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Synthesis and anti-inflammatory activity of some [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid derivatives

Sushilkumar S. Bahekar and Devanand B. Shinde*

Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431 004, MS India

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Abstract—A series of [4,6-(substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid (**4a**–**r**) has been synthesized by the base catalyzed condensation of β-aroylpropionic acid, thiourea with aldehyde in ethanol. Structures of the new compound were established on the basis of ^{1}H NMR and IR spectral data. Anti-inflammatory activity in vivo were evaluated and compared with standard drug diclofenac sodium. Some compounds have shown moderate activity.

In 1893 Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea.[1] The reaction was carried out simply by heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one.

The synthetic potential of this new heterocycle synthesis (now known as Biginelli reaction) remained unexplored for quite some time. In the 1970s and 1980s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines.[2,3]

Since that late 1980s a tremendous increase in activity has again occurred, as evidenced by the growing number of publications and patents on the subject.[3,4] This is mainly due to the fact that the multifunctionalized dihydropyrimidine represents a heterocyclic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives.[5–13] More recently, DHPMs have emerged as, for example, orally active antihypertensive agents.[14–18] A very recent highlight in this context has

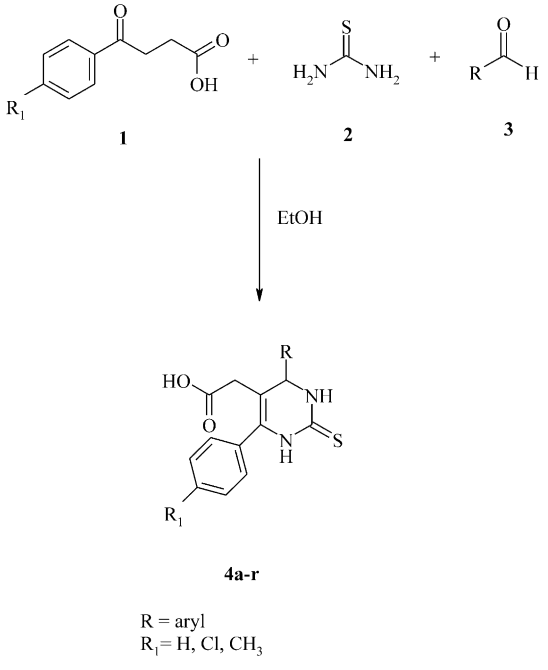

Figure 1.

Keywords: Pyrimidine; Anti-inflammatory activity; Aryl alkanoic acids; NSAIDs.
* Corresponding author. Tel.: +91-2572-50399; fax: +91-2572-50399; e-mail: ssbahekar@rediffmail.com

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Table 1. Characterization data and anti-inflammatory activity of compounds (**1a–r**)

No.	R_1	R	MP (°C)	Yield	Activity in %	Mol. Formula Mol. Wt.	IR-(KBr) cm^{-1}	^1H NMR-($CDCl_3$)
4a	H	Phenyl	197	65	17	$C_{18}H_{16}N_2O_2S$ 324.4	3344 (NH), 2600–3200 (broad-OH), 1684 (–C=O).	2.9 (s, 2H, $-CH_2-$), 4.52 (s, 1H, –CH–), 2.07 (s, 2H, NH broad), 7.0–7.5 (m, 10H, Ar-H), 11.0 (s, 1H, –OH broad)
4b	H	4-Chlorophenyl	222	70	30	$C_{18}H_{15}ClN_2O_2S$ 358.8	3350 (NH), 2600–3200 (broad-OH), 1693 (–C=O).	2.93 (s, 2H, $-CH_2-$), 4.5 (s, 1H, –CH–), 2.02 (s, 2H, NH broad), 7.1–7.6 (m, 9H, Ar-H), 11.0 (s, 1H, –OH)
4c	H	4-Methoxy	207	60	32	$C_{19}H_{18}N_2O_3S$ 354.4	3360 (NH), 2600–3200 (broad-OH), 1680 (–C=O).	2.85 (s, 2H, $-CH_2-$), 3.85 (s, 3H, $-O-CH_3$), 4.51 (s, 1H, –CH–), 2.0 (s, 2H, NH broad), 6.5–7.4 (m, 9H, Ar-H), 11.0 (s, 1H, –OH)
4d	H	2-Thiophene	188	55	21	$C_{16}H_{14}N_2O_2S_2$ 330.4	3380 (NH), 2600–3200 (broad-OH), 1682 (–C=O).	2.9 (s, 2H, $-CH_2-$), 4.46 (s, 1H, –CH–), 2.17 (s, 2H, NH broad), 6.6–7.4 (m, 8H, Ar-H), 11.0 (s, 1H, –OH)
4e	H	Furfural	226	65	19	$C_{16}H_{14}N_2O_3S$ 314.4	3358 (NH), 2600–3200 (broad-OH), 1694 (–C=O).	2.9 (s, 2H, $-CH_2-$), 4.6 (s, 1H, –CH–), 2.2 (s, 2H, NH broad), 6.0–7.3 (m, 8H, Ar-H), 11.2 (s, 1H, –OH)
4f	H	3-Nicotine	181	67	15	$C_{17}H_{15}N_3O_2S$ 325.4	3350 (NH), 2600–3200 (broad-OH), 1699 (–C=O).	2.83 (s, 2H, $-CH_2-$), 4.7 (s, 1H, –CH–), 2.3 (s, 2H, NH broad), 7.0–8.6 (m, 9H, Ar-H), 11.0 (s, 1H, –OH)
4g	Cl	Phenyl	247	71	20	$C_{18}H_{15}ClN_2O_2S$ 358.8	3380 (NH), 2600–3200 (broad-OH), 1680 (–C=O).	2.96 (s, 2H, $-CH_2-$), 4.59 (s, 1H, –CH–), 2.1 (s, 2H, NH broad), 6.8–7.3 (m, 9H, Ar-H), 11.3 (s, 1H, –OH)
4h	Cl	4-Chlorophenyl	251	74	25	$C_{18}H_{14}Cl_2N_2O_2S$ 393.3	3350 (NH), 2600–3200 (broad-OH), 1689 (–C=O).	2.83 (s, 2H, $-CH_2-$), 4.52 (s, 1H, –CH–), 2.09 (s, 2H, NH broad), 7.0–7.5 (m, 8H, Ar-H), 11.0 (s, 1H, –OH)
4i	Cl	4-Methoxy	211	66	35	$C_{19}H_{17}ClN_2O_3S$ 388.9	3375 (NH), 2600–3200 (broad-OH), 1690 (–C=O).	2.91 (s, 2H, $-CH_2-$), 3.8 (s, 3H, $O-CH_3$), 4.59 (s, 1H, –CH–), 1.9 (s, 2H, NH broad), 6.3–7.4 (m, 8H, Ar-H), 11.1 (s, 1H, –OH)
4j	Cl	2-Thiophene	201	69	16	$C_{16}H_{13}ClN_2O_2S_2$ 364.9	3350 (NH), 2600–3200 (broad-OH), 1681 (–C=O).	2.88 (s, 2H, $-CH_2-$), 4.54 (s, 1H, –CH–), 6.07 (s, 2H, NH broad), 6.5–7.4 (m, 7H, Ar-H), 11.3 (s, 1H, –OH)
4k	Cl	Furfural	198	78	09	$C_{16}H_{13}ClN_2O_3S$ 348.8	3340 (NH), 2600–3200 (broad-OH), 1685 (–C=O).	2.95 (s, 2H, $-CH_2-$), 4.56 (s, 1H, –CH–), 1.98 (s, 2H, NH broad), 6–7.4 (m, 7H, Ar-H), 11.1 (s, 1H, –OH)
4l	Cl	3-Nicotine	184	75	11	$C_{17}H_{14}ClN_3O_2S$ 359.8	3350 (NH), 2600–3200 (broad-OH), 1688 (–C=O).	2.94 (s, 2H, $-CH_2-$), 4.6 (s, 1H, –CH–), 2.0 (s, 2H, NH broad), 7.0–8.6 (m, 8H, Ar-H), 11.2 (s, 1H, –OH)
4m	CH_3	Phenyl	229	62	28	$C_{19}H_{18}N_2O_2S$ 338.4	3350 (NH), 2600–3200 (broad-OH), 1681 (–C=O).	2.35 (s, 3H, $-CH_3$), 2.89 (s, 2H, $-CH_2-$), 4.5 (s, 1H, –CH–), 1.9 (s, 2H, NH broad), 7.3–7.7 (m, 9H, Ar-H), 11.0 (s, 1H, –OH)
4n	CH_3	4-Chlorophenyl	213	73	22	$C_{19}H_{17}ClN_2O_2S$ 372.9	3367 (NH), 2600–3200 (broad-OH), 1687 (–C=O).	2.3 (s, 3H, $-CH_3-$), 2.93 (s, 2H, $-CH_2-$), 4.46 (s, 1H, –CH–), 2.2 (s, 2H, NH broad), 6.2–7.4 (m, 8H, Ar-H), 11.1 (s, 1H, –OH)
4o	CH_3	4-Methoxy	199	66	33	$C_{20}H_{20}N_2O_3S$ 368.4	3358 (NH), 2600–3200 (broad-OH), 1684 (–C=O).	2.42 (s, 3H, $-CH_3$), 2.94 (s, 2H, $-CH_2-$), 3.8 (s, 3H, $O-CH_3$), 4.5 (s, 1H, –CH–), 1.9 (s, 2H, NH broad), 7.1–7.6 (m, 8H, Ar-H), 11.0 (s, 1H, –OH)
4p	CH_3	2-Thiophene	194	64	10	$C_{17}H_{16}N_2O_2S_2$ 344.5	3350 (NH), 2600–3200 (broad-OH), 1695 (–C=O).	2.3 (s, 3H, $-CH_3$), 2.9 (s, 2H, $-CH_2-$), 4.6 (s, 1H, –CH–), 2.2 (s, 2H, NH broad), 6.5–7.3 (m, 7H, Ar-H), 11.1 (s, 1H, –OH)
4q	CH_3	Furfural	207	69	11	$C_{17}H_{16}N_2O_3S$ 328.4	3300 (NH), 2600–3200 (broad-OH), 1691 (–C=O).	2.3 (s, 3H, $-CH_3$), 2.98 (s, 2H, $-CH_2-$), 4.8 (s, 1H, –CH–), 2.0 (s, 2H, NH broad), 6.6–7.5 (m, 7H, Ar-H), 10.9 (s, 1H, –OH)
4r	CH_3	3-Nicotine	200	73	07	$C_{18}H_{17}N_3O_2S$ 339.4	3370 (NH), 2600–3200 (broad-OH), 1687 (–C=O).	2.37 (s, 3H, $-CH_3$), 2.9 (s, 2H, $-CH_2-$), 4.63 (s, 1H, –CH–), 2.09 (s, 2H, NH broad), 7.0–8.7 (m, 8H, Ar-H), 11.0 (s, 1H, –OH)

Elemental analysis (±0.4% of the calculated values) was obtained for all the compounds.

been the identification of the structurally rather simple DHPM monastrol as a mitotic kinesin motor protein inhibitor and potential new lead for the development of anticancer drugs.[19] Appropriately functionalized DHPMs have emerged as potent calcium channel blockers.[20,21] Apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated.[22] Most notably among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.[23]

Although the most straightforward protocol to synthesize DHPMs is the one-pot acid-catalyzed Biginelli condensation, this protocol—using ethanol and catalytic amounts of HCl—often provides only low to moderate yields of the desired target molecules, in particular, when substituted aromatic aldehydes or thioureas are employed.[3,23–33] This has led to the recent disclosure of several improved reaction protocols for the synthesis of DHPMs, either by modification of the classical one-pot Biginelli approach it self,[23] or by the development of novel, but more complex multistep strategies.[24–29] In addition, several combinatorial approaches towards DHPMs have been advanced, using solid phase, micro wave conditions.[34–36]

Although aryl alkanoic acids is the most studied class of non steroidal anti-inflammatory drugs which covers the major NSAIDs [37,38] such as diclofenac sodium, naproxen, ibuprofen, etc. Despite intensive research efforts in the past years interest has focused on anti-inflammatory activity of pyrimidine nucleus.[39] The synthesis of titled pyrimidine derivatives was accomplished as shown in Figure 1. Here we report the synthesis and anti-inflammatory activity of some pyrimidine derivatives with acetic acid moiety at fifth position.

The title [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid (**4a–r**) were prepared by acid catalyzed condensation of β-aroylpropanoic acid, thiourea and the appropriate aldehyde with good yield (40–50%) for plane and *p*-substituted halogen analogue derivatives, but it is of poor synthetic value for the preparation of *p*-alkyl and hetero analogue. We have carried out the base catalyzed condensation of the β-aroylpropanoic acid, thiourea with the appropriate aldehyde this method found to be of wide applicability as a number of variously substituted pyrimidine derivatives (**4a–r**) could be prepared in good yield.[41] The structures of the new compounds confirmed by elemental, IR and ^{1}H NMR analysis.

Compounds were subjected to preliminary testing for anti-inflammatory activity according to the method of Winter et al.[40] in albino rats employing the carangeenan induced rat paw edema test. Percentage reduction in the inflammation (i.e., reduction in the left hand paw edema volume of the animals) after 3 h of administration of carangeenan was recorded, and test compound was compared with that of the animals administrated with carangeenan using the reference standard diclofenac sodium. The anti-inflammatory activities of all the compounds have been reported in Table 1.

The anti-inflammatory activity of all the compounds has been recorded on the basis of reference standard drug diclofenac sodium. All the compounds showed tendency to cause a fall in edema and showed anti-inflammatory activity, the anti-inflammatory activity data shows that presence of *p*-methoxy phenyl group at C-4 plays an important role in the activity compounds **4c**, **4i**, **4o** that is, presence of *p*-methoxy phenyl group at C-4 enhances the anti-inflammatory activity. Further it is observed that the presence of phenyl group at C-4 and C-6 reduces the anti-inflammatory activity but phenyl group at C-6 and *p*-chlorophenyl at C-4 increases the activity compounds **4a** and **4b**. Exchange of the positions of these groups reduces the activity compound **4g**. The presence of *p*-chloro phenyl group at C-6 and C-4 gives good anti-inflammatory activity compound **4h**. Also the presence of *p*-methyl phenyl group at C-6 and phenyl group at C-4 gives good anti-inflammatory activity compound **4m**. Further it has been observed that the presence of heterocyclic moiety at C-4 reduces the anti-inflammatory activity.

Anti-inflammatory activity of all title compounds[42] (**4a–r**) was taken by carangeenan-induced rat paw edema test as described by Winter et al. on albino rats.

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41. General procedure [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid (**4a–r**): A reaction mixture of β-aroylpropanoic acid (**1** 0.06 mol) thiourea (**2** 0.06 mol), aldehyde (**3** 0.06 mol) and K_2CO_3 (0.06 mol) in 100 mL ethanol was refluxed in oil bath for 7 h. The reaction mixture was cooled and the solid obtained by filtered was dissolved in hot water and filtered. The filtrate was neutralized with acetic acid. The product thus obtained was recrystallized from ethyl acetate.
42. Carangeenan induced rat paw edema test. 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 a control one and received 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. All the suspensions for oral dose were prepared in the vehicle mentioned above and administered in a constant volume of 0.5 mL per rat.
One h after the administration of the test compound and diclofenac sodium 0.1 mL of 1% w/v suspension of carangeenan was injected in to the subplanatar of left paw of control and test animals. Immediately, the paw volume was measured using plethismometer (initial paw volume), there after the paw volume was measured every half an hour till 3 h. The difference between initial and subsequent readings gave the edema volume for the corresponding time. Percentage inhibition was calculated (see Table 1).