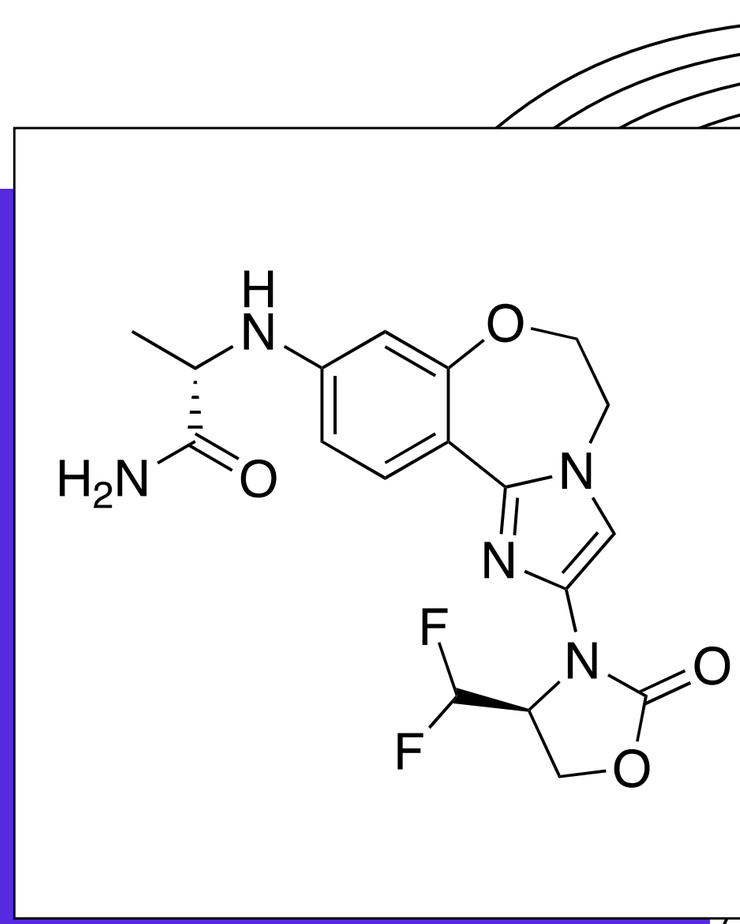
Small Molecules of the Month

May 2021

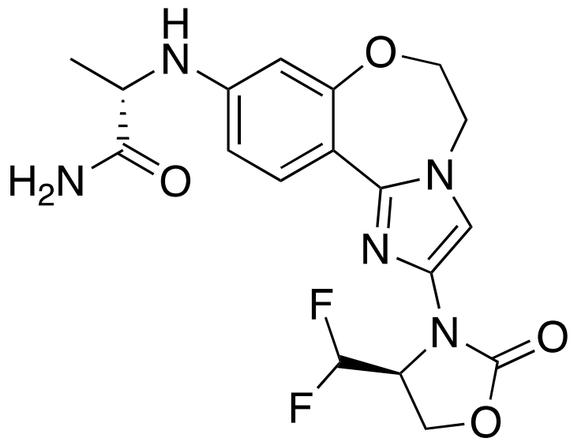


drug hunter

01	mPI3Ka	Genentech
02	RAF	Genentech
03	MEK1/2	Harvard Medical
04	CDC7	Takeda Pharmaceutical
05	CFTR	Novartis
06	ROMK	Merck & Co.
07	RORyt	Janssen R&D
08	LMP7	Merck KGaA
09	CCR2	Bristol Myers Squibb
10	BRAF	Lutris-Parma
11	S1PR2	Galapagos NV
12	pleiotropic	EpicentRx Inc.
13	GO/LDHA	Chinook Therapeutics
14	BTK	X-Chem Inc.

inavolisib

mPI3Kα



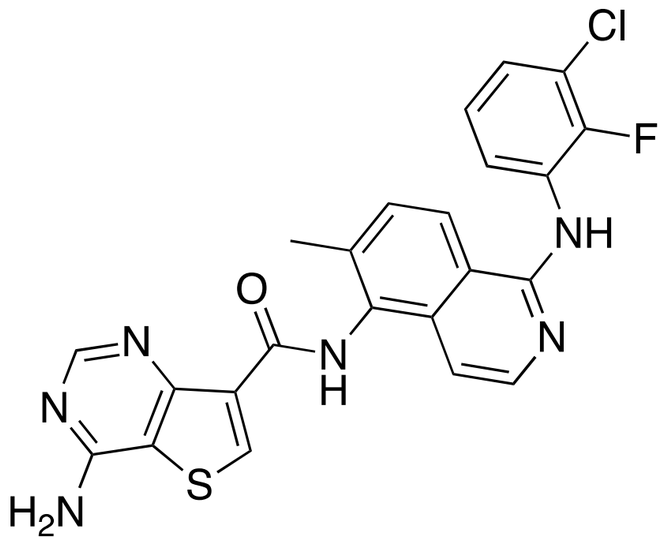
Isoform-selective mutant PI3Kα degrader
Oral <9 mg QD, Ph. III in HR+/HER2- BC
From cellular characterization of PI3Ki and opt.
bioRxiv, May 13, 2021
Genentech, South San Francisco, CA

The Genentech PI3Kα isoform-selective kinase inhibitor and mutant PI3Kα degrader GDC-0077 (inavolisib) selectively depletes the oncogenic mutant p110α catalytic subunit of PI3Kα in cancer cells with active receptor tyrosine kinase (RTK) signaling. The gene encoding p110α, PIK3CA, is one of the most frequently mutated oncogenes, with over 2M cancer patients diagnosed annually with PIK3CA-mutant tumors. PI3Kα has been a target of significant interest for many years, but it has been challenging to identify drugs with significant benefit due to the toxicities associated with wild-type PI3K-family inhibition and negative feedback triggered by PI3K inhibition that activates RTK signaling, counteracting drug activity.

By being highly selective for PI3Kα and selectively degrading mutant p110α by a mechanism that appears to depend on RTK activation, GDC-0077 achieves a greater preclinical therapeutic window than previous PI3K inhibitors, including the recently approved PI3Kα inhibitor alpelisib. The mutant-selective activity observed is assisted by the relative instability of mutant p110α protein vs. WT. GDC-0077 is in several ongoing trials, including a first-in-human study of GDC-0077 in PIK3CA-mutant solid tumors which identified a MTD of 9 mg QD with anti-tumor activity, a Ph. III trial in HR+/HER2- BC in combo. with CDK4/6i and fulvestrant, and a first-in-human study in HER2+ BC with SOC (trastuzumab + pertuzumab). The principle of leveraging the intrinsic instability of certain mutant oncoproteins to identify mutant-selective degraders will likely appear in future pharmacology textbooks.

belvarafenib

RAF



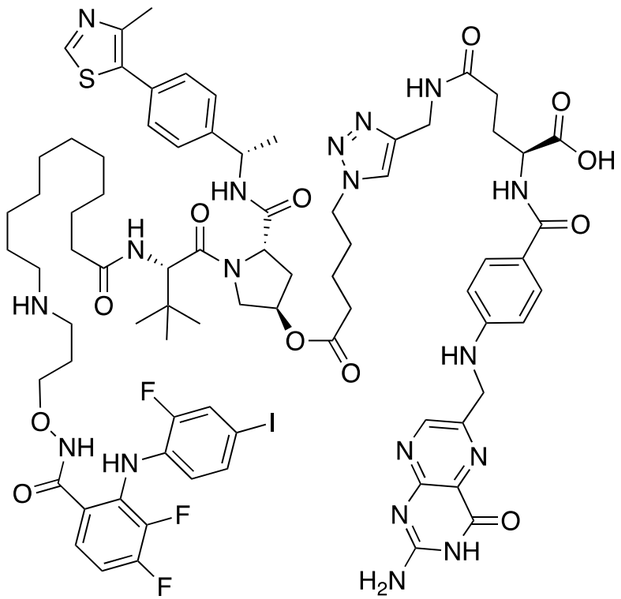
Type II RAF dimer kinase inhibitor
Oral 450 mg BID, Ph. II in BRAF/RAS cancers
Demonstrated activity in NRAS-mut. tumors
Nature, May 5, 2021
Genentech, CA / Hanmi Pharma, KR

The Hanmi/Genentech type II RAF kinase inhibitor, belvarafenib, is a potent and selective inhibitor of RAF dimers. GNE-9815 was covered last month, which was used to validate the biology supporting clinical trials of belvarafenib. This Nature article shares first-in-human results of belvarafenib in BRAF(V600E) and RAS-mutated solid tumors, with a few responses already observed in the dose escalation phase. In agreement with hypothesis that a type II kinase inhibitor would more effectively inhibit RAF dimers than approved type 1.5 inhibitors, belvarafenib demonstrates activity in patients who progressed on prior type 1.5 BRAF(V600E) kinase inhibitors (e.g. vemurafenib, dabrafenib) and against NRAS-mutant tumors in which prior inhibitors are ineffective.

Additionally, in contrast to the type 1.5 inhibitors, no reports of squamous cell carcinoma (SCC) were observed, a known issue with type 1.5 inhibitors due to paradoxical MAPK signaling, caused by the inhibitor-induced formation of catalytically active RAF dimers. A crystal structure confirmed that belvarafenib binds to both RAF monomers in the RAF dimer, in contrast with prior inhibitors which are only able to bind to one subunit of the dimer. Circulating tumor DNA (ctDNA) was tracked during the trial, and helped identify ARAF mutations as a surprising, novel mechanism of RAF inhibitor resistance. A RAF + MEK inhibitor combination is proposed to address this issue. This RAF inhibitor saga is an excellent case study for how small molecule binding modes can lead to dramatically different biological effects even when targeting the same active site via unexpected mechanisms. This is also a great example of how modern ctDNA diagnostic technology is being applied clinically to better understand disease progression mechanisms and generate novel, actionable therapeutic hypotheses.

Folate-MS432

MEK1/2



Folate receptor-dependent PROTAC conjugate
FOLR1-dependent MEK1/2 degrad. in vitro
From conjugation of folate to PROTAC
J. Am. Chem. Soc., May 10, 2021
Harvard Medical / Mt. Sinai

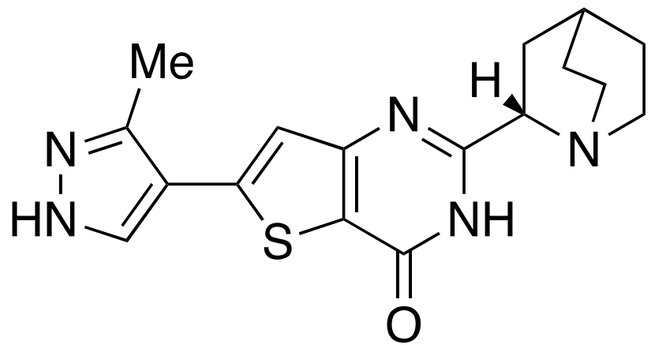
The FOLR1-targeting folate receptor-dependent PROTAC conjugate, folate-MS432, is a MEK1/2 degrader that is targeted to FOLR1, a receptor highly expressed in many cancer cell types but less so in most normal cells. The folate moiety allows the molecule to be taken up into cells via endocytosis, where the inert molecule can be cleaved by intracellular hydrolases to release the active MEK1/2 degrader.

In theory, this strategy could increase the therapeutic windows of degraders against targets with known safety issues upon inhibition, such as MEK1/2. While folate-targeting as a strategy has been attempted in the past (such as in our recent highlight of PDB-folate conjugate EC2629), there has not been much clinical success yet. Like ADCs, there are additional issues to consider, such as bystander effects, the permeability of the released warhead, the relative activity of the released warhead in different cells, and the true expression levels of the receptor of interest.

This adds another valuable entry to the growing toolbox of chimeric molecules, and it will be interesting to watch if improved safety can be reduced to practice in vivo in a manner that differentiates from existing drug conjugate modalities.

simurosertib

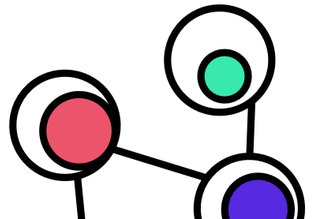
CDC7



CDC7 serine/threonine kinase inhibitor
Oral 50 mg QD, Ph. II in solid tumors compl.
From homology model pharmacophore + opt.
Sci. Adv., May 21, 2021
Takeda Pharmaceutical, Kanagawa, JP

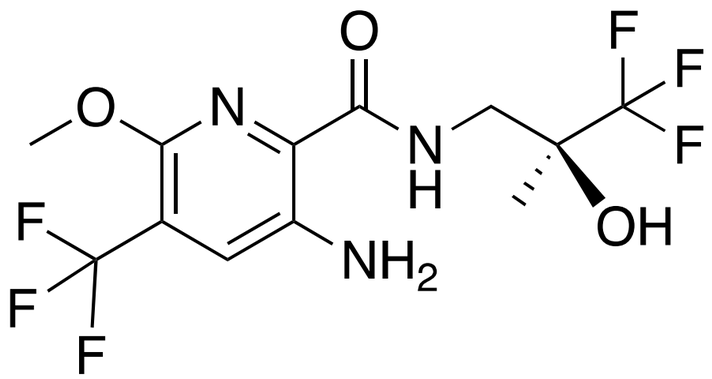
The Takeda CDC7 serine/threonine kinase inhibitor, **simurosertib (TAK-931),** is the first orally active CDC7-selective inhibitor and recently had its Ph. I study results in solid tumors posted. The drug was dosed as a single agent in one study at 50 mg QD with 7-day rest periods on 21-day cycles, and in another study at varying levels with varying rest schedules, suggestive of anticipated on-target tox. Neutropenia and GI adverse events appear to be drug-related (NCT02699749), and most patients did not complete the study due to progressive disease. Though the single-agent results are discouraging, the team published this paper describing their efforts to find a combination regimen and/or cancer subtype where CDC7 inhibition might be effective. Finding the right combination or right tissue type/biomarker can often be key to success in cancer treatment, such as in the examples above or in the now classic case of **CDK4/6 inhibitors in ER+ breast cancer**.

After a systematic evaluation of combination MoA's and cancer cell lines, the authors find that TAK-931 induces a BRCA-mutant-like sensitivity in certain cancer cell lines due to CDC7's role in homologous recombination repair (HRR). DNA-damaging agents and PARPi synergize with TAK-931 both in vitro and in PDX models, in what the authors call "chemical-induced synthetic lethality." It will be interesting to see whether chemical-induced synthetic lethality can lead to improved therapeutic windows in humans, with this particular CDC7 mechanism or with any other drug MoA that chemically impairs DNA-damage repair.



Icenticaftor

CFTR



Mutant + WT CFTR Cl channel potentiator
Oral 300 mg BID, Ph. II in COPD and CF
From 1M cmpd cell-based HTS + opt.
J. Med. Chem., May 24, 2021
Novartis, Horsham, UK / Cambridge, MA

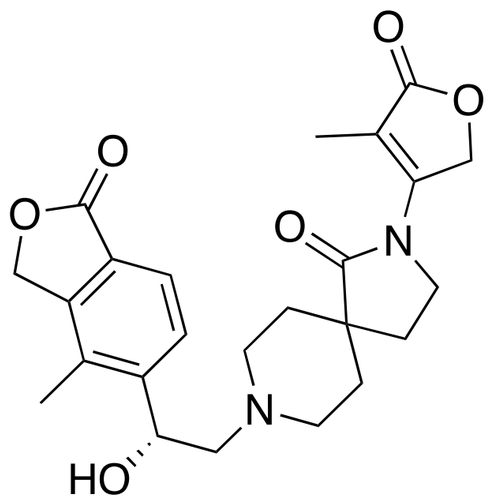
The Novartis mutant and WT CFTR potentiator, icenticaftor (QBW251), is an oral Ph. II clinical candidate for chronic obstructive pulmonary disease (COPD), which is anticipated to become the 3rd leading cause of death globally. The compound had positive proof of concept studies in both cystic fibrosis and COPD, and the advancement of a WT CFTR modulator into the large COPD indication is a significant development. Since there are not good PK/PD models for cystic fibrosis, the candidate was nominated based on in vitro properties and safety studies, but has shown target engagement in humans via biomarkers such as sweat chloride.

This is a great medicinal chemistry case study as the starting point for icenticaftor was objectively unattractive, with furan, aniline, and ester groups. On the way to QBW251, a 2-bromopyridine-containing candidate without detectable GSH adducts in vitro showed GSH adducts in a bile duct cannulation experiment in vivo, and was deselected based on a lower NOAEL in a safety study. Icenticaftor also showed 146% bioavailability in dogs, and though the authors don't comment on it, it's useful to note that >100% F measurements aren't so rare.

The recently highlighted potentiator, GLPG2451, has a similar core structure to icenticaftor, but the two compounds originated from very different looking HTS hits in an interesting example of "convergent" molecular evolution.

MK-8153

ROMK



ROMK potassium channel blocker
Oral eff. in hypertension model (1 mpk QD)
Backup candidate to MK-7145 (Ph. Ib)
J. Med. Chem., May 26, 2021
Merck & Co., Kenilworth, NJ

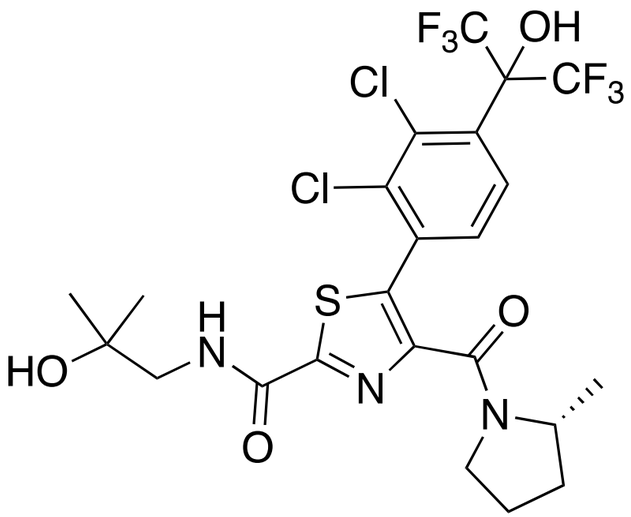
The Merck ROMK potassium channel blocker, MK-8153, is a backup development candidate to MK-7145, whose development as a diuretic was terminated after a Ph. Ib study due to lack of efficacy. Traditional loop diuretic drugs such as furosemide inhibit the Na-K-Cl co-transporter, but carry the risk of life-threatening urinary potassium loss. ROMK is a K channel that feeds K ions to NKCC, facilitating Na absorption, and ROMK inhibitors act as diuretics in animal models without the same levels of potassium loss.

Objectives for the backup molecule included a longer half-life and better permeability to enable an extended release formulation. A lower peak-to-trough ratio was thought to be desirable since high peak-to-trough ratios lead to rebound sodium retention and reduced PD over time. The resulting MK-8153 has a ~14 h projected human half-life with a surprisingly stable vinylogous carbamate group, which also confers greater hERG selectivity to the molecule.

Radiolabeled MK-8153 in bile duct-cannulated rats showed most of it is excreted in urine, and this concentration at the intended site of action is suggested to contribute to in vivo efficacy. MK-8153 currently doesn't appear to be in development.

JNJ-61803534

RORγt



Oral RORγt inverse agonist

Ph. I in HV up to 200 mg w/ PD, discontinued

From HTS + opt.

Scientific Reports, May 26, 2021

Janssen R&D, La Jolla, CA

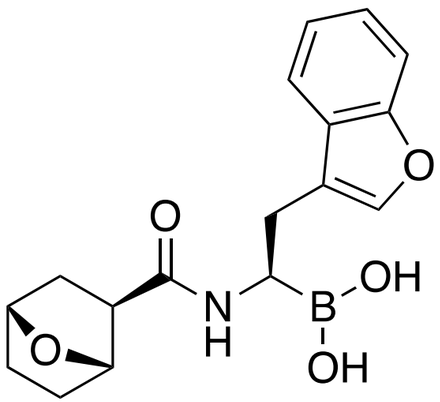
The Janssen RORgt inhibitor, JNJ-61803534, is an oral clinical candidate that was well-tolerated in humans up to 200 mg and demonstrated PD. Unfortunately, development was terminated due to findings in a rabbit embryo-fetal study where fetal development was impacted by JNJ-61803534 treatment. The JNJ team shares a lot of useful human data in the paper, including human PK (half-life of 164-170 h!) and PD. The variability in the human PD data is a good reminder that clinical data is often a lot noisier than preclinical data.

When drug toxicity is a potential concern, the variability in PK and PD in humans makes it more difficult to find an optimal dose in practice than it might sound on paper. JNJ-61803534 was well tolerated in rats with an NOAEL of 400 mg/kg/d, but had a much lower NOAEL in dog (3 mg/kg/d), showing how frustratingly large species differences can be.

Though many RORgt candidates have dropped out now due to safety issues, several continue to be explored in settings from cancer to ocular diseases, in various routes of administration. Though RORgt inhibition has been proposed to carry a risk of lymphoma development based on animal studies, so far the inhibitors that have dropped out have dropped out for other reasons.

M3258

LMP7



Sel. reversible cov. immunoproteosome inh.

Oral efficacy (1 mpk) in xeno., Ph. I in MM

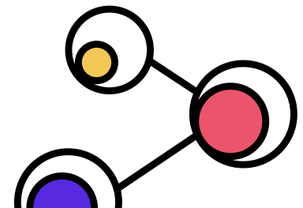
From SBDD

Mol. Cancer Ther., May 27, 2021

Merck KGaA, Darmstadt, DE

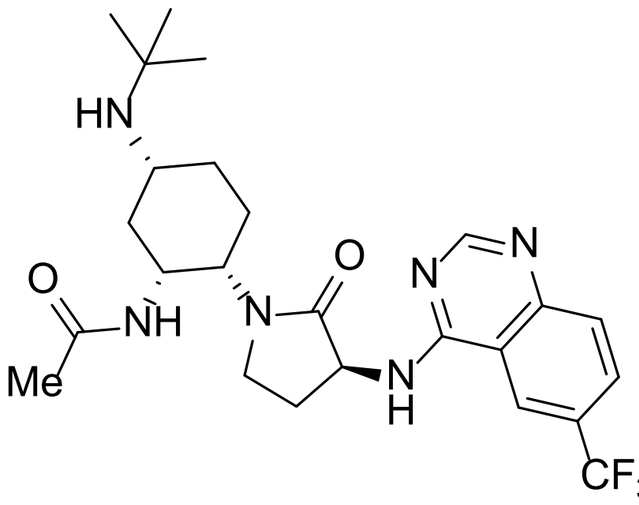
The Merck LMP7 inhibitor, M3258, is an orally available, selective, and reversible inhibitor of the immunoproteasome proteolytic subunit, LMP7. In contrast to the constitutive proteasome, the immunoproteasome is predominantly expressed in hematolymphoid cells such as in multiple myeloma cells. Pan-proteasome inhibitors (pan-PIs) such as bortezomib, carfilzomib, and ixazomib are standard treatments for multiple myeloma, but cause a range of toxicities likely due to constitutive proteasome inhibition.

This selective immunoproteasome inhibitor may lead to similar activity in MM patients but with better tolerability. Non-clinical safety studies in rat and dog identified a smaller spectrum of target organs for M3258 than pan-PIs, supporting this hypothesis. Additionally, while pan-PIs is cytotoxic to immune cells and other cells, M3258 only inhibits proliferation in human B and T cells. A manuscript describing the discovery campaign to M3258 is in preparation.



BMS-753426

CCR2



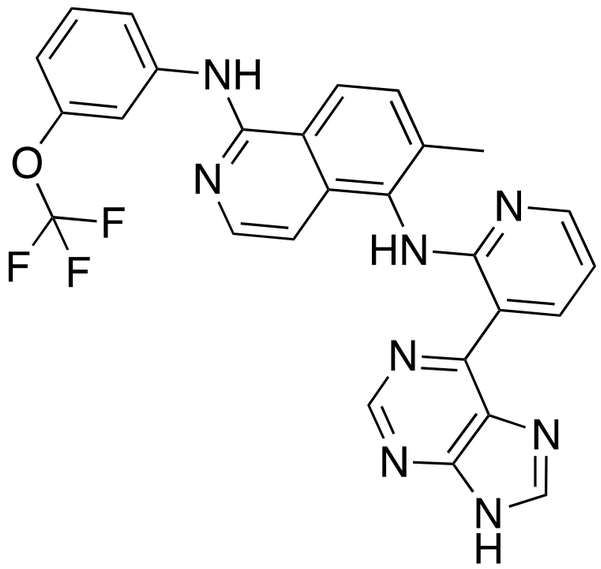
Sel. CCR2 chemokine receptor antagonist
Oral efficacy (25 mpk BID) in inflamm. models
From PK opt. of prior candidate
ACS Med. Chem. Lett., May 25, 2021
Bristol Myers Squibb, Princeton, NJ

The BMS CCR2 inhibitor, BMS-753426, is a potent, oral follow-up molecule to prior clinical candidate, BMS-741672. A small change from a methyl and isopropyl-substituted tertiary amine to a t-butyl secondary amine led to a significant improvement in PK properties including lower clearance and higher bioavailability across species, including cyno.

The compound has four nitrogen-bearing stereocenters but >100 g were prepared without a single column chromatography purification. The authors suggest that dual CCR2 and CCR5 inhibition may be more successful in various indications, and the related molecule BMS-813160 is a dual antagonist in several clinical trials

LUT014

BRAF



Topical BRAF inhibitor (gel) for EGFRi rash

Ph. I in mCRC with EGFRi-related rash

Paradoxical activ. of MAPK to counter EGFRi

Cancer Discovery, May 25, 2021

Lutris-Parma, Tel Aviv, IL / MSKCC, NY

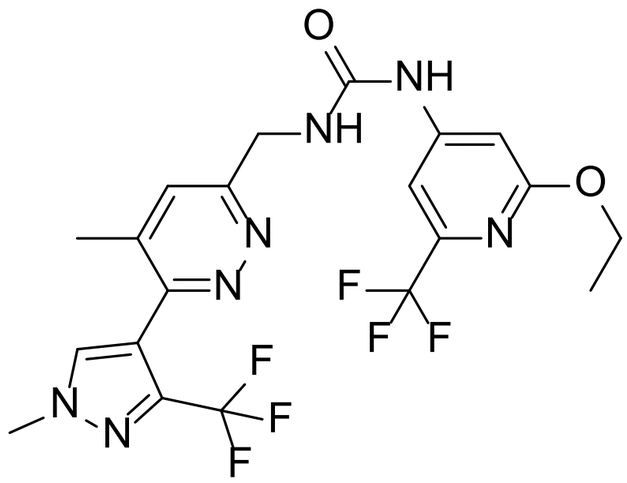
The Lutris-Parma topical BRAF inhibitor, LUT014, is intended to treat rash caused by EGFR inhibitors. Rash is a significant and common side effect of EGFR inhibitor treatment leading to worse quality of life and treatment discontinuations. The rash is on-target, caused by reduced ERK signaling in healthy skin cells.

Interestingly, due to paradoxical MAPK activation which increases ERK signaling discussed above for RAF inhibitors, patients who receive a combination of an EGFR inhibitor with systemic BRAF inhibitors have markedly reduced rash.
The authors hypothesized that topically treating EGFRi drug-related rash with BRAF inhibitors may reduce the severity of dose-limiting rash, and initiated a 10 patient trial with LUT014.

LUT014 was well-tolerated and seems to have a benefit at low concentrations and less benefit at high concentrations, which may be explained by the bell-shaped curve of paradoxical MAPK activation with BRAF monomer inhibitors. A larger controlled trial is likely needed to confirm significance.

GLPG2938

S1PR2



Selective S1PR2 antagonist preclin. candidate

Oral efficacy (1 mpk BID) in fibrosis model

Scaffold hop from literature starting points

J. Med. Chem., May 3, 2021

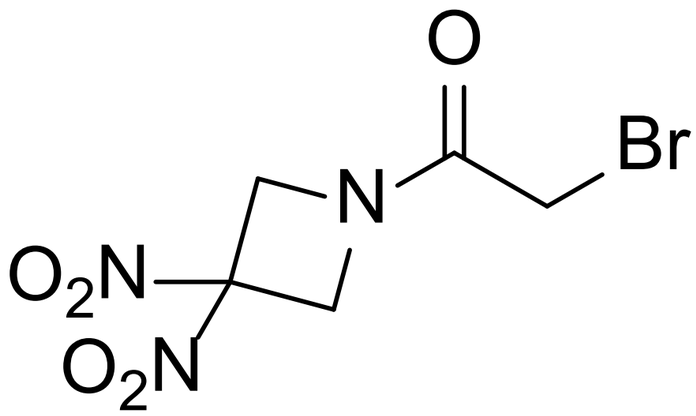
Galapagos NV, Mechelen, Belgium

The Galapagos S1PR2 antagonist GLPG2938 is a preclinical candidate intended for the treatment of idiopathic pulmonary fibrosis (IPF). Though several S1PR1 modulators have been approved, no selective S1PR2 antagonist has entered clinical development yet. The Galapagos team attempted to find a new starting point with two consecutive HTS campaigns, but did not find any advanceable starting points, but were able to develop a literature starting point to a candidate.

A hydrazine motif in the starting point was replaced with a benzylic amine in a surprisingly large property change for a central motif. Improving lipophilic efficiency was key to reducing CYP inhibition. GLPG2938 does not appear to have entered development yet, but should be a useful tool to understand S1PR2 biology.

RRx-001

pleiotropic



Surprisingly well-tolerated clinical molecule
Ph. III candidate in SCLC (4 mg IV QW)
From aerospace compound phenotypic screen
J. Med. Chem., May 27, 2021
EpicentRx Inc., La Jolla, CA

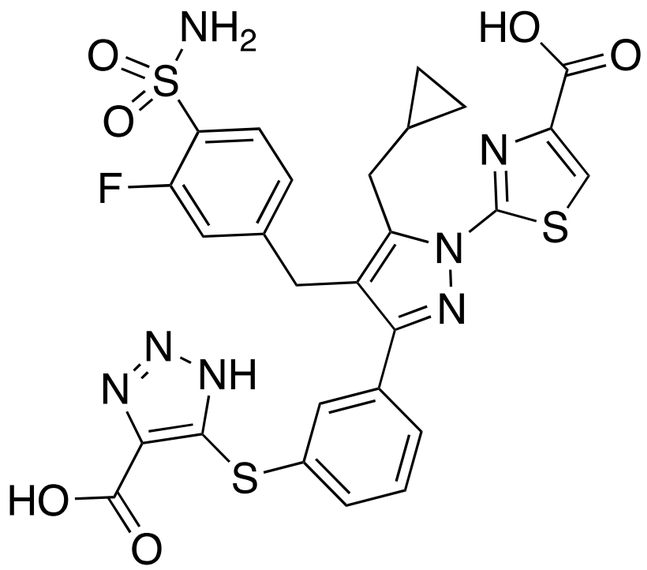
The EpiCentRx Myc and CD47 downregulating molecule with a range of proposed mechanisms, RRx-001, is a Ph. III clinical candidate with an eyebrow-raising chemical structure that originated from an even more eyebrow-raising starting point, trinitroazetidine. The N-nitro motif in the starting point was replaced with the (only slightly) less concerning bromoacetamide group to render the molecule less impact sensitive. Though the molecule is reminiscent of the reactive chemotherapeutics frequently screened in the 60's-80's, it is surprisingly well-tolerated in humans, with over 300 patients having been treated with no dose-limiting toxicities or maximum tolerated dose.

The authors suggest that RRx-001 is a nongenotoxic alkylating agent, reacting with thiol sulfurs to deplete cellular cysteine, thioredoxin, and GSH, indirectly leading to nucleic acid oxidation, and protection of healthy cells by stimulating and upregulating endogenous defense mechanisms. Additionally, by stressing RBCs, multiple protective systems are activated that increase stress tolerance to further doses or chemo or radiation.

Apparently, crocodiles use a similar mechanism of defense against infection and cancer with ROS-producing hemoglobin residues liberated from their RBCs. It will be interesting to see if this molecule can still find a place to demonstrate significant efficacy in the highly competitive, target-focused cancer treatment landscape today.

Compound 7

GO/LDHA



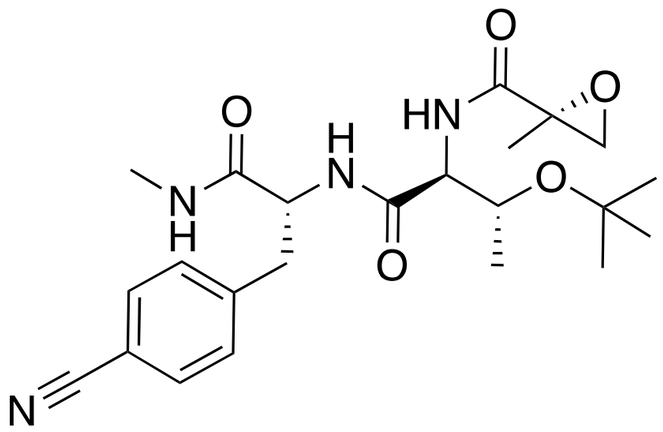
LDHA and GO dual inhibitor
In vitro activity and X-ray vs. both targets
From SBDD of LDHA and GO inhibitors
ACS Med. Chem. Lett., May 20, 2021
Chinook Therapeutics, Seattle, WA

The LDHA/GO dual inhibitor, compound 7, targets two clinically validated targets for hyperoxaluria, a rare genetic disorder that results in oxalate overproduction and sometimes kidney failure. GO is encoded by HAO1, the target of recently approved siRNA drug lumasiran, and LDHA is selectively targeted by Dicerna's nidosiran. The authors aimed to make a small molecule that could target both enzymes simultaneously, and used a structure-based approach to fuse GO and LDHA inhibitors into compounds with in vitro activity and confirmed binding to both enzymes by X-ray crystallography.

Unfortunately, the molecule doesn't demonstrate activity in vivo due to low oral exposure, a property that is challenging to optimize with a large diacid. Also disappointingly, in vitro, dual inhibition of LDHA/GO doesn't appear to have an additive or synergistic effect.

Compound 6

BTK



Epoxide-based covalent BTK inhibitor

Cysteine reactive, Kinact/Ki ~ 6500

From covalent DEL library screening

Bioorg. & Med. Chem. Lett., May 19, 2021

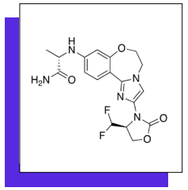
X-Chem Inc., Waltham, MA

The X-Chem covalent BTK inhibitor, compound 6, is an example of a covalent inhibitor discovered using DNA-encoded library chemistry, and is the first epoxide-based covalent inhibitor discovered against BTK. Screening for novel covalent scaffolds is challenging, and many covalent leads are instead discovered from reversible starting points.

This approach applying DNA-encoded library technology to covalent molecule discovery may be useful, especially in identifying non-acrylamide warheads like this example. This paper offers a great case study on how to execute and follow up on such a screen. One eye-catching reagent employed in the screen is “sheared salmon sperm DNA as a general blocking agent.”

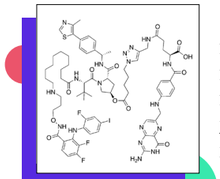
Small Molecules of the Month

May 2021
drughunter.com



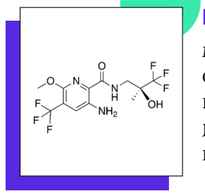
inavolisib | mPI3Kα

Isoform-selective mutant PI3Kα degrader
Oral <9 mg QD, Ph. III in HR+/HER2- BC
From cellular characterization of PI3Ki and opt.
bioRxiv, May 13, 2021
Genentech, South San Francisco, CA



Folate-MS432 | MEK1/2

Folate receptor-dependent PROTAC conjugate
FOLR1-dependent MEK1/2 degrad. in vitro
From conjugation of folate to PROTAC
J. Am. Chem. Soc., May 10, 2021
Harvard Medical / Mt. Sinai



Icenticaftor | CFTR

Mutant + WT CFTR Cl channel potentiator
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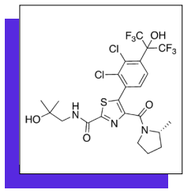
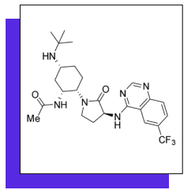
J. Med. Chem., May 24, 2021
Novartis, Horsham, UK / Cambridge, MA



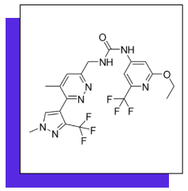
JNJ-61803534 | RORγt

Oral RORγt inverse agonist
Ph. I in HV up to 200 mg w/ PD, discontinued
From HTS + opt.
Scientific Reports, May 26, 2021
Janssen R&D, La Jolla, CA



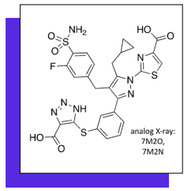
BMS-753426 | CCR2

Sel. CCR2 chemokine receptor antagonist
Oral efficacy (25 mpk BID) in inflamm. models
From PK opt. of prior candidate
ACS Med. Chem. Lett., May 25, 2021
Bristol Myers Squibb, Princeton, NJ



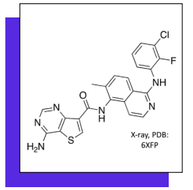
GLPG2938 | S1PR2

Selective S1PR2 antagonist preclin. candidate
Oral efficacy (1 mpk BID) in fibrosis model
Scaffold hop from literature starting points
J. Med. Chem., May 3, 2021
Galapagos NV, Mechelen, Belgium



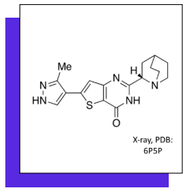
Compound 7 | GO/LDHA

LDHA and GO dual inhibitor
In vitro activity and X-ray vs. both targets
From SBDD of LDHA and GO inhibitors
ACS Med. Chem. Lett., May 20, 2021
Chinook Therapeutics, Seattle, WA



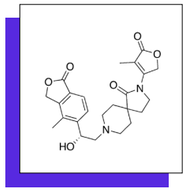
belvarafenib | RAF

Type II RAF dimer kinase inhibitor
Oral 450 mg BID, Ph. II in BRAF/RAS cancers
Demonstrated activity in NRAS-mut. tumors
Nature, May 5, 2021
Genentech, CA / Hanmi Pharma, KR



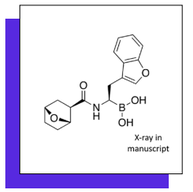
simurosertib | CDC7

CDC7 serine/threonine kinase inhibitor
Oral 50 mg QD, Ph. II in solid tumors compl.
From homology model pharmacophore + opt.
Sci. Adv., May 21, 2021
Takeda Pharmaceutical, Kanagawa, JP



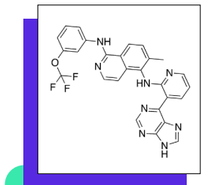
MK-8153 | ROMK

ROMK potassium channel blocker
Oral eff. in hypertension model (1 mpk QD)
Backup candidate to MK-7145 (Ph. Ib)
J. Med. Chem., May 26, 2021
Merck & Co., Kenilworth, NJ



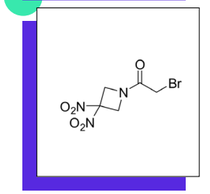
M3258 | LMP7

Sel. reversible cov. immunoproteosome inh.
Oral efficacy (1 mpk) in xeno., Ph. I in MM
From SBDD
Mol. Cancer Ther., May 27, 2021
Merck KGaA, Darmstadt, DE



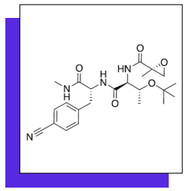
LUT014 | BRAF

Topical BRAF inhibitor (gel) for EGFRi rash
Ph. I in mCRC with EGFRi-related rash
Paradoxical activ. of MAPK to counter EGFRi
Cancer Discovery, May 25, 2021
Lutris-Parma, Tel Aviv, IL / MSKCC, NY



RRx-001 | pleiotropic

Surprisingly well-tolerated clinical molecule
Ph. III candidate in SCLC (4 mg IV QW)
From aerospace compound phenotypic screen
J. Med. Chem., May 27, 2021
EpicentRx Inc., La Jolla, CA



Compound 6 | BTK

Epoxide-based covalent BTK inhibitor
Cysteine reactive, Kinact/Ki ~ 6500
From covalent DEL library screening
Bioorg. & Med. Chem. Lett., May 19, 2021
X-Chem Inc., Waltham, MA

discover together

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