Medicinal Chemistry
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Optimizing Drug-Target Interactions Part - 3

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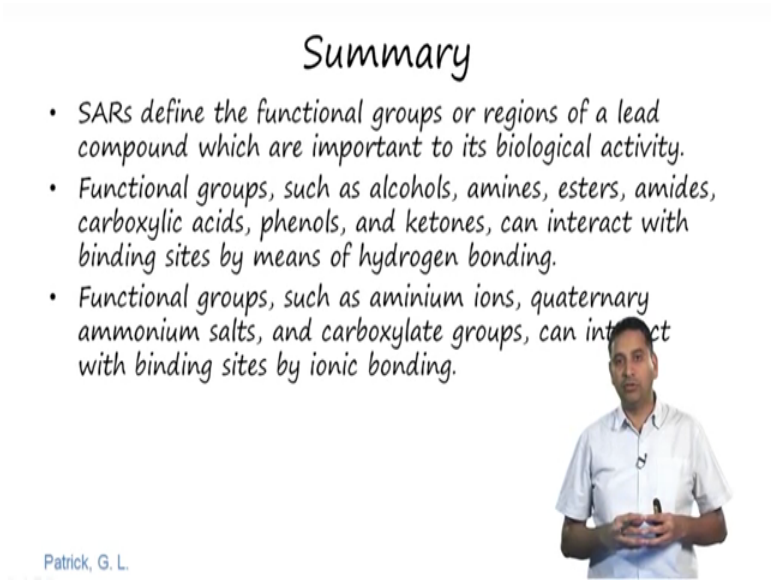

So welcome back. We shall continue to look at how to optimize drug-target interactions. So just to recap what we have been looking at in the past few lectures, so we have sort of defined what structural activity relationships are and these are basically the way in which we want to modify the structure in order to improve the activity of the molecule and we looked at various functional groups such as alcohols, amines, esters and so on and how they can interact with the binding site by hydrogen bonding and by other weak interactions. And we have looked at full cations and anions which can interact by ion bonding.

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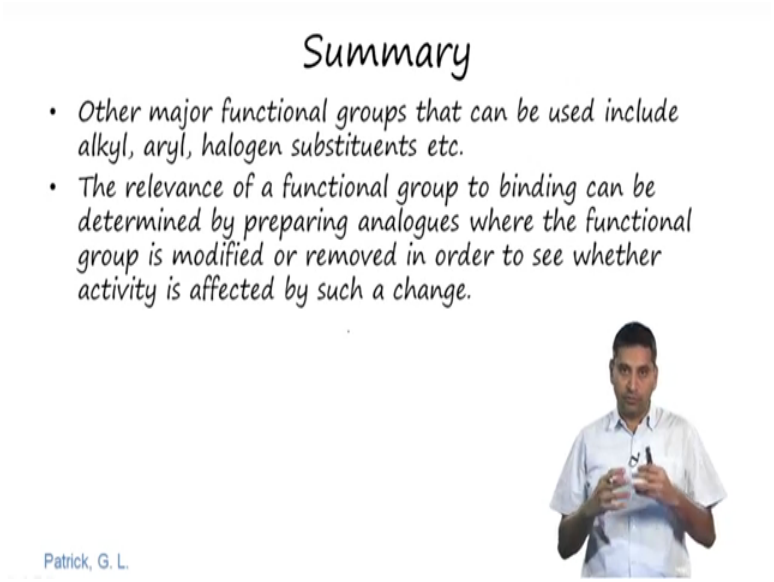

So some of the other major functional groups which can interact in this manner are the alkyl, aryl and halogen substituted compounds and we you also seen that halogen substitute compounds may have a propensity to do alkalization which is not very desirable. So the relevance of the functional group to biding can be understood when we make analogs. So here what we do is we either modify or remove the functional group altogether and see whether the activities affected by such a change. So we have seen all of these concepts in the past few lectures.

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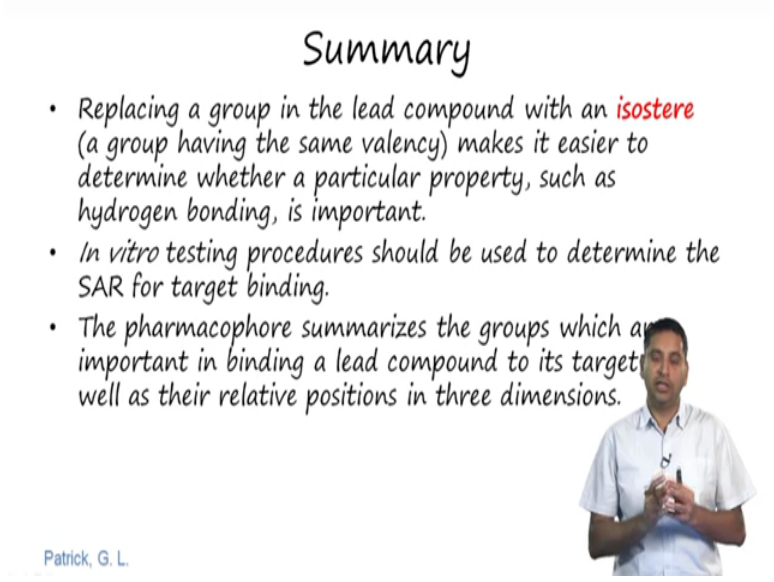

So we also introduced the concept of an isostere which is basically a group that has the same valiancy. So an isostere for an alcohol would be CH2NH2 and so on. So for example, when we want to interrogate whether a particular property such as hydrogen bonding is important, we would replace that molecule with the isostere which does not change the molecular weight of whole lot but would change the polarity and would change the hydrogen bonding capability and so on. And we also understood why In vitro testing procedures and important because once we start looking at animal models that may actually not reach the target and that may be difficult to interpret.

So then finally we were exposed to this concept of pharmacophore which basically summarizes the group which has important for binding and we also looked at the concept of a 3D pharmacophore where you can sort of draw triangles which related these various functional groups.

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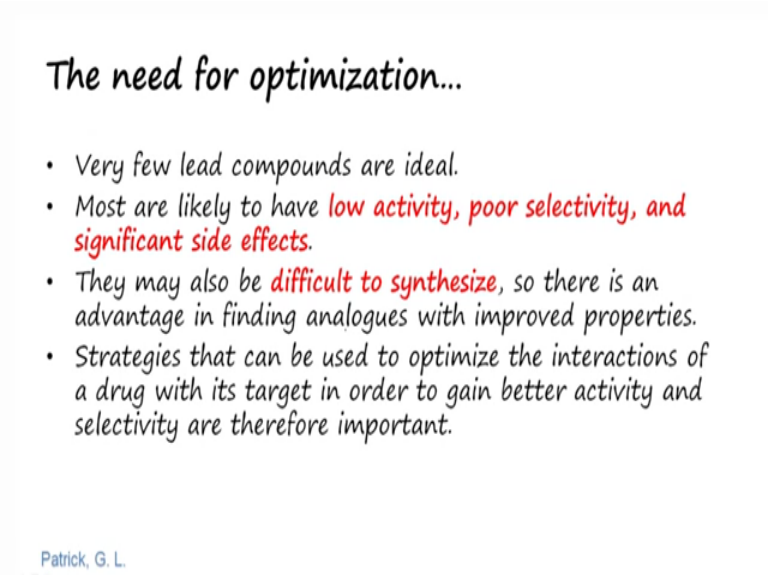

So the need for optimization is very important for us to understand because once we discover a lead maybe through serendipity or through some screening or through some rational design, that lead compound may have good activity but they are far from ideal. So some of the lead compounds although have activity but they may be low and so you need to improve it. And one of the major problems that we face during drug target optimization is poor selectivity and this can also lead to significant side-effects.

So the lead compound may also be difficult to synthesize and so there is an advantage in finding analogs with improved properties. So we have seen thus far number of strategies that one can employ to optimize the interactions of a drug with its target and to impart some level of selectivity.

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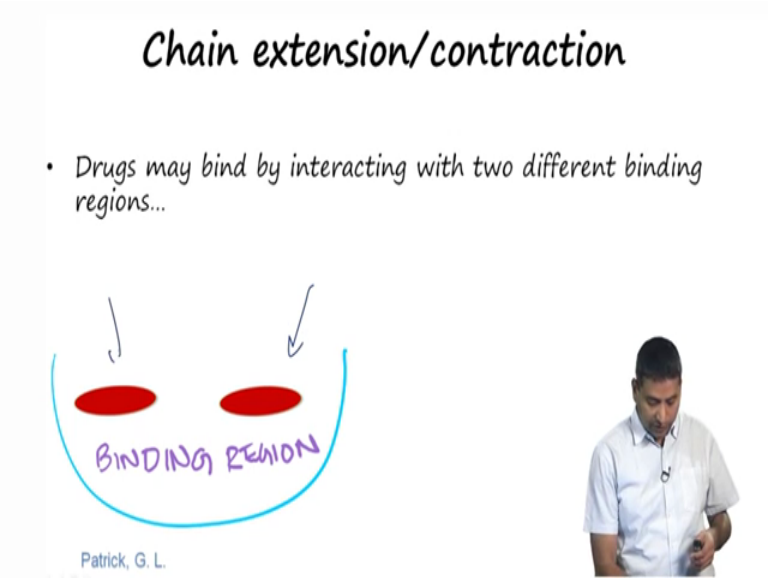

So today we shall continue with this approach and we shall look at various aspects of trying to optimize these interactions. So the first concept that we look at today is chain extension-contraction. So let us imagine that a drug interacts with a particular binding region or a binding site where there are two different binding regions that are present. So here is the first one and here is the second one.

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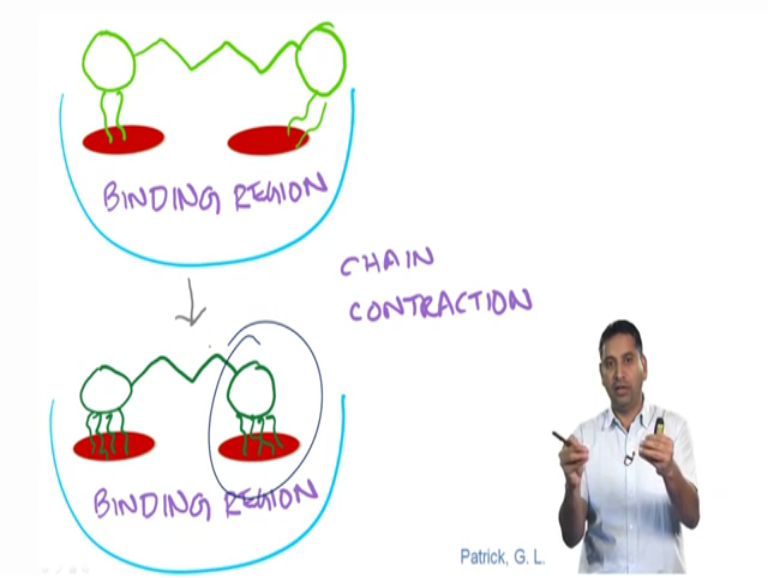

Now if you imagine that there is a drug which binds to this or your lead compound binds to this, so it is possible that one of the regions that is bound is may be strong, let us say this is quite strong. Whereas this region is relatively weakly bound, so by extending the chain what we may be doing is to increase the number of interactions that may occur. So this is one of the strategies that is frequently employed to improve binding to the particular region that of interest.

As a corollary one can also think about a situation where the chain is too long and so you have some weak interactions that are happening over here but once you contract the chain or reduce the length of the chain, then it is possible to arrive at a more optimal interaction. So what to think about here is, is it based on the pharmacophore that we have, there may be one binding interaction that is important and there may be another binding interaction which is important. And so now by modulating the chain length here, we can increase or optimize these features.

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So therefore shortening or lengthening of the chain is useful tactic to try.

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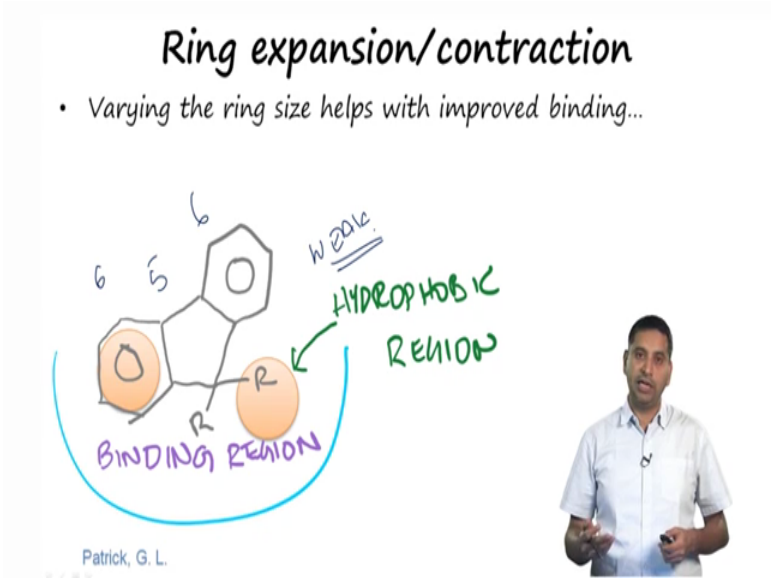

The next concept that we shall look it is ring expansion or contraction. So again here we are going to look at this example where we have couple of binding regions in this binding site. And this is the drug that we have with us or the lead compound that we have with us. And here there is a 6, 5, 6 member ring and so it has a particular orientation that is going to pretty much rigid. So there is a hydrophobic region that is present in the binding pocket in which there is a weak

interaction. So one strategy that we could employ is to improve this binding by changing the ring size in order to improve the binding efficacy.

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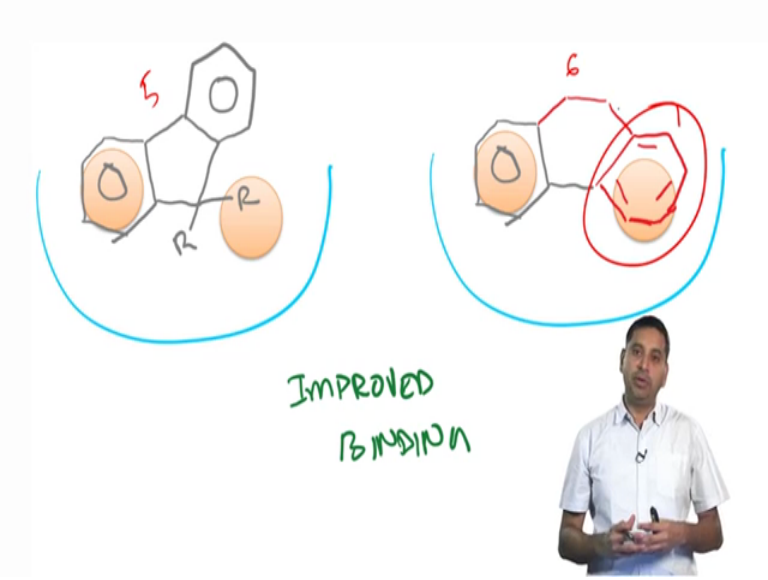

So when we move from 5-membered ring to a 6-membered ring, what we are doing here is we are changing the orientation in which the ring interacts with this hydrophobic region so that it improves the binding efficacy. So therefore this might be a good strategy to employ.

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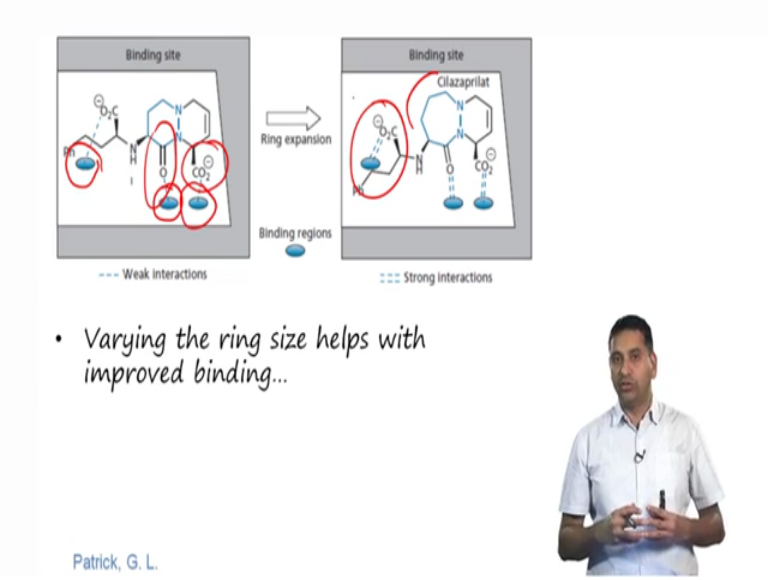

So one example that we can look at here is in the case of this drug which has weak interactions as I have shown here. There is a carboxylate in this molecule and then there is a carbonyl and

there are weak interactions that happen. Now there is another binding region over here which the carboxylate although it is binding, it is not very close enough for it to have effective binding. But once we change the size of this ring and make this 7-membered ring, then what happens is that the molecule is able to access this pocket and it increases the strength of the binding. So this is an example wherein you can use this strategy to your benefit.

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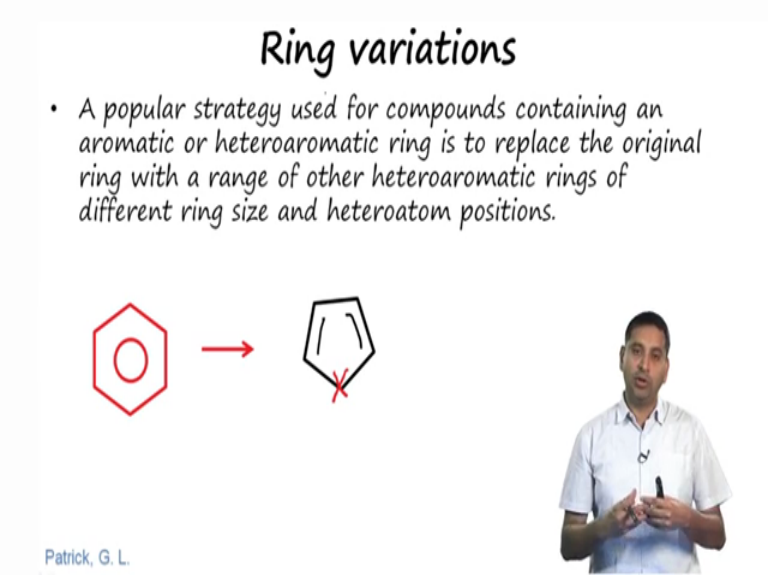

Another popular strategy which is used in order to optimize the drug-target interactions is to vary the ring. So for example, a benzene ring may be important part of your drug. Now the benzene ring can be converted to heteroaromatic ring or we can put in substituent on the benzene for example and this is a very popular method to vary the drug-target interaction.

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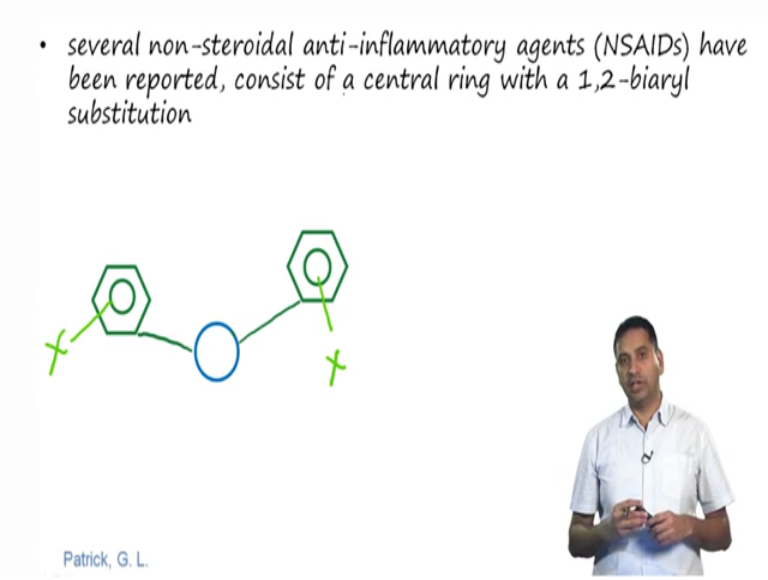

So there are number of non-steroidal inflammatory drugs which have this 1, 2-biaryl system just attached to a central ring. So we shall look at these examples.

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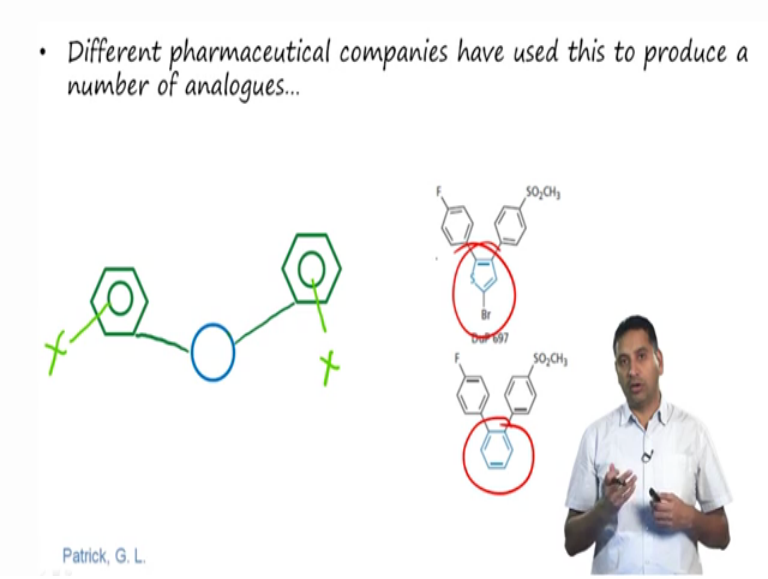

So here then various pharmaceutical companies have tried to make various analogs in order to optimize the drug target interaction. So here are couple of examples over here where this kind of a strategy has been employed and another set of pharmacophore companies had a different approach and here they use the benzene ring and they use this thiophene ring for example to optimize the interactions.

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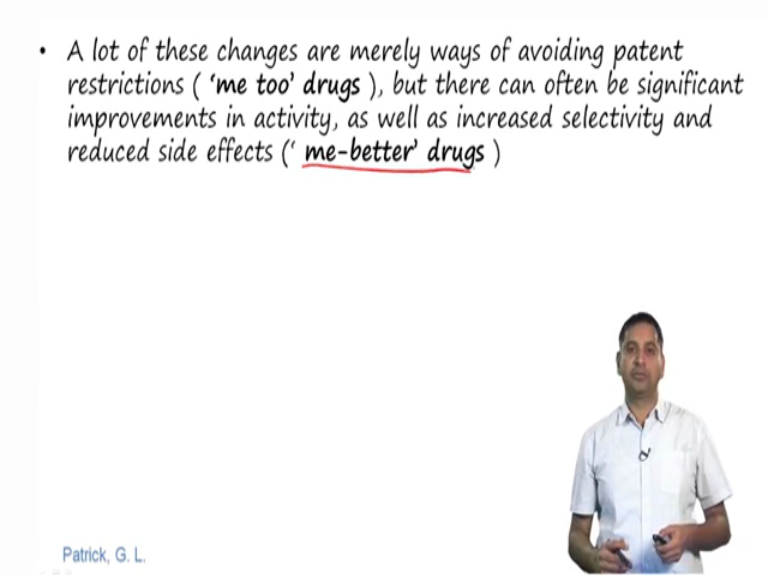

So lot of these changes have been carried out in order to avoid patent restrictions. So keep in mind that patent protection is available for most new drugs and in order for other companies to overcome this, what they do is that they try to make significant changes to the ring or to a particular area of the molecule so that they will be able to avoid the patent restriction. But some of them do indeed result in significant improvements in activity and these are termed as me-better drugs.

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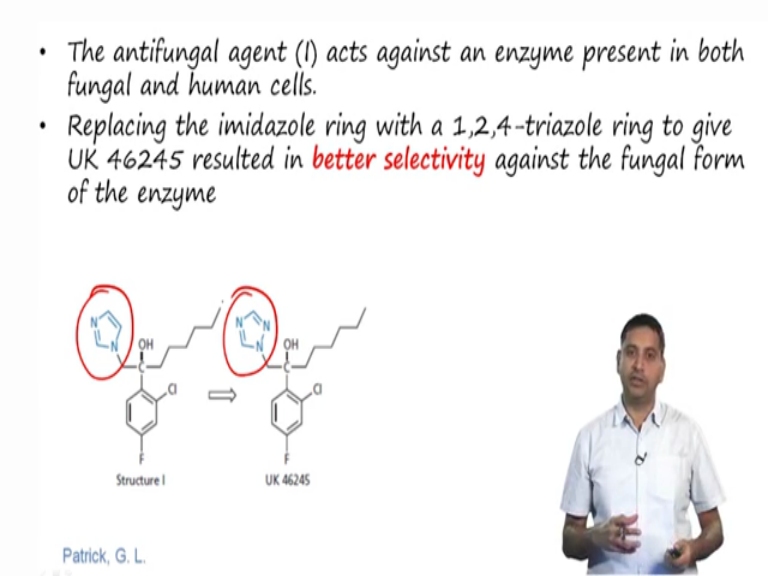

So the example that we can look at here is the antifungal agent which acts against an enzyme that is present in both fungal and human cells. So what was found was that replacing this imidazole ring with a triazole ring results in better selectivity against the fungal form of the enzyme when compared with the human form of the enzyme. So here is that case where the rest of the molecule pretty much remains the same but by changing a particular functional group or a ring we are able to achieve better selectivity.

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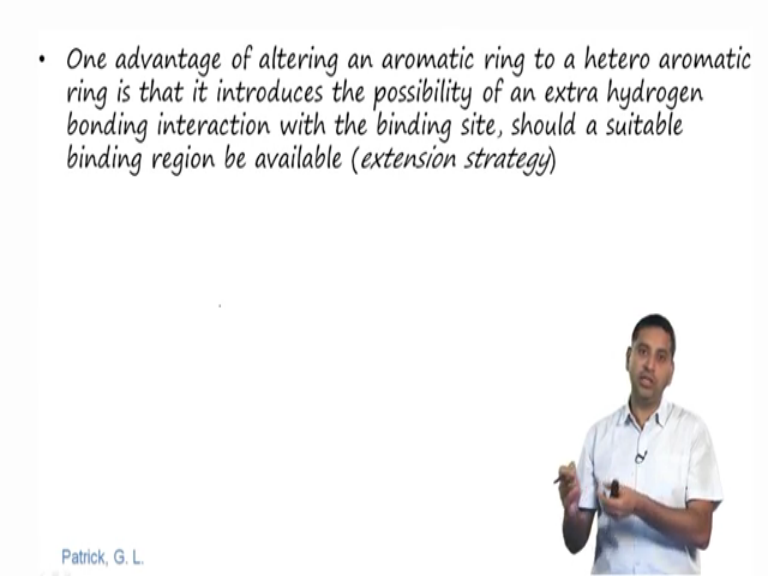

So one advantage of altering an aromatic ring to a hetero aromatic ring is that it also introduces the possibility of extra hydrogen bonding interactions, so herein what we can combine here is the strategy of changing the ring size or changing the ring along with the extension strategy that we have looked at previously, so we not only want to make a change in the binding affinity of the benzene ring, let us say as compared to the heteroaromatic ring, but we also to increase the number of possible interactions through the extension strategy.

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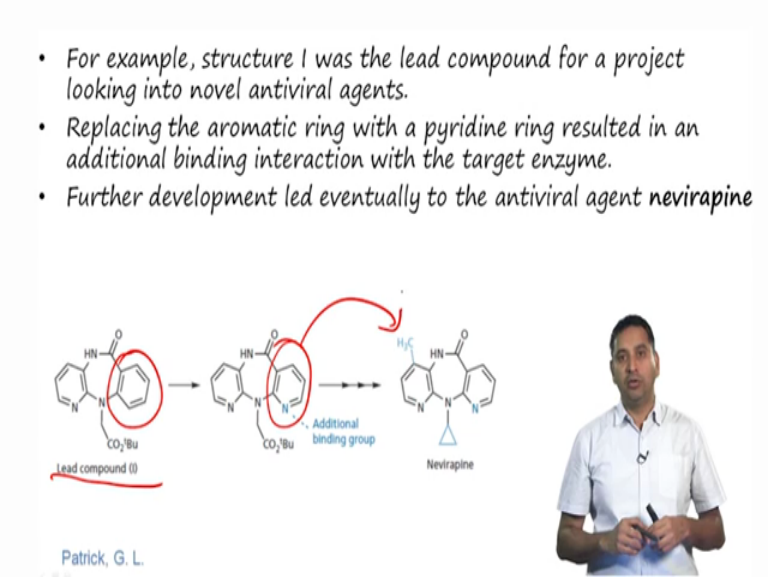

So here is the example that we look at, so the structure 1 was found to be the lead compound, it is a tricyclic molecule with one pyridine ring and one benzene ring which are connected by heterocyclic ring. Here what was suggested was that we convert this benzene ring to a pyridine ring. So the pyridine ring what the advantage of having the pyridine ring is that it actually can have additional binding group because that pyridine ring has a lone pair which can interact through hydrogen bonding perhaps. So this molecule was now the new lead compound and using this molecule the researchers ended up with this nevirapine which is an antiviral agent.

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The next method that is commonly used is called as a ring fusion strategy. So here what happens is that when there is a possibility of using a ring or creating a new ring along with an existing ring, then that can result in different set of interactions. So this may prove to be useful in not just increase interactions but also increase selectivity. So we already looked at previously that there are molecules such as beta blockers which are very useful and these molecules have been developed as replacements of the aromatic ring in adrenaline with a naphthalene ring. So here this is the molecule that we are looking at.

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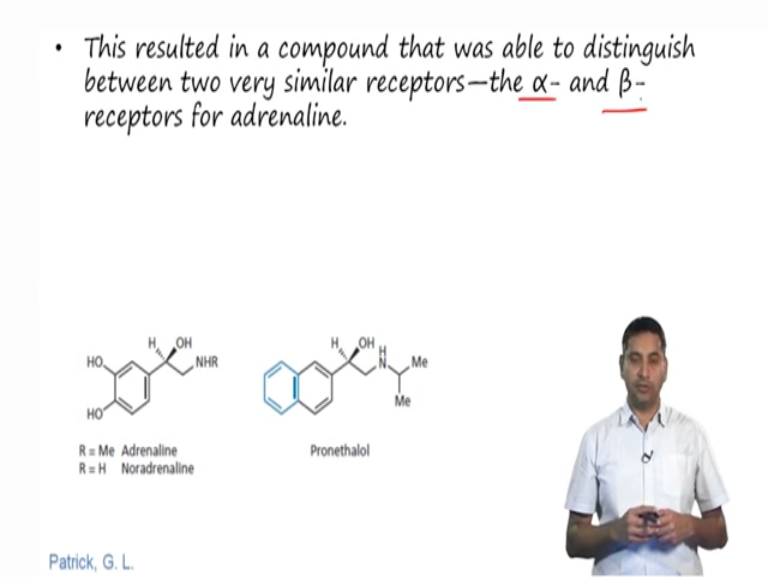

And what happens is that this compound was able to distinguish between two very similar receptors which is the alpha and the beta receptors for adrenaline.

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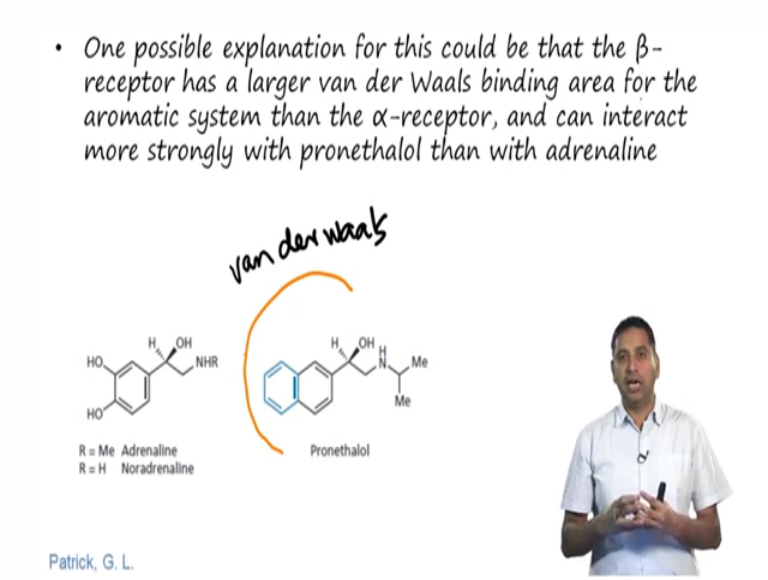

So one of ways in which we can explain this result is that by doing a ring fusion we are actually introducing a new substituent for additional van der waals interactions. So the beta receptor has a larger van der waals biding area compared to the alpha receptor and so it is possible that this binds better and it improves the selectivity.

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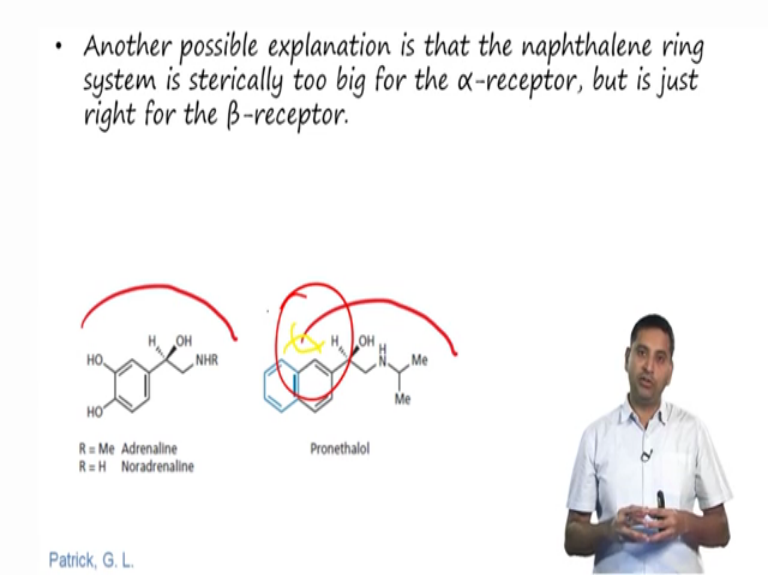

Another possibility is we have looked at previously which is what is known as steric blocking, is that the size of the receptor can be different. So the alpha and beta receptors are going to pick up adrenaline and so they are optimized in that size. But when we develop this drug, it is possible

that you may have some significant steric hindrance to binding. So both these concepts are possible, maybe operational in this case.