Christos Mitsos

Isosteres in Medicinal Chemistry

Group Meeting
2/1/2006

Reviews
G. A Patani, E. J. LaVoie, Chem Rev. 1996, 3147-3176.
C. G. Wermuth, in The Practice of Medicinal Chemistry, Academic Press 1996, pp 203-237.

Definition of Isosterism

Langmuir (1919): Compounds or groups of atoms having the same number of atoms and electrons

Examples: N_2 and CO, N_2O and CO_2, N_3^- and NCO^-

Grimm (1925): "Hydride Displacement Law" addition of hydride to an atom gives to the resulting pseudoatom' the properties of the atom with the next highest atomic number.

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 (1932): atoms, ions or molecules in which the peripheral layers of electrons can be consider identical.

Examples: atoms in the same column of the periodic table, Cl and CN and SCN (despite having different number of atoms)

Definition of Bioisosterism

Friedman (1951): Bioisosteres are atoms or molecules that fit the broadest definition for isosteres and have the same type of biological activity.

Thornber (1979): Groups or molecules which have chemical and physical similarities producing broadly similar biological effects.

Parameters affected with bioisosteric replacements

Size, conformation, inductive and mesomeric effects, polarizability, H-bond formation capacity, pK_a, solubility, hydrophobicity, reactivity, stability.

Bioisosteric replacements: Why?

- Greater selectivity
- Less side effects
- Decreased toxicity
- Improved pharmacokinetics (solubility-hydrophobicity)
- Increased stability
- Simplified synthesis
- Patented lead compounds

H to F replacement

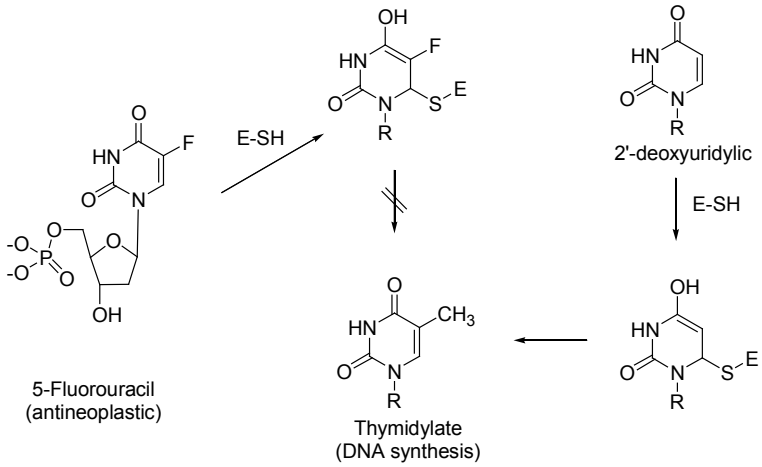
Fluorine: similar size with hydrogen
most electronegative halogen
C-F bond very stable

	H	F	Cl	CH_3	CF_3
Van der Waals radius	1.2	1.35	1.80	2	2
Molecular Refractivity	1.03	0.92	6.03	5.65	5.02
Inductive effect	-	3.08	2.68	0.00	2.85
Resonance effect	0.00	-0.34	-0.15	-0.13	0.19

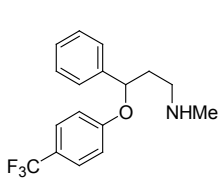
Ideal replacement to study the effect of electronegativity change without affecting steric requirements

F (or other halogens) can be placed on eacily oxidized positions to increase stability during metabolic processes

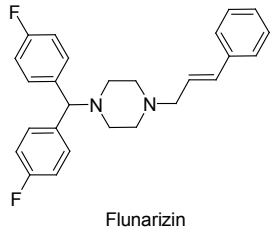
Thus, F (or other halogens when size is not critical) are frequently place on easily oxidized aromatics
Methyl groups often substituted by CF_3



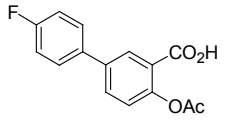
E-SH: Thymidylate synthase



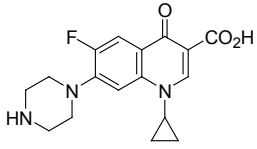
Fluoxetine
(Prozac)
antidepreessant



Flunarizin
(Sibelium)
Ca channel blocker



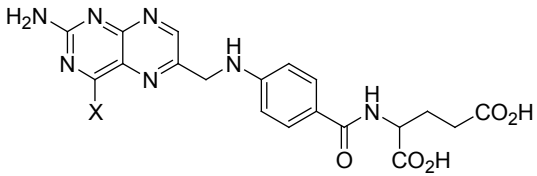
Flufenisal
analgesis



Ciprofloxacin
(Cipro)
antibacterial

-OH to -NH_2 or –SH replacement (also C=O to C=NH or C=S)

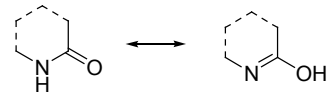
O and NH have similar sizes (but not SH)
All three bear H-bonding donor and acceptor capacities



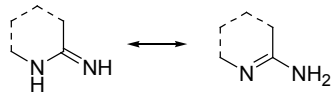
X = NH_2, Aminopterin (Methotrexate)
(an antimetabolite anticancer)

X = OH, Folic acid

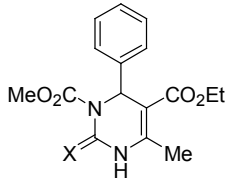
Replacement of OH with NH_2 can stabilize a different tautomer, especially in the case of heterocyclic systems



more stable



more stable



Dihydropyrimidine
calcium channel blockers

X	Van der Waals radius (Å)	IC_{50} (nm)
O	1.40	140
NH	1.50	160
S	1.85	17

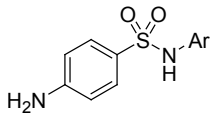
Halogen replacements

CN and CF_3 may be used as alternative electron-withdrawing groups instead of halogens.

The two groups have comparable effects on electronics, but CN will increase the overall hydrophilicity.

Ring replacements

Sulfonamide antebacterials: phenyl group may be replaced by many heterocycclic aromatics to give active compounds



Ar =

Sulfapyridine

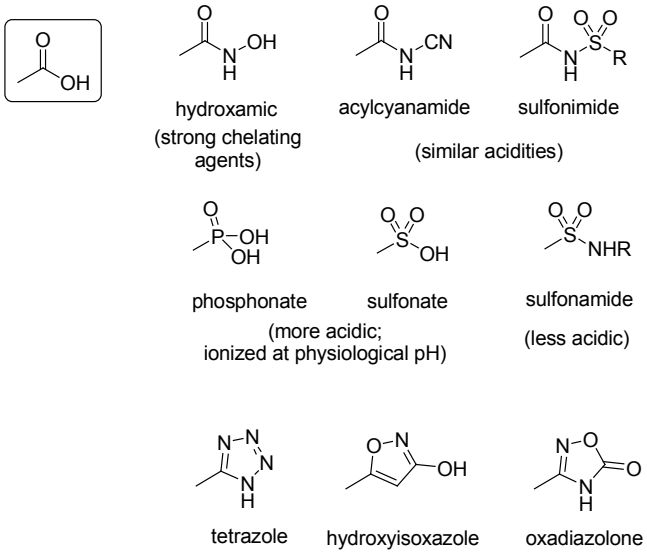
Sulfapyrazine

Sulfathiazole

Sulfapyrimidine

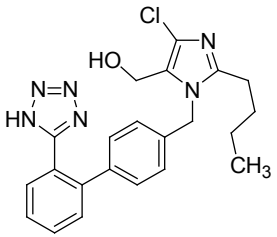
Isosteres in Medicinal Chemistry

COOH replacements



Carboxyl group may be replaced in order to alter acidity, or modify lipophilicity without affecting pKa

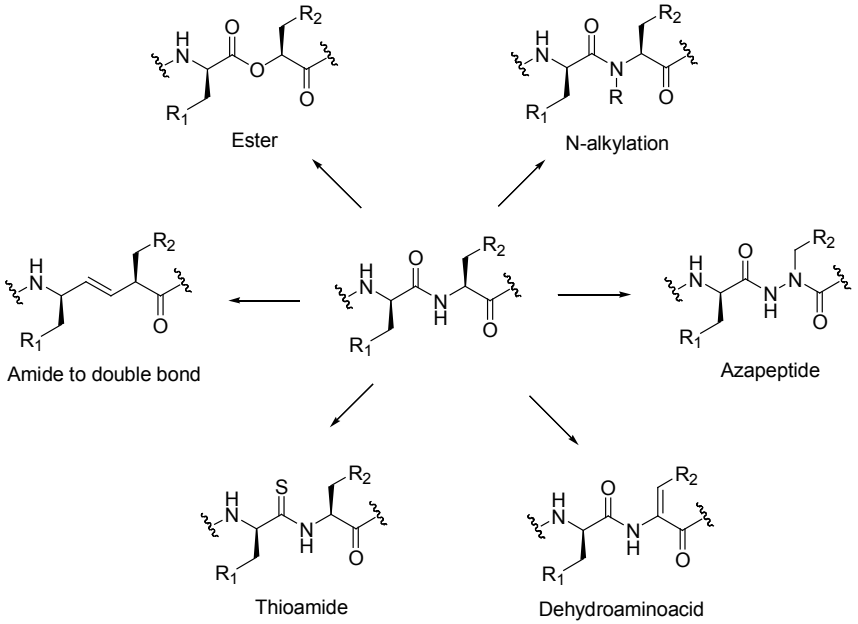
Tetrazoles have comparable pK's with carboxylic acids, but greater lipophilicity



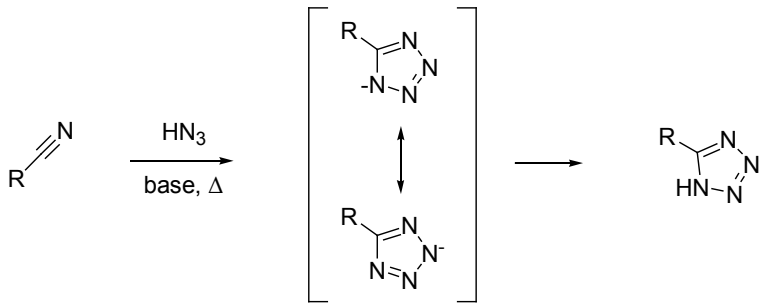
Losartan
(antihypypertensive)

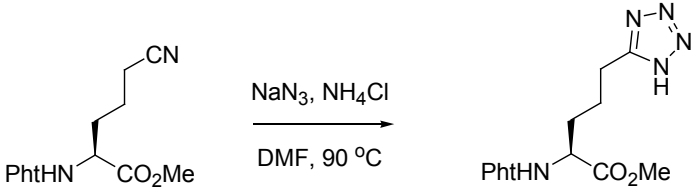
Peptide surrogates

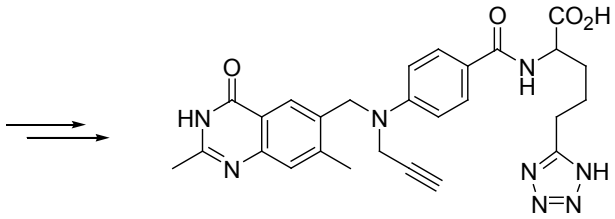
Peptides are characterized by diminished bioavailability when administered orally.
Replacement of the sensitive amide bond by various groups can increase their stability.



Preparation of tetrazoles

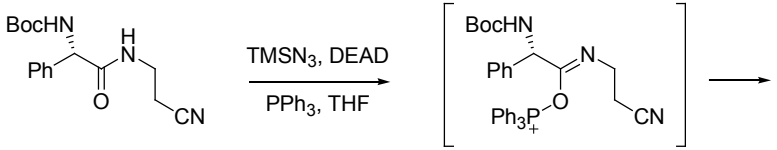




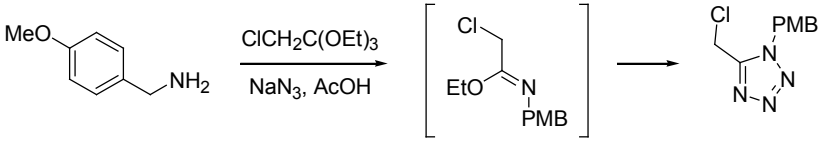


Tomudex analogues

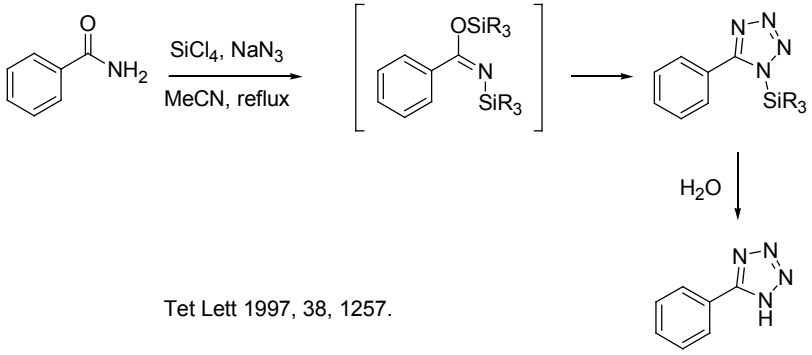
J. Med. Chem. 1999, 42, 3809.



J. Med. Chem 2000, 43, 488.



Tet Lett 1998, 39, 3367.

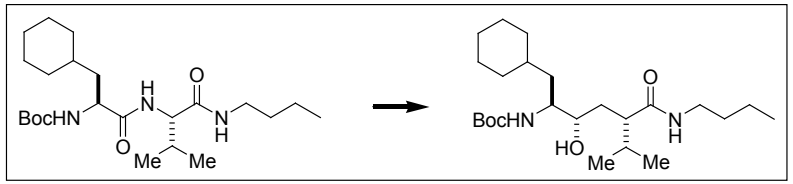


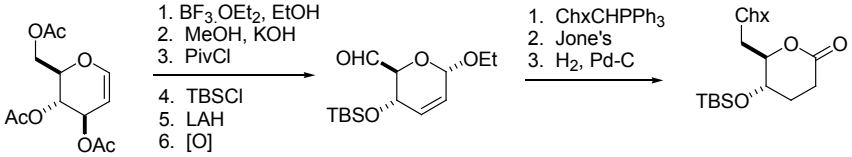
Tet Lett 1997, 38, 1257.

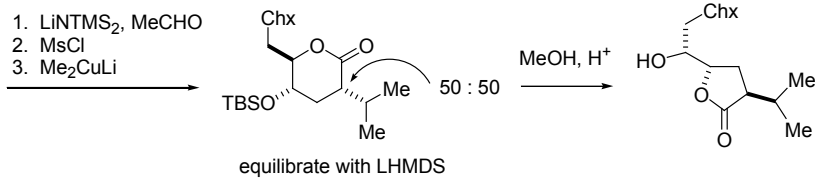
Isosteres in Medicinal Chemistry

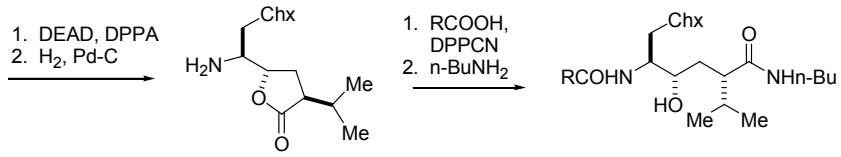
Peptide (amide) repalcements

Amide to hydroxyethyl



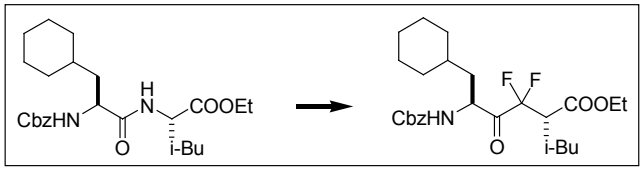


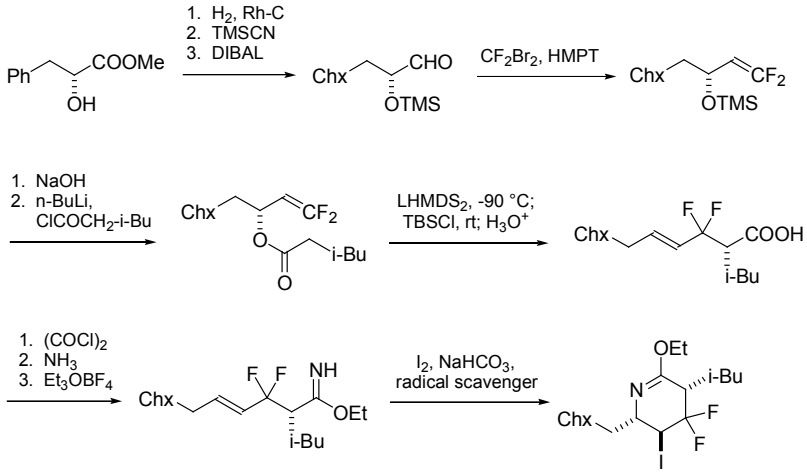




Shiozaki, et.al. Tetrahedron Lett. 1989, 30, 3669-3670.

Amide to alpha-difluoroketone

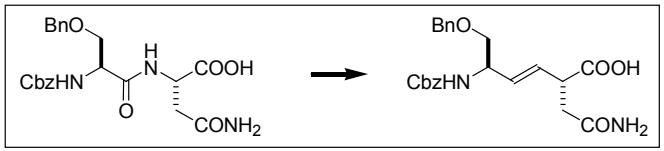


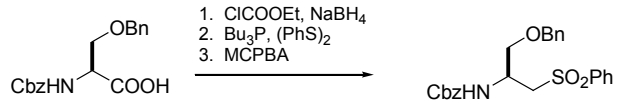


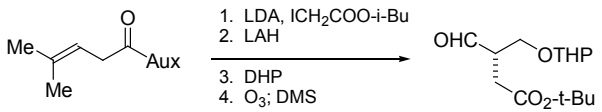
Damon, D. B.; Hoover, D. J. J. Am. Chem. Soc. 1990, 112, 6439-6442.

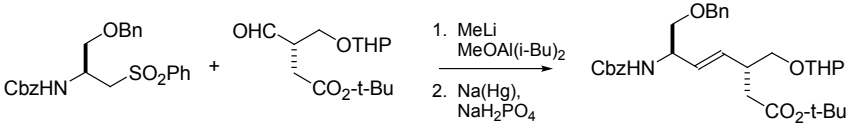
Peptide (amide) repalcements

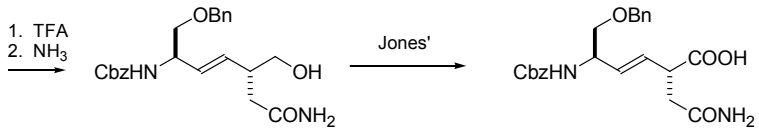
Amide to alkene





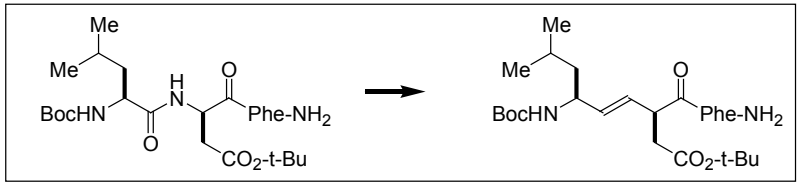


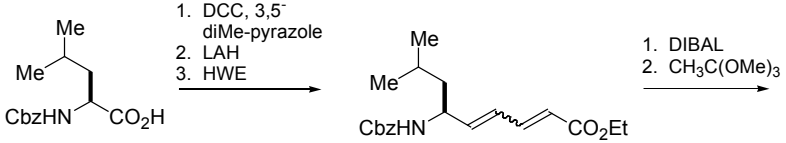


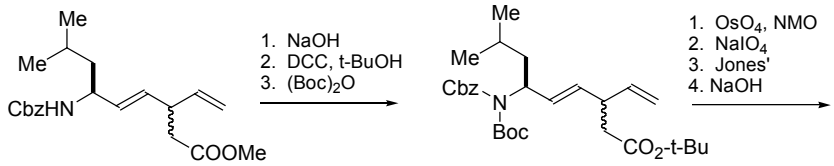


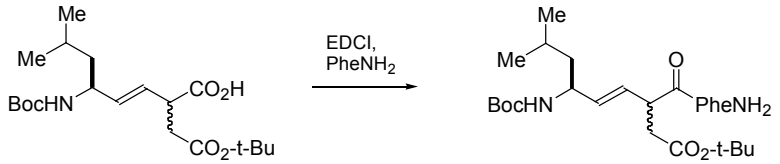
de Gaeta, et.al. J. Org. Chem. 1989, 54, 4004-4005.
Spaltenstein, et.al. J. Org. Chem. 1987, 52, 3759-3766.

Amide to alkene









Separate by Flash Chromatography

Shue, et.al. Tetrahedron Lett. 1988, 29, 4041-4044.