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Synthesis, characterization and biological evaluation of novel C-2 substituted benzimidazole heterocycles

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ABSTRACT

A series of new 1-(1*H*-benzo[*d*] imidazol-2-yl)-3-methyl-4-(substituted phenylhydrazono)-1*H*-pyrazol-5(4*H*)-ones (**4a-i**) were synthesized by the condensation of 2-hydrazinyl-1*H*-benzo[d]imidazole (**2**) with ethyl-2-arylhydrazono-3-oxobutyrates (**3a-i**) in glacial acetic acid. Also, 3-(1*H*-benzo[d]imidazol-2-ylamino)-2-(7-hydroxy-substituted-2-oxo-2H-chromen/quinolin -3-yl)thiazolidin-4-one)s **(7a-d)** were prepared *via* the cyclisation of Schiff bases 3-((2-(1H-benzo[d]imidazol-2-yl)hydrazono)substituted)-7-hydroxy-4-methyl-2H-chromen/quinolin-2-one **(6a-d)** with thioglycolic acid in refluxing benzene. Structural assignments of these synthesized compounds were based on IR, ^{1}HNMR, and Mass spectral data. The newly synthesized compounds (**4a-i**), **(6a-d)** and **(7a-d)** which possess a variety of heterocycles with benzimidazole as core nucleus were evaluated for their antimicrobial and anti-inflammatory activities by cup-plate method and formalin induced rat hind paw oedema method respectively.

Key words: Benzimidazole, pyrazole, coumarin, quinoline, thiazolidine, antimicrobial and anti-inflammatory activity

INTRODUCTION

Benzimidazole and its derivatives have been displayed promising activity in the treatment of several diseases, drawing much attention as important pharmacophore and privileged structure in medicinal chemistry. Benzimidazoles have been found to be effective against various strains of microorganisms based on their biochemical and pharmacological studies as chemotherapeutic agents. The nucleus possesses structural similarity with purine and has been used as biomimetics of guanine residues. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serve as an axial ligand for cobalt in Vitamin B_{12}[1]. Benzimidazoles reported to possess a number of interesting biological activities such as anticancer[2], antioxidant[3-4], antihistaminic[5], analgesic[6], anthelmintics[7], antiaggregant[8], anticonvulsant[9], anti-inflammatory[10-11], antiviral[12], α-glucosidase inhibitory[13] and antimicrobial [14-18]. Many reports have revealed that the influence of the substitution at the 1, 2 & 5 positions of the benzimidazole ring is very important for their pharmacological effects[19-20]. Specifically, 2-substituted benzimidazoles known for their biological activities have been reported[21]. Benzimidazole fused with coumarin reported to possess antibacterial[22], antioxidant[23] and anti-inflammatory[24] activity. In addition, other heterocycles like pyrazole, quinoline and thiazolidine moieties are well known for their biological activities [25-28].

In the light of the above findings and as an extension of our studies on different heterocycles of biological interest[29-32] we herein report the synthesis, antimicrobial and anti-inflammatory activities of C_2 substituted benzimidazole heterocycles.

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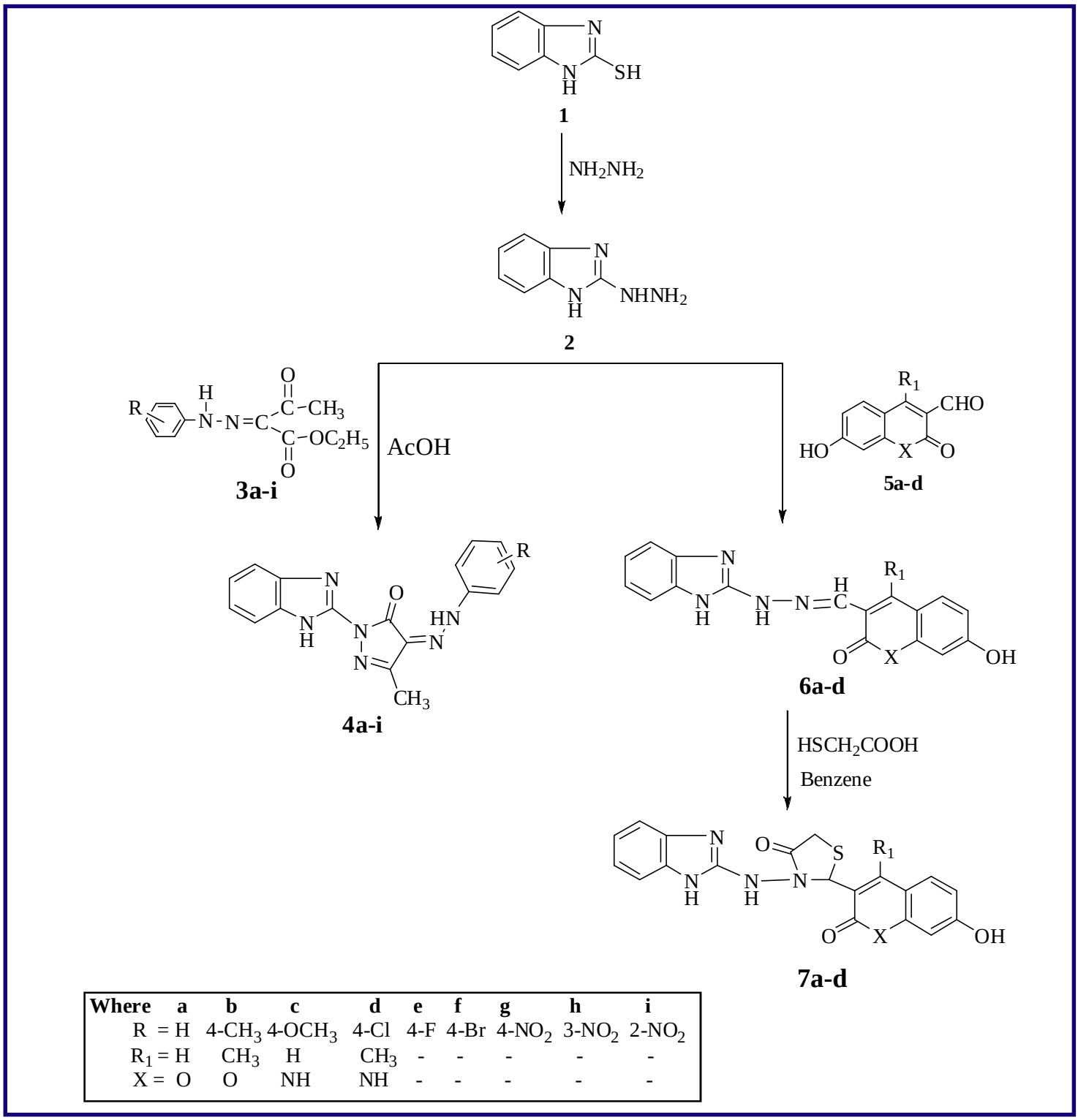
MATERIAL AND METHODS

All the solvents used were of analytical grade and were purified according to standard procedures. Melting points were determined in open capillaries and were uncorrected. IR spectra in KBr disc were recorded on Perkin-Elmer-Spectrum-one FT IR spectrophotometer (υ_{max} in cm^{-1}) and ^{1}HNMR in DMSO-d_6 on BRUKER 500 MHz spectrophotometer using TMS as internal standard (chemical shift in δ or ppm). Mass spectra were recorded on JEOL GC mate EI+ mass spectrophotometer using Argon/Xenon (6 Kv, 10 mA) as the FAB gas. Purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator.

RESULT AND DISCUSSION

Chemistry

1H-Benzo[d]imidazole-2-thiol (**1**) on reaction with excess of hydrazine hydrate gave 2-hydrazinyl-1*H*-benzo[d]imidazole (**2**) in 60 % yield[33]. Compound **2** on reaction with ethyl-2-arylhydrazono-3-oxobutyrates (**3a-i**) in glacial acetic acid under reflux undergoes smooth cyclisation furnishing 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-methyl-4-



Where	a	b	c	d	e	f	g	h	i
R =	H	4-CH_3	4-OCH_3	4-Cl	4-F	4-Br	4-NO_2	3-NO_2	2-NO_2
R_1 =	H	CH_3	H	CH_3	-	-	-	-	-
X =	O	O	NH	NH	-	-	-	-	-

Fig-1: Synthetic scheme for the preparation of C-2 substituted benzimidazole heterocycles

(substituted phenylhydrazono)-1*H*-pyrazol-5(4*H*)-ones (**4a-i**) in 65-75% yield. Reaction of compound **2** in presence of catalytic amount of concentrated hydrochloric acid with 7-hydroxy-4substituted-2-oxo-2H-chromene-3-carbaldehyde/7-hydroxy-4substituted-2-oxo-1,2-dihydroquinoline-3-carbaldehydes (**5a-i**) in refluxing methanol generated Schiff bases **6a-d** in 58-67% yield. Further cyclisation of **6a-d** with thioglycolic acid in refluxing benzene containing a pinch of $ZnCl_2$ gave the desired targeted compounds **7a-d** in 55-62% yield **(Fig-1)**. The formation of 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-methyl-4-(substituted phenylhydrazono)-1*H*-pyrazol-5(4*H*)-ones (**4a-i**) have

been confirmed on the basis of its spectral data. Compound **4a** obtained as pale yellow solid in 71% yield, having melting point 238-240°C. The IR spectrum of compound **4a** exhibited the stretching absorption peaks at 3410, 3131, 3062 and 1732 cm^{-1} due to the presence of phenylhydrazono NH, benzimidazole NH, C=N and C=O groups respectively. The ^1H NMR spectrum revealed characteristic downfield signals at δ 9.0 (s, 1H, NH), 8.7 (s, 1H, benzimidazole NH), 6.9-7.4 (m, 9H, ArH) 2.8 (s, 3H, pyrazole CH_3). The mass spectrum of this compound exhibited molecular ion peak at m/z = 318 (M^+). All these spectral data are in agreement with the structure assigned to **4a**.

Compound **6a** shows absorption peaks at 3444, 2920 and 1766 cm^{-1}due to the presence of OH, benzimidazole NH and C=O group in its IR spectrum. Formation of compound **6a** was confirmed by ^{1}HNMR spectrum signals at δ 10.0 (s, 1H, OH), 9.5 (s, 1H, NH), 8.9 (s, 1H, benzimidazole NH), 6.7-7.5 (m, 8H, ArH, 1H, N=CH). Mass spectrum of compound **6a** exhibited molecular ion peak at m/z =320.

Cyclisation of **6a** with thioglycolic acid in refluxing benzene gave the compound **7a** in 62% yield**.** Structure of compound **7a** in ^{1}HNMR spectrum gave signals at δ 9.9 (s, 1H, OH), 9.3 (s, 1H, NH), 8.6 (s, 1H, benzimidazole NH) and 4.8 (s, 2H, CH_2 of thiazolidine) appears as a new signal indicting the formation of thiazolidine ring. The mass spectrum of compound **7a** exhibited the molecular ion peak at m/z =394. The physical data and spectral of the synthesized compounds were tabulated in the **Table-1** and **Table-2.**

Table-1: Physical data of synthesized compounds

Comp No.	Substitution R	R_1	X	Molecular formula	Yield (%)	M. P. (°C)
4a	H	—		$C_{17}H_{14}N_6O$	72	238-240
4b	4-CH_3	—		$C_{18}H_{16}N_6O$	68	244-246
4c	4-OCH_3	—		$C_{18}H_{16}N_6O_2$	75	218-220
4d	4-Cl	—		$C_{17}H_{13}ClN_6O$	70	236-238
4e	4-F	—		$C_{17}H_{13}FN_6O$	65	202-204
4f	4-Br	—		$C_{17}H_{13}N_7O3$	68	260-262
4g	4-NO_2	—		$C_{17}H_{13}N_7O_3$	71	248-250
4h	3-NO_2	—		$C_{17}H_{13}N_7O_3$	68	232-234
4i	2-NO_2			$C_{17}H_{13}N_7O_3$	66	226-228
6a	—	H	O	$C_{17}H_{12}N_4O_3$	61	221-223
6b	—	CH_3	O	$C_{18}H_{14}N_4O_3$	58	229-230
6c	—	H	NH	$C_{17}H_{13}N_5O_2$	67	192-194
6d	—	CH_3	NH	$C_{18}H_{15}N_5O_2$	64	186-187
7a	—	H	O	$C_{19}H_{14}N_4O_4S$	62	193-195
7b	—	CH_3	O	$C_{20}H_{16}N_4O_4S$	59	209-211
7c	—	H	NH	$C_{19}H_{15}N_5O_3S$	55	196-198
7d	—	CH_3	NH	$C_{20}H_{17}N_5O_3S$	60	224-226

Table-2: Spectral data of synthesized compounds

Comp No	IR (KBr) cm^{-1}	^{1}H NMR (DMSO-d_6) d ppm	MS m/z[M^+]
4a	3410 & 3131, (NH), 1732 (C=O)	9.0 (s, 1H, NH), 8.7 (s, 1H, benzimidazole NH), 6.9-7.4 (m, 9H, ArH), 2.8 (S, 3H, pyrazole CH_3).	318
4b	3410 & 3059, (NH), 1736 (C=O)	10.3 (s, 1H, NH), 8.6 (s, 1H, benzimidazole NH), 6.9-7.7 (m, 9H, ArH), 2.9 (S, 3H, pyrazole CH_3), 2.2 (s, 3H, CH_3).	332
4c	3307 & 3298, (NH), 1700 (C=O)	9.8 (s, 1H, NH), 8.6 (s, 1H, benzimidazole NH), 7.1-8.0 (m, 9H, ArH), 3.7 (S, 3H, pyrazole CH_3). 2.9 (s, 3H, OCH_3).	348
4d	3357 & 3191, (NH), 1705 (C=O)	9.8 (s, 1H, NH), 8.6 (s, 1H, benzimidazole NH), 7.1-8.0 (m, 9H, ArH), 3.7 (S, 3H, pyrazole CH_3). 2.9 (s, 3H, OCH_3).	352
4e	3412 & 3153, (NH), 1746 (C=O)	9.8 (s, 1H, NH), 8.8 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 9H, ArH), 2.9 (S, 3H, pyrazole CH_3).	336
4f	3412 & 3059(NH), 1736 (C=O)	9.6 (s, 1H, NH), 8.8 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 9H, ArH), 2.9 (S, 3H, pyrazole CH_3).	396
4g	3419 & 3374(NH), 1703 (C=O)	9.5 (s, 1H, NH), 8.7 (s, 1H, benzimidazole NH), 7.2-8.9 (m, 9H, ArH), 2.8 (S, 3H, pyrazole CH_3).	363
4h	3440 (OH), 2917 (NH), 1764 (C=O)	9.8 (s, 1H, NH), 8.8 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 9H, ArH), 2.9 (S, 3H, pyrazole CH_3).	363
4i	3412, 3374 (NH), 1744 (C=O)	9.8 (s, 1H, NH), 8.8 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 9H, ArH), 2.9 (S, 3H, pyrazole CH_3).	363
6a	3444 & 2920(NH), 1736 (C=O)	9.9 (s, 1H, OH), 9.3 (s, 1H, NH), 8.9 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 8H, ArH 1H, N=CH).	320
6b	3419 & 2956(NH), 1727 (C=O)	9.9 (s, 1H, OH), 9.1 (s, 1H, NH), 8.7 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 7H, ArH 1H, N=CH).	334
6c	3413 & 3005(NH), 2917 (C=O)	10.0 (s, 1H, OH), 9.3 (s, 1H, quinoline NH), 8.7 (s, 1H, benzimidazole NH), 7.1-8.2 (m, 8H, ArH 1H, N=CH).	319
6d	3447 & 3015(NH), 1764(C=O)	10.0 (s, 1H, OH), 9.2 (s, 1H, quinoline NH), 8.7 (s, 1H, benzimidazole NH), 7.2-8.7 (m, 8H, ArH 1H, N=CH).	333
7a	3315 & 3120(NH), 1720 (C=O)	9.9 (s, 1H, OH), 9.4 (s, 1H, NH), 8.6 (s, 1H, benzimidazole NH), 6.9-7.5 (m, 8H, ArH). 4.8 (s, 2H, thiazolidine CH_2)	394
7b	3410 & 3059(NH), 1736 (C=O)	10.0 (s, 1H, OH), 9.4 (s, 1H, NH), 8.7 (s, 1H, benzimidazole NH), 7.2-7.8 (m, 8H, ArH). 4.8 (s, 2H, thiazolidine CH_2)	408
7c	3447 (NH), 1774 (C=O)	10.5 (s, 1H, OH), 10.0 (s, 1H, NH), 9.3 (s, 1H, quinoline NH), 8.8 (s, 1H, benzimidazole NH) 7.1-8.0 (m, 8H, ArH 1H, N=CH). 4.3 (s, 2H, thiazolidine CH_2)	393
7d	3412&3192(NH), 1746 (C=O)	10.6 (s, 1H, OH), 10.1 (s, 1H, NH), 9.7 (s, 1H, quinoline NH), 8.8 (s, 1H, benzimidazole NH) 7.3-8.1 (m, 8H, ArH 1H, N=CH). 4.9 (s, 2H, thiazolidine CH_2)	407

EXPERIMENTAL

General procedure for the synthesis of 1-(1*H*-benzo[*d*] imidazol-2-yl)-3-methyl-4-(substituted phenylhydrazono)-1*H*-pyrazol-5(4*H*)-ones (4a-i)

To a solution of ethyl-2-arylhydrazono-3-oxobutyrates **(3a-i)** (0.01 mol) in glacial acetic acid (10 ml), a solution of 2-hydrazinyl-1*H*-benzo[*d*]imidazole **(2)** (0.01 mol) in glacial acetic acid (15 ml) was added with stirring. The mixture was refluxed for 7 hours in an oil bath. After completion of reaction confirmed by TLC, the reaction mixture was cooled and allowed to stand overnight. The solid separated was filtered, dried and recrystalliszed from ethanol yielded desired targeted compounds **4a-i**.

General procedure for the synthesis of 3-((2-(1H-benzo[d]imidazol-2-yl)hydrazono)substituted)-7-hydroxy-4-methyl-2H-chromen/quinolin-2-one (6a-d)

To a solution of 2-hydrazinyl-1*H*-benzo[d]imidazole **(2)** (0.01 mole) in methanol, 2-3 drops of concentrated hydrochloric acid, appropriate aldehyde (0.01 mole) were added with stirring. The reaction mixture was refluxed for 6 hours on steam bath. After completion of reaction confirmed by TLC, the reaction mixture was concentrated under reduced pressure. The solid separated was filtered and recrystallized from ethanol provided desired compounds **6a-d.**

General procedure for the synthesis of 3-(1*H*-benzo[d]imidazol-2-ylamino)-2-(7-hydroxy-substituted-2-oxo-2H-chromen/quinolin-3-yl)thiazolidin-4-one)s (7a-d)

To a solution of Compounds **6a-d** (0.01 mole) in dry benzene (10 ml), pinch of $ZnCl_2$ and thioglycolic acid (0.01 mole) was added dropwise with stirring. The reaction mixture was refluxed for 18 hours on steam bath. After completion of reaction confirmed by TLC, the excess of benzene was removed under reduced pressure. The reaction mixture was cooled and triturated with 10% aq. sodium bicarbonate solution. The solid separated was filtered and recrystallized from ethanol furnished desired compounds **7a-d.**

BIOLOGICAL ACTIVITIES

Antimicrobial Activity

The antimicrobial activities were performed by cup plate method[34]. Antibacterial activity screened against two gram positive (*S. aureus* and *B. Subtilis*) and two gram negative *(P. aeruginosa* and *E. coli*) strains. Antifungal activity was carried out against *A. niger, A. flavus* and *A. terrus* under aseptic conditions. The test samples and standard drugs were dissolved in DMF at the concentration 1000 µg/ml. The cups of inoculated plates were then filled with 0.1 ml of the test solution, Gentamycine/Flucanazole solution (standard) and solvent DMF (control). Gentamycine and fluconazole were used as standard drug for antibacterial and antifungal activities respectively. The zone of inhibition was compared with standard drug after 24 hours of incubation at 25^0 C for antibacterial activity and 48 hours at 30^0 C for antifungal activity. The zone of inhibition developed, if any, was measured for the particular compound for each organism. The results of antimicrobial screening of all the newly synthesized compounds were presented in the **Fig-2** and **Fig-3.**

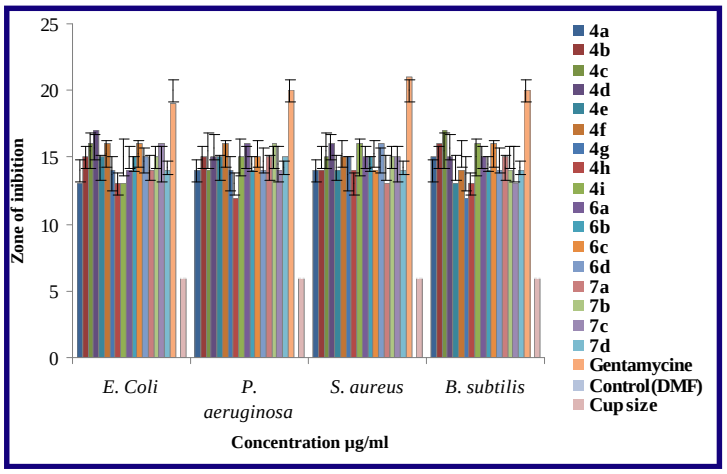


Figure-2: Antibacterial activity of synthesized compounds

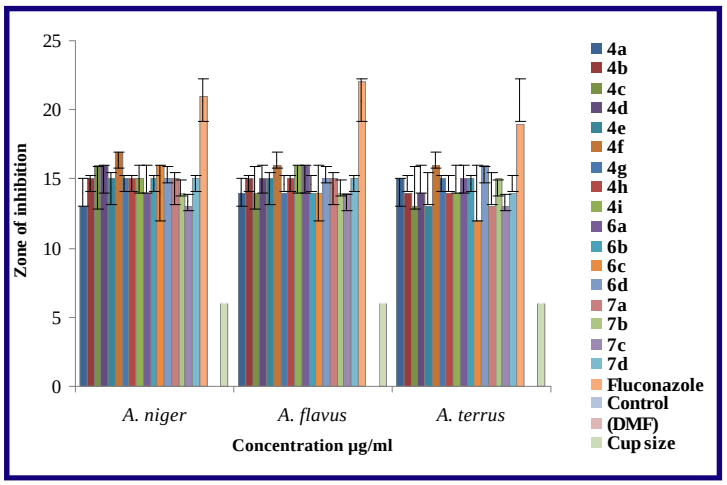


Figure-3: Antifungal activity of synthesized compounds

Anti-inflammatory activity

The anti-inflammatory activity was evaluated by formalin induced rat hind paw oedema method[35-36]. All the animals were maintained under controlled standard animal house conditions with easy access to food and water. The institutional ethical committee for animal cares and use approved for the experimental procedure (Reg. No: 1046/a/07/CPCSEA). This method based on plethysmographic measurement of oedema produced by sub-plantar injection of carrageenan to the hind paw of the rat. Selected albino rats of either sex weighing between 150-180 g were used and divided into 17 groups of six animals each and they were numbered individually.

The animals were fasted for 24 hours with water before the administration of drug. The animals were marked on their hind paws (right and left) just beyond tibio-tarsal junction to ensure the constant dipping at every time in the mercury column up to the fixed mark. Group-I received 0.5 ml of 2% gum acacia suspension orally

Table-3: Anti-inflammatory activity of synthesized compounds

Group	Compound	Dose (mg/kg) Body weight	% Oedema inhibition at different intervals (Mean±SE) 60 min	120 min	180 min	240 min
1	Control	—	0.75 (±0.030)	0.95 (±0.040)	1.10 (±0.100)***	1.15 (±0.03)***
2	Diclofenac sodium	50	0.65 (±0.040) (13)	0.60 (±0.040 (21)***	0.55 (±0.050) (50)***	0.55 (±0.05) (52)***
3	4a	50	0.75 (±0.040) (0)	0.75 (±0.030) (21)***	0.77 (±0.040) (30)***	0.82 (±0.03) (29)***
4	4b	50	0.60 (±0.040) (20)	0.53 (±0.030) (44)*	0.45 (±0.040) (59)***	0.50 (±0.03) (57)
5	4c	50	0.75 (±0.050) (0)	0.75 (±0.040) (21)***	0.75 (±0.050) (31)***	0.80 (±0.04) (30)
6	4d	50	0.80 (±0.050) (0)	0.80 (±0.040) (16)***	0.80 (±0.030) (27)***	0.86 (±0.03) (25)
7	4e	50	0.65 (±0.050) (13)	0.65 (±0.040) (32)	0.60 (±0.030) (45)	0.60 (±0.03) (48)***
8	4f	50	0.75 (±0.040) (0)	0.75 (±0.060) (21)***	0.80 (±0.040) (27)***	0.80 (±0.03) (30)***
9	4g	50	0.85 (±0.050) (0)**	0.85 (±0.041) (10)***	0.85 (±0.027) (23)***	0.90 (±0.03) (22)***
10	6a	50	0.77 (±0.050) (0)	0.75 (±0.041) (21)***	0.70 (±0.027) (36)***	0.70 (±0.03) (39)***
11	6b	50	0.78 (±0.020) (0)	0.75 (±0.035) (21)***	0.73 (±0.022) (34)***	0.73 (±0.02) (37)***
12	6c	50	0.84 (±0.050) (0)**	0.84 (±0.041) (11)***	0.88 (±0.027) (20)***	0.90 (±0.03) (22)***
13	6d	50	0.57 (±0.034) (24)	0.55 (±0.032) (42)	0.50 (±0.032) (54)	0.57 (±0.03) (50)
14	7a	50	0.67 (±0.150) (11)	0.67 (±0.022) (29)*	0.60 (±0.021) (45)	0.60 (±0.02) (48)
15	7b	50	0.74 (±0.050) (1)	0.74 (±0.041) (22)***	0.84 (±0.027) (24)***	0.92 (±0.03) (20)***
16	7c	50	0.60 (±0.150) (20)	0.60 (±0.022) (37)	0.55 (±0.021) (50)	0.55 (±0.02) (52)
17	7d	50	0.60 (±0.340) (20)	0.60 (±0.034) (37)	0.57 (±0.044) (48)	0.62 (±0.04) (46)**

Data represent mean values± SE (n=6).SE, standard error. Data were analyzed using one-way ANOVA.,Percent edema inhibition was calculated as regards saline control group.*Significance levels $^{*}p<0.5$, $^{**}p<0.01$ and $^{***}p< 0.001$ as compared with respective to standard.

which served as control. Group-II injected intra-peritonially with 100 mg/kg body weight of diclofenac sodium and served as reference standard. Remaining 3-17 groups received 15 test compounds at a dose 100 mg/kg body weight administered by oral route. After 30 minutes of inject 0.1 ml of 1% (w/v) carrageenan in the plantar region of let paw of control as well as test compounds treated groups. The right paw served as reference non-inflammed paw for comparison.

The paw volume of control, standard and test group animals was measured at 2 and 4 hours of interval. The percentage increase in oedema over the initial reading was calculated. The increase in oedema of animals administered with standard, test compounds were compared with increase in oedema of control animals with the corresponding intervals of 2 and 4 hours. The results of anti-inflammatory evaluation of all the synthesized compounds were summarized in the **Table-3.**

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