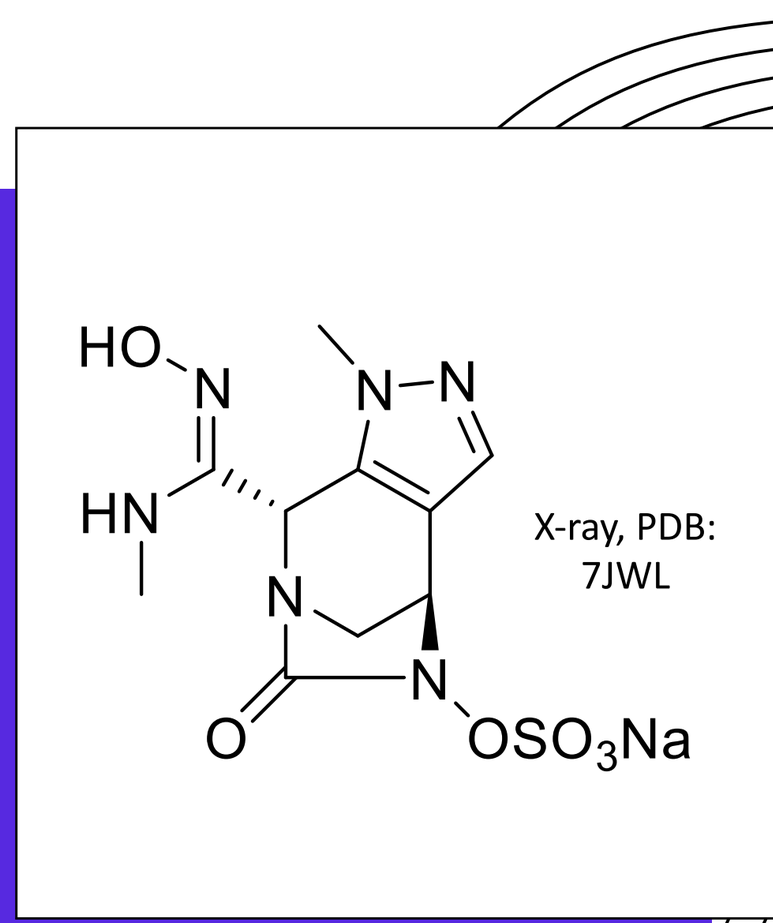
Small Molecules of the Month

September 2021



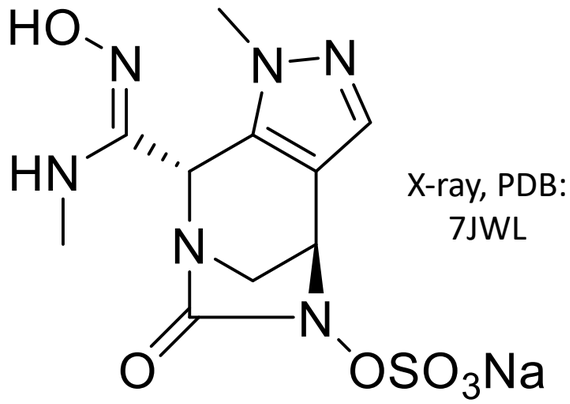
X-ray, PDB:
7JWL

drug
hunter

01	PBP1a/PBP3	Entasis Therapeutics
02	FXIa	Bristol Myers Squibb
03	DNMT1	GlaxoSmithKline
04	PRMT5	Janssen R&D
05	CSF1R	Deciphera Pharmaceuticals
06	AR	University of Michigan
07	PARP1	AstraZeneca
08	S1P1	Sanofi
09	PC1	ImmunoMet Therapeutics
10	BET	Bristol Myers Squibb
11	BACE1	Janssen Pharmaceutica NV
12	γ-secretase	FORUM Pharmaceuticals
13	RORγ	Lycera
14	P2X3	Shionogi

ETX0462

PBP1a/PBP3



X-ray, PDB: 7JWL

penicillin-binding protein + β-lactamase inh.

preclin. eff. at 50 mpk SC, 2,000 mpk tolerated

multitarget SBDD + opt. for porin permeability

Nature

Entasis Therapeutics

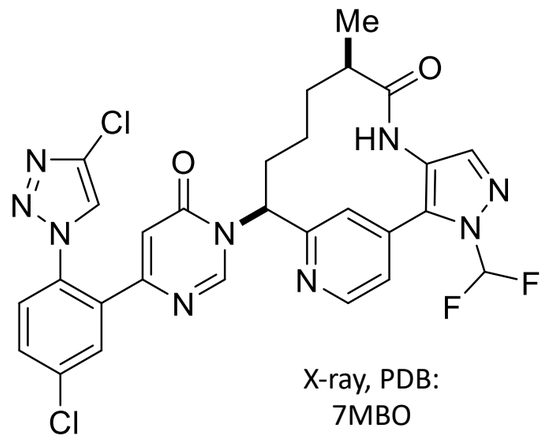
The Entasis broad-spectrum antibiotic, ETX0462, is both an inhibitor of penicillin-binding proteins (PBPs, the target of beta-lactams) and a beta-lactamase inhibitor (BLI). Reviewer Mike Koehler thought this was a substantial disclosure. "A number of BLIs co-formulated with carbapenems and monobactams are currently on the market. There are a number of downsides to co-formulation, not the least of which is that you have to match the PK of the BLI and your beta-lactam in order to be most effective. The diazabicyclooctane (DBO) class includes avibactam, a component of AvyCaz, one of our better options for bacterial infections. Less known is the fact that DBOs can act as single agent antibiotics as well. This stems from the fact that they can inhibit penicillin-binding proteins (PBPs). In the past, this was mostly ignored, as they only bound a subset of PBPs and this lead to a high frequency of resistance (FOR) and poor spectrum of activity when used alone."

The Entasis team designed DBO molecules with an ability to inhibit both PBP1a and PBP3 simultaneously leading to greater efficacy and lower FOR. The resulting molecules were polar and low MW, and poorly permeable. Entasis therefore optimized the new molecules to access their target through porin channels, and found that there was significant SAR in porin permeability. "Some compounds utilize one or a few porins, while other can make use of a much larger number. If a drug is reliant on one or two porins, bacteria can downregulate the expression of a porin or two and develop resistance. If many porins allow access, downregulating a lot of porins will lead to a very substantial fitness cost. Using their system for understanding the reliance of a molecule on a given porin, Entasis were able to optimize for a molecule which utilized a broad range, and arrived at ETX0462."

"The rest of the paper demonstrates the suitability of the compound for further development through an understanding of the PK/PD relationship needed for efficacy (time over MIC of >60% gave 1 log kill at 24h) and running through in vivo models. MIC90 is reported for several relevant bacterial species, and they are impressive. They also report dosing the compound to 2,000 mg/kg over a 14d rat safety study without abnormal clinical signs or microscopic findings." Notably missing is an estimate of human PK for the compound, which may be because there is still PK optimization needed, as the compound was dosed SC once every 3 h in the mouse studies. If a compound of this class is clinically successful, it would be an important new addition to the molecules targeting PBPs, our safest and most highly effective class of antibiotics.

milvexian

FXIa



X-ray, PDB: 7MBO

selective factor Xia serine protease inhib.
oral, phase II, cardiovascular
from opt. of previous macrocyclic FXIa inh.
Journal of Medicinal Chemistry
Bristol Myers Squibb

The BMS factor XIa inhibitor, milvexian (BMS-986177), is an oral antithrombotic with a Ki of 0.11 nM. A member of this macrocyclic series was previously highlighted as one of 2020's Molecules of the Year.

Poor pharmaceutic properties from previous preclinical molecules such as solubility were addressed resulting in this candidate.

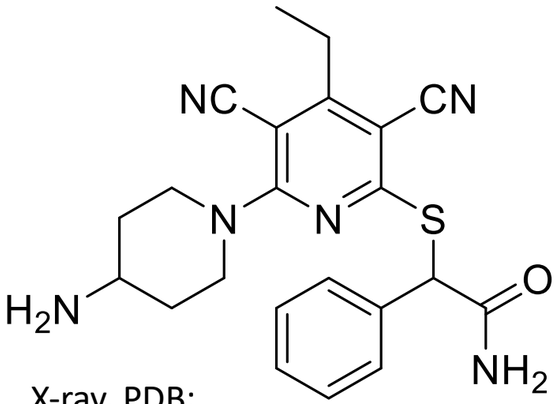
Milvexian is a Ph. II clinical candidate for the prevention and treatment of thromboembolic disorders (secondary stroke prevention (NCT03766581) and venous thromboembolism prevention in total knee replacement surgery (NCT03891524), completed Ph. I study = NCT02608970).

Interesting points from the paper include the introduction of two polar heterocycles from the starting point while improving properties and maintaining potency, and replacement of a pyrazole N-methyl group with a difluoromethyl group to improve metabolic stability. This molecular "rule-breaker" is particularly impressive as an oral candidate given its 6 rings (including 5 aromatic), 9 nitrogen atoms, and macrocyclic core.

The X-ray co-crystal structure (PDB ID: 7MBO) of milvexian bound to FXIa reveals several new hydrogen-bonding interactions relative to the starting point, and its 3D topology from the single crystal X-ray serves as yet another great example that even molecules with low fsp3 and 5 aromatic rings may not be "flat" at all.

GSK3685032

DNMT1



X-ray, PDB:
6X9K

selective rev. DNA methyltransferase inhibitor
preclinical eff. at 30 mpk SC BID (xenograft)
from 1.8M cmpd enzymatic HTS + opt.
Nature Cancer
GlaxoSmithKline

The GSK DNMT1 inhibitor GSK3685032 is a first-in-class, non-nucleoside, reversible and selective inhibitor of the epigenetic target DNA-methyltransferase 1 (DNMT1).

Commonly prescribed hypomethylating agents (HMAs) such as decitabine are incorporated into DNA and inhibit DNMT1, DNMT3A, and DNMT3B irreversibly, and as a consequence are toxic to normal blood cells.

GSK3865032 competes reversibly with the active-site loop of DNMT1 (PDB:6X9K) for penetration into hemi-methylated DNA, and induces robust loss of DNA methylation without affecting DNMT3A or DNMT3B.

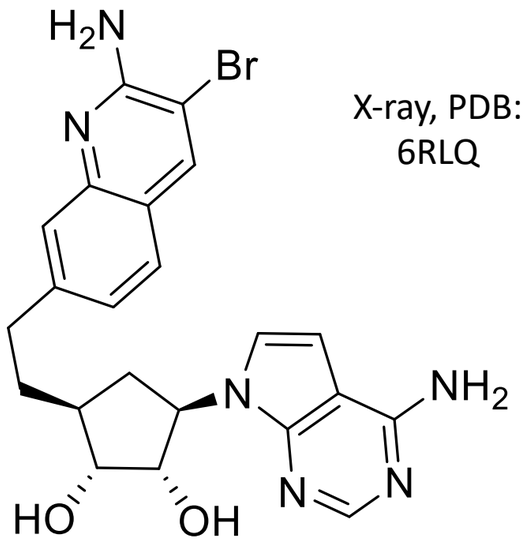
Due to improved in vivo tolerability over hypomethylating agents, GSK3685032 demonstrates superior tumor regression and survival in AML models to decitabine.

Thanks to the improved therapeutic index, it may be potentially viable in solid tumors where HMAs have not been very successful.

This molecule will be a useful tool for better understanding of DNA methylation in various contexts.

JNJ-64619178

PRMT5



X-ray, PDB: 6RLQ

pseudo-irreversible methyltransferase inh.
oral, phase I, cancer
from adenosine derivative library + opt.
Molecular Cancer Therapeutics
Janssen R&D

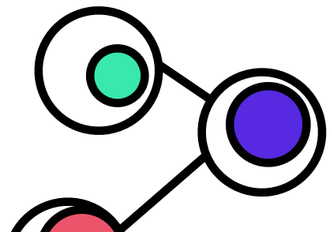
The Janssen PRMT5 inhibitor, onametostat (JNJ-64619178) is a selective, orally active and pseudo-irreversible protein arginine methyltransferase 5 (PRMT5) inhibitor with high selectivity and potency (subnanomolar range, PRMT5-MEP-50 IC50=0.14 nM) under various conditions.

While JNJ-64619178 binds non-covalently in the PRMT5 SAM and substrate-binding sites evidenced by co-crystallography (PDB: 6RLQ), the molecule has a long-residence time, leading to sustained inhibition of PRMT5 even after short compound exposure.

Interestingly, PD was observed for 6 days after treatment cessation, and comparable efficacy was observed with continuous daily dosing as in 7 d on, 7 d off cycles.

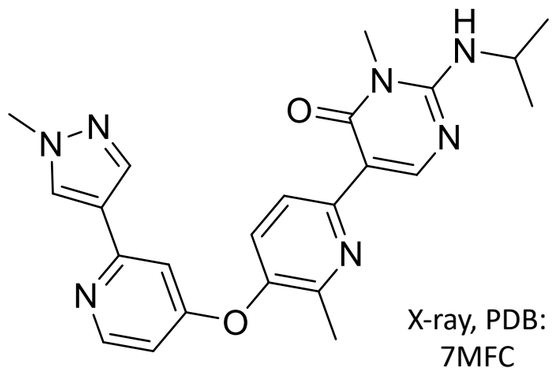
Since PRMT5-dependent methylation events are reversed only by turnover of substrate proteins rather than by demethylases and PRMT5 itself has a long half-life, PRMT5 inhibitors with a long residence time are desirable.

JNJ-64619178 is currently in clinical trials for patients with advanced solid tumors, non-Hodgkin's lymphoma, and lower risk myelodysplastic syndrome (NCT03573310).



vimseltinib

CSF1R



X-ray, PDB: 7MFC

selective CSF1R kinase inhibitor
oral, 30 mg BIW, phase III, cancer
from structure-based design
Molecular Cancer Therapeutics
Deciphera Pharmaceuticals

The Deciphera CSF1R kinase inhibitor, vimseltinib (DCC-3014), is a selective oral TKI that induces an inactive conformation of CSF1R by biomimetically nucleating an array of 17 H-bonds in the switch control region of this switch control kinase.

Several small and large molecule agents targeting CSF1R have been in development, and a small molecule CSF1R inhibitor (pexidartinib) was approved in 2019.

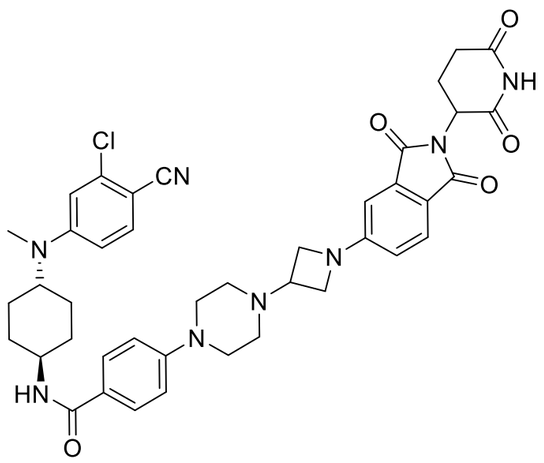
Vimseltinib significantly inhibited CSF1R signaling in PK/PD models at doses as low as 3 mg/kg orally and depletes macrophages in efficacy models. Single agent and combination efficacy with anti-PD1 immunotherapy in a syngeneic mouse colorectal cancer model with effects on the adaptive immune system were also observed, in agreement with the hypothesis that certain macrophages play a role in tumor immune evasion.

In a phase I clinical study, vimseltinib treatment modulated biomarkers of CSF1R inhibition and reduced tumor burden in tenosynovial giant cell tumor (TGCT) patients.

A phase III study with vimseltinib in TGCT is listed but not yet recruiting (NCT05059262).

ARD-2585

AR



oral CRBN-based androgen receptor degrader
preclinical eff. at 10 mpk QD (xenograft)
from previously disclosed AR molecule
Journal of Medicinal Chemistry
University of Michigan

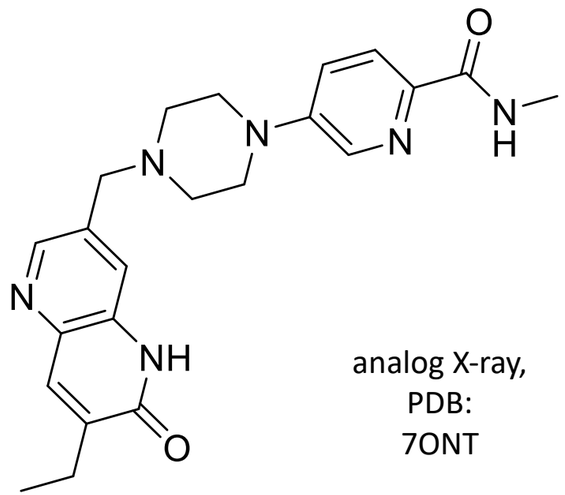
The Michigan bifunctional degrader, ARD-2585, is similar to the Arvinas molecule, ARV-110 that was recently disclosed at AACR 2021. ARV-110 is a first-in-class, potent, and orally active AR degrader in clinical development, but understandably hasn't had much published on it yet given the competitive environment.

The publication of ARD-2585 therefore provides nice insight into the properties of this class of molecules.

ARD-2585 interestingly uses a rigid, linear linked piperidine-azetidine linker to connect the AR ligand and CRBN ligand, and is up to 1000x more potent than ARV-110 in AR reduction in vitro, and is active in a xenograft model at 10 mpk QD PO.

AZD5305

PARP1



analog X-ray,
PDB:
7ONT

oral PARP1-DNA selective trapper
1 mpk QD in PDX model, phase I/II, cancer
from literature starting point
Journal of Medicinal Chemistry
AstraZeneca

The AstraZeneca PARP1-DNA trapper, AZD5305, is a phase I candidate (NCT04644068) for cancer that is selective for PARP1 over PARP2 (>500x).

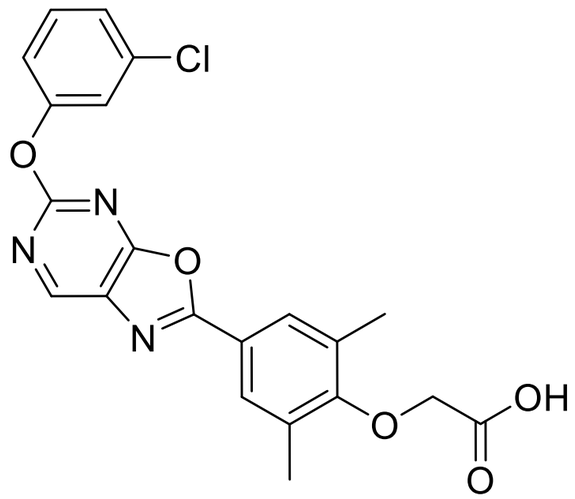
Their study began by profiling the existing clinical and late-stage PARP inhibitors in vitro, finding that the seven leading compounds (olaparib, rucaparib, niraparib, talazoparib, veliparib, NMS-P118 and FR257531) having varying levels of low to modest selectivity for PARP1 over PARP2.

Building on the high selectivity of compound FR257531, the authors optimized potency against BRCA mutant cancer cells, mitigated hERG issues, lowered log D, optimized intrinsic clearance, and removed the phenyl tetrahydropyridine structural alert (MPTP metabolizes to MPP+, which irreversibly causes Parkinson's disease in animals).

The candidate appears to have reduced effects on bone marrow progenitor cells in vitro, and it will be interesting to watch whether this next-generation compound can differentiate in different cancer settings based on overall improved tolerability.

SAR247799

S1P1



G-protein biased GPCR agonist
oral 10 mg QD, phase I, cardiovascular
from HTS and opt.
bioRxiv
Sanofi

The Sanofi S1P1 agonist, SAR247799, is a biased agonist of the S1P1 sphingosine receptor, preferentially activating G-protein signaling over the β-arrestin and internalization pathways.

Commercial S1P1 modulators such as fingolimod and ozanimod exert than immunosuppressive effects in multiple sclerosis and other diseases primarily by downregulating the S1P1 receptor through agonism and receptor internalization.

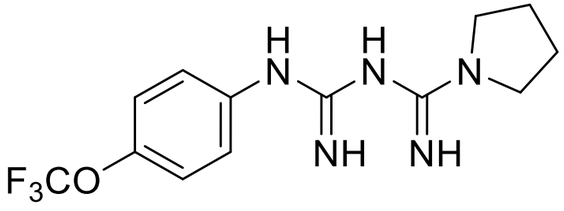
Through biased agonism, SAR247799 exhibits a variety of endothelial-protective properties without reducing lymphocytes in a number of animal models, including a pig coronary microvascular hyperemic response model.

SAR247799 demonstrates good safety and tolerability in healthy subjects (and improves endothelial function, as assessed by flow-mediated dilation in type-2 diabetic patients (NCT03462017).

This is likely an important clinical study for the biased agonism field, which has recently been challenged by the high-profile failures of putative biased mu-opioid receptor agonists.

IM156

PC1



oral protein-complex 1 (OXPHOS) inhibitor
200-800 mg QD, phase I, cancer/IPF
from metformin
J. Pharmacol. Exp. Ther.
ImmunoMet Therapeutics

The ImmunoMet OXPHOS modulator (PC1 inhibitor), IM156, is a derivative of the long-used biguanide diabetes drug, metformin, that appears to have activity in lung fibrosis models.

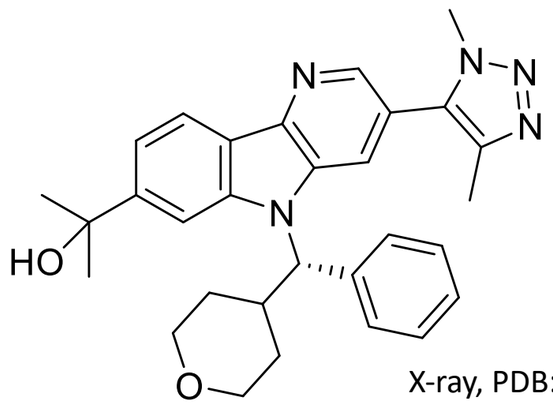
The therapeutic hypothesis for IPF is that myofibroblasts play an essential role in extracellular matrix remodeling and fibrogenesis that lead to loss of pulmonary function.

A complex process of metabolic reprogramming is critical to the myofibroblast phenotype and disruption of myofibroblast metabolic pathways may have anti-fibrotic effects.

A phase I dose escalation study was completed in cancer patients and there are plans to conduct a Ph. II study in IPF.

BMS-986158

BET



X-ray, PDB:
5S9R

oral BET inhibitor

4.5 mg QD, phase I/II for cancer

from bromodomain-focused HTS, SBDD

Journal of Medicinal Chemistry

Bristol Myers Squibb

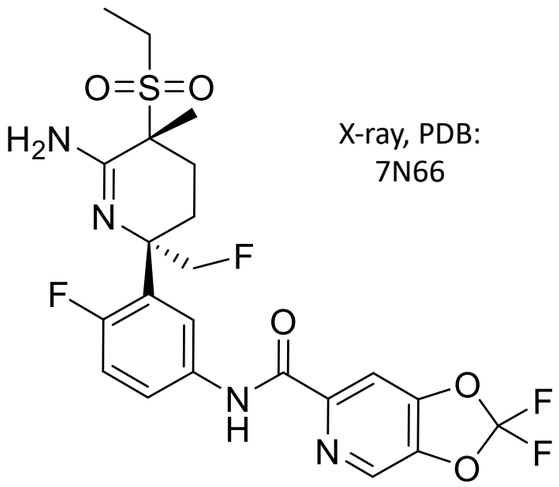
The BMS BET inhibitor, BMS-986158, is in a Ph. I/IIa trial in advanced cancers.

During the optimization of the molecule from a carbazole hit, the authors employed a bold scaffold-hopping strategy involving changing the direction of the carbazole core in order to better access a hydrophobic region of the target.

The proposed new binding mode was confirmed by X-ray co-crystallography.
The molecule's triazole ring also interestingly binds in a manner in which both unsubstituted N atoms appear to be engaged as hydrogen bond acceptors to different hydrogen bond donors in the protein (Asn140 for one, a water-mediated H-bond to Tyr97 for the other).

JNJ-67569762

BACE1



X-ray, PDB: 7N66

oral BACE1-selective inhibitor
preclinical, QTc observed in dogs
from literature starting point
Journal of Medicinal Chemistry
Janssen Pharmaceutica NV

The Janssen BACE1-selective inhibitor, JNJ-67569762, was a preclinical candidate for Alzheimer's disease.

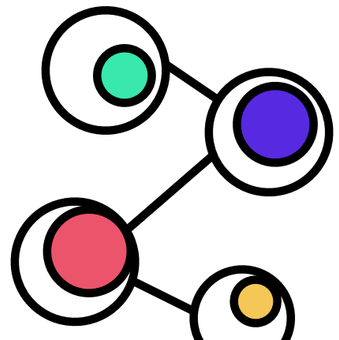
Obtaining BACE1 over BACE2 selectivity was a major challenge in the field, and the molecule is 74x selective thanks to a bicyclic ring system in the S3 pocket.

In in vivo models, BACE1-mediated PD was observed without BACE2-dependent hair depigmentation. The authors chose to work on a 2-amino-tetrahydropyridine scaffold, avoiding the 1,3-thiazine group linked to liver toxicity in clinical trials, and leveraged a sulfonyl group to lower pKa and increase lipophilicity.

Unfortunately, in a 14-day dog study, a prolonged QTc signal was observed, despite a large in vitro window against hERG (patch clamp IC50 = 8.3 uM).

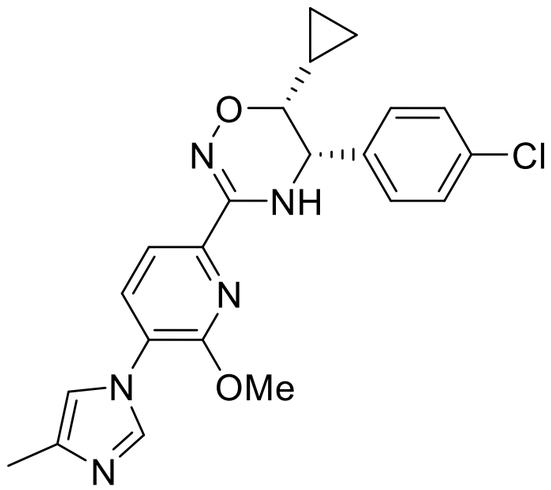
Potential effects on hERG trafficking were postulated but not investigated further.

The report is a valuable example showing that in vivo QTc can still be a major issue even when hERG channel inhibition is not significant in vitro.



FRM-024

γ-secretase



oral gamma secretase modulator
preclinical PD at 30 mpk single dose
from opt. of prior oxadiazine GSM
Journal of Medicinal Chemistry
FORUM Pharmaceuticals

The FORUM Pharmaceuticals CNS-penetrant gamma secretase inhibitor and preclinical candidate, FRM-024, is an advanced example of the use of an oxadiazine as an amide isostere.

While amide isosteres are frequently proposed, it is often difficult to implement them beyond basic heterocyclic replacements.

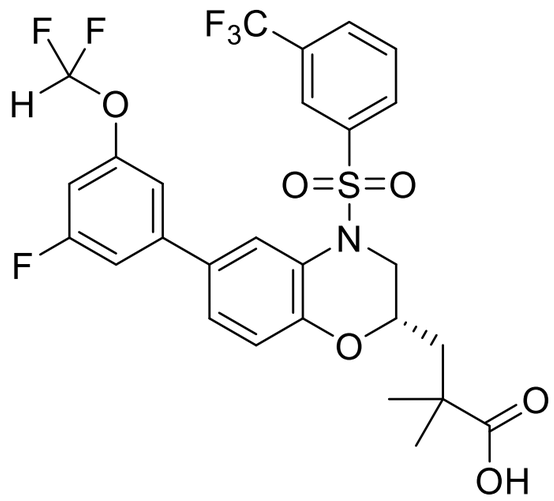
A benzofuran structural alert was successfully replaced with a 4-chlorophenyl group, and the addition of a cyclopropyl group to the oxadiazine core appeared to dramatically improve metabolic stability while maintaining potency and physicochemical properties, making it evidently worth dealing with the additional stereocenter.

It is unlikely that the property improvements found with the oxadiazine could have been found on an amide-based scaffold.

The molecule demonstrates PD in multiple species, was clean in numerous in vitro and in vivo toxicology experiments, and demonstrated a significant safety window in 14-day animal studies (rat, dog).

LYC-55716

RORγ



oral RORγ nuclear receptor agonist

450 mg BID, phase I/II, cancer

from change in MoA of RORγ antagonist + opt.

Journal of Medicinal Chemistry

Lycera

The Lycera ROR gamma agonist, cintirorgon (LYC-55716), is a first-in-class phase 1b clinical candidate for cancer immunotherapy (in combination with pembrolizumab in NSCLC).

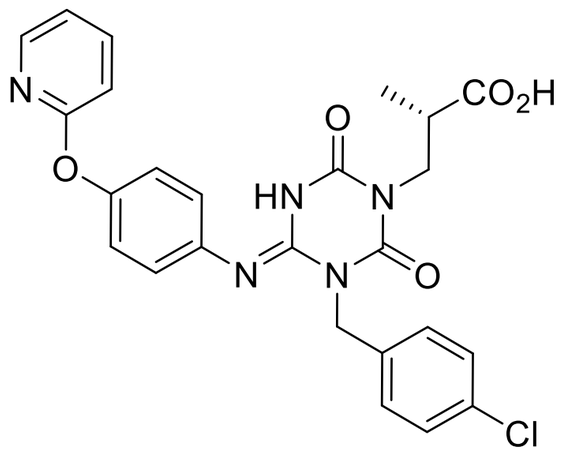
ROR gamma antagonists have been extensively pursued and studied for autoimmune conditions, but ROR gamma agonists have also been recently pursued for "pro-inflammatory" cancer immunotherapy.

An interesting aspect of this story is that the agonists are derived from small changes to antagonists through replacement of an amide by groups without an H-bond donor.

The H-bond donor of antagonist amide is hypothesized to be important to disrupting the structure of the nuclear receptor and disfavoring co-activator binding.

S-600918

P2X3



purinergic receptor (ion channel) antagonist
up to 300 mg PO QD, phase IIb, chronic cough
from opt. of prior P2X3 antagonist
Bioorganic and Medicinal Chemistry Letters
Shionogi

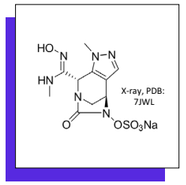
The Shionogi P2X3 ligand-gated ion channel antagonist, sivopixant (S-600918), is an oral Ph. II candidate for refractory chronic cough, which recently completed a its Ph. IIb study, overcoming the projected high dose requirement of a prior preclinical candidate.

The molecule has a very polar core structure with both a dioxotriazine and carboxylic acid, yet is highly bioavailable.

From a chemistry perspective, it is an interesting example where adding another aromatic heterocycle at a late stage of optimization led to a significant lowering of human dose projection, whereas typically at a late stage adding large new groups tends to be avoided.

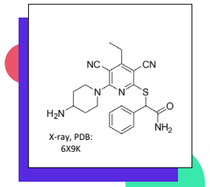
Small Molecules of the Month

September 2021
drughunter.com



ETX0462 | PBP1a/PBP3

penicillin-binding protein + β-lactamase inh.
preclin. eff. at 50 mpk SC, 2,000 mpk tolerated
multitarget SBDD + opt. for porin permeability
Nature
Entasis Therapeutics



GSK3685032 | DNMT1

selective rev. DNA methyltransferase inhibitor
preclinical eff. at 30 mpk SC BID (xenograft)
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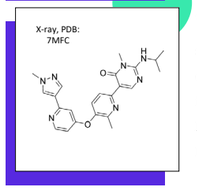
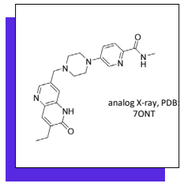
GlaxoSmithKline



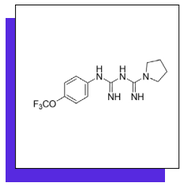
vimseltinib | CSF1R

selective CSF1R kinase inhibitor
oral, 30 mg BIW, phase III, cancer
from structure-based design
Molecular Cancer Therapeutics
Deciphera Pharmaceuticals



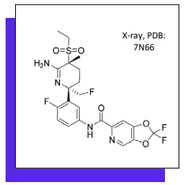
AZD5305 | PARP1

oral PARP1-DNA selective trapper
1 mpk QD in PDX model, phase I/II, cancer
from literature starting point
Journal of Medicinal Chemistry
AstraZeneca



IM156 | PC1

oral protein-complex 1 (OXPHOS) inhibitor
200-800 mg QD, phase I, cancer/IPF
from metformin
J. Pharmacol. Exp. Ther.
ImmunoMet Therapeutics



JNJ-67569762 | BACE1

oral BACE1-selective inhibitor
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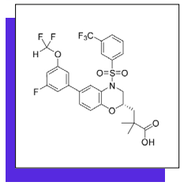
Journal of Medicinal Chemistry
Janssen Pharmaceutica NV



cintirorgon | RORγ

oral RORγ nuclear receptor agonist
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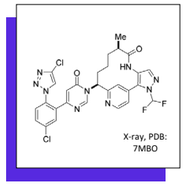
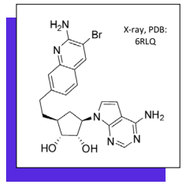
Journal of Medicinal Chemistry
Lycera



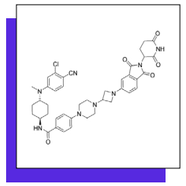
milvexian | FXIa

selective factor Xia serine protease inhib.
oral, phase II, cardiovascular
from opt. of previous macrocyclic FXIa inh.
Journal of Medicinal Chemistry
Bristol Myers Squibb



onametostat | PRMT5

pseudo-irreversible methyltransferase inh.
oral, phase I, cancer
from adenosine derivative library + opt.
Molecular Cancer Therapeutics
Janssen R&D



ARD-2585 | AR

oral CRBN-based androgen receptor degrader
preclinical eff. at 10 mpk QD (xenograft)
from previously disclosed AR molecule
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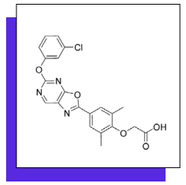
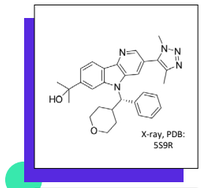
University of Michigan



SAR247799 | S1P1

G-protein biased GPCR agonist
oral 10 mg QD, phase I, cardiovascular
from HTS and opt.
bioRxiv
Sanofi



BMS-986158 | BET

oral BET inhibitor
4.5 mg QD, phase I/II for cancer
from bromodomain-focused HTS, SBDD
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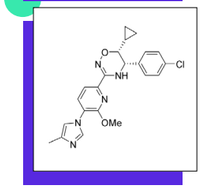

FRM-024 | γ-secretase

oral gamma secretase modulator
preclinical PD at 30 mpk single dose
from opt. of prior oxadiazine GSM
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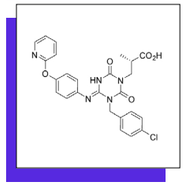
FORUM Pharmaceuticals



sivopixant | P2X3

purinergic receptor (ion channel) antagonist
up to 300 mg PO QD, phase IIb, chronic cough
from opt. of prior P2X3 antagonist
Bioorganic and Medicinal Chemistry Letters
Shionogi

drug hunter

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