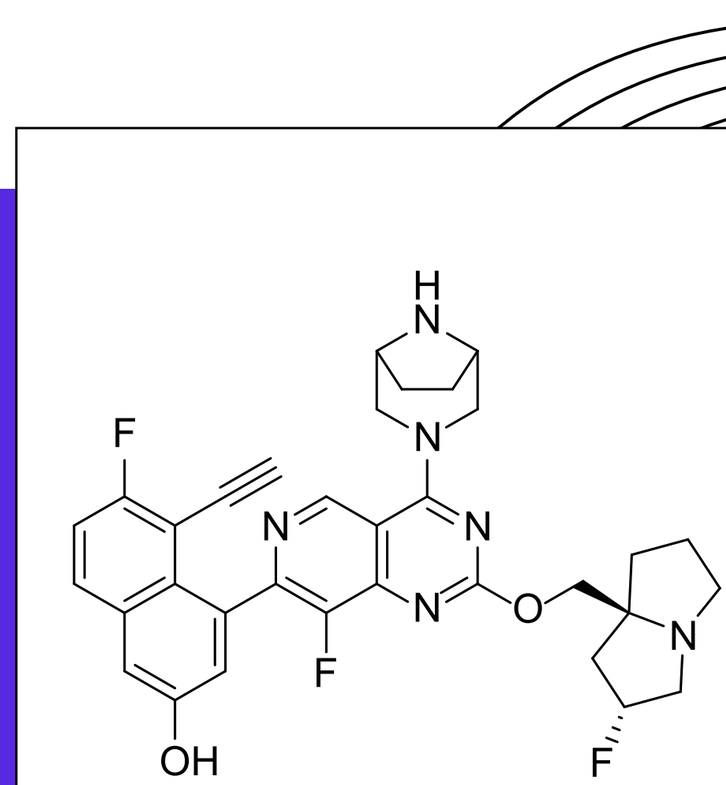
Small Molecules of the Month

December 2021

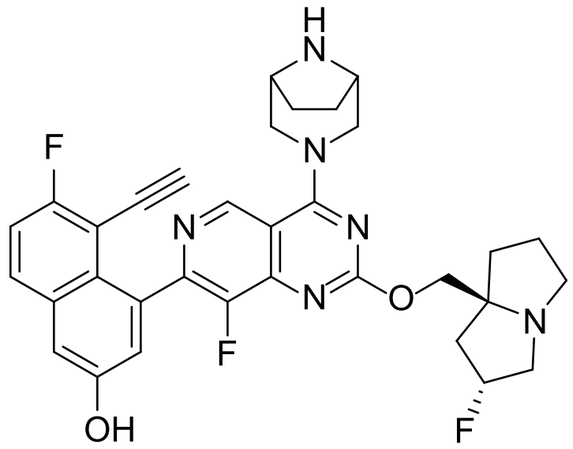


drug hunter

01	$KRAS^{G12D}$	Mirati Therapeutics
02	JNK2	Celgene (Bristol Myers Squibb)
03	HTT	PTC Therapeutics
04	TAAR1	Sunovion Pharmaceuticals
05	GR	AstraZeneca
06	ELOVL1	Vertex
07	RBP4	Takeda
08	ATR	Repare Therapeutics
09	URAT1	Jiangsu Hengrui Medicine Co.
10	JAK	GlaxoSmithKline
11	SGK1	Sanofi
12	Vanin-1	Pfizer
13	LRRK2	Merck & Co.
14	HPK1	Genentech

MRTX1133

Mirati KRAS^{G12D} Inhibitor



reversible KRAS^{G12D} inhibitor
preclinical efficacy in cancer model
from SBDD around KRAS^{G12C} inhibitor
Journal of Medicinal Chemistry
Mirati Therapeutics, San Diego, CA

MRTX1133 was nominated as December 2021's cover molecule by reviewers Joachim Rudolph and Julien Lefranc.

MRTX1133 is a non-covalent inhibitor of KRAS^{G12D} that demonstrated tumor regression in a mouse xenograft model when dosed IP (maximum efficacy at 10-30 mg/kg, activity as low as 3 mg/kg).

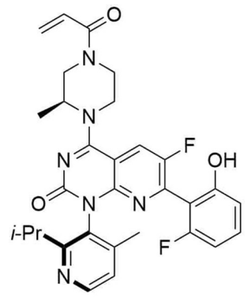
Joachim says, "The discovery of MRTX1133 deserves major credit as the first reported potent and selective non-covalent mutant-specific KRAS inhibitor especially as the targeted G12D mutant is the most prevalent KRAS mutant (33% among KRAS mutant tumors). The paper represents a successful continuation of the work on KRAS G12C inhibitors demonstrating suitability of the same binding site (switch II pocket) for mutants outside of G12C."

"This reflects, in retrospect, the power of covalent screening as an enabler of a stepwise progression from a covalent (G12C) to a corresponding non-covalent target (G12D). While not discussed in this paper, the dibasic nature of MRTX1133 likely compromises oral bioavailability, but following intraperitoneal dosing, the compound demonstrated exposure levels associated with robust PD and efficacy in a KRAS G12D mutant mouse xenograft model (Panc 04.03)."

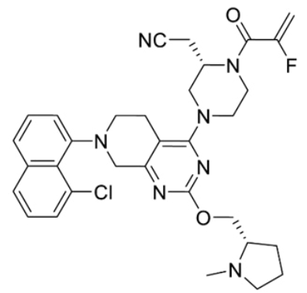
An oral KRAS^{G12D} would be of significant interest, given the clinical success of oral KRAS^{G12C} inhibitors sotorasib and adagrasib, but is technically challenging. While dibasic oral drugs exist, the potency requirements, size, overall properties of the molecule make this challenging. Mirati instead intends to leverage the long predicted human half-life of MRTX1133 (~50 hrs) and identify a long-acting injectable formulation. MRTX1133 remains pre-IND, with an IND planned for 2H 2022.

X-ray structures of analogues are available with PDB codes: 7RPZ, 7RT2, 7RT3, 7RT4, and 7RT5.

Sotorasib (AMG510):

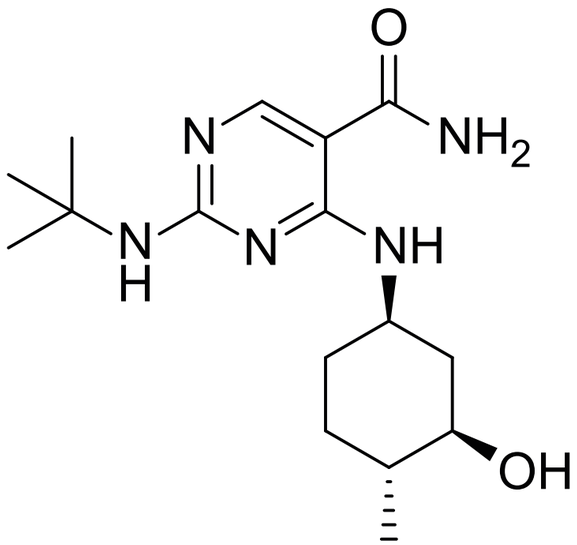


Adagrasib (MRTX849):



CC-90001

BMS c-Jun N-Terminal Kinase Inhibitor CC-90001



oral JNK2 kinase inhibitor
Ph. II candidate for pulmonary fibrosis
from HTS and SBDD
Journal of Medicinal Chemistry
Celgene (Bristol Myers Squibb), San Diego, CA

CC-90001 was nominated by reviewer Christian Kuttruff.

CC-90001 is a JNK (c-Jun N-Terminal Kinase) inhibitor and a Phase II clinical candidate for idiopathic pulmonary fibrosis (NCT03142191).

Christian says, “Preclinical evidence suggests that c-Jun N-terminal kinase (JNK) enzyme function is required for key steps in the pulmonary fibrotic process. Celgene had previously progressed tanzisertib (CC-930) into Phase 2 clinical trials for IPF but eventually stopped the compound because of the benefit/risk profile.”

“With CC-930 displaying a strong JNK2 potency (5 nM over 133 nM for JNK1) and with increasing evidence that JNK1 is the more important isoform to target for fibrotic diseases, the backup program aimed to identify JNK inhibitors with an increased JNK1 bias relative to CC-930. A high throughput screening campaign delivered a 2,4-(diarylamino)pyrimidine starting point showing equal biochemical potency for JNK1/JNK2 but relatively poor kinase selectivity.”

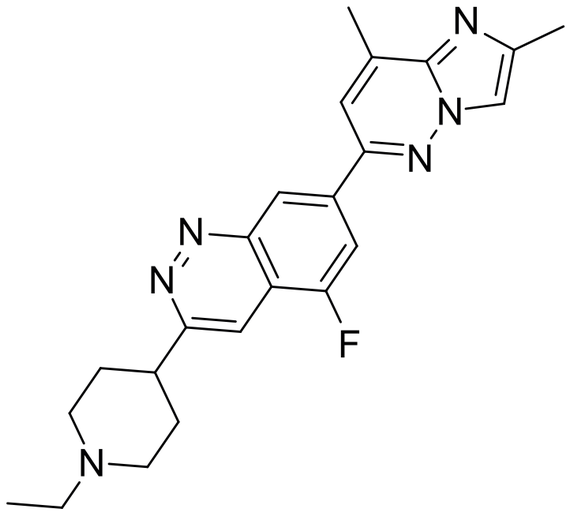
“Supported by crystal structure and SAR data from the tanzisertib program, replacement of the aryl rings with aliphatic moieties led to increased enzyme/cellular potency and improved kinome selectivity. Additional property guided optimization and PK profiling of best-best combinations revealed CC-90001 which not only demonstrated excellent in vivo PK and overall kinase selectivity but also showed >10-fold improvement in cellular JNK1 bias compared to CC-930.”

Though CC-90001 was advanced to Phase II and the trial remains active, CC-90001 is no longer listed in BMS’ pipeline.

PDB codes for relevant structures: tanzisertib (3TTI)

HTT-D3

PTC Therapeutics HTT-lowering splicing modifier



HTT splicing modulator

PD in Huntington's disease model

from HTS and optimization

Nature Communications

PTC Therapeutics, So. Plainfield, NJ

Mutated Huntingtin (HTT) protein is the cause of Huntington's disease (HD).

HTT-D3 is an oral, CNS-penetrant molecule with human HTT lowering activity in vivo used to illustrate the science around PTC Therapeutics' Huntington's disease program. PTC had filed patent applications for the HD program as early as November 2016 (WO201700726).

PTC has an oral, CNS-penetrant molecule for Huntington disease program in Phase II (PTC518). Initial data from the Phase I study showed HTT mRNA and protein lowering in human healthy volunteers as well as PTC518 exposure in the CNS.

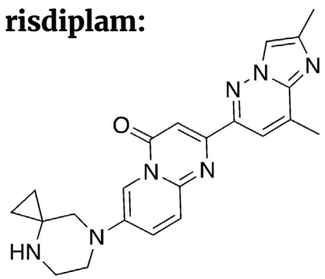
There are no approved disease-modifying treatments for HD, and emerging strategies targeting HTT such as RNAi and ASOs currently cannot penetrate the CNS without an invasive procedure. Treating Huntington's would likely require a drug that is active throughout the body, including the brain.

The molecule was discovered from PTC's splicing platform by screening ~300,000 diverse molecules, filtering out false-positives including Hsp90 inhibitors, and optimization. PTC is well-known for lead discovery for small molecule splicing modifiers, including in the discovery of approved spinal muscular atrophy drug, risdiplam.

The molecule promotes selective splicing of an inducible pseudoexon containing a premature stop codon (psiExon). This reduces mHTT mRNA and protein levels resulting in reduction of mHTT protein levels in the plasma and CSF of Hu97/18 mice.

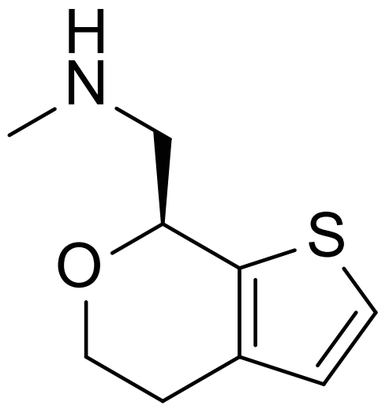
It is encouraging that a degree of systemic HTT reduction appears tolerated in healthy adults, though it is unclear what degree of splicing event selectivity was needed. While another reported compound, HTT-C2, appears to affect 165-215 splicing events, the splicing selectivity of HTT-D3 and PTC518 has not been published.

risdiplam:



ulotaront

Sunovion TAAR1



TAAR1 GPCR agonist
phase III candidate for schizophrenia
from in vivo phenotypic screening
ACS Medicinal Chemistry Letters
Sunovion Pharmaceuticals, Marlborough, MA

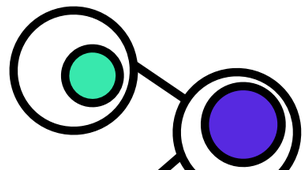
Ulotaront (SEP-363856) is a Phase III candidate with FDA Breakthrough Therapy Designation for the treatment of schizophrenia with demonstrated efficacy based on a physician-rated scale (PANSS) in a 4-week placebo-controlled trial and continued improvement in an open-label extension study.

Reviewer Jake Schwarz says, "ulotaront was developed in collaboration with Psychogenics using their SmartCube® [high-throughput phenotypic screening] technology. By way of background, Psychogenics characterized all marketed CNS drugs using a (proprietary) variety of stimuli in rodents and leveraged machine learning to develop a 'fingerprint' for each drug. Many companies partner with Psychogenics to get a sense of what conditions their novel MOA drugs might be able to treat. That ulotaront continues to progress is great news for patients with schizophrenia, as the road to effective antipsychotics is littered with failures."

The discovery of the drug is an interesting proof-of-concept for this target-agnostic approach in neuroscience, where pharmacology is notoriously hard to attribute to specific targets. Ulotaront turns out to be a TAAR1 GPCR agonist with 5-HT1A receptor activity, but this was not known at the outset. The TAAR family is a relatively new target class (discovered in 2001).

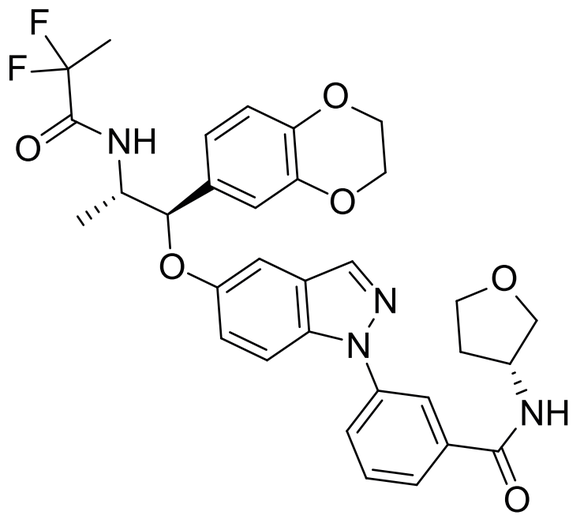
The 5HT1A activity may be relevant as buspirone (5HT1A agonist) is an anxiolytic. However, this agonist doesn't bind to the D2 or 5-HT2A receptors, which is the mechanism of action of second-generation, "atypical" antipsychotics like aripiprazole (Abilify).

It will be interesting to watch if this AI-driven, in vivo phenotypic drug discovery approach can be applied more broadly.



velsecorat

AstraZeneca inhaled glucocorticoid receptor modulator



glucocorticoid receptor modulator
phase II candidate for asthma
from soft drug PK optimization
Drug Metabolism and Disposition
AstraZeneca, Gothenburg, SE

Velsecorat (AZD7594) is an inhaled, non-steroidal glucocorticoid receptor modulator and antedrug (soft drug) for treatment of asthma and other respiratory conditions that has completed several Ph. II studies. While the paper states that the results support progression into Ph. III studies, a Ph. III study does not appear to have started and velsecorat is no longer listed in AstraZeneca's pipeline.

Steroidal GR modulators antedrugs are widely used (e.g. fluticasone propionate, Flonase) but cannot be used for prolonged periods due to side effects including slowed growth in children, bone mineral loss, and type II diabetes in the elderly. Synthetic (non-steroidal) GR modulators may separate desired anti-inflammatory activities from adverse effects by differentially modifying DNA binding vs. coregulator recruitment activities.

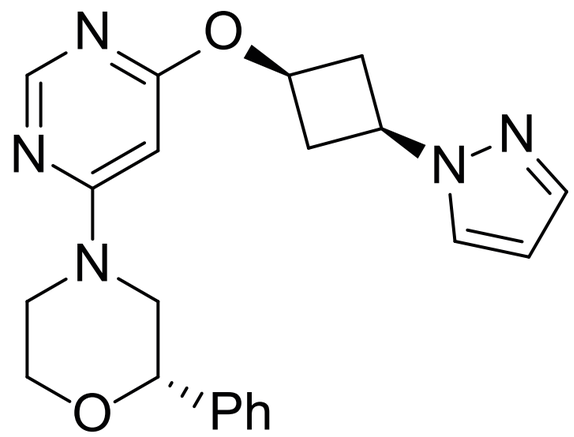
The velsecorat discovery story is a great case study for two strategies for inhaled administration: the antedrug approach, in which the active drug is degraded when it reaches systemic circulation to prevent side effects, and the lung-retention approach, in which a drug is designed to be less permeable across the lung-blood barrier. This report describes the PK of velsecorat in healthy adults, validating these design strategies (inhaled velsecorat $t_{1/2}$ = 27 h, IV $t_{1/2}$ = 2 h). Reviewer Naomi Rajapaksa shares two reviews with strategies for lung-retention here and here.

The medicinal chemistry campaign for velsecorat was reported in 2017 and is a useful case study showing progression from an oral compound to a first-generation inhaled antedrug candidate, and ultimately to velsecorat.

Analog PDB Code: 5NFT

“compound 22”

Vertex ether-based ELOVL1 inhibitors



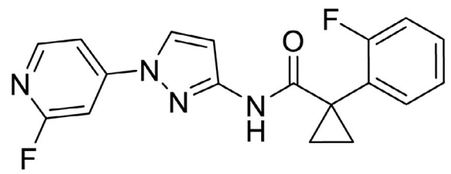
ELOVL1 fatty acid elongase inhibitor
on-target toxicity suggested
from HTS and property-based optimization
Journal of Medicinal Chemistry
Vertex, Boston, MA

Vertex recently disclosed a CNS-penetrant ELOVL1 inhibitor, in which they described preclinical safety findings in rat and cyno. In this article, they disclose a structurally distinct series which displayed similar ocular toxicity in rat, and skin and CNS toxicities in cyno. A third structurally distinct series (undisclosed) also showed toxicities, suggesting a pharmacological class effect.

The remarkable similarity of toxicities despite very structurally different leads is as close to a “smoking gun” for on-target toxicity as you can get, and it is generous of Vertex to share this data with the community. This series of articles will remain useful case studies for target validation and dealing with on-target toxicity for future programs. It is notable that the target organs in rat and cyno are consistently different.

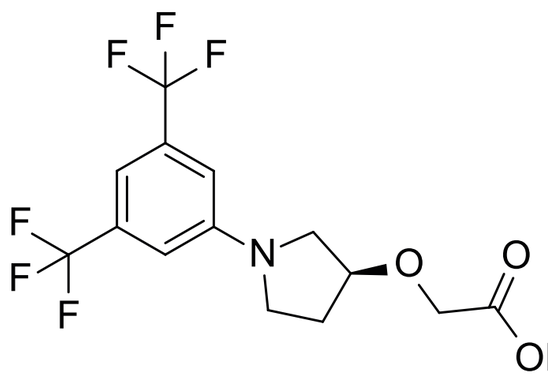
Reviewer Kim Huard comments, “This example also emphasizes the value of investigating safety for a new target as soon as a suitable tool compound is found, allowing the organization to make decisions on the level of risk it’s willing to move forward with or not quickly. The chemical series came from the same screen as the first reported series, and I found interesting that the first SAR exploration was focused on the vectors off of the aromatic core, highlighting the value in having a diversity of chemistry approaches in new programs.”

previously disclosed ELOVL1 inhibitor:



“compound 43b”

Takeda RBP4 reducer



RBP4 reducer targeting RBP4/TTR PPI
preclinical, in vivo RBP4 reduction
from HTS and optimization
Bioorganic and Medicinal Chemistry
Takeda, Fujisawa, JP

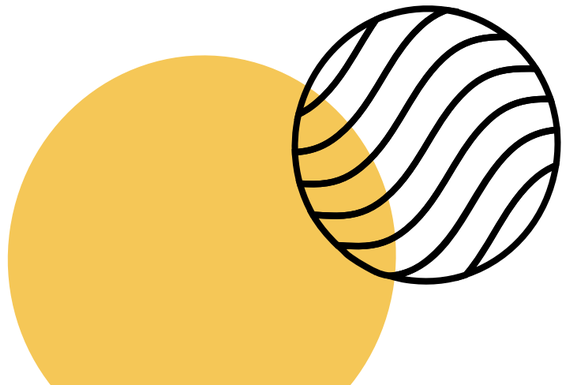
Retinol-binding protein 4 (RBP4) is the sole carrier for retinol (vitamin A). It may also play a role in diabetes and reduction of RBP4 may be beneficial for the ocular disease AMD. Belite Bio had a Ph. III trial ongoing for an oral RBP4 antagonist (LBS-008, tinlarebant) in Stargardt Disease and intends to start a Ph. III trial for AMD in 2022. Stargazer Therapeutics completed a Ph. II study for STG-001 in April.

Retinol-bound RBP4 complexes with transthyretin (TTR) to avoid renal clearance, but after release of retinol, apo-RBP4 is excreted by the kidney. Most apo-RBP4 is reabsorbed and degraded.

“compound 43b” is proposed to disrupt the RBP4-TTR protein-protein interaction (PPI), reducing blood RBP4 levels in mice at orally doses as low as 0.3 mg/kg.

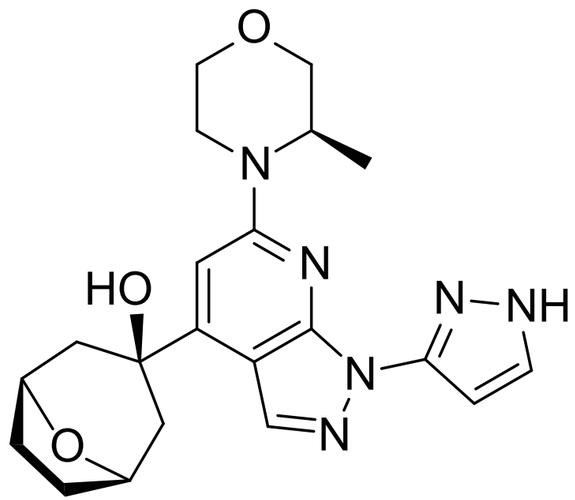
An HTS of the Takeda library led to the starting point. Other RBP4 reducers had been identified by Amgen and others in the past, typically with low MW, carboxylic acid-bearing structures.

Activity around this target was catalyzed by a Nature report in 2005 tying RBP4 to diabetes.
A related patent was filed by Takeda in 2009 and published nearly 10 years ago (US 2011/0251187 A1).



RP-3500

Repare Therapeutics ATR inhibitor



ATR kinase inhibitor

phase I/IIa candidate for advanced solid tumors

from lipid-kinase inhibitor scaffold

Molecular Cancer Therapeutics

Repare Therapeutics, Saint-Laurent, CAN

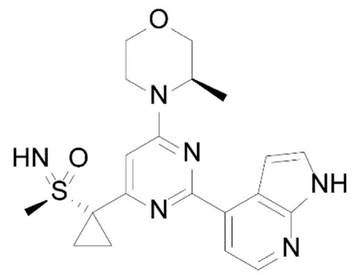
RP-3500 is an oral ATR kinase inhibitor and Ph. II clinical candidate for advanced solid tumors with ATRi-sensitizing mutations, alone or in combination with talazoparib (PARPi) or gemcitabine.

Reviewer Anthony Vaganos says, "An ATR molecule (ceralasertib) is in clinical trials but studies in two different tumors in combination with PARP inhibitors were recently terminated or recommended for closure (see DUETTE, NCT04239014), so a key question will be did Repare design this molecule for combination and if so, will it be able to overcome ceralasertib's failings? Or was this drug designed more for monotherapy? Ceralasertib does have a broad development program so the story definitely isn't over yet."

It is possible that different subsets of tumors may respond better to ATR treatment, and the manuscript suggests different dosing regimens may contribute to better drug combination tolerability.

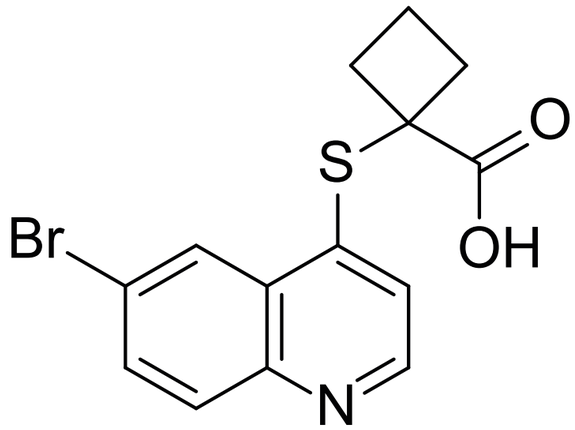
The molecule bears the well-established lipid-kinase inhibitor N-aryl morpholine scaffold present in ceralasertib and other PIK-family kinase inhibitors.

ceralasertib:



HR011303

Jiangsu Hengrui URAT1 inhibitor



human uric acid transporter inhibitor
phase III candidate for hyperuricemia and gout
from pharmacophore-based lead generation
Drug Metabolism and Disposition
Jiangsu Hengrui Medicine Co., Shanghai, CN

Gout is caused by the buildup of uric acid. The main treatments are drugs that increase uric acid secretion (uricosurics, e.g. probenecid) and xanthine oxidase inhibitors which inhibit uric acid production (e.g. allopurinol). URAT1 inhibitors like lesinurad (Ironwood Pharmaceuticals) and dotinurad are emerging treatments, inhibiting uric acid reuptake.

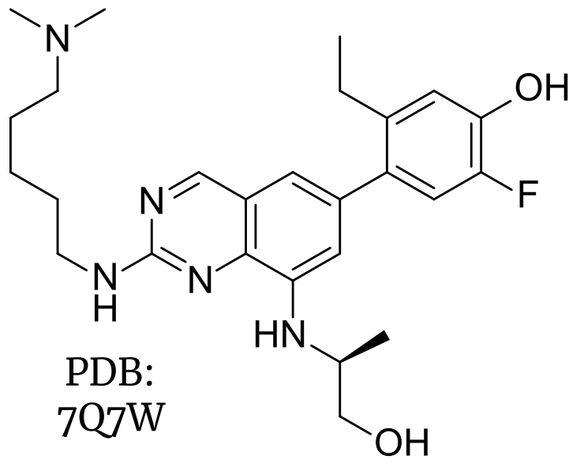
Ironwood discontinued lesinurad for commercial reasons (which carried a black box warning at approval for acute renal failure) in 2019. Pfizer observed acute kidney injury in a Ph. I trial with a URAT1/xanthine oxidase dual inhibitor (PF-06743649). This may not be a class effect, however, as dotinurad (approved in Japan) appears to be well-tolerated.

HR011303 was published in 2016 by Hengrui, and was identified by a pharmacophore-based approach to guide the lead finding effort. The Br atom plays an important role in the binding with the receptor.

This study discloses the PK, mass balance, and metabolism of [14C]HR011303 in six healthy Chinese male subjects. At 216 h post-dose, 91.75% of the administered radioactivity was recovered in the urine (81.50%) and feces (10.26%), indicating complete excretion. Most of the administered radioactivity was recovered within 96 h after dosing, with 79.89% in the urine and 9.50% in the feces. Glucuronidation of the carboxylic acid moiety appears to be the main route of metabolism catalyzed by UGT2B7. HR011303 is currently undergoing Phase III clinical trials in China.

“compound 54c”

GSK inhaled JAK1 inhibitor



PDB:
7Q7W

inhaled JAK inhibitor
reduced AO metabolism in lung
from kinase-focused screening and SBDD
Journal of Medicinal Chemistry
GlaxoSmithKline, Stevenage, UK

JAK kinases are now well-established targets in immunology, but the class has always had safety concerns hanging over it. The safety issues were exacerbated by a recent FDA decision to expand the black box warnings for the class for major cardiovascular events. Inhaled, lung-restricted JAK inhibitors have been of interest because they could leverage the established efficacy of the class while avoiding toxicities due to systemic exposure.

Reviewer Naomi Rajapaksa says, “The GSK paper highlights both an underappreciated role aldehyde oxidase (AO) can play in the lung as well as a challenge of achieving low lung clearance with high systemic clearance.”

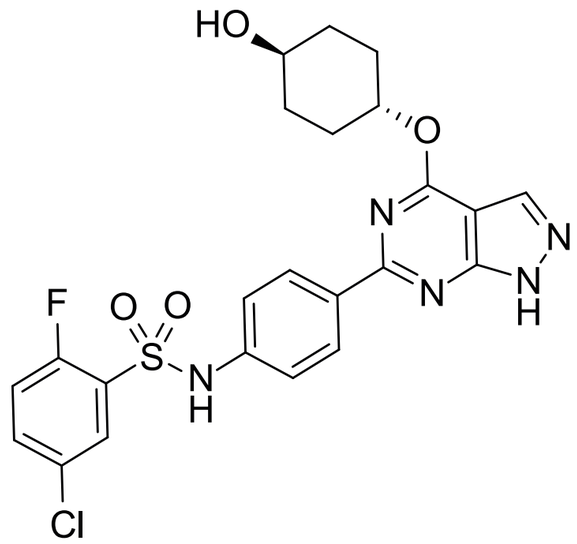
The authors unexpectedly encountered significant aldehyde oxidase metabolism in the lung, and demonstrated that is likely a relevant phenomenon in human lung tissue. Compounds that were not oxidized by AO had greater lung exposure. Interestingly, AO activity was reduced on the molecule by appending groups to a different location on the molecule.

Chris Gampe says, “General consensus is that the lung is not a metabolically active organ, which allows you to dose relatively labile compounds via inhalation and still get good lung exposures while minimizing systemic exposures. This report shows that AO metabolism in the lung can drastically lower lung exposures, so this is helpful for everyone working on inhaled therapies, regardless of the target.”

PDB: 7Q7W

“compound 17a”

Sanofi SGK1 inhibitor



SGK1 kinase inhibitor
preclinical activity in osteoarthritis explant model
from DFG-out virtual screening, SBDD and MPO
Journal of Medicinal Chemistry
Sanofi, Frankfurt am Main, DE

Kinase inhibitors are increasingly being explored for diseases beyond cancer. While SGK1 has been a cancer target, SGK1 has also been implicated in osteoarthritis pathology, and the Sanofi team developed “compound 17a” to interrogate this.

The starting point was identified from ligand-based virtual screening, focusing on the DFG-out conformation, using models built from other SGK1 inhibitors. The pyrazole heterocycle is a two-point hinge binder. Library expansion and further optimization allowed the team to address aryl sulfonamide photostability, selectivity, permeability, and mutagenicity issues leveraging different parts of the molecule.

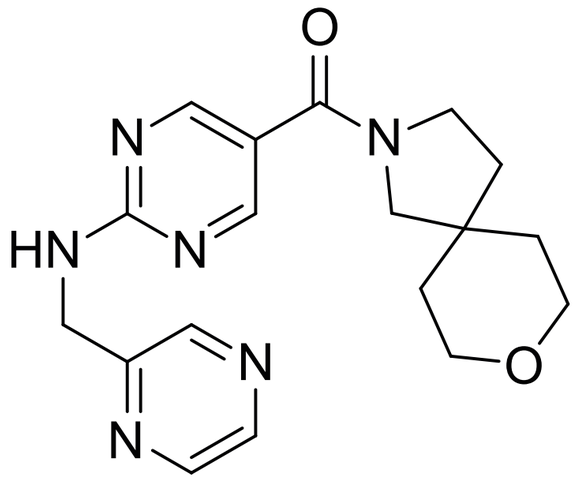
Biological proof of concept was achieved using a mouse femoral head cartilage explant model in which cartilage sections are taken from mice and treated with drug. Significantly reduced disease biomarker (collagen type X) levels were observed above 2 µM, corresponding to cellular potencies below 1 µM.

Interestingly, rodent SGK1 potency is almost 100x lower than human potency (<1 nM). This is not discussed in depth but was likely a challenge to overcome while planning proof-of-concept studies. This also highlights the fact that similar cross-species activity should not be assumed, even for kinase active-site inhibitors.

Analog PDB Code: 7PUE

“compound 3”

Pfizer Vanin-1 inhibitor



vanin-1 pantetheinase inhibitor
preclinical candidate for IBD
from HTS + SBDD
Journal of Medicinal Chemistry
Pfizer, Cambridge, MA + Groton, CT

Vanin-1 is a biotinidase (nitrilase superfamily) that hydrolyzes pantetheine. Despite the critical role of pantetheine, vanin-1 deficient mice don’t appear to have issues, but may be protected in inflammatory disease settings like IBD.

Since human vanin-1 coverage requirements are unknown, the Pfizer vanin-1 program took a “no-regrets” approach to target dose and dose prediction, and deprioritized a ketone-containing lead with high projected human dose (850 mg BID). The ketone was replaced with an amide and optimized to “compound 3.”

The article is an excellent case study for drug discovery on a novel target, with rigorous characterization of properties along the way. For example, vanin-1 is proteolytic, so the hypothesis that the new amide series may be a substrate for vanin-1 was checked.

The differentiation between two late candidates was made based on the identification of a satisfactory crystalline form of “compound 3” for development (no crystalline form was found for the other candidate). “Compound 3” displays is selective over all proteases and wide panels of other targets, and is remarkably efficient (LLE = 8.2, logD = -0.1).

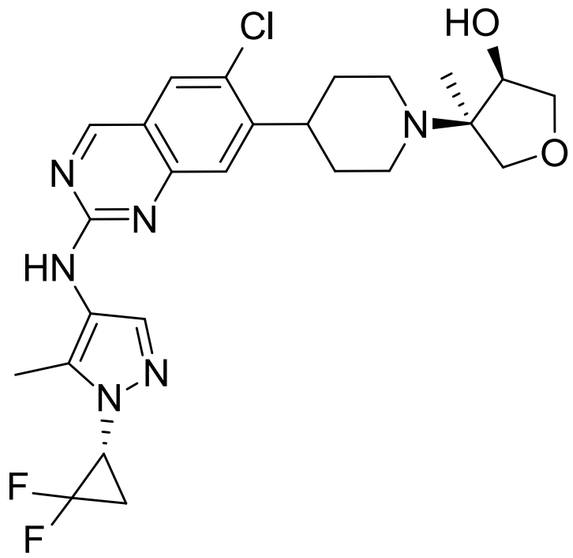
The main route of clearance was predicted to be renal, and the projected human dose was 10-30 mg QD.

Unfortunately, as is common for inflammatory conditions, the mouse disease model used did not provide a clear answer about the therapeutic window for vanin-1 inhibition. No vanin-1 inhibitor appears to be in development.

PDB Code: 7SLV

“compound 24”

Merck LRRK2 inhibitor



LRRK2 kinase inhibitor
preclinical, brain-penetrant
from rational HTL and structure-guided opt.
Journal of Medicinal Chemistry
Merck & Co., Boston, MA

LRRK2 is a target of interest for Parkinson’s disease (e.g. DNL-151), but development had been slowed by concerns about potential lung toxicity of LRRK2 inhibitors. A Phase I study of a LRRK2 inhibitor in healthy volunteers had not shown human toxicity, though, and Biogen/Denali plan to proceed with Ph. III and Ph. IIb trials in 2022. The fact that a healthy volunteer study was allowed suggests that preclinical toxicities observed with DNL-151 were likely different from those observed with previous LRRK2 inhibitors.

“Compound 24” is a brain-penetrant, type I LRRK2 kinase inhibitor with a distinct structure from previously disclosed LRRK2 inhibitors (e.g. GNE-7915, AZD-3759, MLi-2). The molecule has a rat $Kp_{uu,brain}$ of 0.43 and a projected human dose of 19 mg QD, Which is impressive given its relatively large size (6 rings). This is a helpful case study for the development of brain-penetrant kinase inhibitors outside of oncology.

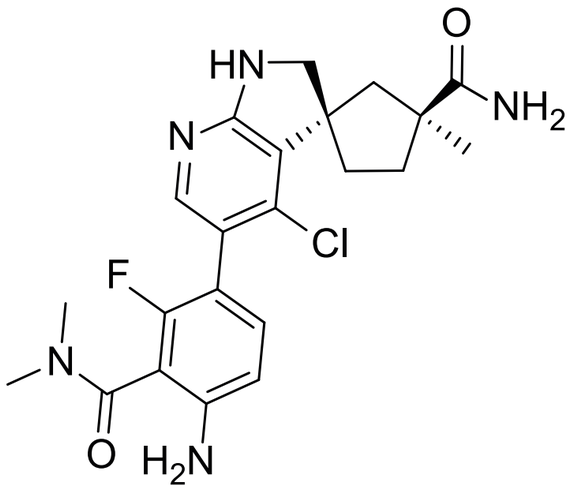
Reviewer Julien Lefranc says, “The MSD team did a great job tackling two big challenges for kinase inhibitors, especially for a non-oncology indication: very high kinase selectivity and brain permeability (along with good oral bioavailability).”

Merck & Co does not appear to have a LRRK2 inhibitor in development.

PDB Code: 7SUJ

“compound 25”

Genentech HPK1 inhibitor



HPK1 kinase inhibitor

unusual P-loop-folded conformation inhibitor

from HTS + SBDD

ACS Medicinal Chemistry Letters

Genentech, South San Francisco, CA

“Compound 25,” inhibits HPK1 via a rare “P-loop folded” active site conformation. The molecule was nominated by reviewer Julien Lefranc, and structural biologist Yoana Dimitrova shares some insight here:

“The ‘folded P-loop’ conformation is considered “extremely unusual” – authors of a 2011 paper looked into this and found it in only 62 out of 2690 complexes for 7 different kinase targets out of 56 covered in the database, an incidence of 12.5%. What is important is that the folded P-loop is found in structures of kinase + compound, so we just may not have found compounds that lead to the folded conformation for the other kinases.”

The P-loop folded conformation may present additional ways to address selectivity in kinase programs. Other HPK1 kinase inhibitors recently highlighted do not target this conformation. Compound 25 has favorable properties including picomolar inhibitory activity (LLE = 8.2) and LCK selectivity (>2500x).

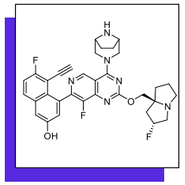
The starting point was identified using a HTS with the kinase domain of HPK1, suggesting that inhibitors of a folded P-loop conformation can be found under normal conditions.

Analog PDB Codes: 7R9L, 7R9P, 7R9T

drug hunter

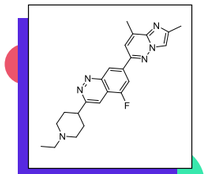
Small Molecules of the Month

December 2021
drughunter.com



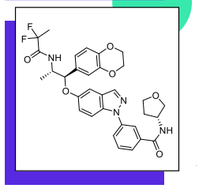
MRTX1133 | KRAS^{G12D}

reversible KRAS^{G12D} inhibitor
preclinical efficacy in cancer model
from SBDD around KRAS^{G12C} inhibitor
Journal of Medicinal Chemistry
Mirati Therapeutics, San Diego, CA



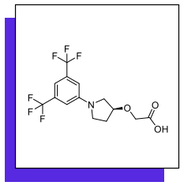
HTT-D3 | HTT

HTT splicing modulator
PD in Huntington's disease model
from HTS and optimization
Nature Communications
PTC Therapeutics, So. Plainfield, NJ



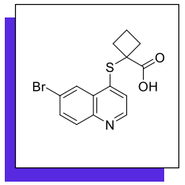
velsecorat | GR

glucocorticoid receptor modulator
phase II candidate for asthma
from soft drug PK optimization
Drug Metabolism and Disposition
AstraZeneca, Gothenburg, SE



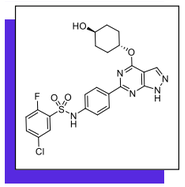
compound 43b | RBP4

RBP4 reducer targeting RBP4/TTR PPI
preclinical, in vivo RBP4 reduction
from HTS and optimization
Bioorganic and Medicinal Chemistry
Takeda, Fujisawa, JP



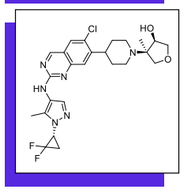
HR11303 | URAT1

human uric acid transporter inhibitor
phase III candidate for hyperuricemia and gout
from pharmacophore-based lead generation
Drug Metabolism and Disposition
Jiangsu Hengrui Medicine Co., Shanghai, CN



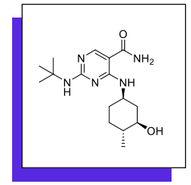
compound 17a | SGK1

SGK1 kinase inhibitor
preclinical activity in osteoarthritis explant model
from DFG-out virtual screening, SBDD and MPO
Journal of Medicinal Chemistry
Sanofi, Frankfurt am Main, DE



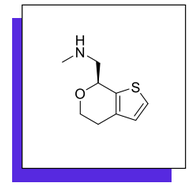
compound 24 | LRRK2

LRRK2 kinase inhibitor
preclinical, brain-penetrant
from rational HTL and structure-guided opt.
Journal of Medicinal Chemistry
Merck & Co., Boston, MA



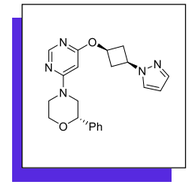
CC-90001 | JNK2

oral JNK2 kinase inhibitor
Ph. II candidate for pulmonary fibrosis
from HTS and SBDD
Journal of Medicinal Chemistry
Celgene (Bristol Myers Squibb), San Diego, CA



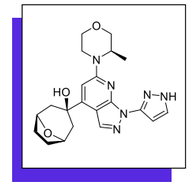
ulotaront | TAAR1

TAAR1 GPCR agonist
phase III candidate for schizophrenia
from in vivo phenotypic screening
ACS Medicinal Chemistry Letters
Sunovion Pharmaceuticals, Marlborough, MA



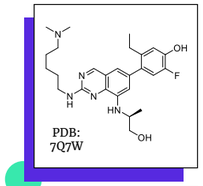
compound 22 | ELOVL1

ELOVL1 fatty acid elongase inhibitor
on-target toxicity suggested
from HTS and property-based optimization
Journal of Medicinal Chemistry
Vertex, Boston, MA



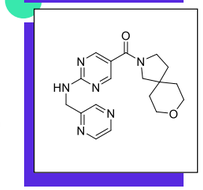
RP-3500 | ATR

ATR kinase inhibitor
phase I/IIa candidate for advanced solid tumors
from lipid-kinase inhibitor scaffold
Molecular Cancer Therapeutics
Repare Therapeutics, Saint-Laurent, CAN



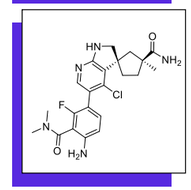
compound 54c | JAK

inhaled JAK inhibitor
reduced AO metabolism in lung
from kinase-focused screening and SBDD
Journal of Medicinal Chemistry
GlaxoSmithKline, Stevenage, UK



compound 3 | Vanin-1

vanin-1 pantetheinase inhibitor
preclinical candidate for IBD
from HTS + SBDD
Journal of Medicinal Chemistry
Pfizer, Cambridge, MA + Groton, CT



compound 25 | HPK1

HPK1 kinase inhibitor
unusual P-loop-folded conformation inhibitor
from HTS + SBDD
ACS Medicinal Chemistry Letters
Genentech, South San Francisco, CA

discover together

drughunter.com
info@drughunter.com