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# SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-SUBSTITUTED BENZIMIDAZOLES

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## ABSTRACT

A set of 2-substituted benzimidazoles were successfully synthesized. Benzimidazoles were prepared by condensation of ortho-phenylenediamine with substituted acids in presence of ring closing agents like Polyphosphoric acid/ HCl. The synthesized compounds were characterized by IR spectroscopy and Elemental analysis. All the synthesized compounds were screened for anthelmenthic activity by using Albendazole as standard.

**KEY WORDS : Benzimidazole, Anthelmenthic activity, Elemental analysis, Spectroscopy.**

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# INTRODUCTION

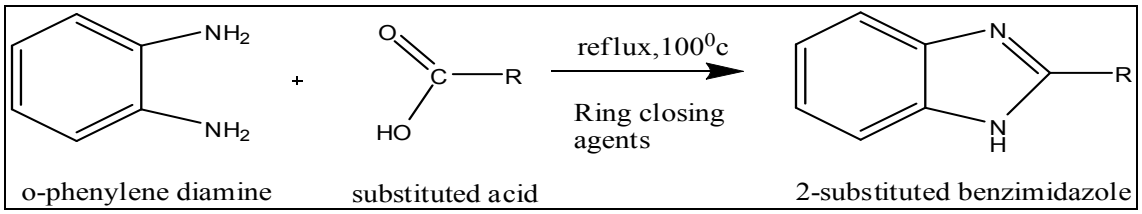
Benzimidazole and its derivatives is an important class of bioactive molecules in the field of Drugs and Pharmaceuticals. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin $B_{12}$.[1]

Benzimidazole, in an extension of the well-elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic carbenes. The NHCs are usually used as ligands for transition metal complexes. Various biological activities reported on benzimidazole derivatives are antioxidant[2,3], anti-inflammatory[4,5], analgesic[6], anti-hepatitis-B-virus[7] antihypertensive[8], anthelmenthic[9,10,11], anti-protozoal[12,13], anticancer[14] and antimicrobial[(15-20)].

A number of methods have been[21, 22] reported for the synthesis of benzimidazoles and its derivatives. These methods include the coupling of o-phenylenediamine with carbonyl compounds in presence of various catalysts like $zrcl_4$, $Sncl_4.5H_2O$, $BF_3Et_2O$, polyethylene glycol, ceric ammonium nitrate[23]. In present study we reported the synthesis of 2-alkyl & aryl substituted benzimidazoles in presence of ring closing agents and screened for anthelmenthic activity.

# MATERIAL AND METHODS

All the chemicals and solvents used for this work were obtained from s d fine-chem limited (SDFCL), MUMBAI. Melting points of synthesized compounds was determined in open capillary tube using kshitij melting point apparatus, expressed in 0c and were uncorrected. Silica gel chromatographic plates were used for TLC and solvent systems were ethylacetate : n-hexane (7:3) for all compounds. The purity of the compounds was checked by TLC and spots were visualised by iodine vapours [24]. IR spectra were recorded in KBr on bruker FT-IR spectrometer. The synthesis of compounds was carried according to **scheme-1.**




**Scheme-1**

***General Procedure for the Synthesis of 2-Substituted Benzimidazoles***

Ortho Phenylenediamine (1mole) was made to condense with carboxylic acid derivatives (1mole) in presence of ring closing agents like hydrochloric acid or polyphosphoric acid. The mixture was kept for reflux and progress of the reaction was monitored by TLC. On completion of reaction, the reaction mixture was cooled and poured on to crushed ice. The cooled mixture was made basic by the gradual addition of concentrated ammonia solution. The precipitated product was then filtered and recrystallized from hot water. Decolourise with charcoal if necessary.

***IR spectral data of synthesized compounds***

1. 1H-benzo[d]imidazole (BZ): IR (KBr) $cm^{-1}$: 3413.67 (aromatic-NH stretching), 1477.77 (-C=C stretching), 1620 (-C=N stretching), 3113.81 (=C-H stretching), 1272.85 (-C-N stretching), 1409.16 (aromatic –NH bending).
2. 2-Methyl-1H-benzo[d]imidazole (MBZ): IR (KBr) $cm^{-1}$: 3445.38 (aromatic-NH stretching), 1462.98 (-C=C stretching), 1556.17 (-C=N stretching), 3176.26 (=C-H stretching), 1270.86 (-C-N stretching), 1477.09 (aromatic –NH bending), 2994.57 and 2874.95 (aliphatic- $CH_3$ stretching), 1386.23 (aliphatic –$CH_3$ bending).

3. 2-(Chloromethyl)-1H-benzo[d]imidazole (ClBZ): IR (KBr) $cm^{-1}$: 3390.67 (aromatic-NH stretching), 1511.60 (-C=C stretching), 1676.80(-C=N stretching), 3055.76 (=C-H stretching), 1271.04 (-C-N stretching), 1430.42(aromatic –NH bending), 742.55 (-C-Cl).
4. 4-(1H-benzo[d]imidazol-2-yl) aniline (PABZ): IR (KBr) $cm^{-1}$: 3385.05 (aromatic-NH stretching), 3470.12 (aromatic – $NH_2$ stretching), 1500.59 (-C=C stretching ), 1605.21 (-C=N stretching), 3143.35 (=C-H stretching), 1274.01 (-C-N stretching), 1444.98 (aromatic –NH bending).

**ANTHELMENTHIC ACTIVITY**

***Worm Collection and Authentication***

Healthy adult Indian earthworms *Pheretima posthuma* due to its anatomical and physiological resemblance with the intestinal roundworm parasites of human beings (Thorn GW et.al., 1977; Chatterjee KD, 1967) used in the present study were collected from Aditya nagar gardens situated in Surampalem. Because of easy availability, earthworms have been used widely for the evaluation of anthelmenthic activity in vitro (Sallaman T 1981). All the earthworms were of approximately equal size. They were collected from local moist place, washed and kept in water and authenticated.

***Test material***

The synthesized compounds were evaluated for their anthelmenthic activity against *Pheretima posthuma*. Various concentrations (10, 20 mg/ml) of synthesized compounds were tested and time of paralysis and time of death of the worms were determined.

***Reference Standard***

Albendazole was used as reference standard. It was procured from Pradeep Organics and chemicals Pvt.Ltd., Hyderabad.

***ANTHELMINTHIC ASSAY[25]***

Anthelmenthic activity was evaluated by exposing the adult *Pheritima posthuma* to different concentrations of synthesized compounds. The anthelmenthic assay was carried as per the method of Ajaiyyeoba et al. [26] with minor modifications. Six earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Distilled water was used as control. The Standard drug and synthesized compounds were dissolved in minimum amount of Water and adjusted the volume up to 20 ml with distilled water to get the two concentrations i.e. 10 mg/ml, 20 mg/ml for each compound. Albendazole (20 mg/ml) was used as reference standard. The standard drug and synthesized compounds were freshly prepared before starting the experiment. Time for paralysis was noted when no movement could be observed except when the worms were shaken vigorously. Time for death of worms were recorded after ascertaining that worms neither moved when shaken vigorously nor when dipped in warm water (50 °C) followed by fading away of their body colours.

## RESULTS AND DISCUSSION

***Chemistry***

Different types of organic acids (aliphatic and aromatic) were used to condense with o-phenylenediamine to synthesise 2-sustituted benzimidazoles[27, 28]. The purity of synthesized compounds was checked by TLC and melting point. The physicochemical data of all synthesized compounds was represented in **table - 1.** The synthesized compounds were characterized by Infrared Spectroscopy & elemental analysis data was represented in **table - 2.**

**Table-1**
***Physicochemical Data***

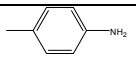
| Entry | Acid | Substitution | Molecular Formula | Molecular Weight | Melting Point | Time [min] | Percentage Yield | $R_f$ Value |
|---|---|---|---|---|---|---|---|---|
| 1. | HCOOH [FORMIC ACID] | -H | $C_7 H_6 N_2$ | 118gms | $170^0$c | 30 | 73.5 | 0.575 |
| 2. | $CH_3COOH$ [ACETIC ACID] | $-CH_3$ | $C_8H_8N_2$ | 132.16gms | $180^0$c | 45 | 50 | 0.68 |
| 3. | $NH_2C_6H_4COOH$ [PABA] |  | $C_{12}H_{22}N_3$ | 209.25gms | $310^0$c | 120 | 31.1 | 0.88 |
| 4. | $ClCH_2COOH$ [CHLORO ACETIC ACID] | $-CH_2Cl$ | $C_8H_7N_2Cl$ | 166.61gms | $210^0$c | 45 | 54.6 | 0.565 |

**Table-2**
***Analytical Data***

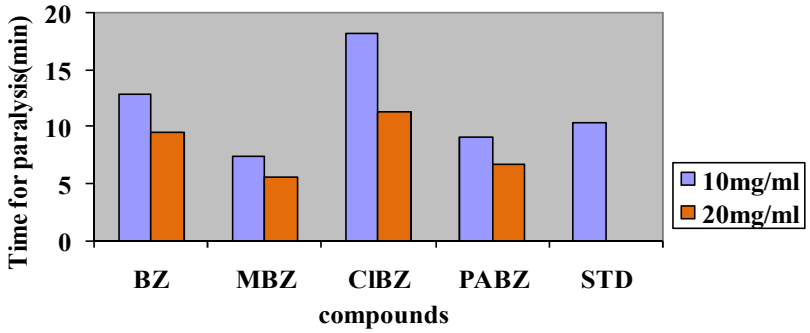
| S.No | Compound Code | Elemental Analysis % | C | H | N | Cl |
|---|---|---|---|---|---|---|
| 1 | BZ | Calculated | 71.17 | 5.12 | 23.71 | - |
| | | Found | 71.10 | 5.01 | 23.52 | - |
| 2 | MBZ | Calculated | 72.70 | 6.10 | 21.20 | - |
| | | Found | 72.55 | 6.02 | 21.12 | - |
| 3 | ClBZ | Calculated | 57.67 | 4.23 | 16.81 | 21.28 |
| | | Found | 57.60 | 4.10 | 16.65 | 21.15 |
| 4 | PABZ | Calculated | 74.62 | 5.30 | 20.08 | - |
| | | Found | 74.55 | 5.15 | 20.01 | - |

Synthesized compounds (10mg/ml, 20mg/ml) were screened for anthelmenthic activity against standard drug albendazole. The results of final compounds for anthelmenthic activity were recorded in table-3 & Graph-1&2. Of all the synthesized compounds MBZ, PABZ showed very high activity. The compound BZ showed moderate activity. MBZ, PABZ showed potent activity than the standard drug. The potent activity is due to presence of electron releasing groups like methyl, aryl, amine on C-2 of benzimidazole ring.

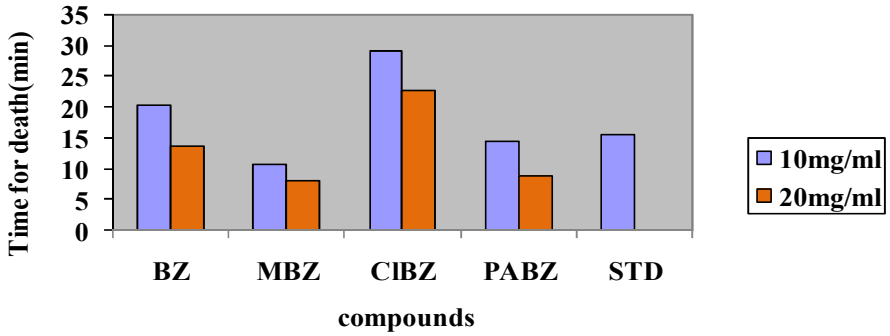
**Table -3**
***Anthelmenthic Activity***

| S.NO | COMPOUND | TIME FOR PARALYSIS (min) | | TIME FOR DEATH (min) | |
|---|---|---|---|---|---|
| | | Concentration | | Concentration | |
| | | 10mg/ml | 20mg/ml | 10mg/ml | 20mg/ml |
| 1. | BZ | 12.89±1.73 | 9.57±0.67 | 20.24±0.41 | 13.67±0.26 |
| 2. | MBZ | 7.45±0.34 | 5.55±0.11 | 10.70±0.25 | 8.12±0.05 |
| 3. | CIBZ | 18.20±1.24 | 11.36±0.83 | 29.13±0.66 | 22.74±0.47 |
| 4. | PABZ | 9.12±0.59 | 6.75±0.32 | 14.36±0.27 | 8.82±0.14 |
| 5. | CONTROL | - | - | - | - |
| 6. | ALBENDAZOLE (STANDARD) | 10.34±0.31 | 7.12±0.15 | 15.45±0.61 | 11.22±0.18 |

**Graph-1**
**Anthelmenthic Activity - Time for paralysis**




**Graph-2**
**Anthelmenthic Activity – Time for death**




***Control – Distilled Water -- No activity***

## CONCLUSION

The present work has demonstrated the use of a simple Cyclocondensation method, Ring closing agents for synthesis of 2-substituted benzimidazoles. All the synthesized compounds were biologically evaluated for anthelmenthic activity. Further analysis of structure by NMR, Mass Spectroscopy is required to interpret the synthesized compounds.

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## REFERENCES

1. (a) Gravatt, G. L.; Baguley, B. C.; Wilson, W. R. Denny, W. A. *J. Med. Chem.* 1994, *37*, 4338. (b) Jayashankara, B.; Rai, K. M. L. *ARKIVOC* 2008, *(xi)*, 75. (c) Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit R. W. Jr.; Michejda, C. J. *J.*

*Med. Chem.* 1997, *40,* 4199. (d) Lin, S. N.; Yang, L. H. *Tetrahedron Lett.* 2005, *46*, 4315. (e) Valdez, J.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Navarrete-Vazquez, G.; Tapia, A.; Cortes, R. Hernandezc, M.; Castilloa, R. *Bioorg. Med. Chem. Lett.* 2002**,** *12,* 2221. (f) Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* 1998, *41,* 1252. (g) Ravindra, K. C.; Vagdevi, H. M.; Vaidya, V. P. *ARKIVOC* 2008, *(xi)*, 1

2. Kus C, Ayhan-Kilcigil G, Can Eke B and Iscan N. *Arch. Pharma*. *Res*. 2004; 27, 156
3. Ates-Alagoz A, Kus C and Coban T. *J. Enzyme Inhib . Med. Chem*. 2005; 20, 325
4. Lazer E S, Matteo M R and Possanza G J. *J. Med, Chem*. 1987; 30, 726
5. Lackner T E and Clissold S P. *Drugs.* 1989; 38, 204
6. Ito K, Kagaya H, Fukuda E, Yoshino K and Nose T. *Arznein. Forsch. Drug Res*. 1982; 32, 49
7. Li Y F, Wang G F, He P L ,Huang W G, zhu F H, Gao H Y, Tang W, Luo Y, Feng C L, Shi L P, Ren Y D, Lu W and Zuo J P. *J. Med. Chem*.1989 2006; 49, 4790
8. Kubo K, Inada Y,Kohara Y, Sugiura Y, Ojima M, Itoh K, Furukawa Y, Nishikawa Y K and Naka T. *J Med. Chem*. 1993; 36, 1772
9. Dubay R, Abuzar S, Sharma S, Chatterjee R K and Katiyar J C. *J.Med. Chem*. 1985; 28, 1748
10. Mavrova A T, Denkova P S, Tsenov Y A, Anichina K K and Vutchev D L. *Bioorg . Med. Chem*. 2007; 15, 6291
11. Ravina E , Sanchez-Alonso R, Fueyo J , Baltar M P ,Bos J,Iglesias R and Sanmartin ML. *Arzneim. Forsch.* 1993; 43, 684
12. Navarette-Vazquez G, Cedilla R, Hernandez-Campos A, Yepez A, Hernandez-luis F, Valdez J, Morels R, Cortes R , Hernandez M and Castillo R. *Bioorg.Med.Chem*. 2001; 11, 187
13. Katiyar S. K., Gordon V. R., Mc Laughlin G. L. and Edlind T. D. *Antimicrob.Agents Chemother*. 1994; 38, 2986
14. Starcevic K, Kraji M, Ester K, Sabol I, grce M, pavelic K and Karminski-zamola G. *Bioorg.Med. Chem*. 2007; 15, 4419
15. Goker H ,kus C , Boykin D W , Yildiz S and Altanlar N. *Bioorg. Med. Chem*. 2002; 10, 2589
16. Goker H, Ozden S, Yildiz S, and Boykin D W 2005 Eur .J. *Med. Chem*. 40 1062
17. Desai K G and Desai K R. *Bioorg. Med. Chem*. 2006; 14, 8271
18. Kazimierczuk Z, Upcroft J A, Upcroft P, Gorska A, Starosciak B and Laudy A. *Acta Biochim. Polon.* 2002; 49, 185
19. Mohammad B G, Hussien M A, Abdel-Alim A A and Hashem M. *Arch. Pharm. Res*. 2006; 29, 26
20. Pawar N S, Dalal D S, Shimpi S R and Mahulikar P P. *Eur. J. Pharm. Sci*. 2004; 21, 115
21. Grimmet M R in (eds) Katritzky A R C W Rees. *Hetero.chem*. 1984; 457
22. Czarny A, Wilson W D and Boykin D W 1996 *J.Heterocyclic chem*. 33 1393
23. (a) Zhang, Z.H.; Yin, L.; Li, Y.; Wang, Y. M. *Catal.Commun.* 2007; 8, 1126. (b) Zhang, Z.H.; Yin, L.; Li, Y.; Wang, Y. M. *Tetrahedron Lett.* 2005; 46, 889
24. Green H, Day AR, The Tautomeric Character of the Imidazole ring, *J.Am.Chem.Soc*, 1942; 64, 1167-1173
25. Srikanth Lingala, Raghunandan Nerella, K.R.S.Sambasiva *Rao International Journal of Pharmaceutical Sciences Review and Research,* 2011; *Volume* 10, Issue 2
26. Ajaiyeoba EO, Onocha PA, Olarenwaju OT.*,In vitro* Anthelmintic properties of *Buchholzia coriaceae and Gynandropsis gynandra* extract.Pharm Biol, 39:217-220,(2001)
27. Furniss BS, Hannaford AJ, Peter WG, Smith, Tetchell AR, *Vogel's Text book of Practical Organic Chemistry*, 1989; 5th ed., 1162-63
28. Ansari K.F., Lal C. *J.Chem.Sci.* 2009; 121(6), 1017-1025