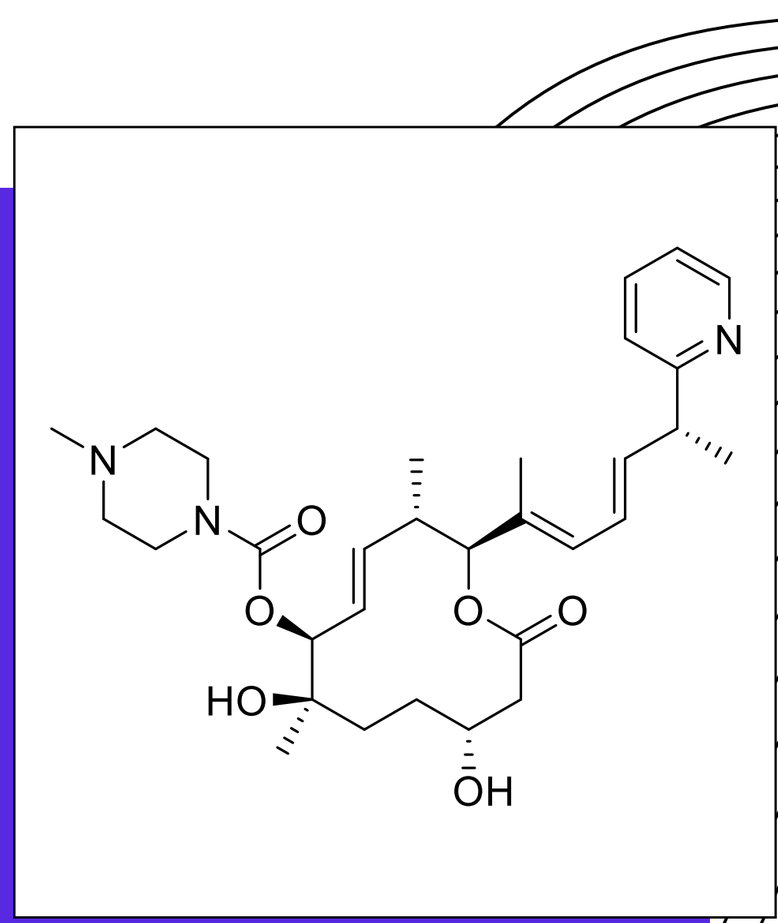
Small Molecules of the Month

June 2021



drug hunter

01	SF3b	H3 Biomedicine
02	ALK	Turning Point Therapeutics
03	mTORC1	Revolution Medicines
04	Polθ	Artios Pharma
05	CDK2/4/6	Pfizer
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07	PI3Kγ,δ	AstraZeneca
08	TLR7	Gilead Sciences
09	menin-MLL	University of Michigan
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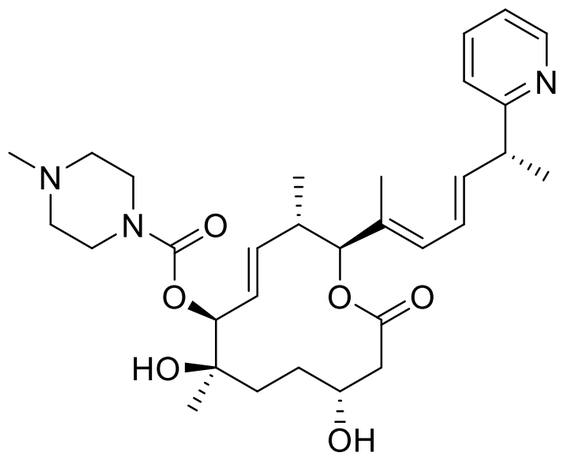
11	β-Lact.	Venatorx Pharmaceuticals
12	β-Lact.	Shionogi
13	ATX	Biogen Inc.
14	PPARγ	Minoryx Therapeutics S.L.

H3B-8800

SF3b



oral splicing modulator (SF3b complex)
7-20 mg 21d+/7d-, Ph. I for myeloid neoplasias
from opt. of pladienolide B natural product
Leukemia
H3 Biomedicine, Cambridge, US

The H3 Biomedicine RNA splicing modulator, H3B-8800, targets the spliceosome SF3b complex containing either wild-type (WT) or mutant SF3B1.

Splicesome inhibition can induce synthetic lethality since cancer cells bearing spliceosome mutations are more dependent on WT spliceosome function.

The compound is derived from the natural product, pladienolide B, optimizing for preferential cytotoxicity in spliceosome-mutant cells.

H3B-8800 completed a Ph. I study in myeloid neoplasias (MDS, CMML, AML) where it was given once-daily in cycles (e.g. 7-20 mg, 21d on, 7d off).

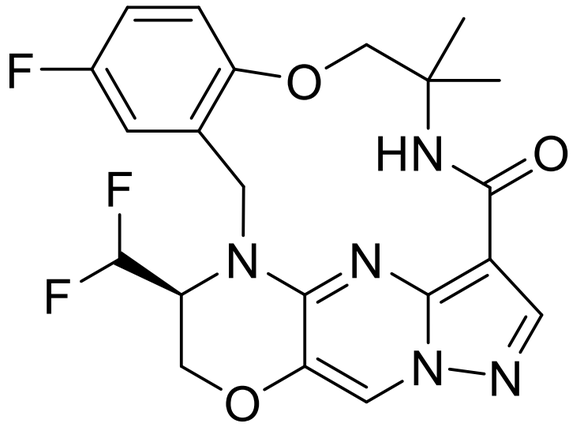
Mostly low-grade treatment-related adverse events (TAEs) were seen but no objective responses were observed, though patients with a TMEM14C biomarker were more likely to become transfusion independent.

The rest cycles in the study design suggest some on-target toxicity was probably anticipated, drug activity was not strong or strongly-defined by a single biomarker, a profile characteristic of many drugs with epigenetic machinery targets.

The optimization of a natural product for selectivity and once-daily oral administration is impressive, and hopefully more medicinal chemistry details will be shared soon.

TPX-0131

ALK



brain-penetrant mutant ALK kinase inhibitor
oral, Ph. I/II in ALK+ pre-treated cancers
undisclosed starting point, SBDD
Molecular Cancer Therapeutics
Turning Point Therapeutics, San Diego, US

The Turning Point Therapeutics CNS-penetrant ALK kinase inhibitor, TPX-0131, is more potent in vitro than all 5 approved ALK inhibitors against WT-ALK and many ALK resistance mutations, including G1202R and gatekeeper mutation L1196M.

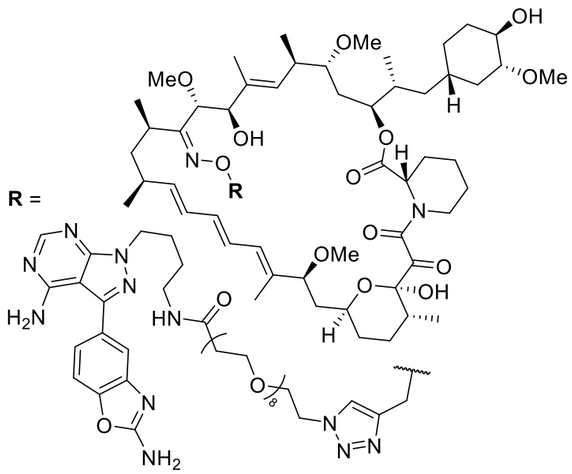
This relatively small macrocycle doesn't rely on the solvent front region of the kinase for activity allowing it to stay active against solvent front mutations like G1202R.

The molecularly efficient structure with low MW, TPSA, and few hydrogen bond donors contributes to its remarkably high brain concentrations (66% of plasma conc. in rat), which may be important in late-stage disease where brain metastases are common.

TPX-0131 is currently in Ph. I/II in ALK+, pre-treated cancers (NCT04849273).

RMC-5552

mTORC1



mTORC1-selective bi-steric mTOR inhibitor
QW IP activity in xeno., 5552 in Ph. I for cancer
from linking of “rapalog” + mTOR inh. + opt
Nature Chemical Biology
Revolution Medicines, Redwood City, US

The Revolution Medicines selective mTORC1 complex inhibitor, RMC-4529, is a “bi-steric” inhibitor that has a rapamycin-derived, FKBP12-recruiting allosteric mTOR inhibitor covalently linked to an active-site (orthosteric) inhibitor of the mTOR kinase.

By inhibiting both binding sites of mTOR, >30-fold selectivity for the mTORC1 complex over mTORC2 complex was found, whereas selective inhibition with “mono-steric” inhibitors has been hard to achieve.

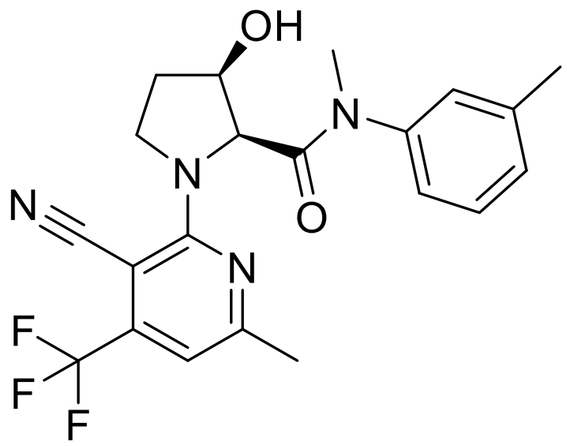
Selective inhibitors of mTORC1 has been desirable since mTORC2 inhibition can lead to hyperglycemia and counterproductive effects in cancer settings, but selective inhibition between complexes which employ the same kinase (mTOR) has been a longstanding challenge.

Interestingly, improved selectivity was ultimately found by reducing the independent affinity of each moiety for their respect target sites (FKBP12/FRB or active site).

This bisteric inhibitor does indeed inhibit tumor growth at doses that do not cause glucose intolerance and does not show signs of RTK induction characteristic of pan-mTOR inhibitors. Hopefully observation of more pronounced anticancer activity with less toxicity will be observed clinically with related molecule RMC-5552, which is entering Ph. I in several tumor types (NCT04774952).

ART558

Polθ



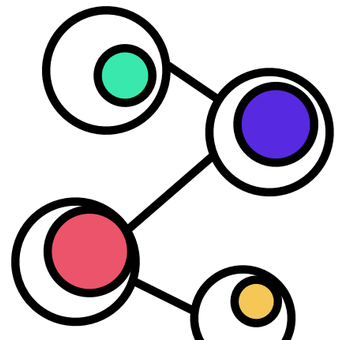
allosteric Polθ DNA polymerase inhibitor
oral activity in BRCA- xenograft (100 mpk QD)
from 165k cmpd biochem. HTS and opt.
Nature Communications
Artios Pharma, Cambridge / ICR, London, UK

The Artios Pharma selective allosteric Polθ DNA polymerase inhibitor, ART558, induces synthetic lethality in BRCA-mutant cancer cells and enhances PARP inhibitor activity.

Defects in the 53BP1/Shieldin complex (which cause PARPi resistance) result in sensitivity to Polθ inhibition.

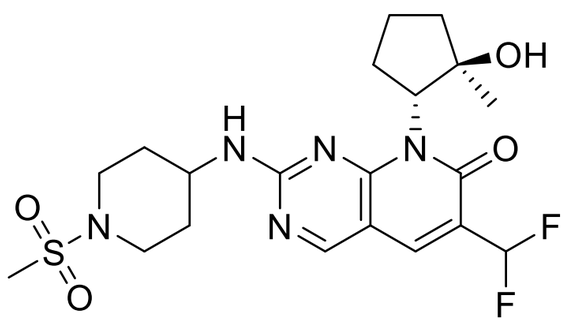
The molecule is orally active in a mouse xenograft model in a BRCA mutant line and Artios aims to have a first-in-human study for a Polθ inhibitor this year.

With the growing success of PARP inhibitors and the synthetic lethality concept there will be interest in seeing clinical data with this new synthetic lethal mechanism.



PF-60873600

CDK2/4/6



X-ray, PDB:
7KJS

selective CDK2/4/6 inhibitor
oral agent in Ph. I/IIa for HR+ HER2- cancers
screen for CDK1/2 sel., SBDD + Free-Wilson
Journal of Medicinal Chemistry
Pfizer, San Diego, US

The Pfizer CDK2/4/6 inhibitor PF-60873600 is orally bioavailable with Ki values of 0.09 nM, 1.3 nM, and 0.16 nM for CDK2, CDK4, and CDK6, respectively, with lower activities against CDK1 (4.5 nM) and CDK9 (20 nM). PF-06873600 entered in Ph. I/IIa in 2018 against HR+ HER2- breast and ovarian cancers.

Control of the cell cycle through selective inhibition of CDK4/6 has proven beneficial in the treatment of breast cancer (e.g. palbociclib, ribociclib), and CDK2 has recently emerged as a therapeutic target in multiple tumor types.

Targeting additional cell cycle CDK isoforms may allow treatment of additional tumor types and overcome resistance to selective CDK4/6 inhibitors.

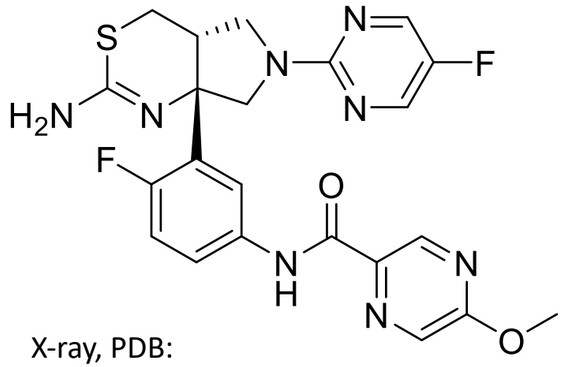
Nonselective CDK inhibitors, however, have a history of failure in clinical trials due to cytotoxicity across gastrointestinal tissues and bone marrow cells which the authors attribute to CDK1.

The starting point was a CDK1-sparing CDK2/4/6 inhibitor related to palbociclib. A cocrystal structure informed the team of vectors to prioritize, and Free-Wilson analysis of existing compounds led to structural modifications that improved the CDK2 potency, LipE, and overall selectivity.

MD simulations suggested that CDK2 selectivity is due to a transient hydrogen bond with a reside which is solvent-exposed in other CDKs.

LY3202626

BACE



X-ray, PDB:
7MYU

low-dose CNS-penetrant BACE inhibitor
90% red. of CSF Aβ in Ph. II at 9.2 mg / discont.
from opt. vs. CatD and dose red. of prior leads
Journal of Medicinal Chemistry
Eli Lilly, Indianapolis, US

The Lilly beta-site APP cleaving enzyme (BACE) inhibitor LY3202626 is an oral, low-dose, CNS-penetrant molecule which entered a Phase II of clinical trial against Alzheimer's disease in 2016.

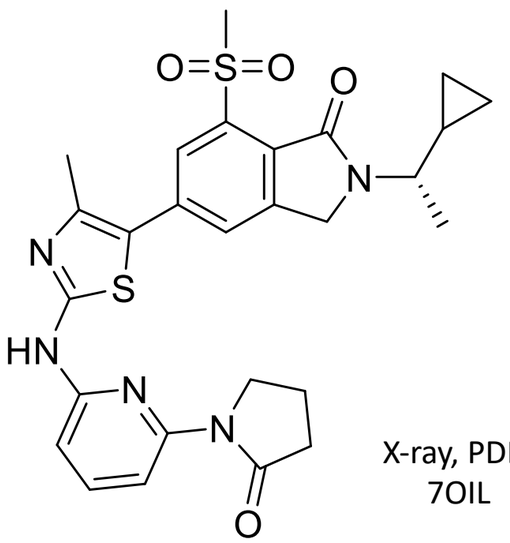
In a Ph. I study, only 9.2 mg of LY3202626 were needed to achieve 90% CSF Aβ reduction. Similar to other BACE inhibitors, development was halted due to a lack of an efficacy signal.

The article shares a lot of preclinical and clinical data (with remarkable alignment between human projections and actual human data) and summarizes many challenges that were overcome including retinal toxicity of earlier molecules due to CatD inhibition as well as a high (>300 mg) dose projection for another candidate.

These "post-humous" program reports are always educational because companies share more data and each company demonstrates a unique approach to solving the same issues. BACE inhibitors were previously highlighted in May 2020 and Feb. 2021 for comparison.

AZD8154

PI3Kγ,δ



X-ray, PDB: 7OIL

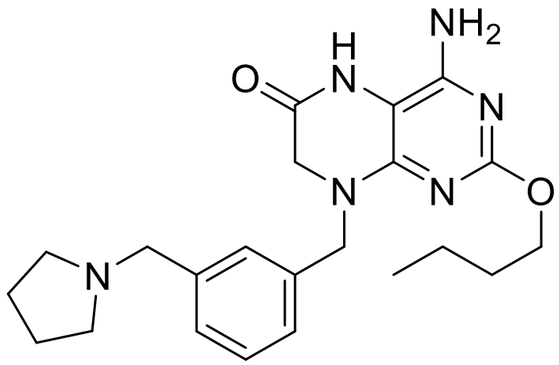
inhaled dual PI3Kγ,δ kinase inhibitor
Ph. II (3 mg QD) for asthma; withdrawn from re-opt. of oral PI3Kγ inhibitor
Journal of Medicinal Chemistry
AstraZeneca, Gothenburg, SE

The AstraZeneca inhaled dual PI3Kγ,δ inhibitor AZD8154 is long-acting in the lung but has low systemic exposure and is selective, potentially avoiding the known side effects of systemic PI3K inhibition.

The molecule is active in cells derived from asthmatic patients as well as in a rat model, and entered Ph. 2 trials (NCT04187508) but was withdrawn due to emerging preclinical toxicology findings.

vesatolimod

TLR7



oral Toll-like receptor TLR7 agonist
3 mg Q2W, Ph. II for HIV/AIDS
from opt. of 8-oxopurine agonist
Science Translational Medicine
Gilead Sciences, Foster City, CA

The Gilead Toll-like receptor 7 (TLR7) agonist, vesatolimod (GS-9620), is a tolerated, low-dose oral TLR7 agonist. It is intended to induce immune cell activation to help eliminate reservoirs of HIV during antiviral therapy.

It was first developed to treat chronic hepatitis B and C infection to induce a liver-targeted antiviral effect without inducing the adverse effects associated with current systemic interferon-α (IFN-α) therapies.

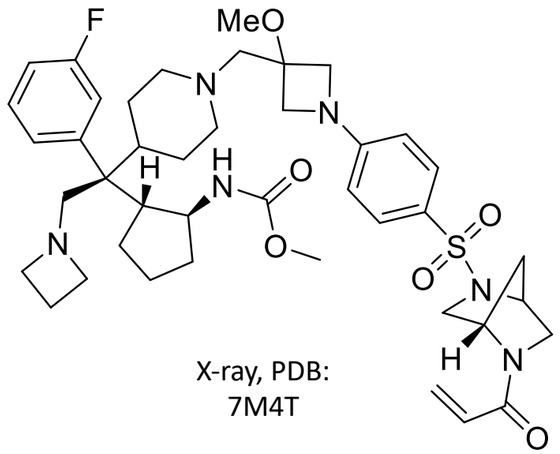
Unfortunately, early clinical data showed it was ineffective against hepatitis B virus (HBV).

Preclinical studies with TLR7 agonists in rhesus macaques infected with SIV or SHIV showed virus control after antiretroviral therapy interruption, and combination regimens resulted in complete elimination of the viral reservoir in some animals.

In Gilead's Ph. II study with vesatolimod, the TLR7 agonist did contribute to the delay of the viral rebound in a subset of HIV patients, suggesting the therapeutic hypothesis might be relevant in humans, though combination treatments might be needed to improve the magnitude of the effect.

M-1121

menin-MLL



X-ray, PDB:
7M4T

orally active covalent menin-MLL PPI inhibitor
efficacy in xenograft (300 mpk PO QD)
warhead addition to rev. inh. and opt.
Journal of Medicinal Chemistry
University of Michigan, Ann Arbor, US

The University of Michigan menin-MLL inhibitor is a covalent protein-protein interaction inhibitor that is orally active and achieves complete tumor regression in a xenograft model (300 mpk PO QD).

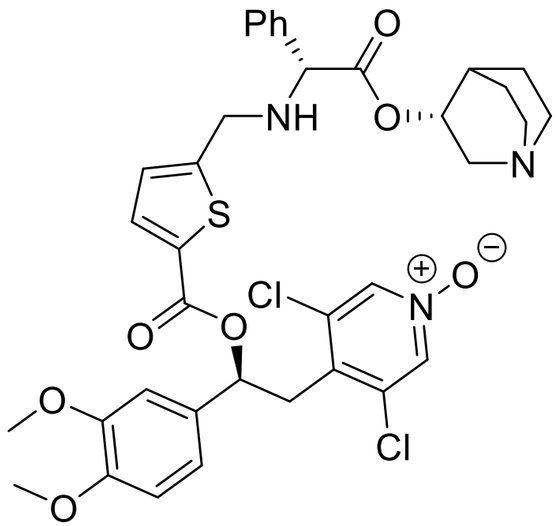
MLL gene fusions are drivers of leukemias via interaction with menin, and small molecule menin-MLL inhibitors have shown preliminary activity in trials (KO-539, NCT04067336 and SNDX-5613, NCT4065399).

M-1121 has a non-covalent scaffold with features reminiscent of prior reversible inhibitors (e.g. MI-503 and VTP-50469) with an acrylamide warhead targeting MLL's Cys329.

Though it is given at a high dose in mouse, the in vivo activity of the molecule is impressive given its large size, acrylamide warhead, the presence of two basic nitrogens, 7 rings, and several hydrogen-bond acceptor and donor groups.

CHF-6001

M3/PDE4



Inhaled dual M3 antagonist/PDE4 inhibitor intratracheal efficacy in model, not developed from linking M3 antag. + PDE inh. and opt.
Journal of Medicinal Chemistry
Chiesi Farmaceutici S.p.A., Parma, IT

The Chiesi M3 antagonist/PDE4 inhibitor dual pharmacology molecule, compound 92a, is an inhaled compound intended for pulmonary diseases. Both M3 and PDE4 are clinically validated targets for COPD (e.g. ipratropium and roflumilast).

Dual pharmacology was thought to be valuable over two independent inhibitors in part due to the potentially better lung retention and lower systemic exposure of larger molecules, as well as the simplified clinical development of one compound with one formulation.

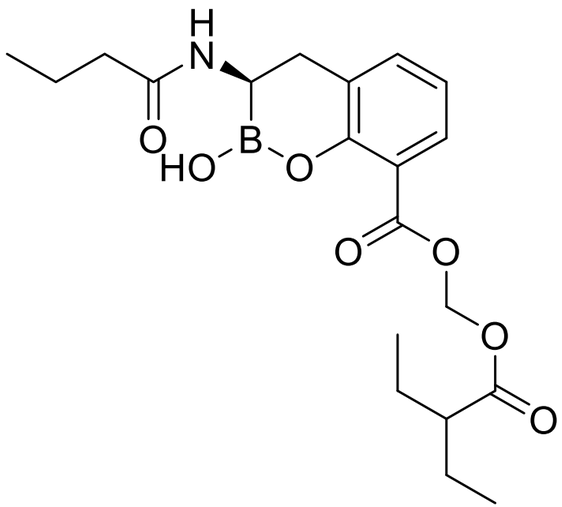
The molecule is derived from the scaffold of prior inhaled PDE4 clinical candidate CHF-6001 and an M3 receptor antagonist and demonstrates in vivo efficacy in bronchoconstriction and inflammation assays in rat after intratracheal administration.

In model animals, 92a seemed to show a lower degree of nausea and GI effects (known side effects of PDE4 inhibitors) than roflumilast.

Unfortunately the quinuclidine ester in the molecule hydrolyzes when stored under accelerated conditions, and this combined with the non-optimal balance between affinity of the two targets resulted in progression being halted.

VNRX-7145

β-Lact.



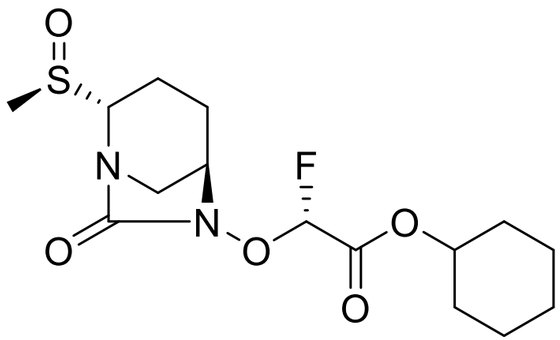
oral serine β-lactamase inh. prodrug
restores ceftibuten activity in model, Ph. I
hydrolysis transition state mimetic
Journal of Medicinal Chemistry
Venatorx Pharmaceuticals, Malvern, US

The Venatorx serine β-lactamase inhibitor VNRX-7145 is an orally bioavailable prodrug of the boronic acid-containing inhibitor VNRX-5236, and is currently in Ph. I. It demonstrates activity in vitro and in vivo covering Enterobacterales expressing key class A or D carbapenemases or class C cephalosporinases.

In preclinical studies, the inhibitor VNRX-7145 restored ceftibuten activity in a mouse model of UTI due to ESBL- and KPC-carbapenemase-producing strains of E. coli and K. pneumoniae. A related molecule, QPX7728, was covered in Apr. 2020.

“compound 21”

β-Lact.



oral serine β-lactamase inh. prodrug
efficacy in murine urinary tract infect. model
from SAR of prior scaffold
Journal of Medicinal Chemistry
Shionogi, Toyonaka, JP

The Shionogi β-lactamase inhibitor (BLI) cyclohexyl ester prodrug, “compound 21,” is a molecule with an interesting sulfinylamide motif on a strained bridgehead nitrogen amide core.

The authors used an interesting radical decarboxylative thiolation to introduce the sulfinyl group.

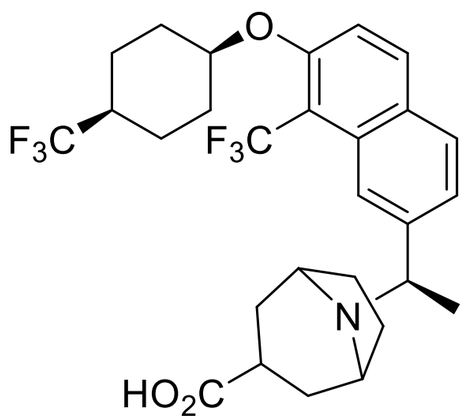
This potent oral BLI restores the antibacterial activity of 3rd-gen. cephalosporin, ceftibuten (CTB) against serine β-lactamase-producing strains including carbapenem-resistant Enterobacteriaceae (CRE).

The molecule is efficacious in a murine urinary tract infection model in combination with CTB, and demonstrated safety in a rat 2 week toxicology study.

A related molecule, ETX0282, was covered in Jul. 2020.

BIO-32546

ATX



X-ray, PDB: 7MFH

CNS-penetrant non-zinc binding ATX inhibitor
oral PK/PD and efficacy in inflamm. pain model
from phosphonic acid hit from S1P library
ACS Medicinal Chemistry Letters
Biogen Inc., Cambridge, US

The Biogen compound BIO-32546 is a potent (IC50 = 1 nM), selective, oral, non-zinc-binding reversible autotaxin (ATX) inhibitor, and is an interesting example of a relevantly large brain-penetrant zwitterion.

The molecule has a distinct structure from ATX inhibitors previously highlighted (e.g. May, Jul., Nov. 2020) and was derived from an phosphonic acid-containing inhibitor hit (28 nM) from a lipid mimetic chemical library.

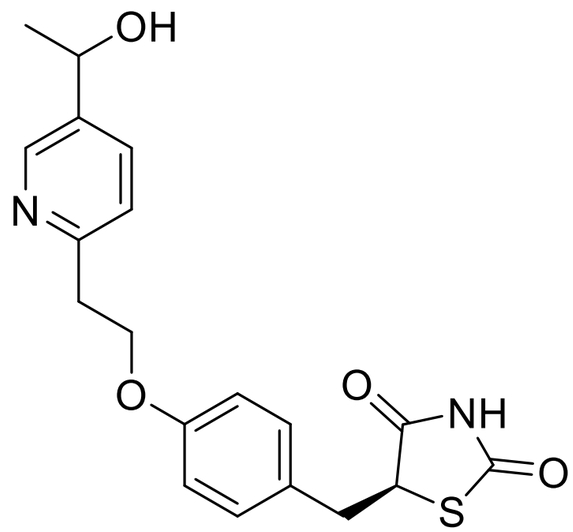
If your first reaction was that this molecule looks like an S1P modulator, you're not crazy – the chemical library was derived from Biogen's S1P program.

Optimization was guided by cocrystal structures and the window against a hERG liability (surprising for an acid-containing molecule) was mitigated with introduction of a benzylic methyl group.

The compound demonstrated in vivo efficacy in a model of acute pain with good PK/PD correlation in a model of acute pain. No brain-penetrant ATX inhibitors appear to be in clinical trials, and Biogen doesn't appear to have advanced an ATX inhibitor into the clinic.

leriglitazone

PPARγ



oral PPARγ agonist for CNS diseases
Ph. II and III ongoing for AMN and cALD
one of the metabolites of pioglitazone
Science Translational Medicine
Minoryx Therapeutics S.L., Barcelona, ES

The Minoryx peroxisome proliferator-activated receptor gamma (PPARγ) agonist, leriglitazone, is one of the several metabolites of pioglitazone, a member of the thiazolidinedione (glitazone) drug class for diabetes.

It is instead being developed for a rare peroxisomal neurodegenerative disease, X-linked adrenoleukodystrophy (X-ALD).

It completed a Ph. I clinical trial (135 and 270 mg/day, 8 days) showing good safety, tolerability and CNS engagement of PPAR gamma receptors at levels equivalent to those required for efficacy in preclinical models, and a Ph. II/III study is currently ongoing to elucidate whether leriglitazone can preventing or delaying the advancement of adrenomyeloneuropathy (AMN) into cALD (childhood cerebral adrenoleukodystrophy).

It is an interesting example of rationally repurposing a species of an established drug class for an entirely different set of indications.

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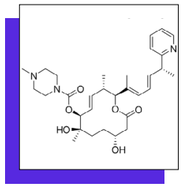
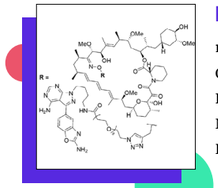
June 2021
drughunter.com



H3B-8800 | SF3b

Oral splicing modulator (SF3b complex)
7–20 mg 21d+/7d–, Ph.I for myeloid neoplasias
From opt. of pladienolide B natural product
Leukemia
H3 Biomedicine, Cambridge, US



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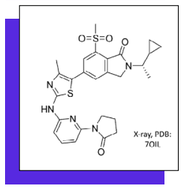
Pfizer, San Diego, US



AZD8154 | PI3Kγ,δ

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From re-opt. of oral PI3Kγ inhibitor
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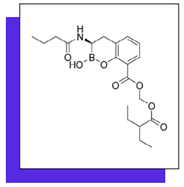
University of Michigan, Ann Arbor, US



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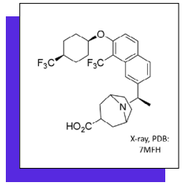

BIO-32546 | ATX

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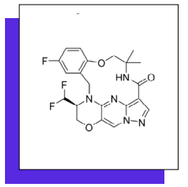
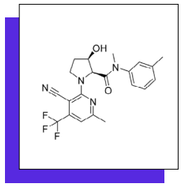


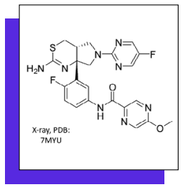
TPX-0131 | ALK

Brain-penetrant mutant ALK kinase inhibitor
Oral, Ph. I/II in ALK+ pre-treated cancers
Undisclosed starting point, SBDD
Molecular Cancer Therapeutics
Turning Point Therapeutics, San Diego, US



ART558 | Polθ

Allosteric Polθ DNA polymerase inhibitor
Oral activity in BRCA– xenograft (100 mpk QD)
From 165k cmpd biochem. HTS and opt.
Nature Communications
Artios Pharma, Cambridge / ICR, London, UK



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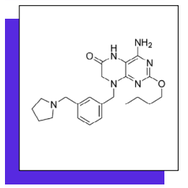
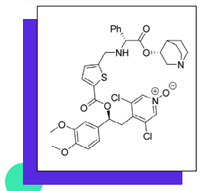
Journal of Medicinal Chemistry
Eli Lilly, Indianapolis, US



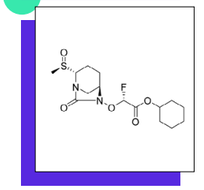
vesatolimod | TLR7

Oral Toll-like receptor TLR7 agonist
3 mg Q2W, Ph. II for HIV/AIDS
From opt. of 8-oxopurine agonist
Science Translational Medicine
Gilead Sciences, Foster City, CA



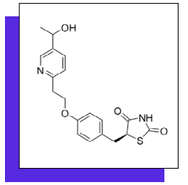
compound 92a | M3/PDE4

Inhaled dual M3 antagonist/PDE4 inhibitor
Intratracheal efficacy in model, not developed
From linking M3 antag. + PDE inh. and opt.
Journal of Medicinal Chemistry
Chiesi Farmaceutici S.p.A., Parma, IT



“compound 21” | β-Lact.

Oral serine β-lactamase inh. prodrug
Efficacy in murine urinary tract infect. model
From SAR of prior scaffold
Journal of Medicinal Chemistry
Shionogi, Toyonaka, JP



Ieriglitazone | PPARγ

Oral PPARγ agonist for CNS diseases
Ph. II and III ongoing for AMN and cALD
One of the metabolites of pioglitazone
Science Translational Medicine
Minoryx Therapeutics S.L., Barcelona, ES

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