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Synthesis and anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones

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Abstract

Several 1,3-thiazolidin-4-ones bearing a 2,6-dihalophenyl group at C-2 and a variously substituted phenyl ring at N-3 have been synthesized and tested as anti-HIV agents. The results of the in vitro tests showed that some of them proved to be effective inhibitors of HIV-1 replication.

Keywords: 2,3-Diaryl-1,3-thiazolidin-4-ones; Anti-HIV activity; NNRTIs

1. Introduction

Reverse transcriptase (RT) is one of the key enzymes packaged within the HIV virion capsid that plays an essential role in the replication of the virus. Consequently, HIV RT has emerged as a prime target for the development of drugs for HIV/AIDS therapy [1]. The HIV RT protein has both RNA-dependent DNA polymerase and RNaseH activities that are required for the conversion of genomic viral RNA to DNA that is subsequently incorporated into the host cell genome.

Inhibitors of HIV RT fall into two main classes: the first, termed nucleoside reverse transcriptase inhibitors (NRTIs), mimic normal active site substrates of RT but lack the 3′-OH group required for DNA chain elongation, which causes premature termination of the growing viral DNA strand [2]. The second class, nonnucleoside reverse transcriptase inhibitors (NNRTIs), binds to a hydrophobic pocket on RT ca. 10–15 Å from the NRTI site. This binding event alters the conformation of active site residues hampering normal enzymatic activity [3].

The use of combinations of NRTIs, NNRTIs, and HIV protease inhibitors, a treatment regimen termed highly active antiretroviral therapy (HAART), is currently the best method for controlling HIV infection. The success of HAART in delaying the onset of AIDS is attributed in part to the suppressed emergence of mutant virus strains in the presence of single inhibitors [4] and by the fact that some inhibitors have been shown to act synergistically toward inhibition of HIV replication [5]. Because mutations in HIV RT affect various NNRTIs differently [6], structurally unique inhibitors are needed that can challenge the swarm of virions in different ways.

The present work is an extension of our ongoing efforts toward the development and the identification of new molecules with anti-HIV activity [7–10]. Recent publications from our laboratory have documented a new class of NNRTIs, 2,3-diaryl-1,3-thiazolidin-4-one derivatives, that proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentrations acting as RT inhibitors [11,12].

From the structure–activity relationship (SAR) point of view, the anti-HIV activity is strongly dependent on the nature of the substituents at C-2 and N-3 of the thiazolidinone ring [11]. In particular, a good activity level is found in compounds having a 2′,6′-dihalophenyl group at C-2 and a phenyl ring at the N-3 (i.e. **1** and **2**). Moreover, we demonstrated that in a series of N-3-(pyridin-2-yl)-derivatives the introduction of a lipophilic substituent at the 4 and 6 positions of the pyridine nucleus led to a substantial increase in antiviral activity.

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Starting from these findings, to shed more light on the SAR of this class of compounds, in the present paper we report the synthesis of an extensive set of 2,3-diaryl-1,3-thiazolidin-4-ones bearing lipophilic substituents at positions 3 and 5 of the phenyl ring at N-3 (corresponding to positions 4 and 6 of pyridin-2-yl derivatives), and an analysis of the biological effects of these variations.

2. Results and discussion

The synthesis of the new 2,3-diaryl-1,3-thiazolidin-4-ones (**1**–**29**) was carried out by reacting a 2,6-dihalo-substituted benzaldehyde with an equimolar amount of a suitable aniline in the presence of an excess of mercaptoacetic acid in refluxing toluene (Fig. 1). The obtained products were isolated by conventional work-up in satisfactory yields. Both analytical and spectral data (^{1}H NMR) of all the synthesized compounds are in full agreement with the proposed structures.

All compounds obtained were tested for anti-HIV activity by determining their ability to inhibit the replication of HIV-1 (III_B) or HIV-2 (ROD) in MT-4 cells.

As shown in Table 1, some of them proved to be effective inhibitors of HIV-1 replication, whereas, as observed for other classes of NNRTIs, none of the tested compounds inhibited the replication of HIV-2 (ROD) in MT-4 cells at subtoxic concentrations (data not shown).

The results reported in Table 1 evidence that the anti-HIV activity of these series of compounds is influenced by the nature of the substituents both on the phenyl ring at C-2 and that at N-3.

Considering first the effect of the nature of the halogen atom on the phenyl ring at C-2, the 2,6-dichlorophenyl derivatives are always more active than the corresponding 2,6-difluoro-substituted ones, analogously to what previously observed in a set of N-3-(pyridin-2-yl) congeners [11]. The favorable effect of the chlorine is confirmed by the finding that 2-chloro-6-fluoro-derivatives possess an intermediate activity between dichloro and difluoro analogues with the sole exception of compound **28**, more active than its two congeners **27** and **29** and also one of the most potent of the series ($EC_{50} = 0.086$ μM).

Turning to the biological effects of changing the substituent on the phenyl ring at N-3, a comparison of the anti-HIV activity results carried out among the three series of derivatives, i.e. compounds having identical substituents on the phenyl ring at C-2, reveals similar trends. The introduction at the *meta* position of lipophilic groups, such as methyl, ethyl or chlorine, positively influences activity and also the 3,5-disubstitution led to compounds endowed with a good activity level. On the contrary, substituents such as methoxy or nitro groups are detrimental for anti-HIV activity. The best results have been recorded in the series of the 2-(2,6-dichlorophenyl)-derivatives: the activity peaks with 3-methyl compound **9** which possesses an $EC_{50} = 0.080$ μM, followed by 3,5-difluoro congener **24** ($EC_{50} = 0.128$ μM), the 3-ethyl analogue **12** ($EC_{50} = 0.156$ μM) and the 3,5-dimethyl derivative **27** ($EC_{50} = 0.190$ μM).

In conclusion, attempts to increase the anti-HIV activity by introducing substituents on the benzene ring at N-3 led to different results depending on the nature and number of the atoms or groups introduced. The obtained results confirm that, as suggested by our preliminary molecular modeling studies [13], the antiviral efficacy of 2,3-diaryl-1,3-thiazolidin-4-ones is related to the presence of lipophilic groups in proper positions of the aromatic ring.

3. Experimental

3.1. Chemistry

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a Carlo Erba Model 1106 Elemental Analyzer and the results are within ±0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-300 spectrometer. Chemical shifts were expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz.

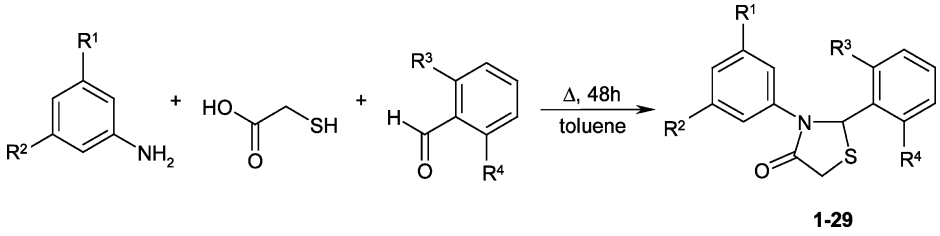
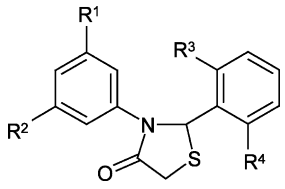


Fig. 1.

Table 1
Anti-HIV-1 activity, cytotoxicity and selectivity index in MT-4 cells for compounds **1**–**29**



Comp.	R^1	R^2	R^3	R^4	EC_{50} (μM) [a]	CC_{50} (M) [b]	SI [c]
1	H	H	Cl	Cl	2.30±0.75	>429	>186
2	H	H	F	F	0.401±0.903	38.1±4.5	95
3	Br	H	Cl	Cl	0.620±0.08	27.78±2.98	44
4	Br	H	Cl	F	0.646±0.25	30.10±2.84	48
5	Br	H	F	F	1.32±0.062	32.68±3.51	25
6	Cl	H	Cl	Cl	0.306±0.011	30.67±7.81	97
7	Cl	H	Cl	F	0.610±0.026	30.10±2.92	48
8	Cl	H	F	F	1.44±0.18	44.20±5.22	31
9	Me	H	Cl	Cl	0.080±0.002	20.8±5.8	260
10	Me	H	Cl	F	0.214±0.115	32.44±2.02	151
11	Me	H	F	F	0.688±0.164	207.8±54.2	302
12	Et	H	Cl	Cl	0.156±0.076	28.95±1.70	184
13	Et	H	Cl	F	0.211±0.077	34.24±1.78	162
14	Et	H	F	F	0.782±0.138	39.14±4.07	51
15	MeO	H	Cl	Cl	1.41±0.08	32.74±3.11	23
16	MeO	H	Cl	F	3.29±1.12	56.54±19.25	17
17	MeO	H	F	F	11.79±4.32	150.61±27.38	13
18	NO_2	H	Cl	Cl	0.731±0.217	15.98±7.85	22
19	NO_2	H	Cl	F	1.33±0.14	32.03±2.83	24
20	NO_2	H	F	F	5.50±0.029	101.69±51.14	19
21	Cl	Cl	Cl	Cl	0.280±0.033	18.06±8.90	66
22	Cl	Cl	Cl	F	0.318±0.029	48.05±21.50	151
23	Cl	Cl	F	F	0.97±0.052	112.72±96.61	115
24	F	F	Cl	Cl	0.128±0.044	43.31±22.77	342
25	F	F	Cl	F	0.247±0.008	33.45±2.32	136
26	F	F	F	F	0.54±0.11	139.02±29.03	254
27	Me	Me	Cl	Cl	0.19±0.11	20.1±12.5	106
28	Me	Me	Cl	F	0.086±0.014	33.35±2.23	394
29	Me	Me	F	F	0.241±0.059	36.2±2.0	150

[a] Concentration required to reduce HIV-1-(III_B) 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}.

*3.1.1. General procedure for the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (**1**–**29**)*

To a stirred solution of aniline (8 mmol) in dry toluene (50 ml), 2-mercaptoacetic acid (16 mmol) and the appropriate aromatic aldehyde (8 mmol) were added. The reaction mixture was refluxed for 48 h and then neutralized by a solution of sodium hydrogen carbonate. After removal of the solvent under reduced pressure, the oily residue was powdered by treatment with a mixture of ethanol and diethyl ether to afford compounds **1**–**12**, **14**–**16** and **18**–**29**. Compounds **13** and **17** were isolated by silica gel column chromatography eluting with chloroform. All compounds were recrystallized from ethanol. Data of compounds **1** and **2** have been previously reported [11].

*3.1.1.1. 3-(3-Bromophenyl)-2-(2,6-dichlorophenyl)-1,3-thiazolidin-4-one (**3**).* Yield 48%, m.p. 121–123 °C; ^{1}H NMR (δ) 3.95 (d, 1H, $J=15.4$, 5-H_A), 4.08 (dd, 1H, $J=2.2$ and 15.4, 5-H_B), 7.10–7.57 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}BrCl_2NOS$) C, H, N.

*3.1.1.2. 3-(3-Bromophenyl)-2-(2-chloro-6-fluorophenyl)-1,3-thiazolidin-4-one (**4**).* Yield 46%, m.p. 74–77 °C; ^{1}H NMR (δ) 3.90 (d, 1H, $J=15.7$, 5-H_A), 4.15 (dd, 1H, $J=2.7$ and 15.7, 5-H_B), 6.85–7.58 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}BrClFNOS$) C, H, N.

*3.1.1.3. 3-(3-Bromophenyl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (**5**).* Yield 71%, m.p. 108–110 °C; ^{1}H NMR (δ) 3.85 (d, 1H, $J=15.4$, 5-H_A), 4.02 (dd, 1H,

$J = 1.6$ and 15.4, 5-H_B), 6.55 (d, 1H, $J = 1.6$, H-2), 6.82–7.50 (m, 7H, ArH). *Anal*. ($C_{15}H_{10}BrF_2NOS$) C, H, N.

*3.1.1.4. 3-(3-Chlorophenyl)-2-(2,6-dichlorophenyl)-1,3-thiazolidin-4-one (**6**).* Yield 67%, m.p. 135–138 °C; ^{1}H NMR (δ) 3.95 (d, 1H, $J = 15.7$, 5-H_A), 4.09 (dd, 1H, $J = 2.2$ and 15.7, 5-H_B), 7.10–7.43 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}Cl_3NOS$) C, H, N.

3.1.1.5. 2-(2-Chloro-6-fluorophenyl)-3-(3-chlorophenyl)-1,3-thiazolidin-4-one (7). Yield 35%, m.p. 82–85 °C; ^{1}H NMR (δ) 3.87 (d, 1H, $J = 15.4$, 5-H_A), 4.11 (dd, 1H, $J = 1.6$ and 15.4, 5-H_B), 6.81–7.39 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}Cl_2FNOS$) C, H, N.

*3.1.2. 3-(3-Chlorophenyl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (**8**)*

Yield 70%, m.p. 125–128 °C; ^{1}H NMR (δ) 3.85 (d, 1H, $J = 15.7$, 5-H_A), 4.13 (dd, 1H, $J = 1.4$ and 15.7, 5-H_B), 6.56–7.35 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}ClF_2NOS$) C, H, N.

*3.1.2.1. 2-(2,6-Dichlorophenyl)-3-(3-methylphenyl)-1,3-thiazolidin-4-one (**9**).* Yield 65%, m.p. 129–132 °C; ^{1}H NMR (δ) 2.28 (s, 3H, CH_3), 3.95 (d, 1H, $J = 15.4$, 5-H_A), 4.08 (dd, 1H, $J = 2.5$ and 15.4, 5-H_B), 6.96–7.28 (m, 8H, ArH and H-2). *Anal*. ($C_{16}H_{13}Cl_2NOS$) C, H, N.

*3.1.2.2. 2-(2-Chloro-6-fluorophenyl)-3-(3-methylphenyl)-1,3-thiazolidin-4-one (**10**).* Yield 32%, m.p. 104–106 °C; ^{1}H NMR (δ) 2.28 (s, 3H, CH_3), 3.86 (d, 1H, $J = 15.4$, 5-H_A), 4.11 (dd, 1H, $J = 1.4$ and 15.4, 5-H_B), 6.81 (d, 1H, $J = 1.4$, H-2), 6.95–7.21 (m, 8H, ArH). *Anal*. ($C_{16}H_{13}ClFNOS$) C, H, N.

*3.1.2.3. 2-(2,6-Difluorophenyl)-3-(3-methylphenyl)-1,3-thiazolidin-4-one (**11**).* Yield 58%, m.p. 89–92 °C; ^{1}H NMR (δ) 2.28 (s, 3H, CH_3), 3.85 (d, 1H, $J = 15.4$, 5-H_A), 4.12 (dd, 1H, $J = 1.4$ and 15.4, 5-H_B), 6.54 (d, 1H, $J = 1.4$, H-2), 6.79–7.23 (m, 7H, ArH). *Anal*. ($C_{16}H_{13}F_2NOS$) C, H, N.

*3.1.2.4. 2-(2,6-Dichlorophenyl)-3-(3-ethylphenyl)-1,3-thiazolidin-4-one (**12**).* Yield 61%, m.p. 108–110 °C; ^{1}H NMR (δ) 1.18 (t, 3H, $J = 7.7$, CH_3), 2.62 (q, 2H, $J = 7.7$, CH_2), 4.00 (d, 1H, $J = 15.4$, 5-H_A), 4.12 (dd, 1H, $J = 1.4$ and 15.4, 5-H_B), 7.03–7.32 (m, 8H, ArH and H-2). *Anal*. ($C_{17}H_{15}Cl_2NOS$) C, H, N.

*3.1.2.5. 2-(2-Chloro-6-fluorophenyl)-3-(3-ethylphenyl)-1,3-thiazolidin-4-one (**13**).* Yield 42%, m.p. 65–67 °C; ^{1}H NMR (δ) 1.14 (t, 3H, $J = 7.7$, CH_3), 2.58 (q, 2H, $J = 7.7$, CH_2), 3.87 (d, 1H, $J = 15.4$, 5-H_A), 4.12 (dd, 1H, $J = 1.6$ and 15.4, 5-H_B), 6.82 (d, 1H, $J = 1.6$, H-2), 6.88–7.23 (m, 7H, ArH). *Anal*. ($C_{17}H_{15}ClFNOS$) C, H, N.

*3.1.2.6. 2-(2,6-Difluorophenyl)-3-(3-ethylphenyl)-1,3-thiazolidin-4-one (**14**).* Yield 58%, m.p. 72–75 °C; ^{1}H NMR (δ) 1.13 (t, 3H, $J = 7.7$, CH_3), 2.57 (q, 2H, $J = 7.7$, CH_2), 3.86 (d, 1H, $J = 15.4$, 5-H_A), 4.12 (dd, 1H, $J = 1.4$ and 15.4, 5-H_B), 6.55 (d, 1H, $J = 1.4$, H-2), 6.78–7.23 (m, 7H, ArH). *Anal*. ($C_{17}H_{15}F_2NOS$) C, H, N.

*3.1.2.7. 2-(2,6-Dichlorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one (**15**).* Yield 49%, m.p. 148–151 °C; ^{1}H NMR (δ) 3.73 (s, 3H, OCH_3), 3.95 (d, 1H, $J = 15.4$, 5-H_A), 4.08 (dd, 1H, $J = 2.5$ and 15.4, 5-H_B), 6.69–7.28 (m, 8H, ArH and H-2). *Anal*. ($C_{16}H_{13}Cl_2NO_2S$) C, H, N.

*3.1.2.8. 2-(2-Chloro-6-fluorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one (**16**).* Yield 63%, m.p. 100–102 °C; ^{1}H NMR (δ) 3.72 (s, 3H, OCH_3), 3.85 (d, 1H, $J = 15.4$, 5-H_A), 4.10 (dd, 1H, $J = 1.6$ and 15.4, 5-H_B), 6.70–7.22 (m, 8H, ArH and H-2). *Anal*. ($C_{16}H_{13}ClFNO_2S$) C, H, N.

*3.1.2.9. 2-(2,6-Difluorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one (**17**).* Yield 16%, m.p. 100–102 °C; ^{1}H NMR (δ) 3.73 (s, 3H, OCH_3), 3.86 (d, 1H, $J = 15.4$, 5-H_A), 4.12 (dd, 1H, $J = 2.0$ and 15.4, 5-H_B), 6.55 (d, 1H, $J = 2.0$, H-2), 6.72-7.24 (m, 7H, ArH). *Anal*. ($C_{16}H_{13}F_2NO_2S$) C, H, N.

*3.1.2.10. 2-(2,6-Dichlorophenyl)-3-(3-nitrophenyl)-1,3-thiazolidin-4-one (**18**).* Yield 50%, m.p. 154–160 °C; ^{1}H NMR (δ) 3.99 (d, 1H, $J = 15.7$, 5-H_A), 4.12 (dd, 1H, $J = 2.2$ and 15.7, 5-H_B), 7.10–8.29 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}Cl_2N_2O_3S$) C, H, N.

*3.1.2.11. 2-(2-Chloro-6-fluorophenyl)-3-(3-nitrophenyl)-1,3-thiazolidin-4-one (**19**).* Yield 50%, m.p. 124–127 °C; ^{1}H NMR (δ) 3.91 (d, 1H, $J = 15.7$, 5-H_A), 4.14 (dd, 1H, $J = 1.7$ and 15.7, 5-H_B), 6.92–8.25 (m, 8H, ArH and H-2). *Anal*. ($C_{15}H_{10}ClFN_2O_3S$) C, H, N.

*3.1.2.12. 2-(2,6-Difluorophenyl)-3-(3-nitrophenyl)-1,3-thiazolidin-4-one (**20**).* Yield 66%, m.p. 130–133 °C; ^{1}H NMR (δ) 3.89 (d, 1H, $J = 15.7$, 5-H_A), 4.15 (dd, 1H, $J = 1.4$ and 15.7, 5-H_B), 6.67 (d, 1H, $J = 1.4$, H-2), 6.83–8.23 (m, 7H, ArH). *Anal*. ($C_{15}H_{10}F_2N_2O_3S$) C, H, N.

*3.1.2.13. 2-(2,6-Dichlorophenyl)-3-(3,5-dichlorophenyl)-1,3-thiazolidin-4-one (**21**).* Yield 32%, m.p. 142–145 °C; ^{1}H NMR (δ) 3.94 (d, 1H, $J = 15.7$, 5-H_A), 4.07 (dd, 1H, $J = 2.2$ and 15.7, 5-H_B), 7.13–7.32 (m, 7H, ArH and H-2). *Anal*. ($C_{15}H_{10}Cl_2N_2O_3S$) C, H, N.

*3.1.2.14. 2-(2-Chloro-6-fluorophenyl)-3-(3,5-dichlorophenyl)-1,3-thiazolidin-4-one (**22**).* Yield 52%, m.p. 121–124 °C; ^{1}H NMR (δ) 3.85 (d, 1H, $J = 15.6$, 5-

H_A), 4.10 (dd, 1H, $J = 1.6$ and 15.6, 5-H_B), 6.78 (d, 1H, $J = 1.6$, H-2), 7.00–7.29 (m, 6H, ArH). *Anal*. ($C_{15}H_{10}ClFN_2O_3S$) C, H, N.

*3.1.2.15. 3-(3,5-Dichlorophenyl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (**23**)*. Yield 51%, m.p. 122–125 °C; ^{1}H NMR (δ) 3.85 (d, 1H, $J = 15.7$, 5-H_A), 4.12 (dd, 1H, $J = 1.4$ and 15.7, 5-H_B), 6.54 (d, 1H, $J = 1.4$, H-2), 6.85–7.29 (m, 6H, ArH). *Anal*. ($C_{15}H_9Cl_2F_2NOS$) C, H, N.

*3.1.2.16. 2-(2,6-Dichlorophenyl)-3-(3,5-difluorophenyl)-1,3-thiazolidin-4-one (**24**)*. Yield 24%, m.p. 151–154 °C; ^{1}H NMR (δ) 3.94 (d, 1H, $J = 15.7$, 5-H_A), 4.08 (dd, 1H, $J = 2.2$ and 15.7, 5-H_B), 6.59–7.30 (m, 7H, ArH and H-2). *Anal*. ($C_{15}H_9Cl_2F_2NOS$) C, H, N.

*3.1.2.17. 2-(2-Chloro,6-fluorophenyl)-3-(3,5-difluorophenyl)-1,3-thiazolidin-4-one (**25**)*. Yield 31%, m.p. 111–113 °C; ^{1}H NMR (δ) 3.85 (d, 1H, $J = 15.4$, 5-H_A), 4.10 (dd, 1H, $J = 1.6$ and 15.4, 5-H_B), 6.59–7.28 (m, 7H, ArH and H-2). *Anal*. ($C_{15}H_9ClF_3NOS$) C, H, N.

*3.1.2.18. 2-(2,6-Difluorophenyl)-3-(3,5-difluorophenyl)-1,3-thiazolidin-4-one (**26**)*. Yield 51%, m.p. 129–131 °C; ^{1}H NMR (δ) 3.85 (d, 1H, $J = 15.7$, 5-H_A), 4.12 (dd, 1H, $J = 1.4$ and 15.7, 5-H_B), 6.54 (d, 1H, $J = 1.4$, H-2), 6.61–7.28 (m, 6H, ArH). *Anal*. ($C_{15}H_9F_4NOS$) C, H, N.

*3.1.2.19. 2-(2,6-Dichlorophenyl)-3-(3,5-dimethylphenyl)-1,3-thiazolidin-4-one (**27**)*. Yield 69%, m.p. 162–164 °C; ^{1}H NMR (δ) 2.22 (s, 6H, CH_3), 3.93 (d, 1H, $J = 15.1$, 5-H_A), 4.06 (dd, 1H, $J = 2.2$ and 15.1, 5-H_B), 6.80–7.29 (m, 7H, ArH and H-2). *Anal*. ($C_{17}H_{15}Cl_2NOS$) C, H, N.

*3.1.2.20. 2-(2-Chloro-6-fluorophenyl)-3-(3,5-dimethylphenyl)-1,3-thiazolidin-4-one (**28**)*. Yield 40%, m.p. 127–129 °C; ^{1}H NMR (δ) 2.23 (s, 6H, CH_3), 3.85 (d, 1H, $J = 15.4$, 5H_A), 4.11 (dd, 1H, $J = 2.7$ and 15.4, 5H_B), 6.78–7.18 (m, 7H, ArH and H-2). *Anal*. ($C_{17}H_{15}ClFNOS$) C, H, N.

*3.1.2.21. 2-(2,6-Difluorophenyl)-3-(3,5-dimethylphenyl)-1,3-thiazolidin-4-one (**29**)*. Yield 61%, m.p. 117–120 °C; ^{1}H NMR (δ) 2.23 (s, 6H, CH_3), 3.84 (d, 1H, $J = 15.1$, 5H_A), 4.12 (dd, 1H, $J = 1.9$ and 15.1, 5H_B), 6.51–7.24 (m, 7H, ArH and H-2). *Anal*. ($C_{17}H_{15}F_2NOS$) C, H, N.

3.2. Pharmacology

The antiviral experiments using MT-4 cells and HIV-1 (III_B) and HIV-2 (ROD) strains were performed following procedures that have already been described [14,15].

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