Medicinal Chemistry
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Tutorial – 12
Optimizing Drug-Target Interactions
Mod08_Lec49

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Alright, so welcome to the tutorial session, so in todays session we are going to solve some problems related to optimizing drug target interactions, so, so far we have looked at number of strategies that people use to optimize how the drug interacts with the target and, so this is obviously important because knows that drugs gets into the bloodstream and reaches the target, how does it interact with the target and how we can optimize those interactions, you know in order to improve the efficacy of the drug.

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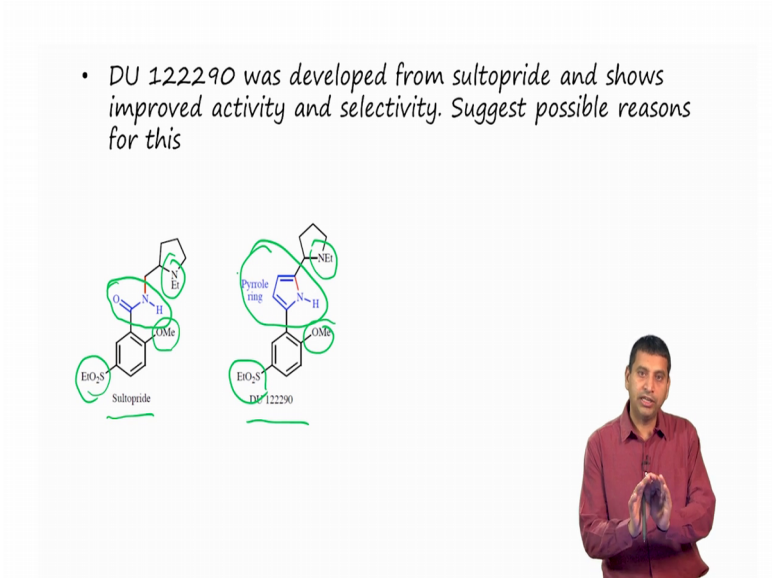

So the first question is this DU 122290 which is a drug shown here was developed from this compound call a sultopride and it shows improved activity and selectivity, so the question is suggest possible reasons for this. Okay, so now look at these two structures, sultopride is shown here and in blue is the amide bond and in the red is the carbon, nitrogen bond and so these are perhaps going to be some things that are important and you also have sulphate ester and you have a methoxy group and N ethyl group, so these are the major functional groups that are present in the molecule.

Now if you look at this DU 122290, which is an analog you see that a number of this functional groups are actually retain, so N ethyl remains as N ethyl, OME remains as OME and this sulphide ester remains as sulphide ester or sulphate, so this functional groups are retained and whereas new pyrrole ring is now been introduced, so once we look at the structure of the molecule we can delineate this differences right away.

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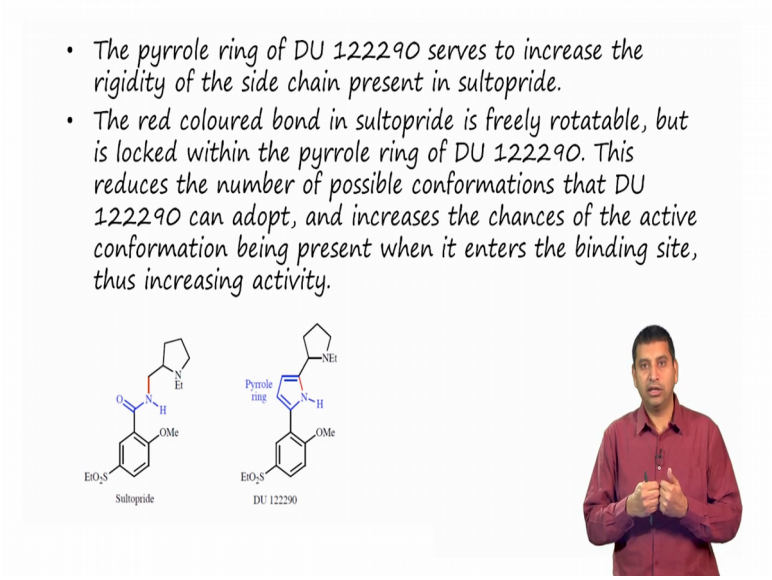

So now one of the strategies that we have looked at previously is called increasing rigidity, so here what we do is we reduce the number of rotatable bonds, so the red bond that is shown here is the carbon, nitrogen bond, is a freely rotatable bond, so in order to increase rigidity, we would want to convert that or reduce the rotation on that bond, so one way we can do it is to make it into a locked pyrrole ring, that is exactly what this analog they have done.

So what this does is that it increases the chances of the active confirmation being present when it enters the binding site, so we have already looked at this concept of active confirmation, what the active confirmation means is that of the infinite possible confirmations, it is possible that a few of them or a subset of them are going to be the ones that are going to interact with the receptor binding site to induce the necessary conformational change and so we want to get to a structure which is as close as possible with the active confirmation, so that we can improve the drug target interaction.

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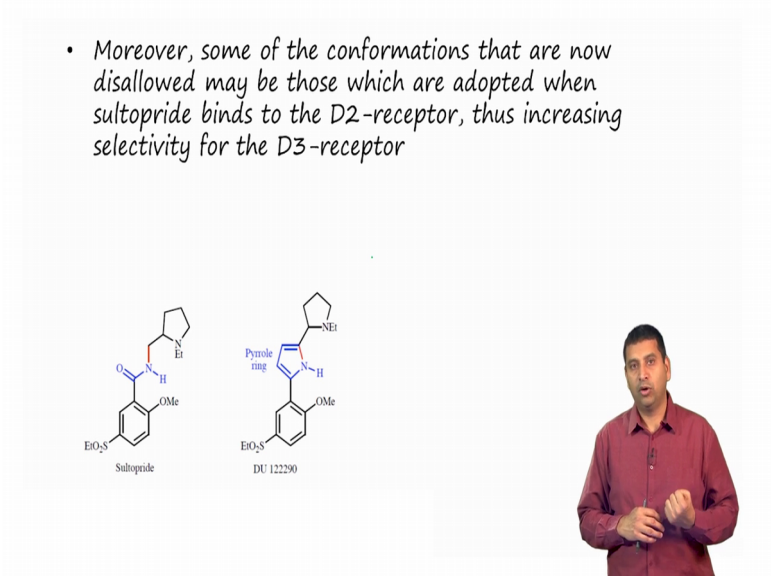

So in the case of the pyrrole some of the confirmations which are possible in sultopride are actually not allowed and so therefore by doing this we are increasing the selectivity of the molecule one particular receptor over the other.

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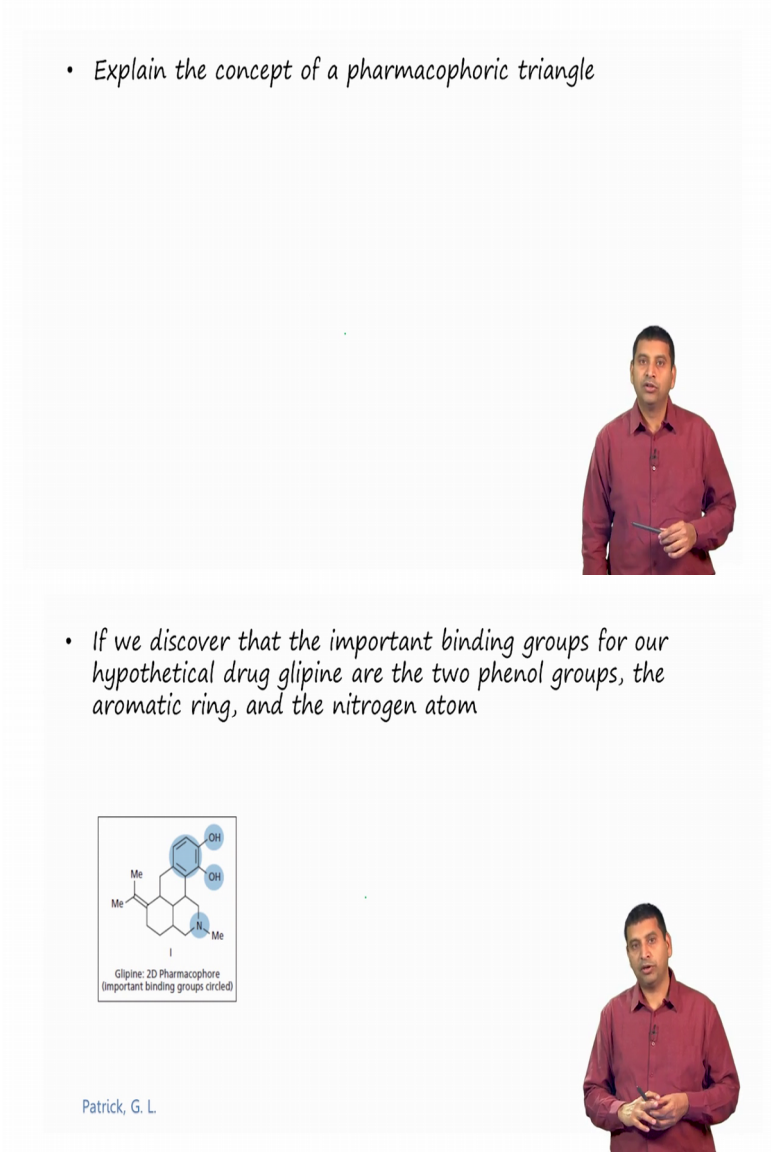

The next question is explain the concept of a pharmacophoric triangle, so in order to address this question, let us go back and look at some of the lecture slides that we encountered previously, so let us go back to our hypothetical drug molecule which is glipine, so it is very easy for us to draw out two-dimensional pharmacophore, so here we have done this N number of times in the course, so you just identify the various functional groups and find out which were the ones that are going to interact with the receptor or removal of which will result in a large decrease in the activity.

So what this means is that, there are certain groups in the molecule which are not that important and there are certain groups the molecule that are important and we define the pharmacophore being the structure of the molecule we shows the activity, so here have

identified the pharmacophore the following manner which is it contains the two phenolic hydroxyl groups, the aromatic ring and the nitrogen atoms, so these are the important parts of the pharmacophore.

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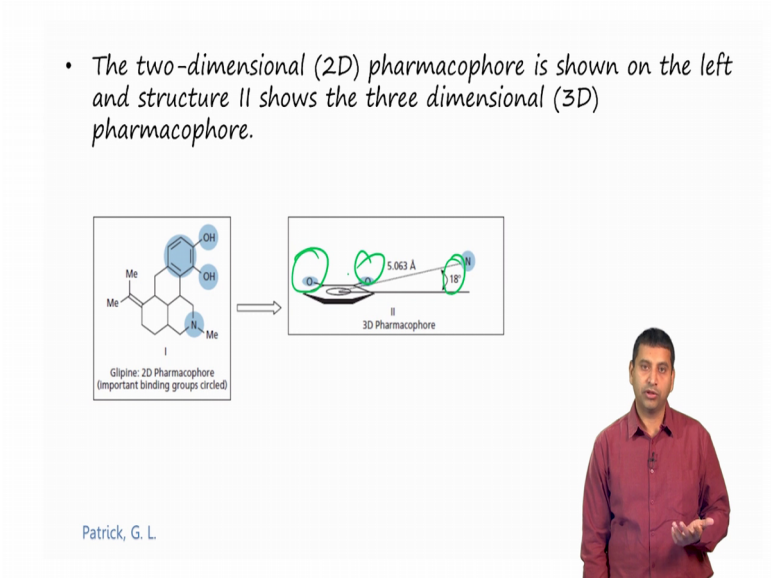

So in order to address the question of the triangle, now what we do is we can now is on the structure of the molecule, we can align it in the form of a 3-D pharmacophore, so here, instead of looking at the molecule as being in a plain, we start looking at the molecule in three dimensions, so we can measure the distance between, let say the aromatic ring and the nitrogen as shown here and we can also start looking at the angle at which the molecule is out of plain, so here for example it is 18° out of plain and you can see here. The other two alcohol groups or phenol groups are also present.

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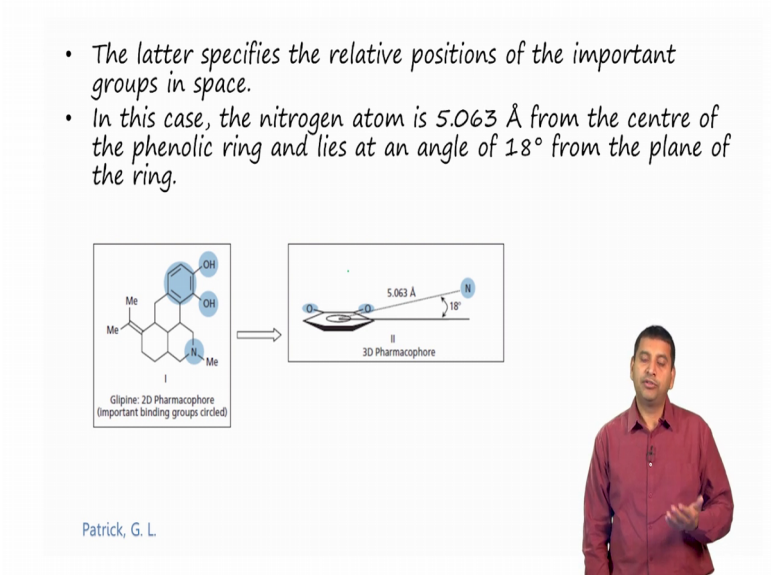

So now based on this can specify the relative positions of the important groups in space and as I mentioned the angle is about 18° from the plane of the ring, now this helps us construct the pharmacophoric triangle.

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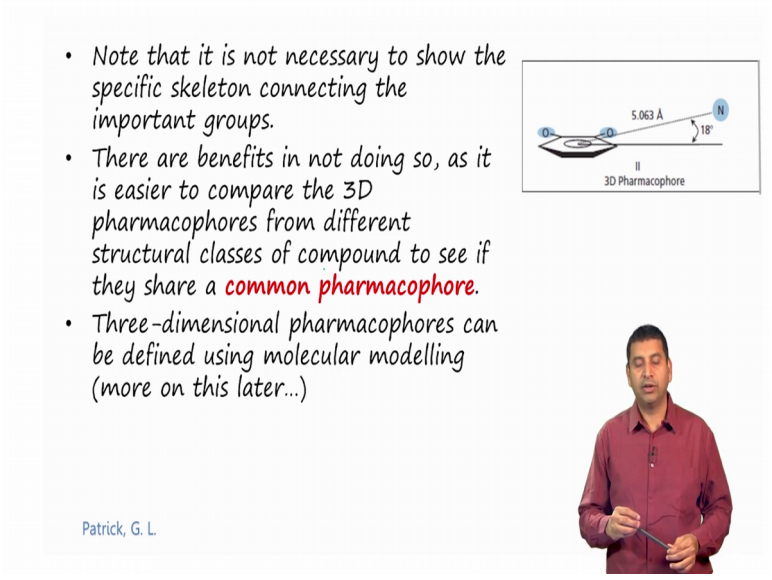

So what we can assume here is that these are the essential functional groups of the pharmacophore and it is possible that they can share are what is known as the common pharmacophore, so this 3-D pharmacophore of course we will discuss it later when we are looking at molecular modelling.

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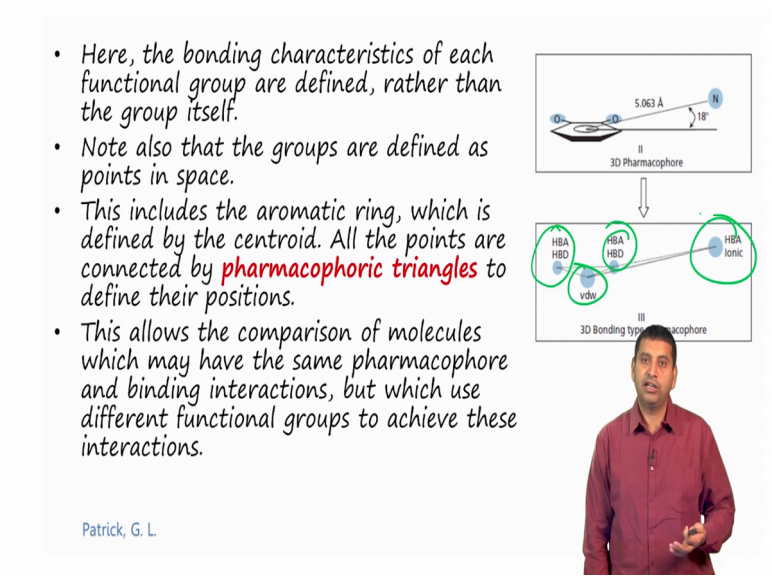

But the triangle approach is shown here where what we start doing is we start constructing triangles. Okay, so you can define this groups in points in space, that means it you can call the van der Waals functional group as a point in space, the hydrogen bond excepted donor is an another point and so on, and now one can start drawing triangles among this three groups which are known as pharmacophoric triangles okay.

And it allows us to compare across, let say library of molecules, so when we define this triangles the way we have done it. It is now possible to take another library of molecules and look for this specific interactions been present in this format. Okay and then we will hypothesise that these are likely to have some drug like molecules.

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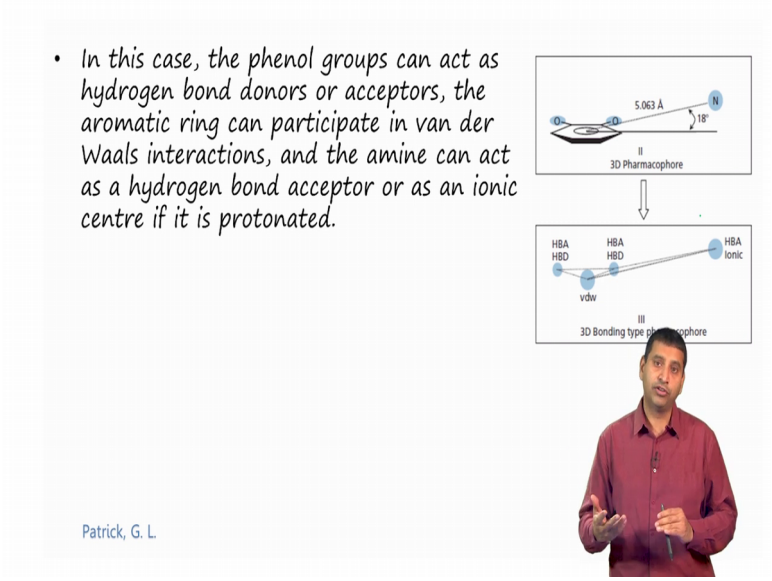

So here, in our case, the phenol groups obviously can act as hydrogen bond donors or acceptors and then the aromatic ring is going to participate in van der Waals interactions and the amine can be a hydrogen bond acceptor and of course it can be an ionic centre if it is protonated.

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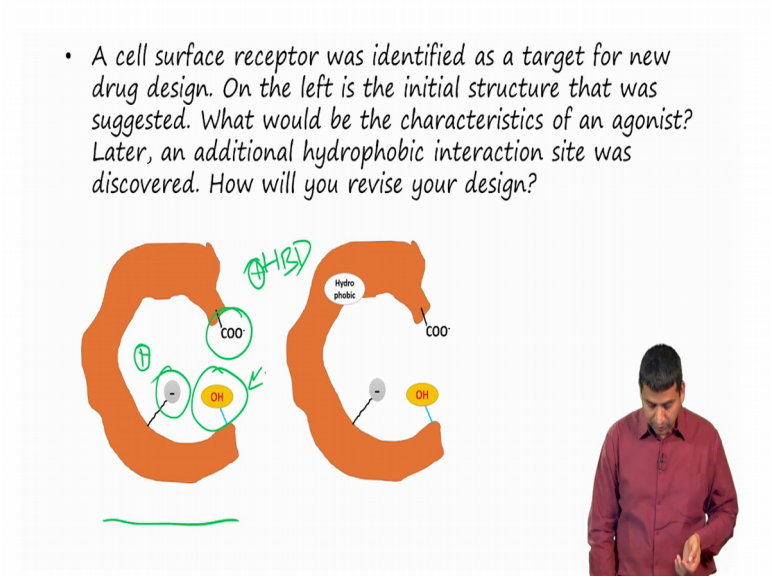

The next question is a cell surface receptor was identified as a target for new drug design, on the left, which is here is shown the initial structure, so what would be the characteristics of an agonist? Okay, so here on the left is this molecule and you can see here that there are, there is a carbolic acid, there is a hydroxyl group and there is a negative charge, which is a probably a substrate for an ionic interactions, so what we would do is if we have to design molecule keeping this in mind than we would place a group which has a positively charged species here, perhaps another positively charged species here or hydrogen bond donor over here and something that interacts with the hydroxyl group over here.

So these are the three characteristics that we would look at and start screening for molecules but the question is that later, while doing this study they found an additional hydrophobic region was discovered, so now the question is how will you revise your design?

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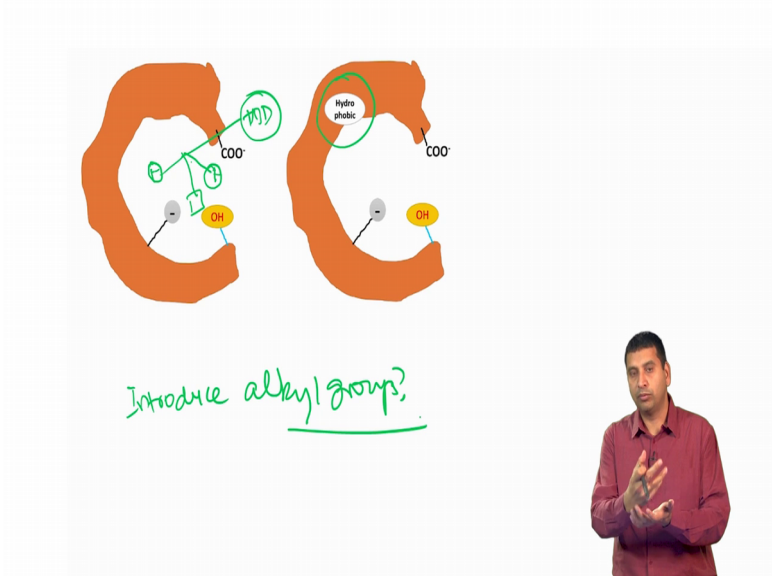

So if you want to revise the design, lets draw out again the molecule that we are looking at, so maybe will have a positively charged species here and there is going to be a another positively charged species or a hydrogen bond donor over here and then there is a going to be a molecule that is going to do, hydrogen bond interaction with the hydroxyl group.

So let say we come up with this type of a molecule, once we discovered this extra hydrophobic group than the logic that we would follow is to introduce alkyl groups, so by introducing alkyl groups what we can do is to sample for this hydrophobic interaction, since the alkyl groups are involved in hydrophobic interactions, so we would be able to improve the binding with this receptor, so this is called an extensional strategy and it works by trying to improve the activity or improve the number of findings that we can achieve.

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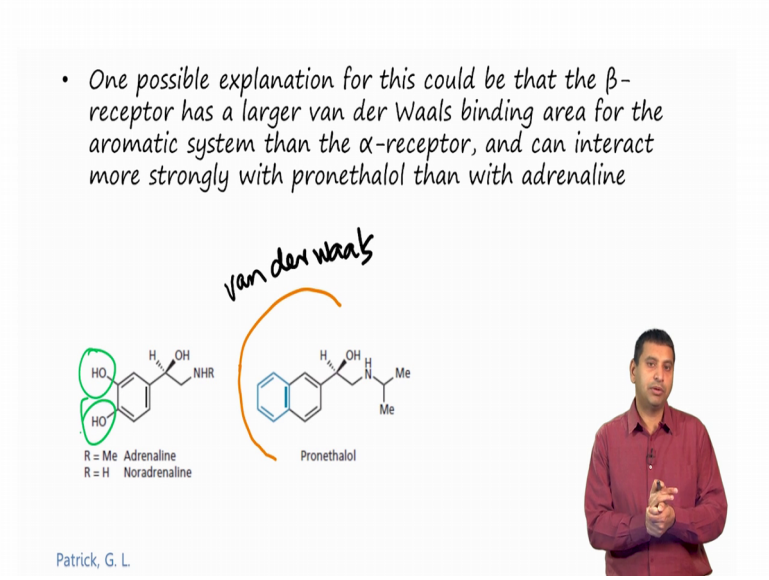

The next question is selective beta-blockers were developed by replacement of the aromatic ring in adrenaline with a naphthalene ring system as shown below, this resulted in a compound that was able to distinguish between two very similar receptors that is the alpha and beta receptors for adrenaline, question is explain, so in order to address this question what we need to do is we need to look at both of these structures carefully and one possible difference, I mean one major difference between this two molecules is that the two hydroxyl groups are gone from adrenaline and you have now situation where you can have van der waals interactions.

So this is something that is distinct between or different between the two molecules, so therefore it is likely that the some van der Waals interactions that is going to be in play, which was not present in the molecules of the left.

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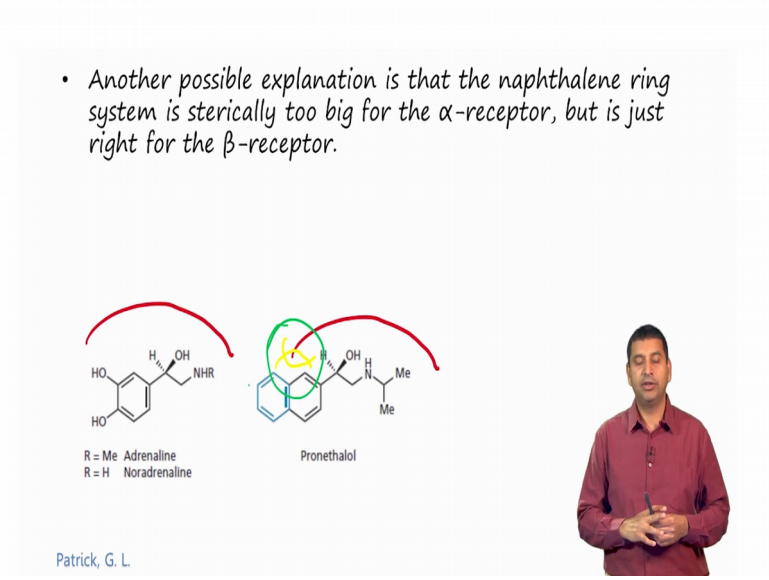

Another possible explanation is that if the receptor is going to interact with this legend than a maybe something that is preventing sterically the interaction as shown here right, so what may happen is that one of the receptor is going to find in a particular way and it fits perfectly, but the other receptor may be binding like this and so what happen is that you have a steric clash which is going to result in some selectivity for one receptor or the other.

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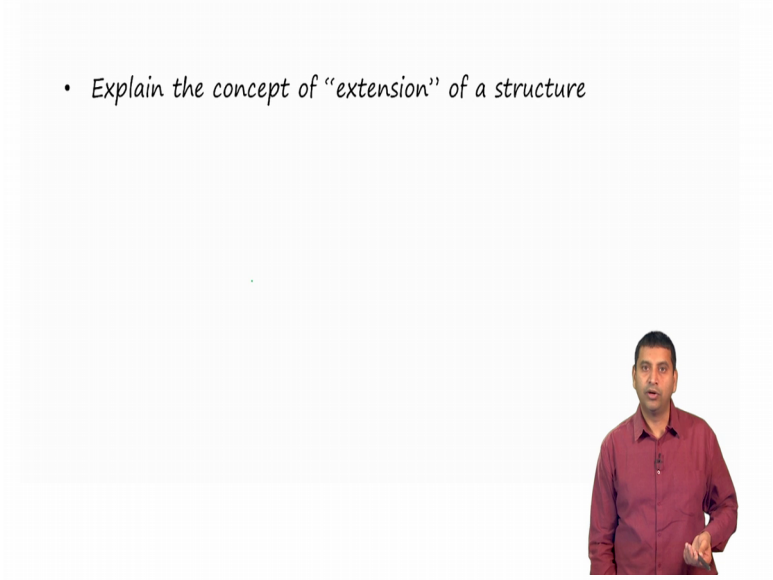

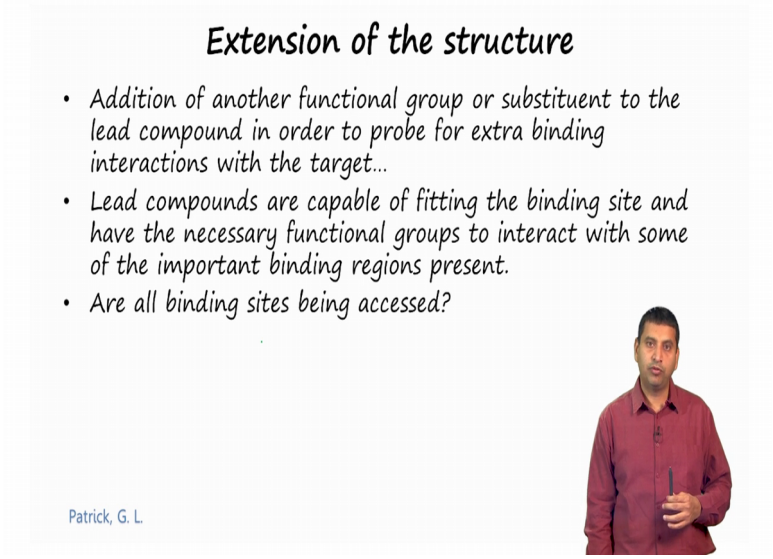

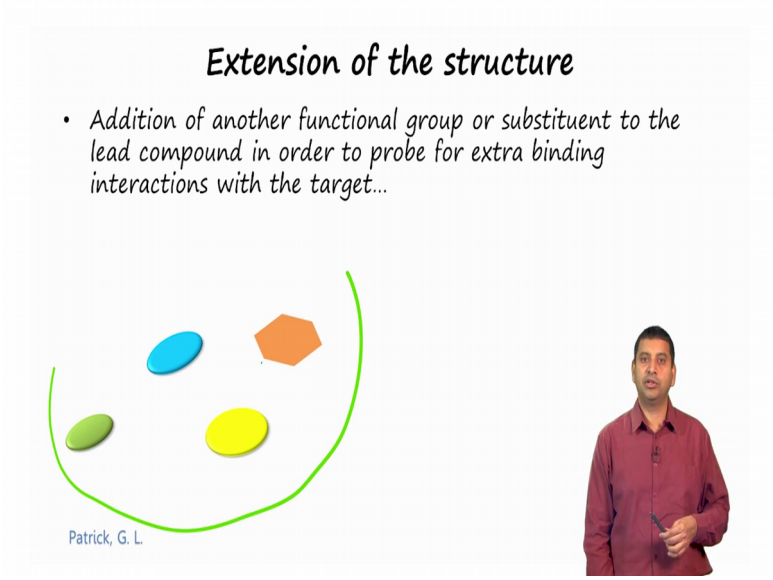

The next question is explain the concept of extinction of a structure, we have already looked at this in the tutorials but let us revisit this, extension is nothing but addition of another functional group or substituent to the lead compound in order to probe for extra binding interactions with the target, so here in the example that we looked at we had three interactions that were already present, but now by adding additional functional groups we may be probing for stronger binding okay, so the basic question that we ask in the extension of structure strategies are all the bindings sites been accessed, so of the answer to that is no, then we can keep adding structures to it to sample for or improve the binding, so here is the pictorial representation, so let say receptor site has these four functional groups which are going to interact with your target.

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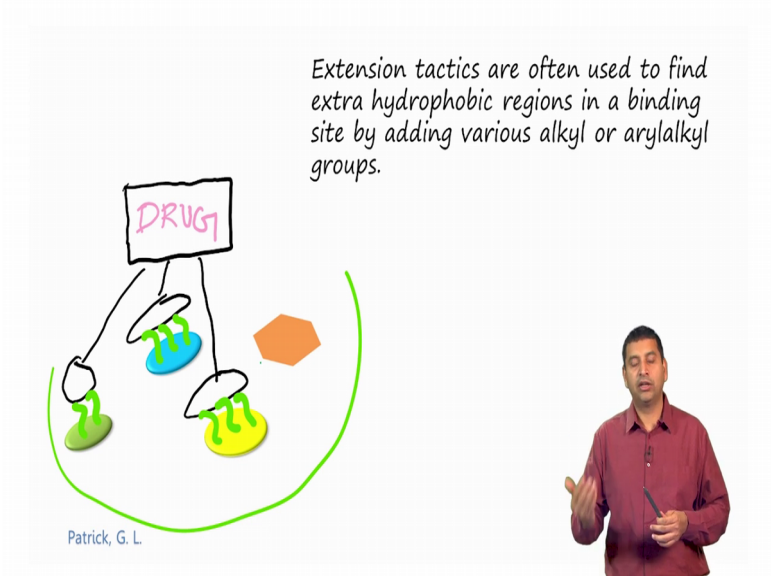

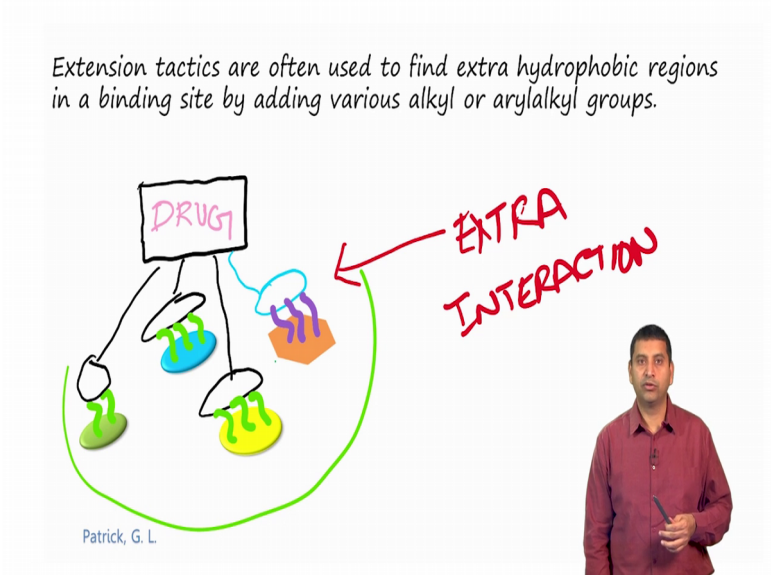

Then what we could do is we can design a drug, let say which interacts with three of these groups in a particular way, now since we are aware we have some idea that they could be an additional binding site, we can use what is known as an extension tactics, so we can add an alkyl or an arylalkyl group, so that the next group that is shown here and also be binding to the target.