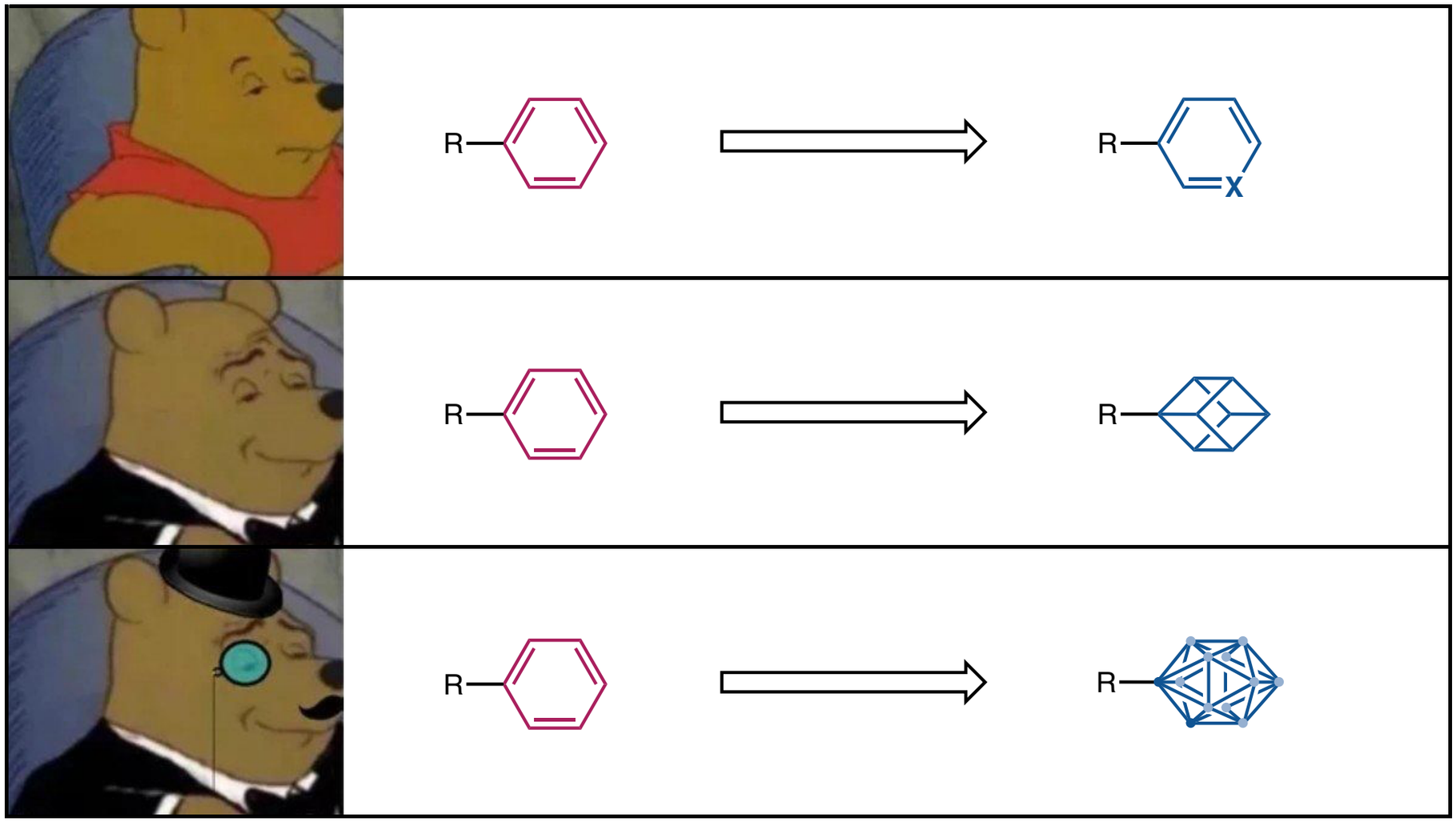
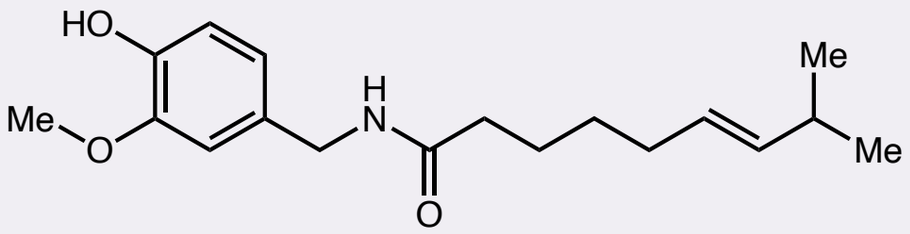
Phenyl Bioisosterism – A Solved Challenge?

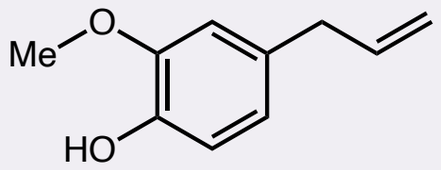


Michael Heilmann
MacMillan Group Meeting
October 20, 2021

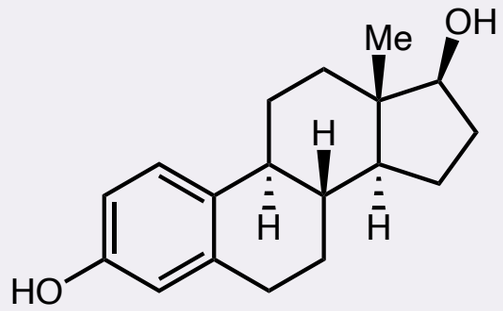
Phenyl Rings as Ubiquitous Building Blocks of Life



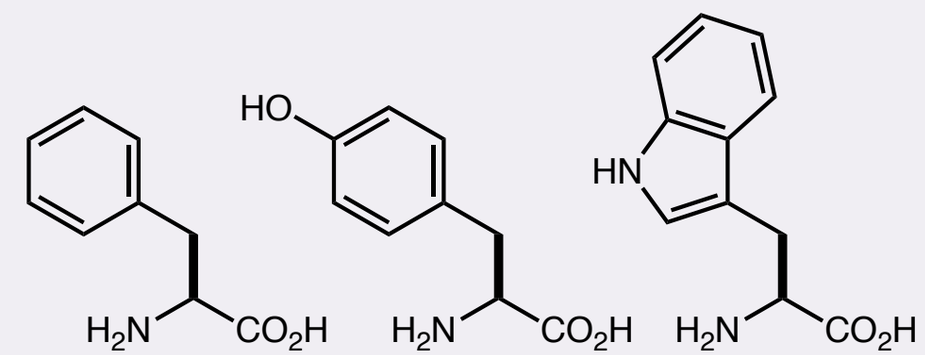
capsaicin
chili pepper alkaloid



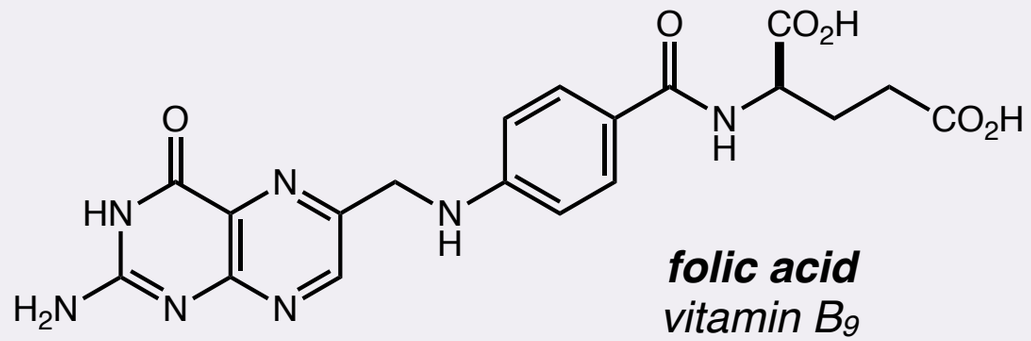
eugenol
natural fragrance



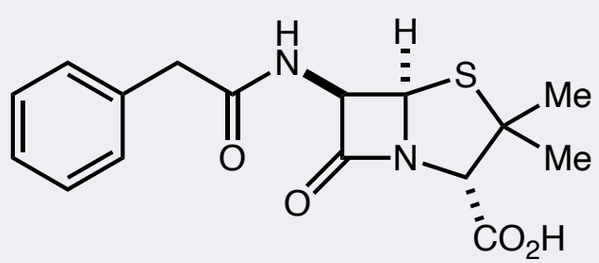
estradiol
hormone



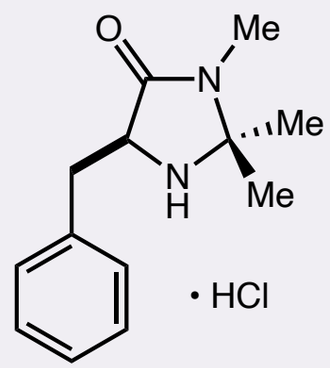
canonical aminoacids
building block, catalyst, signal transducer, …



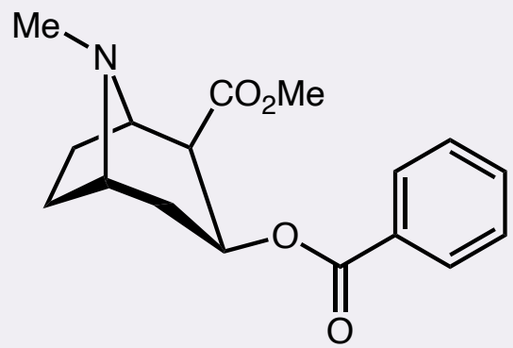
folic acid
vitamin B_9



penicillin G
antibiotic



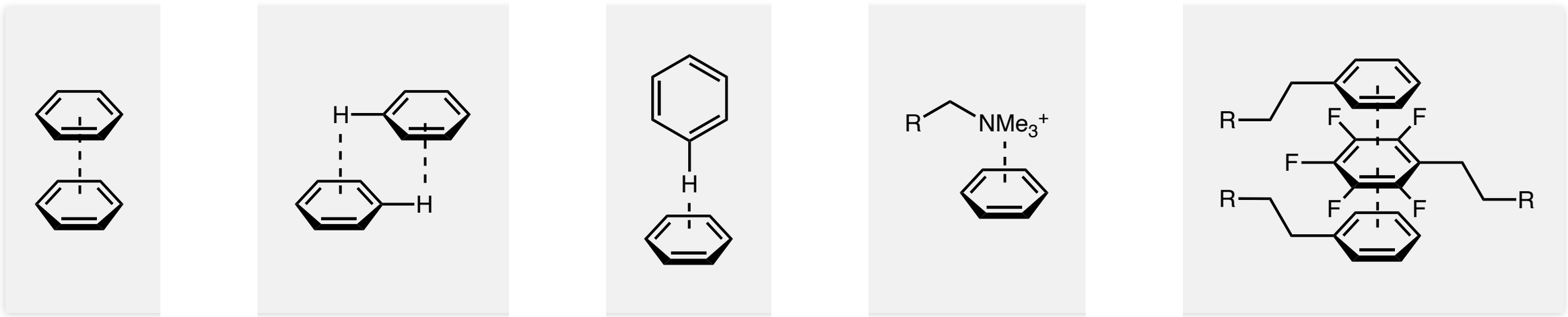
"7"
Nobel Prize winner



cocaine
stimulant

Phenyl Rings as Ubiquitous Building Blocks of Life

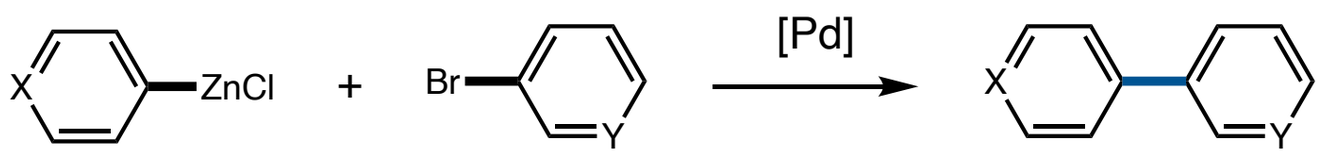
- Phenyl rings engage in numerous different modes of intermolecular interaction

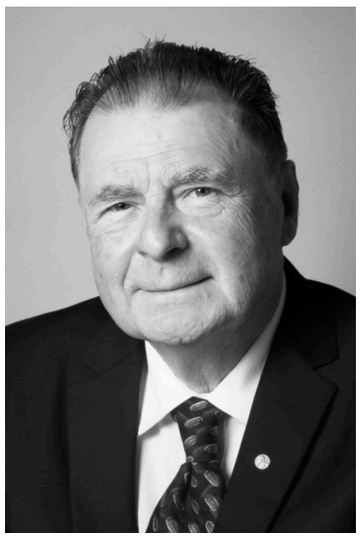


Diederich, F., *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.

Phenyl Rings as Ubiquitous Building Blocks of Life

- We are exceptionally good at forming phenyl–R connections





Richard F. Heck

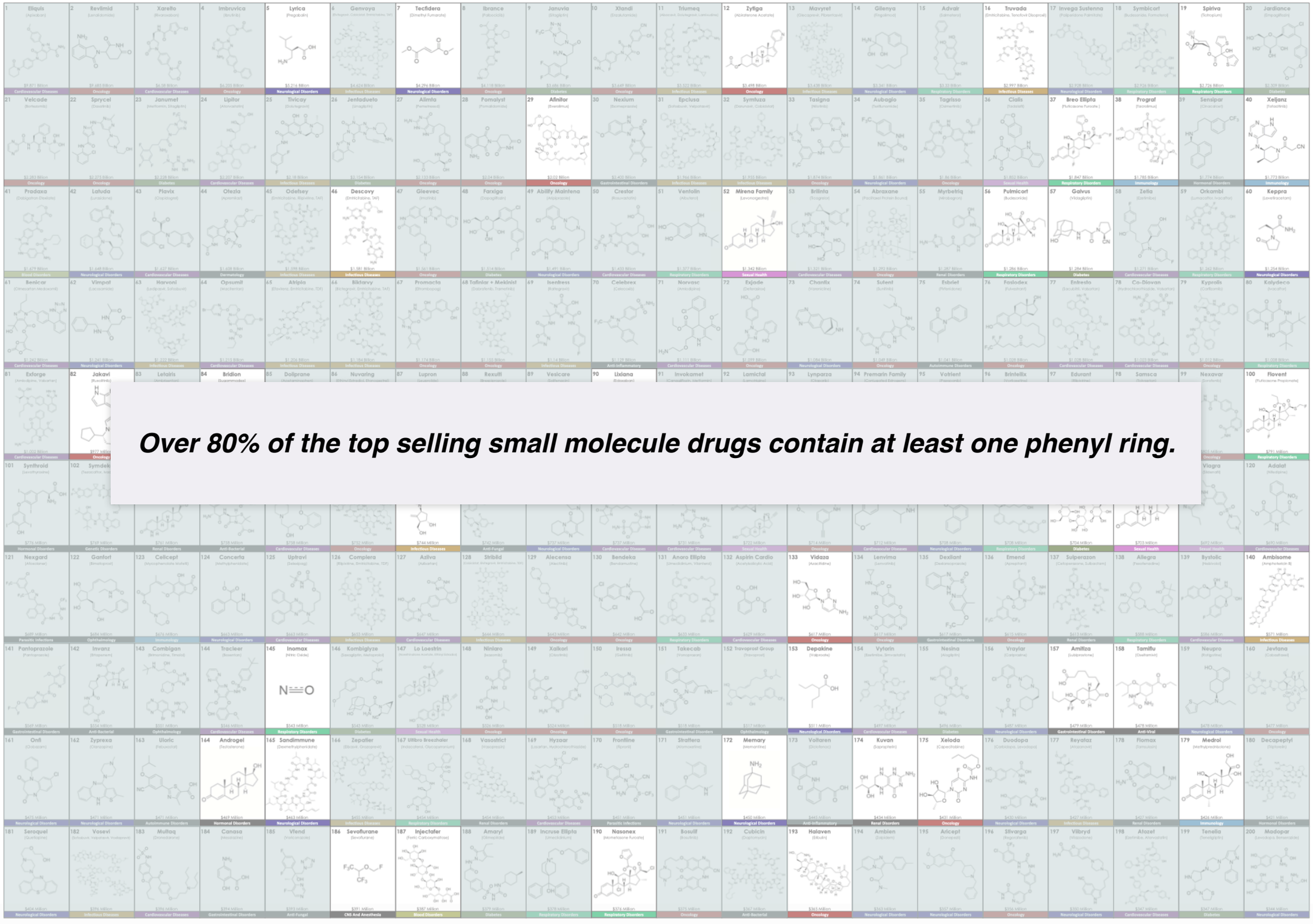
Ei-ichi Negishi

Akira Suzuki

Diederich, F., *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.
The Nobel Prize in Chemistry 2010.

Phenyl Rings as Ubiquitous Scaffolds of Life

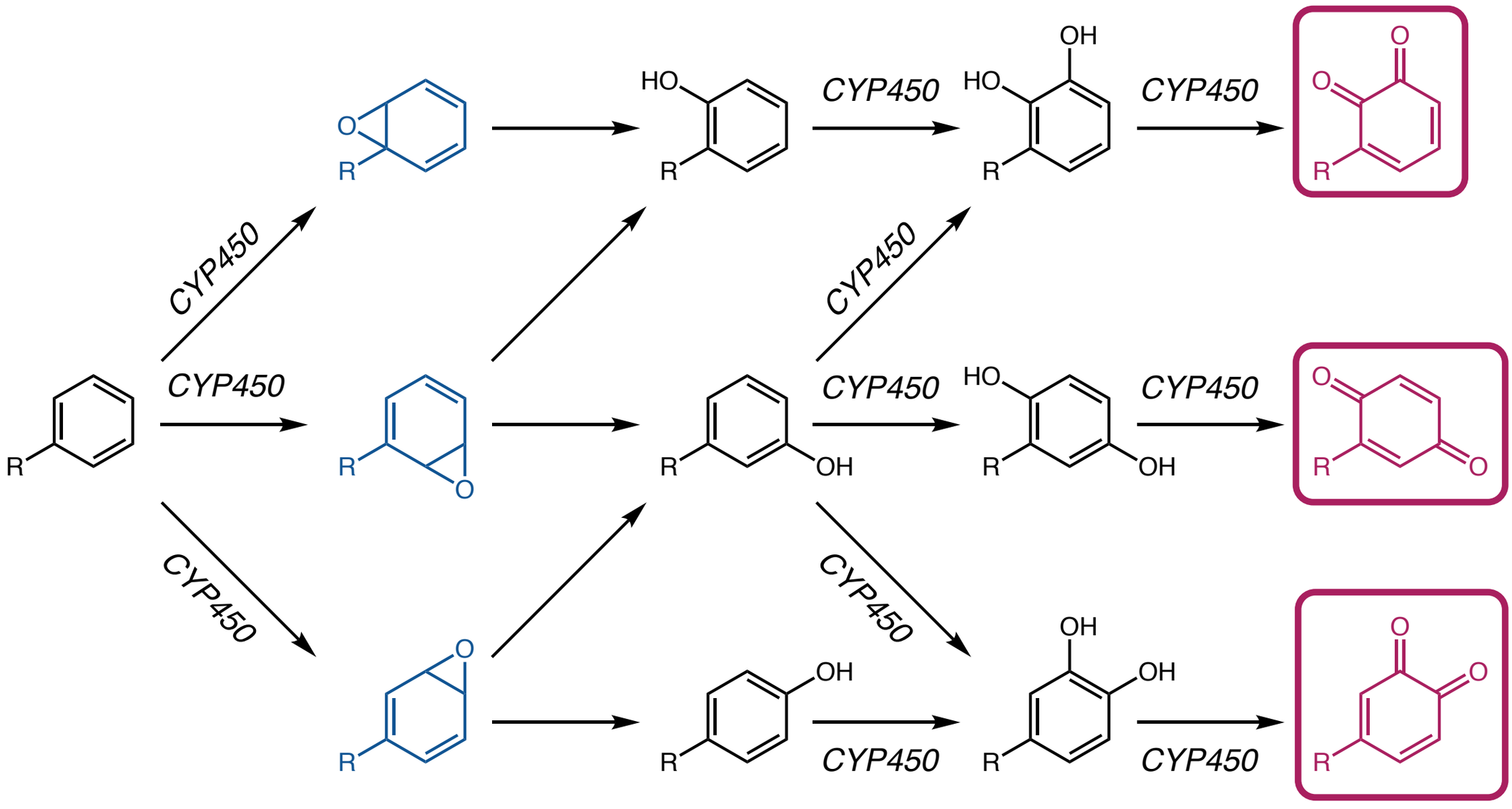
Top 200 Small Molecule Parmaceuticals by Retail Sales in 2018



Over 80% of the top selling small molecule drugs contain at least one phenyl ring.

Njardarson, J. T., *J. Chem. Educ.* **2010**, *87*, 1348.

Phenyl Metabolites and Hepatotoxicity



reactive intermediates

covalent binders

Bolton, J. L., *Chem. Res. Toxicol.* **2017**, *30*, 13.

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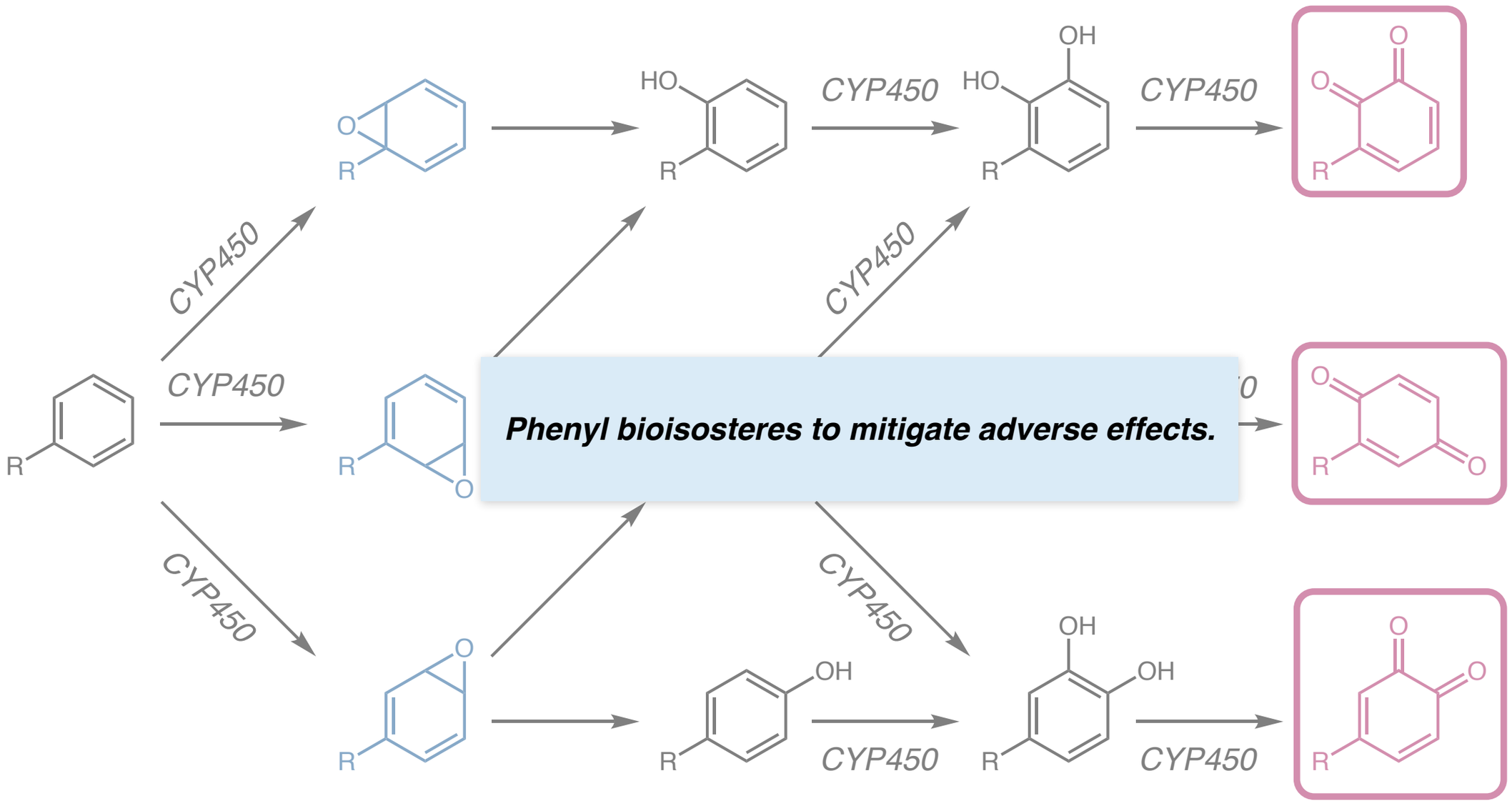

Phenyl bioisosteres to mitigate adverse effects.

reactive intermediates

covalent binders

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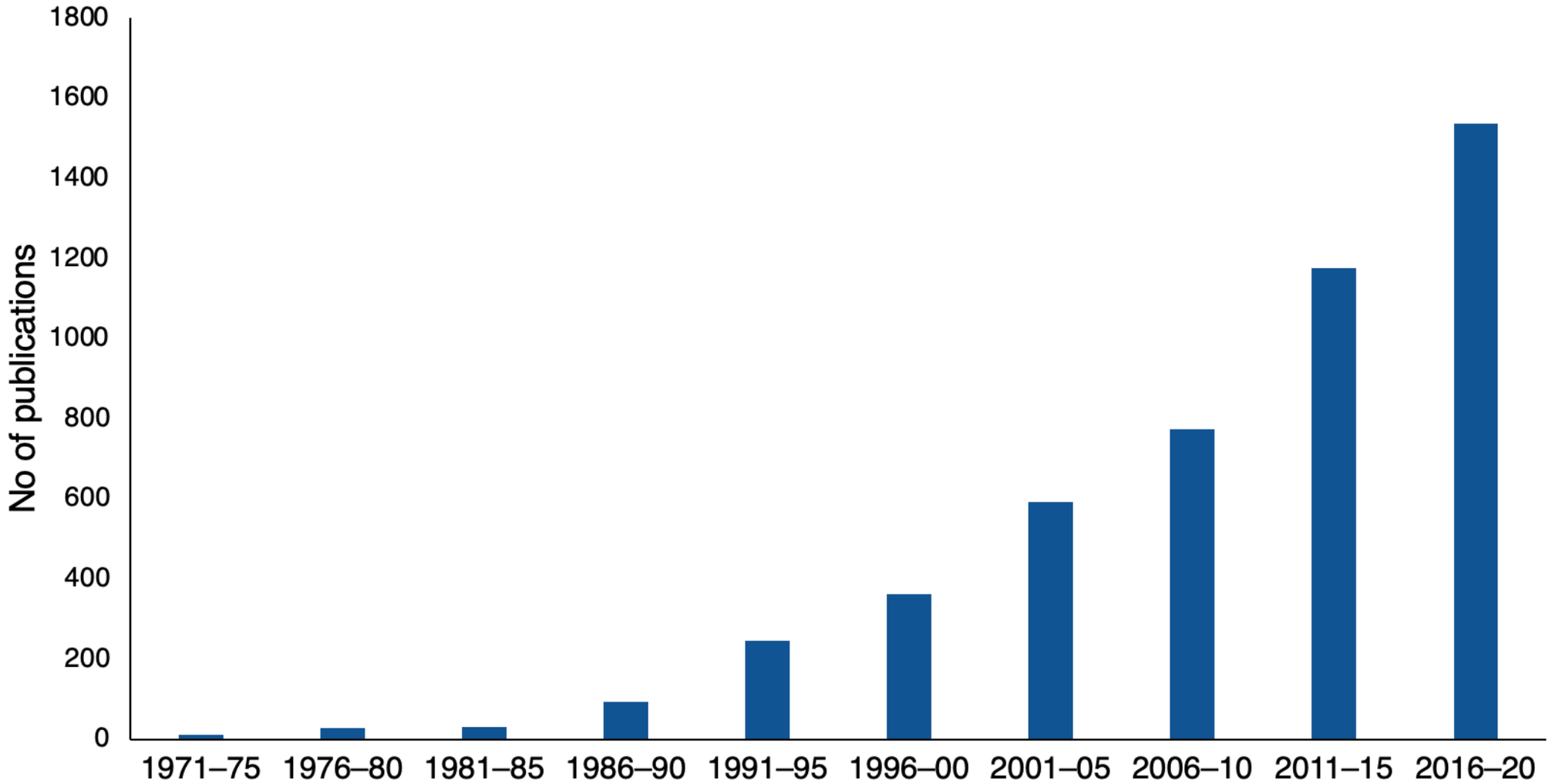
Bioisosteres in the Literature



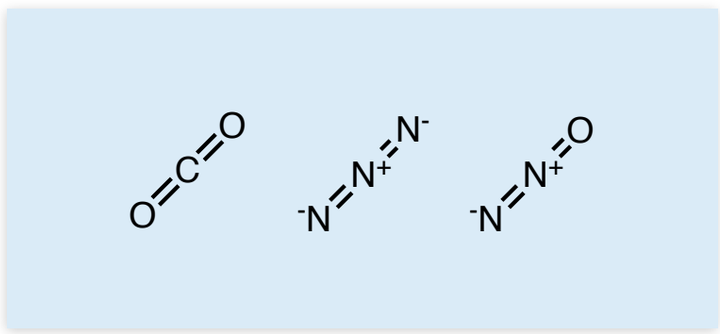
Scifinder; 2021/10.

What Does 'Bioisostere' Mean, Really?

Langmuir *1919*:
isosteres are "compounds or groups of atoms having the same number of atoms and electrons"

groups	isosteres
1	H^-, He, Li^+
2	O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+}
3	S^{2-}, Cl^-, Ar, K^+, Ca^{2+}
4	Cu^{2-}, Zn^{2+}
↓	↓
8	N_2, CO, CN^-
9	CH_4, NH_4^+
10	CO_2, N_2O, N_3^-, CNO^-
↓	↓
20	MnO_4^-, CrO_4^{2-}
21	SeO_4^{2-}, AsO_4^{3-}

1900 *1950* *2000* *2020*



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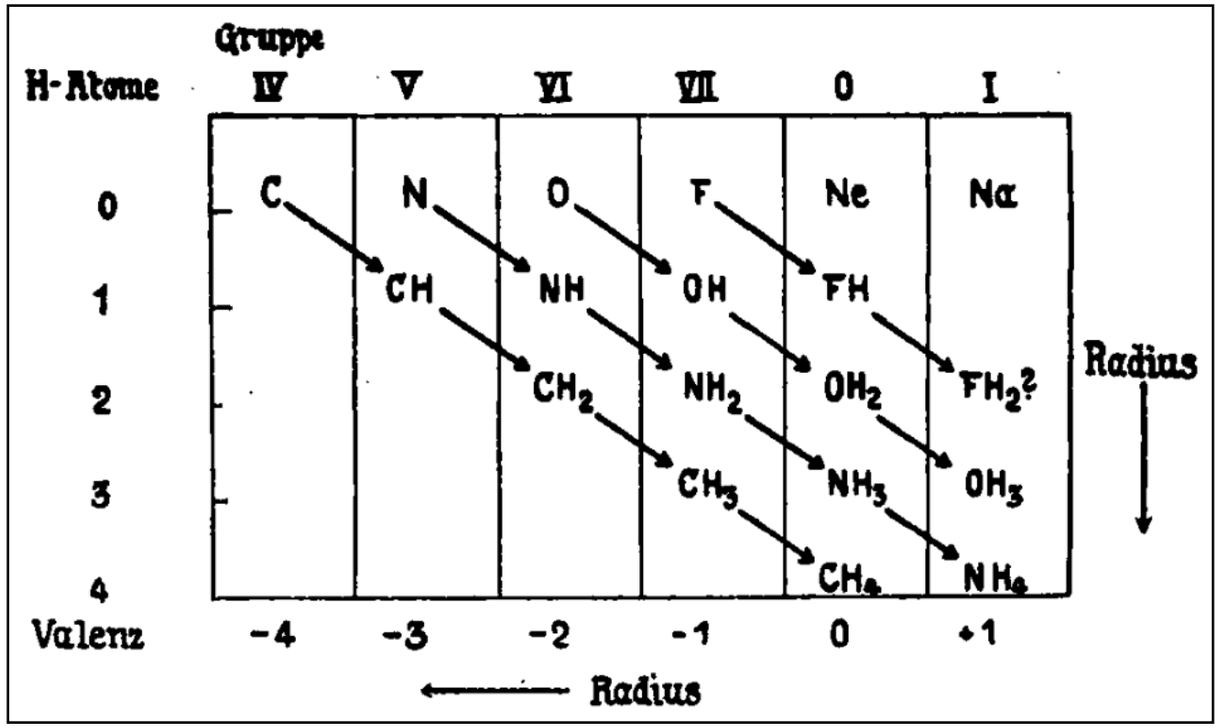
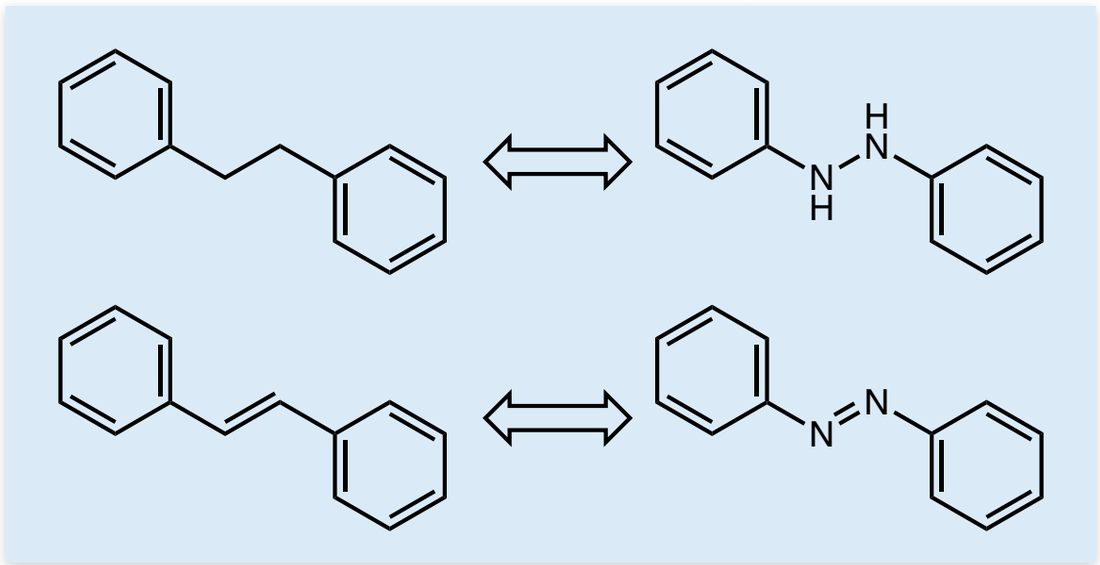


1900 1950 2000 2020

Grimm *1925*:

Hydride replacement law for isosterism



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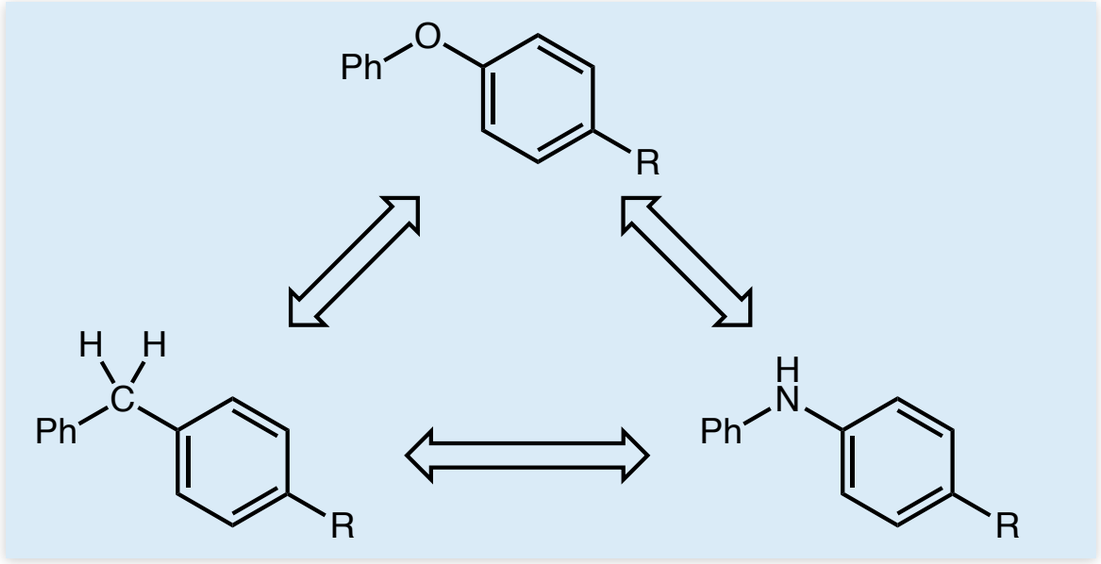
"atoms, ions or molecules in which the peripheral layers of electrons can be considered identical"



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Hydride replacement law for isosterism

no. of peripheral electrons				
4	5	6	7	8
N^+	P	S	Cl	ClH
P^+	As	Se	Br	BrH
S^+	Sb	Te	I	IH
As^+		PH	SH	SH_2
Sb^+			PH_2	PH_3

Langmuir, I., *JACS* **1919**, *41*, 1543.
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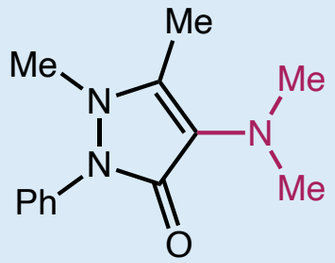
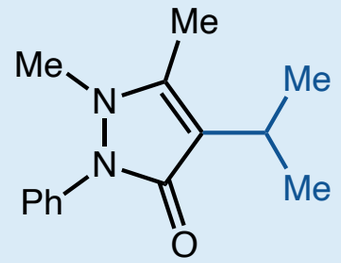


Aminopyrine
analgesic
cancerogenic



Propyphenazone

non-cancerogenic

1900 *1950* *2000* *2020*

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Friedman *1951*:
Bioisosteres are "compounds if they **fit the broadest definition for isosteres** and have the same type of biological activity."

Roche 1933: Saridon

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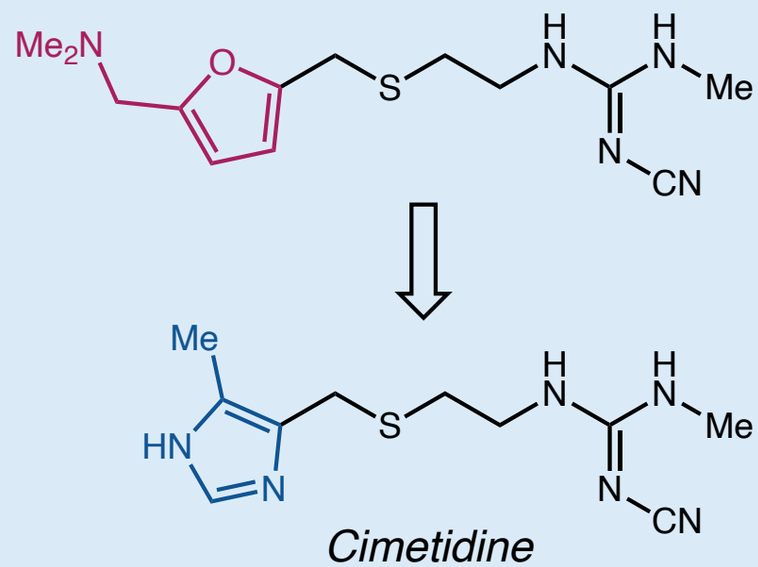

Cimetidine
antihistamine, GSK

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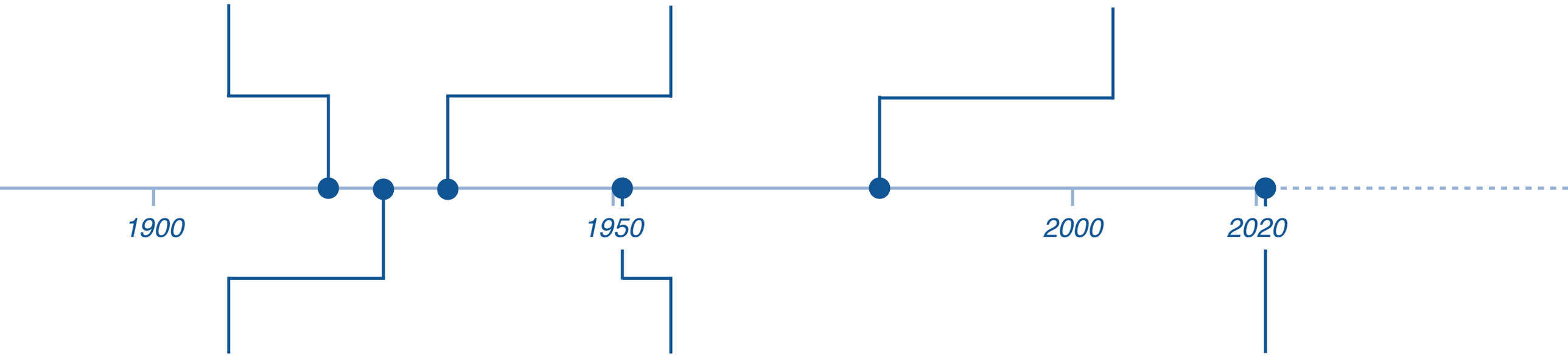

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Meanwell, 2021:
"structural motifs that express similar biological properties or close physicochemical attributes **without the fundamental stipulation that they present a similar shape and size.**"

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Grimm, H. G., *Z. Electrochem.* **1925**, *31*, 474.
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Thornber, C. W., *Chem. Soc. Rev.* **1979**, *4*, 563.
Meanwell, N. A., *J. Med. Chem.* **2021**, *64*, 14046.

A Conventional View of Bioisosteres

classical bioisosteres

monovalent bioisosteres

D and H
F and H
NH and OH
RSH and ROH
F, OH, NH_2 and CH_3
Cl, Br, SH and OH
C and Si

bivalent biososteres in which two single bonds are affected

C═C, C═N, C═O, C═S
$-CH_2-$, −NH−, −O−, −S−
RCOR′, RCONHR′, RCOOR′, RCOSR′

trivalent bioisosteres in which three bonds are affected

R_3CH, R_3N
R_4C, R_4Si, R_4N^+
alkene, imine
−CH═CH−, −S−
−CH═ and −N═C

nonclassical bioisosteres

are structurally distinct, usually comprise different number of atoms and exhibit different steric and electronic properties compared to the functionality being emulated
have been divided into two subgroups:[2]

1. cyclic and noncyclic isosteres
2. exchangeable group isosterism in which the properties of discrete functional elements are emulated

LaVoie, E. J., *Chem. Rev.* **1996**, *96*, 3147.
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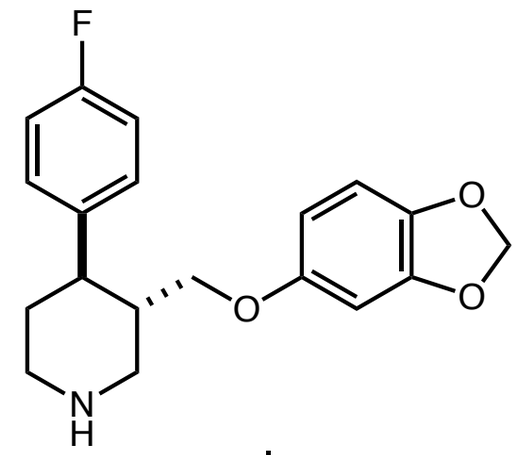
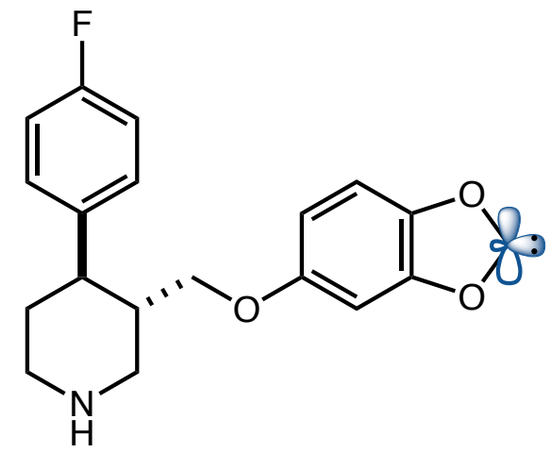


paroxetine
antidepressant

CYP2D6



adverse effects

LaVoie, E. J., *Chem. Rev.* **1996**, *96*, 3147.
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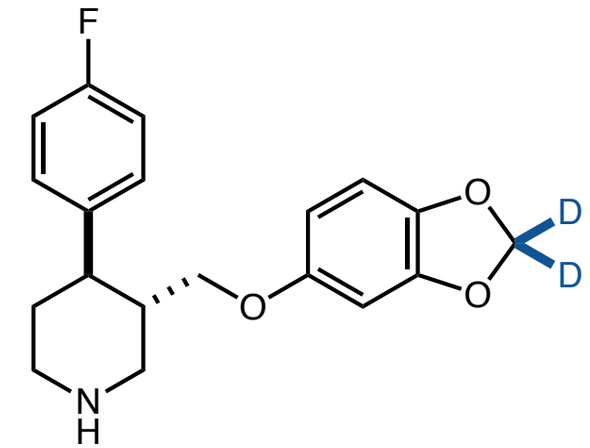
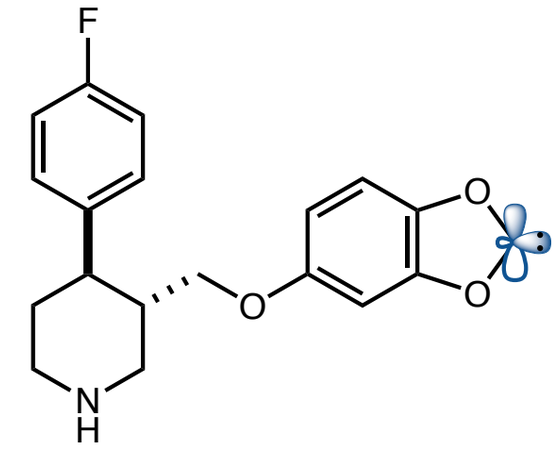


H → D isostere

CYP2D6

strongly reduced metabolization



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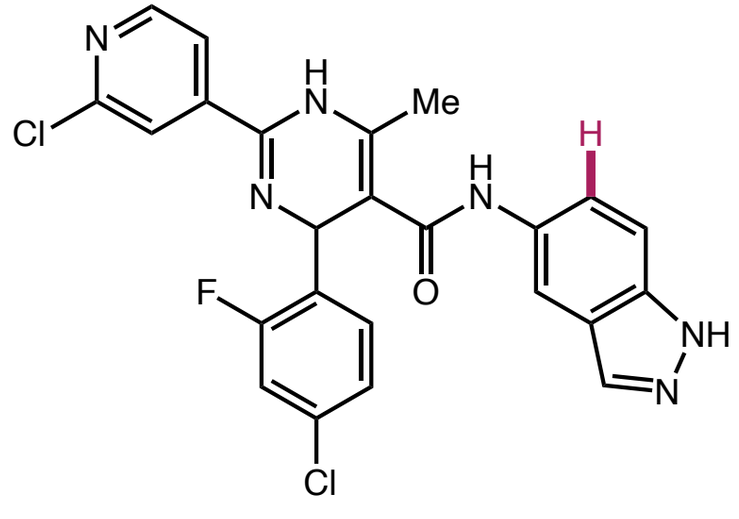
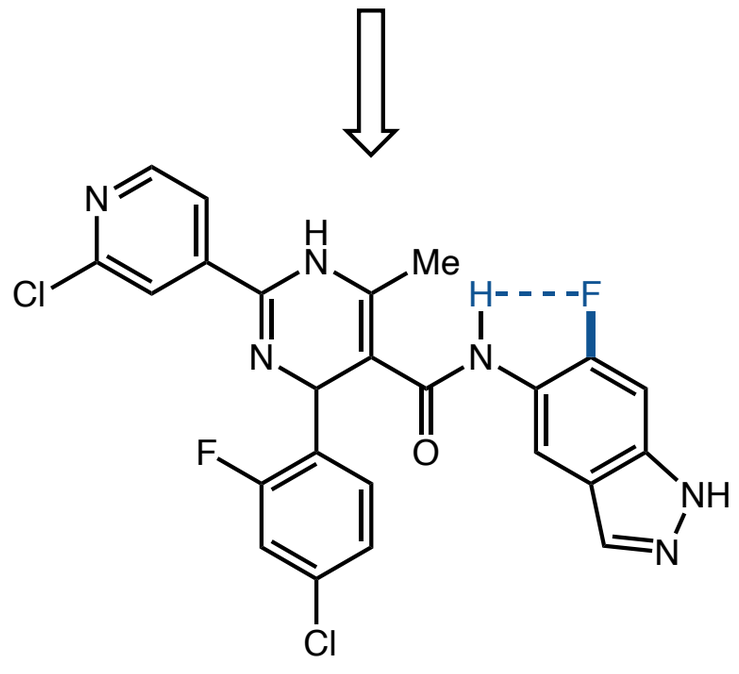


Rho kinase antagonist

liver toxicity
poor oral bioavalability
(F = 7%)



H → F isostere

equipotent

improved
oral bioavalability
(F = 49%)

LaVoie, E. J., *Chem. Rev.* **1996**, *96*, 3147.
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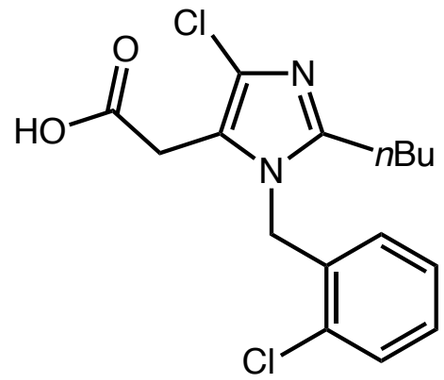
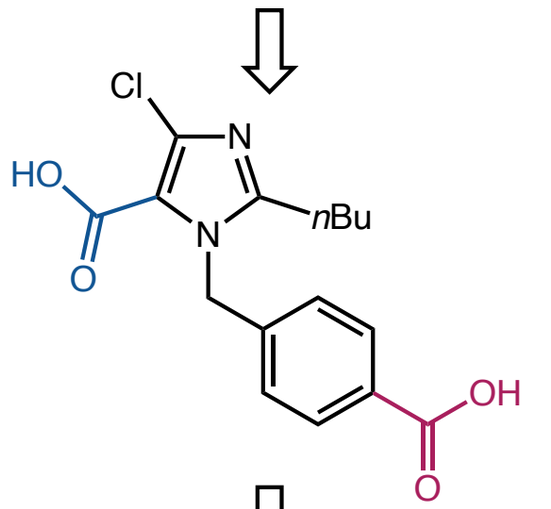
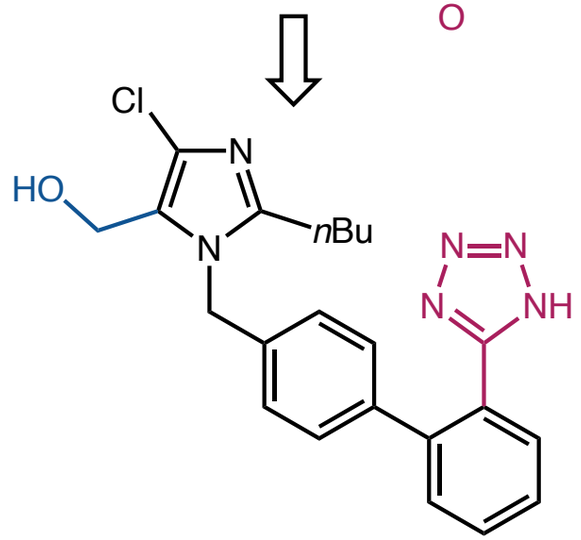


initial lead
AT1R antagonist
IC50 = 40 mM



IC50 = 1.2 mM



Losartan
Merck

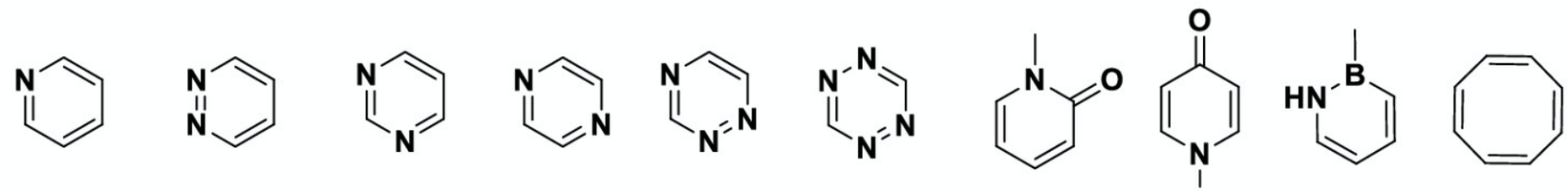
IC50 = 19 uM

60M prescriptions
(US/2018)

LaVoie, E. J., *Chem. Rev.* **1996**, *96*, 3147.
Meanwell, N. A., *J. Med. Chem.* **2011**, *54*, 2529.
Lee, D., *J. Med. Chem.* **2008**, *51*, 6631.
Mavromoustakos, T., *Molecules* **2021**, *26*, 2927.

A Most Likely Incomplete List of Proposed Phenyl Bioisosteres

> *"similar biological properties or close physicochemical attributes without the fundamental stipulation that they present a similar shape and size."*



t ***o, m, p***

t ***o, m, p***

t ***o, m, p***

t ***o, m, p***

t ***o, m, p***

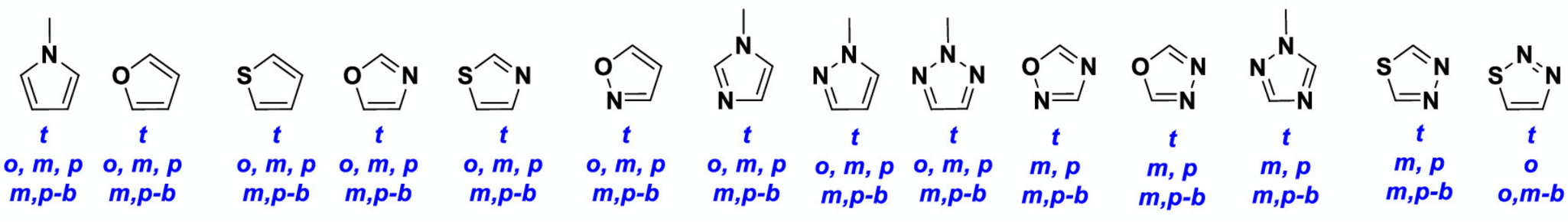
t ***p***

t ***o, m, p***

t ***o, m, p***

t ***o, m, p***

t ***o, m, p***



t ***o, m, p*** ***m,p-b***

t ***o, m, p*** ***m,p-b***

t ***o, m, p*** ***m,p-b***

t ***o, m, p*** ***m,p-b***

t ***o, m, p*** ***m,p-b***

t ***o, m, p*** ***m,p-b***

t ***o, m, p*** ***m,p-b***

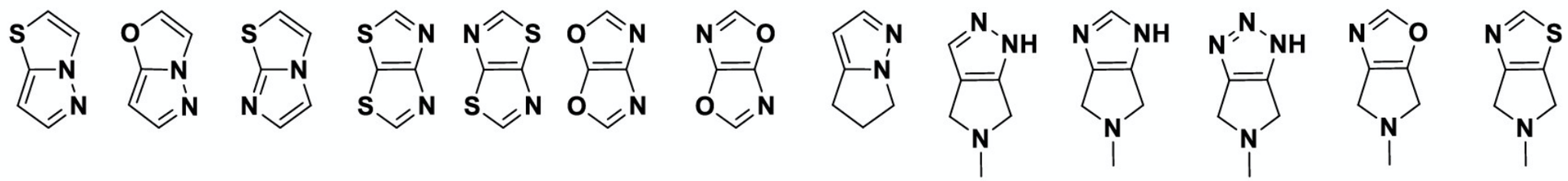
t ***o, m, p*** ***m,p-b***

t ***m, p*** ***m,p-b***

t ***m, p*** ***m,p-b***

t ***m, p*** ***m,p-b***

t ***o*** ***o,m-b***



t ***m, p***

t ***m, p***

t ***o, m, p***

t ***p***

t ***p***

t ***p***

t ***p***

t ***o, m, p***

t ***o, m, p***

t ***o, m, p***

t ***o, m, p***

t ***m, p***

t ***m, p***

Meanwell, N. A., *J. Med. Chem.* **2021**, *64*, 14046.

A Most Likely Incomplete List of Proposed Phenyl Bioisosteres

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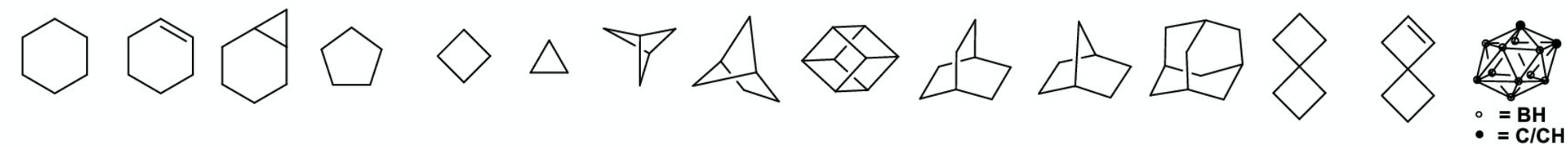

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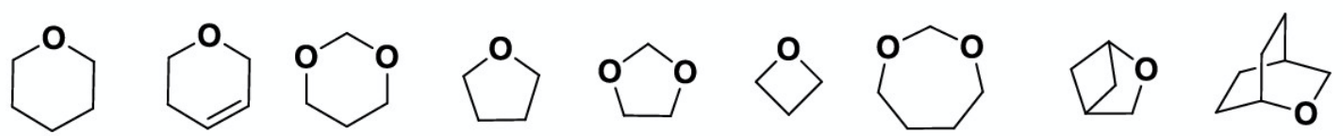
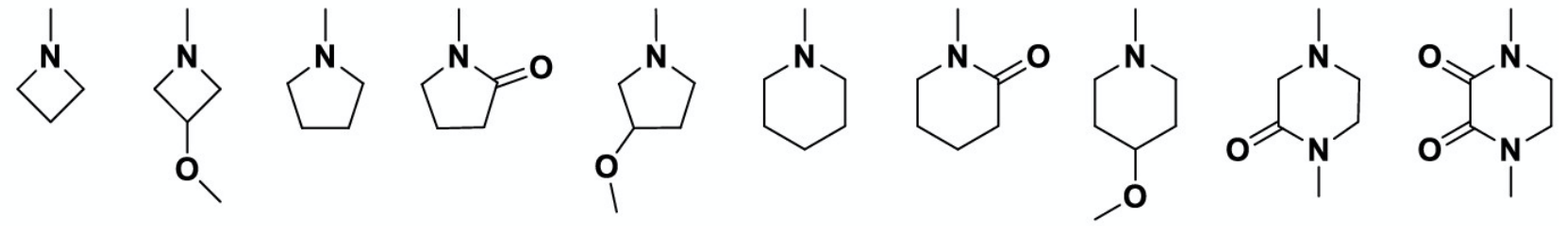
o, m, p	o, m, p	o, m, p	o, m, p m,p-b	o, p	m, p m,p-b	o, p	o, p	o, p	o, m, p	o, m, p	o, m, p	o, m, p	o, m, p	p



t	t	t	t	t	t	t	t	t
o, m, p	o, m, p	o, m, p	o, m, p m,p-b	o, m, p	o, p	o, m, p	o, p	o, m, p

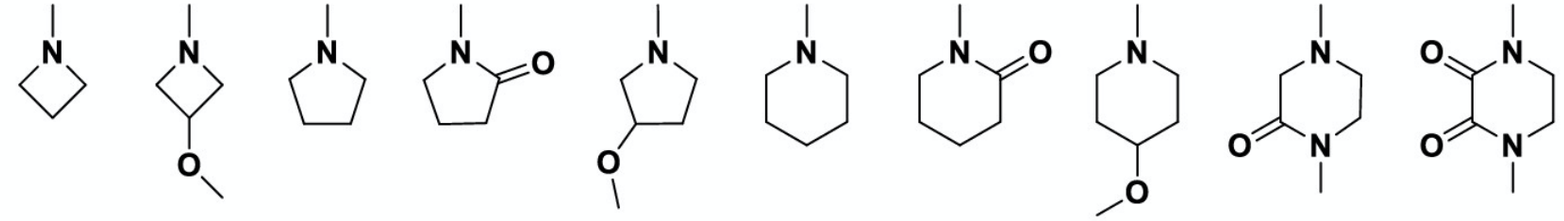


t	t	t	t	t	t	t	t	t	t
o, p	o, p	o, m, p m,p-b	o, m, p m,p-b	o, m, p m,p-b	o, m, p	o, m, p	o, m, p	o, m, p	o, m, p

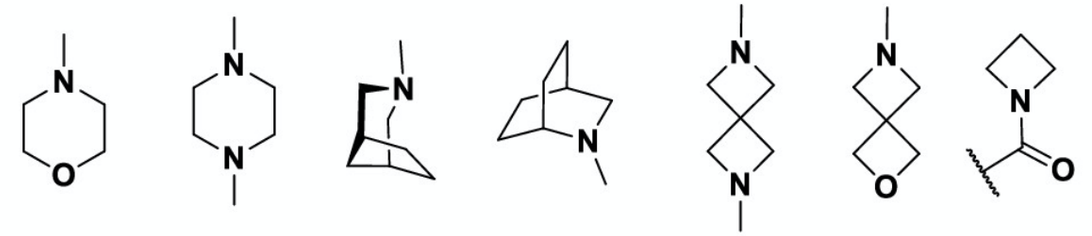
Meanwell, N. A., *J. Med. Chem.* **2021**, *64*, 14046.

A Most Likely Incomplete List of Proposed Phenyl Bioisosteres

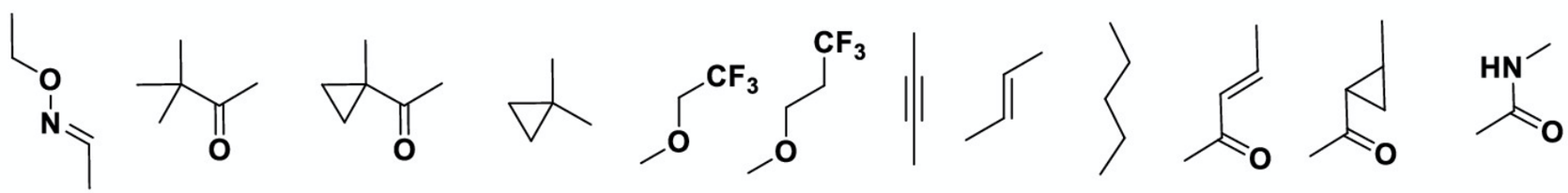
> *"similar biological properties or close physicochemical attributes without the fundamental stipulation that they present a similar shape and size."*



t ***o, p*** | ***t*** ***o, p*** | ***t*** ***o, m, p*** ***m,p-b*** | ***t*** ***o, m, p*** ***m,p-b*** | ***t*** ***o, m, p*** ***m,p-b*** | ***t*** ***o, m, p*** | ***t*** ***o, m, p*** | ***t*** ***o, m, p*** | ***t*** ***o, m, p*** | ***t*** ***o, m, p*** | ***t*** ***o, m, p***



t ***o, m, p*** | ***t*** ***o, m, p*** | ***t*** ***o, p*** | ***t*** ***o, m, p*** | ***t*** ***o, m, p*** | ***t*** ***o, m*** | ***t*** ***o, m, p***

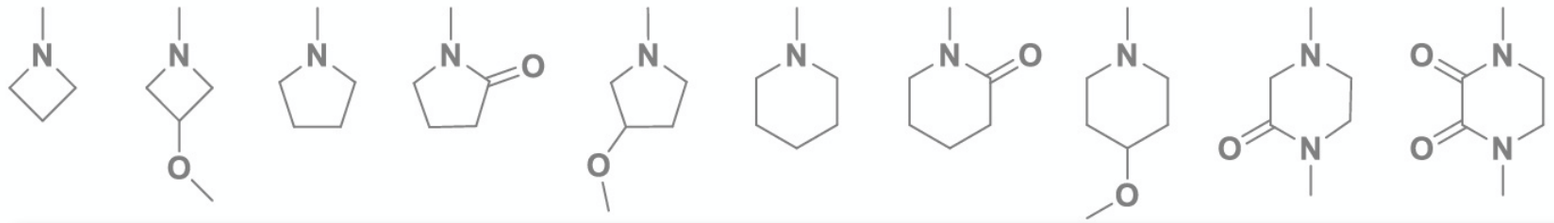


t ***m, p*** | ***t*** ***o*** | ***t*** ***o*** | ***t*** ***o*** | ***t*** | ***t*** | ***t*** ***p*** | ***t*** ***p*** | ***t*** ***o, m, p*** | ***t*** ***m, p*** | ***t*** ***m, p*** | ***t*** ***m, p***

Meanwell, N. A., *J. Med. Chem.* **2021**, *64*, 14046.

A Most Likely Incomplete List of Proposed Phenyl Bioisosteres

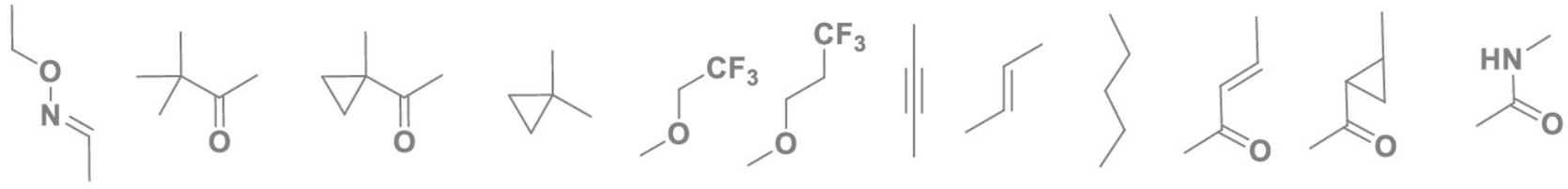
> *"similar biological properties or close physicochemical attributes without the fundamental stipulation that they present a similar shape and size."*



This talk is by no means a complete overview.

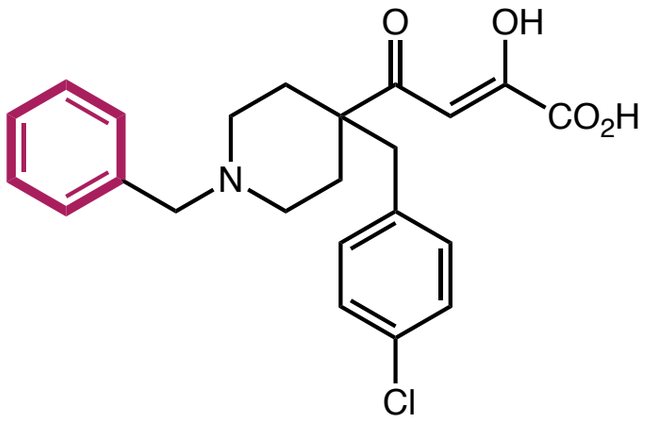
Its goal is to give an idea of how challenging it is to predict the the biological consequences and efficacy of bioisosteric replacements.

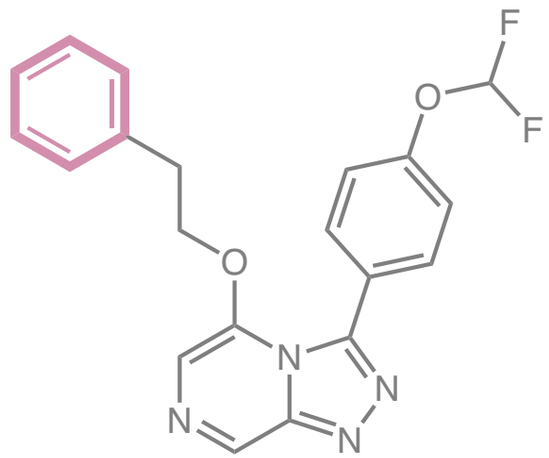
Emphasis will be on a select few more obscure or easily disregarded replacements; replacements the group is well familiar with will only play a minor part.

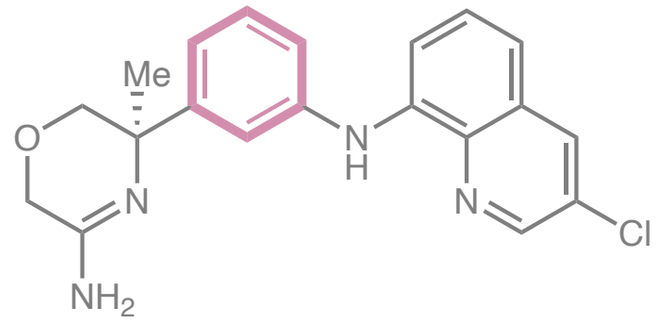


Meanwell, N. A., *J. Med. Chem.* **2021**, *64*, 14046.

Outline

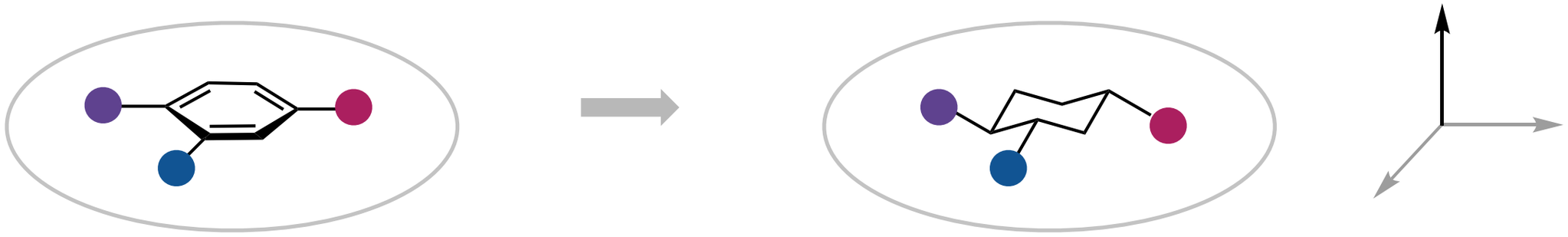




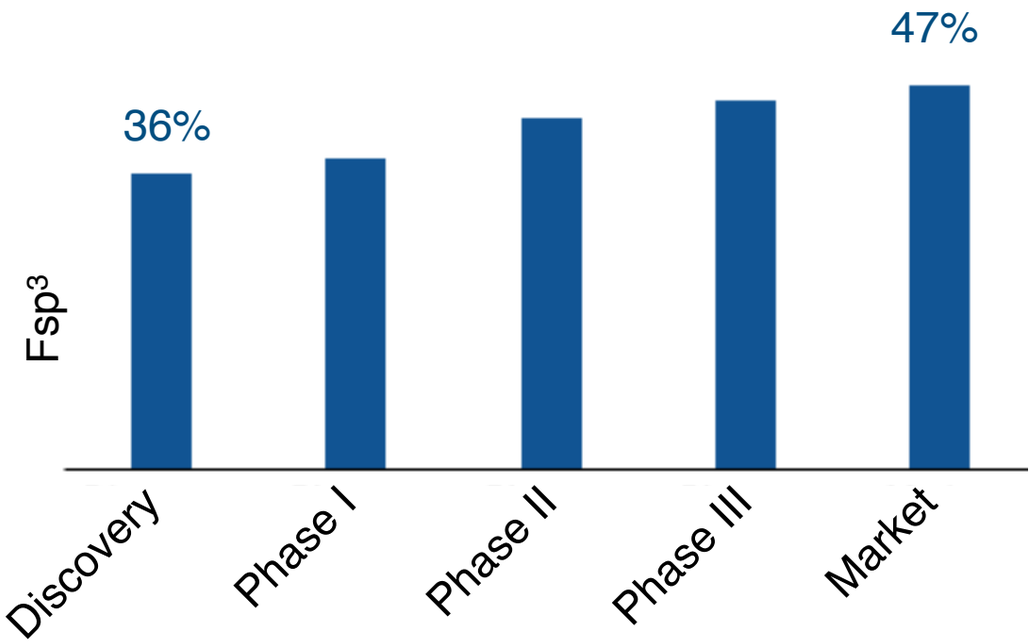


beneficial effects and limitations of an often disregarded bioisostere

The Escape from Flatland

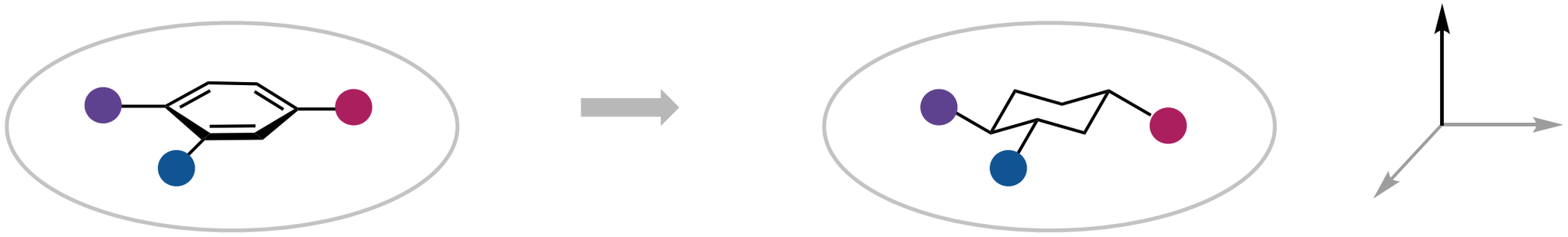


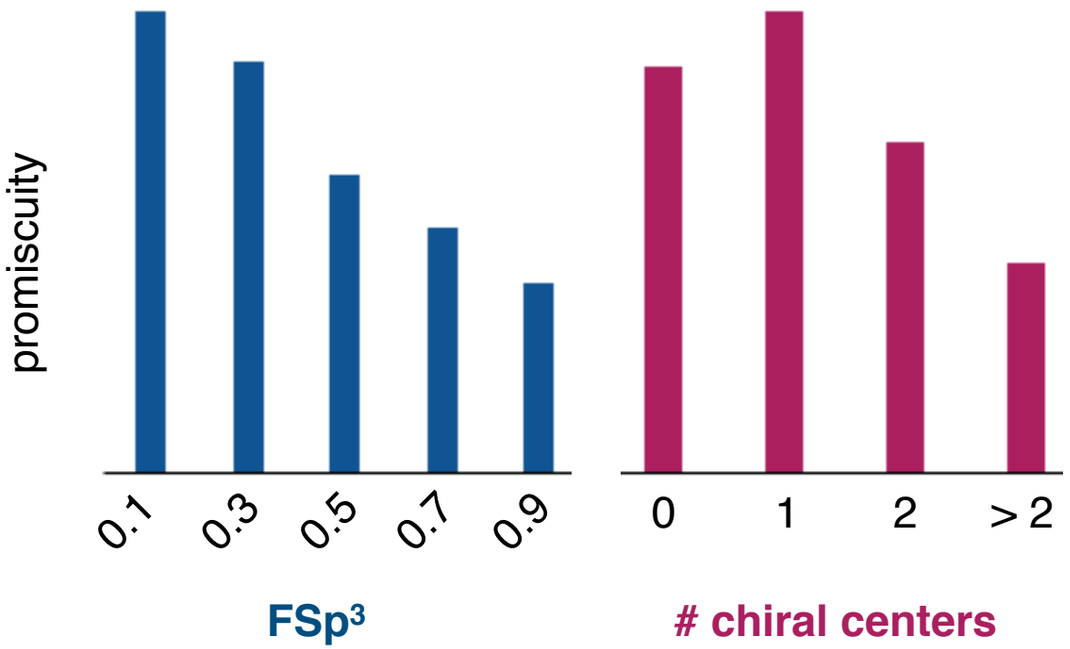
increasing C(sp³) content correlated with clinical success



Lovering, F., *J. Med. Chem.* **2009**, *52*, 6752.
Lovering, F., *Med. Chem. Commun.* **2013**, *4*, 515.
Fraga, C. A. M., *Curr. Top. Med. Chem.* **2019**, *19*, 1712.

The Escape from Flatland





increasing C(sp³) content correlated with clinical success

increasing molecular complexity correlates with selectivity

Lovering, F., *J. Med. Chem.* **2009**, *52*, 6752.
Lovering, F., *Med. Chem. Commun.* **2013**, *4*, 515.
Fraga, C. A. M., *Curr. Top. Med. Chem.* **2019**, *19*, 1712.

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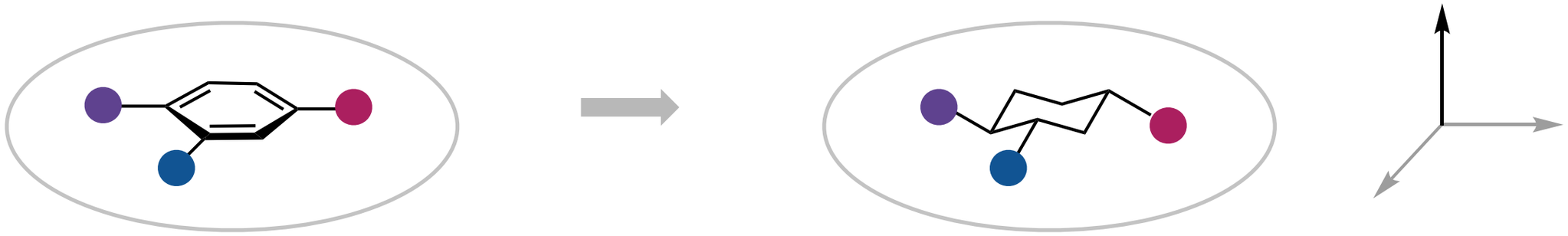

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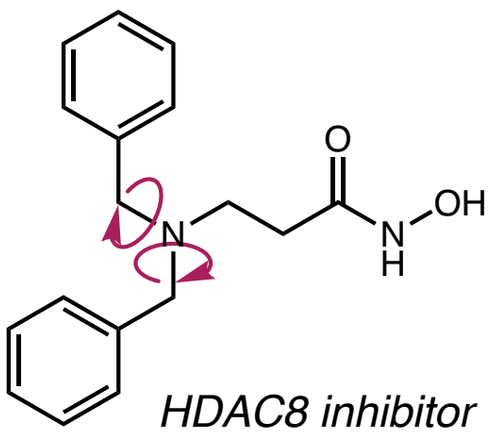
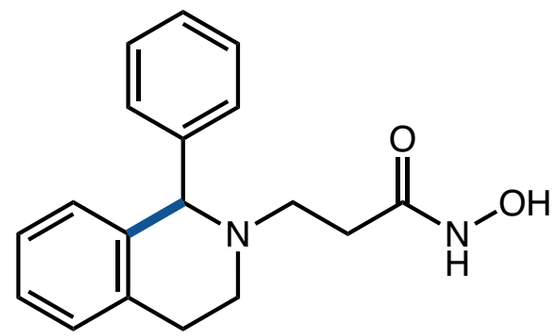


HDAC8 inhibitor

IC50 = 1400 nM



IC50 = 950 nM

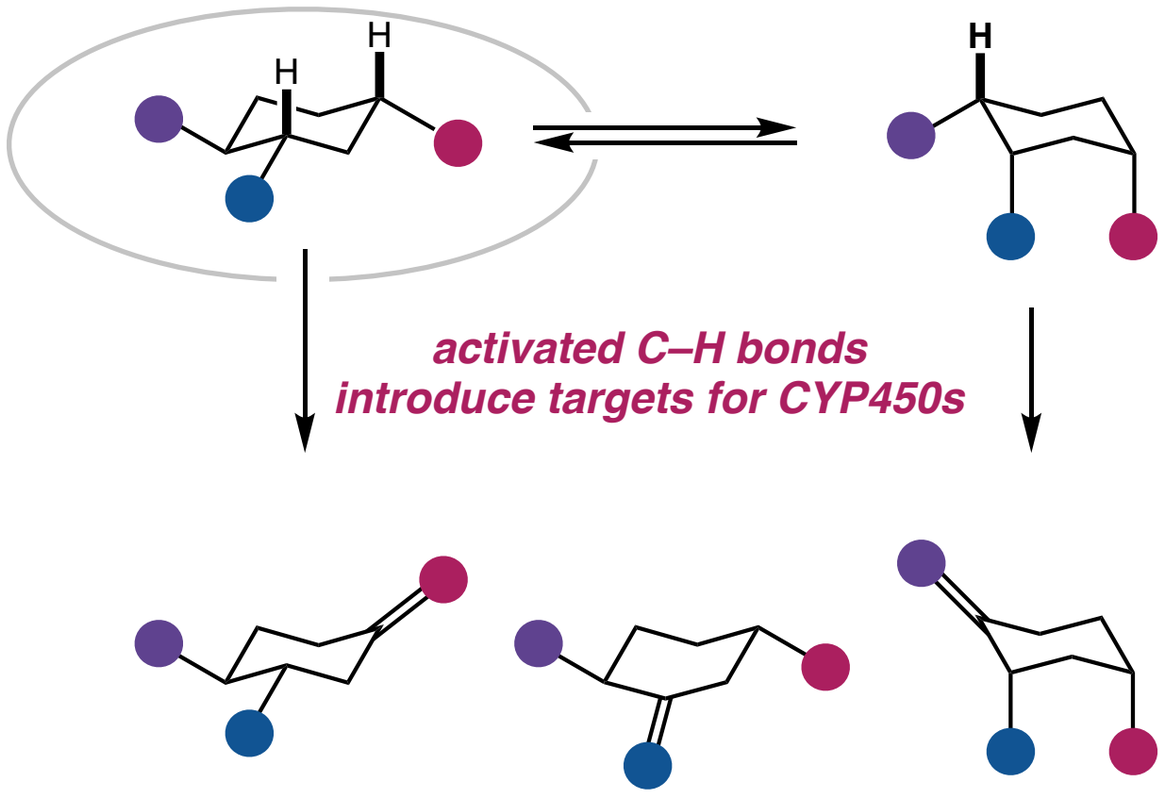
increasing molecular complexity correlates with selectivity

increasing molecular rigidity in scaffolds leads to improved selectivity

Lovering, F., *J. Med. Chem.* **2009**, *52*, 6752.
Lovering, F., *Med. Chem. Commun.* **2013**, *4*, 515.
Fraga, C. A. M., *Curr. Top. Med. Chem.* **2019**, *19*, 1712.

The Escape from Flatland

Is cyclohexyl really that useless as a bioisostere?



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increasing molecular complexity correlates with selectivity

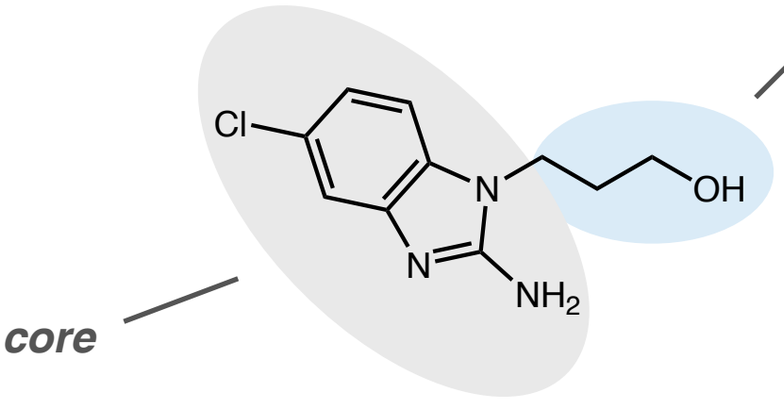
increasing molecular rigidity in scaffolds leads to improved selectivity

Lovering, F., *J. Med. Chem.* **2009**, *52*, 6752.
Lovering, F., *Med. Chem. Commun.* **2013**, *4*, 515.
Fraga, C. A. M., *Curr. Top. Med. Chem.* **2019**, *19*, 1712.

Cyclohexanes as Phenyl Bioisosteres

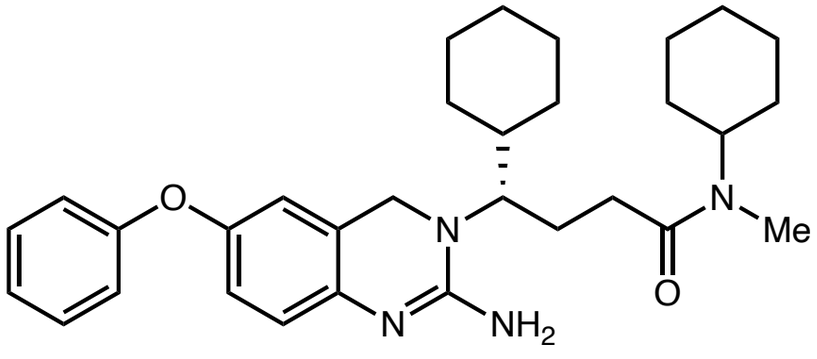
A Case Study on β-Secretase Inhibitors

variable chain

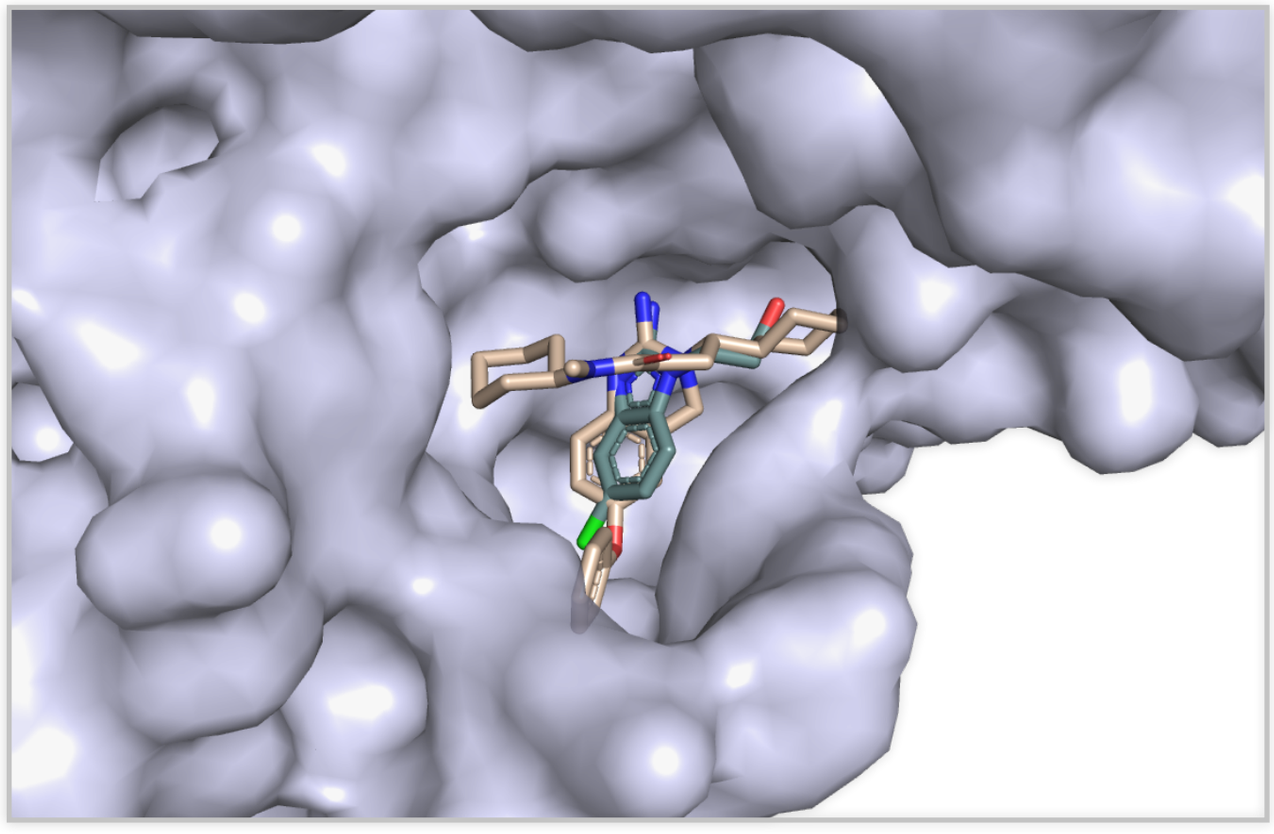


core

initial lead



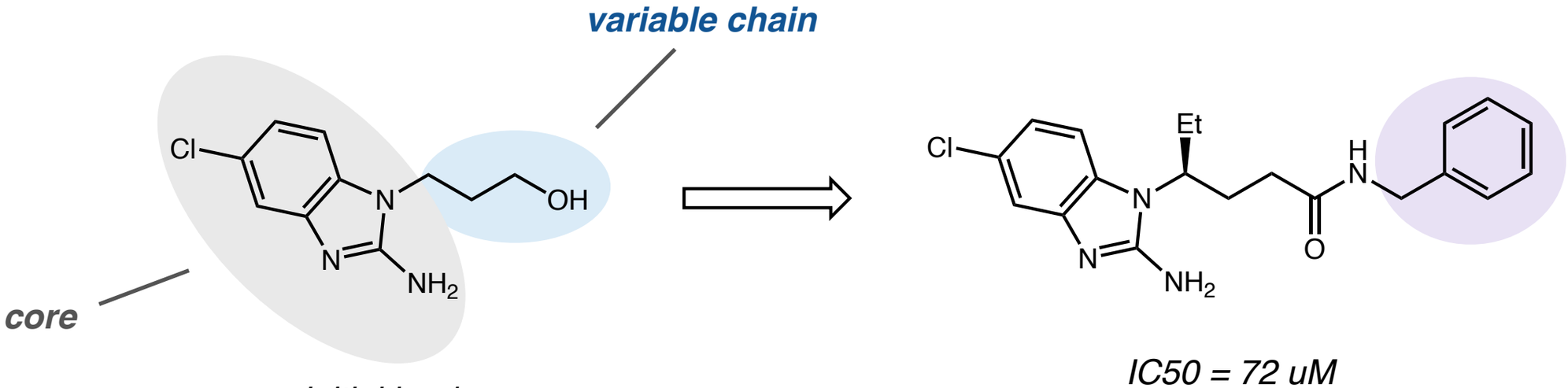
J&J clinical candidate



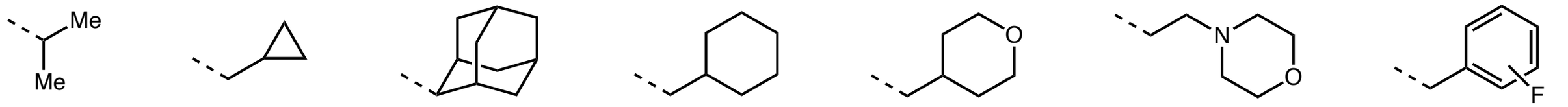
Hesterkamp, T., *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5329.
Reitz, A. B., *J. Med. Chem.* **2007**, *50*, 4261.

Cyclohexanes as Phenyl Bioisosteres

A Case Study on β-Secretase Inhibitors



SAR at Eastern amide



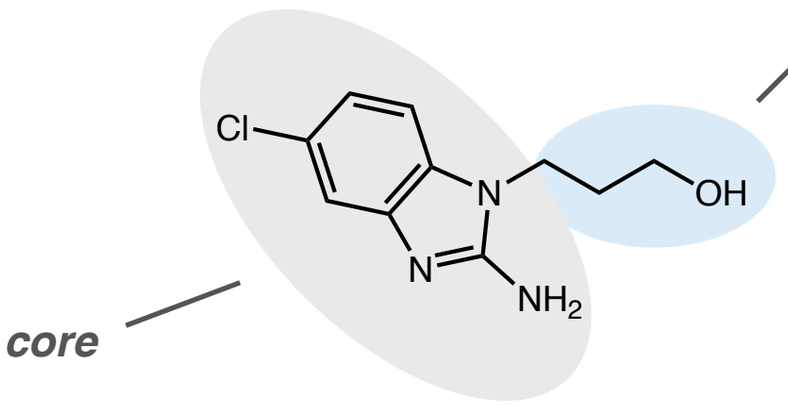
246 uM | *243 uM* | ***8.9 uM*** | ***7.0 uM*** | *> 1000 uM* | *440 uM* | *264…340 uM*

Hesterkamp, T., *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5329.
Reitz, A. B., *J. Med. Chem.* **2007**, *50*, 4261.

Cyclohexanes as Phenyl Bioisosteres

A Case Study on β-Secretase Inhibitors

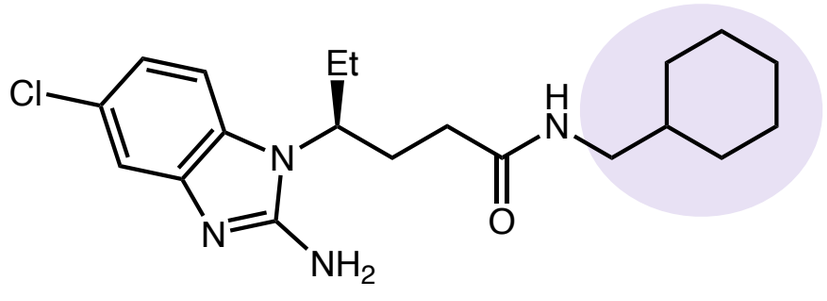
variable chain



core

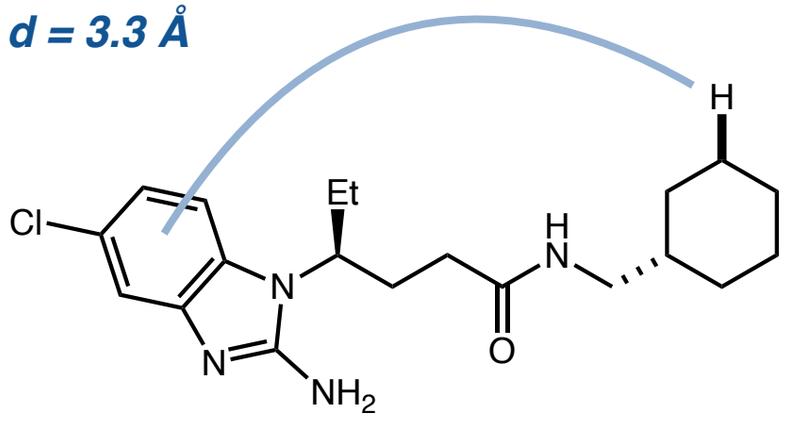
initial lead

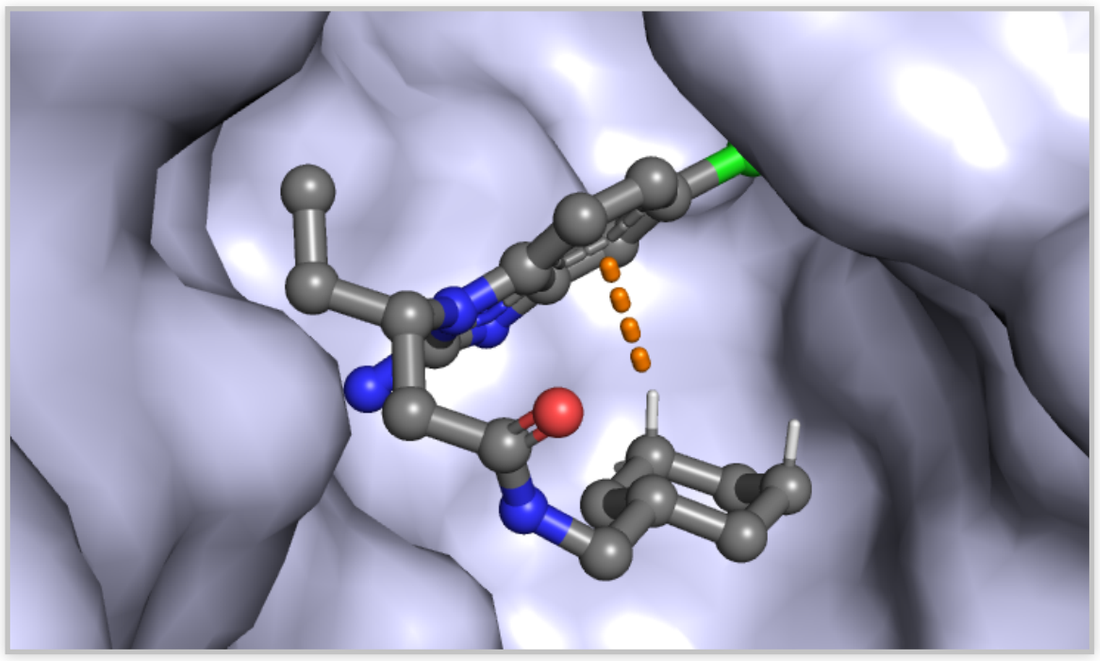
IC50 = 731 uM



IC50 = 7.0 uM

key C–H-π interaction
d = 3.3 Å

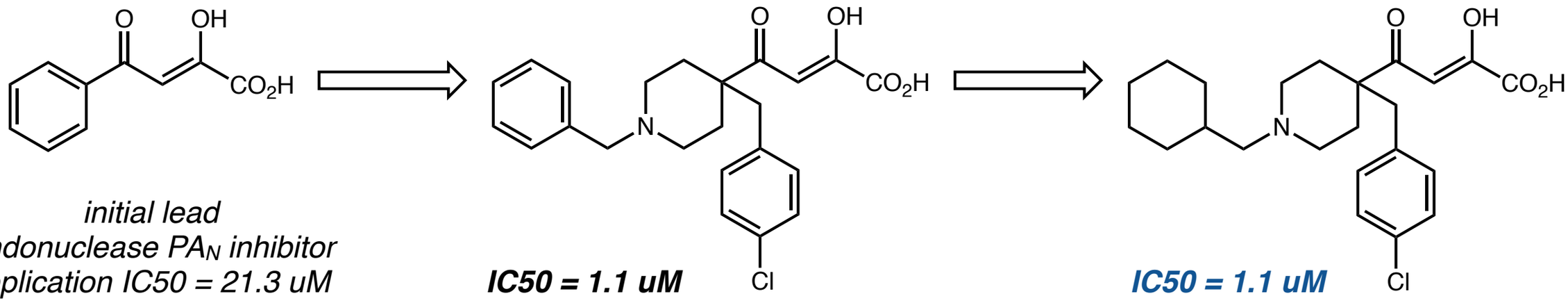




Hesterkamp, T., *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5329.
Reitz, A. B., *J. Med. Chem.* **2007**, *50*, 4261.

Cyclohexanes as Phenyl Bioisosteres

Intermolecular C–H-π Interactions Can Improve Binding

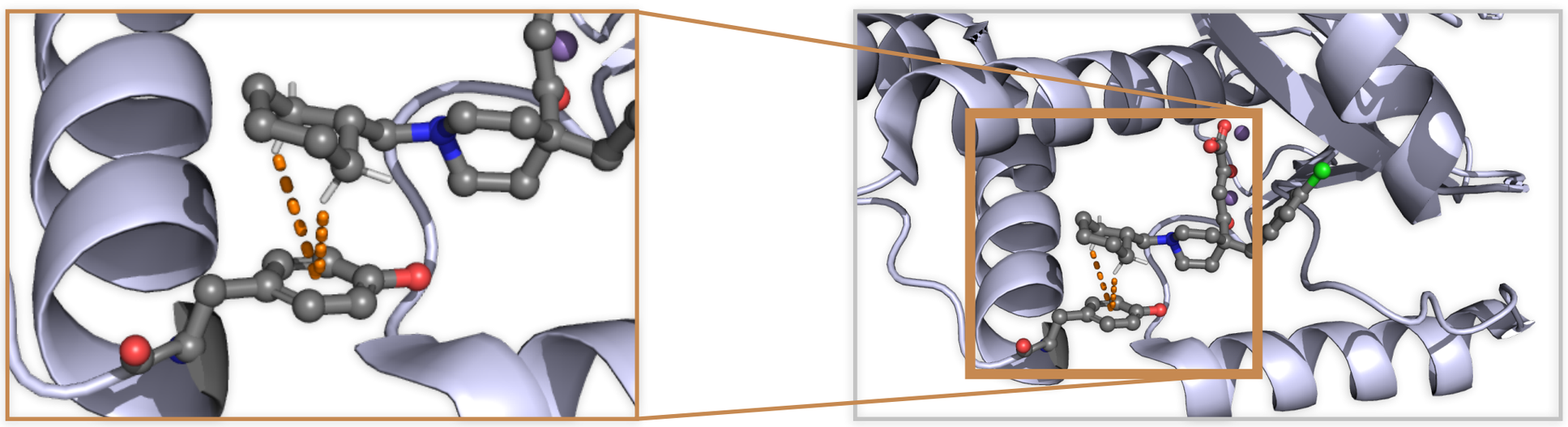


initial lead
endonuclease PA_N inhibitor
replication IC50 = 21.3 uM

IC50 = 1.1 uM

IC50 = 1.1 uM

key C–H-π interaction with Tyr24

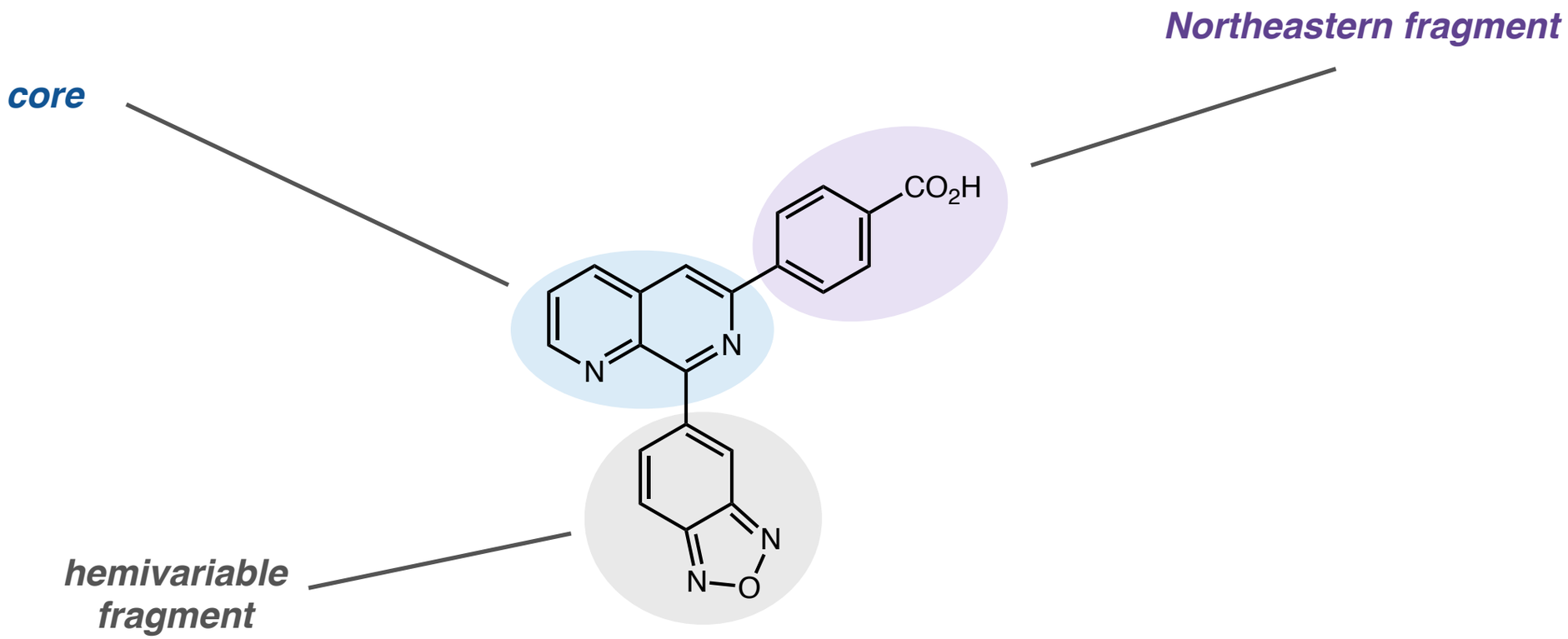


d = 3.4 Å

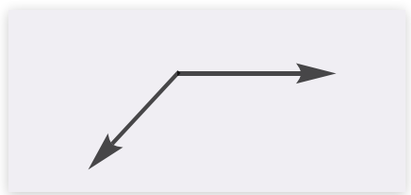
Tomassini, J., *Antimicrob. Agents Chemother.* **1994**, *38*, 2827.
Cusack, S., *PLoS Pathog.* **2012**, *8*, e1002831.

Cyclohexanes as Phenyl Bioisosteres

Viable Scaffolds to Escape Flatland



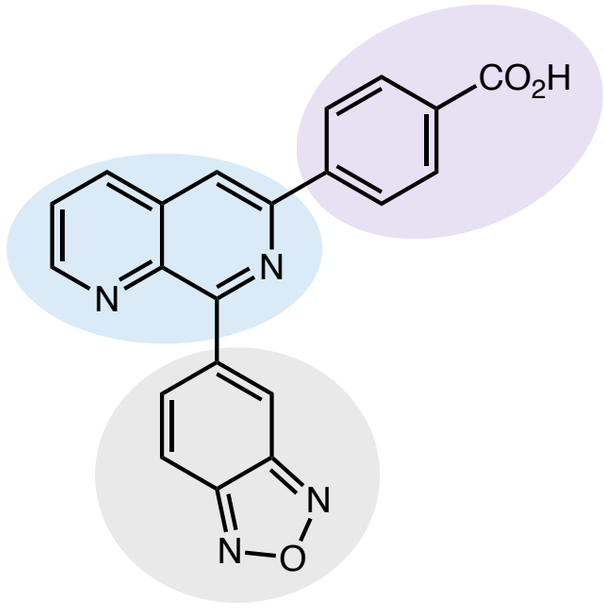
PDE4 inhibitor
initial lead
solubility: 2.3 ug/mL
oral availability: 8%



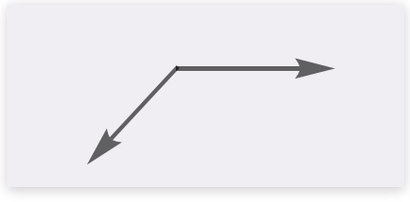
Trifilieff, A., *J. Pharmacol. Exp. Ther.* **2002**, *301*, 241.
Press, N. J. *J. Med. Chem.* **2012**, *55*, 7472.
Press, N. J., *J. Med. Chem.* **2015**, *58*, 6747.

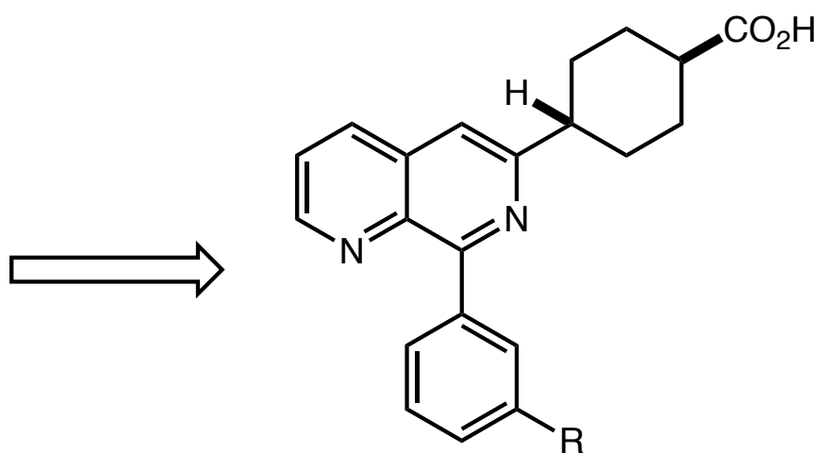
Cyclohexanes as Phenyl Bioisosteres

Viable Scaffolds to Escape Flatland

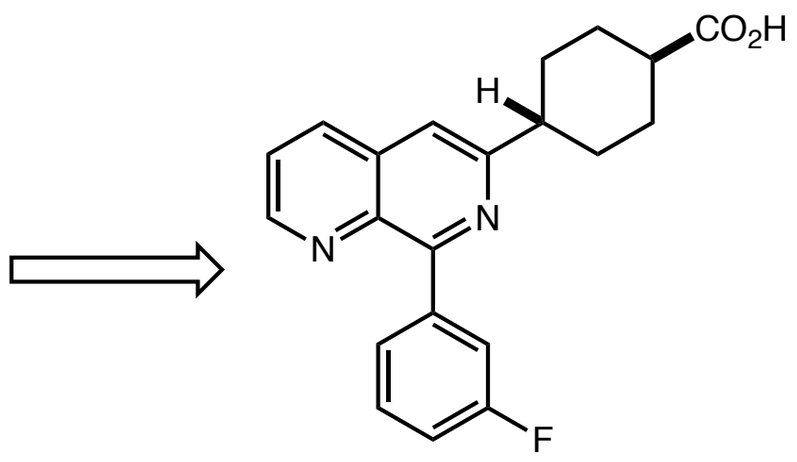


PDE4 inhibitor
initial lead
solubility: 2.3 ug/mL
oral availability: 8%



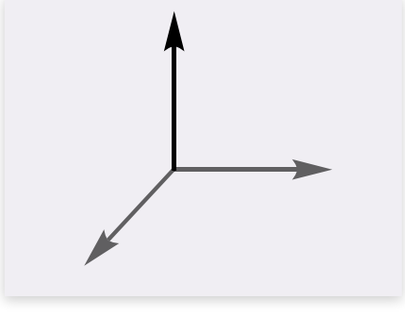


OCF_3	*solubility: 6.0 ug/mL*
OMe	*150 ug/mL*
CN	*430 ug/mL*
SMe	***1100 ug/mL***
	adverse C450P?



clinical candidate

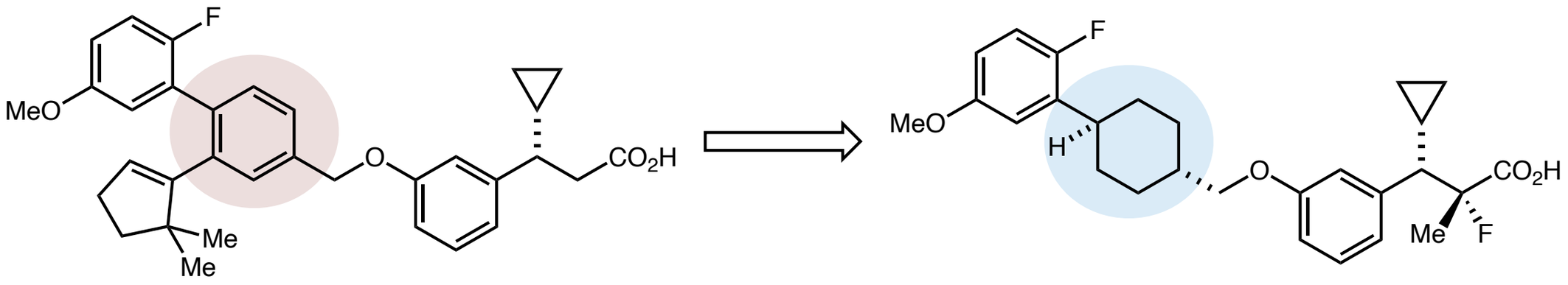
solubility: 920 ug/mL
oral availability: 52%



Trifilieff, A., *J. Pharmacol. Exp. Ther.* **2002**, *301*, 241.
Press, N. J. *J. Med. Chem.* **2012**, *55*, 7472.
Press, N. J., *J. Med. Chem.* **2015**, *58*, 6747.

Cyclohexanes as Phenyl Bioisosteres

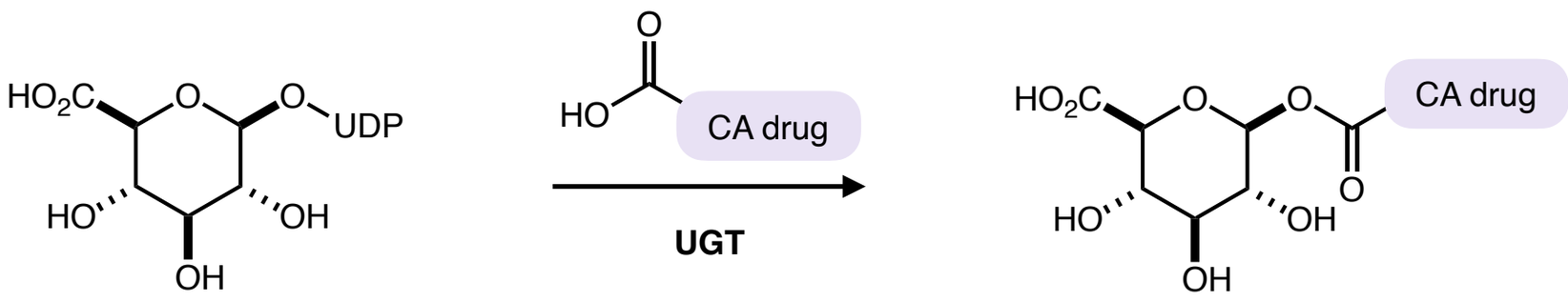
Viable Scaffolds to Escape Flatland



GPR40 agonist

improved activity
increased metabolic stability

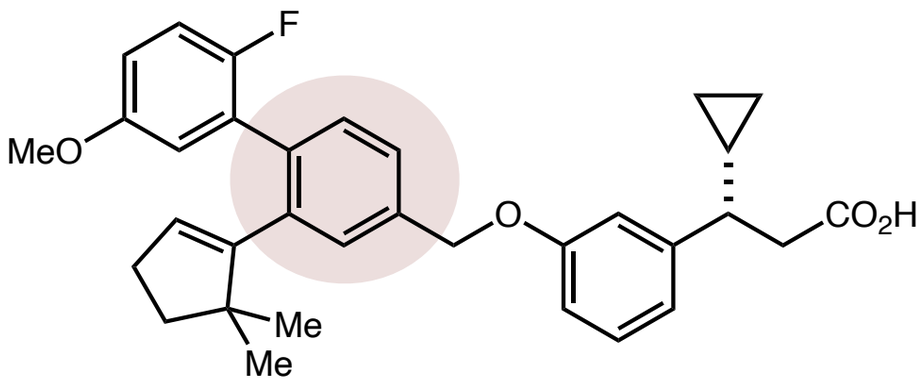
Glucuronide Metabolites



Player, M. R., *ACS Med. Chem. Lett.* **2019**, *10*, 16.
Van Vleet, T. R., *Toxicol. Lett.* **2017**, *272*, 1.

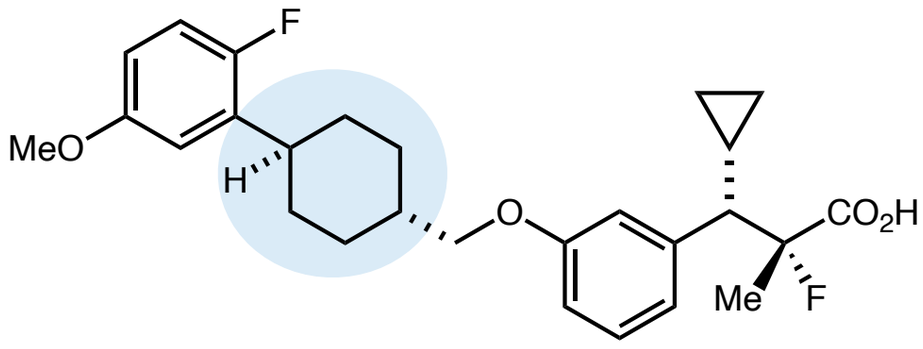
Cyclohexanes as Phenyl Bioisosteres

Viable Scaffolds to Escape Flatland



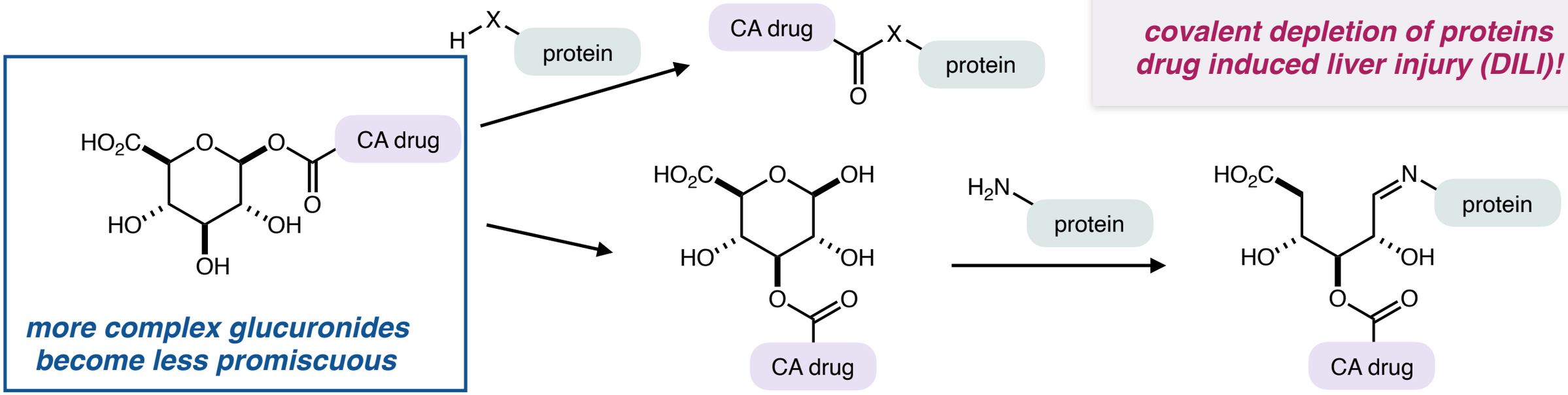
GPR40 agonist

higher Fsp³, added chiral center



improved activity
increased metabolic stability

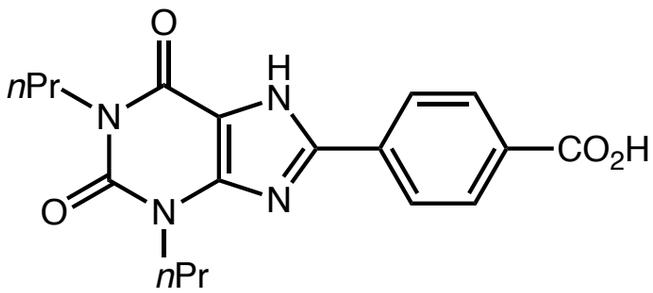
Glucuronide Metabolites



Player, M. R., *ACS Med. Chem. Lett.* **2019**, *10*, 16.
Van Vleet, T. R., *Toxicol. Lett.* **2017**, *272*, 1.

Cyclohexanes as Phenyl Bioisosteres

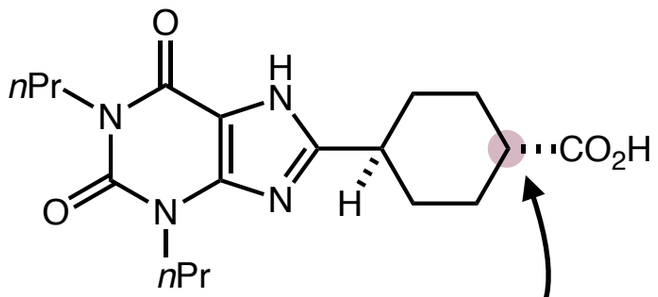
Limitations & Workarounds



A1R antagonist

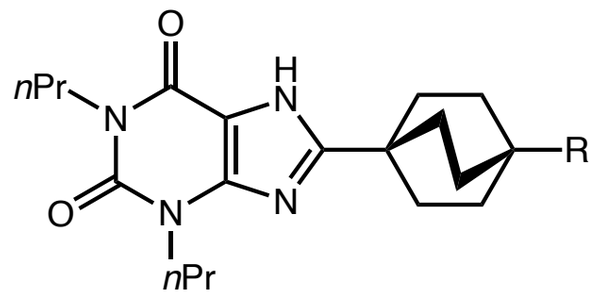
K_i = 6.8 nM

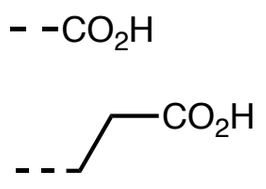
poor solubility



readily isomerizes

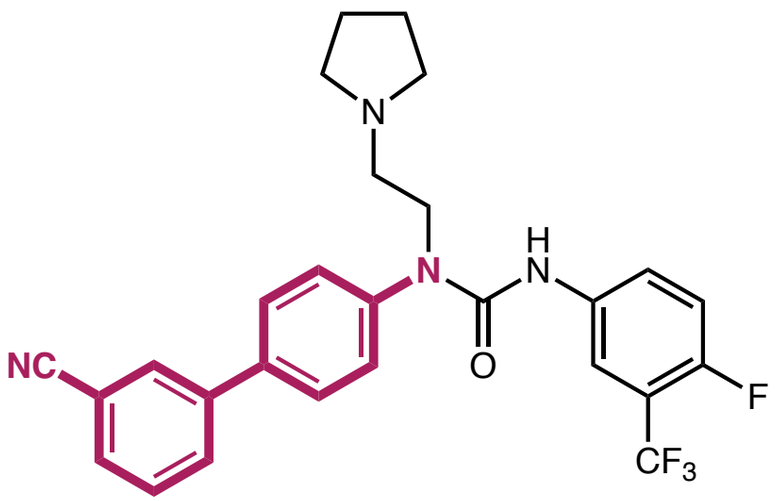
K_i > 500 nM





K_i = 30 nM

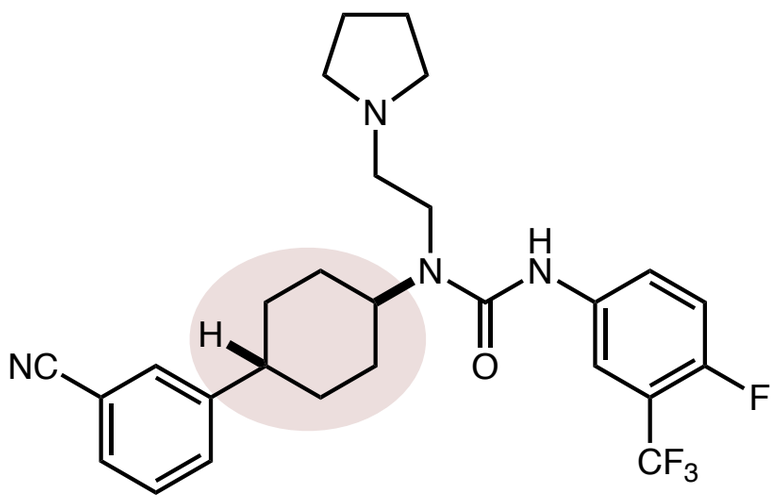
K_i = 7 nM
Tonapofylline



MCHR antagonist

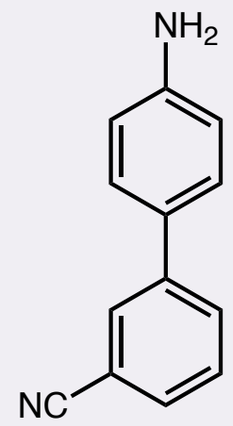
K_i = 2 nM

Ames +



K_i = 297 nM – *too flexible*

Ames + – *desaturation?*

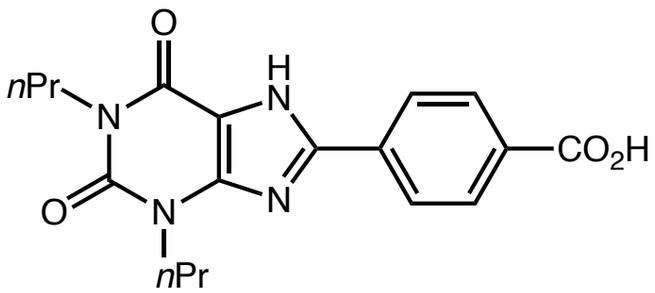


release in vivo?

Jacobsen, K. A., *J. Med. Chem.* **2000**, *43*, 1165.
Kiesman, W. F., *J. Med. Chem.* **2006**, *49*, 7119.
Xu, R., *Bioorg. Med. Chem.* **2006**, *14*, 3285.

Cyclohexanes as Phenyl Bioisosteres

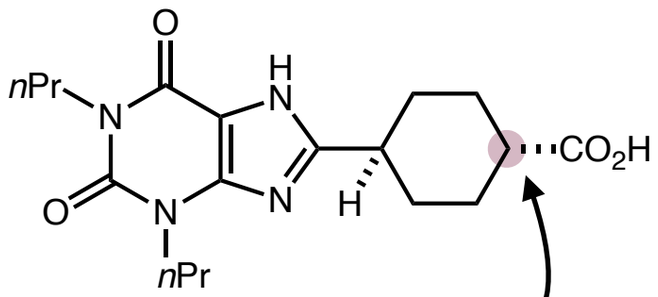
Limitations & Workarounds



A1R antagonist

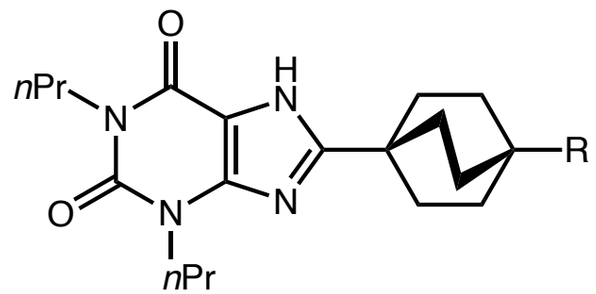
K_i = 6.8 nM

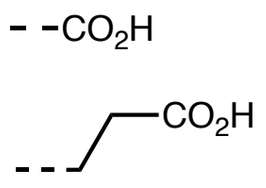
poor solubility



readily isomerizes

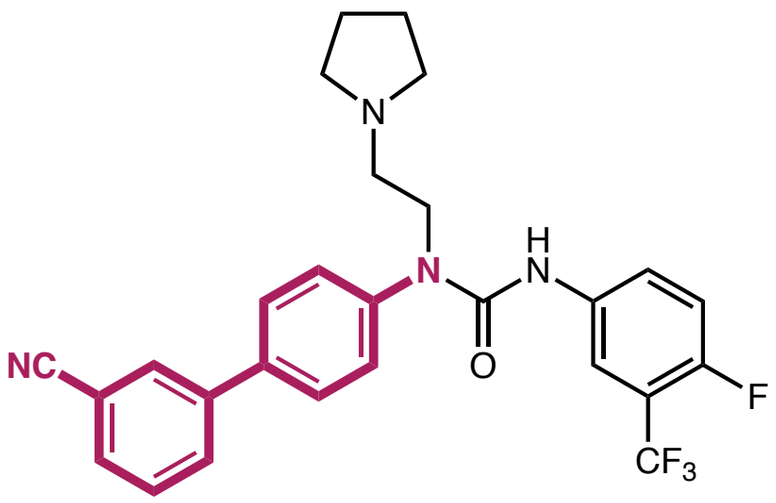
K_i > 500 nM





K_i = 30 nM

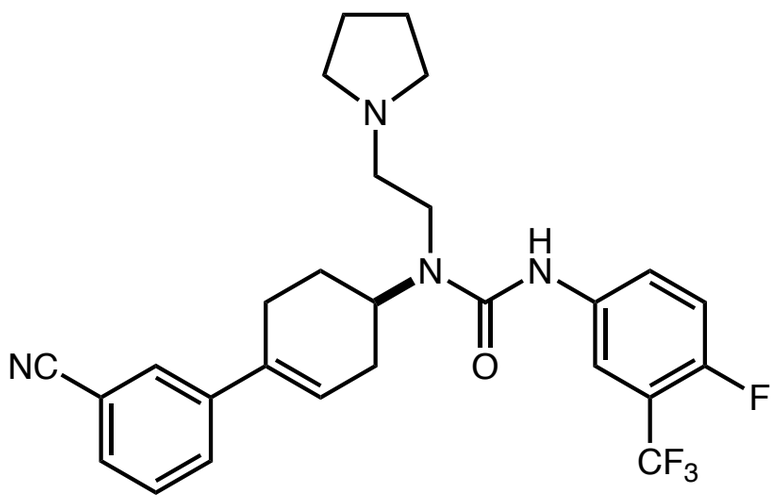
K_i = 7 nM
Tonapofylline



MCHR antagonist

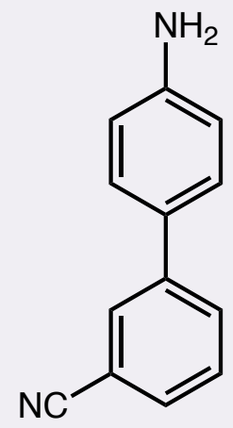
K_i = 2 nM

Ames +



K_i = 3 nM – *increased rigidity*

Ames + – *desaturation?*

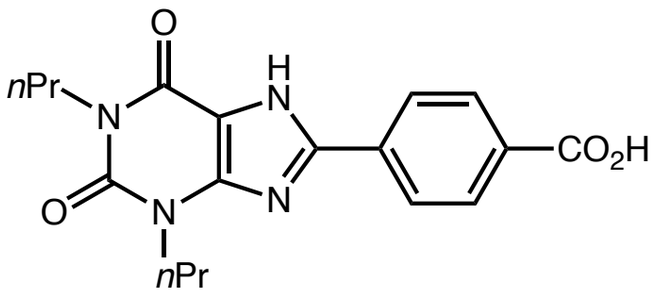


release in vivo?

Jacobsen, K. A., *J. Med. Chem.* **2000**, *43*, 1165.
Kiesman, W. F., *J. Med. Chem.* **2006**, *49*, 7119.
Xu, R., *Bioorg. Med. Chem.* **2006**, *14*, 3285.

Cyclohexanes as Phenyl Bioisosteres

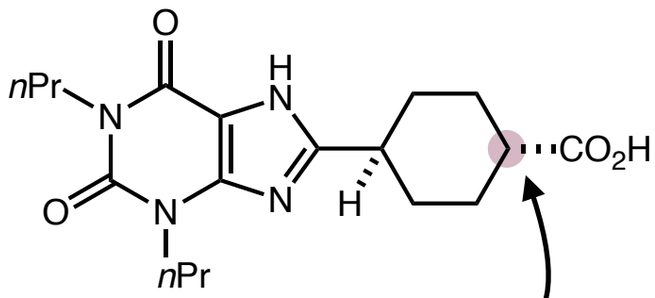
Limitations & Workarounds



A1R antagonist

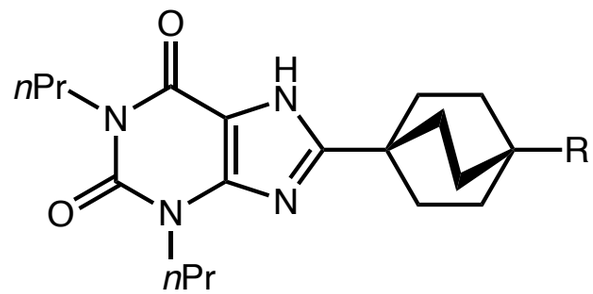
K_i = 6.8 nM

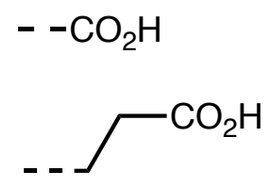
poor solubility



readily isomerizes

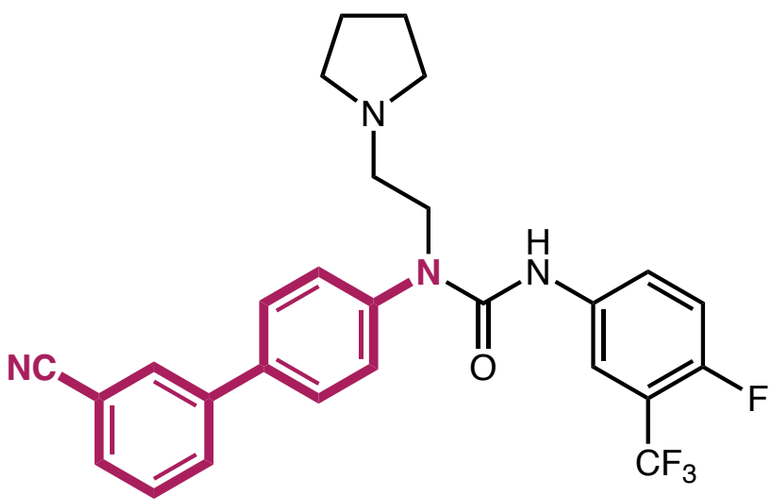
K_i > 500 nM





K_i = 30 nM

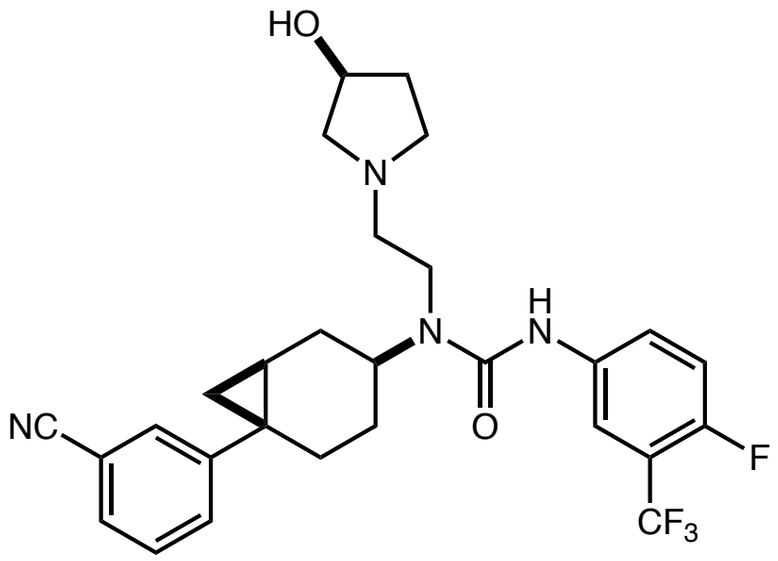
K_i = 7 nM
Tonapofylline



MCHR antagonist

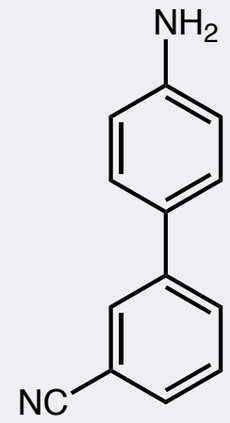
K_i = 2 nM

Ames +



K_i = 8.9 nM – *increased rigidity*

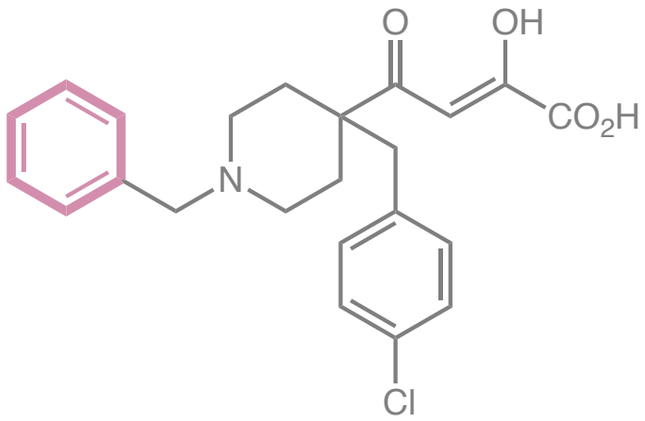
Ames – – *cannot aromatize*

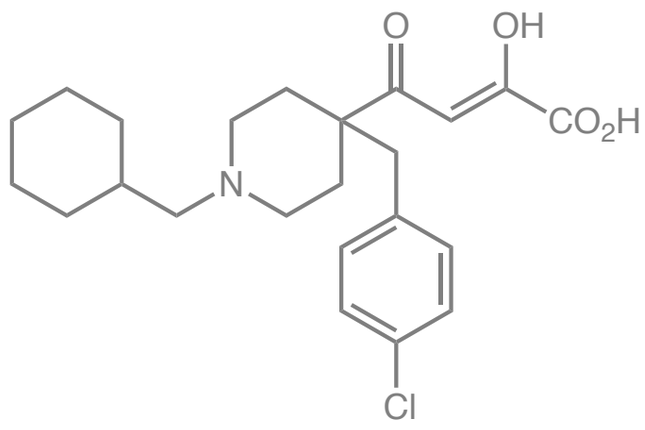


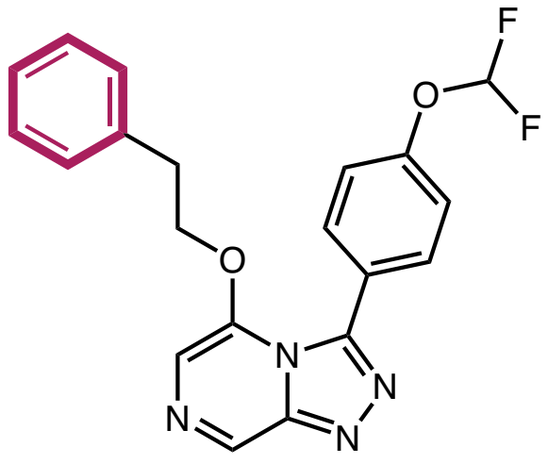
release in vivo?

Jacobsen, K. A., *J. Med. Chem.* **2000**, *43*, 1165.
Kiesman, W. F., *J. Med. Chem.* **2006**, *49*, 7119.
Xu, R., *Bioorg. Med. Chem.* **2006**, *14*, 3285.

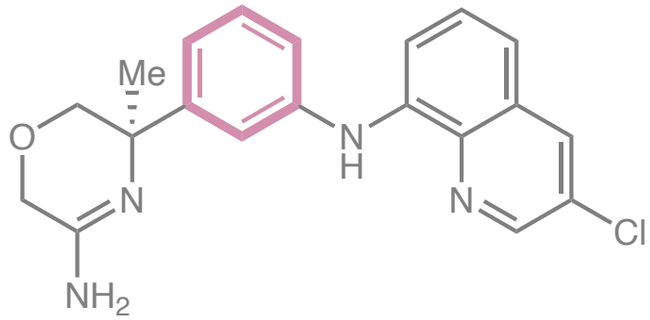
Outline







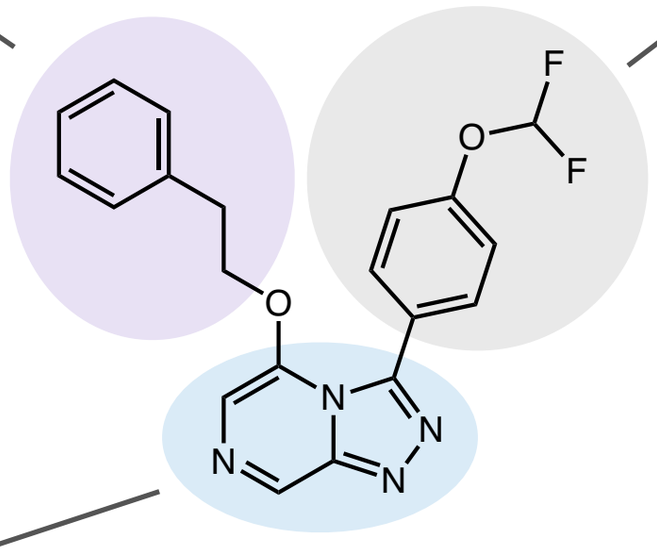
metabolic stability when even the strongest C–H bonds get cleaved



A Case Study in Antimalarial Compounds

Northwestern fragment

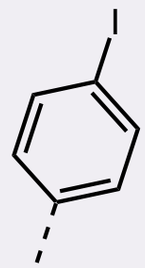
Northeastern fragment



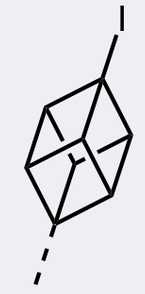
core

Series 4
Open Source Malaria Consortium
PfATP4 inhibitor

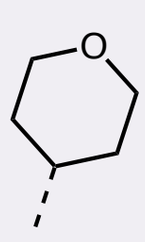
poorly soluble, quickly metabolized

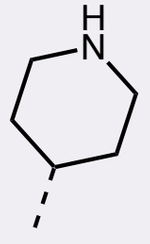


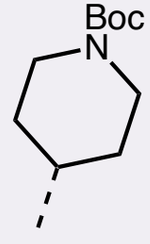
– equipotent
– worse solubility

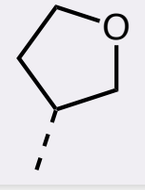


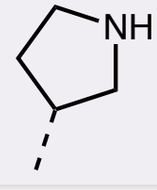
– inactive

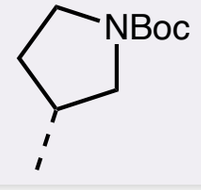








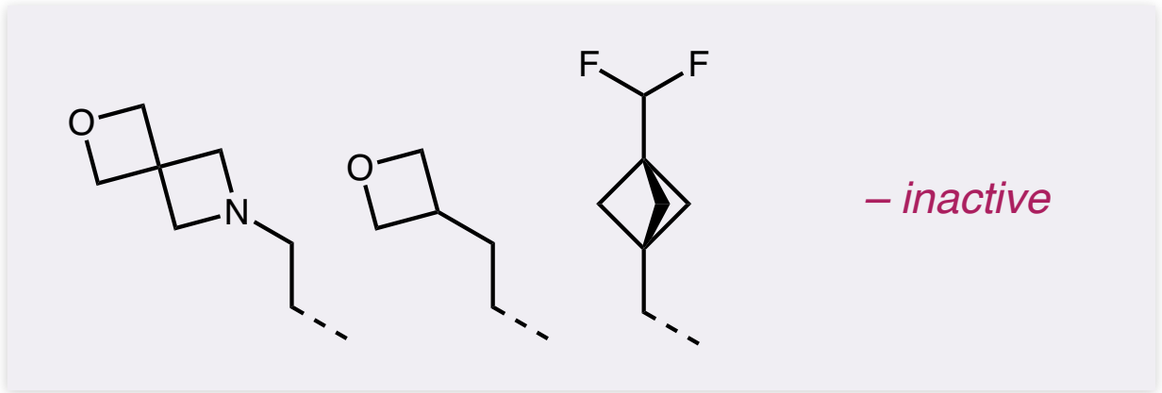




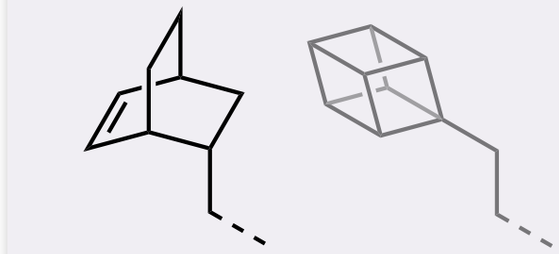
Todd, M. H., *J. Med. Chem.* **2020**, *63*, 11585.

A Case Study in Antimalarial Compounds

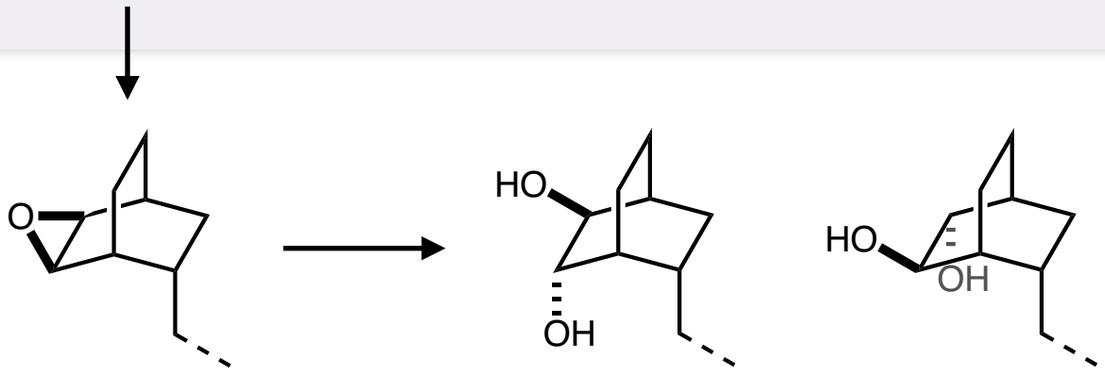
Northwestern fragment

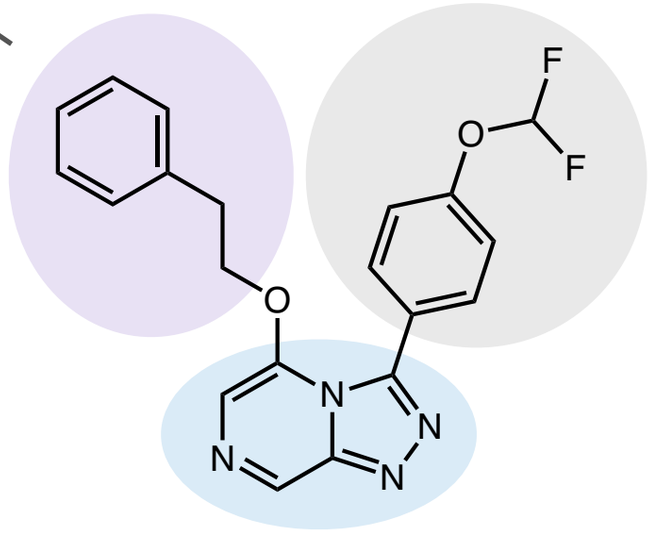


– inactive



– equipotent
– reduced solubility
– fast clearance





Series 4
Open Source Malaria Consortium
PfATP4 inhibitor

poorly soluble, quickly metabolized

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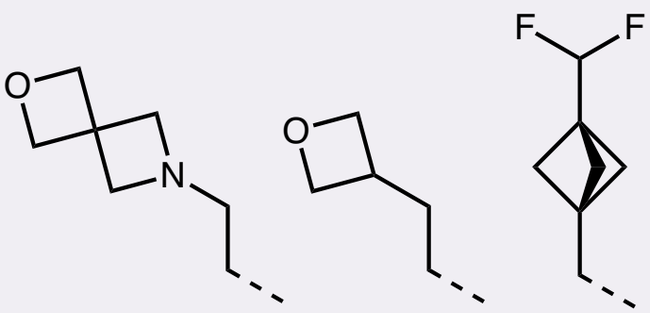
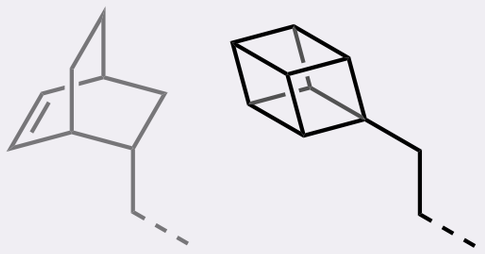
A Case Study in Antimalarial Compounds

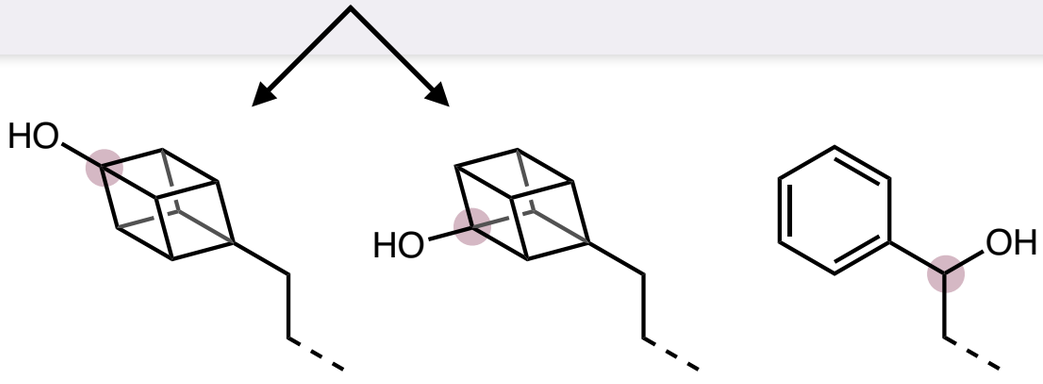
Northwestern fragment

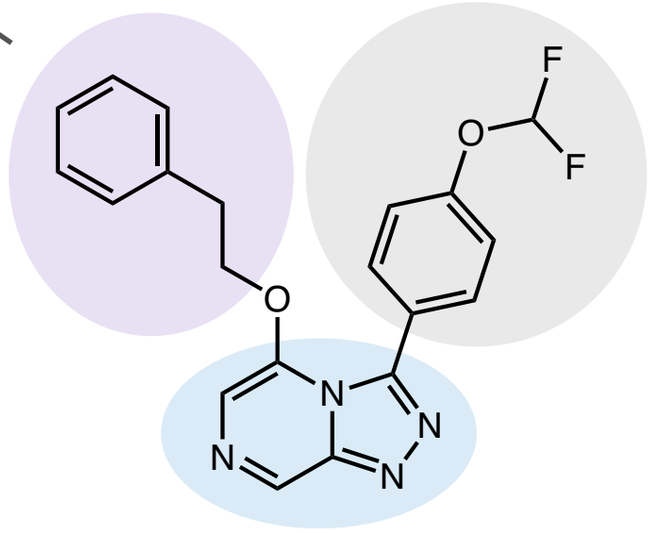


– inactive



– equipotent
– reduced solubility
– fast clearance





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PfATP4 inhibitor

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A Case Study in Antimalarial Compounds

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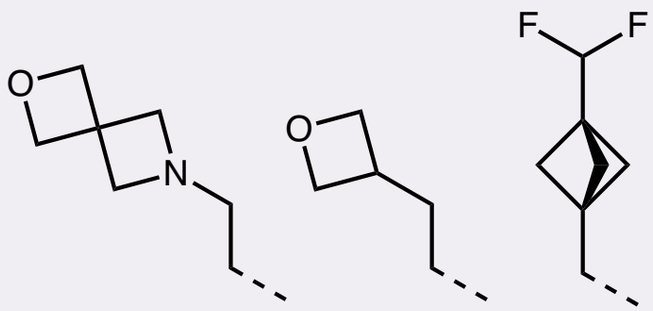
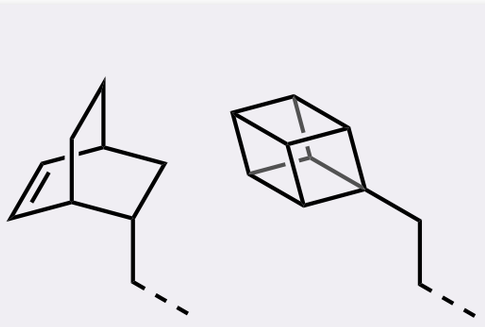
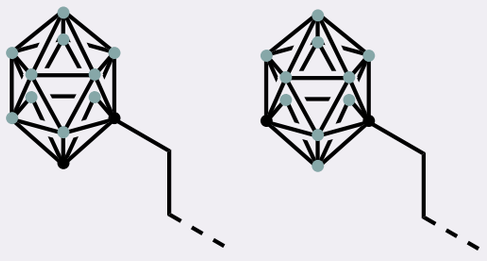


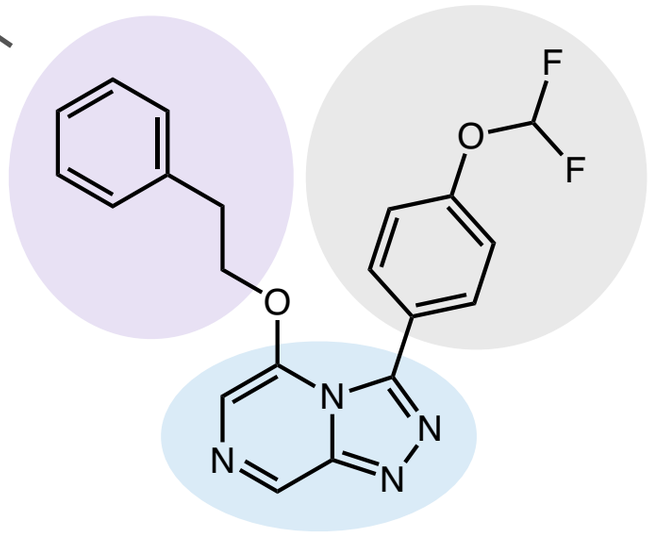
– inactive



– equipotent
– reduced solubility
– fast clearance



– equipotent
– improved stability
– solubility unchanged

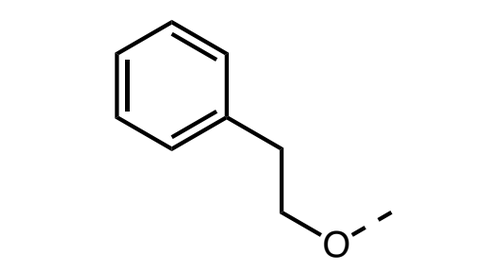
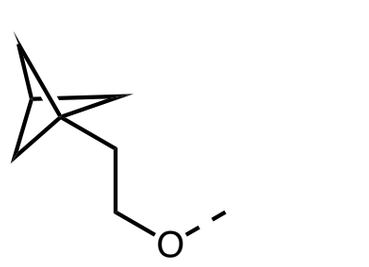
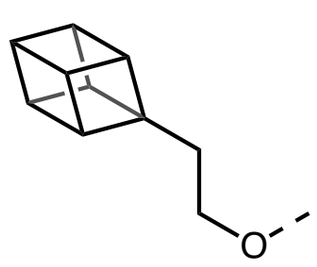
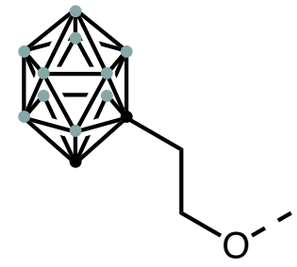


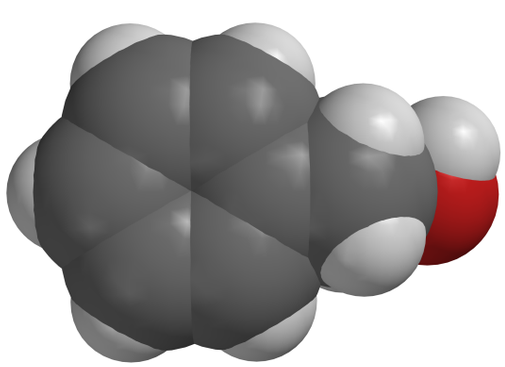
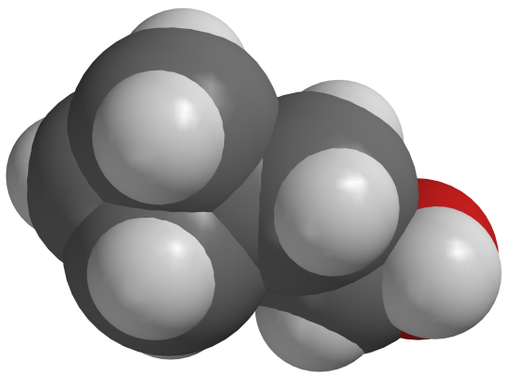
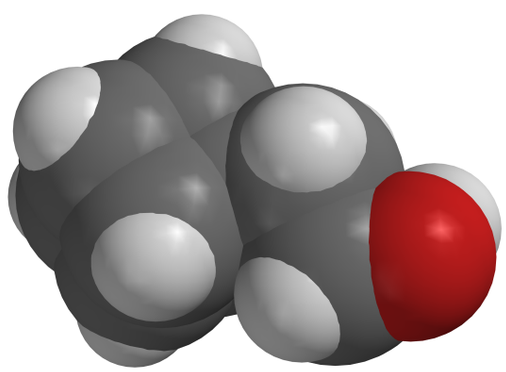
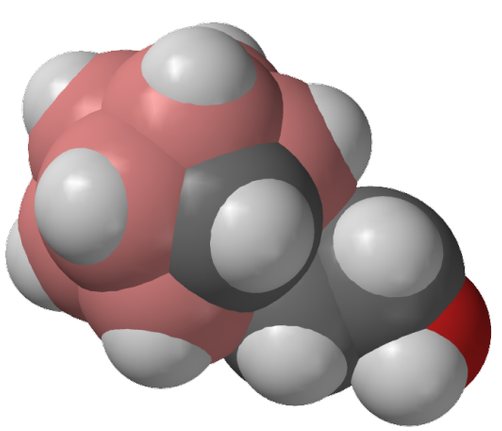
Series 4
Open Source Malaria Consortium
PfATP4 inhibitor

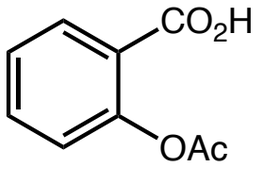
poorly soluble, quickly metabolized

Todd, M. H., *J. Med. Chem.* **2020**, *63*, 11585.

Carboranes as Phenyl Bioisosteres

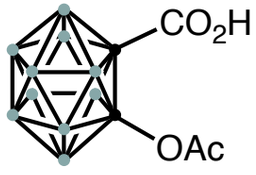







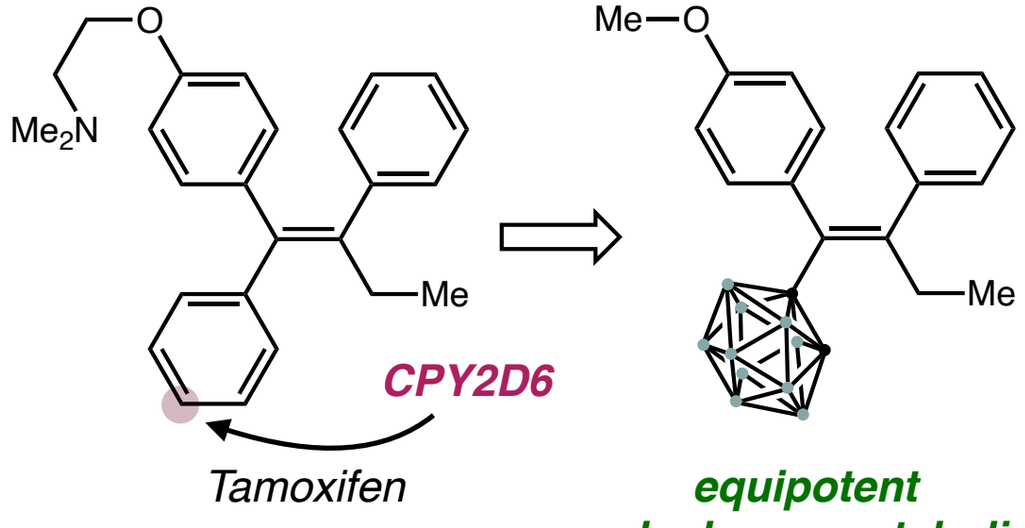
Aspirin

IC50 (COX-1) = 3.57 uM
IC50 (AKR-1A1) > 1000 uM



Asborin

IC50 (COX-1) ≈ 500 uM
IC50 (AKR-1A1) = 1.4 uM

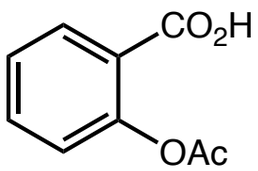


Tamoxifen

equipotent
much slower metabolism

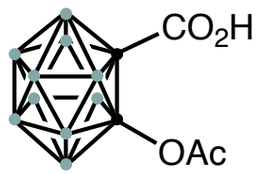
Hey-Hawkins, E., *Chem. Soc. Rev.* **2019**, *48*, 3497.
Ze, S. Q., *J. Med. Chem.* **2012**, *55*, 7290.
Ye, S. Q., *Drug. Des. Devel. Ther.* **2017**, *11*, 629.

Carboranes as Phenyl Bioisosteres



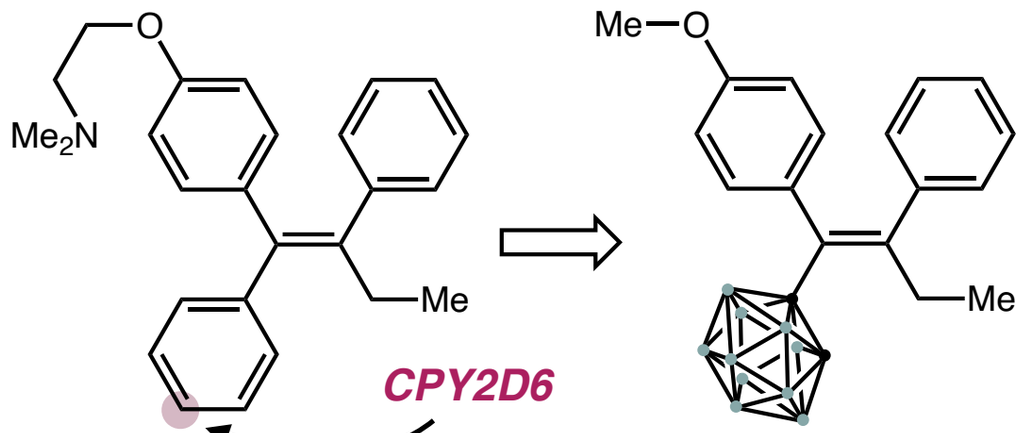
Aspirin

IC50 (COX-1) = 3.57 uM
IC50 (AKR-1A1) > 1000 uM



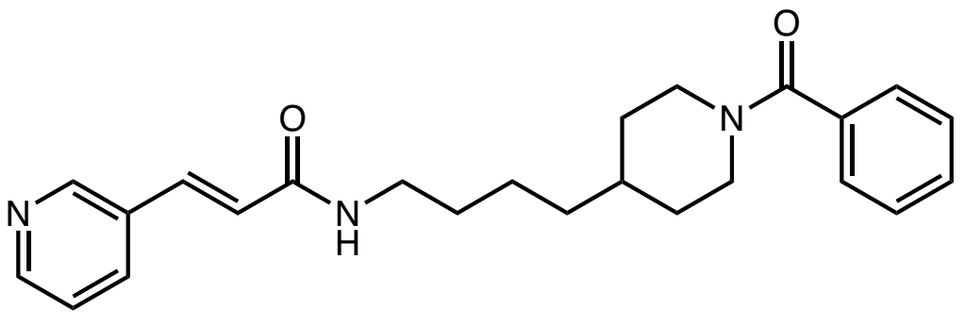
Asborin

IC50 (COX-1) ≈ 500 uM
IC50 (AKR-1A1) = 1.4 uM

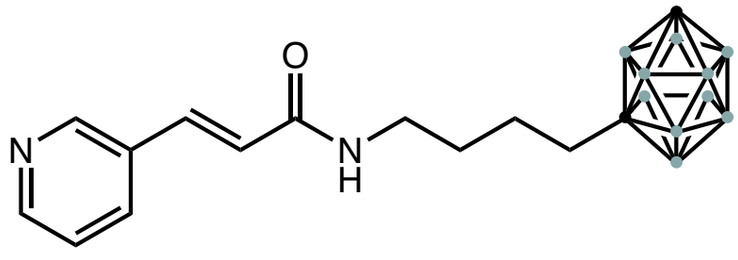


Tamoxifen

equipotent
much slower metabolism



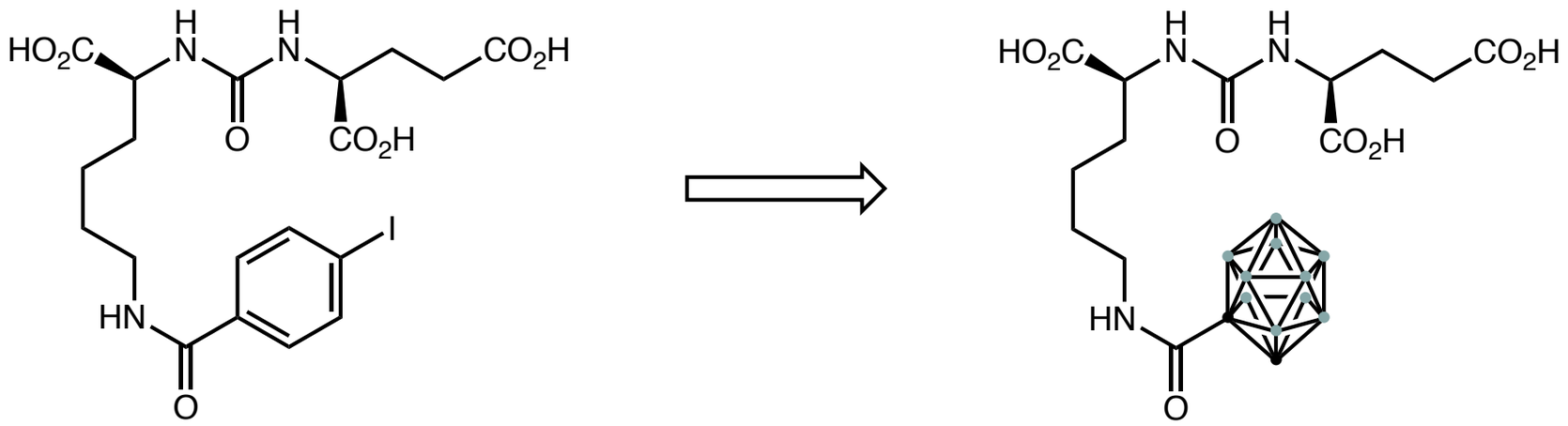
Daporinad
NAMPT antagonist
IC50 0.09 nM
dosage-related adverse effects in P2



equipotent
slower metabolism
→ lower effective dose

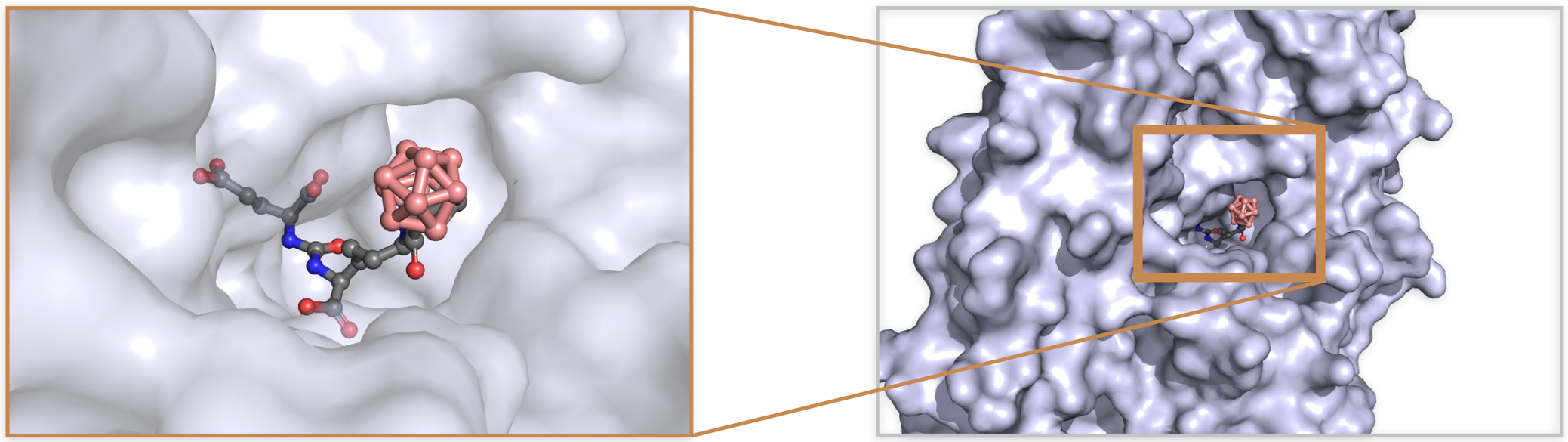
Hey-Hawkins, E., *Chem. Soc. Rev.* **2019**, *48*, 3497.
Ze, S. Q., *J. Med. Chem.* **2012**, *55*, 7290.
Ye, S. Q., *Drug. Des. Devel. Ther.* **2017**, *11*, 629.

Carboranes as Phenyl Bioisosteres



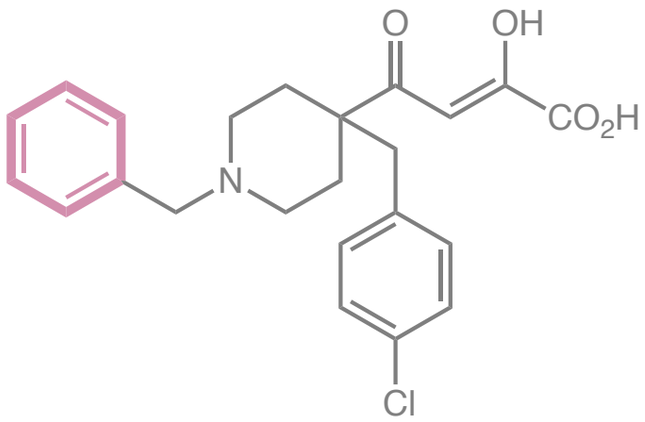
GCPII inhibitor
IC50 ≈ 1 nM

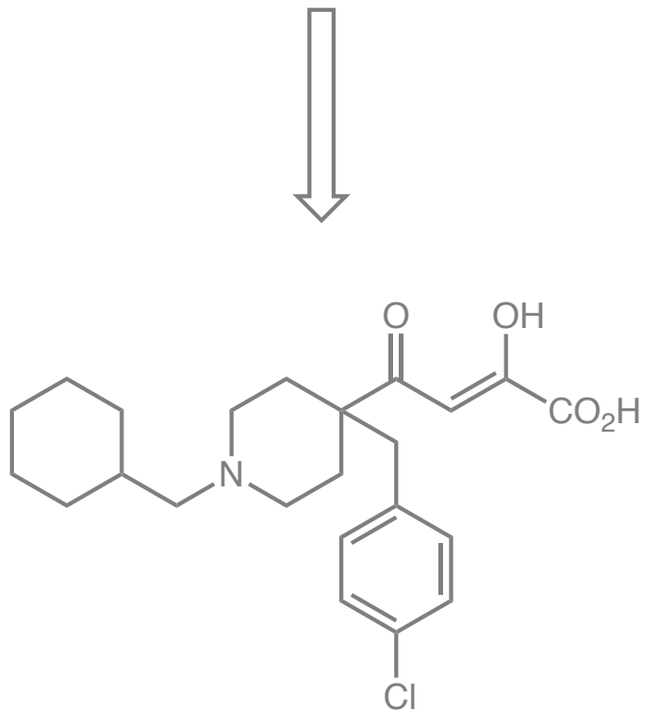
IC50 = 15.6 nM

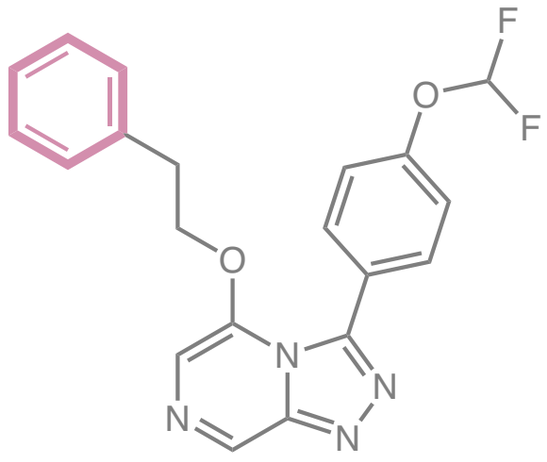


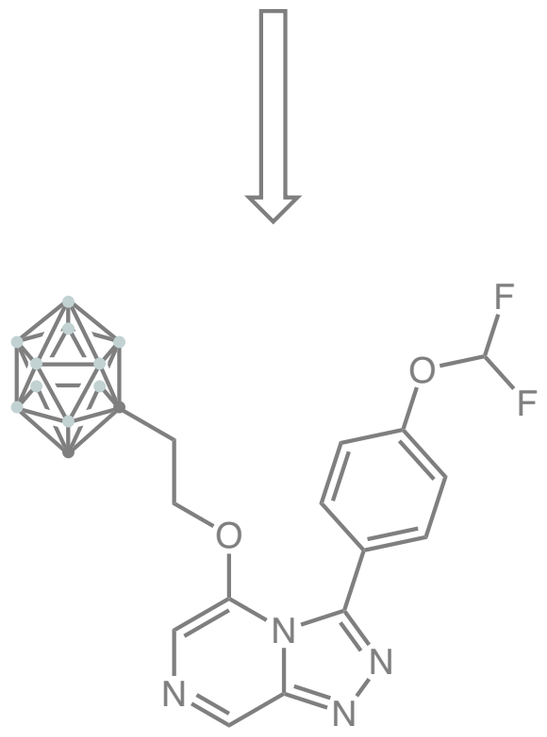
Hey-Hawkins, E., *Chem. Soc. Rev.* **2019**, *48*, 3497.
Ze, S. Q., *J. Med. Chem.* **2012**, *55*, 7290.
Byun, Y., *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5232.

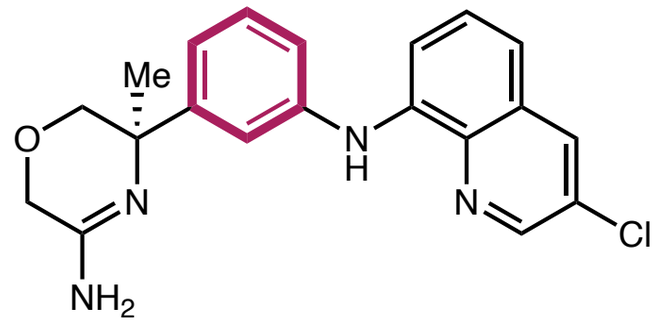
Outline







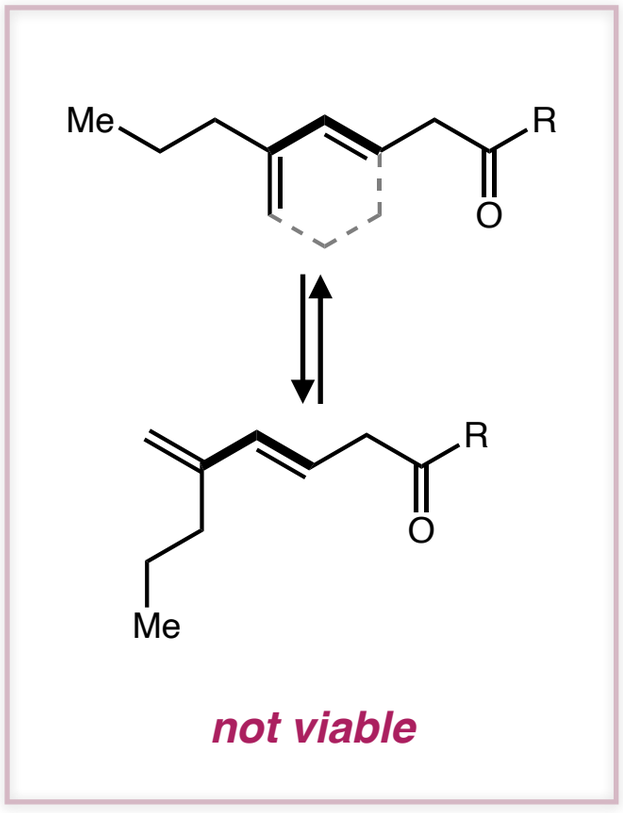




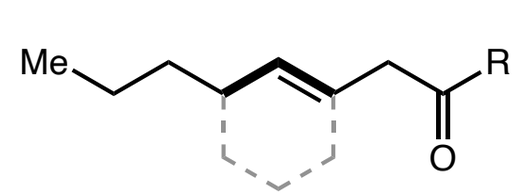
acyclic bioisosteres by reducing open chain flexibility

Open Chain Oximes as Phenyl Bioisosteres

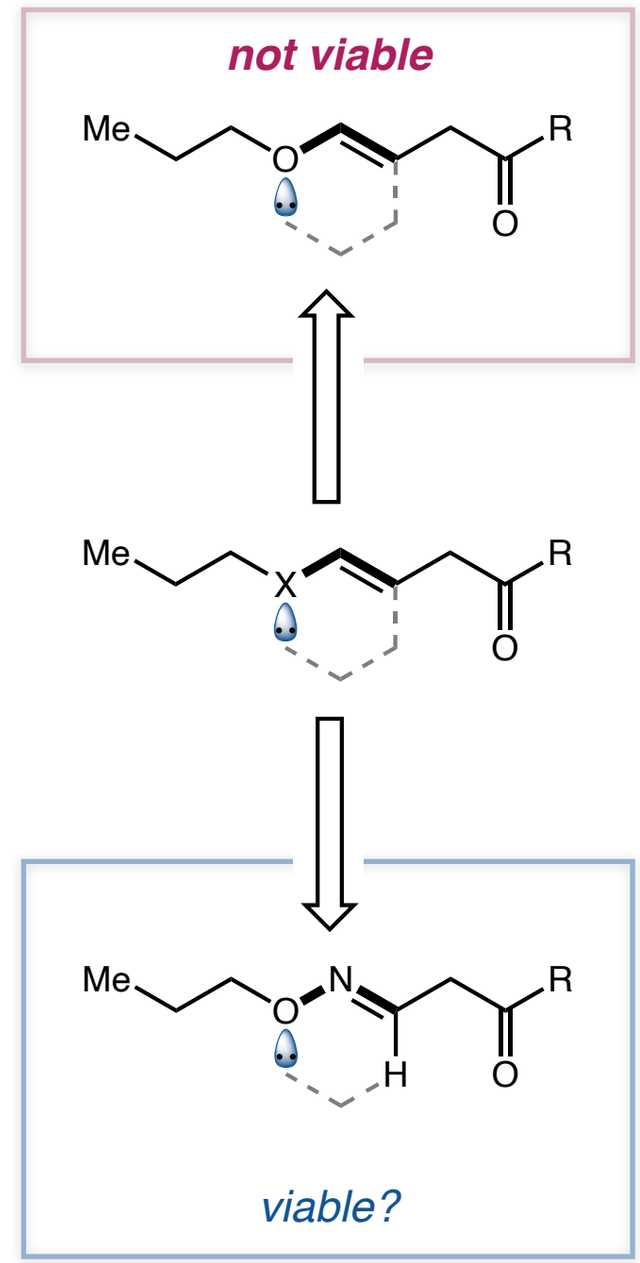
increasing molecular rigidity in scaffolds leads to improved selectivity



not viable



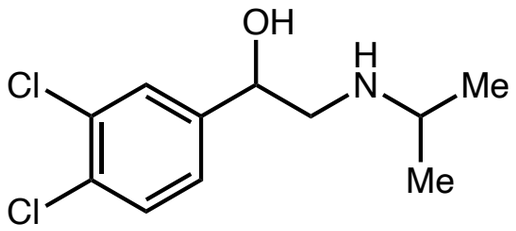
How to introduce rigidity?



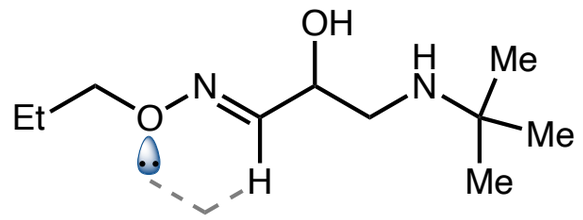
viable?

Balsamo, A., *J. Med. Chem.* **1989**, *32*, 1398.

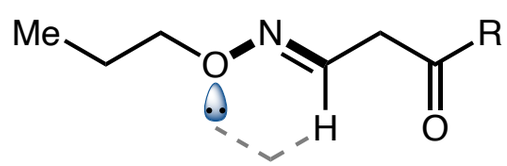
Open Chain Oximes as Phenyl Bioisosteres



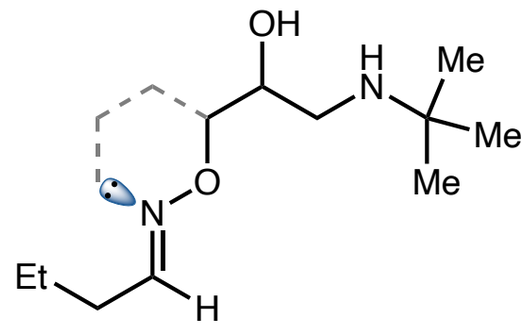
Cl_2-isoprenaline
nonselective β-adrenoceptor agonist
IC50: β_1 = 0.11 uM / β_2 = 0.98 uM



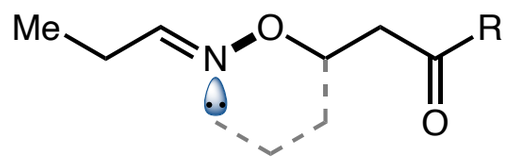
*IC50: β_1 = 8.3 uM / **β_2 = 0.27 uM***



viable



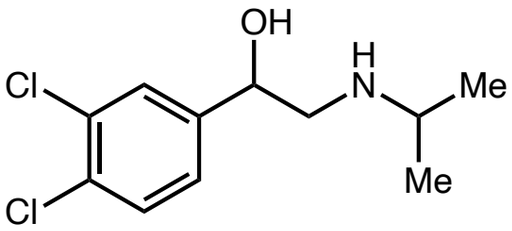
IC50: β_1 = 26 uM / β_2 = 1.5 uM



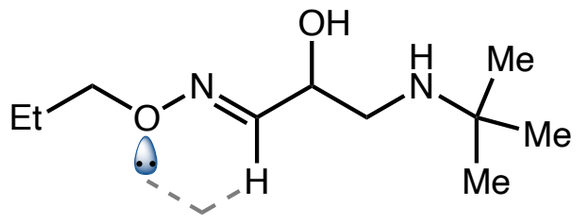
viable, too?

Balsamo, A., *Eur. J. Med. Chem.* **1999**, *34*, 283.
Balsamo, A., *J. Med. Chem.* **1989**, *32*, 1398.

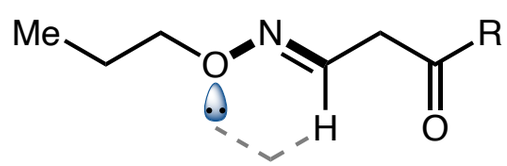
Open Chain Oximes as Phenyl Bioisosteres



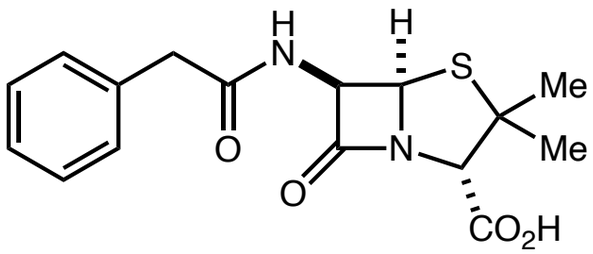
Cl_2-isoprenaline
nonselective β-adrenoceptor agonist
IC50: β_1 = 0.11 uM / β_2 = 0.98 uM



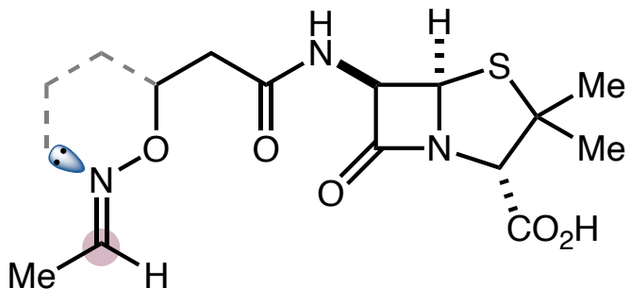
*IC50: β_1 = 8.3 uM / **β_2 = 0.27 uM***



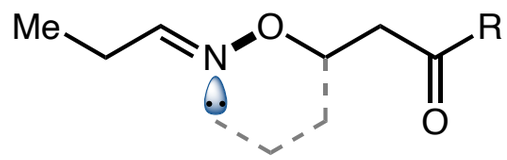
viable



penicillin G
MIC (gram+): 0.05 ug/mL
MIC (gram–): 71 ug/mL



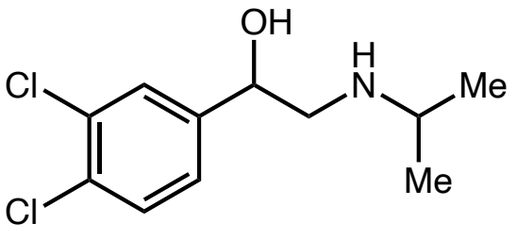
inactive
prone to hydrolysis



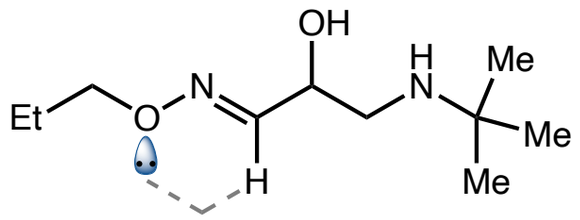
viable, too?

Balsamo, A., *Eur. J. Med. Chem.* **1999**, *34*, 283.
Balsamo, A., *J. Med. Chem.* **1989**, *32*, 1398.

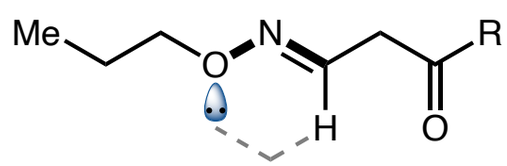
Open Chain Oximes as Phenyl Bioisosteres



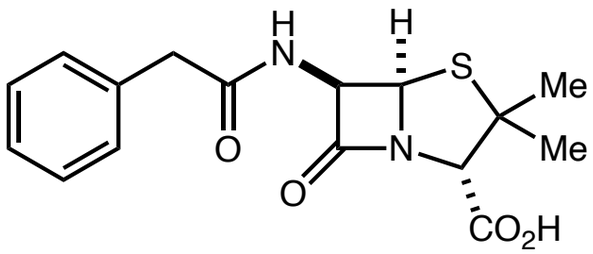
Cl_2-isoprenaline
nonselective β-adrenoceptor agonist
IC50: β_1 = 0.11 uM / β_2 = 0.98 uM



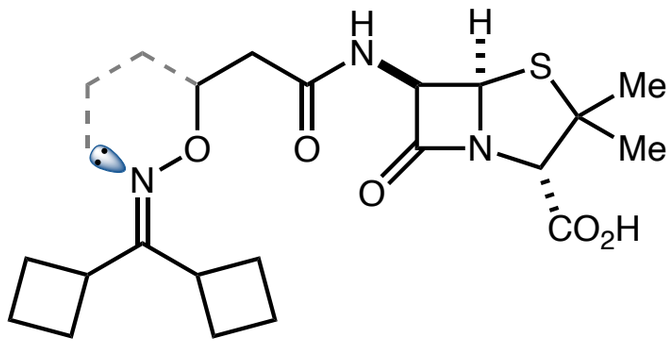
*IC50: β_1 = 8.3 uM / **β_2 = 0.27 uM***



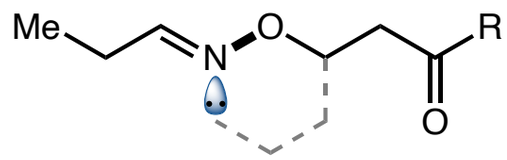
viable



penicillin G
MIC (gram+): 0.05 ug/mL
MIC (gram–): 71 ug/mL



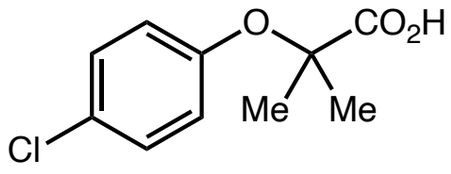
MIC (gram+): 0.06 ug/mL
MIC (gram–): 53 ug/mL



viable

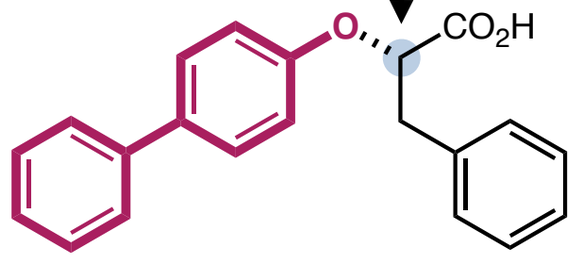
Balsamo, A., *Eur. J. Med. Chem.* **1999**, *34*, 283.
Balsamo, A., *J. Med. Chem.* **1989**, *32*, 1398.

Open Chain Oximes as Phenyl Bioisosteres

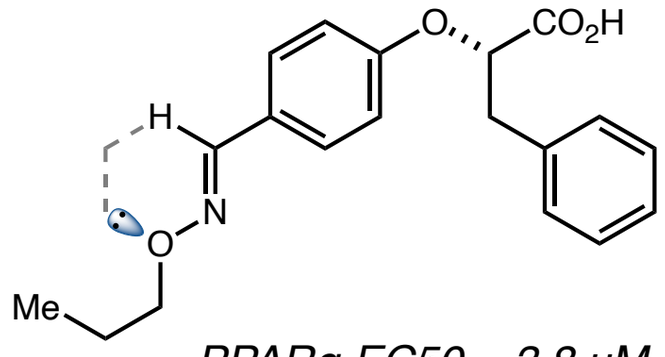


clofibric acid
core of several classes
of PPARα/PPARγ agonists

key stereocenter



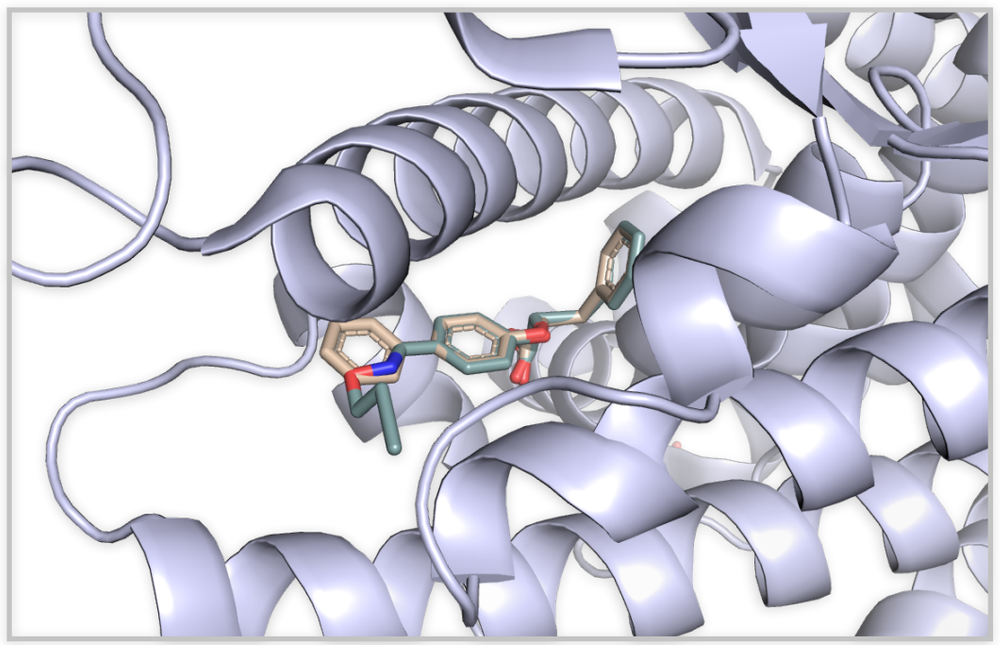
dual agonist
PPARα EC50 = 0.22 uM
PPARγ EC50 = 0.48 uM
metabolism?



PPARα EC50 = 3.8 uM
PPARγ EC50 = 3.8 uM

efficacy relative to biphenyl:
PPARα = 91%
PPARγ = 154%

docking of oxime onto biphenyl co-crystal: additional H-bond with Gln277 rigidifies the complex



Loiodice, F., *J. Med. Chem.* **2005**, *48*,5509.
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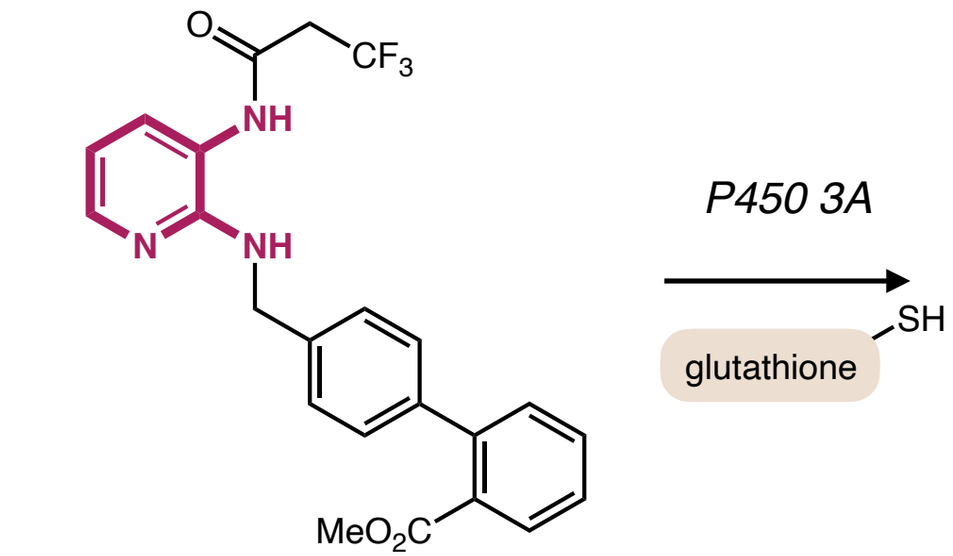
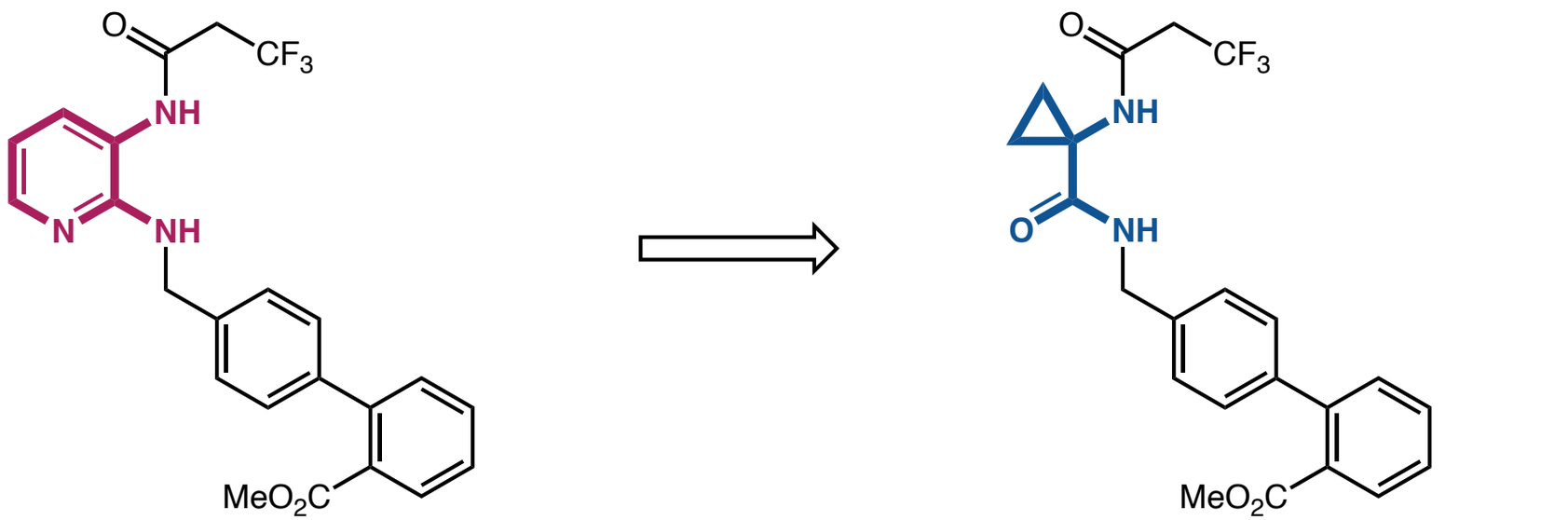
α-Cyclopropyl Carbonyl Compounds



Bradykinin B1 receptor antagonist
K_i = 11.8 nM
Liver Toxicity!

Wood, M. R., *J. Med. Chem.* **2006**, *49*, 1231.
Tang, C., *Chem. Res. Toxicol.* **2005**, *18*. 934.

α-Cyclopropyl Carbonyl Compounds

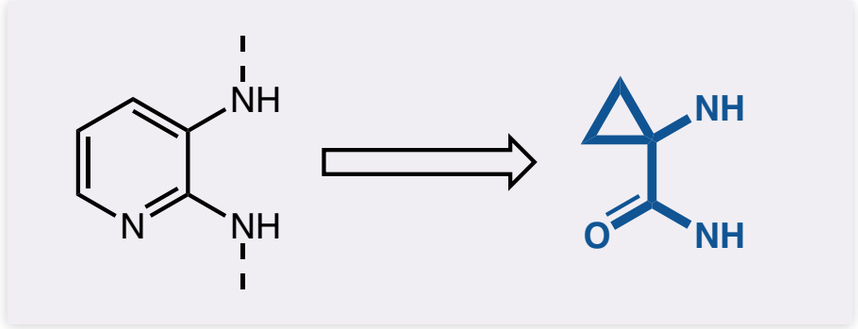


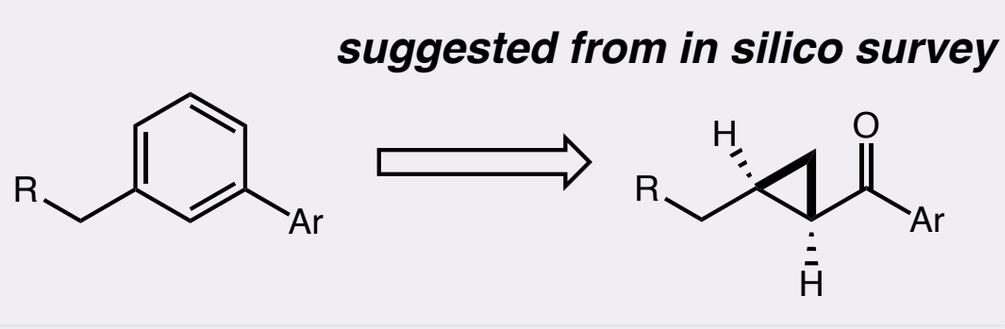
Bradykinin B1 receptor antagonist
K_i = 11.8 nM
Liver Toxicity!

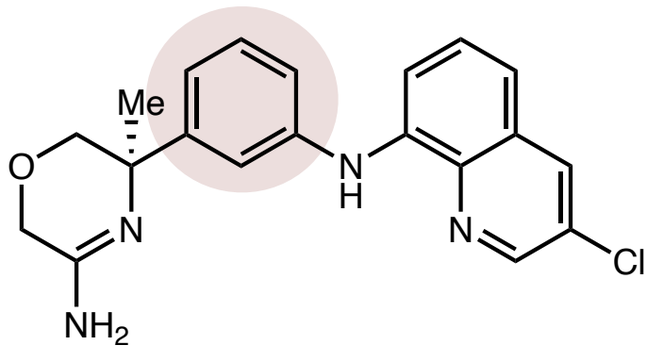
K_i = 63.0 nM
significantly lower GSH metabolism

Wood, M. R., *J. Med. Chem.* **2006**, *49*, 1231.
Tang, C., *Chem. Res. Toxicol.* **2005**, *18*. 934.

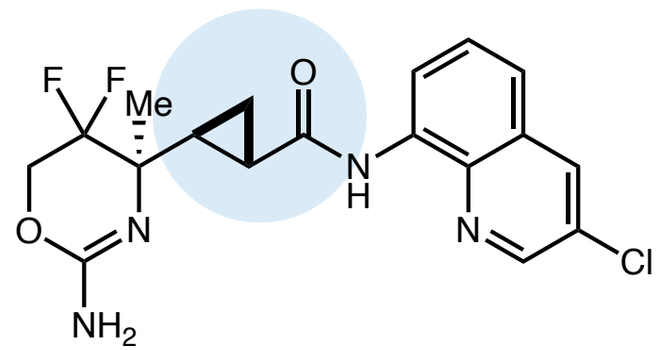
α-Cyclopropyl Carbonyl Compounds







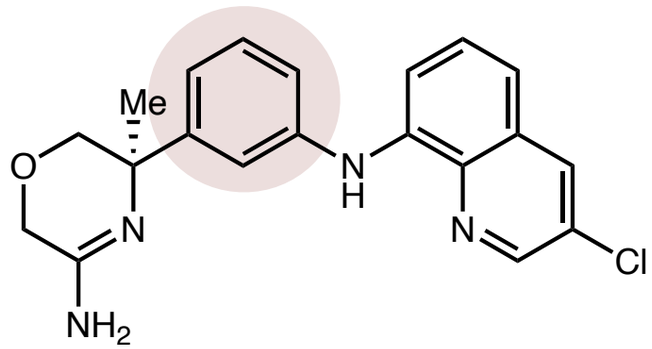
β-secretase antagonist
IC50 = 250 nM
solubility (pH 6.5) < 1 ug/mL



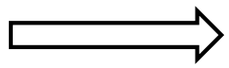
IC50 = 420 nM
solubility (pH 6.5) = 64 ug/mL

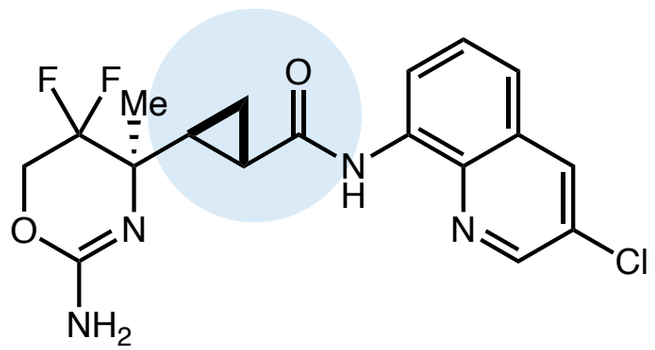
Rarey, M., J. Chem. Inf. Model. 2007, 47, 390.
Stahl, M., *J. Med. Chem.* **2016**, *59*, 4087.

α-Cyclopropyl Carbonyl Compounds



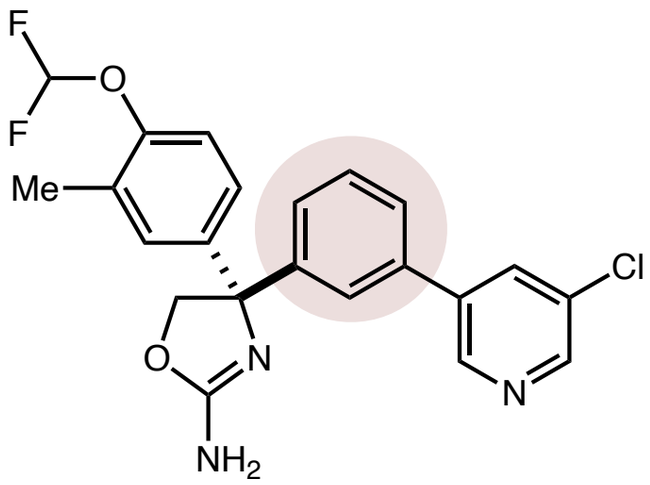
β-secretase antagonist
IC50 = 250 nM
solubility (pH 6.5) < 1 ug/mL



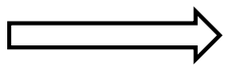


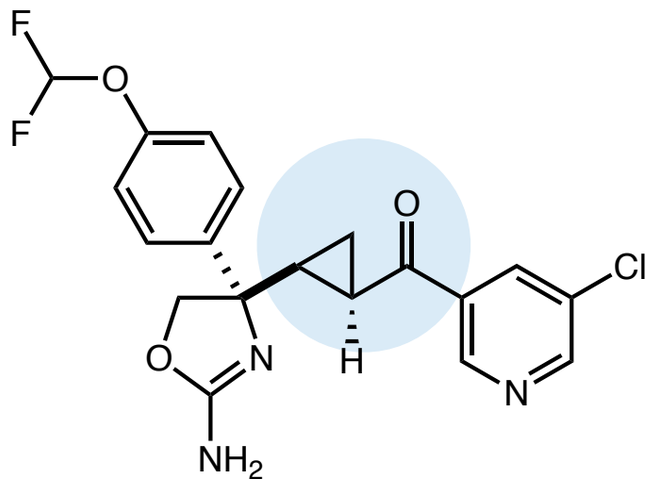
IC50 = 420 nM
solubility (pH 6.5) = 64 ug/mL

2nd Series



IC50 = 145 nM
solubility (pH 6.5) < 1 ug/mL

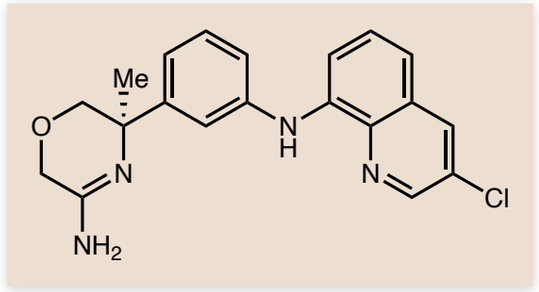


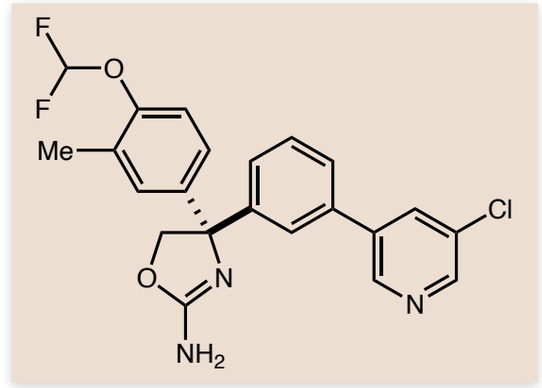


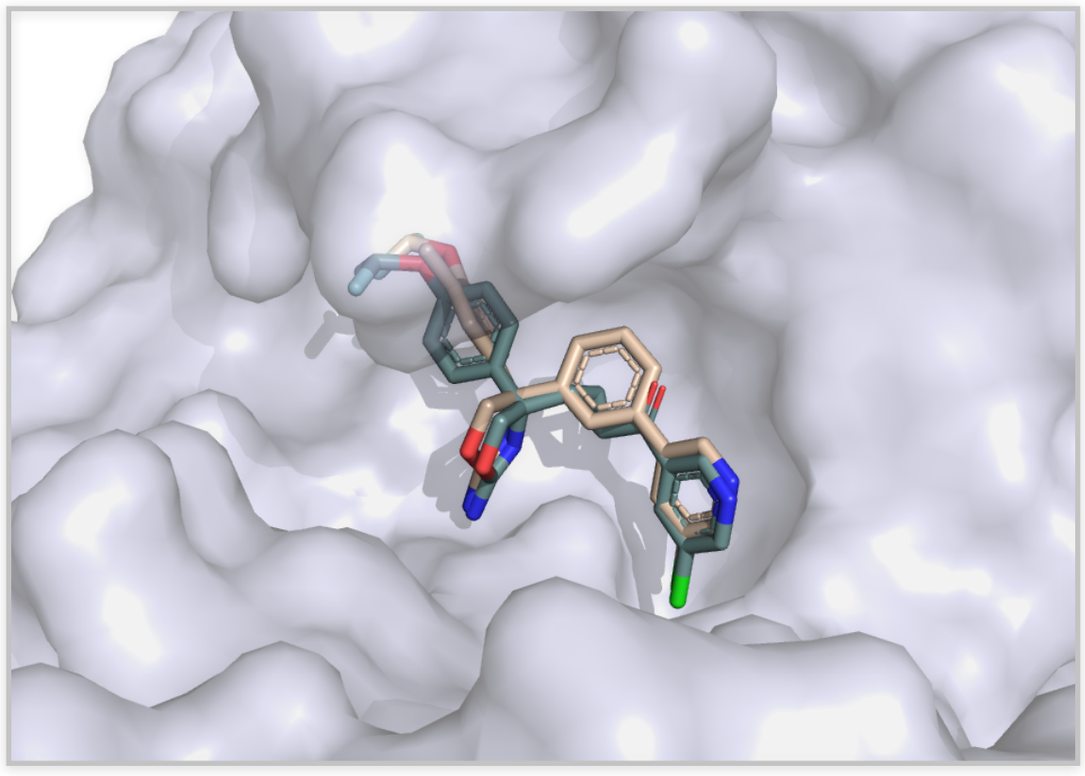
IC50 = 87 nM
solubility (pH 6.5) = 109 ug/mL

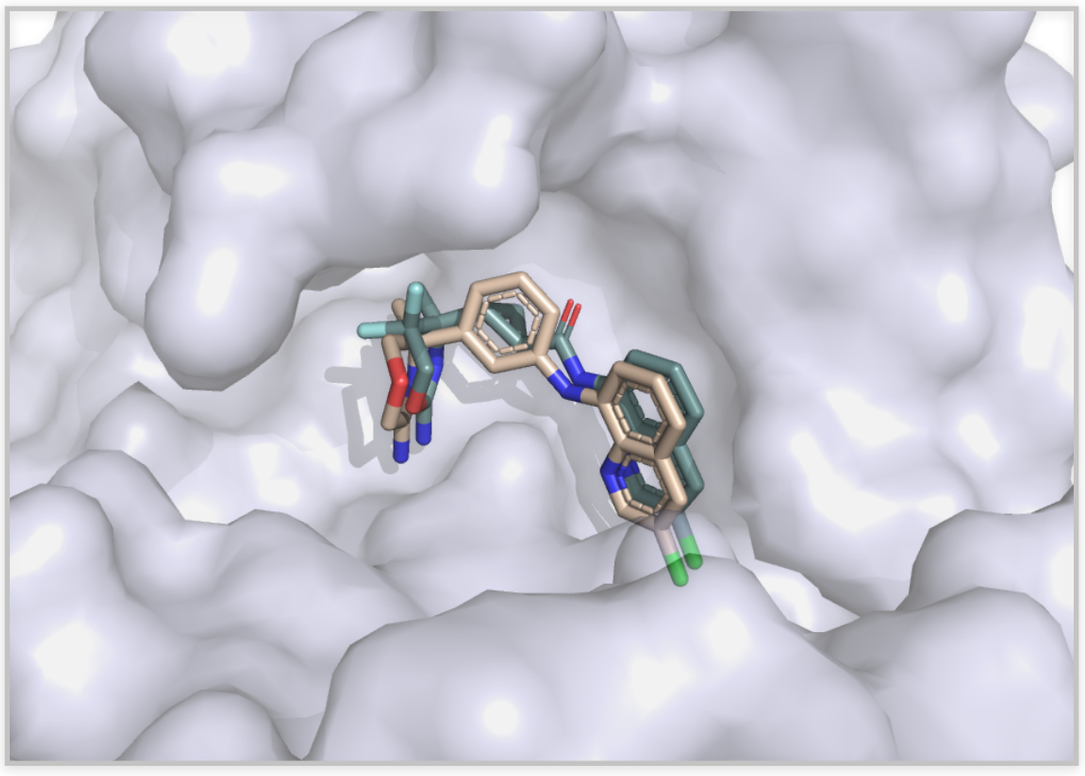
Rarey, M., J. Chem. Inf. Model. 2007, 47, 390.
Stahl, M., *J. Med. Chem.* **2016**, *59*, 4087.

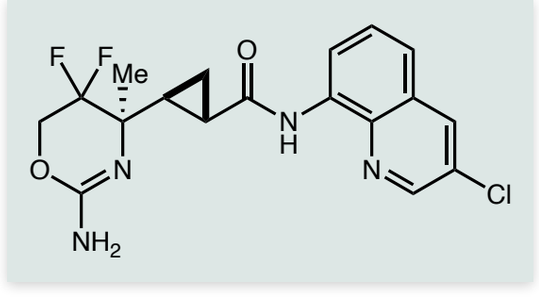
α-Cyclopropyl Carbonyl Compounds

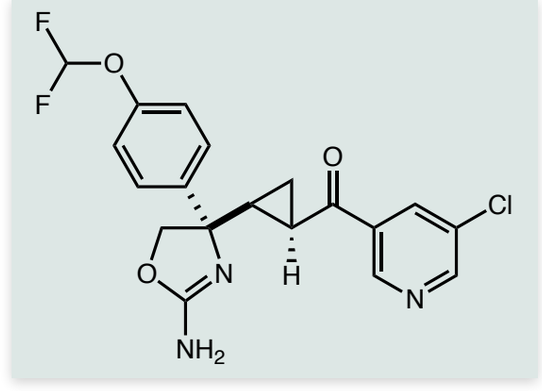






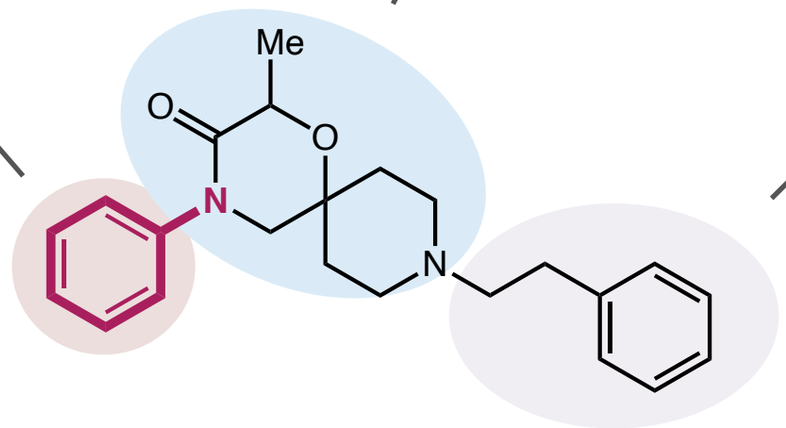






An Analgesia Candidate with Synergistic Activity

N-substituent ***core*** ***Southeastern fragment***

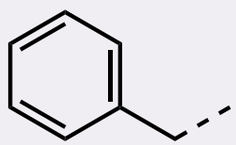


initial lead
μ opioid receptor (MOR) agonist; EC50 = 14 nM
σ_1 receptor antagonist; K_i = 6 nM

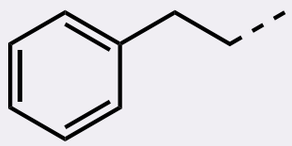
cLogP = 4.2
hERG IC50 = 0.4 uM

H — *loss of activity*

hERG IC50

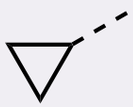


0.1 uM

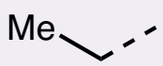


0.2 uM

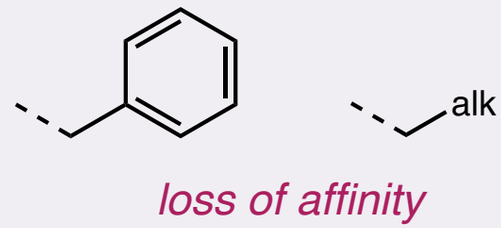
hERG IC50



4.5 uM



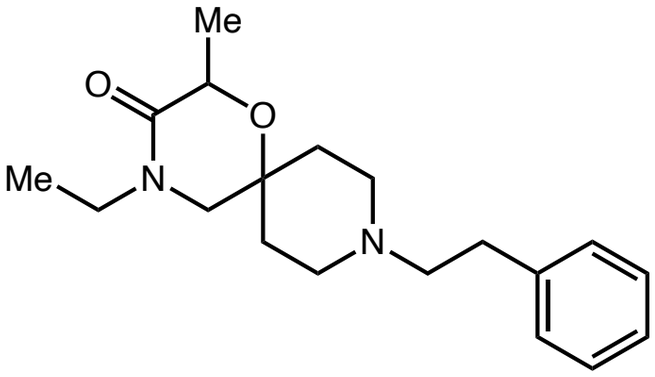
3.1 uM



loss of affinity

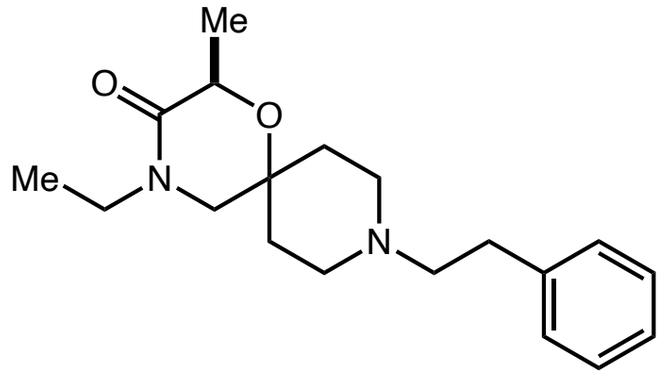
Almansa, C., *J. Med. Chem.* **2020**, *63*, 15508.

An Analgesia Candidate with Synergistic Activity



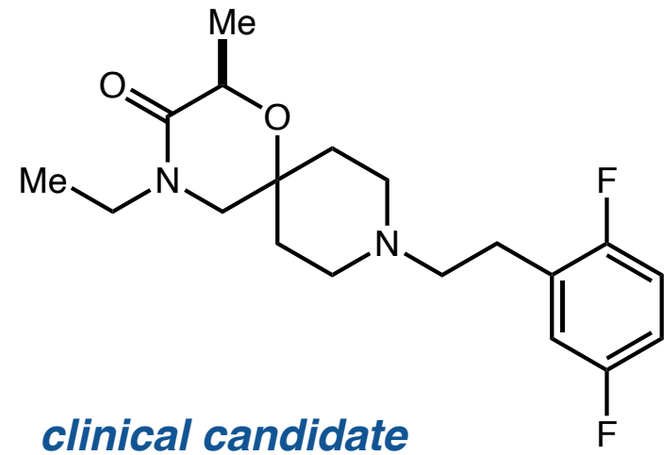
advanced compound
MOR EC50 = 65 nM
σ_1R K_i = 43 nM

cLogP = 2.9
hERG IC50 = 3.1 uM



advanced compound
MOR EC50 = 49 nM
σ_1R K_i = 66 nM

cLogP = 2.9
hERG IC50 = 4.7 uM



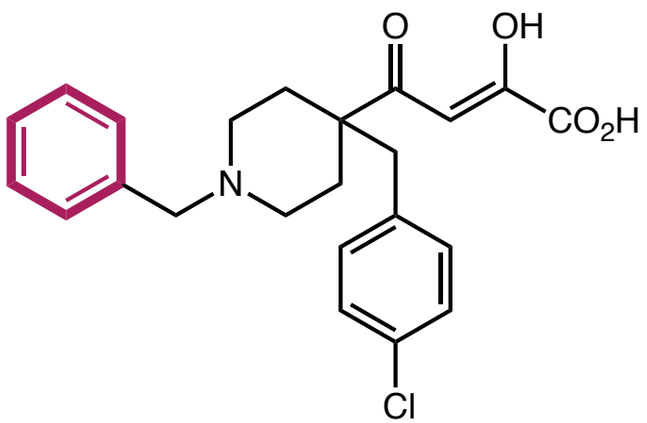
clinical candidate
MOR EC50 = 52 nM
σ_1R K_i = 118 nM

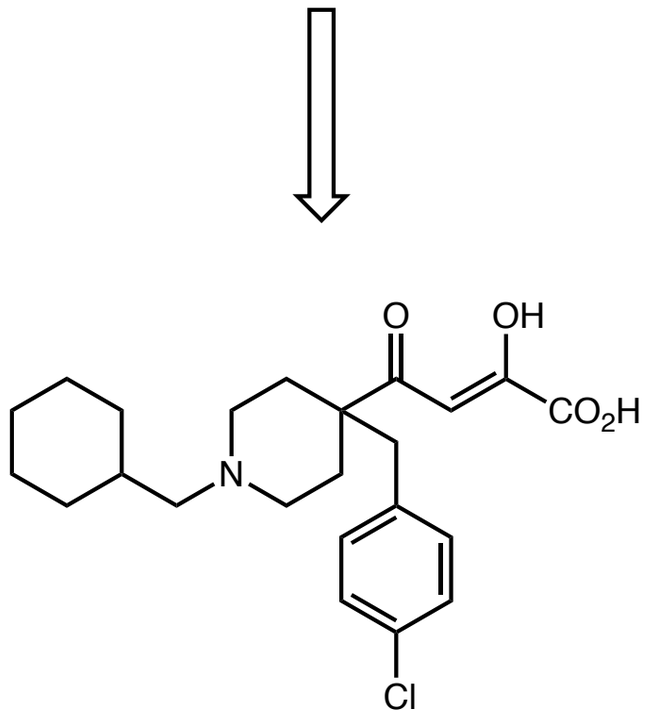
cLogP = 3.2
hERG IC50 > 10 uM

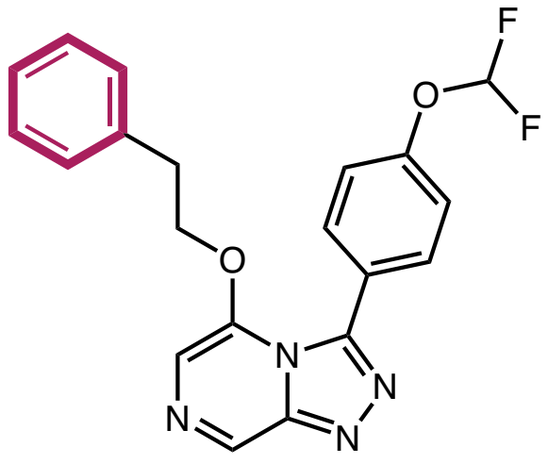
"reduced behavioral signs associated with opioid withdrawal following repeat drug dosing"

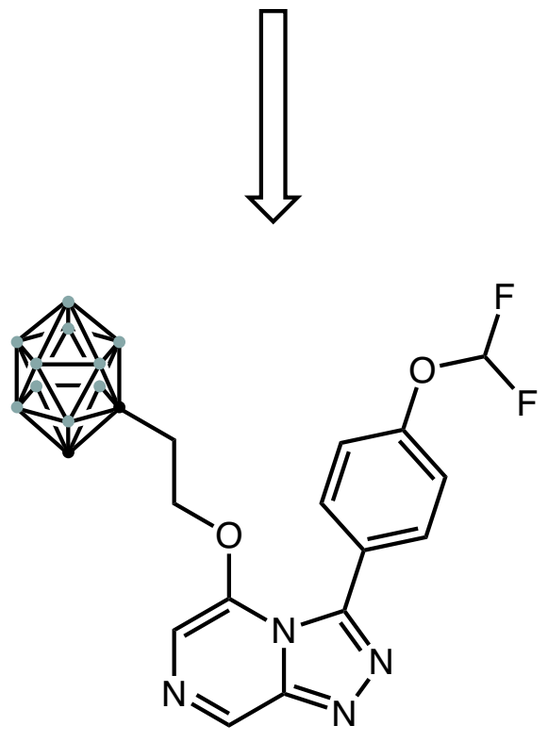
Almansa, C., *J. Med. Chem.* **2020**, *63*, 15508.

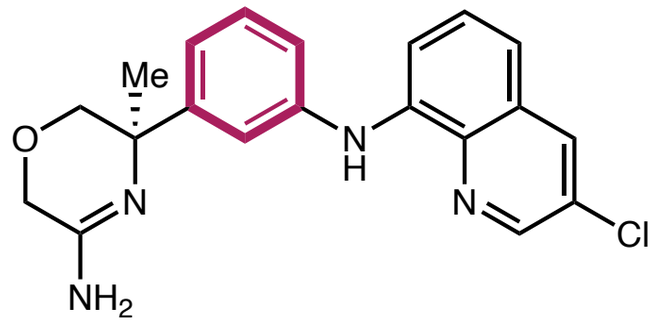
Phenyl Bioisosterism – A Solved Challenge?

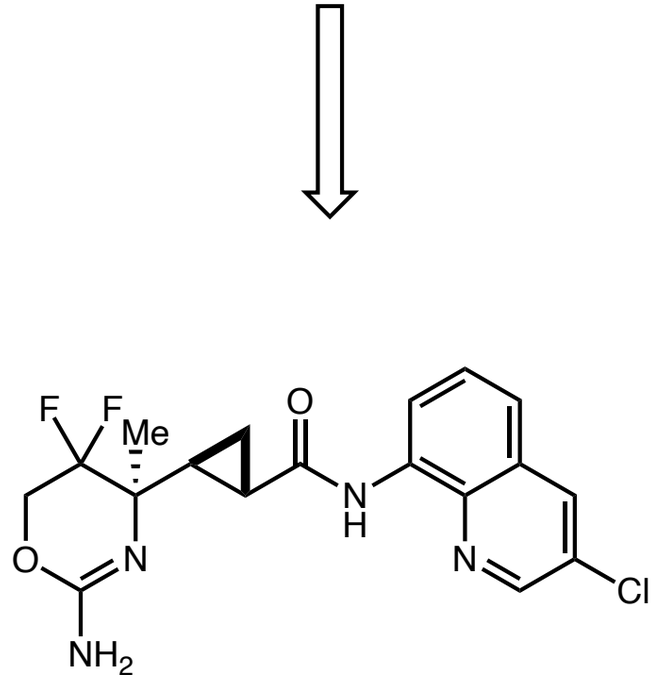












Phenyl Bioisosterism – A Solved Challenge?

Our predictive understanding of SAR and bioisosteric replacement is still in its infancy but the growing amount of data helps both us and machines to improve.

A growing number of scaffolds (and means to synthesize them) does not just lead to better ways to alter physicochemical properties but also to investigate SAR.

There is no “one size fits all” bioisostere. Different bioisosteres may have varying advantages and disadvantages in a given scaffold. An ideal replacement synergizes well with the binding mode.