From RT Inhibitor to RT / IN Dual Inhibitor: A Rational Design

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Introduction

Highly Active Anti-Retroviral Therapy (HAART)

- Standard chemotherapy for HIV / AIDS
- Combine at least 3 drugs and 2 mechanisms of action
- Suppress viral replication
- Improve life quality

Major Drawbacks of HAART

- Regimen complexity
- Side effects
- Cost

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Suboptimal adherence

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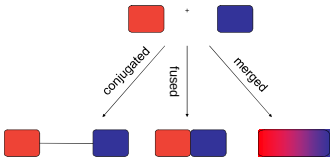
- Viral rebound
- Multi-drug resistance (MDR)

Designed Multiple Ligands (DMLs)



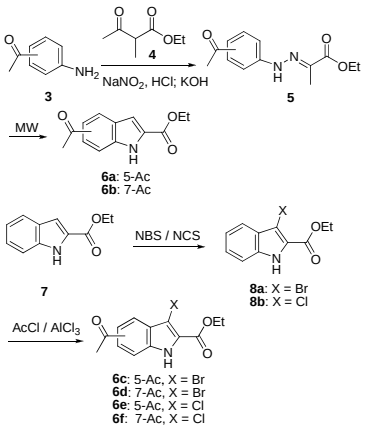
- Capable of inhibiting resistant viral strains
- Less complex dosing
- Fewer side effects
- Lower cost

Major Challenges

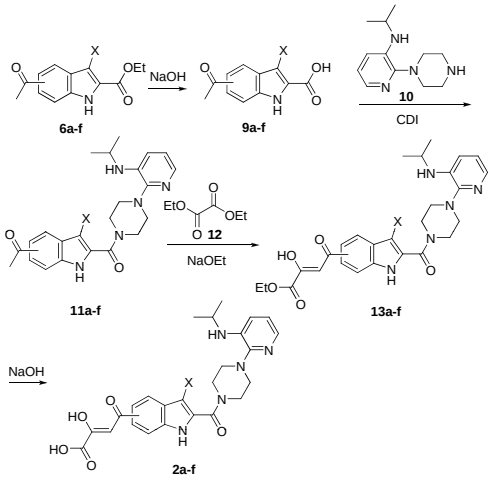
- Minimize binding interference
- Balance binding affinities

Synthesis

Preparation of Acyl Indole-2-carboxylates



Synthesis of Dual Inhibitors



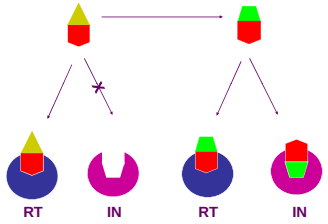
Design

Reverse Transcriptase (RT)

- A primary target for therapeutic intervention
- Structural and binding information well established

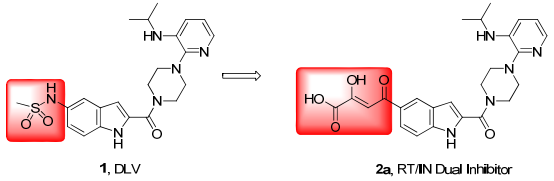
Integrase (IN)

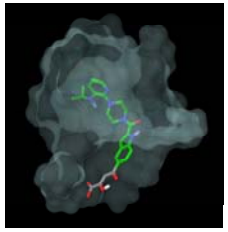
- A newly validated target
- Detailed binding information unknown



Key to The Design of RT/IN Dual Inhibitor

- Identify a tolerate site in RT pharmacophore
- Incorporate a structural motif that induces anti-IN activity





Target Validation

The designed RT/IN dual inhibitor **2a** is docked into the NNRTI binding pocket almost identically to DLV (**1**). It is also shown that the DKA moiety is sitting in an open area and is not directly involved in binding to RT.

Assay

Table 1. Anti-RT, anti-IN and anti-HIV assay results for inhibitors **2a-f**

Inhibitor	X	Sub	RT IC_{50} (μM)	IN IC_{50} (μM)[a]	HIV EC_{50} (μM)	HIV-1_{K103N} EC_{50} (μM)	HIV-1_{L100I} EC_{50} (μM)	HIV-1_{Y181C} EC_{50} (μM)
1(DLV)	--	--	0.036	>100	0.009	>0.10	>0.10	>0.10
2a	H	5	0.0059	11	0.52	5.0	>10	>10
2b	H	7	>100	>100	>10	--	--	--
2c	Br	5	0.12	3.9	0.79	3.2	2.9	>10
2d	Br	7	>100	75	>10	--	--	--
2e	Cl	5	1.1	4.7	0.98	4.1	3.6	9.4
2f	Cl	7	>100	>100	>10	--	--	--

[a] Average activity against 3' processing and strand transfer.

Conclusions

- Replacing methyl sulfonamide group of DLV with a DKA yielded RT/IN dual inhibitor
- The site of DKA incorporation is crucial: C-5 Vs C-7
- Halogenation at C-3 position led to balanced dual activity
- Dual inhibitors with balanced activity demonstrated low fold-resistance against clinically relevant single mutants.