Computational design of novel potent inhibitors of HIV-1 entry

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Summary

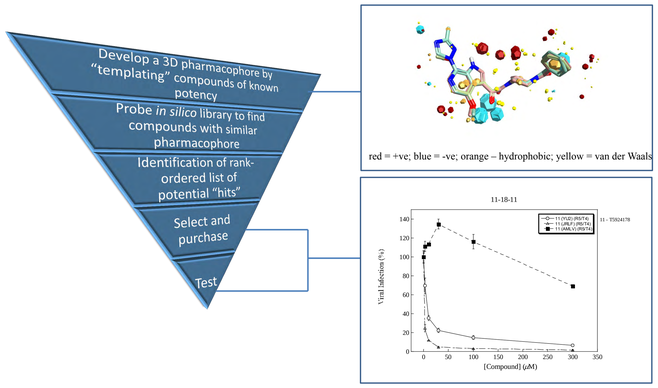
Background: The process of HIV-1 entry is key to the replication of the virus. It is one of the most attractive targets in the search for new drugs to treat HIV-1 infection as entry inhibitors would have utility in both pre- and post-exposure prophylaxis, including woman-controlled microbicides. In the HIV-1 entry field, two main inhibitor chemotypes predominate (BMS-377806- and NBD-556-type compounds) with the BMS-377806 analogues demonstrating superior potency. However, the BMS-377806 analogues suffer from poor solubility and oral bioavailability. Therefore, given the enormous potential of small molecule entry inhibitors, we have designed and tested a series of novel compounds that function as entry inhibitors and have better predicted ADME/PK properties.

Methods: To identify novel compounds that function as entry inhibitors, we performed a high-content pharmacophore virtual screen using Blaze v10 (Cresset, UK) and a pharmacophore derived from templating BMS-377806, BMS-488043, and BMS-626529 using FieldTemplater v3.0 (Cresset, UK). Fifty compounds were purchased for testing in the single round infection assay against HIV-1 pseudotyped with HIV-1 Env and AMLV Env. Spark v10 (Cresset, UK) and StarDrop v5.2 (Optibrium, Ltd., UK) were employed to design a series of next-generation compounds with novel scaffolds. Next-generation compounds were synthesized and tested for potency and specificity in the single-round infection assay.

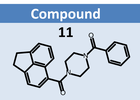
Results: Assessment of the antiviral potencies and specificity of 50 commercially available screening compounds identified 5 novel compounds previously undescribed in the literature. However, each hit contained a core piperazine, a moiety that is shared by the BMS-377806-type inhibitors. Replacement of the core piperazine with a dipyrrolidine yielded a novel inhibitor with high micromolar potency. Sequential replacements of a terminal acenaphthene ring with varying azaindole groups resulted in an inhibitor with low nanomolar potency. However, predicted ADME/PK properties remained poor. Replacement of the dipyrrolidine with a pyrrolo-3,4-pyrazole afforded a compound with improved predicted ADME/PK properties and that retained nanomolar potency.

Conclusions: Using a combination of high-content pharmacophore virtual screening, coupled with scaffold hopping by bioisosteric replacements, and consideration of predicted ADME/PK properties, we have designed a new small-molecule entry inhibitor with a novel scaffold, nanomolar potency, and improved predicted drug-like properties. This new chemotype may provide a blueprint for the future development of small molecule entry inhibitors, whilst characterization of its mechanism of action will yield important basic information about the process of HIV-1 entry.

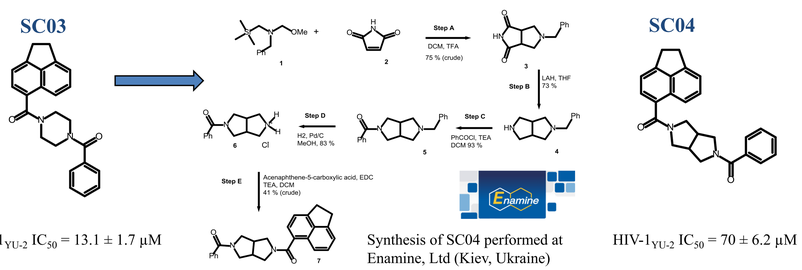
Identification of SC03 by *in silico* "FieldScreening"



Fifty compounds purchased and tested for potency and specificity. Five compounds identified. Compound 11 was most potent.

Compound	IC_{50} YU-2 (μM)	IC_{50} AMLV (μM)
11 	13.1 ± 1.7	N.A.

"Core" scaffold hopping – piperazine to dipyrrolidine

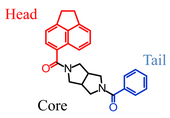


$HIV\text{-}1_{YU\text{-}2}$ IC_{50} = 13.1 ± 1.7 μM

Synthesis of SC04 performed at Enamine, Ltd (Kiev, Ukraine)

$HIV\text{-}1_{YU\text{-}2}$ IC_{50} = 70 ± 6.2 μM

Potency optimization of the dipyrrolidine scaffold

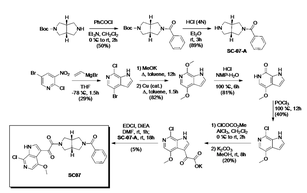


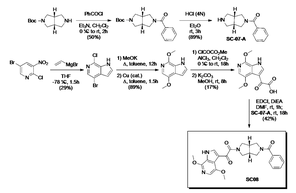
- Successfully changed "core" piperazine to dipyrrolidine
- Acenaphthene group lacks any potential for H+ bonding and can be genotoxic
- Therefore, asked question "Can we make a submicromolar potency molecule with the new core by modifying the head group?"

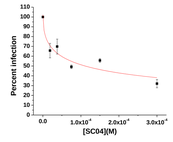
Two new compounds were designed by comparing BMS entry inhibitor head groups to acenaphthene group on **SC04** using Spark v10 (Cresset, UK).
SC07 and **SC08's** head group were chosen on their percentage bioisosteric factor (BIF%). **SC07** = BIF% 57; **SC08** = BIF% 64.

AsisChem Inc. Advancing Science Through Synthesis

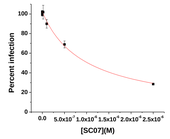
Synthesis of compounds **SC07** and **SC08** was performed at AsisChem, Inc. (Waltham, MA) using the schemes below.



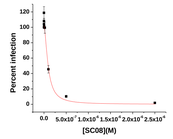




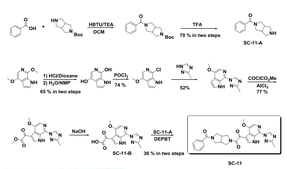
$HIV\text{-}1_{JR\text{-}CSF}$ IC_{50} = 102 ± 31 μM



$HIV\text{-}1_{JR\text{-}CSF}$ IC_{50} = 0.98 ± 0.06 μM

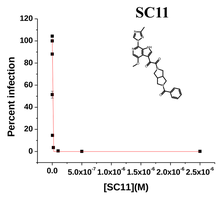


$HIV\text{-}1_{JR\text{-}CSF}$ IC_{50} = 0.09 ± 0.01μM



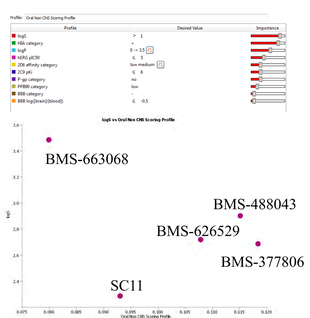
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Synthesis of **SC11** was performed at HD Biosciences (Shanghai, China).



$HIV\text{-}1_{JR\text{-}CSF}$ IC_{50} = 0.8 ± 0.4 nM

In silico ADME analysis of SC11



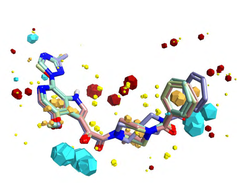
Compounds were analyzed in StarDrop v5.5 (Optibrium, Ltd., Cambridge, UK) against an oral non-CNS drug scoring profile (left).

As can be seen from the graph on the left, plotting logS versus oral non-CNS drug scoring profile, **SC11,** although it has good potency and a new core scaffold, does not offer improvements over current BMS piperazine-based entry inhibitors in terms of predicted ADME.

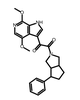
Therefore, we decided to perform further scaffolding, hoping to improve the oral non-CNS drug profile score, and specifically the human intestinal adsorption (HIA) profile, which is the parameter on which all of the compounds score very poorly.

Dipyrrolidine to pyrrolo-3,4-pyrazole scaffold

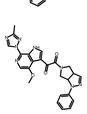
Based on the conformation derived from templating BMS-377806, BMS-488043, BMS-626529, and SC11 (using FieldTemplater, Cresset, UK), two new compounds were designed—**SC10** and **SC12**. These compounds were assessed using StarDrop before synthesis and testing.



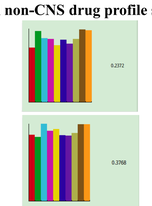
SC10



SC12

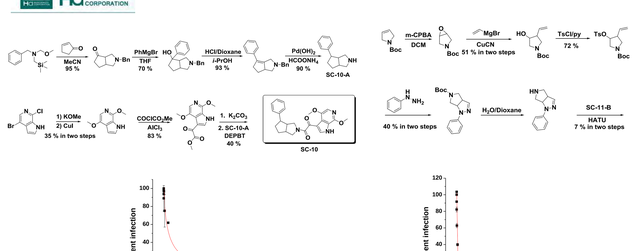


Oral non-CNS drug profile score



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Compounds **SC10** and **SC12** were synthesized at HD Biosciences (Shanghai, China).



$HIV\text{-}1_{JR\text{-}CSF}$ IC_{50} = 0.42 ± 0.11μM

$HIV\text{-}1_{JR\text{-}CSF}$ IC_{50} = 8.0 ± 2.0 nM

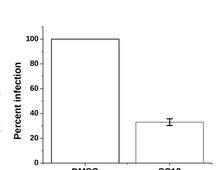
SC12 has a range of potencies against various isolates

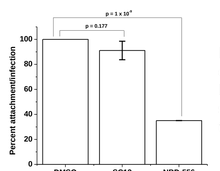
Subtype B isolates

Clade	Isolate	IC_{50}
A	BG505	2.2 ± 0.6 μM
	QG984	507 ± 81 nM
C	DU156	2.5 μM
	DU422	142.5 nM
	ZM53	1.0 ± 0.28 μM
D	QA456	22 nM

SC12 does not appear to block cellular attachment of the virus

Right: Effect of 100 nM of SC12 on the infection of U87.CD4.CXCR4 cells with HxBc2 Env pseudotyped single-round infective HIV-1





Left: Effect of 100 nM of SC12 on the attachment/infection of HxBc2 Env pseudotyped single-round infective HIV-1 to/with U87.CD4.CXCR4 cells

Acknowledgments

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