Tetrahydropyrans in Drug Discovery

Key Points

- Improving drug absorption, distribution, metabolism and excretion
- Modulating drugs' pK_a
- Helping to achieve favorable pharmacokinetic properties

Overview

Tetrahydropyran (THP) is a rigid form of linear ether, thus has lower entropy. As a bioisostere of cyclohexane, THP may gain an additional point of contact with the target by offering oxygen as a hydrogen bond acceptor. In medicinal chemistry, THP substituents, with lower lipophilicity in comparison to the cyclohexyl counterparts, have been employed to modulate the pK_a of drugs and improve their absorption, distribution, metabolism, and excretion (ADME) profiles.

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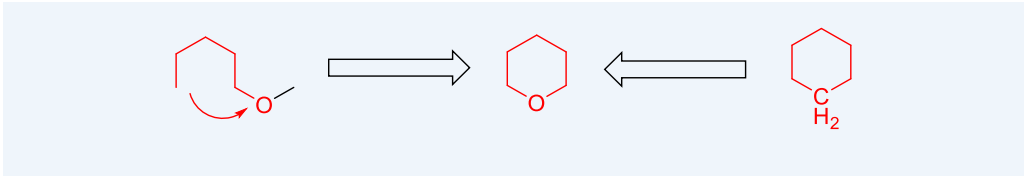
PharmaBlock designs and synthesizes over 1361 THPs, and 218 THP products are in stock. A list of featured THP derivatives is attached at the end of this whitepaper. CLICK HERE to find detailed product information on webpage.

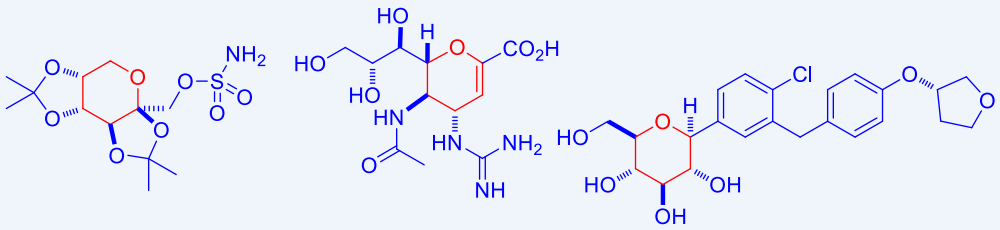
Tetrahydropyran (THP) may be considered as conformationally restraint ether with lower entropy. In the context of drug discovery, THP is a bioisostere of cyclohexane with lower lipophilicity. Having a lower lipophilicity may improve a drug's absorption, distribution, metabolism, and excretion (ADME). Furthermore, by replacing the CH_2 with an oxygen atom, THP may provide an additional point of contact with the target by offering oxygen as a hydrogen bond acceptor.



Tetrahydropyran-containing Drugs

Some THP-containing drugs are closer to carbohydrates than to simple THPs and are not the focus of this review. An early THP-containing drug is anticonvulsant topiramate (Topamax, **1**) as a fructopyranose *O*-alkyl sulfamate.[1] Similarly, neuraminidase inhibitor zanamivir (Relenza, **2**) for treating influenza infection was discovered employing terminal sialic acid, a residue from glucoconjugates, as a starting point. It is the 4-guanadino-derivative of dehydro-2-deoxy-*N*-acetylneuraminic acid (DANA), a transition-state mimetic of neuraminidase.[2]

Selective sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors are one of the most recently approved drug classes for the treatment of type 2 diabetes mellitus (T2DM). All four SGLT-2 inhibitors on the market, Tanabe's canagliflozin (Invokana), BMS's dapagliflozin (Farxiga), Boehringer Ingelheim's empagliflozin (Jardiance, **3**), and Merck's ertugliflozin (Steglatro) are *C*-glycosides, which have improved metabolic stability over metabolically labile *O*-glycosides (e.g., phlorizin).[3]



topiramate (Topamax, **1**)
Mylan, 1996
anticonvulant

zanamivir (Relenza, **2**)
Biota/Glaxo, 1999
neuraminidase inhibitor

empagliflozin (Jardiance, **3**)
Boehringer Ingelheim, 2014
SGLT2 inhibitor

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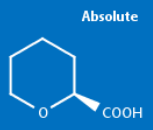

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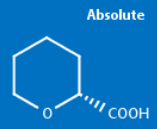

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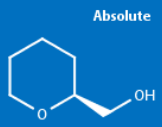

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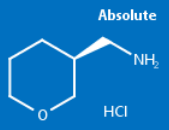

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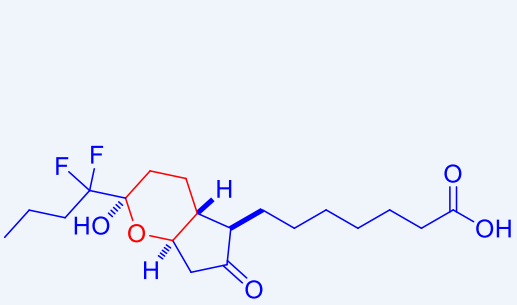
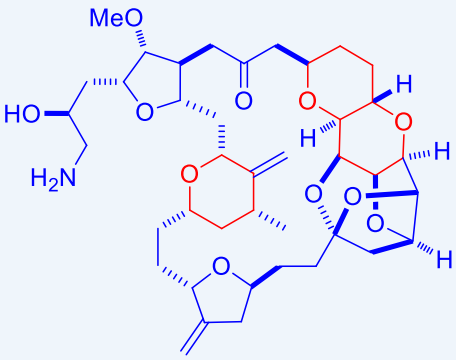
Here, we place emphasis on *bona fide* THP-containing drugs as exemplified by compounds **4**–**9** shown below.

Lubiprostone (Amitiza, **4**), a laxative for the treatment of irritable bowel syndrome with constipation (IBS-c), contains a bicyclic THP-cyclopentanone. Derived from prostaglandin E1, lubiprostone (**4**)'s mechanism of action (MOA) is found to be a chloride channel-2 (ClC-2) opener (activator).[4a] It is not a remarkable drug except its cost, which prompted a physician to publish an article in 2017 with a title: "*$850 Per Bowel Movement?! Hard To Justify That Cost*".[4b] In contrast, few would protest the price for Eisai's eribulin (Halaven, **5**) for the treatment of metastatic breast cancer and liposarcoma. A microtubule dynamics inhibitor, it was discovered through a herculean effort by trimming marine natural product halichondrin B, which has seven THP rings. With three THP rings and 19 chiral centers, eribulin (**5**)'s manufacturing route entails 62 steps and even the longest linear sequence is 30 steps.[5]



lubiprostone (Amitiza, **4**)
Mallinckrodt/Takeda, 2006
chloride channel activator



eribulin (Halaven, **5**)
Eisai, 2010
microtubule dynamics inhibitor

Merck's dipeptidyl peptidase 4 (DPP4) inhibitor omarigliptin (Marizev, **7**) is a more rigid backup for its initial successful drug sitagliptin (Januvia, **6**). Remarkably, omarigliptin (**7**) has such a long half-life that it is taken once weekly whereas its progenitor sitagliptin (**6**) is given qd. Initially, when the cyclohexylamine derivative was installed to replace the linear amine on sitagliptin (**6**), the analogue's selectivity against IKr (IC_{50} = 4.8 μM) was below the desired standard (IC_{50} > 30 μM). In addition, in the CV-dog model, the cyclohexylamine derivative was found to prolong QTc (> 5% at 3 mpk). Replacement of cyclohexylamine with THP-amine reduced the pK_a of the primary amine from 8.6 to 7.3, and the hERG selectivity improved accordingly (IC_{50} = 23 μM). In addition, the THP analogue was devoid of any QTc prolongation in the CV-dog model at doses up to 30 mpk iv.[6]

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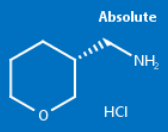

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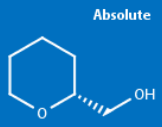

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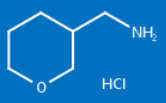

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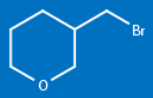

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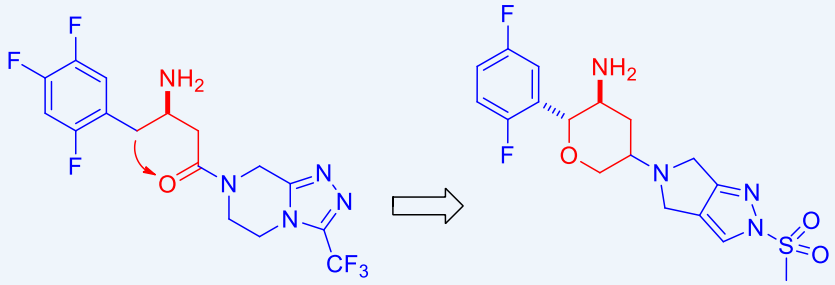
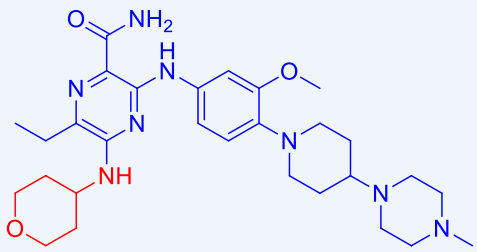


sitagliptin (Januvia, **6**)
Merck, 2006
DPP-4 inhibitor, qd

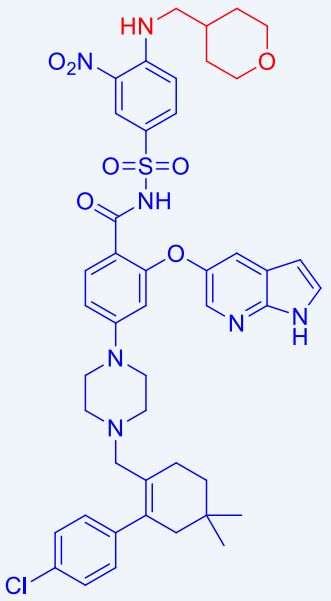
omarigliptin (Marizev, **7**)
Merck, 2015 (Japan)
DPP-4 inhibitor, once weekly

In 2018, Astellas' gilteritinib (Xospata, **8**) garnered the FDA's approval as a treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation. With the popular amino-THP substituent, gilteritinib (**8**) is an AXL receptor tyrosine kinase inhibitor.[7] In addition, it also inhibits FLT3, ALK, LTK and KIT kinases.



gilteritinib (Xospata, **8**)
Astellas, 2018
AXL receptor tyrosine kinase inhibitor

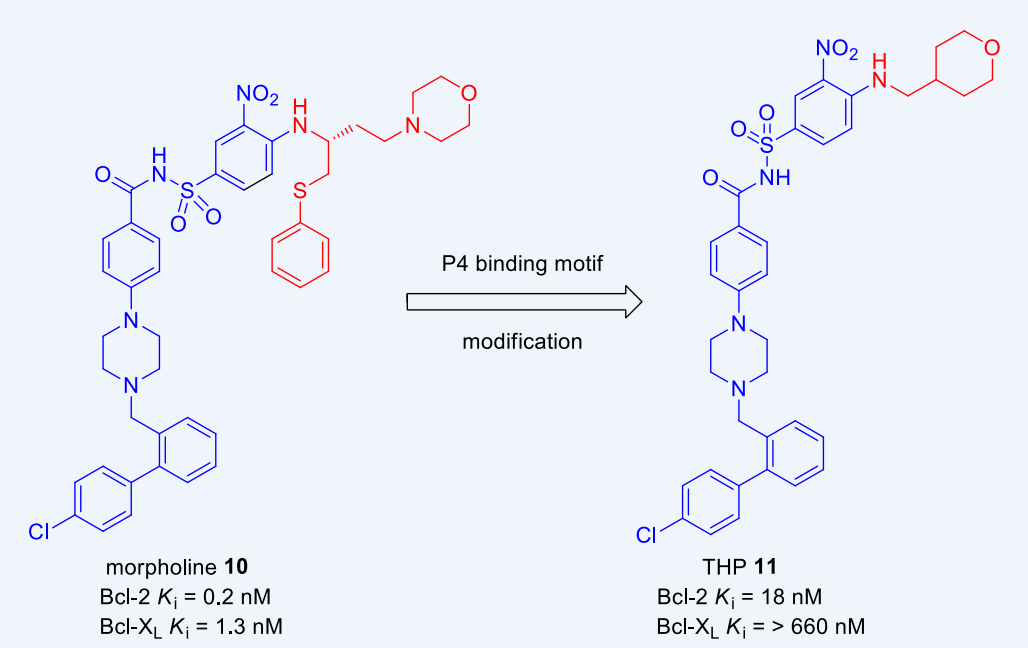
Abbvie's B-cell lymphoma 2 (Bcl-2) inhibitor venetoclax (Venclexta, **9**) is a "wonder" cancer drug for treating chronic lymphocytic leukemia (CLL) with the 17p deletion. Targeting the challenging protein–protein interactions (PPIs), it was discovered from the fragment-based drug discovery (FBDD) strategy under the guidance of the "SAR by NMR" method. Its THP tail fragment played an important role in imparting selectivity against Bcl-X_L (*vide infra*).[8]



venetoclax (Venclexta, **9**)
Abbvie, 2016
Bcl-2 inhibitor

Tetrahydropyrans in Drug Discovery

en route to the discovery of venetoclax (**9**), Abbvie prepared morpholine **10**. While morpholine **10** was a potent Bcl-2 inhibitor (K_i = 0.2 nM), it was not selective against Bcl-X_L (K_i = 1.3 nM). While inhibition of Bcl-2 offered target efficacy in leukemia and lymphoma, inhibition of Bcl-X_L led to dose-limiting thrombocytopenia, a deficiency of platelets (thrombocytes) that may increase the risk of bleeding. From ingenious reverse engineering efforts, Abbvie arrived at THP-containing compound **11**, which lost Bcl-X_L activity. Regrettably, THP **11** also had reduced Bcl-2 affinity and no cell activity. Both of the deficiencies had to be remedied by installing a 7-azaindole ether substituent to occupy the P4 hot spot. Culmination of these efforts eventually provided venetoclax (**9**), which is a potent, selective (Bcl-X_L-sparing and human platelet-sparing), and bioavailable Bcl-2 inhibitor, after an arduous and winding road of discovery.[8]



THP rings have been frequently employed to improve a drug's ADME properties. A series of THP-containing histamine-3 (H_3) receptor antagonists were prepared as a treatment of allergic rhinitis. As represented by dibasic THP **12**, modulation of its partition coefficient achieved an optimal balance of blood clearance (CL = 18 ml/min/kg) and volume of distribution (V_d = 94 L/kg). Remarkably, THP **12** has a half-life of 60 h in dogs and a predicted human half-life of 250 h.[9] Meanwhile, Actelion's THP-based inhibitor **13** of bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) showed antibacterial activity against Gram-negative bacteria. These non-fluoroquinolone topoisomerase inhibitors are of great interest because they may overcome infections inflicted by multidrug resistant (MDR) Gram-negative bacteria.[10]

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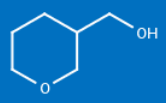

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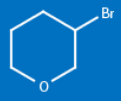

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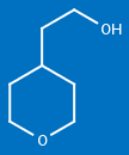

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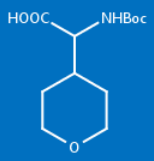

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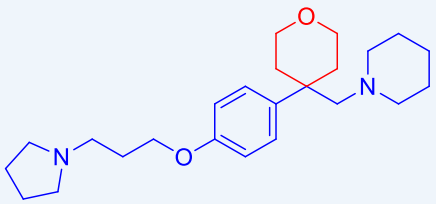
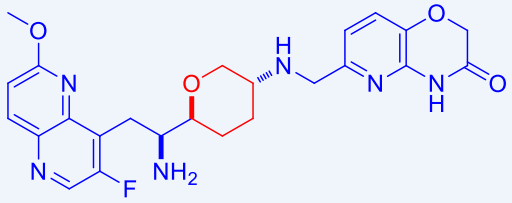
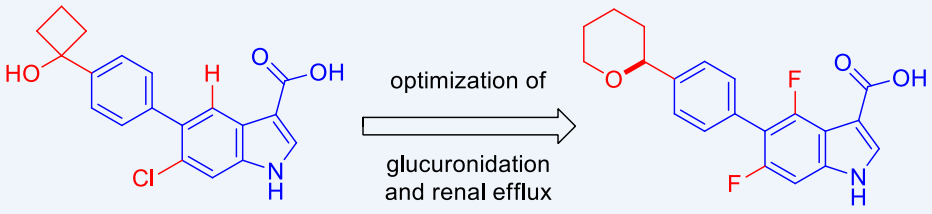


H_3 histamine receptor antagonist **12**



topoisomerase inhibitor **13**

Pfizer's cyclobutanol-containing drug **14** is a direct activator of 5′-adenosine monophosphate activated protein kinase (AMPK). It is potent and selective against β1-containing AMPK isoforms that allosterically activate the enzyme by binding at the "allosteric drug and metabolite" (ADaM) site at the interface of the α- and β-subunits. Its carboxylic acid, the indole N–H, and the cyclobutanol all form hydrogen bonds to protein atoms from the α1 and β1 units. As a clinical candidate for the treatment of diabetes nephropathy associated with T2DM, cyclobutanol **14** is not ideal in terms of ADME. Namely, it undergoes rapid phase II metabolism, forming acyl glucuronide conjugate by uridine glucuronosyltransferase (UGT) isoforms. Renal excretion of unchanged drug is observed in rat, dog, and monkey, and the active renal elimination process is possibly mediated by organic anion transporter (OAT) proteins expressed at the basolateral membrane of proximal tubules.[11a] As a backup drug for **14**, THP-containing analogue PF-06409577 (**15**) may be considered as a conformationally restraint ether, providing an opportunity to balance the lipophilicity without adding additional hydrogen bond donors. In combination with two fluorine substituents on the indole ring, PF-06409577 (**15**) offers favorable *in vitro* ADME properties including decreased CL_{int} in human hepatocytes and increased P_{app} with attenuated binding to human OAT-3 in comparison to the parent drug **14**. PF-06409577 (**15**), now in first-in-human (FIH) clinical trials, emerged from three preclinical candidates (including **14**) as a new investigational drug. Coincidentally, acyl glucuronide metabolites of both **14** and **15** are direct activators of AMPK as well.[11b]



cyclobutanol **14**
$\alpha1\beta1\gamma1$-AMPK EC_{50}, 5.6 nM
rat CL_p, 23 mL/min/kg
rat CL_{renal}, 7.6 mL/min/kg

PF-06409577 (**15**)
$\alpha1\beta1\gamma1$-AMPK EC_{50}, 22 nM
rat CL_p, 1.2 mL/min/kg
rat CL_{renal}, 0.03 mL/min/kg

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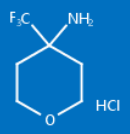

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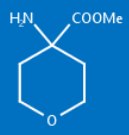

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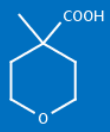

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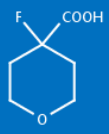

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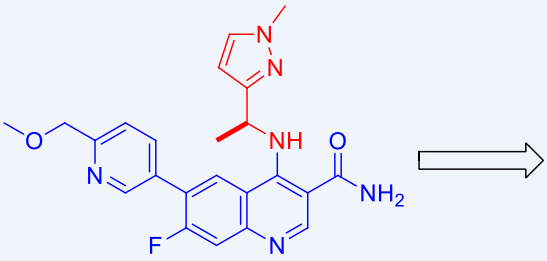
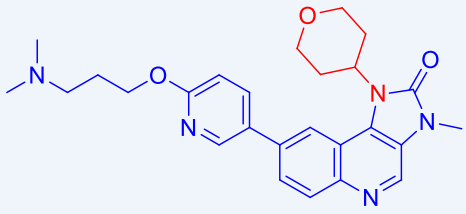
A THP-amine motif helped AstraZeneca to arrive at a potent, selective, and orally bioavailable inhibitor AZD0156 (**17**) of ataxia telangiectasia mutated (ATM) kinase as a potential drug to potentiate the efficacy of the approved drugs irinotecan (a DNA intercalator) and olaparib [a poly ADP ribose polymerase (PARP) inhibitor] in disease-relevant mouse models. ATM kinase is a member of the PI3K-related kinase (PIKK) family of atypical serine/threonine protein kinases (also comprising of mTOR) and plays a central role in both signaling of and the protection of cells against DNA double-strand breaks (DSB) and reactive oxygen species (ROS) that radiotherapy and a wide range of chemotherapies induce. Starting from an initial screening hit with a quinolone carboxamide scaffold, AstraZeneca arrived at ATM inhibitor **16**, which showed *in vivo* efficacy in an HT29 mouse xenograft model. But with a predicted dose of 700 mg qd for **16**, a drug with a better ADME profile and lower predicted dosage would have better chances to succeed in clinical trials. Extensive optimization, including installation of a THP-amine fragment, led to AZD0156 (**17**) with a superior profile in comparison to **16**. AZD0156 (**17**) is potent and selective against closely related kinases such as mTOR and PI3K with superb aqueous solubility, and many other pharmacokinetic parameters. It has a predicted dose of 5 mg qd, bestowing this compound a greater chance of success in clinics.[12a] In 2018, phase I clinical trials for AZD0156 (**17**) in combination with olaparib concluded successfully. Meanwhile, a series of THP-containing 3-cinnoline carboxamides were described as highly potent, selective, and orally bioavailable ATM kinase inhibitors as well.[12b]



ATM inhibitor **16**
ATM IC_{50} = 33 nM
aq. soln. 69 μM
Pred dose = 700 mg qd



AZD0156 (**17**)
ATM IC_{50} = 0.58 nM
aq. soln. > 800 μM
Pred dose = 5 mg qd

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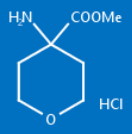

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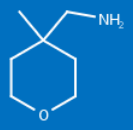

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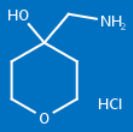

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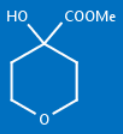

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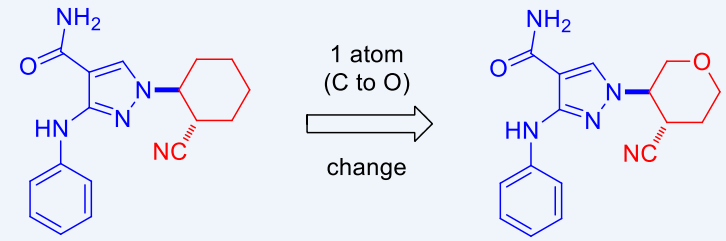
THP played an important role in achieving favorable pharmacokinetic properties during Merck's efforts in optimizing a series of pyrazolyl-carboxamides as Janus kinase 1 (JAK1) selective inhibitors. THP derivative **19**, as a bioisostere of cyclohexyl derivative **18**, introduced a polar oxygen heteroatom, which offered tighter drug–enzyme binding interactions. This was reflected by a 1.4-fold increase of lipophilic ligand efficiency (LLE) although its ligand binding efficiency (LBE) value did not change much. The polarity decrease was subtle (log *D* 2.08 for **19** vs. log *D* 2.66 for **18**), but it translated to improved clearance in both rat and human and a large decrease in unbound *in vivo* rat clearance.[13] This is a good example to highlight that the cyclohexyl–THP switch may bring not only better potencies, but also improved ADME properties (CLp = plasma clearance; r:h Hept CL_{int} = rat and human hepatic intrinsic clearance).

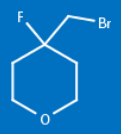


cyclohexyl derivative **18**
JAK1 IC_{50} = 3 nM
LBE = 0.50
LEE = 5.5
HPLC log *D* pH7.0 = 2.66
rat CL_p = 484 mL/min/kg
unbound rat CL = 12,100 mL/min/kg
r:h Hept CL_{int} = 160:25 mL/min/kg

THP derivative **19**
JAK1 IC_{50} = 0.4 nM
LBE = 0.56
LEE = 7.9
2.08
rat CL_p = 20 mL/min/kg
110 mL/min/kg
70:6 mL/min/kg

A THP substituent helped AstraZeneca to reduce the clearance of their interlecukin-1 receptor associated kinase 4 (IRAK4) inhibitors. The cyclopentyl derivative **20**, as a pyrrolopyrimidine-based IRAK4 inhibitor, had a high rate of metabolism in isolated rat hepatocytes (CL_{int} = 71 μL/min/10^6 cells). While the direct oxygen analog employing 2- or 3-tetrahydrofuran (THF) did not show significant improvement of metabolism, 4-THP derivative **21** reduced the rate of metabolism by rat hepatocytes by 5-fold. On a molecular level, the 4-THP moiety showed a lipophilic stacking interaction with Tyr262 as well as a hydrogen bond to Lys213. The optimized IRAK4 inhibitors may serve as treatment of mutant MYD^{L265P} diffuse large B-cell lymphoma (DLBCL).[14]

PharmaBlock Products



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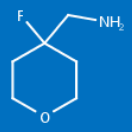

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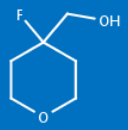

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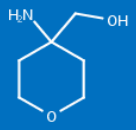

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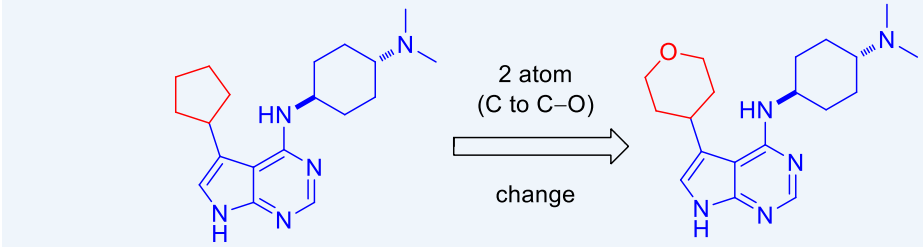
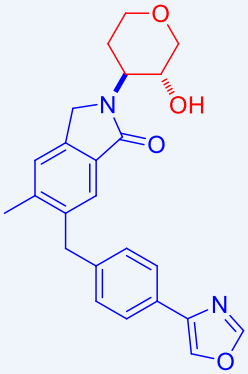


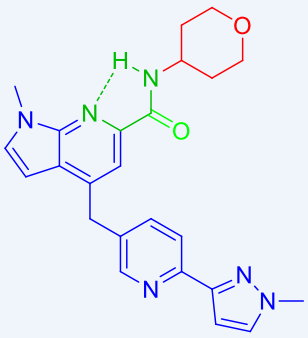
cyclopentyl derivative **20**
IRAK4 enz IC_{50} = 6 nM
IRAK4 cell IC_{50} = 23 nM
rat heps CL_{int} = 71 μL/min/10^6 cells

4-THP derivative **21**
IRAK4 enz IC_{50} = 6 nM
IRAK4 enz IC_{50} = 59 nM
14 μL/min/10^6 cells

THP fragments also made appearance in modulating receptors in addition to the examples on enzymes shown thus far. Muscarinic acetylcholine receptor (mAChR) subtype 1 (M_1) positive allosteric modulators (PAMs) hold great promises of treating Alzheimer's disease (AD) and schizophrenia. But like all potential treatments for AD, this target has encountered many failures in clinical trials. Pfizer's THP-containing M_1-selective PAM PF-06827443 (**22**) is plagued with weak agonist activity, which manifests as seizure and cholinergic adverse events.[15] Another "pure" M_1 PAM THP-containing VU6007477 (**23**) is devoid of agonist activities. Although without the cholinergic toxicity/seizure liability, it is not suitable for translation to the clinic because **23** is a P-glycoprotein (P-gp) substrate (efflux ratio, ER = 4.5) with only moderate permeability (P_{app} = 1.2×10^{-5} cm/s). As a side, 7-azaindole-carboxamide **23** forms an intramolecular hydrogen bond, which helps to maintain the putative bio-activation conformation.[16]



PF-06827443 (**22**)
M_1 PAM EC_{50} = 47 nM
M_1 PAM K_i = 14 nM
M_2–M_5, EC_{50} > 10 μM



VU6007477 (**23**)
M_1 PAM EC_{50} = 230 nM
M_1 agonist EC_{50} > 10 μM
K_i = 0.28 nM, $K_{p,uu}$ = 0.32 nM

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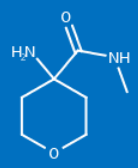

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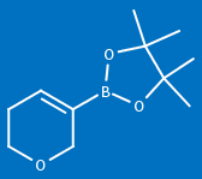

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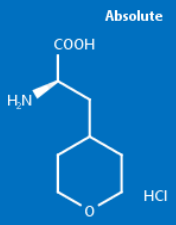

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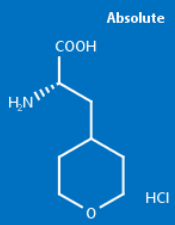
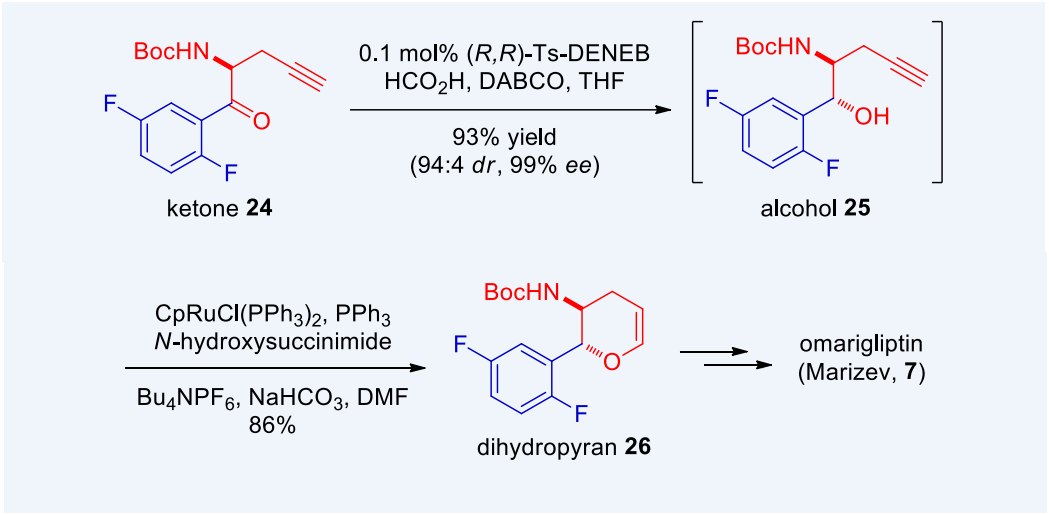


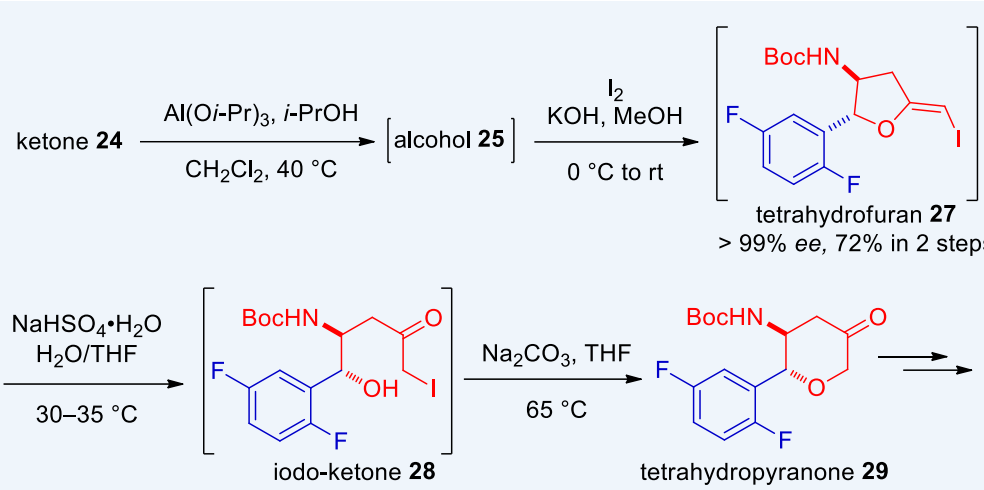
PBLJ0221-1

Synthesis of Some Tetrahydropyran-containing Drugs

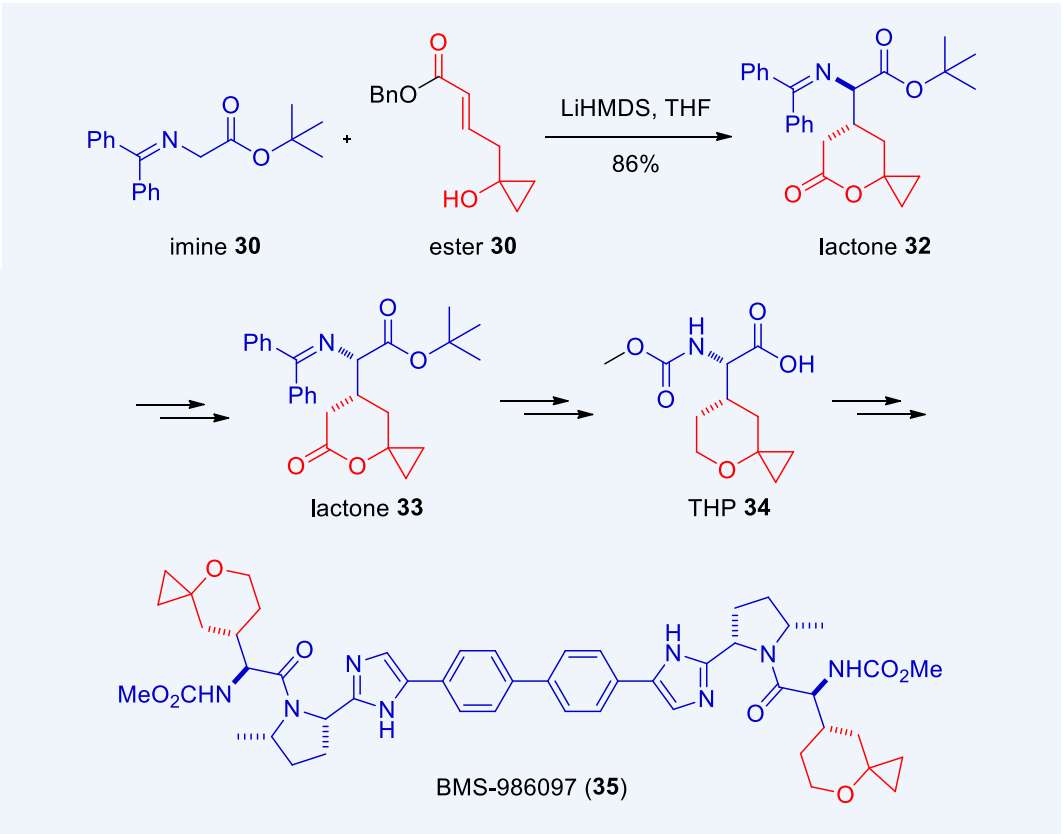
Manufacturing route for an active pharmaceutical ingredient (API) is the gold standard of organic synthesis because it must consider many factors such as synthetic convergence, cost of goods (CoG), scalability, reproducibility, reaction conditions, reactors, and environmental friendliness, etc. Merck's manufacturing route for its DDP-4 inhibitor omarigliptin (Marizev, **7**) serves as a good lesson to learn in devising a commercial production route. Ketone **24** was assembled by reaction between the Grignard reagent (2,5-difluorophenyl)magnesium chloride and the appropriate Weinreb amide. Asymmetric reduction of ketone **24** to alcohol **25** was accomplished via a dynamic kinetic resolution (DKR) asymmetric transfer hydrogenation that was facilitated by an oxo-tethered ruthenium-(II) catalyst, (*R*,*R*)-Ts-DENEB as a highly efficient asymmetric transfer hydrogenation catalyst. Subsequent Ru-catalyzed cyclo-isomerization of alcohol **25** to dihydropyran **26** was carried out in the same pot without workup of the alcohol intermediate.[17]



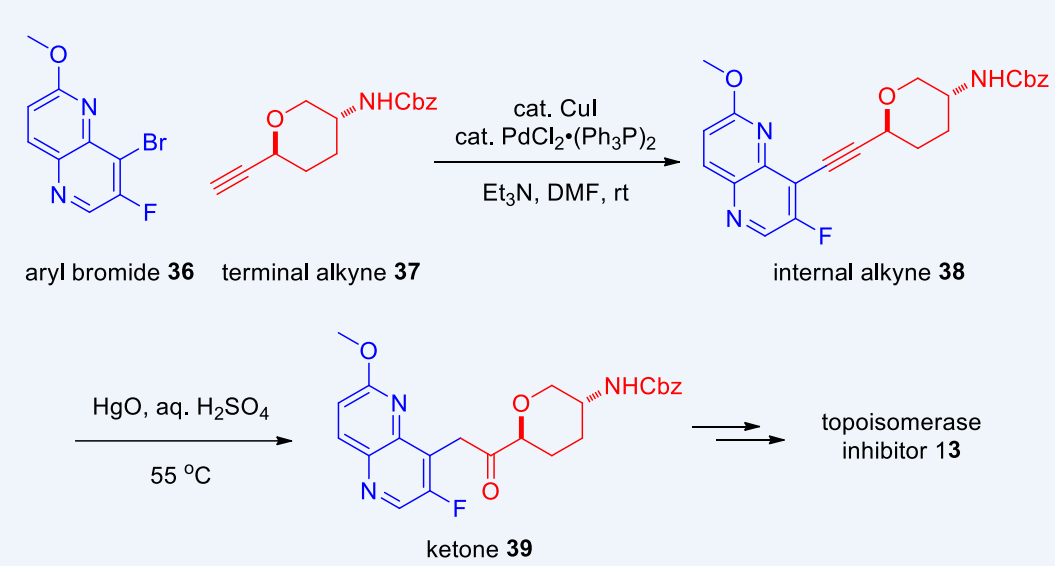
Process Chemistry at HEC Pharma reported an alternative scalable process for the synthesis of the key intermediate of omarigliptin (**7**). Ketone **24** was reduced to alcohol **25** employing a "low-tech" reducing agent via the Meerwein–Ponndorf–Verley reaction. Exposure of alcohol **25** to iodine under basic conditions led to 5-*exo*-*dig* iodocyclization product tetrahydrofuran-vinyl iodide **27**, which was converted to iodoketone **28** via addition of water and a concurrent ring opening reaction promoted by aqueous sodium hydrogen sulfate hydrate. A simple intramolecular S_N2 displacement then gave rise to cycloetherization product tetrahydro-pyranone **29** as an advanced intermediate toward omarigliptin (**7**).[18]



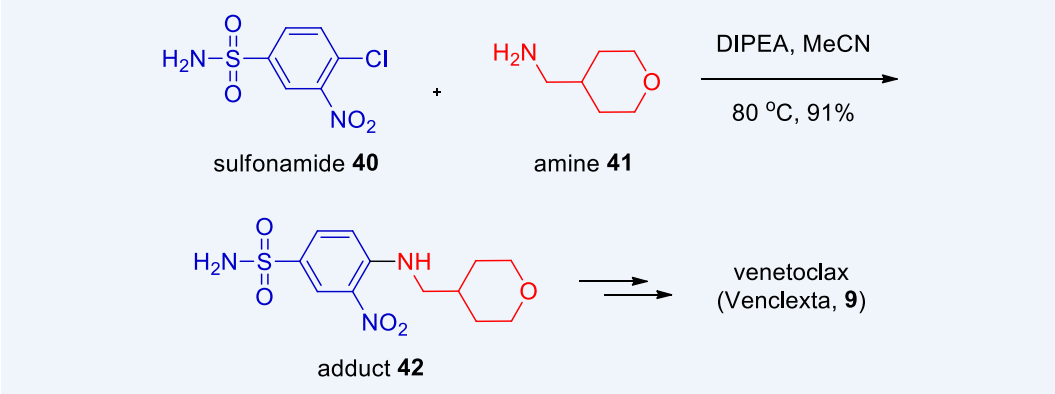
In collaboration with Baran, BMS chemists made a heroic effort in preparing a chiral THP fragment **34** as a building block for the synthesis of the HCV NS5A inhibitor BMS-986097 (**35**). Michael addition of imine **30** as a masked amino acid to α,β-unsaturated ester **31** gave rise to lactone **32** and its enantiomer in a 1:1 ratio. DBU-promoted epimerization and chiral supercritical fluid chromatography (SFC) separation produced lactone **33**, which was manipulated to THP **34** as a single enantiomer. THP **34** served as two tails of the symmetrical BMS-986097 (**35**).[19] For future process and manufacturing routes, an asymmetric synthesis is needed to make THP **34** without the need of epimerization and chiral SFC separations.



Actelion's preparation of the central THP scaffold on topoisomerase inhibitor **13** involved a Sonogashira coupling of aryl bromide **36** and THP-containing terminal alkyne **37** to construct internal alkyne **38**. Hg(II)-promoted hydration under harsher acidic conditions installed ketone **39**, which could be then manipulated to deliver topoisomerase inhibitor **13**.[10,20]



Thankfully, not all THP rings are so complicated to construct, many drug syntheses can take advantage of commercially available THP-containing building blocks. Abbvie's synthesis of the top portion **42** of venetoclax (Venclexta, **9**) entails an S_NAr reaction of 4-chloro-3-nitrobenzene-sulfonamide (**40**) with THP-methylamine **41** at 80 °C. Replacing **40** with 4-fluoro-3-nitrobenzenesulfonamide accelerates the S_NAr reaction, which may be carried out at rt in THF and Et_3N.[21]



PharmaBlock is recognized for its outstanding capability in the design, synthesis, production and commercialization of novel building blocks for use throughout the drug R&D process.

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- 10000+ in stock in both USA and China
- 20000+ supplied within two weeks
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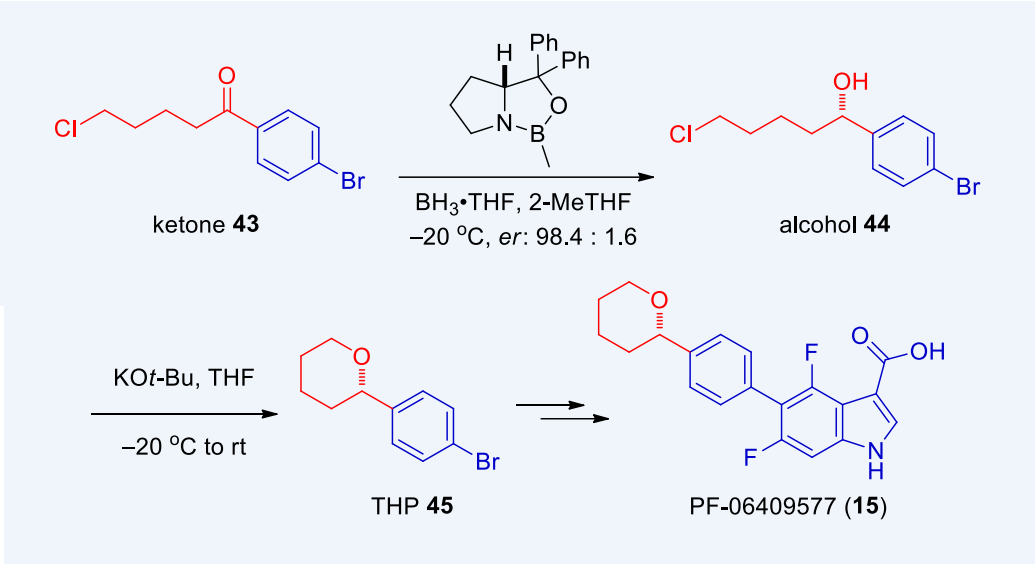
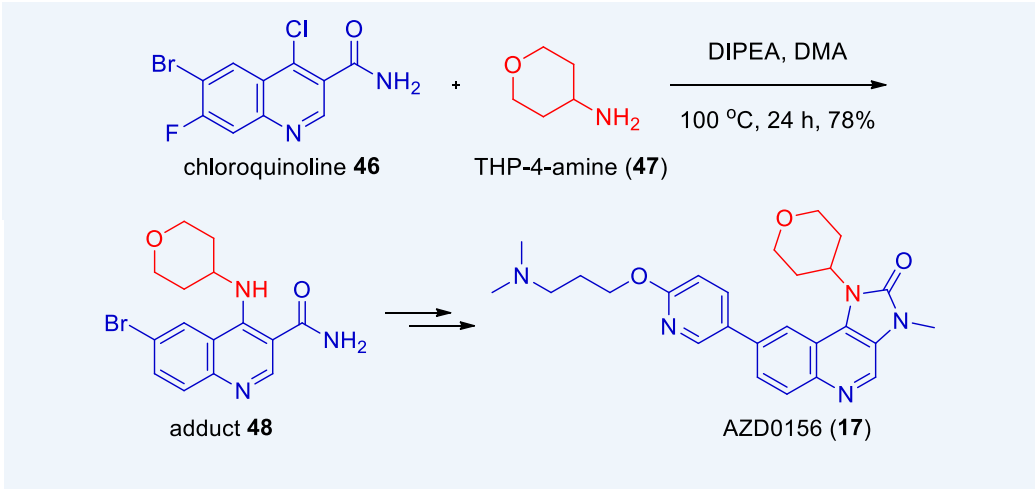
- Novel building blocks designed upon daily monitoring on recent researches and patents
- Keep optimizing cost effective route for better price and sustainable supply
- Fast delivery of custom synthesis
- Enabling technologies of flow chemistry, biocatalysis, photochemistry, electrosynthesis, and fluorination, etc.
- Commercial production with GMP compliance

Pfizer's THP-containing AMPK activator PF-06409577 (**15**) was prepared in kilogram quantities to support its FIH clinical trials. For the reduction of commercially available ketone **43** to make chiral alcohol **44**, Corey–Bakshi–Shibata (CBS) reduction at –20 °C was favored over the Noyori hydrogenation because of the balance of high selectivity, yield, and control over the process. Cyclization of **44** via an intramolecular S_N2 reaction generated THP **45**, which was further manipulated to produce **15**.[22]



An S_NAr reaction between chloroquinoline **46** and the popular THP-4-amine (**47**) was key to construct adduct **48** *en route* to the synthesis of AstraZeneca's ATM kinase inhibitor AZD0156 (**17**).[12]



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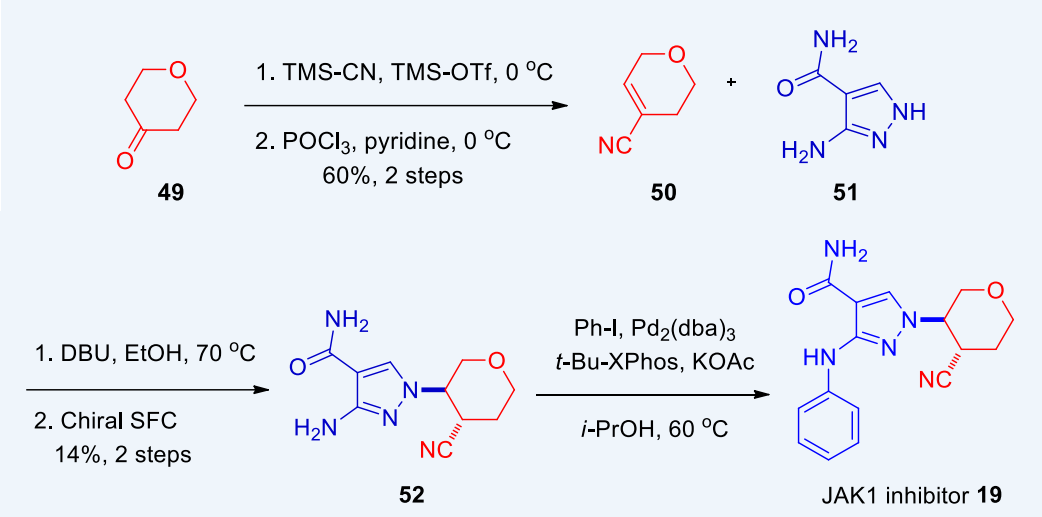
A synthesis of Merck's THP-containing selective JAK1 inhibitor **19** started with treating dihydro-2*H*-pyran-4(3*H*)-one (**49**) with TMS-CN and TMS-OTf to form the cyanohydrin, which was converted to carbonitrile **50** after treating the cyanohydrin with $POCl_3$ in pyridine. Michael addition of pyrazole carboxamide **51** to **50** was induced by DBU to generate a mixture of products, which were separated by chiral SFC to afford enantiomerically pure **52** out of the four possible enantiomers. A Buchwald–Hart coupling between **52** and iodobenzene then produced the JAK1 inhibitor **19**.[13]



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