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Original research paper

Synthesis and biological evaluation of thieno[2,3-*d*]pyrimidine derivatives for anti-inflammatory, analgesic and ulcerogenic activity

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5-Methyl-6-phenyl-2-thioxothieno[2,3-*d*]pyrimidone derivative (**2**) reacted with hydrazonoyl chloride derivatives to afford triazolothienopyrimidones **4a–f**. Also, acetone-1-(2-amino-5-isopropyl-thiophene-3-carbonitrile) (**3**) reacted with functional and bifunctional groups to yield the corresponding compounds **5**–**11**. The new products showed anti-inflammatory, analgesic, and ulcerogenic activities comparable to that of indomethacin and acetylsalicylic acid, respectively.

Keywords: triazolothienopyrimidine, thienopyrimidines, thieno[2,3-*d*][1,3]thiazine, thienopyridines, analgesic, anti-inflammatory, ulcerogenic activity

Pyrimidine and thienopyrimidine derivatives have attracted a great deal of interest owing to their medicinal activities (1–4). Pyrimidine derivatives and heterocyclic annelated pyrimidines continue to attract great interest due to the wide variety of interesting biological activities observed for these compounds, such as anticancer (4), antiviral (5), antitumor (6), anti-inflammatory (7) and antimicrobial activities (8). Also, the rapid growth in the literature dealing with the synthesis and biological activity of the thienopyrimidine derivatives prompted us to synthesize new derivatives of fused pyrimidine, thienopyrimidine and thienopyridine derivatives. In our previous work (9, 10), we reported the behaviour of thienopyrimidine derivatives towards hydrazines, 1,3-diketones, α-haloketones and acids. As part of this work, here we report a new synthesis strategy for the preparation of functionalized thieno[2,3-*d*][1,2,4]triazolo[4,5-*a*]pyrimidines, thieno[2,3-*d*][1,3]thiazine and thienopyrimidine derivatives *via* the reaction of hydrazonyl chloride and cinnamonitriles with thienopyrimidone and 2-amino-5-isopropyl-thiophene-3-carbonitrile.

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EXPERIMENTAL

All melting points were uncorrected and measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). Microanalytical data were performed with a Vario, Elementar apparatus (Shimadzu) (Table I). The IR spectra (KBr) were recorded on a Perkin-Elmer 1650 spectrometer (USA). ^{1}H NMR spectra were determined on a Varian Mercury (300 MHz) spectrometer (Varian, UK) and chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standard. Mass spectra were recorded on 70 ev EI Ms--QP 1000 EX (Shimadzu) (Table II).

The starting materials 2-amino-4-methyl-5-phenyl-thiophene-3-ethylcarboxylate (**1**), 5-methyl-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-4-one (**2**) and acetone-1-(2-amino-5-isopropyl-thiophene-3-carbonitrile (**3**) were prepared according to Gewald *et al.* (11). The hydrazonoyl chloride was prepared as reported (12, 13).

Physico-chemical and spectral data of the synthesized compounds are given in Tables I and II, respectively.

*Synthesis of 2-amino-4-methyl-5-phenyl-thiopene-3-ethylcarboxylate (**1**)*

A mixture of 6-methyl-heptane-2,4-dione, ethylcyanoacetate, sulfur and diethylamine was heated (70 °C) under stirring in absolute ethanol for 4 hours, then the mixture was left for 24 hours at 0 °C. The formed solid was collected by filtration, washed with absolute ethanol (20 mL), dried and yellow crystals were obtained from absolute ethanol.

Synthesis of 5-methyl-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine--4-one

A mixture of compound **1** (0.01 mol) and potassium thiocyanate (0.15 mol) was stirred under reflux in dioxane containing 10% HCl for 15 hours. Poured into 200 mL water, the solid precipitated was filtered off and crystallized from dioxane as yellow powder.

*Synthesis of acetone-1-(2-amino-5-isopropyl-thiophene-3-carbonitrile (**3**)*

A mixture of 6-methyl-heptane-2,4-dione, malononitrile, sulfur and diethylamine was heated (70 °C) under stirring in absolute ethanol for 4 hours, then left for 24 hours at 0 °C. The formed solid was collected by filtration, washed with absolute ethanol (20 mL), dried and crystallized from absolute ethanol as yellow crystals.

*Synthesis of thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one derivatives (**4a–f**). General procedure*

A mixture of compound **2** (2.74 g, 0.01 mol) and the appropriate hydrazonoyl chloride (0.01 mol) was stirred under reflux in dry chloroform (30 mL) with 4 drops of triethylamine for 5 hours. The solvent was evaporated under reduced pressure. The

solid produced was washed three times with 30 mL absolute ethanol and crystallized from an appropriate solvent.

*6-Methyl-1,3,7-triphenyl-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**4a**).* – Compound **4a** was obtained from **2** (2.74 g, 0.01 mol) and *N*-phenylbenzene-carbohydrazonoyl chloride (2.31 g, 0.01 mol) as white needles, and crystallized from dimethylformamide.

*3-Acetyl-1-(4-chlorophenyl)-7-phenyl-6-methyl-thieno[2,3-d][1,2,4]triazolo-[4,3-a]pyrimidin--5-one (**4b**).* – Compound **4b** was obtained from **2** (2.74 g, 0.01 mol) and 2-oxo-N-(4-chlorophenyl)-propane hydrazonoyl chloride (1.96 g, 0.01 mol) as brown powder, and crystallized from dimethylformamide.

*3-Acetyl-1-(4-methoxyphenyl)-7-phenyl-6-methyl-thieno[2,3-d][1,2,4]triazolo-[4,3-a]pyrimidin-5-one (**4c**).* – Compound **4c** was obtained from **2** (2.74 g, 0.01 mol) and 2-oxo-N-(4--methoxy-phenyl)-propane hydrazonoyl chloride (1.91 g, 0.01 mol) as green powder, and crystallized from absolute ethanol.

*3-Acetyl-1-(4-nitrophenyl)-7-phenyl-6-methyl-thieno[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin--5-one (**4d**).* – Product **4d** was obtained from **2** (2.74 g, 0.01 mol) and 2-oxo-N-(4-nitrophenyl)-propane hydrazonoyl chloride (2.06 g, 0.01 mol) as pale red crystals, and crystallized from absolute ethanol.

*1,7-Diphenyl-6-methyl-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one-3-ethylcarboxylate (**4e**).* – Compound **4e** was obtained from **2** (2.74 g, 0.01 mol) and chloro-(phenylhydrazono)-ethyl acetate (2.27 g, 0.01 mol) as white powder, and crystallized from dimethylformamide.

*7-Phenyl-6-methyl-1-(4-tollyl)-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one-3-ethylcarboxylate (**4f**).* – Compound **4f** was obtained from **2** (2.74 g, 0.01 mol) and chloro-(4-tolylhydrazono)-ethyl acetate (2.41 g, 0.01 mol) as yellow powder, and crystallized from absolute ethanol/dioxane.

*Synthesis of 6-isopropyl-5-(2-oxo-propyl)-3*H*-thieno[2,3-d]pyrimidin-4-one (**5a**)*

A mixture of compound **3** (2.22 g, 0.01 mol), formic acid (10 mL) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 12 hours. The reaction mixture was allowed to cool to room temperature, poured into water (100 mL). The formed solid was collected by filtration, washed with absolute ethanol (20 mL), dried and crystallized from dimethylformamide.

*Synthesis of 6-isopropyl-2-methyl-5-(2-oxo-propyl)-3*H*-thieno[2,3-d]pyrimidin-4-one (**5b**)*

A mixture of **3** (2.22 g, 0.01 mol) and glacial acetic acid (30 mL) was stirred under reflux for 12 hours (under TLC analysis). The reaction mixture was allowed to cool to room temperature and was poured into water (100 mL). The solid thus-formed was collected by filtration, washed with etanol (20 mL), dried and crystallized from dimethylformamide.

*Synthesis of 1-(6-isopropyl-2,4-dithioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidin--5-yl)-propan-2-one (**6**)*

A mixture of compound **3** (2.22 g, 0.01 mol) and carbon disulphide (excess 10 mL) was heated under reflux in absolute ethanolic potassium hydroxide solution for 12 hours. The reaction mixture was allowed to cool to 0 °C for 3 hours, the deposited precipitate was filtered off, washed with water (20 mL), dried and crystallized from dioxane.

*Synthesis of 1-(4-imino-6-isopropyl-2-thioxo-1,4-dihydro-2*H*-thieno[2,3-d][1,3]--thiazin-5-yl)-propan-2-one (**7**)*

A mixture of compound **3** (2.22 g, 0.01 mol) and carbon disulphide (excess 10 mL) was heated under reflux on a waterbath (80 °C) in 20 mL pyridine for 8 hours (under TLC control). The reaction mixture was allowed to cool to 0 °C for 3 hours, the deposited precipitate was filtered off, washed with absolute ethanol (20 mL), dried and crystallized from dioxane.

*Synthesis of 4-amino-6-isopropyl-5-(2-oxo-propyl)-1*H*-thieno[2,3-d]pyrimidin-(2-one or 2-thione) (**8a**,**b**). General procedure*

A mixture of compound **3** (2.22 g, 0.01 mol) and urea or thiourea (0.01 mol) was heated at 180 °C in a test tube on sand-bath for 4 hours. The mixture was allowed to cool to room temperature; the product was solidified by cooling and addition of absolute ethanol (50 mL). The precipitate thus-formed was collected by filtration and crystallized from an appropriate solvent.

*4-Amino-6-isopropyl-5-(2-oxo-propyl)-1*H*-thieno[2,3-d]pyrimidin-2-one (**8a**).* – Compound **8a** was obtained from **3** and urea (0.61 g, 0.01 mol), as dark brown crystals and crystallized from dimethylformamide.

*4-Amino-6-isopropyl-5-(2-oxo-propyl)-1*H*-thieno[2,3-d]pyrimidine-2-thione (**8b**).* – Compound **8b** was obtained from **3** and thiourea (0.77 g, 0.01 mol) as brown crystals and crystallized from dioxane.

*Synthesis of 4,6-diamino-2-isopropyl-3-(2-oxo-propyl)-thieno[2,3-b]pyridine-5-carbonitrile (**9**)*

To a solution of **3** (2.22 g, 0.01 mol) in glacial acetic acid (50 mL), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was stirred under reflux for 8 hours, cooled to room temperature, then poured into cold water (100 mL). The solid product was filtered off, washed with water, dried and crystallized from absolute ethanol.

*Synthesis of 4-amino-6-hydroxy-2-isopropyl-3-(2-oxo-propyl)-thieno[2,3-b]pyridine--5-carbonitrile (**10**)*

A mixture of **3** (2.22 g, 0.01 mol) and ethylcyanoacetate (1.13 g, 0.01 mol) in dry dixane (50 mL) containing a catalytic amount of triethylamine was stirred under reflux for 8 hours. The reaction mixture was allowed to cool and poured into cold water (100

mL) and neutralized with acetic acid. The precipitate was filtered off, washed with water, dried and crystallized from dioxane.

*Synthesis of N-[3-cyano-5-isopropyl-4-(2-oxo-propyl)-thiophen-2-yl]-formamidic acid ethyl ester (**11a**)*

A mixture of compound **3** (2.22 g, 0.01 mol) and triethylorthoformate (2.96 g, 20 mmol) was stirred under reflux in acetic anhydride (30 mL) for 6 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL) and neutralized by ammonia solution. The deposited precipitate was collected by filtration, washed with water, dried and crystallized from absolute ethanol.

*Synthesis of N-[3-cyano-5-isopropyl-4-(2-oxo-propyl)-thiophen-2-yl]-acetimidic acid ethyl ester (**11b**)*

A mixture of compound **3** (2.22 g, 0.01 mol) and triethylorthoacetate (2.96 g, 20 mmol) was stirred under reflux in acetic anhydride (30 mL) for 6 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL) and neutralized by ammonia solution. The deposited precipitate was collected by filtration, washed with water, dried and crystallized from benzene.

*Synthesis of N-[3-cyano-5-isopropyl-4-(2-oxo-propyl)-thiophen-2-yl]-formamidine (**12**)*

A mixture of **11a** (2.78 g, 0.01 mol) and ammonia solution (35%, 20 mL) was stirred under reflux in absolute ethanol (20 mL) for 8 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL) and neutrallized by diluted hydrochloric acid. The deposited white powder precipitate was collected by filtration, washed with water, dried and crystallized from absolute ethanol.

*Synthesis of 1-(4-amino-6-isopropyl-thieno[2,3-d]pyrimidin-5-yl)-propan-2-one (**13**)*

To a warmed absolute ethanolic sodium ethoxide solution [prepared by dissolving 0.23 g (0.01 mol) sodium metal in 50 mL absolute ethanol], compound **12** (2.49 g, 0.01 mol) was added. The mixture was stirred under reflux for 8 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL) and neutralized by acetic acid. The deposited precipitate was filtered off, dried and crystallized from benzene.

*Synthesis of 1-(3-amino-4-imino-6-isopropyl-3,4-dihydro-thieno[2,3-d]pyrimidin-5-yl)--propan-2-one (**14**)*

A mixture of **11a** (2.78 g, 0.01 mol) and hydrazine hydrate (99–100%) (10 mL) was stirred in absolute ethanol (20 mL) for 2 hours. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL) and neutralized by acetic acid. The deposited precipitate was collected by filtration, washed with water, dried and crystallized from dioxane.

PHARMACOLOGICAL SCREENING

Animals

Both sexes of Swiss albino mice (25–30 g) were used in analgesic activity testing and adult female Sprague-Dawley rats (150–180 g) were used in anti-inflammatory and ulcerogenic testing. International principle and local regulations concerning the care of used laboratory animals was taken into account (14). The animals had free access to standard commercial diet and water *ad libitum* and were kept in rooms maintained at 22 ± 1 °C with a 12 h light/dark cycle.

Anti-inflammatory activity

The method adopted resembles essentially that described by Winter *et al*. (15). Tween-80 (10%, *V/V*) was selected as vehicle to suspend the standard drug and test compounds. The rats were starved for 18 h prior to the experiment. The animals were weighed, marked for identification and divided into 14 groups, each containing 6 animals. Edema was induced in the left hind paw of all rats by subcutaneous injection of 0.1 mL of 1% (*m/V*) aqueous carrageenean into their footpads. The 1st group was kept as control and was given 1.0 mL of the vehicle. The 2nd to 13th groups were orally administered an aqueous suspension of the synthesized compounds (15 mg kg^{-1} body mass) 1 hour before carrageenean injection. The last group (standard) was administered indomethacin in a dose of 10 mg kg^{-1} body mass, orally as suspension in 10% Tween 80 (16). The paw volume of each rat was measured with a mercury plethysmometer, before carrageenean injection and then hourly for 4 hours post administration of the suspension of synthesized compound in 10% Tween 80.

Analgesic activity

The compounds **4a**–**f**, **5a**,**b**, **6**, **7** and **8a**,**b** were selected for investigating their analgesic activity in acetic acid induced writhing response in mice, following the method of Collier *et al.* (17). Eighty four mice were divided into 14 groups (six in each) and starved for 16 h. The 1st group which served as control was orally given distilled water in an appropriate volume. The 2nd to 13th groups received the aqueous suspension of synthesized compounds orally (15 mg kg^{-1} body mass). The last group received acetylsalicylic acid orally in a dose of 100 mg kg^{-1} body mass. After 30 minutes, each mouse was administerated 0.7% of an aqueous solution of acetic acid (10 mL kg^{-1} body mass) and the mice were then placed in transparent boxes for observation. The number of writhes was counted for 20 min after acetic acid injection. The number of writhes in each treated group was compared to that of the control group. The number of writhings was recorded and the percentage protection was calculated.

Ulcerogenicity

Ulceration in rats was induced as described by *Goel et al*. (18). Rats were divided into 14 groups, of six animals each. The control group of animals was administered only

Table I. Physical and chemical properties of synthesized compounds

Compd. No.	Yield (%)	M.p. (°C)	Mol. formula (M_r)	Found/calcd. (%)		
				C	H	N
1	86	94–96	$C_{14}H_{15}NO_2S$ (262.33)	64,35 64.32	5.78 5.75	5.36 5.38
2	81	313–316	$C_{13}H_{10}N_2OS_2$ (274.35)	56.90 56.80	3.67 4.00	10.21 10.40
3	73	267–270	$C_{11}H_{14}N_2OS$ (222.31)	59.43 59.38	6.35 6.32	12.60 12.56
4a	66	239–241	$C_{26}H_{18}N_4OS$ (434.52)	71.87 71.84	4.17 4.15	12.89 12.76
4b	70	301–303	$C_{22}H_{15}ClN_4O_2S$ (434.90)	60.76 60.64	3.48 3.50	12.88 12.79
4c	68	301–303	$C_{23}H_{18}N_4O_3S$ (430.48)	64.17 64.11	4.21 4.18	13.01 12.89
4d	69	287–290	$C_{22}H_{15}N_5O_4S$ (445.46)	59.32 59.29	3.39 3.30	15.72 15.67
4e	72	276–278	$C_{23}H_{18}N_4O_3S$ (430.49)	64.17 64.13	4.21 4.19	13.01 12.89
4f	70	243–245	$C_{24}H_{20}N_4O_3S$ (444.51)	64.85 64.76	4.53 4.48	12.60 12.54
5a	76	278–281	$C_{12}H_{14}N_2O_2S$ (250.32)	57.58 57.49	5.64 5.61	11.19 11.08
5b	78	256–258	$C_{13}H_{16}N_2O_2S$ (264.35)	59.07 59.02	6.10 6.03	10.60 10.54
6	65	321–324	$C_{12}H_{14}N_2OS_3$ (298.45)	48.29 48.22	4.73 4.67	9.39 9.28
7	59	289–292	$C_{12}H_{14}N_2OS_3$ (298.45)	48.29 48.26	4.73 4.70	9.39 9.35
8a	68	341–343	$C_{12}H_{15}N_3O_2S$ (265.33)	54.32 54.29	5.69 5.71	15.83 15.79
8b	64	316–319	$C_{12}H_{15}N_3OS_2$ (281.40)	51.21 51.18	5.37 5.38	14.93 14.87
9	63	262–264	$C_{14}H_{16}N_4OS$ (288.37)	58.31 58.27	5.59 5.54	19.42 19.36
10	61	278–280	$C_{14}H_{15}N_3O_2S$ (289.36)	58.11 58.08	5.22 5.17	14.52 14.49
11a	74	195–197	$C_{14}H_{18}N_2O_2S$ (278.37)	60.40 60.46	6.51 6.50	10.06 10.11
11b	71	207–209	$C_{15}H_{20}N_2O_2S$ (292.40)	61.61 61.57	6.89 6,84	9.58 9.61
12	56	261–263	$C_{12}H_{15}N_3OS$ (249.33)	57.80 57.77	6.06 6.00	16.85 16.76
13	66	309–311	$C_{12}H_{15}N_3OS$ (249.33)	57.81 57.76	6.06 6.02	16.85 16.91
14	68	259–162	$C_{12}H_{16}N_4OS$ (264.35)	54.52 54.49	6.10 6.09	21.19 21.07

Table II. Spectral data of the synthesized compounds

Compd. No.	Mass (*m/z*)	IR (ν, cm^{-1})	^1H NMR (δ, ppm) (DMSO-d_6)
1	261 (M^+) (100) 188 (M^+-73) (31)	3245 (NH_2) 1710 (C=O)	1.21 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.01 (q, 2H, CH_2), 7.43–7.52 (m, 5H, phenyl), 8.23 (brs, 2H, NH_2, D_2O exchangeable)
2	274 (M^+), (100)	3153 (NH) 1675 (C=O)	2,40 (s, 3H, CH_3), 7.51 (m, 5H, phenyl), 12.45 (s, 1H, NH, D_2O exchangeable), 13.50 (s, 1H, NH, D_2O exchangeable)
3	222 (M^+) (100)	3400 (brs, NH_2) 1704 (C=O) 2217 (CN)	1.00 (d, 6H, $2CH_3$), 2.05 (Septet, 1H, CH), 2.40 (s, 3H, CH_3), 2.50 (s, 2H, CH_2), 13.30 (brs, 1H, NH, D_2O exchangable)
4a	434 (M^+) (100) 357 (M^+-77) (28)	1686 (C=O)	2.11 (s, 3H, CH_3), 7.20–7.30 (m, 6H, phenyl), 7.40–7.56 (m, 9H, phenyl protons)
4b	434 (100) 391 (M^+-43) (54)	1700, 1686 (2C=O)	2.13 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.10–7.15 (d, 2H, phenyl), 7.30–7.35 (m, 2H, phenyl), 7.42–7.44 (m, 3H, phenyl), 7.65–7.68 (d, 2H, phenyl)
4c	430 (100) 399 (M^+-31) (32) 387 (M^+-43) (25)	1702, 1687 (2C=O)	2.11 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.15–7.20 (d, 2H, p-sub-pheny), 7.24–7.30 (m, 3H, phenyl), 7.47–7.56 (m, 2H, phenyl), 7.59–7.63 (d, 2H, phenyl)
4d	456 (M^++1) (34) 445 (100) 402 (M^+-43) (22)	1705, 1683 (2C=O)	2.14 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.16–7.22 (d, 2H, pheny), 7.26–7.35 (m, 3H, phenyl), 7.51–7.57 (m, 2H, phenyl), 7.56–7.60 (d, 2H, phenyl)
4e	430 (M^+) (100)	1714, 1689 (2C=O)	1.27 (t, 3H, CH_3), 2.13 (s, 3H, CH_3), 4.35 (q, 2H, CH_2), 7.25–7.30 (m, 6H, pheny), 7.40–7.75 (m, 4H, phenyl)
4f	444 (M^+) (100) 415 (M^+-29) ((12)	1715, 1689 (2C=O)	1.28 (t, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.38 (q, 2H, CH_2), 7.12–7.16 (d, 2H, phenyl), 7.25–7.35 (m, 3H, pheny), 7.40–7.51 (m, 2H, phenyl), 8.00–8.05 (d, 2H, phenyl)
5a	250 (M^+) (100)	3355 (brs, NH) 1705, 1688 (2C=O)	1.02 (d, 6H, $2CH_3$), 2.07 (Septet, 1H, CH), 2.41 (s, 3H, CH_3), 2.52 (s, 2H, CH_2), 8.21 (s, 1H, pyrimidine proton), 13.10 (brs, 1H, NH, D_2O exchangable)
5b	264 (M^+) (100)	3316 (brs, NH) 1700, 1678 (2C=O)	1.01 (d, 6H, $2CH_3$), 2.06 (Septet, 1H, CH), 2,23 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.48 (s, 2H, CH_2), 8.21 (s, 1H, pyrimidine proton), 13.10 (brs, 1H, NH)
6		3390 (brs, NH) 1702 (C=O) 1350, 1365 (2C=S)	1.00 (d, 6H, $2CH_3$), 2.05 (Septet, 1H, CH), 2.40 (s, 3H, CH_3), 2.50 (s, 2H, CH_2), 8.90 (brs, 1H, NH, D_2O exchangeable), 13.10 (brs, 1H, NH)
7	298 (M^+) (66) 255 (M^+-43) (32) 241 (M^+-57) (42)	3400 (brs, NH) 1706 (CO) 1380 (C=S)	1.00 (d, 6H, $2CH_3$), 2.04 (Septet, 1H, CH), 2.38 (s, 3H, CH_3), 2.50 (s, 2H, CH_2), 8.02 (brs, 1H, NH), 13.00 (brs, 1H, NH)

Table II. continued

Compd. No.	Mass (*m/z*)	IR (ν, cm^{-1})	^1H NMR (δ, ppm) (DMSO-d_6)
8a	266 (M^++1) (34) 265 (M^+) (100)	3450 (brs, 2NH) 1705 1686 (2C=O)	1.03 (d, 6H, $2CH_3$), 2.02 (Septet, 1H, CH), 2.39 (s, 3H, CH_3), 2.48 (s, 2H, CH_2), 8.60 (brs, 2H, 2NH, D_2O exchangeable), 13.20 (brs, 1H, NH)
8b		3397 (brs, 2NH) 1710 (C=O) 1360 (C=S)	1.02 (d, 6H, $2CH_3$), 2.03 (Septet, 1H, CH), 2.41 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 8.45 (brs, 2H, 2NH), 13.30 (brs, 1H, NH)
9	288 (M^+) (100)	3450–3320 (brs, $2NH_2$) 2218 (CN) 1705 (C=O)	1.00 (d, 6H, $2CH_3$), 2.00 (Septet, 1H, CH), 2.38 (s, 3H, CH_3), 2.49 (s, 2H, CH_2), 8.42 (brs, 2H, NH_2), 13.20 (brs, 2H, NH_2)
10	289 (M^+) (100)	3500 (OH) 3400 (brs, NH_2) 2215 (CN) 1712 (C=O)	1.01 (d, 6H, $2CH_3$), 2.04 (Septet, 1H, CH), 2.40 (s, 3H, CH_3), 2.50 (s, 2H, CH_2), 8.23 (brs, 2H, NH_2, D_2O exchangeable), 12.20 (brs, 1H, OH)
11a	279 (M^++1) (29) 278 (M^+) (79)	3390 (brs, NH) 2924, 2213 (CN) 1705 (C=O)	1.02 (d, 6H, $2CH_3$), 1.34 (t, 3H, CH_3), 2.01 (Septet, 1H, CH), 2.41 (s, 3H, CH_3), 2.52 (s, 2H, CH_2), 3.89 (q, 2H, CH_2), 8.00 (s, 1H, methylenic proton), 13.00 (brs, 1H, NH, D_2O exchangeable)
11b		3385 (brs, NH) 2215 (CN) 1708 (C=O)	1.01 (d, 6H, $2CH_3$), 1.35 (t, 3H, CH_3), 2.00 (Septet, 1H, CH), 2.11 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.53 (s, 2H, CH_2), 3.91 (q, 2H, CH_2), 13.10 (brs, 1H, NH)
12		3420 (brs, NH_2) 2216 (CN) 1708 (C=O)	1.03 (d, 6H, $2CH_3$), 2.00 (Septet, 1H, CH), 2.40 (s, 3H, CH_3), 2.51 (s, 2H, CH_2), 8.16 (s, 1H, methylenic proton), 11.50 (brs, 2H, NH_2, D_2O exchangeable)
13	249 (M^+) (100)	3410 (brs, NH_2) 1704 (C=O)	1.00 (d, 6H, $2CH_3$), 2.02 (Septet, 1H, CH), 2.39 (s, 3H, CH_3), 2.50 (s, 2H, CH_2), 8.32 (s, 1H, pyrimidine proton), 11.50 (brs, 2H, NH_2, D_2O exchangeable)
14	264 (M^+) (100) 221 (M^+-43) (43)	3460–3350 (brs, NH+NH_2) 1710 (C=O)	1.04 (d, 6H, $2CH_3$), 2.03 (Septet, 1H, CH), 2.42 (s, 3H, CH_3), 2.53 (s, 2H, CH_2), 8.28 (s, 1H, pyrimidine proton), 8.65, 11.50 (2brs, 3H (NH, NH_2), D_2O exchangeable)

10% (*V/V*) Tween 80 suspension intraperitonially. One group was administered acetylsalicylic acid intraperitoneally in a dose of 200 mg kg^{-1} once daily for 3 days. The remaining groups of animals were administered test compounds intraperitoneally in a dose of 20 mg kg^{-1}. On the fourth day, pylorus was ligated as per the method of Shay *et al*. (19); animals were fasted for 36 h before the pylorus ligation procedure. Four hours after the ligation, animals were sacrificed. The stomach was removed and opened along the greater curvature. Ulcer index was determined by the method of Ganguly and Bhatnagar (20) and is given in Table V.

Table III. Percent anti-inflammatory activity of test compounds[a,b,c]

Compd.	1 hour		2 hours		3 hours		4 hours	
	Edema rate (%)	Pot. (%)	Edema rate (%)	Pot. (%)	Edema rate (%)	Pot. (%)	Edema rate (%)	Pot. (%)
Control	34.8 ± 3.1[f]	0	53.0 ± 1.9[f]	0	82.0 ± 3.3[f]	0	91.6 ± 4.5[f]	0
4a	24.2 ± 0.9[e,f] (30.5)	54	42.0 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.9)	51	74.6 ± 3.3[e,f] (18.6)	40
4b	24.2 ± 0.9[e,f] (30.5)	54	42.0 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.9)	51	74.5 ± 3.3[e,f] (18.6)	40
4c	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f] (1.2)	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	20
4d	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f] (1.2)	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	20
4e	24.2 ± 0.9[e,f] (30.5)	54	42.0 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.8)	51	74.5 ± 3.3[e,f] (18.6)	40
4f	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f] (1.2)	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	20
5a	31.1 ± 1.8[f] (10.5)	15	52.5 ± 1.9[f] (0.9)	2	81.7 ± 4.1[f] (0.1)	0	90.9 ± 3.0 (0.8)	2
5b	24.2 ± 0.9[e,f] (30.5)	54	41.9 ± 2.0[f] (20.8)	36	64.0 ± 1.9[e,f] (21.8)	51	74.5 ± 3.3[e,f] (18.6)	40
6	25.7 ± 1.2[f] (25.9)	46	40.9 ± 3.1[e,f] (22.8)	39	62.3 ± 4.2[e,f] (23.9)	56	71.6 ± 3.3[e,f] (21.8)	47
7	25.7 ± 1.2[e,f] (25.9)	46	40.9 ± 3.1[f] (1.2)	39	62.3 ± 4.2[e,f] (23.9)	56	71.6 ± 3.3[e,f] (21.8)	47
8a	31.2 ± 2.5[f] (10.1)	18	52.3 ± 4.8[f]	2	79.5 ± 2.3[f] (2.8)	7	82.9 ± 1.9[f] (9.5)	21
8b	31.1 ± 1.8[f] (10.5)	15	52.5 ± 1.9[f] (0.9)	2	81.7 ± 4.1[f] (0.1)	0	90.9 ± 3.0 (0.8)	2
Indo-methacin	15.0 ± 0.9[e] (56.9)	100	22.2 ± 0.8[e] (58.2)	100	47.0 ± 5.0[e] (42.6)	100	49.1 ± 2.7[e] (46.4)	100

[a] Vehicle: 1 mL 10% (*V/V*) Tween-80. Dose: 15 mg kg^{-1} b.m. test compound and 10 mg kg^{-1} b.m. of indomethacin.

[b] Values represent the mean ± SEM ($n = 6$).

[c] Each value in parentheses indicates the percentage inhibition rate.

[d] The potency (pot.) was calculated compared to the reference drug indomethacin.

[e] Significantly different from control (Dunnett's test): $p < 0.05$.

[f] Significantly different from indomethacin (Dunnett's test): $p < 0.05$.

RESULTS AND DISCUSSION

According to Gewald *et al.* (11), heating under stirring of a mixture of ethylcyanoacetate, sulfur, benzylmethyl ketone and diethylamine in absolute ethanol for 8 hours afforded 2-amino-4-methyl-5-phenyl-thiophene-3-ethylcarboxylate **1** (85%). The latter compound was cyclized by refluxing in a mixture of potassium thiocyanate and dioxane in

Table IV. Peripheral analgesic activity[a]

Compd.	No. of writhes in 20 min	Protection (%)
Control	48.0 ± 2.2[d]	0
4a	23.2 ± 1.4[c]	52
4b	31.0 ± 1.6[c,d]	35
4c	30.2 ± 1.7[c,a]	37
4d	31.0 ± 1.6[c,d]	35
4e	41.3 ± 2.4[d]	14
4f	45.2 ± 1.8[d]	6
5a	31.3 ± 2.5[c,d]	35
5b	19.6 ± 0.5[c]	59
6	19.0 ± 1.2[c]	60
7	19.6 ± 0.5[c]	59
8a	45.8 ± 2.9[d]	5
8b	45.8 ± 2.9[d]	5
Acetylsalicylic acid	22.6 ± 2.0[c]	53

[a] Vehicle: 1 mL of distilled water. Dose: 15 mg kg^{-1} b.m. of test compound and 100 mg kg^{-1} b.m. of acetylsalicylic acid.

[b] Values represent the mean ± SEM (n = 6).

[c] Significantly different from control (Dunnett's test): $p < 0.05$.

[d] Significantly different from acetylsalicylic (Dunnett's test): $p < 0.05$.

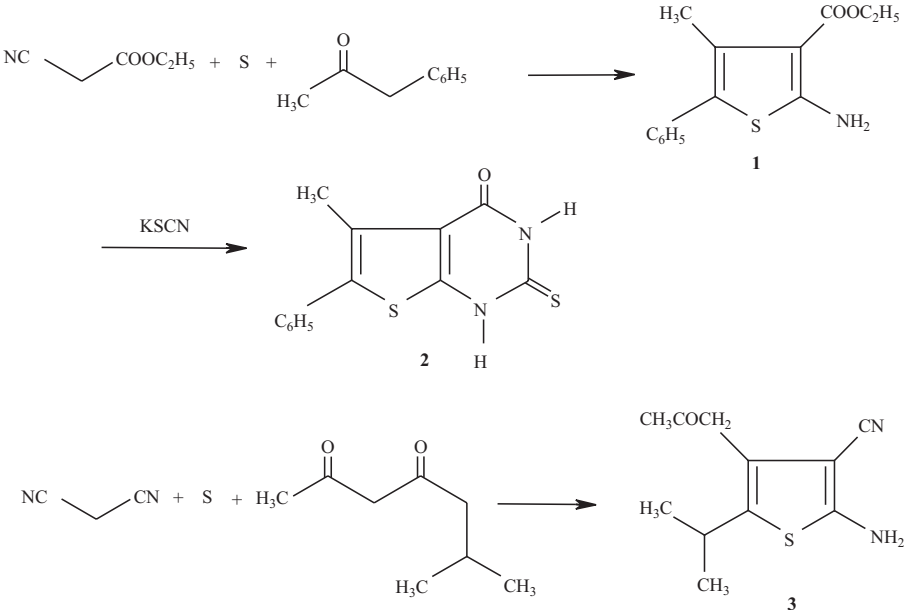
Table V. Ulcerogenicity index

Compd.	Ulcer idex
Control	0.9 ± 0.1[c]
4a	1.1 ± 0.3[d]
4b	0.9 ± 0.3[c]
4c	1.2 ± 0.3[d]
4d	0.7 ± 0.2[c]
4e	1.1 ± 0.2[d]
4f	0.8 ± 0.2[c]
5a	0.9 ± 0.2[c]
5b	1.1 ± 0.2[d]
6	1.1 ± 0.2[d]
7	0.9 ± 0.3[c]
8a	0.9 ± 0.2[c]
8b	1.1 ± 0.3
Acetylsalicylic acid	1.7 ± 0.4[d]

[a] Vehicle: 1 mL of 10% (*V*/*V*) of Tween-80. Dose: 20 mg kg^{-1} b.m. of test compound and 200 mg kg^{-1} b.m. of acetylsalicylic acid.

[b] Each value represents the mean ± SEM (n = 6).

Significantly different from acetylsalicylic acid: [c] $p < 0.05$, [d] $p < 0.01$.

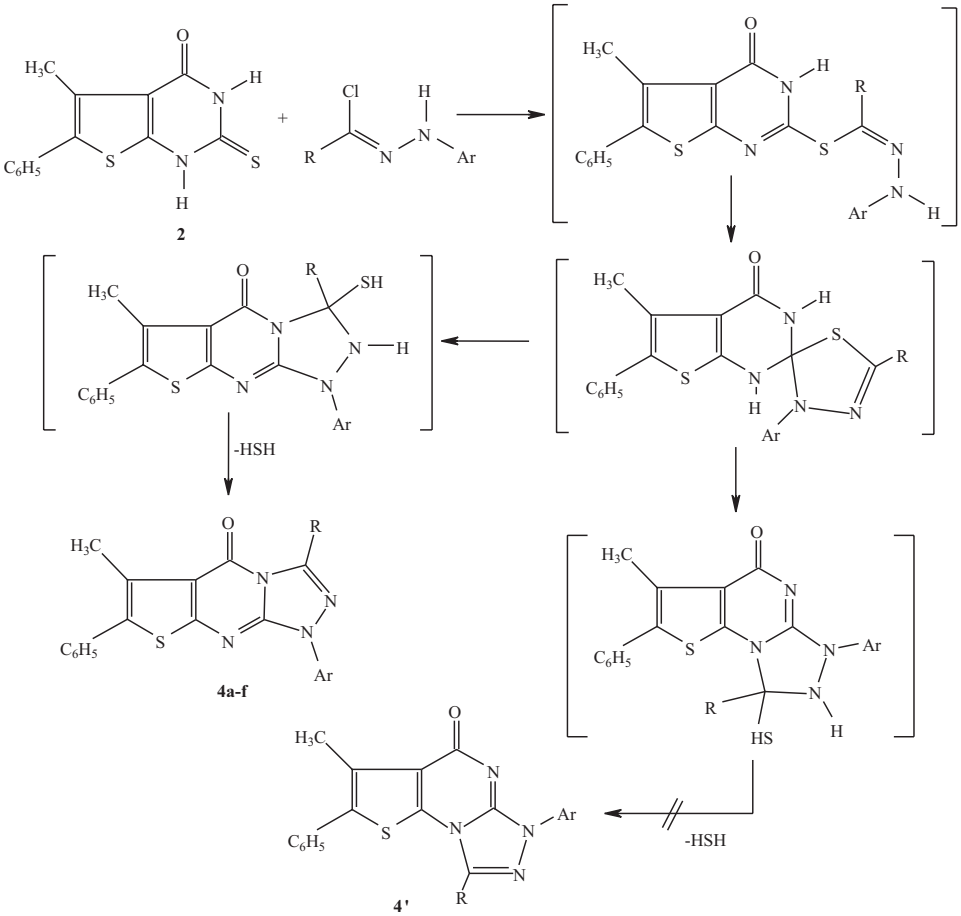


Scheme 1

the presence of concentrated hydrochloric acid affording 5-methyl-6-phenyl-2-thioxo--thieno[2,3-*d*]pyrimidine derivative **2** (Scheme 1). The ^{1}H NMR spectrum of the resulting product **2** is in agreement with the given structure and literature (21). Stirring a mixture of malononitrile, 6-methyl-heptane-2,4-dione, sulfur and diethylamine in absolute ethanol afforded acetone-1-(2-amino-5-isopropyl-thiophene-3-carbonitrile derivative **3** (73%) (Scheme 1). Also, the latter compound was used as a good source to enrich the synthesis of heterocyclic chemistry with several new thieno-pyrimidines, thienothiazine and thieno-pyridine derivatives.

As part of our continuing program on the synthesis of various functionalized mono--heterocyclic and annelated heterocyclic derivatives (22, 23), we report here a new synthetic strategy for the preparation of functionalized thieno[2,3-*d*][1,2,4]-5*H*-1,3-disubstituted-triazolo[4,3-*a*]pyrimidine-5-one derivatives **4a–f** via reactions of hydrazonoyl chlorides with 5-methyl-6-phenyl-2-thioxo-thieno[2,3-*d*]pyrimidine (**2**) (Scheme 2). Beside the correct values of elemental analysis, the IR, ^{1}H NMR and mass spectra of compounds **4a–f** are in agreement with the assigned structures. The N-3 nitrogen atom and not the N-1 nitrogen atom was involved in the cyclization to form adduct **4** and not isomer **4′**.

2-Amino-5-isopropyl-4-(2-oxo-propyl)-thiophene-3-carbonitrile (**3**) behaved as a typical β-enaminonitrile derivative due to the presence of amino and carbonitrile groups at positions 2 and 3, respectively, attached to the thiophene ring, which is considered as a precursor in the synthesis of various heterocyclic derivatives with several new azolo-thienopyrimidines, thienothiazine and thienopyrimidines (24). Therefore, heating under reflux of compound **3** with aliphatic acids, namely, formic and acetic acids for 6 hours

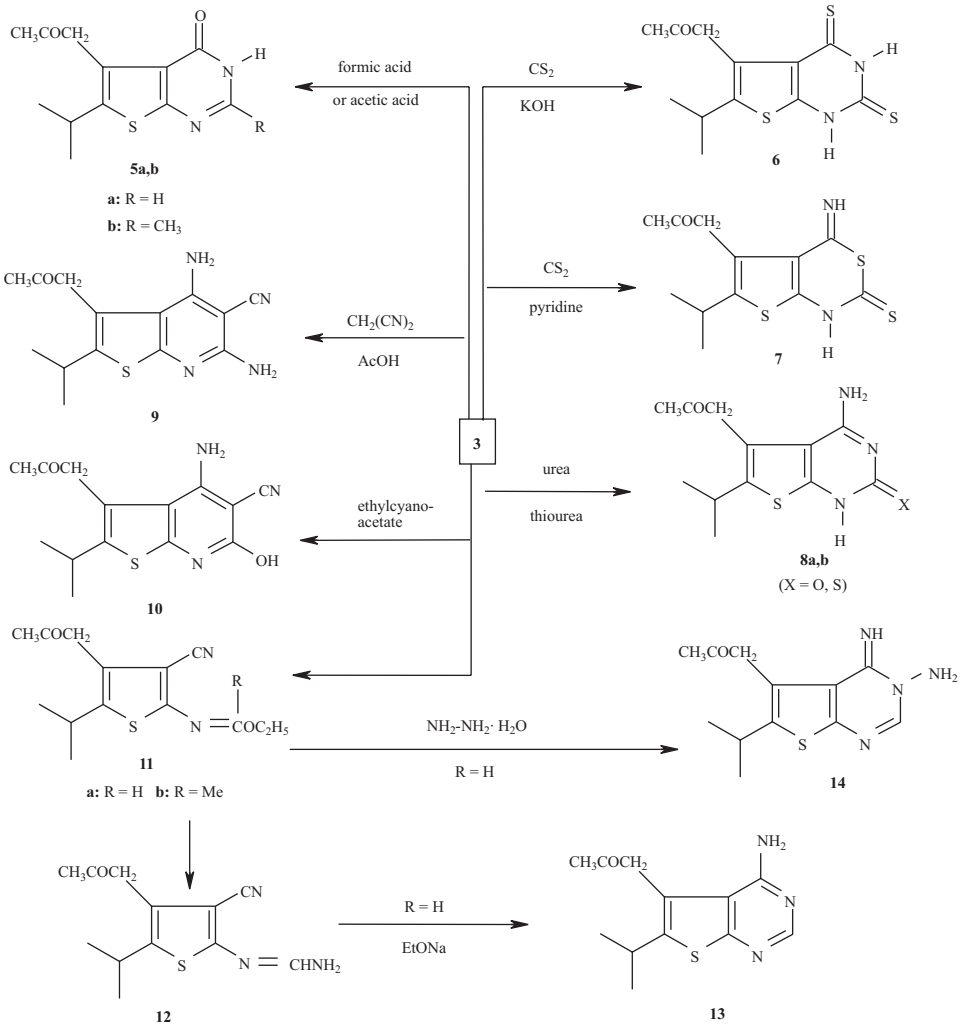


a: R = Ar = C_6H_5
b: R = $COCH_3$, Ar = *p*-C_6H_4-Cl
c: R = $COCH_3$, Ar = *p*-C_6H_4-OCH_3
d: R = $COCH_3$, Ar = *p*-C_6H_4-NO_2
e: R = $COOC_2H_5$, Ar = C_6H_5
f: R = $COOC_2H_5$, Ar = *p*-C_6H_4-CH_3

Scheme 2

yielded thieno[2,3-*d*]-pyrimidin-4-one (**5a**,**b**) (Scheme 3). Besides, the correct values of elemental analyses, the ^{1}H NMR spectrum, IR and mass spectra of the new compounds were in agreement with the assigned structures.

Similarly, compound **3** reacted with carbon disulphide in the presence of potassium hydroxide in absolute ethanol to yield 1-(6-isopropyl-2,4-dithioxo-1,2,3,4-tetrahydro-thieno-[2,3-*d*]pyrimidin-5-yl)-propan-2-one (**6**). IR spectrum of **6** displayed absorption bands at 1350 and 1365 cm^{-1} of two C=S groups. On the other hand, stirring under reflux of com-



Scheme 3

pound **3** with carbon disulphide in dry pyridine afforded the 1-(4-imino-6-isopropyl-2-thioxo-1,4-dihydro-2*H*-thieno[2,3-*d*][1,3]thiazin-5-yl)-propan-2-one (**7**). Also, when heated with urea or thiourea at 180 °C, compound **3** gave 4-amino-6-isopropyl-5-(2-oxo-propyl)--1*H*-thieno[2,3-*d*]pyrimidin-(2-one or 2-thione) derivatives **8a,b**, respectively (Scheme 3).

When compound **3** was reacted with active methylenes, malononitrile in glacial acetic acid and ethylcyanoacetate in dry dioxane in the presence of catalytic amount of tri-

ethylamine, it yielded the corresponding 4,6-diamino-2-isopropyl-3-(2-oxo-propyl)-thieno-[2,3-*b*]pyridine-5-carbonitrile (**9**) and 4-amino-6-hydroxy-2-isopropyl-3-(2-oxo-propyl)-thieno[2,3-*b*]pyridine-5-carbonitrile (**10**), respectively (Scheme 3). Structures **9** and **10** were tentatively preferred for this product based on its ^{1}H NMR spectrum and the IR spectra, which revealed the presence of the cyano-group around 2212 cm^{-1} and NH_2 group around 3500 cm^{-1}. Condensation of **3** with triethyl orthoformate or triethylorthoacetate in boiling acetic anhydride yielded the corresponding N-[3-cyano-5-isopropyl-4-(2-oxo-propyl)-thiophen-2-yl]-formamidic acid ethyl ester (**11a**) and N-[3-cyano-5-isopropyl-4-(2-oxo-propyl)-thiophen-2-yl]-acetimidic acid ethyl ester (**11b**) respectivly, with compatible IR and ^{1}H NMR data. Compound **11a** reacted with ammonium hydroxide solution in absolute ethanol to give N-[3-cyano-5-isopropyl-4-(2-oxo-propyl)-thiophen-2-yl]-formamidine (**12**), which on boiling in absolute ethanolic sodium ethoxide solution underwent cyclization to give 1-(4-amino-6-isopropyl-thieno[2,3-*d*]-pyrimidin-5-yl)-propan-2-one (**13**) (Scheme 3). The IR spectrum of **12** displayed an absorption band at 2216 cm^{-1} (CN), while, that of **13** revealed the absence of CN group. Finally, stirring compound **11a** with hydrazine in absolute ethanol at room temperature gave 1-(3-amino-4-imino-6-isopropyl-3,4-dihydro- thieno[2,3-*d*]pyrimidin-5-yl)-propan-2-one (**14**).

The anti-inflammatory activity data (Table III) indicated that all the test compounds protected rats from carrageenean induced inflammation. Compounds **4a**, **4b**, **4e**, **5b**, **6** and **7** protected rats by 36 to 56% from inflammation while the other tested compounds showed lower anti-inflamatory activity in comparison to indomethacin. This means that the fused triazolo[4,3-*a*]pyrimidine, pyrimidine-2,4-dithione and thieno[2,3-*d*][1,3]thiazine possess good anti-inflammatory activity.

The results of analgesic activity indicate that all the test compounds exhibited high activity (Table IV). Triazolo[4,3-*a*]pyrimidine **4a** with triphenyl substitution showed high activity comparable to that of acetylsalicylic acid. The compounds with acetyl or ethyl-ester group substitution (**4b**–**d**), showed moderate activity. Also, thieno[2,3-*d*]pyrimidines **5b** and **6** and thieno[2,3-*d*][1,3]thiazin **7** were found to be the most active analgesic agents, even more potent than acetylsalicylic acid.

The ulcer index of the test compounds (Table V) reveals that all compounds showed a mild ulcer index as compared to acetylsalicylic acid.

CONCLUSION

New compounds, substituted thieno[2,3-*d*][1,2,4]-triazolo[4,3-a]pyrimidin-5-ones **4a**, **4b**, **4e** 6-isopropyl-2-methyl-5-(2-oxo-propyl)-3*H*-thieno[2,3-*d*] pyrimidin-4-one (**5b**), 1-(6-isopropyl-2,4-dithioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*] pyrimidin-5-yl)propan-2-one (**6**) and 1-(4-imino-6-isopropil-2-thioxo-1,4-dihydro-2H-thieno[2,3-*d*][1,3]thiazin-5-yl)propan-2-one (**7**) showed moderate anti-inflammatory activity. However, thieno[2,3-*d*][1,2,4]-triazolo[4,3-a]pyrimidin-5-ones **4a–d** and 6-isopropyl-5-(2-oxo-propyl)-3*H*-thieno[2,3-*d*] pyrimidin-4-one (**5a**) and compounds **5b**, **6** and **7** showed good to excellent analgesic activity.

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S A Ž E T A K

Sinteza i protuupalno, analgetsko i ulcerogeno djelovanje derivata tieno[2,3-*d*]pirimidina

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Reakcijom derivata 5-metil-6-fenil-2-tioksotieno[2,3-*d*]pirimidona (**2**) s hidrazonoil kloridima dobiveni su triazolotienopirimidoni **4a–f**, a reakcijom aceton-1-(2-amino-5-izopropil-**-**tiopen-3-karbonitrila (**3**) s funkcionalnim i bifunkcionalnim spojevima dobiveni su produkti **5**–**11**. Novi spojevi imaju slično protuupalno, analgetsko i ulcerogeno djelovanje kao i indometacin, odnosno acetilsalicilna kiselina.

Ključne riječi: triazolotienopirimidin, tienopirimidini, tieno[2,3-*d*][1,3]tiazin, tienopiridini, analgetsko, protuupalno, ulcerogeno djelovanje

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