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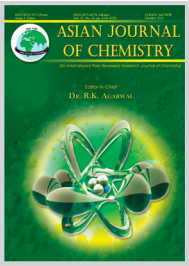

Synthesis and Biological Evaluation of Some New 2,4,6-Trisubstituted Pyrimidines

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In the present study, 3-acetyl-2,5-dimethylfuran on condensation with various aromatic and heterocyclic aldehydes in ethanolic KOH solution yielded the corresponding chalcones (**3a-n**). These chalcones were reacted with guanidine hydrochloride in presence of potassium hydroxide and ethanol to give pyrimidines (**4a-n**). All these compounds were characterized by IR, ^{1}H NMR spectroscopic data and microanalyses. When these compounds were evaluated for anti-inflammatory and antimicrobial activities, some of them were found to possess significant activity, when compared to standard drugs.

Key Words: Pyrimidines, Synthesis, Antimicrobial activity.

INTRODUCTION

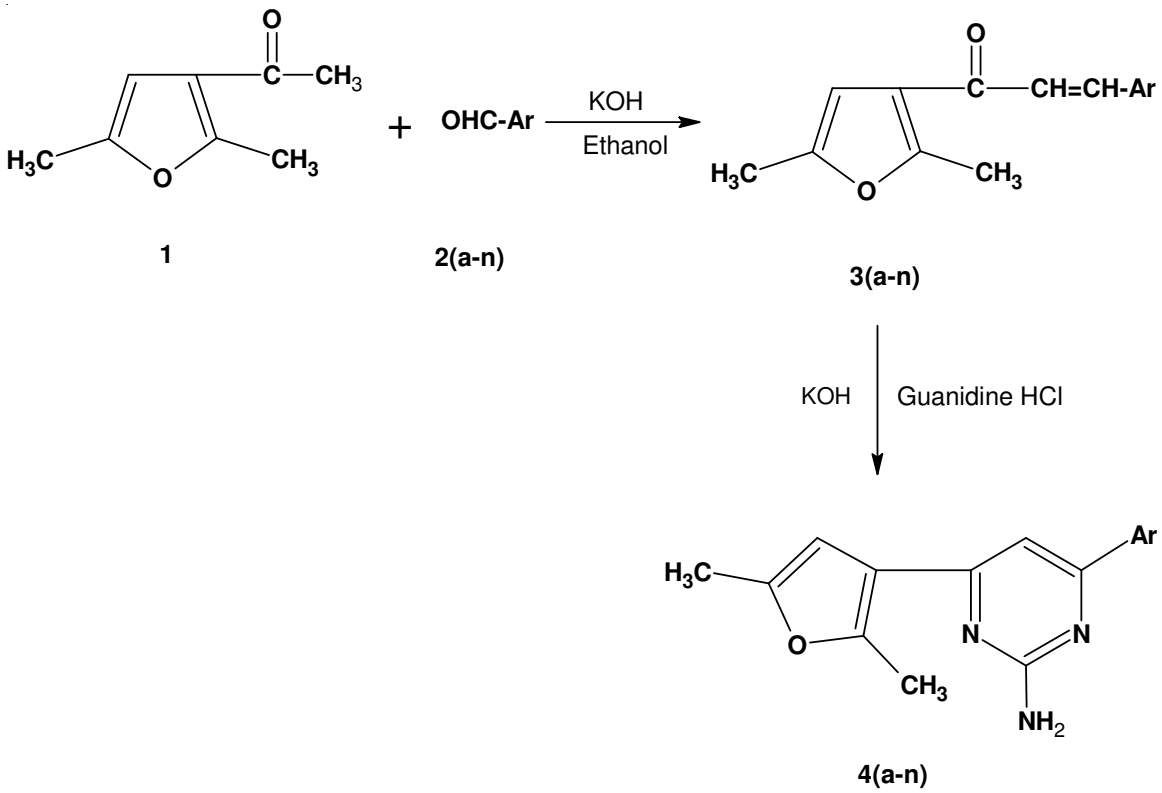
In medicinal chemistry pyrimidine derivatives have been well known for their therapeutic applications. The presence of a pyrimidine base in thymine, cytosine and uracil, which are essential binding blocks of nucleic acids, DNA and RNA is one of the possible reasons for their activity. Many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical use such as antibacterial (sulfadiazines, sulfamerazine and sulfamethazine), anticancer (5-fluorouracil and ftorafur), antiviral (iodoxuridine, trifluoridine and zidovudine), antifungal (flucytocine) and antimalarial agents (pyrimethamine)[1]. Pyrimidines and their derivatives have been found to possess a broad spectrum of biological activities such as antimicrobial, antiinflammatory, analgesic, antiviral and anticancer activities[2-9].

The synthesis of furan derivatives has engrossed substantial attention from organic and medicinal chemists for many years as they belong to a class of compounds with proven utility in medicinal chemistry[10]. Furan derivatives are known to be associated with multiple biological activities[11,12]. Therefore, both the pyrimidine and furan possess worthy and imperative bioactivities, which render them useful substances in drug research.

In view of these observations and in continuation of our research programme on the synthesis of chalcones and their derivatives[13,14], like pyrimidines, pyrazolines and isoxazolines, we report the synthesis of some new pyrimidine derivatives which have been found to possess an interesting profile of antimicrobial and antiinflammatory activities. Synthetic methods for the preparation of pyrimidine derivatives (**4a-n**) are summarized in **Scheme-I**, it is apparent from the scheme that the new heterocyclic compounds possess both a pyrimidine and furan moiety unit. Reaction of chalcones with guanidine seemed to be a convenient route to fulfill this aim[15,16]. Chalcones were synthesized by the reaction of 3-acetyl-2,5-dimethylfuran and various substituted aromatic and hetero cyclic aldehydes in presence of aq.KOH and ethanol. Pyrimidines were obtained in good yield by reacting chalcones (**3a-n**) with guanidine in presence of KOH and ethanol. The structures of the various synthesized compounds were assigned on the basis of elemental analyses, IR and ^{1}H NMR spectral data. These compounds were also screened for their antimicrobial and antiinflammatory activities.

EXPERIMENTAL

All the chemicals used in the synthesis were obtained from standard commercial sources. Melting points were determined in open capillaries, using Boitus melting point apparatus. Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems are indicated at appropriate places. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The ^{1}H NMR spectra of the compounds were recorded on Bruker AMX 400 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in d ppm. Elemental analyses were carried out with a Perkin-Elmer model 2400



Scheme-I

series II apparatus. The results of elemental analyses (C, H, N) were within ± 0.4 % of the calculated values.

General procedure for preparation of 1-(2',5'-dimethyl-3'-furyl)-3-(aryl)-2-propen-1-one 3(a-n): A mixture of 3-acetyl-2,5-dimethylfuran (0.005 mol) (**1**) and appropriate aldehyde (0.005 mol) (**2a-n**) was stirred in ethanol (7.5 mL) and then an aqueous solution of potassium hydroxide (50 %, 7.5 mL) was added to it. The mixture was kept for 24 h and was acidified with 1:1 HCl and H_2O. Then it was filtered under vacuum and the solid was washed with water, purified by column chromatography and crystallized from a mixture of ethyl acetate and hexane (**Scheme-I**).

Synthesis of 2-amino-4-(2',5'-dimethyl-3'-furyl)-6-(aryl)pyrimidine (4a-n): 1-(2',5'-Dimethyl-3'-furyl)-3-(aryl)-2-propen-1-one (**3a-n**) (0.001 mol) was condensed with guanidine hydrochloride (0.001 mol) in the presence of potassium hydroxide (0.002 mol) in absolute ethanol (5 mL) at reflux temperature on a water bath for 3 h. The solvent was evaporated in vacuum and crushed ice was added to the residue while mixing thoroughly, whereupon a bright yellow solid separated out. This solid was filtered under vacuum, dried and purified by column chromatography to give pure pale yellow solid (**Scheme-I**).

Antiinflammatory activity: Spraygue-dawley rats (M/S Gosh Enterprises, Calcutta, West Bengal, India) of either sex weighing between 180-200 g were used in the experiment. 1 % carrageenan sodium gel was prepared with saline water for producing inflammation and gel of 1 % sodium CMC was prepared with saline water for suspending the test compounds and standard drug.

Rats were divided into sixteen groups of five animals each. Inflammation was produced by inducing 0.05 mL of 1 % carrageenan subcutaneously into the sub plantar region of the right hind paw and 0.05 mL of saline was injected into the sub plantar region of the left hind paw for all groups. 1 h prior to carrageenan injection, the groups III-XVI were treated with compounds **(4a-n)** (10 mg/kg). 1 % sodium CMC gel (1 mL/kg) was given to group-I, used as carrageenan treated control and the standard drug aceclofenac (2 mg/kg) was administered to group-II. All the doses were administered orally. Antiinflammatory activity was evaluated by measuring carrageenan induced paw oedema[17,18]. The thickness of raw paw was measured before carrageenan injection and after carrageenan injection at time intervals 0.5, 1, 2, 3, 4 and 6 h using Zeitlin constant loaded lever method[19]. The percentage increase of paw oedema thickness was calculated[20]. The results and statistical analysis of antiinflammatory activity of aceclofenac and the compounds tested were shown in Table-3.

Antimicrobial activity: Cup plate method[21,22] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of (**4a-n**) against *B. subtilis, B. pumilis, S.aureus, E.coli* and *P. vulgaris*. The agar medium was purchased from HI-media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide. Benzylpenicillin was employed as reference standard (1000 µg/mL) to compare the results. The pH of the all the test solutions and control was maintained at 2-3 by using conc. HCl, because the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at a concentration of 0.05 mL (50 µg) and 0.1 mL (100 µg) level and DMSO as control did not show any inhibition.

TABLE-1
PHYSICAL DATA OF THE PREPARED COMPOUNDS 4 (**a-n**)

S. no.	Ar	m.f.	m.p. (°C)	Yield (%)	Calcd. (%)			Found (%)		
					C	H	N	C	H	N
4a	3",4",5"-Trimethoxyphenyl	$C_{19}H_{21}N_3O_4$	312-314	63	64.22	5.91	11.83	64.24	5.92	11.84
4b	4"-Chlorophenyl	$C_{16}H_{14}N_3Ocl$	241-245	57	64.21	4.68	14.01	64.24	4.69	14.11
4c	4"-Dimethylaminophenyl	$C_{18}H_{20}N_4O$	164-165	64	70.12	6.49	18.18	70.14	6.50	18.16
4d	4"-Methylphenyl	$C_{17}H_{17}N_3O$	120-122	54	73.11	5.01	15.05	73.14	5.03	15.15
4e	2",4"-Dichlorophenyl	$C_{16}H_{13}N_3OCl_2$	132-134	60	57.65	3.90	12.61	57.62	3.87	12.64
4f	9"-Anthracenyl	$C_{24}H_{19}N_3O$	223-225	72	78.90	5.20	11.50	78.92	5.21	11.54
4g	4"-Methoxyphenyl	$C_{17}H_{17}N_3O_2$	302-305	68	69.15	5.76	14.23	69.14	5.75	14.22
4h	3",4"-Dimethoxyphenyl	$C_{18}H_{19}N_3O_3$	220-221	70	66.46	5.84	12.92	66.47	5.83	12.93
4i	4"-Fluorophenyl	$C_{16}H_{14}N_3OF$	233-235	53	67.84	4.94	14.84	67.83	4.92	14.82
4j	4"-Nitrophenyl	$C_{16}H_{14}N_4O_3$	260-262	65	61.93	4.51	18.06	61.92	4.54	18.04
4k	2"-Pyridinyl	$C_{15}H_{14}N_4O$	194-196	56	67.66	5.26	21.05	67.62	5.23	21.04
4l	3"-Pyridinyl	$C_{15}H_{14}N_4O$	212-213	46	67.66	5.26	21.05	67.63	5.22	21.03
4m	4"-Pyridinyl	$C_{15}H_{14}N_4O$	233-235	48	67.66	5.26	21.05	67.64	5.25	21.06
4n	2"-Thienyl	$C_{14}H_{13}N_3OS$	240-241	55	61.99	4.79	15.49	61.98	4.78	15.51

TABLE-2
SPECTRAL DATA OF THE PREPARED COMPOUNDS (**4a-n**)

S. no.	IR spectral data (cm^{-1})	^1H NMR spectral data chemical Shift (δ) in ppm
4a	3380 (NH_2), 1591 (C=N), 1503 (C=C)	3.75-4.0 (9H, s, 3 $Xoch_3$), 5.15 (2H, s, -NH_2), 6.45-6.60 (1H, s, C-4'-H), 7.45 (1H, s, C-5-H), 6.40 (2H, S, C-2"-H and C-6"-H), 2.4 (3H, s, Ar-CH_3), 2.9 (3H, s, Ar-CH_3).
4b	3346 (NH_2), 1636 (C=N), 1578 (C=C)	5.45 (2H, s, -NH_2), 6.60 (1H, s, C-4'-H), 7.35 (1H, s, C-5-H), 8.03 (2H, d, *J* = 8.0 Hz, C-3"-H and C-5"-H), 7.48 (2H, d, *J* = 8.0 Hz, C-2"-H and C-6"-H), 2.2 (3H, s, Ar-CH_3), 2.6 (3H, s, Ar-CH_3).
4c	3332 (NH_2), 1610 (C=N), 1570 (C=C), 1178-N $(CH_3)_2$	3.10 (6H, s, -N $(CH_3)_2$), 5.20 (2H, s, -NH_2), 7.2 (1H, s, C-5-H), 6.61 (1H, s, C-4'-H), 8.12 (2H, d, *J* = 8.5 Hz, C-3"-H and C-5"-H), 6.78 (2H, d, *J* = 8.5 Hz, C-2"-H and C-6"-H), 2.65 (3H, s, Ar-CH_3), 2.9 (3H, s, Ar-CH_3).
4d	3335 (NH_2), 1597 (C=N), 1520 (C=C)	2.46 (3H, s, Ar-CH_3), 5.25 (2H, s, -NH_2), 6.67 (1H, s, C-4'-H), 7.45 (1H, s, C-5-H), 8.06 (2H, d, *J* = 8.0 Hz, C-3"-H and C-5"-H), 7.36 (2H, d, *J* = 8.0 Hz, C-2"-H and C-6"-H), 2.15 (3H, s, Ar-CH_3), 2.25 (3H, s, Ar-CH_3).
4e	3326 (NH_2), 1605 (C=N), 1525 (C=C),1372 (C-N), 892 (C-Cl)	5.78 (2H, s, -NH_2), 6.62 (1H, s, C-4'-H), 7.62 (1H, s, -C-3"-H), 7.54 (1H, d, *J* = 8.5 Hz, C-5"-H) 7.41 (1H, d, *J* = 8.5 Hz, C-6"-H), 7.35 (1H, s, C-5-H), 2.4 (3H, s, Ar-CH_3), 2.9 (3H, s, Ar-CH_3).
4f	3328 (NH_2), 1632 (C=N), 1515 (C=C)	5.85 (2H, s, -NH_2), 6.61 (1H, s, C-4'-H), 7.60 (1H, s, C-5-H), 7.22-7.55 (9H, m, Ar-H), 2.2 (3H, s, Ar-CH_3), 2.7 (3H, s, Ar-CH_3).
4g	3414 (NH_2), 1598 (C=N), 1503 (C=C), 1366 (C-N), 1225 (C-O-C)	3.87 (3H, s, C-4"-OCH_3), 5.11 (2H, s, -NH_2), 7.07 (2H, d, *J* = 8.5 Hz, C-3" and 5"-H), 7.37 (1H, s, C-5-H), 6.51 (1H, s, C-4'-H), 8.05 (2H, d, *J* = 8.5 Hz, C-2" and 6"-H), 2.35 (3H, s, Ar-CH_3), 2.7 (3H, s, Ar-CH_3).
4h	3320 (NH_2), 1597 (C=N), 1556 (C=C), 1354 (C-N), 1261 (C-O-C)	5.21 (2H, s, -NH_2), 3.75-4.0 (6H, s, 2x OCH_3), 7.19 (1H, S, C-2"-H), 7.94 (2H, dd, *J* = 8.5 Hz, *J* = 8.5 Hz, C-3" and 5"-H), 6.63 (1H, s, C-4'-H), 7.0 (1H, s, C-5-H), 2.35 (3H, s, Ar-CH_3), 2.7 (3H, s, Ar-CH_3).
4i	3318 (NH_2), 1599 (C=N), 1510 (C=C), 1350 (C-N), 1219 (C-F)	5.21 (2H, s, -NH_2), 7.19 (2H, dd, *J* = 8.5 Hz, C-2" and 6"-H), 6.60 (1H, s, C-4'-H), 8.2 (2H, dd, *J* = 8.5 Hz, C-3" and 5"-H), 7.25 (1H, s, C-5-H), 2.4 (3H, s, Ar-CH_3), 2.8 (3H, s, Ar-CH_3).
4j	3370 (NH_2), 1645 (C=N), 1557 (N=O, asymmetric)	5.22 (2H, s, -NH_2), 6.64-6.65 (1H, s, C-4'-H), 7.35 (1H, s, C-5-H), 7.79 (2H, d, *J* = 8.0 Hz, C-2″ and 6″-H), 8.34 (2H, d, *J* = 8.0 Hz, C-3″and 5″-H), 2.2 (3H,s, Ar-CH_3), 2.6 (3H, s, Ar-CH_3).
4k	3425, 3238 (NH_2), 1656 (C=N), 1510 (C=C)	5.22 (2H, s, -NH_2), 7.53-7.50 (1H, m, C-5"-H), 7.99-7.95 (1H, d, *J* = 8.5 Hz, C-3"-H), 8.33 (1H, m, C-4"-H), 8.73 (1H, d, *J* = 8.5 Hz, C-6"-H), 7.25 (1H, s, C-5-H), 6.60 (1H, s, C-4'-H), 2.4 (3H, s, Ar-CH_3), 2.8 (3H, s, Ar-CH_3).
4l	3415 (NH_2), 1645 (C=N), 1512 (C=C), 1359 (C-N)	5.3 (2H, s, -NH_2), 7.53-7.50 (1H, m, C-5"-H), 6.62 (1H, s, C-4'-H), 7.25 (1H, s, C-5-H), 8.33 (1H, d, *J* = 8.0 Hz, C-4"-H), 7.4 (1H, s, C-2"-H), 8.73 (3H, d, *J* = 8.0 Hz, C-6"-H), 2.4 (1H, s, Ar-CH_3), 2.8 (3H, s, Ar-CH_3).
4m	3418 (NH_2), 1575 (C=N), 1526 (C=C)	5.32 (2H, s, -NH_2), 6.55-6.54 (1H, s, C-4'H), 7.25 (1H, s, C-5-H), 7.46 (2H, d, *J* = 8.5 Hz, C-3"H and 5"H), 7.58 (2H, d, *J* = 8.2 Hz C-2"H and 6"H), 2.4 (3H, s, Ar-CH_3), 2.7 (3H, s Ar-CH_3).
4n	3405 (NH_2), 1565 (C=N), 1516 (C-C), 1360 (C-N), 670 (C-S)	5.3 (2H, s, -NH_2), 6.55-6.58 (1H, s, C-4'H), 7.32 (1H, s, C-5-H), 7.16-7.12 (1H, t, C-4"H), 7.26 (1H, d, *J* = 6 Hz, C-3"H), 7.46 (1H, d, *J* = 8 Hz C- 5"H), 2.3 (3H, s, Ar-CH_3), 2.5 (3H, s, Ar-CH_3).

Same cup plate method using PDA (Potato-Dextrose-Agar) medium was employed to study the preliminary antifungal activity of (**4a-n**) against *A. niger, C. albicans* and *R. oryzae*. The PDA medium was purchased from HI-media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide. Fluconazole employed as

reference standard (1000 µg/mL) to compare the results. The pH of the all the test solutions and control was maintained at 2-3 by using conc. HCl, because the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at a concentration of 0.05 mL (50 µg) and 0.1 mL (100 µg) level and DMSO as control did not show any inhibition.

The cups each of 7 mm diameter were made by scooping out medium with a sterilized cork borer in a Petri dish, which was streaked with the organisms. The solutions of each test compound, control and reference standards (0.05 and 0.1 mL) were added separately in the cups and petri dishes were subsequently incubated at 37 ± 1 ºC for 24 h for antibacterial activity and kept aside at room temperature for 48 h for antifungal activity.

RESULTS AND DISCUSSION

The title compounds 2-amino-4-(2',5'-dimethyl-3'-furyl)-6-(aryl)pyrimidine (**4a-n**) were synthesized in good yields. The physico chemical data of the synthesized compounds and their respective characteristic spectral data are given in Tables 1 and 2. The results of antiinflammatory activity revealed that the compounds (**4a-n**) exhibited moderate to considerable activity when compared to reference standard aceclofenac. In particular, compound **4c** and **4i** possessed maximum activity and this may be due to the presence of a dimethylaminophenyl substituent in the first case and 4-fluorophenyl substituent in the second case.

The antibacterial activity data (Table-4) of pyrimidine derivatives (**4a-n**) indicated that the compounds have some degree of inhibitory activity, when compared with the reference standard benzylpenicillin. Among all the compounds tested, compound **4j** containing 4-nitrophenyl substitution on pyrimidine ring produced maximum inhibitory zone.

The antifungal activity data (Table-5) of pyrimidine derivatives (**4a-n**) revealed that all the compounds in this series have been found to be effective against all fungi, when

TABLE-3
ANTIINFLAMMATORY ACTIVITY OF PYRIMIDINE DERIVATIVES (**4a-n**)

Compound	Per cent inhibition ± SEM at various time intervals					
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
4a	17.89 ± 0.83	24.56 ± 1.02	55.62 ± 1.68	64.36 ± 2.52	81.00 ± 2.61	91.24 ± 2.71
4b	19.82 ± 0.72*	26.46 ± 1.21*	66.32 ± 1.72*	71.51 ± 2.24*	89.56 ± 2.64*	96.73 ± 2.68
4c	22.84 ± 0.85	27.69 ± 1.27	68.12 ± 1.79	70.56 ± 2.26	87.23 ± 2.54*	97.24 ± 2.62
4d	17.34 ± 0.72	19.52 ± 1.43	43.68 ± 2.12	52.43 ± 2.34	86.54 ± 2,59*	89.33 ± 2.76
4e	23.62 ± 0.67	28.64 ± 1.38*	64.67 ± 1.72	72.34 ± 2.07*	86.34 ± 2.47	96.15 ± 1.69
4f	21.32 ± 0.56	24.32 ± 1.27	54.85 ± 1.83	63.332 ± 3.16	76.41 ± 2.52*	92.46 ± 2.61
4g	17.15 ± 1.26	26.31 ± 1.46	55.36 ± 1.82	69.84 ± 2.06	73.24 ± 2.47*	84.39 ± 2.72
4h	19.16 ± 0.93	23.12 ± 1.37	46.24 ± 1.89	69.12 ± 2.35	73.84 ± 2.68	81.15 ± 2.69
4i	23.12 ± 0.91	34.05 ± 1.51	66.32 ± 1.79	78.91 ± 2.59*	84.26 ± 2.54	97.83 ± 2.72
4j	18.67 ± 0.79	23.72 ± 1.31	58.67 ± 1.89	73.18 ± 2.27*	81.34 ± 2.35*	92.76 ± 2.65
4k	16.17 ± 0.85	34.29 ± 1.91*	67.89 ± 1.96	72.16 ± 2.32*	72.45 ± 1.62	84.37 ± 1.71
4l	19.98 ± 0.83	32.84 ± 1.12	44.68 ± 1.56	61.74 ± 2.13	74.12 ± 2.14	84.82 ± 2.61
4m	21.23 ± 0.81	33.14 ± 1.48	55.97 ± 2.31	63.17 ± 1.23	74.87 ± 2.69	83.43 ± 2.89
4n	19.32 ± 0.82	30.12 ± 1.64	57.23 ± 2.51	66.93 ± 2.53	76.24 ± 2.69	85.69 ± 2.79
Aceclofenac	20.26 ± 0.90	23.95 ± 0.97	66.97 ± 2.41	82.97 ± 2.48	88.96 ± 2.52	98.97 ± 2.89

All values are represented as mean ± SEM (n = 6). *P < 0.01 compared to reference standard aceclofenac. Student's t-test. Dosage: aceclofenac-2 mg/kg and test compounds-10 mg/kg body weight of rat

TABLE-4
ANTIBACTERIAL ACTIVITY OF PYRIMIDINE DERIVATIVES (**4a-n**)

Compound	Zone of inhibition (mm)									
	Quantity (µg/mL)									
	B. subtilis		*B. pumilis*		*S. aureus*		*E. coli*		*P. vulgaris*	
	50	100	50	100	50	100	50	100	50	100
4a	12	11	09	10	08	11	11	10	11	08
4b	15	21	17	20	18	23	13	16	14	18
4c	16	18	18	23	20	23	18	23	21	26
4d	20	23	19	18	11	19	18	19	17	18
4e	11	13	14	14	17	21	12	16	11	14
4f	14	18	18	23	14	21	15	17	16	20
4g	19	22	20	24	18	22	16	17	13	16
4h	19	20	18	21	17	17	18	24	25	23
4i	19	21	19	16	21	24	19	21	19	20
4j	19	21	20	24	21	26	21	23	20	25
4k	18	20	17	20	16	21	16	18	15	20
4l	16	20	15	19	15	20	16	18	14	16
4m	14	16	17	20	15	20	18	20	16	18
4n	13	16	15	19	18	19	15	18	20	19
Benzylpenicillin	28	33	31	32	27	30	25	27	28	31

TABLE-5
ANTIFUNGAL ACTIVITY OF PYRIMIDINE DERIVATIVES (**4a-n**)

Compound	Zone of inhibition (mm)					
	Quantity (µg/mL)					
	A. niger		*C. albicans*		*R. oryzae*	
	50	100	50	100	50	100
4a	16	20	17	21	17	19
4b	17	21	15	20	15	18
4c	17	23	24	25	16	18
4d	14	17	16	21	13	18
4e	15	17	21	22	14	16
4f	18	20	22	20	14	19
4g	17	20	21	22	15	18
4h	17	18	20	19	16	18
4i	16	19	21	23	15	19
4j	14	18	19	22	18	21
4k	16	20	22	23	15	18
4l	15	18	19	21	11	16
4m	10	12	12	14	10	15
4n	15	18	18	20	11	17
Fluconazole	24	28	24	28	22	27

compared with reference standard fluconazole. Among all the compounds tested, compound **4c** containing 4-dimethylaminophenyl substitution on pyrimidine ring produced maximum inhibitory zone.

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