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Synthesis, spectral characterization and anthelmintic evaluation of some novel imidazole bearing triazole derivatives

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ABSTRACT

A new series of imidazole containing triazole derivatives ***(7a-7o)*** *was synthesized with the help of different chemical reactions consisting of formation of ester, hydrazide and thiosemicarbazide derivatives of 2,4,5-trisubstituted-1H-imidazoles* ***(2a-2e)****. The proposed structures of newly synthesized compounds were characterized by elemental analysis, IR, NMR and mass spectral data. All the synthesized compounds were screened for their anthelmintic activity against Indian adult earthworms (pheretima posthuma) at different concentrations of 0.150% and 0.300% w/v by using albendazole as standard drug. Most of the compounds of this series have shown reasonable anthelmintic potential when compared with standard drug.*

Keywords: 2,4,5-Trisubstituted-1*H*-imidazole, 1,2,4-triazole, anthelmintic activity.

INTRODUCTION

Helminthic infections like gastrointestinal disturbance (dysentery) and filariasis caused by parasitic warms (helminths) are claiming worldwide deaths of patients and this condition has become more severe because of resistance and availability of very small range of anthelmintics mainly including albendazole and mebendazole [1]. Anthelmintics are drugs that expel parasitic worms (helminths) from the body either by stunning or killing them but treatment with albendazole or mebendazole may show serious side effects in hosts such as epigastric pain, diarrhea, nausea, vomiting, headache, dizziness, edema, rashes and urticaria [2]. These anthelmintic drugs are contraindicated for some patients like pregnant and lactating woman because of low safety profile. Therefore it is the need of hour to synthesize some novel anthelmintic agents to overcome resistance and side effects for safe and effective treatment of anthelmintic infections [3-5].

Literature survey of most recent studies on imidazole and triazole heterocyclic nuclei has proved them to be versatile heterocyclic nuclei having a myriad spectrum of pharmacological activities like anthelmintic, antibacterial, antifungal, antioxidant, anti-inflammatory, anticancer and antiviral activities [6-8]. Keeping in view of these valid observations, it was found significant to club imidazole and triazole nuclei in a single drug molecule by synthesis to ensure their synergistic pharmacological activity thereby reducing dosing frequency, side effects and improving patient compliance which forms the basis of our present research work comprising of synthesis and anthelmintic evaluation of some novel imidazole substituted triazole derivatives in search of better and safer anthelmintic agents.

MATERIALS AND METHODS

Thin layer chromatography was performed on silica plates pre-coated with Merck Silica Gel 60 F254 and column chromatography with silica gel using UV lamp or iodine vapors as visualizing agent to check the progress of reactions. Melting points of synthesized compounds were determined with a Buchi 530 melting point apparatus in an open capillary tube and are uncorrected. Infrared spectra were recorded in KBr pellets on Bruker FTIR. The ^{1}H-NMR spectra were measured in DMSO-d_6 solution on a Bruker DRX-300 MHz spectrometer by using tetramethyl silane (TMS) as an internal reference (chemical shift in δ, ppm). The mass spectra were recorded on a Shimadzu 2010A LC-MS spectrometer. Elemental analyses were realized using Perkin-Elmer 240 elemental analyzer and were in the range of ± 0.4% for each element analyzed. All the chemicals and solvents used for experimental work were supplied by Sigma-Aldrich, Thomas Baker, CDH, E. Merck and S. D. Fine chemicals limited, India.

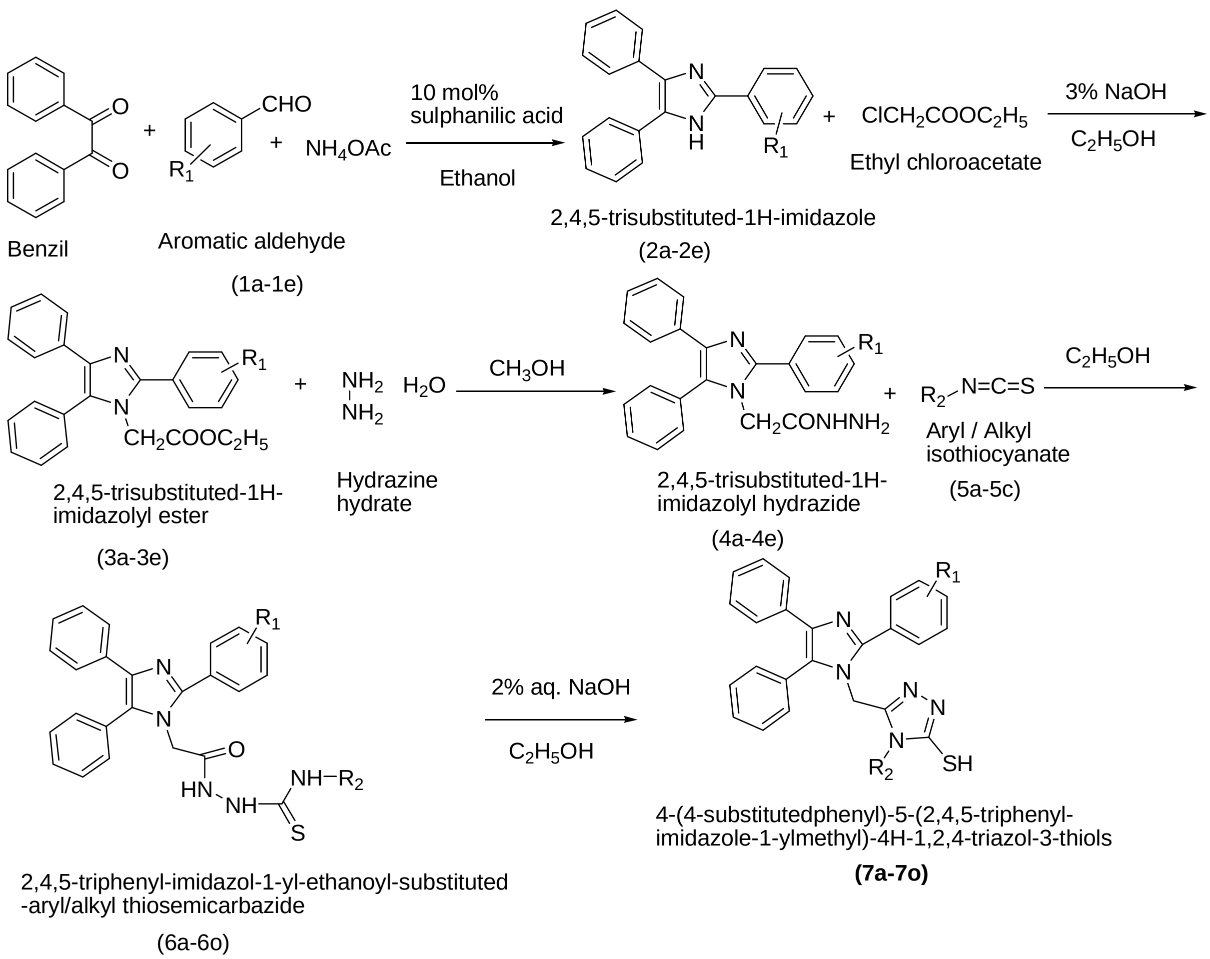
Experimental
All the titled compounds were synthesized by following the scheme of reactions as shown in **Figure 1** and general procedures about all steps involved in synthesis of imidazole substituted triazole derivatives.

General procedure for synthesis of 2,4,5-trisubstituted-1*H*-imidazoles, 2a-2e :
The synthesis of 2,4,5-trisubstituted-1*H*-imidazoles **(2a-2e)** was carried out by refluxing benzil (10 mmol, 2.10 gm) with different aromatic aldehydes **(1a-1e)** (12 mmol), ammonium acetate (40 mmol, 3.08 gm) and sulphanilic acid (10 mol%, 1.73 gm) catalyst in the presence of ethanol (20 mL) in round bottom flask at 80°C for 2 hours. The completion of reaction was checked by Thin Layer Chromatography (TLC) by using silica gel G as stationary phase and solvent system having solvents toluene, ethyl acetate and formaldehyde in ratio 4:4:2. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 mL) to get the solid precipitated. It was collected by filtration, washed with cold water and recrystallized with ethanol.

General procedure for synthesis of 2,4,5-trisubstituted-1*H*-imidazolyl esters, 3a-3e:
The synthesis of 2,4,5-trisubstituted-1*H*-imidazolyl esters **(3a-3e)** was carried out by refluxing different 2,4,5-trisubstituted-1*H*-imidazole derivatives **(2a-2e)** (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 hours. The completion of reaction was checked by Thin Layer Chromatography (TLC) by using silica gel G as stationary phase and solvent system having solvents toluene, ethyl acetate and formaldehyde in ratio 4:4:2. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 mL) to get the solid precipitated. It was collected by filtration, washed with cold water and recrystallized with ethanol.

General procedure for synthesis of 2,4,5-trisubstituted-1*H*-imidazolyl hydrazides, 4a-4e:
The synthesis of 2,4,5-trisubstituted-1*H*-imidazolyl hydrazides **(4a-4e)** was carried out by refluxing different 2,4,5-trisubstituted-1*H*-imidazolyl ester derivatives **(3a-3e)** (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 hours. The completion of reaction was checked by Thin Layer Chromatography (TLC) by using silica gel G as stationary phase and solvent system having solvents toluene, ethyl acetate and formaldehyde in ratio 4:4:2. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 mL) to get the solid precipitated. It was collected by filtration, washed with cold water and recrystallized with ethanol.

General procedure for synthesis of 2,4,5-triphenyl-imidazol-1-yl-ethanoyl-substituted-aryl/alkyl thio - semicarbazides, (6a-6o):
The synthesis of 2,4,5-triphenyl-imidazol-1-yl-ethanoyl-substituted-aryl/alkyl thiosemicarbazides **(6a-6o)** was carried out by refluxing different 2,4,5-trisubstituted-1*H*-imidazolyl hydrazides **(4a-4e)** (10 mmol) with aryl or alkyl isothiocyanate **(5a-5c)** (12 mmol) in the presence of ethanol (25 mL) in round bottom flask at 80°C for 10 hours. The completion of reaction was checked by Thin Layer Chromatography (TLC) by using silica gel G as stationary phase and solvent system having solvents toluene, ethyl acetate and formaldehyde in ratio 4:4:2. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 mL) to get the solid precipitated. It was collected by filtration, washed with cold water and recrystallized with ethanol.



a : R_1 = H
b : R_1 = 4-F
c : R_1 = 4-NO_2
d : R_1 = 2-OH
e : R_1 = 4-CH_3

a : R_2 = C_6H_5
b : R_2 = 4-Cl-C_6H_4
c : R_2 = 4-CH_3-C_6H_4

7a : R_1 = H R_2 = C_6H_5
7b : R_1 = 4-F R_2 = C_6H_5
7c : R_1 = 4-NO_2 R_2 = C_6H_5
7d : R_1 = 2-OH R_2 = C_6H_5
7e : R_1 = 4-CH_3 R_2 = C_6H_5

7f : R_1 = H R_2 = 4-Cl-C_6H_4
7g : R_1 = 4-F R_2 = 4-Cl-C_6H_4
7h : R_1 = 4-NO_2 R_2 = 4-Cl-C_6H_4
7i : R_1 = 2-OH R_2 = 4-Cl-C_6H_4
7j : R_1 = 4-CH_3 R_2 = 4-Cl-C_6H_4

7k : R_1 = H R_2 = 4-CH_3-C_6H_4
7l : R_1 = 4-F R_2 = 4-CH_3-C_6H_4
7m: R_1 = 4-NO_2 R_2 = 4-CH_3-C_6H_4
7n: R_1 = 2-OH R_2 = 4-CH_3-C_6H_4
7o: R_1 = 4-CH_3 R_2 = 4-CH_3-C_6H_4

Figure 1: Synthesis of novel imidazole susbtituted triazole derivatives 7a-7o

General procedure for synthesis of titled compounds 7a-7o:
The synthesis of 4-(4-substitutedphenyl)-5-(2,4,5-triphenyl-imidazole-1-ylmethyl)-4*H*-1,2,4-triazol-3-thiols **(7a-7o)** was carried out by dissolving different 2,4,5-triphenyl-imidazol-1-yl-ethanoyl-substituted-aryl/alkyl thiosemicarbazides **(6a-6o)** (10 mmol) in ethanol (25 mL) and 4 N acqous sodium hydroxide (2-5 mL) resulting in the formation of clear solution. The reaction mixture was refluxed in round bottom flask at 80°C for 12 hours on water bath, concentrated, cooled and filtered. The pH of the filtrate was adjusted between 5 and 6 with acetic acid and kept aside for 2 hours. The reaction mixture was cooled to room temperature and poured on ice-cold water (50 mL) to get the solid precipitated. It was collected by filtration, washed with cold water and recrystallized with ethanol.

Evaluation of anthelmintic activity
Anthelmintic activity of the synthesized compounds was evaluated against Indian adult earthworms (*pheretima posthuma*) of 4-5 cm. in length and 0.1-0.2 cm in width collected from water logged areas of soils in Jalandhar, Punjab, India. The earthworms of equal size and weight were divided into four groups of six earthworms in each group and washed thoroughly to remove mud and fecal matter [9-11].

The standard drug (albendazole) and test compounds were dissolved in minimum quantity of dimethyl sulphoxide (DMSO) and adjusted the volume up to 10 ml with normal saline solution (control) to get the concentrations of 0.150 % w/v and 0.300 % w/v. Six earthworms of nearly equal size were placed in Petri dishes containing standard drug solution and test compound's solutions of above mentioned concentrations at room temperature. The time taken in minutes for complete paralysis and death were recorded and then mean paralysis time and mean lethal time for each sample was calculated. The time taken for worms to become motionless was noted as paralysis time and time taken for worms when they do not respond to any external stimuli was taken as time for death. The mean paralysis time and lethal time of the earthworms for different test compounds and standard drug are tabulated in **Table 3.**

RESULTS AND DISCUSSION

Physicochemical and analytical data of the synthesized compounds **7a-7o** including molecular formula, molecular weight, percentage yield, melting point, R_f value and elemental analysis are shown in **Table 1.** Analytical data including IR, NMR and Mass spectral data is presented in **Table 2** whereas results of anthelmintic studies are tabulated in **Table 3**. It was found in the anthelmintic studies of the titled compounds that compound **7h** was found to be the most potent compound in this series which showed anthelmintic activity comparable to that of standard drug. Whereas compounds like **7c** and **7m** showed high activity, compounds **7b**, **7g** and **7l** showed moderate athelmintic activity and rest of other compounds showed very less anthelmintic activity when compared with standard drug albendazole.

Table 1: Physicochemical and elemental analysis data of the synthesized compounds 7a-7o

Comp.	Molecular Formula	Molecular Weight	% Yield	Melting Point (ºC)	R_f Value	Elemental Analysis (%)
7a	$C_{30}H_{23}N_5S$	486	47	289-291	0.56	C, 74.10; H, 4.47; N, 14.12; S, 6.40
7b	$C_{30}H_{22}FN_5S$	504	51	276-278	0.75	C, 71.35; H, 4.16; F, 3.54; N, 13.35; S, 6.16
7c	$C_{30}H_{22}N_6O_2S$	531	56	277-279	0.58	C, 67.51; H, 4.12; N, 15.27; O, 6.01; S, 6.02
7d	$C_{30}H_{23}N_5OS$	502	71	280-282	0.67	C, 71.45; H, 4.45; N, 13.45; O, 3.11; S, 6.24
7e	$C_{31}H_{25}N_5S$	499	58	290-292	0.61	C, 74.42; H, 5.01; N, 14.01; S, 6.41
7f	$C_{30}H_{22}ClN_5S$	520	65	293-295	0.51	C, 69.15; H, 4.21; Cl, 6.72; N, 13.27; S, 6.07
7g	$C_{30}H_{21}ClFN_5S$	538	60	264-266	0.49	C, 66.83; H, 3.83; Cl, 6.49; F, 3.43; N, 13.01; S, 5.86
7h	$C_{30}H_{21}ClN_6O_2S$	565	64	279-281	0.73	C, 63.67; H, 3.71; Cl, 6.21; N, 14.83; O, 5.62; S, 5.61
7i	$C_{30}H_{22}ClN_5OS$	536	48	274-276	0.78	C, 67.20; H, 4.10; Cl, 6.60; N, 13.01; O, 2.92; S, 5.91
7j	$C_{31}H_{24}ClN_5S$	534	66	260-262	0.71	C, 69.71; H, 4.50; Cl, 6.62; N, 13.10; S, 5.99
7k	$C_{31}H_{25}N_5S$	500	62	267-269	0.64	C, 74.42; H, 5.01; N, 14.01; S, 6.32
7l	$C_{31}H_{24}FN_5S$	518	60	282-284	0.49	C, 71.83; H, 4.61; F, 3.57; N, 13.43; S, 6.09
7m	$C_{31}H_{24}N_6O_2S$	544	48	296-298	0.85	C, 68.26; H, 4.42; N, 15.41; O, 5.82; S, 5.84
7n	$C_{31}H_{25}N_5OS$	516	50	262-264	0.44	C, 72.11; H, 4.69; N, 13.48; O, 3.08; S, 6.12
7o	$C_{32}H_{27}N_5S$	514	68	271-273	0.59	C, 74.81; H, 5.29; N, 13.52; S, 6.21

Table 2: Analytical data of titled compounds 7a-7o

Comp. Code	IR (KBr, cm^{-1})	^{1}H-NMR (DMSO, δ, ppm)	Mass (M^+)
7a	2918.47 (Ar-CH), 1602.74 (C=N), 2584.07 (SH)	4.92 (s, 2H, N-CH_2), 7.21-7.55 (m, 20H, Ar-H), 10.80 (bs, 1H, SH)	487
7b	3173.21 (Ar-CH), 1563.39 (C=N), 2564.05 (SH), 1063.57 (C-F)	4.95 (s, 2H, N-CH_2), 7.20-7.53 (m, 19H, Ar-H), 10.82 (bs, 1H, SH)	505
7c	3124.66 (Ar-CH), 1572.63 (C=N), 2564.63 (SH), 1375.98 (NO_2)	4.91 (s, 2H, N-CH_2), 7.22-7.56 (m, 19H, Ar-H), 10.80 (bs, 1H, SH)	532
7d	3118.47 (Ar-CH), 1552.74 (C=N), 2584.12 (SH), 3279.24 (OH)	5.05 (1H, Ar-OH), 4.92 (s, 2H, N-CH_2), 7.21-7.55 (m, 19H, Ar-H), 10.87 (bs, 1H, SH)	503
7e	2989.17 (Ar-CH), 1607.14 (C=N), 2591.29 (SH)	2.38 (s, 3H, CH_3), 4.97 (s, 2H, N-CH_2), 7.10-7.85 (m, 19H, Ar-H), 10.87 (bs, 1H, SH)	500
7f	3179.24 (Ar-CH), 1604.74 (C=N), 2574.07 (SH), 786.49 (C-Cl)	4.90 (s, 2H, N-CH_2), 7.21-7.57 (m, 19H, Ar-H), 10.85 (bs, 1H, SH)	521
7g	3177.22 (Ar-CH), 1593.32 (C=N), 2554.65 (SH), 773.58 (C-Cl), 1073.58 (C-F)	4.93 (s, 2H, N-CH_2), 7.24-7.57 (m, 18H, Ar-H), 10.83 (bs, 1H, SH)	539
7h	3138.50 (Ar-CH), 1586.51 (C=N), 2580.22 (SH), 772.71 (C-Cl), 1357.52 (NO_2)	4.91 (s, 2H, N-CH_2), 7.20-7.69 (m, 18H, Ar-H), 10.81 (bs, 1H, SH)	566
7i	3179.72 (Ar-CH), 1593.76 (C=N), 2569.26 (SH), 763.28 (C-Cl), 3227.42 (OH)	5.01 (1H, Ar-OH), 7.12-7.84 (m, 18H, Ar-H), 4.92 (s, 2H, N-CH_2), 10.81 (bs, 1H, SH)	537
7j	3169.14 (Ar-CH), 1624.51 (C=N), 2568.23 (SH), 793.57 (C-Cl)	2.41 (s, 3H, CH_3), 4.45 (s, 2H, N-CH_2), 7.11-7.83 (m, 18H, Ar-H), 10.89 (bs, 1H, SH)	535
7k	3184.02 (Ar-CH), 1597.96 (C=N), 2544.15 (SH)	2.31 (s, 3H, CH_3), 7.14-7.83 (m, 19H, Ar-H), 4.96 (s, 2H, N-CH_2), 10.84 (bs, 1H, SH)	501
7l	3133.22 (Ar-CH), 1593.31 (C=N), 2524.02 (SH), 1068.51 (C-F)	2.37 (s, 3H, CH_3), 7.12-7.87 (m, 18H, Ar-H), 4.96 (s, 2H, N-CH_2), 10.88 (bs, 1H, SH)	519
7m	3154.68 (Ar-CH), 1592.67 (C=N), 2534.65 (SH), 1325.90 (NO_2)	2.35 (s, 3H, CH_3), 7.18-7.82 (m, 18H, Ar-H), 4.95 (s, 2H, N-CH_2), 10.86 (bs, 1H, SH)	545
7n	3140.21 (Ar-CH), 1593.53 (C=N), 2561.05 (SH), 3202.21 (OH)	5.01 (1H, Ar-OH), 2.34 (s, 3H, CH_3), 7.14-7.89 (m, 18H, Ar-H), 4.91 (s, 2H, N-CH_2), 10.81 (bs, 1H, SH)	517
7o	3123.16 (Ar-CH), 1585.25 (C=N), 2598.37 (SH)	2.43 (s, 6H, CH_3), 7.16-7.81 (m, 18H, Ar-H), 4.89 (s, 2H, N-CH_2), 10.87 (bs, 1H, SH)	515

Table 3: Anthelmintic activity of test compounds 7a-7o

Comp. Code	R_1	R_2	Time for paralysis (min.) at Conc. in % w/v		Time for death (min.) at Conc. in % w/v	
			0.150 %	0.300 %	0.150 %	0.300 %
7a	H	C_6H_5	32	23	51	41
7b	4-F	C_6H_5	10	8	29	21
7c	4-NO_2	C_6H_5	5	4	15	10
7d	2-OH	C_6H_5	25	15	45	33
7e	4-CH_3	C_6H_5	41	33	56	48
7f	H	4-Cl-C_6H_4	30	20	49	37
7g	4-F	4-Cl-C_6H_4	8	6	23	17
7h	4-NO_2	4-Cl-C_6H_4	4	3	9	6
7i	2-OH	4-Cl-C_6H_4	16	13	43	31
7j	4-CH_3	4-Cl-C_6H_4	39	29	55	46
7k	H	4-CH_3-C_6H_4	37	26	53	43
7l	4-F	4-CH_3-C_6H_4	13	11	38	27
7m	4-NO_2	4-CH_3-C_6H_4	6	5	19	14
7n	2-OH	4-CH_3-C_6H_4	27	17	47	35
7o	4-CH_3	4-CH_3-C_6H_4	45	35	58	50
Control	NA	NA	-	-	-	-
Albendazole	NA	NA	3	2	7	5

CONCLUSION

The proposed imidazole substituted triazole derivatives **7a-7o** were synthesized and evaluated for their anthelmintic activity. All of the synthesized compounds were found to be active as anthelmintic agents and among all the titled compounds, some compounds having electron withdrawing group like compounds **7c**, **7h** and **7m** showed very high anthelmintic activity and compound **7h** being the most potent compound of this series when compared with the standard drug which means that electron withdrawing group is essential for anthelmintic activity. The significant findings of the present research work in this manuscript may be utilized by the researchers for development of better anthelmintic agents for future.

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