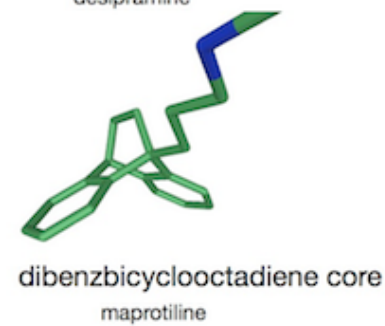
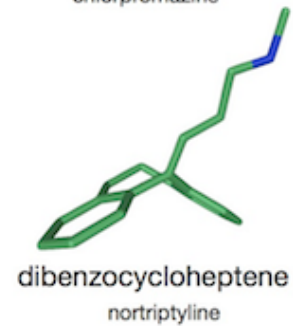
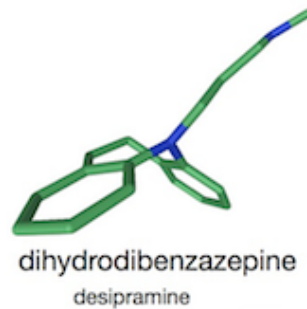
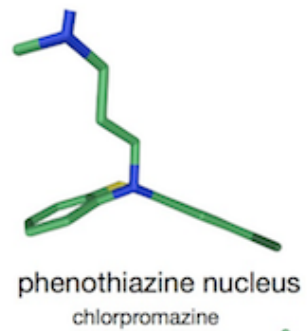
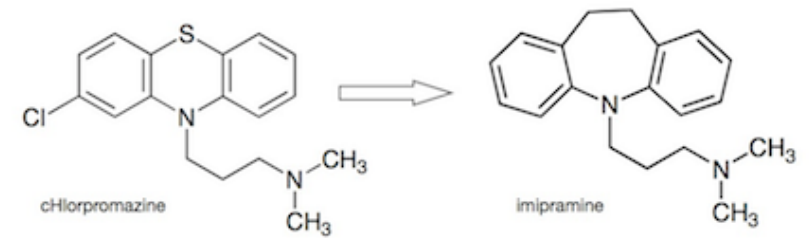
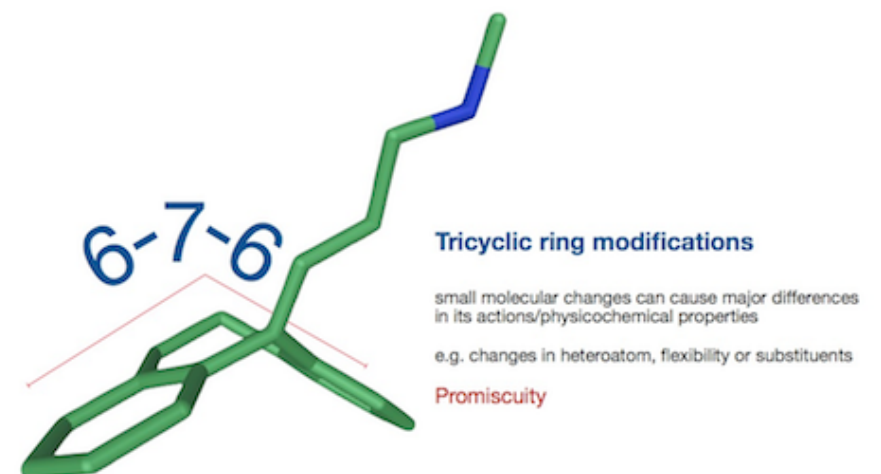


first generations
tricyclic & tetracyclic amines (TCA)

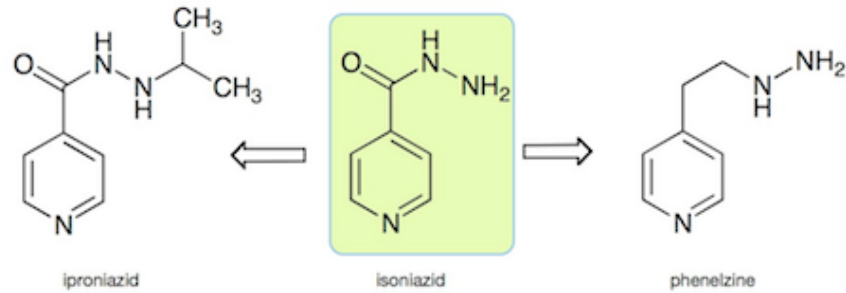


What are the common, key features?



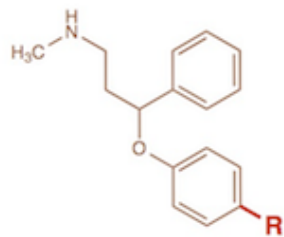
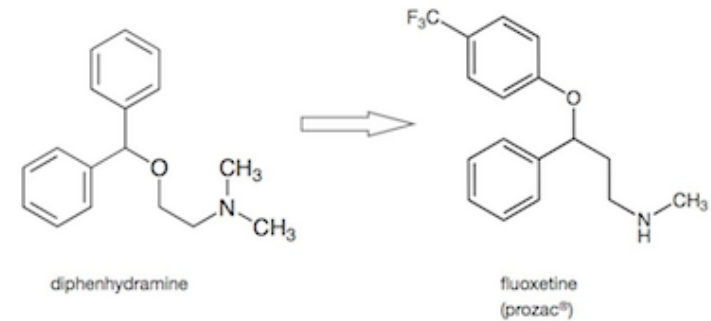
first generations

monoamine oxidase inhibitors



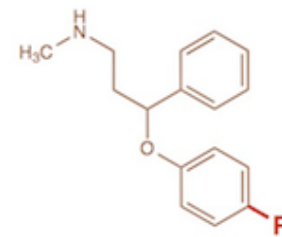
second generations

phenoxyphenylpropylamines



R type & position are critical

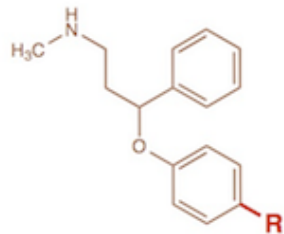
R=	inhibition of reuptake (K_i nM)	
	5-HT	NE
H	102	200
2-OCH ₃	1371	2.4
2-SCH ₃	130	0.2
2-CH ₃	390	3.4
4-CH ₃	95	570
4-OCH ₃	71	1207
2-CF ₃	1489	4467
3-CF ₃	16	1328
4-CF ₃	17	2703
4-CF ₃ , NH ₂	17	2703



unsubstituted R:
weak SSRI, SNRI

R type & position are critical

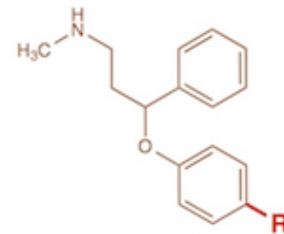
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4-CF ₃ , NH ₂	17	2703



R type & position are critical

2-substituted analogues are weak SSRI, but **potent & selective** towards NE reuptake

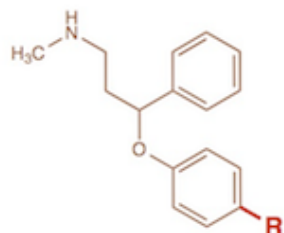
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4-CF ₃	17	2703
4-CF ₃ , NH ₂	17	2703



R type & position are critical

2-CH₃ : weak SSRI;
4-CH₃ : better potency & selectivity towards 5-HT reuptake blockade

R=	inhibition of reuptake (K _i nM)	
	5-HT	NE
H	102	200
2-OCH ₃	1371	2.4
2-SCH ₃	130	0.2
2-CH ₃	390	3.4
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2-CF ₃	1489	4467
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4-CF ₃ , NH ₂	17	2703



R type & position are critical

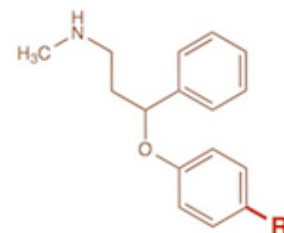
2-CH₃ : weak SSRI;
4-CH₃ : better potency & selectivity towards 5-HT reuptake blockade

as SSRI
also, 2-OCH₃ <<< 4-OCH₃

Ortho substitution

may act as **conformational blocker** - better binding to NE transporter

R=	inhibition of reuptake (K _i nM)	
	5-HT	NE
H	102	200
2-OCH ₃	1371	2.4
2-SCH ₃	130	0.2
2-CH ₃	390	3.4
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2-CF ₃	1489	4467
3-CF ₃	16	1328
4-CF ₃	17	2703
4-CF ₃ , NH ₂	17	2703



R type & position are critical

AS SSRI,
4-CF₃ ≈ 3-CF₃ >>> 2-CF₃

s-fluoxetine, 100X selective as ssRI than R-isomer

R=	inhibition of reuptake (K _i nM)	
	5-HT	NE
H	102	200
2-OCH ₃	1371	2.4
2-SCH ₃	130	0.2
2-CH ₃	390	3.4
4-CH ₃	95	570
4-OCH ₃	71	1207
* 2-CF ₃	1489	4467
* 3-CF ₃	16	1328
* 4-CF ₃	17	2703
fluoxetine * 4-CF ₃	17	2703
norfluoxetine 4-CF ₃ , NH ₂	17	2703

phenoxyphenylpr
opylamines

