99±4.56	18.87±3.52
7e	62.8±9.17	19.05±5.12	17.92±2.40
Ibuprofen	-	15.03±2.1	10.01±3.4
Phenobarbitone	47±5.15	-	-

Table 2: Physical and analytical data of synthesized compounds

Comp. No.	R	m.p. (^{0}C)	Yield(%)	Molecular formula
6a	**H**	**130**	**57%**	**$C_{13}H_{11}N_3$**
6b	-CH_3	116	61%	$C_{14}H_{13}N_3$
6c	-C_2H_5	76	48%	$C_{15}H_{15}N_3$
6d	-C_3H_7	88	51%	$C_{16}H_{17}N_3$
6e	-C_4H_9	70	38%	$C_{17}H_{19}N_3$
7a	H	98	50%	$C_{13}H_{10}N_4O_2$
7b	-CH_3	74	59%	$C_{14}H_{12}N_4O_2$
7c	-C_2H_5	54	53%	$C_{15}H_{14}N_4O_2$
7d	-C_3H_7	72	52%	$C_{16}H_{16}N_4O_2$
7e	-C_4H_9	52	51%	$C_{17}H_{18}N_4O_2$

Compd: 2/3/6/7	R
a	H
b	CH_2
c	C_2H_5
d	C_3H_7
e	C_4H_9



Scheme 1

Table 3: Spectral data of Synthesized Compounds

compound No.	IR (KBr) cm^{-1}	com.. No.	H^1 N.M.R. ($CDCl_3$)
2a	3415 (broad N-H stretching); 3062 (C-H stretching Aromatic); 1500(N-H Bending); 1410 (C=C and C=N ring stretching); 1240(C-N stretching) ; 880(N-H wagging) 700(C=C out of plan)	6a	d = 8.60 (s, 1H, CH imidazole); 8.37 (d, 2H, pyridine); 7.68 (d, 3H, 2 aeromatic + 1 pyridine) ; 7.29 (t, 1H- pyridine); 7.26 (m, 2H, aromatic) ; 2.76 (m, 2H methylene)
2b	3629 (broad N-H stretching); 3206 (C-H stretching aromatic); 2890 (C-H strechinmg aliphatic); 1465 (N-H bending); 1410 (C=C and C=N ring stretching).	6b	d = 8.30 (d, 2H, CH pyridine); 7.57 (d, 3H, 2 aeromatic + 1 pyridine); 7.26 (t, 1H- pyridine); 7.23 (m, 2H, aromatic); 2.76 (m, 2H methylene); 2.65 (3H t, aliphatic)
2c	3612 (broad N-H stretching); 3092 (C-H stretching aromatic); 2802 (C-H strechinmg aliphatic); 1447 (N-H bending); 1410 (C=C and C=N ring stretching).	6c	d = 8.30 (d, 2H, CH pyridine); 7.57 (d, 3H, 2 aeromatic + 1 pyridine); 7.26 (t, 1H- pyridine); 7.23 (m, 2H, aromatic); 2.98 (m, 2H, aliphatic); 2.76 (m, 2H methylene); 1.42 (t, 3H, aliphatic)
2d	3645 (broad N-H stretching); 3100 (C-H stretching aromatic); 2876 (C-H stretching aliphatic); 1457 (N-H bending); 1418 (C=C and C=N ring stretching).	6d	d = 8.30 (d, 2H, CH pyridine); 7.53 (d, 3H, 2 aeromatic + 1 pyridine); 7.26 (t, 1H- pyridine); 7.23 (m, 2H, aromatic); 2.94 (m, 2H, aliphatic); 2.77 (m, 2H methylene); 1.90 (m, 2H,aliphatic); 1.04 (t, 3H, aliphatic)
2e	3626 (broad N-H stretching); 3172 (C-H stretching aromatic); 2862 (C-H strechinmg aliphatic); 1475 (N-H bending); 1423 (C=C and C=N ring stretching).2.78 (m, 2H methylene); 1.85 (m, 2H, aliphatic); 1.41 (t, 2H, aliphatic); 0.91 (m, 3H, aliphatic)	6e	d = 8.30 (d, 2H, CH pyridine); 7.55 (d, 3H, 2 aeromatic + 1 pyridine); 7.29 (t, 1H- pyridine); 7.26 (m, 2H, aromatic); 2.98 (m, 2H, aliphatic);
3a	3425 (broad N-H stretching); 3080(C-H stretching aromatic); 1480 (N-H bending); 1640,1461 (C=C and C=N ring stretching); 1520 (NO_2 asym).		-
3b	3524 (broad N-H stretching); 3122(C-H stretching aromatic); 2971(C-H strechinmg aliphatic); 1425 (N-H bending); 1410 (C=C and C=N ring stretching); 1423 (NO_2 asym).		-
3c	3564 (broad N-H stretching); 3100(C-H stretching aromatic); 2810(C-H strechinmg aliphatic); 1485 (N-H bending); 1401 (C=C and C=N ring stretching); 1440 (NO_2 asym).		-

7a: Yield (50%), m.p. 98°C, IR (cm^{-1}, KBr): 3102(C-H stretching aromatic); 2910(C-H strechinmg aliphatic); 1465 (N-H bending); 1411 (C=C and C=N ring stretching); 1430 (NO_2 asym).

Other compounds 7b-7e were synthesized in similar manner.

Physical and analytical data of synthesized compounds is summarized in Table 2 and spectral data in Table 3.

RESULTS AND DISCUSSION

The required starting material 2-substituted benzimidazole 2a-2e was synthesized by reacting equimolar quantities of o-phenylene diamine 1 and appropriate organic acids i.e. acetic acid, formic acid, propionic acid, butyric acid and valeric acid. Compound 2 was nitrated at position 5 by adopting standard procedures. On the other hand, 3-methyl pyridine was heated under reflux with N-bromo succinimide (NBS) and benzoyl peroxide in CCl_4 to yield bromomethyl pyridine 5. Bromomethyl pyridine was coupled with 2 and 2,5- disubstituted benzimidazoles which yielded the title compounds. All the synthesized compounds were screened for anti-inflammatory activity by carrageenin induced rat paw oedema method[14]. A freshly prepared suspension of carrageenin (0.1 ml, 1%w/v) was injected into planter region of right hind paw of each rat intra-peritonially. The percent inhibiton of oedema between the control group and test groups was calculated, according to the formula given below:

% anti-inflammatory activity=$(V_c\text{-}V_t/V_c) * 100$

Where: V_t, represents the mean increase in paw volume in rats treated with test compound; V_c represents the mean increase in paw volume in control group of rats.

The anticonvulsant screening was carried out by adopting standard protocols[15] against phenylene tetrazole induced convulsions in mice of either sex using phenobarbitone as a reference drug. The data for both the pharmacological activities is expressed as mean ± S.E.M., the student T-test was applied to determine the significance of the difference between the control group and the rat treated with test compounds. The results of pharmacological screening are summarized in Table 1.

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