Eur J Med Chem (1992) 27, 87–92

Synthesis and biological evaluation of new 3,4-dihydro-6-methyl-5-*N*-methylcarbamoyl-4-(substituted phenyl)-2(1*H*)pyrimidinones and pyrimidinethiones*

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(Received 3 September 1990; accepted 3 June 1991)

pyrimidinones / pyrimidinethiones / anti-inflammatory activity / analgesic activity

Introduction

It is observed from the literature that the pyrimidine nucleus plays a vital role in many biological activities such as antimalarial [1], antitumor [2], anti-inflammatory [3], antithyroid [4], diuretic [5] and antifungal activities [6]. It is pertinent to mention that pyrimidine ring systems having a mercapto group occupy a unique position in medicinal chemistry [7]. In view of the biological importance, it was considered worthwhile to synthesise some new pyrimidinones and pyrimidinethiones with certain structural modifications containing the *N*-methylcarbamoyl moiety at the 5-position (**IV**) as possible biologically active compounds.

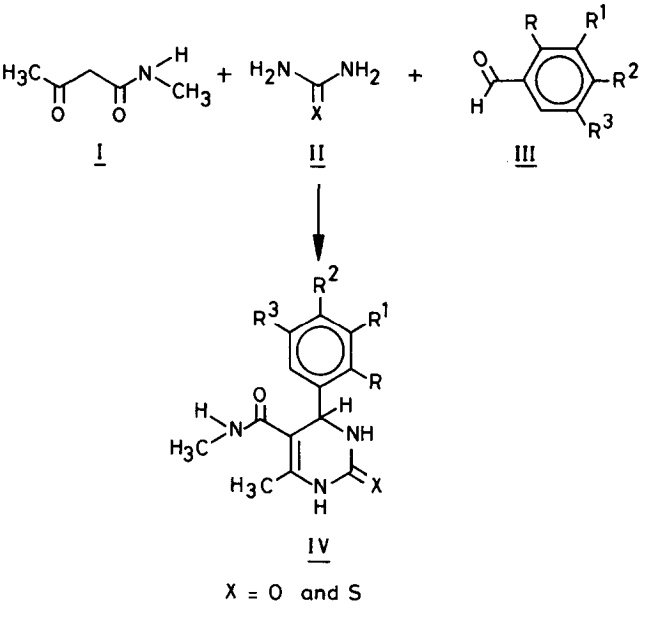
Chemistry

In the present investigation a number of 3,4-dihydro-6-methyl-5-*N*-methylcarbamoyl-4-(substituted phenyl)-2(1*H*)pyrimidinones and pyrimidinethiones (**IV**) were synthesised using conventional methods [8]. The reaction of *N*-methylacetoacetamide (**I**) with urea or thiourea (**II**), and an appropriately substituted benzaldehyde (**III**) in ethanol and hydrochloric acid, resulted in the formation of the desired compounds (**IV**) (scheme 1). All the compounds in tables II and III were characterised on the basis of their elemental analysis and spectroscopic data.

*IICT Communication No 2663

Results and discussion

All the compounds (table I) exhibited an interesting profile of anti-inflammatory and analgesic activity.



Scheme 1.

Table I. Anti-inflammatory and analgesic activities of substituted pyrimidinones and pyrimidinethiones.

Compounds	*Anti-inflammatory action % inhibition of inflammation*	*Analgesic action % protection from pain*
	Carrageenin	*Writhing*
1	14.5	22.3
2	12.1	4.5
6	6.9	8.2
7	19.4	10.1
10	0.0	24.0
11	32.0	12.8
12	5.4	22.5
13	0.0	13.5
14	16.8	8.0
15	30.9	17.0
16	35.1	12.4
19	16.6	19.0
20	19.4	24.9
21	32.4	19.2
23	6.7	20.3
24	19.5	18.4
25	29.0	30.2
26	15.6	12.3
Phenylbutazone	39.5	–
Aspirin	–	57.3

Substituted pyrimidinethiones (table III) possess more potent anti-inflammatory and analgesic activities than the substituted pyrimidinones (table II). Compounds **10** and **13** (table II) having 4-nitro or 3,4-dichloro substitution on the phenyl ring showed no anti-inflammatory activity; they are selective analgesics. Similarly, compound **12** having 2,4-dichloro substitution on the phenyl ring showed substantial reduction in the anti-inflammatory activity (5.5%). In contrast, a chloro substituent on the phenyl ring at the 4-position in compound **11** gave a compound with high anti-inflammatory action (32%) in comparison to the standard phenylbutazone (39.5%).

The pyrimidinones **1**, **10** and **12** (table II), showed mild analgesic activity (22.3, 24.0 and 22.5% respectively) comparable to the standard aspirin (57.3%) while others were less active (table I). However, in the pyrimidinethiones introduction of a 4-hydroxy, 4-methoxy, 2-nitro and 2,4-dichloro substituent into the phenyl ring (compounds **15**, **16**, **21** and **25**, table III) led to high anti-inflammatory activity (30.9, 35.1, 32.4 and 29.0%, respectively; table I) in comparison to phenylbutazone (39.5%). However, substitution of a 4-nitro group into the phenyl ring resulted in compound **23** with a very low anti-inflammatory activity when compared to compound **21** which has 2-nitro substitution in the phenyl ring (6.7 and 32.4%, respectively). Compound **25** exhibited promising analgesic and anti-inflammatory activity.

Experimental protocols

Chemistry

Melting points were determined on an Edmund Bühler melting point apparatus and are uncorrected. Melting points and solvents for recrystallisation are shown in tables II and III. IR spectra were recorded on a Perkin–Elmer model 283 B spectrophotometer in a potassium bromide pellet. Mass spectra were recorded on a VG 7070 H mass spectrometer at 70 eV. The ^{1}H NMR spectra were determined on a Jeol FX 90 Q FT NMR spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. All spectra were consistent with the assigned structures. Elemental analyses were within the acceptable limits of 0.4% of theory.

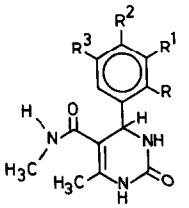
*General procedure for the synthesis of 3,4-dihydro-6-methyl-5-N-methylcarbamoyl-4-(substituted phenyl)-2(1H)-pyrimidinones and pyrimidinethiones (**1–26**, tables II and III)*

A mixture of *N*-methylacetoacetamide (**I**) (0.10 mol), urea or thiourea (**II**) (0.10 mol), substituted benzaldehyde (**III**) (0.10 mol), absolute ethanol (30–50 ml) and concentrated hydrochloric acid (8–15 drops) was stirred and slightly warmed on a steam bath till the mixture became a clear solution. It was allowed to stand overnight at ambient temperature. The product **IV** thus obtained was filtered, dried and recrystallized (tables II and III). When the product did not precipitate, the reaction mixture was refluxed on a steam bath for 3–8 h. It was then cooled, the separated solid was filtered off and the filtrate was poured into 300 ml of water to precipitate the pyrimidinone derivatives. The product was purified by dissolving in a minimum quantity of boiling ethanol and distilling off the solvent until about one-third the volume or to incipient crystallization. Thio analogues were also synthesized by the above procedure. Spectroscopic data for all the compounds were collected (table IV). The data for the pyrimidinone **1** are given: IR bands at 3220 (NH), 1680 (C=O), 1640 (CONH), 1605 (C=C) cm^{-1}. ^{1}H NMR (DMSO–d_6): δ 1.5 (s, 3H, CH_3); 2.4–2.6 (d, 3H, N–CH_3); 5.2 (d, 1H, CH); 6.8–7.0 (m, 5H, arom); 7.4 (br, 1H, NH); 8.2 (br, 1H, NH). MS: 245 (M^+, 75%), 230 (M^+–CH_3, 80), 215 (M^+–CH_3NH, 25), 214 (M^+–CH_3NH_2, 100), 187 [M^+–(CH_3NH+CO), 80], 168 (M^+–C_6H_5, 80), 137 [M^+–(C_6H_5+CH_3NH_2), 95], 109 [M^+–(C_6H_5+CH_3NH_2 + CO), 30], Anal $C_{13}H_{15}N_3O_2$ (C, H, N).

Biological activity

Eighteen selected compounds were screened for anti-inflammatory and analgesic activities (table I). The test compounds were administered orally in 0.5% gum acacia suspension at a dose of 100 mg/kg. Phenylbutazone and aspirin were used as the standards for anti-inflammatory and analgesic tests.

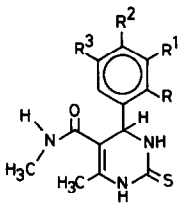
Table II. Physicochemical properties of substituted pyrimidinones **1–13**.



Compound No	*R*	*R¹*	*R²*	*R³*	*Mol formula* (Mol wt)*	*mp (°C)*	*Recryst[a] solvent*	*Yield (%)*
1	H	H	H	H	$C_{13}H_{15}N_3O_2$ (245.27)	256–258	A	90
2	H	H	OH	H	$C_{13}H_{15}N_3O_3$ (261.28)	248–249	B	60
3	H	H	OCH_3	H	$C_{14}H_{17}N_3O_3$ (275.30)	105–107 (dec)	C	60
4	H	OCH_3	OCH_3	H	$C_{15}H_{19}N_3O_4$ (305.33)	194–195	A	60
5	H	OCH_3	OCH_3	OCH_3	$C_{16}H_{21}N_3O_5$ (335.36)	159–160	A	65
6	OH	OCH_3	H	H	$C_{14}H_{17}N_3O_5$ (291.30)	250–252	C	89
7	H	-OCH_2O-		H	$C_{14}H_{15}N_3O_4$ (289.28)	214–215	A	74
8	NO_2	H	H	H	$C_{13}H_{14}N_4O_4$ (290.27)	264–266	A	80
9	H	NO_2	H	H	$C_{13}H_{14}N_4O_4$ (290.27)	250–252	A	90
10	H	H	NO_2	H	$C_{13}H_{14}N_4O_4$ (290.27)	157 (dec)	A	60
11	H	H	Cl	H	$C_{13}H_{14}ClN_3O_2$ (279.71)	165 (dec)	B	60
12	Cl	H	Cl	H	$C_{13}H_{13}Cl_2N_3O_2$ (314.17)	169–170	A	90
13	H	Cl	Cl	H	$C_{13}H_{13}Cl_2N_3O_2$ (314.17)	227–228	A	70

[a]All compounds were analyzed for C, H and N and the results obtained were within ± 0.4% of the theoretical values;
[b]A = ethanol, B = methanol, C = acetone.

Table III. Physicochemical properties of substituted pyrimidinones **14–26**.



Compound No	*R*	*R¹*	*R²*	*R³*	*Mol formula[a] (Mol wt)*	*mp (°C)*	*Recryst[b] solvent*	*Yield (%)*
14	H	H	H	H	$C_{13}H_{15}N_3OS$ (261.33)	215–216	A	85
15	H	H	OH	H	$C_{13}H_{15}N_3O_2S$ (277.30)	248–249	A	89
16	H	H	OCH_3	H	$C_{14}H_{17}N_3O_2S$ (291.37)	280 (dec)	B	62
17	H	OCH_3	OCH_3	H	$C_{15}H_{19}N_3O_3S$ (321.38)	215–216	A	62
18	H	OCH_3	OCH_3	OCH_3	$C_{16}H_{21}N_3O_4S$ (351.24)	217–218	A	79
19	OH	OCH_3	H	H	$C_{14}H_{17}N_3O_3S$ (307.35)	248–249	B	80
20	H	-OCH_2O-		H	$C_{14}H_{15}N_3O_3S$ (306.34)	162–163	A	68
21	NO_2	H	H	H	$C_{13}H_{14}N_4O_3S$ (306.32)	196–197	A	90
22	H	NO_2	H	H	$C_{13}H_{14}N_4O_3S$ (306.32)	262–263	A	91
23	H	H	NO_2	H	$C_{13}H_{14}N_4O_3S$ (306.32)	235–236	B	65
24	H	H	Cl	H	$C_{13}H_{14}ClN_3OS$ (295.77)	270 (dec)	A	68
25	Cl	H	Cl	H	$C_{13}H_{13}Cl_2N_3OS$ (330.26)	249–250	A	80
26	H	Cl	Cl	H	$C_{13}H_{13}Cl_2N_3OS$ (330.26)	260–261	A	64

[a]All compounds were analyzed for C, H and N and the results obtained were within ± 0.4% of the theoretical values; [b]A = ethanol, B = methanol, C = acetone.

Table IV. Spectral data for compounds **2–26**.

Cpd No	*IR (KBr) ν (cm^{-1})*	*^{1}H NMR (solvent/TMS)*
2	3380, 3350, 1680, 1650, 1600 DMSO:	2.0 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 5.1 (d, 1H, CH); 6.8-7.2 (m, 4H, arom); 7.4 (br, 1H, NH); 9.3 (br, 1H, OH); 8.2 (br, 1H, NH)
3	3300, 1670, 1595, 1105 DMSO:	2.1 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 3.6 (s, 3H, OCH_3); 5.2 (d, 1H, CH); 7.1–8.0 (m, 4H, arom); 8.5 (br, 1H, NH); 9.7 (br, 1H, NH)
4	3300, 3210, 1675, 1605, 1107 DMSO:	2.4 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 3.5 (s, 6H, OCH_3); 5.2 (s, 1H, CH); 6.6–6.9 (m, 3H, arom); 7.3 (br, 1H, NH); 10.2 (br, 1H, NH)
5	3265, 3200, 1680, 1620, 1125 DMSO:	2.5 (s, 3H, CH_3); 2.7–2.8 (d, 3H, N-CH_3); 3.7 (s, 9H, OCH_3); 5.8 (s, 1H, CH); 6.6 (s, 2H, arom); 7.5 (br, 1H, NH); 10.27 (br, 1H, NH)
6	3360, 3260, 1670, 1590, 1080 DMSO:	2.2 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 3.7 (s, 3H, OCH_3); 5.5 (d, 1H, CH); 7.0–7.3 (m, 3H, arom); 6.8 (s, 1H, OH); 8.2 (br, 1H, NH); 10.7 (br, 1H, NH)
7	3340, 3240, 1675, 1610, 1107 DMSO:	2.0 (s, 3H, CH_3); 2.4–2.5 (d, 3H, N-CH_3); 5.1 (s, 1H, CH); 5.8 (s, 2H, -OCH_2O-); 6.7–7.0 (m, 3H, arom); 7.4 (br, 1H, NH); 10.3 (br, 1H, NH)
8	3380, 1675, 1620, 1430 DMSO:	2.25 (s, 3H, CH_3); 2.6–2.7 (d, 3H, N-CH_3); 5.9 (d, 1H, CH); 7.3–8.01 (m, 4H, arom); 9.9 (br, 1H, NH)
9	3346, 1650, 1620, 1530, 1350 DMSO:	1.9 (s, 3H, CH_3); 2.4–2.5 (d, 3H, N-CH_3); 5.1 (d, 1H, CH); 7.1 (m, 4H, arom); 9.05 (br, 1H, NH)
10	3280, 1675, 1620, 1435 DMSO:	1.9 (s, 3H, CH_3); 2.4–2.5 (d, 3H, N-CH_3); 5.1 (d, 1H, CH); 7.3 (m, 4H, arom); 9.1 (br, 1H, NH)
11	3280, 1680, 1620, 730 DMSO:	2.1 (s, 3H, CH_3); 2.46–2.7 (d, 3H, N-CH_3); 5.4 (d, 1H, CH); 7.3 (m, 4H, arom); 9.05 (br, 1H, NH)
12	3200, 1670, 1610, 720 DMSO:	2.1 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 5.7 (d, 1H, CH); 7.2–7.4 (m, 3H, arom); 8.4 (br, 1H, NH)
13	3300, 3100, 1670, 1620, 820 DMSO:	2.1 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 5.7 (d, 1H, CH); 7.2–7.4 (m, 3H, arom); 8.4 (br, 1H, NH); 9.0 (br, 1H, NH)
14	3460, 1620, 1405, 1680, 1380 DMSO:	2.1 (s, 3H, CH_3); 2.6–2.7 (d, 3H, N-CH_3); 5.3 (d, 1H, CH); 7.3–7.5 (m, 5H, arom); 9.2 (br, 1H, NH); 9.7 (br, 1H, NH)
15	3410, 3300, 1675, 1620, 1480 DMSO:	2.0 (s, 3H, CH_3); 2.4–2.5 (d, 3H, N-CH_3); 5.1 (d, 1H, CH); 6.9–7.1 (m, 4H, arom); 7.8 (br, 1H, NH); 9.07 (br, 1H, NH)
16	3420, 1675, 1625, 1480, 1120 DMSO:	2.1 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 3.6 (s, 3H, OCH_3); 5.2 (d, 1H, CH); 7.2–8.1 (m, 4H, arom); 8.5 (br, 1H, NH); 10.7 (br, 1H, NH)
17	3410, 1675, 1620, 1480, 1110 DMSO:	2.0 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 3.7 [s, 6H $(OCH_3)_2$]; 5.2 (d, 1H, CH); 6.7–6.8 (m, 3H, arom); 7.6 (br, 1H, NH); 9.75 (br, 1H, NH)
18	3200, 1670, 1590, 1380 DMSO:	2.03 (s, 3H, CH_3); 2.5–2.6 (d, 3H, CH_3); 3.7 (s, 9H, OCH_3); 5.2 (d, 1H, CH); 6.4–6.5 (m, 2H, arom); 9.2 (br, 1H, NH)
19	3440, 3300, 1670, 1620, 1500, 1335 DMSO:	1.6 (s, 3H, CH_3); 2.1–2.2 (d, 3H, N-CH_3); 3.7 (s, 3H, OCH_3); 5.3 (d, 1H, CH); 7.0–7.3 (m, 3H, arom); 8.3 (br, 1H, NH); 10.7 (br, 1H, NH)
20	3420, 1675, 1338, 1620, 1480, 1120 DMSO:	2.0 (s, 3H, CH_3); 2.4–2.5 (d, 3H, N-CH_3); 5.1 (s, 1H, CH); 5.9 (s, 2H, -OCH_2O-); 6.7–7.0 (m, 3H, arom); 8.3 (s, 1H, NH); 10.7 (br, 1H, NH)
21	3420, 3300, 1680, 1620, 1520, 1480, 1345 DMSO:	1.8 (s, 3H, CH_3); 2.3–2.4 (d, 3H, N-CH_3); 5.8 (d, 1H, CH); 7.4–7.8 (m, 4H, arom); 8.3 (br, 1H, NH); 10.3 (br, 1H, NH)
22	3420, 1680, 1625, 1530, 1480, 1347 DMSO:	1.8 (s, 3H, CH_3); 2.3–2.4 (d, 3H, N-CH_3); 5.8 (d, 1H, CH); 7.4–7.8 (m, 4H, arom); 8.3 (br, 1H, NH); 10.3 (br, 1H, NH)
23	3270, 1680, 1620, 1530, 1480, 1380 DMSO:	1.8 (s, 3H, CH_3); 2.4–2.5 (d, 3H, N-CH_3); 5.5 (d, 1H, CH); 7.2–8.1 (m, 4H, arom); 8.5 (br, 1H, NH); 10.7 (br, 1H, NH)
24	3440, 1680, 1620, 1490, 1340, 730 TFA:	1.8 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 5.3 (d, 1H, CH); 6.8–7.2 (m, 4H, arom); 8.5 (br, 1H, NH)
25	3450, 1680, 1610, 1470, 710 TFA:	1.8 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 5.3 (d, 1H, CH); 6.38–7.2 (m, 3H, arom); 8.3 (br, 1H, NH)
26	3450, 1680, 1610, 1470, 720 TFA:	1.8 (s, 3H, CH_3); 2.5–2.6 (d, 3H, N-CH_3); 5.3 (d, 1H, CH); 6.8–7.2 (m, 3H, arom); 8.5 (br, 1H, NH)

All the compounds have been evaluated for antimicrobial and antifungal activities. None of the test compounds showed any appreciable activity.

Anti-inflammatory (anti-edematous) activity carrageenin-induced rat paw edema

The inhibitory activity of the test compounds was studied by using carrageenin-induced rat paw edema as described by Winter *et al* [9]. Wistar rats of both sexes weighing between

150 to 180 g were used. The test compounds were administered orally to the fasted rats at the dose of 100 mg/kg. One hour later, 0.1 ml of 1% carrageenin was injected subcutaneously into the plantar surface of the left hind paw of each rat. The paw volume was measured by a plethysmograph (Ugo Basile, Italy) immediately (0 h) and 3 h later. The percent inhibition of the edema of the treated rats with respect to controls was calculated and compared with phenylbutazone (table I).

Analgesic activity

Writhing (chemical) method

Acetic acid writhing test, modified method of Koster *et al* [10] was used. Groups of five male albino mice, weighing 18–25 g were used. Acetic acid (0.6%) at a dose of 10 mg/kg body weight was injected ip. The animals which showed a stretching episode or writhing were selected for the experiments. The selected animals were fasted for 18 h and an oral dose of the test compound 100 mg/kg was given 1 h prior to the injection. The writhes for each animal were counted for a period of 20 min. The average number of writhes for each group of animals and the percentage change compared with the control group were calculated (table I).

Acknowledgment

We are thankful to Dr AV Rama Rao, Director, IICT, Hyderabad for his kind advice and encouragement.

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