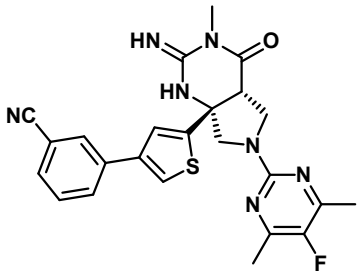
DOTW: Bicyclic Iminopyrimidinone BACE1 Inhibitors



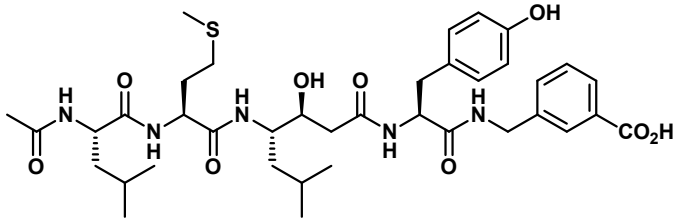
- β-secretase (BACE1) cleaves amyloid precursor protein (APP), leading to an increase in β-amyloid peptides (Aβ)

- Aβ plaques and tau protein tangles have been shown to be directly related to cognitive decline in Alzheimer's disease (AD)

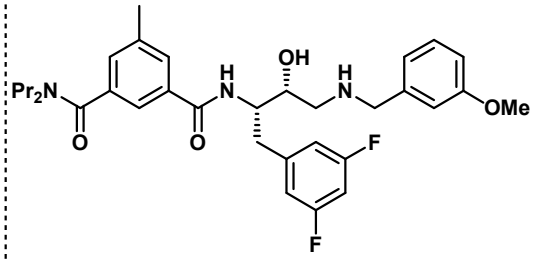
- BACE1 knockout mice do not exhibit the production of Aβ, and show moderate AD phenotypes

Mandal, M. *el al. J. Med. Chem.* **2012**, *55*, 9331.
Mandal, M. *el al. J. Med. Chem.* DOI: 10.1021/acs.jmedchem.8b01326

Peptidomimetic BACE1 Inhibitors



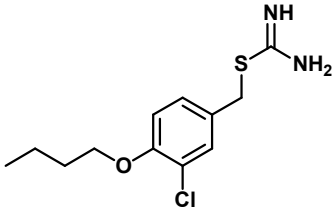
BACE1 IC_{50} = 91 nM



BACE1 IC_{50} = 20 nM

With the success of transition state mimetics of proteases, the first generation $BACE_1$ inhibitors were centered around this structrual feature. However, their high molecular weight, low permeability, and high susceptibility to efflux made these inefficient treatments.

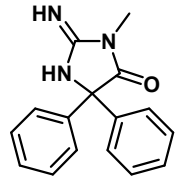
Iminopyrimidinone evolution



BACE1 K_i >200 μM

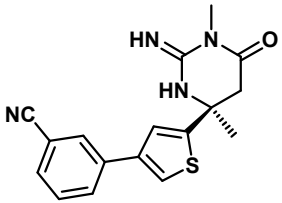
Fragment-based lead generation

MERCK



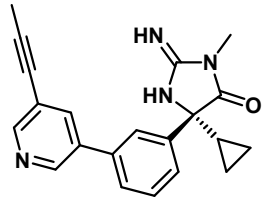
BACE1 K_i = 3.7 μM

Affinity-driven optimization



BACE1 K_i = 56 nM

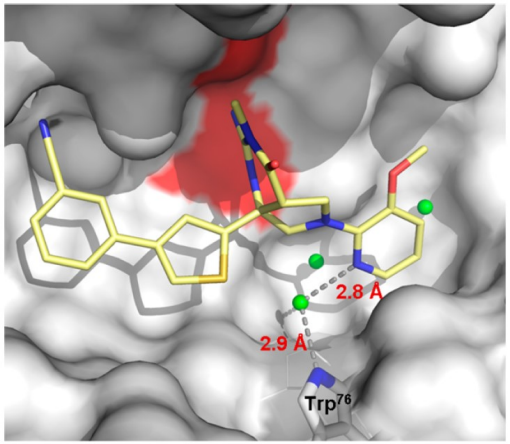
Structurally distinct



BACE1 K_i = 5 nM

Ligand efficiency, bioavailability, selectivity

Co-crystal of ligand bound in BACE1



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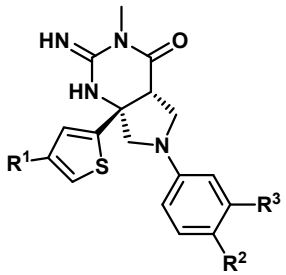
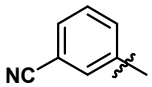
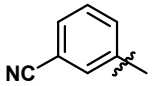
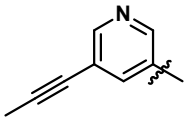
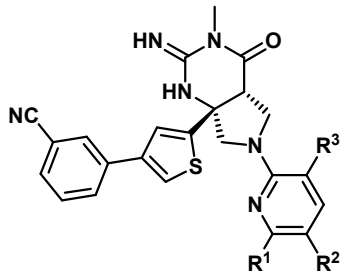
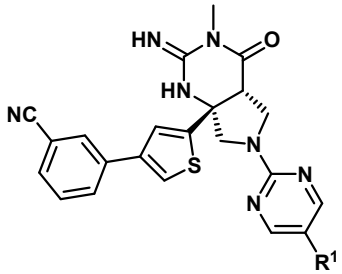


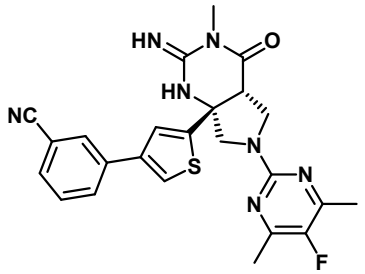
cpd	R^1	R^2	R^3	MW (ClogP)	BACE1 K_i (nM)	CatD/ BACE1	Rat $AUC_{0\text{-}6h}$ (μM.hr)
A		F	H	445 (3.9)	26	12	n.d.
B		H	O-*i*Pr	486 (4.7)	15	17	n.d.
C		H	O-*i*Pr	499 (4.4)	2	82	3.7



cpd	R^1	R^2	R^3	MW (ClogP)	BACE1 K_i (nM)	CatD/ BACE1
A	H	H	H	428 (2.7)	8	23
B	H	H	OMe	458 (3.1)	3	42
C	H	H	CN	454 (2.3)	6	39
D	H	F	H	446 (2.9)	6	15
E	OMe	H	H	458 (3.5)	1	89
F	CF_3	H	H	496 (3.7)	64	n.d.



cpd	R^1	MW (ClogP)	BACE1 K_i (nM)	CatD/ BACE1	Rat $AUC_{0\text{-}6h}$ (μM.hr)	brain 6 h (μM)	brain/plasma	rat PBB (% unbound)
A	H	429 (1.9)	11	28	2.0	0.058	1.0	2.2
B	F	447 (2.1)	4	94	31	0.463	0.1	2.4
C	Cl	464 (2.6)	7	81	90	0.965	0.1	0.4
D	Me	443 (2.4)	9	67	111	0.232	<0.1	n.d.



Prevents CYP3A4 Time-Dependent Inhibition

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