UK-453,061: A NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR FOR THE TREATMENT OF DRUG-RESISTANT HIV INFECTIONS


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Introduction

Non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs) are key components of highly active antiretroviral therapy (HAART). The need to maintain HAART induction in viral load and disease progression are increasingly accompanied by antiretroviral drug resistance and class switching. The recent emergence of novel mutants conferring cross-resistance to NNRTIs and non-nucleoside inhibitors (NNIs) makes it clear that there is a need for new, well tolerated NNRTI with activity clinically specific against drug resistant HIV-1 mutants.

UK-453,061 (Figure 1) was selected as the NNRTI candidate on the basis of its low clearance when used as a single agent and the desire to re-structure the currently distributed compound (Draft-1), which reduces reactivity by blocking the re-association of 2-fold; this reduced reactivity of UK-453,061 can be absorbed into the intestinal tract of the rat, and adsorption to the liver. UK-453,061 has shown negligible interactions with drug hepatoxylin ar and dog liver microsomes, and is relatively stable to metabolites in human liver and rabbit liver homogenates. Overall, UK-453,061 is unlikely to be affected by a combination of glucuronidation and antibiotic interactions previously observed by the cytochrome P450 inhibitors (Simeprevir, 

The data presented below summarize the biochemical and structural optimization of UK-453,061 against panel of clinically relevant HIV-1 RT mutants and the further proctorial characterisation of this emerging NNRTI candidate.

Methods

Isothermal Titration calorimetry (ITC)

UK-453,061 was concentrated to sufficient concentration to TTY typically (0.1-0.5 μM) and Monitor (10 nM-1 μM) in a microtiter plate format (0.2 μL/row). 2 μL of10 μM UK-453,061 was directly solubilized using a Microcal VP-ITC, with 25 μL buffer (10 mM Tris-HCl, 0.1 mM EDTA, pH 7.5) and 25 μl of protein, made every 230 sec, into a final reaction volume of 250 μL. 2

X-ray crystallography

X-ray crystallography

Residues with 100% sequence identity to K10 and K10 of the enzyme in 15 of 18 single- and double-point engineered mutant X-ray structures in complex with other NNRTIs, such as nevirapine (Figure 3b). In both of these structures, residue Y181 of HIV-1 RT is in a "up" conformation and a 1:1 binding mechanism.

In vitro selectivity analysis

UK-453,061 demonstrated anti-viral activity against polymerase (p5) primer extension assay, generating two IC50 values greater than 100 μM (31.0 ng/mL), which are less than 20% of the IC50 of UK-453,061 for inhibition of HIV-1 from 15 to 18 single- and double-point engineered mutant activities by UK-453,061 was observed against both clinically relevant IC100 IC90 (nM) over wt IC90

Results

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Conclusions

UK-453,061 demonstrated anti-viral activity against HIV-1 and HIV-2, and displayed balanced activity against clinically relevant HIV-1 RT single- and double-point mutations in vitro, retaining potency similar to that observed against the clinically relevant mutants K103N, Y181C and G190A. This research was funded by Pfizer Inc.

References

1. Mowbray C et al. Poster presented at the Antiviral Society Conference, Sydney, Australia, July 22-25, 2007. 2. Studies in healthy male subjects found that UK-453,061 was well tolerated. Therefore, we approached studies to no systemic activity of UK-453,061 was observed, and no significant changes in laboratory or clinical data were observed.

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Table 1. Activity profiles of UK-453,061 and reference compounds against panel of HIV-1 reverse transcriptase

![UK-453,061 and reference compounds against panel of HIV-1 reverse transcriptase](attachment://Figure4.png)

![UK-453,061 and reference compounds against panel of HIV-1 reverse transcriptase](attachment://Figure5.png)

![UK-453,061 and reference compounds against panel of HIV-1 reverse transcriptase](attachment://Figure6.png)

![UK-453,061 and reference compounds against panel of HIV-1 reverse transcriptase](attachment://Figure7.png)

![UK-453,061 and reference compounds against panel of HIV-1 reverse transcriptase](attachment://Figure8.png)
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Abstract

Background: NNRTIs are key components of HAART, when combined with other anti-retroviral agents they can lead to sustained reductions in viral load and slow the rate of disease progression. However, NNRTIs are susceptible to mutations in HIV RT, in particular changes that can lead to class resistance. There is a need for a safe and well-tolerated NNRTI with activity against clinically significant drug-resistant viruses, which can be conveniently combined with agents from other classes.

Methods: We utilized biochemical and structural information to optimize a series of pyrazoles against a panel of mutant enzymes encompassing the majority of clinically relevant mutations. Leads were evaluated for efficacy against a panel of 300 recombinant point-mutated and clinical isolates including AntiVirogram™ and PhenoSense™ HIV phenotypic drug susceptibility assays.

Results: The emerging candidate, UK-453,061 inhibits over 60% of viruses bearing key RT mutations with IC_{50} values within 10-fold of wt viruses, as opposed to less than 40% for currently available NNRTIs. In vitro-derived UK-453,061-resistant strains is sensitive to licensed NNRTIs. In non-clinical safety pharmacology studies, the candidate was well tolerated and displayed little interaction with physiologically important receptors or enzymes. Preclinical ADME data indicates that UK-453,061 is likely to be cleared in humans by a combination of glucuronidation and cytochrome P450 metabolism.

Conclusions: Altogether preclinical data suggest that UK-453,061 is a highly potent and selective NNRTI, with excellent efficacy against NNRTI-resistant viruses, and the pharmacokinetic, pharmaceutical and drug safety credentials of a convenient and well-tolerated HAART component. Clinical studies with UK-453,061 are in progress.