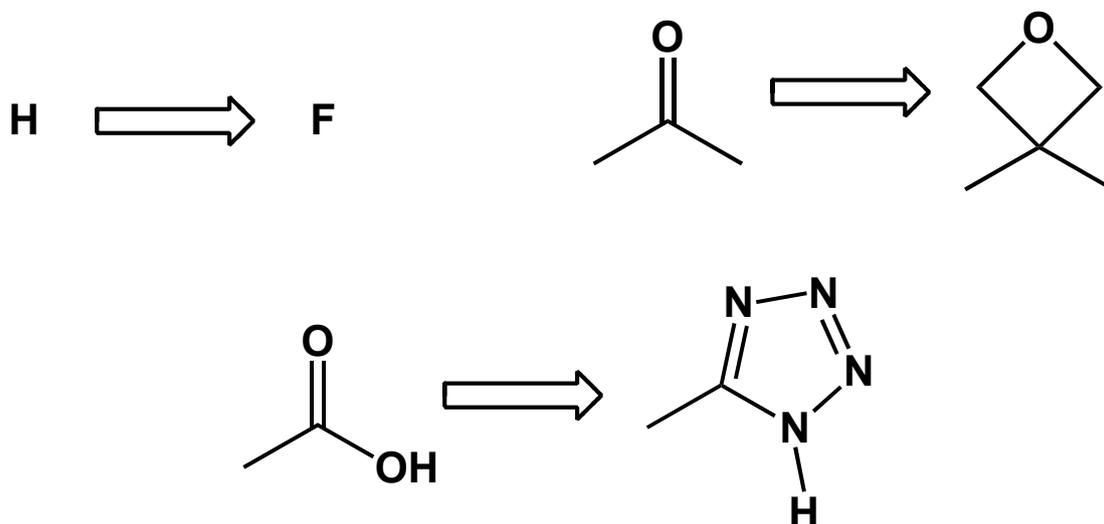


Application of Bioisosteres in Drug Design



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4. Summary

1. Introduction

What are bioisosteres?

Isostere

- The isostere concept was formulated by Irving Langmuir in 1919.



Irving Langmuir

Isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons.

J. Am. Chem. Soc. 1919, 41, 1543

The octet theory of valence indicates that if compounds having the same number of atoms have also the same total number of electrons, the electrons may arrange themselves in the same manner. In this case the compounds or groups of atoms are said to be **isosteric**.

Such compounds should show remarkable similarity in physical properties, that is, in those properties which do not involve a separation of the atoms in the molecule.

Table 1. Groups of Isosteres as Identified by Langmuir

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 ₂ O, N ₃ ⁻ , CNO ⁻
↓	↓
20	MnO ₄ ⁻ , CrO ₄ ²⁻
21	SeO ₄ ²⁻ , AsO ₄ ³⁻

- A further extension to this concept of isosteres came about in 1925 with Grimm's Hydride Displacement Law.

"Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right."

Table 2. Grimm's Hydride Displacement Law

C	N	O	F	Ne	Na
	CH	NH	OH	FH	-
		CH ₂	NH ₂	OH ₂	FH ₂ ⁺
			CH ₃	NH ₃	OH ₃ ⁺
				CH ₄	NH ₄ ⁺

- Erlenmeyer further broadened Grimm's classification in 1932.

Isosteres were redefined as atoms, ions, and molecules in which the peripheral layer of electrons can be considered identical.

Table 3. Isosteres Based on the Number of Peripheral Electrons

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

Bioisostere

The emergence of the concept of bioisosteres as structurally distinct compounds recognized similarly by biological systems has its origins in a series of studies published by Erlenmeyer in the 1930s.

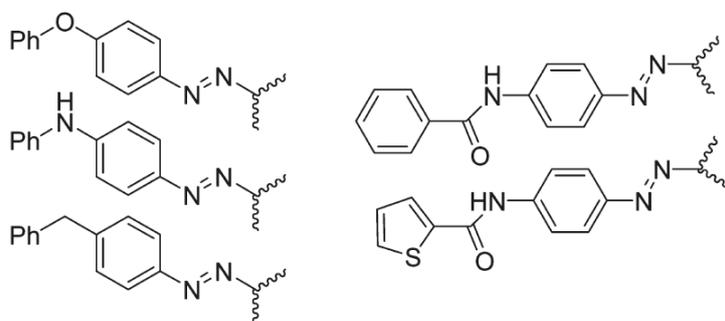
The term "**bioisostere**" was introduced by Harris Friedman in 1950 who defined it as compounds eliciting a similar biological effect.

More recently this definition of bioisosteres has been broadened by Burger as

"Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties."

Prog. Drug Res. 1991, 37, 287

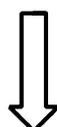
Erlenmeyer showed that antibodies were unable to discriminate between phenyl and thienyl rings or O, NH, and CH₂ in the context of artificial antigens.



the changes induced by the application of bioisosteres

The design of bioisosteres introduces structural changes that can be beneficial or deleterious depending on the context.

**size, shape, electronic distribution, polarizability
dipole, polarity, lipophilicity, pK_a**



In the contemporary practice of medicinal chemistry

The development and application of bioisosteres have been adopted as a fundamental tactical approach useful to address a number of aspects associated with the design and development of drug candidates.

**improving potency, enhancing selectivity, altering physical properties
reducing or redirecting metabolism, eliminating or modifying toxicophores
acquiring novel intellectual property**

Classical and Nonclassical Bioisosteres

classical bioisostere

Chem. Rev. 1996, 96, 3147

Classical bioisosteres represent the results of an early appreciation of the concept and encompass structurally simple atoms or groups.

1) monovalent atoms or groups

D and H
F and H
NH₂ and OH
RSH and ROH
F, OH, NH₂ and CH₃
Cl, Br, SH and OH

2) divalent atoms or groups

C=C, C=N, C=O, C=S
-CH₂-, -NH-, -O-, -S-

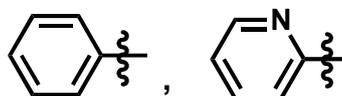
3) trivalent atoms or groups

-CH=, -N=

4) tetrasubstituted atoms

R₄C, R₄Si, R₄N⁺

5) ring equivalent



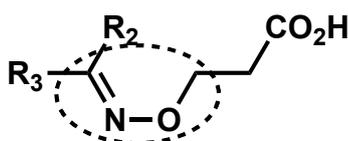
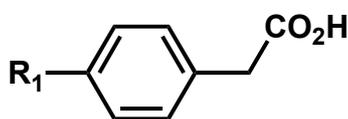
nonclassical bioisostere

Nonclassical bioisosteres are structurally distinct, usually comprise different number of atoms and exhibit different steric and electronic properties.

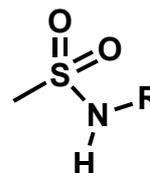
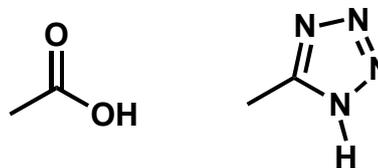
Nonclassical bioisosteres have been divided into two subgroups.

1) cyclic and noncyclic isosteres

2) exchangeable group isosterism in which the properties of discrete functional elements are emulated



MAOMM
(methyleneaminoxy)-methyl moiety



Carboxylic Acid Isosteres

Drug-like Concepts

The application of guidelines linked to the concept of drug-likeness, such as the "rule of five", has gained wide acceptance as an approach to reduce attrition in drug discovery and development.

Lipinski's Rule of Five

Adv. Drug. Del. Rev. 1997, 23, 3

Lipinski's rule states that, poor absorption or permeability is more likely when...

- the molecular weight is greater than **500** daltons
- the clogP (the calculated 1-octanol-water partition coefficient) is greater than **5**
- the number of hydrogen-bond donors (OH, NH) is more than **5**
- the number of hydrogen-bond acceptors (O, N) is more than **10**

Lipophilicity in Drug Discovery

Expert Opin. Drug Discov. 2010, 5, 235

The role of **lipophilicity** in determining the overall quality of candidate drug molecules is of paramount importance. Recent developments suggest that, as well as determining pre-clinical ADMET (absorption, distribution, metabolism, excretion and toxicology) properties, compounds of optimal **lipophilicity** might have increased chances of success in development.

Solubility

- $\log P > 3$ → only 1% were soluble (having kinetic solubility > 250 µg/mL)
- $\log P < 3$ → 50% were soluble

Permeability

- $\log P > 1.7$ for MW 350 - 400
 - $\log P > 3.1$ for MW 400 - 450
 - $\log P > 3.4$ for MW 450 - 500
 - $\log P > 4.5$ for MW > 500
- } to achieve high permeability

Clearance and Metabolism

With respect to metabolic stability, $\log D < 3$ is desirable.

On the other hand, reducing $\log D$ leads to increasing renal clearance.

50% of the compounds that showed net renal **secretion** had calculated $\log D < 0$

50% of the compounds that showed net renal **reabsorption** had calculated $\log D > 1.2$

Bioavailability

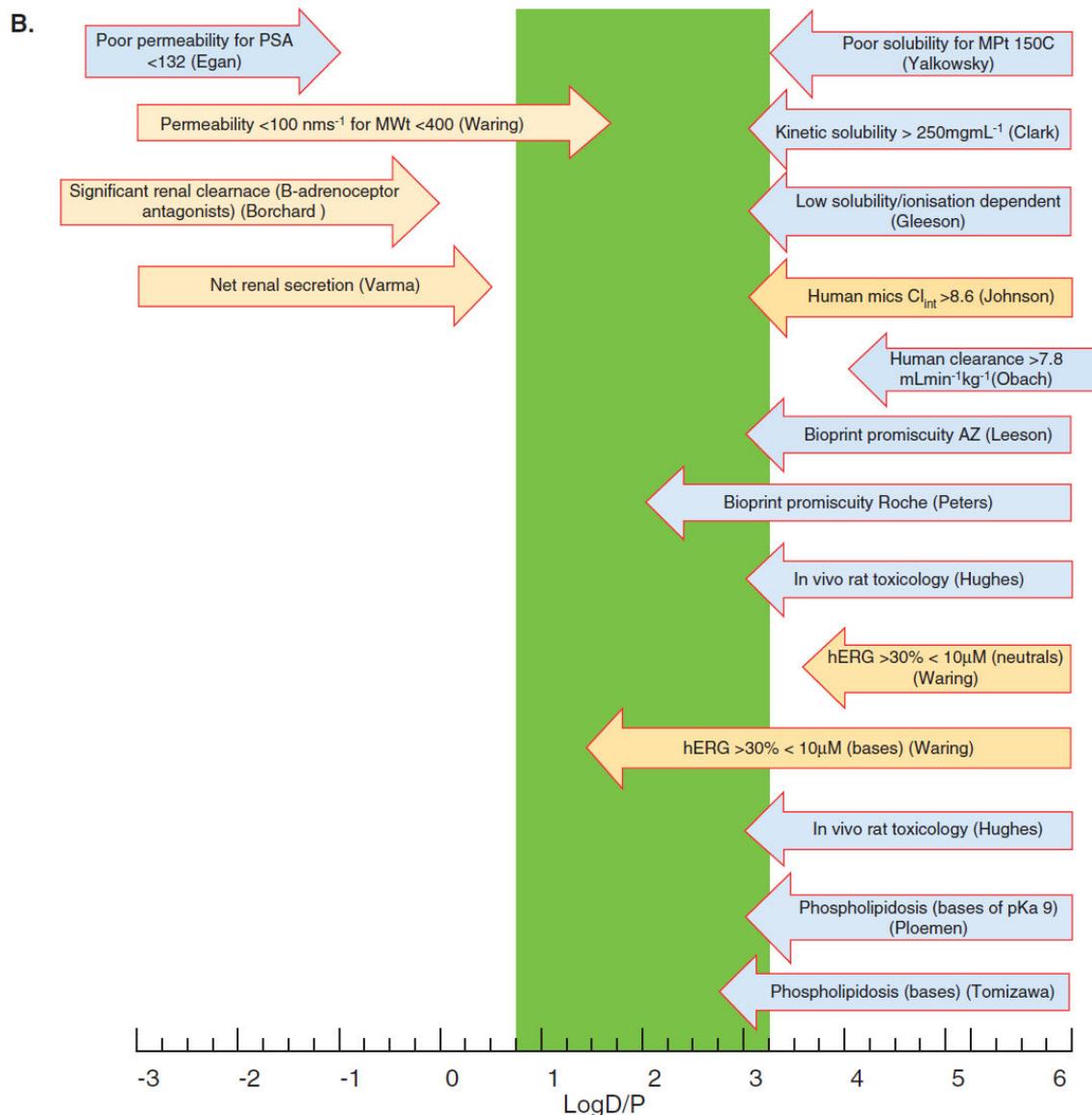
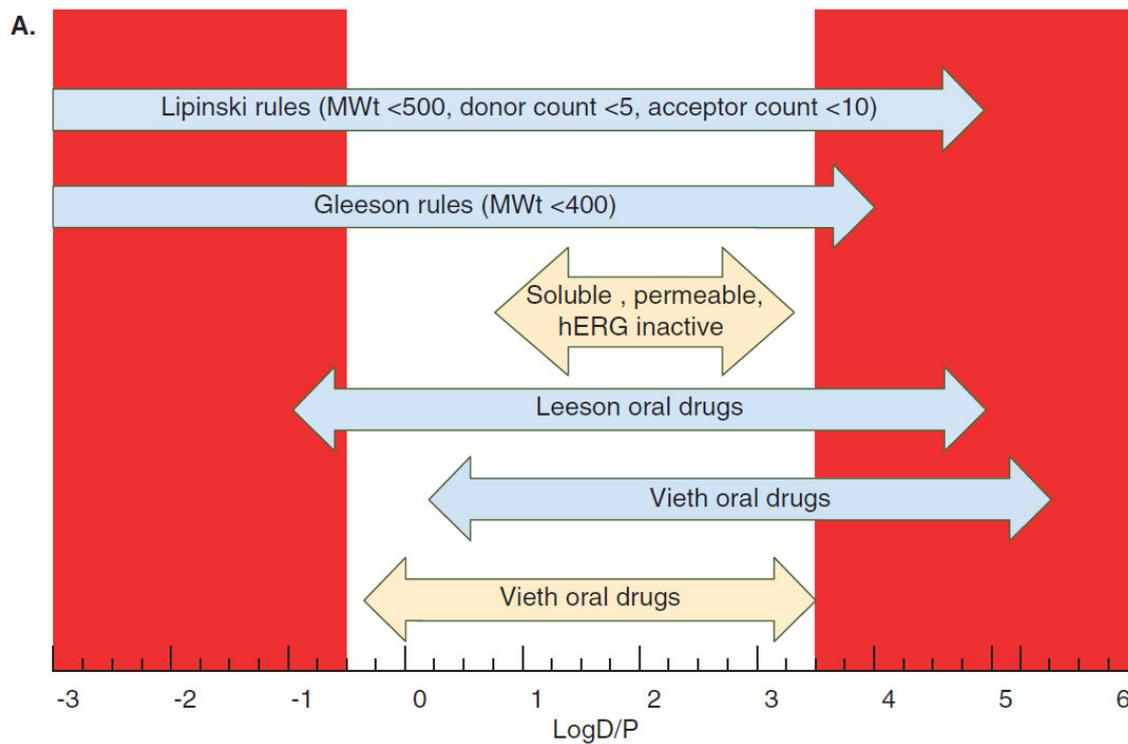
Bioavailability can be considered to be a composite of the effect of solubility, permeability and metabolic stability.

It has been suggested that the optimal range is $0 < \log P < 3$, $1 < \log D < 3$

Toxicity

In principle, more lipophilic compounds might be expected to be more promiscuous, that is, lack of selectivity. So **more lipophilic compounds are likely to be more toxic**.

- **hERG** potencies diminish significantly as $\log D$ increases
- the risk of a compound causing **phospholipidosis** increases if $\log P^2 + pK_a^2$ is > 90
→ for a base with a pK_a of 9, $\log P < 3$ is desirable.
- the average **CYP inhibition** are significantly lower for compounds with $\log P < 3$



(A) shows the regions of lipophilicity where good overall compounds are distributed
(B) shows where properties are compromised for logD(orange) and logP(light blue)

2. Application of Isosteres in Drug Design

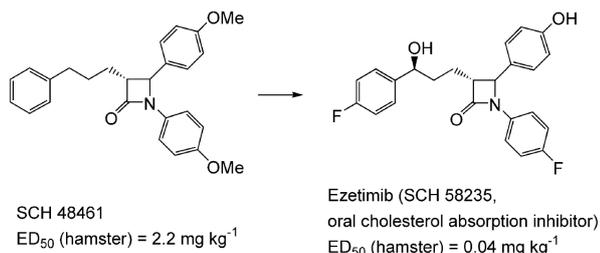
Fluorine as an Isostere of Hydrogen

The unique properties of fluorine have led to its widespread application in drug design as an isostere for hydrogen, since incorporation of fluorine can productively modulate a range of properties of interest to medicinal chemists.

ChemBioChem 2004, 5, 637

Metabolic stability

block the metabolically labile site with a fluorine substituent, hoping that the small fluorine atom will not impair the binding to the target protein



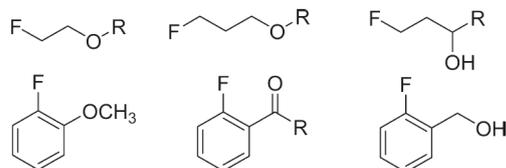
The effect on the pK_a

As the most electronegative atom, fluorine has a very strong effect on the acidity or basicity of nearby functional groups.

amine	pK _a	acid	pK _a
CH ₃ CH ₂ NH ₃ ⁺	10.7	CH ₃ CO ₂ H	4.76
CH ₂ FCH ₂ NH ₃ ⁺	9.0	CH ₂ FCO ₂ H	2.66
CHF ₂ CH ₂ NH ₃ ⁺	7.3	CHF ₂ CO ₂ H	1.24
CF ₃ CH ₂ NH ₃ ⁺	5.7	CF ₃ CO ₂ H	0.23

The effect on molecular lipophilicity

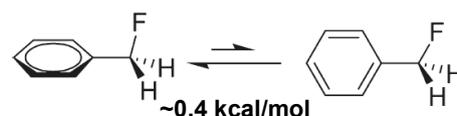
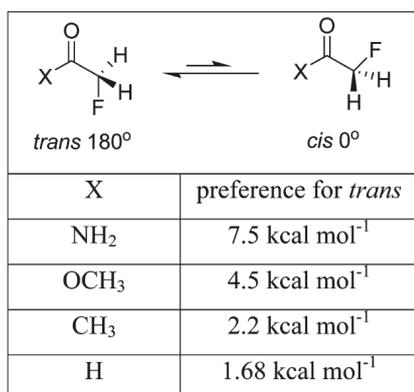
A survey of 293 pairs of molecules that differed only by a F-for-H exchange revealed that the average lipophilicity(logD) increased by 0.25 log units. But there are quite a number of cases (shown below) for which an H to F substitution decreases lipophilicity.



A close inspection of these cases revealed that all compounds were found to have at least one low-energy conformer with an O...F distance smaller than 3.1 Å.

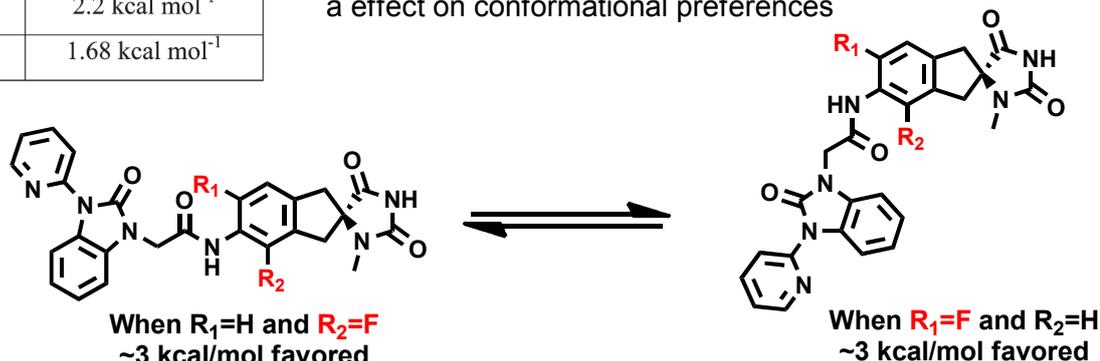
The effect on molecular conformation

α-fluorinated carbonyl derivatives favor a conformation in which the C-F and C=O bonds adopt a trans orientation to align the dipoles in an antiperiplanar.



The modestly preferred (~0.4 kcal/mol) conformation of benzyl fluoride projects the C-F bond orthogonal to the aryl ring, stabilized by donation of electron density from the aryl π-orbital into the σ*_{C-F} antibonding orbital.

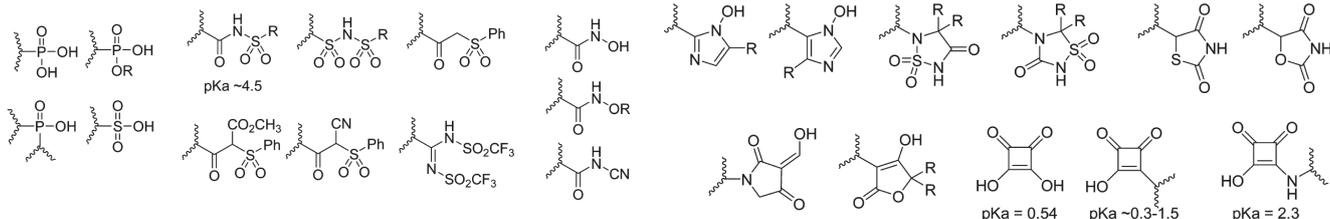
The electrostatic interaction between F(δ⁻) and NH(δ⁺) has a effect on conformational preferences



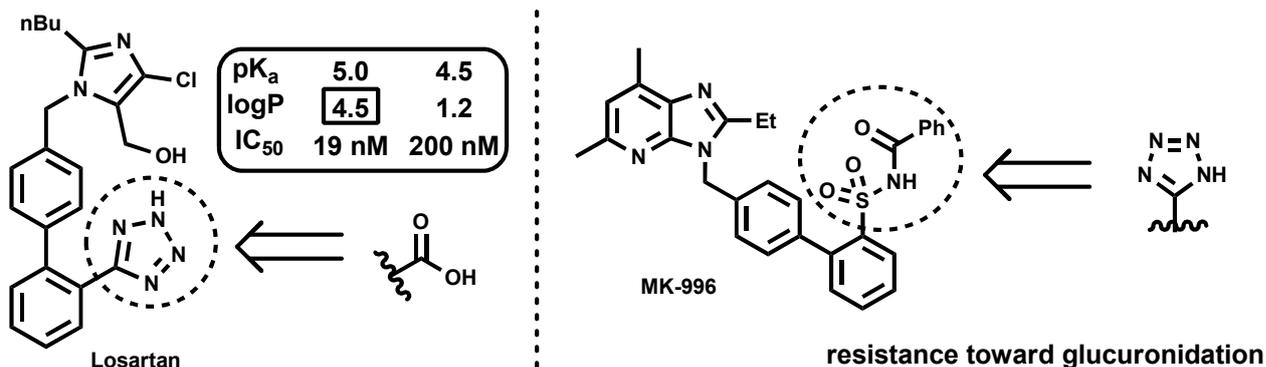
Carboxylic Acid Isosteres

Isosteres of carboxylic acid have been studied extensively. These studies have typically focused on...

- enhancing potency
- reducing polarity
- increasing lipophilicity (improve membrane permeability)
- enhancing pharmacokinetic properties
- reducing the potential for toxicity

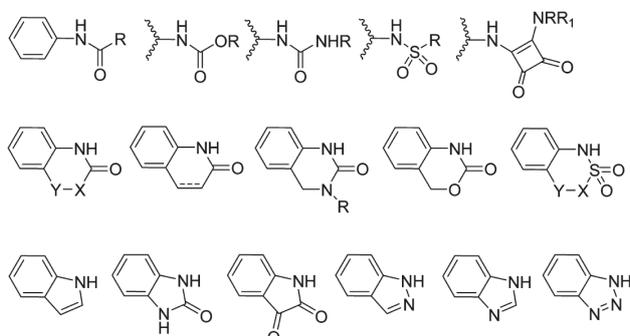


application (Angiotensin II receptor antagonists)



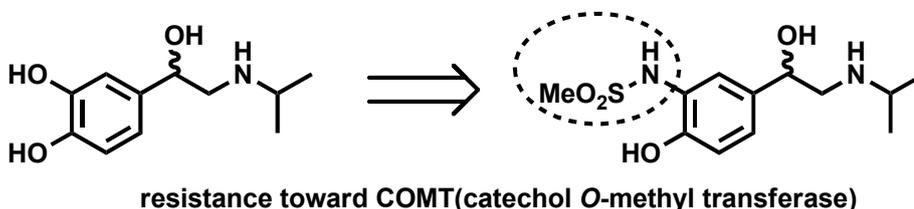
Phenol Isosteres

Phenol and catechol isosteres were typically designed to overcome pharmacokinetic and toxicological limitations.



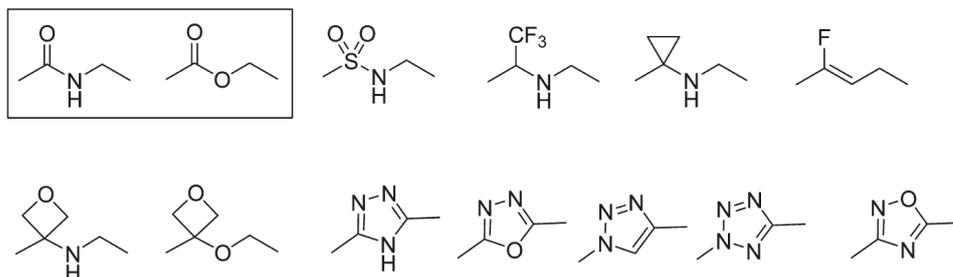
A range of useful surrogates are well-established. The structural diversity, electronic properties, lipophilicity, and size of these functionalities varies widely, providing ample flexibility to customize for a special application.

application (Non-selective β -adrenoceptor agonists)



Amide and Ester Isosteres

Amide isosteres have typically been of interest as a means of modulating polarity and bioavailability, while ester isosteres have frequently been developed to address metabolism issues since esters can be rapidly cleaved in vivo.

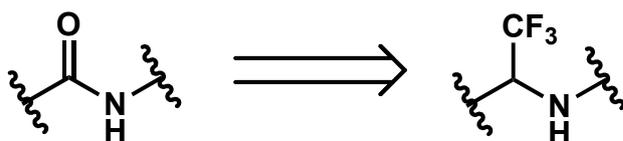


trifluoroethylamines as amide isosteres:

Amide isosteres have been focused on in the context of peptidomimetics.

Many amide replacements are known which retain the **geometry** of the amide bond or maintain the **hydrogen bond-accepting properties** of the amide. However, there are few functional groups, which are capable of preserving the **hydrogen bond-donating properties** of the amide.

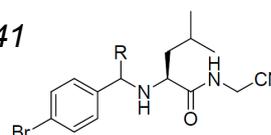
In this situation, trifluoroethylamines were identified as amide isosteres.



- reducing the basicity of the amine without compromising the ability of the NH to function as a H-bond donor
- $\text{CF}_3\text{CH}(\text{R})\text{NHR}'$ bond is close to the 120° observed with an amide
- C-CF₃ bond is as polar as C=O bond

application (inhibitors of cathepsin K)

Bioorg. Med. Chem. 2005, 15, 4741



The replacement of an amide with a trifluoroethylamine leads to high potency, high selectivity and metabolic stability.

The role of the CF₃ group was explored in a brief SAR study. (right Table)
And compound **6** has been modeled into a Cat K crystal structure.

Compound	IC ₅₀ (nM)			
	R	Cat K ^a	R _f ^b	pK _a ^c
6	CF ₃	0.9	0.40	1.3
15	H	802	0.05	6.7
16	CH ₃	988	0.03	6.7
17	CF ₂ CF ₃	2.4	0.42	1.8
18	4-MeSO ₂ Ph	2.5	0.38	4.6
19	CN	30	0.67	0.7

^a Humanized rabbit enzyme.

^b TLC on SiO₂ plates with 40% EtOAc/1% HOAc/hexanes.

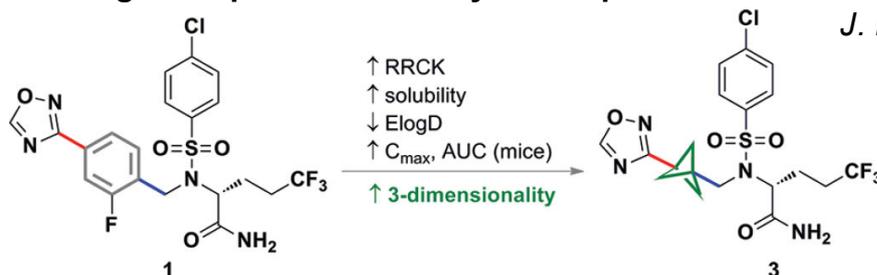
^c Calculated using ACD/pK_a.

- Low basicity allows the excellent H-bond to Gly66.
- The CF₃ group attached to an sp³ carbon orients itself perpendicular to the aromatic ring and stabilizes the aromatic ring in its bioactive conformation.
- The sp³ hybridized nitrogen allows the simultaneous formation of an optimal H-bond.

Phenyl Ring Isosteres

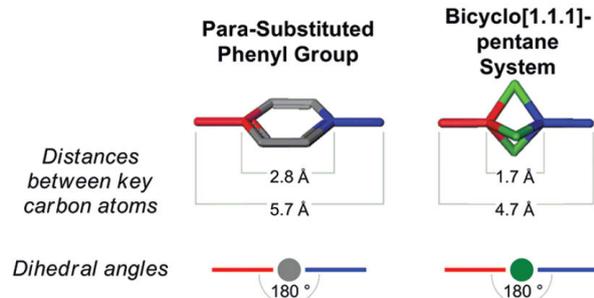
Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ -secretase inhibitor

J. Med. Chem. 2012, 55, 3414



The rationale for the use of the disubstituted bicyclo[1.1.1]pentane motif as a bioisostere for the central fluorophenyl ring derived from generic spatial features.

- comparable dihedral angles
- similar distances between substituents



	1	3
IC ₅₀ (A β ₄₂ , nM) ^{a,b}	0.225 (52)	0.178 (4)
Notch selectivity ^b	350 (14)	178 (4)
human hepatocytes CL _{int,app} (μ L/min/million cells) ^c	15.0	<3.80
HLM CL _{int,app} (mL/min/kg) ^{b,d}	<16.2 (4)	<8.17 (2)
RRCK P _{app} (A to B) (10 ⁻⁶ cm/s) ^e	5.52	19.3
ElogD ^f	4.70	3.80
kinetic solubility (pH = 6.5, μ M)	0.60	216
thermodynamic solubility (pH = 6.5, μ M)	1.70	19.7
thermodynamic solubility (pH = 7.4, μ M)	0.90	29.4
MDR1/MDCK BA/AB ratio ^g	1.72	1.66

^aIC₅₀ values were obtained in a whole cell assay using hu APP_{wt} cells by measuring A β ₁₋₄₂ as previously described.²⁶ ^bNumber of repetitions indicated in parentheses. ^cCL_{int,app} refers to total apparent intrinsic clearance obtained from scaling in vitro half-lives in human hepatocytes.¹⁵ ^dCL_{int,app} refers to total intrinsic clearance obtained from scaling in vitro half-lives in human liver microsomes.¹⁵ ^eRRCK cells with low transporter activity were isolated from Madine-Darby canine kidney cells and were used to estimate intrinsic absorptive permeability.¹⁴ ^fElogD was measured at pH 7.4.¹⁶ ^gMDR1/MDCK assay utilized MDCK cells transfected with the gene that encodes human p-glycoprotein.¹⁴

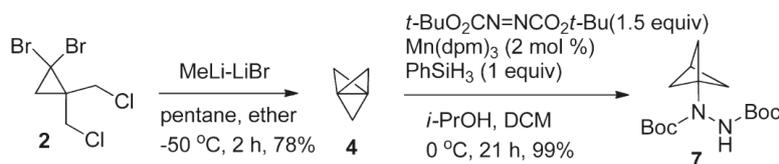
SAR studies into other fluorophenyl replacements indicate the intrinsic advantage of the bicyclo[1.1.1]pentane moiety over conventional phenyl ring isosteres with respect to achieving an optimal balance of properties.

For further application of bicyclo[1.1.1]pentane skeleton to drug discovery

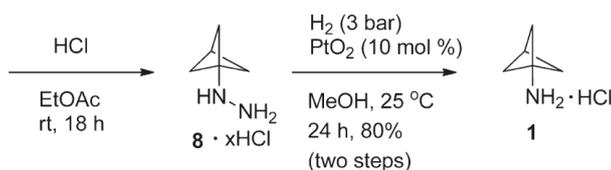
Scalable synthesis of 1-bicyclo[1.1.1]pentylamine was developed.

The key reaction is hydrohydrazination reaction.

Org. Lett. 2011, 13, 4746

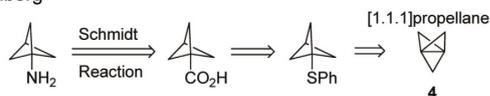


- successfully scaled to 20 g
- overall yield improved to 62%
- a 50-fold reduction in cost

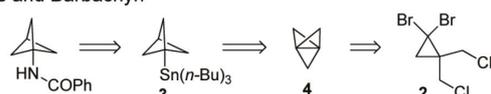


Mn-catalyzed hydrohydrazination:
J. Am. Chem. Soc. 2006, 128, 11693

Wiberg^{3d,f}



Toops and Barbachyn^{5b}



The previous syntheses

- low yield
- complications for scale-up (toxic, explosive...)
- using reversed phase chromatography

3. Oxetanes in Drug Discovery

Oxetanes have recently gained attention as attractive, stable, and less lipophilic molecular for drug discovery.



Physicochemical Properties of Oxetanes

What makes the oxetane a potentially attractive structural motif for drug discovery?

High polarity and outstanding ability to function as **an acceptor of hydrogen bonds**.
Metabolic and chemical **stability**.

Why the oxetane shows the high affinity for hydrogen bonds?

1. For cyclic ethers, a decrease in the ring size is accompanied by a diminution in the corresponding **endocyclic C-O-C angle**. This has the effect of exposing the oxygen atom more effectively to hydrogen-bond donors.
2. An increase in the **s character** of the nonbonding orbitals of the electron lone pairs renders these less available to engage in hydrogen bonding. Several studies suggest that only oxiranes experience a significant change in the hybridization associated with the electron lone pairs on the oxygen atom.



The balance of the two effects makes oxetanes optimal among the cyclic ethers as acceptors of hydrogen bonds.

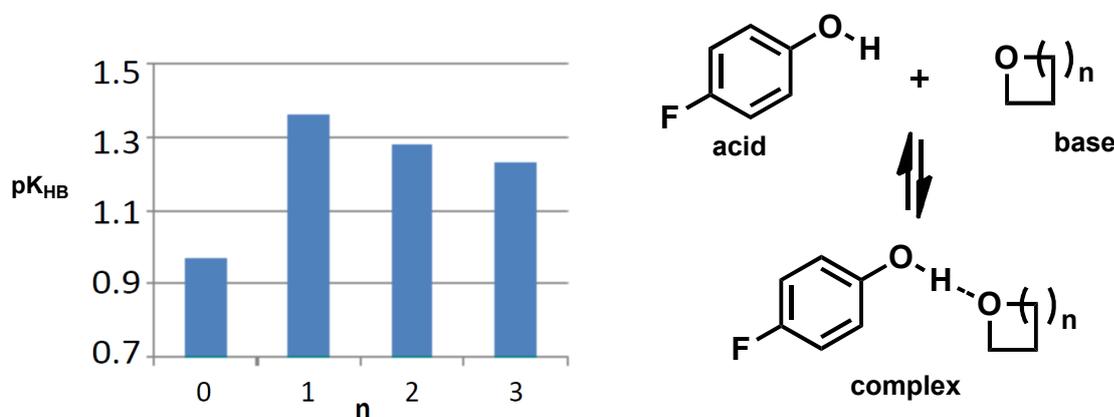
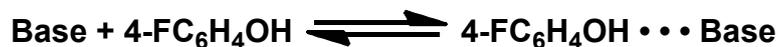


Figure: strength of association with 4-fluorophenol in cyclic ethers against ring-size

pK_{HB} shows the thermodynamic hydrogen-bond basicity.



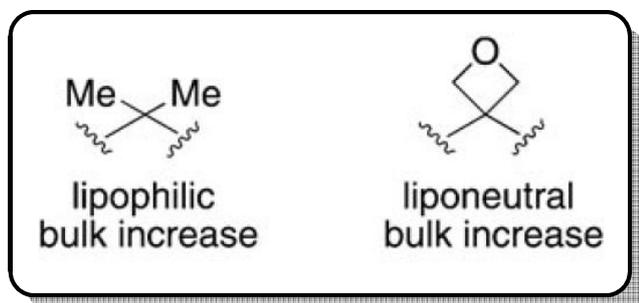
$$K_f = \frac{[\text{Hydrogen-bond complex}]}{[\text{Base}][4\text{-FC}_6\text{H}_4\text{OH}]}$$

$$\text{pK}_{\text{HB}} = -\log_{10} (\text{dissociation constant of the complex}) = \log_{10} K_f$$

Oxetanes as Isosteres

Isosteres of *gem*-dimethyl groups

Initially oxetanes were studied as potential surrogates for *gem*-dimethyl groups, thus allowing the introduction of enhanced polarity with a similar molecular volume.



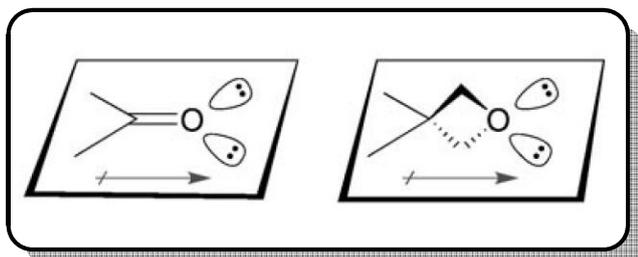
Oxetanes have the ability to graft **bulky substituents** onto a scaffold of interest **without increasing the lipophilicity**.

(Having high lipophilicity leads to low aqueous solubility and fast metabolic degradation.)

Isosteres of carbonyl groups

There are liabilities associated with carbonyl groups that stem from their susceptibility to enzymatic modification and to the epimerization of adjacent stereogenic centers, as well as their inherent electrophilic reactivities and their potential for covalent binding.

So oxetanes are used as chemically and metabolically **stable** isosteres of carbonyl groups.



The oxetane oxygen atom expresses a similar capacity to the C=O moiety to **accept a hydrogen bond**.

(pK_{HB} for oxetane is 1.36
 pK_{HB} for cyclopentanone is 1.27)

pK_{HB} scale of carbonyl groups: *J. Chem. Soc., Perkin Trans. 1998, 101*

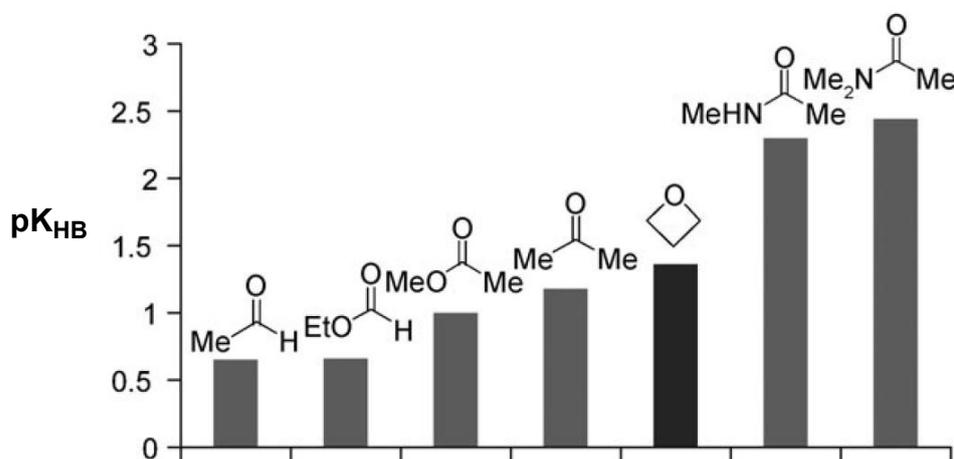
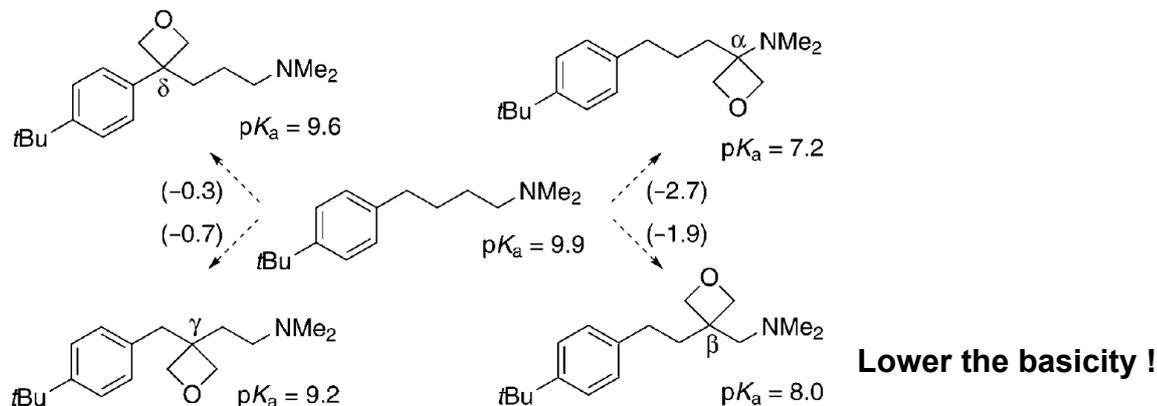


Figure: affinity of oxetane and different carbonyl compounds to act as acceptors for hydrogen bonds

Influence on the basicity of proximal amines

While the oxygen atom of an oxetane can donate electron density as a Lewis base, the oxetane motif itself acts as an electron-withdrawing group on neighboring functional groups. This distant-dependent inductive effect of the oxetane can be used to **temper the basicity of a proximal amine**.

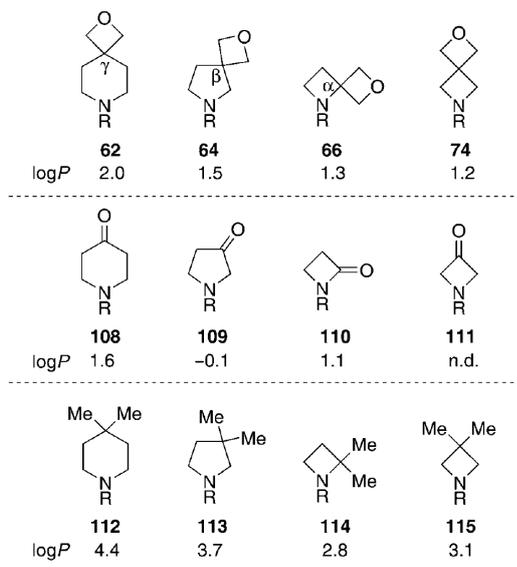
Angew. Chem. Int. Ed. 2006, 45, 7736



Influence on lipophilicity and solubility

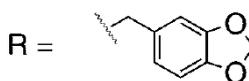
Having seen that the presence of an oxetane can markedly influence the basicity of a proximal amine, it is important to assess its influence on the lipophilicity of the underlying scaffold.

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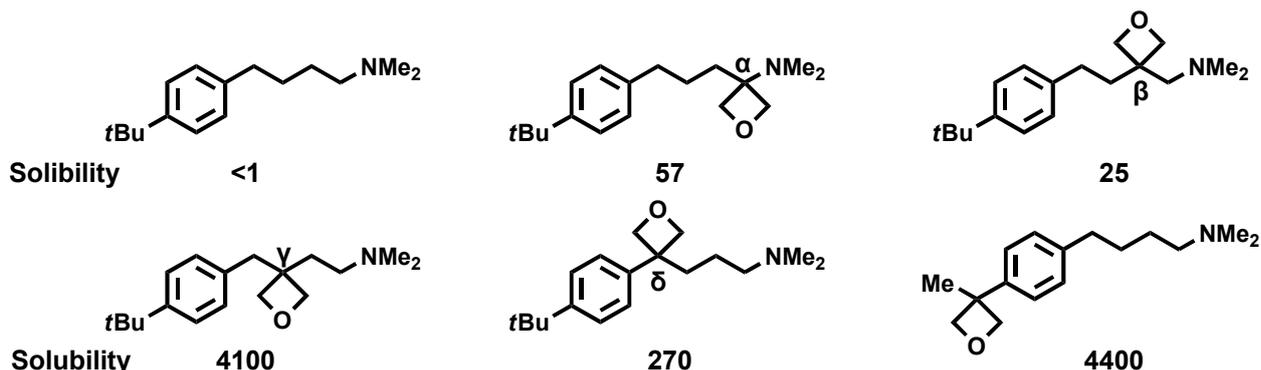
It is shown that an oxetane-containing molecule is typically much **less lipophilic** than the respective *gem*-dimethyl analogue, and that the corresponding carbonyl compounds are even more hydrophilic.

(logP = intrinsic lipophilicity of the neutral base
n.d. = not determined because of chemical instability)



Lower the lipophilicity !

The thermodynamic solubilities measured in buffered solutions at pH9.9 are shown below.

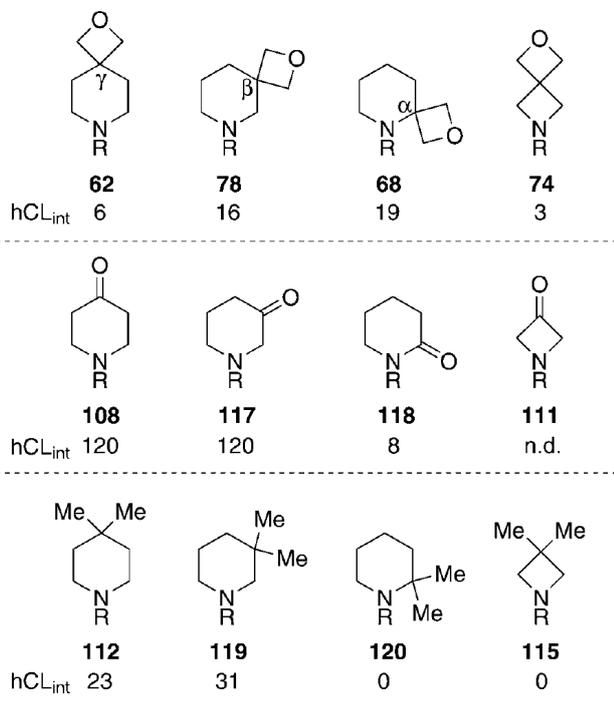


Heighten the solubility !

Metabolic and chemical stability

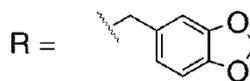
The influence an oxetane has on oxidative phase I metabolism has been studied and compared with compounds having carbonyl or *gem*-dimethyl groups at the corresponding position.

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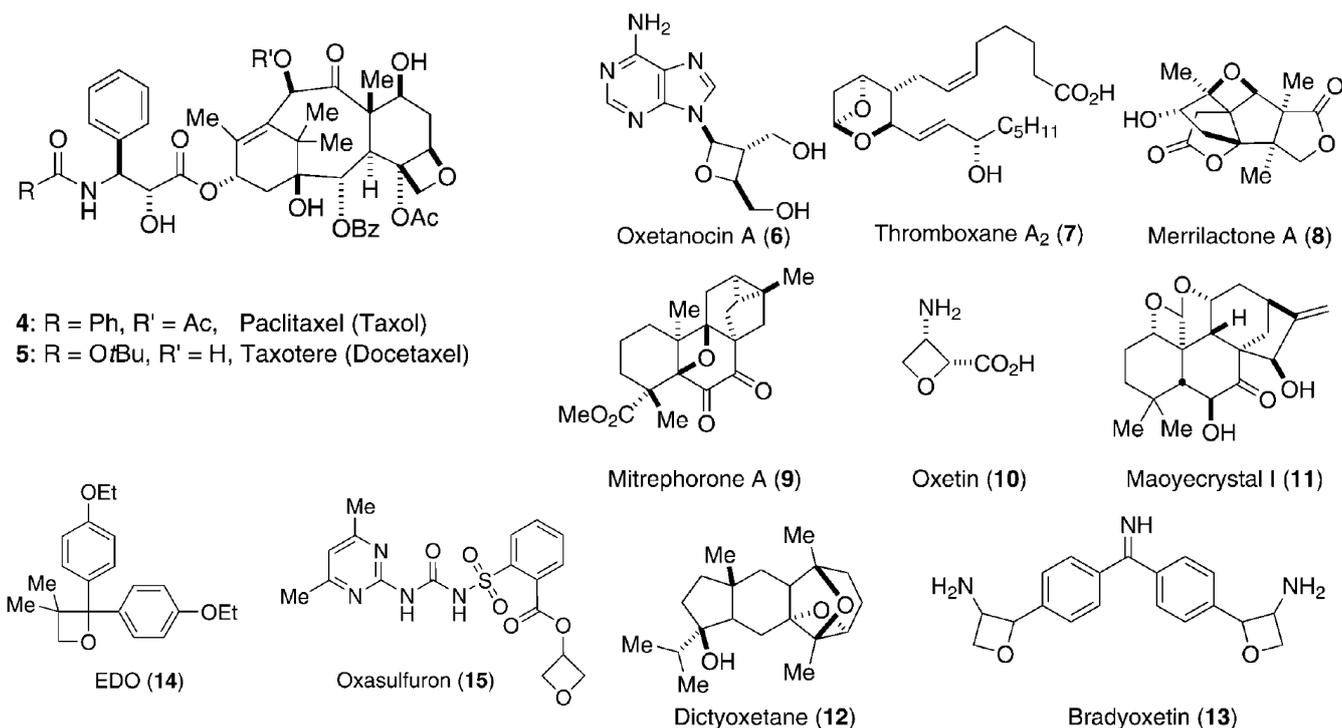
It was found that compounds bearing oxetanes tend to have a low to modest proclivity towards metabolic degradation, and that in many cases the corresponding *gem*-dimethyl or carbonyl compounds have higher intrinsic clearance rates in human liver microsomes.

(hCL_{int} = intrinsic clearance rates [min⁻¹/(mg_{protein}μL⁻¹)]
n.d. = not determined because of chemical instability)



Improve metabolic and chemical stability !

Oxetanes in Drugs and Natural Products

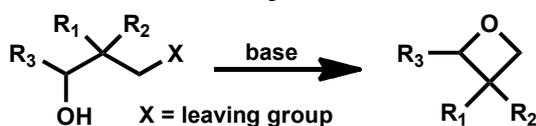


Preparation of Oxetanes

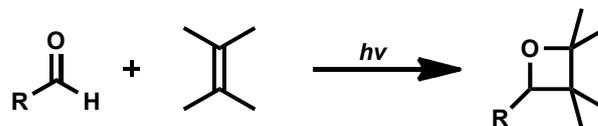
Oxetane has first been reported by Reboul in 1878.

Three general approaches to the synthesis of oxetanes are shown below.

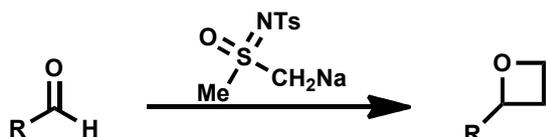
1) Williamson ether synthesis



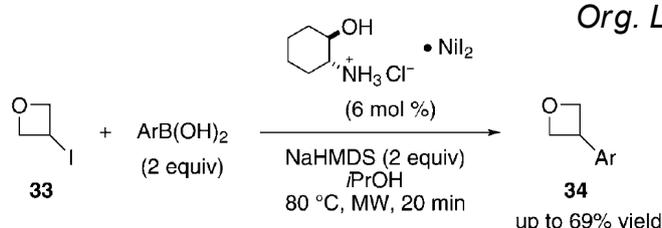
2) Paternó-Büchi reaction



3) sulfonium ylides (via Corey-Chaykovsky reaction)



Preparation of 3-Aryl-substituted Oxetanes

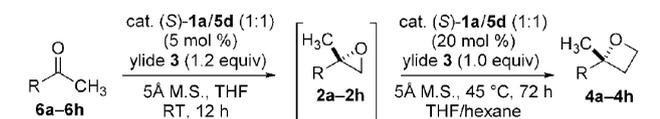


Org. Lett. 2008, 10, 3259

This nickel-mediated Suzuki coupling provides access to a wide range of 3-aryl-substituted oxetanes.

The reaction tolerates a number of common functional groups.

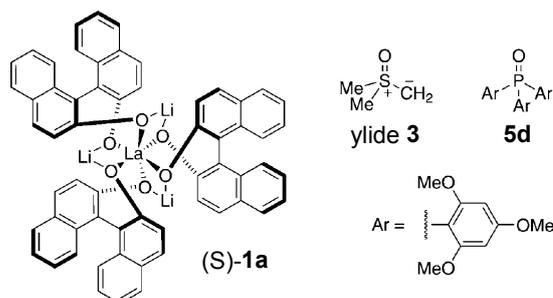
Catalytic Asymmetric Synthesis of 2,2-Disubstituted Oxetanes



Entry	6	R	ee of 2 [%]	4	Yield of 4 [%] ^[b]	ee of 4 [%] ^[c]
1	6a		96	4a	74	99
2	6c		96	4c	62	99
3	6d		94	4d	86	99
4	6e		97	4e	85	99
5	6b		93	4b	88	99
6	6f		93	4f	68	99
7	6g		96	4g	58	> 99.5
8	6h		97	4h	62	> 99.5

[a] Reaction was performed with 1.2 equiv of ylide **3** in THF at room temperature using 5 mol% of (S)-**1a**/**5d** (1:1) for the first step; for the second step, an additional 15 mol% of (S)-**1a**/**5d** (1:1), 1.0 equiv of ylide **3**, and *n*-hexane were added to the reaction mixture. [b] Yield of isolated oxetanes **4** (from ketones **6**) after purification by column chromatography. [c] Determined by GC or HPLC analysis.

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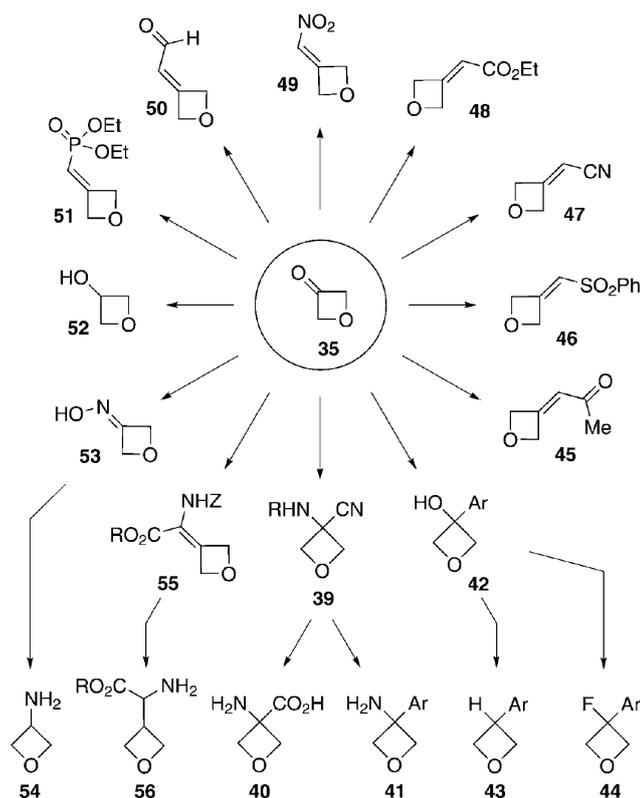
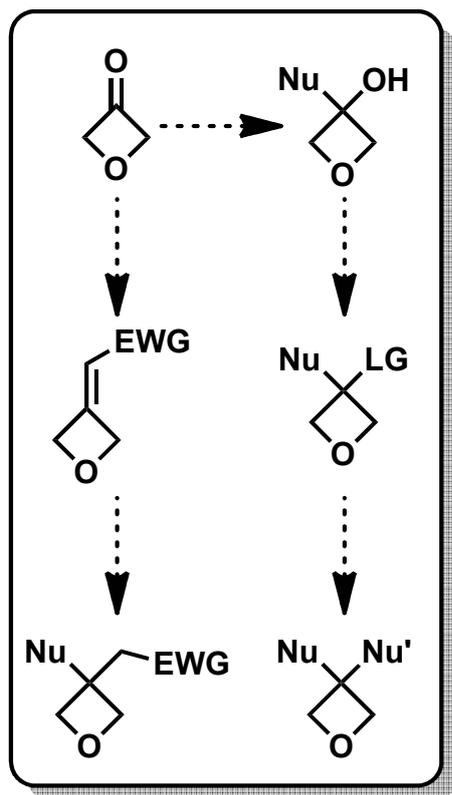
One-pot catalytic asymmetric synthesis of 2,2-disubstituted oxetanes from ketones

Chiral amplification in the second reaction between the epoxide and the ylide occur to afford oxetanes with a higher enantioselectivity than the intermediate epoxides.

In order to get various oxetane derivatives...

Oxetane-3-one is very useful.

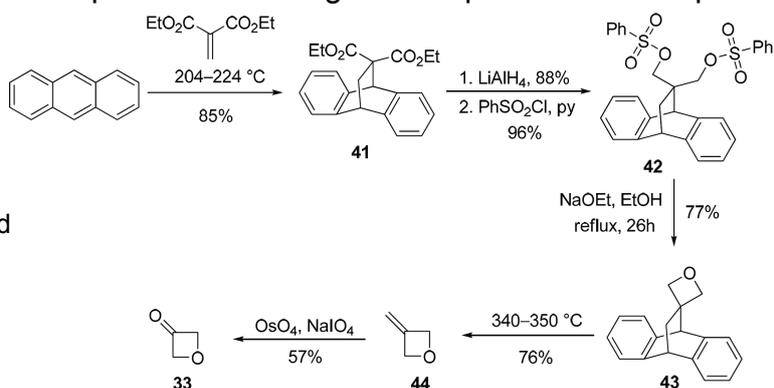
It can be converted to many kinds of 3,3-disubstituted oxetanes.



Why are 3,3-disubstituted oxetanes focused on?

This stems from the aim of not augmenting the complexity by generating a stereogenic center upon grafting an oxetane unit onto a given scaffold.

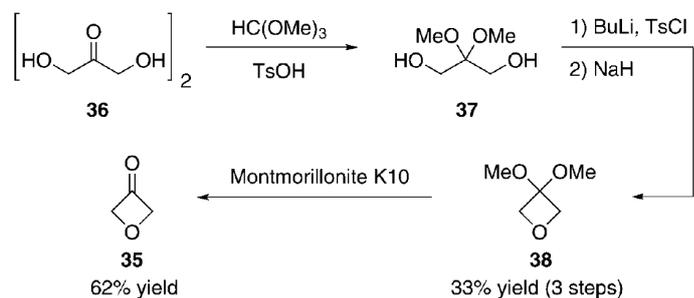
The first synthesis of oxetane-3-one in pure form and significant quantities was reported in a patent from DuPont in 1967.



- intermediate **44** was unstable...
- retro Diels-Alder reaction seemed to be difficult to accomplish with standard laboratory equipment...

Several syntheses of oxetane-3-one was reported; however, each has practical shortcomings, such as the use of preparative gas-chromatographic techniques.

Consequently, a straightforward route was developed starting from dihydroxyacetone dimer.



Angew. Chem. Int. Ed. 2006, 45, 7736

33% yield (3 steps)

4. Summary

The design and application of isosteres have inspired medicinal chemists for almost 80 years, fostering creativity directed toward solving a range of problems in drug design, including understanding and optimizing drug — target interactions and specificity, improving drug permeability, reducing or redirecting metabolism, and avoiding toxicity.

As an established and powerful concept in medicinal chemistry, the application of bioisosteres will continue to play an important role in drug discovery.

Isosterism can also contribute to the productive application in the design and optimization of catalysts in organic chemistry!!

References

review of bioisosteres: *J. Med. Chem.* 2011, 54, 2529

Chem. Rev. 1996, 96, 3147

fluorine in medicinal chemistry: *ChemBioChem* 2004, 5, 637

oxetanes in drug discovery: *Angew. Chem. Int. Ed.* 2010, 49, 9052