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Naphthoxazepine Inhibitors of HIV-1 Integrase: Synthesis and Biological Evaluation

Antonio Garofalo,*[a] Fedora Grande,[b] Antonella Brizzi,[c] Francesca Aiello,[a] Raveendra Dayam,[b] and Nouri Neamati[b]

Two sets of compounds derived from the fusion of a diversely annulated naphthoxazepinedione system with 1,3-thiazole and 1,3-oxazole are described. These compounds are close analogues of previously reported thiazolothiazepine inhibitors of human immunodeficiency virus type 1 integrase (HIV-1 IN). Some of the new derivatives show potency similar to that of the reference compounds, thus gaining further insight into the structure–activity relationship of this class of IN inhibitors.

Introduction

HIV-1 integrase (IN) is an important target for the identification of novel antiretroviral compounds potentially active against HIV-1 replication. Current therapeutic protocols for the treatment of HIV/AIDS are based on combination regimens composed of inhibitors that target reverse transcriptase (RT) and protease (PR). The combination regimens are known to cause severe long-term side-effects in patients. Thus, the discovery of safer antiretroviral drugs active against alternative targets important for viral replication is urgently needed. Raltegravir (MK0518) is a selective IN inhibitor that is expected to be soon approved by the FDA. IN catalyses two reactions, known as 3′-processing and strand transfer, which result in the transfer of retroviral DNA into the host genome.[1,2]

The availability of in vitro assays using recombinant IN has allowed the discovery of numerous IN inhibitors belonging to different chemical classes.[3–6] Several compounds such as S-1360, L-780,810, MK-0518, and GS-9137 thus far have advanced to human clinical trials.[7–11] Previously, we discovered several novel thiazolothiazepine derivatives as IN inhibitors with antiviral activity in cell-based assays.[12] These compounds exerted IN inhibitory activity in the presence of Mg^{2+}, the cofactor most likely used in vivo, unlike many other classes of inhibitors that only inhibit IN in the presence of Mn^{2+}. Due to their low cytotoxicity, low molecular weight, drug-like properties, and structural novelty, we embarked on a study to optimize the original lead compounds.

To perform structure–activity relationship studies, we decided to design simple molecules based on the parent compounds that are as easy to synthesize as the previously reported compounds. The structural motif common to these compounds consists of a central 1,4-thiazepine- or 1,4-oxazepinedione moiety (a) fused to a carbocyclic aromatic system (benzo or naphtho) (b) and to a 1,3-thiazolidine or 1,3-oxazolidine ring (c), as depicted in Figure 1.

The comparison of earlier inhibition data suggested that naphtho derivatives were generally more potent than the benzo analogues against both the 3′-processing and strand transfer reactions of IN with IC_{50} values of ≤ 100 μM. Moreover,

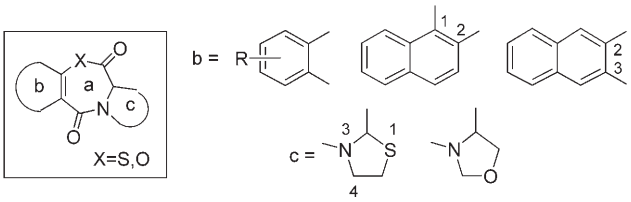


Figure 1. Common structural motif of thiazepinedione and oxazepinedione IN inhibitors.

the shift from a thiazepine to an oxazepine scaffold and the replacement of the thiazole ring with an oxazole did not considerably affect potency. On the other hand, the overall geometry of the tetracyclic system, directly depending on the different modes of annulation of the naphtho moiety, seemed to be more important for activity. In particular, among the three different possible modes, a linear 2,3-naphtho annulation appears to confer the right geometry required for the molecules to be accommodated in the IN active site.

Herein we report the preparation and preliminary biological evaluation of two series of tetracyclic analogues resulting from the fusion of diversely annulated naphthoxazepinedione systems with 1,3-thiazole and 1,3-oxazole, deriving from an elaboration of commercially available 2-thiazolidinecarboxylic acid and in situ preformed 4-oxazolidinecarboxylic acid, respectively. To understand their mode of interactions with the IN active

[a] *Prof. A. Garofalo, Prof. F. Aiello*
Dipartimento di Scienze Farmaceutiche
Università della Calabria, 87036 Arcavacata di Rende, Cs, (Italy)
Fax: (+39) 0984-493-298
E-mail: garofalo@unical.it

[b] *Prof. F. Grande, Prof. R. Dayam, Prof. N. Neamati*
Department of Pharmaceutical Sciences, School of Pharmacy
University of Southern California
1985 Zonal Avenue, Los Angeles, CA 90089 (USA)

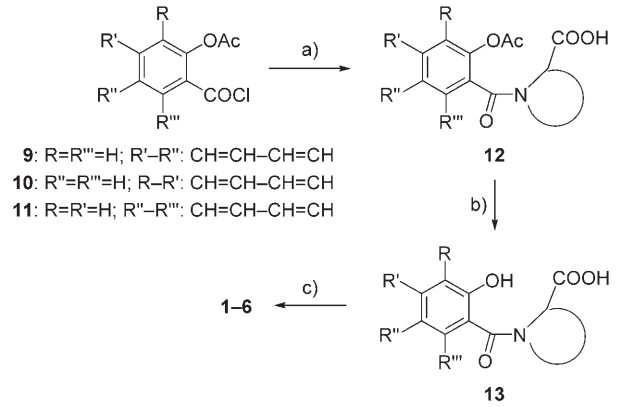
[c] *Prof. A. Brizzi*
Dipartimento Farmaco Chimico Tecnologico
Università di Siena, Via A. Moro, 53100 Siena (Italy)

site, we docked all the compounds onto a previously reported X-ray crystal structure of the core domain of IN.

Results and Discussion

Chemistry

The synthesis of compounds **1**–**6** was accomplished following the general method outlined in Scheme 1 and as previously described using the correct acetoxynaphthoic acid chloride **9**–**11** and an appropriate cyclic amino acid **7** or **8** (Figure 2), as starting materials.[13] Amides of general formula **12** were obtained in good yields. (±)-Thiazolidine-2-carboxylic acid **7** is commercially available, while oxazolidine-4-carboxylic acid **8** was prepared starting from formaldehyde and DL-serine and in situ N-acylated as already described.[14] The hydroxy acid intermediates **13**, in turn obtained by controlled hydrolysis of **12**, were subjected to lactonization using acetic anhydride as dehydrating agents, leading to polycyclic compounds **1**–**6** in generally acceptable yield.[15]



Scheme 1. Reagents and conditions: a) cyclic amino acid, THF/H_2O, pH 8, room temperature; b) Na_2CO_3, H_2O, room temperature; c) Ac_2O, room temperature.

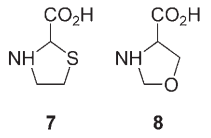


Figure 2. Cyclic amino acid precursors.

Inhibition of IN catalytic activities by naphthoxazepinediones

Chemical structures of naphthoxazepinediones **1**–**6** are reported in Figure 3. Interestingly, the linear compounds **1** and **4** are the most potent IN inhibitors in this series of oxazepinediones showing an activity profile similar to that of previously identified thiazepinediones. Compound **1** inhibited both the 3′-processing and strand transfer activities of IN with IC_{50} values of 110 and 100 μM, respectively. Similarly, compound **4** inhibited both the 3′-processing and strand transfer activities of IN with IC_{50} values of 120 and 90 μM, respectively. Interestingly, both

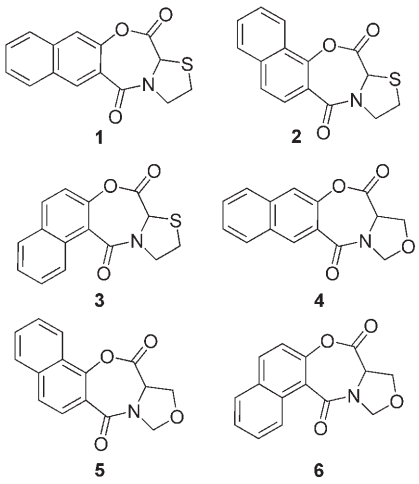


Figure 3. Chemical structures of the new compounds.

the derivatives **1** and **4** showed both anti-IN and antiviral activity with a therapeutic index (TI) value of >4 and >3, respectively. Furthermore, compounds **1** and **4** showed to be active in the presence of Mg^{2+} within the same concentration as in Mn^{2+}. All the other oxazepinediones (**2**, **3**, and **5**) containing slightly bent geometry showed moderate to weak inhibitory activities against both the 3′-processing and strand transfer reactions of IN (IC_{50} > 250 μM) (Table 1). To identify the biologically active conformation of compounds **1**–**6**, we docked all the compounds into the active site of IN using GOLD 3.1.[16] Compounds **1**–**6** occupied a wide cavity surrounded by the active site amino acid residues E152, I151, P142, I141, G140, F139, N117, D116, H114, D64, and Q62. Particularly, the linear compounds **1** and **4** adopted a favorable bound conformation inside the IN active site, so that the oxygen atom of the oxazolidine ring of **4** and, most likely, sulfur of thiazolidine of **1** were suitably positioned to form a coordination bond with Mg^{2+} (Figure 4). This may explain the observed relatively higher IN inhibitory potency of such compounds than that of the analogues with a bent geometry. However, the shift from a thiazepine structure of previously reported derivatives to an oxazepine did not improve the interaction with the enzyme. This

Table 1. Anti-HIV-1 integrase activities of compounds **1**–**6**.

	IN Assay IC_{50} [μM]		Cell Data [μM]	
Compd	3′-Processing	Strand Transfer	EC_{50}[a]	CC_{50}[b]
1	110 ± 24	100 ± 28	80	>330
2	250 ± 25	300 ± 32	>200	>200
3	300 ± 15	330 ± 25	150	>200
4	120 ± 18	90 ± 23	100	>300
5	400	430	150	>150
6	NT[c]	NT[c]	>300	>300

[a] EC_{50}: 50% effective concentration. [b] CC_{50}: 50% cytotoxic concentration. [c] NT: not tested.

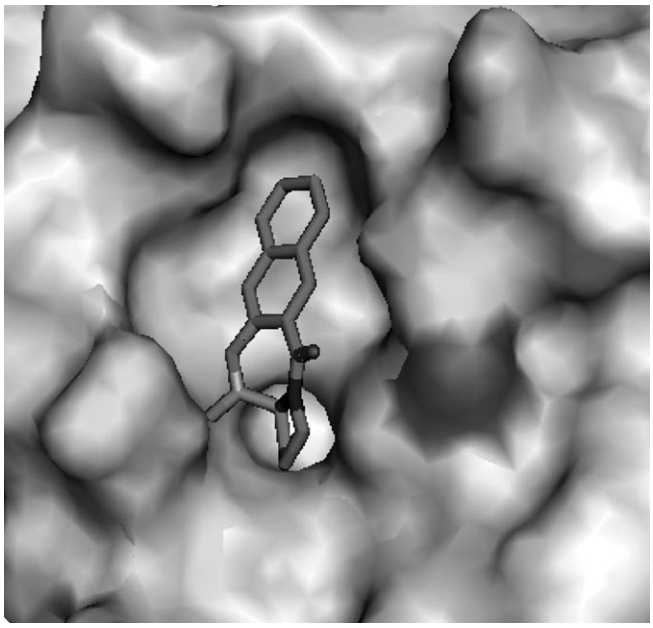


Figure 4. The predicted bound conformation of compound **4** inside the HIV-1 IN active site. Compound **4** is represented as a stick model. The HIV-1 IN active site region is represented as a surface model. The yellow surface shows catalytic triad residues D64, D116, and E152, while the magenta surface indicates a Mg^{2+} ion.

could be due to the overall seven-membered ring contraction. Optimally functionalized derivatives of the linear compounds are expected to exert improved IN inhibitory potency.

Conclusions

We designed and synthesized novel analogues of previously reported thiazolothiazepine IN inhibitors. Some of the new analogues showed a similar range of potency as the reference compounds and are amenable to further structural modifications for enhanced potency and selectivity. Furthermore, our docking studies demonstrate that these compounds may bind to a region of the active site in proximity to the key residues essential for the catalytic activities of IN. Further structural modifications will be reported in due course.

Experimental Section

Chemistry. All reactions were carried out under a nitrogen atmosphere. Progress of the reaction was monitored by TLC on silica gel plates (Riedel-de-Haen, Art. 37341). Organic solutions were dried over $MgSO_4$ and evaporated on a rotary evaporator under reduced pressure. Melting points were measured using an Electrothermal 8103 apparatus and are uncorrected. IR spectra were recorded as thin films on Perkin–Elmer 398 and FT 1600 spectrophotometers. ^{1}H NMR spectra were recorded on a Brüker 300 MHz spectrometer with TMS as an internal standard: chemical shifts are expressed in δ values (ppm) and coupling constants (J) in Hz. Mass spectral data were determined by direct insertion at 70 eV with a VG70 spectrometer. Merck silica gel (Kieselgel 60/230–400 mesh) was used for flash chromatography columns. Elemental analyses were performed on a Perkin–Elmer 240C elemental analyzer, and the results are within $\pm$0.4% of the theoretical values. Yields refer to purified products and are not optimized.

General procedure for the synthesis of compounds 12: The preparation of *N*-(1-acetoxy-2-naphthoyl)oxazolidin-4-carboxylic acid is described as a representative example. A mixture of formaldehyde (37% solution in water, 14.0 mmol, 1.0 mL), DL-serine (1.4 g, 13.3 mmol) and 2 N NaOH (6.5 mL) was stirred overnight at 0 °C. Sodium carbonate (0.7 g, 6.6 mmol) was added in one portion to the cold solution. A solution of 1-acetoxy-2-naphthoic acid chloride (3.3 g, 13.3 mmol) in dry THF (20 mL) was then added dropwise,[13] while a weakly alkaline pH was maintained by the addition of solid sodium carbonate. The mixture was stirred overnight, then concentrated and made acidic (pH 3–4) by adding concentrated HCl. The formed solid was extracted into ethyl acetate, and the resulting solution was washed with water, dried and evaporated. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH/HCO_2H, 86:14:1) to give a waxy yellow solid (2.1 g, 50%); IR (KBr): $\tilde{\nu}$ = 1715, 1700, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 10.05 (1H, bs), 8.05–7.75 (3H, m), 7.82 (1H, d, J = 8.5 Hz), 7.68 (1H, m), 7.48 (1H, d, J = 8.5 Hz), 4.95 (1H, m), 4.45 (2H, t, J = 8.4 Hz), 4.25 (2H, m), 2.49 ppm (3H, s); MS (EI) m/z 329 [M^+]; anal. ($C_{17}H_{15}NO_6$) C, H, N.

General procedure for the synthesis of compounds 13: The preparation of *N*-(1-hydroxy-2-naphthoyl)oxazolidin-4-carboxylic acid is described as a representative example. *N*-(1-acetoxy-2-naphthoyl)-oxazolidin-4-carboxylic acid (2.0 g, 6.0 mmol) was dissolved in a solution of sodium carbonate (0.8 g, 7.5 mmol) in water (20 mL) and stirred overnight at room temperature, then made acidic (pH 3–4) by adding concentrated HCl at 0 °C. The formed solid was extracted with ethyl acetate, and the resulting solution was washed with water, dried and evaporated. The resulting residue was purified by crystallization to give a solid (1.3 g, 74%); mp: 155 °C (acetonitrile/diethyl ether); IR (KBr): $\tilde{\nu}$ = 3335 br, 1760, 1645 cm^{-1}; ^{1}H NMR (CD_3OD): δ = 12.00 (1H, bs), 8.41 (1H, d, J = 8.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.55 (2H, m), 7.30 (2H, m), 5.35 (2H, ABq, J = 13.0, 4.2 Hz), 5.05 (1H, t, J = 7.0 Hz), 4.49 (1H, t, J = 7.5 Hz), 4.25 (1H, dd, J = 6.8, 2.3 Hz), 2.80 ppm (1H, bs); MS (EI) m/z 287 [M^+]; anal. ($C_{15}H_{13}NO_5$) C, H, N.

(±)-2,3-Dihydro-5*H*,13*H*-naphtho[2,3-*f*]thiazolo[2,3-*c*][1,4] oxazepine-5,13(13a*H*)-dione 1: A suspension of *N*-(2-hydroxy-3-naphthoyl)thiazolidin-2-carboxylic acid (121 mg, 0.4 mmol) in acetic anhydride (2 mL) was stirred 24 h at room temperature. The resulting solution was then diluted with chilled-water and left for several hours at 4 °C. The aqueous solution was extracted with chloroform and the organic layer was shaken successively with a 5% sodium bicarbonate solution and brine. The residue obtained after evaporation of the solvent was recrystallized to give pure compound **1** as a white solid (46 mg, 40%): mp 231 °C (dichloromethane/hexanes); IR (KBr): $\tilde{\nu}$ = 1755, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.75 (3H, m), 7.35 (3H, m), 4.50 (1H, dd, J = 6.7, 1.5 Hz), 4.23 (1H, d, J = 10.6 Hz), 4.08 (1H, d, J = 10.6 Hz), 2.92 (1H, dd, J = 12.1, 1.5 Hz), 2.56 ppm (1H, dd, J = 12.1, 6.7 Hz); MS (EI) m/z 285 [M^+]; anal. ($C_{15}H_{11}NO_3S$) C, H, N.

(±)-9,10-Dihydro-7*H*,12*H*-naphtho[2,1-*f*]thiazolo[2,3-*c*][1,4] oxazepine-7,12(11a*H*)-dione 2: Following the identical procedure to that described for compound **1**, but using *N*-(1-hydroxy-2-naphthoyl)thiazolidin-2-carboxylic acid (151 mg, 0.5 mmol), compound **2** was obtained as a white solid (104 mg, 73%); mp: 178 °C (dichloromethane/petroleum ether); IR (KBr): $\tilde{\nu}$ = 1755, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.40 (1H, m), 7.70 (5H, m), 5.40 (1H, s), 4.31 (1H, d, J = 6.1 Hz), 3.99 (1H, d, J = 6.1 Hz), 3.42 (1H, dd, J = 12.1, 1.5 Hz),

2.56 ppm (1H, dd, $J=12.1$, 6.7 Hz); MS (EI) m/z 285 [M^+]; anal. ($C_{15}H_{11}NO_3S$) C, H, N.

(±)-10,11-Dihydro-8*H*,13*H*-naphtho[1,2-*f*]thiazolo[2,3-*c*][1,4] oxazepine-8,13(8a*H*)-dione 3: Following the identical procedure to that described for compound **1**, but using *N*-(2-hydroxy-1-naphthoyl)thiazolidin-2-carboxylic acid (120 mg, 0.4 mmol), compound **3** was obtained as a white solid (75 mg, 59%); mp: 210 °C (dichloromethane/hexanes); IR (KBr): $\tilde{\nu}=1755$, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.03$ (1H, d, $J=8.0$ Hz), 7.91 (1H, d, $J=8.0$ Hz), 7.65 (3H, m), 7.32 (1H, d, $J=8.0$ Hz), 5.45 (1H, s), 4.40 (1H, d, $J=2.4$ Hz), 4.02 (1H, d, $J=6.5$ Hz), 3.42 (1H, d, $J=6.5$ Hz), 3.22 ppm (1H, d, $J=2.4$ Hz); MS (EI) m/z 285 [M^+]; anal. ($C_{15}H_{11}NO_3S$) C, H, N.

(±)-1,13a-Dihydro-3*H*,5*H*,13*H*-naphtho[2,3-*f*]oxazolo[4,3-*c*][1,4]oxazepine-5,13-dione 4: The preparation of this compound is described in Ref. [15].

(±)-11,11a-Dihydro-7*H*,12*H*-naphtho[2,1-*f*]oxazolo[4,3-*c*][1,4] oxazepine-7,12-dione 5: Following the identical procedure to that described for compound **1**, but using *N*-(2-hydroxy-1-naphthoyl)oxazolidin-2-carboxylic acid (115 mg, 0.4 mmol), compound **5** was obtained as a white solid (42 mg, 45%); mp: 158 °C (dichloromethane/petroleum ether); IR (KBr): $\tilde{\nu}=1750$, 1650 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.42$ (1H, d, $J=8.3$ Hz), 7.81 (1H, d, $J=7.8$ Hz), 7.61 (1H, m), 7.52 (1H, m), 7.30 (2H, m), 5.25 (2H, Abq, $J=3.0$ Hz), 4.86 (1H, t, $J=6.6$ Hz), 4.30 ppm (2H, dd, $J=8.0$, 6.5 Hz); MS (EI) m/z 269 [M^+]; anal. ($C_{15}H_{11}NO_4$) C, H, N.

(±)-8a,9-Dihydro-8*H*,13*H*-naphtho[1,2-*f*]oxazolo[4,3-*c*][1,4] oxazepine-8,13-dione 6: Following the identical procedure to that described for compound **1**, but using *N*-(1-hydroxy-2-naphthoyl)oxazolidin-2-carboxylic acid (115 mg, 0.4 mmol), compound **6** was obtained as a white solid (10 mg, 9%); mp: 202 °C (dichloromethane/hexanes); IR (KBr): $\tilde{\nu}=1745$, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.70$ (1H, d, $J=8.0$ Hz), 8.00 (1H, d, $J=8.0$ Hz), 7.80 (1H, d, $J=7.2$ Hz)), 7.60 (2H, m), 7.25 (1H, d, $J=8.6$ Hz), 5.00 (2H, Abq, $J=4.2$ Hz), 4.28 (1H, dd, $J=6.5$, 1.7 Hz), 3.80 (1H, dd, $J=12.0$, 1.7 Hz), 3.40 ppm (1H, dd, $J=12.0$, 6.5 Hz); MS (EI) m/z 269 [M^+]; anal. ($C_{15}H_{11}NO_4$) C, H, N.

Molecular modeling: The structures of all the compounds (Figure 3) were built and minimized using Catalyst (Accelrys, Inc). The poling algorithm implemented within Catalyst was used to generate conformations for all the compounds. For each compound all feasible unique conformations were generated over a 20 Kcal/mol range of energies using the best flexible conformation generation method in Catalyst. The subunit B of the core domain X-ray structure of IN (PDB 1BIS), in which all the active site amino acid residues were resolved, was chosen for docking purpose.[17] All the water molecules present in the protein were removed and hydrogen atoms were added to the protein in consideration of appropriate ionization states for both the acidic and basic amino acid residues. Docking was performed using version 3.1 of the GOLD: Genetic Optimization for Ligand Docking (Cambridge Crystallographic Data Centre) software package.[16] A 20 Å radius active site was defined considering the carboxylate oxygen atom (OD1) of amino acid residue D64 as the centre of the active site. Based on the GOLD fitness score, for each molecule a bound conformation with high fitness score was considered as the best bound conformation. All docking runs were carried out using standard default settings with a population size of 100, a maximum number of 100 000 operations, a mutation and crossover rate of 95. The fitness function that was implemented in GOLD consisted basically of H-bonding, complex energy and ligand internal energy terms.

Biological materials, chemicals, and enzymes: All compounds were dissolved in DMSO and the stock solutions were stored at −20 °C. The [γ-^{32}P]ATP was purchased from either Amersham Biosciences or ICN. The expression system for the wild-type IN was a generous gift of Dr. Robert Craigie, Laboratory of Molecular Biology, NIDDK, NIH, Bethesda, MD.

Preparation of oligonucleotide substrates: The oligonucleotides 21top, 5′-GTG TGG AAA ATC TCT AGC AGT-3′ and 21bot, 5′-ACT GCT AGA GAT TTT CCA CAC-3′ were purchased from Norris Cancer Center Core Facility (University of Southern California) and purified by UV shadowing on polyacrylamide gel. To analyze the extent of 3′-processing and strand transfer using 5′-end labeled substrates, 21top was 5′-end labeled using T_4 polynucleotide kinase (Epicentre, Madison, WI) and [γ-^{32}P]-ATP (Amersham Biosciences or ICN). The kinase was heat-inactivated and 21bot was added in 1.5-molar excess. The mixture was heated at 95 °C, allowed to cool slowly to room temperature, and run through a spin 25 mini-column (USA Scientific) to separate annealed double-stranded oligonucleotide from unincorporated material.

Integrase and antiviral assays: To determine the extent of 3′-processing and strand transfer, wild-type IN was preincubated at a final concentration of 200 nM with the inhibitor in reaction buffer (50 mM NaCl, 1 mM HEPES, pH 7.5, 50 μM EDTA, 50 μM dithiothreitol, 10% glycerol (w/v), 7.5 mM $MnCl_2$, 0.1 mg mL^{-1} bovine serum albumin, 10 mM 2-mercaptoethanol, 10% dimethyl sulfoxide, and 25 mM MOPS, pH 7.2) at 30 °C for 30 min. Then, 20 nM of the 5′-end ^{32}P-labeled linear oligonucleotide substrate was added, and incubation was continued for an additional one hour. Mg^{2+}-based assays were carried out essentially as described.[18] Reactions were quenched by the addition of an equal volume (16 μL) of loading dye (98%) deionized formamide, 10 mM EDTA, 0.025% xylene cyanol and 0.025% bromophenol blue). An aliquot (5 μL) was electrophoresed on a denaturing 20% polyacrylamide gel (0.09 M tris-borate pH 8.3, 2 mM EDTA, 20% acrylamide, 8 M urea). Gels were dried, exposed in a PhosphorImager cassette, and analyzed using a Typhoon 8610 Variable Mode Imager (Amersham Biosciences) and quantitated using ImageQuant 5.2. Percent inhibition (%I) was calculated using the following equation:

$$\%I = 100\,[1-(D-C)/(N-C)] \quad (1)$$

for which C, N, and D are the fractions of 21-mer substrate converted into 19-mer (3′-processing product) or strand transfer products for DNA alone, DNA plus IN, and IN plus drug, respectively. The IC_{50} values were determined by plotting the logarithm of drug concentration *versus* percent inhibition to obtain concentration that produced 50% inhibition. The anti-HIV activity was assessed against CEM cells by an antiviral drug screening, as previously reported.[12]

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Keywords: docking · HIV-1 integrase · inhibitors · naphthoxazepines · thiazolothiazepines

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