Bridge-Fused Rings as *m*-Phenyl Bioisosteres

Key Points

- Offering superior physiochemical properties
- A higher degree of saturation for a molecule may increase receptor–ligand complementarity, which should mitigate off-target effects
- Tend to have lower CYP450 inhibitions, thus reducing DDIs tendency
- May have lower melting point and higher solubility

Overview

While saturated *p*-phenyl isosteres are more and more popular in medicinal chemistry, *m*-phenyl and *o*-phenyl fragments do not have many 3-D-rich isosteres. As this review has shown, saturated *m*-phenyl isosteres such as bicyclo[2.2.1]heptane (**B**, see Fig. 2), bicyclo[2.1.1]hexane (**C**), bicyclo[3.1.1]heptane (**D**), and 2-oxabicyclo[2.1.1]hexane (**E**) are gaining popularity. As most 3-D-rich isosteres, they (a) have a higher degree of saturation for a molecule may increase receptor–ligand complementarity, which should mitigate off-target effects; (b) tend to have lower CYP450 inhibitions, thus reducing DDIs tendency; and (c) may have lower melting point and higher solubility; and (d) oxygen-containing isosteres have added advantage of lower lipophilicity.

With many of those bridge-fused intermediates now commercially available, their utility in drug discovery is destined to bear fruits in the future.

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Merits of sp^3-rich Bioisosteres—Escape from Flatland

Today, it is widely known that a compound's high aromatic ring count is correlated to low aqueous solubility, high lipophilicity, high serum albumin binding, high cytochrome protein (CYP)-450 inhibition, and high hERG inhibition.[1] Being 3-dimensional, fully aliphatic bioisosteres for the 2-dimensional phenyl group may offer superior physiochemical properties. Their fraction of saturated carbon (Fsp^3, defined as equation 1)[2] is 1.0 whereas the Fsp^3 for the aromatic phenyl ring is 0.

Fsp^3 = (number of sp^3-hybridized carbon)/(total carbon count) (1)

For *para*-substituted phenyl ring (*p*-Ph), three popular non-classical 3-D-rich isosteres are cubane-1,4-diyl (CUB, see Fig. 1), bicyclo[2.2.2]-octane-1,4-diyl (BCO), and bicyclo[1.1.1]pentane-1,4-diyl (BCP). Their bridgehead lengths decrease in the following order:

p-Ph (2.79 Å, 100%) > CUB (2.72 Å, 96%) > BCO (2.60 Å, 94%) > BCP (1.85 Å, 65%).

While CUB, BCO, and BCP are reviewed elsewhere, here at the end of this chapter, 2-oxabicyclo[2.2.2]octane (**A**) as another 3-D isostere of *p*-phenyl group will be briefly summarized. The additional oxygen atom on **A** lowers the fragment's lipophilicity.

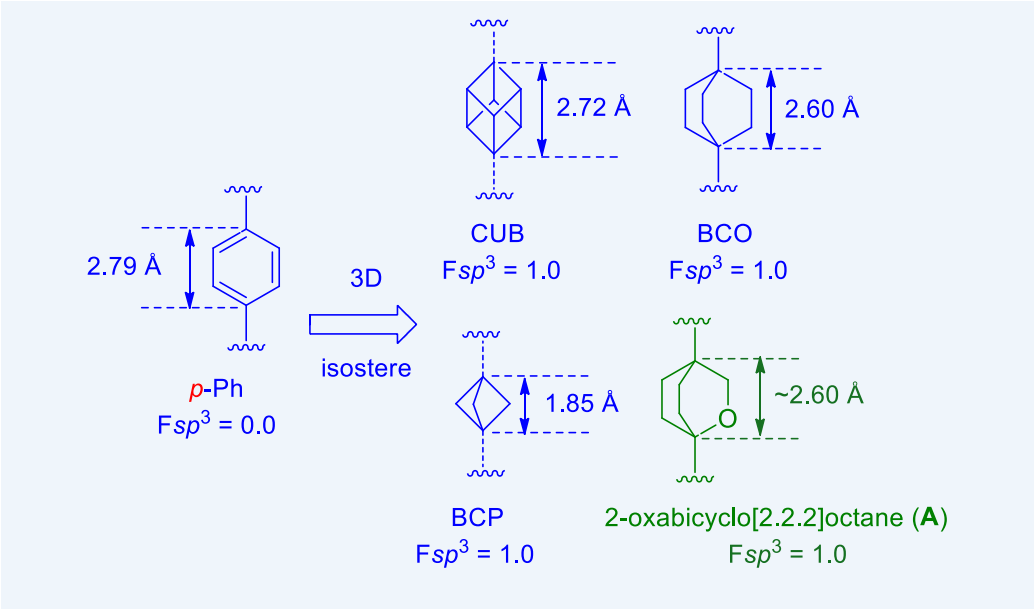


Fig.1. 3-D-rich Isosteres for *p*-Phenyl Fragment

Less known are 3-D-rich bioisosteres for *meta*-substituted phenyl ring (*m*-Ph) and *ortho*-substituted phenyl ring (*o*-Ph).

In literature, at least four bridge-fused rings exist as *m*-phenyl non-classical isosteres: bicyclo[2.2.1]heptane (**B**), bicyclo[2.1.1]hexane (**C**), bicyclo[3.1.1]heptane (**D**), and 2-oxabicyclo[2.1.1]hexane (**E**).[3] Again, the additional oxygen atom on **E** lowers the lipophilicity of the fragment.

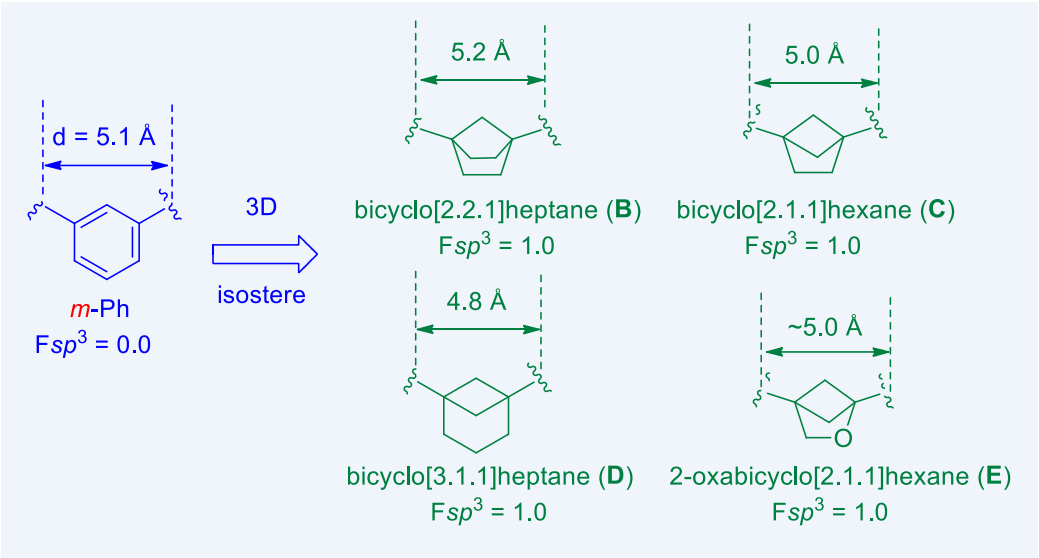


Fig.2. 3-D-rich Isosteres for the *m*-Phenyl Fragment

Whereas all bridge-fused aliphatic isosteres **A**–**E** are potentially subject to CYP450 metabolism, they have several advantages as drug fragments with higher F*sp*^{3} values:

a. A higher degree of saturation for a molecule may increase receptor–ligand complementarity, which should mitigate off-target effects.[1] Saturation (compounds with higher F*sp*^{3} values) also mitigates a drug's promiscuity even for compounds containing ionizable amines that are more promiscuous than neutral ones;[4]

b. Compounds with higher F*sp*^{3} values tend to have lower CYP450 inhibitions, thus reducing drug–drug interaction (DDI) tendency;[4]

c. Disruption of planarity, hence aromaticity, results in lower melting point and higher solubility;

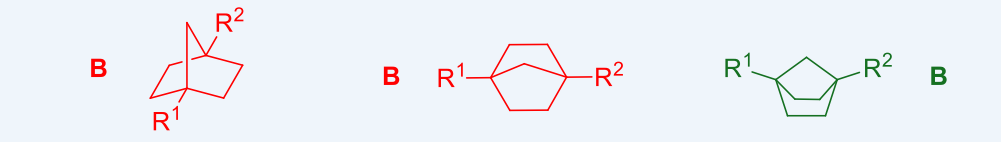
d. Oxygen-containing isosteres have added advantage of lower lipophilicity.

Unfortunately, the last few decades saw cLog*P* getting higher and F*sp*^{3} lower when proper attention was not paid to drugs' physiochemical properties. In order to increase our chances of success in drug discovery, it is essential to get cLog*P* down and F*sp*^{3} up. Employing 3-D-rich isosteres to replace the phenyl fragment is one-step closer to the right

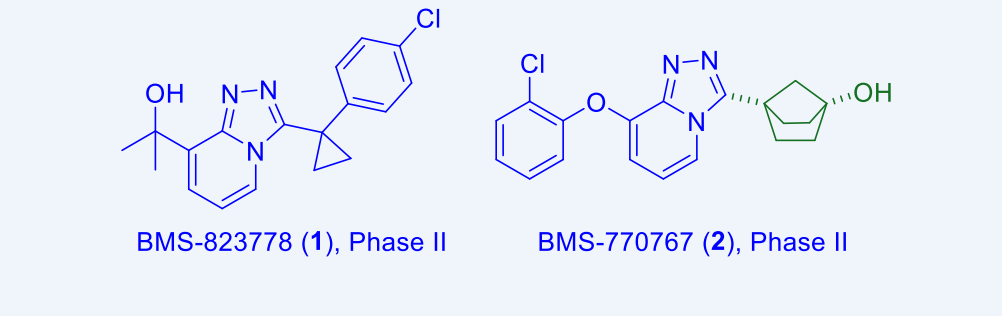
direction.[5] After all, complexity, as measured by both F*sp*^{3} and the presence of chiral centers, impacts the probability of success in the clinic.

3-D-rich Bioisosteres for Phenyl Ring in Drug Discovery

Bicyclo[2.2.1]heptane (**B**) has an interesting geometry. It is most frequently drawn as two red structures below, giving an illusion that the structure is similar to the *para*-phenyl geometry. In fact, this is incorrect because the ring strain renders its geometry closer to the green structure, which is similar to the *meta*-phenyl geometry.



Fragment **B** made an appearance as a substituent of BMS's 11β-HSD-1 inhibitors. 11β-Hydroxysteroid dehydrogenase-type 1 (11β-HSD-1), an enzyme expressed at high levels in the liver and adipose tissue, catalyzes the conversion of inert cortisone to the active glucocorticoid hormone cortisol. Therefore, 11β-HSD-1 inhibitors are actively pursued as pharmacological agents to treat various metabolic diseases. BMS has advanced several 11β-HSD-1 inhibitors with the 1,2,4-triazolopyridine (TZP) core structures to clinical trials for treating patients afflicted with type 2 diabetes, obesity, and the metabolic syndrome. One of them is BMS-823778 (**1**)[6] and the other is BMS-770767 (**2**).[7] Both of them are now in phase II clinical trials. The latter contains fragment **B** as bicyclo[2.2.1]heptanol, which may be viewed as a 3-D rich isostere of an *m*-phenyl ring.



WAY-100635 (**3**) is a potent and selective 5HT$_{1A}$ receptor antagonist with potential as a drug therapy or marker for studying pathophysiology of neuropsychiatric disorders. In order to investigate changes of 5HT$_{1A}$ receptor after binding to WAY-100635 (**3**) using single photon emission computerized tomography (SPECT), **3**'s bulkier analog bicyclo[2.2.1]heptanyl iodide **4**, as well as the corresponding bridge-fused rings such as admantanyl, cubanyl, and bicycle[2,2,2]octanyl

Featured Products

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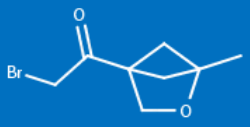
PBLJ0152

PBSQ600065

Featured Products

PBSQ600069



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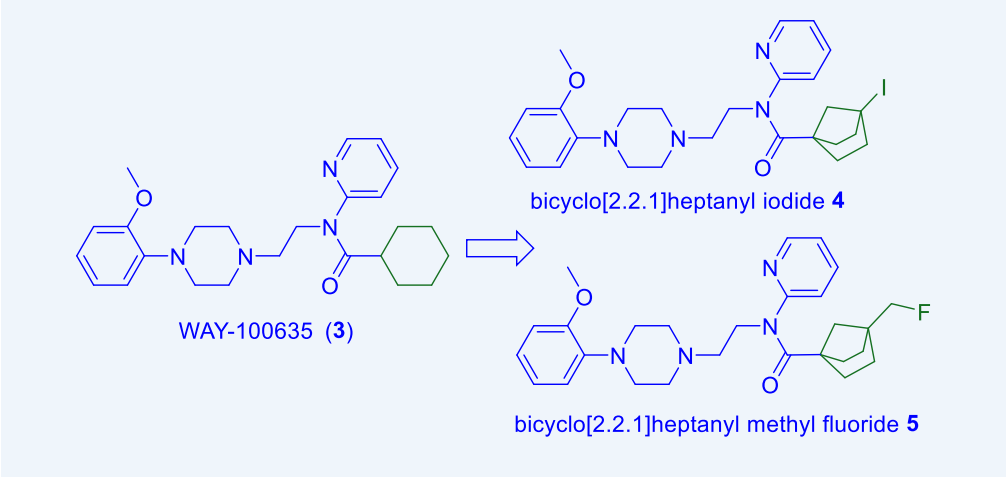
(BCO) analogs were prepared and evaluated. Although compound **4** and other three bulky analogs showed a low propensity for amide hydrolysis, their brain uptake and the specificity for those radioligands were significantly lower than the parent molecule **3**. Therefore, those designed tracers are not suitable for SPECT imaging.[8]

Further efforts to make radiolabeled $5HT_{1A}$ receptor ligands led to the synthesis of bicyclo[2.2.1]heptanylmethyl fluoride **5** and its corresponding bridge-fused rings such as admantanyl, cubanyl, and bicycle[2,2,2]octanyl (BCO) analogs. Among the four analogs, compound **5** was reasonably selective and the cubanyl analog showed a suitable metabolic stability. This endeavor provided a promising starting point for the synthesis of the corresponding ^{18}F-labeled position emission tomography (PET) analogs.[9]



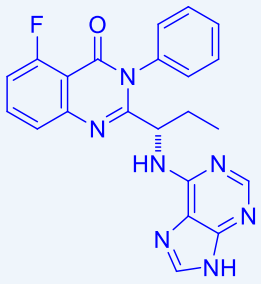
Bicyclo[2.1.1]hexane (**C**) as an *m*-phenyl isostere began to appear only very recently. One of them was among Incyte's phospoinositide-3-kinase (PI3K) inhibitors. Deregulation of the well-known PI3K pathway has been implicated in numerous pathologies such as cancer, diabetes, thrombosis, rheumatoid arthritis, and asthma. Two PI3K inhibitors have been approved by the FDA. One is Gilead's idelalisib (Zydelig, **6**), which is a PI3Kδselective inhibitor and the other is Bayer's copanlisib (Aliqopa, **7**) that is a pan-PI3K inhibitor.[9] In a 2017 patent, Incyte's bicyclo[2.1.1]hexanyl nitrile **8** was claimed to be a selective PI3Kγ inhibitor with an IC_{50} value less than 100 nM.[10] Ironically, bicyclo[3.1.1]heptane (**D**) has made a rare appearance, also in Incyte's 2017 patent on their PI3K inhibitors in the form of bicyclo[3.1.1]heptanyl nitrile **9**.[9] The same goes to 2-oxabicyclo[2.1.1]hexane (**E**), which was represented by 2-oxabicyclo[2.1.1]hexanyl nitrile **10** on the patent.[11] For direct comparison between compounds **8** and **10**, the latter is likely to have better physiochemical properties because the oxygen atom helps reducing the molecule's lipophilicity.

Featured Products

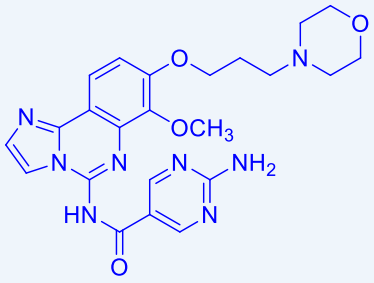
PBWB8143

PBLJ0130

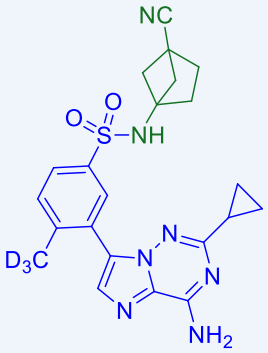
PBLJ0149



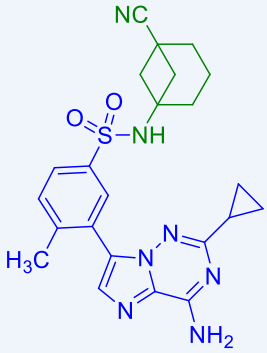
idelalisib (Zydelig, **6**)
Gilead, 2014
PI3Kδ inhibitor



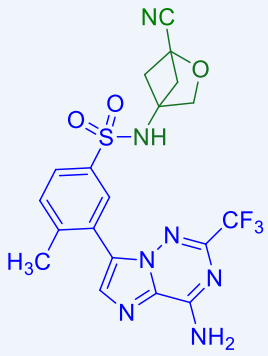
copanlisib (Aliqopa, **7**)
Bayer, 2017
pan-PI3K inhibitor



bicyclo[2.1.1]hexanyl nitrile **8**
PI3Kγ IC_{50} < 100 nM



bicyclo[3.1.1]heptanyl nitrile **9**



2-oxabicyclo[2.1.1]hexanyl nitrile **10**

Now, back to *p*-phenyl isostere 2-oxabicyclo[2.2.2]octane (**A**), which is more popular than fragment **B**–**E** in drug discovery. It is an analog of 2-oxabicyclo[2.1.1]hexane (**E**) with an additional carbon atom and different substitution trajectory. In one case, fragment **E** was employed as a replacement as piperidine to discover novel bacterial topoisomerase inhibitors.[12]

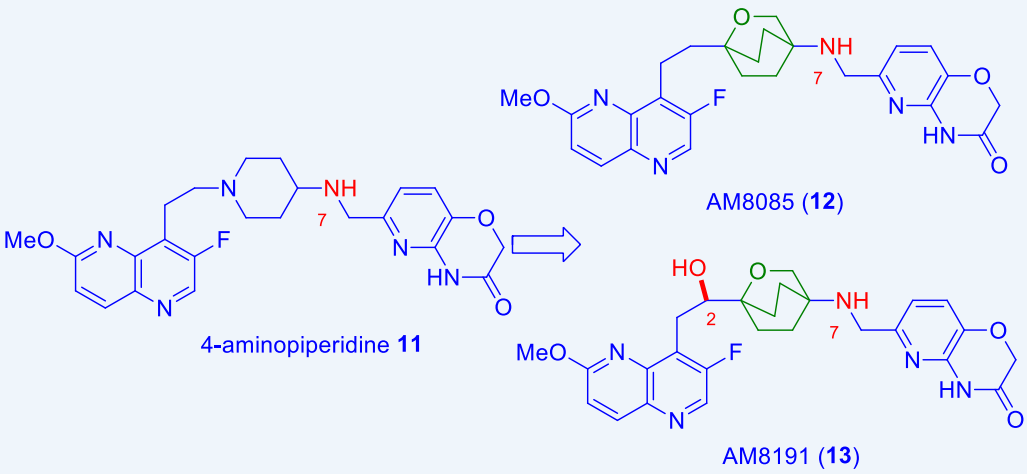
The best known type II topoisomerase inhibitor is probably Bayer's ciprofloxacin (Cipro) among all antibacterials. Much advance has been made to discover new topoisomerase inhibitors, which led to the discovery of 4-aminopiperidine **11**. The hallmark of this linker is the strategic placement of a basic nitrogen atom at position-7 that shows a salt-bridge interaction with Asp83 in the X-ray crystal structure. Employing the 2-oxabicyclo[2.1.1]hexane (**E**) linker provided AM8085 (**12**) with reduced basicity and attenuated hERG activity. Further addition of a hydroxyl group at C-2 gave rise to AM8191 (**13**), which had reduced hERG activity by 30-fold and improved solubility by over 100-fold with minimum loss of antibacterial potency and spectrum.[12]

Featured Products

PBSQ600030-1

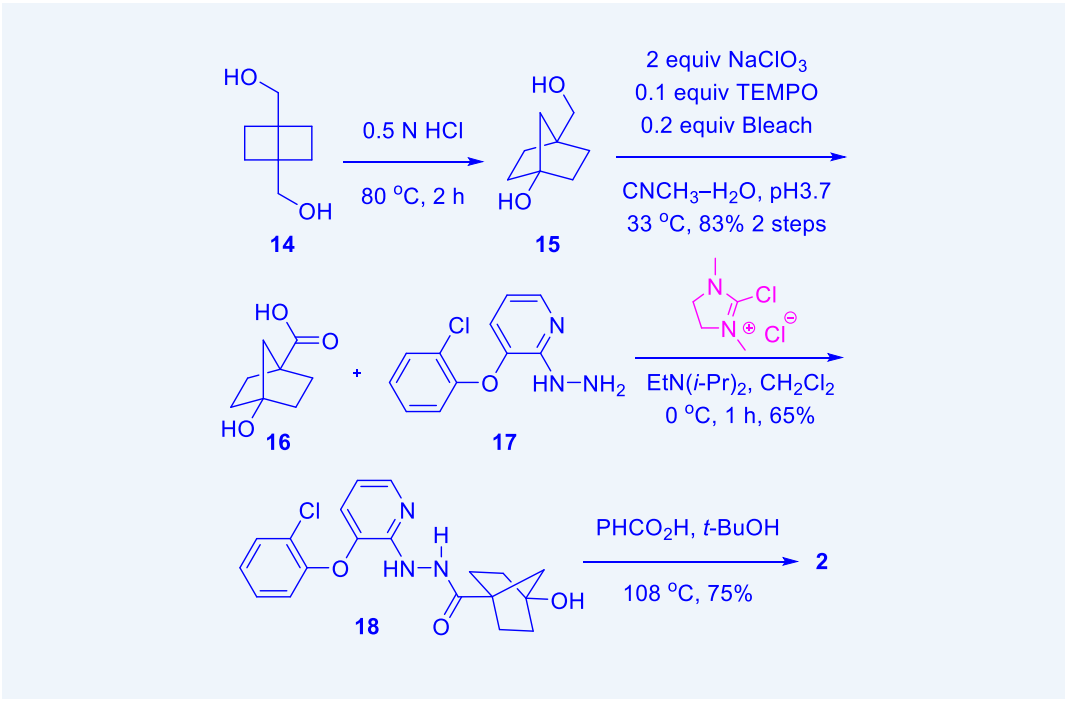
PBSQ600047

PBZ3820



Synthesis of Some Drugs Containing 3-D-rich Bioisosteres for Phenyl Ring

BMS's process procedure to prepare TZP 11HSD-1 inhibitor BMS-770767 (**2**) employed known bicyclo[2.2.0]hexane-1,4-diyldimethanol (**14**)[13] as its starting material. Acid-promoted rearrangement of **14** led to the desired fragment bicyclo[2.2.1]heptane (**B**) in the form of diol **15**, which was readily oxidized to the corresponding acid **16** under environmentally friendly conditions. The union between acid **16** and hydrazine **17** was mediated by 2-chloro-1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium chloride as the coupling agent to provide adduct **18**. Simply treating hydrazide **18** with benzoic acid delivered BMS-770767 (**2**) in good yield.[14]



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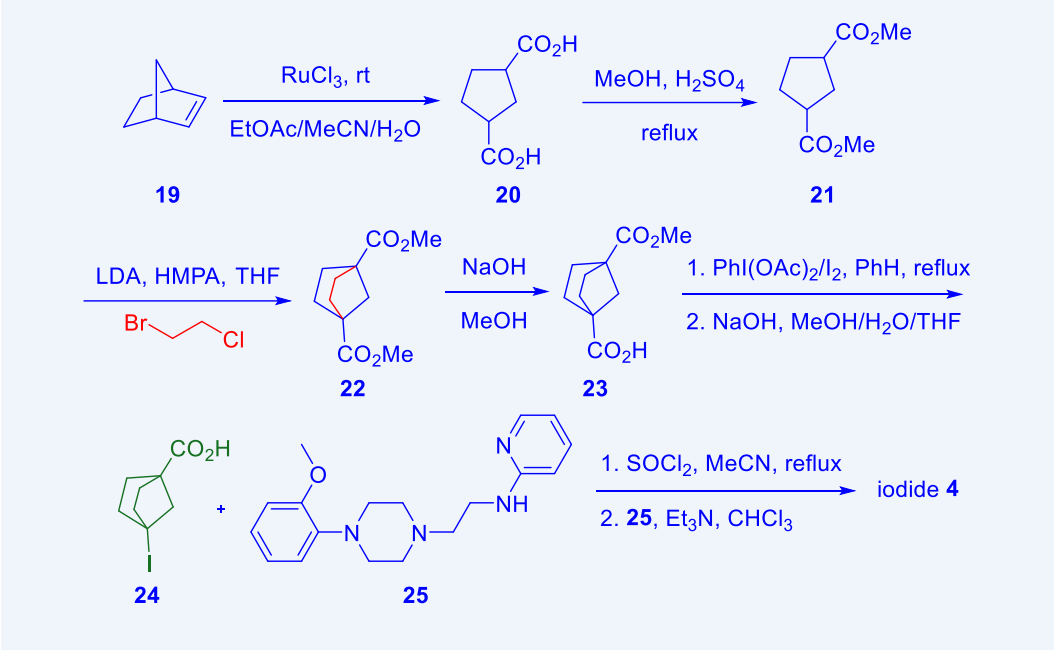
Synthesis of radiolabeled ligand bicyclo[2.2.1]heptanyl iodide **4** began with assembly of fragment **B** as intermediate iodide **24**. Thus, $RuCl_3$-mediated oxidation of norbornene (**19**) afforded di-acid **20**, which was subsequently transformed to di-ester **21**. Alkylation of **21** with 1-bromo-2-chloroethane gave rise to bridge-fused di-ester **22**. After mono-saponification to give **23**, its acid functionality was converted to iodide **24** via a hypervalent iodine iodinative decarboxylation. After converting the acid to the corresponding acid chloride, it was coupled with amine **25** to deliver iodide **4**.[8]



Incyte's preparation of 2-oxabicyclo[2.1.1]hexanyl nitrile **10** as a PI3K inhibitor commenced with production of fragment **E** (2-oxabicyclo-[2.1.1]hexane) in the form of amino-nitrile **30**. Therefore, after protection of amino-alcohol **26** to afford **27**, its alcohol functionality was oxidized employing the Dess–Martin reagent to produce aldehyde **28**. After converting aldehyde **28** to oxime **29**, it was transformed to the key intermediate amino-nitrile **30** upon treatment with methanesulfonyl chloride. Simple exposure of amino-nitrile **30** to pre-fabricated sulfonyl chloride **31** then delivered nitrile **10**.[11]

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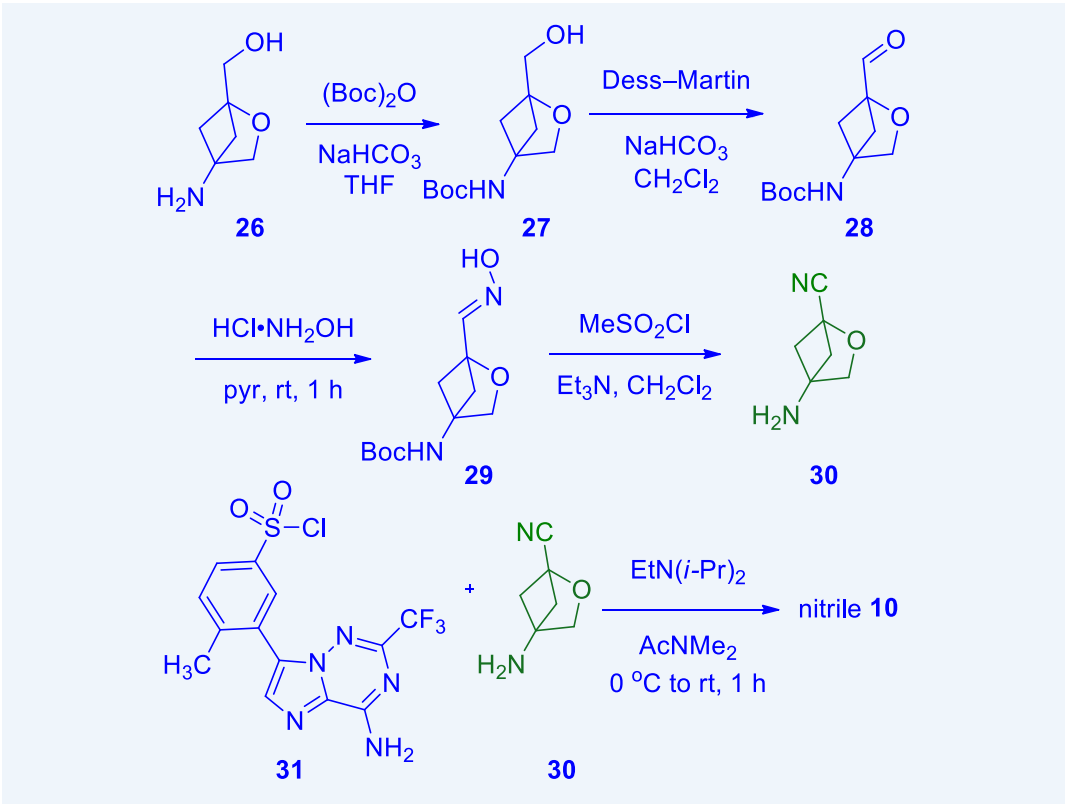
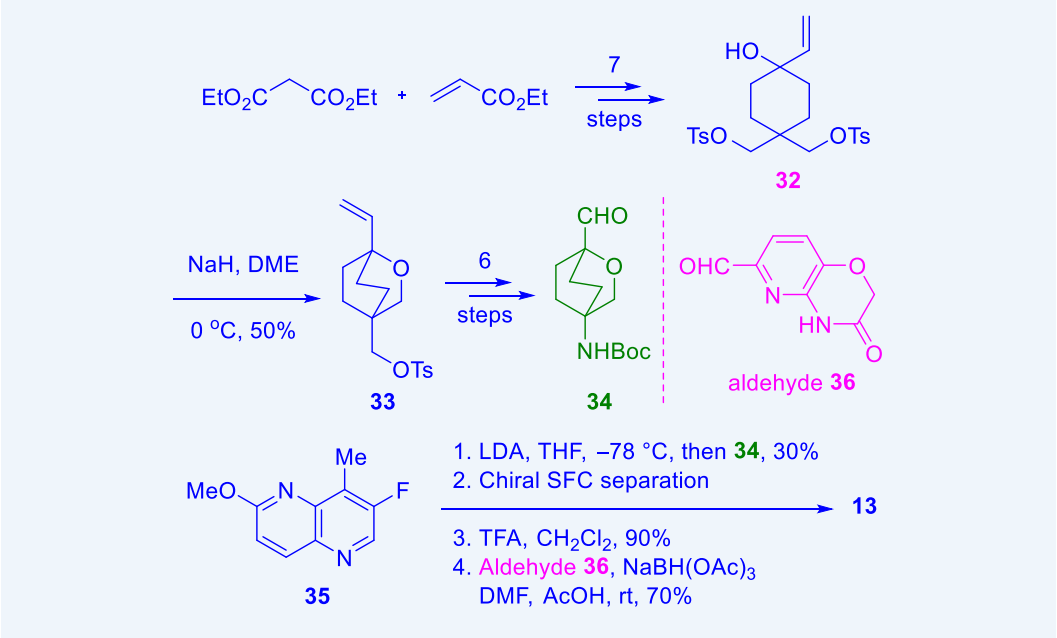


Synthesis of AM8191 (**13**) as a bacterial topoisomerase inhibitor involved a lengthy sequence to prepare fragment **A** (14 steps in total) in the form of aldehyde **34**. As shown below, it took seven steps to assemble intermediate **32** as a bis-tosylate. Exposure of **32** to NaH effected formation of bridge-fused **33**, which was converted to aldehyde **34** in an additional six steps. After deprotonation of the methyl group on aza-quinoline **35**, the resulting carboanion was quenched with aldehyde **34** to afford two enantiomeric alcohols. After SFC separation, one of the enantiomers was deprotected and coupled with aldehyde **36** via reductive amination to deliver AM8191 (**13**).[12]



References

1. Ritchie, T. J.; Macdonald, S. J. F. *Drug Discov. Today* **2009,** *14*, 1011–1020.
2. Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem*. **2009,** *52*, 6752–6756.
3. Mykhailiuk, P. K. *Org. Biomol. Chem.* **2019,** *17*, 2839–2849.
4. Lovering, F. *MedChemCom* **2013,** *4*, 515–519.
5. Auberson, Y. P.; Brocklehurst, C.; Furegati, M.; Fessard, T. C.; Koch, G.; Decker, A.; La Vecchia, L.; Briard, E. *ChemMedChem* **2017,** *12*, 590–598.
6. Li, J.; Kennedy, L. J.; Walker, S. J.; Wang, H.; Li, J. J.; Hong, Z.; O'Connor, S. P.; Ye, X.-y.; Chen, S.; Wu, S.; et al. *ACS Med. Chem. Lett.* **2018,** *9*, 1170–1174.
7. Maxwell, B. D.; Bonacorsi, S. J., Jr. *J. Label. Comp. Radiopharm.* **2016,** *58*, 657–664.
8. Al Hussainy, R.; Verbeek, J.; van der Born, D.; Braker, A. H.; Leysen, J. E.; Knol, R. J.; Booij, J.; Herscheid, J. D. M. *J. Med. Chem.* **2011,** *54,* 3480–3491.
9. Al Hussainy, R.; Verbeek, J.; van der Born, D.; Booij, J.; Herscheid, J. D. M. *Eur. J. Med. Chem.* **2011,** *46,* 5728–5735.
10. Perry, M. W. D.; Abdulai, R.; Mogemark, M.; Petersen, J.; Thomas, M. J.; Valastro, B.; Eriksson, A. W. *J. Med. Chem.* **2019,** *62*, 4783–4814.
11. Buesking, A. W.; Sparks, R. B.; Combs, A. P.; Douty, B.; Falahatpisheh, N.; Shao, L.; Shepard, S.; Yue, E. W. (Incyte) WO2017223414 (2017).
12. Singh, S. B.; Kaelin, D. E.; Wu, J.; Miesel, L.; Tan, C. M.; Meinke, P. T.; Olsen, D.; Lagrutta, A.; Bradley, P.; Lu, J.; et al. *ACS Med. Chem. Lett.* **2014,** *5*, 609–614.
13. Lantos, I.; Ginsburg, D. *Tetrahedron* **1972,** *28*, 2507–2519.
14. Qian, X.; Zhu, K.; Deerberg, J.; Yang, W. W.; Yamamoto, K.; Hickey, M. R. (BMS) US9580420 (2016).