drug hunter

Highlights from Q1 2022

0 intro

1 approvals

2 molecules of the month

3 conference disclosures

4 preview

Outline

Part 1 (This Webinar):

- Highlights from Drug Approvals (2022 Q1)
- Highlights from Molecules of the Month (2022 Q1)
- AACR and ACS Conference Highlights
- Q&A

Part 2 (Next Webinar):

- Emerging Startups, Growing Companies, IPOs
- Clinical Readouts, Positive and Negative
- Acquisitions and Partnerships
- Regulatory Actions and other Industry Lessons

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New Company Financings with Disclosed Focus

septerna

- GPCR native complexes/cryo-EM
- $100M Series A (Third Rock), SSF

Ambagon THERAPEUTICS

- 14-3-3-based molecular glues
- Hit-to-lead
- $85M Series A (Nextech)

- *t*RNA drugs for stop codons (none in clinic)
- $24M (ARCH, Takeda, 8VC), Boston

PRETZEL THERAPEUTICS

- enzyme-based mtDNA modification
- $20M+ (ARCH, GV, ...) Waltham, MA/Gothenburg, SE

NEXTRNA THERAPEUTICS

- SM targeting non-coding RNA/protein interactions (lncRNA)
- $56M, Cambridge, MA

WALKING FISH THERAPEUTICS

- engineered B-cell therapies
- $73M Series A, SSF

AVENGE BIO

- polymer-encapsulated cells making IL-2
- $45M Series A, Natick, MA

Tornado Therapeutics

- rapalogs (mTOR)
- for longevity

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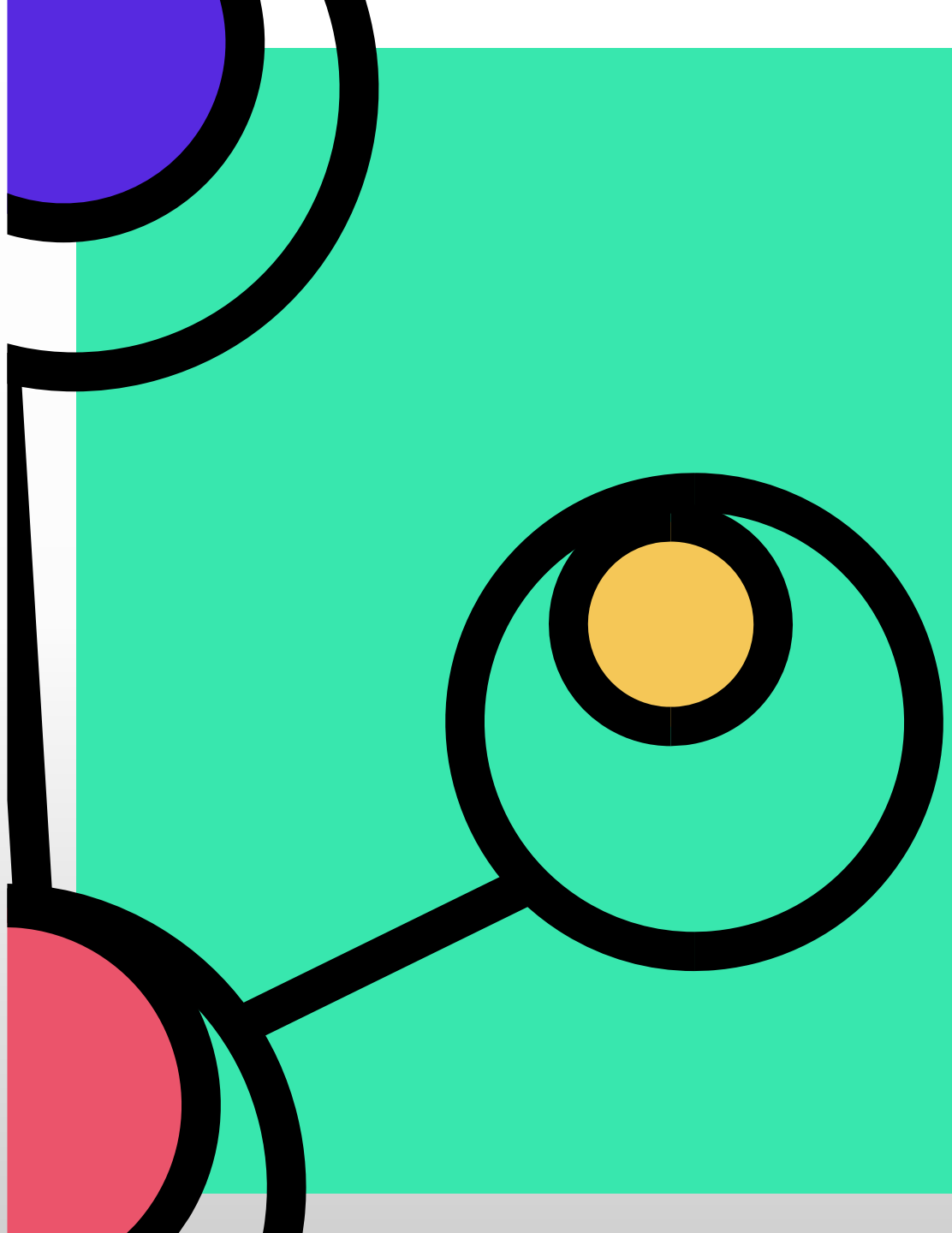


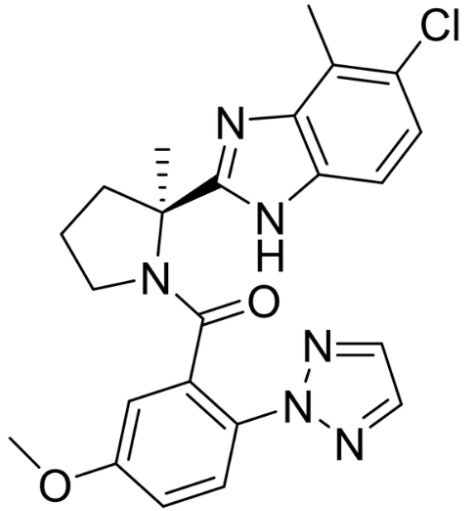
approvals

Highlights from NME Approvals (2022 Q1)

10 NME Approvals, Live Tally Here: https://drughunter.com/resource/2022-drug-approvals/

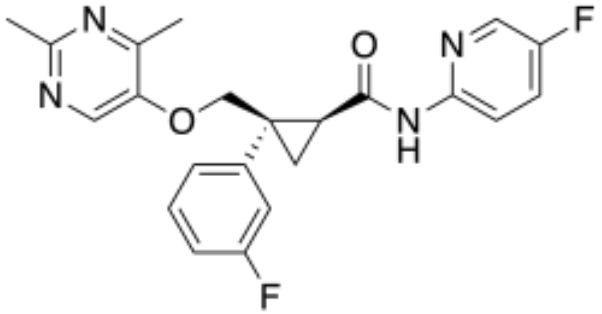
Quviviq (daridorexant)

dual OX1/OX2 blocker

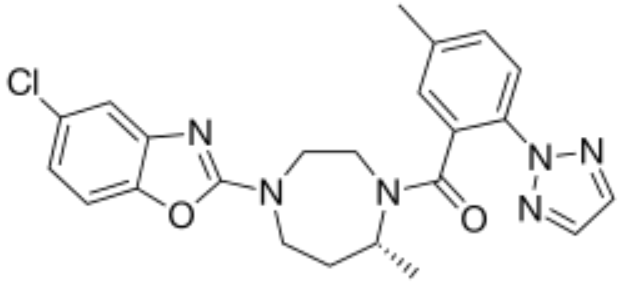


- for insomnia
- oral: 25 or 50 mg

- Shorter half-life (8 h) than suvorexant (12 h) and lemborexant (17 h) to reduce morning grogginess
- Idorsia (formerly Actelion), DataWarrior originators
- November 2020 MOTM



lemborexant (Eisai)



suvorexant (Merck)

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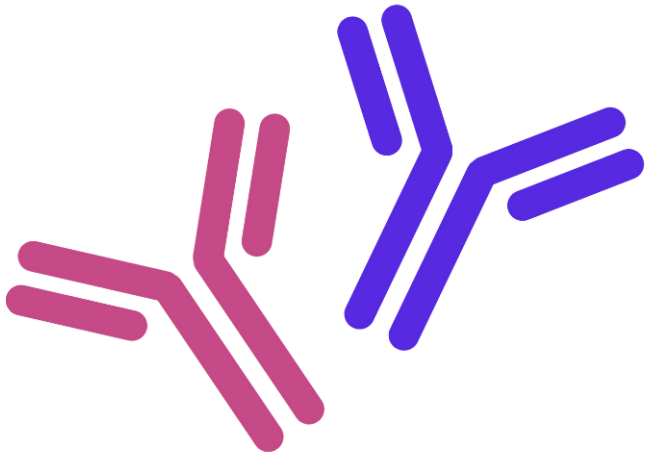
Highlights from NME Approvals (2022 Q1)

relatimab

Lag-3 blocking antibody



- immunotherapy combo. with nivolumab
- 26.5 d half-life, matching 26.5 d of nivo
- OS improvement over nivolumab alone

- First new checkpoint inhibitor immunotherapy mechanism since CTLA-4, PD-1/PD-L1
- TIGIT was widely thought to lead until Roche Ph. III; very active space (TIM-3, OX40, CD73, STING, ...)
- Half-life of Lag-3 antibody matches PD-1 antibody remarkably well!
- OS improvement, ORR = 43% vs. 33% w/ nivolumab monotherapy

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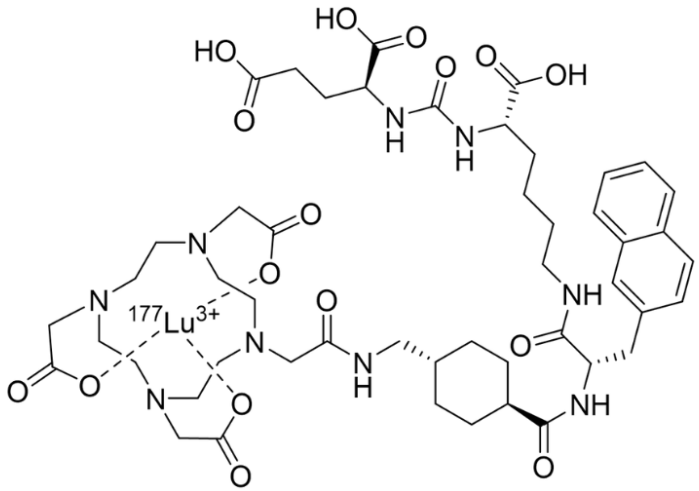
Highlights from NME Approvals (2022 Q1)

Lu 177 vipivotide tetraxetan

PSMA-targeted radiotherapeutic



- for PSMA+ prostate cancer, Mar. 2022
- peptide Ki = 0.37 nM
- PSMA a.k.a. glutamate carboxypeptidase II

- PSMA = "prostate-specific membrane antigen" – widely used as tumor marker for antibodies, ADCs, bispecifics, CAR-Ts, etc.
- Also an enzyme targetable by small molecules!
- ORR = 30% vs. 2% for BSoC
- William Fair, discoverer of PSMA, died of metastatic prostate cancer in 1995

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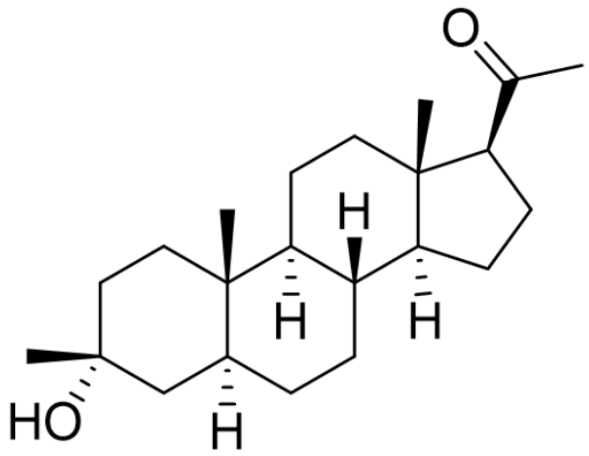
Highlights from NME Approvals (2022 Q1)

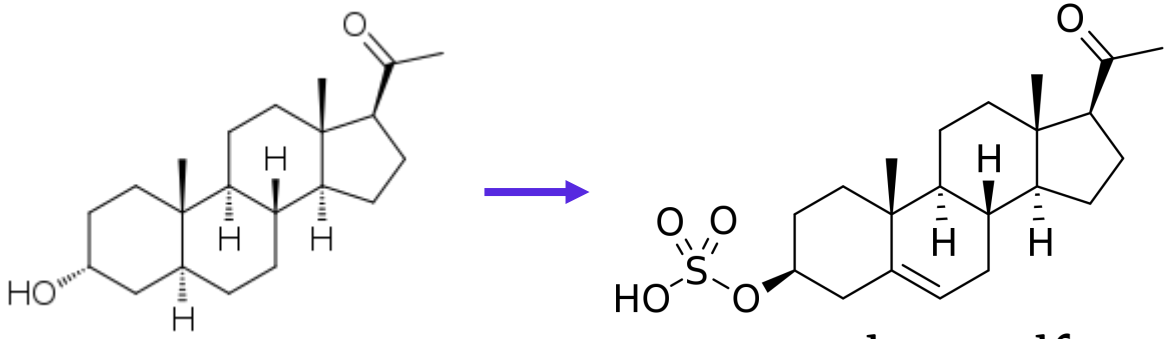
ganaxolone

oral GABAA receptor PAM



- for seizures in CDD, approved Mar. 2022
- 34 hour elimination half-life
- reduced GABAA-inhibiting metabolites

- GABA-A receptor PAM / neurosteroid
- Binds to steroid allosteric site, same site hypothesized to be responsible for AR antagonist seizures (e.g. enzalutamide)
- Does not produce sulfate metabolites that can induce seizures (vs. endogenous allopregnanolone is substrate of isoenzymes)



allopregnanolone (Zulresso), IV, half-life = 9 h

pregnenolone sulfate

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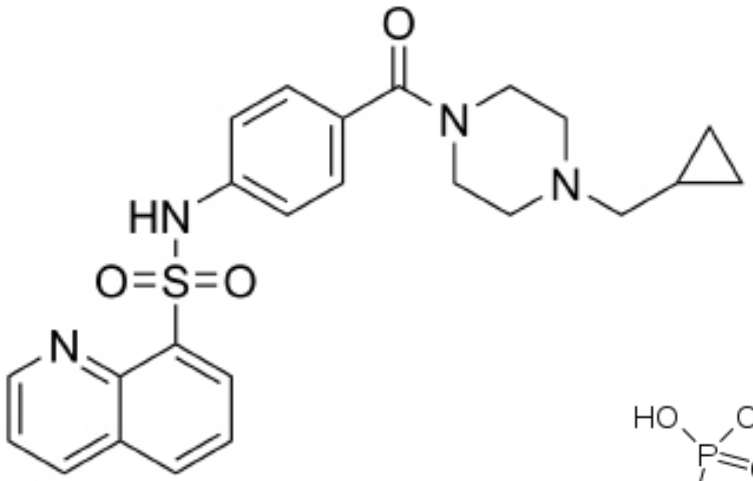
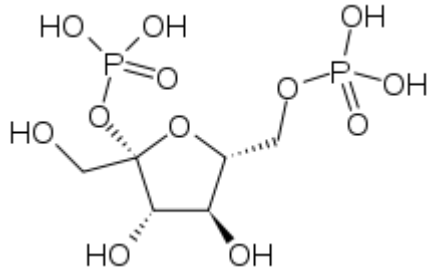
Highlights from NME Approvals (2022 Q1)

mitapivat (Pyrukynd)

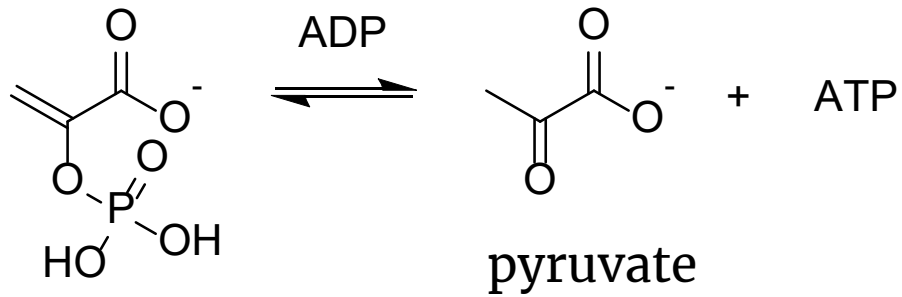
pyruvate kinase (PK) activator



- first-in-class allosteric activator of pyruvate kinase (PK) for hemolytic anemia in pyruvate kinase deficiency
- not a kinase biochemically, mediates last step of glycolysis; mature RBCs lack mitochondria and need glycolysis
- increases activity of both WT and mutant PK enzymes in patient RBCs
- active against broad range of mutants (PK deficiency caused by hundreds of mutations)
- reduction in transfusion burden, first disease-modifying treatment; Forma PKA etavopivat in MOTM March



fructose bis-phosphate
(endogenous agonist of PK)



phosphoenolpyruvate

pyruvate

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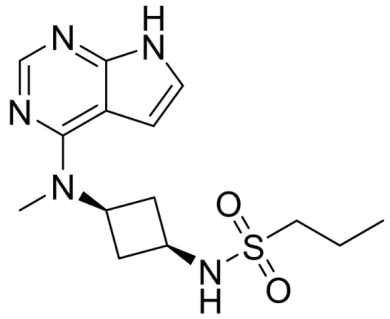
Highlights from NME Approvals (2022 Q1)

Cibinqo (abrocitinib)

JAK1-selective inhibitor



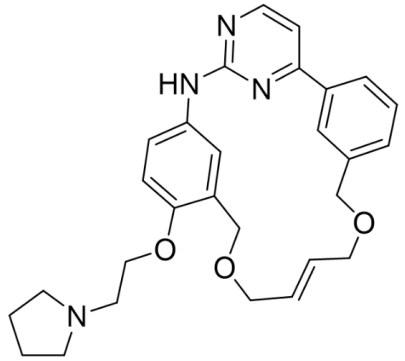
- for refractory AD
- oral: 100 or 200 mg QD

- 9-28x selectivity over JAK2; from pan-JAK inhibitor tofacitinib

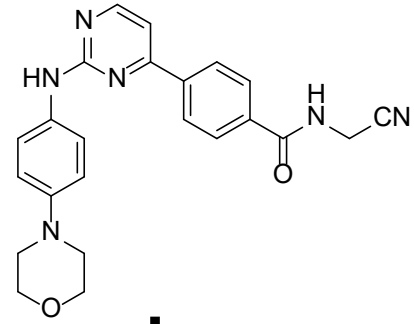
- JAK2 inhibition suspected to cause anemia (role in EPO and TPO signaling)
- JAK1 selectivity pursued for inflammatory diseases
- JAK2 inhibitors (ruxolitinib, fedratinib) paradoxically improve anemia in myelofibrosis patients by inducing apoptosis of pathological blood cell precursors
- Pacritinib shows clinical benefit in myelofibrosis patients with thrombocytopenia, attributed to better JAK1-selectivity (55x biochemically, ~5x in cells)
- Efficacy > elegance

Vonji (pacritinib)

oral JAK2 kinase inhibitor



- for myelofibrosis
- oral: 200 mg BID



momelotinib (Sierra Oncology, $1.7B GSK acq.)

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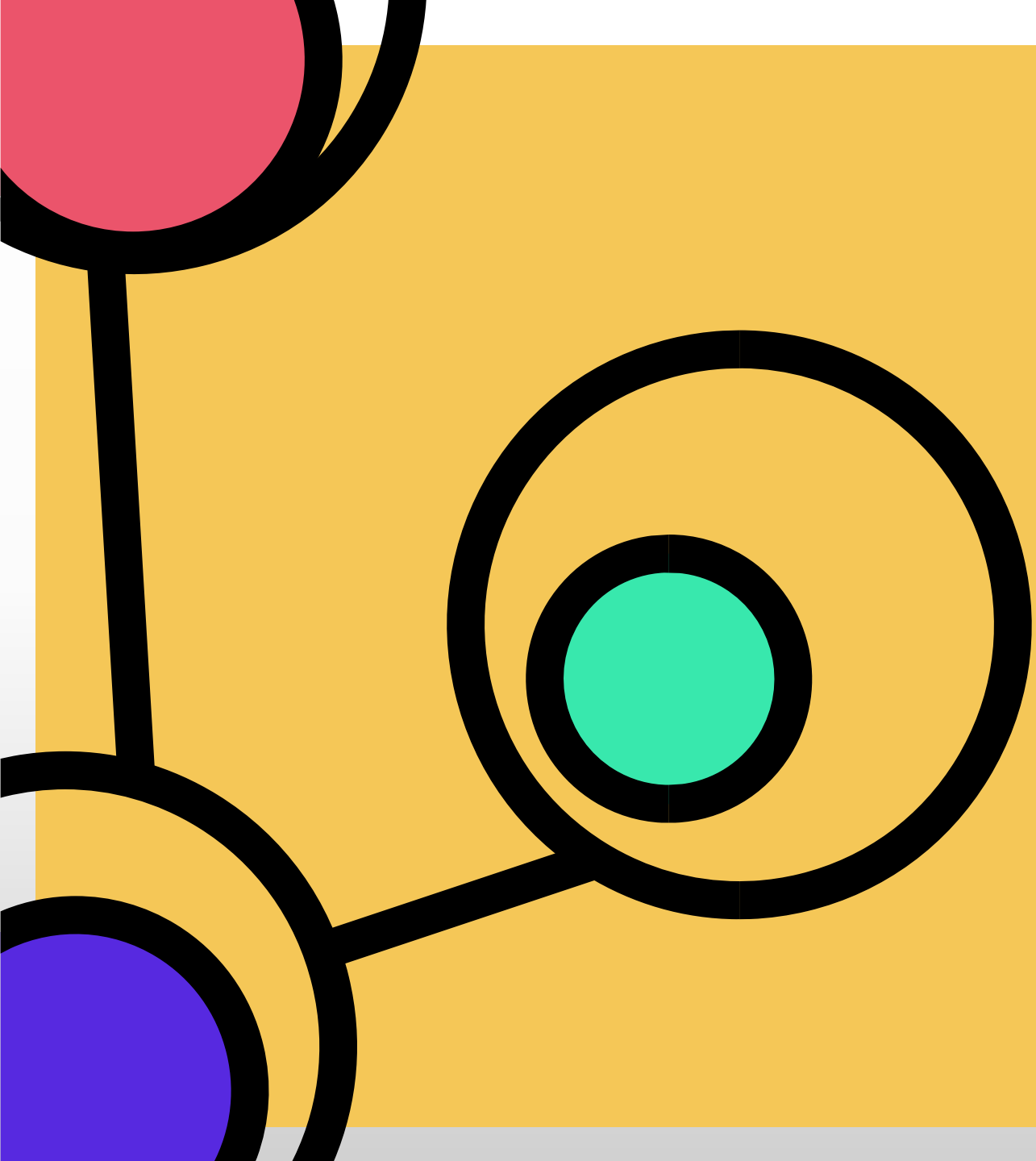
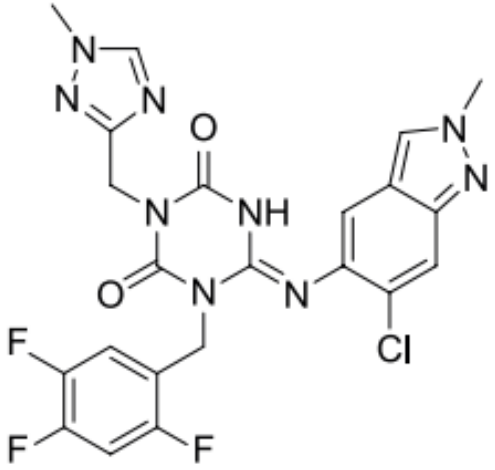


MotM

S-217622

reversible SARS-CoV-2 3CL^{pro} inhibitor



reversible SARS-CoV-2 3CLpro inhibitor

Ph. II/III candidate for COVID-19

virtual + HTS MS screen, SBDD

bioRxiv

Shionogi Pharmaceutical

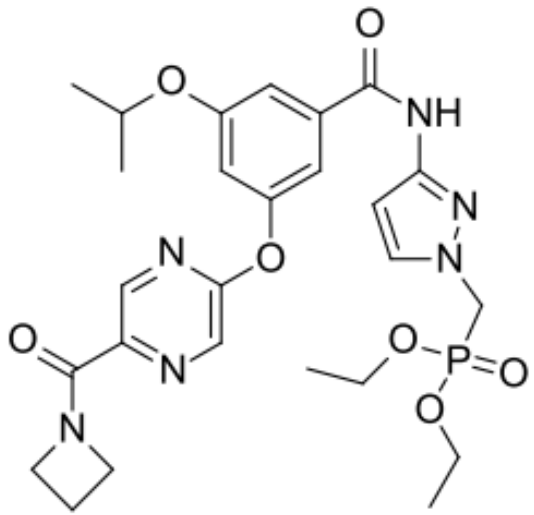
Highlights from Molecules of the Month – Jan.

- Non-peptidic, non-covalent inhibitor, no PK booster needed (in contrast to nirmeltravir + ritonavir)
- Potential for fewer DDIs in COVID patients
- From pharmacophore-guided virtual screening (300 hits confirmed by HT-MS), starting point 8.6 uM

Highlights from Molecules of the Month – Feb.

BMS-820132

GK



oral GK partial activator

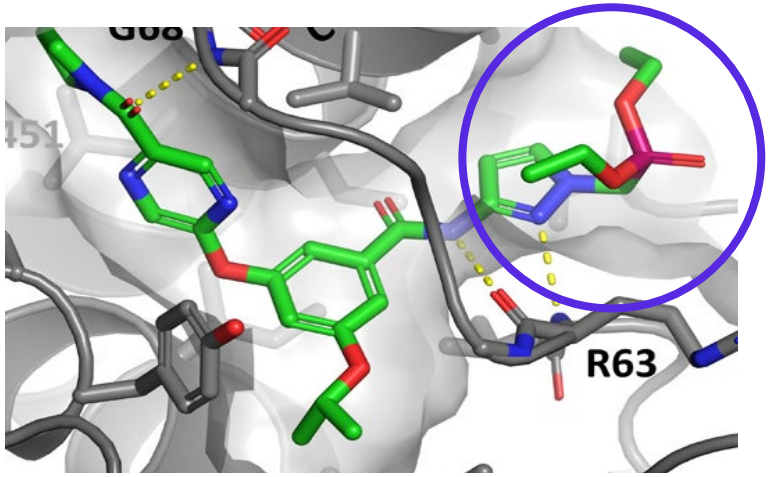
Ph. I candidate for diabetes

from HTS of BMS collection and SBDD

J. Med. Chem.

Bristol Myers Squibb

- Partial GK activator – GK activators hot in the 2000's, problem was hypoglycemia
- Ph. I completed in 2011, 2012, well-tolerated but target class largely halted because of loss of efficacy over time
- Not a prodrug!
- PD correlates w/ parent
- 25 uM hit, nice use of conf. analysis on heterocycle opt.



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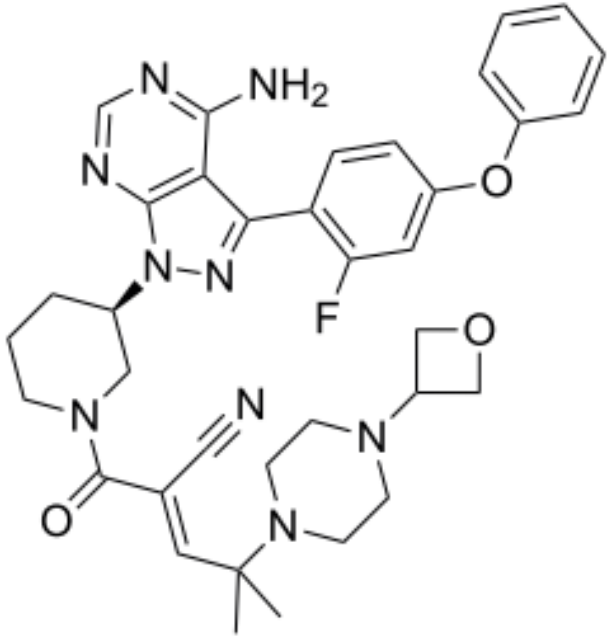
rilzabrutinib (PRN1008)

BTK



oral reversible covalent BTK inhibitor

in Ph. III for immune thrombocytopenia

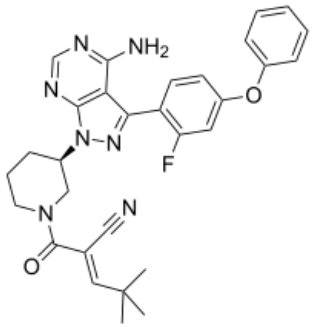
from structure-based drug design + opt.

J. Med. Chem.

Principia Biopharma (Sanofi), So. San Francisco, CA

Highlights from Molecules of the Month – Mar.

- Sanofi bought Principia for $3.7B to obtain these assets
- Interesting case study to watch for the reversible covalent principle – will it prove safer long term?
- BTKi being explored outside of oncology (MS, other immune thrombocytopenia, CU, …) where ibrutinib tox. (cardiac arrhythmias, bleeding, infection, etc.) less tolerated

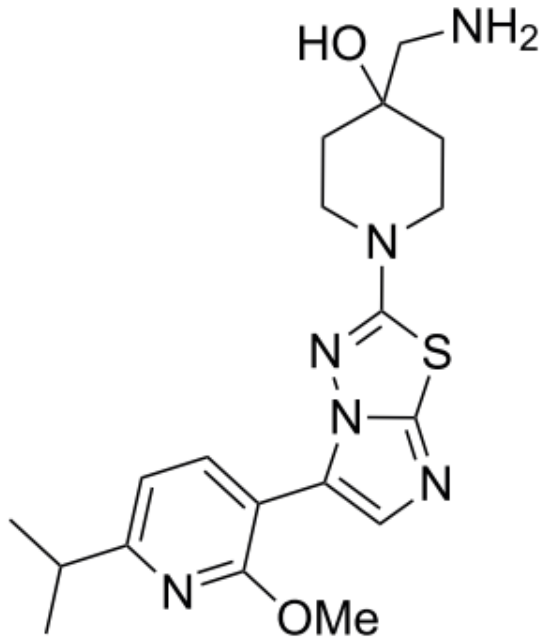


PRN473

drug hunter

INE963

Plasmodium falciparum 3D7



oral blood stage antimalarial

in Ph. I (healthy volunteers)

from 1.5M cmpd phenotypic screen + opt.

J. Med. Chem.

Novartis (NIBR), Emeryville, CA

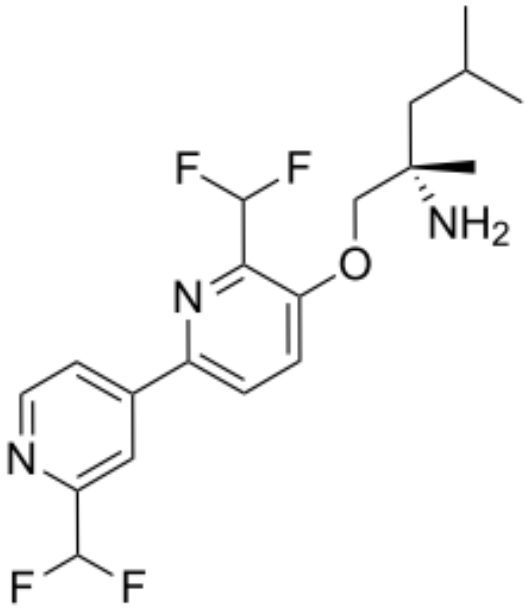
Highlights from Molecules of the Month – Mar.

- Nominated by Dennis Koester:
- Speed of kill – reduces parasite burden fast (no viable parasites within 24 h), important for reducing symptoms and resistance
- No resistance mutants identified yet though multiple selection studies have been performed – active vs. field isolates and drug-resistant strains
- Long human half-life, potential single dose cure
- From 1.5M compound phenotypic screen (0.27 uM hit)

drug hunter

BMS-986176/LX-9211

AAK1



oral CNS-penetrant AAK1 kinase inhibitor

in Ph. II for neuropathic pain

from high-throughput screen + opt.

J. Med. Chem.

Bristol-Myers Squibb, Wallingford, CT

Highlights from Molecules of the Month – Mar.

- Ph. II for neuropathic pain; novel target
- Bold for a CNS-penetrant kinase inhibitor for pain – farthest a kinase inhibitor has gone beyond oncology?
- Other CNS-penetrant kinase inhibitors (LRRK2, DLK, RIPK1) have been for more serious conditions and appear to have had safety issues
- AAK1 inhibition appears to be well-tolerated

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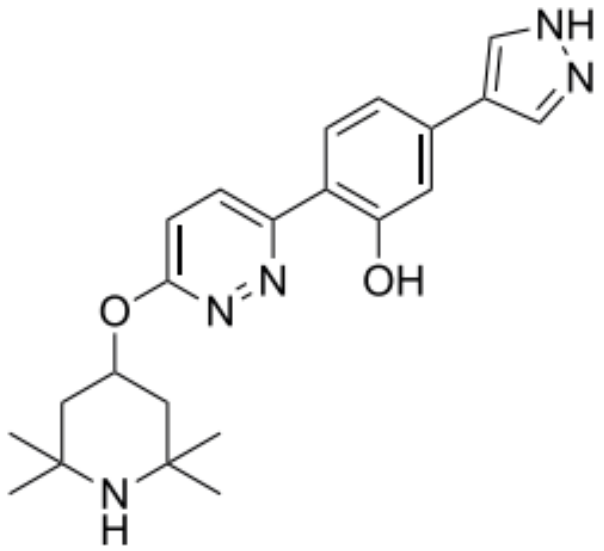
branaplam

SMN2



oral, CNS-penetrant splicing modulator w/ HTT activity

in Ph. II for Huntington's (prev. SMA)

further characterization of SMA candidate

Nat. Commun.

Novartis, Cambridge, MA

Highlights from Molecules of the Month – Mar.

- Previous clinical candidate for SMA
- As also reported by PTC, HTT modulation is a property of splicing modifiers
- HTT modulation observed in SMA patients – now being tested for HD
- Lowers HTT expression – see also HTT-D3 (PTC); PTC has CNS-penetrant Ph. II candidate for HD

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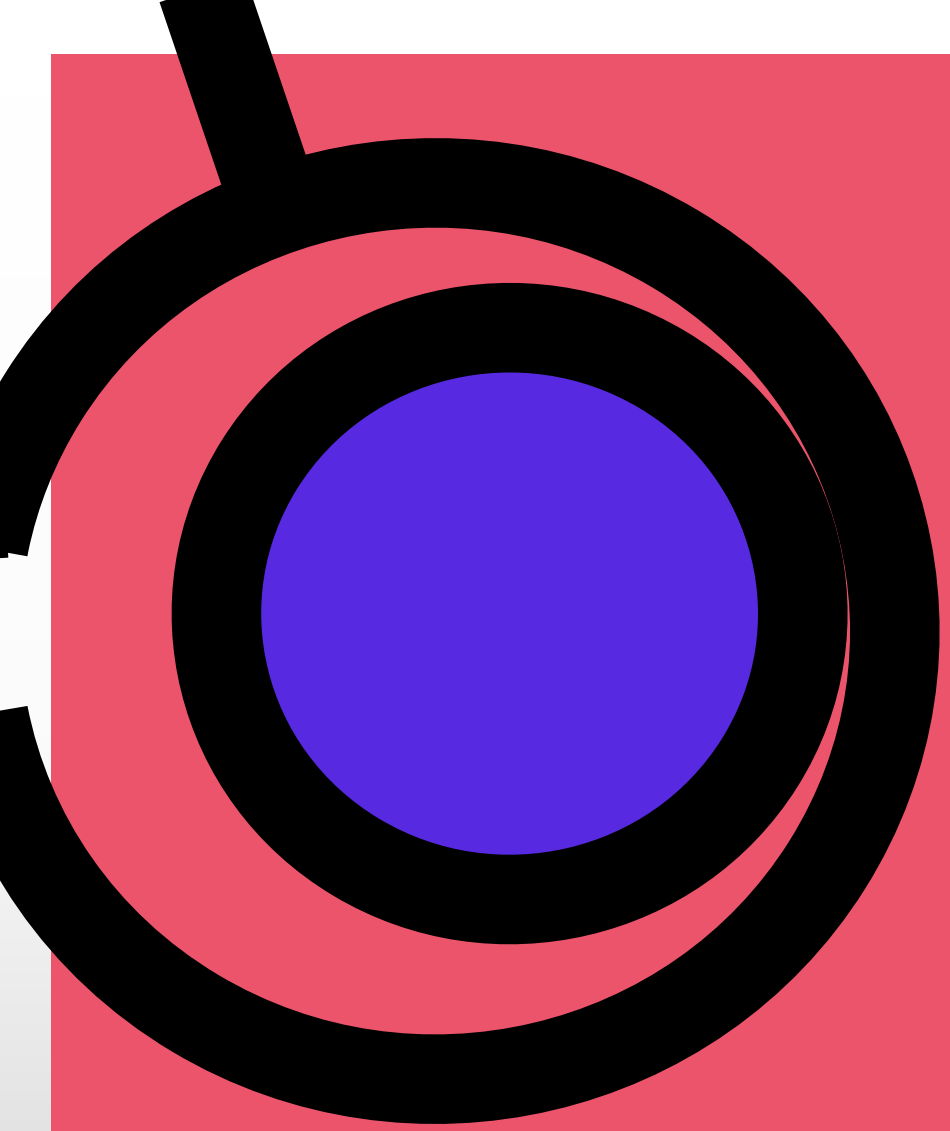
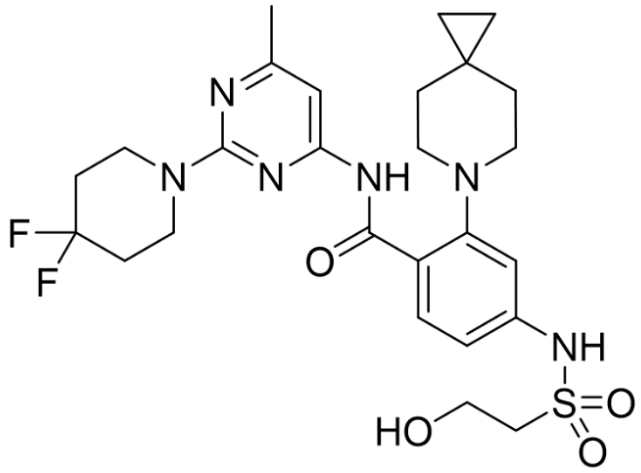


disclosures

AMG 650 (Amgen)

KIF18A motor protein inhibitor



- first-in-class, oral, in Ph. I for cancer
- from 600k cmpd screen vs. motor activity
- non-myosin motor protein target

ACS Spring 2022

- KIF18A is a mitotic kinesin motor protein regulating chromosome positioning
- Synthetic lethal play for chromosomally unstable cancers
- Motor proteins as a class increasingly appear to be actionable (beyond myosin inhibitors and activators like from Myokardia/Cytokinetics)

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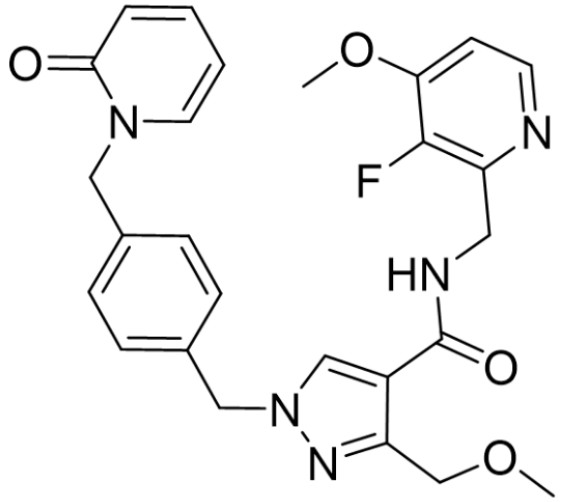
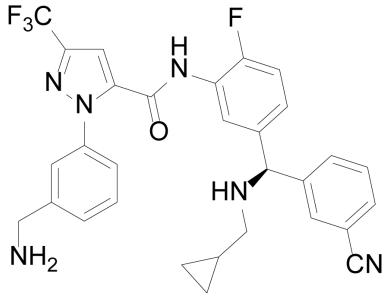
KVD900 (KalVista)

plasma kallikrein inhibitor



- follows BioCryst's berotralstat
- for treatment of attacks vs. prevention
- target inactivation within 20-180 min

ACS Spring 2022



- Differentiating based on fast action (target inactivation between 20 min-30 h)
- For treating acute HAE attacks (Google images)
- Berotralstat specifically limited in label against use in acute HAE attacks
- To demonstrate this profile, KalVista developed faster immunoassay
- Ph. II endpoints met, potential NDA 2024

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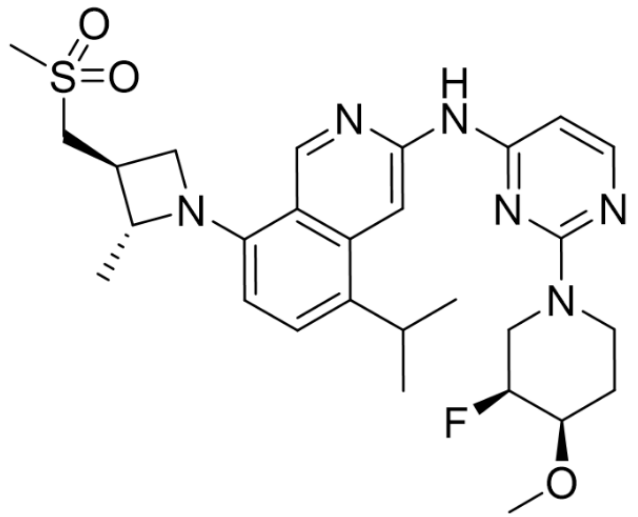
BLU-945 (Blueprint)

EGFR triple-mutant inhibitor



- >1000x selective vs. wild-type EGFR
- intracranial activity in PDCX model
- Ph. I/II alone or combo. w/ osimertinib

ACS Spring 2022

- 4th Generation EGFR inhibitor
- WT-selectivity, mutant activity, and brain-penetration make it a strong contender for best-in-class
- Blueprint pursuing EGFR combos aggressively (e.g. recent acquisition of Lengo for BP exon 20)

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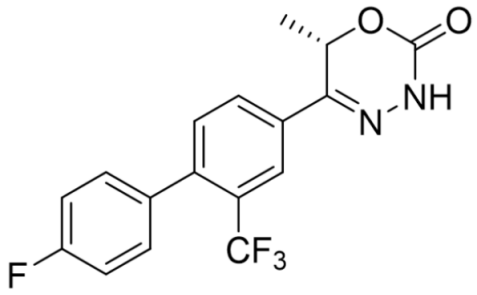
AACR 2022 – Interesting MoAs

BAY 2666605 (Bayer)

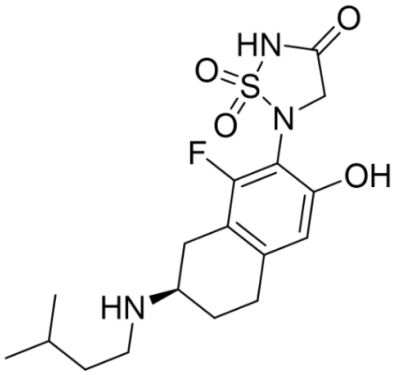
PDE3A-SLFN12 molecular glue



- PDE3A-SLFN12 complex inducer (7 nM)
- Ph. I in metastatic melanoma
- F % = 85, 6.2 h half-life in mouse

ABBV-CLS-484 (ABBV, Calico)

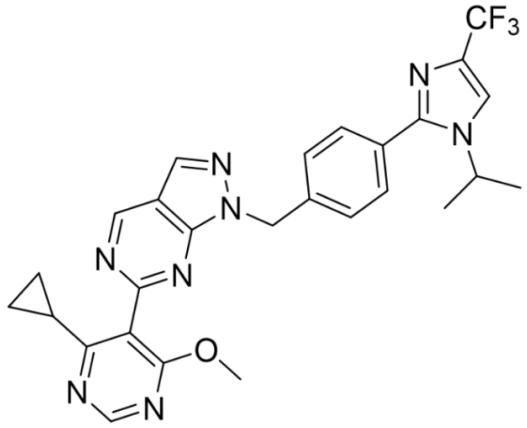
active site PTPN2/N1 inhibitor



- phosphatases notoriously hard to drug
- sub-nanomolar activity, X-ray confirm.
- Ph. I in solid tumors +/- PD-1i

KSQ-4279 (KSQ Therapeutics)

allosteric USP1 inhibitor



- reversible induced fit mechanism
- first-in-class, Ph. I in tumors +/- PARPi
- oral once daily, Ki = 1.2 nM

- PDE3A-SLFN12 molecular glue/velcrin (Broad Institute hit, Bayer going into Ph. I) – stimulates SLFN12 RNAse activity cleaving tRNA-Leu-TAA -> ribosomal pausing – gain of function glue mechanism!
- Phosphatase inhibitor going into clinic (IO + tumor intrinsic activities)
- DUB inhibitor going into clinic

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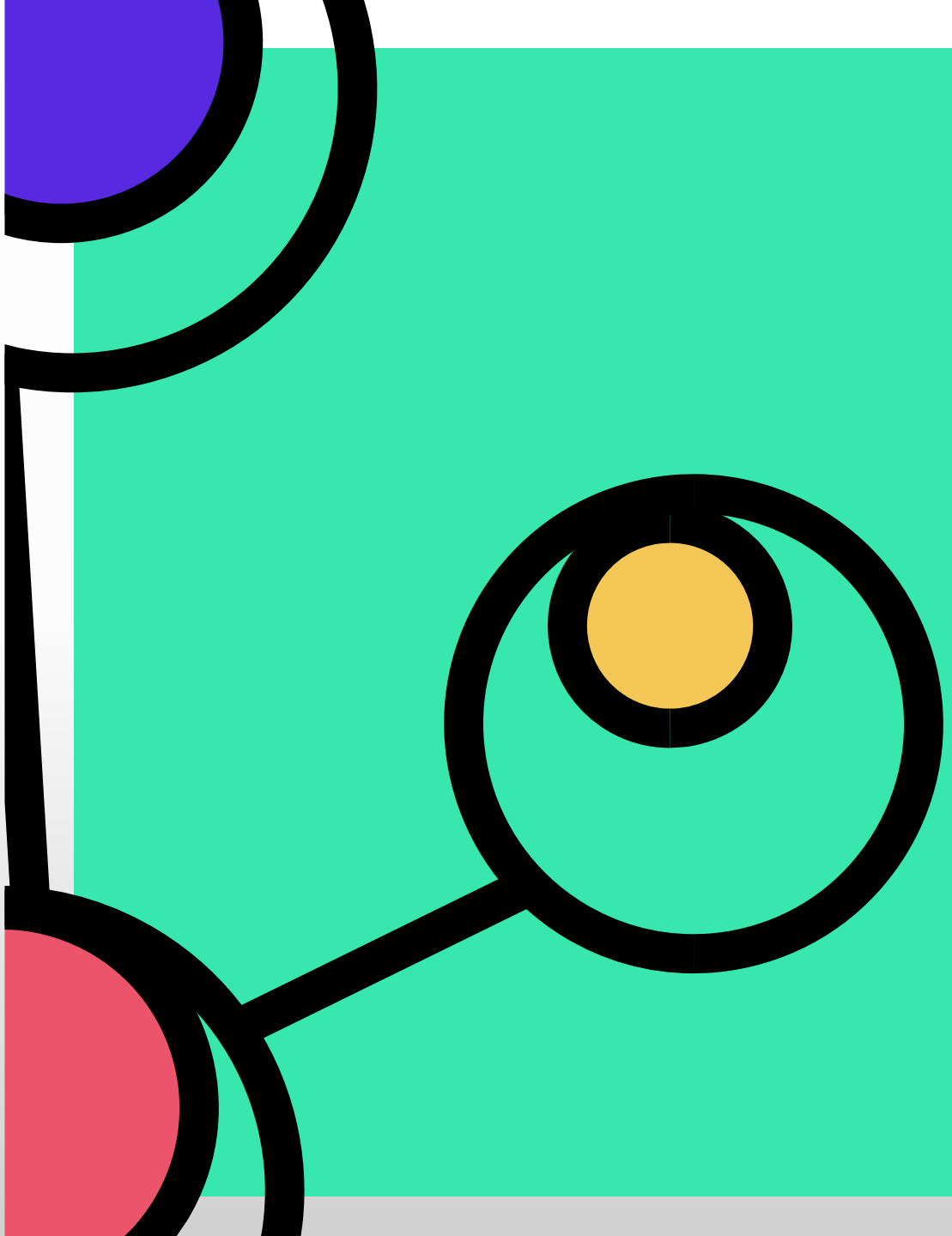
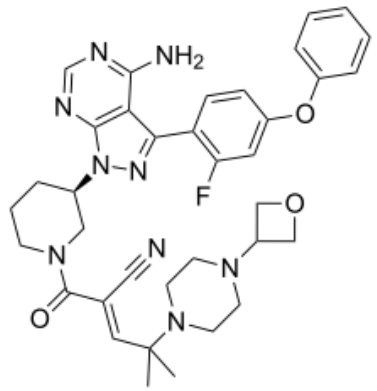


learn more

Deep Dives (MotM)

rilzabrutinib (PRN1008)

BTK



oral reversible covalent BTK inhibitor
in Ph. III for immune thrombocytopenia
from structure-based drug design + opt.
J. Med. Chem.
Principia Biopharma (Sanofi), So. San Francisco, CA

Context. PRN1008 thrombocytopenia target discovery in over the last decad indications (e.g. ibr fenebrutinib (NCT0 as ibrutinib can lea which have been ac

Reviewer Commen ACS meeting in 201 oncology and imm safety and efficacy in rat but well abso dermatitis (Phase I is in Phase III for in was terminated by

Additional Clinical PRN1008 in healthy autoimmune diseas thrombocytopenia, RILECSU study in p warm autoimmune chronic immune th asthma (NCT0510

Mechanism of Acti available in only te inhibitors which ar is being evaluated a activity due to thei common thiols wh

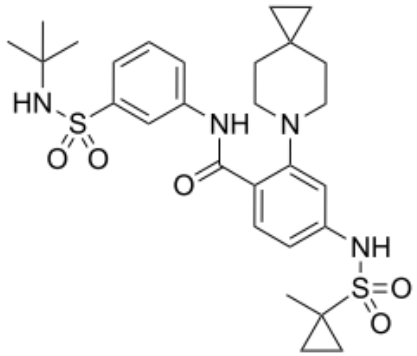
Hit-Finding Strate reversibly to nonca the binding site. In potent and selectiv matter for PRN100 residence times. In in inhibitor residence times; recombinant, full-length BTK was used in the assays. Interestingly, no association was observed between the residual times at the binding site and the IC50 values.

Preclinical Pharmacology. In vivo testing was done using the collagen-induced arthritis (CIA) animal model which has been used to evaluate the ability BTK inhibitors to modulate inflammatory responses. Ankle diameter in female Lewis rats treated at 3, 10, and 30 mg/kg was significantly reduced in all treatment groups vs vehicle controls, with the inhibition being dose dependent. Maximal efficacy was observed with the 30 mg/kg dose. Occupancy studies were conducted by measuring binding of a labeled covalent probe inhibitor to free BTK in rat splenocytes; whereas the concentrations PRN1008 were relatively low at 6 hr and further dropped significantly at 12 hr for all doses tested, occupancy was largely maintained at 12 hr. High occupancy (>80%) at the 30 mg/kg dose was associated with the greatest reduction in ankle diameter; these data and other pharmacokinetic/pharmacodynamic modeling data suggests that optimal activity of the molecule may be dictated by high and sustained occupancy at the BTK binding site.

drug hunter

compound 24

KIF18A



oral kinesin motor protein inhibitor
relative AMG 650 in Ph. I for cancer
from ~600k compounds HTS + opt
J. Med. Chem.
Amgen, Thousand Oaks, CA

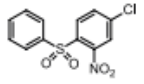
Context. "Compound 24" (Amgen) is a kinesin-like protein 18A (KIF18A) inhibitor being developed for a subset of cancers with chromosomally unstable tumor cells. Their first-in-class, oral clinical candidate, AMG 650, was recently disclosed at ACS Spring 2022 and is in Ph. I for cancer. Both antimitotic drugs targeting microtubules and those targeting essential mitotic kinases have been studied extensively, although the high toxicities associated with these agents and associated moderate efficacy have dampened interests in them over the years. Common events associated with MT inhibitors are dose-limiting neurotoxicities, myelosuppressive, and gastrointestinal effects (almost all approved MT inhibitors have caused one or more of these side-effects in at least 50% of treated patients). These limitations spurred researchers to search for alternative mechanisms of action and mitotic kinesins were identified as potentially viable drug targets, whose inhibition may have a greater therapeutic window by disrupting mitosis without more broadly impacting microtubules. The first lower-quality KIF18A chemical probe was BTB-1, an irreversible, ATP-competitive compound with a 1.7 μM IC_{50}, whose optimization failed to deliver improvements, prompting the search for better molecules.

Target. KIF18A is an ATP-dependent kinesin motor protein that binds tubulin and is involved in chromosome congression, regulating chromosome positioning and spindle length during cell division. KIF18A was first recognized as an microtubule depolymerase based on observations that KIF18A-depleted cell lines harbored aberrantly long mitotic spindles with disrupted chromosome organization. Additional work showed that KIF18A knockdown in cancer cell lines but not normal cell lines induced mitotic vulnerability and led to apoptosis. The protein is overexpressed in a subset of human cancers and has been shown to be required specifically by chromosomally unstable tumors for maintenance of bipolar spindle integrity and proliferation, potentially making it a PARP-like synthetic lethality opportunity to treat certain cancers.

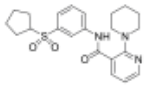
Mechanism of Action. Although a co-crystal structure of KIF18A with this inhibitor class is unavailable, structural predictions support experimental evidence for a binding site that locks the interaction between α-tubulin to KIF18A, preventing it from moving across microtubules, leading to mitotic delays and apoptosis.

Hit-Finding Strategy. The starting point, "compound 3," was discovered through a high-throughput screen of ~600K compounds from the Amgen library, and 800 of these were further analyzed for their effect on cell phenotype. Compounds were screened for inhibition of KIF18A MT-ATPase motor activity using a kinesis motor assay while selectivity against the essential mitotic kinesins Eg5 and CENP-E were assessed. A chromosomally unstable TP53-mutated TNBC cell line (MDA-MB-157) with demonstrated sensitivity to KIF18A knockdown by siRNA was used for the screening.

BTB-1 (KIF18A IC_{50} = 1.7 μM)



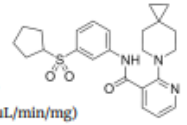
"compound 3" (KIF18A IC_{50} = 6.2 μM)



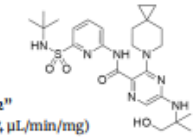
"compound 24" (KIF18A IC_{50} = 0.061 μM)

Lead Optimization. Initial substitution of the piperidine C4 with a spirocyclopropyl group showed >10-fold IC50 improvement with better lipophilicity (compound 6) but was rapidly metabolized. This was addressed by adding a tert-butyl amide plus substitutions at the pyridine ring (compound 22), significantly improving both metabolic stability and potency. Solubility was increased by adding a sulfonamide moiety as well as reformulating using a tween-based IP formulation.

"compound 6" (IC_{50} = 0.41 μM, CL_{int} > 399 μL/min/mg)



"compound 22" (IC_{50} = 0.096 μM, CL_{int} = 64 μL/min/mg)



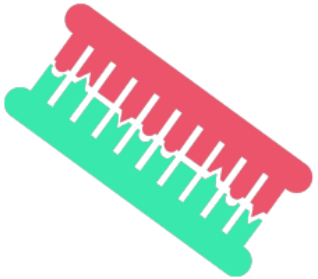
Preclinical Pharmacology. A tumor pharmacodynamic model of mitotic arrest was used to evaluate the late lead compounds, with accumulation of pH3 being used as biomarker and a pharmacodynamic readout of KIF18A inhibition. IP administration of compound 24 at 100 mg/kg in a mouse tumor model resulted in a significantly greater plasma concentration after 24 hrs compared to compound 22 (below the limit of detection) with comparable drug concentrations in tumors as the positive control (PLK-1 inhibitor) BI-2536 (~1 μM). Mice treated with the late lead compounds showed significant increases in pH3 positive cells vs. vehicle alone. Further compound optimization led to the development of "compound 23" and "compound 24", both of which demonstrated a significant and sustained increase in pH3 positive cells at a single dose of 100 mg/kg (intraperitoneal).

drug hunter

Deep Dives (Approvals)

Leqvio

PCSK9 mRNA



(inclisiran)

siRNA

Heterozygous familial hypercholesterolemia

284 mg SC Q3M for 2 cycles, then Q6M

Novartis

Since the discovery
and autosomal dom
it's been an attracti
PCSK9-targeting d
two mAbs (Repatha

PCSK9 regulates b
hepatocytes, leadin
prevents the synth

Modifications to in
inclisiran more sta
The molecular opti
a human half-life o
dosing (of 284 mg
twice monthly inje

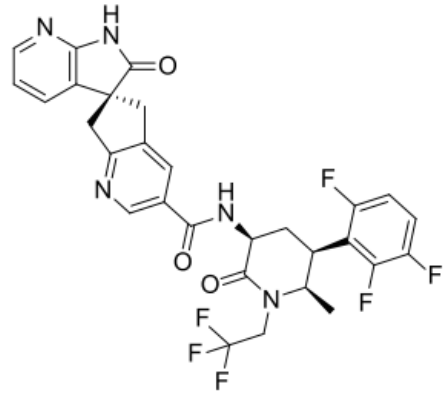
FDA approval was
hypercholesterolen
Leqvio treatment l
in placebo-treated

Merck now has oral PCSK9 inhibitors in the pipeline, which recently demonstrated proof-of-concept in a first-in-human trial. Oral inhibitors may offer a better cost-benefit to society in the long run to large molecules, which have received no shortage of criticism in the past for their high price tags. This twice-a-year injectable option, however, does raise the bar relative to the antibody drugs.

drug hunter

Qulipta

atogepant



Calcitonin gene-related peptide (CGRP)

Receptor antagonist

Migraine

Oral: up to 60 mg QD

drug hunter

Neurology

Qulipta (atogepant), marketed by AbbVie is an oral (10, 20, or 60 mg) calcitonin gene-related peptide (CGRP) receptor antagonist approved in adults for the preventative treatment of episodic migraine. In two Phase III randomized trials, patients who received atogepant experienced, on average, one to two fewer migraine days monthly than patients who received placebo. In one of the studies, patients on atogepant also had fewer monthly medication use days compared with those on placebo.

Approval of Qulipta was predated by two other members of the same drug class, Ubrelvy (ubrogepant) and Nurtec ODT (rimegepant), although these drugs are indicated only for abortive migraine therapy. This makes Qulipta the first and only oral CGRP receptor antagonist approved for preventative use in migraine. The approval of an oral CGRP receptor inhibitor with a sufficiently low dose and safety profile for once-daily, chronic dosing is a major accomplishment in drug discovery given how many gepants were discontinued due to off-target liver toxicity.

CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology, with studies showing that CGRP levels are elevated during migraine attacks. Proof-of-concept for acute migraine treatment was first achieved with Boehringer Ingelheim's olcegepant (the first selective small molecule CGRP antagonist) as early as 2004, though the chemical matter has advanced significantly since then.

The gepants class of small molecules has been observed to have fewer side effects than previous classes of migraine drugs such as triptans and ergots. Atogepant is one of three second-generation gepants, all approved within the last three years having demonstrated better bioavailability and no observable hepatotoxicity. Another gepant, the third-generation agent zavegepant (BHV-3500), recently demonstrated promising safety and efficacy as an intranasal spray in a Phase II/III and Phase III trial, and is currently being prepared for NDA submission.

Brain penetration does not appear to be necessary for the anti-migraine effects of CGRP receptor inhibition, as gepants typically have poor brain exposure, and four monoclonal antibodies (unable to cross the blood-brain barrier, or BBB) targeting either the CGRP ligand (fremanezumab, eptinezumab, galcanezumab) or its receptor (erenumab) have also been approved by the FDA for preventive treatment of episodic migraine. Though migraine originates in the brain, CGRP antagonists are believed to exert their effects at the trigeminal ganglion, which lacks a BBB.

Approval of Qulipta by the FDA was based on data from two randomized, multicenter, double-blind, placebo-controlled trials—the Phase II/III safety study and the Phase III ADVANCE study—as well as data from a Phase III long-term safety study. In the ADVANCE trial, the primary endpoint was change from baseline in mean monthly migraine days across the 12-week treatment period. The changes in the mean monthly migraine days from baseline were significantly higher for all Qulipta dose groups (10 mg: -3.7 days; 30 mg: -3.9 days; 60 mg: -4.2) compared to placebo (-2.5 days).

Although developed and marketed by AbbVie, the patent for synthesis of atogepant is held by Merck Sharp and Dohme Corp. AbbVie acquired rights to atogepant in the acquisition of Allergan, who, in turn, acquired rights to atogepant from MSD for up to $500M in 2015.

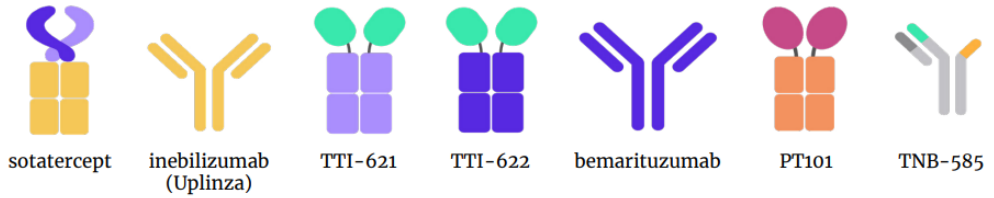
drug hunter

New Additions

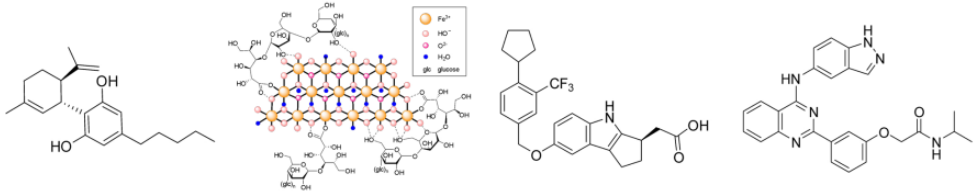
Industry Reviews

2021 Drug Discovery M&A Review – Pt. 1 drughunter.com

Top 10 Overall Mergers & Acquisitions by Value



sotatercept | inebilizumab (Uplinza) | TTI-621 | TTI-622 | bemarituzumab | PT101 | TNB-585



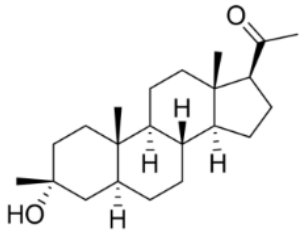
cannabidiol (Epidiolex) | ferric carboxymaltose (Ferinject) | etrasimod | belumosudil (Rezurock)

Company	Acquirer	Lead Molecule	Indication	Lead Mechanism	Stage	Value (M)
Vifor Pharma	CSL	ferric carboxymaltose (Ferinject)	Hematology/ Nephrology	supplemental iron	Commercial	$11,700
Acceleron Pharma	Merck	sotatercept	Cardiovascular	fusion protein; ActRIIA IgG-Fc binds activin type IIA receptor of TGF-β	Ph. III	$11,500
GW Pharmaceuticals	Jazz Pharmaceuticals	cannabidiol (Epidiolex)	Neurology	cannabinoid; unclear MoA	Commercial	$7,200

Monthly Updates

ganaxolone

oral GABAA receptor PAM



- for seizures in CDD, approved Mar. 2022
- 34 hour elimination half-life
- reduced GABAA-inhibiting metabolites

Ztalmy® (ganaxolone) is an oral neuroactive steroid and gamma-aminobutyric acid GABAA receptor positive allosteric modulator, approved for the treatment of seizures caused by cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age or older. It has a recommended dosing frequency of three times a day where dose is titrated based upon the patient's weight.

Endpoints. For patients (ages 2-19 years) with confirmed CDKL5 mutation with seizures not controlled by at least 2 previous treatment regimens, this drug significantly reduced the frequency of major motor seizures when compared to placebo (p= 0.0036), in a randomized double-blinded trial.

Disease Context. CDD is a genetic disorder caused by mutations in the CDKL5 gene, situated on the smaller arm of the X chromosome, and affects one newborn among every 40,000 to 60,000 live births. CDKL5 plays an important role in neuronal development, especially during the early phases of human development. This disease is normally divided into three stages: early epilepsy (stage 1), then infantile spasms (stage 2), and later development of multifocal and refractory epilepsy (stage 3). This disease is manifested by the presence of lengthy tonic-clonic seizures (stage 1), infantile spasms (stage 2), and later multifocal treatment resistant seizures (stage 3). In addition, CDKL5 mutations may lead to repetitive hand movements, decreased head circumference and impaired psychomotor development among a large proportion of patients.

Prior Treatment Options. Treatment options for CDD are normally limited to managing symptoms which include anti-epileptic drugs, vagal nerve stimulators, neurosurgery and diet modifications. According to WHO guidelines,

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Searchable Deep Dives

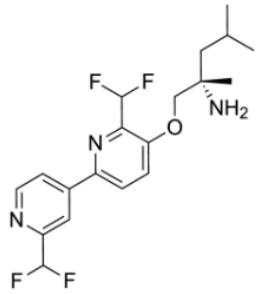
e.g. “CNS-penetrant” or “DEL screen”

cns-penetrant | Molecules | Sort by Date | SEARCH

Search Results

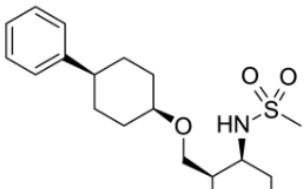
BMS-986176/LX-9211

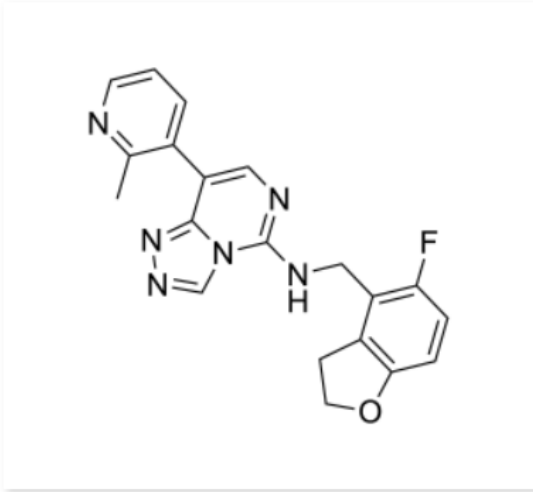
Context. BMS-986176/LX-9211 (BMS) is an oral, CNS-penetrable AAK1 kinase inhibitor being developed for treatment of neuropathic pain. There are six main classes of pain medications, NSAIDs, opioids, ion channel modulators, serotonergic, monoaminergic, and GABAnergic drugs that are broadly used for pain in general, but neuropathic pain due to nerve damage or dysfunction is much harder...



Danavorexton

Context. Danavorexton (Takeda, TAK-925) is a CNS-penetrant, injectable OX2 agonist. Orexin receptor (OX1/OX2) antagonists (e.g. daridorexant) are approved for treatment of insomnia. Orexin agonism would be expected to have the opposite effect, promoting wakefulness rather than sleep, which is helpful for





MAK683

RECENT PUBLICATION

Searchable Deep Dives

oral, allosteric PRC2 inhibitor (EED)
in Ph. I/II for cancer (DLBCL); preliminary efficacy
from micromolar HTS hit
J. Med. Chem.
Novartis, Emeryville, CA

Context. MAK683 is an oral, allosteric and selective PRC2 inhibitor intended for PRC2-dependent cancers. PRC2 is an essential epigenetic regulator of gene expression and enhanced or diminished PRC2 function have been implicated in a number of cancers. Enhancer of zeste homolog 2 (EZH2), one of the four core components of PRC2 that directly trimethylates K27 of histone 3 (H3K27me3), has been the most extensively studied PRC2 subunit and a number of EZH2 mutations and post-translational modifications have reportedly been associated with disease progression. In addition, the approval of the first EZH2 inhibitor, Epizyme's tazemetostat, for advanced/metastatic epithelioid sarcoma and relapsed/refractory follicular lymphoma further validated EZH2 and other PRC2 components as viable drug targets. Resistance mechanisms to EZH2 inhibitors have been observed in cell lines, and the development of other PRC2 inhibitors are underway. Of the five in-development compounds targeting EED, MAK683 is the most clinically advanced. Preliminary clinical data suggest that the drug is tolerable and has signs of efficacy.

Target. The Polycomb Repressive Complex 2 (PRC2) is a polycomb group protein that modulates chromatin structure through repression of its target genes. PRC2 catalyzes the methylation of histone H3 lysine 27 (H3K27) to generate mono-, di-, or trimethylated forms of H3K27; trimethylated H3K27 (H3K27me3) subsequently mediates the suppression of polycomb target genes. PRC2 comprises a catalytic, SET-domain-containing histone methyltransferase (EZH1 or EZH2) as well as two core proteins required for full histone methyltransferase activity: embryonic ectoderm development protein (EED) and suppressor of zeste 12 (SUZ12). EED bridges H3K27me3 binding with EZH2 stimulation and is essential for basal PRC2 activity. It is one of the four core components, together with EZH1/2, SUZ12, and RBBP4/7, that make up the minimal core PRC2 particle. Allosteric activation of PRC2 is initiated by binding of the protein to H3K27me3 through an aromatic cage in EED. The role of PRC2 and polycomb protein deregulation in cancer progression has been extensively studied.

save days to weeks

drughunter.com/contact

dennis@drughunter.com

stay tuned for part II!

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