Bioorganic & Medicinal Chemistry 18 (2010) 3231–3237

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and biological evaluation of novel C5 halogen-functionalized *S*-DABO as potent HIV-1 non-nucleoside reverse transcriptase inhibitors

Hua Qin [a], Chang Liu [b], Ying Guo [c], Ruiping Wang [b], Jianfang Zhang [b], Liying Ma [d], Zhili Zhang [c], Xiaowei Wang [c], Yuxin Cui [a], Junyi Liu [a,c,*]

[a] *State key Laboratory of National and Biomimetic Drug, Peking University, Beijing 100191, PR China*
[b] *College of Pharmaceutical Sciences, Capital Medical University, Beijing 100069, PR China*
[c] *Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, PR China*
[d] *State Key Laboratory for Infection Disease Prevention and Control, National Center for AIDS/STD Control and Prevention (NCAIDS), Chinese Center for Disease Control and Prevention, Beijing 100050, PR China*

ARTICLE INFO

Article history:
Received 1 February 2010
Revised 10 March 2010
Accepted 11 March 2010
Available online 15 March 2010

Keywords:
HIV-1 RT
NNRTIs
S-DABO analogues
Docking

ABSTRACT

A series of novel *S*-DABO analogues (**4a1**–**5a12**) have been synthesized by an efficient method and evaluated as inhibitors of human immunodeficiency virus type-1 (HIV-1). The biological testing results clearly indicated that the substitution of halogen at the C5 position of pyrimidine ring could increase the anti-HIV-1 RT activity. The most active compounds showed activity in the low micromole range with IC_{50} values (IC_{50} 0.18–3.03 μM) comparable to nevirapine (IC_{50} 4.12 μM). The docking showed that a new halogen bond was formed between halogen and carbonyl of TYR188 in the HIV-I RT.

1. Introduction

Since discovery of the human immunodeficiency virus (HIV) as the cause of the acquired immunodeficiency syndrome (AIDS),[1] many efforts have been undertaken to design and synthesize potential agents against HIV. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) serve as an increasingly important role in the therapy of HIV infection, due to their unique antiviral potency, high specificity and low toxicity, such as nevirapine and efavirenz.[2–4] Structure–activity relationship (SAR) studies in this field are documented by the wide number of NNRTIs identified so far include more than fifty structurally different classes of molecules, such as MKC-442 and TMC-125, which are under clinical trials (Fig. 1).[5–7] However, patients treated with NNRTIs can rapidly trigger the emergence of drug resistant HIV-1 variants and the cross-resistance between these structurally unrelated drugs. Therefore, in the NNRTIs field, it is important to develop new agents with higher binding affinity and the capability of inhibiting clinical resistant mutants.

Among NNRTIs, dihydro-alkoxy-benzyl-oxopyrimdines (DABOs) are an interesting class of compounds active at nanomolar concentration. It was first reported in 1992 and further developed during the following years into *S*-DABOs, *N*-DABOs and related analogues (Fig. 1).[8–23] A great number of oxopyrimidines were synthesized and tested as anti-HIV-1 agents to obtain more potent and

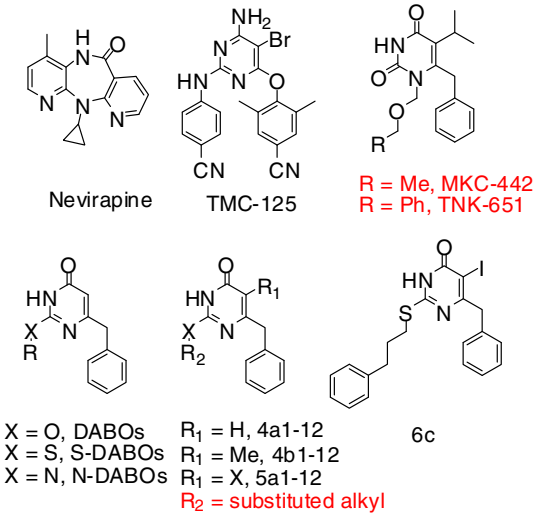


Figure 1. Structures of Nevirapine, TMC-125, MKC-442, TNK-651, DABOs and designed target compounds.

* Corresponding author. Tel.: +86 010 82801706; fax: +86 010 62015548.
E-mail addresses: yxyx@bjmu.edu.cn, oiqh818@sohu.com (J. Liu).

0968-0896/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2010.03.025

selective inhibition compounds, such as *S*-DABOs reported to date (ID_{50} = 3 nM toward the isolated wt enzyme and EC_{50} = 25 pM toward wt NL4-3 virus).[20]

2. Results and discussion

2.1. Drug design

Studies carried out on crystal structures of different RT/NNRTI complexes suggest that these NNRTIs share a common mode of action with the HIV-1 reverse transcriptase.[8–23] Substituting with aryl moiety at C2 and C6 alkyl chains of the pyrimidine ring are structural determinant. The extend side chain at C2 position point toward into a pocket mainly defined by His235, Pro236 and Val106, with the length and size of the C2 side chain having only modulator effects on potency. The chain at C6 position with different substituents on the aromatic or heteroaromatic moieties is located in a hydrophobic region delimited by Tyr181, Tyr188 and Trp229. The NHCO fragment at N3/C4-positions of pyrimidine ring, stabilized by a hydrogen bond between the N3-H function of *S*-DABOs and the carbonyl oxygen of Lys101, cannot be modified without abolishing the antiviral activity of DABO derivatives. These results were reviewed again by our previous work.[24]

The groups at the pyrimidine C5 position furnished a conformational constraint with the aim of enhancing the affinity for the enzyme.[25] A structure–activity relationship (SAR) profile of DABOs together with molecular modeling investigation on their putative binding mode have shown that the groups at C5 position were small alkyl groups such as Me, Et and *i*-Pr, little or no information was available about other C5 substitution, such as halogen atom. However, in recent years the ability of halogen atoms to function as general, effective and reliable sites for directing molecular recognition processes is being given to more and more attention.[26,27] Moreover, no studies are available on the effect of varying both electron effect and the steric hindrance of *S*-DABOs at C5 position using halogen. The halogen group at C5 position of pyrimidine ring may have electron effect with Vall79 and Tyr188 in HIV-1 RT, and the large atomic radius of the halogen group may also help the stabilized conformation of C6 benzyl group on the interaction between the inhibitor and HIV-1 RT.

To investigate the structure and activity relationship of our design compounds, **5a3** was flexibly docked into the binding site of HIV-1 RT (PDB entry 1RT2, complexed with TNK-651) using AUTODOCK 3.05 program.[28] Default parameters were used as described in the AUTODOCK manual unless otherwise specified. The molecule was docked with 100 genetic algorithm runs of up to 250,000 energy evaluations for each run in the docking study of **5a3** with a RT non-nucleoside binding site (NNBS). The studies revealed that the binding mode of **5a3** has approximate conformation as in the TNK-651-RT complex (Fig. 2). The hydrogen bond was formed at the N3-H moiety of **5a3** and the carbonyl group of the Lys101 as stronger as the TNK-651 (distance N3···O 2.73 Å and 2.76 Å, respectively). Besides, a distinct interaction could be formed between the C5-I and the carbonyl of Tyr188 with a 3.25 Å distance that is less than their respective van der Walls radius sums, as well as with halogen bonding angles (∠(C–X···O), 146.77°), which are larger than 120°.[29] There are also a less interaction between the C5-I and the carbonyl of Val179. Based on the docking result, We hypothesized that the introduction of the halogen at C5 position could form a halogen bond, charactered in parallel with a hydrogen bond in terms of strength and directionality, and affect the interaction between **5a3** and the HIV-1 RT by the electron effect and the steric hindrance which should yield more potent anti-HIV agents with higher affinity for the inhibitor binding pocket.

Therefore, we synthesized a new series of C5 halogen-functionalized compounds **5a1**–**12** with different length and size at C2 substituted chain and tested the activity against HIV-1 RT.

2.2. Chemistry

The synthesis of the newly designed compounds is described in Scheme 1. Treatment of benzyl cyanide with 3–5 molar excess of α-bromo esters **1a**, **b** in the present of activated zinc dust in refluxing tetrahydrofuran obtained the β-ketoesters **2a**, **b** in 95% and 85% yields.[30] The compounds **2a**, **b** were converted by reaction with thiourea and sodium in boiling ethanol to 2-thiouracil **3a**, **b** in 86% and 60% yields.[31] Next, selective S-alkylation of **3a**, **b** with appropriate substituted alkyl halide in the present MeONa in anhy-

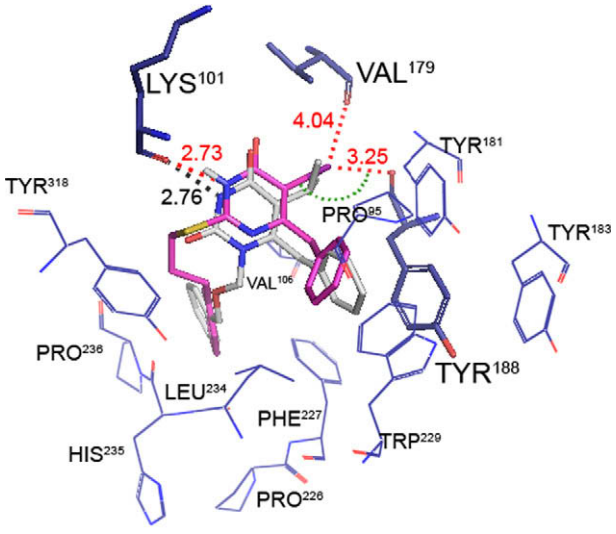
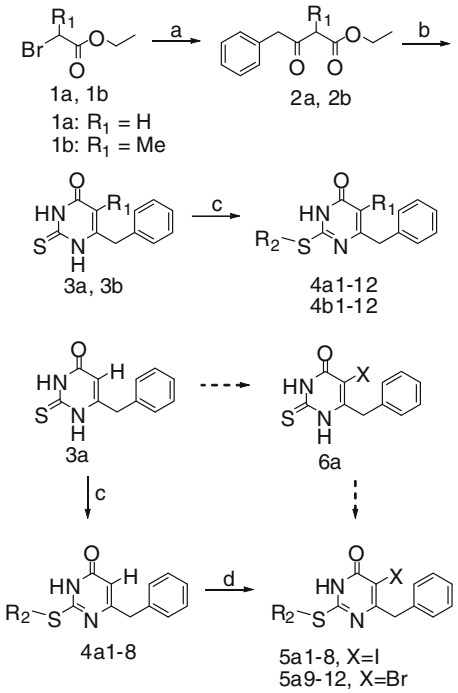


Figure 2. Binding mode of **5a3** (pink) and TNK-651 (white) with HIV-RT. The bonds are shown as red (**5a3**) and black (TNK-651) dashed lines and the halogen bonding angle is shown as green dashed line.



Scheme 1. Reagents and conditions for the chemical synthesis: (a) benzyl cyanide, Zn/THF, reflux; (b) thiourea, EtONa, EtOH, reflux; (c) substituted alkyl halide, Na/MeOH, rt; (d) I_2 or Br_2, PbO_2, rt, overnight.

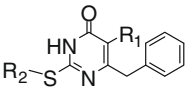
drous MeOH at room temperature afforded the designed compounds **4a1–12**, **4b1–12** in 30–88% yields.[32] Halogenations at C5 position of **4a1–8** by PbO_2 and I_2 or Br_2 in HOAc at room temperature led **5a1–12** in 45–94% yields. The analytical and spectral date showed that the C5-H was substituted by I or Br and no side reactions resulted in the other aromatic rings. However, this halogenation approach was unsuccessful on these compounds which C2 chains were substituted by benzyloxymethyl, ethoxymethyl and allyl such as **4a10–12**. Thus, we decided to halogenate **3a** at C5 position to **6a** before S-alkylation. Unfortunately, some attempts with different reagents and solvent such as NBS/DCM, NBS/DMF, NIS/DCM, Br_2/H_2O and I_2/H_2O at room temperature or heated about 80 °C did not give the halogenated products **6a**, thought to be due to lower aromaticity of compound **3a**.

2.3. Biological activity

The compounds **4a1–12**, **4b1–12** and **5a1–12** were tested for their activity against HIV in RT assay, using a poly(rA)/oligo$(dT)_{15}$ homopolymer template with the HIV antigen detection ELISA method, nevirapine and MKC-442 as references (Table 1).[33] It is interesting to note that three series of compounds reflect obvious structure–activity relationships.

Compared the different substitutions at C5 position, we found that the activity of C5-Me series (**4b1–12**) was a slightly better than C5-H (**4a1–12**) (Table 1). However, if the C5 position was substituted by I or Br, the activity was better than H and Me obviously, and the I was better than Br at concentrations sixfold or more. For example, when the C2 group was 2-naphthyl methyl, the halogen substituent at C5 position was key factor for the activity. The results showed that the anti-HIV-1RT activity was associated with the electrophile and atom radius of the halogen atom. The halogen-functionalized at C5 position of *S*-DABO derivatives could be new HIV-RT inhibitors. These results were accordance with our originally envision and reviewed that the halogen bond functioned as a direction molecular recognition to some degree. The halogen bond acting as a new interaction for rational drug design was discussed by Zhu group recently and our result was also consistent with their experimental result.[29] It was particularly noteworthy that compound **5a3** (IC_{50} = 0.18 μM) was more active than **4a3** (IC_{50} = 8.17 μM) at concentrations 45-fold and 23-fold to nevirapine (IC_{50} = 4.12 μM) by introducing the iodine at the C5 position,. A SAR profile of S-DABAs at C5 position was I > Br >> Me–H. In addition, we found that the small (H) or bulky (*t*-Bu) substituted groups on the benzene ring of the C2 chain were not beneficial for the activity. But maintaining a three-carbon spacer between S and benzene ring was the optimal length for the activity, which demonstrated by **4a3** > **4a2** > **4a1**, **4b3** > **4b2** > **4b1** and **5a3** > **5a2** > **5a1**. Detailed SAR studies on these compounds are under way.

Table 1
Structure and enzymatic activity value[a] of **4a1**–**5a12**



Compd	R_1	R_2	IC_{50}[b] (μM)
4a1	H	$C_6H_5CH_2$	NA[c]
4a2	H	$C_6H_5CH_2$ CH_2	17.45
4a3	H	$C_6H_5CH_2CH_2$ CH_2	8.17
4a4	H	(*O*-CH_3)$C_6H_4CH_2$	47.72
4a5	H	(*m*-CH_3)$C_6H_4CH_2$	91.14
4a6	H	(*m*-OCH_3)$C_6H_4CH_2$	90.85
4a7	H	(*p*-*t*-Bu)$C_6H_4CH_2$	NA
4a8	H	2-Naphthyl methyl	NA
4a9	H	$C_6H_5(CH_3)CH$	>100
4a10	H	$CH_3CH_2OCH_2$	>100
4a11	H	$C_6H_5CH_2OCH_2$	12.12
4a12	H	CH_2=$CHCH_2$	>100
4b1	CH_3	$C_6H_5CH_2$	NA
4b2	CH_3	$C_6H_5CH_2$ CH_2	59.61
4b3	CH_3	$C_6H_5CH_2CH_2CH_2$	2.93
4b4	CH_3	(*O*-CH_3)$C_6H_4CH_2$	>100
4b5	CH_3	(*m*-CH_3)$C_6H_4CH_2$	NA
4b6	CH_3	(*m*-OCH_3)$C_6H_4CH_2$	48.74
4b7	CH_3	(*p*-*t*-Bu)$C_6H_4CH_2$	NA
4b8	CH_3	2-Naphthyl methyl	NA
4b9	CH_3	$C_6H_5(CH_3)CH$	>100
4b10	CH_3	$CH_3CH_2OCH_2$	51.66
4b11	CH_3	$C_6H_5CH_2OCH_2$	19.01
4b12	CH_3	CH_2=$CHCH_2$	NA
5a1	I	$C_6H_5CH_2$	10.12
5a2	I	$C_6H_5CH_2$ CH_2	2.40
5a3	I	$C_6H_5CH_2$ CH_2 CH_2	0.18
5a4	I	(*O*-CH_3)$C_6H_4CH_2$	4.16
5a5	I	(*m*-CH_3)$C_6H_4CH_2$	3.03
5a6	I	(*m*-OCH_3)$C_6H_4CH_2$	8.29
5a7	I	(*p*-*t*-Bu)$C_6H_4CH_2$	5.62
5a8	I	2-Naphthyl methyl	2.04
5a9	Br	$C_6H_5CH_2$ CH_2	13.95
5a10	Br	(*O*-CH_3)$C_6H_4CH_2$	24.94
5a11	Br	(*m*-CH_3)$C_6H_4CH_2$	26.65
5a12	Br	2-Naphthyl methyl	12.26

[a] Nevirapine and MKC-442 were used as the reference compounds here; IC_{50} were 4.12 μM and 0.15 μM, respectively.
[b] Compound dose (μM) required to inhibit the HIV-1 RT activity by 50%; Data represent mean values for three separate experiments, variation among triplicate samples was less than 15%.
[c] No inhibition of reverse transcriptase activity was observed up to a concentration of 100 μM.

3. Conclusions

In summary, we have designed and synthesized three series of novel C5 halogen-functionalized *S*-DABO analogues as new NNRTIs for the first time. The activity result showed that the introduction of halogen atom at C5 position of the pyrimidine ring will increase the activity obviously. A halogen bond could be formed between the halogen atom and the carbonyl of TYR188. Some of the IC_{50} values of the tested compounds were better comparing to the nevirapine, although the activity were suboptimal comparing to the best *S*-DABOs, the SAR exploration encouraged us to the new rational design. Further structure modifications on the C5 position and two chains of the pyrimidine ring are underway. Also, the synthetic route shows combination potential in the synthesis of larger libraries of compounds which is ongoing in our laboratory.

4. Experimental

NMR spectra were recorded on a Bruker Avance II300 or Avance II500 using TMS as an internal standard and chemical shifts are reported in δ (ppm). Mass spectrometer was record on Wasters Quattro Micro 2000. Melting points were measured on a WBS-1B type digital melting-point apparatus and are uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel G plates at 254 nm under a UV lamp. Silica gel (0.040–0.064 mm) used for column chromatography and analytical silica gel TLC plates $60GF_{254}$. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification.

4.1. General procedure for the preparation of compounds 4a1–12

Sodium (225 mg) was dissolved in anhydrous methanol (15 ml), 6-benzyl-2-thiouracil derivatives **3a** (1 mmol) was added followed by addition of appropriate substituted alkyl halide (1.1–3 mmol). After completion of the reaction according to TLC analysis and

evaporation of the solvent, the oil residue was diluted with H_2O (80 ml) followed by addition of HOAc (1 ml). The white precipitate was filtered off and then purified by silica gel column chromatography to afford the white solid products **4a1–12**.

4.1.1. 6-Benzyl-2-(benzylthio)pyrimidin-4(3*H*)-one (4a1)

Yield 80%; mp 188.8–190.5 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 (s, 2H, $ArCH_2$), 4.38 (s, 2H, SCH_2), 5.94 (s, 1H, 5-H), 7.11–7.51 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.61 (CH_2S), 43.96 ($ArCH_2$), 108.46 (C5), 126.84, 127.51, 128.51, 128.63, 129.14, 129.45, 136.51, 136.70 (Ar), 160.21 (C6), 165.32 (C2), 167.94 (C4); *m*/*z* (ESI): 309.0 $(M+H)^+$, 331.0 $(M+Na)^+$; $C_{18}H_{16}N_2OS$ (308.10).

4.1.2. 6-Benzyl-2-(phenethylthio)pyrimidin-4(3*H*)-one (4a2)

Yield 77%; mp 139–140 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.97 (dd, 2H, *J* = 8.1, 9.9 Hz, SCH_2CH_2,), 3.39 (dd, 2H, *J* = 8.4, 9.6 Hz, SCH_2CH_2), 3.86 (s, 2H, $ArCH_2$), 6.02 (s, 1H, 5-H), 7.18–7.34 (m, 10H, ArH), 12.75 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.78 (CH_2S), 35.73 ($ArCH_2$), 44.00 ($ArCH_2CH_2S$), 108.41 (C5), 126.59, 126.86, 128.53, 128.58, 128.62, 129.42, 137.05, 139.74 (Ar), 160.61 (C6), 165.35 (C2), 168.01 (C4); *m*/*z* (ESI): 323.0 $(M+H)^+$, 345.0 $(M+Na)^+$; $C_{19}H_{18}N_2OS$ (322.11).

4.1.3. 6-Benzyl-2-(3-phenylpropylthio)pyrimidin-4(3*H*)-one (4a3)

Yield 88%, mp 149–150 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03 (quintet, 2H, *J* = 7.5 Hz, $CH_2CH_2CH_2$), 2.73 (t, 2H, *J* = 7.5 Hz, $ArCH_2CH_2$), 3.18 (t, 2H, *J* = 7.5 Hz, CH_2CH_2S), 3.81 (s, 2H, $ArCH_2$), 6.00 (s, 1H, 5-H), 7.18–7.33 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.09 (CH_2S), 30.61 (SCH_2CH_2), 34.67 ($CH_2CH_2CH_2S$), 43.98 ($ArCH_2$), 108.23 (C5), 126.05, 126.82, 128.43, 128.47, 129.43, 137.10, 140.99 (Ar), 160.68 (C6), 165.24 (C2), 167.98 (C4); *m*/*z* (ESI): 337.1 $(M+H)^+$, 359.0 $(M+Na)^+$; $C_{20}H_{20}N_2OS$ (336.13).

4.1.4. 6-Benzyl-2-(2-methyl-benzylthio)pyrimidin-4(3*H*)-one (4a4)

Yield 88%; mp 170–172 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3H, $ArCH_3$), 3.98 (s, 2H, $ArCH_2$), 4.67 (s, 2H, SCH_2), 6.10 (s, 1H, 5-H), 7.00–7.63 (m, 9H, ArH), 12.96 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.37 ($ArCH_3$), 33.09 (CH_2S), 43.87 ($ArCH_2$), 108.38 (C5), 126.15, 126.92, 128.01, 128.66, 129.52, 130.27, 130.46, 133.67, 136.83, 136.99 (Ar), 160.68 (C6), 165.33 (C2), 167.82 (C4); *m*/*z* (ESI): 323.1 $(M+H)^+$; $C_{19}H_{18}N_2OS$ (322.11).

4.1.5. 6-Benzyl-2-(3-methyl-benzylthio)pyrimidin-4(3*H*)-one (4a5)

Yield 59%; mp 148.5–149.5 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3H, $ArCH_3$), 3.87 (s, 2H, $ArCH_2$), 4.39 (s, 2H, SCH_2), 6.00 (s, 1H, 5-H), 7.07–7.36 (m, 9-H, ArH), 13.20 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.34 ($ArCH_3$), 34.70 (CH_2S), 44.01 ($ArCH_2$), 108.39 (C5), 126.25, 126.87, 128.33, 128.43, 128.65, 129.47, 129.89, 136.31, 137.06, 138.22 (Ar), 160.49 (C6), 165.63 (C2), 168.05 (C4); *m*/*z* (ESI): 323.1 $(M+H)^+$; $C_{19}H_{18}N_2OS$ (322.11).

4.1.6. 6-Benzyl-2-(3-methoxybenzylthio)pyrimidin-4(3*H*)-one (4a6)

Yield 78%; mp 159–160 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.79 (s, 3H, OCH_3), 3.87 (s, 2H, $ArCH_2$), 4.40 (s, 2H, CH_2S), 5.99 (s, 1H, 5-H), 6.80–7.35 (m, 9H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.75 (CH_2S), 43.93 ($ArCH_2$), 55.22 (OCH_3), 108.39 (C5), 114.66, 121.51, 128.67, 129.46, 129.57, 136.94, 137.88, 160.40 (Ar), 159.70 (C6), 165.47 (C2), 168.00 (C4); *m*/*z* (ESI): 338.9 $(M+H)^+$, 361.0 $(M+Na)^+$; $C_{19}H_{18}N_2O_2S$ (338.11).

4.1.7. 6-Benzyl-2-(4-tert-butylbenzylthio)pyrimidin-4(3*H*)-one (4a7)

Yield 79%; mp 169–170 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (s, 9H, $(CH_3)_3C$), 3.87 (s, 2H, $ArCH_2$), 4.39 (s, 2H, CH_2S), 6.00 (s, 1H, 5-H), 7.06–7.56 (m, 9H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.30 ($(CH_3)_3C$), 34.40 (CH_2S), 34.51 ($ArCH_2$), 44.01 ($(CH_3)_3C$), 108.46 (C5), 125.47, 126.83, 128.64, 128.89, 129.49, 133.36, 137.10, 150.55 (Ar), 160.50 (C6), 165.35 (C2), 167.91 (C4); *m*/*z* (ESI): 365.0 $(M+H)^+$, 387.0 $(M+Na)^+$; $C_{22}H_{24}N_2OS$ (364.16).

4.1.8. 6-Benzyl-2-(naphthalen-2-ylmethylthio)pyrimidin-4(3*H*)-one (4a8)

Yield 65%; mp 213–214 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.84 (s, 2H, $ArCH_2$), 4.55 (s, 2H, CH_2S), 6.02 (s, 1H, 5-H), 7.23–7.33 (m, 5H, ArH), 7.45–7.53 (m, 3H, ArH), 7.80–7.87 (m, 4H, ArH); ^{13}C NMR (75 MHz, pyridine-d_5) δ: 34.73 (CH_2S), 43.75 ($ArCH_2$), 107.61 (C5), 126.15, 126.43, 126.79, 127.53, 127.85, 127.96, 128.02, 128.51, 128.75, 129.62, 132.93, 133.61, 138.38 (Ar), 162.91 (C6), 165.06 (C2), 167.06 (C4); *m*/*z* (ESI): 359.1 $(M+H)^+$, 381.2 $(M+Na)^+$; $C_{22}H_{18}N_2OS$ (358.11).

4.1.9. 6-Benzyl-2-(1-phenylethylthio)pyrimidin-4(3*H*)-one (4a9)

Yield 65%; mp 213–214 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.73 (d, 3H, *J* = 7.0 Hz, CH_3CH), 3.86 (s, 2H, $ArCH_2$), 5.11–5.15 (q, 1H, *J* = 7.2 Hz, CH_3CH), 6.00 (s, 1H, 5-H), 7.24–7.38 (m, 10-H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.01 (CH_3CH), 44.00 (CH_3CH), 44.63 ($ArCH_2$), 108.32 (C5), 126.85, 127.54, 128.50, 128.64, 129.49, 137.13, 141.97 (Ar), 160.37 (C6), 165.72 (C2), 168.14 (C4); *m*/*z* (ESI): 323.0 $(M+H)^+$; $C_{19}H_{18}N_2OS$ (322.11).

4.1.10. 6-Benzyl-2-(ethoxymethylthio)pyrimidin-4(3*H*)-one (4a10)

Yield 53%; mp 130–131 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 3.56 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 3.86 (s, 2H, $ArCH_2$), 5.44 (s, 2H, SCH_2O), 6.02 (s, 1H, 5-H), 7.26–7.35 (m, 5H, ArH), 12.80 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.69 (CH_2CH_3), 43.91 ($ArCH_2$), 65.40 (SCH_2O), 72.25 (OCH_2CH_3), 109.00 (C5), 126.89, 128.63, 129.48, 136.92 (Ar), 159.67 (C6), 165.18 (C2), 168.05 (C4); *m*/*z* (ESI): 277.3 $(M+H)^+$; $C_{14}H_{16}N_2O_2S$ (276.09).

4.1.11. 6-Benzyl-2-(benzyloxymethylthio)pyrimidin-4(3*H*)-one (4a11)

Yield 50%; mp 132–133 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.78 (s, 2H, $ArCH_2$), 4.60 (s, 2H, $ArCH_2O$), 5.46 (s, 2H, SCH_2O), 6.01 (s, 1H, 5-H), 7.26–7.55 (m, 10H, ArH), 12.40 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 43.87 ($ArCH_2$), 71.19 (SCH_2O), 71.54 (OCH_2Ar), 109.19 (C5), 126.93, 128.12, 128.40, 128.53, 128.67, 129.31, 129.47, 136.47, 136.86 (Ar), 159.33 (C6), 164.77 (C2), 167.99 (C4); *m*/*z* (ESI): 339.0 $(M+H)^+$, 361.0 $(M+Na)^+$; $C_{19}H_{18}N_2O_2S$ (338.11).

4.1.12. 2-(Allylthio)-6-benzylpyrimidin-4(3*H*)-one (4a12)

Yield 61%; mp 132–133 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.75 (d, 2H, *J* = 7.2 Hz, SCH_2), 3.77 (s, 2H, $ArCH_2$), 5.05 (d, 1H, *J* = 9.9 Hz, $CH{=}CH_2$), 5.21 (dd, 1H, *J* = 16.8, 1.2 Hz, $CH{=}CH_2$), 5.88 (m, 1H, $CH{=}CH_2$), 6.00 (s, 1H, 5-H), 7.26–7.35 (m, 5H, ArH), 13.26 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.31 (SCH_2), 43.97 (CH_2Ar), 108.34 (C5), 118.79 ($CH{=}CH_2$), 132.39 ($CH{=}CH_2$), 126.86, 128.61, 129.48, 137.00 (Ar), 160.23 (C6), 165.74 (C4), 168.15 (C2); *m*/*z* (ESI): 259.2 $(M+H)^+$, 291.2 $(M+Na)^+$; $C_{14}H_{14}N_2OS$ (258.08).

4.2. Compounds 4b1–12 were prepared by the method used for 4a1–12

4.2.1. 6-Benzyl-5-methyl-2-(benzylthio)pyrimidin-4(3*H*)-one (4b1)

Yield 30%; mp 176.5–177.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.04 (s, 3H, 5-CH_3), 3.96 (s, 2H, $ArCH_2$), 4.38 (s, 2H, CH_2S), 7.23–7.32 (m, 10H, ArH), 12.44 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$)

δ: 10.73 (5-CH_3), 34.54 ($ArCH_2$), 41.04 ($ArCH_2S$), 116.58 (C5), 126.50, 127.41, 128.51, 128.98, 129.09, 136.97, 137.70 (Ar), 155.90 (C6), 162.07 (C2), 165.30 (C4); *m*/*z* (ESI): 323.0 $(M+H)^+$, 345.0 $(M+Na)^+$; $C_{19}H_{18}N_2OS$ (322.11).

4.2.2. 6-Benzyl-2-(benzylthio)-5-methylpyrimidin-4(3*H*)-one (4b2)

Yield 52%; mp 156.5–157.5 °C; white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H, 5-CH_3), 2.97 (t, 2H, *J* = 7.5 Hz, SCH_2), 3.37 (t, 2H, *J* = 7.5 Hz, SCH_2CH_2), 3.98 (s, 2H, $ArCH_2$), 7.16–7.32 (m, 10H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.72 (5-CH_3), 31.81 (CH_2S), 35.83 ($ArCH_2$), 41.05 ($ArCH_2CH_2S$), 116.59 (C5), 126.50, 126.53, 128.49, 128.51, 128.59, 128.91, 137.95, 139.88 (Ar), 156.15 (C6), 162.06 (C2), 165.06 (C4); *m*/*z* (ESI): 337.5 $(M+H)^+$, 359.4 $(M+Na)^+$; $C_{20}H_{20}N_2OS$ (336.13).

4.2.3. 6-Benzyl-5-methyl-2-(3-phenylpropylthio)pyrimidin-4(3*H*)-one (4b3)

Yield 62 °C; mp 152–153 °C; white solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.12 (s, 3H, 5-CH_3), 1.99 (quintet, 2H, *J* = 7.2 Hz, $CH_2CH_2CH_2$), 2.69 (t, 2H, *J* = 7.2 Hz, $ArCH_2CH_2$), 3.14 (t, 2H, *J* = 7.2 Hz, CH_2CH_2S), 3.91 (2H, s, $ArCH_2$), 7.15–7.31 (10H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.68 (5-CH_3), 30.06 (CH_2S), 30.81 (SCH_2CH_2), 34.72 ($ArCH_2CH_2$), 41.01 ($ArCH_2$), 116.32 (C5), 126.00, 126.43, 128.40, 128.44, 128.95, 137.95, 141.07 (Ar), 156.23 (C6), 162.03 (C2), 165.34 (C4); *m*/*z* (ESI): 351.4 $(M+H)^+$, 373.4 $(M+Na)^+$; $C_{21}H_{22}N_2OS$ (350.15).

4.2.4. 6-Benzyl-5-methyl-2-(2-methylbenzylthio)pyrimidin-4(3*H*)-one (4b4)

Yield 74%; mp 173–174 °C; white solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.93 (s, 3H, 5-CH_3), 2.36 (s, 3H, $ArCH_3$), 3.98 (s, 2H, $ArCH_2$), 4.41 (s, 2H, CH_2S), 7.05–7.33 (m, 9H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.74 (5-CH_3), 19.33 ($ArCH_3$), 32.84 (CH_2S), 41.05 ($ArCH_2$), 116.56 (C5), 126.14, 126.51, 127.86, 128.50, 128.99, 130.13, 130.45, 134.27, 136.97, 137.92 (Ar), 156.11 (C6), 162.06 (C2), 165.28 (C4); *m*/*z* (ESI): 337.2 $(M+H)^+$, 359.1 $(M+Na)^+$; $C_{20}H_{20}N_2OS$ (336.13).

4.2.5. 6-Benzyl-5-methyl-2-(3-methylbenzylthio)pyrimidin-4(3*H*)-one (4b5)

Yield 67%; mp 198–199.5 °C; white solid; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.95 (s, 3H, 5-CH_3), 2.22 (s, 3H, $ArCH_3$), 3.90 (s, 2H, $ArCH_2$), 4.29 (s, 2H, CH_2S), 7.02–7.31 (m, 9H, ArH), 12.54 (br s, 1H, NH); ^{13}C NMR (125 MHz, pyridine-d_5) δ: 10.79 (5-CH_3), 21.00 ($ArCH_3$), 34.34 ($ArCH_2$), 40.93 (CH_2S), 115.84 (C5), 126.45, 126.52, 128.17, 128.63, 128.69, 129.24, 123.00, 138.04, 138.13, 138.86 (Ar), 157.88 (C6), 161.22 (C2), 164.67 (C4); *m*/*z* (ESI): 337.1 $(M+H)^+$, 359.1 $(M+Na)^+$; $C_{20}H_{20}N_2OS$ (336.13).

4.2.6. 6-Benzyl-5-methyl-2-(3-methoxybenzylthio)pyrimidin-4(3*H*)-one (4b6)

Yield 43%; mp 162–163 °C; white solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.10 (s, 3H, 5-CH_3), 3.77 (s, 2H, $ArCH_2$), 3.96 (s, 3H, OCH_3), 4.37 (s, 2H, CH_2S), 6.79–6.89 (m, 3H, ArH), 7.14–7.32 (m, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.74 (5-CH_3), 34.67 ($ArCH_2$), 41.09 (CH_2S), 55.21 (OCH_3), 121.44 (C5), 113.09, 114.54, 116.64, 126.50, 128.50, 139.55, 137.82, 138.30, 159.67 (Ar), 155.93 (C6), 162.03 (C2), 165.24 (C4); *m*/*z* (ESI): 353.0 $(M+H)^+$, 374.9 $(M+Na)^+$; $C_{20}H_{20}N_2O_2S$ (352.12).

4.2.7. 6-Benzyl-5-methyl-2-(4-tert-butylbenzylthio)pyrimidin-4(3*H*)-one (4b7)

Yield 55%; mp 188–189 °C; white solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (s, 9H, $(CH_3)_3C$), 1.70 (s, 3H, 5-CH_3), 3.97 (s, 2H, $ArCH_2$), 4.36 (s, 2H, CH_2S), 7.20–7.34 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.72 (5-CH_3), 31.30 ($(CH_3)_3C$), 34.33 ($ArCH_2$), 34.50(CH_2S), 41.00 ($(CH_3)_3C$), 116.64 (C5), 125.46, 126.47, 128.49, 128.80, 128.98, 133.69, 137.89, 155.95 (Ar), 150.45 (C6), 161.88 (C2), 164.87 (C4); *m*/*z* (ESI): 379.0 $(M+H)^+$, 401.0 $(M+Na)^+$; $C_{23}H_{26}N_2O_2S$ (378.18).

4.2.8. 6-Benzyl-5-methyl-2-(naphthalen-2-ylmethyl thio)pyrimidin-4(3*H*)-one (4b8)

Yield 74%; mp 190.5–191.5 °C; white solid; ^1H NMR (500 MHz, DMSO-d_6) δ: 1.96 (s, 3H, 5-CH_3), 3.92 (s, 2H, $ArCH_2$), 4.52 (s, 2H, CH_2S), 7.19–7.26 (m, 5H, ArH), 7.43–7.50 (m, 3H, ArH), 7.76–7.89 (m, 4H, ArH), 12.61 (br s, 1H, NH); ^{13}C NMR (125 MHz, pyridine-d_5) δ: 10.79 (5-CH_3), 34.55 ($ArCH_2$), 40.96 (CH_2S), 115.86 (C5), 126.13, 126.40, 126.53, 127.56, 127.84, 127.94, 128.00, 128.47, 128.71, 129.25, 132.93, 133.62, 135.89, 138.84 (Ar), 157.85 (C6), 161.32 (C2), 164.72 (C4); *m*/*z* (ESI): 373.1 $(M+H)^+$, 395.1 $(M+Na)^+$; $C_{23}H_{20}N_2OS$ (372.13).

4.2.9. 6-Benzyl-5-methyl-2-(1-phenylethylthio)pyrimidin-4(3*H*)-one (4b9)

Yield 50%; mp 165–166 °C; white solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.68 (d, 3H, *J* = 7.2 Hz, CH_3CH), 2.03 (s, 3H, 5-CH_3), 3.94 (s, 2H, $ArCH_2$), 5.06 (q, 1H, *J* = 7.2 Hz, CH_3CH), 7.22–7.35 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.68 (5-CH_3), 22.06 (CH_3CH), 40.96 ($ArCH_2$), 44.73 (CH_3CHS), 116.65 (C5), 126.45, 127.41, 128.46, 128.52, 128.98, 137.91, 142.08 (Ar), 155.75 (C6), 161.93 (C2), 164.88 (C4); *m*/*z* (ESI): 337.0 $(M+H)^+$, 359.0 $(M+Na)^+$; $C_{20}H_{20}N_2OS$ (336.13).

4.2.10. 6-Benzyl-2-(ethoxymethylthio)-5-methyl pyrimidin-4(3*H*)-one (4b10)

Yield 33%; mp 129–130 °C; white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.19 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 2.13 (s, 1H, 5-CH_3), 3.55 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 3.95 (s, 2H, CH_2Ar), 5.38 (s, 2H, SCH_2O), 7.22–7.32 (m, 5H, ArH), 11.99 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.78 (5-CH_3), 14.70 (CH_2CH_3), 40.97 ($ArCH_2$), 65.19 (SCH_2O), 72.32 (OCH_2CH_3), 117.40 (C5), 126.50, 128.47, 128.56, 128.91, 129.18, 137.84 (Ar), 155.36 (C6), 161.90 (C2), 164.82 (C4); *m*/*z* (ESI): 291.0 $(M+H)^+$, 312.9 $(M+Na)^+$; $C_{15}H_{18}N_2O_2S$ (290.11).

4.2.11. 6-Benzyl-2-(benzyloxymethylthio)-5-methyl- pyrimidin-4(3*H*)-one (4b11)

Yield 38%; mp 153–155 °C; white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.14 (s, 3H, 5-CH_3), 3.95 (s, 2H, CH_2Ar), 4.59 (s, 2H, OCH_2Ar), 5.43 (s, 2H, SCH_2O), 7.12–7.52 (m, 1H, ArH), 11.57 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 10.80 (5-CH_3), 40.95 (CH_2Ar), 71.08 (SCH_2O), 71.75 (OCH_2Ar), 117.63 (C5), 126.53, 127.87, 128.36, 128.43, 128.63, 128.90, 129.33, 136.55, 137.76 (Ar), 154.97 (C6), 161.84 (C2), 164.49 (C4); *m*/*z* (ESI): 353.0 $(M+H)^+$, 391.0 $(M+K)^+$; $C_{20}H_{20}N_2O_2S$ (352.12).

4.2.12. 2-(Allylthio)-6-benzyl-5-methylpyrimidin-4(3*H*)-one (4b12)

Yield 53%; mp 150.5–151.5 °C; white solid; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.12 (s, 2H, 5-CH_3), 3.94 (s, 2H, CH_2Ar), 3.80 (d, 2H, *J* = 7.0 Hz, CH_2S), 5.09 (d, 1H, *J* = 10 Hz, CH=CH_2), 5.22 (d, 1H, *J* = 17.0 Hz, CH=CH_2), 5.87 (m, 1H, CH=CH_2), 7.23–7.33 (5H, m, ArH), 12.61 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.68 (5-CH_3), 33.31 (CH_2Ar), 41.05 (SCH_2), 118.45 (C5), 116.49 (CH=CH_2), 132.80 (CH=CH_2), 126.47, 128.44, 128.95, 137.91 (Ar), 155.81 (C6), 162.6 (C2), 165.4 (C4); *m*/*z* (ESI): 273.0 $(M+H)^+$; $C_{15}H_{16}N_2OS$ (272.10).

4.3. General procedure for the preparation of compounds 5a1–8

To a solution of **4a1–8** (0.1 mmol) in HOAc (1 ml) was added the PbO_2 (0.06 mmol) and I_2 (0.06 mmol), and the mixture were

stirred at room temperature for overnight. After completion of the reaction according to TLC analysis, the mixture was poured into H_2O (40 ml). The resulting solid was then filtered, washed with water, and purified by silica gel column chromatography to afford the white solid products **5a1–8**.

4.3.1. 6-Benzyl-2-(benzylthio)-5-iodopyrimidin-4(3*H*)-one (5a1)

Yield 92%; mp 175–177 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.23 (s, 2H, $ArCH_2$), 4.37 (s, 2H, CH_2S), 7.11–7.51 (m, 10H, ArH), 12.00 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.99 ($ArCH_2$), 47.12 ($ArCH_2S$), 85.64 (C5), 126.87, 127.64, 128.50, 128.62, 129.02, 136.28, 137.00 (Ar), 159.63 (C6), 161.82 (C4), 168.62 (C2); *m*/*z* (ESI): 435.0 $(M+H)^+$; $C_{18}H_{15}IN_2OS$ (433.99).

4.3.2. 6-Benzyl-5-iodo-2-(phenethylthio)pyrimidin-4(3*H*)-one (5a2)

Yield 70%; mp 175–177 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.95 (t, 2H, J = 7.5 Hz, SCH_2), 3.36 (t, 2H, J = 7.5 Hz, SCH_2CH_2), 4.24 (s, 2H, $ArCH_2$), 7.13–7.40 (m, 10H, ArH), 11.60 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.19 (CH_2S), 35.55 ($ArCH_2$), 47.16 ($ArCH_2CH_2S$), 85.61 (C5), 126.68, 126.87, 128.47, 128.57, 129.24, 137.10, 139.46 (Ar), 159.94 (C6), 161.69 (C2), 168.66 (C4); *m*/*z* (ESI): 449.2 $(M+H)^+$, 471.2 $(M+Na)^+$; $C_{19}H_{17}IN_2OS$ (448.01).

4.3.3. 6-Benzyl-5-iodo-2-(3-phenylpropylthio)pyrimidin-4(3*H*)-one (5a3)

Yield 45%; mp 155–156 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ:1.97 (quintet, 2H, J = 7.5 Hz, $CH_2CH_2CH_2$), 2.69 (t, 2H, J = 7.5 Hz, $ArCH_2CH_2$), 3.12 (t, 2H, J = 7.5 Hz, CH_2CH_2S), 4.17 (s, 2H, $ArCH_2$), 7.13–7.37 (m, 10H, ArH), 11.65 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.46 (CH_2S), 30.60 ($ArCH_2$), 34.64 (SCH_2CH_2), 47.10 ($CH_2CH_2CH_2S$), 85.26 (C5), 126.11, 126.81, 128.40, 128.44, 128.46, 129.30, 137.12, 140.82 (Ar), 160.07 (C6), 161.74 (C2), 168.62 (C4); *m*/*z* (ESI): 463.1 $(M+H)^+$, 485.1 $(M+Na)^+$; $C_{20}H_{19}IN_2OS$ (462.03).

4.3.4. 6-Benzyl-2-(2-methylbenzylthio)-5-iodo pyrimidin-4(3*H*)-one (5a4)

Yield 53%; mp 176–178 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.34 (s, 3H, $ArCH_3$), 4.23 (s, 2H, $ArCH_2$), 4.38 (s, 2H, CH_2S), 7.03–7.40 (m, 9H, ArH), 11.72 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.28 ($ArCH_3$), 33.36 (CH_2S), 47.13 ($ArCH_2$), 85.60 (C5), 126.22, 126.87, 128.01, 128.48, 129.31, 130.07, 130.54, 133.54, 136.94, 137.04 (Ar), 159.82 (C6), 161.82 (C2), 168.58 (C4); *m*/*z* (ESI): 449.1 $(M+H)^+$, 471.1 $(M+Na)^+$; $C_{19}H_{17}IN_2OS$ (448.01).

4.3.5. 6-Benzyl-5-iodo-2-(3-methylbenzylthio)pyrimidin-4(3*H*)-one (5a5)

Yield 78%; mp 182–183 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3H, $ArCH_3$), 4.21 (s, 2H, $ArCH_2$), 4.34 (s, 2H, CH_2S), 7.02–7.24 (m, 4H, ArH), 7.26–7.40 (m, 5H, ArH), 12.04 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.33 ($ArCH_3$), 35.03 ($ArCH_2$), 47.10 (CH_2S), 85.54 (C5), 126.10, 126.85, 128.48, 128.52, 129.30, 129.69, 136.07, 136.31, 136.99, 138.35 (Ar), 159.88 (C6), 162.06 (C2), 168.63 (C4); *m*/*z* (ESI): 449.1 $(M+H)^+$; $C_{19}H_{17}IN_2OS$ (448.01).

4.3.6. 6-Benzyl-2-(3-methoxybenzylthio)-5-iodo pyrimidin-4(3*H*)-one (5a6)

Yield 76%; mp 161.5–163 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.79 (s, 3H, OCH_3), 4.21 (s, 2H, $ArCH_2$), 4.35 (s, 2H, CH_2S), 6.82–6.87 (m, 3H, ArH), 7.16–7.19 (m, 1H, ArH), 7.26–7.39 (m, 5H, ArH), 12.08 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.06 (CH_2S), 47.11 (ArCH2), 55.23 (OCH_3), 85.59 (C5), 113.23, 114.57, 121.36, 126.85, 129.29, 129.64, 136.94, 137.62 (Ar), 159.76 (C6), 162.05 (C2), 168.66 (C4); *m*/*z* (ESI): 465.0 $(M+H)^+$; $C_{19}H_{17}IN_2O_2S$ (464.01).

4.3.7. 6-Benzyl-2-(4-tert-butylbenzylthio)-5-iodo pyrimidin-4(3*H*) one (5a7)

Yield 48%; mp 180–181 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (s, 9H, $(CH_3)_3C$), 4.24 (s, 2H, $ArCH_2$), 4.34 (s, 2H, CH_2S), 7.17–7.40 (m, 9H, ArH), 11.42 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.29 ($(CH_3)_3C$), 34.53 ($ArCH_2$), 34.75 (CH_2S), 47.13 ($(CH_3)_3C$), 85.70 (C5), 125.57, 126.85, 128.50, 128.77, 129.33, 133.07, 137.04, 150.72 (Ar), 159.69 (C6), 161.54 (C2), 168.53 (C4); *m*/*z* (ESI): 491.3 $(M+H)^+$, 513.2 $(M+Na)^+$; $C_{22}H_{23}IN_2OS$ (490.06).

4.3.8. 6-Benzyl-5-iodo-2-(naphthalen-2-ylmethylthio)pyrimidin-4(3*H*)-one (5a8)

Yield 85%; mp 205–206 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.33 (s, 2H, $ArCH_2$), 4.67 (s, 2H, CH_2S), 7.18–7.34 (m, 3, ArH), 7.45–7.60 (m, 5H, ArH), 7.82–7.92 (m, 4H, ArH), 8.71 (br s, 1H, NH); ^{13}C NMR (75 MHz, pyridine-d_5) δ: 34.88 ($ArCH_2$), 47.01 (CH_2S), 87.28 (C5), 126.23, 126.48, 126.86, 127.96, 128.02, 128.56, 128.68, 129.59, 132.97, 133.61, 135.36, 135.57, 138.04 (Ar), 161.32 (C6), 162.07 (C2), 167.39 (C4); *m*/*z* (ESI): 483.3 $(M-H)^-$; $C_{22}H_{17}IN_2OS$ (484.01).

4.4. Compounds 5a9–12 were prepared by the method used for 5a1–8

4.4.1. 6-Benzyl-5-bromo-2-(phenethylthio)pyrimidin-4(3*H*)-one (5a9)

Yield 60%; mp 154–156 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.95 (t, 2H, J = 7.5 Hz, SCH_2), 3.36 (t, 2H, J = 7.5 Hz, SCH_2CH_2), 4.17 (s, 2H, $ArCH_2$), 7.14–7.39 (m, 10H, ArH), 11.98 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 32.22 (CH_2S), 35.55 ($ArCH_2$), 43.33 ($ArCH_2CH_2S$), 107.72 (C5), 126.69, 126.91, 128.52, 128.58, 129.30, 130.93, 136.80, 139.47 (Ar), 158.76 (C6), 160.73 (C2), 164.77 (C4); *m*/*z* (ESI): 401.2 $(M+H)^+$, 403.1$(M+3)^+$; $C_{19}H_{17}BrN_2OS$ (400.02).

4.4.2. 6-Benzyl-5-bromo-2-(2-methylbenzylthio)pyrimidin-4(3*H*)-one (5a10)

Yield 62%; mp 175–177 °C; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (s, 3H, $ArCH_3$), 4.17 (s, 2 h, $ArCH_2$), 4.39 (s, 2H, CH_2S), 7.03–7.39 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.30 ($ArCH_3$), 33.41 (CH_2S), 43.30 ($ArCH_2$), 107.72 (C5), 126.23, 126.91, 128.13, 128.52, 129.37, 130.08, 130.54, 130.93, 133.48, 136.75, 136.95 (Ar), 159.65 (C6), 160.79 (C2), 164.78 (C4); *m*/*z* (ESI): 401.2 $(M+H)^+$, 403.1 $(M+3)^+$; $C_{19}H_{17}BrN_2OS$ (400.02).

4.4.3. 6-Benzyl-5-bromo-2-(3-methylbenzylthio)pyrimidin-4(3*H*)-one (5a11)

Yield 78%; mp 174–176 °C; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H, $ArCH_3$), 4.15 (s, 2H, $ArCH_2$), 4.34 (s, 2H, CH_2S), 7.04–7.17 (m, 4H, ArH), 7.26–7.37 (m, 5H, ArH), 11.91 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.35 ($ArCH_3$), 35.13 ($ArCH_2$), 43.32 (CH_2S), 107.77 (C5), 126.11, 126.91, 128.52, 128.53, 129.36, 129.69, 135.97, 136.71, 138.39 (Ar), 158.46 (C6), 160.66 (C2), 164.65 (C4); *m*/*z* (ESI): 401.0 $(M+H)^+$, 402.9 $(M+3)^+$; $C_{19}H_{17}BrN_2OS$ (400.02).

4.4.4. 6-Benzyl-5-bromo-2-(naphthalen-2-ylmethylthio)pyrimidin 4(3*H*)-one (5a12)

Yield 50%; mp 180–182 °C; white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.16 (s, 2H, $ArCH_2$), 4.55 (s, 2H, CH_2S), 7.25–7.37 (m, 6H, ArH), 7.48–7.51 (m, 2H, ArH), 7.73–7.84 (m, 4H, ArH); ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 35.44 ($ArCH_2$), 43.33 (CH_2S), 107.98 (C5), 126.18, 126.36, 126.78, 126.93, 127.69, 127.80, 128.55, 129.37, 133.20, 133.54, 136.66 (Ar), 158.56 (C6), 162.62 (C2), 165.04 (C4); *m*/*z* (ESI): 435.2 $(M-H)^-$, 437.1 $(M+1)^-$; $C_{22}H_{17}BrN_2OS$ (436.02).

Acknowledgements

We thank the National Science Foundation of China (20672008, 20972011) and Grants from the Ministry of Science and Technology of China (2005CB523103) for financial support.

References and notes

1. Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500.
2. Tronchet, J. M.; Seman, M. *Curr. Top. Med. Chem.* **2003**, *13*, 1496.
3. Tarby, C. *Curr. Top. Med. Chem.* **2005**, *4*, 1045.
4. Sluis-Cremer, N.; Alpay Temiz, N.; Bahar, I. *Curr. HIV Res.* **2004**, *2*, 323.
5. Campiani, G.; Ramunno, A.; Maga, G.; Nacci, V.; Fattorusso, C.; Catanalotti, E.; Morelli, E.; Novellino, E. *Curr. Pharm. Des.* **2002**, *8*, 615.
6. Talker, R. T.; Clercq, E. D. *Nucleosides Nucleotides* **1995**, *14*, 575.
7. Sankatsing, S. U.; Weverling, G. J.; Peeters, M.; Van't Klooster, G.; Gruzdev, B.; Rakmanova, A.; Danner, S. A.; Jurrianns, S.; Prins, J. M.; Lange, J. M. *AIDS* **2003**, *17*, 2623.
8. Botta, M.; Artico, M.; Massa, S.; Gambacorta, A.; Marogniu, M. E.; Pani, A.; La Colla, P. *Eur. J. Med. Chem.* **1992**, *27*, 251.
9. Artico, A. *Drugs Future* **2002**, *27*, 159.
10. Mai, A.; Artico, M.; Sbardella, G.; Massa, S.; Loi, A. G.; Tramontano, E.; Scano, P.; La Colla, P. *J. Med. Chem.* **1995**, *38*, 3258.
11. Mai, A.; Artico, M.; Sbardella, G.; Massa, S.; Novellino, E.; Greco, G.; Loi, A. G.; Tramontano, E.; Marogiu, M. E.; Ca Colla, P. *J. Med. Chem.* **1999**, *42*, 619.
12. Mai, A.; Artico, G.; Sbardella, G.; Quartarone, S.; Massa, S.; Loi, A. G.; De Montis, A.; Scintu, F.; Putzolu, M.; La Colla, P. *J. Med. Chem.* **1997**, *40*, 1447.
13. Ragno, R.; Mai, A.; Sbardella, S.; Artico, M.; Massa, S.; Musiu, C.; Mura, M.; Marceddu, T.; Cadeddu, A.; La Colla, P. *J. Med. Chem.* **2004**, *47*, 928.
14. He, Y.; Chen, F.; Sun, G.; Wang, Y.; De Clercq, E.; Balzarini, J.; Pannecouque, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3173.
15. Mai, A.; Artico, M.; Ragno, R.; Sbardella, G.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; Maga, G.; La Colla, P. *Bioorg. Med. Chem.* **2005**, *13*, 2065.
16. Manetti, F.; Jose, A. E.; Clotet-Codina, I.; Armand-Ugon, M.; Maga, G.; Crespan, E.; Cancio, R.; Mugnaini, C.; Bernardini, C.; Togninelli, A.; Carmi, C.; Alongi, M.; Petricci, E.; Massa, S.; Corelli, F.; Botta, M. *J. Med. Chem.* **2005**, *48*, 8000.
17. Mugnaini, C.; Manetti, F.; Este, J.; Clotet-Codina, I.; Maga, G.; Cancio, R.; Botta, M.; Corelli, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3541.
18. Togninelli, A.; Carmi, C.; Petricci, E.; Mugnaini, C.; Massa, S.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2006**, *47*, 57.
19. Ji, L.; Chen, F.; De Clercq, E.; Balzarini, J.; Pannecouque, C. *J. Med. Chem.* **2007**, *50*, 1778.
20. Radi, M.; Contemori, L.; Castagnolo, D.; Spinosa, R.; Este, J.; Massa, S.; Botta, M. *Org. Lett.* **2007**, *9*, 3157.
21. Mugnaini, C.; Alongi, M.; Togninelli, A.; Gevariya, H.; Brizzi, A.; Manetti, F.; Bernardini, C.; Angeli, L.; Tafi, A.; Bellucci, L.; Corelli, F.; Massa, S.; Maga, G.; Samuele, A.; Facchini, M.; Clotet-Codina, I.; Armand-Ugón, M.; Esté, J.; Botta, M. *J. Med. Chem.* **2007**, *50*, 6580.
22. Wang, Y.; Chen, F.; De Clercq, E.; Balzarini, J.; Pannecouque, C. *Bioorg. Med. Chem.* **2008**, *16*, 3887.
23. Mai, A.; Artico, M.; Rotili, D.; Tarantino, D.; Clotet-Codina, I.; Armand-Ugón, M.; Ragno, R.; Simeoni, S.; Sbardella, G.; Nawrozkij, M. B.; Samuele, A.; Maga, G.; Este, J. *J. Med. Chem.* **2007**, *50*, 5412.
24. Qin, H.; Liu, C.; Zhang, J.; Guo, Y.; Zhang, S.; Zhang, Z.; Wang, X.; Zhang, L.; Liu, J. *Bioorg. Med. Chem. Lett.* **2009**, doi:10.1016/j.bmcl.2009.04.051.
25. Mai, A.; Sbardella, G.; Artico, M.; Ragno, R.; Massa, S.; Novellino, E.; Greco, G.; Lavecchia, A.; Musiu, C.; La Colla, M.; Murgioni, C.; La Colla, P.; Loddo, R. *J. Med. Chem.* **2001**, *44*, 2544.
26. Auffinger, P.; Hays, F. A.; Westhof, E.; Ho, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16789.
27. Himmel, D. M.; Das, K.; Clark, A. D.; Hughes, S. H.; Benjahad, A.; Oumouch, S.; Guillemont, J.; Coupa, S.; Poncelet, A.; Csoka, I.; Meyer, C.; Andries, K.; Nguyen, C. H.; Grierson, D. S.; Arnold, E. *J. Med. Chem.* **2005**, *48*, 7582.
28. Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. *J. Comput. Chem.* **1998**, *19*, 1639.
29. Lu, Y.; Shi, T.; Wang, Y.; Yang, H.; Yan, X.; Luo, X.; Jiang, H.; Zhu, W. *J. Med. Chem.* **2009**, *52*, 2854.
30. Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.
31. Danel, K.; Larsen, E.; Pedersen, E. B. *Synthesis* **1995**, 934.
32. Danel, K.; Pedersen, E. B.; Nielsen, C. *J. Med. Chem.* **1998**, *41*, 191.
33. Lu, X.; Chen, Y.; Guo, Y.; Liu, Z.; Shi, Y.; Xu, Y.; Wang, X.; Zhang, Z.; Liu, J. *Bioorg. Med. Chem.* **2007**, *15*, 7399.