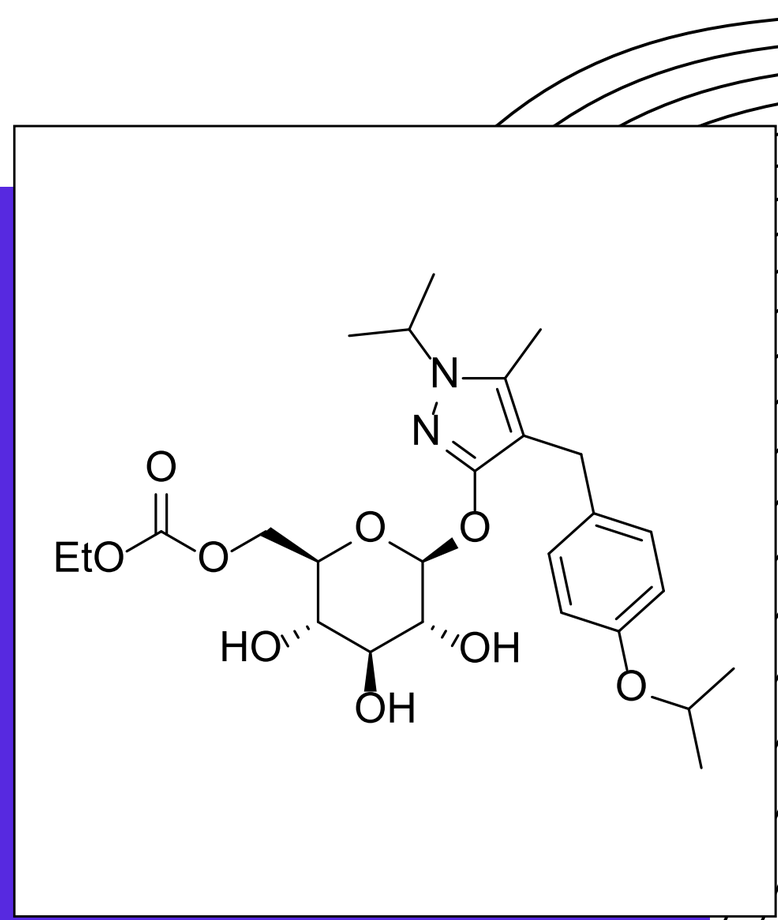
Small Molecules of the Month

January 2021



drug hunter

01	remogliflozin etabonate	Kissei Pharma
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03	BI 730357	Boehringer Ingelheim
04	MLi-2	Merck & Co.
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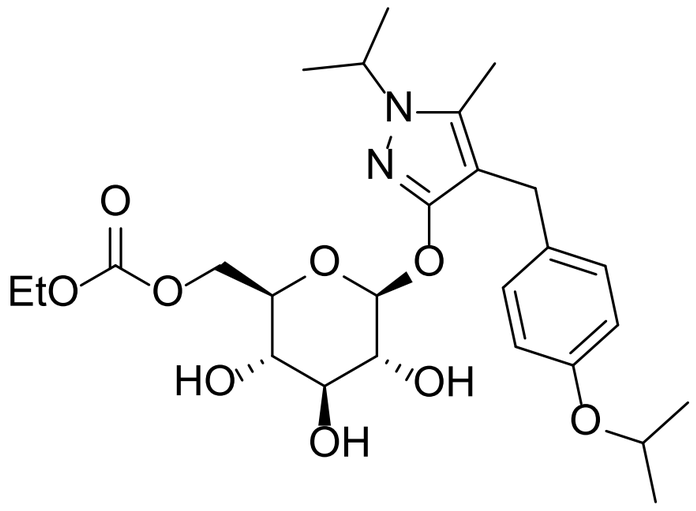
remogliflozin etabonate

Kissei Pharma



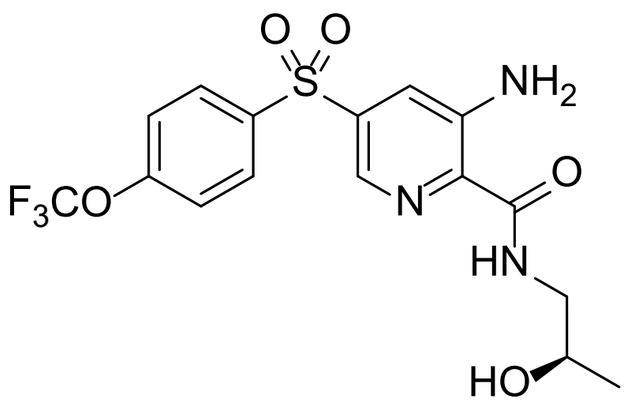
SGLT1-sparing oral SGLT2 inhibitor prodrug
Launched in India for diabetes, 100 mg BID
From mouse urine drug metabolite and opt.
Bioorg. Med. Chem., Jan. 22, 2021
Kissei Pharma / Toho University, JP

The Kissei SGLT2 inhibitor prodrug, remogliflozin etabonate, is an SGLT1-sparing oral drug launched in 2019 in India for the treatment of type 2 diabetes.

Interestingly, the lead for this drug was a metabolite identified from mouse urine after treatment with a Wyeth-Ayerst antihyperglycemic agent of previously unknown mechanism.

GLPG2451

Galapagos



Oral CFTR ABC transporter potentiator

Ph. II for cystic fibrosis (5-80 mg QD), discont.

Similarity screen of 589 cmpds + scaffold hop

J. Med. Chem., Jan. 5, 2021

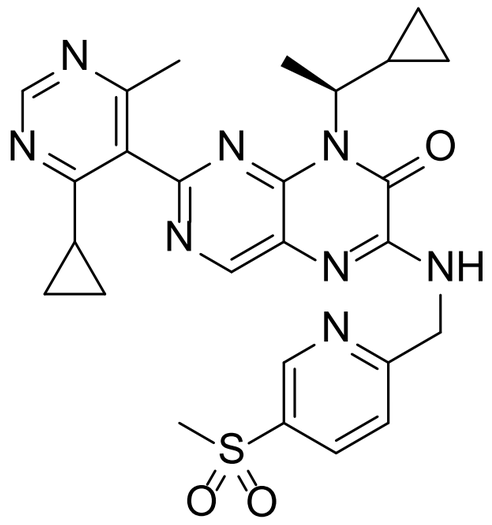
Galapagos NV, Mechelen, BE

The Galapagos CFTR potentiator, GLPG2451, is an oral, once-daily clinical candidate for cystic fibrosis (5-80 mg QD). It was advanced into a high-profile Ph. II triple-combo study with the CFTR correctors GLPG2737 and GLPG2222 in partnership with AbbVie, and was seen as a potential competitor to Vertex's CF franchise, but unfortunately weak efficacy data appears to have ended development.

The GLPG team was able to get away from their original thiophene core by conducting an interesting scaffold hop in which a hydrogen bond donor and acceptor were swapped across a ring, resulting in their much nicer looking final scaffold.

BI 730357

Boehringer Ingelheim



Oral RORγ nuclear receptor antagonist

On-going Ph. II for psoriasis (QD dosing)

50k cmpd high-conc. frag. screen + scaff. hop

ACS Med. Chem. Lett., Jan. 5, 2021

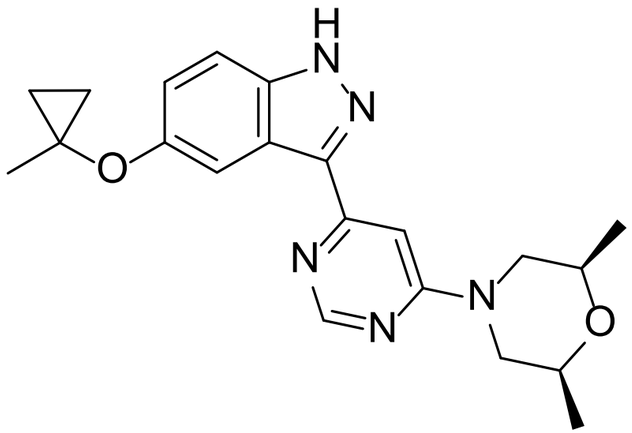
Boehringer Ingelheim, Ridgefield, CT

The Boehringer RORγ antagonist, BI 730357, is an oral once-daily clinical candidate from a new compound class in development for plaque psoriasis. We highlighted two other RORγ modulators last year in February and March.

While most clinical RORγ modulators have discontinued development after reaching Ph. II, BI 730357's Ph. II trial appears to be on-going.

MLi-2

Merck & Co.

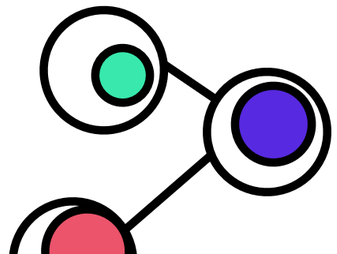


Oral, brain-penetrant LRRK2 kinase inhibitor
Recapitulated LRRK2 lung tox. in model
Discovery details manuscript in preparation
J. Pharmacol. Exp. Ther., Jan. 28, 2021
Merck & Co., Inc., Boston, MA

The Merck LRRK2 inhibitor, **MLi-2**, is an orally available tool compound that is structurally distinct from the LRRK2 inhibitor GNE-7915. LRRK2 had been a highly attractive target for treating Parkinson's disease, but pulmonary toxicity observed with LRRK2 inhibition in non-human primates (NHP) cast a shadow on the utility of LRRK2 inhibitors.

Since NHP studies are cost and resource-intensive, it was difficult to study the toxicity in depth. The Merck team was able to recapitulate the pulmonary toxicity in rodents with MLi-2, and found that the lung effects were due to chronic LRRK2 inhibition and were mild and readily reversible.

This study provides a higher-throughput method to assess new LRRK2 inhibitor scaffolds and more broadly understand on-target effects of LRRK2 inhibition.



GSK 3008348 ("cmpd 1")

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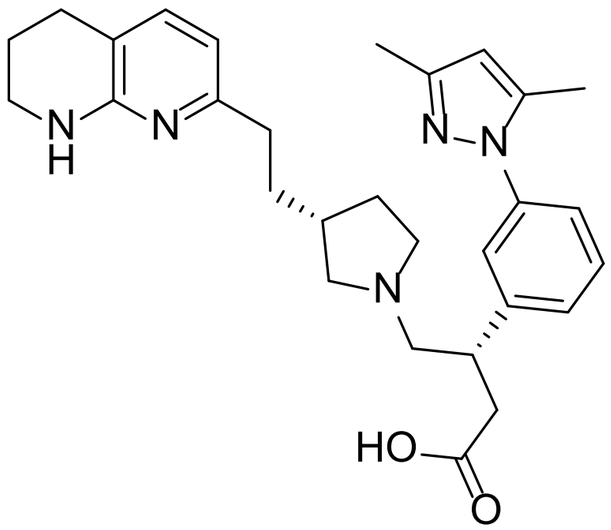


avB6 integrin inhibitor + lysosomal degrader

In vitro degradation, Ph. I completed, discont.

Derived from prior integrin inhibitors

J. Pharmacol. Exp. Ther., Jan. 26, 2021

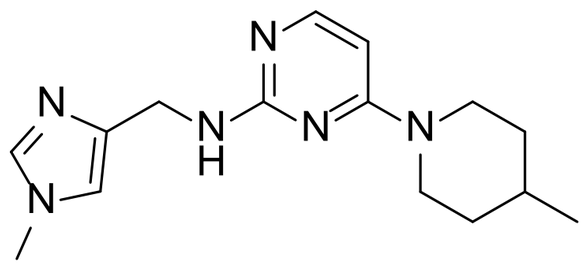
GlaxoSmithKline, Stevenage, UK

The GSK avB6 integrin inhibitor, "compound 1," or GSK 3008348 is a previously reported IPF clinical candidate that is a picomolar binder to avB6 with slow dissociation kinetics. The recent report highlights the fact that the compound results in prolonged effects in cells by triggering integrin internalization and lysosomal degradation.

While this phenomena of small molecule-induced receptor internalization/ degradation has been characterized in other transmembrane receptors such as GPCRs, it hasn't been well-studied in integrins. Small molecule integrin modulators are seeing renewed interest for indications such as fibrosis, and this induced lysosomal degradation pharmacology is worth keeping in the mental toolbox for targeting integrins and other transmembrane proteins.

“compound 5i”

Takeda Pharmaceutical



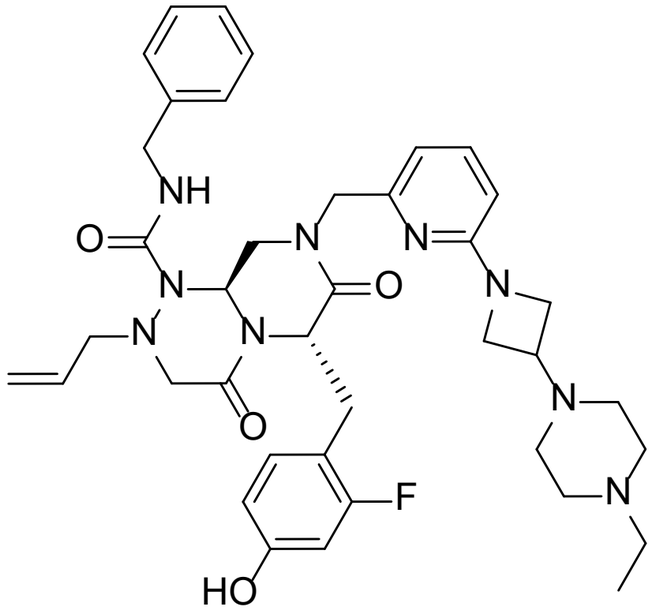
Oral, brain-penetrant O-GlcNAcase (OGA) inh.
Structurally distinct in vivo tool
From virtual screen of 100k cmpd, testing 2681
J. Med. Chem., Jan. 6, 2021
Takeda Pharmaceutical, Fujisawa, JP

The Takeda O-GlcNAcase (OGA) inhibitor, “compound 5i,” binds to the same site as prior sugar-based OGA inhibitors, but has surprisingly different chemical properties and a unique binding mode. The Takeda team realized that polar, sugar-based OGA inhibitors would be challenging to get into the brain where they would be needed for neurodegenerative diseases, and so used an elegant virtual-screening and structure-based approach to make the leap to the distinct, CNS-friendly starting point for compound 5i.

The less basic pyrimidine N(1) nitrogen (pKa ~ 4.9) surprisingly appears to be protonated in the binding site, making a bidentate interaction with a carboxylate, likely helped by the presence of a second Asp residue. The article is a great case-study for identifying distinct new chemical matter through a rational approach, and the new brain-penetrant OGA inhibitor should be a useful in vivo tool compound for understanding the treatment of neurodegenerative disorders.

E7386

Eisai Co.



Oral, selective B-catenin/CBP PPI inhibitor

Synergy w/ PD-1i in model, in Ph. I for cancer

Opt. of prior peptidomimetic candidate

Cancer Res., Jan. 6, 2021

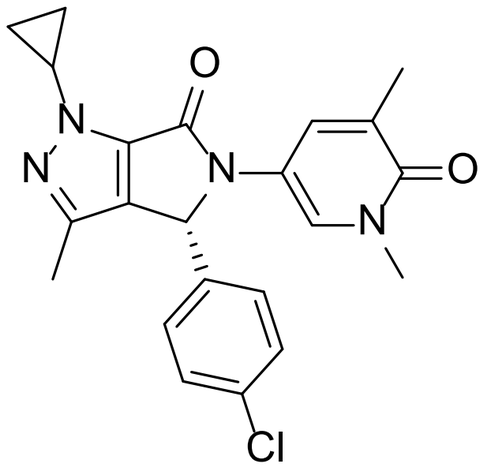
Eisai Co., Ltd., Tsukuba, JP

The Eisai B-catenin/CBP inhibitor, E7386, is an orally active and selective inhibitor of the B-catenin/CBP protein-protein interaction, a key node in the long studied Wnt/B-catenin pathway in cancer. Prior attempts to drug Wnt directly were met with severe toxicity in clinical trials.

The pathway has seen a resurgence in interest due to its potential role in tumor immune evasion, and the Eisei team demonstrates that E7386 synergizes with anti-PD-1 in a syngeneic model. E7386 is currently in a Ph. I study as a monotherapy for solid tumors.

NVS-BET-1

Novartis (NIBR)



BRD4 (BD1/2) BET bromodomain inhibitor
Wound-heal. at 1 mpk QD, bell-shaped pharm.
From phenotypic screen (MDM2 inhibitor hit)
Nat. Chem. Biol., Jan. 18, 2021
Novartis (NIBR), Basel, CH

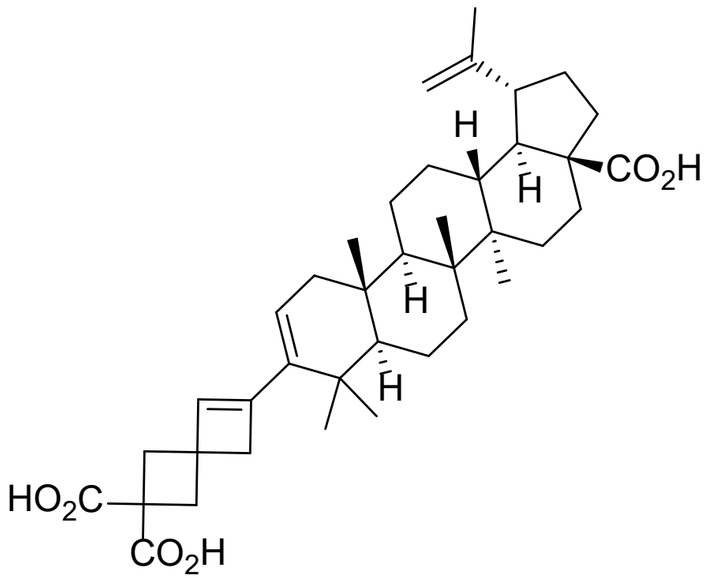
The Novartis BET bromodomain inhibitor, NVS-BET-1, is a new chemotype of BRD4 (BD1 and BD2) inhibitor. While we recently highlighted a few high-profile, selective bromodomain inhibitors from AbbVie and GSK, the Novartis team took a different approach to reaching their molecules.

The Novartis team was looking for mechanisms that influence keratinocyte differentiation to treat wound healing, and identified BET inhibitors in a phenotypic screen. Interestingly, their proprietary matter emerged from a BRD4 biochemical screen that identified a totally unrelated p53-MDM2 inhibitor as a moderately potent hit. Optimization led to NVS-BET-1 which potently influences wound healing when administered orally at doses as low as 1 mg/kg.

The wound-healing effects however, were lost at higher concentrations, recapitulating the “bell-shaped” dose-response curves from in vitro assays.

“compound 16”

Bristol Myers Squibb



Nanomolar HIV-1 maturation inhibitor

Interesting structure

Derivative of GSK3532795/BMS955176

Bioorg. Med. Chem. Lett., Jan. 26, 2021

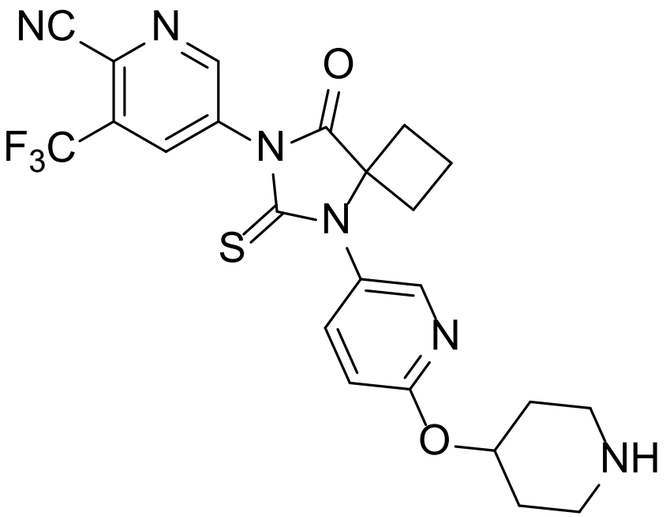
Bristol Myers Squibb, CT + NJ

The BMS HIV-1 maturation inhibitor, “compound 16,” is a potent derivative of the clinical candidate GSK3532795/955176, with double-digit nanomolar activity in cells.

The spiro[3.3]hept-5-ene effectively replaces a phenyl ring its parent molecule. Though it wasn’t taken beyond an in vitro assay, the structure is worth noting in the mental isostere toolbox.

JNJ-63576253 / TRC-253

Janssen R&D



Oral WT and F877L mut. AR inhibitor

Completed Ph. I/II trial in mCPRC

No hepatotox. vs. bioactivated prior lead

J. Med. Chem., Jan. 20, 2021

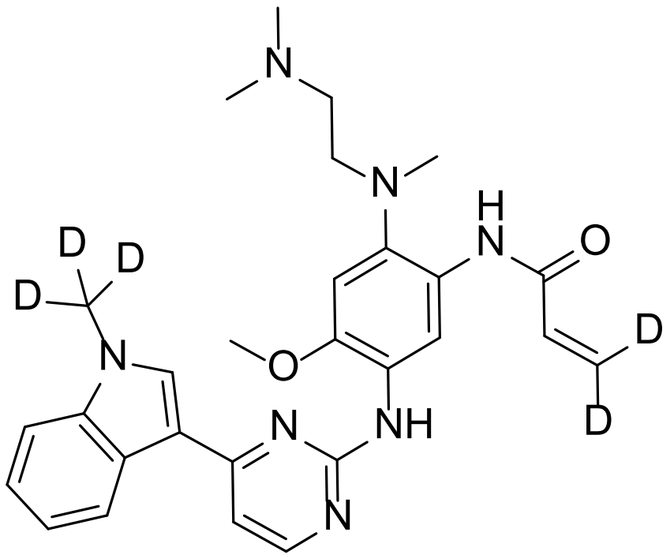
Janssen R&D, Spring House, PA

The JNJ AR antagonist, JNJ-63576253, is a clinical molecule for prostate cancer that is active against both wild-type androgen receptor as well as the clinically relevant AR mutant, F877L. F887L is a devious resistance mechanism that transforms antagonists of AR into agonists.

The parent compound from which 6253 is derived was found to be unacceptably hepatotoxic, which was suspected to be due to bioactivation of an electron rich phenyl ring. Replacing the phenyl ring with a pyridine, an often-effective strategy for mitigating bioactivation of aryl amines, led to the dramatically improved safety window observed for JNJ-63576253. JNJ-63576253/TRC-253 recently completed a Ph. I/II trial in mCRPC.

dosimertinib

ZZU / HNU / Henan Genuine Biotech Co.



Deuterated covalent mut. EGFR inhibitor

Wider TI in model, Ph. I in China

Deuteration reduces less sel. metabolite

J. Med. Chem., Jan. 18, 2021

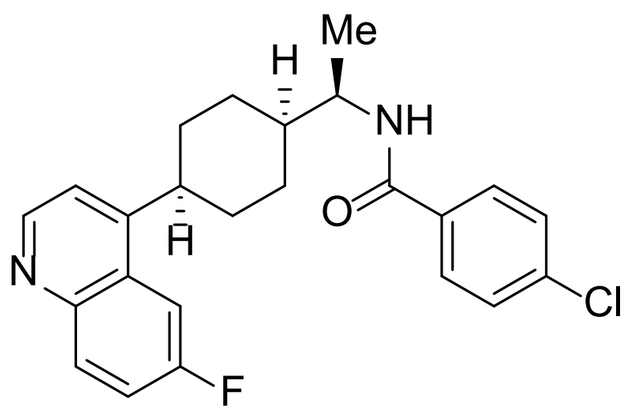
ZZU / HNU / Henan Genuine Biotech Co., CN

The Henan EGFR inhibitor, dosimertinib, is a deuterated derivative of the approved covalent inhibitor, osimertinib. A metabolite of osimertinib, AZ5104, has lower selectivity for WT EGFR than mutant EGFR, which the authors suggest may contribute to some adverse events. Deuteration of osimertinib appears to reduce the formation of the AZ5104-like metabolite in vitro and in vivo.

Dosimertinib appears to have a wider therapeutic window in mice than osimertinib based on doses at which mouse body weight loss is observed, and is currently starting a Ph. I trial in China to evaluate this hypothesis in humans.

BMS-986242

Bristol Myers Squibb



Oral IDO1 inhibitor

Clinical candidate in Ph. I/II combo for cancer

Reversed amide of linrodostat

ACS Med. Chem. Lett., Jan. 28, 2021

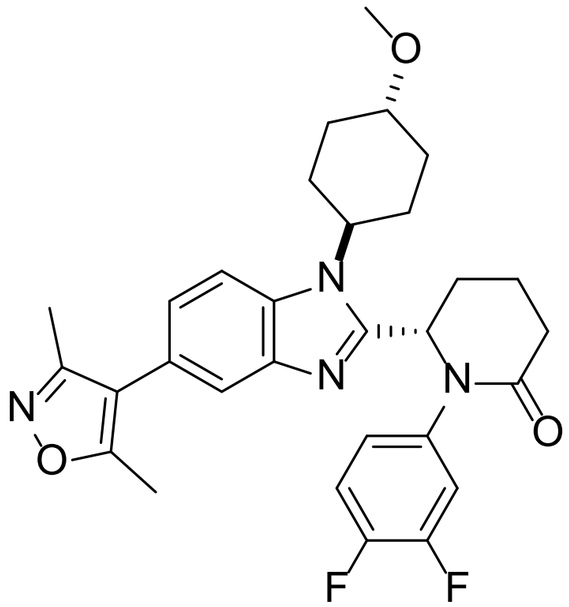
Bristol Myers Squibb, Lawrence Township, NJ

The BMS IDO1 inhibitor, BMS-986242, is a clinical candidate in a Ph. I/II study in combination with nivolumab for cancer. Like me, you probably had to look twice at this molecule since it's so similar to linrodostat, which we covered recently. Forming the reverse amide of linrodostat appears to improve the PK profile and also removes a potential reactive aniline metabolite.

Making the reverse amide of an amide starting point is a med. chem. tactic that's often suggested, but it's rare to see it play out so well, especially when both the amide H-bond donor and acceptor making interactions with the target.

CCS1477

ICR / Royal Marsden / CellCentric



P300/CBP bromodomain inhibitor

PD observed in serial biopsies from Ph. I

50 mg QD, 3-d-on-4-off; origin not discussed

Cancer Discovery, Jan. 11, 2021

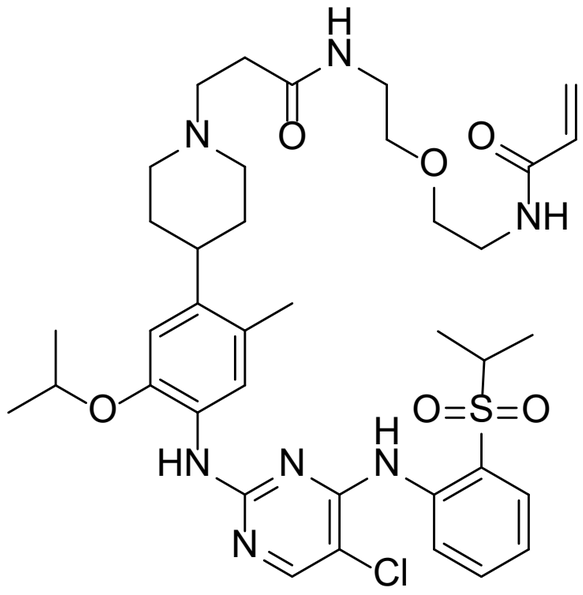
ICR / Royal Marsden / CellCentric, UK

The CellCentric p300/CBP inhibitor, CCS1477, is an orally available drug in early development for advanced prostate cancer, and is structurally distinct from the p300/CBP inhibitor we covered in Apr. 2020. In agreement with its proposed MoA, it impacts AR and MYC signaling in serial tumor biopsies acquired from its first-in-human Ph. I trial.

It will be interesting to see whether the agent is able to demonstrate a significant survival and quality-of-life benefit in late-stage disease given the likely on-target effects of p300/CBP inhibition on certain healthy cells.

Con B-1

Sichuan University / Tsinghua University



Covalent inh. of remote ALK kinase cysteine

Thought-provoking proposed MoA

From ceritinib and linker opt.

J. Med. Chem., Jan. 20, 2021

Sichuan University / Tsinghua University, CN

The academic covalent ALKi inhibitor, **Con B-1**, is thought-provoking initial proof-of-concept that remote kinase cysteines might be targetable from an active-site inhibitor. The authors show that a derivative of ceritinib with a remote electrophile attached can inhibit ceritinib more potently than a non-reactive control compound, that linker length significantly impacts activity, and that a 1:1 compound:ALK adduct can be detected on incubuation with an excess of reactive compound.

The proposed MoA would be more convincing with an X-ray co-crystal structure rather than a docking model, or with a comparison to an appropriate Cys->Ala mutant, but it is worth considering this strategy in other contexts.

drug hunter

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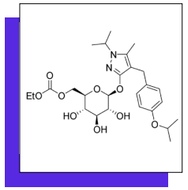
drughunter.com



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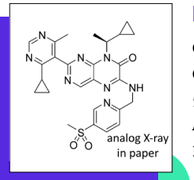

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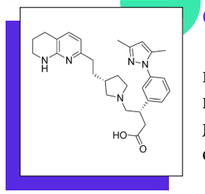

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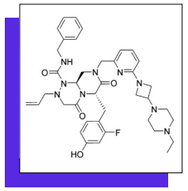

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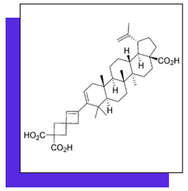

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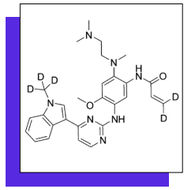

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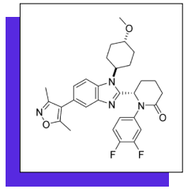

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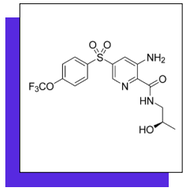

GLPG2451

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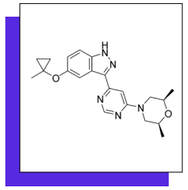

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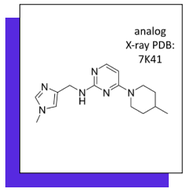

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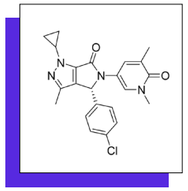

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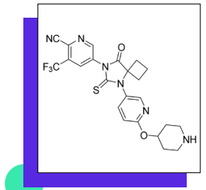

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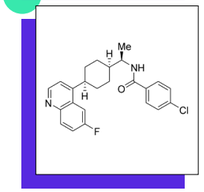
J. Med. Chem., Jan. 20, 2021
Janssen R&D, Spring House, PA



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Oral IDO1 inhibitor
Clinical candidate in Ph. I/II combo for cancer
Reversed amide of linrodostat
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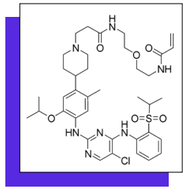

Con B-1

Covalent inh. of remote ALK kinase cysteine
Thought-provoking proposed MoA
From ceritinib and linker opt.
J. Med. Chem., Jan. 20, 2021
Sichuan University / Tsinghua University, CN

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