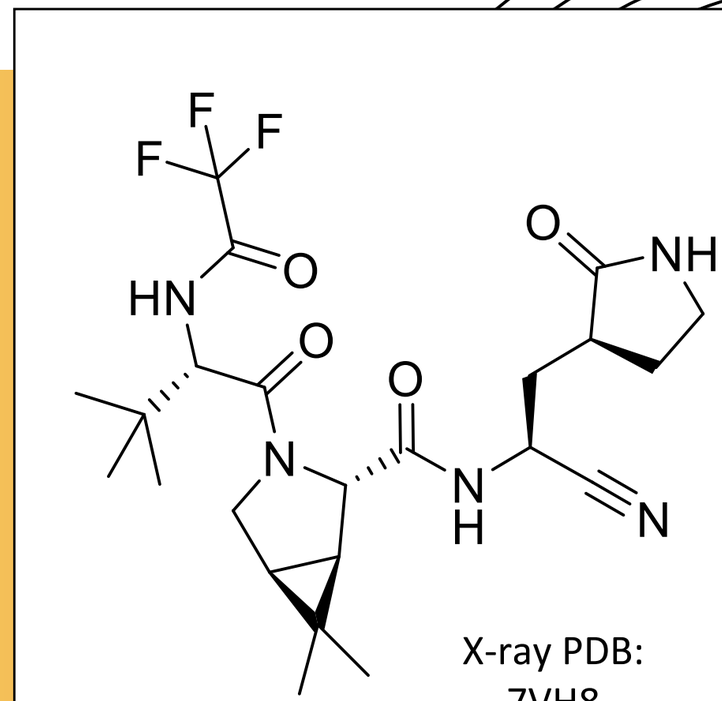
Molecules of the Year

2021

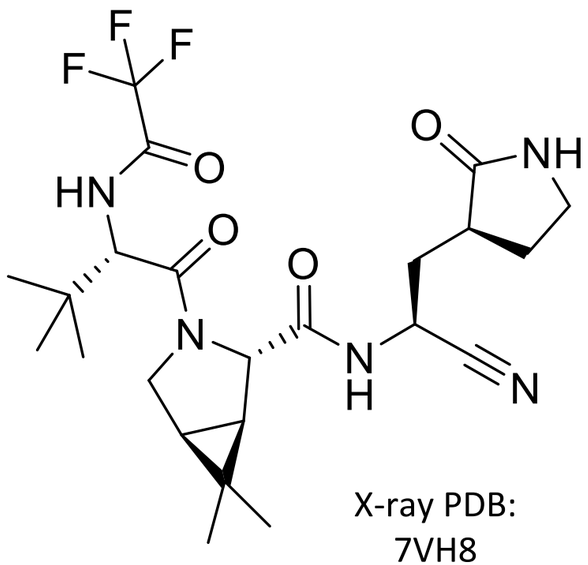


drug hunter

01	paxlovid (PF-07321332)	Pfizer
02	ARV-471	Arvinas
03	KB-0742	Kronos Bio
04	compound 44	Merck & Co.
05	MRTX1133	Mirati Therapeutics
06	mobocertinib	ARIAD/Takeda
07	LSN3318839	Lilly Research Laboratories
08	RM-018	Revolution Medicines
09	inovalisib (GDC-0077)	Genentech
10	H3B-8800	H3 Biomedicine
11	berotralstat	BioCryst
12	giredestrant (GDC-9545)	Genentech

paxlovid (PF-07321332)

Pfizer CoV-2 MPro Inhibitor



X-ray PDB:
7VH8

oral pan-coronavirus antiviral, rev. covalent

Ph. III candidate for COVID-19 (300 mg BID)

from SARS-CoV-1 inhibitor (WO2005113580)

paxlovid (PF-07321332)

Pfizer Worldwide Research

Pfizer's PF-07321332 (API of Paxlovid) is an oral, reversible covalent SARS-CoV-2 main protease inhibitor, which received emergency use authorization from the FDA for Covid treatment at the end of 2021. Clinical data showed Paxlovid reducing Covid hospitalization and death by 89%.

It was nominated for November's cover by Mike Koehler, Christian Kuttruff, and Callie Bryan. "Paxlovid sets a speed record in development that may never be broken!" said Mike Koehler. Their Science paper describing the development came out in the same month that their clinical trial was ended early due to strong efficacy. "I looked up some other recent molecules with rapid development times, and the standouts are the CFTR modulators, which were in trials for only about three years (but took a very long time to go from the phenotypic screens to development) and remdesivir, which received rapid approval, but was developed years earlier as a general antiviral therapy and repurposed."

Paxlovid became more important after molnupiravir showed sharply reduced efficacy in the final analysis of its trial data relative to the interim analysis. The reduction in hospitalization risk for molnupiravir patients had fallen from 48% to just 30% in the bigger data set.

Reviewer Ron Li says, "The reality is that the vaccines, although extremely helpful, have shown lower effectiveness against omicron, especially for immunocompromised patients. I recently took care of two fully vaccinated patients (with boosters), but were taking immunosuppressants. Both were hospitalized with severe Covid. It would be a gamechanger for our fight against Covid if Paxlovid can demonstrate a significant benefit for this patient population.

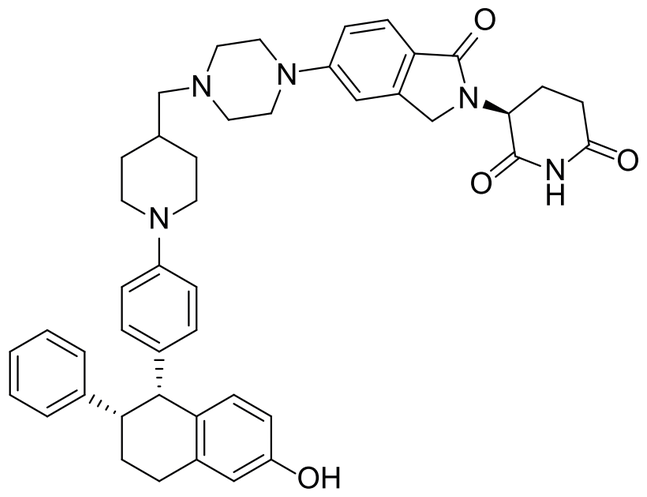
There is also growing evidence that initial severity of disease is associated with persistent symptoms and chronic complications (this includes the constellation of symptoms commonly referred to as long covid, but also complications such as heart disease and blood clots). It will be interesting to see whether Paxlovid impacts of these long term outcomes.

Decreased hospitalizations, improved outcomes for immunocompromised patients, and decreased risk of chronic complications of Covid would be a triple win!"

The molecule originated from a preclinical candidate for SARS (SARS-CoV-1) (WO2005113580) in the early 2000's, the further development of which was halted due to the end of the SARS outbreak. PK and pharmaceutics optimization led to PF-07321332, which is a rare example of a clinical candidate with a reversible covalent nitrile warhead. The nitrile warhead resulted in greatly improved permeability and oral absorption over the α-hydroxymethyl ketone-bearing starting point. The molecule was first made on July 22, 2020, only months after the project was initiated, and the first 1.4 kg was prepared by early November. In an industry where we are accustomed to 12-year development timeframes, the pace of this molecule's discovery and development by the Pfizer team is truly breathtaking.

ARV-471

Arvinas ER Chimeric Degrader



CRBN-based heterobifunctional ER degrader
oral Ph. II candidate for ER+/HER2- BC
from ER ligand and CRBN ligand
ARV-471
Arvinas, New Haven, CT

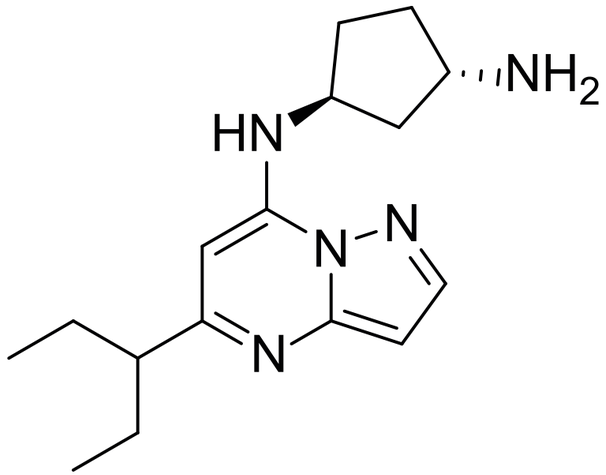
The Arvinas ER chimeric degrader, ARV-471, is an oral, bioavailable ER degrading CRBN-based PROTAC for the treatment of patients with ER+/HER2- breast cancer. Along with ARV-110, it is one of the first chimeric degraders to enter a Ph. II clinical trial. It was first disclosed at AACR in early 2021, and though the molecules have not been formally published yet, related analogs have been published and characterized.

ER degradation with SERDs like fulvestrant is a well-validated mechanism, but fulvestrant doesn't appear to achieve complete degradation of ER. ARV-471 achieves deeper tumor regression in preclinical models over fulvestrant, at much lower doses, and has a more prominent effect in combination with CDK4/6 inhibitor palbociclib.

In humans, the molecule has an effective half life of 28 h, and antitumor activity is observed in patients at doses as low as 120 mg QD. While ARV-471 will face strong competition from next-generation SERDs currently in trials like giredestrant (also featured here), the demonstration of oral activity at a reasonable dose in humans is an important proof-of-principle for the PROTAC strategy. For a long time, the scientific community was skeptical that PROTACs could be rendered suitable for once-daily oral dosing, and molecules like ARV-471 have ended that dogma.

KB-0742

Kronos CDK9 Inhibitor



selective CDK9 inhibitor
oral Ph. I candidate for MYC-amp tumors
from microarray binding assay with lysate
KB-0742
Kronos Bio, Cambridge, MA

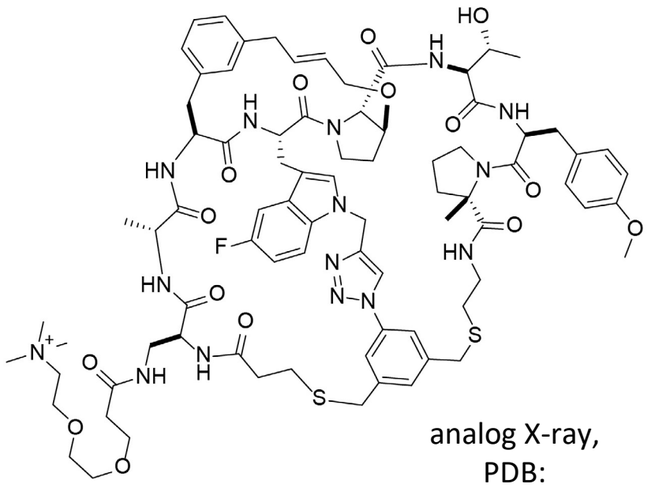
The Kronos CDK9 inhibitor, KB-0742, is an ultraselective inhibitor of cyclin-dependent kinase CDK9. The CDK family of kinases have been pursued as cancer drug targets for decades, but family selectivity within the highly conserved kinase family has made it difficult to identify highly selective molecules, resulting in less than ideal tolerability. The molecule has a remarkably efficient, simple structure, rare among selective kinase inhibitors. The nearest off-targets are CDK13 and CDK2 with >60x selectivity, and it is selective against all other CDKs with >200x selectivity (including CDKs 1, 7, 4, and 6). It is currently in Ph. I for MYC-amplified solid tumors.

Kronos published the discovery story and preclinical evaluation of this selective CDK9 inhibitor in Cell Chemical Biology in early 2021, and demonstrated that the molecule has enhanced potency in MYC-amplified cell lines. The Kronos team also announced positive interim results from their dose-escalation studies, including excellent PK properties and target engagement demonstrated by modulation of pPolII. No serious adverse events have been observed to date.

The fragment starting point was identified using a microarray binding assay with cell lysates, and is a good example of how the strategy used to find a good starting point is often key to success in drug discovery, and that bigger molecules are not better.

compound 44

Merck PCSK9 Inhibitors



analog X-ray, PDB: 7S5H

macrocyclic PCSK9/LDLR PPI inhibitor
oral PD in Ph. I with MK-0616
from mRNA display screen and SBDD
published example: compound 44
Merck & Co.

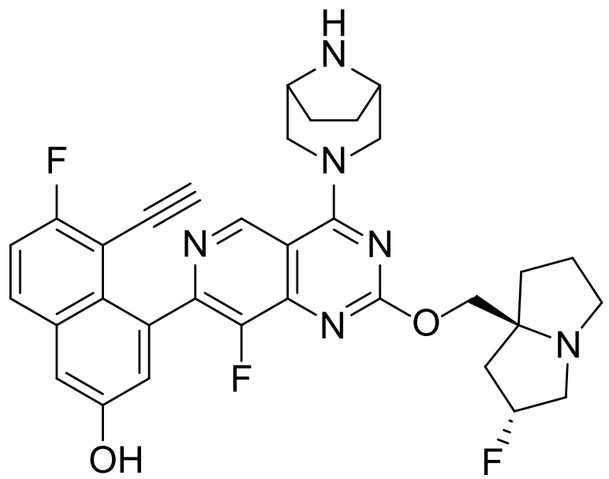
MK-0616 is a macrocyclic PCSK9 inhibitor with demonstrated once-daily PCSK9-lowering and LDL-cholesterol-lowering activities in a human clinical trial (<300 mg QD). Currently PCSK9-targeting therapies are only available by injection, and the cost-benefit of using large molecules to lower cholesterol has been hotly debated. Identification of oral PCSK9 inhibitors has been something of a "holy grail" for the field, but difficult to achieve due to the poor ligandability of the target.

While MK-0616 has not been formally published, related macrocycles have been disclosed that illustrate the concept. The Merck bicyclic macrocyclic peptide PCSK9 inhibitor, "compound 44," is a highly potent (Ki = 0.00239 nM) and orally bioavailable (cyno %F = 2.9, t1/2 = 10 h) agent that demonstrated in vivo target engagement comparable to approved PCSK9 antibodies.

The discovery of such molecules is an interesting proof of concept for this emerging area of drug space (rationally designed oral macrocyclic peptides), with hits generated by a relatively new technology (mRNA display screen) and advanced with structure-based design (potency increased by 100,000x). Several off-target issues were addressed while simultaneously lowering clearance, lipophilicity, and improving oral bioavailability. Interestingly, the clearance of the molecules was shifted over time from predominantly hepatic to renal by reducing OATP 1B1 transporter activity. This PCSK9 drug discovery campaign is a tour de force from the team at Merck and will remain a "classic" in bRO5 drug discovery.

MRTX1133

Mirati KRAS^{G12D} Inhibitor



reversible KRAS^{G12D} inhibitor

preclinical efficacy in cancer model

from SBDD around KRAS^{G12C} inhibitor MRTX1133

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 said, "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."

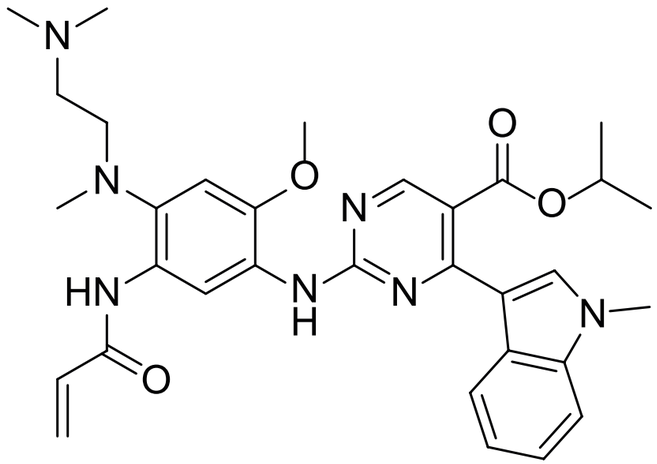
"This reflects, in retrospect, the power of covalent screening as an enabler of a stepwise progression from a covalent (G12C) to a corresponding non-covalent target (G12D). While not discussed in this paper, the dibasic nature of MRTX1133 likely compromises oral bioavailability, but following intraperitoneal 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.

mobocertinib

Takeda EGFRex20 Inhibitor



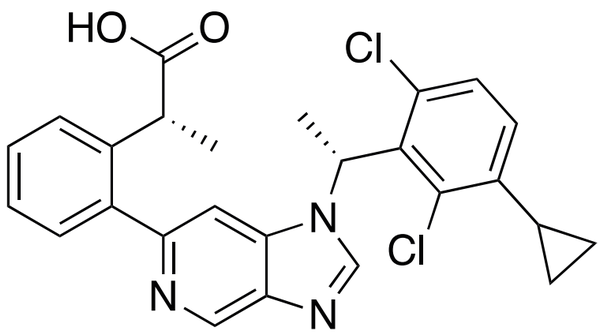
EGFR exon 20 mutant inhibitor, oral once-daily
Breakthrough Therapy for ex20+ NSCLC (Ph. I)
from cellular screening + SBDD
mobocertinib
ARIAD/Takeda, Cambridge, MA

The ARIAD/Takeda EGFR exon 20 insertion mutant (EGFR ex20 in) inhibitor TAK-788 is a Breakthrough Therapy for patients with advanced non-small cell lung cancer (NSCLC) whose tumors harbor EGFR exon 20 insertion mutations. The appearance of exon 20 insertions is a common resistance mechanism to earlier generations of EGFR inhibitors including osimertinib, to which TAK-788 is structurally related.

1st and 2nd generation EGFR inhibitors partly depend on the fact that mutant forms of EGFR have destabilized inactive forms with reduced ATP affinity relative to wild-type (WT) EGFR, making the mutant forms easier to drug in cells. EGFR exon 20 mutants, however, have active sites that are very similar to WT, making tumors bearing these mutations difficult to drug without significant side effects due to WT inhibition. This oral covalent inhibitor is more potent against exon 20 mutants than WT in cells, and is also active against a range of other common EGFR mutations. While the selectivity is still modest and side effects that seem related to WT EGFR inhibition are observed clinically, the significant responses in exon 20 insertion-bearing tumors is encouraging.

LSN3318839

Lilly GLP Molecular Glue

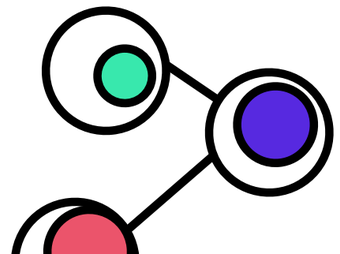


GLP-1R/GLP molecular glue agonist (PAM)
oral blood glucose↓, additive w/ sitaglipin
from 220k cmpd cell-based screen + PK opt.
LSN3318839
Lilly Research Laboratories, Indianapolis, IN

The Lilly glucagon-like peptide-1 receptor (GLP-1R) agonist (LSN3318839) is a positive allosteric modulator intended to treat type 2 diabetes. This drug candidate has an interesting proposed mechanism as a molecular glue between GLP-1R and GLP peptide, enhancing endogenous peptide activity. GLP-1 agonism is a well-established mechanism for treatment of diabetes, with most drugs being injectable peptides (glucagon or its derivatives).

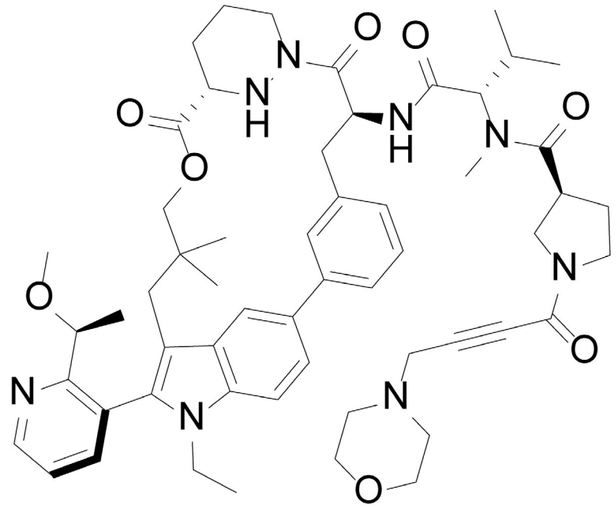
The starting point was identified from a 220k compound cell-based screen in the presence of GLP-1 peptide, and optimization of PK of prior lead LSN3160440 led to LSN3318839. Oral administration of LSN3318839 (30 mg/kg) results in a blood glucose lowering effect in animal models, which is additive with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

It is the first characterized molecular glue for GPCRs with demonstrated in vivo efficacy. An oral option for GLP agonism could be a valuable alternative to the injections currently employed frequently by diabetics, though it remains to be seen whether the typically slower speed of action of an oral drug would impact adoption.



RM-018

RevMed KRAS^{G12C} Tricomplex Inhibitor



KRAS(G12C)ON-cyclophilin A tri-complex inh. overcomes KRAS resist. mut. in PDX model natural product related (sanglifehrin); undiscl.
RM-018
Revolution Medicines, Redwood City, CA

The Revolution Medicines KRASG12C inhibitor, RM-018, "glues" KRASG12C to the highly abundant chaperone protein, cyclophilin A, in a tri-complex (KRAS- inhibitor-cyclophilin A) stabilized by protein-protein interactions. An undisclosed molecule in their pipeline with a related mechanism, RMC-6291, has been reported to be orally bioavailable in multiple species, with oral activity in PDX models.

KRAS is a driver of cancer cell growth, and mutants including KRAS^{G12C} have been hot targets due to the newfound ability to drug them selectively over wild type KRAS, which is important for healthy cell division. The first KRAS^{G12C} inhibitor, sotorasib, was approved in 2021.

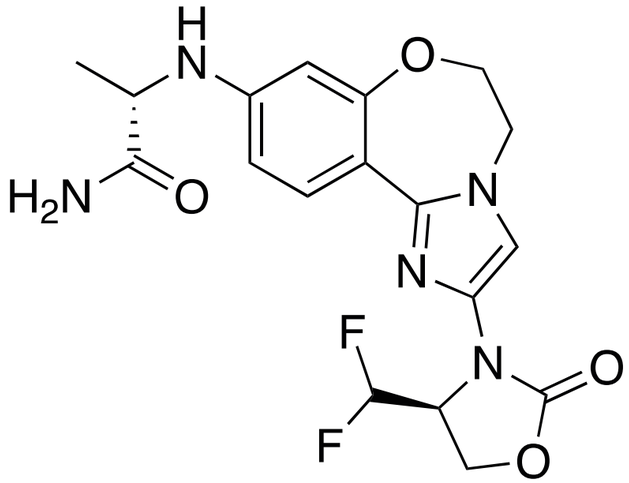
While GTP-OFF inhibitors of KRAS^{G12C} which bind to a switch-II have demonstrated clinical efficacy (including 2020 Small Molecule of the Year Finalist, MRTX849), resistance to such inhibitors was inevitable due to switch- II mutations. Because RM-018 targets the GTP-ON state of KRAS^{G12C} with a unique mechanism, it overcomes GTP-OFF resistance mutations such as KRAS$^{G12C/Y96D}$ in patient-derived xenografts.

While the discovery story hasn't been published, based on the cyclophilin- binding MoA and structure it's likely that the compound was inspired by the natural product sanghlifehrin A.

RevMed appears to be advancing related compounds toward clinical development, and KRAS is likely not the only target this fascinating tri- complex mechanism will be applied to. Whether this new mechanism will be as well-tolerated in humans as mutant-selective inhibition remains to be seen.

inovalisib (GDC-0077)

Genentech mPI3Kα Degrader



isoform-selective mutant PI3Kα degrader
oral <9 mg QD, Ph. III in HR+/HER2- BC
from cellular characterization of PI3Ki and opt.
inovalisib (GDC-0077)
Genentech, South San Francisco, CA

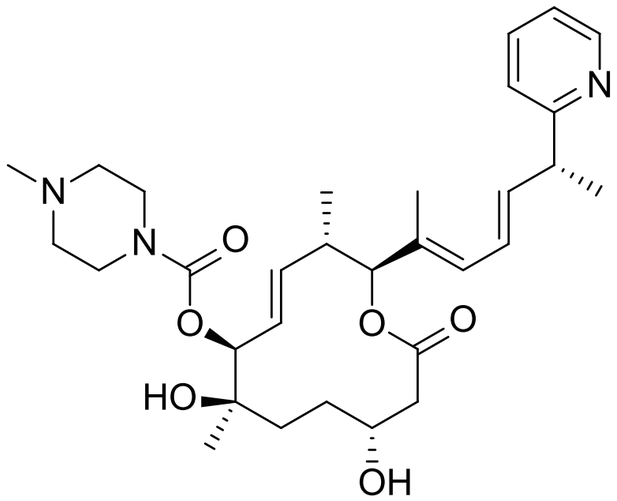
The Genentech PI3Kα isoform-selective kinase inhibitor and mutant PI3Kα degrader inavolisib selectively depletes the oncogenic mutant p110α catalytic subunit of PI3Kα in cancer cells with active receptor tyrosine kinase (RTK) signaling. The gene encoding p110α, PIK3CA, is one of the most frequently mutated 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, inovalisib 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 inovalisib 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.

H3B-8800

H3Bio SF3b Splicing Modulator



oral splicing modulator (SF3b complex)
7-20 mg 21d+/7d-, Ph. I for myeloid neoplasias
from opt. of pladienolide B natural product
H3B-8800
H3 Biomedicine, Cambridge, MA

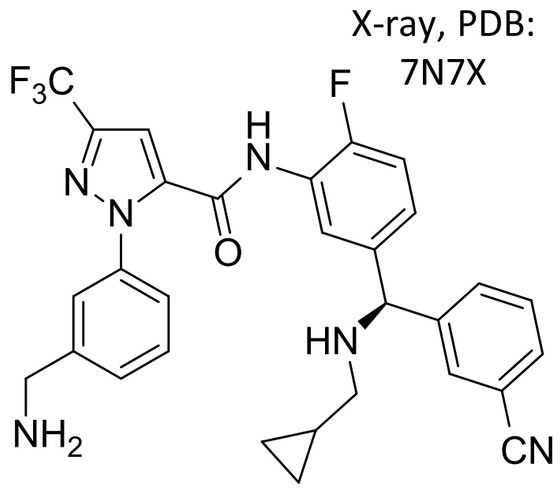
The H3 Biomedicine RNA splicing modulator, H3B-8800, targets the spliceosome SF3b complex containing either wild-type (WT) or mutant SF3B1. Splicesome inhibition can induce synthetic lethality since cancer cells bearing spliceosome mutations are more dependent on WT spliceosome function. The compound is derived from the natural product, pladienolide B, optimizing for preferential cytotoxicity in spliceosome-mutant cells.

H3B-8800 completed a Ph. I study in myeloid neoplasias (MDS, CMML, AML) where it was given once-daily in cycles (e.g. 7-20 mg, 21d on, 7d off). Mostly low-grade treatment-related adverse events (TAEs) were seen but no objective responses were observed, though patients with a TMEM14C biomarker were more likely to become transfusion independent. The rest cycles in the study design suggest some on-target toxicity was probably anticipated, drug activity was not strong or strongly-defined by a single biomarker, a profile characteristic of many drugs with epigenetic machinery targets.

The optimization of a natural product for selectivity and once-daily oral administration is impressive, and hopefully more medicinal chemistry details will be shared soon.

berotralstat

BioCryst Kallikrein Inhibitor



oral plasma kallikrein serine protease inhibitor
approved for prevention of HAE attacks
from structure-based drug design
berotralstat
BioCryst, Birmingham, AL

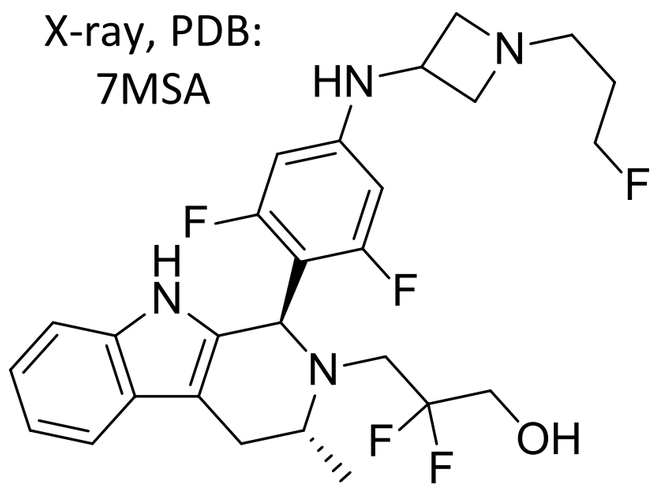
The Biocryst oral plasma kallikrein inhibitor, berotralstat (BCX7353), was recently approved as the first non-steroidal treatment for prevention of hereditary angioedema attacks. The molecule is given orally (150 mg QD) despite having two basic amines.

Interestingly for a chronically administered drug, the molecule is noted to have QT prolongation risk at ~3x the recommended dose (450 mg), which appears acceptable for this rare and underserved indication. The molecule was discovered after a structure-based drug design campaign starting with knowledge from a previously poorly bioavailable benzamidine-containing zwitterion, avoralstat (BCX4161).
The benzamidine was successfully replaced with a similarly basic benzylamine, and the new benzylamine-containing fragment was elaborated into molecule with a highly dissimilar structure and binding mode from the original drug.

There are several interesting features from the crystal structures including the fact that the highly hydrophilic primary amine is buried in a polar cleft of the protein. This approved drug is another great example of a “rule-breaker” succeeding in a rare disease setting.

giredestrant (GDC-9545)

Genentech ER Degrader



selective ER degrader (SERD) + full antag.
oral (30 mg QD), Ph. III for ER+, HER2- BC
from profiling >4k cmpds for desired MoA
giredestrant (GDC-9545)
Genentech, San Francisco, US

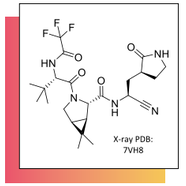
The Genentech next generation oral SERD (selective estrogen receptor degrader) and full antagonist, giredestrant (GDC-9545), is a potential best-in-class Ph. III candidate for ER+, HER2- breast cancer (NCT04546009). It is the third SERD clinical candidate from Genentech (after GDC-0810 and GDC-0927) and a number of oral SERDs have previously been highlighted on *Drug Hunter* (including SAR439659, AZD9833, GNE-149).

The oral, once-daily molecule has been well-tolerated at doses up to 250 mg and a standardized 30 mg dose has been selected for development. Interim analysis and updated data from trials NCT03916744 and NCT03332797 show promising activity including in the presence of ESR1 mutations. Hormone therapy is a mainstay of treatment for breast cancer, but side effects have a significant quality of life impact and affect treatment adherence. A well-tolerated, easily combinable, and effective ER degrader could be beneficial, especially in preoperative (adjuvant) settings where quality of life is particularly important, and patients are expected to do relatively well vs. later stage cancers.

drug hunter

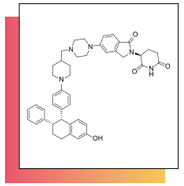
2021 Small Molecules of the Year

drughunter.com



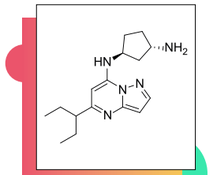
Pfizer CoV-2 M^{Pro} Inhibitor

oral pan-coronavirus antiviral, rev. covalent
Ph. III candidate for COVID-19 (300 mg BID)
from SARS-CoV-1 inhibitor (WO2005113580)
paxlovid (PF-07321332)
Pfizer Worldwide Research



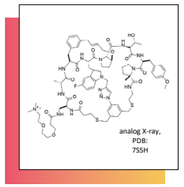
Arvinas ER Chimeric Degrader

CRBN-based heterobifunctional ER degrader
oral Ph. II candidate for ER+/HER2- BC
from ER ligand and CRBN ligand
ARV-471
Arvinas, New Haven, CT



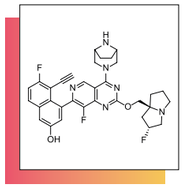
Kronos CDK9 Inhibitor

selective CDK9 inhibitor
oral Ph. I candidate for MYC-amp tumors
from microarray binding assay with lysate
KB-0742
Kronos Bio, Cambridge, MA



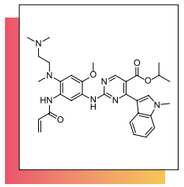
Merck PCSK9 Inhibitors

macrocyclic PCSK9/LDLR PPI inhibitor
oral PD in Ph. I with MK-0616
from mRNA display screen and SBDD
published example: compound 44
Merck & Co.



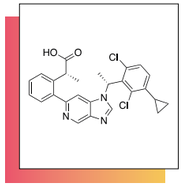
Mirati $KRAS^{G12D}$ Inhibitor

reversible $KRAS^{G12D}$ inhibitor
preclinical efficacy in cancer model
from SBDD around $KRAS^{G12C}$ inhibitor
MRTX1133
Mirati Therapeutics, San Diego, CA



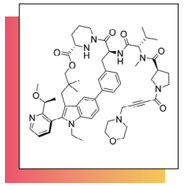
Takeda EGFR ex20 Inhibitor

EGFR exon 20 mutant inhibitor, oral once-daily
Breakthrough Therapy for ex20+ NSCLC (Ph. I)
from cellular screening + SBDD
mobocertinib
ARIAD/Takeda, Cambridge, MA



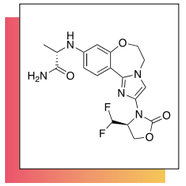
Lilly GLP Molecular Glue

GLP-1R/GLP molecular glue agonist (PAM)
oral blood glucose↓, additive w/ sitaglipin
from 220k cmpd cell-based screen + PK opt.
LSN3318839
Lilly Research Laboratories, Indianapolis, IN



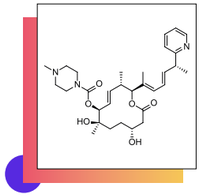
RevMed $KRAS^{G12C}$ Tricomplex Inhibitor

KRAS(G12C)ON-cyclophilin A tri-complex inh.
overcomes KRAS resist. mut. in PDX model
natural product related (sanglifehrin); undiscl.
RM-018
Revolution Medicines, Redwood City, CA



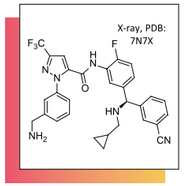
Genentech mPI3Kα Degrader

isoform-selective mutant PI3Kα degrader
oral <9 mg QD, Ph. III in HR+/HER2- BC
from cellular characterization of PI3Ki and opt.
inovalisib (GDC-0077)
Genentech, South San Francisco, CA



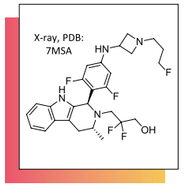
H3Bio SF3b Splicing Modulator

oral splicing modulator (SF3b complex)
7-20 mg 21d+/7d-, Ph. I for myeloid neoplasias
from opt. of pladienolide B natural product
H3B-8800
H3 Biomedicine, Cambridge, MA



BioCryst Kallikrein Inhibitor

oral plasma kallikrein serine protease inhibitor
approved for prevention of HAE attacks
from structure-based drug design
berotralstat
BioCryst, Birmingham, AL



Genentech ER Degrader

selective ER degrader (SERD) + full antag.
oral (30 mg QD), Ph. III for ER+, HER2- BC
from profiling >4k cmpds for desired MoA
giredestrant (GDC-9545)
Genentech, San Francisco, US

discover together

drughunter.com
info@drughunter.com