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Synthesis and biological evaluation of phosphonate analogues of nevirapine

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ABSTRACT

A series of nevirapine-based analogues containing the phosphonate functionality were prepared and evaluated in vitro against HIV RT. The effect of the phosphonate was evaluated against the wild type and Y181C HIV replication. An in vivo PK study was performed on a select analogue.

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Tremendous advances in therapeutic options for the treatment of human immunodeficiency virus (HIV) infection have been achieved.[1] There are now more than twenty antiretroviral agents covering six classes marketed to treat HIV, with the non-nucleoside reverse transcriptase inhibitors (NNRTI) remaining one of the key components of highly active antiretroviral therapy (FDA approved NNRTIs **1**–**5** shown in Fig. 1).[2,3] However, rapid emergence of drug-resistant viruses that are cross-resistant to other members of this class limit the broad usage of NNRTI.[4] Toward this end, the goal of our project was to identify an NNRTI with activity against major HIV-1 reverse transcriptase (RT) mutants.

Recently in our HIV protease inhibitor (PI) project, the phosphonate functional group was explored as a pro-drug handle, designed to increase half-life ($t_{1/2}$) through higher intracellular loading.[5a] Protease inhibitors containing a diethyl phosphonate were shown to have favorable resistance profiles (Fig. 2). GS-8374, a darunavir analogue, which has a diethyl phosphonate with optimal projection installed at the P2 site of the darunavir scaffold, is markedly more potent against mutant HIV protease enzymes including most of the clinically relevant strains.[5b] Interestingly, when the diethyl phosphonate-containing inhibitors were co-crystallized with wild type and mutant HIV protease enzymes, the phosphonate group itself was found to have no interactions with the active site. Instead the group was entirely exposed to solvent at the end of a long, hydrophobic active site channel. It was hypothesized that the observed increased potency was due to a 'solvent anchoring' affect provided by the phosphonate moiety.[5]

According to the authors, solvent anchoring enhanced the degeneracy of the inhibitor binding states and allowed the molecule to effectively adapt to the altered active site of the mutant enzyme, which endowed a favorable resistance profile. We set out to improve upon existing NNRTIs by implementing this phosphonate strategy in hopes of obtaining a desirable resistance profile. We herein report the synthesis and evaluation of phosphonate-containing NNRTIs based on nevirapine scaffold.

Prior data from Boehringer Ingelheim detailed novel modifications of nevirapine (Viramune®, **3**) that improved its resistance profile toward a key clinical mutant Y181C. This included modifying the core and installing an aryl group separated from the core by a linker of varying atom composition and length (Fig. 3).[6] These second generation nevirapine analogues, such as literature compound **6**, were shown to be very active against the RT enzyme as well as the wild-type virus in cell based assays. Compared with **3**, compound **6** was >200-fold more active against the Y181C mutant (Table 1).[6] Our modeling studies with compound **6** suggested that a phosphonate group appended on these second generation nevirapine compounds would potentially further enhance the compound's affinity for RT and improve its resistance profile through solvent anchoring effects.

We investigated phosphonate-containing nevirapine analogues by examining SAR with two- or three-atom linkers (containing C, O, or N) between the nevirapine core and the aryl group. As such,

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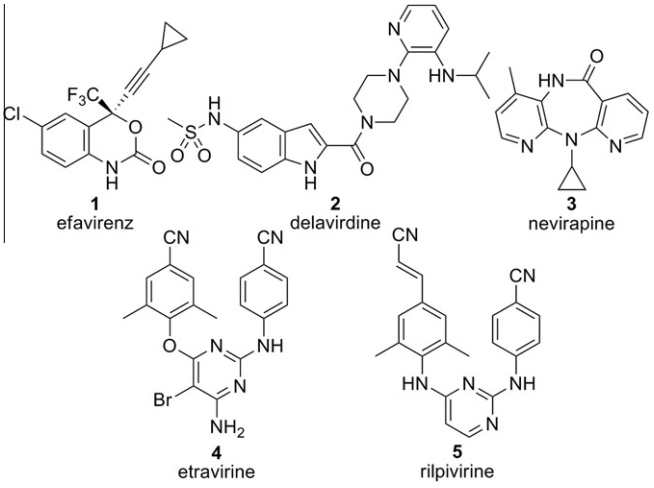


Figure 1. Marketed HIV NNRTI's.

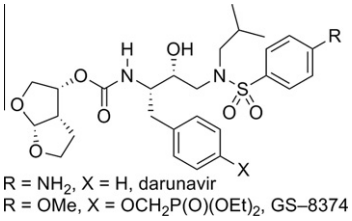


Figure 2. Darunavir and GS–8374.

the synthesis for the two-atom C-linked series is detailed in Scheme 1. Starting from known compound **7**, Sonogashira coupling to the acetylene adduct, followed by a two-step reduction provided phenol **8** in moderate yield.[7] Alkylation of **8** installed the desired diethyl phosphonate moiety to give **9** in 54%, which was then hydrolyzed using TMSBr buffered with 2,6-lutidine to reveal diacid **10** in nearly quantitative yield. The highly polar diacids were isolated via HPLC (0–100% MeCN–H_2O gradient, 5% TFA modifier).

The synthesis for the two-atom N-linked series is detailed in Scheme 2. Diethyl hydroxymethylphosphonate was triflated at low temperature in high yield. The resulting triflate was reacted with 4-hydroxybenzaldehyde in the presence of Cs_2CO_3 to afford **A**. Next, reduction of nitro group in compound **11** (prepared according to literature procedures),[7] followed by a one-pot reductive amination of the resulting amine gave diethyl phosphonate **12** in good yield. The phosphonate was unmasked with buffered TMSBr to afford diacid **13** in 95%.

The inhibitory activity against both the RT enzyme and HIV replication of the two-atom linker (C- and N-linked) series is shown in Table 1. Non-phosphonate, second generation compounds **8** and **14** (synthesis not shown), prepared as references, showed cell-based activity on par with nevirapine (**3**) against the WT virus. Yet both compounds demonstrated a significant improvement in resistance profile against the Y181C mutant relative to compound **3** (16- and 13-fold reduction comparing with >100-fold decrease). Incorporating the diethyl phosphonate moiety gave **9**, which had a further improvement in activity against WT (1.5- to 3-fold) and Y181C (1.5- to 2-fold) when compared with **8** and **14**. In addition, it is >40-fold more active against the Y181C mutant than **3**, and resistance was improved to 7-fold from >100-fold.

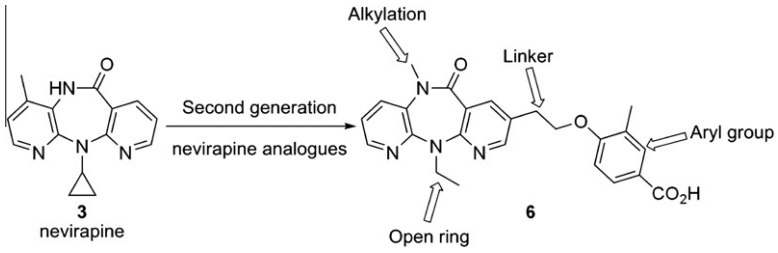
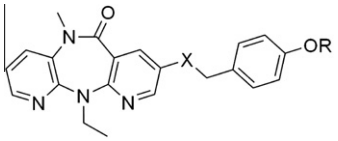


Figure 3. Second generation nevirapine compounds.

Table 1
Two-atom linker SAR for C- and N-linked nevirapine analogues



Compound	X	R	IC_{50} (nM)	EC_{50} (nM)		Fold change	CC_{50} (μM)
				WT	Y181C		
Efavirenz (**1**)	—	—	30	0.55	1.6	3.0	—
Nevirapine (**3**)	—	—	309	74	>10,000	>100	—
6	—	—	69	8	53	7	—
8	CH_2	H	—	43	670	16	—
14	CH_2	CH_3	—	100	1273	13	—
9	CH_2	$CH_2P(O)(OEt)_2$	100	33	234	7	—
10	CH_2	$CH_2P(O)(OH)_2$	1810	>5000	>5000	n/a	71
12	NH	$CH_2P(O)(OEt)_2$	70	10	94	9	—
13	NH	$CH_2P(O)(OH)_2$	3800	>5000	>5000	n/a	—

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