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Synthesis and evaluation of 2-(2,6-dihalophenyl)-3-pyrimidinyl-1,3-thiazolidin-4-one analogues as anti-HIV-1 agents

Ravindra K. Rawal,[a] Rajkamal Tripathi,[b] S. B. Katti,[a,*] Christophe Pannecouque[c] and Erik De Clercq[c]

[a]*Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India*
[b]*Microbiology Division, Central Drug Research Institute, Lucknow 226 001, India*
[c]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, 10 Minderbroedersstraat, B-3000 Leuven, Belgium*

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Abstract—A series of 2-(2,6-dihalophenyl)-3-(substituted pyrimidinyl)-1,3-thiazolidin-4-ones were designed on the prediction of quantitative structure–activity relationship (QSAR) studies, synthesized, and evaluated as HIV-1 reverse transcriptase inhibitors. Our attempts in correlating the identified molecular surface features related properties for modeling the HIV-1 RT inhibitory activity resulted in some statistically significant QSAR models with good predictive ability. The results showed that compounds **4m** and **4n** were highly active in inhibiting HIV-1 replication with EC_{50} values in the range of 22–28 nM in MT-4 as well as in CEM cells with selectivity indexes of >10,000. The derived models collectively suggest that the compounds should be compact without bulky substitution on its peripheries for better HIV-1 RT inhibitory activity. These models also indicate a preference for hydrophobic compounds to obtain good HIV-1 RT inhibitory activity.

1. Introduction

Non-nucleoside reverse transcriptase (RT) inhibitors (NNRTIs) of HIV-1 RT are an important part of currently available anti-HIV therapies because of their diversity and specificity in targeting this enzyme.[1] However, the efficacy of NNRTIs is seriously hampered by the emergence of mutant viral strains.[2,3] Therefore, it is imperative to look for new chemical entities having broad-spectrum activity against a variety of clinically relevant mutant RT enzymes with minimal cytotoxicity. Recently, Berraca et al. and our group reported thiazolobenzimidazole (TBZ) derived 2,3-(diaryl-substituted)-1,3-thiazolidin-4-one scaffold as selective HIV-1 NNRTIs (Fig. 1).[4–8] Subsequently, a systematic QSAR effort was made by our group and others to rationalize the biological activity and to define the biophoric space around the 4-thiazolidinone skeleton, indicating the importance of overall hydrophobicity of the analogues, and steric and electronic features of meta-/para-substituents of N-3-aryl moiety.[9–11] It was also suggested that a heteroaryl system would be a preferred one for the 3-aryl moiety for better HIV-1 RT inhibitory activity. The studies carried out with the topological descriptors of these compounds suggested that less extended or compact saturated structural templates would be better for the activity. Therefore, the compounds having high hydrophobicity at N-3-aryl moiety were designed, synthesized, and evaluated for RT inhibitory activity and the results are presented in this paper.

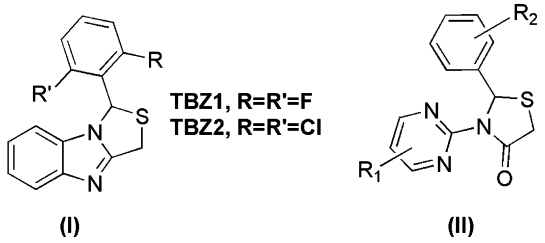

Figure 1. Structures of TBZ1 and TBZ2 (**I**) and 2-(2,6-dihalophenyl)-3-pyrimidinyl-1,3-thiazolidin-4-one derivatives (**II**).

Keywords: 4-Thiazolidinones; Anti-HIV-1 activity; HIV-1 RT; NNRTIs; QSAR.
* Corresponding author. Tel.: +9152226220586; e-mail: setu_katti@yahoo.com

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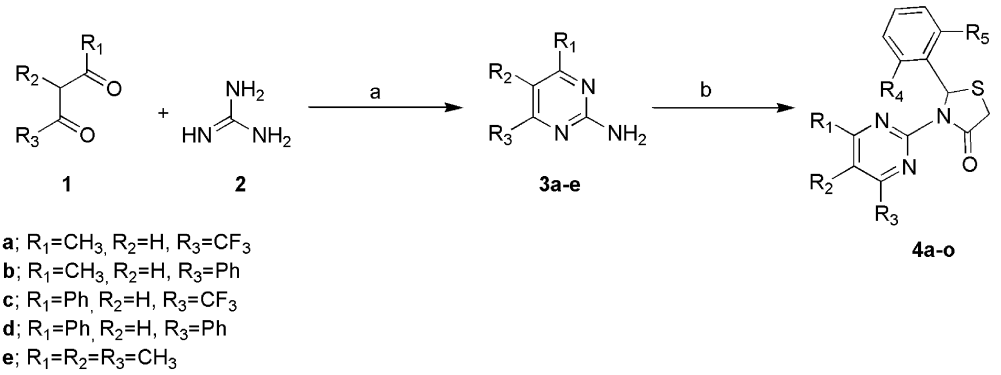


Scheme 1. Synthesis of 2-aminopyrimidines and 2-(2,6-dihalophenyl)-3-pyrimidinyl-1,3-thiazolidin-4-ones. Reagents and conditions: (a) EtOH, reflux, 8 h, 55–80% yields; (b) 2,6-dihalo-substituted benzaldehyde (1.5 equiv), mercaptoacetic acid (2 equiv), toluene reflux at 120 °C, 24 h, 28–56%.

2. Results and discussion

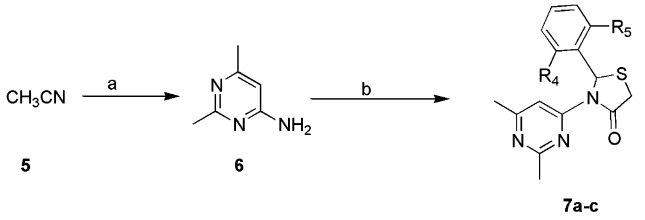
2.1. Method

2.1.1. Chemistry. To synthesize the di- and tri-substituted 2-aminopyrimidine compounds (**3a–e**), free base guanidine (**2**) solution in ethanol was refluxed with different 1,3-dicarbonyl compounds (**1a–e**) for 8 h to yield the corresponding 2-aminopyrimidine (**3a–e**) as shown in Scheme 1.[12] The synthesis of 4-amino-2,6-dimethylpyrimidine (**6**) was carried out, according to reported procedure (Scheme 2),[13] by heating the mixture of acetonitrile and NaOMe for 14 h at 150 °C in a glass sealed tube. The obtained product was isolated by conventional workup in satisfactory yield. The synthesis of new 2-(2,6-dihalophenyl)-3-(substituted pyrimidin-2-yl)-1,3-thiazolidin-4-ones (**4a–o** and **7a–c**) was carried out according to the reported procedure,[5] by reacting a suitably substituted 2-aminopyrimidine (**3a–e**, **6**) with 2,6-dihalo-substituted benzaldehyde in the presence of an excess of mercaptoacetic acid in reflux toluene for 24 h (Schemes 1 and 2). After completion of the reaction, desired final products were obtained by conventional workup procedure followed by flash column chromatography purification on silica-gel (230–400 mesh size) in moderate to excellent yields. All the synthesized compounds were well characterized by spectroscopic methods and elemental analysis.

2.1.2. Anti-HIV activity evaluation

2.1.2.1. In vitro HIV-RT kit assay.[14] 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 (Roche Kit). 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 mix was transferred to streptavidine-coated microtiter 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 anti-digoxigenin–peroxidase (DIG–POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template were 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 catalyzed 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 the formula given below

$$\% \text{ Inhibition} = 100 - \left[\frac{\text{OD 405 nm with inhibitor}}{\text{OD 405 nm without inhibitor}} \times 100\right]$$



Scheme 2. Synthesis of 4-amino-2,6-dimethylpyrimidine and 2-(2,6-dihalophenyl)-3-(2,6-dimethylpyrimidin-4-yl)-1,3-thiazolidin-4-ones. Reagents and conditions: (a) MeONa, reflux at 150 °C, 14 h, 90% yield; (b) 2,6-dihalo-substituted benzaldehyde (1.5 equiv), mercaptoacetic acid (2 equiv), toluene reflux at 120 °C, 24 h, 38–54% yields.

2.1.2.2. In vitro anti-HIV assay. The methodology of the anti-HIV assays has been previously described.[15] Briefly, MT-4 or CEM cells were infected with HIV-1_{IIIB} and HIV-2_{ROD} at 100 times the $CCID_{50}$ (50% cell culture infective dose) per milliliter of cell suspension. Then, 100 μl of the infected cell suspension was transferred to microtiter plate wells, mixed with 100 μl of the appropriate dilutions of test compounds, and further incubated at 37 °C. In CEM cells, after 4 days of incubation, HIV-1-induced syncytium formation was recorded. The 50% effective concentration (EC_{50}) was defined as the compound concentration required to inhibit virus-induced syncytium formation by 50%.[16] After 5 days of incubation of MT-4 cells, the number of viable cells

was determined. The 50% effective concentration (EC_{50}) was defined as the concentration of compound required to reduce 50% cell viability in MT-4 cells. The cytotoxic concentration CC_{50} was determined as the concentrations of compound to inhibit by 50% the number of viable cells in mock-infected MT-4 and CEM cell cultures.

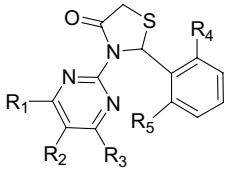
2.2. Biological activity

All compounds (**4a**–**o** and **7a**–**c**) were evaluated for HIV-1 RT inhibitory activity by determining their percentage inhibition of HIV-1 RT activity in HIV-1 RT kit.[14] The HIV-1 RT inhibition assay gave data in agreement with the in vitro anti-HIV activity in MT-4 and CEM cell line.[15,16] Those compounds showing inhibitory activity against RT in HIV-1 RT kit also showed anti-HIV-1 activity in both cell lines (Tables 1 and 2). The cytotoxicity of compounds was also measured in MT-4 and CEM cells in parallel with the HIV RT-inhibitory activity[15,16] (Tables 1 and 2).

As predicted by the molecular modeling studies,[9–11] the overall hydrophobicity of the analogues, and steric and electronic features of *meta*-/*para*-substituents of 3-hetero-aryl moiety led to a substantial increase in antiviral activity. In terms of the structure–activity relationships (SARs), introducing a 2-pyrimidinyl substituent at the N-3 atom of the thiazolidinone ring led to enhanced anti-HIV activity. In particular, the 2,6-dihalophenyl substituted compounds **4m** and **4n** were more active than the other analogues including the lead compounds TBZs (**TBZ1 and TBZ2**). Considering the effect of the substituents on the pyrimidine ring at N-3, introduction of 4-methyl-6-trifluoromethylpyrimidin-2-yl moiety (**4a**–**c**) led to moderate activity. Introduction of the 4-methyl-6-phenylpyrimidin-2-yl moiety (**4d**–**f**) led to a decrease in the activity. Introduction of the 4-phenyl-6-trifluoromethylpyrimidin-2-yl and 4,6-diphenylpyrimidin-2-yl (**4g**–**l**) also led to a substantial decrease in activity. The compounds with the best combination of high potency and low toxicity were the 4,5,6-trimethylpyrimidin-2-yl derivatives **4m**, **4n**, and **4o**. Compounds **4m** and **4n** proved to be 12.5- to 14-fold more effective than **TBZ1** and 21- to 23.5-fold more effective than **TBZ2** in inhibiting the HIV-1 replication in MT-4 cells. In CEM cells, compounds **4m** and **4n** are 50 times more active than **TBZ1**.

Compounds **4m** and **4n** thus emerged as the most potent compounds of this series with EC_{50} values in the range of 22–28 nM. Probably the flexibility of these molecules

Table 1. Anti-HIV-1 activity, cytotoxicity, and selectivity index in MT-4 cells and HIV-RT kit assay for compounds (**4a**–**o** and **7a**–**c**)



Compound	R_1	R_2	R_3	R_4	R_5	Yield (%)	Anti-HIV-1 activity			Inhibition rate (%) (HIV-RT kit assay)	
							EC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]	100 μg/ml	10 μg/ml
4a	Me	H	CF_3	Cl	Cl	50	1.0 ± 0.3	46.4 ± 3.1	46	43.7	32.9
4b	Me	H	CF_3	Cl	F	47	1.3 ± 0.3	16.9 ± 14.5	13	93.7	46.3
4c	Me	H	CF_3	F	F	38	5.0 ± 0.6	125.4 ± 45.7	25	38.9	32.3
4d	Me	H	Ph	Cl	Cl	48	6.1 ± 2.8	35.3 ± 2.9	6	51.5	18.0
4e	Me	H	Ph	Cl	F	41	3.9 ± 0.6	145.5 ± 129.3	38	79.9	32.7
4f	Me	H	Ph	F	F	37	6.4 ± 0.1	36.5 ± 0.8	6	54.2	47.4
4g	Ph	H	CF_3	Cl	Cl	46	>80.2	140.4 ± 97.6	<1	39.4	25.4
4h	Ph	H	CF_3	Cl	F	42	>10.8	93.9 ± 58.4	9	20.6	43.9
4i	Ph	H	CF_3	F	F	32	>122.8	74.3 ± 60.4	<1	6.6	15.6
4j	Ph	H	Ph	Cl	Cl	38	>194.8	192.7 ± 15.9	<1	51.4	31.6
4k	Ph	H	Ph	Cl	F	30	>242.5	>200.9	<1	66.7	55.6
4l	Ph	H	Ph	F	F	28	>167.2	176.6 ± 25.0	<1	44.0	30.1
4m	Me	Me	Me	Cl	Cl	56	0.03 ± 0.02	>320.4	>11456	100	94.8
4n	Me	Me	Me	Cl	F	50	0.02 ± 0.01	216.2 ± 53.5	8669	100	99.3
4o	Me	Me	Me	F	F	45	0.4 ± 0.04	341.1 ± 45.6	880	100	96.3
7a	2,6-Dimethyl-pyrimidin-4-yl			Cl	Cl	54	4.3 ± 1.1	41.3 ± 1.1	10	51.9	6.6
7b	2,6-Dimethyl-pyrimidin-4-yl			Cl	F	49	4.3 ± 0.3	47.6 ± 1.5	11	48.6	9.3
7c	2,6-Dimethyl-pyrimidin-4-yl			F	F	38	25.5 ± 4.1	271.6 ± 93.3	11	58.1	27.2
	TBZ-1					—	0.35 ± 0.1	19.2 ± 2.8	54.5	—	—
	TBZ-2					—	0.6 ± 0.09	9.4 ± 6.5	16	—	—

[a] Concentration required to reduce HIV-1-induced cytopathic effect by 50% in MT-4 cells.
[b] Concentration required to reduce MT-4 cell viability by 50%.
[c] Selectivity index or ratio of CC_{50} to EC_{50}.

Table 2. Anti-HIV-1 activity, cytotoxicity, and selectivity index in CEM cells for selected compounds

Compound	Anti-HIV-1 activity		
	EC_{50}[a] (μM)	CC_{50}[b] (μM)	SI[c]
4a	0.8 ± 0.5	46.7 ± 2.8	62
4b	1.1 ± 0.5	19.3 ± 13.6	18
4c	4.4 ± 1.1	140.4 ± 51.9	32
4d	5.8 ± 2.1	35.3 ± 2.9	6
4e	3.9 ± 0.4	171.9 ± 126.6	44
4f	5.6 ± 1.3	36.5 ± 0.8	6
4m	0.02 ± 0.01	>339.4	>15281
4n	0.02 ± 0.01	249.6 ± 79.8	10989
4o	0.3 ± 0.2	>372.7	>1222
7a	3.8 ± 1.2	42.0 ± 1.9	11
7b	4.1 ± 0.4	47.6 ± 1.3	12
7c	20.3 ± 9.5	271.6 ± 93.3	13
TBZ-1	1.10 ± 0.3	50.0 ± 3.2	45

[a] Concentration required to reduce HIV-1-induced cytopathic effect by 50% in CEM cells.
[b] Concentration required to reduce CEM cell viability by 50%.
[c] Selectivity index ratio CC_{50}/EC_{50}.

enables them to be better accommodated into the HIV-1 RT allosteric binding site. In addition, these compounds were minimally toxic, and their selectivity indexes were remarkably high (up to >10,000). As observed for other classes of NNRTIs, none of the compounds inhibited the replication of HIV-2 (ROD) in MT-4 cells at subtoxic concentrations.

2.3. QSAR and modeling studies

For the QSAR study 26 identified molecular surface features related descriptors[17] belonging to 2D- and 3D-descriptor classes from MOE[18] have been considered to parameterize the compounds (Table 1). A complete list of all 26 2D molecular descriptors along with 3D descriptors included in the present QSAR study is given in supporting information. Among the descriptors considered, several properties of van der Waals surface Area of these compounds have taken part in the regression equations. Among these, the descriptors prefixed with partial equalization of orbital electronegativities (PEOE) having resulted from the PEOE method of calculating atomic partial charges and the descriptor prefixed with Q having resulted from the partial charges on the atoms of the structure have shown strong correlation (r is 0.74–0.97) with HIV-RT inhibitory activity of the compounds. The activity of these compounds is best explained by these descriptors as shown in the following models (Table 3).

Model 1

$$-\log EC_{50} = 11.83 - 0.078(0.009)\text{PEOE\_VSA} + 2 - 0.027(0.002)Q\text{\_VSA\_NEG}$$
$$n = 18,\ r = 0.96,\ Q^2 = 0.88,$$
$$s = 0.38,\ F = 91.53 \quad (1)$$

Model 2

$$-\log EC_{50} = 11.671 - 0.084(0.009)\text{PEOE\_VSA} + 2 - 0.029(0.002)Q\text{\_VSA\_NEG} - 0.004(0.002)\text{ASA\_P}$$
$$n = 18,\ r = 0.97,\ Q^2 = 0.90,$$
$$s = 0.34,\ F = 77.94 \quad (2)$$

In the equations, n is the number of compounds, r is the correlation coefficient, Q^2 is cross-validated R^2 from the leave-one-out (LOO) cross-validation procedure, s is the standard error of the estimate, and F is the F-ratio between the variances of calculated and observed activities. The values given in the parentheses are the standard errors of the regression coefficients. In both the models PEOE_VSA+2 represents the sum of VSA with partial atomic charges in the range of 0.10–0.15. It has participated in model with a negative regression coefficient suggesting in favor of decreased positively charged and increased

Table 3. Physicochemical properties and anti-HIV activity of compounds **4a**–**o** and **7a**–**c** in MT-4 cells

Compound	PEOE_VSA+2	Q_VSA_NEG	ASA_P	$-\log EC_{50}$		
				(Obsd)	Eq. (1) (Calcd)	Eq. (2) (Calcd)
4a	11.8	190.8	176.5	6.0	5.7	5.9
4b	20.8	173.1	183.2	5.9	5.5	5.7
4c	29.9	155.5	188.6	5.3	5.3	5.5
4d	5.1	216.4	92.9	5.2	5.6	5.5
4e	14.1	198.7	101.0	5.4	5.3	5.2
4f	23.2	181.0	106.3	5.2	5.1	5.0
4g	11.8	252.1	196.2	3.8	4.1	4.4
4h	20.8	234.4	203.8	4.7	3.7	3.9
4i	29.9	216.7	208.5	3.6	3.6	3.9
4j	5.1	277.6	91.8	3.4	4.0	3.8
4k	14.1	260.0	100.2	3.3	3.7	3.5
4l	23.2	242.3	104.1	3.5	3.4	3.1
4m	5.1	145.0	91.4	7.6	7.4	7.4
4n	14.1	127.4	97.4	7.6	7.2	7.1
4o	23.2	109.7	99.8	6.4	7.2	7.1
7a	27.5	155.1	103.0	5.4	5.5	5.3
7b	36.5	137.4	106.9	5.4	5.2	5.0
7c	45.5	119.7	110.1	4.6	5.2	5.0

negatively charged surface areas for better inhibitory activity. The regression coefficient of Q_VSA_NEG suggests a preference for negatively charged/polarized surface areas as desirable for HIV-RT inhibitory activity same as inferred by PEOE_VSA+2. Interestingly in model 2, water accessible surface area of all polar ($|q_i| \geqslant 0.2$) atoms (ASA_P) indicates that partially positively charged/polarized atomic regions of the compounds are undesirable for better activity. This is in agreement with the earlier observation.[17] The models suggest that 4-thiazolidinone skeleton offers scope for further modulation.

3. Conclusion

In conclusion, novel 2-aminopyrimidine and 2-(2,6-dihalophenyl)-3-(pyrimidin-2-yl)-1,3-thiazolidin-4-ones were synthesized, characterized, and tested. The developed QSAR equations suggest molecules with higher lipophilicity would be better for the activity. This may suggest favorable nature of compact conformations/structural analogues for the activity. The inferences from the regression coefficients of PEOE_VSA+2, Q_VSA_NEG, and ASA_P are in general agreement with our previous studies. Two compounds **4m** and **4n** were found to be highly potent and selective anti-HIV-1 agents, inhibiting virus replication at a concentration of 22–28 nM and selectivity indexes of $\geqslant$10,000 in MT-4 as well as in CEM cells. Hence, compounds **4m** and **4n** were more than 10-fold active in MT-4 and 50-fold more active in CEM cells than **TBZ1**. It may be mentioned that 4-thiazolidinone skeleton holds promise for further activity optimization studies.

4. Experimental

Melting points (mp) were determined on a Complab melting point apparatus and are uncorrected. The C, H, N analyses were carried out on CARLO-ERBA EA1108 elemental analyser. Infrared (IR) spectra were recorded on an FT-IR Perkin-Elmer (model) spectrometer. The ^{1}H spectra were recorded on a DPX-200 and DPX-300 Bruker FT-NMR spectrometer. The chemical shifts are reported as parts per million (δ ppm) from $(CH_3)_4Si$ (TMS) as an internal standard. The ^{13}C NMR spectra were recorded on a DPX-300 Bruker FT-NMR (75 MHz) spectrometer. Mass spectra were obtained by electron spray ionization mass spectroscopy (ESI-MS) and fast atom bombardment (FAB positive) techniques. Column chromatography separations were obtained on silica-gel (230–400 mesh).

4.1. QSAR and modeling studies

QSAR descriptor module of MOE was used to calculate about 26 descriptors for each compound presented in Table 1. The 2D molecular descriptors use the atoms and connection information of the molecules. 3D molecular descriptors of MOE include internal 3D (i3D), which use 3D coordinate information about each molecule, and external 3D (x3D), which use 3D coordinate information with an absolute frame of reference. The HIV-1 RT inhibitory activity was used as EC_{50} in micromolar units, where EC_{50} was the concentration required to reduce HIV-1 induced cytopathic effect by 50% in MT-4 cells. For the present QSAR study the observed EC_{50} was converted to negative logarithm ($-\log EC_{50}$) in molar units. The observed values of compounds **4g–l** are greater than the written values. In the QSAR study, the EC_{50} value of **4g–l** was made double (before the transformation to $-\log EC_{50}$) in molar units to check whether these compounds are less active even at double the dose. The observed activity was considered as dependent variable and the calculated physicochemical properties as independent variables while modeling statistically significant relationships to explore the selectivity requirements among these compounds. In this study, the structures of 2-(2,6-dichlorophenyl)-3-pyrimidin-2-yl-thiazolidin-4-one, 2-(2-chloro-6-fluorophenyl)-3-pyrimidin-2-yl-thiazolidin-4-one, and 2-(2,6-difluorophenyl)-3-pyrimidin-2-yl-thiazolidin-4-one have been considered as the common basic core templates for the generation of 3D-structures of the analogues. These core structures have been constructed in MOE using molecular builder of the software followed by systematic conformational search under default conditions with energy minimization (force field: MMFF94x) to identify the minimum energy conformer. The structures of all analogues of Table 1 have been generated by appropriately modifying the corresponding core structures and then subjected to energy minimization (force field:MMFF94x) to obtain their final conformer. The QSAR model building is limited to triparametric for HIV-RT inhibitory activity. All the computational works were performed on molecular operating environment (MOE 2004.03), supplied by the Chemical Computing Group Inc., using Compaq Pentium 4 workstation. The structures of the compounds were sketched using the molecular builder of MOE and each structure was subjected to energy minimization with a convergence criterion of 0.01 kcal/mol Å using the MMFF94 force field. All energy-minimized structures were saved into a database for descriptor calculation. The correlation analysis of various physicochemical descriptors and biological activity data was accomplished by CP-MLR protocol.[19]

4.2. General synthetic procedure for compounds (3a–e)

The synthesis of compounds (**3a–e**) was performed according to the previously reported procedure.[12] The appropriate 1,3-dicarbonyl compounds (**1a–e**) (1.0 mmol) and free base guanidine (**2**) solution in ethanol (1.0 mmol) were refluxed at 78 °C for 8 h. The reaction mixture was then concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with water and then finally with brine. The organic layer was dried over sodium sulfate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica-gel using chloroform–methanol as eluent.

4.2.1. 4-Methyl-6-trifluoromethylpyrimidin-2-ylamine (3a). This compound was obtained as solid in 80% yield, mp 138 °C; IR (KBr): ν_{max} C=O 1583, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3H, CH_3 at C_4-pyrimidine), 5.69 (br s, 2H, NH_2), 6.80 (s, 1H, H_5-pyrimidine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.02 (1C), 161.84 (1C), 155.27 (C1), 154.81 (1C), 105.03 (1C), 23.01 (1C); ESI-MS: *m/z* 178 $[M+1]^+$.

4.2.2. 4-Methyl-6-phenylpyrimidin-2-ylamine (3b). This compound was obtained as solid in 78% yield, mp 135 °C; IR (KBr): ν_{max} C=O 1595, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H, CH_3 at C_4-pyrimidine), 5.33 (br s, 2H, NH_2), 6.93 (s, 1H, H_5-pyrimidine), 7.45 (t, 3H, Ph), 7.97 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.31 (1C), 164.11 (1C), 162.01 (C1), 136.26 (1C), 129.05 (1C), 127.40 (2C), 125.77 (2C), 106.02 (1C), 22.83 (1C); ESI-MS: *m/z* 186 $[M+1]^+$.

4.2.3. 4-Phenyl-6-trifluoromethylpyrimidin-2-ylamine (3c). This compound was obtained as solid in 72% yield, mp 130–132 °C; IR (KBr): ν_{max} C=O 1597, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.66 (br s, 2H, NH_2), 7.35 (s, 1H, H_5-pyrimidine), 7.48 (m, 3H, Ph), 8.03 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.89 (1C), 162.18 (1C), 156.18 (C1), 155.71 (1C), 134.91 (1C), 130.22 (1C), 127.67 (2C), 125.99 (2C), 101.70 (1C); ESI-MS: *m/z* 240 $[M+1]^+$.

4.2.4. 4,6-Diphenylpyrimidin-2-ylamine (3d). This compound was obtained as solid in 68% yield, mp 138–140 °C; IR (KBr): ν_{max} C=O 1593, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.25 (br s, 2H, NH_2), 7.48 (s, 1H, H_5-pyrimidine), 7.49 (m, 6H, Ph), 8.04 (m, 4H, Ph); ESI-MS: *m/z* 248 $[M+1]^+$.

4.2.5. 4,5,6-Trimethylpyrimidin-2ylamine (3e). This compound was obtained as solid in 76% yield, mp 208 °C; IR (KBr): ν_{max} C=O 1597, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.06 (s, 3H, CH_3 at C_5-pyrimidine), 2.29 (s, 6H, $2CH_3$ at C_4 and C_6-pyrimidine), 5.06 (br s, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.18 (2C), 159.17 (1C), 115.20 (C1), 20.90 (2C), 11.80 (1C); ESI-MS: *m/z* 138 $[M+1]^+$.

4.3. General synthetic procedure for compound 6

The synthesis of compound **6** was performed according to the previously reported procedure.[13] A mixture of acetonitrile (19.6 gm) and NaOMe (0.4 gm) was heated for 14 h in a glass sealed tube at 150 °C. The reaction mixture from the cooled glass tube was taken out. The reaction mixture was taken up in ethyl acetate. The organic layer was successively washed with water and then finally with brine. The organic layer was dried over sodium sulfate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica-gel using chloroform–methanol as eluent.

4.3.1. 2,6-Dimethyl-pyrimidin-4-ylamine (6). This compound was obtained as solid in 90% yield, mp 181–183 °C; IR (KBr): ν_{max} C=O 1583, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3H, CH_3 at C_6-pyrimidine), 2.51 (s, 3H, CH_3 at C_2-pyrimidine), 5.11 (br s, 2H, NH_2), 6.10 (s, 1H, H_5-pyrimidine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.99 (1C), 164.44 (1C), 161.91 (1C), 99.46 (1C), 24.34 (1C), 22.52 (1C); ESI-MS: *m/z* 124 $[M+1]^+$.

4.4. General synthetic procedure for compounds (4a–o and 7a–c)

The synthesis of compounds (**4a**–**o** and **7a**–**c**) was performed according to the previously reported procedure.[5] The appropriate (hetero)aromatic amine (1.0 mmol) and 2,6-dihalo-substituted benzaldehyde (1.2 mmol) were stirred in dry toluene under reflux condition followed by addition of mercapto acid (2.0 mmol). The reaction mixture was refluxed under stirring for an additional 24–48 h untill the complete consumption of (hetero)aromatic amine. The reaction mixture was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 5% aq citric acid, water, 5% aq sodium hydrogen carbonate, and then finally with brine. The organic layer was dried over sodium sulfate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica-gel using hexane–ethyl acetate as eluent. The structures of synthesized compounds were characterized by means of TLC, IR, FAB-MS, ^1H NMR, ^{13}C NMR, and elemental analysis.

4.4.1. 2-(2,6-Dichlorophenyl)-3-(4-methyl-6-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one (4a). This compound was obtained as solid in 50% yield, mp 111–115 °C; IR (KBr): ν_{max} C=O 1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.60 (s, 3H, CH_3), 3.87 (d, J = 15.90 Hz, 1H, 5-H_A), 4.12 (dd, J = 1.67 and 15.91 Hz, 1H, 5-H_B), 7.05–7.20 (m, 3H, H_3, H_4 and H_5-Ph), 7.28 (d, J = 1.66 Hz, 1H, H-2), 7.41 (s, 1H, H_5-pyrimidine); ESI-MS: *m/z* 408 $[M+1]^+$ and 430 $[M+Na^+]$.

4.4.2. 2-(2-Chloro-6-fluorophenyl)-3-(4-methyl-6-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one (4b). This compound was obtained as solid in 47% yield, mp 92–94 °C; IR (KBr): ν_{max} C=O 1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.60 (s, 3H, CH_3), 3.85 (d, J = 16.00 Hz, 1H, 5-H_A), 4.17 (d, J = 16.00 Hz, 1H, 5-H_B), 6.81 (s, 1H, H-2), 6.90–6.97 (m, 1H, H_4-Ph), 7.14–7.17(m, 2H, H_3 and H_5-Ph), 7.19 (s, 1H, H_5-pyrimidine); ESI-MS: *m/z* 392 $[M+1]^+$ and 414 $[M+Na^+]$.

4.4.3. 2-(2,6-Difluorophenyl)-3-(4-methyl-6-trifluoromethyl-pyrimidin-2-yl)thiazolidin-4-one (4c). This compound was obtained as solid in 38% yield, mp 124–127 °C; IR (KBr): ν_{max} C=O 1726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.60 (s, 3H, CH_3), 3.85 (d, J = 15.97 Hz, 1H, 5-H_A), 4.17 (d, J = 15.97 Hz, 1H, 5-H_B), 6.81 (s, 1H, H-2), 6.90–6.97 (m, 1H, H_4-Ph), 7.14–7.21(m, 2H, H_3 and H_5-Ph), 7.29 (s, 1H, H_5-pyrimidine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.82, 168.71, 161.03, 157.71, 155.79, 154.32, 128.64, 120.62, 116.33, 111.33, 110.62,

110.28, 51.77, 33.26, 23.44; ESI-MS: *m/z* 376 $[M+1]^+$ and 398 $[M+Na^+]$.

4.4.4. 2-(2,6-Dichlorophenyl)-3-(4-methyl-6-phenylpyrimidin-2-yl)thiazolidin-4-one (4d). This compound was obtained as solid in 48% yield, mp 168–170 °C; IR (KBr): ν_{max} C=O 1717 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.53 (s, 1H, CH_3), 3.91 (d, J = 15.75 Hz, 1H, 5-H_A), 4.16 (dd, J = 1.75 and 15.77 Hz, 1H, 5-H_B), 7.08 (t, 2H, H_3 and H_5-Ph), 7.19 (s, 1H, H_5-pyrimidine), 7.22 (m, 1H, H_4-Ph), 7.28–7.43 (m, 3H, Ar-H), 7.49 (d, J = 1.60 Hz, 1H, H-2), 7.85–7.90 (dd, J = 2.23 and 7.95 Hz, 2H, Ar-H); ESI-MS: *m/z* 416 $[M+1]^+$ and 438 $[M+Na^+]$. Anal. Calcd for $C_{20}H_{15}Cl_2N_3OS$: C, 57.70; H, 3.63; N, 10.09. Found: C, 57.46; H, 3.49; N, 9.95.

4.4.5. 2-(2-Chloro-6-fluorophenyl)-3-(4-methyl-6-phenylpyrimidin-2-yl)thiazolidin-4-one (4e). This compound was obtained as solid in 41% yield, mp 138–140 °C; IR (KBr): ν_{max} C=O 1718 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.54 (s, 1H, CH_3), 3.84 (d, J = 15.67 Hz, 1H, 5-H_A), 4.17 (d, J = 15.81 Hz, 1H, 5-H_B), 6.89 (m, 2H, H_3 and H_5-Ph), 6.92–7.14 (m, 2H, H_4-Ph and H_5-pyrimidine), 7.30 (s, 1H, H-2), 7.36–7.43 (m, 3H, Ar-H), 7.86–7.91 (dd, J = 2.30 and 7.85 Hz, 2H, Ar-H); ESI-MS: *m/z* 400 $[M+1]^+$ and 422 $[M+Na^+]$.

4.4.6. 2-(2,6-Difluorophenyl)-3-(4-methyl-6-phenylpyrimidin-2-yl)thiazolidin-4-one (4f). This compound was obtained as solid in 37% yield, mp 165–168 °C; IR (KBr): ν_{max} C=O 1717 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.54 (s, 1H, CH_3), 3.82 (dd, J = 1.77 and 17.79 Hz, 1H, 5-H_A), 4.21 (d, J = 17.79 Hz, 1H, 5-H_B), 6.81 (t, 2H, H_3 and H_5-Ph), 7.06 (s, 1H, H_5-pyrimidine), 7.15 (m, 1H, H_4-Ph), 7.31 (s, 1H, H-2), 7.40–7.46 (m, 3H, Ar-H), 7.90–7.95 (dd, J = 2.73 and 7.83 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.96, 168.02, 163.34, 160.97, 157.66, 155.89, 134.82, 129.76, 128.09, 127.49 (2C), 125.89 (2C), 117.31, 111.33, 110.70, 110.37, 52.22, 33.42, 23.12; ESI-MS: *m/z* 384 $[M+1]^+$ and 406 $[M+Na^+]$.

4.4.7. 2-(2,6-Dichlorophenyl)-3-(4-phenyl-6-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one (4g). This compound was obtained as solid in 46% yield, mp 206–208 °C; IR (KBr): ν_{max} C=O 1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.93 (d, J = 16.06 Hz, 1H, 5-H_A), 4.18 (dd, J = 1.57 and 16.00 Hz, 1H, 5-H_B), 7.10–7.18 (t, 2H, H_3 and H_5-Ph), 7.31 (m, 1H, H_4-Ph), 7.46 (m, 3H, Ar-H), 7.52 (s, 1H, H-2), 7.70 (s, 1H, H_5-pyrimidine), 8.03–8.08 (dd, J = 1.96 and 8.16 Hz, 2H, Ar-H); ESI-MS: *m/z* 470 $[M]^+$ and 492 $[M+Na^+]$.

4.4.8. 2-(2-Chloro-6-fluorophenyl)-3-(4-phenyl-6-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one (4h). This compound was obtained as solid in 42% yield, mp 157–160 °C; IR (KBr): ν_{max} C=O 1727 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.93 (d, J = 16.06 Hz, 1H, 5-H_A), 4.19 (d, J = 15.96 Hz, 1H, 5-H_B), 6.90 (m, 1H, H_4-Ph), 7.15–7.18 (m, 2H, H_3 and H_5-Ph), 7.48 (m, 3H, Ar-H), 7.51 (d, J = 1.86 Hz, 1H, H-2), 7.71 (s, 1H, H_5-pyrimidine), 8.03–8.08 (dd, J = 1.88 and 7.58 Hz, 2H, Ar-H); ESI-MS: *m/z* 454 $[M]^+$, and 476 $[M+Na^+]$.

4.4.9. 2-(2,6-Difluorophenyl)-3-(4-phenyl-6-trifluoromethylpyrimidin-2-yl)thiazolidin-4-one (4i). This compound was obtained as solid in 32% yield, mp 156–158 °C; IR (KBr): ν_{max} C=O 1726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.93 (d, J = 16.06 Hz, 1H, 5-H_A), 4.18 (d, J = 16.00 Hz, 1H, 5-H_B), 6.86 (t, 2H, H_3 and H_5-Ph), 7.01 (s, 1H, H-2), 7.23 (m, 1H, H_4-Ph), 7.49 (m, 3H, Ar-H), 7.71 (s, 1H, H_5-pyrimidine), 8.06–8.11 (dd, J = 1.96 and 8.06 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.00, 168.02, 166.72, 160.87, 157.56, 155.89, 133.78, 131.06, 128.31, 127.86 (2C), 126.43 (2C), 117.11, 111.33, 110.70, 110.37, 106.98, 57.71, 34.21; ESI-MS: *m/z* 437 $[M]^+$ and 460 $[M+Na^+]$.

4.4.10. 2-(2,6-Dichlorophenyl)-3-(4,6-diphenylpyrimidin-2- yl)thiazolidin-4-one (4j). This compound was obtained as solid in 38% yield, mp 206–208 °C; IR (KBr): ν_{max} C=O 1717 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.93 (d, J = 15.74 Hz, 1H, 5-H_A), 4.19 (dd, J = 1.54 and 16.11 Hz, 1H, 5-H_B), 7.09–7.50 (m, 11H, Ar-H), 7.84 (s, 1H, H-2), 7.99–8.04 (m, 2H, Ar-H and 1H, H_5-pyrimidine); ESI-MS: *m/z* 478 $[M+1]^+$ and 500 $[M+Na^+]$. Anal. Calcd for $C_{25}H_{17}Cl_2N_3OS$: C, 62.77; H, 3.58; N, 8.78. Found: C, 62.73; H, 3.74; N, 8.55.

4.4.11. 2-(2-Chloro-6-fluorophenyl)-3-(4,6-diphenylpyrimidin-2-yl)thiazolidin-4-one (4k). This compound was obtained as solid in 30% yield, mp 176–178 °C; IR (KBr): ν_{max} C=O 1723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.93 (d, J = 15.74 Hz, 1H, 5-H_A), 4.19 (dd, J = 1.54 and 16.11 Hz, 1H, 5-H_B), 7.09 (m, 1H, H_4-Ph), 7.15-7.22 (m, 2H, H_3 and H_5-Ph), 7.44-7.50 (m, 8H, Ar-H), 7.85 (s, 1H, H-2), 8.01–8.06 (m, 2H, Ar-H and 1H, H_5-pyrimidine); ESI-MS: *m/z* 462 $[M]^+$ and 484 $[M+Na^+]$.

4.4.12. 2-(2,6-Difluorophenyl)-3-(4,6-diphenylpyrimidin-2-yl)thiazolidin-4-one (4l). This compound was obtained as solid in 28% yield, mp 192–194 °C; IR (KBr): ν_{max} C=O 1726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.86 (dd, J = 1.76 and 15.85 Hz, 1H, 5-H_A), 4.24 (d, J = 15.65 Hz, 1H, 5-H_B), 6.83 (t, 2H, H_3 and H_5-Ph), 7.12–7.20 (m, 1H, H_4-Ph), 7.45–7.51 (m, 8H, Ar-H), 7.86 (s, 1H, H-2), 8.04–8.09 (m, 2H, Ar-H and 1H, H_5-pyrimidine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.00, 164.59 (2C), 161.07, 157.56, 156.36, 135.26 (2C), 129.85 (2C), 128.16, 127.58 (4C), 126.09 (4C), 117.61, 110.81, 110.51, 107.32, 52.28, 33.44; ESI-MS: *m/z* 446 $[M+1]^+$ and 468 $[M+Na^+]$.

4.4.13. 2-(2,6-Dichlorophenyl)-3-(4,5,6-trimethylpyrimidin-2-yl)thiazolidin-4-one (4m). This compound was obtained as solid in 56% yield, mp 202–204 °C, IR (KBr): ν_{max} C=O 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.10 (s, 3H, CH_3 at C_5-pyrimidine), 2.36 (s, 6H, $2CH_3$ at C_4 and C_6-pyrimidine), 3.90 (dd, J = 3.42 and 15.66 Hz, 1H, 5-H_A), 4.13 (dd, J = 2.04 and 15.66 Hz, 1H, 5-H_B), 7.05 (t, 1H, H_4-Ph), 7.18–7.21 (dd, J = 1.08 and 7.95 Hz, 1H, H_3-Ph), 7.25–7.28 (dd, J = 1.35 and 7.74 Hz, 1H, H_5-Ph), 7.48 (d,

J = 2.07 Hz, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.00, 164.47 (2C), 152.34, 134.34, 133.27, 133.10, 129.26, 127.94, 126.98, 122.79, 57.71, 34.21, 21.00 (2C), 12.34; ESI-MS: m/z 368 $[M+1]^+$ and 390 $[M+Na^+]$. Anal. Calcd for $C_{16}H_{15}Cl_2N_3OS$: C, 52.18; H, 4.11; N, 11.41. Found: C, 52.33; H, 3.96; N, 11.15.

4.4.14. 2-(2-Chloro-6-fluorophenyl)-3-(4,5,6-trimethylpyrimidin-2-yl)thiazolidin-4-one (4n). This compound was obtained as white solid in 50% yield, mp 199–200 °C, IR (KBr): ν_{max} C=O 1717 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.11 (s, 3H, CH_3 at C_5-pyrimidine), 2.37 (s, 6H, 2CH_3 at C_4 and C_6-pyrimidine), 3.90 (dd, J = 2.04 and 15.66 Hz, 1H, 5-H_A), 4.15 (d, J = 15.66 Hz, 1H, 5-H_B), 7.05 (m, 1H, H_4-Ph), 7.11–7.14 (m, 2H, H_3 and H_5-Ph), 7.16 (s, 1H, H-2); ESI-MS: m/z 352 $[M]^+$ and 374 $[M+Na^+]$.

4.4.15. 2-(2,6-Difluorophenyl)-3-(4,5,6-trimethylpyrimidin-2-yl)thiazolidin-4-one (4o). This compound was obtained as solid in 45% yield, mp 194–198 °C; IR (KBr): ν_{max} C=O 1718 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.11 (s, 3H, CH_3 at C_5-pyrimidine), 2.37 (s, 6H, CH_3 at C_4 and C_6-pyrimidine), 3.79 (d, J = 15.60 Hz, 1H, 5-H_A), 4.10 (d, J = 15.60 Hz, 1H, 5-H_B), 6.78 (t, 2H, H_3 and H_5-Ph), 6.98 (s, 1H, H-2), 7.17 (m, 1H, H_4-Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.79, 164.50 (2C), 161.07, 157.75, 152.57, 128.30, 122.61, 116.99, 110.50, 110.16, 51.98, 33.46, 21.08 (2C), 12.30; ESI-MS: m/z 336 $[M+1]^+$ and 358 $[M+Na^+]$.

4.4.16. 2-(2,6-Dichlorophenyl)-3-(2,6-dimethylpyrimidin-4-yl)thiazolidin-4-one (7a). This compound was obtained as solid in 54% yield, mp 140–142 °C, IR (KBr): ν_{max} C=O 1708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3 at C_6-pyrimidine), 2.48 (s, 3H, CH_3 at C_2-pyrimidine), 3.91 (d, J = 16.14 Hz, 1H, 5-H_A), 4.15 (dd, J = 1.92 and 16.17 Hz, 1H, 5-H_B), 7.11 (t, 1H, H_4-Ph), 7.17–7.20 (dd, J = 1.35 and 8.01 Hz, 1H, H_3-Ph), 7.32–7.35 (dd, J = 1.44 and 7.86 Hz, H_5-Ph), 7.52 (d, J = 1.86 Hz, 1H, H-2), 7.98 (s, 1H, H_5-pyrimidine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.05, 167.15, 165.20, 155.33, 134.31, 133.52, 131.79, 129.16, 127.97, 127.21, 105.77, 57.33, 34.46, 23.93, 23.26; FAB-MS: m/z 354 $[M]^+$. Anal. Calcd for $C_{15}H_{13}Cl_2N_3OS$: C, 50.86; H, 3.70; N, 11.86. Found: C, 50.78; H, 3.68; N, 11.73.

4.4.17. 2-(2-Chloro-6-fluorophenyl)-3-(2,6-dimethylpyrimidin-4-yl)thiazolidin-4-one (7b). This compound was obtained as solid in 49% yield, mp 118–120 °C; IR (KBr): ν_{max} C=O 1710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.43 (s, 3H, CH_3 at C_6-pyrimidine), 2.46 (s, 3H, CH_3 at C_2-pyrimidine), 3.80 (d, J= 16.11 Hz, 1H, 5-H_A), 4.16 (d, J = 16.11 Hz, 1H, 5-H_B), 6.89 (m, 1H, H_4-Ph), 7.13 (m, 2H, H_3 and H_5-Ph), 7.25 (d, J = 2.51 Hz, 1H, H-2), 8.03 (s, 1H, H_5-pyrimidine); FAB-MS: m/z 338 $[M]^+$.

4.4.18. 2-(2,6-Difluorophenyl)-3-(2,6-dimethylpyrimidin-4-yl)thiazolidin-4-one (7c). This compound was obtained as solid in 38% yield, mp 120–122 °C; IR (KBr): ν_{max} C=O 1711 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.44 (s, 3H, CH_3 at C_6-pyrimidine), 2.45 (s, 3H, CH_3 at C_2-pyrimidine), 3.79 (d, J = 16.08 Hz, 1H, 5-H_A), 4.19 (d, J = 16.11 Hz, 1H, 5-H_B), 6.80 (m, 2H, H_3 and H_5-Ph), 7.05 (m, 1H, H_4-Ph), 7.15 (d, J = 1.54 Hz, 1H, H-2), 7.98 (s, 1H, H_5-pyrimidine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.83, 167.21, 165.31, 160.93, 157.52, 155.28, 128.37, 116.90, 110.60, 110.28, 105.17, 51.47, 33.66, 24.07, 23.25; FAB-MS: m/z 322 $[M+1]^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.02.044.

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