Medicinal Chemistry
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Optimizing Drug-Target Interactions Part-1

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Alright, so welcome back. In today's lecture we are going to continue to look at optimizing drug target interactions. So in connection with this we need to be able to first think about how the structural analogues that we are going to make are going to behave with the target. So let us say we have an enzyme that we have identified as a target and we want to start screening for drug candidates, then we would need to be able to think about what effect changing the structure has on the inhibition of the enzyme?

So in today's lecture we will be looking at some detail what are the various interactions that are in play and what are the various ways in which these can effect (the efficacy of the molecule and the potency of the molecule, okay.

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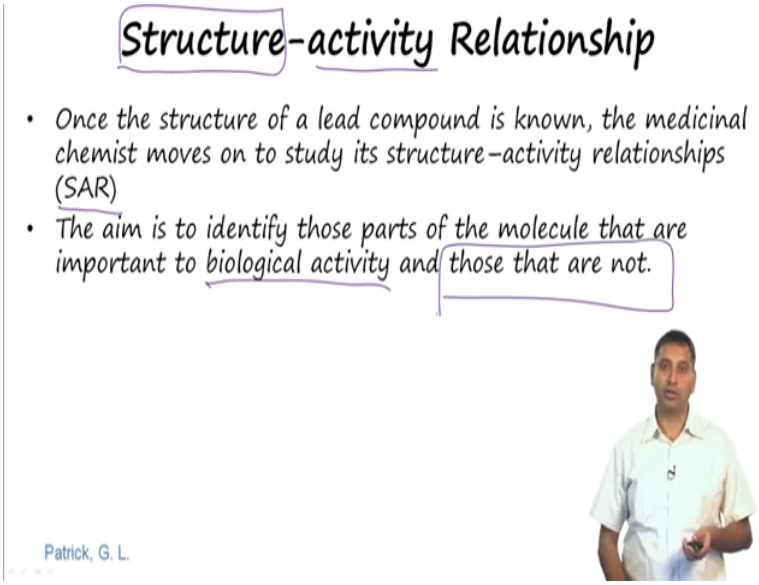

So we will start with defining something called as the structure activity relationship, so structure activity relationship is something that is very commonly used in medicinal chemistry and it is essentially describes the entire medicinal chemistry in a nutshell because all of medicinal chemistry is basically trying to understand structure activity relationship. So the activity here can be reduction of fever. For example if you are looking at that as a phenol type or it can be inhibition of an enzyme or it can be reduction in pain or anything that we look for that is defined as activity or inhibition of receptor or neurotransmission and so on.

And structure is something that we as chemists would understand very well how the molecule is placed? So there are certain areas of the molecule which seem to be more important than others and that is something that we try to (())(1:54) in doing a SAR. So the aim of SAR is to be able to identify the most important parts of the molecule that contribute to the biological activity and more importantly we also want to find out those that are not important so that we can cut it out.

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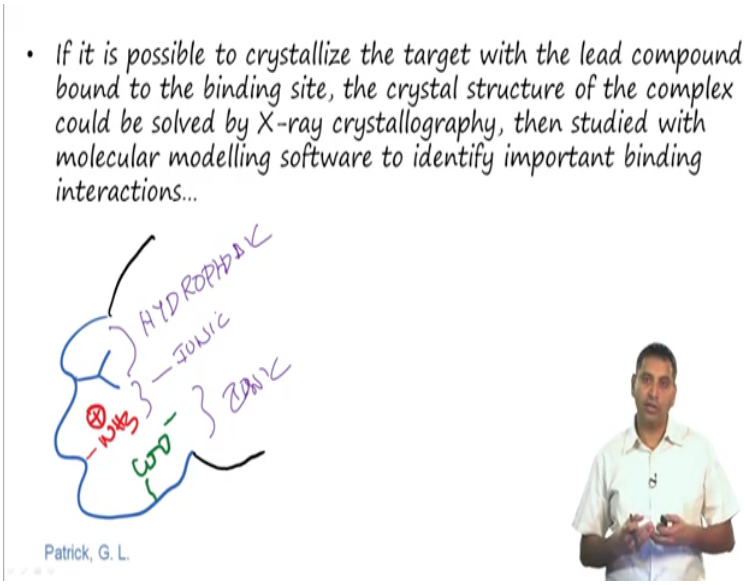

So just to think about this as a concept let us say we have a target, let us say we have a protein and we have the crystal structure of the protein which is bound to the substrate or top be inhibitor. Now what we can do is we have let us say an active side of this enzyme and this is what the active side of the enzyme looks like for example. Then one can start thinking about the various types of interactions that may be in play, so just for example would be hydrophobic and this would be an ionic and this would again be ionic but maybe you need a negatively charged species to interact with this and so on.

So once we have the active side and once we have the ligands that are bound to the active side then it is possible to identify the important binding interactions. So that is something that we can try to do by using help from software.

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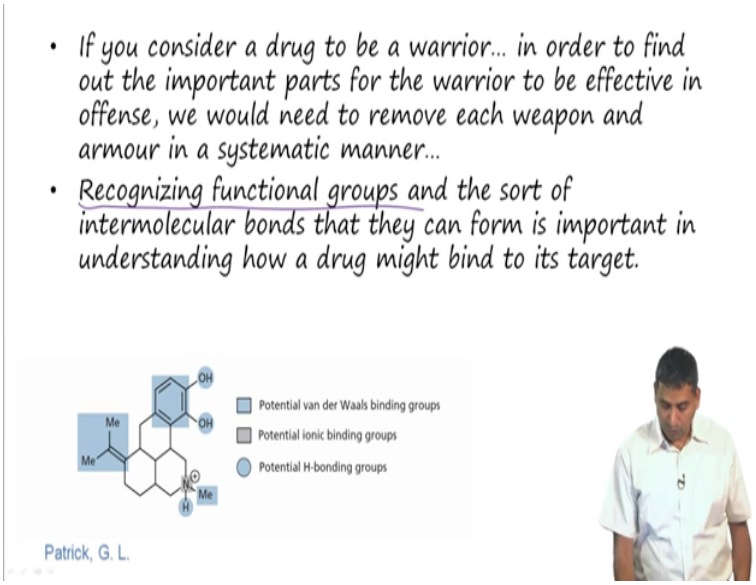

So if you consider the drug to be a warrior and warrior has lot of armour and equipments and weapons and so on, this process allows us to find out what are the important parts of the warrior that are effective in offence, in this case let us say binding receptor to activate it and inhibitor to inhibit the enzyme and so on. So now we start removing each weapon from the armour and see what are the weapons that are really important for the offence to occur.

So this is essentially the process of structure activity relationship. So we need to be able to recognize functional groups that forms these intermolecular bonds. So remember we are not looking at covalent bonds, there are of course irreversible inhibitors but a large majority of the molecules that we want to look for are reversible or molecules that go and bind through week intermolecular interactions.

So if we know what are the important molecules that are (())(4:11) contribute what are the important functional groups that are going to contribute to this then this might help to develop a full understanding of how the drug might binds to its target. So we will just take this hypothetical molecule called as glyph which is shown here. so you can think about various functional groups that are present. So let us look at this molecule in a little bit more detail in the next slide.

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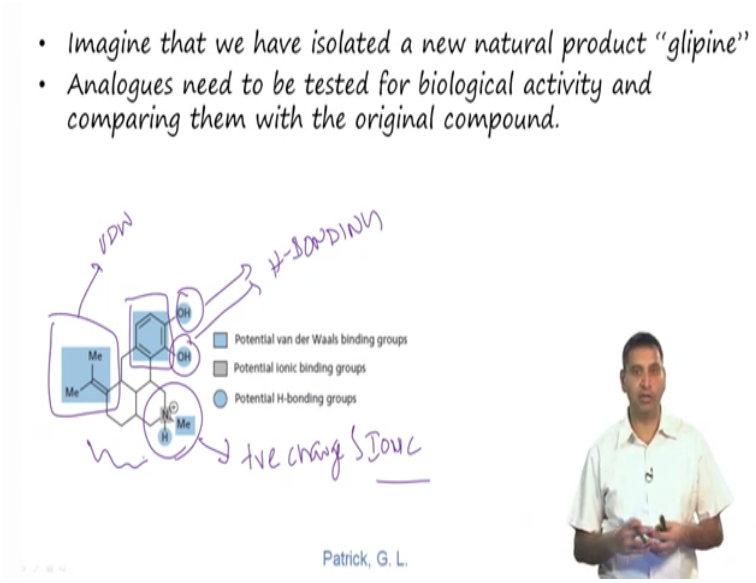

So here we have this part of the molecule here which is important for Van der Waals interactions, this also is important for Van der Waals interactions and you can see here there are couple of hydroxyl groups, here potentially hydrogen bonding interactions are possible and lastly you have here a very nice protonated tertiary amine which would have a full positive charge which can do ionic interactions.

So therefore in this molecule we can break this down into simpler parts where we can identify the functional groups that are going to play a role. We also have to keep in mind that there is a scaffold that holds these functional groups together and so the important of the scaffold is also needs to be determined. So for example if you remove this 3 rings over here and just connect it by a linear chain because the molecule act the same way it does.

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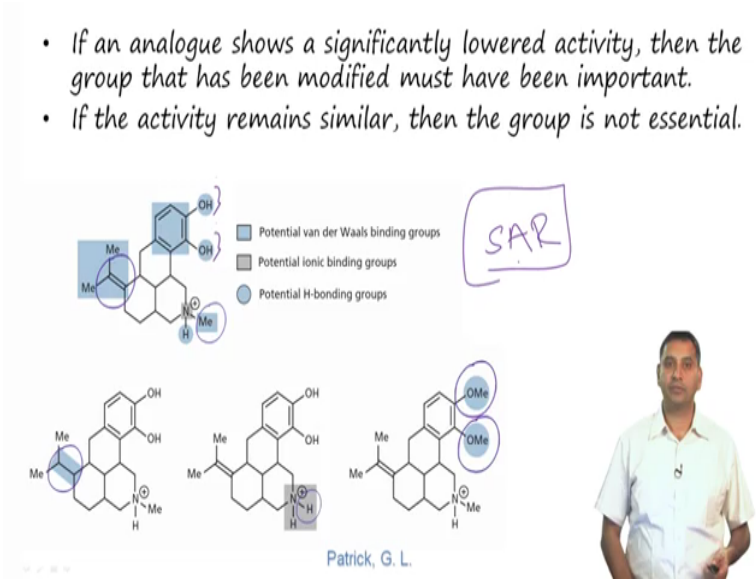

So in order to systematically study this what we would do is to be able to change these functional groups one at a time. So then if the activity remains similar then the group is perhaps not important for the molecule to act, but if there is a dramatic change or there is a significant change in the activity then it is likely that the group is essential. So we can just in our own mind we can think off many of these possibilities.

So if you want to study what happens when I remove this Van der Waals interaction, I can reduce this double bond to a single bond and then find out whether the Van der Waals interaction play the important role or not. If you wish to study what happens with this ionic interaction, what you can do is this methyl group here can be sort of removed and then you can convert it to a hydrogen over here and that will change the way in which the hydrogen bonding can occur.

Lastly if you want these hydrogen bonding interactions to be studied then this OMe-OMe groups can then be prepared where the OH is converted to OMe and therefore the hydrogen bonding is not possible. So these are again you know nutshell we can think about this as conceptually few experiments that one could do to identify the most important functional groups, so such a study is called structure activity relationship.

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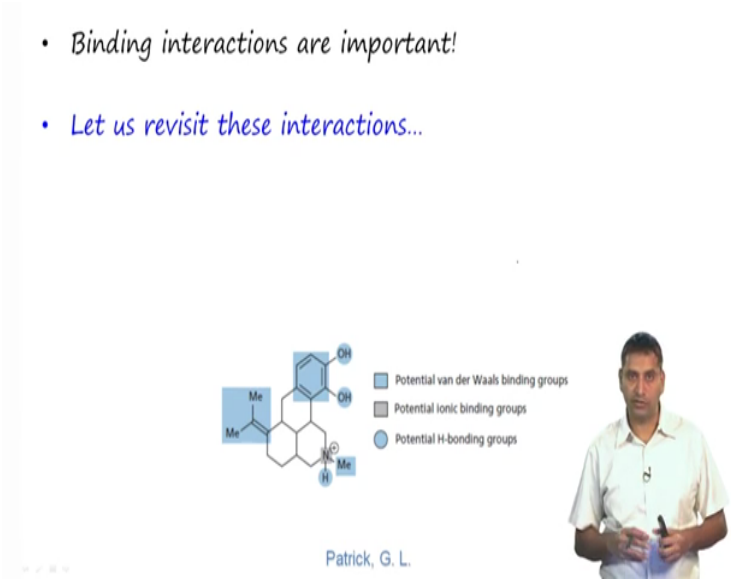

So let us now revisit these interactions, we have already looked at in some detail several weeks back about how the various interactions occur inside a protein for example and these are absolutely necessary for us to get a better understanding of this and therefore we shall revisit these interactions.

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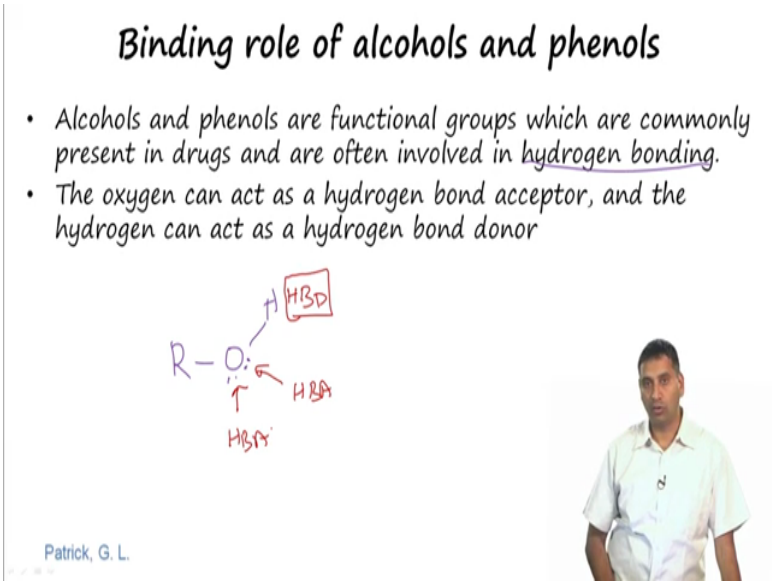

So first major functional group that we shall visit is an alcohol, alcohols and phenols are commonly found in many drugs and they are often involved in hydrogen bonding. So the oxygen can act as a hydrogen bond acceptor, so now let us draw out the structure of an alcohol which is R-O-H and keep in mind there are two lone pairs that are sitting over here and this hydrogen here is a hydrogen bond donor we are already familiar with this

terminology and these are hydrogen bond acceptors. So together in an alcohol you have two hydrogen bond acceptor possibilities and one hydrogen bond donor possibility.

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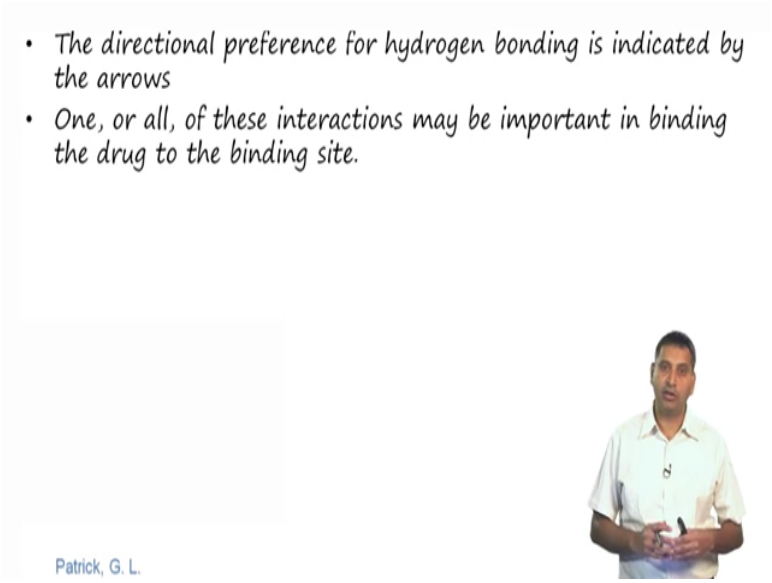

It is important at this point to recognize that there is a directional preference for hydrogen bonding. So the lone pair has particular orientation through which the hydrogen bonding interaction occurs and therefore if the functional group is positioned in the right manner then it can involve itself in hydrogen bonding, but if it is not then it is possible that there may be protein residue or amino acid residue that is capable of hydrogen bonding but because the orientation is not correct the hydrogen bonding may not occur or it may be very weak, so all these interactions, one or all of these interactions may be important in binding the drug to its binding site.

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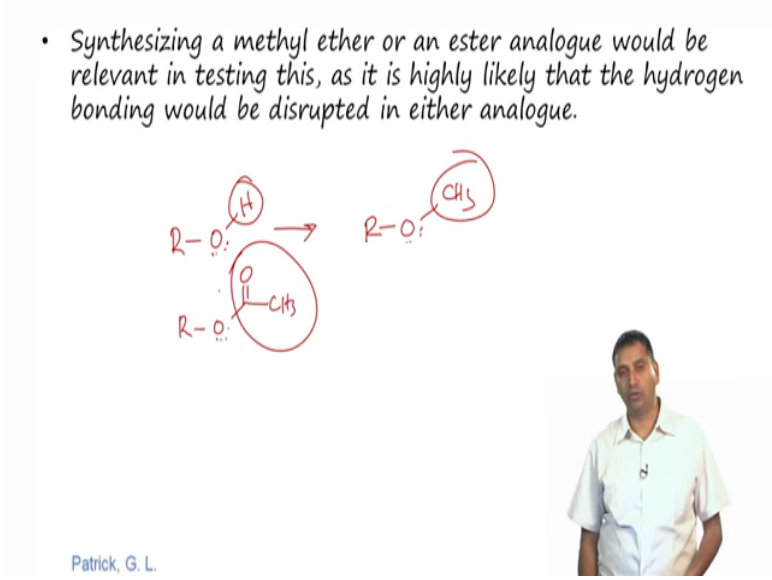

So if we make an ether or an ester of an alcohol, then it is impossible for us to interrogate whether there is an effect of hydrogen bonding or not? So let us look at the structure of an ether. So R-O-H is what we start with, if you convert this to R-O-CH 3 for example it is a methyl ether the two lone pairs remain the same as you can see here, but the hydrogen now has become a methyl group.

The alternative would be to make an ester wherein these two lone pairs are still there but this hydrogen is now being converted to an acetyl group. So these are couple of analogues that can be perhaps synthesized without much difficultly to study this.

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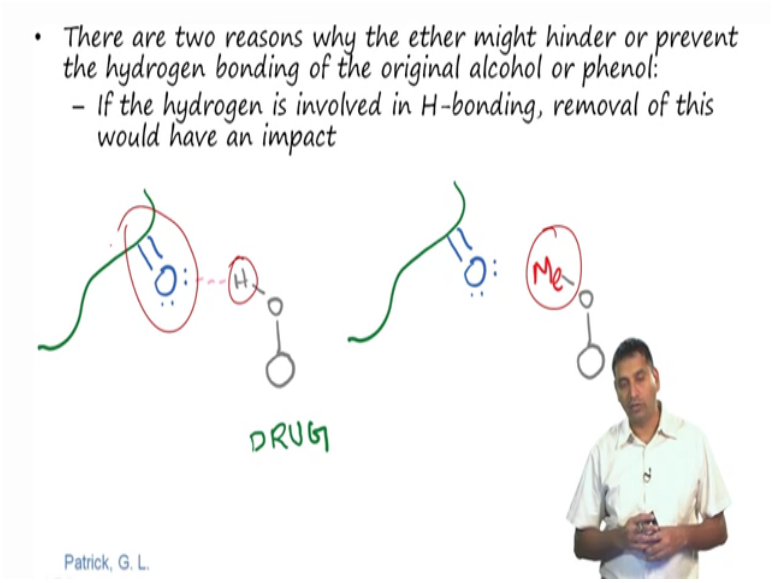

Now there are two reasons why the ether might hinder or prevent the hydrogen bonding of the original alcohol or phenol. The first one is if the hydrogen is involved in the hydrogen bonding, then if you remove this hydrogen altogether and replace it with a methyl then you have the situation where the entire hydrogen bond itself has been removed. So here is for example a carbonyl group in protein active side which is going to interact with this hydrogen.

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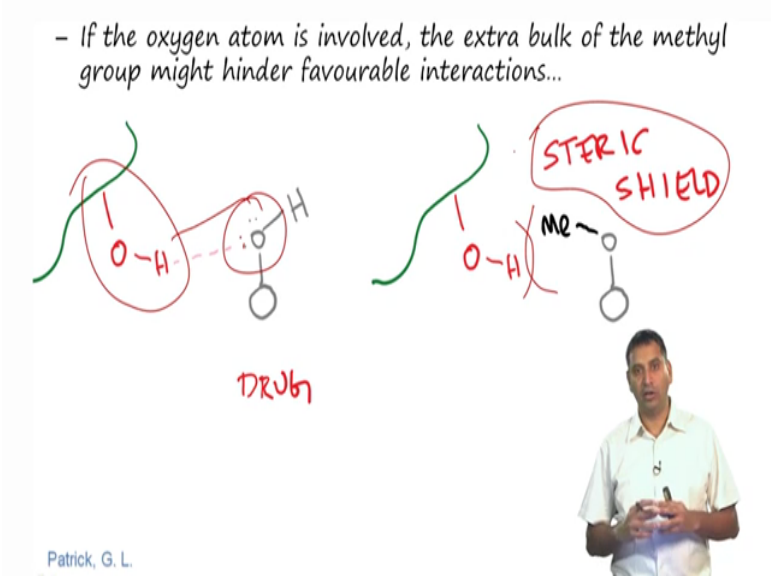

The second possibility is that if a drug interacts with a hydroxyl group in the receptor site or the binding site then our oxygen of the drug is involved in hydrogen bonding as you can see here. If you now replace the hydrogen with a methyl group, then it is possible that you have some steric hindrance which prevents this lone pair from interacting with the O-H, so this is called as the steric shield and this will help us understand what are the kind of favourable interactions that happen in a drug receptor interaction.

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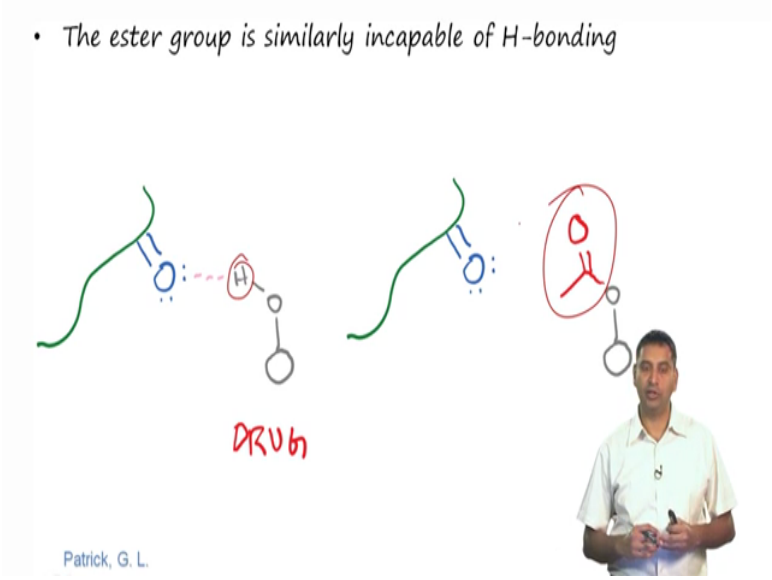

The ester is also incapable of hydrogen bonding. So here if you replace this hydrogen with an acetyl group this is going to completely remove the possibility of intermolecular hydrogen bonding.

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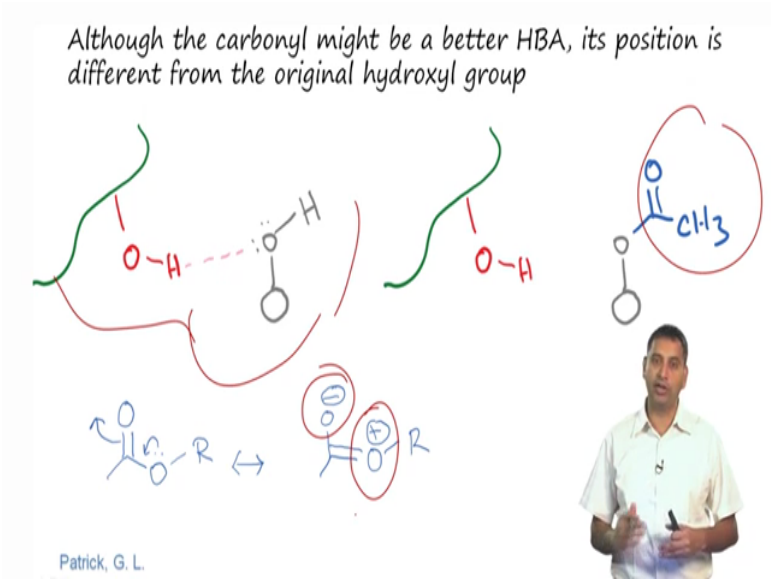

But when you look at the other possibility that is if the alcohol through the oxygen is going to be involved in hydrogen bonding by making an ester we are doing a few thing, first thing is that we have now converted this alcohol to an ester and we can draw this resonance form where there is a full negative charge on this oxygen and a full positive charge on the other oxygen.

So a full negative charge in the resonance form would translate to delta minus on the carbonyl and so the carbonyl is a very good hydrogen bond acceptor, but this may not be in the right orientation so if the rest of the drug is for example held by a particular residue in some manner, so the rest of the drug is held by other interactions and then there is a (()) (11:44) hydrogen bonding that is important for example, then the acetyl group is going to be in a position where the hydrogen bonding efficacy is not that great and keep in mind the original oxygen has now a delta plus and it is going to reduce the hydrogen bonding capability.

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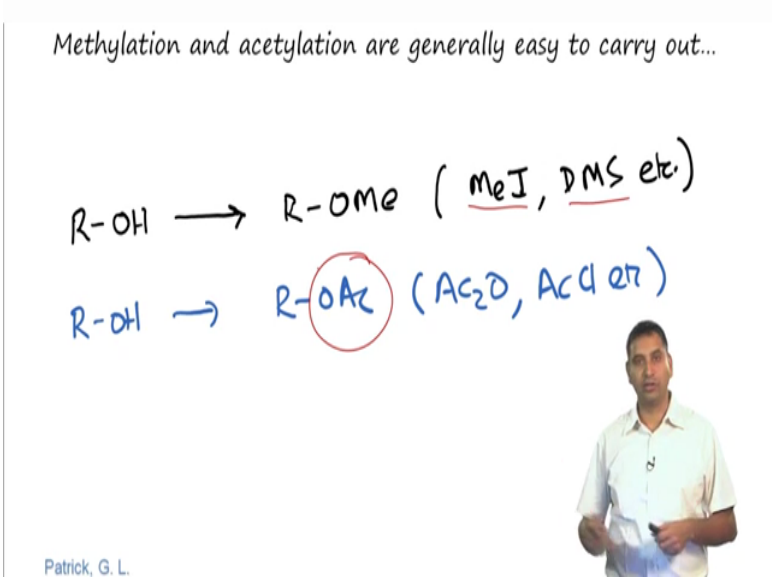

So these reactions that is conversion of an alcohol to an ether or a conversion of an alcohol to an ester are fairly easy and they can be done by commonly available reagents such as methyl iodide in the presence of a weak base or dimethyl sulphate in the presence of a base. And acetylation can be carried out by acetic anhydride or acetyl chloride or other reagents.

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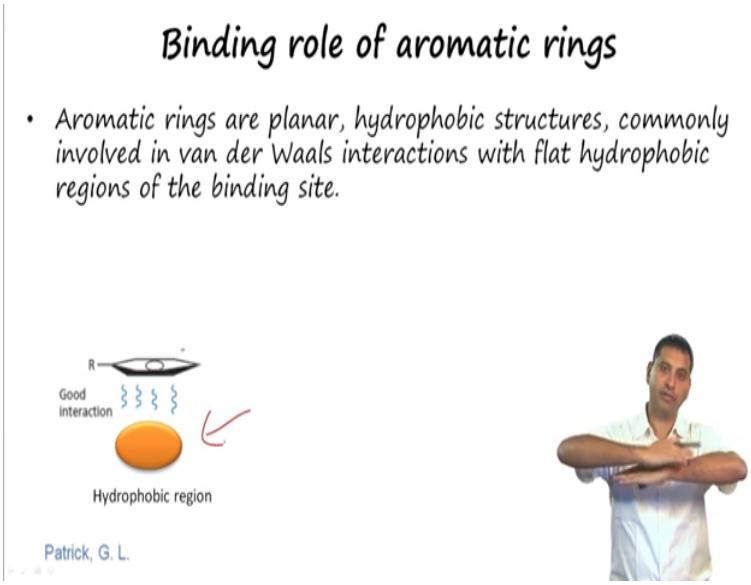

So the next major functional group that is available in drugs is an aromatic ring. So if there is a hydrophobic region in a binding pocket then it can interact with the (())(12:34) cloud of the benzene ring and these hydrophobic interactions or Van der Waals interactions are fairly common.

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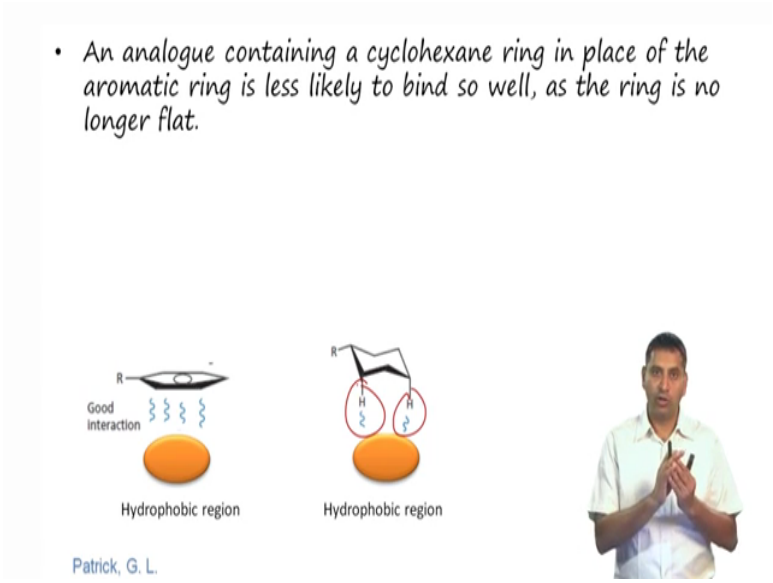

Now if you convert or if you synthesize a cyclohexane compound, where the aromatic interaction is completely removed you are replacing it with a hydrogen interaction with a hydrophobic region, but the molecule is no longer flat.

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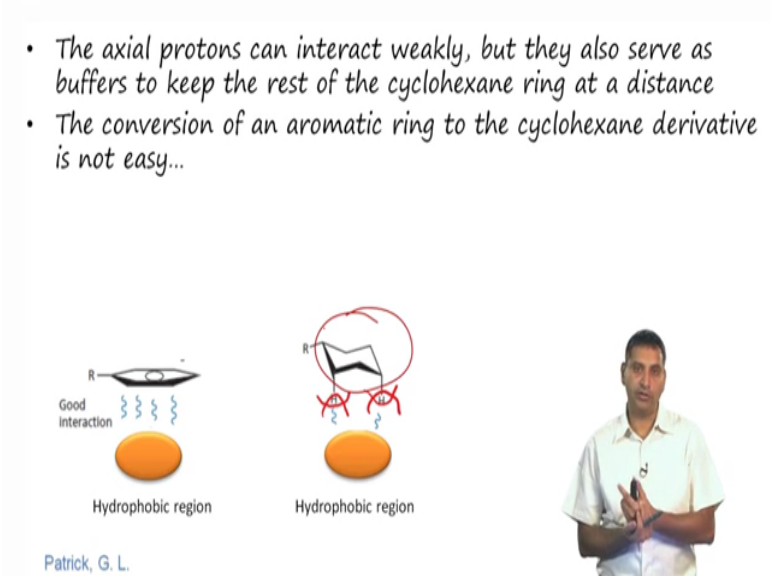

So what happens is that because there is some interaction with the axial hydrogens and the cyclohexane not being planar the rest of the molecule that is this part of the molecule does not interact with the hydrophobic region. So by converting a benzene ring which has very good interaction with the hydrophobic region to a cyclohexane, it is possible that we may be disrupting the favourable interactions and it is possible that the analogue may not be very efficacious in what we wanted to carry out.

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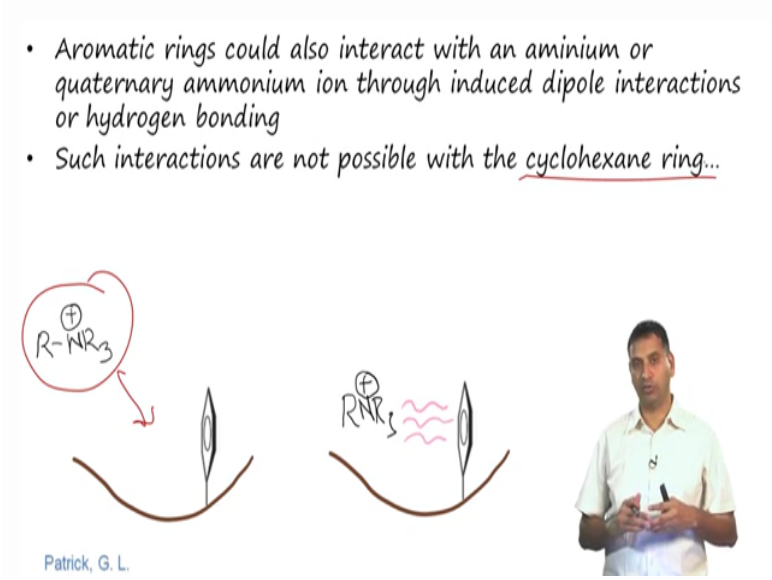

Aromatic rings can also interact with aminium ions or quaternary ammonium through induced dipole or hydrogen bonding. So let us look at this case now. So here is a quaternary ammonium salt and once it get closer to an aromatic ring then it can interact with what is

known as a dipole induced dipole interaction. Aromatic rings can also do this through hydrogen bonding, there are cases where there are some weak interactions that can occur, but such interactions are not possible with a cyclohexane ring and therefore replacing a benzene ring with a cyclohexane ring may be a good way to study this.

However, conversion of a benzene ring to cyclohexane is not easy, so one will need to go back to synthesize a separate analogue which does this.

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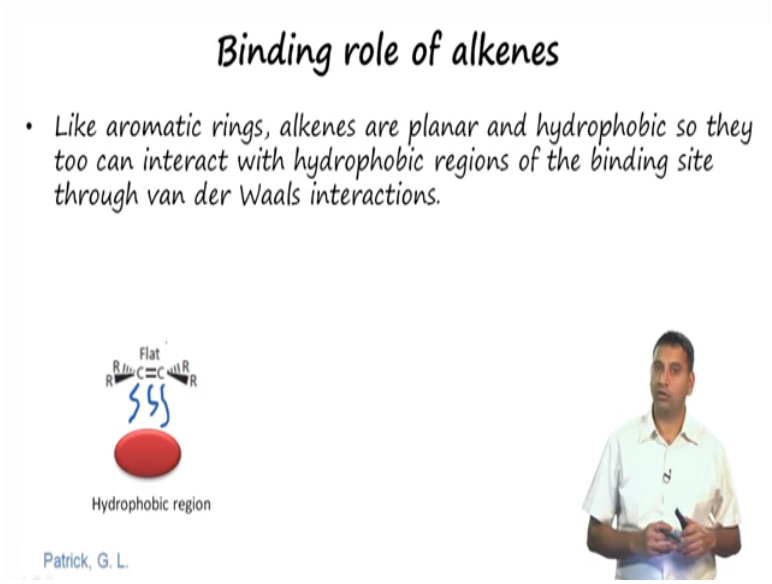

Next we shall look at alkenes, alkenes like aromatic rings are planar and they are also hydrophobic and so they can involve themselves in these hydrophobic interactions or Van der Waals interactions.

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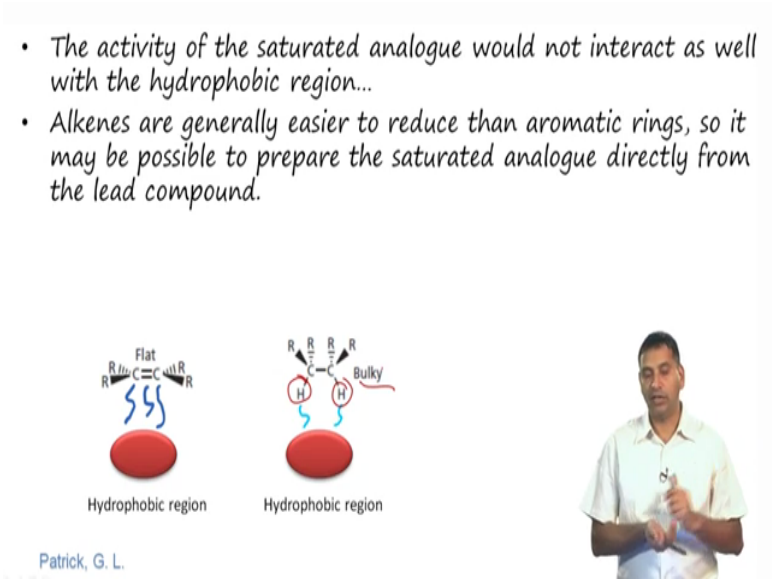

So the activity of the saturated analogue which is shown here would not be as strong, so you are replacing a Pi bond with this again these two C-H's which are good in interacting but they are not as good and again the rest of the molecule is not going to interact because of the steric bulk, so alkenes are easier to reduce than aromatic rings, so it may be possible to prepare the saturated analogue directly from the lead compound.

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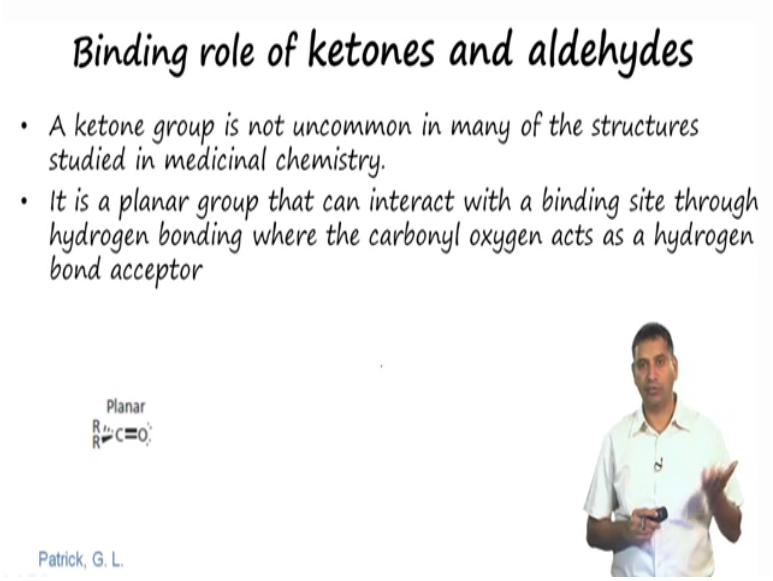

The next functional group that we will look at is ketone or aldehyde, ketone is not very uncommon in many drugs so it is a important functional group. Again it is a planar molecule and it has a carbonyl oxygen which can act as a hydrogen bond acceptor as we have seen previously.

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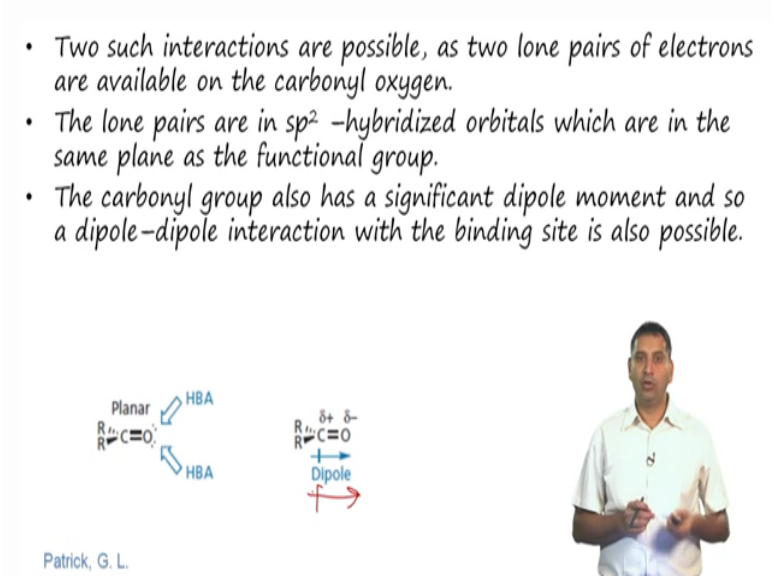

The carbonyl functional group is also a dipole because you have a electronegative oxygen atom pulling electrons and so there is a dipole in this molecule, the lone pair of the carbonyl are in the sp 2 hybrid orbitals and which are in the same plane as the functional group, this leads to two interactions that is one through the lone pair of the carbonyl oxygen and the other one is through the dipole interaction, so we will look at this now.

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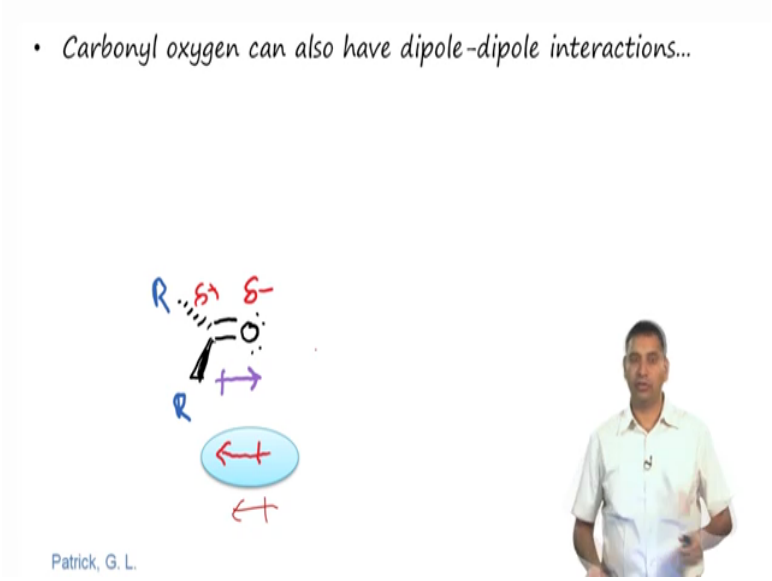

So when you have the carbonyl compound coming in and let us say there is an alcohol on the binding site so this is the binding area. Now the carbonyl can come in and it can involve itself in these weak hydrogen bonds and this is favourable and the second possibility is that if there is an dipole in the binding pocket than the carbonyl can interact to itself in a manner that is

favourable. So you have the dipole in this direction interacting with the dipole in this direction because you have delta minus and delta plus which is going to interact with the counter charge.

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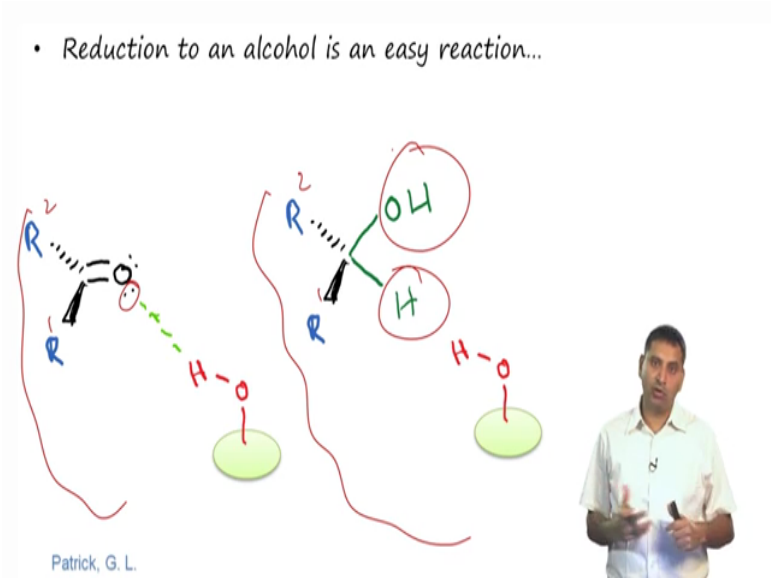

If you convert the carbonyl to an alcohol through a process of reduction one could use sodium borohydride for example, then what we have done is we have potentially replaced this lone pair with a hydrogen. So this disrupts the hydrogen bonding altogether and since we shall assume that there is some binding preference over here and let us say this is R 1 and R 2 rather than two R's then it is possible that the orientation in which the drug is coming in is going to be important.

So now in order for the this hydroxyl group to be involved in hydrogen bonding it has to flip around which may or may not be easy to carry out.

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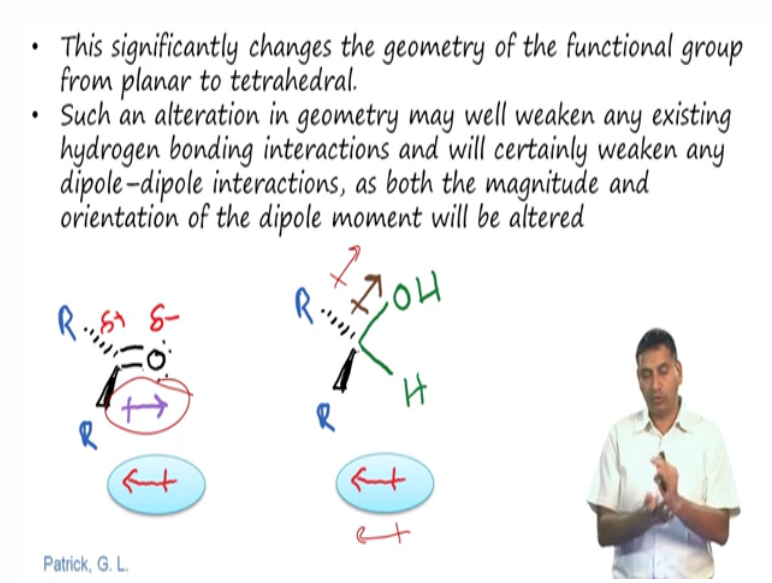

So the geometry of the functional group completely changes so we have converted this to a tetrahedral carbon and such a alteration in the geometry will also weaken any existing hydrogen bonding interactions and will certainly weaken any dipole interactions that can occur because if you have this the induced dipole in the binding site in this area in this direction. Now the new dipole that you have created is actually in a direction which is different from the original dipole. So therefore the magnitude of the interaction will certainly go around.

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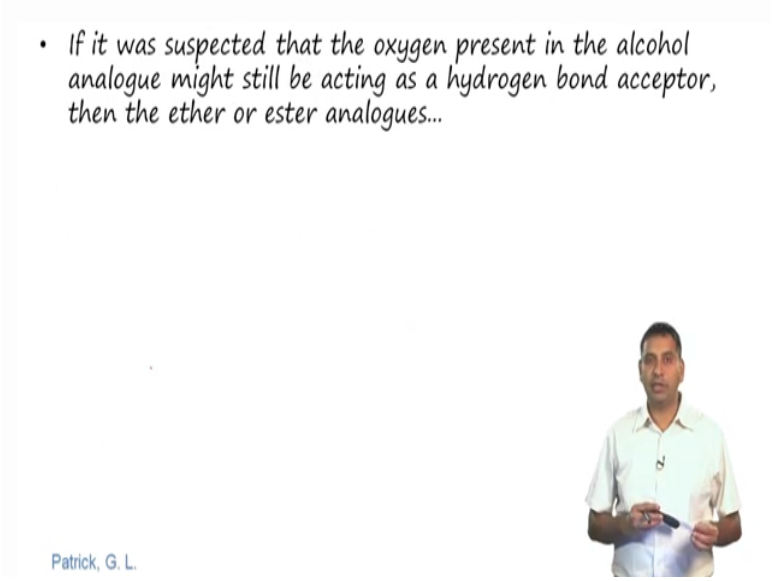

So if it was suspected that the oxygen present in the alcohol analogue might still be acting as a hydrogen bond acceptor, then what we could do is convert that oxygen to an ether or an ester as we have already seen previously those are again going to disrupt this.

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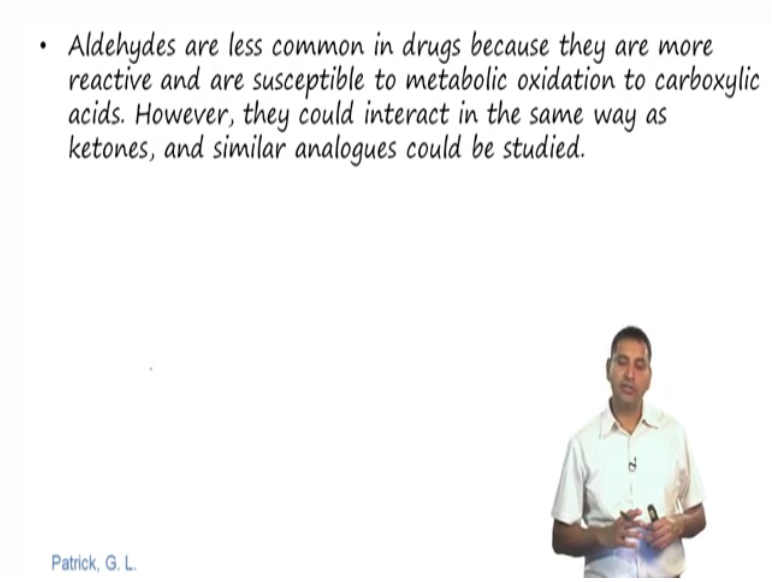

Aldehydes (())(17:49) are quite uncommon in drugs because they are quite reactive and they are susceptible to metabolic oxidation. However, they could interact the same way as ketones and similar analogues could be studied.

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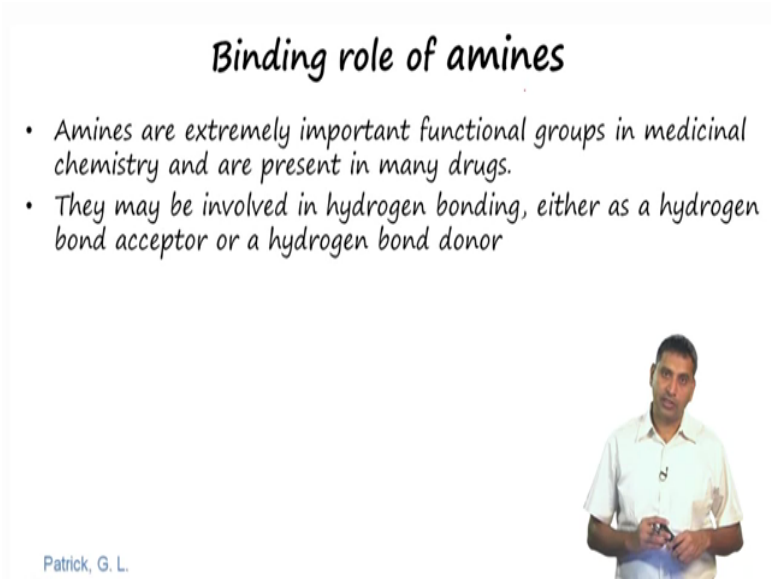

Amines is the next functional group, which are extremely important functional groups in medicinal chemistry and are present in many drugs, they may be involved in hydrogen bonding either as a hydrogen bond acceptor, or as a hydrogen bond donor we shall look now.

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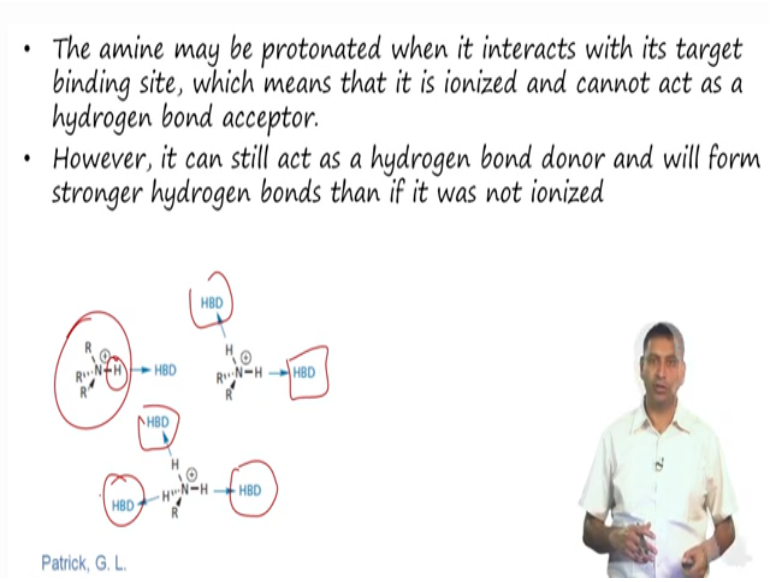

So the way in which the amine can act as a hydrogen bond acceptor is because it has a lone pair of electrons and therefore it can interact with the hydrogen. The way in which an amine especially a secondary amine or a primary amine act as a hydrogen bond donor is through the hydrogens which are next to the nitrogen. So both of these are possible in amines, of course in tertiary amine it can only act as a hydrogen bond acceptor.

The amine in many cases depending on the (())(18:46) can be protonated and when it is protonated then the hydrogen bond acceptor capability of the lone pair is not present and instead it becomes a hydrogen bond donor. So in the case of a tertiary amine you have converted this hydrogen bond accepting lone pair since it is now protonated it becomes a hydrogen bond donor.

Similarly you have a situation with the primary and secondary amines where you have additional hydrogen bonding donor possibilities. However, this molecule can also have a hydrogen bond interaction if it is not ionized.

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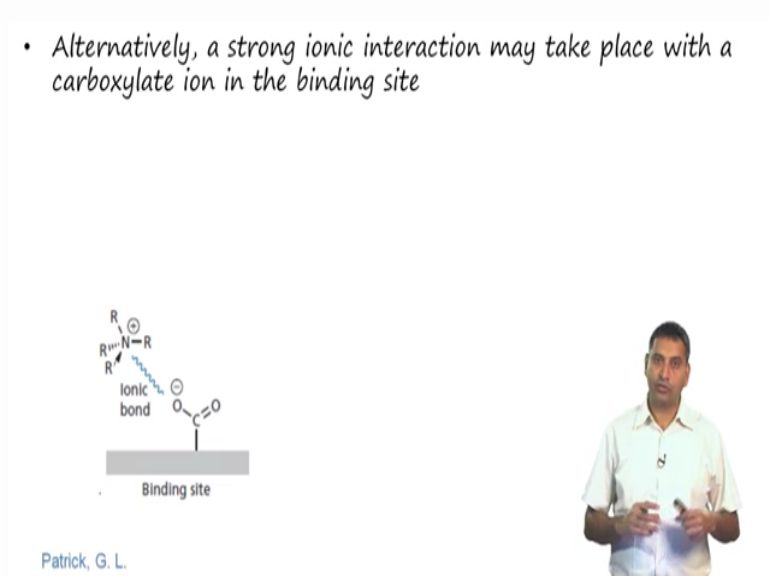

Alternatively, a strong interaction which is of ionic in nature can occur with a carboxylic binding site. So here is the representation of that and this is something that we have looked at previously.

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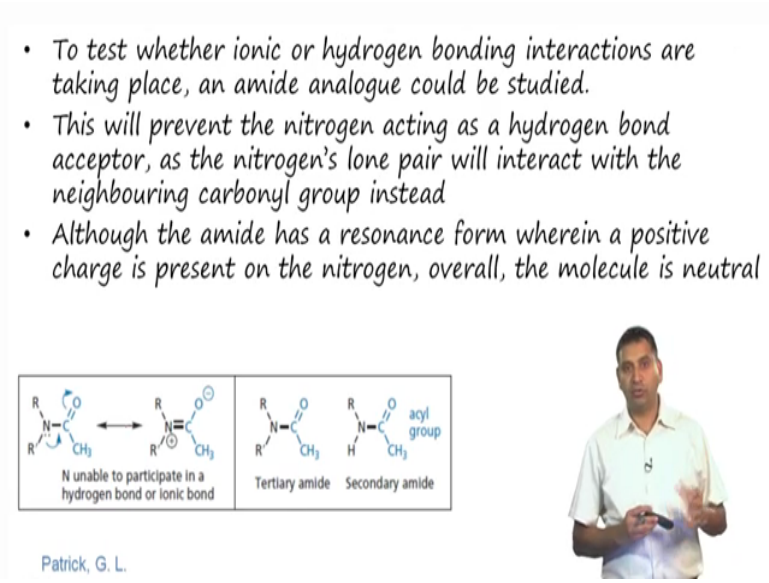

So to test whether the ionic or hydrogen bonding interactions are taking place one could convert the amine to an amide, so this will prevent the nitrogen from acting as a hydrogen bond acceptor because the nitrogen's lone pair will interact with the neighbouring carbonyl instead of the target. So here we have seen this already the amide nitrogen, the lone pair is going to be delocalized when you generate a resonance form such as this and so the nitrogen

lone pair is really not available to participate in hydrogen bonding, but neither it is possible that it is present as a ionic bond because this nitrogen is not going to get protonated.

So the tertiary amide or secondary amide which are derivatives of the secondary and the primary amines respectively are useful compounds to make if you want to study this.

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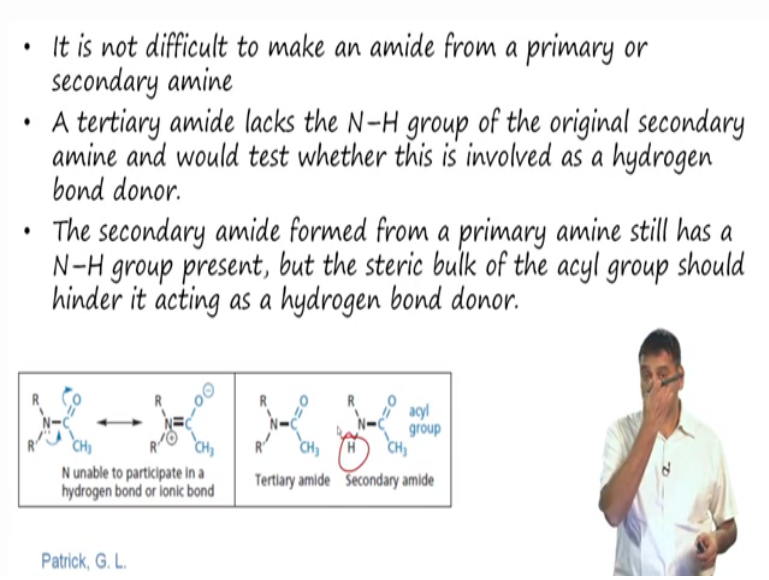

It is not difficult to make an amide from a primary or secondary amine. The tertiary amide lacks the N-H of the original secondary amine and would test whether this is involved in hydrogen bond donor. The secondary amide which is found from a primary amine still has a N-H present but because of the steric bulk of the acyl group we should hinder it acting as the hydrogen bond donor.

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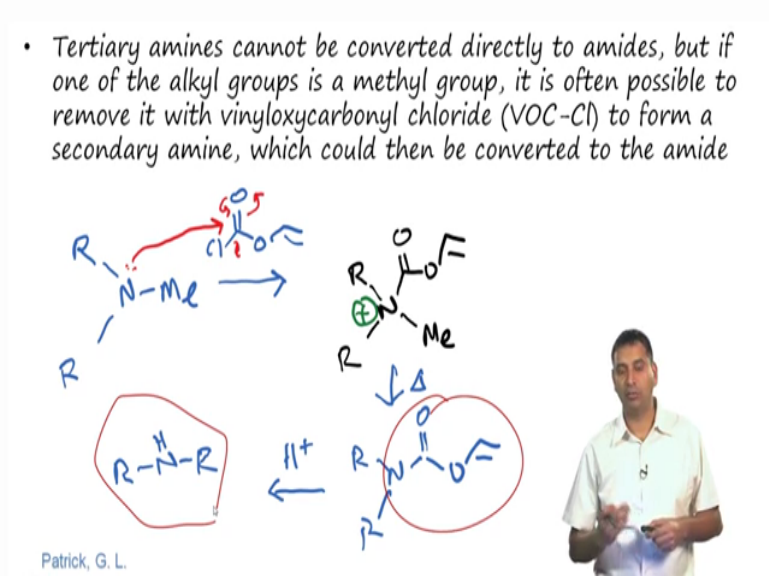

Tertiary amines cannot be directly converted to amides for obvious reasons, but if one of the alkyl groups is a methyl group, then it is possible to cleave it using this vinyloxycarbonyl chloride reagent. So one of the ways in which you can clear the methyl group is by using this reagent and the mechanism is as follows the lone pair on the nitrogen attacks the carbonyl chloride and then forms the intermediate as shown here which then upon heating methyl group is removed and then you get this carbomate over here, which then it hydrolysed in acidic pH to give you back the amine, somewhat harsh conditions to do this, but in principle it can be done.

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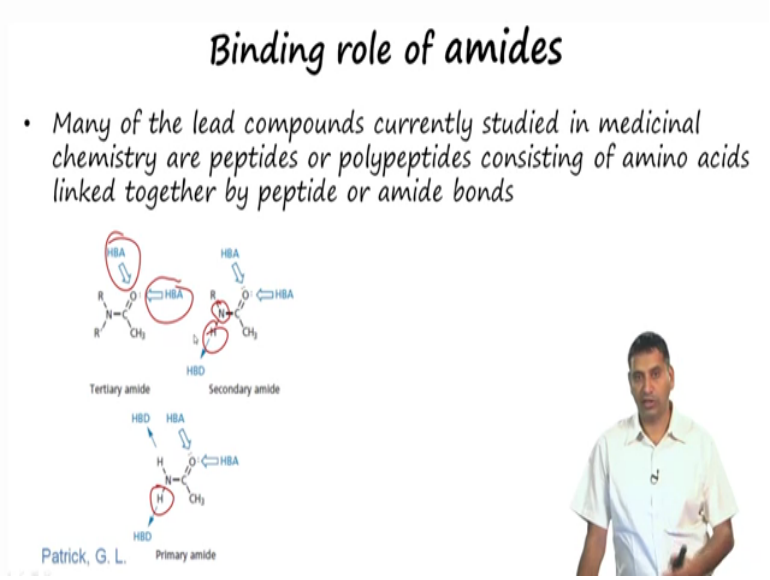

The next major functional group that we will look at is amides, we have already looked at the resonance form of amides and so there are two major hydrogen bond acceptors here which is basically this two lone pairs on the carbonyl oxygen and we already saw that the nitrogen is not very important, but if you have an N-H in the case of a secondary or a primary amide then the H can act as a hydrogen bond donor, so tertiary amides have somewhat of a different role compared secondary or primary.

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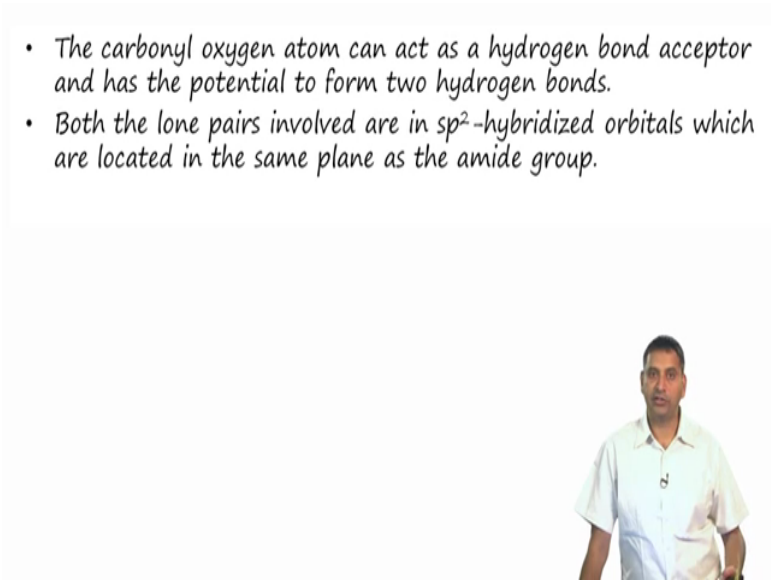

And since the large number of peptides have this functional group involved it is important functional group for people to understand. So the lone pairs are involved in sp 2 hybridized orbitals which are located in the same plane as the amide group. So that is an important point for us to note when we are looking at hydrogen bond interaction capability.

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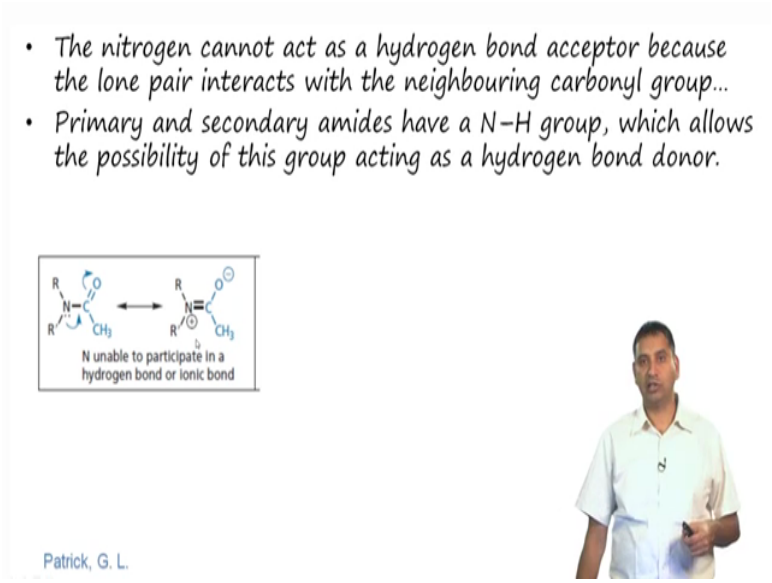

The nitrogen cannot act as a hydrogen bond acceptor because the lone pair interacts with the neighbouring carbonyl group we have already looked at this. So the primary and secondary amides have an N-H group which allow the possibility of this group to act as a hydrogen bond donor.

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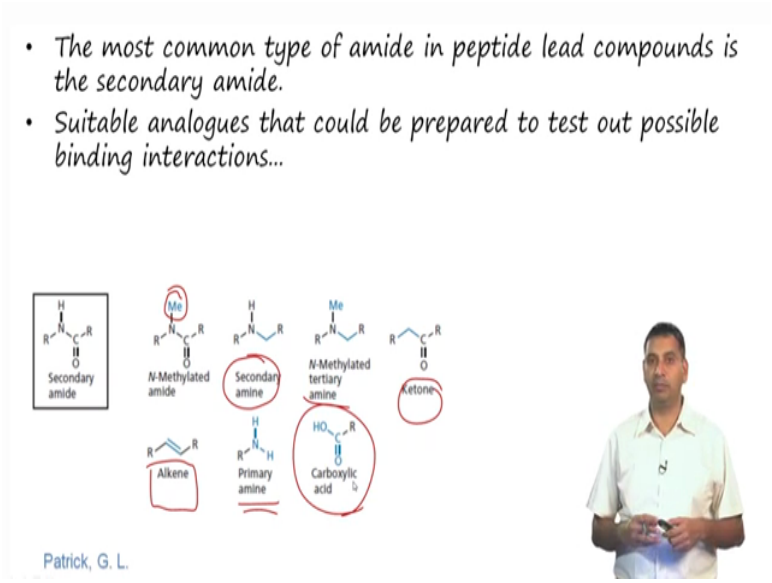

So the most common type of amide in peptide compounds is the secondary amide. So we can think about some suitable analogues that can be prepared to test out the binding interactions. So just to list them we can methylate it over here, we can convert it to a secondary amine, we can make the N-methylated tertiary amine, we can remove the nitrogen altogether and make a ketone, we can remove the carbonyl as well as the nitrogen but keep the double bond, you

can convert it all the way to the primary amine or make a carboxylic acid. So these are some of the analogues that we can think off and now let us look at them in some detail.

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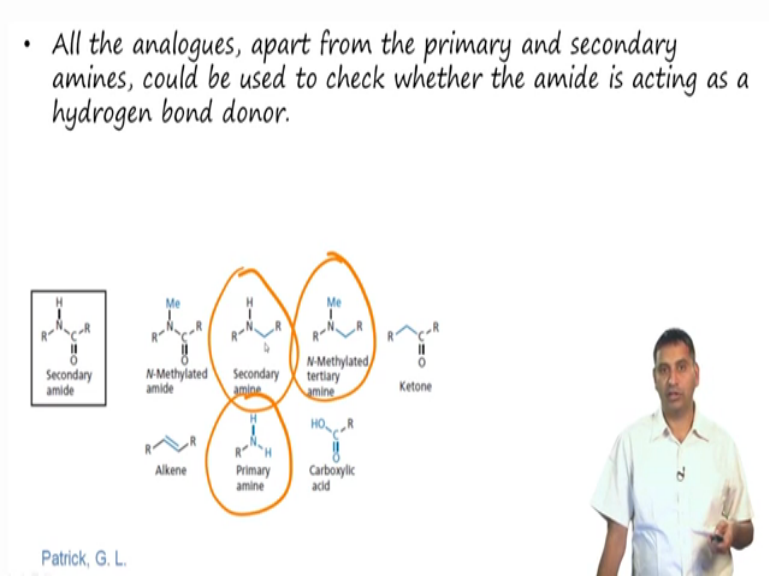

So all analogues apart from the primary and secondary amines could be used to check whether the amide is acting as a hydrogen bond donor or not, so if you think about the N-methylated compound it is not going to present any possibility for a hydrogen bond. So therefore this will be a good analogue and this compound here the primary amine and secondary amine can also be used to check whether it is a hydrogen bond donor.

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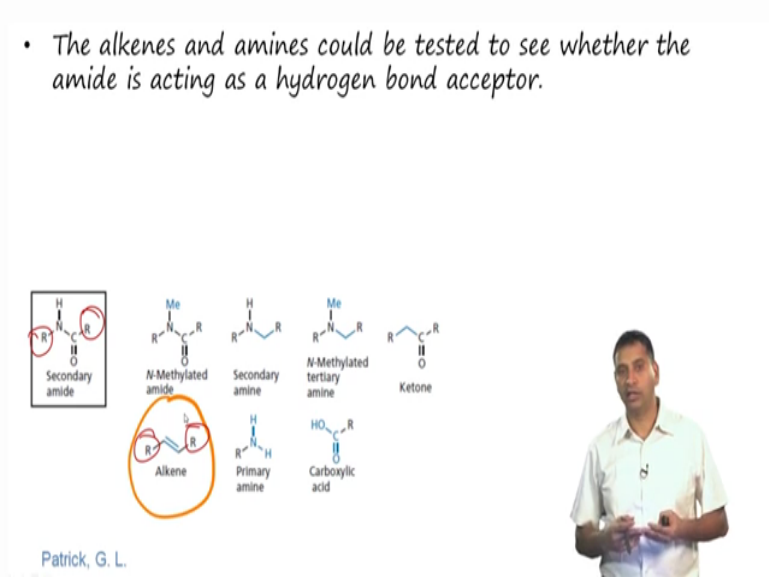

The alkenes are useful because they have a double bond and the geometry of the double bond is useful. So the R here and the R here are in the same geometry and so therefore it is going to perhaps can be involved in interactions. So if the amide is involved in interactions wherein this geometry is important than one could find the load, also because you have completely eliminated the possibility of hydrogen bonding, then this molecule if it is not active then it is possible that the amide was important.

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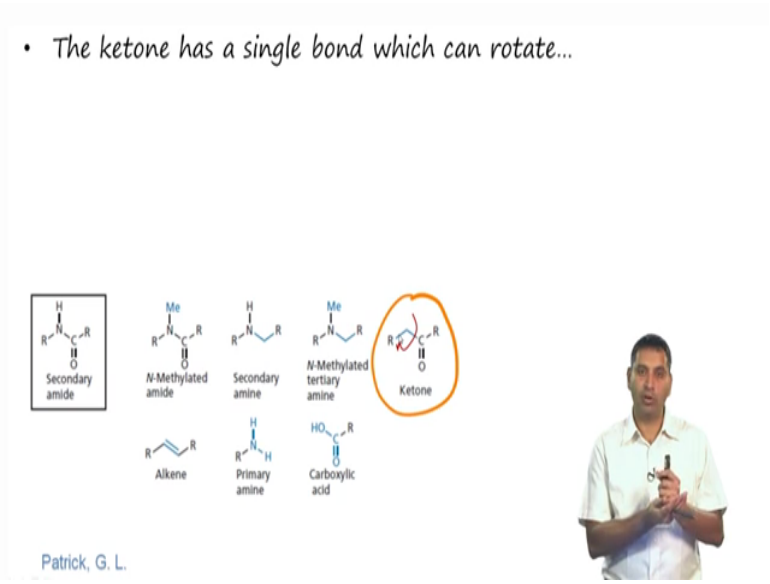

The ketone has a single bond right next to it which can rotate as opposed to the amide and so therefore this makes a good case for us to study how important the rigidity of the amide bond is in the interaction.

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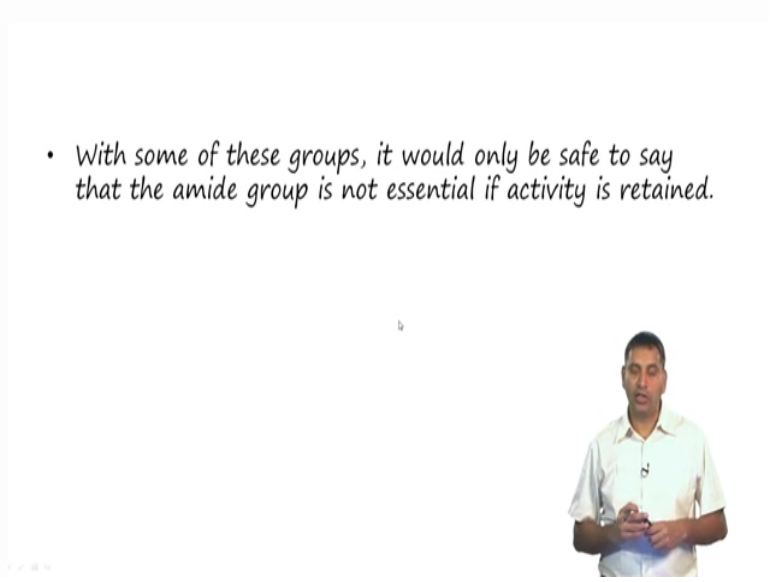

So with some of these groups, it would only be safe to say that the amide group is not essential if activity is retained.

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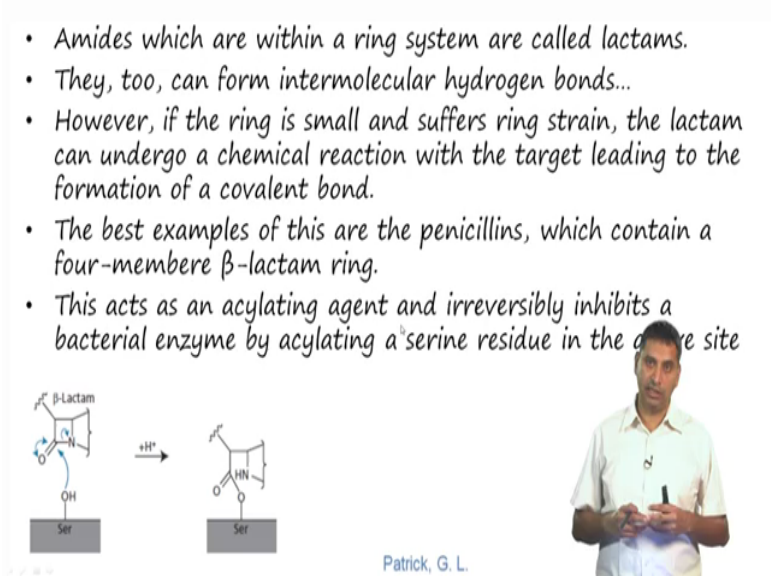

So amides which are within a ring system are called as lactams. And these lactams can also form intermolecular hydrogen bonds. However, if the ring is small and has ring strain, then the lactam can undergo chemical reaction with the target leading to the formation of a covalent bond. So the classic examples are penicillins which contain a four membered beta lactam ring and this also acts as an acylating agent and irreversibly inhibits by acylating a serine residue in the active site, we shall look at this in more detail when we discuss anti-bacterial agent.

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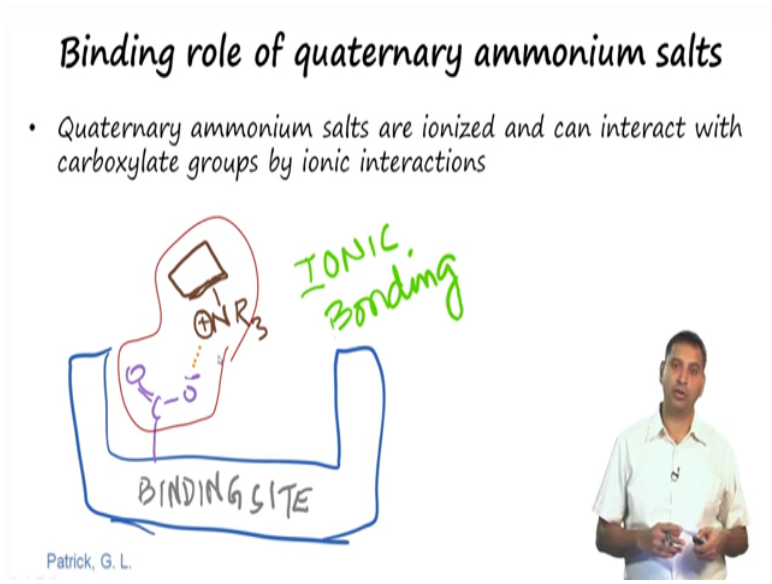

So the next class of compounds that we are going to look at is quaternary ammonium salts and we have already discussed this but this quaternary ammonium salts are basically permanent fully positively charged species and therefore they would be expected to interact with binding sites where there is a carboxylate, this is an example of an ionic bonding.

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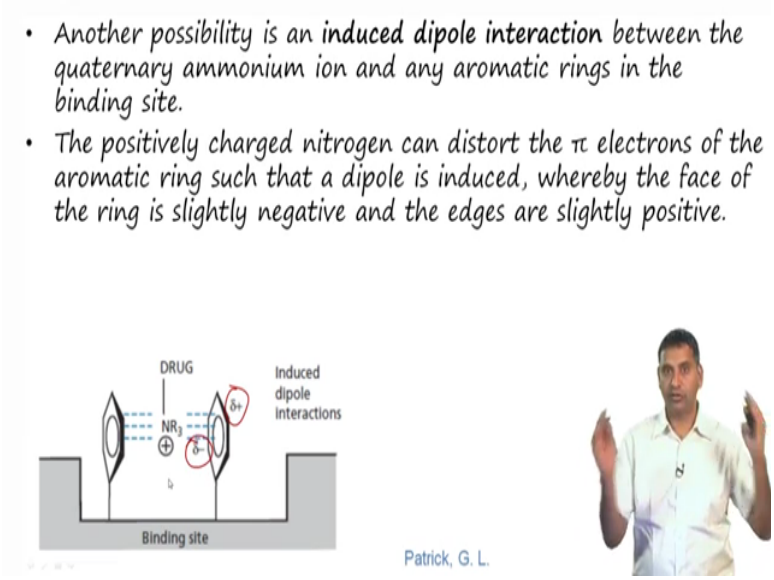

It's another possibility is that they can be involved in interactions with aromatic rings, we have already looked at this previously. So the positively charged nitrogen can distort the pi electrons of aromatic ring such that a dipole is induced. So the phase of the ring is slightly negative, the edges are slightly positive, so you see here this is slightly delta plus, this is delta minus and therefore this interaction can occur.

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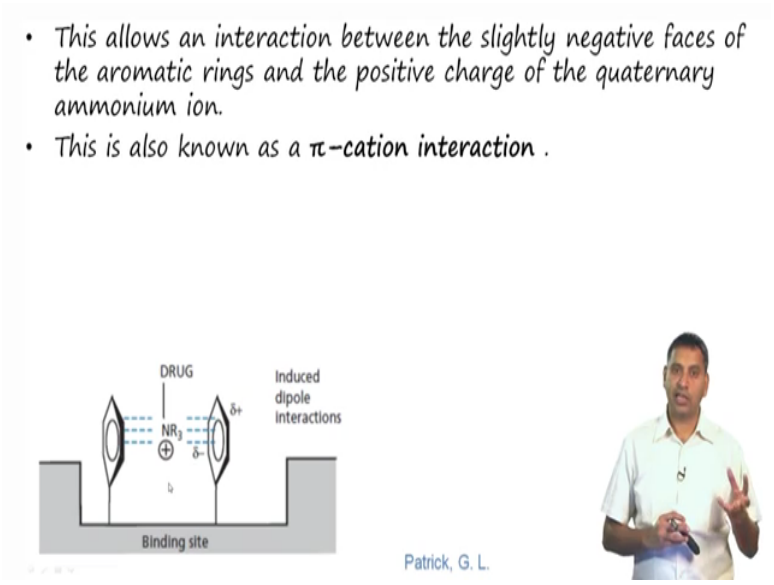

So this is called as cation pi interaction and this can play a role in certain cases where you have these residues appropriately aligned.

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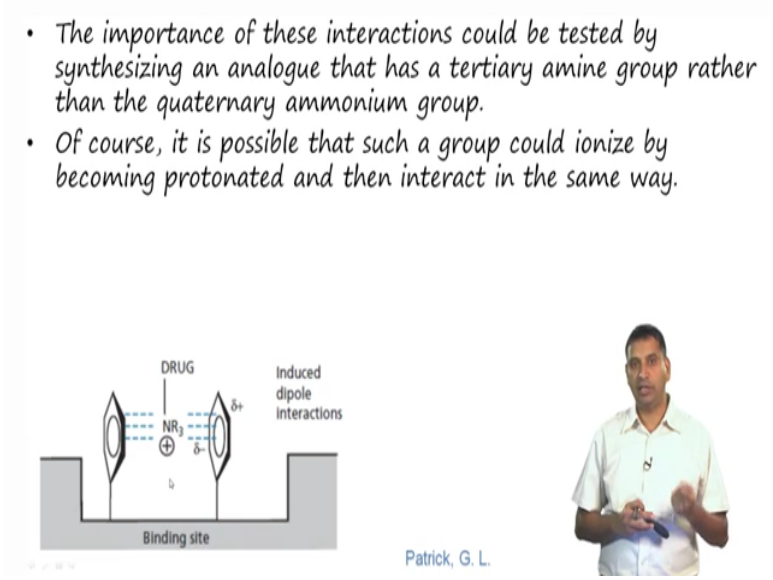

The importance of these interactions can be tested by synthesizing an analogue that has a tertiary amine group, rather than a quaternary ammonium group. Of course it is possible that such group can get protonated and interact in the same way, but it would help us understand whether this interaction is important or not.

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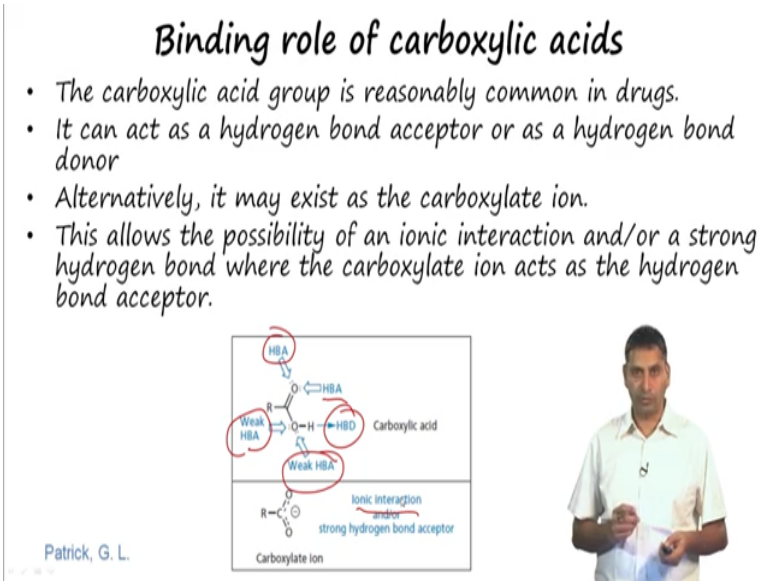

The next major functional group that we will look at is a carboxylic acid, there are number of drugs which have carboxylic acids in them and one of the things aspects of carboxylic acids

is that it has multiple hydrogen bond donor and acceptor capabilities. So here is the HBA's the hydrogen bond acceptors and this O-H is a hydrogen bond donor and here this oxygen as we looked at previously is a weak hydrogen bond acceptor and similarly these are the lone pair here on the same oxygen is also a weak hydrogen bond acceptor.

Frequently carboxylic acids are in the deprotonated state the (())(26:52) of this are sufficiently low that in physiological pH they would be in the carboxylate and so these carboxylates are going to have very strong ionic interactions. For example protonated amines and they can also act as hydrogen bond acceptors.

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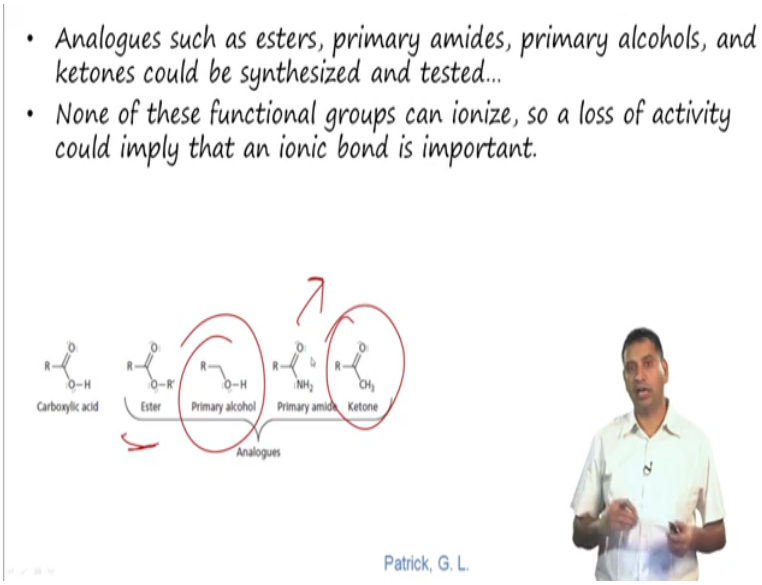

So some of the analogues that we could synthesize to study the role of carboxylic acid would be to make an ester shown here, or you can reduce it all the way to the primary alcohol one can also make an amide keep in mind that the when we were trying to study the role of an amide we proposed that you can make a carboxylic acid and now we are looking at the opposite situation, we can also make a ketone and so on, so none of these functional groups can ionize, so loss of activity may imply that the ionic bond was important.

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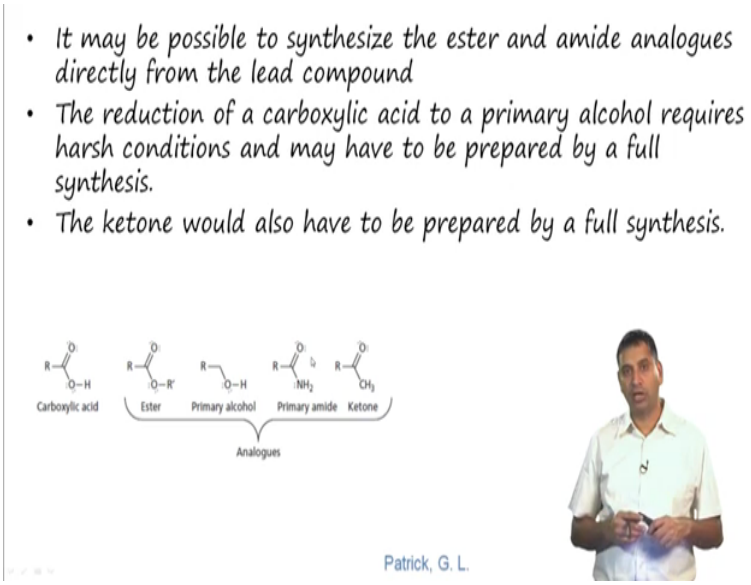

The primary alcohol could shed light on whether the carbonyl oxygen is involved in hydrogen bonding, whereas the ester and ketone could indicate whether the hydroxyl group of the carboxylic acid is involved in hydrogen bonding. It may be possible to synthesize the ester and amide analogues directly from the lead compound, but the reduction of the carboxylic acid is the primary alcohol requires pretty harsh conditions and if you are not sure that the other functional groups in the drug may survive these conditions, we may have to go back and prepare it and of course the ketone would have to be prepared by a full synthesis.

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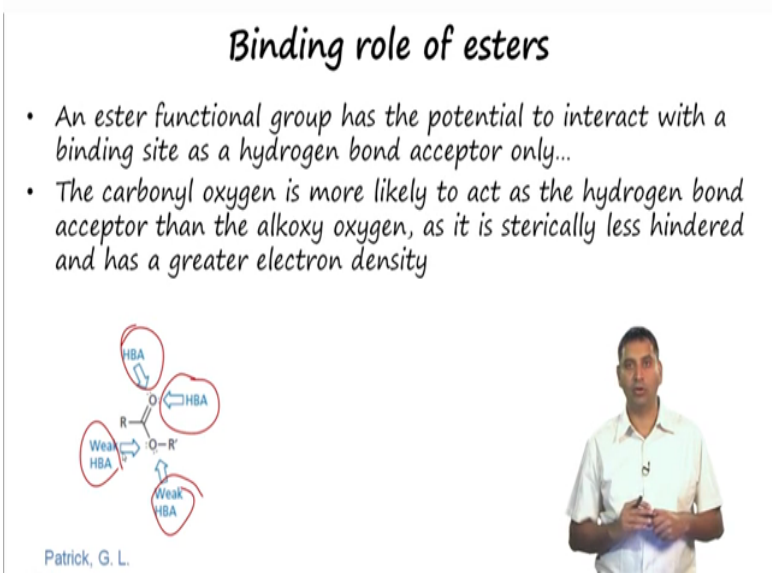

The next functional group that we will look at is an ester. An ester functional group has the potential to do a hydrogen bond acceptance in the carbonyl like much like the other carbonyl

functional groups and there are couple of weak hydrogen bond accepting groups on the oxygen and the carbonyl is also sterically less hindered compared to the ester oxygen so that is O-R and therefore it is more likely that the carbonyl oxygen will be involved in hydrogen bonding.

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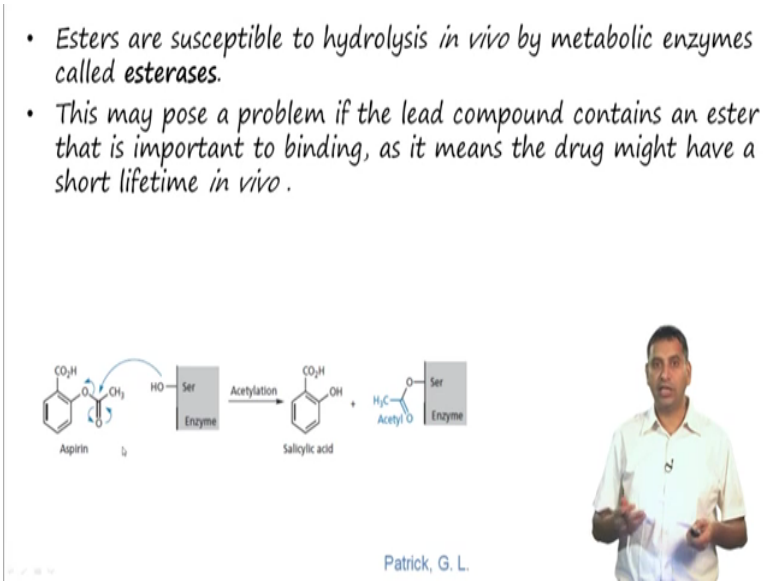

Many esters are susceptible to hydrolysis in vivo by metabolic enzymes known as esterases. And this may pose a problem if the lead compound contains an ester and it may convert it to be carboxylic acid and the alcohol.

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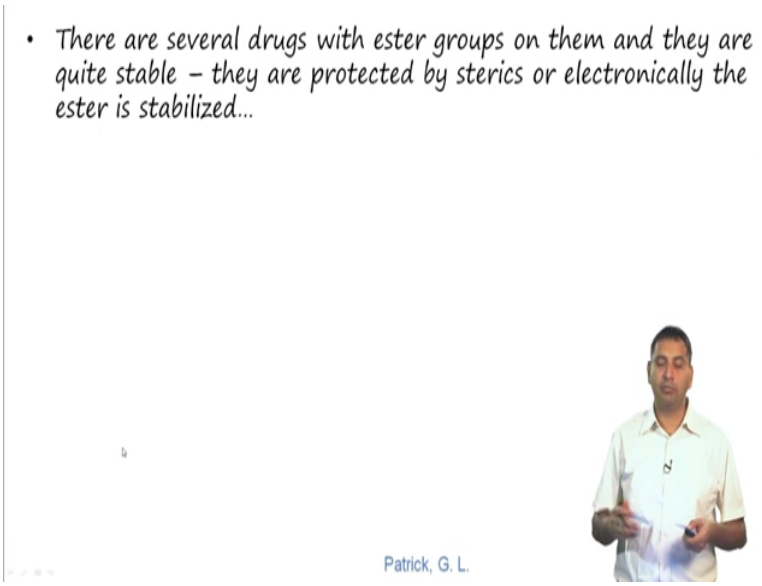

But there are many drugs which do contain an ester and these esters are made in such a way that they are protected by sterics or electronics to prevent the ester hydrolysis under these conditions.

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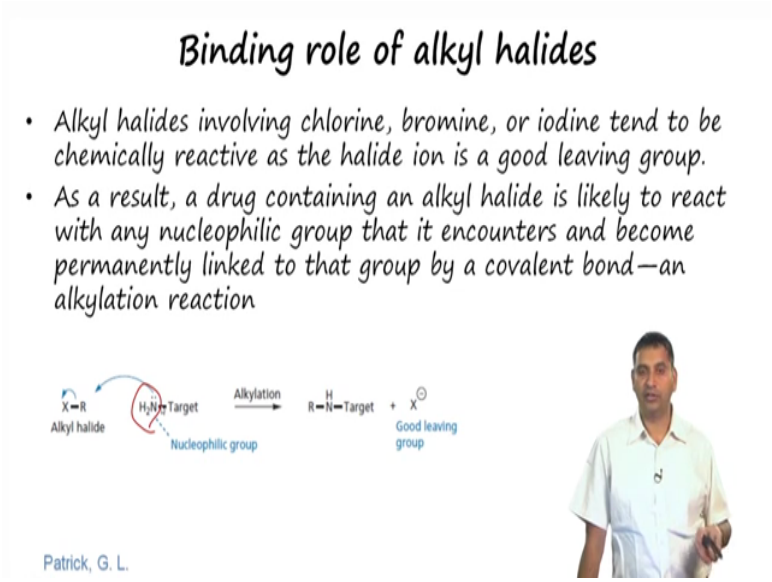

So alkyl halides is the next functional group and they are not as common in variety of drugs and one of the problems with this is that they are actually sometimes good leaving groups. So when you have a new nucleophile such as an amine in the let us say in the target they can react with the alkyl halide and form a covalent bond. So this is something that one needs to consider when we incorporate halides in the molecule.

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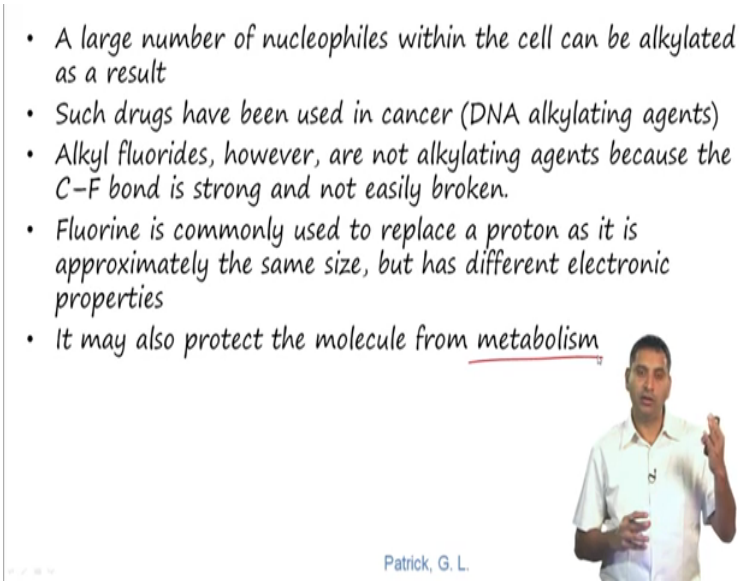

So such drugs have actually been used in cancer, so we have already looked at examples of DNA alkylating agents. So chlorine, bromine and iodine have this problem, but fluorides are not alkylating agents because the carbon fluorine bond is quite strong and not easily broken. So many times a fluorine is used to replace a proton as it is approximately the same size but it has very different electronic properties. In several cases it also protects the molecule from metabolism. So there is a difference between fluorine and the other three halogens.

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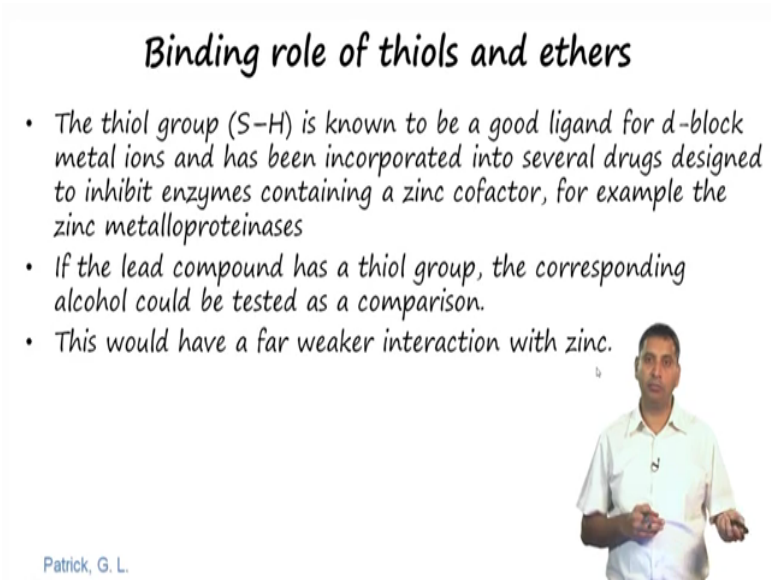

The next functional group we will look at is thiols and ethers, so thiol is known to be a good ligand for d-block metal ions, especially zinc for example and zinc containing enzyme such as metalloproteinases can be inhibited by using a thiol. So these thiols may go and bind to the zinc and prevent the enzyme from acting. So if we suspect that this is happening then what we could do is convert the thiol to the alcohol and test it for comparison, we would predict that the alcohol would have far weaker interaction in zinc compared to the thiol.

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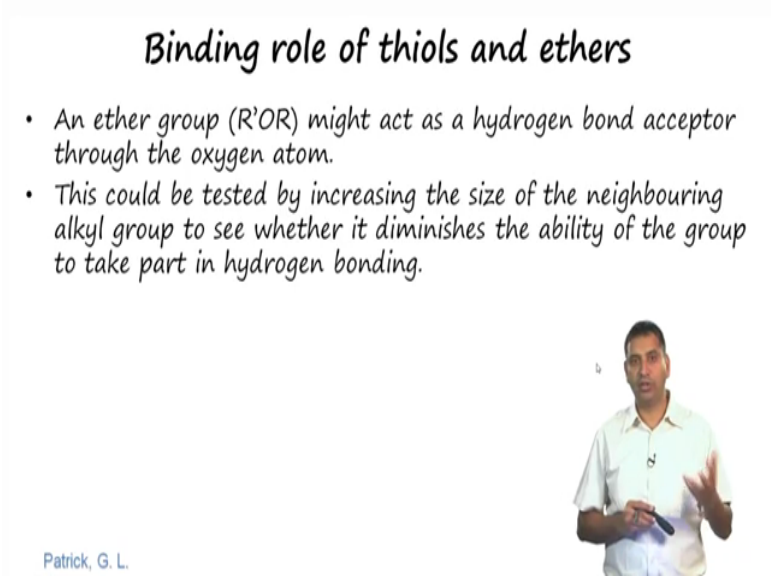

The ether functional group we have already seen this is going to act as a hydrogen bond acceptor and what we could do is to increase the size of the neighbouring alkaline group and see whether it diminishes the ability of the group to take part in hydrogen bonding. So this will tell us whether the ether group is important or not.

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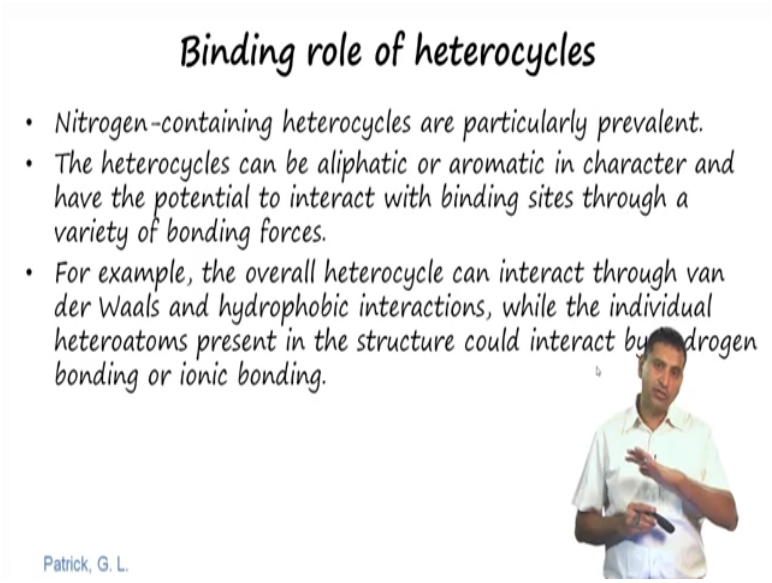

So this large number of drugs contain heterocycles, so the next topic that we are going to take but not in much detail is heterocycles because it is a completely fast area where the number of heterocycles that can be studied. Heterocycles can be aliphatic or aromatic in character and therefore there are heterocycles which can interact through Van der Waals interactions or

hydrophobic interactions and also by hydrogen bonding or in some cases but ionic bonding, so each of this heterocycle will have to be treated in on its own.

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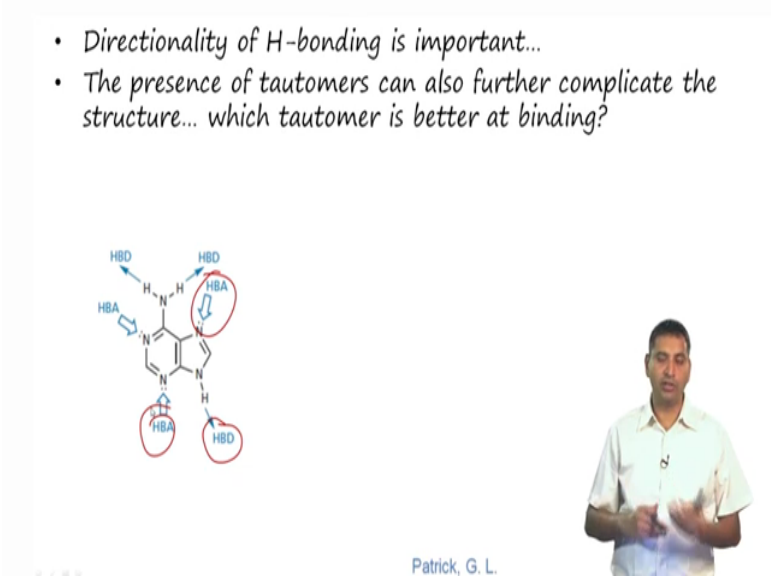

So the directionality of the hydrogen bonding is also important. So for example if you look at adenine, here you have number of hydrogen bond acceptors and donors but they are all placed in a manner in which their directionality that is induced which is going to be important in binding, there is also a possibility of tautomerizm and so then (what) which tautomer is better at binding all these questions become important to answer.