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Synthesis and anti-inflammatory activity of some [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl]-acetic acid derivatives*

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Dihydropyrimidines **4a-r** have been synthesized by base catalysed condensation of β-aroylpropanoic acid, guanidine nitrate and aromatic aldehyde. Structures of the new compounds were established on the basis of ^{1}H NMR and IR spectral data. Anti-inflammatory activity *in vivo* was evaluated and compared with standard drug diclofenac sodium.

Keywords: dihydropyrimidines, aryl alkanoic acids, anti-inflammatory activity

Similar groups/structures often exhibit similar biological activities. However, they usually exhibit different potency. The traditional structure activity relationship (SAR) investigations are a useful tool in the search for new drugs. However, SAR is usually determined by making minor changes to the structure of the existing compound and assessing the effect on its biological activity (1). Heterocyclic compounds have been reported for anti-inflammatory activity (2, 3). Among them aryl alkanoic acids are the most studied class of compounds (4, 5). Pyrimidines have also been reported to possess antifolate (6), antimicrobial (7), leishmanicide (8), anticonvulsant (9), anti-Rubella (10), anti-HIV-1 (11), calcium channel modulating (12) and selective hepatitis B virus inhibiting activities (13). Literature survey reveals that less attention is given to the synthesis and activity of the pyrimidine nucleus having the acetic acid group at its fifth position. Here we report on the synthesis of [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl]-acetic acids **4a-r** and their anti-inflammatory activity.

* This work is dedicated to Prof. M. S. Shingare, Dr. B. A. M. University, Aurangabad
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EXPERIMENTAL

Melting points were taken in an open capillary and are uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded on a JASCO spectrophotometer (Japan) using KBr pellets. ^{1}H NMR spectra in $CDCl_3$ were recorded on a multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker, Germany), 300 MHz, using TMS as an internal standard.

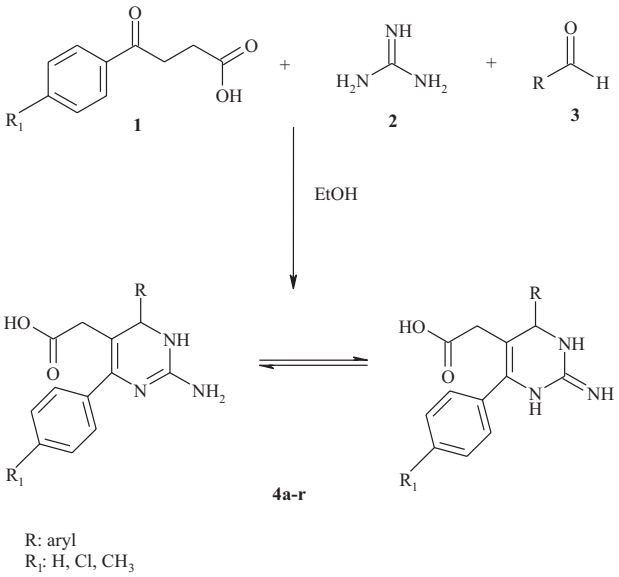
Satisfactory elemental analyses (± 0.4% of the calculated values) were obtained for all compounds.

*General synthetic procedure for [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl]-acetic acid derivatives (**4a-r**)*

A mixture of β-benzoylpropanoic acid (**1**, 0.06 mol), guanidine nitrate (**2**, 0.06 mol), aldehyde (**3**, 0.06 mol) and K_2CO_3 (0.06 mol) in 100 mL ethanol (95%) was refluxed in oil bath. It was cooled, the crystalline solid thus obtained was filtered off, dried and dissolved in hot water. It was filtered again and neutralised with acetic acid. The solid thus obtained was filtered off, washed with cold water, dried and recrystallised from a suitable solvent.

All compounds **4a-r** were synthesised following the same procedure (see Scheme 1). The analytical data for compounds **4a-r** are given in Table I.

The newly synthesised compounds were racemic mixtures and were not separated into chiral molecules.



Scheme 1

Anti-inflammatory activity

Anti-inflammatory activity of all title compounds was taken by the carageenan-induced rat paw edema test as described by Winter *et al.* (14). Albino rats of either sex (150–200 g) were divided into different groups, containing six animals each. Animals were fasted for 12 h before experiment and only water was allowed. While the first group was the control and received the vehicle (Tween 80 in propylene glycol, 10%, *V/V*, 0.5 mL per rat), the second group received diclofenac sodium (10 mg kg^{-1} body mass). All the remaining groups received the test compounds at the same dose orally (10 mg kg^{-1} body mass). All the suspensions for the oral dose were prepared in the vehicle mentioned above and administered in a constant volume of 0.5 mL per rat. One hour after the administration of the test compounds and diclofenac sodium, 0.1 mL of 1% *(m/V)* suspension of carageenan was injected into the left paw subplantar of control and test animals. The paw volume was measured immediately using a plethismometer (initial paw volume), and thereafter the paw volume was measured every half an hour for three hours. Percentage edema inhibition is reported in Table I.

RESULTS AND DISCUSSION

When [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidin-5-yl]-acetic acids (**4a-r**) were prepared by acid catalysed condensation, which usually gives good yields (40–50%) for phenyl and *p*-substituted halogen derivatives, it was of poor synthetic value for the preparation of *p*-alkyl and hetero analogues. We therefore attempted the base catalysed condensation of the β-aroylpropanoic acid and guanidine nitrate with the appropriate aldehyde. This method was found to be of wide applicability (15) for preparing various substituted pyrimidine derivatives **4a-r** in good yield. The title compounds thus prepared were confirmed by elemental, IR and ^{1}H NMR analyses (Table I).

The newly synthesised compounds were subjected to preliminary testing for their anti-inflammatory activity in comparison with the reference drug, dicklofenac sodium. The percentage reduction in the inflammation (*i.e.* reduction in the left hand paw edema volume of the animals) 3 h after administration of carageenan was recorded. All the compounds showed a tendency to causing a reduction in edema. Compounds having the phenyl and *p*-methoxyphenyl group at C-4 and the phenyl, *p*-chlorophenyl and *p*-tolyl group at C-6 (compounds **4c**, **4i** and **4o)** showed remarkable anti-inflammatory activity. It was observed that the methoxy groups attached to the *para* position of the aryl ring at C-4 enhanced the anti-inflammatory activity. It was also observed that the presence of the phenyl group at C-4 and the *p*-chlorophenyl and *p*-tolyl group at C-6 exerted good activity (compounds **4g** and **4m**). Further, it was observed that the presence of heterocyclic moiety at C-4 reduced the activity (compounds **4d**, **4e**, **4f**, **4j**, **4k**, **4l**, **4p**, **4q** and **4r**).

Table I. Characterisation data and anti-inflammatory activity of compounds ***4a-r***

Compound No.	R_1	R	Mol. formula (M_r)	M. p. (°C)	Yield (%)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$, δ, ppm)	Activity $\bar{x} \pm SD$ (%)
4a	H	Phenyl	$C_{18}H_{17}N_3O_2$ (307.35)	185–187	60[a] 37[b]	3350 (NH), 2600–3300 (b–OH), 1681 (C=O)	2.9 (s, 2H, CH_2), 4.52 (s, 1H, CH), 5.96 (s, 3H, NH b), 7.0–7.5 (m, 10H, ArH), 11.03 (s, 1H, OH b)	22.2 ± 1.2
4b	H	4-Chloro-phenyl	$C_{18}H_{16}ClN_3O_2$ (341.79)	172–176	57[a] 35[b]	3350 (NH), 2680–3300 (b–OH), 1689 (C=O)	2.9 (s, 2H, CH_2), 5.58 (s, 1H, CH), 5.92 (s, 3H, NH b), 7.0–7.6 (m, 9H, ArH), 11.0 (s, 1H, OH b)	20.5 ± 2.0
4c	H	4-Methoxy	$C_{19}H_{19}N_3O_3$ (337.37)	177–182	45[a] 25[b]	3380 (NH), 2600–3260 (b–OH), 1690 (C=O)	2.8 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 5.52 (s, 1H, CH), 6.0 (s, 3H, NH b), 6.5–7.3 (m, 9H, ArH), 11.0 (s, 1H, OH b)	28.2 ± 2.4
4d	H	2-Thiophene	$C_{16}H_{15}N_3O_2S$ (313.37)	171–173	65[a] 40[b]	3385 (NH), 2650–3300 (b–OH), 1710 (C=O)	2.9 (s, 2H, CH_2), 5.56 (s, 1H, CH), 5.97 (s, 3H, NH b), 6.6–7.4 (m, 8H, ArH), 11.1 (s, 1H, OH b)	17.1 ± 1.9
4e	H	Furfural	$C_{16}H_{15}N_3O_3$ (297.31)	165–168	40[a] 35[b]	3350 (NH), 2580–3230 (b–OH), 1720 (C=O)	2.9 (s, 2H, CH_2), 5.6 (s, 1H, CH), 6.2 (s, 3H, NH b), 6.0–7.3 (m, 8H, ArH), 11.0 (s, 1H, OH b)	19.2 ± 2.1
4f	H	3-Nicotine	$C_{17}H_{16}N_4O_2$ (308.33)	189–193	48[a] 35[b]	3340 (NH), 2590–3330 (b–OH), 1672 (C=O)	2.9 (s, 2H, CH_2), 5.7 (s, 1H, CH), 5.97 (s, 3H, NH b), 7.0–8.67(m, 9H, ArH), 11.03 (s, 1H, OH b)	11.4 ± 1.8
4g	Cl	Phenyl	$C_{18}H_{16}ClN_3O_2$ (341.79)	166–168	50[a] 30[b]	3355 (NH), 2658–3350 (b–OH), 1675 (C=O)	2.96 (s, 2H, CH_2), 5.59 (s, 1H, CH), 5.87 (s, 3H, NH b), 7.0–7.3 (m, 9H, ArH), 11.0 (s, 1H, OH b)	26.2 ± 2.4
4h	Cl	4-Chloro-phenyl	$C_{18}H_{15}Cl_2N_3O_2$ (376.24)	187–190	55[a] 37[b]	3370 (NH), 2690–3300 (b–OH), 1689 (C=O)	2.93 (s, 2H, CH_2), 5.52 (s, 1H, CH), 5.88 (s, 3H, NH b), 7.0–7.4 (m, 8H, ArH), 11.0 (s, 1H, OH b)	22.6 ± 2.7
4i	Cl	4-Methoxy	$C_{19}H_{18}ClN_3O_3$ (371.82)	180–184	60[a] 40[b]	3350 (NH), 2750–3350 (b–OH), 1688(C=O)	2.9 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 5.59 (s, 1H, CH), 5.9 (s, 3H, NH b), 6.5–7.4 (m, 8H, ArH), 11.1 (s, 1H, OH b)	31.2 ± 1.3

4j	Cl	2-Thiophene	$C_{16}H_{14}ClN_3O_2S$ (347.81)	154–156	50[a] 39[b]	3380–(NH), 2650–3220 (b–OH), 1674 (C=O)	2.88 (s, 2H, CH_2), 5.54(s, 1H, CH), 6.07 (s, 3H, NH b), 6.5–7.4 (m, 7H, ArH), 11.0 (s, 1H, OH b)	20.1 ± 1.5
4k	Cl	Furfural	$C_{16}H_{14}ClN_3O_3$ (331.75)	162–166	40[a] 28[b]	3357 (NH), 2600–3330 (b–OH), 1730 (C=O)	2.95 (s, 2H, CH_2), 5.56 (s, 1H, CH), 5.9 (s, 3H, NH b), 6–7.4 (m, 7H, ArH), 11.0 (s, 1H, OH b)	18.1 ±1.9
4l	Cl	3-Nicotine	$C_{17}H_{15}ClN_4O_2$ (342.78)	182–184	50[a] 36[b]	3360 (NH), 2700–3210 (b–OH), 1697 (C=O)	2.9 (s, 2H, CH_2), 5.55 (s, 1H, CH), 6.0 (s, 3H, NH b), 7.0–8.6 (m, 8H, ArH), 11.1 (s, 1H, OH b)	17 ± 2.3
4m	CH_3	Phenyl	$C_{19}H_{19}N_3O_2$ (321.37)	175–178	60[a] 30[b]	3340 (NH), 2600–3340 (b–OH), 1680 (C=O)	2.35 (s, 3H, CH_3), 2.9 (s, 2H, CH_2), 5.63 (s, 1H, CH), 5.9 (s, 3H, NH b), 7.0–7.3 (m, 9H, ArH), 11.1 (s, 1H, OH b)	29.3 ± 2.1
4n	CH_3	4-Chloro-phenyl	$C_{19}H_{18}ClN_3O_2$ (355.82)	166–171	55[a] 25[b]	3370 (NH), 2750–3360 (b–OH), 1688 (C=O)	2.3 (s, 3H, CH_3), 2.93 (s, 2H, CH_2), 5.6 (s, 1H, CH), 6.0 (s, 3H, NH b), 6.5–7.4 (m, 8H, ArH), 11.1 (s, 1H, OH b)	21.4 ± 2.3
4o	CH_3	4-Methoxy	$C_{20}H_{21}N_3O_3$ (351.40)	173–175	45[a] 29[b]	3350 (NH) 2600–3290 (b–OH), 1687 (C=O)	2.4 (s, 3H, CH_3), 2.9 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 5.56 (s, 1H, CH), 5.9 (s, 3H, NH b), 7.0–7.3 (m, 8H, ArH), 11.0 (s, 1H, OH b)	30.1 ± 1.5
4p	CH_3	2-Thiophene	$C_{17}H_{17}N_3O_2S$ (327.40)	163–165	50[a] 35[b]	3380 (NH), 2600–3360 (b–OH), 1695 (C=O)	2.35 (s, 3H, CH_3), 2.9 (s, 2H, CH_2), 5.56 (s, 1H, CH), 5.9 (s, 3H, NH b), 6.5–7.3 (m, 7H, ArH), 11.1 (s, 1H, OH b)	21.2 ± 1.8
4q	CH_3	Furfural	$C_{17}H_{17}N_3O_3$ (311.34)	156–159	55[a] 30[b]	3340 (NH), 2600–3300 (b–OH), 1735 (C=O)	2.3 (s, 3H, CH_3), 2.98 (s, 2H, CH_2), 5.5 (s, 1H, CH), 6.0 (s, 3H, NH b), 6.0–7.5 (m, 7H, ArH), 10.9 (s, 1H, OH b)	18.2 ± 1.4
4r	CH_3	3-Nicotine	$C_{18}H_{18}N_4O_2$ (322.36)	197–202	50[a] 27[b]	3367 (NH), 2670–3330 (b–OH), 1691 (C=O)	2.37 (s, 3H, CH_3), 2.91 (s, 2H, CH_2), 5.56 (s, 1H, CH), 6.09 (s, 3H, NH b), 7.0–8.7 (m, 8H, ArH), 11.1 (s, 1H, OH b)	19.2 ± 2.0

Reference standard diclofenac sodium 48.1 ± 2.1.

[a] Acid catalysed, [b] Base catalysed, [c] All test compounds and diclofenac sodium were administered at the dose level of 10 mg kg^{-1} body mass.

[d] Number of individual results, $n = 6$.

CONCLUSIONS

In this work, we have demonstrated that condensation of β-benzoylpropanoic acid, guanidine nitrate and aldehyde in the presence of K_2CO_3 afforded [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidin-5-yl]-acetic acid derivatives with promising anti-inflammatory activity. The activity data obtained during the study will be certainly useful for structure activity relationship studies of new anti-inflammatory compounds and for drug designing.

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S A Ž E T A K

Sinteza i protuupalno djelovanje derivata [2-amino-6-(4-supstituiranih aril)-4-(4-supstituiranih fenil)-1,6-dihidropirimidin-5-il]-octene kiseline

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Bazno kataliziranom kondenzacijom β-aroilpropanske kiseline, gvanidin nitrata i aromatskog aldehida sintetizirani su dihidropirimidini **4a**-**r**. Strukture novih spojeva potvrđene su ^{1}H NMR i IR spektroskopijom. Protuupalno djelovanje sintetiziranih spojeva određeno je *in vivo* i uspoređeno s djelovanjem diklofenak-natrija.

Ključne riječi: dihidropirimidini, aril alkanske kiseline, protuupalno djelovanje

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