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Substituted tetrahydroquinolines as potent allosteric inhibitors of reverse transcriptase and its key mutants

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ABSTRACT

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are key elements of multidrug regimens, called HAART (Highly Active Antiretroviral Therapy), that are used to treat HIV-1 infections. Elucidation of the structure–activity relationships of the thiocarbamate moiety of the previous published lead compound **2** provided a series of novel tetrahydroquinoline derivatives as potent inhibitors of HIV-1 RT with nanomolar intrinsic activity on the WT and key mutant enzymes and potent antiviral activity in infected cells. The SAR optimization, mutation profiles, preparation of compounds, and pharmacokinetic profile of compounds are described.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are key elements of multidrug regimens, called HAART (Highly Active Antiretroviral Therapy), that are used to treat HIV-1 infections. HAART consists of combinations of nucleoside HIV reverse transcriptase inhibitors (NRTIs), NNRTIs, and protease inhibitors (PIs). However, due to the propensity of HIV to rapidly mutate, the efficacy and durability of HAART can be compromised. The most frequent HIV RT mutations observed in patients failing therapy with first generation NNRTIs are K103N and Y181C. Therefore, new agents with better activity profiles against both wild type (WT) HIV-1 and the RT K103N and Y181C strains are needed.

Tetrazole and triazole thioacetanilides, **1**, were reported as potent NNRTIs against WT and K103N mutant (Scheme 1).[1] It is also known that the tetrazole and triazole moiety in **1** can be replaced by tertiary thiocarbamates (**2**), amides, and carbamates.[1c] This Letter reports the discovery and SAR of a structurally novel class of compounds related to compound **2** that exhibit good antiviral efficacy against the WT enzyme and the clinically relevant mutants K103N and Y181C.

Compound **2** exhibited desirable intrinsic potency against the WT and key mutant K103N and was about 10-fold less potent against Y181C (IC_{50}: 8 nM (WT), 9 nM (K103N), 80 nM (Y181C)).[2] In a cell based antiviral assay (Spread assay),[3] compound **2** also demonstrated good activities and had a minimal shift between 10% fetal bovine serum (FBS) and 50% normal human serum (NHS) (CIC95: WT, 31 nM (10% FBS), 62 nM (50% NHS)). Conformational analysis of **2** suggested that the *N*-methyl group of the thiocarbamate and the *ortho*-methyl group of the mesitylene could be in close proximity. Therefore it appeared reasonable to form a bond between the two methyl groups, to generate a tetrahydroquinoline motif which led to compound **3** (Scheme 1 and Table 1). Compound **3** showed improved potency against the WT and K103N enzymes. However, this modification decreased potency against the Y181C mutant enzyme compared to the unconstrained analogue **2**. Compound **3** also displayed a five-fold decrease in potency in the presence of 50% NHS in the Spread assay presumably due to its high

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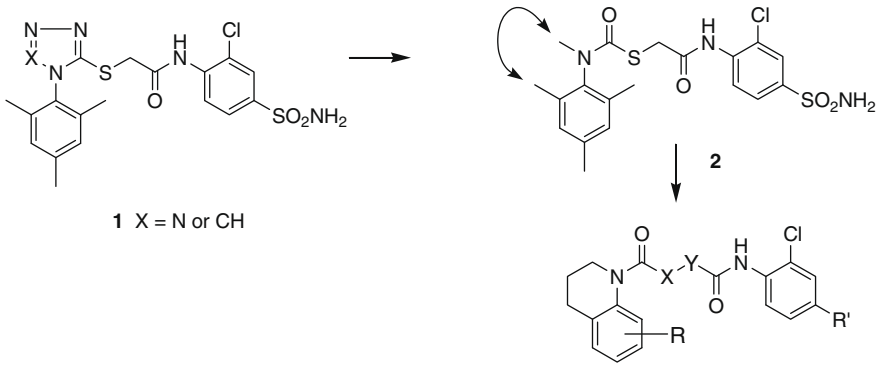
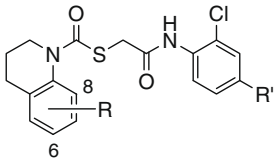


Scheme 1.

Table 1
SAR results



Compounds	R	R′	RT_Pol[a] IC_{50} (nM)			Antiviral Activity[b] CIC_{95} (nM)	
			WT	K103N	Y181C	10% FBS	50% NHS
3	6-Me	SO_2NH_2	3	3	1300	78	396
4	8-Me	SO_2NH_2	6	4	61	47	219
5	6-Cl	SO_2NH_2	8	—	—	141	1250
6	8-Cl	SO_2NH_2	2	4	31	23	47
7	6,8-Cl	SO_2NH_2	1	1	4	13/18[c]	40/33[c]
8	6,8-Cl	H	4	—	175	125	406
9	6,8-Cl	CN	7	14	95	156	1250
10	6,8-Cl	CONHBn	2	2	4	63[c]	307[c]
11	6,8-Cl	SO_2CH_3	4	3	11	5.6[c]	5.7[c]
12	6,8-Cl	$CONH(CH_2)_3NH_2$	2	2	7	97[c]	34[c]

[a] Compounds were evaluated in a standard SPA assay. The values are the geometric mean of at least two determinations. All individual values are within 25% of the mean.
[b] CIC95 (cell culture inhibitory concentration) is defined as the concentration at which the spread of virus is inhibited by >95% in MT-4 human T-lymphoid cells maintained in RPMI 1640 medium containing either 10% fetal bovine serum (FBS) or 50% normal human serum (NHS). The antiviral activity of compound against wild-type (H9IIIB) virus was measured. The values are the geometric mean of at least two determinations. All individual values are within 25% of the mean.
[c] The antiviral activity of compound against wild-type (R8) virus was measured.

protein binding (99% in human plasma). Introducing a methyl group at the 8-position (**4**) maintained WT and K103N potency, and regained activity versus the Y181C mutant. It is known that the mesitylene group can be replaced with a mono- or di-chloro substituted phenyl ring.[1] Therefore, a chlorine atom was introduced into this series at the 6 and 8 position (**5** and **6**). A similar trend was observed in this series of chlorine analogues, where the 8-chloro compound (**6**) was significantly more potent than the 6-chloro isomer (**5**). The 8-Chloro analogue was also more potent than the corresponding methyl analogue (**6** vs **4**). Combining the 6- and 8-chlorine substitution on the aryl ring provided compound **7** with a further increase in potency. Compound **7** exhibited good potency against WT enzyme, K103N, and in particular Y181C mutants. These improvements translated into excellent antiviral activities in cell culture.

Co-crystallization[4] of compounds **3** and **7** with WT RT revealed that the 6-substitutent (methyl group in **3** and chlorine atom in **7**) of the phenyl group interacts with Trp-229 and the anilide side chain is accommodated within the solvent channel lying under Pro-236 (Fig. 1). The anilide carbonyl group in both **3** and **7** is positioned to interact with Lys-103 backbone NH via a hydrogen bond, and this interaction is considered to contribute to the excellent potency of both **3** and **7** against the K103N mutant. The thiocarbamate carbonyl group in **7** is orientated differently compared to the one in **3** presumably to minimize its interaction with the 8-chlorine atom.

Since the 4-position of the sulfonamide is solvent exposed, we further explored the SAR of the anilide moiety using a library-based approach to replace the primary sulfonamide. Selected results are listed in Table 1. Deletion of the sulfonamide led to compound **8** and reduced potency against the Y181C enzyme and activity in cell based assays. Replacement of the sulfonamide with a small cyano group (**9**) or a large benzyl amide (**10**) was tolerated. Replacement of the sulfonamide with methyl sulfone yielded compound **11** with improved antiviral activities compared to **7** and no shift in potency in the presence of 50% human serum in the Spread assay. Incorporation of an amide side chain with a basic amine group (**12**) was tolerated and its antiviral activity was maintained. This result is consistent with the observation from the co-crystal structures that the *para* position of the anilide is solvent exposed and therefore tolerates a variety of substituents (Fig. 1).

We then initiated an effort to replace the thiocarbamate and selected results are summarized in Table 2. Replacement of the thiocarbamate with carbamate (**13**), amide (**14**) and urea (**15**) linkers showed modest activities in the enzyme assay, and all had significant potency shifts in the Spread assay in the presence of 50% NHS. A cyclopropane ring has been used successfully as a