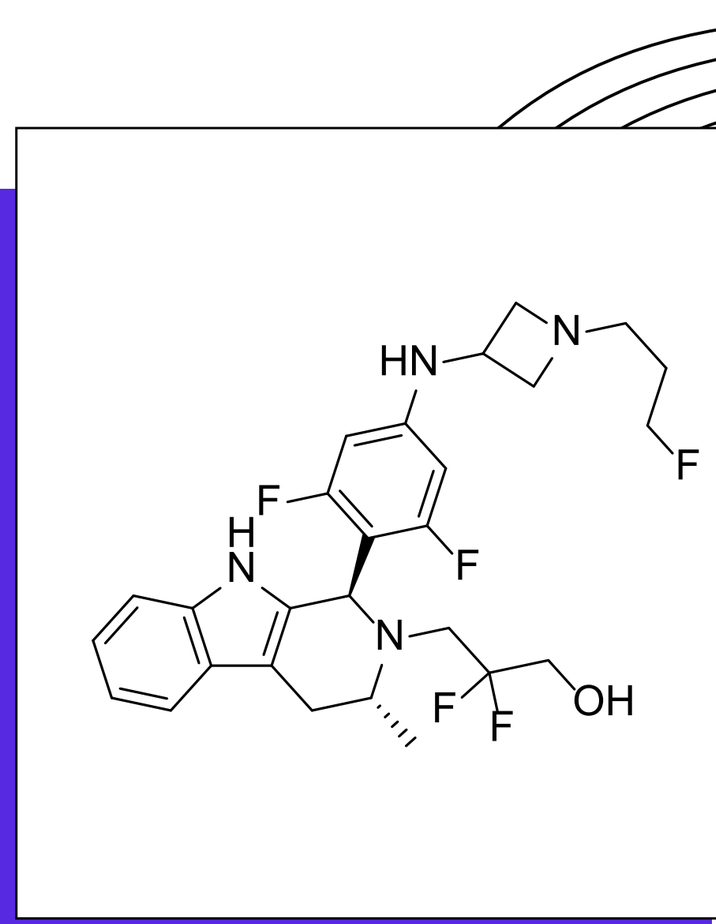
Small Molecules of the Month

July 2021



drug hunter

01	ERα	Genentech
02	FGFR2	Incyte Corporation
03	ATR	AstraZeneca
04	CDK9	Bayer, Berlin, DE / Vincerx
05	AMPA-R	Takeda Pharmaceutical
06	M1R	Takeda Pharmaceutical
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09	LMP2/7	Kezar Life Sciences
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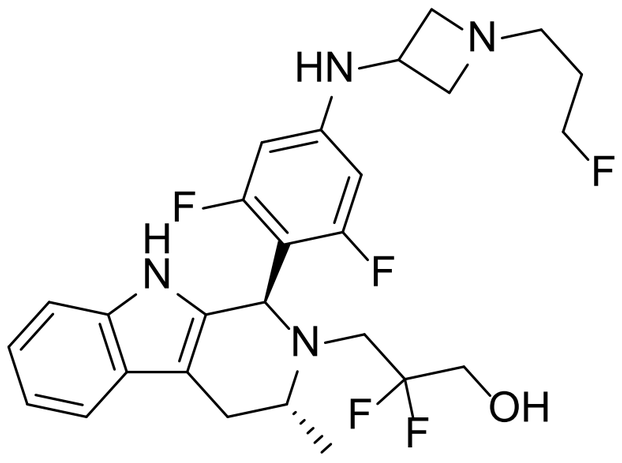
11	tubulin	PTC Therapeutics
12	COX-2	Janssen
13	BD2	GlaxoSmithKline
14	AAK1	Bristol Myers Squibb

giredestrant

ERα



Selective ER degrader (SERD) + full antag.
Oral (30 mg QD), Ph. III for ER+, HER2- BC
From profiling >4k cmpds for desired MoA
Journal of Medicinal Chemistry
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).

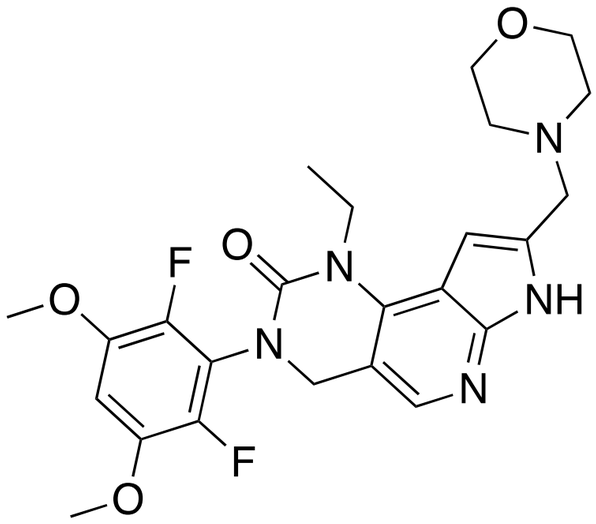
It is the third SERD clinical candidate from Genentech (after GDC-0810 and GDC-0927) and a number of oral SERDs have previously been highlighted here (including SAR439659, AZD9833, GNE-149). The oral, once-daily molecule has been well-tolerated at doses up to 250 mg and a standardized 30 mg dose has 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.

pemigatinib

FGFR2



Oral FGFR1/2/3 kinase inhibitor
Approved in oncology, 13.5 mg QD (14d+, 7d-)
From focused screen of ~20k cmpds and SBDD
Journal of Medicinal Chemistry
Incyte Corporation, Wilmington, US

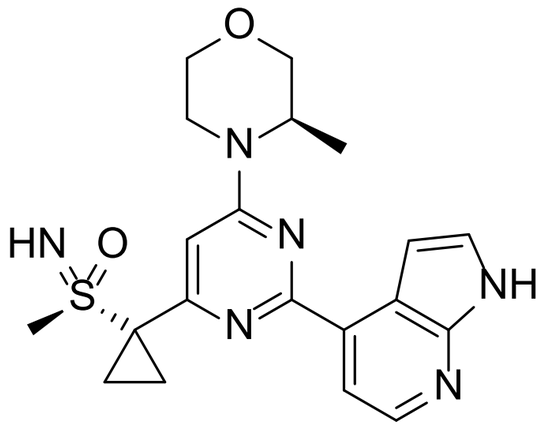
The Incyte FGFR1/2/3 kinase inhibitor, pemigatinib, is an oral kinase inhibitor that obtained an FDA accelerated approval in 2020 for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma (bile duct cancer) with FGFR2 fusion or other rearrangement as detected by an FDA-approved test. There were no FDA-approved drugs for second-line treatment of patients with unresectable or metastatic cholangiocarcinoma, and no treatments approved specifically for cholangiocarcinomas with an FGFR2 gene fusion or rearrangement. Pemigatinib was approved concurrently with a Foundation Medicine companion diagnostic assay for FGFR2 rearrangements.

The molecule was approved primarily based on data from the Ph. II FIGHT-202 study (NCT02924376) of 107 patients (est. ORR of 36%), and took only 3 years from trial initiation to reach accelerated approval, serving as yet another example of the relative efficiency of trials leveraging genetic biomarkers. Safety was supported by data from 320 additional patients in other clinical trials. One important risk of pemigatinib considered in the FDA multidisciplinary review was ocular toxicity (retinal pigment epithelial detachment, RPED), which occurred in 6% of patients (out of 466).

The median time to first onset of RPED was 62 days, and the RPED was manageable and largely reversible with dose modification and supportive care. Comprehensive ophthalmologic monitoring is therefore recommended during treatment. During optimization, a CYP3A4 TDI signal (45% inh. at 25 uM) was observed with a piperazine analog, which was addressed by replacing the piperazine with the morpholine motif present in the drug.

ceralasertib

ATR



ATR serine/threonine kinase inhibitor
Oral agent in Ph. II for cancer
From mTOR-program derived hit + opt.
Clinical Cancer Research
AstraZeneca, Cambridge, UK

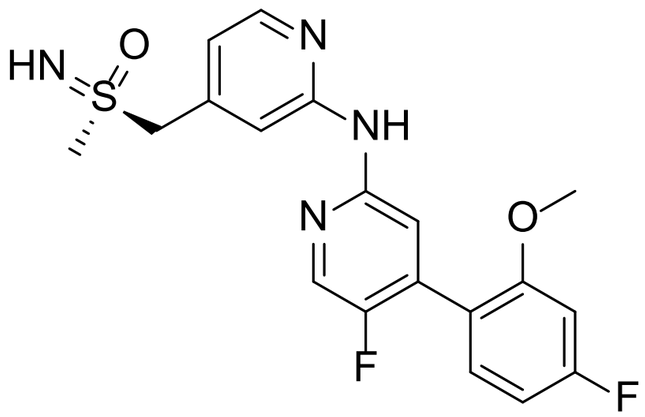
The AstraZeneca ATR serine/threonine kinase inhibitor, ceralasertib (AZD6738), is a potent (1 nM biochemical IC50), orally bioavailable, ATP-competitive inhibitor, and is one of the most clinically advanced sulfoximines with ~32 registered clinical studies. An indole to azaindole change was key to mitigating CYP TDI during discovery, which was important due to the number of drug combinations the molecule ended up being involved in. The molecule is broadly selective against other kinases (0/442 kinases with >50% inh. at 1 uM) likely thanks to the morpholine hinge-binding element which is a privileged motif for PI3K-like kinases.

Though the structure and discovery campaign were disclosed years ago, this publication shares valuable data from its Ph. I study including human PK and its recommended Ph. II dose (40 mg QD) with carboplatin. A higher Ph. II dose (160 mg PO QD) was used in combination with olaparaib. The difference in dose is notable for synthetic lethality programs as an example of how different DNA-damage mechanisms result in different tolerabilities in combination due to synergistic toxicity.

One interesting comment from the article is that rats are believed to be better models of bone marrow toxicity than mouse, and preclinically ceralasertib was not well-tolerated in combination with carboplatin in rats, leading to the 3-day dosing gap used in human trials. Another novel ATR inhibitor, M4344, was also published on in July and is worth checking out.

VIP152

CDK9



>50x family-selective CDK9 kinase inhibitor
IV agent (5-30 mg QW) in Ph. I for cancer
Scaffold hop from atuveciclib
Journal of Medicinal Chemistry
Bayer, Berlin, DE / Vincerx, Palo Alto, US

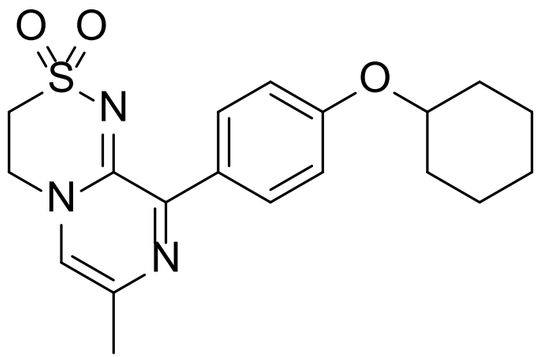
The Vincerx Pharma/Bayer CDK9 inhibitor, VIP152 (BAY 1251152), is a once-weekly (5-30 mg) IV agent in Ph. I for cancer with >50x family-selectivity. The sulfoximine-containing molecule is derived from the oral candidate atuveciclib (interestingly with opposite sulfoximine stereochemistry) and is significantly more potent under high ATP conditions.

To maximize the therapeutic index, the team targeted a short half-life molecule to enable acute CDK9 inhibition for antitumor activity without prolonged transcription inhibition (oncogenic shock), with IV administration to reduce exposure variability.

Solubility is key to IV administration, and the pyridine of VIP152 allowed it to have comparable solubility to atuveciclib at pH 4 (within the physiologically acceptable range for IV administration in humans), while the improved potency enabled a low IV dose. A 38% disease control rate was already observed in the first 31 patients in the VIP152 first-in-human (FIH) study, with several patients having benefit beyond 15 cycles.

TAK-653

AMPA-R



Potent AMPA-R potentiator w/ min. agonism
6 mg PO QD in Ph. II (withdrawn, biz decision)
From biochemical screen + opt.
Scientific Reports
Takeda Pharmaceutical, Fujisawa, JP

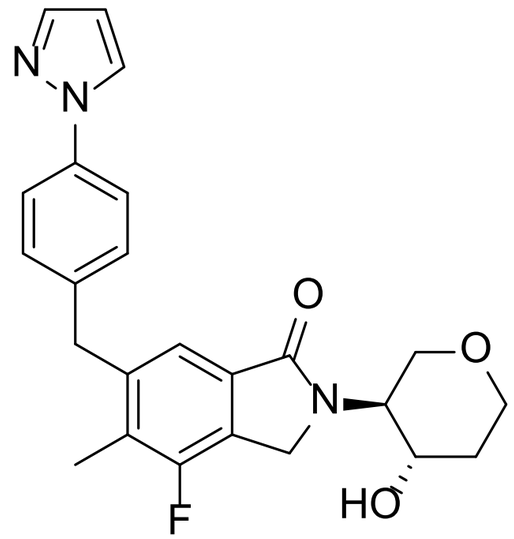
The Takeda AMPA-R potentiator, TAK-653, is a glutamate-dependent potentiator that exhibits minimal agonism. AMPA-R agonism is associated with seizure risk and bell-shaped dose-response effects. As reviewer Jake Schwarz notes, companies including Cortex Pharmaceuticals (now RespireRx) and Lilly have been trying to develop AMPA modulators for decades, testing both "low-impact" AMPA modulators with a wider therapeutic window but lower potency and "high-impact" compounds with a narrow therapeutic window but higher potency.

The Takeda team was able to identify compounds with a wide safety margin against convulsion (400-1000x), behaving like "low-impact" modulators, but with significant efficacy and potency to enable a 6 mg oral dose. They suggest that selectively enhancing AMPA-R activation by physiological glutamate is key to enhancing cognition, as nonselective activation of resting AMPA-R's may have a detrimental effect.

Unfortunately, while the molecule was taken into Ph. II studies for depression (e.g. NCT03312894), it was withdrawn in a business decision. The interesting thiadiazine dioxide starting point of TAK-653 was identified in a biochemical screen using GluA2o LBD protein.

TAK-071

M1R



Low **α**- M1R positive allosteric modulator

7.5 mg+ PO QD in Ph. II for Parkinson's

From eval. of M1R PAMs w/ low cooperativity

British Journal of Clinical Pharmacology

Takeda Pharmaceutical, Cambridge, USA

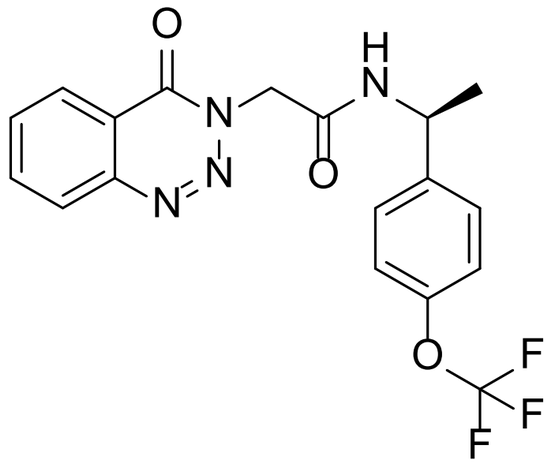
The Takeda brain-penetrant M1R positive allosteric modulator (PAM), TAK-071, was optimized for lower cooperativity (**α**) with the native ligand to theoretically reduce the side effect of diarrhea from M1R activation. In animal models, higher cooperativity on M1R was associated with diarrhea, while lower cooperativity led to a wider margin.

In this first-in-human study, TAK-071 appears to safe and well tolerated in humans, with notably uncommon nausea, vomiting, or diarrhea effects typical of cholinergic agents. TAK-071 demonstrates a long half-life of ~46-60 h with excellent brain penetration at a low dose, which is impressive for a molecule containing a secondary alcohol and THP ring. A Ph. II trial for Parkinson's appears to be actively enrolling (NCT04334317) with a sentinel dose of 7.5 mg QD.

Overall, this story is a nice example of a biological hypothesis for cooperativity optimization playing out a drug's human safety profile. It is especially remarkable given the typical concentration difference between the intended CNS-site of action vs. the gut target organ for safety.

TAK-041

GPR139



GPR139 GPCR agonist

Oral (40-160 mg QD) Ph. II for schizophrenia

625k-cmpd cell-based screen (21 nM hit) + opt

Journal of Medicinal Chemistry

Takeda, San Diego, US

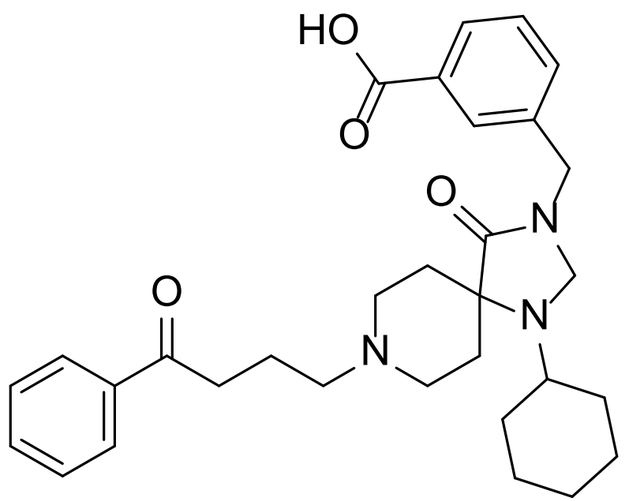
The Takeda GPR139 agonist, TAK-041, is a CNS-penetrant GPCR agonist being explored for schizophrenia symptoms and is an interesting example of a triazinone-containing clinical candidate. GPR139 is an orphan GPCR that's highly expressed in the human habenula, which plays a major role in avoidance behavior. Lesions in the habenula cause deficits in social behavior and cognitive abilities, and GPR139 KO's demonstrate behavior deficits related to SCZ.

Jake Schwarz notes: "While GPCRs are highly druggable, the agonist route is fraught with peril. Full agonism rarely mimics the natural state of a healthy receptor, where the agonist is not constantly present at the receptor. Partial agonists and PAMs have enjoyed much more success."

This first-in-class molecule is a notable example of clinical development of a challenging mechanism of action in a challenging therapeutic area (SCZ), and so far, has completed a Ph. II study with the latest results posted in Mar. 2021 (NCT03319953). Neurocrine plans to move the molecule (NBI-1065845) into Ph. II studies for depression in 2H 2021.

TAK-906

D2/D3



Peripherally-restricted D2/D3 antagonist
Oral agent for gastroparesis in Ph. II
Up to 100 mg PO BID
JPET, Clinical Pharmacology
Altos Therapeutics / Takeda, Cambridge

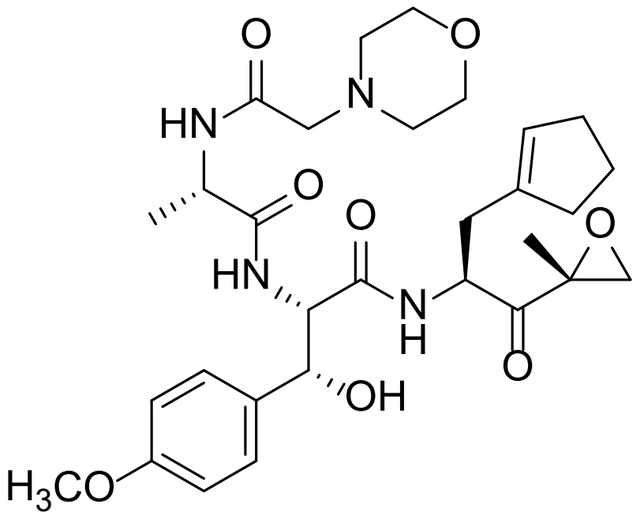
The Altos Therapeutics/Takeda D2/D3 receptor antagonist, TAK-906, is a peripherally-restricted, non-BBB penetrant molecule, targeting the stomach and vomiting center in the area postrema to treat gastroparesis. Gastroparesis is a chronic condition characterized by delayed gastric emptying, resulting in nausea, vomiting, pain, and anorexia. Cisapride was used off-label in the past (but was famously withdrawn due to cardiac side effects).

Metoclopramide, a dopamine receptor antagonist, is approved for short term use (up to 12 weeks) and up to 5 days by the EMA, due to the increased risk of tardive dyskinesia. Peripheral restriction was employed due to known CNS side effects of D2/D3 antagonism (e.g., tardive dyskinesia). It is a great example of a peripherally-restricted drug targeting a former CNS target in a new indication.

Reviewer Jake Schwarz notes that eluxadoline (Viberzi) is another great example for irritable bowel syndrome (IBS), which targets opioid receptors in the enteric nervous system. Reviewer Kim Huard notes that the PK, DDI, and safety evaluation was done in healthy volunteers, and it would be interesting to compare the data to studies in gastroparesis patients as this is an example where the disease state may have different absorption and exposure profiles to the healthy volunteers.

KZR-616

LMP2/7



Covalent immunoproteasome inhibitor
Subcutaneous agent in Ph. I/II for SLE and LN
Designed from proteasome inhibitors
Drug Metabolism and Disposition
Kezar Life Sciences, San Francisco, US

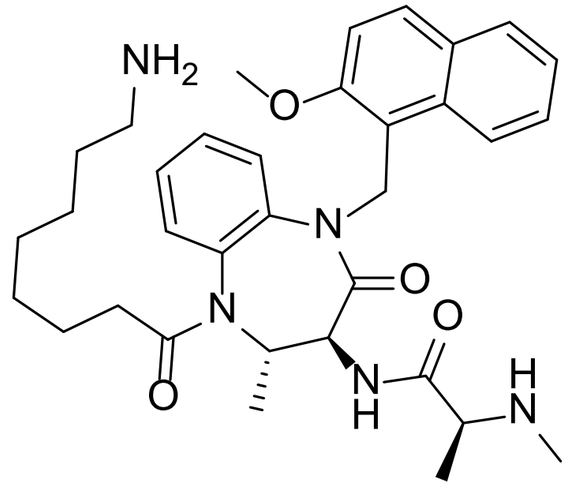
The Kezar Life Sciences covalent immunoproteasome inhibitor, KZR-616, licensed from Onyx, targets the LMP7 and LMP2 active sites of the immunoproteasome, and is currently in Ph. II trials for autoimmune disorders (30 mg SC QW for 2 weeks, then 45 mg SC weekly for 14 weeks). More subunit-selective, proteasome-sparing reversible-covalent LMP7 inhibitors (including Molecule of the Month M3258 and these examples) have recently been reported but are not being developed in autoimmune diseases.

Interestingly, the molecule's epoxide is primarily metabolized by microsomal epoxide hydrolase (mEH), and not CYPs or soluble epoxide hydrolase (sEH) as might be expected, adding complexity to PK prediction. Though KZR-616 was disclosed a few years ago, this article is a nice case study for how to distinguish metabolic routes of an epoxide-containing molecule.

It will be interesting to see with more clinical data whether this molecule is able to sufficiently avoid constitutive proteasome inhibition to provide a suitable safety profile for many autoimmune diseases.

“compound 10”

XIAP



XIAP E3-ligase degrader via SM ubiquitylation

Novel mechanism of induced degradation

From derivatization of XIAP-binder

Journal of the American Chemical Society

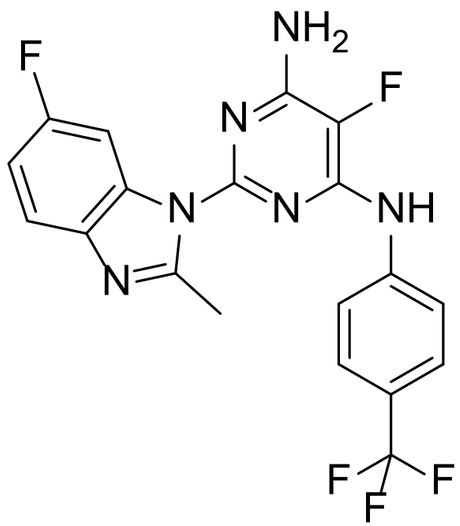
Genentech, San Francisco, US

The Genentech XIAP E3-ligase degrader, [compound 10], has an interesting mechanism of action, triggering the degradation of its target (XIAP) by ubiquitylation of the small molecule. The molecule behaves as a lysine mimetic, accepting ubiquitin from the targeted E3 complex, promoting XIAP’s own degradation.

As E3 ligases are often difficult to drug, this “K-tag” approach adds an interesting new concept to the toolbox, which may be easier to translate into drugs than heterobifunctional degraders which tend to be much larger and less synthetically accessible.

PTC596

tubulin



CNS-penetrant tubulin-binder (colchicine site)

Oral agent in Ph. I for leiomyosarcoma

Not a P-gp substrate, formerly BMI-1 inh.

Molecular Cancer Therapeutics

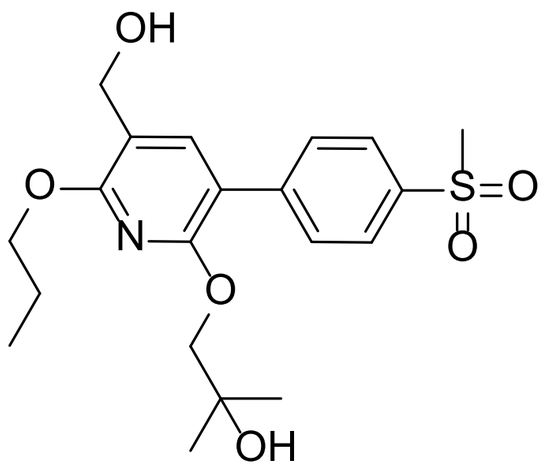
PTC Therapeutics, South Plainfield, US

The PTC Therapeutics oral, brain-penetrant tubulin-binding agent, PTC596, is in Ph. I clinical studies for advanced solid tumors (starting dose of 200 mg PO BIW). We recently highlighted encequidar, a P-gp inhibitor co-dosed with paclitaxel to render paclitaxel orally bioavailable. A directly orally bioavailable tubulin-binder would circumvent the need for two drugs and reduce potential drug-drug interactions.

One of the 2020 small molecule FDA approvals, cedazuridine, similarly induces a DDI to render the traditional IV chemo agent decitabine orally available. The adoption of "oral chemo" combination regimens may catalyze the development of single agent oral chemotherapies such as PTC596 as well. A topical synthetic tubulin inhibitor (tirbanibulin) was also approved last year for actinic keratosis. It will be interesting to watch if synthetic tubulin-binders will start to displace natural products in chemotherapy.

“compound 10”

COX-2



Gut-restricted, selective COX-2 inhibitor

In vivo showed no inhibition of gut COX-2

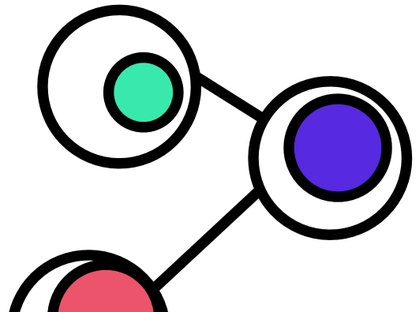
From modification of etoricoxib

Journal of Medicinal Chemistry

Janssen, Spring House, US

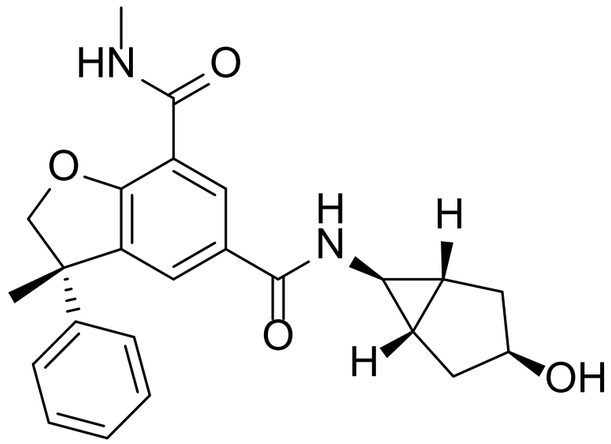
The Janssen gut-restricted COX-2 inhibitor, compound 10, is a tool compound used to test the hypothesis that gut-restricted COX-2 inhibition would be beneficial for cancer without the cardiovascular risk of systemic COX-2 inhibition. Unfortunately, IVIVC of several compounds demonstrated that in vivo efficacy was not driven by gut COX-2 inhibition, but by residual systemic activity.

Reviewer Mike Koehler found this story particularly interesting this month. Though it was not a positive result, this is a great case study for getting decision-making biological data quickly using medicinal chemistry.



GSK852

BD2



>1000x BD2-selective BET bromodomain inh.

Orally available in dog

Rational design from prior lead

Journal of Medicinal Chemistry

GlaxoSmithKline, Stevenage, UK

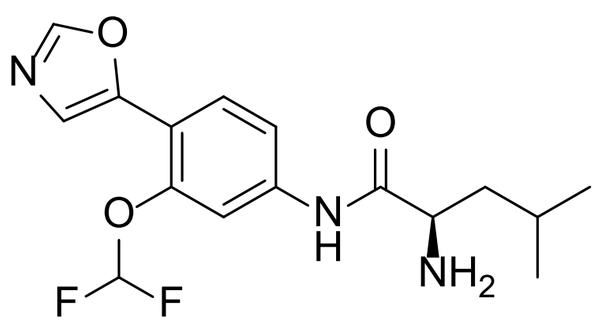
The GSK BET BD2 inhibitor, GSK852, is one of a series of BD2-targeting compounds published last month by GSK (see a fragment-based approach here, a DEL screening approach here, and a pincolinamide molecule here).

Each of these campaigns is impressive and educational in different ways, and the collective GSK BD2 effort is a tour de force of lead finding and optimization strategies (for additional BET efforts recently published by GSK and others, see May 2020, Mar. 2020, Feb. 2020, and Jan. 2021).

GSK852 was particularly interesting for its chemical structure, the use of a quaternary center to block metabolism and improve solubility. GSK has invested significant resources into drugging epigenetic modulators and the publication of their efforts will be helpful to the community in understanding the challenging biology of many of these pathways.

“compound 59”

AAK1



The BMS AAK1 kinase inhibitor, compound 59, is brain-penetrant and acts on the CNS. The target was identified from a phenotypic screen of mouse knockouts, and a non-brain penetrant inhibitor doesn’t show in vivo activity, confirming the central activity needed on the target.

Targeting a kinase in the CNS for pain is bold due to the high bar for safety required, but recent advances in achieving selectivity with kinase inhibitors for broader therapeutic areas such as inflammation makes it seem achievable.
As Jake points out, an increasing number of kinase inhibitors are entering the clinic for non-cancer CNS indications such as for LRRK2, DLK, and RIPK1.

Brain penetrant AAK1 kinase inhibitor

Efficacious in neuropathic pain model

From biochemical screen of in-house library

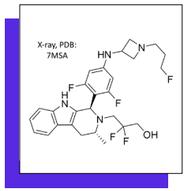
Journal of Medicinal Chemistry

Bristol Myers Squibb, Wallingford, US

drug hunter

Small Molecules of the Month

July 2021
drughunter.com



giredestrant | ERα

Selective ER degrader (SERD) + full antag.
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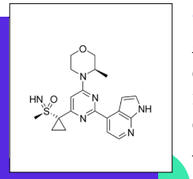
From profiling >4k cmpds for desired MoA
Journal of Medicinal Chemistry
Genentech, San Francisco, US



ceralasertib | ATR

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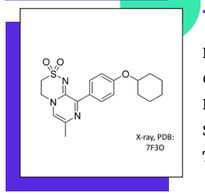
AstraZeneca, Cambridge, UK



TAK-653 | AMPA-R

Potent AMPA-R potentiator w/ min. agonism
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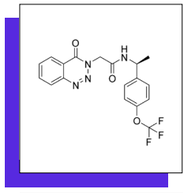
Takeda Pharmaceutical, Fujisawa, JP



TAK-041 | GPR139

GPR139 GPCR agonist
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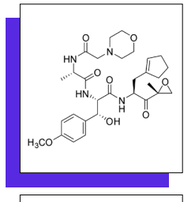
Takeda, San Diego, US



KZR-616 | LMP2/7

Covalent immunoproteasome inhibitor
Subcutaneous agent in Ph. I/II for SLE and LN
Designed from proteasome inhibitors
Drug Metabolism and Disposition
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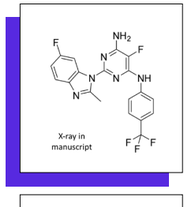

PTC596 | tubulin

CNS-penetrant tubulin-binder (colchicine site)
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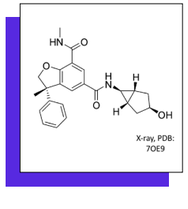
Not a P-gp substrate, formerly BMI-1 inh.
Molecular Cancer Therapeutics
PTC Therapeutics, South Plainfield, US



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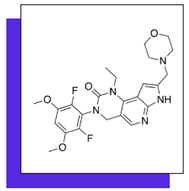
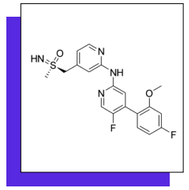


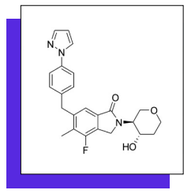
pemigatinib | FGFR2

Oral FGFR1/2/3 kinase inhibitor
Approved in oncology, 13.5 mg QD (14d+, 7d-)
From focused screen of ~20k cmpds and SBDD
Journal of Medicinal Chemistry
Incyte Corporation, Wilmington, US



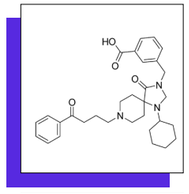
VIP152 | CDK9

>50x family-selective CDK9 kinase inhibitor
IV agent (5-30 mg QW) in Ph. I for cancer
Scaffold hop from atuveciclib
Journal of Medicinal Chemistry
Bayer, Berlin, DE / Vincerx, Palo Alto, US



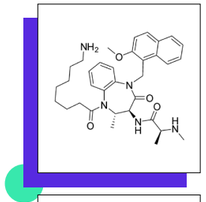
TAK-071 | M1R

Low α- M1R positive allosteric modulator
7.5 mg+ PO QD in Ph. II for Parkinson's
From eval. of M1R PAMs w/ low cooperativity
British Journal of Clinical Pharmacology
Takeda Pharmaceutical, Cambridge, USA



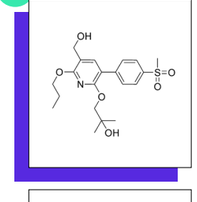
TAK-906 | D2/D3

Peripherally-restricted D2/D3 antagonist
Oral agent for gastroparesis in Ph. II
Up to 100 mg PO BID
JPET, Clinical Pharmacology
Altos Therapeutics / Takeda, Cambridge



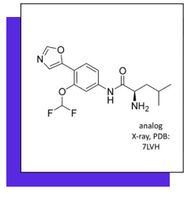
"compound 10" | XIAP

XIAP E3-ligase degrader via SM ubiquitylation
Novel mechanism of induced degradation
From derivatization of XIAP-binder
Journal of the American Chemical Society
Genentech, San Francisco, US



"compound 10" | COX-2

Gut-restricted, selective COX-2 inhibitor
In vivo showed no inhibition of gut COX-2
From modification of etoricoxib
Journal of Medicinal Chemistry
Janssen, Spring House, US



"compound 59" | AAK1

Brain penetrant AAK1 kinase inhibitor
Efficacious in neuropathic pain model
From biochemical screen of in-house library
Journal of Medicinal Chemistry
Bristol Myers Squibb, Wallingford, US

drug hunter

discover together

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info@drughunter.com