Perspective

From 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*](1,4)benzodiazepin-2(1*H*)-one (TIBO) to Etravirine (TMC125): Fifteen Years of Research on Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase†

Bart L. De Corte‡

Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, Welsh and McKean Roads, Spring House, Pennsylvania 19477-0776

Received July 7, 2004

Introduction

Dr. Paul Janssen was very passionate about the discovery and development of new drugs in many disease areas. Under his leadership, numerous breakthrough drugs in analgesia, anesthesia, psychiatry, fungal infections, gastrointestinal disorders, and anthelmintic remedies were discovered, developed, and introduced into the market place, and his contributions have been recognized around the world. In the past 17 years of his life, Dr. Paul (as he was affectionally called) focused on the search for better treatments for patients with acquired immune deficiency syndrome (AIDS). Beginning in 1987, Dr. Paul and his collaborators pioneered the field of non-nucleoside inhibitors of HIV reverse transcriptase (NNRTIs) with the discovery of the 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*](1,4)-benzodiazepin-2(1*H*)-one (TIBO) series. The original lead compounds emanated from an antiviral screening approach without knowledge of the molecular target(s) involved. However, with the first potent anti-HIV agents of this type in hand, the mechanism of action was elucidated and a new anti-HIV therapeutic approach was born.[1] This Perspective discusses the history of anti-HIV research up to the discovery of etravirine (TMC125) at Janssen Pharmaceutica, the Janssen Research Foundation, the Center for Molecular Design (Vosselaar, Belgium), the Rega Institute for Medical Research (Leuven, Belgium), Tibotec (Mechelen, Belgium), and the Center for Advanced Biotechnology and Medicine (Rutgers University, NJ).

Discovery of the TIBO Series: The First Anti-HIV NNRTIs

In the early 1980s, strong evidence developed for the causative agent of AIDS being an immunologically destructive retrovirus called HIV.[2] Since this virus depends on RNA to convey its genetic signature, reverse transcriptase is a critical enzyme for its replication. Hence, nucleoside analogues that were known to inhibit reverse transcriptase from other viruses soon appeared as therapeutic agents for the treatment of HIV.[2−7] Dideoxynucleosides proved to be especially effective in inhibiting HIV-1 replication and in preventing the associated destruction of infected T cells.[8−11] In 1987, zidovudine (3′-azido-2′,3′-dideoxythymidine; AZT) was approved by the Food and Drug Administration (FDA) for treating AIDS patients in the U.S.

When Janssen Pharmaceutica entered the area of HIV research in 1987, the understanding of the replication cycle of the HIV virus was very limited and the molecular targets that are known today to be central to HIV replication had not been identified. By use of a pragmatic approach, 600 molecules were selected from the Janssen compound collection for screening in the virology laboratories of Prof. Eric De Clercq and Dr. Rudi Pauwels at the Rega Institute at the Catholic University of Leuven.[12] These selected compounds fulfilled two criteria: (1) they covered a wide range of chemical diversity and (2) they did not show significant biological activity in a battery of unrelated pharmacological assays. The compounds were tested for their ability to protect MT-4 cells infected with HIV. This strategy, which obviated the lack of knowledge about the biology of HIV and was unbiased toward specific molecular targets, led to the discovery of R14458 (**1**), a TIBO derivative (Figure 1).[1] Although the potency of **1** was rather weak, with an EC_{50} of 62 μM, the activity was specific, as determined by a cytotoxicity screen. The enantiomers of **1** were prepared via a stereoselective synthesis,[13] and it was established that the anti-HIV activity resided almost exclusively in the (+)-(*S*) isomer.

Since the biological target was unknown, the lead optimization program was conducted by a conventional medicinal chemistry approach under the direction of Dr. Michael Kukla. This effort led to a much more potent compound against HIV-1, R82913 (**2**).[1] Mechanistic studies established that the potent TIBO compounds did not mask the CD4/HIV receptor on MT-4 cells, and effects on binding of HIV-1 to MT-4 cells were also excluded. By use of detergent-disrupted virus particles, it was found that the TIBO compounds markedly inhibited poly(rA)·oligo$(dT)_{12-18}$-directed reverse transcriptase (RT) activity. At that point, the TIBO compounds became the first NNRTIs with specific inhibition of HIV-1 replication. From further structure−activity relationship (SAR) studies, R86183 (**3**), a compound

† This paper is dedicated to the memory of Dr. Paul A. J. Janssen.

‡ Contact information. Phone: 215-628-5513. Fax: 215-628-3297. E-mail: bdecorte@prdus.jnj.com.

10.1021/jm040127p CCC: $30.25
Published on Web 02/08/2005

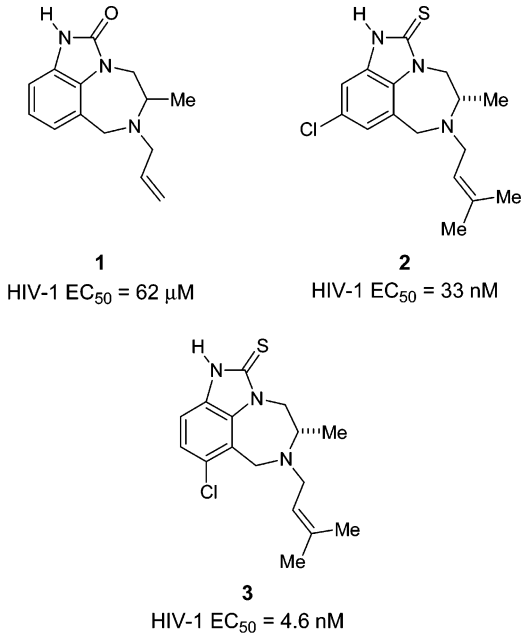


Figure 1. Prototype TIBO compounds and their inhibition of HIV-1 replication in HIV-infected MT-4 cells.

whose activity equals that of AZT,[13−19] was discovered and ultimately selected for clinical evaluation.

Non-Nucleoside Reverse Transcriptase Inhibitors

Not surprisingly, the disclosure of the TIBO compounds inspired the search for more potent and selective RT inhibitors in many industrial and academic institutions. More than 30 structurally different classes of NNRTIs have now been identified.[20−22] Three chemical entities from such series, nevirapine, delavirdine, and efavirenz, have been approved by the FDA for clinical use, while a number of other compounds are in preclinical or clinical development (Figure 2). Emivirine (MKC-442) is the clinically most advanced representative of the pyrimidinedione class.[23] Thiocarboxanilide UC-781 has been identified as a (retro)virucidal agent capable of reducing the infectivity of HIV-1 virions.[24,25] DPC 083, a close analogue of efavirenz, has proven to reduce the viral load in patients who harbor NNRTI-resistant mutants.[26,27] Capravirine is also distinguished by its activity against such mutant HIV strains.[28] Capravirine is undergoing advanced clinical trials and has proven to be effective in both NNRTI-naive and NNRTI-experienced patients.[29]

The desire to understand the binding mode of the TIBO compounds with the RT enzyme led Dr. Paul to initiate a collaboration with Prof. Eddy Arnold of the Center for Advanced Biotechnology and Medicine at Rutgers University in Piscataway, NJ. The X-ray crystal structure of HIV-1 RT complexed with **3** was solved at 3.0 Å resolution, and the binding mode was found to be strikingly similar to that previously reported for the complex of nevirapine and HIV-1 RT.[30−32] Each compound binds in a hydrophobic pocket close to, but distinct from, the substrate binding site, and each compound adopts a butterfly-like shape (Figure 3). In the case of the TIBO compounds, the dimethylallyl substituent interacts with the side chains of Tyr181, Tyr188, and Trp229, and the chlorophenyl group interacts with Leu100, Lys101, and Tyr318. Nevirapine is positioned in the allosteric binding pocket in much the same way; the 4-methylpyridyl fits into the western part of the pocket, and the unsubstituted pyridyl group occupies the eastern part.[33,34] The thiourea NH group of TIBO forms a critical hydrogen bond with the main-chain carbonyl oxygen atom of Lys101. The latter arrangement is in contrast to that of nevirapine, where no hydrogen bonds occur between the ligand and the HIV-1 RT protein.[35]

A Second Lead Series: The α-Anilinophenylacetamides (α-APAs)

While the TIBO compounds were being evaluated clinically, high-throughput, cell-based screening systems were installed at the Rega Institute.[36] This setup allowed for a more extensive evaluation of the Janssen compound library and led to the identification of a second class of HIV-1 RT inhibitors. As for the TIBO series, the lead compound here, R15345 (**4**), was originally synthesized in an unrelated medicinal chemistry project (Figure 4). This α-anilinophenylacetamide (α-APA) exhibits an EC_{50} against HIV-1 of 610 nM.[37] The simplicity of its structure and the relative ease of its

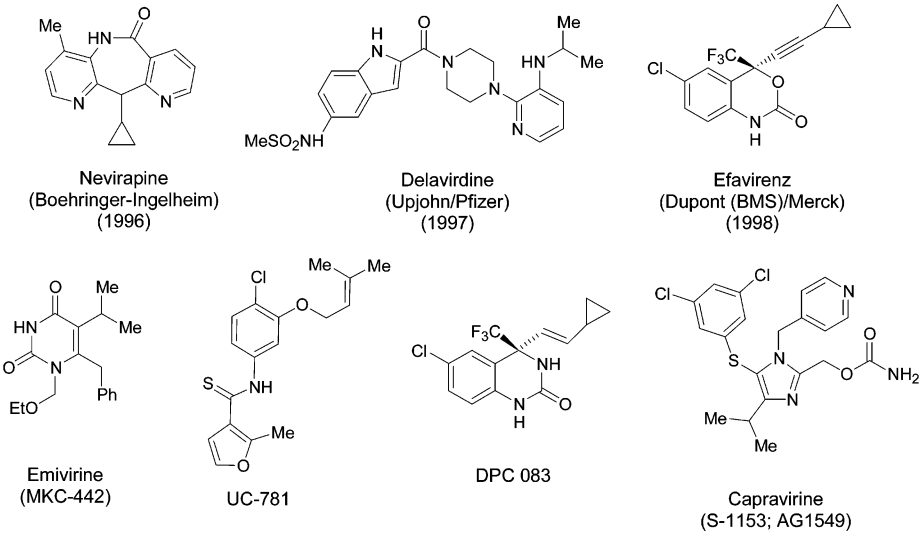


Figure 2. Chemical structures of marketed NNRTIs and selected NNRTIs under clinical development.

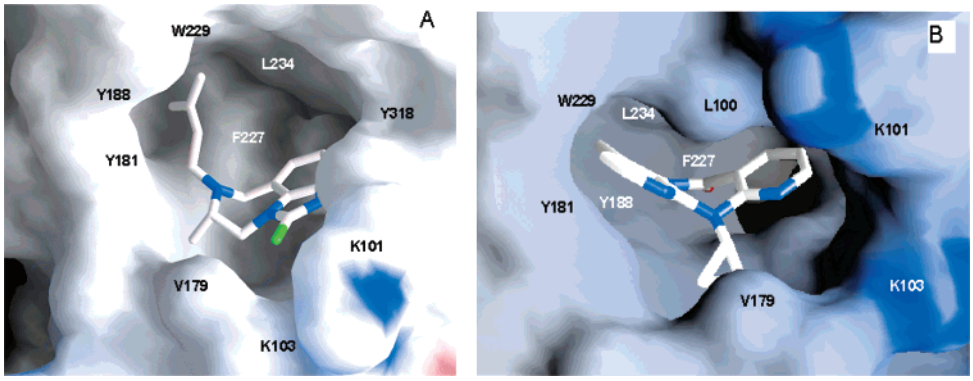


Figure 3. Molecular surface diagram showing the structure of the non-nucleoside inhibitor binding pocket and the interactions with (A) **3** and (B) nevirapine.[30]

4 HIV-1 EC_{50} = 610 nM

5 HIV-1 EC_{50} = 13 nM

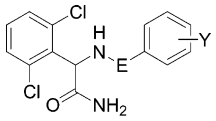
Figure 4. Prototype α-APA compounds and their inhibition of HIV-1 replication.

synthesis made the α-APA series attractive for lead optimization. This effort resulted in loviride (**5**; R89439), a compound with an EC_{50} of 13 nM, which became a clinical candidate (Figure 4). X-ray analysis of a cocrystal of loviride analogue R95845 (**6**) with HIV-RT revealed that the 4-methylacetophenone group occupies the western section of the binding pocket, whereas the 2,6-dihalophenyl substituent is positioned in the eastern section (Figure 5).[38] However, the development of loviride was abandoned when it became apparent that it did not offer a sufficient advantage over nevirapine and delavirdine, the two NNRTIs approved for clinical use at that time.[39−42]

From α-APAs to Imidoyl Thioureas (ITUs)

As SAR studies continued with the α-APA series, an unexpected observation was made. In general, increasing the spacer length between the two aryl groups in loviride resulted in a considerable decrease in activity. However, there was one exception with R93514 (**7h**), which did not fit this trend; in fact, **7h** was surprisingly active compared to all other analogues tested (Table 1).

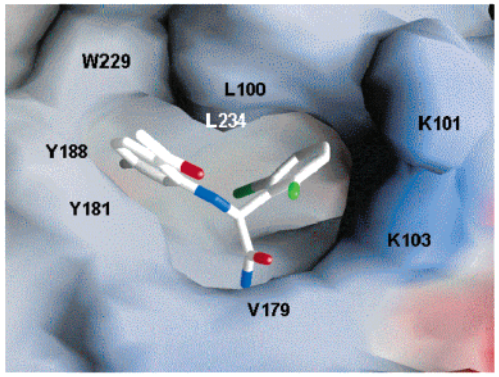
Table 1. Activity of Selected α-Aminophenylacetamides vs HIV-1

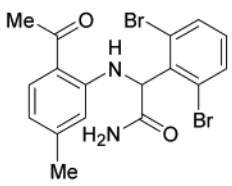


compd	E	Y	EC_{50} (μM)
7a		*o*-NO_2	0.1
7b		*o*-Cl	0.4
7c		*p*-Cl	>50
7d	CH_2	*o*-NO_2	>50
7e	CO	*o*-NO_2	>50
7f	CONH	*o*-NO_2	>50
7g	CSNH	*o*-Cl	>50
7h	CSNH	*p*-Cl	0.16

Further investigation of this anomaly led to a series of imidoyl thioureas (ITUs).[43] With proper choice of the substitution pattern on both aryl groups (e.g., R100943, **8a**, Figure 7), these ITUs were potent inhibitors of the wild-type HIV-1. The activity of **8a** was cause for excitement because its activity profile against a number of clinically relevant single mutants compared quite favorably to the profiles of nevirapine, delavirdine, and loviride (Table 2).

The X-ray crystal structure of HIV-1 RT complexed with **8a** explained the apparent anomaly observed with the ITU compounds and revealed that the aryl wings of such compounds were switched compared with compounds in the loviride series (Figure 6).[44] The RT-bound conformation of **8a** resembles a "U" or horseshoe shape in contrast to the butterfly-like shape of **3**, **5**, or nevirapine. Interestingly, the 2,6-dichlorophenyl sub-





6

Figure 5. Molecular surface diagram showing the structure of the non-nucleoside inhibitor binding pocket and the interactions with loviride analogue **6**.[38]

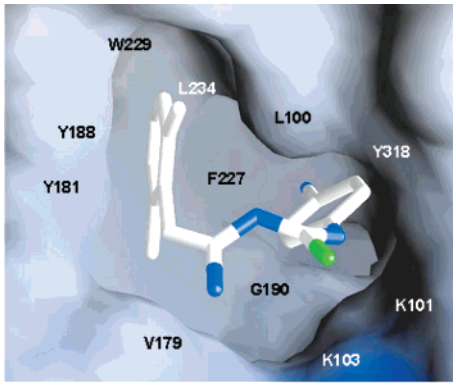
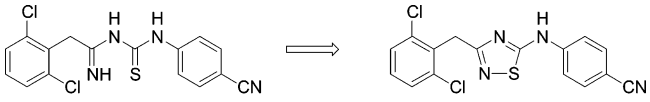


Figure 6. Molecular surface diagram showing the structure of the non-nucleoside inhibitor binding pocket and the interactions with **8a**.[44]



8a **9**

Figure 7. Structures of **8a** and metabolite **9**.

Table 2. Activity (EC_{50}, μM) of Nevirapine, Delavirdine, Loviride (**5**), **8a**, and **10** vs HIV-1 and Selected Single Mutants[a]

compd	LAI	L100I	K103N	Y181C	Y188L
nevirapine	0.032	0.32	6.3	10	>100
delavirdine	0.063	2.5	2.5	2.0	1.3
5	0.013	0.05	1.3	16	50
8a	0.003	0.51	0.59	0.51	0.32
10	0.006	0.40	0.04	0.20	0.32

[a] The LAI strain is the wild-type HIV-1. Other infecting viral strains with mutations in the RT enzyme are characterized according to the mutated amino acid position (one-letter codes). The first amino acid is present in the wild-type HIV-1. The second amino acid is present in the mutated strain. For example, Y181C refers to replacement of the tyrosine at position 181 with cysteine.

stituent now resides in the western section of the binding pocket, and the 4-cyanophenyl group resides in the eastern section. In fact, the 4-cyanophenyl group proved to be the optimal eastern-section substituent and was kept constant in the succeeding generations. The in vitro activity profile of **8a** justified consideration of it for clinical development. Unfortunately, oxidative ring closure of the imidoyl thiourea functionality proved to be a major liability. The product of oxidative cyclization, thiadiazole **9**, was inactive (EC_{50} > 1 μM vs HIV-1; Figure 7).

The Diaryltriazine (DATA) Series

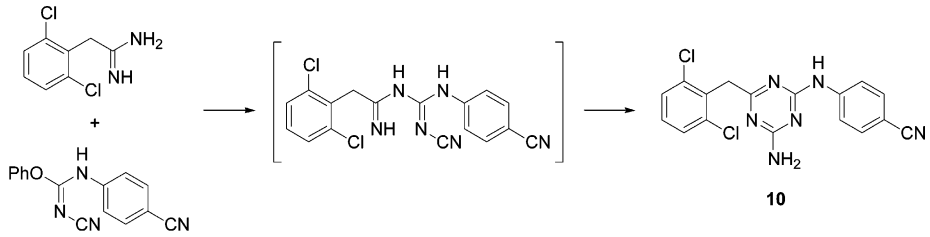
Soon after the NNRTIs were being used in clinical settings, it became apparent that this class of RT inhibitors is vulnerable to HIV's high mutation rate, which results in a rapid selection of resistant strains.[45] Mutations in the NNRTI binding pocket render the inhibitors inactive without affecting adversely the catalytic competency of the RT enzyme. In response to this clinical reality, Dr. Paul relied on a key collaboration with Dr. Rudy Pauwels at Tibotec. Tibotec had an expanded viral panel available that included all clinically relevant mutants, and it was appreciated that any future NNRTI drug would need to tackle most, if not all, of the clinically relevant mutants.

To improve the metabolic properties of **8a** and protect against the unproductive ring closure, an attempt was made to synthesize the cyanoguanidine isostere as outlined in Scheme 1.[46] Unexpectedly, the intended cyanoguanidine was never isolated; it presumably was an intermediate that spontaneously cyclized to form diaryltriazine (DATA) **10**.[47] It was surprising that **10** was equally potent to **8a** given that thiadiazole **9** was inactive (Table 2). A possible explanation may be that the presence of the triazine reduces a number of potentially redundant torsional degrees of freedom.[44] This entropically favorable restriction of flexibility may explain why the DATA analogues are, in general, more potent than their precursors against both wild-type and NNRTI-resistant HIV-1 mutants (vide infra).

When **10** was identified, Dr. Paul had formally retired from Janssen Pharmaceutica. Now fully convinced of the power of computer-aided drug design, he worked to establish and lead the newly formed Center for Molecular Design (CMD). At the CMD, Dr. Paul, Dr. Paul Lewi, and collaborators employed a variety of computational modeling tools to help advance the NNRTI project. Around this time, efavirenz reached the market place, and this drug was considered to be a second-generation NNRTI. The activity of efavirenz against a number of clinically relevant single mutants made it the new "gold standard" in the field. An important challenge now was to equal or improve on the profile of efavirenz. The single greatest weakness facing efavirenz was its lack of efficacy against the K103N mutant.

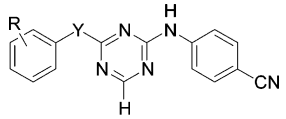
Synthetic work in the Janssen Research Foundation (JRF) initially focused on exploring the substituents on the triazine core of **10**, and it became apparent that the 2,6-dichlorobenzyl group could easily be replaced by 2,6-disubstituted or 2,4,6-trisubstituted anilines, phenols, or thiophenols. At the same time, molecular modeling and X-ray crystallography studies suggested that the primary amino group in **10** is probably not interacting with the RT enzyme. This prediction was confirmed when the disubstituted triazines proved to be very potent inhibitors of HIV-1 and several clinically important single mutant strains. Compounds **11a**–**c** inhibited both wild-type HIV-1 and the clinically important L100I, K103N, Y181C, and Y188L single mutants with low nanomolar potency (Table 3). However, excitement surrounding these disubstituted triazines was some-

Scheme 1. Synthesis of **10**



10

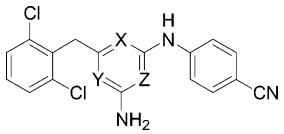
Table 3. Activity (EC_{50}, μM) of Selected Disubstituted Triazines **11** vs HIV-1 and Selected Single and Double Mutants[a]



compd	R	Y	LAI	L100I	K103N	Y181C	Y188L	L100I + K103N	K103N + Y181C
11a	2,4,6-tri-Me	NH	0.0003	0.013	0.003	0.008	0.04	1.3	0.05
11b	2,4,6-tri-Me	O	0.0006	0.020	0.003	0.02	0.063	2.5	0.13
11c	2,6-di-Me-4-CN	NH	0.001	0.25	0.008	0.05	0.05	>10	nd

[a] The LAI strain is the wild-type HIV-1. Other infecting viral strains with mutations in the RT enzyme are characterized according to the mutated amino acid position (one-letter codes). The first amino acid is present in the wild-type HIV-1. The second amino acid is present in the mutated strain. For example, Y181C refers to replacement of the tyrosine at position 181 with cysteine. nd = not determined.

Table 4. Activity (EC_{50}, μM) of Isomeric Pyrimidines **12** vs HIV-1 and Selected Single Mutants[a]



compd	X	Y	Z	LAI	L100I	K103N	Y181C	Y188L
12a	N	CH	N	0.001	0.30	0.012	0.18	0.071
12b	CH	N	N	0.010	>10	>10	>10	>10
12c	N	N	CH	0.45	>10	>10	>10	>10

[a] The LAI strain is the wild-type HIV-1. Other infecting viral strains with mutations in the RT enzyme are characterized according to the mutated amino acid position (one-letter codes). The first amino acid is present in the wild-type HIV-1. The second amino acid is present in the mutated strain. For example, Y181C refers to replacement of the tyrosine at position 181 with cysteine.

what tempered by the appearance of double mutants of the HIV-1 virus in clinical settings around that time. The prevalent L100I + K103N and K103N + Y181C double mutants were not appreciably affected by these disubstituted triazines.

The Diarylpyrimidines (DAPYs): Discovery of Etravirine

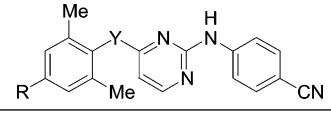
Three isomeric pyrimidines can be generated by replacing any one nitrogen atom in the triazine core of the DATA series with a carbon atom. All three regioisomers, **12a**−**c**, were prepared, but only **12a** possessed an anti-HIV activity comparable to that of **10** (Table 4).[48] Compound **12a** is the only isomer that fulfills two critical requirements for binding. First, it has two hydrogen bonds with Lys101: the NH group linking the pyrimidine and the 4-cyanophenyl group interacts with the main-chain carbonyl oxygen of Lys101, and the pyrimidine nitrogen serves as hydrogen acceptor to the Lys101 side chain amine. Second, it has a proper positioning of the two phenyl rings in the eastern and western hydrophobic binding pockets.

When the primary amino group was omitted from the pyrimidine nucleus, potency was maintained, supporting the observation made with the disubstituted triazines that the exocyclic NH_2 group is not intimately involved in binding. Compounds **13a**−**d** were very potent inhibitors of both HIV-1 and a number of clinically important single mutant strains. Although the activity of the 2,4-disubstituted pyrimidines against the K103N + Y181C double mutant was encouraging, the activity against the L100I + K103N double mutants was not significant (Table 5). Pyrimidine **13a** (TMC120, R147681) is currently being evaluated as a topical microbicide for the prevention of vaginal HIV transmission.[49,50]

Replacement of the triazine core in the DATAs with a pyrimidine also allowed for exploration of the impact of substitution at the 5-position of the pyrimidine ring. Introduction of a bromine atom in the 5-position of the pyrimidine proved to be the secret to obtaining potent inhibitors of the L100I + K103N and K103N + Y181C double mutants (Table 6). In particular, the activity of **14b** and **14c** against the very recalcitrant L100I + K103N double mutant was reason for excitement.

Finally, introduction of an amino group at the 6-position afforded etravirine (**15**, TMC125, R165335), a compound with low-nanomolar potency against wild-type HIV-1 and a large panel of clinically relevant HIV single and double mutants. Etravirine is a potent, next-generation NNRTI. The first-generation NNRTIs, nevirapine and delavirdine, owe their clinical utility largely to activity against the HIV-1 wild-type strain. The second-generation NNRTI efavirenz possesses a much-improved activity profile against wild-type HIV-1 and several clinically relevant HIV-1 mutants. Etravirine is extraordinary by virtue of its potency against

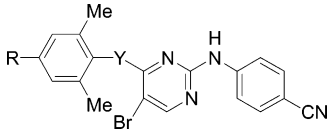
Table 5. Activity (EC_{50}, μM) of Selected 2,4-Disubstituted Pyrimidines **13** vs HIV-1 and Selected Single and Double Mutants[a]



compd	R	Y	LAI	L100I	K103N	Y181C	Y188L	L100I + K103N	K103N + Y181C
13a	Me	NH	0.001	0.018	0.004	0.008	0.048	>10	0.044
13b	Me	O	0.003	0.022	0.003	0.038	0.055	8.2	1.1
13c	CN	NH	0.0004	0.034	0.002	0.007	0.008	1.1	0.037
13d	CN	O	0.001	0.073	0.003	0.037	0.019	0.80	0.094

[a] The LAI strain is the wild-type HIV-1. Other infecting viral strains with mutations in the RT enzyme are characterized according to the mutated amino acid position (one-letter codes). The first amino acid is present in the wild-type HIV-1. The second amino acid is present in the mutated strain. For example, Y181C refers to replacement of the tyrosine at position 181 with cysteine.

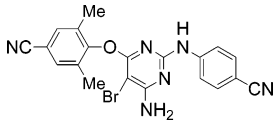
Table 6. Activity (EC_{50}, μM) of Selected 2,4,5-Trisubstituted Pyrimidines **14** vs HIV-1 and Selected Single and Double Mutants[a]



compd	R	Y	LAI	L100I	K103N	Y181C	Y188L	L100I + K103N	K103N + Y181C
14a	Me	NH	0.006	0.011	0.007	0.036	0.027	0.35	0.28
14b	CN	O	0.001	0.007	0.001	0.022	0.006	0.049	0.025
14c	CN	NH	0.0004	0.007	0.0004	0.010	0.003	0.037	0.032

[a] The LAI strain is the wild-type HIV-1. Other infecting viral strains with mutations in the RT enzyme are characterized according to the mutated amino acid position (one-letter codes). The first amino acid is present in the wild-type HIV-1. The second amino acid is present in the mutated strain. For example, Y181C refers to replacement of the tyrosine at position 181 with cysteine.

Table 7. Activity (EC_{50}, μM) of Marketed NNRTIs and **15** (Etravirine) vs HIV-1 and Selected Single and Double Mutants[a]

compd	LAI	L100I	K103N	Y181C	Y188L	L100I + K103N	K103N + Y181C
nevirapine	0.032	0.32	6.31	10	>10	nd[b]	>10
delavirdine	0.063	2.5	2.5	2.0	1.3	nd[b]	>10
efavirenz	0.001	0.04	0.04	0.002	0.16	>10	0.040
 **15** (etravirine)	0.001	0.003	0.001	0.007	0.005	0.019	0.004

[a] The LAI strain is the wild-type HIV-1. Other infecting viral strains with mutations in the RT enzyme are characterized according to the mutated amino acid position (one-letter codes). The first amino acid is present in the wild-type HIV-1. The second amino acid is present in the mutated strain. For example, Y181C refers to replacement of the tyrosine at position 181 with cysteine. [b] nd = not determined.

the single mutants K103N and Y181C and the double mutants K103N + Y181C and L100I + K103N (Table 7). In fact, etravirine retains meaningful activity (EC_{50} < 100 nM) against 97% of 1081 clinically derived recombinant viruses resistant to at least one of the currently marketed NNRTIs.[51]

The exceptional spectrum of activity of etravirine might be attributed to its ability to bind the RT enzyme in more than one conformationally distinct mode.[52−54] This hypothesis may explain why X-ray diffraction of the wild-type HIV-1 RT/etravirine crystals has only been obtained with poor resolution (6−8 Å). It is thought that the structures of etravirine and closely related DAPY compounds can adapt to changes in the NNRTI binding pockets. The torsional flexibility of the DAPY structure permits access to numerous conformational variants, and their compact structure permits repositioning and reorientation when mutations in the binding pocket are present.[44]

Preliminary clinical investigations have confirmed the therapeutic potential of etravirine.[55] Treatment of patients harboring NNRTI-resistant HIV-1 variants with etravirine (900 mg, b.i.d. for 7 days) results in a median decrease in the plasma HIV-1 RNA of −0.89 $\log_{10}$ units.[56] This observation challenges the existing belief that resistance to NNRTIs is a class phenomenon and that resistance to one particular NNRTI will result in resistance to all the members of this class of RT inhibitors. Thus, etravirine has the potential for use in individuals infected with NNRTI-resistant HIV-1.[57]

Beyond Etravirine. The Discovery of Rilpivirine (TMC278)

Drug discovery efforts have continued since the discovery of etravirine. The primary goal of further analogue work has been to improve the pharmacokinetic properties of etravirine while maintaining its activity profile against wild-type HIV-1 and clinically relevant HIV-1 mutants. This effort has led to the discovery of rilpivirine, a novel DAPY NNRTI with an exceptional activity profile and very desirable druglike properties. The discovery and attributes of rilpivirine are the subject of another manuscript.[58]

Conclusion

During the 17 years of HIV research, under the leadership of Dr. Paul Janssen, several new classes of NNRTIs were discovered. The TIBOs were the first inhibitors of the HIV-1 virus to be identified as belonging to the NNRTI class. Shortly thereafter, loviride, a representative of the α-APA family of NNRTIs, was discovered. SAR studies around the α-APAs produced the ITUs, a third class of promising NNRTIs. An effort to improve the metabolic stability of the ITUs led to the serendipitous discovery of **10**, the first DATA compound. Structural modification of the DATA compounds eventually provided **15** (etravirine), a prototypical DAPY compound that is highly potent and effective against wild-type and drug-resistant HIV-1 variants. Thus, etravirine has the potential for use in individuals infected with NNRTI-resistant HIV-1. A common thread throughout these notable achievements was Dr. Paul's scientific brilliance, creativity, and perseverance. To be sure, the memory of Dr. Paul will remain a constant inspiration for all of us.

Acknowledgment. The discovery of the TIBOs, α-APAs, DATAs, and DAPYs under the leadership of Dr. Paul Janssen was the result of a collaboration between scientists from many different backgrounds who shared a common goal of scientific excellence. Without their contributions, etravirine would never have been identified. Special thanks go to Eddy Arnold and Kalyan Das for providing the X-ray crystallography

pictures and to Bruce Maryanoff, Donald Ludovici, Robert Kavash, Henry Breslin, Paul Lewi, Eddy Arnold, Karen Manson, Marie-Pierre de Béthune, and Robert Galemmo, Jr. for helpful suggestions and critical review of this manuscript.

Biography

Bart L. De Corte is a native of Belgium. He completed his undergraduate education in the Department of Agricultural and Chemical Engineering at the State University of Gent, Belgium. After receiving a Diplome d'Etudes Approfondies at the Université de Rennes in France, he obtained his Ph.D. in 1992 under the guidance of Prof. John Welch at the University at Albany, State University of New York. He performed postdoctoral research in the laboratory of Prof. Tom Harris at the Center of Molecular Toxicology at Vanderbilt University in Nashville, TN. He joined Janssen Research Foundation and the Johnson & Johnson family of companies in 1993. He is currently a Principal Scientist at Johnson & Johnson Pharmaceutical Research & Development in Spring House, PA.

References

(1) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. Potent and selective inhibition of HIV-1 replication in vitro by a novel series of TIBO derivatives. *Nature* **1990**, *343*, 470−474.

(2) Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* **1983**, *220*.

(3) Mitsuya, H. Progress in antiviral therapy in AIDS: dideoxynucleosides and azidothymidine. *Med. Immunol.* **1987**, *14*, 297−305.

(4) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. 3′-Azido-3′-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096−7100.

(5) Mitsuya, H.; Broder, S. Strategies for antiviral therapy in AIDS. *Nature* **1987**, *325*, 773−778.

(6) Gallo, R. C.; Montagnier, L. AIDS in 1988. *Sci. Am.* **1988**, *259*, 41−48.

(7) Gallo, R. C.; Montagnier, L. The chronology of AIDS research. *Nature* **1987**, *326*, 435−436.

(8) Yarchoan, R.; Mitsuya, H.; Broder, S. AIDS therapies. *Sci. Am.* **1988**, *259*, 110−119.

(9) Yarchoan, R.; Berg, G.; Brouwers, P.; Fischl, M. A.; Spitzer, A. R.; Wichman, A.; Grafman, J.; Thomas, R. V.; Safai, B.; Brunetti, A. Response of human-immunodeficiency-virus-associated neurological disease to 3′-azido-3′-deoxythymidine. *Lancet* **1987**, *1* (8525), 132−135.

(10) Yarchoan, R.; Klecker, R. W.; Weinhold, K. J.; Markham, P. D.; Lyerly, H. K.; Durack, D. T.; Gelmann, E.; Lehrman, S. N.; Blum, R. M.; Barry, D. W. Administration of 3′-azido-3′-deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. *Lancet* **1986**, *1* (8481), 575−580.

(11) Sharma, P. L.; Nurpeisov, V.; Hernandez-Santiago, B.; Beltran, T.; Schinazi, R. F. Nucleoside Inhibitors of Human Immunodeficiency Virus Type 1 Reverse Transcriptase. *Curr. Top. Med. Chem.* **2004**, *4*, 895−921.

(12) Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds. *J. Virol. Methods* **1988**, *20*, 309−321.

(13) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Miranda, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) derivatives. 2. *J. Med. Chem.* **1991**, *34*, 3187−3197.

(14) Kukla, M. J.; Breslin, H. J.; Pauwels, R.; Fedde, C. L.; Miranda, M.; Scott, M. K.; Sherrill, R. G.; Raeymaekers, A.; Van Gelder, J.; Andries, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) derivatives. *J. Med. Chem.* **1991**, *34*, 746−751.

(15) White, E. L.; Buckheit, R. W., Jr.; Ross, L. J.; Germany, J. M.; Andries, K.; Pauwels, R.; Janssen, P. A. J.; Shannon, W. M.; Chirigos, M. A. A TIBO derivative, R82913, is a potent inhibitor of HIV-1 reverse transcriptase with heteropolymer templates. *Antiviral Res.* **1991**, *16*, 257−266.

(16) Pauwels, R.; Andries, K.; Debyser, Z.; Kukla, M. J.; Schols, D.; Breslin, H. J.; Woestenborghs, R.; Desmyter, J.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. New tetrahydroimidazo[4,5,1-*jk*][1,4]-benzodiazepin-2(1*H*)-one and -thione derivatives are potent inhibitors of human immunodeficiency virus type 1 replication and are synergistic with 2′,3′-dideoxynucleoside analogs. *Antimicrob. Agents Chemother.* **1994**, *38*, 2863−2870.

(17) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G.; Gauthier, D. A.; Ho, C. Y.; Scott, M. K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. J. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo-[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one (TIBO) Derivatives. 3. *J. Med. Chem.* **1995**, *38*, 771−793.

(18) Ho, W.; Kukla, M. J.; Breslin, H. J.; Ludovici, D. W.; Grous, P. P.; Diamond, C. J.; Miranda, M.; Rodgers, J. D.; Ho, C. Y.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. J. Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-*jk*)][1,4]benzodiazepin-2(1*H*)-one (TlBO) Derivatives. 4. *J. Med. Chem.* **1995**, *38*, 794−802.

(19) Breslin, H. J.; Kukla, M. J.; Kromis, T.; Cullis, H.; De Knaep, F.; Pauwels, R.; Andries, K.; De Clercq, E.; Janssen, M. A. C.; Janssen, P. A. J. Synthesis and anti-HIV activity of 1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (TBO) derivatives. Truncated 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-ones (TIBO) analogues. *Bioorg. Med. Chem.* **1999**, *7*, 2427−2436.

(20) De Clercq, E. The role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 infection. *Antiviral Res.* **1998**, *38*, 153−179.

(21) Hajos, G.; Riedl, Z.; Molnar, J.; Szabo, D. Nonnucleoside reverse transcriptase inhibitors. *Drugs Future* **2002**, *25*, 47−62.

(22) Balzarini, J. Current Status of Non-nucleoside Reverse Transcriptase Inhibitors of Human Immunodeficiency Virus Type 1. *Curr. Top. Med. Chem.* **2004**, *4*, 921−944.

(23) Szczech, G. M.; Furman, P.; Painter, G. R.; Barry, D. W.; Borroto-Esoda, K.; Grizzle, T. B.; Blum, M. R.; Sommadossi, J.; Endoh, R.; Niwa, T.; Yamamoto, M.; Moxham, C. Safety assessment, in vitro and in vivo, and pharmacokinetics of emivirine, a potent and selective nonnucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1. *Antimicrob. Agents Chemother.* **2000**, *44*, 123−130.

(24) Balzarini, J.; Naesens, L.; Verbeken, E.; Laga, M.; Van Damme, L.; Parniak, M.; Van Mellaert, L.; Anne, J.; De Clercq, E. Preclinical studies on thiocarboxanilide UC-781 as a virucidal agent. *AIDS* **1998**, *12*, 1129−1138.

(25) Borkow, G.; Barnard, J.; Nguyen, T. M.; Belmonte, A.; Wainberg, M. A.; Parniak, M. A. Chemical barriers to human immunodeficiency virus type 1 (HIV-1) infection: Retrovirucidal of UC781, a thiocarboxanilide nonnucleoside inhibitor of HIV-1 reverse transcriptase. *J. Virol.* **1997**, *71*, 3023−3030.

(26) Ruiz, N.; Nusrat, R.; Lauenroth-Mai, E.; Berger, D.; Walworth, C.; Bacheler, L. T.; Ploughman, L.; Tsang, P.; Labriola, D.; Echols, R.; Levy, R. DPC 083-203 Study Team. Study DPC 083-201: A phase II comparison of 100 and 200 mg once-daily DPC 083 and 2 NRTIs in patients failing a NNRTI-containing regimen. Presented at the 9th Conference of Retroviruses and Opportunistic Infections, Seattle, WA, February 24−28, 2002; Abstract No. 6.

(27) Ruiz, N.; Nusrat, R.; Lazzarin, A.; Arasteh, K.; Goebel, F.-D.; Audagnotto, S.; Rachlis, A.; Arribas, J.; Ploughman, L.; Fiske, W.; Labriola, D.; Levy, R.; Echols, R. DPC 083-203 Study Team. Study DPC-083-203: A phase II double-blind (DB) comparison of 3 once-daily doses of NNRTI DPC 083 vs 600 mg efavirenz (EFV) in combination with 2 NRTIs in HIV antiretroviral (ARV) treatment naive patients. Presented at the 9th Conference of Retroviruses and Opportunistic Infections, Seattle, WA, February 24−28, 2002; Abstract No. 7.

(28) Fujiwara, T.; Sato, A.; el-Farrash, M.; Miki, S.; Abe, K.; Isaka, Y.; Kodama, M.; Wu, Y.; Chen, L. B.; Harada, H.; Sugimoto, H.; Hatanaka, M.; Hinuma, Y. S-1153 inhibits replication of known drug-resistant strains of human immunodeficiency virus type 1. *Antimicrob. Agents Chemother.* **1998**, *42*, 1340−1345.

(29) Sorbera, L. A.; Castaner, J.; Bayes, M. Capravirine. *Drugs Future* **2003**, *28*, 1149−1158.

(30) Ding, J.; Das, K.; Moereels, H.; Koymans, L.; Andries, K.; Janssen, P. A. J.; Hughes, S. H.; Arnold, E. Structure of HIV-1 RT/TIBO R 86183 complex reveals similarity in the binding of diverse nonnucleoside inhibitors. *Nat. Struct. Biol.* **1995**, *2*, 407−415.

(31) Kohlstaedt, L. A.; Wang, J.; Friedman, J. M.; Rice, P. A.; Steitz, T. A. Crystal structure at 3.5 Å resolution of HIV-1 reverse transcriptase complexed with an inhibitor. *Science* **1992**, *256*, 1783−1790.

(32) Arnold, E.; Das, K.; Ding, J.; Yadav, P. N. S.; Hsiou, Y.; Boyer, P. L.; Hughes, S. H. Targeting HIV reverse transcriptase for anti-AIDS drug design: structural and biological considerations for chemotherapeutic strategies. *Drug Des. Discovery* **1996**, *13*, 29−47.

(33) Tantillo, C.; Ding, J.; Jacobo-Molina, A.; Nanni, R. G.; Boyer, P. L.; Hughes, S. H.; Pauwels, R.; Andries, K.; Janssen, P. A. J.; Arnold, E. Locations of anti-AIDS drug binding sites and resistance mutations in the three-dimensional structure of HIV-1 reverse transcriptase: implications for mechanisms of drug inhibition and resistance. *J. Mol. Biol.* **1994**, *243*, 369−387.

(34) Nanni, R. G.; Ding, J.; Jacobo-Molina, A.; Hughes, S. H.; Arnold, E. Review of HIV-1 reverse transcriptase three-dimensional structure: Implications for drug design. *Perspect. Drug Discovery Des.* **1993**, *1*, 129−150.

(35) Smerdon, S. J.; Jager, J.; Wang, J.; Kohlstaedt, L. A.; Chirino, A. J.; Friedman, J. M.; Rice, P. A.; Steitz, T. A. Structure of the binding site for nonnucleoside inhibitors of the reverse transcriptase of human immunodeficiency virus type 1. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3911−3915.

(36) Pauwels, R.; de Bethune, M.-P.; Andries, K.; Stoffels, P.; Janssen, P.; De Clercq, E. Discovery, development and characterization of agents active against the AIDS virus. *J. Recept. Signal Transduction Res.* **1995**, *15*, 609−616.

(37) Pauwels, R.; Andries, K.; Debyser, Z.; Van Daele, P.; Schols, D.; Stoffels, P.; De Vreese, K.; Woestenborghs, R.; Vandamme, A. M.; Janssen, C. G. M.; Anne, J.; Cauwenbergh, G.; Desmyter, J.; Heykants, J.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. Potent and highly selective human immunodeficiency virus type 1 (HIV-1) inhibition by a series of α-anilinophenylacetamide derivatives targeted at HIV-1 reverse transcriptase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1711−1715.

(38) Ding, J.; Das, K.; Tantillo, C.; Zhang, W.; Clark, A. D., Jr.; Jessen, S.; Lu, X.; Ysiou, Y.; Jacobo-Molina, A.; Andries, K.; Pauwels, R.; Moereels, H.; Koymans, L.; Janssen, P. A. J.; Smith, R. H., Jr.; Kroeger Smith, M. B.; Koepke, M.; Michejda, C. J.; Hughes, S. H.; Arnold, E. Structure of HIV-1 reverse transcriptase in a complex with the non-nucleoside inhibitor α-APA R 95845 at 2.8 Å resolution. *Structure* **1995**, *3*, 365−379.

(39) Romero, D. L.; Morge, R. A.; Genin, M. J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I. W.; Reusser, F.; Thomas, R. C.; Tarpley, W. G. Bis(heteroaryl)piperazine (BHAP) reverse transcriptase inhibitors: structure−activity relationships of novel substituted indole analogues and the identification of 1-[(5-methanesulfonamido-1*H*-indol-2-yl)-carbonyl]-4-[3-[(1-methylethyl)amino]-pyridinyl]piperazine monomethanesulfonate (U-90152S), a second-generation clinical candidate. *J. Med. Chem.* **1993**, *36*, 1505−1508.

(40) Dueweke, T. J.; Poppe, S. M.; Romero, D. L.; Swaney, S. M.; So, A. G.; Downey, K. M.; Althaus, I. W.; Reusser, F.; Busso, M.; Resnick, L. U-90152, a potent inhibitor of human immunodeficiency virus type 1 replication. *Antimicrob. Agents Chemother.* **1993**, *37*, 1127−1131.

(41) Freimuth, W. W. Delavirdine mesylate, a potent non-nucleoside HIV-1 reverse transcriptase inhibitor. *Adv. Exp. Med. Biol.* **1996**, *394*, 279−289.

(42) Nottet, H. S.; Oteman, M. H.; Visser, M. R.; Verhoef, J. Anti-human immunodeficiency virus type 1 activities of novel non-nucleoside reverse transcriptase inhibitors. *J. Antimicrob. Chemother.* **1994**, *33*, 366−368.

(43) Ludovici, D. W.; Kukla, M. J.; Grous, P. G.; Krishnan, S.; Andries, K.; de Bethune, M. P.; Azijn, H.; Pauwels, R.; De Clercq, E.; Arnold, E.; Janssen, P. A. J. Evolution of anti-HIV drug candidates. Part 1: From α-Anilinophenylacetamide (α-APA) to imidoyl thiourea (ITU). *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2225−2228.

(44) Das, K.; Clark, A. D., Jr.; Lewi, P. J.; Heeres, J.; De Jonge, M. R.; Koymans, L. M. H.; Vinkers, H. M.; Daeyaert, F.; Ludovici, D. W.; Kukla, M. J.; De Corte, B.; Kavash, R. W.; Ho, C. Y.; Ye, H.; Lichtenstein, M. A.; Andries, K.; Pauwels, R.; De Bethune, M.-P.; Boyer, P. L.; Clark, P.; Hughes, S. H.; Janssen, P. A. J.; Arnold, E. Roles of conformational and positional adaptability in structure-based design of TMC125-R165335 (Etravirine) and related non-nucleoside reverse transcriptase inhibitors that are highly potent and effective against wild-type and drug-resistant HIV-1 variants. *J. Med. Chem.* **2004**, *47*, 2550−2560.

(45) Deeks, S. G. International perspectives on antiretroviral resistance. Nonnucleoside reverse transcriptase inhibitor resistance. *J. Acquired Immune Defic. Syndr.* **1999**, *26* (Suppl. 1), S25−S33.

(46) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. Cyanoguanidine-thiourea equivalence in the development of the histamine H2-receptor antagonist, cimetidine. *J. Med. Chem.* **1977**, *20*, 901−906.

(47) Ludovici, D. W.; Kavash, R. W.; Kukla, M. J.; Ho, C. Y.; Ye, H.; De Corte, B. L.; Andries, K.; de Bethune, M. P.; Azijn, H.; Pauwels, R.; Moereels, H. E. L.; Heeres, J.; Koymans, L. M. H.; de Jonge, M. R.; Van Aken, K. J. A.; Daeyaert, F. F. D.; Lewi, P. J.; Das, K.; Arnold, E.; Janssen, P. A. J. Evolution of anti-HIV drug candidates. Part 2: Diaryltriazine (DATA) analogues. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2229−2234.

(48) Ludovici, D. W.; De Corte, B. L.; Kukla, M. J.; Ye, H.; Ho, C. Y.; Lichtenstein, M. A.; Kavash, R. W.; Andries, K.; de Bethune, M. P.; Azijn, H.; Pauwels, R.; Lewi, P. J.; Heeres, J.; Koymans, L. M. H.; de Jonge, M. R.; Van Aken, K. J. A.; Daeyaert, F. F. D.; Das, K.; Arnold, E.; Janssen, P. A. J. Evolution of anti-HIV drug candidates. Part 3: diarylpyrimidine (DAPY) analogues. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2235−2239.

(49) Di Fabio, S.; Van Roey, J.; Giannini, G.; van den Mooter, G.; Spada, M.; Binelli, A.; Pirillo, M. F.; Germinario, E.; Belardelli, F.; de Bethune, M.-P.; Vella, S. Inhibition of vaginal transmission of HIV-1 in hu-SCID mice by the non-nucleoside reverse transcriptase inhibitor TMC120 in a gel formulation. *AIDS* **2003**, *17*, 1597−1604.

(50) van Herrewege, Y.; Vanham, G.; Michiels, J.; Fransen, K.; Kestens, L.; Andries, K.; Janssen, P.; Lewi, P. A series of diaryltriazines and diarylpyrimidines are highly potent non-nucleoside reverse transcriptase inhibitors with possible applications as microbicides. *Antimicrob. Agents Chemother.* **2004**, *48*, 3684−3689.

(51) Andries, K.; Azijn, H.; Thielemans, T.; Ludovici, D.; Kukla, M.; Heeres, J.; Janssen, P.; De Corte, B.; Vingerhoets, J.; Pauwels, R.; de Bethune, M.-P. TMC125, a novel next-generation non-nucleoside reverse transcriptase inhibitor active against non-nucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob. Agents Chemother.* **2004**, *48*, 4680−4686.

(52) Udier-Blagovic, M.; Tirado-Rives, J.; Jorgensen, W. L. Validation of a model for the complex of HIV-1 reverse transcriptase with nonnucleoside inhibitor TMC125. *J. Am. Chem. Soc.* **2003**, *125*, 6016−6017.

(53) Lewi, P. J.; De Jonge, M.; Daeyaert, F.; Koyman, L.; Vinkers, M.; Heeres, J.; Janssen, P. A. J.; Arnold, E.; Das, K.; Clark, A. D.; Hughes, S. H.; Boyer, P. L.; De Bethune, M. P.; Pauwels, R.; Andries, K.; Kukla, M.; Ludovici, D.; De Corte, B.; Kavash, R.; Ho, C. On the detection of multiple-binding modes of ligands to proteins, from biological, structural, and modeling data. *J. Comput.-Aided Mol. Des.* **2003**, *17*, 398.

(54) Das, K.; Lewi, P. J.; Hughes, S. H.; Arnold, E. Crystallography and the design of anti-AIDS drugs: Conformational flexibility and positional adaptability are important in the design of non-nucleoside HIV-1 reverse transcriptase inhibitors. *Prog. Biophys. Mol. Biol.* **2005**, *88*, 209−231.

(55) Gruzdev, B.; Rakhmanova, A.; Doubovskaya, E.; Yakovlev, A.; Peeters, M.; Rinehart, A.; de Dier, K.; Baede-Van Dijk, P.; Parys, W.; van't Klooster, G. A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naive, HIV-1 infected subjects. *AIDS* **2003**, *17*, 2487−2494.

(56) Gazzard, B. G.; Pozniak, A. L.; Rosenbaum, W.; Yeni, G. P.; Staszewski, S.; Arasteh, K.; De Dier, K.; Peeters, M.; Woodfall, B.; Stebbing, J.; van't Klooster, G. A. An open-label assessment of TMC 125, a new, next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance. *AIDS* **2003**, *17*, 49−54.

(57) Two recent publications discuss the pharmacological profile and clinical potential of etravirine in detail: (a) Pauwels, R. New non-nucleoside reverse transcriptase inhibitors (NNRTIs) in development for the treatment of HIV infections. *Curr. Opin. Pharmacol.* **2004**, *4*, 437−446. (b) Haslinger, B. A.; Arendt, G. TMC-125 (Tibotec). *Curr. Opin. Invest. Drugs* **2004**, *5*, 208−213.

(58) Janssen, P. A. J.; Lewi, P. J.; Arnold, E.; Daeyaert, F.; de Jonge, M.; Heeres, J.; Koymans, L.; Vinkers, M.; Guillemont, J.; Pasquier, E.; Kukla, M.; Ludovici, D.; Andries, K.; de Béthune, M.-P.; Pauwels, R.; Das, K.; Clark, A. D., Jr.; Volovik Frenkel, Y.; Hughes, S. H.; Medaer, B.; De Knaep, F.; Bohets, H.; De Clerck, F.; Lampo, A.; Williams, P.; Stoffels, P. In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]amino]benzonitrile (R278474, Rilpivirine). *J. Med. Chem.* **2005**, *48*, xxx−xxx.

JM040127P