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Synthesis, Characterization and Biological Evaluation of Novel Benzimidazole Derivatives

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ABSTRACT

*The research envisaged in the present study is the synthesis and evaluation of novel benzimidazole derivatives for anthelmintic activity. The title compounds were synthesized in a good yield. The synthesized Compounds 4a-4l was characterized by FT-IR, LC-MASS and ^{1}H NMR data and evaluated for their antimicrobial and anthelmintic activities by standard protocol available in literature. All the compounds were subjected for anthelmintic screening, among this series of compounds **4h and 4j** showed high activity against.*

***Key Words**: O-Phenylene diamine, P-Amino benzoic acid and 4-Nitrobenzaldehyde, Anthelmintic activities.*

INTRODUCTION

Heterocyclic compounds containing a ring made up, in addition to carbon atoms, other elements (heteroatoms), 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 [1-3].

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 [4, 5]. 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 [6].

MATERIALS AND METHODS [7-9]

The synthesized compounds were screened for anthelmentic activities. Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400-4000 cm^{-1} Using KBr pellets and values are reported in cm^{-1} and the spectra were interpreted. ^{1}H-NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d_6 and chemical shifts (δ) are reported in parts per million down field from internal reference Tetramethylsilane (TMS) and the Spectra were interpreted. Mass spectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra were interpreted. Precoated Silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds**:** Chloroform: Methanol (1:3).

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General procedures:

Step I: Synthesis of 4-(1H-Benzoimidazol-2-yl)-phenylamine:

2-(4-aminophenyl) benzimidazole was synthesized by the condensation of O-phenylenediamine and para amino benzoic acid in 4N hydrochloric acid (40 ml) and refluxed for 4 hrs, then cooled at room temperature. The completion of this reaction was monitored by thin layer chromatography. The pH was adjusted to 7.2 using Sodium Hydroxide pellets. The resulting solid was filtered and washed with water, dried in vacuum and re crystallized from methanol[20].The yield of 2-(4-aminophenyl) benzimidazole was found to be 64% and the melting point is 168ºC -170ºC.

Step II: Synthesis of N-[4-(1H-Benzoimidazol-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 10ºC. 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.

Step III: 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. The reaction mixture was refluxed for 5 hrs 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 IV: Synthesis of Some Novel N-[4-(1H-Benzoimidazol-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 with stirring for 2 h. The crude products were separated out by evaporating dichloromethane and recrystallized from ethanol to yield the pure compounds [40]. The physical data are reported in **Table No. 1**.

4a-IR 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*). ^{1}H-NMR (DMSO δ 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).

4b- IR Cm^{-1} (KBr): 3412(-NH *Str*), 3012(-CH *Str*, benzene), 2901(-CH_3 *Str*), 1698 (C=O *Str*), 1665(-CH=CH-), 1538(C=N *Str*), 1383C-N *Str*). ^{1}H-NMR (DMSO δ 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_3). Mass (EI-MS): 458(M+1, 100%), 481(M+Na).

4c- IR 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_3 *Str*). ^{1}H-NMR (DMSO δ 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_3). Mass (EI-MS): 478(M+1, 100%), 493(M+Na, 60%).

4d- IR 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_3 *Str*).^{1}H-NMR (DMSO δ 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_3). Mass (EI-MS): 504(M+1, 100%), 530(M+Na).

4e- IR Cm^{-1} (KBr): 3428(-NH *Str*), 3082(-CH *Str*, benzene), 1732(C=O *Str*), 1606(-CH=CH-), 1505(-NO_2 *Str*), 1498(C=N *Str*), 1310(C-N *Str*).^{1}H-NMR (DMSO δ ppm): 12.02(1H, -NH), 8.42- 6.23 (12H, Ar-H), 4.89 (2H, -CH_2), 2.34(1H, -CH). Mass (EI-MS): 489(M+1, 100%), 511(M+Na).

4f- IR 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*),. ^{1}H-NMR (DMSO δ 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%).

4g-IR Cm^{-1} (KBr): 3471(-OH *Str*), 3419(-NH *Str*), 3072(-CH *Str*, benzene), 2845(-CH_3 *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1582(C=N *Str*), 1357(C-N *Str*). ^{1}H-NMR (DMSO δ 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_3). Mass (EI-MS): 474(M+1, 100%), 496(M+Na).

4h- IR Cm^{-1} (KBr): 3399(-NH *Str*), 3057(-CH *Str*, benzene), 2884(-CH_3 *Str*), 1746 (C=O *Str*), 1621(-CH=CH-), 1534(C=N *Str*), 1322(C-N *Str*). ^{1}H-NMR (DMSO δ ppm): 11.13(1H, -NH indole), 8.23-7.52(17H, Ar-H), 6.26-6.01 (2H, CH=CH), 2.83-2.32 (6H, -CH_3). Mass (EI-MS): 487(M+1, 100%), 509(M+Na, 40%).

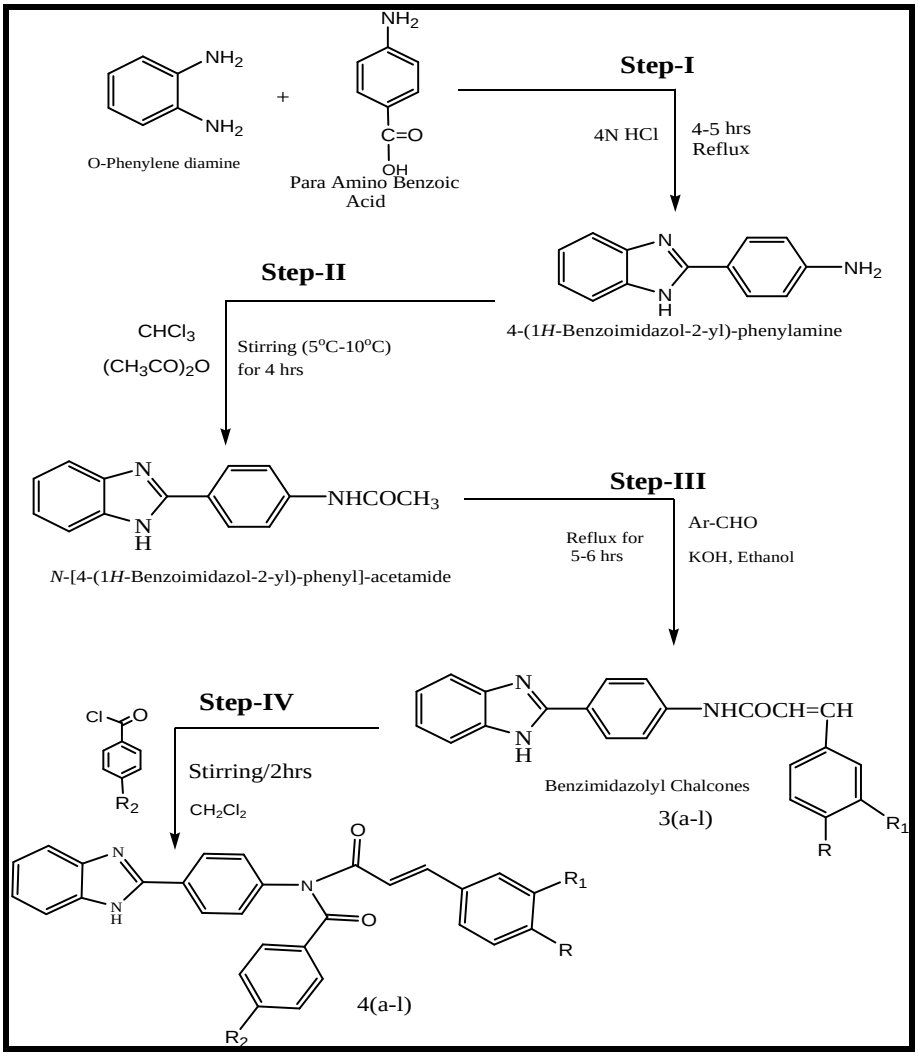
4i- IR Cm^{-1} (KBr): 3419 (-NH *Str*), 3070(-CH *Str*, benzene), 2848(-CH_3 *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1525(C=N *Str*), 1310(C-N *Str*). ^{1}H-NMR (DMSO δ ppm): 11.02(1H, -NH indole) 7.80- 7.02(17H, Ar-H), 6.45-6.62(2H, CH=CH), 2.10-1.92 (3H, -CH_3). Mass (EI-MS): 458(M+1, 100%), 480(M+Na, 40%).

4j- IR Cm^{-1} (KBr): 3407 (-NH *Str*), 3033(-CH *Str*, benzene), 2842(-CH_3 *Str*), 1703 (C=O *Str*), 1629(-CH=CH-), 1551(C=N *Str*), 1323(C-N *Str*), 1054(C-N *Str*). ^{1}H-NMR (DMSO δ ppm): 10.25(1H, -NH indole),8.12- 7.56(16H, Ar-H), 6.23-6.10 (2H, CH=CH), 2.56-2.24 (3H, -CH_3).Mass (EI-MS): 492(M+1, 100%), 514(M+Na, 40%).

4k- IR Cm^{-1} (KBr): 3427 (-NH *Str*), 3083(-CH *Str*, benzene), 2852(-CH_3 *Str*), 1741 (C=O *Str*), 1603(-CH=CH-), 1582(-NO_2 *Str*), 1573(C=N *Str*), 1330(C-N *Str*). ^{1}H-NMR (DMSO δ ppm): 11.02(1H, -NH indole),802- 7.45(16H, Ar-H), 6.12-6.04 (2H, CH=CH), 2.19-2.034 (3H, -CH_3). Mass (EI-MS): 503(M+1, 100%), 525(M+Na, 40%).

4l- IR Cm^{-1} (KBr): 3419 (-NH *Str*), 3070(-CH *Str*, benzene), 2848(-CH_3 *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1525(C=N *Str*), 1310(C-N *Str*). ^{1}H-NMR (DMSO δ 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_3). Mass (EI-MS): 472(M+1, 100%), 494(M+Na, 40%).

Scheme of synthesis:



R= H, -NO_2, -CH_3, -Cl, -OCH_3, **R_1**= H, -OH, -OCH_3, **R_2** = H, -CH_3

Anthelmintic activity: [10-12]

The synthesized compounds are screened for anthelminthic 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 (**Fig. 1, 2**). The mean lethal time for each test compound was recorded and compared with standard drug.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. 2**.

RESULTS AND DISCUSSION

Synthesis:

The characterization data of all compounds **4a-4ls** 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, ^{1}H NMR data. The present work which involve reaction between o-Phenylene diamine with para amino benzoic acid in the presence of HCl to get Benzimidazole, which on reaction 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 anthelmentic activities.

Spectroscopy:

The structures of all the newly synthesized compounds were characterized as **4a-4l** on the basis of satisfactory analytical and spectral data including IR, LC-MASS, ^{1}H NMR data. The IR spectra of the compound **4l** 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_3 *Str*), 1715 (C=O *Str*), 1631(-CH=CH-), 1525(C=N *Str*), 1310(C-N *Str*) groups respectively. The ^{1}H NMR spectra of **(4l)** 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_2), 3.45-3.23 (3H, -OCH_3), 2.10 (1H, -CH) assigned to the each particular set of protons. The molecular ion peak in their mass spectra was **m/z** = (M^+, 100%) & (M+1) peaks identified respectively.

Table No. 1: Physical data of (4a-4l)

Code	R	R_1	R_2	Mol. Formula	Mol. wt (g.mol^{-1})	M.P (^{0}C)
4a	H	H	H	$C_{29}H_{21}N_3O_2$	443	212-214
4b	-CH_3	H	H	$C_{30}H_{23}N_3O_2$	457	232-234
4c	-OCH_3	H	H	$C_{30}H_{23}N_3O_3$	473	198-200
4d	-OCH_3	-OCH_3	H	$C_{31}H_{25}N_3O_4$	503	243-240
4e	-NO_2	H	H	$C_{29}H_{20}N_4O_4$	488	208-210
4f	-Cl	H	H	$C_{29}H_{22}N_3O_2$	477	218-220
4g	-CH_3	-OH	H	$C_{30}H_{23}N_3O_3$	473	225-228
4h	-$N(H_3)_2$	H	H	$C_{31}H_{26}N_4O_2$	486	192-194
4i	H	H	-CH_3	$C_{30}H_{23}N_3O_2$	457	238-240
4j	-Cl	H	-CH_3	$C_{30}H_{22}N_3ClO_2$	491	274-276
4k	-NO_2	H	-CH_3	$C_{30}H_{22}N_4O_4$	502	184-186
4l	-CH_3	H	-CH_3	$C_{31}H_{25}N_3O_2$	471	225-227

Anthelmintic activity:

The synthesised compounds (4a-4l) were evaluated for anthelmintic activity on Indian earthworms (*Pheretima 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 **4h** and **4j** having more activity and compounds **4d, 4k, 4l** and **4f** showed moderate activity. After all, the synthesized compounds in overall estimation confirm the better activity against *peritima posthuma.*

Table No. 2: Antihelmintic activity of Novel Benimidazole derivatives

S.No.	Name	Time in minutes					
		For paralysis			For death		
		% Concentration			% Concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
1	**Control**	-	-	-	-	-	-
2	**Albendazole**	15	12	8	44	34	26
3	**4a**	24	20	18	60	50	42
4	**4b**	20	18	16	53	49	45
5	**4c**	22	19	14	56	45	47
6	**4d**	18	14	12	48	40	30
7	**4e**	19	20	14	51	39	32
8	**4f**	21	22	15	49	52	58
9	**4g**	20	24	15	50	42	44
10	**4h**	15	13	10	46	37	28
11	**4i**	22	19	18	58	48	46
12	**4j**	16	12	10	46	36	30
13	**4k**	19	20	15	50	48	38
14	**4l**	22	20	18	58	49	40

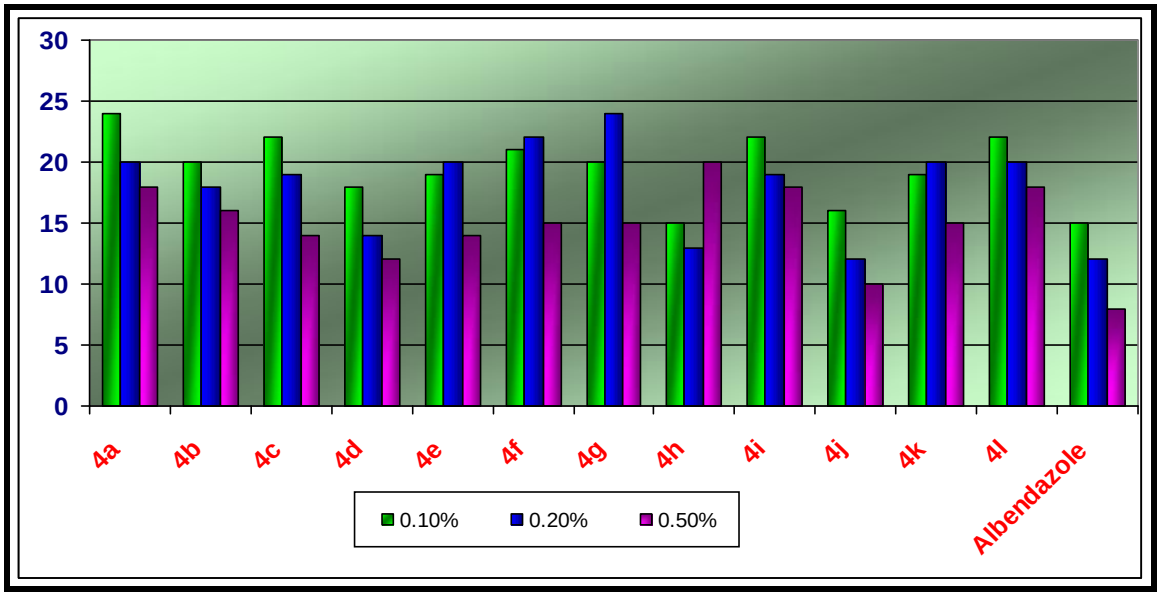


Fig. 1: Graphical representation of anthelmentic activity of compounds (4a-4l) – Paralysis time (min)

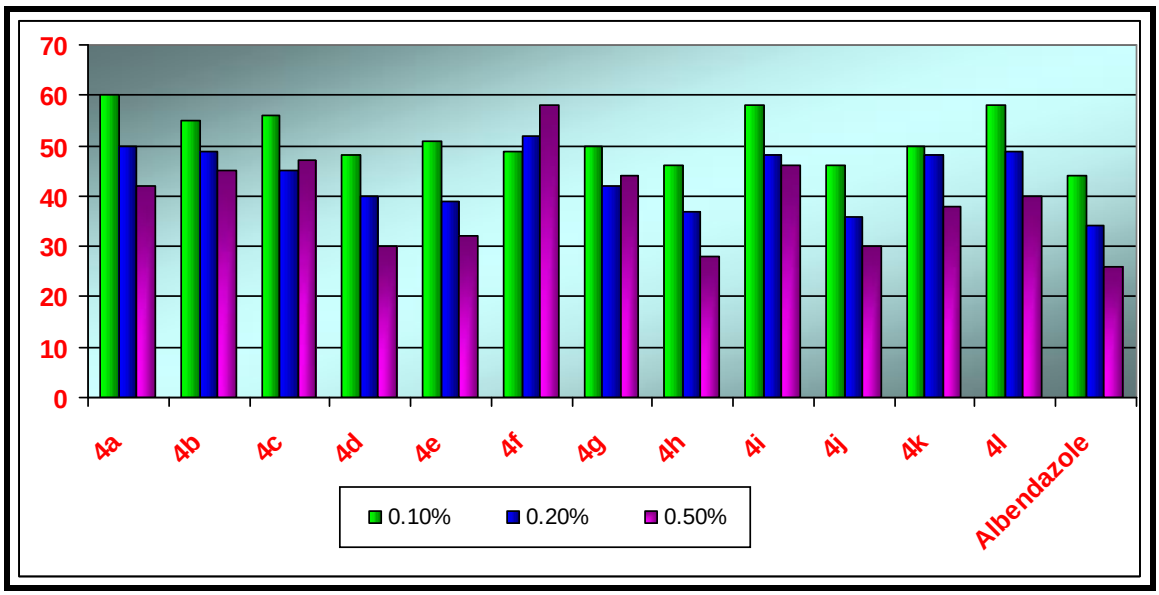


Fig. 2: Graphical representation of anthelmentic activity of compounds (4a-4l) - Death time(min)

Fig. 3: Photographs of various Novel Benzimidazoles derivatives –Anthelmintic activity

CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of Benzimidazoles. The yield of the synthesized compound was found to be in the range from 60-87 %. In conclusion, the present study highlights the importance of Benzimidazoles derivatives having various heterocyclic moiety features responsible for the anthelmintic activities and may serve as a lead molecule for further modification to obtain clinically useful novel entities.

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