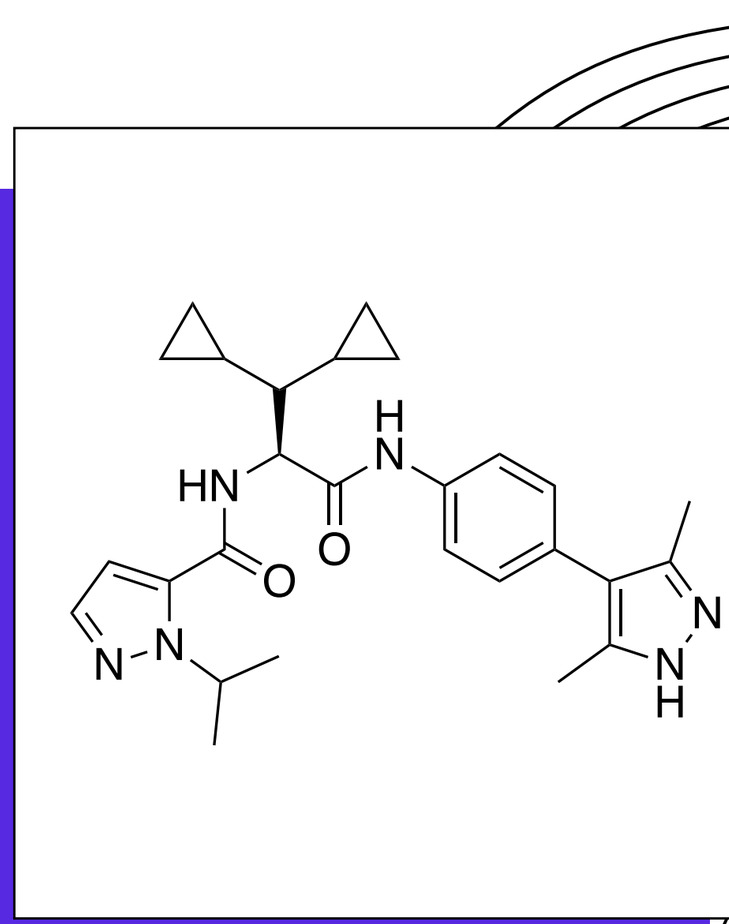
Small Molecules of the Month

June 2022

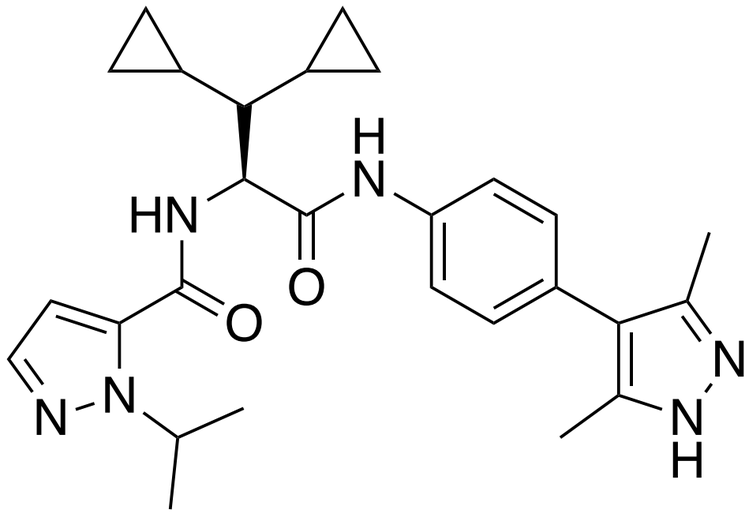


drug hunter

01	IL-17A	Leo Pharma
02	PAR4	Bristol-Myers Squibb
03	SETD2	Epizyme Inc
04	LRRK2	Denali Therapeutics
05	GlyT1	Boehringer Ingelheim
06	FXR	Biocon-Bristol Myers Squibb
07	CD38	Mitobridge
08	RNR	Taiho Pharmaceutical
09	Akt	Nanjing Chia-Tai Tianqing
10	MR	Mitsubishi Tanabe

Compound 23

IL-17A



oral interleukin 17A modulator

favorable in vivo PK profile in multiple species

from a previous patent and SBDD

J. Med. Chem.

LEO Pharma Research & Early Development, Ballerup, DK

featured article: doi.org/10.1021/acs.jmedchem.2c00422

drug hunter

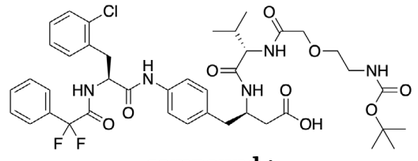
Context. "Compound 23" (LEO Pharma) is an oral IL-17A protein-protein interaction modulator being developed for psoriasis and other inflammatory diseases. Like most cytokines, the involvement of IL-17A in chronic inflammatory diseases has been well-researched. IL-17A is the key cytokine that mediates psoriasis, and targeting it or its receptor has led to the approval of the highly effective monoclonal antibodies secukinumab (Cosentyx), ixekizumab (Taltz), and brodalumab (Siliq) by the FDA and EMA, and bimekizumab (Bimzelx) by the EMA. Owing to the phenomenon of biologic fatigue caused by anti-drug antibodies, which has been associated with anti-psoriatic antibody treatment, oral small molecule inhibitors with similar efficacy and safety have been explored as an alternative therapy. However, modulating protein-protein interactions (PPIs) with small molecules, as is being done for IL-17A, is not without its challenges, such as finding starting points that are within Ro5 space. "Compound 23" is Ro5 compliant and was found to have good oral bioavailability, with data on in vivo efficacy and safety yet to be reported. In the meantime, DICE Therapeutics' S011806, which is in Ph. I studies, appears to be leading the way in the race to the first approved IL-17A oral small molecule inhibitor, although LEO Pharma has disclosed another candidate.

Reviewer Commentary. Reviewer Christian Gampe states "compound 23" is a great example of a small molecule that modulates a protein that has only been targeted with antibodies so far (see Dr. Gampe's discussion of small molecule immunomodulators on the Drug Hunter website). What it took to get there is some excellent medicinal chemistry: meticulous SBDD to significantly trim the original hit and employment of suitable amide isosteres to get into a more palatable phys-chem space, as well as identification of lipophilic substituents to drive potency while keeping oxidative metabolism in check."

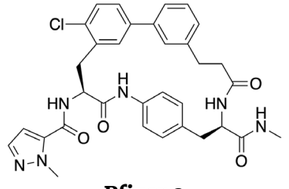
Target. IL-17A is one of six structurally-related members (IL-17A–F) of the IL-17 family of cytokines and is considered its founding member. IL-17 receptors typically exist as heterodimers and are designated as IL-17RA–RE, with the heterodimeric 17RA/IL-17RC believed to be the receptor for IL-17A and IL-17F homo- and heterodimers. As a cytokine, the role of IL-17 in inflammatory diseases is well-validated. Particularly, extensive human genetic validation studies have implicated dysregulated IL-17A expression in psoriasis.

Mechanism of Action. Activation of IL-17R by the corresponding IL-17 cytokine leads to activation of downstream pathways, such as those involving NFκB, MAPKs, and C/EBPs, resulting in the subsequent expression of antimicrobial peptides, other cytokines, and chemokines. Currently approved IL-17 inhibitors, all of which are monoclonal antibodies, either bind to the monomeric units of the cytokine and preclude activation of its receptor or bind to the receptor to disrupt activation by the cytokine itself. "Compound 23" binds to the IL-17A dimer interface and prevents binding of the cytokine to 17RA/IL-17RC.

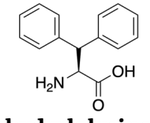
Hit-Finding Strategy. Compound 1 (**PDB: 7AMG**) and the macrocyclic compound Pfizer 3 (**PDB: 5HI5**) occupy the same central pocket of IL-17A, maintaining hydrogen bonds with Leu120 and Trp90. The main difference is the orientation of Phe85, which in 7AMG has flipped to make space for the long tail of "compound 1". In 5HI5, this residue instead caps the binding site and forms an edge-to-face pi-pi interaction with one of the aromatic rings of Pfizer 3. The chlorophenyl ring, constrained in a macrocyclic ring, is also oriented differently than that of "compound 1". It was this observation that led to the design of improved compounds. LEO Pharma scientists combined the orientations of "compound 1" and Pfizer 3 to obtain a core benzhydrylglycine moiety which allowed each phenyl group to occupy either the chlorophenyl of "compound 1" or Pfizer 3.



compound 1



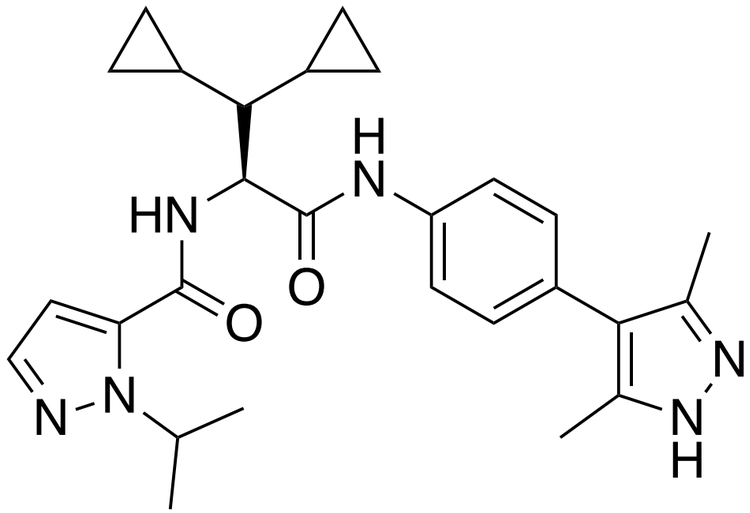
Pfizer 3



benzhydrylglycine core

Compound 23

IL-17A



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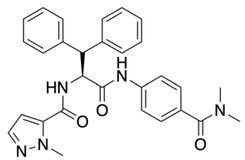
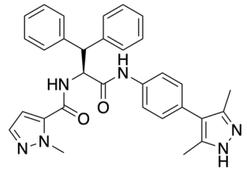
featured article: doi.org/10.1021/acs.jmedchem.2c00422

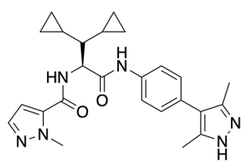
Lead Optimization. Initial optimization focused on shortening the aniline subunit to generate a Ro5-compliant molecule with reduced molecular size and PSA, as well as increasing the probability of oral bioavailability. This led to "compound 3", which had an EC_{50} of 5610 nM. Further optimization explored heteroaryl isosteres of the *N,N*-dimethylbenzamide moiety, with dimethylpyrazole analog 7 giving significant improvement (EC_{50} = 117 nM). To further reduce lipophilicity, SAR around the central benzhydrylglycine was then investigated. Removal of one, then both of the benzene rings, followed by systematic evaluation of aliphatic rings, which were better able to occupy the central lipophilic pocket, ultimately led to biscyclopropylalanine 19, which showed both good potency (EC_{50} = 53 nM) and metabolic stability. Finally, optimization of the pyrazole provided "compound 23" (EC_{50} = 14 nM)



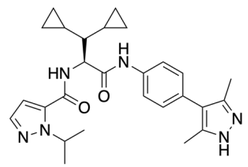
compound 3
(EC_{50} = 5610 nM)



compound 7
(EC_{50} = 117 nM)



compound 19
(EC_{50} = 53 nM)



compound 23
(EC_{50} = 14 nM)

Binding mode: "Compound 23" binds in the central pocket between the residues of chains A and B of IL-17A (**PDB: 7AMA**). The x-ray structure shows the presence of hydrogen bonds between the amides of "compound 23" and Leu120 residue. Other hydrogen bonds can be observed in the other molecular extremity, in the dimethylpyrazole moiety that interacts with the amide nitrogen and carbonyl oxygen atoms of Trp90 of chain B.

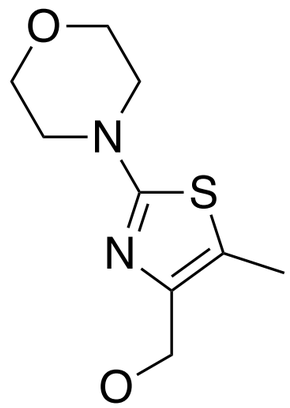
Preclinical Pharmacology. In vivo PK studies were done in male Sprague-Dawley rats and other undisclosed preclinical species. Rats were dosed orally at 2.4 mg/kg or intravenously at 0.1 mg/kg with "compound 23". Despite demonstrating low in vitro aqueous solubility at pH 6.5, the compound was completely absorbed following oral dosing. Clearance of the molecule was 7.4 mL/min/kg with an associated volume of distribution of 2.6 L/kg, resulting in a half-life of 3.7 h. In vivo safety and efficacy data are yet to be reported by LEO Pharma scientists.

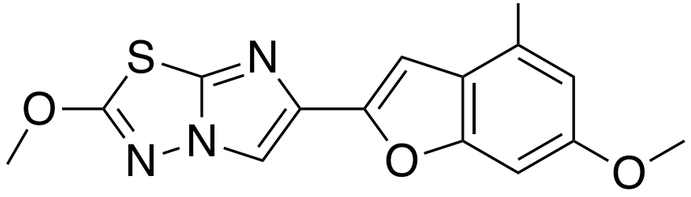
Clinical Development. Preclinical compound

Patent. Leo Pharma has filed a patent application that describes a series of IL-17A modulators (WO2020127685A1) to treat dermal diseases.

BMS-986120

PAR4





oral PAR4 antagonist

Ph. II completed in thrombosis (discontinued)

HTS, potency, and PK opt.

J. Med. Chem.

Bristol-Myers Squibb, Princeton, NJ

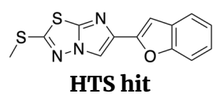
featured article: doi.org/10.1021/acs.jmedchem.2c00359

Context. BMS-986120, (BMS) is an oral protease-activated receptor 4 (PAR4) inhibitor that was being developed for arterial thrombosis. PAR4 was long considered a redundant "backup" receptor to the more popular and well-researched PAR1 receptor, owing in part to the higher thrombin levels required for activation and the slower signaling response the receptor induces. However, a new hypothesis, also espoused by BMS scientists in developing BMS-986120, suggests that targeting PAR4 may offer an improved window between antithrombotic efficacy and bleeding time due to its signaling kinetics. Given its role in sustained thrombin signaling, blocking PAR4 is expected to preclude unwanted stable thrombus growth, while transient signaling through PAR1 is left untouched to preserve initial thrombus formation. Preclinical data seem to lend support to this theory, with a marked improvement in therapeutic window observed, when compared to the widely used standard clopidogrel. Should these successes continue during clinical development, which is currently ongoing for BMS–986141, the backup to BMS-986120, the resulting drug will likely be a valuable addition to the antiplatelet therapy space, particularly since the only approved PAR inhibitor, vorapaxar (Zontivity), has a black box warning due to high bleeding risk.

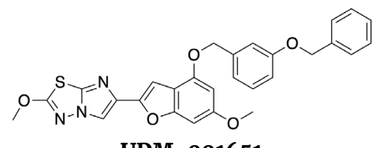
Target. PAR4 is the most recently discovered member of the PAR family of G-protein-coupled receptors and is highly expressed on platelets. The receptor is activated by thrombin, which mediates processes such as blood coagulation, inflammation, and wound healing. In a mouse model of thrombosis, PAR4 was found to be essential for platelet thrombus propagation, while inhibition of the protein in another study was found to protect against myocardial ischemia. Unlike PAR1, which is also abundantly expressed on platelets and responds to subnanomolar thrombin concentrations, PAR4 requires ~10 fold more thrombin for activation, a feature BMS scientists, and others focusing on PAR4, believe makes the protein a superior antithrombotic target with regards to the window between efficacy and bleeding time.

Mechanism of Action. Thrombin activates human platelets through proteolysis of the *N*-terminus of PAR1 and PAR4 to expose a new *N*-terminus, which serves as a "tethered peptide ligand"; the ligand then self-activates the receptor through intramolecular binding, effecting transmembrane signaling. Although both receptors are activated through this mechanism, each interacts with thrombin distinctly, which affects the rates of proteolysis. This differing kinetics allows the fine-tuning of thrombin signaling in platelets where PAR1 activation results in a rapid transient signal, whereas activation of PAR4 causes prolonged signaling. Therefore, blocking sustained thrombin signaling through PAR4 as done with BMS-986120 and BMS-986141 may limit thrombosis but allow transient signaling through PAR1 to continue to maintain homeostasis as well as limit bleeding.

Hit-Finding Strategy. An HTS screen, using a calcium mobilization assay (PAR4 fluorescent imaging plate reader (FLIPR)), identified an imidazothiadiazole-containing hit (PAR4 IC_{50} = 11 nM). Initial optimization of the hit resulted in UDM-001651 (PAR4 IC_{50} = 2.4 nM), a potent, selective, and orally bioavailable tool compound.



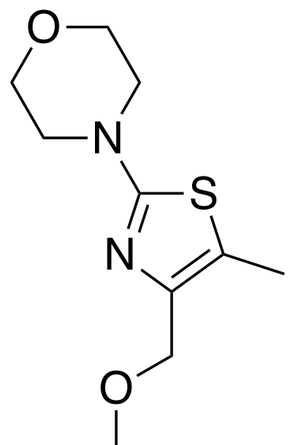
HTS hit
(IC_{50} = 11 nM)



UDM-001651
(IC_{50} = 2.4 nM)

BMS-986120

PAR4



oral PAR4 antagonist

Ph. II completed in thrombosis (discontinued)

HTS, potency, and PK opt.

J. Med. Chem.

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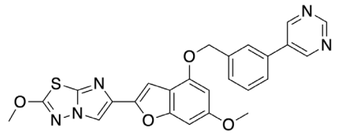
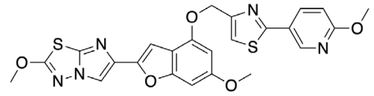
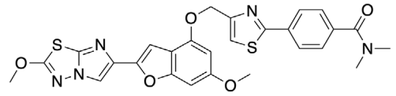
Lead Optimization. Lead optimization focused exclusively on the bis-benzyloxy substituent in UDM-001651, with a focus on hydrophobic substituents at the meta position. "Compound 3" was an important early hit (IC_{50} = 1.1 nM) but suffered from low microsome stability. Replacement of a benzylic ether with a thiazole ring resulted in improved metabolic stability while maintaining potency ("compound 20", IC_{50} = 0.8 nM) but introduced CYP3A4 liabilities (IC_{50} = 0.1 µM). However, further exploration of the thiazole ring resulted in the morpholinothiazole seen in BMS-986120 (IC_{50} = 0.4 nM) and the para-linked *N,N*-dimethylamide, BMS-986141 (IC_{50} = 0.4 nM), which had nearly identical potency.



compound 3
(IC_{50} = 1.1 nM)



compound 20
(IC_{50} = 0.8 nM)



BMS-986141
(IC_{50} = 0.4 nM)

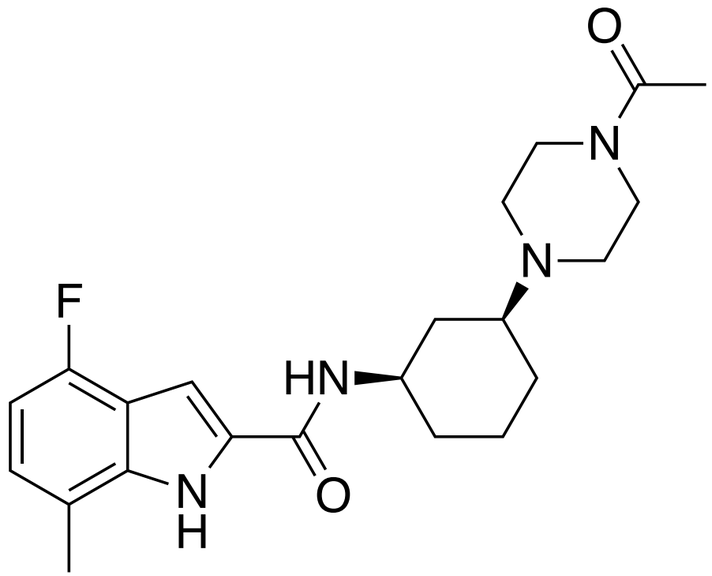
Preclinical Pharmacology. An electrolytic-mediated carotid arterial thrombosis (ECAT) model was used in cynomolgus monkeys to evaluate the antithrombotic efficacy of both molecules vs. the standard arterial thrombosis treatment clopidogrel. BMS-986120 was dosed at 0.2, 0.5, and 1 mg/kg, BMS-986141 at 0.05, 0.1, and 0.5 mg/kg, and clopidogrel at 0.1, 0.3, 1, and 3 mg/kg; all compounds were dosed orally. Following treatment with the three compounds, an 8 mg carotid artery thrombus in the vehicle group was reduced to below 2 mg, suggesting strong antithrombotic efficacy. At 0.5 mg/kg, BMS-986141 demonstrated close to full efficacy compared with BMS-986120 at 1 mg/kg. Bleeding time was assessed using the cynomolgus monkey kidney bleeding time model. A dose-dependent prolongation of bleeding time was seen, with animals dosed with clopidogrel experiencing the longest bleeding times (>1000 s for the 1 and 3 mg/kg doses).

Clinical Development. BMS-986120 has completed two Ph. I studies in healthy subjects, one to determine tolerability, pharmacokinetics, pharmacodynamics, and gene variant effects in humans, and one to examine ex vivo thrombus formation in a human model (NCT02208882, NCT02439190). BMS-986120 was tolerated as a single oral dose up to 180 mg PO and in multiple doses up to 100 mg for 14 days, and no difference in PAR4-mediated platelet response was observed in those with AA120 versus TT120 PAR4 variants. BMS-986120 reduced total thrombus area significantly compared to aspirin alone, or in combination with clopidogrel at high shear, but not at low shear stress.

Patent. An imidazothiadiazole and imidazopyrazine derivatives series for treating platelet aggregation was patented by the Universite de Montreal and Bristol Myers Squibb (US9688695B2).

EZM0414

SETD2



oral SETD2 Inhibitor

Ph. I candidate in oncology

in-house library screening and SBDD

ACS Med. Chem. Lett.

Epizyme Inc., Cambridge, MA

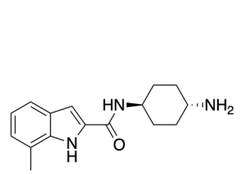
featured article: doi.org/10.1021/acsmedchemlett.2c00167

Context. EZM0414 (Epizyme, Inc.) is an oral SETD2 inhibitor being developed for hematological malignancies. Although several genetic studies have proposed that the histone methyltransferase SETD2 is a tumor suppressor in solid cancers, inhibition of the enzyme may be desirable in some hematological malignancies such as leukemia and lymphoma. In particular, certain mutations in multiple myeloma (MM) and diffuse large B-cell lymphoma (DLBCL) that result in dysregulation of histone H3 lysine 36 (H3K36) methylation are thought to be key to tumorigenesis in these malignancies. The FDA recently granted Fast Track Status to EZM0414, which is currently being evaluated in a Ph I study. Epizyme, and with it EZM0414, was recently acquired by Ipsen as part of a $247 million deal that also included the acquisition of the approved first-in-class EZH2 inhibitor tazemetostat (Tazverik).

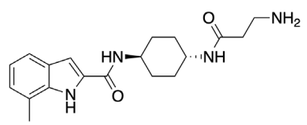
Target. SETD2 is a lysine *N*-methyltransferase that mediates cellular processes such as transcriptional elongation and regulation, alternative RNA splicing, and DNA damage repair. The protein catalyzes the methylation of dimethylated H3K36 (H3K36me2) to the trimethylated form H3K36me3. It is the only known enzyme that catalyzes the trimethylation of H3K36. SETD2 has been studied widely as a tumor suppressor, and loss of function of the enzyme has most often been associated with solid malignancies such as renal carcinoma and thyroid cancer. However, other studies, have suggested that SETD2 may be required for the proliferation of hematological malignancies such as leukemia, lymphoma, and multiple myeloma.

Mechanism of Action. Epizyme scientists posit that inhibiting SETD2 could be desirable in B-cell malignancies where dysregulation of H3K36 methylation is key for tumorigenesis. These include DLBCL, where histone H1 mutations are prevalent, as well as high-risk MM containing the t(4;14) chromosomal translocation. In t(4;14) MM, the translocation results in high expression of NSD2, another histone methyltransferase responsible for H3K36me1 and H3K36me2 synthesis, which overall leads to the accumulation of both histones. Since H3K36me2 is the substrate for SETD2, inhibiting the enzyme is hypothesized to lead to inhibition of tumor growth in t(4;14) MM. If true, it would establish proof of concept for targeting the protein in other B cell malignancies with perturbed H3K36 methylation.

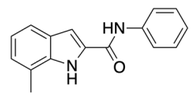
Hit-Finding Strategy. A screening campaign of the Epizyme library against SETD2 using a radiometric assay that monitored histone methylation, identified a series of hits containing a 2-amidoindole core. X-ray analysis of hit "2" showed that it resided within the enzyme's peptide binding site, and the 7-methylindole occupies part of the lysine channel where H3K36 is methylated by S-adenosylmethionine (SAM). Initial SAR optimization found that fluorine substitution on the indole was well tolerated, with substitution at the 4-position having the highest activity. Subsequent optimization of physicochemical and DMPK properties focused compounds related to HTS hit "4", as efforts using other series proved difficult. Ultimately, it was found that meta-substitution on the arene provided the best activity, leading to "compound 24" as a lead molecule.



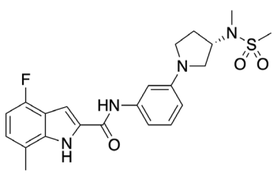
HTS hit 1
(IC_{50} = 166 µM)



HTS hit 2
(IC_{50} = 22.1 µM)



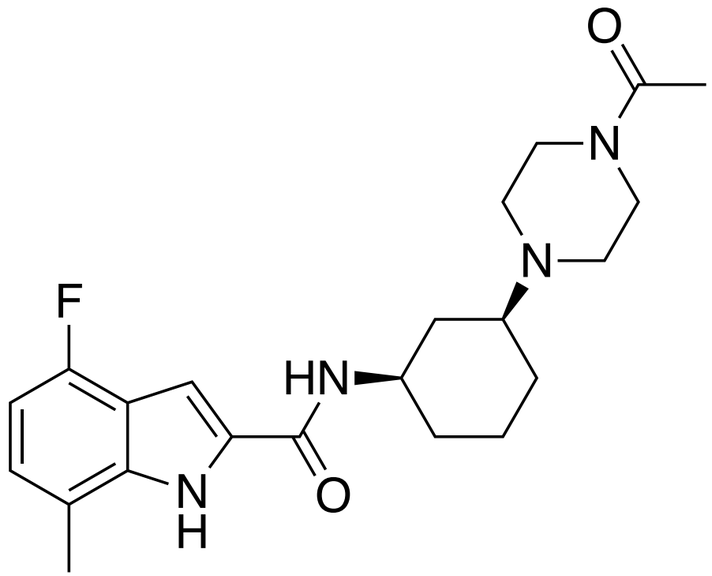
HTS hit 4
(IC_{50} = 4.25 µM)



compound 24
(IC_{50} = 0.012 µM)

EZM0414

SETD2



oral SETD2 Inhibitor

Ph. I candidate in oncology

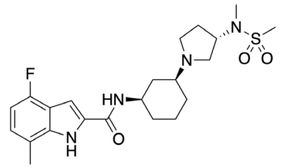
in-house library screening and SBDD

ACS Med. Chem. Lett.

Epizyme Inc., Cambridge, MA

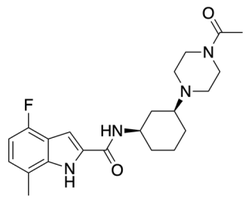
featured article: doi.org/10.1021/acsmedchemlett.2c00167

Lead Optimization. Lead optimization focused on addressing the high lipophilicity and potential metabolism-derived toxicities of "compound 24". Switching the central aromatic ring back to the saturated system seen in hits "1" and "2" improved these properties, leading to EPZ-719. Analogs containing a cis-cyclohexane were prioritized, as they were predicted to mimic the planar aromatic ring found in the earlier hits. This was supported by molecular dynamics simulations that indicated the 1,3-cis-cyclohexane would have minimal 1,3-diaxial strain compared with the 1,3-trans-cyclohexane. Furthermore, molecular modeling predicted that the cis-isomer would better fit into the ligand pocket and stabilize the Tyr1671 residue in an "out" position via a hydrophobic interaction. A final set of optimizations led to a series of piperazine analogs and ultimately to EZM0414 as their clinical candidate.



EPZ-719
(IC_{50} = 0.008 µM)

equatorial vs. axial configurations



EZM0414
(IC_{50} = 0.018 µM)

Binding mode: The x-ray structure (PDB:7TY2) revealed that the indole moiety is located deep within the lysine pocket. H-bonds can be observed between the indole nitrogen, the oxygen of the amide group, and Phe1606 residue.

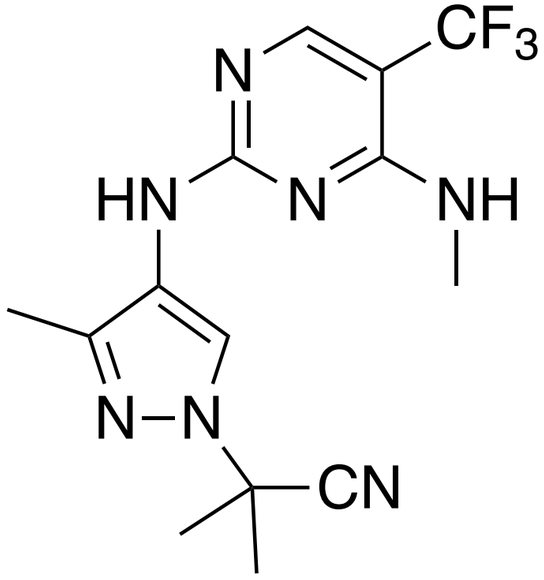
Preclinical Pharmacology. In vitro safety testing of the compound in a 47-target panel and another panel comprising 72 kinases showed IC_{50} >25 µM for all targets, with the exception of dopamine D2 (IC_{50} = 13.0 µM, antagonist) and 5-HT1B (IC_{50} = 3.2 µM, agonist). NOD SCID mice implanted with human MM KMS-11 cells were used for in vivo efficacy studies. Daily dosing of the animals at 15 and 30 mg/kg BID led to 60% and 90% reductions in tumor growth, respectively.

Clinical Development. EZM0414 has progressed through IND-enabling studies and is currently recruiting for a Ph. I clinical trial (NCT05121103). This study will evaluate the safety, tolerability, pharmacokinetics, efficacy, MTD, DLT, and RP2D in subjects with relapsed/refractory MM and DLBCL. The dose-expansion study will be executed with six dose levels: 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg.

Patent. Epizyme described their substituted indoles series and methods of use to treat cancer in a patent published in 2019 (WO2020037079A1).

DNL201

LRRK2



oral LRRK2 kinase inhibitor

Ph. I completed in Parkinson's Disease

HTS, SBDD, and CNS-focused opt.

Sci. Transl. Med.

Denali Therapeutics Inc., South San Francisco, CA

featured article: doi.org/10.1126/scitranslmed.abj2658

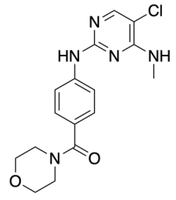
drug hunter

Context. DNL201 (Denali Therapeutics) is an oral, CNS-penetrating, ATP-competitive leucine-rich repeat kinase 2 (LRRK2) inhibitor being developed for Parkinson's disease (PD). PD remains incurable; current treatment options only alleviate disease symptoms and do not prevent progression. Due to its well known involvement in familial and even sporadic/idiopathic PD, LRRK2, particularly the G2019S variant, has been a hotly pursued target in the last decade, with at least a dozen promising agents having been reported (e.g., Merck's MLi-2 and "compound 24" which we have previously featured). However, clinical advancement of these molecules has been hampered by concerns about potential lung toxicity. Although a previous preclinical study evaluating pulmonary toxicity in macaques seemed to validate these concerns, data provided by Denali scientists in the current publication, which includes clinical data, seem to allay these concerns. DNL201 is being developed together with another LRRK2 inhibitor DNL151 (BIIB122; Biogen/Denali), which is currently undergoing Ph. II evaluation. With the safety and efficacy observed for DNL201 in Ph. I studies (NCT04551534), the compound is expected to enter advanced clinical development shortly. These potential first-in-class agents present uncommon case studies of selective brain-penetrating kinase inhibitors outside of cancer, and offer the best chance to test the LRRK2 hypothesis in PD so far.

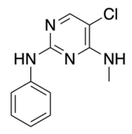
Target. LRRK2, widely expressed in many body organs and tissues, including the brain, is a large multidomain scaffolding protein containing ankyrin, leucine-rich, and WD40 repeats, as well as a catalytic region with Ras/GTPase and serine-threonine kinase activities. Since LRRK2 mutations were first implicated in the 2000s as one of the most common genetic risk factors for Parkinson's disease pathogenesis and progression, the gene has been studied preclinically as a drug target. The G2019S LRRK2 mutation is the one of the most common variants, with a prevalence of up to 42%, depending on the population, but perhaps more interestingly, it seems to show Mendelian genetics. Additionally, genetic studies have shown that common noncoding variants at the LRRK2 locus are associated with an increased risk for Parkinson's disease. Increased LRRK2 activity has also been found in patients with other genetic forms of Parkinson's disease as well as in those with sporadic non-familial disease.

Mechanism of Action. The G2019S mutation is associated with increased kinase activity, resulting in sustained phosphorylation of downstream substrates that ultimately impact membrane trafficking and lysosomal function. Other mutations have been associated with decreased GTPase activity of the protein. Like most LRRK2 inhibitors in development, DNL201 targets the kinase activity of the enzyme to improve membrane trafficking and lysosomal function.

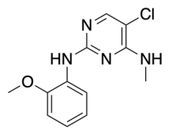
Hit-Finding Strategy. "Compound 1" was first reported by a group at Genentech following a biochemical LRRK2 high-throughput screening assay. However, the potential for kinase selectivity was a concern, as the diaminopyrimidine moiety is well-established in the kinase inhibition literature. Using homology modeling and ATP-binding site analysis, a series of phenyl diaminopyrimidines were synthesized to probe the Leu1949 selectivity pocket. Substitution on the aniline ring showed that high selectivity (vs. JAK2) could be obtained while reducing molecular weight and TPSA, giving properties consistent with CNS penetration. However, removal of the morpholino amide did result in a 2-fold loss in potency against LRRK2 ("compounds 9" and "11"). Adding the morpholino amide back ultimately provided the lead structure, "compound 19".



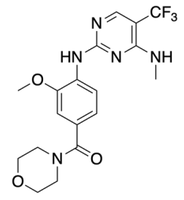
compound 1
(K_i = 6 nM)



compound 9
(LRRK2 K_i = 11 nM
JAK2 K_i = 64 nM)



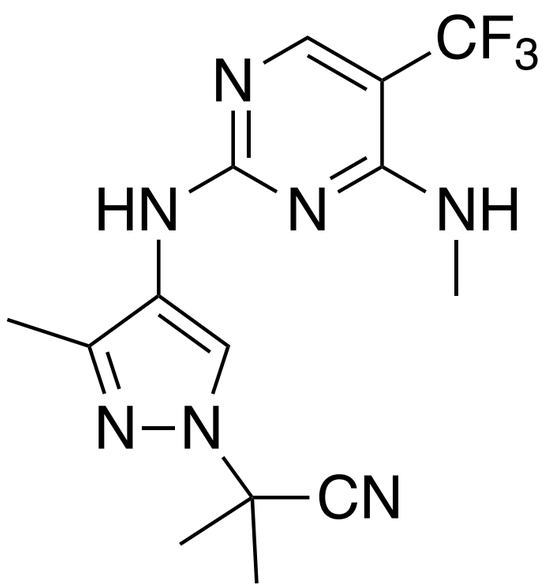
compound 11
(LRRK2 K_i = 6 nM
JAK2 K_i = >3.2 µM)



compound 19
(LRRK2 K_i = 1 nM
JAK2 K_i = >3.2 µM)

DNL201

LRRK2



oral LRRK2 kinase inhibitor

Ph. I completed in Parkinson's Disease

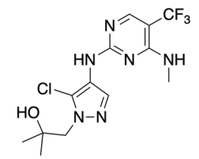
HTS, SBDD, and CNS-focused opt.

Sci. Transl. Med.

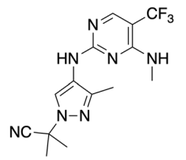
Denali Therapeutics Inc., South San Francisco, CA

featured article: doi.org/10.1126/scitranslmed.abj2658

Lead Optimization. In an effort to further reduce molecular size, improve aqueous solubility, and remove the potential for reactive metabolites via ortho-quinoneimine formation, a series of aminopyrazoles was investigated. "Compound 18" displayed excellent brain penetration and stability, as well as acceptable clearance and oral bioavailability. A docking overlay using "compound 18" helped rationalize the final modifications that led to DNL201. The exchange of the chlorine atom for a methyl group and the hydroxyl for a nitrile group significantly improved human hepatocyte stability, rat free brain exposure, CYP inhibition, and induction liabilities. The resulting molecule has a remarkably simple structure for a kinase inhibitor clinical candidate.



compound 18
(LRRK2 K_i = 9 nM)



DNL201
(LRRK2 K_i = 0.7 nM)

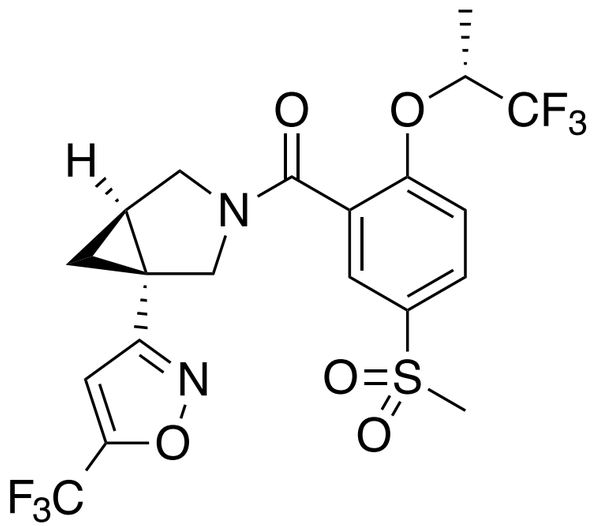
Preclinical Pharmacology. Animal experiments were conducted in rodent and macaques models and assessed the restoration of lysosomal function, inhibition of LRRK2 activity in the PNS and CNS, secretion of a marker of LRRK2 activity (bis[monoacylglycerol] phosphate; BMP) in urine and kidneys, and overall safety. One hour following oral dosing of the compound at 3, 10, 30, or 60 mg/kg in rats, dose-dependent inhibition of LRRK2 activity was seen, which translated into an unbound IC_{50} of 52 nM in brain tissue. Treatment with the compound, in human H4 neuroglioma cells, also significantly restored lysosome size and morphology to those in controls expressing wild-type LRRK2, while lysosomal protein degradation was significantly normalized to wild-type levels. Safety was evaluated over a 39-week period. DNL201 dosed at 16 mg/kg BID over the period was well-tolerated and with a C_{max} of around 7.33 µM/hour. Due to concerns about pulmonary toxicity of LRRK2 kinase inhibitors, safety assessments in lung tissues of cynomolgus macaques treated with the molecule were done. Consistent with a previous preclinical study, microscopic lung changes consisting of type II pneumocytes were seen; however, these were found in the current study to be non-adverse and reversible.

Clinical Development. DNL201 has completed two Ph. I clinical trials. A Ph. I study (NCT04551534) was directed to study the safety, tolerability, and PK/PD in healthy volunteers, wherein single ascending and multiple-dose regimens tested up to 100 mg PO BID. No serious adverse effects were reported, and at the highest tested doses, DNL201 inhibited LRRK2 by 90% and 50% at peak and trough blood concentrations. Furthermore, the CSF-to-unbound plasma ratio of 1.0 ± 0.13 in elderly volunteers receiving 80 mg of DNL201 BID, suggests a high level of brain exposure. The second Ph. I study (NCT03710707) investigated the safety, tolerability, and PK/PD of multiple oral doses in subjects with Parkinson's disease with a 30 and 50 mg PO TID dose regimen for 28 days. At the highest dose, more than 50% LRRK2 inhibition was reported, although a higher incidence of mild or moderate adverse events was observed. Evidence of impact on lysosomal function was noticed based on a dose-dependent reduction in urinary BMP concentration in both healthy volunteers and patients with the disease.

Patent. Denali Therapeutics' novel heteroaryl-substituted pyrimidines inhibitors of LRRK2 to treat Parkinson's disease were described in patent US9932325B2, granted with expiration in 2037.

Iclepertin

GlyT1



oral GlyT1 inhibitor

Ph. III candidate in schizophrenia

10 and 25 mg PO QD efficacy in CIAS improv.

J. Pharmacol. Exp. Ther.

Boehringer Ingelheim Pharma, Biberach an der Riss, DE

featured article: doi.org/10.1124/jpet.121.001071

drug hunter

Context. Iclepertin (BI 425809; Boehringer Ingelheim) is an oral glycine transporter-1 (GlyT1) inhibitor being developed for cognitive impairment associated with schizophrenia (CIAS). The ineffectiveness of currently available antipsychotic medications in improving negative symptoms and cognitive deficits leaves a significant unmet need for patients with CIAS. Based on the glutamate *N*-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis, several agents have been explored to reverse deficits in sensory processing and improve cognition in these patients. Notably, the transporter GlyT1, which depletes extracellular glycine, has been actively pursued. None have survived clinical development, however, with the most notable being ex-Roche agent bitopertin, which was discontinued following poor efficacy in two Ph. III studies (the molecule is currently being developed by Disc Medicine for rare genetic disorders). Iclepertin has already achieved success in a Ph. II study while several Ph. III studies are underway, and it will be interesting to see if the potential first-in-class drug can succeed in a new indication after bitopertin's past disappointments.

Target. GlyT1 is one of two transporters that control the extracellular levels of glycine in the brain, glial cells, and neuronal pre- and post-synaptic sites of NMDA synapses. NMDA plays a pivotal role in cognition and sensory processing by providing excitatory input to GABA inhibitory neurons, which contributes to the generation of gamma oscillations in cortical regions, and plays a role in working memory and cognitive function. The finding that NMDA receptor antagonists induced schizophrenic symptoms in humans led to the coining of the NMDA receptor hypofunction hypothesis. Since endogenous glycine and its precursor D-serine are co-agonists at the NMDA receptors, GlyT1, which controls the transport of glycine, was proposed as an ideal target for schizophrenia treatment. In support of the theory, schizophrenia animal model experiments with GlyT1 inhibitors have observed improved cognitive performance.

Mechanism of Action. Activation of NMDA receptors is associated with increased intracellular calcium levels, which activates several downstream signaling pathways involved in the regulation of several physiological processes. GlyT1 inhibitors increase extracellular and hence synaptic glycine levels, which enhances NMDA receptor function and ultimately improves cognitive performance in schizophrenia.

Hit-Finding Strategy. Not described

Lead Optimization. Not described

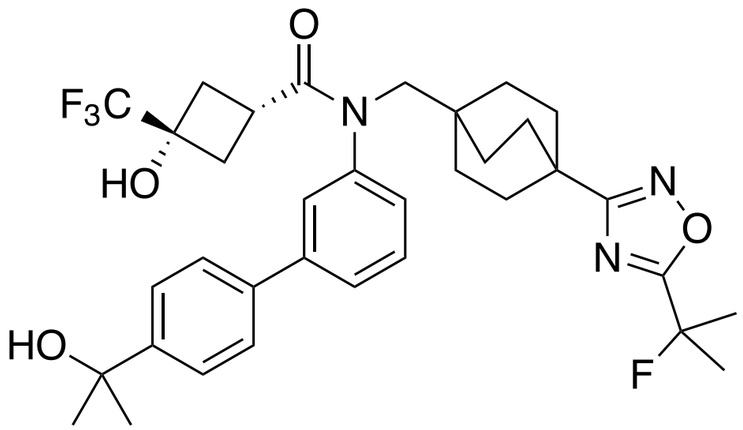
Preclinical Pharmacology. Efficacy studies evaluated iclepertin's ability to reverse MK-801 (NMDA antagonist)-induced deficiencies in auditory sensory processing and cortical network function as measured using electroencephalography in male C57BL/6JRj mice, as well as its improvement of spatial memory performance in MK-801-treated male CD-1 mice, which was measured via the T-maze spontaneous alternation test. Iclepertin was associated with significant ($P < 0.05$) reversal of MK-801-induced deficits as measured by the auditory event-related potentials readouts N1 amplitude and N1 gating at all tested doses (0.3, 1, and 4 mg/kg); overall, this translated into an IC_{50} on GlyT1 of 5.2 nM. For reversal of memory deficits, treatment with the molecule at 0.5-4.5 mg/kg significantly improved or reversed ($P < 0.05$) a previous MK-801-induced reduction in spontaneous alternation. The molecule also demonstrated favorable PK in male Han Wistar rats dosed at 2.6 mg/kg, with a C_{max} of 1010 nM and T_{max} of 1.67 h.

Clinical Development. Iclepertin has completed several Ph. I and II clinical trials and is now being tested in a Ph. III trial to treat the cognitive impairment associated with schizophrenia in the Connex trials (Connex-1 NCT04846868, Connex-2 NCT04846881, Connex-3 NCT04860830, Connex-X long term safety study NCT05211947). As previously reported in the Ph. II study, doses of 10 mg and 25 mg PO QD significantly improved the cognition in patients with schizophrenia showing the largest statistical separation from placebo after 12 weeks of treatment. Thus, Boehringer Ingelheim is planning a dosing regimen of 10 mg PO QD to be randomized between placebo and intervention arm in the Ph. III Connex studies.

Patent. The Boehringer Ingelheim International patent US9012489B2 describes substituted phenyl-3-aza-bicyclo[3.1.0]hex-3-yl-methanones series of glycine transporter-1 inhibitors useful for the treatment of schizophrenia, Alzheimer's Disease, and other neurological and psychiatric disorders.

BMS-986339

FXR



oral nonbile acid FXR agonist

FGF15 induction in a BDL mouse model

SBDD

J. Med. Chem.

Biocon-Bristol Myers Squibb Research and Development Center, Bangalore, IN

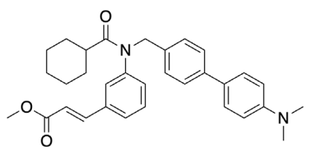
featured article: https://doi.org/10.1021/acs.jmedchem.2c00165

Context. BMS-986339 (BMS) is an oral farnesoid X receptor (FXR) agonist being developed for nonalcoholic steatohepatitis (NASH). Considered the master regulator of bile acid homeostasis, the nuclear receptor FXR may be an attractive target for diseases such as NASH, where bile acid dysregulation has been implicated. Currently, the only approved FXR agonist is Intercept's bile acid-derived Obeticholic acid (Ocaliva), which is yet to be indicated for NASH, likely due to safety concerns; however, the company recently announced positive results from a Ph. III study. Other FXR agonists in clinical development include Novartis' tropifexor (LJN452) and Gilead's cilofexor, both of which are non-bile acid-derived. This is an interesting approach to indirectly treat the liver via influencing bile acid homeostasis in the intestines. A previous lead agent, BMS-986318 has activity in both tissues and was withdrawn from a planned Ph. I study. BMS scientists believe this differentiated pharmacological profile may be the key to a better safety profile.

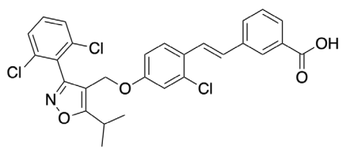
Target. FXR, a nuclear receptor expressed highly in the liver and intestines, controls bile acid synthesis, transport, and detoxification. Since dysregulation of bile acid synthesis plays a role in several debilitating diseases such as NASH, targeting the protein may be an ideal therapeutic strategy. FXR knockout mice have been found to be hypercholesterolemic due to increased HDL cholesterol levels. Further, in transgenic apolipoprotein-A-I (apoA-I) mice, activation of FXR reduced total HDL cholesterol levels and decreased total cholesterol, while activators of FXR were negative regulators of apoA-I. In a clinical study, 45% of patients with NASH who received the endogenous bile acid derivative obeticholic acid had improved liver histology vs. 21% who received a placebo.

Mechanism of Action. In the liver, FXR suppresses lipogenesis and promotes the oxidation of fatty acids. Activation of the protein also represses bile synthesis and promotes its accelerated excretion and detoxification. In the intestines, activation of the receptor increases the expression of the gut hormone fibroblast growth factor 19 (FGF19), ultimately suppressing bile acid synthesis. BMS-986339 selectively differentiates itself from other known agonists in development due to the tissue-specificity of its pharmacological profile (i.e., poor activity in the liver vs. intestines), a property BMS scientists theorize could reduce undesirable effects such as pruritus associated with other anti-FXR agents.

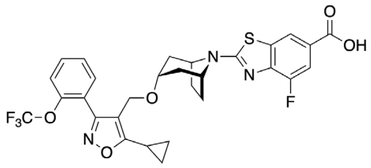
Hit-Finding Strategy. A multipronged approach to hit-finding was used, including HTS, fragment-based drug design, and pharmacophore modeling (using previously disclosed FXR agonists, such as fexaramine, GW4064, and tropifexor). X-ray analysis revealed a hydrophobic barrel-shaped pocket that provided an opportunity to replace the phenyl linker with moieties that increased the hydrophobic volume and potentially improved potency. Pharmacophore modeling ultimately led to a series of compounds containing phenyl isosteric motifs, with [2.2.2]bicyclooctane the most potent, giving "compound 8" as the primary lead.



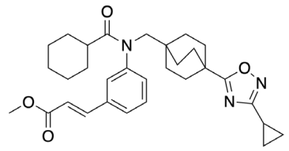
fexaramine



GW064



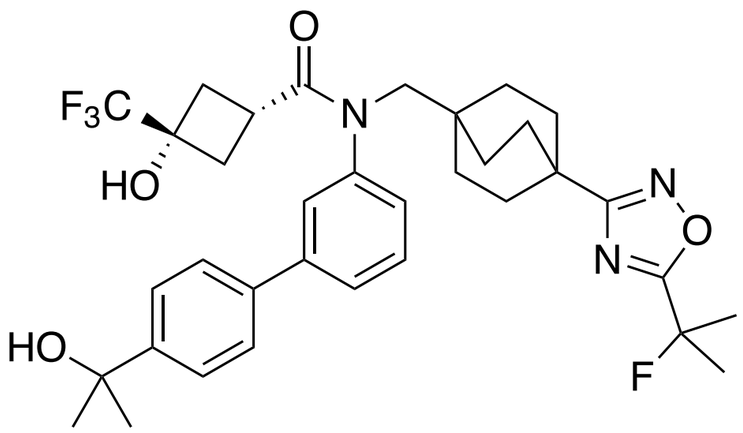
tropifexor



compound 8
(EC_{50} = 27 nM)

BMS-986339

FXR



oral nonbile acid FXR agonist

FGF15 induction in a BDL mouse model

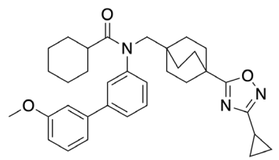
SBDD

J. Med. Chem.

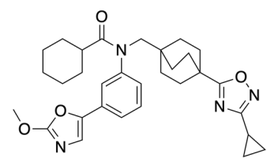
Biocon-Bristol Myers Squibb Research and Development Center, Bangalore, IN

featured article: https://doi.org/10.1021/acs.jmedchem.2c00165

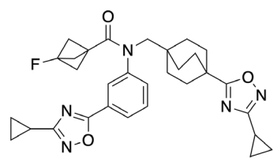
Lead Optimization. Optimization began with the replacement of the α,β-unsaturated ester in "compound 8" with suitably substituted aryl rings, such that interactions of the protein with the ester methoxy group would be maintained. Initially, a 3-fold drop in potency was observed with a methoxy-substituted aryl ring (ex., "compound 9'). However, potency was regained when 5-membered heteroaryl rings were introduced (ex., "compound 14'). Not only did this improve potency, but it offered the potential for improved PK properties, lower ClogP, and better aqueous solubility. Further optimization focused on metabolic stability, specifically that of the cyclohexyl moiety, ultimately leading to "compound 21". A final round of optimization to balance potency and in vitro liabilities, including PXR transactivation, and CYP_{2C9} inhibition, led to BMS-986399.



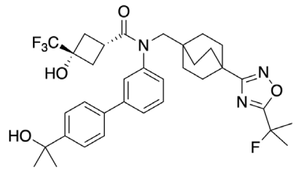
compound 9
(EC_{50} = 92 nM)



compound 14
(EC_{50} = 25 nM)



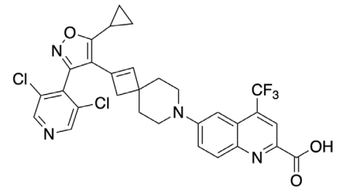
compound 21
(EC_{50} = 93 nM)



BMS-986399
(EC_{50} = 34 nM)

Binding mode: A co-crystal structure of BMS-986339 with the hFXR revealed that it binds in a hydrophobic pocket (**PDB:7TRB**), similar to other inhibitors, and highlights the importance of H-bond interactions between the hydroxyl and carbonyl groups with Asn287 and His298, as well as an edge-to-face pi-stacking interaction of oxadiazole ring with Trp458.

Preclinical Pharmacology. In vivo experiments were conducted in a mouse bile duct ligation model, with dosing at 0.3, 1, 3, and 10 mg/kg for 9 days. At 10 mg/kg, both BMS-986339 and a previous lead, BMS-986318, used as a positive control, induced Fgf15 (mouse FGF19 homolog) expression to a similar extent in the intestine; however, BMS-986339 was ~50-fold less efficacious in the liver. FXR is known to positively regulate the expression of tumor suppressors involved in gastrointestinal and liver cancers, so having this differential activity is welcomed.



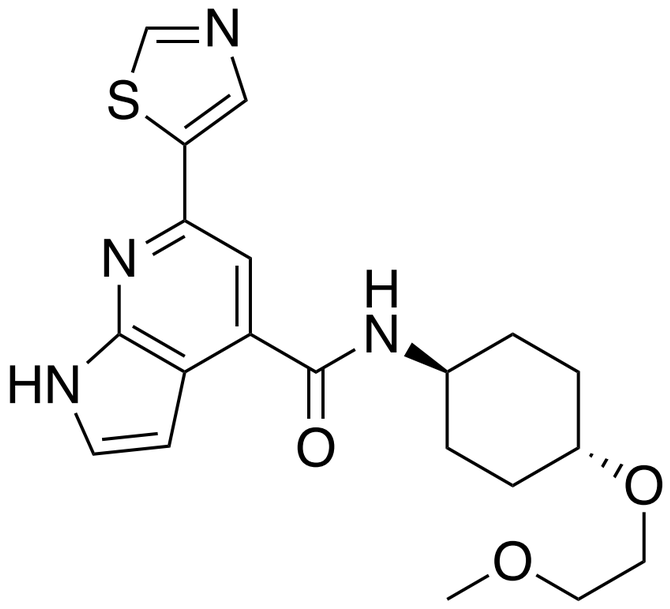
BMS-986318
(EC_{50} = 53 nM)

Clinical Development. Preclinical compound

Patent. Bristol Myers Squibb has described a series of substituted bicyclic compounds as farnesoid X receptor modulators in patent US11254663B2.

MK-0159

CD38



oral CD38 inhibitor

in vivo efficacy in a murine model of cardiac I/R

from the previously disclosed inhibitor CD38i

J. Med. Chem.

Mitobridge (an Astellas Company), Cambridge, MA

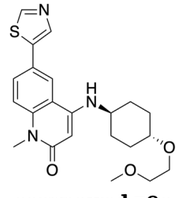
featured article: https://doi.org/10.1021/acs.jmedchem.2c00688

Context. MK-0159 (Mitobridge) is an oral CD38 inhibitor being developed for cardiovascular diseases. Due to its $NADP^+$ depleting activity, which has implications for calcium homeostasis, the cell surface marker CD38 has attracted attention as a suitable target for developing cardiovascular disease agents. Although two monoclonal antibodies targeting CD38 (daratumumab and isatuximab) have been approved, both for cancer indications, the search for the first small molecule CD38 inhibitor is still ongoing. MK-0159 demonstrated potent activity against human CD38 enzymes (IC_{50} = 22 nM) while it significantly increased blood and heart NAD^+ levels. Furthermore, it protected treated mice from cardiac ischemia/reperfusion injury, making the compound the first to demonstrate in vivo cardioprotective effects in a mouse cardiac ischemia/reperfusion injury model.

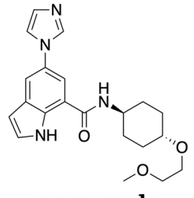
Target. In addition to its role as a cell surface marker, CD38 also has both ADP-ribosyl cyclase and $NADP^+$ hydrolase activities, allowing the enzyme to deplete NAD^+ and $NADP^+$ levels in non-hematopoietic tissues where it is widely expressed. Interest in the protein as a suitable cardiovascular disease target stems from numerous studies that have observed an association between its upregulation and certain cardiac disorders. Depletion of its substrates has been associated with cardiac ischemia/reperfusion injury and other cardiac disorders, while CD38 knockout mice had reduced arrhythmia through a reduction of spontaneous calcium release in cardiomyocytes.

Mechanism of Action. CD38 catalyzes the generation of the second messengers adenosine diphosphate ribose (ADPR), cyclic ADPR, and nicotinic acid adenine dinucleotide phosphate, which stimulate the synthesis of cellular Ca^{2+}, a key mediator of cardiac excitation-contraction coupling as well as contraction-relaxation of vascular smooth muscles. MK-0159 targets the $NADP^+$ hydrolase activity of the enzyme.

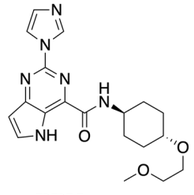
Hit-Finding Strategy. Evaluation of the known CD38 inhibitors, "compound 78c" and "compound 2" (first reported by GSK), led Mitobridge scientists to reason that the indole seen in "compound 2" might serve in a similar binding capacity to the qunolin-2-one ring of 78c, and that, given the relative similarity of these two compounds, it might be possible to replace the indole moiety with some other heterocycle to generate a new inhibitor with improved properties. Ribon Therapeutics published a patent detailing RBN013209, which may have been derived using similar rationale. However, there was a lack of SAR data in these reports that necessitated the design and synthesis of new analogs to fully understand the structural requirements needed in a potent and selective inhibitor.



compound 78c



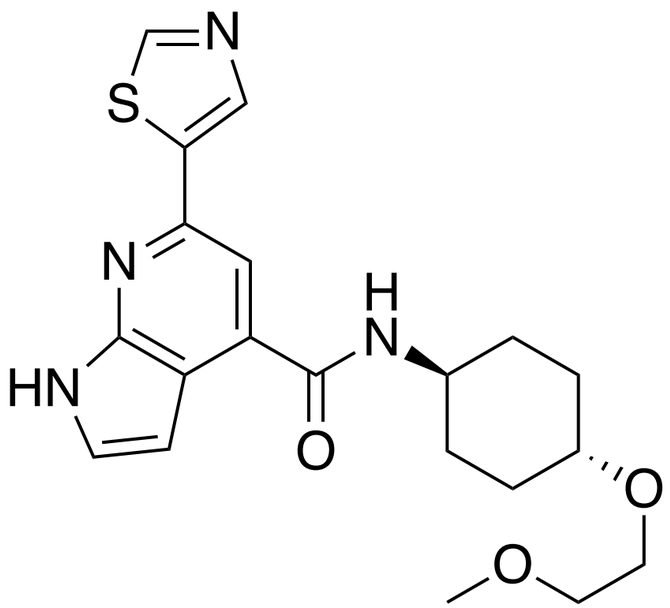
compound 2



RBN013209

MK-0159

CD38



oral CD38 inhibitor

in vivo efficacy in a murine model of cardiac I/R

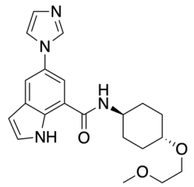
from the previously disclosed inhibitor CD38i

J. Med. Chem.

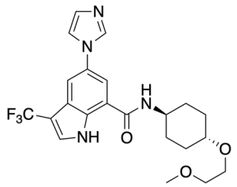
Mitobridge (an Astellas Company), Cambridge, MA

featured article: https://doi.org/10.1021/acs.jmedchem.2c00688

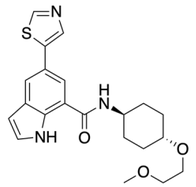
Lead Optimization. Optimization first introduced electron-withdrawing substituents at the 3-position of the indole ring, leading to a slight improvement in potency (compound 6). Concern that the imidazole at the 5-position might lead to CYP450 activity, a series of analogs were investigated using heteroaromatic moieties other than azoles. Surprisingly, replacement of the imidazole with anything other than the thiazole in compound 21 resulted in severe loss of activity. Finally, in an attempt to improve plasma exposure (AUC, h*ng/mL) and oral bioavailability, a series of indole analogs were designed, ultimately leading to MK-0159.



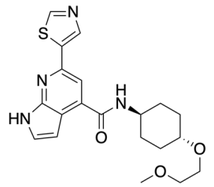
compound 2
(IC_{50} = 60 nM)



compound 6
(IC_{50} = 41 nM)



compound 21
(IC_{50} = 13 nM
AUC = 7,375)



MK-0159
(IC_{50} = 22 nM
AUC = 10,410)

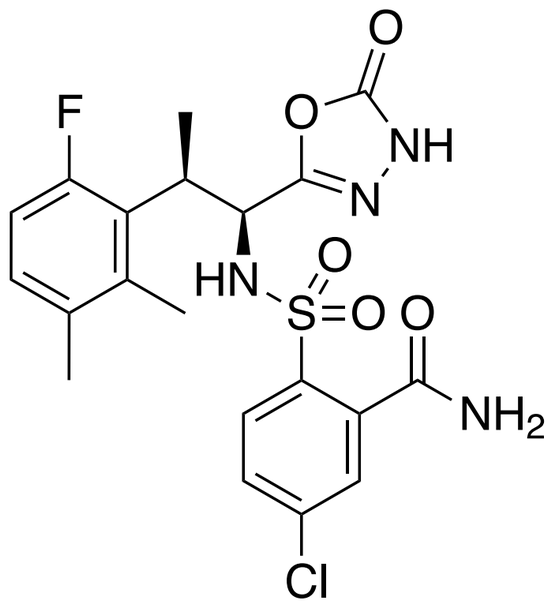
Preclinical Pharmacology. Oral administration of the molecule in a cardiac ischemia/reperfusion mouse model at 3, 10, and 30 mg/kg was associated with a significant (>2-fold) increase in NAD^+ levels in the blood and a ~1.4-fold increase in the heart (30 mg/kg dose), with significant concomitant decreases in ADPR levels in the blood (EC_{50} = 40 nM) and heart (EC_{50} = 181 nM) at all doses. Mice treated with MK-0159 alone or combined with an NAD^+ precursor prior to induction of ischemia had a significantly reduced infarct size, although similar tissue areas were at risk for an infarction by all animals.

Clinical Development. Preclinical compound

Patent. CD38 inhibitors were described in patent application WO2021207186A1 assigned to Mitobridge, Inc.

TAS1553

RNR



oral RNR subunit interaction inhibitor

Ph. I candidate in oncology

HTS and SBDD

Commun. Biol.

Taiho Pharmaceutical Co., Ltd., Tsukuba, JP

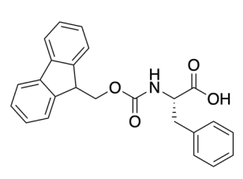
featured article: https://doi.org/10.1038/s42003-022-03516-4

Context. TAS1553 (Taiho Pharmaceutical) is an oral ribonucleotide reductase (RNR) inhibitor with antitumor activity. As the enzyme that catalyzes the rate-limiting step for deoxyribonucleotide triphosphate (dNTP) synthesis in cells, RNR has long been of interest to anticancer drug discovery efforts, especially since unlimited dNTP supply is key to one the most recognized hallmarks of cancer: uncontrolled proliferation. Currently, the 5 FDA-approved RNR inhibitors target either the large catalytic R1 subunit (gemcitabine, clofarabine, cladribine, fludarabine; all nucleoside analogs) or the small free radical-containing R2 subunit (hydroxyurea) of the protein, with these inhibitors showing negligible cross-reactivity between the subunits. The novel TAS1553 differentiates itself from these and other reported agents by targeting the R1-R2 protein-protein interaction (IC_{50} = 9.22 ± 1.40 µmol/L). Since the compound doesn't target either the free radical or substrate binding sites, Taiho scientists believe it will be associated with less off-target effects vs. current agents. Whether this theory holds may be revealed in the near future as the molecule is currently in early clinical development (Ph. I).

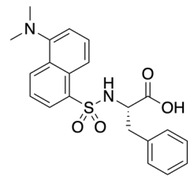
Target. RNR is a highly expressed multisubunit enzyme that catalyzes the rate-limiting step for de novo dNTP production. The protein comprises 2 subunits (α and β) which are also referred to as R1 (or B1) and R2 (or B2), respectively. The activity of the enzyme is regulated tightly through control of the expression of the R2 subunit. In mice, overexpression of the R2 subunit was associated with tumorigenesis and progression. In clinical samples, the expression of the enzyme is upregulated in tumor vs. normal tissues, while its expression is also associated with poor prognosis.

Mechanism of Action. The enzyme catalyzes the reduction of nucleotide diphosphate to deoxyribonucleotide diphosphate which is subsequently converted to dNTP by a kinase. Agents that target the protein are typically radical scavengers such as hydroxyurea, iron chelators such as triapine, and nucleoside analogs such as the popular cancer treatment gemcitabine. TAS1553 is believed to disrupt the RNR's R1-R2 protein-protein interaction, leading to identification of the non-nucleoside analogue TAS1553. The molecule was found to deplete cellular deoxy-ATP (dATP) pools, then induce replication stress, subsequently triggering apoptosis in tumors.

Hit-Finding Strategy. A high-throughput fluorescence polarization (FP) binding assay using R1 and fluorescently labeled P7 heptapeptide (*N*-AcFTLDADF) was used to screen a small, focused library of various amino acid derivatives, based on a report that Fmoc-L-Phe competes with P7 for binding to R1. The screen confirmed that Fmoc-L-Phe and similar amino acids, such as Dansyl-L-Phe, had a weak but concentration-dependent inhibitory activity.



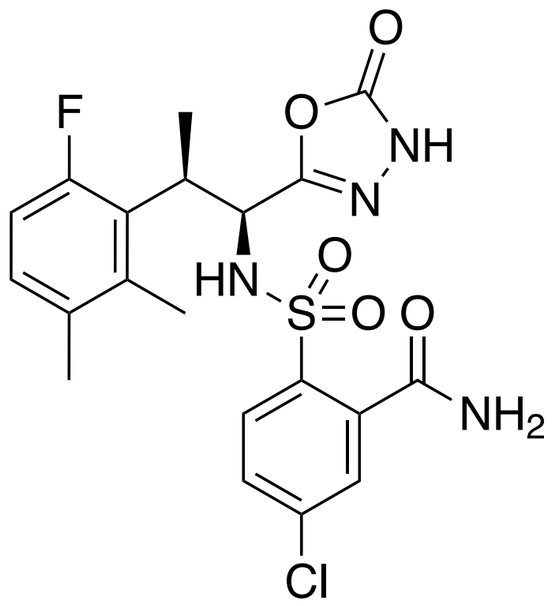
Fmoc-L-Phe



Dansyl-L-Phe

TAS1553

RNR



oral RNR subunit interaction inhibitor

Ph. I candidate in oncology

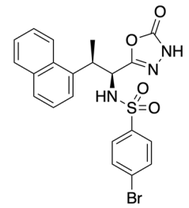
HTS and SBDD

Commun. Biol.

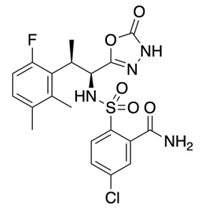
Taiho Pharmaceutical Co., Ltd., Tsukuba, JP

featured article: https://doi.org/10.1038/s42003-022-03516-4

Lead Optimization. A medicinal chemistry effort that focused on improving the binding, enzymatic, and cellular activity led to the discovery of "compound 1", a unique β-methyl-α-amino acid derivative. Analysis of the X-ray cocrystal structure of "compound 1" with R1 allowed for structure-based lead optimization. Several highly potent nanomolar inhibitors were identified through lead optimization (details undisclosed). Exchange of the bromine for chlorine and addition of an amide moiety on the phenylsulfonamide and replacement of the naphthalene ring with a 6-fluoro-2,3-dimethylbenzene resulted in the preclinical candidate TAS1553.



compound 1
(IC_{50} = 0.527 µM)



TAS1553
(IC_{50} = 0.054 µM)

Binding mode: X-ray cocrystal structure was solved for a TAS1553 analogue and early lead molecule "compound 1" and hRRM1 (**PDB:6L3R**). The crystal structure showed that this compound binds similarly to the P7 peptide, being accommodated in the *C* terminus R2 binding site at R1.

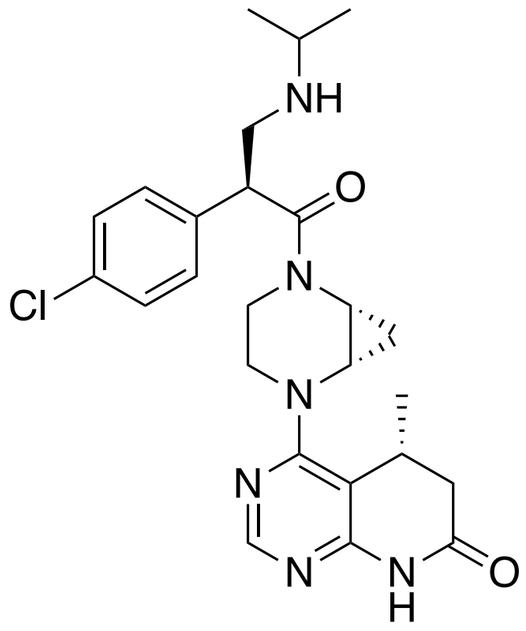
Preclinical Pharmacology. In MV-4-11 xenograft mice dosed 50 and 200 mg/kg of the molecule, both doses resulted in a significant ~3-fold reduction in intratumor dATP levels after 1 h, although the levels recovered after 4 h. At 50, 100, and 200 mg/kg, the percent reduction of mean tumor volume vs controls following QD dosing for 14 days was 52, 45, and 29%, respectively. These antitumor properties of TAS1553 was also observed in solid tumor models. Further, in an acute myeloid leukemia mice model, the molecule dosed at 100 mg/kg significantly increased survival time by ~20 days, corresponding to a ~38% lifespan increase.

Clinical Development. TAS1553 is currently being evaluated in a first-in-human Ph. I clinical study (NCT04637009) in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) and other myeloid neoplasms.

Patent. The Taiho Pharmaceutical novel sulfonamide series having ribonucleotide reductase inhibitory activity for solid tumors and blood cancers treatments were covered in patents US20200157066A1 and WO2017209155A1.

NTQ1062

Akt



oral Akt inhibitor

Ph. I in advanced solid tumors

scaffold hopping and PK opt.

J. Med. Chem.

Nanjing Chia-Tai Tianqing Pharmaceutical Co., Ltd., Nanjing, CN

featured article: https://doi.org/10.1021/acs.jmedchem.2c00527

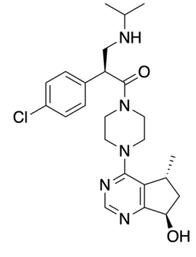
Context. NTQ1062 (Nanjing Chia-Tai Tianqing; CTTQ) is an oral ATP-competitive Akt inhibitor being developed for cancer. Because the PI3K/Akt/mTOR pathway is one of the most commonly disrupted pathways in cancer, inhibitors targeting one or more of the three kinases have been hotly pursued. To date, five PI3K and three mTOR inhibitors have been approved, but favorable PK and safety data have hindered the approval of an Akt inhibitor for cancer. The compound, which is currently being evaluated in a Ph. I study in China (CTR20211999), joins a select list of Akt inhibitors being evaluated in various stages of clinical development. It remains to be seen whether the promising preclinical data will translate into decent efficacy and safety in patients.

Editor Commentary. This is an interesting example of a 2,5-diazabicyclo[4.1.0]heptane in a clinical candidate. To our knowledge, it is the first compound containing this moiety to advance to the clinical stage, although there have been a couple of other reports in the primary literature detailing their use in drug discovery.

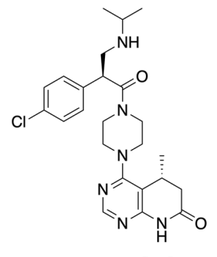
Target. The serine/threonine kinase Akt, which plays a key role in the P13K/Akt/mTOR signaling pathway, is an extensively validated cancer target. Overactivation of the oncogene has been associated with multiple cancers.

Mechanism of Action. Known Akt inhibitors either bind to the allosteric site or compete for binding to the ATP site of the kinase. The ATP-competitive inhibitor NTQ1062 was found to exert its antiproliferative activity through induction of apoptosis and G_0-G_1 cell cycle arrest.

Lead Generation Strategy. The Genentech drug GDC-0068, developed in collaboration with Array BioPharma, already in Ph. III trials (NCT04060862), was used as a starting point in a campaign to enhance the potency further and improve the PK profile of novel Akt inhibitors. A scaffold hopping strategy, using conformational constraints, was used to target specific features of the ATP binding pocket in Akt. This led to the identification of "compound 4b"; however, its less than optimal PK properties required further optimization.



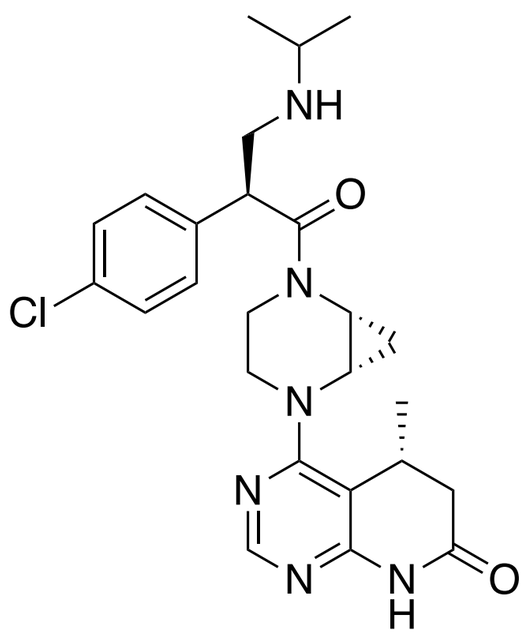
GDC-0068
(Akt1/2/3 IC_{50} = 3.8/48/22 nM)



compound 4b
(Akt1/2/3 IC_{50} = 1.6/24/0.3 nM)

NTQ1062

Akt



oral Akt inhibitor

Ph. I in advanced solid tumors

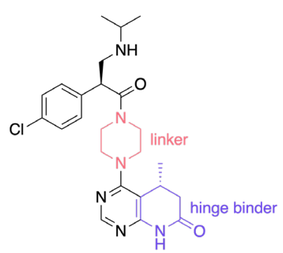
scaffold hopping and PK opt.

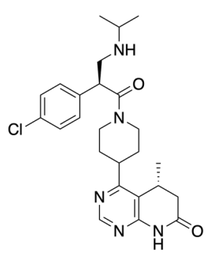
J. Med. Chem.

Nanjing Chia-Tai Tianqing Pharmaceutical Co., Ltd
Nanjing, CN

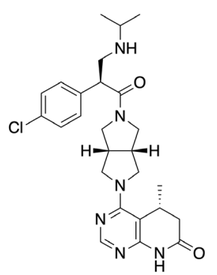
featured article: https://doi.org/10.1021/acs.jmedchem.2c00527

Lead Optimization. Optimization centered on trying to block the metabolically labile sites of "compound 4b". Initial modifications within the hinge-binding region proved fruitless, as substitution of the methyl group with a trifluoromethyl, modification of its stereochemistry, or changing its position from 5 to 6 led to compounds with lower inhibitory potency. Attention was then focused on the linker region. It was quickly determined that the both nitrogens of the piperazine were critical, as removal of even one of them significantly reduced the potency (ex., "compound 12"). Furthermore, if the linker length was expanded beyond that of piperazine (ex., "compound 13"), potency dropped as well. Metabolic lability was finally addressed by adding methyl groups, or making bridged piperazines, with the fused piperazine of "compound 22b" (NTQ1062) giving the best results.

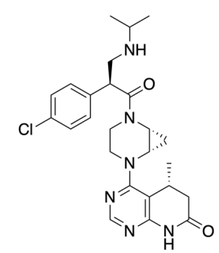




compound 12
(Akt1/2/3
IC_{50} = >1000/>1000/0.1 nM)



compound 13
(Akt1/2/3
IC_{50} = 285/167/6.6 nM)



NTQ1062
(Akt1/2/3
IC_{50} = 0.4/6.3/0.1 nM)

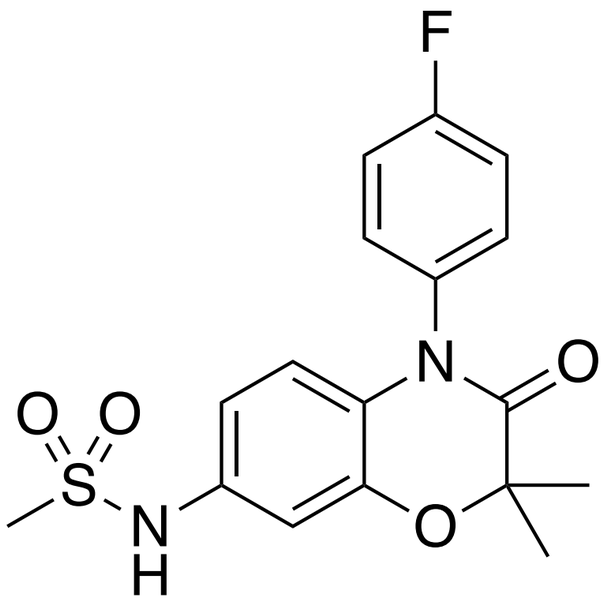
Preclinical Pharmacology. Selectivity of the compound was assessed against 185 kinases spanning 7 families. Inhibition of more than 90% mediated by the compound was seen with only 4 kinases, all in the AGC family. In vivo experiments were done in a LNCaP prostate xenograft tumor mice model. Dosed at 12.5, 25, and 50 mg/kg, the molecule was associated with tumor growth inhibition of 58.4%, 84.1%, and 95.5%. The molecule also had a favorable toxicity profile in animals.

Clinical Development. NTQ1062 is currently being assessed in a Ph. I study for the treatment of advanced solid tumors in China (CTR20211999).

Patent. In the patent US20220144821A1 assigned to Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd were described Akt inhibitors series for the treatment of a disease mediated by this kinase.

Apararenone

MR



oral nonsteroidal MR antagonist

Ph. II candidate in DN and NASH (discontinued)

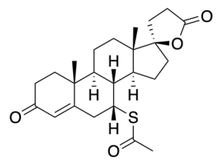
previous literature and hypothesis-driven opt.

J. Med. Chem.

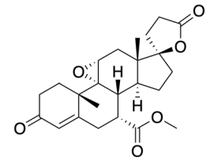
Mitsubishi Tanabe Pharma Corporation, Yokohama, JP

featured article: https://doi.org/10.1021/acs.jmedchem.2c00402

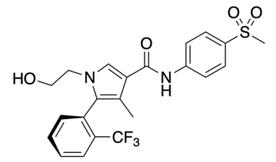
Context. Apararenone (Mitsubishi Tanabe) is an oral nonsteroidal mineralocorticoid receptor (MR) antagonist. Agents with the ability to modulate the nuclear receptor MR have been pursued for at least 80 years. Spironolactone, the first-in-class MR (steroidal) antagonist, was approved in 1960, with the more selective eplerenone (also steroidal) being approved in 2002, 42 years later. Since steroidal MR antagonists (MRAs) are known to distribute primarily to the kidneys and have been associated with an increased risk of hyperkalemia, attention has shifted to nonsteroidal MR antagonists. Research efforts in this regard culminated in the approval of the first nonsteroidal MR antagonist finerenone (Kerendia) for CKD associated with type 2 diabetes in 2021. Another agent, Sankyo's esaxerenone, is approved in Japan for hypertension and diabetic nephropathies. Apararenone was designed based on the interesting hypothesis that T-shaped compounds with one polar functionality flanking a hydrophobic core structure, along with a bulky middle substituent, could act as an MRA. Although positive results were reported in a recently completed Ph. II study in patients with diabetic nephropathy and NASH, the compound appears to have been discontinued by Mitsubishi Tanabe.



spironolactone



eplerenone

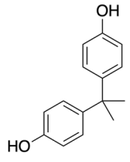


esaxerenone

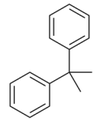
Target. The MR is a nuclear receptor family member that acts as a ligand-activated transcription factor. Hyperactivation of the receptor by aldosterone and cortisol has been observed in several disorders such as cardiovascular disease, kidney disease, nonalcoholic steatohepatitis (NASH), fibrosis, inflammation, and type 2 diabetes.

Mechanism of Action. MR antagonists are either steroidal or nonsteroidal. The inhibitors act by blocking the action of aldosterone, thus reversing the overactivation of the receptor, which ultimately results in decreased sodium reabsorption in the kidneys, heart, and blood vessels.

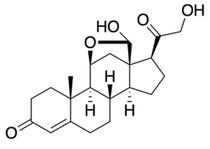
Hit-Finding Strategy. Using their hypothesis as a guide, Mitsubishi Tanabe scientists evaluated the known estrogen receptor (ER) agonist bisphenol A and 2,2-diphenylpropane as the hydrophobic core structure. Additionally, the X-ray structure of MR with aldosterone (**PDB:2AA2**) indicated the 3-keto functionality engages in a hydrogen bonding interaction with Gln776, Arg817, and Ser810 via a water molecule, while the 18- and 21-hydroxy groups participate in a hydrogen bonding interaction with Asn770, Cys942, and Thr945, suggesting that these residues may be important to engage. SAR studies using 2,2-diphenylpropane as a core led to the installation of a sulfonamide and the initial lead "compound 2".



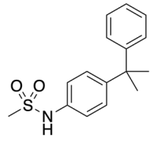
bisphenol A



2,2-diphenylpropane



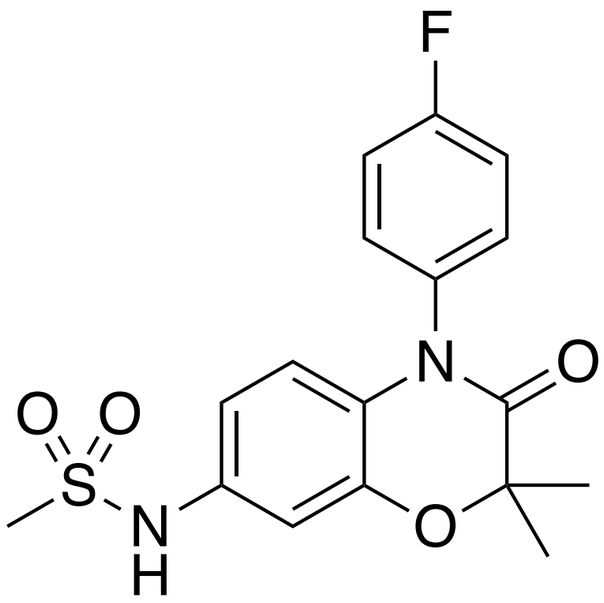
aldosterone



compound 2
hMR binding
(K_i = 0.74 μM)

Apararenone

MR



oral nonsteroidal MR antagonist

Ph. II candidate in DN and NASH (discontinued)

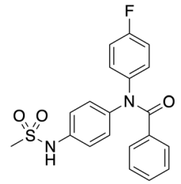
previous literature and hypothesis-driven opt.

J. Med. Chem.

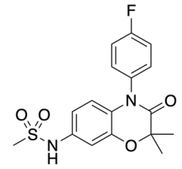
Mitsubishi Tanabe Pharma Corporation, Yokohama, JP

featured article: https://doi.org/10.1021/acs.jmedchem.2c00402

Lead Optimization. Lead optimization began with the replacement of the 2,2-diphenylpropane with diphenylamine since derivatization and optimization for MR binding are more straightforward. SAR studies conducted with these derivatives found that a 4-fluoro substituent on the phenyl ring, coupled with the introduction of an amide moiety, provided the best results ("compound 15"). Further SAR studies focused on determining how to best employ the amide to maximize the interaction between the compound and MR. Cyclization to the 1,4-benzoxazin-3-one proved highly advantageous and ultimately delivered apararenone.



compound 15
hMR binding
(K_i = 0.611 µM)



apararenone
hMR binding
(K_i = 0.104 µM)

Preclinical Pharmacology. To investigate the anti-aldosterone effect of the compound, adrenalectomized rats were first dosed orally with MT-3995 at 0.3, 1, 3, or 10 mg/kg or with the steroidal MR antagonist eplerenone at 1, 3, 10, or 30 mg/kg, followed by subcutaneous injection of aldosterone at 0.5 and 3 h. Significant reversal of the decrease in Na^+/K^+ ratio caused by MR overactivation was observed even at the lowest dose of the compound, translating to a potency that was ~10-fold more than that of eplerenone based on ED_{50} values (MT-3995, 1.1 mg/kg [95% CI 0.36 – 3.4]; eplerenone, 11 mg/kg [95% CI 3.5 – 34]). The compound was also found to significantly inhibit the progression of aldosterone-induced hypertension in rats.

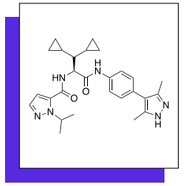
Clinical Development. Apararenone completed several Ph. I and II clinical trials for diabetic nephropathy and nonalcoholic steatohepatitis. Efficacy and long-term safety in patients with stage 2 diabetic nephropathy were assessed in two Ph. II trials (NCT02517320 and NCT02676401). The trial's primary and secondary endpoints were the 24-week percent change from baseline in urine albumin to creatine ratio and 24 and 52-week remission rates. The intervention arm received 2.5 mg, 5 mg, or 10 mg PO QD. The drug was well-tolerated, and urine albumin to creatine ratio significantly decreased to 62.9%, 50.8%, and 46.5% in the 2.5 mg, 5 mg, and 10 mg treatment arms after 24 weeks. The remission rates at this point were 7.8%, 29.0%, and 28.1% to apararenone 2.5 mg, 5 mg, and 10 mg groups. After 52 weeks, the percent reduction from baseline in urine albumin to creatine ratio was approximately 60% in apararenone 5 mg and 10 mg groups.

Apararenone was also investigated in patients with NASH (NCT02923154). The patients were randomized to receive 10 mg PO QD or placebo for 72 weeks. The trial primary endpoint was 24 weeks percent change in serum alanine aminotransferase (ALT) from baseline. The apararenone proved to be well tolerated at this dose regimen. The intervention group showed a higher percentage of change than the placebo group (-13.7% versus -3.0%) and improved multiple potential fibrosis markers. Furthermore, apararenone was previously studied for the treatment of hypertension, but development was halted. On July 26, 2021, Mitsubishi Tanabe communicated that development for DN and NASH was also discontinued, but provided no explanation.

Patent. Mitsubishi Tanabe Pharma mineralocorticoid receptor modulating agents were covered in the granted patent US7998956B2, with an expiration date of 2028-02-23.

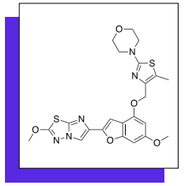
Small Molecules of the Month

June 2022
drughunter.com



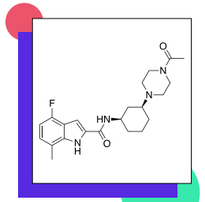
Compound 23 | IL-17A

oral interleukin 17A modulator
favorable in vivo PK profile in multiple species
from a previous patent and SBDD
J. Med. Chem.
LEO Pharma Research & Early Development, Ballerup, DK



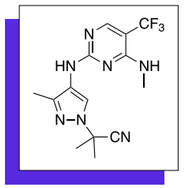
BMS-986120 | PAR4

oral PAR4 antagonist
Ph. II completed in thrombosis (discontinued)
HTS, potency, and PK opt.
J. Med. Chem.
Bristol-Myers Squibb, Princeton, NJ



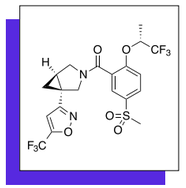
EZM0414 | SETD2

oral SETD2 Inhibitor
Ph. I candidate in oncology
in-house library screening and SBDD
ACS Med. Chem. Lett.
Epizyme Inc., Cambridge, MA



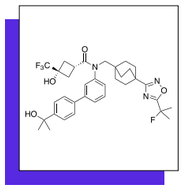
DNL201 | LRRK2

oral LRRK2 kinase inhibitor
Ph. I completed in Parkinson's Disease
HTS, SBDD, and CNS-focused opt.
Sci. Transl. Med.
Denali Therapeutics Inc., South San Francisco, CA



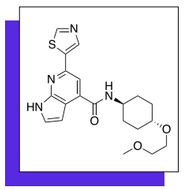
Iclepertin | GlyT1

oral GlyT1 inhibitor
Ph. III candidate in schizophrenia
10 and 25 mg PO QD efficacy in CIAS improv.
J. Pharmacol. Exp. Ther.
Boehringer Ingelheim Pharma, Biberach an der Riss, DE



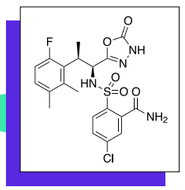
BMS-986339 | FXR

oral nonbile acid FXR agonist
FGF15 induction in a BDL mouse model
SBDD
J. Med. Chem.
Biocon-Bristol Myers Squibb Research and Development Center, Bangalore, IN



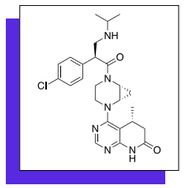
MK-0159 | CD38

oral CD38 inhibitor
in vivo efficacy in a murine model of cardiac I/R
from the previously disclosed inhibitor CD38i
J. Med. Chem.
Mitobridge (an Astellas Company), Cambridge, MA



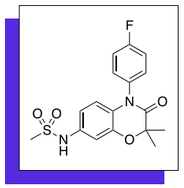
TAS1553 | RNR

oral RNR subunit interaction inhibitor
Ph. I candidate in oncology
HTS and SBDD
Commun. Biol.
Taiho Pharmaceutical Co., Ltd., Tsukuba, JP



NTQ1062 | Akt

oral Akt inhibitor
Ph. I in advanced solid tumors
scaffold hopping and PK opt.
J. Med. Chem.
Nanjing Chia-Tai Tianqing Pharmaceutical Co., Ltd., Nanjing, CN



Apararenone | MR

oral nonsteroidal MR antagonist
Ph. II candidate in DN and NASH (discontinued)
previous literature and hypothesis-driven opt.
J. Med. Chem.
Mitsubishi Tanabe Pharma Corporation, Yokohama, JP

drug hunter

drug hunter

discover together

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