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Synthesis of 4-substituted pyrido[2,3-*d*]pyrimidin-4(1*H*)-one as analgesic and anti-inflammatory agents

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ABSTRACT

4-Substituted-pyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **4a–c** were synthesized by oxidation of 4-substituted-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **3a–c** which were in turn prepared from arylidenemalononitriles **1a–c** and 6-aminothiouracil **2**. The reactivity of compounds **4a–c** towards some reagents such as formamide, carbon disulfide, urea, thiourea, formic and acetic acids were studied. All the synthesized compounds were characterized by spectroscopic means and elemental analysis. Compound **4c** exhibited 64% and 72% analgesic activity. Also, compound **4b** showed 50% and 65% anti-inflammatory activity. Interestingly these compounds showed one-third of ulcer index of the reference aspirin and diclofenac.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain and fever. However, long-term clinical usage of NSAIDs is associated with significant side effects such as gastrointestinal lesions, bleeding, and nephrotoxicity. Therefore, discovery of new safer anti-inflammatory drugs represents a challenging goal in a research area.[1–3] In our ongoing medicinal chemistry research program, we found that pyrimidines and condensed pyrido[2,3-*d*]pyrimidines exhibit potent central nervous system (CNS) activity, including analgesic, anti-inflammatory and anticonvulsant behavior.[4,5] Pyridopyrimidines with 7-(6-morpholin-4-ylpyridin-3-yl)-substitutions are reported to possess significant analgesic, anti-inflammatory and anticonvulsant activitiy.[6,7] We have earlier documented that some lead 2-pyrazolyl-pyridopyrimidines,[8] 2-thioxopyridipyrimidines, 2-thioxopyrimidoquinolines exhibited good analgesic and anti-inflammatory properties.[9,10]

Both pyrimidine and heterocyclic uracil structural analogues such as 2-thioxo-pyrido[2,3-*d*]pyrimidin-4-one and pyrrolo[2,3-*d*]pyrimidines have shown a wide range of biological applications. The use of Sangivamicine or Toyocamicine as antibiotics is well known, and the antiviral application of their analogues has been reported.[11] Besides, other pyrido[2,3-*d*]pyrimidine ring system is present in a number of biologically active compounds which includes antipyretic,[12] bactericides,[13] medicinal,[14] and antitumoral,[15] antihistaminic,[16] diuretic,[17,18] activities and can even be used in the treatment of neuronal diseases.[19]

In this work, we present the synthesis of several pyrido[2,3-*d*]pyrimidine derivatives from 6-aminouracil and arylidenemalononitrile derivatives. These reactions have two points of interest: first, to obtain new derivatives with potential biological applications, and second to explore into the reactivity of 6-aminouracil with electron-deficient alkenyl compounds; these reactions, as we previously reported in the case of electron-deficient α,β-unsaturated dienophiles,[20–22] could evolve through two different ways via a Michael addition at the C(5) atom of the pyrimidine ring.[23] The synthesis of pyrido[2,3-*d*]pyrimidine derivatives from 6-aminouracil and ketones, DMFDMA,[24] α,β-unsaturated ketones,[25] and via Mannich bases (arylalkanone),[26] has been reported. In our case we have used arylidenemalononitrile derivatives **1** as electron-deficient reactants with 6-aminouracil **2**.

6-Aminothiouracil **2** was reacted with an equimolar amount of arylidenemalononitrile **1a–c** according to the reported procedure.[20] We performed this reaction under dry conditions and refluxing for long time in order to prevent the formation of the 1,4-dihydropyrido[2,3-*d*]pyrimidin-4-ones **3a–c**, thus it was not necessary to purified the reaction mixture by column chromatography. The most probable mechanism to afford pyridopyrimidines **3**, which is shown in Scheme 1, involves two steps, the first a Michael addition reaction of the pyrimidine ring C-5 carbon atom to **1** to give, via zwitterionic structure **I**, the intermediate **II**, which then undergoes ring closing resulting in product **3**. The prolonged duration reaction is required to furnish the oxidized form **4a–c**.

Various 7-amino-6-cyano-5-sbstituted-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-ones (**4a–c,** Scheme 2) were synthesized by condensation of arylidenemalononitriles **1a–c** and 6-aminothiouracil **2** as reported in the literature.[9] 6-Aminothiouracil on

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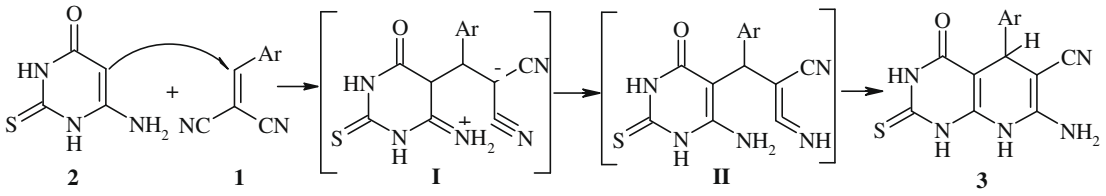
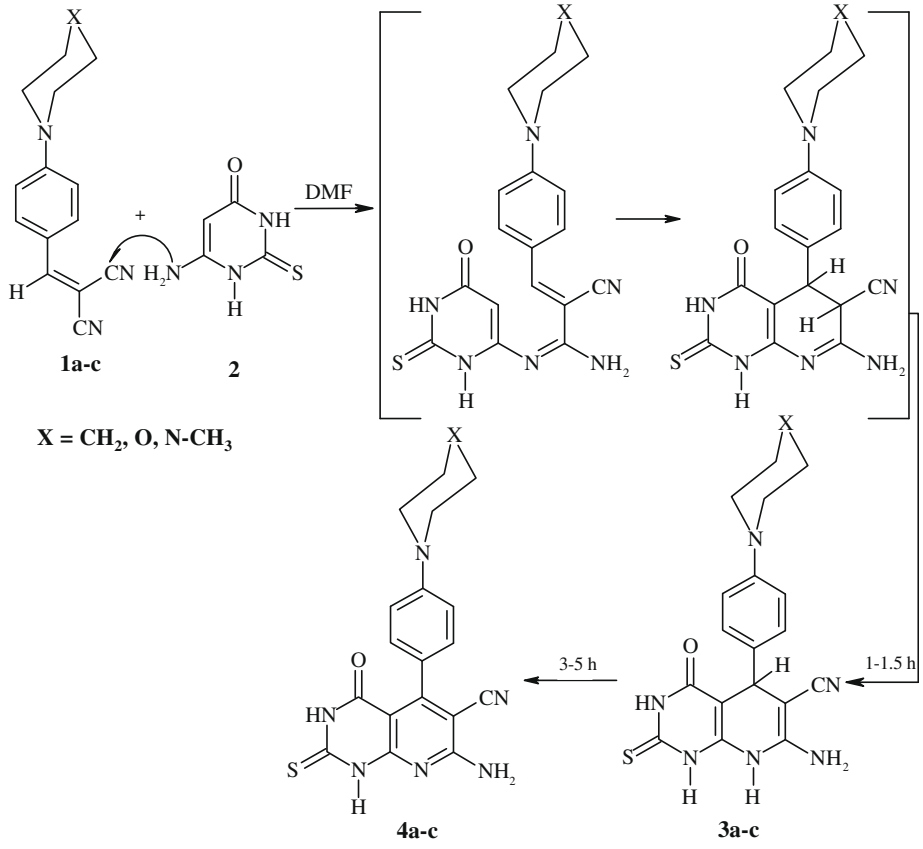


Scheme 1. Mechanism postulated for the reaction of 6-aminouracil and arylidenemalononitrile.



Scheme 2. Reaction of 6-aminouracil with arylidenemalononitriles **1a**–**c**.

refluxing with arylidenemalononitrile **1a** in dimethylformamide for 3–5 h gave condensed product **4a** after usual workup. Compound **4a** was purified by crystallization from dioxane to give pure 7-amino-6-cyano-5-[4-(1-piperidinyl)-phenyl]-2-thioxopyrido [2,3-*d*]pyrimidin-4(1*H*)-ones (**4a**) in 78% yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **4a** showed signals at δ 1.56 (br s, 6H, piperidinyl 3 CH_2), 3.25 (br s, 4H, piperidinyl 2 NCH_2), 6.88 (AA′BB′, 2H, Ar–*H*, *J* = 8.6 Hz), 7.10 (AA′BB′, 2H, Ar–*H*, *J* = 8.6 Hz), 7.62 (br s, 2H, NH_2), 8.45 (br s, H, N*H*), 12.05 (br s, H, N*H*). Also, ^{13}C NMR (500 MHz; DMSO-d_6) of **4a** showed signals at δ 23.86, 25.09, 25.81 (3 CH_2), 48.15, 48.67 (2 NCH_2), 107.68 (CN), 113.63, 114.83, 115.64, 117.12, 120.83, 121.92, 129.18, 151.4, 153.07, 167.30, 160.98 (11 signals for 11 sp^2 carbon), 172.7 (C=O), 183.05 (C=S). IR spectra show absorption band at 3450 (NH's), 2218 (CN) and 1680 (C=O) cm^{-1}. Spectral data of **4a** fully support the structure assigned to it. Similarly the others –(4-morpholinyl) and –(4-methylpiperazinyl), that is, **4b,c** (Scheme 2) were synthesized and purified by crystallization. Spectral and analytical data of compounds **4a–c** reported in Reference and notes of this Letter fully support the structures assigned to them.

Compounds **4a–c** as a typical β-enaminonitrile derivative, reacted with formamide and aliphatic acids namely, formic and acetic acids, afforded 5-substituted-pyrido[2,3-*d*:6,5-*d*]dipyrimidine-4,6-dione derivatives (**5a–c**, **7a–f**), respectively. The IR spectra of compounds **5** displayed absorption bands around 3500 cm^{-1} (NH, NH_2) and around 1685 cm^{-1} for carbonyl group, However the IR spectra of compounds **7** displayed absorption bands around 3450 cm^{-1} (NH) and around 1670, 1685 cm^{-1} for two carbonyl groups. The ^{1}H NMR (DMSO-d_6) spectrum of **5b** showed the signals at δ 3.29 (t, 4H, morpholinyl 2 NCH_2, *J* = 5.0 Hz), 3.90 (t, 4H, morpholinyl 2 OCH_2, *J* = 5.0 Hz), 6.98 (AA′BB′, 2H, Ar–*H*, *J* = 8.7 Hz), 7.18 (AA′BB′, 2H, Ar–*H*, *J* = 8.7 Hz), 7.75 (br, s, 2H, NH_2), 8.06 (s, 1H, pyrimidine-*H*), 8.65 (br s, H, NH), 12.30 (br s, H, N*H*). Also, the ^{1}H NMR (DMSO-d_6) spectrum of compound **7b** as an example showed signals at 1.60 (br, s, 6H, piperidinyl 3 CH_2), 2.26 (s, 3H, pyrimidine-CH_3), 3.32 (br s, 4H,

piperidinyl 2 NCH_2), 7.10 (d, 2H, Ar–*H*, *J* = 8.6 Hz), 7.25 (d, 2H, Ar–*H*, *J* = 8.6 Hz), 8.50 (br s, H, N*H*), 9.70 (br s, 1H, N*H*), 11.80 (br s, H, N*H*).

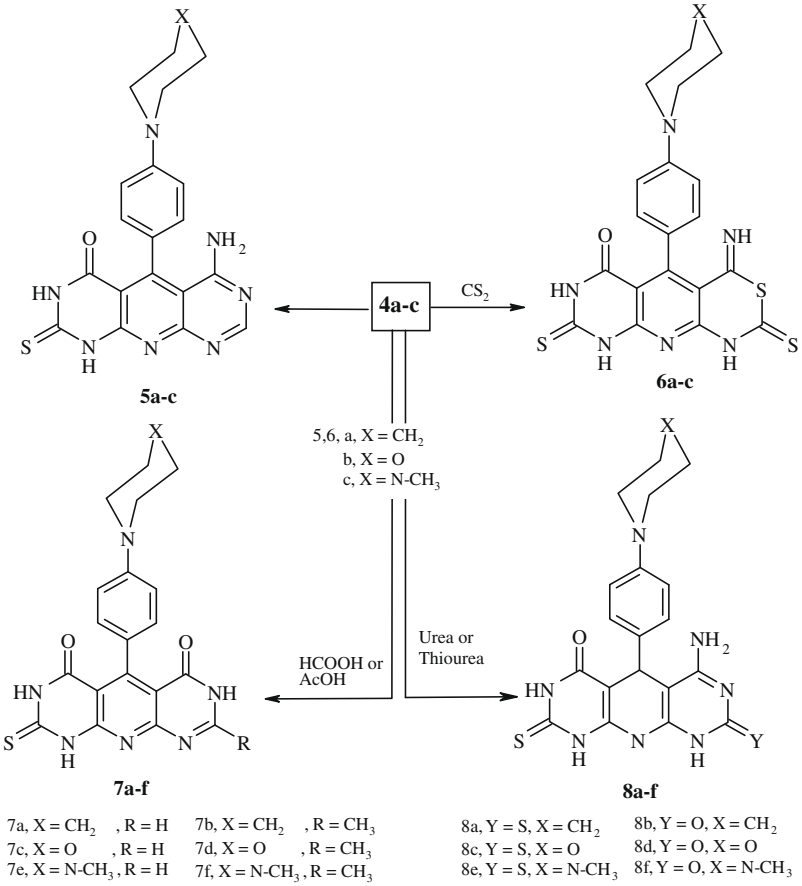
Also, when compound **4a–c** was heated with carbon disulfide in pyridine, 6-Imino-5-substituted-2-thioxopyrimido[4′,5′:2,3]pyrido[6,5-*d*][1,3]thiazin-13-one **(6a–c)**, was obtained. The ^{1}H NMR (DMSO-d_6) spectrum of **6c** showed signals at δ 2.29 (s, 3H, piperazinyl NCH_3), 2.57 (br s, 4H, piperazinyl 2 CH_3NCH_2), 3.38 (br s, 4H, piperazinyl 2 ArNCH_2), 7.18 (AA′BB′, 2H, Ar–*H*, *J* = 8.6 Hz), 7.42 (AA′BB′, 2H, Ar–*H*, *J* = 8.6 Hz), 8.45 (br s, H, N*H*), 8.90 (s, 1H, N*H*), 9.25 (br s, H, N*H*), 11.80 (br s, H, N*H*).

Finally, compound **4a–c** reacted with thiourea or urea at 180 °C, it gave 6-amino-5-substituted-2,8-dithiopyrido[2,3-*d*:6,5-*d*]dipyrimidin-4-one (**8a,c,e**), and 6-amino-5-substituted-2-thiopyrido[2,3-*d*:6,5-*d*]dipyrimidine-4,8-dione (**8b,d,f**), respectively, (Scheme 3). The ^{1}H NMR (DMSO-d_6) spectrum of **8f**, as an example, showed signals at 2.26 (s, 3H, piperazinyl NCH_3), 2.58 (br, s, 4H, piperazinyl 2 CH_3NCH_2), 3.39 (br s, 4H, piperazinyl 2 ArNCH_2), 7.07 (AA′BB′, 2H, Ar–*H*, *J* = 9.0 Hz), 7.33 (AA′BB′, 2H, Ar–*H*, *J* = 9.0 Hz), 8.23 (br s, 2H, NH_2), 8.70 (br s, H, N*H*), 9.37 (br s, H, N*H*), 11.82 (br s, H, N*H*). Also, its IR spectra for the compounds **8** displayed absorption bands around 3500 (NH, NH_2) and 1670, 1685 cm^{-1} (2 C=O).

Test for analgesic activity was performed by tail-flick technique using Wistar albino mice. The results of analgesic activity indicate that test compounds exhibited moderate analgesic activity at 30 min of reaction time; the activity increased at 1 h, further it reached to peak level at 2 h and declining in activity was observed at 3 h (Table 1). Compound **4b** with morpholine substituent showed good activity; with the increased lipophilicity (*N*-methylpiprazine group, compound **4c**) showed increased in activity. Replacement of *N*-methylpiprazine group with piperidinyl group (compound **4a**) retains the activity. 4-Aminopyrimidine ring formation at *C*-2 and *C*-3 (compounds **5a–c**) leads to moderate decrease in activity. Imino-pyrimido[1,3]thiazine formation and pyrimidin-4-one formations (compounds **6a–c** and **7a–c**) also results in decreasing activity. 2-Thioxopyrimidines ring formation (compound **8a–c**) leads to further decrease of activity. Compound 7-amino-6-cyano-5-[4-(4-methylpiperazinyl)-phenyl]-2-thioxo-pyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**4c**) emerged as the most active analgesic agent and it is moderately more potent when compared to the reference standard diclofenac sodium.

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test in rats.[27] The anti-inflammatory activity data (Table 2) indicated that all the test compounds protected rats from carrageenan-induced inflammation moderately at 30 min of reaction time; the activity increased at 1 h and it reached to peak level at 2 h. Declining in activity was observed at 3 h. The compound with morpholine substituent **4b** showed moderately more potent anti-inflammatory activity when compared to the reference standard diclofenac sodium. The compound 7-amino-6-cyano-5-[4-(4-methylpiperazinyl)-phenyl]-2-thioxopyrido[2,3-*d*]pyrimi-din-4(1*H*)-one (**4c**) showed equipotent anti-inflammatory activity when compared to the reference standard diclofenac sodium.

The ulcer index of the test compounds (Table 2) reveals that the 2-amino-3-cyano-pyrido[2,3-*d*]pyrimidines **4a–c** and 6-amino-5-



Scheme 3. Reactions of 2-aminopyrido[2,3-*d*]pyrimidine-3-carbonitriles **4a–c** with some reagents.

Table 1
Percent analgesic activity of the synthesized compounds (tail-flick technique)

Compound	Dose (mg/kg)	Percent analgesic activity			
		30 min	1 h	2 h	3 h
4a	10	46 ± 1.39*	51 ± 1.73*	55 ± 1.26**	39 ± 1.25*
	20	63 ± 1.54***	64 ± 1.26***	69 ± 1.73***	47 ± 1.37*
4b	10	45 ± 1.69*	47 ± 1.32*	53 ± 1.15**	31 ± 1.92*
	20	59 ± 1.51***	63 ± 1.67***	66 ± 1.59***	43 ± 1.38*
4c	10	53 ± 1.79**	60 ± 1.73**	64 ± 1.32***	44 ± 1.36*
	20	67 ± 1.91***	68 ± 1.57***	72 ± 1.51***	52 ± 1.58*
5a	10	41 ± 1.71*	49 ± 1.24*	52 ± 1.64*	32 ± 1.66*
	20	55 ± 1.62**	57 ± 1.93**	59 ± 1.93**	38 ± 1.90*
5b	10	38 ± 1.57*	43 ± 1.90*	46 ± 1.73*	27 ± 1.73*
	20	55 ± 1.25**	57 ± 1.84**	58 ± 1.66**	36 ± 1.56*
5c	10	39 ± 1.71*	43 ± 1.72*	45 ± 1.56*	36 ± 1.96*
	20	50 ± 1.93*	58 ± 1.66**	58 ± 1.25*	43 ± 1.71*
6a	10	38 ± 172*	42 ± 1.28*	48 ± 1.71*	34 ± 1.23*
	20	51 ± 1.83*	53 ± 1.73**	56 ± 1.58**	39 ± 1.73*
6b	10	39 ± 1.23*	41 ± 1.28*	44 ± 1.90*	32 ± 1.44*
	20	49 ± 1.74*	53 ± 1.84*	56 ± 1.26**	44 ± 1.52*
6c	10	32 ± 1.72*	35 ± 1.23*	38 ± 1.23*	29 ± 1.41*
	20	42 ± 1.11*	46 ± 1.70*	49 ± 1.58*	38 ± 1.89*
7a	10	32 ± 1.62*	36 ± 1.81*	45 ± 1.26*	33 ± 1.32*
	20	40 ± 1.31*	50 ± 1.32*	55 ± 1.36**	39 ± 1.82*
7b	10	37 ± 1.09*	43 ± 1.83*	48 ± 1.39*	35 ± 1.32*
	20	48 ± 1.22*	56 ± 1.24*	56 ± 1.58**	42 ± 1.71*
7c	10	30 ± 1.69*	38 ± 1.74*	45 ± 1.18*	29 ± 1.71*
	20	44 ± 1.93*	47 ± 1.24*	53 ± 1.23*	36 ± 1.56*
8a	10	38 ± 1.39*	43 ± 1.53*	46 ± 1.26*	34 ± 1.29*
	20	43 ± 1.92*	49 ± 1.24**	52 ± 1.35*	41 ± 1.31*
8b	10	39 ± 1.71*	43 ± 1.82*	46 ± 1.71*	33 ± 1.71*
	20	48 ± 1.93*	51 ± 1.28*	53 ± 1.63**	44 ± 1.93*
8c	10	42 ± 1.76*	45 ± 1.62*	49 ± 1.57*	33 ± 1.63*
	20	48 ± 1.25*	49 ± 1.63*	55 ± 1.29**	46 ± 1.51*
Control		2 ± 0.35	6 ± 0.49	4 ± 0.59	4 ± 0.91
Diclofenac	10	37 ± 1.69*	43 ± 1.42*	45 ± 0.94*	33 ± 0.96*
	20	46 ± 0.95*	55 ± 1.16**	62 ± 1.49***	39 ± 1.13*

Each value represents the mean ± SEM ($n = 6$).
Significance levels $^{*}p < 0.5$, $^{**}p < 0.01$ and $^{***}p < 0.001$ as compared with the respective control.

Table 2
Percent anti-inflammatory activity of the synthesized compounds (Carrageenan-induced paw oedema test in rats)

Compound	Dose (mg/kg)	Percent protection				Ulcer index
		30 min	1 h	28 h	3 h	
4a	10	35 ± 1.96*	37 ± 1.36*	45 ± 1.54*	29 ± 1.26*	0.58 ± 1.39*
	20	45 ± 1.08*	49 ± 1.32**	51 ± 1.58**	36 ± 1.27*	
4b	10	41 ± 1.21*	48 ± 1.39*	50 ± 1.30**	36 ± 1.72*	0.54 ± 1.56*
	20	50 ± 1.52**	61 ± 1.54***	63 ± 1.52***	47 ± 1.96*	
4c	10	39 ± 1.26*	40 ± 1.54*	46 ± 1.63*	31 ± 1.63*	0.51 ± 1.47*
	20	48 ± 1.32**	55 ± 1.62***	60 ± 1.39***	37 ± 1.35*	
5a	10	33 ± 1.31*	39 ± 1.57*	40 ± 1.37*	32 ± 1.63*	0.58 ± 1.39*
	20	42 ± 1.29*	45 ± 1.53*	48 ± 1.71*	39 ± 1.23*	
5b	10	35 ± 1.28*	40 ± 1.18*	42 ± 1.39*	30 ± 1.71*	0.70 ± 1.37*
	20	43 ± 1.34*	47 ± 1.74*	49 ± 1.22**	38 ± 1.36*	
5c	10	35 ± 1.28*	37 ± 1.32*	38 ± 1.37*	31 ± 1.29*	0.69 ± 1.17*
	20	43 ± 1.34*	48 ± 1.18*	50 ± 1.56*	38 ± 1.37*	
6a	10	33 ± 1.28*	38 ± 1.57*	39 ± 1.73*	25 ± 1.91*	0.73 ± 1.34*
	20	37 ± 1.71*	40 ± 1.31*	46 ± 1.32*	33 ± 1.24*	
6b	10	25 ± 1.73*	28 ± 1.91*	31 ± 1.72*	21 ± 1.41*	0.89 ± 1.62*
	20	30 ± 1.26*	34 ± 1.57*	42 ± 1.74*	30 ± 1.30*	
6c	10	31 ± 1.27*	32 ± 1.18*	37 ± 1.31*	22 ± 1.33*	0.85 ± 1.32*
	20	39 ± 1.93*	40 ± 1.21*	46 ± 1.28*	31 ± 1.47*	
7a	10	30 ± 1.71*	34 ± 1.53*	38 ± 1.61	27 ± 1.18*	0.89 ± 1.41*
	20	35 ± 1.60*	41 ± 1.27*	44 ± 1.71*	32 ± 1.73*	
7b	10	29 ± 1.71*	33 ± 1.73*	34 ± 1.64*	26 ± 1.61*	0.90 ± 1.51*
	20	36 ± 1.83*	39 ± 1.72*	41 ± 1.25*	34 ± 1.74*	
7c	10	31 ± 1.29*	36 ± 1.57*	38 ± 1.22*	29 ± 1.51	0.86 ± 1.33*
	20	39 ± 1.33*	42 ± 1.26*	46 ± 1.36*	36 ± 1.30*	
8a	10	35 ± 1.27*	37 ± 1.42*	40 ± 1.97*	28 ± 1.71*	0.69 ± 1.27*
	20	41 ± 1.31*	47 ± 1.56*	51 ± 1.23*	39 ± 1.69*	
8b	10	33 ± 1.26*	39 ± 1.62*	43 ± 1.73*	29 ± 1.31*	0.72 ± 1.61*
	20	40 ± 1.83*	46 ± 1.51**	48 ± 1.62**	35 ± 1.70*	
8c	10	33 ± 1.54*	40 ± 1.72*	43 ± 1.11*	29 ± 1.25*	0.67 ± 1.23*
	20	39 ± 1.26*	46 ± 1.60*	49 ± 1.29**	38 ± 1.56*	
Control		5.1 ± 0.29	6.1 ± 0.27	5.7 ± 0.32	3.2 ± 0.93	0.15 ± 0.32**
Diclofenac	10	32 ± 0.63*	38 ± 1.58*	39 ± 1.97*	33 ± 0.93*	
	20	45 ± 1.63**	52 ± 0.92***	60 ± 1.52***	42 ± 1.36**	1.65 ± 0.59**
Aspirin	—	—	—	—	—	1.73 ± 0.41*

Each value represents the mean ±SEM ($n = 6$).
Significance levels $^{*}p < 0.5$, $^{**}p < 0.01$ and $^{***}p < 0.001$ as compared with the respective control.

[4-(1-piperidinyl)phenyl]-2-thioxopyrido[2,3-*d*:6,5-*d*] dipyrimidine (**5a**) showed negligible ulcer index, whereas compounds **5b,c**, **6a** and **8a–c** exhibited little increase in ulcer index and the compounds **6b,c** and **7a–c** exhibited higher ulcer index over other test compounds. When compared to the reference standard aspirin (ulcer index 1.73 ± 0.41) and diclofenac (ulcer index 1.6 ± 0.59) the test compounds exhibited about 35–50% of the ulcer index of reference standards. Compounds 5-[4-(4-methylpiperazinyl)-phenyl]-2-thioxopyrido[2,3-*d*]pyrimidine (**4c**) and 5-[4-(4-morpholinyl)-phenyl]-2-thioxopyrido-[2,3-*d*]pyrimidine (**4b**) exhibited least ulcer index (0.54 ± 1.56 and 0.51 ± 1.47, respectively)among the test compounds, which is about one-third of the ulcer index of reference standards aspirin and diclofenac. The compound 5-[4-(1-piperidinyl)phenyl]-2-thioxopyrido[2,3-*d*:6,5-*d*]dipyrimidine-4,6-dione (**7a**) showed the highest ulcer index (0.90 ± 1.51) among the test compounds which is about 50% of the ulcer index of reference standards aspirin and diclofenac.

In summary, a new series of pyrido[2,3-*d*]pyrimidine derivatives has been prepared an fully assigned by analytical and spectral data.[28] The results of the analgesic and anti-inflammatory activities of the present series showed that moderate enhancement of the activity. Compound **4c** exhibited 64% and 72% analgesic activity at 10 and 20 mg/kg dose level, respectively, at the reaction time of 2 h. The compound **4b** showed 50% and 65% anti-inflammatory activity at the dose 10 and 20 mg/kg, respectively, at the reaction time 2 h. Interestingly these compounds showed one-third of ulcer index of the reference aspirin and diclofenac. Hence this series could be developed as a novel class of analgesic and anti-inflammatory agents. However, further structural modification is planned to increase the analgesic and anti-inflammatory activities with the decreased ulcerogenic index.

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28. *General*: All melting points were measured using an Electrothermal IA 9100 apparatus (Shimadzu, Japan). The ^{1}H NMR and ^{13}C NMR spectra were recorded on *JEOL* ECA-500 and chemical shifts were expressed as δ values against $Si(CH_3)_4$ as internal standard (*p*-substituted phenyl are assigned as AA′BB′ system). IR spectra were recorded as KBr pellets on a Perkin–Elmer 1430 spectrometer, (National Research Center and Department of Chemistry Cairo University). Mass spectra were run at 70ev on HP-5988A Mass spectrometer, Micro-analytical Centre, Cairo University. The pharmacological data were analyzed in Pharmacological Unit National Research Centre, Egypt. The starting materials **1a**–**c** were prepared according to the reported procedure.[29]
Synthesis of 7-amino-6-cyano-5-sbstituted-2-thioxopyrido[2,3-d]pyrimidin-4(1H)-ones ***4a–c****; General procedure*: A mixture of equimolar of arylidenemalononitrile **1** and 6-aminothiouracil **2** (10 mmol) in dimethylformamide (50 mL) was boiled under reflux for 3–5 h (under *TLC* control). The reaction mixture was allowed to cool; the formed precipitate was filtered off, washed with ethanol and dried, and crystallized from appropriate solvent to produce **4a–c** in good yields.
7-Amino-6-cyano-5-[4-(1-piperidinyl)phenyl]-2-thioxopyrido[2,3-d]pyrimidin-4(1H)-one (**4a**): It was obtained from **1a**, as a yellow powder, crystallized from dioxane; in 78% yield, mp 287–289 °C, IR, ν_{max}/cm^{-1}: 3450 (br s, NH, NH_2), 3028 (CH aryl), 2218 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6) ppm: δ 1.56 (br s, 6H, piperidinyl 3 CH_2), 3.25 (br s, 4H, piperidinyl 2 NCH_2), 6.88 (d, 2H, Ar–H, J = 8.6 Hz), 7.10 (d, 2H, Ar–H, J = 8.6 Hz), 7.62 (br s, 2H, NH_2), 8.45 (br s, H, NH), 12.05 (br s, H, NH); ^{13}C NMR (DMSO-d_6) ppm: δ 23.86, 25.09, 25.81 (3 CH_2), 48.15, 48.67 (2 NCH_2), 107.68 (CN), 113.63, 114.83, 115.64, 117.12, 120.83, 121.92, 129.18, 151.4, 153.07, 167.30, 160.98 (11 signals for 11 sp^2 carbon), 172.7 (C=O), 183.05 (C=S); The MS, [M$^+$], m/z 378 (67%); $C_{19}H_{18}N_6OS$ (378.4); requires (Found): C, 60.29 (60.26); H, 4.79 (4.77); N, 22.23 (22.19).
7-Amino-6-cyano-5-[4-(4-morpholinyl)phenyl]-2-thioxopyrido[2,3-d]pyrimidin-4(1H)-one (**4b**): It was obtained from **1b**, as a yellow powder, crystallized from dioxane; in 81% yield, mp 303–305 °C, IR, ν_{max}/cm^{-1}: 3430 (br s, NH, NH_2), 3045 (CH aryl), 2216 (CN), 1684 (CO); ^{1}H NMR (DMSO-d_6) ppm: δ 3.25 (t, 4H, morpholinyl 2 NCH_2, J = 5.1 Hz), 3.84 (t, 4H, morpholinyl 2 OCH_2, J = 5.0 Hz), 6.92 (d, 2H, Ar–H, J = 8.8 Hz), 7.14 (d, 2H, Ar–H, J = 8.8 Hz), 7.80 (br s, 2H, NH_2), 8.39 (br s, H, NH), 12.00 (br s, H, NH); The MS, [M$^+$], m/z 380 (100%); $C_{18}H_{16}N_6O_2S$ (380.4); requires (Found): C, 56.83 (56.79); H, 4.24 (4.19); N, 22.09 (22.11).
7-Amino-6-cyano-5-[4-(4-methylpiperazinyl)phenyl]-2-thioxopyrido[2,3-d]pyrimi-din-4(1H)-one (**4c**): It was obtained from **1c**, as a yellow powder, crystallized from ethanol, in 76% yield, mp 273-275 °C, IR, ν_{max}/cm^{-1}: 3430 (br s, NH, NH_2), 3029 (CH aryl), 2215 (CN), 1682 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 2.31 (s, 3H, piperazinyl NCH_3), 2.57 (br s, 4H, piperazinyl 2 CH_3NCH_2), 3.34 (br s, 4H, piperazinyl 2 $ArNCH_2$), 7.06 (d, 2H, Ar- H, J = 8.7 Hz), 7.37 (d, 2H, Ar–H, J = 8.7 Hz), 7.88 (br s, 2H, NH_2), 8.75 (br s, H, NH), 11.80 (br s, H, NH); The MS, [M$^+$], m/z 393 (100%); $C_{19}H_{19}N_7OS$ (393.4); requires (Found): C, 57.99 (57.94); H, 4.86 (4.79); N, 24.92 (24.96).
Synthesis of 6-amino-5-substituted pyrido[2,3-d:6,5-d]dipyrimidin-4-one (**5a–c**); *General procedure*: A mixture of compound **4** (10 mmol), formamide (10 mL) and formic acid (2 mL) was stirred under reflux in DMF (50 mL) for 12 h. The reaction mixture was allowed to cool to room temperature, poured into water (100 mL) and neutralized with ammonia solution. The precipitate was collected by filtration washed with water and ethanol, dried and crystallized.
6-Amino-5-[4-(1-piperidinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4-one (**5a**): It was obtained from **4a**, as a pale yellow powder, crystallized from dioxane, in 67% yield, mp 311–313 °C, IR, ν_{max}/cm^{-1}: 3485 (br s, NH, NH_2), 3034 (CH aryl), 1680 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 1.58 (br s, 6H, piperidinyl 3 CH_2), 3.27 (br s, 4H, piperidinyl 2 NCH_2), 6.96 (d, 2H, Ar–H, J = 9.0 Hz), 7.14 (d, 2H, Ar–H, J = 9.0 Hz), 7.80 (br s, 2H, NH_2), 8.30 (s, 1H, pyrimidine-*H*), 8.68 (br s, H, NH), 11.70 (br s, H, NH); The MS, [M$^+$], m/z 405 (76%); $C_{20}H_{19}N_7OS$ (405.4); requires (Found): C, 59.24 (59.21); H, 4.72 (4.69); N, 24.18 (24.16).
6-Amino-5-[4-(4-morpholinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4-one (**5b**): It was obtained from **4b**, as a yellow powder, crystallized from dioxane, in 64% yield, mp 269–271 °C, IR, ν_{max}/cm^{-1}: 3500 (br s, NH, NH_2), 3039 (CH aryl), 1675 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 3.29 (t, 4H, morpholinyl 2 NCH_2, J = 5.0 Hz), 3.90 (t, 4H, morpholinyl 2 OCH_2, J = 5.0 Hz), 6.98 (d, 2H, Ar–H, J = 8.7 Hz), 7.18 (d, 2H, Ar–H, J = 8.7 Hz), 7.75 (br s, 2H, NH_2), 8.06 (s, 1H, pyrimidine-*H*), 8.65 (br s, H, NH), 12.30 (br s, H, NH); The MS, [M$^+$], m/z 407 (100%); $C_{19}H_{17}N_7O_2S$ (407.4); requires (Found): C, 56.01 (55.98); H, 4.21 (4.19); N, 24.06 (24.11).
6-Amino-5-[4-(4-methylpiperazinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4-one (**5c**): It was obtained from **4c**, as a pale yellow powder, crystallized from ethanol, in 70% yield, mp 261–263 °C, IR, ν_{max}/cm^{-1}: 3445 (br s, NH, NH_2), 3025 (CH aryl), 1685 (CO); ^{1}H NMR (DMSO-d_6) ppm: δ 2.29 (s, 3H, piperazinyl NCH_3), 2.59 (br s, 4H, piperazinyl 2 CH_3NCH_2), 3.36 (br s, 4H, piperazinyl 2 $ArNCH_2$), 7.12 (d, 2H, Ar–H, J = 8.5 Hz), 7.40 (d, 2H, Ar–H, J = 8.5 Hz), 8.00 (br s, 2H, NH_2), 8.32 (s, 1H, pyrimidine-*H*), 8.90 (br s, H, NH), 11.65 (br s, H, NH); The MS, [M$^+$], m/z 420 (100%); $C_{20}H_{20}N_8OS$ (420.5); requires (Found): C, 57.12 (57.09); H, 4.79 (4.81); N, 26.65 (26.59).
6-Imino-5-substituted-2-thioxopyrimido[4′,5′:2,3]pyrido[6,5-d][1,3]thiazin-13-one (**6a–c**); *General procedure*: A mixture of compound **4** (10 mmol) and carbon disulfide (excess 10 mL) was heated under reflux on a water-bath (80 °C) in 40 mL pyridine for 12 h (TLC control). The reaction mixture was allowed to cool to 0 °C for 12 h the precipitate was filtered off, washed with ethanol (40 mL), dried and crystallized from the proper solvent.
6-Imino-5-[4-(1-piperidinyl)phenyl]-2-thioxopyrimido[4′,5′:2,3]pyrido[6,5-d][1,3]-thiazin-13-one (**6a**): It was obtained from **4a**, as a dark brown substance and crystallized from DMF in 65% yield, mp 317–319 °C, IR, ν_{max}/cm^{-1}: 3500 (br s, NH's), 3036 (CH aryl), 1680 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 1.53 (br s, 6H, piperidinyl 3 CH_2), 3.24 (br s, 4H, piperidinyl 2 NCH_2), 7.02 (d, 2H, Ar–H, J = 8.7 Hz), 7.14 (d, 2H, Ar–H, J = 8.7 Hz), 8.39 (br s, H, NH), 8.85 (br s, H, NH), 9.50 (br s, H, NH), 11.20 (br s, H, NH); The MS, [M$^+$], m/z 452 (100%); $C_{20}H_{16}N_6OS_3$ (452.5); requires (Found): C, 53.07 (53.02); H, 3.56 (3.54); N, 18.57 (18.49).
6-Imino-5-[4-(4-morpholinyl)phenyl]-2-thioxopyrimido[4′,5′:2,3]pyrido[6,5-d][1,3]-thiazin-13-one (**6b**): It was obtained from **4b**, as a dark yellow powder and crystallized from DMF in 62% yield, mp 339–341 °C, IR, ν_{max}/cm^{-1}: 3480 (br s, NH's), 3039 (CH aryl), 1676 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 3.32 (t, 4H, morpholinyl 2 NCH_2, J = 4.9 Hz), 3.86 (t, 4H, morpholinyl 2 OCH_2, J = 4.9 Hz), 7.08 (d, 2H, Ar–H, J = 8.9 Hz), 7.22 (d, 2H, Ar–H, J = 8.9 Hz), 8.20 (br s, H, NH), 8.86 (br s, H, NH), 9.30 (br s, H, NH), 12.10 (br s, H, NH); The MS, [M$^+$], m/z 456 (53%); $C_{19}H_{16}N_6O_2S_3$ (456.5); requires (Found): C, 49.98 (49.89); H, 3.53 (3.50); N, 18.41 (18.37).
6-Imino-5-[4-(4-methylpiperazinyl)phenyl]-2-thioxopyrimido[4′,5′:2,3]pyrido-[6,5-d][1,3]thiazin-13-one (**6c**): It was obtained from **4c**, as a brown powder and crystallized from DMF in 60% yield, mp 291–293 °C, IR, ν_{max}/cm^{-1}: 3520 (br s, NH's), 3037 (CH aryl), 1678 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 2.29 (s, 3H, piperazinyl NCH_3), 2.57 (br s, 4H, piperazinyl 2 CH_3NCH_2), 3.38 (br s, 4H, piperazinyl 2 $ArNCH_2$), 7.18 (d, 2H, Ar–H, J = 8.6 Hz), 7.42 (d, 2H, Ar–H, J = 8.6 Hz), 8.45 (br s, H, NH), 8.90 (s, H, NH), 9.25 (br s, H, NH), 11.80 (br s, H, NH); The MS, [M$^+$], m/z 469 (58%); $C_{20}H_{19}N_7OS_3$ (469.5); requires (Found): C, 51.15 (51.09); H, 4.08 (4.05); N, 20.87 (20.79).
Synthesis of 5-substituted pyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7a**,**c**,**e**)*; General procedure*: A mixture of compound **4** (10 mmol), formic acid (10 mL) and a catalytic amount of concentrated hydrochloric acid was heated under reflux for 16 h. The reaction mixture was allowed to cool to room temperature, poured into cold water (100 mL). The formed solid was collected by filtration, washed by ethanol (20 mL), dried and crystallized.
5-[4-(1-Piperidinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7a**): It was obtained from **4a**, as a yellow powder, crystallized from DMF in 63% yield, mp 320–323 °C, IR, ν_{max}/cm^{-1}: 3450 (br s, NH's), 3029 (CH aryl), 1675, 1684 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 1.56 (br s, 6H, piperidinyl 3 CH_2), 3.31 (br s, 4H, piperidinyl 2 NCH_2), 6.94 (d, 2H, Ar–H, J = 8.8 Hz), 7.18 (d, 2H, Ar–H, J = 8.8 Hz), 8.24 (s, 1H, pyrimidine-*H*), 8.65 (br s, H, NH), 9.30 (br s, H, NH), 12.10 (br s, H, NH); The MS, [M$^+$], m/z 406 (100%); $C_{20}H_{18}N_6O_2S$ (406.4); requires (Found): C, 59.09 (59.11); H, 4.46 (4.41); N, 20.67 (20.64).
5-[4-(4-Morpholinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7c**): It was obtained from **4b**, as a yellow powder, crystallized from DMF in 57% yield, mp 271–273 °C, IR, ν_{max}/cm^{-1}: 3480 (br s, NH), 3029 (CH aryl), 1678, 1688 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 3.27 (t, 4H, morpholinyl 2 NCH_2, J = 4.9 Hz), 3.89 (t, 4H, morpholinyl 2 OCH_2, J = 4.9 Hz), 7.03 (d, 2H, Ar–H, J = 8.4 Hz), 7.31 (d, 2H, Ar–H, J = 8.4 Hz), 8.16 (s, 1H, pyrimidine-*H*), 8.55 (br s, H, NH), 9.00 (br s, H, NH), 12.25 (br s, H, NH); The MS, [M$^+$], m/z 408 (49%); $C_{19}H_{16}N_6O_3S$ (408.4); requires (Found): C, 55.87 (55.85); H, 3.95 (3.98); N, 20.58 (20.61).
5-[4-(4-Methylpiperazinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7e**): It was obtained from **4c**, as a yellow powder, crystallized from dioxane in 59% yield, mp 263–265 °C, IR, ν_{max}/cm^{-1}: 3465 (br s, NH), 3036 (CH aryl), 1673, 1682 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 2.32 (s, 3H, piperazinyl NCH_3), 2.63 (br, s, 4H, piperazinyl 2 CH_3NCH_2), 3.38 (br s, 4H, piperazinyl 2

ArNCH_2), 7.15 (d, 2H, Ar–H, J = 8.6 Hz), 7.38 (d, 2H, Ar–H, J = 8.6 Hz), 8.28 (s, 1H, pyrimidine-*H*), 8.85 (br s, H, NH), 9.35 (br s, H, NH), 12.15 (br s, H, NH); The MS, [M$^+$], *m/z* 421(64%); $C_{20}H_{19}N_7O_2S$ (421.4); requires (Found): C, 56.99 (56.95); H, 4.54 (4.49); N, 23.26 (23.28).

Synthesis of 8-methyl-5-substituted pyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7b**,**d**,**f**); *General procedure*. A mixture of compound **4** (10 mmol) and acetic acid (80 mL) was heated under reflux for 28 h. The reaction mixture was allowed to cool to room temperature and poured into cold water (100 mL). The formed solid was collected by filtration, washed with ethanol (20 mL), dried and crystallized.

8-Methyl-5-[4-(1-piperidinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7b**): It was obtained from **4a**, as a yellow powder, crystallized from dioxane in 62% yield, mp 289–291 °C, IR, ν_{max}/cm^{-1}: 3475 (br s, NH), 3026 (CH aryl), 1668, 1683 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 1.60 (br s, 6H, piperidinyl 3 *CH*$_2$), 2.26 (s, 3H, pyrimidine-*CH*$_3$), 3.32 (br s, 4H, piperidinyl 2 NCH_2), 7.10 (d, 2H, Ar–H, J = 8.6 Hz), 7.25 (d, 2H, Ar–H, J = 8.6 Hz), 8.50 (br s, H, NH), 9.70 (br s, H, NH), 11.80 (br s, H, NH); The MS, [M$^+$], *m/z* 420 (100%); $C_{21}H_{20}N_6O_2S$ (420.4); requires (Found): C, 59.98 (59.96); H, 4.79 (4.73); N, 19.99 (19.94).

8-Methyl-5-[4-(4-morpholinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7d**): It was obtained from **4b**, as a yellow powder, crystallized from dioxane, mp 253–255 °C, IR, ν_{max}/cm^{-1}: 3450 (br s, NH), 3029 (CH aryl), 1670, 1686 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 2.27 (s, 3H, pyrimidine-*CH*$_3$), 3.30 (t, 4H, morpholinyl 2 NCH_2, J = 5.1 Hz), 3.93 (t, 4H, morpholinyl 2 OCH_2, J = 5.1 Hz), 7.08 (d, 2H, Ar–H, J = 8.7 Hz), 7.36 (d, 2H, Ar–H, J = 8.7 Hz), 8.80 (br s, H, NH), 9.150 (br s, H, NH), 12.20 (br s, H, NH); The MS, [M$^+$], *m/z* 410 (39%); $C_{19}H_{18}N_6O_3S$ (410.4); requires (Found): C, 55.59 (55.46); H, 4.42 (4.39); N, 20.48 (20.45).

8-Methyl-5-[4-(4-methylpiperazinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,6-dione (**7f**): It was obtained from **4c**, as a yellow powder, crystallized from dioxane, mp 259–261 °C, IR, ν_{max}/cm^{-1}: 3445 (br s, NH), 3027 (CH aryl), 1672, 1683 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 2.29 (s, 3H, pyrimidine-*CH*$_3$), 2.34 (s, 3H, piperazinyl NCH_3), 2.61 (br s, 4H, piperazinyl 2 CH$_3$NCH_2), 3.40 (br s, 4H, piperazinyl 2 ArNCH_2), 7.09 (d, 2H, Ar–H, J = 8.8 Hz), 7.39 (d, 2H, Ar–H, J = 8.8 Hz), 8.68 (br s, H, NH), 9.23 (br s, H, NH), 12.00 (br s, H, NH); The MS, [M$^+$], *m/z* 435 (43%); $C_{21}H_{21}N_7O_2S$ (435.4); requires (Found): C, 57.91 (57.86); H, 4.86 (4.79); N, 22.51 (22.49).

Synthesis of 6-amino-5-substituted-2,8-dithiopyrido[2,3-d:6,5-d]dipyrimidin-4-one (***8a***,***c***,***e***) *and 6-amino-5-substituted-2-thiopyrido[2,3-d:6,5-d]dipyrimidine-4,8-dione* (***8b***,***d***,***f***); *General procedure*: A mixture of compound **4** (0.01 mol) and thiourea or urea (10 mmol) was heated at 180 °C in a test tube on a sand-bath for 6 h. The mixture was allowed to cool to room temperature; the product was solidified by cooling and addition of methanol (50 mL). The precipitate was collected by filtration and crystallized from the proper solvent.

6-Amino-5-[4-(1-piperidinyl)phenyl]-2,8-dithioxopyrido[2,3-d:6,5-d]dipyrimidin-4-one (**8a**): It was obtained from **4a** and thiourea, as a yellow powder and crystallized from DMF, in 63% yield, mp 290–293 °C, IR, ν_{max}/cm^{-1}: 3490 (br s, NH, NH$_2$), 3031 (CH aryl), 1679 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 1.56 (br s, 6H, piperidinyl 3 *CH*$_2$), 3.29 (br s, 4H, piperidinyl 2 NCH_2), 7.11 (d, 2H, Ar–H, J = 8.7 Hz), 7.38 (d, 2H, Ar–H, J = 8.7 Hz), 8.05 (br s, 2H, NH$_2$), 8.55 (br s, H, NH), 8.95 (br s, H, NH), 11.05 (br s, H, NH); The MS, [M$^+$], *m/z* 437 (47%); $C_{20}H_{19}N_7OS_2$ (437.5); requires (Found): C, 54.90 (54.86); H, 4.37 (4.39); N, 22.41 (22.36).

6-Amino-5-[4-(1-piperidinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,8-dione (**8b**): It was obtained from **4a** and urea, as a brown powder and crystallized from DMF, in 65% yield, mp 268–270 °C, IR, ν_{max}/cm^{-1}: 3500 (br s, NH, NH$_2$), 3038 (CH aryl), 1684, 1668 (2C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 1.60 (br s, 6H, piperidinyl 3 CH$_2$), 3.32 (br s, 4H, piperidinyl 2 NCH_2), 7.08 (d, 2H, Ar–H, J = 8.6 Hz), 7.36 (d, 2H, Ar–H, J = 8.6 Hz), 8.15 (br s, 2H, NH$_2$), 8.85 (br s, H, NH), 9.45 (br s, H, NH), 11.75 (br s, H, NH); The MS, [M$^+$], *m/z* 421 (100%); $C_{20}H_{19}N_7O_2S$ (421.4); requires (Found): C, 56.99 (56.95); H, 4.54 (4.52); N, 23.26 (23.29).

6-Amino-5-[4-(4-morpholinyl)phenyl]-2,8-dithioxopyrido[2,3-d:6,5-d]dipyrimidin-4-one (**8c**): It was obtained from **4b** and thiourea, as a yellow powder and crystallized from DMF, in 60% yield, mp 297-300 °C, IR, ν_{max}/cm^{-1}: 3470 (br s, NH, NH$_2$), 3029 (CH aryl), 1680 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 3.28 (t, 4H, morpholinyl 2 NCH_2, J = 5.2 Hz), 3.94 (t, 4H, morpholinyl 2 OCH$_2$, J = 5.1 Hz), 7.08 (d, 2H, Ar–H, J = 8.9 Hz), 7.43 (d, 2H, Ar–H, J = 8.9 Hz), 8.25 (br s, 2H, NH$_2$), 8.86 (br s, H, NH), 9.34 (br s, H, NH), 11.70 (br s, H, NH); The MS, [M$^+$], *m/z* 439 (61%); $C_{19}H_{17}N_7O_2S_2$ (439.5); requires (Found): C, 51.92 (51.87); H, 3.89 (3.91); N, 22.30 (22.26).

6-Amino-5-[4-(4-morpholinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,8-dione (**8d**): It was obtained from **4b** and urea, a yellow powder and crystallized from DMF, in 58% yield, mp 281–283 °C, IR, ν_{max}/cm^{-1}: 3510 (br s, NH, NH$_2$), 3028 (CH aryl), 1686, 1675 (2 C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 3.30 (t, 4H, morpholinyl 2 NCH_2, J = 5.1 Hz), 3.96 (t, 4H, morpholinyl 2 OCH_2, J = 5.1 Hz), 7.07 (d, 2H, Ar–H, J = 8.8 Hz), 7.40 (d, 2H, Ar–H, J = 8.8 Hz), 8.32 (br s, 2H, NH$_2$), 8.95 (br s, H, NH), 9.65 (br s, H, NH), 11.85 (br s, H, NH); The MS, [M$^+$], *m/z* 423 (100%); $C_{19}H_{17}N_7O_3S$ (423.4); requires (Found): C, 53.89 (53.91); H, 4.04 (4.02); N, 23.15 (23.09).

6-Amino-5-[4-(4-methylpiperazinyl)phenyl]-2,8-dithioxopyrido[2,3-d:6,5-d]dipyrimi-din-4-one (**8e**): It was obtained from **4c** and thiourea, as a yellow powder and crystallized from DMF, in 64% yield, mp 307–309 °C, IR, ν_{max}/cm^{-1}: 3480 (br s, NH, NH$_2$), 3025 (CH aryl), 1683 (CO). ^{1}H NMR (DMSO-d_6) ppm: δ 2.23 (s, 3H, piperazinyl NCH$_3$), 2.57 (br s, 4H, piperazinyl 2 CH$_3$NCH_2), 3.35 (br s, 4H, piperazinyl 2 ArNCH_2), 7.10 (d, 2H, Ar–H, J = 8.6 Hz), 7.36 (d, 2H, Ar–H, J = 8.6 Hz), 8.19 (br s, 2H, NH$_2$), 8.62 (br s, H, NH), 9.15 (br s, H, NH), 11.45 (br s, H, NH); The MS, [M$^+$], *m/z* 452 (75%); $C_{20}H_{20}N_8OS_2$ (452.5); requires (Found): C, 53.07 (53.11); H, 4.45 (4.42); N, 24.76 (24.71).

6-Amino-5-[4-(4-methylpiperazinyl)phenyl]-2-thioxopyrido[2,3-d:6,5-d]dipyrimidine-4,8-dione (**8f**): It was obtained from **4c** and urea, a yellow powder and crystallized from DMF, in 71% yield, mp 327–329 °C, IR, ν_{max}/cm^{-1}: 3460 (br s, NH, NH$_2$), 3019 (CH aryl), 1685, 1678 (2C=O). ^{1}H NMR (DMSO-d_6) ppm: δ 2.26 (s, 3H, piperazinyl NCH$_3$), 2.58 (br s, 4H, piperazinyl 2 CH$_3$NCH_2), 3.39 (br s, 4H, piperazinyl 2 ArNCH_2), 7.07 (d, 2H, Ar–H, J = 9.0 Hz), 7.33 (d, 2H, Ar–H, J = 9.0 Hz), 8.23 (br s, 2H, NH$_2$), 8.70 (br s, H, NH), 9.37 (br s, H, NH), 11.82 (br s, H, NH); The MS, [M$^+$], *m/z* 436 (100%); $C_{20}H_{20}N_8O_2S$ (436.4); requires (Found): C, 55.03 (55.05); H, 4.61 (4.65); N, 25.67 (25.63).

Pharmacology: The synthesized compounds were evaluated for analgesic, ulcergenic index and anti-inflammatory activities. One-way analysis of variance (ANOVA) was performed to certain the significance of all the exhibited activities. The test compounds and the standard drugs were administered in the form of a suspension (1% carboxy methyl cellulose as a vehicle) by oral route of administration for analgesic and anti-inflammatory but for ulcerogenicity studies by intraperitoneally as suspension in 10% v/v Tween-80. Each group consisted of six animals. The animals were procured from Animal Home (National Research Center Egypt), and were maintained in colony cages at 25 ± 2 °C, relative humidity of 45–55%, under a 12-h light and dark cycle; were fed standard animal feed.[30] All the animals were acclimatized for a week before use. The institutional Animal Ethics Committee approved the protocol adopted for the experimentation of animals.

Analgesic assay: The analgesic activity was performed by tail-flick technique using Wister albino mice (25–35 g) pf either sex selected by random sampling technique.[31,32] Diclofenac sodium at a dose level of 10 and 20 mg/kg was administered orally as reference drug for comparison. The test compounds at two dose levels (10, 20 mg/kg) were administered orally. The reaction times were recorded at 30 min, 1, 2 and 3 h after the treatment. And cut-off time was 10 s. The percent analgesic activity (P) was calculated by the following formula. $P = [T_2 - T_1/10 - T_1] \times 100$; where T_1 is the reaction time (s) before treatment, and T_2 is the reaction time (s) after treatment.

Anti-inflammatory activity: Anti-inflammatory activity was evaluated by carrageenan-induced paw oedema test in rats.[27] Diclofenac sodium 10, 20 mg/kg was administered as standard drug for comparison. The test compounds were administered at two dose levels (10, 20 mg/kg). The paw volumes were measured using the mercury displacement technique with the help of plethysmograph (Model PLYAN; Buxco, USA) immediately before and 30 min, 1, 2 and 3 h after carrageenan injection. The percent inhibition of paw oedema was calculated according to the following formula, (percent inhibition I = 100[1 − (a − x)/(b − y)] where x is the mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group), a is the mean paw volume of rats after the administration of carrageenan in the test group (drug treated), b is the mean paw volume of rats after the administration of carrageenan in the control group, y is the mean paw volume of rats before the administration of carrageenan in the control group. *Ulcerogenicity*: Ulceration in rats was induced as described by Goyal et al. Albino rats of wistar strain weighing 150–200 g of either sex were divided into various groups each of six animals.[33] Control group of animals were administered only with 10% v/v Tween-80 suspension intraperitoneally. One group was administered with Aspirin intraperitoneally in a dose of 200 mg/kg once daily for three days. The remaining group of animals was administered with test compounds intraperitoneally in a dose of 20 mg/kg. On fourth day, Pylorus was ligated as per the method of Shay et al..[34] 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 with the greater curvature. Ulcer index was determined by the method of Ganguly and Bhatnagar.[35]

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