Chimie Médicinale

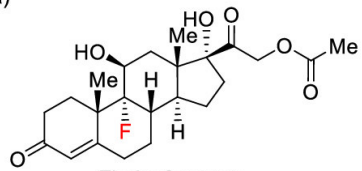
Introduction et principes généraux

- Introduction : le développement pharmaceutique
- Mode d'action : nature des interactions molécule-cible
- « Drug Discovery »
- « Drug Design »
- Chimie médicinale : Développements en chimie organique
  1. *Le Fluor en chimie médicinale*
  2. *Le groupement Méthyle en chimie médicinale*
  3. *Nouveaux motifs : oxétane, cyclopropane, « escape from flatland »*
- Fonctionnalisation C-H en chimie médicinale

• Le fluor : un atome essentiel

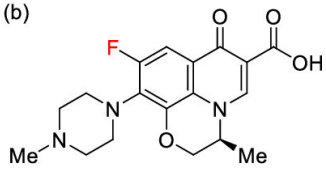
Avant les années 50 : fluor absent de la chimie pharmaceutique

(a)



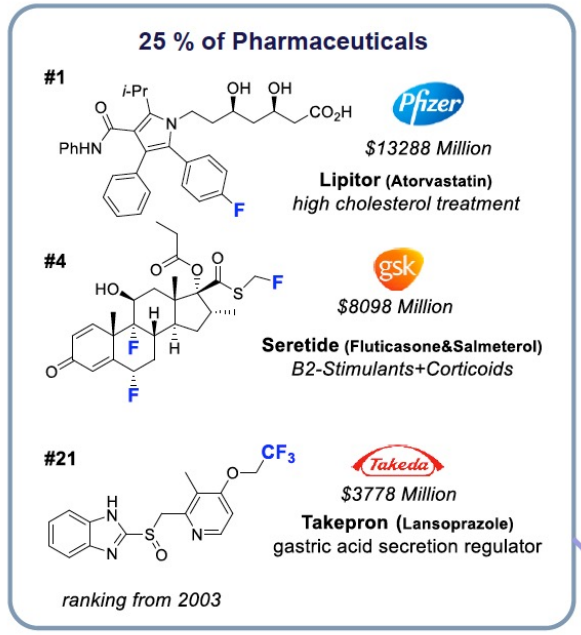
Florinef acetate
1954

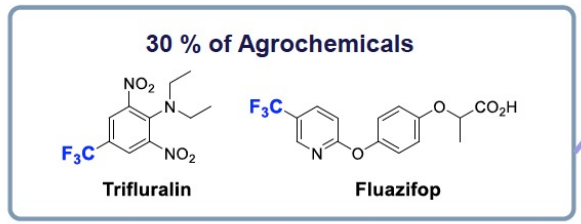
(b)

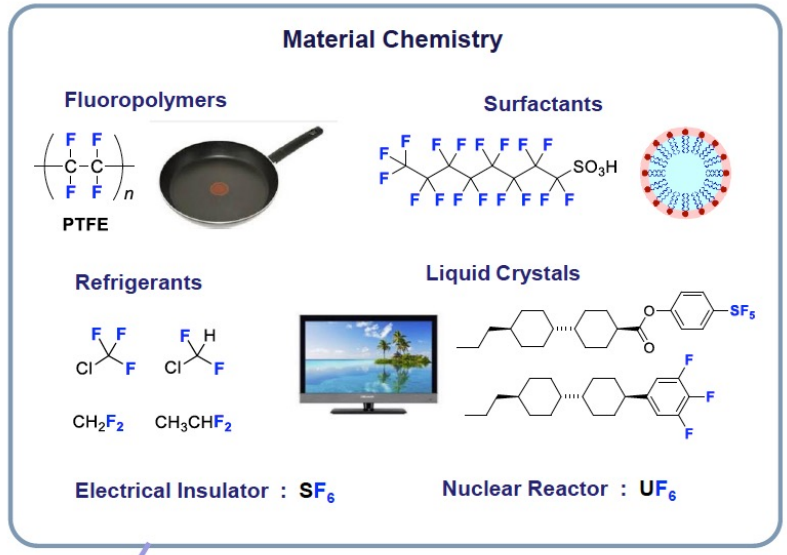


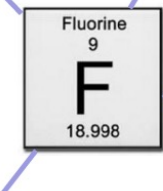
levofloxacin
1993

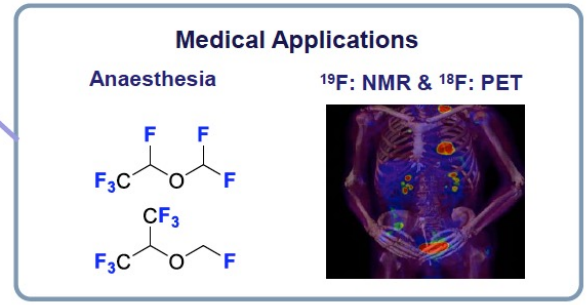
The first fluoro-pharmaceutical was fludrocortisone, Florinef (Florinef acetate), which was brought to market in 1954. Florinef is a synthetic corticosteroid that exhibits potent mineralocorticoid properties and high glucocorticoid activity for the treatment of adrenogenital syndrome, adrenal insufficiency, and postural hypotension. Fluoroquinolones such as levofloxacin, were introduced in the 1980s and represent a second historically significant group of fluoro-pharmaceuticals. Fluoroquinolones act as potent antibacterial agents by inhibiting the activity of DNA gyrase and topoisomerase, and this mechanism of action is fundamentally different from that of β-lactam antibiotics such as penicillin, cephalosporin, and antibacterial sulfur drugs.







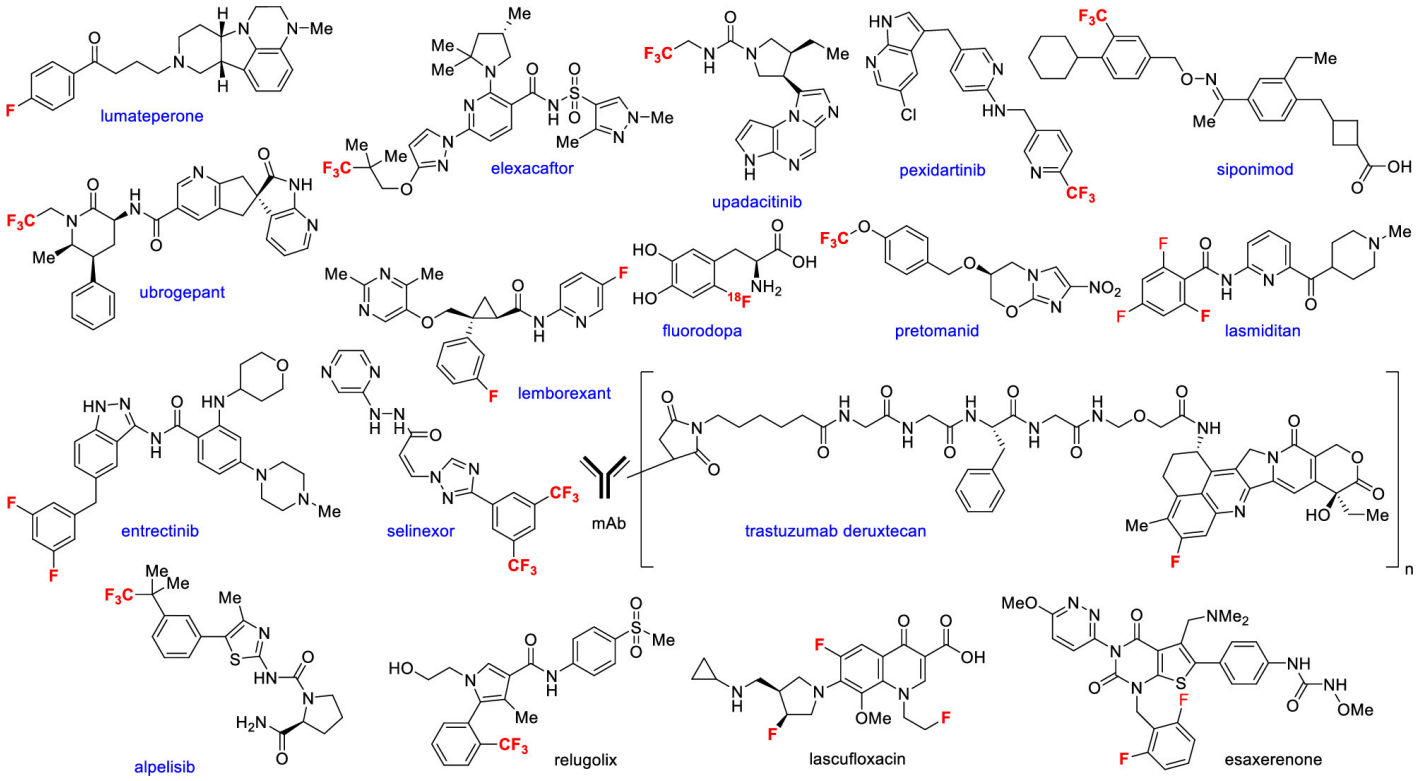


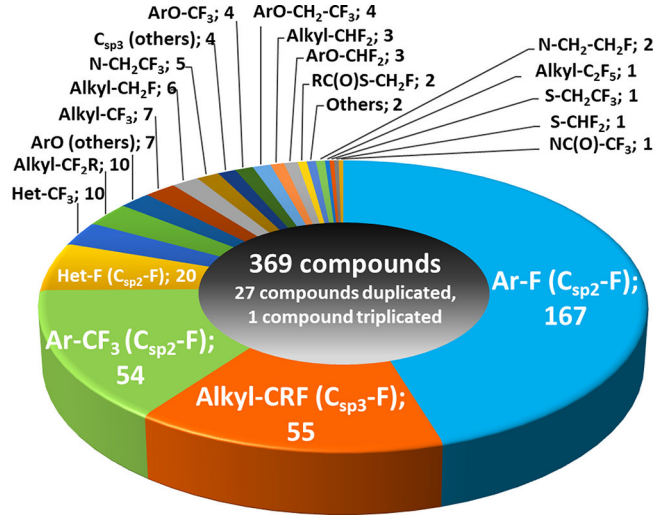


> « Contribution of Organofluorine compounds to Pharmaceuticals » *ACS Omega* **2020**, *5*, 10633

- **Le fluor : un atome essentiel**

Avant les années 50 : fluor absent de la chimie pharmaceutique





Chemotype distribution of fluoro-pharmaceuticals.

17 fluoro-pharmaceuticals globally registered in 2019 including one fluorinated-biologic drug, trastuzumab deruxtecan.

> « Contribution of Organofluorine compounds to Pharmaceuticals » *ACS Omega* **2020**, *5*, 10633

• Pourquoi une telle importance de l'atome de fluor ?

Substitution d'un atome d'hydrogène par un atome de fluor

• Pourquoi substituer un atome d'hydrogène par un atome de fluor ?

L'atome de fluor est souvent utilisé en chimie médicinale comme un mime d'atome d'hydrogène ou un mime de fonction OH. Il est cependant déconseillé d'en tirer une règle générale.

F *vs* H

Du point de vue stérique, malgré un rayon de Van der Waals supérieur
le F n'induit pas de fortes perturbations stériques lorsqu'il se substitue à un H, comparativement au cas des autres halogènes. En revanche, un méthyle diffère fortement d'un trifluorométhyle, plus comparable à un isopropyle.
Le faible rayon de VdW du F est lié à sa forte charge nucléaire (9 protons) qui induit une contraction des orbitales 2p.

La comparaison des énergies de liaison indique que l'introduction du F induit une meilleure résistance vis-à-vis des transformations métaboliques.

L'électronégativité du fluor perturbe aussi la distribution électronique au sein de la molécule étudiée (basicité ou acidité de fonctions voisines, moment dipolaire, …) ainsi que les propriétés physiques (volatilité et lipophilicité plus grandes, …).

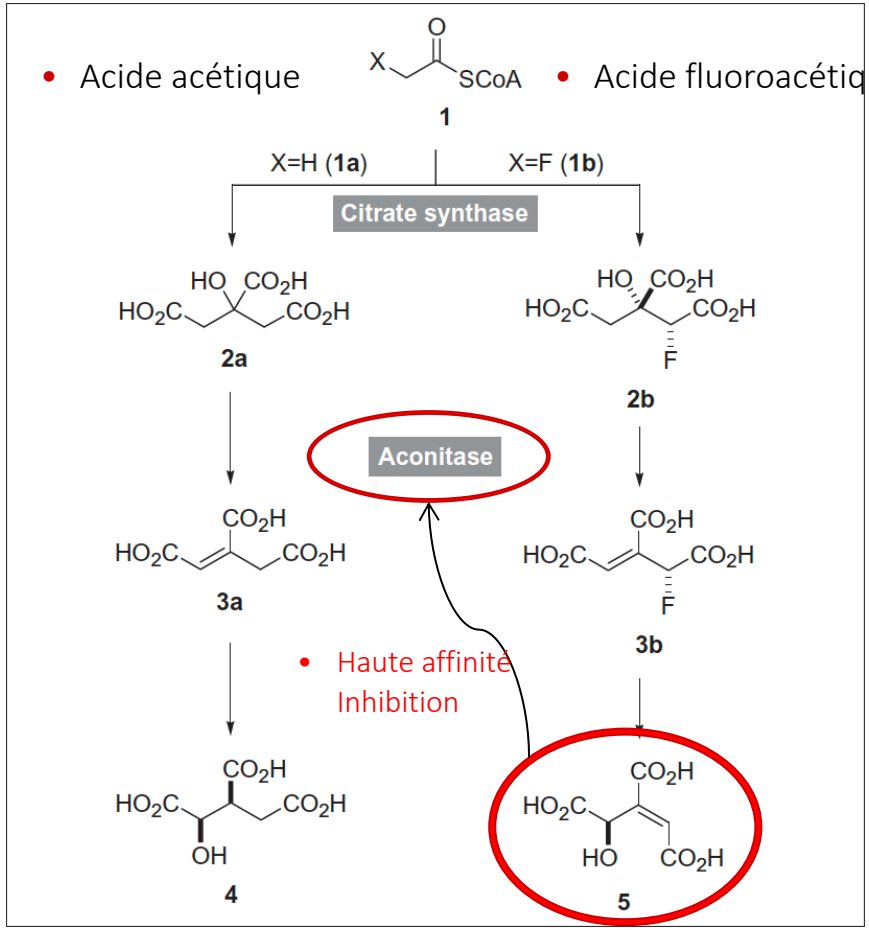
Atom	Pauling's electronegativity χ_p	Electron Affinity (kcal/mol)	Ionisation Potential (kcal/mol)	Van der Waals Radii (Å)	Atom Polarisability (Å^3)
H	2.20	17.7	313.6	1.20	0.667
F	**3.98**	**79.5**	**401.8**	**1.47**	**0.557**
Cl	3.16	83.3	299.0	1.74	2.18
Br	2.96	72.6	272.4	1.85	3.05
I	2.66	70.6	241.2	1.98	4.70
C	2.55	29.0	240.5	1.70	1.76
N	3.04	- 6.2	335.1	1.55	1.10
O	3.44	33.8	314.0	1.52	0.82

D^0(C-X)	Bond Dissociation Energy kcal/mol
CH_3-H	104.3
CH_3-F	108.3
CH_3-Cl	82.9
CH_3-Br	69.6
CH_2F-F	119.5
CHF_2-F	127.5
CF_3-F	130.5

> F. Diederich *et al.* « Fluorine in Pharmaceuticals: looking beyond intuition » *Science* 2007, *317*, 1881-1886

- **Pourquoi une telle importance de l'atome de fluor ?**

  Exemple illustrant l'analogie H ≈ F : toxicité de l'acide fluoroacétique



- L'ensemble des dérivés fluorés et non fluorés reconnus par les enzymes du cycle de Krebs

> F. Diederich *et al.* « Fluorine in Pharmaceuticals: looking beyond intuition » *Science* 2007, *317*, 1881-1886

- **Pourquoi une telle importance de l'atome de fluor ?**

Substitution d'une fonction OH par un atome de fluor

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X	Bond Length C-X (Å)
H	1.09
F	1.35
Cl	1.77
O	1.43
S	1.82
C	1.54
Si	1.85

F *vs* OH

Le fluor pourrait, en quelques rares occasions, mimer une fonction OH car :

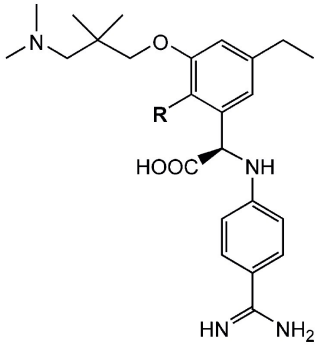
Elément le plus électronégatif, le fluor peut être un accepteur de liaison hydrogène. Cette liaison hydrogène sera cependant (au moins 2 fois) plus faible que celle dans le cas d'une fonction OH.

Cette analogie OH-F est aussi fondée sur la comparaison des longueurs de liaison. ***Longueur de liaison : C-O (1,43 Å) ≈ C-F (1,38 Å)***
Le remplacement d'un OH par un fluor permettrait d'éviter les dégradations oxydantes que peuvent subir les composés hydroxylés.
Cependant, le caractère « accepteur » de liaison hydrogène du fluor a été plus que remis en cause (faible affinité du fluor pour l'hydrogène, …)

> F. Diederich *et al.* « Fluorine in Pharmaceuticals: looking beyond intuition » *Science* 2007, *317*, 1881-1886

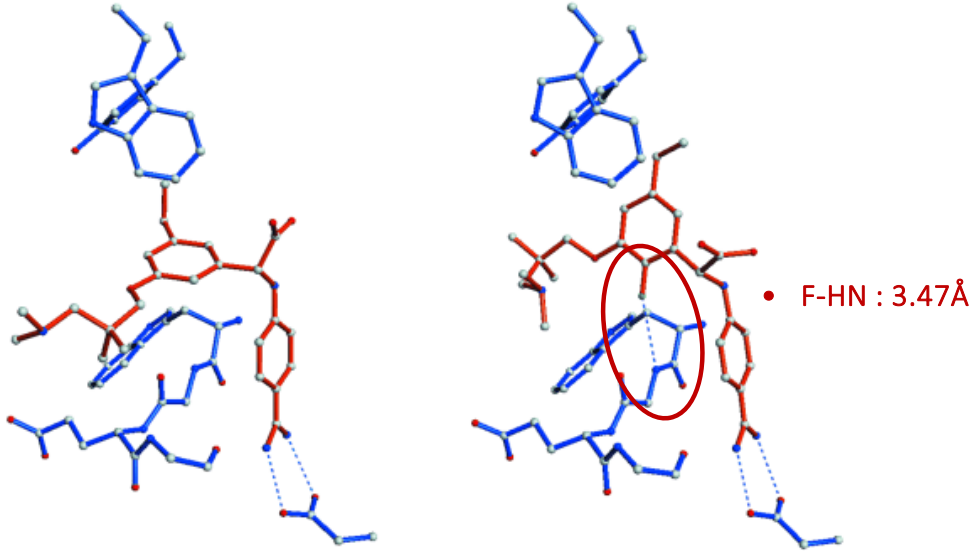
• Effet du fluor sur les propriétés pharmacodynamiques

> Liaison hydrogène



R	K_i - Thrombin [μM]
H	1.6
F	0.26

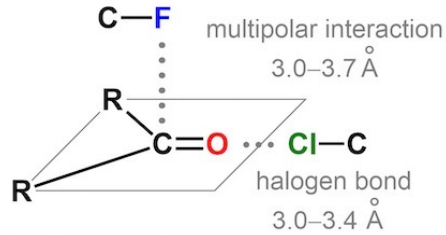
Figure 4. *Structure and binding affinity of a pair of thrombin inhibitors with and without fluorine substituent.*



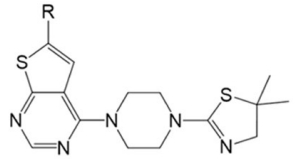
• F-HN : 3.47Å

> Interactions électrostatiques

• Orthogonal Multipolar Interaction

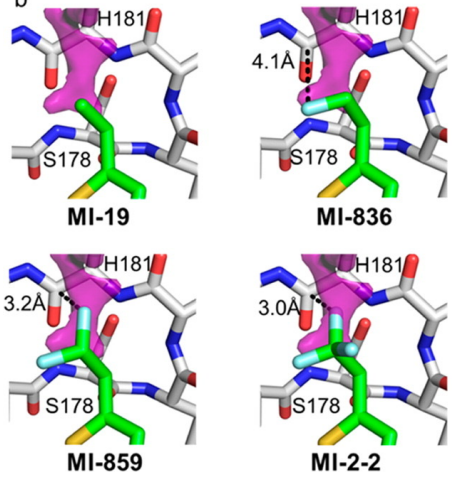


a

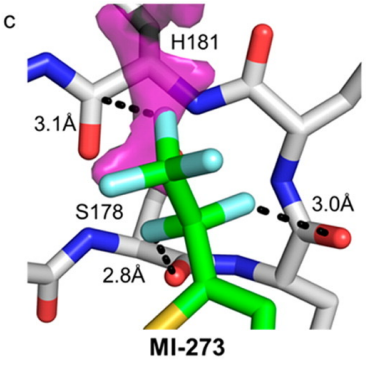


	R	IC_{50} (nM)	ΔΔG (kcal/mol)
MI-19	$-CH_2CH_3$	1200 ± 70	0
MI-836	$-CH_2CH_2F$	260 ± 13	-0.90
MI-859	$-CH_2CHF_2$	65 ± 20	-1.7
MI-2-2	$-CH_2CF_3$	46 ± 16	-1.9
MI-273	$-CF_2CF_3$	674 ± 158	-0.34

b



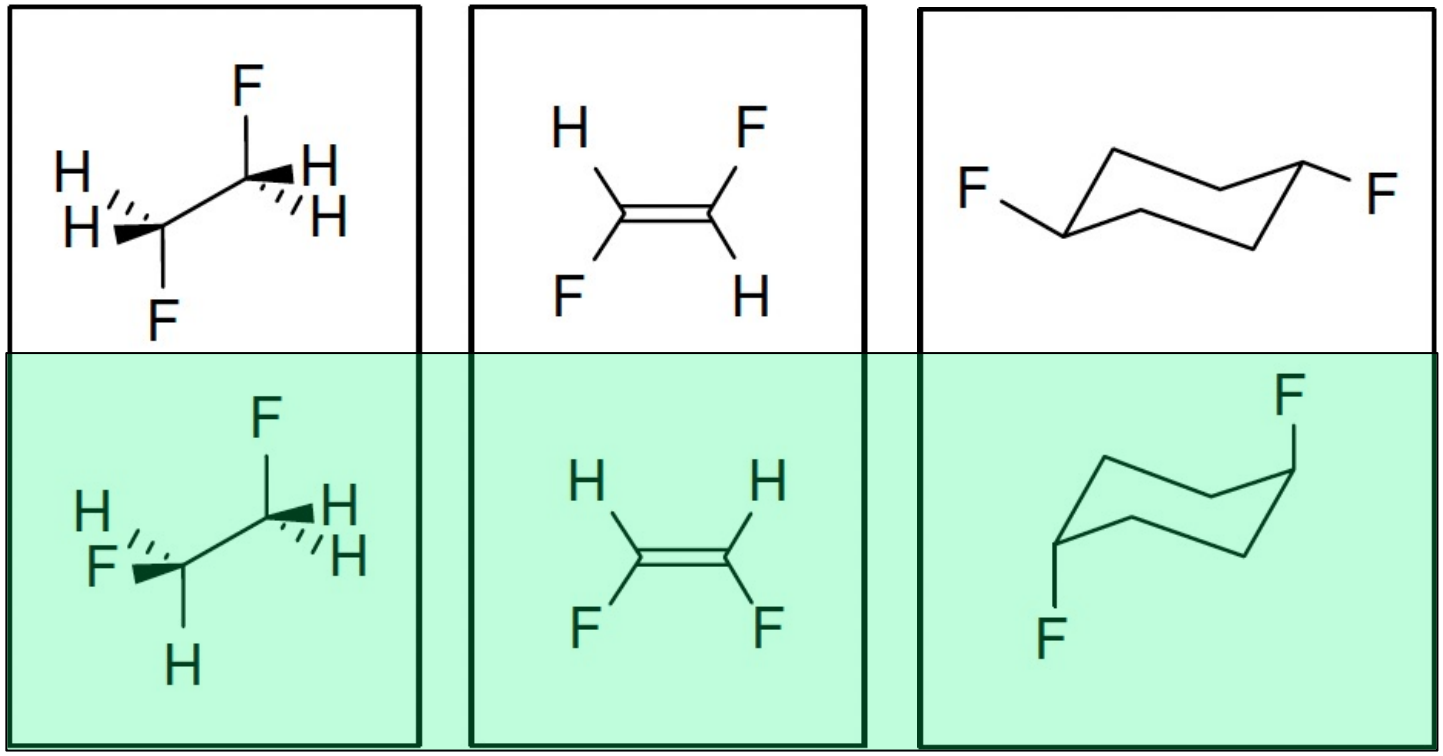
c



> « Fluorine in Medicinal Chemistry » *ChemBioChem* **2004**, *5*, 637-643 & *Chem. Soc. Rev.* **2008**, *37*, 320-330.

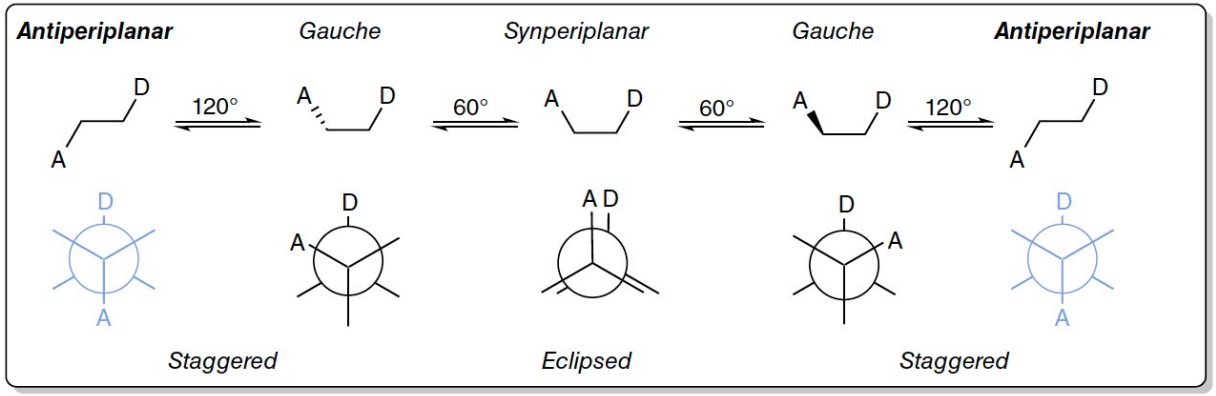
- Effet du fluor sur les propriétés pharmacodynamiques
  > Petit quizz

Quels sont les produits les plus stables (pour chaque paire) ?



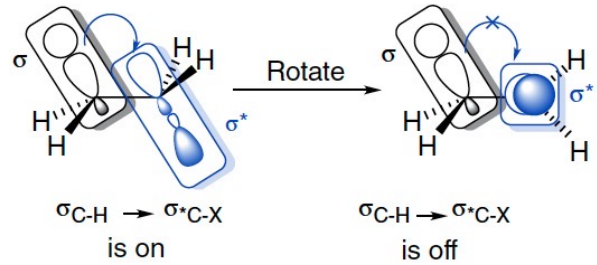
- **Effet du fluor sur les propriétés pharmacodynamiques**
  > Effet gauche

Stereoelectronic preference for conformations in which the best donor lone pair or bond is antiperiplanar to the best acceptor bond

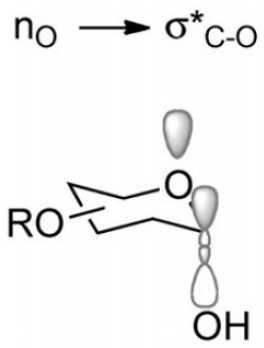


*H's not shown

Orbital interactions:



- **anomeric effect**



■ Since the antibonding C–O orbital is a better acceptor orbital than the antibonding C–H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

> « Fluorine in Medicinal Chemistry » *ChemBioChem* **2004**, *5*, 637-643 & *Chem. Soc. Rev.* **2008**, *37*, 320-330.

• Effet du fluor sur les propriétés pharmacodynamiques
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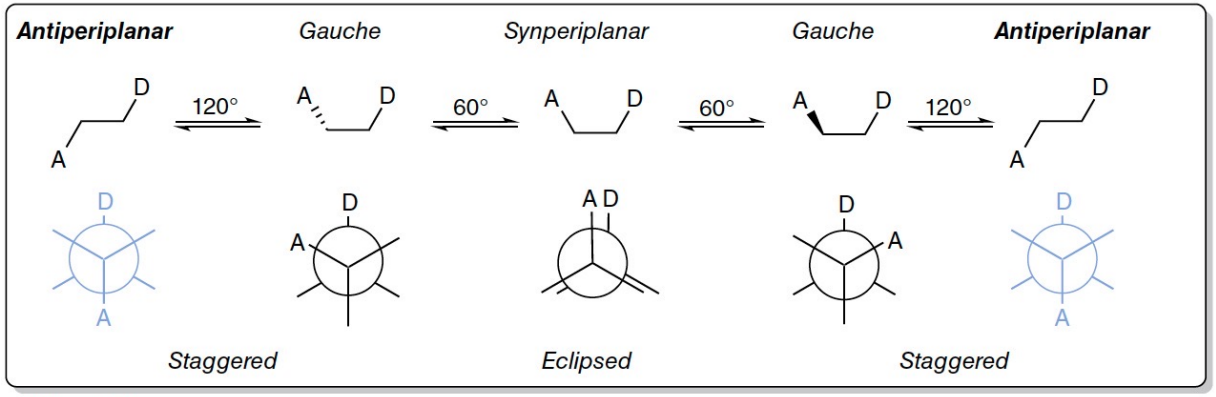

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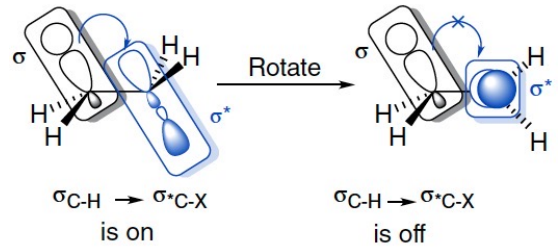
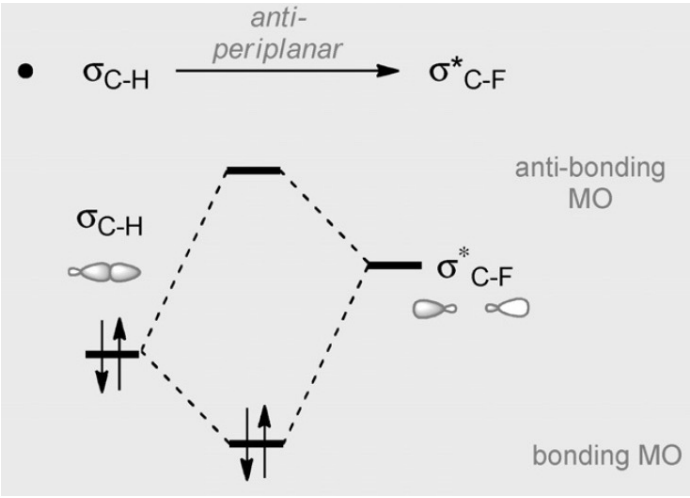
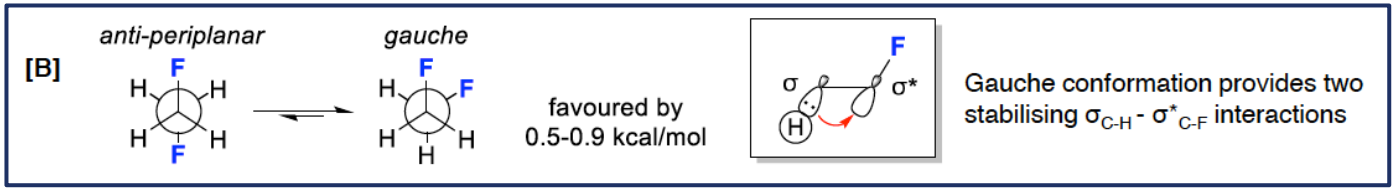




Stereoelectronic effects are dependent on the orientation/overlap and relative energies of orbitals. If this difference in energy is small and the overlap is large, the interaction between the two orbitals will be significant (e.g., σ_{C-H} -> σ_{C-F*}).

The Gauche effect is an atypical situation where a gauche conformation (groups separated by a torsion angle of approximately 60) is more stable than the anti conformation (180).



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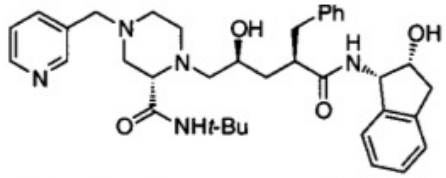
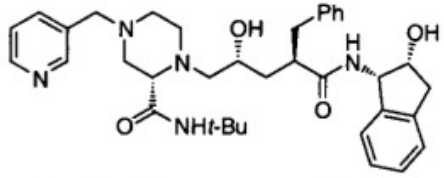
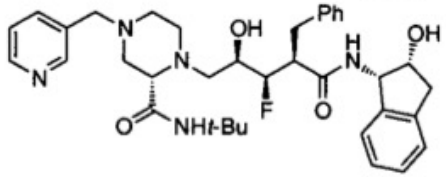
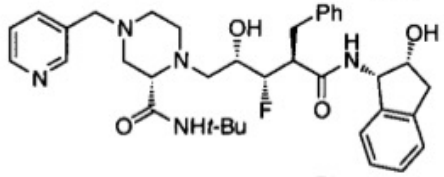
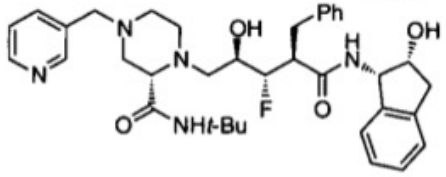
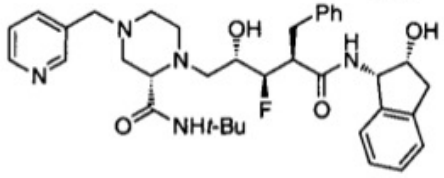
- Effet du fluor sur les propriétés pharmacodynamiques
  > Effet gauche

Inhibition Constants (K_i) for Inhibition of HIV-1 Protease by Indinavir and Analogues

Compound	Structure	K_i (nM)	Compound	Structure	K_i (nM)
Indinavir (**3**)		1.9	C_{17}-*epi*-Indinavir (**48**)		160
syn,syn-4		2.0	**syn,anti-4**		20
anti,anti-4		27	**anti,syn-4**		5900

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- Effet du fluor sur les propriétés pharmacodynamiques
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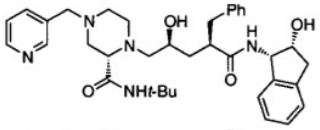
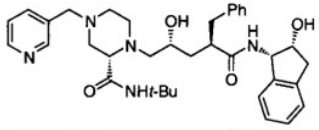
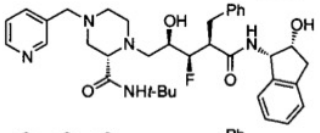
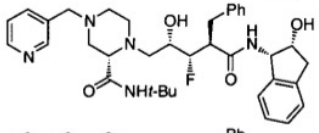
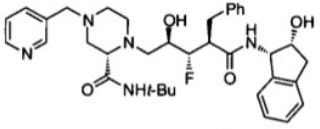
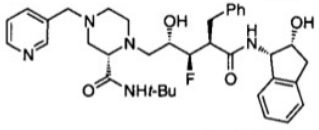
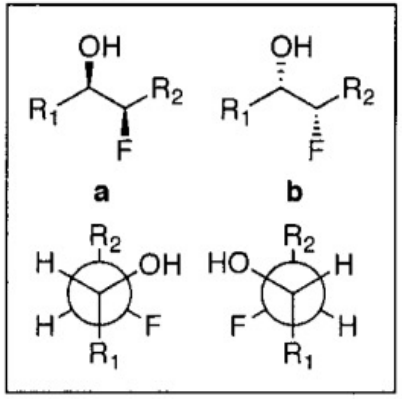
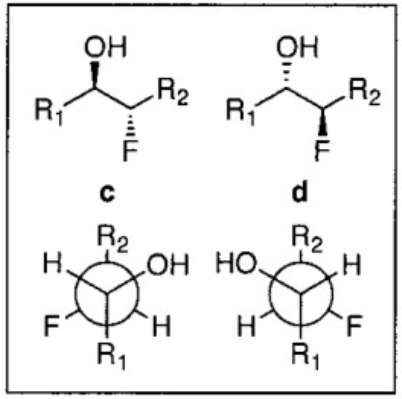
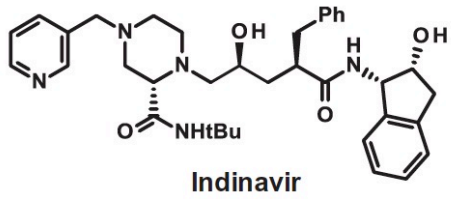
Indinavir (3)		1.9	C_{17}-*epi*-Indinavir (48)		160
syn,syn-4		2.0	syn,anti-4		20
anti,anti-4		27	anti,syn-4		5900

Syn fluorohydrins

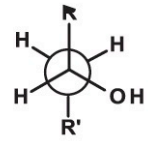


Anti fluorohydrins

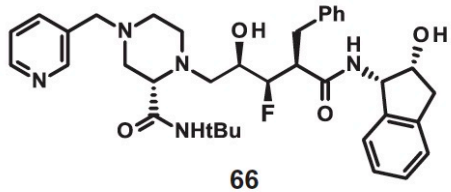




Indinavir

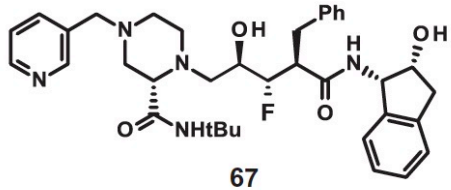


Binding conformation

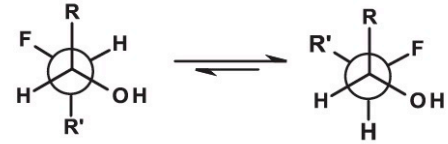


66

Binding conformation favoured



67

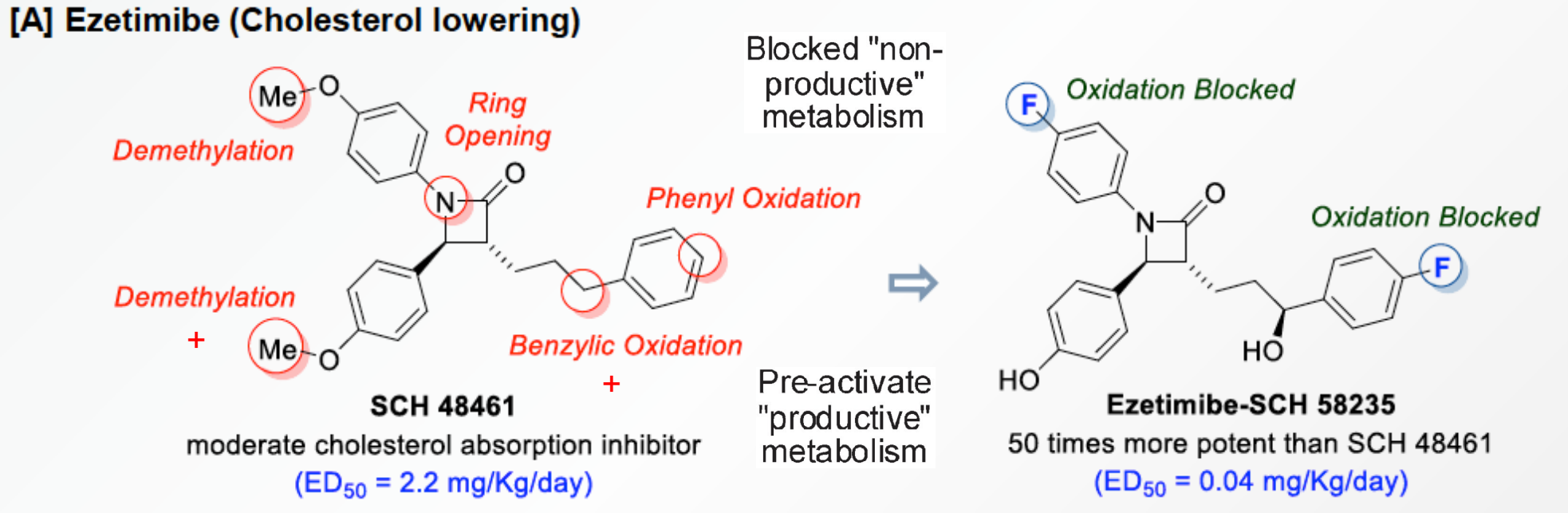


Binding conformation disfavoured

> « Fluorine in Medicinal Chemistry » *ChemBioChem* **2004**, *5*, 637-643 & *Chem. Soc. Rev.* **2008**, *37*, 320-330.

- Effet du fluor sur les propriétés pharmacocinétiques
  > Protection des sites sensibles vis-à-vis des réactions de métabolisation

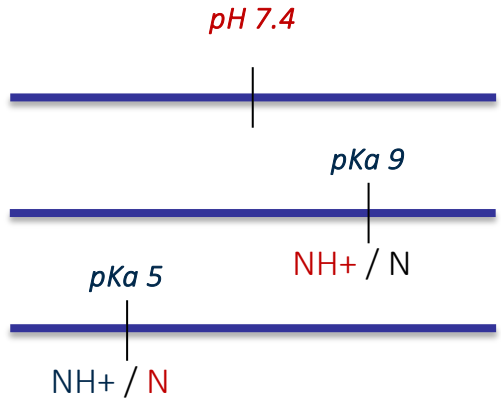
	H	F
Van de Waals radius	1.2	**1.47**
Electronegativity	2.1	**4**
Bond strength to C	98	**105**

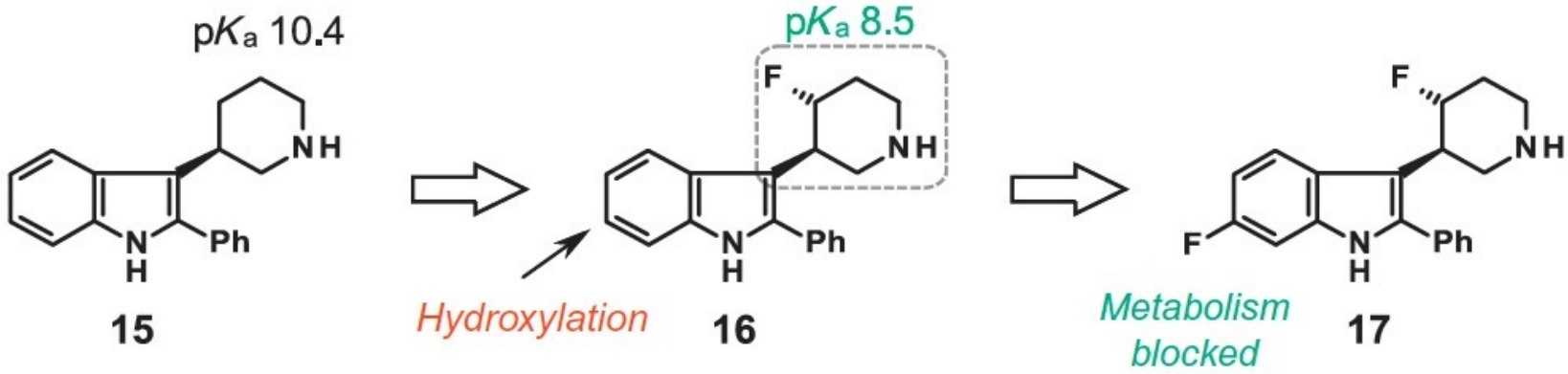


> « Fluorine in Medicinal Chemistry » *ChemBioChem* 2004, *5*, 637-643 & *Chem. Soc. Rev.* 2008, *37*, 320-330.

- **Effet du fluor sur les propriétés pharmacocinétiques**
  > Modulation du pK_a des fonctions acide/basiques environnantes

Compound	pK_a	Compound	pK_a	Compound	pK_a
CH_3COOH	4.76	CH_3CH_2COOH	4.87	$(CH_3)_2CHOH$	17.1
CH_2FCOOH	2.59	CF_3CH_2COOH	3.06	$(CF_3)_2CHOH$	9.3
$CH_2ClCOOH$	2.87	C_6H_5COOH	4.21	$(CH_3)_3COH$	19.0
$CH_2BrCOOH$	2.90	C_6F_5COOH	1.70	$(CF_3)_3COH$	5.4
CHF_2COOH	1.33	CH_3CH_2OH	15.93	C_6H_5OH	9.99
CF_3COOH	0.50	CF_3CH_2OH	12.39	C_6F_5OH	5.5

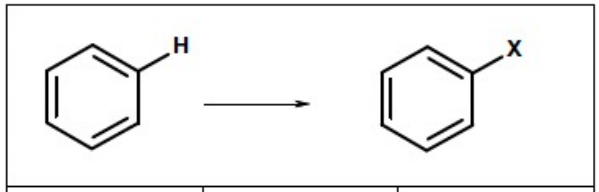




Bioavailability (F)	Poor F%	F = 18%	F = 80%
	(K_i= 0.99 nM)	(K_i= 0.43 nM)	(K_i= 0.06 nM)

> « Fluorine in Medicinal Chemistry » *ChemBioChem* **2004**, *5*, 637-643 & *Chem. Soc. Rev.* **2008**, *37*, 320-330.

- Effet du fluor sur les propriétés pharmacocinétiques
  > Modulation de la lipophilie



X	Π	σ_I
H	0.00	0.00
F	0.14	0.52
Cl	0.71	0.47
CH_3	0.56	0.04
CF_3	0.88	0.42
OCH_3	–0.02	0.29
OCF_3	1.04	0.39
SO_2CH_3	–1.63	0.48
SO_2CF_3	0.55	0.73

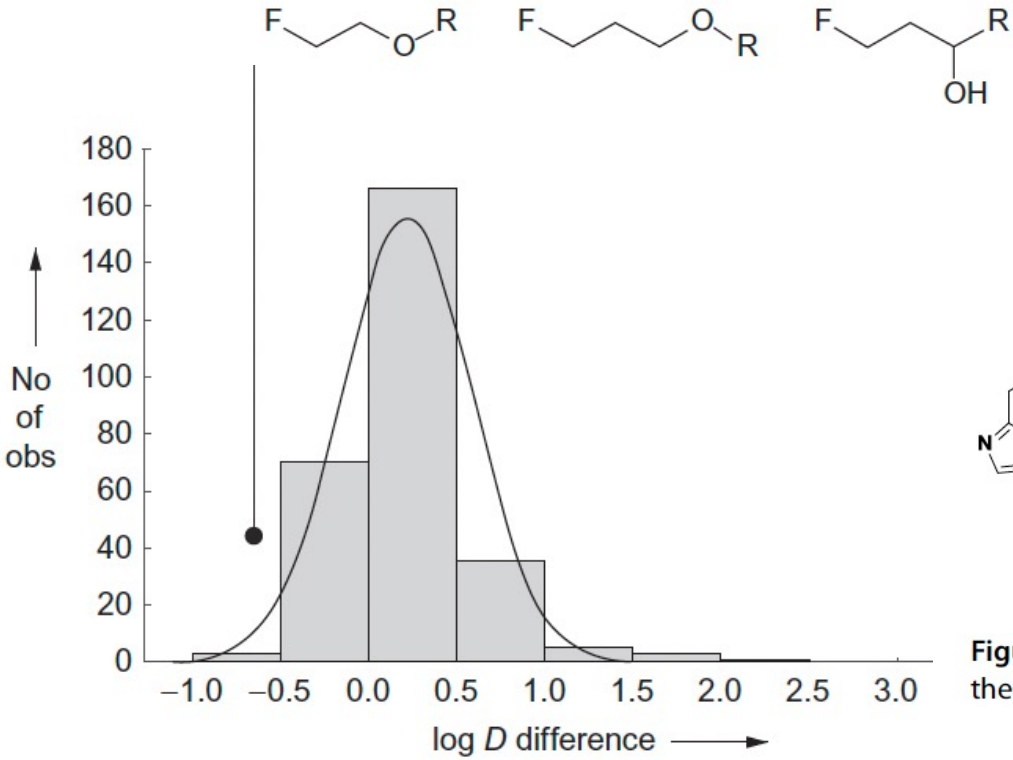
Figure 5 Lipophilicity substituent constant π and inductive parameter σ_I for common fluorine substituents compared to close analogues.

Augmentation de la lipophilie avec la présence d'atomes de fluor
Applicable aux composés aromatiques (C(sp^2)-F)

Attention aux composés aliphatiques (C(sp^3)-F)

> « Fluorine in Medicinal Chemistry » *ChemBioChem* 2004, *5*, 637-643 & *Chem. Soc. Rev.* 2008, *37*, 320-330.

• Effet du fluor sur les propriétés pharmacocinétiques
> Modulation de la lipophilie



Histogram of change in log D observed upon substitution of a H atom by a F atom.
On average, log D is increased by roughly 0.25.

Fragments associated with reduction in log D in this sample are highlighted.
*A possible explanation is that **fluorine in close vicinity to an oxygen atom** increases the overall polarity of the molecule, leading to a more pronounced gain in solvation energy in the polar medium relative to the nonpolar solvent. However, it is also possible that the fluorine polarizes the neighboring oxygen atoms and this leads to stronger hydrogen bonds between the oxygen and neighboring water molecules.*

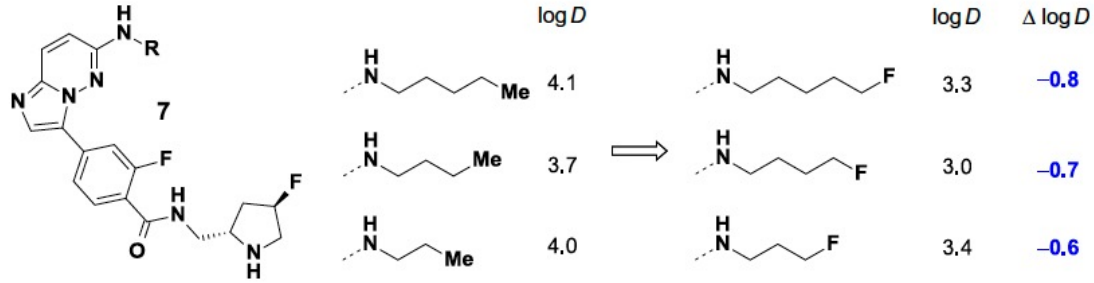


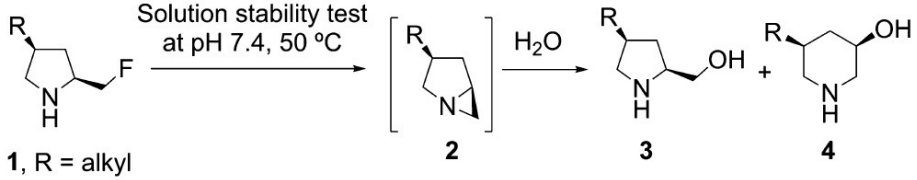
Figure 9 IKKβ inhibitors showing lowering of log *D* through introduction of fluorine into the terminal position of alkyl group.

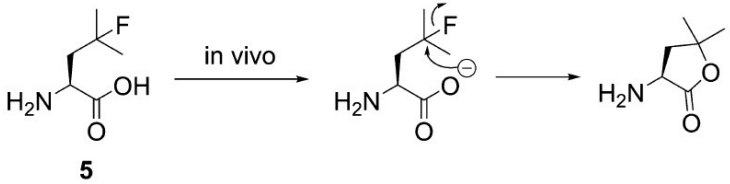
> « Fluorine in Medicinal Chemistry » *ChemBioChem* **2004**, *5*, 637-643 & *Chem. Soc. Rev.* **2008**, *37*, 320-330.

- Effet du fluor
  > The dark side of fluorine

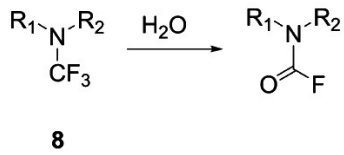
FDA in 2018, 18 contain fluorine. As the C–F bond-dissociation energy (BDE) is very high (typically 109 kcal/mol or above), fluorine is often used by medicinal chemists to block a metabolic soft spot, which can reduce a molecule's metabolic clearance and/or prevent the formation of reactive metabolites. However, such high BDE measures the homolytic cleavage of the C–F bond, and dissociation of fluorine from carbon is typically heterolytic under physiological conditions. In the presence of a nucleophile or drug-metabolizing enzymes, the release of fluoride can be facile, which is often observed in more easily tracked. For a drug suffering from significant C–F bond cleavage, fluoride's strong affinity for bones may lead to safety issues such as skeletal fluorosis. For example, there is

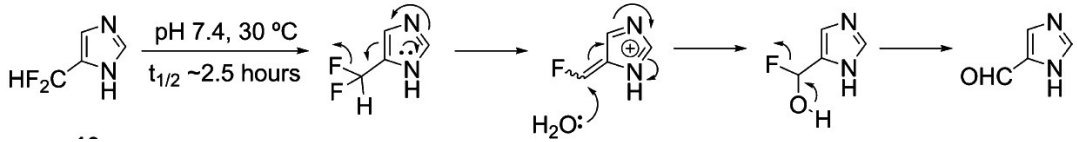
A. S_N2 reactions involving monofluorinated alkyls





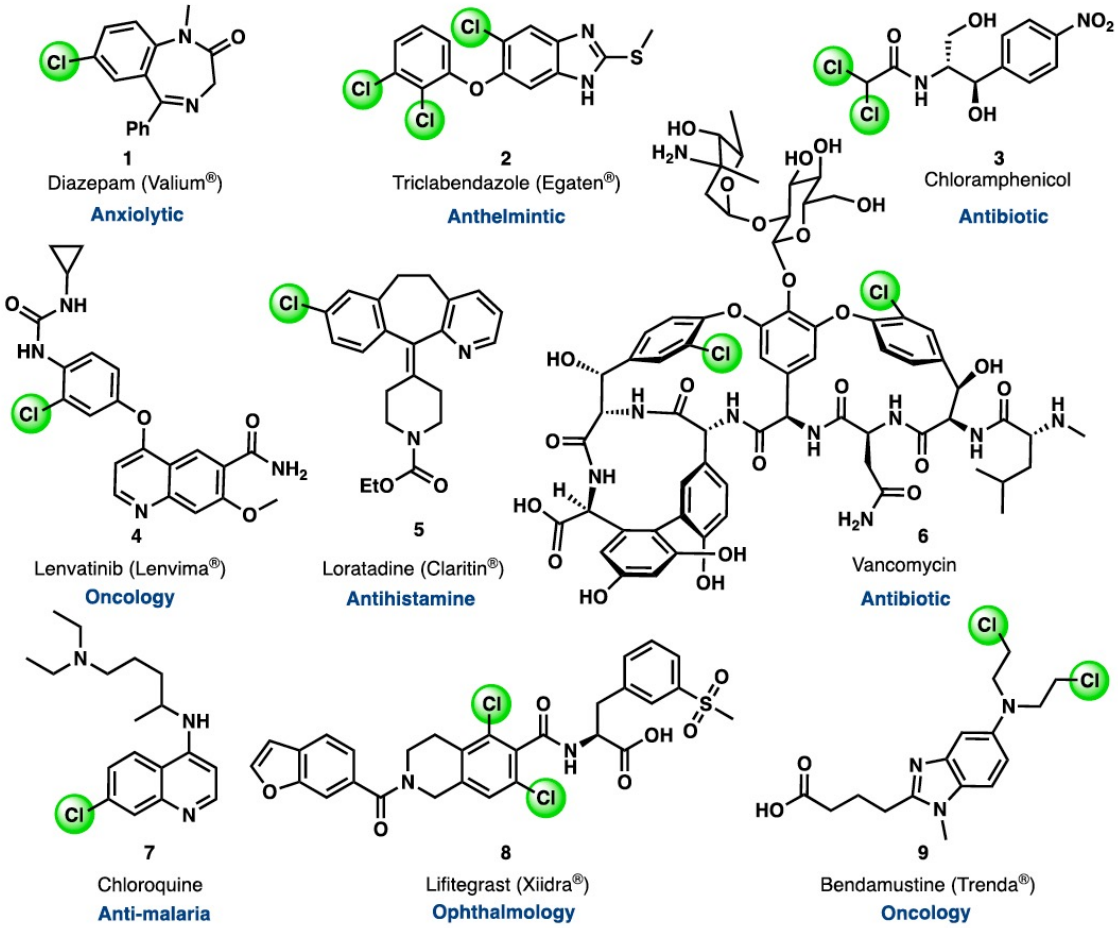
B. Lone pair of electrons or δ^- at fluorine's β- or other vinylogous positions may lead to loss of F^-

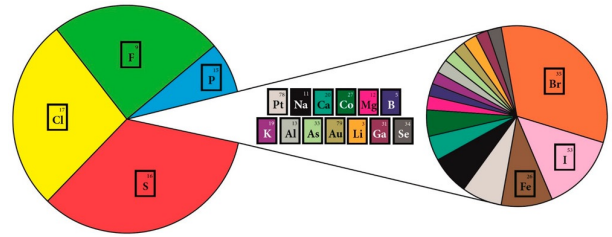


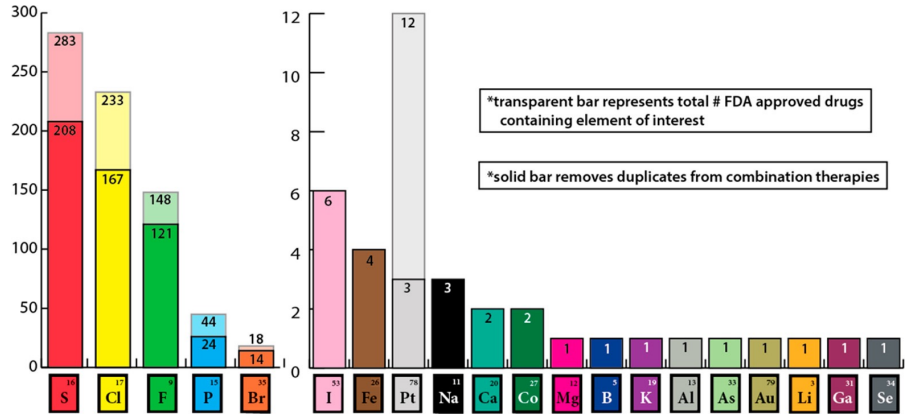


> «The dark side of fluorine » *ACS Med. Chem. Lett.* **2019**, *10*, 1016.

- Et pourquoi pas le Chlore ?
  > Un élément utile en chimie médicinale







> «Magic Chloro»: profound effects of the Cl atom in drug discovery *J. Med. Chem.* **2023**, *66*, 5305.

- Et pourquoi pas le Chlore ?
  > Un élément utile en chimie médicinale

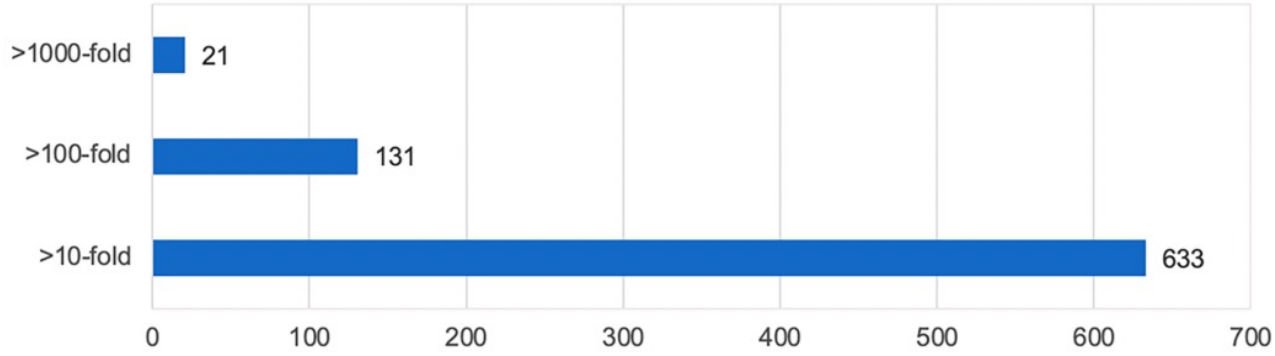
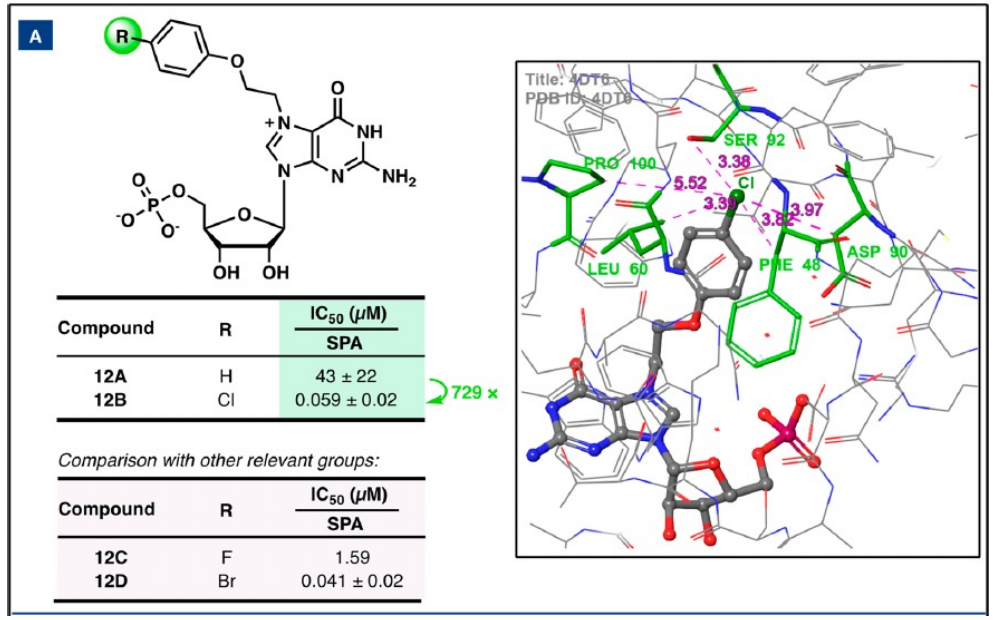


Figure 2. Number of articles in the years 2010–2022 showing a potency improvement of >10-fold, >100-fold, and >1000-fold when a molecule of interest underwent one or two H-to-Cl substitutions.



Compound	R	IC_{50} (μM) SPA
12A	H	43 ± 22
12B	Cl	0.059 ± 0.02

729 ×

Comparison with other relevant groups:

Compound	R	IC_{50} (μM) SPA
12C	F	1.59
12D	Br	0.041 ± 0.02

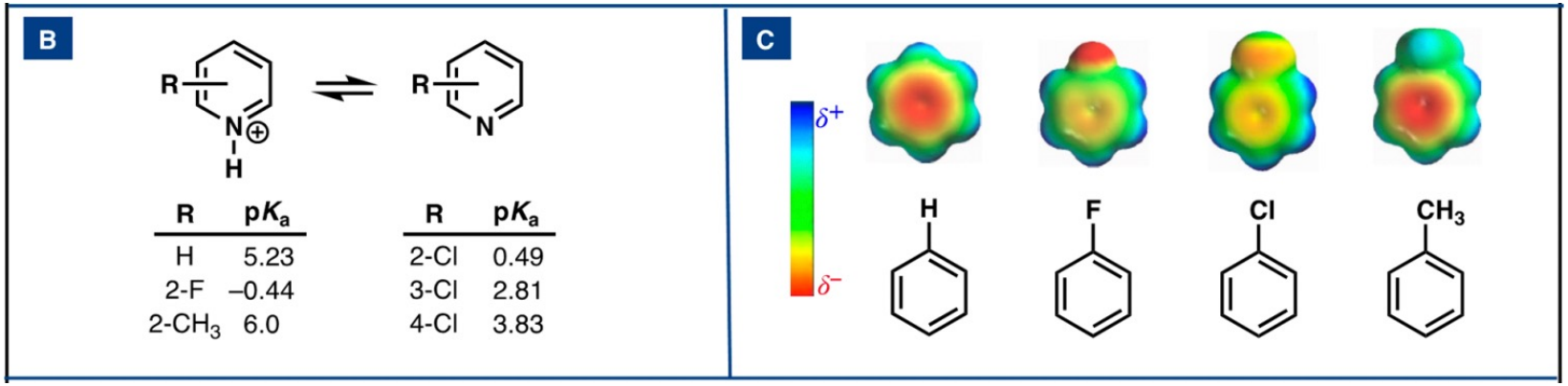
> «Magic Chloro»: profound effects of the Cl atom in drug discovery *J. Med. Chem.* **2023**, *66*, 5305.

- Et pourquoi pas le Chlore ?

Although fluorine, chlorine, and methyl substituents each have unique characteristics, The chlorine atom is able to combine the beneficial effects of a fluorine atom (e.g., electronegativity/electron-withdrawing ability, metabolic stability, increased acidity), a methyl group (e.g., lipophilicity, van der Waals interactions, steric effect)

Table 3. Substituent Constants for R = H, F, Cl, and CH_3

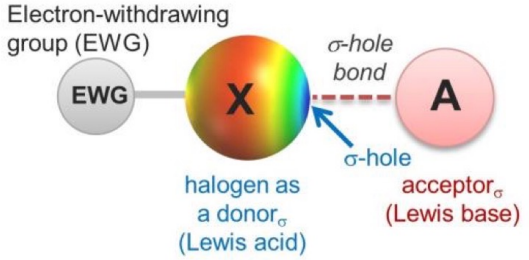
substituent	H	F	Cl	CH_3
electronegativity	2.20	3.98	3.16	2.55
Hammett σ_{meta} [34,35]	0.00	0.34	0.37	−0.07
Hammett σ_{para} [34,35]	0.00	0.06	0.23	−0.17
van der Waals radius (Å) [75,136]	1.10	1.47	1.75	2.0
steric parameters, E_S [35]	0.00	−0.46	−0.97	−1.24
molar refraction, MR [34,35]	1.03	0.92	6.03	5.65
hydrophobic parameter π [34,35]	0.00	0.14	0.71	0.56
bond length of carbon substituent bond (Å) [140]	1.09	1.35	1.77	1.54

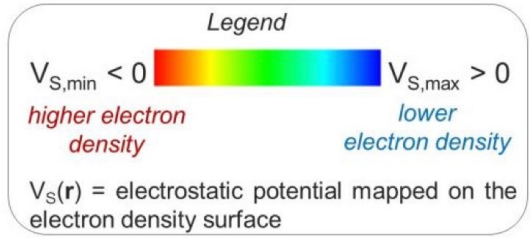


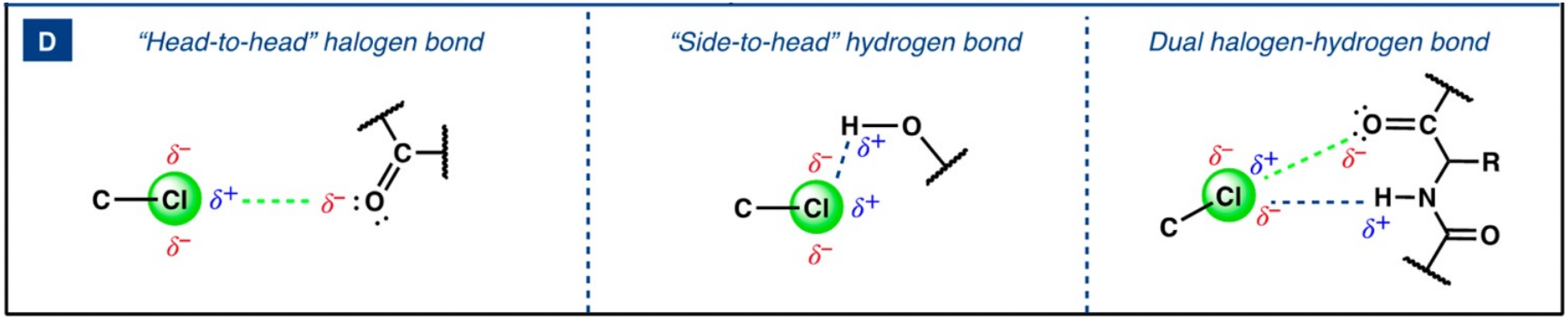
> «Magic Chloro»: profound effects of the Cl atom in drug discovery *J. Med. Chem.* **2023**, *66*, 5305.

- Et pourquoi pas le Chlore ?

Quite notably, the most unique feature of a chlorine atom is that it can engage in halogen bonding, which distinguishes it from both fluorine and a methyl group.







> «Magic Chloro»: profound effects of the Cl atom in drug discovery *J. Med. Chem.* **2023**, *66*, 5305.

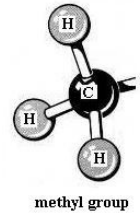
Chimie Médicinale

Introduction et principes généraux

- Introduction : le développement pharmaceutique
- Mode d'action : nature des interactions molécule-cible
- « Drug Discovery »
- « Drug Design »
- Chimie médicinale : Développements en chimie organique
  1. *Le Fluor en chimie médicinale*
  2. *Le groupement Méthyle en chimie médicinale*
  3. *Nouveaux motifs : oxétane, cyclopropane, « escape from flatland »*
- Fonctionnalisation C-H en chimie médicinale

- **Importance en chimie médicinale :**
  Le groupement METHYLE présent dans plus de 75% des principes actifs

Lipophilie
Solubilité
Conformation
Interaction
Métabolisation



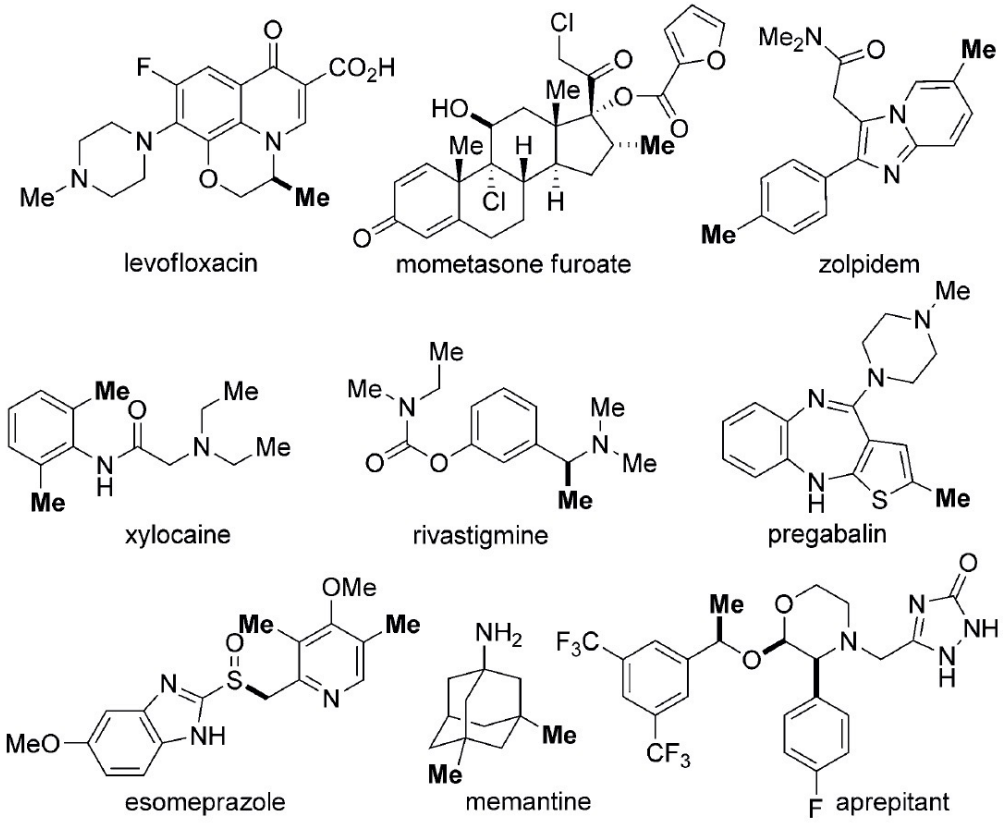
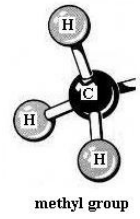


Figure 1. Small-molecule drugs containing a carbon-bound methyl group. Methyl groups that would be challenging to install without resorting to de novo synthesis are in bold.

> « The Magic Methyl Effect » *Angew. Chem. Int. Ed.* **2013**, *52*, 1225

- Propriétés pharmacocinétiques

Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



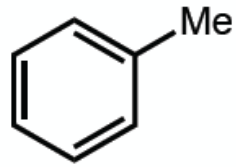
Lipophilicity

"lipid loving", hydrophobic

benzene

Log *P* = 2.13

toluene



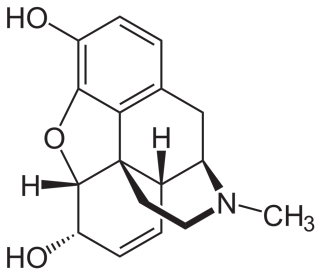
Log *P* = 2.69

Log *P* is logarithm of the partition coefficient between n-octanol and water

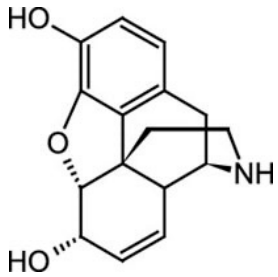
■ important for crossing biomembranes to get to target tissues and for transport through bloodstream

> « Methylation effect in medicinal chemistry » *Chem. Rev.* **2011**, *111*, 5215

• Propriétés pharmacocinétiques

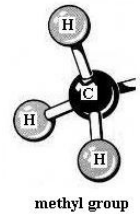


Morphine : R = Me
ED_{50} = 4.8 mg/kg

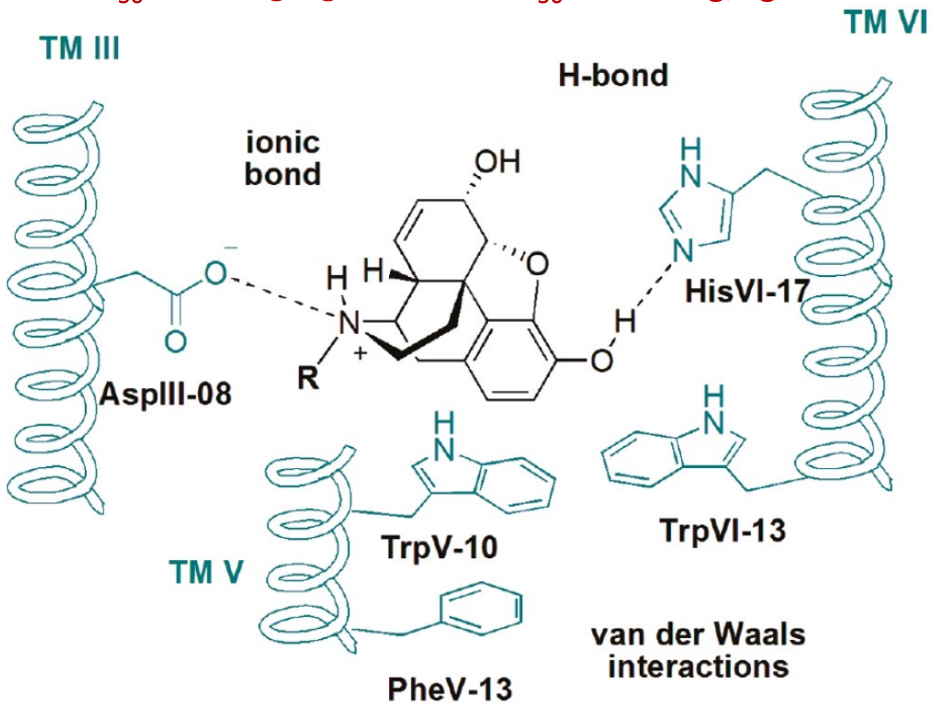


Normorphine : R = H
ED_{50} = 31.5 mg/kg

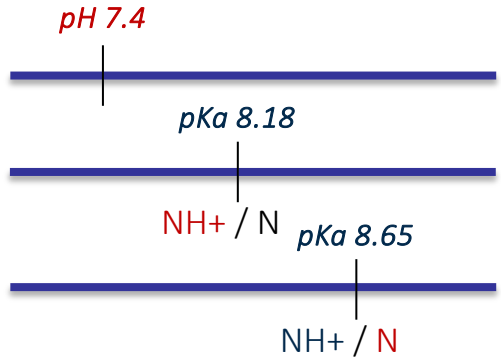
Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



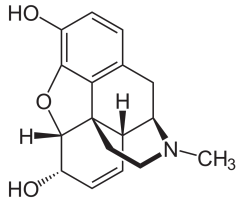
Analysis of the binding mode of morphine to opioid receptors revealed that this reduction of activity is not due to interactions with the target bioreceptor, because the main interactions with the catalytic site such as ionic ligation are maintained.

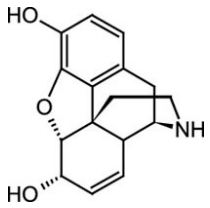


pKa morphine = 8.18 & pKa normorphine = 8.66.
The reduced activity of normorphine is due to its more polar secondary nitrogen. Consequently, normorphine has greater difficulty passing through the bloodbrain barrier, where its target receptors are located



> « Methylation effect in medicinal chemistry » *Chem. Rev.* 2011, *111*, 5215





pKa morphine = 8.18 & pKa normorphine = 8.66

When pK_a values are measured in the gas phase, where there are no hydrogen bonding effects, they are found to follow the predictions based solely on electron-donating effects. In water, mono-, di-, and

J. Am. Chem. Soc. **1971**, *93*, 3914

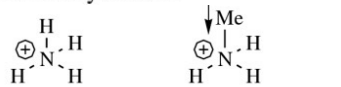
Abstract: Relative gas-phase basicities of some aliphatic amines have been determined by ion cyclotron resonance spectroscopy.

; trimethyl-

amine > dimethylamine > methylamine; triethylamine > diethylamine > ethylamine;

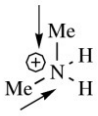
It is concluded that increasing alkyl substitution increases basicity if similar substituents are compared, that increasing alkyl group size increases basicity,

The pK_a values for the **amines** ammonia, methylamine, dimethylamine, and trimethylamine are 9.2, 10.6, 10.7, and 9.8 respectively. The electron-donating effect of the methyl substituents increases the basic strength of methylamine over ammonia by about 1.4 pK_a units, i.e. by a factor of over 25 ($10^{1.4} = 25.1$). However, the introduction of a second methyl substituent has a relatively small effect, and the introduction of a third methyl group, as in trimethylamine, actually reduces the basic strength to nearer that of methylamine.

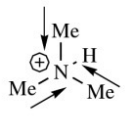


ammonium
pK_a 9.2

methylammonium
pK_a 10.6



dimethylammonium
pK_a 10.7

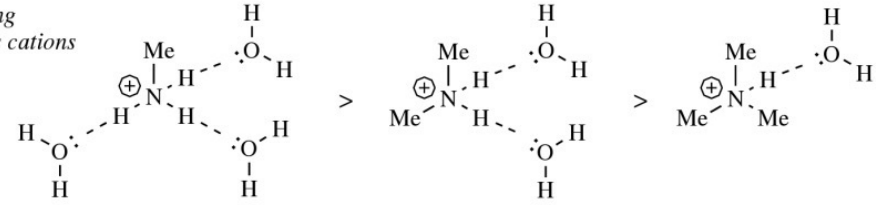


trimethylammonium
pK_a 9.8

electron-donating effects of alkyl groups stabilize positive charge

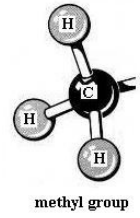
This apparent anomaly is a consequence of measuring pK_a values in aqueous solution, where there is more than ample opportunity for hydrogen bonding with water molecules. Hydrogen bonding helps to stabilize a positive charge on nitrogen, and this effect will decrease as the number of alkyl groups increases. Therefore, the observed pK_a values are a combination of increased basicity with increasing alkyl groups (as predicted via electron-donating effects) countered by a stabilization of the cation through hydrogen bonding, which decreases with increasing alkyl groups. Note that we saw solvent molecules influencing the acidity of alcohols by stabilizing the conjugate base (see Section 4.3.3).

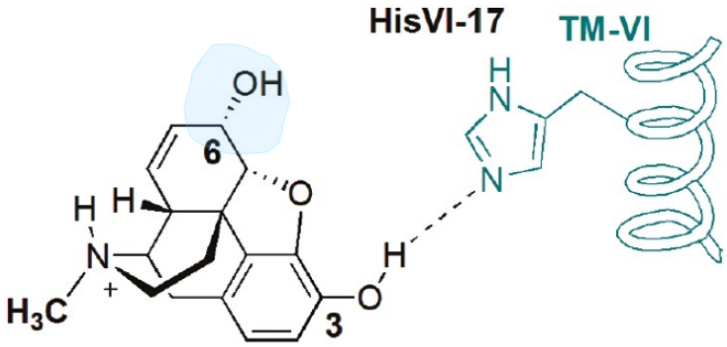
H-bonding stabilizes cations



• Propriétés pharmacocinétiques

Lipophilie
Solubilité
Interaction
Conformation
Métabolisation

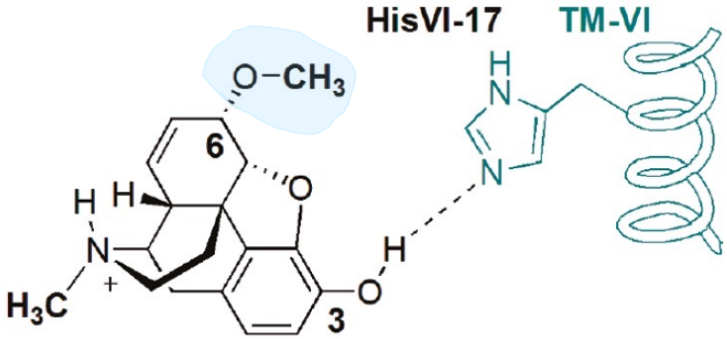




Morphine : OH
ED_{50} = 0.75 mg/kg

Heterocodeine, an O-methylated derivate at C-6, exhibits 2-fold more activity *in vivo* than morphine.
But Heterocodeine's *in vitro* potency is roughly equivalent.

O_6-methylation



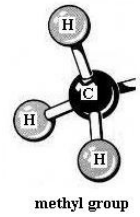
Heterocodeine : OMe
ED_{50} = 0.48 mg/kg

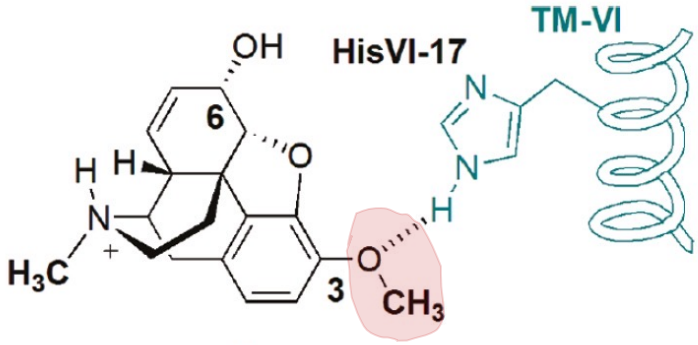
Methylation must effect its pharmacokinetic parameters, leading to increased lipophilicity and facilitating its passage into the central nervous system.

> « Methylation effect in medicinal chemistry » *Chem. Rev.* **2011**, *111*, 5215

- Propriétés pharmacocinétiques… mais aussi pharmacodynamiques

Lipophilie
Solubilité
Interaction
Conformation
Métabolisation

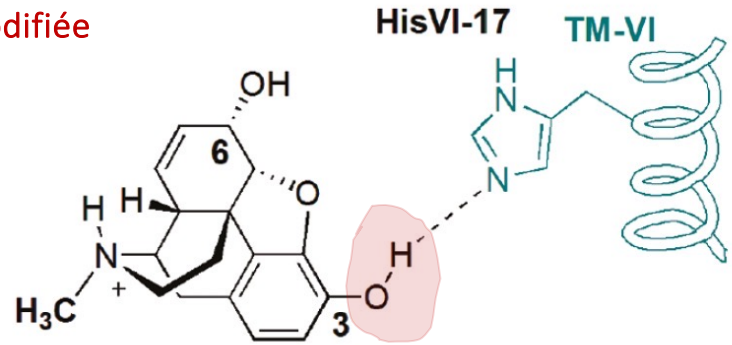




Codeine : OMe
Ki μ-receptor = 0.35 μM ED_{50} = 14.5 mg/kg

O_3-methylation

Perte d'activité d'un facteur 200
Liaison H modifiée



Morphine : OH
Ki μ-receptor = 0.0018 μM ED_{50} = 4.8 mg/kg

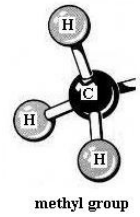
Despite being 200-fold less potent in vitro, codeine is only 3-fold less potent than morphine in vivo

Codeine can be considered as a PRODRUG of Morphine

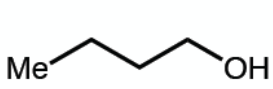
> « Methylation effect in medicinal chemistry » *Chem. Rev.* 2011, *111*, 5215

- Propriétés pharmacocinétiques… mais aussi pharmacodynamiques

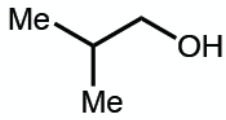
Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



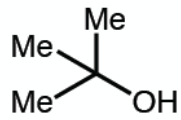
Hydrophilic Effect



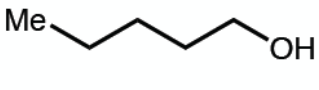
n-butanol
8.2g/100g H_2O



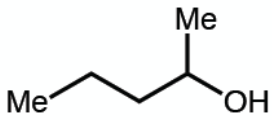
isobutanol
5g/100g H_2O



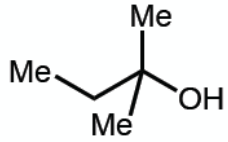
tert-butanol
miscible



n-pentanol
2.4g/100g H_2O

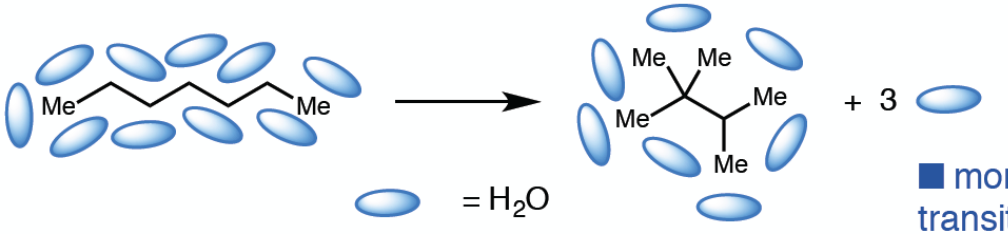


2-pentanol
4.9g/100g H_2O



neopentanol
12.2g/100g H_2O

The small improvements in binding affinity observed upon introducing a methyl group have been attributed to desolvation effects.[12] Increased methylation reduces the free energy of desolvation required to strip a ligand of solvated water molecules when it transfers from an aqueous environment to the greasy cavity of a protein (Figure 2 b).[13] In this way, methylation can energetically favor binding and lower the IC_{50} value. Estimates place the value for $\Delta\Delta G_{transfer}$ upon a proton for methyl replacement at about 0.8 kcal mol^{-1} for transfer from water to a protein.[14] This corresponds to an approximate 3.5-fold boost in potency from methylation based on $\Delta\Delta G_{transfer}$ alone. A more empirical evaluation of

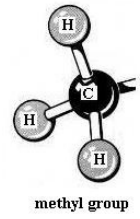


- fewer water molecules needed to be organized, entropic gain with "globular" shape
- more negative $\Delta G_{desolvation}$ when transitioning from aqueous to membrane

> « Methylation effect in medicinal chemistry » *Chem. Rev.* 2011, *111*, 5215

- Propriétés pharmacodynamiques

Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



■ The bigger picture of methylation and potency improvements

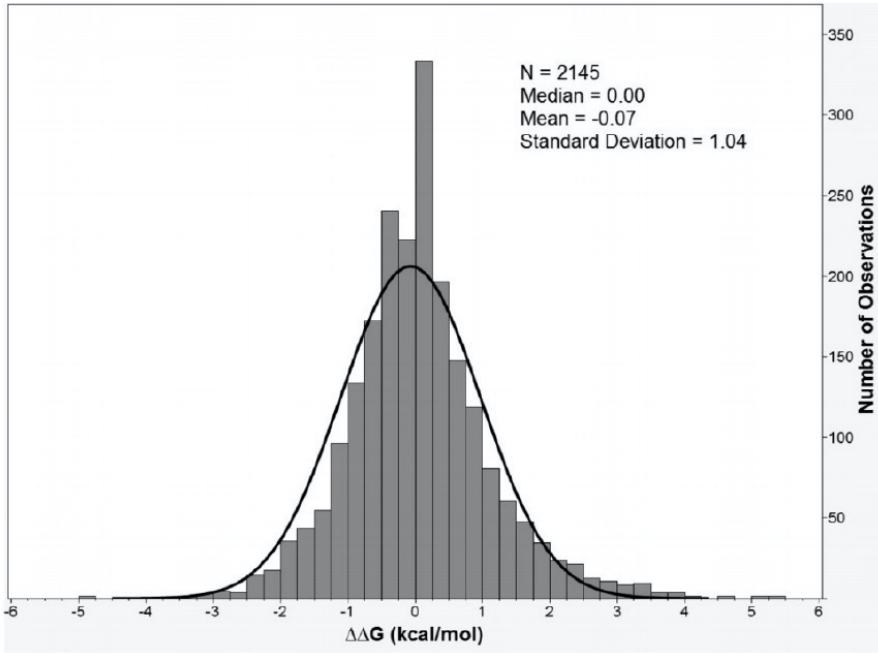


Figure 1. Distribution of free energy changes on activity for substitutions of a hydrogen atom by a methyl group in publications in the *Journal of Medicinal Chemistry* and *Bioorganic Medicinal Chemistry Letters* during 2006–2011.

■ methylation just as likely to decrease binding affinity as it is to increase

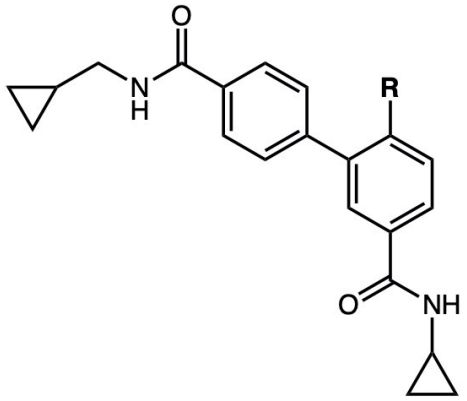
■ rare for addition of Me group to give free energy gain greater than 3 kcal/mol (4 cases, 0.0019%

■ 10 fold boost (1.36 kcal/mol) - 8%

■ 100 fold boost (2.7 kcal/mol) - 0.4%

> « Methylation effect in medicinal chemistry » *Chem. Rev.* **2011**, *111*, 5215

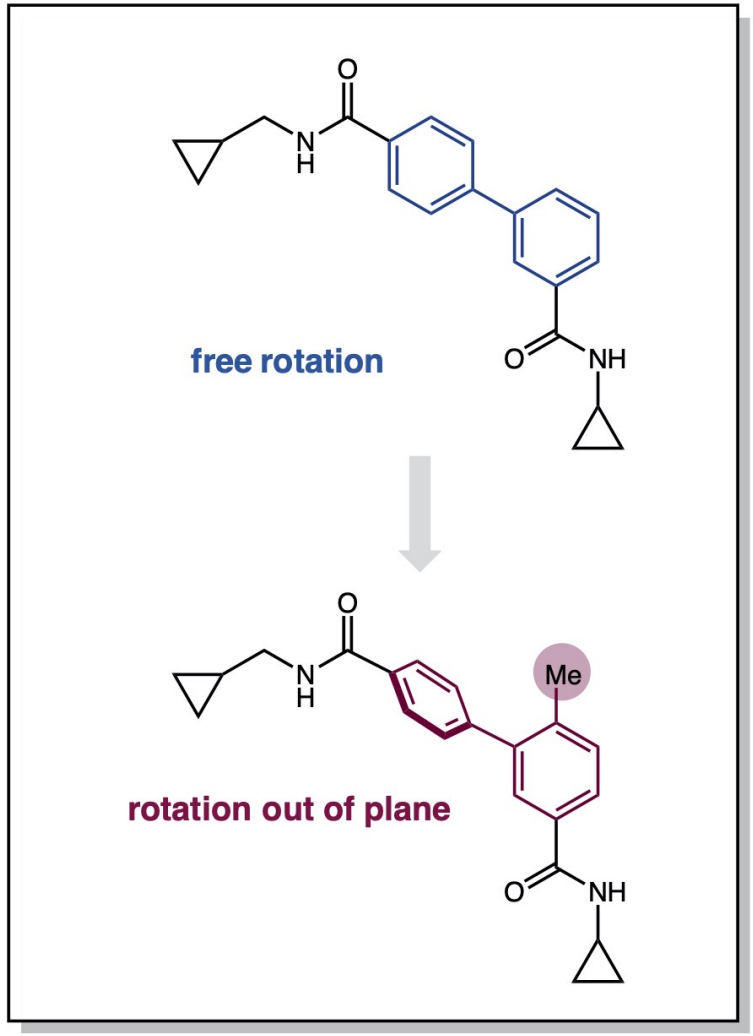
- Propriétés pharmacodynamiques



biphenyl amide inhibitors of p38α kinase

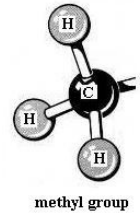
R	K_i (nM)	IC_{50}
H	>2500	>16,000
Me	12	75
Cl	25	160
F	460	2900
OMe	520	3300

(inhibitor constant, nM needed to achieve 1/2 max inhibition)



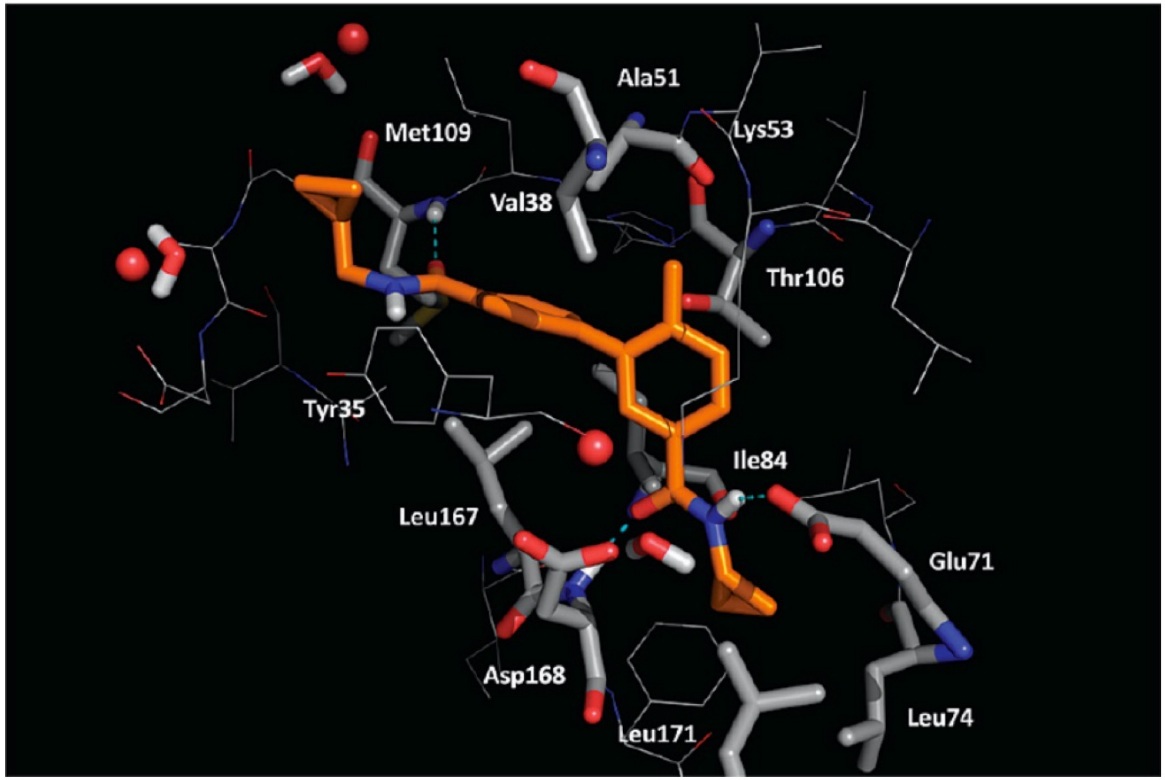
■ Conformational preorganization leads to ~200-fold boost

Lipophilie
Solubilité
Interaction
Conformation
Métabolisation

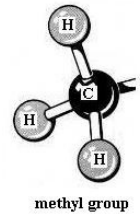


> « Methylation effect in medicinal chemistry » *Chem. Rev.* 2011, *111*, 5215

- Propriétés pharmacodynamiques
  - Conformational preorganization leads to ~200-fold boost



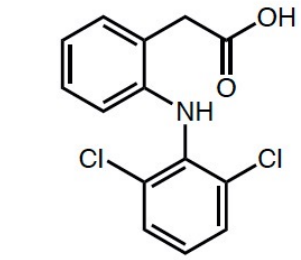
Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



- methyl in lipophilic pocket - larger groups do not fit
- several hydrophobic interactions with biphenyl
- dihedral angle of *o*-Me-biphenyl free drug matches the bound conformer best

> « Methylation effect in medicinal chemistry » *Chem. Rev.* 2011, *111*, 5215

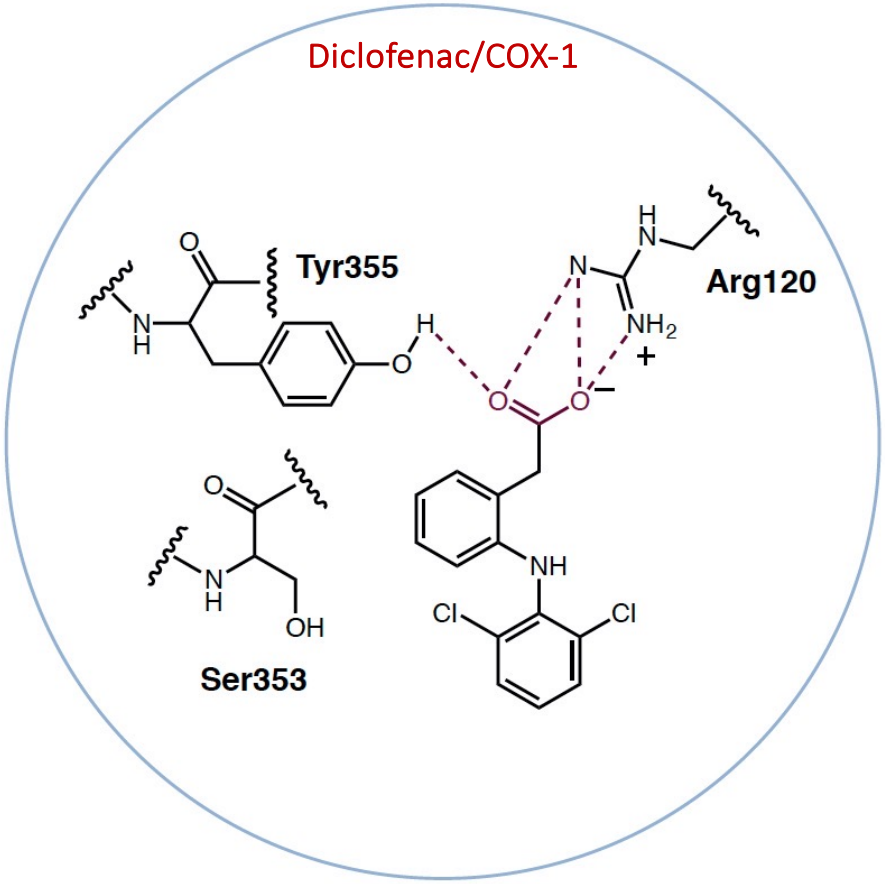
- Propriétés pharmacodynamiques : problème de sélectivité
  - Use of methyl group to decrease binding affinity



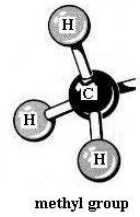
diclofenac

K_i (μM) COX-1 = 0.01
K_i (μM) COX-2 = 0.01

NSAID



Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



> « Methylation effect in medicinal chemistry » *Chem. Rev.* **2011**, *111*, 5215

- Propriétés pharmacodynamiques : problème de sélectivité
  - Use of methyl group to decrease binding affinity

Lipophilie
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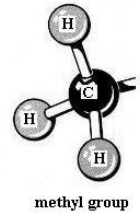
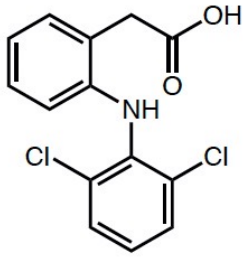
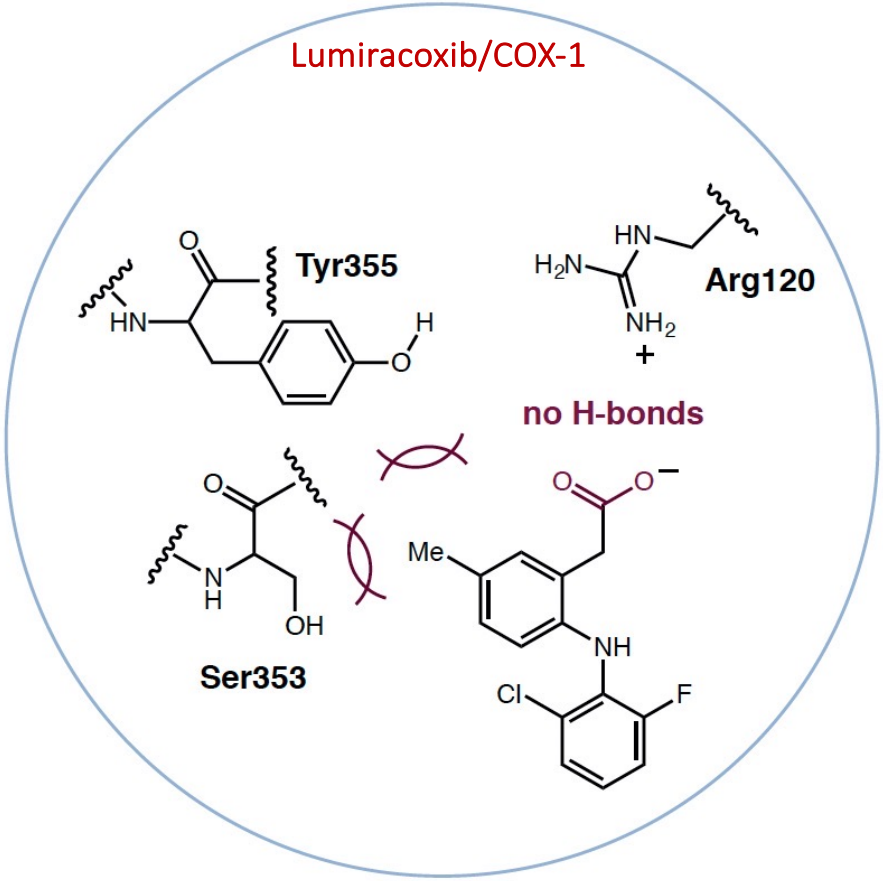


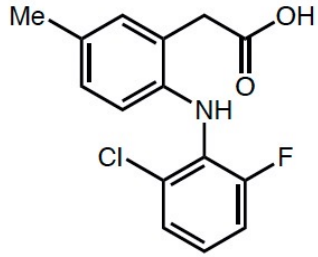


diclofenac

K_i (μM) COX-1 = 0.01
K_i (μM) COX-2 = 0.01

NSAID





lumiracoxib

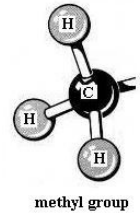
K_i (μM) COX-1 = 3.2
K_i (μM) COX-2 = 0.06

NSAID, but taken off market due to liver damage

> « Methylation effect in medicinal chemistry » *Chem. Rev.* **2011**, *111*, 5215

- Propriétés pharmacocinétiques : problème de stabilité

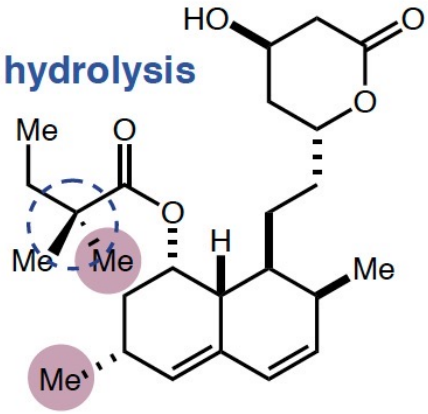
Lipophilie
Solubilité
Interaction
Conformation
Métabolisation



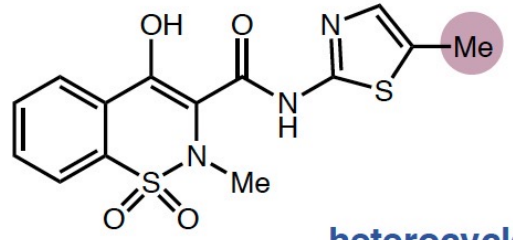
Methyl Groups as Protecting group

Protection of adjacent functional group:

prevention of hydrolysis



simvastatin



meloxicam

heterocycle susceptible to oxidation

> « Methylation effect in medicinal chemistry » *Chem. Rev.* 2011, *111*, 5215

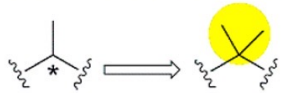
• Le groupement *gem*-diméthyle

PHARMACODYNAMICS

van der Waals contacts with a small pocket of the target protein leading to extended target engagement, and increased potency and selectivity.

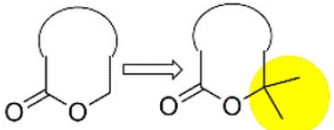
Rotational barrier imposed on nearby rotatable bonds and functional groups to enforce local restriction to an entropically favorable bioactive conformation.

STRUCTURAL ROLE



Chiral center — Chiral center abolished

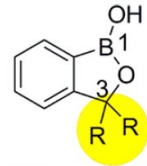
DRUG METABOLISM AND PHARMACOKINETICS



Prone to hydrolytic cleavage in plasma — Reduced rate of hydrolytic cleavage in plasma

Metabolic oxidation of the methylene is blocked. Also the sterically hindered *tert*-alcohol less susceptible to undergo Phase II conjugation reactions.

To modulate the pK_a of a nearby ionizable functional group



199 and **200**

Compd	R	aqueous pK_a
199	H	7.3
200	CH_3	8.3

> « The *gem*-Dimethyl group in medicinal chemistry » *J. Med. Chem.* **2018**, *61*, 2166

• Le groupement *gem*-diméthyle

APPLICATION OF THE THORPE-INGOLD EFFECT TO THE DESIGN OF PRODRUGS

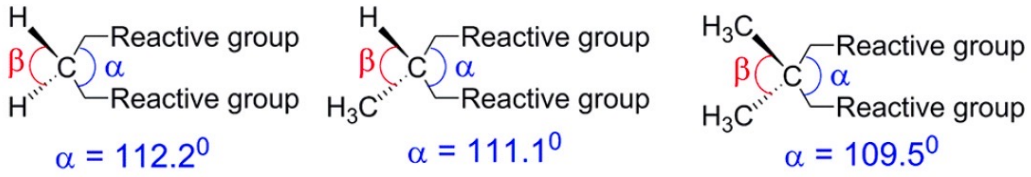
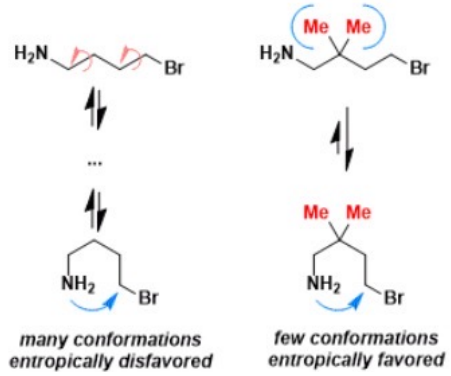
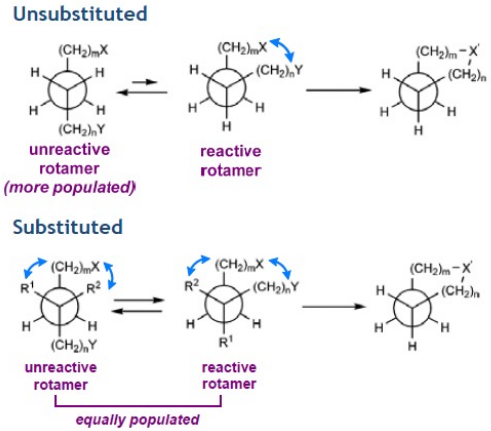
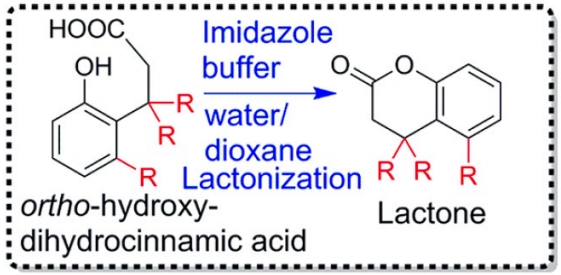
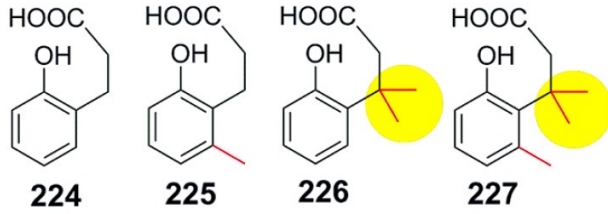


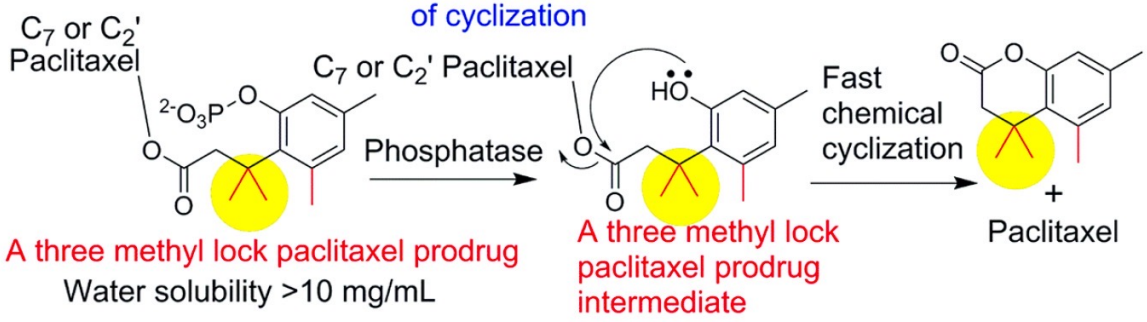
Figure 69. Thorpe–Ingold conformational effect by a *gem*-dimethyl substituent at the noncyclic methylene group.











> « The *gem*-Dimethyl group in medicinal chemistry » *J. Med. Chem.* **2018,** *61,* 2166

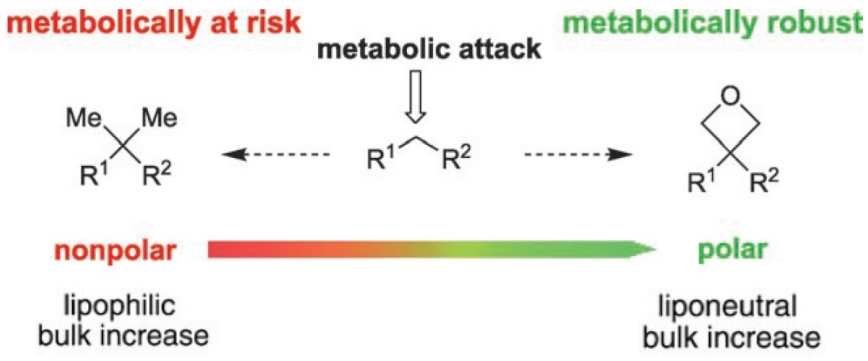
Chimie Médicinale

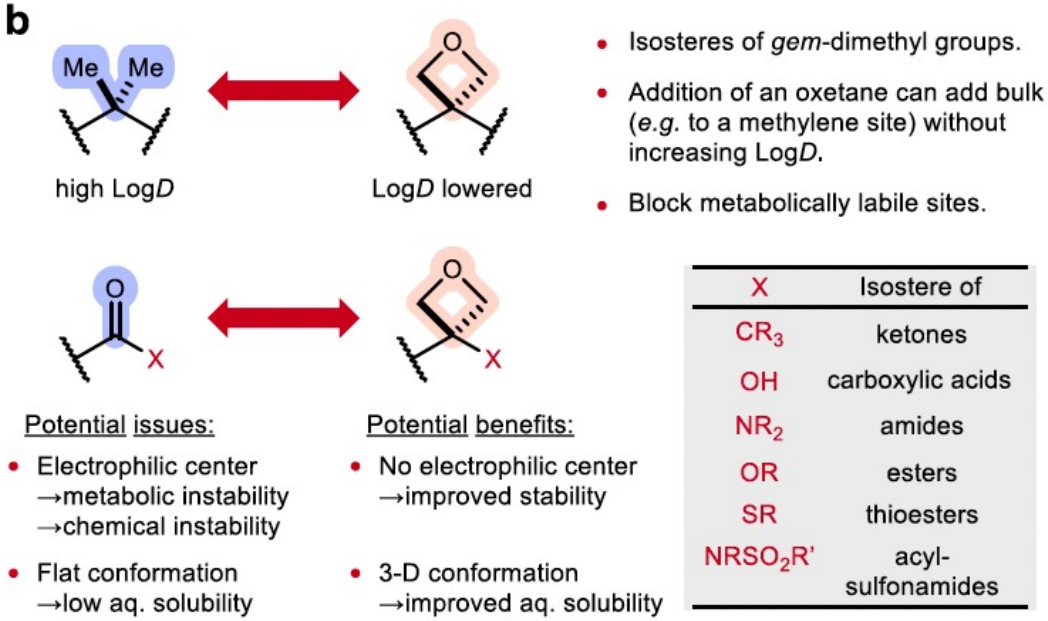
Introduction et principes généraux

- Le développement pharmaceutique
- Mode d'action : nature des interactions molécule active-cible biologique
- Chimie médicinale : « Drug Discovery »
- Chimie médicinale : « Drug Design »
- Chimie médicinale : Développements en chimie organique
  1. *Le Fluor en chimie médicinale*
  2. *Le groupement Méthyle en chimie médicinale*
  3. *Nouveaux motifs : oxétane, cyclopropane, « escape from flatland »*

- Agents anticancéreux : Mécanisme d'action-Etudes de cas

- Le motif *Oxetane* en chimie médicinale



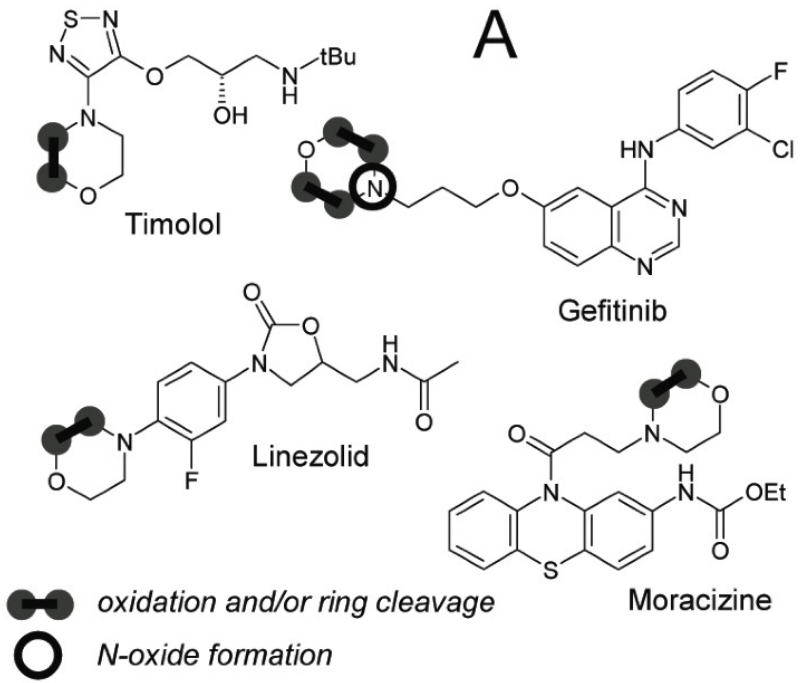


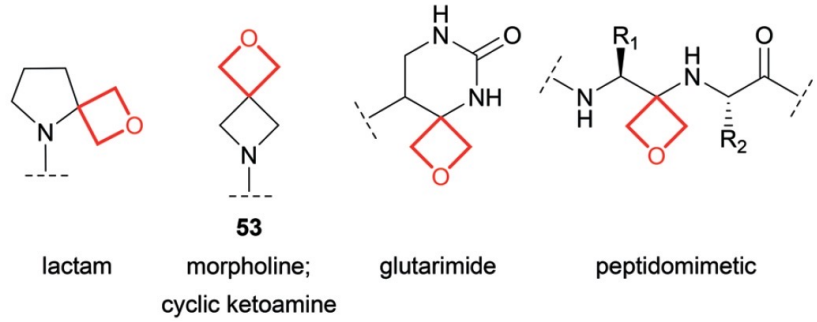
- Isosteres of *gem*-dimethyl groups.
- Addition of an oxetane can add bulk (*e.g.* to a methylene site) without increasing Log*D*.
- Block metabolically labile sites.

Potential issues:
- Electrophilic center →metabolic instability →chemical instability
- Flat conformation →low aq. solubility

Potential benefits:
- No electrophilic center →improved stability
- 3-D conformation →improved aq. solubility

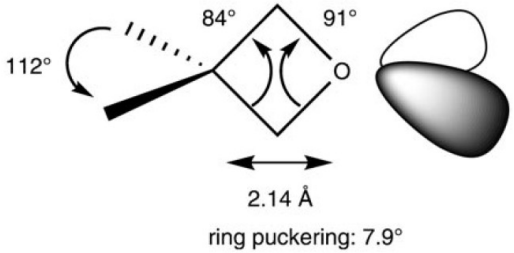
X	Isostere of
CR_3	ketones
OH	carboxylic acids
NR_2	amides
OR	esters
SR	thioesters
$NRSO_2R'$	acyl-sulfonamides

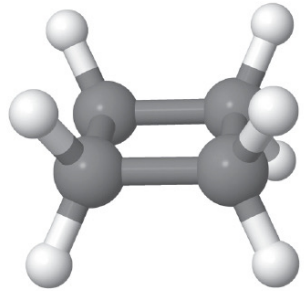




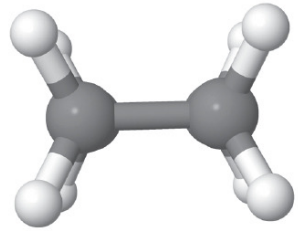
> E.M. Carreira *et al.* « Oxetanes as versatile elements in drug discovery and synthesis » *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

- Le motif *Oxetane* en chimie médicinale
  - La question de la conformation



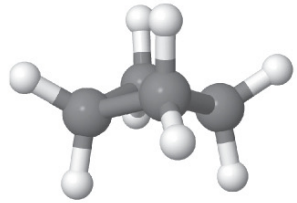


view along C–C

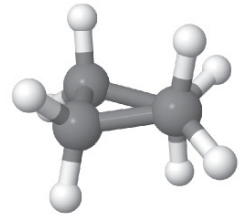


planar cyclobutane (not the real conformation)

side-on view of planar cyclobutane shows eclipsing C–H bonds



view along C–C



the puckered 'wing' conformation of cyclobutane

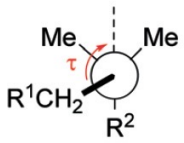
C–H bonds no longer fully eclipsed

> E.M. Carreira *et al.* « Oxetanes as versatile elements in drug discovery and synthesis » *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

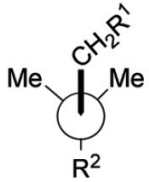
• Le motif *Oxetane* en chimie médicinale

• Propriétés pharmacodynamiques

• Préférence conformationnelle

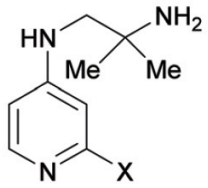


τ = ±120 ±30°



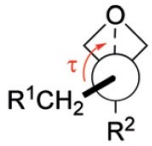
τ = 0 ±30°

gauche and antiperiplanar conformations equally likely



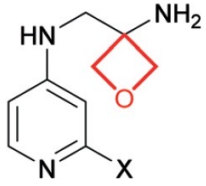
51

RSVF EC_{50} = 12 nM



τ = ±120 ±30°

gauche conformation preferred



52

RSVF EC_{50} = 2 nM

Conformation gauche reconnue préférentiellement par la cible biologique

• Liaison Hydrogène

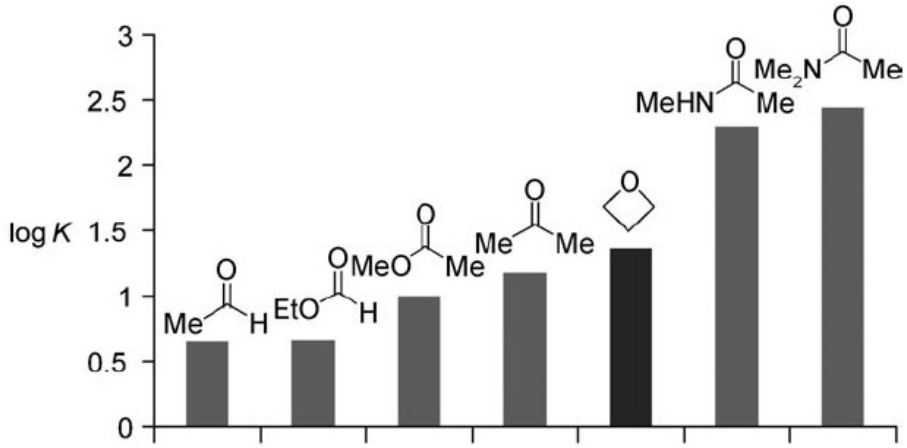
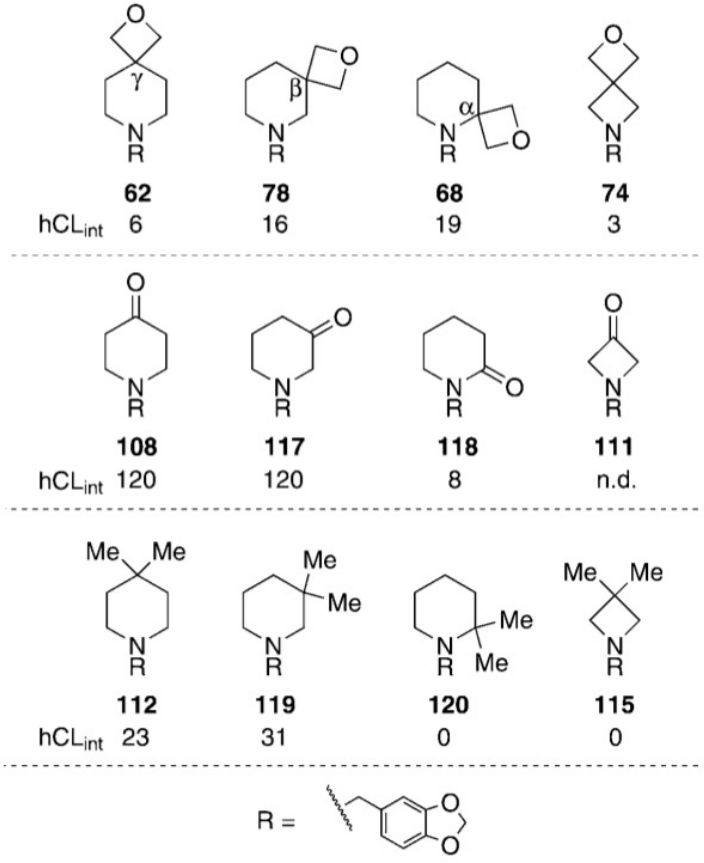


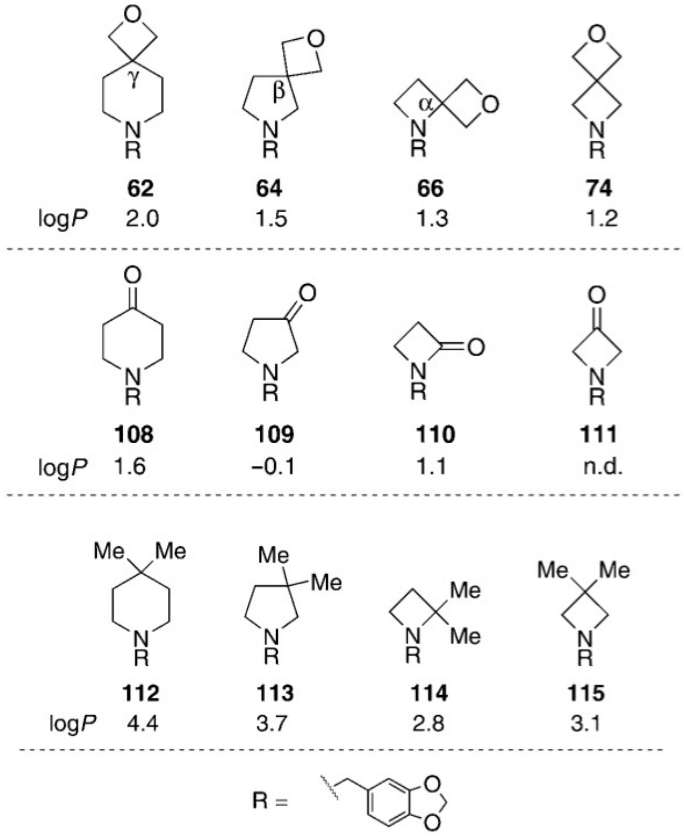
Figure 5. Affinity of oxetane and different carbonyl compounds to act as acceptors for hydrogen bonds.

> E.M. Carreira *et al.* « Oxetanes as versatile elements in drug discovery and synthesis » *Angew. Chem. Int. Ed.* **2010,** *49*, 9052-9067.

- Le motif *Oxetane* en chimie médicinale
  - Propriétés pharmacocinétiques
    - Influence sur la stabilité métabolique



    - Influence sur la lipophilie

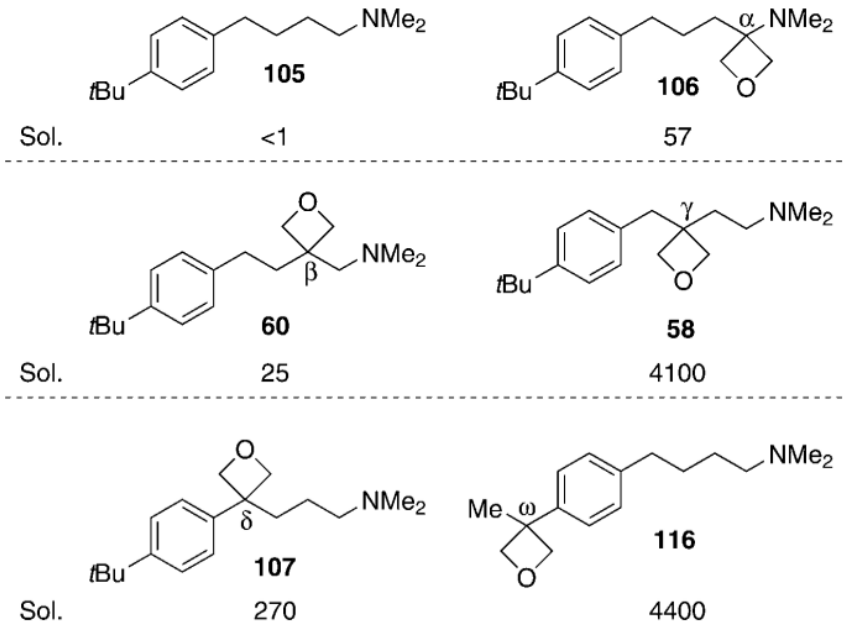


> E.M. Carreira *et al.* « Oxetanes as versatile elements in drug discovery and synthesis » *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

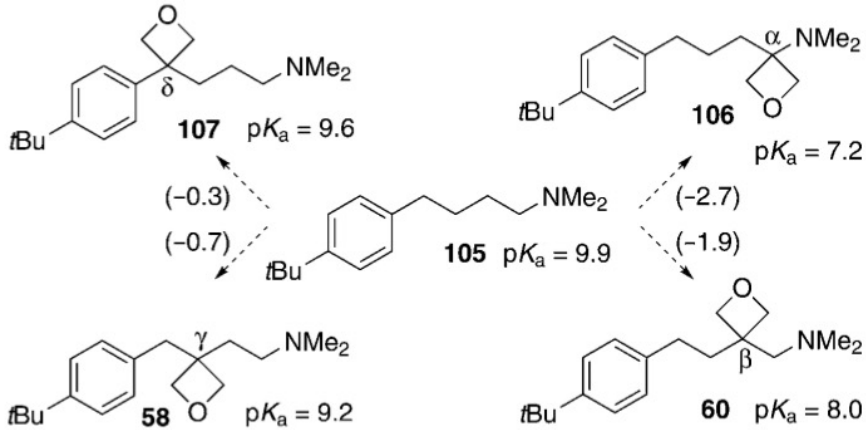
• Le motif *Oxetane* en chimie médicinale

• Propriétés pharmacocinétiques

• Influence sur la solubilité

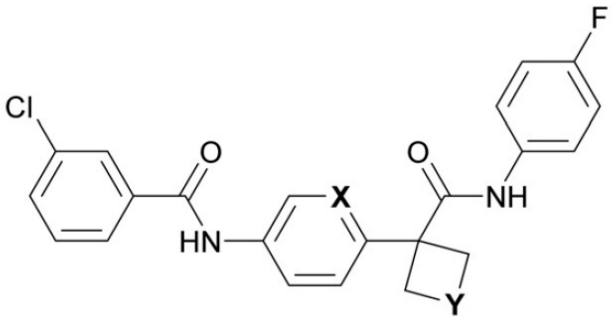


• Influence sur le pK_a

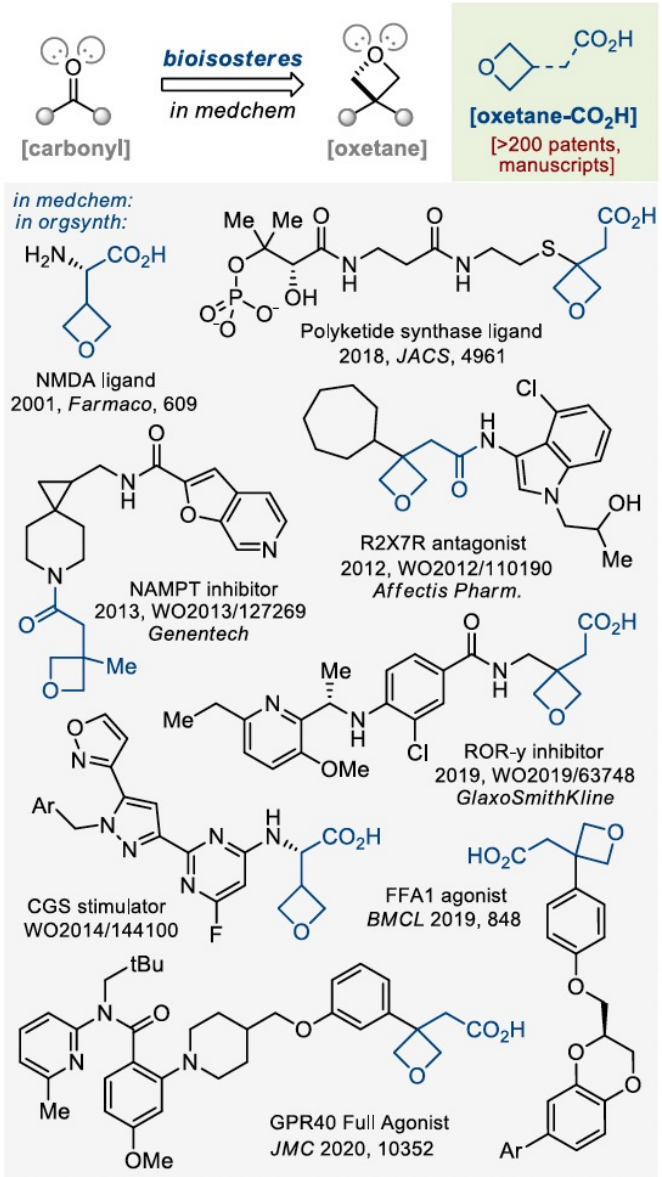


> E.M. Carreira *et al.* « Oxetanes as versatile elements in drug discovery and synthesis » *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

- Le motif *Oxetane* en chimie médicinale
  - Propriétés pharmacocinétiques



Cmpd	X	Y	LogP[a]	Solubility[b] (µM)	Hep $Cl_{int,u}$ human/rat (mL/min/kg)
36	C	CH_2	5.3	2	2000/2000
37	C	O	3.8	76	420/250
38	N	O	3.1	170	<44/<84

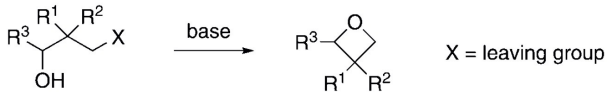


> E.M. Carreira *et al.* « Oxetanes as versatile elements in drug discovery and synthesis » *Angew. Chem. Int. Ed.* **2010**, *49*, 9052-9067.

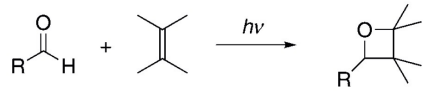
• Le motif *Oxetane* en chimie médicinale

• Synthèses

a) Williamson ether synthesis



b) Paternò-Büchi reaction



Scheme 1. Fundamental synthetic pathways towards oxetanes.

The mechanism of the *Paterno-Büchi reaction* has been extensively studied. The current understanding of the process involves the following steps: 1) the carbonyl functionality (S_0) is excited by a UV photon *via* n *-absorption to afford the corresponding singlet state (S_1); 2) the carbonyl singlet state can be converted to the carbonyl triplet state (T_1) *via* intersystem crossing (ISC); 3) when the carbonyl singlet reacts with the alkene (mostly in the case of aliphatic aldehydes and ketones and a very high alkene concentration is required in order to quench the singlet state efficiently) the photocycloaddition is stereospecific and the stereochemical information of the alkene substrate is translated into the oxetane product; 4) in the overwhelming majority of the *Paterno-Büchi reactions*, however, the intersystem crossing gives rise to the carbonyl triplet state, which upon addition to the alkene affords a 1,4-biradical (these species have been studied spectroscopically);[33] and 5) finally the most stable 1,4-biradical conformer collapses to the oxetane product.

Start here:

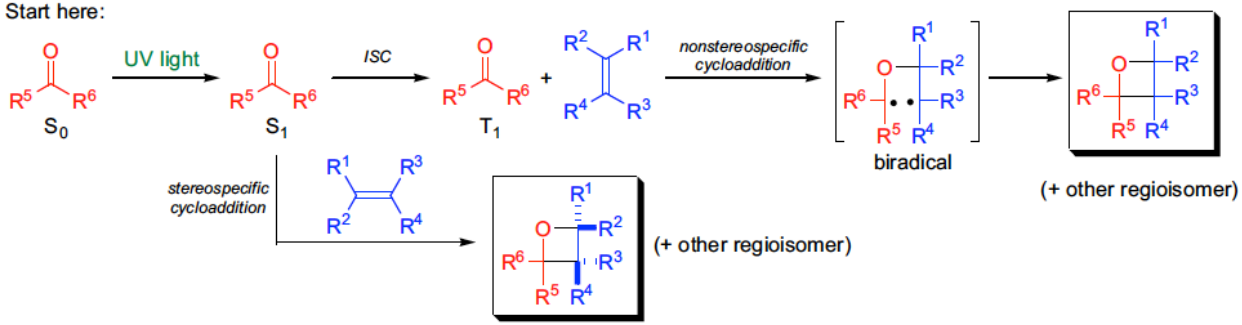
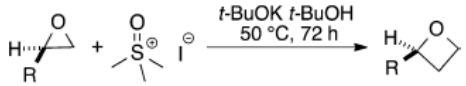


Table 3. Expanded Scope of Oxetanes Accessed through Epoxide Ring Opening with Trimethyloxosulfonium Ylide



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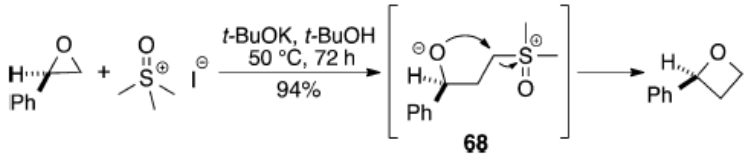
entry		yield (%)
1	$CH_2OCH(CH_3)OC_2H_5$	70
2	$CH_2OCH_2CH{=}CH_2$	65
3	$CH_2OC_6H_5$	83
4	$CH_2CH_2CH{=}CH_2$	56
5	$CH(OC_2H_5)_2$	59

Mécanisme ?

COREY-CHAYKOVSKY EPOXIDATION

Scheme 19. Oxetane Formation through Epoxide Opening with Trimethyloxosulfonium Ylide



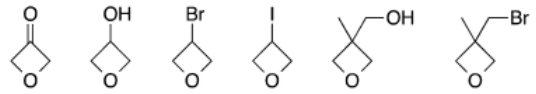
68

> J. A. Bull *et al.* « Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry » *Chem. Rev.* **2016**, *116*, 12150-12233.

• Le motif *Oxetane* en chimie médicinale

• Synthèses

Readily available, inexpensive oxetane building blocks



Less available and costly

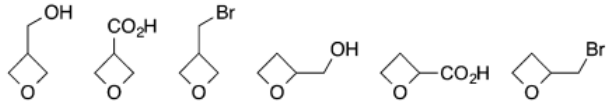
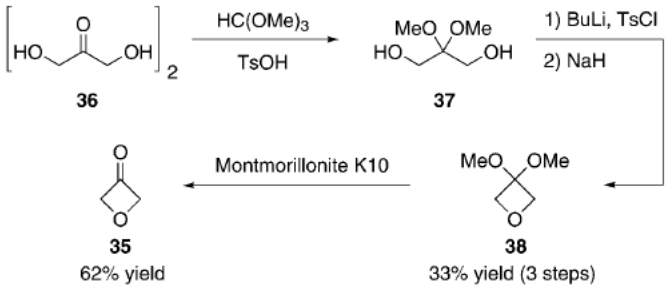
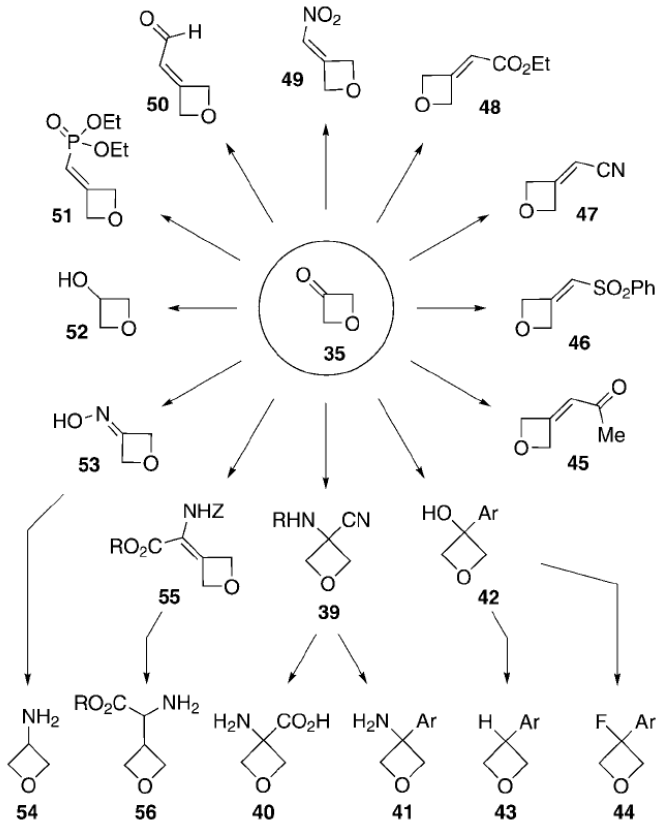


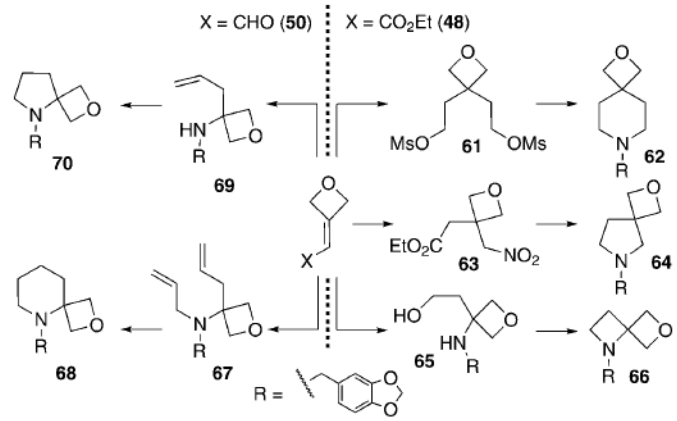
Figure 15. Some commercially available oxetane-containing building blocks.



Scheme 7. Synthesis of oxetan-3-one.

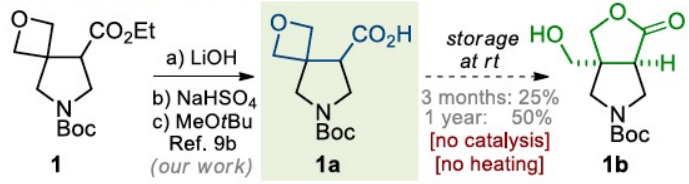


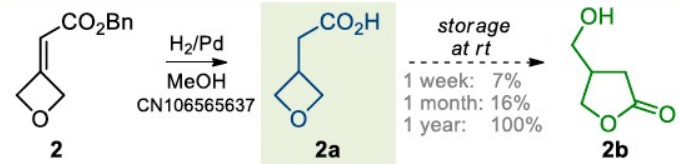
Scheme 8. Reactions of oxetan-3-one in the literature.[47b,48] Z = benzyloxycarbonyl.



Scheme 10. Synthesis of spirocyclic oxetanes starting from Michael acceptors **48** and **50**. Ms = methanesulfonyl.

Unexpected observations:





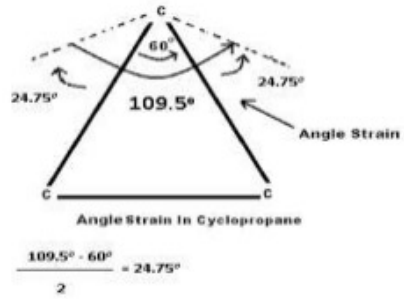
> J. A. Bull *et al.* « Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry » *Chem. Rev.* **2016**, *116*, 12150-12233.

- Le motif *Cyclopropane* en chimie médicinale
  - *Théorie de BAEYER sur la TENSION DE CYCLE*

$$\text{Total Strain Energy} = \left(\left[\text{Sample } \Delta H_{comb} \text{ per } -CH_2- \right] - \left[\text{Reference } \Delta H_{comb} \text{ per } -CH_2- \right] \right) \bullet n$$

Baeyer Strain for selected ring sizes

size of ring	Ht of Combustion (kcal/mol)	Total Strain (kcal/mol)	Strain per CH_2 (kcal.mol)	"angle strain" deviation from 109°28'
3	499.8	27.5	9.17	24°44'
4	656.1	26.3	6.58	9°44'
5	793.5	6.2	1.24	0°44'
6	944.8	0.1	0.02	-5°16'
7	1108.3	6.2	0.89	
8	1269.2	9.7	1.21	
9	1429.6	12.6	1.40	
10	1586.8	12.4	1.24	
11	1743.1	11.3	1.02	
12	1893.4	4.1	0.34	
13	2051.9	5.2	0.40	
14	2206.1	1.9	0.14	
15	2363.5	1.9	0.13	



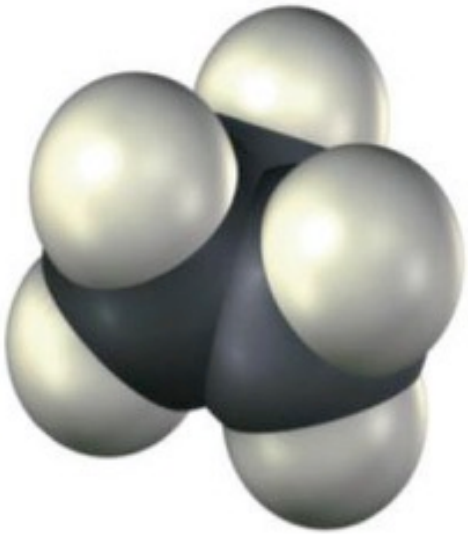
Distortion or strain = ½ ($109^0 28'$ – bond angle of ring).

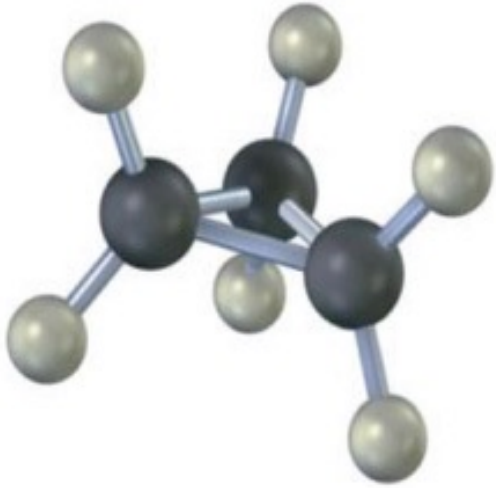
Heat of combustion for open chain alkanes: 157.4 kcal/CH_2

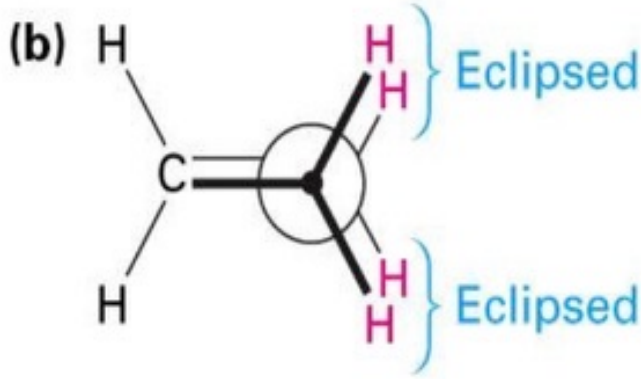
> « The Cyclopropyl fragment » *J. Med. Chem.* 2016, *59*, 8712-8756.

- Le motif *Cyclopropane* en chimie médicinale

  - *Attention: la tension de cycle est aussi le résultat de la conformation éclipsée*

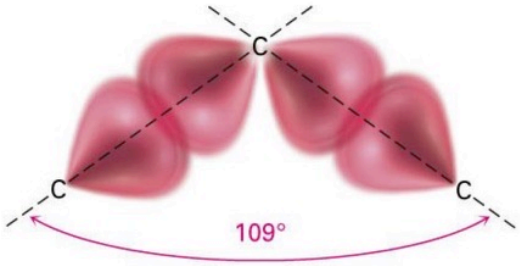




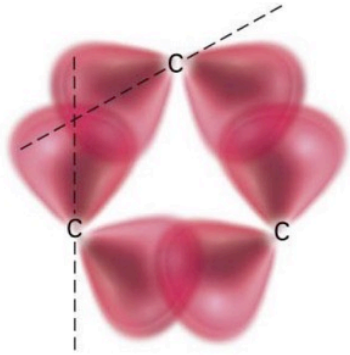


> « The Cyclopropyl fragment » *J. Med. Chem.* **2016**, *59*, 8712-8756.

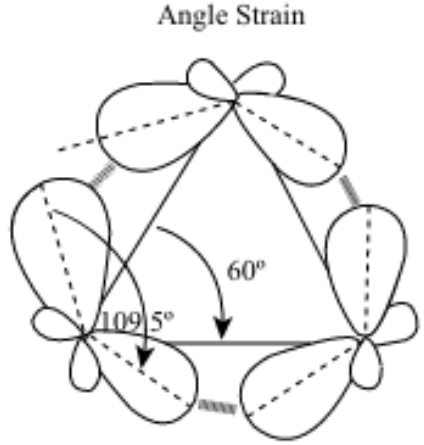
- Le motif *Cyclopropane* en chimie médicinale
  - *Considérations orbitalaires*

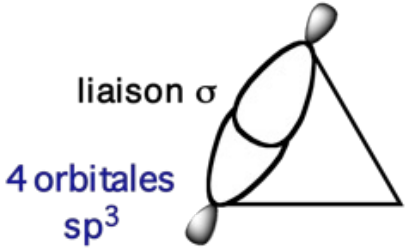


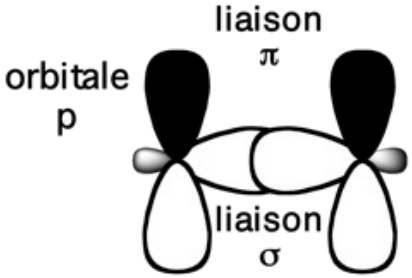
Typical alkane C–C bonds



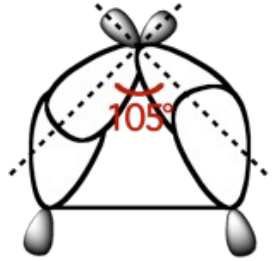
Typical bent cyclopropane C–C bonds







Augmentation du caractère p de la liaison σ



2 orbitales C-C
$sp^{3,7}$
2 orbitales C-H
$sp^{2,3}$

Liaison C-C : caractère « p » plus élevé
Analogie avec double liaison

Liaisons C-H : caractère « s » exacerbé
Donc plus courte et forte
106 kcal/mol
(éthane : 101 kcal/mol)

Que peut-on déduire pour le pKa ?

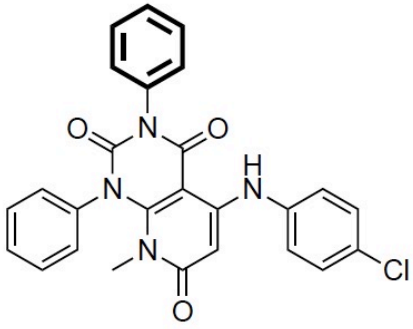
> « The Cyclopropyl fragment » *J. Med. Chem.* 2016, *59*, 8712-8756.

- Le motif *Cyclopropane* en chimie médicinale
  - Isostérie et lipophilie

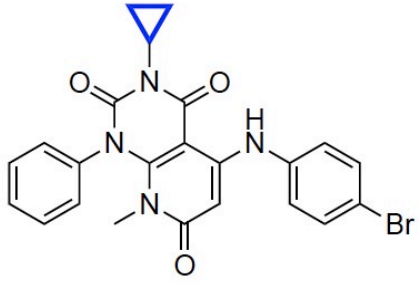
Lipophilie

Iso-propyl	clogP ~ 1.5
Phenyl	clogP ~ 2.0
Cyclopropyl	clogP ~ 1.2

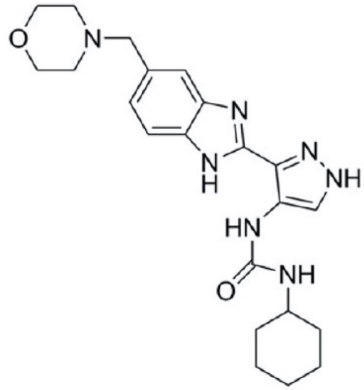
Conformation plane du cyclopropane
> isostère d'un phényle ou C=C



clogP = 6.3
IC_{50} (ACHN) = 4800 (68)
IC_{50} (HT-29) = 990 (39)

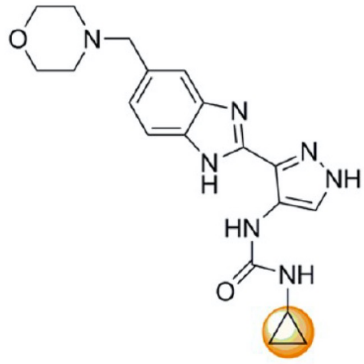


clogP = 5.0
IC_{50} (ACHN) = 1270 (5)
IC_{50} (HT-29) = 100 (2)



17

Aurora A IC_{50} = 5.7 nM,
Aurora B IC_{50} = 5.2 nM,
Cell-based activity:
HCT116 polyploidy inhibition at 0.1 μM,
Ligand Efficiency = 0.36,
clogP = 3.9

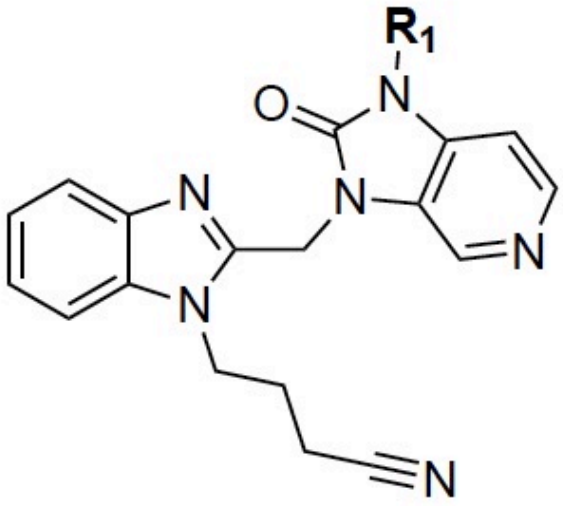


18 (AT9283)

Aurora A IC_{50} ~ 3 nM,
Aurora B IC_{50} <3 nM,
Cell-based activity:
HCT116 polyploidy inhibition at 0.03 μM, Ligand Efficiency = 0.42,
clogP = 2.2

> « The Cyclopropyl fragment » *J. Med. Chem.* 2016, *59*, 8712-8756.

- Le motif *Cyclopropane* en chimie médicinale
  - stabilité métabolique



Metabolic stability

R_1	HLM $t_{1/2}$ (min)	EC_{50} (HEp-2) (μM)	clogP
i-Pr	7.4	0.004	2.21
t-Bu	4.0	0.003	2.61
***c*-Pr**	**39**	**0.010**	**1.72**
c-Bu	4.6	0.016	2.28

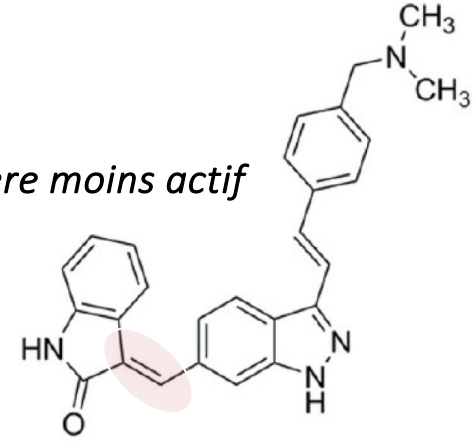
Liaisons C-H : caractère « s » exacerbé
Donc plus courte et forte
106 kcal/mol
(éthane : 101 kcal/mol)

> « The Cyclopropyl fragment » *J. Med. Chem.* **2016**, *59*, 8712-8756.

- Le motif *Cyclopropane* en chimie médicinale
  - Stabilité conformationnelle et solubilité

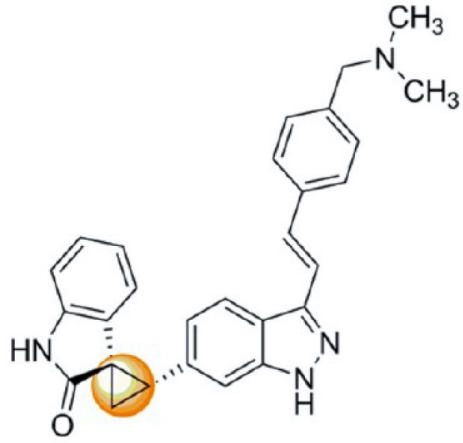
Isostère double liaison > bloque l'isomérisation possible

Isomérisation E > Z : isomère moins actif



8

PLK4, IC_{50} = 4 nM



9

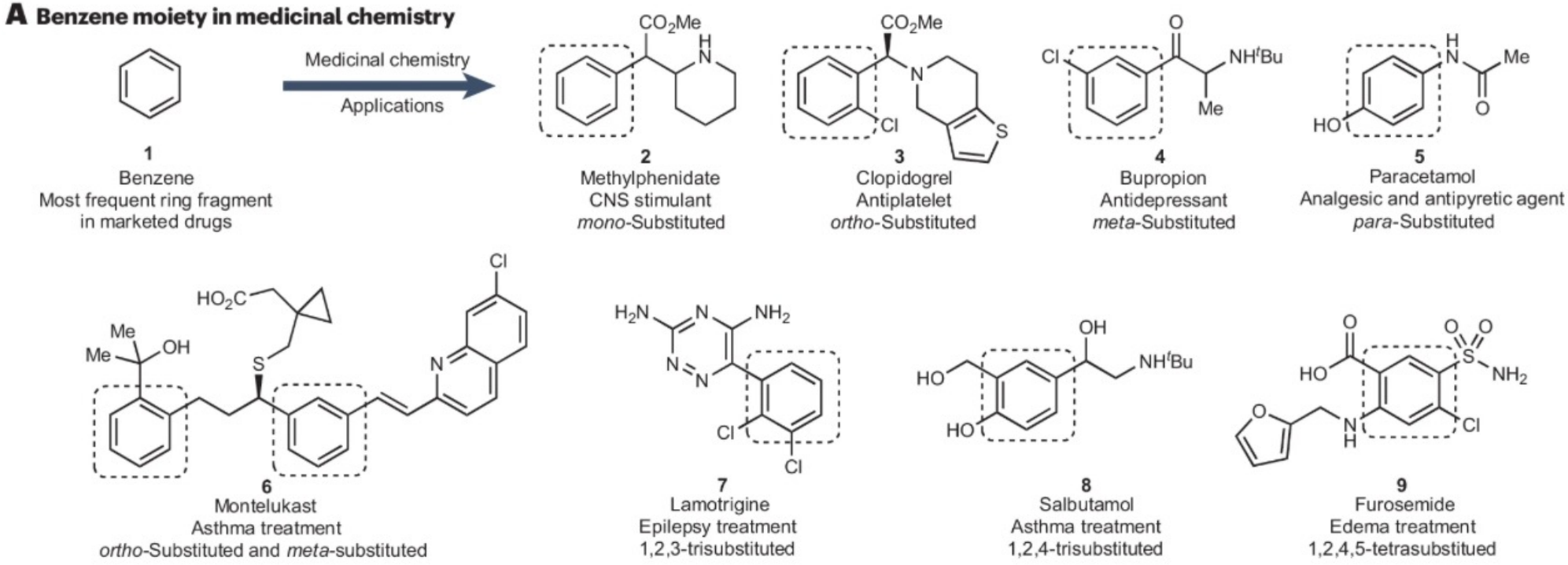
PLK4 IC_{50} = 1.8 nM

Cyclopropane / alcène :
augmentation du caractère sp^3
> Hausse solubilité aqueuse

> « The Cyclopropyl fragment » *J. Med. Chem.* **2016**, *59*, 8712-8756.

- Escape from flatland

The phenyl ring appears in approximatively 45% of marketed small-molecule drugs



> « Saturated bioisosteres of benzene: where to go next?» *Org. Biomol. Chem.* **2019**, *17*, 2839

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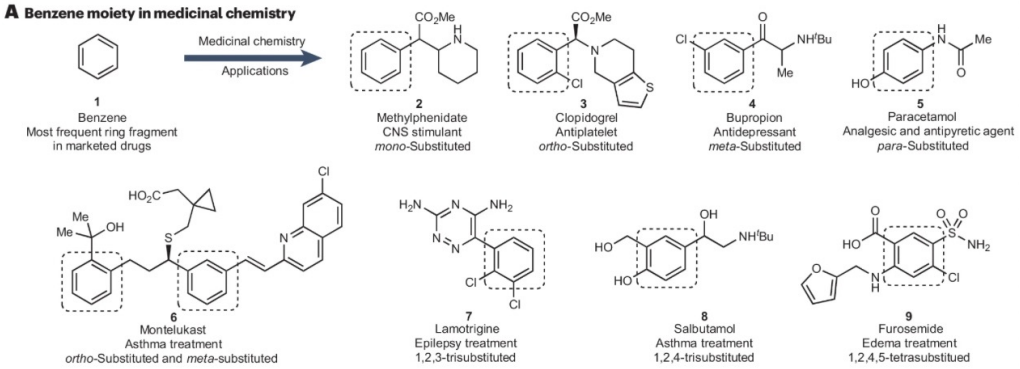
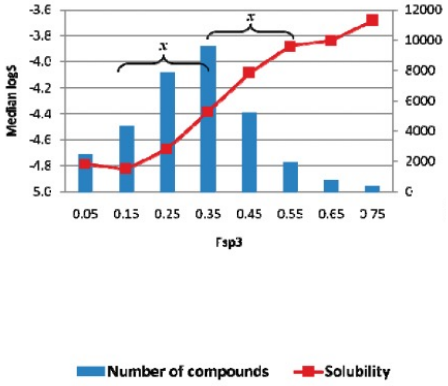
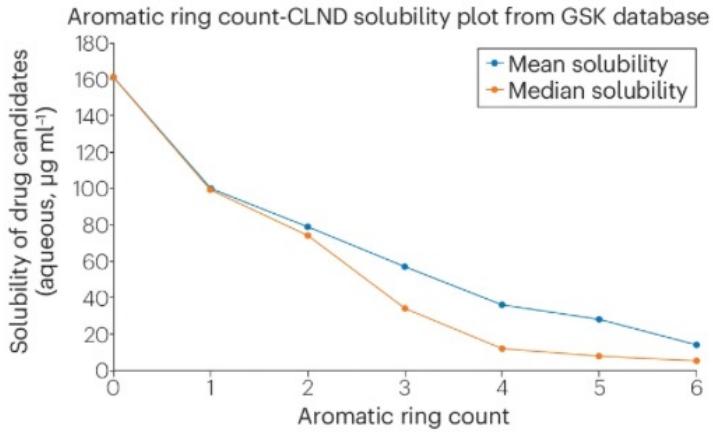


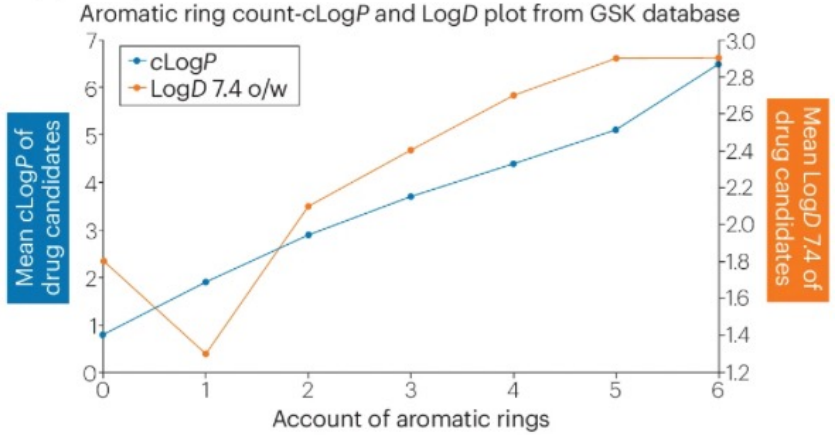


B Problems with aromatic structures in drug candidates

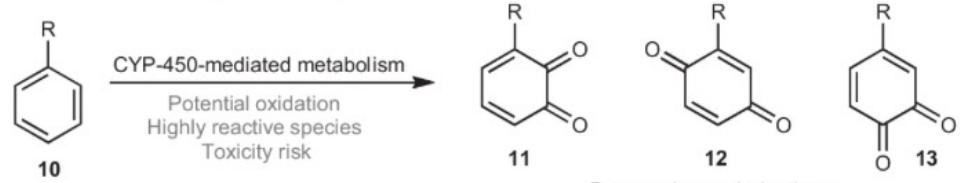
Ba Solubility concern:

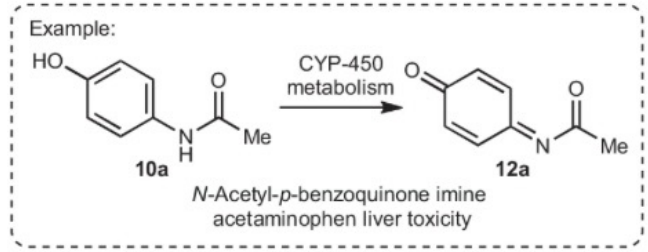


Bb Lipophicility concern:



Bc Metabolic stability and safety concern:





> « Saturated bioisosteres of benzene: where to go next?» *Org. Biomol. Chem.* 2019, *17*, 2839

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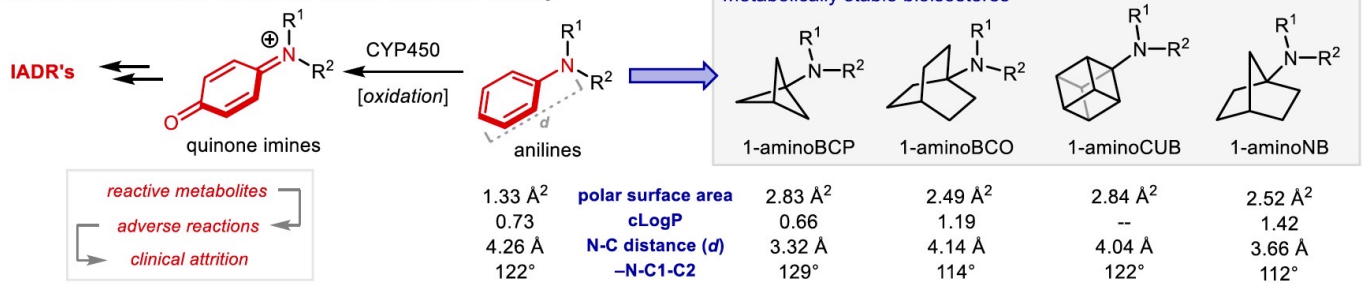
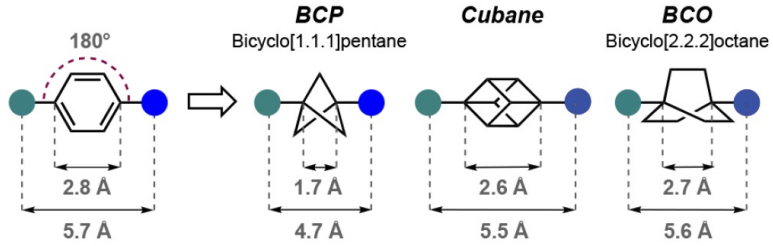
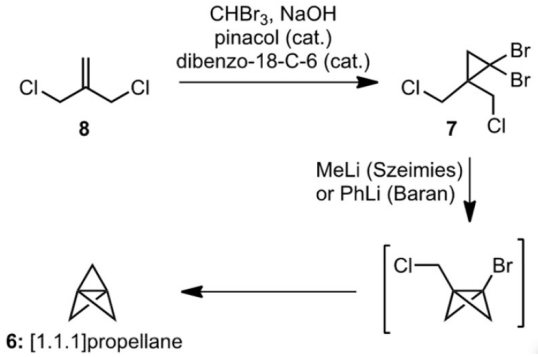
A. Saturated isosteres to overcome aniline metabolic liability

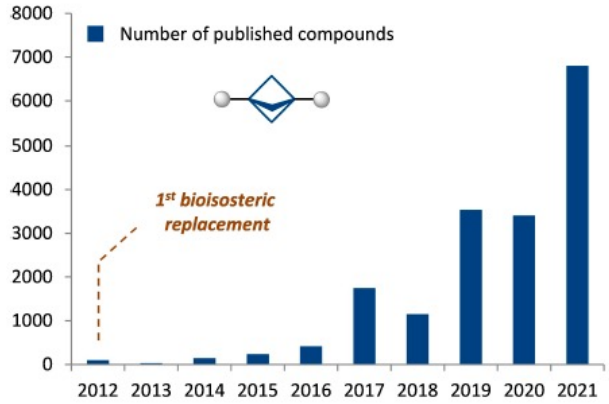


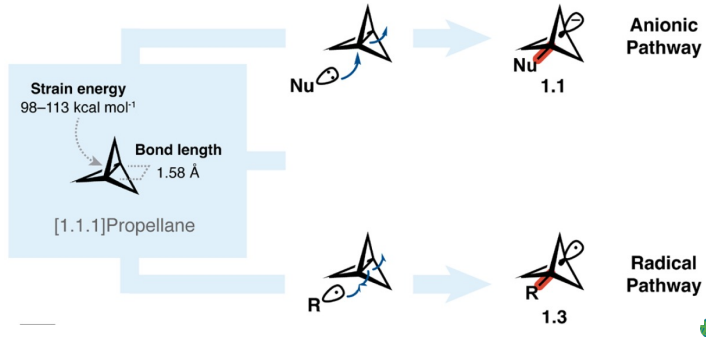
When replacing the benzene ring in bioactive compounds with saturated bioisosteres, several factors must be kept in mind. First, such replacement will increase the compound's (a) metabolic stability and (b) water solubility. For example, derivatives of phenol and aniline are often metabolically labile due to the fast *in vivo* oxidation to 1,4-benzoquinone by cytochrome-p450.[27] Indeed, aliphatic linkers cannot degrade this way and hence are more stable. On the other hand, derivatives of





While hydrocarbons such as cubane and bicyclo[2.2.2]octane more accurately mimic the substituent separation, they are significantly harder to access with diversity at the bridgehead positions





> « Saturated bioisosteres of benzene: where to go next?» *Org. Biomol. Chem.* 2019, *17*, 2839

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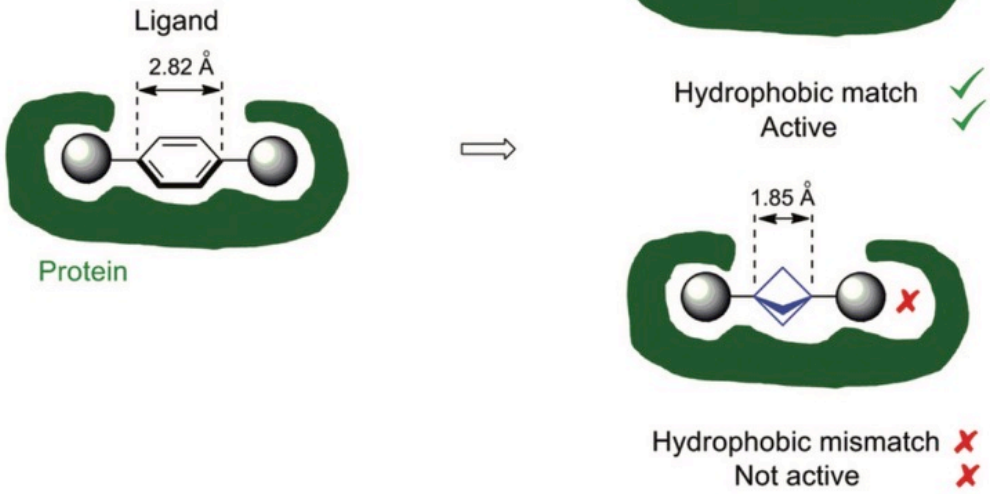
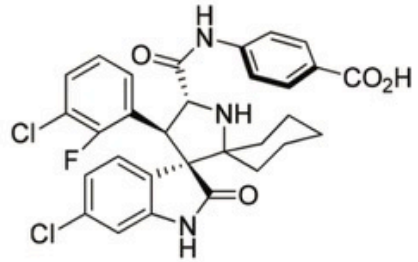
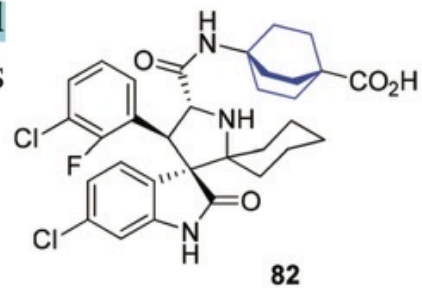
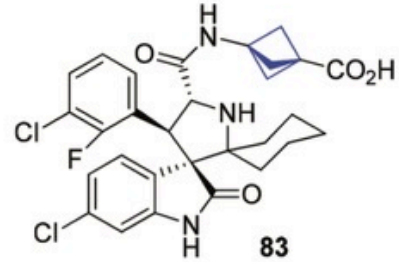
The influence of the replacement of the benzene ring in a bioactive compound with a saturated linker on the activity and selectivity is hard to predict, however. Two simplified scenarios

(a) - Benzene as a spacer;
- WITHOUT aryl-protein interractions:









	Comp. **81**	Comp. **82**	Comp. **83**
IC_{50} (MDM2, nM)	4.4	3.7	6.4
IC_{50} (SJSA-1, nM)	100	89	542
C_{max} (ng/mL)	1553	8234	*n.d.*
CL (L h^{-1} kg^{-1})	1.16	0.119	*n.d.*

> « Saturated bioisosteres of benzene: where to go next?» *Org. Biomol. Chem.* 2019, *17*, 2839

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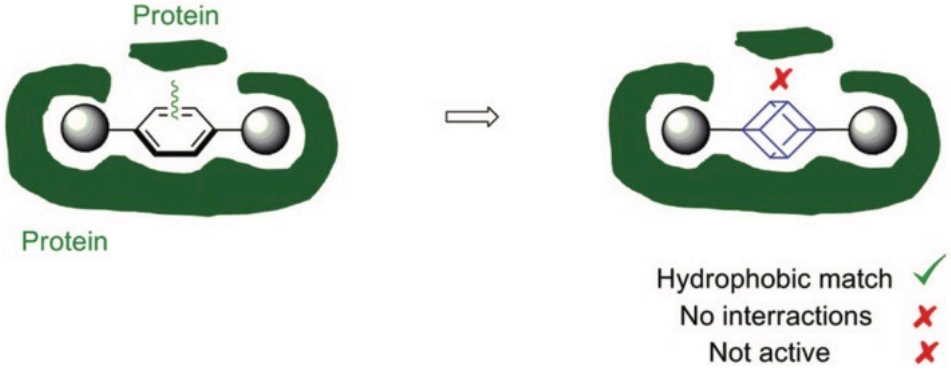
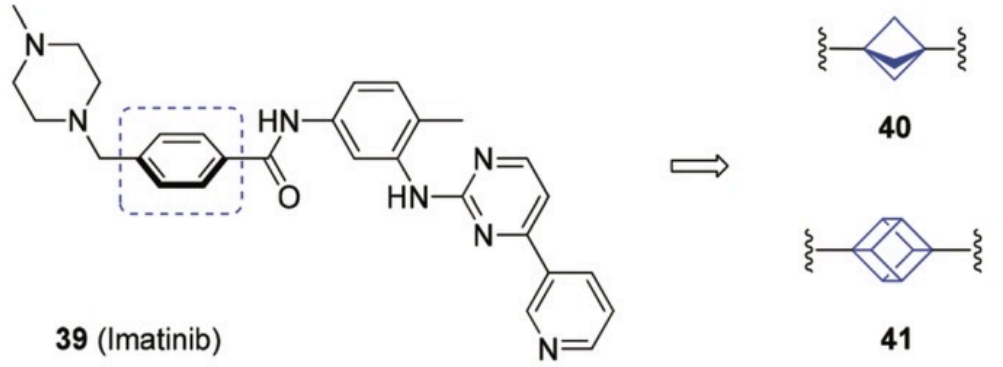
The influence of the replacement of the benzene ring in a bioactive compound with a saturated linker on the activity and selectivity is hard to predict, however. Two simplified scenarios

(b) - Benzene as a spacer;
- Benzene in aryl-protein interractions (~~~):





	Imatinib **39**	Comp. **40**	Comp. **41**
IC_{50} (ABL1 kinase)	371 nM	>1 µM	>30 µM
logD (pH = 7.4)	2.45	1.51	1.67
thermod. solub. (pH = 7.4, µM)	30.7	2680	356
HLM CL_{int} (mL/min/kg)	18.7	<16.6	37.0

Scheme 6 Anticancer drug imatinib (**39**) and its analogues **40** and **41**.

> « Saturated bioisosteres of benzene: where to go next?» *Org. Biomol. Chem.* 2019, *17*, 2839

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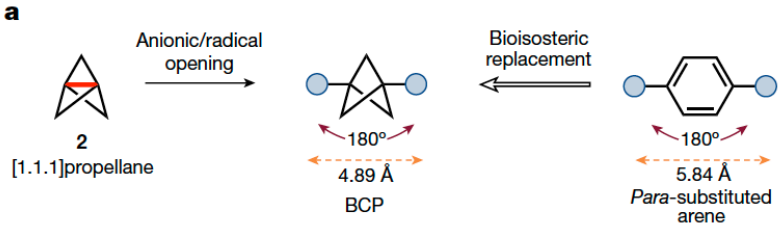

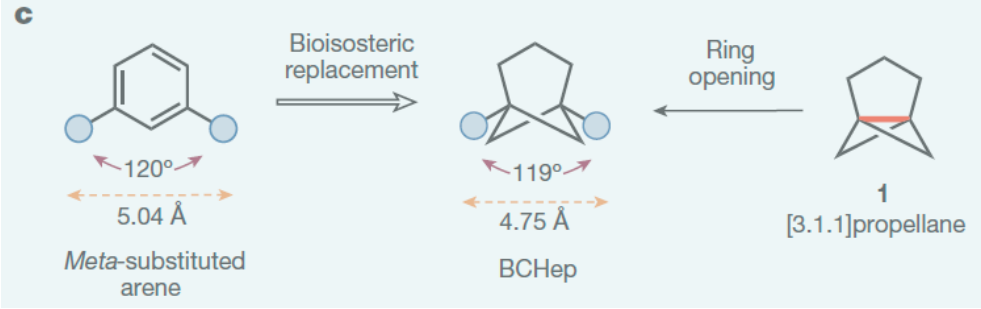

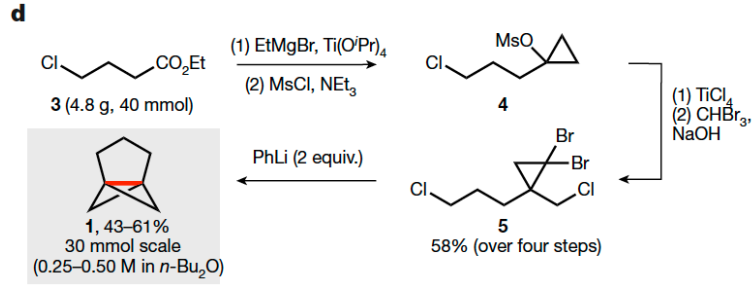

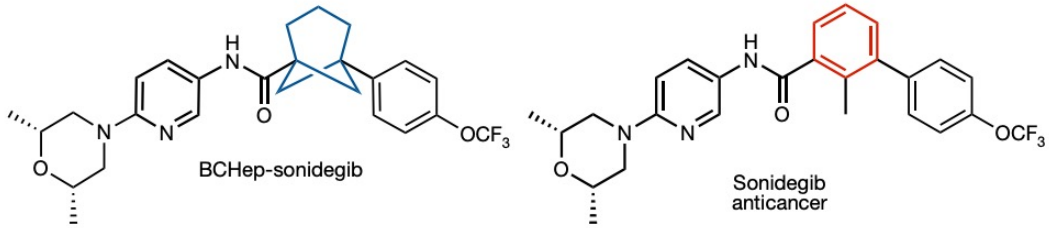

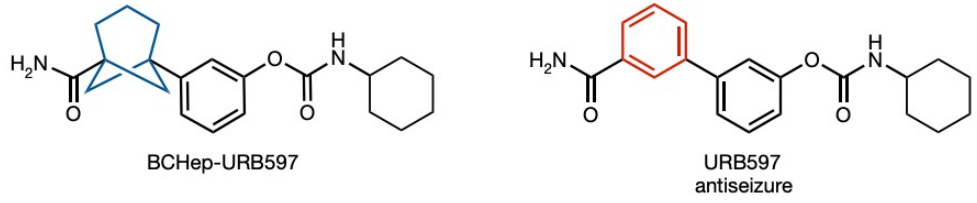

BCHeps show reduced clearance rates and better half-time in mouse and human liver microsomes compared to their arene equivalents, and membrane permeability is improved.

	Sonidegib	BCHep-Sonidegib	URB597	BCHep-URB597
Molecular weight (Da)	485.5	489.5	338.4	356.5
clog*P*	6.8	6.2	3.8	3.7
Topological polar surface area (Å^2)	63.7	63.7	81.4	81.4
Aqueous solubility (μg ml^{-1})/(μM)	<0.8 / <1.6	<0.8 / <1.6	<0.5 / <1.6	<0.6 / <1.6
Mouse liver microsomal stability, Cl_i (μl min^{-1} per mg protein)/$T_{1/2}$ (min)	26/53	19/75	180/8	77/18
Human liver microsomal stability, Cl_i (μl min^{-1} per mg protein)/$T_{1/2}$ (min)	20/70	18/76	54/26	17/80
Caco-2, AB/BA P_{app} (10^{-6} cm s^{-1})	0.6/0.7	3.7/2.7	18.7/11.1	15.3/24.4

> «Synthesis of meta-substituted arene bioisosteres from [3.1.1]propellane» *Nature* 2022, *611*, 721

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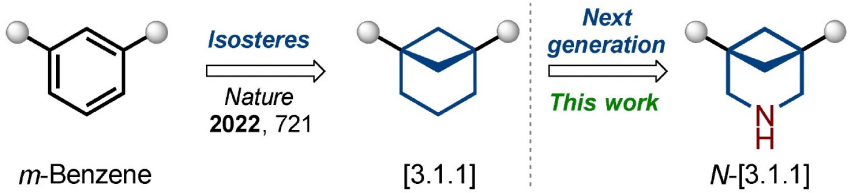


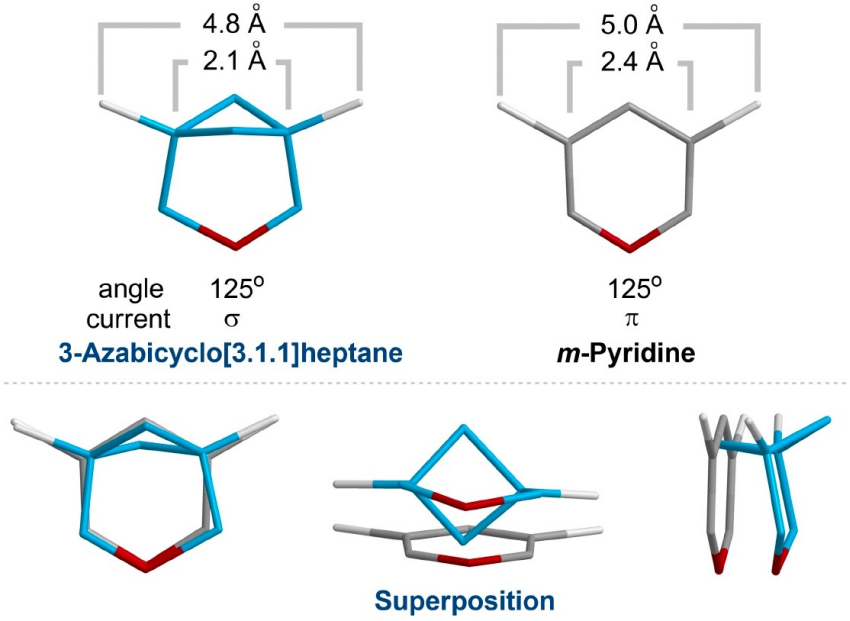
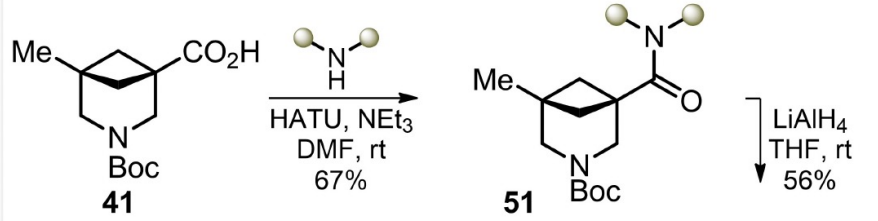
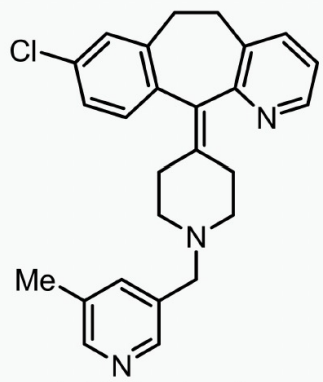


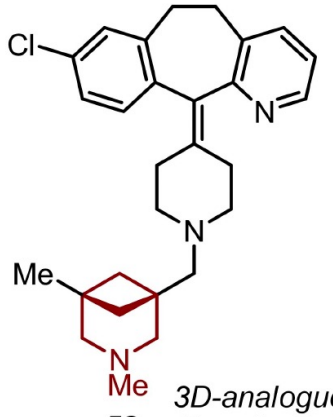
Figure 2. Visualized comparison of 3-azabicyclo[3.1.1]heptane and 3,5-disubstituted pyridine.

Saturated analogue of a drug





Antihistamine drug
Rupatadine



52 ***3D-analogue*** **Rupatadine**

Compound	*Sol.*	*clogP*	*logD (7.4)*	CL_{int}	$t_{1/2}$
Rupatadine	29±1	5.1	>4.5	517	3.2
52 *N*-[3.1.1]	365±1	5.2	3.8	47	35.7

> «3-azabicyclo[3.1.1]heptanes & evaluation of their properties as saturated isosteres» *Angew. Chem. Int. Ed.* **2023**, *62*, e202304246

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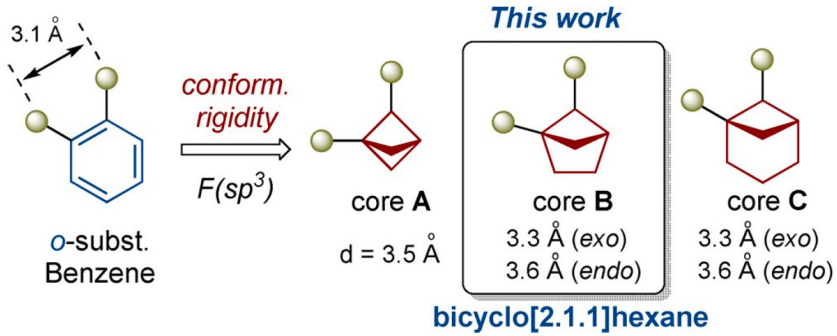
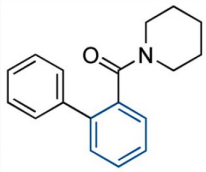
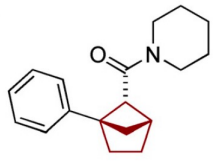
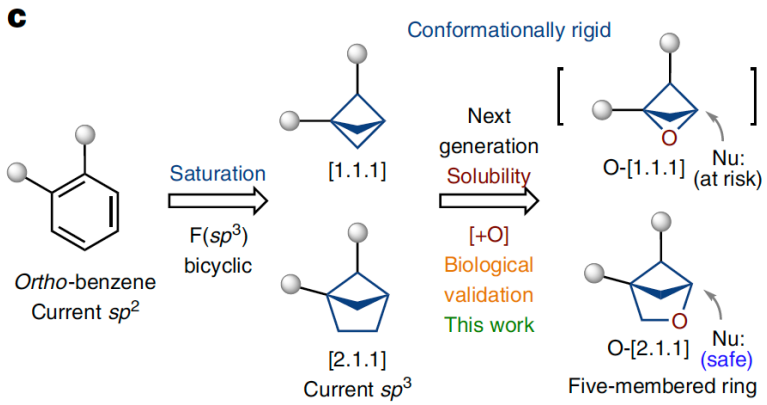
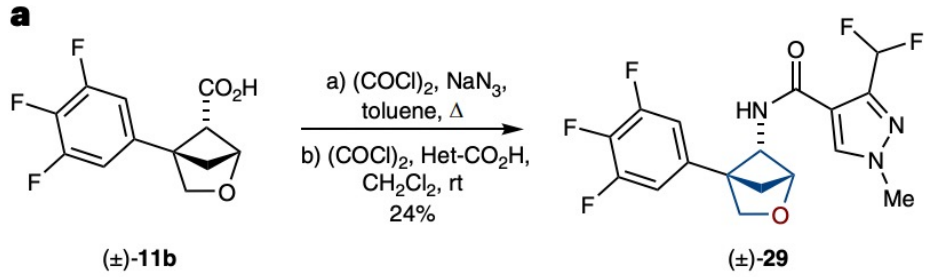
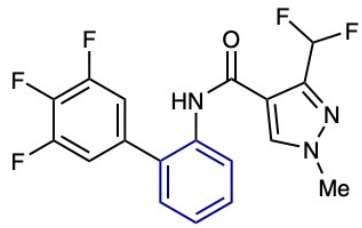
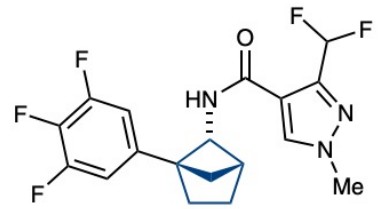


Model compound	 **24**	 **25**
Water solubility (7.4)[a]	397	492
Lipophilicity, logD(7.4)[b]	3.5	3.7






Fluxapyroxad
Fungicide (BASF)


(±)-28

Compound	Solubility	clogP	logD (7.4)	Cl_{int}
Fluxapyroxad	25 ± 1.1	2.2	3.5 ± 0.1	28
(±)-**28**	34 ± 0.4	2.9	4.3 ± 0.2	35
(±)-**29**	155 ± 3.2	1.3	2.8 ± 0.1	23

> « Saturated bioisosteres of *ortho*-substituted benzenes » *Angew. Chem. Int. Ed.* **2020**, *59*, 20515