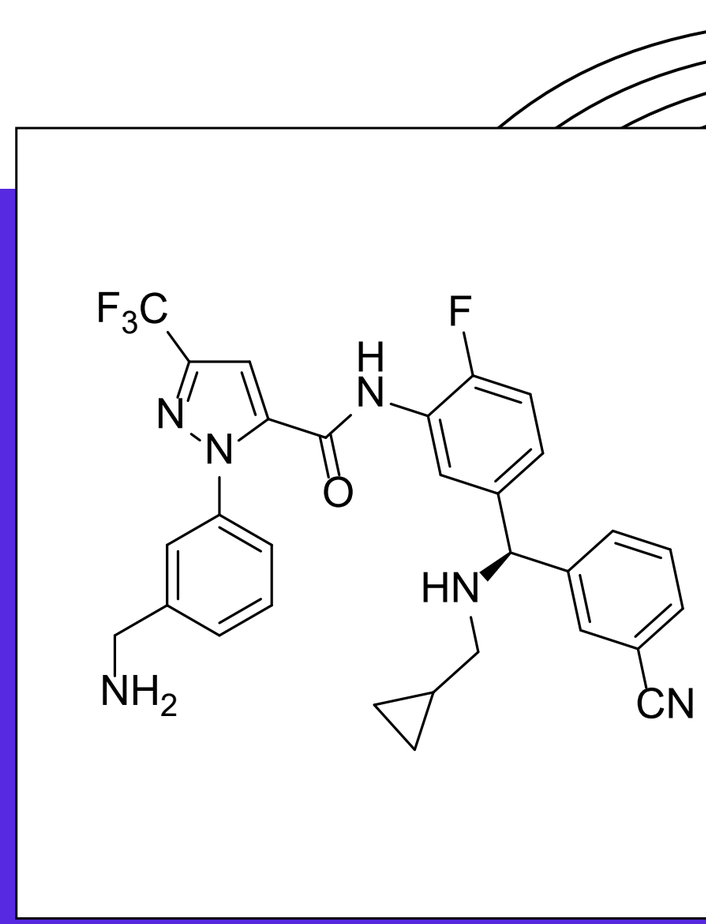
Small Molecules of the Month

August 2021



drug hunter

01	kallikrein	BioCryst
02	RIPK2	GlaxoSmithKline
03	PKCθ	Celgene/BMS
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12	BTK	Takeda
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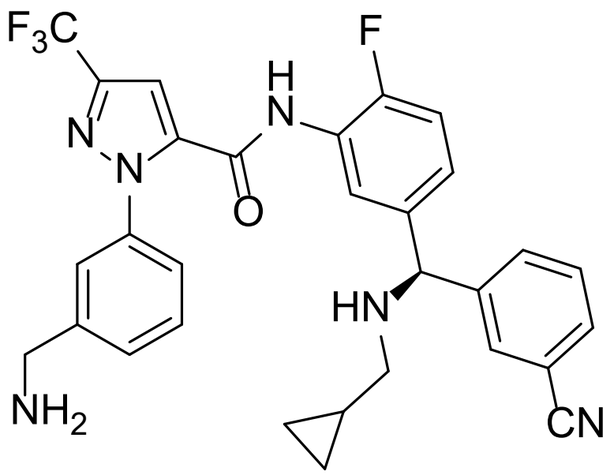
14	MCT4	Merck Healthcare KGaA

berotralstsat

kallikrein



Oral plasma kallikrein serine protease inhibitor
Approved for prevention of HAE attacks
From structure-based drug design
Journal of Medicinal Chemistry
BioCryst, Birmingham, AL, USA

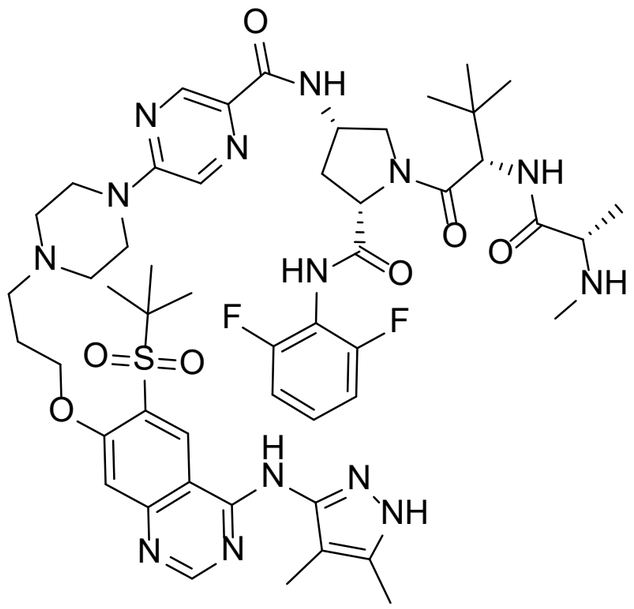
The Biocryst oral plasma kallikrein inhibitor, berotralstat (BCX7353), was recently approved as the first non-steroidal treatment for prevention of hereditary angioedema attacks. The molecule is given orally (150 mg QD) despite having two basic amines. Interestingly for a chronically administered drug, the molecule is noted to have QT prolongation risk at ~3x the recommended dose (450 mg), which appears acceptable for this rare and underserved indication.

The molecule was discovered after a structure-based drug design campaign starting with knowledge from a previously poorly bioavailable benzamidine-containing zwitterion, avoralstat (BCX4161). The benzamidine was successfully replaced with a similarly basic benzylamine, and the new benzylamine-containing fragment was elaborated into molecule with a highly dissimilar structure and binding mode from the original drug.

There are several interesting features from the crystal structures including the fact that the highly hydrophilic primary amine is buried in a polar cleft of the protein. This approved drug is another great example of a “rule-breaker” succeeding in a rare disease setting.

“compound 20”

RIPK2



Long-acting RIPK2 degrader (SC admin.)

In vivo degradation of RIPK2 over 60 days

IAP binder linked to RIPK2 binder

Journal of Medicinal Chemistry

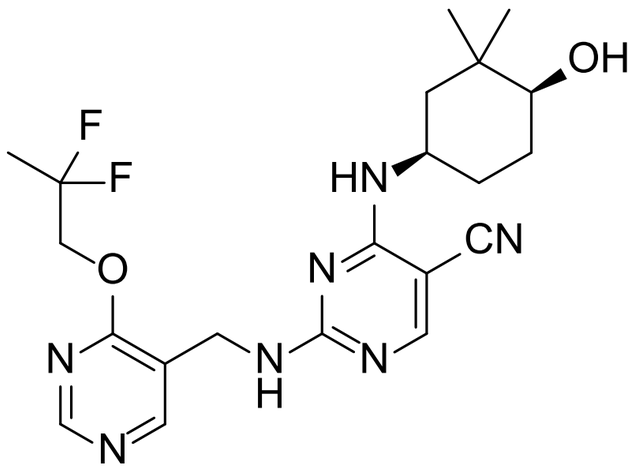
GlaxoSmithKline, Stevenage, UK

The GSK RIPK2 PROTAC, “compound 20”, demonstrates in vivo degradation of RIPK2 over 60 days after a single compound dose when administered SC in slow-release PLGA microparticles. This degrader was previously highlighted as a Molecule of the Month, voted by our readers as a final contender for Molecule of the Year in 2020 thanks to its remarkable in vivo PD.

This article shares more details about the optimization campaign and identification of the molecule, as well as proof-of-concept on the use of the slow-release matrix, and is worth a read for all interested in targeted protein degradation.

CC-90005

PKCθ



Oral, selective PKCθ kinase inhibitor

Ph. I candidate for Psoriasis

From screen of internal library and SBDD

Journal of Medicinal Chemistry

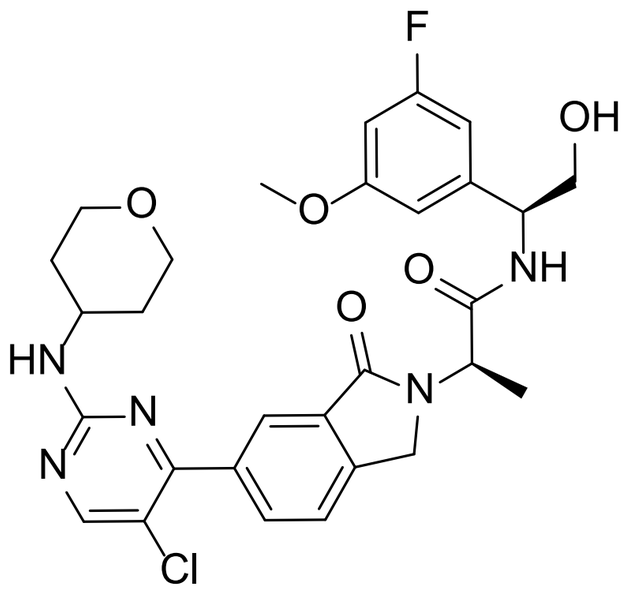
Celgene/BMS, San Diego, CA, USA

The Celgene/BMS PKCθ kinase inhibitor, CC-90005, highlighted by Julien Lefranc, is a clinical candidate in Ph. I for psoriasis, with some dosing being conducted in healthy volunteers. The safety profile is impressive given how fraught with selectivity issues previous PKC inhibitors have been.

The molecule is >550-fold selective for PKCθ over PKCδ, and has relatively high sp3 character for a kinase inhibitor. The advancement of a PKC kinase inhibitor into healthy volunteers and with an intended chronic inflammation indication is testament to how far kinase inhibition has come in 20 years with respect to achievable selectivity and safety.

ASTX029

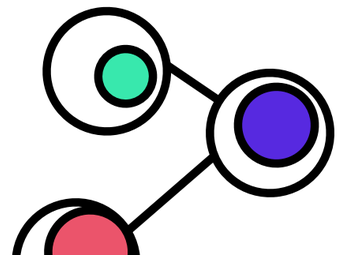
ERK1/2



Oral ERK1/2 kinase and phosphorylation inhib.
Ph. 1/2 candidate for solid tumors
from SBDD from prior lead
Journal of Medicinal Chemistry
Astex Pharmaceuticals, Cambridge, UK

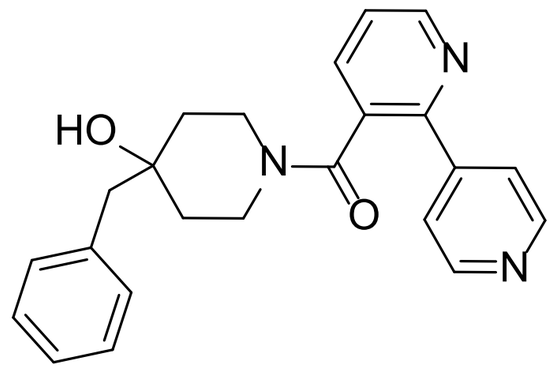
The Astex ERK1/2 kinase inhibitor, ASTX029, is an oral Ph. I-II candidate for patients with advanced solid tumors. The molecule was derived from fragment screening together with structure-based design. Interestingly, the molecule also blocks the phosphorylation/activation of ERK1/2 in addition to inhibiting its kinase activity, making it potentially more effective. Addressing CYP3A4-mediated metabolism while maintaining favorable physicochemical properties was a key aspect of lead optimization.

Though metabolism studies highlighted the oxan ring as a key site of metabolism in lead molecule, the sp3-rich moiety was necessary for potency and physicochemical properties. It was found that replacement of a different region of the molecule improved stability, demonstrating that oxan metabolism is context dependent and serving as another example of a molecule having decent half-life despite having an ether moiety. It will be interesting to see whether the different MoA of this ERK1/2 inhibitor improves the therapeutic index relative to traditional ERK1/2 kinase inhibitors.



soticlestat

CH24H



Brain-penetrant CH24H inhibitor

Ph. 2 for epilepsies (up to 300 mg PO QD)

From SBDD

Journal of Medicinal Chemistry

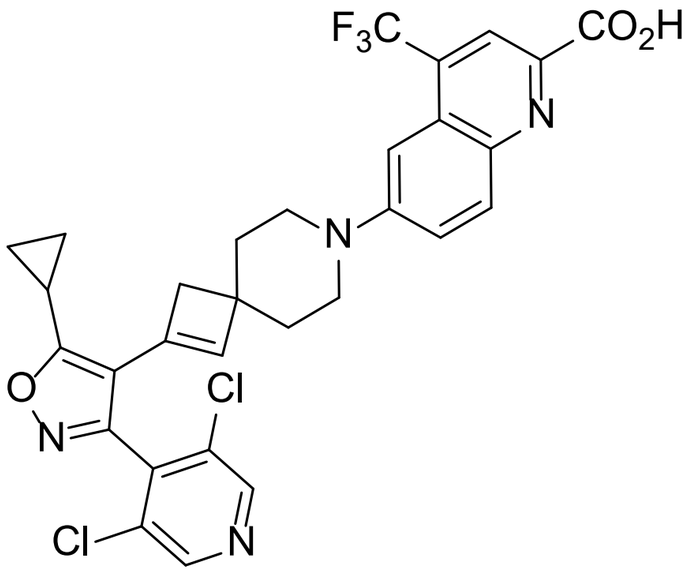
Takeda, Fujisawa, Japan

The Takeda cholesterol 24-hydroxylase inhibitor, soticlestat (TAK-935, previously OV935) is a potent, highly selective, first-in-class inhibitor of the brain-specific enzyme cholesterol 24-hydroxylase (CH24H). Cholesterol 24-hydroxylase converts cholesterol to 24S-hydroxycholesterol, which acts as a positive allosteric modulator of N-methyl-D-aspartate (NMDA) receptors.

Soticlestat blocks 24S-hydroxycholesterol production in the brain in an in vivo mouse model in a dose-dependent manner (1, 3, and 10 mg/kg). It is in Ph. III as a novel anti-epileptic, for pediatric epilepsies such as in Dravet syndrome and Lennox-Gastaut syndrome. The compound (IC50 = 7.4 nM) came from 4-arylpyridine derivatives identified in a high-throughput screening (HTS) campaign with further optimization utilizing structure based drug design (SBDD).

BMS-986318

FXR



Oral FXR agonist for NASH

Robust in vivo PD, phase I HV study withdrawn

From prior FXR agonists

ACS Med. Chem. Lett

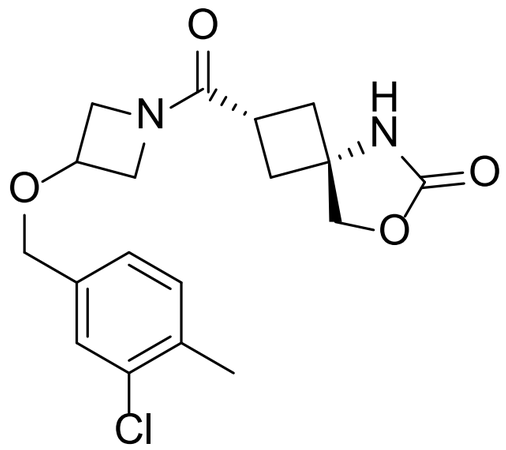
Bristol Myers Squibb, Princeton, NJ, USA

The BMS spirocyclobutene-containing FXR agonist, BMS-986318, appears to have been intended as a clinical candidate, but was withdrawn from a planned Ph. I study. The molecule exhibits potent in vitro and in vivo activation of FXR (FXR Gal4 reporter EC50 = 53 nM, SRC-1 recruitment assay EC50 = 350 nM) and demonstrates efficacy in the mouse bile duct ligation model of liver cholestasis and fibrosis.

This novel molecule displayed robust target engagement in vivo and is a rare example of a cyclobutene-containing, rationally designed drug-like molecule.

“compound 4f”

MAGL



Oral, brain-penetrant, reversible MAGL inh.
in vivo PK/PD in CNS (0.3-10 mpk PO)
from HTS and SBDD
Journal of Medicinal Chemistry
Takeda, Fujisawa, Japan

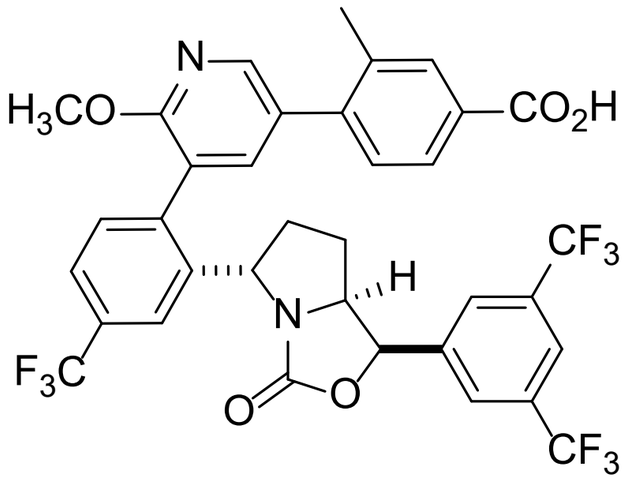
The Takeda MAGL inhibitor, [“compound 4f”], was selected by reviewer [Joachim Rudolph]. “MAGL (monoacylglycerol lipase) is implicated in neuroinflammation, and inhibitors of this enzyme are of interest as therapeutics in neurodegenerative and other neurological diseases. Most of the advanced compounds, including the clinically evaluated ABX-1431, are irreversible inhibitors, but chronic blockade has been found to lead to undesirable desensitization.

There is therefore a need for potent, selective reversible inhibitors of MAGL to assess their clinical viability as an alternative to irreversible inhibitors. This work by Takeda scientists reports new potent reversible MAGL inhibitors with good in vivo PK and PD profiles. The chemical structure of the lead 4f and related compounds also use interesting cyclobutyl/azetidine spiro scaffolds.”

The molecule started from an HTS hit and was advanced using structure-based drug design. Compound 4f shows good oral absorption, blood-brain-barrier penetration, and significant PD at 0.3-10 mpk PO in mice which correlated with drug brain concentrations.

MK-8262

CETP



Potential best-in-class CETP inh. (<1 mg QD)

Completed Ph. I in HV; discont. as backup

From anacetrapib

Journal of Medicinal Chemistry

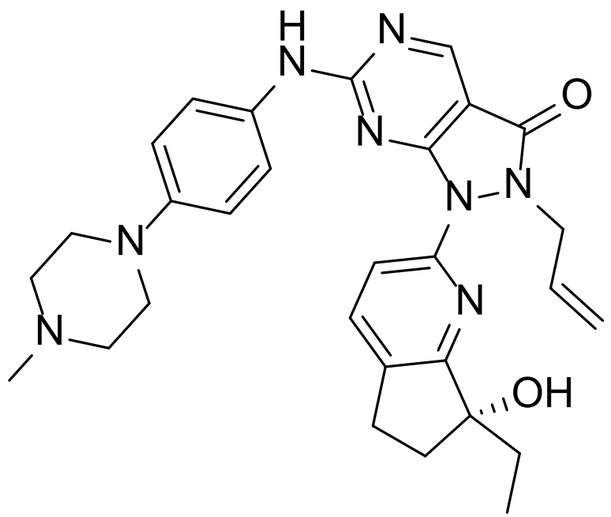
Merck & Co., Kenilworth, NJ, USA

The Merck CETP inhibitor backup, MK-8262, is potential best-in-class CETP inhibitor, which was only discontinued as a backup due to the success of its predecessor, anacetrapib in Ph. III.

Reviewer Kim Huard thought this CETP inhibitor was a great piece of work from Merck, and is a great example how to deal with a very lipophilic binding site, optimizing total rather than unbound exposure and using TPSA as a surrogate for lipophilicity since the molecules were outside the reliably measurable range for LogD. “I also liked their strategy of adding a carboxylic acid to reduce lipophilicity while shifting non-specific binding from tissue towards plasma proteins,” which likely contributes to the long half-life observed. MK-8262 completed a Ph. I study in healthy volunteers and was found to be safe and likely fully efficacious at the very low projected dose of <1 mg QD.

ZN-c3

Wee1



Selective oral Wee1 kinase inh. (300 mg QD)

Ph. II candidate for uterine serous carcinoma

From literature starting point

Journal of Medicinal Chemistry

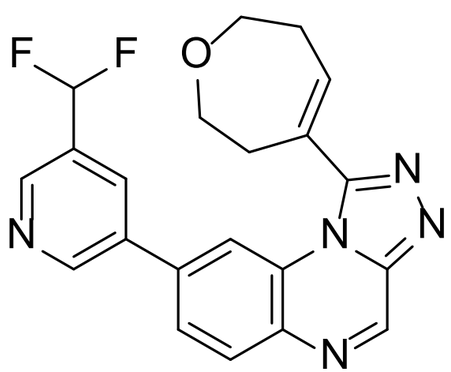
Zentalis Pharmaceuticals, San Diego, CA, USA

The Zentalis Wee1 inhibitor, ZN-c3, is a highly selective kinase inhibitor that is currently being evaluated in Ph. II clinical trials in adult women with recurrent or persistent uterine serous carcinoma (USC).

The starting pyrazolopyrimidinone series was from the WO2013126656 patent, and while the molecule is similar to other kinase inhibitors (e.g. adavosertib, AZD1775), the ethyl group of the tertiary alcohol provided an unexpected improvement of potency while allowing maintenance of other properties including intrinsic clearance. It is an interesting example of navigating tight IP space to find a development candidate.

BAY-8400

DNA-PK



Oral selective DNA-PK kinase inhibitor

Synergy with radiotherapy in model

From library screen

Journal of Medicinal Chemistry

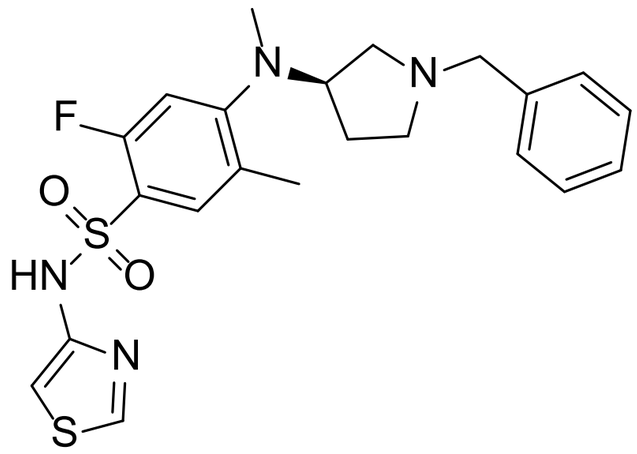
Bayer AG, Berlin, Germany

The Bayer DNA-PK inhibitor, BAY-8400, is an orally active and selective DNA-PK kinase inhibitor that synergistically enhances the efficacy of radiotherapeutics in xenograft models. The program started with a campaign to identify ATR inhibitors, which resulted in hits against ATR, ATM, and DNA-PK, all of which are of interest due to their roles in DNA damage repair.

It will be interesting to watch this active space to see whether ATR, ATM, or DNA-PK inhibition can improve therapeutic indexes or efficacy of various DNA-damaging treatments clinically.

NBI-921352

NaV1.6



Highly selective NaV1.6 sodium channel inh.
Entering Ph. II for seizures (100 mg TID)
Arylsulfonamide class
bioRxiv
Xenon Pharmaceuticals, Burnaby, Canada

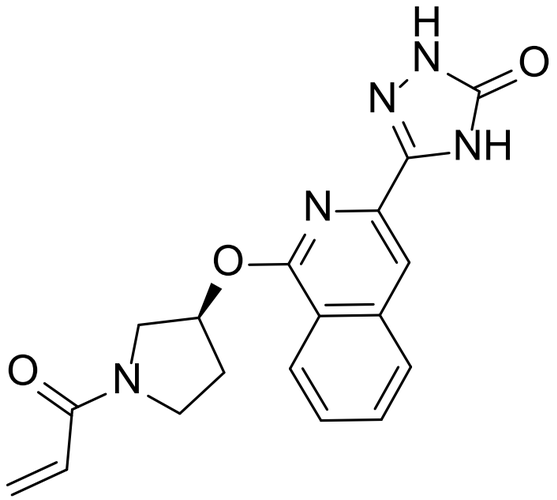
The Xenon NaV1.6 Inhibitor, NBI-921352, is remarkably selective for the NaV1.6 sodium channel over other isoforms (IC50 = 51 nM, 756x vs. NaV1.1, 134X vs. NaV1.2, 276X vs. NaV1.7, >583X vs. 1.3, 1.4, 1.5). The molecule is It is being developed to treat pediatric patients with SCN8A developmental and epileptic encephalopathy (SCN8A-DEE) and other indications such as adult focal epilepsy.

The molecule is an arylsulfonamide and has a similar structure to NaV1.7 arylsulfonamide inhibitors, and is a state-dependent inhibitor, preferentially inhibiting activated channels.

The molecule was well-tolerated in a Ph. I study at plasma concentrations greater than required for efficacy in preclinical studies, and efficacy will soon be evaluated in Ph. II. NBI-921352 appears to be effective in preventing seizures at lower brain and plasma concentrations than commonly prescribed sodium channel inhibitor antiseizure medicines (ASMs) carbamazepine, phenyltoin, and lacosamide, and was tolerated at higher multiples of effective plasma/brain concentrations than these prior drugs.

TAK-020

BTK



Oral covalent BTK inhibitor

>80% BTK occupancy <5 mg (Ph. I dose esc.)

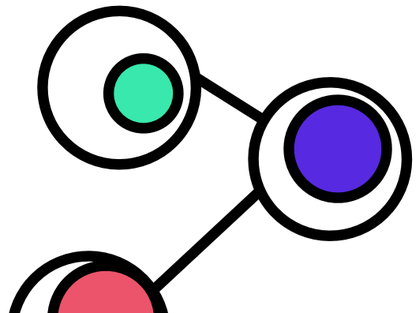
From fragment-based screen of 11k cmpds

Journal of Medicinal Chemistry

Takeda, San Diego, CA, USA

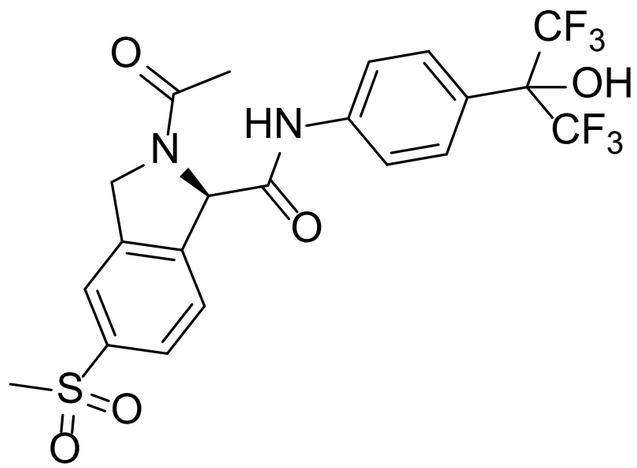
The Takeda covalent BTK inhibitor clinical candidate, TAK-020, is a highly selective oral covalent BTK inhibitor with safety and tolerability profiles that are promising for both hematologic malignancies and autoimmune diseases based on a study in healthy volunteers. The molecule originated from a simple triazolone fragment, and overall is a remarkably efficient inhibitor.

The triazolone fragment binds in an interesting way to the kinase with the highly polar triazolinone buried near the gatekeeper residue, likely contributing to its high kinase selectivity given that most kinases prefer more lipophilic motifs in that region. TAK-020 is anticipated to be efficacious at a very low dose (<5 mg) and it will be interesting to watch how it progresses in the highly competitive BTK landscape.



AZD0284

RORC2



Oral RORC2 inverse agonist for psoriasis

100 mg PO BID, Ph. I term. due to preclin. data

From opt. of lit. inverse agonist

Journal of Medicinal Chemistry

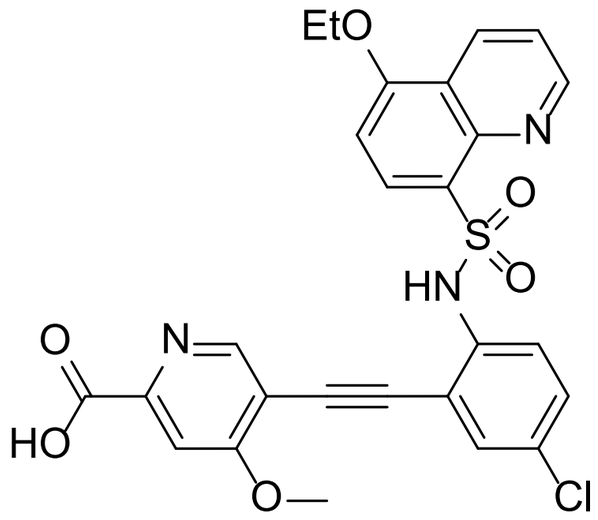
AstraZeneca, Gothenburg, Sweden

The AstraZeneca oral RORgt inverse agonist, AZD0284, is an inverse agonist of the nuclear receptor RORC2 (RORγt). Reviewer Chris Gampe says, "targeting the activation and function of Th17 cells has been successful for the treatment of autoimmune disease (cf. IL-17, IL-17R, IL-23 Abs). RORC2 is the transcription factor that controls Th17 function and is a target of high interest in immunology and immuno-oncology, with at least 12 compounds in clinical development worldwide, and the first signs of clinical efficacy being reported for a compound called VTP-43742."

AZD0284 was well-tolerated in a Ph. I study with biomarker changes observed at low doses (4-238 mg). It will be interesting to see if the molecule is advanced further.

“compound 18n”

MCT4



Monocarboxylate transporter 4 inhibitor
In vivo PD but limited eff. in xenograft model
From cell-based screen and opt.
Journal of Medicinal Chemistry
Merck Healthcare KGaA, Darmstadt, Germany

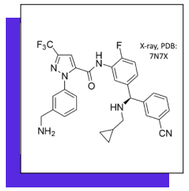
The Merck KGaA MCT4 chemical probe, “compound 18n”, is a novel inhibitor of the monocarboxylate transporter MCT4. Large quantities of lactic acid need to be transported out of tumor cells due to their dependence on glucose metabolism, and this transport is mediated by MCTs. Overexpression of MCT4 is a marker for poor prognosis in cancer, and hence it has been considered as an oncology target, though tools to test the hypothesis were lacking.

The Merck team found a starting point in a submicromolar hit (600 nM IC50), which was optimized to an in vivo tool compound. Unfortunately, while treatment with the MCT4 tool in combination with an MCT1/2 tool resulted in an increase in tumor lactate concentration, no significant effect on tumor growth was seen. This new tool will be helpful to help understand the role MCT4 plays in various biological contexts and whether certain tumors are more susceptible to inhibition or certain combination partners are more effective.

drug hunter

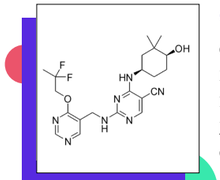
Small Molecules of the Month

August 2021
drughunter.com



berotralstsat | kallikrein

Oral plasma kallikrein serine protease inhibitor
Approved for prevention of HAE attacks
From structure-based drug design
Journal of Medicinal Chemistry
BioCryst, Birmingham, AL, USA



CC-90005 | PKCθ

Oral, selective PKCθ kinase inhibitor
Ph. I candidate for Psoriasis
From screen of internal library and SBDD
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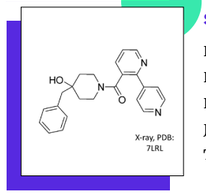
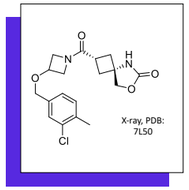


soticlestat | CH24H

Brain-penetrant CH24H inhibitor
Ph. 2 for epilepsies (up to 300 mg PO QD)
From SBDD
Journal of Medicinal Chemistry
Takeda, Fujisawa, Japan



"compound 4f" | MAGL

Oral, brain-penetrant, reversible MAGL inh.
in vivo PK/PD in CNS (0.3-10 mpk PO)
from HTS and SBDD
Journal of Medicinal Chemistry
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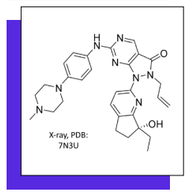
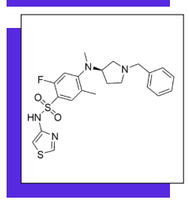


ZN-c3 | Wee1

Selective oral Wee1 kinase inh. (300 mg QD)
Ph. II candidate for uterine serous carcinoma
From literature starting point
Journal of Medicinal Chemistry
Zentalis Pharmaceuticals, San Diego, CA, USA



NBI-921352 | NaV1.6

Highly selective NaV1.6 sodium channel inh.
Entering Ph. II for seizures (100 mg TID)
Arylsulfonamide class
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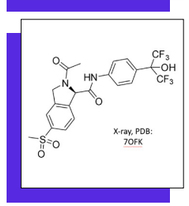
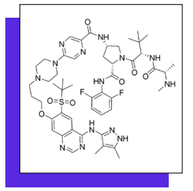


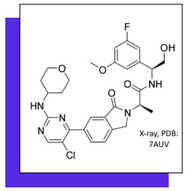
AZD0284 | RORC2

Oral RORC2 inverse agonist for psoriasis
100 mg PO BID, Ph. I term. due to preclin. data
From opt. of lit. inverse agonist
Journal of Medicinal Chemistry
AstraZeneca, Gothenburg, Sweden



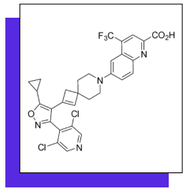
"compound 20" | RIPK2

Long-acting RIPK2 degrader (SC admin.)
In vivo degradation of RIPK2 over 60 days
IAP binder linked to RIPK2 binder
Journal of Medicinal Chemistry
GlaxoSmithKline, Stevenage, UK



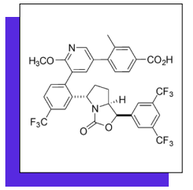
ASTX029 | ERK1/2

Oral ERK1/2 kinase and phosphorylation inhib.
Ph. 1/2 candidate for solid tumors
from SBDD from prior lead
Journal of Medicinal Chemistry
Astex Pharmaceuticals, Cambridge, UK



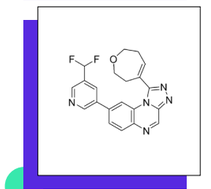
BMS-986318 | FXR

Oral FXR agonist for NASH
Robust in vivo PD, phase I HV study withdrawn
From prior FXR agonists
ACS Med. Chem. Lett
Bristol Myers Squibb, Princeton, NJ, USA



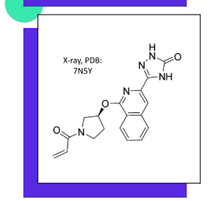
MK-8262 | CETP

Potential best-in-class CETP inh. (<1 mg QD)
Completed Ph. I in HV; discont. as backup
From anacetrapib
Journal of Medicinal Chemistry
Merck & Co., Kenilworth, NJ, USA



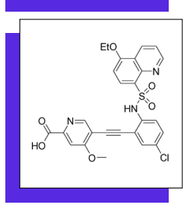
BAY-8400 | DNA-PK

Oral selective DNA-PK kinase inhibitor
Synergy with radiotherapy in model
From library screen
Journal of Medicinal Chemistry
Bayer AG, Berlin, Germany



TAK-020 | BTK

Oral covalent BTK inhibitor
>80% BTK occupancy <5 mg (Ph. I dose esc.)
From fragment-based screen of 11k cmpds
Journal of Medicinal Chemistry
Takeda, San Diego, CA, USA



"compound 18n" | MCT4

Monocarboxylate transporter 4 inhibitor
In vivo PD but limited eff. in xenograft model
From cell-based screen and opt.
Journal of Medicinal Chemistry
Merck Healthcare KGaA, Darmstadt, Germany

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