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Pyridin-2(1*H*)-ones: A Promising Class of HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors

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Introduction

The acquired immune deficiency syndrome (AIDS) continues to be a major health problem worldwide with approximately 40 million people infected with the human immunodeficiency virus (HIV).[1] A vast amount of research has lead to the identification of several molecular targets for the treatment of HIV infections.[2] Current approved drugs are targeted to the retroviral enzymes reverse transcriptase (RT) and protease, and there is one fusion inhibitor.[3] Treatment of AIDS involves a combination of three or more drugs in a regimen called highly active antiretroviral treatment (HAART), typically including RT and protease inhibitors. Despite the fact that HAART has significantly improved the levels of patient mortality, there are several problems to solve, with the emergence of clinical resistance a major challenge.[3]

The enzyme RT is responsible for the conversion of single-stranded RNA viral genome into a double-stranded DNA copy. RT inhibitors are classified as nucleoside and non-nucleoside, depending on their mechanism of action. Nucleoside inhibitors bind and inhibit the active site through chain termination of DNA synthesis whereas the non-nucleoside binds to a hydrophobic nonactive site pocket, about 10 Å away from the catalytic site (Figure 1). Non-nucleoside RT inhibitors (NNRTIs) are very attractive as anti-HIV agents because of their high selectivity, relatively low toxicity, and activity in the nanomolar range.[3] Three NNRTIs have been approved for clinical use namely, nevirapine (VIRAMUNE), delavirdine (RESCRIPTOR), and efavirenz (SUSTIVA, STOCRIN) approved in 1996, 1997, and 1998, respectively (Figure 2).[2,3] However, all these induce drug resistant variants of HIV-1. Examples of common mutations in the binding site of NNRTIs that confer resistance are Y181C, Y188C, K103N, and L100 A. Significant progress has been made in the search for the next generation of NNRTIs able to overcome resistance mutations, which are a major challenge in the design of new NNRTIs. Examples of such efforts is the development of TMC-125 (etravirine) (Figure 2) and the structurally related TMC-278 (rilpivirine) that are currently in phase III and phase II clinical trials, respectively.[4,5] A second example is the potent RT inhibitor UC781 (Figure 2) active against several mutant strains. This molecule is being developed as a microbicide to prevent HIV-1 transmission.[4] In addition to approved drugs and compounds in clinical studies, there are several other molecules, covering more than 50 different structural classes, that have been identified as NNRTIs.[6] The reader is referred to recent excellent reviews regarding NNRTIs in Ref. [4–7] and references therein.

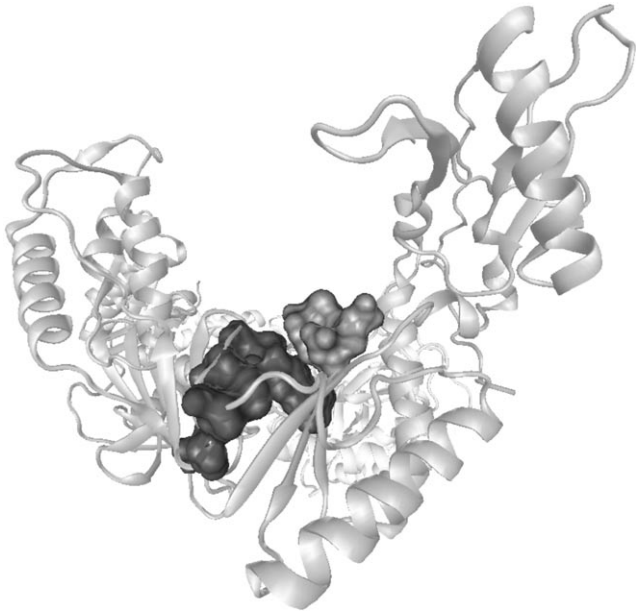

Figure 1. Structure of HIV-1 reverse transcriptase. Residues of the active site are represented as a light gray surface and residues of the NNRTIs binding site as a dark gray surface.

Pyridin-2(1*H*)-ones, a class of NNRTIs, were discovered in a screening program at Merck and the first potent analogues advanced into clinical trials. Despite the development of Merck pyridinones being suspended because of the emergence of resistance, the pyridin-2(1*H*)-one ring remained a promising core

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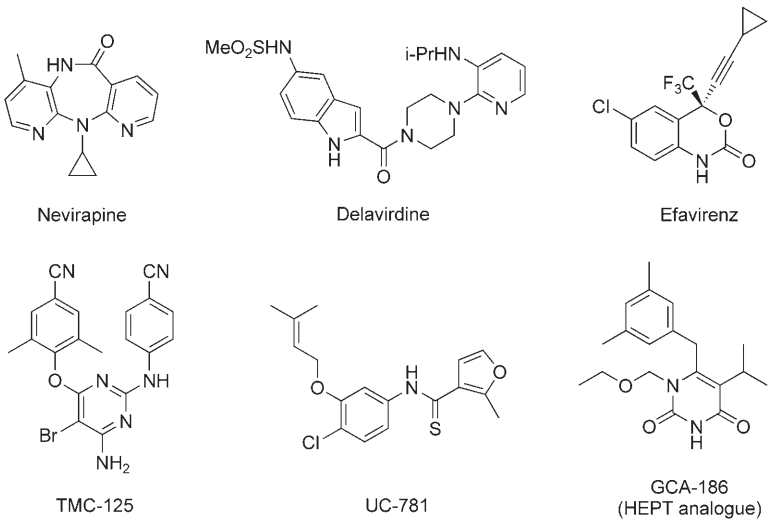


Figure 2. Approved and other potent NNRTIs.

for further synthetic programs that have culminated in the development of potent inhibitors against resistant strains. Computational structure-based design has also played an important role in the optimization of these analogues. This review focuses on the progress in the research of pyridin-2(1*H*)-ones as NNRTIs. The first part describes the discovery and subsequent synthetic efforts to overcome resistance of Merck pyridinones. Table 1 summarizes representative pyridin-2(1*H*)-ones discussed throughout the paper. The second section presents the studies directed to elucidate the binding mode with RT. The third section shows the structure-based design of pyridinone analogues based on docking results and other computational studies.

Discovery and Development

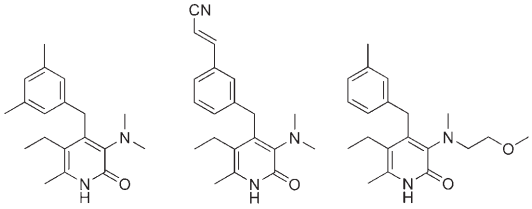
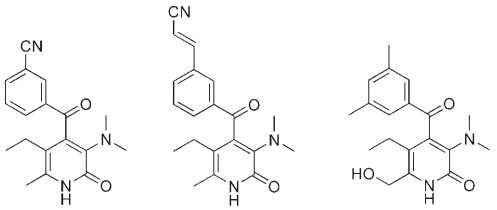
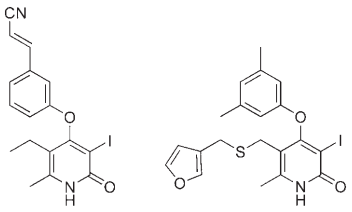
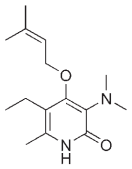
Dawn of pyridin-2(1*H*)-ones as NNRTIs: Merck pyridinones

Pyridin-2(1*H*)-one derivatives were identified as NNRTIs in an enzyme-based screening program conducted by Merck. In 1991 compound L-345,516 (**1**) was the first potent and selective HIV-1 RT inhibitor described of this class. However, this molecule was hydrolytically unstable.[8] Subsequent synthetic efforts focused on the development of more stable analogues and the phthalimide ring of L-345,516 was replaced by several other heterocyclic groups.[9,10] In general, these molecules were obtained by the condensation of the appropriate pyridin-2(1*H*)-one ring with the corresponding heterocycle. The nature and size of the linker between the pyridinone ring and the second heterocyclic moiety were also modified. A significant amount of structure–activity relationship (SAR) studies[10–12] lead to the development of L-697,661 (**2**), L-697,639 (**3**), and L-696,229 (**4**). Noteworthy, the three molecules have a benzoxazole group attached by a two atom

Table 1. Representative non-nucleoside reverse transcriptase inhibitors of the pyridin-2(1*H*)-one class.

Type (subtype)	Chemical Structure	Ref.
Merck pyridinone (phtalidimide)	**1** L-345,516	[8]
Merck pyridinone (benzoxazole)	**2** L-697,661; **3** L-697,639; **4** L-696,229	[8,9]
Pyridinone–efavirenz hybrid	**5**	[19]
Pyridinone–HEPT hybrid (4-arylthiopyridin-2(1*H*)-one)	**6**; **7**	[20]

Table 1. (Continued)

Type (subtype)	Chemical Structure	Ref.
Pyridinone–HEPT hybrid (4-benzylpyridin-2(1*H*)-one)	 **8** **9** **10** R157208	[22–24]
Pyridinone–HEPT hybrid (4-benzoylpyridin-2(1*H*)-one)	 **11** **12** **13**	[22–24]
Pyridinone–HEPT hybrid (4-aryloxypyridin-2(1*H*)-one)	 **14** R165481 **15** R221239	[25, 26]
Pyridinone–UC781 hybrid[a]	 **16**	[32]

[a] Type derived from docking studies with promising inhibitory activity against mutant strains. An example molecule is shown (see text for details).

linker to the pyridin-2(1*H*)-one ring at position 3 and are potent at nanomolar concentrations.[8,11] SAR studies emphasized the importance of the linker size and the 5-ethyl, 6-methyl substituents on the pyridin-2(1*H*)-one ring.[11,12] Also, the dichloro or dimethyl substitution of the benzoxazole ring of L-697,661 and L-697,639 plays a critical role in the activity of these analogues.[10,11]

L-697,661 was a subject of clinical studies showing good activity in patients. However, rapid resistant strains of the virus emerged.[13,14] The main mutations identified as responsible for the emergence of resistance were the residues at positions 103 and 181 not only for L-697,661 but also for other pyridinones such as L-697,639 and L-696,229.[13,15–18] From kinetic studies and analysis of resistance mutations it was concluded that this type of inhibitor should bind in the same pocket as other NNRTIs.[8,15,17]

Pyridinone–efavirenz hybrids

To optimize Merck pyridinones against resistant strains, a series of 3-alkoxymethyl and 3-aryloxymethyl-2-pyridin-2(1*H*)-ones were synthesized.[19] Prepared molecules incorporate structural features such as a trifluoromethyl and cyclopropyl alkynyl groups that improved the resistance profiles of efavirenz (Figure 2) and other related analogues. In this series of pyridinone–efavirenz hybrids, compound **5** showed an interesting inhibitory profile against mutant strains including the increased activity over the Merck pyridinone L-697,661 against the mutant K103N. However, **5** and other 3-alkoxymethyl and 3-aryloxymethyl-2-pyridin-2(1*H*)-ones did not outperform the inhibitory profile of efavirenz.[19]

Pyridinone–HEPT hybrids

Considering the partial structure similarity of Merck pyridinones and 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) derivatives such as GCA-186 (Figure 2), a very extensive synthetic program was initiated leading to the development of a series of potent pyridinone–HEPT hybrids. Subtypes of these hybrids include 4-arylthiopyridin-2(1*H*)-ones,[20,21] 4-benzylpyridin-2(1*H*)-ones,[22–24] 4-aryloxypyridin-2(1*H*)-ones,[25,26] and 4-benzoylpyridin-2(1*H*)-ones.[23,24] 4-Benzylpyridin-2(1*H*)-ones

were further coupled with the nucleoside RT inhibitor azidothymidine (AZT) to test a hypothesis of "mixture site" inhibitors. However, the pyridinone–AZT conjugates were inactive.[27] A common structural feature of the pyridinone–HEPT hybrids is the substitution at position 4 of the pyridinone ring by a one-atom linker to a phenyl ring. Several potent pyridinone–HEPT molecules contain a dimethylamine or iodo group at position 3 of the pyridin-2(1*H*)-one ring. During the development of these analogues, the presence of the dimethylamine group was inspired by the structural similarity to the isopropyl group at the corresponding position of GCA-186.[24,28] Interestingly, during the optimization steps of several molecules in this series it was observed that the 3′,5′-dimethyl groups at the phenyl ring (for example, **6**, **7**, **8**, **13**, **15**) led to an enhanced inhibitory activity such is the case for the same substitution pattern at the phenyl ring of GCA-186 (Figure 2).[24,28] Similar to the Merck pyridinones, several leads in the pyridinone–HEPT hybrids series contain the 5-ethyl, 6-methyl substituents on the pyridin-2(1*H*)-one ring that seem to be the optimum in several pyridinone derivatives. Notable exceptions are R221239 (**15**), that has a furfuryl methyl thioether group at position 5, and **13** that has a hydroxymehtyl group at position 6.

Biological studies revealed that the pyridinone–HEPT hybrids are NNRTIs.[20,22] The crystal structures for HIV-1 RT in complex with R157208, R165481, and R221239 have been published recently showing that these molecules actually bind into the NNRTIs binding site (vide infra).[26]

A very attractive feature of the pyridinone–HEPT hybrids is that recently developed 4-benzoylpyridin-2(1*H*)-ones such as **11**, **12**, and **13** show activity against a large panel of clinically relevant HIV-1 mutant strains and seem to display a more attractive inhibitory profile than efavirenz.[23,24] Furthermore, the 4-aryloxypyridin-2(1*H*)-ones R165481 (**14**) and R221239 (**15**) show activity against mutant strains K103N and Y181C and the double mutant K103N + Y181C at nanomolar concentrations.[26]

Binding Mode into the NNRTIs Binding Pocket

Automated docking and 3D-QSAR of Merck pyridinones

As mentioned earlier, biological experiments showed that L-697,661, L-697,639, L-696,229, and other related Merck pyridinones should bind in the NNRTIs pocket. Several two-dimensional quantitative structure–activity relationship analyses (2D-QSAR) have been performed for this subtype of pyridinone analogue,[9,11,12,29] suggesting a hydrophobic character of their binding site.[30,31] However, no crystal structures of HIV-1 RT in complex with Merck pyridinones are available.

Before the crystal structures of HIV-1 RT in complex with pyridinone–HEPT hybrids were published (vide infra) an automated docking study of potent Merck pyridinones including L-697,661, L-697,639, and L-696,229 with the NNRTIs binding site was conducted.[32] Docking results showed a good agreement with previous 2D-QSAR studies. According to the binding model, pyridinone analogues adopt a butterfly-like conformation in the binding pocket, a common feature of several NNRTIs,[6] and have a similar binding mode to other NNRTIs such as nevirapine (Figure 3).[32] The docking model suggested a key interaction that helps the stabilization of the pyridin-

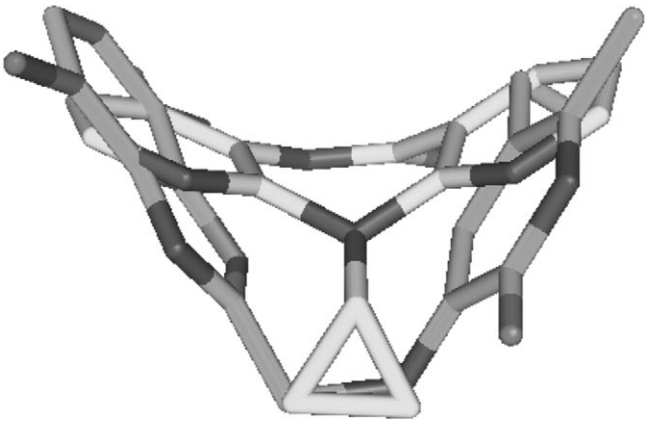


Figure 3. Binding mode model of L-697,661 (carbons in dark gray) compared to the binding mode of nevirapine (carbons in light gray) found in the crystal structure. Figure created with the program Pymol.[33a]

2(1*H*)-one ring into the NNRTI pocket, namely hydrogen bonding of the nitrogen at the pyridinone ring with the main chain oxygen of K101. From the binding model it was also concluded that hydrophobic contacts between the aromatic ring of Y181 and the benzoxazole ring of the potent Merck pyridinones may stabilize the complex and also be responsible for the decrease in activity upon mutation of this residue.[32]

Automated docking studies were extended to a series of 40 Merck pyridinones. Docked conformations were the starting point of three-dimensional quantitative structure–activity relationship analyses (3D-QSAR).[34] Docking results further support the binding model developed for L-697,661 and other potent inhibitors including the calculated hydrogen bonding of the nitrogen at the pyridinone ring with the main chain oxygen of K101. 3D-QSAR models also suggested that the proposed interaction between Y181 and the benzoxazole ring of the potent pyridinone derivatives may stabilize the complex.

Pyridinone–efavirenz and –HEPT hybrids: modelling studies and crystal structures

To aid in the understanding at the molecular level of the biological activity of pyridinone–efavirenz and pyridinone–HEPT hybrids, molecules **5** and **8** were docked into the NNRTIs binding pocket using an automated procedure with the program AutoDock 3.0.[32] Noteworthy, the binding model for **8** was proposed before the crystal structures of HIV-1 RT in complex with other pyridinone–HEPT hybrids were published (vide infra). Docking results showed that both hybrids adopt a butterfly-like conformation into the binding pocket. It was concluded that the cyclopropylpropynyl group of **5** and the benzyl group of **8** occupy the arene pocket formed by Y181, Y188, W229, and F227 making contacts with the conserved residue W229 (Figure 4). It was also predicted that the *N*-dimethyl substituent of **8** occupys the same binding pocket as the linker of Merck pyridinones.[32]

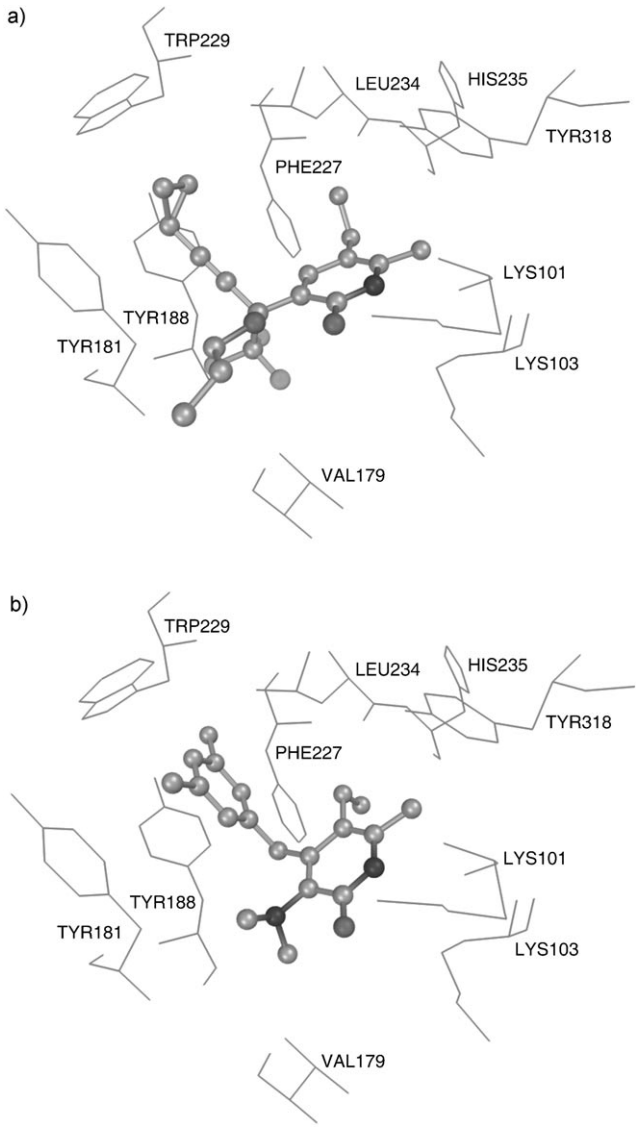


Figure 4. Binding mode proposed for a) pyridinone-efavirenz hybrid **5** and b) pyridinone–HEPT hybrid **8** into the NNRTIs binding pocket.[32] Figure created with the program AutoDockTools.[33b]

In a recent work, compounds **8** and R157208 (**10**) were manually docked into the NNRTIs binding pocket and the derived models were geometrically optimized.[24] Results suggested that both molecules bind in the same general orientation as that previously calculated for **8**.[32] Notably, the benzyl group occupy the pocket formed by Y181, Y188, W229, and F227, and the NH-group of the pyridinone ring forms a hydrogen bond with the carbonyl oxygen of K101.[26] Analysis of the X-ray crystal structure of the R157208–RT complex confirmed the proposed binding orientation.[26] Further computational studies involved the modelling of **13** into the NNRTIs binding site helping to explain, at the molecular level, the activity of this molecule against different mutant strains, in particular the K103N mutant. Key molecular interactions, in addition to the hydrogen bonding between the pyridinone ring and K101, are the hydrogen bond between the hydroxyl group of **13** with the backbone carbonyl of P236 and the hydrophobic interactions made by the dimethylphenyl group with residues Y181 and W229.[24]

Three crystal structures of HIV-1 RT in complex with pyridin-2(1*H*)-one analogues are currently available (Table 2). The three ligands are pyridinone–HEPT hybrids namely R157208, R165481, and R221239. The structures show that these molecules adopt a butterfly-like conformation into the binding pocket and the NH-group of the pyridinone ring forms a hydrogen bond with the carbonyl oxygen of K101. As mentioned above, the binding orientation observed in the crystal structures is the same proposed previously in the docking study of the pyridinone–HEPT hybrid **8**[32] (Figure 5). A distinctive feature of R165481–RT and R221239–RT complexes is that Y181 does not make significant contacts with these molecules, helping to explain the activity against the Y181C mutation at nanomolar concentrations. In addition, favourable interactions between the iodine atom at position 3 of the pyridin-2(1*H*)-one ring and RT seem to be critical to the activity of these molecules against the native form and several mutant strains.[26] Moreover, the crystal structures reveal the importance of the furfuryl methyl thioether group of R221239 that makes interactions with K103, V106, F227, L234, and P236; and the acrylonitrile substitution of R165481 that makes extensive contacts with V108, Y188, F227, L228, and W229.[26]

Table 2. Crystal structures of pyridin-2(1*H*)-one analogues in complex with HIV-1 RT.[26]

Pyridinone	PDB Code	Resolution Å
R157208	2BAV	2.95
R165481	2B5J	2.90
R221239	2BE2	2.43

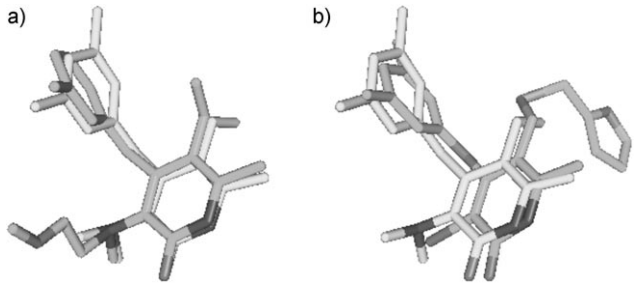


Figure 5. Binding conformation of **8** (carbons in light gray) calculated by automated docking compared to the binding conformation of a) R157208 and b) R221239 found in the crystal structures. Figure created with the program Pymol.[33a]

Computer-aided Design of NNRTIs Based on Pyridin-2(1*H*)-one Analogues

QSAR-based database mining

A 2D-QSAR study using the *k* nearest neighbour QSAR approach was conducted for more than 40 Merck pyridinones.[35]

Best QSAR models were used to search the National Cancer Institute database[36] for novel putative NNRTIs leads. Predicted promising leads include pyrazolo[3,4-d]pyrimidines.[37] Docking analysis of the predicted molecules into the NNRTIs binding pocket further support the hypothesis that these types of molecules could be attractive NNRTIs.[35] Additional QSAR models have been reported recently to predict successfully the activity of Merck pyridinones.[38]

Structure-based design of novel pyridin-2(1*H*)-ones

Docking and 3D-QSAR studies of L-697,661 and related Merck pyridinones served as the basis to perform a structure-based design of novel pyridin-2(1*H*)-ones as promising NNRTIs active against mutant strains.[32] An example of a designed molecule is the pyridinone–UC781 hybrid **16** (Figure 6) where the benzoxazol ring of the potent Merck pyridinones is replaced by a nonaromatic moiety, such as a (3-methylbut-2-enyl)oxy group, that does not make strong interactions with Y181. The reduction of binding dependence on interactions with Y181 has been shown to favour activity against the mutant Y181C.[39,40] Automated docking of **16** and other molecules with the structure of RT shows that the pyridinone–UC781 hybrids adopt the expected binding mode within the NNRTIs including a butterfly-like conformation and the hydrogen-bond formation between the nitrogen at the pyridinone ring with the oxygen of K101. In addition, the (3-methylbut-2-enyl)oxy group could make hydrophobic contacts with the conserved residue W229. Noteworthy, the design principles of the pyridinone–UC781 hybrids are in agreement with the general design considerations of NNRTIs pointed out recently, namely placement of an unsaturated group in the arene pocket formed by Y181, Y188, W229, and F227; a hydrogen bond interaction with the main chain oxygen of K101; small size of the inhibitor; and some degree of flexibility to allow the inhibitor to adjust to the mutations.[41] In fact, the molecular flexibility of TMC-125 (Figure 2) is considered to play an important role in the activity of this molecule against mutant strains.[40] Experimental development of pyridin–UC781 hybrids is in progress.

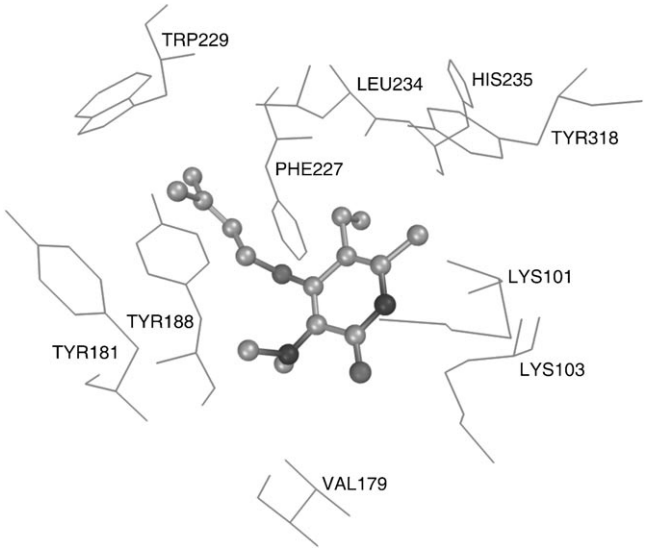


Figure 6. Binding mode calculated for **16** into the NNRTI binding pocket. Figure created with the program AutoDockTools.[33b]

Conclusions

Since the first pyridinones were reported by Merck as potent NNRTIs, the pyridin-2(1*H*)-one ring has been of interest for the development of NNRTIs. Early pyridin-2(1*H*)-one analogues containing a benxozazole ring advanced into clinical studies. Despite their discontinued development because of the generation of resistance, extensive SAR data collected through enormous synthetic efforts lead to the development of pyridione–efavirenz and pyridinone–HEPT hybrids with promising activity profiles against resistant mutant strains. A notable example is compound R221239 that shows activity against mutant strains at nanomolar concentrations. Pyridin-2(1*H*)-one analogues have been the subject of intensive computational studies in our group including automated docking, QSAR studies, and database mining. In silico approaches have led to the design of potentially active molecules such as the pyridinone–UC781 hybrids. Docking models of several pyridinones including L-697,661, **5**, and **8**, and three currently available crystal structures of pyridinone–HEPT hybrids within the NNRTIs binding site, reveal the formation of a hydrogen bonding of the nitrogen at the pyridinone ring with the main chain oxygen of K101. The crystal structures of pyridinone–HEPT hybrids are in agreement with the previous insights of the binding mode proposed for **8** and provide valuable avenues for the future development of novel pyridin-2(1*H*)-ones as promising candidates for the treatment of AIDS.

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Keywords: AIDS · biologically active compounds · computer-aided drug design · docking · structure–activity relationships

[1] AIDS Epidemic Update: December 2005. Joint United Nations Programme on HIV/AIDS and World Health Organization 2005.
[2] E. De Clercq, *J. Med. Chem.* **2005**, *48*, 1297 – 1313.
[3] D. C. Meadows, J. Gervay-Hague, *ChemMedChem* **2006**, *1*, 16 – 29.
[4] A. Basavapathruni, K. S. Anderson, *Curr. Pharm. Des.* **2006**, *12*, 1857 – 1865, and references therein.
[5] L. R. Boone, *Curr. Opin. Invest. Drugs* **2006**, *7*, 128 – 135, and references therein.
[6] J. Balzarini, *Curr. Top. Med. Chem.* **2004**, *4*, 921 – 944.
[7] R. Pauwels, *Curr. Opin. Pharmacol.* **2004**, *4*, 437 – 446.
[8] M. E. Goldman, J. H. Nunberg, J. A. O'Brien, J. C. Quintero, W. A. Schleif, K. F. Freund, S. L. Gaul, W. S. Saari, J. S. Wai, J. M. Hoffman, P. S. Anderson, D. J. Hupe, E. A. Emini, A. M. Stern, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6863 – 6867.
[9] W. S. Saari, J. M. Hoffman, J. S. Wai, T. E. Fisher, C. S. Rooney, A. M. Smith, C. M. Thomas, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintero,

W. A. Schleif, E. A. Emini, A. M. Stern, P. S. Anderson, *J. Med. Chem.* **1991**, *34*, 2922 – 2925.
[10] W. S. Saari, J. S. Wai, T. E. Fisher, C. M. Thomas, J. M. Hoffman, C. S. Rooney, A. M. Smith, J. H. Jones, D. L. Bamberger, M. E. Goldman, J. A. Obrien, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, P. S. Anderson, *J. Med. Chem.* **1992**, *35*, 3792 – 3802.
[11] J. M. Hoffman, A. M. Smith, C. S. Rooney, T. E. Fisher, J. S. Wai, C. M. Thomas, D. L. Bamberger, J. L. Barnes, T. M. Williams, J. H. Jones, B. D. Olson, J. A. O'Brien, M. E. Goldman, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, P. S. Anderson, *J. Med. Chem.* **1993**, *36*, 953 – 966.
[12] J. M. Hoffman, J. S. Wai, C. M. Thomas, R. B. Levin, J. A. O'Brien, M. E. Goldman, *J. Med. Chem.* **1992**, *35*, 3784 – 3791.
[13] R. T. Davey, Jr, R. L. Dewar, G. F. Reed, M. B. Vasudevachari, M. A. Polis, J. A. Kovacs, J. Falloon, R. E. Walker, H. Masur, S. E. Haneiwich, D. G. O'Neill, M. R. Decker, J. A. Metcalf, M. A. Deloria, O. L. Laskin, N. Salzman, H. C. Lane, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5608 – 5612.
[14] M. S. Saag, E. A. Emini, O. L. Laskin, J. Douglas, W. I. Lapidus, W. A. Schleif, R. J. Whitley, C. Hildebrand, V. W. Byrnes, J. C. Kappes, K. W. Anderson, F. E. Massari, G. M. Shaw, *N. Engl. J. Med.* **1993**, *329*, 1065 – 1072.
[15] J. H. Nunberg, W. A. Schleif, E. J. Boots, J. A. O'Brien, J. C. Quintero, J. M. Hoffman, E. A. Emini, M. E. Goldman, *J. Virol.* **1991**, *65*, 4887 – 4892.
[16] V. V. Sardana, E. A. Emini, L. Gotlib, D. J. Graham, D. W. Lineberger, W. J. Long, A. J. Schlabach, J. A. Wolfgang, J. H. Condra, *J. Biol. Chem.* **1992**, *267*, 17526 – 17530.
[17] J. H. Condra, E. A. Emini, L. Gotlib, D. J. Graham, A. J. Schlabach, J. A. Wolfgang, R. J. Colonno, V. V. Sardana, *Antimicrob. Agents Chemother.* **1992**, *36*, 1441 – 1446.
[18] V. W. Byrnes, V. V. Sardana, W. A. Schleif, J. H. Condra, J. A. Waterbury, J. A. Wolfgang, W. J. Long, C. L. Schneider, A. J. Schlabach, B. S. Wolanski, *Antimicrob. Agents Chemother.* **1993**, *37*, 1576 – 1579.
[19] J. W. Corbett, K. J. Kresge, S. Pan, B. C. Cordova, R. M. Klabe, J. D. Rodgers, S. K. Erickson-Viitanen, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 309 – 312.
[20] V. Dolle, E. Fan, C. H. Nguyen, A.-M. Aubertin, A. Kirn, M. L. Andreola, G. Jamieson, L. Tarrago-Litvak, E. Bisagni, *J. Med. Chem.* **1995**, *38*, 4679 – 4686.
[21] V. Dolle, A.-M. Aubertin, O. Ludwig, C. H. Nguyen, E. Bisagni, M. Legraverend, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 173 – 178.
[22] V. Dolle, C. H. Nguyen, M. Legraverend, A.-M. Aubertin, A. Kirn, M. L. Andreola, M. Ventura, L. Tarrago-Litvak, E. Bisagni, *J. Med. Chem.* **2000**, *43*, 3949 – 3962.
[23] A. Benjahad, K. Courte, J. Guillemont, D. Mabire, S. Coupa, A. Poncelet, I. Csoka, K. Andries, R. Pauwels, M.-P. de Bethune, C. Monneret, E. Bisagni, C. H. Nguyen, D. S. Grierson, *J. Med. Chem.* **2004**, *47*, 5501 – 5514.
[24] A. Benjahad, M. Croisy, C. Monneret, E. Bisagni, D. Mabire, S. Coupa, A. Poncelet, I. Csoka, J. Guillemont, C. Meyer, K. Andries, R. Pauwels, M.-P. de Bethune, D. M. Himmel, K. Das, E. Arnold, C. H. Nguyen, D. S. Grierson, *J. Med. Chem.* **2005**, *48*, 1948 – 1964.
[25] A. Benjahad, J. Guillemont, K. Andries, C. H. Nguyen, D. S. Grierson, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4309 – 4312.
[26] D. M. Himmel, K. Das, A. D. Clark, Jr., S. H. Hughes, A. Benjahad, S. Oumouch, J. Guillemont, S. Coupa, A. Poncelet, I. Csoka, C. Meyer, K. Andries, C. H. Nguyen, D. S. Grierson, E. Arnold, *J. Med. Chem.* **2005**, *48*, 7582 – 7591.
[27] R. Pontikis, V. Dolle, J. Guillaumel, E. Dechaux, R. Note, C. H. Nguyen, M. Legraverend, E. Bisagni, A.-M. Aubertin, D. S. Grierson, C. Monneret, *J. Med. Chem.* **2000**, *43*, 1927 – 1939.
[28] A. L. Hopkins, J. Ren, H. Tanaka, M. Baba, M. Okamato, D. I. Stuart, D. K. Stammers, *J. Med. Chem.* **1999**, *42*, 4500 – 4505.
[29] J. S. Wai, T. M. Williams, D. L. Bamberger, T. E. Fisher, J. M. Hoffman, R. J. Hudcosky, S. C. MacTough, C. S. Rooney, W. S. Saari, C. M. Thomas, M. E. Goldman, J. A. O'Brien, E. A. Emini, J. H. Nunberg, J. C. Quintero, W. A. Schleif, P. S. Anderson, *J. Med. Chem.* **1993**, *36*, 249 – 255.
[30] R. Garg, S. P. Gupta, H. Gao, M. S. Babu, A. K. Debnath, C. Hansch, *Chem. Rev.* **1999**, *99*, 3525 – 3601.
[31] S. P. Gupta in *Progress in Drug Research, Vol. 58* (Ed.: E. Jucker), Birkhäuser Verlag, Basel, **2002**, pp. 252 – 253.
[32] J. L. Medina-Franco, S. Rodríguez-Morales, C. Juárez-Gordiano, A. Hernández-Campos, J. Jiménez-Barbero, R. Castillo, *Bioorg. Med. Chem.* **2004**, *12*, 6085 – 6095.
[33] a) DeLano, W. L. The PyMOL Molecular Graphics System (2002) DeLano Scientific, Palo Alto, CA, USA. http://www.pymol.org; b) M. F. Sanner, *J. Mol. Graphics Modell.* **1999**, *17*, 57 – 61.
[34] J. L. Medina-Franco, S. Rodríguez-Morales, C. Juárez-Gordiano, A. Hernández-Campos, R. Castillo, *J. Comput.-Aided Mol. Des.* **2004**, *18*, 345 – 360.
[35] J. L. Medina-Franco, A. Golbraikh, S. Oloff, R. Castillo. A. Tropsha, *J. Comput.-Aided Mol. Des.* **2005**, *19*, 229 – 242.
[36] NCI/NIH Developmental Therapeutics Program. http://dtp.nci.nih.gov/.
[37] C. C. Cheng, R. K. Robins, *J. Org. Chem.* **1956**, *21*, 1240 – 1256.
[38] S. Bajaj, S. S. Sambi, S. Gupta, A. K. Madan, *QSAR Comb. Sci.* **2006**, *25*, 813 – 823.
[39] J. Ren, R. M. Esnouf, A. L. Hopkins, J. Warren, J. Balzarini, D. I. Stuart, D. K. Stammers, *Biochemistry* **1998**, *37*, 14394 – 14403.
[40] P. A. J. Janssen, P. J. Lewi, E. Arnold, F. Daeyaert, M. de Jonge, J. Heeres, L. Koymans, M. Vinkers, J. Guillemont, E. Pasquier, M. Kukla, D. Ludovici, K. Andries, M.-P. de Bethune, R. Pauwels, K. Das, A. D. Clark, Jr., Y. V. Frenkel, S. H. Hughes, B. Medaer, F. De Knaep, H. Bohets, F. De Clerck, A. Lampo, P. Williams, P. Stoffels, *J. Med. Chem.* **2005**, *48*, 1901 – 1909.
[41] W. L. Jorgensen, J. Ruiz-Caro, J. Tirado-Rives, A. Basavapathruni, K. S. Anderson, A. D. Hamilton, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 663 – 667.

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