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RESEARCH PAPER

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME IMIDAZOLE BEARING HYDRAZONES AS POSSIBLE ANTIMICROBIAL AND ANTHELMINTIC AGENTS

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Hydrazones have been of considerable scientific interest due to their momentous biological activities. A number of imidazole bearing hydrazone derivatives were synthesized and characterized in the present investigation. Synthetic protocols were undertaken to react benzil with benzaldehyde and ammonium acetate in the presence of sulphanilic acid as catalyst to yield suitable imidazoles. Further, in the proceeding steps, reactions of imidazole were carried out to yield ester, then hydrazide and finally the hydrazone derivatives. Spectral methods were used to characterize the synthesized compounds appropriately. The synthesized hydrazones were screened for antibacterial, antifungal, anthelmintic activities. Most of the synthesized compounds showed moderate to good biological activities.

Key words: Imidazoles, Hydrazides, Hydrazones, Antimicrobial activity, Anthelmintic activity.

INTRODUCTION

A wide variety of antibiotics have been developed to combat against bacterial infections. But unfortunately, in the absence of an effective platform for antibiotic discovery and after years of misuse and overuse of antibiotics in humans and animals, bacteria are becoming antibiotic resistant. The fast resistance of bacteria against antibiotics has become a prevailing medical problem over the world (Desai *et al* 2014; Abdel-Aziz *et al* 2015). Treatment options for these infections are often insufficient particularly in immune compromised patients. In the past few decades, the extremely increasing multi-drug resistant microbial infections have become a serious health issue. The discovery of novel antimicrobial compounds still remains a challenging task to the medicinal chemistry research scientists (Kethireddy *et al* 2015).

In the field of heterocyclic chemistry, nitrogen containing heterocyclic compounds such as imidazoles have occupied an inimitable position due to their versatile properties in chemistry and pharmacology and their presence in, pharmaceuticals and natural products (Dahiya and Pathak, 2007; Dahiya, 2008; Dahiya *et al* 2008; Mehta and Pathak, 2011; Kumar, 2011; Verma *et al* 2013). Imidazole nucleus is privileged scaffold commonly found in biomolecules and amino acids such as biotin, purine, pilocarpine, histamine, histidine alkaloids, and other alkaloids (Vichier-Guerre *et al* 2014; Patel *et al* 2014; Tang *et al* 2014). These compounds possess various biological activities such as nitric-oxide synthase inhibition, antidepressant, anti-parasitic, antifungal,

anti-inflammatory, antiviral, antibacterial, antitubercular, antiallergic, anticancer, anti-helmintic, antiprotozoal, analgesics activities (Jourshari *et al* 2013; Ziarani *et al* 2015; Sharma *et al* 2016a). Therefore, synthesis of substituted imidazoles has attracted considerable interest in recent years and a large number of novel chemotherapeutic agents have been developed by medicinal chemists to largely exploit this versatile motif (Verma *et al* 2013).

Hydrazides and hydrazones have been considered as a category of unique compounds for the discovery of innovative therapies due to their significant pharmacological and biological activities. Nifuroxazide, verazide and salinazid are examples of hydrazone-containing antibacterial and antimycobacterial drugs which have been clinically approved. Moreover, isonicotinoyl hydrazide (INH) and its isonicotinoyl hydrazone analogs, are well-established antitubercular agents, which are related to the hydrazide class. INH also exhibits bacteriostatic effects on bacillus (Abdel-Aziz *et al* 2015; Rollas and Kucukguzel, 2007). Hydrazones and their derivatives have been demonstrated to possess interesting diverse biological activities like antioxidant, antimicrobial, anticancer, anticonvulsant, analgesic, antiprotozoal, cardioprotective, antiparasitic, antidepressant, anti-HIV, anti-inflammatory, antitubercular and trypanocidal etc (Rollas and Kucukguzel, 2007). Hydrazones are also emerging as moiety of interest in medical biotechnology (Kajal *et al* 2014).

In continuation to our interest (Kumar *et al* 2011; Sharma *et al* 2011) in this field, recently we have reported synthesis and biological evaluation of some thiazolidin-4-ones as possible antimicrobial and anthelmintic agents (Sharma *et al* 2016b). All the synthesized compounds have depicted moderate to good biological activities. These findings prompted us to evaluate the hydrazones obtained in the previous step employing the same synthetic methodology. Hence, in this paper, we report synthesis of some imidazolyl hydrazone derivatives and their biological evaluation for antibacterial, antifungal and anthelmintic activities.

EXPERIMENTAL

Chemistry

All the chemicals and solvents used in this study were procured from SD Fines (Mumbai, India) and Qualigens (Navi Mumbai, India), Himedia (Mumbai, India). Labindia MR-VIS visual melting range apparatus was used to determine melting points. The IR spectra were obtained on a Perkin Elmer IR spectrophotometer (potassium bromide disk). 1H NMR spectra were recorded using a Bruker Avance II 400 spectrometer (Fallanden, Switzerland) and chemical shifts are expressed as δ (ppm) with tetramethylsilane as an internal standard. Mass spectra were recorded on Waters Q-TOF micro mass spectrometer (Manchester, UK), using electron spray ionisation method.

General procedure for the synthesis of title compounds

2,4,5-Triphenyl-1H-imidazoles (1)

A mixture of benzil (10 mmol, 2.10 g) with benzaldehyde (10 mmol, 1.3 ml), ammonium acetate (40 mmol, 3.08 g) and sulphanilic acid (10 mol%, 1.73 g) as catalyst in the presence of ethanol (20 ml) were refluxed in a round bottom flask at 80°C for 2 h. The completion of reaction was checked by thin layer chromatography (TLC) by using silica gel G as stationary phase and using appropriate solvent system. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 ml) to get the solid precipitates. It was collected by filtration, washed with cold water and recrystallized with ethanol.

2,4,5-Triphenyl-1H-imidazolyl esters (2)

Refluxing of 2,4,5-triphenyl-1*H*-imidazole **1** (10 mmol) with ethyl chloroacetate (12 mmol, 1.2 ml) in the presence of 3% sodium hydroxide (10 ml) and ethanol (15 ml) in round bottom flask at 80°C for 8 h yielded the 2,4,5-triphenyl-1*H*-imidazolyl ester. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 ml) to get the solid precipitates as product which was then collected by filtration, washed with cold water and recrystallized with ethanol.

2,4,5-Triphenyl-1H-imidazolyl hydrazide (3)

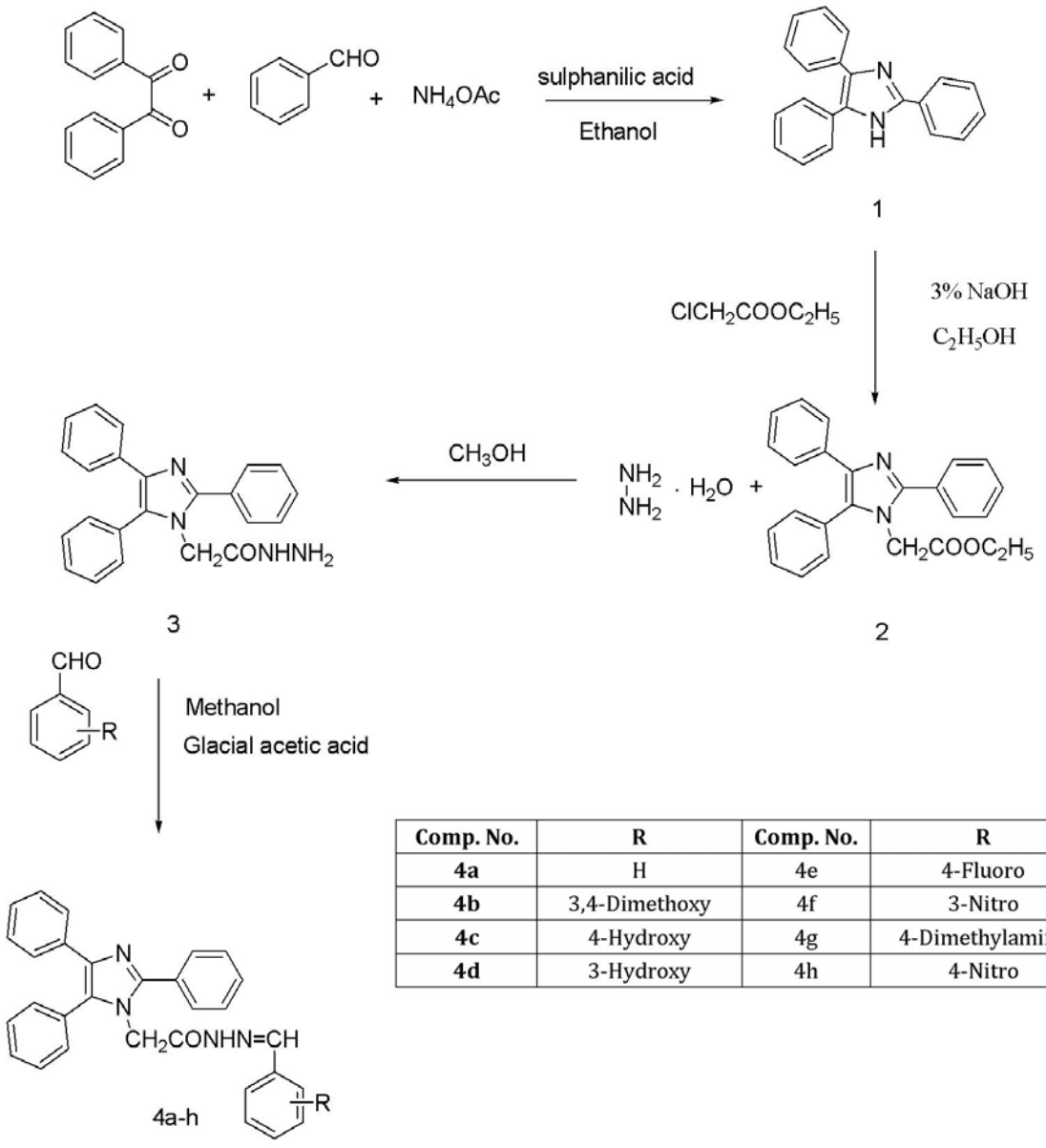
The synthesis of title compound was carried out by refluxing 2,4,5-triphenyl-1*H*-imidazolyl ester **2** (10 mmol) with hydrazine hydrate (0.1 mol, 5 ml) in the presence of methanol (15 ml) in round bottom flask at 80°C for 6 h. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 ml) to get the solid precipitates as product. It was collected by filtration, washed with cold water and recrystallized with ethanol.

2,4,5-Triphenyl-1H-imidazolyl hydrazones (4a-h)

For synthesis of 2,4,5-triphenyl-1*H*-imidazolyl hydrazones, heating under reflux was done for a mixture of 2,4,5-triphenyl-1*H*-imidazolyl hydrazide (10 mmol) with different substituted aldehydes (10 mmol) in the presence of small amount of glacial acetic acid and methanol (15 ml) in a round bottom flask at 80°C for about 2 h.

The mixture was cooled and poured in 50 ml of ice cold water. The solid thus obtained was separated by filtration and recrystallized appropriately.

Synthetic steps for preparation of title compounds are shown in **Scheme 1**.



Comp. No.	R	Comp. No.	R
4a	H	4e	4-Fluoro
4b	3,4-Dimethoxy	4f	3-Nitro
4c	4-Hydroxy	4g	4-Dimethylamino
4d	3-Hydroxy	4h	4-Nitro

Scheme 1. Synthetic scheme for preparation of compounds **4a-h**

Spectral Characterization of synthesized compounds

N'-benzylidene-2-(2,4,5-triphenyl-1H-imidazol -1yl) acetohydrazide (4a)

Yield 75%; m.p. 212-214°C; IR (cm^{-1}, KBr): 3260 (N-H of -CONH), 3070 (C-H of aromatic), 1665 (C=O of -CONH), 1460 (C=N); ^{1}H NMR (DMSO-d_6): 4.28 (2H, s, NCH_2), 7.25-8.17 (20H, m, aromatic), 8.29 (1H, s, N=CH), 8.60 (1H, s, CONH).

N'-(3,4-Dimethoxybenzylidene)-2-(2,4,5-tri-phenyl-1H-imidazol-1yl)acetohydrazide (4b)

Yield 80%; m.p. 158-160°C; IR (cm^{-1}, KBr): 3268 (N-H of -CONH), 3063 (C-H of aromatic), 1667 (C=O of -CONH), 1445 (C=N); ^{1}H NMR (DMSO-

d_6): 3.59 (6H, s, OCH_3), 4.25 (2H,s, NCH_2), 6.90-8.01 (18H, m, aromatic), 8.32 (1H, s, N=CH), 8.55 (1H, s, CONH).

N'-(4-Hydroxybenzylidene)-2-(2,4,5-triphenyl-1H-imidazol-1yl)acetohydrazide (4c)

Yield 72%; m.p. 202-206°C; IR (cm^{-1}, KBr): 3265 (N-H of -CONH), 3198 (OH), 3027 (C-H of aromatic), 1643 (C=O of -CONH), 1445 (C=N); ^{1}H NMR (DMSO-d_6): 4.23 (2H, s, NCH_2), 7.15-8.24 (19H, m, aromatic), 8.28 (1H, s, N=CH),8.49 (1H s, CONH), 9.24 (1H, s, OH).

N'-(3-Hydroxybenzylidene)-2-(2,4,5-triphenyl-1H-imidazol-1yl)acetohydrazide (4d)

Yield 75%; m.p. 213-217°C; IR (cm^{-1}, KBr): 3233 (N-H of -CONH), 3194 (OH), 3012 (C-H of aromatic), 1657 (C=O of -CONH), 1445 (C=N); ^{1}H NMR (DMSO-d_6): 4.24 (2H, s, NCH_2), 7.15-8.26 (19, m, aromatic), 8.35 (1H, s, N=CH), 8.63 (1H, s, CONH), 9.31 (1H, s, OH).

N'-(4-Fluorobenzylidene)-2-(2,4,5-triphenyl-1H-imidazol-1yl)acetohydrazide (4e)

Yield 70%; m.p. 138-140°C; IR (cm^{-1}, KBr): 3252 (N-H of -CONH), 3029 (C-H of aromatic), 1638 (C=O of -CONH), 1427 (C=N), 1109 (C-F); ^{1}H NMR (DMSO-d_6): 4.17 (2H, s, NCH_2), 7.15-8.19 (19H, m, aromatic), 8.31 (1H, s, N=CH),8.85 (1H, s, CONH).

N'-(3-Nitrobenzylidene)-2-(2,4,5-triphenyl-1H-imidazol-1yl)acetohydrazide (4f)

Yield 68%; m.p. 260-262°C; IR (cm^{-1}, KBr): 3252 (N-H of -CONH), 3014 (C-H of aromatic), 1643 (C=O of -CONH), 1439 (C=N) 1378 (NO_2); ^{1}H NMR (DMSO-d_6): 4.19 (2H, S, NCH_2), 7.12-8.25 (19H, m, aromatic), 8.27 (1H, s, N=CH), 8.71 (1H, s, CONH).

N'-(4-Dimethylaminobenzylidene)-2-(2,4,5-triphenyl-1H-imidazol-1yl)acetohydrazide (4g)

Yield 64%; m.p. 142-146°C; IR (cm^{-1}, KBr): 3261 (N-H of -CONH), 3035 (C-H of aromatic), 1652 (C=O of -CONH), 1452 (C=N); ^{1}H NMR (DMSO-d_6): 2.53 (6H, s, CH_3), 4.21 (2H, s, NCH_2), 6.95-8.11 (19H, m, aromatic), 8.33 (1H, s, N=CH), 8.67 (1H, s, CONH).

N'-(4-Nitrobenzylidene)-2-(2,4,5-triphenyl-1H-imidazol-1yl)acetohydrazide (4h)

Yield 67%; m.p. 245-250°C; IR (cm^{-1}, KBr): 3263 (N-H of -CONH), 3022 (C-H of aromatic), 1645 (C=O of -CONH), 1462 (C=N) 1359 (NO_2); ^{1}H NMR (DMSO-d_6): 4.24 (2H, s, NCH_2), 7.01-8.15 (19H, m, aromatic), 8.31 (1H, s, N=CH), 8.57 (1H, s, CONH).

BIOLOGICAL EVALUATION

Evaluation of antimicrobial activity

Procurement and maintenance of test pathogens

Human pathogenic bacterial and fungal microorganisms were purchased from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh. The tested pathogens include two Gram positive bacteria *Staphylococcus aureus* (MTCC 7443), *Bacillus subtilis* (MTCC 121); two Gram negative bacteria *Escherichia coli* (MTCC 40) and *Pseudomonas fluorescens* (MTCC 1748); two fungal pathogens *Candida glabrata* (MTCC3814), *Candida albicans* (MTCC 227). All pathogenic microorganisms were preserved in slants of brain heart infusion agar at 4°C in the refrigerator for future use. *For standardization of inoculums*, pathogenic microorganisms were grown for 24 h, in LBB medium and adjusted at a concentration according to 0.5 McFarland standards. McFarland standards are used to adjust the turbidity of bacterial suspensions to obtain a required population of cells in broth medium. McFarland standards were prepared by mixing 0.05 ml of 1.175% barium chloride dihydrate ($BaCl_2.2H_2O$), with 9.95 ml of 1% sulfuric acid (H_2SO_4) together. The reaction between these two compounds resulted in barium sulfate precipitate, which causes turbidity in the solution. The standard could be compared visually to a suspension of bacteria in sterile saline or nutrient broth (Andrews, 2001).

Determination of antimicrobial activity

Antibacterial and antifungal activities of the synthesized compounds were tested using agar well diffusion method (Andrews, 2001). For this purpose, 100 μl of test pathogen (bacterial or fungal species) was aseptically introduced and spread using cotton swabs on surface of gelled sterile Muller Hilton agar plates. A well of about 6.0 mm diameter with sterile cock borer was aseptically punched on each agar plate. Test compounds (100 μl, 2mg/ml) were introduced into the wells in the plates. Another well was used for filling DMSO as a negative control. Positive control was made by placing antibiotic disc (erythromycin) on agar plate. Plates were kept in laminar flow for 30 min for pre diffusion of compounds to occur and then for bacteria, the inoculated plates were incubated for 24 h at

37°C and, for fungi, the inoculated plates were incubated for 48 h at 25°C. Clear inhibition zones around discs indicated the presence of antimicrobial activity. For optimal fidelity of results, each assay was repeated three times. The diameter of resulting zone of inhibition were measured in terms of millimetre (mm.) using a Hi-media zone scale. The antimicrobial action was assessed by the diameter (mm) of growth inhibition zones and compared with commercially available antibacterial and antifungal agents like erythromycin and fluconazole. Results of antimicrobial activity of the synthesized compounds are given in **Table 1**.

Table 1. Antimicrobial activity of synthesized compounds

Compound No.	Antibacterial Activity (Zone of inhibition in mm)				Antifungal Activity	
	Gram Positive Bacteria		Gram Negative Bacteria			
	Staphylococcus aureus (MTCC 7443)	*Bacillus subtilis* (MTCC 121)	*Pseudomonas fluorescens* (MTCC 1748)	*Escherichia coli* (MTCC 40)	*Candida albicans* (MTCC 227)	*Candida glabrata* (MTCC 3814)
4a	12.5±0.4	12.9±0.4	ND	ND	17.9±1.6	15.4±0.5
4b	14.1±1.1	13.5±0.5	ND	21.7±1.5	16.1±0.8	14.1±0.9
4c	18.4±0.4	15.8±0.3	17.1±1.6	17.7±0.6	17.4±1.2	16.8±1.2
4d	21.1±0.3	18.1±1.3	16.5±1.4	16.9±0.8	20.4±1.4	21.8±0.5
4e	ND	ND	13.0±0.8	14.5±0.5	ND	ND
4f	16.7±0.7	18.1±1.6	18.2±1.2	20.1±0.9	19.2±1.5	15.9±0.7
4g	15.4±0.7	17.6±0.9	21.0±0.8	21.2±0.7	22.4±0.8	20.8±0.9
4h	21.3±0.6	19.8±1.2	28.3±1.1	24.3±0.9	19.2±1.3	17.5±1.3
Positive control*	24.4±0.4	33.4±0.5	32.3±0.3	29.0±0.5	-	-
Positive control**	-	-	-	-	25.7±0.4	26.4±0.4
Negative control***	0	0	0	0	0	0

*Standard Antibacterial Drug Ciprofloxacin (15 *µ*g disc) **Standard Antifungal Drug Fluconazole (10 *µ*g disc)
***DMSO Data given as Mean±S.E.M. (n=3)

Evaluation of anthelmintic activity

For the experimentation purpose, required number of groups consisting of six Indian earthworms (*Pheretima postuma)* each of nearly equal size (8±1cm) in length and 0.1-0.2 cm in width) were taken and washed with normal saline to remove all faecal materials. They were placed in standard drug solution and test compounds solutions taken in Petri dish (4" size) at room temperature. Earthworms tested in normal saline were taken used as a control group. The standard drug and test compounds were dissolved in minimum quantity of dimethyl sulfoxide (DMSO) and adjusted the volume up to 15 ml with normal saline solution to get the concentration of 0.15% *w/v* and 0.3% *w/v*. Piperazine citrate 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. The time taken by worms to become motionless was noted as paralysis time and death time was the time when they died. To ascertain the death of the motionless worms, they were immersed in the water at 50°C, which stimulate and induce movement in the worms, if alive. The failure of earthworms to respond to this stimulus was considered as the death time (Chaluvaraju and Bhat, 2011). The lethal time and paralysis time of the earthworms for different test compounds and standard drug are given in **Table 2**.

RESULTS AND DISCUSSION

All the hydrazones reported in the present investigation have been synthesized by adopting suitable synthetic chemical procedures. Reaction between aromatic aldehydes and benzil produced triphenyl imidazole which was further reacted with ethylchloroacetate to yield the corresponding ester. This ester was treated with excess of hydrazine hydrate to yield the imidazolyl hydrazide. Finally, reaction of this hydrazide with different substituted aromatic

Table 2. Anthelmintic activity of synthesized compounds

Compound No.	Concentration (150 mg/dl)		Concentration (300 mg/dl)	
	Time in min		Time in min	
	For Paralysis	For Death	For Paralysis	For Death
4a	69.6±1.3	77.5±1.2	57.8±0.9	60.5±1.2
4b	ND	ND	ND	ND
4c	ND	ND	ND	ND
4d	45.2±1.4	68.8±1.4	40.3±1.1	55.4±0.9
4e	45.9±1.5	75.4±1.3	39.4±1.5	65.7±1.3
4f	55.6±1.2	71.3±0.9	46.8±1.3	59.2±0.9
4g	45.4±0.9	71.2±0.9	41.9±1.2	68.4±0.9
4h	47.9±1.4	75.7±0.8	35.2±0.5	65.1±1.1
Control	–	–	–	–
Piperazine citrate	28.5±0.3	37.1±0.7	17.9±0.3	28.2±0.5

*Data given as Mean+S.E.M. (n=6)

aldehydes yielded the title compounds which were characterized by appropriate spectral techniques such as IR and NMR. In the IR spectra peaks observed in the range of 1427cm^{-1} to 1462 cm^{-1} confirmed the presence of C=N. In proton NMR spectra peak at around 8.49 to 8.85 confirmed the presence of CONH group in the title compounds. These hydrazones were tested for antibacterial and antifungal activities using agar well diffusion method and their zone of inhibition was determined against two Gram positive, two Gram negative and two fungal strains. The synthesized compounds have demonstrated moderate anthelmintic activities. At 300 mg/dl concentration, compound **4h** showed most effective paralysis time of 35.2±0.5 min. Compound **4d** was observed to be most potent in causing death of these organisms with mean death time of 55.4±0.9 at this concentration. It was followed by compound no. **4f** with mean death time of 59.2±0.9. Interesting antimicrobial activity profile has also been observed with these compounds. Antibacterial activity data suggested that the electron withdrawing group nitro bearing compound **4h** was most active against Gram positive bacterial strain *S. aureus* (zone of inhibition 21.3±0.6) and *B. subtilus* (zone of inhibition 19.8±1.2). Interestingly, this compound was also found to be most active against tested Gram negative bacterial strains *E. coli* and *P. fluorescens* with zone of inhibition 24.3±0.9 and 28.3±1.1 mm respectively. Compound **4e** was found inactive against Gram positive bacterial strains and compound **4a** with no substitution was observed to be inactive against tested Gram negative bacterial strains. Compound **4g** with a dimethyl amino substitution demonstrated most potent zone of inhibition of 22.4±0.8 against *C. albicans* followed by compound **4d** with a hydroxy substitution which was found most active against another fungal strain *C. glabrata* with zone of inhibition 21.8±0.5 mm.

CONCLUSION

Synthesis of some triphenyl imidazole clubbed hydrazone derivatives has been described in this paper. All the synthesized compounds were characterized by suitable methods. The compounds have been screened for antibacterial, antifungal and anthelmintic activities. Some of the synthesized compounds have shown promising potential and can further be explored for their anti-infective activities.

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