Medicinal Chemistry
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Optimizing Drug-Target Interactions Part-2

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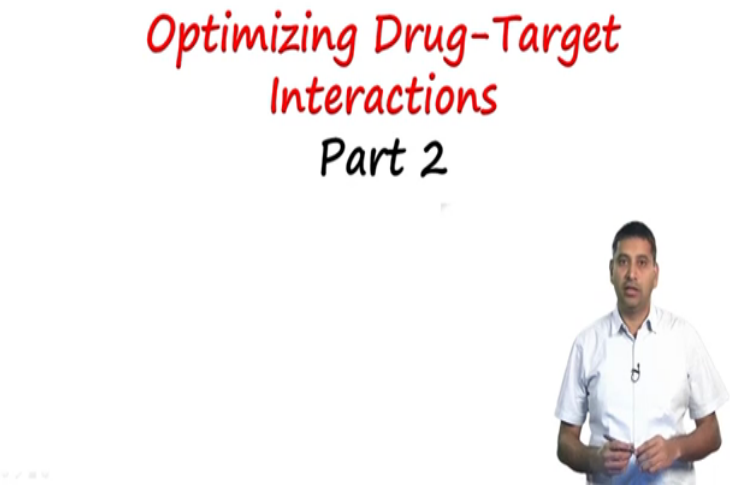

Alright, so welcome back. In today's lecture we are going to continue to look at how to optimize drug target interactions and we have spent a fair amount of time in trying to figure out what are the best ways to understand, how a drug interacts with its targets and now what we would need to do is we 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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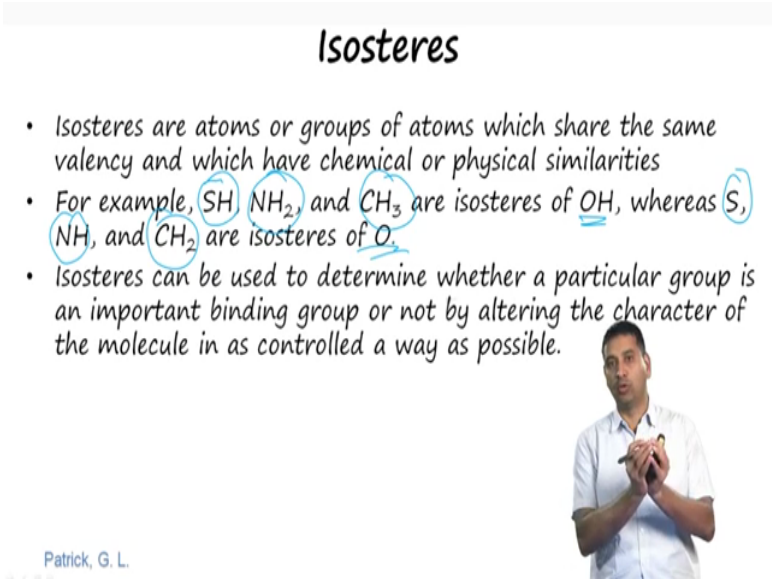

Now in this connection we shall first introduce the concept of isosteres, isosteres are basically atoms or groups of atoms which share the same valency and which have the chemical and physical similarities. So simple example here is that thiol SH, NH 2 and CH 3 would be good isosteres of alcohols. So 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 CH 2 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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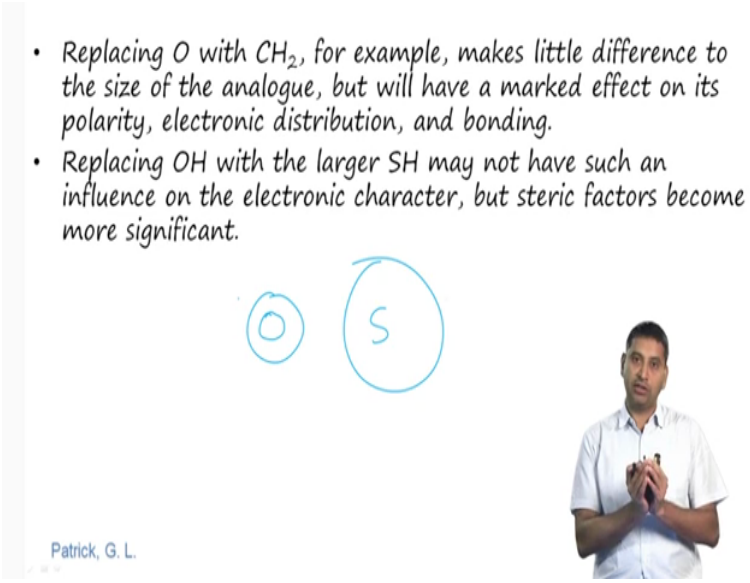

So for example is you replace an oxygen with a CH 2 then it would make a little difference to the size of the compound, but now the polarity, electronic distribution and bonding are all going to change. So for example an oxygen has to lone pairs which are going to be involved in potentially hydrogen bonds, whereas CH 2 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 a 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 has of the group has gone up, there is going to be sterics which are going to start playing a role.

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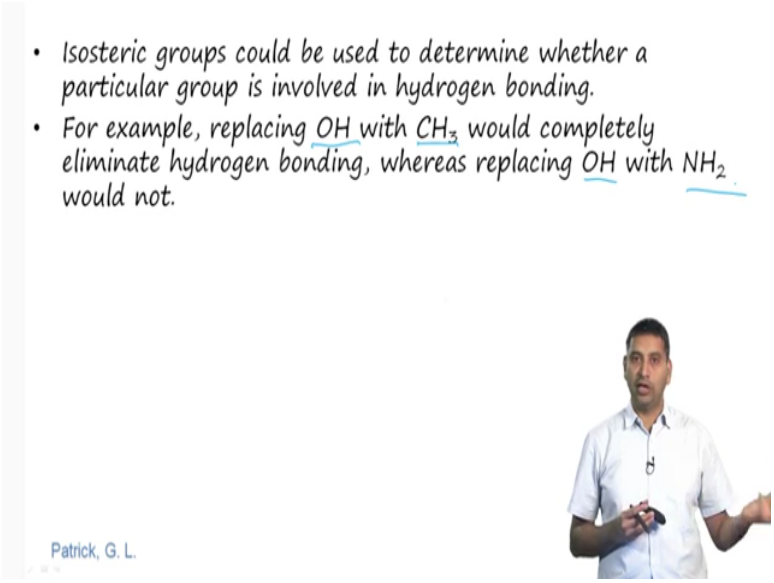

So isosteric groups could be used to determine whether a particular group is involved in hydrogen bonding. So if we have an OH and if that hydrogen bonding is important, now replacing the alcohol with the methyl group would completely eliminate hydrogen bonding and whereas replacing an OH with NH 2 would 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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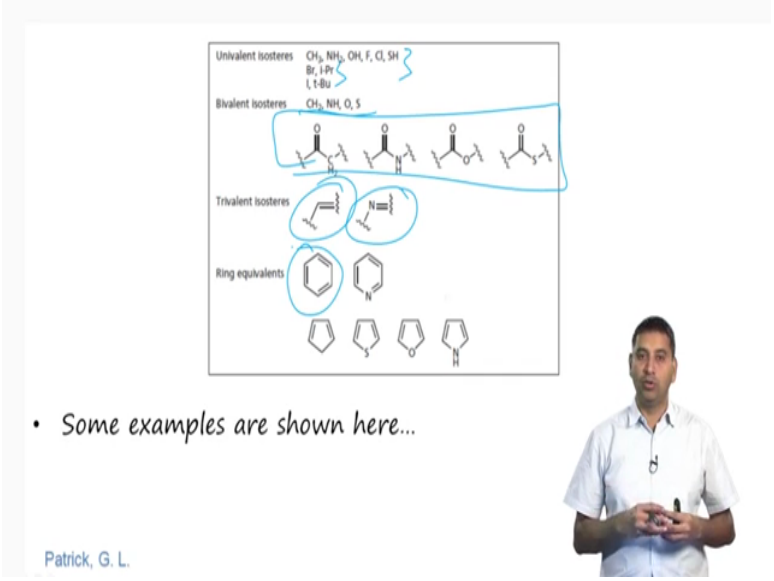

So in this figure we have some examples of isosteres, and so we have already looked at some of the univalent isosteres that is CH 3, NH 2, OH you can also replace the group with a fluorine, chlorine or even a thiol and other halogens such as BR. Now you can replace a methyl group with isopropyl or tertiary butyl for example. And then there are bivalent

isosteres which wherein you have CH 2, 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 (())(4:22) then you have three potential groups which can be placed on the (())(4:26), whereas in isostere of an (())(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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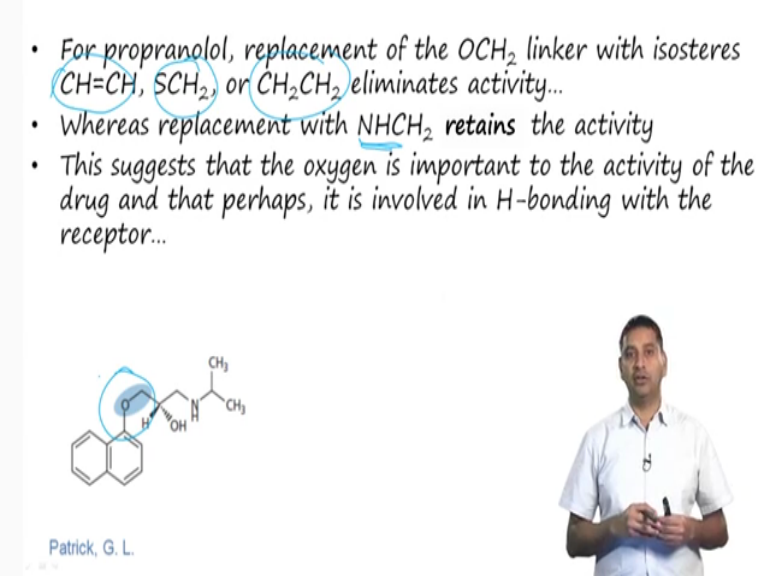

So let us take an example so for propranolol whose structure is shown here, replacement of the OCH 2 linker with isosteres CH double bond CH, SCH 2, or CH 2 CH 2 eliminates activity, whereas replacement with NHCH 2 reduces the activity. So from these two experiments what we can sort of conclude is that 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 (())(5:21) or even a thio S ether then these two functional groups are not capable of doing hydrogen bonding. And similarly CH 2 CH 2 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 these set of experiments one get 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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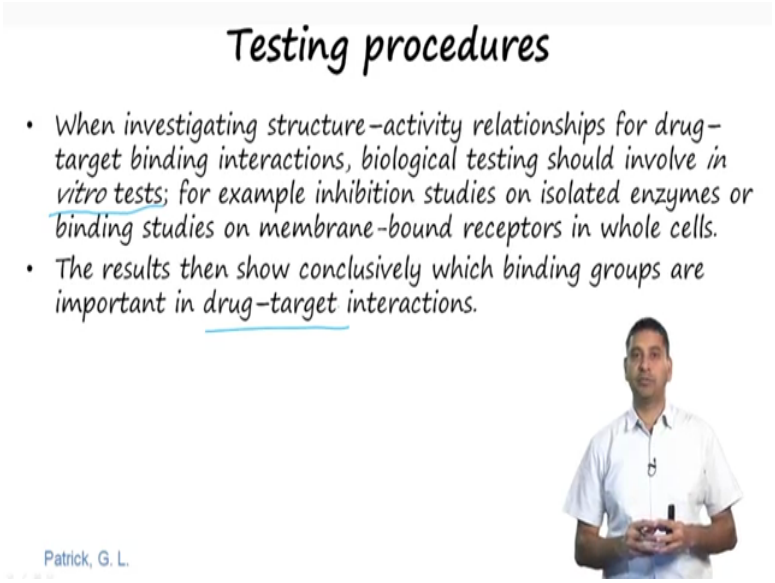

Now we shall spend a little bit of time and understand what are the various testing procedures that we would use in investigating isosteres? So when doing such structure activity relationships, we should restrict ourselves to in vitro tests. So if you are looking at a particular receptor or we are looking 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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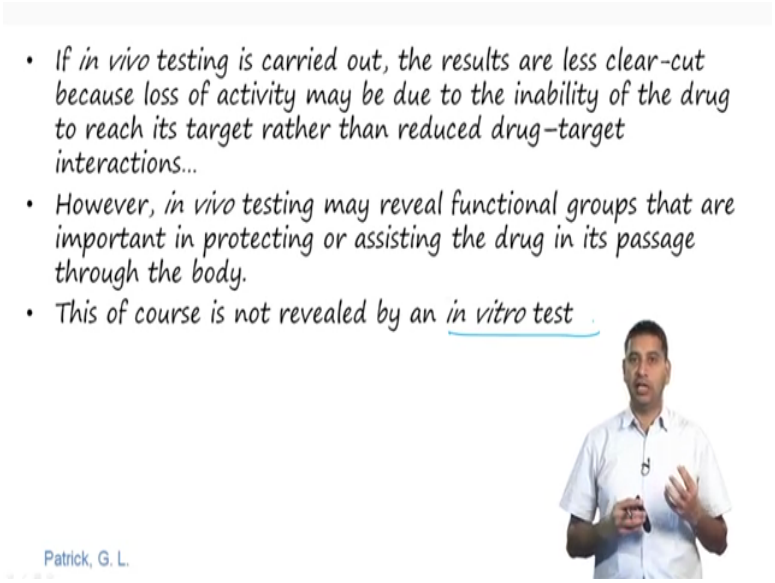

So if we were to resolve to in vivo testing then the results become less clear because what is possible is that the compound may not reach that target and so we would not get an idea about whether the lower activity is due to the reduced drug target interactions or because of metabolism that the compound 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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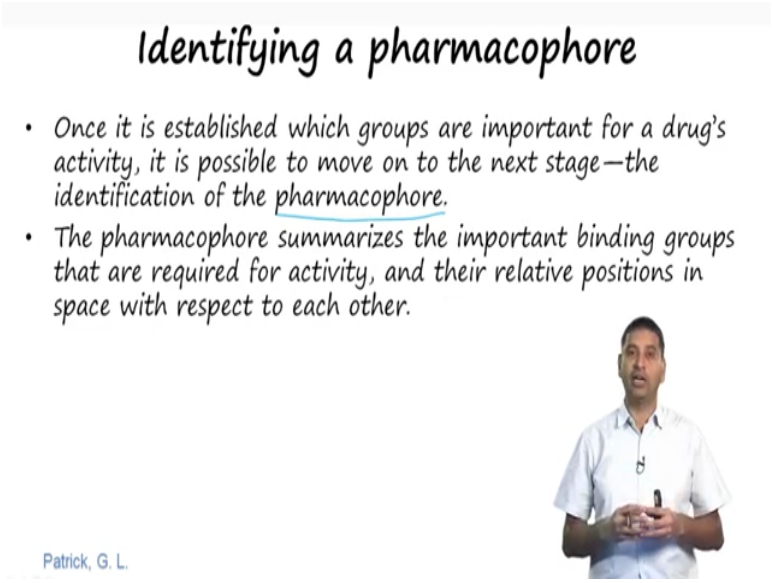

So the next step in our drug target optimization would be to identify a pharmacophore, we have already defined what a pharmacophore is, but we shall look at it once again. So pharmacophore basically summarizes the important binding groups that are required for activity and more importantly their relative position in space with respect to each other. So for this we need to establish what groups are important for a drugs 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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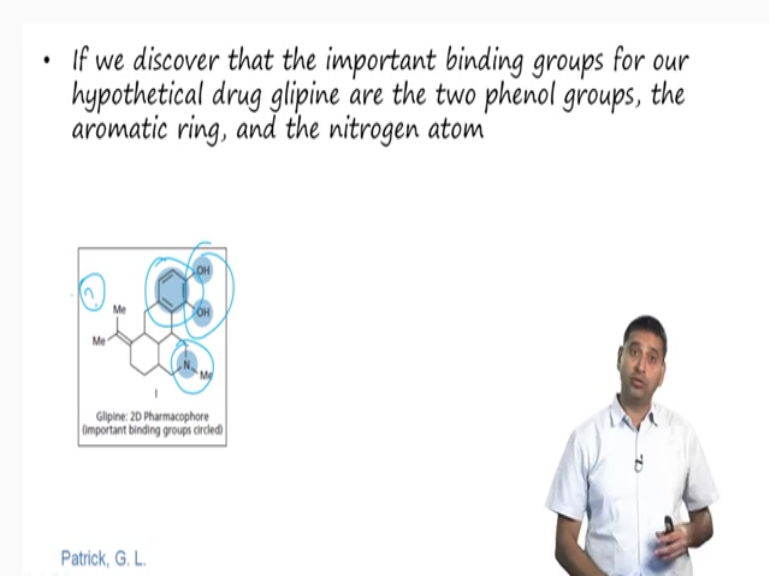

So if we discover that the important binding groups for example the hypothetical drug that we looked at, we looked at the important functional groups which are the two phenol functional groups, the aromatic ring and the nitrogen atom. So they are all shown here for us to understand. Now what this means 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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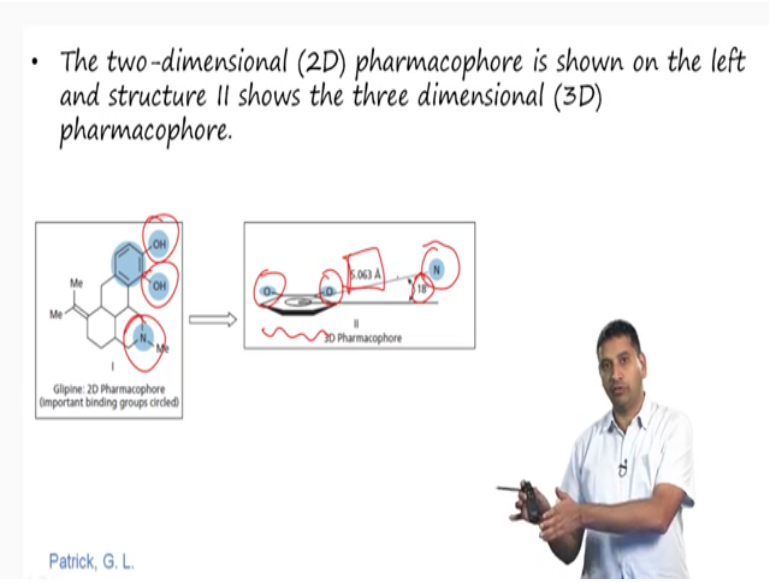

So now if I have to construct the 2D pharmacophore which is shown here, then we can think about the 3D pharmacophore. So if we have the bond distances in our hand then one could draw out a structure which is going to be something like this where you have a 3D

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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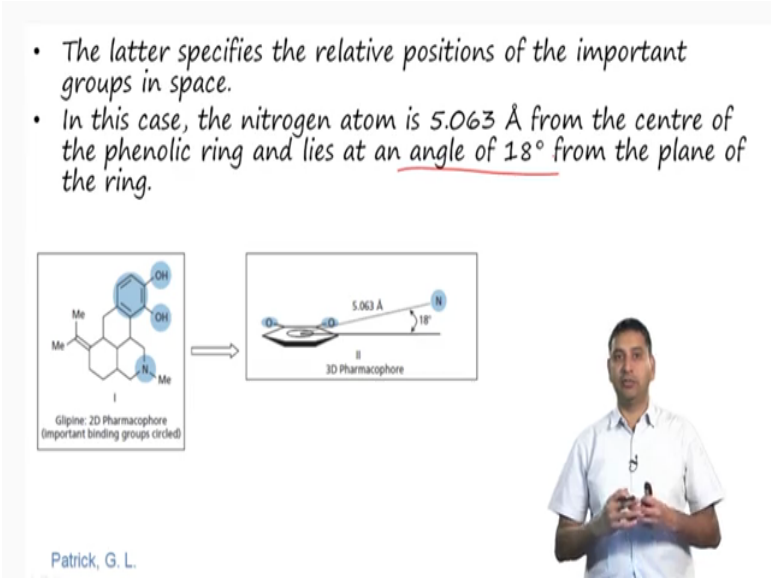

So the distance of 5.063 angstrom is something that is very important in identifying the pharmacophore because once we know the target then we would try to position this molecule in such a way that this distance may have a role to play. So as we looked at previously the angle that we found was 18 degrees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

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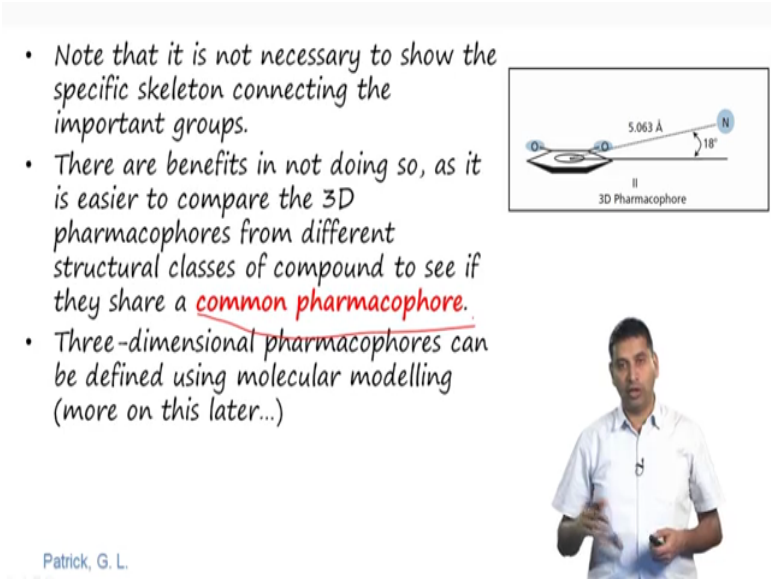

So it is not necessary to show the specific skeleton connecting the important groups. So this is the major benefit of using 3D pharmacophores. So then what we could start doing is to compare various 3D pharmacophores from different structural classes which share a common pharmacophore. So what we would 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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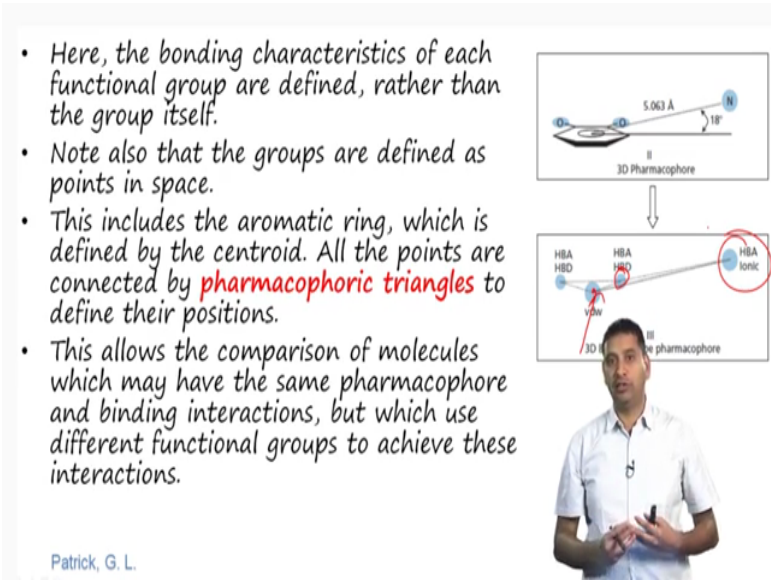

So the bonding characteristics of each functional group is defined, rather than the group itself. So what we will next we will do is, we will define this OH group as a hydrogen bond acceptor as well as a hydrogen bond donor. Then the aromatic ring, which was there for Van der Waals interactions the centre 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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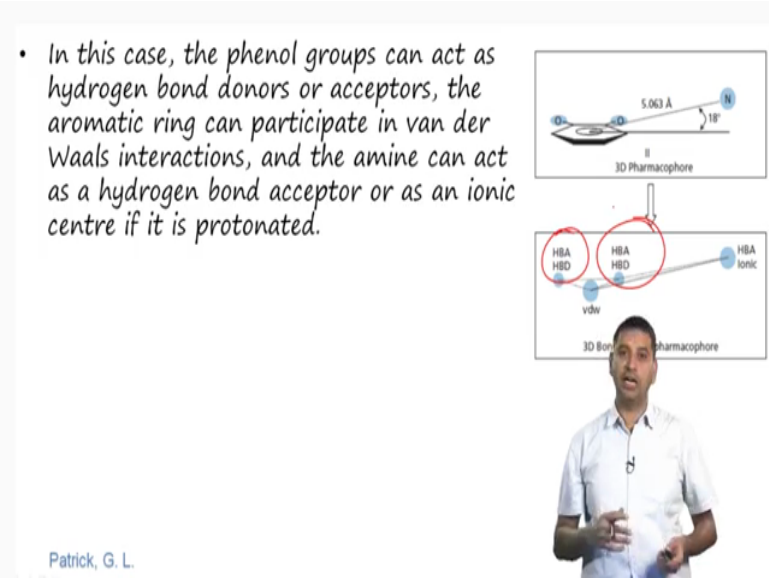

So in this case we are looking at the phenol groups which can act as hydrogen bond donors or acceptors, the aromatic ring which can participate in Van der Waals interactions and the amine which can act as a hydrogen bond acceptor or as an ionic centre if protonated. But we can now replace the phenol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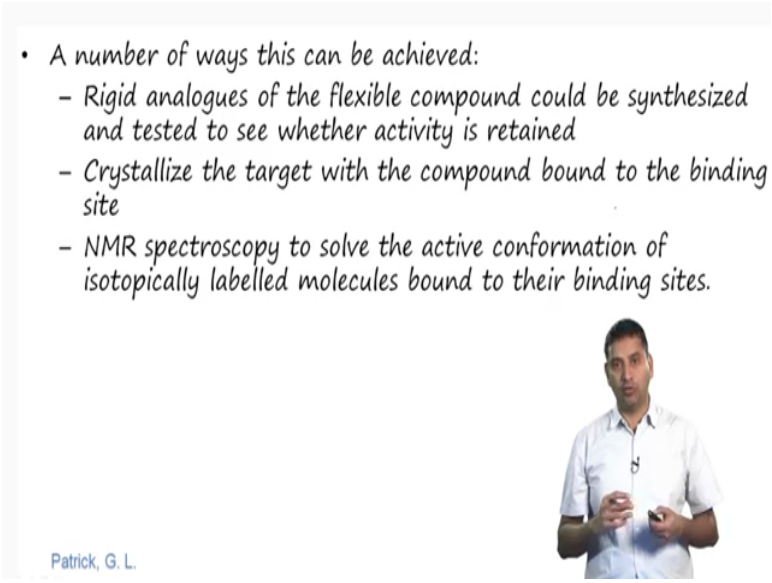

So a number of ways in which we can identify these pharmacophores is what we can do is we can now make rigid analogues of the flexible molecule and then test and see whether they are going to act in the same way, if we are lucky we can also crystalize the target molecule with the compound and then find 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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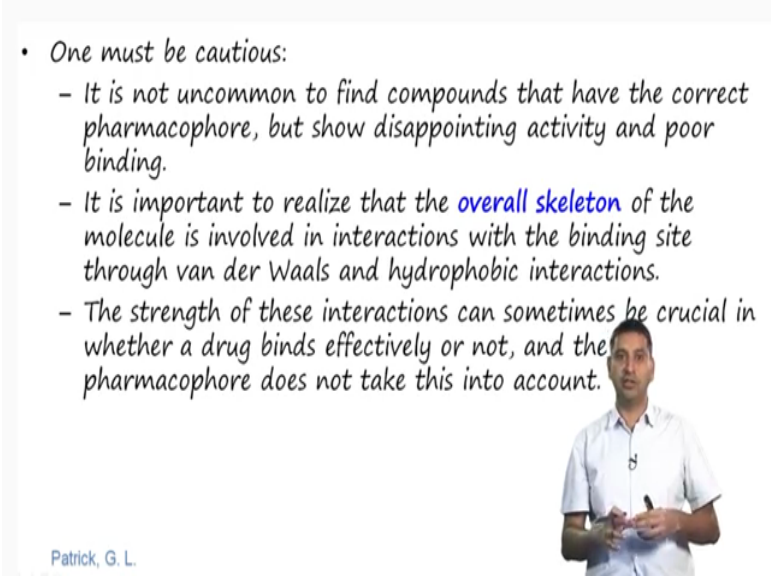

So in doing all of this one must be cautious because it is not uncommon to find compounds that have the correct pharmacophore, but do not show any activity or binding because we have to understand that in glipine there are three other rings that are important, we do not know how the positioning of those 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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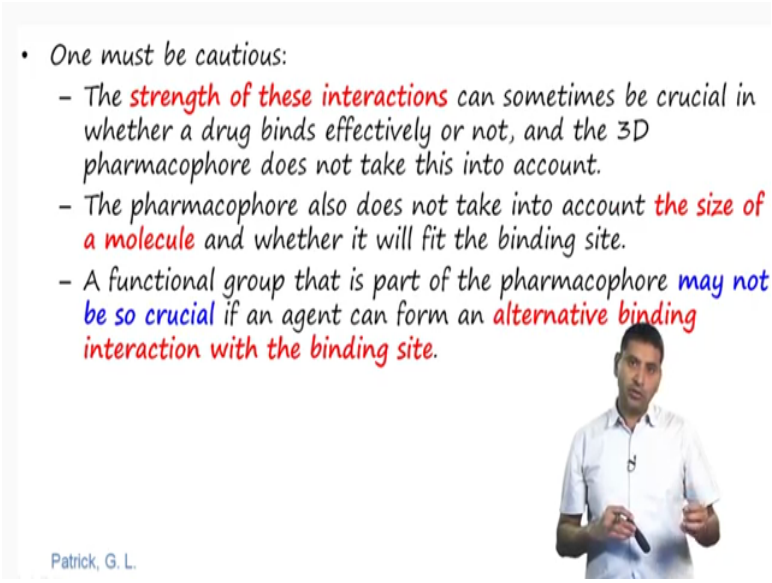

So therefore the strength of the interactions which are very crucial is not taken into account when we are constructing a 3D pharmacophore and the pharmacophore also does not take into account the size of the molecule and whether it will fit into the binding site. So a functional group that is part of 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 three are some caveats when we are doing this analysis with the 3D pharmacophore which one must be cautious about.

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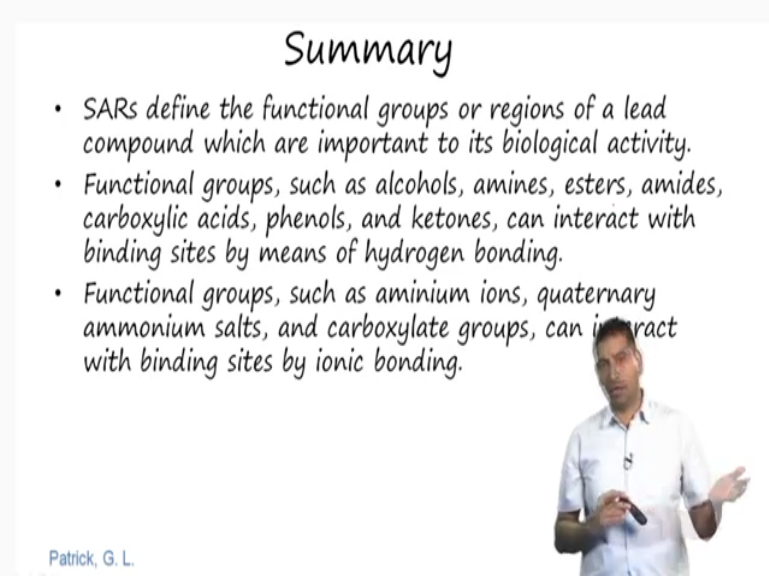

So to summarize the past few topics that we have looked at, we have looked at structure activity relationship or SAR and what this does is this defines the functional group or the regions of a lead compound which are important towards biological activity. So we have looked at various functional groups 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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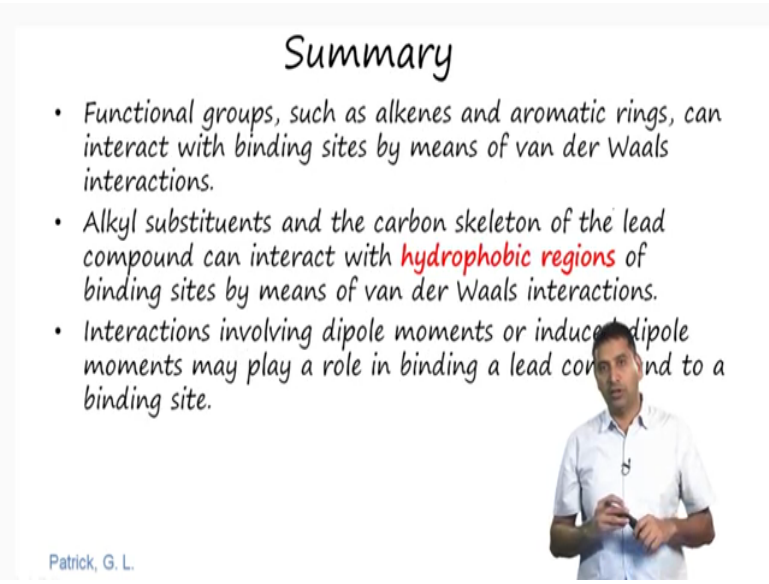

There are functional groups which interact through Van der Waals interactions and examples of these are (())(18:05) or alkenes and aromatic rings and alkenes substituents which are present on may drugs are very important regions for hydrophobic interactions and this actually may play a role the way in 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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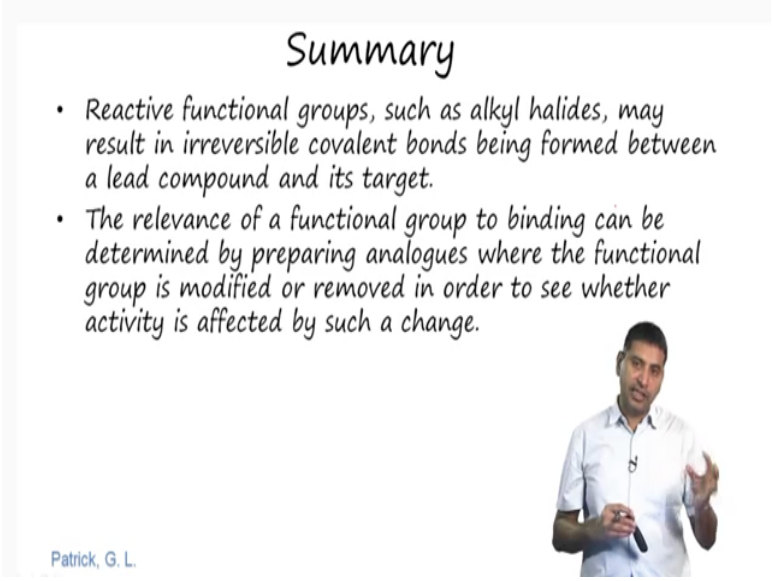

And we have looked at certain reactive functional groups, such as alkyl halides and what this can do is that they can irreversibly modify the target and therefore they are not very useful in certain drug development cases. So the relevance of a particular functional group which is part of the lead may 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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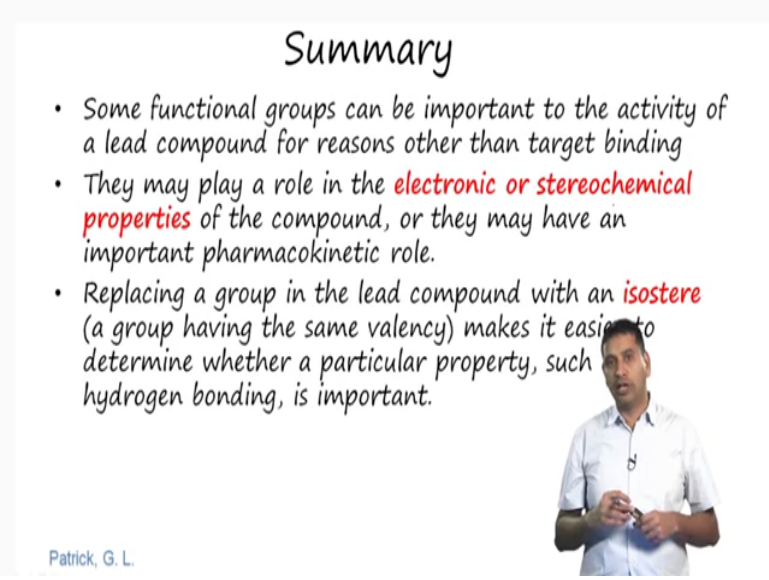

And some functional groups can be important to the activity of a lead compound for reasons other than target binding. So for example there may be some important electronic effect of the functional group or there may be stereochemical properties of the group which may play a role. Now replacing a group 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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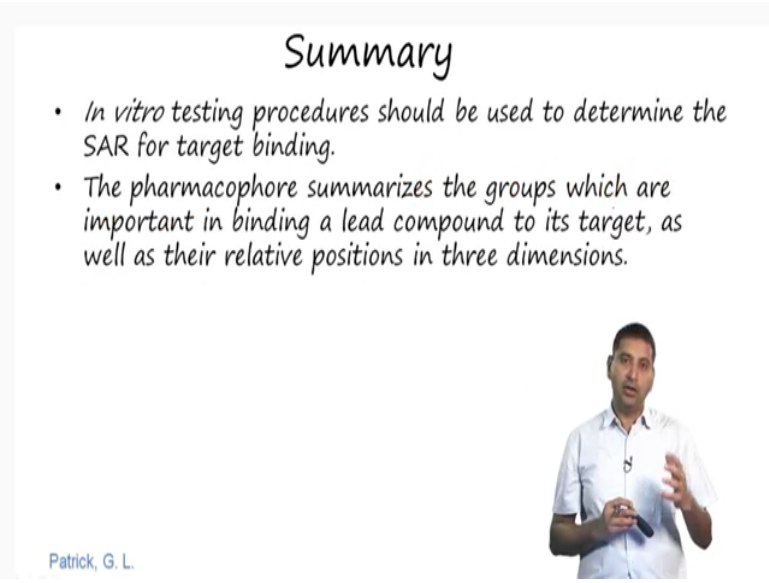

And it is recommended that in vitro test procedures are used when we are doing the structure activity relationship because that will avoid the some of the complications that are associated

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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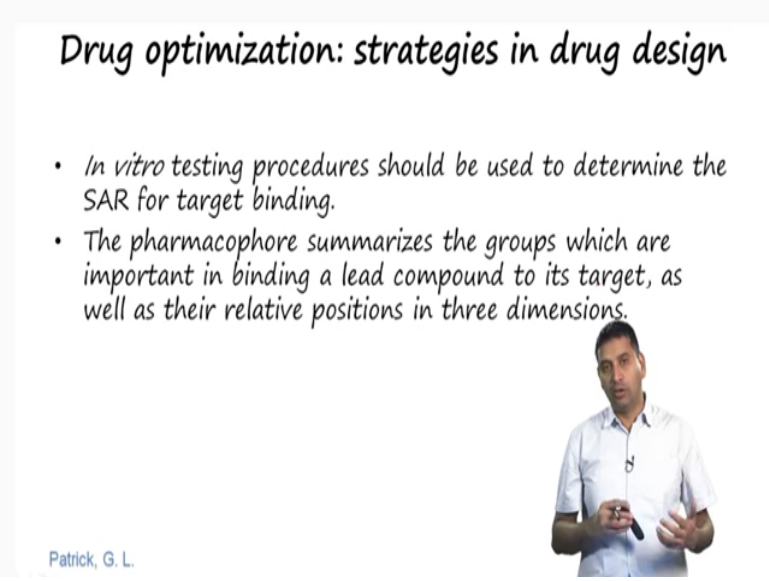

Now what we will do is we will look at how these strategies can be used in drug design. So the pharmacophore summarizes the groups which are important in binding a lead compound towards target as well as the relative positions in three dimensions.

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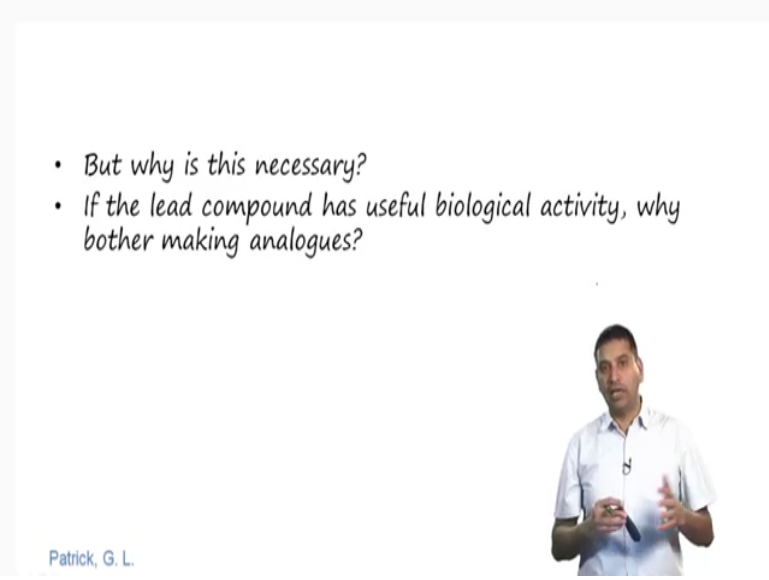

But why is this necessary? If the lead compound has useful biological activity, why even bother making analogues? So this is an important question that we need to answer.

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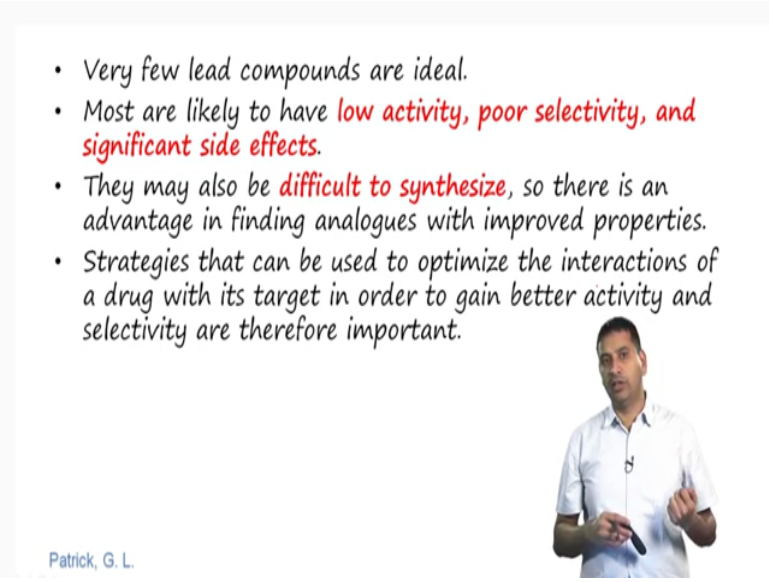

And the reason for this is that there are very few lead compounds which are ideal. So some of them have low activity, some of them have poor selectivity and more importantly because they have poor selectivity they may also have significant side effects. We have not covered these aspects but some of the 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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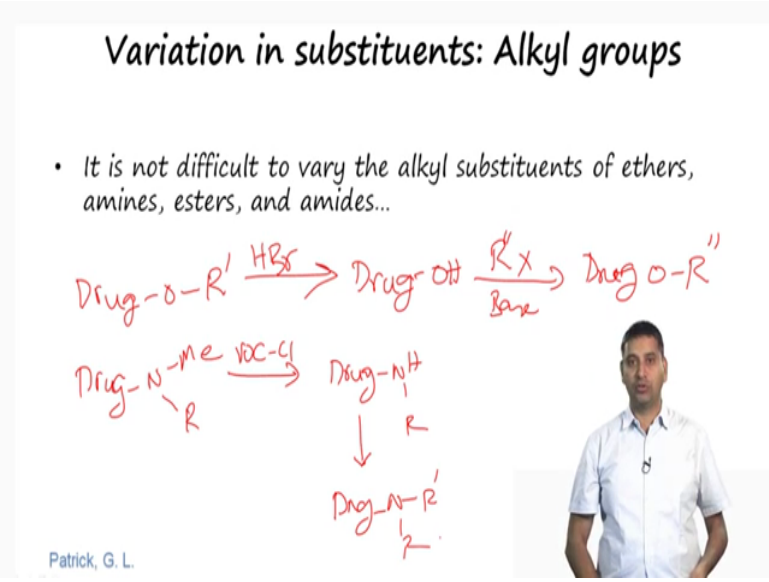

So some of the ways in which we do this optimization in drug design is to vary substituents. So the first variation in substituents is to vary alkyl groups. So if you have a drug with an ether which I am referring to as R prime then what we could do is to deprotect this ether to convert it to the alcohol, 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 ad try to find out whether those alkyl group 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 vinyloxy 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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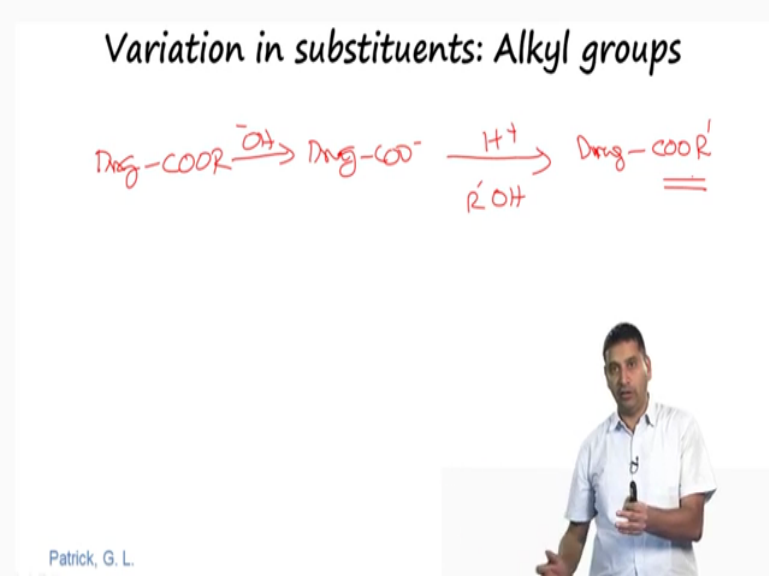

Now you can also vary alkyl groups on esters. So the way we would do this is take let us say a drug has an ester you would first hydrolyse of the ester you would use some base so you will get drug COO minus which then can subsequently be esterified perhaps with un residic conditions with an R prime and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

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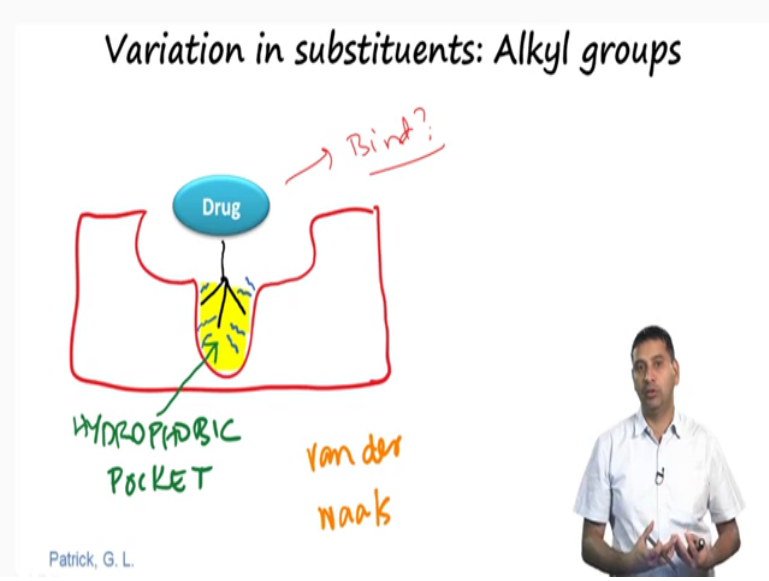

Now what happens for example is when we change the alkyl group imagine this is a protein which has a hydrophobic pocket and now you have a drug which has a methyl group pendent methyl group. Now this methyl group can interact with the hydrophobic pocket and this may be your lead compound. Now if this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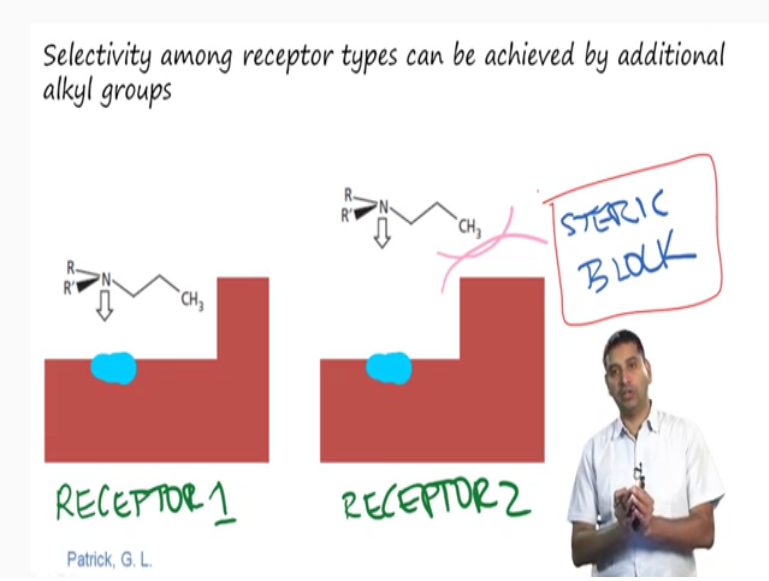

There is also possible that we may have two different kinds of receptors, so let us say taking hypothetically receptor 1 and receptor 2 and they have very similar binding regions where an amine is going to bind. So if you see here this is a smaller group and this is a larger group over here and so the 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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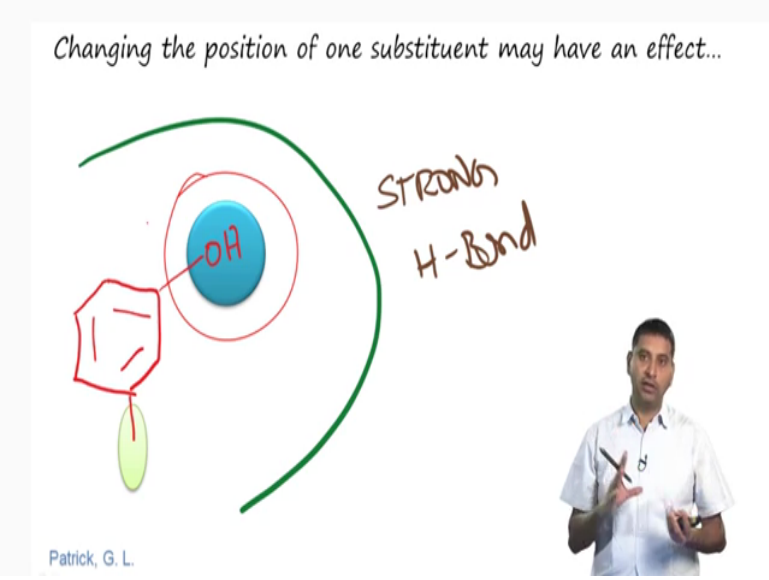

It is also possible that when you have aromatic substituents you can position the substituents such that the orientation can change. So here is again a hypothetical example where you have a hydrogen bonding region which is going to interact with the hydroxyl group and one could imagine that this group 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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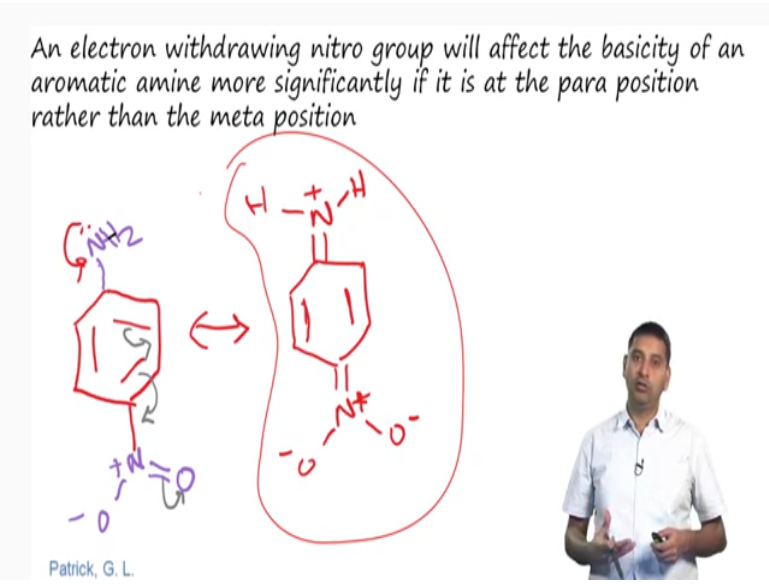

The next case is when you have an electron withdrawing nitro group will affect the basicity of the aromatic amine far more when it is in the para position when it is compared to the meta position. So now let us look at the para position, so you can push electrons and you get a structure such as this 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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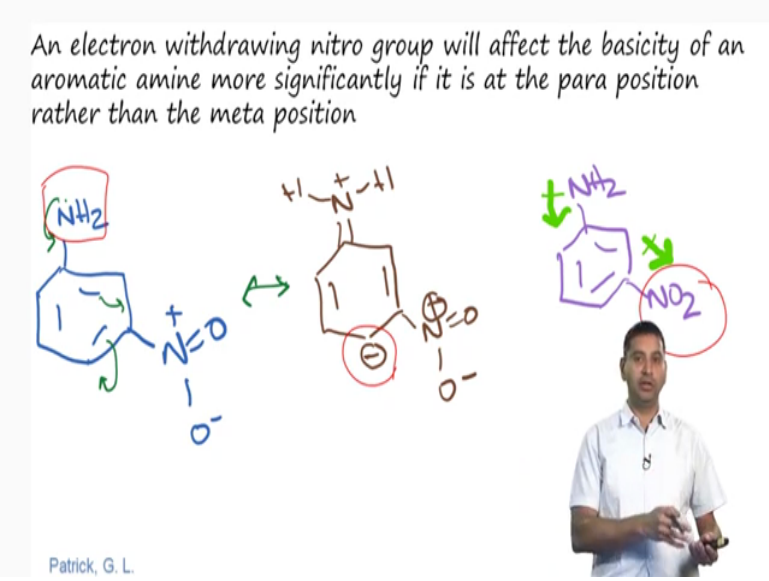

Whereas if you have it in the meta position, if you push electrons you get a resonance form such as this, but this resonance form is not going to contribute very significantly because it has a full negative charge on the carbon which is not very useful. So the major effect by which this nitro group is 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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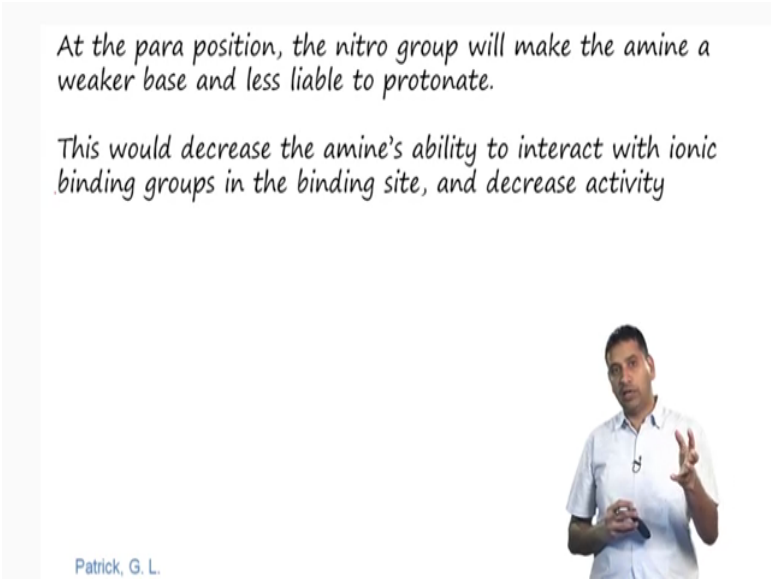

So therefore the amines ability to interact with the perhaps an ionic binding group will change and you can actually modulate the activity by changing the position of the electron withdrawing functional group.

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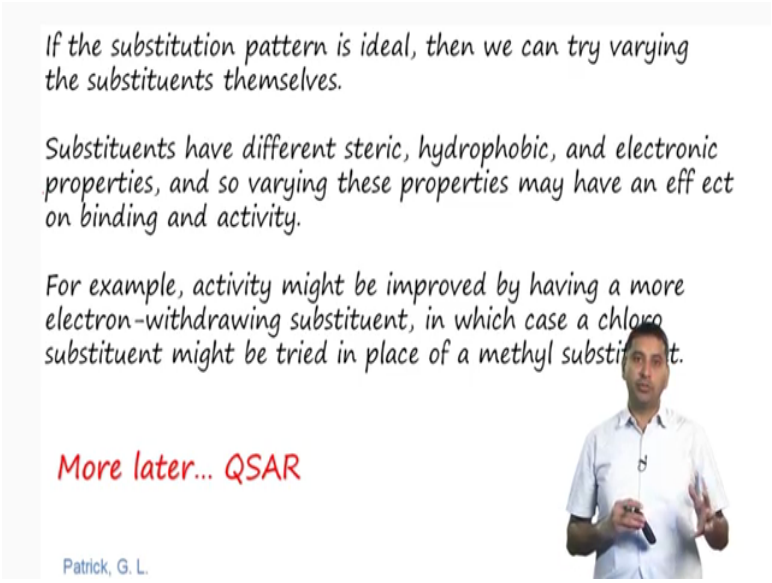

So if the substitution pattern is ideal then we can try varying the substituents themselves. So for example substituents which can have different steric, or may be hydrophobic, or electronic properties can be varied and this will have an effect on the binding and the activity. So one way is to have let 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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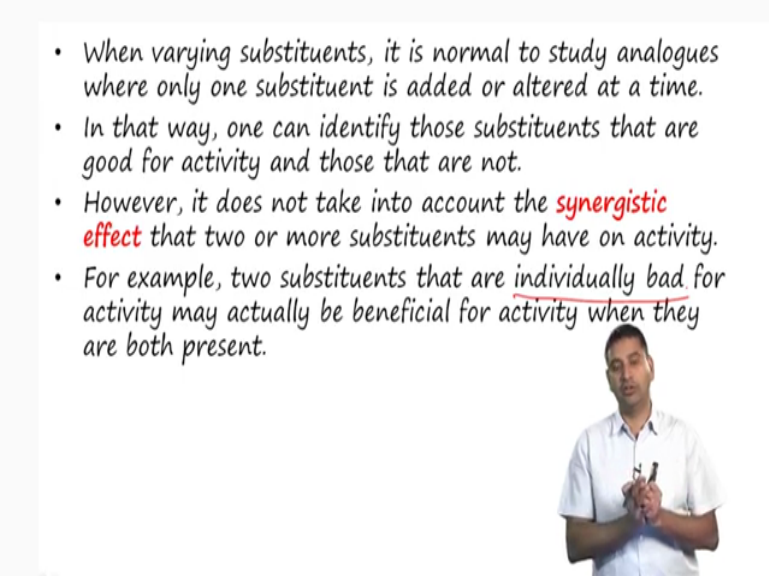

But when we are varying substituents, it is normal to study analogues where only one substituent is added. So when we are trying to figure out variation one would do it in a very systematic way that is we vary one functional group at a time, but sometimes when there are two different groups which are 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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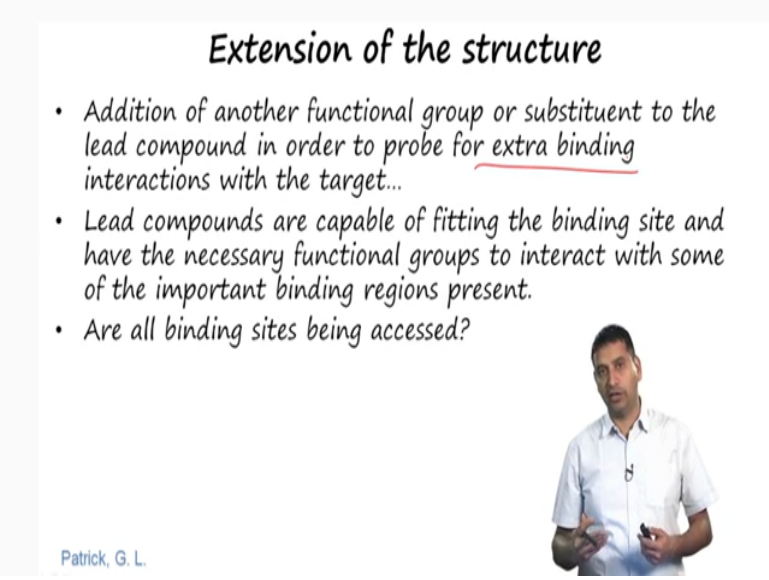

The next concept which we are going to look at is extension of the structure, so we already looked at in part when we are looking at the longer alkyl group, but there is a systematic way to do the extension of the structure. So here the concept is that when we are identifying a lead compound and we are 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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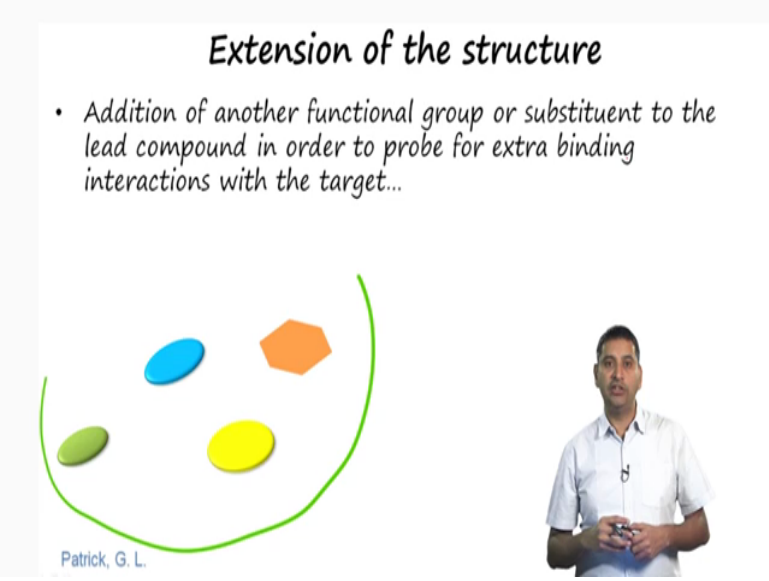

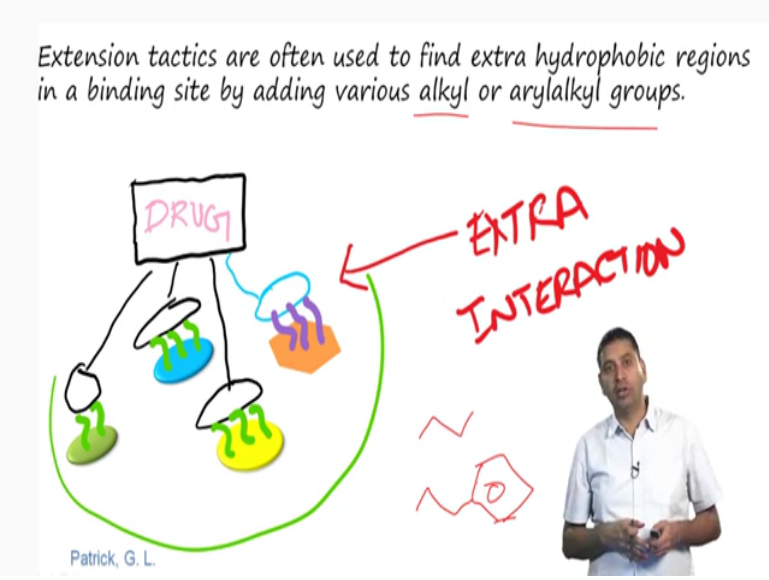

So let us imagine that there is a target which has these four major binding areas that we have identified, when we have a lead compound what we perhaps may identify is there can be three of these interactions that are in play. So one can imagine that this is let us say this is Van der Waals interaction 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 (())(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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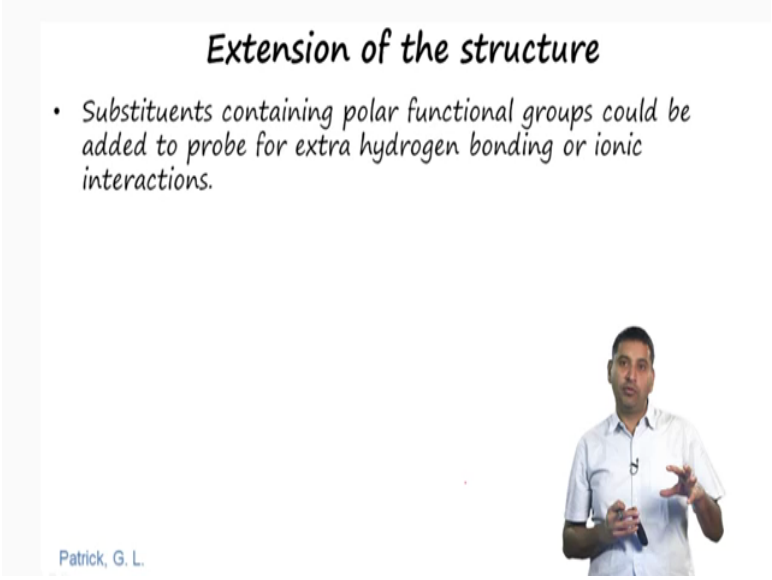

So substituents which contain polar functional groups could be added to the lead compound such as an extra hydrogen bonding or extra ionic interaction and then we could potentially probe for better binding to the target.

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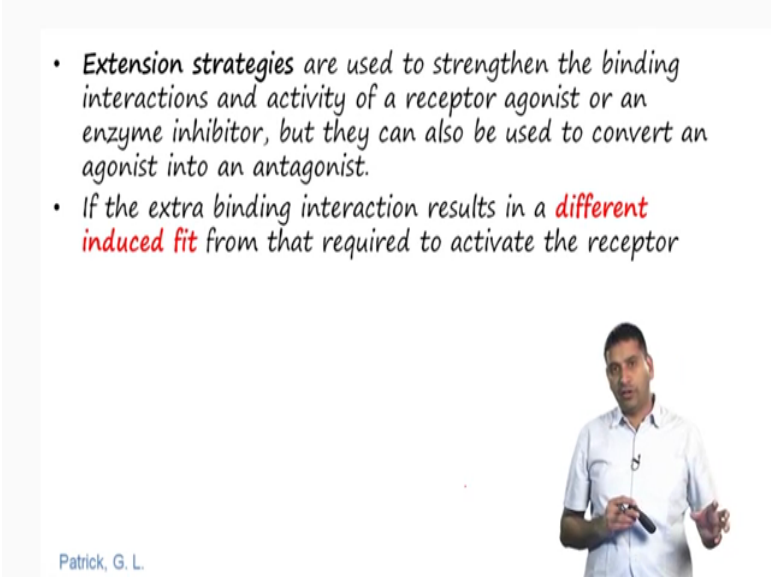

So extension strategies are used to strengthen the binding interactions and this would help in improving the activity for example when we are looking at a receptor agonist then since you have a stronger binding then you are going to perhaps do the conformational change more efficiently, or when you are 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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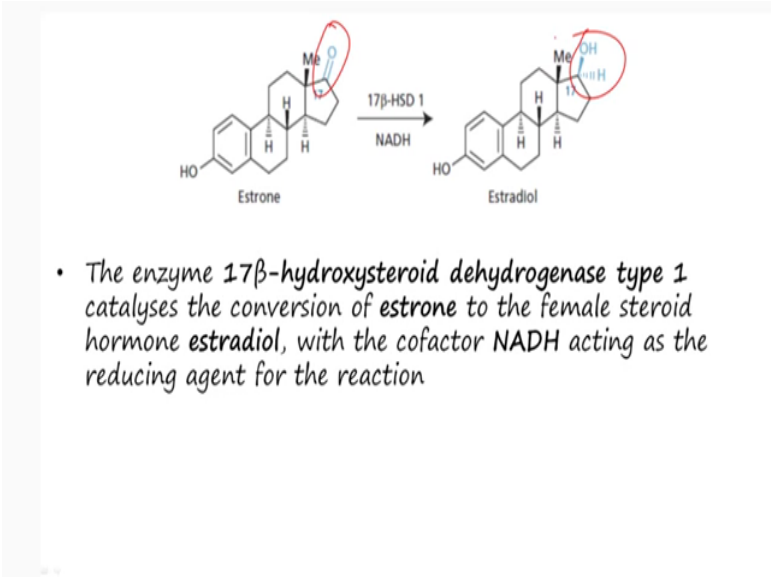

Now here let us look at an example of this enzyme, so this enzyme is basically a 17 beta hydroxysteroid dehydrogenase. So this uses NADH as a co factor we have already looked at how NADH acts and it is a source of (())(32:42). So what happens is that this carbonyl becomes a alcohol. So this is let us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

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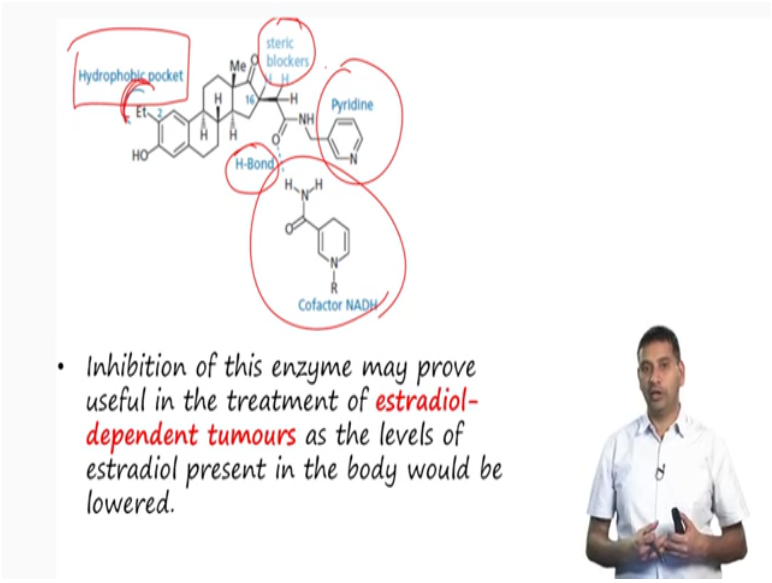

Now what we could do in this extension strategy is to add a potential group which is going to bind to a hydrophobic pocket which is present in the enzyme and you can also add what are known as steric block that is you add extra methyl group which we have already looked at and since we know that the co 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.