

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: N₂ and CO, N₂O and CO₂, N₃⁻ 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

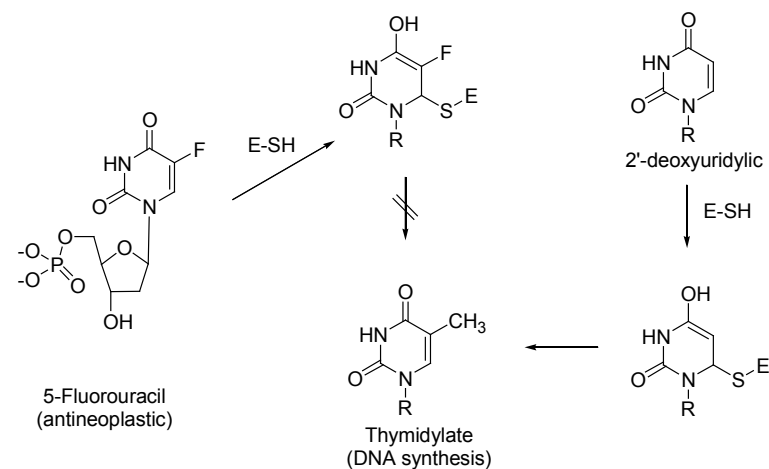
Fluorine: similar size with hydrogen
most electronegative halogen
C-F bond very stable

	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

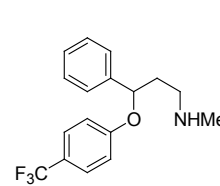
Ideal replacement to study the effect of electronegativity change without affecting steric requirements

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

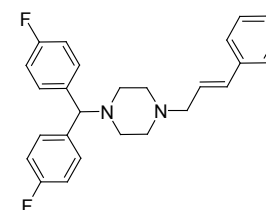
Thus, F (or other halogens when size is not critical) are frequently placed on easily oxidized aromatics
Methyl groups often substituted by CF₃



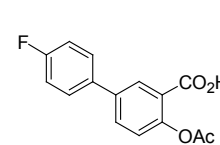
E-SH: Thymidylate synthase



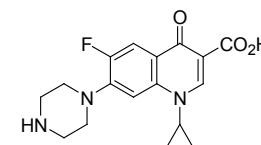
Fluoxetine
(Prozac)
antidepressant



Flunarizin
(Sibelium)
Ca channel blocker



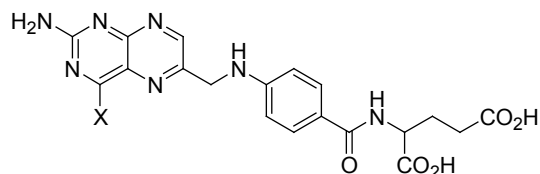
Flufenisal
analgesic



Ciprofloxacin
(Cipro)
antibacterial

**-OH to -NH₂ or -SH replacement
(also C=O to C=NH or C=S)**

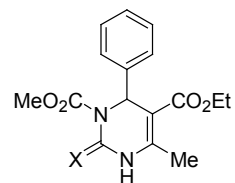
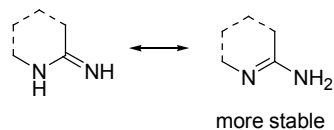
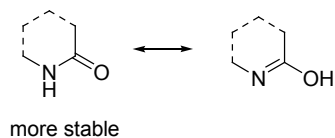
O and NH have similar sizes (but not SH)
All three bear H-bonding donor and acceptor capacities



X = NH₂, Aminopterin (Methotrexate)
(an antimetabolite anticancer)

X = OH, Folic acid

Replacement of OH with NH₂ can stabilize a different tautomer, especially in the case of heterocyclic systems



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

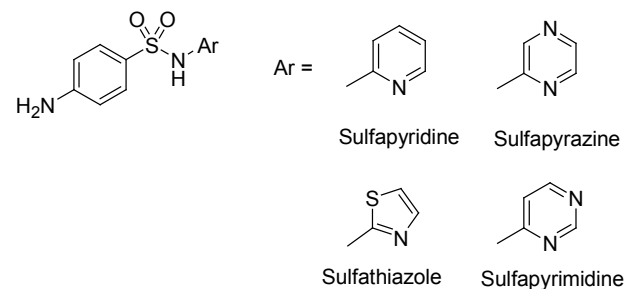
Halogen replacements

CN and CF₃ may be used as alternative electron-withdrawing groups instead of halogens.

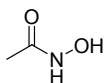
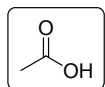
The two groups have comparable effects on electronics, but CN will increase the overall hydrophilicity.

Ring replacements

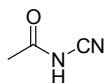
Sulfonamide antibiotics: phenyl group may be replaced by many heterocyclic aromatics to give active compounds



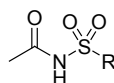
COOH replacements



hydroxamic
(strong chelating
agents)



acylcyanamide



sulfonamide

(similar acidities)



phosphonate

(more acidic;
ionized at physiological pH)



sulfonate

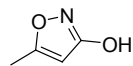


sulfonamide

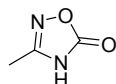
(less acidic)



tetrazole



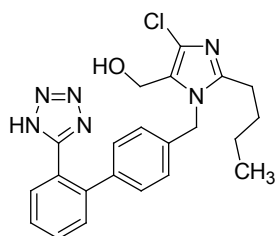
hydroxyisoxazole



oxadiazolone

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

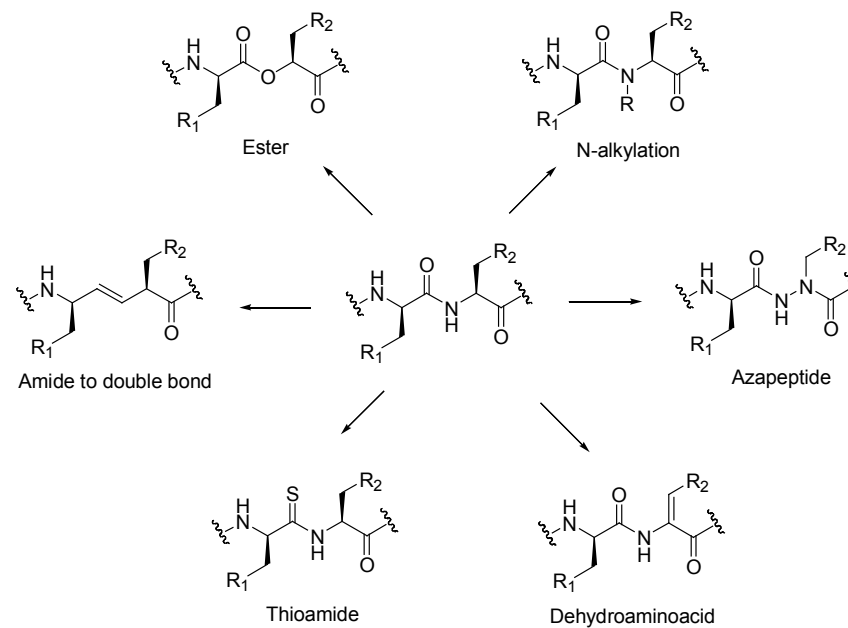
Tetrazoles have comparable pK's with carboxylic acids, but greater lipophilicity



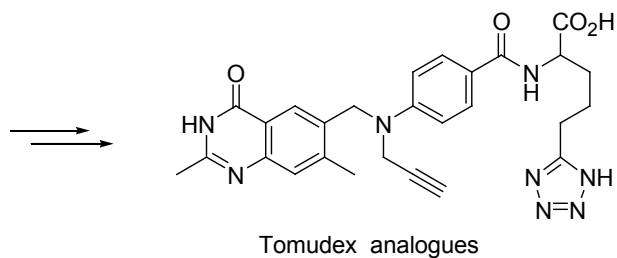
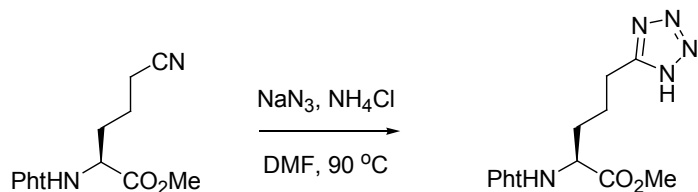
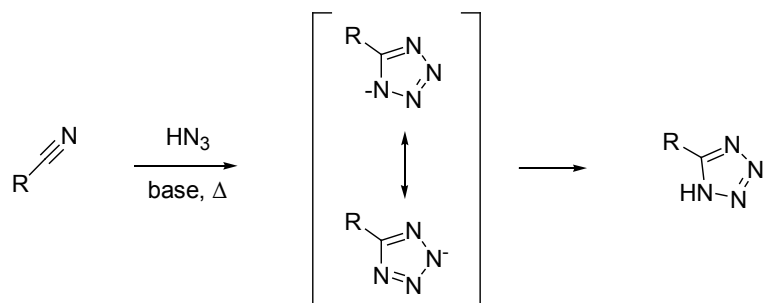
Losartan
(antihypertensive)

Peptide surrogates

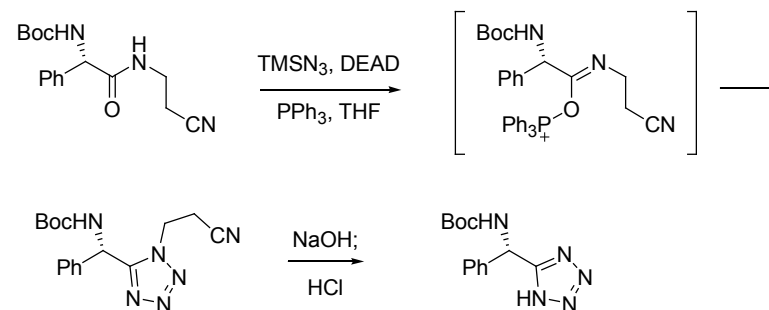
Peptides are characterized by diminished bioavailability when administered orally. Replacement of the sensitive amide bond by various groups can increase their stability.



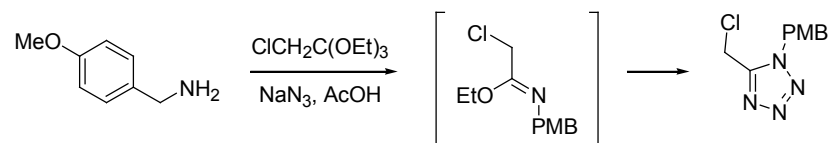
Preparation of tetrazoles



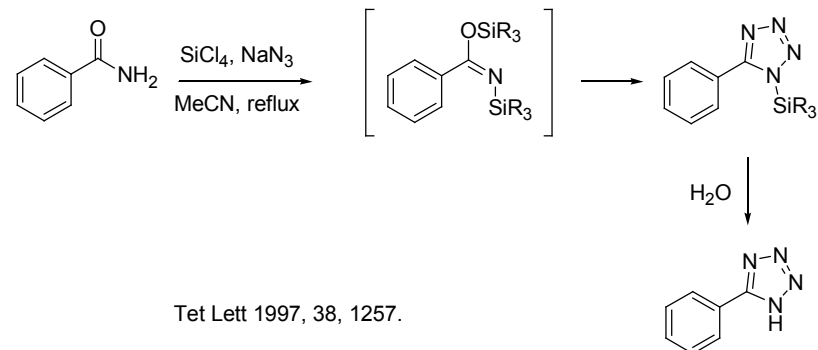
J. Med. Chem. 1999, 42, 3809.



J. Med. Chem 2000, 43, 488.



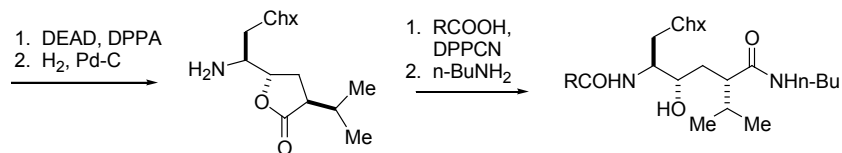
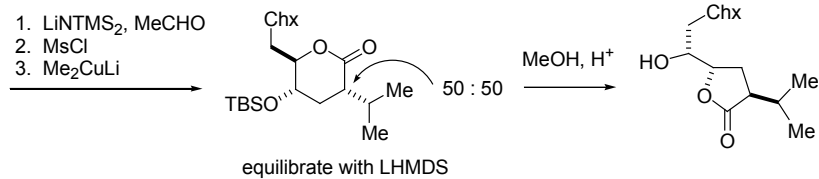
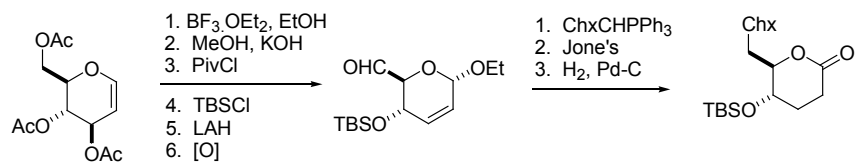
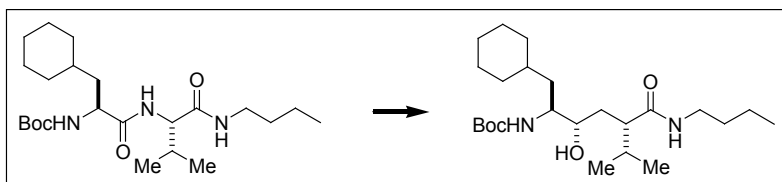
Tet Lett 1998, 39, 3367.



Tet Lett 1997, 38, 1257.

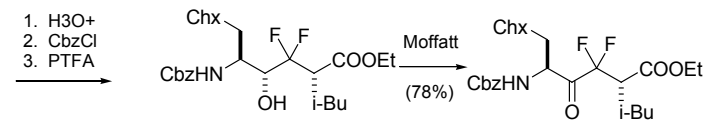
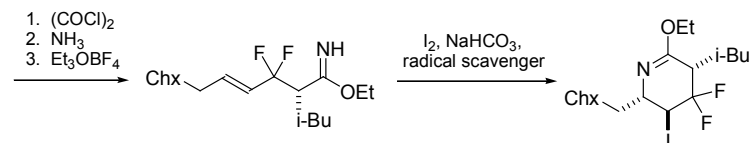
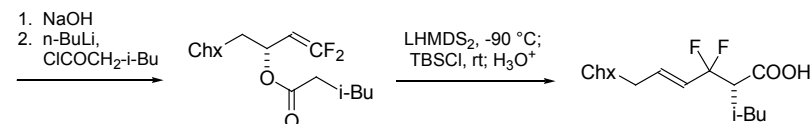
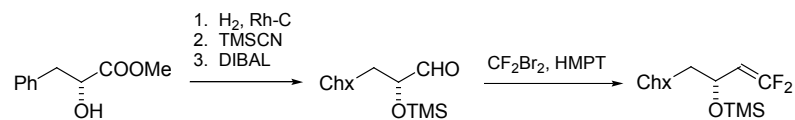
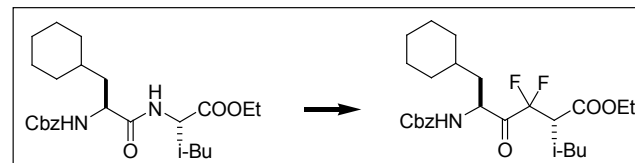
Peptide (amide) replacements

Amide to hydroxyethyl



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

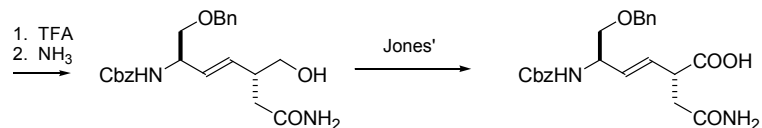
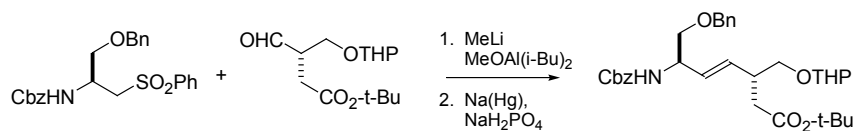
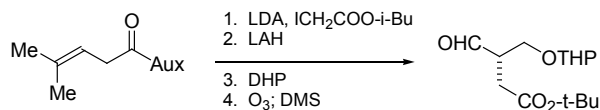
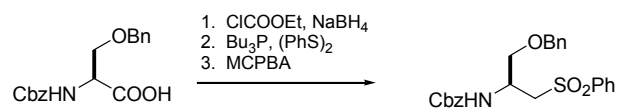
Amide to alpha-difluoroketone



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

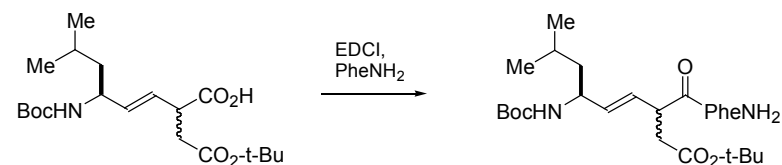
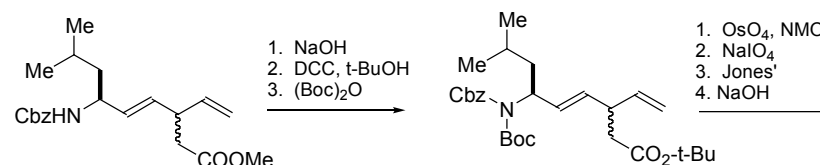
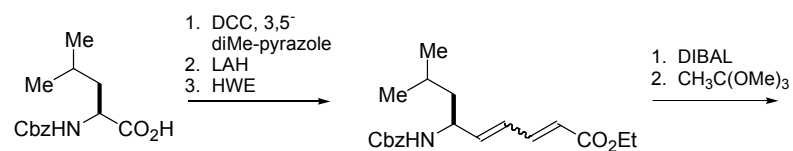
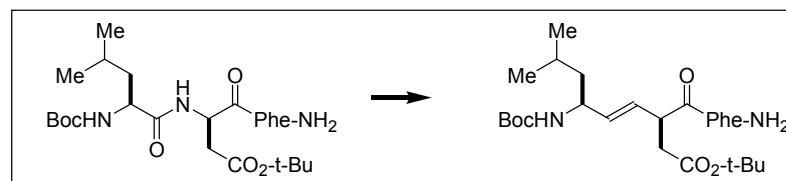
Peptide (amide) replacements

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.