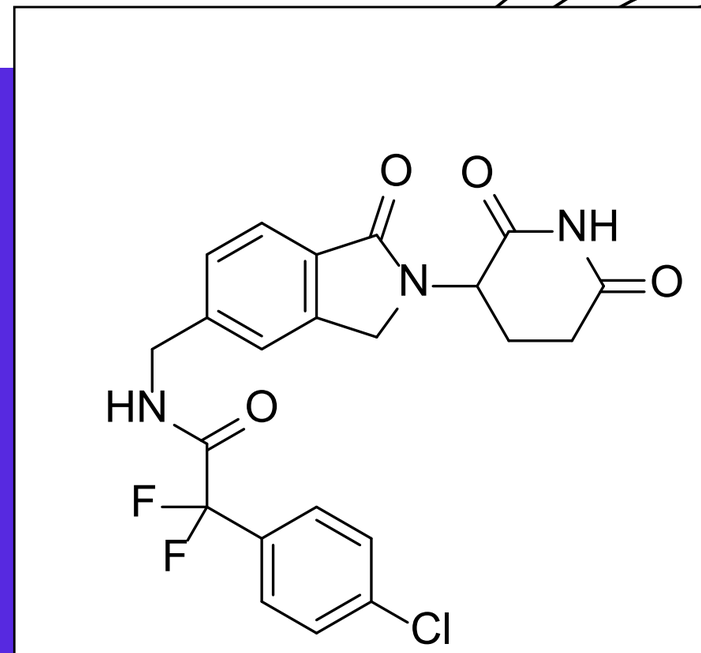
Small Molecules of the Month

February 2021



drug hunter

01	CC-90009	Celgene/Bristol Myers Squibb
02	LYS006	Novartis
03	E7766 (STING)	Eisai Inc.
04	mobocertinib (TAK-788)	ARIAD/Takeda
05	TAK-981	Millenium/Takeda
06	"compound 24"	Bristol Myers Squibb
07	ARB-272572	Arbutus Biopharma Inc.
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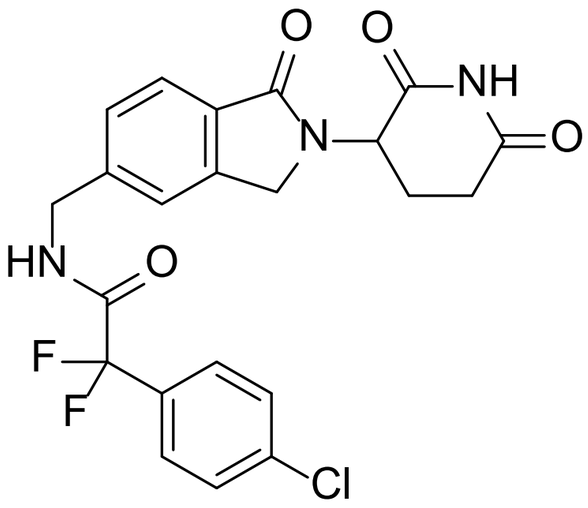
14	NITD-688	Novartis (NITD)

CC-90009

Celgene/Bristol Myers Squibb



CRBN-based GSPT1 molecular glue degrader
Intravenous agent in Ph. I for AML + MDS
From phenotypic screen of CRBN mod library
J. Med. Chem., Feb. 16, 2021
Celgene/Bristol Myers Squibb, San Diego, CA

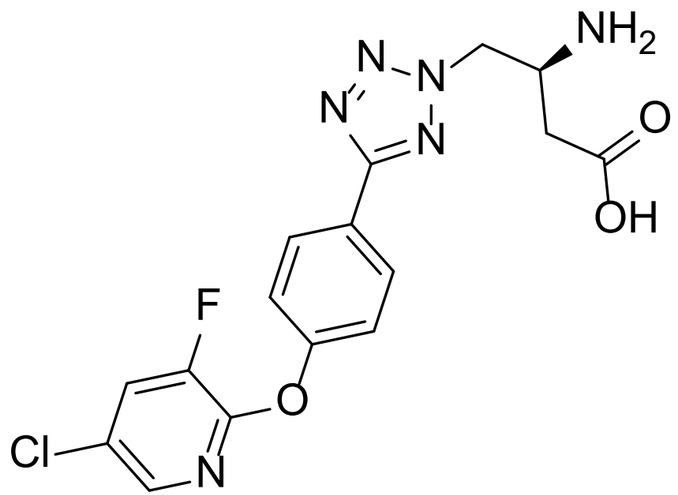
The Bristol Myers Squibb (BMS)/Celgene GSPT1 degrader (CC-90009) is a CRBN-based molecular glue (CELMoD). It is a clinical candidate in Ph. I for AML and MDS, and in contrast to CC-92480 highlighted last March, spares the primary targets of prior imide drugs (IKZF1/3) and instead selectively degrades GSPT1.

The starting point was identified through a phenotypic screen against a panel of AML cell lines using their cereblon (CRBN) modulator library and the nontumor human epithelial cell line (THLE-2) as a counterscreen.

Clinically, at a dose of 2.4 mg, 90% GSPT1 reduction was observed, representing an important proof-of-concept for expanding the scope of molecular glue-type degraders.

LYS006

Novartis



Selective oral LTA4H metalloenzyme inhibitor

In multiple inflamm. Ph. II incl. colitis + NASH

1800 cmpd fragment screen + frag. merging

J. Med. Chem., Feb. 16, 2021

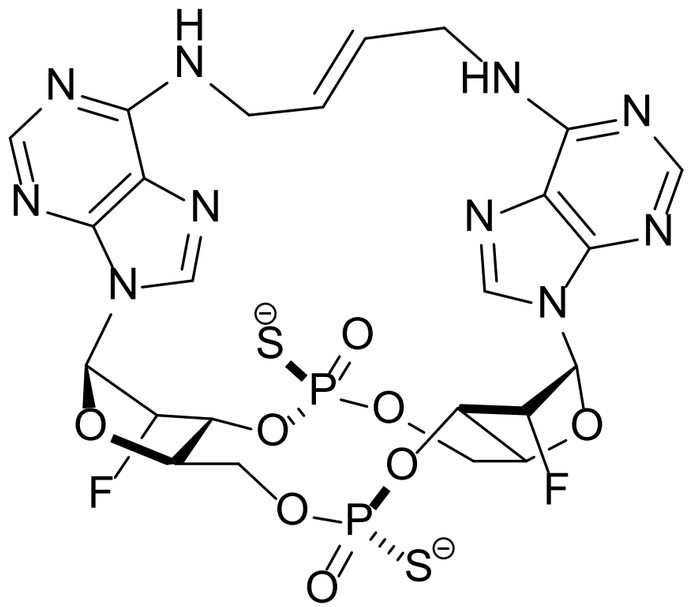
Novartis, Basel, CH

The Novartis LTA4H metalloenzyme inhibitor, LYS006, is a selective oral agent in multiple Ph. II studies to treat inflammatory diseases including ulcerative colitis and NASH. The starting points for this picomolar inhibitor were identified through a fragment based approach using differential scanning fluorimetry (DSF) as an initial binding assay, confirming hits with X-ray crystallography.

Structure based fragment-merging led to a remarkably potent amine lead, and early hERG and CYP inhibition signals were dealt with by introducing a carboxylic acid to the molecule.

E7766 (STING)

Eisai Inc



Intratumoral STING receptor agonist

In Ph. I for adv. solid tumors as single agent

From macrocyclization of cyclic dinucleotide

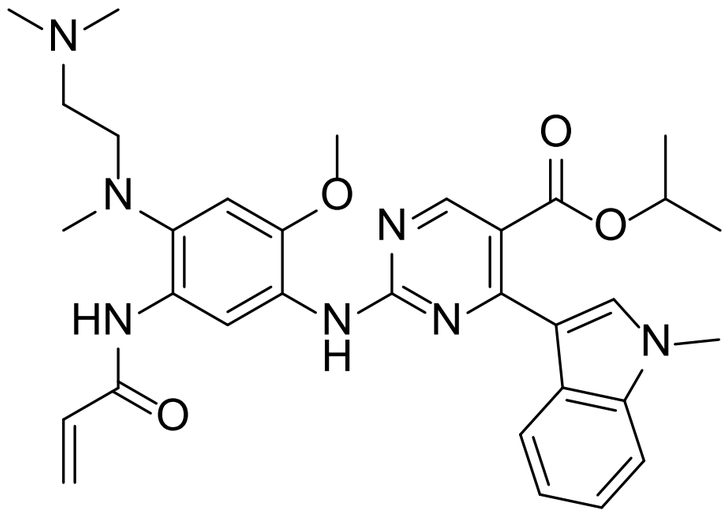
ChemMedChem., Jan. 31, 2021

Eisai Inc., Cambridge, MA

The Eisai STING agonist E7766 leads to tumor eradication in 9/10 treated animals in a syngeneic model when injected intratumorally, and is currently in a Ph. I study for advanced solid tumors. The molecule has an interesting macrocyclic structure, and behaves as a cyclic dinucleotide mimic with potent activity on all four human STING variants.

mobocertinib (TAK-788)

ARIAD/Takeda

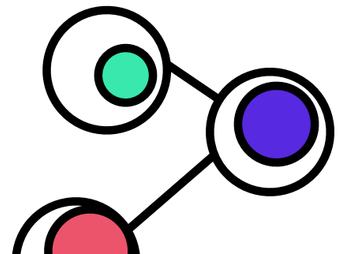


EGFR exon 20 mutant inhibitor, oral once-daily
Breakthrough Therapy for ex20+ NSCLC (Ph.I)
From cellular screening + SBDD
Cancer Discovery, Feb. 25, 2021
ARIAD/Takeda, Cambridge, MA

The ARIAD/Takeda EGFR exon 20 insertion mutant (EGFRex20ins) inhibitor TAK-788 is a Breakthrough Therapy for patients with advanced non-small cell lung cancer (NSCLC) whose tumors harbor EGFR exon 20 insertion mutations. The appearance of exon 20 insertions is a common resistance mechanism to earlier generations of EGFR inhibitors including osimertinib, to which TAK-788 is structurally related.

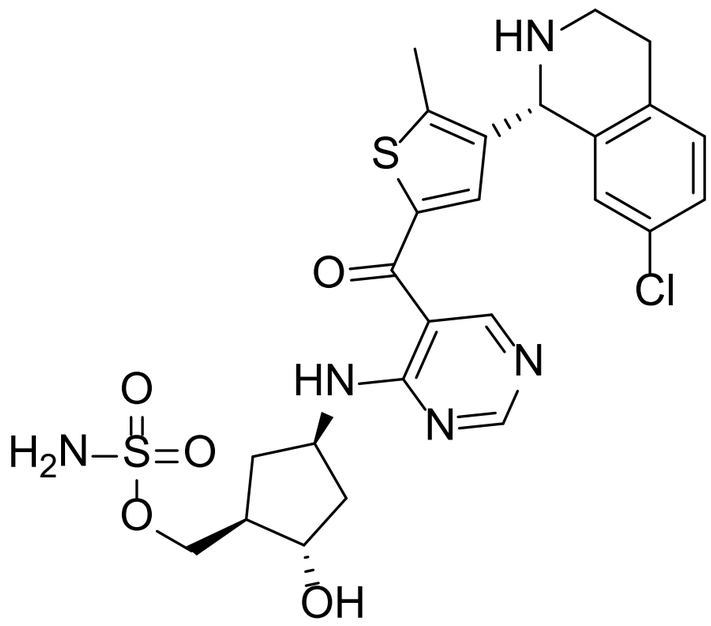
1st and 2nd generation EGFR inhibitors partly depend on the fact that mutant forms of EGFR have destabilized inactive forms with reduced ATP affinity relative to wild-type (WT) EGFR, making the mutant forms easier to drug in cells. EGFR exon 20 mutants, however, have active sites that are very similar to WT, making tumors bearing these mutations difficult to drug without significant side effects due to WT inhibition.

This oral covalent inhibitor is more potent against exon 20 mutants than WT in cells, and is also active against a range of other common EGFR mutations. While the selectivity is still modest and side effects that seem related to WT EGFR inhibition are observed clinically, the significant responses in exon 20 insertion-bearing tumors is encouraging.



TAK-981

Millenium/Takeda



Mechanism-based SAE E1 ligase inhibitor
First-in-class, Ph. II (IV) for adv. solid tumors
From phenotypic screen and scaffold hop
J. Med. Chem., Feb. 25, 2021
Millenium/Takeda, Cambridge, MA

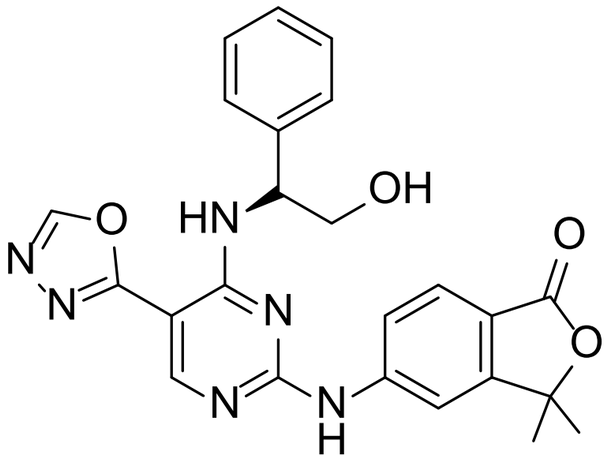
The Millenium/Takeda SUMO-activating enzyme (SAE) inhibitor TAK-981 is a mechanism-based inhibitor that covalently forms a SUMO substrate-inhibitor adduct that potently inhibits SAE, rather than reacting with SAE directly.

The Takeda team has been able to successfully leverage this fascinating mechanism to develop potent inhibitors against a range of E1 enzymes including ATG7 and NEDD8-activating enzyme (NAE), one of which (pevonedistat) is currently in a Ph. III trial for AML. TAK-981 is currently in combination Ph. II trials for advanced solid tumors as an intravenous infusion.

This Takeda platform is another great example of how chasing down mechanisms from a phenotypic screen can lead to a rich pipeline of new targets and clinical candidates beyond what was originally intended.

"compound 24"

Bristol Myers Squibb



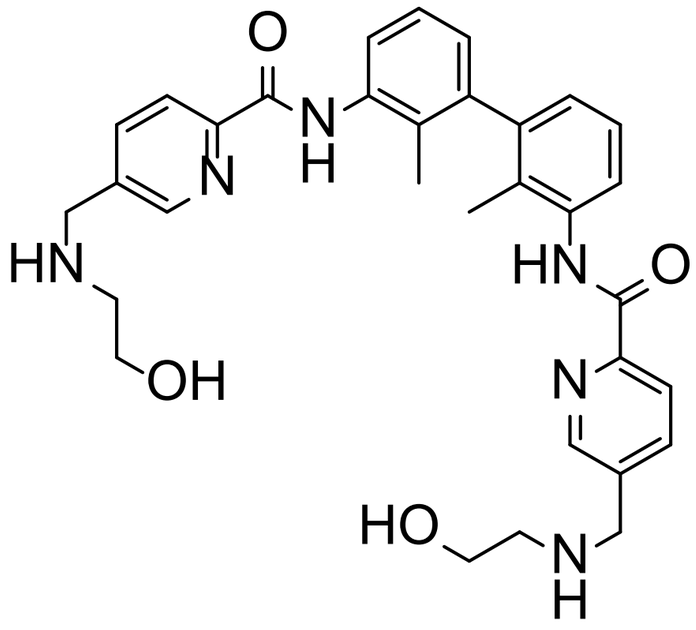
>50x family-selective HPK1 kinase inhibitor
Tumor clearance w/ PD-1i (oral 100 mpk BID)
From IRAK4 inhibitor and homology modeling
ACS. Med. Chem. Lett., Feb. 19, 2021
Bristol Myers Squibb, Cambridge, MA

The Bristol Myers Squibb (BMS) HPK1 kinase inhibitor, "compound 24" is an oral tool compound intended for cancer immunotherapy, with >50x selectivity against family members including GLK. The starting point was an IRAK4 kinase inhibitor identified from historical kinome selectivity data. A homology-model based on MST1 was used for optimization.

Interestingly this uncharged kinase inhibitor possesses a cyclic lactone which binds to a backbone N-H in a co-crystal structure without hydrolizing and a primary alcohol which binds to a front-pocket aspartate. Oral BID dosing (100 mg/kg) in combination with an anti-PD-1 antibody led to a 100% cure rate in a syngeneic tumor model.

ARB-272572

Arbutus Biopharma Inc.



PD-L1 inhibitor via induced internalization

Oral activity (10 mpk QD) in humanized model

From biochemical HTRF screening

Nat. Comm., Feb. 22, 2021

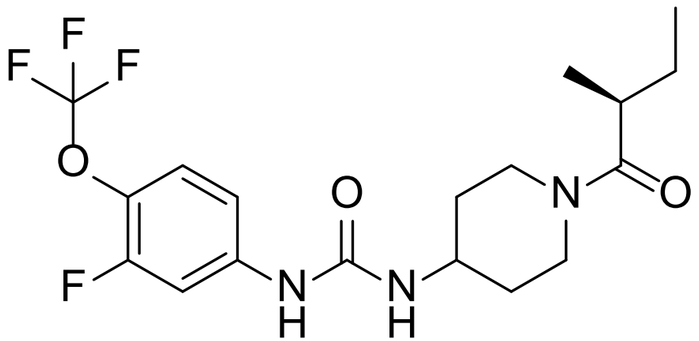
Arbutus Biopharma Inc, Warminster, PA

The Arbutus PD-L1 inhibitor ARB-272572 is a preclinical molecule that potently induces PD-L1 dimerization and internalization and demonstrates oral activity (10 mg/kg QD) in a humanized mouse model. Biologic PD-1/PD-L1 inhibitors have had incredible success as cancer immunotherapy agents, and there has been significant accompanying interest in small molecule inhibitors.

Given the crowdedness of the field, however, the Arbutus team also makes the case that small molecule PD-L1 inhibitors could be useful in alternate settings such as chronic hepatitis B, and demonstrate activity in an in vitro HBV assay as well.

EC5026

EicOsis Human Health Inc.



pM oral sEH epoxide hydrolase inhibitor

Completed Ph. I HV study + in animal health

Epoxide-opening transition-state mimic

J. Med. Chem., Feb. 7, 2021

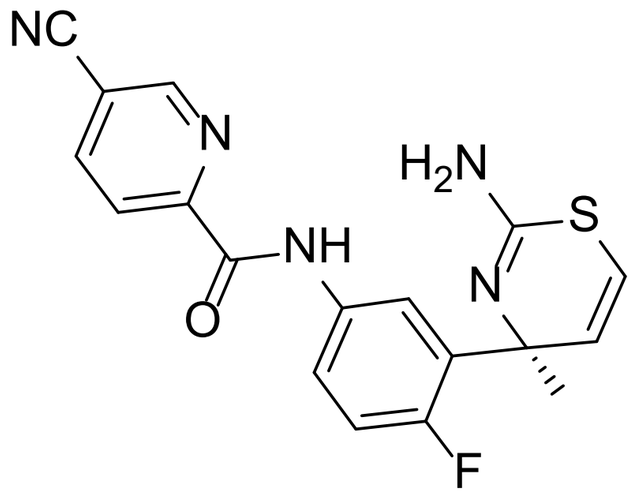
EicOsis Human Health Inc., Davis, CA

The EicOsis oral soluble epoxide hydrolase (sEH) inhibitor, EC5026, is a compound currently intended as a non-opioid analgesic and anti-inflammatory agent.
It recently completed a Ph. I study in healthy volunteers without drug-related adverse events. Despite its small size, it has picomolar binding activity with the urea acting as an epoxide-opening transition-state mimic.

The authors discuss a range of development considerations including their selection of a clinical path, IND-enabling studies, clinical findings, and even animal health development. This is a must-read for anyone interested in the overall drug discovery process beyond medicinal chemistry.

atabecestat

Shionogi Pharmaceutical



First patented BACE1 protease inhib. of series

Ph. II/III in Alzheimer's, discontinued (tox.)

From phenotypic screen and SBDD

J. Med. Chem., Feb. 15, 2021

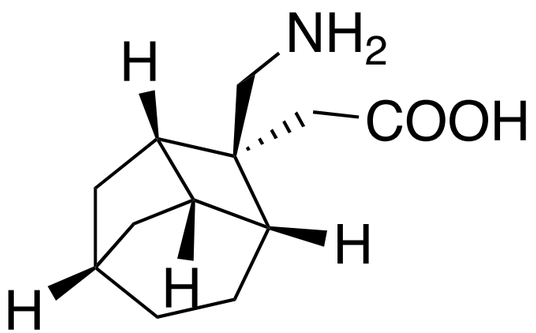
Shionogi Pharmaceutical, Osaka, JP

The Shionogi BACE1 aspartyl protease inhibitor, atabecestat (JNJ-54861911) is an oral, brain-penetrant compound that was advanced into the EARLY Ph. IIb/III clinical trial for treatment of preclinical Alzheimer's disease (AD) patients. The starting point was identified from a phenotypic HTS, and was the first thiazine-based BACE1 disclosed in the patent literature.

The Shionogi team discloses that the trial was discontinued due to liver enzyme elevation, and subsequent analysis showed that the treatment group actually had dose-related cognitive worsening, in agreement with other company's findings. The Shionogi team shares a lot of helpful development details including their studies to de-risk an early 500 nM in vitro hERG signal.

HSK16149

Haisco Pharmaceutical



Oral, brain-penetrant VGCC inhibitor

Ph. II/III for diabetic neuropathic pain in China

Gabapentenoid

J. Pharmacol. Exp. Ther., Mar. 1, 2021

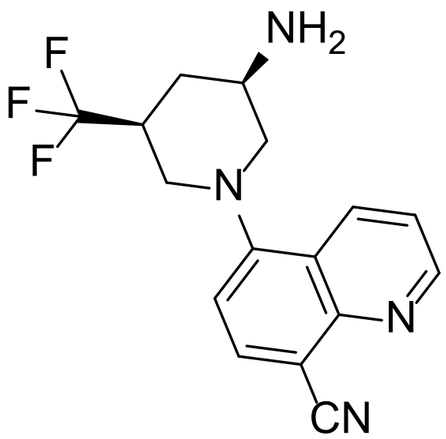
Haisco Pharmaceutical, Chengdu, CN

The Haisco voltage-gated calcium channel (VGCC) alpha-2-delta subunit inhibitor, HSK16149, is a potent and potentially longer-acting gabapentinoid drug candidate for chronic pain over pregabalin, with a potentially wider therapeutic index for the central nervous system (CNS).

The molecule is planned for a Ph. II/III trial in China for diabetic peripheral neuropathic pain. Identifying novel chemical matter around small ligands like pregabalin is challenging, but the Haisco team appears to have found a nice niche in this brain-penetrant molecule's interesting bridged cyclobutane structure. Chemists here may enjoy the structure of a recently approved-in-Japan competitor molecule from Daiichi Sankyo, mirogabalin as well.

M5049

EMD Serono/Merck KGaA



Selective TLR7/8 inhibitor (dimer stabilizer)

In Ph. I for lupus (oral twice-daily)

From screening for TLR7/8-selective agents

J. Pharmacol. Exp. Ther., Mar. 1, 2021

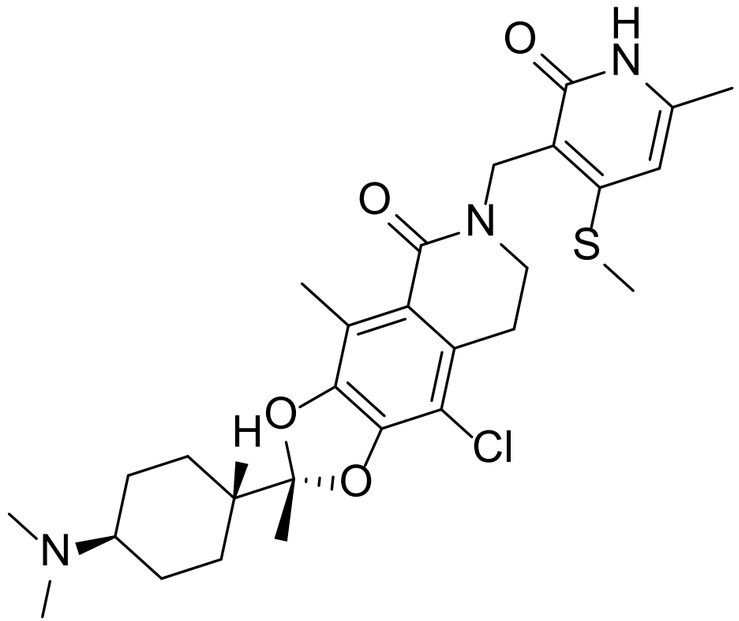
EMD Serono/Merck KGaA, Billerica, MA

The EMD Serono/Merck KGaA toll-like receptors TLR7/TLR8 inhibitor M5049 is an oral, twice-daily anti-inflammatory agent currently in a Ph. I trial for Lupus. The molecule potently blocks both synthetic ligands and natural endogenous RNA ligands such as microRNA and Alu RNA. TLR7 and TLR8 selective modulators (both agonists and antagonists) have been of significant recent interest due to the TLR's key roles in immune signaling but have been challenging to develop since TLR7/8 are membrane proteins that are difficult to express, purify, and crystallize.

The Serono team however was able to generate an interesting crystal structure showing that the molecule binds to the interface between two monomers, stabilizing an inactive dimer, preventing receptor activation.

CPI-1328

Constellation Pharma



Femtomolar EZH2 hist. methyltransferase inh.

Oral activity (10-25 mg/kg QD) in xenograft

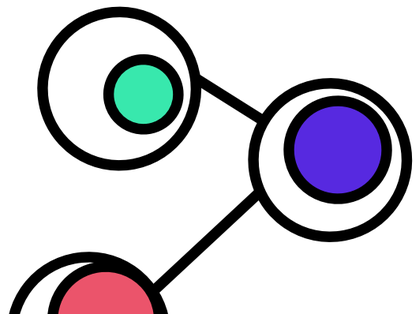
From opt. of prior ligand

J. Bio. Chem., Jan. 30, 2021

Constellation Pharma, Cambridge, MA

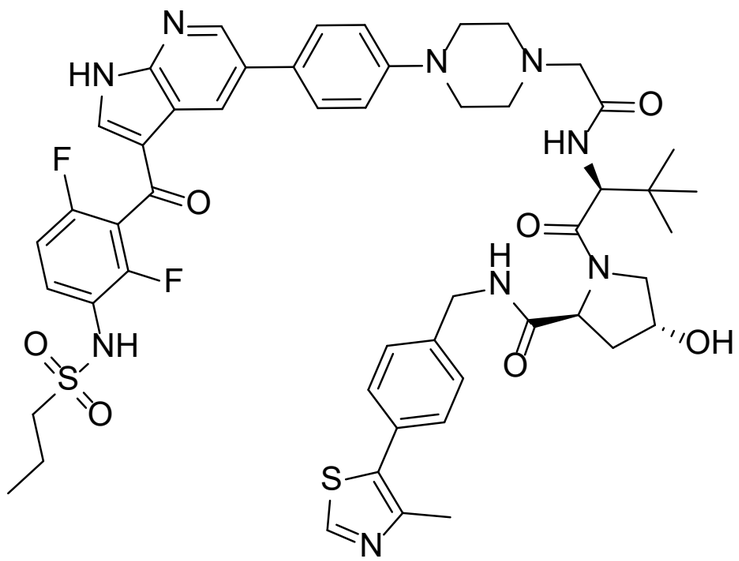
The 2nd generation Constellation EZH2 histone methyltransferase inhibitor, CPI-1328, is an extremely potent tool compound with reversible femtomolar activity against EZH2, and is one of the most potent reversible small inhibitors ever reported. Previous analyses have suggested an empirical barrier for non-covalent inhibitors around 10 pM.

The molecule builds on a finding from their previous paper that a thiomethyl group is critical for increased drug residence time. This activity translated to in vivo activity at 25 mg/kg QD despite the comprehensive target coverage thought to be needed against EZH2 to elicit an effect.



SJF-0628

Yale University



Mut. BRAF sel. heterobifunctional degrader

Efficacy in xenograft at 50 mg/kg IP BID

VHL-based degrader from vemurafenib

Nat. Comm., Feb. 10, 2021

Yale University, New Haven, CT

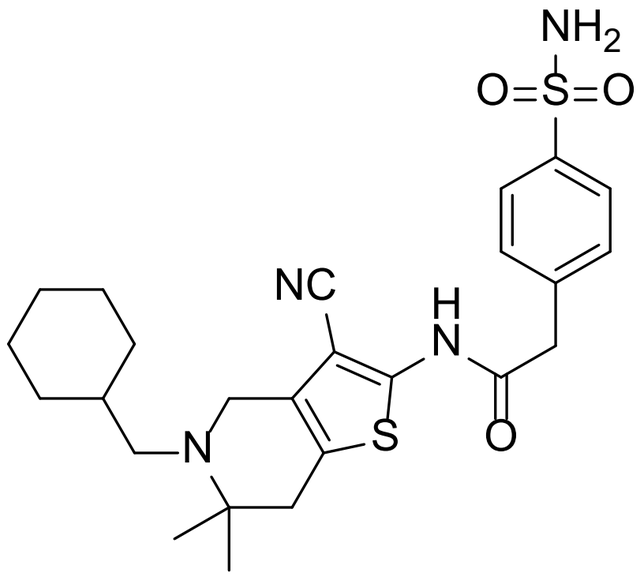
The Yale BRAF-targeting PROTAC SJF-0628 is a VHL-based heterobifunctional degrader with in vivo activity in a xenograft model (50 mg/kg BID IP). Though mutant BRAF is a well-validated target, drugging mutant forms selectively over wild-type continues to be a challenge. It had been hypothesized that modalities such as targeted degradation might be a viable strategy to achieve functional selectivity for mutant forms of BRAF.

Interestingly, the authors show here that BRAFWT is degraded to a far lower extent due to a weaker ternary complex between the compound and E3 ligase in cells, despite lower selectivity of the parent BRAF inhibitor, vemurafenib. However, under different cellular contexts, the authors show that wild-type still appears to be degraded, which may still present a safety issue if healthy human dividing cells are still affected in vivo, or in certain combination regimens.

Like any important proof-of-concept, this article raises new questions for the modality, such as how to predict or optimize a therapeutic index preclinically given such mechanistic complexity.

NITD-688

Novartis (NITD)



Pan-serotype dengue virus NS4B inhibitor
Oral preclin. candidate, trial planned
From 1.5M cmpd phenotypic screen + opt.
Sci. Transl. Med., Feb. 3, 2021
Novartis (NITD), Emeryville, CA

The Novartis pan-serotype dengue virus (DENV) NS4B protein inhibitor, NITD-688, is a preclinical candidate with strong activity against all four serotypes of DENV in vitro and excellent oral efficacy in a mouse model. The starting point was identified through phenotypic screening of 1.5M compounds and counterselection against host factors and cytotoxicity.

The target was identified through resistance mutations and binding confirmed by 15N-NMR. Allometric scaling was used to predict a human efficacious dose of 35 mg QD. Non-GLP studies showed good tolerability in dog up to 80 mg/kg, and QTc prolongation was not observed despite partial inhibition of hERG in vitro.

The authors allude to designing a trial to ensure patients are recruited within 48 h of fever onset to make sure the inhibitor can be administered early enough to affect outcomes.

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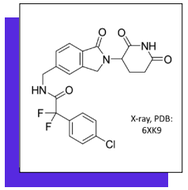
drughunter.com



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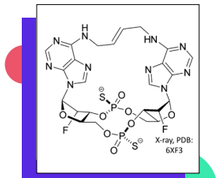

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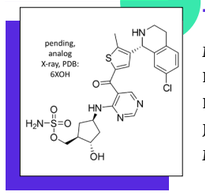

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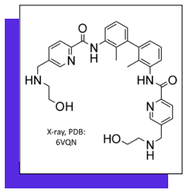

ARB-272572

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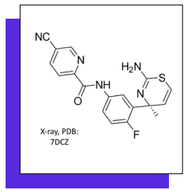
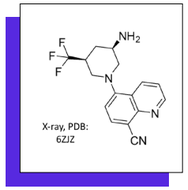


atabecestat

First patented BACE1 protease inhib. of series
Ph. II/III in Alzheimer's, discontinued (tox.)
From phenotypic screen and SBDD
J. Med. Chem., Feb. 15, 2021
Shionogi Pharmaceutical, Osaka, JP



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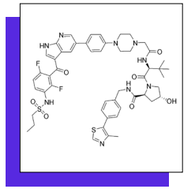

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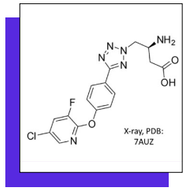

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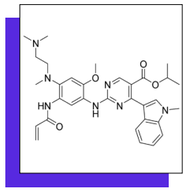

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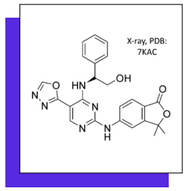

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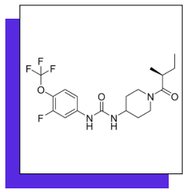
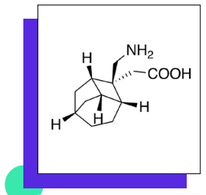


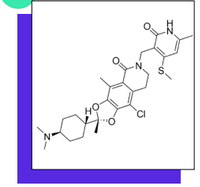
EC5026

pM oral sEH epoxide hydrolase inhibitor
Completed Ph. I HV study + in animal health
Epoxide-opening transition-state mimic
J. Med. Chem., Feb. 7, 2021
EicOsis Human Health Inc., Davis, CA



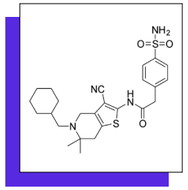
HSK16149

Oral, brain-penetrant VGCC inhibitor
Ph. II/III for diabetic neuropathic pain in China
Gabapentenoid
J. Pharmacol. Exp. Ther., Mar. 1, 2021
Haisco Pharmaceutical, Chengdu, CN



CPI-1328

Femtomolar EZH2 hist. methyltransferase inh.
Oral activity (10-25 mg/kg QD) in xenograft
From opt. of prior ligand
J. Bio. Chem., Jan. 30, 2021
Constellation Pharma, Cambridge, MA



NITD-688

Pan-serotype dengue virus NS4B inhibitor
Oral preclin. candidate, trial planned
From 1.5M cmpd phenotypic screen + opt.
Sci. Transl. Med., Feb. 3, 2021
Novartis (NITD), Emeryville, CA

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