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2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT Inhibitors

Ravindra K. Rawal,[a] Yenamandra S. Prabhakar,[a] S. B. Katti[a,*] and E. De Clercq[b]

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

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Abstract—A series of 4-thiazolidinones were evaluated as selective inhibitors of the HIV-RT enzyme. Our attempt in correlating the derived physicochemical properties with the HIV-RT inhibitory activity resulted in some statistically significant QSAR models with good predictive ability. The QSAR studies indicated the role of lipophilicity, dipole moment and out-of-plane potential energy of the compounds in rationalizing the activity. One of the compounds, **1**, inhibited the enzyme at 0.204 μM concentration with minimal toxicity to MT-4 cells.
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1. Introduction

Since the discovery of human immunodeficiency virus (HIV-1) and its role in the development of AIDS, considerable research efforts have been made towards understanding viral biology with a view to identify drug targets for clinical intervention.[1] In this endeavour, viral enzymes are the prime targets in the search for effective drugs to treat HIV/AIDS. One such essential enzyme is human immunodeficiency virus type-1 reverse transcriptase (HIV-1 RT), which enables the integration of viral genetic information into the host genome.[2] Non-nucleoside reverse transcriptase inhibitors (NNRTIs)[3] inter alia have been extensively investigated, and several NNRTIs have been approved by the FDA and are used clinically. Unfortunately, the virus rapidly develops resistance to existing drugs through mutation. Therefore, it is imperative to look for new chemical entities having broad-spectrum HIV-RT inhibitory activity (see Fig. 1). More recently E. De Clercq and his group have reported that 2,3-diaryl substituted 4-thiazolidinone derived from reterosynthetic opening of thiazolobenzimidazole (TBZ) selectively inhibit HIV-RT activity.[4] Subsequently from our group a systematic effort was made through QSAR to rationalize the biological activity and to define the biophoric space around the 4-thiazolidinone skeleton.[5,6]

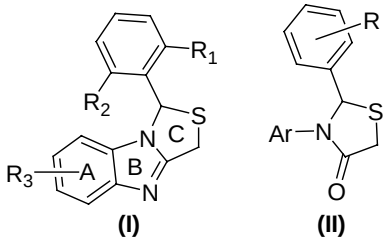

Figure 1. Structure of TBZs (**I**) and 2,3-diaryl-1,3-thiazolidin-4-one derivatives (**II**).

A detailed structure–activity relationship study of the HIV-1 Reverse Transcriptase (RT) inhibitory activity of two series of 2,3-diaryl-thiazolidin-4-ones in terms of physicochemical and structural descriptors has been carried out using combinatorial protocol interfaced multiple linear regression (CP-MLR) and partial least-squares (PLS) analysis. The models developed in the study indicate a preference for hydrophobic compounds for better inhibitory activity and also for compounds having propensity for a butterfly-like conformation.[5] The HIV-1 RT inhibitory activity of 2-(2,6-dihalophenyl)-3-(substituted pyridin-2-yl)-thiazolidin-4-ones has been analyzed with different topological descriptors obtained from DRAGON software.[6] The correlations obtained from the TOPO class descriptors suggest that

Keywords: 4-thiazolidinones; HIV-RT; NNRTIs; Dicyclohexylcarbodiimide; QSAR.
* Corresponding author. Tel.: +91 05 22 26 20 58 6; fax: +91 05 22 22 34 05; e-mail: setu_katti@yahoo.com

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less extended or compact saturated structural templates would be better for activity. The physicochemical weighting components of these descriptors suggest homogeneous influence of mass, volume, electronegativity and/or polarizability on the activity.[6]

In the above background and because of our continued interest in the medicinal aspects of thiazolidinones, we thought it appropriate to explore the synthesis and HIV-RT inhibitory activity of 2,3-diaryl-thiazolidin-4-ones. Furthermore, we have attempted to rationalize the activity of these compounds using the molecular descriptors generated in MOE.[7] The synthesis, biological activities and QSAR studies of these compounds are presented in this paper.

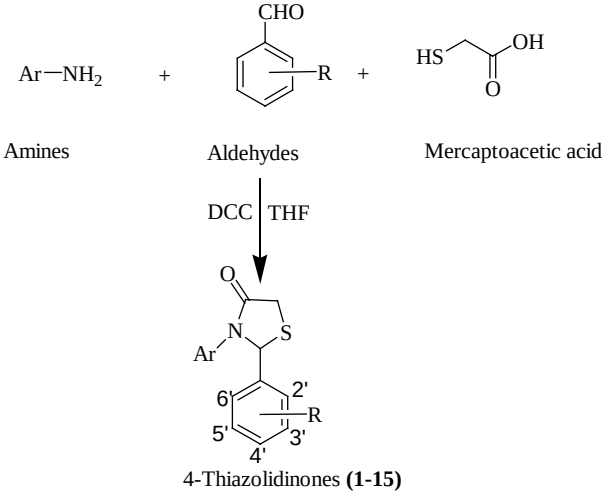
2. Result and discussion

2.1. Chemistry

The compounds reported (**1**–**15**) in this study were synthesized by the multi-component reaction protocol reported earlier from this laboratory. The reactions were performed by reacting the appropriate amine, aldehyde and mercapto acid (Scheme 1) in the presence of dicyclohexylcarbodiimide (DCC) at room temperature.[8] After completion of the reaction, which is usually 1.0 h, the desired products were obtained in excellent yield and purity. The spectral data, including the elemental analysis of the compounds reported in this study, correlate with the expected structure.

2.2. Antiviral activity assay

The methodology of anti-HIV assays has been described previously.[9] Briefly, MT-4 cells were infected with HIV-1 (IIIB) at 100 times the $CCID_{50}$ (50% cell culture infective dose) per millilitre of cell suspension. One hundred microlitres of the infected cell suspension was then transferred to microtitre plate wells, mixed with 100 μl of the appropriate dilutions of test compounds and



Scheme 1.

further incubated at 37 °C. After 5 days of incubation, the number of viable cells was determined. The 50% effective concentration (EC_{50}) and 50% cytotoxic concentration (CC_{50}) were defined as the concentrations of compound required to reduce the number of viable cells in the virus-infected and mock-infected cell cultures, respectively.

2.3. Biological activity

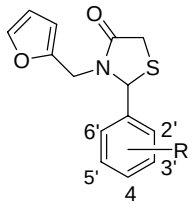
Compounds **1**–**15** were evaluated for HIV-RT inhibitory activity by determining their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells. Compound induced cytotoxicity was also measured in MT-4 cells in parallel with the HIV-RT inhibitory activity[10] (Table 1). As observed for other classes of NNRTIs, none of the compounds inhibited the replication of HIV-2 (ROD) in MT-4 cells at subtoxic concentration. From the biological activity data reported in Table 1, it may be inferred that the anti-HIV activity is strongly dependent on the nature of the substituent at C-2 and N-3 of the thiazolidinone ring. In particular, a high activity level was observed for compounds possessing a 2,6-dihalophenyl group at C-2 and a pyridine-2-yl or pyrimidine-2-yl ring at N-3. Compounds **1**, **2** and **3** prevented the cytopathic effect of HIV-1 (IIIB) at nanomolar concentrations and were minimally toxic to MT-4 cells resulting in a remarkably high selectivity indices. It is worth noting that compound **1** is 1.7 times more active than the corresponding TBZ lead compounds and possessed a selectivity index of about 216.

Considering the effect of the substituents on the Phenyl ring at C-2 and by keeping the furfuryl substituent at the N-3 position constant, the substituent methyl at 2′, and 2′ and 6′ (**12** and **13**) led to moderate activity. When the methoxy group was introduced at 2′; 4′; 2′, 4′ and 5′; 3′, 4′ and 5′ and 2′,4′ and 6′ led to a decrease in activity. The effect of halogen substituent on the phenyl ring at C-2, the 2′,6′-dichlorophenyl derivative (**1**), was more active than the corresponding 2′,6′-difluoro substituted (**2**), the favourable effect of chlorine is confirmed by the finding that 2′-chloro, 6′-fluoro derivative (**3**) possessed intermediate activity between dichloro and difluoro analogues. On the other hand, the introduction of the pentafluorophenyl group (**14**) and naphthyl substituent (**15**) at C-2 led to a substantial decrease in activity than the compounds **1**, **2** and **3**. To obtain a better rational for the activity, a detailed QSAR was done on the present dataset.

2.4. QSAR and modeling studies

For the QSAR study, 193 descriptors belonging to 2D- and 3D-descriptor classes from MOE have been considered to parameterize the compounds (Table 1). A complete list of all the 2D molecular descriptors along with 3D descriptors included in the present QSAR study is given in supporting information. Among the descriptors considered, log*P*(O/W) (log of the octane/water partion coefficient), MNDO_dipole (the dipole moment calculated using the MNDO Hamiltonian), E_oop (out-of-plane potential energy) have shown strong

Table 1. Anti-HIV-1 activity, cytotoxicity and selectivity index in MT-4 cells for compounds **1**–**15**



Compound	R					EC_{50} (μM)[a] HIV-1 III_B	CC_{50} (μM)[b]	SI[c]
	2′	3′	4′	5′	6′			
1	Cl	H	H	H	Cl	0.204 ± 0.0	44.8 ± 2.96	216
2	F	H	H	H	F	2.88 ± 0.576	208.47 ± 27.59	74
3	Cl	H	H	H	F	0.576 ± 0.16	97.76 ± 47.6	192
4	H	H	Cl	H	H	43.54	43.54 ± 4.354	<1
5	Cl	H	H	H	H	6.43 ± 1.77	111.73 ± 61.77	22
6	H	Cl	H	Cl	H	42.16	42.16 ± 2.378	<1
7	OMe	H	H	H	H	57.78	57.78 ± 11.70	<1
8	H	H	OMe	H	H	85.64	85.64 ± 52.42	<1
9	OMe	H	OMe	OMe	H	262.69	262.69 ± 54.81	<1
10	H	OMe	OMe	OMe	H	358.167	358.167	<1
11	OMe	H	OMe	H	OMe	6.88	6.88 ± 0.860	<1
12	Me	H	H	H	H	29.08 ± 10.62	159.89 ± 37.216	7
13	Me	H	H	H	Me	7.8 ± 1.39	42.787 ± 3.345	6
14	F	F	F	F	F	46.85 ± 9.91	82.636 ± 47.306	2
15			1-Naphthyl			5.53 ± 0.744	39.32 ± 4.85	8
			TBZ			0.35 ± 0.14	19.20 ± 2.80	54.5

[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 ratio CC_{50}/EC_{50}.

correlation (r is 0.74–0.94) 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 2).

Model 1

$$-\log EC_{50} = -1.191 + 1.479(0.206)\log P(O/W) + 0.649(0.114)\ \text{MNDO\_dipole}$$
$$n = 15, r = 0.920, Q^2 = 0.742, s = 0.501, F = 33.30 \quad (1)$$

Model 2

$$-\log EC_{50} = -1.244 + 1.408(0.173)\log P(O/W) + 7.358(2.900)\ \text{E\_oop} + 0.640(0.094)\ \text{MNDO\_dipole}$$
$$n = 15, r = 0.951, Q^2 = 0.806, s = 0.434, F = 34.40 \quad (2)$$

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, log$P$(O/W) indicates the favourability of hydrophobic nature for the interactions. The regression coefficient of MNDO_dipole suggests a preference for compounds with positive dipole moment for better inhibitory activity in these compounds. Interestingly, out-of-plane potential Energy term (E_oop) in model 2 indicates the compounds having the ability to go out of plane show better inhibitory activity. This is in agreement with the earlier observations as well.[5] The models suggest that 4-thiazolidinone skeleton offers scope for any modulation.

3. Conclusions

The results presented in this study indicate that changes at C-2 of thiazolidinone moiety, except for 2′,6′-dihalophenyl may lead a to reduction in HIV-RT inhibitory activity of these compounds. However, introduction of furfuryl moiety at the N-3 position in the thiazolidinone ring is well-tolerated. The developed QSAR equations suggest molecules with higher lipophilicity would be better for the activity. This may suggest the favourable nature of compact conformations/structural analogues for the activity. The inferences from the regression coefficients of log$P$(O/W), MNDO_dipole and E_oop are in general agreement with our previous studies. 2-(2,6-Dichloro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (**1**) was found to be the most promising of the series with an EC_{50} of 0.204 μM and selectivity index of 216. The out-of-plane potential energy term (E_oop), associated with flexibility of the molecule is about six times more for compound **1** (0.094), as compared to TBZ (0.015).

Table 2. Physicochemical properties and anti-HIV activity of compounds **1**–**15**

Compound	Log*P*(O/W)	MNDO_dipole	E_oop	−Log EC_{50}		
				(Obs.)	Eq. (1) (Calcd)	Eq. (2) (Calcd)
1	3.485	3.169	0.094	6.690	6.021	6.383
2	2.607	3.758	0.006	5.541	5.104	4.875
3	3.327	4.463	0.030	6.239	6.626	6.516
4	2.897	1.779	0.034	4.060	4.249	4.224
5	2.895	3.376	0.065	5.192	5.282	5.473
6	3.600	0.778	0.009	4.074	4.639	4.389
7	2.259	3.147	0.008	3.938	4.193	4.008
8	2.261	3.221	0.006	3.767	4.244	4.049
9	1.995	2.424	0.028	3.280	3.333	3.324
10	1.746	2.841	0.051	3.145	3.236	3.406
11	2.243	0.012	4.189	4.862	4.845	4.684
12	2.601	2.210	0.081	4.537	4.091	4.432
13	2.897	2.209	0.100	5.108	4.528	4.988
14	3.058	1.038	0.005	4.330	4.006	3.767
15	3.525	2.467	0.027	5.257	5.624	5.502

Hence, compound **1** is found to be more active than TBZ. It may be mentioned that 4-thiazolidinone skeleton holds promise for further activity optimization studies.

4. Experimental

Melting points (mp) were determined with a Complab melting point apparatus and are uncorrected. The C, H and N analyses were carried out on CARLO-ERBA EA1108 elemental analyser. Thin-layer chromatography (TLC) was performed on readymade silica gel plates (Merck) using ethyl acetate–hexane (2:8) as the solvent system. Iodine was used as the developing reagent. Infrared (IR) spectra were recorded on an FT-IR Perkin-Elmer (model) spectrometer. The ^{1}H spectra were recorded on a DPX-200 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-200 Bruker FT-NMR (50 MHz) spectrometer. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive) technique. 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 193 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 micro molar 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 activity was considered as dependent variable and the calculated physicochemical properties as independent variables, while modelling statistically significant relationships to explore the selectivity requirements among these compounds. 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 structure of the compounds was sketched using the molecular builder of MOE and each structure was subjected to energy minimization with a convergence criteria of 0.01 kcal/mol Å using the MMFF94 force field. All energy-minimized structures were saved in a database for descriptor calculation. The correlation analysis of various physicochemical descriptors and biological activity data was accomplished by the CP-MLR protocol. It is a 'filter' based variable selection procedure involving selected subset regressions for model development in QSAR and QSPR studies.[10] In this procedure, a combinatorial strategy with appropriately placed 'filters' has been interfaced with MLR to result in the extraction of diverse structure–activity models, each having a unique combination of descriptors from the dataset under study. So, developed models have been used in explaining the HIV RT inhibitory activity of the compounds.

4.2. General synthetic procedure for compounds 1–15

The appropriate amine (1.0 mmol) and aldehyde (2.0 mmol) were stirred in THF under ice-cold conditions for 5 min, followed by addition of mercapto acid (3.0 mmol). After 5 min, dicyclohexylcarbodiimide (1.2 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for an additional 50 min at room temp. Dicyclohexylurea (DCU) was removed by filtration and the filtrate 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 the

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 final compounds were characterized by TLC, IR, FAB-MS, ^{1}H NMR, and ^{13}C NMR.

4.3. 2-(2,6-Dichloro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (1)

This compound was obtained as gummy in 92% yield, IR (Neat): ν_{max} C=O 1664 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.65 (d, J = 15.46 Hz, 1H, CH_2furfuryl), 3.81 (s, 2H, CH_2), 4.91 (d, J = 15.47 Hz, 1H, CH_2furfuryl), 6.09 (s, 1H, CH), 6.25–7.39 (m, 6H, Ar–H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.6, 148.7, 143.3, 136.2, 135.5, 132.5, 131.2, 130.5, 129.2, 110.8, 109.9, 58.7, 39.7, 34.5; FAB-MS m/z 328 $[M+H]^+$. Anal. Calcd for $C_{14}H_{11}Cl_2NO_2S$: C, 51.23; H, 3.38; N, 4.27. Found: C, 51.22; H, 3.40; N, 4.23.

4.4. 2-(2,6-Difluoro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (2)

This compound was obtained as a white solid in 82% yield, mp 80 °C; IR (KBr): ν_{max} C=O 1688 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.65 (d, J = 15.47 Hz, 1H, CH_2furfuryl), 3.82 (dd, 2H, CH_2), 4.87 (d, J = 15.47 Hz, 1H, CH_2furfuryl), 6.00 (s, 1H, CH), 6.15–7.36 (m, 6H, Ar–H); FAB-MS m/z 296 $[M+H]^+$. Anal. Calcd for $C_{14}H_{11}F_2NO_2S$: C, 56.94; H, 3.75; N, 4.74. Found: C, 57.06; H, 3.58; N, 4.70.

4.5. 2-(2-Chloro-6-fluoro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (3)

This compound was obtained as gummy in 84% yield, IR (Neat): ν_{max} C=O 1683 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.65 (d, J = 15.46 Hz, 1H, CH_2furfuryl), 3.81 (dd, 2H, CH_2), 4.86 (d, J = 15.47 Hz, 1H, CH_2furfuryl), 6.14 (s, 1H, CH), 6.23–7.29 (m, 6H, Ar–H); FAB-MS m/z 312 $[M+H]^+$. Anal. Calcd for $C_{14}H_{11}ClFNO_2S$: C, 53.94; H, 3.56; N, 4.49. Found: C, 53.81; H, 3.47; N, 4.40.

4.6. 2-(4-Chloro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (4)

This compound was obtained as gummy in 79% yield, IR (Neat): ν_{max} C=O 1683 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.62 (d, J = 15.40 Hz, 1H, CH_2furfuryl), 3.76–3.81 (d, 2H, CH_2), 4.93 (d, J = 15.46 Hz, 1H, CH_2furfuryl), 5.50 (s, 1H, CH), 6.10–7.78 (m, 7H, Ar–H); FAB-MS m/z 294 $[M+H]^+$. Anal. Calcd for $C_{14}H_{11}Cl_2NO_2S$: C, 57.24; H, 4.12; N, 4.77. Found: C, 57.11; H, 4.03; N, 4.68.

4.7. 2-(2-Chloro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (5)

This compound was obtained as gummy in 80% yield, IR (Neat): ν_{max} C=O 1685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.71 (d, 2H, J = 15.52 Hz, CH_2), 3.78 (d, J = 15.42 Hz, 1H, CH_2furfuryl), 4.99 (d, J = 15.48 Hz, 1H, CH_2furfuryl), 6.00 (s, 1H, CH), 6.14 (d, J = 3.15Hz, 1H, Ar–H), 6.26 (d, J = 3.18Hz, 1H, Ar–H), 7.22–7.39 (m, 5H, Ar–H); FAB-MS m/z 294 $[M+H]^+$. Anal. Calcd for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12; N, 4.77. Found: C, 57.33; H, 4.05; N, 4.63.

4.8. 2-(3,5-Dichloro-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (6)

This compound was obtained as gummy in 82% yield, IR (Neat): ν_{max} C=O 1686 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.67 (d, J = 15.44 Hz, 1H, CH_2furfuryl), 3.75 (dd, J = 16.70 2H, CH_2), 4.91 (d, J = 15.44 Hz, 1H, CH_2furfuryl), 5.45 (s, 1H, CH), 6.14 (d, J = 3.18 Hz, 1H, Ar–H), 6.30 (d, J = 3.18 Hz, 1H, Ar–H), 7.16–7.78 (m, 4H, Ar–H); FAB-MS m/z 328 $[M+H]^+$. Anal. Calcd for $C_{14}H_{11}Cl_2NO_2S$: C, 51.23; H, 3.38; N, 4.27. Found: C, 51.38; H, 3.52; N, 4.34.

4.9. 3-Furan-2-ylmethyl-2-(2-methoxy-phenyl)-thiazolidin-4-one (7)

This compound was obtained as gummy in 89% yield, IR (Neat): ν_{max} C=O 1680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.67 (d, J = 15.45 Hz, 1H, CH_2furfuryl), 3.73 (dd, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.96 (d, J = 15.44 Hz, 1H, CH_2furfuryl), 5.88 (s, 1H, CH), 6.11–7.35 (m, 7H, Ar–H); FAB-MS m/z 290 $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.19; H, 5.32; N, 4.75.

4.10. 3-Furan-2-ylmethyl-2-(4-methoxy-phenyl)-thiazolidin-4-one (8)

This compound was obtained as gummy in 92% yield, IR (Neat): ν_{max} C=O 1681 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.60 (d, J = 15.40 Hz, 1H, CH_2furfuryl), 3.75–3.80 (d, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.92 (d, J = 15.38Hz, 1H, CH_2furfuryl), 5.51 (s, 1H, CH), 6.10 (d, J = 3.10 Hz, 1H, Ar–H), 6.27 (d, J = 3.09 Hz, 1H, Ar–H), 6.88 (d, J = 8.65 Hz, 2H, Ar–H), 7.22–7.35 (m, 3H, Ar–H); FAB-MS m/z 290 $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.21; H, 5.04; N, 4.89.

4.11. 3-Furan-2-ylmethyl-2-(2,4,5-trimethoxy-phenyl)-thiazolidin-4-one (9)

This compound was obtained as a white solid in 86% yield, mp 82–84 °C; IR (KBr): ν_{max} C=O 1677 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.70 (d, J = 15.40 Hz, 1H, CH_2furfuryl), 3.80 (s, 9H, OCH_3), 3.81 (s, 2H, CH_2), 4.87 (d, J = 15.38 Hz, 1H, CH_2furfuryl), 5.91 (s, 1H, CH), 6.09–7.31 (m, 5H, Ar–H); FAB-MS m/z 350 $[M+H]^+$. Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.52; H, 5.39; N, 4.01.

4.12. 3-Furan-2-ylmethyl-2-(3,4,5-trimethoxy-phenyl)-thiazolidin-4-one (10)

This compound was obtained as a white solid in 90% yield, mp 128 °C; IR (KBr): ν_{max} C=O 1679 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.74 (d, J = 15.46 Hz, 1H,

CH_2furfuryl), 3.80 (s, 2H, CH_2), 3.85 (s, 9H, OCH_3), 4.90 (d, J = 15.47 Hz, 1H, CH_2furfuryl), 5.49 (s, 1H, CH), 6.13 (s, , 1H, Ar–H), 6.29 (s, 1H, Ar–H), 6.51 (s, 2H, Ar–H), 7.34 (s, 1H, Ar–H); FAB-MS m/z 350 $[M+H]^+$. Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.52; H, 5.51; N, 3.97.

4.13. 3-Furan-2-ylmethyl-2-(2,4,6-trimethoxy-phenyl)-thiazolidin-4-one (11)

This compound was obtained as a white solid in 89% yield, mp 120–122 °C; IR (KBr): ν_{max} C=O 1669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.60 (d, J = 15.34 Hz, 1H, CH_2furfuryl), 3.75 (s, 9H, OCH_3), 3.81 (s, 2H, CH_2), 4.79 (d, J = 15.35 Hz, 1H, CH_2furfuryl), 6.04 (s, 1H, CH), 6.09–7.30 (m, 5H, Ar–H); FAB-MS m/z 350 $[M+H]^+$. Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.28; H, 5.53; N, 3.85.

4.14. 3-Furan-2-ylmethyl-2-*o*-tolyl-thiazolidin-4-one (12)

This compound was obtained as gummy in 84% yield, IR (Neat): ν_{max} C=O 1682cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.26 (s, 3H, CH_3), 3.66 (d, J = 15.38 Hz, 1H, CH_2furfuryl), 3.77 (s, 2H, CH_2), 5.03 (d, J = 15.34 Hz, 1H, CH_2furfuryl), 5.80 (s, 1H, CH), 6.09 (s, 1H, Ar–H), 6.28 (s, 1H, Ar–H), 7.16–7.45 (m, 5H, Ar–H); FAB-MS m/z 274 $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.81; H, 5.66; N, 5.12.

4.15. 2-(2,6-Dimethyl-phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one (13)

This compound was obtained as a white solid in 75% yield, mp 85 °C; IR (KBr): ν_{max} C=O 1681 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.21 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.48 (d, J = 15.19 Hz, 1H, CH_2furfuryl), 3.74 (s, 2H, CH_2), 5.00 (d, J = 15.18 Hz, 1H, CH_2furfuryl), 6.02 (s, 2H, Ar–H), 6.18 (s, 1H, CH), 6.27–7.35 (m, 5H, Ar–H); FAB-MS m/z 288 $[M+H]^+$. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.98; H, 6.08; N, 4.74.

4.16. 3-Furan-2-ylmethyl-2-pentafluorophenyl-thiazolidin-4-one (14)

This compound was obtained as gummy in 70% yield, IR (Neat): ν_{max} C=O 1691 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.66 (dd, 2H, J = 15.83, CH_2), 4.09 (d, 1H, J = 15.59, CH_2furfuryl), 4.72 (d, J = 15.50 Hz, 1H, CH_2furfuryl), 5.95 (s, 1H, CH), 6.19–6.27 (m, 3H, Ar–H); FAB-MS m/z 350 $[M+H]^+$. Anal. Calcd for $C_{14}H_8F_5NO_2S$: C, 48.14; H, 2.31; N, 4.01. Found: C, 48.16; H, 2.28; N, 4.02.

4.17. 3-Furan-2-ylmethyl-2-naphthalen-1-yl-thiazolidin-4-one (15)

This compound was obtained as gummy in 80% yield, IR (Neat): ν_{max} C=O 1685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.78–3.89 (m, 1H, CH_2furfuryl and 2H, CH_2), 5.10 (d, J = 14.78 Hz, 1H, CH_2furfuryl), 6.06 (s, 1H, CH), 6.24–7.94 (m, 10H, Ar–H); FAB-MS m/z 310 $[M+H]^+$. Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 70.01; H, 4.88; N, 4.64.

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References and notes

1. Turner, B. G.; Summers, M. F. *J. Mol. Biol.* **1999**, *285*, 1.
2. Arnold, E.; Das, K.; Ding, J.; Yadav, P. N. S., et al. *Drug Design Disc.* **1996**, *13*, 29–47.
3. Ren, J.; Esnouf, R.; Garman, E.; Somers, D.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Jones, Y.; Stuart, D.; Stammers, D. *Nat. Struct. Biol.* **1995**, *2*, 293–302.
4. (a) Barreca, M. L.; Chimirri, A.; Luca, L. D.; Monforte, A. M.; Monforte, P.; Rao, A.; Zappala, M.; Balzarini, J.; De Clercq, E.; Pannecouque, C.; Witvrouw, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1793–1796; (b) Barreca, M. L.; Balzarini, J.; Chimirri, A.; De Clercq, E.; Luca, L. D.; Holtje, M. H.; Holtje, M.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Rao, A.; Zappala, M. *J. Med. Chem.* **2002**, *45*, 5410–5413.
5. (a) Prabhakar, Y. S.; Solomon, V. R.; Rawal, R. K.; Gupta, M. K.; Katti, S. B. *QSAR Comb. Sci.* **2004**, *23*, 234–244; (b) Rawal, R. K.; Solomon, V. R.; Raja, V.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. *Combinatorial Chemistry and High-throughput screening* **2005**, *8*, 439–443.
6. Prabhakar, Y. S.; Rawal, R. K.; Gupta, M. K.; Solomon, V. R.; Raja, V.; Katti, S. B. *Combinatorial Chemistry and High-throughput screening* **2005**, *8*, 431–437.
7. MOE: The Molecular Operating Environment from Chemical Computing Group Inc., 1255 University Street, Suite 1600, Montreal, Quebec, Canada H3B 3X3.
8. (a) Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619–7624; (b) Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, S. B. *J. Chem. Res.* **2004**, 368.
9. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijin, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309.
10. Prabhakar, Y. S. *SAR Comb. Sci.* **2003**, *22*, 583–595.