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Synthesis and Biological Activity of 4,6-Substituted aryl-1-acetyl pyrimidine-2-ols

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The synthesis of 4-(4'-bromophenyl)-6-substituted aryl-1-acetyl-pyrimidine-2-ols have been reported. The synthesized derivatives were characterized by elemental analysis and spectral data (IR and ^{1}H NMR). All the synthesized derivatives have been evaluated for their antimicrobial and anthelmintic activities against microbes and helminthes.

Key Words: Pyrimidine-2-ols, Biological activities, Helminthes.

INTRODUCTION

Pyrimidine and its derivatives represents one of the important class of heterocyclic system which is associated with the wide range of biological and pharmacological activities such as antimicrobial[1-3], anticancer[4], antihypertensive[5], antipyretic[6], analgesic[7], antiinflammatory[8], insecticidal[9,10] and anthelmintic[11] activities. These versatile biological significance inspired us to synthesize 4,6-substituted aryl-1-acetyl pyrimidine-2-ol derivatives.

Present paper describes the synthesis of 4-(4'-bromophenyl)-6-substituted aryl-1-acetyl pyrimidine-2-ol derivatives (**Scheme-I**), characterization and investigation for their antimicrobial and anthelmintic activities.

EXPERIMENTAL

The melting points (ºC) were recorded by open capillary method and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Shimadzu FTIR 8300 spectrophotometer using KBr pellets. The ^{1}H NMR spectra were recorded on a DRX-300 (300 MHZ) instrument using $CDCl_3$ as solvent (chemical shift in δ ppm), and TMS as internal standard. The completion of reactions was monitored by TLC.

Synthesis of 4-bromo chalcones 1(a-k): 4-Bromoacetophenone (0.01 mol) and anisaldehyde (0.01 mol) were stirred in ethanol (10-20 mL) and 10 mL of 40 % NaOH solution was added to it. The mixture was kept overnight at room temperature. The contents were then poured on crushed ice and acidified with dil. HCl. The solid was filtered, dried and recrystallized from ethanol. The other chalcones were prepared with the same procedure using different aromatic aldehydes. The purity of the compounds has been checked by TLC.

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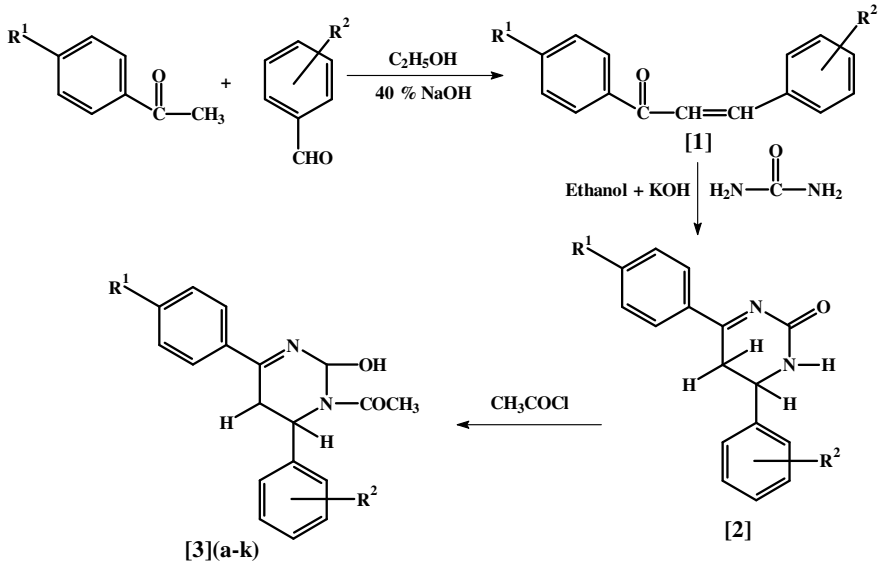

where, R^1 = bromo, R^2 = 4-O-CH_3, 4-OH-3-OCH_3, H, 4-Cl, 2-Cl, 4-N$(CH_3)_2$, 2-NO_2, 3-NO_2, furyl, 2-OH, 4-OH.

Scheme-I

Synthesis of 4-(4'-bromophenyl)-6-substituted phenyl-1,5,5,6-tetrahydro pyrimidine-2-ones 2(a-k): The chalcones (0.01 mol) prepared in step-1, urea (0.01 mol) and KOH (1 g) in ethanol (20 mL) was refluxed on waterbath for 6 h and completion of the reaction was monitored by TLC. After keeping in ice-cold condition, the solid was collected and recrystallized from ethanol. Yield 78 %, m.p. 190 ºC, m.w. 358.9 g, elemental analysis (%): found (calcd.) C: 56.80, (56.84), H: 4.11, (4.17), N: 7.76, (7.80), IR (KBr, ν_{max}, cm^{-1}): 3350-3300 (-N-H *str.*), 1590-1510 (C=N *str.*), 1610-1590 (C=C *str.*), 1750-1640 (C=O *str.*), 820-740 (Ar-H def), 600-536 (Ar-Br *str.*). Similarly other derivatives were prepared with different chalcones applying the same procedure.

4-(4'-Bromophenyl)-6-substituted phenyl-1-acetyl-5,6-dihydropyrimidine-2-ols 3(a-k): The different pyrimidine-2-ones, **2(a-k)** from step- 2 (0.005 mol) and acetyl chloride (16 mL) were heated at 30-40 ºC, under reflux on waterbath for 2 h. Completion of the reaction was monitored by TLC. Excess of acetyl chloride was evaporated and the oily product obtained, was treated with pet ether. The solid obtained was filtered off, dried and recrystallized from ethanol. The physical and spectral data of the synthesized derivatives have been given in Table-1.

Spectral data of compounds 3(a-k)

4-(4'-Bromophenyl)-6-(4''-methoxy phenyl)-1-acetyl-5, 6-dihydro-pyrimidine-2-ol (3a): IR (KBr, ν_{max}, cm^{-1}): 3488 (Ar-O-H *str.*), 1685 (N-C=O *str.*), 1602 (C=C *str.*), 1585 (C=N *str.*), 532 (Ar-Br *str.*), 3052 (Ar-H *str.*), 1278 (C-O-C *str.*). ^{1}H

NMR ($CDCl_3$) δ (ppm): 2.15 (d, 3H, N-CO-CH_3), 2.60 (d, 3H, Ar-O-CH_3), 4.80 (d, 1H, Ar-OH), 5.54 (d, 1H, H-C_6 pyrimidine), 6.73 (d, 1H, H-C_5 pyrimidine), 7.11-7.50 (m, 8H, Ar-H).

TABLE-1
PHYSICAL DATA OF COMPOUNDS **3a-k**

Comp.	R^2	m.f.	m.w.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Found (calcd.)		
						C	H	N
3a	4-O-CH_3	$C_{19}H_{17}N_2O_3Br$	400.9	196	88	56.85 (56.87)	4.21 (4.24)	6.95 (6.98)
3b	4-OH-3-OCH_3	$C_{19}H_{17}N_2O_4Br$	416.9	192	89	54.64 (54.68)	4.01 (4.07)	6.69 (6.71)
3c	H	$C_{18}H_{15}N_2O_2Br$	370.9	158	86	58.21 (58.23)	4.00 (4.04)	7.51 (7.54)
3d	4-Cl	$C_{18}H_{14}N_2O_2BrCl$	405.4	184	89	53.25 (53.28)	3.41 (3.45)	6.89 (6.90)
3e	2-Cl	$C_{18}H_{14}N_2O_2BrCl$	405.4	149	65	53.24 (53.28)	3.42 (3.45)	6.88 (6.90)
3f	4-$N(CH_3)_2$	$C_{20}H_{20}N_3O_2Br$	413.9	110	78	57.94 (57.98)	4.80 (4.83)	10.11 (10.14)
3g	2-No_2	$C_{18}H_{14}N_3O_4Br$	415.9	160	79	51.90 (51.93)	3.31 (3.36)	10.00 (10.09)
3h	3-No_2	$C_{18}H_{14}N_3O_4Br$	415.9	214	86	51.91 (51.93)	3.32 (3.36)	10.01 (10.09)
3i	6-Furyl	$C_{16}H_{13}N_2O_3Br$	360.9	222	89	53.19 (53.20)	3.59 (3.60)	7.71 (7.75)
3j	2-OH	$C_{18}H_{15}N_2O_3Br$	386.9	218	60	55.80 (55.82)	3.84 (3.87)	7.20 (7.23)
3k	4-OH	$C_{18}H_{15}N_2O_3Br$	386.9	210	86	55.80 (55.82)	3.83 (3.87)	7.19 (7.23)

4-(4'-Bromophenyl)-6-(4''-hydroxy-3-methoxyphenyl)-1-acetyl-5,6-dihydropyrimidine-2-ol (3b): IR (KBr, ν_{max}, cm^{-1}): 3409 (Ar-O-H *str.*), 1683 (N-C=O *str.*), 1600 (C=C *str.*), 1589 (C=N *str.*), 592 (Ar-Br *str.*), 3084 (Ar-H *str.*), 1265 (C-O-C *str.*), 2943 (C-H *str.* -CH_3); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.19 (d, 3H, N-CO-CH_3), 2.71 (d, 3H, Ar-O-CH_3) 4.88 (d, 1H, Ar-OH), 5.56 (d, 1H, H-C_6 pyrimidine), 6.75 (d, 1H, H-C_5 pyrimidine), 7.00-7.55 (m, 7H, Ar-H).

4-(4'-Bromophenyl)-6-phenyl-1-acetyl-5,6-dihydropyrimidine-2-ol (3c): IR (KBr, ν_{max}, cm^{-1}): 3488 (Ar-O-H *str.*), 1683 (N-C=O *str.*), 1602 (C=C *str.*), 1585 (C=N *str.*), 532 (Ar-Br *str.*), 3061 (Ar-H *str.*), 2928 (C-H *str.* -CH_3); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.10 (d, 3H, N-CO-CH_3), 4.82 (d, 1H, Ar-OH), 5.55 (d, 1H, H-C_6 pyrimidine) 6.74 (d, 1H, H-C_5 pyrimidine), 7.20-7.55 (m, 9H-Ar-H).

4(4'-Bromophenyl)-6-(4''-chlorophenyl)-1-acetyl-5,6-dihydropyrimidine-2-ol (3d): IR (KBr, ν_{max}, cm^{-1}): 3419 (Ar-O-H *str.*), 1681 (N-C=O *str.*), 1604 (C=C *str.*), 1583 (C=N *str.*), 570 (Ar-Br *str.*), 717 (Ar-Cl *str.*), 3086 (Ar-H *str.*), 2929 (C-

H *str.* -CH_3). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.15 (d, 3H, N-CO-CH_3), 4.84 (d, 1H, Ar-OH), 5.56 (d, 1H, H-C_6 pyrimidine) 6.75 (d, 1H, H-C_5 pyrimidine), 7.17-7.60 (m, 8H-Ar-H).

4-(4'-Bromophenyl)-6-(2'-chlorophenyl)-1-acetyl-5,6-dihydropyrimidine-2-ol (3e): IR (KBr, ν_{max}, cm^{-1}): 3052 (Ar-O-H *str.*), 1681 (N-C=O *str.*), 1608 (C=C *str.*), 1583 (C=N *str.*), 592 (Ar-Br *str.*), 727 (Ar-Cl *str.*), 3064 (Ar-H *str.*), 2926 (C-H *str.* -CH_3). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.16 (d, 3H, N-CO-CH_3), 4.86 (d, 1H, Ar-OH), 5.57 (d, 1H, H-C_6 pyrimidine) 6.76 (d, 1H, H-C_5 pyrimidine), 7.27-7.55 (m, 8H-Ar-H).

4-(4'-Bromophenyl)-6-(4''-dimethylaminophenyl)-1-acetyl-5,6-dihydropyrimidine-2-ol (3f): IR (KBr, ν_{max}, cm^{-1}): 3380 (Ar-O-H *str.*), 1682 (N-C=O *str.*), 1604 (C=C *str.*), 1584 (C=N *str.*), 570 (Ar-Br *str.*), 852 (C-N str in dimethylamino group), 3024 (Ar-H *str.*), 2956 (C-H *str.* -CH_3). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.03 (d, 3H, N-CO-CH_3), 3.02 (d, 6H, N-$(CH_3)_2$), 4.80 (d, 1H, Ar-OH) 5.54 (d, 1H, H-C_6 pyrimidine), 6.73 (d, 1H, H-C_5 pyrimidine), 6.80-7.55 (m, 8H-Ar-H).

4-(4'-Bromophenyl)-6-(2'-nitrophenyl)-1-acetyl-5,6-dihydropyrimidine-2-01 (3g): IR (KBr, ν_{max}, cm^{-1}): 3410 (Ar-O-H *str.*), 1681 (N-C=O *str.*), 1606 (C=C *str.*), 1587 (C=N *str.*), 549 (Ar-Br *str.*), 1572 (Ar-NO_2 *str.*, asym), 1319 (Ar-NO_2 *str.*, sym), 3091 (Ar-H *str.*), 2899 (C-H *str.* -CH_3), ^{1}H NMR ($CDCl_3$) δ (ppm): 2.05 (d, 3H, N-CO-CH_3), 4.91 (d, 1H, Ar-OH), 5.56 (d, 1H, H-C_6 pyrimidine), 6.74 (d, 1H, H-C_5 pyrimidine), 7.27-8.07 (m, 8H, Ar-H).

4-(4'-Bromophenyl)-6-(3'-nitrophenyl)-1-acetyl-5,6-dihydropyrimidine-2-ol (3h): IR (KBr, ν_{max}, cm^{-1}): 3489 (Ar-OH *str.*), 1689 (N-C=O *str.*), 1610 (C=C *str.*), 1580 (C=N *str.*), 605 (Ar-Br *str.*), 1560 (Ar-NO_2 *str.*, asym), 1373 (Ar-NO_2 *str.*, sym), 3063 (Ar-H *str.*), 2875 (C-H *str.* -CH_3), ^{1}H NMR ($CDCl_3$) δ (ppm): 2.04 (d, 3H, N-CO-CH_3), 4.90 (d, 1H, Ar-OH), 5.55 (d, 1H, H-C_6 pyrimidine), 6.73 (d, 1H, H-C_5 pyrimidine), 7.27-8.12 (m, 8H, Ar-H).

4-(4'-Bromophenyl)-6-furyl-1-acetyl-5, 6-dihydro- pyrimidine-2-ol (3i): IR (KBr, ν_{max}, cm^{-1}): 3378 (Ar-OH *str.*), 1683 (N-C=O *str.*), 1614 (C=C *str.*), 1585 (C=N *str.*), 558 (Ar-Br *str.*), 1010 (furyl ring C-O-C *str.*), 3063 (Ar-H *str.*), 2933 (C-H *str.* -CH_3); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.10 (d, 3H, N-CO-CH_3), 4.89 (d, 1H, Ar-OH), 5.56 (d, 1H, H-C_6 pyrimidine), 6.30 (d, 1H, H-C_5 pyrimidine), 7.01-7.65 (m, 7H, Ar-H).

4-(4'-Bromophenyl)-6-(2-hydroxyphenyl)-1-acetyl-5,6-dihydropyrimidine-2-ol (3j): IR (KBr, ν_{max}, cm^{-1}): 3358 (Ar-OH *str.*), 1730 (N-C=O *str.*), 1608 (C=C *str.*), 1539 (C=N *str.*), 590 (Ar-Br *str.*), 3032 (Ar-H *str.*), 2904 (C-H *str.* -CH_3); ^{1}H NMR ($CDCl_3$) δ (ppm), 2.08 (d, 3H, N-CO-CH_3), 5.36 (d, 2H, Ar-OH), 5.58 (d, 1H, H-C_6 pyrimidine), 6.74 (d, 1H, H-C_5 pyrimidine), 6.92-7.76 (m, 8H, Ar-H).

4-(4'-Bromophenyl)-6-(4''-hydroxyphenyl)-1-acetyl-5,6-dihydropyrimidine -2-ol (3k): IR (KBr, ν_{max}, cm^{-1}): 3458 (Ar-O-H *str.*), 1680 (N-C=O *str.*), 1583 (C=C *str.*), 1489 (C=N *str.*), 534 (Ar-Br *str.*), 3084 (Ar-H *str.*), 2916 (C-H *str.* -CH_3); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.02 (d, 3H, N-CO-CH_3), 5.35 (d, 2H, Ar-O-H), 5.60 (d, 1H, H-C_6 pyrimidine), 6.73 (d, 1H, H-C_5 pyrimidine), 6.90-7.7 (m, 8H, Ar-H).

Antimicrobial activity[12,13]: The synthesized compounds **3a-k** were screened for their *in vitro* antimicrobial activity against, *B. subtilis*, *E. coli*, *K. pneumoniae* and *S. aureus* and antifungal activity against, *A. niger*, *A. flavus*, *T. viride*, *C. albicans*. The antimicrobial activity was performed by standard filter paper disc diffusion method and zone of inhibition has been reported in the Table-3. Streptomycin and nystatin were used as standard drugs for antibacterial and antifungal activities respectively. Nutrient agar was employed as culture medium and DMSO were used as solvent.

***In vitro* anthelmintic activity[14]:** *In vitro* anthelmintic screening study of compounds **3a-j** were performed by the Watkins technique, against common Indian earthworm '*P. posthuma*".

For this purpose 4 and 2 % solutions of the synthesized pyrimidine derivatives and standard drug piperazine hydrochloride in ethylene glycol were used. The experiments were performed in duplicate and an average paralytic time and lethal time in minutes have been given in the table.

RESULTS AND DISCUSSION

It has been inferred from the Tables 2 and 3, the synthesized pyrimidine derivatives **3 (a-k)** have exhibited pronounced antibacterial,while moderate antifungal activities, moderate to good anthelmintic activities against microbes and helminthes selected, as compared to standard drugs. Derivatives with methoxy, amino, furyl, imidazolo and chloro groups have been exhibited better antibacterial activity than the rest.

TABLE-2
ANTIMICROBIAL DATA OF COMPOUNDS **3a-k**

Compounds	Antibacterial				Antifungal			
	B. Subtilis	*E. Coli*	*K. Pneumoniae*	*S. Aureus*	*A. niger*	*A. Flavus*	*T. viride*	*C. albicans*
3a	+	++	+	++	+++	++	++	+++
3b	+	++	+	++	+++	+++	+++	++
3c	++	+++	++	+++	++	–	+	++
3d	++	+++	++	+++	++	++	+	++
3e	++++	+++	++	+++	+	+++	+	+
3f	++++	+++	++	+++	+	+++	+	+
3g	+++	++	+++	+++	+++	++	++	+
3h	++	+++	++	++	++	+	+++	–
3i	+++	+++	++	+++	+++	++	++	++
3j	+++	+++	+++	+++	+++	++	+++	++
3k	+++	++	++	++	++	+	+	–
Streptomycin	++++	+++	+++	++++	–	–	–	–
Nystatin	–	–	–	–	++++	+++	++++	+++

Zone of inhibition was measured in mm. ++++: (18-20 mm) strong activity, +++: (15-18 mm) good activity, ++: (10-15 mm) moderate activity, +: (8-10) poor activity, –: (< 8) inactive.

TABLE-3
ANTHELMINTIC ACTIVITY OF COMPOUNDS **3a-k** (IN MINUTES)

Compound	R^2	Concentration			
		4 %		2 %	
		Paralytic time	Lethal time	Paralytic time	Lethal time
3a	4-O-CH_3	10	16	11	19
3b	4-OH-3-OCH_3	8	14	9	17
3c	H	12	17	13	20
3d	4-Cl	10	16	12	20
3e	2-Cl	9	14	11	18
3f	4-N$(CH_3)_2$	8	14	9	18
3g	2-NO_2	9	15	10	18
3h	3-NO_2	12	16	11	17
3i	6-furyl	9	15	10	17
3j	2-OH	10	14	11	17
3k	4-OH	11	16	12	20
Std. drug	Piperazine hydrochloride	6	13	7	15

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