

Medicinal Chemistry
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Optimizing Drug-Target Interactions Part-2

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*Optimizing Drug-Target
Interactions*
Part 2



Alright, so welcome back. In today's lecture we are going to continue to look at how to optimize drug target interactions and we have spent a fair amount of time in trying to figure out what are the best ways to understand, how a drug interacts with its targets and now what we would need to do is we need to optimize this because there are certain properties of the drug that are not very desirable in the context of further development and so one would need to have you know better understanding of how to enhance the properties as far as how well it interacts with the target, as well as being able to survive the on slot by the metabolic process in order to get there.

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Isosteres

- Isosteres are atoms or groups of atoms which share the same valency and which have chemical or physical similarities
- For example, SH, NH₂, and CH₃ are isosteres of OH, whereas S, NH, and CH₂ are isosteres of O.
- Isosteres can be used to determine whether a particular group is an important binding group or not by altering the character of the molecule in as controlled a way as possible.





Patrick, G. L.

Now in this connection we shall first introduce the concept of isosteres, isosteres are basically atoms or groups of atoms which share the same valency and which have the chemical and physical similarities. So simple example here is that thiol SH, NH₂ and CH₃ would be good isosteres of alcohols. So if you see the similarity you have one oxygen attached to hydrogen and therefore you can think about a thiol which is sulphur based molecule or an amine which is a nitrogen based molecule or methyl group which is a carbon based molecule and they all have hydrogens attached to them and this can potentially act as isosteres of alcohols, whereas if you think about ether such as R-O-R here just a sulphur NH and CH₂ would be the isosteres of oxygen.

So isosteres are very important because they can be used to determine whether the group is important in binding, or not. And so if one were to replace the molecule with the isostere then we could you know fairly controlled way find out whether that group is important or not?

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- Replacing O with CH₂, for example, makes little difference to the size of the analogue, but will have a marked effect on its polarity, electronic distribution, and bonding.
- Replacing OH with the larger SH may not have such an influence on the electronic character, but steric factors become more significant.



Patrick, G. L.

So for example if you replace an oxygen with a CH₂ then it would make a little difference to the size of the compound, but now the polarity, electronic distribution and bonding are all going to change. So for example an oxygen has two lone pairs which are going to be involved in potentially hydrogen bonds, whereas CH₂ is not capable of doing that. So such replacements will have a tremendous impact on the polarity, electronic distribution but will not have much of an impact on the size.

Similarly replacing an OH with a larger thiol SH group may not have an influence on the electronic character, but because you are starting with an oxygen and then replacing it with the sulphur since the size of the molecule of the group has gone up, there is going to be sterics which are going to start playing a role.

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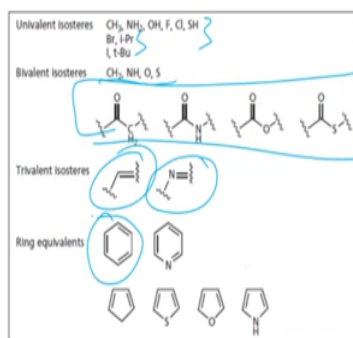
- *Isosteric groups could be used to determine whether a particular group is involved in hydrogen bonding.*
- *For example, replacing OH with CH₃ would completely eliminate hydrogen bonding, whereas replacing OH with NH₂ would not.*

Patrick, G. L.



So isosteric groups could be used to determine whether a particular group is involved in hydrogen bonding. So if we have an OH and if that hydrogen bonding is important, now replacing the alcohol with the methyl group would completely eliminate hydrogen bonding and whereas replacing an OH with NH₂ would not. So using this kind of a trial and error method one would be able to figure out whether hydrogen bonding is important?

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- *Some examples are shown here...*

Patrick, G. L.



So in this figure we have some examples of isosteres, and so we have already looked at some of the univalent isosteres that is CH₃, NH₂, OH you can also replace the group with a fluorine, chlorine or even a thiol and other halogens such as BR. Now you can replace a methyl group with isopropyl or tertiary butyl for example. And then there are bivalent

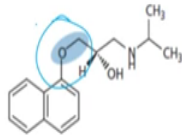
isosteres which wherein you have CH₂, NH, O and S which can work with two different functional groups I mean two different groups on both sides.

And if you think about it then you can also have these are the isosteres where you have various esters and amides and thio esters for example they are all going to be bivalent isosteres. You can also have trivalent isosteres, so for example if you have an (O)(4:22) then you have three potential groups which can be placed on the (O)(4:26), whereas in isostere of an (O)(4:29) would be an amine, so where you have again a trivalent situation.


So if your molecule has a ring such as a benzene ring then one could replace it with various heterocyclic rings as shown here and these would be good ring equivalence.

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- For propranolol, replacement of the OCH₂ linker with isosteres CH=CH, SCH₂, or CH₂CH₂ eliminates activity...
- Whereas replacement with NHCH₂ retains the activity
- This suggests that the oxygen is important to the activity of the drug and that perhaps, it is involved in H-bonding with the receptor...



Patrick, G. L.



So let us take an example so for propranolol whose structure is shown here, replacement of the OCH₂ linker with isosteres CH double bond CH, SCH₂, or CH₂CH₂ eliminates activity, whereas replacement with NHCH₂ reduces the activity. So from these two experiments what we can sort of conclude is that it is possible that the hydrogen bonding capability is important.

So when you have an oxygen present then it can involve itself in hydrogen bonding and when you replace this with an (O)(5:21) or even a thio S ether then these two functional groups are not capable of doing hydrogen bonding. And similarly CH₂CH₂ also is an example because that also tells you that hydrogen bonding is important because that is not going to play a role. And more importantly when you replace the oxygen with a nitrogen which is still capable of doing hydrogen bonding the activity does not go down.

So from this set of experiments one can conclude that the hydrogen bonding of this group is going to be an important factor in the activity of the compound.

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Testing procedures

- When investigating structure-activity relationships for drug-target binding interactions, biological testing should involve in vitro tests; for example inhibition studies on isolated enzymes or binding studies on membrane-bound receptors in whole cells.
- The results then show conclusively which binding groups are important in drug-target interactions.

Patrick, G. L.



Now we shall spend a little bit of time and understand what are the various testing procedures that we would use in investigating isosteres? So when doing such structure activity relationships, we should restrict ourselves to in vitro tests. So if you are looking at a particular receptor or we are looking at a particular enzyme then it is better for us to restrict ourselves to the enzyme or to the receptor as the case may be because these would help us understand whether the binding groups are important in the drug target interactions.

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- If *in vivo* testing is carried out, the results are less clear-cut because loss of activity may be due to the inability of the drug to reach its target rather than reduced drug-target interactions...
- However, *in vivo* testing may reveal functional groups that are important in protecting or assisting the drug in its passage through the body.
- This of course is not revealed by an in vitro test.

Patrick, G. L.



So if we were to resolve to in vivo testing then the results become less clear because what is possible is that the compound may not reach that target and so we would not get an idea about whether the lower activity is due to the reduced drug target interactions or because of metabolism that the compound is not getting to the place where it supposed to get in. So in vivo functional groups are useful of course because they will reveal whether the functional groups are important in protecting or assisting the drug in its passage through the body and this obviously is not revealed by an in vitro test.

But when we are looking at isosteres, when we are trying to understand or optimize drug target interactions it is very important that we restrict ourselves at this point to in vitro (7:23) because one can make far more conclusions from the (7:26) with respect to the drug target interaction than an in vivo (7:31).

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Identifying a pharmacophore

- Once it is established which groups are important for a drug's activity, it is possible to move on to the next stage—the identification of the pharmacophore.
- The pharmacophore summarizes the important binding groups that are required for activity, and their relative positions in space with respect to each other.

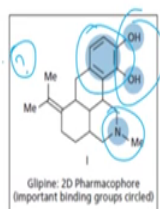
Patrick, G. L.



So the next step in our drug target optimization would be to identify a pharmacophore, we have already defined what a pharmacophore is, but we shall look at it once again. So pharmacophore basically summarizes the important binding groups that are required for activity and more importantly their relative position in space with respect to each other. So for this we need to establish what groups are important for a drug's activity and then since we are aware of the structure, we would be able to sort of suggest what is the relative position of these groups with respect to each other? So a lot of optimization process would involve the identification of a pharmacophore.

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- If we discover that the important binding groups for our hypothetical drug glipine are the two phenol groups, the aromatic ring, and the nitrogen atom



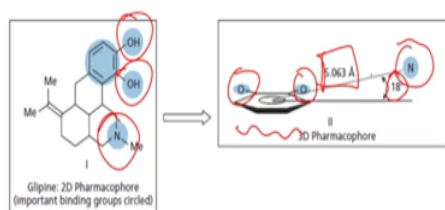
Patrick, G. L.



So if we discover that the important binding groups for example the hypothetical drug that we looked at, we looked at the important functional groups which are the two phenol functional groups, the aromatic ring and the nitrogen atom. So they are all shown here for us to understand. Now what this means is that if these are the only important functional groups then perhaps the other parts of it can actually be cut out, that is the question that one could ask.

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- The two-dimensional (2D) pharmacophore is shown on the left and structure II shows the three dimensional (3D) pharmacophore.



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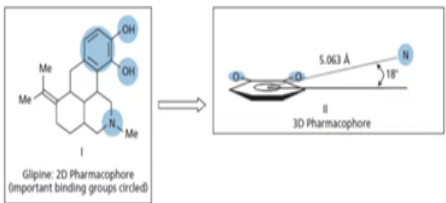
So now if I have to construct the 2D pharmacophore which is shown here, then we can think about the 3D pharmacophore. So if we have the bond distances in our hand then one could draw out a structure which is going to be something like this where you have a 3D

pharmacophore. So here is the nitrogen of the NMe, here are the two phenols that we see here and this as you can see is the aromatic ring.

So if we were to measure the distance between the nitrogen group and the centre of the aromatic ring, this turns out to be 5.063 angstrom. And because the compound is not planar you know the nitrogen group is bend out of plane and if you measure the angle at which this nitrogen is present they turns out to be around 18 degrees. So what we are doing in this process is we are identifying the most important functional groups and then we are trying to locate them in 3 dimensional space and from this process we are going to try to identify the 3 dimensional pharmacophore.

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- The latter specifies the relative positions of the important groups in space.
- In this case, the nitrogen atom is 5.063 Å from the centre of the phenolic ring and lies at an angle of 18° from the plane of the ring.



I
Gilpine: 2D Pharmacophore
(important binding groups circled)

II
3D Pharmacophore

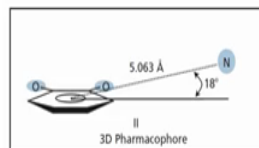
Patrick, G. L.



So the distance of 5.063 angstrom is something that is very important in identifying the pharmacophore because once we know the target then we would try to position this molecule in such a way that this distance may have a role to play. So as we looked at previously the angle that we found was 18 degrees from the plane of the ring.

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- Note that it is not necessary to show the specific skeleton connecting the important groups.
- There are benefits in not doing so, as it is easier to compare the 3D pharmacophores from different structural classes of compound to see if they share a **common pharmacophore**.
- Three-dimensional pharmacophores can be defined using molecular modelling (more on this later...)



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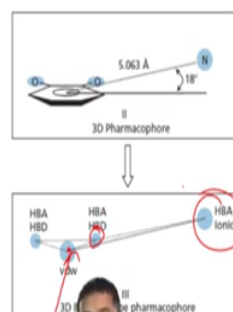


So it is not necessary to show the specific skeleton connecting the important groups. So this is the major benefit of using 3D pharmacophores. So then what we could start doing is to compare various 3D pharmacophores from different structural classes which share a common pharmacophore. So what we would need to do is to basically arrive upon a aromatic ring with perhaps two hydrogen bonding groups on it and then about 5.063 angstrom if there should be a nitrogen present.

So these are some basic structural characteristics which you can start identifying in the pharmacophore, we will look at this in more detail when we are discussing molecular modeling later on in this course.

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- Here, the bonding characteristics of each functional group are defined, rather than the group itself.
- Note also that the groups are defined as points in space.
- This includes the aromatic ring, which is defined by the centroid. All the points are connected by **pharmacophoric triangles** to define their positions.
- This allows the comparison of molecules which may have the same pharmacophore and binding interactions, but which use different functional groups to achieve these interactions.



Patrick, G. L.



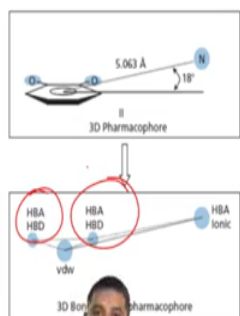
So the bonding characteristics of each functional group is defined, rather than the group itself. So what we will next we will do is, we will define this OH group as a hydrogen bond acceptor as well as a hydrogen bond donor. Then the aromatic ring, which was there for Van der Waals interactions the centre of the aromatic ring can now be important because then we can start drawing triangles. So all the functional groups can now be positioned in the right manner.

So what we do is, we can start drawing triangles among these three points. For example this is the centre of the aromatic ring so that can be a vertex and then one of the hydrogen bond donors and acceptor which is the OH group can be another vertex and the third one over here can be the third vertex, so you get a triangle there. Similarly you can take this hydrogen bond acceptor the centre of this benzene ring and the hydrogen bond acceptor slash ionic group which is a nitrogen group can be the third vertex and then you can draw second triangle.

So we are now condensed or brought down the molecule into two triangles that are going to be important in the pharmacophore. So then this process helps us compare molecules which have the same pharmacophore and binding interactions. But now we can then start looking at different functional groups to achieve the same result.

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In this case, the phenol groups can act as hydrogen bond donors or acceptors, the aromatic ring can participate in van der Waals interactions, and the amine can act as a hydrogen bond acceptor or as an ionic centre if it is protonated.



Patrick, G. L.


So in this case we are looking at the phenol groups which can act as hydrogen bond donors or acceptors, the aromatic ring which can participate in Van der Waals interactions and the amine which can act as a hydrogen bond acceptor or as an ionic centre if protonated. But we can now replace the phenol for example with an amine because what we are looking for is a

hydrogen bond acceptor, hydrogen bond donor or we can replace it with a thiol perhaps if the H is important and then we can replace the aromatic ring for example with various heterocyclic rings that we looked at, they would all produce the right sort of Van der Waals interaction and then the nitrogen can also be replaced if necessary.

So I think in this process we are able to figure out that you can now think about the molecule in terms of the various functional groups that are present which are important for activity and again these functional groups have been brought identified based on various synthetic modifications that we have made previously and then studying the activity and then once we find that the activity is not changed then we would assume that the group is not important and so on.

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- Identifying 3D pharmacophores is relatively easy for rigid cyclic structures, such as the hypothetical glipine.
- With more **flexible structures**, it is not so straightforward because the molecule can adopt a large number of **shapes or conformations** which place the important binding groups in different positions relative to each other.
- Normally, only one of these conformations is recognized and bound by the binding site.
- This conformation is known as the **active conformation**.



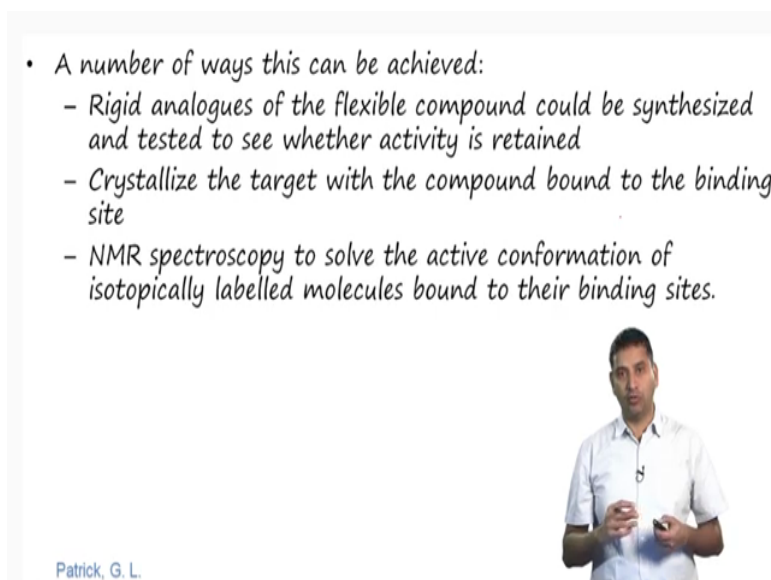
Patrick, G. L.

So identifying 3D pharmacophores is not very difficult for rigid cyclic structures. For example the glipine example that we looked at, but when you have flexible structures then the problem is not as straight forward because what happens as we know is that there is going to be a large number of shapes or conformations that the molecule is going to possibly take up.

So this then become more complicated to interpret because the important binding groups may actually be a particular conformation which can be the active conformation and if they are not present in that conformation then the molecule may not be active. So again we will look at this in little bit of more detail later, but what one may safely assume is that only one or may be a few of the conformations of the molecule is recognized and bound by the binding site

and so if you have a linear molecule it becomes a little bit more complicated to make interpretations around this concept.

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A slide with handwritten text and a presenter. The text is as follows:

- A number of ways this can be achieved:
 - Rigid analogues of the flexible compound could be synthesized and tested to see whether activity is retained
 - Crystallize the target with the compound bound to the binding site
 - NMR spectroscopy to solve the active conformation of isotopically labelled molecules bound to their binding sites.

Patrick, G. L.


The slide also features a small video inset of a man in a white shirt, identified as Patrick G. L., who is speaking and gesturing with his hands.

So a number of ways in which we can identify these pharmacophores is what we can do is we can now make rigid analogues of the flexible molecule and then test and see whether they are going to act in the same way, if we are lucky we can also crystalize the target molecule with the compound and then find out what the important interactions are in the binding sites. So here we would need to use a combination of X ray crystallography and computational tools.

One can also use NMR spectroscopy, so what we could do is we could take isotopically labelled molecules and find out how they are going to bind to target. So this is a relatively new phenomenon and but this can also be used to solve the or to identify the active conformation.

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- *One must be cautious:*
 - *It is not uncommon to find compounds that have the correct pharmacophore, but show disappointing activity and poor binding.*
 - *It is important to realize that the overall skeleton of the molecule is involved in interactions with the binding site through van der Waals and hydrophobic interactions.*
 - *The strength of these interactions can sometimes be crucial in whether a drug binds effectively or not, and the pharmacophore does not take this into account.*




Patrick, G. L.

So in doing all of this one must be cautious because it is not uncommon to find compounds that have the correct pharmacophore, but do not show any activity or binding because we have to understand that in glipine there are three other rings that are important, we do not know how the positioning of those rings has helped in contribution to the activity. So when we are making analogues it is important for us to understand that the overall skeleton of the molecule may change when we are making new analogues.

And it is also possible that the for example the ring in glipine can be involved in Van der Waals interactions or hydrophobic interactions and those also may contribute to the activity. So the strength of even these weak interactions can sometimes be crucial in whether a drug binds effectively or not and the 3D pharmacophore will not take this into account because we are trying to sort of minimize the variables in constructing the 3D pharmacophore.

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- One must be cautious:
 - The **strength of these interactions** can sometimes be crucial in whether a drug binds effectively or not, and the 3D pharmacophore does not take this into account.
 - The pharmacophore also does not take into account **the size of a molecule** and whether it will fit the binding site.
 - A functional group that is part of the pharmacophore **may not be so crucial** if an agent can form an **alternative binding interaction with the binding site**.



Patrick, G. L.


So therefore the strength of the interactions which are very crucial is not taken into account when we are constructing a 3D pharmacophore and the pharmacophore also does not take into account the size of the molecule and whether it will fit into the binding site. So a functional group that is part of the pharmacophore may not be so crucial if an agent can form an alternating binding interaction with the binding site.

So it is possible that you know when we are having a functional group that is part of the pharmacophore and in our initial studies it shows that group is important, but when we make an analogue it is possible that an alternate binding interaction occurs in the binding site which compensates for this. So there are some caveats when we are doing this analysis with the 3D pharmacophore which one must be cautious about.

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Summary

- SARs define the functional groups or regions of a lead compound which are important to its biological activity.
- Functional groups, such as alcohols, amines, esters, amides, carboxylic acids, phenols, and ketones, can interact with binding sites by means of hydrogen bonding.
- Functional groups, such as aminium ions, quaternary ammonium salts, and carboxylate groups, can interact with binding sites by ionic bonding.



Patrick, G. L.


So to summarize the past few topics that we have looked at, we have looked at structure activity relationship or SAR and what this does is this defines the functional group or the regions of a lead compound which are important towards biological activity. So we have looked at various functional groups which are such as alcohols, amines, esters, amides, carboxylic acids, phenols and ketones and these can potentially interact with the site by hydrogen bonding.

There are also other functional groups such as aminium ions, quaternary ammonium salts and carboxylates which have a full positive charge or a full negative charge and this can bind by ionic binding.

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Summary

- Functional groups, such as alkenes and aromatic rings, can interact with binding sites by means of van der Waals interactions.
- Alkyl substituents and the carbon skeleton of the lead compound can interact with **hydrophobic regions** of binding sites by means of van der Waals interactions.
- Interactions involving dipole moments or induced dipole moments may play a role in binding a lead compound to a binding site.




Patrick, G. L.

There are functional groups which interact through Van der Waals interactions and examples of these are (O)(18:05) or alkenes and aromatic rings and alkenes substituents which are present on many drugs are very important regions for hydrophobic interactions and this actually may play a role the way in which the molecule is going to enter the active site for example. The interactions involving dipole moments or induced dipole moments although they are quite weak in nature may play an important role in certain lead compounds.

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Summary

- *Reactive functional groups, such as alkyl halides, may result in irreversible covalent bonds being formed between a lead compound and its target.*
- *The relevance of a functional group to binding can be determined by preparing analogues where the functional group is modified or removed in order to see whether activity is affected by such a change.*




Patrick, G. L.

And we have looked at certain reactive functional groups, such as alkyl halides and what this can do is that they can irreversibly modify the target and therefore they are not very useful in certain drug development cases. So the relevance of a particular functional group which is part of the lead may be determined by preparing analogues. So for example you can convert a hydroxyl group to a methyl group and then you can study whether the hydroxyl group is important for the activity or not and we have looked at this systematically how to change these groups and understand what is the effect of this.

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Summary

- Some functional groups can be important to the activity of a lead compound for reasons other than target binding
- They may play a role in the **electronic or stereochemical properties** of the compound, or they may have an important pharmacokinetic role.
- Replacing a group in the lead compound with an **isostere** (a group having the same valency) makes it easier to determine whether a particular property, such as hydrogen bonding, is important.




Patrick, G. L.

And some functional groups can be important to the activity of a lead compound for reasons other than target binding. So for example there may be some important electronic effect of the functional group or there may be stereochemical properties of the group which may play a role. Now replacing a group in the lead compound with what is known as an isostere helps us understand whether that particular property or the functional group is important or not. The most common example is hydrogen bonding.

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Summary

- *In vitro* testing procedures should be used to determine the SAR for target binding.
- The pharmacophore summarizes the groups which are important in binding a lead compound to its target, as well as their relative positions in three dimensions.



Patrick, G. L.

And it is recommended that *in vitro* test procedures are used when we are doing the structure activity relationship because that will avoid the some of the complications that are associated


with in vivo experiments because keep in mind the objective of structure activity relationship at this point is to understand how well the drug interacts with the target.

And we have looked at the concept of the pharmacophore which basically summarizes where the groups are and how they are going to bind to the target and the relative position of these functional groups can be defined in three dimensions, we have looked at the 3D pharmacophore definition, we will look at this in more detail when we are looking at computational studies. So with this we have sort of figured out how to optimize this interactions between drug and its target.

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Drug optimization: strategies in drug design

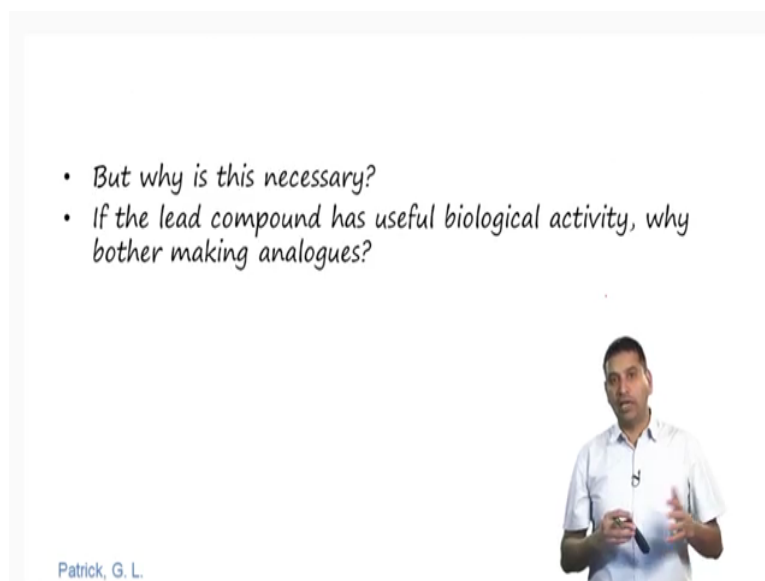
- In vitro testing procedures should be used to determine the SAR for target binding.*
- The pharmacophore summarizes the groups which are important in binding a lead compound to its target, as well as their relative positions in three dimensions.*



Patrick, G. L.

Now what we will do is we will look at how these strategies can be used in drug design. So the pharmacophore summarizes the groups which are important in binding a lead compound towards target as well as the relative positions in three dimensions.

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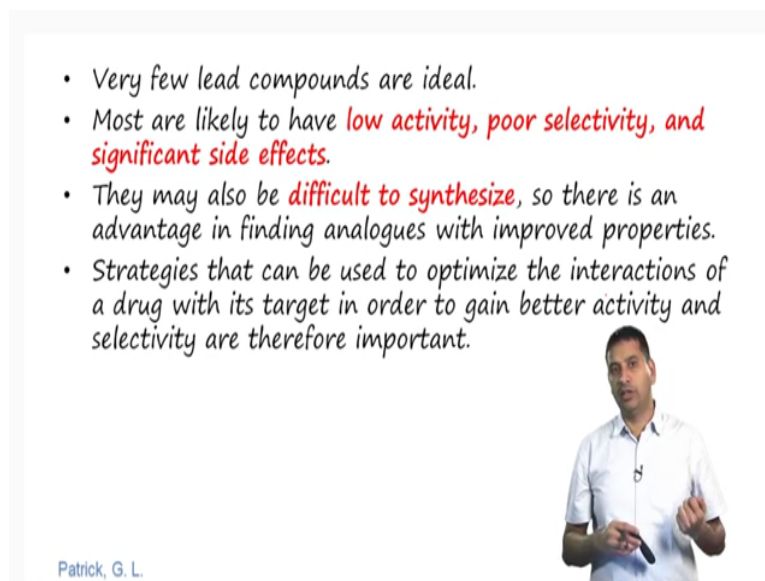
A slide with a white background and a thin grey border. It contains two bullet points in a handwritten-style font. The first bullet point asks 'But why is this necessary?'. The second bullet point asks 'If the lead compound has useful biological activity, why bother making analogues?'. In the bottom right corner, there is a small video inset of a man in a white shirt speaking. The name 'Patrick, G. L.' is written in the bottom left corner.

- *But why is this necessary?*
- *If the lead compound has useful biological activity, why bother making analogues?*

Patrick, G. L.

But why is this necessary? If the lead compound has useful biological activity, why even bother making analogues? So this is an important question that we need to answer.

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A slide with a white background and a thin grey border. It contains four bullet points in a handwritten-style font. The second bullet point has some words in red: 'low activity, poor selectivity, and significant side effects'. The third bullet point has 'difficult to synthesize' in red. The fourth bullet point is about optimizing interactions. In the bottom right corner, there is a small video inset of a man in a white shirt speaking. The name 'Patrick, G. L.' is written in the bottom left corner.

- *Very few lead compounds are ideal.*
- *Most are likely to have low activity, poor selectivity, and significant side effects.*
- *They may also be difficult to synthesize, so there is an advantage in finding analogues with improved properties.*
- *Strategies that can be used to optimize the interactions of a drug with its target in order to gain better activity and selectivity are therefore important.*

Patrick, G. L.

And the reason for this is that there are very few lead compounds which are ideal. So some of them have low activity, some of them have poor selectivity and more importantly because they have poor selectivity they may also have significant side effects. We have not covered these aspects but some of the compounds may actually be difficult to synthesize and so scaling it up might be a problem. So finding a compound with improved properties is always something that medicinal chemistry look to do.

So strategies that can be used to optimize the interactions of a drug with its target helps us gain better activity and perhaps in the process we also may get better selectivity and so therefore this is a very important exercise that we use in drug design.

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Variation in substituents: Alkyl groups

- It is not difficult to vary the alkyl substituents of ethers, amines, esters, and amides...

$$\text{Drug-O-R}' \xrightarrow{\text{HBr}} \text{Drug-OH} \xrightarrow[\text{Base}]{\text{R}''\text{X}} \text{Drug-O-R}''$$

$$\text{Drug-N-Me} \xrightarrow{\text{VOC-Cl}} \text{Drug-NH} \xrightarrow{\text{R}} \text{Drug-N-R}'$$

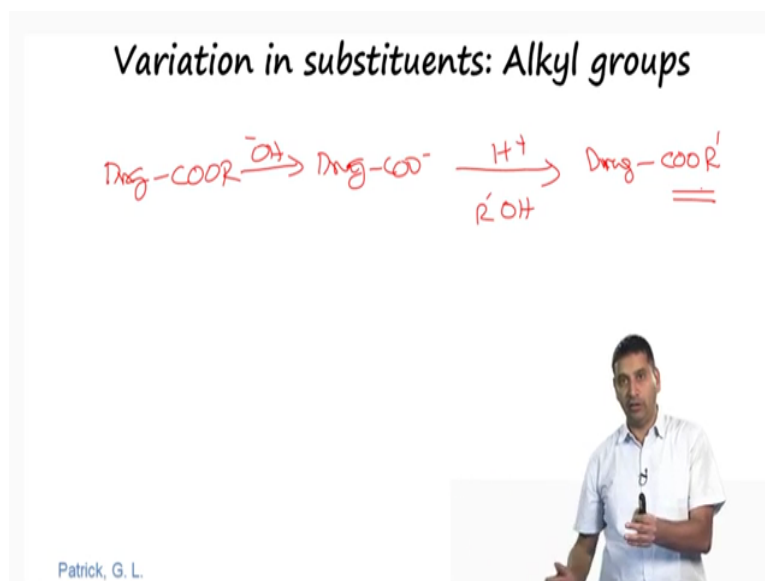
Patrick, G. L.



So some of the ways in which we do this optimization in drug design is to vary substituents. So the first variation in substituents is to vary alkyl groups. So if you have a drug with an ether which I am referring to as R prime then what we could do is to deprotect this ether to convert it to the alcohol, so you will get drug over each which then can be reacted with various alkyl halides perhaps in the presence of a base to give you drug with O-R double prime.

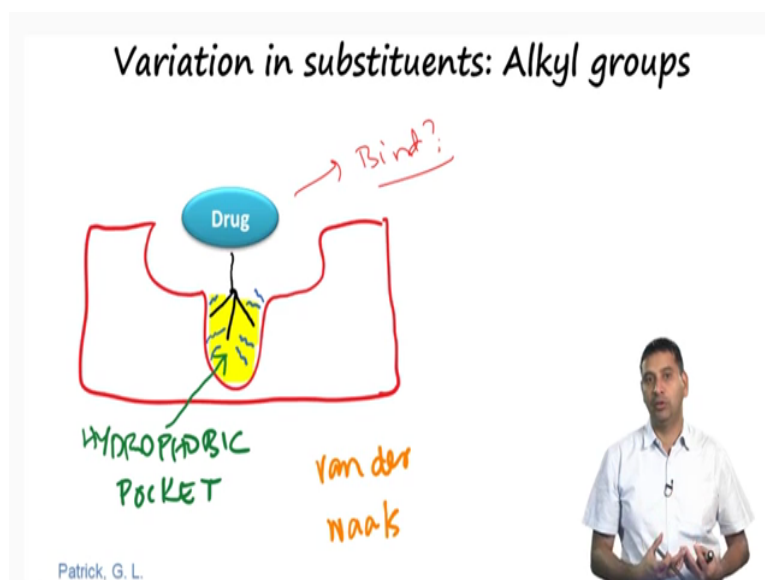
So what this will tell us is that let us say I have a methoxy group I can convert it ethoxy, isopropoxy, tertiary butoxy and so on and try to find out whether those alkyl groups can help with improve properties or not? Similarly if we have a drug with an amine the methyl amine for example what we could do is we have already looked at this vinyl oxy carbonyl chloride which gives you drug with an N H and R which can then subsequently be converted to drug with N R prime R so this helps us get a new series of compounds.

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Now you can also vary alkyl groups on esters. So the way we would do this is take let us say a drug has an ester you would first hydrolyse of the ester you would use some base so you will get drug COO minus which then can subsequently be esterified perhaps with an residic conditions with an R prime and you get COOR prime, so in doing so we can systematically increase the chain length of the ester.

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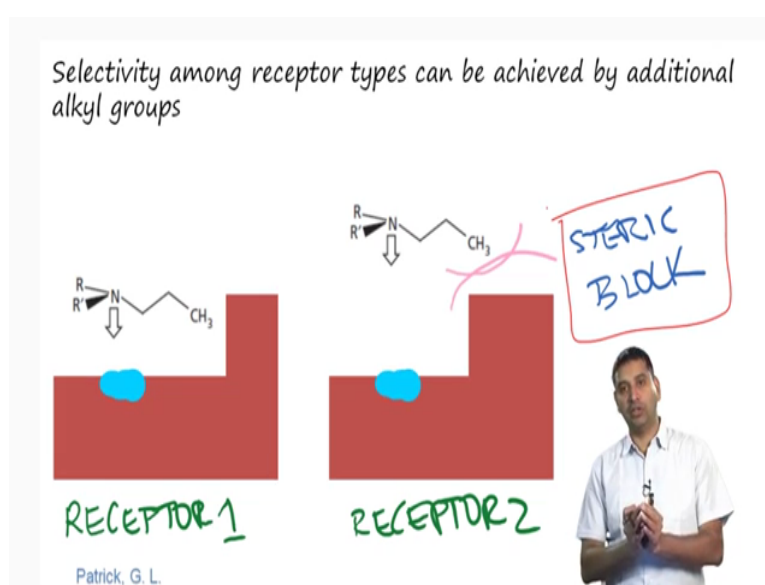


Now what happens for example is when we change the alkyl group imagine this is a protein which has a hydrophobic pocket and now you have a drug which has a methyl group pendent methyl group. Now this methyl group can interact with the hydrophobic pocket and this may be your lead compound. Now if this hydrophobic pocket is important than one could design a

compound where you can extend the chain so that you can improve the binding to the hydrophobic pocket.

So what we would do is to convert the methyl group for example into a tertiary butyl group. So in doing so what we have done is to increase the number of interactions Van der Waals interactions that could occur. So now the question is will this bind better? And that can be answered by doing the experiment, but if we are able to identify a hydrophobic pocket which is important then we could increase the interactions by changing a methyl group to a tertiary butyl group.

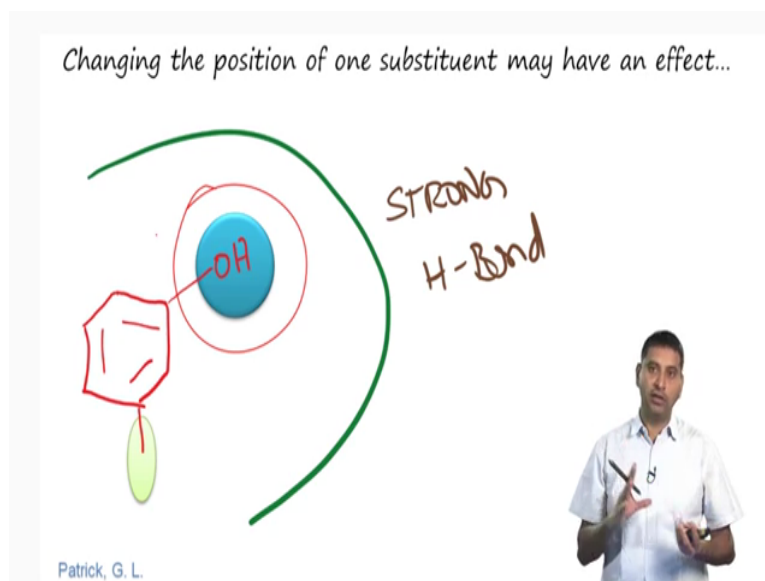
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There is also possible that we may have two different kinds of receptors, so let us say taking hypothetically receptor 1 and receptor 2 and they have very similar binding regions where an amine is going to bind. So if you see here this is a smaller group and this is a larger group over here and so the cavity size is going to be larger here compared to the cavity size here. So if this is something that distinguishes the receptors then what we could do is to increase the number of alkyl groups let us say this methyl group can be converted to a longer chain and it is possible that we can achieve selectivity.

So in the present case by using this molecule we would not be able to achieve selectivity because the binding is going to be identical, whereas if you now increase the carbon chain then it is possible that you may be blocking access to the smaller cavity while retaining the access to the larger cavity. So this concept is called the steric block.

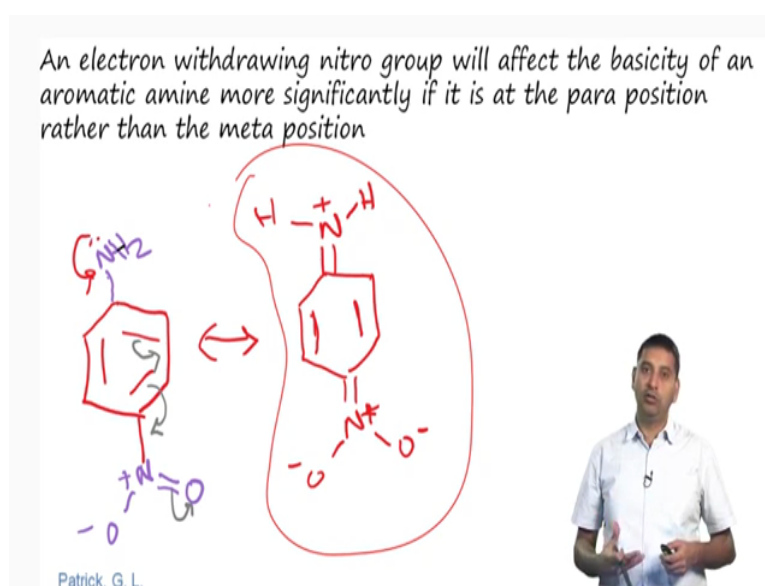
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It is also possible that when you have aromatic substituents you can position the substituents such that the orientation can change. So here is again a hypothetical example where you have a hydrogen bonding region which is going to interact with the hydroxyl group and one could imagine that this group is going to be weak, keep in mind that there is another interaction here with the drug molecule which is going to be important and therefore we want to keep that interaction intact.

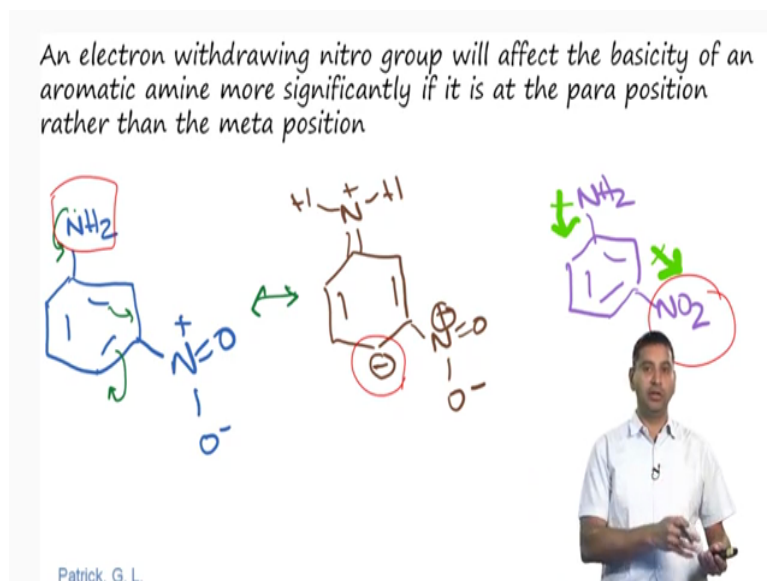
Now when we design the next analogue what we could do is we could change the substituent to the meta position. So here the access to the hydrogen bonding functional group is going to be stronger and then therefore it is possible that this molecule is going to bind much better.

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The next case is when you have an electron withdrawing nitro group will affect the basicity of the aromatic amine far more when it is in the para position when it is compared to the meta position. So now let us look at the para position, so you can push electrons and you get a structure such as this where there is a full positive charge on the nitrogen and there is going to be an extended conjugation. So the lone pair on this nitrogen is clearly not available for donation.

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Whereas if you have it in the meta position, if you push electrons you get a resonance form such as this, but this resonance form is not going to contribute very significantly because it has a full negative charge on the carbon which is not very useful. So the major effect by which this nitro group is going to act is through induction, so it is going to be an electron withdrawing group but it is going to act through induction. So therefore this lone pair is far more available when you have the nitro group in the meta position as compared to the para position.

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At the para position, the nitro group will make the amine a weaker base and less liable to protonate.

This would decrease the amine's ability to interact with ionic binding groups in the binding site, and decrease activity



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So therefore the amines ability to interact with the perhaps an ionic binding group will change and you can actually modulate the activity by changing the position of the electron withdrawing functional group.

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If the substitution pattern is ideal, then we can try varying the substituents themselves.

Substituents have different steric, hydrophobic, and electronic properties, and so varying these properties may have an effect on binding and activity.

For example, activity might be improved by having a more electron-withdrawing substituent, in which case a chloro substituent might be tried in place of a methyl substituent.

More later... QSAR



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So if the substitution pattern is ideal then we can try varying the substituents themselves. So for example substituents which can have different steric, or may be hydrophobic, or electronic properties can be varied and this will have an effect on the binding and the activity. So one way is to have let us say a more electron withdrawing substituents such as the chloro substituent can be tried out instead of a methyl group. So we will look at more of these in

detail when we are studying about or when we are looking about quantitative structure activity relationships in a few lectures from now.

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- When varying substituents, it is normal to study analogues where only one substituent is added or altered at a time.
- In that way, one can identify those substituents that are good for activity and those that are not.
- However, it does not take into account the **synergistic effect** that two or more substituents may have on activity.
- For example, two substituents that are individually bad for activity may actually be beneficial for activity when they are both present.




But when we are varying substituents, it is normal to study analogues where only one substituent is added. So when we are trying to figure out variation one would do it in a very systematic way that is we vary one functional group at a time, but sometimes when there are two different groups which are varied it can result into what is known as the synergistic effect, so both the groups may not contribute much or may not have a substantially increased activity, but when you place them together they are going to have a stronger effect.

So this is something that one needs to be aware of and so individually they may actually be bad for the activity, but when you place them in the right orientation they can have a synergistic effect.

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Extension of the structure

- Addition of another functional group or substituent to the lead compound in order to probe for extra binding interactions with the target...
- Lead compounds are capable of fitting the binding site and have the necessary functional groups to interact with some of the important binding regions present.
- Are all binding sites being accessed?





Patrick, G. L.

The next concept which we are going to look at is extension of the structure, so we already looked at in part when we are looking at the longer alkyl group, but there is a systematic way to do the extension of the structure. So here the concept is that when we are identifying a lead compound and we are going to see what are the major interactions inside the receptor or the enzyme but it is possible that there are some binding sites which are not being accessed. So can we look for extra binding interactions with the target so that is the concept that we want to use here.

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Extension of the structure

- Addition of another functional group or substituent to the lead compound in order to probe for extra binding interactions with the target...



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Extension tactics are often used to find extra hydrophobic regions in a binding site by adding various alkyl or arylalkyl groups.

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So let us imagine that there is a target which has these four major binding areas that we have identified, when we have a lead compound what we perhaps may identify is there can be three of these interactions that are in play. So one can imagine that this is let us say this is Van der Waals interaction and this could be a hydrogen bonding, and this could be an ionic, so this could be any of these combinations are possible but these are the three major interactions that are going to be important.


But we can also identify perhaps another group where may be there is an aromatic pi pi interaction that is possible then what we could do is to add that extra interaction by making a new compound. So by systematically understanding the binding areas one could design compounds that may have an extra interaction which might be useful. So this can be achieved by adding various alkyl or arylalkyl groups.

So if you want to add a may be a (O)(30:51) group or you could also add a group with a benzene ring. So now if this benzene ring is going to go and may be do some stacking interactions with the binding site then it is possible that you can have an extra interaction. So these are some ways to do an extension to get to improved analogue.

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Extension of the structure

- *Substituents containing polar functional groups could be added to probe for extra hydrogen bonding or ionic interactions.*




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So substituents which contain polar functional groups could be added to the lead compound such as an extra hydrogen bonding or extra ionic interaction and then we could potentially probe for better binding to the target.

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- *Extension strategies are used to strengthen the binding interactions and activity of a receptor agonist or an enzyme inhibitor, but they can also be used to convert an agonist into an antagonist.*
- *If the extra binding interaction results in a **different induced fit** from that required to activate the receptor*

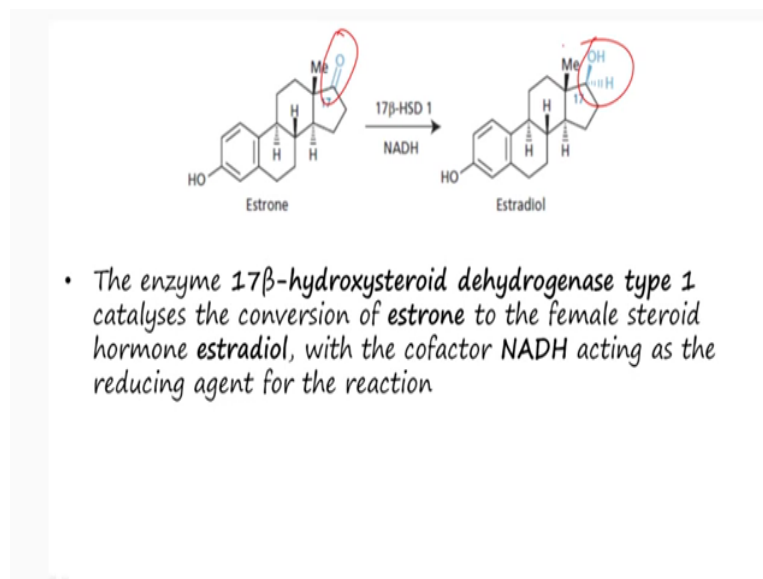


Patrick, G. L.

So extension strategies are used to strengthen the binding interactions and this would help in improving the activity for example when we are looking at a receptor agonist then since you have a stronger binding then you are going to perhaps do the conformational change more efficiently, or when you are looking at an enzyme inhibitor because it is going to go and bind to the enzyme active site, then it is going to be able to inhibit the enzyme better, but you can also use this extension strategy to convert an agonist to an antagonist.

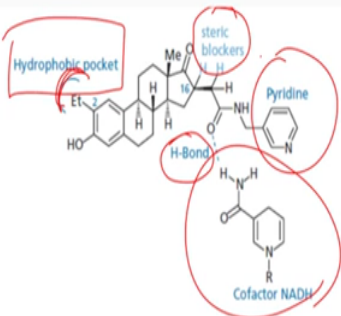
So what may happen is that because you are trying to factor in more interactions, this extra binding interaction can result in a different induced fit. So once you have a different induced fit, it may not activate let us say an ion channel or a GPCR in the same way. So what may happen is the receptor will undergo a conformational change, but it may not be the desired conformational change for the signal to be transmitted. So extension strategies can be used to convert an agonist to an antagonist.

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Now here let us look at an example of this enzyme, so this enzyme is basically a 17 beta hydroxysteroid dehydrogenase. So this uses NADH as a co factor we have already looked at how NADH acts and it is a source of (H⁻)(32:42). So what happens is that this carbonyl becomes an alcohol. So this is let us say an important enzyme in cancer therapy.

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- Inhibition of this enzyme may prove useful in the treatment of **estradiol-dependent tumours** as the levels of estradiol present in the body would be lowered.



Now what we could do in this extension strategy is to add a potential group which is going to bind to a hydrophobic pocket which is present in the enzyme and you can also add what are known as steric block that is you add extra methyl group which we have already looked at and since we know that the co factor is bound to the co factor binding region, so you can position the group such that you have an extra hydrogen bonding capability and you also have a pyridine ring which is present. So this compound was designed to help with inhibiting this enzyme.

So by factoring in extra interactions that could potentially occur what we could do is we could design a better compound. So this compound has been used as a candidate for the treatment of estradiol dependent tumours.