Urea−PETT Compounds as a New Class of HIV-1 Reverse Transcriptase Inhibitors. 3. Synthesis and Further Structure−Activity Relationship Studies of PETT Analogues

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The further development of allosteric HIV-1 RT inhibitors in the urea analogue series of PETT (phenylethylthiazolylthiourea) derivatives is described here. The series includes derivatives with an ethyl linker (**1**−**5**) and racemic (**6**−**16**) and enantiomeric (**17**−**20**) *cis*-cyclopropane compounds. The antiviral activity was determined both at the RT level and in cell culture on both wild-type and mutant forms of HIV-1. Most compounds have anti-HIV-1 activity on the wt in the nanomolar range. Resistant HIV-1 was selected in vitro for some of the compounds, and the time for resistant HIV-1 to develop was longer for urea−PETT compounds than it was for reference compounds. Preliminary pharmacokinetics in rats showed that compound **18** is orally bioavailable and penetrates well into the brain. The three-dimensional structure of complexes between HIV-1 RT and two enantiomeric compounds (**17** and **18**) have been determined. The structures show similar binding in the NNI binding pocket. The propionylphenyl moieties of both inhibitors show perfect stacking to tyrosine residues 181 and 188. The cyclopropyl moiety of the (+)-enantiomer **18** exhibits optimal packing distances for the interactions with leucine residue 100 and valine residue 179.

Introduction

The life cycle of HIV has been extensively studied, and a number of stages identified for possible intervention to prevent viral replication.[1] These include formation of proviral DNA by the reverse transcriptase enzyme (RT), integration of proviral DNA into the host DNA by the integrase enzyme, and cleavage of the precursor viral proteins by the protease enzyme. Clinically relevant agents which have been successfully developed are RT inhibitors and protease inhibitors. RT inhibitors are divided into two categories: nucleoside (NRTIs) and nonnucleoside (NNRTIs) reverse transcriptase inhibitors. NRTIs are phosphorylated by cellular enzymes to an active metabolite, analogous to a natural nucleotide, for incorporation into the growing viral DNA chain by HIV RT in a competitive reaction. Once inserted into the chain, no further nucleosides can be added, and therefore viral replication ceases. NNRTIs are a diverse group of compounds which inhibit HIV RT by an allosteric mechanism of action. NNRTIs are not incorporated into the growing strand of HIV DNA but directly inhibit the viral RT by binding to an allosteric site.

Thus far, three NNRTIs, nevirapine (Viramune),[2] delavirdine (Rescriptor),[3] and DMP-266 (Sustiva),[4] have been approved for treatment of HIV-1-infected adults in combination with nucleoside analogues. A number of such agents are or have been in clinical trials including 3,4-dihydroquinoxaline-2(1*H*)-thione derivative (HBY 097),[5] α-anilinophenylacetamide (α-APA, loviridine),[6] tetrahydroimidazobenzodiazepinthione (tivirapine),[7] and isopropyluracil derivatives (HEPT, MKC-442),[8] and some of the other more recent additions to the group include alkenyldiarylmethane derivative (ADAM),[9] 1*H*-imidazol-2-ylmethyl carbamate derivative (S-1153),[10] and thiocarboxanilide derivatives (UC 84, UC 38).[11]

Because NNRTIs interact with a specific binding site on the enzyme, any slight variation brought about by a single point mutation can have a significant impact on the sensitivity of virus to members of this group, and high-level resistance can develop quickly.[1] The rapid development of resistance to NNRTIs is an important factor influencing the failure of today's treatment approaches to HIV infection.[12a,b] As part of the preclinical evaluation of new treatments for HIV, the activity of all new agents are investigated in combination with other antiretroviral compounds against a number of both laboratory and clinical HIV isolates, to evaluate potential synergistic or antagonistic activity.[13,14] Combination therapy can slow the selection of drug-resistant strains and is associated with significant clinical benefit.[15] Several combinations are used, and several are currently undergoing clinical evaluation, including combinations of two or more RT inhibitors and combinations of RT inhibitors with protease inhibitors.[2d,16] There is a further need for the discovery and development of improved NNRTIs.

We have recently described a series of thiourea

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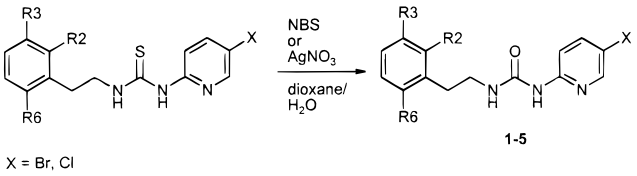
Scheme 1



derivatives, the PETT (phenylethylthiazolylthiourea) compounds, which belong to the NNRTIs.[17−20] The lead compound in this series was LY73497 which inhibited wild-type HIV-1 with ED_{50} of 1.3 μM and HIV-1 RT with IC_{50} of 0.9 μM. The first generation of PETT compounds resulted in trovirdine with ED_{50} of 20 nM and IC_{50} of 15 nM. The further optimization of the PETT series has led to urea analogues briefly described in our preliminary paper.[21] We can now more comprehensively confirm that urea analogues have better toxicological and pharmacokinetic properties than the thiourea compounds and their antiviral activity in cell culture in the presence of human serum is better than that of the thiourea compounds.

In this study we report the synthesis and anti-HIV-1 activity of 20 urea−PETT compounds including both phenethyl and phenylcyclopropyl derivatives, development of resistant HIV-1 in vitro for some of the compounds, and also pharmacokinetic studies for one of the compounds. The three-dimensional structure of the complexes between HIV-1 RT and an enantiomeric pair of a PETT cyclopropane compound has been determined.

Chemistry

Compounds **1**−**5** (Table 1) with an ethyl linker described in the present study were synthesized according to Scheme 1. Conversion of the previously reported thiourea compounds[20] to the corresponding urea analogues was achieved either with *N*-bromosuccinimide (NBS) or with silver nitrate ($AgNO_3$). The yields of these reactions were only about 30%, but both agents were efficient and rapid to afford these urea compounds. It was important that the products of these reactions were purified carefully, because it was known that the starting materials were highly potent HIV-1 RT inhibitors.

A representative synthesis for racemic cyclopropane compounds **6**−**16** is described in Scheme 2. Ethylation of 2-chloro-4-fluorophenol (**28**) with ethyl iodide in the presence of potassium carbonate in refluxing acetone afforded intermediate **29** which was converted to aldehyde **30** using *n*-BuLi and DMF. 2-Chloro-3-ethoxy-6-fluorostyrene (**31**) was prepared from 2-chloro-3-ethoxy-6-fluorobenzaldehyde (**30**) by reaction with an appropriate Wittig reagent. The yields of the three first steps were high: 89−98%. Cyclopropanation of the styrene **31** with ethyl diazoacetate in dichloroethane using copper(I) iodide and palladium(II) acetate as catalysts afforded the ester **32** (*cis*/*trans* ratio 0.45). *cis*-Ester was purified by column chromatography (the yield of pure *cis*-ester was 12%) and then hydrolyzed with potassium hydroxide in ethanol/water to give cyclopropanecarboxylic acid **33**. Curtius reaction on the acid using diphenyl phosphorazidate followed by reaction with 2-amino-5-cyanopyridine afforded compound **10**. The unoptimized yield of this reaction was 9%. The corresponding coupling reactions with 2-amino-5-bromopyridine and 2-amino-5-chloropyridine gave higher yields.

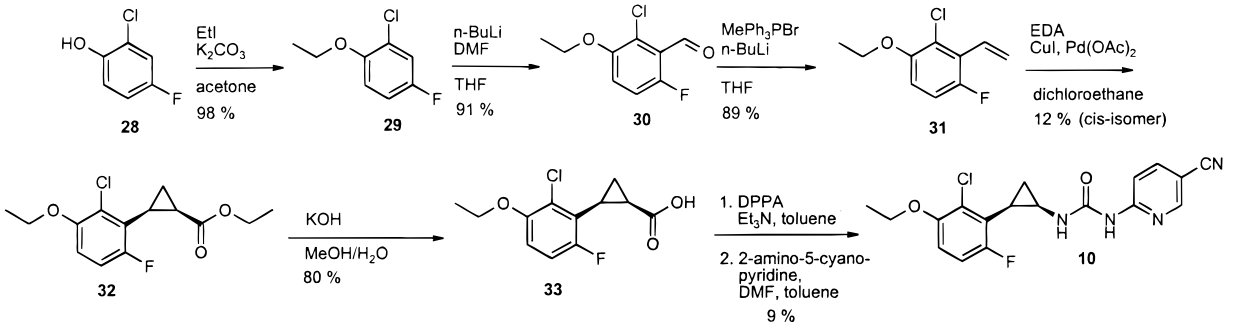
The synthesis of compound **17** described in Scheme 3 is representative for the enantiomeric cyclopropane compounds **17**−**20**. Acylation of 3-fluorophenol (**34**) with propionyl chloride followed by Fries rearrangement with $AlCl_3$ afforded intermediate **36** in very high yield without formation of any regioisomers. Compound **36** was alkylated with methyl iodide to give 4′-fluoro-2′-methoxypropiophenone (**37**). This compound was acetal-protected by reaction with ethylene glycol, and further reaction of the resulting intermediate **38** with *n*-BuLi and DMF afforded aldehyde **39**. A Wittig reaction on compound **39** gave styrene **40**. The next step, asymmetric cyclopropanation reaction with ethyl diazoacetate, catalyzed by copper(I) triflate and enantiomeric ligand[22] gave ester **41** (*cis*/*trans* ratio of 3.0, *cis* purified by column chromatography, the yield of pure *cis*-ester was 45%). It was notable that the *cis*/*trans* ratio of the product in this asymmetric cyclopropanation reaction was reversed compared to the above-mentioned. We have no explanation for this high *cis*-selectivity, but one speculation is that substituents of the phenyl ring stabilize a transition state that leads to the *cis*-compound. The corresponding reaction using styrene gives a *cis*/*trans* ratio of 0.3.[22] Cyclopropanecarboxylic acid **43** was obtained by hydrolysis of *cis*-ester **41** first with HCl/dioxane/water to give deketalized compound **42**, followed by hydrolysis with lithium hydroxide in methanol/water. Curtius reaction on the acid **43** followed by reaction with 2-amino-5-bromopyridine as outlined also in Scheme 2 yielded compound **44**, which was demethylated with boron trichloride in methylene chloride to afford the desired compound **17**. The enantiomeric purity of this compound was determined by high-performance liquid chromatography (HPLC) on a Chiral-AGP column to be 98.6% ee.

Biological Results and Discussion

Antiviral Activity. All compounds **1**−**20** in this study were tested in HIV-1 RT enzyme assays with wild-type and three constructed mutants, Ile100, Cys181,[23] and Asn103, and in cell culture using MT-4 cells[24] and both wild-type virus and virus containing a mutation in residue 100, 181, or 103. The amino acid substitutions Ile100 and Cys181 were observed at an early stage when studying PETT compounds in cell culture,[20] and virus carrying Cys181 or Asn103 has been identified in clinical isolates after administration of nevirapine, delavirdine, and DMP-266.[1,12a,b] The most active compounds were tested in a cell culture assay containing 50% human serum to simulate protein binding in the physiological environment. DMP-266, HBY-097, nevirapine, and delavirdine were chosen as reference compounds. The IC_{50} and ED_{50} values from these assays are presented in Table 1.

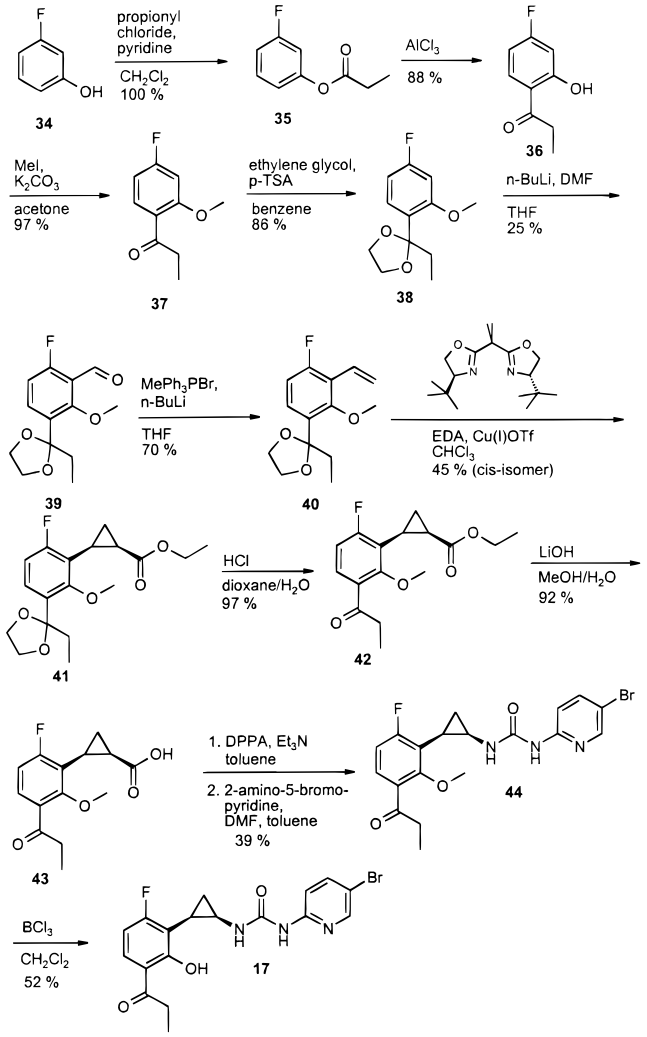
All the present compounds can be divided into four groups: (i) phenethyl derivatives, compounds **1**−**5**, (ii) racemic cyclopropane derivatives with 2,6-dihalogen-3-alkoxy or 2,6-dihalogen-3-hydroxy substitution of the phenyl ring, compounds **6**−**12**, (iii) racemic cyclopropane derivatives with 2-hydroxy-3-acetyl or propionyl-6-fluoro

Scheme 2[a]



[a] The compounds are racemic; only one enantiomer of the *cis*-compound is shown.

Scheme 3



substitution of the phenyl ring, compounds **13**−**16**, and (iv) enantiomeric cyclopropane derivatives, compounds **17**−**20**.

Compound **2** with a 2-fluoro-3,6-dimethoxy-substituted phenyl ring was the most active of the phenethyl derivatives in the first group but not as active as its thiourea analogue as we have reported earlier.[20] 3-Acetyl substitution of the phenyl ring in compounds **4** and **5** decreased activity significantly on both wild-type and mutant HIV-1 RT and virus. Compound **1** with a dimethylamino group in the 3-position of the phenyl ring was synthesized to enhance water solubility, but this substituent was not favorable for activity.

As we have found earlier the *cis*-cyclopropane derivatives are more potent than the ethyl-linked analogues especially on mutants.[21] *cis*-Cyclopropane compounds have a more restricted conformation compared with ethyl analogues which appears to lead to better interaction with the mutant enzymes. The most favorable substitution of the phenyl ring in the second group, which contained *cis*-cyclopropane derivatives, was the 2-fluoro-3-ethoxy-6-fluoro substitution of compounds **7** and **8**. Replacement of the pyridyl ring on the right-hand side of the molecule with a pyridazine ring, compounds **9** and **11**, and replacement of the 3-ethoxy substituent with a 3-hydroxy substituent on the phenyl ring, compound **12**, led to decreased activity.

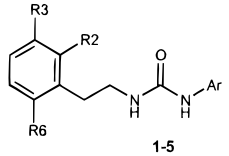
Racemic *cis*-cyclopropane derivatives described in this paper, compounds **13**−**16** of the third group, represent a new type of 2-hydroxy-3-acetyl- or propionyl-6-fluorophenyl ring substitution. They represent a very potent group of PETT-urea compounds on both wild-type and mutant HIV-1 RT and virus. All of them were more active on mutant HIV-1 RT (Asn103) than any compound hitherto. Hydrogen bonding between the 2-hydroxy and 3-acetyl or 3-propionyl substituent of the phenyl ring contributes to the stability of the compounds and consequently is beneficial for activity.

The last group, compounds **17**−**20**, included pure (−)- and (+)-enantiomers of 2-hydroxy-3-propionyl-6-fluorophenyl *cis*-cyclopropane derivatives with bromo- and chloropyridine rings on the opposite side of the urea function, herein referred to as the right-hand side of the molecule. Both (−)- and (+)-enantiomers were very active. (+)-Enantiomers, compounds **18** and **20**, were about 10-fold more potent on RT mutant (Ile100) and 2−3-fold more potent on mutant HIV-1 (Ile100) than (−)-enantiomers, compounds **17** and **19,** while (−)-enantiomers were 2−4-fold more potent on mutant HIV-1 (Asn103) than (+)-enantiomers.

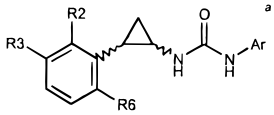
Enantiomeric *cis*-cyclopropane compounds **17**−**20** were also tested in a wild-type HIV-1 assay which contained 50% human serum. The same assay in our earlier work contained 15% human serum.[21] The presence of human serum resulted in a slight decrease in activity, which was less than that observed with delavirdine and DMP-266.

3-D Structure of HIV-1 RT Inhibitor Complexes. The three-dimensional structures of the complexes between HIV-1 RT and inhibitors **17** and **18** have been determined with 2.9 and 2.8 Å diffraction data, respectively. The structures show similar binding of the two inhibitors in the NNI binding pocket (Figure 1). The

Table 1. Inhibition of HIV-1 RT and HIV-1 (IIIB) Replication



1-5



6-20

compd	R_2	R_3	R_6	Ar	optical activity	HIV−1 RT (rCdG), IC_{50} (μM)[b] wt	Ile100	Cys181	Asn103	HIV-1 MT-4 cells, ED_{50} (μM)[c] wt	wt[d]	Ile100	Cys181	Asn103
1	F	NMe2	F	5-bromopyrid-2-yl		0.0250	>2.5	1.5	>2.5	0.500	nd[e]	>20	>20	>20
2	F	OMe	OMe	5-chloropyrid-2-yl		0.0030	0.140	0.140	0.224	0.028	nd	3.8	>5	1.13
3	Cl	OEt	F	5-bromopyrid-2-yl		0.0040	1.68	0.240	>2.4	0.070	nd	>10	>5	>5
4	OMe	COMe	F	5-chloropyrid-2-yl		0.224	26.2	12.7	>2.7	0.819	nd	>5	>5	>5
5	F	COMe	OMe	5-chloropyrid-2-yl		0.109	11.2	10.1	>2.7	0.273	nd	>20	>20	3.28
6	F	OEt	F	5-chloropyrid-2-yl	(+,−)	0.0016	0.081	0.014	0.473	0.031	nd	0.816	0.163	0.544
7	F	OEt	Cl	5-chloropyrid-2-yl	(+,−)	0.0013	0.052	0.021	0.237	0.009	nd	0.139	0.104	0.780
8	F	OEt	Cl	5-cyanopyrid-2-yl	(+,−)	0.0027	0.027	0.020	0.192	0.004	nd	0.053	0.200	0.400
9	F	OEt	Cl	5-chloropyridazin-2-yl	(+,−)	0.0052	1.0	1.0	>2.6	0.018	nd	>5	>5	>5
10	Cl	OEt	F	5-cyanopyrid-2-yl	(+,−)	0.0043	0.200	0.130	0.183	0.008	nd	0.234	0.270	>5
11	Cl	OEt	F	5-chloropyridazin-2-yl	(+,−)	0.0160	0.140	0.260	>2.6	0.078	nd	4.4	2.3	>5
12	Cl	OH	F	5-chloropyrid-2-yl	(+,−)	0.135	4.1	4.3	>2.7	0.110	nd	>5	>5	>5
13	OH	COEt	F	5-chloropyrid-2-yl	(+,−)	0.0090	0.076	0.051	0.057	0.027	nd	0.220	0.340	0.350
14	OH	COEt	F	5-cyanopyrid-2-yl	(+,−)	0.0068	0.032	0.016	0.097	0.003	nd	0.069	0.046	0.137
15	OH	COMe	F	5-cyanopyrid-2-yl	(+,−)	0.0053	0.013	0.016	0.098	0.008	nd	0.040	0.230	0.104
16	OH	COMe	F	5-bromopyrid-2-yl	(+,−)	0.0035	0.018	0.008	0.070	0.021	nd	0.050	0.113	0.561
17	OH	COEt	F	5-bromopyrid-2-yl	(−)	0.0038	0.171	0.016	0.083	0.008	0.058	0.100	0.069	0.080
18	OH	COEt	F	5-bromopyrid-2-yl	(+)	0.0048	0.014	0.010	0.041	0.012	0.056	0.053	0.095	0.358
19	OH	COEt	F	5-chloropyrid-2-yl	(−)	0.0032	0.115	0.019	0.082	0.009	0.051	0.100	0.100	0.200
20	OH	COEt	F	5-chloropyrid-2-yl	(+)	0.0027	0.014	0.004	0.077	0.013	0.080	0.075	0.100	0.470
DMP-266						0.0040	0.050	0.006	0.061	0.005	0.050	0.060	0.016	0.140
HBY-097						0.008	0.009	0.009	0.056	0.009	0.320	0.072	0.073	0.500
delavirdine						0.0013	0.130	0.114	0.625	0.176	>5	>5	>5	>5
nevirapine						0.170	17.1	>50	3.8	0.230	0.850	1.6	>20	>20

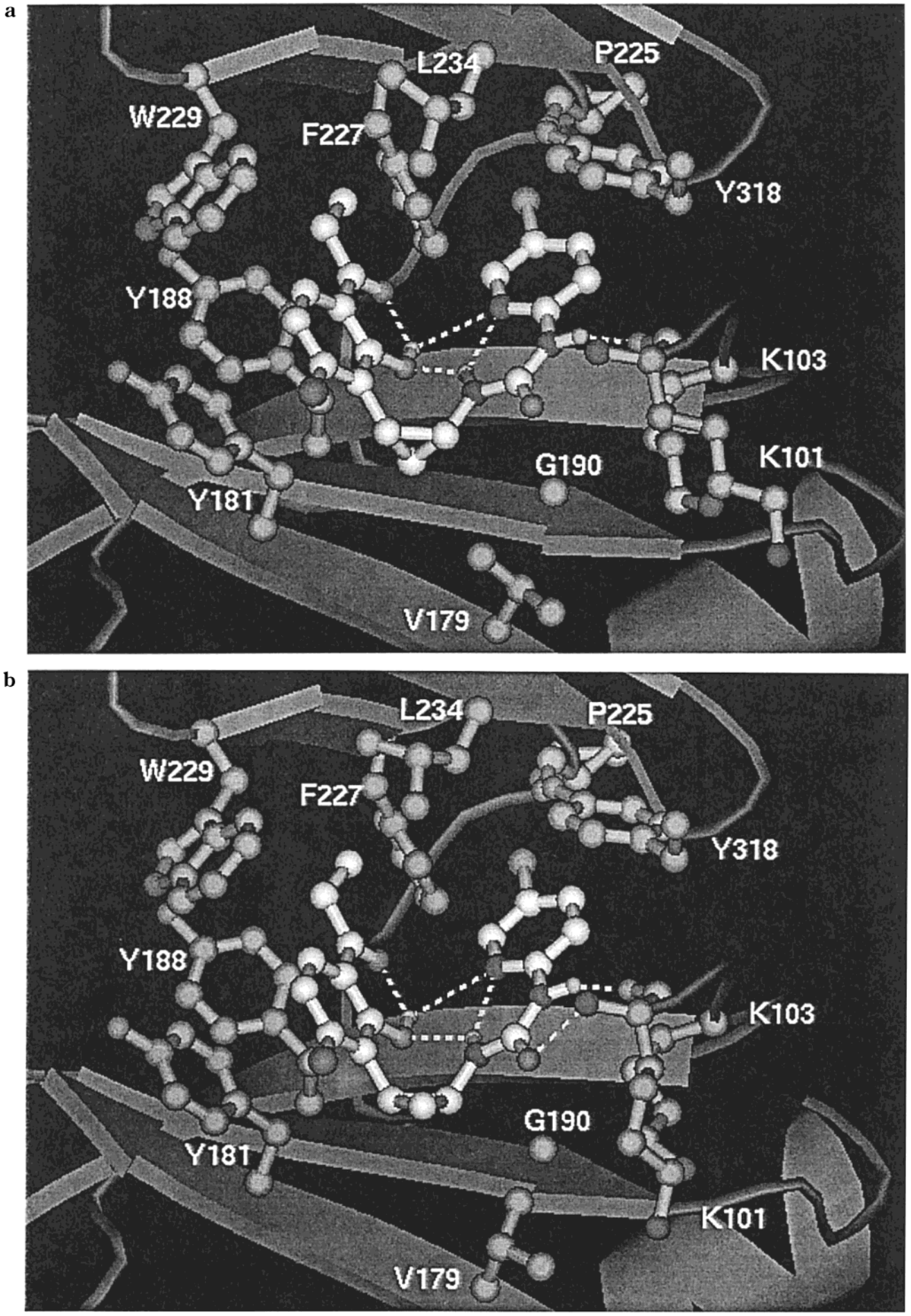
[a] All compounds have the *cis*-configuration, + and − reflecting the 1*S*,2*S* and 1*R*,2*R* configurations respectively. [b] The HIV-1 RT assay which used (poly)rC·(oligo)dG as the template/primer is described in ref 23. [c] Anti-HIV activity assay: MT4 cells (human T cell line) grown in RPMI 1640 medium supplemented with 10% fetal calf serum, penicillin, and streptomycin were seeded into 96-well microplates (2×10^4 cells/well) and infected with 10−20 $TCID_{50}$ of HIV-1 (IIIb) per well. Test compounds in different concentrations were added. The cultures were incubated at 37 °C in CO_2 atmosphere, and the viability of cells was determined at day 5 or 6 with XTT vital dye.[24] The anti-HIV-1 activity was measured as the reduction in cytopathic effect caused by the virus. Mutant HIV-1 was achieved by passaging the virus in MT4 cells in stepwise increasing concentrations of different NNRTIs. When virus was growing in highest possible, nontoxic concentration of the compound, it was passaged once without compound. Cellular DNA was analyzed with respect to nucleotide sequence in the HIV-1 RT gene, and the supernatant was frozen in aliquots at −70 °C for cross-resistance studies. [d] The assay contains 50% human AB serum. [e] Not determined.

conformation of both inhibitors is stabilized by a hydrogen bond network involving one amide hydrogen of the urea moiety, the nitrogen in the pyridine ring, the hydrogen of the phenolic hydroxyl, and the carbonyl oxygen of the propionyl moiety. The hydrogen bond interactions to the protein differ between compounds **17** and **18**. Compound **18** has two hydrogen bonds to the protein. One of the urea nitrogen atoms and the carbonyl oxygen atom bind to the main chain carbonyl oxygen (2.6 Å) and amide nitrogen of K101 (3.0 Å), respectively. Compound **17** has only one hydrogen bond to the protein, namely between one of the urea nitrogens and the carbonyl oxygen of K101 (2.8 Å).

The propionylphenyl moiety of the inhibitor stacks to the tyrosine residues 181 and 188 and shows also van der Waals interaction perpendicular to W229. The pyridine moiety close packs to P236 and the oxygen of H235 on the side and to K103 side and main chain atoms. The packing to the H235 oxygen and to the phenolic oxygen of Y318 forces the plane of the pyridine ring to deviate from planarity with the plane of the urea moiety by an angle of 10°. The inhibitor is covered from above by the side chains of L100, L234, and Y318. V106 interacts with the inhibitor from below. The bromo moiety of the pyridyl ring and the propionylphenyl moiety of the phenyl ring pack against F227 and the backbone of P235. The fluoro substituent of the phenyl ring packs in both complexes against the carbon chain of E1138 (residue 138 in the p51 subunit) (Figure 2).

The orientation of the cyclopropyl ring differs between **17** and **18**. It points downward relative to the plane of the inhibitor in compound **17**, and in the enantiomeric compound **18** it points up. The cyclopropyl ring close packs to L100, V179, and Y181 in compound **17**. In addition to these interactions this ring in compound **18** close packs extensively to E1138 (Figure 2). This causes a small alteration in the positioning of the propionylphenyl moiety.

Study of Resistance Development. Selection of resistant HIV-1 in vitro was performed for phenethylurea compound **2** and racemic cyclopropane compounds **8** and **13**. Delavirdine and nevirapine were used as reference compounds. A curve showing maximal concentration of test compound permitting virus growth in each passage is presented in Figure 3. The time before virus appeared in 0.1 μg/mL delavirdine, nevirapine, and compounds **2**, **8**, and **13** was 2, 5, 6, 13, and 17 weeks, respectively. There is a correlation between the activity on mutant forms of HIV-1 and the length of time for resistance development for urea−PETT compounds. The results depicted in Figure 3 clearly demonstrate the superiority of compounds **8** and **13** compared to the reference compounds in terms of resistance development. This makes the cyclopropyl-


a
L234
P225
W229
F227
Y318
Y188
K103
G190
K101
Y181
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b
L234
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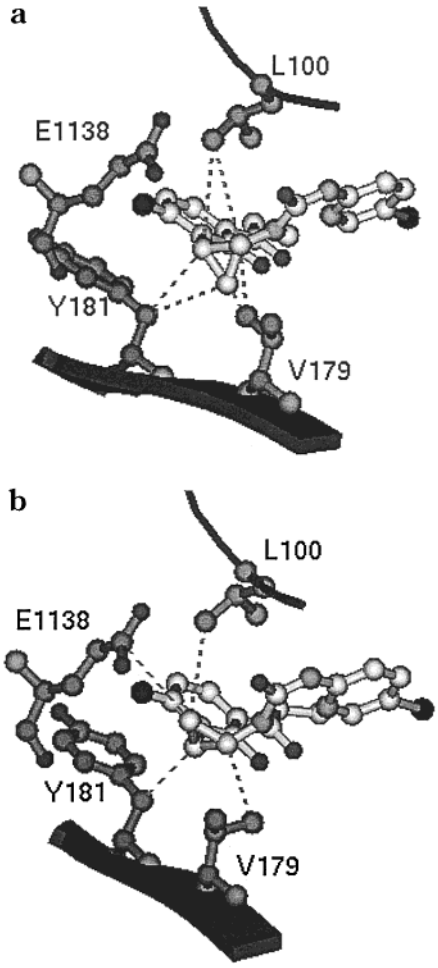

Figure 2. Cyclopropyl moiety, which differs in conformation between the two enantiomeric inhibitors **17** (a) and **18** (b), has close-packing interactions (dotted lines) with L100 and V179 and Y181 in both cases, but in addition to these interactions the cyclopropyl moiety of **18** has extensive hydrophobic close-packing interactions with E1138. The program Molscript was used for drawing the figures.[33]

urea−PETT compounds very interesting potential drugs against HIV/AIDS. Resistant virus from four cultures exposed to compound **13** were isolated after 23 passages. Sequence analysis of a portion of the RT gene coding for aa 90−250 showed the following aa changes: (L100I, Y181N), (L100I, Y181N), (K101E, I132L, Y181N), or (Y181C, Y188H).

Pharmacokinetic Studies. Compound **18** was selected for preliminary pharmacokinetic studies in male rats. These studies also included determination of concentration in the brain since it is of great importance that drugs against HIV/AIDS can penetrate into the brain. A DMSO solution of compound **18** was intravenously injected at a dose of 13 mg/kg into three rats. The rats were sacrificed after 18.5, 62, and 120 min, respectively, and concentrations in brain and plasma

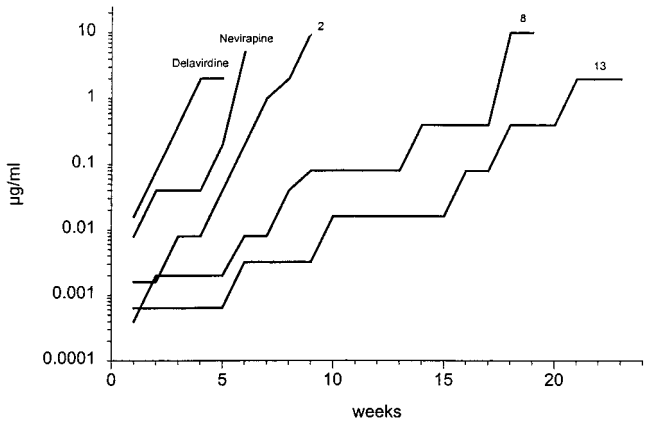

Figure 3. Selection of resistant HIV-1 in vitro. MT4 cells were seeded into microplates (2×10^4 cells/well) and infected with 10−20 $TCID_{50}$/well of HIV-1(IIIb) in the presence of 5-fold serial dilutions of a test compound. RT activity was determined in the supernatant after 6 days. Virus replicating in wells containing subinhibitory concentrations of test compound was passaged into (a) cells without test compound, (b) cells with test compound at the same concentration as used in the preceding selection, and (c) cells with test compound at 5-fold higher concentration. Virus was passaged once a week until replicating virus was detected in cells cultured in the presence of the highest nontoxic concentration of the test compound. Finally, virus was grown to give a virus stock, and sequence analysis of the RT gene was performed.

were analyzed. High levels of **18** were detected in both brain and plasma: i.e., at 18.5 min the concentration of **18** was 1.2 μg/mL in plasma and 5 μg/g in brain tissue, at 62 min 1.2 μg/mL and 6 μg/g, respectively, and at 120 min 0.7 μg/mL and 2 μg/g, respectively. These results clearly indicate that compound **18** penetrates well into the brain, and levels comparable with the concentration in plasma are detected. This compound was also dosed orally at 11.4 mg/kg in 10% ethanol, 10% Capmul, and 80% oleic acid. These studies show that this compound is orally available, and a rather flat AUC curve was observed, thus making it hard to calculate the absolute oral availability. C_{max} values of 0.07 μg/mL (0.17 μM) at 4 and 6 h were detected indicating that the compound is slowly absorbed which is most likely due to its expected poor water solubility.

Conclusions

In conclusion, cyclopropane urea analogues were more potent than the ethyl-linked urea compounds. A study of conformationally restricted cyclopropane thiourea compounds has been communicated.[25] In that study all compounds with significant activity were *cis*-isomers and they were more potent than phenethyl compounds with the same substitution pattern on the phenyl ring and the same right-hand side of the molecule. The same pattern is found for urea cyclopropane compounds. Compounds bearing 2-hydroxy-3-acetyl or propionyl-6-

Figure 1. Three-dimensional structure of the complex between HIV-1 RT and (a) **17** and (b) **18**. Positioning of HIV-1 RT inhibitors **17** and **18** in the NNI binding site of the palm subdomain. In order to make the figure less complex, the residues L100, E1138 (residue 138 in the p51 subunit), H235, and P236 have been excluded, though they are important ligands. The two inhibitors bind similarly. The striking features of the binding mode of these inhibitors are the internal stabilizing hydrogen bond network, the hydrogen bonds between the inhibitor urea moiety and the main chain atoms of K101, and the efficient utilization of the van der Waals interactions with the propionylphenyl moiety of the inhibitor and the aromatic amino acid residues Y181, Y188, and W229. Moreover, there is an extensive utilization of close-packing interactions of predominantly hydrophobic nature between these inhibitors and the protein. The program Molscript was used for drawing the figures.[33]

fluoro substituents on the phenyl ring on the left-hand side of the molecule and 5-bromo-, 5-chloro-, or 5-cyanopyridine on the right-hand side of the molecule were most potent inhibitors of HIV-1. The time for resistance development was longer for our compounds than for reference compounds, and the pharmacokinetic properties were promising. Further development aimed at a drug against HIV/AIDS is ongoing in our laboratories.

Experimental Section

Chemistry. All melting points were determined on an Electrothermal 9100 capillary melting point apparatus and are uncorrected. Analytical results are indicated by atom symbols and are within 0.4% of theoretical values except where indicated. ^{1}H NMR spectra were recorded on a Bruker AC-250 spectrometer (250 MHz) using TMS as the internal standard. Hewlett-Packard 5890 series II gas chromatograph equipped with fused silica capillary column and thin-layer chromatography with precoated silica gel 60 F_{256} from Merck were used for monitoring reactions. The high-performance liquid chromatography (HPLC) analyses of enantiomeric compounds were performed on a Chiral-AGP column. Optical rotations were determined on Perkin-Elmer polarimeter 241. Merck silica gel, 230−400 mesh, was used for chromatography. Yields were not optimized.

General Procedure for Synthesis of 1−3 from Thiourea Analogues. The corresponding thiourea compound (1 equiv) was dissolved in dioxane (7 mL/mmol) and H_2O (1.4 mL/mmol), and *N*-bromosuccinimide (4.7 equiv) dissolved in H_2O (2 mL/mmol) was added. The reaction mixture was stirred at room temperature for 20 min. The mixture was washed with 0.01 N NaOH and brine, dried over Na_2SO_4, and evaporated. The crude material was crystallized from acetone.

***N*-[2-(2,6-Difluoro-3-(dimethylamino)phenethyl)]-*N′*-[2-(5-bromopyridyl)]urea (1).** The title compound was prepared from the corresponding thiourea analogue:[20] mp 135 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.21 (br s, 1H), 8.13 (d, 1H), 7.65 (dd, 1H), 6.86−6.75 (m, 3H), 3.63 (q, 2H), 3.01 (t, 2H), 2.75 (s, 6H). Anal. ($C_{16}H_{17}BrF_2N_4O$) H, N; C: calcd, 48.1; found, 47.6.

***N*-[2-(3,6-Dimethoxy-2-fluorophenethyl)]-*N′*-[2-(5-chloropyridyl)]urea (2).** The title compound was prepared from the corresponding thiourea analogue:[20] mp 185 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 9.07 (br s, 1H), 8.02 (d, 1H), 7.52 (dd, 1H), 6.88 (d, 1H), 6.79 (t, 1H), 6.53 (dd, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.60 (q, 2H), 3.00 (dt, 2H). Anal. ($C_{16}H_{17}ClFN_3O_3$) C, H, N.

***N*-[2-(2-Chloro-3-ethoxy-6-fluorophenethyl)]-*N′*-[2-(5-bromopyridyl)]urea (3).** The title compound was prepared from the corresponding thiourea analogue:[20] mp 202 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.26 (br s, 1H), 8.29 (d, 1H), 7.92 (dd, 1H), 7.70 (t, 1H), 7.57 (d, 1H), 7.28−7.08 (m, 2H), 4.20 (q, 2H), 3.53 (q, 2H), 3.08 (t, 2H), 1.47 (t, 3H). Anal. ($C_{16}H_{16}BrClFN_3O_2$) C, H, N.

***N*-[2-(3-Acetyl-6-fluoro-2-methoxyphenethyl)]-*N′*-[2-(5-chloropyridyl)]urea (4).** The title compound was prepared from the corresponding thiourea analogue[20] which was synthesized from 4-fluoro-2-methoxyacetophenone. The thiourea analogue (1.0 g, 2.6 mmol) was dissolved in H_2O/dioxane (1:10, 20 mL). $AgNO_3$ (2.0 g, 11.8 mmol) dissolved in H_2O (5 mL) was added. The reaction mixture was stirred at room temperature for 2 h. EtOAc was added to the mixture and it was filtered through Celite, washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The crude material was purified by column chromatography (silica gel, 50% EtOAc in *n*-hexane followed by EtOAc) to give 0.3 g (32%) of the title compound: mp 180 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.74 (br s, 1H), 8.81 (br s, 1H), 8.06 (s, 1H), 7.62 (d, 1H), 7.54 (t, 1H), 7.09 (d, 1H), 6.88 (t, 1H), 3.80 (s, 3H), 3.58 (q, 2H), 3.01 (t, 2H), 2.56 (t, 3H). Anal. ($C_{17}H_{17}ClFN_3O_3$) C, H, N.

***N*-[2-(3-Acetyl-2-fluoro-6-methoxyphenethyl)]-*N′*-[2-(5-chloropyridyl)]urea (5).** The title compound was prepared from corresponding thiourea analogue[20] which was synthesized from 2-fluoro-4-methoxyacetophenone.The thiourea compound was converted to corresponding urea compound as described for compound **4**: mp 189 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.18 (br s, 1H), 8.98 (br s, 1H), 7.96 (d, 1H), 7.80 (t, 1H), 7.52 (dd, 1H), 6.90 (d, 1H), 6.70 (d, 1H), 3.82 (s, 3H), 2.98 (m, 4H), 2.50 (d, 3H). Anal. ($C_{17}H_{17}ClFN_3O_3$) C, H, N.

General Procedure for Synthesis of Cyclopropane Compounds 6−12: *N*-[*cis*-2-(2-Chloro-3-ethoxy-6-fluorophenyl)cyclopropyl]-*N′*-[2-(5-cyanopyridyl)]urea (10). 2-Chloro-4-fluorophenol (**28**) (25 g, 170.6 mmol), ethyl iodide (27.3 mL, 341.2 mmol), and K_2CO_3 (47.2 g, 341.2 mmol) in acetone (350 mL) were stirred at 55 °C overnight. The reaction mixture was filtered and evaporated. *n*-Hexane was added and the mixture was filtered again. The evaporation gave 29.26 g (98%) of crude 1-chloro-2-ethoxy-5-fluorobenzene (**29**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15−7.11 (m, 1H), 6.93−6.86 (m, 2H), 4.07 (q, 2H), 1.46 (t, 3H).

Compound **29** (29.26 g, 167.7 mmol) was dissolved in dry THF (350 mL) and the mixture was cooled to −65 °C; 2.5 M *n*-BuLi in hexanes (73.8 mL, 184.5 mmol) was added under nitrogen and the mixture was stirred at the same temperature for 0.5 h. DMF (14.3 mL, 184.5 mmol) was added to the mixture and it was allowed to warm to room temperature. The reaction mixture was poured onto ice and extracted with diethyl ether. The organic layer was washed with 0.01 N HCl, H_2O, and brine, dried over Na_2SO_4, and evaporated. Crystallization from *n*-hexane gave 30.8 g (91%) of 2-chloro-3-ethoxy-6-fluorobenzaldehyde (**30**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.12−7.01 (m, 2H), 4.09 (q, 2H), 1.46 (t, 3H).

Dry methyltriphenylphosphonium bromide (54.6 g, 151.6 mmol) was mixed with THF (750 mL) under nitrogen at room temperature; 2.5 M *n*-BuLi in hexanes (65.6 mL, 164.0 mmol) was added dropwise and the temperature of the reaction mixture rose to 36 °C. The temperature was then allowed to fall to 30 °C. Compound **30** (30.7 g, 151.6 mmol) was dissolved in THF (100 mL) and added dropwise to the reaction mixture. The temperature of the mixture rose to 45 °C. The mixture was stirred for 20 min. It was evaporated to the volume of about 200 mL, diethyl ether (700 mL) was added, and the mixture was washed with H_2O and brine, filtered twice through an Al_2O_3 column, and evaporated to give 27.18 g (89%) of 2-chloro-3-ethoxy-6-fluorostyrene (**31**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99−6.75 (m, 3H), 6.01−5.92 (m, 1H), 5.69−5.63 (m, 1H), 4.08 (q, 2H), 1.46 (t, 3H).

Compound **31** (27.0 g, 134.6 mmol) was dissolved in 1,2-dichloroethane (400 mL), and Cu(I)I (40 mg) and $Pd(OAc)_2$ (40 mg) were added. The mixture was heated to reflux. Ethyl diazoacetate (28.3 mL, 269.2 mmol) in 1,2-dichloroethane (100 mL) was added dropwise under 2 h and the mixture was refluxed for 1 h. The cooled mixture was evaporated, and the *cis*-ester was purified by column chromatography (silica gel, 5−50% EtOAc in *n*-hexane) to give 4.0 g (12%) of the ethyl ester of *cis*-2-(2-chloro-3-ethoxy-6-fluorophenyl)cyclopropanecarboxylic acid (**32**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.88 (t, 1H), 6.76 (dd, 1H), 4.01 (qq, 4H), 2.26−2.19 (m, 2H), 1.79−1.68 (m, 1H), 1.62−1.53 (m, 1H), 1.43 (t, 3H), 1.10 (t, 3H).

Compound **32** (3.0 g, 11.6 mmol) was added to the mixture of KOH (1.95 g, 34.8 mmol) in EtOH (30 mL) and H_2O (10 mL). The mixture was refluxed overnight. The cooled mixture was washed twice with *n*-hexane, acidified with concentrated HCl, extracted with diethyl ether, dried over Na_2SO_4, and evaporated to give 2.4 g (80%) of *cis*-2-(2-chloro-3-ethoxy-6-fluorophenyl)cyclopropanecarboxylic acid (**33**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.88 (t, 1H), 6.77 (dd, 1H), 4.05 (q, 2H), 2.32−2.17 (m, 2H), 1.72−1.61 (m, 2H), 1.45 (t, 3H).

Compound **33** (0.3 g, 1.16 mmol), diphenyl phosphorazidate (0.28 mL, 1.28 mmol), and triethylamine (0.18 mL, 1.28 mmol) in toluene (7 mL) were refluxed for 40 min. 2-Amino-5-cyanopyridine[20] (152 mg, 1.28 mmol) in 2 mL of DMF was added, and reflux was continued for 4 h. Toluene was evaporated and diethyl ether was added to the mixture which was washed with 0.01 N HCl, H_2O, and brine, dried over Na_2SO_4, and evaporated. Crude material was crystallized from acetone and recrystallized from acetonitrile to give 40 mg (9%) of the

title compound: mp 201 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.83 (br s, 1H), 9.36 (br s, 1H), 8.14 (d, 1H), 7.71 (dd, 1H), 6.98−6.78 (m, 3H), 4.11 (q, 2H), 3.29 (m, 1H), 2.11 (q, 1H), 1.64 (q, 1H), 1.53 (t, 3H), 1.33 (m, 1H). Anal. ($C_{18}H_{16}ClFN_4O_2$) C, H, N.

***N*-[*cis*-2-(2,6-Difluoro-3-ethoxy)cyclopropyl]-*N*′-[2-(5-chloropyridyl)]urea (6).** The title compound was prepared from 2,4-difluorophenol as described for compound **10**. 2-Amino-5-chloropyridine was used instead of 2-amino-5-cyanopyridine: mp 158 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.89 (br s, 1H), 7.87 (d, 1H), 7.48 (dd, 1H), 6.86−6.73 (m, 3H), 4.04 (q, 2H), 3.30 (m, 1H), 2.10 (q, 1H), 1.54 (m, 1H), 1.45 (t, 3H), 1.35 (m, 1H). Anal. ($C_{17}H_{16}ClF_2N_3O_2$) C, H, N.

***N*-[*cis*-2-(6-Chloro-3-ethoxy-2-fluorophenyl)cyclopropyl]-*N*′-[2-(5-chloropyridyl)]urea (7).** The title compound was prepared from 4-chloro-2-fluorophenol as described for compound **10**. 2-Amino-5-chloropyridine was used instead of 2-amino-5-cyanopyridine: mp 176.9 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 9.27 (br s, 1H), 7.81 (d, 1H), 7.46 (dd, 1H), 7.14 (dd, 1H), 6.81 (t, 2H), 4.06 (q, 2H), 3.33 (m, 1H), 2.09 (q, 1H), 1.62 (m, 1H), 1.45 (t, 3H), 1.33 (m, 1H). Anal. ($C_{17}H_{16}Cl_2FN_3O_2$) C, H, N.

***N*-[*cis*-2-(6-Chloro-3-ethoxy-2-fluorophenyl)cyclopropyl]-*N*′-[2-(5-cyanopyridyl)]urea (8).** The title compound was prepared from 4-chloro-2-fluorophenol as described for compound **10**: mp 211−212 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.77 (br s, 1H), 9.32 (br s, 1H), 8.16 (d, 1H), 7.71 (dd, 1H), 7.15 (dd, 1H), 6.98−6.78 (m, 2H), 4.08 (q, 2H), 3.34 (m, 1H), 2.12 (q, 1H), 1.65 (q, 1H), 1.47 (t, 3H), 1.31 (m, 1H). Anal. ($C_{18}H_{16}ClFN_4O_2$) H, N; C: calcd 57.7; found, 57.2.

***N*-[*cis*-2-(6-Chloro-3-ethoxy-2-fluorophenyl)cyclopropyl]-*N*′-[2-(5-chloropyridazinyl)]urea (9).** The title compound was prepared from 4-chloro-2-fluorophenol as described for compound **10**. 2-Amino-5-chloropyridazine was used instead of 2-amino-5-cyanopyridine: mp 218.9 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.10 (d, 1H), 7.81 (d, 1H), 7.33 (d, 1H), 7.17 (t, 1H), 7.01 (s, 1H), 4.16 (q, 2H), 3.33 (m, 1H), 2.15 (q, 1H), 1.60 (q, 1H), 1.41 (t, 3H), 1.22 (m, 1H). Anal. ($C_{16}H_{15}Cl_2FN_4O_2$) C, H, N.

***N*-[*cis*-2-(2-Chloro-3-ethoxy-6-fluorophenyl)cyclopropyl]-*N*′-[2-(5-chloropyridazinyl)]urea (11).** The title compound was prepared from 2-chloro-4-fluorophenol as described for compound **10**. 2-Amino-5-chloropyridazine was used instead of 2-amino-5-cyanopyridine: mp 192 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.88−10.54 (m, 2H), 8.08−7.90 (m, 1H), 7.37 (d, 1H), 6.86 (t, 1H), 6.76−6.67 (m, 1H), 4.04 (q, 2H), 3.44 (m, 1H), 2.16 (q, 1H), 1.64 (q, 1H), 1.52−1.40 (m, 4H). Anal. ($C_{16}H_{15}Cl_2FN_4O_2$) C, H, N.

***N*-[*cis*-2-(2-Chloro-6-fluoro-3-hydroxyphenyl)cyclopropyl]-*N*′-[2-(5-chloropyridyl)]urea (12).** The title compound was prepared from 2-chloro-4-fluorophenol as described for compound **10**. The last step, dealkoxylation, was carried out as in the last step for the compound **17** and 2-amino-5-chloropyridine was used instead of 2-amino-5-cyanopyridine: mp 206.5 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.44 (br s, 1H), 8.03 (br s, 1H), 7.88 (d, 1H), 7.72 (dd, 1H), 7.20 (d, 1H), 7.01 (t, 1H), 6.90 (dd, 1H), 3.13 (m, 1H), 2.03 (q, 1H), 1.46 (m, 1H), 1.02 (m, 1H). Anal. ($C_{15}H_{12}Cl_2FN_3O_2$) C, H; N: calcd, 11.8; found, 11.3.

***N*-[*cis*-2-(6-Fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-chloropyridyl)]urea (13).** The title compound was prepared from 3-fluorophenol as described for compound **17**. The cyclopropanation step was carried out as described for compound **10**. 2-Amino-5-chloropyridine was used instead of 2-amino-5-cyanopyridine: mp 223 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.21 (d, 1H), 9.42 (br s, 1H), 8.01−7.88 (m, 2H), 7.83 (d, 1H), 7.71 (dd, 1H), 7.24 (d, 1H), 6.82 (dd, 1H), 3.17−2.98 (m, 3H), 1.91 (q, 1H), 1.42 (m, 1H), 1.15−1.01 (m, 4H). Anal. ($C_{18}H_{17}ClFN_3O_3$) C, H; N: calcd, 11.1; found, 10.6.

***N*-[*cis*-2-(6-Fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-cyanopyridyl)]urea (14).** The title compound was prepared from 3-fluorophenol as described for compound **17**. The cyclopropanation step was carried out as described for compound **10**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.2 (d, 1H), 9.81 (br s, 1H), 8.30 (d, 1H), 8.06−7.94 (m, 2H), 7.83 (br s, 1H), 7.41 (d, 1H), 6.84 (dd, 1H), 3.18−3.01 (m, 3H), 1.94 (q, 1H), 1.43 (m, 1H), 1.16−1.03 (m, 4H). Anal. ($C_{19}H_{17}FN_4O_3$) C, H, N.

***N*-[*cis*-2-(3-Acetyl-6-fluoro-2-hydroxyphenyl)cyclopropyl]-*N*′-[2-(5-cyanopyridyl)]urea (15).** The title compound was prepared from 3-fluorophenol as described for compound **17**. Acetyl chloride instead of propionyl chloride was used in the first step and the cyclopropanation step was carried out as described for compound **10**: mp 236.4 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.14 (s, 1H), 9.79 (br s, 1H), 8.34 (d, 1H), 8.04 (dd, 1H), 7.96 (dd, 1H), 7.71 (br s, 1H), 7.46 (d, 1H), 6.85 (dd, 1H), 3.07 (m, 1H), 2.65 (s, 3H), 1.94 (q, 1H), 1.42 (m, 1H), 1.09 (m, 1H). Anal. ($C_{18}H_{15}FN_4O_3$) H, N; C: calcd, 61.0; found, 60.5.

***N*-[*cis*-2-(3-Acetyl-6-fluoro-2-hydroxyphenyl)cyclopropyl]-*N*′-[2-(5-bromopyridyl)]urea (16).** The title compound was prepared as described for compound **15**. 2-Amino-5-bromopyridine was used instead of 2-amino-5-cyanopyridine: mp 226 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.13 (s, 1H), 9.51 (br s, 1H), 7.98−7.92 (m, 2H), 7.84−7.79 (m, 2H), 7.24 (d, 1H), 6.83 (dd, 1H), 3.04 (m, 1H), 2.65 (s, 3H), 1.92 (q, 1H), 1.41 (m, 1H), 1.07 (m, 1H). Anal. ($C_{17}H_{15}BrFN_3O_3$) C, H; N: calcd, 10.3; found, 9.7.

General Procedure for Synthesis of Enantiomeric Cyclopropane Compounds 17−20: 3-Fluoro-1-propionyloxybenzene (35). Propionyl chloride (20 mL, 0.255 mol) was added to a solution of 3-fluorophenol (**34**) (22.4 g, 0.2 mol) and pyridine (24 mL, 0.3 mol) in dichloromethane (200 mL) at room temperature over a period of 5 min. The reaction was exothermic. The solution was stirred for 30 min at room temperature, dichloromethane was added, and the solution was washed with saturated $NaHCO_3$ and H_2O, dried over $MgSO_4$, and concentrated in vacuo to give 33.8 g (100%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 1H), 6.98−6.83 (m, 3H), 2.60 (q, 2H), 1.27 (t, 3H).

4′-Fluoro-2′-hydroxypropiophenone (36). Compound **35** (33.8 g of crude material from the previous step) was reacted with $AlCl_3$ (33.3 g, 0.25 mol) at 150 °C for 10 min. After careful quenching with water, the reaction mixture was extracted with diethyl ether; the organic layer was dried over $MgSO_4$ and evaporated to give 29.5 g (88%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.68 (d,1H), 7.77 (dd, 1H), 6.67−6.56 (m, 2H), 2.99 (q, 2H), 1.23 (t, 3H).

4′-Fluoro-2′-methoxypropiophenone (37). Compound **36** (29.5 g, 0.176 mol) was dissolved in 200 mL of acetone, and K_2CO_3 (42.0 g, 0.3 mol) and methyl iodide (25.0 mL, 0.4 mol) were added. The reaction mixture was heated at 40 °C for 12 h and filtered, and acetone was evaporated. The residue was dissolved in diethyl ether, washed with 0.01 N NaOH and H_2O, dried over $MgSO_4$, and evaporated to give 31.2 g (97%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82−7.73 (m, 1H), 6.72−6.63 (m, 2H), 3.40 (s, 3H), 2.97 (q, 2H), 1.17 (t, 3H).

1-[1,1-(Ethylenedioxy)propyl]-4-fluoro-2-methoxybenzene (38). A solution of compound **37** (31.2 g, 0.171 mol), ethylene glycol (10.5 mL, 0.188 mol), and *p*-toluenesulfonic acid (1 g) in benzene (300 mL) was refluxed in a Dean−Stark apparatus for 12 h. After cooling the reaction mixture was washed several times with 1 M NaOH and dried over Na_2SO_4 and K_2CO_3. Evaporation gave 38 g (86%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46−7.40 (m, 1H), 6.68−6.56 (m, 2H), 4.02 (t, 2H), 3.85 (s, 3H), 3.84 (t, 2H), 2.12 (q, 2H), 0.82 (t, 3H).

3-[1,1-(Ethylenedioxy)propyl]-6-fluoro-2-methoxybenzaldehyde (39). 2.5 M *n*-BuLi in hexanes (128 mL, 0.32 mol) was added dropwise to a solution of compound **38** (38 g, 0.168 mol) in THF (450 mL) at −65 °C under nitrogen. The temperature was allowed to reach −40 °C and then recooled to −65 °C. While keeping the temperature at about −65 °C, a solution of DMF (25 mL, 0.32 mol) in THF (50 mL) was added. The reaction mixture was allowed to reach room temperature slowly and no starting material was left after 30 min as monitored by GC. After an additional 1 h the reaction mixture was quenched with saturated NH_4Cl solution, extracted with

diethyl ether, and dried over Na_2SO_4. Evaporation gave the residue which was purified on a silica gel column eluting with EtOAc/*n*-hexane (1:9) to give 10 g (25%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.8−7.7 (m, 1H), 6.9 (t, 1H), 4.15−4.0 (m, 2H), 3.97 (s, 3H), 3.95−3.8 (m, 2H), 2.1 (q, 2H), 0.85 (t, 3H).

3-[1,1-(Ethylenedioxy)propyl]-6-fluoro-2-methoxystyrene (40). 2.5 M *n*-BuLi in hexanes (16 mL, 40 mmol) was added to a suspension of methyltriphenylphosphonium bromide (14.3 g, 40 mmol) in THF (250 mL) at room temperature under nitrogen followed by the addition of compound **39** (10 g, 39.5 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 2 h. *n*-Hexane and brine were added to the mixture and the organic phase was washed twice with brine and once with water. After evaporation of the solvent the residue was filtered through a funnel filled with alumina (aluminum oxide 90 acc. Brockmann from Merck) and eluting with EtOAc/*n*-hexane (1:9) to remove the generated triphenylphosphine oxide. Evaporation of the organic solvent gave a residue which was finally purified on silica gel eluting with EtOAc/*n*-hexane (1:9) to give 6.9 g (70%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4−7.3 (m, 1H), 6.85−6.7 (m, 2H), 6.05−5.95 (m, 1H), 5.65−5.55 (m, 1H), 4.1−4.0 (m, 2H), 3.95−3.8 (m, 2H), 3.8 (s, 3H), 2.1 (q, 2H), 0.85 (t, 3H).

Ethyl Ester of (1*R*,2*S*)-*cis*-2-[3-(1,1-(Ethylenedioxy)-propyl)-6-fluoro-2-methoxyphenyl]cyclopropanecarboxylic Acid (41). Cu(I)OTf (100 mg, 0.2 mmol) (very sensitive to air)[26] was added to 40 mL of chloroform (chloroform used in this reaction was ethanol-free, degassed, and purified through a basic alumina column), and the mixture was stirred at room temperature under argon for 15 min. The chiral ligand 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (commercially available from Aldrich) (295 mg, 1.0 mmol) was added and the mixture, which became green, was stirred for 30 min at room temperature under argon. Compound **40** (5.0 g, 19.8 mmol) in 20 mL of chloroform was added and the solution was cooled to 0 °C on ice. Ethyl diazoacetate (8.0 mL, 80 mmol) in 40 mL of chloroform was added dropwise under a period of 4 h. The color of the reaction mixture became yellow and then dark brown. The mixture was stirred at room temperature for 2 h (GC showed complete reaction and *cis*/*trans* ratio of 3.0) and then evaporated. The residue was dissolved in 200 mL of EtOAc, washed with saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel by eluting with 5−10% EtOAc in *n*-hexane to give 3.0 g (45%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 1H), 6.80 (m, 1H), 4.12−3.68 (m, 7H), 2.31−1.98 (m, 4H), 1.69−1.45 (m, 3H), 1.33 (m, 1H), 1.10 (t, 3H), 0.81 (t, 3H).

Ethyl Ester of (1*R*,2*S*)-*cis*-2-(6-Fluoro-2-methoxy-3-propionylphenyl)cyclopropanecarboxylic Acid (42). Compound **41** (2.2 g, 6.5 mmol) was dissolved in 1,4-dioxane (13 mL). 6M HCl (2.6 mL) was added and the mixture was stirred for 1.5 h at room temperature. The mixture was extracted with diethyl ether, the organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give 1.85 g (97%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54−7.48 (m, 1H), 6.85 (t, 1H), 4.03−3.95 (m, 2H), 3.86 (t, 3H), 2.94 (q, 2H), 2.26−2.18 (m, 2H), 1.71−1.52 (m, 2H), 1.20−1.08 (m, 6H).

(1*R*,2*S*)-*cis*-2-(6-Fluoro-2-methoxy-3-propionylphenyl)-cyclopropanecarboxylic Acid (43). Compound **42** (1.8 g, 6.12 mmol) was dissolved in solution of LiOH (0.59 g, 24.5 mmol) in MeOH (25 mL)/H_2O (10 mL) and stirred at 80 °C for 2.5 h. The reaction solution was concentrated and acidified with 4 N HCl. The mixture was extracted with CH_2Cl_2; the organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give 1.5 g (92%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51−7.45 (m, 1H), 6.84 (t, 1H), 3.82 (s, 3H), 2.93 (q, 2H), 2.29 (q, 1H), 2.15 (q, 1H), 1.63−1.57 (m, 2H), 1.16 (t, 3H).

(1*R*,2*R*)-*N*-[*cis*-2-(6-Fluoro-2-methoxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-bromopyridyl)]urea (44). Triethylamine (0.41 mL, 2.94 mmol) and diphenyl phosphorazidate (0.635 mL, 2.94 mmol) were added to a solution of compound **43** (0.782 g, 2.94 mmol) in dry toluene (2.5 mL). The solution was stirred at room temperature under argon for 30 min and then heated to 120 °C. After 15 min a solution of 2-amino-5-bromopyridine (0.56 g, 3.23 mmol) in DMF (1 mL) was added and heating was continued for 3 h. Toluene was evaporated; the residue was dissolved in benzene, washed with 1 N HCl, H_2O, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel by eluting with EtOAc/*n*-hexane (1:2 to 1:1) to give 0.49 g (39%) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.72 (br s, 1H), 9.08 (br s, 1H), 7.80 (d, 1H), 7.62−7.47 (m, 2H), 6.92−6.78 (m, 2H), 3.91 (s, 3H), 3.42 (m, 1H),2.90 (q, 2H), 2.12 (q, 1H), 1.56 (q, 1H), 1.38 (q, 1H), 1.13 (t, 3H).

(1*R*,2*R*)-*N*-[*cis*-2-(6-Fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-bromopyridyl)]urea (17). A 1 M solution of BCl_3 in CH_2Cl_2 (3.3 mL, 3.3 mmol) was added to a solution of compound **44** (0.49 g, 1.1 mmol) in CH_2Cl_2 (10 mL) at −60 °C under argon. Stirring was continued overnight and the temperature was allowed to rise slowly to room temperature. The solution was diluted with CH_2Cl_2 and washed with an aqueous solution of $NaHCO_3$, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified by chromatography on silica gel by eluting with EtOH/CH_2Cl_2 (1:10) and by crystallization from acetonitrile to give 0.24 g (52%) of the titled compound: ee 98.6% as determined by HPLC on a chiral-AGP column, eluent 11% acetonitrile in sodium phosphate buffer, flow 0.9 mL/min, UV detection at 254 nm, t_R 14.26 min; mp 198.9 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 13.22 (s, 1H), 9.42 (br s, 1H), 8.04−7−77 (m, 4H), 7.16 (d, 1H), 6.78 (t, 1H), 3.11 (q, 2H), 3.02 (m, 1H), 1.93 (q, 1H), 1.42 (q, 1H), 1.11 (t, 3H), 1.00 (m, 1H). Anal. ($C_{18}H_{17}BrFN_3O_3$) C, H, N. $[\alpha]_D^{22} = -153.8°$ (c = 0.005 g/mL, CH_2Cl_2).

(1*S*,2*S*)-*N*-[*cis*-2-(6-Fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-bromopyridyl)]urea (18). The title compound was prepared as described for compound **17**. The chiral ligand that was used in the cyclopropanation step was 2,2′-isopropylidenebis[(4*R*)-4-*tert*-butyl-2-oxazoline] (for preparation see the Supporting Information in ref 22): ee 98.6% as determined by HPLC on a chiral-AGP column, eluent 11% acetonitrile in sodium phosphate buffer, flow 0.9 mL/min, UV detection at 254 nm, t_R 20.56 min; mp 198−199 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 13.32 (d, 1H), 9.10 (br s, 1 H), 8.53 (br s, 1H), 7.83 (br s, 1H), 7.72−7.67 (m, 1H), 7.57 (dd, 1H), 6.76 (br s, 1 H), 6.60 (t, 1H), 3.20−3.17 (m, 1H), 3.06−2.97 (m, 2H), 2.05−1.94 (m, 1H), 1.62−1.52 (m, 2H), 1.28 (t, 3H). Anal. ($C_{18}H_{17}BrFN_3O_3$) C, H, N. $[\alpha]_D^{22} = +149.8°$ (c = 0.005 g/mL, CH_2Cl_2).

(1*R*,2*R*)-*N*-[*cis*-2-(6-Fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-chloropyridyl)]urea (19). The title compound was prepared as described for compound **17**. 2-Amino-5-chloropyridine was used instead of 2-amino-5-bromopyridine: ee of the corresponding ester 98.4% as determined by HPLC on a chiral column, eluent 11% acetonitrile in sodium phosphate buffer, flow 0.9 mL/min, UV detection at 220 nm, t_R 33.42 min; mp 196.5−198.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 13.32 (d, 1H), 9.30−8.66 (m, 2H), 7.78−7.67 (m, 2H), 7.46 (dd, 1H), 6.81 (m, 1H), 6.58 (t, 1H), 3.20 (m, 1H), 3.00 (q, 2H), 2.01 (q. 1H), 1.57 (q, 1H), 1.33−1.19 (m, 4H). Anal. ($C_{18}H_{17}ClFN_3O_3$) C, H, N. $[\alpha]_D^{22} = -176.8°$($c$ = 0.005 g/mL, CH_2Cl_2).

(1*S*,2*S*)-*N*-[*cis*-2-(6-Fluoro-2-hydroxy-3-propionylphenyl)cyclopropyl]-*N*′-[2-(5-chloropyridyl)]urea (20). The title compound was prepared as described for compound **18**. 2-Amino-5-chloropyridine was used instead of 2-amino-5-bromopyridine: ee of the corresponding ester 96.0% as determined by HPLC on a chiral column, eluent 11% acetonitrile in sodium phosphate buffer, flow 0.9 mL/min, UV detection at 220 nm, t_R 20.61 min; mp 196−197 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 13.34 (d, 1H), 9.14 (br s, 2H), 7.79.7.62 (m, 2H), 7.42 (dd, 1H), 6.79 (m, 1H), 6.59 (t, 1H), 3.21 (m, 1H), 3.04 (q, 2H),

2.00 (q, 1H), 1.58 (q, 1H), 1.36−1.19 (m, 4H). Anal. ($C_{18}H_{17}ClFN_3O_3$) C, H, N. $[\alpha]_D^{22} = +176.8°$ ($c = 0.005$ g/mL, CH_2Cl_2).

Pharmacokinetic Evaluation. Brain sample preparation: Brains were weighed and homogenized in approximately 30 mL of methanol/chloroform (1/1). Internal standard (compound **13**) was added, and the homogenate was filtered. The tissue precipitate was extracted three times with 5 mL of methanol/chloroform (1/1) and the combined extracts were added to the filtrate. One part of water was added to 5 parts of the filtrate and the mixture was shaken in 5 min. An aliquot (0.5 mL) of the organic phase was evaporated to dryness and the residue was dissolved in 20 μL of DMSO and 0.5 mL of the mobile phase. The sample was centrifuged (1 min, 14 000 rpm) and 50 μL of the supernatant was injected into a reversed-phase HPLC system using UV detection at 250 nm.

Plasma sample preparation: 40−100 μL of plasma was mixed with an equal volume of acetonitrile (10 s; Vibrofix). The sample was centrifuged (3 min, 14 000 rpm) and 30−50 μL of the supernatant was injected into a reversed-phase HPLC system using UV detection at 250 nm.

Crystallography. The details of the crystallization and the structure determination will be published elsewhere. Briefly, complexes of HIV-1 RT with the compounds **17** and **18** were crystallized in the space group *C*2221. The cell parameters were $a = 119.5$ Å, $b = 156.6$ Å, and $c = 156.4$ Å. X-ray diffraction data to 2.95 and 2.7 Å resolution, respectively, were collected at the synchrotron stations D41 at LURE Paris, France (compound **18**), and 1711 at MAX-lab Lund, Sweden (compound **17**). Data were processed with DENZO and scaled with Scalepack.[27,28] The completeness of data was 99% with an R_{sym} value[29] of 16.1% for the RT/**17** complex, and for the RT/**18** complex the corresponding values were 94% and 10.2%. The protein model coordinates from 1hni were used for rotation and translation functions and refinements using the program package XPLOR.[30] The structures were refined to R_{cryst}-values[31] of 21.4% ($R_{free} = 29.1\%$) using 2.95 Å data for the RT/**17** complex and 24% ($R_{free} = 28.3\%$) using 2.7 Å data for the RT/**18** complex. Model construction employed the program O.[32]

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