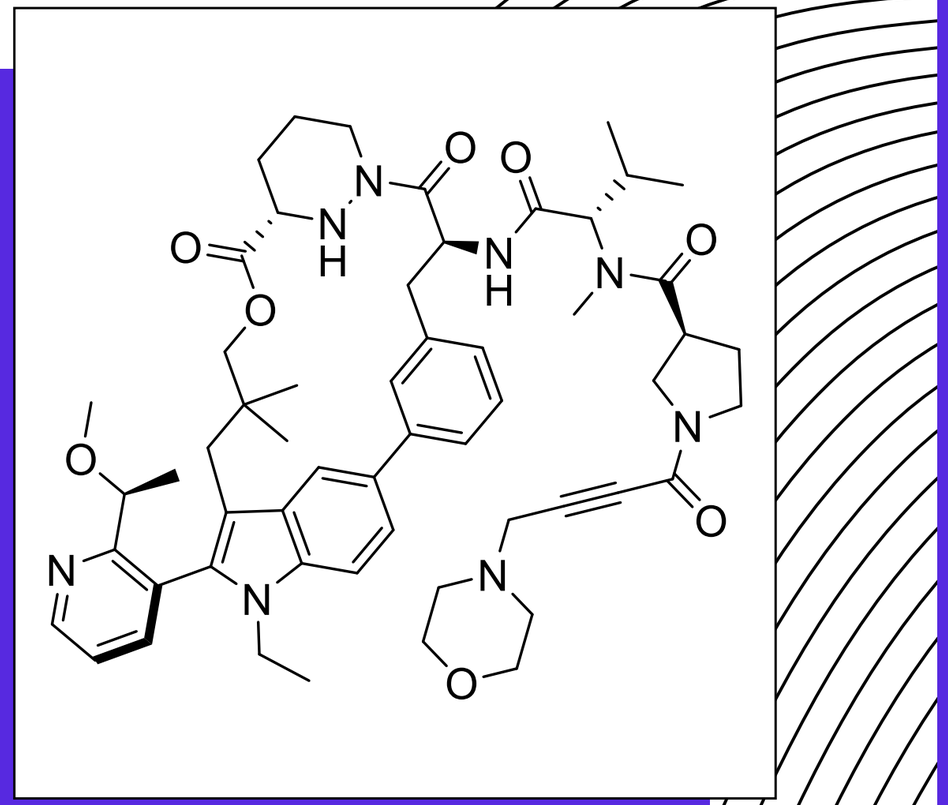
Small Molecules of the Month

April 2021



drug hunter

01	KRASG12C	RevMed
02	TRPA1	Genentech
03	sGC	Bayer
04	MAT2A	Agios
05	DUBTAC	Berkeley/Novartis
06	GABA	Roche
07	METTL3	Storm/Cambridge
08	MAT2A	AstraZeneca
09	TEAD	Vivace
10	p97	Cleave
11	FXR/TGR5	Fuji Yakuhin
12	RORγ	Eternity/Hengrui
13	RAF	Genentech
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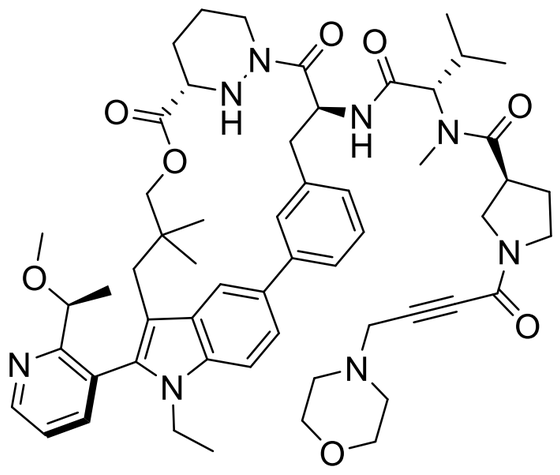
RM-018

KRASG12C



KRAS(G12C)ON-cyclophilin A tri-complex inh. Overcomes KRAS resist. mut. in PDX model Natural product related (sanglifehrin); undiscl. Cancer Discov., Apr. 6, 2021 Revolution Medicines, Redwood City, CA

The Revolution Medicines KRASG12C inhibitor, RM-018, "glues" KRASG12C to the highly abundant chaperone protein, cyclophilin A, in a tri-complex (KRAS-inhibitor-cyclophilin A) stabilized by protein-protein interactions.

KRAS is a driver of cancer cell growth, and mutants including KRASG12C have been hot targets due to the newfound ability to drug them selectively over wild type KRAS, which is important for healthy cell division.

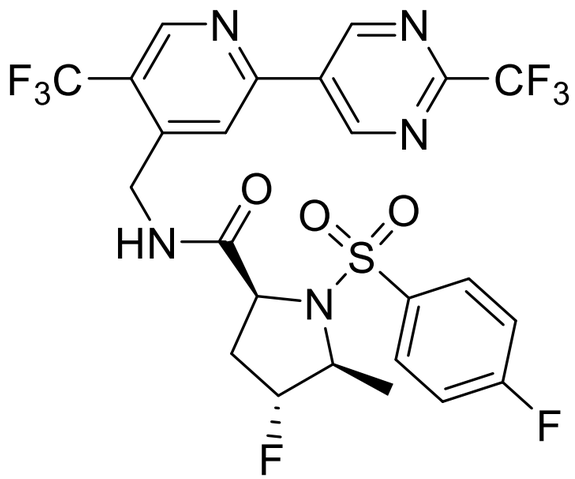
While GTP-OFF inhibitors of KRASG12C which bind to a switch-II have demonstrated clinical efficacy (including 2020 Small Molecule of the Year Finalist, MRTX849), resistance to such inhibitors was inevitable due to switch-II mutations. Because RM-018 targets the GTP-ON state of KRASG12C with a unique mechanism, it overcomes GTP-OFF resistance mutations such as KRASG12C/Y96D in patient-derived xenografts.

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

RevMed appears to be advancing related compounds toward clinical development, and KRAS is likely not the only target this fascinating tri-complex mechanism will be applied to.

GDC-0334

TRPA1



Oral TRPA1 ion-channel inhibitor
For asthma, target engagement in HV Ph. I
From ligand-based design, cryo-EM structure
J. Exp. Med., Apr. 5, 2021
Genentech Inc., South San Francisco, CA

The Genentech TRPA1 ion-channel inhibitor, GDC-0334, is an oral candidate for asthma that demonstrated target engagement in a non-invasive skin-based Ph. I study. It reduces TRPA1 agonist-induced symptoms in healthy volunteers, with near complete TRPA1 inhibition at 600 mg.

TRPA1 is most well-known as a receptor activated by irritants such as allyl isothiocyanate, the irritant in wasabi.

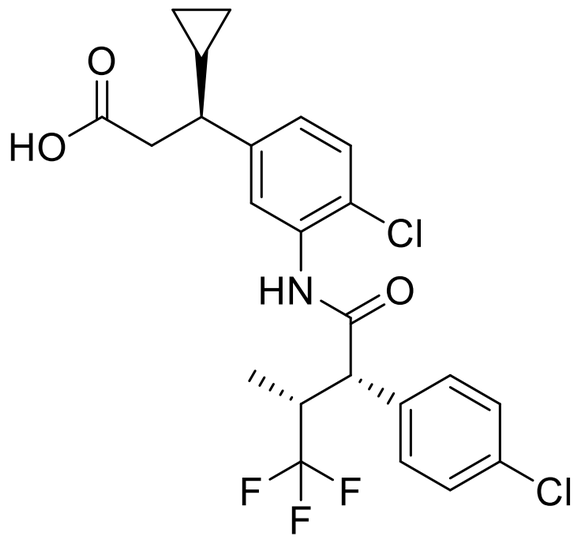
Though there has been significant interest in targeting TRPA1 for various conditions including pain, validating the biology preclinically has been challenging due to species expression differences, the possibility of different inhibitor sites of action, and the difficulty in identifying inhibitors with suitable in vivo profiles.

The authors describe evaluation of GDC-0334 across multiple developed species models, disclose human data, and characterize the binding mode of GDC-0334 by cryo-EM, revealing a different binding site from the TRPA1 inhibitor recently highlighted.

This is a great case study on the use of sentinel tissue (skin) biomarkers across species including humans to assess target engagement quickly and non-invasively prior to enrolling a lengthier trial in the intended indication (asthma).

BAY 1101042

sGC



Oral once-daily sGC activator

Ph. II for CKD + diabetic neuropathy

From cell-based HTS + opt.

J. Med. Chem., Apr. 19, 2021

Bayer AG, Wuppertal, DE

The Bayer soluble guanylate cyclase (sGC) activator, BAY 1101042 (runcaciguat), is a once-daily (50 mg), oral clinical candidate in Ph. II for chronic kidney disease and diabetic retinopathy.

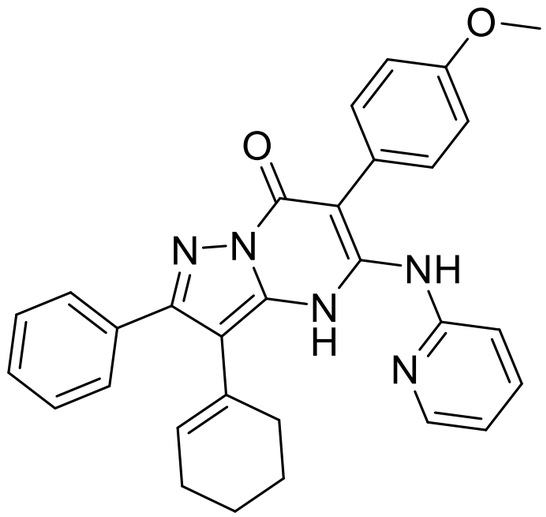
sGC is an intracellular receptor for nitric oxide (NO), binding NO via a heme-cofactor, which activates a catalytic domain that leads to production of second messenger cGMP.

This NO-sGC-cGMP axis is a key pathway regulating the cardiovascular system. Runcaciguat acts by displacing the heme-cofactor, but binding in a way that activates sGC as if NO had bound heme, turning on cGMP production.

This conveniently dosed candidate can be useful in evaluating the NO-sGC-cGMP axis in humans in multiple disease contexts.

AG-270

MAT2A



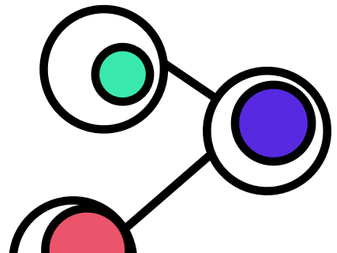
First-in-class oral MAT2A allosteric inhibitor
Synthetic lethal candidate in Ph. I for MTAP-
From>2000 fragment library and SBDD
J. Med. Chem., Apr. 8, 2021
Agios Pharmaceuticals, Cambridge, MA

The Agios first-in-class oral MAT2A enzyme allosteric inhibitor, AG-270, is a Ph. I clinical candidate for tumors with MTAP gene loss.

The inhibitor works on a synthetic lethality principle: the MTAP-loss which drives tumors also makes them particularly sensitive to reduction in S-adenosyl methionine (SAM) levels, and since MAT2A is the primary producer of SAM, inhibition of MAT2A leads to MTAP- tumor killing while healthy tissues are largely unaffected.

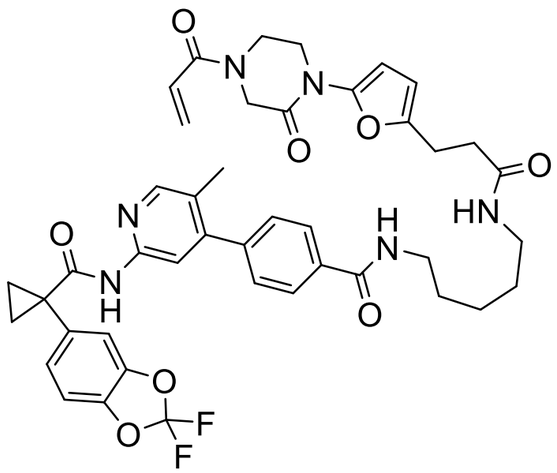
Remarkably, the program started from a 620 µM fragment hit detected by SPR, and the challenging pyrazolopyrimidone core structure with multiple tautomeric states was carried through to the clinical candidate (despite multiple attempts to replace it).

Though MAT2A inhibition has previously been shown to result in a feedback loop resulting in MAT2A upregulation, AG-270 appears to be potent enough to overcome this effect (though this effect might also be beneficial for maintaining overall drug tolerability).



NJH-2-057

DUBTAC



Covalent allosteric OTUB1-recruiting DUBTAC
Induced deubiq./stabilization of ΔF508-CFTR
From gel-based screen of 702 covalent ligands
bioRxiv, Apr. 30, 2021
UC Berkeley / Novartis (NIBR)

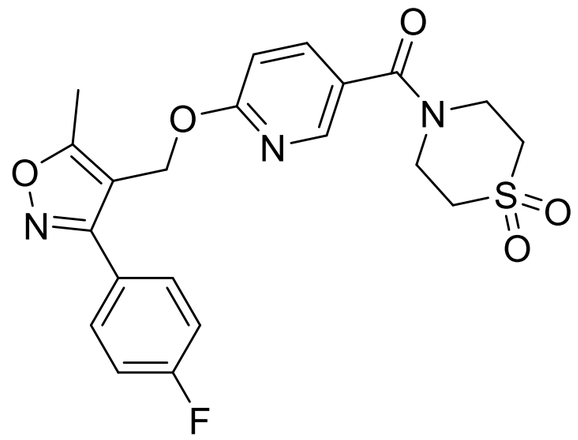
The UC Berkeley and Novartis deubiquitinating enzyme-recruiting chimera (DUBTAC), NJH-2-057, has a warhead that covalently targets a non-catalytic allosteric cysteine on the deubiquitinase (DUB) OTUB1.

The CFTR-binding moiety recruits OTUB1 to the mutant ion channel, ΔF508-CFTR, stabilizing the protein by preventing its polyubiquitination and degradation. This work provides an interesting proof of concept for targeted protein stabilization rather than degradation via DUB recruitment.

We recently highlighted a number of new chimeric modalities, including ribonuclease recruiting chimeras (RIBOTACs), phosphatase recruiting chimeras (PhoRCs), LYTACs, and AUTACs, and this introduction of a deubiquitinating enzyme-recruiting chimera will add another valuable concept to the pharmacological toolbox.

basmisanil

GABAA-α5



CNS-pen. GABAA-α5 neg. allo. mod. (NAM)
Ph. II for Down syndrome (240 mg BID)
From 56k cmpd competition binding HTS
Sci. Rep., Apr. 8, 2021
Roche Innovation Center, Basel, CH

The Roche $GABA_A$-α5 selective negative allosteric modulator (NAM), **basmisanil**, is a Ph. II candidate for intellectual disability in Down syndrome.

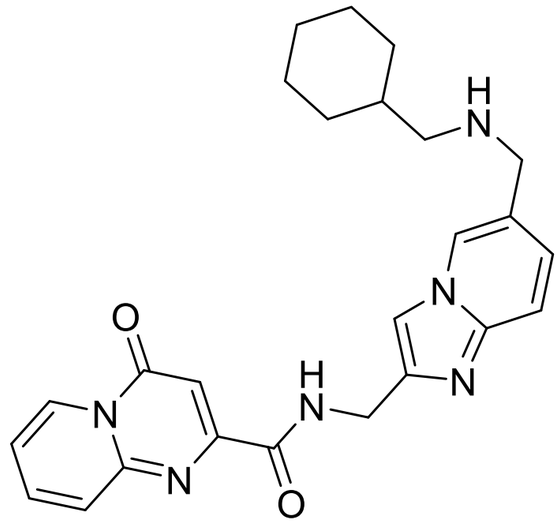
$GABA_A$ receptors assemble as pentamers of subunits, and non-subunit selective compounds have anxiogenic or convulsive side effects.

Basimasil is the only safe and selective $GABA_A$-α5 inhibitor that has entered clinical development. It is highly selective for the $GABA_A$-α5 receptor subtype and is >90x selective against -α1, -α2, and -α3 subunit-containing receptors, and accordingly demonstrated good tolerability in healthy volunteers at maximum target occupancy, confirmed with a [^{11}C]-radiolabeled PET tracer.

The team reports human PET and EEG data in this paper, providing evidence for functional target engagement in the human brain for this well-tolerated compound.

STM-2457

METTL3



METTL3 RNA modifying enzyme inhibitor
Efficacy in AML PDX model (50 mg/kg IP)
From 250k compound HTS
Nature, Apr. 26, 2021
Storm Therapeutics / University of Cambridge

The Storm Therapeutics/Cambridge METTL3 RNA methyltransferase inhibitor, STM-2457, is a first-in-class catalytic inhibitor of the METTL3 RNA modifying enzyme.

DNA-methyltransferase and other epigenetic targets such as HDACs have been explored for their potential roles in cancer and other diseases, and this compound brings RNA modifying enzymes into the druggable target space.

The compound is highly specific for METTL3, with no inhibition of other RNA, DNA, or protein methyltransferases, despite being competitive with the ubiquitous SAM-cofactor.

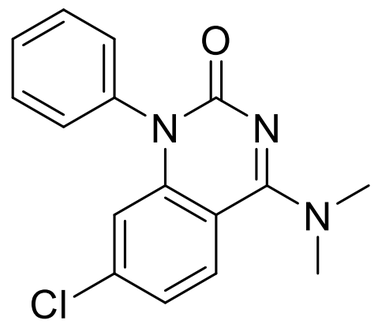
Human cellular target engagement was demonstrated with a thermal-shift experiment, and an X-ray co-crystal structure helps explain the selectivity observed.

While the compound demonstrates activity in patient-derived xenografts (PDX) and on leukaemic stem cell populations, no significant effects were observed in normal hematopoietic stem cells (HSCs).

More in vivo safety data and an understanding of the mechanism of differentiation between healthy and cancer cells will tell whether this mechanism can be clinically impactful.

“compound 28”

MAT2A



Potent MAT2A inhibitor in vivo tool

Efficacy in MTAP-mut. xenograft (50 mpk SC)

From fragment-based DD (frag. merging)

J. Med. Chem., Apr. 26, 2021

AstraZeneca, Cambridge, UK

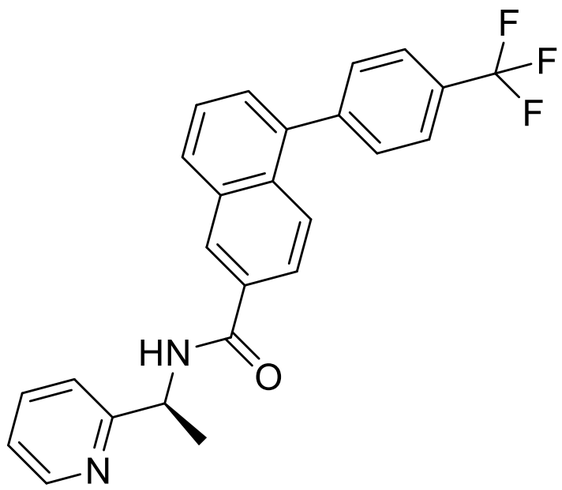
The AstraZeneca MAT2a allosteric inhibitor, compound 28, is a remarkably potent (25 nM in cells) in vivo tool compound generated from merging of two weak fragments (Kd = 250 µM and 6.2 µM).

The molecule binds in the same site as AG-270 (above) and has a relatively uncommon quinazolinone core, which makes several polar interactions in the binding site.

The identification of this highly efficient inhibitor is a great case study for fragment-based lead generation.

VT-104

TEAD



Oral pan-TEAD auto-palmitoylation inhibitor
Tumor regression at 3 mg/kg QD
From 160k compound cell-based HTS
Mol. Cancer. Ther., Apr. 13, 2021
Vivace Therapeutics, San Mateo, CA

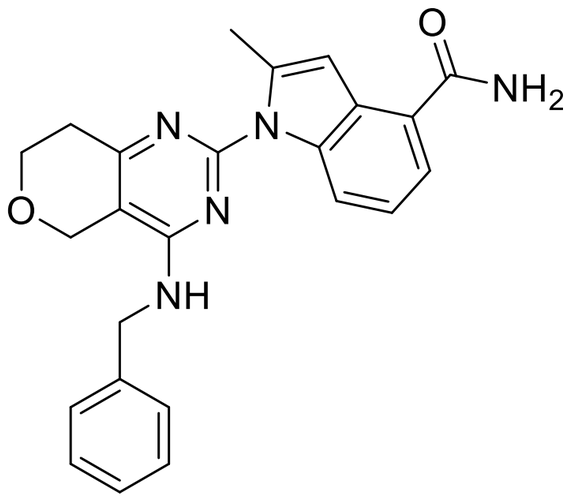
The Vivace Therapeutics pan-TEAD transcription factor inhibitor, VT-104, binds to a lipid pocket on TEAD, preventing its auto-palmitoylation, similar to a previously highlighted TEAD inhibitor.

In contrast to previously published TEAD inhibitors, VT104 has high oral bioavailability (78%) and a long half-life (24 h) in mice, and demonstrates in vivo tumor regression at a low daily dose of 3 mg/kg.

Interestingly in the paper, the authors refer to an NF2 mutant tumor being “lost” due to the difficulty in growing the tumors - these things happen in real life drug discovery.

CB-5083

p97/VCP



P97/VCP ATPase inhibitor (PDE6 off-target)
Ph. I in cancer (discont., dyschromatopsia)
From HTS of NIH compound library
J. Pharmacol. Exp. Ther., Apr. 30, 2021
Cleave Therapeutics, San Francisco, CA

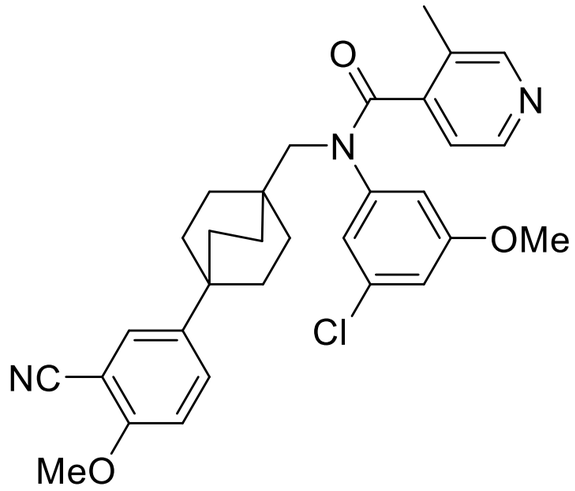
The Cleave Therapeutics p97 (VCP) inhibitor, CB-5083, was a Ph. I clinical candidate for cancer that was terminated due to vision side effects including causing patients to see unusual colors (dyschromatopsia).

In this paper, the authors suggest that the visual impairment was due to the compounds inhibition of the phosphodiesterase-6 (PDE6), which is involved in photoreceptor signal transduction.

Fortunately, the effect on vision appears to be reversible, and the authors suggest CB-5083 should be re-evaluated in the clinic. This work suggests that PDE6 should be a more routinely screened against off-target, and preclinical ERG recordings can be used to assess functional safety relevance for compounds with in vitro PDE6 signals.

“cmpd 20p”

FXR/TGR5



FXR nucl. receptor + TGR5 GPCR dual agonist

Dual in vivo effects at 100 mpk PO

From merger of literature agonist fragments

Sci. Rep., Apr. 28, 2021

Fuji Yakuhin Co., Ltd., Saitama, JP

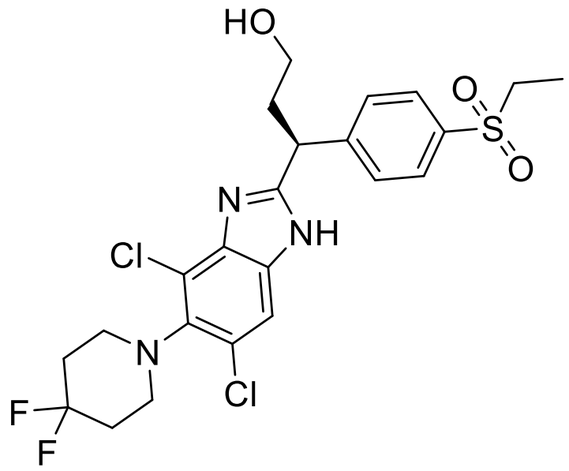
The Fuji Yakuhin FXR/TGR5 non-bile acid dual agonist, **compound 20p**, simultaneously activates the FXR nuclear receptor and the unrelated TGR5 GPCR receptor when dosed orally in vivo. FXR has been a important target for liver disease, and a number of agonists have been in development, including one of last year’s **Molecules of the Year**.

TGR5 is a receptor that stimulates GLP-1 peptide secretion when activated. Oral GLP-1R agonists have similarly been hotly pursued, and have also been featured a few times on *Drug Hunter.*

The combined effect on both agonists was thought to be beneficial for hepatic diseases. By merging elements of FXR and TGR5 agonists, the authors were able to identify this potent dual agonist while maintaining properties for oral dosing. While dual inhibition of related targets is more commonly observed, dual activation of unrelated targets by a single compound in vivo is conceptually remarkable.

SHR168442

RORγ



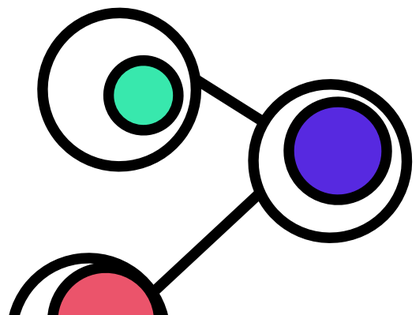
Topical (skin-restricted) ROR_{γ} antagonist
Efficacy in psoriasis model / minipig PK
From GSK-805 and met. stability reduction
Sci. Rep., Apr. 28, 2021
Eternity Bioscience, NJ / Shanghai Hengrui, CN

The Eternity Bioscience/Shanghai Hengrui RORγ antagonist, SHR168442, is a skin-restricted, topical compound intended to treat psoriasis.

As a master regulator of Th17 immune cells which are significantly involved in allergic diseases, both positive and negative oral modulators of RORγt had been hotly pursued, though many have ceased clinical development.

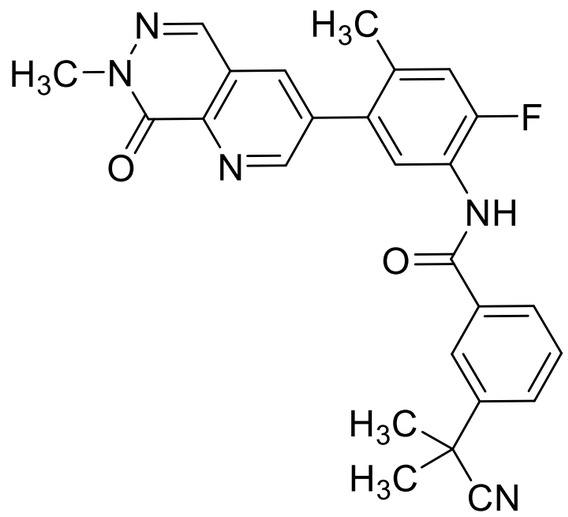
SHR168442 was "optimized" to be rapidly cleared compared to its starting point, GSK-805. A skin-restricted compound may address the safety concerns of systemic exposure.

Another topical RORγ antagonist, GSK2981278, had failed in Ph. I for psoriasis, but the target may not have been fully engaged. SHR168442 does not seem to have entered clinical development yet.



GNE-9815

RAF



Oral pan-RAF Type II kinase inhibitor tool
Combo. efficacy in KRAS+ models w/ MEKi
SBDD from literature ligands
ACS Med. Chem. Lett., Apr. 21, 2021
Genentech, South San Francisco, CA

The Genentech pan-RAF Type II kinase inhibitor, GNE-9815, is an oral chemical probe and among the most highly kinase-selective inhibitors of RAF reported. Interestingly, it minimally engages the hinge region of the kinase with a weak hydrogen bond acceptor and a polarized C-H···O=C hydrogen bond.

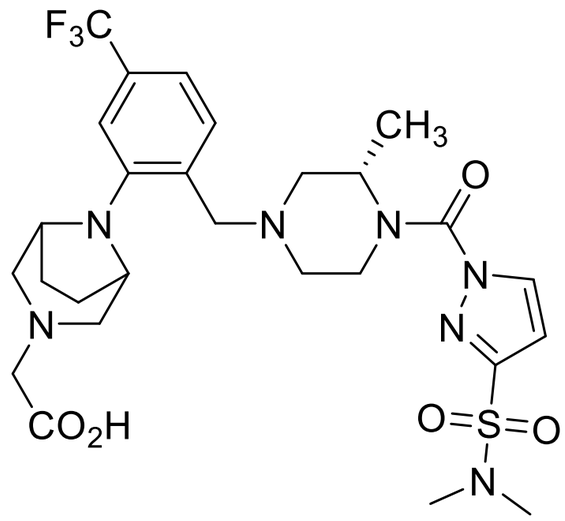
Type I BRAF inhibitors targeting $BRAF^{V600E}$ have been successfully used in melanoma, but not in KRAS mutant cancers. In fact, in KRAS mutant tumors, Type I BRAF inhibitor treatment paradoxically activates the MAPK signaling pathway by promoting the formation of RAF dimers.

Using Type II pan-RAF tools including GNE-9815, the authors were able to validate the combination of Type II pan-RAF inhibitors with MAPK pathway inhibitors in KRAS mutant tumors.

A trial of a Type II RAF inhibitor, belvarafenib (HM95573/GDC-5573) in combination with a MEK inhibitor, cobimetinib is listed (NCT04835805).

ABD957

ABHD17



ABHD17 serine hydrolase covalent inhibitor
Reduction of N-Ras signaling, AML cell growth
5k cmpd ser. hydrolase directed screen + opt.
Nature Chem. Biol., Apr. 29, 2021
Scripps (TSRI) / UCSF / Lundbeck

The TSRI/UCSF/Lundbeck pan-ABHD17 serine hydrolase covalent inhibitor, ABD957, impairs N-Ras depalmitoylation in AML cells, reducing N-Ras signaling and growth of NRAS-mutant AML cells.

This pyrazole urea is significantly more selective for ABHD17 than previously used beta-lactone and phosphonylfluoride tools, and helps clarify the biological role of these enzymes.

Chemically, the use of a pyrazole urea as a covalent inhibitor is interesting as it allowed the authors to tune the reactivity and selectivity of the compound by altering the pyrazole leaving group. This tuning is not available on warheads such as acrylamides, beta-lactones, or other reactive species.

drug hunter

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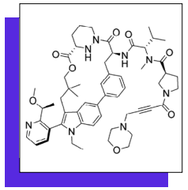
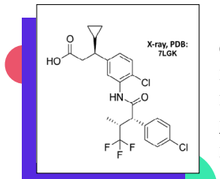
drughunter.com



RM-018 | KRAS^{G12C}

KRAS(G12C)ON-cyclophilin A tri-complex inh.
Overcomes KRAS resist. mut. in PDX model
Natural product related (sanglifehrin); undiscl.
Cancer Discov., Apr. 6, 2021
Revolution Medicines, Redwood City, CA



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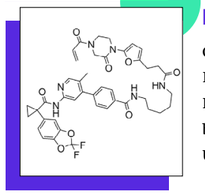

NJH-2-057 | DUBTAC

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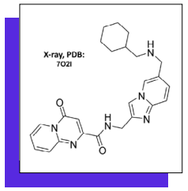
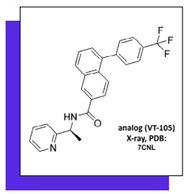


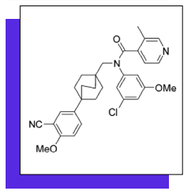
STM-2457 | METTL3

METTL3 RNA modifying enzyme inhibitor
Efficacy in AML PDX model (50 mg/kg IP)
From 250k compound HTS
Nature, Apr. 26, 2021
Storm Therapeutics / University of Cambridge



VT-104 | TEAD

Oral pan-TEAD auto-palmitoylation inhibitor
Tumor regression at 3 mg/kg QD
From 160k compound cell-based HTS
Mol. Cancer. Ther., Apr. 13, 2021
Vivace Therapeutics, San Mateo, CA



"cmpd 20p" | FXR/TGR5

FXR nucl. receptor + TGR5 GPCR dual agonist
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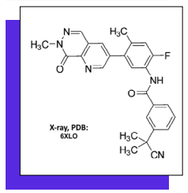

GNE-9815 | RAF

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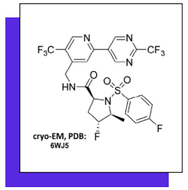
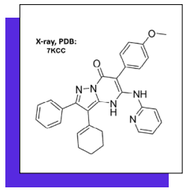


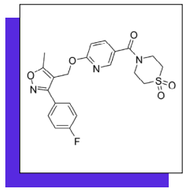
GDC-0334 | TRPA1

Oral TRPA1 ion-channel inhibitor
For asthma, target engagement in HV Ph. I
From ligand-based design, cryo-EM structure
J. Exp. Med., Apr. 5, 2021
Genentech Inc., South San Francisco, CA



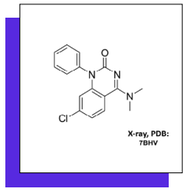
AG-270 | MAT2A

First-in-class oral MAT2A allosteric inhibitor
Synthetic lethal candidate in Ph. I for MTAP-
From >2000 fragment library and SBDD
J. Med. Chem., Apr. 8, 2021
Agios Pharmaceuticals, Cambridge, MA



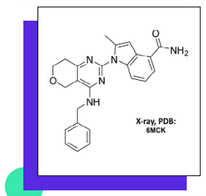
basmisanil | GABAA-α5

CNS-pen. GABAA-α5 neg. allo. mod. (NAM)
Ph. II for Down syndrome (240 mg BID)
From 56k cmpd competition binding HTS
Sci. Rep., Apr. 8, 2021
Roche Innovation Center, Basel, CH



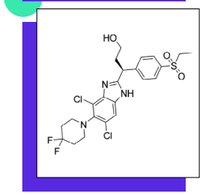
"compound 28" | MAT2A

Potent MAT2A inhibitor in vivo tool
Efficacy in MTAP-mut. xenograft (50 mpk SC)
From fragment-based DD (frag. merging)
J. Med. Chem., Apr. 26, 2021
AstraZeneca, Cambridge, UK



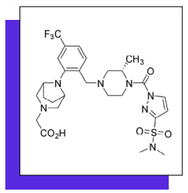
CB-5083 | p97/VCP

P97/VCP ATPase inhibitor (PDE6 off-target)
Ph. I in cancer (discont., dyschromatopsia)
From HTS of NIH compound library
J. Pharmacol. Exp. Ther., Apr. 30, 2021
Cleave Therapeutics, San Francisco, CA



SHR168442 | RORγ

Topical (skin-restricted) RORγ antagonist
Efficacy in psoriasis model / minipig PK
From GSK-805 and met. stability reduction
Sci. Rep., Apr. 28, 2021
Eternity Bioscience, NJ / Shanghai Hengrui, CN



ABD957 | ABHD17

ABHD17 serine hydrolase covalent inhibitor
Reduction of N-Ras signaling, AML cell growth
5k cmpd ser. hydrolase directed screen + opt.
Nature Chem. Biol., Apr. 29, 2021
Scripps (TSRI) / UCSF / Lundbeck

drug hunter

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