

**MICROWAVE ASSISTED SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVITY OF NOVEL BENZIMIDAZOLE DERIVATIVES**

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**ABSTRACT**

A new class of potentially biological active novel bezimidazole derivatives containing Benzimidazole moiety has been synthesized and evaluation of novel Benzimidazole derivatives for Anthelmintic activity. The title compounds were synthesized in a good yield. The synthesized Compounds **3a-3h** was characterized by FT-IR, Mass and <sup>1</sup>H NMR data and evaluated for their anthelmintic activities by standard protocol available in literature. All the compounds were subjected for Anthelmintic screening, among this series of compounds **3d** and **3e** showed high activity against.

**Keywords:** 4-(1H-Benzoimidazol-2-yl)-phenyl amine, Substituted benzaldehyde, Substituted benzyl chloride, Anthelmintic activities.

**INTRODUCTION**

Heterocyclic compounds containing a ring made up, in addition to carbon atoms, other elements (heteroatom's), most often nitrogen, oxygen, and sulfur, and less frequently phosphorus, boron, and silicon. The ring system in which a benzene ring is fused to the 4, 5-positions of imidazole is designated as benzimidazole<sup>1</sup>. The benzimidazole nucleus, which is a useful structure for research and development of new pharmaceutical molecules, has received much attention in last decade. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Owing to the immense importance and varied by bioactivities exhibited by Benzimidazoles, efforts have been made from time to time to generate libraries of these compounds and screened them for potential biological activities.

Due to their antimicrobial activities, new

Benzimidazoles have been synthesized and investigated for medical applications. As resistance to antimicrobial drugs is wide spread; there is an increase necessity for identification of novel structure which could lead to the design of new, potent and less toxic antimicrobial agents. Numerous attempts have been made to develop new structural prototypes to search for more effective antimicrobials. The Benzimidazoles still remains one of the most versatile classes of compounds against microbes and, therefore are useful substructures for further molecular exploration. The exhibit a range of biological activities.<sup>2-5</sup>

**EXPERIMENTAL:**

Melting points were determined in open capillaries, using Toshniwal melting point apparatus, expressed in °C and are uncorrected. The IR spectra of the compounds were recorded on thermo Nicolet Nexus 670S series, FT-IR spectrometer using KBr disc. <sup>1</sup>H NMR was scanned on Avance-400 MHz instrument.

Chemical shifts are expressed in  $\delta$  (ppm) relative to TMS as an internal standard using DMSO- $d_6$  as solvent. Mass spectra's were recorded on a ES-MSD-Trap-SL. The purity of the compounds was checked on silica gel-coated aluminum sheets (Merck, 1.005554, silica gel HF254-361, Type 60, 0.25 mm, Darmstadt, Germany) by thin-layer chromatography (TLC). TLC was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (short wave length, 254 nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60-120 mesh).

### General procedures:

#### Step I: Synthesis of N-[4-(1H-Benzimidazol-2-yl)-phenyl]-acetamide:

Dissolve 2-(4-aminophenyl) benzimidazole (2.09 g, 0.01 mole) in chloroform (50 ml) and acetic anhydride (1.02 g, 0.01 mole) was added drop wise with constant stirring at 5 to 10°C. Then the reaction mixture was subjected for microwave irradiation for 10 cycles for 10sec (2min) at 160W. The reaction mixture was stirred for 4 hours. The excess solvent was distilled off and the solid product was filtered, dried and recrystallized from ethanol to give N-(4-(1H-benzo[d]imidazol-2-yl) phenyl) acetamide.<sup>6-7</sup>

#### Step II: Synthesis of benzimidazolyl Chalcones:

Dissolve N-(4-(1H-benzo[d]imidazol-2-yl) phenyl) acetamide (2.51 g, 0.01 mol) in ethanol (30 ml) and various aromatic aldehydes (0.01 mole) were taken and then an aqueous solution of KOH (2%, 5 ml) added to it. Then the reaction mixture was subjected for microwave irradiation for 10 cycles for 10sec (3min) at 160W and then the excess solvent was removed by vacuum distillation and then it was poured into crushed ice and acidified with dilute HCl. The solid separated was filtered and recrystallized from ethanol.

#### Step III: Synthesis of Some Novel N-[4-(1H-Benzimidazol-2-yl)-phenyl]-N-(3-phenyl-acryloyl)-benzamide:

The benzimidazolyl Chalcones 3(a-l) 0.01 mol) obtained above was dissolved in dichloromethane to which an equimolar amount of benzoyl chloride was added. Then the reaction mixture was subjected for microwave irradiation for 10 cycles for 10sec (3min) at 160W. The crude products were separated out by evaporating dichloromethane and recrystallized from ethanol to yield the pure compounds.<sup>8</sup> The physical data are reported in **Table 1**.

**3a**-IR  $\text{Cm}^{-1}$  (KBr): 3402 (-NH *Str*), 3045(-CH *Str*, benzene), 1724 (C=O *Str*), 1656(-CH=CH-), 1509(C=N *Str*), 1325(C-N *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$

ppm): 10.06(1H, -NH indole), 7.98-7.00(16H, Ar-H), 6.00-5.98 (2H, CH=CH). Mass (EI-MS): 444(M+1, 100%), 466(M+Na).

**3b**- IR  $\text{Cm}^{-1}$  (KBr): 3412(-NH *Str*), 3012(-CH *Str*, benzene), 2901(-CH<sub>3</sub> *Str*), 1698 (C=O *Str*), 1665(-CH=CH-), 1538(C=N *Str*), 1383C-N *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 11.06(1H, -NH indole), 8.15-7.41(17H, Ar-H), 6.32-6.00 (2H, CH=CH), 2.03-1.98 (3H, -CH<sub>3</sub>). Mass (EI-MS): 458(M+1, 100%), 481(M+Na).

**3c**- IR  $\text{Cm}^{-1}$  (KBr): 3406(-NH *Str*), 3092(-CH *Str*, benzene), 1701 (C=O *Str*), 1620(-CH=CH-), 1536(C=N *Str*), 1323(C-N *Str*), 1158(-OCH<sub>3</sub> *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 10.51(1H, -NH indole), 7.99-7.30(17H, Ar-H), 6.16-6.04 (2H, CH=CH), 3.62-3.08(3H, -OCH<sub>3</sub>). Mass (EI-MS): 478(M+1, 100%), 493(M+Na, 60%).

**3d**- IR  $\text{Cm}^{-1}$  (KBr): 3442 (-NH *Str*), 3008(-CH *Str*, benzene), 1712 (C=O *Str*), 1624(-CH=CH-), 1553(C=N *Str*), 1334(C-N *Str*), 1095(-OCH<sub>3</sub> *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 11.23(1H, -NH indole), 8.02-7.34(16H, Ar-H), 6.16-6.04 (2H, CH=CH), 3.84-3.20 (6H, -OCH<sub>3</sub>). Mass (EI-MS): 504(M+1, 100%), 530(M+Na).

**3e**- IR  $\text{Cm}^{-1}$  (KBr): 3428(-NH *Str*), 3082(-CH *Str*, benzene), 1732(C=O *Str*), 1606(-CH=CH-), 1505(-NO<sub>2</sub> *Str*), 1498(C=N *Str*), 1310(C-N *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 12.02(1H, -NH), 8.42- 6.23 (12H, Ar-H), 4.89 (2H, -CH<sub>2</sub>), 2.34(1H, -CH). Mass (EI-MS): 489(M+1, 100%), 511(M+Na).

**3f**- IR  $\text{Cm}^{-1}$  (KBr): 3427 (-NH *Str*), 3063(-CH *Str*, benzene), 1729(C=O *Str*), 1663(-CH=CH-), 1546(C=N *Str*), 1328(C-N *Str*), 1055(-Cl *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 10.45(1H, -NH indole), 8.02- 7.52(17H, Ar-H), 6.92-6.31 (2H, CH=CH). Mass (EI-MS): 478(M+1, 100%), 500(M+Na, 60%).

**3g**-IR  $\text{Cm}^{-1}$  (KBr): 3471(-OH *Str*), 3419(-NH *Str*), 3072(-CH *Str*, benzene), 2845(-CH<sub>3</sub> *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1582(C=N *Str*), 1357(C-N *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 10.19(1H, -NH indole), 7.94- 7.10(18H, Ar-H), 7.03-6.78 (2H, CH=CH), 3.82(1H,-OH), 2.60-2.18 (3H, -CH<sub>3</sub>). Mass (EI-MS): 474(M+1, 100%), 496(M+Na).

**3h**- IR  $\text{Cm}^{-1}$  (KBr): 3419 (-NH *Str*), 3070(-CH *Str*, benzene), 2848(-CH<sub>3</sub> *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1525(C=N *Str*), 1310(C-N *Str*). <sup>1</sup>H-NMR (DMSO  $\delta$  ppm): 10.00(1H, -NH indole), 7.99-7.38(16H, Ar-H), 6.86-6.62 (2H, CH=CH), 2.30-2.23 (6H, -CH<sub>3</sub>). Mass (EI-MS): 472(M+1, 100%), 494(M+Na, 40%).

**Biological Evaluation:**

**Anthelmintic Activity:** Synthesized compounds are screened for anthelmintic activity by using Earth worms. Six earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl sulfoxide (DMSO) and adjusted the volume up to 10 ml with normal saline solution to get the concentration of 0.1% w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug.<sup>9-10</sup>

The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms were frequently applied with external stimuli, which stimulate and induce movement in the worms, if alive. The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are tabulated in **Table No.1**.

**RESULTS AND DISCUSSION**

**Synthesis:** The characterization data of all compounds **3a-3h** are given the experimental section. All the synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their elemental analysis by FT-IR, LC-MASS, <sup>1</sup>H NMR data. The present work which involve reaction between Benzimidazole with acetic anhydride and then which on react with substituted benzoldihyde to get intermediates, which on rection with Benzoyl chloride to give respective title compounds. The synthesized compounds were screened for anthelmintic activities.

**Spectroscopy:** The structures of all the newly synthesized compounds were characterized as **3a-3h** on the basis of satisfactory analytical and spectral data including IR, LC-MASS, <sup>1</sup>H NMR data. The IR

spectra of the compound **3h** N-[4-(1H-Benzoimidazol-2-yl)-phenyl]-4-methyl-N-(3-p-tolyl-acryloyl)-benzamide show characteristic absorption bands at 3419 (-NH *Str*), 3070(-CH *Str*, benzene), 2848(-CH<sub>3</sub> *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1525(C=N *Str*), 1310(C-N *Str*) groups respectively. The <sup>1</sup>H NMR spectra of (**3h**) N-[4-(1H-Benzoimidazol-2-yl)-phenyl]-4-methyl-N-(3-p-tolyl-acryloyl)-benzamide 11.053 (1H, -NH), 8.9- 7.10 (13H, Ar-H), 5.572 (2H, -CH<sub>2</sub>), 3.45-3.23 (3H, -OCH<sub>3</sub>), 2.10 (1H, -CH) assigned to the each particular set of protons. The molecular ion peak in their mass spectra was **m/z** = (M<sup>+</sup>, 100%) & (M+1) peaks identified respectively.

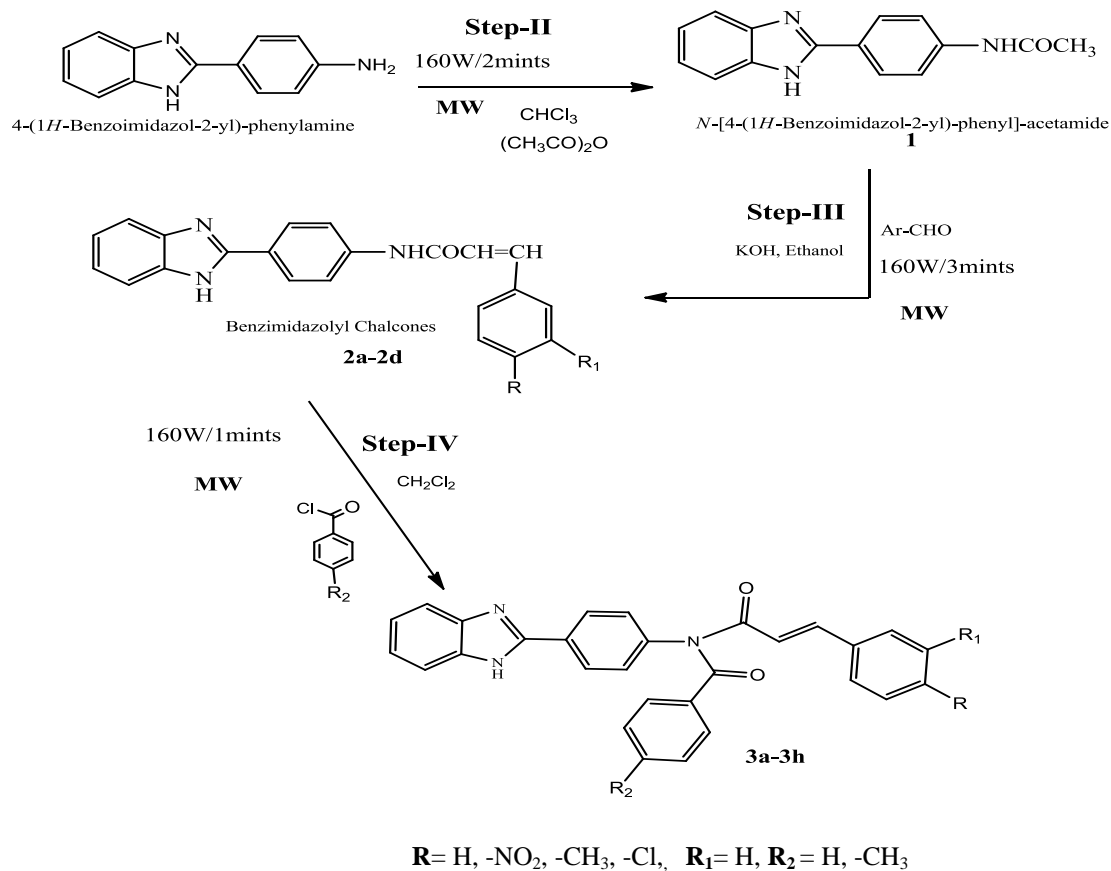
**Anthelmintic activity:** The synthesised compounds (**3a-3h**) were evaluated for anthelmintic activity on Indian earthworms (*Peretima posthuma*). All compounds showed anthelmintic activity is shown in table. Among the compounds tested all the compounds were showed significant paralytic time of earthworms, compared to standard drug albendazole at 0.1%, 0.2% and 0.5% concentrations of compounds.

A closer inspiration of data from this table indicated that compound **3d** and **3e** having more activity and compounds **3a**, **3b**, and **4f** showed moderate activity. After all, the synthesized compounds in overall estimation confirm the better activity against *peritima posthuma*.

**CONCLUSION**

In the present study, a series of N-[4-(1H-Benzoimidazol-2-yl)-phenyl]-4-methyl-N-(3-p-tolyl-acryloyl)-benzamide were synthesized according to the above mentioned procedures by conventional methods as mentioned in the scheme by the present work which involve reaction between Benzimidazole with acetic anhydride and then which on react with substituted benzoldihyde to get intermediates, which on rection with Benzoyl chloride to give respective title compounds. The synthesized compounds are responsible for the anthelmintic activities and may serve as a lead molecule for further modifications to obtain clinically useful novel entities.

## Chemistry:



Scheme-I

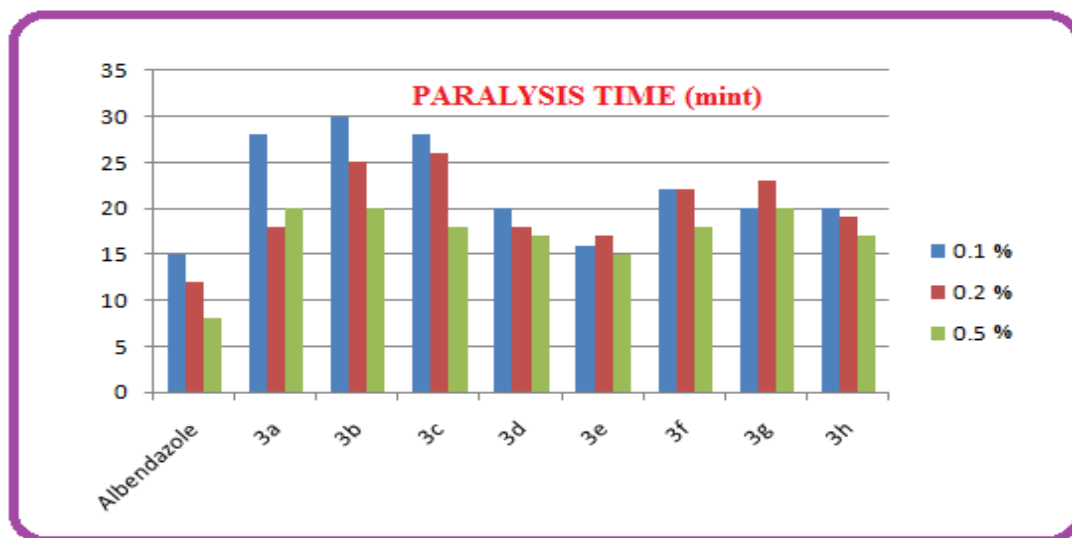
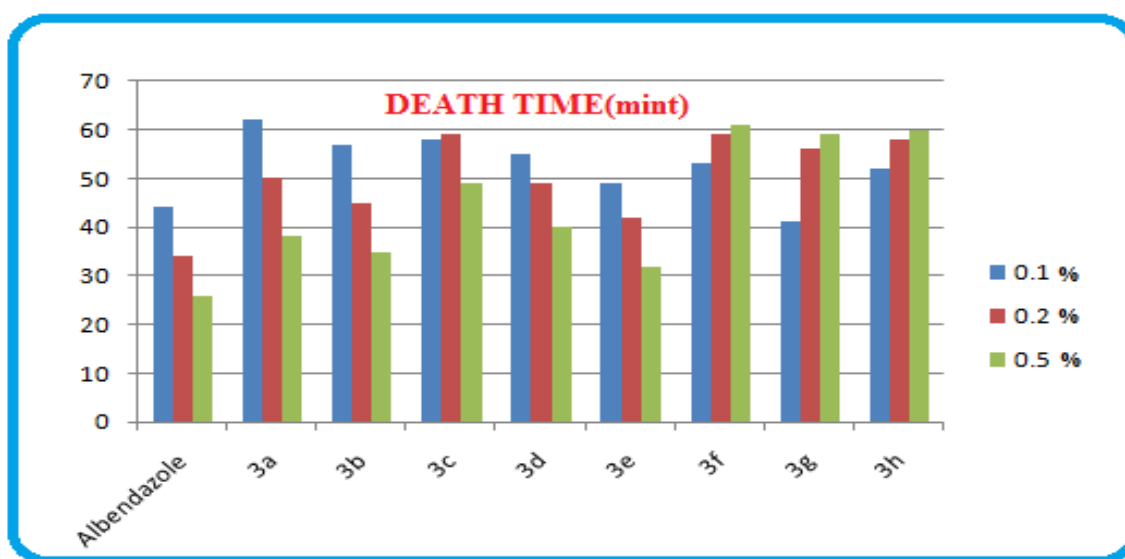


Figure 1: Graphical representation of anthelmintic activity of compounds ( 3a-3h) – Paralysis time (min).

**Table 1. Antihelmintic activity of novel Benzimidazole derivatives**

S.No.	Name	Time in minutes					
		For paralysis % Concentration			For death % Concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
	Control	-	-	-	-	-	-
	Albendazole	15	12	8	44	34	26
1	3a	28	18	20	62	50	38
2	3b	30	25	20	57	45	35
3	3c	28	26	18	58	59	49
4	3d	20	18	17	55	49	40
5	3e	16	17	15	49	42	32
6	3f	22	22	18	53	59	61
7	3g	20	23	20	41	56	59
8	3h	20	19	17	52	58	60

**Figure 2:** Graphical representation of anthelmintic activity of compounds (3a-3h) - Death time(min)



**Fig.3: Photographs of various novel Benzimidazole derivatives–Anthelmintic activities.**

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