Medicinal Chemistry
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Optimizing Drug-Target Interactions Part - 4

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So welcome back. So continuing on the topic of optimizing drug-target interactions, we are going to look at various strategies that we would use. And to begin with in today's lecture, we look at the concept of isostere, we have already looked at it previously that isosteres are basically, it is a group that has the same valency and so it makes it easier to determine whether that particular property, for example hydrogen bonding is important or not. And so replacing a group in the lead compound with an appropriate isostere will help us optimize the drug-target interactions. So if hydrogen bonding is going to be quite important, then we may want to put in a group that will enhance hydrogen bonding and so on.

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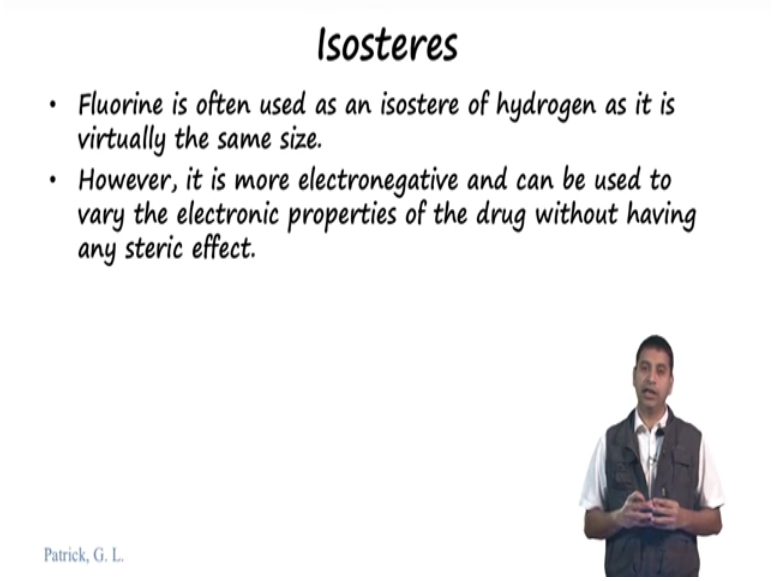

The fluorine, fairly electronegative atom is fairly commonly used as an isostere of hydrogen. So interestingly although it is much more electronegative, it has very similar size as hydrogen. So therefore by replacing hydrogen with a fluorine, will sort of keep the steric effect to be similar but it can substantially vary the electronic properties of the drug. So by doing this, one can figure out if the hydrogen is important in any interaction or not.

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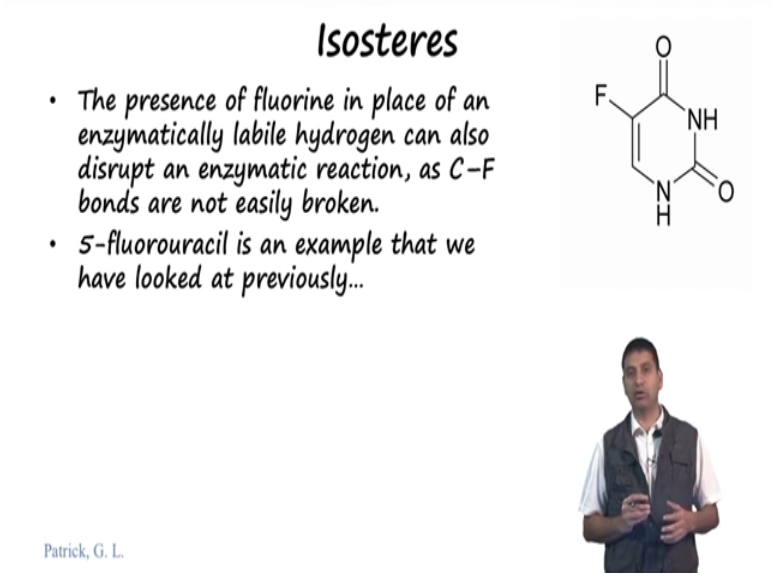

So the presence of fluorine is also useful when we are looking at enzymatically labeled hydrogens. So if you want to disrupt an enzymatic reaction where the carbon-hydrogen bond is broken, we could replace it with a carbon-fluorine bond and we have already looked at previously about this molecule called as 5-flurouracil which is shown here.

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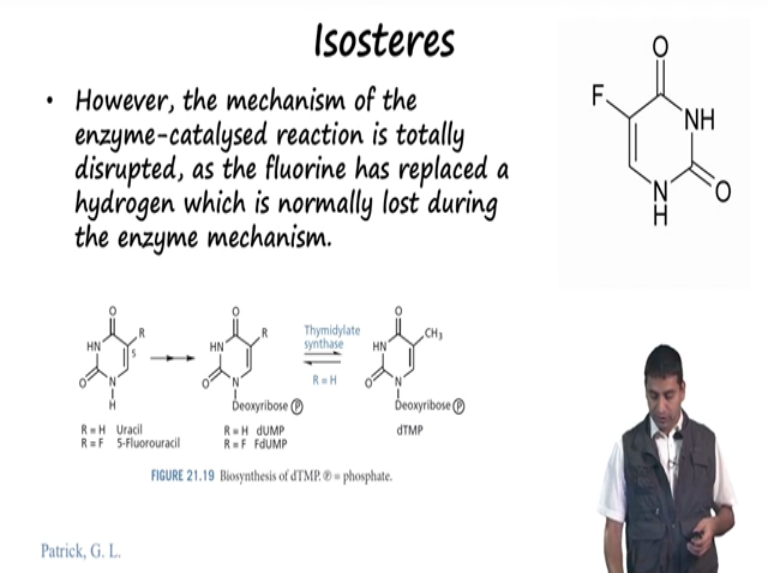

So because we are replacing hydrogen with fluorine, the mechanism of the enzyme-catalyzed reaction is disrupted. So again we have looked at this previously but we just recap very quickly here. So during this reaction of uracil going to TMP, what happens is that there is an enzyme called Thymidylate synthase which is important in this process. So here this group where R equals hydrogen is replaced by a metal group.

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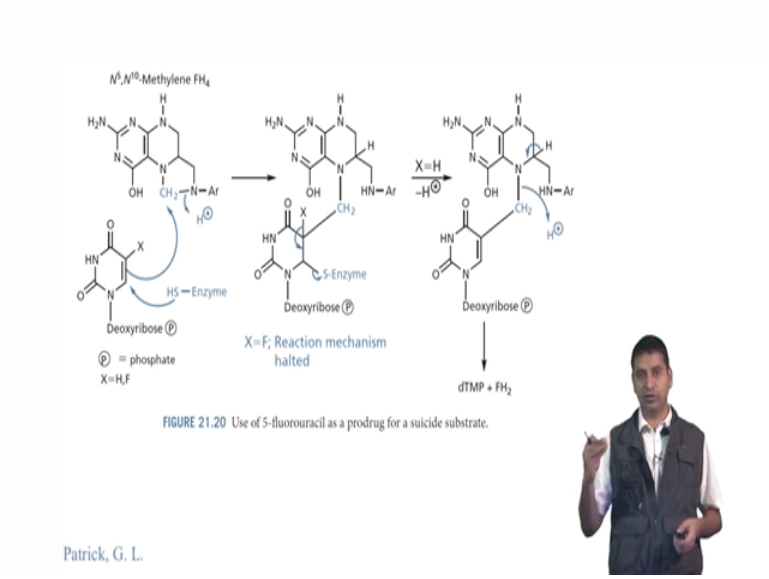

Let us look at the mechanism of this reaction. So this is a cysteine based process and so the thiol of the cysteine attacks this molecule here and then interacts with the CH2 and introduces a CH2 group here. And the next step is when excess hydrogen it is going to lose H plus and reform the double bond as shown

here. But when we do this reaction with fluorine, the second step is not possible and so the reaction mechanism is halted. So here the isostere also plays a role of disrupting the mechanism.

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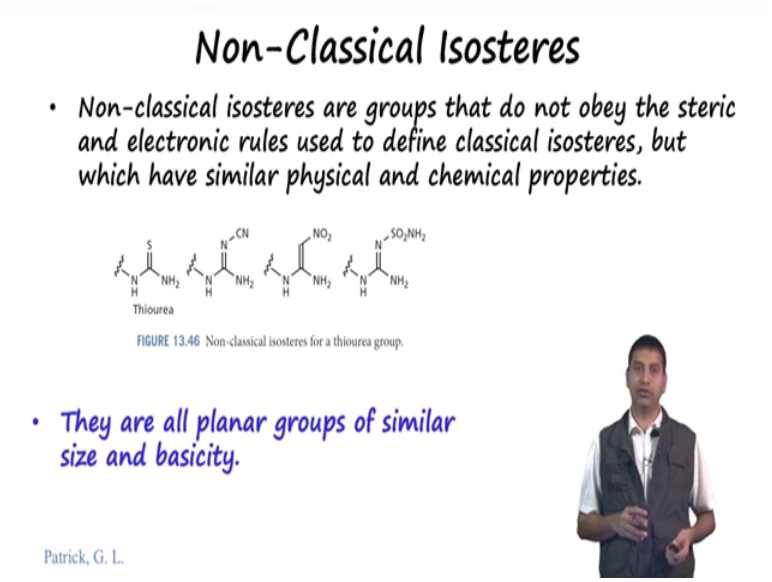

Other than the classical isosteres, there are also molecules known as non-classic isosteres and these are groups that do not obey the steric and electronic rules that are usually used to define classical isosteres but which have very similar physical and chemical properties. So for example, if you have a thio urea in your drug, then you could replace it with any of these groups because they are all planar, as you can see they all have a CP2 carbon and they all have similar basicity. And the size also might be quite similar because of the nature of the functional groups that are involved here. So these molecules do not have the same valency clearly and so therefore they are not classical isosteres and they are called as non-classical isosteres.

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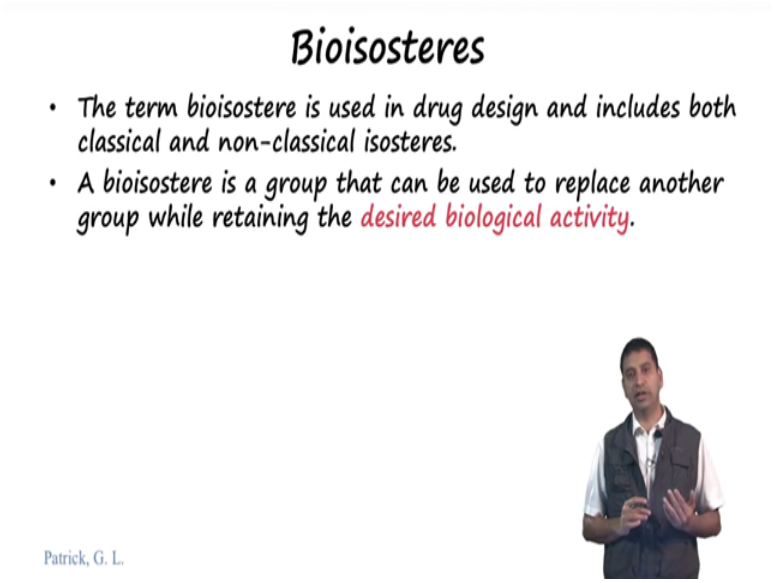

In addition to that, there is another concept of isosteres which is known as bioisostere, so the term bioisostere is commonly used in drug design and it is a super set of both classical as well as non-classic isosteres. So in common terms, in drug discovery bioisostere is a group that can be used to replace another group while retaining the same biological activity. That means that if I replace a molecule with another molecule or functional group, then the activity of that molecule does not change or it can improve and the desired biological activity can be achieved.

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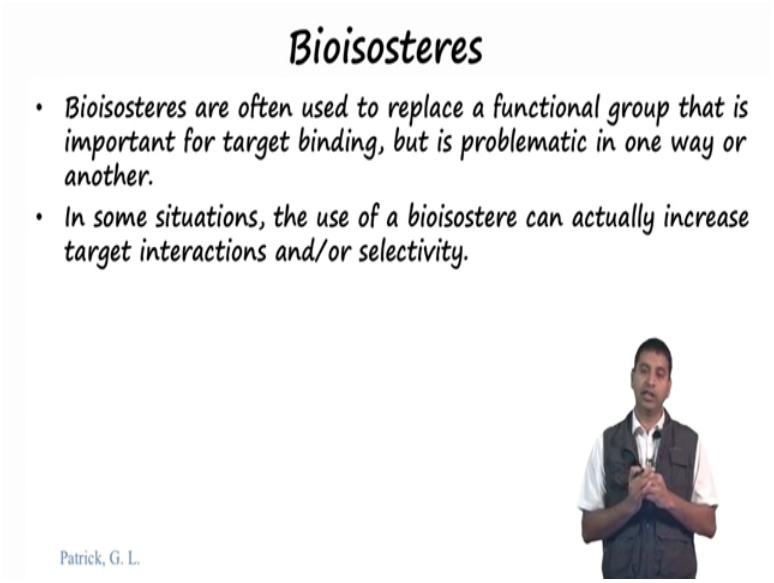

So bioisosteres are often used to replace functional groups that are important for binding in a target. So for example, it is possible that your functional group is very important for binding but it has other

problems during metabolism. So here the use of a bioisostere can actually increase the target drug interactions and may also help with increased selectivity.

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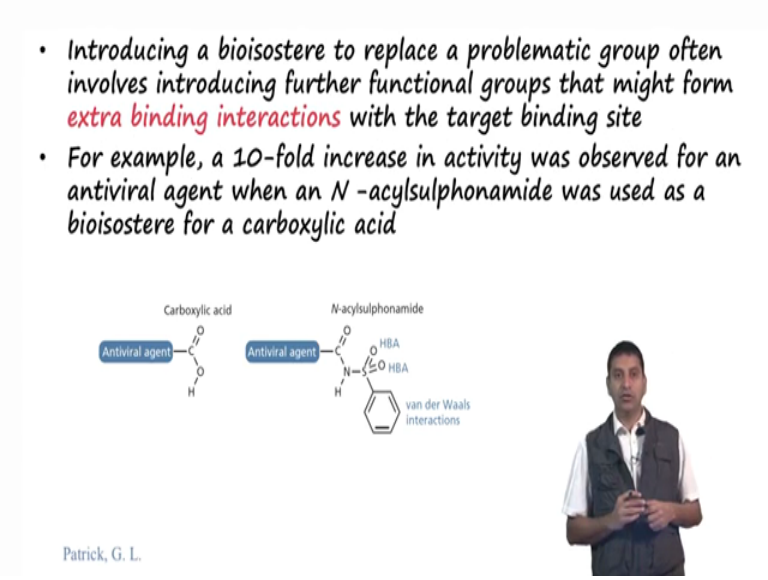

So for example, the pyrrole ring has frequently been used as a bioisostere of an amide. So if you see here, this is the amide that we are interested in and this example which is of sultopride which is antagonist and here what happens is that this is the amide that is of interest. And if you replace this with a pyrrole ring, so as you can see here, there are number of common elements in these two functional groups. So you have the C double bond which is aligned in this direction and the new C double bonds, C in pyrrole ring is also aligned in the same direction.

And then you are introducing a planarity. This pyrrole ring can be used as a bioisostere for an amide. And these agents have shown promise as antipsychotic agents that do not have the side-effects that are associated with the dopamine D 2 receptor which is associated with this molecule sultopride.

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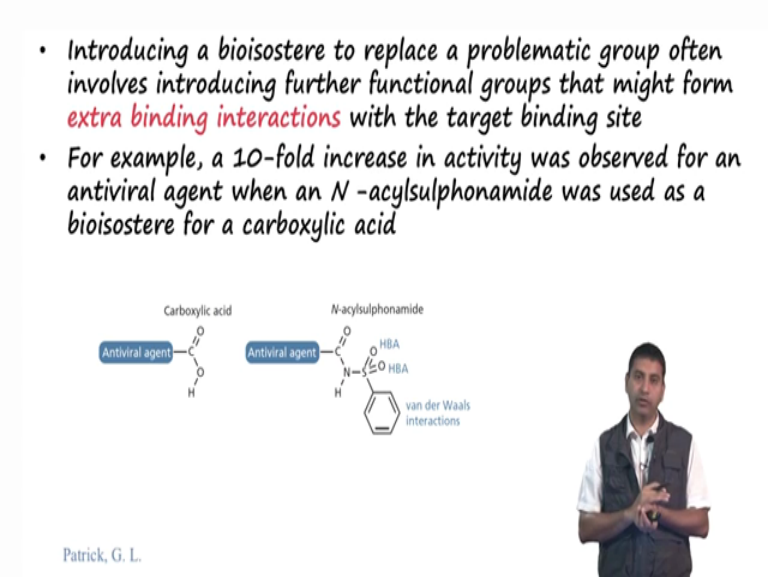

So introducing a bioisostere to replace a problematic group also involves introducing further functional groups that might form extra binding interactions. So for example, if you take this molecule which is an antiviral agent which has a carboxylic acid, now by replacing this carboxylic acid with an N-acylsulphonamide, so this is in this case it is a non-classical isostere and it would be classified under the umbrella of bioisostere. And so this N-acylsulphonamide actually mimics the carboxylic acid in many respects. But not just that, it also introduced a new functional group which is for van der waals interaction. So as we know from previous discussions the van der waals interactions can be important in the case of aromatic rings.

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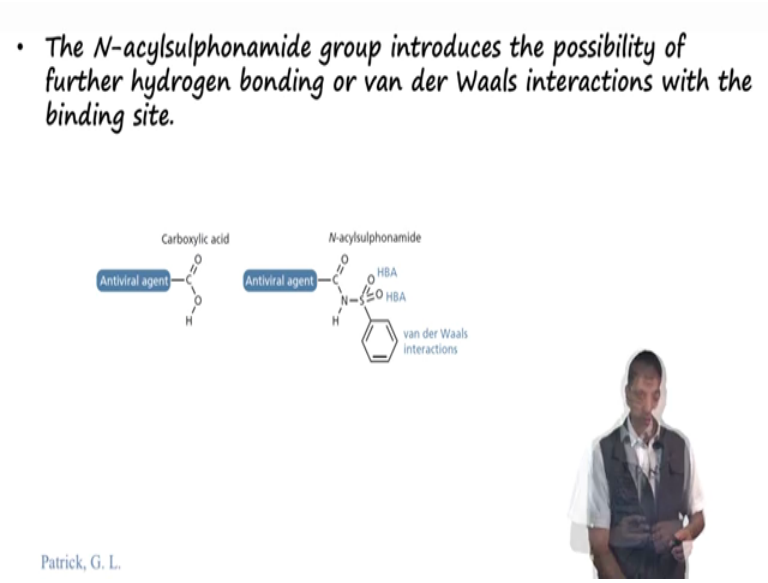

So N-acylsulphonamide groups keeps the hydrogen bonding pretty much intact because of this but introduces new interactions with the binding site.

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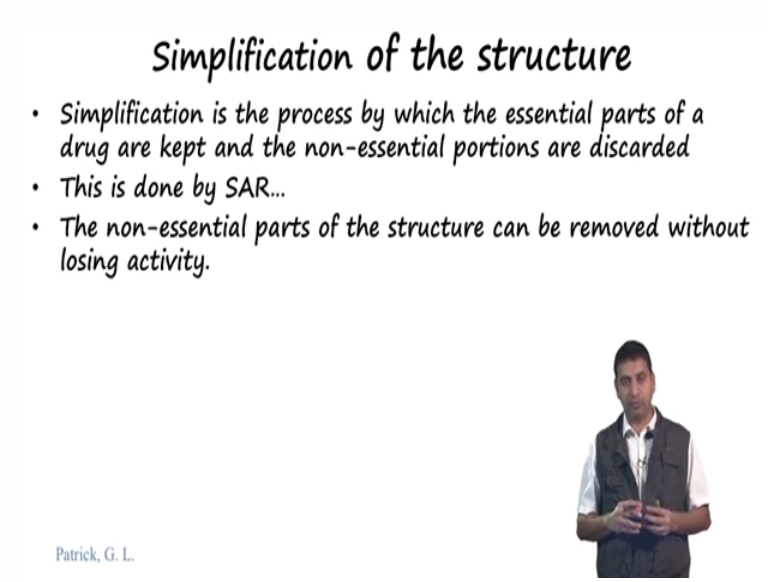

The next strategy that we would employ is simplification of the structure. As the name suggest, simplification is a process by which only the essential parts of a drug are kept and the non-essential parts are discarded. So of course this is done by detailed structure activity relationship or SAR. So the way we would identify the non-essential parts is that we would one by one remove the parts and then find out which one is important for activity. So if you remove a particular part of the molecule and the activity is not changed, then we would classify that as a non-essential part.

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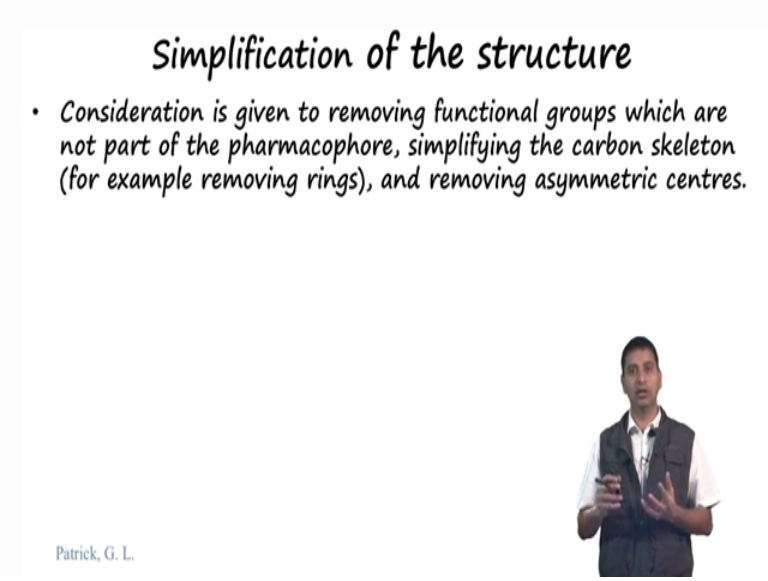

So lot of consideration is given to removing functional groups which are not part of the pharmacophore. So keep in mind we have already discussed the concept of pharmacophore in detail previously and so therefore by keeping the pharmacophore intact we can remove the other groups, for example a ring which is not very essential for the binding can be removed. Also we are very much interested at this stage to remove asymmetric centers. So as we know asymmetric centers are going to create problems because during synthesis you are going to end up with a racemic mixture and the racemic mixture to be separated and each of them has to be tested individually for the activity.

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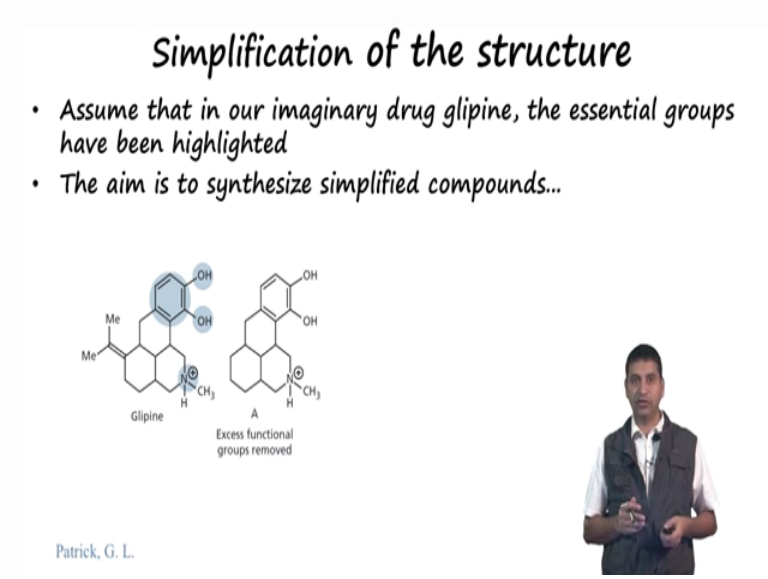

So let us go back to our imaginary drug glipine, where the essential groups are shown here that is the ones that are in this diagram below. So you have possibility of ionic interaction with this quandary ammonium salt and you have both hydrogen bonding as well as van der waals interactions. So let us assume that these are the essential interactions that are important for activity. So now one can remove the excess functional groups in a systematic manner.

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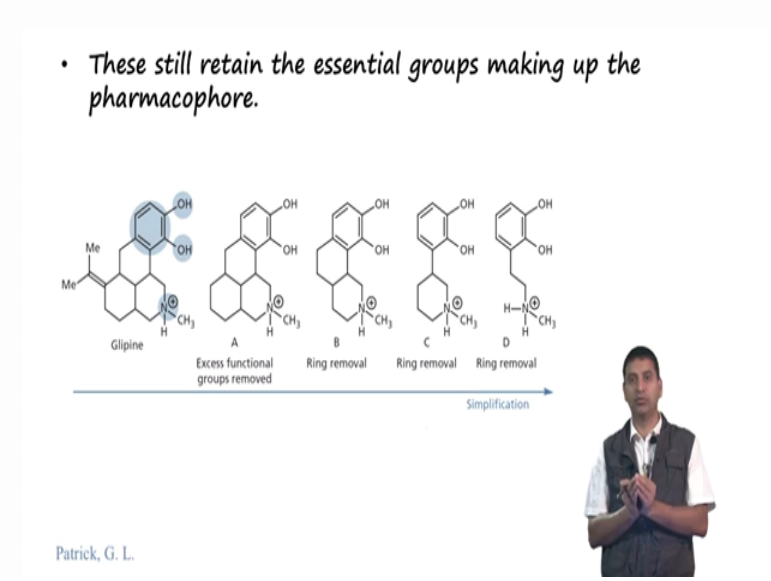

So here what we are doing is that for example, this colophonic structure here can be removed and you end up with structure A. Now you can then go further and remove this extra ring over here because this ring does not seem to be important for activity based on structural activity relationship. And you are further simplifying the structure and making it a tricyclic core that is as shown in structure B. Now in structure C you have even removed third ring over here. And you are making this molecule as a bicyclic by T.

So now since we know that the amine is the important part, one can go further and remove this ring as well and find out whether that is going to be important for activity. So therefore identifying the pharmacophore is really essentially and then one can think about systematically removing various functional groups which are not essential parts of the pharmacophore.

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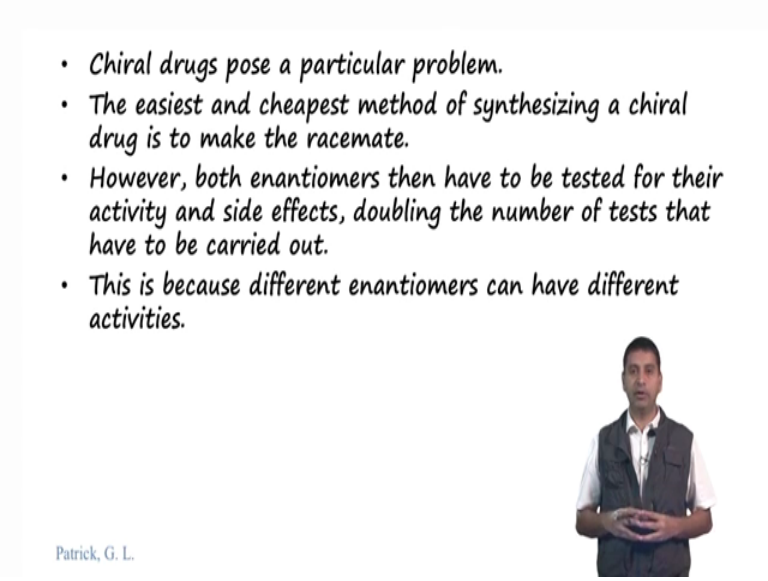

So as I have mentioned earlier, chiral drugs pose a particular problem. Now the simplest way to make a chiral drug is to make the racemate. Lot of the reagents that are used for asymmetric synthesis are quite expensive. And so for example, if I would want to do reduction of a ketone, then I would use sodium borohydride which is quite cheap but if I have to make one enantiomer of the ketone of the alcohol starting from the ketone, then I would need to use an expensive reagent, asymmetric reagent and that also gives me a possibility of having 5 to 10 percent of the undesirable isomer which anyway I have to separate.

So now the other problem is that if you are using the drug as a racemate, we have discussed this previously, both enantiomers have to be tested for activity and side-effects. So therefore let us say we have a preclinical investigation in an animal model, and we would need to use let us say 25 animals in the case of a particular drug, because I am dealing with both enantiomers I have to now double the number of tests which means I would have to use 50 animals.

So this not only increase the cost but also is not useful from a standpoint of ethics. So as we very well recognize, enantiomers can have different activities. And so therefore if it is possible to simplify the structure wherein this chiral center can be removed altogether, then this might be a good strategy to follow.

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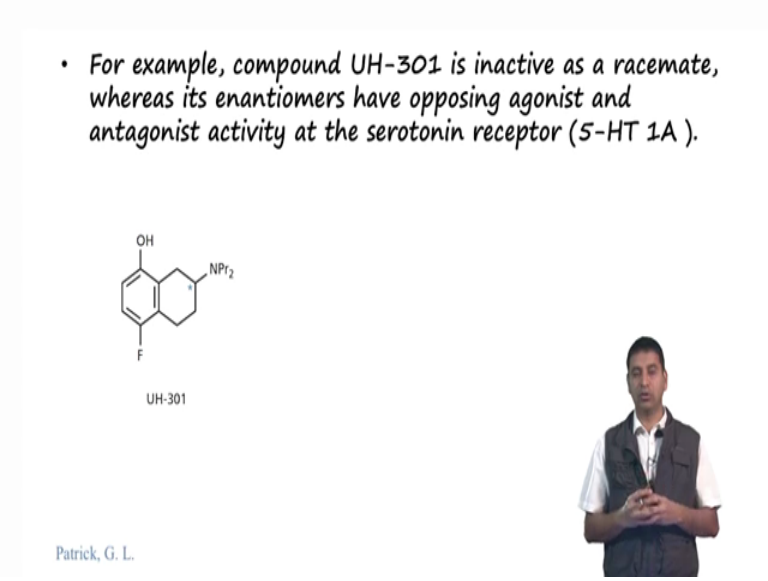

So here is an example of this molecule, UH-301 which is actually inactive as a racemate, this is very interesting example because the opposing enantiomers, the R and S enantiomers actually have opposing activity against the serotonin receptor. So the R version of this has exactly the opposite activity as the S version. So therefore when you actually tested it as a racemate, on the whole it is inactive.

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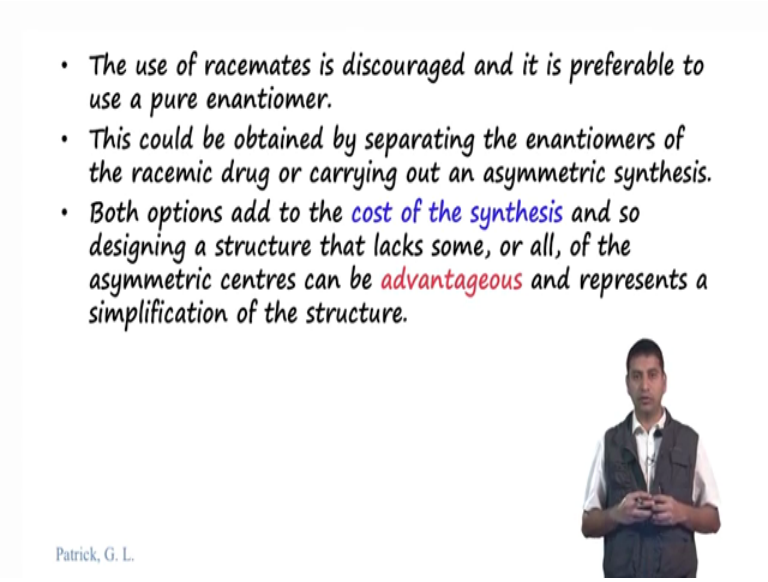

So the racemate is discouraged therefore and it is preferable to use a pure enantiomer. Now of course what we can do is we have already looked at in detail that we can separate out these enantiomers of the racemate drug but this is going to increase the cost of the synthesis and also you are going to lose 50 percent of your molecule in terms of the yield. So therefore designing a structure that lacks some or all of

the asymmetric centers can be hugely advantageous and it is an important part of simplification of the structure.

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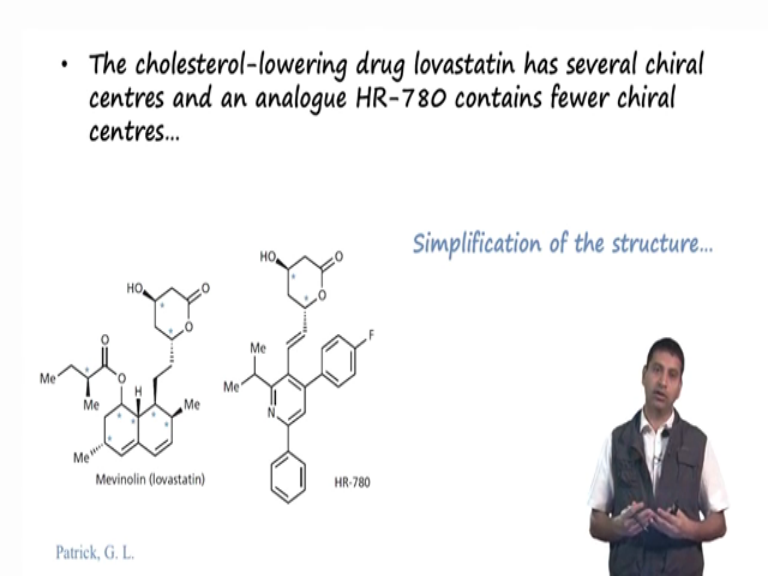

So the cholesterol lowering drug lovastatin which is shown here has chiral centers, so you can see here that it has 1, 2, 3, 4, 5, 6, 7, 8 chiral centers. During structure activity relationship using this concept of simplification, we are now substantially lowering the number of chiral centers and it is basically we have come down from 8 to 2 and this molecule has pretty much the same activity as the parent compound. So it is highly desirable to use this analog in terms of taking it forward as a drug compared to lovastatin.

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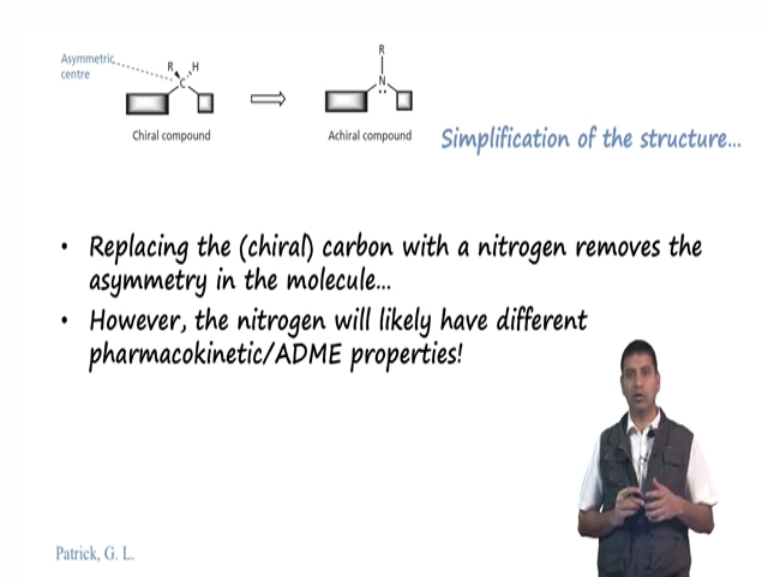

Another approach that we can use is to remove the chiral center altogether by replacing the carbon with a nitrogen. So as we know nitrogen is going to undergo ring flipping and therefore the molecule is going to be a chiral. So this may be a very important way to remove asymmetry or introduce symmetry in the molecule. However there is a risk here, so nitrogen as we know has very different pharmacokinetics and of course ADME properties and so one has to be careful while doing this kind of a modification.

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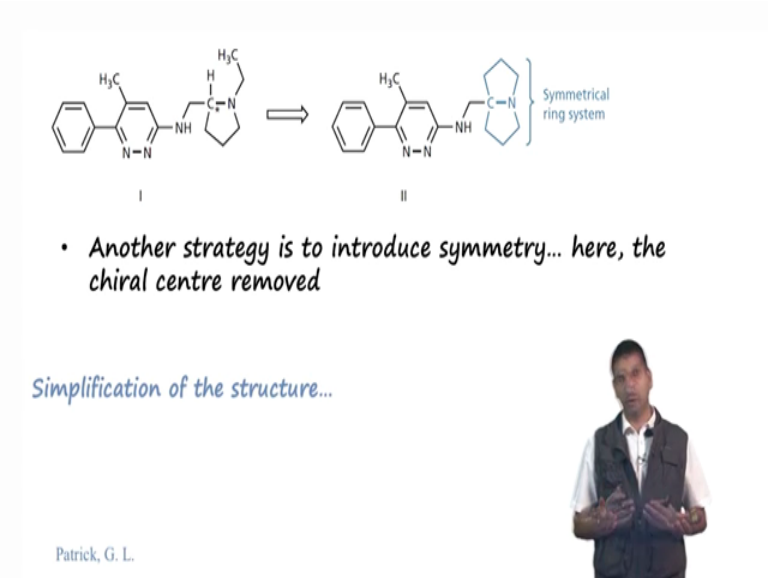

So another strategy is to introduce a symmetry. That is a molecule has asymmetric center such as the one shown here, what we could do is to convert this to a molecule which has a plane of symmetry or any element of symmetry which makes it a chiral. So here in this example what we have done is we have introduced two 5-membered rings here which are basically mirror images and you can draw a plane which is a plane of symmetry which is going to sort make the molecule on the whole a chiral.

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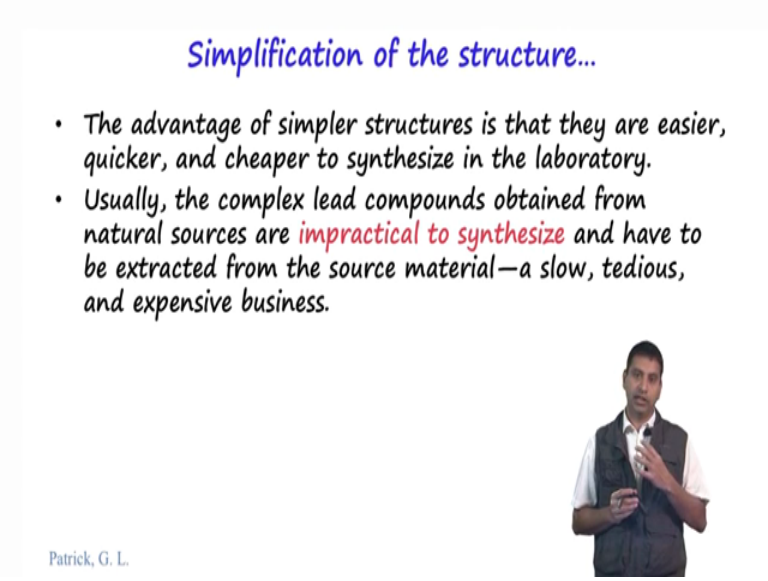

Again this is classified under simplification of the structure. So the advantage of simpler molecules is that they are easier, quicker, and cheaper to synthesize in the lab. Usually the natural products that we are extracting from natural sources are pretty much impractical to synthesize and what is typically done is that they are extracted from the source material and which is an extremely slow TDS and quite expensive.

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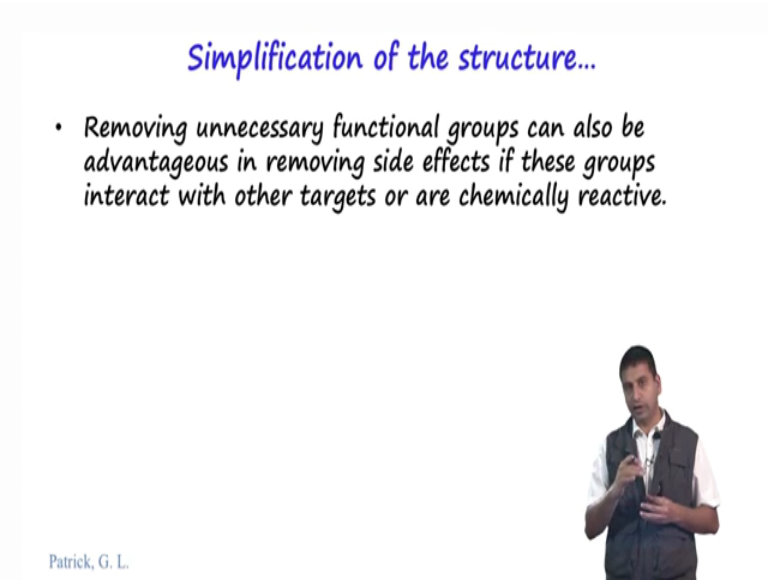

So removing unnecessary functional groups can also be in some cases advantageous to removing side-effects. So when we are doing ADME, we might discover that the molecule has some unwanted side-effects and these may be due to a particular functional group that is in the molecule which is not

important for the activity. So these side-effects or these functional groups that interact with other targets, or which are chemically reactive can be removed.

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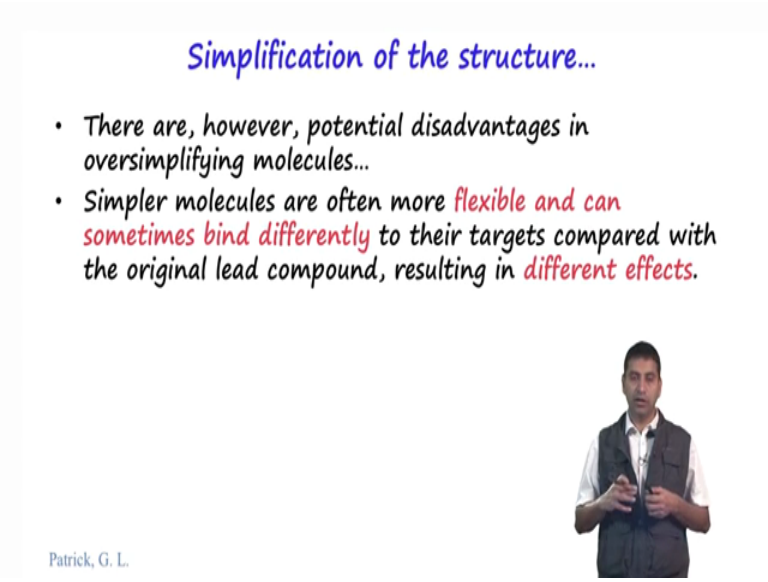

However there is a major word of caution here, in that the disadvantages in oversimplifying molecules are plenty. So once you have made the molecule simpler, for example in the glipine case we have removed all the rings and now the rings, the molecule is going to be rotate quite easily and it makes it more flexible. So once you make it more flexible, then the active conformation is going to change. So if the active conformation is going to change, then the efficacy of the molecule might go down because it is going to bind differently.

So it is possible that you might see different effects compared to the original lead compound. So this must be kept in mind while we are trying to simplify the structure.

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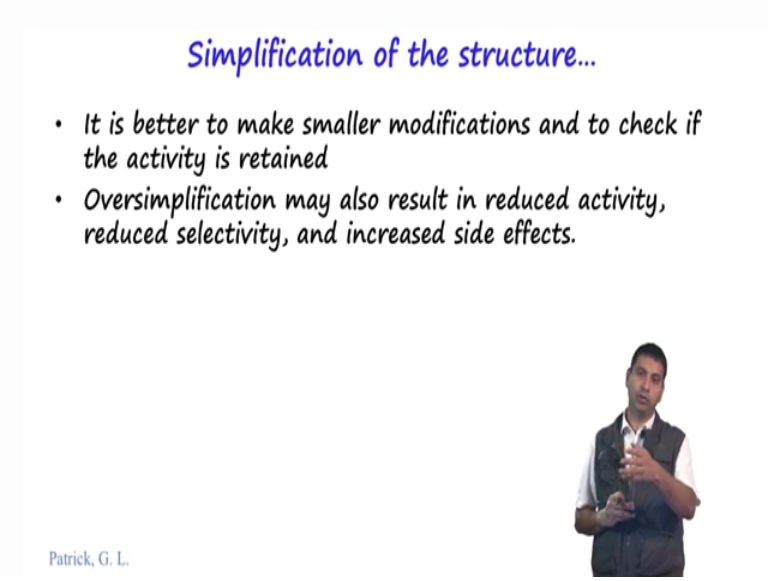

So therefore it is better to make small modifications, take small steps and then check again if the activity is retained or not and then proceed further because oversimplification may result in reduced activity also selectivity may go down and sometimes the side-effects may also go up because of promiscuous interaction.

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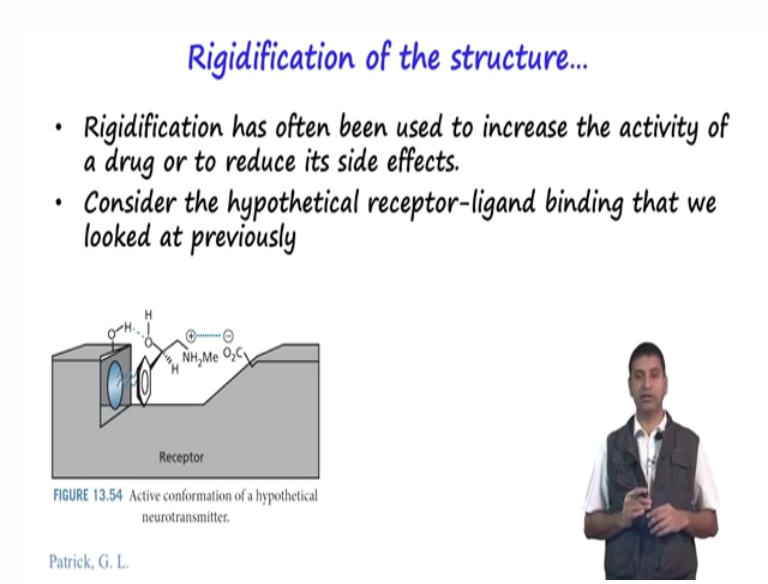

The next strategy that we will use is called as Rigidification. So rigidification is nothing but trying to introduce elements inside the lead molecule which are going to make the molecule more rigid this is typically done to increase the ligand receptor or ligand enzyme binding interactions and so in order to understand this better let us look at this example. So this is our hypothetical receptor and hypothetical

molecule and as you can see there are number of interactions that we have looked at previously which are important for the binding of the molecule to the receptor. So for example, you have a hydrogen bonding interaction as well as van der waals interactions and a salt bridge.

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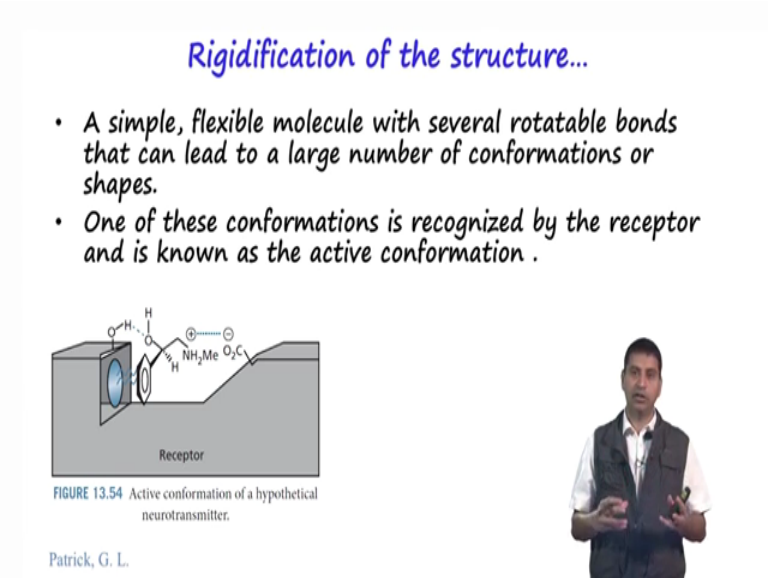

So a simple, flexible molecule with several rotatable bonds will lead to a large number of conformations and of course large number of shapes. But we have discussed previously that there may be what is known as an active conformation wherein there is a specific shape of the molecule and a specific structure which is going to interact with the receptor. So this is called the active conformation and ideally we would like to mimic this active conformation.

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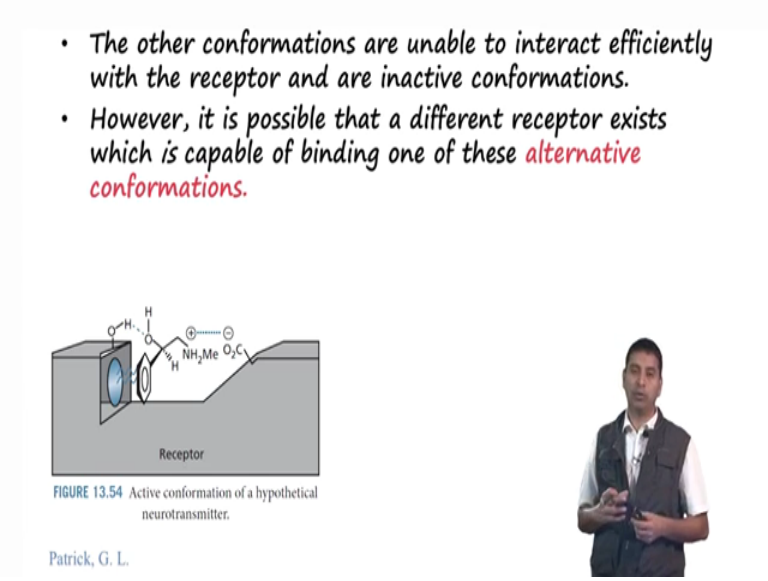

The corollary to this is that the other conformations which are theoretically possible are unable to interact efficiently with the receptor and therefore called as inactive conformations. So it is possible that a different receptor can bind to these alternative conformations. So this may lead to a situation where there is going to be potential side-effects because we are going to have some receptor which is interacting with one particular conformation and another receptor which is going to interact with alternative conformations leading to possible problems.

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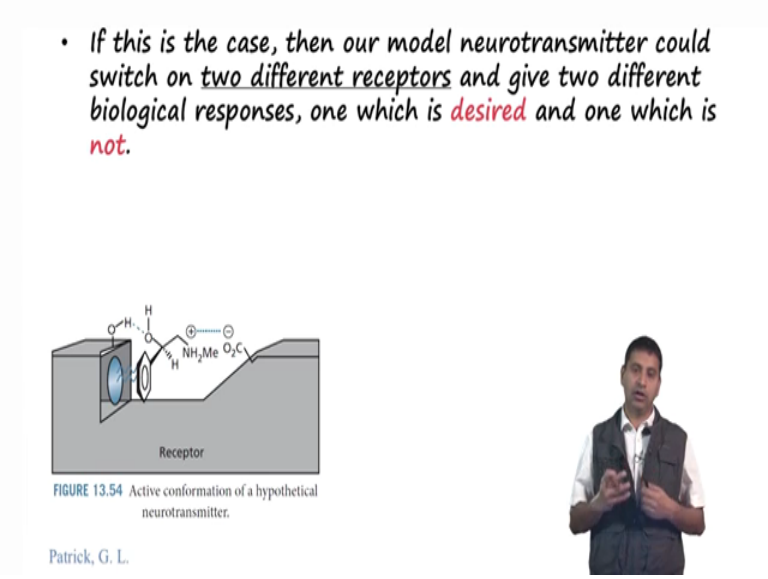

So if this is the case, then our model neurotransmitter can switch on two different receptors at the same time. So what will happen is that this may result in two different biological responses and only one of them is desired and the other one is not. So in order to solve to this problem, we are looking at rigidification of the structure.

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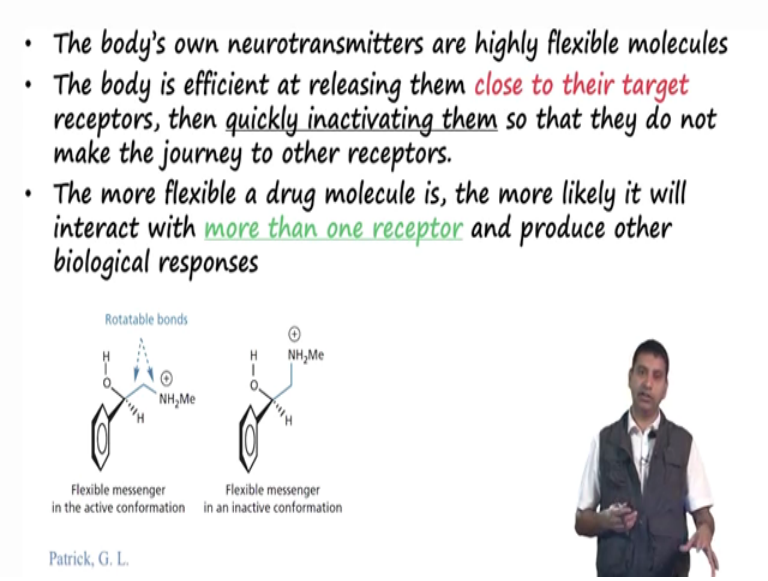

In our own body these neurotransmitters are highly flexible molecules are very useful because they are released very close to the target receptors. So we have already looked at this previously that there is a synapse interneuron area and that is where the receptor is going to bind to the surface of the neuron. So as soon as the signal is transmitted, then it is taken back into the cell and also this is going to be highly localized. But when we are developing a drug, we need to be able to consume this drug and the drug interacts with number of part of the body before it gets to the target. So one has to be careful when we are looking at designing these types of ligands which are for these kinds of receptors.

So the more flexible a drug molecule is, it is perhaps more likely that it will interact with more than one receptor. So in order to address this let us look at the hypothetical receptor. So imagine that at this molecule is going to undergo a carbon-carbon bond rotation. So if it does that, then the NH2ME which is located below here is going to go up. So let us assume that this is the active conformation and this is an inactive conformation. So if this is the inactive conformation, it is possible that this inactive conformation interacts with a different receptor. So in order to avoid this what we could do is to make this molecule more rigid so that it interacts only with the desired receptor.

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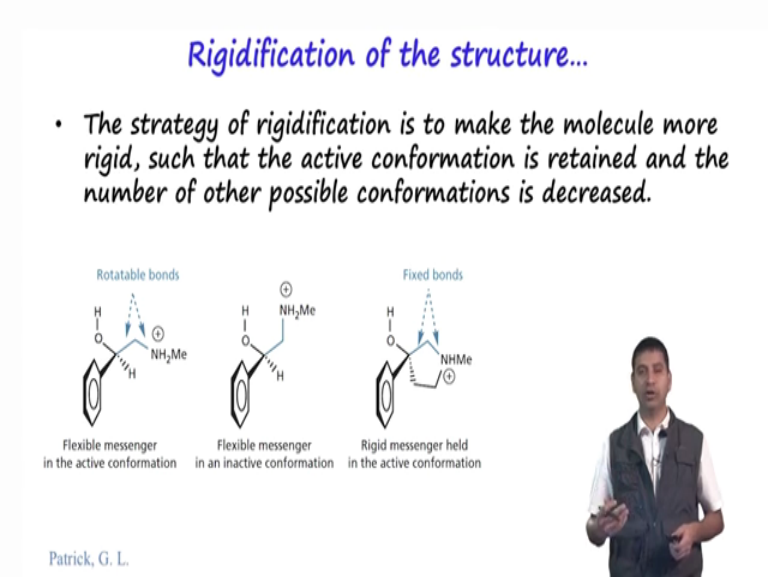

So we could introduce for example a cyclic system. So here what we have done is basically we have made a ring over here and made this molecule. So instead of allowing the molecule to rotate, we have now made the molecule rigid. Here the molecule that is rigid is held in the active conformation. So keep in mind that the nitrogen is still capable of picking up a proton and forming a salt and therefore we may not be tremendously changing the way in which the molecule is going to interact through the salt bridge. But what we have done is that the number of conformations that are possible for this molecule has been greatly reduced.

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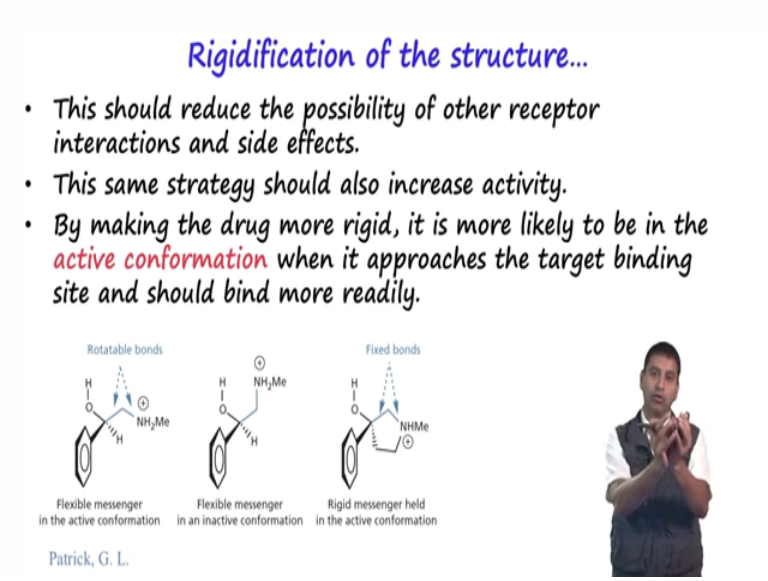

So what one could expect is that it would reduce the number of interactions with other receptors and this can lead to side-effects. So a similar strategy can also result in increased activity because what we are doing is we are locking the molecule in the active conformation. So when it approaches the target to bind, it is perhaps more likely that it will bind more readily because what we have understood from our receptor drug interaction is that the receptor after it binds is going to undergo a conformations change and this conformation change is actually induced by this active conformation.

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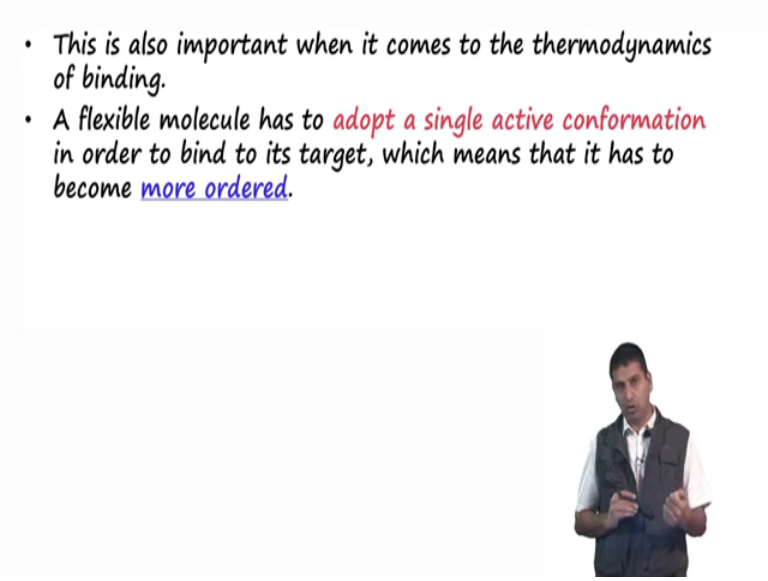

So it also is important when it comes to thermodynamics of binding. So a flexible molecule has to adopt a single active conformation which means that it has to become more ordered.

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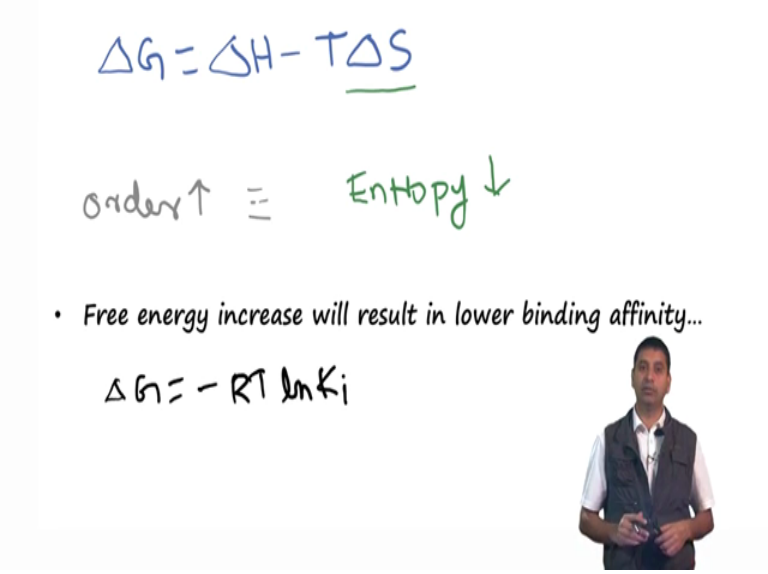

And we know that delta G is nothing but delta H minus T delta S. So when order is increased, entropy goes down. So this will result in an increase in free energy because we also know that the free energy is related to the equilibrium constant in the following manner that is delta G equals minus RT ln K.

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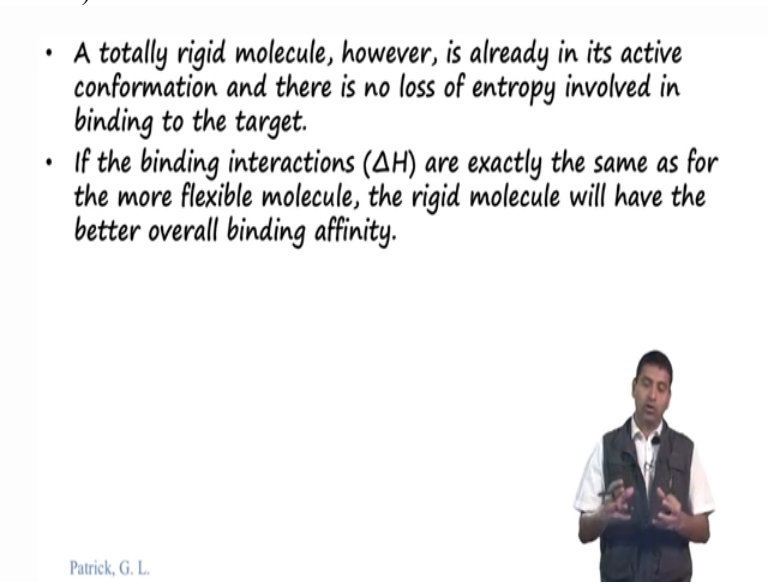

So totally rigid molecule is already present in its active conformation and therefore there is no loss of entropy involved during binding to the target. So if we assume that the binding interactions which is the enthalpic component is pretty much the same for the more flexible molecule as well as rigid molecule, then overall the binding affinity will actually improve.

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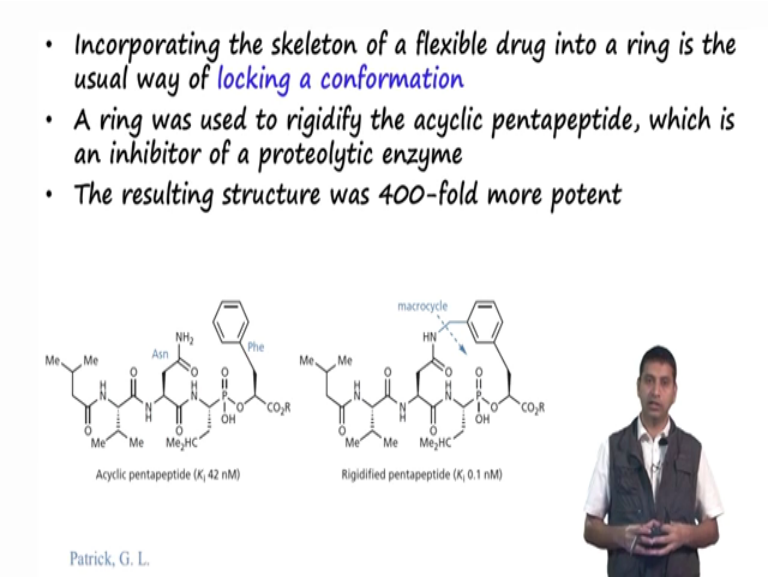

Incorporating skeleton of a flexible drug into a ring is also used to locking a conformation. So for example, here is the acyclic pentapeptide which is an inhibitor of a proteolytic enzyme. So as shown here, it has a number of rotatable bonds and it is quite flexible. But once you connect two portions of this peptide, so by introducing what is known as microcycle here what we are doing is we are restricting the number of possible conformations. So here in this case the rigidified peptide was 400-fold more potent than the acyclic peptide.

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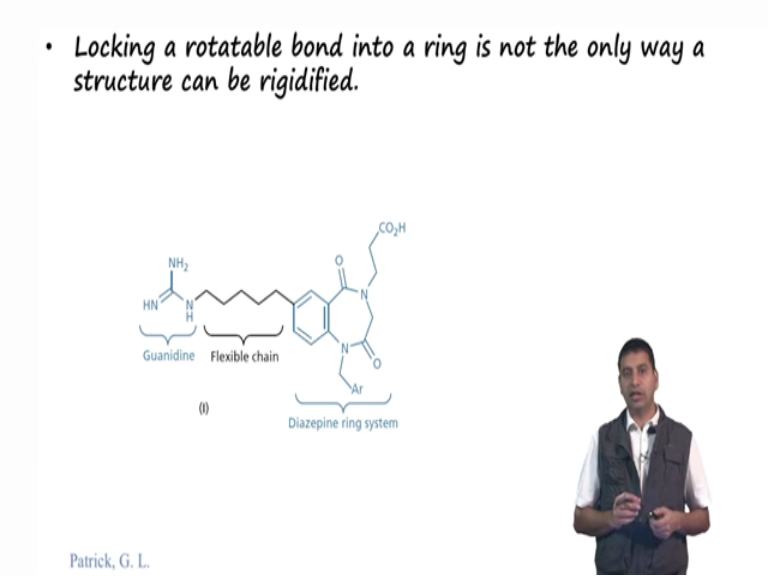

Locking a rotatable bond into a ring is not the only way that the structure can be rigidified. So one thing that we can do is to be able to partially rigidify by incorporating a double bond an alkyne, amide or an aromatic ring.

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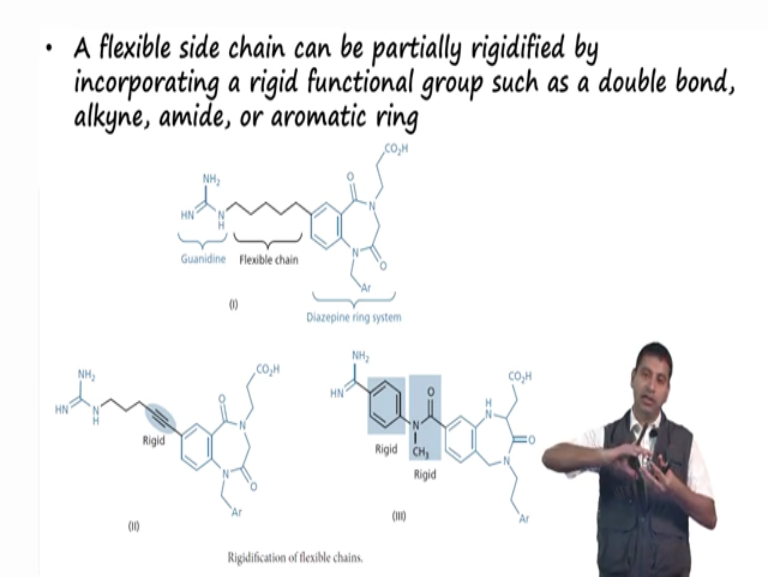

So here the common theme is that we are introducing SP2 or SP3 hybridized bonds. So if you have a flexible chain as shown here, if we want to make it more rigid, then one of the ways is to introduce an alkyne. So the alkyne restricts the number of rotatable bonds and that may help in rigidification or partial rigidification of the structure. Alternatively we can also introduce an amide along with a benzene ring. So what this does is that it is going to reduce the flexibility because the benzene ring, the carbon-nitrogen has to undergo a rotation and because there is partial double bond character associated with this bond, it is likely that it will go very fast. And therefore it may result in partial rigidification.

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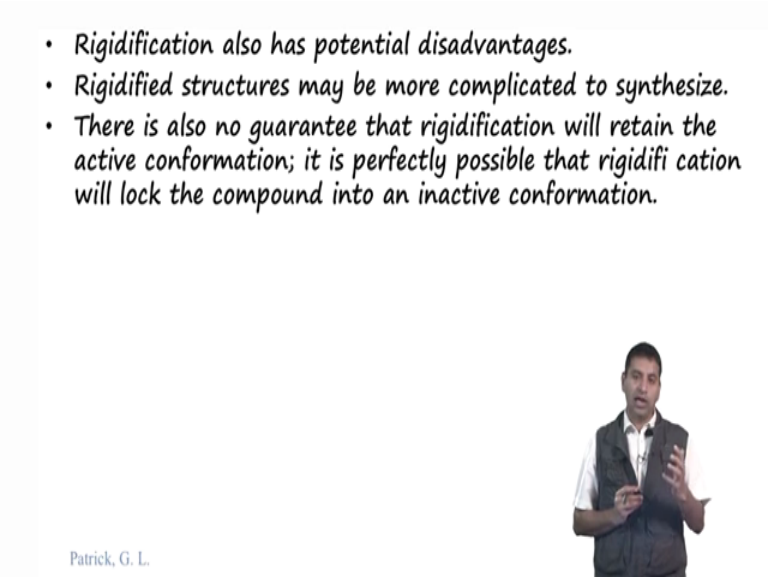

Of course we must also discuss the disadvantages of this approach. Some of the structures are actually not very easy to synthesize. And so it may add to the complexity of the synthesis. Also there is not guarantee that rigidification will retain the active conformation. It is entirely possible that rigidification will lock the molecule into an inactive conformation. So before we enter into this exercise of rigidification, we would need to identify what the active conformation is.

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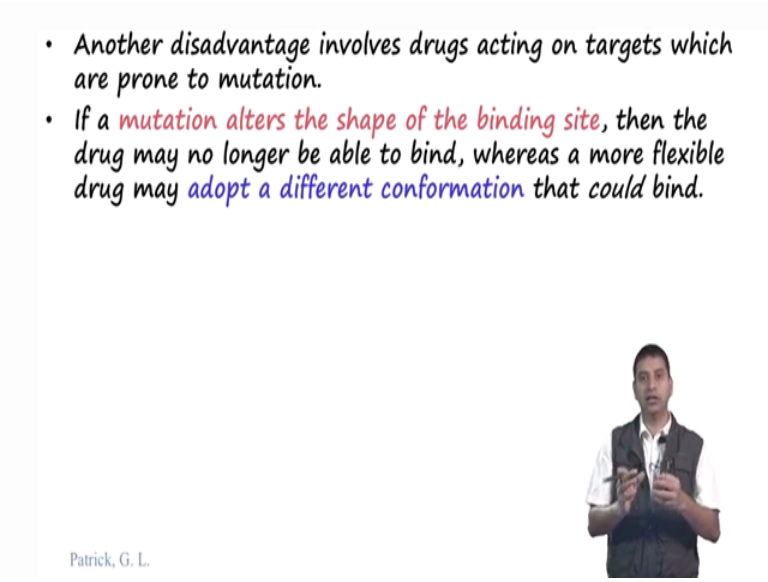

Another potential disadvantage is that if the case that drugs which are acting on targets which are prone to mutation, so what we have discussed previously is that when in response to a drug sometimes a residue in a protein undergoes mutation and this sort of changes the shape of binding site and the original drug may actually no longer be able to bind, whereas the more flexible drug may actually adopt a different conformation that could help with binding so one possible disadvantage of using the highly rigid drugs is that if the protein is prone to mutation or changing in the active site, then this will not be able to adopt accordingly.

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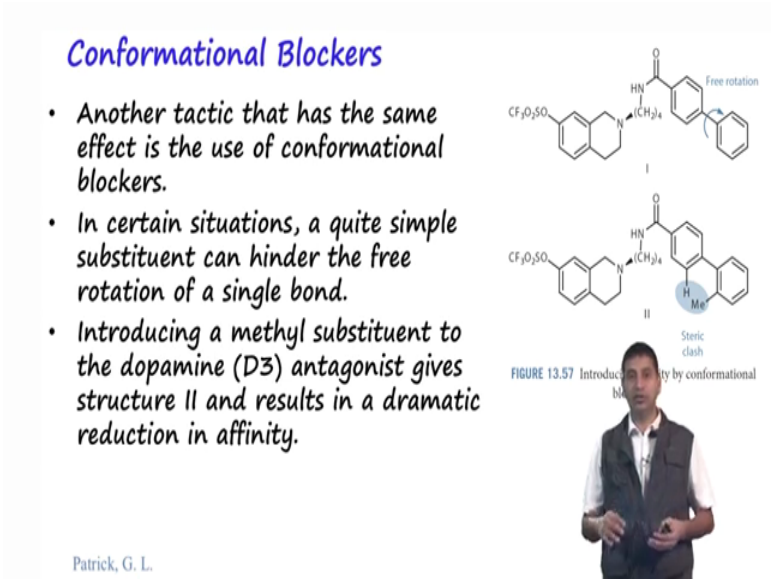

The next strategy that we look at is blocking of conformation. So we have been looking at how to sort of reduce the number of rotatable bonds and this is along the same lines. So here let us assume that there is a particular conformation. For example, in this biphenyl system there is going to be free rotation along the benzene-benzene ring. But if we introduce a metal group over here in one of the positions, what happens is that the metal group now, the van der waals area are going to overlap and so the metal group is going to create or going to slow down the rotation. So this is known as conformational blocking. So introducing this metal substituent to the dopamine antagonist gives the structure, a reduced affinity towards original receptor.

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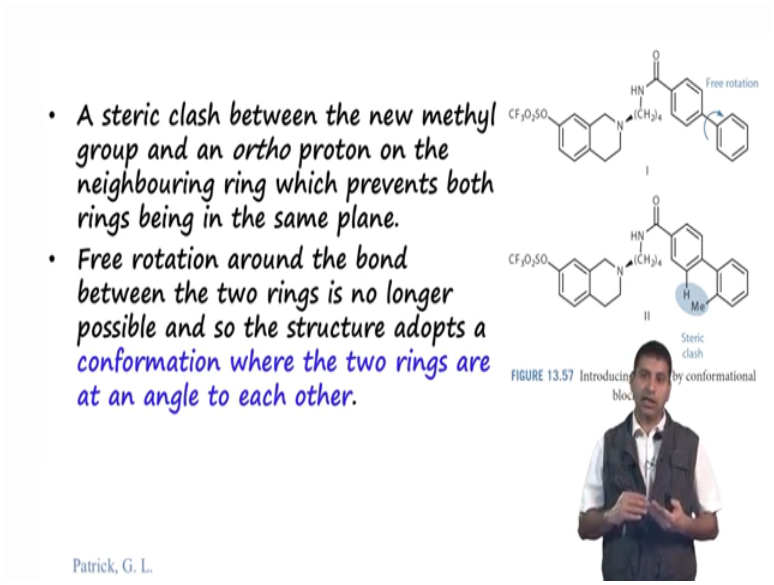

So a steric clash between the new methyl group and the ortho proton prevents the rings from being in the same plane and therefore the ring is not able to adopt a conformation where the two rings are going to be planar. So they are always going to be at an angle with one to each other.

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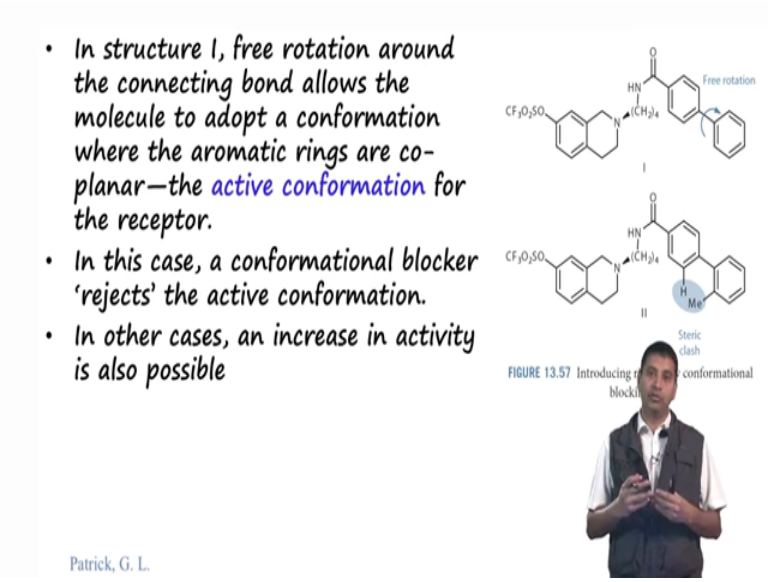

So in this case the conformational blocker actually rejects the active conformation. But it is also possible that in other cases such a modification can increase the activity.

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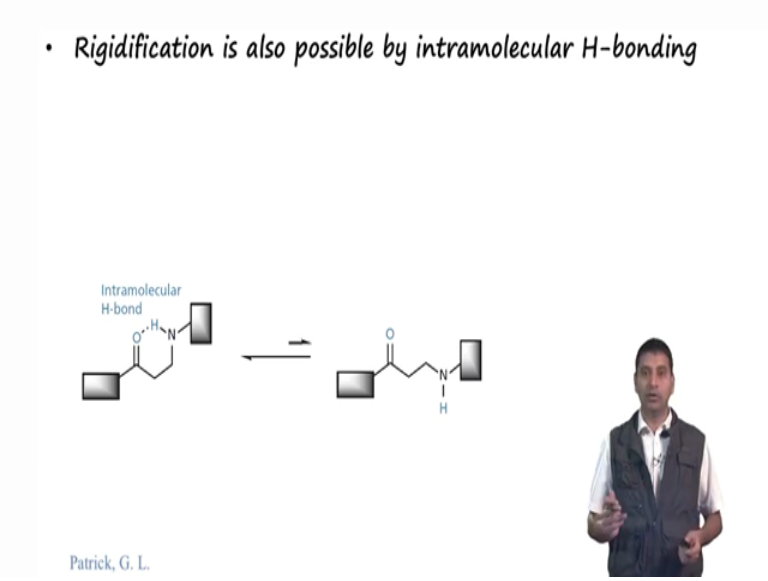

So rigidification is also possible by introducing a intramolecular hydrogen bond. So as you can imagine that intramolecular hydrogen bonds are something that are not weak because they are going to be in the

right, for example here there is a 6-membered ring and these 6-membered rings are quite favored and therefore introducing an intramolecular hydrogen bond with 6-members in the ring is very useful way of rigidifying the structure. So here this was the open chain compound and once it is involved in intramolecular hydrogen bond, it is going to become more rigid.

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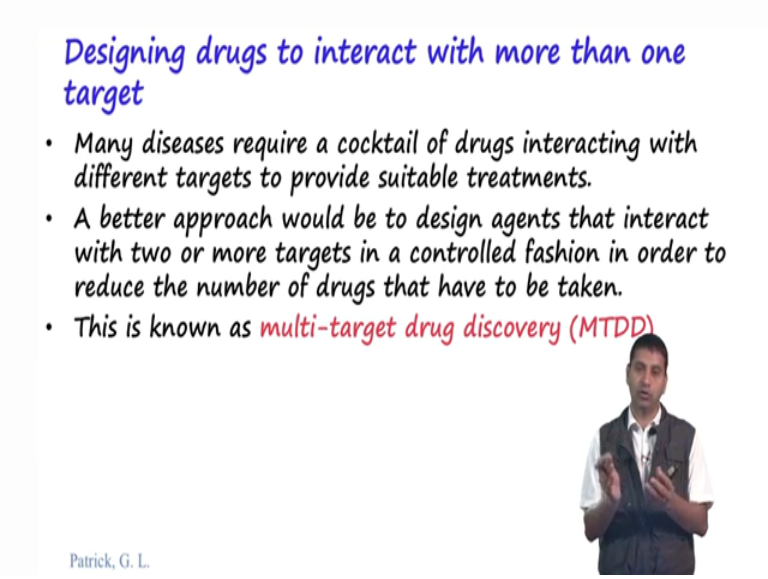

Now the next strategy is called as multi-target drug discovery or MTDD, so here the concept is designing drugs to interact with more than one target. So frequently when one is diagnosed with diseases such as cancer or even infectious diseases, the treatment for this usually requires a cocktail of drugs. For example, with HIV they give you a cocktail of drugs. And now what happens here is that these drugs are going to interact with different targets and perhaps these targets obviously going to be important and once you inhibit them they are going to result in the cure.

But a possible improvement instead of giving a cocktail of drugs is to be able to make a single molecule which can do all of these together. So here we would be able to design agents that interact with two or more targets in a very controlled manner. And these may potentially reduce the number of drugs because it is difficult for people to even manufacture and keep track of so many different kinds of drugs. So if you have a single drug which can do both, then it may have potential advantages.

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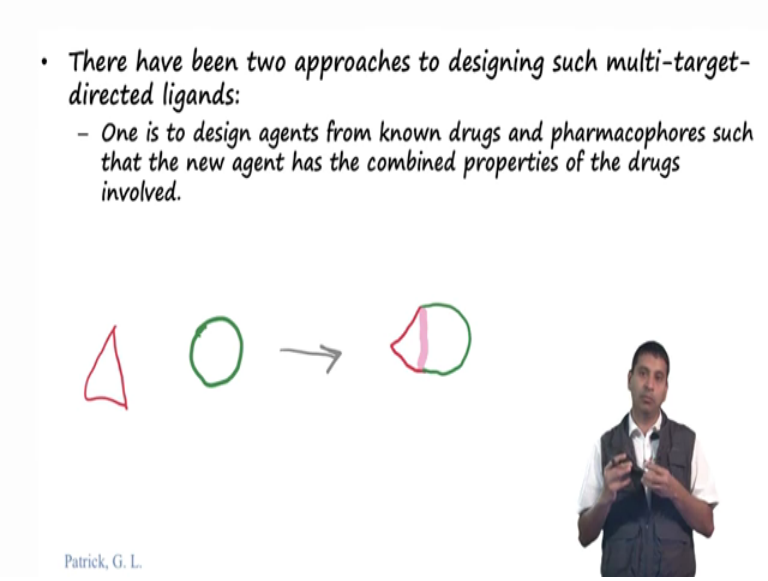

So here is the example. So what we have done is that for example, this is one of the drugs that is used and these others is the other drug that is used. And now can I make a molecule which is going to look like this, which is going to be interacting with both the targets? So here the pharmacophores are the important components of these drugs and now I can fuse this pharmacophore so to speak, and hopefully this will have combined properties of both the drugs involved.

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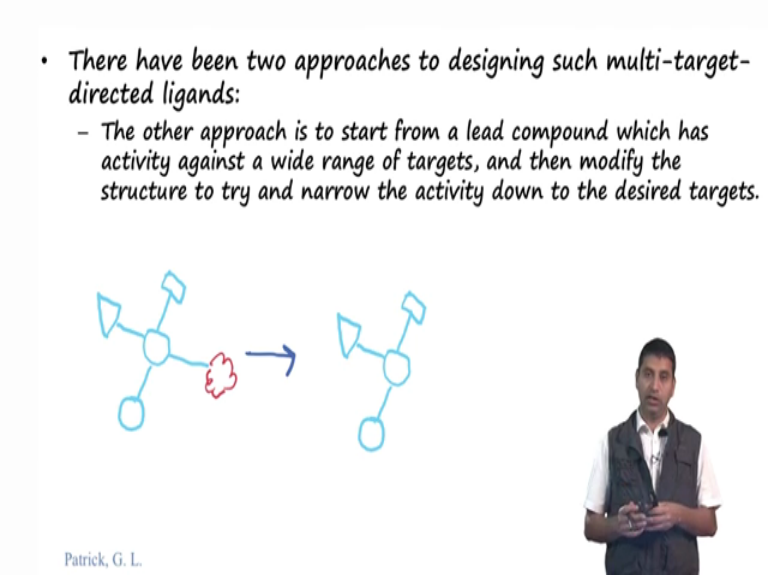

Another way to do this is to be able to design multi-targeted directed ligands. So here we start from a lead compound which has activity against a number of different targets. And then we modify the structure so that we can narrow down the activity to the desired targets. So for example, in this drug this has multi-

target drug, now if this component is not useful, then I can remove this and prepare a new drug which is going to have less unwanted effects.

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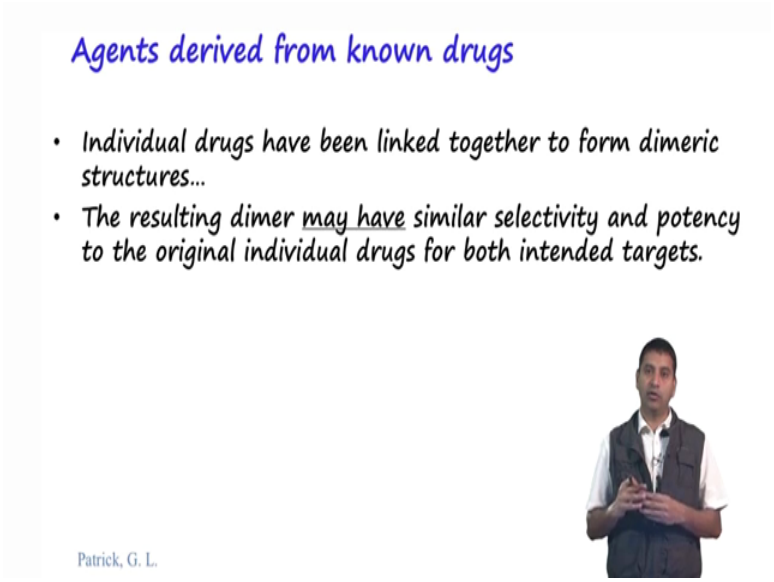

The next strategy is to be able to use known drugs and make to improve drug target interactions by improving on these known drugs. So some drugs can be linked together to form dimeric structures. Now the dimer may actually have similar selectivity as well as potency compared to the original drug for intended targets.

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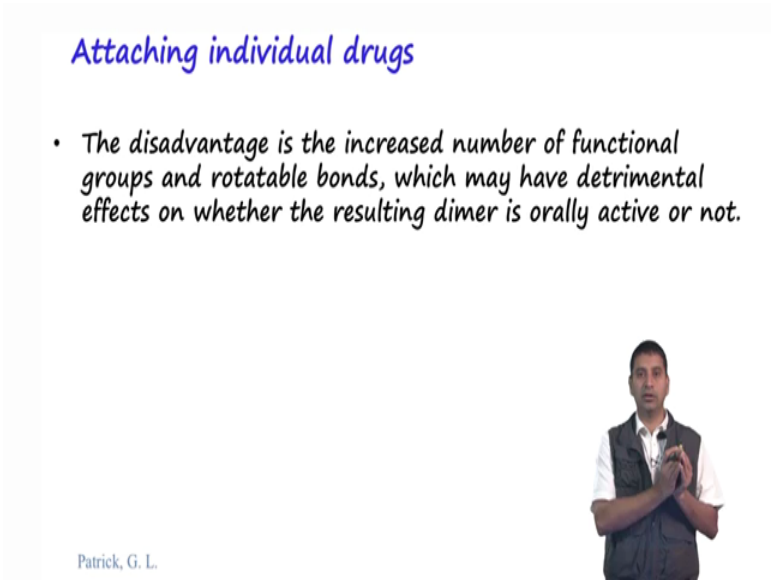

So the disadvantage of this method is that we are increasing the number of functional groups and rotatable bonds which may actually make the molecule perhaps less orally active, so one needs to be careful in designing these molecules so that we can continue to retain the ADME properties.

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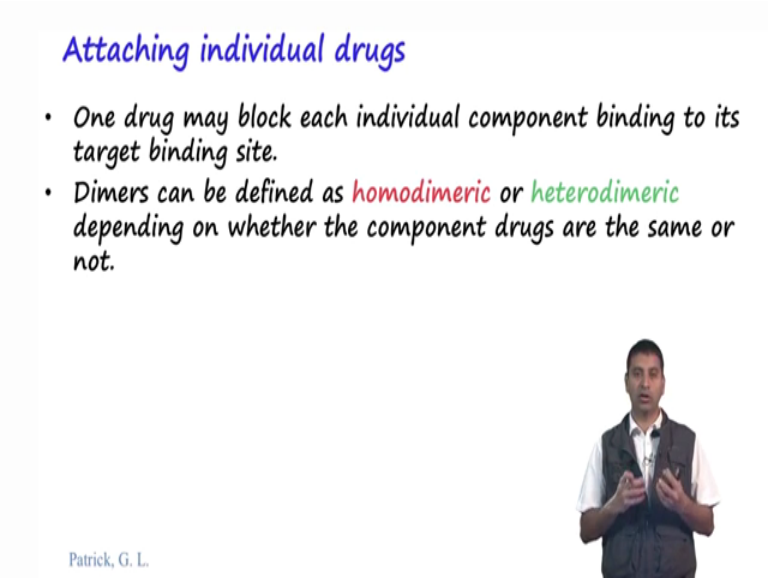

One drug may also block the individual binding of the other drug. So therefore sometimes it is desirable to use homodimeric molecules instead of heterodimeric molecules where you have the same component in the dimer. So of course they are classified as homodimeric and heterodimeric depending on what the components of the dimer are.

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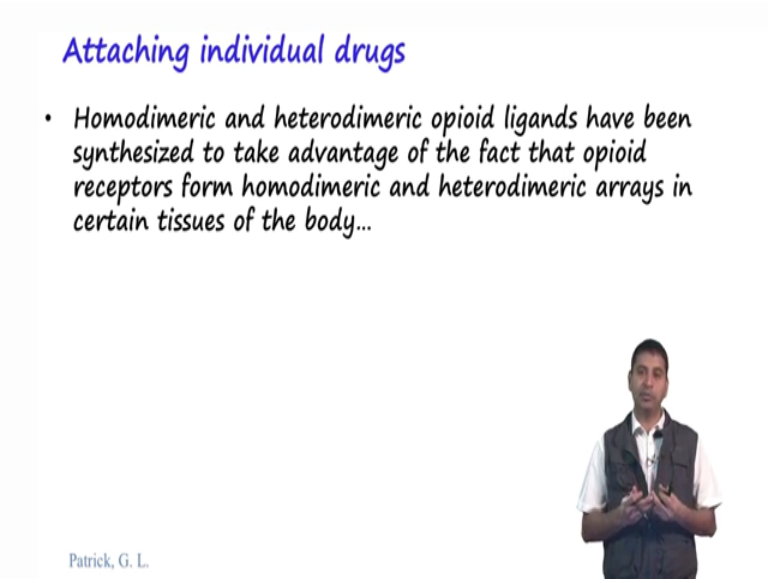

So in case of opioid ligands, homodimeric or even heterodimeric ligands have been used which have an advantage because the receptors themselves present themselves as aroids. And therefore by using these kind of ligands we may be able to interact with multiple receptors in the body.

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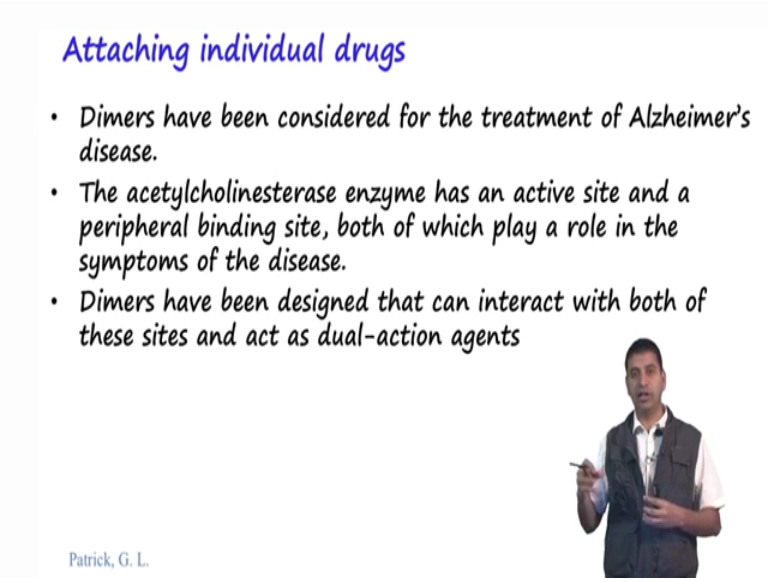

Dimers have also been considered for the treatment of Alzheimer's disease. So the acetylcholinesterase enzyme which we have looked at previously has an active site and the peripheral binding site and both of these are suggested to play a role in symptoms of the disease. So what we could do is we could use what is known as dual action agent wherein one of the components interacts with the active site while the other one interacts with the peripheral site.

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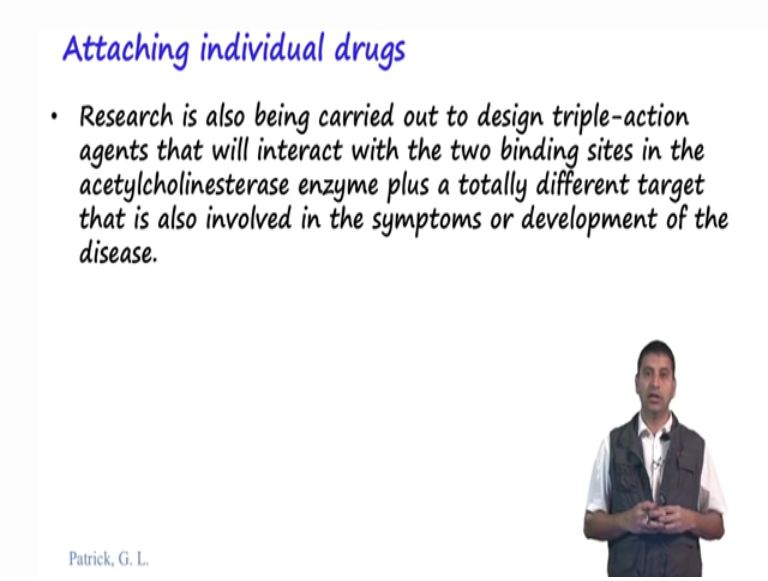

Research is also being carried out to design triple-action drugs wherein this will interact with two different binding sites in the acetylcholine enzyme active site and also a different target which is involved in the symptoms or the development of the disease.

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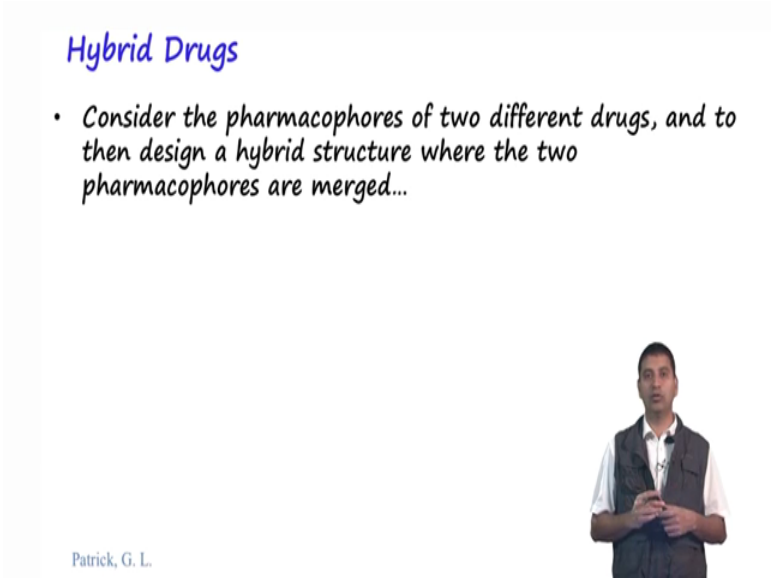

So the next concept is hybrid drugs. Here this is similar to the dimeric or heterodimeric drugs that we have looked at previously. And here what we do is we want to design a hybrid structure, so where the two pharmacophores are actually merged.

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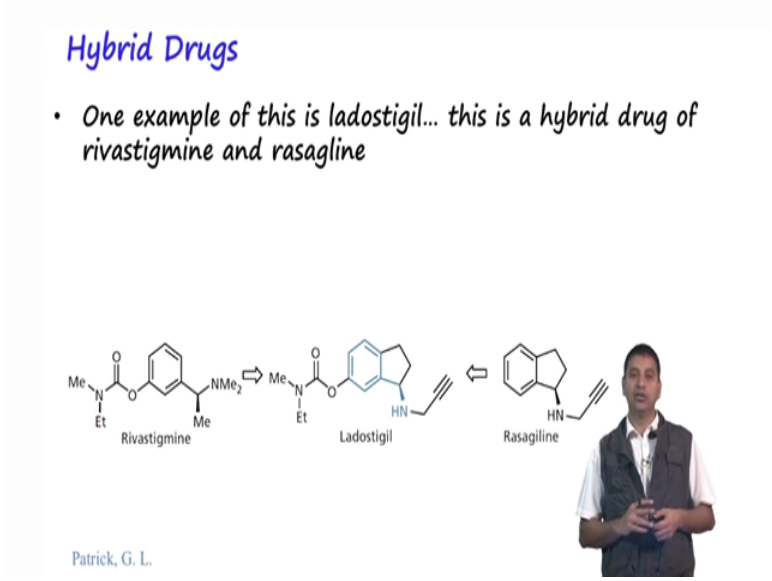

So here is an example of this molecule which is ladostigil. So here is actually a hybrid of these two molecules here. So here this aromatic ring and the main part of it is retained whereas we have introduced this extra functional group here from the other drug and when you merge these two, you get this new molecule as shown here. So this is called as hybrid molecule.

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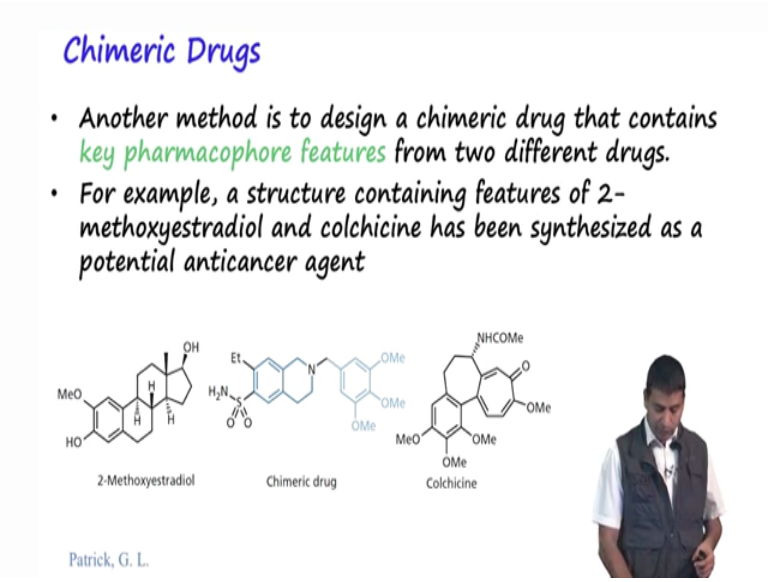

The next methodology that we would use is the use chimeric drugs. So here this contains key pharmacopho features from two different drugs. And the example here is this 2-methoxyestradiol as well as colchicine and both of these are potential anticancer drugs but now when you make a chimer of these two, you mix some of the components or the essential features of the colchicine as well as the essential components of 2-methoxyestradiol and you make this chimeric drug which has some of these features in it.

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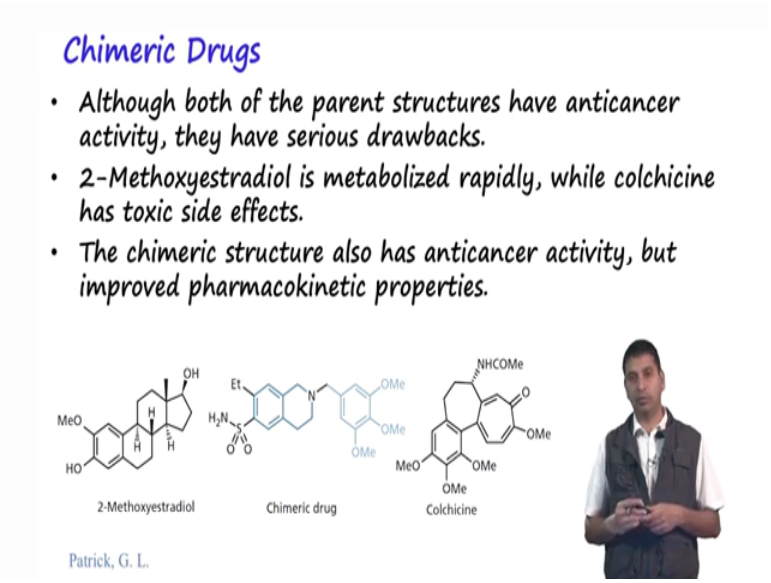

So although both the parent structures are very important, they have some serious drawbacks such as side-effects. So the chimeric structure also has anticancer activity but because we have merged only the important functional groups of these molecules it seems to have better pharmacokinetic properties.