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2-(Aryl Oxy Methyl)-1H- Benzimidazoles: Synthesis, Characterization and Biological Evaluation

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Abstract

Helminthiasis is a macro, parasitic disease of humans and animals in which a part of the body is infected with Helminth parasites. It is one of the most deadly, neglected, tropical diseases and many die annually from this disease. The total eradication from this problem is very difficult. The drugs which expel Helminth parasites from the body either by stunning or killing them without causing significant damage to the host are called Anthelmintics. The most commonly used class of Anthelmintics are Benzimidazoles, whose mode of action is by blocking transportation of secretory granules and movement of other cell organelles by binding to beta-tubulin and inhibit polymerization of microtubules in the cytoskeleton of the Helminthic parasite. Most of the Anthelmintics are non-selective, with a narrow spectrum of activity, high toxicity, unsafe for undernourished children and pregnant women, requires follow up purgation and development of resistance by the parasite. So there is a need for search and development of new Anthelmintics preferably with a novel mode of action and minimum side effects. Because of this, a scheme was designed which involved synthesis, characterization and Anthelmintic evaluation of some 2-(Aryl Oxy Methyl)-1H-Benzimidazoles. The identification and characterization of the synthesized compounds were carried out by a melting point, thin layer chromatography, FT-IR, ^{1}H-NMR, to ascertain that the synthesized compounds are of different chemical nature than the respective parent compound. The synthesized compounds were preliminarily screened for the *in vitro* anthelmintic activity using Piperazine Citrate as standard.

Keywords: Aryl oxy acetic acid • Benzimidazole • FT-IR • ^{1}H-NMR • Anthelmintic activity

Introduction

Medicinal chemistry is one of the branches of science which deals with the study of discovery, identification, development, and interpretation of mode of action of biologically active compounds at the molecular level. Medicinal chemistry is concerned with improving older drugs and formulating newer drugs [1]. Medicinal chemistry involves synthesis, characterization, biological evaluation and SAR studies. Helminthiasis is a macro, parasitic disease of humans and animals in which a part of the body is infected with Helminth parasites. It is one of the most deadly, neglected, tropical diseases and many die annually from this disease. The total eradication of this problem is very difficult. The drugs which expel Helminth parasites from the body either by stunning or killing them without causing significant damage to the host are also called Anthelmintics. The most commonly used class of Anthelmintics are Benzimidazoles whose mode of action is by blocking the transportation of secretory granules and movement of other cell organelles by binding to beta-Tubulin and inhibit polymerization of microtubules in the cytoskeleton of Helmintic parasite [2]. Most of the Anthelmintics are non-selective, with a narrow spectrum of activity, high toxicity, not safe for undernourished children pregnant women, and requires follow up purgation. So there is a need for search and development of new Anthelmintics preferably with a novel mode of action and minimum side effects. Benzimidazoles are an aromatic, condensed, bicyclic, heterocyclic, organic compounds consisting of Benzene ring fused to 4,5 positions of Imidazole ring [3]. Benzimidazoles are the privileged structures in synthetic medicinal chemistry because they have multifarious applications. They are synthesized mostly by Philips condensation by treating ortho phenylenediamine with Carboxylic acids using mineral acid [4]. Sampath had prescribed *in vitro* Anthelmintic activity on *Pheretima posthuma* with slight modifications [5] (Figure 1).

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Materials and Methods

All the reagents and solvents used were of laboratory grade. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (60 F254), visualized with an ultraviolet light or iodine spray. The melting points of synthesized compounds were determined by the open capillary method and were uncorrected. The purity and homogeneity of compounds were checked using the TLC technique. IR spectra of compounds were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer.^{1}H-NMR spectra were recorded on Bruker Advance 300 MHz Spectrophotometer using Deuterated

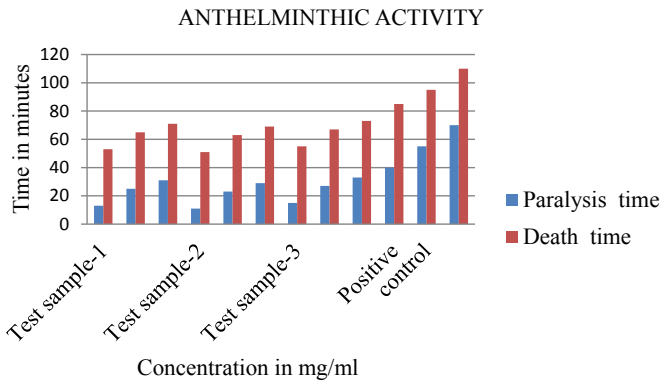


Figure 1. Anthelmintic activity of the synthesized compounds.

Chloroform as a solvent. Proton chemical shifts (d) are relative to tetra methyl silane (TMS, d = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet) and m (multiplet) as well as b (broad). The synthesized compounds (test samples) was tested for their *in vitro* anthelmintic activity according to the methods described by Sampath with slight modifications.

Synthesis of phenoxy acetic acids

A total of 0.01 moles of Phenol was measured and dissolved in 3.5 ml of 33% sodium hydroxide, taken in a clean and dry round-bottomed flask fitted with a reflux condenser along with condenser pipes. 2.5 ml of 50% mono Chloro Acetic acid was added and the reaction mixture was heated on a water bath to reflux for about one hour. The reaction mixture was cooled and poured it into a beaker containing 10 ml of ice-cold water followed by acidification of the solution using dilute hydrochloric acid. The compound was extracted from the resultant solution using 25 ml of diethyl ether, washed the ethereal extract with little water to remove impurities. 25 ml of 5% sodium carbonate was added to the ethereal solution. The sodium carbonate layer was separated from the ether layer and the sodium carbonate layer was acidified using dilute hydrochloric acid. Crude Phenoxy acetic acid separated as solid which was filtered at suction, washed with cold water, dried and recrystallized from suitable recrystallizing solvent to obtain the pure Phenoxy acetic acid [6].

Synthesis of 2-(Aryl Oxy Methyl)-1H-Benzimidazoles

A total of 0.01 moles of O-Phenylene di amine was weighed and dissolved in 25 ml of 4 N Hydrochloric acid taken in a clean and dry round-bottomed flask fitted with reflux condenser along with condenser pipes. 0.01 moles of Phenoxy acetic acid was added and the reaction mixture was heated on wire gauze. The completion of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into 50 ml of ice water and basified using a saturated sodium bicarbonate solution. Crude 2-(Aryl oxy alkyl)-1H-benzimidazole separated as solid which was filtered at suction, washed with cold water, dried and recrystallized the crude from the suitable recrystallizing solvent using activated charcoal [7].

Evaluation of *in vitro* anthelmintic activity

The synthesized compounds (test samples) were tested for their *in vitro* anthelmintic activity by the Motility inhibition method according to the methods described by Sampath with slight modifications. The assay was performed *in vitro* on Indian adult earthworm *Pheretima posthuma* since it has anatomical and physiological resemblance with the intestinal helminth parasites of human beings. Earthworms were collected from the waterlogged areas of soil from the agricultural fields in Karimnagar. The worms were acclimatized to the laboratory conditions before experimentation. They were washed with saline to remove fecal matter, mud, etc and were authenticated as *Pheretima posthuma* by the department of Zoology of SRR Degree College Karimnagar. Adult Indian earthworm *Pheretima posthuma* of nearly equal length and equal width were selected for the experimental protocol in five groups of six earthworms in each group. All the test sample solutions and standard drug solutions of different concentrations were prepared freshly before starting the experiment. Standard drugs used for the anthelminthic activity were Piperazine citrate which serves as a positive control. Normal saline (0.9% NaCl) serves as negative control. Solutions of test samples and solutions of the standard drug were poured into the Petri dishes. Earthworms were introduced into the six Petri dishes containing the solutions of known concentration kept at room temperature. The time taken by worms to become motionless and fading of color was noted as paralytic time. The time taken by worms to become motionless and with a faded color was noted as lethal time. Anthelminthic activity was expressed in terms of paralytic time and lethal time expressed in minutes. Paralytic and lethal time taken for worms was observed taking two hours' time period as the maximum time for animal response to the compound. The paralytic and lethal time for test samples were recorded, tabulated and compared with standard drug.

Results and Discussion

2-(Phenoxy Methyl)-1H-Benzimidazole (JS1)

Brown Solid; M.P: 188ºC; Percentage of yield : 86; R_f value: 0.66; IR (KBr) $\nu_{max/}$ cm^{-1}: C-H stretching of hetero aromatic ring at 3049, N-H stretching of hetero aromatic ring at 3355, C-H stretching of CH_2 at 2898 and C-O of Aryl alkyl ether at 1250 and 1056; H^1-NMR CH_2 S 4.66 2H; Ar-H m 7.40; Formula weight 224.25; Elemental analysis calculated: C (74.98%) H (5.39%) N (12.49%) O (7.13%); Molecular formula: $C_{14}H_{12}N_2O$; TLC eluent: Chloroform and Ethyl acetate -3:1; Recrystallizing solvent: Ethanol.

2-[(4-Methyl Phenoxy) Methyl]-1*H*-Benzimidazol (JS2)

Brown Solid; M.P: 180ºC; Percentage of yield: 86; R_f value: 0.68; IR (KBr) ν_{max}/ cm^{-1}: C-H stretching of hetero aromatic ring at 3037, N-H stretching of hetero aromatic ring at 3372, C-H stretching of CH_2 at 2859, C-O of Aryl alkyl ether at1241 and 1041, and C-H stretching of CH_3 at 2919,1441,1345; H^1-NMR CH_2 S 4.72 2H, CH_3 S 3.04 3H, Ar-H m 7.56; Formula weight:238.28; Elemental analysis calculated: C (75.61%) H (5.92%) N (11.76%) O (6.71%); Molecular formula: $C_{15}H_{14}N_2O$; TLC eluent: Chloroform and Ethyl acetate -3:1; Recrystallizing solvent: Ethanol.

2-[(4-Nitro Phenoxy) Methyl]-1H-Benzimidazole (JS3)

Yellow Solid; M.P: 98ºC; Percentage of yield: 76; R_f value: 0.57; IR (KBr) ν_{max}/ cm^{-1}: C-H stretching of hetero aromatic ring at 3063, N-H stretching of hetero aromatic ring at 3347, C-H stretching of CH_2 at 2983, C-O of Aryl alkyl ether at 1220 and 1044,NO_2 of Aromatic ring at 1623,1387; H^1-NMR CH_2 S 4.60 2H Ar-H m 7.11; Formula weight: 269.25; Elemental analysis calculated: C (62.45%) H (4.12%) N (15.61%) O (17.83%); Molecular formula: $C_{14}H_{11}N_3O_3$, TLC eluent: Chloroform and Ethyl acetate -3:1; Recrystallizing solvent: Ethanol (Table 1).

Etherification

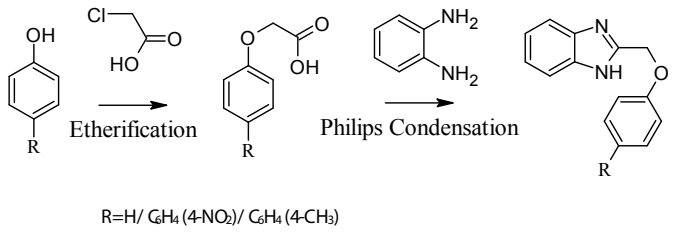
Synthesis of Aryl Oxy Acetic acid (asymmetrical ether) from Phenols using Mono Chloro Acetic acid and strong base involves the etherification principle. Etherification is a coupling reaction that involves an S_N^2 reaction mechanism. The rate of reaction depends on the concentration of phenol (aryl oxide anion) as well as the concentration of Mono Chloro Acetic acid. A strong base is used to remove proton of phenol and to generate aryl oxide anion *in situ* which acts as a nucleophile and it displaces the chloride ion of mono chloroacetic acid. Polar aprotic solvents enhance the rate of reaction. Electron releasing group destabilize the intermediate aryl oxide anion and thereby the presence of the electron releasing group in the phenol enhances the rate of reaction. An electron-withdrawing group stabilizes the intermediate aryl oxide anion and thereby the presence of the electron-withdrawing group in the phenol retards the rate of reaction (Scheme 1).

Condensation

Philips-Ladenburg reaction is an organic named reaction that involves a

Table 1. Computational data of molecular properties and bioactivity scores from Mol inspiration.

Variables	JS1	JS2	JS3
Log P	3.19	3.63	3.15
Total polar surface area	37.92	37.92	83.74
Number of oxygen and nitrogen atoms	3	3	6
Number of Hydrogen attached to O and N	1	1	1
Number of rotatable bonds	3	3	4
GPCR ligand score	-0.16	-0.15	-0.19
Ion channel modulator score	0.09	-0.01	0.01
Kinase inhibitor score	-0.28	-0.27	-0.27
Nuclear receptor ligand score	-0.45	-0.41	-0.36
Protease inhibitor score	-0.54	-0.53	-0.49
Enzyme inhibitor score	-0.07	-0.12	-0.15



R=H/ C_6H_4 (4-NO_2)/ C_6H_4 (4-CH_3)

Scheme 1. Synthesis of 2-(Aryl Oxy Methyl)-1H- Benzimidazoles.

synthesis of Benzimidazole and their derivatives from 1, 2-di-amino benzene and carboxylic acids in the presence of dilute mineral acids. It is a condensation reaction. Higher yields are obtained with aliphatic acids. Lesser yields are obtained with aromatic acids. The yield from aromatic acids can be improved by carrying out the reaction in sealed tubes.

Conclusion

In conclusion, we have described the design and synthesis of several 2-(Aryl Oxy Methyl)-1H-Benzimidazoles of potential Anthelmintic activity. These compounds were prepared from phenols via a two-step process involving the etherification of phenols using mono chloroacetic acid followed by Philips condensation of Phenoxy Acetic acids using ortho phenylenediamine. The purity and homogeneity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected), thin-layer chromatography. The chemical structure of the synthesized compounds was confirmed by infrared absorption spectra, and 1H spectra. Some of the synthesized showed better *in vitro* anthelmintic activity than the Piperazine standard drug.

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