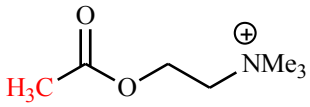
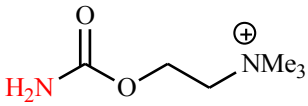
Answers to end-of-chapter questions

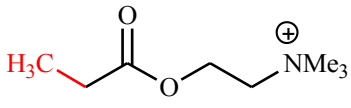
1) The three molecules are very similar to each other. Structures I and II differ from acetylcholine in having an amino group and an ethyl group respectively instead of a methyl group.



Acetylcholine



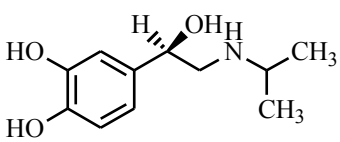
I



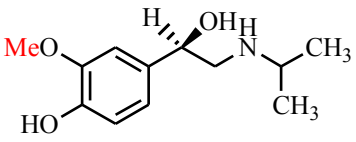
II

One might expect structure II to be active since a methyl and ethyl group are more similar to each other than to an amino group. Both are hydrophobic groups that can interact by van der Waals interactions. In contrast, the NH_2 group is a polar group that is more likely to interact by hydrogen bonding. The fact that structure I is active and structure II is inactive suggests that it is not the type of binding that is crucial here but that the difference in activity is due to the sizes of the different groups. The methyl and amino groups are similar in size, whereas the ethyl group is larger. If the space available in the binding site is limited, structure II may not fit due to the larger ethyl group. Further details can be found in sections 22.5-22.7.

2) The inactive metabolite has a methyl ether rather than a phenol group. This indicates that the phenol group is an important binding group when isoprenaline interacts with the adrenergic receptor. For example, the hydrogen atom of the phenol group may act as a hydrogen bond donor to a corresponding hydrogen bond acceptor in the binding site. This interaction is no longer possible for the inactive metabolite. Another possibility is that the phenolic oxygen acts as a hydrogen bond acceptor and that the methyl group in the metabolite prevents this interaction due to its size and bulk (see also sections 14.2.6 and 23.10.3).



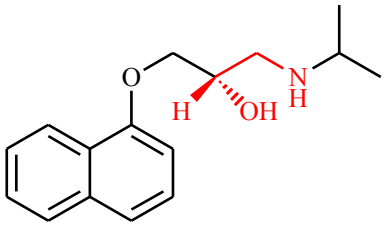
Isoprenaline



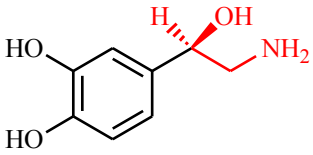
Inactive metabolite

3) This question is related to question 3 in Chapter 4. Larger and bulkier *N*-alkyl groups result in selectivity for the β-receptors (see also section 23.10.3)

4) Both molecules contain the identical moiety shown in red.

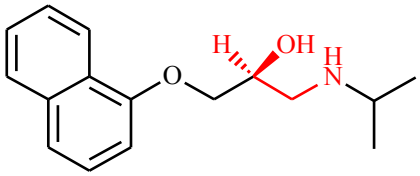


Propranolol



Noradrenaline

The carbon bearing the alcohol group is an asymmetric centre has the same configuration in each molecule. This is demonstrated by redrawing propranolol as follows:

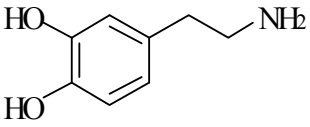


Propranolol

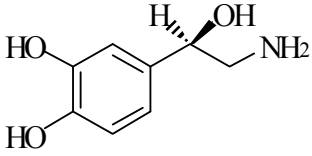
Therefore, it is possible for this moiety in both molecules to form similar interactions with the receptor. However, the aromatic systems are different and so different interactions are possible here. This can account for propranolol acting as an antagonist rather than as an agonist if a different induced fit results.

Propranolol is likely to show β-adrenergic selectivity due to the fact that it has a bulky *N*-alkyl substituent (compare question 3 above and section 23.11.3)

5) There are clear structural similarities between dopamine and noradrenaline.

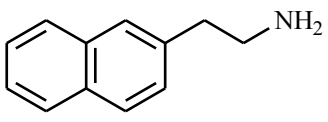


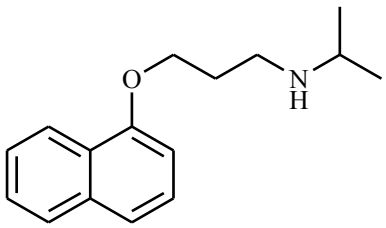
Dopamine

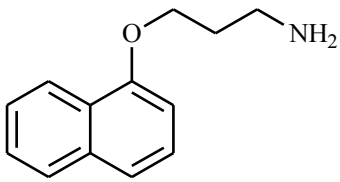


Noradrenaline

For that reason, it is possible that dopamine has similar binding interactions with its receptor. Taking this argument further, strategies that led to antagonists for adrenergic receptors might also work in designing antagonists for the dopamine receptor. Replacing the catechol ring system of noradrenaline with a naphthalene ring resulted in adrenergic antagonists, so similar tactics with dopamine might also be successful. The following structures would be worth investigating.

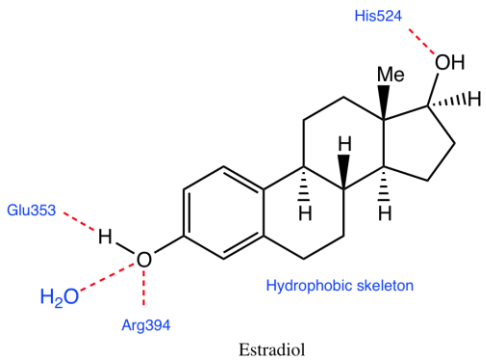




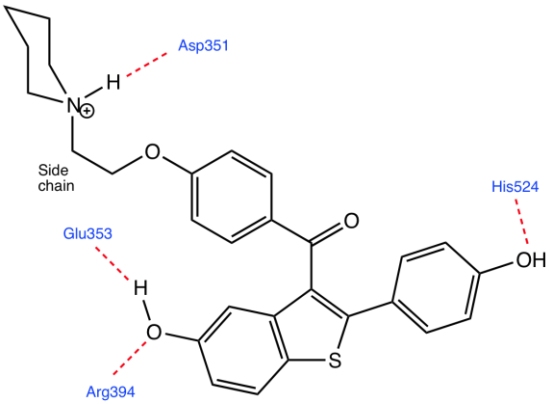


The first structure is a straight replacement of the catechol ring of dopamine with a naphthalene ring. The other two structures are based on the adrenergic antagonist propranolol, where the alcohol and/or *N*-alkyl groups have been removed.
Since all these structures lack the side chain alcohol, they are unlikely to bind to adrenergic receptors.

6) It is worth considering the interactions of estradiol and raloxifene with the estrogen receptor (box 8.2) in order to answer this question.



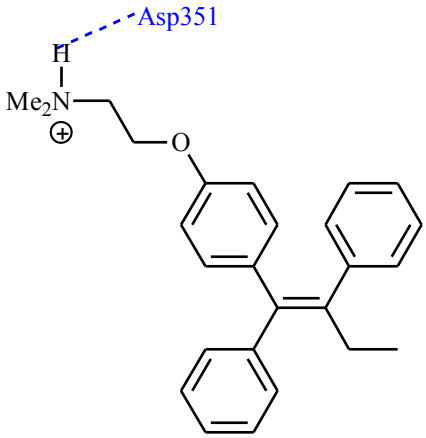
Estradiol



Raloxifene

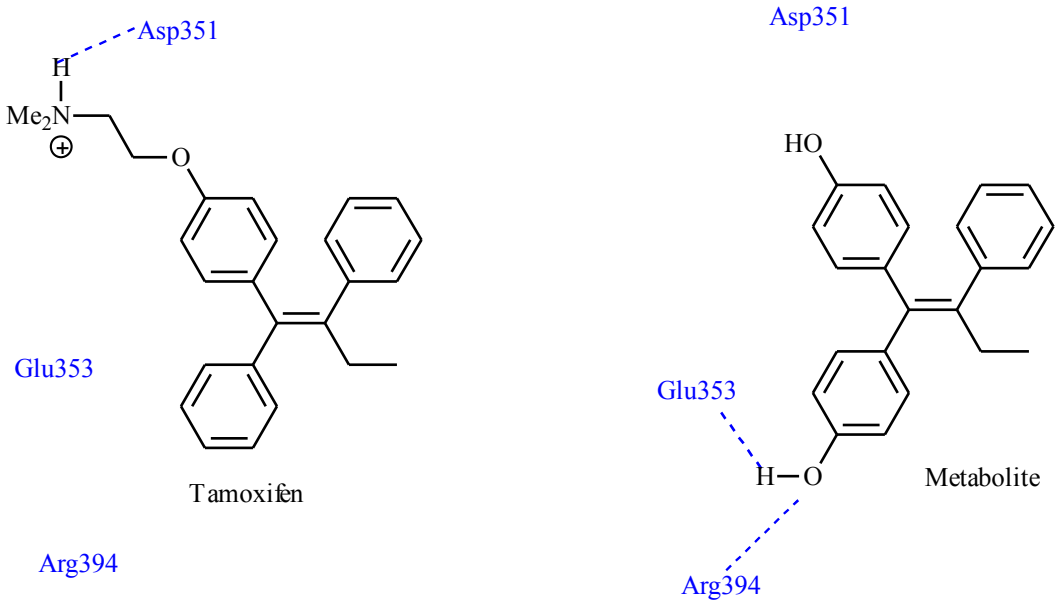
(Modified diagram)

Both estradiol and raloxifene contain functional groups that interact through hydrogen bonding to the amino acids Glu-353, Arg-394 and His-524. Both molecules have hydrophobic skeletons that position these groups correctly and match the hydrophobic nature of the binding site. Estradiol is an agonist whereas raloxifene is an antagonist. This is due to the extra interaction with Asp-351 that is possible for raloxifene.
Turning now to tamoxifen, this molecule is also hydrophobic and of a similar size to the above, allowing it to fit the hydrophobic binding site. It does not have the phenol or alcohol functional groups present in estradiol or raloxifene, but it does have a group that can interact with Asp-351 in the same way as raloxifene. Therefore, it binds as an antagonist.



Tamoxifen

7) Although tamoxifen itself is an antagonist, its metabolite is an agonist. This is because it has lost the group that is so crucial for antagonist activity (the side chain containing the amine). It also contains a phenol group which can mimic the phenolic group of estradiol (see above Q6).



8)
The data required to create Schild plots are the following

Normorphine and naloxone

[I]	dose ratio	log[I]	1/dose ratio	log(1/dose ratio)
1×10^{-6}	0.0018	-6	555.6	2.75
1×10^{-7}	0.0178	-7	56.2	1.75
3.162×10^{-8}	0.1122	-7.5	8.91	0.95

Metkephamid and naloxone

[I]	dose ratio	log[I]	1/dose ratio	log(1/dose ratio)
3.16×10^{-7}	0.0562	-6.5	17.8	1.25
1×10^{-7}	0.1585	-7	6.31	0.8
3.162×10^{-8}	0.7943	-7.5	1.26	0.1

Met-enkephalin and naloxone

[I]	dose ratio	log[I]	1/dose ratio	log(1/dose ratio)
3.16×10^{-7}	0.0398	-6.5	25.13	1.4
1×10^{-7}	0.2512	-7	3.98	0.6
3.162×10^{-8}	0.8913	-7.5	1.12	0.05

The Schild plots have the following intersections with the x-axis. These correspond to the values for pA_2
Normorphine and naloxone -8.36
Metkephamid and naloxone -7.61
Met-enkephalin and naloxone -7.50
The values of pA_2 are similar for metkephamid and Met-enkephalin indicating that these have similar target selectivities.