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SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVITY OF NOVEL IMIDAZOLE-5-ONE DERIVATIVES

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ABSTRACT

Objective: *To synthesize and evaluate the Anthelmintic activity of novel Imidazole derivatives.* ***Methods:*** *Synthesis of Benzoyl glycine derivatives involves the N-Benzoylation of equimolar quantities of substituted benzoyl chloride with glycine in the presence of aqueous NaOH (10%). Benzoyl glycine derivatives undergo Erlenmeyer condensation reaction with Substituted Benzaldehydes in the presence of acetic anhydride and anhydrous sodium acetate to yield 2-Oxazoline-5-one derivatives. It undergoes dehydration reaction with thiosemicabazide and 1-pheny-3-thiosemicabazide to yield final compound. The Anthelmintic activity of all synthesized compounds was carried by using an Indian earthworm (Pheretima posthuma). And Albendazole used as standard drug.* ***Results:*** *All compounds synthesized are obtained in crystalline form with good practical yield. The purity and homogeneity of compounds synthesized were determined by sharp melting points and TLC method. The chemical structures were confirmed by FTIR, [1]HNMR, and Mass spectrum.* ***Conclusion:*** *The synthesized compound* ***1b, 1d*** *and* ***2d*** *showed good Anthelmintic activities whereas others exhibited significant activities.*

KEY WORDS

Benzoyl glycine, 4-aminobenzoyl glycine, Imidazole-5-one derivatives, Anthelmintic activity.

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. Imidazoles are five membered heterocyclics that contain in their structure two nitrogen atoms. Imidazole is very useful units in the fields of medicinal and pharmaceutical chemistry and has been reported to exhibit a variety of biological activities. The imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar, five membered heteroaromatic molecule with 3C and 2N atom in 1 and 3 positions[1-2]. It was first named as gluoxaline (first synthesis with glyoxal and ammonia). Amphoteric nature is susceptible to electrophilic and nucleophilic attack. Highly stable to thermal, acid, base, oxidation and reduction conditions. It has extensive intramolecular hydrogen bonding. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Imidazole a heterocyclic compound and subsequently their derivatives have been used as antiproliferative [3], anticonvulsant [4], antitubercular [5], antimicrobial [6], antiviral [7], Further Immidazole-5-one core moieties have remarkable potential of anti-radiation agents and also used in various organic synthesis and transformations as reaction intermediates.

Anthelmintics are drugs that force out parasitic worms (helminths) and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host. Moreover, the discovery of an anthelmintic vaccine, frequently delayed by difficulties in drug development, has made the fight

against parasites a major economic and food security issue. Helminthes infections, repetitively entitled helminthiasis is among the most invasive infection and a prime degenerative disease for a large proportion of world's population. In developing countries, they poing a large threat to public health and contribute to the prevalence of malnutrition, anemia, eosinophilia, and pneumonia. The helminthes mainly survive in the human body in the intestinal tract, but they are also found in tissue, as their larvae migrate toward them. Most diseases caused by helminthes are of a chronic, unbearable nature; they most likely cause more morbidity and better economic and social deficiency among humans and animals than any single group of parasites. Chemical control of helminthes coupled with the better administration has been the important worm control strategy throughout the world. However, development of resistance in helimitic against conventional anthelmintics is a leading problem in the treatment of helimintic diseases. Despite this prevalence of parasitic infections, the search on the anthelmintic drug is sparse. Helminths have complex life cycles, special knowledge of which is required for the treatment of the infections caused by them. Therefore, it is important to look for alternative strategies against gastrointestinal nematodes, which have led to the anthelmintic activity. The constitution of derivatives has been supported by IR, H-NMR and Mass spectral data.

MATERIALS AND METHODS:

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 was scanned on Avance-400 MHz instrument. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-d_6 as solvent. 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 (9:1) used as a mobile phase.

Experimental procedures: [8-9]

Step-1: Synthesis of Benzoylglycine derivatives:

The compound, glycine (0.03 mol) was dissolved in 10% sodium hydroxide solution in a conical flask. To this flask benzoyl chloride (0.03 mol) was added slowly in five portions with constant stirring. The reaction mixture was transferred to a beaker containing few pieces of crushed ice. Then hydrochloric acid was added slowly with stirring until the reaction mixture is acid to congo red paper. The precipitate thus formed was filtered on Buchner funnel washed with ice cold water and dried.

Step II: Synthesis of Oxazoline-5-one derivatives:

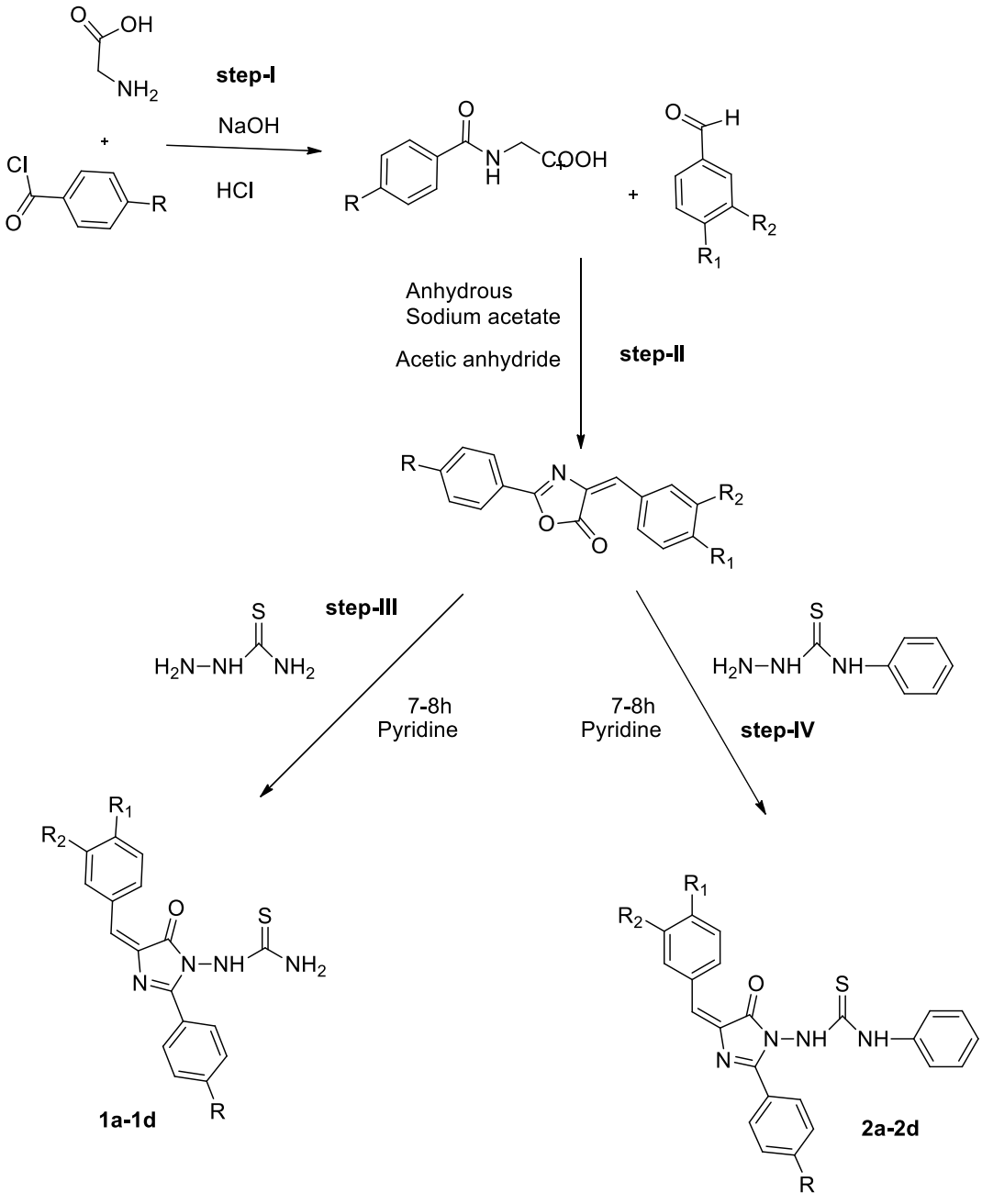
An equimolar mixture of substituted benzaldehydes (0.01 mol), benzoyl glycine derivatives (0.01mol), anhydrous sodium acetate (0.82, 0.01mol) and acetic anhydride (2.85ml , 0.03 mol) was heated on electric hot plate with constant shaking in a conical flask . As soon as the mixture was liquified completely, the flask was heated on water bath for two hours. Cool and 20 ml of ethanol was added slowly to the contents of the flask, mixture was allowed to stand overnight. The separated crystalline product was filtered, washed with ice cold ethanol and then finally washed with boiling water, dried at 100^0C.

Step-III: Synthesis of novel Imidazole-5-one derivatives:

A mixture of equimolar quantities of Oxazoline-5-one derivatives (0.01mol) and thiosemicabazide (0.01mol) in pyridine with a pinch of KOH in a round bottom flask and refluxed for 7-8 hours. The progress of the reaction was monitored by TLC. After completion of the reaction resulting mass was poured into crushed ice and neutralized with dil. HCl. The precipitate thus formed was filtered, dried and the product was recrystallized from methanol.

Step-IV: Synthesis of novel Imidazole derivatives:

A mixture of equimolar quantities of Oxazoline-5-one derivatives (0.01mol) and phenyl-3-thiosemicarbazide (0.01mol) in pyridine with a pinch of KOH in a round bottom flask and refluxed for 7-8 hours. The progress of the reaction was monitored by TLC. After completion of the reaction resulting mass was poured into crushed ice and neutralized with dil. HCl. The precipitate thus formed was filtered, dried and the product was recrystallized from methanol.



R= H, NH_2 , R_1 = H, CH_3, NO_2, OCH_3 , $N(CH_3)_2$, R_2 = H

Scheme

Spectral data:

1a. IR, Cm^{-1} (KBr): 3415(-NH *Str*, NH_2), 3302(-CH *Str*, NH), 3084(-CH *Str*, aromatic), 2761(-CH *Str*, Benzyl), 1693(C=O *Str*), 1572(C=N *Str*), 1347(C-N *Str*). 1261(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 12.08(1H, -NH-CS), 8.35(1H, Benzyl), 8.03-7.02(10H, Ar-H), 2.42(2H, NH_2). **Mass (EI-MS):** 322(M), 323(M + 1), 321(M -1).

1b. IR, Cm^{-1} (KBr): 3400(-NH *Str*, NH_2), 3282(-CH *Str*, NH), 3103(-CH *Str*, aromatic), 2775(-CH *Str*, Benzyl), 1696(C=O *Str*), 1627(NO_2 *str*), 1586(C=N *Str*), 1375(C-N *Str*). 1255(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 11.86(1H, -NH-CS), 8.32(1H, Benzyl), 8.23-6.92(8H, Ar-H), 2.43(4H, NH_2). **Mass (EI-MS):** 382(M), 383(M + 1), 381(M -1).

1c. IR, Cm^{-1} (KBr): 3424(-NH *Str*, NH_2), 3282(-CH *Str*, NH), 3054(-CH *Str*, aromatic), 2967(-CH *Str*, aliphatic), 2764(-CH *Str*, Benzyl), 1710(C=O *Str*), 1543(C=N *Str*), 1353(C-N *Str*). 1283(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 11.76(1H, -NH-CS), 8.69(1H, Benzyl), 8.02-6.98(9H, Ar-H), 2.52(2H, NH_2). **Mass (EI-MS):** 336(M), 337(M+1), 335(M -1).

1d. IR, Cm^{-1} (KBr): 3421(-NH *Str*, NH_2), 3265(-CH *Str*, NH), 3093(-CH *Str*, aromatic), 2978(-CH *Str*, aliphatic), 2756(-CH *Str*, Benzyl), 1702(C=O *Str*), 1568(C=N *Str*),

1343(C-N *Str*). 1245(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 11.25(1H, -NH-CS), 8.65(1H, Benzyl), 8.44-6.83(8H, Ar-H), 2.32(4H, NH_2). **Mass (EI-MS):** 397(M), 398(M+1), 396(M -1).

2a. IR, Cm^{-1} (KBr): 3343(-NH *Str*, NH), 3282(-NH *Str*, NH), 3162(-CH *Str*, aromatic), 2973(-CH *Str*, aliphatic), 2827(-CH *Str*, Benzyl), 1695(C=O *Str*), 1574(C=N *Str*), 1329(C-N *Str*). 1255(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 12.66(1H, -NH-CS), 11.17(1H, -NH-C_6H_5), 8.09(1H, Benzyl), 7.40-6.83(14H, Ar-H), 2.32(6H, -CH_3). **Mass (EI-MS):** 441(M), 442(M+1), 440(M -1).

2b. IR, Cm^{-1} (KBr): 3382(-NH *Str*, NH), 3246(-NH *Str*, NH), 3063(-CH *Str*, aromatic), 2983(-CH *Str*, aliphatic), 2804(-CH *Str*, Benzyl), 1699(C=O *Str*), 1565(C=N *Str*), 1356(C-N *Str*). 1268(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 12.48(1H, -NH-CS), 11.23(1H, -NH-C_6H_5), 8.05(1H, Benzyl), 7.98-6.54(14H, Ar-H). **Mass (EI-MS):** 412(M), 413(M+1), 411(M -1).

2c. IR, Cm^{-1} (KBr): 3303(-NH *Str*, NH), 3276(-NH *Str*, NH), 3053(-CH *Str*, aromatic), 2865(-CH *Str*, Benzyl), 1710(C=O *Str*), 1632(NO_2 *Str*), 1582(C=N *Str*), 1343(C-N *Str*). 1275(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 12.03(1H, -NH-CS), 11.65(1H, -NH-C_6H_5), 8.12(1H, Benzyl), 8.23-7.02(13H, Ar-H), 2.02(2H, -NH_2). **Mass (EI-MS):** 458(M), 459(M+1), 457(M -1).

2d. IR, Cm^{-1} (KBr): 3365(-NH *Str*, NH), 3272(-NH *Str*, NH), 3093(-CH *Str*, aromatic), 2939(-CH *Str*, aliphatic), 2798(-CH *Str*, Benzyl), 1702(C=O *Str*), 1587(C=N *Str*), 1343(C-N *Str*). 1265(C=S *Str*). **^{1}HNMR** (DMSO, δppm)**:** 12.98(1H, -NH-CS), 11.76(1H, -NH-C_6H_5), 8.23(1H, Benzyl), 8.03-6.93(13H, Ar-H), 2.56(6H, -OCH_3). **Mass (EI-MS):** 458(M), 459(M+1), 457(M -1).

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 (**Figure 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 **1a-1d** and **2a-2d** 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 and ^{1}H NMR data. The present work which involves reaction Synthesis of Benzoyl glycine derivatives involves the N-Benzoylation of equimolar quantities of substituted benzoyl chloride with glycine in the presence of aqueous NaOH (10%). Benzoyl glycine derivatives undergo Erlenmeyer condensation reaction with Substituted Benzaldehydes in the presence of acetic anhydride and anhydrous sodium acetate to yield Oxazoline-5-one derivatives. It undergoes dehydration reaction with thiosemicabazide and 1-pheny-3-thiosemicabazide to yield final compound. The Anthelmintic activity of all synthesized compounds was carried by using on Indian earthworms (Pheretima posthuma). And Albendazole used as standard drug. The structures of all the newly synthesized compounds were characterized as **1a-1d** and **2a-2d** on the basis of satisfactory analytical and spectral data including IR, LC-MASS and ^{1}H NMR data.

Table 1: Physical data of Novel Imidazole derivatives (1a-1d and 2a-2d)

All the Novel Imidazole derivatives are dissolved in ethanol and methanol and the TLC solvent system was Chloroform: methanol (9:1)

Code	R	R_1	R_2	Mol. Wt ($g.mol^{-1}$)	M.P (^0C)	% Yield
1a	H	H	H	322	110-112	72
1b	NH_2	NO_2	H	382	142-144	76
1c	H	H	CH_3	336	102-105	68
1d	NH_2	OCH_3	OCH_3	397	165-168	76
2a	H	$N(CH_3)_2$	H	441	152-154	74
2b	H	CH_3	H	412	128-130	80
2c	NH_2	NO_2	H	458	185-187	72
2d	H	OCH_3	OCH_3	458	168-170	78

Anthelmintic activity:

The synthesised compounds (**1a-1d and 2a-2d**) 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 the synthesized compound **1b, 1d** and **2d** showed good Anthelmintic activities whereas others showed significant activities. After all, the synthesized compounds in overall estimation confirm the better activity against *peritima posthuma.*

Table 2. Antihelmintic activity of novel Imidazole derivatives

S.No.	Name	Time in minutes					
		For paralysis % Concentration			For death % Concentration		
	Concentration	**0.1**	**0.2**	**0.5**	**0.1**	**0.2**	**0.5**
	Control	-	-	-	-	-	-
	Albendazole	15	12	8	44	34	26
1	**1a**	27	19	17	60	50	40
2	**1b**	**20**	**17**	**12**	**48**	**39**	**32**
3	**1c**	28	26	17	59	58	49
4	**1d**	**19**	**16**	**15**	**47**	**36**	**30**
5	**2a**	28	20	18	58	50	42
6	**2b**	22	20	18	61	59	53
7	**2c**	28	25	22	59	56	50
8	**2d**	25	20	20	53	40	38

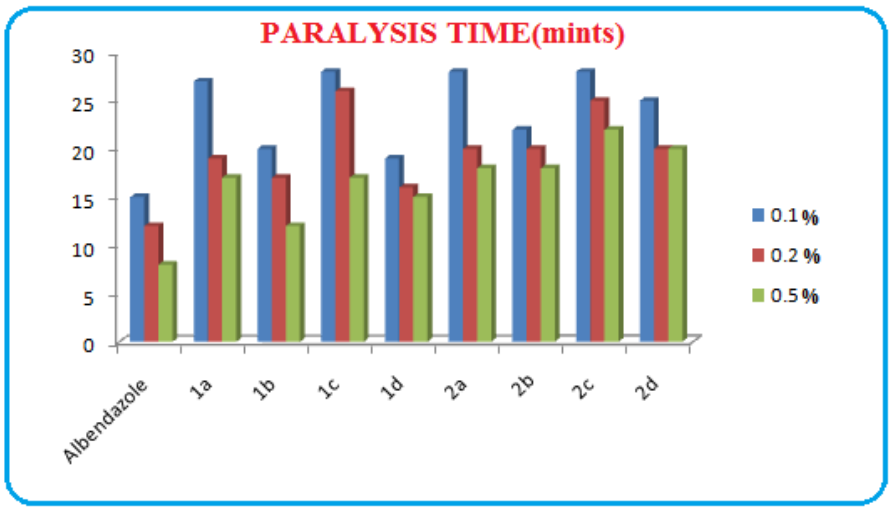


Figure 1: Graphical representation of anthelmentic activity of compounds (**1a-1d and 2a-2d**) – Paralysis time (min).

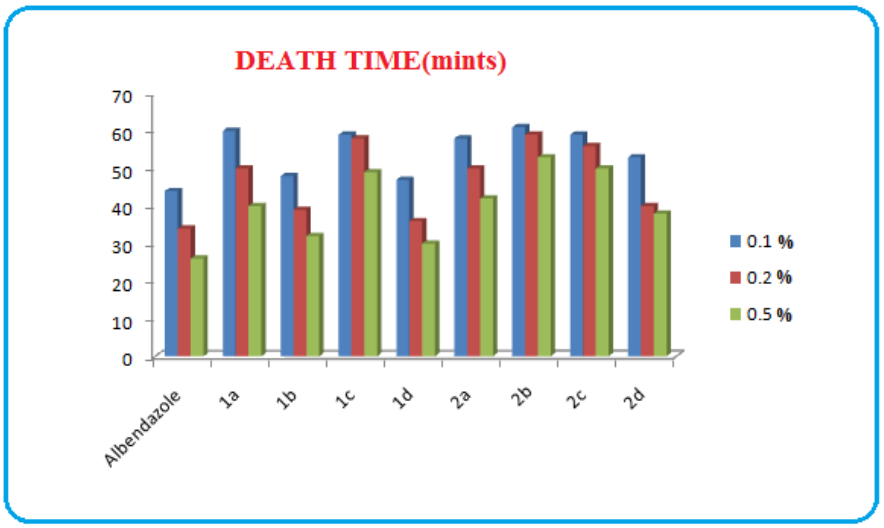


Figure 2: Graphical representation of anthelmintic activity of compounds (**1a-1d** and **2a-2d**) – Death time (min).

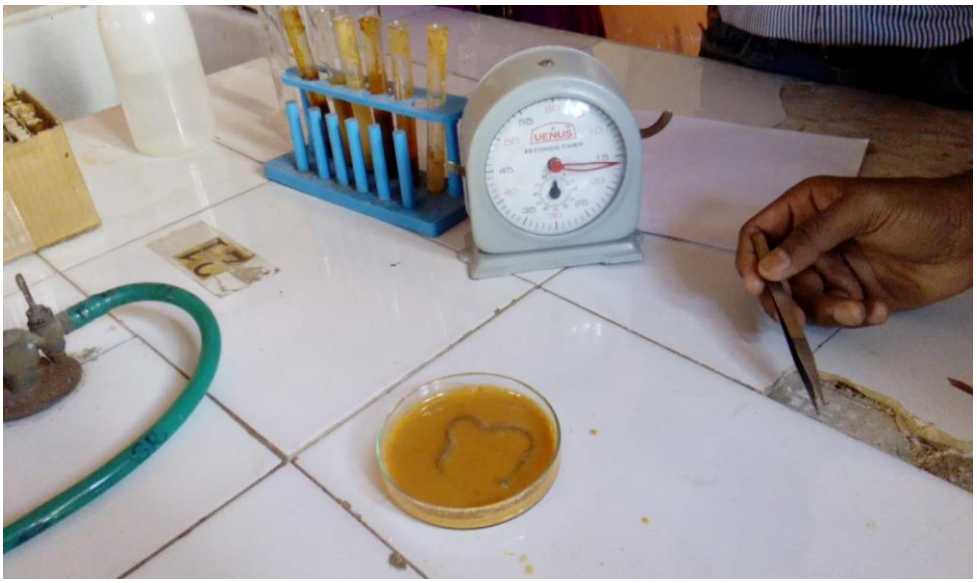


Fig.3: Photographs of various Novel Imidazole derivatives –Anthelmintic activity**.**

CONCLUSION:

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of Imidazole derivatives. The yield of the synthesized compounds was found to be in the range from 64-82 %. In conclusion, the present study highlights the importance of Imidazole 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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