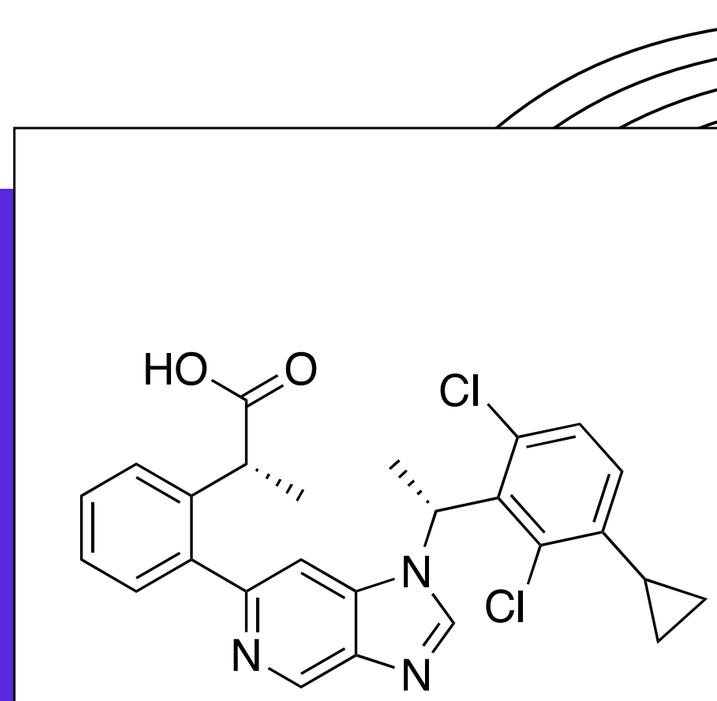
Small Molecules of the Month

March 2021

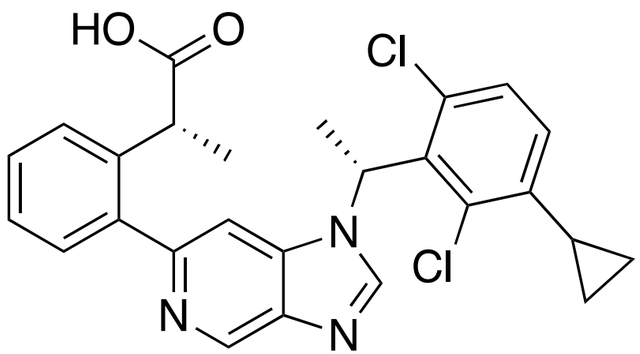


drug hunter

01	LSN3318839	Lilly Research Laboratories
02	GLPG1972 / S201086	Galapagos SASU
03	BMS-986224	Bristol Myers Squibb
04	encequidar	Athenex / Hanmi Pharmaceutical
05	S62798	Servier
06	CVN424	Cerevance / Takeda California
07	ABBV-167	AbbVie
08	GDC-0310	Genentech
09	“compound 72”	Merck & Co
10	“compound 20”	Genentech
11	TAK-418	Takeda Pharmaceuticals
12	GSK716 (13)	GlaxoSmithKline
13	RBN-012759	Ribon Therapeutics
14	sisunatovir	Reviral Ltd.

LSN3318839

Lilly Research Laboratories



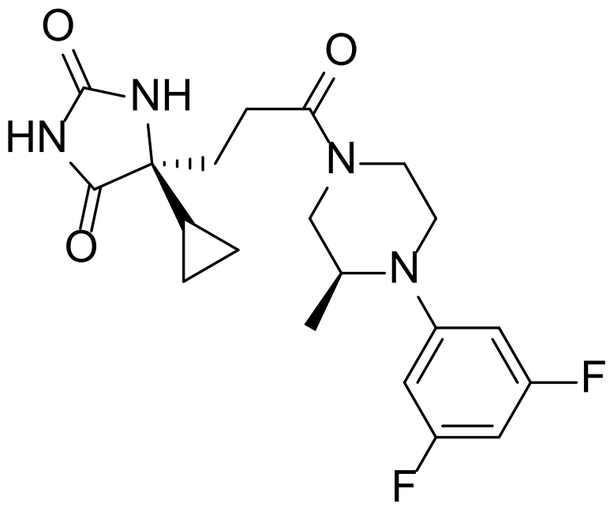
The Lilly glucagon-like peptide-1 receptor (GLP-1R) agonist (LSN3318839) is a positive allosteric modulator intended to treat type 2 diabetes. This drug candidate has an interesting proposed mechanism as a molecular glue between GLP-1R and GLP peptide, enhancing endogenous peptide activity.

The starting point was identified from a 220k compound cell-based screen in the presence of GLP-1 peptide, and optimization of PK of prior lead LSN3160440 led to LSN3318839. Oral administration of LSN3318839 (30 mg/kg) results in a blood glucose lowering effect in animal models, which is additive with sitaglipin administration. It is the first characterized molecular glue for GPCRs with demonstrated in vivo efficacy.

GLP-1R/GLP molecular glue agonist (PAM)
Oral blood glucose↓, additive w/ sitaglipin
From 220k cmpd cell-based screen + PK opt.
J. Med. Chem., Mar. 15, 2021
Lilly Research Laboratories, Indianapolis, IN

GLPG1972 / S201086

Galapagos SASU



Zinc-binding ADAMTS-5 metalloproteinase inh.

Oral candidate in Ph. II for osteoarthritis

50k cmpd HTS enriched for zinc-binding + opt.

J. Med. Chem., Mar. 15, 2021

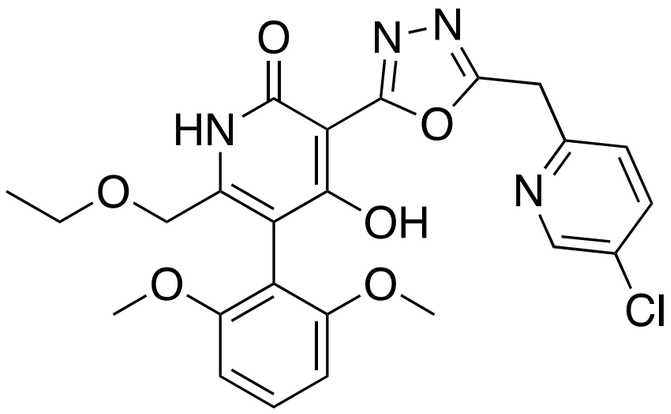
Galapagos SASU, FR / Servier, FR

The Galapagos-Servier selective ADAMTS-5 metalloproteinase inhibitor (GLPG1972) recently completed a Ph. II study for knee osteoarthritis. Identification of small molecule clinical candidates for metalloproteinases is challenging due to selectivity issues and the chemical properties of needed metal-binding groups.

The hydantoin is proposed to act as a bidentate zinc-binding motif (see this paper for an X-ray co-crystal structure of a hydantoin inhibitor coordinated to zinc). The mechanism of action targeting cartilage is interesting but the compound did not meet its primary or secondary endpoints in its recent Ph. II trial.

BMS-986224

Bristol Myers Squibb



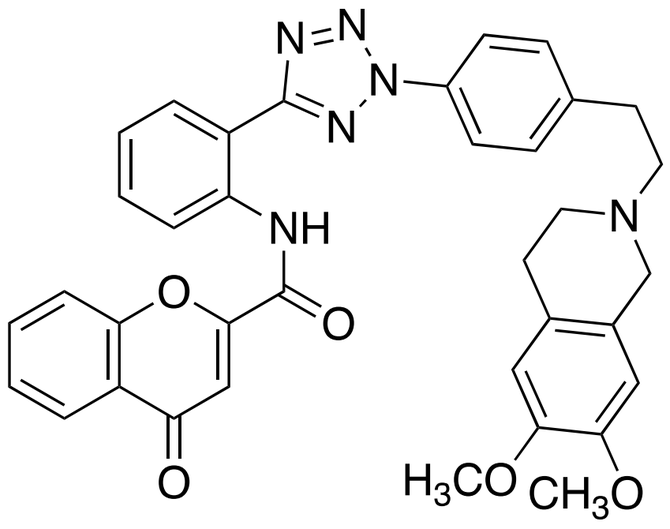
Oral apelin receptor GPCR agonist
Completed Ph. I for heart failure, discontinued
From cell-based HTS and opt.
J. Med. Chem., Mar. 19, 2021
Bristol Myers Squibb, Princeton, NJ

The Bristol Myers Squibb apelin receptor (APJ) GPCR agonist (“compound 14”) is a clinical candidate for heart failure which completed a Ph. I study. Endogenous pyroglutamated apelin-13 peptide has been shown to be beneficial in cardiovascular disease models, and this small molecule agonist was intended to treat heart failure by mimicking apelin-13 peptide without the stability and delivery issues of a peptide approach.

This drug candidate has impressive PK in preclinical species despite its structure containing several groups that can be difficult to deal with, including a phenol, pyridine, several ethers, a pyridine, and two benzylic positions. In a rat model, compound 14 treatment results in an increase in cardiac output without significant increase in heart rate in contrast to currently used inotropes such as dobutamine. Development appears to have been discontinued.

encequidar

Athenex / Hanmi Pharmaceutical



Gut-restrict. P-gp inh. for oral paclitaxel combo

Efficacious in Ph. III, NDA filed but CRL issued

From opt. of tariquidar

J. Med. Chem., Mar. 17, 2021

Athenex / Hanmi Pharmaceutical, Seoul, KR

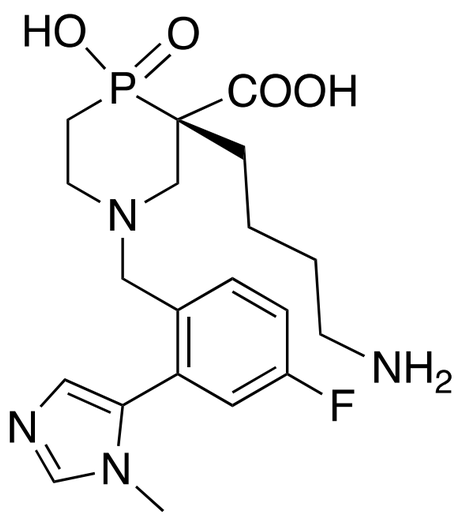
The Athenex/Hanmi Pharmaceutical P-gp transporter inhibitor (encequidar) is a gut-restricted compound intended to reduce efflux and increase absorption of the IV drug, paclitaxel to enable oral paclitaxel delivery. The use of transporter inhibitors in preclinical settings to improve drug exposure is well-established, and similar use in humans in various contexts has been often discussed but has seen little success.

This drug is an interesting overall case study for deliberately inducing a DDI, leveraging a transporter inhibitor to make an IV drug (paclitaxel) orally bioavailable, and the paper covers preclinical and clinical development in detail.

Oral combination of encequidar and paclitaxel demonstrated efficacy and tolerability with reduced neuropathy and no hypersensitivity (since the IV excipient polyoxyl-35 castor oil was obviated) in a Ph. III study in metastatic breast cancer. While the drug appears to work as intended and an NDA was filed, the FDA recently issued a complete response letter recommending additional studies.

S62798

Servier



Fibrinolytic TAFIa carboxypeptidase inhibitor

Ph. II candidate for pulm. embolism; discont.

From literature pharmacophore and SBDD

J. Med. Chem., Mar. 25, 2021

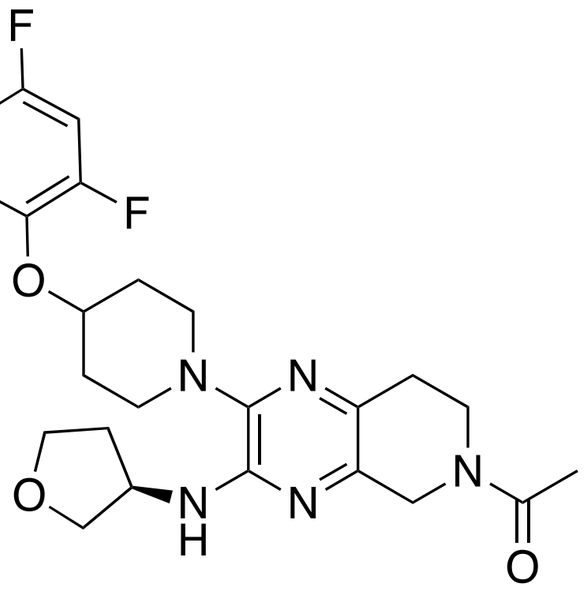
Servier, Croissy-sur-Seine, FR

The Servier thrombin activatable fibrinolysis inhibitor (TAFIa) inhibitor (S62798) is a fibrinolytic (clot degrading) agent which entered Ph. II in the EU for pulmonary embolism, but development appears to have been cancelled. TAFIa inhibitors are suggested to reduce clotting risk without the risk of major hemorrhage since they don't interfere with platelet activation and blood coagulation. The phosphinic acid acts as a zinc binding motif, and was cyclized in order to reduce conformational flexibility and increase selectivity against other carboxypeptidases.

This phosphorus-containing molecule has interesting drug properties as it is a highly polar, renally excreted compound possessing two acidic sites and multiple potentially basic atoms. The binding mode is also interesting with numerous highly polar interactions including zinc metal-binding within a short distance of one another. I.V. administration of S62798 in mice accelerated clot degradation and blood vessel recanalization as intended, which could be useful for treating pulmonary embolism or ischemic stroke.

CVN424

Cerevance / Takeda California



CNS pen. GPR6 GPCR inverse agonist
Oral QD Ph. II candidate for Parkinson's
From 360k cmpd cell-based HTS + opt.
J. Pharmacol. Exp. Ther., Apr. 1, 2021
Cerevance / Takeda California, San Diego, US

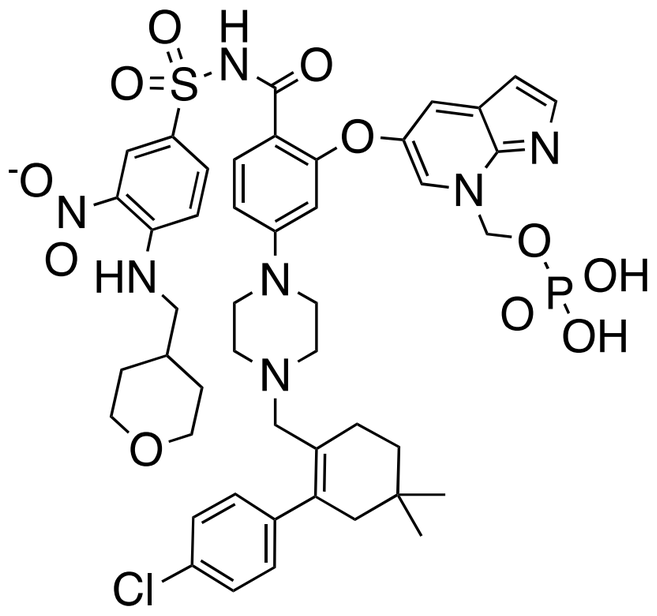
The Cerevance/Takeda GPR6 inverse agonist (CVN424) is an oral, once-daily clinical candidate in Ph. II for Parkinson's disease after completing a Ph. I in healthy volunteers. Its >40 µM starting point was discovered through a 360k compound cell-based HTS targeting human GPR6 (an orphan GPCR).

The molecule CVN424 is interesting because it is brain penetrant and orally available even with five rings and numerous polar atoms and metabolic soft spots. In vivo, CVN424 increases locomotor activity, reverses haloperidol induced catalepsy and restores mobility in a bilateral 6-OHDA lesion model of Parkinson's disease.

With its non-dopaminergic mechanism, CVN424 is a potential drug for treating the motor symptoms of PD with a reduced risk of adverse effects such as L-DOPA induced dyskinesias.

ABBV-167

AbbVie



Venetoclax prodrug with reduced food effect

Enhanced bioavailability in healthy volunteers

From venetoclax heterocycle N-alkylation

Mol. Cancer. Ther. Mar. 30, 2021

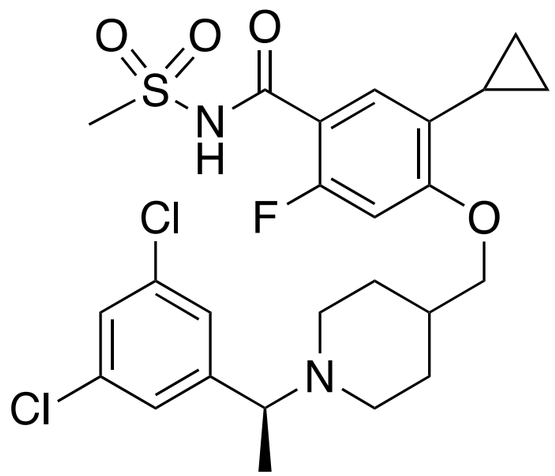
AbbVie, North Chicago, IL

The AbbVie BCL-2 inhibitor prodrug (ABBV-167) is a phosphate prodrug of venetoclax used for treatment of chronic lymphocytic leukemia (CLL). This molecule has an interesting prodrug mechanism, masking an azaindole heterocycle through heterocycle N-alkylation.

By improving the solubility, the dose needed of this prodrug relative to parent was greatly reduced, nicely illustrated with pill pictures in the manuscript. A clinical study on healthy volunteers revealed that both solid and liquid dosage forms of ABBV-167 significantly improve the bioavailability of venetoclax under fasted conditions and reduce the food effect with respect to venetoclax.

GDC-0310

Genentech



Zwitterionic oral selective Nav1.7 inh. for pain

Predicted QD dosing, completed Ph. I, discont.

PK optimization of prior scaffold

J. Med. Chem., Mar. 8, 2021

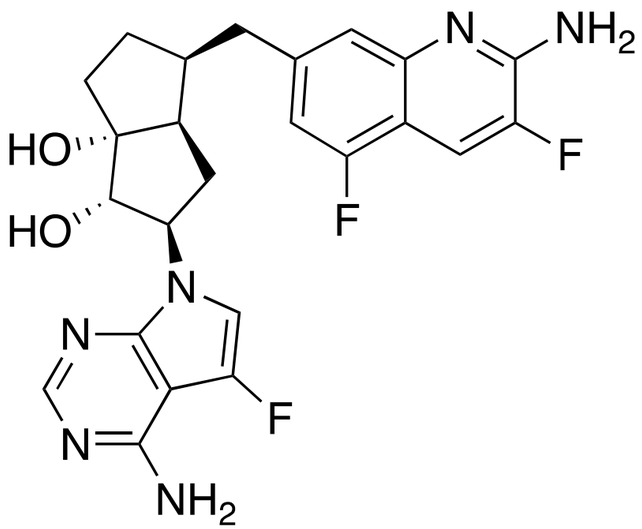
Genentech, South San Francisco, CA / Xenon

The Genentech Nav1.7 inhibitor (GDC-0310) is a oral Ph. I clinical candidate for pain. Nav1.7 has been a hot target for pain, and we previously highlighted a Nav1.7 inhibitor as one of 2020's Small Molecules of the Year. It is interesting among Nav1.7 inhibitors due to the presence of a very polar amine group where highly lipophilic elements were formerly incorporated, and is also an interesting example of an orally available zwitterion with a membrane-bound target.

This acyl-sulfonamide derivative demonstrates >300-fold selectivity over Nav1.1, Nav1.5, and Nav1.6. Preclinical studies of GDC-0310 were conducted based on measuring its ability to block a response to aconitine (a plant alkaloid that causes abnormal opening of sodium channels). Unfortunately development of this molecule has been discontinued.

“compound 72”

Merck & Co



Oral PRMT5 inh. for treating cancers

Projected human dose of 15 mg QD w/ 6 HBD

SBDD from SAM cofactor

J. Med. Chem., Mar. 23, 2021

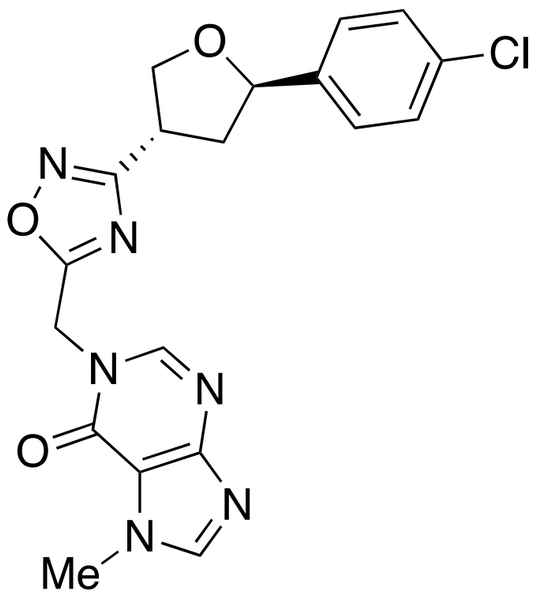
Merck & Co, Boston, MA

The Merck protein arginine methyltransferase 5 (PRMT5) inhibitor (“compound 72”) is a SAM cofactor-mimetic with a novel 5,5-fused carbon-based bicyclic scaffold. PRMT5 is an actively pursued epigenetic target for cancer with a flurry of research programs being published recently and several trials being initiated.

Remarkably, compound 72 has an excellent oral PK profile in higher species with a low predicted human dose of 15 mg QD, despite having 6 hydrogen bond donors and 6 rings.

“compound 20”

Genentech



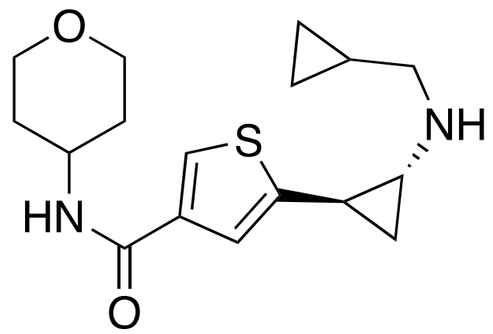
Cryo-EM-characterized TRPA1 ion channel inh.
Oral efficacy (10 mpk BID) in asthma model
Rational design from literature starting point
J. Med. Chem., Mar. 22, 2021
Genentech, South San Francisco, CA

The Genentech transient receptor potential ankyrin 1 (TRPA1) inhibitor (“compound 20”) is an ion channel inhibitor with a binding site and mechanism of action characterized by cryo-EM. Structural information for ion-channel targets is rare as X-ray co-crystal structures of membrane-bound proteins are difficult to obtain.

The article is an interesting case study for using conformational analysis to improve drug molecules, and the authors highlight several interesting attempted linker rigidification strategies. Compound 20 is orally efficacious in a guinea pig asthma model demonstrating a substantial reduction in inflammatory response due to BALF infiltrates in the airways around 10 mg/kg BID.

TAK-418

Takeda Pharmaceuticals



Brain-penetrant LSD1 inh. for neuro. disorders

Sociability ↑ in vivo, completed Ph. I in HV

Tranylcypromine class mechanism-based inh.

Sci. Adv., Mar. 12, 2021

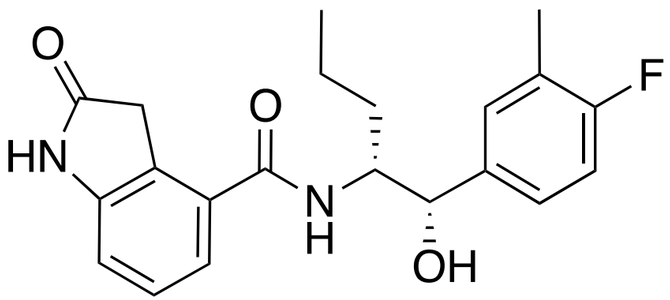
Takeda Pharmaceuticals, Fujisawa, JP

The Takeda lysine-specific demethylase 1 (LSD1) inhibitor (TAK-418) is an oral CNS-penetrant clinical candidate for neurodevelopmental disorders such as autism spectrum disorder. We previously highlighted irreversible and reversible LSD1 inhibitors intended to treat cancer.

This tranylcypromine-derived clinical candidate is interesting because it is a relatively rare example of a mechanism-based CNS-acting drug. Oral administration of TAK-418 at only 1 mg/kg normalized mRNA expression in neurodevelopmental disorder model rodents and improved sociability. The proposed mechanism of action for neurodevelopmental disorders (restoring gene expression homeostasis by inhibiting a stabilizer of faulty epigenetic machinery) will be interesting to watch.

GSK716 (13)

GlaxoSmithKline



The GlaxoSmithKline (GSK) Z a1-antitrypsin stabilizer (“compound 13,” GSK716) acts by blocking the formation of polymers within the endoplasmic reticulum of hepatocytes for treatment of a1-antitrypsin deficiency. It was identified through a DNA-encoded library screen with a nominal diversity of 2 trillion components. Compound 13 showed an excellent selectivity profile toward a1-antitrypsin.

The 1 mg/kg i.v. infusion of compound 13 demonstrated moderate bioavailability in rat and was predicted to have high oral bioavailability in human. This molecule is interesting as the starting point came from a DEL screen and has a rare corrector mechanism of action.

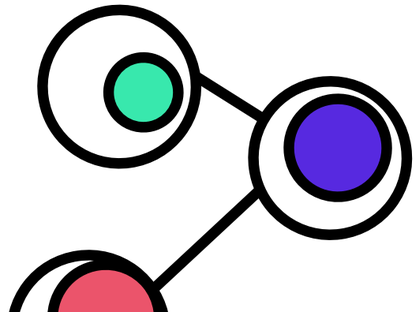
Mutant a1-antitrypsin folding corrector

Sub-μM in cell, high predicted human %F

From 2T component DEL + SBDD

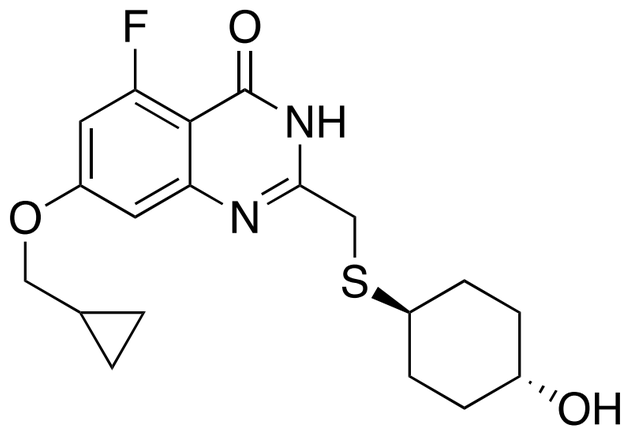
Bioorg. Med. Chem. Lett., Mar. 19, 2021

GlaxoSmithKline, Stevenage, UK / UCL



RBN-012759

Ribon Therapeutics



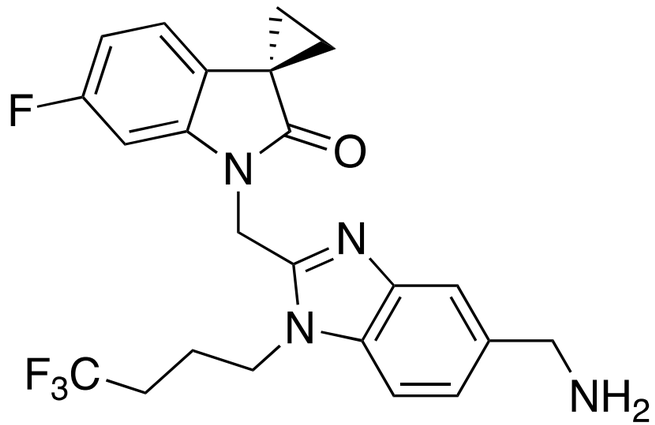
>300-fold family-selective PARP14 inh. tool
90x IC50 coverage at 500 mpk BID PO in vivo
From PARP-preferring directed library + SBDD
Cell Chem. Bio., Mar. 10, 2021
Ribon Therapeutics, Cambridge, MA

The Ribon Therapeutics PARP14 inhibitor (RBN-012759) is a tool compound with >300x selectivity over all PARP family members. While PARP1/2 are well-known to drug hunters as synthetic lethal targets due to their role in DNA damage repair, there are 17 PARP enzymes with many other biological roles without as much pharmacological exploration.

The starting point for RBN-012759 was identified by screening a PARP-preferring directed library and structure-based design led to RBN-012759. Preclinical studies in mice demonstrated modest oral bioavailability of RBN-012759, but it was well tolerated over several days at 500 mg/kg BID orally, a dose that provides 90-fold coverage of the mouse PARP14-free IC50 value (15 ng/mL) at 8 h. This tool should help elucidate the role of PARP14 in anti-tumor immunity.

sisunatovir

Reviral Ltd



Oral lung penetrant RSV fusion inhibitor
Ph. II candidate (50 mg BID) for RSV infect.
Opt. from literature starting point
J. Med. Chem., Mar. 17, 2021
Reviral Ltd, Hertfordshire, UK

The Reviral respiratory syncytial virus (RSV) fusion inhibitor (sisunatovir) is an oral Ph. II clinical candidate that demonstrated reduction in viral load and total symptom score in RSV-infected patients and has received the Fast Track designation from the FDA. Crowded areas for development such as for RSV often lead to interesting chemical structures.

This molecule is interesting because of some less common structural motifs including a potentially reactive spirocyclic cyclopropyl oxindole and a primary amine. Despite the potential for hERG inhibition, no QT effects were observed in the guinea pig model or dog telemetry studies, and the molecule was taken through human proof of concept.

The paper describes the discovery and development thought process in detail and is a great drug discovery process case study from a smaller organization.

drug hunter

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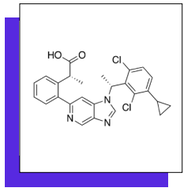

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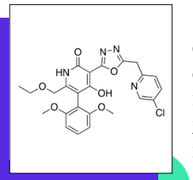

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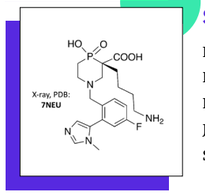

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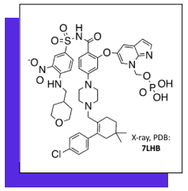

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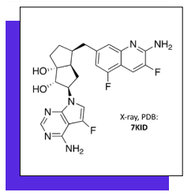

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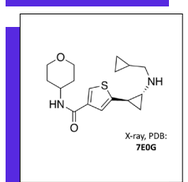

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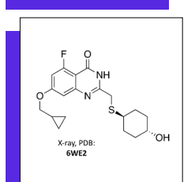

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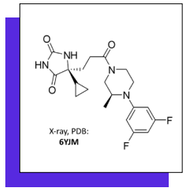

GLPG1972 / S201086

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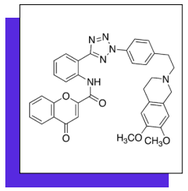

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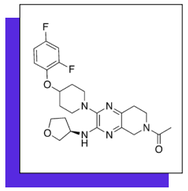

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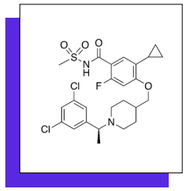

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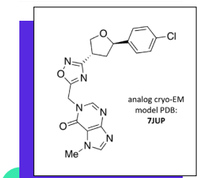
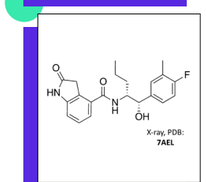
Predicted QD dosing, completed Ph. I, discont.
PK optimization of prior scaffold
J. Med. Chem., Mar. 8, 2021
Genentech, South San Francisco, CA / Xenon



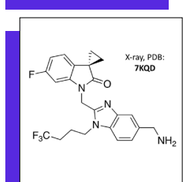
"compound 20"

Cryo-EM-characterized TRPA1 ion channel inh.
Oral efficacy (10 mpk BID) in asthma model
Rational design from literature starting point
J. Med. Chem., Mar. 22, 2021
Genentech, South San Francisco, CA



GSK716 (13)

Mutant α1-antitrypsin folding corrector
Sub-μM in cell, high predicted human %F
From 2T component DEL + SBDD
Bioorg. Med. Chem. Lett., Mar. 19, 2021
GlaxoSmithKline, Stevenage, UK / UCL



sisunatovir

Oral lung penetrant RSV fusion inhibitor
Ph. II candidate (50 mg BID) for RSV infect.
Opt. from literature starting point
J. Med. Chem., Mar. 17, 2021
Reviral Ltd, Hertfordshire, UK

drug hunter

discover together

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