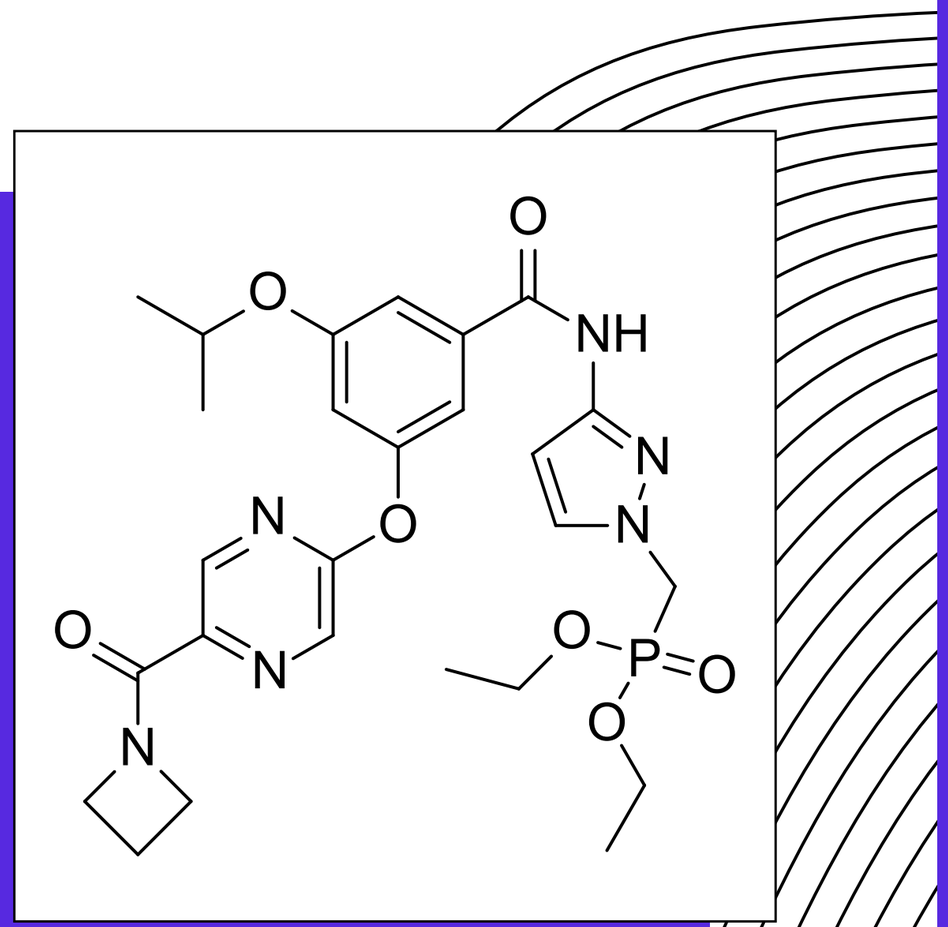
# Small Molecules of the Month

## February 2022

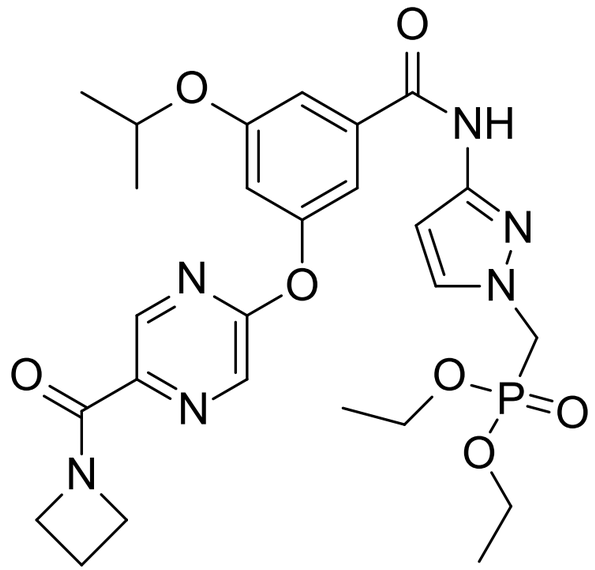



drug hunter

| | | |
|---|---|---|
| 01 | GK | Bristol Myers Squibb |
| 02 | ChemR23 | Kyowa Kirin |
| 03 | SGLT2 | GC Pharma |
| 04 | D1 | Eli Lilly |
| 05 | OX2 | Takeda |
| 06 | ATAD2 | AstraZeneca |
| 07 | FGFR | Astellas Pharma |
| 08 | DNA-PK | AstraZeneca |
| 09 | GCS | Takeda |
| 10 | MEK1/2 | Novartis (NIBR) |

# 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

**Context.** BMS-820132 (Bristol Myers Squibb) is an oral glucokinase (GK) partial activator intended for diabetes. GK activators for diabetes were hotly pursued in the late 2000's, with well over 100 industry patents on GK activators by 2009. The pursuit was triggered by the discovery of the first allosteric activators of glucokinase from an enzymatic screen of 120k compounds at Roche in 2003, leading to the first GK activator studied in diabetes patients. Initial clinical glucokinase full activators were challenged by hypoglycemia and loss of efficacy over time, leading to alternative strategies such as hepatoselective molecules, and the partial activation approach employed here.

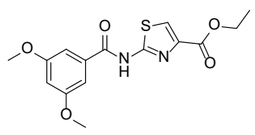
**Target**. Unlike protein kinases, glucokinase (GK, hexokinase IV) phosphorylates glucose to glucose-6-phosphate. GK is not saturated at physiological glucose levels (~5 mM, enzyme $K_m$ ~8 mM) allowing it to have a role in "sensing" glucose levels. GK's role in glucose control and relevance to diabetes is validated by human genetics: loss of function results in a form of diabetes called MODY-2, and gain of function results in persistent hypoglycemia. GK activation reduces blood sugar levels, but too much GK activation can lead to hypoglycemia (low blood sugar).

**Mechanism of Action**. To mitigate the risk of hypoglycemia, the BMS team, like some others, sought "partial" GK activators, rather than "full" activators. A partial GK activator would avoid lowering GK's glucose $K_m$ too much, making GK activity still dependent on physiological glucose concentrations.

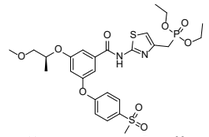
**Hit-Finding Strategy.** A GK activator hit (compound 10, $AC_{50}$ = 25 uM) was identified from a high-throughput screen of the BMS compound collection. An enzymatic activation assay with recombinant human GK was used, detecting the GK reaction product G6P in a secondary reaction with G6P dehydrogenase, measuring conversion of the G6P dehydrogenase co-factor, thio-NADH.

**Lead Optimization**. A full GK activator (compound 11, $AC_{50}$ = 38 nM) with in vivo activity in mice was discovered first, but had issues including ion channel inhibition (hERG, Na) and poor metabolic stability (path from 10 to 11 not reported). Optimization focused on maintaining potency while reducing lipophilicity. Key changes to this effect included replacement of a thiazole with a pyrazole, and replacement of the benzenesulfonyl group with a pyrazine amide. The final compound has comparable potency to the full activator (29 nM) but a lower % maximum activation.

Reviewer Kim Huard says, "I like that they chose to include in the publication a conformational analysis of compounds 29-33 (Figure 5). The potency SAR seems to correlate with the energy and conformational landscape of the biarylether and amide functionalities rather than specific interactions of the central aryl ring with the protein. This kind of analysis can be done on a small set of compounds to help define the bioactive conformation, which can be particularly valuable in the absence of structural information."



**"compound 10"**



**"compound 11"**

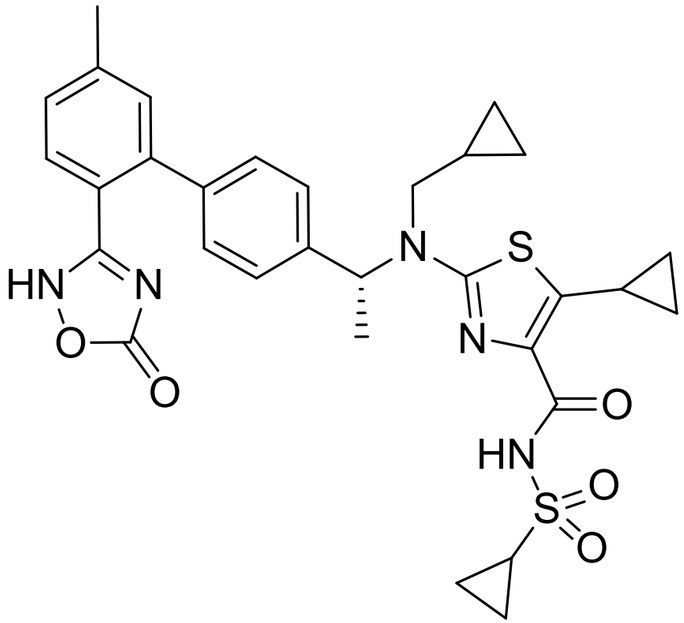
**Binding Mode.** Interestingly, the molecule binds to human GK with the phosphonate ester intact **(PDB: 7T78)**. It is not a prodrug as might be expected at first glance. It is a rare example of a phosphonate ester clinical candidate where the phosphonate is part of the drug.

**Preclinical Pharmacology**. Preclinical toxicology studies were challenged by the fact that the intended population for the drug has higher blood sugar levels than healthy subjects, making it unclear whether toxicities observed with a GK activator preclinically in non-diabetic animals would translate to diabetic patients. BMS-820132 in healthy, euglycemic Sprague-Dawley rats and beagle dogs in 1 mo. tox. studies showed extended hypoglycemia and associated toxicities and degeneration in histopathological studies, including in the sciatic nerve, myocardium, stomach, and stomach muscle at exposures comparable to expected clinical therapeutic exposures. However, no hypoglycemia or associated AEs were observed in diabetes model rates (ZDF rats).

**Clinical Development**. The molecule completed two Ph. I studies (NCT01290575, NCT01105429) in 2011 and 2012. The molecule was generally well tolerated at doses from 10 to 450 mg, with glucose reduction starting at 10 mg. At 30 mg, serum insulin increase was detected, and at 75 mg, mild hypoglycemia was observed, which resolved either spontaneously or with oral sugar. The glucose reduction without insulin increase at low doses and with insulin increase at high doses support its hypothesized dual effect on the liver and pancreas. Despite the potential therapeutic window, the molecule stalled, likely due to the challenges observed with other molecules after longer term dosing.

# Compound 14f

## ChemR23




oral ChemR23 inhibitor

preclinical, immunology

from HTS, scaffold hopping and opt.

Bioorg. Med. Chem.

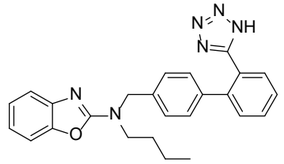
Kyowa Kirin

**Context.** Compound 14f (Kyowa Kirin) is an oral ChemR23 inhibitor with two acidic sites. Nominated by Bryan McKibben, this article describes a scaffold hopping exercise to address the short half-life of previously described chemical matter, and the successful development of in-vivo tool inhibitors to probe ChemR23 biology in animal models of inflammatory disease. An earlier ChemR23 inhibitor from Kyowa was previously highlighted in Jul. 2020. This article also describes the design of a fluorescein-labeled probe for the target.

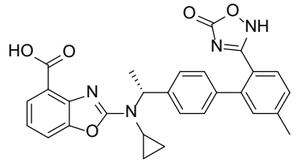
**Target.** ChemR23 (CMKLR1) is a chemokine-like, GPCR receptor implicated in dendritic, macrophage and NK-cell related inflammatory diseases including systemic lupus erythematosus (SLE), psoriasis and atherosclerosis. The ChemR23 inhibitor was developed with the intention of suppressing the migration of plasmacytoid dendritic cells (pDCs), which may be useful in certain autoimmune diseases.

**Mechanism of Action**. The ChemR23 molecules trigger receptor internalization after binding, resulting in a decrease in ChemR23 signaling.

**Hit-Finding Strategy**. A triazole hit (compound 1, $IC_{50}$ = 3.3 µM) was discovered in a high-throughput screen using a human pDC-like cell line (CAL-1).




**"compound 1"** ($IC_{50}$ = 3.3 µM)



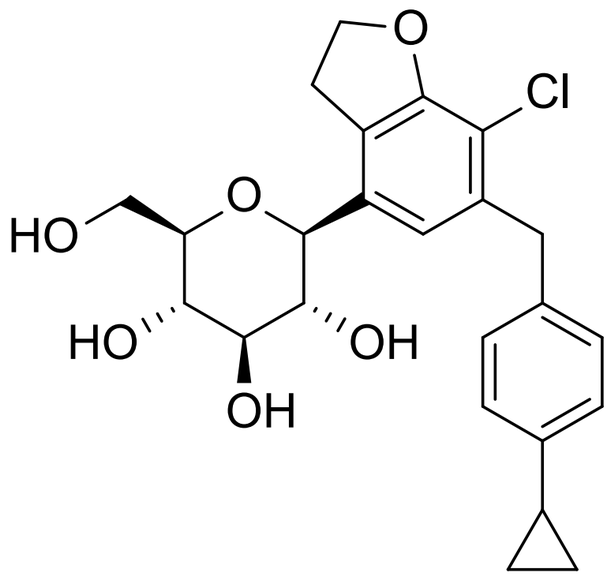

**"compound 2"** ($IC_{50}$ = 3.2 nM)

**Lead Optimization**. The optimization to a compound with two acidic substituents, compound 2 ($IC_{50}$ = 3.2 nM), was previously reported. The two acidic groups are key for potency, and surprisingly, the carboxylic acid was key for improving bioavailability in cynos, though compound 2 had a short half-life. Scaffold hoping from the benzoxazole acid to the thiazole N-acylsulfonamide led to improved PK. During optimization, the team targeted >80% receptor internalization, the level needed for complete chemotaxis inhibition. This is a rare example of optimization of a diacid to an orally bioavailable tool compound, and an interesting example of two carboxylic acid isosteres being employed in the same molecule.

**Preclinical Pharmacology**. Oral administration of 14f at 30 mg/kg in cynomolgus monkeys resulted in a sustained effect on ChemR23 internalization on pDCs until 8 h after dosing, a longer effect than the previous generation of 2-aminobenzoxazole-based inhibitors. ChemR23 expression was not detected 4 h after administration, with levels recovering to ~20% by 6-8 h. No ChemR23 modulators currently appear to be in clinical development.

# GCC5694A

**SGLT2**



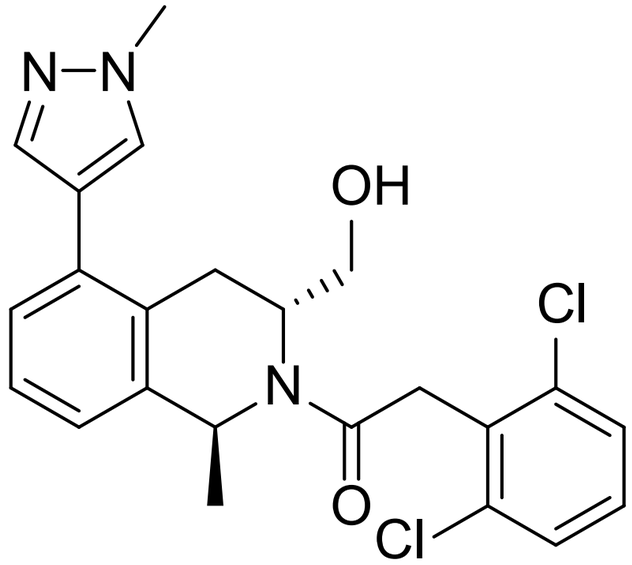

oral SGLT2 inhibitor
clinical candidate for diabetes
from literature SGLT2 inhibitor
Bioorganic Med. Chem. Lett.
GC Pharma (Green Cross)

**Context**. GCC5694A (GC Pharma (Green Cross)) is an oral SGLT2 inhibitor. SGLT2 inhibitors help glycemic control in diabetes by preventing reabsorption of glucose in the kidney. Dapagliflozin was the first SGLT2 inhibitor approved in the EU (2012), and canagliflozin was the first to be approved in the US (2013). We recently highlighted remogliflozin, an SGLT1-sparing drug launched in India in 2019 with a unique origin, and a Janssen dual SGLT1/2 inhibitor based on the natural product phlorizin. There are now eight gliflozins approved for clinical use worldwide. GCC5694A is reported to be in clinical trials in South Korea, though it is not in GC Pharma's pipeline.

Though it is not clear from the data presented how GCC5694A differentiates from previous SGLT2 inhibitors for diabetes, it is an interesting example of a molecule developed for the Korean market by a Korean company. GC Pharma is also more well-known for biologics, and this is an example of a small molecule research program from them. The Korean biotech landscape has evolved rapidly, which Samsung Biologics' recent purchase of Biogen's biosimilars JV stake brought into public conscience. It will be interesting to watch the small molecule capabilities of Korean companies develop over time, a space currently led by Hanmi, Chong Kun Dang (CKD Pharma), Daewoong, and Ildong.

# LY3154885

D1




oral D1 modulator

Ph. I candidate for neurological disorders

opt. against DDI w/ hepatocyte Cl assay

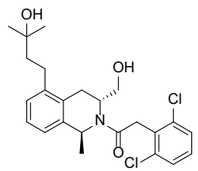
J. Med. Chem.

Eli Lilly and Company

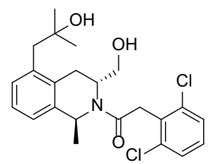
**Context**. LY3154885 (Eli Lilly and Company) is an oral D1 modulator. Lilly recently completed several clinical trials with LY3154207 (mevidalen), the first D1 positive allosteric modulator (D1PAM) with published clinical data, in Parkinson's disease (NCT02562768), sleep (NCT02603861), and lewy body dementia (LBD) (NCT03305809). In nonclinical studies, mevidalen was found to be mainly cleared by CYP3A4, creating a risk for it being a victim drug to DDIs when co-dosed with CYP3A4 inhibitors or inducers. LY3154885 was a backup compound to address this DDI risk, with metabolism shifted from CYP-mediated to predominantly UGT-mediated by changing the tertiary alcohol-bearing group to a pyrazole. The molecule was advanced to Ph. I, but terminated early due to a business decision.

**Mechanism of Action**. The D1 dopamine receptor is the most abundant dopamine receptor in the CNS. While D1 antagonism is a well-known property of antipsychotics, D1 agonism and selective D1 modulation have had less clinical application. An orthosteric, catecholamine-derived D1-selective partial agonist has been approved as an IV, postoperative antihypertensive agent (fenoldopam, 1997), but these types of catecholamine-derived compounds have seen limited development success due to poor PK, bell-shaped pharmacology, and tachyphylaxis (rapidly developed drug tolerance).

**Hit-Finding Strategy**. Lilly scientists pioneered D1 positive allosteric modulators (WO2014193781A1) from a non-catecholamine scaffold. When their program was initiated, there was no precedent in the primary or patent literature for small molecule, allosteric D1 activation. A single hit was identified from an HTS of 421000 molecules from the Lilly library, and developed into mevidalen, a highly potent, subtype selective, D1 positive allosteric modulator with no bell-shaped pharmacology or tachyphylaxis.




**mevidalen:**



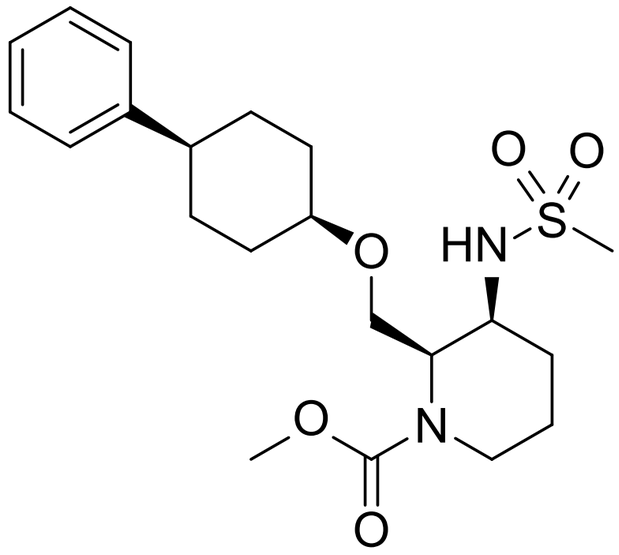

**DPTQ:**

**Lead Optimization**. To reduce DDI risk related to CYP3A4, the team sought to increase the fraction of metabolism by other liver enzymes. Designs were assisted by a machine learning model based on internal data in a CYP3A4 substrate loss assay, but no clear SAR emerged and compounds metabolized by additional CYPs just tended to be cleared faster. Using a hepatocyte clearance assay +/- the CYP inhibitor ABT, it was discovered that DPTQ was mainly cleared by glucuronidation. Clinically, for drugs cleared by glucuronidation, DDI risks are rare, and UGT-based DDIs are less significant than CYP-mediated DDIs. Unfortunately, DPTQ induced CYP3A4 mRNA in hepatocytes and was deprioritized. Further exploration of tertiary alcohol replacements led to LY3154885, which also appears to be more brain penetrant ($Kp_{u,u}$ = 0.85 vs. 0.25 for mevidalen), possibly due to the reduced hydrogen bond donor count.

**Pharmaceutics**. Interestingly, though LY3154207 is very weakly basic (pyrazole pKa <2), a stable HBr monohydrate salt was identified, which was taken into development.

# Danavorexton

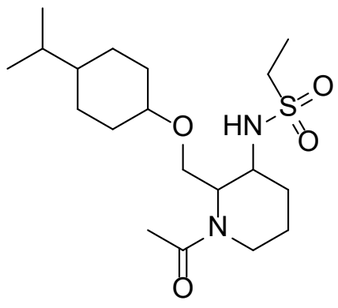
**OX2**




injectable OX2 agonist
Ph. I candidate for narcolepsy
from HTS and optimization
ACS Med. Chem. Lett.
Takeda

**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 patients with narcolepsy (difficulty staying awake). TAK-925 was the first orexin agonist tested in people with narcolepsy type 1. Interestingly, TAK-925 is an injectable molecule, since sleeping or anesthesized patients can't swallow pills (NCT05025397). The IV molecule demonstrated proof of concept in promoting wakefulness in narcolepsy patients, and an oral version (TAK-994) was planned (with a targeted launch in 2024) but discontinued due to an undisclosed safety signal.

**Hit-Finding Strategy**. The OX2R-selective starting point (compound 2, $EC_{50}$ = 570 nM as a mixture) was identified from a high throughput screen using a calcium flux assay for OX2R agonism second in a fluorometric imaging plate reader (FLIPR) assay system.

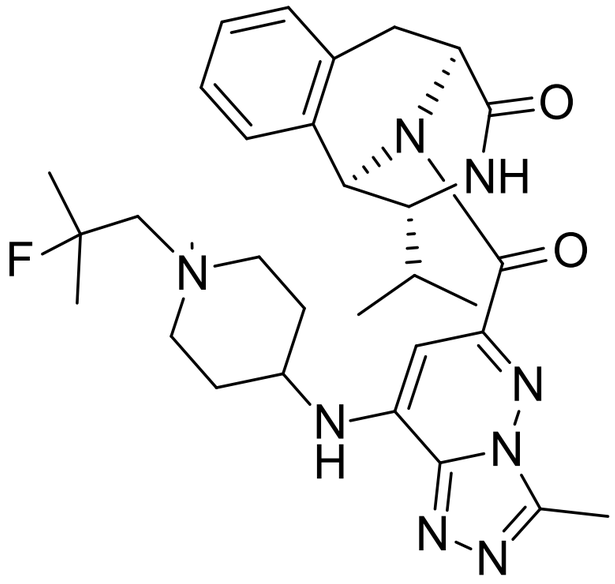



**"Compound 2"**

**Lead Optimization**. Defining the stereochemistry of the piperidine ring was a key step in lead optimization. Interestingly, it was found that the piperidine C2-methylene group and the cyclohexyl-ether stereocenter are both stably axial, due to A(1,2)-strain in the N-carbamoylpiperidine and the large phenyl substituent on the cyclohexyl group.

# AZ13824374

## ATAD2




in vitro ATAD2 inhibitor

preclinical, oncology

from 1.8 million compound HTS and opt.

J. Med. Chem.

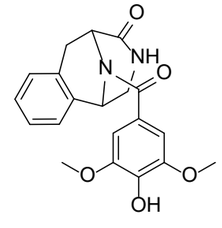
AstraZeneca

**Context.** AZ13824374 (AstraZeneca) is an in vitro ATAD2 inhibitor. Reviewer and nominator Julien Lefranc says, "several ATAD2 probes have been published in the past (including GSK 8814, GSCK388, and BAY-850), but so far no compounds have reached clinical trials." ATAD2 is a bromodomain-containing, chromatin-binding target that is overexpressed in many cancers due to c-Myc coamplification. While ATAD2 inhibition is supported by siRNA target modulation, there is limited pharmacological evidence to support it as a bona fide cancer target.

Prior literature molecules showed limited cellular activity, or activity that is confounded by potential off-target activities. This tool compound is the first to demonstrate significant cellular ATAD2 activity while also being highly selective against BRD4 and other bromodomains, which could confound interpretation of anti-proliferative activity data. Unfortunately, both ATAD2-amplified and ATAD2 non-amplified cells were found to be similarly affected by inhibitor, challenging the initial thesis that ATAD2 expression may be a useful biomarker.

**Target**. Computational analysis indicates ATAD2 is distinct from other bromodomain-containing proteins, and it has a relatively poor ligandability score due to its more open binding pocket. Instead of a lipophilic Trp-Pro-Phe motif present in other bromodomain-containing proteins, it has a significantly more polar Arg-Val-Phe motif.

**Hit-Finding Strategy**. When the AZ ATAD2 program was initiated, no potent ATAD2 inhibitors had been reported. The initial hit (compound 6) was obtained through a TR-FRET assay run as an HTS at 10 μM against the 1.8M compound AZ screening collection. The screen was noisy, with a large number of FRET artifacts. Elimination of interference compounds led to an overall hit rate of <0.3%. The hits were clustered and 60 representatives were tested by $^{15}$N 2D HSQC NMR using 40μM $^{15}$N-labeled ATAD2. Virtually all hits were determined to be false positives, with the only exception being compound 6. Many of the false positives caused the bound protein spectrum to collapse, suggestive of protein unfolding and aggregation. This was attributed to the instability of the truncated ATAD2 construct used for screening by AZ and other groups. Protein re-engineering led to a more stable construct that reduced the false positive rate, allowing identification of more true actives.

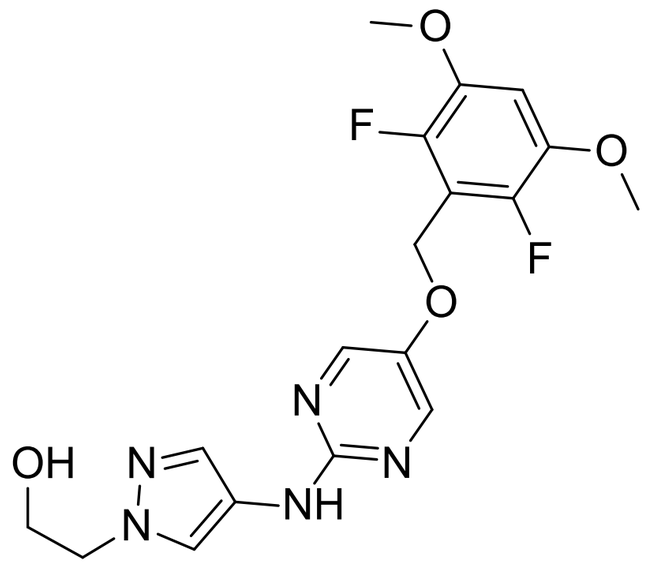



**"Compound 6" (PDB: 7Q6U)** **AZ13824374 (PDB: 7Q6T)**

**Lead Optimization**. Phenol replacement was accomplished with a bicyclic heterocycle. The aminopiperidine side chain brought in two additional hydrogen bonds (including a water-mediated hydrogen bond to ASP1071). Overall, lead optimization from compound 5 to AZ13824374 took place in 1 year.

# ASP5878

## FGFR




oral FGFR inhibitor

Ph. I candidate for solid tumors

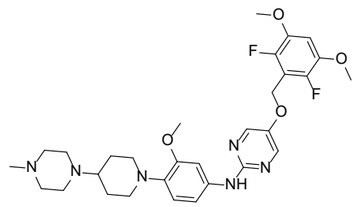
opt. from previously disclosed lead

Bioorg. Med. Chem.

Astellas Pharma Inc.

**Context**. ASP5878 (Astellas Pharma Inc.) is an oral pan-FGFR inhibitor. The four FGFRs have emerged as attractive targets for cancer in recent years, and we've covered several recently. FGFR3 has had less dedicated effort disclosed on it specifically relative to FGFRs 1, 2, and 4, but genetic alterations of FGFR3 have been noted in bladder cancer. In late stage metastatic bladder cancer, metastasis to the brain is an issue that is not addressed well with antibodies or ADCs. This program targeted a brain-penetrant FGFR3 inhibitor (regardless of FGFR selectivity) while addressing hERG cardiotoxicity concerns of a previous pan-FGFR lead. ASP5878 entered a phase I clinical trial for the treatment of urothelial carcinoma, hepatocellular carcinoma and squamous cell lung carcinoma patients in 2013 (NCT02038673) but there have been no updates since 2018.

**Starting Point**. The starting point, pan-FGFR compound 1 (FGFR3 $IC_{50}$ = 1.2 nM) was previously reported, identified using structure-based design (SBDD). This molecule, a basic amine with a hERG pharmacophore, had what the authors considered potent ($IC_{50}$ = 10 μM) hERG channel inhibition. The starting point also had high intrinsic clearance in human liver microsomes (171 mL/min/kg).



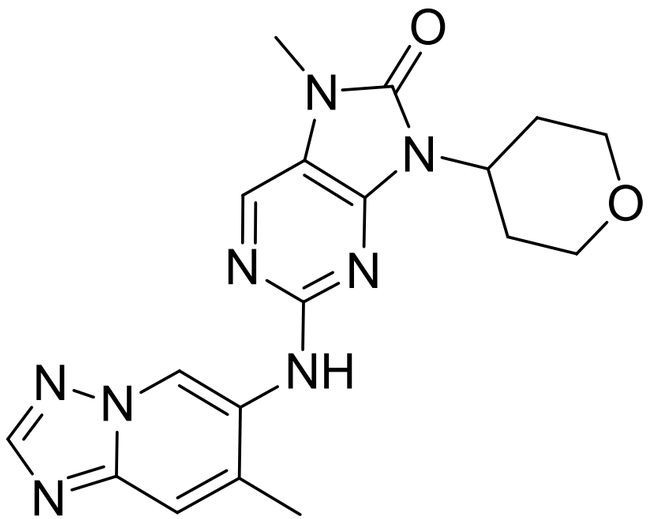

**"compound 1"**

**Lead Optimization**. To improve in vitro metabolic stability, the carbon-based ethylene linker was replaced with an ether linker, which resulted in a significant improvement in in vitro clearance (171 to 40 mL/min/kg). The replacement of the hinge-binding nitrogen's phenyl ring with alternative, pyrazole-based amines or alcohols resulted in compounds with reduced hERG activity – other heterocycles with the same basic amine positioning were less effective at mitigating hERG.

**Preclinical Pharmacology**. ASP5878 did not affect the hERG current up to 10 μM in a patch-clamp assay, and a single oral dose of ASP5878 at 1, 10, and 100 mg/kg did not induce serious side effects on the CNS or the cardiovascular and respiratory systems in dogs. ASP5878 exhibited sub-hepatic clearance, high oral bioavailability in rats and dogs (94%), and modest brain penetration in rats ($K_{p,brain}$ = 0.69 at 24 h). Interestingly, the $K_{p,brain}$ was significantly higher at 24 h than between 1-4 h (0.15-0.20).

# AZD7648

**DNA-PK**



oral DNA-PK inhibitor

Ph. I/II candidate for advanced tumors

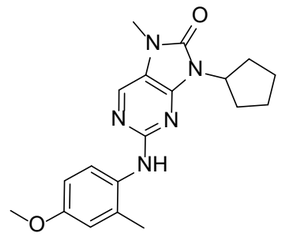
from screening for selectivity vs. PI3Ka

Mol. Cancer Ther.

AstraZeneca

**Context.** AZD7648 (AstraZeneca) is an oral DNA-PK inhibitor. DNA-PK, ATR, and ATM are all kinases involved in DNA damage repair and have been of significant recent interest due to the success of PARP inhibitors and the concept of synthetic lethality. We have highlighted a few DNA-PK inhibitors and ATR inhibitors recently. The discovery of AZD7648 has previously been reported. This recent article highlights the in vivo pharmacology of the molecule in several ovarian cancer patient-derived xenograft (PDX) models, extending prior work, showing in vivo potentiation of activity of olaparib in BRCA- PDXs, but not BRCA+ PDXs, suggesting that an olaparib/DNA-PK inhibitor combination could be effective in ovarian cancer. Two trials involving AZD7648 have been posted and appear to be recruiting.

**Hit-Finding Strategy.** An HTS of ~500k compounds from AZ's internal collection focusing on selectivity vs. PI3Kα led to the identification of PIK-family selective inhibitor "compound 1" (DNA-PK $pIC_{50}$ = 8.3). The nearest off-targets were CSF1R ($pIC_{50}$ = 7.6) and TTK ($pIC_{50}$ = 7.7). Interestingly, the compound appears to have a "flipped" binding mode in CSF1R (PDB **6T2W**) vs. the PIK-family kinases (**PDB 6T3B**), which includes DNA-PK. Crystal structures of PI3Kγ were used as a model for DNA-PK due to the challenge of crystallizing the large protein.

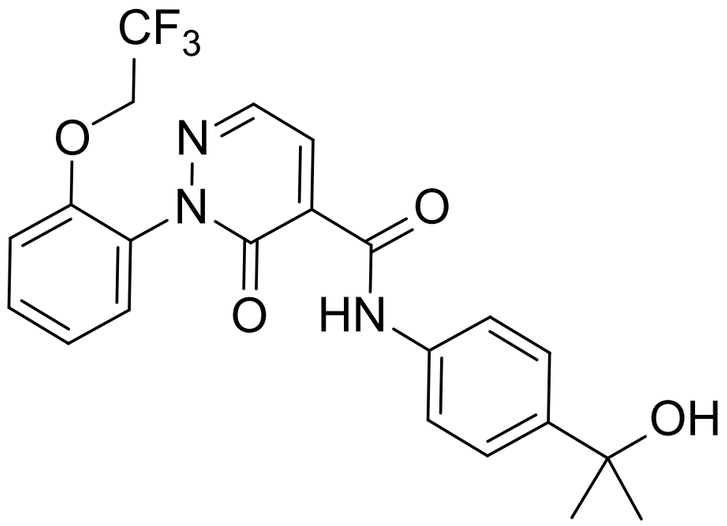


**"compound 1"**

**Lead Optimization.** The methyl group ortho- to the aniline was found to be a "magic methyl," leading to 10-100x increases in biochemical potency relative to compounds without it. The effect is attributed to a conformational effect, inducing a twisted conformation, as well as filling a lipophilic pocket. Exploration of heterocyclic replacements of the aniline group led to an imidazopyridine ($pK_a$ = 7.1) with a hERG signal (8.1 μM), which disappeared when moving to the less basic triazolopyridine ($pK_a$ = 3.4). The optimized compound, AZD7648, is potent (DNA-PK $IC_{50}$ = 0.6 nM, $pIC_{50}$ 9.2) and relatively polar (logD = 1.3).

# T-690

## GCS




oral GCS inhibitor

preclinical, neurodegeneration

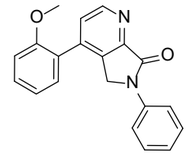
scaffold hop from prev. reported GCS inhibitor

J. Med. Chem.

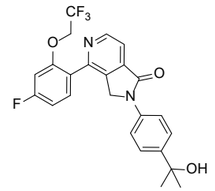
Takeda

**Context**. T-690 (Takeda) is an oral GCS inhibitor that is brain-penetrant, non-basic, and non-competitive with UDP-glucose. We recently highlighted a glucosylceramide synthase (GCS, aka CGT) inhibitor in Ph. III (Sanofi's venglustat). GCS inhibition may reduce glycosphingolipid levels downstream of its product, glucosylceramide (GlcCer). GCS inhibitors have been clinically explored in diseases where accumulation of glycosphingolipids may contribute to pathology, including GBA-mutant Parkinson's disease and various rare genetic diseases. The Takeda molecule has a distinct structure from previously reported GCS inhibitors (Eliglustat, EXEL-0346, venglustat and BZ1). Existing GCS inhibitors such as miglustat and eliglustat do not treat the neuropathic symptoms of diseases like Gaucher's Disease (GD), but the Takeda team suggests that a brain-penetrant GCS inhibitor (like venglustat or Merck's BZ1) might.

**Hit-Finding Strategy**. The starting point, compound 1 (17 µM), was discovered from a high-throughput screen using a cellular assay to measure GlcCer formation in GD patient fibroblasts. Target confirmation was done based on GCS enzyme inhibition. Previous GCS inhibitors like miglustat and eliglustat were discovered from the natural product 1-deoxynojirimycin or mimicking substrates of GCS.




**"compound 1" (17 µM)**




**T-036 (31 nM)**

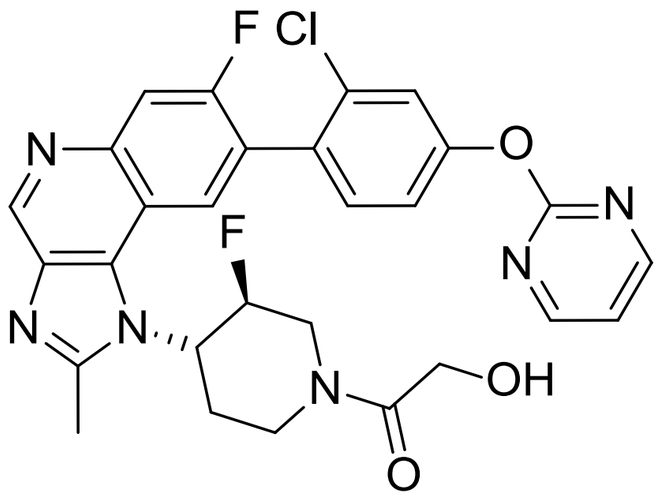
To reduce safety-associated risks (off-target effects) they performed pharmacophore-based scaffold hopping of T-036 that led to the T-690 discovery.

**Lead Optimization**. The optimization of hit 1 to T-036 was previously described. The tertiary alcohol of T-036 was important for mitigating hERG activity. Unfortunately T-036 led to body weight loss in mice after 3 days of treatment, likely due to off-target effects, though a panel of 47 targets showed T-036 was generally clean. T-036 did have activity against the serotonin transporter, SERT (310 nM), inhibition of which has been reported to reduce appetite and body weight in rats. SERT was therefore used as a sentinel off-target for overall selectivity. Scaffold hopping was conducted using an interesting internal hydrogen bonding strategy to maintain key binding interactions while significantly changing the properties of the core.

**Preclinical Pharmacology**. T-690 had no SERT inhibitory activity ($IC_{50}$ > 10 µM) and no body weight loss in a rodent tox. study, though the relationship is not clearly causal. Interestingly, T-690 showed a species different between mouse and human, with 12.7x weaker activity on mouse GCS enzyme. Brain penetration of T-690 was improved ($Kp_{uu,brain}$ =0.26) compared with T-036 ($Kp_{uu,brain}$ = 0.11). T-690 is a moderate MDR-1 efflux substrate (ER = 8.8). The non-cationic structure of these Takeda molecules is unique among GCS inhibitors, and may be beneficial to avoid potential CV or other off-target risks. T-690 activity on GCS is also not affected by concentration of substrates C8-ceramide or UDP-glucose, indicating that it is a noncompetitive inhibitor with a new binding site, in contrast to eliglustat which has significantly weaker activity at elevated UDP-glucose concentrations.

# MAP855

## MEK1/2




oral MEK1/2 inhibitor

preclinical, oncology

from HTS and SBDD

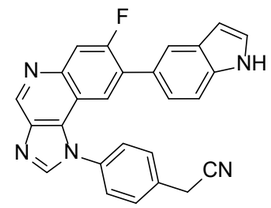
J. Med. Chem.

Novartis Institutes for BioMedical Research

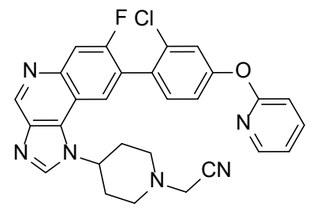
**Context**. MAP855 (Novartis Institutes for BioMedical Research) is an oral MEK1/2 active-site inhibitor. Several MEK inhibitors (e.g. cobimetinib, trametinib) have been approved for cancer, generally derived from the same allosteric pharmacophore. MEK inhibitors continue to be explored in combination with new drug mechanisms, with recent interest particularly around combinations with KRAS and RAF inhibitors. Resistance to clinical MEK combinations can involve activating mutations on MEK1/2, which the Novartis team hypothesizes results in shifting of equilibrium toward an active enzyme state. Clinical mutations tend to cluster around an autoinhibitory helix.

**Mechanism of Action**. An ATP-competitive, conformation-agnostic MEK inhibitor might therefore help address resistance. This is an interesting approach, as kinase drug discovery programs typically prefer to start with allosteric starting points when available due to selectivity benefits. Literature ATP-competitive MEK inhibitors have generally been of low quality/selectivity.

**Hit-Finding Strategy**. The starting point (compound 4, MEK1 $IC_{50}$ = 2.6 µM) was identified from high-throughput screening with a MEK1-ERK2 cascade assay, filtering with activity against BRAF and ERK2, and confirming in a cellular phospho-ERK assay. The starting point had promising selectivity against a small panel of 37 kinases (7 of 37 with activity at 5 µM), but had unmeasurable solubility and a high logP of 6.9.




**"compound 4," MEK1 $IC_{50}$ = 2.6 µM:**



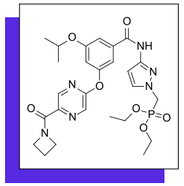

**"compound 6," MEK1 $IC_{50}$ = 70 nM**

**Lead Optimization**. Replacing the indole and phenyl groups to the ortho-substituted aryl ether and piperidine present in compound 6 led to greatly improved solubility and potency. A co-crystal structure of an analog (PDB 7PQV) confirmed the active-site binding mode (the center nitrogen on the tricyclic ring is the hinge-binding element). It took only another three heavy atom changes from compound 6 to remove CYP3A4 liabilities, increase cellular potency by >100x, and reduce logP by 5 units. This illustrates well how small changes can make significant impacts in medicinal chemistry.

Notably, fluorination of the piperidine ring led to a 10x increase in potency while maintaining favorable properties. The resulting tool compound has comparable in vivo activity to clinical MEK1/2 inhibitors.

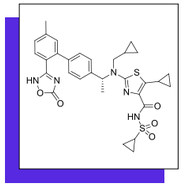
# Small Molecules of the Month

February 2022
drughunter.com



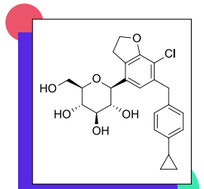
## BMS-820132 | GK

oral GK partial activator
Ph. I candidate for diabetes
from HTS of BMS collection and SBDD
J. Med. Chem.
Bristol Myers Squibb



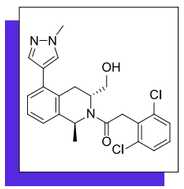
## Compound 14f | ChemR23

oral ChemR23 inhibitor
preclinical, immunology
from HTS, scaffold hopping and opt.
Bioorg. Med. Chem.
Kyowa Kirin



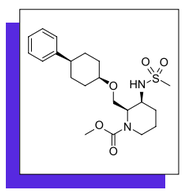
## GCC5694A | SGLT2

oral SGLT2 inhibitor
clinical candidate for diabetes
from literature SGLT2 inhibitor
Bioorganic Med. Chem. Lett.
GC Pharma (Green Cross)



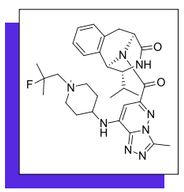
## LY3154885 | D1

oral D1 modulator
Ph. I candidate for neurological disorders
opt. against DDI w/ hepatocyte Cl assay
J. Med. Chem.
Eli Lilly and Company



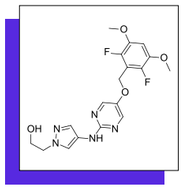
## Danavorexton | OX2

injectable OX2 agonist
Ph. I candidate for narcolepsy
from HTS and optimization
ACS Med. Chem. Lett.
Takeda



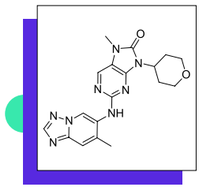
## AZ13824374 | ATAD2

in vitro ATAD2 inhibitor
preclinical, oncology
from 1.8 million compound HTS and opt.
J. Med. Chem.
AstraZeneca



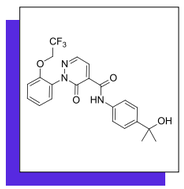
## ASP5878 | FGFR

oral FGFR inhibitor
Ph. I candidate for solid tumors
opt. from previously disclosed lead
Bioorg. Med. Chem.
Astellas Pharma Inc.



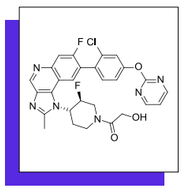
## AZD7648 | DNA-PK

oral DNA-PK inhibitor
Ph. I/II candidate for advanced tumors
from screening for selectivity vs. PI3Ka
Mol. Cancer Ther.
AstraZeneca



## T-690 | GCS

oral GCS inhibitor
preclinical, neurodegeneration
scaffold hop from prev. reported GCS inhibitor
J. Med. Chem.
Takeda



## MAP855 | MEK1/2

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Novartis Institutes for BioMedical Research

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