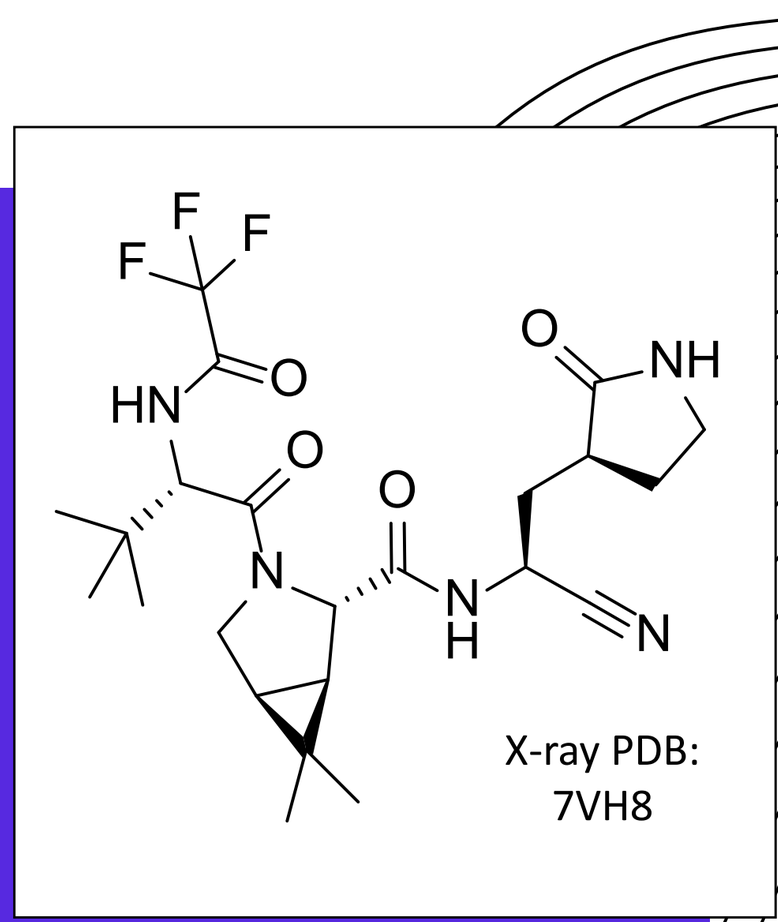
Small Molecules of the Month

November 2021

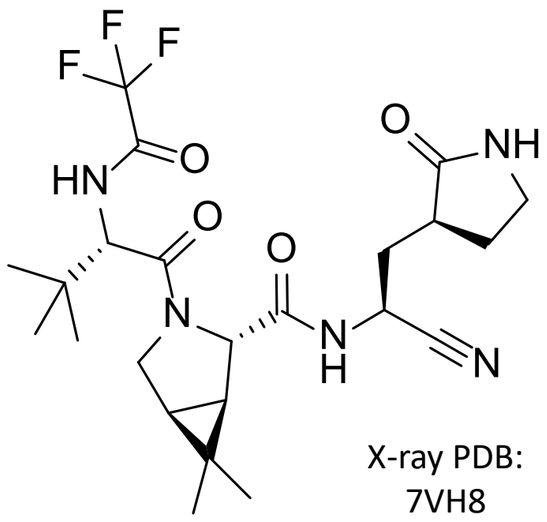


drug hunter

01	SARS-CoV-2 M^{pro}	Pfizer Worldwide Research
02	SARS-CoV-2	Gilead Sciences Inc.
03	$KRAS^{G12C}$	Astellas Pharma Inc.
04	CDK7	Syros Pharmaceuticals Inc.
05	BTK	Biogen
06	BRAF	Roche
07	CDK8	Daiichi Sankyo Co. Ltd.
08	ELOVL1	Vertex Pharmaceuticals Inc.
09	MET	Merck KGaA
10	PRMT5	Pfizer Oncology
11	VPS34	Genentech Inc.
12	TRPM8	Dompé Farmaceutici S.p.A
13	PfeEF2	Merck Institute for Pharmacometrics
14	RET	Novartis Genomics Institute

PF-07321332

SARS-CoV-2 M^{pro}



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)

Science

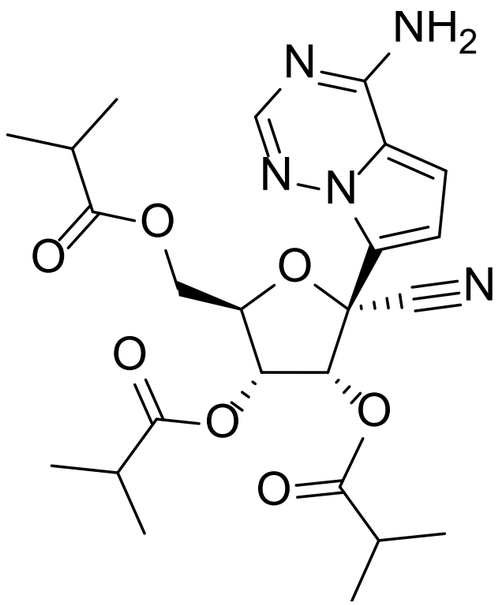
Pfizer Worldwide Research

This month's cover molecule, Pfizer's PF-07321332 (API of Paxlovid) is an oral, reversible covalent SARS-CoV-2 main protease inhibitor, which has been submitted to the FDA by Pfizer for emergency approval for Covid treatment. Interim data showed Paxlovid reducing Covid hospitalization and death by 89%. It was nominated for this month's cover by Mike Koehler, Christian Kuttruff, and Callie Bryan. "Paxlovid sets a speed record in development that may never be broken!" says 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.

Paxlovid may be more important now that 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 has fallen from 48% to just 30% in the bigger data set. 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. If approved, PF-07321332 is likely to be a significant tool in addressing Covid.

GS-621763

SARS-CoV-2



oral antiviral prodrug of remdesivir
effective in a ferret SARS-CoV-2 model
from remdesivir nucleoside (GS-441524)
Nature Communications
Gilead Sciences Inc.

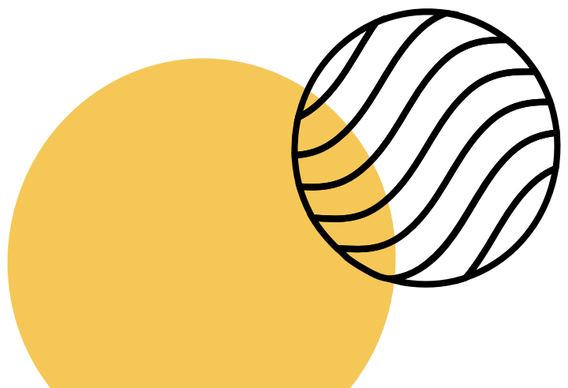
The Gilead SARS-CoV-2 drug, GS-621763, is an oral prodrug of the parent nucleoside of remdesivir (GS-441524) which demonstrated therapeutic and prophylactic efficacy in a ferret model of SARS-CoV-2 infection, significantly reducing viral load to near-undetectable levels with twice-daily administration.

Remdesivir is already FDA approved as an IV medication, and this orally available counterpart would greatly improve its utility in combating Covid especially in outpatient settings.

GS-621763 is pre-systemically hydrolyzed to provide high systemic exposures of GS-441524, which is converted in lungs to the triphosphate metabolite; identical to the metabolite generated by remdesivir.

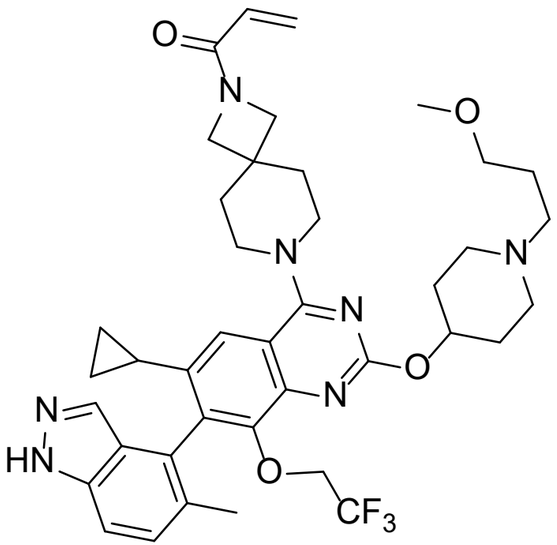
The potential human daily oral dose of this molecule is estimated to be roughly 250 mg.

This is another proof-of-concept that suggests that oral pills and combinations of multiple mechanisms are on their way to address SARS-CoV-2 and its mutants.



ASP2453

KRAS^{G12C}



oral drug, covalent inhibitor of KRAS^{G12C}

effective in KRAS^{G12C}-mutated cancer models

SBDD utilizing KRAS proto-oncogene, GTPase

British Journal of Cancer

Astellas Pharma Inc.

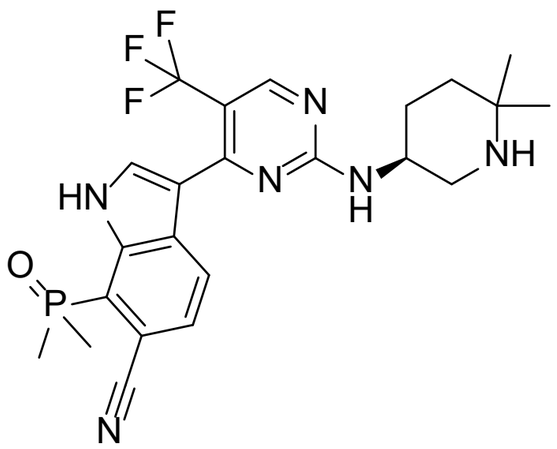
The Astellas KRAS^{G12C} covalent inhibitor, ASP2453, is an oral molecule with activity in preclinical mouse models of KRAS^{G12C}-mutated cancer at lower doses than sotorasib (AMG 510).

Several KRAS inhibitors have been highlighted recently.

ASP2453 possesses an interesting spirocyclic azetidine-containing acrylamide warhead, and the authors note that ASP2453 is likely more reactive than piperazine-bearing AMG 510. ASP2453 does not appear to have entered clinical development yet.

SY-5609

CDK7



oral picomolar & reversible CDK7 inhibitor
Ph. I candidate in breast cancer comb. therapy
from previous CDK7 inhibitor SY-1365
Journal of Medicinal Chemistry
Syros Pharmaceuticals Inc.

The Syros Pharmaceuticals CDK7 kinase inhibitor, SY-5609, is a picomolar, reversible, and highly selective molecule with slow off-rate kinetics.

It follows a prior covalent clinical candidate from Syros.

The molecule is >4000x selective vs. the nearest known off-target among 485 kinases profiled.

Cyclin-dependent kinase inhibitors have seen a resurgence in interest recently as previous issues with family selectivity and potential toxicity now seem surmountable.

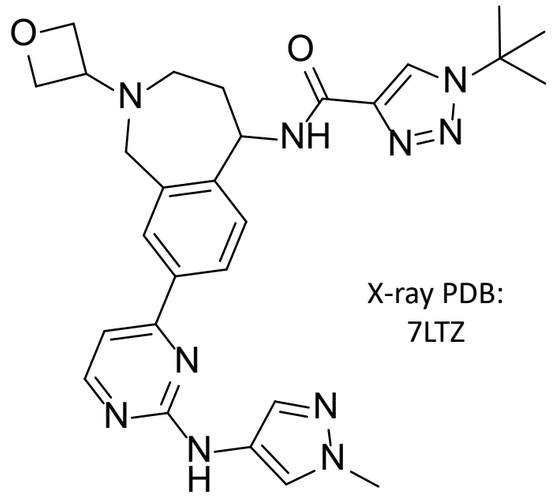
This is thanks to a combination of biomarker-focused clinical development and the success of combination regimens and patient selection for CDK4/6 inhibitors as well as wealth of industry kinase drug discovery experience.

This inhibitor is a rare example of a phosphine-oxide containing clinical candidate, though the motif is likely to be more frequently used due to the precedent set by brigatinib.

The molecule entered clinical development in 2020 (NCT04247126) in patients with advanced solid tumors and in combination with fulvestrant in patients with HR+, HER2- breast cancer.

BIIB091

BTK



X-ray PDB:
7LTZ

oral reversible BTK kinase inhibitor
Ph. I candidate for multiple sclerosis
from prior BTK inhibitor BIIB0685
Journal of Medicinal Chemistry
Biogen

The Biogen reversible BTK kinase inhibitor, BIIB091, is a highly selective, phase I clinical candidate for multiple sclerosis.

Irreversible BTK inhibitors have been explored and developed extensively, primarily in cancer.

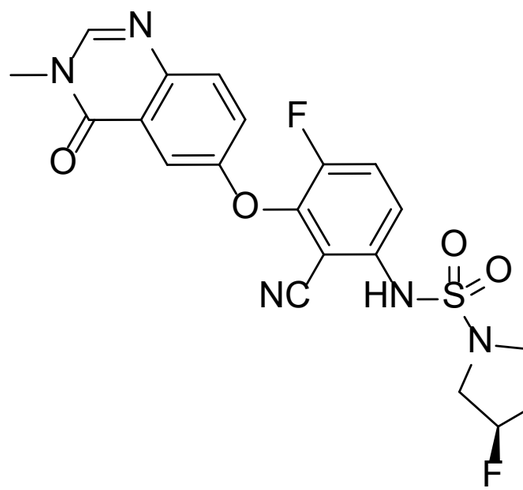
Reversible molecules have been less common, with the most clinically advanced molecule being fenebrutinib (phase III).

This molecule possesses an uncommon benzoazepine core and triazine amide, whose polarity contribute to favorable overall drug properties.

The amine is rendered non-basic by the oxetane and other substitutions (pKa = 2.8), and the molecule is more polar than the typical active-site kinase inhibitor with corresponding properties (e.g. solubility >50 ug/mL, logD = 2.2, PPB f_u = 18%) The Biogen team reported good safety in two preclinical species with a high NOAEL of 250 mg/kg in cyno (>10x over projected human efficacious dose) and efficacy in a mouse TI2 immunization model (there are no animals that recapitulate multiple sclerosis, a human disease). Human safety data has not yet been reported.

compound Ia

BRAF



oral BRAF inhibitor, brain penetrant
effective in A375-derived mouse models
from prior paradox inducing BRAF inhibitors
Clinical Cancer Research
Roche

The Roche BRAF inhibitor, compound Ia, is designed to address the limitations of existing BRAFi/MEKi inhibitor combinations.

It is a RAF paradox breaker (see belvarafenib) and is brain penetrant, offering the potential to address several mechanisms of resistance to approved agents and potentially reducing the need for MEKi combination (which brings in additional side effects).

Preclinical superiority was demonstrated over approved BRAFi in macro-metastatic and disseminated micro-metastatic brain tumor models.

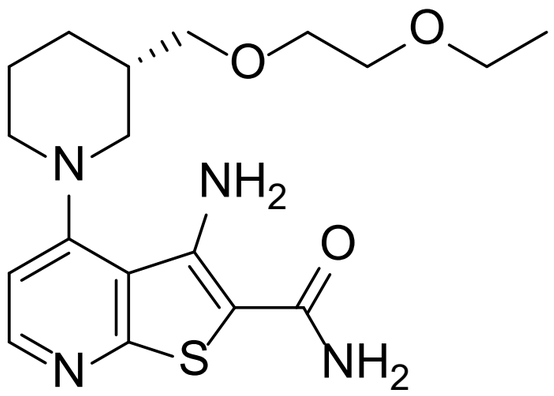
The high CNS permeability could extend the duration of response in melanoma patients for whom brain metastases are a fatal and frequent outcome.

Compound Ia was well-tolerated in mice at all doses tested (up to 180 mg/kg).

CNS drug hunter Jake Schwarz says, “Limiting HBDs is a key component of brain penetration, and this beauty only has one.”

DS96432529

CDK8



oral CDK8 kinase inhibitor
effective in ovariectomized rat model
CDK8 identified as MoA after screen
Bioorganic & Medicinal Chemistry Letters
Daiichi Sankyo Co. Ltd.

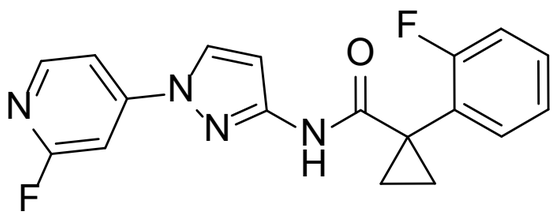
The Daiichi Sankyo CDK8 kinase inhibitor, DS96432529, is intended to be a bone anabolic agent.

The molecule shows preclinical efficacy and synergy with alendronate or parathyroid hormone.

The discovery program was initiated well before the likely target (CDK8) was identified and provides an interesting retrospective case study for phenotypic drug discovery.

compound 27

ELOVL1



oral ELOVL1 inhibitor for ALD, CNS penetrant

toxicities observed in higher species

internal HTS and LBDD

Journal of Medicinal Chemistry

Vertex Pharmaceuticals Inc.

The Vertex ELOVL1 inhibitor, compound 27, is a potent (13 nM) CNS-penetrant compound that reduces very long chain fatty acid (VLCFA) levels in the CNS, which are believed to be pathological in the rare disease adrenoleukodystrophy (ALD).

The starting point came from an HTS on compounds from an internal collection.

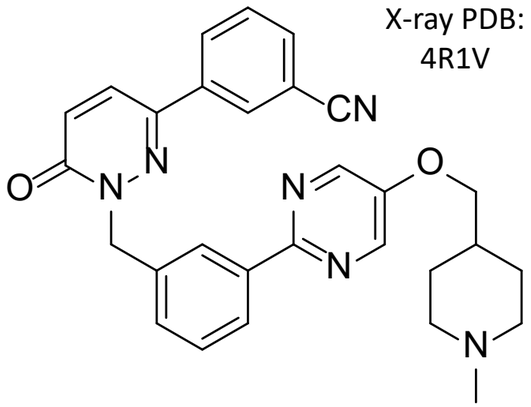
The molecule demonstrated activity in patient fibroblasts, lymphocytes, and microglia, as well as PD in mouse models of ALD.

Unfortunately, preclinical safety findings in the skin, eye, and CNS including irreversible corneal damage in rat as well as seizures and skin lesions in cyno are significant risks to further development.

A comparison of the findings to genetic models and data suggests on-target safety liabilities. The Vertex team generously shares safety details in this article which is rare but will be very helpful to the community in assessing this pathway in drug discovery.

tepotinib

MET



oral MET kinase inhibitor
approved for clinical use in NSCLC
internal HTS and SBDD
Clinical Cancer Research
Merck KGaA

The Merck KGaA MET kinase inhibitor, tepotinib, was approved earlier this year for METex14 positive NSCLC patients, and is administered once-daily in contrast to capmatinib, which was approved in 2020.

Both molecules were approved based on small numbers of patients (tepotinib pivotal trial: NCT02864992) due to the significance of the response in trials.

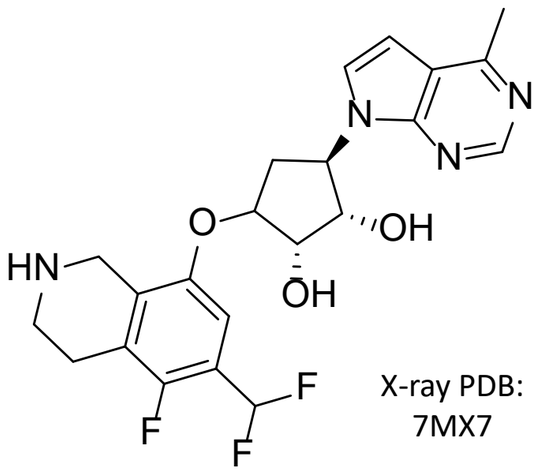
MET is a great case study for small molecules being approved before large molecules for a surface receptor – anti-MET antibodies were expected to lead in this area and were initially thought to be more clinically advanced.

MET antibodies surprisingly failed to demonstrate efficacy in later trials, which may be due to a number of factors including the fact that antibodies can in certain cases be agonists for their target receptor and small molecules may be better for amplification mutants as well as other mutants that do not depend on ligand activation.

Both capmatinib and tepotinib demonstrate meaningful intracranial activity (favorable results in 13/15 evaluable patients for tepotinib).

PF-06939999

PRMT5



X-ray PDB:
7MX7

oral SAM-competitive PRMT5 inhibitor
Ph. I candidate for solid tumors (adv. or met.)
SBDD utilizing PRMT5:MEP50 w/ A9145C
Molecular Cancer Therapy
Pfizer Oncology

The Pfizer SAM-competitive PRMT5 inhibitor, PF-06939999 is a Ph. I clinical candidate in dose escalation in solid tumors. Ph. I data has been reported showing signs of early efficacy with cytopenias as common adverse events.

This is in agreement with Ph. I data that was recently reported for a JNJ SAM-competitive PRMT5 inhibitor in which thrombocytopenia was identified as a dose-limiting toxicity and an early efficacy signal may have been detected.

The Pfizer team suggests that PRMT5i may be especially beneficial in cancers which are dependent on alternative splicing pathways.

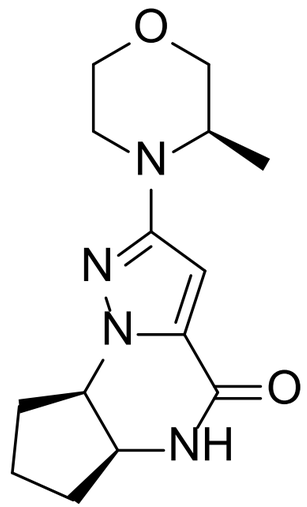
Furthermore, preclinical resistance studies suggest that complete resistance to SAM site inhibitors may be prevented due to structural constraints in the co-factor binding site.

The discovery campaign began with the published crystal structure of PRMT5:MEP50 complexed with the nucleoside A9145C. To minimize the synthetic complexity associated with A9145C and AdoMet analogs, a ligand truncation strategy was employed to define a minimum pharmacophore.

For an excellent recent review of the PRMT5/MAT2A pathway by Agios and Novartis scientists, see here. Clinical development appears to continue at the moment.

compound 5

VPS34



X-ray PDB:
7RSV

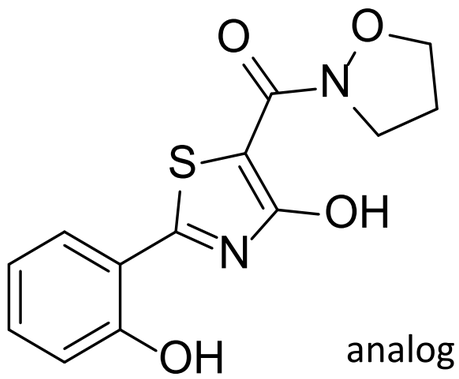
oral selective VPS34 kinase inhibitor
discontinued due to potential toxicity
SBDD and SAR optimization
Journal of Medicinal Chemistry
Genentech Inc.

The Genentech VPS34 kinase inhibitor, compound 5, is a selective kinase inhibitor that is unusually polar for a kinase inhibitor (logD = 1.0, PPB = 23%) but maintains low clearance.

The article was nominated by reviewers Joachim Rudolph, Callie Bryan, Christian Kuttruff, and Julien Lefranc for its interesting tricyclic structure and disclosure of tolerability findings related to VPS34 inhibiton.

compound 59

TRPM8



analog X-ray
PDB:
6NR2

TRPM8 blocker for ocular administration
effective w/ ocular admin. in animal model
cell-based screen. and opt. of thiazoles series
Journal of Medicinal Chemistry
Dompé Farmaceutici S.p.A

The Dompé Farmaceutici TRPM8 blocker, compound 59 is a potent (IC_{50} = 11 nM) compound for painful ocular conditions, with ocular efficacy in a preclinical behavioral model.

TRPM8 is a cation channel which is the predominant in mammalian cold thermosensor and it is activated by well-known molecules like menthol, eucalyptol, and geraniol. The starting points were previous drug candidates tetrazole DFL23448 and ketone DFL23693.

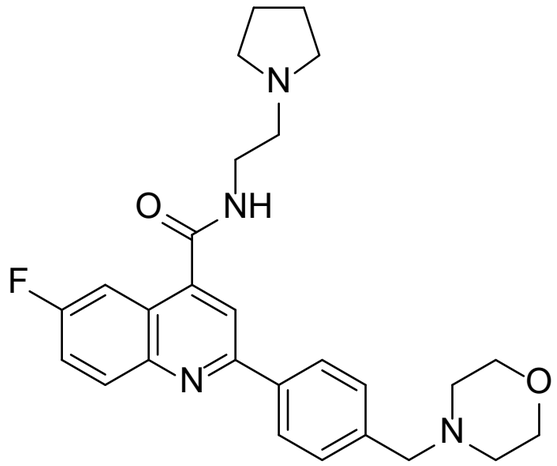
The molecule possesses an unusual hydroxythiazole which was found to be critical for activity.

An unusual N-alkoxy amide was also employed, with surprisingly sharp SAR.

The compound shows rapid activity in a preclinical model (15 min post dose) and is an rare case study for ocular drug discovery.

M5717

PfeEF2



oral plasmodium eEF2 inhibitor
Ph. I candidate for malaria treatment
from phenotypic screen & optimization
The Lancet
Merck Institute for Pharmacometrics

The Merck Institute antimalarial compound, M5717, is the first plasmodium eEF2 inhibitor to reach clinical development, and is a good example of an orally available dibasic compound as well as an antimalarial with a discrete target identified after traditional phenotypic screening.

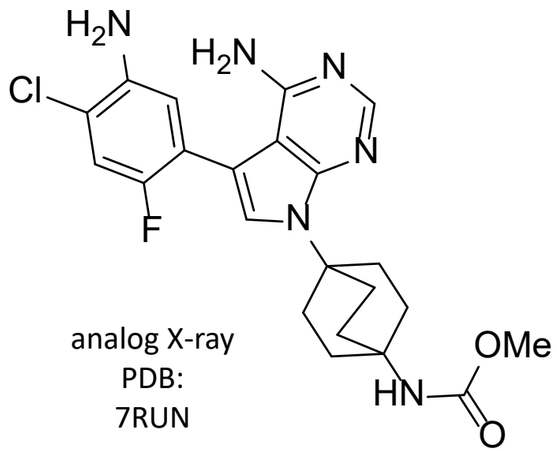
It was well-tolerated in healthy volunteers and has a long half-life (146-193 h at doses ≥200 mg).

Single oral doses of M5717 (150 mg, 400 mg, or 800 mg) resulted in clearance of asexual blood-stage parasites.

The molecule may be a valuable component of single-dose antimalarial combination therapy or malaria prophylaxis in the future.

compound 1

RET



analog X-ray
PDB:
7RUN

oral RET kinase inhibitor
effective in tumor xenograft model
from scaffold hopping & optimization
ACS Medicinal Chemistry Letters
Novartis Genomics Institute

The Novartis RET inhibitor, compound 1, demonstrated robust oral in vivo efficacy in RET-driven tumor xenografts at low doses (10 mpk QD).

RET inhibitors (selpercatinib and pralsetinib) have recently been approved in RET+ cancers based on significant efficacy in selected patients.

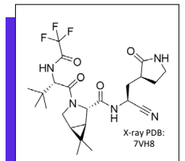
Compound 1 was advanced through preclinical studies including rat toxicology but does not appear to have progressed further.

It possesses a significantly different structure from the approved RET inhibitors and has interesting bicyclooctane and aniline motifs.

The aniline appears to make two critical hydrogen-bonding interactions deep into the active site [based on an analog's X-ray crystal structure (PDB = 7RUN)] and would be non-trivial to replace.

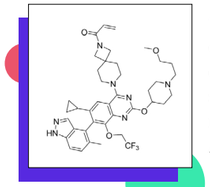
Small Molecules of the Month

November 2021
drughunter.com



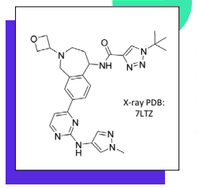
PF-07321332 | SARS-CoV-2 M^{pro}

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



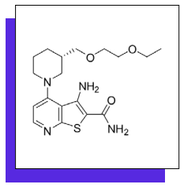
ASP2453 | $KRAS^{G12C}$

oral drug, covalent inhibitor of $KRAS^{G12C}$
effective in $KRAS^{G12C}$-mutated cancer models
SBDD utilizing KRAS proto-oncogene, GTPase
British Journal of Cancer
Astellas Pharma Inc.



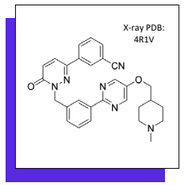
BIIB091 | BTK

oral reversible BTK kinase inhibitor
Ph. I candidate for multiple sclerosis
from prior BTK inhibitor BIIB0685
Journal of Medicinal Chemistry
Biogen



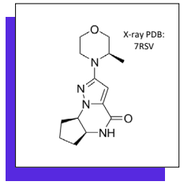
DS96432529 | CDK8

oral CDK8 kinase inhibitor
effective in ovariectomized rat model
CDK8 identified as MoA after screen
Bioorganic & Medicinal Chemistry Letters
Daiichi Sankyo Co. Ltd.



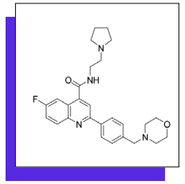
tepotinib | MET

oral MET kinase inhibitor
approved for clinical use in NSCLC
internal HTS and SBDD
Clinical Cancer Research
Merck KGaA



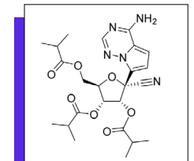
compound 5 | VPS34

oral selective VPS34 kinase inhibitor
discontinued due to potential toxicity
SBDD and SAR optimization
Journal of Medicinal Chemistry
Genentech Inc.



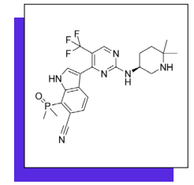
M5717 | PfeEF2

oral plasmodium eEF2 inhibitor
Ph. I candidate for malaria treatment
from phenotypic screen & optimization
The Lancet
Merck Institute for Pharmacometrics



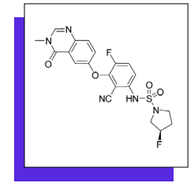
GS-621763 | SARS-CoV-2

oral antiviral prodrug of remdesivir
effective in a ferret SARS-CoV-2 model
from remdesivir nucleoside (GS-441524)
Nature Communications
Gilead Sciences Inc.



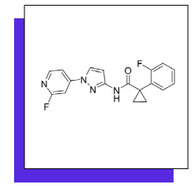
SY-5609 | CDK7

oral picomolar & reversible CDK7 inhibitor
Ph. I candidate in breast cancer comb. therapy
from previous CDK7 inhibitor SY-1365
Journal of Medicinal Chemistry
Syros Pharmaceuticals Inc.



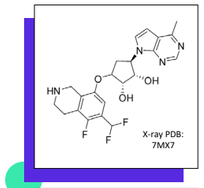
compound Ia | BRAF

oral BRAF inhibitor, brain penetrant
effective in A375-derived mouse models
from prior paradox inducing BRAF inhibitors
Clinical Cancer Research
Roche



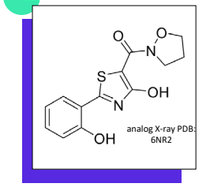
compound 27 | ELOVL1

oral ELOVL1 inhibitor for ALD, CNS penetrant
toxicities observed in higher species
internal HTS and LBDD
Journal of Medicinal Chemistry
Vertex Pharmaceuticals Inc.



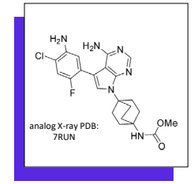
PF-06939999 | PRMT5

oral SAM-competitive PRMT5 inhibitor
Ph. I candidate for solid tumors (adv. or met.)
SBDD utilizing PRMT5:MEP50 w/ A9145C
Molecular Cancer Therapy
Pfizer Oncology



compound 59 | TRPM8

TRPM8 blocker for ocular administration
effective w/ ocular admin. in animal model
cell-based screen. and opt. of thiazoles series
Journal of Medicinal Chemistry
Dompé Farmaceutici S.p.A



compound 1 | RET

oral RET kinase inhibitor
effective in tumor xenograft model
from scaffold hopping & optimization
ACS Medicinal Chemistry Letters
Novartis Genomics Institute

drug hunter

HIGHLIGHTS FROM DRUG DISCOVERY ARTICLES PUBLISHED ONLINE | NOV. 2021

discover together

drughunter.com
info@drughunter.com