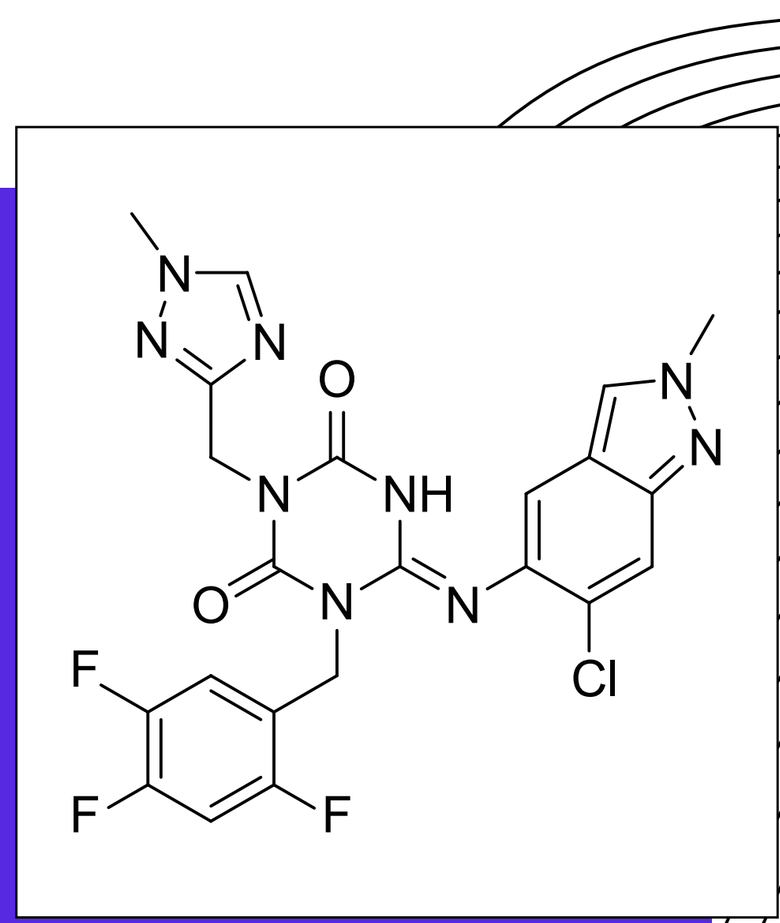
Small Molecules of the Month

January 2022

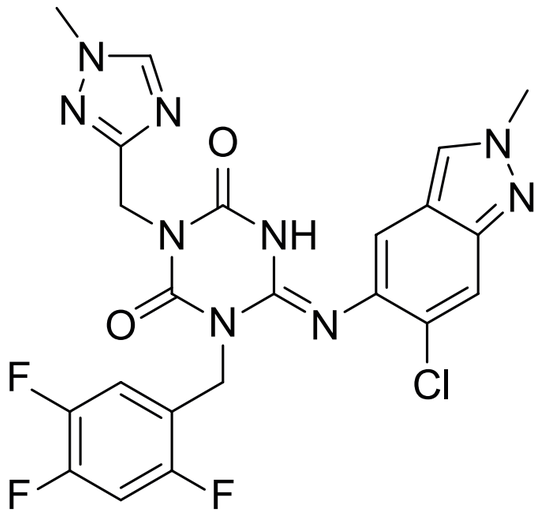


drug hunter

01	CoV-2 M^{pro}	Shionogi
02	Factor XI	Bayer AG
03	CD33	Pfizer
04	HIV CA/SP1	ViiV Healthcare (GSK)
05	STING	Aduro (Chinook)
06	PRMT5	Mirati
07	NaPi2b	Kyowa Kirin
08	GPR38	Daiichi Sankyo
09	GR	LEO Pharma
10	α7-nAChR	Johns Hopkins

S-217622

reversible SARS-CoV-2 3CL^{pro} inhibitor



reversible SARS-CoV-2 3CLpro inhibitor
Ph. II/III candidate for COVID-19
virtual + HTS MS screen, SBDD
bioRxiv
Shionogi Pharmaceutical

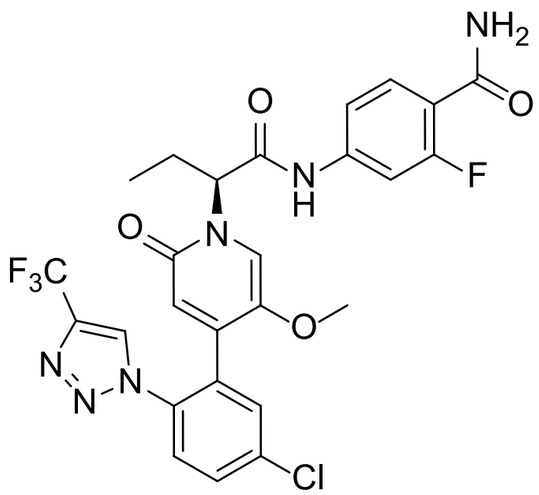
S-217622 is the first oral, non-covalent, non-peptidic SARS-CoV-2 3CL (main protease) inhibitor clinical candidate, currently in Ph. II/III trials as a once-daily oral treatment for COVID-19. Unlike paxlovid, the molecule is a non-covalent inhibitor, which may lead to a better safety profile in large populations, though there is no reason to expect issues with the reversible covalent paxlovid today. Paxlovid is also the combination of the peptidic drug PF-07321332 with a PK booster, ritonavir, and a single drug with sufficient PK for standalone oral dosing would be ideal for broadest adoption.

The starting point was identified by virtual screening, with the top 300 hits being confirmed by high-throughput mass spectrometry. The starting point was weakly biochemically active ($3CL_{pro}$ IC_{50} of 8.6 uM). Structure-based design was leveraged to improve the potency by ~500x to 13 nM with surprisingly small changes relative to the starting point. Remarkably, the compound has oral %F of 97% in rat, 106% in monkey, and 65% in dog. The molecule is broadly active in vitro against the WT, alpha, beta, gamma, delta, and omicron strains, with comparable activity in each.

Shionogi has historically been a leader in the anti-infectives space and the identification of this molecule adds to their prestige in the area.

asundexian (BAY2433334)

factor XI inhibitor



factor XI inhibitor
Ph. II candidate for CV (fibrillation, stroke, MI)
related to previous series
Br. J. Clin. Pharmacol.
Bayer AG

asundexian (BAY2433334) is a reversible Factor XIa active site inhibitor previously disclosed at the 2021 EFMC-ISMC conference. This article highlights the Ph. I data of asundexian in healthy volunteers, showing that the drug is well tolerated, with no clinically relevant bleeding-related adverse events or any relevant CYP3A4 modulation.

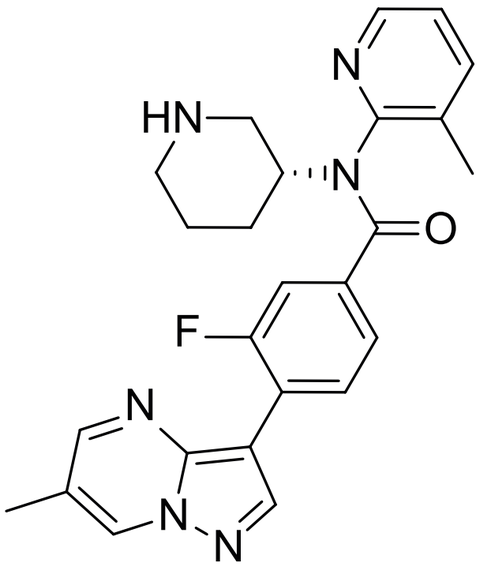
The molecule is suitable for once daily dosing (20, 50 mg PO QD), and is currently being tested in more than 4000 patients in several phase 2 studies (NCT04304534, NCT04510987, NCT04304508, NCT04218266). This program follows Bayer's success with rivaroxaban (Factor Xa inhibitor), another key target in the coagulation cascade.

In contrast to factor Xa, factor XIa is not required for homeostasis. The molecule's discovery story has not been published yet (conference report only, patent: US10421742B2). This chemical class was identified using internal X-ray cocrystal structures of two tool compounds with human FXIa. Extensive use of Water Map analysis helped the team identify the Ester Binding Pocket and the P1' pocket as key areas to investigate SAR for. A sub-micromolar hit was optimized to their first clinical candidate, which had a carboxylic acid. Unfortunately, in a phase I clinical trial in healthy volunteers, the first candidate showed a very short half-life in humans.

To address this, the team decided to replace the carboxylic functional group filling the P2' pocket with a non-acidic substituent. After several rounds of optimization, BAY2433334 (asundexian) was identified as a second clinical candidate.

compound 1

CD33 pre-MRNA splicing modulator



CD33 splicing modulator
preclinical (neurodegeneration)
from 3.1M cmpd phenotypic CD33 splicing screen
ACS Med. Chem. Lett.
Pfizer Inc.

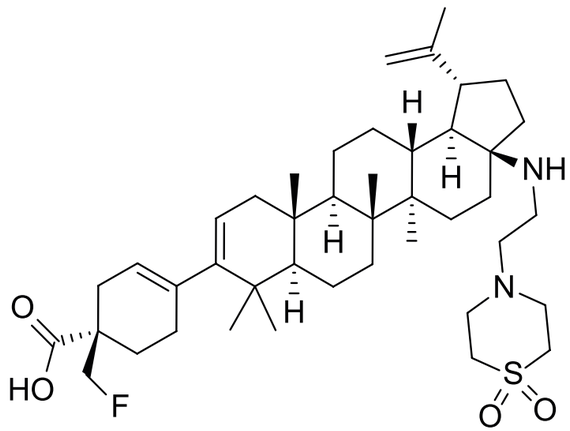
compound 1 is a CD33 pre-mRNA splicing modulator that increases CD33 exon 2 skipping in cells. CD33/Siglec 3 regulates microglia activity, and genetic alterations of CD33 are associated with protection from Alzheimer's. Alternative splicing of CD33 with exclusion of exon 2 is hypothesized to copy the protective effect of the human genetic variants.

The hit is an interesting proof-of-concept for pre-mRNA splicing manipulation by a small molecule. It was identified from an HTS of the full Pfizer library of 3.1M compounds, using a reporter-gene-based phenotypic CD33 splicing assay. The hit was derived from a previous PCSK9 translational stalling project. A high-content imaging assay for cytotoxicity was used to qualify hits.

Unfortunately, despite promising initial SAR, the program was discontinued and no further characterization of the molecules was undertaken. However, this shows that RNA splicing modulation by small molecules is a strategy that should continue to be explored more broadly for targets that are otherwise challenging to drug directly.

GSK3640254

HIV maturation inhibitor



HIV maturation inhibitor
Ph. II candidate for HIV
from prior clinical candidate
Antimicrob. Agents Chemother.
ViiV Healthcare (GSK)

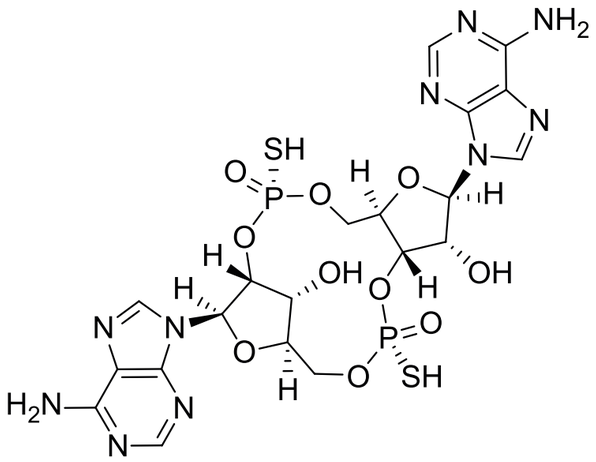
GSK3640254 is an HIV maturation inhibitor and Ph. IIb clinical candidate (60-180 mg PO QD) with activity against a range of HIV strains with Gag polymorphisms. The first HIV maturation inhibitor to read out clinically was bevirimat (Myriad Genetics), derived from a natural product first isolated from a Chinese herb. Maturation inhibitors like GSK3640254 work by binding to the cleavage site of the Gag protein, preventing release of p24 and formation of proper HIV capsids.

Unfortunately, the initial drug was not efficacious enough due to polymorphisms in HIV Gag protein leading to resistance (response in only ~50% of patients). GSK had another clinical candidate, GSK3532795 in clinical trials, but this was discontinued due to GI tolerability issues in a Ph. IIb study when combined with emtricitabine and tenofovir. GSK3640254 is believed to be safer and also has deeper target coverage at trough exposure (150 nM) on a broader range of polymorphisms, hopefully leading to more durable efficacy.

The molecule is an interesting example of a clinical candidate with three olefins and a primary alkyl fluoride. The primary differences between GSK3532795 and GSK3640254 structurally are on the left-hand portion, with a benzoic acid replaced by the semi-saturated motif present in ‘254.

MIW815 (ADU-S100)

STING agonist



STING agonist
Ph. II candidate for met. H&N cancer
from SBDD of endogenous ligand
Clin. Cancer Res.
Aduro (Chinook Therapeutics)

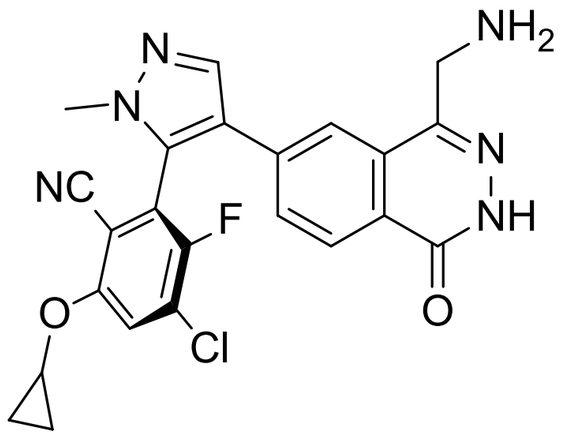
[MIW815 (ADU-S100)] is a first-in-class STING agonist for cancer immunotherapy. Agonism of the STING (stimulator of IFN genes) receptor, true to its name, leads to [stimulation of type I IFN production], aiding the antitumor immune response. Systemic activation of STING, however, may lead to negative immunologic effects such as [cytokine storm].

In part due to the possibility of side effects and in part due to the PK properties of STING agonists, most STING agonists have been tested with intratumoral administration, with the hope of priming the immune system to trigger an [abscopal effect] that would allow a broader response. Unfortunately, while partial responses were seen at the site of injection, no substantial activity was observed, resulting in the termination of studies with ADU-S100 and the collapse of Aduro Biotech.

Like most other clinical STING agonists, ADU-S100 is an analog of the natural cyclic dinucleotide ligand for STING. The molecules possess an interesting thiophosphate linkage that is important for stability (though the half-life after injection is still short, <30 min). The original data around ADU-S100 is now being published and will be helpful to other research. The STING saga is an interesting case study for intratumoral administration, as drugs needed to be developed to have low systemic exposure for safety, but sufficient stability to have an effect at the site of injection.

MRTX1719

PRMT5 inhibitor



PRMT5 inhibitor
preclinical (MTAP-deleted cancers)
from fragment-based design + SBDD
J. Med. Chem.
Mirati Therapeutics

MRTX1719 is PRMT5-MTA complex inhibitor for the treatment of MTAP-deleted cancers currently in IND-enabling studies. PRMT5 is a target of active interest with several molecules recently highlighted here. Inhibition of PRMT5 is expected to induce synthetic lethality in MTAP-deleted tumors – however, PRMT5 is also an essential gene for hematopoesis, and therefore most PRMT5 inhibitors also lead to dose-limiting cytopenias.

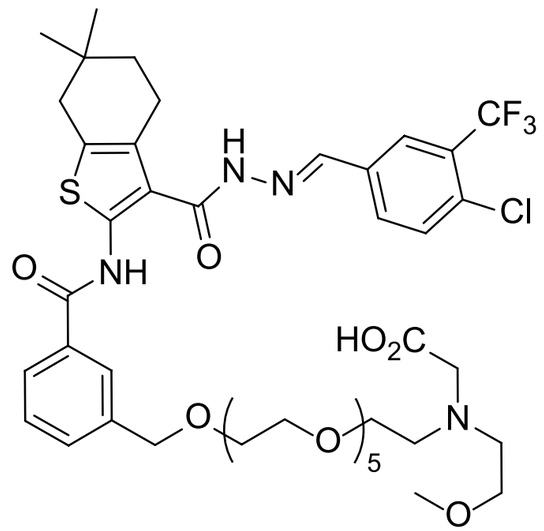
MRTX1719, in contrast, inhibits PRMT5 cooperatively with MTA (methylthioadenosine), which is accumulated in MTAP-deleted cells. This mechanism of action may allow greater differentiation between MTAP-deleted tumor cells and healthy hematopoetic stem cells. The molecule is orally active in a preclinical model with once daily dosing.

The molecule emerged from a fragment-based drug discovery campaign specifically focused on the PRMT5-MTA complex, and is an excellent case study for the FBDD approach. Initial fragment screening suggested PRMT5-MTA was ligandable, and fragment-growing from the 10 uM initial hit supported by X-ray crystallography led to compounds with nanomolar cellular activity, picomolar Kd's and a long dissociation half life of >14 days. Importantly, MRTX1719 appears to be selective for MTAP-deleted cancer cells, though it remains to be seen whether this will translate to a better therapeutic window vs. cytopenia and greater efficacy in humans (activity on bone marrow colony forming units was not reported).

This is an impressive technical achievement and a compound to watch for in the clinic.

compound 15

NaPi2b inhibitor



NaPi2b inhibitor
preclinical (hyperphosphatemia)
in-house compound screen + optimization
J. Med. Chem.
Kyowa Kirin Co., Ltd.

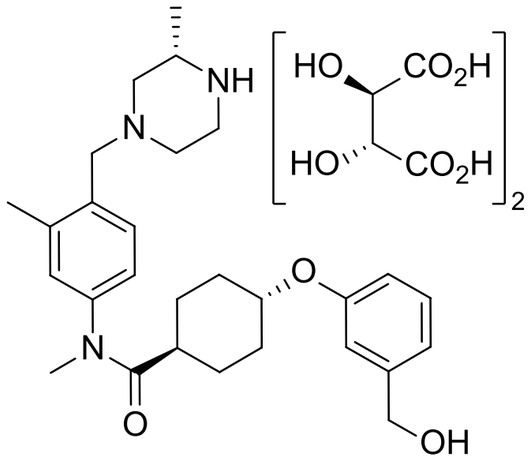
[Compound 15](#) is a gut-restricted inhibitor of NaPi2b, a sodium-dependent phosphate transport protein in the solute carrier (SLC) family. NaPi2b is expressed on the apical side of the small intestine and contributes to absorption of inorganic phosphate in the diet. Chronic kidney disease patients have elevated serum phosphate levels and need dialysis to remove excess phosphate. Oral phosphate binder therapies such as sevelamer hydrochloride and lanthanum carbonate that prevent phosphate absorption have non-ideal patient adherence due to pill burden and GI side effects.

NaPi2b, however, is also expressed in the lungs and testes, and systemic inhibition is undesirable from a safety perspective. One systemic NaPi2b inhibitor with an undisclosed structure, ASP3325, has been tested in humans but was ineffective in end-stage renal disease (ESRD) patients, but there is not enough disclosed data to draw conclusions about the efficacy of the mechanism.

Compound 15 is negligibly orally absorbed due to membrane impermeability by design, but demonstrates phosphate-lowering efficacy in vivo (rat intestinal loop assay) with comparable activity to sevelamer hydrochloride. The molecule does not appear to be in development.

DS-3801b

GPR38 agonist



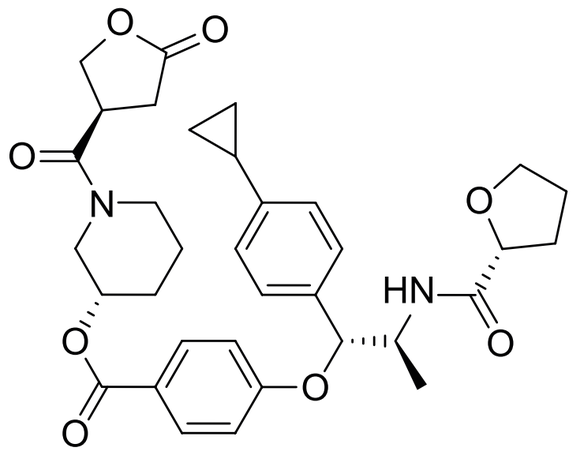
GPR38 agonist
Ph. I candidate for chronic constipation
from previously disclosed GPR38 agonists
Bioorg. Med. Chem. Lett.
Daiichi Sankyo Co., Ltd.

DS-3801b is a non-macrolide GPR38 agonist and a Ph. I clinical candidate for treatment of chronic constipation (SAD 1-100 mg PO). GPR38 is the receptor for the GI hormone motilin, which as the name suggests, regulates GI motility. Agonism of GPR38 is expected to reduce constipation by activating GI tract smooth muscle cells to move things along. DS-3801b was found to be safe and well tolerated after doses up to 50 mg, with mild GI adverse events.

The molecule was optimized from a previously disclosed GPR38 agonist, and has significantly greater sp3 character than its starting point. Though the side chains are similar, there was a dramatic core change. A “magic methyl” effect was also observed by installing a methyl group at the 3-position of the phenyl ring. Interestingly, the solid form employed in clinical trials is the bis-tartrate salt (two tartaric acids per unit of DS-3801b).

LEO 134310

glucocorticoid receptor agonist



glucocorticoid receptor agonist
Ph. I candidate for psoriasis
dual-soft drug
Sci. Rep.
LEO Pharma A/S

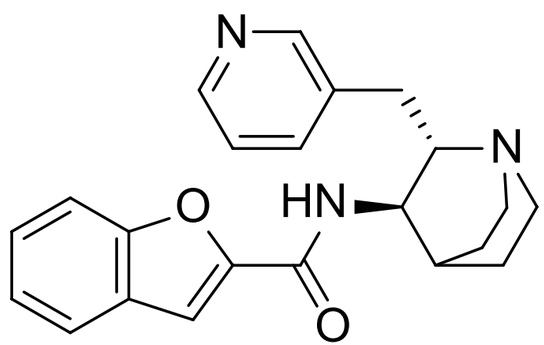
LEO 134310 is a non-steroidal, selective glucocorticoid receptor (GR) agonist in Ph. I for plaque psoriasis. Glucocorticoid receptor modulators are widely used in tissue-restricted forms (think Flonase) for their acute effects, but prolonged engagement of GR is undesirable. Previously LEO Pharma described the identification of this topical clinical candidate through a dual-soft drug strategy (rapid metabolism in both blood and liver) to limit systemic exposure and shorten skin residence time.

The campaign started with a previously disclosed inhaled GR agonist (AZD7594), but the N1-aryl-indazole needed to be replaced for skin use due to strong UV absorbance. Amides were successfully used as isosteres of the indazole (which is interesting as normally chemists try to go in the opposite direction for metabolic stability). As desired, the compound is rapidly hydrolyzed in the blood and further metabolized in the liver.

In minipigs, topical administration did not lead to any reduction in skin thickness in contrast to corticosteroids betamethasone (BMV foam) and clobetasol propionate (CP foam). The molecule is also highly selective among a panel of nuclear receptors including against mineralocorticoid receptor (MR) which is associated with skin atrophy. LEO 134310 may therefore be a better tolerated option for long term use in skin diseases than prior GR modulators.

bradanicline (ATA-101 or TC-5619)

alpha-7 nicotinic receptor agonist



alpha-7 nicotinic receptor agonist
Ph. II candidate for chronic cough
drug repurposing
J. Pharmacol. Exp. Ther.
Johns Hopkins

bradanicline (ATA-101 or TC-5619) is a molecule first disclosed a decade ago by Targacept.It is a selective agonist of the alpha-7 neuronal nicotinic acetylcholine receptor, and was intended as a drug candidate for treatment of cognitive impairment in neurological disorders. It is highly selective for the CNS over peripheral receptor subtypes.

Interestingly, in this article, the authors show that the molecule dose-dependently inhibits coughing in guinea pigs. Nicotine has been demonstrated to have anti-tussive properties, and it is suggested that this nicotinic receptor subtype is responsible for that effect.

In humans, ATA-101 was well-tolerated in several clinical studies when given daily for several weeks at doses as high as 125 mg QD, and entered Ph. II to evaluate efficacy in patients with refractory chronic cough. Unfortunately, the molecule has not shown an anti-tussive effect in humans.

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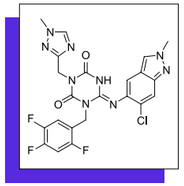
drughunter.com



S-217622 | CoV-2 M^{pro}

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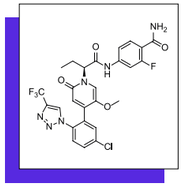

asundexian | factor XI

factor XI inhibitor
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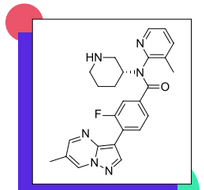

compound 1 | CD33 pre-mRNA

CD33 splicing modulator
preclinical (neurodegeneration)
from 3.1M cmpd phenotypic CD33 splicing screen
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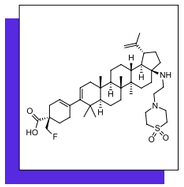

GSK3640254 | HIV Gag

HIV maturation inhibitor
Ph. II candidate for HIV
from prior clinical candidate
Antimicrob. Agents Chemother.
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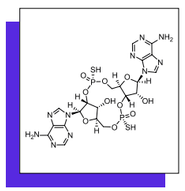
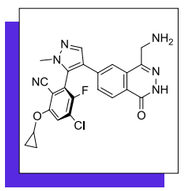


ADU-S100 | STING

STING agonist
Ph. II candidate for met. H&N cancer
from SBDD of endogenous ligand
Clin. Cancer Res.
Aduro (Chinook Therapeutics)



MRTX1719 | PRMT5-MTA

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preclinical (MTAP-deleted cancers)
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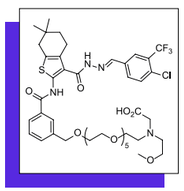

compound 15 | NaPi2b

NaPi2b inhibitor
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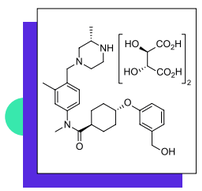

DS-3801b | GPR38

GPR38 agonist
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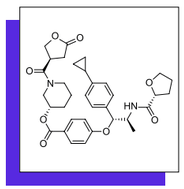
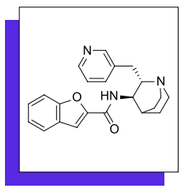


LEO 134310 | GR

glucocorticoid receptor agonist
Ph. I candidate for psoriasis
dual-soft drug
Sci. Rep.
LEO Pharma A/S



ATA-101 | α-7 nAChR

alpha-7 nicotinic receptor agonist
Ph. II candidate for chronic cough
drug repurposing
J. Pharmacol. Exp. Ther.
Johns Hopkins

drug hunter

discover together

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