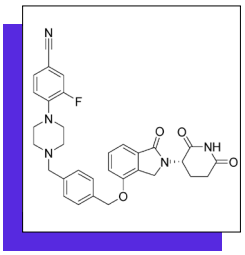
Small Molecules of the Month

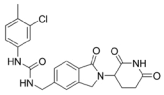
March 2020
drughunter.com



CC-92480

CRBN-based selective IKZF1/3 degrader
Oral efficacy in lenalidomide-resist. xenograft
From phenotypic screen and optimization
J. Med. Chem., Mar. 4, 2020
Celgene, San Diego, CA

Activity in lenalidomide-resistant cells. In vivo toxicity.

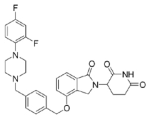


Aiolos EC_{50}: 59 nM
GSPT1 EC_{50}: 1 nM

Screen of CRBN mod. library for activity in lenalidomide-resist. cell line.

Counterscreen against toxicity to PBMCs

Rapid degradation kinetics. Activity on off-target receptors.



Aiolos EC_{50}: 0.1 nM
GSPT1 EC_{50}: >10000 nM

Reduced off-target binding

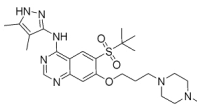
CC-94280

Ph. 1 in RR-multiple myeloma

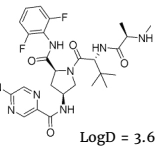
"PROTAC 6"

IAP-based selective RIPK2 degrader
Prolonged PD w/ 0.15 mpk SC Q3D dosing
E3 binder switch and property-based opt.
Commun. Biol., Mar. 20, 2020
GlaxoSmithKline, Stevenage, UK / PMCC

RIPK2 binder



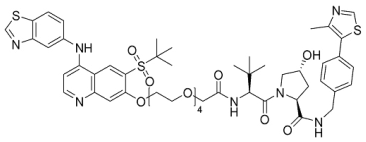
IAP binder



RIPK2 DC_{50}: 0.4 nM
hWB EC_{50}: 3.2 nM
Rat $T^1/_2$ = 16 h

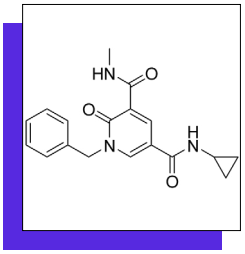
LogD = 3.6
Sol. = 346 µM

RIPK2 binder



VHL binder

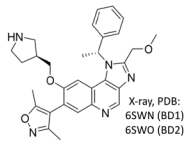
RIPK2 DC_{50}: 2 nM



GSK620

BD2 domain selective BET inhibitor
Oral efficacy in 3 inflammation models
From SBDD of a BD2-selective HTS hit
Science, Mar. 19, 2020
GlaxoSmithKline, Stevenage, UK

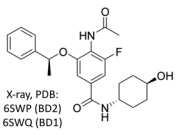
BD1-selective tool (GSK778)



X-ray, PDB: 6SWN (BD1) 6SWO (BD2)

BRD4 BD1 IC50: 40 nM
BRD4 BD2 IC50: 6300 nM

BD2-selective tool (GSK046)

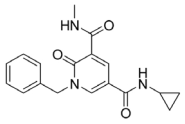


X-ray, PDB: 6SWP (BD2) 6SWQ (BD1)

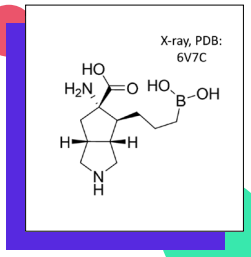
BRD4 BD1 IC_{50}: >50000 nM
BRD4 BD2 IC_{50}: 50 nM

+%F

Oral efficacy in arthritis, psoriasis, liver fibrosis models



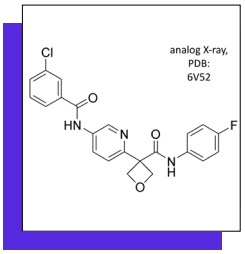
BRD4 BD1 IC_{50}: 16000 nM
BRD4 BD2 IC_{50}: 79 nM



X-ray, PDB: 6V7C

"Compound 3"

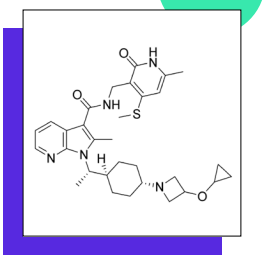
Human arginase 1 inhibitor
%F > 20 in higher species, oral mouse PD
From SBDD of literature starting point
ACS Med. Chem. Lett., Mar. 23, 2020
Merck, Boston, MA



analog X-ray, PDB: 6V52

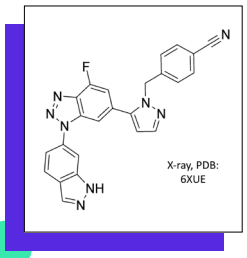
"Compound 13"

Heme-displacing IDO1 inhibitor
Human predicted QD dose of 26 mg
From 260k MS-based screen and SBDD
ACS Med. Chem. Lett. Mar. 10, 2020
Merck, Boston, MA



"Compound 21"

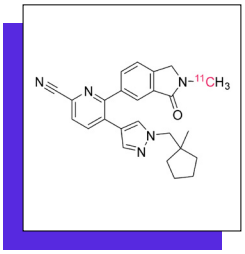
Long-residence time EZH2 inhibitor
Oral efficacy in xenograft model
From optimization of prior EZH2 inhibitor
ACS Med. Chem. Lett., Mar. 26, 2020
Constellation Pharma., Cambridge, MA



X-ray, PDB: 6XUE

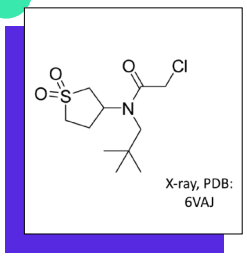
"Compound 74"

Non-nucleoside CD73 inhibitor
HCD73 cell potency of 19 nM
Cell-based HTS of >200k compounds and opt.
J. Med. Chem., Mar. 26, 2020
Arcus Biosciences, Hayward, CA



[^{11}C]MK-6884

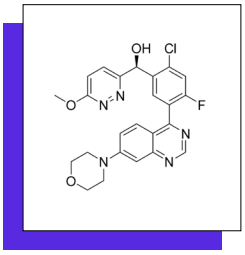
M4 positive allosteric modulator PET tracer
Good uptake and brain signal, BP_{ND} = 0.83
From optimization of prior M4 PAM
J. Med. Chem., Mar. 12, 2020
Merck, West Point, PA



X-ray, PDB: 6VAJ

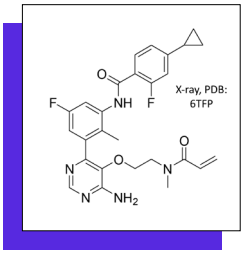
Sulfopin

Selective covalent Pin1 inhibitor
Oral efficacy in xenograft model
From covalent fragment screen and opt.
bioRxiv, Mar. 21, 2020
Weizmann Institute / Harvard Medical



M3814

DNA-PK-selective kinase inhibitor
Oral efficacy in xenograft radiation models
Undisclosed screening and optimization
Mol. Cancer Ther., Mar. 27, 2020
Merck KGaA, Darmstadt, DE



X-ray, PDB: 6TFP

Remibrutinib (LOU064)

BTK-selective covalent kinase inhibitor
Ph. I completed in HV, in Ph. II
SBDD from reversible BTK inhibitor and opt.
J. Med. Chem., Mar. 4, 2020
Novartis, Basel, CH

drug hunter