# Selective Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors. New 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones and Related Compounds with Anti-HIV-1 Activity[1]

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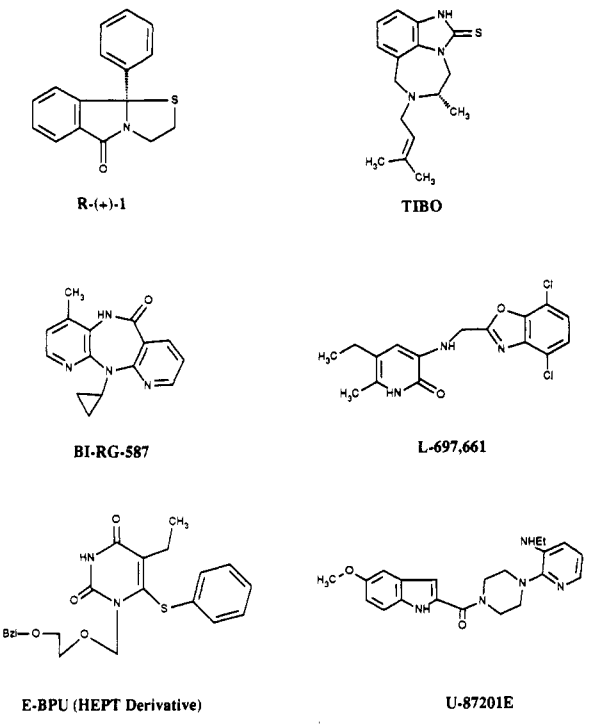
A series of substituted 2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones and related compounds **1–73** were synthesized and evaluated for their ability to inhibit reverse transcriptase (RT) of the human immune deficiency virus 1 (HIV-1) and replication of HIV-1 in MT2 cells. The antiviral activity of these compounds depends on the stereoselective configuration of the substituent in position 9b. Structure–activity studies were done within these series of compounds to determine the optimum substituents for antiviral activity. The most potent inhibitors were found in the class of 2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones bearing a phenyl ring system in position 9b optionally substituted with one or two methyl groups or a chlorine atom in position 8. The most active analogues (*R*)-(+)-**1**, (*R*)-(+)-**6**, (*R*)-(+)-**13**, (*R*)-(+)-**26**, and (*R*)-(+)-**53** inhibit the HIV-1 RT with an $IC_{50}$ between 16 and 300 nM and an $IC_{50}$ between 10 and 392 nM in MT2 cells, respectively.

## Introduction

The human immune deficiency virus 1 is the causative agent of the acquired immune deficiency syndrome (AIDS).[2] The epidemic spread of this disease is dramatically increased by recent estimates of the WHO.[3] So far, the only approved drugs for the therapy of HIV-1 infection are 3′-azidothymidine (AZT, Zidovudine)[4] and recently 2′,3′-didesoxyinosine (ddI, Didanosine)[5] and 2′,3′-didesoxycytidine (ddC, Zalcitabine).[6] Unfortunately, these drugs suffer from severe side effects as thrombocytopenia, bone marrow toxicity,[7] and peripheral neuropathy.[8] All these nucleosides block the replication of HIV-1 by interfering with the HIV-1 encoded enzyme reverse transcriptase, and since the clinical relevance of the inhibition of this enzyme is well documented,[9] we chose this target for our drug development program. In a high throughput enzymatic screening assay using a part of the original heteromeric RNA of HIV-1 as a template and a synthetic 18mer oligonucleotide complementary to the primer binding site (PBS) as the primer,[10] we identified a lead structure, 9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]-isoindol-5(9b*H*)-one (**1**, BM 21.1298).[11] By substantial chemical modification this first lead compound **1** was further optimized relative to the inhibition of the HIV-1 RT screening assay and subsequently in HIV-1-infected MT2 cells.

At the time of our study, additional support was available from several already known selective non-nucleoside HIV-1 RT inhibitors, 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (TIBO),[12] 11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one (BI-RG-587),[13] 1-[[2-(benzyloxy)ethoxy]methyl]-5-ethyl-6-(phenylthio)pyrimidine-2,4(1*H*,3*H*)-dione (E-BPU, HEPT derivative),[14] 3-[[(4,7-dichlorbenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (L-697,661),[15] 5-methoxyindole-2-carboxylic acid [*N*′-[3-(aminoethyl)pyridin-2-yl]piperazide] (U-87201E)[16] (Scheme I).

**Scheme I**




All these compounds including **1** do not inhibit other retroviral, bacterial, or mammalian polymerases as well as HIV-2 RT.[17] They specifically bind to an allosteric site of HIV-1 RT close to but not identical with the active site of this enzyme. We now publish here the recent results in optimizing our lead structure **1**.

## Chemistry

An appropriate substituted benzophenone-2-carboxylic acid always served as starting material for compounds bearing a sulfur, oxygen, or nitrogen atom in ring C (structure I).

These precursors could be easily cyclized to the end products by condensation with bifunctional, optionally

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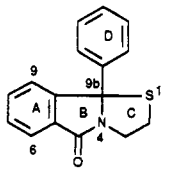


I

branched mercaptoalkylamines,[18,19] hydroxyalkylamines,[18] diaminoalkyls,[18] or aminothiophenol, respectively (Scheme II).

Most of the above-mentioned benzophenone-2-carboxylic acids, leading to end products substituted in ring D, were prepared according to standard literature procedures. Some of these reactions include the Friedel–Crafts acylation of substituted benzenes with phthalic anhydride, metal organic reaction of substituted (het)aryls with phthalic anhydride, or the oxidation of 1-methyl-2-(het)arylmethylbenzene derivatives.

Substituted phthalic anhydrides were usually not appropriate precursors for end products bearing substituents in ring A, since metal organic as well as Friedel–Crafts reactions predominantly lead to isomers, which could not be easily separated. Therefore, we generally synthesized compounds III ($R_6$–$R_9$ not hydrogen) starting from 2-aminobenzophenone[21] derivatives IV, which were conveniently converted via the nitrile to the carboxylic acids (Scheme III).

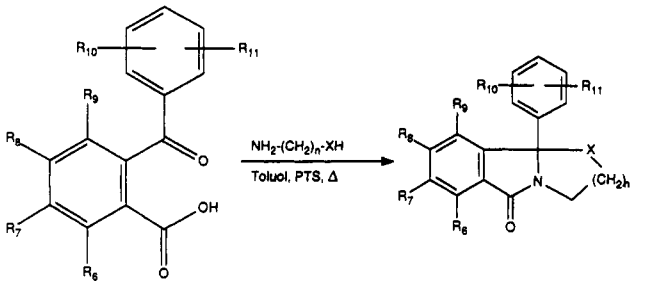
In case of 2,3-dihydropyrrolo[2,3-*a*]isoindol-5(9b*H*)-ones (X = $CH_2$ in structure III) the synthesis followed that outlined Scheme IV. Actually, 3-aryl-substituted isoindolinones were the starting material for a stepwise alkylation of these precursors. The first alkylation takes place on the nitrogen atom with a weak base. These intermediates can either be isolated or directly cyclized with a second equivalent of a strong base.

Intermediate 2-(2-pyridinoyl)pyridine-3-carboxylic acids X (Scheme V) as precursors for 2,3-dihydrothiazolo-[3′,2′:1,2]pyrrolo[3,4-*b*]pyridin-5(9b*H*)-one derivatives (aza analogues **71–73**, Table IV) were readily prepared starting with compounds VIII by hydrolytic cleavage and decarboxylation to IX,[22] which were subsequently oxidized with potassium permanganate to 2-(2-pyridinoyl)pyridine-3-carboxylic acids X.

All compounds listed in Tables I–IV are chiral and were first obtained as racemic mixtures. The separation of both enantiomers can be easily achieved by a simple chromatography of these compounds on cellulose triacetate with alcohol or alcohol/water as eluents.

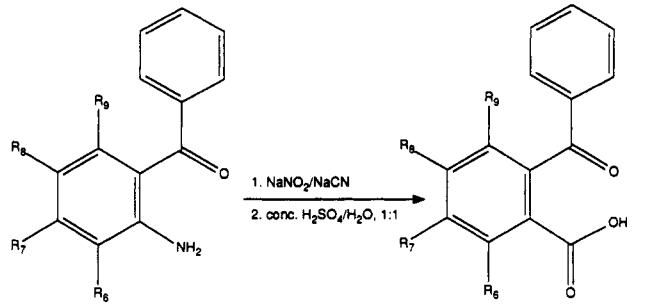
**Structure–Activity Relationships (SAR).** When we started our SAR study, we first decided to separate the enantiomers of **1** and to prove the stereoselective antiviral activity of this novel lead structure. Chromatographic separation of the racemic mixture led to pure enantiomers from which crystals could be grown for use in X-ray analysis.[23] These results enabled us to assign the (*R*)-(+)-configuration to the more active enantiomer. (*R*)-(+)-**1** ($IC_{50}$ = 0.28 μM) was about twice as active as the racemic mixture ($IC_{50}$ = 0.7 μM), whereas the (*S*)-(−)-**1** enantiomer ($IC_{50}$ = 39.3 μM) was at least 50 times less active in the RT assay (Table I). From several active racemic mixtures **6**, **13**, **26**, and **53**, we have also determined the absolute configuration of the purified enantiomers by X-ray analysis, and we could always confirm the (*R*)-(+)-configuration for the active antipodes (*R*)-(+)-**6**, (*R*)-(+)-**13**, (*R*)-(+)-**26**, and (*R*)-(+)-**53**, respectively. For further discussion of this SAR study, however, we will always correlate the activity of the racemate **1** to the other racemates **2–73**.

**Scheme II**



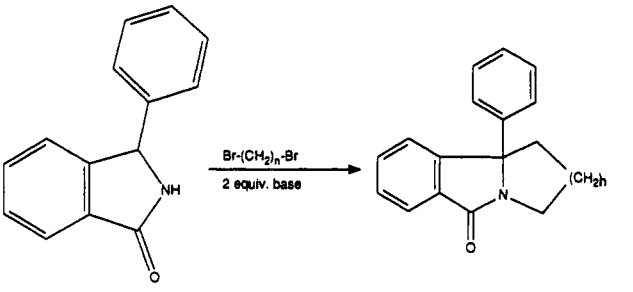

II III

**Scheme III**



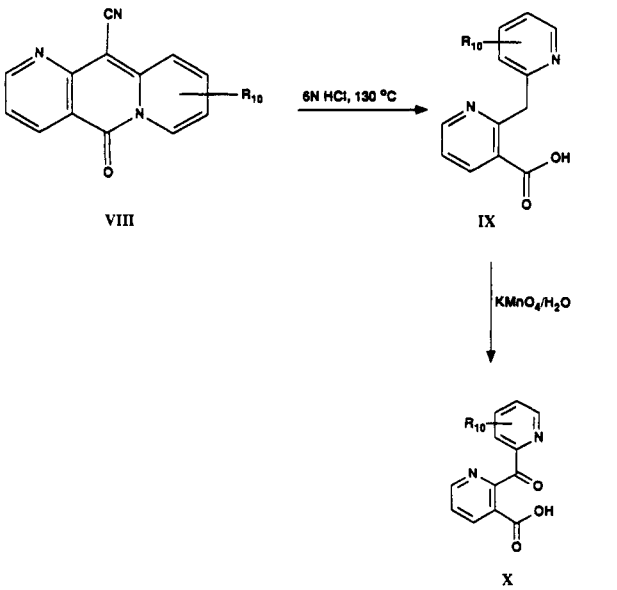

IV V

**Scheme IV**



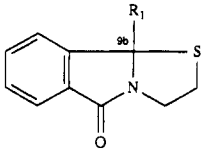

VI VII

**Scheme V**




VIII IX X

**Table I.** Structure and Antiviral Activity of 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones




| no. | $R_1$ | prep method[a] | yield, % | mp, °C | recryst solvent | RT $IC_{50}$,[b] μM |
|---|---|---|---|---|---|---|
| 1 | phenyl | A | 77 | 108–10[j] | ethanol | 0.7 |
| (*R*)-(+)-1 | phenyl | B | 40 | 99–100 | ethanol | 0.28 |
| (*S*)-(−)-1 | phenyl | B | 40 | 99–100 | ethanol | 39.6 |
| 2 | phenyl, thiocarbonyl | D | 29 | 151–5 | *c* | 3.5 |
| 3 | 2-thienyl | A | 63 | 150–1 | *e* | 2.65 |
| 4 | 2-furanyl | A | 23 | 113–4 | *c* | 1.35 |
| 5 | 2-pyrrolyl | A | 7 | 200–5 | *c* | >100 |
| 6 | 1-naphthyl | C | 67 | 151–2 | ethanol | 0.13 |
| (*R*)-(+)-6 | 1-naphthyl | B | 38 | 175–6 | *g* | 0.15 |
| 7 | 9-anthracenyl | C | 21 | 197–8 | ethanol | 0.9 |
| 8 | 4-chlorophenyl | A | 25 | 127–31[k] | *c* | 4.0 |
| 9 | 4-methylphenyl | A | 65 | 72–5[k] | *c* | 0.77 |
| 10 | 4-isopropylphenyl | A | 51 | *d* | *c* | 10 |
| 11 | 4-methoxyphenyl | A | 33 | *d*[k] | *c* | >30 |
| 12 | 3-chlorophenyl | A | 49 | 132–4[k] | ethanol | 0.14 |
| 13 | 3-methylphenyl | C | 78 | 120–2[k] | ethanol | 0.035 |
| (*R*)-(+)-13 | 3-methylphenyl | B | 40 | 98–101 | ethanol | 0.035 |
| 14 | 3-methoxyphenyl | C | 49 | 140–1[k] | *c* | 0.97 |
| 15 | 3-ethylphenyl | A | 6 | *d* | *c* | 1.1 |
| 16 | 3-isopropylphenyl | A | 37 | 99–101 | ethanol | 2.1 |
| 17 | 3-(trifluoromethyl)phenyl | A | 44 | 104–5[k] | *h* | 1.05 |
| 18 | 3-hydroxyphenyl | Y | 11 | 138–40[k] | *c* | 12.7 |
| 19 | 3-aminophenyl | X | 39 | 184–6 | $CH_2Cl_2$ | 4.6 |
| 20 | 3-nitrophenyl | A | 33 | 91–7 | ethanol | 0.86 |
| 21 | 3-cyanophenyl | Z[f] | 11 | *d* | *c* | 1.81 |
| 22 | 2-methylphenyl | A | 29 | 109–10 | *h* | 6.3 |
| 23 | 2,3-dimethylphenyl | A | 9 | 191–5 | *c* | 1.65 |
| 24 | 2,5-dimethylphenyl | A | 39 | 90–1[k] | *h* | 0.97 |
| 25 | 3,4-dimethylphenyl | A | 67 | 155–7[k] | ethanol | 0.39 |
| 26 | 3,5-dimethylphenyl | A | 76 | 165–6 | *i* | 0.084 |
| (*R*)-(+)-26 | 3,5-dimethylphenyl | B | 40 | 174–5 | ethanol | 0.016 |
| 27 | 4-indanyl | A | 13 | 151–3 | ethanol | 0.9 |
| 28 | 3,5-dichlorophenyl | C | 30 | 105–8 | ethanol | 0.59 |
| 29 | 3,4-dichlorophenyl | A | 77 | *d*[k] | *c* | 4.0 |

[a] See Experimental Section. [b] The HIV RT assay was performed as previously described.[20] Reported $IC_{50}$ values are the mean of at least two experiments. [c] Sample purified by column chromatography and did not require recrystallization. [d] Amorphous or oily product. [e] Ethanol/water. [f] Equimolar amounts of benzophenone-2-carboxylic acid derivative and cysteamine were used. [g] Methanol. [h] Isohexane. [i] Diisopropyl ether. [j] Reference 18. [k] Reference 19.

Our strategy in improving the antiviral potency of **1** first focused on the substituents in position 9b (Table I).

We soon observed that an aromatic residue is absolutely necessary for potent HIV-1 RT inhibitory activity. A couple of aliphatic derivatives in position 9b completely lack antiviral activity,[24] and we did not put additional efforts in the variation of aliphatic side chains. Attempts to improve potency by replacement of the phenyl ring by thiophene, furan, and pyrrole, to give **3**, **4**, and **5** as well as the substitution of the carbonyl oxygen in **1** to sulfur **2**, were also not effective.

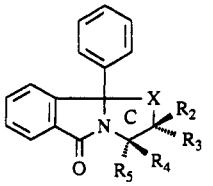
Having identified the phenyl ring as a suitable moiety, we next considered the exploration of the spacial requirements in position 9b by synthesizing the bulky naphthyl and anthracenyl derivatives **6** and **7**. To our surprise, **6** ($IC_{50}$ = 0.13 μM) was already about five times more potent than **1**, and the even bulkier compound **7** ($IC_{50}$ = 0.9 μM) almost showed the same activity as **1**.

These results clearly imply a large hydrophobic pocket for these substituents at the enzyme binding site. In addition, force field calculations of the naphthyl derivative determined two preferential conformations of the naphthyl residue,[23] which are simultaneously incorporated in the anthracenyl derivative. The improved activity of **6** over **7** therefore led to the hypothesis that **6** exhibits a preferred conformation of the naphthyl group by binding to the enzyme.

**6** and **7** did not give any information on requirements in the para position of the phenyl ring in lead structure **1**. We therefore synthesized the *p*-chloro **8**, *p*-methyl **9**, and *p*-methoxy **11** derivatives with various inductive and/or mesomeric properties of the substituents as well as the more hydrophobic and bulkier isopropyl compound **10**. As indicated in Table I, none of these derivatives clearly improved the antiviral activity. Only the aliphatic methyl group in **9** showed comparable potency to the parent compound, whereas the bulkier isopropyl derivative already dropped in activity.

In the meta-substituted series **12–21**, we again prepared first the chloro **12**, methyl **13**, and methoxy **14** entities. Both **12** and even more dramatically **13** enhanced the potency in our RT enzyme assay with an $IC_{50}$ of 140 and 35 nM, respectively. Systematic introduction of hydrophilic, polar, and bulkier substituents **15–21** in this position generally produced less active analogues. Even the trifluoromethyl derivative **17** which is most comparable to **13** drastically fell in activity. One should mention here that our molecular modeling investigation and the knowledge of the structures of (*R*)-(+)-**13**, TIBO, and BI-RG-

**Table II.** Structure and Antiviral Activity of 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones and Derivatives Modified in Ring C




| no. | $-XCR_2R_3CR_4R_5-$ | prep method[a] | yield, % | mp, °C | recryst solvent | RT $IC_{50}$,[b] μM |
|---|---|---|---|---|---|---|
| **1** | $-SCH_2CH_2-$ | A | 77 | 108–10 | ethanol | 0.7 |
| **30** | $-SOCH_2CH_2-$ | E | 11 | 174–7 | *c* | 1.45 |
| **31** | $-SO_2CH_2CH_2-$ | F | 5 | 190–3 | *c* | >10 |
| **32** | $-OCH_2CH_2-$ | G | 75 | 148–50[k] | ethanol | 6.1 |
| **33** | $-NHCH_2CH_2-$ | H | 63 | 152–4[k] | ethanol | >100 |
| **34** | $-CH_2CH_2CH_2-$ | I | 13 | 96–7 | *c* | 15 |
| **35** | $-SCH_2CH_2CH_2-$ | J | 9 | 164–7[l] | *c* | 2.2 |
| **36** | $-OCH_2CH_2CH_2-$ | K | 40 | 129–30[k] | ethanol | 51 |
| **37** | $-NHCH_2CH_2CH_2-$ | L | 61 | 183–7[k] | ethanol | >10 |
| **38** | $-CH_2CH_2CH_2CH_2-$ | M | 26 | 162–4 | *c* | 75.5 |
| **39** | $-OCH(CH_3)CH_2-$[d] | N[e] | 35 | 153–4 | ethanol | 37.6 |
| **40** | $-OC(CH_3)HCH_2-$[h] | O[f] | 28 | 153–4 | ethanol | >100 |
| **41** | $-OCH_2CH(CH_3)-$[m] | P | 45 | 141–2 | *g* | 73 |
| **42** | $-OCH_2C(CH_3)H-$[n] | Q | 48 | 140–1 | *g* | 40 |
| **43** | $-SCH_2CH(COOCH_3)-$[j] | R | 23 | 116–7 | ether | 0.22 |
| **44** | $-SCH_2CH(COOH)$[i] | S | 44 | 96–8 | ethanol | >100 |
| **45** | $-SCH_2CH(CONH_2)-$[j] | T | 21 | 160–2 | *o* | 59 |
| **46** |  | U | 5 | 163–4[k] | *c* | 40 |

[a–c] See footnotes *a–c*, Table I. [d] Since the $IC_{50}$ of the other diastereomer was >100 μM, we suppose that the absolute configuration of the carbon atom in position 9b is (*R*). [e] The mixtures of diastereomers were separated by RP HPLC. **39** $[\alpha]^{20}_D = +261.1°$ ($CHCl_3$). [f] The mixtures of diastereomers were separated by chromatography on cellulose triacetate. **40** $[\alpha]^{20}_D = -263°$ ($CHCl_3$). [g] 2-Propanol. [h] Both isolated diastereomers yielded $IC_{50}$ > 100 μM. Since **40** is the epimer of **39**, we conclude that the absolute configuration of the carbon atom in position 9b is (*R*). [i] Only one diastereomer as detected by $^1$H-NMR spectroscopy. [j] We assume that the absolute configuration of the carbon atom in position 9b is (*R*), since these compounds were prepared from **43**. [k] Reference 18. [l] Reference 19. [m] **41**: $[\alpha]^{20}_D = -318.5°$ ($CHCl_3$). [n] **42**: $[\alpha]^{20}_D = +313.0°$ ($CHCl_3$). [o] Ethyl acetate.

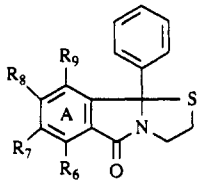
587 resulted in a high three-dimensional similarity of these compounds. Superimposition of these three structures led to the prediction of a methyl group in meta position, which was impressively verified by the activity of (*R*)-(+)-**13**.[23]

Since the methyl group was most effective in increasing the antiviral activity, we also tested the 9b *o*-methylphenyl derivative **22**. However, this compound was considerably less potent than **13**. Having identified the *m*-methyl and *m*-chloro substituents as most suitable, we next explored disubstitution **23–29** of these residues in the aromatic ring. All dimethyl compounds bearing one substituent in the meta position **23–26** are potent RT inhibitors with an optimum for compound **26**, which as pure enantiomer (*R*)-(+)-**26** yielded an $IC_{50}$ of 16 nM. The indanyl derivative **27** resembles **23** in its antiviral activity and is even less potent than the naphthyl compound **6**. The dichloro derivatives **28** and **29** could not reach the inhibitory constants of the monochloro compound **12**. Taking together all the information from the systematic substitution of position 9b, we assume that these residues fit into a hydrophobic pocket of the enzyme.

Evaluations of representative examples from modification of ring C are summarized in Table II.

Oxidation of the sulfur atom led to the sulfoxide with equivalent potency relative to **1**, if one considers the four possible diastereomers of **30**. Further oxidation to the sulfone **31** completely inactivates the molecule. Replacement of the sulfur by O, NH, and $CH_2$ **32–34** as well as ring enlargement of the same series by a methylene group yielded the less active 2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one (**32**), 2,3-dihydroimidazo[2,1-*a*]isoindol-5-(9b*H*)-one (**33**), 1,2,3,9b-tetrahydro-5*H*-pyrrolo[2,1-*a*]-isoindol-5-one (**34**), 3,4-dihydro-2*H*-[1,3]thiazino[2,3-*a*]isoindol-6(10b*H*)-one (**35**), 3,4-dihydro-2*H*-[1,3]-oxazino[2,3-*a*]isoindol-6(10b*H*)-one (**36**), 1,2,3,10b-tetrahydropyrimido[2,1-*a*]isoindol-6(2*H*)-one (**37**), and 1,2,3,-10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (**38**). In general, five-membered rings were more potent than six-membered rings, and the antiviral activity decreased in the series S > O > $CH_2$ > NH. Although thiazoloisoindolinones appeared to be the best ring system, we synthesized 2- and 3-methyl-substituted derivatives in the oxazoloisoindolinone series **39–42** because of the commercial availability of enantiomeric pure aminopropanols needed. By this strategy, we expected only two diastereomers of each compound with (*R*)- or (*S*)-configuration in position 9b. In the case of **41** and **42**, hints from the literature even predicted the predominant formation of only one diastereomer.[25] As can be seen from Table II, all methyl-substituted derivatives **39–42** were not effective in enhancing the potency of the parent compound **32**. Since **39** is more active than its epimer ($IC_{50}$ > 100 μM), we suggest the (*R*)-configuration for the carbon atom in position 9b. From this point of view and from our analytical data, we also can propose the (*R*)-configuration for **40**. The synthesis of **41** and **42**, however, led to only one single diastereomer, and we are not absolutely sure about the configuration in position 9b. Some information in this regard can be derived from the condensation product of L-cysteine methyl ester with benzophenone-2-carboxylic acid. The only isolated diastereomer **43** surprisingly yielded high inhibitory activity in our RT assay and obviously suggests the (*R*)-configuration of the carbon atom 9b. However, this hypothesis was not further proved by X-ray analysis. Subsequent modifications of this methyl

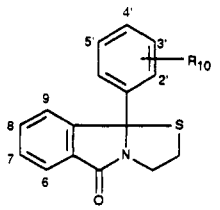
**Table III.** Structure and Antiviral Activity of 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones and Derivatives Modified in Ring A




| no. | $R_6$ | $R_7$ | $R_8$ | $R_9$ | prep method[a] | yield, % | mp, °C | recryst solvent | RT $IC_{50}$,[b] μM |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | H | A | 77 | 108–10 | ethanol | 0.7 |
| 47 | $CH_3$ | H | H | H | A | 46 | 114–5 | *c* | 8.0 |
| 48 | H | $CH_3$ | H | H | A | 45 | 97–8 | *g* | 10.0 |
| 49 | H | Cl | H | H | A | 48 | 122–3 | ethanol | 24 |
| 50 | H | $OCH_3$ | H | H | A | 55 | *d* | *c* | 4 |
| 51 | H | Cl | Cl | H | A | 67 | 112–4 | ethanol | 4.48 |
| 52 | H | H | $CH_3$ | H | A | 75 | 115–8 | ethanol | 0.72 |
| 53 | H | H | Cl | H | A | 68 | 133–6 | ethanol | 0.19 |
| (*R*)-(+)-53 | H | H | Cl | H | B | 38 | 87–93 | ethanol | 0.09 |
| 54 | H | H | $OCH_3$ | H | A | 43 | *d* | *c* | 3.60 |
| 55 | H | H | $CF_3$ | H | A | 30 | 120–1 | ethanol | 17.7 |
| 56 | H | H | $NO_2$ | H | A | 73 | 205–11 | *e* | 10 |
| 57 | H | H | $NH_2$ | H | V | 25 | 230–3 | *f* | 4.5 |
| 58 | H | H | H | Cl | A | 18 | 128–30 | ethanol | 0.29 |
| 59 |  | | H | H | C | 30 | 124–5 | ethanol | >100 |
| 60 | H |  | | H | A | 20 | 115–7 | *c* | 10 |
| 61 | H | H |  | | W | 24 | 185–90 | *h* | 26 |

[a–d] See footnotes *a–d*, Table I. [e] Methanol. [f] Ethyl acetate. [g] 2-Propanol. [h] 50% acetone–50% toluene.

**Table IV.** Structure and Antiviral Activity of Aza Derivatives of 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones




| no. | position of N-atom | $R_{10}$ | prep method[a] | yield, % | mp, °C | recryst solvent | RT $IC_{50}$,[b] μM |
|---|---|---|---|---|---|---|---|
| 1 | none | H | A | 77 | 108–10 | ethanol | 0.7 |
| 62 | 6-aza | H | A | 83 | 178–9 | ethanol | >100 |
| 63 | 7-aza | H | A[g] | 20 | 120–1 | *c* | >100 |
| 64 | 8-aza | H | A | 63 | 228–9[f] | *e* | 17 |
| 65 | 9-aza | H | A | 62 | 172–6 | ethanol | 3.45 |
| 66 | 2′-aza | H | A | 61 | 117–9 | ethanol | 5.85 |
| 67 | 3′-aza | H | A | 57 | 149–52 | ethanol | 28 |
| 68 | 4′-aza | H | A | 68 | 113–4 | ethanol | >30 |
| 69 | 2′-aza | 3′-$CH_3$ | A | 65 | 123–7 | *c* | 4.1 |
| 70 | 2′-aza | 5′-$CH_3$ | A | 40 | *d* | *c* | 1.0 |
| 71 | 2′,9-diaza | H | A | 11 | 149–50 | ether | 23 |
| 72 | 2′,9-diaza | 3′-$CH_3$ | A | 53 | 134–5 | ethanol | 6.6 |
| 73 | 2′,9-diaza | 5′-$CH_3$ | A | 32 | 129–30 | ethanol | 4.6 |

[a–d] See footnotes *a–d*, Table I. [e] Ethanol/HCl. [f] HCl salt. [g] The product was purified by HPLC, since it was contaminated with the 8-aza derivative **64**.

carboxylate to **44** and **45** as well as several other alkyl carboxylate and amid derivatives[24] unfortunately did not improve the interesting antiviral activity of **43**. Conversion of the slightly twisted conformation of the thiazolidine ring in **1** to the more planar derivative **46** also decreased potency.

The effect of introducing nuclear substituents into the phenyl ring A of the isoindole system was explored next. Systematic insertion of substituents with inductive and/or mesomeric behavior yielded compounds **47–61** listed in Table III.

As can be seen from these results, the most promising entities are substituted in either position 8 or 9 with the methyl and chlorine compounds **52**, **53**, and **58** as the most potent derivatives. Again, the position of the chlorine atoms is predictable from the superimposition of structure **1** and TIBO and supports our three-dimensional model of these RT inhibitors.

The data so far imply that a 3′-methyl-8-chloro derivative should result in an even better inhibitor of RT. However, this compound was 2–10 times less active than **13** and **53**, respectively.[24] An additive effect could therefore not be detected by introducing both substituents into one molecule.

Having identified the criteria set of highly potent substituted derivatives, we finally decided to improve the

Table V. Antiviral Activity of Selected Compounds in the RT Assay and in HIV-1 Infected MT2 Cell Cultures

| | $IC_{50}$, μM | |
|---|---|---|
| no. | RT[a] | MT2 cells[b] |
| (*R*)-(+)-1 | 0.28 | 0.392 |
| (*R*)-(+)-6 | 0.15 | 0.046 |
| (*R*)-(+)-13 | 0.035 | 0.051 |
| (*R*)-(+)-26 | 0.016 | 0.01 |
| (*R*)-(+)-53 | 0.09 | 0.074 |
| 73 | 4.6 | 7.8[c] |
| TIBO | 0.16 | 0.217 |
| BI-RG-587 | 0.43 | 0.303 |
| L-697,661 | 0.001[c] | 0.08 |
| E-BPU | 0.003[c] | <0.027[c] |
| U-87201 | 0.14 | 1.59 |

[a] See footnote *b*, Table I. [b] Cell culture inhibitory concentrations ($IC_{50}$) are defined as those which inhibit by 50% the spread of HIV-$1_{IIIb}$ infection in susceptible cell culture. Assays were performed as previously described.[20] [c] Data from only one experiment.

water solubility of these 2,3-dihydrothiazolo[2,3-*a*]isoindol-5-(9b*H*)-ones by synthesizing aza derivatives **62–73**, since (*R*)-(+)-**1**, (*R*)-(+)-**13**, and (*R*)-(+)-**53** unfortunately produced only moderate serum levels after po administration to rats due to weak oral bioavailability of these highly lipophilic compounds. As summarized in Table IV, we successively introduced nitrogen atoms into all aromatic ring positions.

Focusing first on the series **62–65**, we clearly observed a continuous improvement of the antiviral activity moving the nitrogen from position 6 to 9. The same strategy in the exocyclic phenyl ring apparently showed a decrease of potency from 2′-aza **66** to 3′-aza **67** and 4′-aza **68**. Nevertheless, the most potent entities **62** and **66** did not reach the activity of the parent entity **1**. We therefore synthesized the two *m*-methyl-substituted 2′-aza derivatives **69** and **70** to find out whether the methyl group can again improve the potency in this series. **70** with the methyl group para to the 2′-aza nitrogen was slightly more effective than **66** and parallels findings in the BI-RG-587 series. The three-dimensional similarity of our structures to BI-RG-587 finally induced us to prepare the 2′,9-diaza analogues **71–73**. As can be drawn from Table IV, the parent compound **71** dramatically loses antiviral activity in comparison to **1**, whereas a methyl group again improves the inhibitory potency of these molecules. However, since the antiviral activity of BI-RG-587 is more pronounced (Table V) than that of **73**, we suppose a rotation of the revolving methylpyridine residue in position 9b leading to a different conformation in comparison to BI-RG-587, where the conformation of the two pyridines is frozen by the tricyclic ring system.

Compounds inhibiting in vitro HIV-1 RT activity were subsequently evaluated for antiviral potency in MT2 cell cultures (Table V).

As shown in Table V, 2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones that were potent enzyme inhibitors effectively prevented the spread of HIV-$1_{IIIb}$ infection in MT2 cells. No evidence of cytotoxicity[24] was observed in these experiments at concentrations as high as 50 μM. The same order of magnitude between the RT inhibitory potency and the inhibition in cell culture suggests that the antiviral effect of these compounds is mediated via direct inhibition of RT. As already published with TIBO, BI-RG-587, and all the other non-nucleoside inhibitors, serial passage of the HIV-1 virus in cell culture in the presence of 2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones have yielded viral strains which are resistant to these compounds. In fact, resistant HIV-1 mutants with 100-fold increased $IC_{50}$-values were generated after eight passages in MT2 cells. Comparison of the deduced amino acid sequences with wild type sequence exhibited an amino acid substitution at position 181 (Cys for Tyr), whereas amino acid 188 and the residues 101–104 remained unchanged. However, in the enzymatic assay substitutions of amino acids Lys-101 and Lys-103 as well as Tyr-181 and/or Tyr-188 in the reverse transcriptase by site directed mutagenesis also led to resistance against these thiazoloisoindolinones.[20]

## Conclusions

We have identified the novel structure of 2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-ones as selective HIV-1 RT inhibitors, which also potently prevent the spread of the virus infection in MT2 cells. The oral bioavailability of these compounds is only moderate in rats, and the attempt to reduce the lipophilicity of these entities by preparing aza analogues suffered from a loss in potency. These compounds show a high degree of three-dimensional homology to TIBO and BI-RG-587, and further X-ray studies of these structures eventually as cocrystals with the RT[26] will probably produce additional similiarities with L-697,661, HEPT, and U-87201E. The most potent inhibitors were found in the class of 2,3-dihydrothiazolo-[2,3-*a*]isoindol-5(9b*H*)-ones bearing a phenyl ring system in position 9b optionally substituted with one or two methyl groups in the meta position or a chlorine atom in position 8. Cross resistance of our compounds and among all of the known non-nucleoside inhibitors[27] clearly indicates that these compounds bind to the same allosteric site of HIV-1 RT. Further clinical trials will clarify whether these non-nucleosides RT inhibitors will help to treat HIV-1 infection in man in combination with nucleosides, protease inhibitors, or tat inhibitors.

## Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. The identity of all compounds was confirmed by $^1$H NMR (250 MHz, Bruker AC-250, solvents DMSO-$d_6$ or $CDCl_3$, TMS = 0 ppm) and mass spectra (Finnigan MAT 312, data system SS300), which were provided by the Analytical Department of the Boehringer Mannheim Research Laboratories. The $^1$H NMR spectra of compounds **1–73** are available as supplementary material. All reactions were followed by TLC carried out on Merck F 254 silica gel plates. Merck silica gel, 200–400 mesh, was used for the chromatographies. Yields were not optimized. Several benzophenone-2-carboxylic acid derivatives used in the preparation of these compounds were commercially available in the cases of **1**, **6**, **8**, **9**, **12**, **22**, **24**, **32**, **33**, **35–37**, **39–43**, **46**, and **66**. Most of the other benzophenone-2-carboxylic acids were prepared by (a) Friedel–Crafts reaction with phthalic anhydride, (b) metal organic reaction with phthalic anhydride, (c) oxidation of 2-methylbenzophenones, and (d) the synthesis of 2-picolinylbenzoic acid as described by Aeberli et al.[28] An alternative route starting from substituted 2-aminobenzophenones[21] via the nitriles to the carboxylic acids as well as the synthesis of 2-benzoylpyridine-3-carboxylic acid and substituted 2-(2-pyridinoyl)pyridine-3-carboxylic acids are described in this section. As far as original synthetic procedures are known for these substituted benzophenone-2-carboxylic acids, the references thereof are indicated in the following list: **3**,[29] **4**,[30] **5**,[31] **7**,[32] **10**,[33] **11**,[34] **13**,[35] **14**,[19] **15**,[36] **16**,[36] **17**,[37] **20**,[38] **21**,[30] **23**,[39] **25**,[40] **26**,[41] **27**,[36] **28**,[28] **29**,[42] **47**,[43] **48**,[44] **49**,[28] **50**,[45] **51**,[28] **52**,[44] **53**,[28] **54**,[45] **55**,[46] **56**,[47] **58**,[48] **59**,[49] **60**,[50] **61**,[49] **62**,[51] **63**,[52] **64**,[52] **67–70**.[53] 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepine-2(1*H*)-thione (TIBO),[12] 11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (BI-RG-587),[13] 1-[[2-(benzyloxy)ethoxy]methyl]-5-ethyl-6-(phenylthio)pyrimidine-

2,4(1*H*,3*H*)-dione (E-BPU, HEPT derivative),[14] 3-[[(4,7-dichlorobenzoxazol-2-yl)methyl]amino]-5-ethyl-6-methylpyridin-2(1*H*)-one (L-697,661),[15] and 5-methoxyindole-2-carboxylic acid [*N*'-[3-(aminoethyl)pyridin-2-yl]piperazide] (U-87201E)[16] were prepared by the Chemical Department of Boehringer Mannheim. The following methods (A-Z) are described for specific products. However, identical procedures may be applied to analogous compounds.

**Preparation of Substituted 2,3-Dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one Derivatives. Method A. 9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (1).**[11] Cysteamine (15.4 g, 0.20 mol), benzophenone-2-carboxylic acid (22.6 g, 0.10 mol), 150 mL of toluene, and a catalytic amount of toluene-4-sulfonic acid (0.5 g) were placed in a flask equipped with a stirrer and a Dean-Stark tube. The mixture was stirred and refluxed until the level of the water layer in the side arm remained constant (5–24 h). The reaction was allowed to cool to room temperature, and the resultant solid was removed by filtration. If a solid was not obtained on cooling the solvent was removed under reduced pressure. The resultant residue was taken up in $CH_2Cl_2$, washed with saturated $NaHCO_3$ and water, dried, and concentrated. The crude product was recrystallized from ethanol to yield 20.5 g (77%) of pure product: mp 108–110 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.22–3.40 (m, 2 H), 3.49–3.60 (m, 1 H), 4.28–4.38 (m, 1 H), 7.30–7.44 (m, 3 H), 7.48–7.66 (m, 5 H), 7.70–7.76 (m, 1 H); MS *m/e* 267 ($M^+$).

**Separation of Stereoisomers. Method B. (*S*)- and (*R*)-9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (*S*)-(−)-1 and (*R*)-(+)-1.** A solution of racemic 9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (500 mg) in ethanol (10 mL) was subjected to chromatography on cellulose triacetate (Merck, 15–25 $\mu$m, 250 g) and eluated with ethanol (flow 7.5 mL/min, 1.5 bar). The appropriate fractions of (*S*)-(−)-1 and (*R*)-(+)-1 were concentrated and crystallized from ethanol: (*S*)-(−)-1, $[\alpha]^{20}_D = -342°$ ($CHCl_3$), (*R*)-(+)-1, $[\alpha]^{20}_D = +344°$ ($CHCl_3$). Enantiomeric excess (ee) > 99%.

(*R*)-(+)-**6** (200 mg in 15 mL methanol), eluent methanol, $[\alpha]^{20}_D = +454°$ ($CHCl_3$), ee > 99.6%.

(*R*)-(+)-**13** (500 mg in 10 mL ethanol), eluent ethanol, $[\alpha]^{20}_D = +313°$ ($CHCl_3$), ee > 98.5%.

(*R*)-(+)-**26** (200 mg in 15 mL methanol), eluent 80% methanol–20% $H_2O$, $[\alpha]^{20}_D = +319°$ ($CHCl_3$), ee > 99%.

(*R*)-(+)-**53** (200 mg in 10 mL ethanol), eluent ethanol, $[\alpha]^{20}_D = +259°$ ($CHCl_3$), ee > 99.7%.

**Method C.** The procedure described in method A was followed except that toluene was substituted for xylene.

**Method D. 9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindole-5(9b*H*)-thione (2).** A mixture of 9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (1) (2 g, 7.5 mmol) and Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] (3.8 g, 9.4 mmol) in dry dioxane (100 mL) was stirred at 60 °C for 5 h. After cooling and filtering, the solution was concentrated and flash chromatographed over silica gel, and product (1.24 g, 58%) was eluated with 84% heptane–16% methyl ethyl ketone: mp 151–155 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.31–3.43 (m, 1 H), 3.56–3.68 (m, 2 H), 4.80–4.94 (m, 1 H), 7.20–7.58 (m, 8 H), 7.94–8.02 (m, 1 H); MS *m/e* 283 ($M^+$).

**Method E. 9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one 1-Oxide (30).** A solution of 9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isodinol-5(9b*H*)-one (1) (0.5 g, 1.87 mmol) and 30% $H_2O_2$ (0.2 mL) in glacial acetic acid (5 mL) was stirred at room temperature for 10 h. After half of this time a second portion of 30% $H_2O_2$ (0.2 mL) was added. Subsequently, the solution was concentrated and chromatographed over silica gel. Elution with 97% $CH_2Cl_2$–3% methanol yielded 58 mg (11%) of pure product: mp 174–177 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.75–2.89 (m, 1 H), 3.36–3.50 (m, 1 H), 3.65–3.77 (m, 1 H), 4.61–4.74 (m, 1 H), 7.40–7.62 (m, 8 H), 7.83–7.90 (m, 1 H); MS *m/e* 283 ($M^+$).

**Method F. 9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one 1,1-Dioxide (31).** To a solution of 9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (1) (1.3 g, 4.86 mmol) in $CH_2Cl_2$ (12.5 mL) was added a solution of $KMnO_4$ (1.54 g) in water (25 mL) and benzyltriethylammonium chloride (0.6 g). The mixture was stirred at room temperature for 4 h, and then the organic phase was separated, washed twice with water, dried, and concentrated. The residue was chromatographed over silica gel. Elution with 90% $CH_2Cl_2$–10% methanol yielded 73 mg (5%) of pure product: mp 190–193 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.18–3.32 (m, 1 H), 3.45–3.60 (m, 1 H), 3.80–3.91 (m, 1 H), 4.65–4.78 (m, 1 H), 7.45–7.72 (m, 8 H), 7.84–7.92 (m, 1 H); MS *m/e* 299 ($M^+$).

**Method G.** The procedure described in method A was followed except that cysteamine was substituted for aminoethanol.

**Method H.** The procedure described in method A was followed except that cysteamine was substituted for diaminoethane.

**Method I. 1,2,3,9b-Tetrahydro-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (34).** (a) A mixture of 3-phenyl-2,3-dihydroisoindolin-1-one[51] (0.5 g, 2.39 mmol), toluene (10 mL), DMF (0.5 mL), 1-bromo-3-chloropropane (0.29 mL), and NaH (70 mg, 2.91 mmol) was stirred at 130 °C for 2 h. The mixture was cooled, poured into water (150 mL), and extracted with ethyl acetate. The organic phase was dried and evaporated to yield 2-(3-chloropropyl)-3-phenyl-2,3-dihydroisoindolin-1-one (0.6 g, 88%) as crude product: MS *m/e* 285 ($M^+$).

(b) A mixture of crude 2-(3-chloropropyl)-3-phenyl-2,3-dihydroisoindolin-1-one (0.6 g, 3.5 mmol), NaH (120 mg, 5 mmol), and DMF (3 mL) was stirred at 80 °C for 3 h. The mixture was diluted with water, acidified with 2 N acetic acid, and extracted with ethyl acetate. The organic phase was washed with water, dried, and concentrated. The residue was chromatographed over silica gel. Elution with 34% ethyl acetate–66% isohexane yielded 115 mg (13%) of pure product: mp 96–97 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.60–1.78 (m, 1 H), 1.93–2.12 (m, 1 H), 2.26–2.40 (m, 1 H), 2.67–2.80 (m, 1 H), 3.30–3.42 (m, 1 H), 3.85–3.98 (m, 1 H), 7.25–7.46 (m, 6 H), 7.48–7.55 (m, 2 H), 7.73–7.80 (m, 1 H); MS *m/e* 249 ($M^+$).

**Method J.** The procedure described in method A was followed except that cysteamine was substituted for 1-mercapto-3-propanamine.

**Method K.** The procedure described in method A was followed except that cysteamine was substituted for 1-hydroxy-3-propanamine.

**Method L.** The procedure described in method A was followed except that cysteamine was substituted for 1,3-diaminopropane.

**Method M. 1,2,3,10b-Tetrahydropyrido[2,1-*a*]isoindol-6-(2*H*)-one (38).** A mixture of 3-phenyl-2,3-dihydroisoindolin-1-one[54] (0.7 g, 3.34 mmol), toluene (15 mL), DMF (1 mL), 1,4-dibromobutane (0.47 mL), and NaH (200 mg, 8.33 mmol) was stirred at 130 °C for 2 h. The mixture was cooled, diluted with water, acidified with 2 N acetic acid, and extracted with ethyl acetate. The organic phase was washed with water, dried, and concentrated. The residue was chromatographed over silica gel. Elution with 34% ethyl acetate–66% isohexane yielded 228 mg (26%) of pure product: mp 162–164 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.40–1.85 (m, 5 H), 2.77–2.90 (m, 1 H), 2.98–3.07 (m, 1 H), 4.42–4.55 (m, 1 H), 7.15–7.45 (m, 8 H), 7.82–7.90 (m, 1 H); MS *m/e* 263 ($M^+$).

**Method N.** The procedure described in method A was followed except that cysteamine was substituted for (*S*)-(+)-1-amino-2-propanol.

**Method O.** The procedure described in method A was followed except that cysteamine was substituted for (*R*)-(−)-1-amino-2-propanol.

**Method P.** The procedure described in method A was followed except that cysteamine was substituted for (*R*)-(−)-2-amino-1-propanol.

**Method Q.** The procedure described in method A was followed except that cysteamine was substituted for (*S*)-(+)-2-amino-1-propanol.

**Method R. 5(9b*H*)-Oxo-9b-phenyl-2,3-dihydrothiazolo-[2,3-*a*]isoindole-3-carboxylic Acid Methyl Ester (43).** To a solution of benzophenone-2-carboxylic acid (1 g, 4.4 mmol) in xylene (10 mL) was added portionwise over 10 h L-cysteine methyl ester hydrochloride (1.7 g, 9.9 mmol) and sodium acetate (1.35 g) at 100 °C. After an additional 3 h at 100 °C, the mixture was concentrated under reduced pressure and the resultant residue was taken up in $CH_2Cl_2$, washed with saturated $NaHCO_3$ and water, dried and concentrated. An analytical sample was obtained upon crystallization from ether: mp 116–117 °C; $[\alpha]^{20}_D = -57°$ ($CH_3OH$); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.40–3.50 (m, 1 H), 3.57 (s, 3 H), 3.90–4.00 (m, 1 H), 5.08–5.15 (t, 1 H), 7.28–7.40 (m, 4 H), 7.50–7.63 (m, 2 H), 7.67–7.80 (m, 3 H); MS *m/e* 325 ($M^+$).

**Method S. 5(9b*H*)-Oxo-9b-phenyl-2,3-dihydrothiazolo-[2,3-*a*]isoindole-3-carboxylic Acid 44.** A solution of 5(9b*H*)-Oxo-9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid methyl ester (**43**) (327 mg, 1 mmol as crude product) in ethanol (5 mL) and 2 N NaOH (2 mL) was stirred at 40 °C for 2 h. After evaporation of ethanol, the water solution was acidified with 6 N HCl and the acid isolated by filtration to yield upon recrystallization from ethanol 138 mg (44%) of pure product: mp 96–98 °C; $[\alpha]^{20}_D$ = −212° ($CH_3OH$); $^1H$ NMR (DMSO-$d_6$) δ 3.35–3.45 (m, 1 H), 3.90–4.00 (m, 1 H), 4.91–5.01 (t, 1 H), 7.25–7.42 (m, 4 H), 7.50–7.65 (m, 2 H), 7.72–7.82 (m, 3 H); MS *m/e* 311 ($M^+$).

**Method T. *N*-Methyl-5(9b*H*)-oxo-9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindole-3-carboxylic Acid Amide (45).** To a solution of 5-(9b*H*)-oxo-9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid (**44**) (311 mg, 1.00 mmol of pure product) and 4-methylmorpholine (0.11 mL, 1.00 mmol) in dry $CH_2Cl_2$ (10 mL) was added isobutylchloroformiate (0.148 mL, 1.10 mmol) at −15 °C. After 15 min methylamine (34.7 mg, 1.10 mmol) in $CH_2Cl_2$ (0.27 mL) was added, and the temperature was slowly increased to 25 °C over 5 h. The solution was diluted with $CH_2Cl_2$, washed with $NaHCO_3$ solution and water, dried, and concentrated. The residue was recrystallized from ethyl acetate to yield 67 mg (21%) of pure product: mp 160–162 °C; $[\alpha]^{20}_D$ = −7.1° ($CH_3OH$); $^1H$ NMR (DMSO-$d_6$) δ 2.52–2.58 (d, 3 H), 3.35–3.44 (m, 1 H), 3.86–3.96 (m, 1 H), 4.72–4.82 (t, 1 H), 7.28–7.40 (m, 4 H), 7.50–7.65 (m, 2 H), 7.74–7.98 (m, 4 H); MS *m/e* 324 ($M^+$).

**Method U.** The procedure described in method A was followed except that cysteamine was substituted for 2-mercaptoaniline and xylene was used as solvent.

**Method V. 8-Amino-9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (57).** To a mixture of 8-nitro-9b-phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (**56**) (3.3 g, 11 mmol) in ethanol (33 mL) was rapidly added $Na_2S_2O_4$ (48 g, 39 mmol) in water (33 mL) at reflux temperature. After 15 min, ethanol was removed under reduced pressure, and water (300 mL) was added. The solution was extracted three times with $CH_2Cl_2$ (300 mL), and subsequently the organic phase was washed with 2 N HCl and water, dried, and evaporated to yield after trituration with ethyl acetate 775 mg (25%) of pure product: mp 230–233 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.15–3.27 (m, 2 H), 3.39–3.50 (m, 1 H), 4.23–4.38 (m, 1 H), 6.78 (s, 1 H), 6.86–6.90 (m, 1 H), 7.30–7.60 (m, 8 H), MS *m/e* 282 ($M^+$).

**Method W. 9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*][5,6]-benzoisoindol-5(9b*H*)-one (61).** (a) A mixture of 1-benzoylnaphthaline-2-carboxylic acid (830 mg, 3 mmol), $SOCl_2$ (7.3 mL), and DMF (2 mL) was refluxed for 1 h to yield after evaporation 820 mg (92%) of the acid chloride: mp 90–95 °C. (b) A mixture of crude 1-benzoylnaphthaline-2-carboxylic acid chloride (820 mg, 3 mmol), cysteamine (300 mg, 3.9 mmol), $NEt_3$ (2.1 mL, 15 mmol), and $CH_2Cl_2$ (10 mL) was stirred at room temperature for 2 h. After filtering, the organic phase was washed four times with water, concentrated, acidified with toluene-4-sulfonic acid, and diluted with toluene. This mixture was refluxed for 2 h, cooled to room temperature, washed with saturated $NaHCO_3$ and water, dried, and concentrated. The crude product was triturated with 50% acetone–50% toluene to yield 230 mg (24%) of pure product: mp 185–190 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.15–3.28 (m, 1 H), 3.43–3.62 (m, 2 H), 4.41–4.52 (m, 1 H), 7.27–7.45 (m, 4 H), 7.49–7.59 (m, 2 H), 7.66–7.73 (m, 2 H), 7.85–8.00 (m, 3 H); MS *m/e* 317 ($M^+$).

**Method X. 9b-(3-Aminophenyl)-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (19).** To a solution of 9b-(3-nitrophenyl)-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (**20**) (23.4 g, 75 mmol) in methanol (600 mL) was rapidly added $Na_2S_2O_4$ (48 g) in water (150 mL) at reflux temperature. After 15 min, methanol was removed under reduced pressure and water (300 mL) was added. The solution was extracted three times with $CH_2Cl_2$ (300 mL), and subsequently the organic phase was washed with water, dried, and evaporated to yield 8.21 g (39%) of pure product: mp 184–186 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.23–3.38 (m, 2 H), 3.48–3.60 (m, 1 H), 4.22–4.36 (m, 1 H), 5.18 (s, 2 H), 6.45–6.52 (m, 1 H), 6.74–6.80 (m, 2 H), 6.98–7.06 (m, 1 H), 7.40–7.61 (m, 3 H), 7.65–7.72 (m, 1 H); MS *m/e* 282 ($M^+$).

**Method Y. 9b-(3-Hydroxyphenyl)-2,3-dihydrothiazolo-[2,3-*a*]isoindol-5(9b*H*)-one (18).** To a mixture of 9b-(3-aminophenyl)-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (**19**) (2.5 g, 8.85 mmol), water (13 mL), and concentrated HCl (2 mL) was slowly added $NaNO_2$ (0.65 g, 9.42 mmol) in water (2 mL) at 0–3 °C. After 30 min, the mixture was refluxed for 15 min, cooled to room temperature, extracted with $CH_2Cl_2$, dried, and concentrated. The residue was chromatographed over silica gel. Elution with 91% toluene–9% methanol yielded 265 mg (11%) of pure product: mp 138–140 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.23–3.38 (m, 2 H), 3.48–3.60 (m, 1 H), 4.25–4.38 (m, 1 H), 6.65–6.72 (m, 1 H), 6.95–7.05 (m, 2 H), 7.12–7.22 (m, 1 H), 7.41–7.63 (m, 3 H), 7.68–7.74 (m, 1 H), 9.52 (s, 1 H); MS *m/e* 283 ($M^+$).

**Method Z.** The procedure described in method A was followed except that equimolar amounts of 2-(3-cyanobenzoyl)benzoic acid and cysteamine was used.

**Synthesis of Substituted Benzophenone-2-carboxylic Acids Starting from 2-Aminobenzophenones. 2-Benzoyl-4-chlorobenzoic Acid.** (a) To a mixture of 2-amino-5-chlorobenzophenone (25.5 g, 110 mmol) in glacial acetic acid (82 mL) was first slowly added a solution of concentrated $H_2SO_4$ (19.5 mL) in water (18.2 mL) at 10 °C and then dropwise a solution of $NaNO_2$ (9.8 g, 142 mmol) in water (19.5 mL) between 0 and 5 °C. This diazonium salt mixture and a solution of $Na_2CO_3$ (72.9 g) in water (200 mL) were simultaneously added from two separate dropping funnels to a solution of $CuSO_4 \cdot 5H_2O$ (52.3 g, 209 mmol) and KCN (57.4 g, 880 mmol) in water (440 mL) at 10 °C. The pH of the solution was adjusted to 5 by controlling the rate of addition from the dropping funnels. The resulting precipitate was collected by filtration, triturated with a mixture of ethyl acetate and 2 N HCl, and again filtered through Celite. The organic phase was separated, washed with 2 N NaOH and water, dried, and evaporated. The residue was chromatographed over silica gel. Elution with 20% ethyl acetate–80% isohexane yielded 21.4 g (81%) of 2-benzoyl-4-chlorobenzonitrile: mp 74–78 °C. (b) A mixture of this nitrile (10.7 g, 44 mmol) in concentrated $H_2SO_4$ (40 mL) and water (54 mL) was refluxed for 6 h. After cooling, the mixture was diluted with water, extracted with ethyl acetate, dried, and evaporated to yield 9.7 g (84%) of pure product: mp 174–179 °C (lit.[28] mp 175–177 °C).

**Synthesis of 2-Benzoylpyridine-3-carboxylic Acid.** A mixture of 3-(methoxycarbonyl)pyridine-2-carboxylic acid chloride (2.6 g, 13 mmol), $AlCl_3$ (5.2 g, 39 mmol), and benzene (20 mL) was heated at 80 °C for 3 h. The solvent was decanted, and the residue was resolved in hot water, treated with charcoal, and filtered. After evaporation of the solvent the residue was chromatographed over silica gel. Elution first with 50% ethyl acetate–50% isohexane followed by 90% ethyl acetate–10% methanol yielded 0.8 g (27%) of pure product: mp 154–157 °C; $^1H$ NMR (DMSO-$d_6$) δ 7.27–7.33 (m, 1 H), 7.48–7.58 (m, 2 H), 7.62–7.73 (m, 3 H), 8.35–8.41 (m, 1 H), 8.79–8.83 (m, 1 H), 13.57 (s, 1 H).

**Synthesis of Substituted 2-(2-Pyridinoyl)pyridine-3-carboxylic Acids.** (a) A solution of 2-(2-pyridinemethyl)-pyridine-3-carboxylic acid[22] (927 mg, 4.3 mmol), $KMnO_4$ (917 mg, 5.8 mmol), and water (20 mL) was stirred at 90 °C for 3 h. The precipitate was removed by filtration, and the water solution was concentrated to a volume of 10 mL and acidified with 2 N HCl to pH 4. The solids were collected by filtration to yield 350 mg (36%) of 2-(2-pyridinoyl)pyridine-3-carboxylic acid:[55] $^1H$ NMR (DMSO-$d_6$) δ 7.30–7.50 (m, 2 H), 7.85–8.15 (m, 3 H), 8.35–8.50 (m, 2 H).

(b) 2-(6-Methyl-2-pyridinoyl)pyridine-3-carboxylic acid: mp 211–219 °C; $^1H$ NMR (DMSO-$d_6$) δ 2.32 (s, 3 H), 7.42–7.47 (m, 1 H), 7.61–7.67 (m, 1 H), 7.90–7.97 (m, 2 H), 8.39–8.35 (m, 1 H), 8.75–8.80 (m, 1 H).

(c) 2-(4-Methyl-2-pyridinoyl)pyridine-3-carboxylic acid: mp 210–212 °C; $^1H$ NMR (DMSO-$d_6$) δ 2.45 (s, 3 H), 7.38–7.44 (m, 1 H), 7.60–7.68 (m, 1 H), 7.98–8.04 (m, 1 H), 8.30–8.41 (m, 2 H), 8.75–8.81 (m, 1 H).

**HIV-1 Reverse Transcriptase Enzyme Assay.** In brief, 1 μg of HIV-1 template RNA (1080 nucleotides) and 20 ng of 18-*mer*-deoxy-oligo primer (complementary to the primer binding site on the template) were annealed by heating to 90 °C and slowly cooling to 37 °C. Primer/template were added to the reaction mixture [40 ng of HIV-1 RT (p66/p51 expressed in *E.*

*coli*), nucleotides, and buffers according to the nonradioactive RT-Kit, Boehringer Mannheim] and incubated in a streptavidin-coated microtiter plate for 60 min at 37 °C with the different inhibitors. Plates were washed five times with 0.1% Tween 20 in PBS. After washing, 100 μL of anti-DIG-peroxidase conjugate (150 mU/mL, diluted with 100 mM Tris–HCl pH 7.7, 150 mM NaCl) was added to each well and the resulting mixture incubated for 30 min at room temperature. After additional washing (see above), 100 μl of 2,2′-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) solution (1 g/L of ABTS in ABTS–buffer) were delivered to each well and subsequently incubated in an ELISA reader at 405 nm. The inhibitors were dissolved in DMSO and added to the assay mixture to get the desired concentration, maintaining the DMSO concentration below 5% in the assay. The concentration of inhibitors that produced 50% inhibition ($IC_{50}$) are the mean values from at least two independent assays.

**HIV-1 Cell Culture Growth and Testing of Antiviral Compounds.** HIV-1 infectivity studies were performed in MT2 T-lymphoid cells. In brief, MT2 cells were infected with $HTLV_{IIIB}$ at a MOI of 0.01. Syncytium formation and cell viability using a MTT-test [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] were determined 7 days after infection. Stock solutions were prepared by dissolving the inhibitors in 50% DMSO/50% culture medium. In cell culture supernatant, DMSO concentration was below 1%. $IC_{50}$-doses are mean values from at least two different assays. Infected, nontreated cells served as a control for 100% infection.

**Supplementary Material Available:** $^1$H-NMR spectra of compounds 1–73 (73 pages). Ordering information is available on any current masthead page.

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