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Discovery and optimization of 2-pyridinone aminal integrase strand transfer inhibitors for the treatment of HIV

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ABSTRACT

HIV integrase strand transfer inhibitors (InSTIs) represent an important class of antiviral therapeutics with proven efficacy and excellent tolerability for the treatment of HIV infections. In 2007, Raltegravir became the first marketed strand transfer inhibitor pioneering the way to a first-line therapy for treatment-naïve patients. Challenges with this class of therapeutics remain, including frequency of the dosing regimen and the genetic barrier to resistance. To address these issues, research towards next-generation integrase inhibitors has focused on imparting potency against RAL-resistent mutants and improving pharmacokinetic profiles. Herein, we detail medicinal chemistry efforts on a novel class of 2-pyridinone aminal InSTIs, inpsired by MK-0536, which led to the discovery of important lead molecules for our program. Systematic optimization carried out at the amide and aminal positions on the periphery of the core provided the necessary balance of antiviral activity and physiochemical properties. These efforts led to a novel aminal lead compound with the desired virological profile and preclinical pharmacokinetic profile to support a once-daily human dose prediction.

Over the past five years, HIV-1 integrase strand transfer inhibitors (InSTIs) have been established as important first-line components of combination antiretroviral (ARV) therapy in treatment-naïve patients.[1,2] Merck pioneered research and development in the field, launching Raltegravir (RAL, Fig. 1) in 2007 as the first marketed InSTI.[3,4] Recent efforts have focused on the discovery of next-generation InSTIs to address the emergence of RAL-resistant mutants as well as its requirement for twice-daily (b.i.d.) dosing.[5,6] To this end, Dolutegravir (DTG), recently launched jointly by Shionogi-ViiV Healthcare and GlaxoSmithKline, became the first marketed next-generation InSTI.[7] DTG displays good potency against RAL-resistant mutants as well as a human pharmacokinetic profile enabling once-daily (QD) dosing without need for PK boosting.

In our laboratories, efforts towards a next-generation InSTI have focused on identifying structurally novel chemical matter with coverage of key RAL resistant mutants. Specifically, we have targeted good intrinsic wild-type (WT) potency as well as potency against the most common RAL-resistant single mutations (E92Q, Y143R, Q148R, Q148K, N155H) and the most common double mutant, G140S/Q148H. Additionally, we have focused on structural classes with a preclinical PK profile that would project un-boosted QD oral dosing in humans. We have previously disclosed the discovery of a novel 2-pyridinone aminal class of InSTI, inspired by our clinical candidate, MK-0536.[8,9] Efforts in this structurally diverse series culminated in the discovery of two lead molecules (**1** and **2**).[10] In the present manuscript, we present a detailed overview of the medicinal chemistry efforts which led to the discovery of **1**; the discovery of **2** will be the subject of a forthcoming report.

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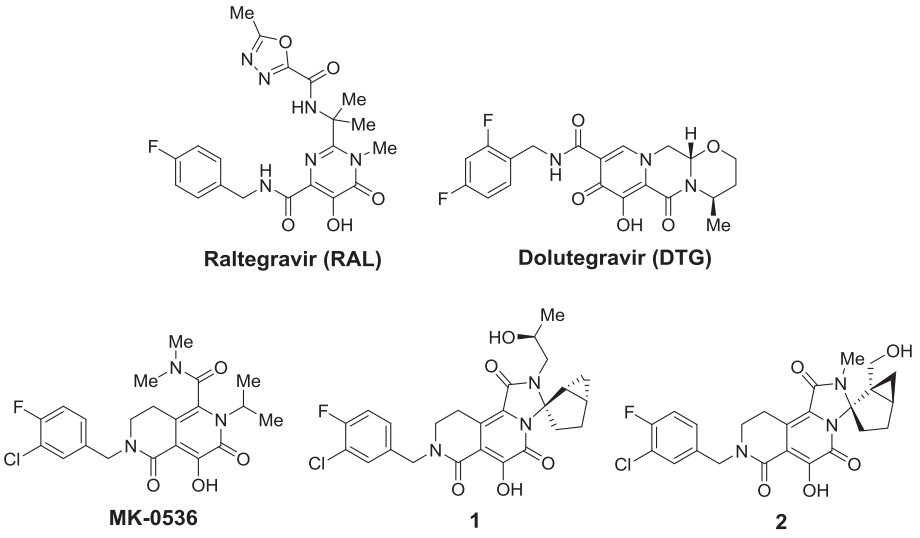


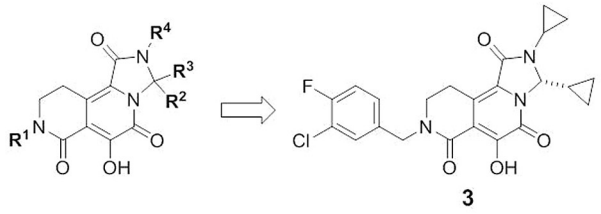
Fig. 1. Marketed HIV integrase strand transfer inhibitors and current lead 2-pyridinone aminals.

As we initiated medicinal chemistry efforts on the 2-pyridinone aminal class, compound **3** was identified as an early and promising lead (Fig. 2), displaying a good PK profile in beagle dogs (low CL, good %F) and predicted human PK. However, significant improvements in serum-shifted potency and in its intrinsic resistance profile were desired. The 2-pyridinone core underwent extensive optimization around its tricyclic periphery while retaining the key bidentate metal-binding pharmacophore. While efforts were made to improve the overall profile by modification of the benzyl region (R^1, data not shown), these proved unsuccessful for this class and we retained the 4-fluoro-3-chlorobenzyl group in all compounds of interest. This halo-benzyl moiety is similar in structure to all historically optimal R^1 substituents (RAL, DTG, MK-0536), and so the lack of tolerated structural variation was not surprising.

Optimization efforts in this class were focused at the R^2/R^3 (herein referred to as the aminal) and R^4 (herein referred to as the amide) positions. As is common in the early lead optimization space, many compounds were characterized as racemates *in vitro* (Table 1 and Table 3), a strategy that has proven successful to triage new HIV Integrase inhibitors. Efforts in the R^2/R^3 region are shown in Table 1. In general, simple aminals derived from aldehydes (Table 1, Entries **4** and **5**) provided inferior WT and mutant virological profiles compared to ketone-based aminals. A survey of aminal ring sizes (Table 1, Entries **6**–**8**) indicated that the smaller cyclobutyl or larger cycloheptyl ring systems exhibited suboptimal mutation profiles compared to cyclopentyl ring system. Installation of a methyl group at the 3-position of the cyclopentyl ring (Table 1, entry **9**) improved the virological profile modestly. Finally, we discovered that by tying back the methyl group into novel bicyclo[3.1.0]hexane ring system (Table 1, Entries **10** and **11**), a further improvement in the mutation profile was realized. Upon characterization of all four possible stereoisomers of this ring system, compounds **10** and **11** were confirmed as providing the optimal overall balance of properties.

The profile of compound **11** is shown in Fig. 3 and highlights the improved intrinsic WT potency and mutation profile compared to compound **3**. Like **3**, compound **11** was highly bound to plasma proteins and displayed moderate aqueous solubility. Not surprisingly, **11** exhibited an improved beagle dog PK profile over **3**, with extremely low clearance of 0.12 mL/min/kg and a long half-life of 13 h, driven by its very low unbound fraction. The low-dose oral bioavailability of **11** was 15%. With this profile, compound **11** became an important benchmark compound for future compounds in the aminal series, however we sought to improve the physical properties and virological profile.

The synthesis of **11**, shown in Scheme 1, is performed by heating the previously reported amide **12**[10] with excess (1*R*,5*S*)-bicyclo[3.1.0]hexan-2-one **13**[11] in DMA with one equivalent of sulfuric acid at 105 °C. Under these forcing conditions, the reaction provided separable diastereomers in a ~1:1 ratio, and **11** was isolated in 17% overall yield.



WT IP[a]		95 / 1729 nM
Mutant IP[b]		123 / 142 / 1006 / 820 / 271 / 1545 nM
Mutant Fold Shift[c]		1 / 2 / 11/ 9 / 3 / 16
PPB (d,h)		97.6, 99.9%
Solubility (pH 2,7)		40, 34 μM
PSA		79 Å^2
Dog PK (0.5/1 mpk iv/p.o.)	CL	1.4 mL/min/kg
	V_d	0.7 L
	$t_{1/2}$	7.5 h
	F%	44 %

Fig. 2. Profile of initial aminal lead compound **3**. [a] Kinetic HIV replication assay IP in 10/50% NHS. [b] IP fold shift in 10% NHS compared to WT enzyme of E92Q, Y143R, Q148R, Q148K, N155H, and G140S/Q148H.

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