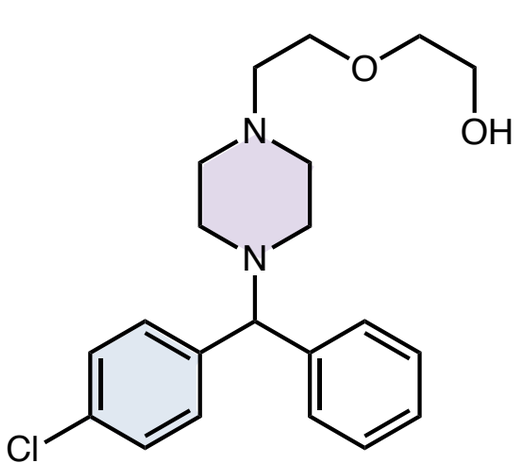
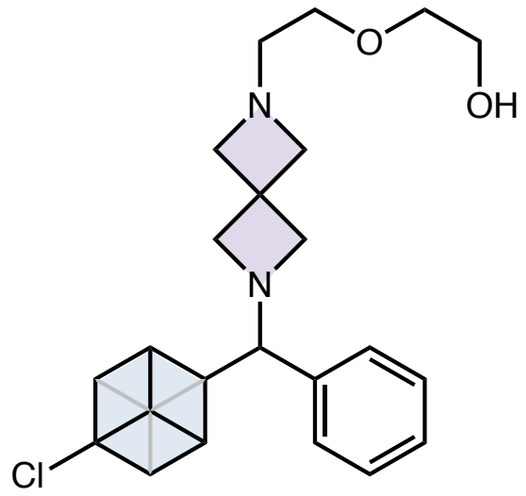
Bioisosteres of Common Functional Groups



Hydroxyzine



Ian Perry

MacMillan Group Meeting

May 16th, 2019

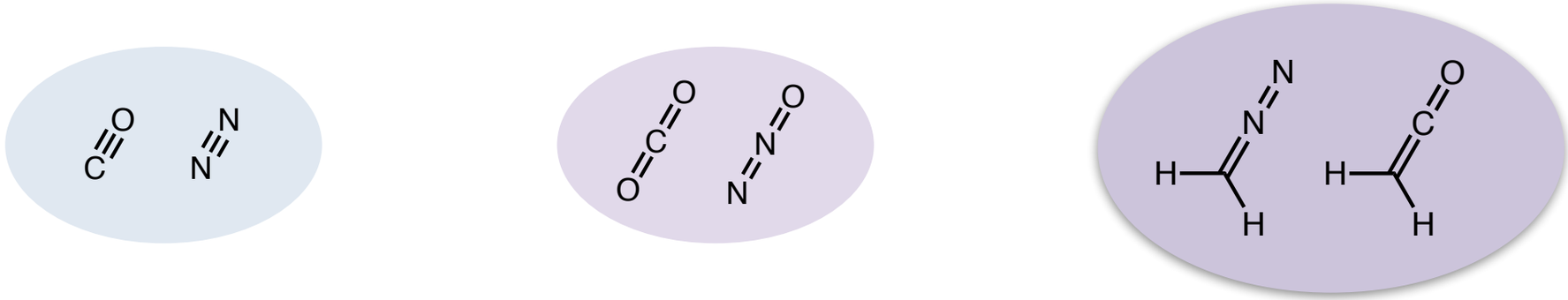
Introduction to Isosterism

Irving Langmuir

1932 Nobel Prize in Chemistry *for Discoveries in Surface Chemistry*

JACS 1919: “The Arrangement of Electrons in Atoms and Molecules”

JACS 1919: “Isomorphism, Isosterism and Covalence

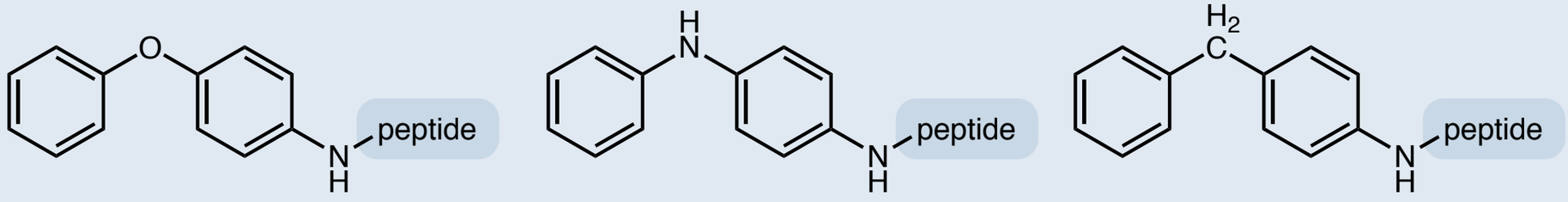


Compounds showing a relationship to one another like that between carbon dioxide and nitrous oxide will be called isosteric compounds, or isosteres.

Langmuir, I. *J. Am. Chem. Soc.*, **1919**, 41, 1543

Introduction to Bioisosterism

1932: Erlenmeyer Demonstrates Bioisosterism of some of Langmuir's Isosteres -
Antibodies were found to not discriminate in the binding of several artificial antigens



1951: H. L. Friedman coins "Bioisostere" - Molecules or groups "which fit the broadest definition of isosteres and have the same type of biological activity."

Erlenmeyer, H., Berger, E., *Biochem Z.* **1932**, 252, 22
Friedman, H. L. *NASNRS.*, **1951**, 206, 358

Talk Outline

Part 1 - Classical Bioisosteres

3 case studies of isosteric atom substitution:

Procaine vs. Procainamide

Haloperidol vs. Silahaloperidol

The importance of Celebrex-CH_3

Part 2 - Nonclassical Bioisosteres

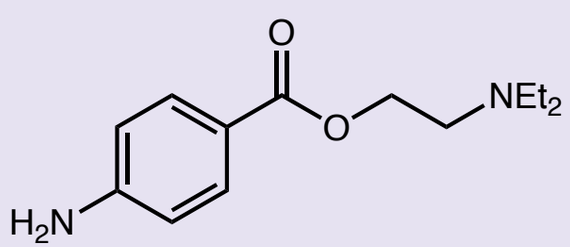
Common examples of
Nonclassical Bioisosteres

Strained (hetero)cycles as
Bioisosteres

Bioisosteres of Aromatic Rings

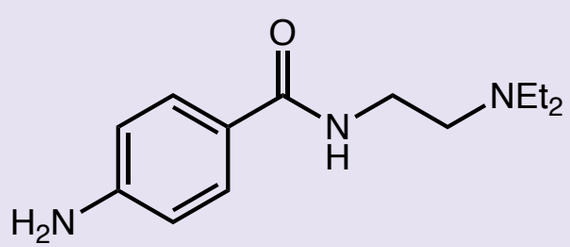
examples of bioisosterism are abundant in medicinal chemistry, this talk is not comprehensive.
For a more detailed review, see:
Meanwell, N. A. *J. Med. Chem.* **2011**, 54, 2529

Case Study in Classical Bioisosteres: Procaine vs. Procainamide



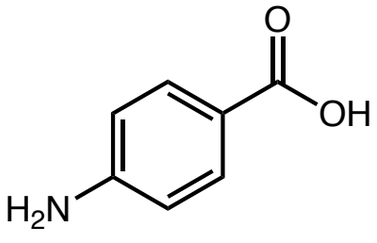
procaine

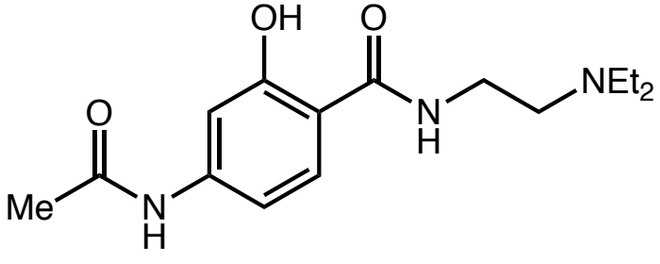
substitution of
a divalent atom



procainamide

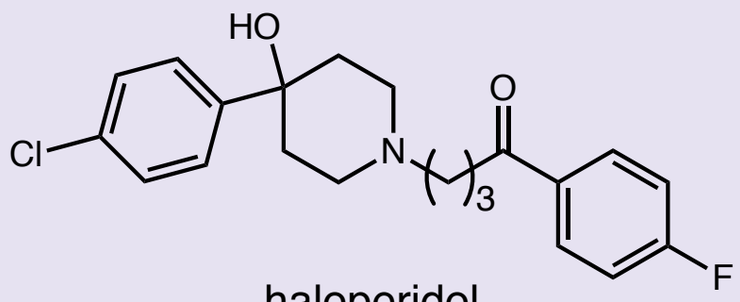
Analgesic		Analgesic
Nav channel blocker		Nav channel blocker
Metabolsim via ester hydrolysis *(pseudocholinesterase)*		***Metabolsim via Acylation or oxidation*** *(P450)*





Imming, P., Sinning, C., Meyer, A. *Nat. Rev. Drug Discov.* **2006**, 6, 126

Case Study in Classical Bioisosteres: Haloperidol vs. Sila-haloperidol



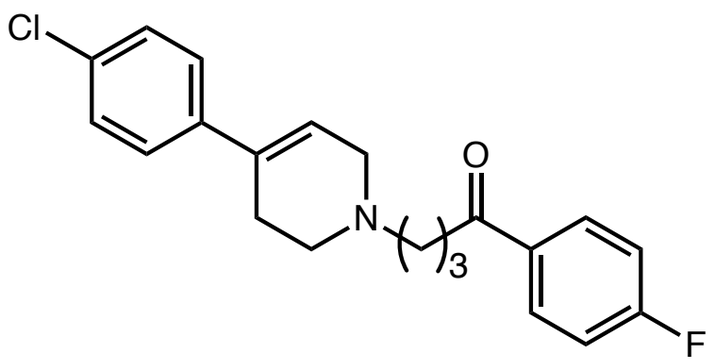
haloperidol

Antipsychotic

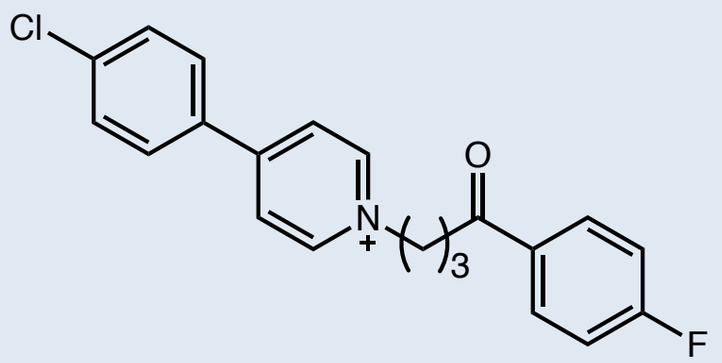
Developed for the treatment of neuropsychiatric disorders

Alleviates hallucinations and delusions
associated with schizophrenia

Irreversible side effects associated with long-term use



aromatization

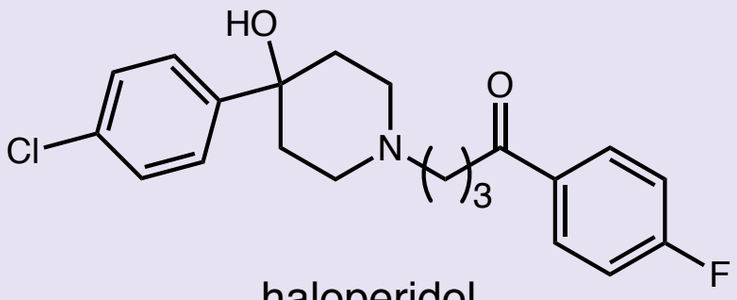


HPP^+

neurotoxin associated with dyskinesia

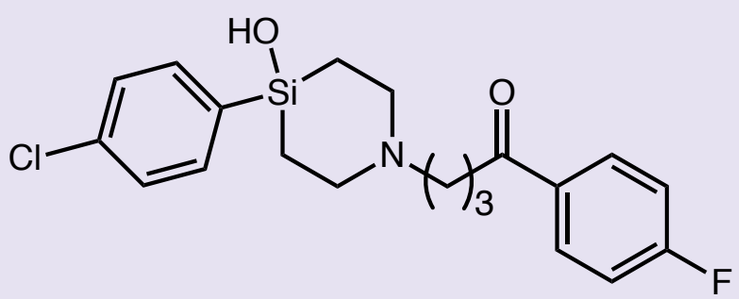
Janssen, P. A. J., *J. Med. Chem.* **1958,** 1, 105
Tacke, R. *et al. ChemMedChem* **2008**, 3, 152

Case Study in Classical Bioisosteres: Haloperidol vs. Sila-haloperidol



haloperidol

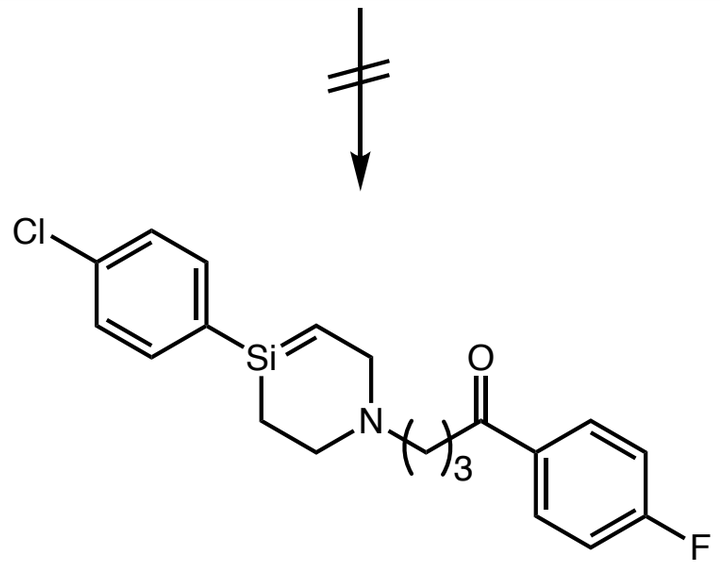
Antipsychotic



Silahaloperidol

substitution of carbon for silicon has limited effect on pharmacokinetic properties

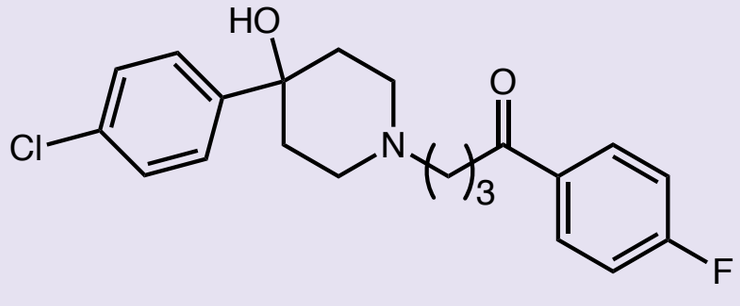
strong Si-OH bond and weak Si=C bond disfavors elimination compared to carbon analogue



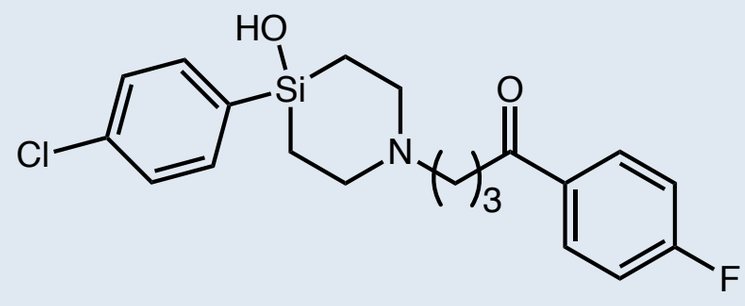
no detected neurotoxic metabolites

Janssen, P. A. J., *J. Med. Chem.* **1958,** 1, 105
Tacke, R. *et al. ChemMedChem* **2008**, 3, 152

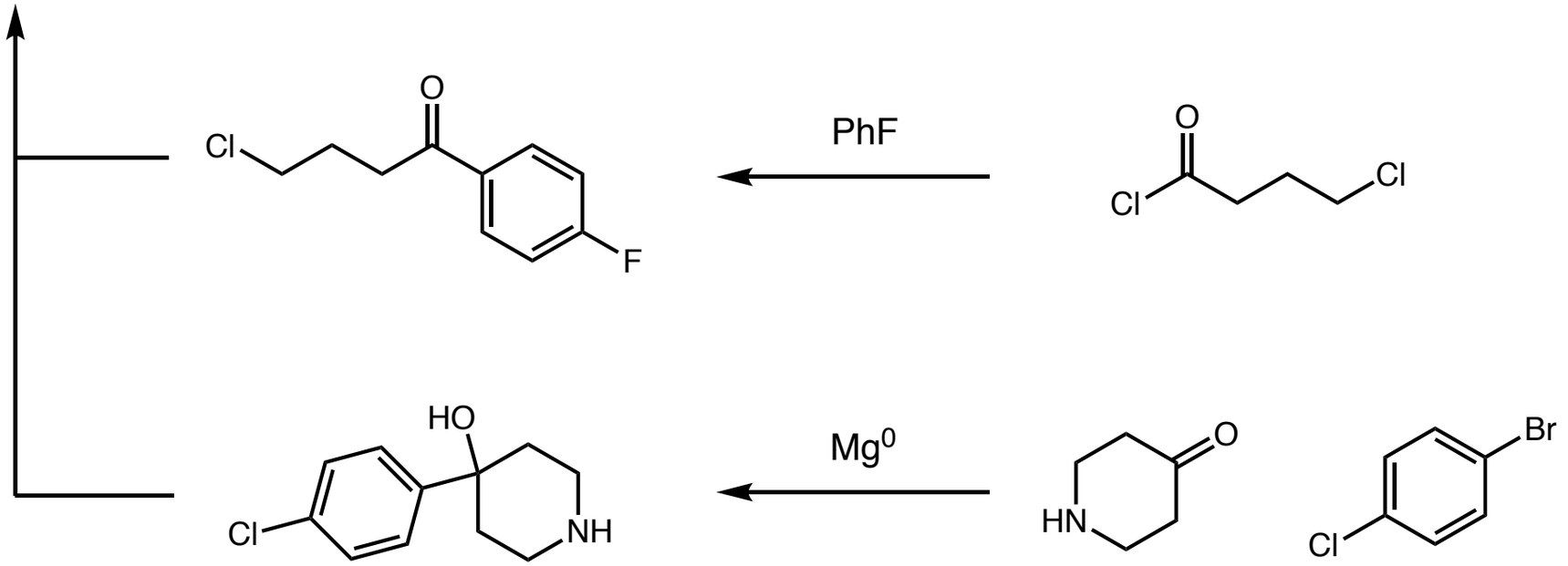
Case Study in Classical Bioisosteres: Haloperidol vs. Sila-haloperidol



Haloperidol



Silahaloperidol



Janssen, P. A. J., *J. Med. Chem.* **1958,** 1, 105
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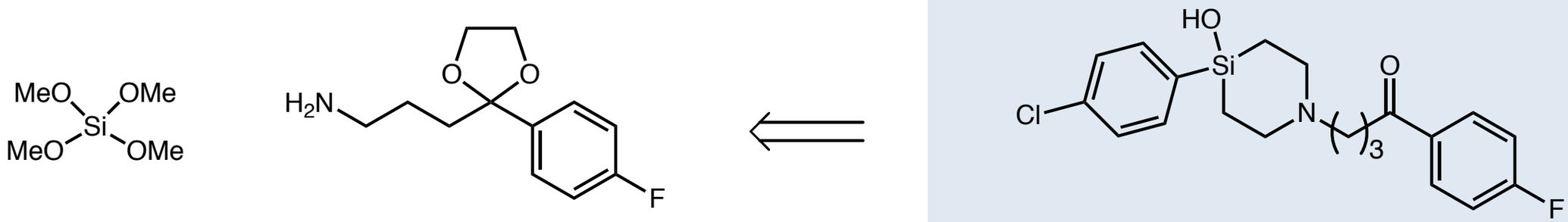
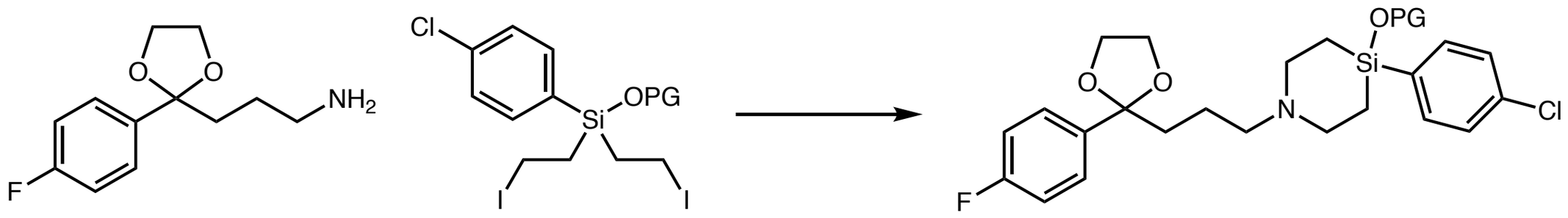


Silahaloperidol

12 steps, *7% overall yield*

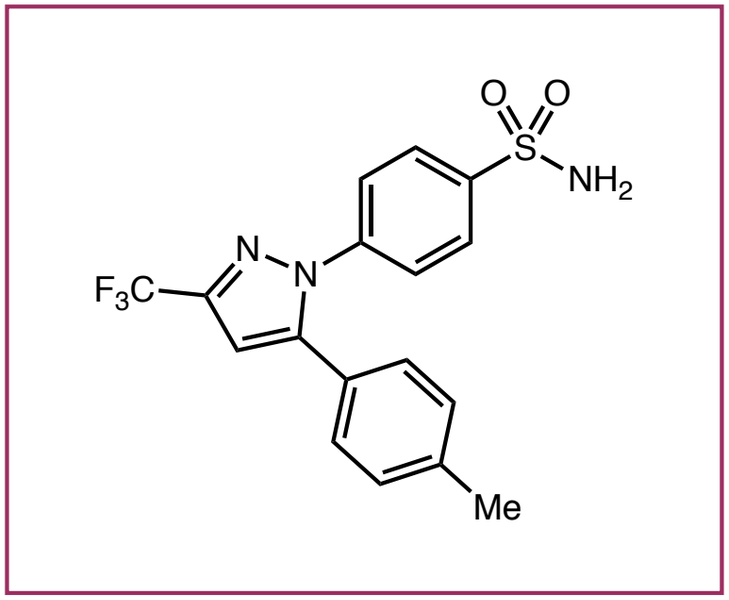
key silacycle formation



incorporation of ***non-native functionality*** *as bioisosteres often involves lengthy syntheses*

Janssen, P. A. J., *J. Med. Chem.* **1958,** 1, 105
Tacke, R. *et al. ChemMedChem* **2008**, 3, 152

Case Study in Classical Bioisosteres: Celecoxib

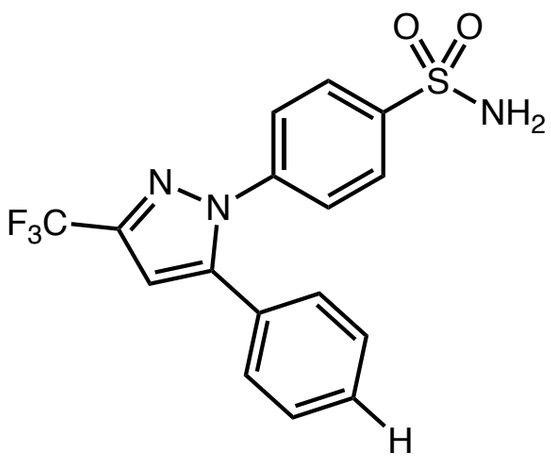


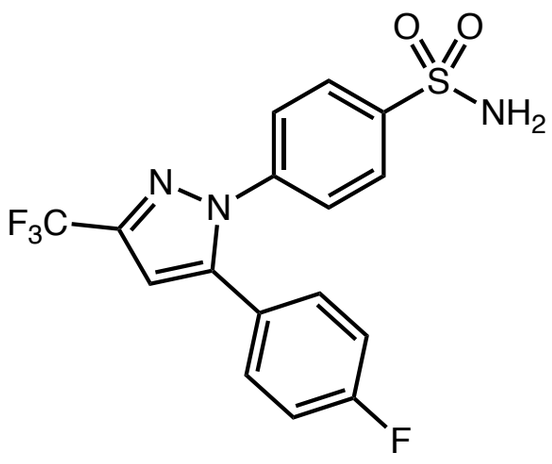
NSAID developed by Pfizer

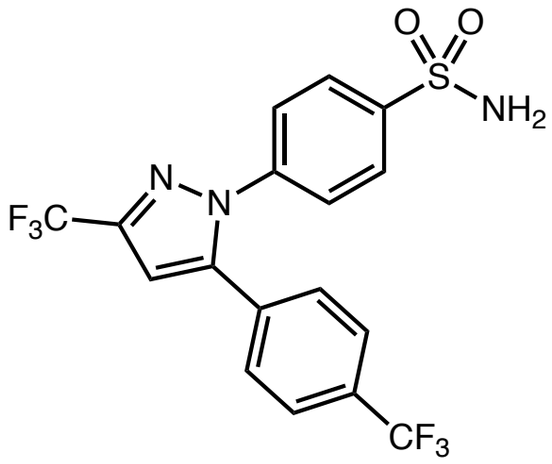
Selective COX-2 inhibitor

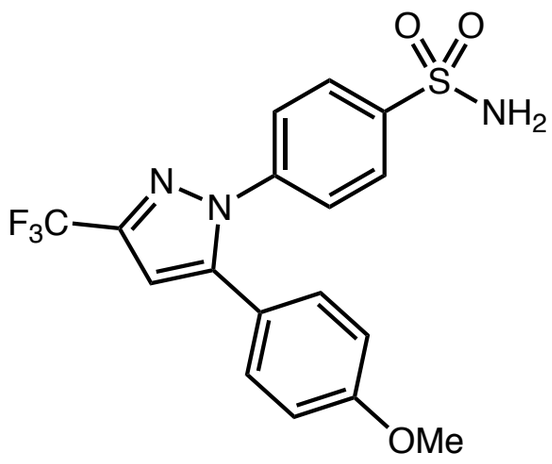
Marketed for the treatment of Arthritis

μM level IC_{50} for COX-2 in all cases





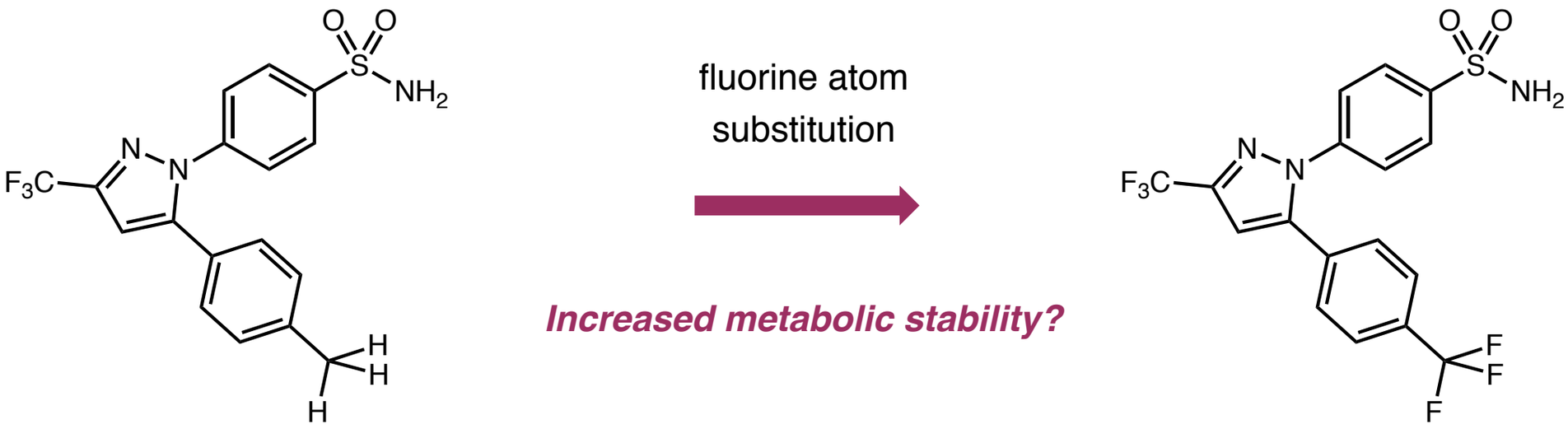




high specificity for COX-2 vs. COX-1

Penning, T. D., *J. Med. Chem.* **1997**, 40, 1347

Case Study in Classical Bioisosteres: Celecoxib



isosteric substitution that removes benzylic metabolic handle results in undesirable pharmacokinetic properties

For an excellent review on rational incorporation of fluorine as a hydrogen isostere, see:

Meanwell, N. A. *J. Med. Chem.* **2018**, *61,* 5822

Penning, T. D., *J. Med. Chem.* **1997**, 40, 1347

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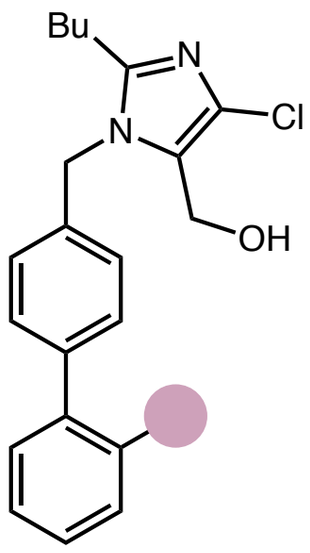
Bioisosteres of Aromatic Rings

Introduction to Nonclassical Bioisosteres

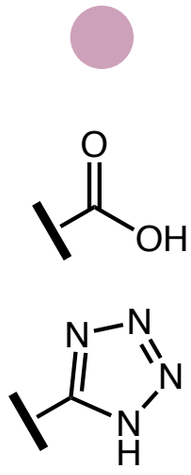
Unlike their classical counterparts, nonclassical bioisosteres do not conform to Langmuir's broad definition of "isostere."

Nonclassical bioisosteres are groups capable of emulating the steric or electronic profile of the original functional group

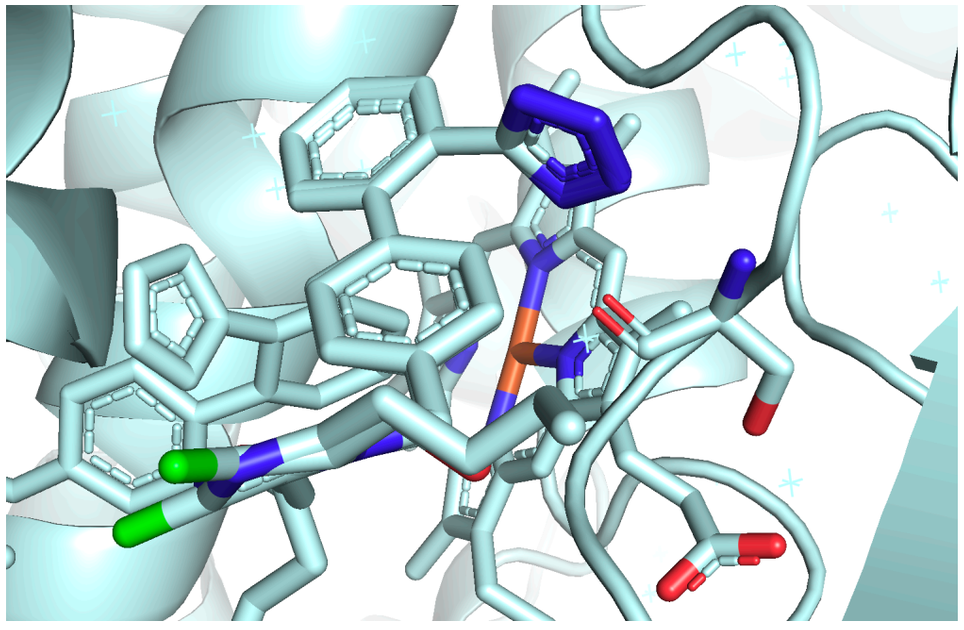


losartan scaffold

high blood pressure



	pKa	IC_{50} [μM]	dose [mg/kg]
	4.2	0.23	3
	4.5	0.019	0.8



Ballatore, C., Huryn, D. M. & Smith, A. B. *ChemMedChem* **2013**, 8, 385

Introduction to Nonclassical Bioisosteres

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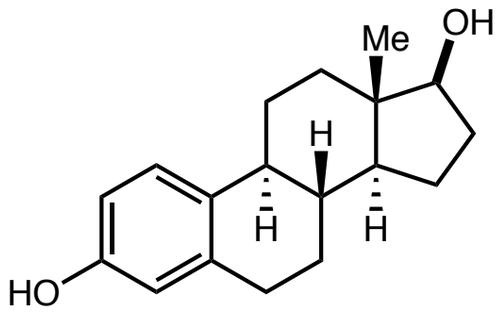
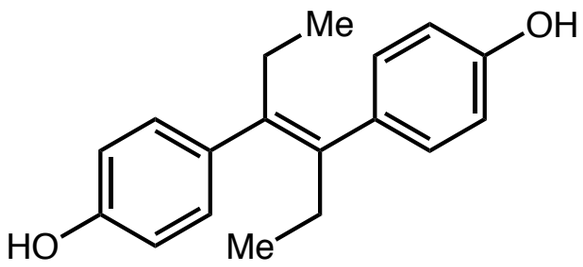


estrogen
primary female sex hormone



diethyl stilbestrol
"synthetic estrogen"

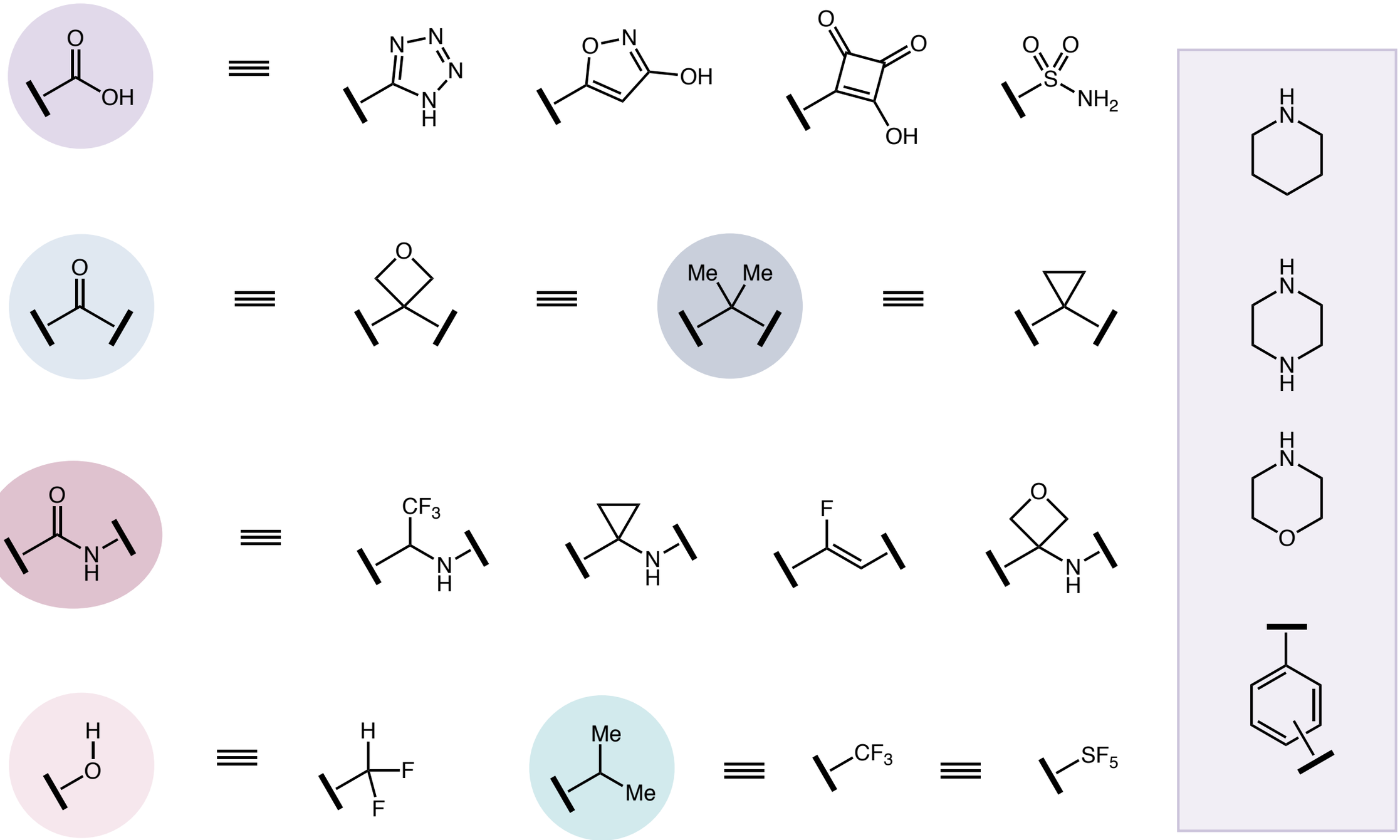
Prescribed to pregnant women
1940-1970

Thought to prevent miscarriages
in pregnant women with low estrogen

Use discontinued after DES linked to development of clear cell carcinoma by women exposed *in utero*

Am. J. Med., **1976**, 10, 1107

Bioisosteres of Common Functional Groups

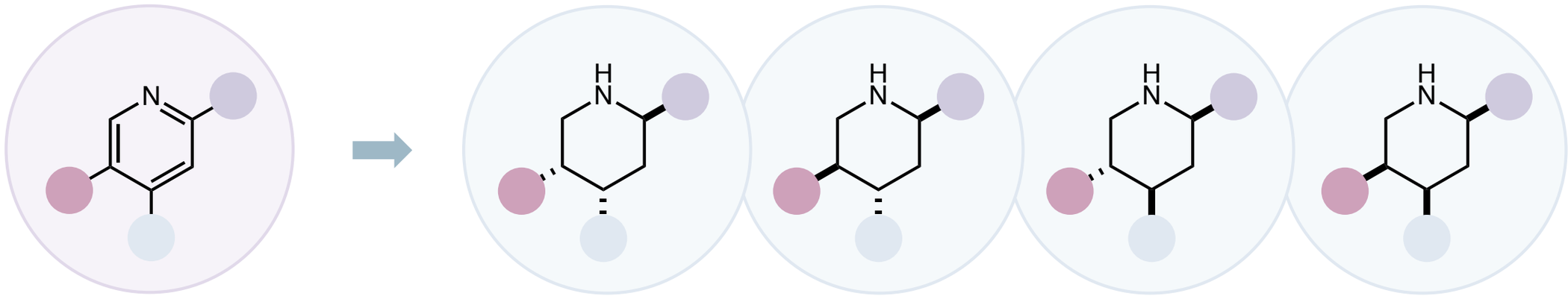


…and many more

Escaping Flatland

Incorporating highly saturated fragments in drug discovery correlates with clinical success

Greater three-dimensionality imparts higher specificity in binding

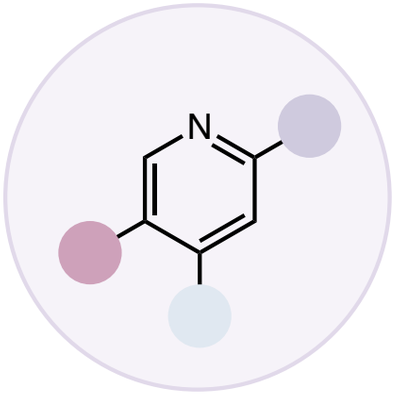


& enantiomers

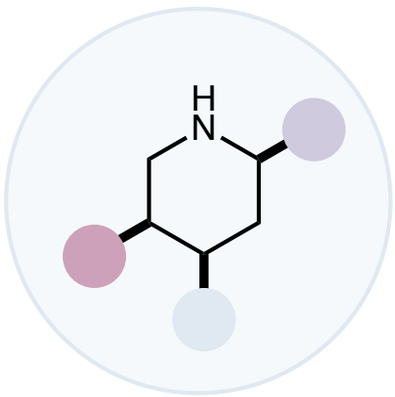
Aside from synthetic accessibility, is there a caveat to increased sp^3 character?

Lovering, F., Bikker, J. & Humblet, C., *J. Med. Chem.* **2009**, 52, 6752

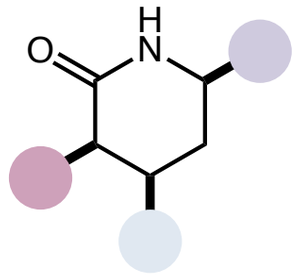
Escaping Flatland

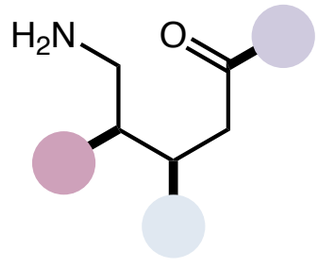


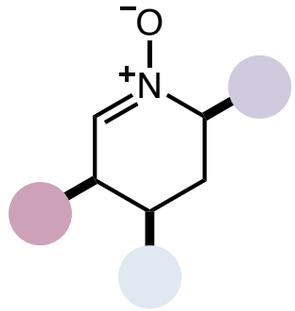
easily synthetically accessed



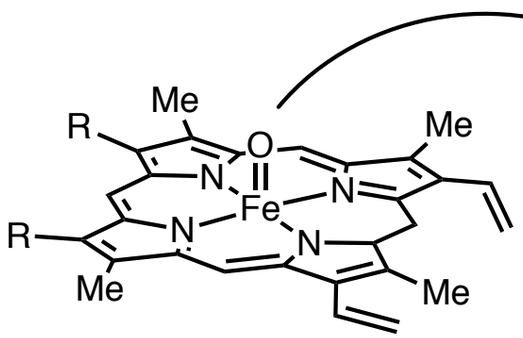
high likelihood of clinical success



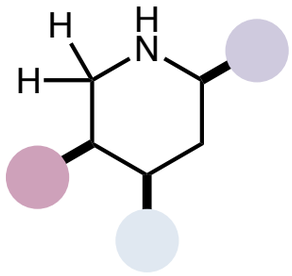


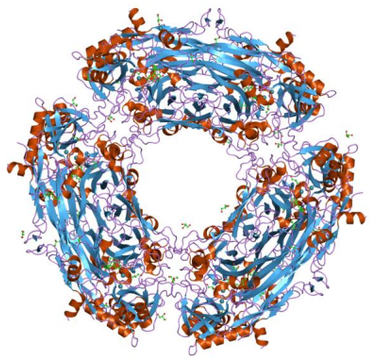


more pathways available for oxidative metabolism



cytochrome P450





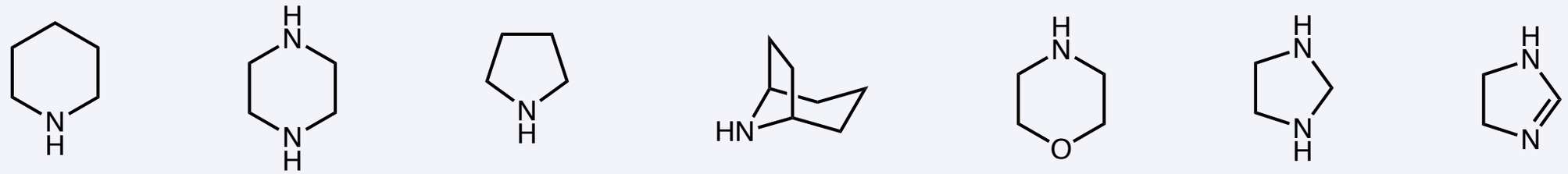
amine oxidase

Bolleddula, J. *et al. Drug Metab. Rev.* **2014**, 46, 379

Escaping Flatland

Despite metabolic instability, saturated heterocycles remain some of the most utilized functionality in medicinal chemistry

Most frequiently used saturated nitrogen heterocycles in FDA approved pharmaceuticals



72	59	37	13	12	11	10

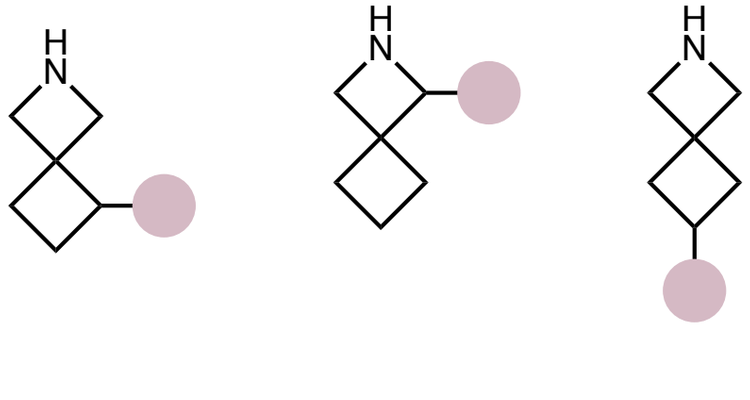
number of approved drugs containing each saturated heterocyclic core

expanding the scope of accessible functionality toward saturated heterocycles of increased metabolic stability could greatly impact the rate of success in drug development

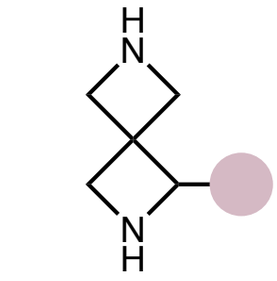
Vitaku, E., Smith, D. T., Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257
Bolleddula, J. *et al. Drug Metab. Rev.* **2014**, 46, 379

Spirocyclic Azetidines as Bioisosteres of Nitrogen Heterocycles

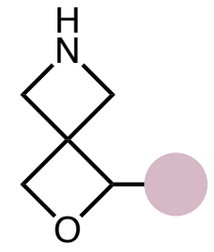
2, 3 & 4-substituted piperidine analogues

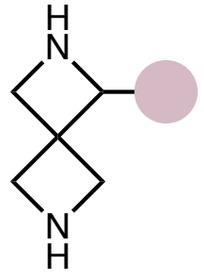


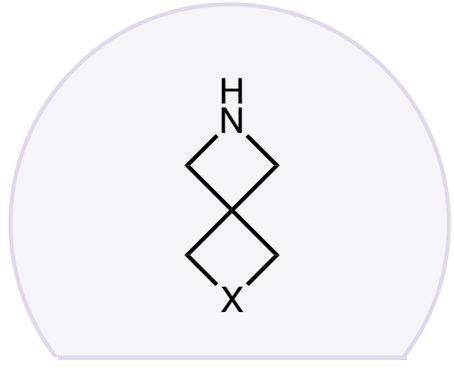
2 & 3 substituted piperazine analogues

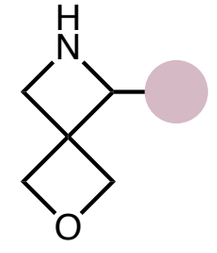


2 & 3 substituted morpholine analogues









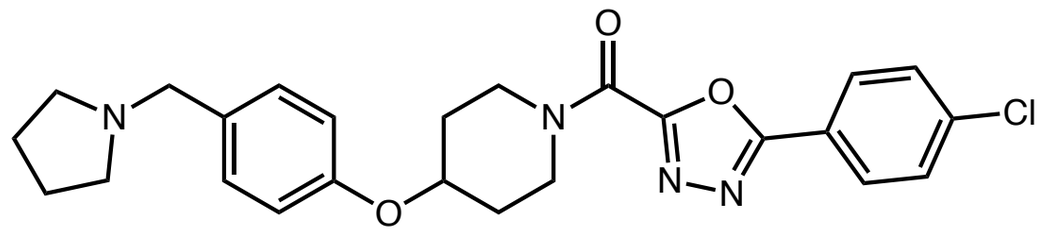
2-azaspiro[3.3]heptane core

6-oxa-2-azabicyclo[3.3]heptane in an MCHr1 Antagonist

Melanin concentrating hormone receptor 1 (MCHr1) has been linked to regulation of appetite.

Small molecule antagonists of this receptor have been shown to prevent obesity

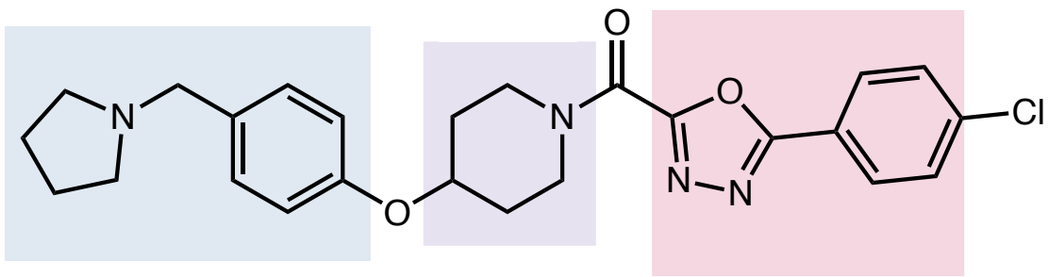
*High throughput screening at AstraZeneca generated **compound 1** for lead optimization*



compound 1 - *antagonist of MCHr1*

Johansson, A. *et al. J. Med. Chem.* **2016**, 59, 2497

6-oxa-2-azabicyclo[3.3]heptane in an MCHr1 Antagonist

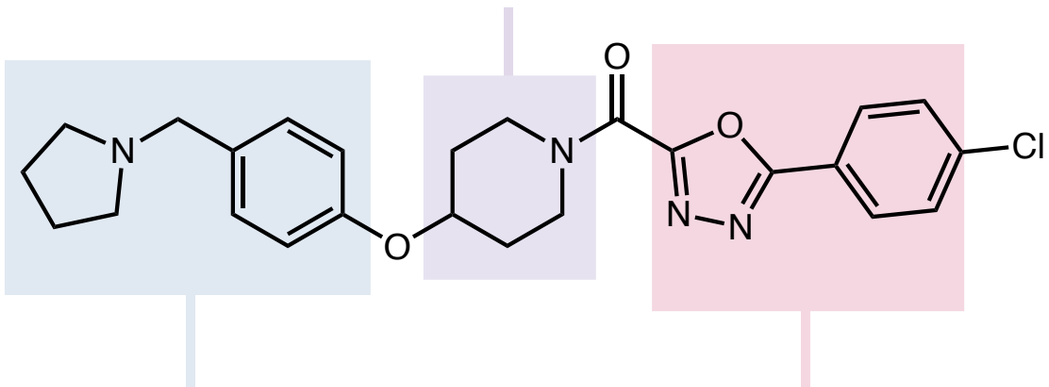


reduction of HERG activity (off target binding resulting in cardiac arrhythmia) is a priority

Johansson, A. *et al. J. Med. Chem.* **2016**, 59, 2497

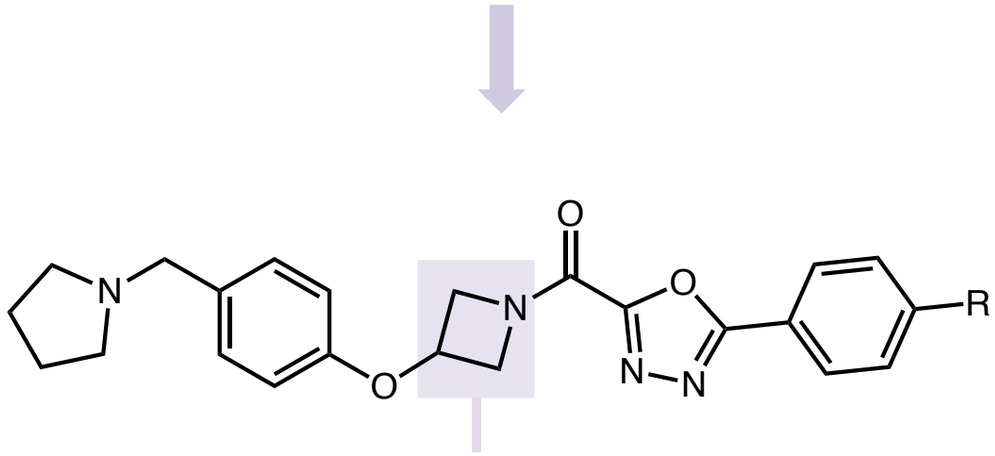
6-oxa-2-azabicyclo[3.3]heptane in an MCHr1 Antagonist

high degree of piperidine lipophilicity
limited degrees of freedom in exploring SAR



basic, benzylic amine
critical for MCHr1 activity

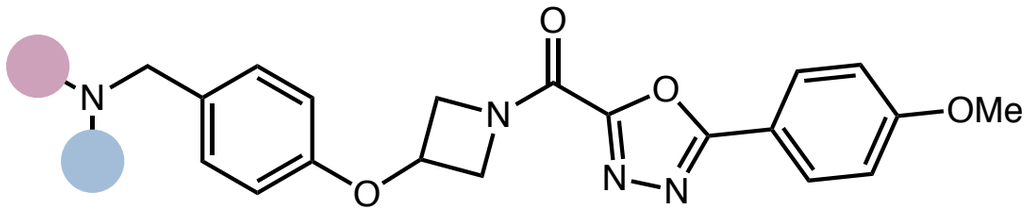
low tolerance for
structural modification

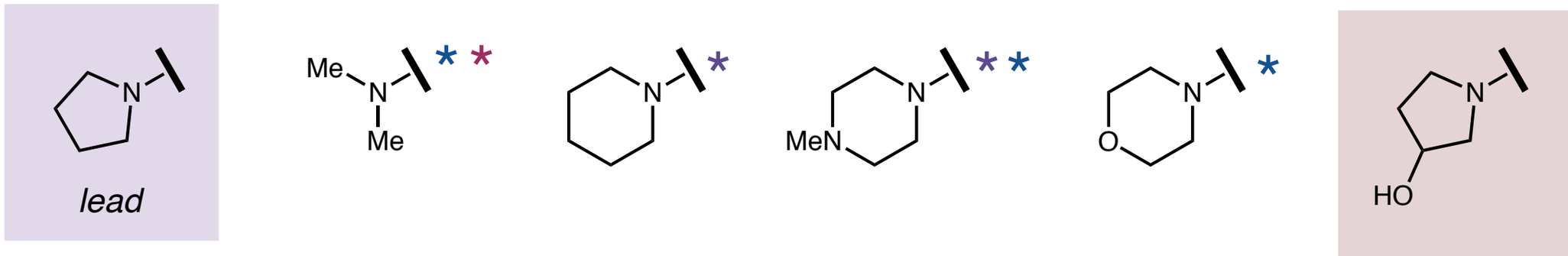


azetidine substitution had limited effect on activity, but allowed for
greater freedom in exploring benzylic amine functionality

Johansson, A. *et al. J. Med. Chem.* **2016**, 59, 2497

6-oxa-2-azabicyclo[3.3]heptane in an MCHr1 Antagonist





lead

reduced metabolic stability *

no reduction in hERG interaction *

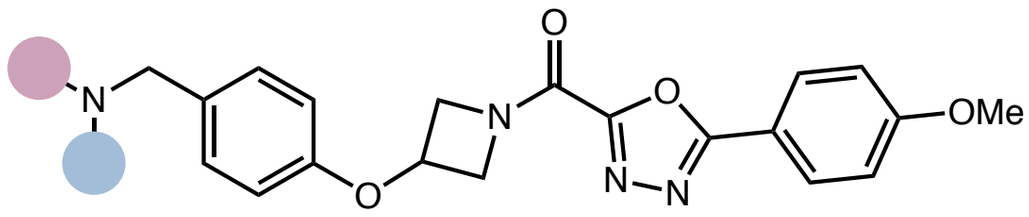
reduced MCHr1 potency *

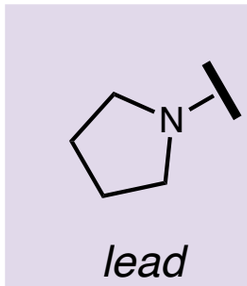
low receptor
occupancy (efflux)

hydrogen bond donors
or acceptors improve potency

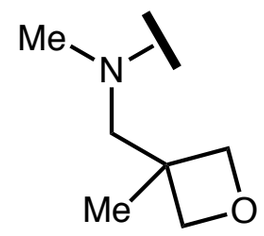
Johansson, A. *et al. J. Med. Chem.* **2016**, 59, 2497

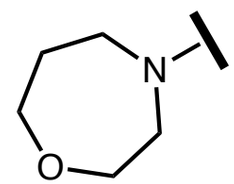
6-oxa-2-azabicyclo[3.3]heptane in an MCHr1 Antagonist

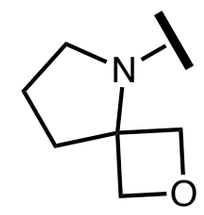


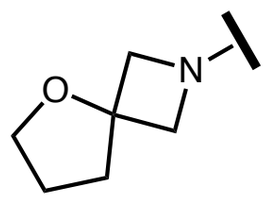


lead





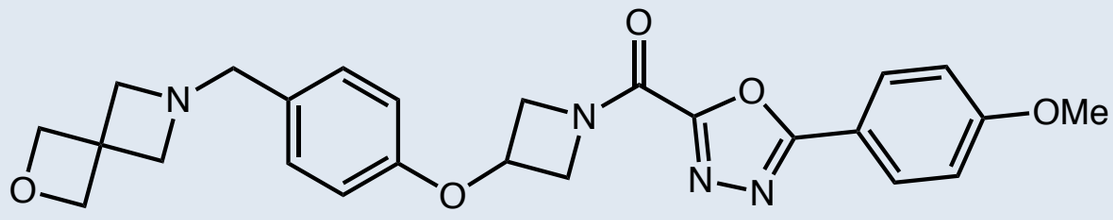




high levels of activity, but no marked improvement in metabolic stability

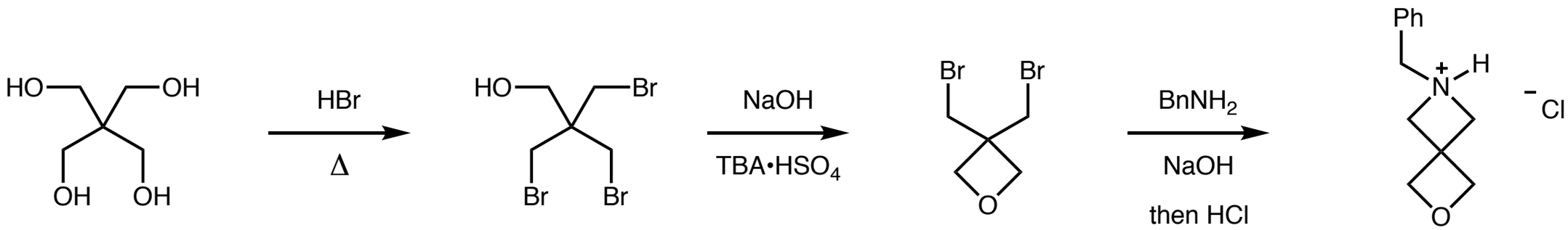
Johansson, A. *et al. J. Med. Chem.* **2016**, 59, 2497

6-oxa-2-azabicyclo[3.3]heptane in an MCHr1 Antagonist



increased metabolic stability - high MCHr1 activity - moved to phase 1

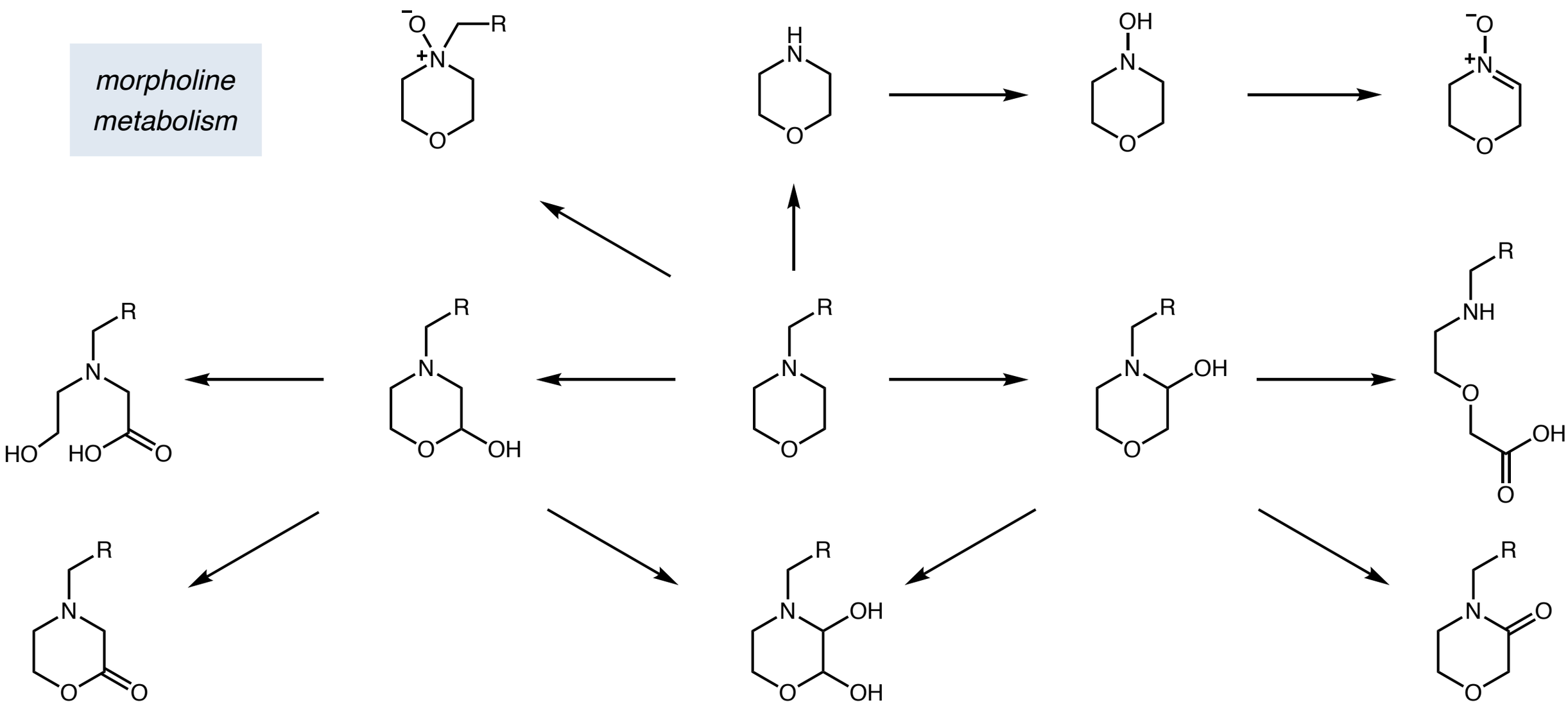
synthetic route to spirocycle:



Golden, M. *et al. Org. Proc. Res. Dev.* **2016**, 20, 675

“Spiromorpholine” metabolism

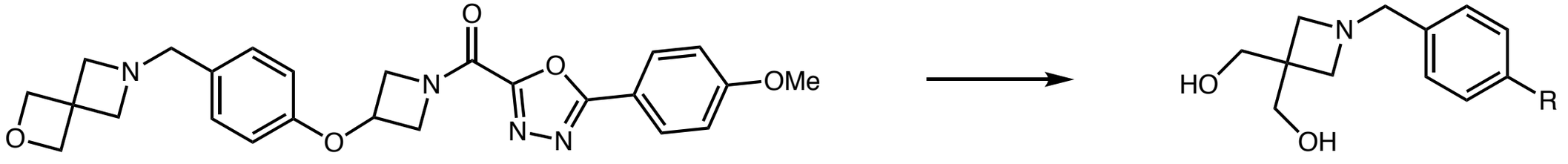
morpholine metabolism

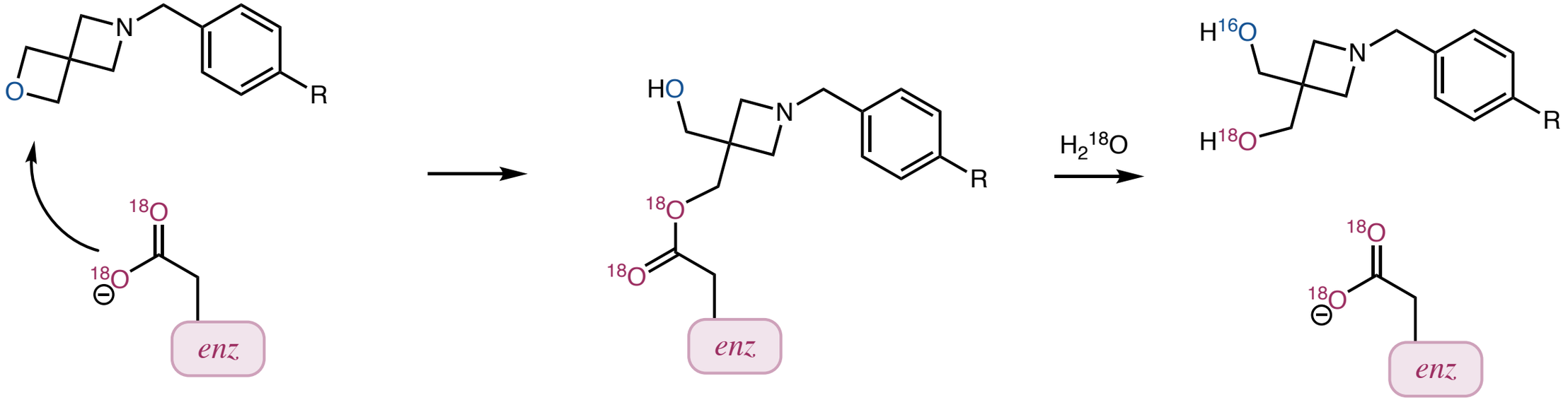


metabolism of morpholine dominated by C–H oxidation

Bolleddula, J. et al. Drug Metab. Rev. **2014,** 46, 379
Li, X.-Q. *et al. Drug Metab. Dispos.* **2016**, *44*, 1341

“Spiromorpholine” metabolism

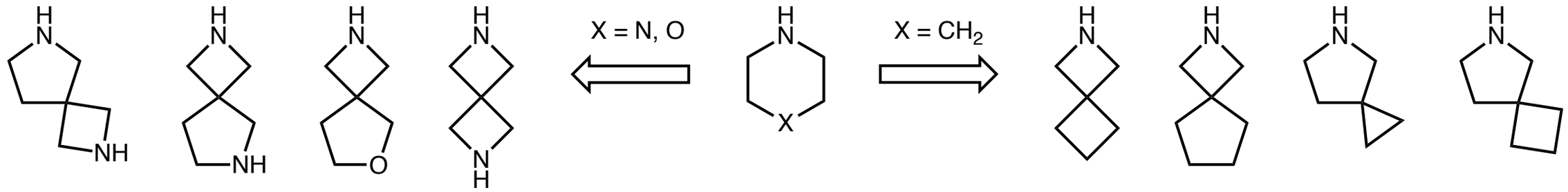


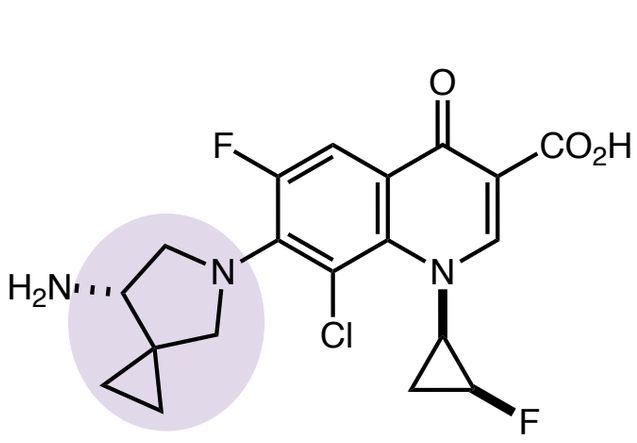


enz = epoxide hydrolase

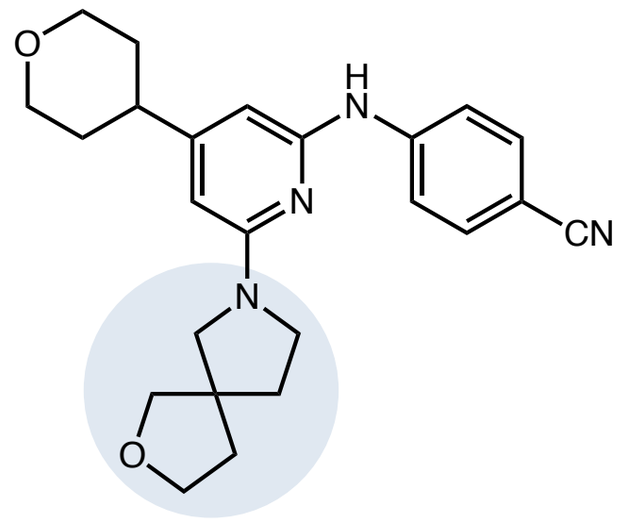
Li, X.-Q. *et al. Drug Metab. Dispos.* **2016**, *44*, 1341

Other Analogues of Saturated Heterocycles

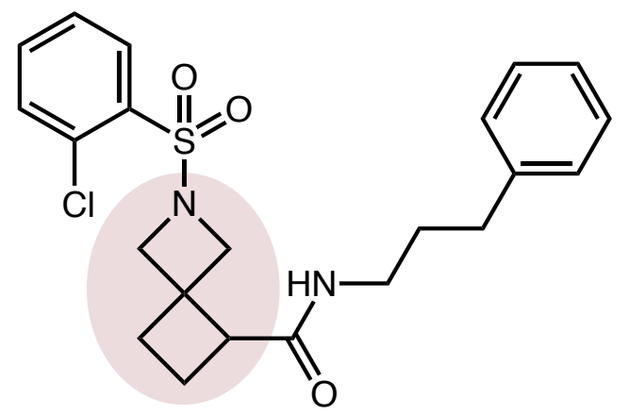




antibacterial drug
Daiichi Sankyo

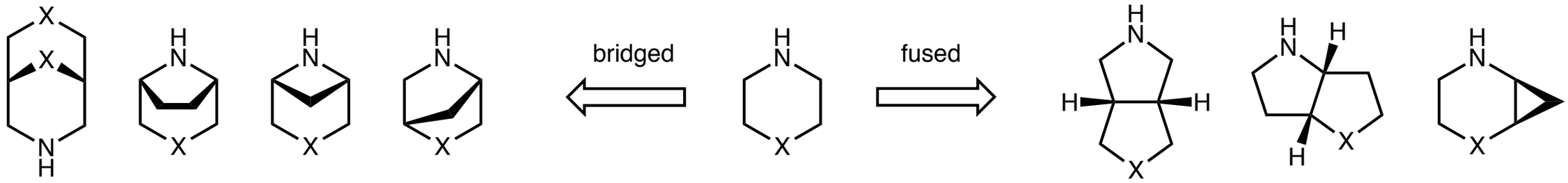


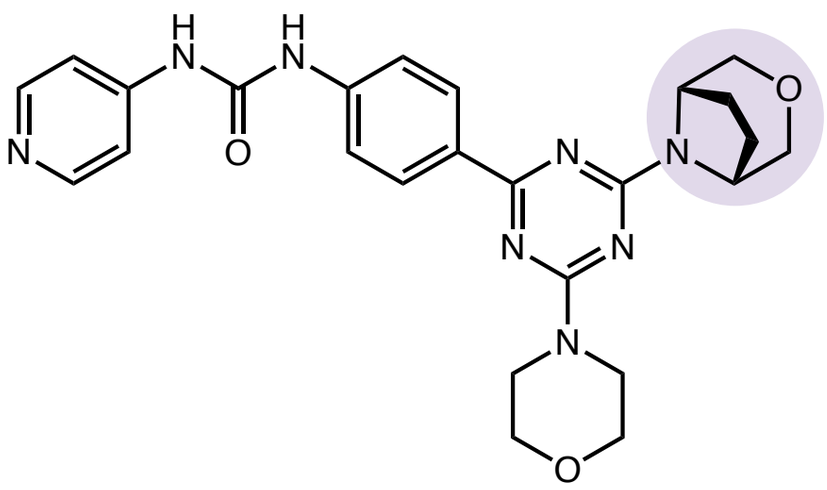
antineurodegenerative
Roche



epoxide hydrolase inhibitor
Merck

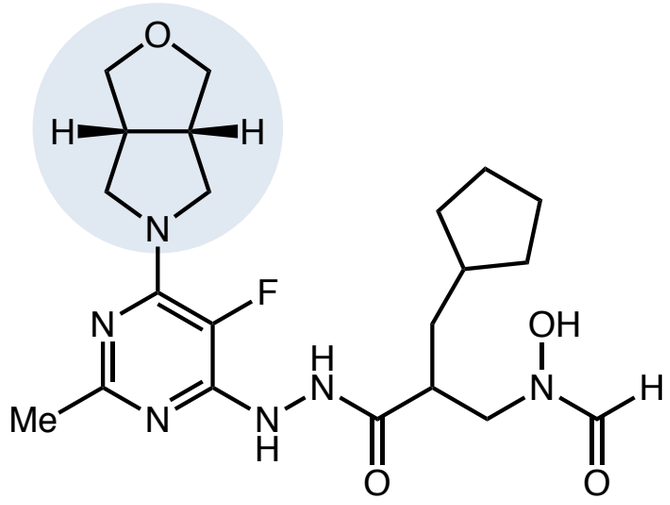
Other Analogues of Saturated Heterocycles





PI3K inhibitor

Pfizer

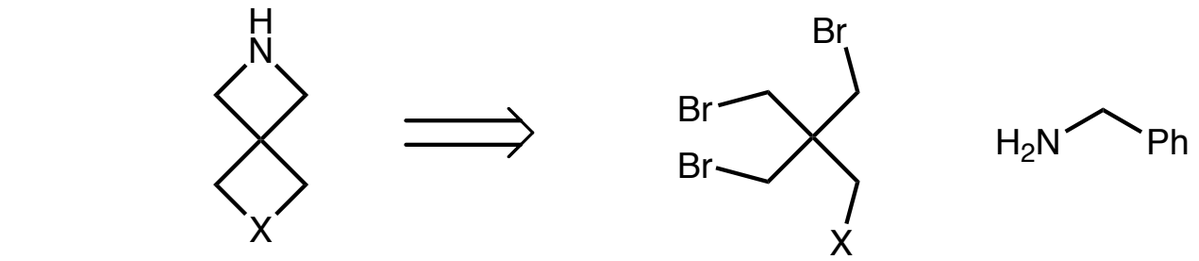


Peptide deformylase inhibitor

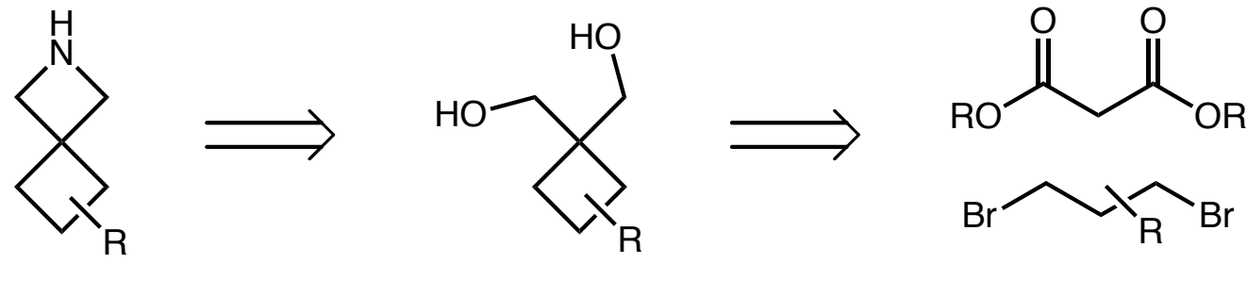
GSK

spiro, fused, and bridged bicyclic compounds - lower oxidative lability, higher conformational rigidity

Synthesis of Complex Isosteres of Saturated Heterocycles



affords access to N-substituted spiro-morpholines and spiro-piperazines

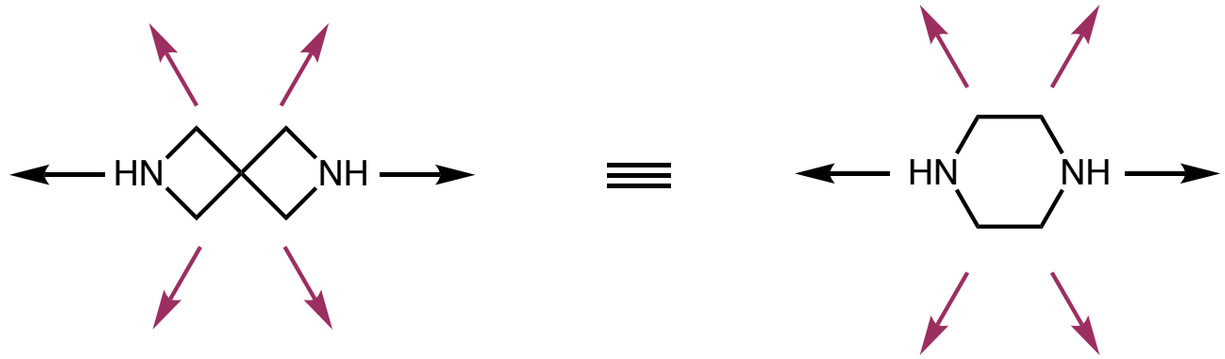


modular approach to spiro-piperidine affords greater substitutional diversity

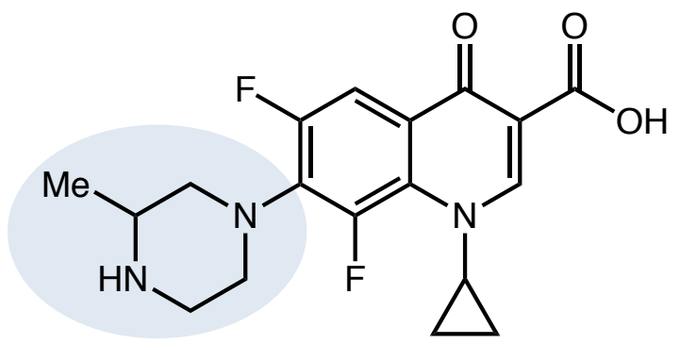
---

can a more modular approach to spiroheterocycles afford a broader range of medicinally relevant isosteres?

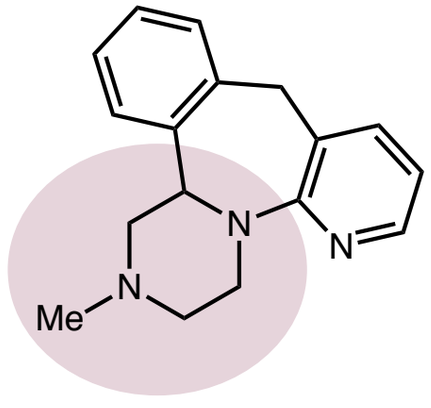
Synthesis of Complex Isosteres of Saturated Heterocycles



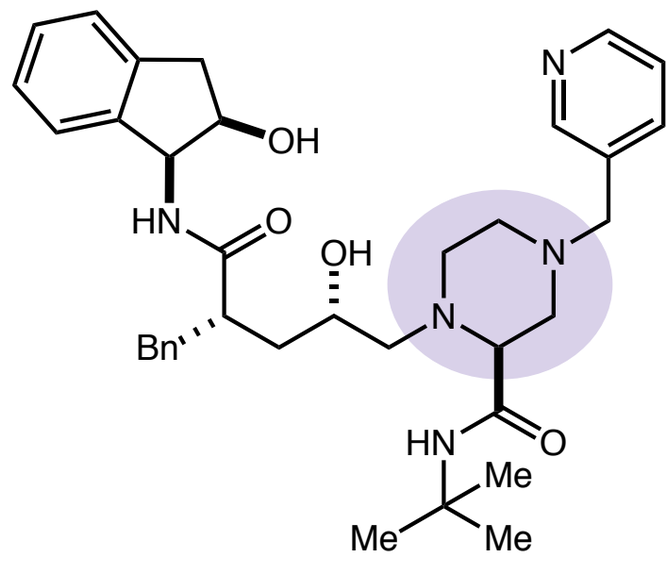
synthetically challenging exit vectors



Gatifloxacin (BMS)
antibiotic

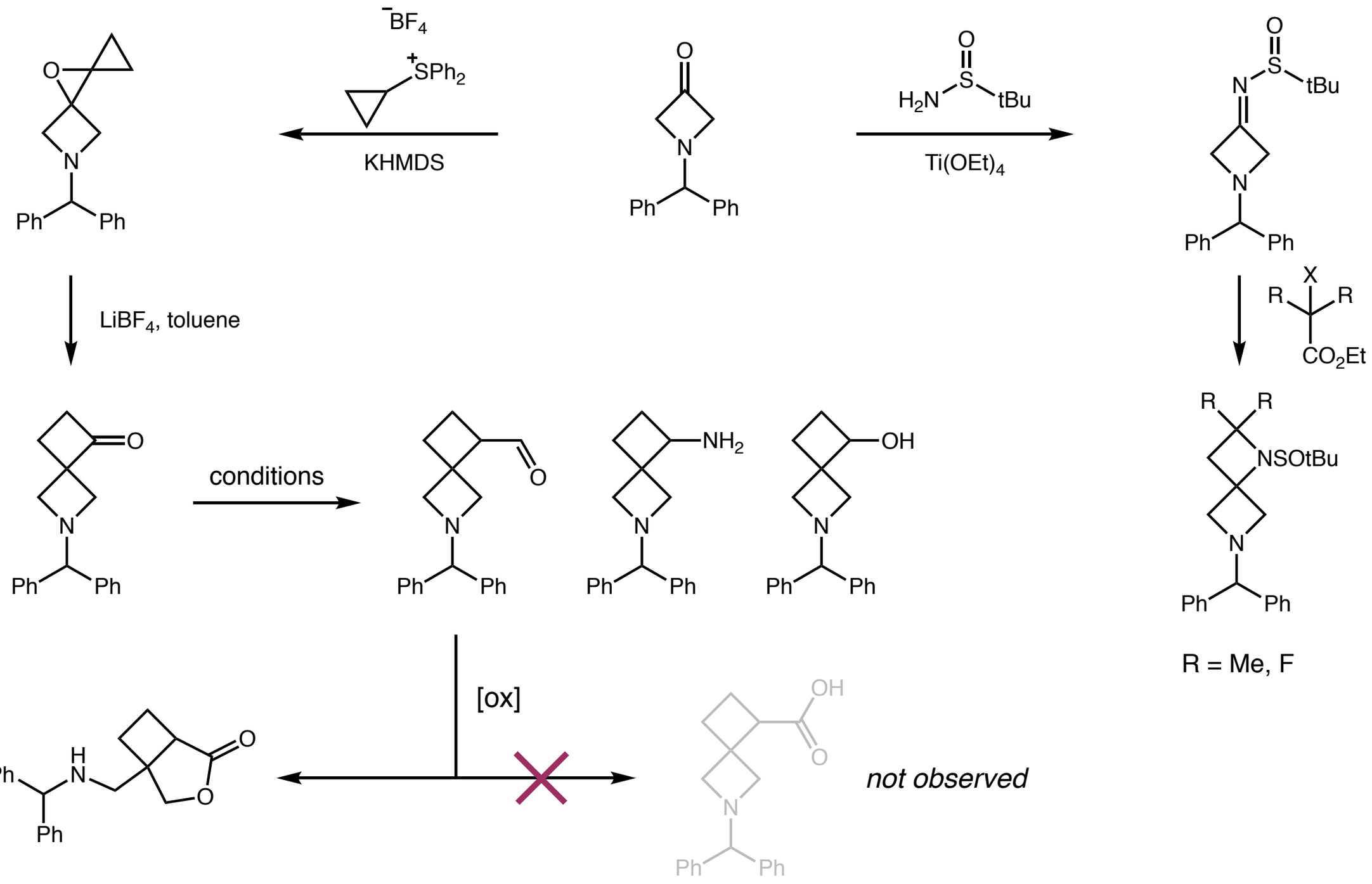


Mirtazapine (Organon)
antidepressant



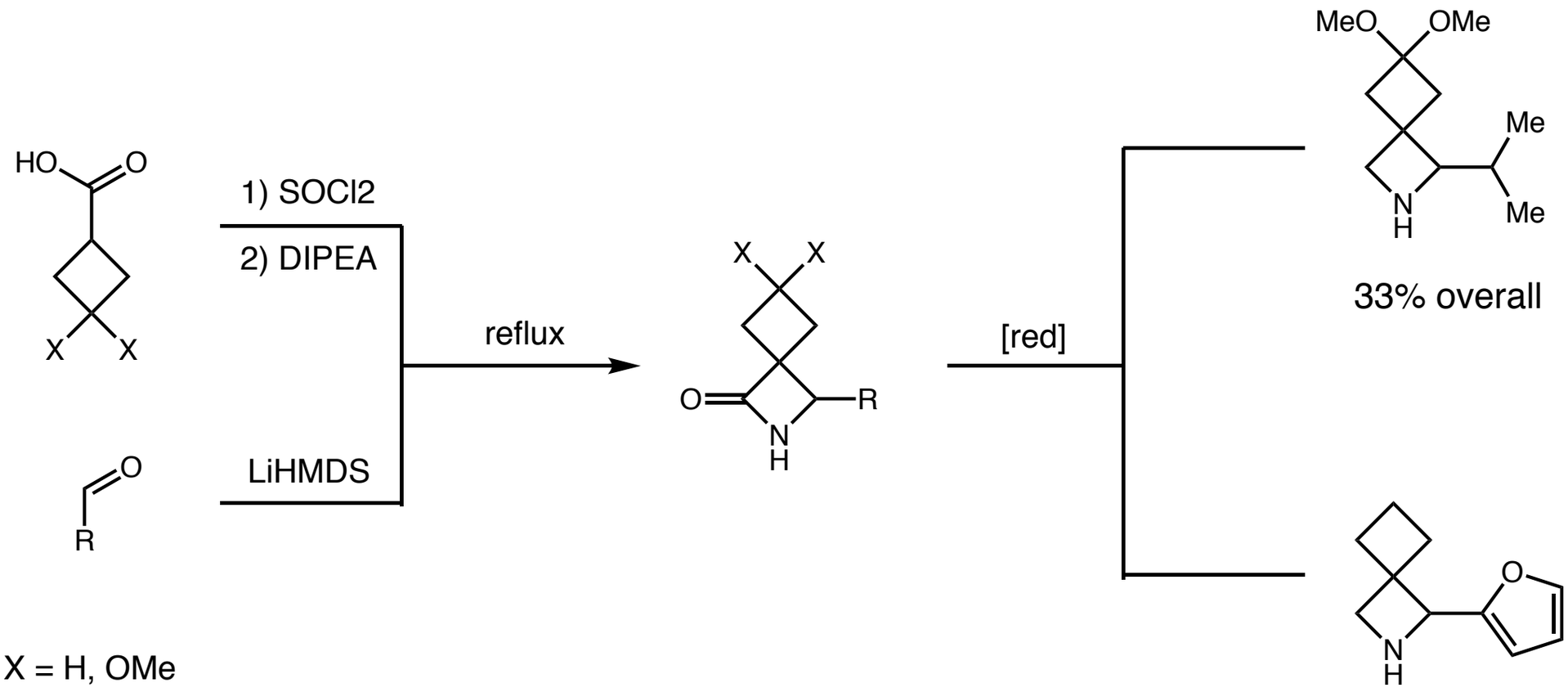
Indinavir (Merck)
antiretroviral

Synthesis of Complex Isosteres of Saturated Heterocycles



Guérot, C., Tchitchanov, B. H., Knust, H & Carreira, E. M. *Org Lett* **2011**, 13, 780

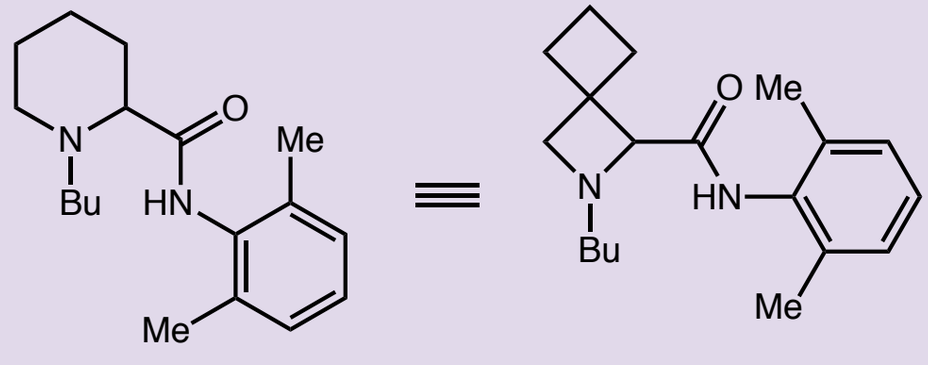
Synthesis of Complex Isosteres of Saturated Heterocycles



X = H, OMe

R = alkyl, aryl

Mykhailiuk Group has since expanded this platform to [4.3], [5.3], and [6.3] spirocyclic azetidines



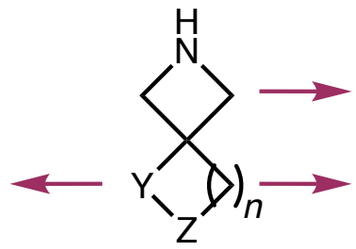
Bupivacaine *19% yield*

Kirichok, A. A. *et al. Chem. Eur. J.* **2018**, 24, 5444

Kirichok, A. A. *et al. Angew. Chem. Int. Ed.* **2017**, 56, 8865

Synthesis of Complex Isosteres of Saturated Heterocycles

spirocycles with exit vectors off of terminal heteroatoms are straightforward to synthesize from feedstock materials

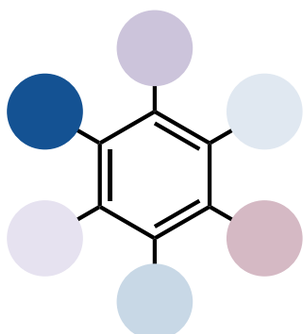


pathways toward strained spirocycles with exit vectors on carbon and at orthogonal angles are limited, novel developments in this arena are in great demand

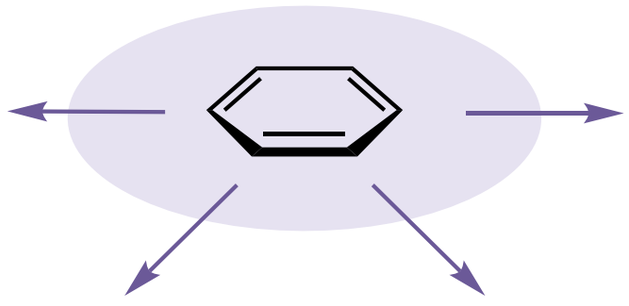
For additional examples of spiroheterocycle construction, see:
Carreira,E. M. & Fessard, T. C. *Chem. Rev.* **2014**, *114,* 8257

Bioisosteres of Benzene Rings

While many pharmaceutical compounds contain saturated heterocycles, many, many more contain benzene rings (>500 as of 2014)



- high structural rigidity
- 6 exit vectors
- many methods for incorporation and functionalization



2D vectorial space

Taylor, R. D., MacCoss, M. & Lawson, A. D. G. *J. Med. Chem.* **2014**, 57, 5845

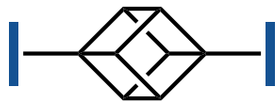
Bioisosteres of Benzene Rings

some guidelines for phenyl isosteres

retained structural rigidity

reduced cLogP (lipophilicity) as compared to Ph

increased sp^3 incorporation without intoducing metabolic instability

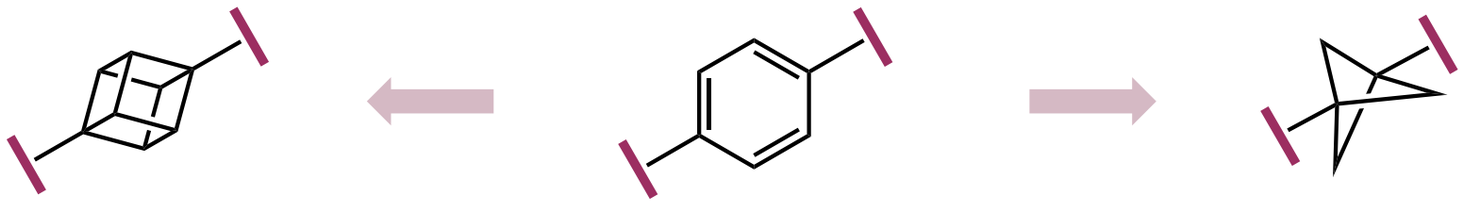


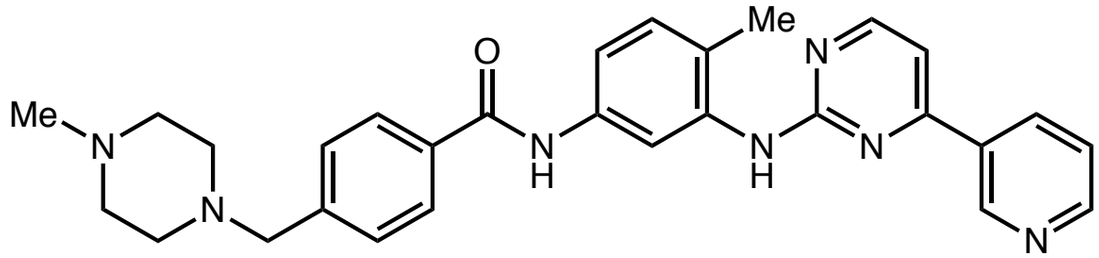
Eaton, *ACIE* ***1992***

Stephan, *J. Med. Chem.* **2012**

Taylor, R. D., MacCoss, M. & Lawson, A. D. G. *J. Med. Chem.* **2014**, 57, 5845

1,4-disubstituted Benzene Bioisosteres





Imatinib - ABL1 kinase inhibitor - anticancer

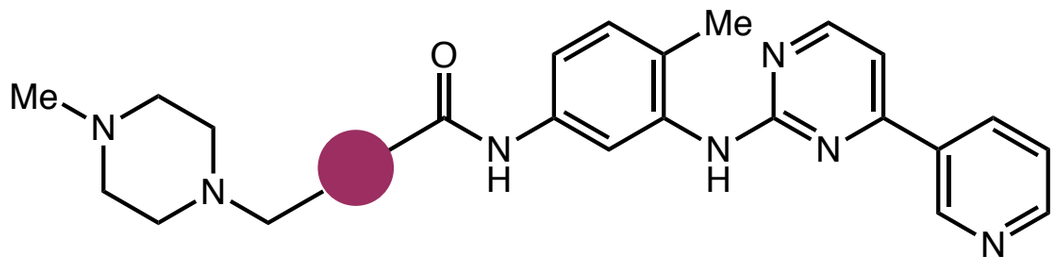
4 aromatic rings, low fraction of sp^3–hybridized carbon atoms

cLogP = 4.53 (upper end of Lipinski's rule of 5)

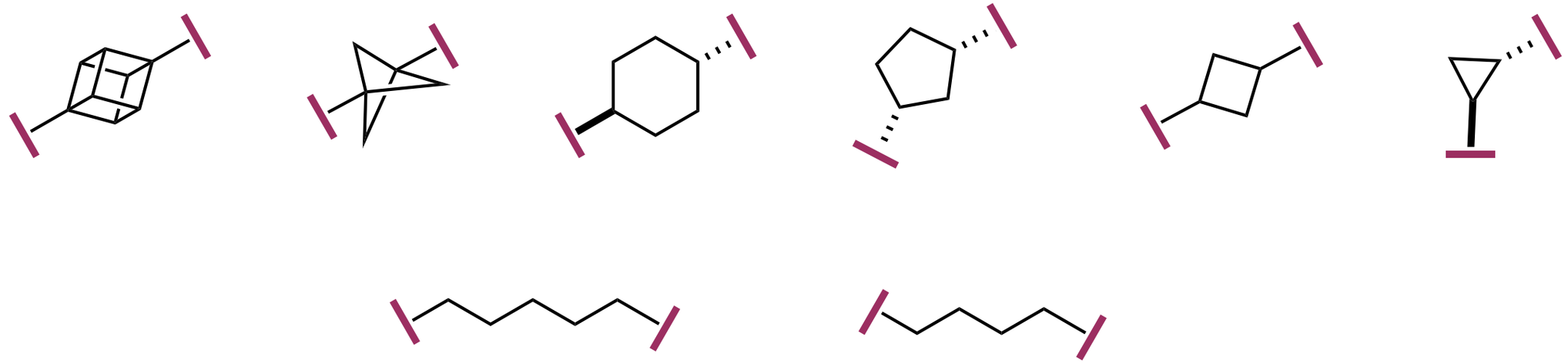
nearly insoluble in neutral aqueous media

Nicolau, K. C. *et al. ChemMedChem* **2016**, *11*, 31

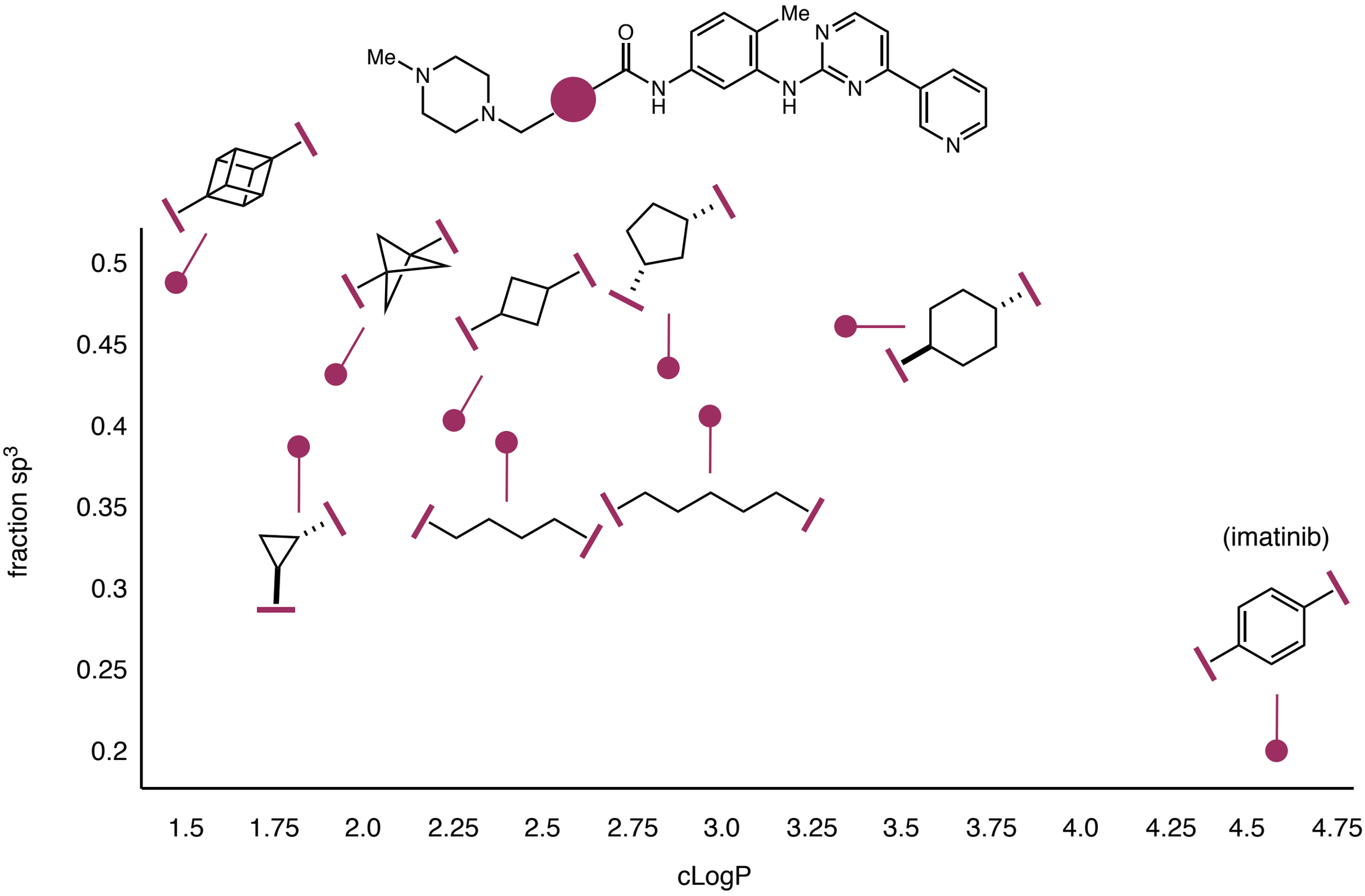
1,4-disubstituted Benzene Bioisosteres



incorporated linkers:

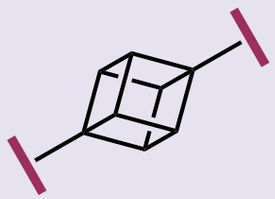


1,4-disubstituted Benzene Bioisosteres

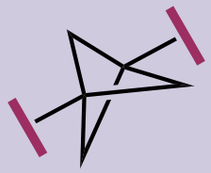


Nicolau, K. C. *et al. ChemMedChem* **2016**, *11*, 31

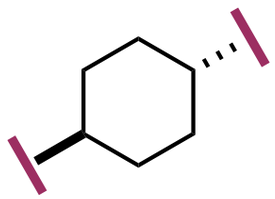
1,4-disubstituted Benzene Bioisosteres

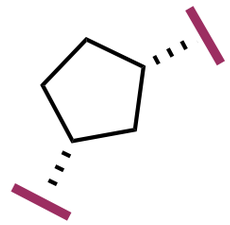


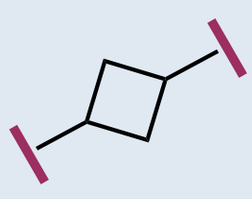
10-fold increase
in solubility



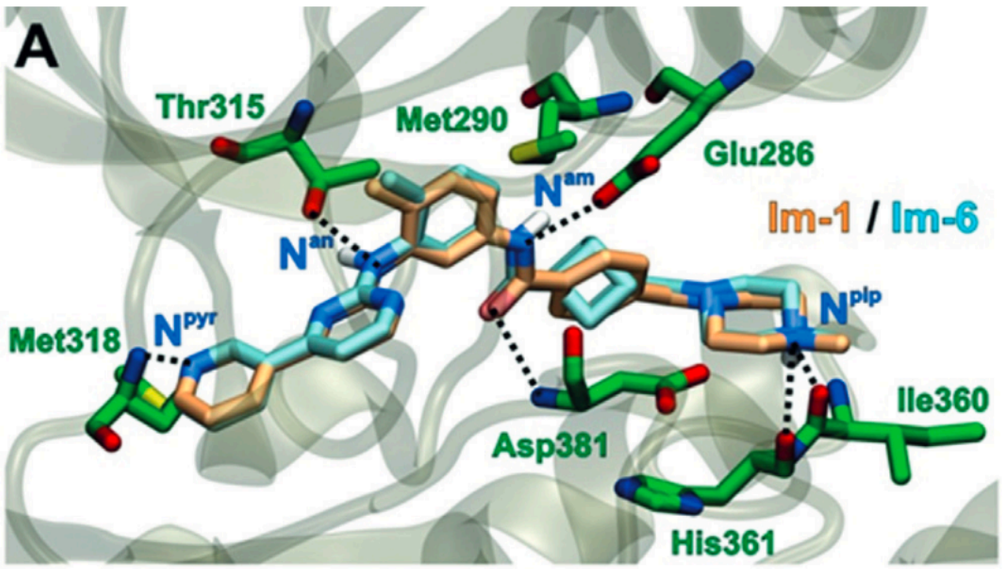
>80-fold increase
in solubility

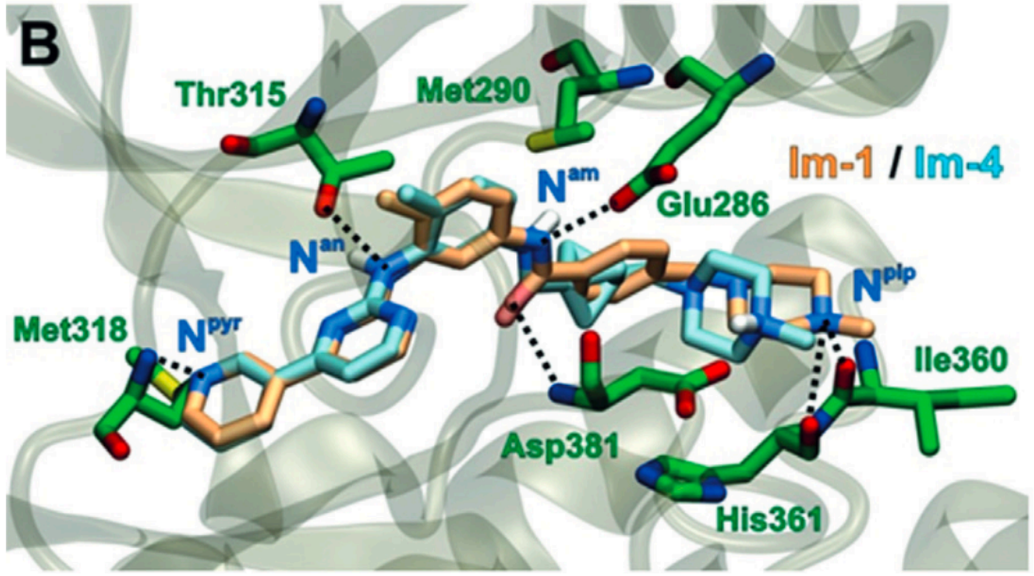






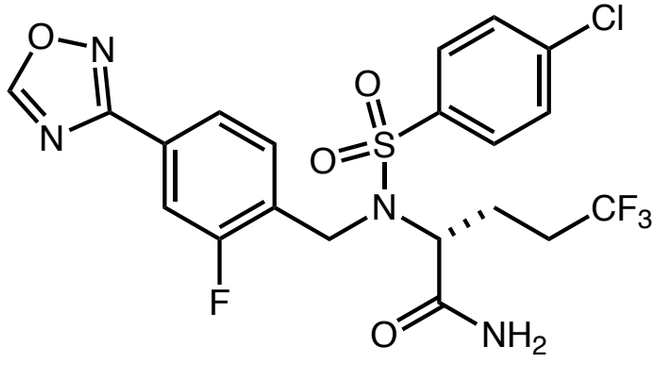
50-fold increase
in solubility



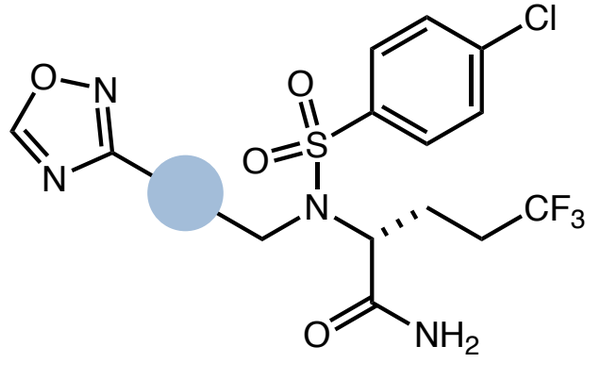


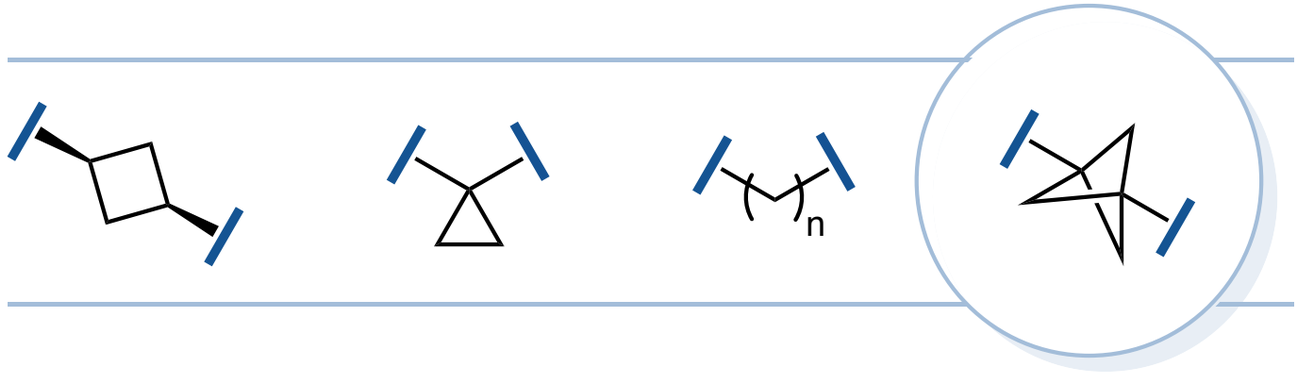
Nicolau, K. C. *et al. ChemMedChem* **2016**, *11*, 31

Bioisosteres of Benzene Rings



BMS 708,163
γ-secretase inhibitor
(anti-Alzheimer's)



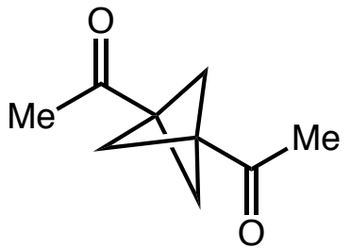


equipotent to BMS 708,163
improved permeability
improved aqueous solubility

fluoro substitution in parent compound
not required in bicyclic analogue

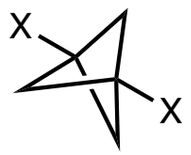
Stephan, A. F. *et al. J. Med. Chem.* **2012**, 55, 3414

Synthesis of Benzene Bioisosteres: [1.1.1]-bicyclopentane



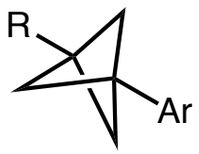
Michl & Kaszynski, *J. Org. Chem.*
1988, *53*, 4593

diacetyl
hv



X_2

Thirumoorthi, N. T.,
Chem Commun.
2015, *51*, 3139



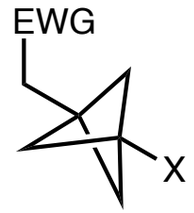
1) R—MgBr
1) Pd, ArI

[1.1.1]-propellane

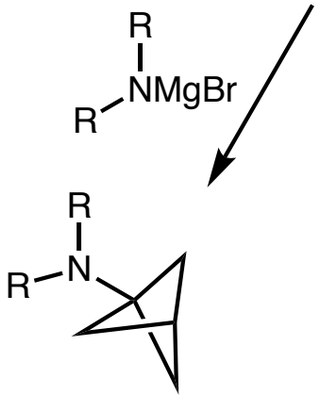
de Meiere, *et al.*
Eur. J. Org. Chem.
2000, 1137

EWG X

BEt_3

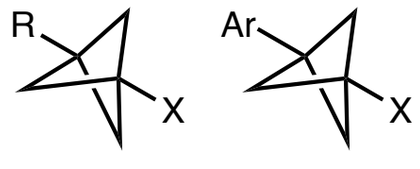


Recent reports: Anderson Group
Chem. Sci., **2018**, *9,* 5259
Org. Lett. **2019**, *21*, 2408



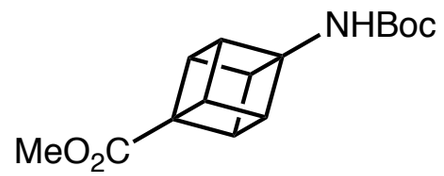
Gianatassio, R. *et al.*
Science, **2016**, *351*, 241

Ar/R—X
$Ir(ppy)_3$



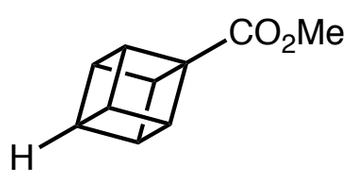
Nugent, J. *et al*.
ChemRXiv, **2019**

Synthesis of Benzene Bioisosteres: cubane

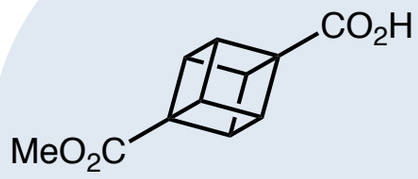


Eaton, P. E. *et al*
J. Org. Chem.
1984, *49,* 185.

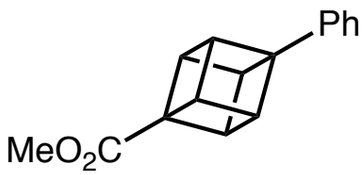
$(PhO)_2P(O)N_3$
tBuOH



multiple reports



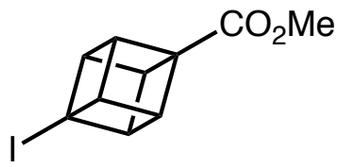
methyl-1,4-cubane dicarboxylate



$Pb(OAc)_4$
PhH, *hv*

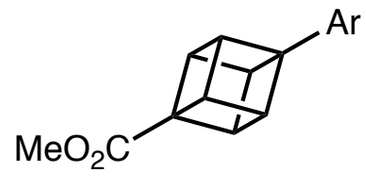
Moriarty, R. M. & Khosrowshahi, J. S.
JACS **1989**, *111*, 8944

PIDA
I_2



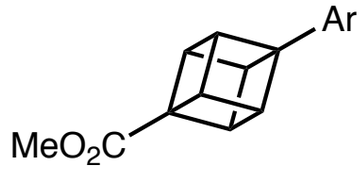
Eaton, P. E. & Maggini, M. J.
JACS, **1988**, *110*, 7230

1) TCNHPI
DCC
2) Ar_2Zn
$Fe(acac)_3$



Toriyama, F *et al.*
JACS, **2016**, *138*, 11132

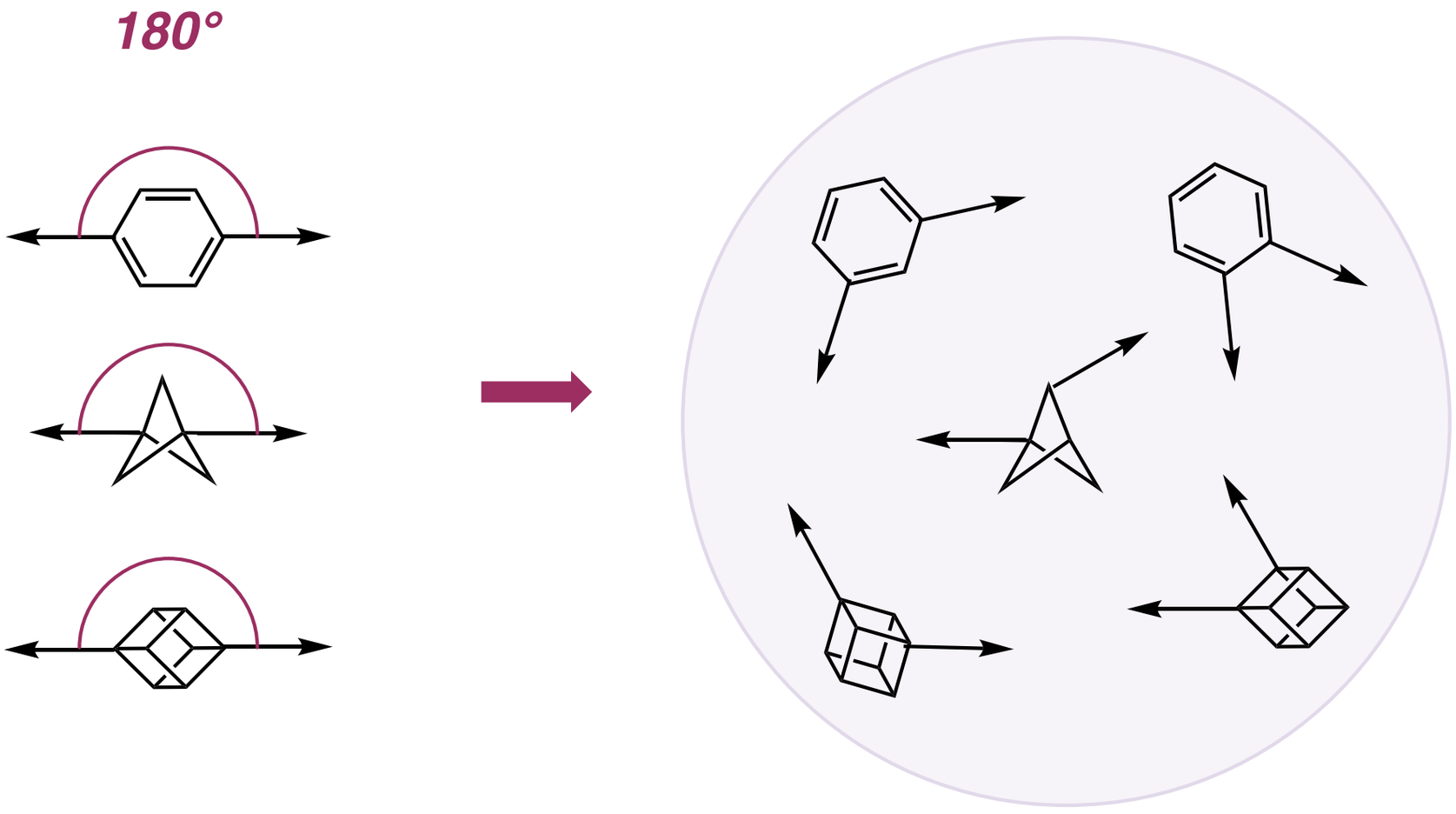
1) TCNHPI
DCC
2) ArZnCl
$NiCl_2{\bullet}dCO_2Mebpy$



Bernhard, S. S. R. *et al*
Chem. Eur. J., **2018**, *24*, 1026

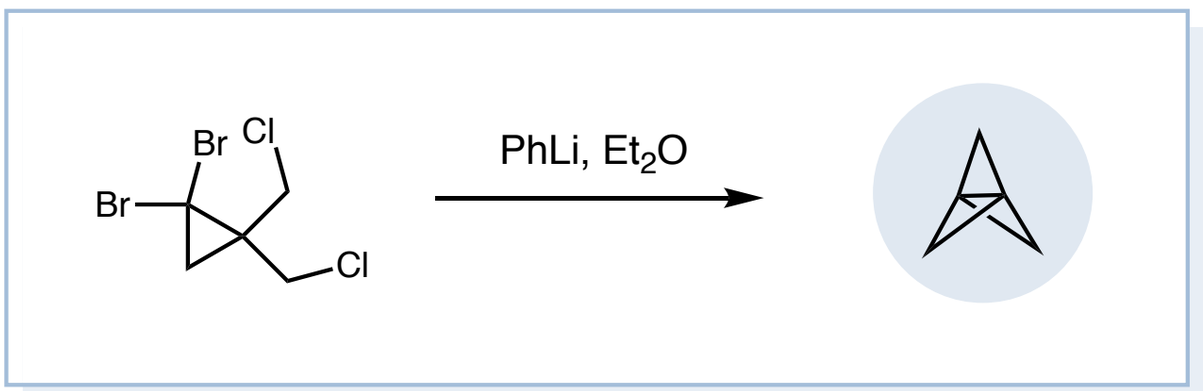
Synthesis of Benzene Bioisosteres: Escaping Straightland?

incorporation of strained sp^3-rich scaffolds has a major limitation: nonlinear exit vectors

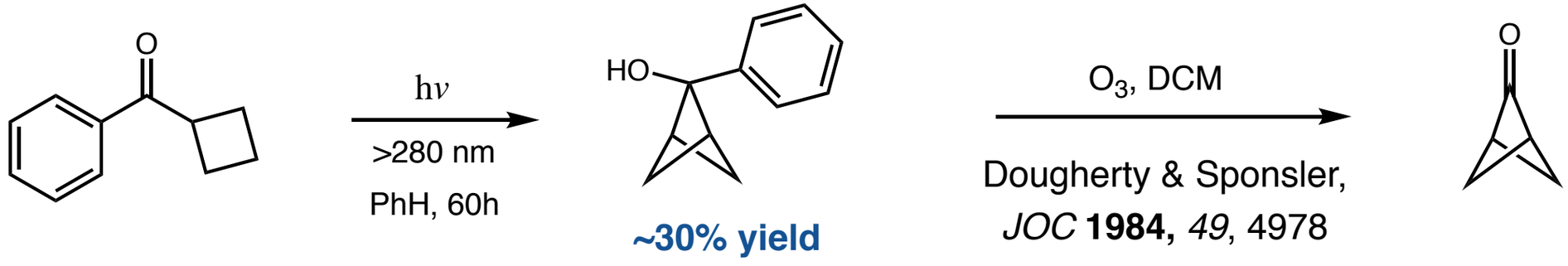


Synthesis of Benzene Bioisosteres: Escaping Straightland?

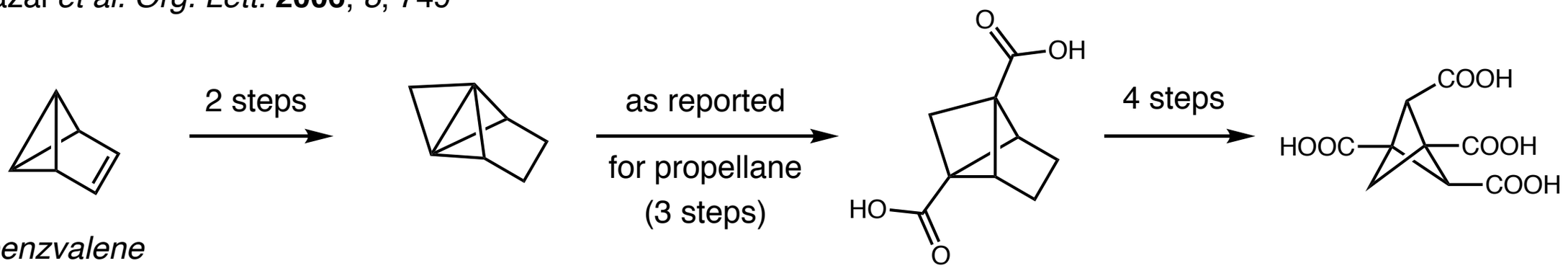
nonlinear exit vectors from bicyclopentane



Padwa *et al. JACS*, **1968,** *90*, 3717



Mazal *et al. Org. Lett.* **2006**, *8*, 749

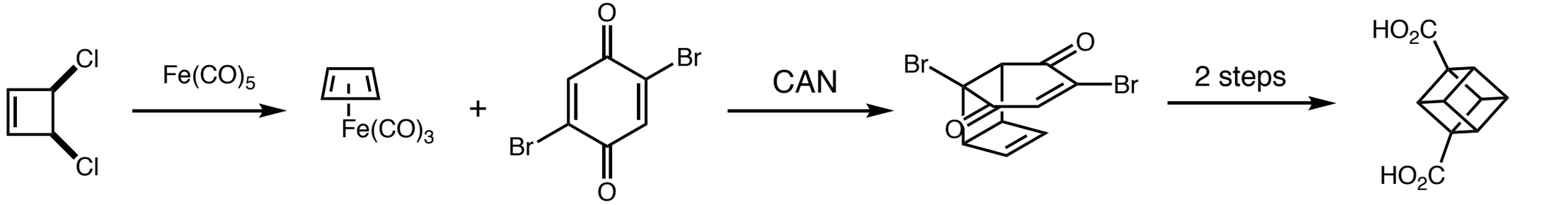


benzvalene

Synthesis of Benzene Bioisosteres: Escaping Straightland?

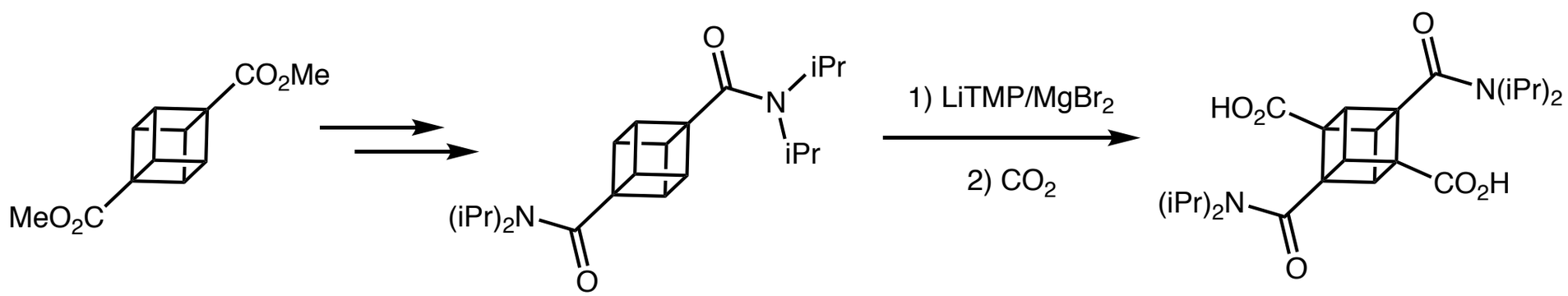
nonlinear exit vectors from bicyclopentane

Barborak *et al. J. Am. Chem. Soc.* **1966**, *88*, 1328

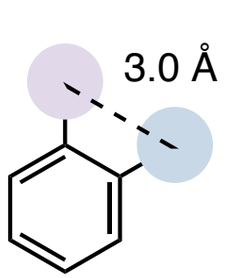


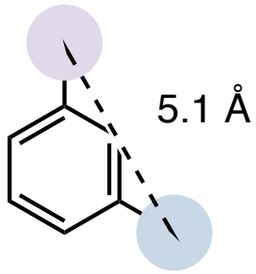
~50% yield from quinone

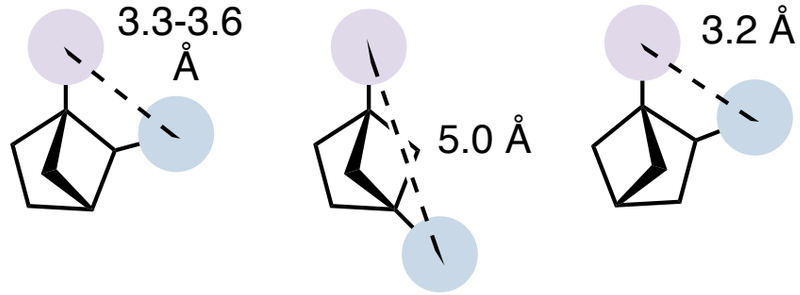
Bashir-Hashemi, *J. Am. Chem. Soc.* **1988**, *110,* 7234



Additional Benzene Bioisosteres: Ortho and Meta

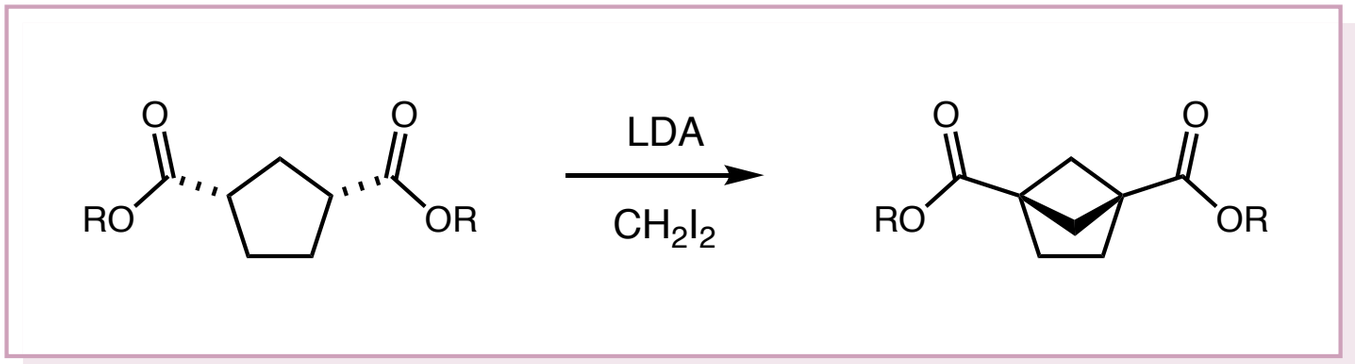


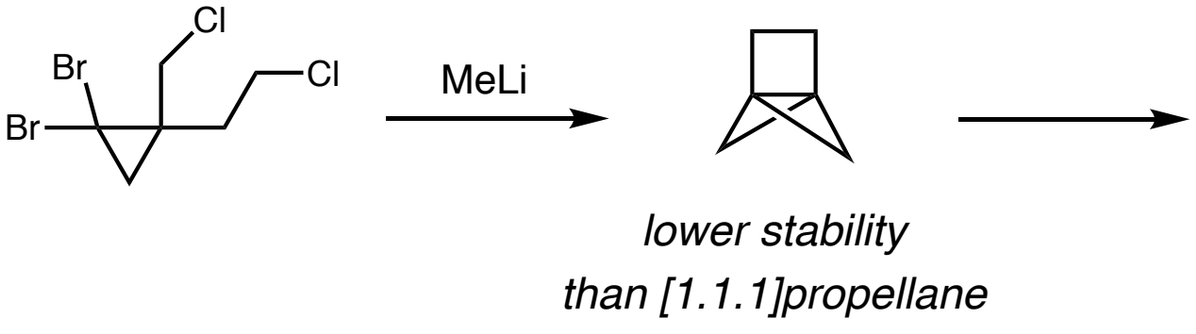




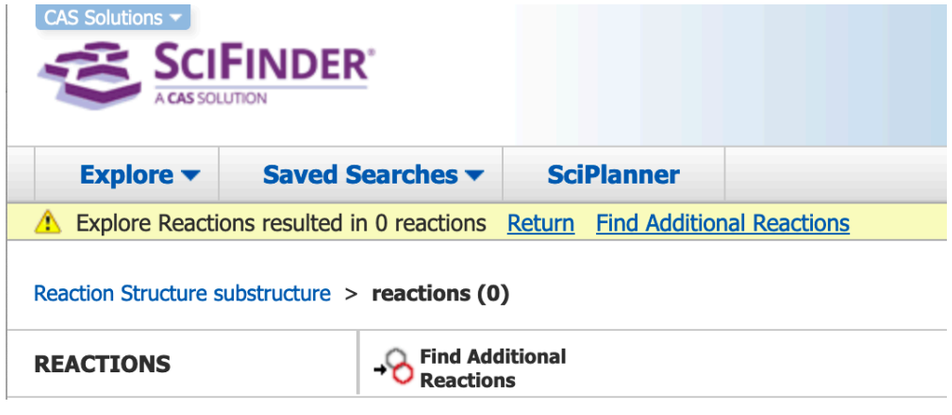
rigidity, increased 3 dimensionality

improved physico-chemical properties?





lower stability
than [1.1.1]propellane



Fuchs, J. & Szeimies, G. *Chem. Ber.* **1992**, *125*, 2517
Mykhailiuk, P. K. *Org. Biomol. Chem.* **2019**,17, 2839

Bioisosteres of Common Functional Groups

Bioisosteres are frequently employed in a medicinal chemistry setting to improve or alter physico-chemical properties of lead compounds

The abundance and diversity of bioisosteres is continuously growing as novel chemical methods for the installation of complex functionality are developed

While important in elucidating stucture-activity relationships, bioisosteres can often have hard-to-predict effects on the activity and properties of bioactive molecules

Synthetic strategies toward installation of novel exit vectors on spirocyclic, bridged-bicyclic, and polycyclic sp^3-rich scaffolds are in high demand in the medicinal chemistry community