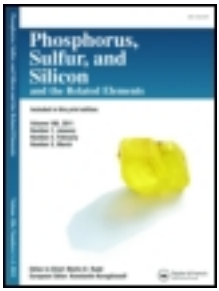

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Synthesis and Anti-HIV Activity of New 6-Thioarylpyrimidines and Related Compounds

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*A series of new 5-nitro- and 5-amino-6-arylsulfanyl-1-propyl-1*H*-pyrimidin-2,4-diones **(4–9)** were synthesized with the aim to develop new non-nucleoside reverse transcriptase inhibitors (NNRTIs). Similarly, 6-arylsulfanyl-1,3-dimethyl-5-nitro-1*H*-pyrimidin-2,4-diones **(12–15)** were prepared from **10**. A new 2-amino-2-phenyl-7-phenylsulfanyl-imidazo[1,2-a]pyrimidin-5-one **(18)** has been synthesized from reaction of **17** with α-bromoacetophenone in the presence of NaH. The newly synthesized compounds were evaluated for their anti HIV-1 and HIV-2 activity in MT-4 cells.*

Keywords 6-arylsulphanyl-pyrimidones; anti-HIV activity; imidazo[1,2-*a*]pyrimidin-5-one; non-nucleoside reverse transcriptase inhibitors (NNRTIs)

INTRODUCTION

To the chemotherapist, the revelation of a new chemical class with potent activity against the HIV-1 reverse transcriptase, the key enzyme in the HIV replication, and the target for developing anti-HIV drugs, is always exciting; meanwhile, the attempts are continuing to discover drugs that can interfere with a stage in the viral replicative cycle without damaging the normal processes of the host cell.

Two types of reverse transcriptase inhibitors have been developed,[1–3] nucleoside reverse transcriptase inhibitors (NRTIs)

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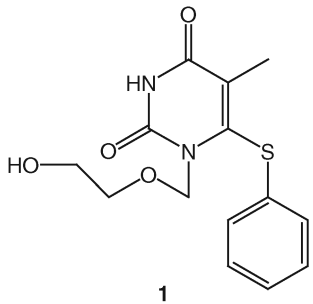
and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Three NNRTIs, nevirapine,[4] delaviridine,[5,6] and efavirenz[7] have been approved by the FDA for the treatment of HIV infection. However, significant resistance has been developed against the current NNRTIs and therefore there is an urgent need to develop new anti-HIV agents that are effective against these resistant mutants.[8,9] Several potent 6-alkylsulfanyl or sulphonyl-5-nitrouracil family attracts significant attention due to their chemotherapeutic importance against HIV. Benhida et al.[10] have reported the synthesis of various derivatives of 1-ethoxymethyl-6-alkylsulphanyl and 6-arylsulphonyl-1*H*-pyrimidine-2,4-diones and the 5-nitro analogues with potent anti-HIV-1 activities in CEM/SS cells. On the other hand, Yousif and Yamamoto[11] have prepared similar 6-alkyl or arylsulfanyl analogues with different substituentes at N-1. However, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (**1**) (HEPT) has been synthesized by Miyasaka et al.[12] and Al-Soud and Al-Masoudi[13] with high anti-HIV inhibitory activity as an interesting example in this series. In our recent work, we reported new 5-nitro-1-propyl- or 1,3-dimethyl-5-nitro-1*H*-pyrimidin-2,4-diones having 6-arylsulfanyl groups and their amino analogues as HIV-1 and HIV-2 replication inhibitors.



1

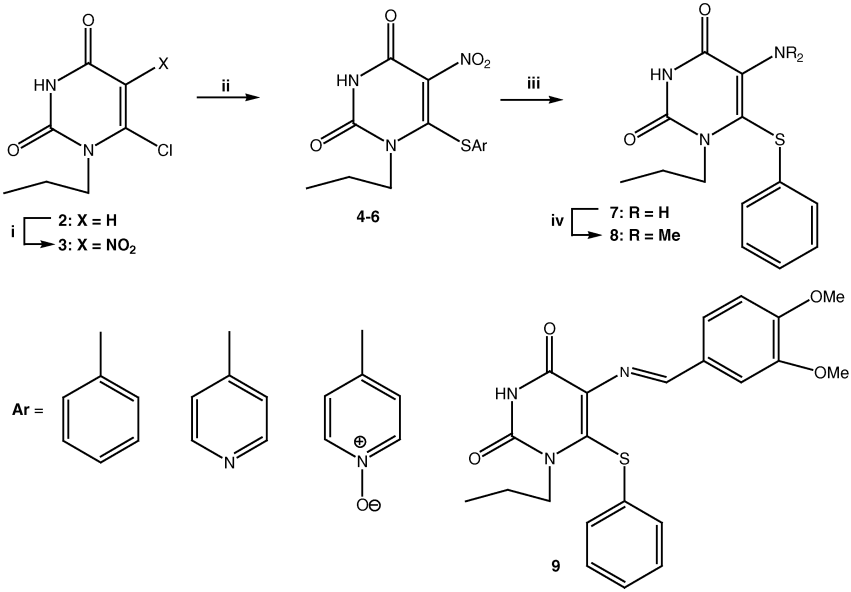
RESULTS AND DISCUSSION

Chemistry

Various 5-alkyl- and 5-arylsulfanyl derivatives of 4-nitroimidazole derivatives as well as the 5-substituted-piperazine analogues have been prepared recently in our laboratory[14–19] via nucleophilic displacements of the bromine group activated by an adjacent nitro group. Several alternative potential heterocylic bases, other than imidazole derivatives, such as pyrimidine bases substituted by various potential groups[20–28] were prepared from their chloro analogue[20] via nucleophilic

displacements. Analogously, our efforts are focused on the preparation of new pyrimidines carrying arylsulfanyl groups, which might lead to biological active candidates. 6-Chloro-5-nitro-1-propyl-1*H*-pyrimidin-2,4-dione (**3**), prepared from nitration of **2**,[11] has been selected for the synthesis of our targets by treatment with different arylsulfanyl nucleophiles, such as sodium phenylthiolate, 4-pyridinethiol and 4-(*N*-oxidepyridine)thiol in the presence potassium carbonate in hot DMF or ethanol to give, after purification, **4–6** in 69, 55, and 51% yield, respectively. Reduction of **4** with H_2/Pd-C in methanol for 5 h afforded, after purification, **7** (79%).

Treatment of **7** with formaldehyde in acetonitrile followed by reduction of the inseparable product with sodium cyanoborohydride ($NaBH_3CN$) under reflux for 3 h afforded, after chromatographic purification, **8** (74%). On the other hand, refluxing of **7** with 3,4-dimethoxyphenylaldehyde in ethanol gave **9** (77%) (Scheme 1).

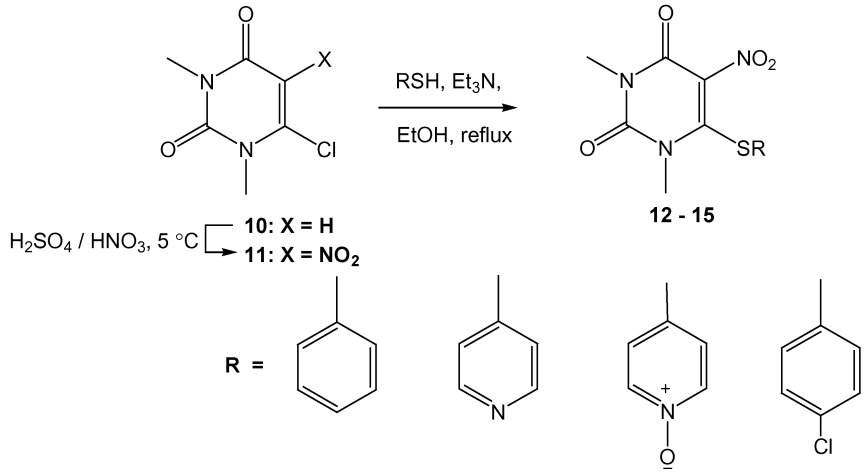


SCHEME 1 *Reagents and conditions:* (i) HNO_3/H_2SO_4, 5°C; (ii) ArSNa or ArSH, DMF (120°C) or EtOH (reflux); (iii) H_2/Pd-C, MeOH, 5 h; (iv) HCOH (10 equiv.), $NaBH_3CN$ (3 equiv.), MeCN, reflux, 3 h.

The structures of the newly synthesized compounds **4–9** were assigned by the ^1H, ^{13}C NMR and mass spectra. The ^1H NMR spectra of **4–9** showed rather similar patterns for the N-1 propyl protons. Thus, the multiplets in the region δ 3.67–3.38 ppm and δ 1.49–1.42 ppm were

attributed to the methylene protons of C-1′ and C-2′, respectively; meanwhile the triplets resonated in the region δ 0.83–0.81 ppm ($J \sim 7.0$ Hz) were attributed to CH_3 of N-1-propyl group. The resonances of the aryl moiety of **4, 7–9** appeared as multiplets in the region δ 7.63–7.22 ppm, meanwhile the same moiety of **4** and **5** were appeared as doublets in the region δ 8.76–7.30 ppm (J =7.6 Hz). In the ^{13}C NMR spectra of **4–9**, C-2 and C-4 of the pyrimidine ring resonated at the region δ 166.8-157.0 ppm, and δ 151.1–148.1 ppm, respectively. C-6 of **4-6** resonated at δ 159.1, 156.9, and 158.2 ppm, respectively, while it appeared at δ 127.2 and 125.8 ppm, respectively, for **7** and **8**. C-5 bearing nitro group of **4–8** resonated at δ 116.0–106.9 ppm, while appeared at δ 90.8 ppm for **9**.

Next, other models of 6-arylsulfanyl pyrimidine derivatives bearing N-1 and N-3 substituted methyl groups were prepared. Thus, treatment of **11**,[29,30] prepared from nitration of **10**, with sodium phenylthiolate, 4-pyridinethiol, 4-(*N*-oxidepyridine)thiol, and 4-chlorophenylthiolate in the presence of triethylamine in hot ethanol gave, after purification, **12–15** in 69, 52, 61, and 53% yield, respectively (Scheme 2).

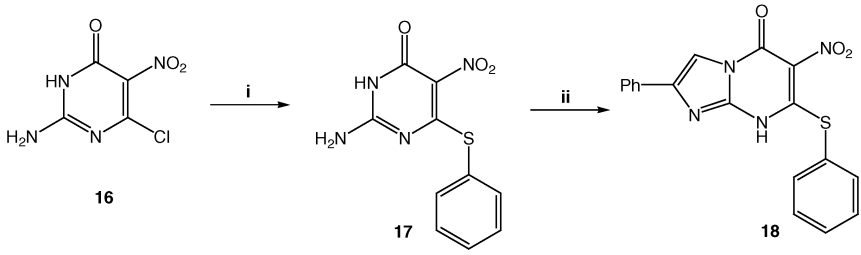


SCHEME 2

The assignment of protons and carbons of the pyrimidine ring, and the substituents were deduced in comparison to compounds **4–6** and the previously reported data on 6-arylsulfanyl pyrimidines.[11,12]

In the ^{1}HNMR spectra of **12–15**, the N-1 and N-3 methyl groups were resonated at the region δ 3.11–3.00 ppm. The ^{13}C NMR spectra of **12–15** were almost similar to those of the analogues **4–6**.

Gross et al.[31] have described the identification of pyrrolopyrimidones, 2-arylimidazol[1,2-*a*]-pyrimidone series and imidazolo [1,2-*a*]-pyrimid-5-ones as potent GnRH receptor antagonists by reaction of 2-amino-pyrimidone derivatives with α-bromoacetophenone. We has selected 2-amino-6-chloro-5-nitro-pyrimid-4-one (**16**) as a key intermediate in synthesis of new 5-nitro-6-phenylsulfanyl-imidazo[1,2-*a*]-pyrimid-4-one (**18**) in attempt to evaluate its anti-HIV activity. Thus, treatment **16** with PhSNa in DMF at 120°C, afforded **17** (65%). Compound **17** was converted into 2-amino-2-phenyl-7-phenylsulfanyl-imidazo[1,2-*a*]pyrimidin-5-one (**18**) (51%) by treatment with α-brmoacetophenone in the presence of NaH in DMF (Scheme 3).



SCHEME 3 *Reagents and conditions.* (i) PhSNa, DMF, 120°C, 3 h; (ii) α-bromoacetophenone, DMF, NaH, 23°C, 5 h, followed by addition of NH_4OH at 23°C.

The structures of **17** and **18** were confirmed by the ^{1}H-, ^{13}C NMR, and mass spectra. In the ^{13}C NMR spectrum of **18**, C-5 and C-7 appeared at the higher field δ 188.2 ppm and δ 173.2 ppm, respectively, in comparison to the same atoms of the adduct **17** (C-4: δ 163.6 ppm and C-6: 142.8 ppm). The bridge carbon atom C-9 of **18** resonated at the lower field (δ 124.3 ppm) compared to C-2 of the adduct **17** (δ 150.2 ppm). The structure of **18** was further confirmed by the homo- and heteronuclear NMR study. The gradient selected HMBC[32] spectrum allowed $^2J_{C,H}$ coupling the assignment of C-2 at δ_C 139.8 ppm by correlation with H-3 at δ_H 7.15 ppm, while it showed $^3J_{C,H}$ between H-3 and C-5 and C-9 at δ_C 188.2 ppm and δ_C 144.6 ppm, respectively. Its mass spectra exhibited the correct molecular ion $[M+H]^+$ (426).

In-vitro Anti-HIV Assay

Various compounds have been reported to inhibit the replication of human immunodeficiency virus type 1 (HIV-1) in vitro.[33] Among these, compound is HEPT 1, a potent and selective inhibitor of HIV-1 in

TABLE I In Vitro Anti-HIV-1[a] and HIV-2[b] of Some New 6-Arylthiopyrimidines

Compound	Virus strain	EC_{50}(μg/mL)[c]	CC_{50}(μg/mL)[d]	SI[e]
3	III_B	>62.40	≥ 62.40	≤ 1
	ROD	>62.40	≥ 62.40	≤ 1
4	III_B	>72.90	>72.90	≤ 1
	ROD	>72.90	>72.90	≤ 1
5	III_B	>76.63	76.63	<1
	ROD	>76.63	76.63	<1
6	III_B	>0.313	0.313	<1
	ROD	>0.313	0.313	<1
7	III_B	>44.30	≥ 44.30	<1
	ROD	>44.30	≥ 44.30	<1
12	III_B	>81.20	≥ 81.20	≤ 1
	ROD	>81.20	≥ 81.20	≤ 1
13	III_B	>11.60	11.60 ± 1.07	<1
	ROD	2.54	11.60 ± 1.07	5
14	III_B	>0.275	0.275 ± 0.233	<1
	ROD	>0.275	0.275 ± 0.233	<1
17	III_B	>88.07	88.07 ± 39.77	<1
	ROD	>88.07	88.07 ± 39.77	<1
18	III_B ROD	>2.56 >2.56	2.56 2.56	<1
Efavirenz	III_B	0.003	40	13333
Capravirine	III_B	0.0014	11	7857

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.
[c]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect.
[d]Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e]SI: Selectivity index (CC_{50}/EC_{50}).

various T4 cells cultures, including peripheral blood lymphocyte (PBL) cells.[34]

In this study, we explored new analogues resemble in their structure to HEPT. The new synthesized analogues **3–7**,**12–14, 17,** and **18** were evaluated for their in vitro anti-HIV-1 activity by using the IIIB strain for HIV-1 and the ROD strain for the HIV-2, and monitored by the inhibition of the virus-induced cytopathic effect in the human T-lymphocyte (MT-4) cells. The results are summarized in Table I, in which the data for efavirenz[7] and capravirine[35] were included for comparison purposes. Compound **6**, **13** and **14** were found to be the only compounds from the series inhibiting HIV-1 replication in cell culture. Compounds **6** and **14** showed anti-HIV-1 and HIV-2 with $EC_{50} > 0.313$ μg/mL and >0.275 μg/mL, respectively, but with no selectivity can be witnessed (SI < 1).

Compound **13** showed higher value of EC_{50} against HIV-2 (2.54μg/ml), with $CC_{50} = 11.60$ μg/ml, resulting with selectivity value (SI) of 5.

CONCLUSIONS

Compound **6** and **14** are equipotent against HIV-1 and HIV-2 replication in vitro, and therefore, it is not likely an NNRTI, meanwhile compound **13** showed some selectivity (SI = 5) against HIV-2 ($EC_{50} =$ 2.54 μg/mL), confirming the typical first generation NNRTI mode of action of this compound. The structure-activity relationships (SARs) of 6-arylparimidine derivatives have suggested the importance of thioaryl group on the pyrimidine ring, especially the pyridine-*N*-oxide residue, for potent inhibitory activity against RT, then lead to the discovery of more potent and selective analogues that will allow the elucidation of their molecular mode of action.

EXPERIMENTAL

General Procedure

Melting points were measured on a Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland) and are uncorrected. Microanalytical data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (^{1}H) and at 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Heteronuclear assignments were verified by ^{1}H-^{13}C HMBC experiment. Mass spectra were recorded on 70 eV EI and FAB MAT 8200 spectrometers (Finnigan MAT, USA), using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrix. Some molecular ions were detected by doping the sample with Na^+ ion.

6-Chloro-5-nitro-1-propyl-1H-pyrimidin-2,4-dione (3)[11]

6-Chloro-1-propyluracil (**2**) (1.0 g, 5.29 mmol) was added in a portion to a stirred concentration of H_2SO_4 (3.0 mL), kept below 15°C by cooling in ice. Fuming HNO_3 (3.0 mL) was added slowly—being maintained at 0–5°C, and the solution was then poured onto ice (40 g) with stirring. The product was at once extracted with chloroform (2 × 30 mL) and the combined extract was dried (Na_2SO_4), filtered and quickly evaporated to give **3** (78%) as a yellow solid; m.p. 90–92°C. ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H, NH); 3.59 (m, 2H, CH_2-1′); 1.45 (m, 2H, CH_2-2′); 0.80 (t, 3H, $J = 7.5$ Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 157.6 (C-4); 150.6 (C-2); 150.1 (C-6); 123.9 (C-5), 42.0 (C-1′); 21.0 (C-2′); 11.1 (C-3′). Anal. calcd.

for $C_7H_8ClN_3O_4$ (233.61): C, 35.99; H, 3.45; N, 17.99. Found: C, 35.78; H, 3.32; N, 17.79.

5-Nitro-6-arylsulfanyl-1-propyl-1*H*-pyrimidin-2,4-diones (4–9, 11)—General Procedure

A solution of **3** (4.28 mmol) in DMF (20 mL) or ethanol (20 mL) and arylmercaptan (6.42 mmol) was heated at 120°C (DMF) or under reflux (ethanol) for 8–10 h. After cooling, the solution was evaporated to dryness and the residue was recrystallized from ethanol or ethanol/methanol to give the desired product.

5-Nitro-6-phenylsulfanyl-1-propyl-1H-pyrimidin-2,4-dione (4)

From sodium phenylthiolate (0.85 g). Yield: 1.36 g (69%), m.p. 109–111°C. ^{1}H NMR (DMSO-d_6): δ 7.59 (m, 2H, Ar-H); 7.31 (m, 3H, Ar-H); 3.61 (m, 2H, CH_2-1'); 1.45 (m, 2H, CH_2-2'); 0.81 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 162.1 (C-4); 159.1 (C-6); 148.1 (C-2); 129.5, 128.6, 128.4, 126.1 (Ar—C); 113.8 (C-5), 50.8 (C-1'); 21.8 (C-2'); 11.8 (C-3'). Anal. Calcd. for $C_{13}H_{13}N_3O_4S$ (307.33): C, 50.81; H, 4.26; N, 13.67. Found: C, 50.60; H, 4.13; N, 4.02. MS: m/z (FAB) 308 $(M+H)^+$.

5-Nitro-1-propyl-6-(pyridin-4-ylsylfanyl)-1H-pyrimidin-2,4-dione (5)

From 4-pyridinethiol (0.72 g). Yield: 55%, m.p. 311–312°C. ^{1}H NMR (DMSO-d_6): δ 9.89 (s, 1H, NH); 8.76 (d, 2H, J = 7.6 Hz, Ar-H); 7.55 (d, 2H, J = 7.6 Hz, Ar—H); 3.45 (m, 2H, CH_2-1′); 1.49 (m, 2H, CH_2-2′); 0.83 (t, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 163.2 (C-4); 156.9 (C-6); 150.3 (C-2); 129.5, 128.6, 128.4, 126.1 (Ar-C); 116.0 (C-5), 45.2 (C-1′); 21.1 (C-2′); 11.1 (C-3′). Anal. calcd. for $C_{12}H_{12}N_4O_4S$ (308.32): C, 46.74; H, 3.92; N, 18.17. Found: C, 46.52; H, 3.79; N, 17.88. MS: m/z (FAB) 309 $(M+H)^+$.

5-Nitro-1-propyl-6-(pyridin-N-oxide-4-ylsulfanyl)-1H-pyrimidin-2,4-dione (6)

From 4-(*N*-oxidepyridine)thiol (0.81 g). Yield: 1.06 g (51%), m.p. 95–98 dec.°C. ^{1}H NMR (DMSO-d_6): δ 8.00 (d, 2H, J = 7.6 Hz, Ar-H); 7.30 (d, 2H, J = 7.6 Hz, Ar—H); 3.58 (m, 2H, CH_2-1′); 1.43 (m, 2H, CH_2-2′); 0.81 (t, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 166.8 (C-4); 158.2 (C-6); 150.2 (C-2); 138.2 (Ar-C$c_{,e}$); 131.3 (Ar-C$_{b,f}$); 113.5 (C-5); 48.5 (C-1′); 21.1 (C-2′); 11.1 (C-3′). Anal. calcd. for $C_{12}H_{12}N_4O_5S$ (324.31): C, 44.44; H, 3.73; N, 17.28. Found: C, 44.22; H, 3.68; N, 17.05. MS: m/z (FAB) 325 $(M+H)^+$.

5-Amino-6-phenylsulfanyl-1-propyl-1H-pyrimidin-2,4-dione (7)

A solution of **3** (0.70 g, 2.27 mmol) in methanol (20 mL) and Pd/C (150 mg) was stirred under H_2 for 5 h The solid was filtered and the solution was evaporated to dryness. The residue was recrystallized from ethanol to give **7** (0.50 g 79%), m.p. 143–146°C. ^{1}H NMR (DMSO-d_6): δ 9.95 (s, 1H, NH); 8.83 (br s., 2H, NH_2); 7.41–7.32 (m, 5H, Ar-H); 3.59 (m, 2H, CH_2-1′); 1.45 (m, 2H, CH_2-2′); 0.81 (t, 3H, $J = 7.1$ Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 163.5 (C-4); 150.2 (C-6); 133.8; 127.8, 125.0, 121.0 (Ar-C, C-6); 106.9 (C-5); 48.5 (C-1′); 21.1 (C-2′); 11.2 (C-3′). Anal. calc. for $C_{13}H_{15}N_4O_2S$ (277.34): C, 56.30; H, 5.45; N, 15.15. Found: C, 50.02; H, 5.37; N, 14.89. MS: m/z (FAB) 300 $(M+Na)^+$.

5-(Dimethylamino)-6-phenylsulfanyl-1-propyl-1H-pyrimidin-2,4-dione (8)

To a suspension of **6** (0.50 g, 1.80 mmol) in acetonitrile (10 mL) were added 37% aqueous formaldehyde (0.54 g, 18.00 mmol, 10 equiv.) and the mixture was heated under reflux for 1 h. After cooling, sodium cyanoborohydride ($NaBH_3CN$) (0.34 g, 5.4 mmol, 3.0 equiv.) and the mixture was stirred at reflux temperature for 2 h. After cooling, the reaction mixture was evaporated to dryness and the residue was partitioned between chloroform (3 × 20 mL) and water (20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness, and the residue was poured onto SiO_2 column.

Elution, in gradient, with methanol (0–10%) and chloroform, as eluent, afforded **8** (0.40 g, 74%), m.p. 139-143°C. ^{1}H NMR (DMSO–d_6): δ 7.48 (m, 2H, Ar-H); 7.32 (m, 3H, Ar-H); 3.38 (m, 2H, CH_2-1′); 3.21 (s, 6H, NMe_2); 1.48 (m, 2H, CH_2-2′); 0.83 (t, 3H, $J = 7.0$ Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 161.6 (C-4); 151.1 (C-2); 135.6; 129.5, 129.0 (Ar-C); 126.8 (C-6); 125.8 (C-6, ArC); 106.9 (C-5); 48.0 (C-1′); 40.1 (NMe_2); 21.7 (C-2′); 11.1 (C-3′). Anal. calcd. for $C_{15}H_{19}N_3O_2S$ (305.4): C, 58.99; H, 6.27; N, 13.76. Found: C, 58.73; H, 6.16; N, 13.51. MS: m/z (FAB) 328 $(M+Na)^+$.

(E)-5-(3,4-Dimethoxybenzylideneamino)-6-phenylsulfanyl-1-propyl-1H-pyrimidin-2,4-dione (9)

A solution of **7** (0.50 g, 1.80 mmol) in EtOH (20 mL) containing 2,4-dimethoxybenzaldehyde (0.33 g, 2.00 mmol) was heated under reflux for 3 h. After cooling, the crystals was filtered and washed with cold EtOH to give **9** (0.59 g, 77%), m.p. 155–158°C. ^{1}H NMR (DMSO-d_6): δ 7.63–7.25 (m, 9H, Ar-H + CH=N); 3.86, 3.82 (2xs, 6H, 2xOMe); 3.67 (m, 2H, CH_2-1′); 1.42 (m, 2H, CH_2-2′); 0.81 (t, 3H, $J = 7.0$ Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 160.3 (CH=N); 157.0 (C-4); 148.1 (C-2, C-6); 128.3 (Ar–*C*–OMe), 127.7, 127.6, 125.4, 123.9 (Ar-C); 90.8 (C-5), 60.0 (OMe);

45.7 (C-1′); 21.2 (C-2′); 11.3 (C-3′). Anal. calc. for $C_{22}H_{23}N_3O_4S$ (425.5): C, 62.10; H, 5.45; N, 9.88. Found: C, 61.89; H, 5.39; N, 9.71. MS: m/z (FAB) 426 $(M+H)^+$.

6-Chloro-1,3-dimethyl-5-nitro-1H-pyrimidin-2,4-dione (11)

Compound **11** was prepared by Pfleiderer et al.[29] and Clark et al.[30]

6-Arylsulfanyl-1,3-dimethyl-5-nitro-1H-pyrimidin-2,4-diones (12–15)—General Procedure

A solution of chloro compound **11** (1.71 g, 9.37 mmol) in DMF (20 mL) and arylmercaptan (18.74 mmol) was heated at 120°C (DMF) for 12 h. After cooling, the solution was evaporated to dryness and the residue was recrystallized from ethanol or ethanol/methanol to give the desired products **12–15**.

1,3-Dimethyl-5-nitro-6-phenylsulfanyl-1H-pyrimidin-2,4-dione (12)

From sodium phenylthiolate (2.47 g). Yield: 1.89 g (69%), m.p. 308–311°C. ^{1}H NMR (DMSO-d_6): δ 7.58 (m, 2H, Ar-H); 7.31 (m, 2H, Ar-H); 3.07, 3.00 (2s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): δ 159.4 (C-4); 156.2 (C-2); 148.1 (C-6); 130.8, 128.3, 127.5, 125.4 (Ar-C); 105.5 (C-5); 27.0, 26.7 (Me). Anal. Calc. for $C_{12}H_{11}N_3O_4S$ (293.3): C, 49.14; H, 3.78; N, 14.33. Found: C, 48.89; H, 3.70; N, 14.01. MS: m/z (FAB) 328 $(M+Na)^+$.

1,3-Dimethyl-5-nitro-6-(pyridin-4-ylthio)-1H-pyrimidin-2,4-dione (13)

From 4-pyridinethiol (2.08 g). Yield: 1.43 g (52%), m.p. 211–214 dec.°C. ^{1}H NMR (DMSO-d_6): δ 8.60 (d, 2H, $J = 7.5$ Hz, Ar-Hc,e); 7.61 (d, 2H, $J = 7.5$ Hz, Ar-Hb,f); 3.11, 3.09 (2s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): δ 162.2 (C-4); 157.1 (C-2); 148.6 (C-6); 129.8, 128.7, 128.9, 126.7 (Ar-C); 108.1 (C-5); 27.5, 27.0 (Me). Anal. calcd. for $C_{11}H_{10}N_4O_4S$ (294.29): C, 44.89; H, 3.43; N, 19.04. Found: C, 44.65; H, 3.33; N, 18.87. MS: m/z (FAB) 295 $(M+H)^+$.

1,3-Dimethyl-5-nitro–6-(pyridin-N-oxide-4-ylsulfanyl)-1H-pyrimidin-2,4-dione (14)

From 4-(*N*-oxidepyridine)thiol (2.38 g). Yield: 1.77 g (61%), m.p. 200–202 dec.°C. ^{1}H NMR (DMSO-d_6): δ 8.08 (d, 2H, $J = 8.1$ Hz, Ar-Hc,e); 7.37 (d, 2H, $J = 8.1$ Hz, Ar-Hb,f); 3.09, 3.01 (2s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): δ 164.2 (C-4); 157.9 (C-2); 150.1 (C-6); 136.2 (Ar-$C_{c,e}$), 131.1 (Ar-$C_{b,f}$); 112.9 (C-5); 27.7, 27.2 (Me). Anal. calcd. for $C_{11}H_{10}N_4O_5S$

(310.29): C, 42.58; H, 3.25; N, 18.06. Found: C, 42.32; H, 3.09; N, 17.89. MS: m/z (FAB) 311 $(M+H)^+$.

6-(4-Chlorophenylsulfanyl)-1,3-dimethyl-5-nitro-1H-pyrimidin-2,4-dione (15)

From 4-chlorophenylmercaptan (2.69 g). Yield: 1.62 (53%), m.p. 132-137°C. ^{1}H NMR (DMSO-d_6): δ 8.08 (d, 2H, $J = 8.1$ Hz, Ar-Hc,e); 7.37 (d, 2H, $J = 8.1$ Hz, Ar-Hb,f); 3.09, 3.01 (2s, 6H, 2xCH_3). ^{13}C NMR (DMSO-d_6): δ 157.2 (C-4); 151.0 (C-2); 145.0 (C-6); 131.0, 129.5 (Ar-C), 111.9 (C-5); 27.0, 26.9 (Me). Anal. calcd. for $C_{12}H_{10}ClN_3O_4S$ (327.74): C, 43.98; H, 3.08; N, 12.82. Found: C, 43.69; H, 2.92; N, 12.61. MS: m/z (FAB) 350 $(M + Na)^+$.

2-Amino-5-nitro-6-phenylsulfanyl-1*H*-pyrimidin-4-one (17)

This compound was prepared from **16** (0.65 g, 2.96 mmol) according ro the procedure of preparation of **3**. Yield: 0.51 g (65%), m.p. 233–235°C. ^{1}H NMR (DMSO-d_6): δ 11.27 (br s., 2H, NH_2); 7.40–7.34 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 188.2 (C-5); 173.2 (C-7); 144.6 (C-9); 139.8 (C-2); 135.0, 133.1, 129.3, 129.1, 128.7, 127.2, 125.4 (Ar-C), 124.3 (C-3); 115.1 (C-6). Anal. calcd. for $C_{10}H_8N_4O_3S$ (264.26): C, 45.45; H, 3.05; N, 21.20. Found: C, 45.19; H, 3.98; N, 20.98. MS: m/z (FAB) 328 $(M+Na)^+$.

2-Amino-2-phenyl-7-phenylsulfanyl-imidazo[1,2-α]pyrimidin-5-one (18)

To a solution of **17** (0.30 g, 1.13 mmol) in anhydrous DMF (10 mL) containing NaH (0.06 g, 2.5 mmol) was added α-bromoacetophenone (0.32 g, 1.6 mmol). The reaction mixture was stirred at 23°C for 5 h, followed by the addition of NH_4OH solution (7 mL) at 23°C to give, after chromatography, **18** (0.21 g, 51%), m.p. 192–195°C. ^{1}H NMR (DMSO-d_6): δ 7.45–7.41 (m, 5H, C_8—Ar-H); 7.26-71.8 (m, 5H, S—Ar-H); 7.15 (s, 1H, H-3). ^{13}C NMR (DMSO-d_6): δ 188.2 (C-4); 173.2 (C-6); 144.6 (C-2); 139.8 (C-8); 135.0, 133.1, 129.3, 129.1, 128.7, 127.2, 125.4 (Ar-C), 124.3 (C-7); 115.1 (C-5). Anal. calcd. for $C_{18}H_{12}N_4O_3S$ (364.38): C, 59.33; H, 3.32; N, 15.38. Found: C, 58.92; H, 3.19; N, 15.09. MS: m/z (FAB) 365 $(M+H)^+$.

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