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ARTICLE

Synthesis, Characterization and Anti-inflammatory Activity of New Pyrimidines

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ABSTRACT

The synthesis of some pyrimidine derivatives was achieved by condensation of 2-hydroxyacetophenone and cinnamic acid as starting materials through 1,3-diketones as intermediates. The resulting diketones have been converted into substituted pyrimidines by reaction with urea, thiourea and guanidine in the presence of trace of triethylamine and pyridine in calculated quantity. The synthesized compounds were characterized by their physical properties, NMR and LC-mass spectroscopic studies and also screened for their anti-inflammatory activity.

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KEYWORDS

Pyrimidines, 1,3-Diketones, Cinamoyloxyacetophenones, Triethylamine, Pyridine, Anti-inflammatory activity, Paw edema.

INTRODUCTION

Heterocyclic compounds containing "N" atom are most abundantly distributed in nature and compound having pyrimidine nucleus possesses broad range of biological activities [1-7]. Derivatives of pyrimidine have played crucial roles in the history of heterocyclic chemistry and used extensively as important pharmacophores and synthons in the field of organic chemistry and drug design. The pyrimidine nucleus also constitutes the major part of vital molecules including vitamins such as thiamine [8], riboflavin [9] and folic acid [10]. Recently, structurally simple dihydropyrimidinone (DHPM) derivative monastrol has emerged as a mitotic kinesin Eg5 motor protein inhibitor for the development of anticancer drugs [11] and also identified as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest [12].

Pyrimidines have high electron-accepting property induced by C=N double bonds and its coordination ability [13], due to which they play a key role as an organic semiconductor or semiconducting material and also using as a building block in phosphorescent emitters, fluorescent emitters, bipolar host materials, and electron transporting materials in organic light-emitting devices (OLEDs). The early reports and many important contributions describing a variety of synthetic strategies for preparation of pyrimidine derivatives have been published. Many of these prevailing strategies rely on condensation of N-C-N fragments, most often amidines or guanidines with 1,3-dicarbonyl derivatives [14-16].

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We have prepared total nine new pyrimidines in three steps, using cinnamic acids and *o*-hydroxyacetophenones as starting materials. The substituted cinnamic acids were prepared from commercially available benzaldehydes and melonic acid using Knoevengal-Doebner reaction conditions. Then substituted cinnamic acids were treated with *o*-hydroxyacetophenone in pyridine solution using $POCl_3$ as condensing agent to obtain 2′-cinnamoyloxyacetophenones. These 2′-cinnamoyloxyacetophenones were treated with powdered KOH in pyridine to get 1,3-diketones [17], and then finally converted into the desired pyrimidine by treating with different amides and finally they were tested for their anti-inflammatory activity.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus in an open capillary tubes are uncorrected. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Joel JNM λ-300 spectrometer using TMS as internal reference. The values for chemical sifts (δ) being given in ppm and coupling constants (*J*) in hertz (Hz). LC-MS was recorded on an Agilent-1100 periods LC/MSD (VL). Elemental analysis was performed on a Vario EL-III. TLC was carried out on GF_{254} silica gel plates. Column chromatography was performed with Merck silica gel 60-120, 100-200 mesh. All other chemicals and solvents used were obtained from commercial sources and used as received standard procedures.

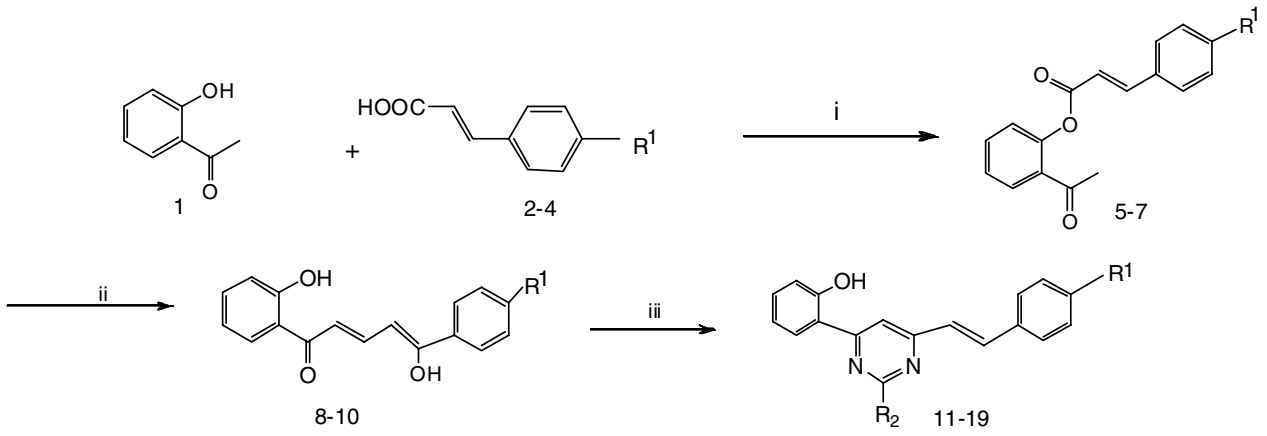
Synthesis of substituted pyrimidines (11-19): The obtained diketone (1 mmol) was mixed with urea, thiourea, or guanidine hydrochloride, in pyridine and then stirred on electromagnetic stirrer for about 4 h with catalytic amount of triethylamine (**Scheme-I**). The completion of reaction was monitored by TLC and the reaction mixture was poured into crushed ice with stirring and acidified with 10 % HCl. The obtained precipitate was filtered and recrystallized from ethanol.

Characterization data

4-(2-Hydroxyphenyl)-6-(4-methoxystyryl)pyrimidine-2-thiol (11): Following the above mentioned procedure, compound **11** was obtained from 1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.503 g), thiourea (1 mmol, 0.258 g) as bright yellow colour solid. Yield: 0.536 g (94 %), m.p. 116-118 ºC. ^{1}H NMR (DMSO-d_6): δ 15.55 (1H, br, s, Ar-OH), 11.47(1H, SH), 7.7-7.4 (4H, m), 7.2-6.9 (4H, m), 7.61 (1H, d, *J* = 16.0 Hz, H-α), 7.65 (1H, d, *J* = 16.0 Hz, H-β), 6.8(1H, s, pyrimidine), 3.8(1H, s, OCH_3). ^{13}C NMR (DMSO-d_6): δ 170.91 (pyrimidine), 160.4, 159.7, 158.3, 155.3, 134.7, 130.1, 129.4, 128.9, 127.9, 124.5, 123.2, 120.4, 117.7, 115.6, 114.3, 55.5 (OCH_3). LC-MS (ESI, negative ion mode): *m/z* 335 $(M-H)^-$. Elemental analysis: calcd. (found) for $C_{19}H_{16}N_2O_2S$: C 67.80 (66.69); H 4.70 (4.39); N 8.30 (7.83), S 9.50 (9.25).

4-(2-Hydroxyphenyl)-6-(4-methoxystyryl)-2-hydroxypyrimidine (12): Following the general procedure, compound **12** was obtained from 1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.355 g), urea (1 mmol, 0.144 g) as light yellow colour solid. Yield: 0.328 g, (88.8 %), m.p.: 120-122 ºC. ^{1}H NMR (DMSO-d_6): δ 15.57 (1H, br, s, Ar-OH), 11.44 (1H, OH),7.7-7.6 (2H, d), 7.4-7.2 (4H, m), 7.0 (2H, d), 7.60 (1H, d, *J* = 16.0 Hz, H-α), 7.64 (1H, d, *J* = 16.0 Hz, H-β), 6.8 (1H, s, pyrimidine), 3.8 (1H, s, OCH_3). ^{13}C NMR (DMSO-d_6): δ 168.94 (pyrimidine), 160.4, 159.7, 158.1, 155.3, 134.7, 130.1, 129.1, 128.9, 128.7, 124.5, 123.3, 120.6, 117.4, 115.8, 114.3, 55.35 (OCH_3). LC-MS (ESI, positive ion mode): *m/z* 321 $(M+H)^+$. Elemental analysis: calcd. (found) for $C_{19}H_{16}N_2O_3$: C 71.2 (71.30); H 5.0 (5.17); N 8.7 (8.48).

4-(2-Hydroxyphenyl)-6-(4-methoxystyryl)-2-aminopyrimidine (13): Following the general procedure, compound **13** was obtained from 1-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-3-hydroxy-2,4-pentadiene-1-one (0.355 g), guanidine hydrochloride (1 mmol, 0.114 g) as yellow colour solid. Yield: 0.347 g, (91.6 %), m.p. 98-100 ºC. ^{1}H NMR (DMSO-d_6): δ 15.57 (1H, br, s, Ar-OH), 9.4 (2H, NH_2), 7.7-7.6 (2H, d), 7.4-7.2 (4H, m), 7.0 (2H, d), 7.60 (1H, d, *J* = 16.0 Hz, H-α), 7.64 (1H, d, *J* = 16.0 Hz, H-β), 6.8 (1H, s, pyrimidine), 3.8 (1H, s, OCH_3). ^{13}C NMR (DMSO-d_6): δ 163.0 (pyrimidine), 161.4, 159.7, 158.1, 155.3, 134.9, 130.0, 129.2, 128.9, 127.4, 124.5, 123.3, 120.3, 117.7, 115.5, 114.5, 55.3 (OCH_3). LC-MS (ESI,



(11) R^1= OCH_3, R^2= SH; (12) R^1=OCH_3, R^2 =OH; (13) R^1=OCH_3, R^2=NH_2; (14) R^1=Cl, R^2=SH; (15) R^1=Cl, R^2=OH; (16) R^1=Cl, R^2=NH_2; (17) R^1=H, R^2= SH; (18) R^1=H, R^2=OH; (19) R^1=H, R^2=NH_2

Reagents & conditions: (i) Pyridine; $POCl_3$, room temperature, 4 h; (ii) Dry pyridine, KOH, room temperature, 1-2 h; (iii) Urea, thiourea, or guanidine hydrochloride pyridine, triethylamine, 4 h stirring at room temperature

Scheme-I

positive ion mode): *m/z* 318 $(M+H)^+$. Elemental analysis: calcd. (found) for $C_{19}H_{17}N_3O_2$: C 71.4 (71.30); H 5.30 (5.15); N 13.10 (12.98).

4-(2-Hydroxyphenyl)-6-(4-chlorostyryl)pyrimidine-2-thiol (14): Following the general procedure, compound **14** was obtained from 1-(2-hydroxyphenyl)-5-(4-chlorophenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.510 g), thiourea (1 mmol, 0.258 g) as brownish yellow colour solid. Yield 0.54 g (94.7 %). m.p. 142-146 ºC. ^{1}H NMR (DMSO-d_6): δ 12.46 (1H, br, s, Ar-OH), 11.39 (1H, s, SH), 7.8-7.7 (4H, m), 7.4-7.2 (4H, m), 7.57 (1H, d, *J* = 16.0 Hz, H-α), 7.61 (1H, d, J=16.0 Hz, H-β), 6.58 (1H, s, pyrimidine). ^{13}C NMR (DMSO-d_6): δ 167.33 (pyrimidine, SH), 161.11, 158.80, 155.00, 135.70, 133.50, 132.40, 130.43, 129, 128, 124.50, 123.60, 120.09, 116.40, 114.60. LC-MS (ESI, positive ion mode): *m/z* 341.5 $(M+H)^+$. Elemental analysis: calcd. (found) for $C_{18}H_{13}N_2OSCl$: C 63.40 (63.84); H 3.80 (3.25); N 8.20 (8.40); S 9.30 (9.13); Cl 10.40 (10.39).

4-(2-Hydroxyphenyl)-5-(4-chlorostyryl)-2-hydroxypyrimidine (15): Following the general procedure, compound **15** was obtained from 1-(2-hydroxyphenyl)-5-(4-chlorophenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.510 g), urea (1 mmol, 0.204 g), greenish yellowcolour solid. Yield: 0.53 g, (96.5 %). m.p. 102-104 ºC. ^{1}H NMR (DMSO-d_6): δ 15.46 (1H, br, s, Ar-OH), 11.35 (1H, s, pyrimidine, OH), 7.7 (4H, m), 7.5-7.4 (4H, m), 7.61 (1H, d, *J* = 16.0 Hz, H-α), 7.65 (1H, d, *J* = 16.0 Hz, H-β), 6.8 (1H, s, pyrimidine). ^{13}C NMR (DMSO-d_6): δ 165.1 (pyrimidine, OH), 159.6, 158.8, 155.3, 135.15, 134.66, 133.79,130.42, 129.8, 128.0, 124, 120.51, 117.71, 114.6. LC-MS (ESI, positive ion mode): *m/z* 325.5 $(M+H)^+$. Elemental analysis: calcd. (found) for $C_{18}H_{13}N_2O_2Cl$: C 66.5 (66.78); H 4.0 (4.10); N 8.6 (8.48); Cl 10.9 (10.85).

4-(2-Hydroxyphenyl)-5-(4-chlorostyryl)-2-aminopyrimidine (16): Following the general procedure, compound **16** was obtained from 1-(2-hydroxyphenyl)-5-(4-chlorophenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.510 g), guanidine hydrochloride (1 mmol, 0.162 g), as brownish colour solid. Yield: 0.49 g (89 %). m.p. 159-161 ºC. ^{1}H NMR (DMSO-d_6): δ 12.01 (1H, br, s, Ar-OH), 9.01 (1H, s, NH_2), 7.7 (4H, m), 7.5-7.4 (4H, m), 7.61 (1H, d, *J* = 16.0 Hz, H-α), 7.65 (1H, d, *J* = 16.0 Hz, H-β), 6.8 (1H, s, pyrimidine). ^{13}C NMR (DMSO-d_6): δ 163.8 (pyrimidine, OH), 159.68, 158.8, 155.3, 135.7, 134.3, 132.98, 130.2, 129.8, 128.8, 127.2, 123.6, 121.9, 120.6, 116.4, 114.6. LC-MS (ESI, negative ion mode): *m/z* 322.5 $(M-H)^-$. Elemental analysis: calcd. (found) for $C_{18}H_{14}N_3OCl$: C 66.70 (66.47); H 4.30 (4.25); N 12.90 (12.88); Cl 10.90 (10.89).

4-(2-Hydroxyphenyl)-6-styrylpyrimidine-2-thiol (17): Compound **17** was obtained from 1-(2-hydroxyphenyl)-5-phenyl-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.798 g), thiourea (1 mmol, 0.456 g), greenish yellow colour solid. Yield: 0.840 g (91.50 %). m.p.: 96-97 ºC. ^{1}H NMR (DMSO-d_6): δ 12.13 (1H, br, s, Ar-OH), 11.39 (1H, s, SH), 7.9-7.8 (2H, d), 7.7 (2H, d,), 7.5-7.3 (5H, m), 7.63 (1H, d, *J* = 16.0 Hz, H-α), 7.67 (1H, d, *J* = 16.0 Hz, H-β), 6.9 (1H, s, pyrimidine). ^{13}C NMR (DMSO-d_6): δ 168.87 (SH), 159.74, 158.10, 155.08, 135.13, 134.79, 130.12, 128.97, 126.06, 124.50, 123.30, 120.44, 117.72, 115.80. LC-MS (ESI, negative ion mode): *m/z* 305 $(M-H)^-$. Elemental analysis: calcd. (found) for $C_{18}H_{14}N_2OS$: C 70.50 (70.51); H 4.50 (4.27); N 9.10 (9.17); S 10.40 (10.36).

4-(2-Hydroxyphenyl)-6-styryl-2-hydroxypyrimidine (18): Compound **18** was obtained from 1-(2-hydroxyphenyl)-5-(phenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.665 g), urea (1 mmol, 0.3 g), yellow colour solid. Yield: 0.66 g, (92 %). m.p.: 108-110 ºC. ^{1}H NMR (DMSO-d_6): δ 15. 46 (1H, br, s, Ar-OH), 11.41 (1H, s, OH), 7.9-7.8 (2H, d), 7.7 (2H, d), 7.5-7.4 (5H, m), 7.63 (1H, d, *J* = 16.0 Hz, H-α), 7.67 (1H, d, *J* = 16.0 Hz, H-β), 6.9 (1H, s, pyrimidine). ^{13}C NMR (DMSO-d_6): δ 160.21 (pyrimidine OH), 159.77, 158.79, 155.23, 135.13, 134.79, 130.11, 128, 126.14, 124.50, 123.28, 120.45, 117.73, 115.80. LC-MS (ESI, negative ion mode): *m/z* 291 $(M-H)^-$. Elemental analysis: calcd. (found) for $C_{18}H_{14}N_2O_2$: C 74.40 (74.43); H-4.80 (4.57); N 9.60 (9.48).

4-(2-Hydroxyphenyl)-6-styryl-2-aminopyrimidine (19): Compound **19** was obtained from 1-(2-hydroxyphenyl)-5-(phenyl)-3-hydroxy-2,4-pentadiene-1-one (1 mmol, 0.931 g), guanidine hydrochloride (1 mmol, 0.13 g), yellow colour solid. Yield: 0.89 g (89 %). m.p. 112-114 ºC. ^{1}H NMR (DMSO-d_6): δ 15.46 (1H, br, s, Ar-OH), 9.4 (2H, s, NH_2), 7.9-7.8 (2H, d), 7.7 (2H, d), 7.5-7.3 (5H, m), 7.63 (1H, d, *J* = 16.0 Hz, H-α), 7.67 (1H, d, *J* = 16.0 Hz, H-β), 6.89 (1H, s, pyrimidine). ^{13}C NMR (DMSO-d_6): δ 163.80 (pyrimidine, NH_2), 159.77, 158.79, 155.23, 135.13, 134.79, 130.11, 128, 126.45, 124.50, 123.30, 120.43, 117.72, 115.80. LC-MS (ESI, negative ion mode): *m/z* 290 $(M+H)^+$. Elemental analysis: calcd. (found) for $C_{18}H_{15}N_3O$: C 74.70 (74.59); H 5.10 (5.12); N 14.50 (14.48).

Anti-inflammatory activity: All the newly synthesized compounds were studied for anti-inflammatory activity by the carrageenan induced hind paw edema test [18] in mice. A 0.5 % w/v of sodium carboxyl methylcellulose (CMC) suspension was used as vehicle for the control group. All mices have been divided into eleven groups. Group I served as control to administered vehicle only. The standard drug ibuprofen (dose 50 mg/kg) was administered to Group II animals. The synthesized compounds **11-19** were administered to Group III to XI animals, respectively. The rats were dosed with test drugs orally including the reference standard with help of oral feeding needle. After 30 min of drug administration, 0.1 mL of 1 % w/v carrageenan solution in saline was injected in the sub-plantar region of left hind paw of control as well as standard and test groups. The volume of injected paws was measured at 0 and 3 h after induction of edema by using a plethysmometer. The volume of edema was expressed for each animal as the difference between zero and three hours volume. The percent inhibition of edema was calculated by following formula:

$$\text{Inhibition of edema (\%)} = \frac{V_c - V_t}{V_c} \times 100$$

where V_t = Mean paw volume of treatment group; V_c = Mean paw volume of control group.

RESULTS AND DISCUSSION

This work reports a simple and effective method for the synthesis of pyrimidines. Our purpose was to synthesize a series of pyrimidine derivatives through 1,3-diketone intermediates starting from substituted cinnamic acids and 2-hydroxyacetophenone. Total nine new pyrimidines in three steps, using cinnamic acids and *o*-hydroxyacetophenone as the starting

materials. The substituted cinnamic acids were prepared from commercially available benzaldehydes and melonic acid using Knoevengal-Doebner reaction conditions.

Later the above synthesized cinnamic acids were treated with *o*-hydroxyacetophenone in pyridine solution using $POCl_3$ as condensing agent to obtain 2′-cinnamoyloxyacetophenones.These 2′-cinnamoyloxyacetophenones were treated with powdered KOH in pyridine to get 1,3-diketones and then finally converted into the desired pyrimidine by treating with respective amides.

In this process triethylamine is very helpful in increasing yield as well as purity of product within the less time relatively. The completion of chemical reaction was monitored by thin-layer chromatography. The final products have been confirmed from their spectral analysis *viz*. ^{1}H NMR, ^{13}C NMR and LC-mass. The spectral value in proton NMR at δ 6.58-6.90 (1H, s) indicate proton in pyrimidine ring. The δ value at 7.57-7.60 ppm is due to shielding of α-protons in styryl group, whereas β-protons resonate at relatively higher δ values because of polarization of π-electrons, in the range 7.61-7.67 ppm. The Trans configuration of H_α & H_β was conformed from *J* values at 16.0 Hz. The aromatic protons give signals at various δ values depending on nature and position of substituent. Phenolic protons are noticed at 15.55-12.46 ppm. The methoxyl protons give strong signal at 3.80 ppm.

The ^{13}C NMR values obtained at 170, 159, 158,115 ppm conforms the presence of pyrimidine group. The high δ values at 160, 155, 135, *etc*. conformed that aromatic carbons substituted to -OH, -OCH_3 and -Cl groups. All the synthesized final products show strong peaks in their LC-mass spectra at respective mass values in positive ion and negative ion modes.

Pyrimidine derivatives exhibited normal to moderate anti-inflammatory in comparison with standard drug. The presence of methoxyl group and thiol in pyrimidine play the major role in inhibitory effects. The anti-inflammatory activities of compounds **11-19** were studied in carrageenan induced edema model of inflammation in mice. The percent inhibition of edema was calculated against the control on the basis of experimental data obtained. All the pyrimidine derivatives showed significant anti-inflammatory activity. The compound **11** showed better activity may be due to the presence of methoxyl in styryl ring at 4-position and thiol group at 2nd position of pyrimidine. The compounds **13**, **14**, **16**, **17** exhibited moderate activity may be due to the presence of chlorine in styryl group and amino groups in pyrimidine nucleolus (Table-1). Hence, the anti-inflammatory activity of pyrimidine derivatives was increased with styryl group substituted by electron releasing group at 4th position. The other pyrimidine derivatives **12**, **15**, **18** and **19** showed low activity.

TABLE-1
ANTI-INFLAMMATORY ACTIVITY
OF PYRIMIDINE DERIVATIVES

Group	Compound	V_c-V_t	% Inhibition of edema at the end of 3 h
Group-1	Control	1.43±0.0070	–
Group-2	Std. Ibuprofen	1.4370-0.3075	78.60
Group-3	**11**	1.4370-0.4914	65.80
Group-4	**12**	1.4370-0.7593	47.16
Group-5	**13**	1.4370-0.5371	62.93
Group-6	**14**	1.4370-0.5082	64.95
Group-7	**15**	1.4370-0.9153	36.30
Group-8	**16**	1.4370-0.5832	59.41
Group-9	**17**	1.4370-0.5216	63.70
Group-10	**18**	1.4370-0.7132	50.36
Group-11	**19**	1.4370-0.6583	54.18

Values expressed as mean ± SEM, n = 3 in each group, *P < 0.05 compared with control.

Conclusion

A total of nine pyrimidine derivatives were synthesized containing styryl groups at one position of pyrimidine ring. The yield and purity of final products were enhanced by using trace amount of triethylamine at third stage of preparation. All the reactions gave their target products in good to excellent yield. The reactions are rapid and facile and accomplished at room temperature. Among the nine synthesized compounds, compounds **11**, **14** and **17** showed better activities which may be due to the presence of thiol and other electron donating groups. These studies can be utilized for further biological studies of synthesized pyrimidines.

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