Trifluoromethylpyridines in Drug Discovery

Key Points

- May offer tighter binding to the target protein
- May improve drug solubility, metabolism, stability, and other drug-like properties

Overview

Trifluoromethylpyridine fragment exists in at least three marketed drugs: Agios' isocitrate dehydrogenase 2 (IDH2) allosteric inhibitor enasidenib (Idhifa, **1**), Upjohn's HIV protease inhibitor tipranavir (**4**), and Janssen's androgen receptor antagonist apalutamide (**5**). The trifluoromethyl group may form tetrel bonding with heteroatoms on target proteins and the nitrogen atom on pyridine can serve as a hydrogen bond acceptor, establishing further binding points to target proteins. As a consequence, trifluoromethylpyridine is a privileged structure in drug discovery. It may offer tighter binding to the target protein, improving a drug's solubility, metabolism, stability, and other drug-like properties.

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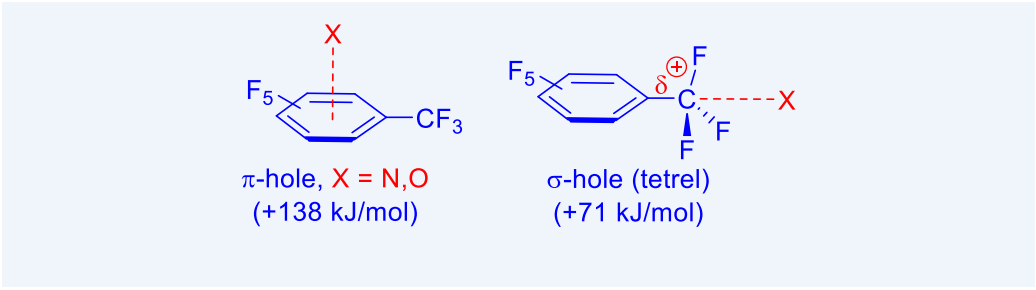
Trifluoromethyl substituent can have non-covalent interactions (NCIs) with heteroatoms such as oxygen and nitrogen. Take perfluorotoluene as an example, in addition to the well-known π-hole interactions (+138 kJ/mol) afforded by the phenyl motif, the trifluoromethyl carbon atom can partake α-hole interactions (+71 kJ/mol) with the neighboring heteroatom, albeit not as strong as the π-hole interactions. The α-hole interactions, also known as *tetrel bonding*, is a testimony to the fact that the three fluorine atoms attached directly to the carbon atom are so electron-withdrawing that they make it partially positive.[1]



Agios' isocitrate dehydrogenase 2 (IDH2) allosteric inhibitor enasidenib (Idhifa, **1**) complexed to the mutant IDH2 enzyme can dramatically reduce (IC_{50} = 10–20 nM) the production of the oncometabolite, (*R*)-2-hydroxyglutarate (2HG), in a cellular assay. Interestingly, it has been demonstrated that compound **2**, a "naked" analog of enasidenib without the $-CF_3$ groups presents a higher IC_{50} value (30 nm), suggesting that the $-CF_3$ group modulates the binding ability of the inhibitor, increasing the affinity to the IDH active site. Frontera and coworkers carried out docking experiments and discovered that the O⋯ CF_3 distance is shorter than the sum of van der Waals radii and the directionality is adequate to establish a favorable interaction with the σ-hole (165.1°) of the CF_3. They speculated that one of two CF_3 groups present in the inhibitor interacts with an aspartate amino acid (ASP_{312}) of the active site via the tetrel bonding.[1,2]

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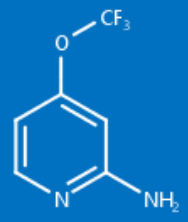

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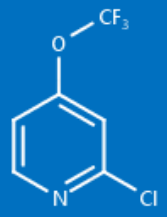

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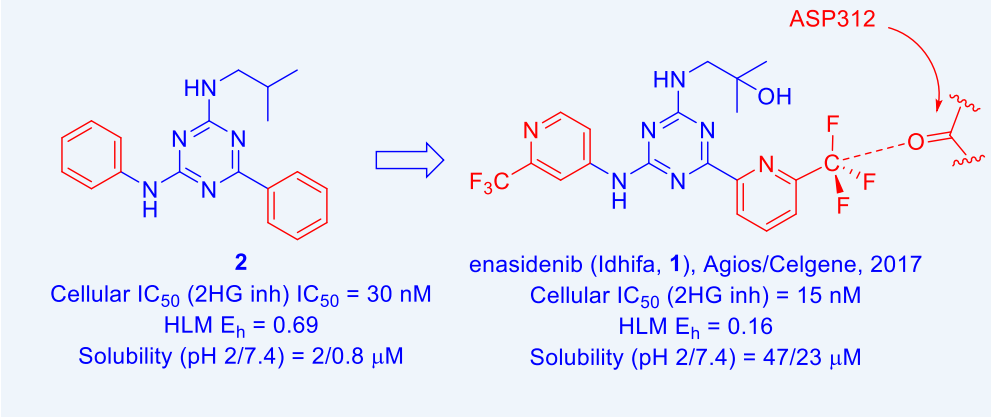
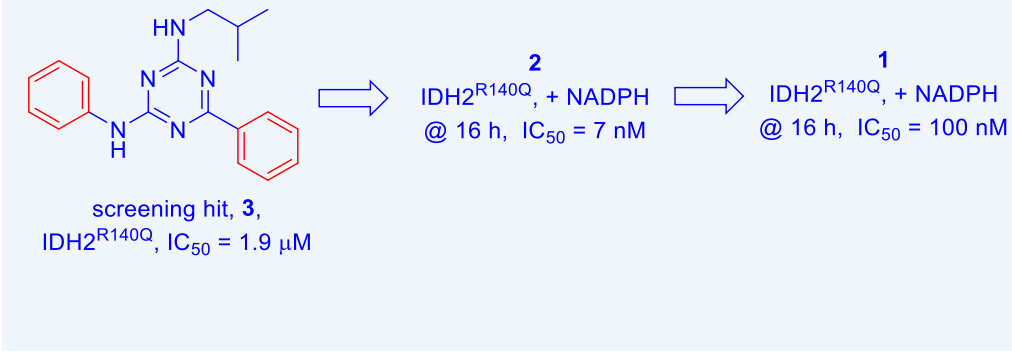


Agios identified triazine **3** as a high-throughput screening (HTS) hit. Their initial hit-to-lead chemistry led to compound **2**, the first sub-100 nM inhibitor of $IDH2^{R140Q}$. However, despite its potency in enzymatic and cellular assays, it was highly lipophilic, resulting in solubility-limited absorption *in vivo*. To make things worse, its *in vitro* liver microsomal instability translated to high clearance *in vivo*. X-Ray co-crystal structure of **2** and $IDH2^{R140Q}$ provided invaluable insight for further optimization. Installation of two trifluoromethylpyridine substituents and a 2-methyl-2-propanol led to enasidenib (**1**) with excellent potency for 2-HG inhibition, improved solubility, low clearance (0.83 L/h/kg), and good oral bioavailability (41%) *in vivo* in rats.[3]



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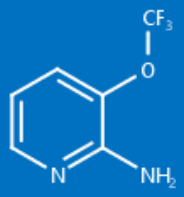

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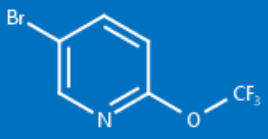

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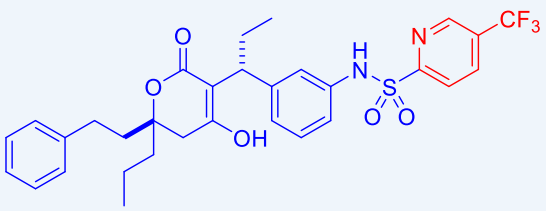
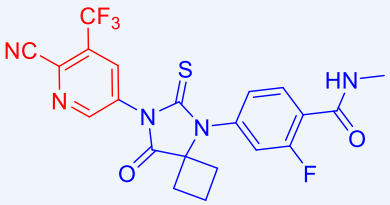
Trifluoromethylpyridine-containing Drugs

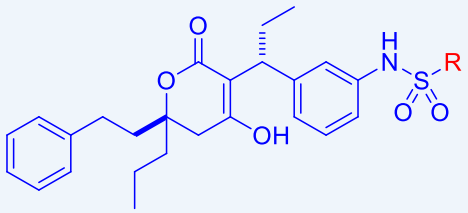
In addition to enasidenib (**1**), two additional trifluoromethylpyridine-containing drugs are currently on the market. One is Upjohn's HIV protease inhibitor tipranavir (Aptivus, **4**).[4] The other is Janssen's androgen receptor antagonist apalutamide (Erleada, **5**) for treating castration-resistant prostate cancer (CRPC).[5]

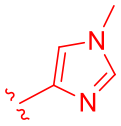
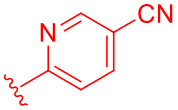
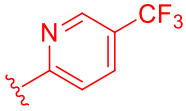


Tipranavir (Aptivus, **4**)
Upjohn, 2005
HIV protease inhibitor



apalutamide (Erleada, **5**)
Janssen, 2018
Anti-androgen



R	K_i (nM)	IC_{50} (nM)	IC_{90} (nM)
 **6**	60	130	560
 **7**	7	40	260
 **4**	8	30	100

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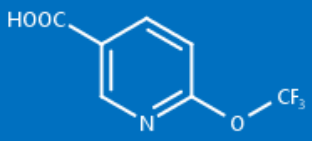

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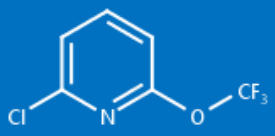

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During their structure–activity relationship (SAR) investigations, Upjohn explored three bioisosteres for the arylsulfonamide moiety R. One was 1-methylimidazol-4-yl **6**, another was 5-cyano-2-pyridyl **7**, and the third was 5-trifluoromethyl-2-pyridyl **4**. Although compounds **7** and **4** had similar values for their K_i, IC_{50}, and IC_{90}, early safety studies suggested advantages of compound **4** over compound **7**. Therefore, compound **4** was selected as a development candidate, which eventually became tipranavir (Aptivus).[4]

The structure of apalutamide (**5**), discovered by Jung's group at UCLA in the 2000s, is similar to that of enzalutamide (Xtandi, developed by Medivation and approved in 2012), also discovered by Jung. However, in murine xenograft models of metastasized-CRPC (mCRPC), apalutamide (**5**) demonstrated greater antitumor activity than enzalutamide. Furthermore, apalutamide (**5**) penetrates less effectively the blood–brain barrier (BBB) than enzalutamide, suggesting that the chance of developing seizures may be less than with enzalutamide. At the end, the fact that both Janssen and Medivation were able to secure intellectual properties for their respective AR antagonists also speaks volume of the power of phenyl–pyridyl switch.[5]

Trifluoromethylpyridines in Drug Discovery

The constitutively active PI3K–AKT–mTOR signaling pathway is one of the key deregulation pathways important to cancer intervention. As shown below, phosphatidylinositol 3-kinases (PI3K) play a central role in a broad cellular functions including cell growth, proliferation, differentiation, survival and intracellular trafficking. Here RTK stands for receptor tyrosine kinase, GFR is the acronym for growth factor receptors, and mTOR is short for mammalian target of rapamycin. Gilead's PI3Kδ selective inhibitor idelalisib (Zydelig) was approved in 2014 and Bayer's pan-PI3K inhibitor copanlisib (Aliqopa) in 2017.

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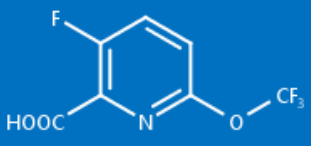

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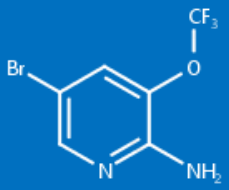

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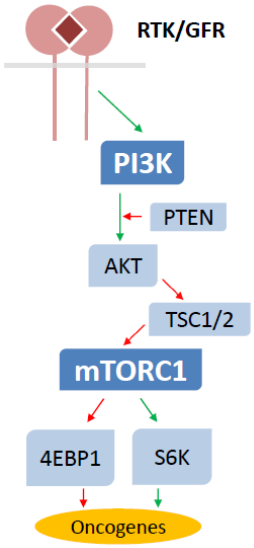

The PI3K–AKT–mTOR Signaling Pathway

Trifluoromethylpyridine fragment has made appearances in several advanced PI3K/mTOR inhibitors.

In 2011, Novartis disclosed NVP-BKM120 (buparlisib, **8**), with a pyrimidine core structure and a 4-(trifluoromethyl)pyridin-2-amine substituent, as a potent, selective, and orally bioavailable class I PI3 kinase inhibitor for treating cancer. One of the morpholines binds to the hinge at Val_{882}. The trifluoromethyl group here imparted superior solubility (132 μM for **8**) in comparison to the corresponding chloro-analog (45 μM) and the nitrile-analog (11 μM).[6] In 2018, Novartis sold buparlisib (**8**)'s right to China's Adlai Noryte, possibly because of some toxicity issues observed in phase III clinical trials for treating blood cancers and solid tumors. The culprit was likely due to buparlisib (**8**)'s microtubule interactions.

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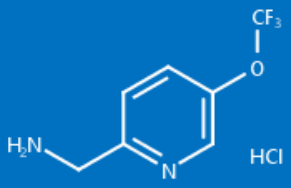

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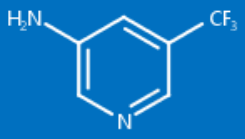

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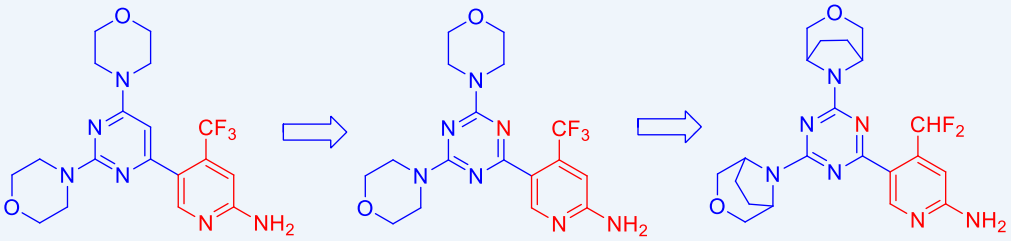

Wymann and colleagues at Basel sought to improve upon existing PI3K inhibitors while dialing in mTOR inhibition as well. They chose the triazine core structure aimed to (a) maximize compound solubility and bioavailability, (b) achieve blood–brain barrier penetration, (c) avoid microtubule interactions as observed for buparlisib (**8**), and (d) introduce moderate mTOR inhibition. The fruit of their labor led to the discovery of PQR309 (bimiralisib, **9**) as a potent, brain-penetrant, orally bioavailable, pan-class I PI3K inhibitor.[7] It was in phase II clinical trials in 2017 for the treatment of advanced solid tumors and refractory lymphoma.

In another successful medicinal chemistry maneuver, Wymann et al. dialed out bimiralisib (**9**)'s PI3K activities via installation of bulkier substituted morpholines and replacing the trifluoromethyl substituent on pyridine with the corresponding difluoromethyl group. They arrived at PQR620 (**10**), which showed excellent selectivity for mTOR over PI3K and protein kinases and efficiently prevented cancer cell growth in a 66 cancer cell line panel.[8]

The trifluoromethylpyridine fragment seems to be a really fruitful substituent for PI3K inhibitors. In addition to pan-PI3K inhibitors mentioned above, Novartis discovered CDZ173 (leniolisib, **11**) as a structurally novel class of PI3Kδ selective inhibitor.[9] In 2019, it was in clinical trials for treating Sjörgren's syndrome.

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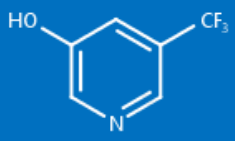

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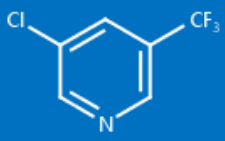

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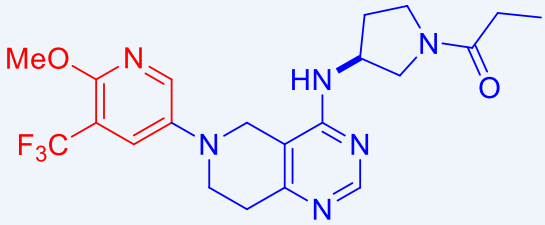
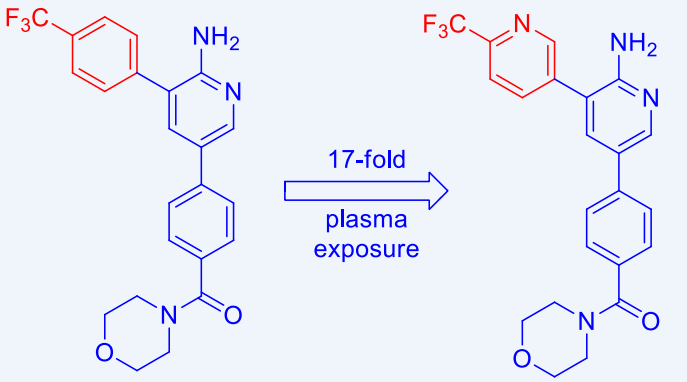


CDZ173 (leniolisib, **11**)

The trifluoromethylpyridine fragment was helpful in boosting a series of anti-malarial drugs' overall profiles. Replacing the trifluoromethylphenyl fragment on compound **12** with the corresponding trifluoromethylpyridyl group led to analog **13** with improved hERG binding (from 3 μM to 20.2 μM). Furthermore, the aza-analog **13** (C_{avg}, 3.4 μM) enjoyed a 17-fold boost of plasma concentration over **12** (C_{avg}, 0.20 μM) after a single 30 mg/kg oral dose.[10]



12
hERG IC_{50} = 3 μM
$C_{avg\ 0–8\ h}$ = 0.20 μM

13
hERG IC_{50} = 20.2 μM
$C_{avg\ 0–8\ h}$ = 0.20 μM

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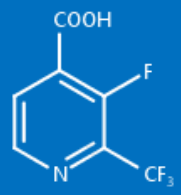

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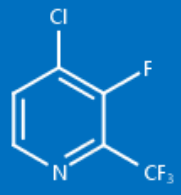

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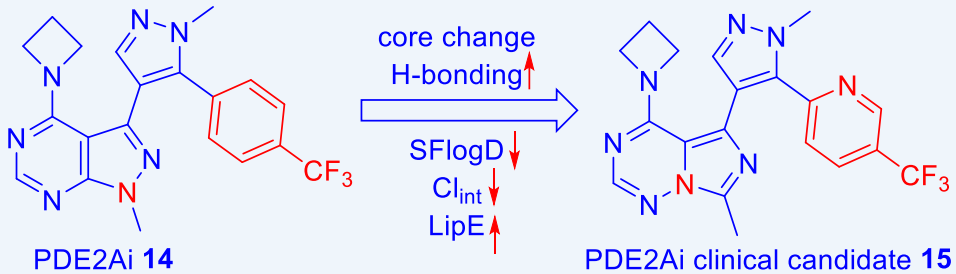
The phenyl–pyridine switch has done wonders in medicinal chemistry to improve a drug's *in vitro* binding affinity; *in vitro* functional affinity; *in vitro* PK/ADME profile; *in vitro* safety profile; and *in vivo* pharmacological profile.[11] The tactic made an *encore* appearance for Pfizer's phosphodiesterase 2A inhibitor (PDE2Ai) program. The PDE enzymes are well known now due to the success of sildenafil (Viagra, a PDE5 inhibitor for treating erectile dysfunction) and apremilast (Otezla, a PDE4 inhibitor for treating psoriasis). PDE2A inhibitors, on the other hand, have potential to treat cognitive impairment associated with schizophrenia (CIAS). While one of Pfizer's PDE2Ai lead compounds pyrazolopyrimidine **14** had desired potency, selectivity, and brain penetration for a preclinical candidate, they sought to reduce the estimated human dose (180 mg/day). During SAR investigations, simply switching the trifluoromethylphenyl group on **14** to the corresponding trifluoromethyl-pyridyl analog indeed reduced clearance in human liver microsomes (HLMs) from 85 to 30 mL/min/kg, but the potency suffered a 4.5-fold loss. With the aid of computer-assisted drug design (CADD) and chemistry innovation to avoid using high-energy intermediates, they eventually arrived at imidazotriazine analog **15** as a potent, highly selective, and brain penetrant PDE2Ai clinical candidate.[12]



PDE2Ai **14**
PDE2A IC_{50} = 2 nM
HLM Cl_{int} = 85 mL/min/kg
MDR BA/AB = 1.4
estimated human dose = 180 mg/day
SFlogD = 2.9
LipE = 6.1

PDE2Ai clinical candidate **15**
PDE2A IC_{50} = 1.6 nM
HLM Cl_{int} = 52 mL/min/kg
MDR BA/AB = 1.4
49 mg/day
SFlogD = 2.3
LipE = 6.5

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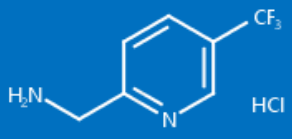

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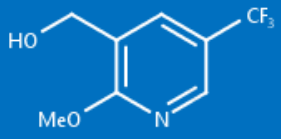

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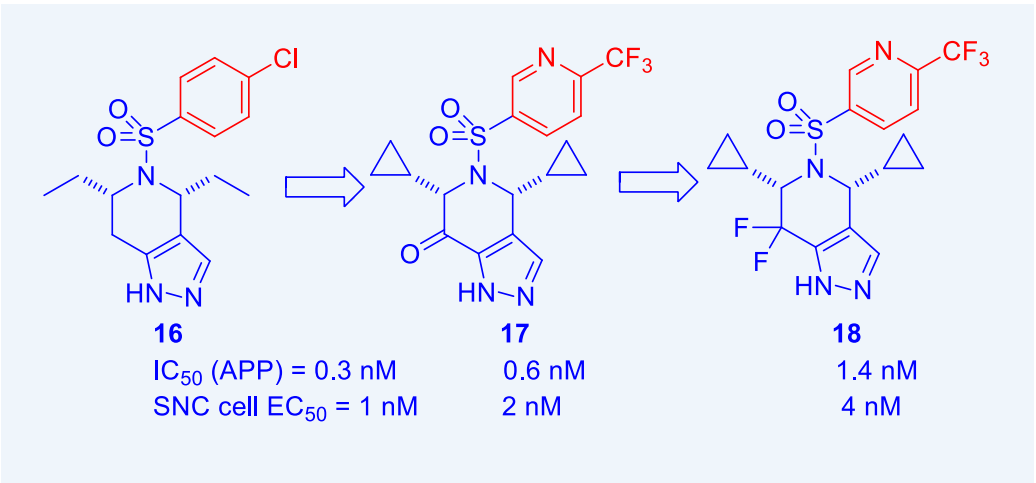
Semko and colleagues at Élan discovered a novel series of sulfonamide-pyrazolopiperidines as potent and efficacious γ-secretase inhibitors. Although an early inhibitor **16** reduced brain Aβ40 levels by 25% in a wild-type FVB mouse model, its bioavailability was low (2.5%) because its ethyl group was readily oxidized and the chlorine atom on the phenyl ring was displaced by glutathione (GSH). For this particular series, cyclopropyl group was an effective replacement for the ethyl group to achieve better stability while maintaining potency and the trifluoromethyl group helped to alleviate the glutathione conjugation issue. Therefore, trifluoromethyl-pyridyl analog **17** became less susceptible to glucuronidation at the NH site of the pyrazole ring but had low cellular activity since the core structure was easily oxidized to the aromatic hydroxypyridine. Thankfully, replacing the ketone with difluoromethylene led to compound **18**, which was bestowed with HLM stability (likely due to the two fluorine atoms that also lowered the susceptibility of the nearby moieties to CYP450 enzymatic oxidation) and lowered brain Aβ40 levels by 27% in a mouse model following oral administration of a dose of 1 mg/kg.[13]



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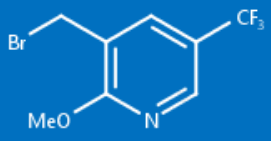

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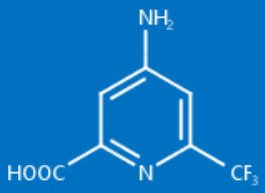
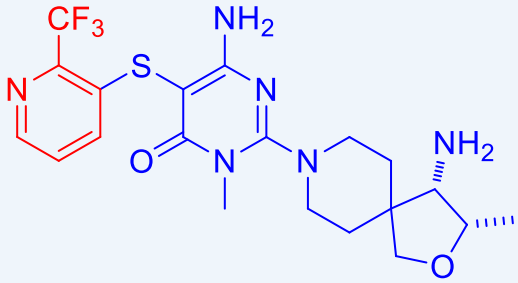


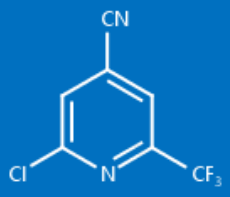
PBU1747

Novartis made a splash by revealing their allosteric SHP2 (Src homology region 2-containing protein tyrosine phosphatase) inhibitors in 2016. SHP2 is a non-receptor protein tyrosine phosphatase and scaffold protein. It is comprised of three domains: N-SH2, C-SH2, and PTP (PTP is short for PTPase, i.e., *p*rotein *t*yrosine *p*hosphatase), where the active site resides. Since the phosphate group binding site is highly positively charged and often does not have a distinctive small molecule pocket, competitive SHP2 inhibitors mimicking phosphate are very challenging. The initial competitive SHP2 inhibitors discovered during the last two decades invariably possessed ionizable functional groups, and thus had difficulty crossing cell membranes or enter bloodstream. Novartis reported an allosteric SHP2 inhibitor SHP099, which occupies a tunnel-like binding site (a pocket formed by the confluence of the three domains) in SHP2's closed conformation. Because SHP2 is only active when adopting the open conformation, SHP099 behaves like a molecule glue that preventing the opening of SHP2. As an allosteric inhibitor, SHP099 does not need to be phosphate-like. It has appropriate affinity, cell permeability, and other properties that enable oral administration.[14] One of Novartis' allosteric SHP2 inhibitors, TNO155, went on to phase I clinical trials in 2017 and the world awaits the outcome. In 2019, they reported 3-amino-3-methylpyrimidinones such as **19** as potent, selective, and orally efficacious SHP2 inhibitors.[15]

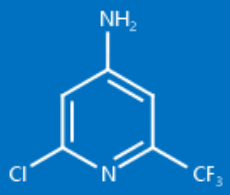


SHP2 inhibitor **19**

PharmaBlock Products



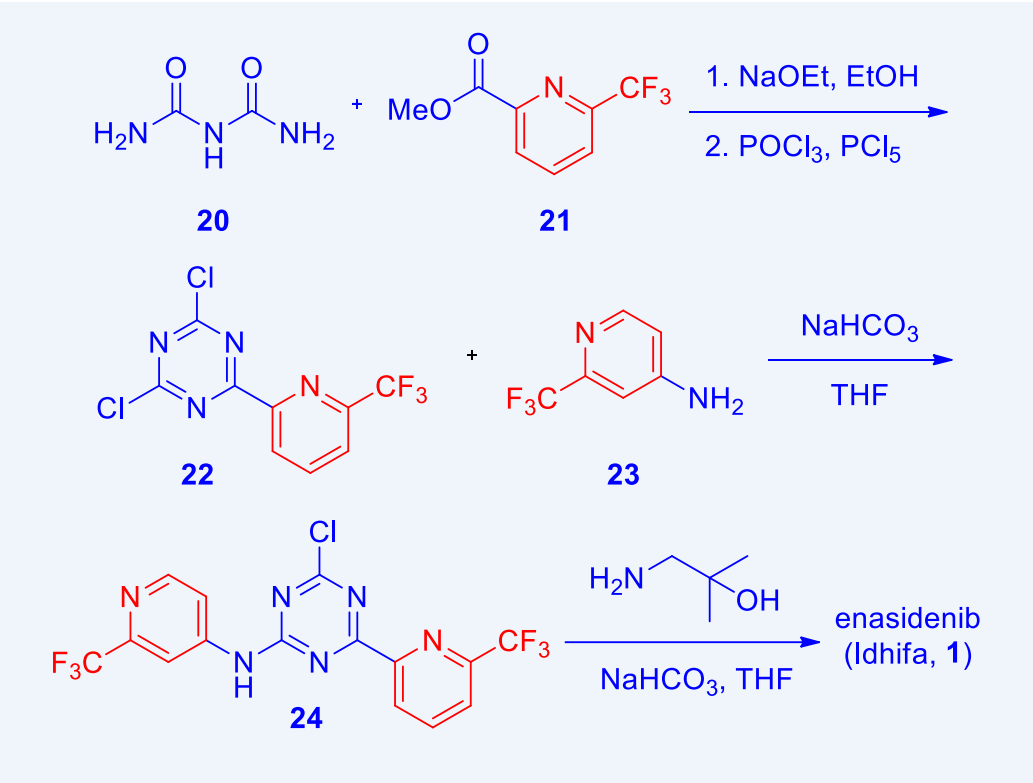
PB90831



PBYS1021

Synthesis of Some Trifluoromethylpyridine-containing Drugs

Agios' preparation of their IDH2 allosteric inhibitor enasidenib (Idhifa, **1**) commenced with installation of the triazine core on **22** from condensation of carbamylurea (**20**) with methyl 6-(trifluoromethyl)picolinate (**21**), followed by chlorination using $POCl_3$ to offer dichlorotriazine **22**. An S_NAr displacement of the first chlorine on dichlorotriazine **22** with 4-amino-2-trifluoromethylpyridine (**23**) gave monochlorotriazine **24**. Another S_NAr displacement of the remaining chlorine with 1-amino-2-methyl-2-propanol then completed the synthesis of enasidenib (**1**).[3]



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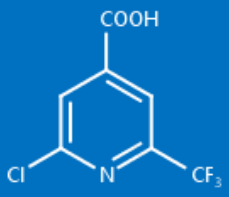
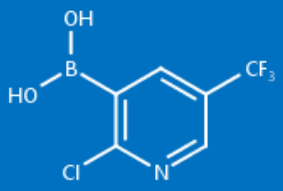
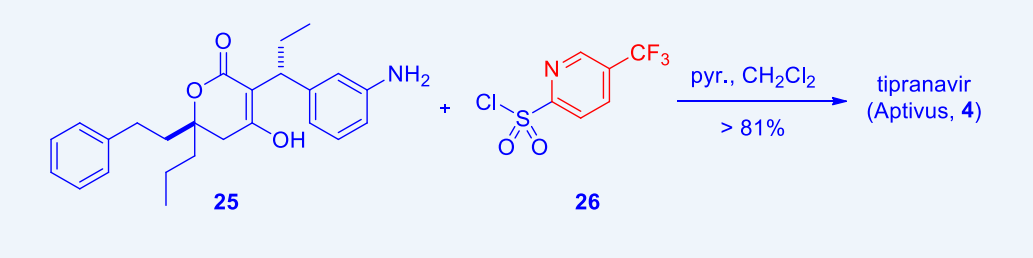


PBYS1201



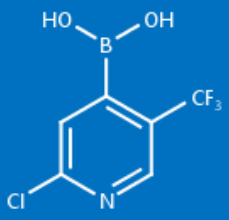
PBYS1656

With regard to the synthesis of Upjohn's HIV protease inhibitor tipranavir (Aptivus, **4**), the major challenge was installation of the two chiral centers on the left-hand portion **25**. Once that achieved, simply mixing aniline **25** with 5-(trifluoromethyl)pyridine-2-sulfonyl chloride (**26**) in the presence of pyridine as the base delivered the desired tipranavir (**4**) in excellent yield (81% yield includes the previous step for concurrently reducing the nitro group and a double bond).[16]



Jung's initial route on the patent was not amenable to process and manufacturing. Therefore, many process chemistry patents have been filed to improve the original route. In one case, hydrolysis of commercially available 2-chloro-3-(trifluoromethyl)pyridine (**27**) afforded pyridone **28**, which offered requisite reactivity and regioselectivity for nitration to produce 5-nitropyridone **29**. Refluxing **29** with a mixture of $POCl_3$ and PCl_5 restored the chloropyridine functionality on **30**, which was then reduced to 6-chloro-5-(trifluoromethyl)pyridin-3-amine (**31**). The choice of Raney nickel as the catalyst for hydrogenation was a wise one because a palladium-based catalyst would have caused concurrent dechlorination. After Boc protection of the amine as **32**, an S_NAr reaction took place to install 6-cyano-pyridine on **33**, which underwent an acidic deprotection to unmask the amine on **34**. Transformation of **34** to isothiocyanate **35** was accomplished by treating it with thiophosgene. Coupling between isothiocyanate **35** and aniline **36** then delivered apalutamide (**7**) after acidic hydrolysis.[5]

PharmaBlock Products



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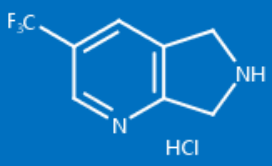

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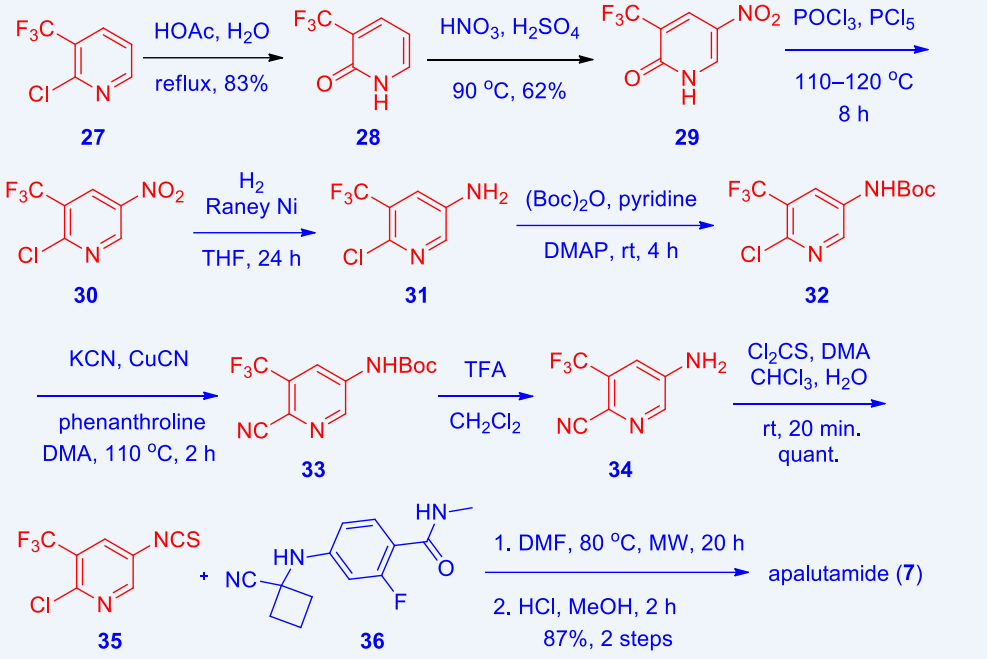
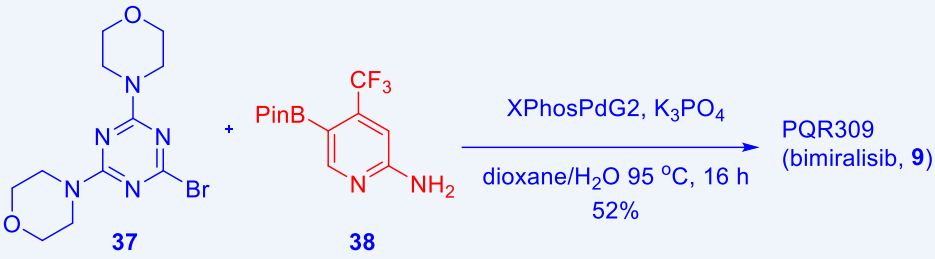
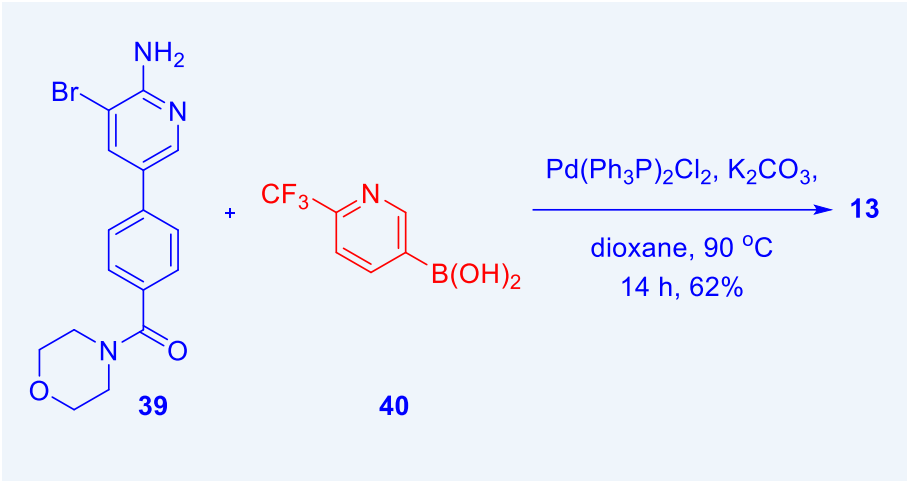


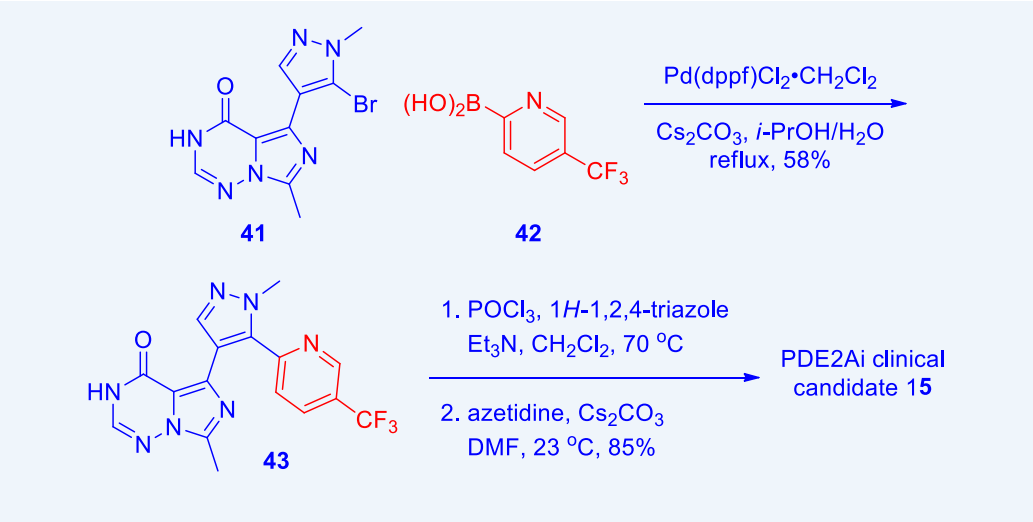
Synthesis of Basel's PI3K/mTOR inhibitor PQR309 (bimiralisib, **9**) is reasonably straightforward. The Suzuki coupling between triazine-bromide **37** and pinacol-borane of the trifluoromethylpyridyl fragment **38** was promoted by XPhosPdG2 as the catalyst to afford bimiralisib (**9**) in 52% yield.[7]



The Suzuki coupling was also key to assemble antimalarial drug **13**. The union between 3-pyridylbromide **39** and trifluoromethylpyridyl-boronic acid **40** took place with relative ease, only requiring the simple $Pd(Ph_3P)Cl_2$ catalyst.[10]



The Suzuki coupling is so ubiquitous in drug discovery, I wonder how we managed before it was discovered? Pfizer's synthesis of their PDE2Ai clinical candidate **15** resorted to the Suzuki coupling between pyrazole bromide **41** and (5-(trifluoromethyl)pyridin-2-yl)boronic acid (**42**) to afford adduct **43**. Subsequent chlorination of **43** was followed by an S_NAr replacement with azetidine to produce the API **15**.[12]



Novartis' synthesis of its SHP2 inhibitor **19** involved a copper-catalyzed Ullman coupling between 2-(trifluoro-methyl)pyridine-3-thiol (**44**) and 5-iodopyrimidinone **45** to prepare the thioether. Subsequent acidic Boc deprotection then delivered **19**.[15]

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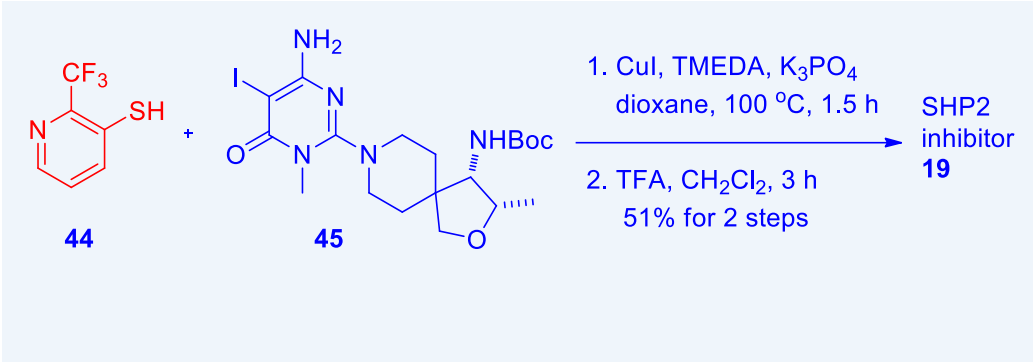

44 **45**

To conclude, trifluoromethylpridine fragment exists in at least three marketed drugs: Agios' IDH2 allosteric inhibitor enasidenib (Idhifa, **1**), Upjohn's HIV protease inhibitor tipranavir (**4**), and Janssen's androgen receptor antagonist apalutamide (**5**). The trifluoromethyl group may form tetrel bonding with heteroatoms on target proteins and the nitrogen atom on pyridine can serve as a hydrogen bond acceptor, establishing further binding to target proteins. As a consequence, trifluoromethylpridine is a privileged structure in drug discovery. It may offer tighter binding to the target protein, improve upon a drug's solubility, metabolism, stability, and other drug-like properties.

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