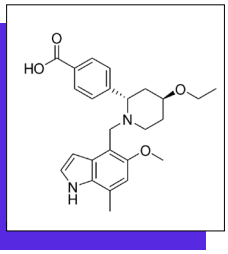
Small Molecules of the Month

February 2020
drughunter.com



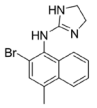
LNP023

Selective factor B serine protease inhibitor
Orally available, retinal barrier penetrant
From 250k compound HTS and SBDD lead op.
J. Med. Chem., Feb. 19, 2020
Novartis (NIBR), Cambridge, MA

Hit-Finding:
"Full deck" HTS of 1.1M compounds in ELISA assay.

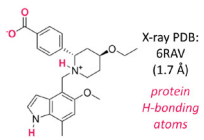
Targeted HTS of 250k compounds in CVF-Bb inhib. assay.

Fragment-based screen (NMR, X-ray).



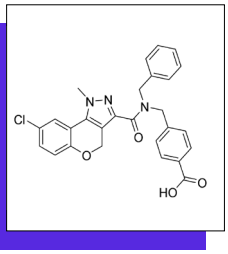
X-ray PDB: 6QSW (1.64 Å)

Factor B SPR K_d: 10 μM
hERG RLB IC_{50}: 7.1 μM
α1a IC_{50}: 0.3 μM
α2c IC_{50}: 0.18 μM
>30 μM vs. 17 other proteases



X-ray PDB: 6RAV (1.7 Å)
protein H-bonding atoms

Factor B SPR K_d : 7.9 nM
hERG, α1a, α2c IC_{50}: >30 μM
>30 μM vs. 41 other proteases
completed Ph. 1 in HV

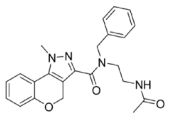


LMB763 (nidufexor)

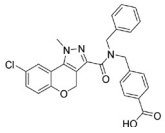
Selective FXR partial agonist
Orally efficacious in NASH models
From two 3M compound HTS and LBD
J. Med. Chem., Jan. 15, 2020
Novartis (GNF), San Diego, CA

Hit-Finding:
"Full deck" HTS of ~3M compounds in FXR/SRC1 HTRF biochemical assay.

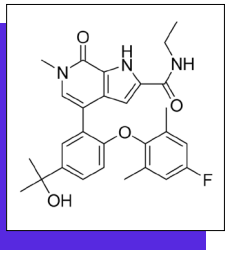
"Full deck" HTS of ~3M compounds in FXR BSEP-luc reporter cellular assay.



FXR HTRF EC_{50}: 480 nM
FXR Cell EC_{50}: 690 nM
Overlapping HTS hit



FXR HTRF EC_{50}: 7 nM
FXR Cell EC_{50}: 32 nM
completed Ph. 1 in HV

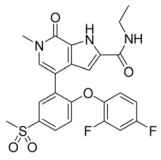


ABBV-744

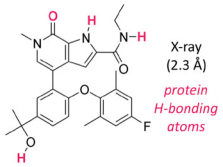
BD2 domain selective BET inhibitor
Orally efficacious in XG w/o platelet, GI tox
From SBDD of BD1/2 dual inhibitors
Nature, 2020, 578, 306-310
AbbVie, North Chicago, IL

Starting Point:

Re-evaluation of 2500 dual-bromodomain BET inhibitors

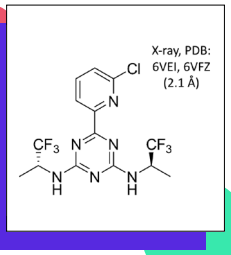


BRD4 BD2 IC_{50}: 1.2 nM
BRD4 BD1 IC_{50}: 22 nM



X-ray (2.3 Å)
protein H-bonding atoms

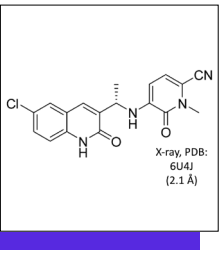
BRD4 BD2 IC_{50}: 28 nM
BRD4 BD1 IC_{50}: 20700 nM



X-ray, PDB: 6VEI, 6VFZ (2.1 Å)

AG-881 (vorasidenib)

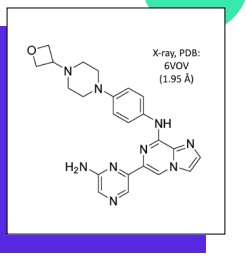
Allosteric mutant IDH1/2 dual inhibitor
Oral, brain penetrant, completed Ph. I in HV
From SBDD of prior mIDH inhibitor
ACS Med. Chem. Lett., 2020, 11, 101-107
Agios Pharmaceuticals, Cambridge, MA



X-ray, PDB: 6U4J (2.1 Å)

FT-2102 (olutasidenib)

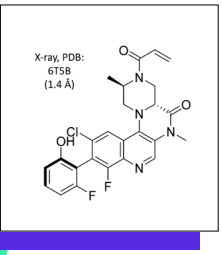
Allosteric mutant-selective IDH1 inhibitor
Oral, in clinical development
From SBDD of prior mIDH inhibitor
J. Med. Chem. 2020, 63, 1612-1623
FORMA Therapeutics, Watertown, MA



X-ray, PDB: 6VOV (1.95 Å)

GS-9876 (lanraplenib)

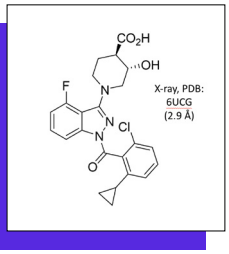
SYK-selective kinase inhibitor
Oral, completed Ph. I in HV
From optimization of prior candidate
ACS Med. Chem. Lett. Feb. 12, 2020
Gilead Sciences, Seattle, WA



X-ray, PDB: 6T5B (1.4 Å)

"Compound 25"

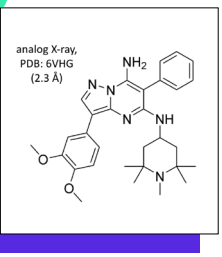
Mutant KRASG12C allosteric covalent inhibitor
Orally efficacious in XG model
From optimization of literature starting point
J. Med. Chem. Feb. 5, 2020
AstraZeneca, Cambridge, UK



X-ray, PDB: 6UCG (2.9 Å)

"Compound 25"

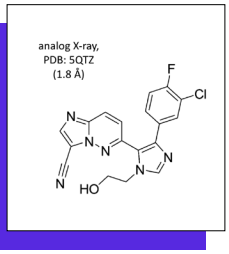
RORγt allosteric inhibitor
Orally bioavailable in higher species
From HTS and ligand-based design
ACS Med. Chem. Lett. 11, 114-119
Merck, Boston, MA



analog X-ray, PDB: 6VHG (2.3 Å)

WF-47-JS03

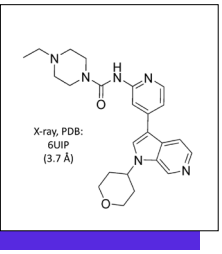
RET kinase inhibitor
Orally efficacious in XG but narrow TI
From data mining of internal matter and opt.
ACS Med. Chem. Lett. Feb. 12, 2020
Novartis (GNF), San Diego, CA



analog X-ray, PDB: 5QTZ (1.8 Å)

BMS-986260

Selective TGFβR1 kinase inhibitor
Completed oral CV studies in higher species
From data mining of internal matter and opt.
ACS Med. Chem. Lett. 11, 172-178
Bristol-Myers Squibb, Princeton, NJ



X-ray, PDB: 6UIP (3.7 Å)

GNF2133

GSK3β-sparing DYRK1A kinase inhibitor
Orally efficacious in proliferation model, but non-specific proliferation observed
from cellular phenotypic screen and opt.
J. Med. Chem. Feb. 20, 2020
Novartis (GNF), San Diego, CA

drug hunter