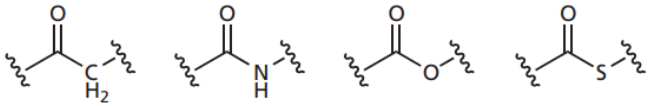
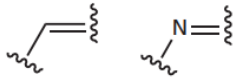
Classical isosteres

Univalent isosteres CH_3, NH_2, OH, F, Cl, SH
Br, i-Pr
I, t-Bu

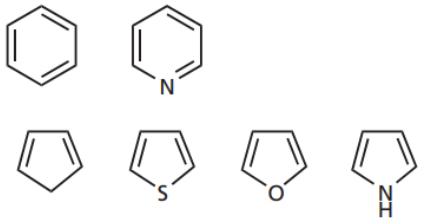
Bivalent isosteres CH_2, NH, O, S



Trivalent isosteres



Ring equivalents



Non-classical isosteres

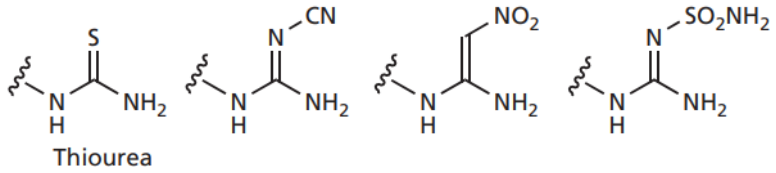


FIGURE 13.46 Non-classical isosteres for a thiourea group.

Bioisostere

both classical and non-classical isosteres
a group that can be used to replace another group while retaining the desired biological activity

often used to replace a functional group that is important for target binding, but is problematic in one way or another (e.g. Toxicity)

replacing a functional group with a bioisostere is NOT guaranteed to retain activity for every drug at every target

In some situations, the use of a bioisostere can actually increase target interactions and/or selectivity

The results of bioisosteric replacement

1) **Structural**: conformation; size; bond angle
   Scaffold hopping can be seen as an example
2) **Receptor interactions**: most relevant parameters will be size, shape, electronic properties, pKa, chemical reactivity, and hydrogen bonding.
3) **Pharmacokinetics**: optimization of absorption, transport, and excretion properties of the molecule the most important parameters to consider are lipophilicity, hydrophilicity, hydrogen bonding, pKa
4) **Metabolism**: Chemical reactivity is an important property to optimize

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

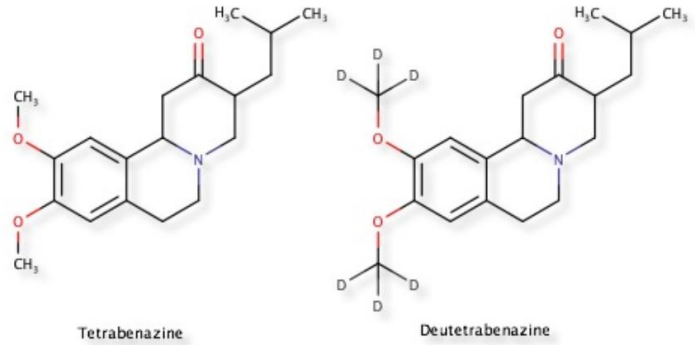
C=C, C=N, C=O, C=S
$-CH_2-$, $-NH-$, $-O-$, $-S-$
RCOR′, RCONHR′, RCOOR′, RCOSR′

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 $-N=C$

Replacement of Hydrogen by Deuterium

- minor impact on the physicochemical properties
- usually introduced to modulate metabolism
- If the bond to the H being replaced is broken during the rate-determining step – **Kinetic isotopic effect**
- Slow epimerization



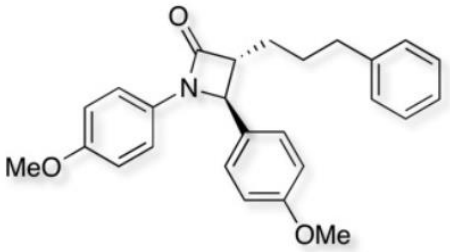
Tetrabenazine (treatment of Huntington's Disease-Related Chorea) is well absorbed but it has relatively low bioavailability and the primary route for metabolism is via oxidation by CYP2D6. Deutetrabenazine from Teva - the half-life nearly twice that of tetrabenazine, allowing it to be administered twice rather than three times a day, and at lower doses, thus reducing peak concentration adverse effects while maintaining efficacy.

https://www.cambridgemedchemconsulting.com/resources/bioisoteres/

Replacement of Hydrogen by Fluorine

Fluorine

- introduced to reduce basicity of proximal amines or increase acidity of proximal acids
- to introduce a conformational bias in molecules
- C-F bond is strong and thus resistant to metabolic cleavage
- is highly electron-withdrawing - serves to reduce the potential for oxidative metabolism

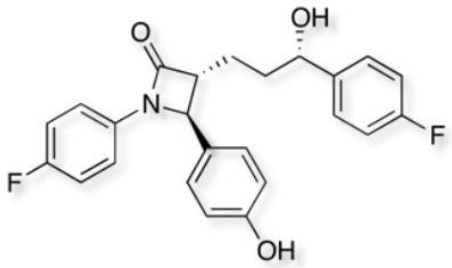


ED50 2.2 mg/kg (Hamster)

ED50 2.0 mg/kg (Rat)

ED50 0.2 mg/kg (Monkey)

ED50 0.1 mg/kg (Dog)



Ezetimibe ED50 0.04 mg/kg (Hamster)

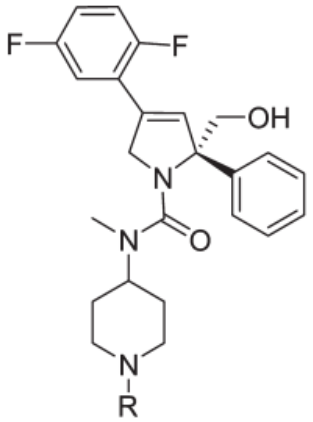
ED50 0.03 mg/kg (Rat)

ED50 0.0005 mg/kg (Monkey)

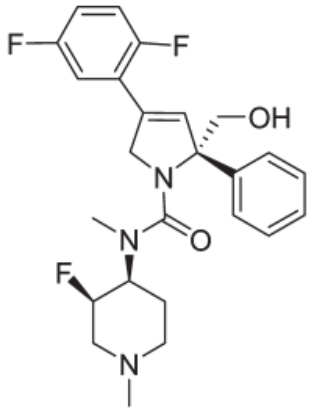
ED50 0.007 mg/kg (Dog)

Review: K.L. Kirk *Current Topics in Medicinal Chemistry*, **2006**, *6* (14), 1447
Fluorine as a bioisotere of H: N.A. Meanwell *J. Med. Chem.* **2018**, *61*, 5822

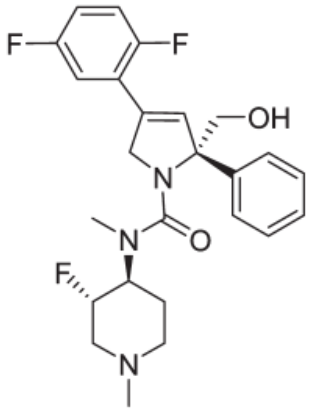
The strategic deployment of a fluorine atom to modulate basicity was probed in the context of inhibitors of kinesin spindle protein (KSP)



22: R = cyclopropyl
23: R = CH_2CH_2F
24: R = H



25



26

23 was dealkylated in rat liver microsomes (RLM) as the major metabolic pathway to afford **24** and fluoroacetaldehyde, which was oxidized to fluoroacetic acid, a highly toxic substance

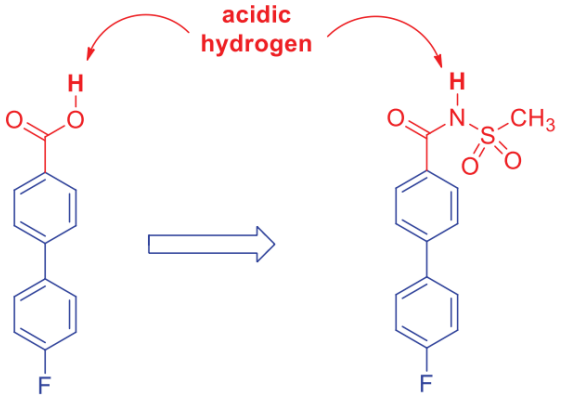
F substituent in the piperidine ring where the effect on pKa was dependent on stereochemical disposition. In the trans analogue **26**, the F in equatorial position - reduction in basicity from pKa = 8.8 to pKa = 6.6. In contrast, in the cis isomer **25**, the F is disposed axially, effect on basicity - pKa = 7.6. This compound, MK-0731 (**25**), was subsequently advanced into clinical trials.

N. A. Meanwell *J. Med. Chem.* **2011**, *54*, 2529–2591

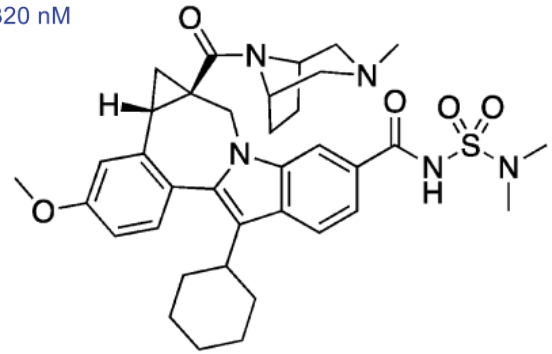
Carboxylic acid isosteres

Effect:

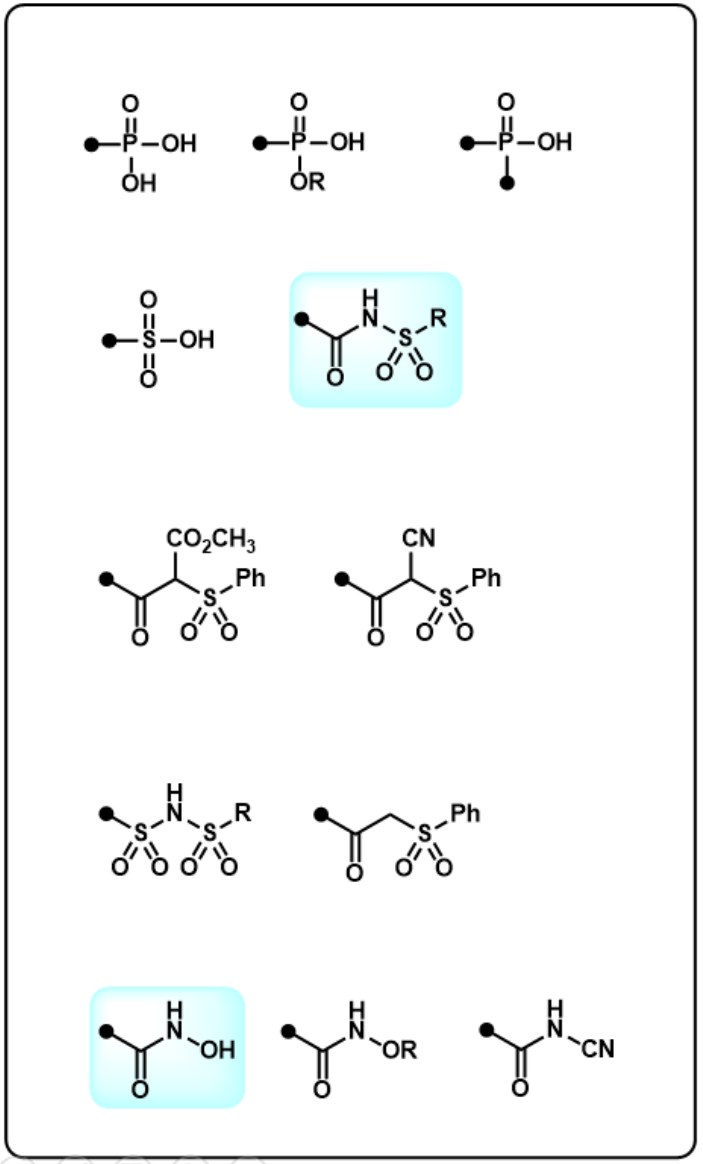
- Enhancing potency
- Reducing polarity
- Increasing lipophilicity (improve membrane permeability)
- Enhancing pharmacokinetic properties
- Reducing the potential for toxicity



acid **118**, K_d = 300 μM acylsulfonamide **119**, K_d = 320 nM

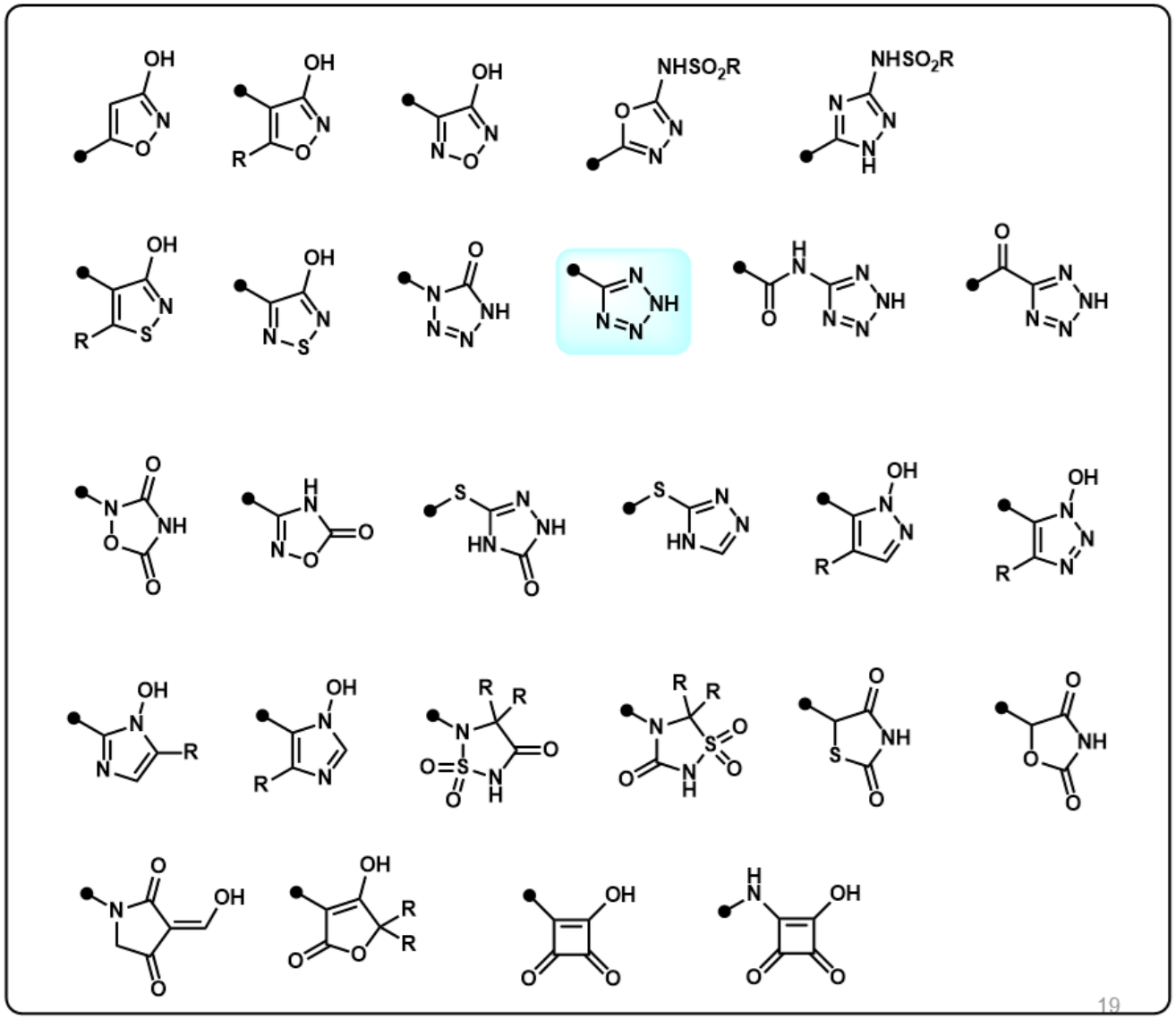


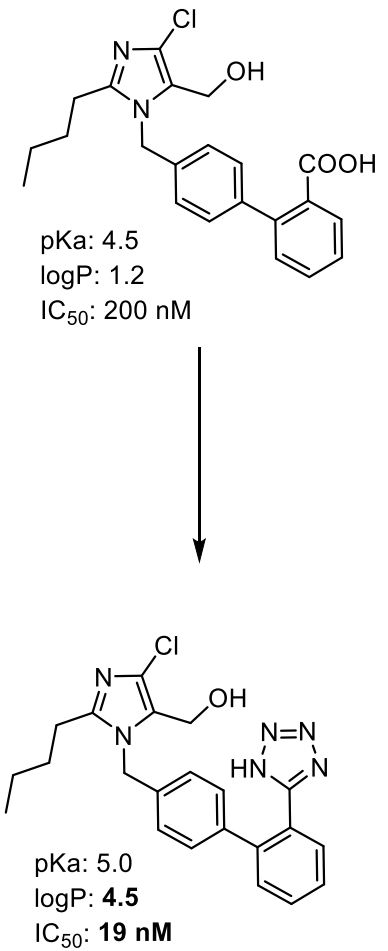
Beclabuvir
(*Anti-HCV*)



N. A. Meanwell *J. Med. Chem.* **2011**, *54*, 2529–2591

Carboxylic acid isosteres

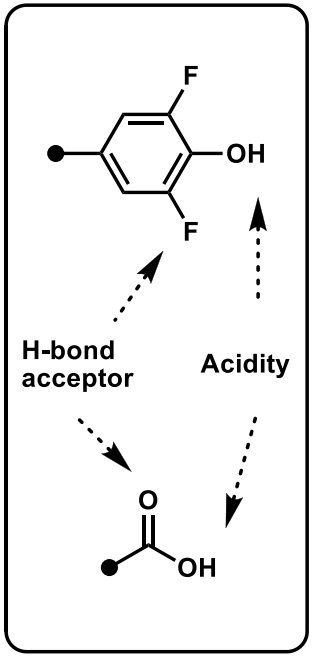


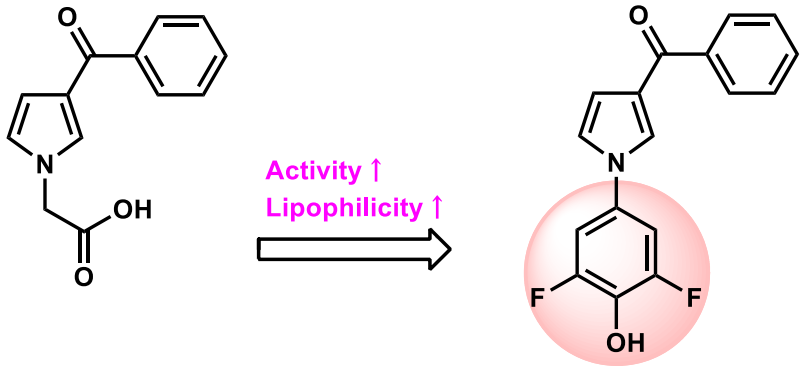


Losartan
(Angiotensin II receptor antagonist)

N. A. Meanwell *J. Med. Chem.* **2011**, *54*, 2529–2591

Carboxylic acid isosteres





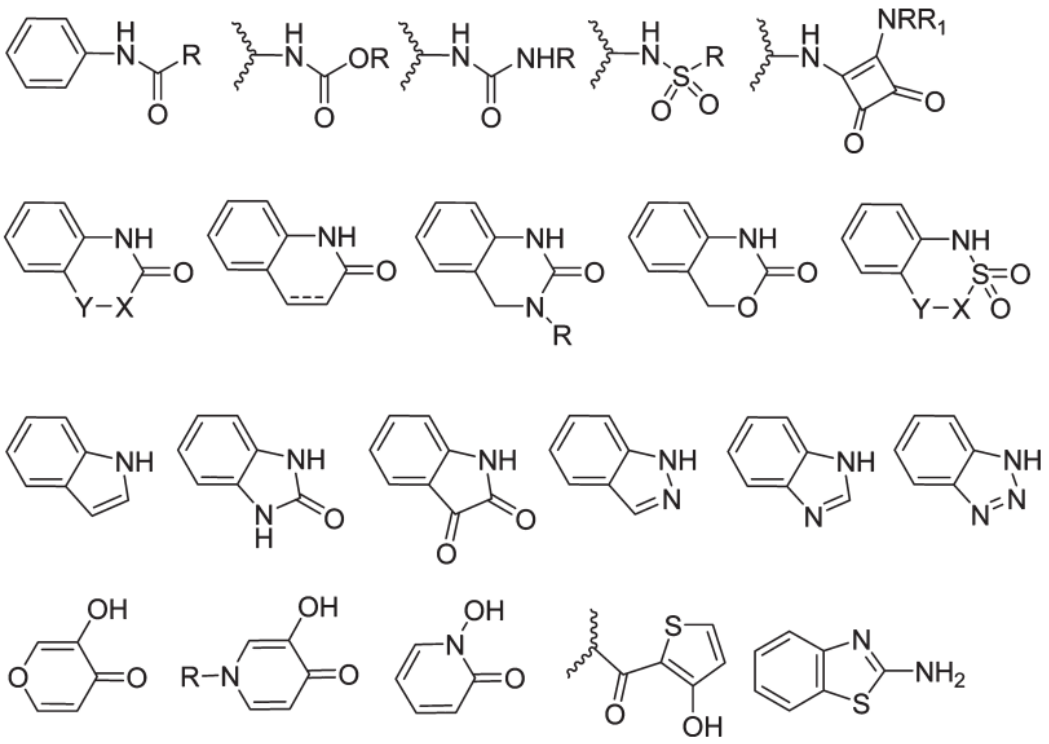
IC_{50} = 2.4 μM
logP = 1.23

IC_{50} = 0.39 μM
LogP = 3.56

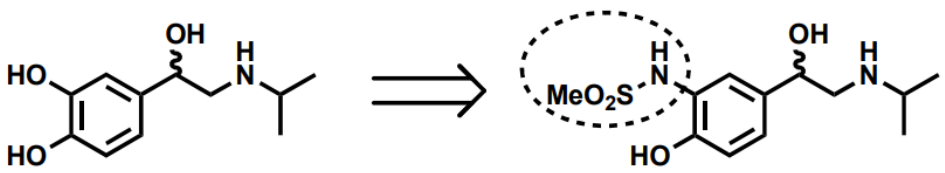
Aldose reductase inhibitors (Diabetes)

N. A. Meanwell *J. Med. Chem.* **2011**, *54*, 2529–2591

Replacement phenol or catechol



application (Non-selective β-adrenoceptor agonists)

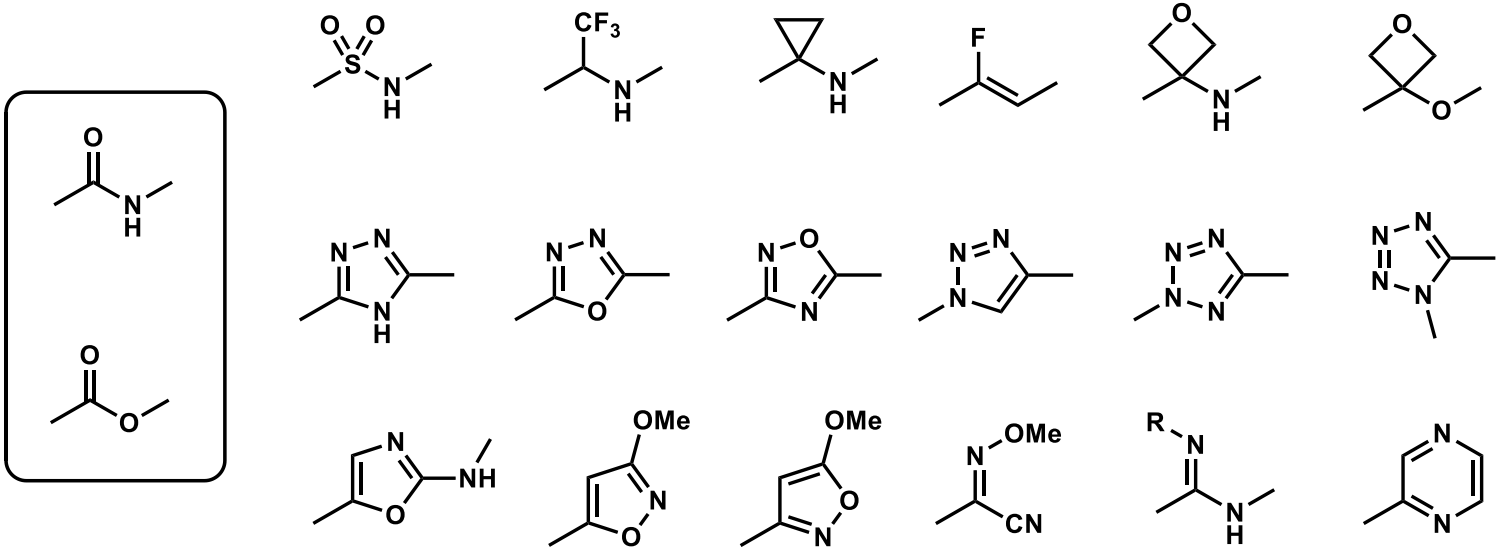


resistance toward COMT(catechol *O*-methyl transferase)

N. A. Meanwell *J. Med. Chem.* **2011**, *54*, 2529–2591

Replacement of amides and esters

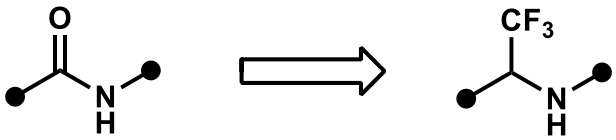
Amide isosteres - modulating polarity and bioavailability
Ester isosteres - address metabolism issues (esters can be rapidly cleaved in vivo)



C.R.J. Stephenson et al. *ACS Med. Chem. Lett.* **2020**, 11, 10, 1785–1788

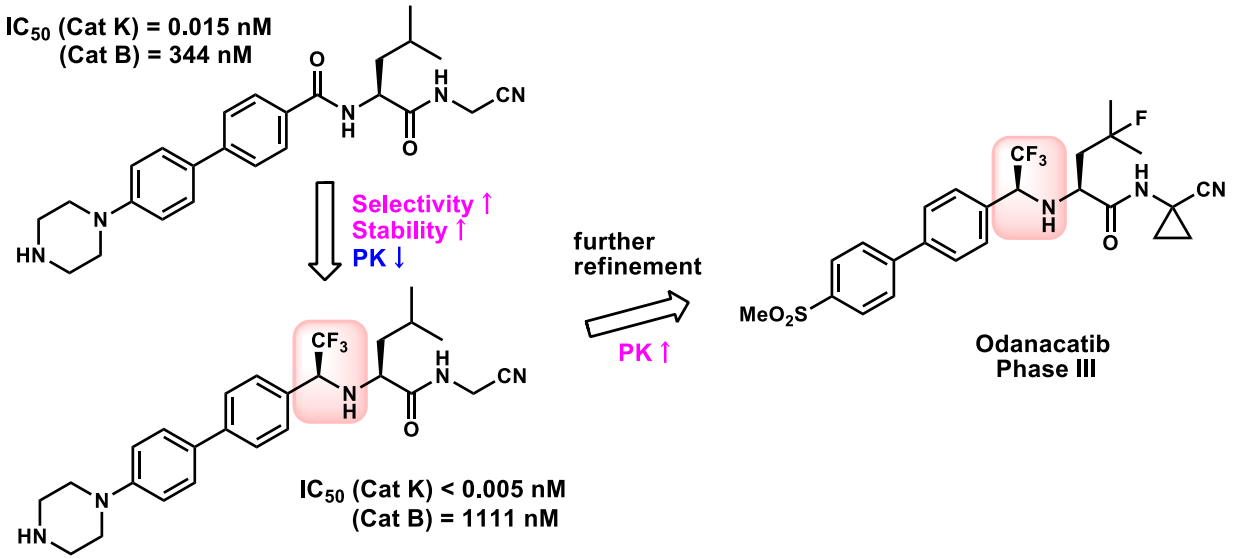
Replacement of amides and esters

The trifluoroethylamine can act as an isostere of an amide moiety in peptide-based molecules.



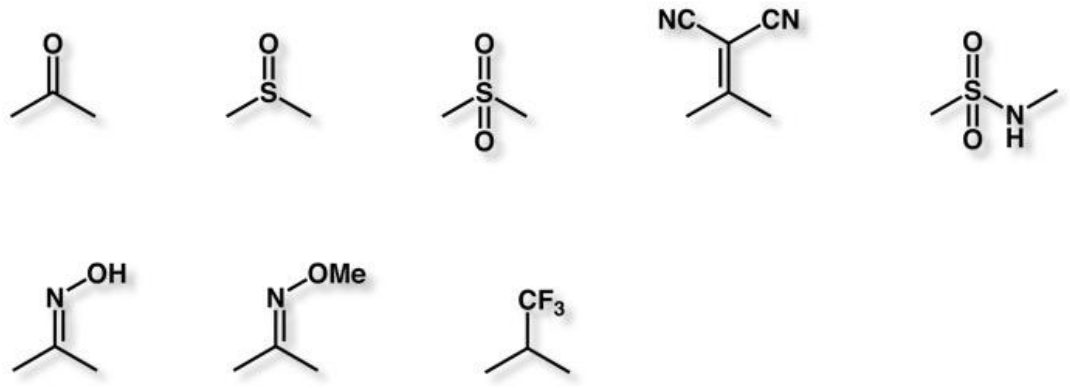
- Reducing the basicity of the amine without compromising of the NH to function as a H-bond donor
- $CF_3CH(R)NHR'$ bond is close to 120° observed with an amide
- C-CF_3 bond is as polar as C=O bond

Cathepsin K inhibitor (Osteoporosis)

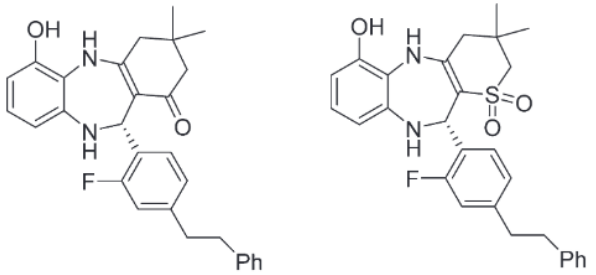


C.R.J. Stephenson et al. *ACS Med. Chem. Lett.* **2020**, 11, 10, 1785–1788

Replacement of carbonyl



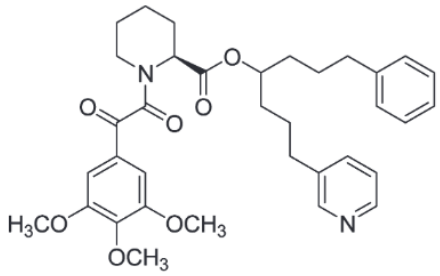
Simple ketones and aldehydes - typically low prevalence in drugs because of their potential chemical reactivity (e.g. reduction/oxidation)



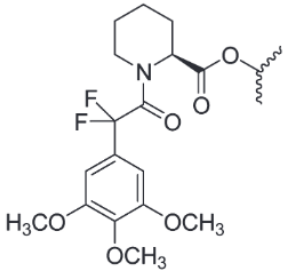
303
IC_{50} = 74 nM
EC_{50} = 400 nM
K_D = 15 nM

304
IC_{50} = 26 nM
EC_{50} = 29 nM
K_D = 0.8 nM

K. Vandyck et al. *J. Med. Chem.* **2009**, *52*, 4099–4102



310

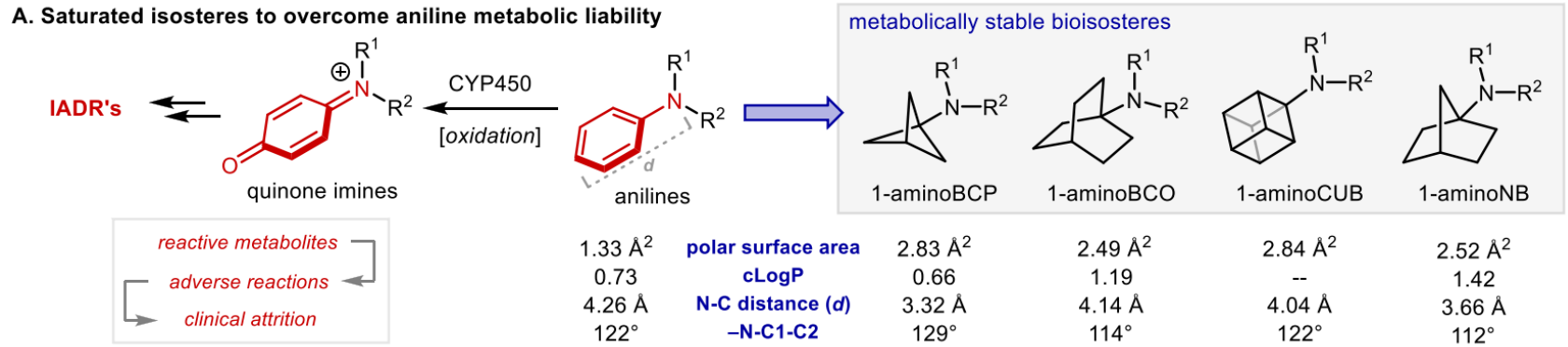


311

G. M. Dubowchik et al. *Org. Lett.* **2001**, *3*, 3987–3990

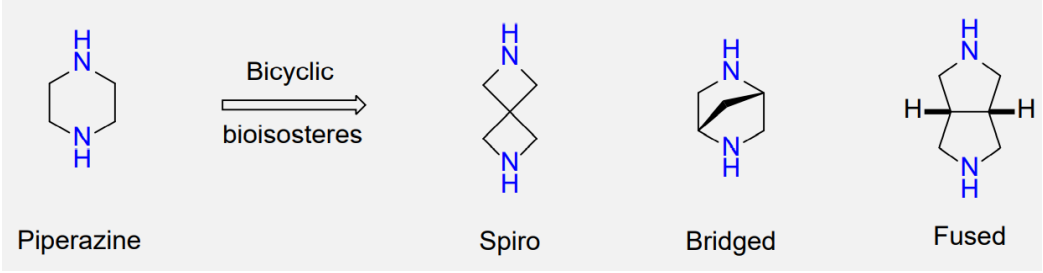
N. A. Meanwell *J. Med. Chem.* **2011**, *54*, 2529–2591

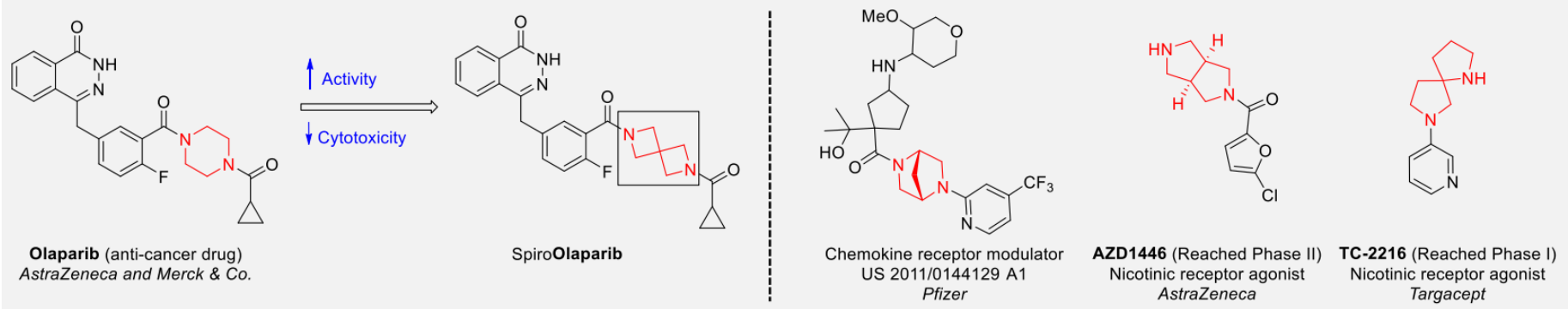
Replacement of aniline



C.R.J. Stephenson et al. *ACS Med. Chem. Lett.* **2020**, 11, 10, 1785–1788

Replacement of piperazine





Olaparib (anti-cancer drug)
AstraZeneca and Merck & Co.

SpiroOlaparib

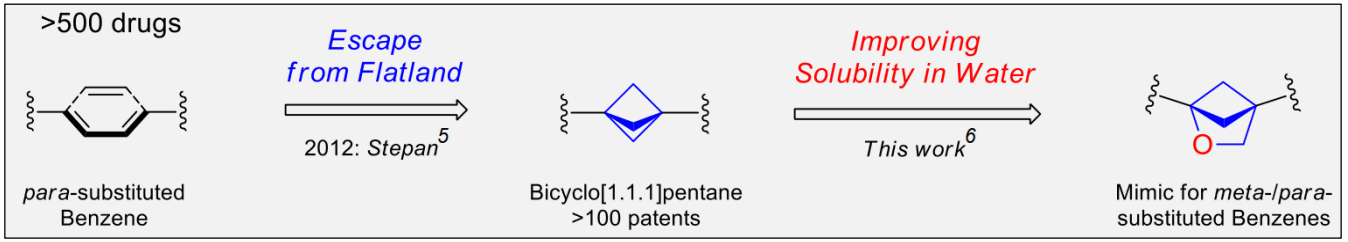
Chemokine receptor modulator
US 2011/0144129 A1
Pfizer

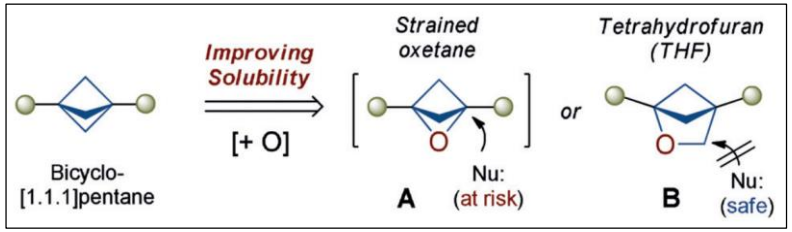
AZD1446 (Reached Phase II)
Nicotinic receptor agonist
AstraZeneca

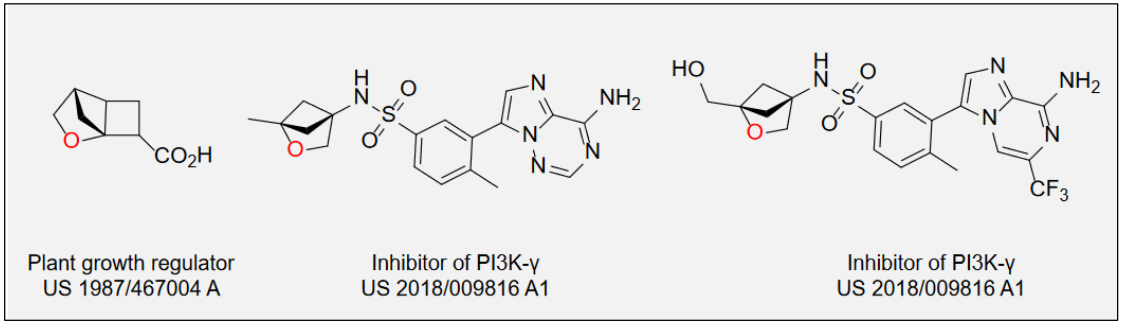
TC-2216 (Reached Phase I)
Nicotinic receptor agonist
Targacept

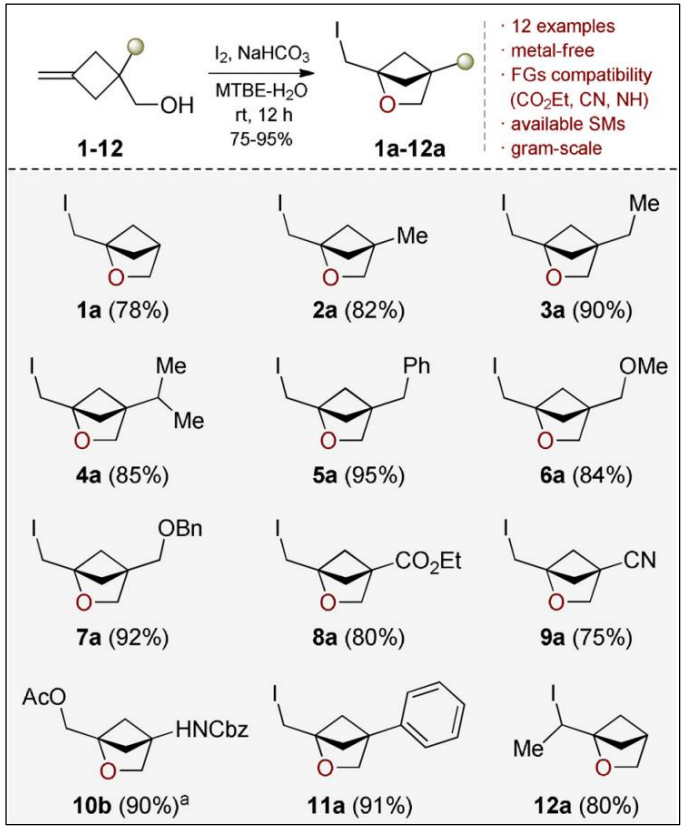
https://enamine.net/download/MedChem/Enamine_Piperazine-Bioisosteres-2019.pdf
P.H. Mykhailiuk et al *Angew. Chem. Int. Ed.* **2020**, *59*, 7161 –7167

Replacement of *para*-substituted benzene





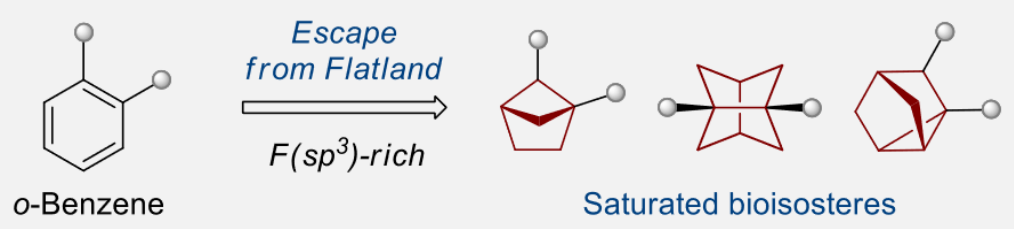


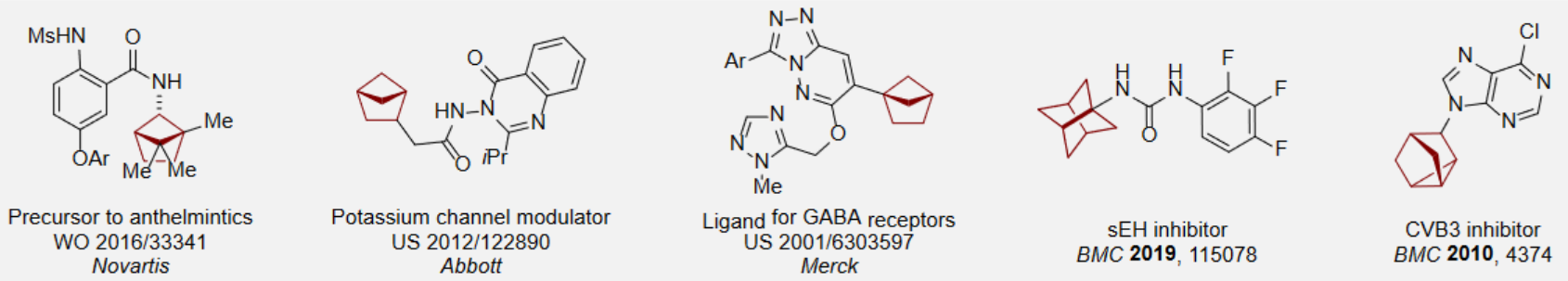


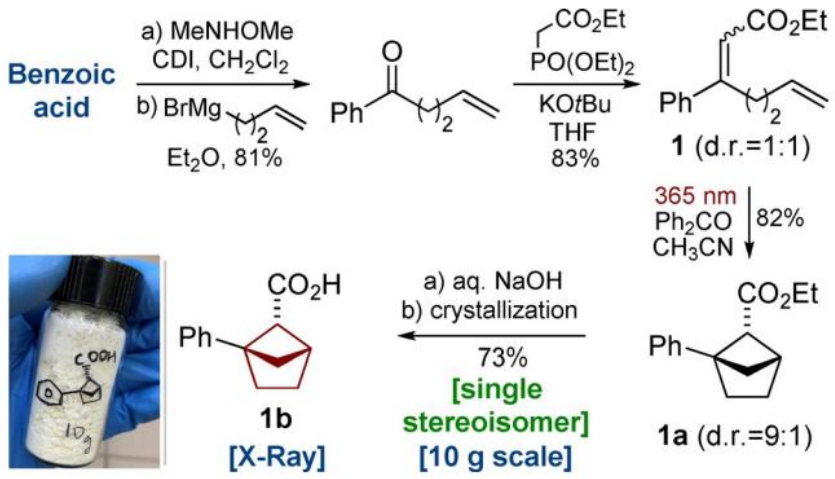
https://enamine.net/download/MedChem/Enamine-Water-Soluble-benzene-mimics-2020.pdf

P.H. Mykhailiuk et al *Angew. Chem. Int. Ed.* **2020**, *59*, 7161 –7167

Replacement of *ortho*-substituted benzene

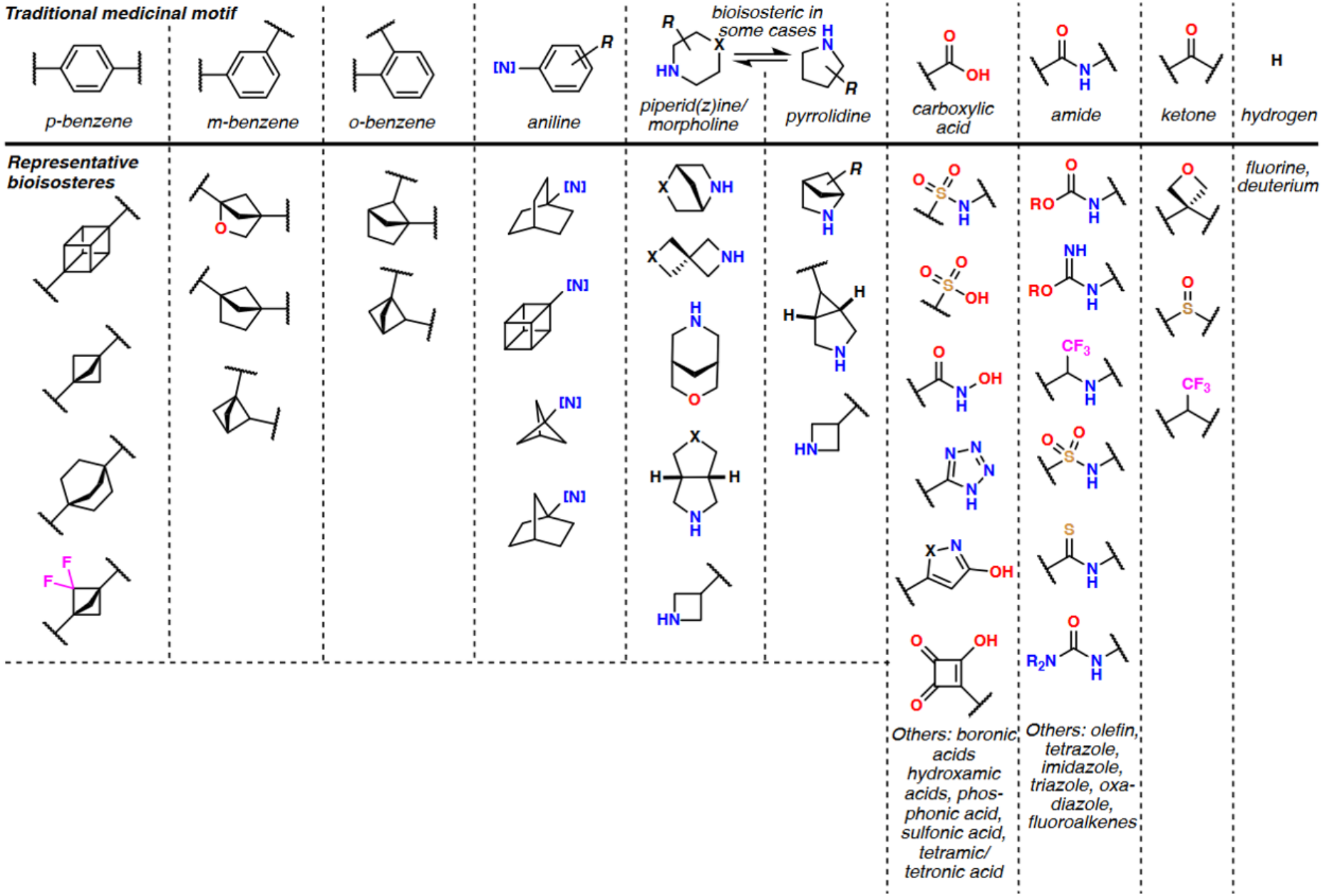






https://enamine.net/download/MedChem/Enamine_Saturated_Bioisosteres_of_o-benzene-2020.pdf
P.H. Mykhailiuk et al *Angew. Chem. Int. Ed.* **2020**, *59*, 20515 – 20521

Bioisosteres



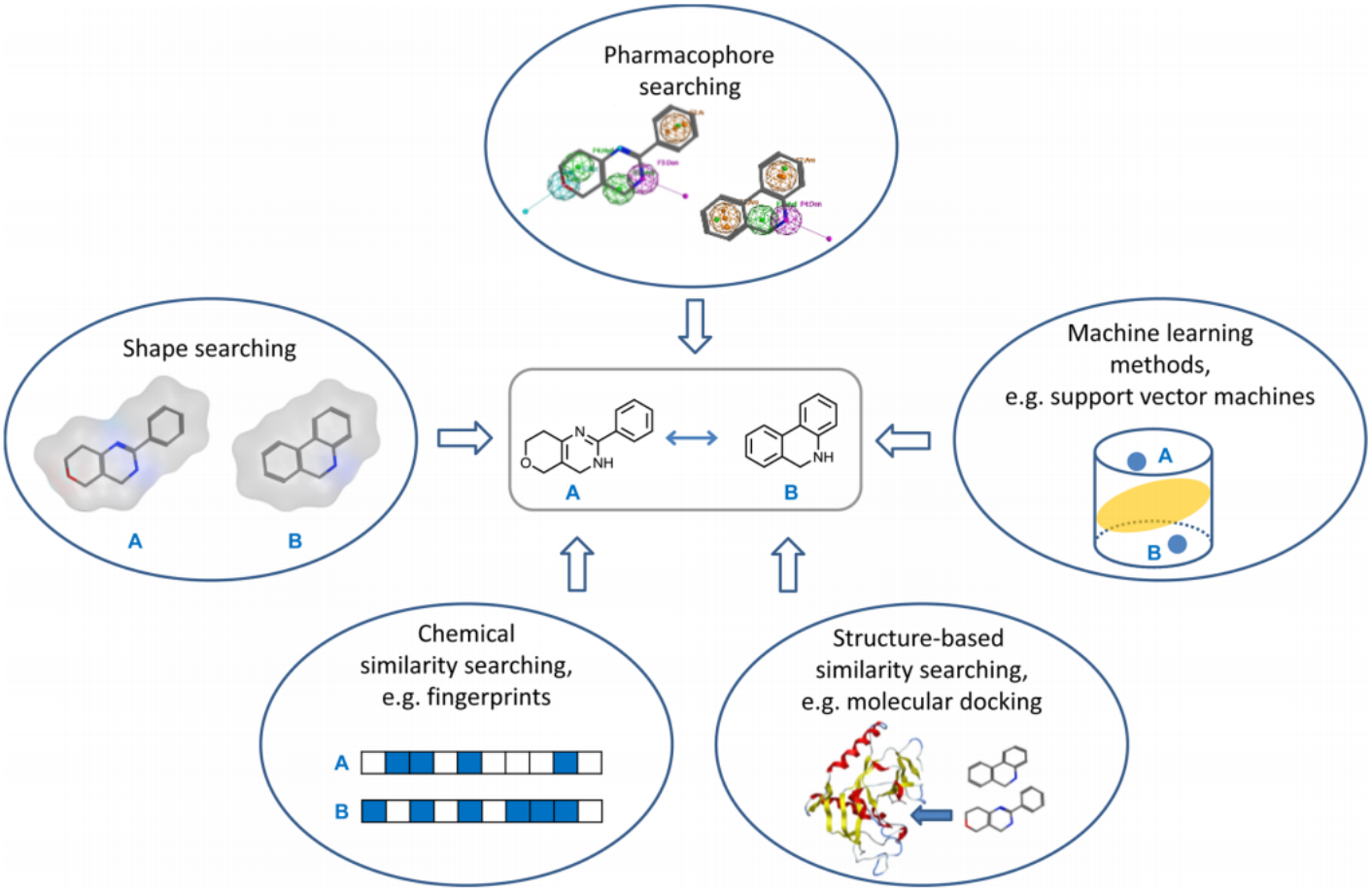
Bioisostere web database

http://www.swissbioisostere.ch

- Scaffold hopping is a strategy for discovering structurally novel compounds
- starts with known active compounds and end with a novel chemotype by modifying the central core structure of the molecule
- computer-aided search for active compounds containing different core structures
- can also be attempted on a case-by-case basis from a chemical viewpoint

- compounds with different structures but similar activity
- Reasons: circumventing an intellectual property; replacing a chemically complex natural product; improving pharmacological properties of known actives

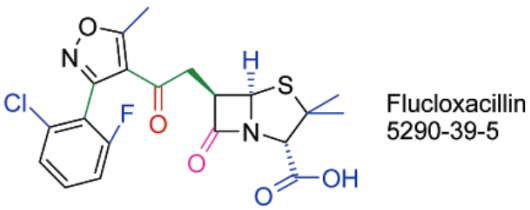
The concept of scaffold hopping can be applied to structure-based virtual screening



J. Bajorath et al. *J. Med. Chem.* **2017**, *60*, 1238−1246

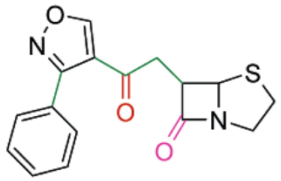
Scaffolds are extracted from compounds by removal of all substituents while retaining ring systems and linker moieties between rings

The Scaffold Tree algorithm - rules how to systematically decompose a scaffold



Flucloxacillin
5290-39-5

terminal sidechain
linker
exocyclic double bond
exolinker double bond

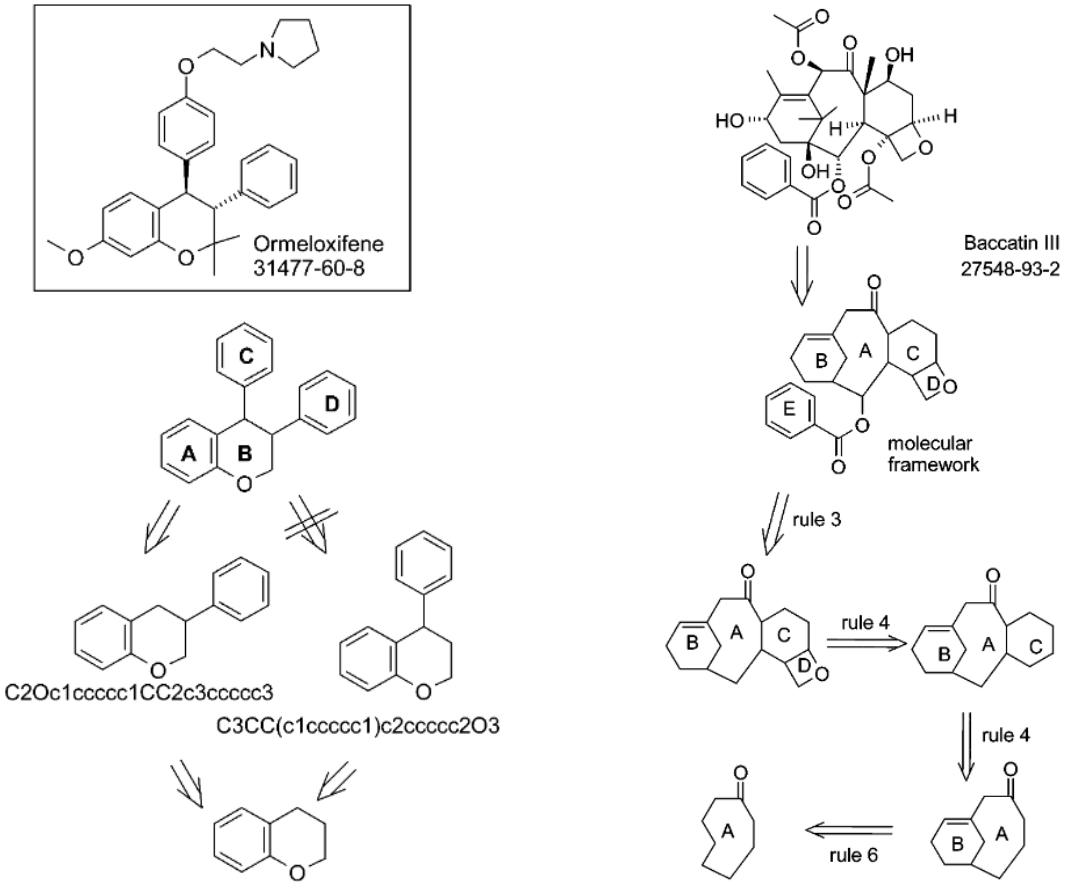


molecular framework

1. Remove Heterocycles of Size 3 First
2. Do Not Remove Rings with g 12 Atoms if There Are Still Smaller Rings To Remove
3. Choose the Parent Scaffold Having the Smallest Number of Acyclic Linker Bonds
4. Retain Bridged Rings, Spiro Rings, and Nonlinear Ring Fusion Patterns with Preference
5. Bridged Ring Systems Are Retained with Preference over Spiro Ring Systems
6. Remove Rings of Sizes 3, 5, and 6 First
7. A Fully Aromatic Ring System Must Not Be Dissected in a Way That the Resulting System Is Not Aromatic Any More
8. Remove Rings with the Least Number of Heteroatoms First
9. If the Number of Heteroatoms Is Equal, the Priority of Heteroatoms to Retain is N > O > S.
10. Smaller Rings are Removed First
11. For Mixed Aromatic/Nonaromatic Ring Systems, Retain Nonaromatic Rings with Priority
12. Remove Rings First Where the Linker Is Attached to a Ring Heteroatom at Either End of the Linker

A. Schuffenhauer et al. *J. Chem. Inf. Model.* **2007**, *47*, 47-58
J. Bajorath et al. *J. Med. Chem.* **2017**, *60*, 1238−1246

Scaffolds are extracted from compounds by removal of all substituents while retaining ring systems and linker moieties between rings



A. Schuffenhauer et al. *J. Chem. Inf. Model.* **2007**, *47*, 47-58
J. Bajorath et al. *J. Med. Chem.* **2017**, *60*, 1238−1246

Scaffold hopping events are often of different magnitude

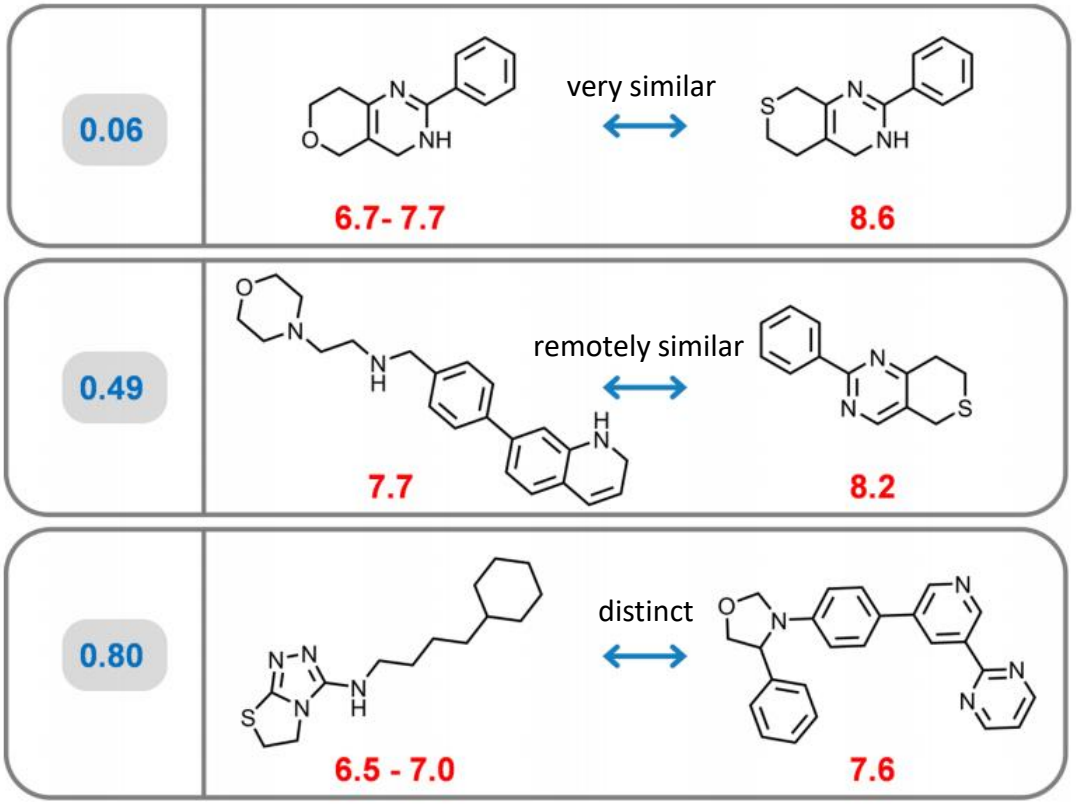
Scaffolds might be very similar, e.g. distinguished by a heteroatom in a ring.

Scaffolds might be completely distinct, e.g. consist of different ring systems with different topology

Detecting compounds that contain distantly related scaffolds but share similar activity would be considered a meaningful scaffold hopping event.

Structural distance between two scaffolds is represented by a number in range 0 – 1 (blue).

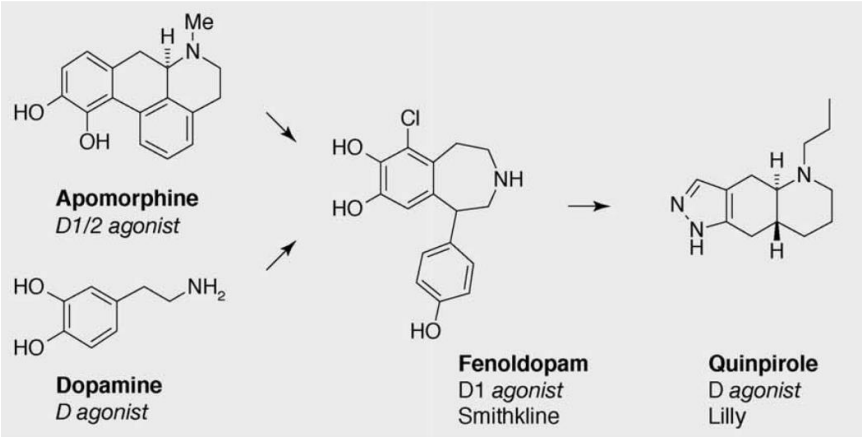
Values ≤ 0.34 = similar scaffolds
Values ≥ 0.74 = dissimilar scaffolds



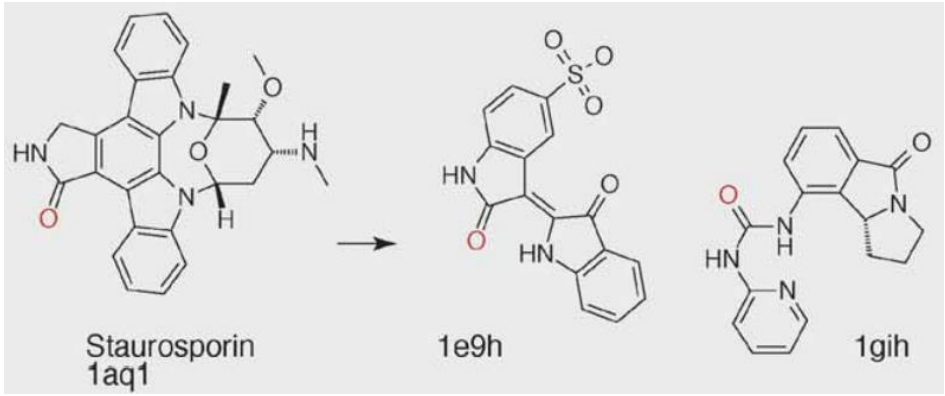
A. Schuffenhauer et al. *J. Chem. Inf. Model.* **2007**, *47*, 47-58
J. Bajorath et al. *J. Med. Chem.* **2017**, *60*, 1238−1246

Dopamine agonists

- Starting from the natural ligand
- Fenoldopam - structural similarity to dopamine
- Quinpirole - completely novel structure

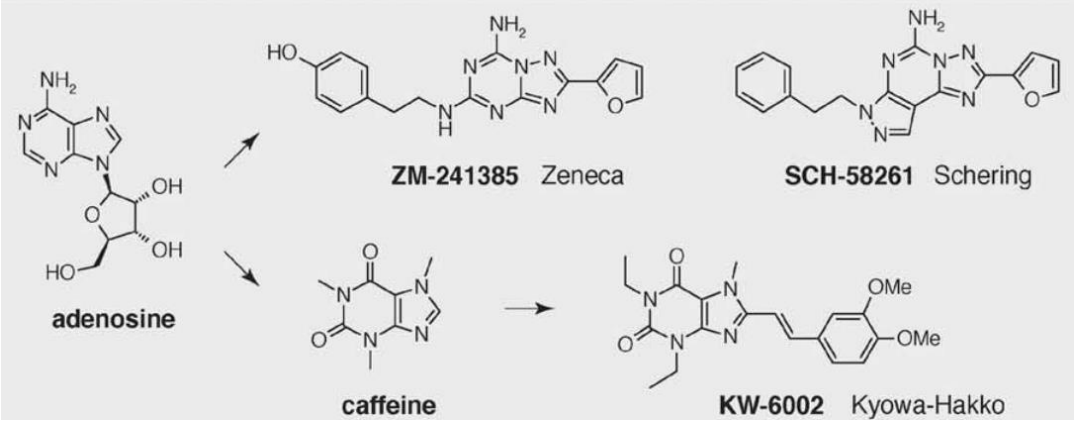


Inhibitors of CDK2



Adenosine A2a-antagonists

- starting form the natural ligand adenosine (an agonist)
- or the natural product caffeine (a subtype-unselective antagonist)



M. Stahl et al. *Drug Discov. Today Technol.*, **2004**, *1* (3), 217-224

Computational approaches

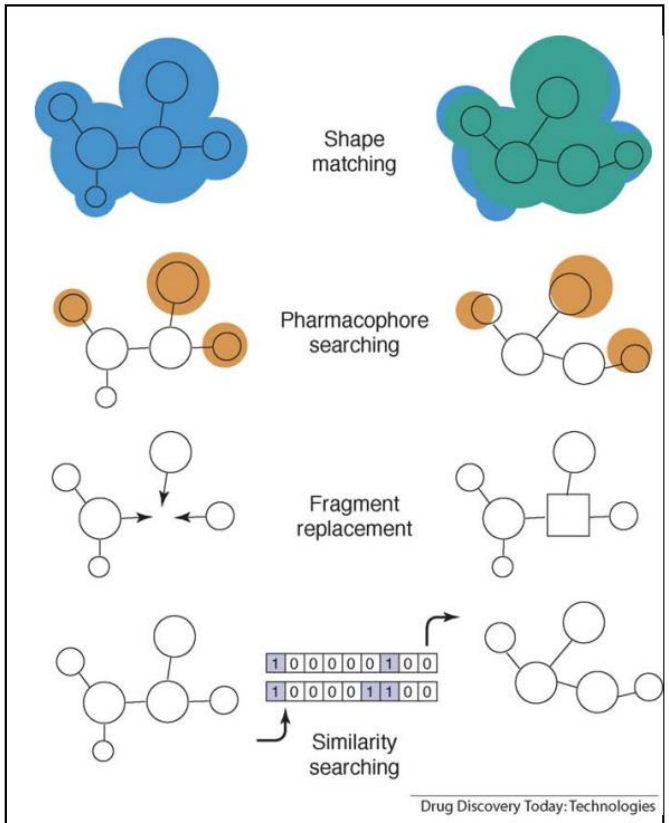


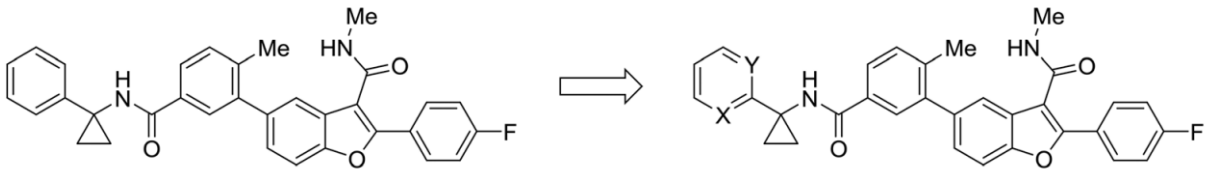
Figure 3. Schematic representation of four principal computational approaches to scaffold hopping. Many software programs offer combinations of several approaches, for example, pharmacophore searching combined with a shape filter can be a very powerful approach. Although shape matching and pharmacophore searching require 3D coordinates, fragment replacement can also be performed on planar chemical structures. Similarity searching is the most abstract of the three methods, because the molecular structure is intermediately encoded in a set of descriptors.

Method	Pros	Cons	Software
Shape matching	Fast, high success rate for small or rigid compounds	Requires knowledge about bioactive conformation	BioSolveIT www.biosolveit.de ROCS www.eyesopen.com
Pharmacophore searching	Yielding clear answers, based on a maximum of information	Requires knowledge about bioactive conformation and alignment	Catalyst www.accelrys.com Unity www.tripos.com
Fragment replacement	Can be performed on 2D or 3D structure, high success rate	Calculations might yield many or no results depending on tolerance	CAVEAT cchem.Berkeley.edu/pabgrp/index.html
Similarity searching	Fast and always applicable	High degree of uncertainty because of high abstraction from chemical structure	Daylight Fingerprints www.daylight.com

M. Stahl et al. *Drug Discov. Today Technol.*, **2004**, *1* (3), 217-224

Scaffold hopping for imparting metabolic stability

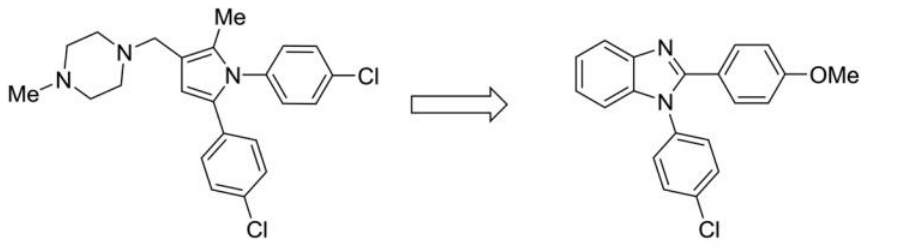
Replacement of a phenyl substituent with a pyridyl or pyrimidyl substituent



1 HLM $t_{1/2}$: 11 min

2 X = N, Y = CH HLM $t_{1/2}$: 108 min
3 X = N, Y = N HLM $t_{1/2}$: >120 min

Benzimidazole, imidazole, and imidazopyridine were identified as potential replacements for pyrrole core—which can generate toxic metabolites



14 (BM212)

M. tuberculosis H37Rv MIC: 5 μM
Cytotoxicity HepG2 Cells IC_{50}: 7.8 μM
MIC = Minimum inhibitory concentration

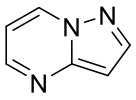
15

M. tuberculosis H37Rv MIC: 2.3 μM
Cytotoxicity HepG2 Cells IC_{50}: 203 μM

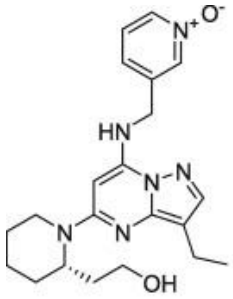
For more examples see the review: T. W. Moore, et al. *RSC Med. Chem.*, **2020**, *11*, 18-29

In 1988, Evans mentioned the term 'privileged structures', describing them as simple structural subunits present in the molecules of several drugs, with distinctive therapeutic uses, or affinities to several different receptors.

In medicinal chemistry some scaffolds may have privileged characteristics, being recognized molecularly by distinctive receptors without being important pharmacophores

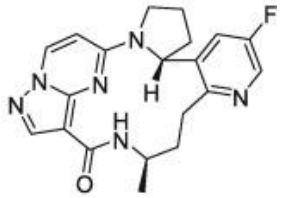


pyrazolo[1,5-a]pyrimidine

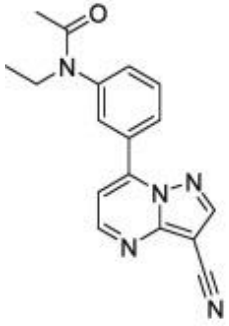


dinaciclib
CDK inhibitor

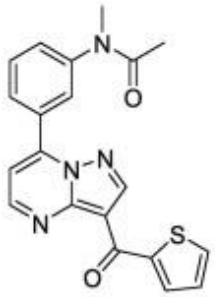
Vitrakvi® (larotrectinib)
TrkA, TrkB and TrkC inhibitor



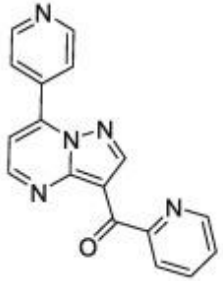
Selitrectinib (Loxo-195)
TrkA, TrkB and TrkC inhibitor



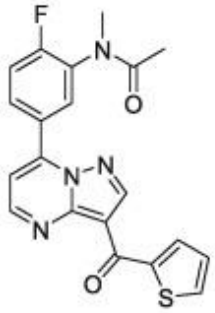
Zaleplon
insomnia



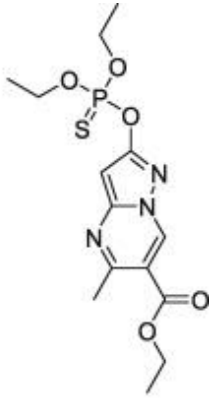
Indiplon
insomnia



Ocinaplon
anxiolytic



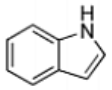
Loredipion
insomnia



Pyrazophos
fungicide

B. E. Evans et al. *J. Med. Chem.*, **1988**, *31*, 2235, A. Gumus et al. *Bioorg. Med. Chem. Lett.* **2021**, *49*, 128309

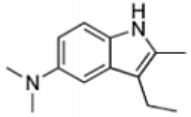
Privileged Scaffold



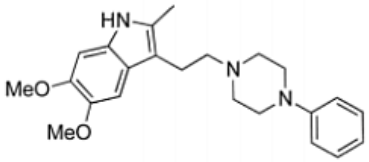
Indole

Structures

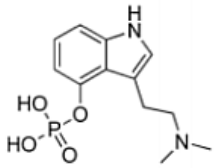
Drugs



Medmain
Therap Cat: Serotonin inhibitor

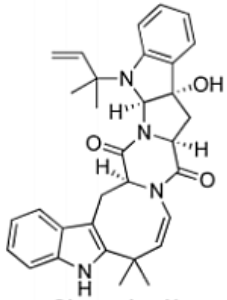


Oxypertine
Therap Cat: Antidepressant

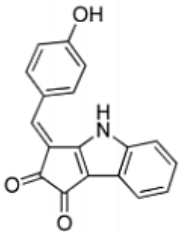


Psilocybin
Therap Cat: Psychomimetic

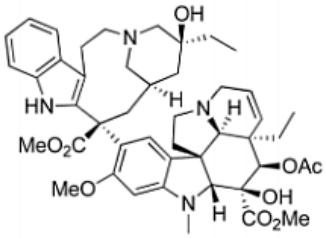
Natural Products



Okaramine N
Source: Penicillium simplicissium
Biological Activity: Insecticidal activity



Nostodione A
Source: The terrestrial blue-green algae Nostoccommune
Biological Activity: Mitotic spindle posion



Vinblastine
Source: Leaves of Madagascar periwinkle plant (Cantharanthus roseus)
Biological Activity: Anticancer agent; causes apoptosis by stopping spindle formation during mitosis

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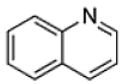
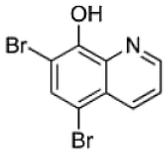
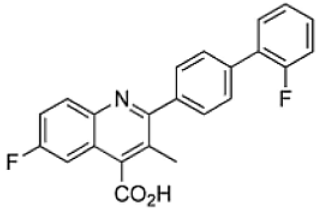


Quinoline

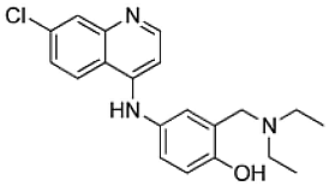
Drugs



Broxyquinoline
Therap Cat: Antiseptic; disinfectant

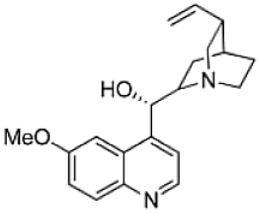


Brequinar
Therap Cat: Immunosuppressant

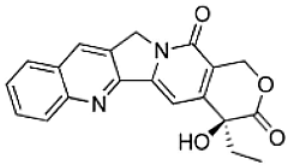


Amodiaquin
Therap Cat: Antimalarial

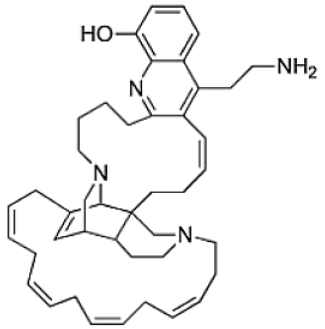
Natural Products



Quinine
Source: Quina Bark
Biological Activity: Anti-malarial



Camptothecin
Source: The Chinese tree Camptotheca acuminata Decne
Biological Activity: Anti-cancer activity



Njaoamine F
Source: Neopetrosia
Biological Activity: Cytotoxic

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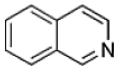
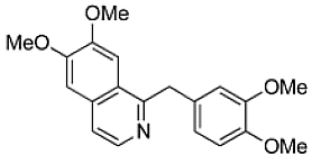
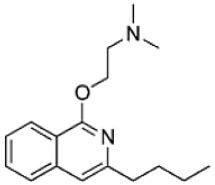


Isoquinoline

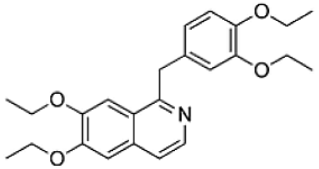
Drugs



Papaverine
Therap Cat: Vasodilator (cerebral)

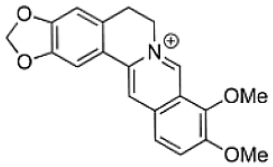


Dimethisoquin
Therap Cat: Anesthetic (topical)

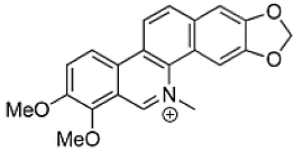


Ethaverine
Therap Cat: Antispasmodic

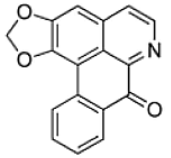
Natural Products



Berberine
Source: Berberis and Mahonia
Biological Activity: Causes Respiratory stimulation, transient hypotension, and convulsion. Cholinesterase and tyrosine decarboxylase inhibitor.



Chelerythrine
Source: The plant Greater celandine, Chelidonium majus
Biological Activity: Potent protein kinase C inhibitor.



Liriodenine
Source: The tulip tree Liriodendron tulipifera
Biological Activity: Leishmanicidal activity.

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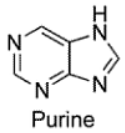
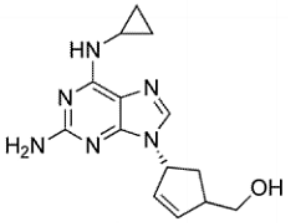
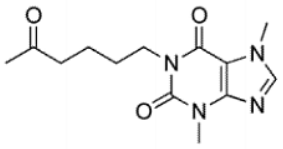
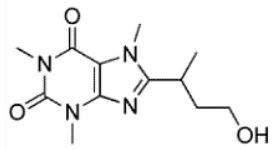

Purine

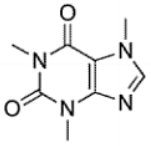
Drugs

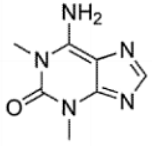

Abacavir
Therap Cat: Antiviral (HIV)

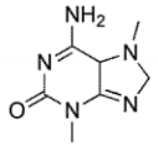

Pentoxifylline
Therap Cat: Hemorheologic agent


Cafaminol
Therap Cat: Decongestant (nasal)

Natural Products


Caffeine
Source: Coffee beans, tea leaves
Biological Activity: Stimulant


1,3 Dimethylisoguanine
Source: Amphimedon viridis
Biological Activity: Cytoxic to human ovarian cancer cells


3,7 Dimethylisoguanine
Source: Agelas longissima
Biological Activity: Antibacterial

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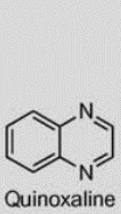
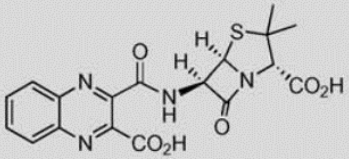
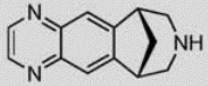


Quinoxaline

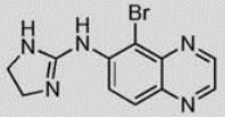
Drugs



Quinacillin
Therap Cat: Antibacterial

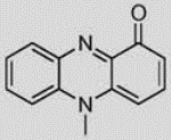


Varenicline
Therap Cat: Aid in smoking cessation

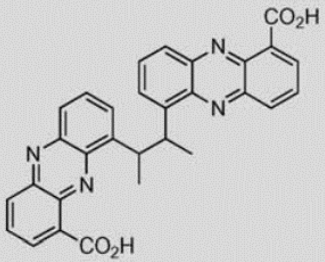


Brimonidine
Therap Cat: Antiglaucoma

Natural Products



Pyocyanine
Source: Pseudomonas aeruginosa
Biological Activity: Antibiotic activity against Gram-positive and Gram-negative bacteria, fungi, and protozoa



6,6'-(1,2-dimethyl-1,2ethanediyl)bis [1-phenazinecarboxylic acid]
Source: Streptomyces
Biological Activity: Phosphodiesterase inhibitor

CNB-253
Source: Streptomyces
Biological Activity: Antibacterial

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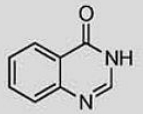
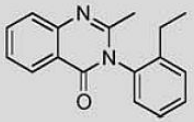
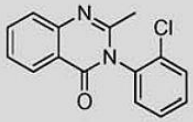
Drugs



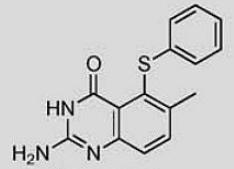
Quinazolinone



Etaqualone
Therap Cat: Sedative; hypnotic

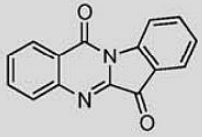


Mecloqualone
Therap Cat: Sedative; hypnotic

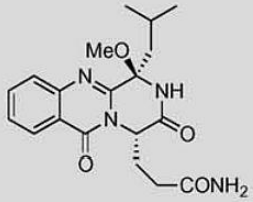


Nolatrexed
Therap Cat: Antineoplastic

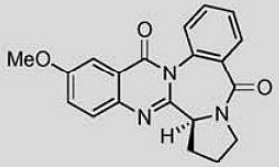
Natural Products



Tryptanthrin
Source: Various plant sources
Biological Activity: Active against African trypanosomes



Aurantiamide A
Source: Penicillium aurantiogriseum
Biological Activity: Cytotoxic to tumor cell lines



(-)-Circumdatin H
Source: The fungus Aspergillus ochraceus
Biological Activity: Inhibits mitochondrial respiratory chain

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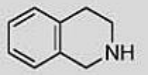
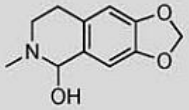
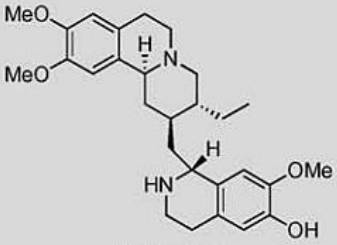
Drugs



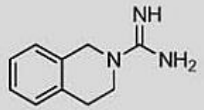
Tetrahydroisoquinoline



Hydrastinine
Therap Cat: Hemostatic

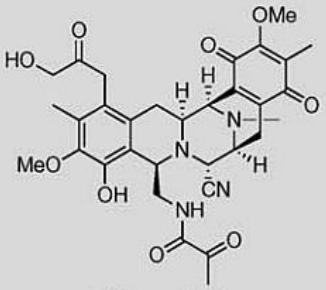


Cephaeline
Therap Cat: Emetic; antiamebic

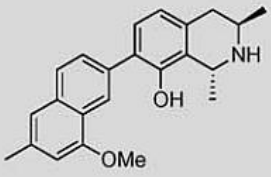


Debrisoquin
Therap Cat:Antihypertensive

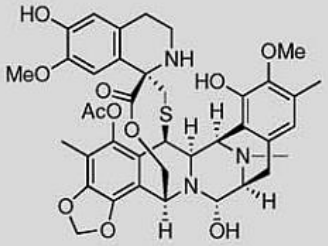
Natural Products



Saframycin R
Source: Streptomyces lavendulae
Biological Activity: Anti-tumor agent



Dioncophylline B
Source: Triphophyllum peltatum (Dioncophyllaceae)
Biological Activity: Activity against P. falciparum, Leishmania, and Trypanosoma



Ecteinascidin 743
Source: The tunicate Ecteinascidia turbinata
Biological Activity: Anti-tumor agent

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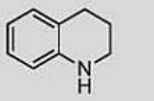
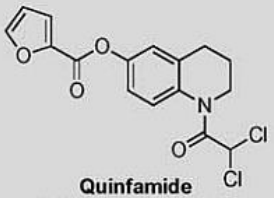
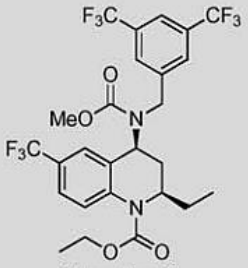
Drugs



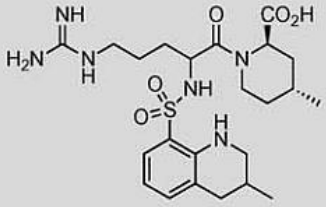
Tetrahydroquinoline



Quinfamide
Therap Cat: Antiamebic

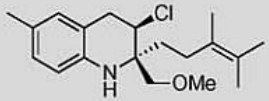


Torcetrapib
Therap Cat: Antilipemic; antiatherosclerotic

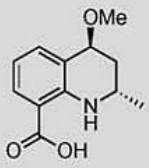


Argatroban
Therap Cat: Antithrombotic

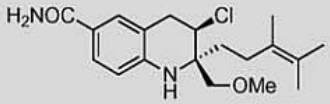
Natural Products



Virantmycin
Source: Streptomyces nitrosporeus
Biological Activity: Inhibits growth of DNA and RNA viruses and has weak anti-fungal activity



Helquinoline
Source: Janibacter limosus
Biological Activity: Antibiotic



Benzastatin C
Source: Streptomyces nitrosporeous
Biological Activity: Inhibitatory activity against glutamate toxicity and lipid peroxidation

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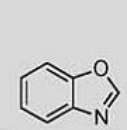
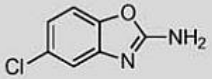
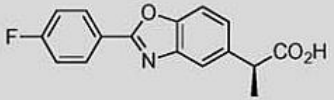


Benzoxazole

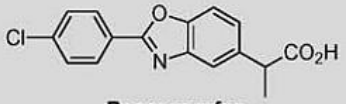
Drugs



Zoxazolamine
Therap Cat: Muscle relaxant (skeletal); uricosuric

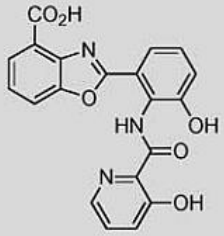


Flunoxaprofen
Therap Cat: Anti-inflammatroy

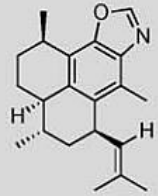


Benoxaprofen
Therap Cat: Anti-inflammatory; analgestic

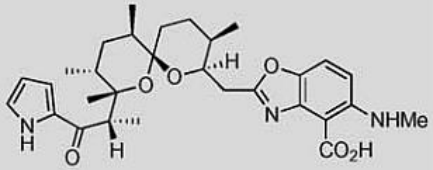
Natural Products



Antibiotic A 16886A
Source: Streptomyces
Biological Activity: Active against gram-positive bacteria and viruses



Pseudopteroxazole
Source: West Indian gorgian coral Pseudoterogoria
Biological Activity: Anti-tuberculosis activity



Antibiotic A23187
Source: Streptomyces chartreusis
Biological Activity: Antibiotic

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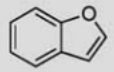
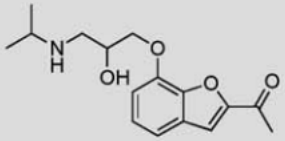
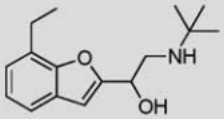


Benzofuran

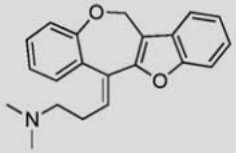
Drugs



Befunolol
Therap Cat: Antiglaucoma

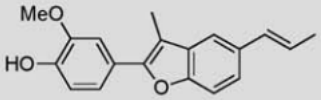


Buturalol
Therap Cat: Antianginal; antihypertensive

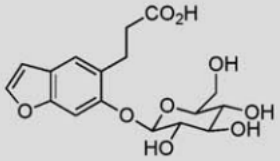


Oxetorone
Therap Cat: Analgesic (specific in migraine)

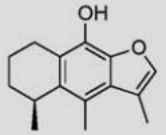
Natural Products



Eupomatenoid-5
Source: Piper regnellii
Biological Activity: Anti-fungal activity



Cnidioside A
Source: Leaves of Peucedanum japonicum Thunb
Biological Activity: Anti-oxidant activity



Cacalol
Source: Psacalium decompositum
Biological Activity: Anti-inflammatory activity

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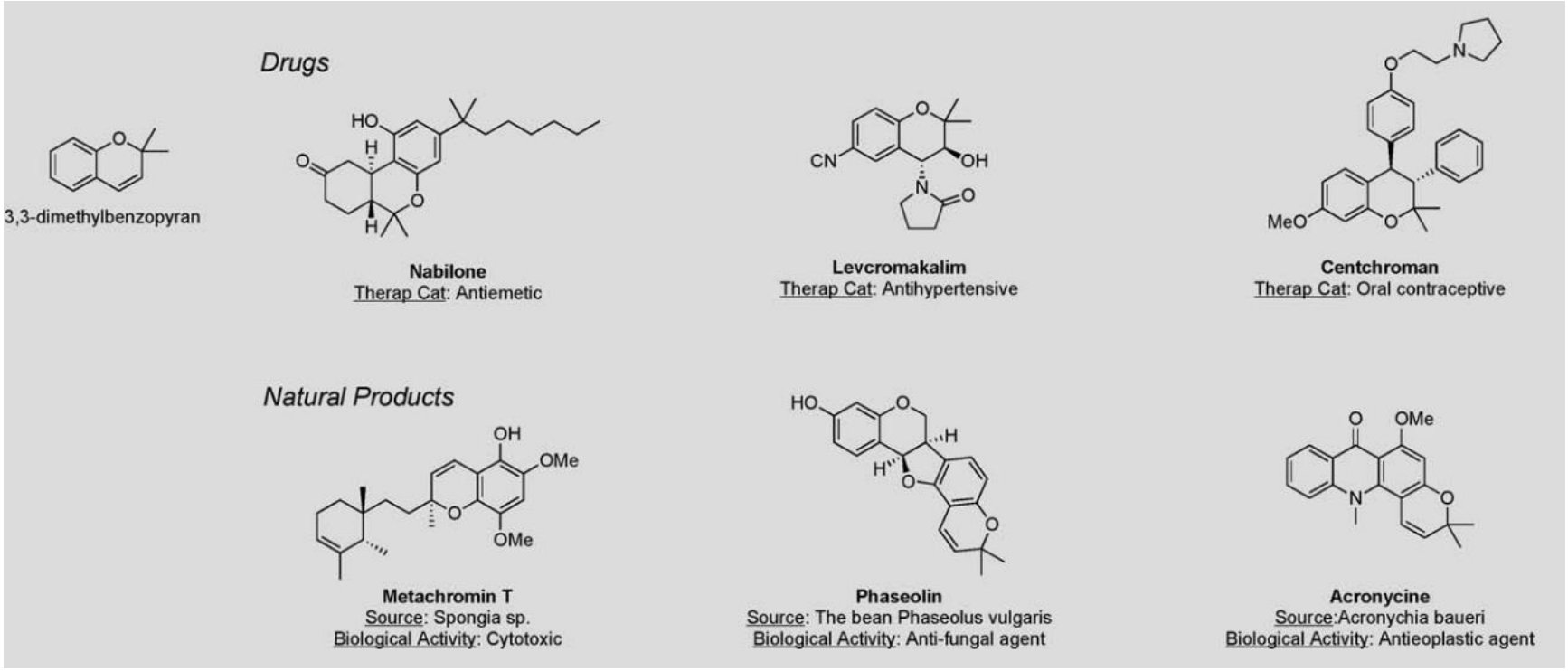

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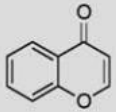
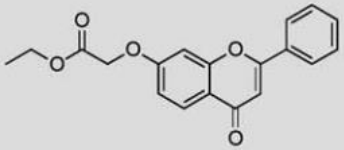
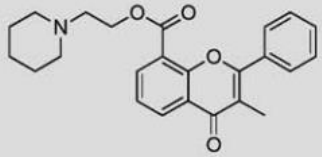


Chromone

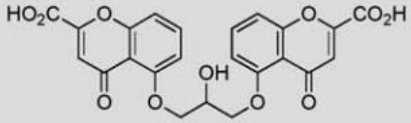
Drugs



Efloxate
Therap Cat: Vasodilator (coronary)

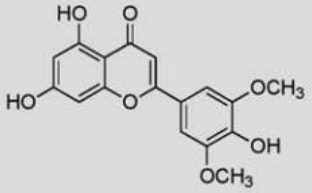


Flavoxate
Therap Cat: Antispasmodic

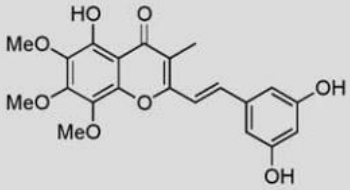


Cromolyn
Therap Cat: Antiasthmatic; antiallergic

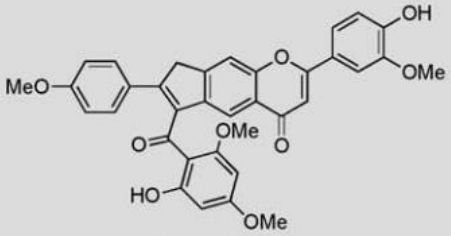
Natural Products



Tricin
Source: Wikstremia indica
Biological Activity: Anti-leukemic agent



Hormothamnione
Source: The marine cryptophye Crsophaeum talyori
Biological Activity: Anticancer agent



Cissampelflavone
Source: Cissampelos pareira
Biological Activity: Active against African trypanosomes

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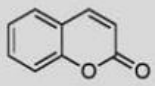
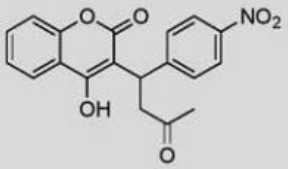
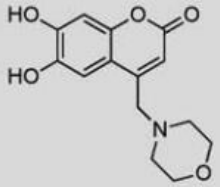
Drugs



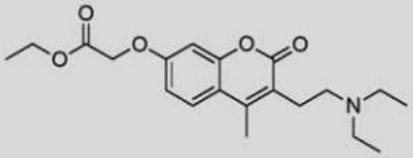
Coumarin



Acenocoumarol
Therap Cat: Anticoagulant

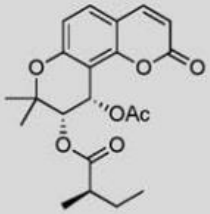


Folescutol
Therap Cat: Capillary protectant

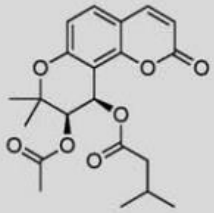


Chromonar
Therap Cat: Vasodilator (coronary)

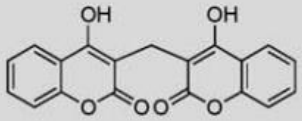
Natural Products



Visnadin
Source: Fruits of Ammi visnaga and Phlododicarpus
Biological Activity: Blocks calcium channels



Suksdorfin
Source: Lomatium suksdorfii
Biological Activity: Anti-HIV agent



Dicoumarol
Source: Isolated from spoiled hay
Biological Activity: Anticoagulant

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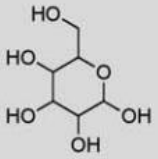
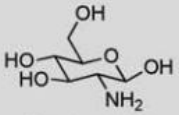
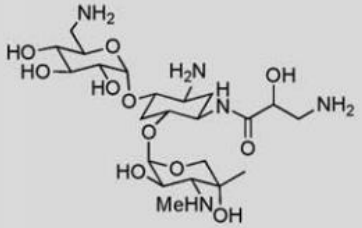
Drugs



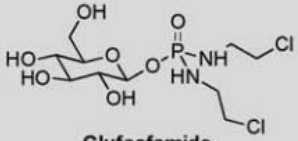
Carbohydrate



Glucosamine
Therap Cat: Antiarthritic

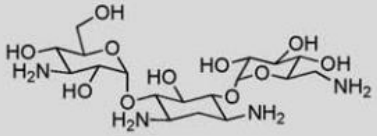


Isepamicin
Therap Cat: Antibacterial

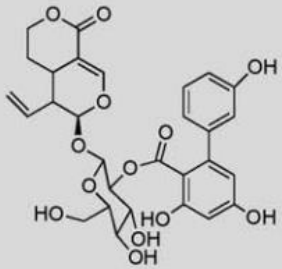


Glufosfamide
Therap Cat: Antieoplastic

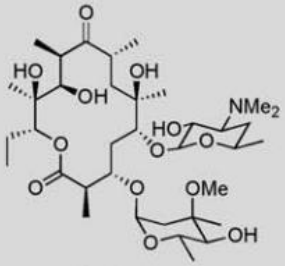
Natural Products



Kanamycin A
Source: Streptomyces Griseus
Biological Activity: Antibiotic



Amarogentin
Source: Upper parts of Sweria chirata (Loganiaceae)
Biological Activity: Leishmanicidal activity



Erythromycin
Source: Saccharopolyspora erythraea
Biological Activity: Antibiotic

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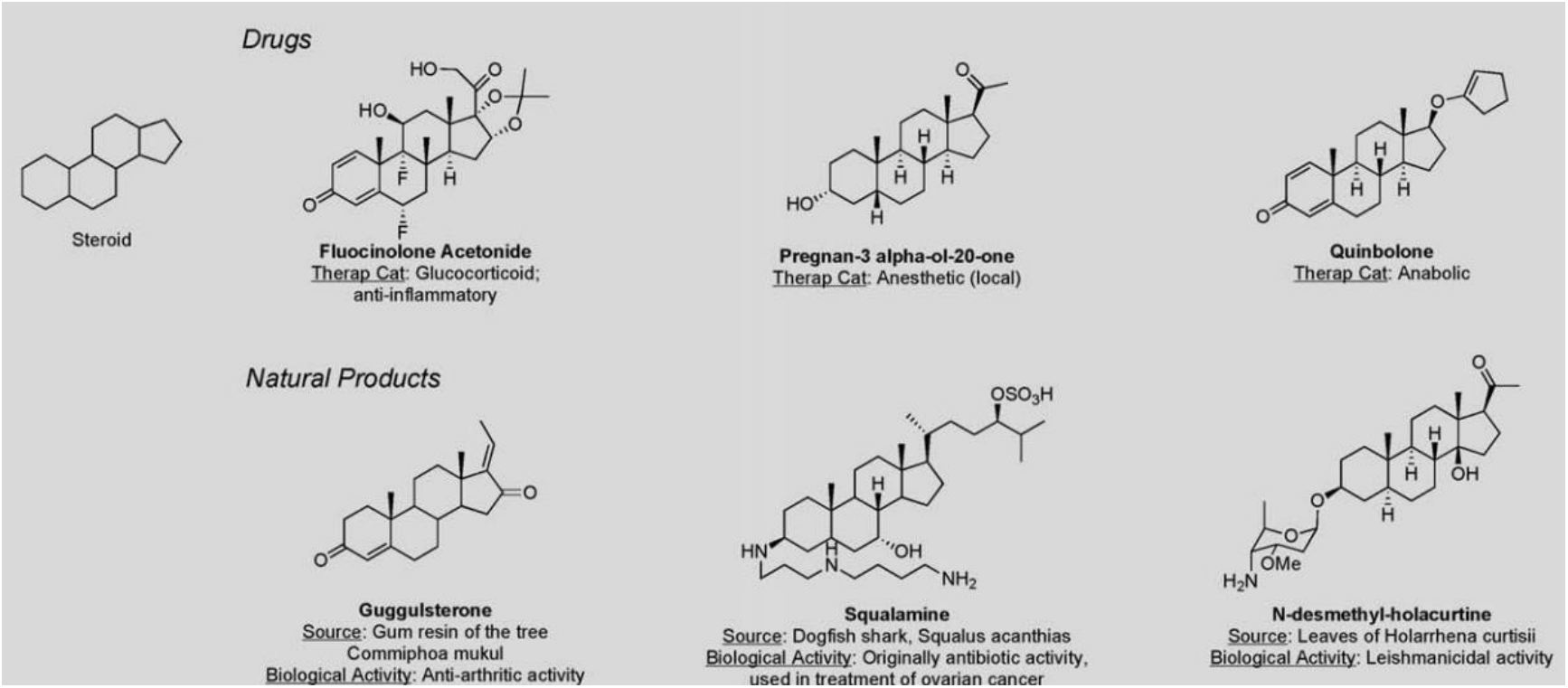

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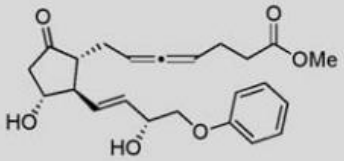
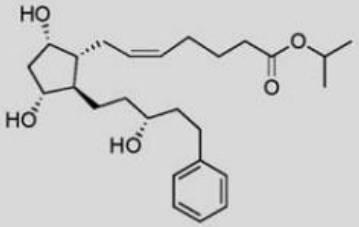
Drugs

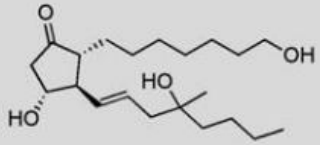
Prostanoic acid



Enprostil
Therap Cat: Antiulcerative, anti-secretory agent

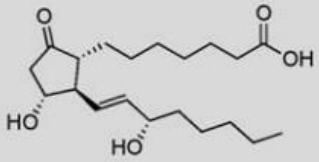


Latanoprost
Therap Cat: Antiglaucoma

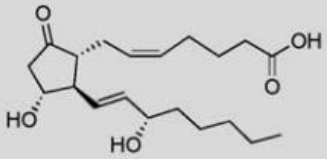


Rioprostil
Therap Cat: Antiulcerative

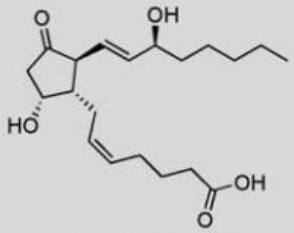
Natural Products



Prostaglandin E1
Source: Various mammalian sources
Biological Activity: Vasodilator (peripheral)



Prostaglandin E2
Source: Various mammalian sources
Biological Activity: Oxytocic; abortifacient



Prostaglandin D2
Source: Various mammalian sources
Biological Activity: Neuromodulator

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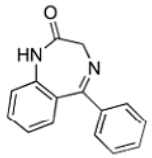
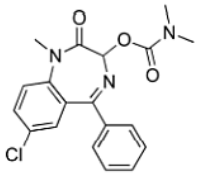
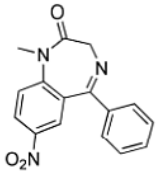
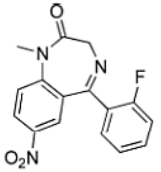
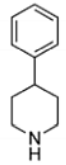
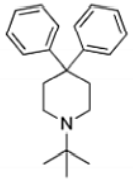
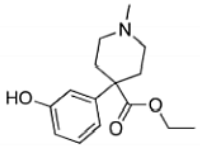
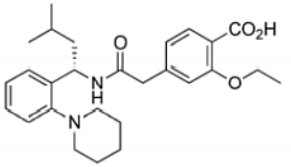
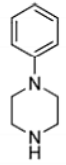
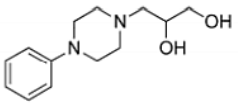
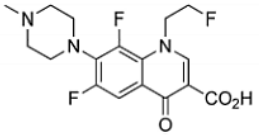
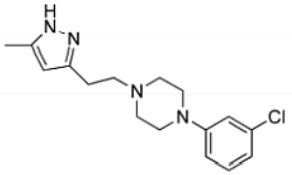
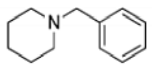
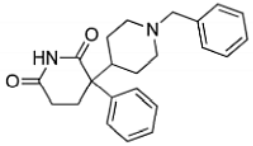
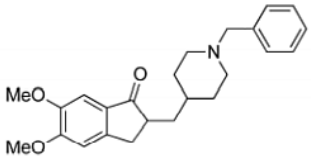
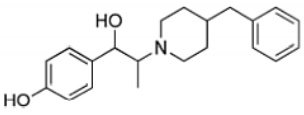
Examples of Privileged Scaffolds Found Primarily in Drugs

Privileged Scaffold	Structures		
 Benzodiazepine	 **Camazepam** Therap Cat: Anxiolytic	 **Nimetazepam** Therap Cat: Sedative, hypnotic	 **Flunitrazepam** Therap Cat: Hypnotic
 Arylpiperidine	 **Butdipine** Therap Cat: Antiparkinsonian	 **Hydroxypethidine** Therap Cat: Analgesic (narcotic)	 **Repaglinide** Therap Cat: Antidiabetic
 Arylpiperazine	 **Dropropizine** Therap Cat: Antitussive	 **Fleroxacin** Therap Cat: Antibacterial	 **Mepiprazole** Therap Cat: Tranquilizer
 Benzylpiperidine	 **Benzetimide** Therap Cat: Antiparkinsonian	 **Donepezil** Therap Cat: Nootropic	 **Ifenprodil** Therap Cat: Vasodilator (cerebral and peripheral)

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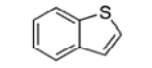
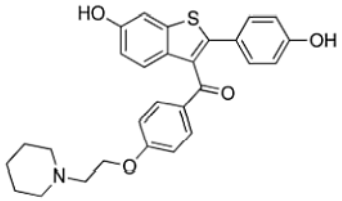
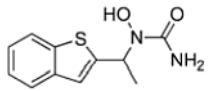
Examples of Privileged Scaffolds Found Primarily in Drugs



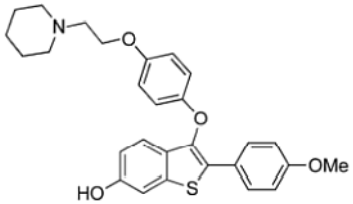
Benzothiophene



Raloxifene
Therap Cat: Antiosteoporotic

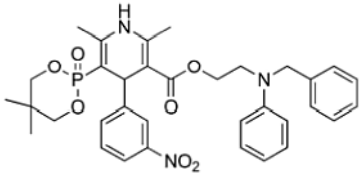


Zileuton
Therap Cat: Antiasthmatic

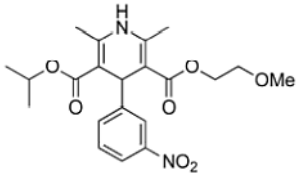


Arzoxifene
Therap Cat: Antineoplastic (hormonal)

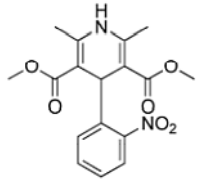
Dihydropyridines



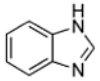
Efonidipine
Therap Cat: Antihypertensive



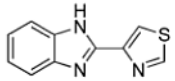
Nimodipine
Therap Cat: Vasodilator (cerebral)



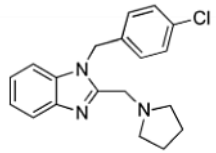
Nifedipine
Therap Cat: Antianginal; antihypertensive



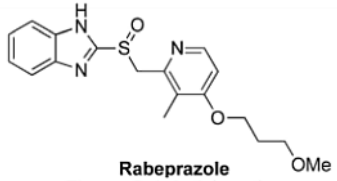
Benzimidazole



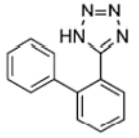
Thiabendazole
Therap Cat: Antihelmintic



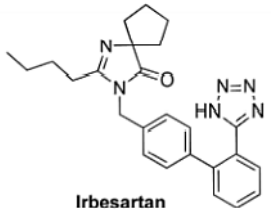
Clemizole
Therap Cat: Antihistaminic



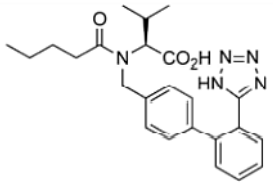
Rabeprazole
Therap Cat: Antiulcerative



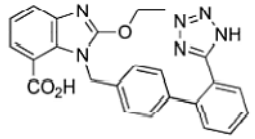
Biphenyltetrazole



Irbesartan
Therap Cat: Antihypertensive



Valsartan
Therap Cat: Antihypertensive



Candesartan
Therap Cat: Antihypertensive. In treatment of congestive heart failure.

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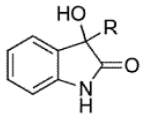
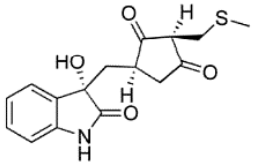
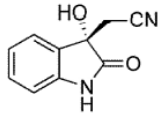
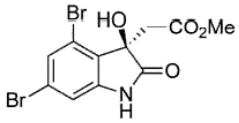
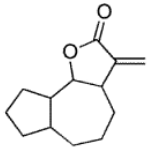
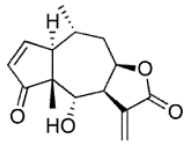
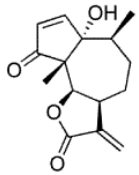
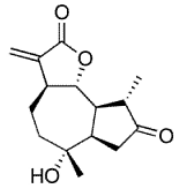
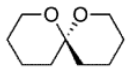
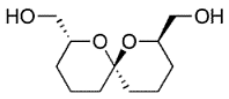
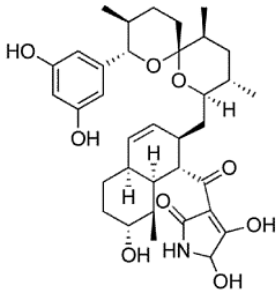
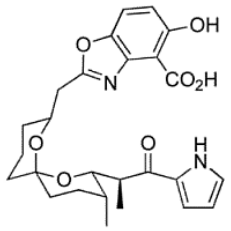
Examples of Privileged Scaffolds in Natural Products

Privileged Scaffold	Structures
 3-substituted-3-hydroxy-2 -oxindole	 **3-(*R*)-maremycin B** Source: Terrestrial Streptomyces Biological Activity: Cytotoxic
	 **(*R*)-(+)-3-cyanomethyl-3-hydroxindole** Source: Rheum maximowiczii Biological Activity: Activation/inhibition of specific cytokines.
	 **(*R*)-convolutamydine A** Source: Amathia Convoluta (maine bryozoan) Biological Activity: Inhibits diffentiation promyelocytic leukimia cells HL-60.
 5-7-5 lactone ring system	 **Helenalin** Source: Arnica montana and Arnica chamissonis Biological Activity: anti-inflammatory, inhibits the activation of the transcription factor NF-kB
	 **Parthenin** Source: Arnica montana Biological Activity: anti-Leishmanial and Trypanosomal activity
	 **Chinensiolide B** Source: Ixeris chinensis Nakai
 6,6-spiroacetal	 **Spiket-P** Source: Spongistatins Biological Activity: Antimitotic
	 **Integramycin** Source: Actinoplanes Biological Activity: HIV-1 integrase inhibitor
	 **Routiennocin** Source: Streptomyces routienni Biological Activity: In vitro activity against gram positive and anaerobic bacteria

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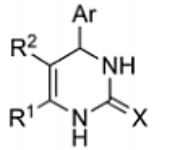
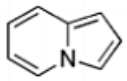
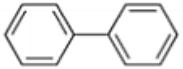
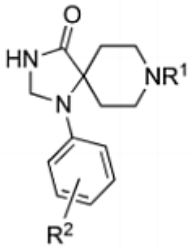
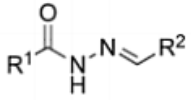
Other examples

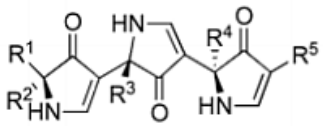

Dihydropyrimidone
[X = S or O]

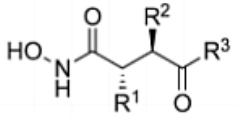

Indolizine

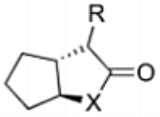

Biphenyl

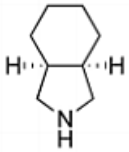

Triazaspirodecanone

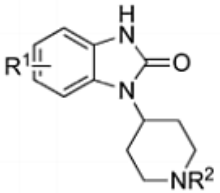

N-Acylhydrazone

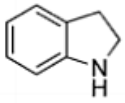

Pyrrolinone

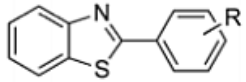

Hydroxyamate

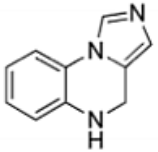

trans-Lactam/Lactone
[X = N or O]

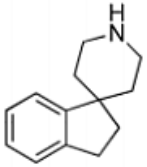

Hexahydroisoindole

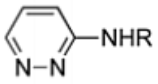

Benzimidazolone

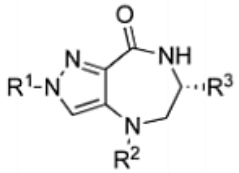

Indoline

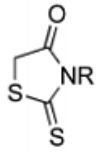

2-Arylbenzothiazole

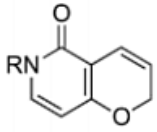

Imidazolequinoxaline

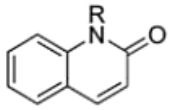

Spiroindanylpiperidine


Aminopyridazine


1,4-Pyrazolodiazepin-8-one

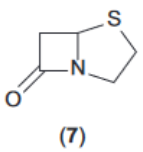

Rhodanine


Pyranopyridone

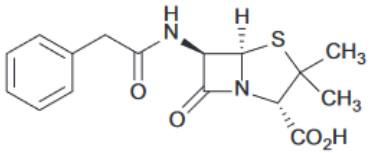

Pyranoquinolone

B. R. Stockwell *et al. Curr. Opin. Chem. Biol.* **2010**, *14(3)*, 347–361

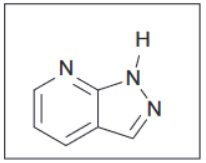
Other examples



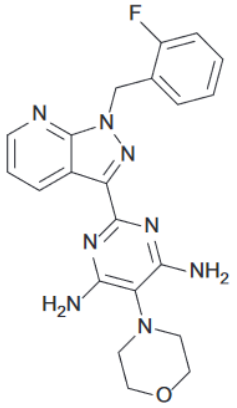
(**7**)



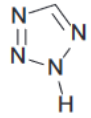
penicillin-G (**8**)



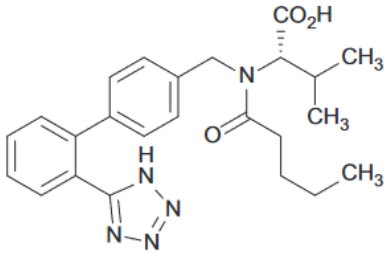
1*H*-pyrazolo[3,4-*d*]pyridine (**36**)



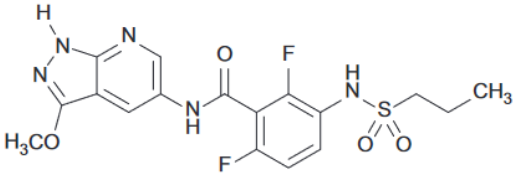
BAY 418543 (**37**)



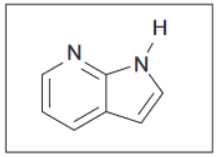
tetrazole (**24**)



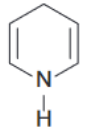
valsartan (**25**)



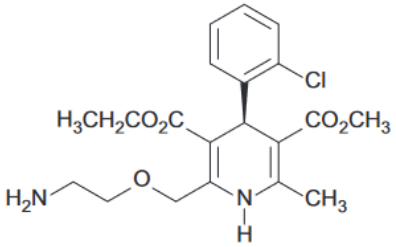
38



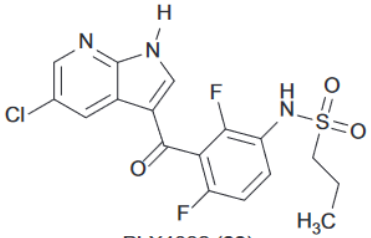
pyrrolo-pyridine (**40**)



1,4-dihydropyridine (**26**)



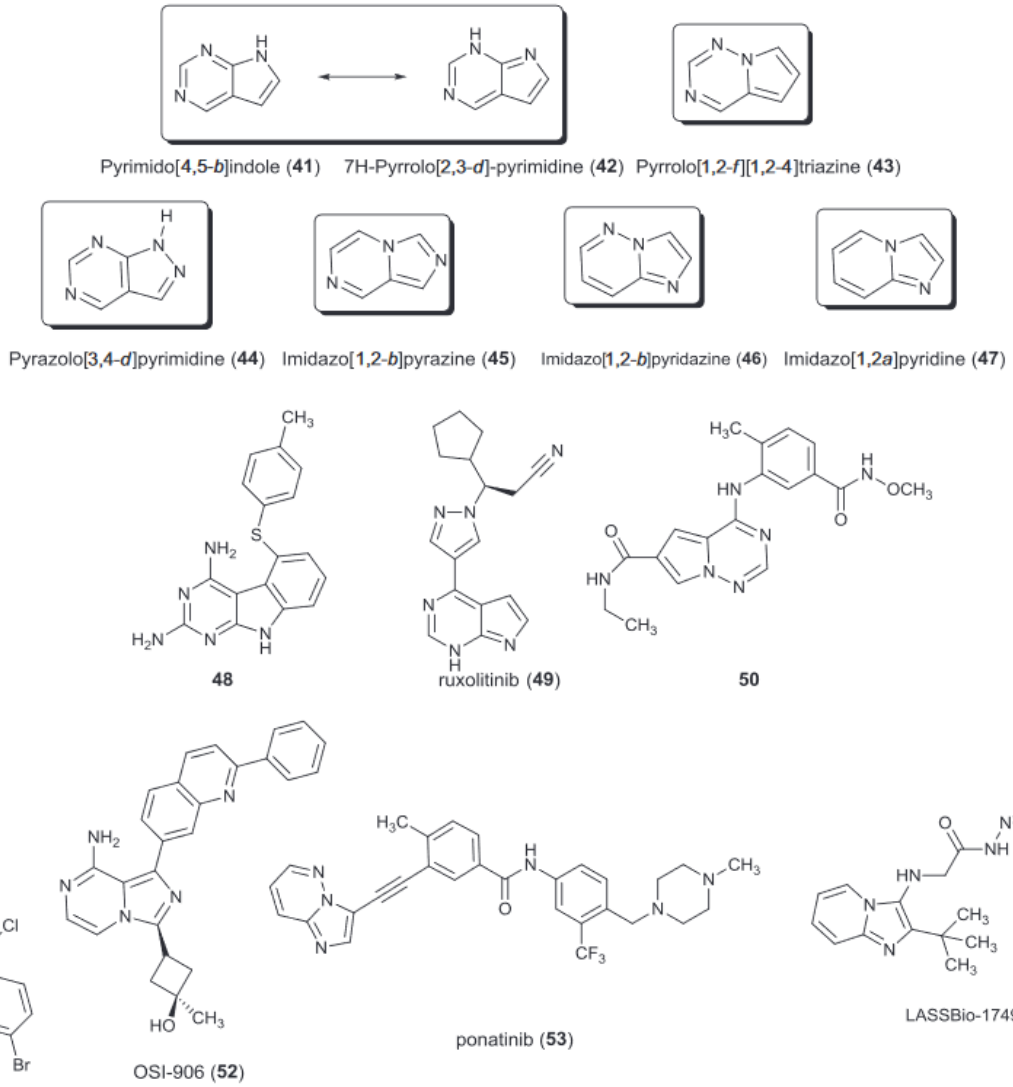
amlodipine (**27**)



PLX4032 (**39**)

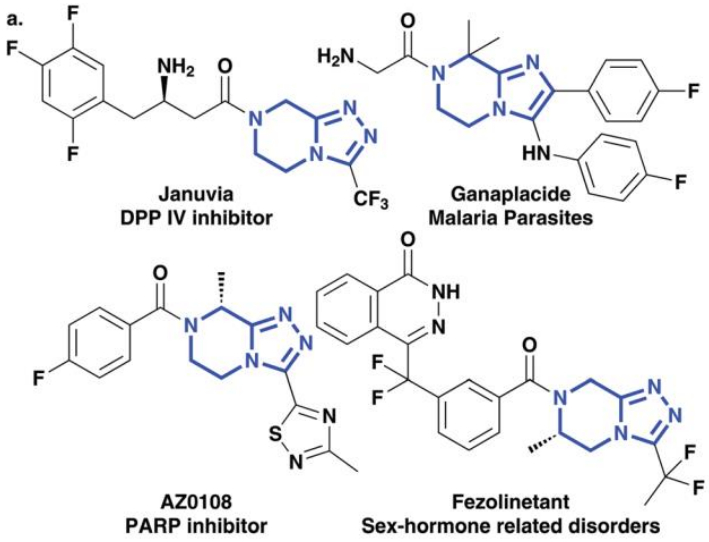
E. J. Barreiro, Chapter 1:Privileged Scaffolds in Medicinal Chemistry: An Introduction , in Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation, 2015, pp. 1-15 DOI: 10.1039/9781782622246-00001

Other examples



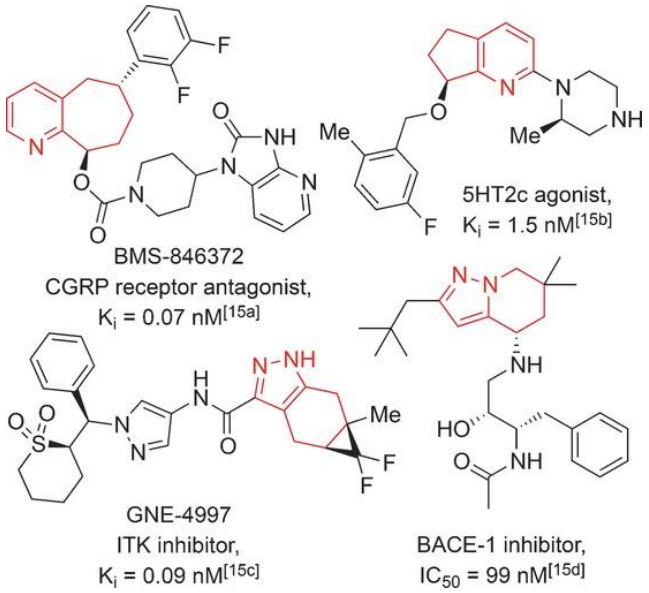
E. J. Barreiro, Chapter 1:Privileged Scaffolds in Medicinal Chemistry: An Introduction , in Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation, 2015, pp. 1-15 DOI: 10.1039/9781782622246-00001

Partially saturated privileged scaffolds

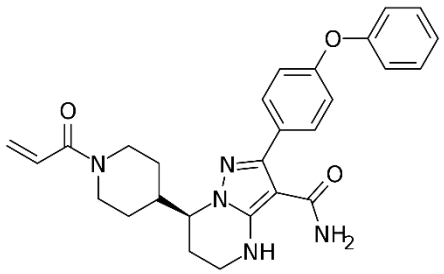


piperazine-based

D. R. Spring et al *Chem. Commun.*, **2020**, *56*, 6818-6821



D. R. Spring et al *ACIE* **2016**, *55*, 12479 –12483

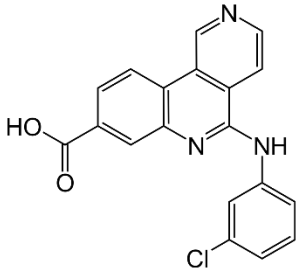


Zanubrutinib
Bruton's tyrosine
kinase (BTK) inhibitor

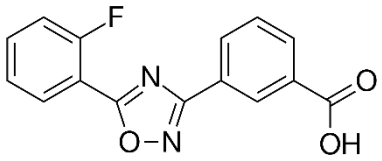
Y. Y. Syed et al *Drugs* **2020**, *80*, 91–97

COOH has been considered problematic for cell-based activity;

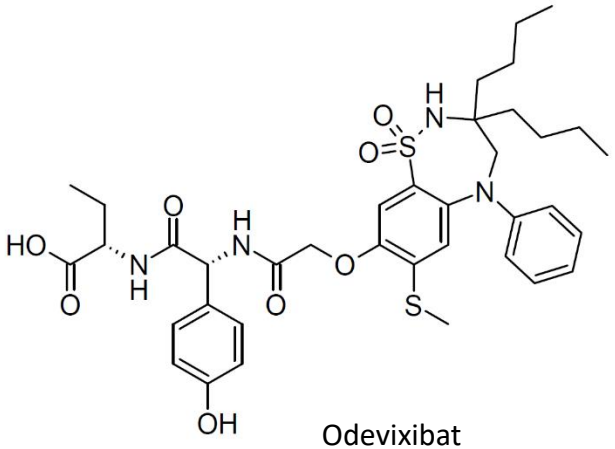
but it is not always the case



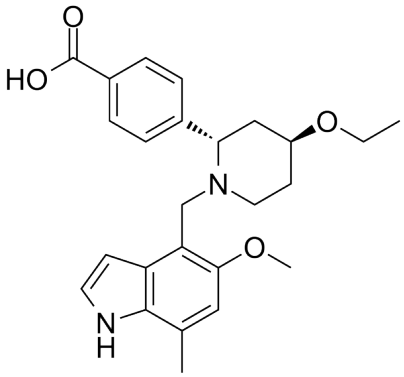
Silmitasertib
inhibitor of protein kinase CK2



Ataluren
treatment of Duchenne muscular dystrophy.



Odevixibat
reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT)



Iptacopan
factor B inhibitor