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Synthesis and biological evaluation of new hydrazone

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Abstract

Synthesis of new hydrazone derivatives, starting from 2-(3,4-Dichloro-benzoyl)-benzoic acid to 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester than converted into 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide with substituted aromatic ketones. The structures of the newly synthesized compounds were confirmed by analytical and spectral analysis of IR, ¹H NMR and MASS spectroscopy. The in-vitro antibacterial screening of synthesized compounds was performed against the following standard bacterial strains *Escherichia coli* (MTCC 1573), and *Staphylococcus aureus* (MTCC 1430). Compound 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-bromo-phenyle)-ethylidene]-hydrazide (BP-10), gives the highest activity on *Escherichia coli* (MTCC 1573) and *Staphylococcus aureus* (MTCC 1430). The in-vitro anthelmintic activity was evaluated on Adult earthworms (*Pheretima posthuma*). Compound 2-(3,4-dichloro-benzoyl)-benzoic acid (2-oxo-1,2-diphenyl-ethylidene)-hydrazide (BP-7), and 2-(3,4-dichloro-benzoyl)-benzoic acid (2-oxo-1,4-chlorophenyle-ethylidene)-hydrazide (BP-13), gives the highest activity and other is gives the moderate activity against Adult earthworms (*Pheretima posthuma*).

Keywords: Hydrazone, antibacterial, anthelmintic, Ketones

1. Introduction

Hydrazones are standard compounds for drug technique, as attainable ligands for metal complexes, organ catalysis and as well for the synthesis of heterocyclic compounds [1]. The simplicity of analysis, improved hydrolytic strength virtual to mines, and affinity toward crystalline are the fascinating characteristics of hydrazones [2, 3]. Due to these affirmative traits, hydrazones have been beneath study for a long time, however abundant of their basic chemistry remains unknown [4]. Hydrazones a division of organic compounds having the basic structure $R_1R_2C=NNH_2$ [5, 6]. They are joined to aldehydes and ketones, by the substitute of the chemical element with the $-NNH_2$ cluster [7, 8]. They are resulting in the contraction of substitute of the chemical element with carbonyl compounds for the most part aldehydes and ketones [9]. They are fashioned by the action of reductant of ketones or aldehydes. Hydrazones are azomethines characterized by the presence of the tri atomic grouping $>C=N-N<$ [10, 11]. They are distinguished from alternative member of this category (imines, Oximes etc.) by the presence of the two inter joined ($-N-N-$) element atoms [12]. According to the wants of a polydentate matter, the cluster functionalities are increased by condensation and substitution [13, 14]. Hydrazones are typically named once the carbonyl compounds from that they are obtained [15]. They are necessary intermediates heterocyclic chemistry [16, 17]. Hydrazones moiety plays an anassociate degree necessary key role in heterocyclic chemistry. Hydrazones contain the universal formula specified under [18, 19].

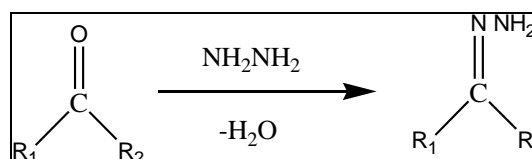


Fig 1: General formation and formula of hydrazones [20].

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2. Materials and Methods

All the chemicals and solvents, purchased from Merck (India), CDH, Sigma-Aldrich, Qualigens and S.D. Fine was used without further purification. The progress of reaction was monitored by thin layer chromatography performed on a silica gel coated slides. All melting points were determined by using open capillary melting point apparatus and uncorrected.

The $^1\text{H-NMR}$ spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m). All exchangeable protons were confirmed by addition of D_2O . The Perkin Elmer spectrum IR ES Version 10.6.0 was used for IR spectroscopy. Mass spectroscopy was recorded by ACQ Method.

2.1. Pharmacology

Anti-bacterial and Anthelmintic activity

2.1.1. Antimicrobial Activity

In vitro Antimicrobial Screening

The *in-vitro* antibacterial screening of synthesized compounds was performed against the following standard bacterial strains *Escherichia coli* (MTCC 1573) and *Staphylococcus aureus* (MTCC 1430), were used.

2.1.2 Preparation of inoculums

The gram positive *Staphylococcus aureus* (MTCC 1430) and gram negative bacteria *Escherichia coli* (MTCC 1573), were pre-cultured in agar medium in Petri dish after mixing the bacteria in distilled water. Poured it in agar medium and centrifuged it 48-72 hr at 35°C [21].

2.1.3 Cup-plate method

In to the fresh nutrient agar media (cooled at 40°C) a specific volume of the microbial suspension (inoculums) was poured and mixed thoroughly [22]. In the Petri plates about 20 ml of this suspension was poured aseptically and reserved till the solidification. Using a germ-free stopper bit on the surface of agar plates was pierced [23]. The primed wells were filled with an equal volume of a solution of synthesized compounds and standard drugs; separately [24, 25]. After a period of pre-incubation diffusion, the plates were incubated face up for a definite time about (48-72 hr) under specific conditions ($32-36^\circ\text{C}$) [26]. The zones of inhibition were calculated as parameters of antimicrobial properties of synthesized derivatives. The resulting compounds are shown in table-3.

2.1.4 Anthelmintic Activity.

Animal

Adult earthworms (*Pheretima posthuma*), were used to evaluate anthelmintic activity *in vitro*. Earthworms were collected from the S.D College of pharmacy & vocational studies muzaffarnagar in the month of July. The average size of earthworm was 6-8 cm.

2.1.5 Drug and chemical

Piperazine citrate was used as a standard drug in experimental protocol.

2.1.6 Anthelmintic Activity procedure

The anthelmintic assay was performed *in vitro* using adult earthworm (*Pheretima posthuma*) due to its physiological and anatomical similarity with the intestinal round worm parasites of human beings for start costing anthelmintic activity [27].

The test sample of the drug was prepared at different concentration, 10, 25, 50 mg/ml in DMSO. Containing six groups, each has six earthworms. Near about equal size of earthworm are placed in a Petri dish at room temperature ($20-25^\circ\text{C}$), after washing with normal saline to remove all facial matter, containing 25 ml of test solution of drug. Piperazine citrate is used as standard 10, 25 and 50 mg/ml in DMSO, distilled water was used as control. All test and standard solution were ready newly prior to the test. By the inspection time taken of paralysis was noted when no movement of any genus could be observed excluding when the worms were shaken vigorously. Times for death of worms were recorded after ascertaining that worms neither moved when shaken vigorously nor when dipped in warm water (50°C). All the results were shown in Table.4 and expressed as a mean \pm SEM of six worms in each group [28].

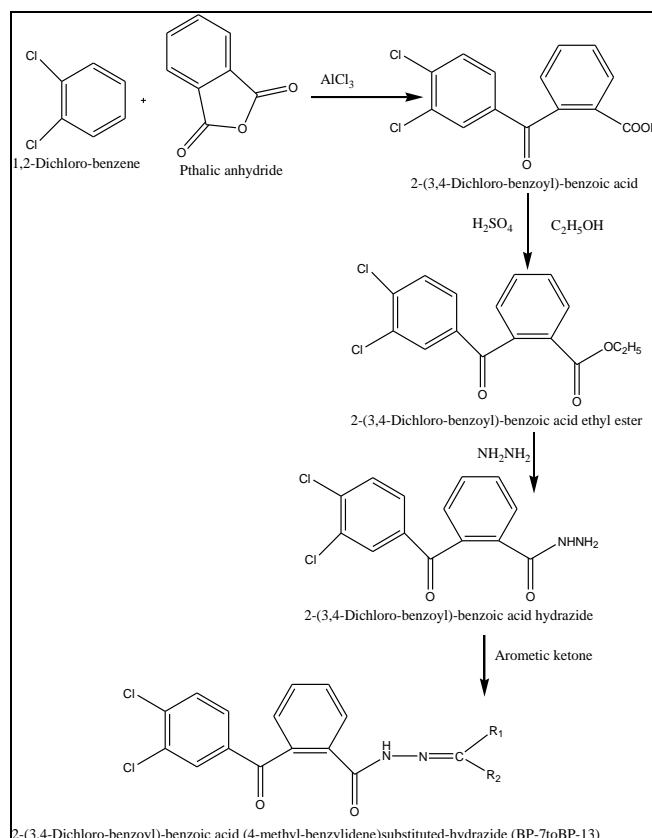
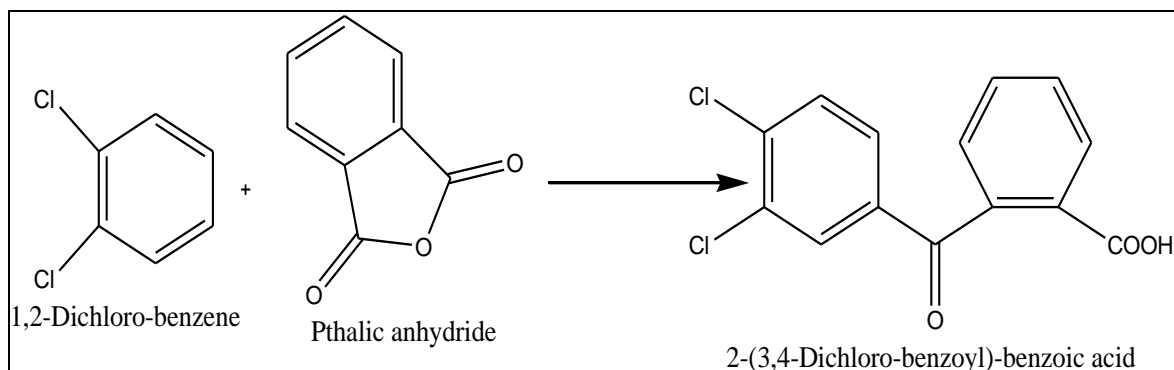


Fig 2: Synthetic Procedure For Hydrazone Derivatives [29].

Experimental

Step-1 Synthesis of 2-(3, 4-Dichloro-benzoyl)-benzoic acid

2-(3, 4-Dichloro-benzoyl)-benzoic acid was synthesized from respective phthalic anhydride dissolved in nitro benzene with heat and continuous stirring on magnetic stirrer then add Dichlorobenzene. Cool at room temperature and add Aluminum tri chloride with continuous stirring till the removal of HCL fumes. Then add water take it on distillation for the removal of nitro benzene, the clear solution cool and add diluted HCL. The white shiny 2-(3,4-Dichloro-benzoyl)-benzoic acid crystals were appeared.

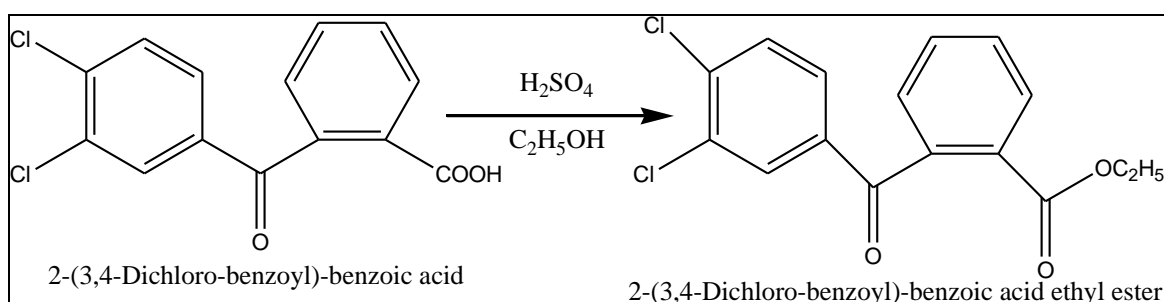


Step 1: Synthetic procedure

Step-2 Synthesis of 2-(3, 4-Dichloro-benzoyl)-benzoic acid ethyl ester

2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester was synthesized from their respective 2-(3,4-Dichloro-benzoyl)-

benzoic acid ethyl ester, using an excess of ethanol in the presence of H_2SO_4 under reflux for 20-24 hours, the white semisolid solution with fruity smell is prepared.

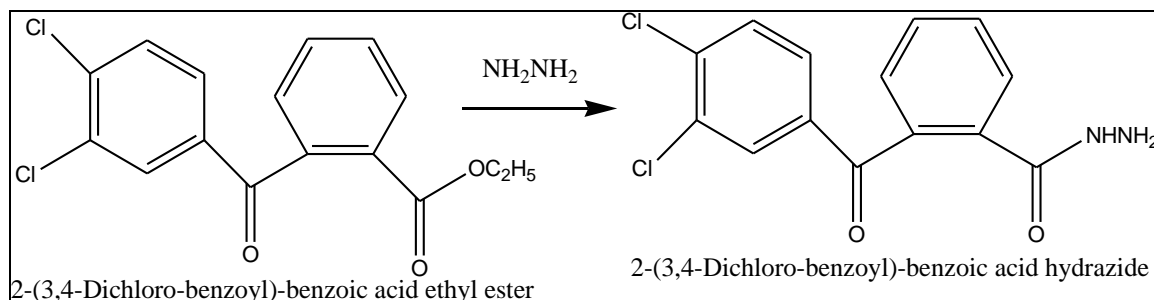


Step 2: Synthetic procedure

Step-3 Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide

Synthesis of 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide

from 2-(3,4-Dichloro-benzoyl)-benzoic acid ethyl ester with Hydrazine hydrate 99% in ethanol under reflux for 20-24 hours. The white semisolid solution has appeared.



Step 3: Synthetic procedure

Step-4 synthesis of hydrazones derivatives (BP-7-BP-13)

Synthesis of hydrazone derivatives from 2-(3,4-Dichloro-benzoyl)-benzoic acid hydrazide (0.1 mol) with different ketones (0.1 mol), add in 15ml ethanol and 15ml glacial acetic acid in 100 ml R.B.F refluxing for 45 min. Identify by TLC in benzene/acetone at every 20 min. pour in ice- cold water. The different color solid products were collected by filtration under suction. The product was re-crystallized in chloroform. The colored fine crystals were produced. All designed molecules are given in table no-1.

3. Results and Discussion**Compound characterization**

After synthesizing the designed compounds, percentage yield, retention factor (Rf), melting point and elemental analysis (CHNS analysis) were performed. The findings of physical and elemental data of the compounds are reported in Table 2.

Spectral characterization of 2-(3,4-dichloro-benzoyl)-benzoic acid (2-oxo-1,2-diphenyl-ethylidene)- substituted hydrazone

Compound no BP-7 2-(3,4-dichloro-benzoyl)-benzoic acid (2-oxo-1,2-diphenyl-ethylidene)-hydrazide

Mol. Formula - $C_{28}H_{18}Cl_2N_2O_3$, 1H NMR- ($CDCl_3$, 300MHz) 7.97-7.22(m, 17H, Ar-H) 4.40(S, 1H, N-H), IR- (KBr, cm-1) 1083 (C-Cl), 1352 (C-N), 1680 (C=O), MASS- [M+1] at m/z- 502.

Compound no BP-8. 2-(3,4-dichloro-benzoyl)-benzoic acid (2-hydroxy-1,2-diphenyl-ethylidene)-hydrazide

Mol. Formula- $C_{28}H_{20}Cl_2N_2O_3$, 1H NMR-($CDCl_3$, 300MHz) 7.99-7.22 (m, 17 H, -Ar-H) 4.38 (S, 1H, N-H), 4.88 (S, 1H, -OH), 2.63 (S, 1H, -CH), IR- (KBr, cm-1) 1085 (C-Cl), 1352 (C-N), 1685 (C=O).

Compound no BP-9. 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-methoxy-phenyle)-ethylidene]-hydrazide.

Mol. Formula- $C_{23}H_{18}Cl_2N_2O_3$, 1H NMR- ($CDCl_3$, 300MHz) 7.95-6.92 (m, 11 H, -Ar-H) 4.07 (s, 1H, N-H), 3.50 (s, 3H, -OCH₃), 2.1 (s, 3H, -CH₃), IR- (KBr,cm-1) 1081 (C-Cl), 1353 (C-N), 1686 (C=O).

Compound no BP-10. 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-bromo-phenyle)-ethylidene]-hydrazide

Mol. Formula- $C_{22}H_{15}Cl_2N_2O_3$, 1H NMR-($CDCl_3$, 300MHz)7.83-7.26 (m, 11 H, -Ar-H) 4.80 (s, 1H, N-H), 1.8 (s, 3H, -CH₃), IR- (KBr,cm-1) 1081 (C-Cl), 1353 (C-N), 1686 (C=O).

Compound no BP-11. 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-chloro-phenyle)-ethylidene]-hydrazide

Mol. Formula- $C_{22}H_{15}Cl_3N_2O_2$, 1H NMR-($CDCl_3$, 300MHz)7.90-7.25 (m, 11 H, -Ar-H) 4.38 (s, 1H, N-H), 1.37 (s, 3H, -CH₃), IR- (KBr,cm-1) 1084 (C-Cl), 1350 (C-N), 1684 (C=O).

3.1. Biological Evaluation of the prepared molecules

3.1.1. Antibacterial activity against gram negative bacteria *Escherichia coli*

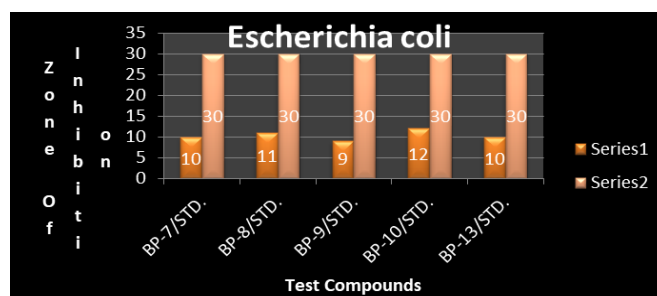


Fig 3: Antibacterial activity against gram negative bacteria *Escherichia coli* [30].

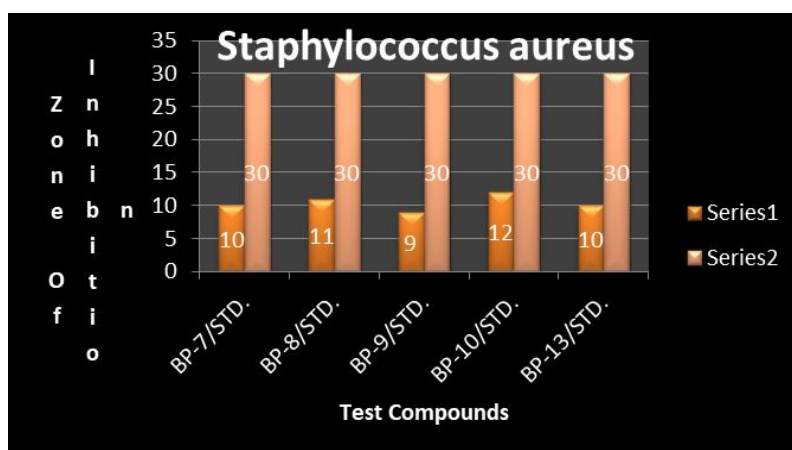
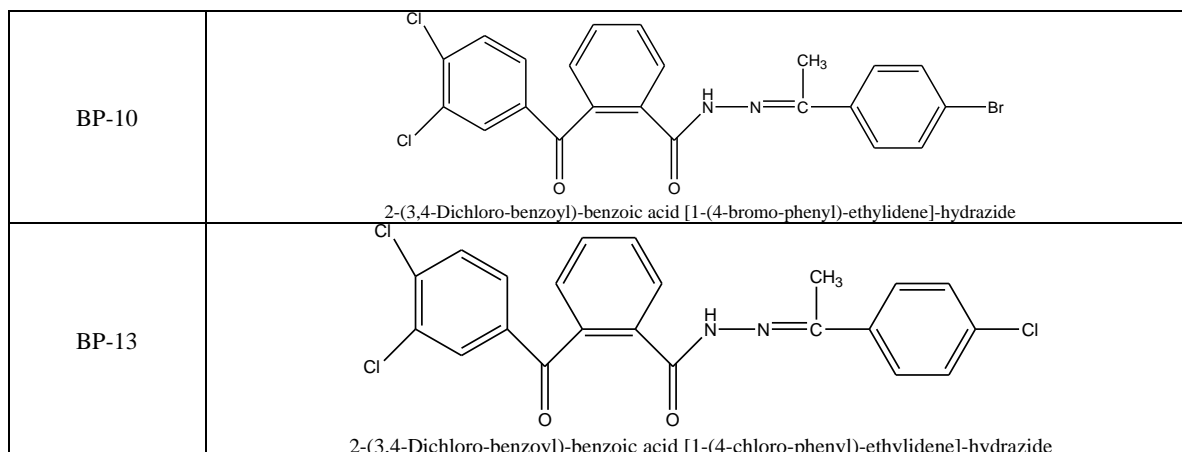


Fig 4: Antibacterial activity against gram positive bacteria *Staphylococcus aureus* [31].

A list of designed molecules has been shown in Table-1

Table 1: Designed molecules

Compounds	Structure
BP-7	
BP-8	2-(3,4-Dichloro-benzoyl)-benzoic acid (2-hydroxy-1,2-diphenyl-ethylidene)-hydrazide
BP-9	2-(3,4-Dichloro-benzoyl)-benzoic acid [1-(4-methoxy-phenyl)-ethylidene]-hydrazide

**Table 2:** Physical data of the compounds (BP 7-13).

Compounds	R ₁	R ₂	MP (°C)	R _f B:A (3:1)	Yield (%)	Mol. Formula (MW)
BP-7			144-146°C	0.85	50	C ₂₈ H ₁₈ Cl ₂ N ₂ O ₃ (501.36)
BP-8			132-136°C	0.54	45	C ₂₈ H ₂₀ Cl ₂ N ₂ O ₃ (503.38)
BP-9		CH ₃	138-140°C	0.74	49	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₃ (441.31)
BP-10		CH ₃	159-161°C	0.71	45	C ₂₂ H ₁₅ Cl ₂ N ₂ O ₃ (490.18)
BP-13		CH ₃	125-126°C	0.67	51	C ₂₂ H ₁₅ Cl ₃ N ₂ O ₂ (445.73)

Table 3: Anti-bacterial Activity (Zone of inhibition) of BP 7 to BP 13.

Compounds	Zone of inhibition (mm)	
	Gram negative bacteria	Gram positive bacteria
	Escherichia coli (MTCC-1573)	Staphylococcus aureus (MTCC-1430)
BP-7	10	10
BP-8	11	11
BP-9	09	09
BP-10	12	12
BP-13	10	10
Ofloxacin	30	30
Control	00	00

Table 4: Anthelmintic activity.

S.NO.	Groups	Concentration (mg/ml)	Earthworm (<i>Pheretimaposthuma</i>)	
			Time taken for paralysis (P) in min. (mean & seam)	Time taken for death (D) in min. (mean & seam)
01.	Control (water only)
02.	BP-7	10	33.5 ± 0.99**	63.33 ± 0.88**
		25	24.33 ± 1.23	47.5 ± 0.77
		50	13.5 ± 0.66	32.66 ± 0.88
03.	BP-8	10	38.5 ± 0.76	67.5 ± 0.76
		25	26.5 ± 0.76	52.5 ± 0.77
		50	13.8 ± 0.60	26.5 ± 0.76
04.	BP-9	10	44.6 ± 1.40	73.5 ± 0.78
		25	32.5 ± 0.75	67.5 ± 0.77
		50	13.33 ± 0.66	27.5 ± 0.76

05.	BP-10	10	47.66 ± 1.40	68.05 ± 1.11
		25	27.00 ± 1.73	33.00 ± 1.26
		50	14.00 ± 0.57	31.66 ± 1.43
06.	BP-13	10	33.00 ± 1.46**	62.00 ± 1.16**
		25	24.88 ± 1.13	31.83 ± 1.73
		50	15.83 ± 0.70	28.83 ± 1.72
07.	Piperazine citrate (standard)	10	22.5 ± 0.76***	63.5 ± 0.88***
		25	17.5 ± 0.75	32.5 ± 0.76
		50	12.5 ± 0.74	17.5 ± 0.75

Each value represents mean ± SEM (N=6).

4. Conclusions

All synthesized compounds displayed antibacterial activity and gives highest activity for both gram negative bacteria (*Escherichia coli* MTCC 1573), and gram positive bacteria (*Staphylococcus aureus* MTCC 1430). Compounds 2-(3,4-dichloro-benzoyl)-benzoic acid (2-oxo-1,2-diphenyl-ethylidene)-hydrazide (BP-7), 2-(3,4-dichloro-benzoyl)-benzoic acid (2-hydroxy-1,2-diphenyl-ethylidene)-hydrazide (BP-8), 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-methoxy-phenyle)-ethylidene]-hydrazide (BP-9), 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-bromo-phenyle)-ethylidene]-hydrazide (BP-10), 2-(3,4-dichloro-benzoyl)-benzoic acid [1-(4-chloro-phenyle)-ethylidene]-hydrazide (BP-9), gives the good anthelmintic activity.

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