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Design, microwave-assisted synthesis and HIV-RT inhibitory activity of 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5-(un)substituted-pyrimidin-2-yl)-thiazolidin-4-ones

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ABSTRACT

A series of novel thiazolidin-4-ones bearing a hydrophobic substituent at 5-position on the 4,6-dimethylpyrimidine ring at N-3 (**5c–i** and **6c–i**) were designed on the prediction of QSAR studies, synthesized in good yields of 60.1–85.3% by microwave-assisted one-pot protocol with the combination of using dicyclohexylcarbonimide (DCC) as the promotor, and evaluated as HIV-1 reverse transcriptases inhibitors. The results of in vitro HIV-1 RT kit assay showed that some of the new compounds, such as **5c**, **6c**, **5d**, **6d**, **5g**, **5h** and **6i**, could effectively inhibit RT activity. Among them, compounds **5c** and **6c** where ethyl group existed at 5-position on N-3 pyrimidine ring were the best ones with the IC_{50} value of 0.26 μM and 0.23 μM, respectively. Structure-activity relationship analysis of these analogues suggested that the overall hydrophobicity and steric factor were important to the anti-HIV RT activity. The mechanism of the intramolecular cycloamidation promoted by DCC was also investigated with the key uncyclized intermediate **13**.

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1. Introduction

2,3-(Diaryl-substituted)-1,3-thiozolidin-4-one scaffold, a mimic of thiazolobenzimidazole (TBZ) (**1** and **2**) (Fig. 1) has drawn many attentions due to its' potent and selective inhibition against the HIV-1 and low toxicity by binding to the allosteric site of the reverse transcriptase (RT) as a non-nucleoside RT inhibitor (NNRTI).[1–8] Recently, the systematic QSAR study revealed that the overall hydrophobicity of the molecule, and steric and electronic features of *meta*-/*para*-substituents on N-3-aryl moiety were important to enhance the biological activity.[9–14] For examples, the thiazolidin-4-ones bearing a lipophilic adamantyl substituent have exhibited good anti-HIV activity,[15,16] and a series of 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-pyrimidin-2-yl) thiazolidin-4-ones (**3**–**6**) have been observed with higher anti-HIV activity compared to the other aryl substituted ones (Fig. 1).[17–21] Among them, **4a**, **5b** and **6b** exhibited the most activity and high selectivity index (**4a**: EC_{50} = 0.02 ± 0.01 μM, CC_{50} = 184.76 ± 42.22 μM, SI = 7123; **5b**: EC_{50}=0.03 ± 0.02 μM, CC_{50} > 320 μM, SI > 11456; **6b**: EC_{50} = 0.02 ± 0.01 μM, CC_{50} = 216.2 ± 53.5 μM, SI = 8669), implying that they would be potential anti-HIV drug candidates.[17,18] These promising antiviral activities of **3**–**6** demanded to synthesize their novel derivatives to meet the ever-growing requirements for the structure–activity relationship (SAR) study and the anti-HIV drug discovery. Therefore, in this paper the compounds possessing *para*-alkyl substituent of N-3-pyrimidine moiety (**5c–i** and **6c–i**) were designed, synthesized and evaluated for HIV-RT inhibitory activity for further investigating the SAR analysis between the RT inhibitory activity and the hydrophobicity of the thiazolidin-4-one derivatives.

2,3-Diaryl-1,3-thiozolidin-4-one derivatives have been conveniently synthesized by the three component one-pot reaction with aromatic amine, aromatic aldehyde and mercaptoacetic acid in refluxing toluene.[22] Some new synthetic methods and reagents such as microwave-assisted,[23–25] DCC,[26] Hünig's base,[27] ion liquids,[28] and KSF clay[29] have been used for effectively improving the synthesis of such compounds. For instance, in the case of **3**–**6** bearing a 4,6-dimethylpyrimidinyl group, while the reaction could not provide satisfactory result with moderate yields in refluxing toluene for long time (24–48 h) probably due to the low reactivity of the 2-aminopyrimidine,[1,18] under microwave-irradiation the synthesis could produce **5a** in yield of 56% within 12 min.[23] More recently, we have also reported an efficient microwave assisted synthesis of 2,3-diaryl-1,3-thiozolidin-4-ones.[30,31] Herein, we would like to present an improved microwave assisted synthesis of 2-(2,6-dihalophenyl)-3-(5-(un)substitued-4,6-dimethyl pyrimidin-2-yl)thiazolidin-4-ones (**5** and **6**) in good yields promoted by DCC (Scheme 1), and the reaction process of such intramolecular cycloamidation via the key uncyclized intermediate **13**.

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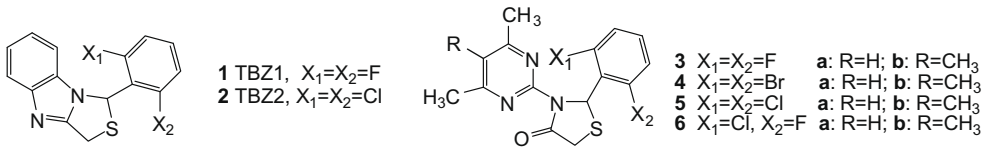
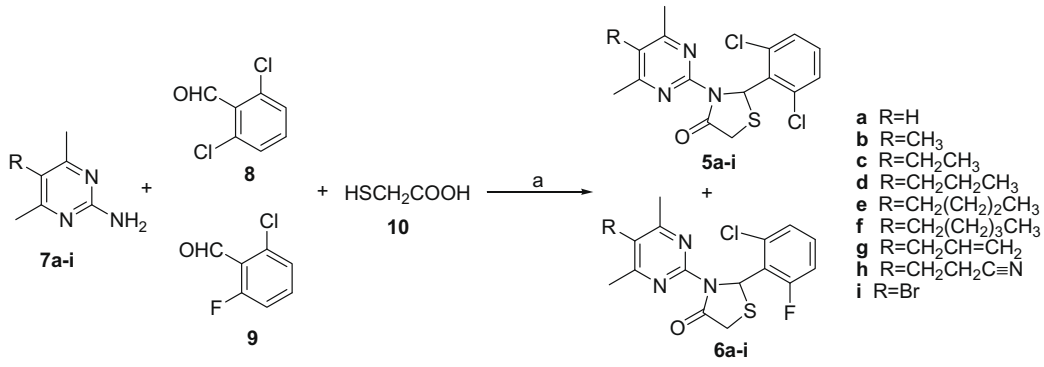


Figure 1. Structures of TBZ (**1** and **2**) and 2-(2,6-dihalorophenyl)-3-(pyrimidin-2-yl) thiazolidin-4-ones (**3**–**6**).



Scheme 1. Synthesis of **5** and **6**. Reagents and conditions (a) (1) MW, 140 °C in sealed tube, 10 min, **7a**:**8**:**10** = 1:1:2; (2) MW, 140 °C in sealed tube, 2 equiv DCC, 5 min.

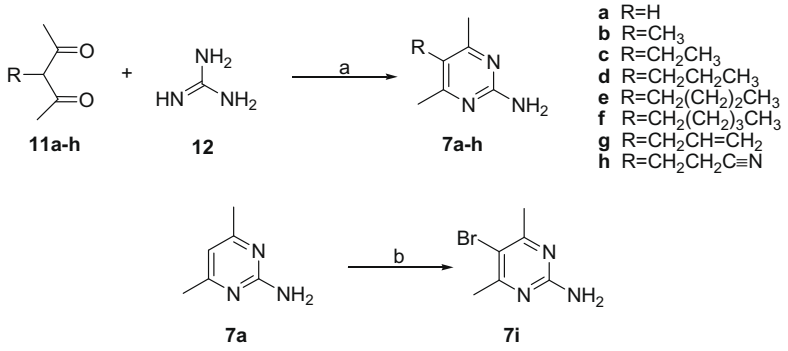
2. Result and discussion

2.1. Chemistry

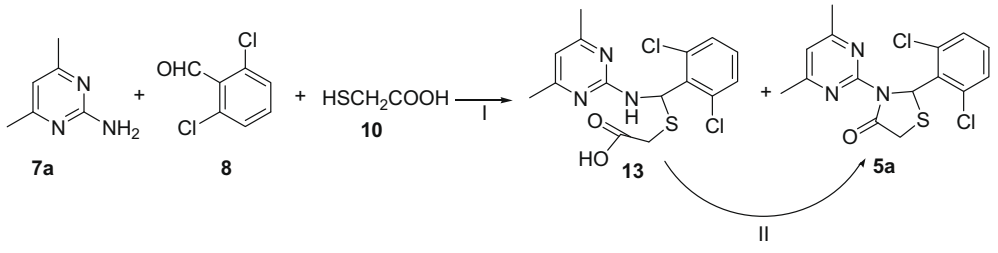
The 2-aminopyrimidines (**7a–h**) were prepared by refluxing an ethanolic solution of free base guanidine (**12**) with different 1,3-dicarbonyl compounds (**11a–h**) as shown in Scheme 2 according to the literature,[32] and the synthesis of 2-amino-4,6-dimethyl-5-bromopyrimidine (**7i**) was carried out according to the reported procedure (Scheme 2).[33]

The synthesis of 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5-(un)substituted-pyrimidin-2-yl) thiazolidin-4-ones (**5** and **6**) was firstly examined for optimizing the reaction condition as exampli-fied with (**5a**) using **7a**, **8** and **10** as the starting materials under microwave irradiation following our reported procedure[30,31] (Scheme 3 and Table 1). However, the reaction could not proceed effectively with a poor yield of the desired product **5a**, insteadly, an uncyclized addition intermediate **13** was obtained as a predominant product.

According to the proposed mechanism of the reaction (Scheme 3), the intermediate **13** was produced from the nucleophilic addition of mercaptoacetic acid **10** to the imine in situ generated from **7a** and **8**, and further intramolecular condensation of **13** would afford the desired product **5a**. The results (Table 1) indicated that the reactivity for **13** to form the target product **5a** was not so high possibly because of the existence of the electron deficient pyrimidine



Scheme 2. Synthesis of 2-aminopyrimidines **7**. Reagents and conditions: (a) anhydrous EtOH, reflux, 8 h, 8.8–85.2% yields; (b) Br_2, anhydrous $CHCl_3$, rt, stirred in the dark, 20 h, 65.1% yields.



Scheme 3. Synthesis of compound **5a**.

Table 1
The microwave assisted synthesis of **5a**

Entry	Temperature (°C)	Time (min)	Yield[a] of **5a** (%)	Yield[a] of **13** (%)
1	140 °C in sealed tube[b]	10	13.6	67.8
2	Reflux	20	10.5	63.2
3	140 °C in sealed tube	10[c]	33.7	31.5

[a] Isolated yield.
[b] All the reaction could proceeded with the reactant ratio of **7a**:**8**:**10** = 1:1:2 in dry toluene under microwave irradiation.
[c] Total reaction time: after the condensation of **7a** and **8** was carried out at 140 °C in sealed tube stirring for 5 min, mercaptoacetic acid **10** was added for other 5 min.

group. Accordingly, we examined the cycloamidation of **13** by using Lewis acid catalysts, condensation agent and microwave irradiation for promotion (Table 2). Although Lewis acids could not catalyze the cyclo-condensation, DCC has remarkably promoted the reaction. Furthermore by using the combination of the condensation agent (DCC) and microwave irradiation the cycloamidation of **13** could proceed very effectively and provided **5a** in excellent yield of 80.2% (Table 2, entry 4). Subsequently, we approached the microwave assisted one-pot three components reaction with **7a**, **8** and **10** in the presence of DCC, but the yield of **5a** was 18.5% without detecting the intermediate **13** (entry 5). Considering above results, the one-pot synthesis would take place with two steps as shown in Scheme 3. Firstly, the mixture of **7a**, **8** and **10** was irradiated to form the intermediate **13** with minor product **5a** (Scheme 3 step I), then a certain amount of DCC was added to the reaction mixture and the reaction mixture was exposured to microwave irradiation again for a given time to afford the product **5a** in good yield (Scheme 3 step II). It should be noted that the additional solvent should be added to dissolve DCC and to decrease the concentration of the final mixture solution from 1.0 mmol/mL to 0.25 mmol/mL. With this procedure, the reaction conditions were optimized by examining the equivalent of DCC, the reaction time and the temperature (Table 2).

Thus, the one-pot three component synthesis could proceed effectively firstly with the reactant ratio of **7a**:**8**:**10** = 1:1:2 at 140 °C in dry toluene in sealed tube under microwave irradiation for 10 min, subsequently, DCC (2 equiv) was added and some dry toluene was added again which made the concentration of the reaction mixture to be in 0.25 mmol/mL, and then the reaction solution was irradiated for another 5 min. After simply work up and purification by silica gel column chromatography, the product **5a** was obtained in the high yield of 73.7%. Under the same conditions, the compounds **5** and **6** were synthesized in the yields of 60.1–85.3% within 15 min, providing a convenient and practical one pot procedure for accessing to 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5-(un)substituted-pyrimidin-2-yl)thiazolidin-4-ones (Table 3).

All the synthesized compounds were characterized by spectroscopic methods and elemental analysis.

2.2. HIV-RT inhibitory activity evaluation

All the new compounds (**5c–i** and **6c–i**) were evaluated for HIV-RT inhibitory activity in HIV-RT kit[34] by comparison with the documented compounds **5b** and **6b** (the most active ones among the reported thiozolidin-4-one derivatives), and the results are showed in Table 4.

It could be seen from the table that most of the new compounds showed notable HIV-RT inhibitory activity, such as **5c**, **6c**, **5d**, **6d**, **5g**, **5h** and **6i**. Among them, compound **5c** and **6c** where ethyl group existed at 5-position on the pyrimidine ring at N-3 showed a more significant HIV-RT inhibitory activity and their IC_{50} values were 0.26 μM and 0.23 μM, respectively, even better than those of the known analogues **5b** and **6b** (IC_{50}: 0.83 μM and 0.38 μM,

Table 2
The synthesis of **5a**

Entry	Lewis acid (equiv)	Condensation agent (equiv)	Solvent	Conditions	Time (min)	Yield of **5a** (%)
1[a]	Na_2SO_4 (1)	—	THF	rt	30	Trace
2[a]	$ZnCl_2$ (1)	—	THF	rt	30	Trace
3[a]	—	DCC (1)	THF	rt	30	41.8
4[a,b]		DCC (1)	Toluene	140 °C, MW	10	80.2
5[c]	—	DCC (2)	Toluene	140 °C, MW	10	18.5
6[d]	—	DCC (2)	Toluene	140 °C, MW	10	56.3
7	—	DCC (2)	Toluene	140 °C, MW	5	73.7
8	—	DCC (2)	Toluene	140 °C, MW	2.5	48.8
9	—	DCC (2)	Toluene	150 °C, MW	5	50.5
10	—	DCC (2)	Toluene	130 °C, MW	5	71.2
11	—	DCC (2)	Toluene	120 °C, MW	5	65.5

[a] The reaction was carried out with the pure **13** as the starting material.
[b] The reaction was performed in sealed tube under MW.
[c] All the reactants were added at the same time. The reaction conditions were same with those in entry 1 (Table 1).
[d] DCC was added in step II in Scheme 3 and the corresponding conditions were discussed. The reactions were performed in sealed tube under MW. The conditions of step I were also same with those in entry 1 (Table 1).

Table 3
The microwave assisted synthesis of **5** and **6**

R	Yield of **5** (lit.) (%)	Mp of **5** (lit.) (°C)	Yield of **6** (lit.) (%)	Mp of **6** (lit.) (°C)
a	73.7 (56[23])	208.5–210.5 (200–202[23])	85.3(22[1])	162.0–164.0 (165–166[1])
b	73.8 (56[18])	208.5–210.5 (202–204[18])	82.5(50[18])	178.0–179.5 (199–200[14])
c	70.2	174.5–176.5	80.8	127.0–128.5
d	67.0	139.5–141.0	71.1	154.0–155.5
e	71.4	139.5–141.5	70.6	110.0–112.5
f	63.7	128.5–130.0	63.2	129.5–131.5
g	66.1	135.5–137.5	67.8	110.0–111.5
h	60.1	195.3–197.2	67.3	182.6–184.2
i	71.5	199.0–201.0	70.9	153.5–155.0

Table 4
HIV-RT kit assay for compounds (**5b–i** and **6b–i**)

Compounds	R	IC_{50} (μM) (HIV-RT kit assay)	Compounds	IC_{50} (μM) (HIV-RT kit assay)
5b	CH_3	0.83 ± 0.03	**6b**	0.38 ± 0.09
5c	CH_2CH_3	0.26 ± 0.02	**6c**	0.23 ± 0.04
5d	$CH_2CH_2CH_3$	0.77 ± 0.35	**6d**	0.85 ± 0.35
5e	$CH_2(CH_2)_2CH_3$	4.29 ± 3.57	**6e**	15.96 ± 3.99
5f	$CH_2(CH_2)_3CH_3$	74.39 ± 4.42	**6f**	16.15 ± 4.95
5g	$CH_2CH{=}CH_2$	1.22 ± 0.15	**6g**	2.92 ± 0.14
5h	$CH_2\ CH_2C{\equiv}N$	1.02 ± 0.13	**6h**	2.01 ± 0.57
5i	Br	9.82 ± 2.67	**6i**	1.52 ± 0.25

respectively), implying that **5c** and **6c** may be better accommodated into the HIV-1 RT allosteric binding site. It's also suggested that the compounds with high hydrophobicity would be better for the HIV-RT inhibitory activity. However, as the alkyl chain of R group at 5-position on the pyrimidine ring prolonged, the RT inhibitory activity decreased. For instance, the introduction of 5-pentyl (**5f** and **6f**) led to a markedly loss in the activity, which indicated that the bulky substituents at this position, such as butyl and pentyl group, would be a detrimental effect in anti-HIV-RT activity. In the cases of 5-propyl (**5d** and **6d**), 5-allyl (**5g** and **6g**) and 5-propanenitrile group (**5h** and **6h**), their activity were lightly decreased. Furthermore, compounds **5h** and **6h** with nitrile group are more active than **5g** and **6g** bearing a double bond, respectively, although the former have the more bulky substituent ($CH_2CH_2C{\equiv}N$) then that ($CH_2CH{=}CH_2$) of the later at 5-position on the pyrimidine ring at N-3. The inhibitory activity of compounds **5i** and **6i** is less active than those of **5b** and **6b**, suggesting that the hydrophobic but electron withdrawing halo atom such as Br at 5-position on the pyrimidine ring at N-3 may be unfavorable to anti-HIV-RT activity. The above structure–activity relationships (SAR) analysis may be helpful to guide further modification of thiazolidinone analogs.

In conclusion, this paper presented an improved microwave-assisted one-pot protocol combining with the use of DCC for synthesizing 2-(2,6-dihalophenyl)-3-(4,6-dimethyl-5-(un)substituted-pyrimidin-2-yl) thiazolidin-4-ones in good yields. A majority of the new compounds, such as **5c**, **6c**, **5d**, **6d**, **5g**, **5h** and **6i**, showed notable HIV-1 RT inhibitory activity and compound **5c** and **6c** were the best ones with the IC_{50} value of RT inhibitory activities of 0.26 μM and 0.23 μM, respectively, higher than those of **5b** and **6b**. SAR analysis indicated that the results were in agreement with those predicted by molecular modeling studies[9–14] which suggested the overall hydrophobicity of the analogues, and steric and electronic features of *meta*-/*para*-substituents of 3-hetero-aryl moiety on thiazolidin-4-one led to a substantial increase in antiviral activity. The further synthesis and biological activity measurement are under way.

3. Experimental

3.1. General experimental procedures

All microwave-assisted reactions were carried out on a CEM Discover S-Class Synthesizer (CEM Co. Ltd, USA). Melting points were measured in an open capillary on a SGW® X-4 melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz in $CDCl_3$ solutions on a AC-P400 Bruker FT-NMR spectrometer. The chemical shifts are as parts per million (δ ppm) from TMS as an internal standard. ESI-MS were determined using a Quayyro mass spectrometer, and signals were recorded in m/z. IR spectra were determined on a WQF-510 as KBr tablets for solid samples and were expressed in cm^{-1} scale. Element analysis was performed using a Hekaeus (CHNO, rapid) elemental analyzer. The optical densities for examining the activities of HIV-RT inhibition was measured on a BioRad Model 3550 microplate spectrophotometer. The silica gel (300–400 mesh) for flash column chromatography was from Qingdao Marine Chemical (China).

3.2. The synthesis of compounds 7a–i

The synthesis of compounds **7a–h** was carried out according to the reported procedure,[32] and the synthesis compound **7i** was proceeded as the literature.[33]

3.2.1. 2-Amino-4,6-dimethylpyrimidine (7a)

White solid, 85.2%, mp 152–153 °C, lit. mp 152–154 °C,[35] ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.52 (s, 2H, NH_2), 2.35 (s, 6H, $2CH_3$), 6.22 (s, 1H, Ar-H).

3.2.2. 2-Amino-4,5,6-trimethylpyrimidine (7b)

White solid, 70.5%, mp 206–208 °C, lit. mp 208 °C,[32] ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.03 (s, 2H, NH_2), 2.28 (s, 6H, $2CH_3$), 2.05 (s, 3H, CH_3).

3.2.3. 2-Amino-4,6-dimethyl-5-ethylpyrimidine (7c)

White solid, 32.8%, mp 142–144 °C, lit. mp 148–149 °C,[32] ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.97 (s, 2H, NH_2), 2.32 (s, 6H, $2CH_3$), 1.07 (t, 3H, J = 7.2 Hz, CH_3), 2.54–2.48 (q, 2H, J = 7.2 Hz, CH_2).

3.2.4. 2-Amino-4,6-dimethyl-5-propylpyrimidine (7d)

White solid, 26.3%, mp 160-162 °C, lit. mp 165–167 °C,[36] ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.90 (s, 2H, NH_2), 2.33 (s, 6H, $2CH_3$), 0.99 (t, 3H, J = 7.2 Hz, CH_3), 1.52–1.42 (m, 2H, CH_2), 2.47(t, 2H, J = 7.6 Hz, CH_2).

3.2.5. 2-Amino-4,6-dimethyl-5-butylpyrimidine (7e)

White solid, 24.1%, mp 109–110 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.85 (s, 2H, NH_2), 2.33 (s, 6H, $2CH_3$), 0.96 (t, 3H, J = 7.2 Hz, CH_3), 1.41–1.45 (m, 4H, $2CH_2$), 2.48 (t, 2H, J = 7.6 Hz, CH_2). MS (ESI) m/z: 180.2 ($[M+H]^+$).

3.2.6. 2-Amino-4,6-dimethyl-5-pentylpyrimidine (7f)

White solid, 15.7%, mp 150–151 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.88 (s, 2H, NH_2), 2.33 (s, 6H, $2CH_3$), 0.91 (t, 3H, J = 6.8 Hz, CH_3), 1.35–1.44 (m, 6H, $3CH_2$), 2.48 (t, 2H, J = 7.6 Hz, CH_2). MS (ESI) m/z: 194.4 ($[M+H]^+$).

3.2.7. 2-Amino-4,6-dimethyl-5-allylpyrimidine (7g)

White solid, 22.4%, mp 129–131 °C, lit. mp 131–134 °C,[36] ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.85 (s, 2H, NH_2), 2.34 (s, 6H, $2CH_3$), 3.27 (d, 2H, J = 4.8 Hz, CH_2), 4.78 (d, 1H, J = 17.2 Hz, $=CH_2$), 5.02 (d, 1H, J = 10.4 Hz, $=CH_2$), 5.72–5.82 (m, 1H, $=CH$).

3.2.8. 2-Amino-4,6-dimethyl-5-propanenitrilepyrimidine (7h)

White solid, 8.8%, mp decomposed at 209 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.68 (t, 2H, J = 4.8 Hz, CH_2), 2.46 (t, 2H, J = 4.8 Hz, CH_2), 2.21 (s, 6H, CH_3). MS (ESI) m/z: 177.1 ($[M+H]^+$).

3.2.9. 2-Amino-4,6-dimethyl-5-bromopyrimidine (7i)

White solid, 65.1%, mp 180–182 °C, lit. mp 186–188 °C,[33] ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.10 (s, 2H, NH_2), 2.43 (s, 6H, $2CH_3$).

3.3. The synthesis of compound 13

A mixture of 2-amino-4,6-dimethylpyrimidine compound (**7a**) (0.5 mmol), 2,6-dichlorophenyl aldehyde **8** (0.5 mmol) and mercaptoacetic acid **10** (1.0 mmol) were stirred at 140 °C using dry toluene (0.5 mL) as solvent in sealed tube by irradiating in a CEM Discover S-Class Synthesizer for 10 min. After cooled to room temperature, a yellow solid was precipitated, which was crystallized from ethanol to afford compound.

3.3.1. 2-((4,6-Dimethylpyrimidin-2-ylamino)(2,6-dichlorophenyl)methylthio)acetic acid (13)

White solid, 67.8%, mp: decomposed at 190 °C, IR (KBr) ν: 1702 cm^{-1} (C=O); 3279 cm^{-1} (NH); 3458 cm^{-1} (OH), ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.56 (brs, 1H, COOH), 7.45 (m, 2H, CH; NH), 7.01–7.33 (m, 3H, Ar-H), 6.49 (s, 1H, pyrimidinyl-H), 3.70 (d, 1H, J = 16.2 Hz, CH_2), 3.93 (d, 1H, J = 16.2 Hz, CH_2), 2.22 (s, 6H, CH_3). MS (ESI) m/z: 372.4 ([M+H]$^+$). Anal. Calcd for $C_{15}H_{15}Cl_2N_3O_2S$: C, 48.40; H, 4.06; N, 11.29; Found: C, 48.32; H, 4.10; N, 11.32.

3.4. General procedure for the synthesis of compounds 5 and 6

A mixture of 5-(un)substituted-2-amino-4,6-dimethylpyrimidine compounds (**7a-i**) (0.5 mmol), aromatic aldehydes (0.5 mmol) and mercaptoacetic acid (1.0 mmol) were firstly stirred at 140 °C using dry toluene (0.5 mL) as solvent in sealed tube by irradiating in a CEM Discover S-Class Synthesizer for 10 min. Subsequently, DCC (206 mg) and additional dry toluene were added and the last concentration was 0.25 mmol/mL. The mixture were stirred at 140 °C in sealed tube by irradiating microwave for 5 min reaction. Then, after cooled to room temperature, DCU was removed by filtration and the mixture was neutralized with solid K_2CO_3. Solvent was removed under reduced pressure to get a crude product, which was isolated by silica gel column chromatography eluting with cyclohexane–ethyl acetate as eluent. Compounds **5** and **6** were obtained as white solids.

3.4.1. 2-(2,6-Dichlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5a)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47 (s, 1H, CH), 7.28–7.05 (m, 3H, Ar-H), 6.72 (s, 1H, pyrimidinyl-H), 4.16 (d, 1H, J = 15.8 Hz, CH_2), 3.93 (d, 1H, J = 15.8 Hz, CH_2), 2.36 (s, 6H, CH_3).

3.4.2. 2-(2,6-Dichlorophenyl)-3-(4,5,6-trimethylpyrimidin-2-yl)thiazolidin-4-one (5b)

^{1}H NMR ($CDCl_3$) δ: 7.47 (d, 1H, J = 1.7 Hz, CH), 7.28–7.06 (m, 3H, Ar-H), 4.16 (dd, 1H, J = 15.7 Hz, 2.0 Hz, CH_2), 3.93 (d, 1H, J =15.7 Hz, CH_2), 2.36 (s, 3H, CH_3), 2.10 (s, 6H, CH_3).

3.4.3. 2-(2,6-Dichlorophenyl)-3-(5-ethyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5c)

IR (KBr) ν: 1710 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.46 (d, 1H, J = 1.8 Hz, CH), 7.29–7.06 (m, 3H, Ar-H), 4.16 (dd, 1H, J = 15.7 Hz, 2.0 Hz, CH_2), 3.92 (d, 1H, J = 15.7 Hz, CH_2), 2.54 (q, 2H, J = 7.2 Hz, CH_2), 2.39 (s, 6H, CH_3), 1.06 (t, 3H, J = 7.2 Hz, CH_3). MS (ESI) m/z: 404.9 ([M+Na]$^+$). Anal. Calcd for $C_{17}H_{17}Cl_2N_3OS$: C, 53.41; H, 4.48; N, 10.99. Found: C, 53.37; H, 4.41; N, 11.05.

3.4.4. 2-(2,6-Dichlorophenyl)-3-(5-propyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5d)

IR (KBr) ν: 1710 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.46 (d, 1H, J = 1.8 Hz, CH), 7.29–7.06 (m, 3H, Ar-H), 4.16 (dd, 1H, J = 15.7 Hz, 2.0 Hz, CH_2), 3.93 (d, 1H, J = 15.7 Hz, CH_2), 2.50–2.43 (m, 2H, CH_2), 2.38 (s, 6H, CH_3), 1.49–1.39 (q, 2H, J = 7.2 Hz, CH_2), 1.08–1.04 (t, 3H, J = 7.2 Hz, CH_3). MS (ESI) m/z: 419.3 ([M+Na]$^+$). Anal. Calcd for $C_{18}H_{19}Cl_2N_3OS$: C, 54.55; H, 4.83; N, 10.60. Found: C, 54.62; H, 4.81; N, 10.55.

3.4.5. 2-(2,6-Dichlorophenyl)-3-(5-butyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5e)

IR (KBr) ν: 1722 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.45 (d, 1H, J = 1.9 Hz, CH), 7.28–7.05 (m, 3H, Ar-H), 4.15 (dd, 1H, J = 15.7 Hz, 2.0 Hz, CH_2), 3.92 (d, 1H, J = 15.7 Hz, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.37 (s, 6H, CH_3), 1.38–1.36 (m, 4H, CH_2), 0.94–0.90 (t, 3H, J = 6.8 Hz, CH_3). MS (ESI) m/z: 433.0 ([M+Na]$^+$). Anal. Calcd for $C_{19}H_{21}Cl_2N_3OS$: C, 55.61; H, 5.16; N, 10.24. Found: C, 55.58; H, 5.10; N, 10.31.

3.4.6. 2-(2,6-Dichlorophenyl)-3-(5-pentyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5f)

IR (KBr) ν: 1722 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.46 (d, 1H, J = 1.9 Hz, CH), 7.28–7.06 (m, 3H, Ar-H), 4.16 (dd, 1H, J = 15.7 Hz, 2.0 Hz, CH_2), 3.93 (d, 1H, J = 15.7 Hz, CH_2), 2.53–2.42 (m, 2H, CH_2), 2.38 (s, 6H, CH_3), 1.41–1.32 (m, 6H, CH_2), 0.87–0.91 (t, 3H, J = 6.8 Hz, CH_3). MS (ESI) m/z: 447.4 ([M+Na]$^+$). Anal. Calcd for $C_{20}H_{23}Cl_2N_3OS$: C, 56.60; H, 5.46; N, 9.90. Found: C, 56.52; H, 5.47; N, 9.86.

3.4.7. 2-(2,6-Dichlorophenyl)-3-(5-allyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5g)

IR (KBr) ν: 1710 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.47 (s, 1H, CH), 7.27–7.07 (m, 3H, Ar-H), 5.72–5.82 (m, 1H, =CH), 5.02 (d, 1H, J = 10.4 Hz, =CH_2), 4.78 (d, 1H, J = 17.2 Hz, =CH_2), 4.15 (dd, 1H, J = 15.6 Hz, 1.6 Hz, CH_2), 3.93 (d, 1H, J = 14.8 Hz, CH_2), 3.26–3.27 (m, 2H, CH_2), 2.36 (s, 6H, CH_3). MS (ESI) m/z: 416.8 ([M+Na]$^+$). Anal. Calcd for $C_{18}H_{17}Cl_2N_3OS$: C, 54.83; H, 4.35; N, 10.66. Found: C, 54.91; H, 4.34; N, 10.71.

3.4.8. 2-(2,6-Dichlorophenyl)-3-(5-propanenitrile-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5h)

IR (KBr) ν: 1718 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.44 (s, 1H, CH), 7.30–7.07 (m, 3H, Ar-H), 4.19 (dd, 1H, J = 16.0 Hz, 2.0 Hz, CH_2), 3.93 (d, 1H, J = 15.6 Hz, CH_2), 2.95 (t, 2H, J = 7.6 Hz, CH_2), 2.48 (t, 2H, J = 7.6 Hz, CH_2), 2.44 (s, 6H, CH_3). MS (ESI) m/z: 428.3 ([M+Na]$^+$). Anal. Calcd for $C_{20}H_{18}Cl_2N_2OS$: C, 59.26; H, 4.48; N, 6.91. Found: C, 59.41; H, 4.40; N, 6.99.

3.4.9. 2-(2,6-Dichlorophenyl)-3-(5-bromo-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (5i)

IR (KBr) ν: 1727 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ: 7.42 (d, 1H, J = 1.6 Hz, CH), 7.31–7.08 (m, 3H, Ar-H), 4.16 (dd, 1H, J = 15.6 Hz, 1.6 Hz, CH_2), 3.93 (d, 1H, J = 15.8 Hz, CH_2), 2.48 (s, 6H, CH_3). MS (ESI) m/z: 456.1 ([M+Na]$^+$). Anal. Calcd for $C_{15}H_{12}BrCl_2N_3OS$: C, 41.59; H, 2.79; N, 9.70. Found: C, 41.54; H, 2.77; N, 9.68.

3.4.10. 2-(2-Chloro-6-fluorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6a)

^{1}H NMR ($CDCl_3$) δ: 7.15–7.12 (m, 3H, Ar-H; CH), 6.93–6.90 (m, 1H, Ar-H), 6.72 (s, 1H, pyrimidinyl-H), 4.17 (d, 1H, J = 15.8 Hz, CH_2), 3.84 (d, 1H, J = 14.7 Hz, CH_2), 2.36 (s, 6H, CH_3).

3.4.11. 2-(2-Chloro-6-fluorophenyl)-3-(4,5,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6b)

^{1}H NMR ($CDCl_3$) δ: 7.17–7.13 (m, 3H, Ar-H; CH), 6.95–6.90 (m, 1H, Ar-H), 4.18 (d, 1H, J = 15.7 Hz, CH_2), 3.85 (d, 1H, J = 14.8 Hz, CH_2), 2.37 (s, 3H, CH_3), 2.11 (s, 6H, CH_3).

3.4.12. 2-(2-Chloro-6-fluorophenyl)-3-(5-ethyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6c)

IR (KBr) ν: 1714 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.17–7.13 (m, 3H, Ar-H; CH), 6.95–6.90 (m, 1H, Ar-H), 4.18 (d, 1H, J = 15.7 Hz, CH_2), 3.85 (d, 1H, J = 14.1 Hz, CH_2), 2.56 (q, 2H, J = 7.6 Hz, CH_2), 2.40 (s, 6H, CH_3), 1.07 (t, 3H, J = 7.6 Hz, CH_3). MS (ESI) m/z: 389.2 ($[M+Na]^+$). Anal. Calcd for $C_{17}H_{17}ClFN_3OS$: C, 55.81; H, 4.68; N, 11.49. Found: C, 55.73; H, 4.62; N, 11.54.

3.4.13. 2-(2-Chloro-6-fluorophenyl)-3-(5-propyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6d)

IR (KBr) ν: 1712 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.15–7.13 (m, 3H, Ar-H; CH), 6.95–6.90 (m, 1H, Ar-H), 4.18 (d, 1H, J = 15.7 Hz, CH_2), 3.85 (d, 1H, J = 15.3 Hz, CH_2), 2.49 (t, 2H, J = 7.8 Hz, CH_2), 2.39 (s, 6H, CH_3), 1.45 (q, 2H, J = 7.2 Hz, CH_2), 0.97 (t, 3H, J = 7.2 Hz, CH_3). MS (ESI) m/z: 402.9 ($[M+Na]^+$). Anal. Calcd for $C_{18}H_{19}ClFN_3OS$: C, 56.91; H, 5.04; N, 11.06. Found: C, 56.95; H, 5.12; N, 11.07.

3.4.14. 2-(2-Chloro-6-fluorophenyl)-3-(5-butyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6e)

IR (KBr) ν: 1712 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.17–7.14 (m, 3H, Ar-H; CH), 6.95–6.90 (m, 1H, Ar-H), 4.18 (dd, 1H, J = 15.7 Hz, 1.6 Hz, CH_2), 3.84 (d, 1H, J = 14.9 Hz, CH_2), 2.55–2.48 (m, 2H, CH_2), 2.39 (s, 6H, CH_3), 1.40–1.38 (m, 4H, CH_2), 0.93 (t, 3H, J = 6.8 Hz, CH_3). MS (ESI) m/z: 417.6 ($[M+Na]^+$). Anal. Calcd for $C_{19}H_{21}ClFN_3OS$: C, 57.93; H, 5.37; N, 10.67. Found: C, 57.90; H, 5.34; N, 10.62.

3.4.15. 2-(2-Chloro-6-fluorophenyl)-3-(5-pentyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6f)

IR (KBr) ν: 1718 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.12–7.10 (m, 3H, Ar-H; CH), 6.92–6.87 (m, 1H, Ar-H), 4.15 (d, 1H, J = 15.7 Hz, CH_2), 3.82 (d, 1H, J = 15.4 Hz, CH_2), 2.50–2.486 (m, 2H, CH_2), 2.37 (s, 6H, CH_3), 1.40–1.30 (m, 6H, CH_2), 0.87 (t, 3H, J = 6.87 Hz, CH_3). MS (ESI) m/z: 432.3 ($[M+Na]^+$). Anal. Calcd for $C_{20}H_{23}ClFN_3OS$: C, 58.89; H, 5.68; N, 10.30. Found: C, 58.85; H, 5.67; N, 10.36.

3.4.16. 2-(2-Chloro-6-fluorophenyl)-3-(5-allyl-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6g)

IR (KBr) ν: 1713 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.16–7.15 (m, 3H, Ar-H; CH), 6.96–6.90 (m, 1H, Ar-H), 5.75–5.82 (m, 1H, =CH), 5.04 (d, 1H, J = 10.4 Hz, $=CH_2$), 4.80 (d, 1H, J = 17.2 Hz, $=CH_2$) 4.18 (d, 1H, J = 15.6 Hz, CH_2), 3.85 (d, 1H, J = 14.8 Hz, CH_2), 3.28–3.29 (m, 2H, CH_2), 2.39 (s, 6H, CH_3). MS (ESI) m/z: 401.3 ($[M+Na]^+$). Anal. Calcd for $C_{18}H_{17}ClFN_3OS$: C, 57.21; H, 4.53; N, 11.12. Found: C, 57.29; H, 4.48; N, 11.07.

3.4.17. 2-(2-Chloro-6-fluorophenyl)-3-(5-propanenitrile-4,6-dimethylpyrimidin-2-yl) thiazolidin-4-one (6h)

IR (KBr) ν: 1715 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.15 (m, 3H, CH, Ar-H), 6.93 (m, 1H, Ar-H), 4.19 (d, 1H, J = 15.6 Hz, CH_2), 3.85 (d, 1H, J = 14.4 Hz, CH_2), 2.96 (t, 2H, J = 7.2 Hz, CH_2), 2.49 (t, 2H, J = 7.6 Hz, CH_2), 2.46 (s, 6H, CH_3). MS (ESI) m/z: 388.9 ($[M+H]^+$). Anal. Calcd for $C_{20}H_{18}ClFN_2OS$: C, 61.77; H, 4.67; N, 7.20. Found: C, 61.82; H, 4.61; N, 7.09.

3.4.18. 2-(2-Chloro-6-fluorophenyl)-3-(5-bromo-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one (6i)

IR (KBr) ν: 1736 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ: 7.17–7.12 (m, 3H, Ar-H; CH), 6.96–6.91 (m, 1H, Ar-H), 4.18 (d, 1H, J = 15.8 Hz, CH_2), 3.85 (d, 1H, J = 15.4 Hz, CH_2), 2.53 (s, 6H, CH_3). MS (ESI) m/z: 438.9 ($[M+Na]^+$). Anal. Calcd for $C_{15}H_{12}BrClFN_3OS$: C, 43.24; H, 2.90; N, 10.08. Found: C, 43.27; H, 2.89; N, 10.05.

3.5. In vitro HIV-RT kit assay[34]

The HIV-RT inhibition assay was performed by using an RT assay kit (Roche), and the procedure for assaying RT inhibition was performed as described in the kit protocol. Briefly, the reaction mixture consists of template/primer complex, 2′-deoxy-nucleotide-5′-triphosphates (dNTPs) and reverse transcriptase (RT) enzyme in the lysis buffer with or without inhibitors. After 1 h incubation at 37 °C the reaction mixture was transferred to streptavidine-coated microtitre plate (MTP). The biotin labeled dNTPs that are incorporated in the template due to activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer and antidigoxigenin-peroxidase (DIG-POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template was bound to anti-DIG-POD antibody. The unbound anti-DIG-POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyses by a peroxide enzyme. The absorbance of the sample was determined at OD 405 nM using microtiter plate ELISA reader. The resulting color intensity is directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by comparing to a sample that does not contain an inhibitor. The percentage inhibition was calculated by formula as given below: % Inhibition = 100 − [(OD 405 nm with inhibitor/OD 405 nm without inhibitor) × 100].

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References and notes

1. Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. *Antivir. Res.* **2004**, *63*, 79.
2. Rao, A.; Balzarini, J.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. *Il Farmaco* **2004**, *59*, 33.
3. Barreca, M. L.; Chimirri, A.; De Clercq, E.; De Luca, L.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappalà, M. *Il Farmaco* **2003**, *58*, 259.
4. Rao, A.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. *Il Farmaco* **2003**, *58*, 115.
5. Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; De Luca, L.; Höltje, H. D.; Höltje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappalà, M. *J. Med. Chem.* **2002**, *45*, 5410.
6. Rao, A.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. *Il Farmaco* **2002**, *57*, 747.
7. Barreca, M. L.; Chimirri, A.; De Luca, L.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappala, M.; Balzarini, J.; De Clercq, E.; Pannecouque, C.; Witvrouw, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1793.
8. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 1725.
9. Rawal, R. K.; Solomon, V. R.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. *Comb. Chem. High Throughput Screening* **2005**, *8*, 439.
10. Prabhakar, Y. S.; Solomon, V. R.; Rawal, R. K.; Gupta, M. K.; Katti, S. B. *QSAR Comb. Sci.* **2004**, *23*, 234.
11. Prabhakar, Y. S.; Rawal, R. K.; Gupta, M. K.; Solomon, V. R.; Katti, S. B. *Comb. Chem. High Throughput Screening* **2005**, *8*, 431.
12. Roy, K.; Leonard, J. T. *QSAR Comb. Sci.* **2005**, *24*, 579.
13. Ravichandran, V.; Prashantha Kumar, B. R.; Sankar, S.; Agrawal, R. K. *Eur. J. Med. Chem.* **2009**, *44*, 1180.
14. Murugesan, V.; Prabhakar, Y. S.; Katti, S. B. *J. Mol. Graphics Modell.* **2009**, *27*, 735.
15. Balzarini, J.; Orzeszko-Krzesińska, B.; Maurin, J. K.; Orzeszko, A. *Eur. J. Med. Chem.* **2009**, *44*, 303.
16. Balzarini, J.; Orzeszko-Krzesińska, B.; Maurin, J. K.; Orzeszko, A. *Eur. J. Med. Chem.* **2007**, *42*, 993.
17. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Eur. J. Med. Chem.* **2008**, *43*, 2800.
18. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Bioorg. Med. Chem.* **2007**, *15*, 3134.
19. Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. *Bioorg. Med. Chem.* **2005**, *13*, 6771.

20. Rawal, R. K.; Tripathi, R. K.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Med. Chem.* **2007**, *3*, 355.
21. Rawal, R. K.; Tripathi, R.; Kulkarni, S.; Paranjape, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Chem. Biol. Drug. Des.* **2008**, *72*, 147.
22. Verma, A.; Saraf, S. K. *Eur. J. Med. Chem.* **2008**, *43*, 897.
23. Rao, A.; Chimirri, A.; Ferro, S.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappalà, M. *Arkivoc* **2004**, 147.
24. Sriram, D.; Yogeeswari, P.; Kumar, T. G. A. *J. Pharm. Pharm. Sci.* **2005**, *8*, 426.
25. Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. *Org. Biomol. Chem.* **2004**, *2*, 2809.
26. Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619.
27. Gududuru, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. *Synlett* **2004**, 2357.
28. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121.
29. Dandia, A.; Singh, R.; Khaturia, S.; Me-rienne, C.; Morgantc, G.; Loupyd, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409.
30. Chen, H.; Bai, J.; Zhao, L.; Yuan, X. G.; Li, X. L.; Cao, K. Q. *Chin. J. Org. Chem.* **2008**, *28*, 1092 (in Chinese).
31. Chen, H.; Bai, J.; Zhao, L.; Yuan, X. G.; Li, X. L.; Cao, K. Q. *Chin. J. Org. Chem.* **2009**, *29*, 94 (in Chinese).
32. Stewart, R.; Thomas, W. S. L. *J. Org. Chem.* **1982**, *47*, 2075.
33. Nasielski, J.; Standaert, A.; Nasielski-Hinkens, R. *Synth. Commun.* **1991**, *21*, 901.
34. Reverse Transcriptase Assay, Colorimetric kit, Roche Diagnostics GmbH, Roche Applied Science, Sandhofer Strasse 116, D-68305 Mannheim, Germany.
35. Haley, C. A. C.; Maitland, P. *J. Chem. Soc.* **1951**, 3155.
36. Brown, D. J.; England, B. T. *J. Chem. Soc.* **1967**, 1922.