Poster #00637

Discovery of GS-9770 – a Novel, Unboosted, Once Daily Oral HIV-Protease Inhibitor

Xiaochun Han*; Ron Aoyama; Jacob Cha; Aesop Cho; Ana Z Gonzalez; Salman Jabri; Michael Lee; Albert C. Liclican; Ryan McFadden; Andrew Mulato; Zach E. Newby; Jie Xu; Johannes Voigt; Lianhong Xu; Hong Yang

Gilead Sciences, Inc., Foster City, CA

Conclusions

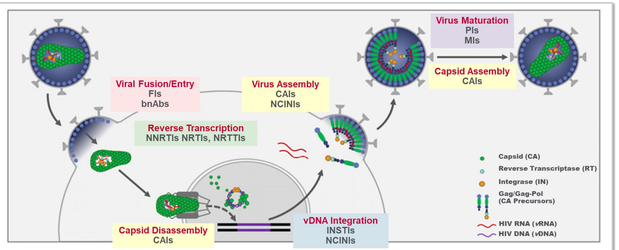
A novel, potent, selective, non-peptidomimetic, unboosted once daily (QD) oral HIV-PI was discovered

GS-9770 demonstrated high activity against all drug resistant viruses tested

Metabolic stability was hard earned and necessitated careful blockage of key hot spots

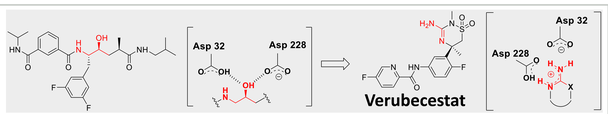
Background

- HIV-protease inhibitors (PIs) block the cleavage of precursor proteins needed for viral maturation and infectivity



Cell, **2021**, *184*, 1032–1046

- Traditional PIs require PK boosting with a CYP inhibitor to enable QD dosing
- Guanidine as novel transition state mimic for aspartic proteases was exemplified in unboosted QD β-secretase (BACE) inhibitors

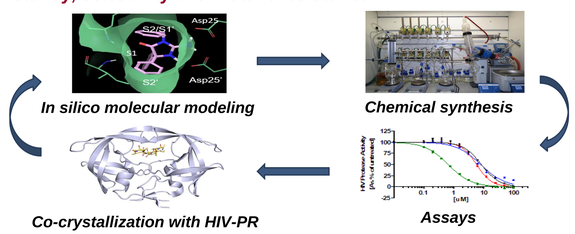


>85% Hepatic Extraction **<10% Hepatic Extraction**

- **Goal: to discover Guanidine-based unboosted QD HIV-PIs**

Methods

Potency, selectivity and mutant resistance

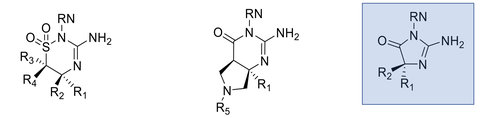


Metabolic stability

- *in vitro* stability assays (hMS), Met ID (hMS/ hHep)
- *in vivo* PK studies on pre-clinical species

Results

1. Identifying iminohydantoin "core" scaffold via molecular modeling



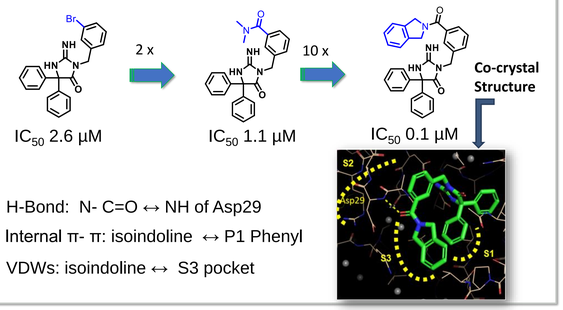
❑Flexible core ❑Good vectors ❑Low LE*

❑Rigidified core ❑Good vectors ❑Low LE

❑Rigidified core ❑Good vectors ❑High LE

(LE – Ligand efficiency)*

2. Gaining biochemical potency with P2-benzamide



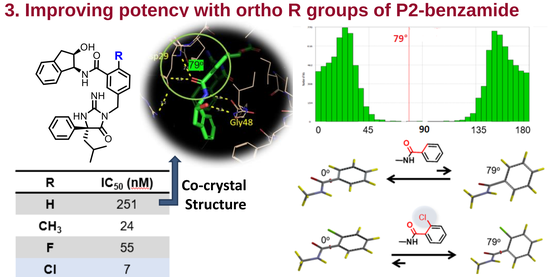
IC_{50} 2.6 μM IC_{50} 1.1 μM IC_{50} 0.1 μM

H-Bond: N- C=O ↔ NH of Asp29

Internal π- π: isoindoline ↔ P1 Phenyl

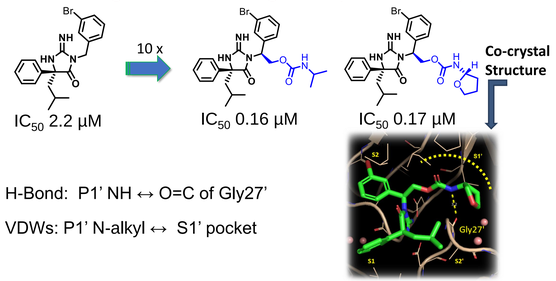
VDWs: isoindoline ↔ S3 pocket

3. Improving potency with ortho R groups of P2-benzamide



R	IC_{50} (nM)
H	251
CH_3	24
F	55
Cl	7

4. Establishing "4-point" binding mode (P1/P1'/P2/P2')

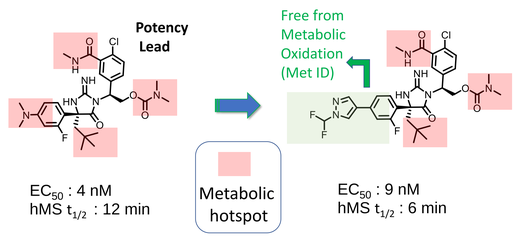


IC_{50} 2.2 μM IC_{50} 0.16 μM IC_{50} 0.17 μM

H-Bond: P1' NH ↔ O=C of Gly27'

VDWs: P1' N-alkyl ↔ S1' pocket

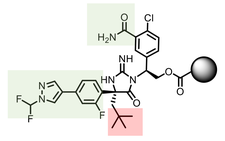
5. Optimizing P1 – metabolically stable "bi-aryl"



EC_{50} : 4 nM
hMS $t_{1/2}$: 12 min

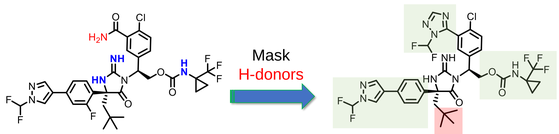
EC_{50} : 9 nM
hMS $t_{1/2}$: 6 min

6. Optimizing P1' – CF_3 substituted cyclopropyl on carbamate improves metabolic stability



	CD_3 CD_3			CF_3
EC_{50} (nM)	23	58	45	40
hMS $t_{1/2}$ (min)	4	43	100	342

7. Optimizing P2 – N-CF_2H substituted 1,2,4-triazole as an amide isostere improves bioavailability

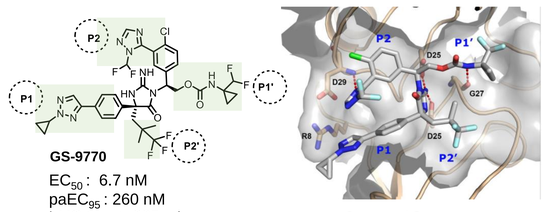


Caco-2 AB/BA [ER*]: 0.8 /10 [14]
F% (rat): <10 %

Caco-2 AB/BA [ER]: 9.7 /14 [1.4]
F% (rat): 47%
EC_{50} : 7.7 nM
hMS $t_{1/2}$: 230 min

** ER: efflux ratio = BA/AB*

8. Optimizing P2' – fluorination improves metabolic stability / fine tuning at P1 and P1' reduces protein binding

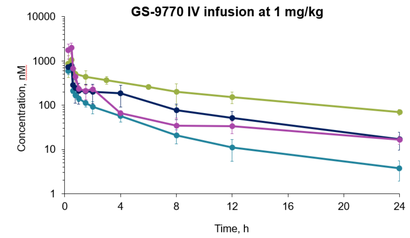


GS-9770
EC_{50} : 6.7 nM
$paEC_{95}$: 260 nM
hMS $t_{1/2}$: > 395 min

9. GS-9770 displays high selectivity against off-target aspartic proteases

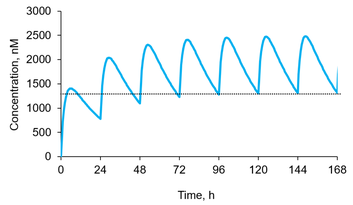
HIV protease K_i(app), pH 5.3, nM	Fold selectivity over off-target				
	BACE	Cathepsin D	Cathepsin E	Pepsin	Renin
0.14	>710000	390000	13000	480000	980

10. GS-9770 displays good PK profiles in pre-clinical species



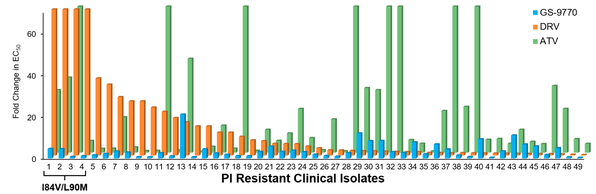
	$t_{1/2}$ hours	%F (5 mg/kg)
Rat	10.6	46
Cyno	7.4	100
Rhesus	11.7	—
Dog	6.7	100

11. GS-9770 reaches the projected human efficacious QD dose



	GS-9770 400 mg
Target C_{trough}	1.3 μM (IQ5)
Plasma CL	0.09 L/h/kg
Bioavailability	60%
$t_{1/2}$	18.5 h

12. GS-9770 displays superior resistance profile



Fold Change in EC_{50}	GS-9770	DRV	ATV
Mean (SD)	3.8 (3.8)	52.8 (154.9)	16.4 (23.2)
Range	0.4–21	0.3–615	0.6–>132
Viruses with >10-fold change in EC_{50}, n/N (%)	3/49 (6)	17/49 (35)	23/49 (47)

Presented at CROI 2024; March 3-6, 2023; Denver, Colorado