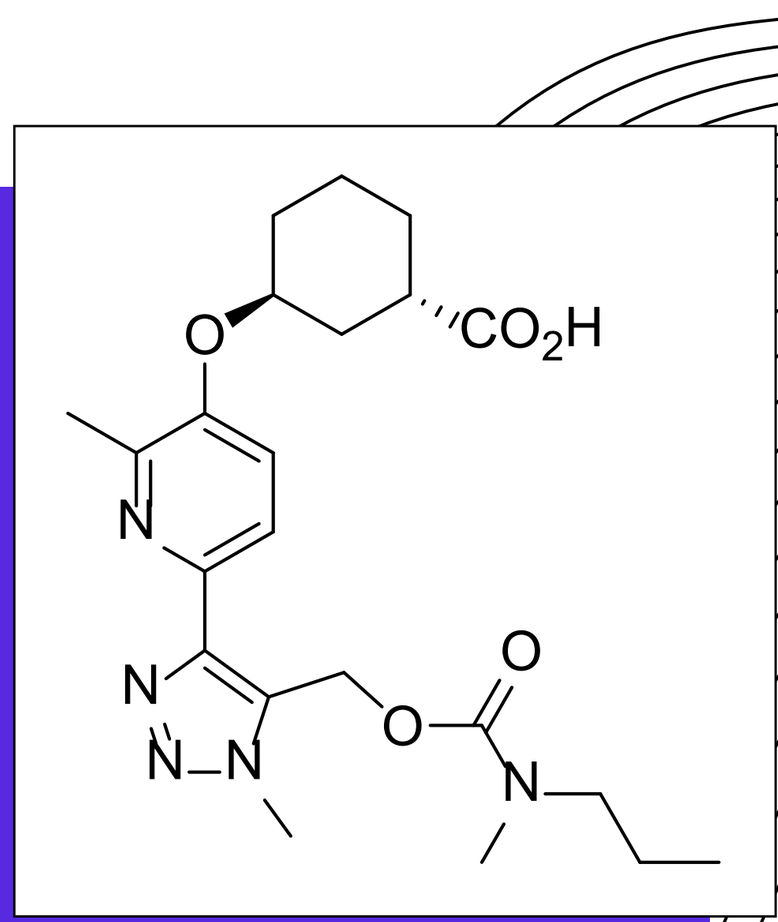
Small Molecules of the Month

October 2021

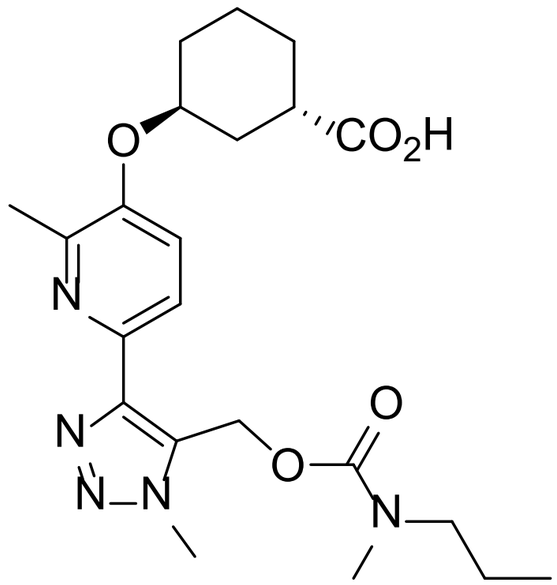


drug hunter

01	LPA_1	Bristol Myers Squibb
02	CRBN/BET	Saint Jude Children’s Hospital
03	CDC7	Carna Biosciences
04	myosin	Cytokinetics
05	CFTR	Pfizer
06	troponin	Cytokinetics
07	NS3-NS4B	Janssen Pharmaceutica
08	P2X3	Bayer AG
09	TRK	Turning Point Therapeutics
10	TGFβR	Bristol Myers Squibb
11	GCS	Sanofi
12	IBAT	Mirum / Pfizer / Pharmacia / Sear
13	PCSK9	Merck & Co.
14	HPK1	Janssen R&D

BMS986278

LPAR1 antagonist



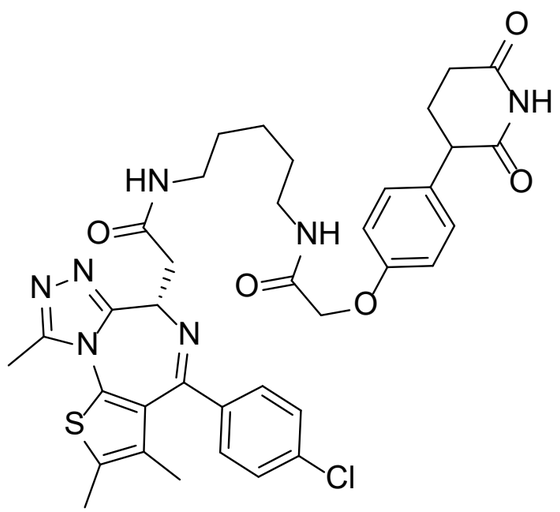
oral LPA_1 GPCR receptor antagonist
Ph. II candidate for IPF (60 mg BID)
from addressing tox. of prior candidate
Journal of Medicinal Chemistry
Bristol Myers Squibb, Princeton, NJ

This month's cover molecule, BMS-986278, is an LPA_1 antagonist and oral (up to 125 mg BID) Ph. II clinical candidate for idiopathic pulmonary fibrosis (IPF) (NCT04308681). Reviewer and nominator Christian Kuttruff says: "While there are two approved molecules for the treatment of IPF (pirfenidone from Roche and nintedanib from BI), there is still a significant medical need for IPF/PF-ILD patients. Alongside current Phase III assets targeting IPF (Fibrogen's pamrevlumab, Roche's pentraxin and United Therapeutics' teprostinil), this BMS LPAR1 antagonist is a promising compound in development for IPF due to the fact that their previous frontrunner molecule (BMS-986020) showed promising proof-of-efficacy in a 6 month Ph. II trial in IPF patients, slowing the decline of FVC by 69% vs. placebo. BMS-986020's trial was stopped due to hepatobiliary toxicity, which BMS-986278 may address."

"The hepatobiliary tox. is believed to be an off-target effect specific to BMS-986020, which can most likely be attributed to increased plasma bile acids, possibly due to the fact that the compound has significant inhibitory activity at several key bile acid transporters (incl. BSEP, MRP4, MDR3). Their chemical optimization approach therefore included a decrease in lipophilicity and increase in $C(sp^3)$ to decrease transporter inhibition and a lower dose via replacement of the amino-isoxazole carbamate which was metabolically labile.
By systematically optimizing the individual parts of the molecule (going from biphenyl acid to 3-oxycyclohexyl acid; phenyl-ring to methyl-pyridine, isoxazole to polar methyl-triazole and installation of optimal O-carbamate) they ended up with BMS-986278 which has reduced clogP, increased PSA and increased $C(sp^3)$ vs. BMS-986020, which resulted in the improved liability profile (particularly protein binding & bile salt export pump activities)."

compound 4c

phenyl-glutarimide-based degrader



degrader with simpler CRBN warhead

BRD4 DC50 = 0.87 nM, D_{max} = 99%

from structure-based design

Angewandte Chemie Int. Ed.

Saint Jude Children's Hospital, Memphis, TN

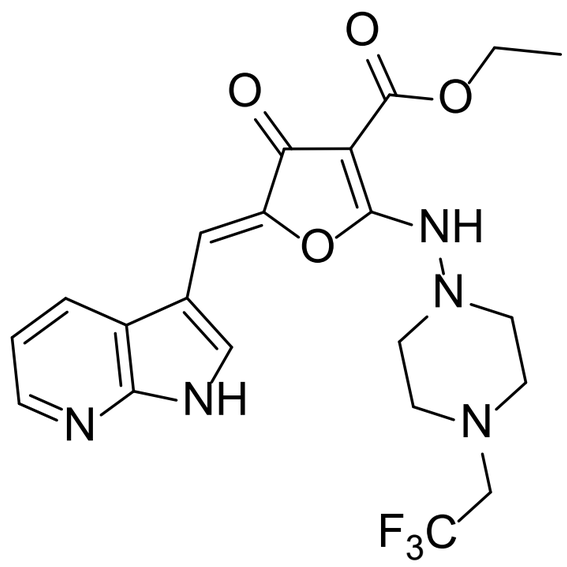
The bifunctional degrader, SJ995973, was nominated by Joachim Rudolph. "Instead of the thalidomide-based cereblon binder present in the established BET degrader tool dBET1, SJ995973 uses a novel cereblon binder containing a simple phenyl ring instead of the hydrolytically labile phthalimide group.

Not only is SJ995973 an extremely potent BET degrader (BRD4 DC50 = 0.87 nM (Dmax = 99%)), but the alternative cereblon binder offers key advantages over thalidomide (and classical IMiDs used in PROTAC design in general), including chemical stability, smaller size and TPSA, and synthetic feasibility."

This novel cereblon binding motif is likely to be reused in many new applications.

AS-0141

CDC7 kinase inhibitor



oral, slow-off, selective CDC7 kinase inhibitor
Ph. I candidate for solid tumors
from HTS and PK optimization
Journal of Medicinal Chemistry
Carna Biosciences, Kobe, JP

The Carna Biosciences CDC7 kinase inhibitor, AS-0141, is a clinical candidate for cancer with a structure that contains a hydrazine, furenone, and ester, all rare functional groups for an oral molecule.

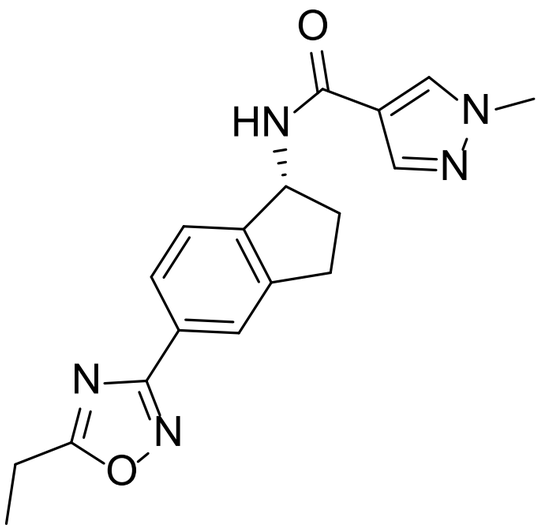
The molecule has a long residence time on the kinase, and despite a short half-life in mouse, extended target engagement is observed >24 h post-dose.

The unusual structure of the molecule was confirmed by single crystal X-ray diffraction.

This is also an interesting example of a drug candidate being developed by a drug discovery product supplier – reagents for some of the assays used were supplied by Carna Biosciences' assay products division.

aficamten

myosin inhibitor



oral QD myosin inhibitor (IC50 = 1.4 μM)
Ph. II candidate for cardiomyopathy (5-30 mg)
from HTS w/ bovine cardiac muscle myofibrils
Journal of Medicinal Chemistry
Cytokinetics, South San Francisco, CA

The Cytokinetics next-generation myosin inhibitor, aficamten, is a phase II candidate for genetic hypertrophic cardiomyopathies, and is orally dosed between 5-30 mg QD.

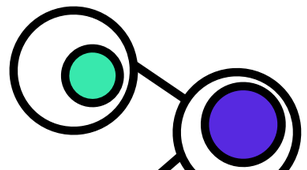
It follows BMS's mavacamten (acquired from Myokardia in a $13.1B deal), whose NDA is under review by the FDA.

This class of molecules is intended to address hypertrophic cardiomyopathy (in which thickening of the left ventricular walls limits cardiac output) by inhibiting cardiac sarcomere contractility.

The molecule is reaches steady state within two weeks of dosing in a Ph. I trial rather than over six weeks for mavacamten, is safe and well-tolerated in healthy volunteers, and has low risk of DDIs with no significant cytochrome P450 induction or inhibition risk.

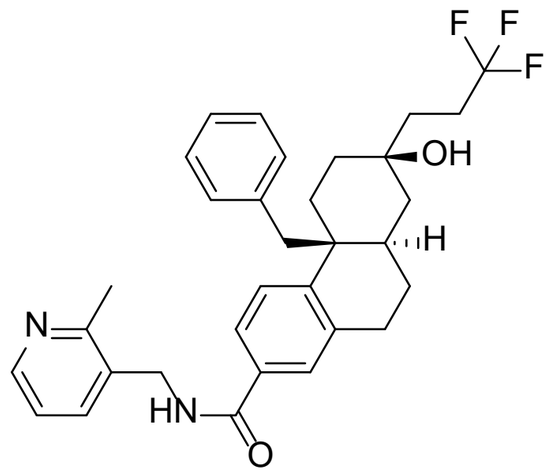
The indoline starting point was discovered in a high-throughput phenotypic screen using bovine cardiac muscle myofibrils measuring the rate of ATP hydrolysis. Selectivity against cardiac myofibrils was inherent to the scaffold, with no measurable inhibition against smooth muscle myosin detected throughout optimization.

This is an excellent modern example of empirical screening being employed boldly and successfully for a novel mechanism, with the follow-through to a clinical molecule.



CP-628006

CFTR potentiator



CFTR potentiator w/ diff. MoA from ivacaftor
preclinical synergy w/ iva. on G551D-CFTR
from 150k cmpd HTS
British Journal of Pharmacology
Pfizer, Cambridge, UK

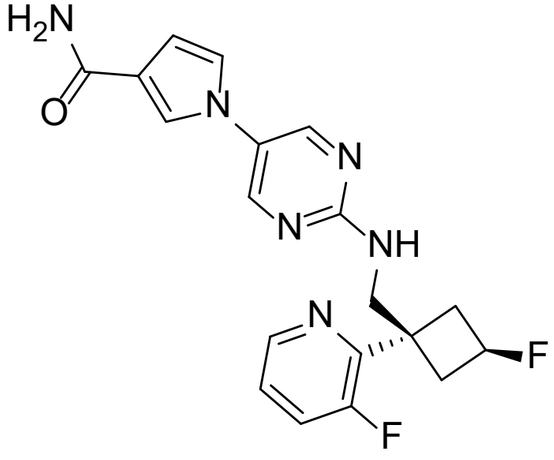
The Pfizer CFTR potentiator, CP-628006, enhances CFTR function in cystic fibrosis patient-derived airwell cells with a distinct mechanism of action from existing potentiators such as ivacaftor.

It has a unique chemical structure, and in contrast to other potentiators does not seem to inhibit the channel at high concentrations of drug and appears to improve the plasma membrane stability of F508del-CFTR rather than destabilize it.

Greater clinical benefit in CF might be achieved with combinations of different classes of potentiators such as CP-628006, making it an interesting albeit synthetically challenging starting point for further investigation.

reldesemtiv

troponin activator



second gen. oral troponin activator
Ph. III candidate for ALS (300 mg BID)
from HTS in muscle assay and reducing BP
Journal of Medicinal Chemistry
Cytokinetics, South San Francisco, CA

The Cytokinetics second generation troponin activator, reldesemtiv, is intended to treat muscle weakness by directly activating skeletal muscle.

A high concentration of free drug is expected to be needed due to the large amount of fast skeletal muscle troponin in the body, making safety and selectivity critical. Reldesemtiv demonstrated robust activity in a Ph. I PD assessment of muscle response (with a maximum conc. reached at 4000 mg dose of 26 μM) and a reduction in decrease of ALSFRS-R scores in a Ph. II study for ALS patients with more advanced disease across all dose groups, supporting its advancement to a Ph. III trial despite the primary endpoint of slow upright vital capacity not being achieved.

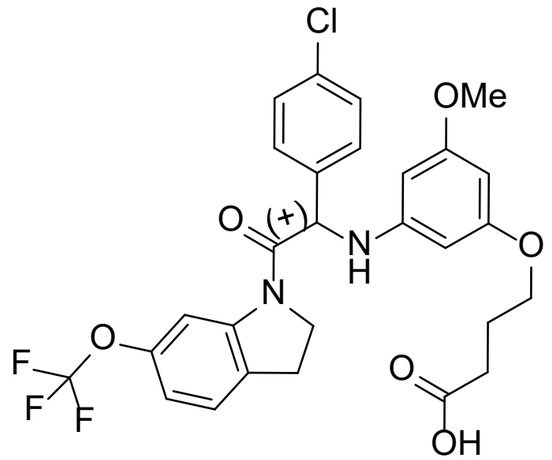
The molecule looks quite different from its thiadiazole starting point identified by HTS, and the focus of optimization was on improving selectivity and distribution to muscle rather than brain tissue since the first-generation molecule tirasemtiv caused what appear to be off-target CNS effects. Chemically the molecule is an interesting example of a pyrrole and fluoro-cyclobutane-containing drug candidate, and is completely structurally different from first-generation molecule.

Development-wise, the molecule is also a good example of a molecule succeeding in human despite high rodent clearance (particularly in male rather than female rats).

The drug is another example of a fascinating and bold mechanism of action being pursued with a small molecule by Cytokinetics.

JNJ-A07

dengue virus inhibitor



pan-genotype, pan-serotype dengue virus inh.
high barrier to resistance, efficacious in vivo
from phenotypic antiviral screen
Nature
Janssen Pharmaceutica, Beerse, BE

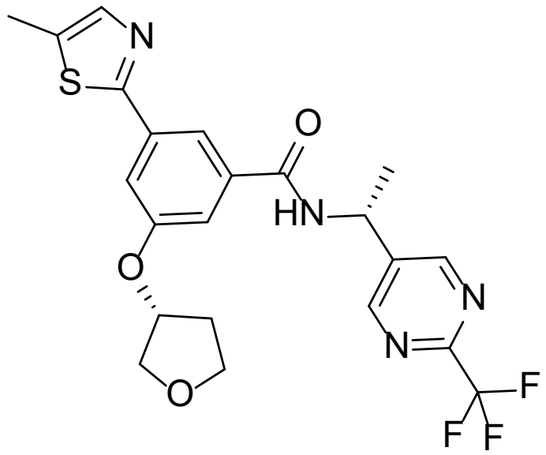
The Janssen pan-genotype, pan-serotype dengue virus inhibitor, JNJ-A07, demonstrates broad activity against a panel of 21 clinical isolates and has a high barrier to resistance.

It blocks the interaction between the non-enzymatic NS4B protein and NS3, preventing them from forming an NS3-NS4B complex which is essential for replication (though it does not appear to dissociate formed NS3-NS4B complexes).

The mechanism is another recent success for phenotypic screening and if developed, this class of molecules could be a significant tool against dengue disease, which affects >96M individuals worldwide.

eliapixant

P2X3 antagonist



oral P2X3 ion channel antagonist
Ph. II, multiple settings (50-750 mg BID)
from literature P2X3 antagonists
Scientific Reports
Bayer AG, Berlin, DE

The Bayer P2X3 purinoreceptor antagonist, eliapixant (BAY1817080), is intended to treat various disorders associated with hypersensitive nerve fibers, including endometriosis.

The hypothesis is that P2X3 receptor antagonism can inhibit cycles of pain causing neurogenic inflammation, causing pain, etc. modifying the underlying disease in endometriotic lesions.

Endometriosis is an area of significant unmet medical need but with a high bar for safety.

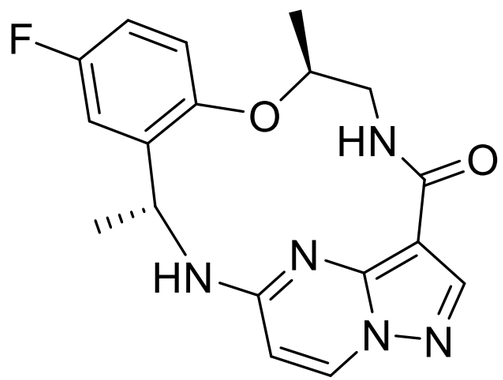
Eliapixant is highly potent and selective for P2X3 over other P2X subtypes in vitro, including P2X2/3.

The molecule completed a phase I safety study and is in several ongoing phase II trials in different conditions including endometriosis (NCT04614246); other hypersensitive nerve fiber-associated disorders, including refractory or unexplained chronic cough (RUCC) (NCT04562155); diabetic neuropathic pain (DNP) (NCT04641273) and overactive bladder (OAB) (NCT04545580).

Eliapixant given 75 mg BID appears to significantly decrease cough frequency in patients with refractory chronic cough.

repotrectinib

TRK inhibitor



X-ray, PDB:
7VKO

oral, CNS-penetrant TRK(A-C) kinase inhibitor
Ph. II candidate for solid tumors (160 mg QD)
from literature starting point
Molecular Cancer Therapeutics
Turning Point Therapeutics, San Diego, CA

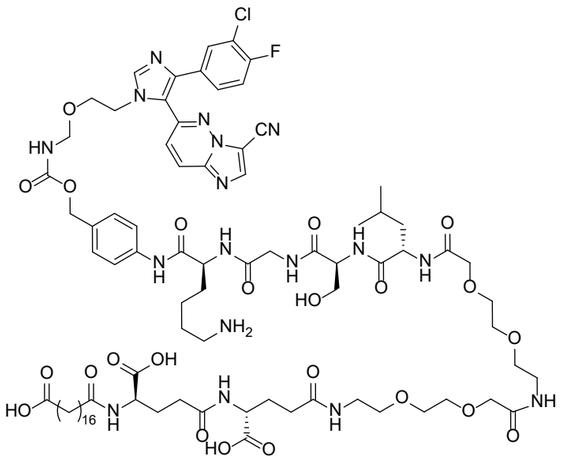
The Turning Point Therapeutics oral, brain-penetrant ALK/ROS1/TRK kinase inhibitor, repotrectinib (TPX-0005), is a macrocyclic molecule with a small size intended to limit adverse interactions with resistance mutation hotspots near kinase active sites.

TRK fusion proteins are driver mutations in certain cancers (which respond well to larotrectinib and entrectinib) but resistance is anticipated to be a problem.

This molecule inhibits TRKA, TRKB, TRC, ROS1, and various forms of ALK, and durable responses were observed in both TKI-naïve and pretreated patients with NTRK+ cancers (NCT03093116).

compound 10

tumor-activated TGFBR inhibitor



tumor specific prodrug of TGFβR inhibitor
QW dosing, improved tumor-to-heart ratio
BMS-986260 prodrug w/ self-immolative link.
Journal of Medicinal Chemistry
Bristol Myers Squibb, Princeton, NJ

The BMS TGFβR inhibitor prodrug, "compound 10," demonstrates antitumor efficacy comparable to the parent compound (BMS-986260) in a syngeneic model with once-weekly dosing, while reducing the systemic exposure of BMS-986260.

Reducing the systemic exposure of a TGFβR inhibitor is important due to previously observed mechanism-based cardiac toxicity.

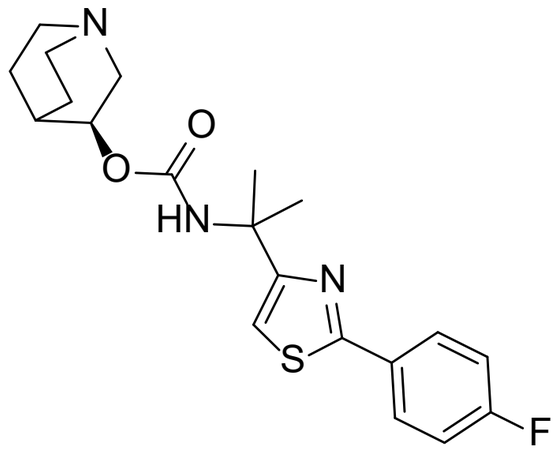
This prodrug is preferentially cleaved by proteases overexpressed in tumors, and results in a prolonged, favorable tumor-to-heart ratio of the active drug in distribution studies.

This is an interesting proof-of-concept for tumor-targeted prodrugs as an approach to improving the therapeutic index of cancer drugs.

It is especially interesting in the immune-oncology setting where the initiation of anticancer activity in a tumor may lead to an abscopal effect and broader systemic responses due to antitumor immune activation.

venglustat

GCS inhibitor



potential BIC oral GCS inhibitor

Ph. III in genetic diseases (15 mg QD)

brain-penetrant, allosteric inhibitor

Scientific Reports

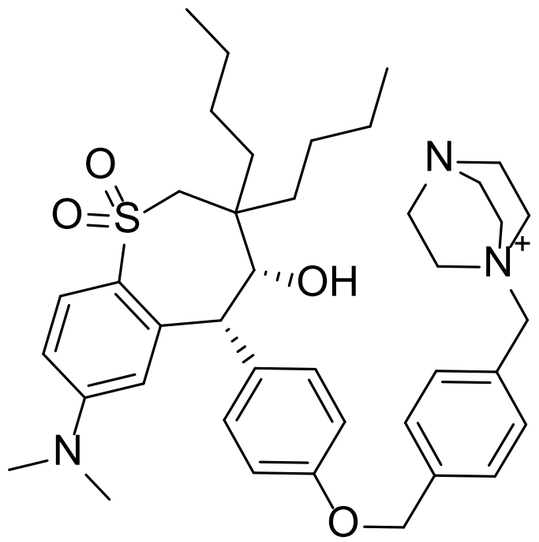
Sanofi

The Sanofi glucosylceramide synthase (GCS) inhibitor, venglustat, is an oral, brain-penetrant clinical candidate for GBA-mutant Parkinson's disease and other diseases where GBA-mutations are relevant.

Though the molecule did not demonstrate efficacy within one year in early GBA-PD patients and was discontinued in this indication (NCT02906020), it continues to be tested in various rare genetic diseases including Gaucher disease type 3 (NCT02843035), Fabry disease (NCT02228460), GM2 gangliosidosis (NCT04421451), and autosomal-dominant polycystic kidney disease (NCT04705051), as its safety has already been demonstrated.

maralixibat

IBAT inhibitor



oral gut-restricted bile acid transporter inh.
approved for cholestatic pruritis in Sep. 2021
repurposed (first patented in 1994)
The Lancet
Mirum / Pfizer / Pharmacia / Searle

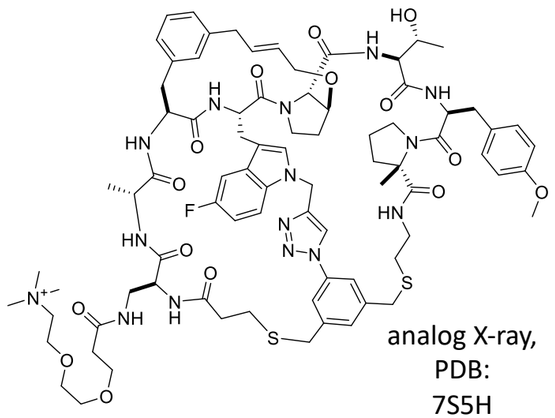
The Mirum Pharmaceuticals IBAT bile acid transporter inhibitor, maralixibat, has a long history, having been first patented by scientists at Searle in 1994 and published by the time Searle became part of Pharmacia in 2005.

It was finally approved in Sep. 2021 for treatment of cholestatic pruritis in patients with Alagille Syndrome, and is estimated to reach annual sales of $536M by 2026, a nice success story for repurposing of old mechanisms by a biotech.

The drug is a bile acid transport inhibitor, preventing enterohepatic bile acid recirculation, and was originally designed to have minimal systemic exposure after oral administration.

compound 44

PCSK9 inhibitor



analog X-ray,
PDB:
7S5H

bioavailable bicyclic macrocycle PCSK9 inh.
%F cyno = 2.9, MW 1612, preclinical
from mRNA display screen and SBDD
Journal of Medicinal Chemistry
Merck & Co.

The Merck bicyclic macrocyclic peptide PCSK9 inhibitor, "compound 44," is a highly potent (Ki = 0.00239 nM) and orally bioavailable (cyno %F = 2.9, t1/2 = 10 h) agent against a notoriously difficult target for small molecules, demonstrating target engagement comparable to approved PCSK9 antibodies.

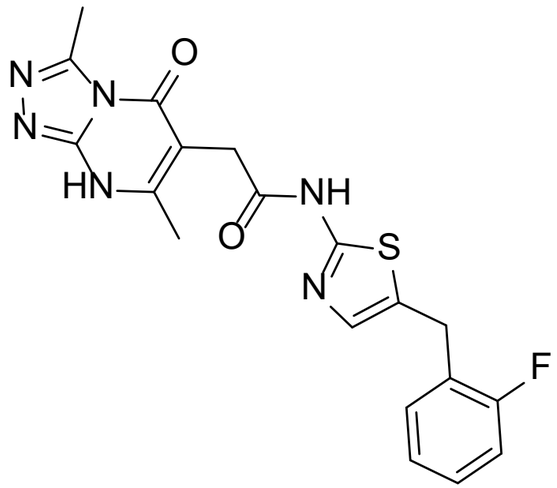
The discovery of this molecule is an interesting proof of concept for this emerging area of drug space (oral macrocyclic peptides), with hits generated by a relatively new technology (mRNA display screen) and advanced with structure-based design (potency increased by 100,000x).

Several off-target issues were addressed while simultaneously lowering clearance, lipophilicity, and improving oral bioavailability. Interestingly, the clearance of the molecules was shifted over time from predominantly hepatic to renal by reducing OATP 1B1 transporter activity.

This PCSK9 drug discovery campaign is a tour de force from the team at Merck and a must-read for anyone interested in bRO5 chemical matter.

compound 1

allosteric HPK1 inhibitor



selective inhibitor of unphosphorylated HPK1
non-ATP competitive, IC50 = 1.2 μM
from 700k cmpd HTS for non-ATP comp. inh.
Biochemistry
Janssen R&D, Spring House, PA

The Janssen non-ATP competitive HPK1 inhibitor, "compound 1," was identified from a screening cascade specifically looking for allosteric inhibitors, which may provide a selectivity advantage over ATP-competitive starting points.

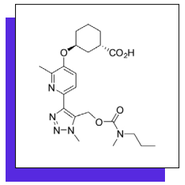
Reviewer Adi Murthy says, "Specificity may prove challenging for HPK active site inhibitors since it belongs to a large family of Ste20 genes that act as MAP4Ks, all with high kinase domain homology."

Reviewer and nominator Callie Bryan says, "The publication summarizes work towards allosteric inhibitors of HPK1 targeting the inactive conformation through application of a cascade assay designed to target full-length, inactive HPK1. In doing so, molecules that attenuate autophosphorylation and potentially interfere with active HPK1 dimer formation were discovered without strong competition with ATP.

This strategy could prove fruitful to other kinases where allosteric inhibition may provide higher likelihood of selective inhibition."

Small Molecules of the Month

October 2021
drughunter.com



BMS-986278 | LPA_1

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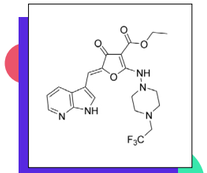

AS-0141 | CDC7

oral, slow-off, selective CDC7 kinase inhibitor
Ph. I candidate for solid tumors
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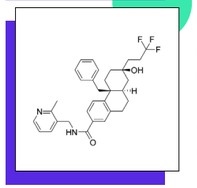

CP-628006 | CFTR

CFTR potentiator w/ diff. MoA from ivacaftor
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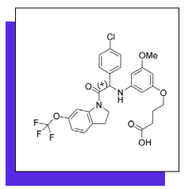
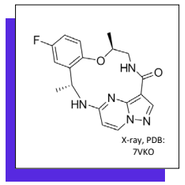
Pfizer, Cambridge, UK



JNJ-A07 | NS3-NS4B

pan-genotype, pan-serotype dengue virus inh.
high barrier to resistance, efficacious in vivo
from phenotypic antiviral screen
Nature
Janssen Pharmaceutica, Beerse, BE



repotrectinib | TRK

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Ph. II candidate for solid tumors (160 mg QD)
from literature starting point
Molecular Cancer Therapeutics
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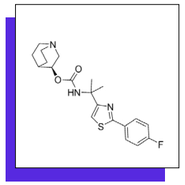
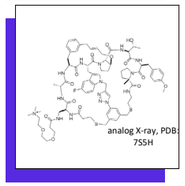


venglustat | GCS

potential BIC oral GCS inhibitor
Ph. III in genetic diseases (15 mg QD)
brain-penetrant, allosteric inhibitor
Scientific Reports
Sanofi



"compound 44" | PCSK9

bioavailable bicyclic macrocycle PCSK9 inh.
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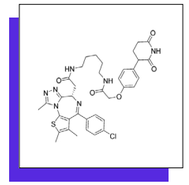
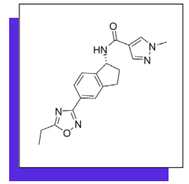
Journal of Medicinal Chemistry
Merck & Co.



SJ995973 | CRBN/BET

degrader with simpler CRBN warhead
$BRD4$ $DC50$ = 0.87 nM, D_{max} = 99%
from structure-based design
Angewandte Chemie Int. Ed.
Saint Jude Children's Hospital, Memphis, TN



aficamten | myosin

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Ph. II candidate for cardiomyopathy (5-30 mg)
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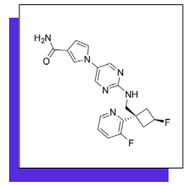

reldesemtiv | troponin

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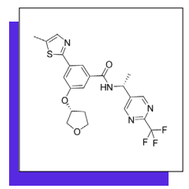
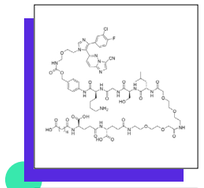
from HTS in muscle assay and reducing BP
Journal of Medicinal Chemistry
Cytokinetics, South San Francisco, CA



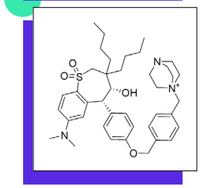
eliapixant | P2X3

oral P2X3 ion channel antagonist
Ph. II, multiple settings (50-750 mg BID)
from literature P2X3 antagonists
Scientific Reports
Bayer AG, Berlin, DE



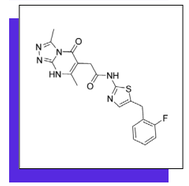
"compound 10" | TGFβR

tumor specific prodrug of TGFβR inhibitor
QW dosing, improved tumor-to-heart ratio
BMS-986260 prodrug w/ self-immolative link.
Journal of Medicinal Chemistry
Bristol Myers Squibb, Princeton, NJ



maralixibat | IBAT

oral gut-restricted bile acid transporter inh.
approved for cholestatic pruritis in Sep. 2021
repurposed (first patented in 1994)
The Lancet
Mirum / Pfizer / Pharmacia / Searle



"compound 1" | HPK1

selective inhibitor of unphosphorylated HPK1
non-ATP competitive, $IC50$ = 1.2 µM
from 700k cmpd HTS for non-ATP comp. inh.
Biochemistry
Janssen R&D, Spring House, PA

drug hunter

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