Thiazolothiazepine Inhibitors of HIV-1 Integrase

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A series of thiazolothiazepines were prepared and tested against purified human immunodeficiency virus type-1 integrase (HIV-1 IN) and viral replication. Structure−activity studies reveal that the compounds possessing the pentatomic moiety SC(O)CNC(O) with two carbonyl groups are in general more potent against purified IN than those containing only one carbonyl group. Substitution with electron-donating or -withdrawing groups did not enhance nor abolish potency against purified IN. By contrast, compounds with a naphthalene ring system showed enhanced potency, suggesting that a hydrophobic pocket in the IN active site might accommodate an aromatic system rather than a halogen. The position of sulfur in the thiazole ring appears important for potency against IN, as its replacement with an oxygen or carbon abolished activity. Further extension of the thiazole ring diminished potency. Compounds **1**, **19**, and **20** showed antiviral activity and inhibited IN within similar concentrations. These compounds inhibited IN when Mn^{2+} or Mg^{2+} was used as cofactor. None of these compounds showed detectable activities against HIV-1 reverse transcriptase, protease, virus attachment, or nucleocapsid protein zinc fingers. Therefore, thiazolothiazepines are potentially important lead compounds for development as inhibitors of IN and HIV replication.

Introduction

Human immunodeficiency virus type-1 integrase (HIV-1 IN), one of the three *pol* gene products, is required for the efficient insertion of the retroviral genome into host cell DNA.[1] Upon viral adsorption and reverse transcription, the viral DNA is processed by IN, which removes the terminal 3′-dinucleotides. Following nuclear entry, transesterification of phosphodiester bonds is catalyzed by IN, which cleaves the host DNA and joins it to the processed 3′-viral termini. These two steps, known as 3′-processing and 3′-end joining (or DNA strand transfer), can be reproduced using in vitro assays, which have sought to identify inhibitors of IN. Such assays utilize purified IN protein and oligonucleotides corresponding to the sequence of the U5 or U3 ends of the HIV long terminal repeat (LTR).[2,3] In addition, IN is able to catalyze an apparent reversal of the strand-transfer reaction, a process known as disintegration.[4] In this reaction, a branched oligonucleotide substrate consisting of viral and target DNA is resolved into its constituents. Since IN is unique to retroviruses and required for viral replication, identifying potent inhibitors selective for IN should provide novel therapeutic strategies for the treatment of AIDS.

Several classes of inhibitors have been reported to date. Although, none has yet proven to be highly selective for IN[5,6] and useable for therapeutic development, much information has been gained regarding specific structural requirements for potential leads. For example, a majority of hydroxylated aromatics such as catechol-containing compounds have been demonstrated to possess potency against the 3′-processing and 3′-strand-transfer reactions catalyzed by IN.[6] However, despite such promising initial results, compounds containing this moiety can also cross-link protein,[7] chelate metal,[8,9] and thus generally lack the desired selectivity.[5,6] As opposed to the catechol-containing compounds, non-catechol-containing structures are excellent leads to develop a selective potent IN inhibitor, for they possess considerably less cytotoxicity (e.g. structures below).

Among these, several sulfonamides,[10,11] diaryl sulfones,[12] and aromatic disulfides[13] were found to inhibit IN function at low micromolar concentrations. However, only the 2-mercaptobenzenesulfonamides[13] and to a lesser extent the naphthalene disulfonate exhibited antiviral activity.[11,14]

In our continuing efforts to identify novel non-catechol-containing inhibitors of IN from compounds shown to possess antiviral activity in the NCI Antiviral Drug Screening Program, we discovered benzothiazepine **1** as a "lead". Subsequently, a series of compounds were designed and synthesized to establish a structure−activity relationship among thiazolothiazepines. Herein, we present the synthesis and anti-IN activity of 31 thiazepines.

Results and Discussions

Chemistry. The synthesis of compounds **1**, **5**, **11**, **13**, **14**, **21**−**25**, and **28**−**30** has been accomplished according

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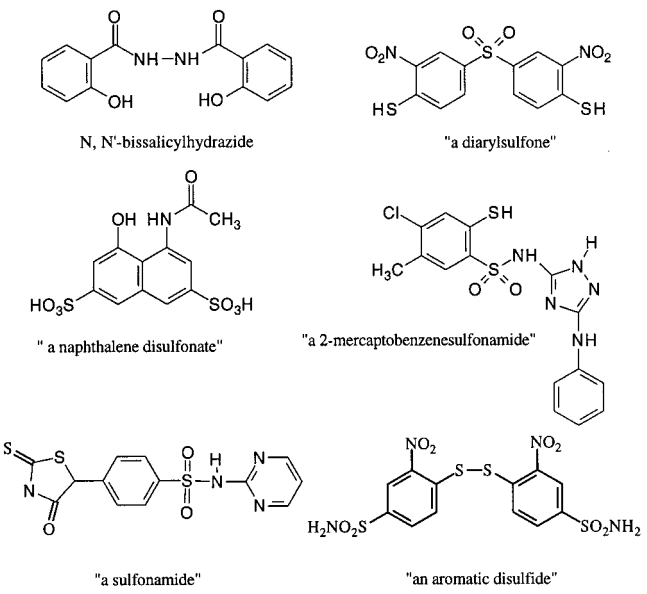
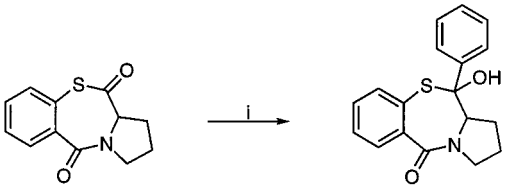


to procedures reported elsewhere.[15−20] Compounds **2**−**4**, **6**−**10**, **12**, **19**, and **20** have been prepared following the general method outlined in Scheme 1, described in ref 15. Schotten−Baumann reaction between the (un)-substituted 2,2′-dithiobis(benzoic acid chloride) or 3,3′-dithiobis(2,2′-naphthoic acid chloride), in turn obtained from corresponding acids **32a**−**g**[21−25] and thionyl chloride, and L-thiaproline (Aldrich) (**33**) or thiazolidine-2-carboxylic acid (**34**)[26] or 1,3-oxazolidine-4-carboxylic acid (**35**)[27] gave disulfides **36**. NaBH4 reduction of the crude disulfides gave the corresponding thiophenols in very good yield. Disulfides **36** and subsequent thiophenols were obtained as amorphous solids by ion-exchange chromatography and were then used without a thorough characterization. The eventual cyclization reaction was carried out using *N*,*N*′-carbonyldiimidazole (CDI) in dry THF leading to optically inactive tricyclics **2**−**4**, **6**−**10**, **12**, and **19**, and **20** because of racemization at C-11a (C-13a in the case of compounds **19** and **20**).

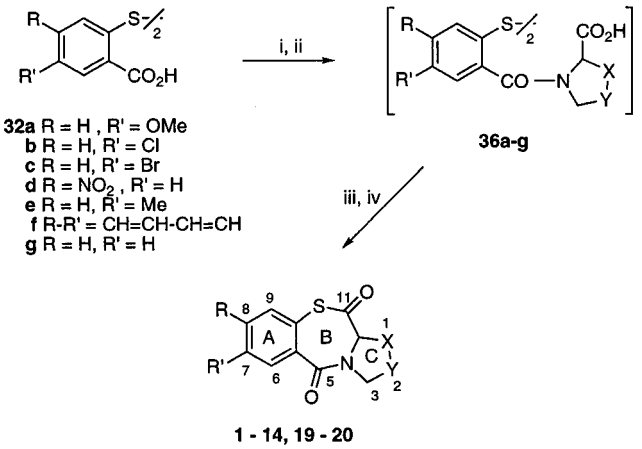
Controlled 3-chloroperbenzoic acid (MCPBA) oxidation of the tricyclic sulfides **4**−**6** and **10** gave sulfoxides **15**−**18** (Scheme 2) which were tentatively assigned a trans configuration on the basis of ^{1}H NMR experiments and Dreiding stereomodels inspection. This would reflect a preferred approach of the electrophile from the less hindered face of the tricyclic, namely the one taken up by the C-11a proton. Compound **26** was obtained as a racemic mixture by reaction of previously described (±)-1,2,3,11a-tetrahydro-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine-5,11-dione (**37**)[16] with phenylmagnesium bromide (eq 1).

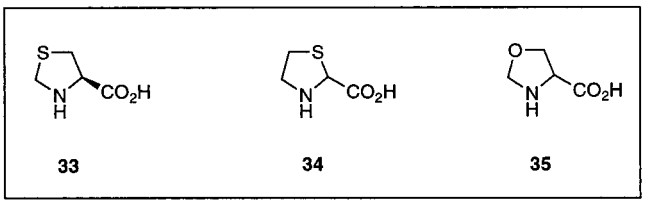


(1)[a]

[a]Reagents: (i) PhMgBr/Et_2O.

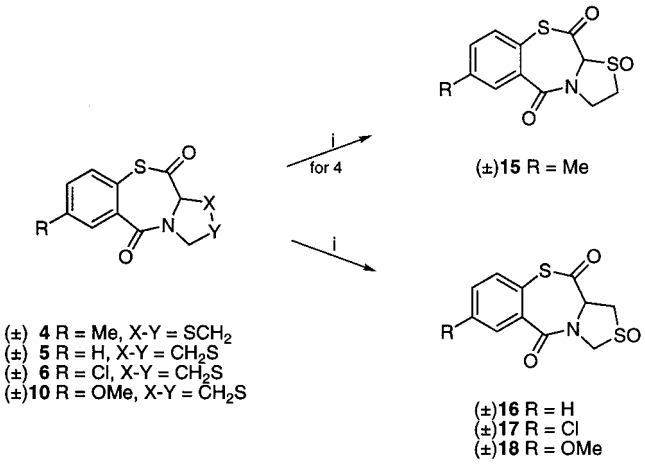
Scheme 1[a]





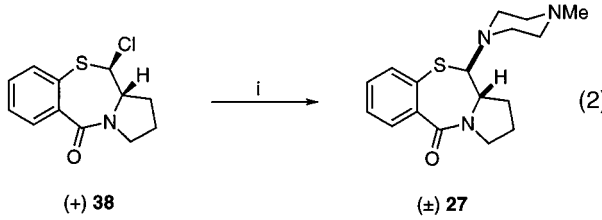
[a] Reagents: (i) $SOCl_2$/reflux; (ii) **33** or **34** or **35**/Na_2CO_3/THF/H_2O/rt; (iii) $NaBH_4$/EtOH/reflux; (iv) CDI/THF/reflux.

Scheme 2[a]



[a] Reagents: (i) MCPBA/CH_2Cl_2/0 °C.

No effort was made in order to elucidate relative configuration for **26**. The basic side chain of compound **27** was installed by means of reaction of 1-methylpiperazine on optical active chloro derivative **38**[15] (eq 2).

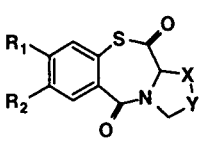


(2)[a]

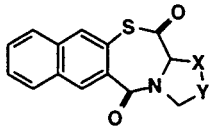
[a]Reagents: (i) $HN(CH_2CH_2)_2NMe/Na_2CO_3/NaI/MeCN$/reflux/20 h.

In the reaction conditions used, a racemic mixture of *trans*-27 was the sole product obtained. Finally, the synthesis of compound **31** was carried out by Mannich

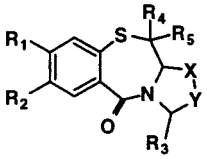
Table 1. Anti-HIV-1 Integrase Activities of Thiazepines **1**−**31**



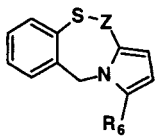
1-18



19-20



21-27

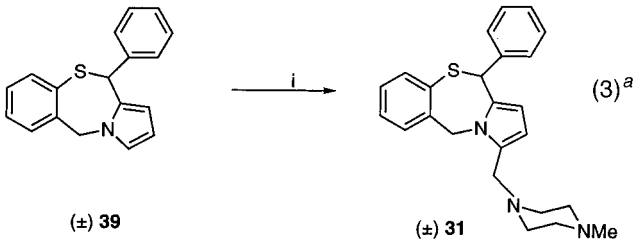


28-31

									integrase assay IC_{50} (μM)		cell data (μM)	
compd	R_1	R_2	R_3	R_4	R_5	R_6	−X−Y−	Z	3′-processing	3′-end joining	EC_{50}[a]	CC_{50}[b]
1	H	H					$-S-CH_2-$		110 ± 12	146 ± 79	107	>200
2	H	Cl					$-S-CH_2-$		151; 105	120; 60	>50	>50
3	H	Br					$-S-CH_2-$		58 ± 15	48 ± 18		
4	H	Me					$-S-CH_2-$		64 ± 47	55 ± 29		
5	H	H					$-CH_2-S-$		208 ± 24	227 ± 104	>200	>200
6	H	Cl					$-CH_2-S-$		158; 111	160; 110	>100	>100
7	H	Br					$-CH_2-S-$		87 ± 24	74 ± 32	>200	>200
8	H	Me					$-CH_2-S-$		52	63	NR[c]	35
9	NO_2	H					$-CH_2-S-$		90 ± 27	100 ± 36	>50	>50
10	H	OMe					$-CH_2-S-$		155; 275	155; 245	>200	>200
11	OMe	OMe					$-CH_2-S-$		670; 630	333; 330	>50	>50
12	H	H					$-CH_2-O-$		>333	>333		
13	OMe	OMe					$-(CH_2)_2-$		>1000	>1000	>200	>200
14	H	H					$-(CH_2)_3-$		406; 495	343 ± 109	>200	>200
15	H	Me					$-S(O)-CH_2-$		590 ± 350	590 ± 350	>100	>100
16	H	H					$-CH_2-S(O)-$		200; 185	215; 222		
17	H	Cl					$-CH_2-S(O)-$		260; 215	280; 200		
18	H	OMe					$-CH_2-S(O)-$		84.5	142		
19							$-S-CH_2-$		40 ± 10	47 ± 6	60	>316
20							$-CH_2-S-$		92 ± 30	100 ± 40	280	>316
21	H	H	H	OAc	H		$-(CH_2)_2-$		>1000	>1000	>200	>200
22	H	H	H	OMe	H		$-(CH_2)_2-$		>1000	>1000	>200	>200
23	H	H	Ph	H	H		$-CH_2-S-$		372; 111	376; 268		
24	OMe	OMe	H	H	H		$-(CH_2)_2-$		>1000	>1000	>200	>200
25	H	H	H	OH	H		$-(CH_2)_2-$		>1000	>1000	>200	>200
26	H	H	H	OH	Ph		$-(CH_2)_2-$		>1000	>1000		
27	H	H	H	H	$N(CH_2CH_2)_2NMe$		$-(CH_2)_2-$		>1000	>1000	>125	>125
28						H		>CO	590	300	146	>200
29						H		$>CHCO_2Et$	>1000	>1000		
30						CH_2NMe_2		$>CHC_6H_4$-*p*F	>1000	>1000		
31						$CH_2N(CH_2CH_2)_2NMe$		>CHPh	>1000	>1000		

[a] EC_{50}: 50% effective concentration. [b] CC_{50}: 50% cytotoxic concentration. [c] NR: not reached due to cytotoxicity.

reaction on the α-pyrrole position of (±)-11-phenyl-5*H*,-11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine (**39**)[20] by means of paraformaldehyde and 1-methylpiperazine dihydrochloride in methanol (eq 3).



[a]Reagents: (i) $CH_2O/HN(CH_2CH_2)_2NMe.2HCl/MeOH/reflux$ 48h.

Biology. Benzothiazepine **1** was originally identified as an IN inhibitor (IC_{50} values for 3′-processing and 3′-end joining: 110 and 146 μM, respectively) from testing a series of compounds that were shown to have antiviral activity in the NCI Antiviral Drug Screening against CEM cells. Compound **1** with a therapeutic index (TI) value of >1.8 (50% effective concentration (EC50) value of 107 ± 26 and 50% cytotoxic concentration (CC50) value of >200 μM) is moderately active in HIV-1-infected CEM cells. Because of its lack of cytotoxicity, this compound served as a "lead" for the design and testing of derivatives. Although **1** was not a potent antiviral compound, its unique structure and the fact that it differed from other reported IN inhibitors warranted designing other inhibitors based on this compound. To establish a structure−activity relationship, 30 analogues were prepared and tested in an assay specific for IN as well as against HIV-1-infected CEM cells. Several important modifications were made to determine the importance of each ring and the nature of the substituents. The first modifications were aimed at the A and B rings (compounds **1**−**18**). In a second class of compounds, an extra ring was added and the importance of the sulfur's position was analyzed (**19** and **20**). The third group contains substitutions on all the rings (**21**−**27**), and the last group (**28**−**31**) was designed to determine whether the thiazolothiazepine ring system is required for activity (Table 1). The chloro-, bromo-, and the methyl-substituted derivatives **2**−**4**, although exhibiting potency similar to that of the parent compound **1** against purified IN, were inactive against viral replication and also showed no detectable cytotoxicity at the highest concentrations tested. Comparable results were obtained when sulfur was moved to position

2 as in compounds **5**−**11** (Table 1). However, the removal of sulfur (compounds **12**−**14**) abolished anti-IN and antiviral activities. Oxidation of the sulfur atom also generally reduced potency (compounds **15**−**18**). Interestingly, both the naphtho derivatives **19** and **20** showed both antiviral and anti-IN activity. Compound **19** with an IC_{50} value of 40 μM against IN was more active than the parent compound **1** against HIV-1 infected cells. Compound **19** with a TI value of > 5 was the best in this series (EC_{50}: 60 and CC_{50}: > 316 μM). Additionally, the naphthalene-substituted **20** was also active against both purified IN (IC_{50} values of 92 and 100 μM against 3′-processing and 3′-strand transfer, respectively) and HIV-1-infected cells (EC_{50}: 279−286 and CC_{50}: >316 μM). Other modifications of the ring system (compounds **21**−**31**) abolished both antiviral and anti-IN activities.

Role of Divalent Metals. Divalent metal ions, such as Mn^{2+} or Mg^{2+}, coordinate with the acidic residues (D, D, E) of IN's active site.[28−30] Metals are involved in the catalytic functioning because the enzyme is unable to perform 3′-processing and 3′-strand transfer without Mn^{2+} or Mg^{2+}. Previous studies have implied that the reported hydroxylated aromatic inhibitors of IN are potentially metal chelators.[8,9,14,31] Thus, chelating metals at the active site of IN have been proposed to be responsible for the inhibition of IN function. However, hydroxylated aromatics are generally active only when Mn^{2+} is used as a cofactor.[8] The results of this study indicate that the thiazolothiazepines are equally active in Mg^{2+}-based assays. Figure 1 shows a representative gel comparing the inhibition of IN in the presence of Mn^{2+} or Mg^{2+}. Compounds **1**, **19**, and **20** were active in the presence of Mg^{2+} within the same concentration range as in Mn^{2+}, thus indicating that these compounds differ from hydroxylated aromatics and perhaps act at different sites on IN. Inhibition of IN in the presence of Mg^{2+} by thiazolothiazepines sets this class of compounds apart from other IN inhibitors.[32,33] The activity in Mg^{2+} might be related to the antiviral activity of the thiazolothiazepine derivatives because Mg^{2+} has been proposed to be the metal used in vivo by IN.

Selectivity. The selectivity of compounds **1**, **19**, and **20** was examined against other sites on the HIV replication cycle. When tested against reverse transcriptase, protease, virus attachment, or nucleocapsid protein zinc fingers, none of the compounds exhibited any detectable activities at 100 μM, suggesting selectivity against IN. Thus, thiazolothiazepines are potentially important lead inhibitors of IN.

Conclusions

In an attempt to identify inhibitors of HIV-1 IN, we tested compounds that were shown to possess antiviral activity in the NCI Antiviral Drug Screening program. Compound **1** was identified as a lead in both in vitro and in vivo studies. In this study we have synthesized and evaluated a series of thiazolothiazepines as potential antiviral compounds with activity against purified IN. On the basis of the structure of tested compounds, we can conclude that the best substituent for both antiviral and anti-IN activity is the addition of a benzene ring to the A ring. Further structure−activity relationships provided evidence that geometry, size, and shape of compounds is as important as their substituents. The fact that thiazolothiazepines are equally potent in Mg^{2+}- and Mn^{2+}-based assays suggests that the IN binding site by these compounds differs from previously reported inhibitors. Testing these compounds against other viral proteins (reverse transcriptase, protease, virus attachment, or nucleocapsid zinc fingers) suggested selectivity for IN. Another advantage of this class of compounds is that they are amenable for preparation of chemical libraries using recent advances in combinatorial chemistry. Cumulatively, this study demonstrates that thiazolothiazepines are novel leads for designing drugs against IN and HIV replication.

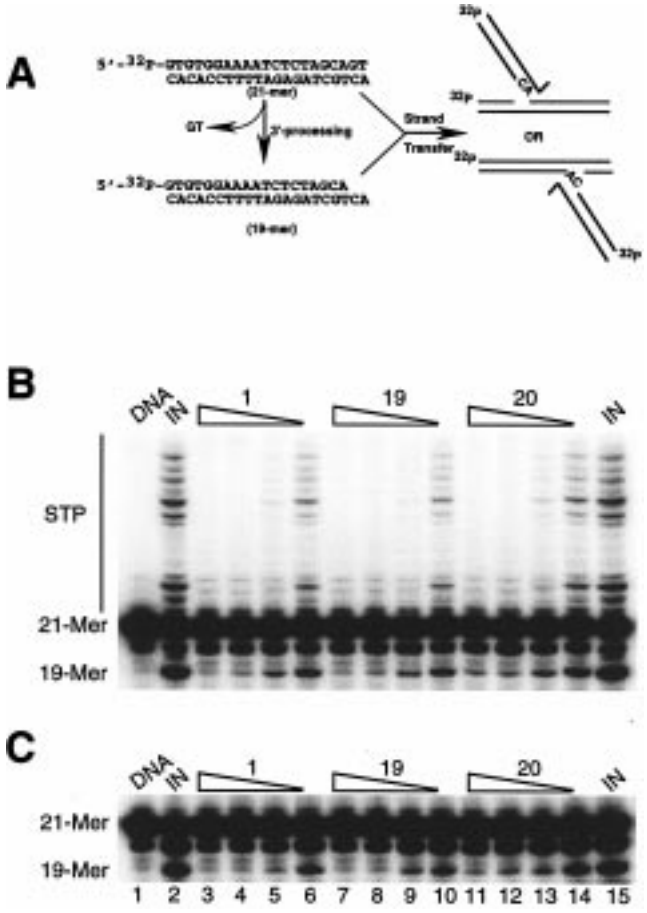


Figure 1. Inhibition of HIV-1 IN catalytic activities by thiazolothiazepines. (A) IN assays: A 21-mer blunt-end oligonucleotide corresponding to the U5 end of the HIV-1 proviral DNA, 5′ end-labeled with ^{32}P, is allowed to react with purified HIV-1 IN. The initial step involves nucleolytic cleavage of two bases from the 3′-end, resulting in a 19-mer oligonucleotide. Subsequently, 3′-ends are then covalently joined to another identical oligonucleotide, which serves as the target DNA. (B, C) Concentration-dependent inhibition of HIV-1 IN by thiazolothiazepines **1**, **19**, and **20** using Mn^{2+} (B) and Mg^{2+} (C) as cofactor: lane 1, DNA alone; lanes 2 and 15, DNA and integrase; lanes 3−6, 7−10, and 11−14, DNA, integrase, and compounds **1**, **19**, and **20** at 1000, 333, 111, and 37 μM, respectively.

Experimental Section

General. Where necessary, solvents were dried and purified according to the recommended procedures. All reactions were carried out under an argon atmosphere. Progress of the reaction was monitored by TLC on silica gel plates (Riedel-de-Haen, Art. 37341). Organic solutions were dried over $MgSO_4$; evaporation refers to removal of solvent on a rotary

evaporator under reduced pressure. Melting points were determined 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 Bruker 200-MHz spectrometer with TMS as internal standard. 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. Dowex 50 × 2 200 resin (Aldrich) was used for ion-exchange chromatography. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer, and the results are within ±0.4% of the theoretical values. Yields refer to purified products and are not optimized.

Chemicals. All compounds were dissolved in DMSO, and all aliquots were also made in DMSO prior to each experiment. The stock solutions were kept at −20 °C.

Preparation of Oligonucleotide Substrates. The HPLC-purified oligonucleotides AE117, 5′-ACTGCTAGAGATTTTC-CACAC-3′, and AE118, 5′-GTGTGGAAAATCTCTAGCAGT-3′, were purchased from Midland Certified Reagent Co. (Midland, TX). The expression system for the wild-type HIV-1 IN was a generous gift of Drs. T. Jenkins and R. Craigie, Laboratory of Molecular Biology, NIDDK, NIH, Bethesda, MD. To analyze the extents of 3′-processing and 3′-strand transfer using 5′-end labeled substrates, AE118 was 5′-end labeled using T4 polynucleotide kinase (Gibco BRL) and [γ-^{32}P]ATP (DuPont-NEN). The kinase was heat-inactivated, and AE117 was added to the same final concentration. The mixture was heated at 95 °C, allowed to cool slowly to room temperature, and run on a G-25 Sephadex quick spin column (Boehringer Mannheim, Indianapolis, IN) to separate annealed double-stranded oligonucleotide from unincorporated label.

Reference Reagents for Mechanistic and Target-Based Assays. All positive control compounds for individual assays except AZTTP were obtained from the NCI chemical repository. The reference reagents for the individual assays are as follows: attachment, Farmitalia (NSC 65016)[34] and dextran sulfate (NSC 620255); reverse transcriptase inhibition, rAdT template/primer-AZTEC (Sierra BioResearch, Tuscon, AZ) and rCdG template/primer-UC38[35] (NSC 629243); protease inhibition, KNI-272[36] (NSC 651714); IN inhibitor, ISIS 5320[37] (NSC 665353) and DIBA-1[38] (NSC 654077), a NCp7 Zn finger inhibitor.

IN Assay. 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 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 1 h. Mg^{2+}-based assays were carried essentially as described.[39] Reactions were quenched by the addition of 8 μL of loading dye (98% deionized formamide, 10 mM EDTA, 0.025% xylene cyanol, 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 Molecular Dynamics PhosphorImager cassette, and analyzed using a Molecular Dynamics PhosphorImager (Sunnyvale, CA). Percent inhibition was calculated using the following equation:

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

where C, N, and D are the fractions of 21-mer substrate converted to 19-mer (3′-processing product) or 3′-strand-transfer products for DNA alone, DNA plus IN, and IN plus drug, respectively. IC_{50} values were determined by plotting the drug concentration versus percent inhibition and determining the concentration that produced 50% inhibition.

HIV-1 Cell and Target-Based Assays. The cell-based p24 attachment assay has been described in detail elsewhere.[38] Assays for activity against HIV-1 reverse transcriptase rAdT (template/primer) and rCdG (template/primer) using recombinant HIV-1 reverse transcriptase (a kind gift from S. Hughes, ABL Basic Research, NCI−FCRDC, Frederick, MD) have been previously described.[40] The substrate cleavage of recombinant HIV-1 protease in the presence of test compounds was quantified using an HPLC-based methodology with the artificial substrate Ala-Ser-Glu-Asn-Try-Pro-Ile-Val-amide (Multiple Peptide Systems, San Diego, CA) and has been previously described.[38,41] The anti-HIV drug testing performed at NCI is based on a protocol described by Weislow et al.[42]

General Procedure for the Preparation of Thiazepines 2−4, 6−10, 12, 19, and 20. This procedure is illustrated for the preparation of (±)-1,11a-dihydro-7-methoxy-3*H*,5*H*,-11*H*-thiazolo[4,3-*c*][1,4]benzothiazepine-5,11-dione (**10**). A mixture of 2,2′-dithiobis(5-methoxybenzoic acid) (5.5 g, 15 mmol) (**32a**)[21] and thionyl chloride (40 mL) was refluxed for 1.5 h. After cooling, the excess of thionyl chloride was removed under vacuum with the aid of dry benzene (2 × 5 mL). The resulting solid was dissolved in dry THF (40 mL), and the solution was added dropwise to a mixture of L-thiaproline (**33**) (4.0 g, 30.0 mmol) and sodium carbonate (3.2 g, 15.0 mmol) in water (50 mL). Additional sodium carbonate was added from time to time to maintain a weakly alkaline pH. The mixture was stirred overnight, then concentrated, and made acidic (pH 3−4) by adding concentrated HCl. The gummy solid was extracted into ethyl acetate, and the resulting solution was washed with water, dried, and evaporated to give a foam. Ion-exchange column chromatography using methanol as the eluent gave almost pure disulfide **36a** as an amorphous solid. Such a material (8.95 g, 15 mmol), was dissolved in 85% ethanol (100 mL) containing NaOH (1.2 g, 30 mmol) and to this was added a solution of $NaBH_4$ (1.14 g, 30 mmol) in ethanol (50 mL). The mixture was gently refluxed for 0.5 h, then concentrated, and diluted with chilled water. The cold solution was left at room temperature for 15 min before being filtered and made acidic (pH 3−4) by concentrated HCl. The gummy solid was treated exactly as described before for purification of compound **36a** and then thoroughly dried under vacuum before being subjected to the successive reaction without further manipulation. Crude thiophenol derivative (6.0 g, 20.0 mmol) was dissolved into dry THF (80 mL), and *N*,*N*′-carbonyldiimidazole (3.24 g, 20.0 mmol) was added in portions. The solution was stirred for 24 h at room temperature and for 2 h under reflux. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ and 0.5 N HCl. The organic solution was separated and washed with $NaHCO_3$-saturated solution and water. After drying and evaporation of the solvent, a pasty residue was obtained and purified by flash chromatography (8% methanol in EtOAc) to give 4.2 g (74% yield from the thiophenol precursor) of **10** as a white powder: mp 145−147 °C (benzene); IR (KBr) 1700, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1 H, J = 2.8 Hz), 7.35 (m, 1 H), 7.04 (dd, 1 H, J = 8.1, 2.8 Hz), 4.88 (half of AB q, 1 H, J = 10.2 Hz), 4.67 (half of AB q, 1 H, J = 10.2 Hz), 4.60 (dd, 1 H, J = 6.6, 1.5 Hz), 3.87 (s, 3 H), 3.64 (dd, 1 H, J = 12.7, 1.5 Hz), 3.15 (dd, 1 H, J = 12.7, 6.6 Hz). Anal. ($C_{12}H_{11}NO_3S_2$) C, H, N.

(±)-7-Chloro-2,3-dihydro-5*H*-thiazolo[2,3-*c*][1,4]-benzothiazepine-5,11(11a*H*)-dione (2). Starting from 2,2′-dithiobis(5-chlorobenzoic acid) (**32b**)[22] (5.6 g, 15 mmol), the title compound **2** was obtained (3.6 g, 63% yield from the thiophenol precursor) adopting the same procedure as for **10** but using thiazolidine-2-carboxylic acid (**34**)[26] instead of L-thiaproline (**33**): mp 231−232 °C (benzene); IR (KBr) 1695, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1 H, J = 2.4 Hz), 7.52−7.38 (m, 2 H), 5.35 (s, 1 H), 4.03 (m, 2 H), 3.16 (m, 2 H). Anal. ($C_{11}H_8ClNO_2S_2$) C, H, N.

(±)-7-Bromo-2,3-dihydro-5*H*-thiazolo[2,3-*c*][1,4]-benzothiazepine-5,11(11a*H*)-dione (3). Starting from 2,2′-dithiobis(5-bromobenzoic acid) (**32c**)[22] (7.0 g, 15 mmol), the title compound **3** was obtained (4.0 g, 70% yield from the thiophenol precursor) adopting the same procedure as for **10** but using thiazolidine-2-carboxylic acid (**34**)[26] instead of L-thiaproline (**33**): mp 219−220 °C (benzene); IR (KBr) 1695, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.11 (d, 1 H, J = 2.2 Hz), 7.62 (dd, 1 H, J = 8.3, 2.2 Hz), 7.32 (dd, 1 H, J = 8.3, 2.2 Hz), 5.33 (s, 1 H), 4.00 (m, 2 H), 3.18 (m, 2 H). Anal. ($C_{11}H_8BrNO_2S_2$) C, H, N.

(±)-2,3-Dihydro-7-methyl-5*H*-thiazolo[2,3-*c*][1,4]-benzothiazepine-5,11(11a*H*)-dione (4). Starting from 2,2′-dithiobis(5-methylbenzoic acid) (**32e**)[24] (5.0 g, 15.0 mmol), the title compound **4** was obtained (5.6 g, 76% yield from the thiophenol precursor) adopting the same procedure as for **10** but using thiazolidine-2-carboxylic acid (**34**)[26] instead of L-thiaproline (**33**): mp 197−199 °C (benzene−petroleum ether); IR (KBr) 1690, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (s, 1 H,), 7.29 (m, 2 H), 5.36 (s, 1 H), 4.02 (m, 2 H), 3.12 (m, 2 H), 2.42 (s, 3 H). Anal. ($C_{12}H_{11}NO_2S_2$) C, H, N.

(±)-7-Chloro-1,11a-dihydro-3*H*,5*H*,11*H*-thiazolo[4,3-*c*]-[1,4]benzothiazepine-5,11-dione (6). Starting from 2,2′-dithiobis(5-chlorobenzoic acid) (**32b**)[22] (5.6 g, 15 mmol), the title compound **6** was obtained (4.0 g, 70% yield from the thiophenol precursor) using the same procedure as for **10**: mp 204−205 °C (benzene); IR (KBr) 1705, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (d, 1 H, J = 2.0 Hz), 7.51−7.38 (m, 2 H), 4.72 (half of AB q, 1 H, J = 10.7 Hz), 4.57 (dd, 1 H, J = 6.9, 1.7 Hz), 3.67 (dd, 1 H, J = 11.9, 1.7 Hz), 3.19 (dd, 1 H, J = 11.9, 6.9 Hz). Anal. ($C_{11}H_8ClNO_2S_2$) C, H, N.

(±)-7-Bromo-1,11a-dihydro-3*H*,5*H*,11*H*-thiazolo[4,3-*c*]-[1,4]benzothiazepine-5,11-dione (7). Starting from 2,2′-dithiobis(5-bromobenzoic acid) (**32c**)[22] (7.0 g, 15 mmol), the title compound **7** was obtained (4.1 g, 63% yield from the thiophenol precursor) using the same procedure as for **10**: mp 213−214 °C (benzene); IR (KBr) 1700, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (t, 1 H, J = 1.0 Hz), 7.63 (dd, 1 H, J = 8.0, 1.0 Hz), 7.34 (d, 1 H, J = 8.0 Hz), 4.90 (half of AB q, 1 H, J = 10.6 Hz), 4.71 (half of AB q, 1 H, J = 10.6 Hz), 4.55 (dd, 1 H, J = 6.0, 1.9 Hz), 3.67 (dd, 1 H, J = 11.8, 1.9 Hz), 3.18 (dd, 1 H, J = 11.8, 6.0 Hz). Anal. ($C_{11}H_8BrNO_2S_2$) C, H, N.

(±)-1,11a-Dihydro-7-methyl-3*H*,5*H*,11*H*-thiazolo[4,3-*c*]-[1,4]benzothiazepine-5,11-dione (8). Starting from 2,2′-dithiobis(5-methylbenzoic acid) (**32e**)[24] (5.0 g, 15.0 mmol), the title compound **8** (6.1 g, 82% yield from the thiophenol precursor) was obtained as a thick oil, using the same procedure as for **10**: IR (KBr) 1695, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (s, 1 H,), 7.30 (m, 2 H), 4.87 (half of AB q, 1 H, J = 10.2 Hz), 4.66 (half of AB q, 1 H, J = 10.2 Hz), 4.60 (dd, 1 H, J = 6.8, 1.7 Hz), 3.62 (dd, 1 H, J = 12.1, 1.7 Hz), 3.23 (dd, 1 H, J = 12.1, 6.8 Hz), 2.40 (s, 3 H). Anal. ($C_{12}H_{11}NO_2S_2$) C, H, N.

(±)-1,11a-Dihydro-8-nitro-3*H*,5*H*,11*H*-thiazolo[4,3-*c*]-[1,4]benzothiazepine-5,11-dione (9). Starting from 2,2′-dithiobis(4-nitrobenzoic acid) (**32d**)[23] (5.9 g, 15 mmol), the title compound **9** was obtained (2.0 g, 34% from the thiophenol precursor) using the same procedure as for **10**: mp 231−232 °C (benzene−petroleum ether); IR (KBr) 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (s, 1 H), 8.32 (dd, 1 H, J = 8.1, 2.0 Hz), 8.16 (d, 1 H, J = 8.1 Hz), 4.90 (half of AB q, 1 H, J = 10.5 Hz), 4.77 (half of AB q, 1 H, J = 10.5 Hz), 4.54 (dd, 1 H, J = 6.4, 1.5 Hz), 3.70 (dd, 1 H, J = 11.9, 1.5 Hz), 3.23 (dd, 1 H, J = 11.9, 6.4 Hz). Anal. ($C_{11}H_8N_2O_4S_2$) C, H, N.

(±)-1,11a-Dihydro-3*H*,5*H*,11*H*-oxazolo[4,3-*c*][1,4]-benzothiazepine-5,11-dione (12). Starting from commercial 2,2′-dithiodibenzoic acid (**32g**) (4.6 g, 15.0 mmol), the title compound **12** was obtained as a thick oil (3.0 g, 42% yield from the thiophenol precursor) adopting the same procedure as for **10** but using freshly prepared 1,3-oxazolidine-4-carboxylic acid (**32**)[27] (3.5 g, 30.0 mmol) instead of L-thiaproline (**33**): IR (KBr) 1690, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (m, 1 H), 7.22 (m, 3H), 5.27 (half of AB q, 1 H, J = 5.3 Hz), 5.17 (half of AB q, 1 H, J = 5.3 Hz), 4.81 (dd, 1 H, J = 8.8, 1.7 Hz), 4.25 (dd, 1 H, J = 5.9, 1.6 Hz), 3.98 (dd, 1 H, J = 8.9, 5.9 Hz); MS m/z 235 (M^+), 207, 177, 150, 136 (100), 108. Anal. ($C_{11}H_9NO_3S$) C, H, N.

(±)-2,3-Dihydro-5*H*-naphtho[2,3-*f*]thiazolo[2,3-*c*][1,4]-thiazepine-5,13(13a*H*)-dione (19). Starting from 3,3′-dithiobis(2,2′-naphthoic acid)[25] (**32f**) (1.22 g, 1.5 mmol), the title compound **19** (0.27 g, 30% yield from the thiophenol precursor) was obtained, adopting the same procedure as for **10** but using thiazolidine-2-carboxylic acid (**34**) instead of L-thiaproline (**33**) and carrying out the $NaBH_4$ reduction of the disulfide overnight at room temperature: mp 196−198 °C; IR (KBr) 1700, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.52 (s, 1 H), 7.99 (s, 1 H), 7.93 (m, 1 H), 7.84 (m, 1 H,), 7.63 (m, 2 H), 5.40 (s, 1 H), 4.11 (m, 2 H), 3.16 (m, 2 H); MS m/z 301 (M^+), 273 (100), 186, 158, 142, 114. Anal. ($C_{15}H_{11}NO_2S_2$) C, H, N.

(±)-1,13a-Dihydro-3*H*,5*H*,13*H*-naphtho[2,3-*f*]thiazolo-[4,3-*c*][1,4]thiazepine-5,13-dione (20). Starting from 3,3′-dithiobis(2,2′-naphthoic acid) (**32f**) (1.22 g, 1.5 mmol), the title compound **20** (0.34 g, 38% yield from the thiophenol precursor) was obtained, using the same procedure as for **10** but carrying out the $NaBH_4$ reduction of the disulfide overnight at room temperature: mp 200−203 °C; IR (KBr) 1695, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.51 (s, 1 H), 7.98 (s, 1 H), 7.94 (m, 1 H), 7.84 (m, 1 H), 7.58 (m, 2 H), 4.97 (half of AB q, 1 H, J = 10.6 Hz), 4.73 (half of AB q, 1 H, J = 10.6 Hz), 4.66 (dd, 1 H, J = 6.9, 1.6 Hz), 3.65 (dd, 1 H, J = 11.8, 1.5 Hz), 3.14 (dd, 1 H, J = 12.1, 6.7 Hz); MS m/z 301 (M^+), 273 (100), 186, 158, 142, 114. Anal. ($C_{15}H_{11}NO_2S_2$) C, H, N.

General Procedure for the Preparation of Sulfoxides 15−18. This procedure is illustrated for the preparation of (±)-*trans*-1,11a-dihydro-3*H*,5*H*,11*H*-thiazolo[4,3-*c*][1,4]benzothiazepine-5,11-dione 2-oxide (**16**). To a stirred and cooled (0 °C) solution of compound **5**[15] (0.5 g, 2.0 mmol) in dry dichloromethane (5 mL) was added ∼80% 3-chloroperbenzoic acid (0.43 g, ∼2 mmol) in 8 mL of the same solvent dropwise over about 15 min. After an additional 2 h at 0 °C, the reaction mixture was filtered and the filter cake was rinsed with dichloromethane. The combined solution was washed twice with 5% aqueous K_2CO_3, dried, and evaporated to give the crude **16** (0.47 g, 89% yield), which solidified on trituration with hexane: mp 191−194 °C (benzene); IR (KBr) 1695, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (m, 1 H), 7.55 (m, 3 H), 5.75 (dd, 1 H, J = 13.1, 3.0 Hz), 5.14 (t, 1 H, J = 7.6 Hz), 3.91 (d, 1 H, J = 13.1 Hz), 3.72 (dd, 1 H, J = 14.6, 7.6 Hz), 3.23 (ddd, 1 H, J = 14.6, 7.6, 3.0 Hz). Anal. ($C_{11}H_9NO_3S_2$) C, H, N.

(±)-*trans*-2,3-Dihydro-7-methyl-5*H*-thiazolo[2,3-*c*][1,4]-benzothiazepine-5,11(11a*H*)-dione 1-Oxide (15). Starting from **4** (0.53 g, 2.0 mmol), the title compound **15** (0.39 g, 73% yield) was obtained using an identical procedure as for **16**: mp 211−212 °C (benzene); IR (KBr) 1690, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, 1 H, J = 2.5 Hz), 7.38 (m, 2 H), 5.25 (s, 1 H), 4.52 (m, 1 H), 3.40 (m, 1 H), 3.10 (m, 1 H), 2.47 (t, 3 H). Anal. ($C_{12}H_{11}NO_3S_2$) C, H, N.

(±)-*trans*-7-Chloro-1,11a-dihydro-3*H*,5*H*,11*H*-thiazolo-[4,3-*c*][1,4]benzothiazepine-5,11-dione 2-Oxide (17). Starting from **6** (0.57 g, 2.0 mmol), the title compound **17** (0.41 g, 68% yield) was obtained using an identical procedure as for **16**: mp 213-215 °C (benzene); IR (KBr) 1695, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (d, 1 H, J = 2.7 Hz), 7.50 (m, 2 H), 5.75 (dd, 1 H, J = 12.9, 2.9 Hz), 5.13 (t, 1 H, J = 7.8 Hz), 3.91 (d, 1 H, J = 13.0 Hz), 3.73 (dd, 1 H, J = 14.7, 7.2 Hz), 3.23 (ddd, 1 H, J = 14.7, 7.8, 2.9 Hz). Anal. ($C_{11}H_8ClNO_3S_2$) C, H, N.

(±)-*trans*-1,11a-Dihydro-7-methoxy-3*H*,5*H*,11*H*-thiazolo-[4,3-*c*][1,4]benzothiazepine-5,11-dione 2-Oxide (18). Starting from **10** (0.56 g, 2.0 mmol), the title compound **18** (0.42 g, 71%yield) was obtained using an identical procedure as for **16**: mp 172−174 °C (benzene); IR (KBr) 1690, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (d, 1 H, J = 2.7 Hz), 7.40 (d, 1 H, J = 8.3 Hz), 7.09 (dd, 1 H, J = 8.3, 2.7 Hz), 5.76 (dd, 1 H, J = 12.9, 2.8 Hz), 5.17 (t, 1 H, J = 7.6 Hz), 3.91 (d, 1 H, J = 12.9 Hz), 3.89 (s, 3 H), 3.73 (dd, 1 H, J = 14.7, 7.1 Hz), 3.23 (ddd, 1 H, J = 14.7, 7.6, 2.8 Hz). Anal. ($C_{12}H_{11}NO_4S_2$) C, H, N.

(±)-2,3,11,11a-Tetrahydro-11-hydroxy-11-phenyl-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzothiazepin-5-one (26). A solution of compound **37**[16] (0.88 g, 3.8 mmol) in dry THF (10 mL) was dropwise added to a solution of PhMgBr in ethyl ether (obtained from 1.23 g of PhBr, 0.185 g of Mg turnings, and 8 mL of Et_2O). The mixture was refluxed for 30 min, then cooled to room temperature, and quenched by the addition of NH_4Cl-saturated solution. Chloroform extraction and evaporation gave a residue which was purified by column chromatography to give the title compound **26** (0.7 g, 59% yield) along with some other unidentified byproducts. The title compound was obtained as colorless crystals by crystallization: mp 137−141 °C (ethanol); IR (KBr) 3210 broad, 1620 cm^{-1}; ^1H NMR

($CDCl_3$) δ 8.02 (m, 1 H), 7.85 (m, 1 H), 7.60−7.10 (m, 7 H), 3.87 (m, 1 H), 3.55 (m, 2 H), 3.08 (br s, 1 H), 1.95 (m, 4 H). Anal. ($C_{18}H_{17}NO_2S$) C, H, N.

(±)-*trans*-2,3,11,11a-Tetrahydro-11-(4-methylpiperazino)-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzothiazepin-5-one (27). A mixture of (+)-11-chloro-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzothiazepin-5-one (**38**)[15] (0.6 g, 2.4 mmol), freshly distilled 1-methylpiperazine (0.34 mL, 3.1 mmol), Na_2CO_3 (1.06 g, 10.0 mmol), and NaI (0.36 g, 2.4 mmol) in dry CH_3CN (30 mL) was gently refluxed for 20 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was successively washed with a 2% solution of $Na_2S_2O_3$, water, and brine. The residue obtained after evaporation was chromatographed on silica gel eluting with 5% methanol in CH_2Cl_2. The title compound **27** was obtained as a white solid (0.55 g, 73% yield): mp 188−190 °C (2-propanol−isopropyl ether); IR (KBr) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (m, 1 H), 7.50 (m, 2 H), 7.61 (m, 1 H), 7.33 (m, 2 H), 4.36 (d, 1 H, J = 11.2 Hz), 3.70 (m, 3 H), 2.58 (m, 4 H), 2.38 (m, 4 H), 2.27 (s, 3 H), 2.02 (m, 4 H); MS *m*/*z* 317 (100, M^+), 217, 180, 139, 99, 70. Anal. ($C_{17}H_{23}N_3OS$) C, H, N.

(±)-3-[(4-Methylpiperazin-1-yl)methyl]-11-phenyl-5*H*,-11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine (31). A solution of compound **39**[20] (0.55 g, 2.0 mmol), paraformaldehyde (0.1 g), and 1-methylpiperazine dihydrochloride (0.52 g, 3.0 mmol) in CH_3OH (20 mL) was refluxed for 48 h. After cooling, the mixture was diluted with water and made alkaline (pH 9−10) by dropwise addition of 1 N NaOH. The oil formed was extracted with ethyl acetate. The organic layer was washed with water and dried. After evaporation of the solvent, the residue obtained was chromatographed (5% CH_3OH in CH_2Cl_2) to give the title compound **31** as a white solid (0.7 g, 91% yield): mp 161−162 °C (2-propanol); ^1H NMR ($CDCl_3$) δ 7.50−7.00 (m, 9 H), 5.97 (s, 1 H), 5.86 (d, 1 H, J = 3.5 Hz), 5.53 (d, 1 H, J = 3.5 Hz), 5.44 (half of AB q, 1 H, J = 14.5 Hz), 5.31 (half of AB q, 1 H, J = 14.5 Hz), 3.52 (half of AB q, 1 H, J = 13.5 Hz), 3.52 (half of AB q, 1 H, J = 13.5 Hz), 2.52 (m, 8 H), 2.30 (s, 3 H). Anal. ($C_{24}H_{27}N_3S$) C, H, N.

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