physicochemical properties

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Isosterism

Definition of Isosterism

Langmuir (1919):

Cpd.s or grp.s of atoms having the same no. of atoms and electrons

Ex.:

N_2 & CO , N_2O & CO_2,

N^-_3 & NCO^-

Grimm (1925): "Hydride Displacement Law"

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):

Ex.: atoms in the same column of the periodic table :

(despite having different number of atoms

no. of peripheral electrons				
4	5	6	7	8
N^+	P	S	Cl	ClH
P^+	As	Se	Br	BrH
S^+	Sb	Te	I	IH
As^+		PH	SH	SH_2
Sb^+			PH_2	PH_3

Harris Friedman in 1950 who defined the term "**bioisostere**" as compounds eliciting a similar biological effect.

bioisosteres has been broadened by Burger as

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

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,
- pKa,
- 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

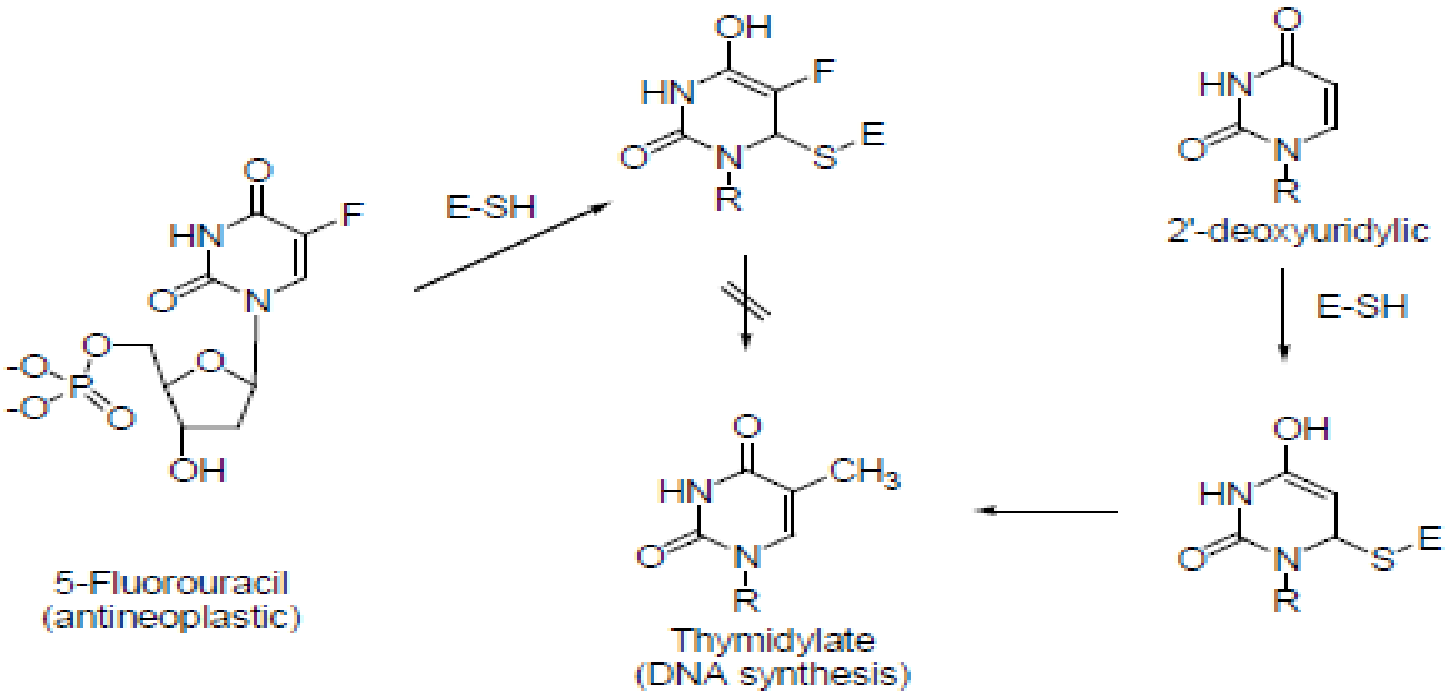
H to F replacement

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.

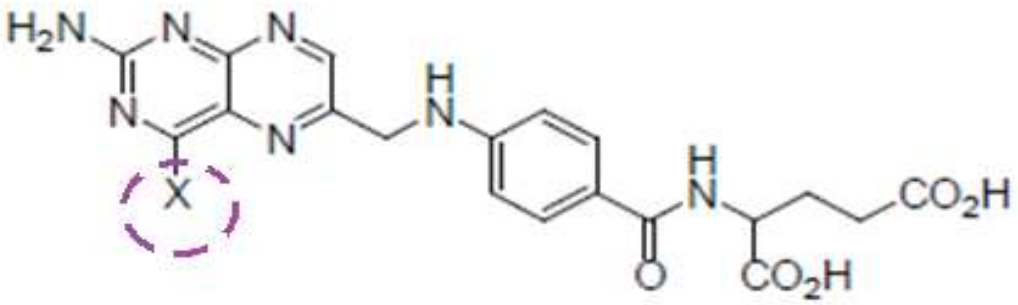
F ⟶ can be placed on easily oxidized positions to increase stability during metabolic processes.



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

** O and NH have similar sizes

All three bear H-bonding donor and acceptor capacities

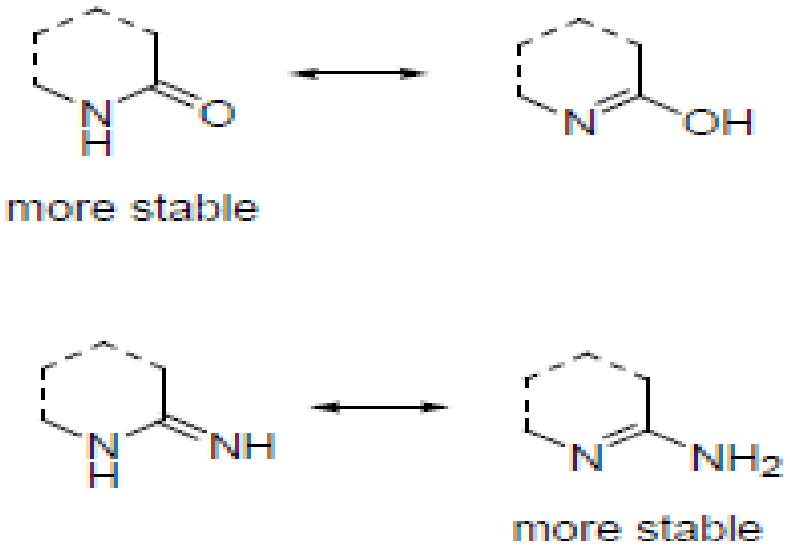


X = NH_2, **Methotrexate**

(an antimetabolite anticancer)

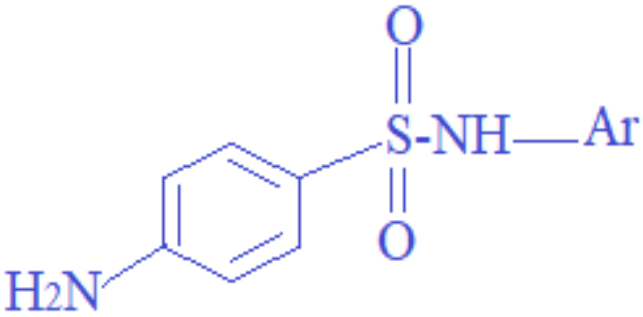
X = OH, **Folic Acid**

Replacement of OH with NH_2

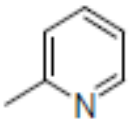


Ring replacements

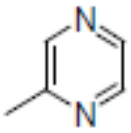
Sulfonamide antibacterials



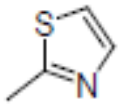
Ar =



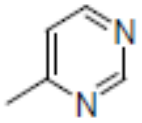
Sulfapyridine



Sulfapyrazine

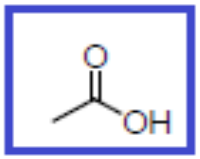


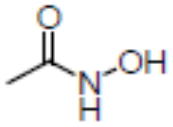
Sulfathiazole



Sulfapyrimidine

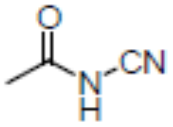
COOH replacements





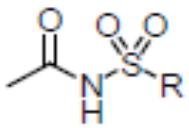
Hydroxamic

(strong chelating agents)

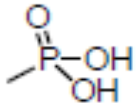


Acylcyanamide

(similar acidities)

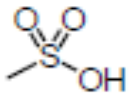


Sulfonimide

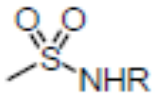


Phosphonate

(more acidic; ionized at physiological pH)

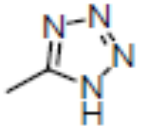


Sulfonate

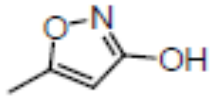


Sulfonamide

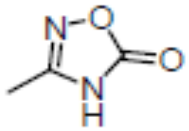
(less acidic)



Tetrazole



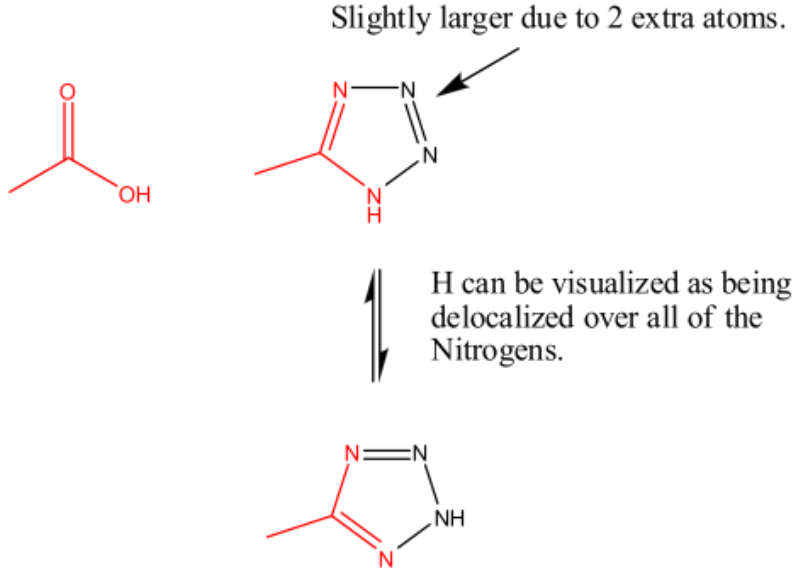
Hydroxyisoxazole

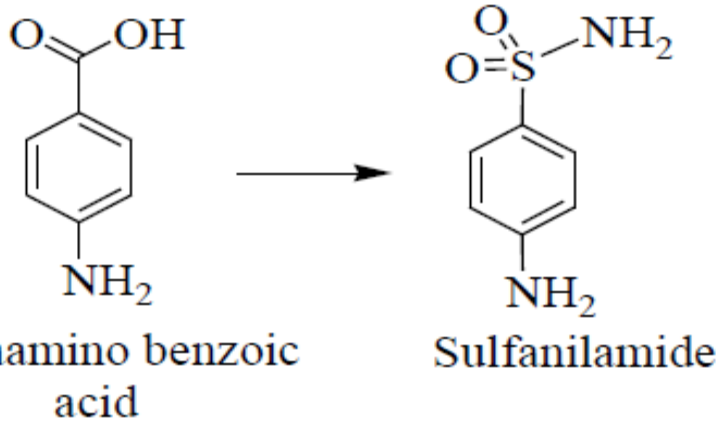


Oxadiazolone

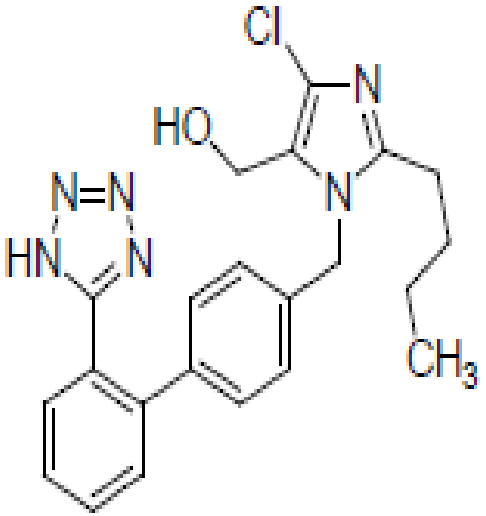
Tetrazoles

stable in-vivo
pka: 4.90 (Acetic acid is 4.76)
Slightly larger than an acid





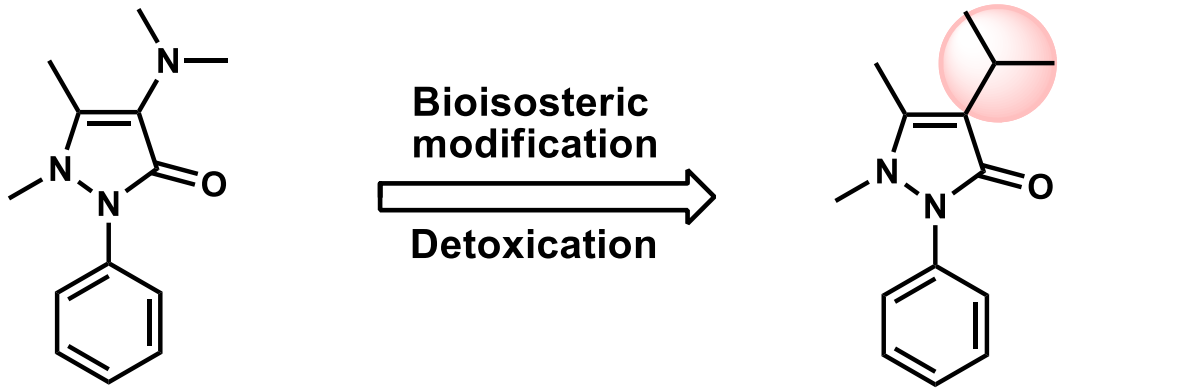
Tetrazoles have comparable pK's with carboxylic acids,



Losartan
(antihypypertensive)

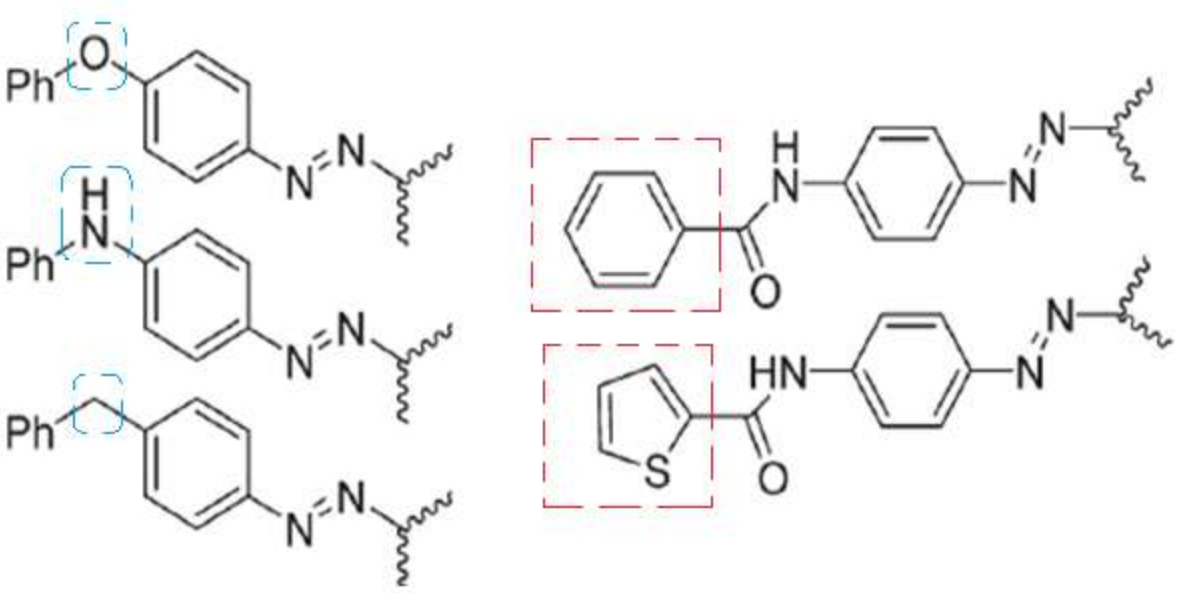
Aminopyrine Marketed as an analgesic and anti-inflammatory drug in 1896.

In 1922, It was revealed that Aminopyrine was a carcinogen .

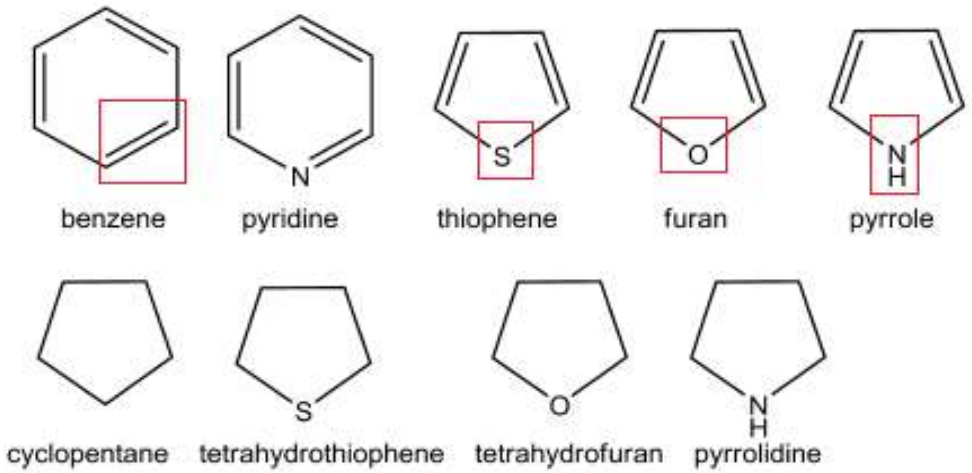


Aminopyrine **Propylphenazone**

Erlenmeyer showed that antibodies were unable to discriminate between phenyl and thienyl rings or O, NH, and CH_2 in the context of artificial antigens.

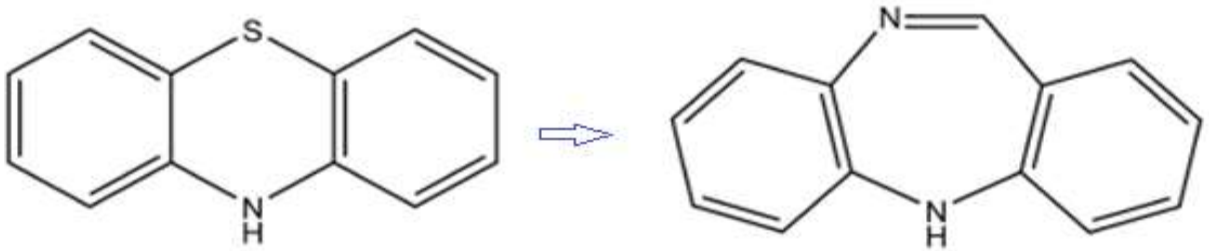


* Grp.s of atoms that impart similar physical or chemical properties to a molecule because of similarities in size, electronegativity, or stereochemistry accordingly $H_2C=CH_2$ equivalent divalent. **[aromatic character significantly decreased]**



ring equivalents

replacement of the sulfur atom in the phenothiazine ring system of tranquilizing agents with the vinylene grp.



phenothiazine

tranquilizing agent

dibenzodiazepam

antidepressant agent

* $CH_2=CH_2$ in Ar. Ring can replace by S, O (furan), NH(pyrrole) in such cases, aromatic character is significantly decreased .

*isosteric pairs that possess similar steric and electronic configurations are

-(COO^-) and (SO_2NR^-) ions;

ketone (C=O) and sulfone(O=S=O);

(Cl^-) and trifluoromethyl (CF_3);

(-H) and (-F);

(-OH) and ($-NH_2$);

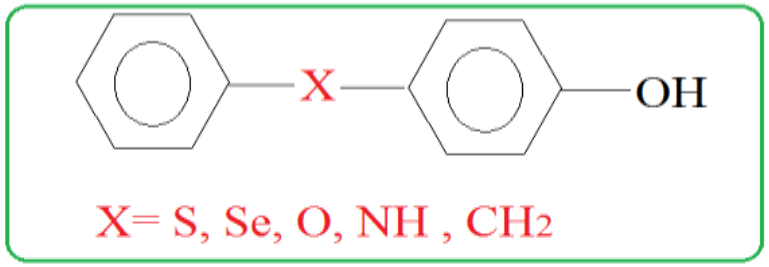
(-OH) and (-SH).

Divalent ether (-O-), sulfide (-S-),

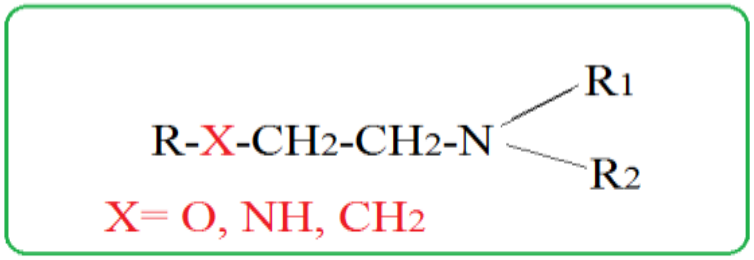
(-NH-), and ($-CH_2-$) groups,

although dissimilar electronically, are sufficiently alike in their steric nature to be frequently interchangeable in designing new drugs.

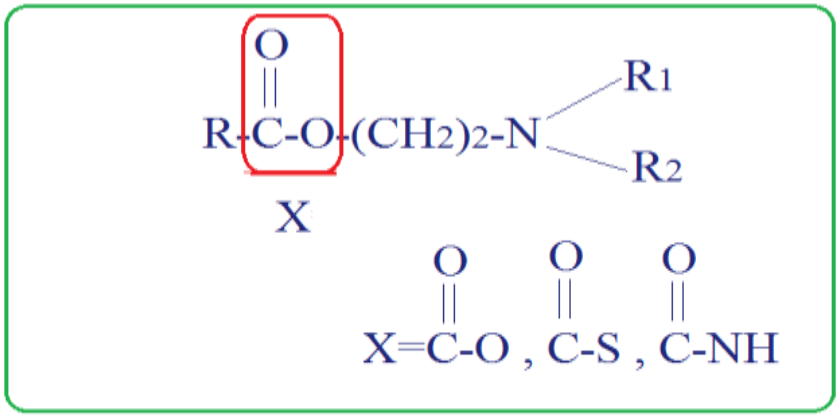
Application of isoster concepts in the synthesis of biologicaly active cpds can be illustrated w¯ :



All isosters are antibacterial Agents



All isosters are antihistaminic agents



All isosters are Anticholinergic agent

Effect on the pKa

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

	amine	pKa
Ethylamine	$CH_3CH_2NH_3^+$	10.7
	$CH_3FCH_2NH_3^+$	9.0
	$CHF_2CH_2NH_3^+$	7.3
	$CF_3CH_2NH_3^+$	5.7

	acid	pKa
Acetic acid	CH_3COOH	4.7
	CH_2FCOOH	2.6
	CHF_2COOH	1.2
	CF_3COOH	0.2

Phenols

H-Bond donors

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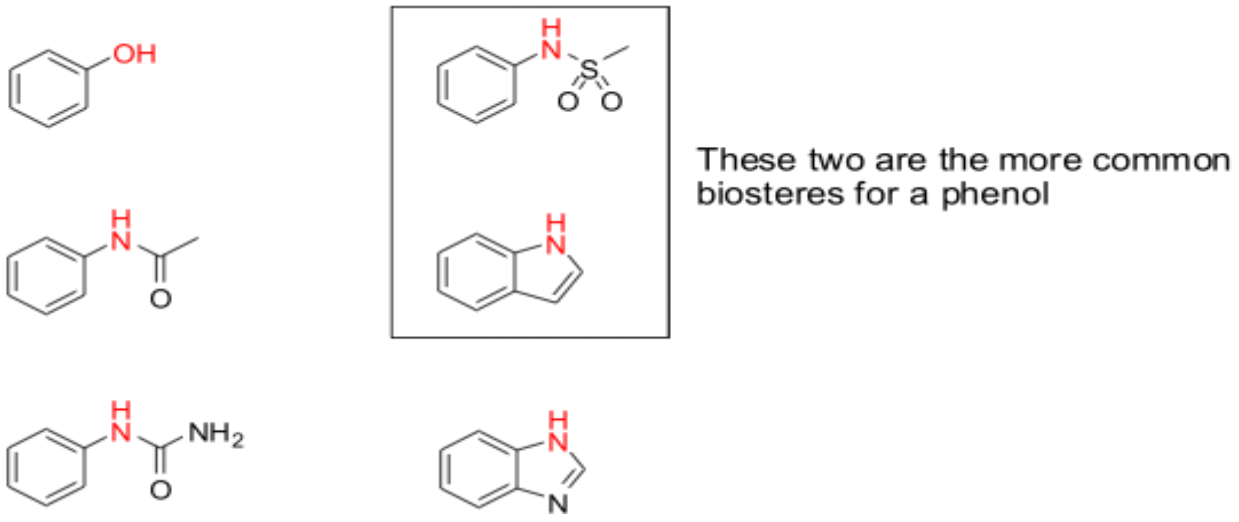
Generally the biostere is an ‘N-H’ with an electron withdrawing group attached to the nitrogen.

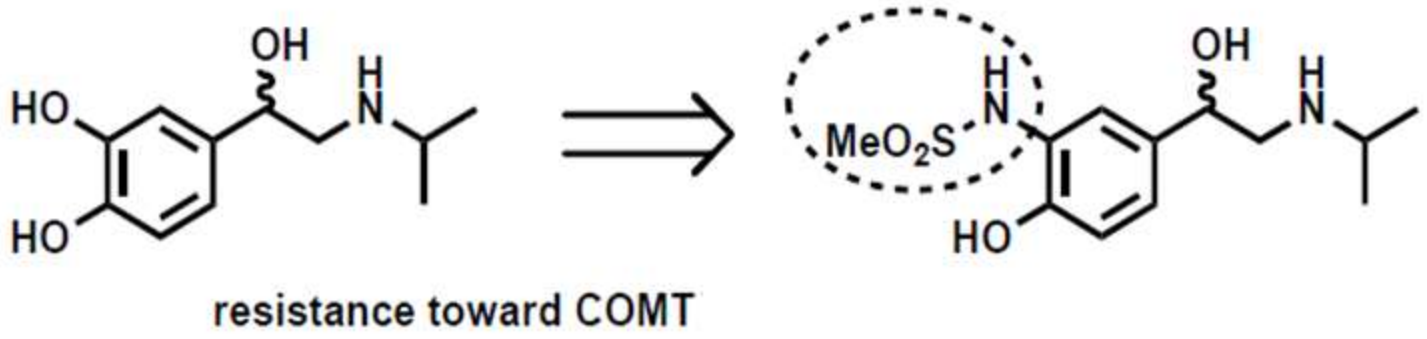


These two are the more common biosteres for a phenol

Phenol Isosteres

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

Non-selective β-adrenoceptor agonists



resistance toward COMT