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Design and synthesis of pyridone inhibitors of non-nucleoside reverse transcriptase

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ABSTRACT

Next generation NNRTIs are sought which possess both broad spectrum antiviral activity against key mutant strains and a high genetic barrier to the selection of new mutant viral strains. Pyridones were evaluated as an acyclic conformational constraint to replace the aryl ether core of MK-4965 (**1**) and the more rigid indazole constraint of MK-6186 (**2**). The resulting pyridone compounds are potent inhibitors of HIV RT and have antiviral activity in cell culture that is superior to other next generation NNRTI's.

HIV (human immunodeficiency virus) has a high rate of mutation due to its infidelity during replication. As a result, single drug therapy is ineffective due to the rapid selection of resistant mutant viral strains.[1] The more effective regimen, highly active antiretroviral therapy (HAART), uses at least two anti-HIV drugs simultaneously. This therapy significantly reduces HIV viral load and has led to a dramatic decrease in AIDS related mortality.[2] The emergence of HIV-1 strains resistant to at least one antiretroviral drug highlights the need for further development of antiviral agents with improved efficacy against these mutant strains.[3]

Reverse transcriptase (RT) inhibitors block the conversion of single stranded viral RNA to double stranded DNA, a prerequisite to integration into host DNA.[4] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) interact with the RT enzyme at an allosteric site to induce a change in the substrate binding site which interferes with polymerase activity.[5] A common consequence of NNRTI use is the emergence of resistant mutant forms of HIV.[6] Next generation NNRTIs are sought which possess both broad spectrum antiviral activity against key mutant strains (especially K103N and Y181C) and a high barrier to the selection of new mutant strains. Additionally, facilitating patient compliance dictates that next generation NNTRIs are efficacious with once daily oral administration. The current leader in the pursuit of improved NNRTI's is Tibotec's Rilpivirine® (TMC278)[7] which was recently approved by the FDA to be administered orally once daily.

In recent years, several groups have reported NNRTI's which feature a biaryl ether.[8] Specifically, Tucker et. al. reported a series of biaryl ethers (Fig. 1) which feature a pyrazolopyridine, as exemplified by MK-4965 (**1**), and have excellent broad spectrum antiviral activity against key mutant strains of RT. We[9] have also shown that conformationally constrained inhibitors (Fig. 1) such as MK-6186 (**2**) have comparable antiviral activity with good pharmacokinetics when dosed orally to preclinical species. Visual inspection of the X-ray crystal structures of **1** (PDB entry 3DRP) and **3**, a benzotriazole analog of **2** containing an aminomethyl group, complexed to wt RT (Fig. 2) shows the importance of the positioning of the pyrazolopyridine moiety with respect to the central phenyl ring

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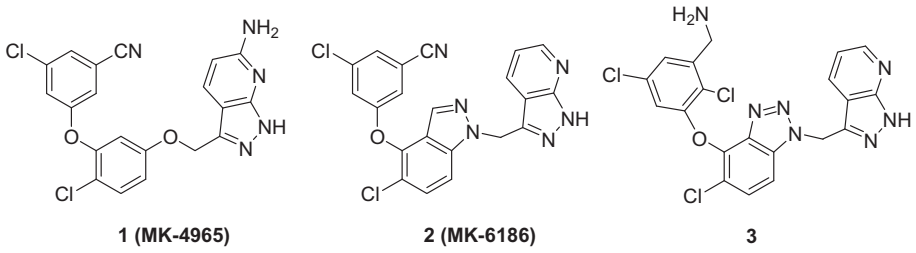


Figure 1. Structures of lead NNRTI inhibitors.

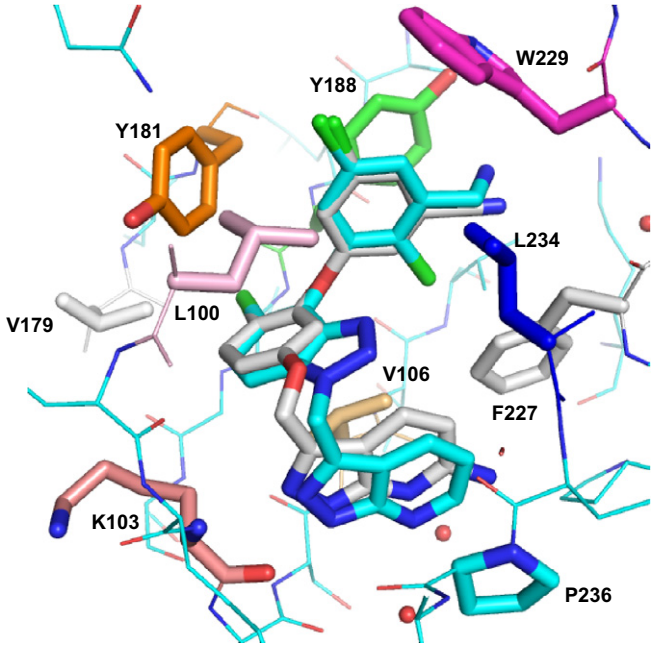


Figure 2. The bound conformation of **3** (teal) (from crystal structure complex with wt-RT) superimposed with the crystal structure of **1** (gray) complexed with wt-RT (PDB entry 3DRP). Active site residues within 7 Å are displayed. Key active site residues are highlighted and labeled in black. W239 and Y318 are hidden for clarity.

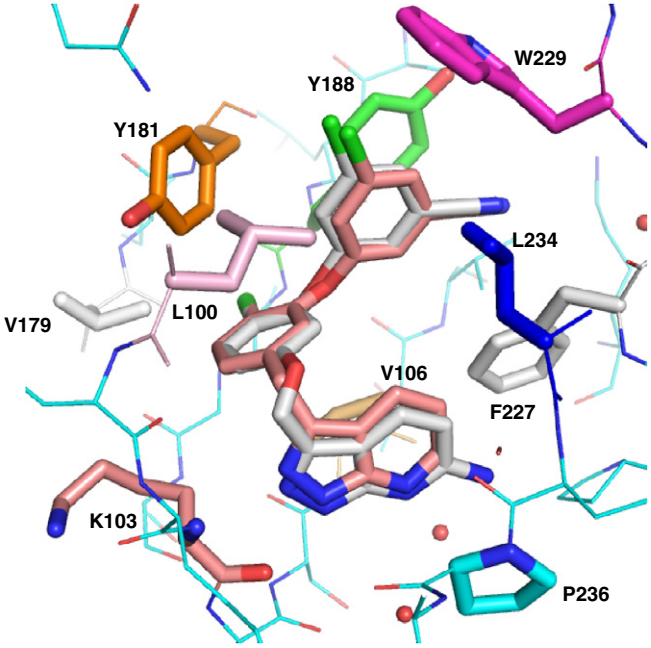
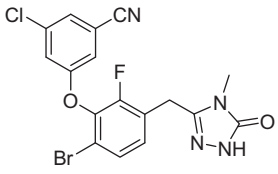


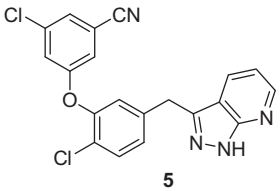
Figure 4. Docked conformation of **5** (salmon) superimposed with the bound conformation of **1** (gray) complexed with wt RT. Active site residues within 7 Å are displayed. Key active site residues are highlighted and labeled in black. W239 and Y318 are hidden for clarity.



4

RT inhibition EC_{50} (nM)

WT	2
K103N/Y181C	9



5

RT inhibition Ki (nM)

WT	0.24
K103N	0.48
Y181C	0.51

RT Antiviral Cell (CIC_{95} nM)

WT	22
K103N	211

Figure 3. Structures and RT inhibition of methylene linked NNRTI inhibitors.

as the resulting hydrogen bonds to the K103 backbone are essential for binding. The bound conformations of **1** and **3** complexed with wt RT show dihedral angles of 150° and 180° with respect to the linker between the pyrazolopyridine and the central phenyl ring.

Sweeney et. al.[10] have found that methylene linked inhibitors such as **4** (Fig. 3) are potent inhibitors of RT. These compounds contain a triazolinone moiety which presumably forms hydrogen bond interactions with the K103 backbone in an analogous fashion to the pyrazolopyridine of **1** and **3**. We[11] and others[12] have shown that one atom linkers between the pyrazolopyridine and the central phenyl ring are also potent inhibitors of RT. In particular, the methylene linked **5** (Fig. 3) has sub-nanomolar enzyme inhibition against both wt-RT and the two most clinically relevant mutants, K103N and Y181C. Compound **5** was docked[13] in the binding site of **1** complexed with wt-RT. This docked conformation of **5** is superimposed with the bioactive conformation of **1** (Fig. 4) and shows exceptional alignment of the terminal rings. The linker to the pyrazolopyridine of the docked conformation of **5** shows a dihedral angle of 81° with respect to the central ring and indicates the need for a nearly orthogonal disposition for a one atom linker relative to the central core ring. This contrasts with the bound conformations of the 2 atom linked inhibitors, **1** and **3,** which are more planar with the linkers having measured dihedral angles of 150° and 180° with respect to the central ring. **5** was unfortunately less active in cell culture than **1**, especially against the virus containing the K103N mutant (211 nM), and had suboptimal pharmacokinetics in rat. These shortcomings may be due to the nature of the central phenyl ring and linker since the related compounds **1** and **2** have superior profiles. We sought to change the nature of the central ring and linker of **5** in order to improve the antiviral activity in cell culture and the pharmacokinetics in our preclinical species.