Experimental Section

Chemistry. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a C. Erba Model 1106 Elemental Analyzer and the results were within ± 0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for TLC. ^{1}H NMR spectra were measured with a Varian Gemini 300 spectrometer in $CDCl_3$ with TMS as internal standard: chemical shifts are expressed in δ (ppm) and coupling constants (*J*) in hertz.

General Procedure for 2,3-Diaryl-1,3-thiazolidin-4-ones 4-34. To a stirred solution of aromatic amine (**1**) (8 mmol) in dry toluene (50 mL), 2-mercaptoacetic acid (**2**) (16 mmol) and the appropriate aromatic aldehyde (**3**) (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. All compounds were recrystallized from ethanol.

Physical and spectral data of compounds 4-34

2-(2,6-Dichlorophenyl)-3-phenyl-1,3-thiazolidin-4-one (4). Mp: 128-129 °C, yield 78%. ^{1}H NMR: 3.96 (d, 1H, *J* = 15.4, 5-H_A), 4.09 (dd, 1H, *J* = 2.2 and 15.4, 5-H_B), 7.06-7.35 (m, 9H, ArH and H-2). Anal. ($C_{15}H_{11}Cl_2NOS$) C, H, N.

2-(2,6-Difluorophenyl)-3-phenyl-1,3-thiazolidin-4-one (5). Mp: 144-145 °C, yield 65%. ^{1}H NMR: 3.87 (d, 1H, *J* = 15.4, 5-H_A), 4.14 (dd, 1H, *J* = 1.9 and 15.4, 5-H_B), 6.58 (d, 1H, *J* = 1.9, H-2), 6.82 (m, 2H, H-3',5'), 7.17-7.34 (m, 6H, ArH). Anal. ($C_{15}H_{11}F_2NOS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-pyridin-2-yl-1,3-thiazolidin-4-one (6). Mp: 135-138 °C, yield 8%. ^{1}H NMR: 3.94 (d, 1H, *J* = 15.7, 5-H_A), 4.17 (dd, 1H, *J* = 2.2 and 15.7, 5-H_B), 6.98-7.40 (m, 4H, ArH and H_5-Py), 7.63 (d, 1H, *J* = 2.2, H-2), 7.67 (m, 1H, H_4-Py), 8.13 (d, 1H, *J* = 8.5, H_3-Py), 8.20 (m, 1H, H_6-Py). Anal. ($C_{14}H_{10}Cl_2N_2OS$) C, H, N.

2-(2-Chloro,6-fluorophenyl)-3-pyridin-2-yl-1,3-thiazolidin-4-one (7). Mp: 112-114 °C, yield 45%. ^{1}H NMR: 3.84 (d, 1H, *J* = 15.9, 5-H_A), 4.19 (dd, 1H, *J* = 1.4 and 15.9, 5-H_B), 6.88-7.35 (m, 5H, ArH, H-2 and H_5-Py), 7.68 (m, 1H, H_4-Py), 8.23 (m, 2H, $H_{3,6}$-Py). Anal. ($C_{14}H_{10}ClFN_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-pyridin-2-yl-1,3-thiazolidin-4-one (8). Mp: 115-118 °C, yield 18%. ^{1}H NMR: 3.84 (d, 1H, J = 15.9, 5-H_A), 4.22 (dd, 1H, J = 1.1 and 15.9, 5-H_B), 6.81 (m, 2H, H-3',5'), 7.0 (m, 1H, H_5-Py), 7.16 (m, 1H, H-4'), 7.20 (d, 1H, J = 1.1, H-2), 7.67 (m, 1H, H_4-Py), 8.20 (d, 1H, J = 8.5, H_6-Py), 8.24 (m, 1H, H_3-Py),. Anal. ($C_{14}H_{10}F_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-pyridin-3-yl-1,3-thiazolidin-4-one (9). Mp: 129-130 °C, yield 10%. ^{1}H NMR: 4.00 (d, 1H, J = 15.7, 5-H_A), 4.13 (dd, 1H, J = 2.2 and 15.7, 5-H_B), 7.13-7.31 (m, 5H, ArH, H-2 and H_5-Py), 7.81 (m, 1H, H_4-Py), 8.44 (dd, 1H, J = 1.6 and 4.8, H_6-Py), 8.64 (m, 1H, J = 2.5, H_2-Py). Anal. ($C_{14}H_{10}Cl_2N_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-pyridin-3-yl-1,3-thiazolidin-4-one (10). Mp: 171-173 °C, yield 40%. ^{1}H NMR: 3.91 (d, 1H, J = 15.7, 5-H_A), 4.17 (dd, 1H, J = 1.4 and 15.7, 5-H_B), 6.65 (d, 1H, J = 1.4, H-2), 6.87 (m, 2H, H-3',5'), 7.21-7.32 (m, 2H, H-4' and H_5-Py), 7.72 (m, 1H, H_4-Py), 8.46 (dd, 1H, J = 1.4 and 4.7, H_6-Py), 8.58 (d, 1H, J = 2.4, H_2-Py). Anal. ($C_{14}H_{10}F_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-pyridin-4-yl-1,3-thiazolidin-4-one (11). Mp: 137-138 °C, yield 14%. ^{1}H NMR: 3.95 (d, 1H, J = 15.9, 5-H_A), 4.12 (dd, 1H, J = 2.1 and 15.9, 5-H_B), 7.11-7.31 (m, 4H, ArH, H-2), 7.39 (d, 2H, J = 6.4, $H_{3,5}$-Py), 8.51 (d, 2H, J = 6.4, $H_{2,6}$-Py). Anal. ($C_{14}H_{10}Cl_2N_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-pyridin-4-yl-1,3-thiazolidin-4-one (12). Mp: 114-117 °C, yield 15%. ^{1}H NMR: 3.85 (d, 1H, J = 15.9, 5-H_A), 4.20 (dd, 1H, J = 1.4 and 15.9, 5-H_B), 6.67 (d, 1H, J = 1.4, H-2), 6.86 (m, 2H, H-3',5'), 7.25 (m, 1H, H-4'), 7.41 (d, 2H, J = 6.4, $H_{3,5}$-Py), 8.52 (d, 2H, J = 6.4, $H_{2,6}$-Py). Anal. ($C_{14}H_{10}F_2N_2OS$) C, H, N.

3-(5-Chloropyridin-2-yl)-2-(2,6-dichlorophenyl)-1,3-thiazolidin-4-one (13). Mp: 138-141 °C, yield 53%. ^{1}H NMR: 3.93 (d, 1H, J = 15.9, 5-H_A), 4.16 (dd, 1H, J = 2.2 and 15.9, 5-H_B), 7.05-7.31 (m, 3H, ArH), 7.55 (d, 1H, J = 2.2, H-2), 7.64 (dd, 1H, J = 2.5 and 8.7, H_4-Py), 8.14 (d, 1H, J = 2.5, H_6-Py), 8.17 (d, 1H, J = 8.7, H_3-Py). Anal. ($C_{14}H_9Cl_3N_2OS$) C, H, N.

2-(2-Chloro-6-fluorophenyl)-3-(5-chloropyridin-2-yl)-1,3-thiazolidin-4-one (14). Mp: 91-94 °C, yield 41%. ^{1}H NMR: 3.84 (d, 1H, J = 15.9, 5-H_A), 4.18 (dd, 1H, J = 2.2 and 15.9, 5-H_B), 6.87-7.16 (m, 4H, ArH and H-2), 7.64 (dd, 1H, J = 2.5 and 8.9, H_4-Py), 8.17 (d, 1H, J = 2.5, H_6-Py), 8.26 (d, 1H, J = 8.9, H_3-Py). Anal. ($C_{14}H_9Cl_2FN_2OS$) C, H, N.

3-(5-Chloropyridin-2-yl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (15). Mp: 95-98 °C, yield 66%. ^{1}H NMR: 3.84 (d, 1H, J = 15.9, 5-H_A), 4.22 (dd, 1H, J = 1.1 and 15.9, 5-H_B), 6.83 (m,

2H, H-3',5'), 7.12 (d, 1H, J = 1.1, H-2), 7.18 (m, 1H, H-4'), 7.64 (dd, 1H, J = 2.8 and 9.1, H_4-Py), 8.19 (d, 1H, J = 2.8, H_6-Py), 8.26 (d, 1H, J = 9.1, H_3-Py). Anal. ($C_{14}H_9ClF_2N_2OS$) C, H, N.

3-(5-Bromopyridin-2-yl)-2-(2,6-dichlorophenyl)-1,3-thiazolidin-4-one (16). Mp: 148-151 °C, yield 79%. ^{1}H NMR: 3.93 (d, 1H, J = 15.9, 5-H_A), 4.16 (dd, 1H, J = 2.2 and 15.9, 5-H_B), 7.06-7.31 (m, 3H, ArH), 7.54 (d, 1H, J = 2.2, H-2), 7.77 (dd, 1H, J = 2.6 and 8.8, H_4-Py), 8.13 (d, 1H, J = 8.8, H_3-Py), 8.24 (d, 1H, J = 2.6, H_6-Py). Anal. ($C_{14}H_9BrCl_2N_2OS$) C, H, N.

3-(5-Bromopyridin-2-yl)-2-(2-chloro-6-fluorophenyl)-1,3-thiazolidin-4-one (17). Mp: 90-91 °C, yield 41%. ^{1}H NMR: 3.84 (d, 1H, J = 15.9, 5-H_A), 4.18 (dd, 1H, J = 1.6 and 15.9, 5-H_B), 6.88-7.25 (m, 4H, ArH and H-2), 7.78 (dd, 1H, J = 2.5 and 9.1, H_4-Py), 8.23 (d, 1H, J = 9.1, H_3-Py), 8.27 (d, 1H, J = 2.5, H_6-Py). Anal. ($C_{14}H_9BrClFN_2OS$) C, H, N.

3-(5-Bromopyridin-2-yl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (18). Mp: 88-90 °C, yield 68%. ^{1}H NMR: 3.83 (d, 1H, J = 15.8, 5-H_A), 4.21 (dd, 1H, J = 1.4 and 15.8, 5-H_B), 6.83 (m, 2H, H-3',5'), 7.12 (d, 1H, J = 1.4, H-2), 7.19 (m, 1H, H-4'), 7.77 (dd, 1H, J = 2.4 and 8.2, H_4-Py), 8.22 (d, 1H, J = 8.2, H_3-Py), 8.29 (d, 1H, J = 2.4, H_6-Py). Anal. ($C_{14}H_9BrF_2N_2OS$) C, H, N.

3-(6-Bromopyridin-2-yl)-2-(2,6-dichlorophenyl)-1,3-thiazolidin-4-one (19). Mp: 162-164 °C, yield **10%**. ^{1}H NMR: 3.94 (d, 1H, J = 15.9, 5-H_A), 4.16 (dd, 1H, J = 2.2 and 15.9, 5-H_B), 7.07-7.36 (m, 4H, ArH and H_5-Py), 7.53 (dd, 1H, J = 7.8 and 8.2, H_4-Py),7.54 (d, 1H, J = 2.2, H-2), 8.19 (d, 1H, J = 8.2, H_3-Py). Anal. ($C_{14}H_9BrCl_2N_2OS$) C, H, N.

3-(6-Bromopyridin-2-yl)-2-(2-chloro-6-fluorophenyl)-1,3-thiazolidin-4-one (20). Mp: 104-106 °C, yield 74%. ^{1}H NMR: 3.85 (d, 1H, J = 15.9, 5-H_A), 4.19 (dd, 1H, J = 2.2 and 15.9, 5-H_B), 6.89-7.19 (m, 5H, ArH, H-2 and H_5-Py), 7.52 (dd, 1H, J = 7.8 and 8.2, H_4-Py), 8.26 (d, 1H, J = 8.2, H_3-Py). Anal. ($C_{14}H_9BrClFN_2OS$) C, H, N.

3-(6-Bromopyridin-2-yl)-2-(2,6-difluorophenyl)-1,3-thiazolidin-4-one (21). Mp: 126-130 °C, yield 60%. ^{1}H NMR: 3.84 (d, 1H, J = 15.9, 5-H_A), 4.23 (dd, 1H, J = 1.4 and 15.9, 5-H_B), 6.86 (m, 2H, H-3',5'), 7.08 (d, 1H, J = 1.4, H-2), 7.16-7.25 (m, 2H, H-4' and H_5-Py), 7.52 (dd, 1H, J = 7.9 and 8.2, H_4-Py), 8.29 (d, 1H, J = 8.2, H_3-Py). Anal. ($C_{14}H_9BrF_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-(3-methylpyridin-2-yl)-1,3-thiazolidin-4-one (22). Mp: 159-160 °C, yield 20%. ^{1}H NMR: 2.26 (s, 3H, Me), 3.94 (d, 1H, J = 15.6, 5-H_A), 4.14 (dd, 1H, J = 2.2 and 15.6, 5-H_B), 7.05-7.33 (m, 4H, ArH and H_5-Py), 7.49 (dd, 1H, J = 1.4 and 7.6, H_4-Py), 7.65 (d, 1H, J = 2.2, H-2), 8.25 (dd, 1H, J = 1.4 and 4.7, H_3-Py). Anal. ($C_{15}H_{12}Cl_2N_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-(3-methylpyridin-2-yl)-1,3-thiazolidin-4-one (23). Mp: 131-133 °C, yield 21%. ^{1}H NMR: 2.17 (s, 3H, Me), 3.84 (d, 1H, 15.4, 5-H_A), 4.18 (dd, 1H, J = 1.9 and 15.4, 5-H_B), 6.81 (m, 2H, H-3',5'), 7.05 (d, 1H, J = 1.9, H-2), 7.09 (dd, 1H, J = 4.7 and 7.7, H_5-Py), 7.20 (m, 1H, H-4'), 7.49 (dd, 1H, J = 1.4 and 7.7, H_4-Py), 8.27 (dd, 1H, J = 1.7 and 4.7, H_5-Py),. Anal. ($C_{15}H_{12}F_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-(4-methylpyridin-2-yl)-1,3-thiazolidin-4-one (24). Mp: 192 °C, yield 71%. ^{1}H NMR: 2.38 (s, 3H, Me), 3.97 (d, 1H, J = 15.6, 5-H_A), 4.20 (dd, 1H, J = 1.9 and 15.6, 5-H_B), 6.85 (d, 1H, J = 4.9, H_5-Py), 7.08-7.33 (m, 3H, ArH), 7.67 (d, 1H, J = 1.9, H-2), 7.96 (s, 1H, H_3-Py), 8.09 (d, 1H, J = 4.9, H_6-Py). Anal. ($C_{15}H_{12}Cl_2N_2OS$) C, H, N.

2-(2-Chloro-6-fluorophenyl)-3-(4-methylpyridin-2-yl)-1,3-thiazolidin-4-one (25). Mp: 130-133 °C, yield 40%. ^{1}H NMR: 2.34 (s, 3H, Me), 3.84 (d, 1H, J = 15.4, 5-H_A), 4.18 (dt, 1H, J = 1.6 and 15.4, 5-H_B), 6.82 (d, 1H, J = 5.2, H_5-Py), 6.86-7.34 (m, 4H, ArH and H-2), 8.02 (s, 1H, H_3-Py), 8.08 (d, 1H, J = 5.2, H_6-Py). Anal. ($C_{15}H_{12}ClFN_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-(4-methylpyridin-2-yl)-1,3-thiazolidin-4-one (26). Mp: 108-110 °C, yield 42%. ^{1}H NMR: 2.33 (s, 3H, Me), 3.83 (d, 1H, 15.9, 5-H_A), 4.21 (dd, 1H, J = 1.6 and 15.9, 5-H_B), 6.70-6.83 (m, 3H, H-3',5' and H_5-Py), 7.14 (m, 1H, H-4'), 7,20 (d, 1H, J = 1.6, H-2), 8.00 (s, 1H, H_3-Py), 8.08 (d, 1H, J = 5.0, H_6-Py). Anal. ($C_{15}H_{12}F_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-(5-methylpyridin-2-yl)-1,3-thiazolidin-4-one (27). Mp: 157-159 °C; yield 85%. ^{1}H NMR: 2.22 (s, 3H, Me), 3.93 (d, 1H, J = 15.7, 5-H_A), 4.15 (dd, 1H, J = 2.2 and 15.7, 5-H_B), 7.02-7.29 (m, 3H, ArH), 7.47 (dd, 1H, J = 1.9 and 8.5, H_4-Py), 7.61 (d, 1H, J = 2.2, H-2), 7.97 (d, 1H, J = 8.5, H_3-Py), 8.03 (d, 1H, J = 1.9, H_6-Py). Anal. ($C_{15}H_{12}Cl_2N_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-(5-methylpyridin-2-yl)-1,3-thiazolidin-4-one (28). Mp: 99-101 °C, yield 18%. ^{1}H NMR: 2.21 (s, 3H, Me), 3.83 (d, 1H, 15.6, 5-H_A), 4.20 (dd, 1H, J = 1.4 and 15.6, 5-H_B), 6.80 (m, 2H, H-3',5'), 7.15 (m, 1H, H-4'), 7,17 (d, 1H, J = 1.4, H-2), 7.47 (dd, 1H, J = 2.2 and 8.5, H_4-Py), 8.03 (d, 1H, J = 8.5, H_3-Py), 8.06 (d, 1H, J = 2.2, H_6-Py). Anal. ($C_{15}H_{12}F_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-(6-methylpyridin-2-yl)-1,3-thiazolidin-4-one (29). Mp: 142-144 °C, yield 38%. ^{1}H NMR: 2.29 (s, 3H, Me), 3.94 (d, 1H, J = 15.9, 5-H_A), 4.16 (d, 1H, J = 2.2 and 15.9, 5-H_B), 6.82 (d, 1H, J = 7.7, H_5-Py), 7.02-7.30 (m, 3H, ArH), 7.54 (dd, 1H, J = 7.7 and 8.2, H_4-Py), 7.63 (d, 1H, J = 2.2, H-2), 7.94 (d, 1H, J = 8.2, H_3-Py). Anal. ($C_{15}H_{12}Cl_2N_2OS$) C, H, N.

2-(2-Chloro-6-fluorophenyl)-3-(6-methylpyridin-2-yl)-1,3-thiazolidin-4-one (30). Mp: 100-103 °C, yield 56%. ^{1}H NMR: 2.32 (s, 3H, Me), 3.85 (d, 1H, J = 15.6, 5-H_A), 4.20 (d, 1H, J = 15.6, 5-H_B), 6.83 (d, 1H, J = 7.4, H_5-Py), 6.87-7.36 (m, 4H, ArH and H-2), 7.55 (dd, 1H, J = 7.4 and 8.0, H_4-Py), 8.03 (d, 1H, J = 8.0, H_3-Py). Anal. ($C_{15}H_{12}ClFN_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-(6-methylpyridin-2-yl)-1,3-thiazolidin-4-one (31). Mp: 88-89 °C, yield 46%. ^{1}H NMR: 2.32 (s, 3H, Me), 3.84 (d, 1H, J = 15.9, 5-H_A), 4.23 (dd, 1H, J = 1.6 and 15.9, 5-H_B), 6.81 (t, 2H, J = 8.8, H-3',5'), 6.83 (d, 1H, J = 7.4, H_5-Py), 7.15 (m, 1H, H-4'), 7.20 (d, 1H, J = 1.6, H-2), 7.54 (dd, 1H, J = 7.4 and 8.2, H_4-Py), 8.03 (d, 1H, J = 8.2, H_3-Py). Anal. ($C_{15}H_{12}F_2N_2OS$) C, H, N.

2-(2,6-Dichlorophenyl)-3-(4,6-dimethylpyridin-2-yl)-1,3-thiazolidin-4-one (32). Mp: 156-158 °C, yield 87%. ^{1}H NMR: 2.25 and 2.82 (2s, 6H, Me), 3.93 (d, 1H, J = 15.9, 5-H_A), 4.15 (dd, 1H, J = 2.2 and 15.9, 5-H_B), 6.66 (s, 1H, H_5-Py), 7.02-7.28 (m, 3H, ArH), 7.63 (d, 1H, J = 2.2, H-2), 7.75 (s, 1H, H_3-Py). Anal. ($C_{16}H_{14}Cl_2N_2OS$) C, H, N.

2-(2-Chloro-6-fluorophenyl)-3-(4,6-dimethylpyridin-2-yl)-1,3-thiazolidin-4-one (33). Mp: 143-145 °C, yield 65%. ^{1}H NMR: 2.28 (s, 6H, Me), 3.84 (d, 1H, J = 15.7, 5-H_A), 4.19 (d, 1H, J = 15.7, 5-H_B), 6.67 (s, 1H, H_5-Py), 6.84-7.36 (m, 4H, ArH and H-2), 7.84 (s, 1H, H_3-Py). Anal. ($C_{16}H_{14}ClFN_2OS$) C, H, N.

2-(2,6-Difluorophenyl)-3-(4,6-dimethylpyridin-2-yl)-1,3-thiazolidin-4-one (34). Mp: 122 °C, yield 80%. ^{1}H NMR: 2.27 (s, 6H, Me), 3.84 (d, 1H, J = 15.9, 5-H_A), 4.23 (dd, 1H, J = 1.2 and 15.9, 5-H_B), 6.67 (s, 1H, H_5-Py), 6.80 (t, 2H, J = 8.5, H-3',5'), 7.15 (m, 1H, H-4'), 7.20 (d, 1H, J = 1.2, H-2), 7.84 (s, 1H, H_3-Py). Anal. ($C_{16}H_{14}F_2N_2OS$) C, H, N.

Computational studies.

Structures: 1. Protein. The X-ray structure of RT complexed with the inhibitor Nevirapine was retrieved from the Brookhaven Protein Data Bank (code 1VRT, 2.20 Å resolution) and used as target for our modeling studies. The ligand and water molecules were discarded and missing side chains of the unbound enzyme were manually completed using the InsightII/Biopolymer module.[1] Using the Biopolymer utility within the software package Sybyl 6.7,[2] "Essential_only" hydrogen atoms were added to the protein and later "KOLLUA" partial charges were assigned. **2. Ligands.** Coordinates for Nevirapine were taken directly from the X-ray structure of its complex with the

HIV-1 RT. The structures of the ligands **21** and **29** were constructed using standard bond lengths and angles from the Sybyl fragment library and fully optimized by semiempirical quantum mechanical method AM1. The flexible torsions identified by the docking procedure for the two inhibitors correspond to those defined by the two aromatic nuclei.

GRID studies. The calculations of the main intermolecular interactions involved in the RT inhibition were performed using the GRID software.[3] This approach is useful for determining energetically favourable binding sites for small chemical groups (probes) and a macromolecule target of known three-dimensional structure (i.e. RT enzyme). The probe groups are small, distinct chemical entities and correspond to the functional groups of the inhibitors, as methyl, hydroxyl or carbonyl groups. In the GRID method, the probe is moved through a regular grid of points in a region of interest around the target molecule and, at each point, the interaction energy between the probe and the target molecule is calculated using a classical empirical energy function. All GRID calculations were performed with several probes in a box with dimensional equal 32 Å and a grid spacing of 1 Å. The interaction energies were contoured at an energy level of –0.3 Kcal/mol for the hydrophobic DRY probe, and –3.5 Kcal/mol for both aliphatic methyl and aromatic probes

Docking calculations. Docking studies to RT were carried out using the package AutoDock 3.0, a program that allows torsional flexibility in the ligand, while the protein is kept rigid.[4] The dimensions of the grid were 60Å×60Å×60Å with grid points separated by 0.375 Å. The grid was centered on the allosteric site, using the Nevirapine crystallographic position as reference. The AutoGrid program generated separate grid maps for all atom types of the ligand structures plus one for electrostatic interactions. Our inhibitors present fluorine, chlorine and bromine atoms, but the AutoDock force field is based on a version of the AMBER force field[5] which lacks parameters for halogens. However, AutoDock provides the actual values of the non-bond parameters for halogens derived from the Merck force field, MMFF.[6] In order to allow the software to use these atom type parameters, we edit the atom names of the appropriate HETATM records in our PDBQ file, so that the first letter corresponded to the AutoDock single-letter code (i.e. "F" for fluorine, "c" for chlorine and "b" for bromine). We used the so-called Lamarckian genetic algorithm (LGA), which combines a traditional genetic algorithm (GA) with a local search method. For both ligands, the docking simulation was composed of 100 independent runs, starting each time from a different position and orientation chosen randomly. Clustering of the docked conformations was performed

with a tolerance of 1.5 Å. All the other values were used as default settings and the results were ranked by the lowest energy representative of each cluster combined with the root mean square deviation.

In vitro anti-HIV assay. The antiviral experiments using MT-4 cell cultures and HIV-1 (III_B) and HIV-2 (ROD) or CEM cell cultures and NNRTI-resistant mutant HIV-1 strains were performed following previously described procedures.[7-9]

RT assay. The RT assay using recombinant HIV-1 RT was essentially performed as described.[10]

Supporting References

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