Pyrrolobenzothiazepinones and Pyrrolobenzoxazepinones: Novel and Specific Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors with Antiviral Activity

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Two novel classes of pyrrolobenzothiazepinones and pyrrolobenzoxazepinones were investigated as potential anti-AIDS drugs. These compounds were found to inhibit HIV-1 reverse transcriptase (RT) enzyme *in vitro* and to prevent HIV-1 cytopathogenicity in T4 lymphocytes, without appreciable activity on HIV-2 cytopathic effects, and against HBV as well as calf-thymus DNA α-polymerase. Their potency is influenced by substituents at position 6 and on the fused aromatic ring. Specifically, small lipophilic substituents at C-6 were preferred, whereas substitutions on the benzo-fused ring were found to be detrimental to activity, with respect to the unsubstituted compounds. Modification of the π-system at C-6 is well tolerated, although the replacement of the benzo-fused with a [2,3]naphtho-fused ring leads to a less active compound. Maximum potency and specificity is achieved with a phenyl and an ethyl group at position 6 of the pyrrolobenzoxazepinone system. In the enzymatic assay the oxazepinone derivative (±)-6-ethyl-6-phenylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one **16e** (IC_{50} = 0.25 μM) was found to be more potent than nevirapine (IC_{50} = 0.5 μM), tested in the same experimental conditions using rC·dG as a template-primer. In cell culture assay benzoxazepine **16e** was active against HIV-1, both wild type and AZT-sensitive, and HIV-1 (IIIB) strains, but not against HIV-2. In enzyme assay although **16e** inhibited HIV-1 RT, it was inactive against the nevirapine-resistant recombinant RT Y181C at 50 μM. Molecular modeling studies suggest that these derivatives present a 3D pharmacophoric arrangement similar to that of other non-nucleoside inhibitors such as nevirapine.

Introduction

Acquired immune deficiency syndrome (AIDS) is a pandemic disease whose primary etiological agent is the human immune deficiency virus type 1 (HIV-1).[1] This retrovirus causes immunosuppression by destroying the T-lymphocytes. Clinical signs are a generalized lymphodenopathy, opportunistic infections, Kaposi's sarcoma, a non-Hodgkin lymphosarcoma,[2] and an AIDS-related dementia.[3] In the life cycle of this retrovirus the reverse transcriptase (RT) is a key multifunctional enzyme, and it has been a major pharmacological target for the development of antiretroviral agents.[4,5] Its inhibition is considered one of the most practicable approaches in order to prevent the spreading of the infection.[6] One of the antiretroviral drugs currently employed in the treatment of AIDS is AZT (zidovudine) **1**, a competitive inhibitor of the viral RT. Despite its clinical usefulness, its toxicity and a low specificity, due to the inhibition of cellular polymerases,[7] its poor blood−brain barrier penetration (AZT is unsuccessful in the case of cephalic virus infection),[8,9] and the emergence of viral resistance[10] have limited the therapeutic application of this nucleoside analogue. In order to bypass the disadvantages inherent in nucleoside analogues, several non-nucleoside RT inhibitors have been developed. These include dibenzo- and dipyridodiazepinones, such as nevirapine **2**,[11] TIBO compounds **3**,[12] and pyridinone derivatives **4**.[13] Although structurally unrelated, these compounds are highly specific for HIV-1 RT and are inactive against HIV-2 cytopathic effects. They inhibit the RT by a noncompetitive mechanism, interacting with the enzyme through a common binding site.[6,14] These compounds are promising therapeutic agents for the treatment of HIV-1 infection and exhibit low levels of toxicity, though the emergence of resistance is a limiting factor for their therapeutic effectiveness.[14] Now, since there is an increasing need for more effective drugs, we began a random search for non-nucleoside RT inhibitors in order to provide novel structural leads. Several tricyclic compounds were screened, and pyrrolobenzothiazepinones (e.g. **6a**) were found to be weak inhibitors of the RT enzyme. Thus, the objective of this study is the development of novel classes of non-nucleoside RT inhibitors (**5**), specific for HIV-1, through optimization of our leads. We detail herein the synthesis of pyrrolobenzothiazepinone and pyrrolobenzoxazepinone derivatives **5** (Chart 1) and structure−activity relationships (SAR) for antiretroviral activity related to the variation of the substituents on the heterocyclic systems.

Chemistry

The synthesis of pyrrolo[2,1-*d*][1,5]benzothiazepinones **6** has been accomplished according to literature procedures.[15] C-6 alkylation of **6** by exposure of the corresponding potassium enolates to methyl or ethyl iodide afforded ketones **7**. O-Alkylation was a persistent side reaction: the O-alkylated regioisomers were obtained

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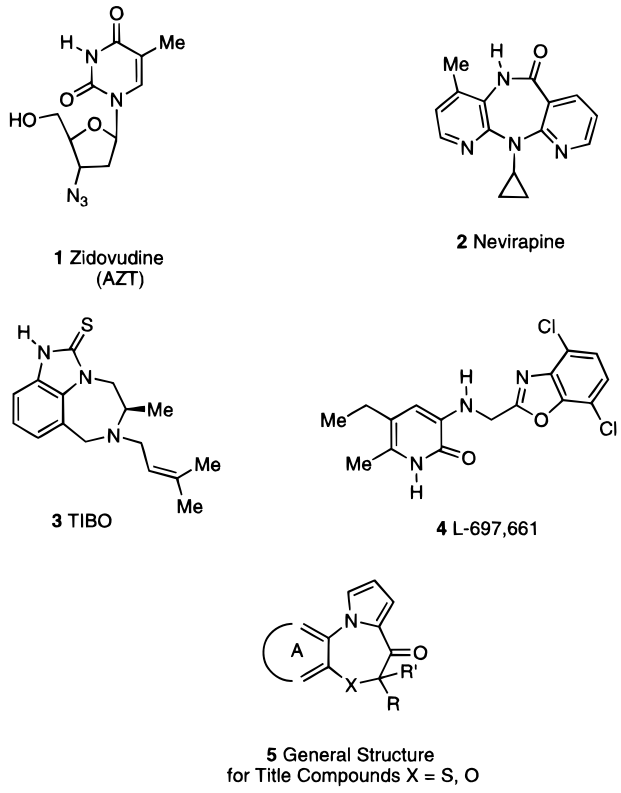
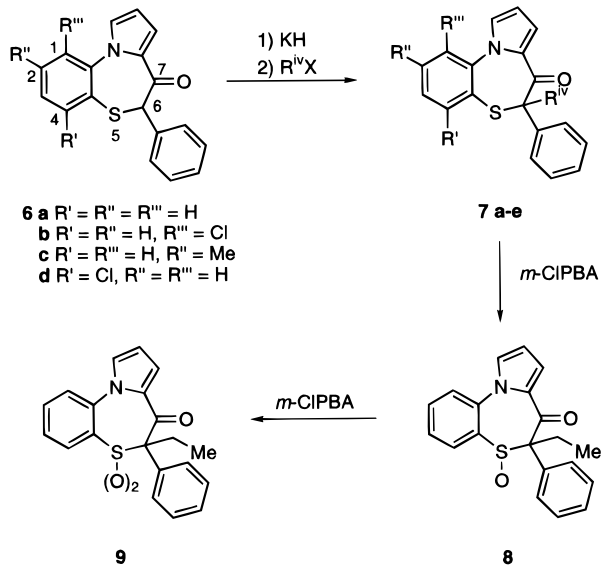
Chart 1

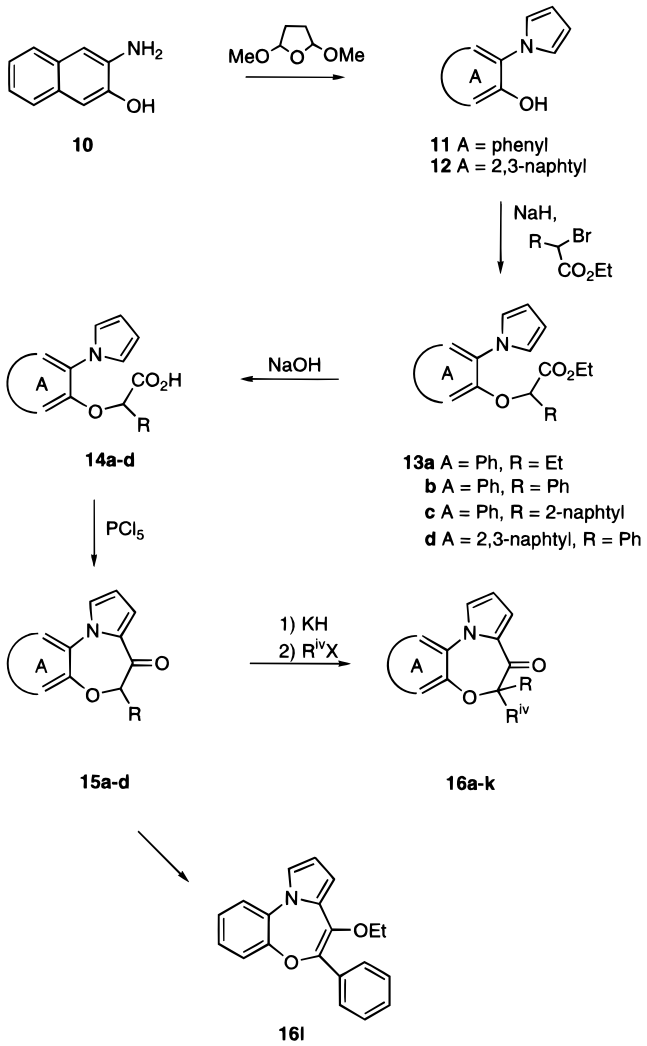


Scheme 1



in 20−30% yield. Compounds **7** were the focus of our attention owing to their ability to inhibit HIV-1 RT (*vide infra*). Thus, ketone **7b** was further examined and served as a key intermediate to explore SAR at position 5. In fact, monooxidation of the sulfur-bridged atom of **7b** occurred with an equimolar amount of *m*-chloroperbenzoic acid at 0 °C (**8**). Subsequent overoxidation provided the corresponding sulfone **9** (see Scheme 1). The pyrrolo[2,1-*d*][1,5]benzoxazepinones **16** were synthesized as shown in Scheme 2. Accordingly, starting from the 1-(2-hydroxyphenyl)pyrrole **11**, previously described by Artico,[16] and from the pyrrole derivative **12**, obtained starting from 3-amino-2-naphthol **10** by the same procedure described for compound **11**, the esters **13a**−**d** were prepared by O-alkylation with the appropriate ethyl α-bromo ester (see refs 15a−c). Saponi-

Scheme 2



fication of the ethyl ester group (NaOH, H_2O) (**14a**−**d**) and subsequent intramolecular cyclization using phosphorus pentachloride gave ketones **15a**−**d**. Treatment of the corresponding potassium enolates with alkyl halides finally yielded the desired oxazepinones **16a**−**k** (see Table 1). The corresponding O-alkylated compounds were also obtained as byproducts (15−25% yield) (e.g. **16l**).

Results and Discussion

The new cyclic compounds were tested in an *in vitro* HIV-1 RT enzyme assay to evaluate their potential as anti-AIDS drugs. Table 2 summarizes the test results. Selected compounds were further tested for their ability to block the proliferation of HIV-1 infection on T4 lymphocytes (CEM, MT-2, and MT-4 cell lines) *in vitro* (Tables 2 and 3). A direct correlation between the anti-enzymatic and cellular activity on T4 cells was observed, and the data support the hypothesis that the described compounds block the HIV-1 infection through inhibition of the RT enzyme. These RT inhibitors displayed a HIV-1 specificity; in fact, they were not effective against HIV-2 cytopathic effects on T4 cells. In the enzymatic assay the inhibitory potency of these compounds toward RT was dependent upon the template-primer substrate: the most potent inhibition was observed with rC·dG while the same compounds showed higher IC_{50} values with rA·dT (these data are not reported). Futhermore, **16b,c,e,j,k** proved to be highly specific for

Table 1. Physical Data for Compounds **7**−**16**

compd	A	R	R′	R″	R‴	R^{iv}	% yield[a]	mp (°C)	recryst solvent	formula	anal.[b]
7a			H	H	H	Me	66	143−144	EtOH	$C_{19}H_{15}NOS$	C,H,N
7b			H	H	H	Et	63	137−139	EtOH	$C_{20}H_{17}NOS$	C,H,N
7c			H	H	Cl	Et	60	151−152	ethyl ether/hexanes	$C_{20}H_{16}ClNOS$	C,H,N
7d			H	Me	H	Et	57	132−134	EtOH	$C_{21}H_{19}NOS$	C,H,N
7e			Cl	H	H	Et	72	165−167	EtOH	$C_{20}H_{16}ClNOS$	C,H,N
8							69	178−179	EtOH	$C_{20}H_{17}NO_2S$	C,H,N
9							74	201−202	EtOH	$C_{20}H_{17}NO_3S$	C,H,N
12							48	106−107	hexanes	$C_{14}H_{11}NO$	C,H,N
13a	Ph	Et					66			$C_{16}H_{19}NO_3$	C,H,N
13b	Ph	Ph					67			$C_{20}H_{19}NO_3$	C,H,N
13c	Ph	2-naphthyl					76			$C_{24}H_{21}NO_3$	C,H,N
13d	2,3-naphthyl	Ph					65			$C_{24}H_{21}NO_3$	C,H,N
14a	Ph	Et					93	91−92	ligroin	$C_{14}H_{15}NO_3$	C,H,N
14b	Ph	Ph					94	125−126	hexanes	$C_{18}H_{15}NO_3$	C,H,N
14c	Ph	2-naphthyl					71	68−70	ethyl ether/hexanes	$C_{22}H_{17}NO_3$	C,H,N
14d	2,3-naphthyl	Ph					76	83−84	hexanes	$C_{22}H_{17}NO_3$	C,H,N
15a	benzo	Et					60	50−51	hexanes	$C_{14}H_{13}NO_2$	C,H,N
15b	benzo	Ph					58	102−103	EtOAc/hexanes	$C_{18}H_{13}NO_2$	C,H,N
15c	benzo	2-naphthyl					52	135−137	EtOH	$C_{22}H_{15}NO_2$	C,H,N
15d	[2,3]naphtho	Ph					57	165−167	EtOH	$C_{22}H_{15}NO_2$	C,H,N
16a	benzo	Et				*n*-propyl	69			$C_{17}H_{19}NO_2$	C,H,N
16b	benzo	Et				allyl	51	59−61	hexanes	$C_{17}H_{17}NO_2$	C,H,N
16c	benzo	Et				2-isopentenyl	60	100−102	hexanes	$C_{19}H_{21}NO_2$	C,H,N
16d	benzo	Ph				Me	61	135−136	hexanes	$C_{19}H_{15}NO_2$	C,H,N
16e	benzo	Ph				Et	69	112−114	EtOH	$C_{20}H_{17}NO_2$	C,H,N
16f	benzo	Ph				*n*-propyl	77	146−147	hexanes	$C_{21}H_{19}NO_2$	C,H,N
16g	benzo	Ph				allyl	71	130−131	hexanes	$C_{21}H_{17}NO_2$	C,H,N
16h	benzo	Ph				2-isopentenyl	66	162−163	hexanes	$C_{23}H_{21}NO_2$	C,H,N
16i	benzo	Ph				cyclopropyl-methyl	57	142−144	dichloromethane/ hexanes	$C_{22}H_{19}NO_2$	C,H,N
16j	benzo	2-naphthyl				Et	52	179−180	EtOH	$C_{24}H_{19}NO_2$	C,H,N
16k	[2,3]naphtho	Ph				Et	59	106−107	hexanes	$C_{24}H_{19}NO_2$	C,H,N
16l							27	114−115	hexanes	$C_{20}H_{17}NO_2$	C,H,N

[a] Yields refer to isolated and purified materials. [b] All the compounds analyzed were within ±0.4% of the theoretical values.

HIV-1 RT without inhibiting *in vitro* calf-thymus DNA α-polymerase and HBV-polymerase activity at 500 μM concentration.

Compounds **7b** and **16e** were further used in *in vitro* studies to assess their inhibitory effect in a panel of selected HIV strains. This panel included HIV strains both sensitive (HIV-1 (6S)) and resistant (HIV-1 (6R)) to AZT, a strain (A-17) resistant to the pyridinone RT inhibitors, HIV-1 (IIIB), HIV-1 RF, HIV diphenyl sulfone resistant, N119, SIV (MAC 251), and HIV-2 (ROD), by means of the MT-2, MT-4, and CEM-SS cell lines. Compound **7b** was moderately active only against HIV-1 (6S) strain, sensitive to AZT, with an ED_{50} of 8.7 μM, while **16e** proved to be active against HIV-1 RF, HIV-1 (6S) AZT sensitive, and HIV-1 (IIIB) with ED_{50}s of 0.12, 0.42, and 0.13 μM, respectively (see Table 3). In enzyme assay although **16e** inhibited HIV-1 RT, it was inactive against the pyridinone-resistant recombinant RT Y181C at 50 μM.

***In Vitro* SAR Study.** To identify the structural requirements capable of improving the inhibitory potency of our thiazepinones and oxazepinones toward HIV-1 RT and HIV-1 cytopathic effects, the SAR study was carried out as a function of (i) the nature of the 5-bridged heteroatom, (ii) the nature and position of substituents in the benzo-fused ring, (iii) the nature and length of the alkyl chain at position 6, (iv) the nature of the π-system at C-6, and (v) the modification of the fused aromatic ring.

(i) In general, benzothiazepinones (e.g. **7b**) proved to be weaker inhibitors of HIV-1 RT than the corresponding benzoxazepinones (e.g. **16e**), although **7b** was likewise less cytotoxic to CEM cells ($IC_{50} = 100$ μM) with respect to **16e** ($IC_{50} = 4.9$ μM). Oxidation of the sulfur atom to sulfoxide or sulfone resulted in a dramatic reduction in potency (**8** and **9** *vs* **7b**).

(ii) In the thiazepinones series the introduction of a substituent in the benzo-fused ring was detrimental to activity; 1-chloro, 4-chloro, and 3-methyl substituents provided compounds (**7c**−**e**) with decreased potency if compared to the unsubstituted **7a,b**.

(iii) In these series of compounds the inhibitory potency is dramatically dependent upon the nature and the length of the substitution at C-6 (**7a,b** *vs* **6a** and **16d,e** *vs* **16f**−**i**). Specifically, small lipophilic substituents, such as methyl or ethyl, are generally preferred. Larger alkyl groups at C-6 (i.e. propyl, allyl, 2-isopentenyl, and cyclopropylmethyl) result in weak or inactive compounds (**16f**−**i**). The ethyl group is required for optimum activity.

(iv) Geometrically, these novel inhibitors present two π-systems arranged in a "butterfly-like" orientation (see Molecular Modeling Section).[17] The combination of a phenyl ring with the ethyl side chain at C-6 provided the most active compounds (**7b**, **16e**), although the reduction of this π-region by introduction of a 2-isopentenyl group in the place of the C-6 phenyl ring was well tolerated, providing an analogue whose affinity to RT was remarkably high (**16c**). Substitution of the π-system at C-6 with an alkyl chain provided a weaker inhibitor of RT (**16a** *vs* **16c** or **16e**). Therefore, the rank order of potency in the C-6-substituted benzoxazepines for RT inhibition is aryl−alkyl (**16e**) > alkenyl−alkyl (**16c**) > dialkyl (**16a**) ≫ aryl−alkenyl (**16g**) > alkyl (**15a**) > aryl (**15b**). Apparently, the enzyme is also able to accommodate greater steric bulk around position 6 of the oxazepinones since the extension of the π-system at C-6 by replacement of the 6-phenyl ring with a

Table 2. Inhibition of HIV-1 RT Activity[a] and Inhibition of HIV-1 Infection in Cell Culture[b]

compd	HIV-1 RT IC_{50} (μM)[c] poly rC (dG)	IC_{50} (μM)[d]	EC_{50} (μM)[e]	SI (μM)[f]
6a	100.0 ± 10	18.3	ND	–
7a	5.0 ± 1	ND	0.81	–
7b	15.0 ± 2	100.1	1.80	55.2
7c	600 ± 50		NA	
7d	>600		NA	
7e	500 ± 35	NT		
8	500 ± 10	NT		
9	>300	NT		
15a	100 ± 15	NT		
15b	>300	NT		
15c	>300	NT		
15d	>300	NT		
16a	10 ± 1	NT		
16b	5 ± 2	NT		
16c	0.3 ± 0.04	45.2	1.35	35.0
16d	10 ± 1	6.9	0.35	19.7
16e	0.25 ± 0.03	4.9	0.47	10.4
16f	500 ± 20	>150	ND	
16g	25 ± 2	6.4	0.71	9.0
16h	>500	120	ND	
16i	>500	11.8	ND	
16j	0.5 ± 0.1	37.3	0.85	44.0
16k	150 ± 20	NT		
16l	>300	NT		
L-697,661	0.15 ± 0.02			
nevirapine	0.5 ± 0.1			
AZT		>1	0.0019	526

[a] Testing was performed by Screening Laboratory of IRBM. [b] Testing was performed by the National Cancer Institute's Developmental Therapeutics Program, AIDS antiviral screening program. All the data listed were compared to the corresponding test results for AZT which served as the treated control, performed at the same time. [c] Inhibition of HIV-1 RT activity. All the data listed were compared to the corresponding test results for nevirapine and L-697,661, performed at the same time. The IC_{50} is stated as the mean of at least three experiments. [d] The IC_{50} value is the test drug concentration which results in a 50% survival of uninfected untreated control CEM-SS cells (e.g. cytotoxicity of the test drug). [e] The EC_{50} value is the test drug concentration which produces a 50% survival of HIV 1 infected cells relative to uninfected untreated controls (e.g. in vitro anti-HIV-1 activity). [f] SI = selectivity index (IC_{50}/EC_{50}). NA = not active. ND = not determined. NT = not tested.

Table 3. *In Vitro* Studies of Compounds **7b** and **16e** in a Panel of Selected HIV Strains (IC_{50}s and ED_{50}s in μM)[a]

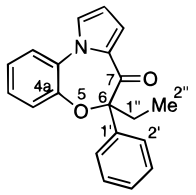
HIV strain		**7b**	cell line	**16e**	cell line
SIV (Mac 251)		NT		NA	MT-4
HIV-2 (ROD)		NA	CEM-SS	NA	CEM-SS
HIV-1 (A-17)		NA	MT-2	NA	MT-4
MER-RT					
N119[b]		NT		NA	MT-4
HIV DSRes[b]		NT		NA	MT-4
HIV-1 (6S)					
AZT-sensitive	IC_{50}	110	MT-2	3.30	MT-4
	ED_{50}	8.70		0.42	
	SI	12.6		8	
HIV-1 RF	IC_{50}			10.40	CEM-SS
	ED_{50}	NT		0.12	
	SI			86	
HIV-1 (IIIB)	IC_{50}		MT-2	3.31	MT-4
	ED_{50}	NA		0.13	
	SI			25	
HIV-1 (6R)					
AZT-resistant	IC_{50}		MT-2	2.90	MT-4
	ED_{50}	NA		1.60	
	SI			1.7	

[a] Testing was performed by the National Cancer Institute's Developmental Therapeutics Program, AIDS antiviral screening program. [b] N119 and diphenyl sulfone resistant HIV-1 (HIV DSRes) are two strains with a mutation at position 181 of the RT.

2-naphthyl group led to a slightly less potent oxazepinone (**16j**), if compared to **16e**. The alteration of the geometric property of the tricyclic skeleton by means of a C-6−C-7 double bond led to an inactive compoud (**16l**) (Scheme 2, and Table 2).

(v) Extension of the π-fused system through the replacement of the benzo-fused ring with a [2,3]naphtho-fused ring system was detrimental to activity (**16k**) (see Table 2).

Chart 2



τ_1 = τ(C7, C6, O5, C4a)
τ_2 = τ(C7, C6, C1', C2')
τ_3 = τ(C7, C6, C1'', C2'')

16e

Molecular Modeling

Computational studies were performed to deduce the active conformation and relative orientation of **16e** with respect to the enzyme-bound conformation of nevirapine.[18,19] Since the structure of the nevirapine/HIV-1 RT complex has been solved,[18,19] a superimposition model of **16e** upon nevirapine might greatly facilitate successive docking studies of the inhibitor into the non-nucleoside binding site of HIV-1 RT.[18−26] Both *R*- and *S*-enantiomers of **16e** had to be modeled because all the investigated compounds were assayed as racemic mixture. A conformational analysis was preliminary performed on the *S*-enantiomer of **16e** by scanning the following torsional angles: $\tau_1 = \tau$(C7, C6, O5, C4a), $\tau_2 = \tau$(C7, C6, C1′, C2′), and $\tau_3 = \tau$(C7, C6, C1″, C2″) (see Chart 2 for atoms labeling). Energies were computed through the molecular mechanics Tripos force field[27] using Gasteiger−Hückel charges.[28,29]

According to our calculation, the lowest-energy conformation of *S*-**16e** is characterized by a pseudoaxial disposition of the pendant phenyl ring (Ph-ax). The torsional angles defining this conformation are $\tau_1 = 77°$, $\tau_2 = 2°$, and $\tau_3 = 58°$. However, conformers not far in energy from the global minimum (about 2 kcal/mol) were also found featuring the phenyl ring in a pseudoequatorial orientation (Ph-eq).

Recently, Ren *et al.* have described in detail the binding mode of five non-nucleoside inhibitors cocrystallized with HIV-1 RT (nevirapine, its analogue 1051U91,[11] the α-anilinophenylacetamide R90385,[30] HEPT,[31] and 9-chloroTIBO).[12a] Inspection of these complexes reveals that the inhibitors are embedded into a largely hydrophobic cleft where they assume a similar three-dimensional arrangement. Specifically, their structures consist of two hydrophobic essentially planar moieties folded in a "roof-like/butterfly" disposition. The angle subtended by the planes of these two pharmacophoric elements is around 110°.[17] A third moiety of relatively small size, generally hydrophobic, extends out from the top of the "roof" (in nevirapine it corresponds to the cyclopropyl group). It seemed reasonable to assume that the ethyl substituent of **16e** had its equivalent in the cyclopropyl group of nevirapine. Identifying the two pharmacophoric rings making up the roof in **16e** required a careful analysis of the conformational and steric features of this molecule. In our database of *S*-**16e** conformers we detected two geometries mimicking the "butterfly" shape of nevirapine: a Ph-ax one (the global minimum) and a Ph-eq one

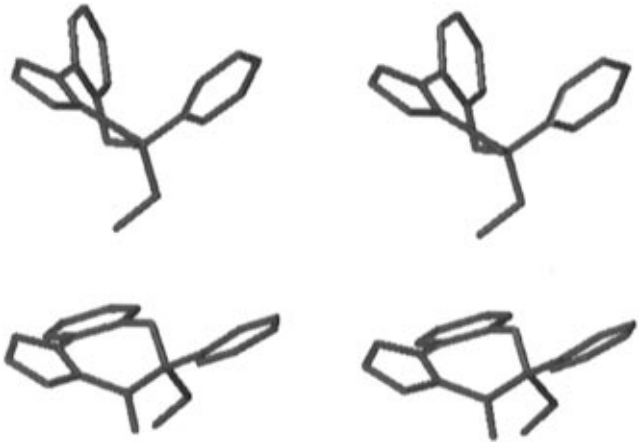


Figure 1. The phenyl-axial (top) and the phenyl-equatorial (bottom) conformers of *S*-**16e** mimicking the butterfly arrangement of nevirapine.

higher in energy by 2.2 kcal/mol. Both of them are shown in Figure 1. The torsional angles defining the global minimum conformer have already been given. In the selected Ph-eq conformation $\tau_1 = -68°$, $\tau_2 = 0°$, $\tau_3 = 41°$. Depending on the puckering of the oxazepine ring the pendant phenyl ring may be folded against the fused benzene (Ph-ax) or the fused pyrrole ring (Ph-eq). The Ph-ax conformation deviates significantly from the pharmacophore geometry as the planes of the two facing benzene rings form a too sharp solid angle (55°). In the Ph-eq conformation the angle between the pendant phenyl and pyrrole rings is 129°, a value close to that subtended by the pyridine rings of nevirapine (121°).[18,19] These results convinced us that the Ph-eq conformation of **16e** is the one bound to the enzyme.

The Ph-eq conformer of S-**16e** reported in Figure 1 was then converted into its mirror image, thus obtaining an isoenergetic *R*-conformer differing only in the sign of the torsional angles. Both *S*- and *R*-structures were superimposed on nevirapine about the pharmacophoric rings yielding the two alignments shown in Figure 2. The *S*-enantiomer overlays the C and A pyridine rings of nevirapine with the fused pyrrole and, respectively, the pendant phenyl ring. The pairwise correspondences between aromatic rings are inverted for *R*-enantiomer. Owing to the symmetry of the three-point pharmacophore, our model is not able to predict differences in activity, if any, between the enantiomers of **16e**. However, the superpositions shown in Figure 2 represent valuable starting points for docking the inhibitor into the non-nucleoside binding pocket of the HIV-1 RT and design new analogues. These theoretical studies are in progress while synthetic strategies to obtain the pure enantiomers have been planned.

Conclusions

New classes of non-nucleoside HIV-1 RT inhibitors, specific for HIV-1, exhibiting no activity in an HIV-2 cell culture assay and on calf-thymus DNA α-polymerase have been described. Summarizing the SARs, optimum enzyme inhibition is obtained with polycyclic compounds containing phenyl and ethyl moieties at position 6. Larger substituents at this position as well as alteration of the benzo-fused ring reduce activity. Oxazepinone **16e** is the most active noncompetitive HIV-1 RT inhibitor of this series ($IC_{50} = 250$ nM). In the enzymatic assay, it proved to be a more potent inhibitor than nevirapine ($IC_{50} = 500$ nM),[32] an inhibitor

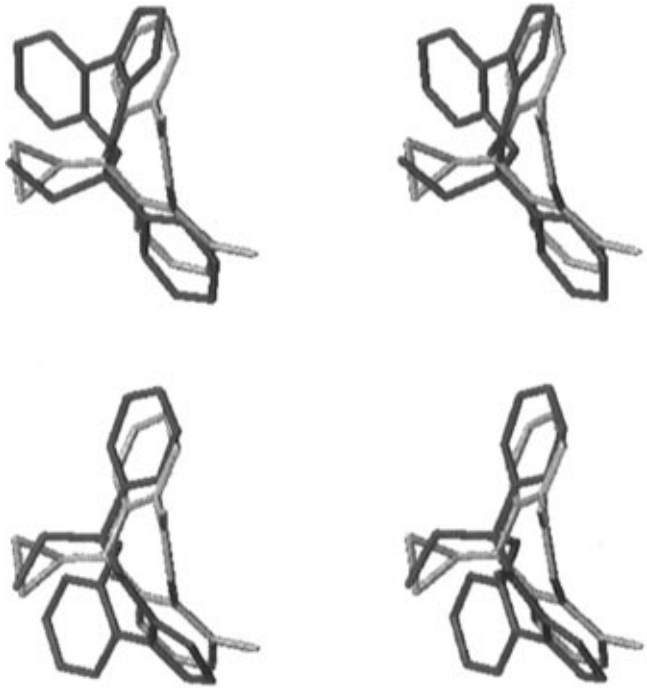


Figure 2. The Ph-eq conformations of *S*-**16e** (top) and *R*-**16e** (bottom) superimposed on the enzyme-bound conformation of nevirapine. Nevirapine and **16e** are depicted in gray and red, respectively.

currently undergoing clinical evaluation, although **16e** was less active than the pyridinone L-697,661 ($IC_{50} = 150$ nM),[13] tested in the same experimental conditions. **16e** blocks the HIV-1 replication in T4 lymphocytes, with an ED_{50} value of 470 nM, although in the same assay it proved to be less active than AZT ($ED_{50} = 1.9$ nM) (see Table 2). Furthermore, when tested in a panel of selected HIV strains, **16e** proved to be active against HIV (IIIB), HIV-1 (6S), and HIV-RF with ED_{50}s of 130, 420, and 120 nM, respectively. When tested against the rRT from HIV-1 mutant resistant to pyridinone and nevirapine (Y181C), compoud **16e** did not inhibit at 50 μM concentration, behaving like the other non-nucleoside nevirapine, TIBO, and pyridinones. The cross-resistance of resistant viruses to structurally unrelated compounds such as nevirapine, pyridinones, and benzoxazepines (**16e**) suggest that these unrelated HIV-1 inhibitors may share a common binding site. Moreover, molecular modeling studies showed that the investigated compounds present a "butterfly-like" orientation for the polycyclic ring system similar to that of nevirapine.[17,21−26] This three-dimensional arrangement together with the cross-resistance shown in enzyme assay would make them interact with the enzyme through a binding site occupied by other non-nucleoside inhibitors such as nevirapine and TIBO. However, we believe that the pharmacophoric pattern of these compounds is not yet optimal. A different-sized π-system at C-6 or differently fused aromatic rings might possibly lead to further optimization of the antiretroviral activity of these heterocycles. Work in this line is currently in progress in our laboratories.

Experimental Section

Melting points were determined using an Electrothermal 8103 apparatus and are uncorrected. IR spectra were taken with Perkin-Elmer 398 and FT 1600 spectrophotometers. ^{1}H-NMR spectra were recorded on a Bruker 200 MHz spectrometer with TMS as internal standard; the values of the chemical

shifts (δ) are given in ppm and coupling constants (J) in hertz. All reactions were carried out in an argon atmosphere. Progress of the reaction was monitored by TLC on silica gel plates (Riedel-de-Haen, Art. 37341). Merck silica gel (Kieselgel 60) was used for chromatography (70−230 mesh) and flash chromatography (230−400 mesh) columns. Extracts were dried over $MgSO_4$, and solvents were removed under reduced pressure. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer, and the results are within ±0.4% of the theoretical values, unless otherwise reported. Yields refer to purified products and are not optimized. Physical data for compounds **7a**−**16l** are reported in Table 1.

General Procedure for Preparation of Compounds 7a−e. This procedure is illustrated for the preparation of (±)-6-methyl-6-phenylpyrrolo[2,1-*d*][1,5]benzothiazepin-7(6*H*)-one (**7a**). To a suspension of potassium hydride (119 mg, 1.0 mmol, 35% in oil) in anhydrous THF (3 mL) was added ketone **6a** (300 mg, 1.0 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at room temperature for 2 h, and then methyl iodide (130 μL, 2.09 mmol) was added. After 12 h of stirring at room temperature, 10% NH_4Cl was added (1 mL), the solvent was removed under vacuum, and the residue was extracted with EtOAc. The organic solution was washed with brine, dried, and concentrated. The residue was flash chromatographed (dichloromethane) and recrystallized to afford 210 mg of **7a** as a white solid: IR (Nujol) 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 6.45 (m, 1 H), 7.08 (m, 1 H), 6.97−7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 26.2, 62.8, 111.0, 122.0, 124.1, 126.4, 126.6, 127.0, 127.1, 128.2, 128.7, 129.8, 134.6, 135.9, 140.5, 141.8, 190.1.

(±)-6-Ethyl-6-phenylpyrrolo[2,1-*d*][1,5]benzothiazepin-7(6*H*)-one (7b). Starting from **6a** (150 mg, 0.5 mmol), the title compound was obtained according to the procedure described for **7a**: IR (Nujol) 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3 H, J = 7.2 Hz), 2.23 (m, 1 H), 2.56 (m, 1 H), 6.42 (m, 1 H), 6.92−7.48 (m, 11 H).

(±)-1-Chloro-6-ethyl-6-phenylpyrrolo[2,1-*d*][1,5]-benzothiazepin-7(6*H*)-one (7c). Starting from **6b** (85 mg, 0.26 mmol), the title compound was obtained following an identical procedure as for **7a**. Ketone **7c** was chromatographed using 20% EtOAc in hexanes as eluant: IR (Nujol) 1635 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3 H, J = 7.1 Hz), 2.27 (m, 2 H), 6.41 (m, 1 H), 6.84−7.29 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 10.0, 34.2, 71.5, 109.4, 119.9, 127.0, 127.2, 127.5, 128.0, 128.6, 129.2, 130.4, 131.7, 135.0, 135.7, 138.8, 140.3, 191.0.

(±)-6-Ethyl-2-methyl-6-phenylpyrrolo[2,1-*d*][1,5]-benzothiazepin-7(6*H*)-one (7d). Starting from **6c** (250 mg, 0.82 mmol), **7d** was obtained according to the procedure described above for **7a**: IR (Nujol) 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3 H, J = 7.1 Hz), 2.20 (m, 1H), 2.24 (s, 3 H), 2.51 (m, 1 H), 6.42 (m, 1 H), 6.80−7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 10.0, 21.1, 33.7, 68.7, 110.7, 121.7, 122.5, 124.4, 126.8, 127.2, 127.6, 127.8, 128.3, 135.5, 136.1, 139.8, 140.0, 141.7, 189.7.

(±)-4-Chloro-6-ethyl-6-phenylpyrrolo[2,1-*d*][1,5]-benzothiazepin-7(6*H*)-one (7e). Starting from **6d** (300 mg, 0.92 mmol), the ketone **7e** was obtained following an identical procedure as for **7a**. Compound **7e** was chromatographed using CH_2Cl_2 and hexanes 1:1 as eluant: IR (Nujol) 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3 H, J = 7.0 Hz), 2.31 (m, 1 H), 2.62 (m, 1 H), 6.43 (m, 1 H), 6.89−7.55 (m, 10 H).

(±)-6-Ethyl-6-phenylpyrrolo[2,1-*d*][1,5]benzothiazepin-7(6*H*)-one 5-Oxide (8). To a solution of **7a** (100 mg, 0.31 mmol) in dry chloroform (1.5 mL), cooled at 0 °C was slowly added a solution of *m*-chloroperbenzoic acid (53 mg, 0.31 mmol) in dry chloroform (1.6 mL). After 12 h at 0 °C, the suspension was filtered off and the filtrate was washed twice with 5% K_2CO_3 solution, dried, and evaporated. The solid residue was chromatographed (EtOAc) and recrystallized to give 120 mg of sulfoxide **8** as colorless prisms: IR (Nujol) 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7.0 Hz), 2.70 (m, 2 H), 6.52 (m, 1 H), 6.80−7.50 (m, 11 H).

(±)-6-Ethyl-6-phenylpyrrolo[2,1-*d*][1,5]benzothiazepin-7(6*H*)-one 5,5-Dioxide (9). To a solution of ketone **8** (37 mg, 0.11 mmol) in dry chloroform (0.5 mL) was slowly added a solution of *m*-chloroperbenzoic acid (60 mg, 0.347 mmol) in dry chloroform (1.6 mL). After 10 h at room temperature, the suspension was filtered off and the filtrate was washed twice with 5% K_2CO_3 solution, dried, and evaporated. The solid residue was chromatographed (EtOAc) and recrystallized to give 20 mg of sulfone **9** as colorless prisms: IR (Nujol) 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.1 Hz), 2.77 (m, 2 H), 6.53 (m, 1 H), 7.0−7.60 (m, 11 H).

1-(2-Hydroxy-3-naphthyl)pyrrole (12). To a solution of 3-amino-2-naphthol **10** (5.0 g, 31.4 mmol) in 200 mL of water and glacial acetic acid (1:9) was added 2,5-dimethoxytetrahydrofuran (4.1 g, 31.4 mmol) in glacial acetic acid (10 mL). The mixture was heated at 110 °C for 30 min, the solvent was removed *in vacuo*, and the residue was extracted with EtOAc. The organic layers were washed with 10% Na_2CO_3 solution and brine, dried, and evaporated. The residue was flash chromatographed (dichloromethane) and recrystallized to give 3.2 g of pyrrole **12** as pale pink prisms: IR (neat) 3490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 1 H), 6.44 (m, 2 H), 6.97 (m, 2 H), 7.25−7.95 (m, 6 H).

General Procedure for Preparation of Compounds 13a−d. This procedure is illustrated for the preparation of (±)-α-[[2-(1*H*-pyrrol-1-yl)phenyl]oxy]phenylacetic acid ethyl ester (**13b**). Sodium hydride (332 mg, 13.8 mmol) was added to a solution of 1-(2-hydroxyphenyl)pyrrole **11** (2 g, 12.5 mmol) in anhydrous THF (60 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then a solution of ethyl α-bromophenylacetate (3.05 g, 12.5 mmol) in anhydrous THF (20 mL) was added dropwise. After 17 h at room temperature, the solvent was removed *in vacuo*, and the residue was taken up in dichloromethane. The organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (toluene) to give 2.7 g of **13b** as a colorless oil: IR (neat) 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 6.9 Hz), 4.10 (q, 2 H, J = 6.9 Hz), 5.51 (s, 1 H), 6.31 (m, 2 H), 6.94−7.47 (m, 11 H).

(±)-α-[[2-(1*H*-Pyrrol-1-yl)phenyl]oxy]butyric Acid Ethyl Ester (13a). Starting from **11** (5.0 g, 31.3 mmol), the title compound was obtained (reaction time 15 h) following the procedure described for **13b**. After flash chromatography (30% ethyl ether in hexanes), **13a** was obtained as a colorless oil: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7.2 Hz), 1.23 (t, 3 H, J = 7.0 Hz), 1.92 (m, 2 H), 4.20 (q, 2 H, J = 7.2 Hz), 4.56 (t, 1 H, J = 5.8 Hz), 6.30 (m, 2 H), 6.85−7.35 (m, 6H).

(±)-α-[[2-(1*H*-Pyrrol-1-yl)phenyl]oxy]-2-naphthylacetic Acid Ethyl Ester (13c). Starting from **11** (790 mg, 5 mmol), the title compound was obtained (reaction time 15 h) following the procedure described for **13b**. After flash chromatography (toluene), **13c** was obtained as a colorless oil: IR (neat) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7.1 Hz), 4.12 (m, 2 H), 6.15 (s, 1 H), 6.30 (m, 2 H), 6.35−8.25 (m, 13 H).

(±)-α-[[3-(1*H*-Pyrrol-1-yl)-2-naphthyl]oxy]phenylacetic Acid Ethyl Ester (13d). Starting from **12** (3.12 g, 14.9 mmol), the title compound was obtained (reaction time 18 h) following the procedure described for **13b**. After flash chromatography (30% ethyl ether in hexanes), **13d** was obtained as a colorless oil: IR (neat) 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3 H, J = 6.9 Hz), 4.18 (m, 2 H), 5.76 (s, 1 H), 6.37 (m, 2 H), 7.23 (m, 2 H), 7.26−7.86 (m, 11 H).

General Procedure for Preparation of Compounds 14a−d. This procedure is illustrated for the preparation of (±)-α-[[2-(1*H*-pyrrol-1-yl)phenyl]oxy]phenylacetic acid (**14b**). The ester **13b** (2.7 g, 8.4 mmol) was dissolved in 26 mL of EtOH/THF mixture (1:1), and 5% aqueous NaOH (22.4 mL) was slowly added. The reaction mixture was stirred at room temperature for 1 h, concentrated, and acidified with 4 N HCl until pH 3−4. The suspension was extracted with EtOAc, and the organic phase was washed with brine, dried, and concentrated. The residue was crystallized to give the acid **14b** (2.3 g) as colorless prisms: IR (Nujol) 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.48 (s, 1 H), 6.33 (m, 2 H), 6.90−7.50 (m, 11 H).

(±)-α-[[2-(1*H*-Pyrrol-1-yl)phenyl]oxy]butyric Acid (14a). Starting from **13a** (4.6 g, 16.8 mmol), the title compound was obtained (reaction time 4 h) following the procedure as for **14b**. After purification by flash chromatography (10% EtOAc in chloroform), **14a** crystallized as colorless prisms: IR (KBr)

1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 3.5 Hz), 1.97 (m, 2 H), 4.58 (t, 1 H, J = 5.5 Hz), 6.30 (m, 2 H), 6.87−7.35 (m, 6 H).

(±)-α-[[2-(1*H*-Pyrrol-1-yl)phenyl]oxy]-2-naphthylacetic Acid (14c). Similarly to **14b**, the acid **14c** was prepared starting from 1.6 g (4.3 mmol) of **13c** (reaction time 3 h). **14c** was obtained as colorless prisms: IR (neat) 3410, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50 (br s, 1 H), 6.10 (s, 1 H), 6.32 (m, 2 H), 6.92−7.15 (m, 4 H), 7.21−7.60 (m, 6 H), 7.84 (m, 2 H), 8.15 (m, 1 H).

(±)-α-[[3-(1*H*-Pyrrol-1-yl)-2-naphthyl]oxy]phenylacetic Acid (14d). Starting from **13d** (2.65 g, 6.9 mmol), the title compound was obtained (reaction time 4 h) following the procedure as for **14b**. After purification by flash chromatography (benzene), **14d** crystallized as colorless prisms: IR (KBr) 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s, 1 H), 6.04 (m, 2 H), 6.90−7.60 (m, 13 H).

General Procedure for Preparation of Compounds 15a−d. This procedure is illustrated for the preparation of (±)-6-phenylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (**15b**). Phosphorus pentachloride (400 mg, 1.92 mmol) was added to a solution of acid **14b** (500 mg, 1.89 mmol) in dry 1,2-dichloroethane (8.5 mL) within 20 min. The reaction mixture was stirred at room temperature for 5 h, and then was poured into crushed ice, basified with 10% NaOH solution, and extracted with chloroform. The organic layers were washed with brine, dried, and evaporated. The residue was chromatographed (dichloromethane and hexanes, 2/1) and recrystallized to yield 300 mg of oxazepinone **15b** as colorless prisms: IR ($CHCl_3$) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.47 (s, 1 H), 6.43 (m, 1 H), 6.80−7.40 (m, 11 H).

(±)-6-Ethylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (15a). Similarly to **15b**, the oxazepinone **15a** was prepared starting from 4.0 g (16.3 mmol) of **14a** (reaction time 6 h at 80 °C). **15a** was obtained as pale brown prisms: IR ($CHCl_3$) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 7.0 Hz), 1.89 (m, 1 H), 2.16 (m, 1 H), 4.30 (dd, 1 H, J = 8.8, 3.9 Hz), 6.44 (m, 1 H), 7.18−7.40 (m, 6 H).

(±)-6-(2-Naphthyl)pyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (15c). Similarly to **15b**, the oxazepinone **15c** was prepared starting from 2.38 g (6.94 mmol) of **14c** (reaction time 7 h at 80 °C). **15c** was obtained as white prisms: IR ($CHCl_3$) 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (s, 1 H), 6.55 (m, 1 H), 6.76 (dd, 1 H, J = 9.0 Hz), 6.95 (m, 1 H), 7.09−7.63 (m, 10 H), 8.23 (m, 1 H).

(±)-5-Phenylnaphtho[2,3-b]pyrrolo[1,2-*d*][1,4]oxazepin-4(5*H*)-one (15d). Similarly to **15b**, the oxazepinone **15d** was prepared starting from 1.14 g (3.2 mmol) of **14d** (reaction time 4 h at 80 °C). **15d** was obtained as colorless prisms: IR ($CHCl_3$) 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.57 (s, 1 H), 6.56 (m, 1 H), 7.25−7.86 (m, 13 H).

General Procedure for the Preparation of Oxazepinones 16. This procedure is illustrated for the preparation of (±)-6-ethyl-6-phenylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (**16e**). A solution of **15b** (366 mg, 1.33 mmol) in anhydrous THF (5 mL) was added to a suspension of potassium hydride (153 mg, 1.33 mmol, 35% in oil) in anhydrous THF (2.5 mL). The reaction mixture was stirred for 2 h at room temperature, and then ethyl iodide (204 mg, 1.33 mmol) was added. After an additional 30 min at room temperature the solvent was removed, and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography (dichloromethane) to give 280 mg of ketone **16e** which crystallized as pale yellow prisms: IR (Nujol) 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7.2 Hz), 2.42 (m, 2 H), 6.45 (m, 1 H), 6.80−7.40 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 18.3, 32.3, 96.0, 111.6, 120.5, 121.6, 125.2, 125.5, 126.0, 126.8, 127.5, 128.1, 133.8, 134.1, 138.2, 146.7, 192.6. The O-alkylated regioisomer **16l** was also isolated by flash chromatography and recrystallized as colorless prisms: IR ($CHCl_3$) 1599, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 6.9 Hz), 3.88 (q, 2 H, J = 6.8 Hz), 6.45 (m, 1 H), 6.61 (m, 1 H), 7.15−7.36 (m, 9 H), 8.04 (m, 1 H).

(±)-6-Ethyl-6-*n*-propylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (16a). Starting from 140 mg (0.61 mmol) of **15a**, the title compound was obtained following the procedure as for **16e**. After flash chromatography (dichloromethane), **16a** was obtained as colorless oil: IR 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 7.0 Hz), 0.94 (t, 3 H, J = 7.2 Hz), 1.40 (m, 2 H), 1.77 (m, 4 H), 6.42 (m, 1 H), 7.16−7.37 (m, 6 H) ; ^{13}C NMR ($CDCl_3$) δ 7.7, 14.3, 16.5, 29.0, 37.9, 93.6, 111.5, 120.3, 121.6, 125.2, 125.3, 125.4, 127.0, 133.8, 134.0, 146.5, 193.4.

(±)-6-Allyl-6-ethylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (16b). Starting from 280 mg (1.23 mmol) of **15a**, the title oxazepinone was obtained following the procedure as for **16e**. After flash chromatography, **16b** was obtained as colorless prisms: IR 1646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.3 Hz), 1.69−2.00 (m, 2H), 2.46−2.67 (m, 2 H), 5.07 (m, 2 H), 5.70−5.92 (m, 1 H), 6.41 (m, 1 H), 7.14−7.37 (m, 6 H).

(±)-6-Ethyl-6-(2-isopentenyl)pyrrolo[2,1-*d*][1,5]-benzoxazepin-7(6*H*)-one (16c). Starting from 140 mg (0.61 mmol) of **15a**, the title compound was obtained following the procedure as for **16e**. After flash chromatography (dichloromethane), **16c** was obtained as colorless prisms: IR 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.3 Hz), 1.53 (s, 3 H), 1.67 (s, 3 H), 1.85 (m, 2 H), 2.48 (d, 2 H, J = 6.9 Hz), 5.19 (t, 1 H, J = 7.8 Hz), 6.41 (m, 1 H), 7.0−7.36 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 7.8, 18.0, 25.9, 29.4, 34.2, 93.6, 111.5, 117.3, 120.5, 121.6, 125.2, 125.4, 127.1, 133.7, 134.0, 135.1, 146.5, 193.3.

(±)-6-Methyl-6-phenylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (16d). Starting from **15b** (300 mg, 1.1 mmol), the title compound was prepared (reaction time 12 h) following the procedure described for **16e** and was recrystallized as colorless prisms: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 6.46 (m, 1 H), 6.90−7.45 (m, 11 H).

(±)-6-Phenyl-6-*n*-propylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (16f). Starting from 200 mg (0.72 mmol) of **15b**, the title compound was obtained (reaction time 12 h), following the procedure as for **16e**, as colorless prisms: IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.0 Hz), 1.61 (m, 2 H), 2.43 (m, 2 H), 6.45 (m, 1 H), 6.90−7.40 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 17.1, 41.7, 95.7, 11.6, 120.5, 121.6, 125.2, 125.5, 126.0, 126.8, 127.5, 128.0, 133.8, 134.0, 138.4, 146.7, 192.7.

(±)-6-Allyl-6-phenylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-one (16g). Similarly to **16e**, the ketone **16g** was prepared starting from 200 mg (0.72 mmol) of **15b** (reaction time 12h). Oxazepinone **16g** was obtained as colorless prisms: IR (Nujol) 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15 (m, 2 H), 5.10 (dd, 1 H, J = 10.7, 1.4 Hz), 5.20 (d, 1 H, J = 1.6 Hz), 5.89 (m, 1 H), 6.45 (m, 1 H), 6.95−7.40 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 43.4, 94.8, 111.8, 119.0, 120.7, 121.5, 125.3, 125.6, 126.3, 126.7, 127.5, 128.1, 128.3, 132.4, 133.7, 137.8, 146.4, 191.8.

(±)-6-(2-Isopentenyl)-6-phenylpyrrolo[2,1-*d*][1,5]-benzoxazepin-7(6*H*)-one (16h). Starting from 300 mg (1.09 mmol) of oxazepinone **15b**, the title compound was obtained as colorless prisms (reaction time 10 h), following the procedure described for **16e**. **16h** was purified by flash chromatography (35% chloroform in hexanes): IR (Nujol) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (s, 3 H), 1.66 (s, 3 H), 2.97 (m, 1 H), 3.16 (m, 1 H), 5.23 (m, 1 H), 6.44 (m, 1 H), 6.95−7.45 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 37.2, 95.2, 111.7, 118.0, 120.5, 121.5, 125.3, 125.6, 126.2, 126.8, 127.5, 128.0, 133.6, 133.9, 135.0, 138.4, 146.5, 192.5.

(±)-6-(Cyclopropylmethyl)-6-phenylpyrrolo[2,1-*d*][1,5]-benzoxazepin-7(6*H*)-one (16i). Starting from **15b** (287 mg, 1.04 mmol), the title compound was obtained (reaction time 15 h) following the procedure described for **16e**. After flash chromatography (30% dichloromethane in hexanes), **16i** was obtained as colorless prisms: IR (film) 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.2 (m, 2 H), 0.46 (m, 2 H), 1.08 (m, 1 H), 2.23 (m, 1 H), 2.58 (m, 1 H), 6.46 (m, 1 H), 6.80−7.35 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 5.0, 5.7, 6.2, 45.3, 96.1, 111.6, 120.5, 121.4, 125.1, 125.4, 126.2, 126.7, 127.7, 128.0, 128.3, 134.0, 134.5, 138.2, 147.0, 192.7.

(±)-6-Ethyl-6-(2-naphthyl)pyrrolo[2,1-*d*][1,5]-benzoxazepin-7(6*H*)-one (16j). Similarly to **16e**, the oxazepinone **16j** was prepared starting from 120 mg (0.37 mmol) of **15c** (reaction time 15 h) and, after purification by flash chromatography (dichloromethane and hexanes, 1:1), was obtained as colorless prisms: IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 7.0 Hz), 2.60 (m, 1 H), 3.03 (m, 1 H), 6.52 (m, 1 H), 6.73−7.88 (m, 12 H), 8.80 (d, 1 H, J = 8.5

Hz); ^{13}C NMR ($CDCl_3$) δ 9.0, 31.4, 97.4, 112.0, 121.0, 121.4, 124.5, 125.1, 125.3, 125.5, 126.0, 126.4, 127.3, 129.2, 130.0, 131.3, 133.3, 133.7, 134.0, 135.1, 147.0, 191.4.

(±)-5-Ethyl-5-phenylnaphtho[2,3-*b*]pyrrolo[1,2-*d*][1,4]-oxazepin-4(5*H*)-one (16k). Starting from **15d** (300 mg, 0.92 mmol), the title compound was obtained (reaction time 12 h) following the procedure as for **16e**. After purification by flash chromatography (dichloromethane), **16k** crystallized as colorless prisms: IR (Nujol) 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3 H, J = 7.0 Hz), 2.44 (m, 2 H), 6.47 (m, 1 H), 7.0−7.80 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 8.3, 32.0, 95.7, 112.0, 119.7, 120.6, 123.1, 126.0, 126.2, 127.2, 127.3, 127.5, 128.0, 130.6, 132.0, 133.4, 138.2, 145.2, 193.0.

***In Vitro* Anti-HIV Assay.** The ability of the test compounds to protect HIV-1-infected T4 lymphocytes (CEM cells) from cell death was determined following the reported procedure.[33] All compounds are compared with a positive (AZT-treated) control performed at the same time under identical conditions.

***In Vitro* HIV-1 RT Assay.** The standard assay was performed at 37 °C for 30 min in a 50 μL reaction mixture containing 50 mM Tris·HCl (pH 8.2), 1 mM dithiothreitol, 80 mM KCl, 12 mM $MgCl_2$, 0.01% Triton X-100, 0.5 μCi of either [^{3}H]dTTP (NEN) or [^{3}H]dGTP (NEN), 2.5 μg of either poly(rA)/$(dT)_{12-18}$ (Pharmacia) or poly(rC)/$(dG)_{12-18}$ (Pharmacia), test compounds dissolved in DMSO (final concentration 10%), and 0.1 unit of recombinant HIV-1 RT (Boehringer Mannheim). The reaction was stopped with 100 μL of 20% (v/v) trichloroacetic acid, and the precipitated material was analyzed for radioactivity.[12a,34] The concentration that caused 50% inhibition (IC_{50}) is stated as the mean of at least three experiments.

***In Vitro* α-Polymerase Assay.** The standard assay was performed at 37 °C for 15 min in a 50 μL reaction mixture containing 20 mM Tris acetate (pH 7.3), 1 mM dithiothreitol, 75 mM KCl, 1 mM $MgCl_2$, 100 μg/mL bovine serum albumin (BSA) DNAase-free, 1 μM dNTPs, 0.3 μL of [^{32}Pd]CTP 3000 Ci/mmol (Amersham), 0.006 unit of activated calf-thymus DNA (Pharmacia), test compounds dissolved in DMSO (final concentration 10%), and 0.06 unit of calf-thymus DNA α-polymerase (HT Biotechnology, LTD). The reaction was stopped with 100 μL of 20% (vol/vol) trichloroacetic acid, and the precipitated material was analyzed for radioactivity.[35]

***In Vitro* DNA-Dependent Hepatitis B Virus-Polymerase Assay. Purification of HBV Particles from HBV-DNA Positive Serum.** Serum from HBV-DNA positive patients was clarified by 15 min centrifugation at 10.000 rpm. Clarified serum (15 mL) was loaded onto a discontinuous sucrose gradient: 3 mL of 30% sucrose, 5 mL of 20% sucrose, and 10 mL of 10% sucrose in 10 mM Tris·HCl (pH 7.5). After centrifugation for 18 h at 25.000 rpm at 4 °C in a SW28 Beckman rotor, the pellet was resuspended in 1.5 mL of 20% glycerol in 10 mM Tris·HCl (pH 7.5) and stored in aliquots at −80 °C.

The standard assay was performed at 37 °C for 2 h in a 50 μL reaction mixture containing 50 mM Tris·HCl (pH 7.5), 100 mM KCl, 30 mM $MgCl_2$, 0.2% Triton X-100, 1 μM dNTPs, 0.3 μL of [^{32}Pd]CTP 3000 Ci/mml (Amersham), the test compounds dissolved in DMSO (final concentration 10%), and 2 μL of purified HBV particles. The reaction was stopped with 100 μL of 20% (v/v) trichloroacetic acid and the precipitated material was analyzed for radioactivity.[36]

Molecular Modeling. All molecular modeling was performed with use of the software package SYBYL[37] running on a Silicon Graphics Iris Indigo XS24 workstation. A starting model of compound **16e** was built using the SKETCH routine. Conformational energies were calculated through the molecular mechanics TRIPOS force field.[27] Partial atomic charges were computed with the Gasteiger−Hückel method.[28,29] Full geometry optimizations were realized with the SYBYL/MAXIMIN2 minimizer by applying the BFGS (Broyden, Fletcher, Goldfarb, and Shannon) algorithm with a change in energy value of 0.001 kcal/mol as convergence criterion. The conformational analysis of **16e** was performed by scanning the torsional angles τ_1, τ_2, and τ_3 (definitions are given in Chart 2). Using the SYBYL/GRIDSEARCH routine, τ_2 and τ_3 were scanned through 30° steps within intervals of 0−330° and 0−150°, respectively. The endocyclic bond associated with τ_1 was rotated manually. The geometry of nevirapine was extracted from a 2.9 Å resolution structure of the HIV-1 RT/ complex[19] retrieved from the Brookhaven Protein Data Bank (entry code 3HVT).[38]

Enantiomeric geometries were automatically generated using the SYBYL/INVERT option. Low-energy conformations of **16e** (both *S*- and *R*-enantiomers) were overlapped on the nevirapine enzyme-bound conformation using the SYBYL/FIT command.

The fitting points for aromatic rings were pseudoatoms placed at 1.0 Å distance along the normal to each ring passing through the ring centroid.

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