GSK2838232, a second generation HIV-1 maturation inhibitor with an optimized virology profile

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Abstract

Background

The first generation HIV-1 maturation inhibitor bevirimat demonstrated clinical efficacy in infected subjects. However, gag polymorphisms in both capsid (p24) and Sp1 regions were liabilities for bevirimat potency against a broad range of HIV-1 isolates; therefore limiting the clinical utility of bevirimat to 40% of HIV patients without polymorphisms in the 369-370 region of gag.

Methods

We aimed to improve the virology profile of an HIV-1 maturation inhibitor by combining a medicinal chemistry approach with a virology triage strategy focused on activity against gag polymorphisms. Initial anti-viral activity was assessed in an MT4 assay using NL4-3 with a consensus clade B capsid/Sp1 region and compared to a V370A mutant. Compounds with no loss of potency against V370A were progressed into mechanism of action studies and a panel of HIV-1 isolates in a PBMC anti-viral assay.

Results

GSK2838232 was identified using this strategy with an NL4-3 IC50 at 0.81nM and a similar IC50 against V370A at 0.71nM. The effect of human serum addition was assessed on GSK2838232 potency and showed no effect with increasing serum concentrations up to 40%. When tested in a panel of 26 HIV-1 isolates covering a diversity of capsid/Sp1 genotypes in clades A, AE, B, and C using a PBMC based assay, GSK2838232 had a mean IC50 of 1.6nM (IC50 range 0.8nM to 4.3nM). The broad spectrum isolate coverage was confirmed by an external contract research group in a panel of 60 isolates covering various clades with only 1 isolate (92BR014) not inhibited by GSK2838232. The external panel also included viruses with known resistance genotypes to show that GSK2838232 is not cross resistant with marketed anti-retroviral products. Based on previous observations of bevirimat potency and HIV protease inhibitor (PI) treatment, GSK2838232 was tested against a panel of viruses isolated from subjects prior to and post PI treatment and did not have a correlation in potency depending on PI experience.

Conclusions

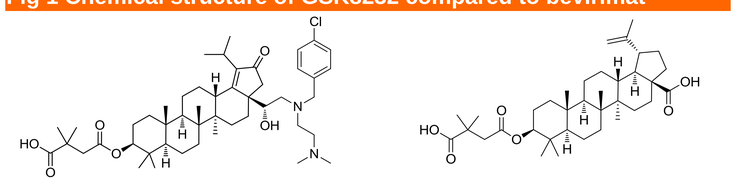
These data demonstrate the optimized anti-viral properties of GSK2838232 and support the further assessment of this compound as a second generation maturation inhibitor for the treatment HIV-1 infected subjects.

Assay details

- The MT4 assay was modified from Averett ,1989 (1)
- The effect of protein binding on anti-viral potency was determined by adding serial dilutions of human serum up to 40% to the standard anti-viral assay and measuring the IC_{50}
- PBMC anti-viral assays were performed as previously described in Muniz-Medina 2009 (2)
- Data in Figures 4 & 6 were generated at SRI (Frederick, Maryland)
- Data in Figure 7 were generated by the lab of Dr. Nijhuis
- IC_{50} plots contain potency ≥ the maximum value on the y-axis

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consent

Fig 1 Chemical structure of GSK8232 compared to bevirimat



GSK2838232

Bevirimat (BVM)

Fig 2 Mechanism of action: GSK8232 inhibits cleavage of CA/Sp1

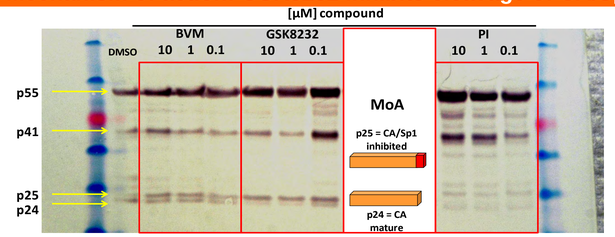


Fig 3 GSK8232 maintains potency against QVT polymorph V370A

Assay	Virus	GSK8232 IC_{50} [nM]	BVM IC_{50} [nM]
MT4 anti-viral	NL.wt	0.81	263
MT4 anti-viral	NL.V370A	0.71	5,200
MT4 cell viability	-	5130	>10,000

Fig 4 GSK8232 has no human serum effect on antiviral potency

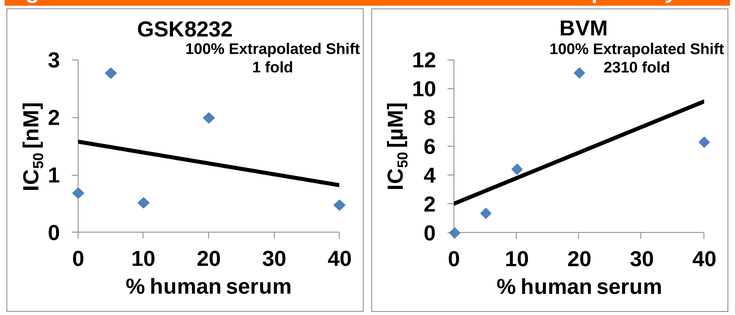
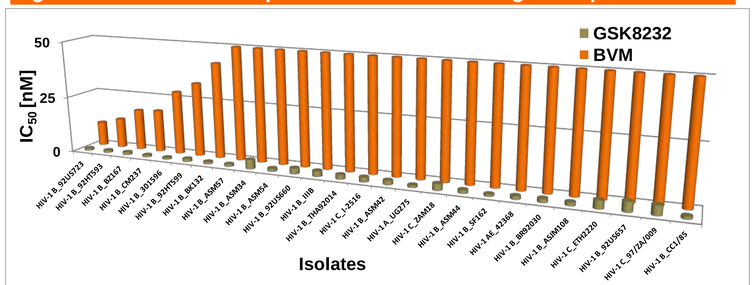
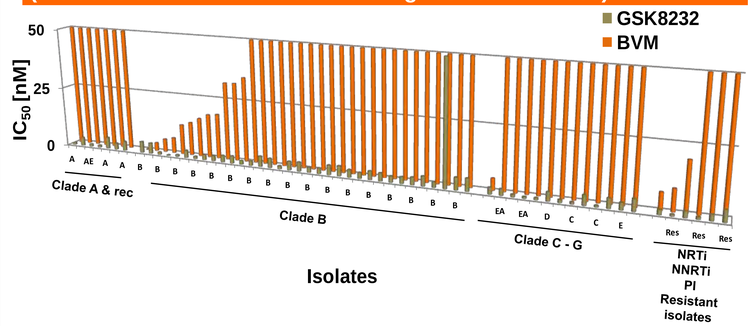


Fig 5 GSK8232 has an optimized isolate coverage compared to BVM



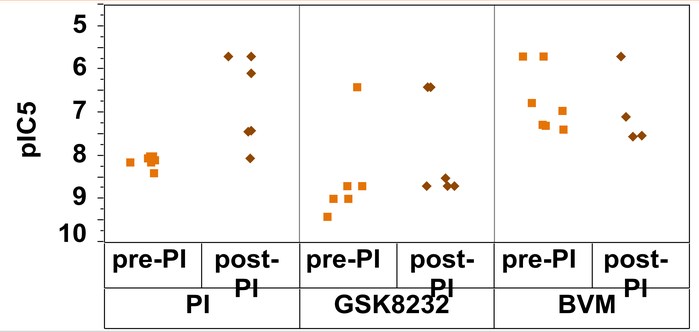
GSK8232 inhibits clades A, AE, B, & C HIV-1 isolates with mean IC_{50} = 1.6nM

Fig 6 GSK8232 has an optimized profile in a larger virus panel (includes additional clades and drug resistant viruses)



GSK8232 has optimized cross clade potency, and does not display cross-resistance to viruses with resistance mutations to common marketed anti-retrovirals

Fig 7 GSK8232 potency is not affected by PI therapy



Viruses prior to or post Protease Inhibitor (PI) therapy do not correlate with GSK8232 potency (pIC50=-log(IC50 M)) Note: not all pre/post viruses are paired by subject

Conclusions

- Mechanism of action for GSK8232 is consistent with maturation inhibition
- GSK8232 anti-viral IC50 is not affected by human serum up to 40% by volume
- GSK8232 has an optimized virology profile compared to BVM
- GSK8232 IC50 ≤ 5nM for 97 of 101 viruses tested in vitro
- GSK8232 is potent against viruses resistant to marketed anti-retrovirals
- GSK8232 is potent against 10/12 PI resistant isolates (data combined from Figures 6 & 7)
- GSK8232 is in Phase I clinical development as a second generation maturation inhibitor

References

1. Averett, D. Anti-HIV compound assessment by two novel high-capacity assays. J Virol Methods 1989; 23:263-76
2. Muniz-Medina, V. The relative activity of “Function Sparing” HIV-1 entry inhibitors on viral entry and CCR5 internalization: Is allosteric functional selectivity a valuable therapeutic property? Mol Pharmacol 2009; 75:490-501

Acknowledgements

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