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Synthesis and anti-inflammatory activity of some 3-(4,6-disubtituted-2 -thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives

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ABSTRACT

A series of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives has been synthesized by condensation of thiourea, 5-(4-subtituted phenyl)-5-oxopentanoic acid and substituted aldehyde. The synthesized compounds were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant (p <0.05) anti-inflammatory activity.

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) exhibit their effect by inhibiting COX enzymes and by blocking the synthesis of prostaglandins. The use of NSAIDs for the treatment of inflammation and pain[1] is often accompanied by gastrointestinal ulceration,[2] bleeding[3] and suppression of renal function.[4] Commonly, gastrointestinal adverse effects can be reduced through suppressing acid production, by concomitant use of a proton pump inhibitor, for example, omeprazole or the prostaglandin analogue Misoprostol.

From the literature survey, it was found that large number of pyrimidine derivatives of pharmacological importance was synthesized.[5–9] Pyrimidine forms an integral part of a large number of therapeutically important compounds like thiamine, riboflavin, purine bases, sulfadiazine etc.

It was also observed that aryl acetic acid or propanoic acid derivatives have major contribution in non-steroidal anti-inflammatory agents. Acid side chain was frequently used to have more potent anti-inflammatory agent. We have reported acetic acid containing 2-thioxo/amino-1,2,3,4-tetrahydropyrimidine moiety (Fig. 1) as anti-inflammatory agent.[5,7] But it is observed that these compounds show moderate anti-inflammatory activity due to its lower lipophilicity. In view of this, it was proposed to synthesize propanoic acids containing 2-thioxo-1,2,3,4-tetrahydropyrimidine moiety (Fig. 2) with improved lipophilicity.

The present work employed the base catalyzed modification for Biginelli reaction, that is, the condensation of the 5-(4-subtituted phenyl)-5-oxopentanoic acid (**Ia**–**Ie**), urea and substituted aldehyde.[5] The structures of the new compounds were confirmed by ^{1}H NMR and Mass spectral analysis. All the synthesized compounds were subjected to preliminary testing for anti-inflammatory activity according to the method of Winter et al.[10]

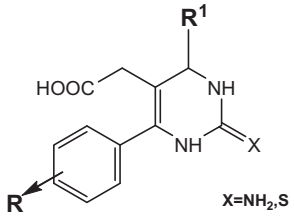

Figure 1.

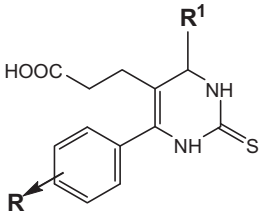

Figure 2.

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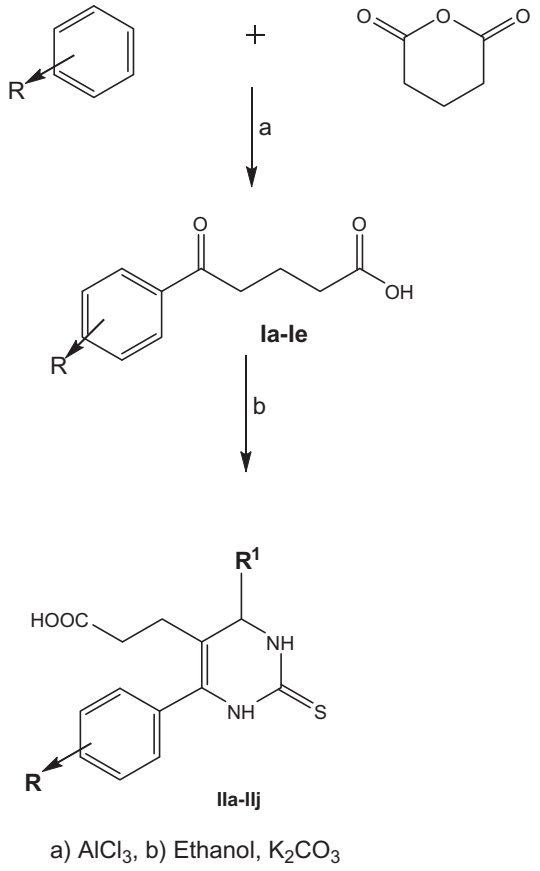
Table 1
Mean paw volume (ml) and % inhibition of compounds **IIa–IIj**

No.	Mean paw volume (ml) ± SEM					% Inhibition of edema				
	1 h	2 h	3 h	4 h	24 h	1 h	2 h	3 h	4 h	24 h
Control	1.925 ± 0.1011	1.905 ± 0.046	1.63 ± 0.059	1.44 ± 0.046	1.39 ± 0.053	—	—		—	—
IIa	1.45 ± 0.035**	1.63 ± 0.045**	1.57 ± 0.038	1.56 ± 0.028	1.48 ± 0.064	24.67%	14.21%	3.68	—	—
IIb	1.96 ± 0.044	1.87 ± 0.022	1.79 ± 0.019	1.69 ± 0.044	1.55 ± 0.06	—	1.57%	—	—	—
IIc	1.34 ± 0.021**	1.56 ± 0.017**	1.54 ± 0.037	1.47 ± 0.087	1.39 ± 0.035	30.38%	17.89%	5.52%	—	—
IId	1.74 ± 0.074**	1.62 ± 0.039**	1.61 ± 0.047	1.58 ± 0.045	1.46 ± 0.028	9.61%	14.73%	1.22%	—	—
IIe	1.53 ± 0.076**	1.63 ± 0.06**	1.37 ± 0.046**	1.44 ± 0.068	1.54 ± 0.051	20.51%	14.21%	15.95%	—	—
IIf	1.29 ± 0.04**	1.37 ± 0.077**	1.46 ± 0.058	1.38 ± 0.068	1.19 ± 0.024*	32.98%	28.08%	10.42%	4.16%	14.38%
IIg	1.29 ± 0.012**	1.36 ± 0.009**	1.42 ± 0.043*	1.49 ± 0.025	1.36 ± 0.043	32.98%	28.60%	12.88%	—	2.15%
IIh	1.37 ± 0.038**	1.49 ± 0.027**	1.47 ± 0.035	1.36 ± 0.036	1.16 ± 0.02*	28.83%	21.78%	9.81%	5.55%	16.54%
IIi	1.50 ± 0.063**	1.49 ± 0.1**	1.54 ± 0.022	1.60 ± 0.025	1.3 ± 0.052	22.07%	21.78%	5.52%	—	6.47%
IIj	1.38 ± 0.068**	1.39 ± 0.072**	1.29 ± 0.084**	1.33 ± 0.06	1.20 ± 0.085	28.31%	27.03%	20.85%	7.63%	13.66%
Diclofenac	1.51 ± 0.017**	1.56 ± 0.028**	1.29 ± 0.08**	1.34 ± 0.032	1.51 ± 0.035	21.55%	17.89%	20.85%	6.94%	—

Test compounds = 20 mg/kg.
Reference standard, Diclofenac sodium = 20 mg/kg.
Mean ± SEM $n = 6$, [$^{**}p < 0.05$].
Statistical analysis is done by one-way ANOVA.

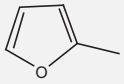
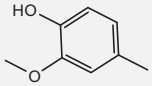
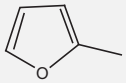
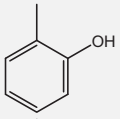
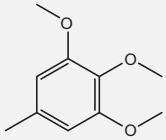
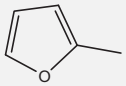
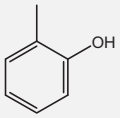
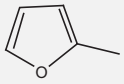
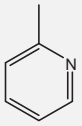
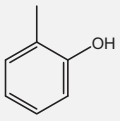


Scheme 1.

Table 2
Characterization data for 5-(4-subtituted phenyl)-5-oxopentanoic acid derivatives

S. no	R	Molecular formula	Molecular weight	% Yield	Melting point (°C)
Ia	H	$C_{11}H_{12}O_3$	370	82	126–129
Ib	CH_3	$C_{12}H_{14}O_3$	384	86	105–107
Ib	Cl	$C_{11}H11O_3Cl$	227	81	124–127
Id	F	$C_{11}H11O_3F$	210	82	140–143
Ie	OCH_3	$C_{12}H_{14}O_4$	222	90	126–128

Table 3
4,6-(4-Substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl-propanoic acid

Compound	R	R^1	Molecular formula molecular weight	% Yield	Melting point (°C)
IIa	F		$C_{17}H_{15}FN_2O_3S$ 346	65	171–172
IIb	CH_3		$C_{21}H_{22}N_2O_4S$ 398	73	195–198
IIc	Cl		$C_{17}H_{15}ClN_2O_3S$ 363	70	291–294
IId	Cl		$C_{19}H_{17}ClN_2O_3S$ 388	71	190–193
IIe	CH_3		$C_{23}H_{26}N_2O_5S$ 442	74	135–137
IIf	CH_3		$C_{18}H_{18}N_2O_3S$ 342	80	245–248
IIg	H		$C_{19}H_{18}N_2O_3S$ 354	76	217–219
IIh	H		$C_{17}H_{16}N_2O_3S$ 328	80	169–172
IIi	Cl		$C_{18}H_{16}ClN_3O_2S$ 373	76	227–230
IIj	OCH_3		$C_{20}H_{20}N_2O_4S$ 384	76	>300

The final compounds 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIa–IIj**) have been synthesized by the reaction of the 5-(4-subtituted phenyl)-5-oxopentanoic acid (**Ia–Ie**) with urea and substituted aldehyde in alcohol in presence of potassium carbonate (Scheme 1).

In conclusion, a new series of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives has been prepared and fully assigned by analytical and spectral data.[11] The present investigation showed significant anti-inflammatory action to all compound of the series except **IIb**, when compared against vehicle treated control. The results were found to be equipotent with diclofenac (Table 1). The anti-inflammatory effect was found to be most significant (p <0.05) at 1 h and gradually reduced at subsequent hours. Overall looking at duration of action and percent inhibition, the sustained and significant (p <0.05) action was reported with **IIe**, **IIf**, **IIg**, **IIh** and **IIj**. Moreover, **IIc** and **IId** were also significant (p <0.05) but had shown short duration of action.

Hence the present series could be developed as a novel class of anti-inflammatory agents. However, further structural modification is planned to increase the anti-inflammatory activities.

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11. *General*:
Melting points of compounds were taken in open capillaries on Scientific Melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded using Bruker avance II 400 spectrometer with TMS as internal standard. The mass spectra were obtained using time of Flight Mass Spectrometer.
Synthesis of 5-(4-subtituted phenyl)-5-oxopentanoic acid (**Ia–Ie**):
Place substituted benzene (0.5 M) and glutaric anhydride (0.75 M) in RBF provided with a reflux condenser and calcium chloride guard tube. Stir the mixture and add powdered anhydrous $AlCl_3$ (0.165 M) all at once. The reaction starts immediately. HCl was evolved and the mixture became hot. Heat the reaction mixture on oil bath to gentle refluxing, with continued stirring for 1 h. Allow the reaction mixture to cool, immersed the flask in a bath of cold water and slowly add water and conc. HCl. This leads to separation of the benzene layer. Separate the benzene layer and keep it for overnight to form solid mass. The crude acid was dissolved in a solution of sodium carbonate by boiling it for 10–15 min. The solution was then filtered and washed with two portions of hot water to remove the small amount of aluminium hydroxide. Treat the hot filtrate with decolorizing carbon, boil it for 5 min and filter. Cool the hot filtrate to about 50 °C and cautiously acidified with concn HCl and keep it for cooling to 0 °C in a freezing mixture of ice and salt. Thus the product obtained was filtered, washed thoroughly with cold water and dried. All the other compounds of this series were synthesized using same procedure. The physical characteristics of the compounds (**Ia–Ie**) are given in Table 2.
Synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIa–IIj**):
A mixture of 5-(4-subtituted phenyl)-5-oxopentanoic acid (**Ia–Ie**) (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 8–12 h. The reaction mixture was cooled and the solid obtained was filtered. The solid was dissolved in hot water and filtered. The filtrate was neutralized with acetic acid. The solid obtained was filtered, dried and recrystallized from ethyl acetate. All the other compounds of this series were synthesized using same procedure and characterized using ^{1}H NMR and Mass spectrometry. The physical characteristics of the compounds (**IIa–IId**) are given in Table 3.
The spectral data of each compound is given below.
3-(6-(4-Fluorophenyl)-4-(furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIa**):
^{1}H NMR (400 MHz, DMSO): d = 10.21 (s, 1H), 6–8.5 (m, 7H), 5.2 (s, 1H), 4.6 (s, 1H), 2.8 (d, 2H), 2.42 (d, 2H), 2.01 (br s, 1H); MS: m/z = 447 (m+1).
3-(4-(4-Hydroxy-3-methoxyphenyl)-2-thioxo-6-p-tolyl-1,2,3,4-tetrahydropyrimidin-5yl) propanoic acid (**IIb**):
^{1}H NMR (400 MHz, DMSO): d = 10.21 (s, 1H), 6.3–8.88 (m, 7H), 5.61 (s, 1H), 5.30 (s, 1H), 4.68 (s, 1H), 3.65 (s, 3H), 2.91 (s, 3H), 2.61 (d, 2H), 2.24 (d, 2H), 2.00 (br s, 1H); MS: m/z = 399 (m+1).
3-(6-(4-Chlorophenyl)-4-(furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)propanoic acid (**IIc**):
^{1}H NMR (400 MHz, DMSO): d = 10.22 (s, 1H), 6.1–8.2 (m, 7H), 5.3 (s, 1H), 4.65 (s, 1H), 2.85 (d, 2H), 2.45 (d, 2H), 2.10 (br s, 1H); MS: m/z = 363 (m+1).
3-(6-(4-Chlorophenyl)-4-(2-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IId**):
^{1}H NMR (400 MHz, DMSO): d = 10.31 (s, 1H), 6.2–8.1 (m, 9H), 5.26 (s, 1H), 4.70 (s, 1H), 2.91 (d, 2H), 2.44 (d, 2H), 2.12 (br s, 1H); MS: m/z = 389 (m+1).
3-(2-Thioxo-6-p-tolyl-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIe**):
^{1}H NMR (400 MHz, DMSO): d = 10.21 (s, 1H), 6.24–8.78 (m, 6H), 5.63 (s, 1H), 5.30 (s, 1H), 4.68 (s, 1H), 3.55 (s, 9H), 2.92 (s, 3H), 2.62 (d, 2H), 2.26 (d, 2H), 2.00 (br s, 1H); MS: m/z = 443 (m+1).
3-(4-(Furan-2-yl)-2-thioxo-6-p-tolyl-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIf**):
^{1}H NMR (400 MHz, DMSO): d = 10.21 (s, 1H), 6.2–8.35 (m, 7H), 5.31 (s, 1H), 4.62(s, 1H), 2.9 (d, 2H), 2.75 (d, 2H), 2.51 (s, 3H), 2.09 (br s, 1H); MS: m/z = 343 (m+1).
3-(4-(2-Hydroxyphenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIg**):
^{1}H NMR (400 MHz, DMSO): d = 10.23 (s, 1H), 6.2–8.7 (m, 9H), 5.12 (s, 1H), 4.18 (s, 1H), 2.79 (d, 2H), 2.45 (d, 2H), 2.10 (br s, 1H); MS: m/z = 355 (m+1).
3-(4-(Furan-2-yl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIh**):
^{1}H NMR (400 MHz, DMSO): d = 10.25 (s, 1H), 6.22-8.27 (m, 8H), 5.18 (s, 1H), 4.20 (s, 1H), 2.81 (d, 2H), 2.50 (d, 2H), 2.14 (br s, 1H); MS: m/z = 329 (m+1).
3-(6-(4-Chlorophenyl)-4-(pyridin-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid (**IIi**):
^{1}H NMR (400 MHz, DMSO): d = 10.28 (s, 1H), 6.23–8.29 (m, 8H), 5.20 (s, 1H), 4.22 (s, 1H), 2.82 (d, 2H), 2.52 (d, 2H), 2.19 (br s, 1H); MS: m/z = 374 (m+1).
3-(4-(2-Hydroxyphenyl)-6-(4-methoxyphenyl)-2-thioxo-1,2,3,4 tetrahydropyrimidin-5-yl) propanoic acid (**IIj**):
^{1}H NMR (400 MHz, DMSO): d = 10.27 (s, 1H), 6.12–8.67 (m, 8H), 5.40 (s, 1H), 5.12 (s, 1H), 4.18 (s, 1H), 3.20 (s, 3H), 2.81 (d, 2H), 2.49 (d, 2H), 2.12 (br s, 1H); MS: m/z = 385 (m+1).
Anti-inflammatory activity:
All the synthesized compounds were subjected to preliminary testing for anti-inflammatory activity using Albino rats. 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. The first group was a control one and received vehicle [Tween80 in propylene glycol (10%, v/v), 0.5 ml per rat], the second group received diclofenac sodium 20 mg kg^{-1} body weight. 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. After 1 h of 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 plethysmometer (initial paw volume), there after the paw volume was measured every hour till 24 h. The difference between initial and subsequent readings gave the edema volume for the corresponding time. Percentage inhibition was calculated.