Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase: Molecular Modeling and X-ray Structure Investigations

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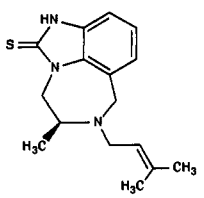
The structural features of a new class of non-nucleoside HIV-1 reverse transcriptase inhibitors (3) are presented. Comparison of the structural and electronic properties with those of TIBO (1) and Nevirapine (2) yields a common three-dimensional model. This model permits the improvement of the lead compound 3 by chemical modification (5, 6). Additionally, two new types of inhibitors (4, 7) with similar biological activity can be derived from this model. The structures of the new compounds, including their absolute configuration, are determined by X-ray crystallography.

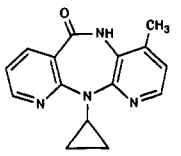
Introduction

Reverse transcriptase (RT[1]) is a key enzyme in the replication of HIV and therefore the main target in the investigation of drugs against AIDS.[2] So far, the only effective drugs are nucleoside analogs such as AZT (azidothymidine). Although it is not clear whether such substances are simply incorporated into a DNA strand or act by a different mechanism, toxic side effects are almost inevitably connected with their chain-terminating property. Therefore, a different approach to the inhibition of this enzyme is highly desirable.

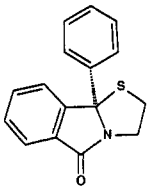
A second generation of inhibitors such as TIBO (1) and Nevirapine (2) have been developed that seem to attack a different site of the enzyme.[3] Common effort of chemical



1 (TIBO)



2 (Nevirapine)



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synthesis and screening of natural products and synthetic compounds recently lead to isoindolinone 3 which in vitro inhibits the activity of HIV-1 RT in the same order of magnitude as 1 and 2.[4] The activity data of this compound as well as those of 1 and 2 and the molecules discussed below are given in Table I. For sake of comparability, the data of 1 and 2 have been remeasured in the same test system.[4b,5] In all cases (except 2 which is achiral) the enantiomers were separated by chromatography[4] and their absolute configuration identified by X-ray crystallography. The inactive enantiomers are not included in the table.

Although on a two-dimensional basis compounds 1, 2, and 3 exhibit almost no similarities, preliminary comparison of the geometries of these molecules indicates some structural elements that are common to all molecules: two

Table I. In Vitro Activity of the Active Enantiomers of Inhibitors 1-7 on HIV-1 Reverse Transcriptase

compd	absolute config	IC_{50} (μM)	compd	absolute config	IC_{50} (μM)
1	*S*[a]	0.16	5	*R*	0.15
2		0.43	6	*R*	0.03
3	*R*	0.28	7	*R*	0.83
4	–[b]	8.70			

[a] From Ref 3e. [b] Not determined.

π systems arranged in a butterfly-like orientation, an additional lipophilic region between them, and a carbonyl or thiocarbonyl group.

In order to establish a common three-dimensional model that could be used to derive new active compounds, we decided to study the structures of the three molecules in detail using X-ray crystallography and semiempirical calculations (MNDO[6]).

Unfortunately, a high-resolution X-ray structure of HIV-RT is still unknown. Consequently, the design of RT inhibitors by use of molecular modeling is restricted to the comparison of properties of the inhibitor molecules alone. If this approach includes molecules with conformational flexibility, as in the case of 1, a procedure of this type is easily subject to overinterpretation. Structural models derived from such an approach must therefore be supported by experimental facts.

Structure of 3. It is quite reasonable to determine the structure of this compound by calculation since it contains only few degrees of freedom. Its geometry depends mainly on the orientation of the exocyclic phenyl ring and the pseudorotation of the thiazolidine. Therefore a conformational analysis of the torsion of the phenyl ring with optimization of all remaining geometrical parameters was performed using MNDO. The obtained torsion potential is depicted in Figure 1 (top). The minimum represents a structure in which the plane of the phenyl ring approximately bisects the amide bond.

Independently, an X-ray analysis of 3 was performed. Two different conformers were found in the unit cell that differ slightly in the thiazolidine pucker and the orientation of the phenyl ring. In general, both X-ray analysis and MNDO calculation lead to a consistent picture of the structure of this molecule. Most interestingly, experiment as well as calculation show a considerable deviation of the amide nitrogen from planarity.[7] Other computational procedures such as molecular mechanics did not reproduce

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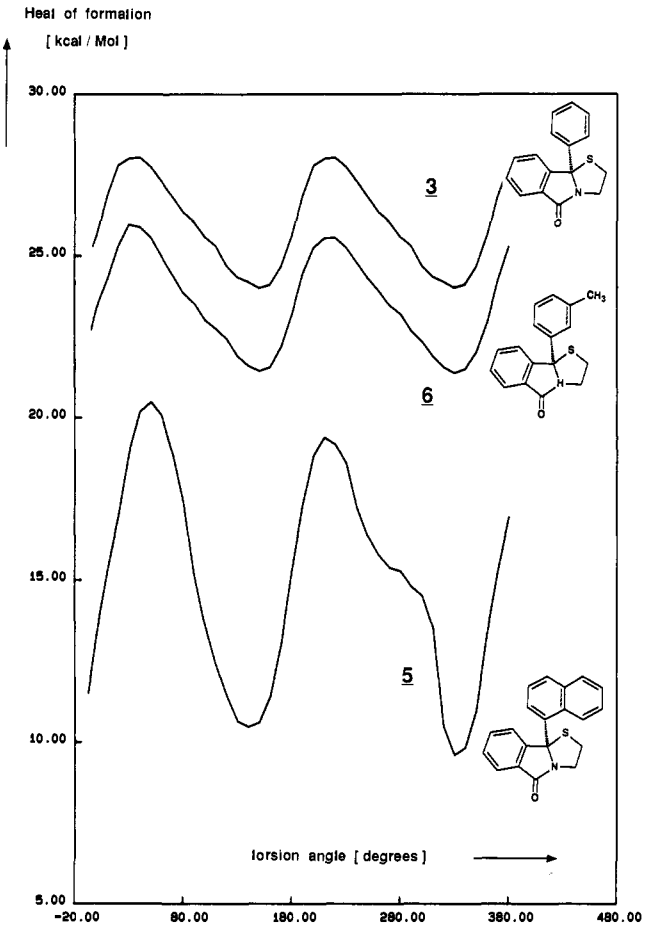


Figure 1. Torsion potentials (heat of formation) of **3** (top), **5** (bottom), and **6** (middle) using MNDO in kilocalories per mole. The torsion angle is defined: N–C(bridgehead)–C(1′)–C(2′) for **3** and **5**, N–C(bridgehead)–C(1′)–C(6′) for **6**, respectively. 0 degrees denotes structures where the 3′-methyl group in **6** or the second benzene ring in **5** is located anti to the amide nitrogen. The relative energy scale is the same for all compounds; the absolute heat of formation values refer to **3**.

this result. We assign this deviation to the highly strained bicyclic core of the molecule. The two crystallographically determined conformations of **3** are displayed in Figure 2.

Structure of TIBO (1). For sake of comparison with **2** and **3** a conformational analysis of **1** was performed. Since three atoms of the seven-membered ring are part of the planar benzimidazole system, the conformational flexibility of the diazepine moiety should mainly be determined by the remaining four saturated atoms and therefore resemble the structural properties of cyclohexene. Thus we expect two conformers that are related to the two cyclohexene twist forms. Variation of the torsion angle between the methyl substituent and the dimethylallyl side chain between −180° and 180° was performed using MNDO, all remaining structural parameters being optimized. By this method only two minima could be located. These two structures were subsequently fully optimized by the same method. The resulting structures are indeed similar to the two cyclohexene twist conformations, one having an axial, the other an equatorial methyl group (see Figure 3). As a consequence of the nitrogen inversion, in both structures the dimethylallyl groups occupy an equatorial position.

For the discussion below we will use the first structure which represents the energy minimum. It should be noted, however, that **1** exhibits a lot of conformational freedom and the active conformation cannot really be determined. Especially the position of the dimethylallyl side chain cannot be predicted.

During this investigation, the X-ray structure analysis of the 9-chloro derivative of TIBO was published.[8] The two crystallographically determined conformers of this compound exhibit close similarity to the results of our calculations.

Structure of Nevirapine (2). This achiral molecule was simply optimized by MNDO since there are only two reasonable conformations (and their mirror images). The two orientations of the cyclopropyl group—syn or anti to the seven-membered ring—lead to structures with approximately the same energy. The syn conformer seems to be almost identical to the X-ray structure of this molecule which was recently published.[9] The selection of the "enantiomer" used in our comparisons (see below) is, of course, arbitrary; the discussions are valid for both orientations of the cyclopropyl group.

Comparison of the Electrostatic Potentials of 1, 2, and 3 and Construction of a Three-Dimensional Model. In order to examine whether the three compounds might interact with the enzyme in a similar way, we compared the electrostatic potentials of **1**, **2**, and **3**. The charges were calculated by the MNDO method. Subsequently, the electrostatic potentials were calculated using a point charge model. Although such a model is only a crude approximation, a high similarity between the potentials of very different compounds is indicative for a similar charge distribution.

The obtained isopotential surfaces were moved in space together with the underlying molecules in order to obtain maximal overlap. The results are displayed in Figure 4 as stereo pictures (see legend). Some surprising results can be derived from this approach:

1. Although the three molecules exhibit no chemical similarity, the electrostatic potential distributions are almost identical.

2. If the potentials are superimposed in space, the atom positions of the underlying molecules (see Figure 5) do not match. Especially the thiocarbonyl group of **1** does not, as one might have expected, occupy the same position as the carbonyl groups of the other two compounds.

3. As a result of the superimposition of the isopotential surfaces, the methyl substituent of **1**, the thiazolidine ring of **3**, and the cyclopropyl group of **2** are shifted into the same region and now occupy equivalent positions.

From these results a three-dimensional model was constructed which is presented in Figure 6. An aromatic ring and a second extended π-system should be arranged in a roof-like orientation. The distance between the midpoints of the two systems should be 4.5–5 Å, and the angle between the two planes should be around 110°. Additionally, the molecule should contain a carbonyl or thiocarbonyl group, an extra lipophilic site, and a methyl group. We are quite sure about the position of the methyl group indicated in the model since upon only slight conformational change of **1** the methyl group of **2** and one of the dimethylallyl methyl groups in **1** match exactly. The absolute configuration used in this model is derived from the active enantiomer of compound **3**.

Test of the Model. In order to check the validity of the model before synthesizing new compounds, we decided first to test it by use of simple, commercially available

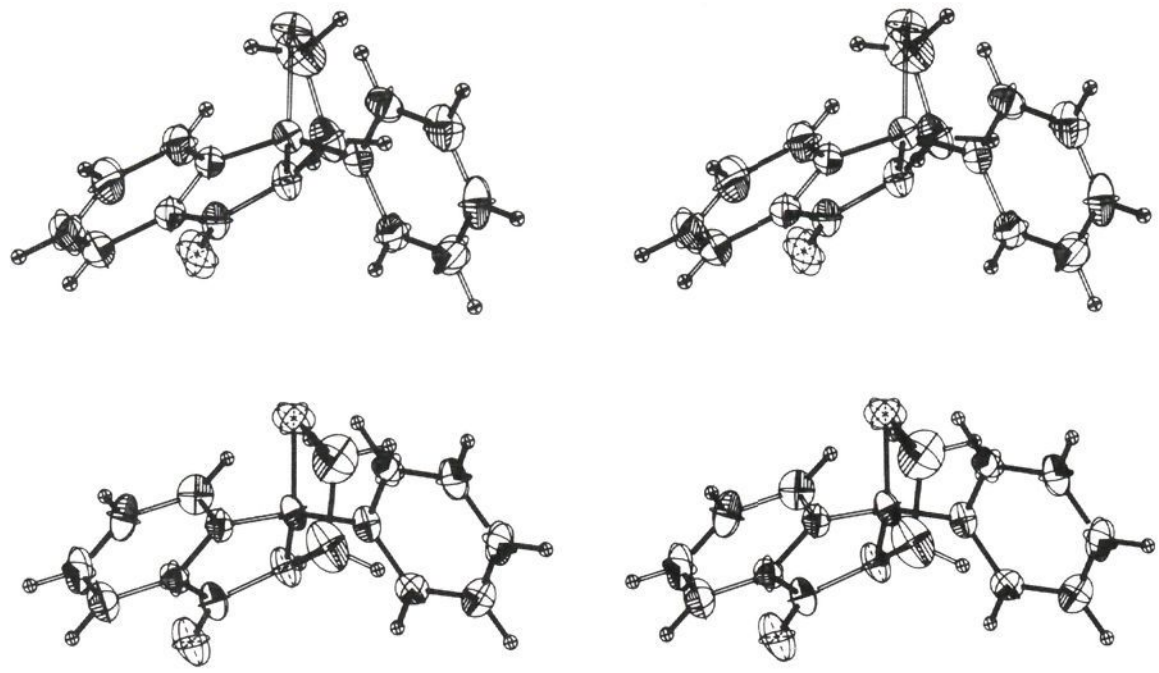


Figure 2. The two independent molecules in the unit cell of the X-ray structure of (*R*)-**3** (active enantiomer).

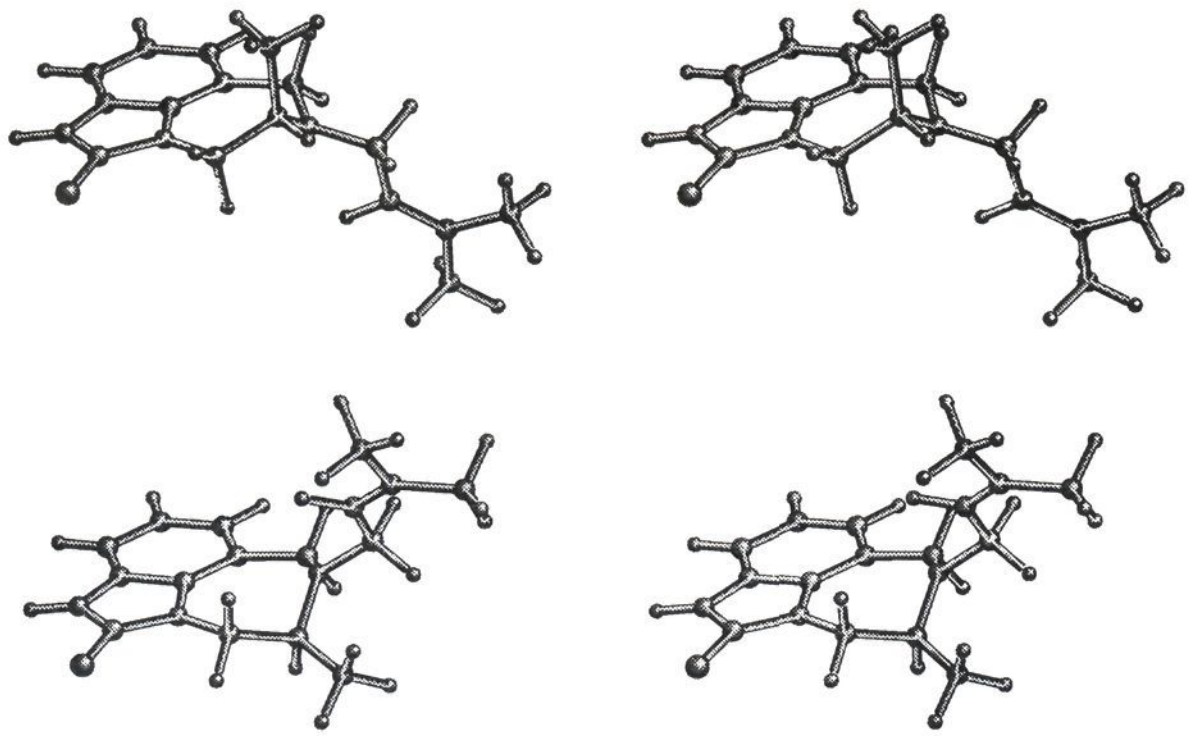


Figure 3. The two energetically lowest conformations of TIBO (**1**) calculated by MNDO. A different graphical representation has been used in order to distinguish calculational from experimental results. Top: conformation employed in the construction of the model.

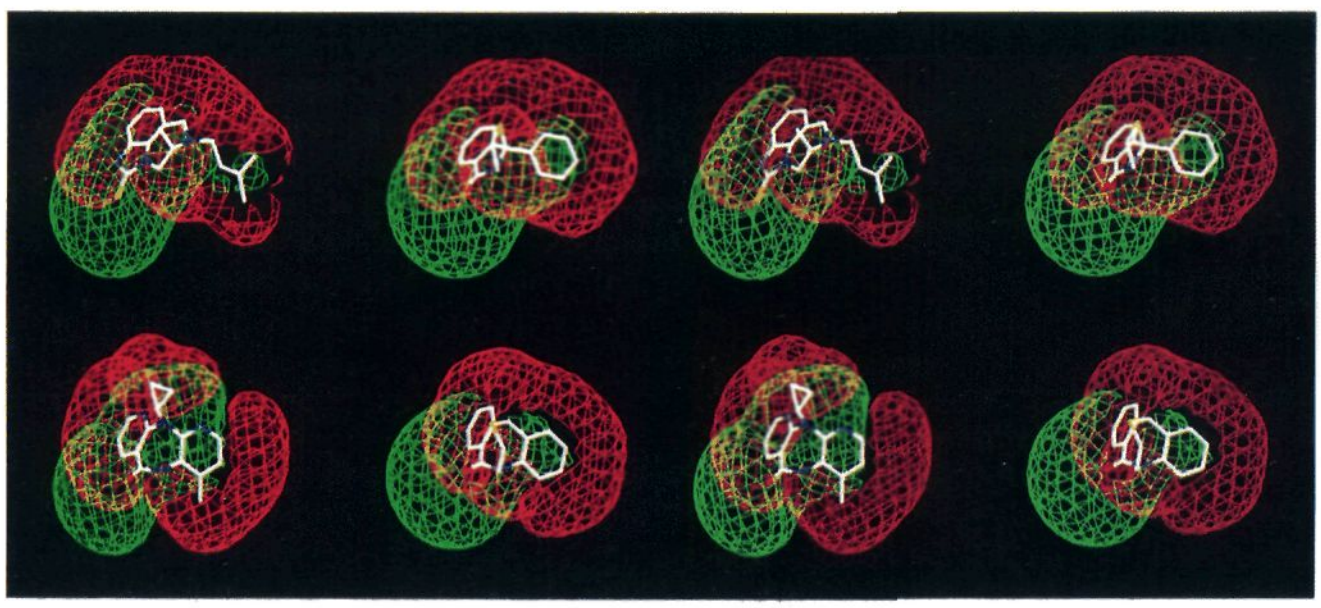


Figure 4. Electrostatic isopotential maps derived from a point charge model using MNDO charges: −5 kcal/mol green, +5 kcal/mol red. Hydrogen atoms omitted for clarity. Top left, **1**; top right, **3**; bottom left, **2**; bottom right, **7**.

compounds that should not exhibit conformational degrees of freedom. Therefore the Fine Chemicals Directory[10] of commercially available compounds was searched.

In a first step, the database was accessed by the substructure search feature of MACCS.[10] The candidates found by this method were subsequently subjected to geometry optimization by MNDO[6] and SYBYL[11] and compared with the model. Finally one single compound (**4**) out of 73 000 could be located that matches all requirements of the model in Figure 6 except the methyl group.[12] The two enantiomers of this compound were separated by chromatography and tested. As expected,

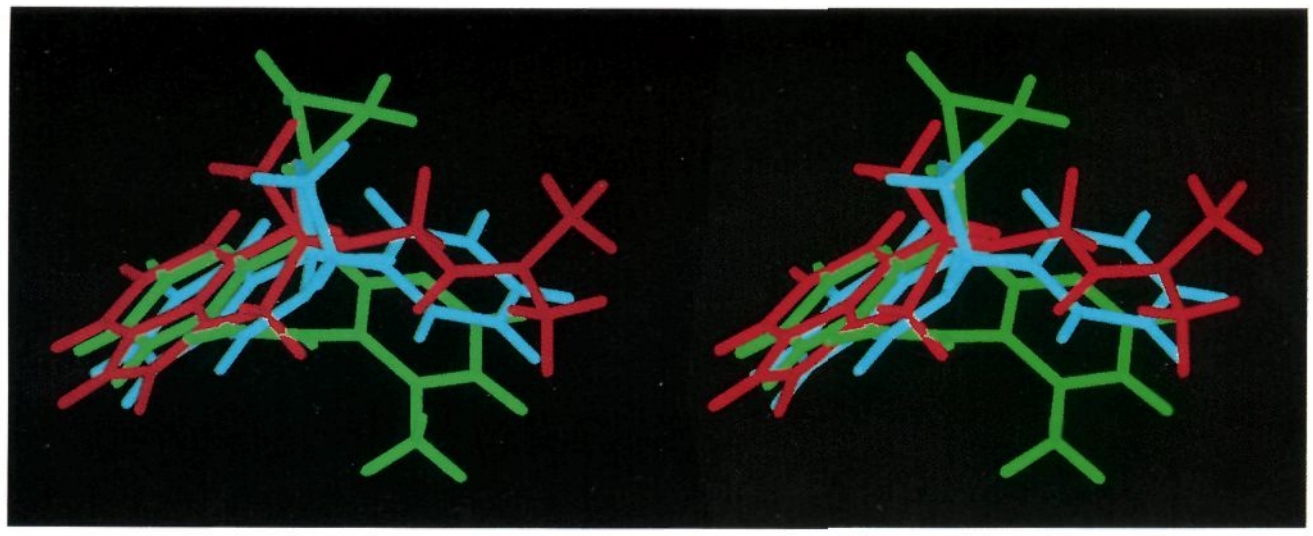


Figure 5. Superimposition of the MNDO structures of **1** (red), **3** (blue), and **2** (green) as derived from Figure 4.

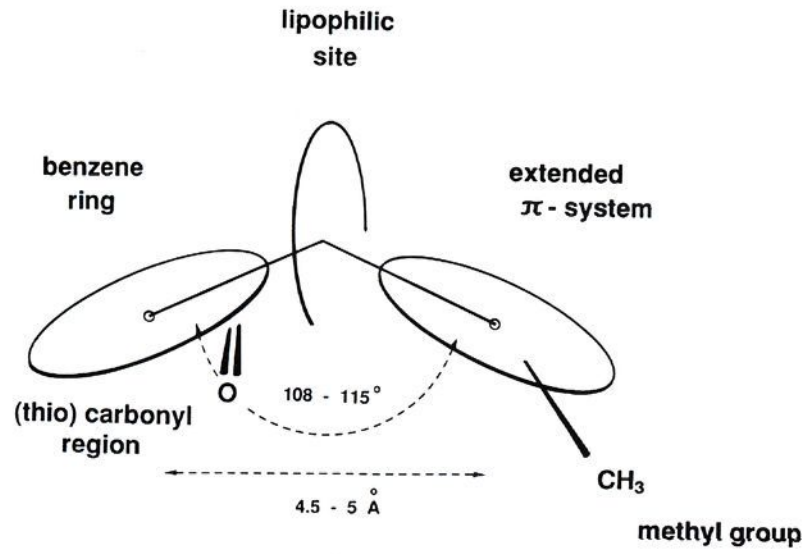
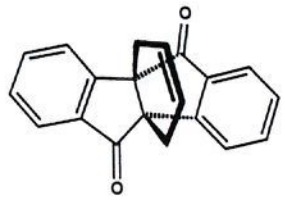


Figure 6. The common three-dimensional model derived from the comparison of **1**, **2**, and **3** (see text).



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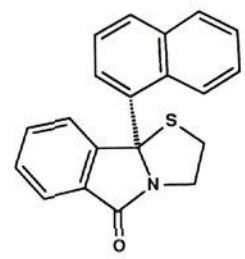
one enantiomer showed in vitro RT inhibition activity (see Table I), the other was inactive (IC_{50} > 100 μM). Although the activity is lower than that of **1**, **2**, and **3**, we can assume that our model is reasonable. In analogy to the other compounds we tried to determine the absolute configuration by X-ray crystallography. Unfortunately, several experiments lead only to structures with poor resolution.[13] Thus the configuration of the biologically active enantiomer cannot be determined by this method, although we assume the configuration given in Figure 7. A superimposition of compounds **3** and **4** is given in Figure 8.

Two consequences for the optimization of **3** follow immediately from the comparison:

1. Compounds **3** and **4** are quite unflexible molecules. If we superimpose the left aromatic systems as well as the carbonyl groups, the thiazolidine ring of **3** and the butene-bridge of **4** occupy the same region denoted as "lipophilic site" in the model (Figure 6). In this case the right benzene moieties of both molecules cannot be superimposed. If we assume that both compounds bind to the same receptor, we have to conclude that the two different orientations of the right benzene group are equally accepted. Thus it is reasonable to design a compound that contains both possible orientations at the same time. Therefore we decided to synthesize the naphthalene derivative **5**, a compound which is directly suggested by inspection of Figure 8.

2. Since compound **4** does not contain the methyl group indicated in the model, the *m*-methyl derivative of **3** should be synthesized and tested as well (compound **6**).



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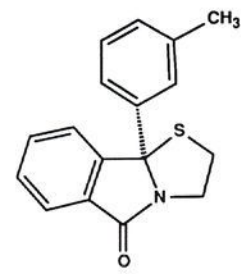

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Although the position of the methyl group (ortho or meta) cannot be deduced from Figure 5 with certainty, preference for the meta substitution is suggested by the side chain of **1** (see Figure 3, top).[14]

Optimization of 3. The results of the in vitro RT test of the aforementioned compounds are included in Table I. In the case of the naphthyl derivative **5** the activity is increased by a factor of 2, in the case of the *m*-methyl compound **6** by a factor of 10 as compared to the lead compound **3**.

Since the orientations of the 3′-methyl group in **6** and the naphthalene system in **5** are not clear, we performed MNDO calculations and X-ray analyses of both compounds. The torsion barriers obtained by the same procedure as in the case of **3** (see above) are included in Figure 1. As can be seen from the figure, the positions of the minima are the same as in **3**. There is no preference for one of the two possible conformations. The X-ray analysis of **6** yields a structure with the methyl group syn to the amide bond (see Figure 9), whereas in the naphthalene compound the second benzene ring is located anti to the nitrogen (see Figure 10). Thus the active conformations of both molecules remain unclear, although, considering the model and the comparisons discussed above, we assume a syn conformation for both molecules.

Design of a New RT Inhibitor. Apart from the optimization of the lead compound **3** by variation of substituents, we have tried to design molecules that fit into the model discussed above but belong to different chemical classes and might serve as new leads.

Structures and potential distributions of various molecules were calculated and compared to the model. Finally a structure was found that fits both the electronic as well

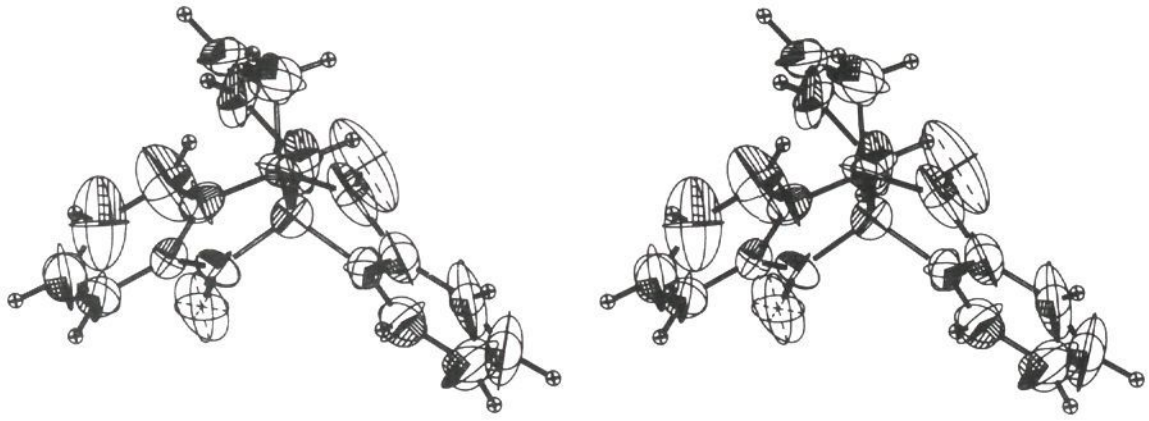


Figure 7. X-ray structure of **4**.

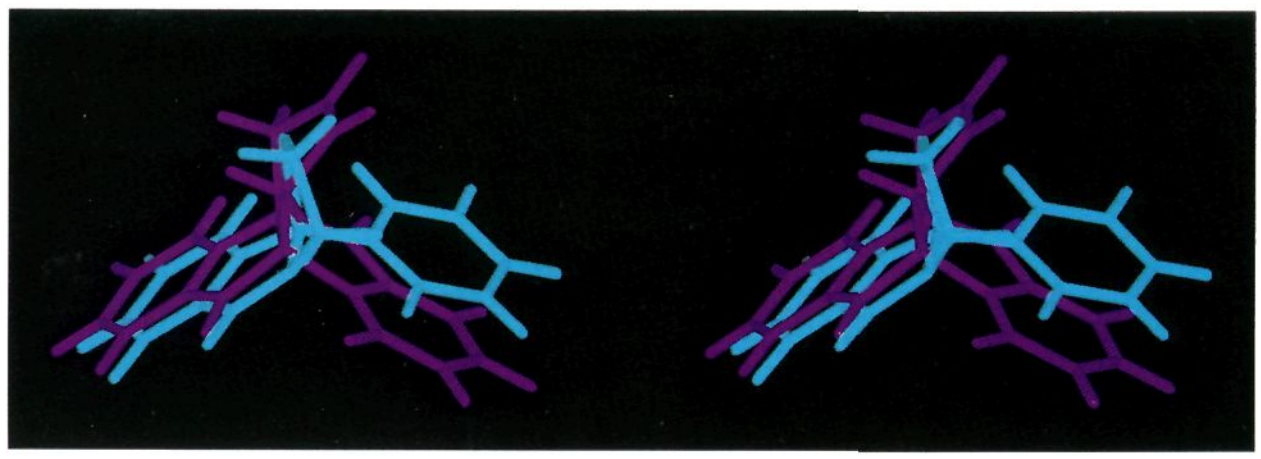


Figure 8. Superimposition of the MNDO structures of **3** (blue) and **4** (magenta).

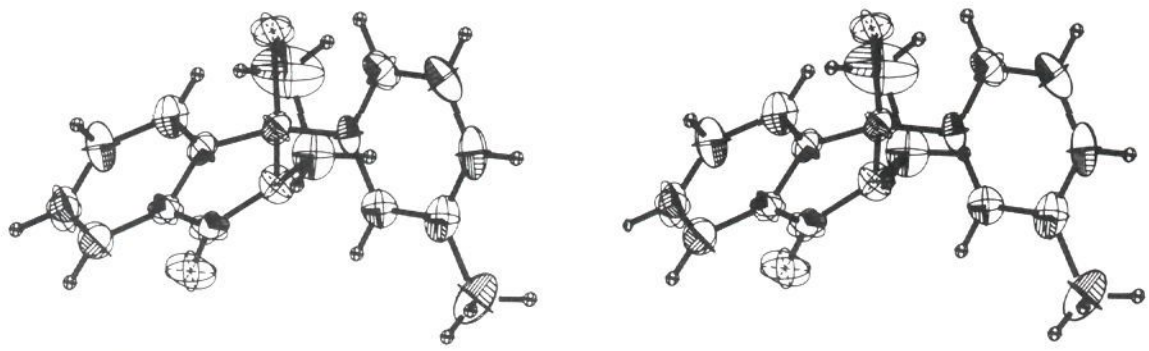


Figure 9. X-ray structure of (*R*)-**6** (active enantiomer).

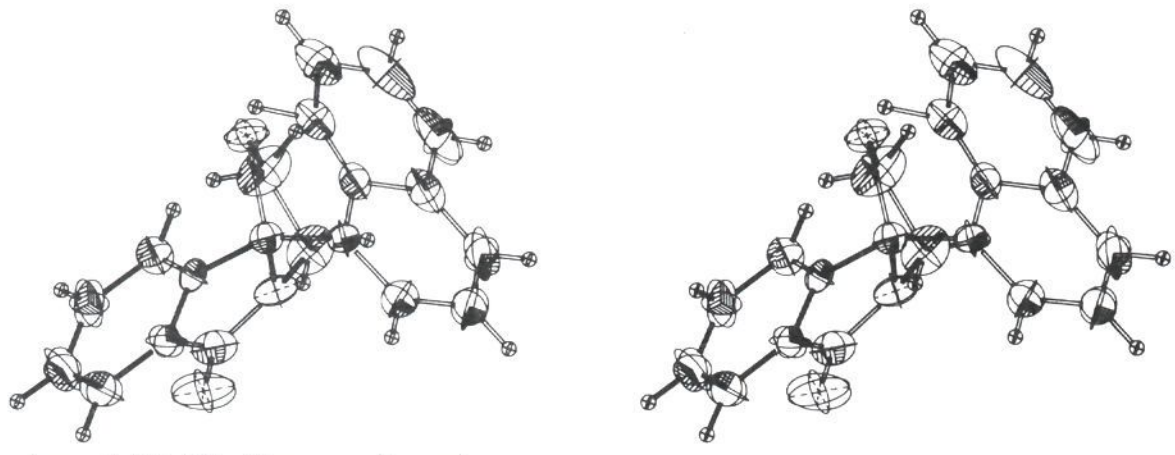
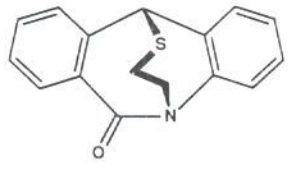


Figure 10. X-ray structure of (*R*)-**5** (active enantiomer).

as the geometrical requirements. Therefore **7** was proposed for synthesis.



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As in the case of the comparison of **1**, **2**, and **3**, there seem to be only few relations between the compounds **3** and **7** as long as only the two-dimensional structures are considered. In a three-dimensional superimposition however, the structures are almost identical (Figure 11).

To further compare this compound with the other molecules, the charges obtained from a MNDO calculation of **7** were used to derive a point charge based electrostatic potential distribution. Comparison of the isopotential surfaces (Figure 4) indicates a strong similarity of **7** to the other compounds. The compound was synthesized, and the enantiomers were separated and tested in the RT assay. As can be seen in Table I, the inhibitory activity of this compound is indeed equivalent to the activities of compounds **1**, **2**, and **3** from which the model was derived.

The structure of **7**, including its absolute configuration, was determined by X-ray crystallography (see Figure 12). We would like to emphasize that **7** was deduced solely by theoretical methods. It is therefore an impressive example

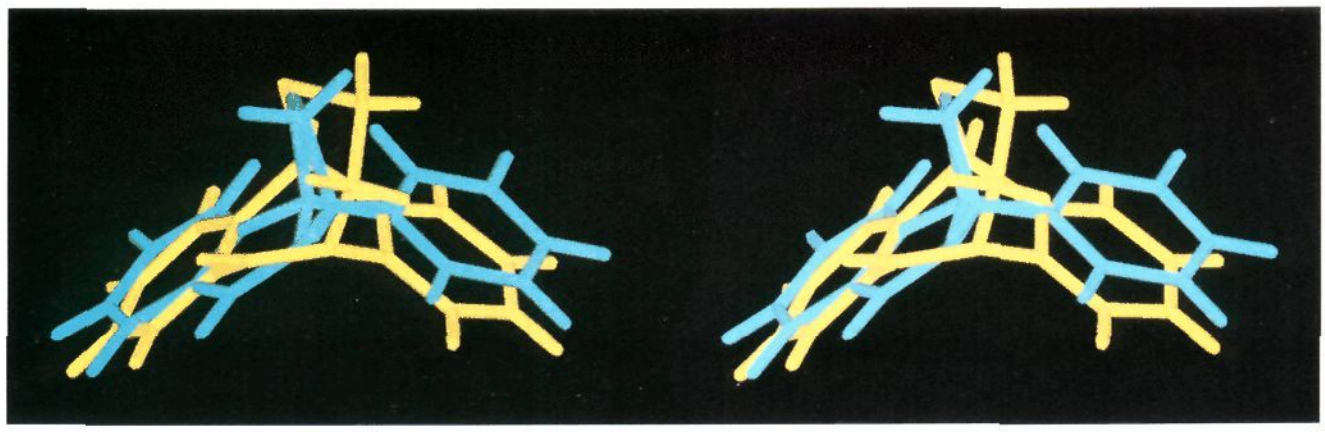

Figure 11. Superimposition of the MNDO structures of **3** (blue) and **7** (yellow).

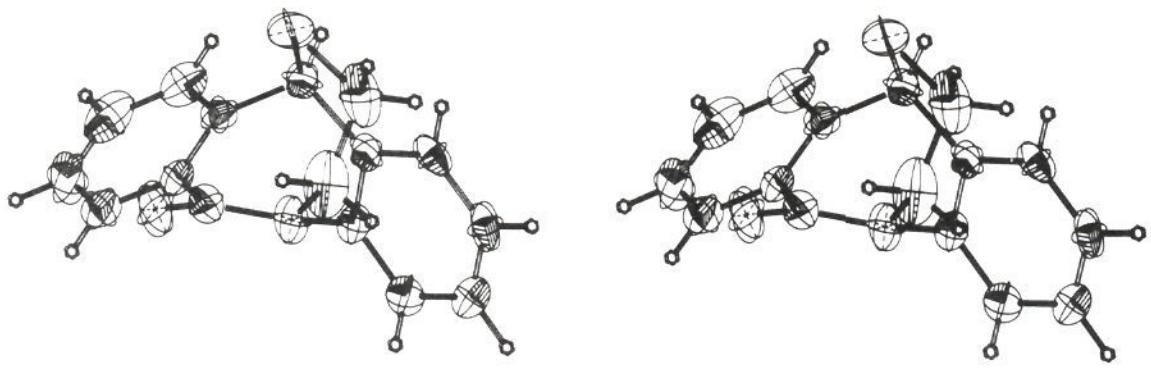

Figure 12. X-ray structure of (*R*)-**7** (active enantiomer).

Table II. Crystal Data and Data Collection Parameters for Compounds **3**–**7**

	3	**4**	**5**	**6**	**7**
mol formula	$(C_{16}H_{13}NOS)_2$	$C_{20}H_{14}O_2$	$C_{20}H_{15}NOS$	$C_{17}H_{15}NOS$	$C_{16}H_{13}NOS$
mol weight	267.35 × 2	286.33	317.41	281.38	267.35
crystal system	monoclinic	rhombic	monoclinic	monoclinic	rhombic
space group	$P2_1$-C_2^2 (no. 4)	$P2_12_12_1$-D_2^4 (no. 19)	$P2_1/c$-C_{2h}^5 (no. 14)	$P2_1/c$-C_{2h}^5 (no. 14)	$P2_12_12_1$-D_2^4 (no. 19)
cell dimensions					
a, Å	8.768 (2)	9.960 (5)	8.175 (6)	8.367 (3)	7.250 (3)
b, Å	10.627 (2)	11.077 (6)	22.46 (2)	13.771 (4)	9.511 (3)
c, Å	15.055 (2)	13.542 (7)	8.540 (6)	12.922 (2)	18.844 (9)
β, deg	103.24 (1)		99.49 (6)	107.40 (2)	
v, Å^3	1365.5	1494.1	1546.6	1420.8	1299.4
Z	2	4	4	4	4
d_{calc}, g cm^{-3}	1.30	1.27	1.36	1.31	1.37
linear abs, μ, mm^{-1}	0.22	0.08	0.20	0.21	0.23
F(000)	560	600	664	592	560
diffractometer	Syntex R3	Syntex R3	AED II	Syntex R3	Syntex R3
scan type	ω	ω	$\theta - \omega$	ω	ω
rflns measd (h_{min}:h_{max},k_{min}:k_{max},l_{min}:l_{max})	0:13,0:16,−23.:23	−13:13,0:14,0:17	−11:11,0:30,0:12	0:11,0:18,−17:17	0:10,0:13,0:26
2θ (from:to), deg	3:63	3:52.5	3:57.5	3:53	3:57.5
no. of rflns measd	4955	3302	4144	3257	1971
absorp corr; range of transmiss (min:max)	empir, 8 rflns; 0.84:1.00	empir, 7 rflns; 0.97:1.00	empir, 6 rflns; 0.85:1.00	empir, 6 rflns; 0.93:1.00	empir, 7 rflns; 0.88:1.00
no. of uniq obsd data with $I > 2.5\ \sigma(I)$	4123	1237	2225	1995	1137
no. of parms (NV)	343	200	209	182	173
R(*F*)	0.059	0.076	0.042	0.063	0.045
$R_w(F)$	0.047	0.063	0.033	0.053	0.038
weighting scheme	$1/\sigma^2(F)$	$1/\sigma^2(F)$	$1/\sigma^2(F)$	$1/\sigma^2(F)$	$1/\sigma^2(F)$
goodness of fit	3.08	2.41	2.50	2.97	1.82
ρ residual, e Å^{-3} (min:max)	−0.30:0.36	−0.32:0.32	−0.23:0.28	−0.61:0.59	−0.25:0.21

for rational drug design even if the structure of the biological target is not known.

Discussion of a Different Model

Recently, Mui et al.[9] published a comparison of the X-ray structures of **2** and 9-chloro-TIBO.[8] The superimposition of the two molecules presented by the author is, however, completely different from our model. Their comparison is mainly based upon a match of the carbonyl and thiocarbonyl groups and the methyl substituents of both molecules and a superimposition of the cyclopropyl and the dimethylallyl groups. We have tried to include our inhibitors into this model. However it was not possible to derive a consistent picture that covers all compounds, especially if we use the knowledge of the absolute configurations. In addition, the structures of **2** ("enantiomer" as in Figure 5) and **7** are extremely similar, and a superimposition of these two compounds according to our proposition is straightforward. Therefore we prefer the three-dimensional model presented above. We cannot, of course, be certain about the validity of our model as long as high-resolution X-ray structures of RT cocrystallized with the inhibitors are not yet available.

Conclusions

In this paper we have shown that by comparison of geometric and electronic properties of drugs it is possible to develop molecules with improved biological activity even if the three-dimensional structure of the biological receptor is not known. Additionally, by use of rational drug design methods combined with experimental structure determinations totally new structures can be deduced.

Experimental Section

Chemical syntheses, separation of the enantiomers, design of the test system, and test of the biological activity will be described elsewhere.[4,5] In all cases the biologically inactive enantiomers were used for crystallization, and the active enantiomers were saved for further biological experiments.

Semiempirical calculations were performed using a MNDO version by Bischof and Friedrich[6b] on VAX 3100e and Silicon Graphics SGI 4D/310 VGX computers.

The color pictures and the isopotential maps were created with the molecular modeling software package SYBYL[11] which was also used to perform the force field calculations. The X-ray structures were displayed with program ORTEP.[15]

Crystallography. In all cases, Mo Kα radiation (λ = 0.710 73 Å) was used. Crystallographic calculations were performed using the SHELXTL PLUS program package[16] (January 1989 release) on a MICROVAX II computer. Empirical absorption corrections were carried out. The structures were solved by direct methods. Hydrogen atoms were located by option HFIX of the SHELXTL program. Crystallization conditions are given below; crystal data are collected in Table II. Fractional coordinates are available as supplementary material.

(*S*)-(−)-9b-Phenyl-2,3-dihydrothiazolo[2,3-*a*]isoindol-5-(9b*H*)-one (3): single crystals of dimensions 0.5 × 0.7 × 0.8 mm obtained from ethanol.

Dibenzo[*h*,*l*]tricyclo[4.3.3.0^{1,6}]dodec-3-ene-7,10-dione (4): single crystals of dimensions 0.15 × 0.4 × 0.6 mm obtained from tetrahydrofuran.

(*S*)-(−)-9b-(1-Naphthyl)-2,3-dihydrothiazolo[2,3-*a*]isoindol-5(9b*H*)-one (5): single crystals of dimensions 0.45 × 0.78 × 0.91 mm obtained from methanol.

(*S*)-(−)-9b-(3-Methylphenyl)-2,3-dihydrothiazolo[2,3-*a*]-isoindol-5(9b*H*)-one (6): single crystals of dimensions 0.1 × 0.8 × 0.8 mm obtained from ethanol.

(*S*)-(−)-5,6-Dihydro-11,5-thioethano-11*H*-dibenz[*b*,*e*]azepin-6-one (7): single crystals of dimensions 0.17 × 0.21 × 0.63 mm obtained from 2-propanol.

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Supplementary Material Available: Tables of the fractional coordinates of **3–7** (11 pages). Ordering information is given on any current masthead page.

References

(1) Abbreviations used in this paper: RT = reverse transcriptase, HIV = human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, MNDO = modified neglect of diatomic differential overlap.

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(7) If the three atoms bonded to the nitrogen atom are being used to define a plane, the distance between this plane and the nitrogen amounts to 0.3 Å.

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(10) Supplied by Molecular Design Ltd., San Leandro, CA. The model presented in Figure 6 could, in principle, be an example for the use of three-dimensional databases in drug design. Since we do not yet have access to 3D databases we had to do very unspecific substructure searches as a first step. The large majority of hits had to be sorted out by hand.

(11) Tripos Associates Inc., St. Louis, MO.

(12) Compound **4** is available from Aldrich Chemical Comp., Inc.

(13) Determination of the absolute configuration of an organic compound consisting only of C, H, and O (all other molecules reported here contain sulfur) is difficult because of the small differences of the real and imaginary part of the dispersion corrections of C and O with Mo Kα radiation (Table 2.3.1. in *International Tables for Xray Crystallography*, Vol. IV, Birmingham, 1974). Additionally only a few, weak reflections could be measured (see Table II).

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