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Synthesis and Anthelmintic Activity of Benzimidazole Derivatives

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Abstract

In this study we had synthesized some Benzimidazole derivatives and screened for their anthelminitic activity. o-Phenylenediamine was condensed with acids in presence of Polyphosphoric acid and solvents like water and dilute hydrochloric acid. The presence of specific functional group were analysed by IR spectroscopy. The determination of structure for the synthesized compounds by NMR and Mass spectroscopy is in progress. All the synthesized compounds showed significant anthelmintic activity.

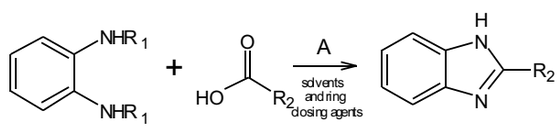
Keywords: Benzimidazole, Anthelminitic, o-Phenylenediamine

Introduction

Benzimidazole and their derivatives were reported to have wide biological activities like antitumor, antiviral, antifungal, antioxidant, antiulcer, antiamoebic, antihistaminic, anthelmintic and anti hypertensive activity. Various substituted benzimidazole was synthesized in the presence of different solvents and catalytic agents had been reported. In the present investigation, we reported the synthesis of 2-alkyl and aryl substituted benzimidazole derivatives in the presence of ring closing agents eg: (poly phosphoric acid and other solvents) and the synthesized compounds were screened for their anthelmintic activity.

Materials and Methods

All the chemicals and solvents used for this work were obtained from E. Merck Ltd., Mumbai and Loba Chemie Pvt. Ltd. The reagents were of analytical grade purity. Melting points of the synthesized compounds were determined in open capillary tubes using ROLEX melting point apparatus expressed in ^{o}C and were uncorrected. Silica gel chromato plates were used for TLC and the solvent systems were ethyl acetate: n-hexane (7:3) for compound 1 and ethyl acetate: n-hexane (7:2) for compounds 2,3,4,. The purity of the compounds was checked by TLC and the spots were visualized by iodine vapours. IR absorption spectra were recorded on FTIR- 8400 S Shimadzu spectrophotometer using potassium bromide pellets and were expressed in cm^{-1}. The synthesis of compounds were carried according to the scheme - I.



Synthesis of 2-methylbenzimidazole[6]

A mixture of 5.43g (0.03 mol) of o-phenylenediamine dihydrochloride, 20 ml of water and 5.4g (0.09 mol) of acetic acid was refluxed for 45 minutes. Then the reaction mixture was poured over crushed ice with stirring. The cooled mixture was made basic by the gradual addition of concentrated ammonia solution. The precipitated product was then filtered and recrystallised from 10% aqueous ethanol, yield: 50%, m.pt: 177-180^{0}C, Rf value: 0.469, IR (KBr) cm^{-1}:3295.16(N-H), 1500.15(C=C), 1593.09(C=N), 752.19(C-H), 1248.82(C-N), 1156.25(CH_3).

Synthesis of 2-benzylbenzimidazole

A mixture of 5.43g (0.03 mol) of o-phenylenediamine dihydrochloride, 20 ml of water and 12.3g (0.09 mol) of phenyl acetic acid was refluxed for 45 minutes. Then the reaction mixture was poured over crushed ice with stirring. The cooled mixture was made basic by the gradual addition of concentrated ammonia solution. The precipitated product was then filtered and recrystallised from 40% aqueous ethanol, yield: 48% m.pt: 235-236^{0}C, Rf value: 0.315, IR (KBr)cm^{-1}:3416.66 (N-H),1486.05 (C=C),1645.17 (C=N), 1185.18 (C-N), 857.30 (Ar-H), 2884.35 (CH_2).

Synthesis of 2-phenylbenzimidazole

A mixture of 6g o-Phenylenediamine, 6g of benzoic acid and 25ml of 4N dilute hydrochloric acid was refluxed for 2

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hours at 180-185^{0}c. The reaction mixture was cooled and poured on to the crushed ice. Then the product was filtered and washed with water. The product was recrystallised in boiled water using charcoal, yield: 33.58%, m.p.: 238-239^{0}C, R_f value: 0.272, IR (KBr) cm^{-1}:3062.75 (N-H), 1454.23 (C=C), 1584.41 (C=N), 1128.28 (C-N), 934.45 (C-H)

Synthesis of 2-(4-amino phenyl) benzimidazole

A mixture of Para amino benzoic acid (4.5g, 33 mM) and o-Phenylenediamine (3.8g, 34 mM) were stirred in a syrupy phosphoric acid (45ml) at 200 c for 2 hours. The reaction mixture was cooled and poured on to the crushed ice. The bulky white precipitate obtained was stirred in cold water (400 ml) and sodium hydroxide solution (5M) was added until the pH 7. The resulting solid was filtered and recrystallised from methanol, yield: 56.55%, m. p: 248-250^{0}C, $R_f$value: 0.250, IR (KBr) cm^{-1}:3327.94 (N-H), 3461.08 (NH_2), 1530.41(C=C), 1621.06 (C=N), 1193.85 (C-N), 894.91 (Ar-H).

Anthelmintic activity[7,8]

The anthelmintic activity was evaluated on adult Indian earth worm *Pheretima posthuma* due to its anatomical resemblance with the intestinal roundworm parasites of human beings. The activity was carried out using Mathew *et al* method. Four groups of Indian earth worms each containing six earthworms approximately of equal size was used for the study. Each group of earth worms were treated with vehicle (1% CMC), synthesized compounds (10, 50,100mg/ml conc.) and piperazine citrate (15mg/ml).

Observations were made for the time taken for paralysis and death of individual worms (Table 1). Paralysis was said to occur when the worms do not revive even in normal saline. Death was concluded when the worms lost their motility, followed with fading away of their body colour.

Results and Discussion

All the synthesized compounds showed significant anthelmintic activity. Among the synthesized compounds 2-phenylbenzimidazole showed potential anthelminitic activity 0.931±0.231 & 1.317±0.149 minutes for paralysis and death respectively when compared with the standard piperazine citrate. The synthesized compounds were analyzed mainly by IR spectral reading, physical and chromatography readings. Further analysis of structure by NMR, Mass spectroscopy is required to interpret the synthesized compounds.

Table-1

Anthelmintic activity of Benzimidazole Derivatives

Sl.No.	Parameters	Concentration mg/ml	2-methyl benzimidazole	2-benzyl benzimidazole	2-phenyl benzimidazole	2-(4-amino phenyl) benzimidazole	Piperazine Citrate
1	Time taken for paralysis in minutes	100	1.59±0.117	1.87±0.291	0.931±0.231	1.79±0.445	
		50	3.88±0.430	3.98±0.48	31.125±0.304	4.01±0.339	
		10	11.56±0.429	10.98±0.99	12.30±0.5762	10.86±0.115	
		15					41.53±0.52
2	Time taken for death in minutes	100	2.08±0.314	2.81±0.284	1.317±0.149	2.11±0.430	
		50	4.52±0.114	4.23±0.59	4.575±0.304	4.82±0.515	
		10	12.01±0.526	11.74±0.989	13.50±0.6614	11.44±0.693	
		15					45.±0.36

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