Medicinal Chemistry
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Optimizing Access to the Target
Mod09_Lec50

Okay, so in the past few lectures we have been looking at number of aspects about how to optimise drug target interactions, of course we must recognised that unless the drug is to the target it is not going to be able to interact with it.

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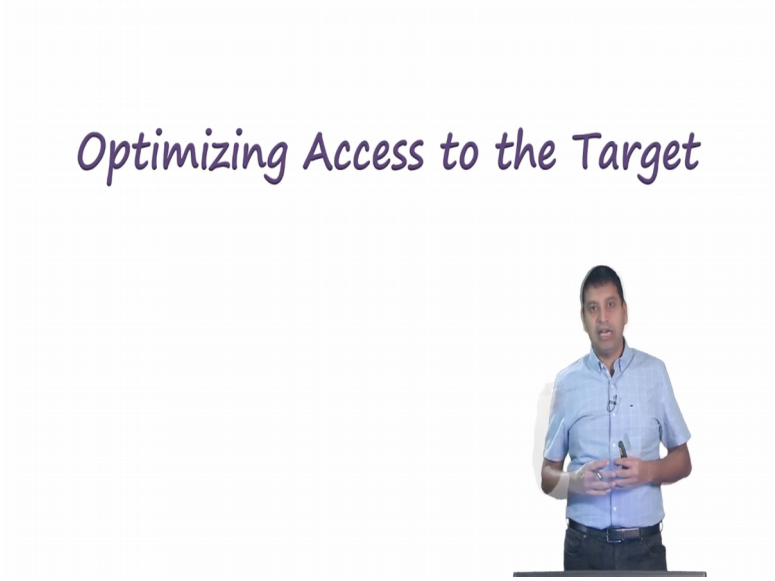

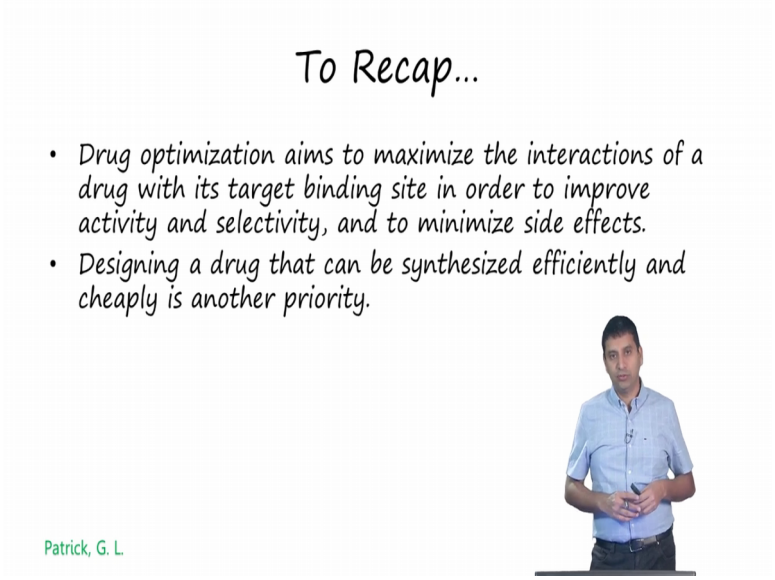

So in todays lecture will very importantly look at how to optimize the access to the target, but before we get started, let us quickly recap what we have done in the past few lectures, so the

major concept that we have been dealing with is drug optimization, so drug optimization basically looks to maximize the interactions of a drug with its target binding site and as we know this will help improve the activity of the drug, so if you have the right kind of interactions to the drug than you are going to have perhaps the best efficacy, it also might improve the selectivity.

So if you have two different kinds of active sites or two different kinds of receptors then if you can optimize the drug to selectively act on one that might be useful and as a corollary, it will also minimize side effects because as the selectivity of the drug goes up the side-effects presumably go down, now the second part of it is to be able to design a drug that can be synthesized efficiently. Okay, so this is not something that you really take into account during the first identification of a lead but after you identify a lead then you may want to really, seriously think about how to synthesise the drug efficiently and of course cost is a major issues, so you want to make sure that the cost is less

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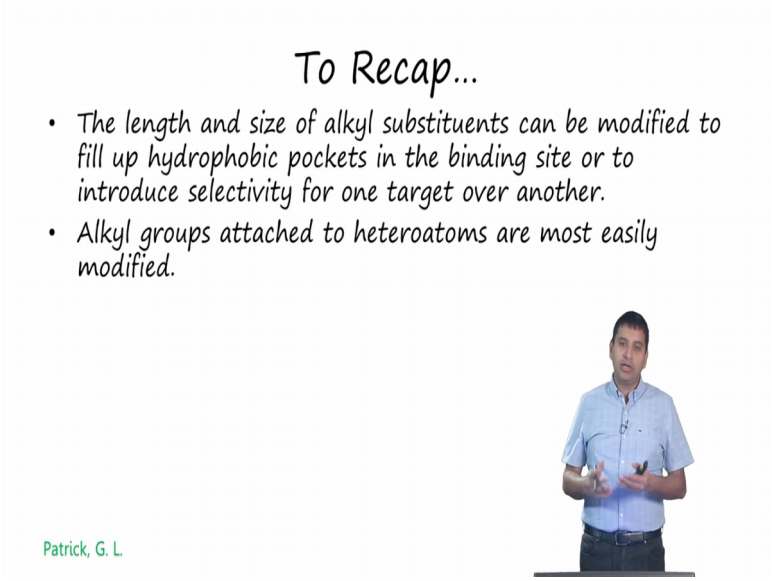

And now in order to do this, there are very systematic ways of optimizing the interaction and that is what is we looked at previously, so for example if there is a hydrophobic pocket in the binding site, then we can change the length and the size of the alkyl subsequent, so that we can fill up the hydrophobic pocket in the binding site and this also may help with introducing selectivity of one target over the other, now alkyl groups which are attached to heteroatoms are actually easier to modify because you can do through nuclear felix substitution for example, you can convert it to an ethyl, butyl and so on.

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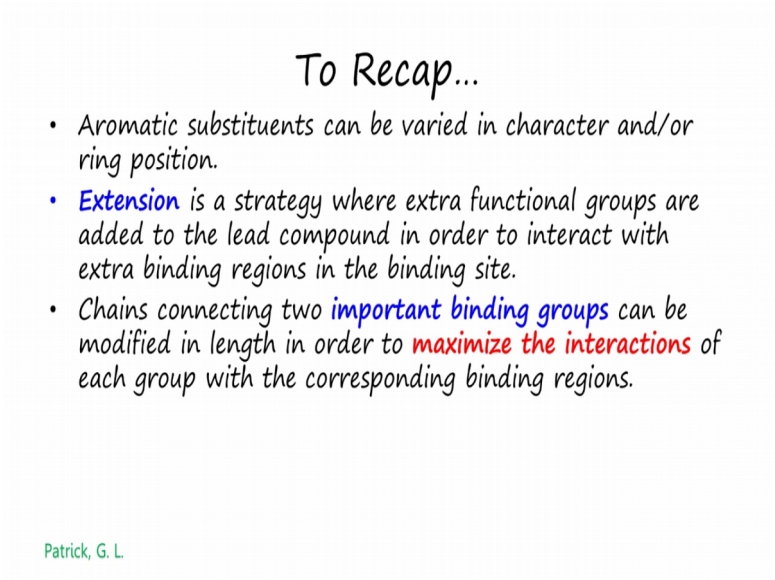

Now the second major functional group other than alkyl groups is the aromatic substituents, now we can change the position of the aromatic substituents for example, we can go from Ortho to Meta to Para and that would vary the character of the ring, the next strategy that we encountered was what is known as extension, so your extension is a strategy where an extra functional group is added to the lead compound to increase the levels of interaction, so during the optimization studies or structure activity relationship studies, one may discovers some extra binding, regions in the binding site in order to access those binding regions you would and more functional groups, now change containing two important and binding groups can be modified in length, so if you have group A and group B which are binding with two different regions then you can change the length between these two binding regions to maximize the interaction,

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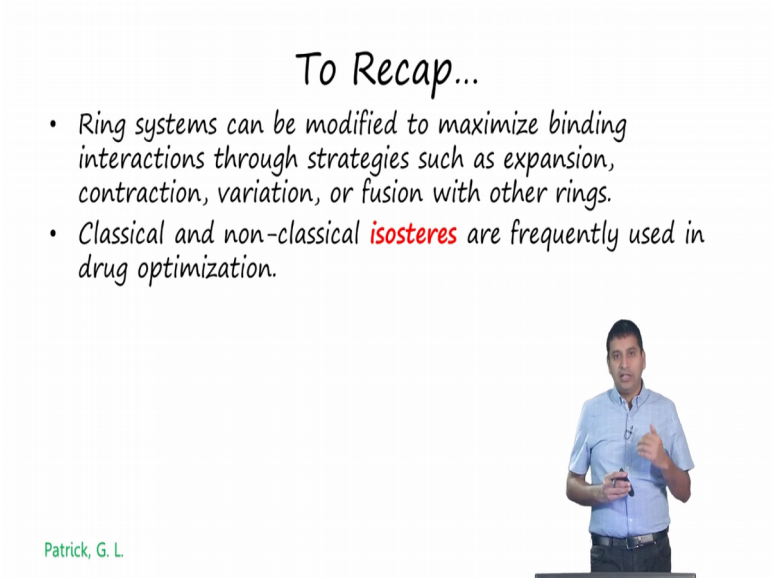

We can also modify ring systems to increase the binding and this can be achieved by doing ring expansion, so we can make a six number ring or seven number ring, we looked at examples of those, we can convert to six number ring to a five number ring for example, or you can also vary the ring, so you can convert completely alkyl or a carbon-based ring system to somewhat of a heterocyclic ring system or you can also fuse it with other ring, so if there are two rings which are close to one another and if that is the degrees of freedom is quite high, you can use it with other things to reduce that, we encountered this concepts of classical and non-classical isostere and these are very frequently used in drug optimization.

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Now replacing a group in the lead compound with an isostere makes it easier to data mine whether a particular property, such as hydrogen bonding is important, we looked at several examples of this, one way to do this is to replace it with a methyl group because it has the same valence.

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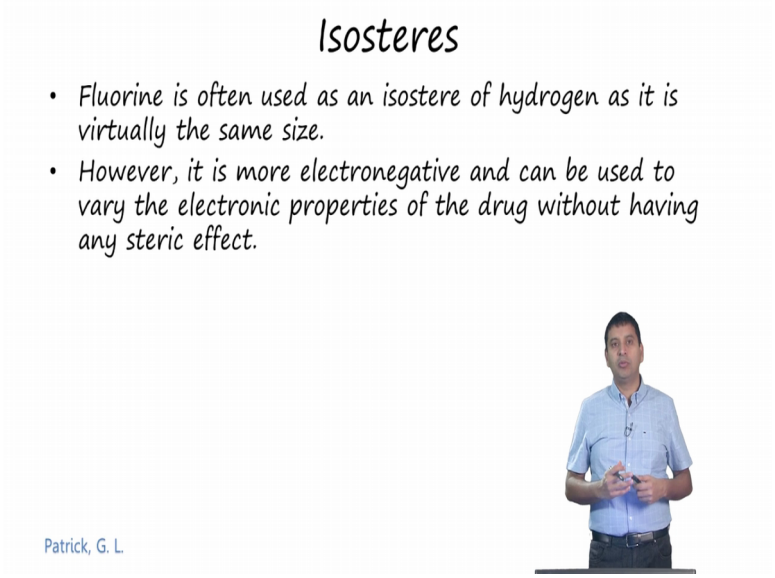

Fluorine, we discussed is often used as an isostere of hydrogen because it is of similar size and since it is more electronegative, it can be used to vary the electronic properties of the drug without having any major steric effect, so fluent is a very commonly used isosteres this concept.

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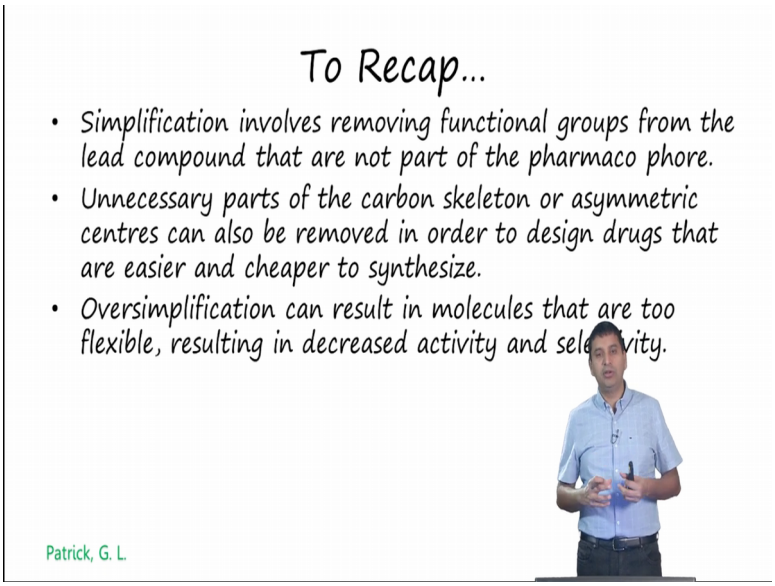

The next concept is simplification, so simplification involves removing functional groups from the lead compound that are not part of the pharmacophore, so here what we need to identify is to see what the major aspects of the pharmacophore are and then we can one by one, chopped the regions which are not necessary, so this could be not so useful parts of the carbons skeletons, they can also be a asymmetric centres, which can be removed because it is easier to synthesise this compounds, however, one must be cautious that oversimplification can result in molecules that are too flexible, which will result in decreased activity and selectivity.

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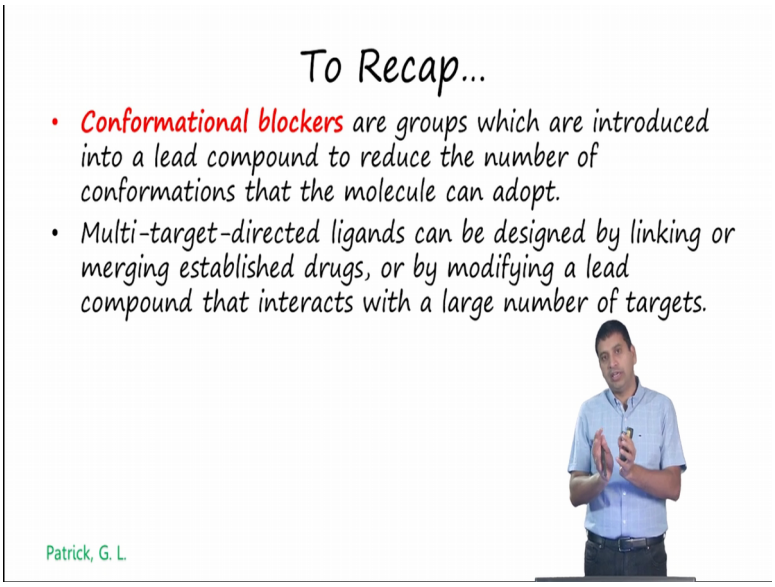

The next major strategy that one would use is rigidification, so you have a lead molecule which has number of conformations and we work under hypothesis that there must be an active conformation and the closer we get in structure to active conformation, the better the interactions would be, so here what would we do is we would remove the possibility of rotation or lock it into a rigid ring and so on, all of these constitute rigidification.

The also looked at conformational blockers, so here the number of conformations that are molecule and adopt is majorly reduced, so for example if you have a bi funnel system then you add a methyl groups so that the rotation is going to be inhibited and therefore your number of conformations that can be adopted would be lower and we looked at this multi-target-directed ligands which means that is molecules which can be linked or merging as established drugs to be able to target multiple sites in the cell, so here the way we would do this we would modify the lead compound basically, so that it interacts with a large number of targets.

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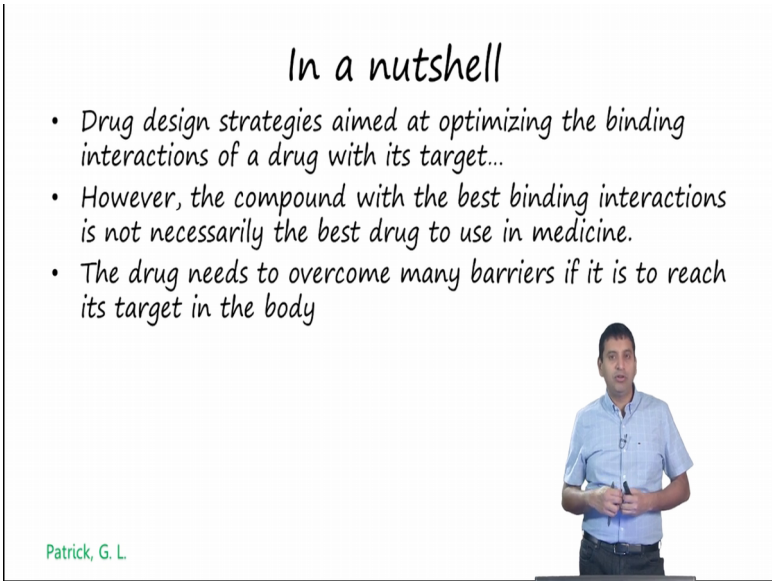

Now, in a nutshell, drug design strategies are basically aimed at optimising the binding interactions of a drug with its target, now we can do this and we can find the best molecule which binds to the target, however, the compound need not be the best drug because we have already looked at in detail through a lectures in ADME that the drug will need to undergo many barriers to reach the target in the body, so now we should look at how to address this issue.

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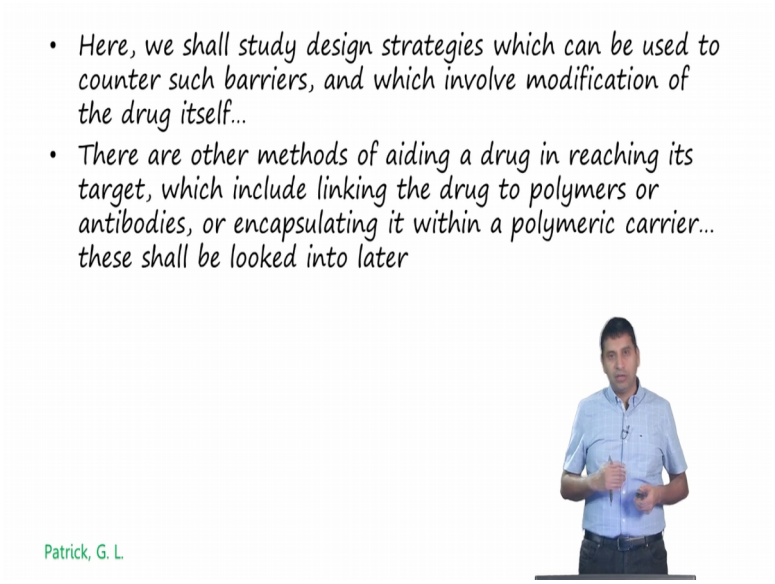

So we shall study some design strategies which can be used to counter such barriers and there are other methods which help with getting the drug to its target and some of these includes

linking of drugs to polymers or antibodies, so polymers will help with encapsulation and this will help get it to its target. Perhaps, antibodies are very specific to certain cells of its receptors and then by conjugating are molecule to the antibody we may be localising the drug better and also we can also do correlate modification to our polymer or oligomer and so on, so we should look into this in more detail later.

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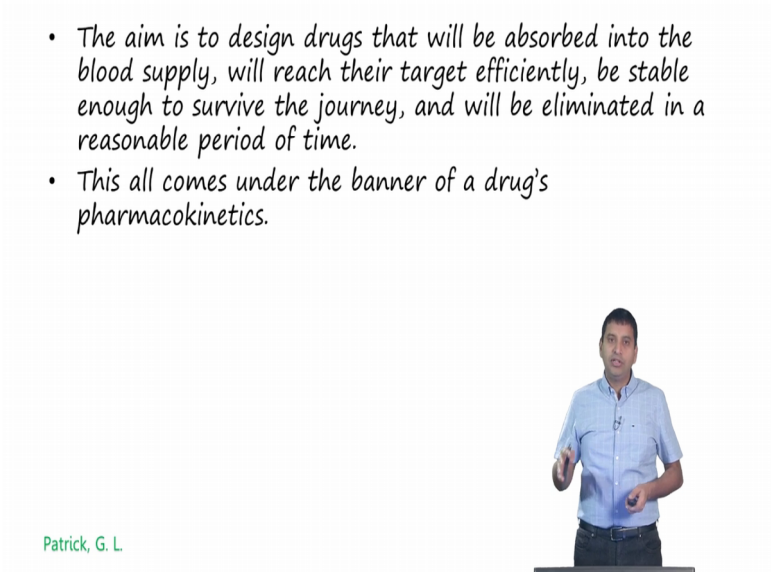

The fundamental aim of this strategies is to able to design pounds that would be absorbed into the blood supply because unless it is absorbed in the blood supply, it is not going to be distributed efficiently, now it should also is stable, so that it can survive the journey and more importantly should be able to optimize the elimination properties, so that it remains in the body for a reasonable amount of time until it achieves its a goal, but it should not remain there for too long, which may also cause some side effects, so all of these comes under the banner of drugs pharmacokinetics.

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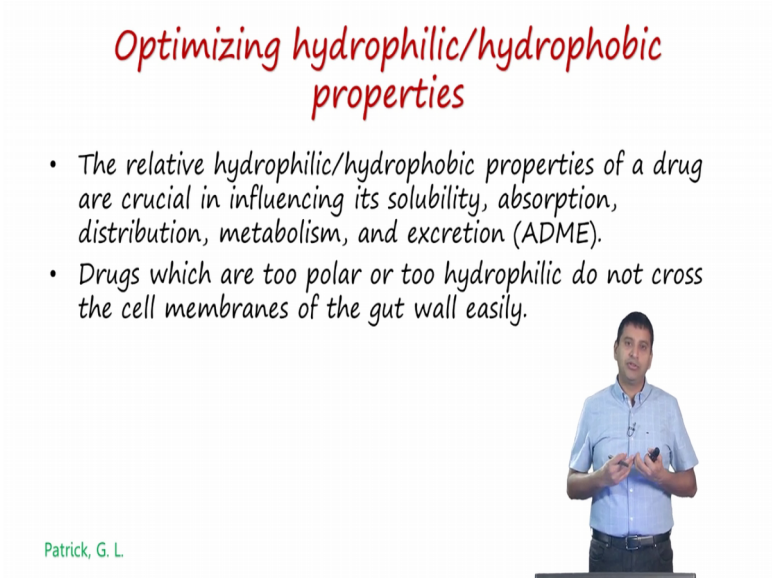

So in order to optimize a drug, the first major thing that we would look at is to optimize the hydrophilic or hydrophobic property, so the relative hydrophilic, hydrophobic property is crucial to influence its solubility because unless you get the molecule into water or aqueous medium, it is not possible for it to be administered in some cases, then it also has to have optimize absorption and distribution, metabolism and excretion a DME all this properties are going to be influenced by the relative hydrophilicity and hydrophobicity, so we have already looked at this previously, but with drugs which are to polar are going to have problem because they are not going to get across the cell membrane.

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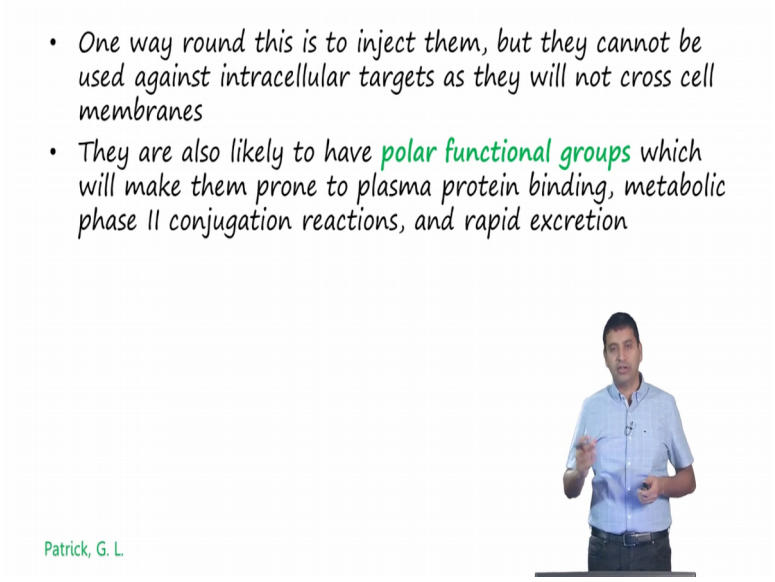

Similarly the drugs which are too hydrophobic will get absorbed in fact globules, of course, for molecules which are hydrophilic you can inject them, but then they may not be able to reach the target because they have to cross cell membranes to get into the target perhaps, so there are also likely to have polar functional groups which will make them prone to find to plasma protein, so once the pomp ode binds to the plasma protein then it circulates in the body for a long time without releasing into the area where it is supposed to interact with the target, so also having polar functional groups can also make a candidate for phase II conjugation reactions, which will also result in rapid excretion.

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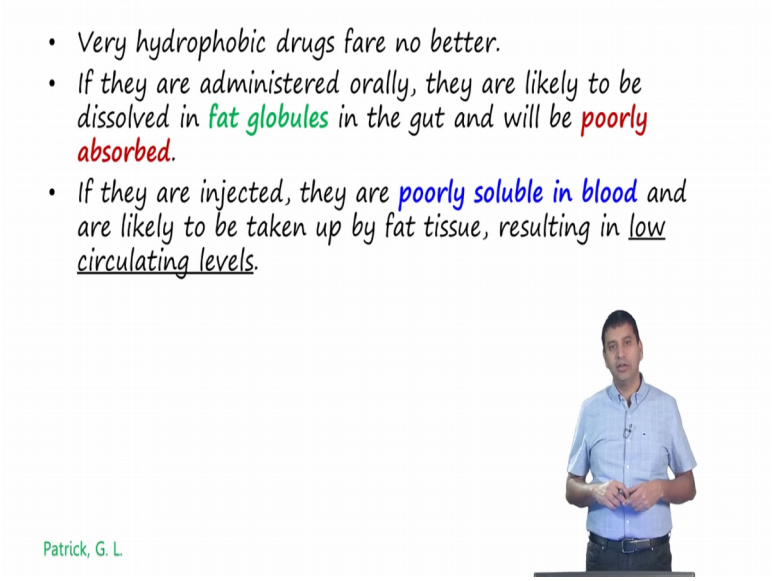

And we just looked at it briefly that very hydrophobic drugs are also problematic because they are going to be poorly absorbed and now if they are injected then they are poorly soluble in blood and they are likely to be taken up by fat tissue, this is again going to result in low circulating levels.

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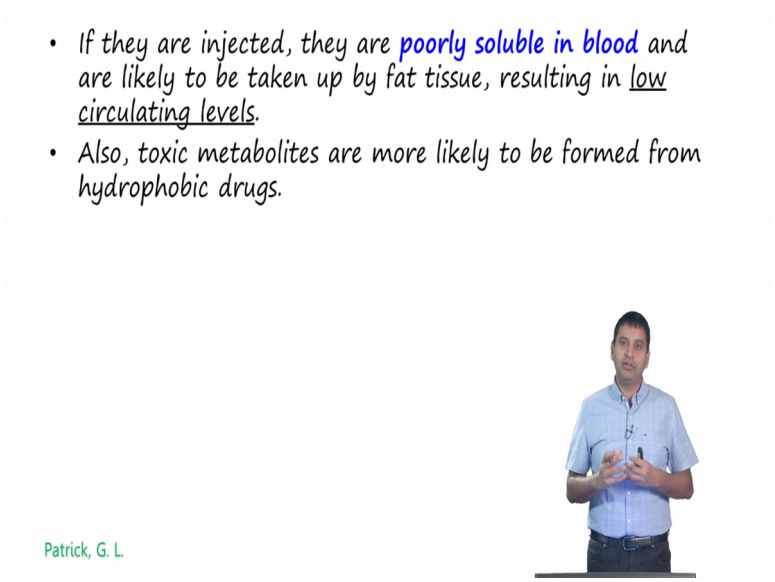

So therefore they need to be in optimize based on these, so you toxic metabolites are also more likely to be formed using hydrophobic drugs, so to summarise, we need to be able to figure out their optimal hydrophobicity and hydrophilicity, so that we can achieve the desired properties.

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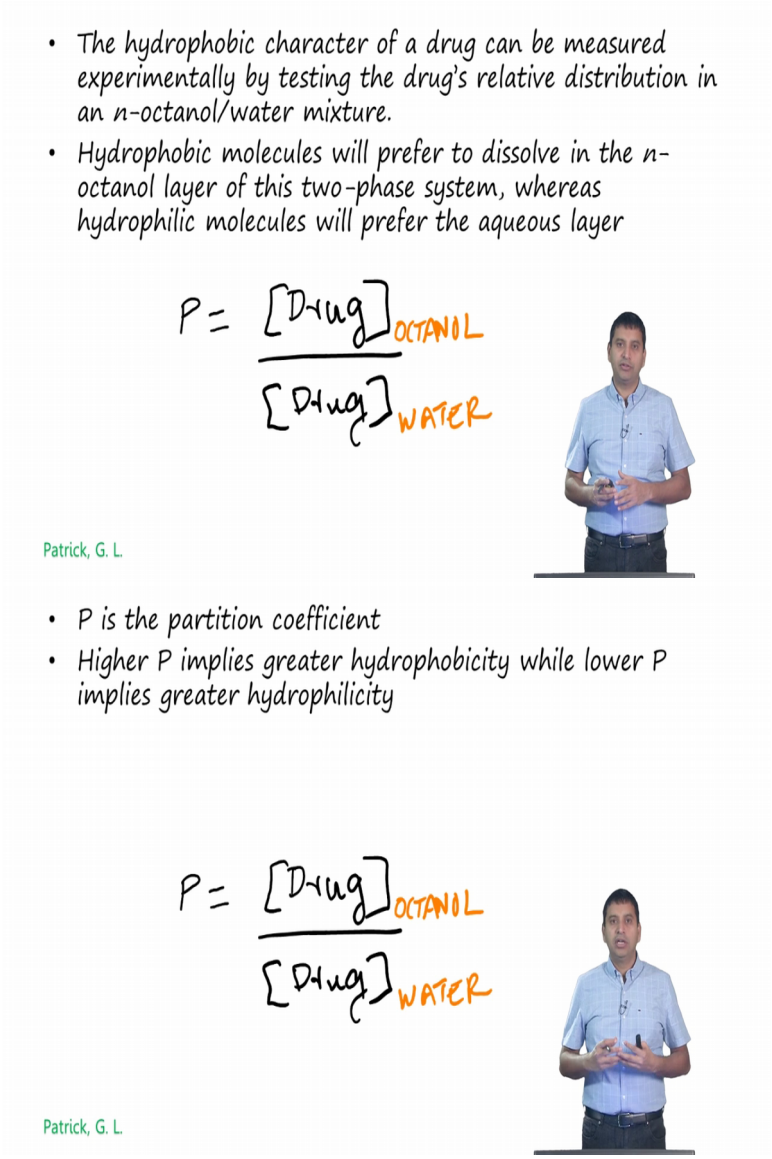

Now the hydrophobic character of a drug can be measured in anyways, one of the ways to do it is to have a mixture of n-octanol and water, so when you have this mixture these are immiscible liquids and therefore they going to form a layer that means it will have n-octanol layer and the water layer, now when you add your compound to this, the compound will either dissolve completely in n-octanol or if it is equal soluble it may completely dissolve water or there may be some part of the molecule, which will dissolve in water and some part of the molecule that will dissolve in the octanol layer.

So therefore we can define this parameter P which is nothing but the concentration of the drug in the octanol layer divided by the concentration of the drug in water layer, so this P is called as the partition coefficient, so if you imagine that the number P is very large, that

means that the concentration of the drug in the octanol layer is significantly higher than the concentration of the drug in the water layer, which would imply that the molecule essentially dissolves in octanol compare to water, which again suggest that because octanol has eight carbon in its chain, it implies that the molecule is preferentially binding to octanol which would suggest that there would be greater hydrophobicity, as a corollary, the lower the value that means the higher the concentration of the drug in water, it would mean that the molecule is more hydrophilic.

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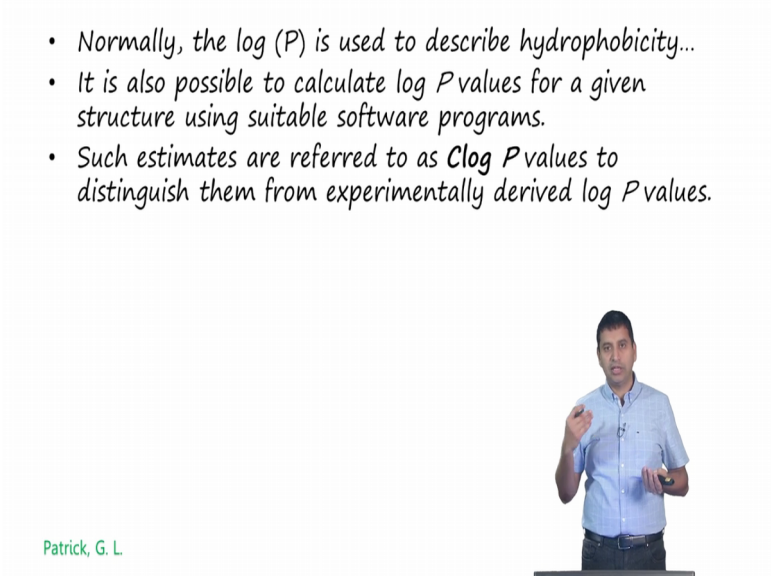

Normally we use this term called as log P which is used to describe the hydrophobicity, we can also calculate log P, by using some software programs and these are reference to as Clog P because they are called as a calculated log P values, now, so therefore we can distinguish the experimentally derived log P values from the calculated now P values.

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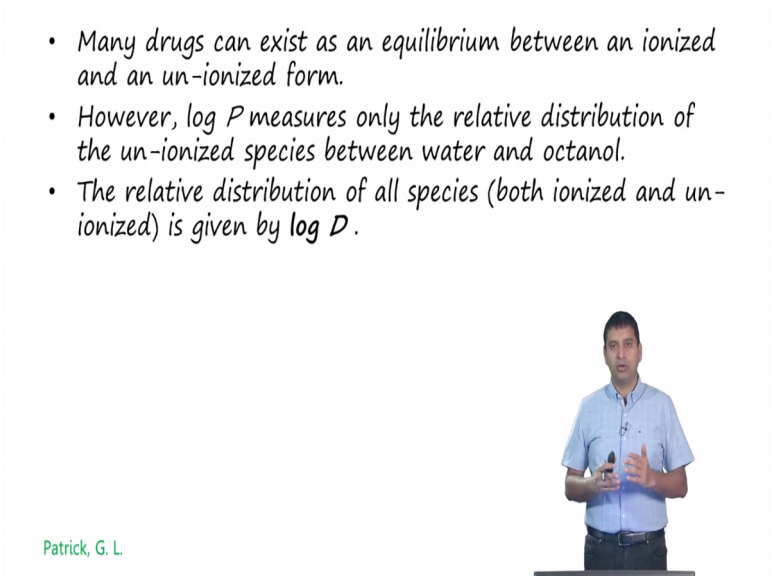

Now we have already looked at that many drugs can exist as an equilibrium between an ionized and un-ionized form, for example, you have a amine, it can be protonated and it will form exist as an ammonium ion and so you will have this equilibrium between these two, so log P measures only the relative distribution of the un-ionized species because we are taking water, but if you take buffer instead of water, then you will be able to determine what is known as a log D which gives us an idea about how it partitions into octanol and buffer during the dissolution process.

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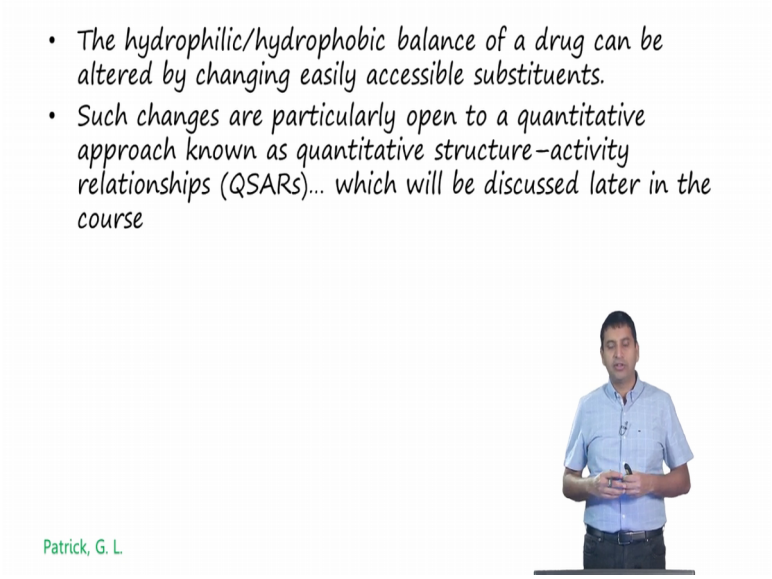

So the hydrophobic, hydrophilic balance in the altered by changing accessible substituents, so such changes are particularly open to what is known as a quantitative approach because we

can start looking at systematically how the values can be changed and how the partition can be modified and such an approach is known as the quantitative structure activity relationships, which will discussed later in the course.

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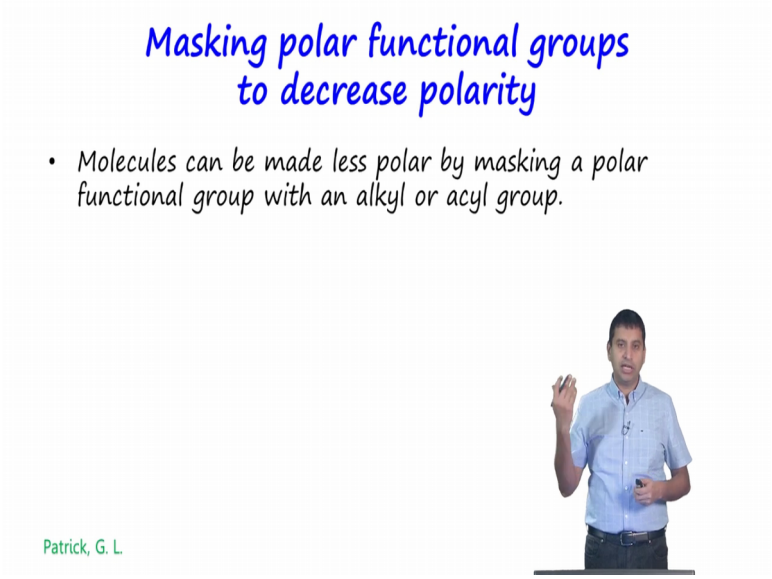

Now we have looked that the case where you are able to determine the log P value by looking at the partition between octanol and water, but you can also, once you determine this, let say you will find that the molecule is too polar, then you may want to decrease the polarity, so the way in which you want to decrease the polarity is you have to mask the polar functional groups, so the polar functional group, for example an alcohol can be masked by making it into an astom, like a asyl ester for example, you can remove the functional group altogether and put an alkyl group as we know that the alkyl group contributes to hydrophobicity significantly.

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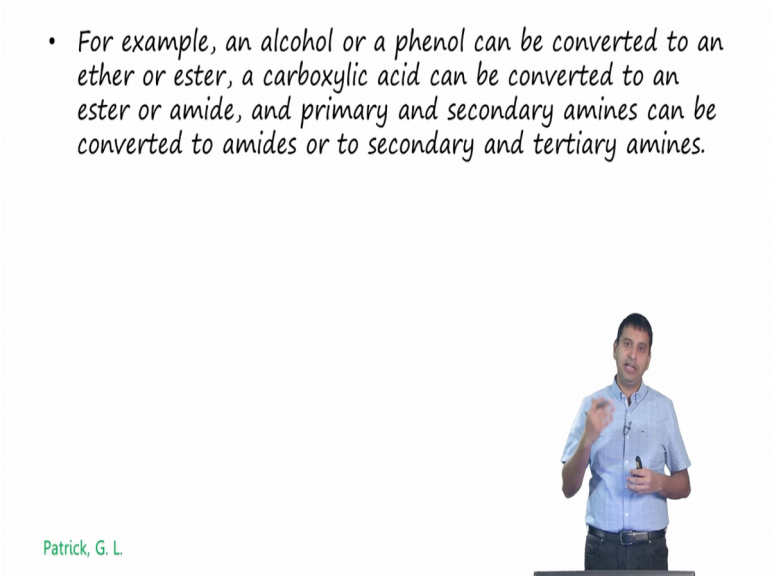

So an a phenol or an alcohol can be converted to an ether or an ester or a carboxylic acid can be converted to an ester or amide because carboxylic acid is likely to exist in equilibrium as carboxylate and so therefore by make it into an ester or amide you are going to reduce the polarity of the molecule, similarly primary or secondary amines can be converted into amides or to secondary and tertiary amines by adding more alkyl groups.

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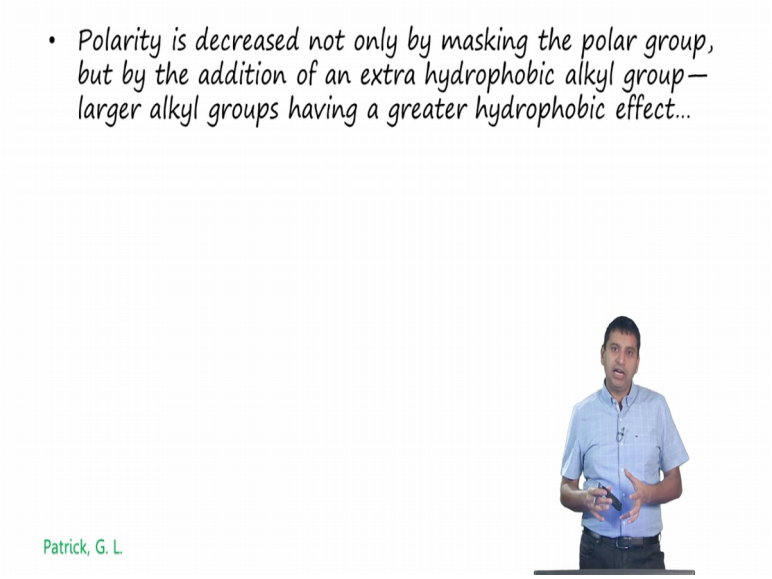

Polarity is not only by masking the polar group, but by also by adding extra hydrophobic alkyl groups, so the larger the alkyl groups that we had, the greater the hydrophobic effect.

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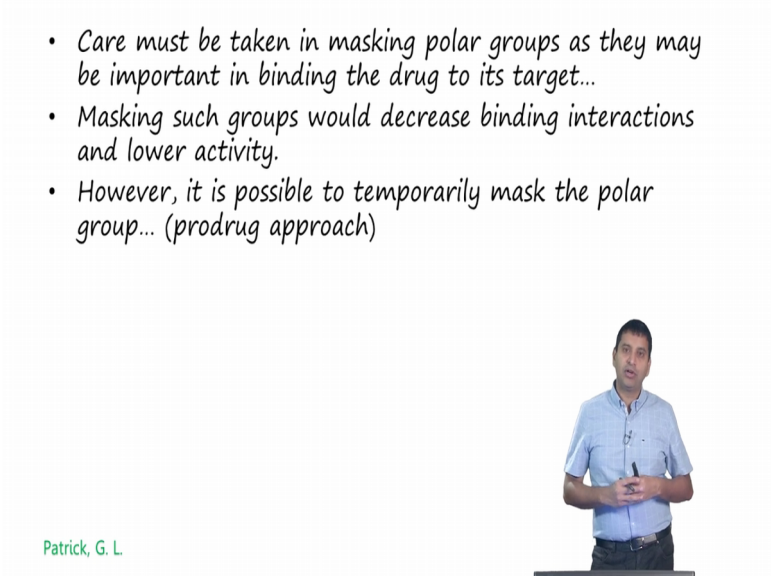

Of course a can must be taken in masking this polar groups because it may be important in binding to its target, so masking such groups would then decrease the binding interactions and it would defeat the purpose of doing this modification, however, it is also possible to temporarily mask this group, so you put this group on for some time and after sometime the group is cleaved and then it presents itself to the target and it can interact better, such an approach is called as the proddrug approach.

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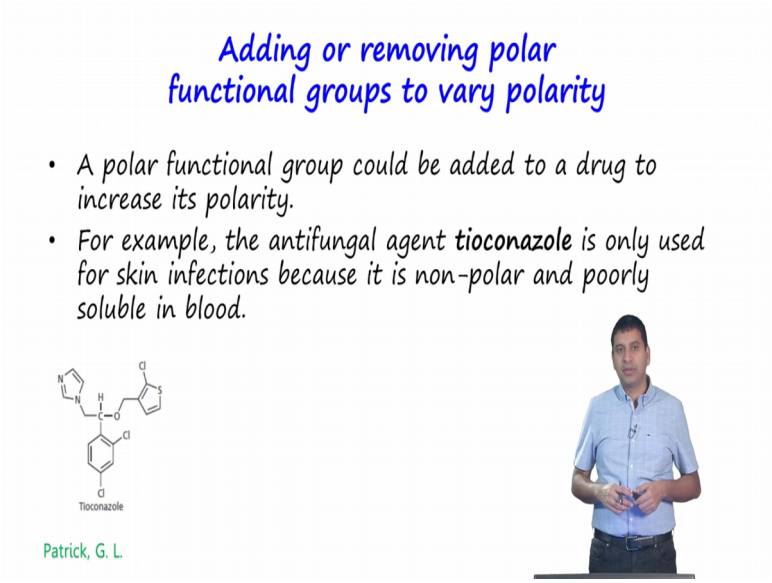

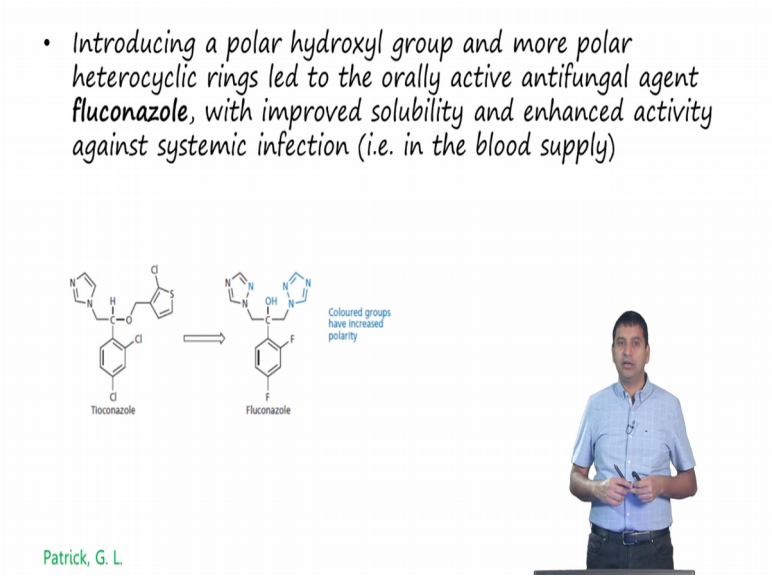

Now you can also add or remove polar functional groups to very polarity, so a polar functional group can be added to increase its polarity, so for example this molecule, which is an antifungal molecule is not used because it is non-polar and poorly soluble in blood, so what was done was to convert it to a more polar subsequent, this molecule is known as a fluconazole and this can be used as an antifungal agent which leads it to make it orally bioavailable molecule and it also has an enhanced infection against systemic that is in blood supply infections, so the change we make here is to convert heterocyclic ring on the left to try nitrogen ring on the right.

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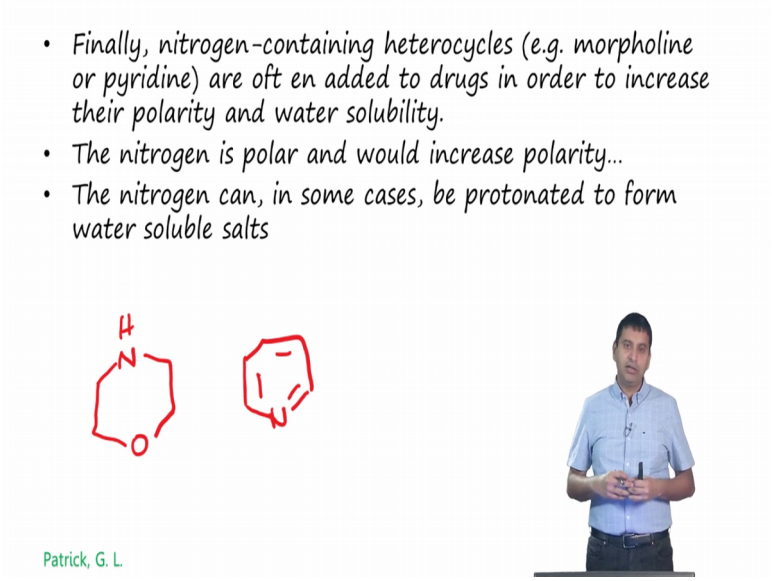

Finally nitrogen-containing heterocycles, such as morpholine or pyridine are often added to drugs to increase their polarity, so morpholine is a structure shown, which has oxygen and a

nitrogen in the ring and this greatly increases the polarity, so because the nitrogen is polar and so you going to increase a polarity, but also nitrogen can be protonated and it will form a water-soluble salt.

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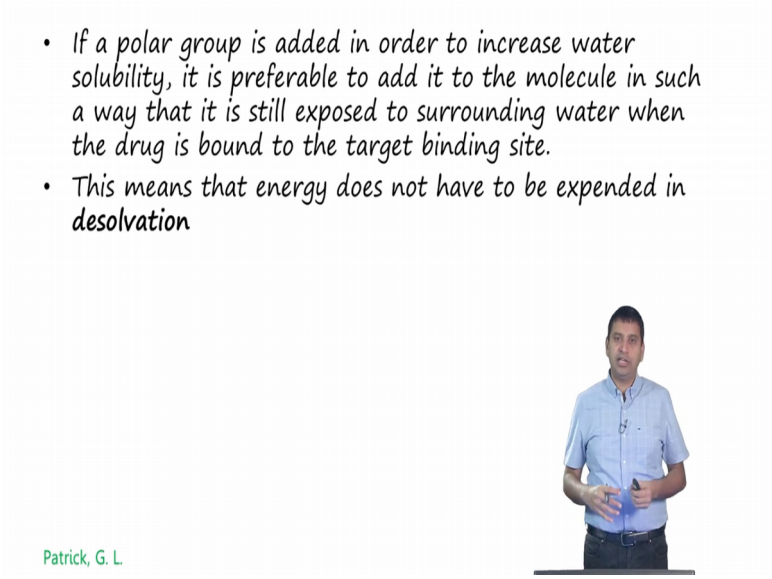

If a polar group is added in order to increase the water solubility, it is preferable to add eight to the molecule in such a way that it is still exposed to the surrounding water when the drug is bound to the target, so what this means is that the energy does not have to be expended in desolvation, so when the molecule goings binds to the target it has to get the rid of the water molecules and so this cost some energy, if you are putting the drug, you put it in a place where it does not hamper this interaction so that desolvation is not a problem.

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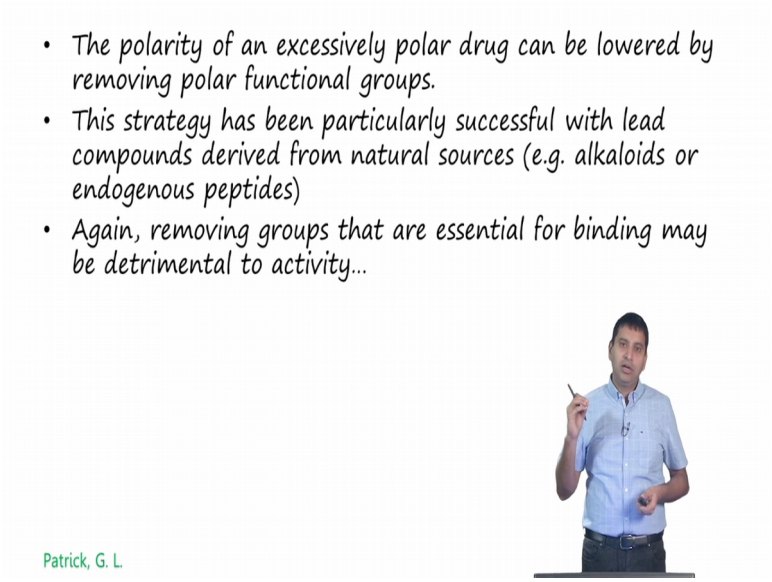

The polarity of an excessively polar group can be lowered by removing polar functional groups, now we can use this very much in modifying a lead compound they had from natural sources, which are typically alkaloid or peptides, so all of these have many polar functional groups, so we can remove somehow this polar functional groups to reduce the polarity, now of course we need to keep in mind that we need to be able to remove the groups only the groups which are not important for activity.

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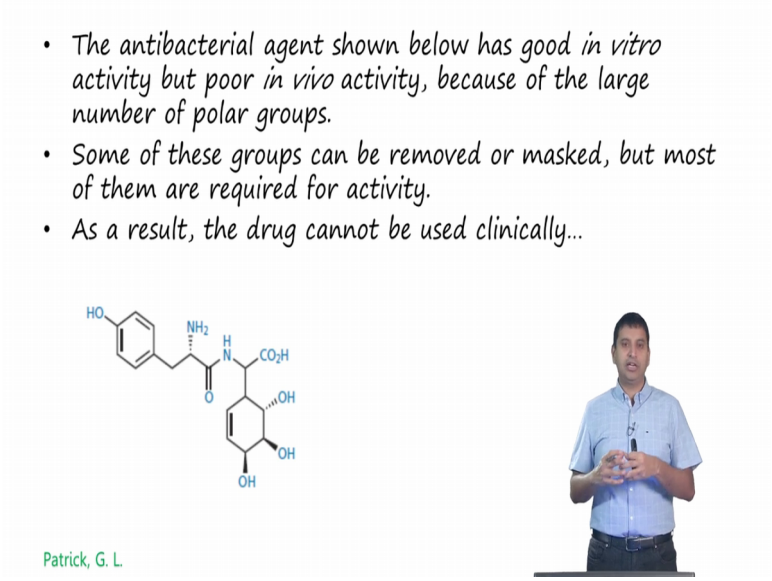

So the antibacterial agent which is shown below has good in vitro activity, but it has very poor in vivo activity and this is because of the large number of polar groups, so some of these groups be removed or masked, so if you see the structure, it has a number of carboxylic acids and alcohols and it also has a phenol, so on the whole the molecule is quite polar, so we cannot use this molecule in clinically because this is going to be a problem, so one approach to improve this molecule would be to masked it in a way such that it is able to you administered and it is able to reach the target and perhaps before it reaches the target we can un-masked the polar groups.

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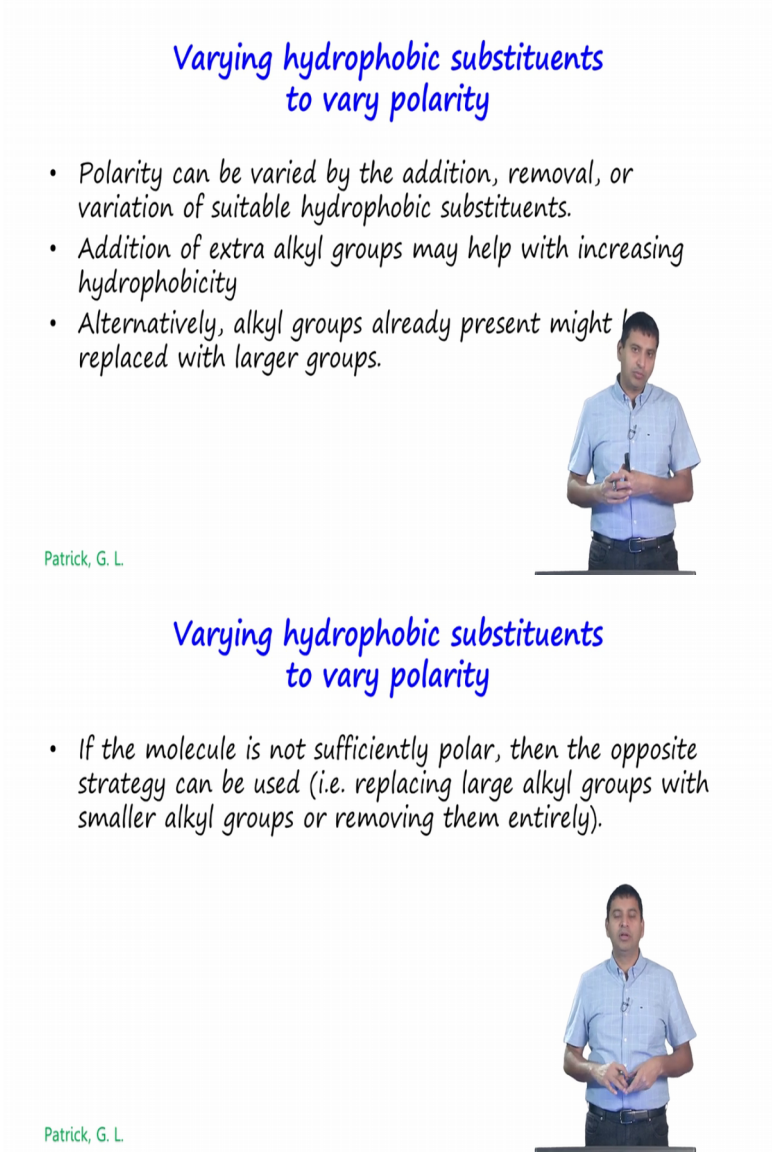

The next approach is to be able to any the hydrophobic substituents to very polarity, so polarity can be varied by addition, removal or variation of hydrophobic substituents, so the alkyl group that you added will help with increasing hydrophobicity, the alkyl group already present can also be replaced with larger groups, if you have an isopropyl group can you can converted to a tertiary butyl group or a neopentyl group and so on, if the molecule is not sufficiently polar than the opposite strategy can be used that is be replaces large alkyl groups with the smaller alkyl group or removing them altogether.

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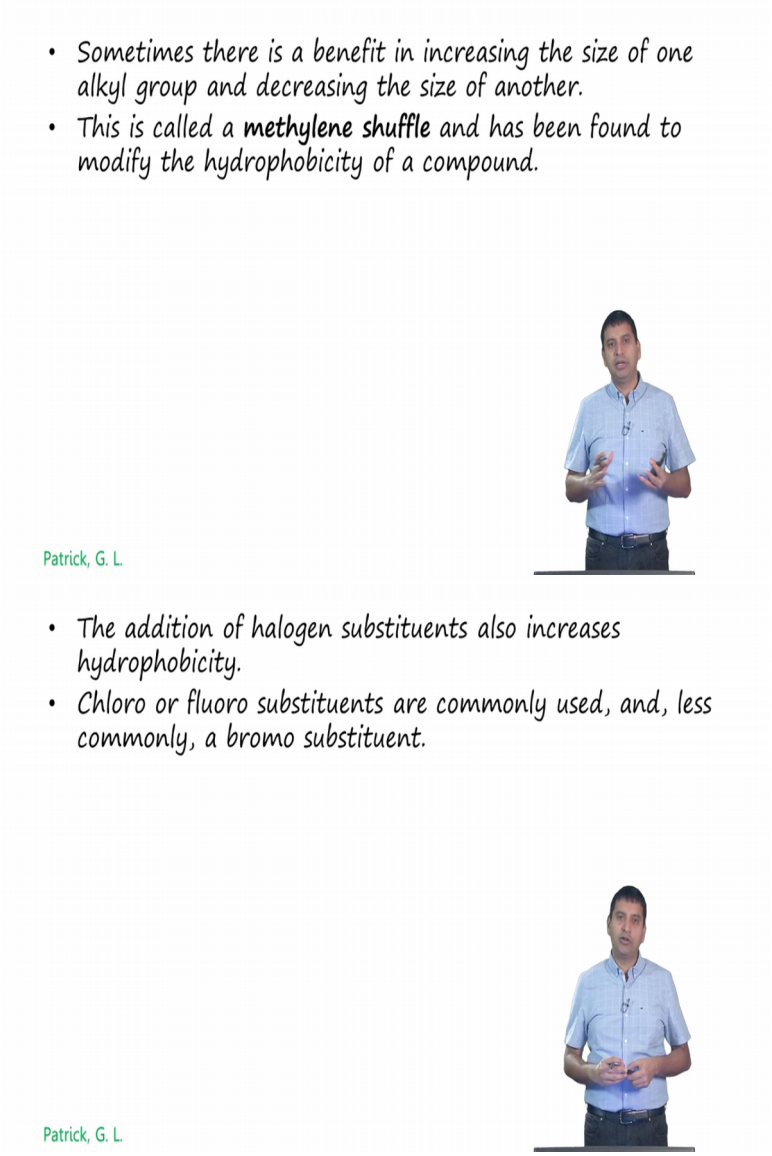

Sometimes there is a benefit in increasing the size of one of the alkyl groups and decreasing the size of the other, so this is known as methylene shuffle and it is been found to modify the hydrophobicity of a molecule, the addition of halogen substituents also increases hydrophobicity, so in many cases chloro or fluoro substituents are commonly used and far less commonly is to use a bromo substituent.

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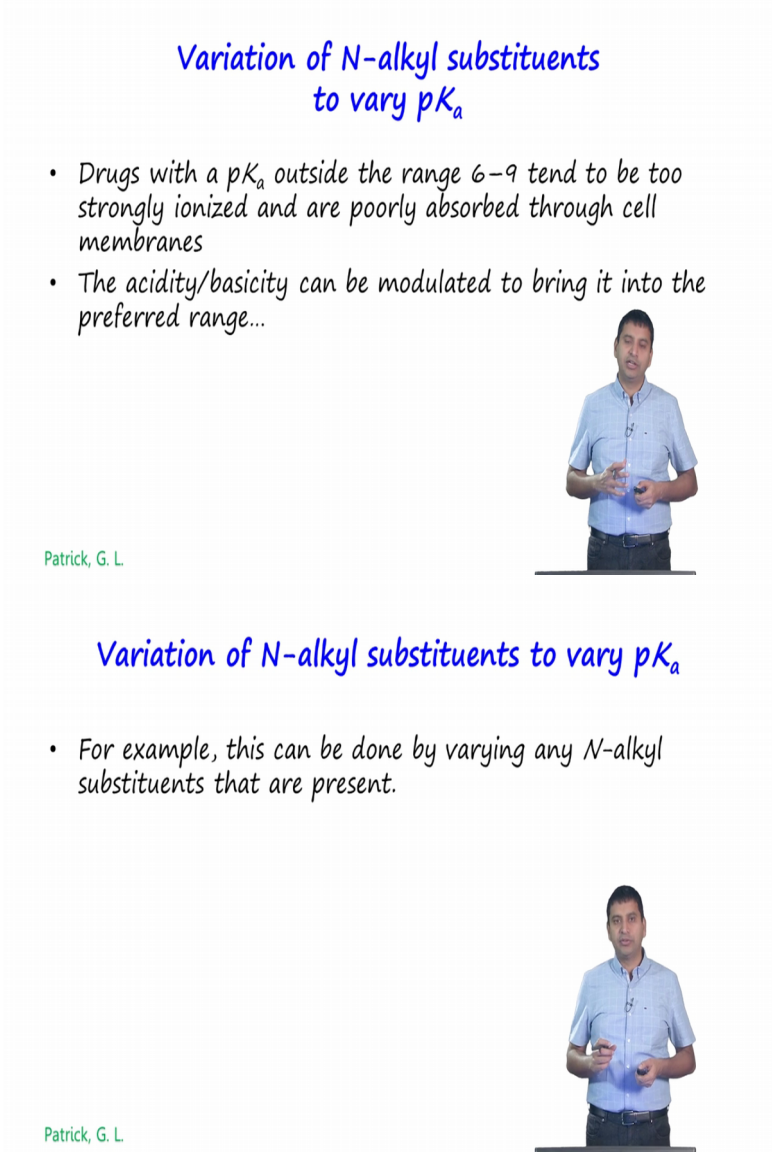

Next we can change the n-alkyl substituents to very PKa, so drugs with their PKa, outside the range of 6 to 9 are considered either strongly ionized and therefore they are poorly soluble or absorbed through the cell membrane, so we have again looked at a number of such case studies previously, so now by changing the alkyl substituent, we can then what you read the acidity or basicity and bring it into the preferred range, so can do this by varying the alkyl substituent that are present.

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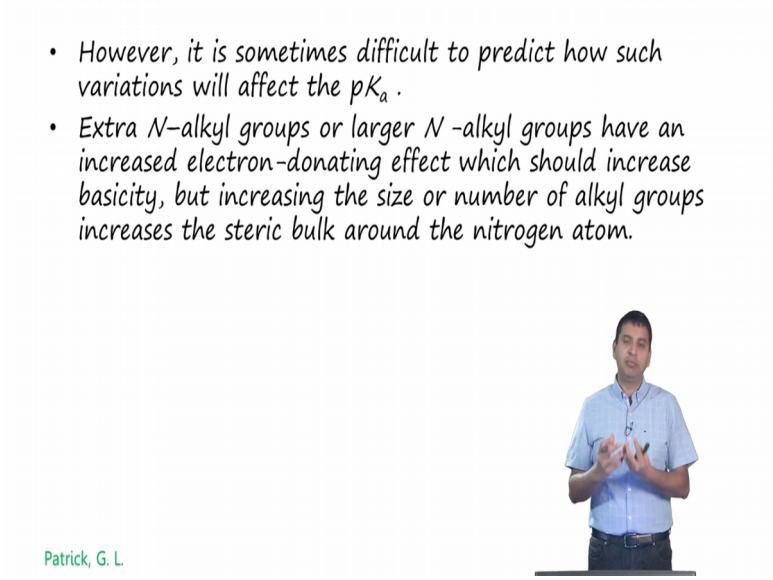

However, it is sometimes difficult to predict how such variations will affect PKa, so for example when you add an extra methyl group or an alkyl group to an amine because of the electron donating the effect of the alkyl group, the basicity will increase, but you are also increasingly the steric bulk around the nitrogen, so therefore the ability of the lone paired to interact with a proton also goes down, so this sometimes can have opposite effects and therefore it makes it a little bit unpredictable as to what will happen.

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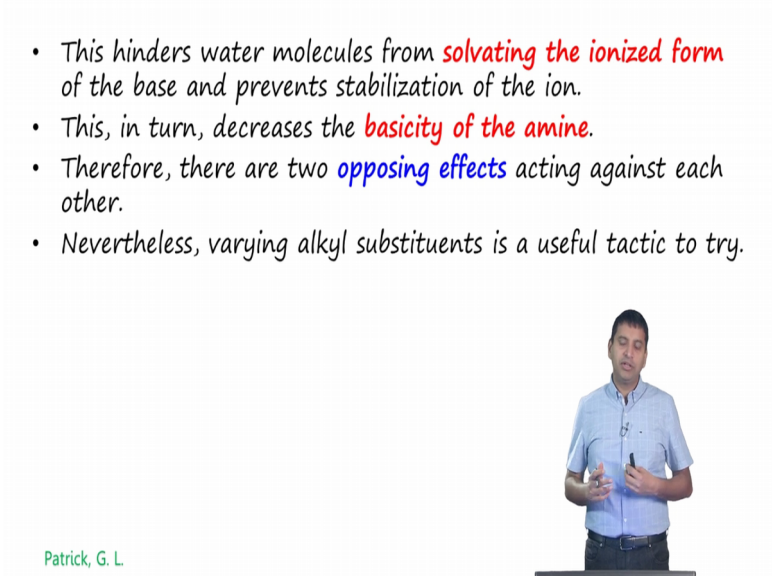

So because you are going to do this, it will hinders the water molecules from solvating the ionized form of the base and it prevents stabilization of the ion and this in turn decreases the basicity of the amine, so nevertheless varying alkyl substituents is a useful tactic to try.

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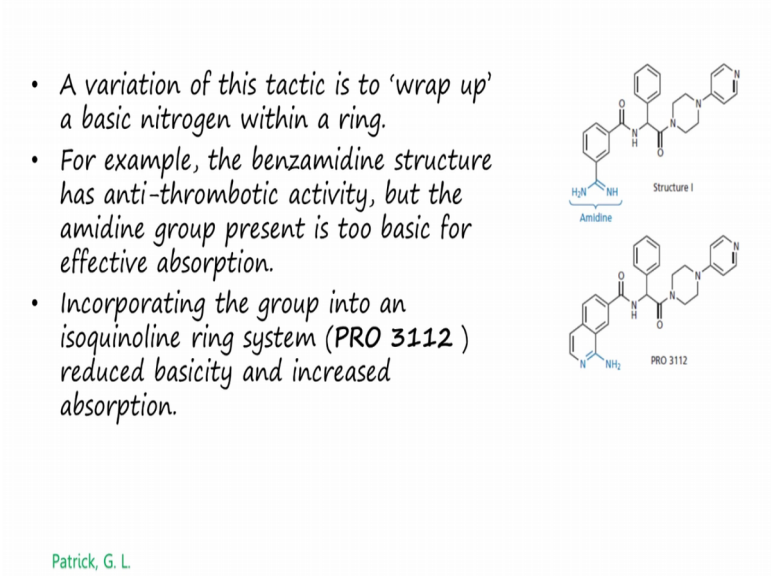

A variation of this tactic is called as the wrap up, here what we do is we wrap up a basic nitrogen within a ring, so if you have an aromatic ring to begin with, then what we could do is to convert this aromatic ring into a pyridine ring so that you can make it into a more polar group, now for example in the benzamidine structure which has anti-thrombotic activity which is structure one but the amidine group is too basic for effective absorption, so what we do is to convert this amidine group into a pyridine group, it is compound which is known as PRO 3112 has reduced basicity and much better absorption.

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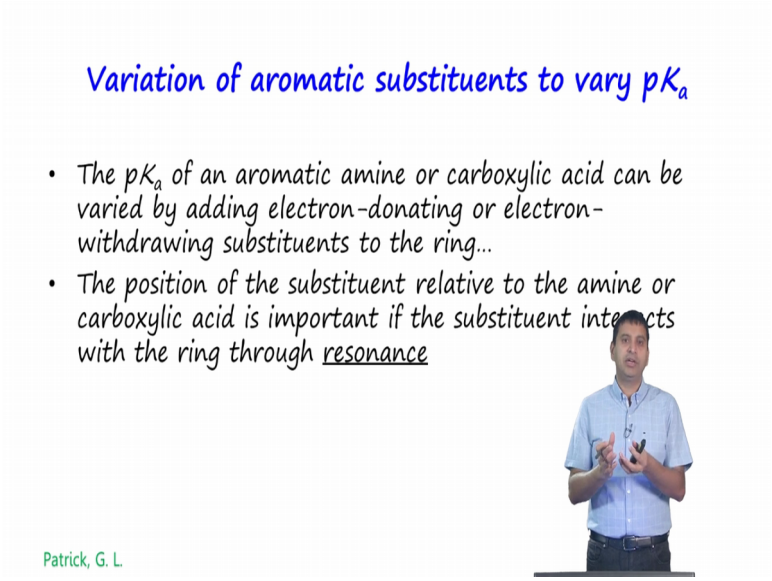

Aromatic substituents can also be varied to change PKa, so PKa of an aromatic amine or carboxylic acid can be varied by adding electron donating or electron withdrawing

substituents, so the position of the substituent relative to the amine or carboxylic acid is very important in determining if the subsequent interacts with the ring through resonance.

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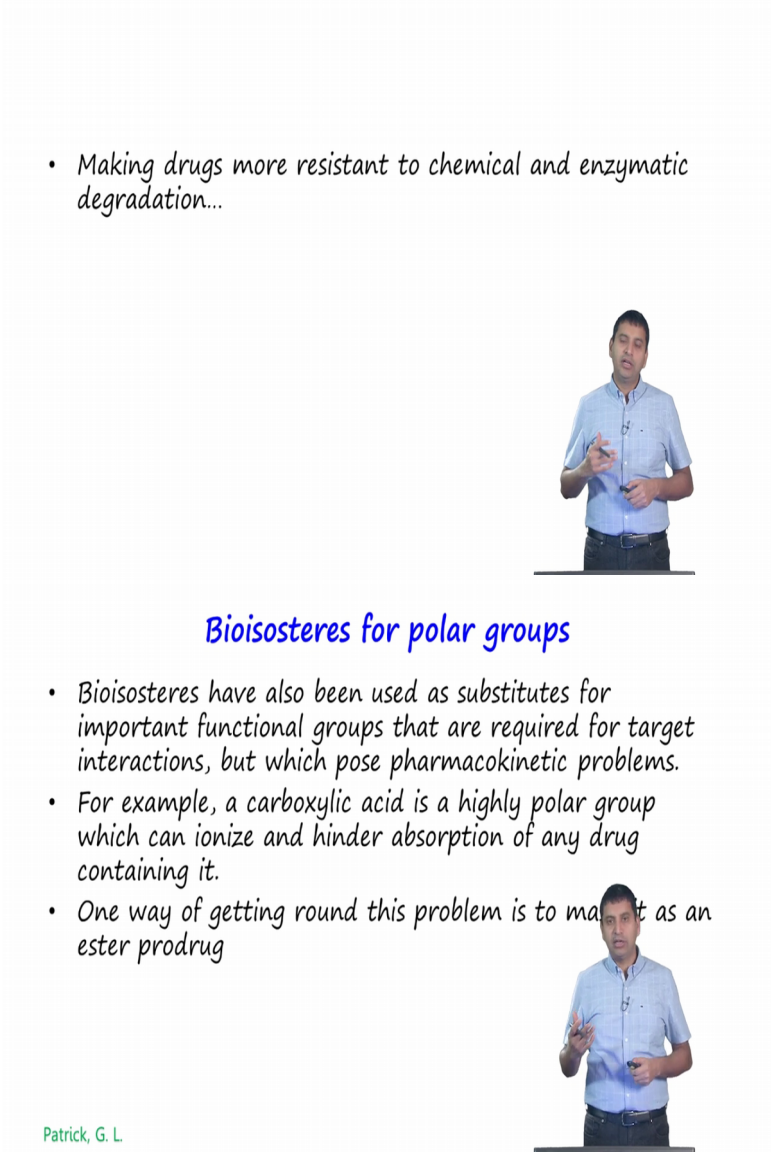

Now bioisosteres are used for polar groups, so bioisosteres which we have looked at previously have been used as a substitute for important functional groups that are required for target interactions, but these pose pharmacokinetic problems, for example if you replaced carboxylic acid, which is a highly polar group, it can ionize and it can hinder absorption and you may need to replace this in order to address these points, so one way to address this is to masked as an ester prodrug, we looked at prodrugs later in the course.

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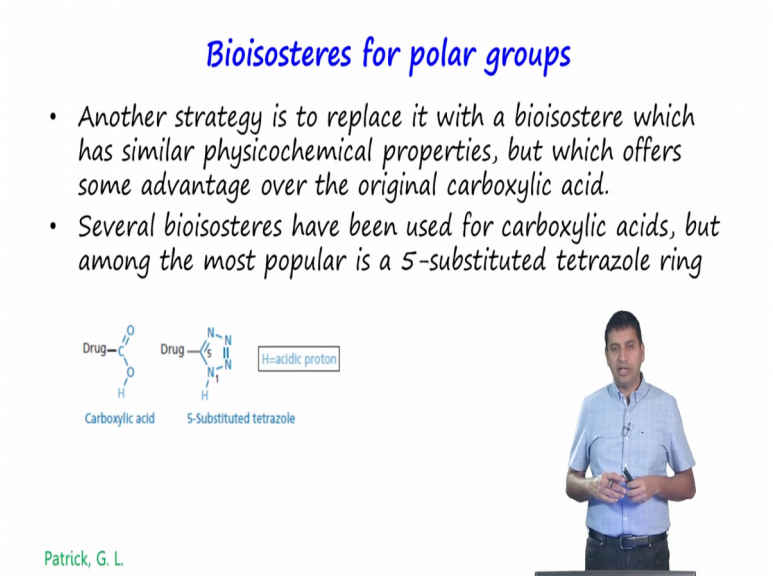

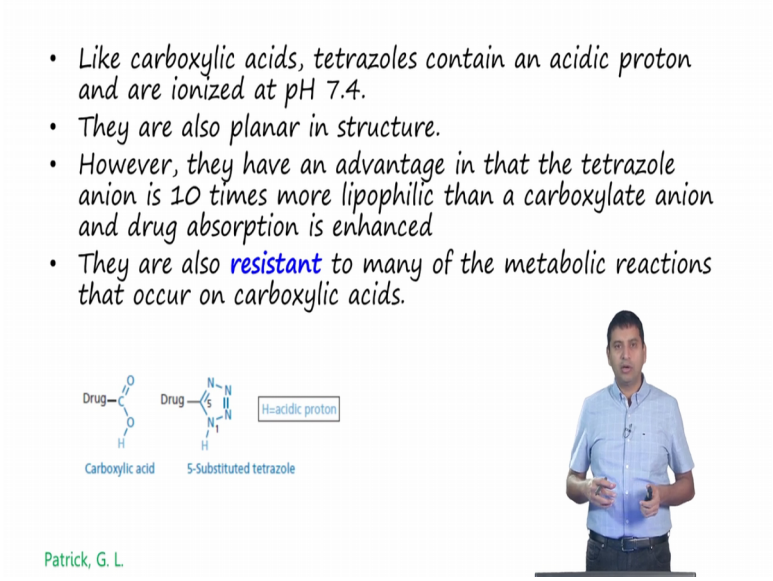

Another strategy is to replace it with a while bioisostere which has a similar physicochemical properties, but which offers the same advantage over the original carboxylic acid, so here for example this carboxylic acid can be replaced with this that tetrazole ring as shown here, so like the carboxylic acid the tetrazole ring contain an acidic proton and its ionized at pH 7.4 but there also planar in structure, however, they have an advantage that the tetrazole is 10 times more lipophilic than a carboxylate anion and so therefore the drug absorption is enhanced, there also quite resistant to many of the metabolic reactions that can occur on carboxylic acids.

So making drugs resistant to chemical and enzymatic degradation is the next in which we can help the drug get to its target.

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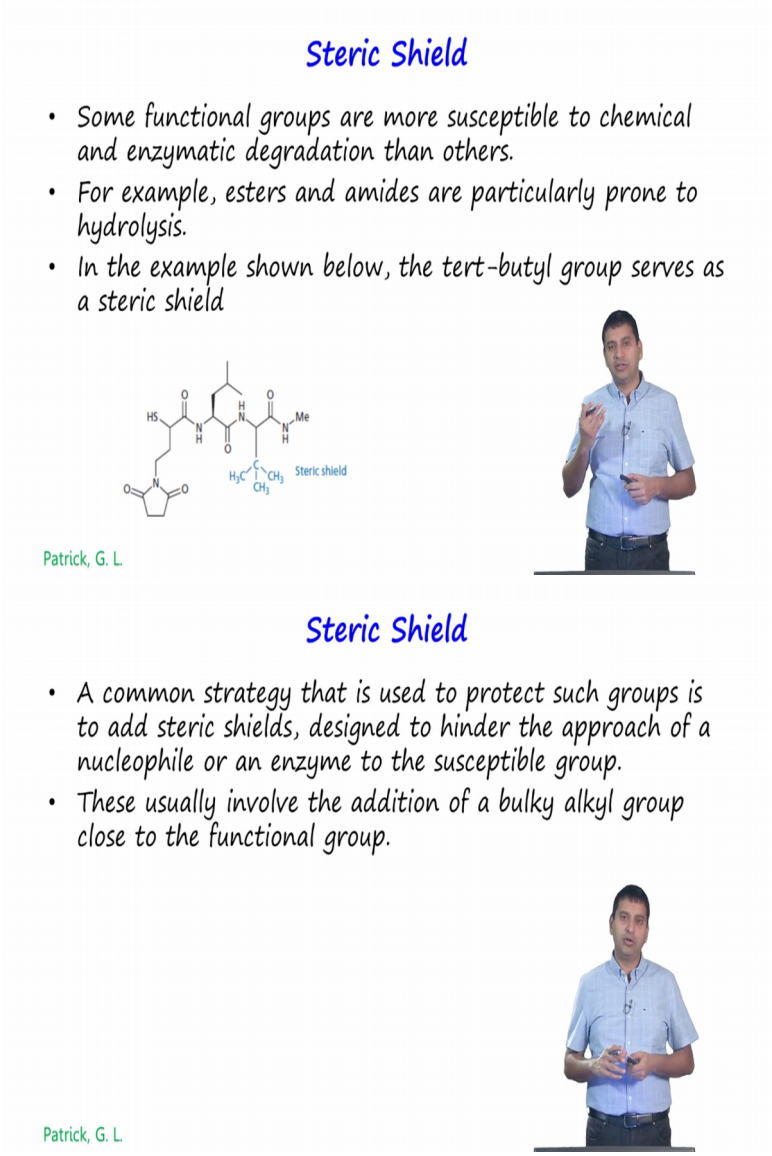

So one way to do this is to introduce what is known as a steric shield, so some functional groups are more susceptible to chemical and enzymatic degradation than others, so for example asters and amides are particularly prone to hydrolysis, in the example shown below we have added tertiary butyl group next to an amide to prevent its physile hydrolysis.

Another common strategy that is used to protect such group is to add steric shields, designed to hinder the approach of a nucleophile or an enzyme to the susceptible group, so these usually involves the addition of a bulky alkyl group close to the functional groups, like we have added this tertiary butyl group next to the amide.

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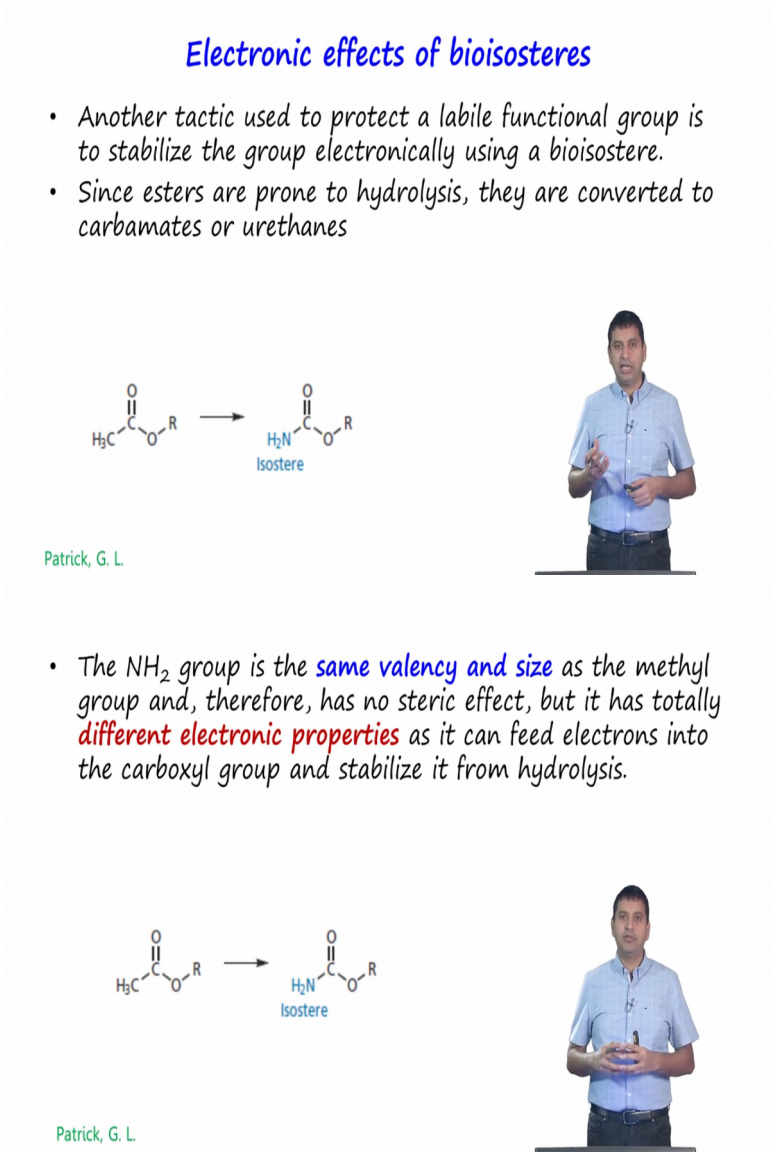

The other way in which we can do this is to exploit the electronic effects of bioisosteres, so what we can do for an example is that esters are prone to hydrolysis and they converted to carbamates or urethanes, so here we have replace the methyl group with an NH2, which is an isostere, the NH2 has the same valency and size, but it has no steric effect and it has very different electronic properties and therefore what it does is it is an electronic donating group, it stabilizes it from hydrolysis.

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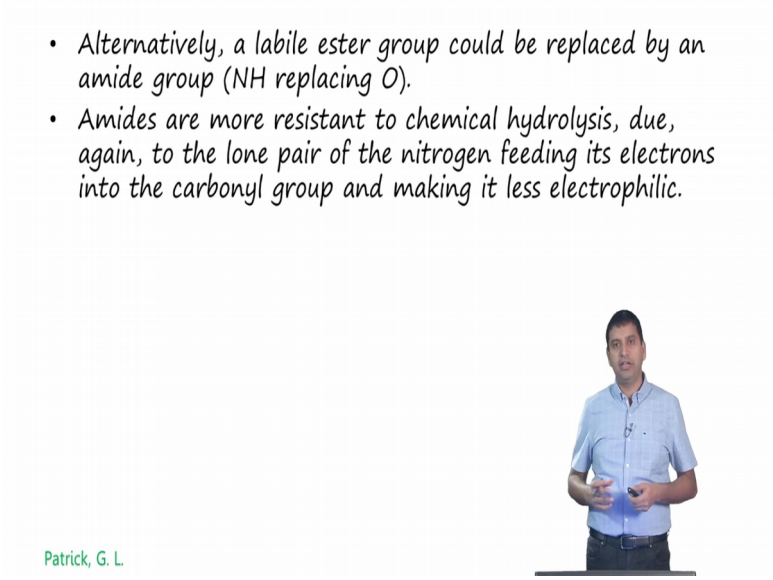

Alternatively a labile ester group can also be replaced by an amide, which is converting an oxygen to an NH, amides are significantly more resistant to hydrolysis compared to esters, again, this is the same effect because nitrogen can read its lone pair into the carbonyl.

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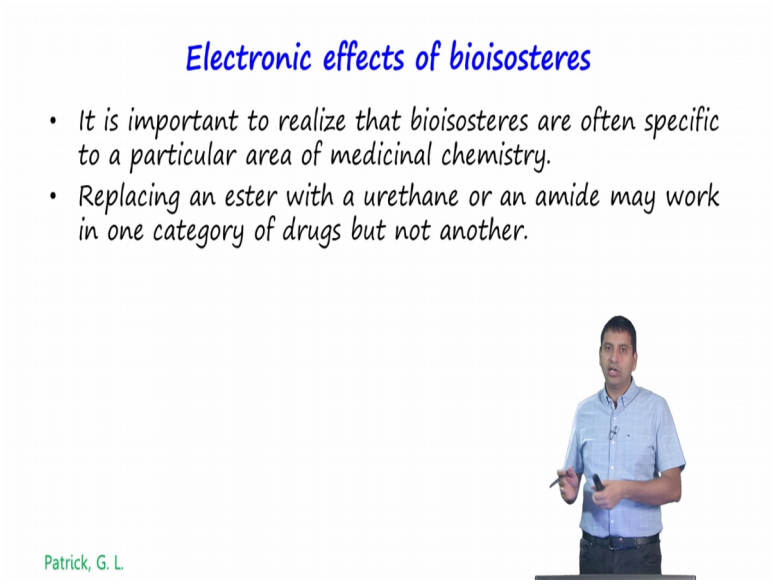

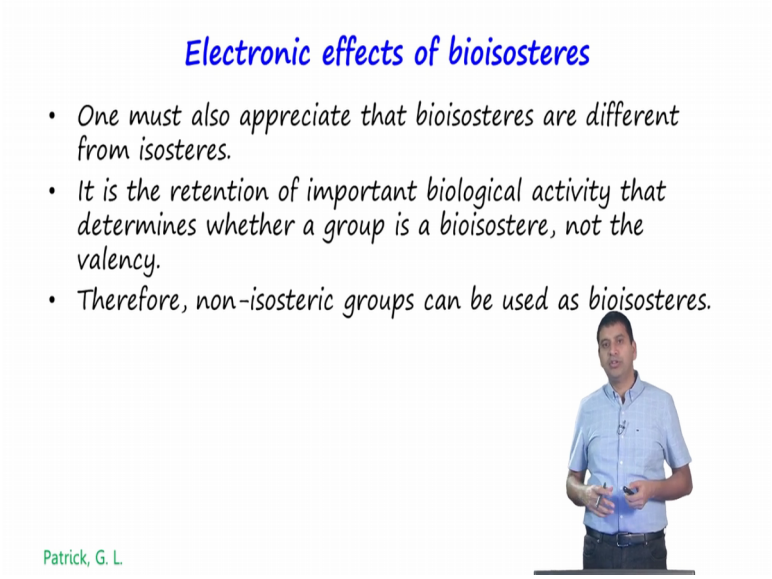

It is also important to realize that bioisosteres are often specific to a particular area of medicinal chemistry, so for example replacing an ester with a urethane or an amide may work in one category of drugs, but it may not work in another category, also one must appreciate that bioisosteres are different from isosteres, so because an isosteres have the same valency one could vary this property in a predictable manner. But in case of bioisosteres we do not particularly have this valency condition and therefore they can be varied based on other parameters, so it is the retention of the important biological activity that determines whether a group is a bioisostere or not, so non-isosteric groups can also be used as bioisosteres.

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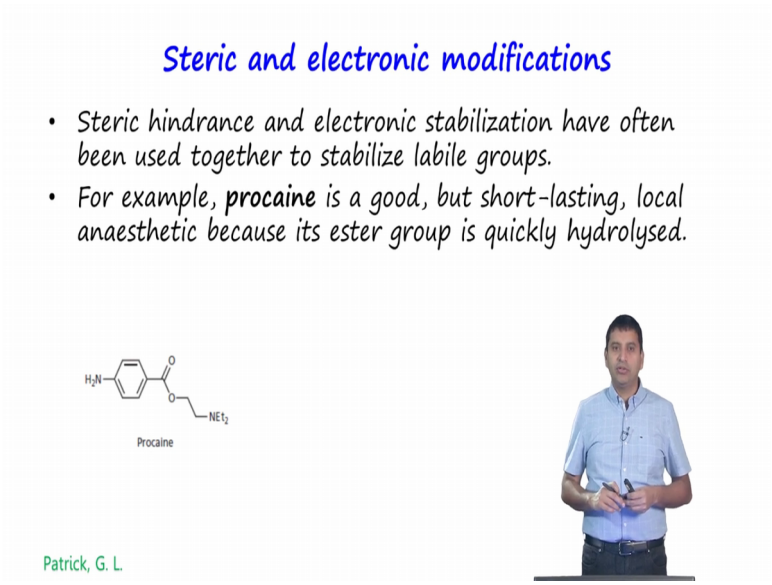

Steric hindrance and electronic stabilization have often been used to gather to stabilise labile groups, so here is an example of procaine, which is a good but it is a very short lasting local anaesthetic that is because it has an ester that can be hydrolysed.

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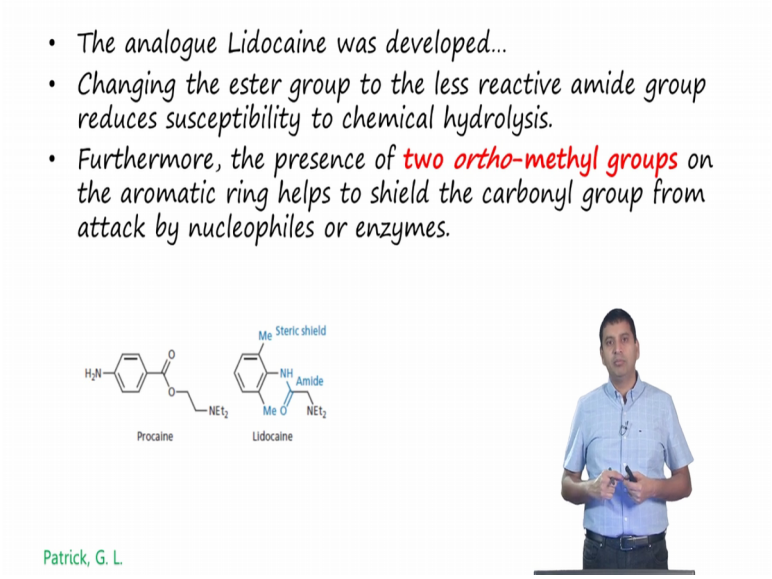

The analogue lidocaine, which was developed has far improved properties, so what they have done here is to convert the ester to the less reactive amide group which reduces the susceptibility to chemical hydrolysis, they have also added two ortho-methyl groups on the aromatic ring which helps to shield the carbonyl group from attack by the nucleophiles.

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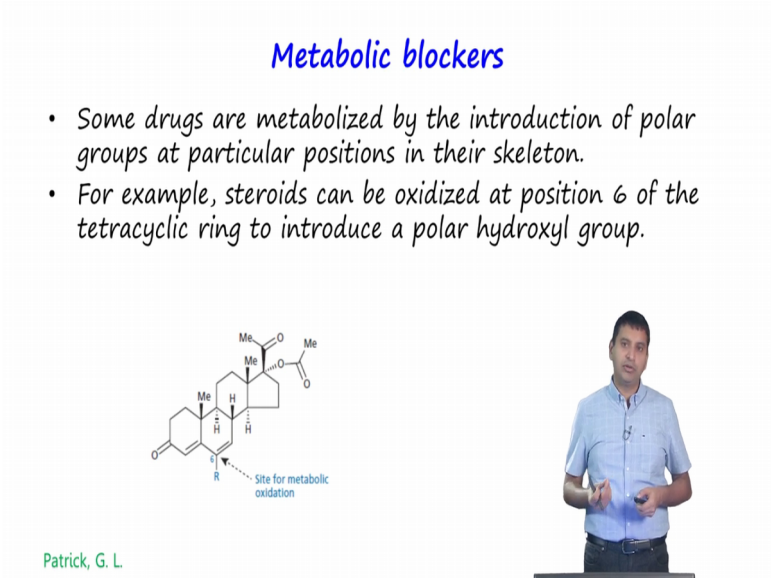

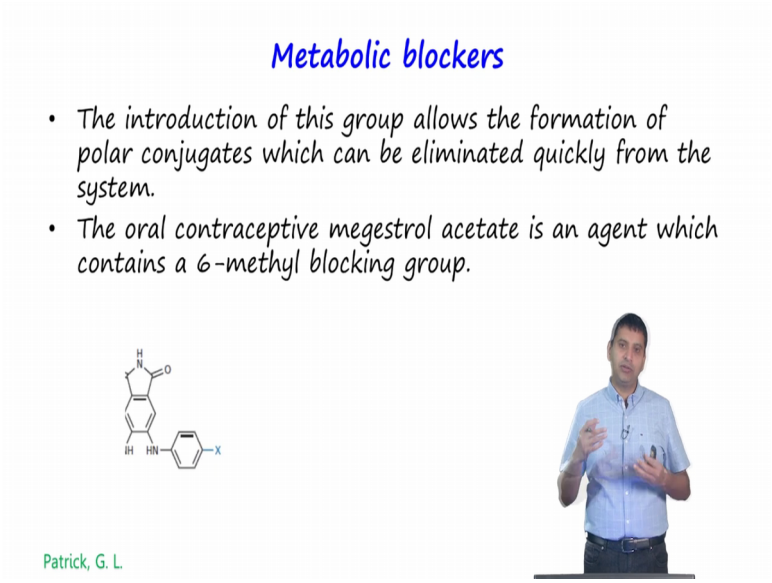

The next concept we are going to look at is a metabolic blockers, so some drugs are metabolized by the introduction of polar groups at particular positions in the skeleton, so for example, steroids can be oxidized at this position 6 as shown here of the tetracyclic ring and then what it does is it greatly increases the polarity because it introduces the polar hydroxyl group.

The introduction of this group allows the formation of polar conjugates, which can help with eliminating it quickly, so the oral contraceptive megestrol acetate is an agent which contains the 6-methyl group here, so here R is actually a methyl, so what it does here is to prevent the oxidation reaction, which greatly improves its properties.

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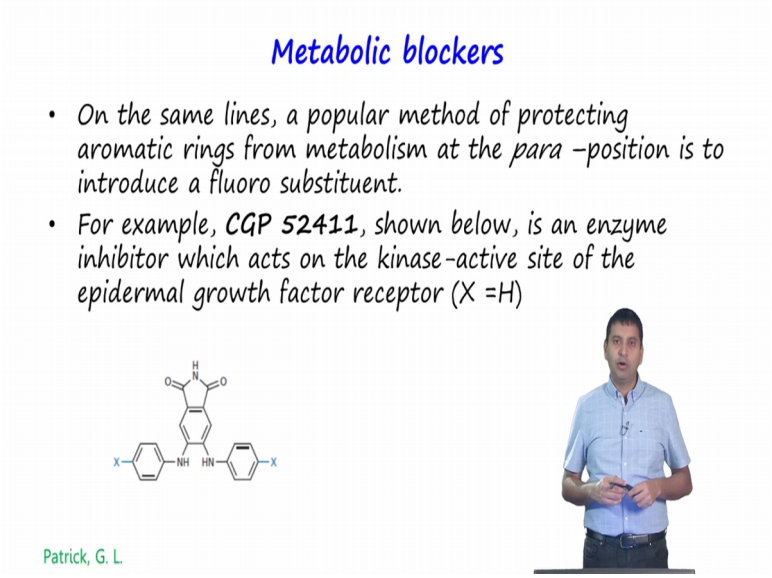

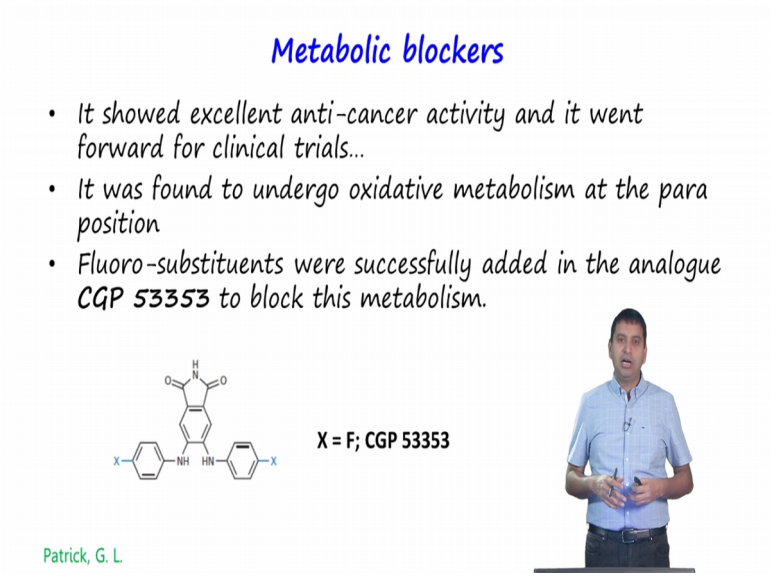

On the same lines, a popular method of protecting aromatic rings from metabolism at the para-position is to introduce a fluoro substituent, so in our previous ADME discussions we have seen that aromatic rings with a substituent on it are particularly prone to oxidization at the para-position, so what we can do is we can introduce a substituent in the para-position to prevent this from happening, so that example here is the CGP 52411 which is an enzyme inhibitor and acts on the kinase active side of a epidermal growth factor receptor.

So here X is hydrogen, but now when you replace X equals fluorine, then you have a pretty interesting molecule because it has the same anti-cancer properties of the same parent compound but it does not undergo the oxidative metabolism than the parent compound undergoes.

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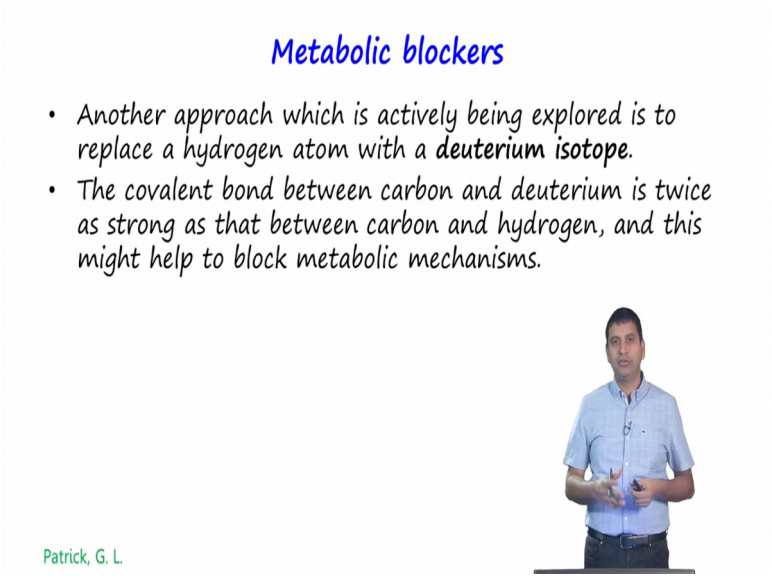

Another approach, which is being actively explored is to replace a hydrogen with deuterium, so we already know that from kinetic acidophilic that replacing a hydrogen with a deuterium is going to make the want stronger, so since the covalent bond is about twice as strong than this will help with reducing the metabolic reactions.

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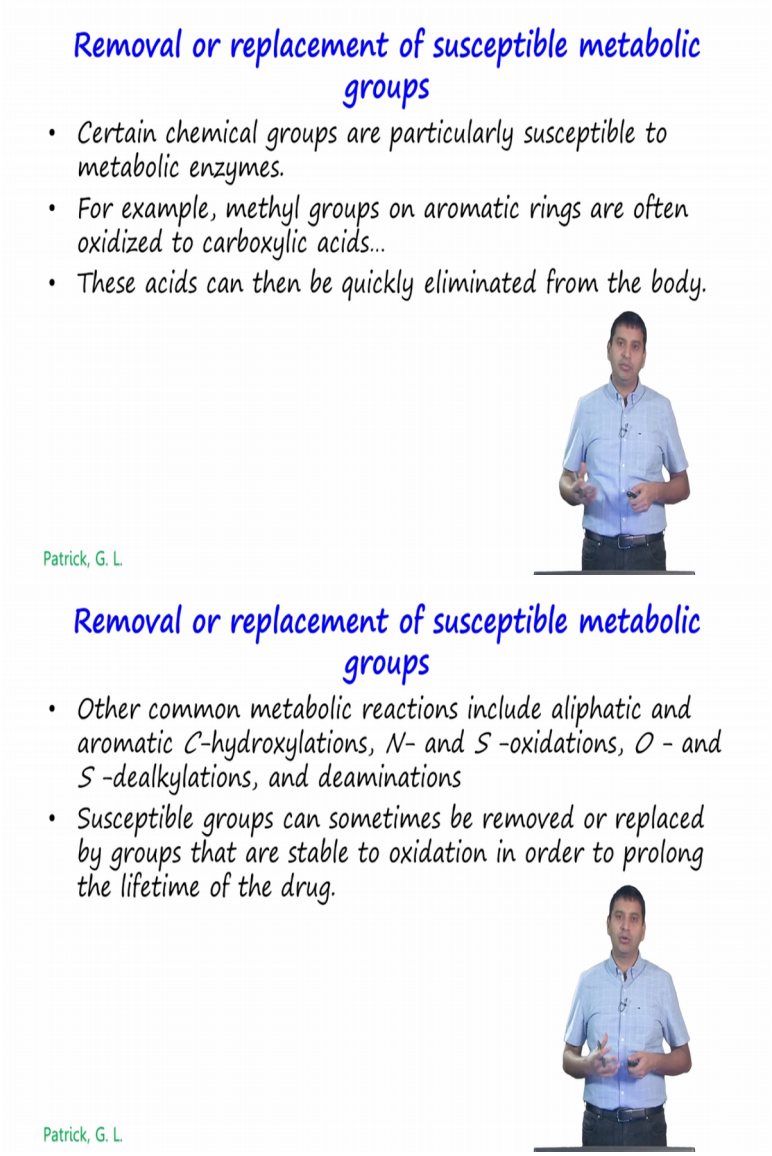

The next approach is to remove or replaced the susceptible metabolic group, so certain chemical groups are particularly susceptible to metabolic enzymes, so methyl groups on aromatic rings, for example, are oxidized all the way up to the carboxylic acid and once they are oxidized, this acids can be quickly eliminated from the body.

The other common metabolic reactions include aliphatic and aromatic C- hydroxylations, N or nitrogen or sulphur based oxidation that means convert amine to an N oxide, you can also have sulphur oxidations, sulphunic acids, sulphonic acids and so on, you can also have dealkylations which are next to hydro atom and deaminations, so these groups if they are not going be to important, you can actually remove them or replaced them by other groups which are not prone to oxidation.

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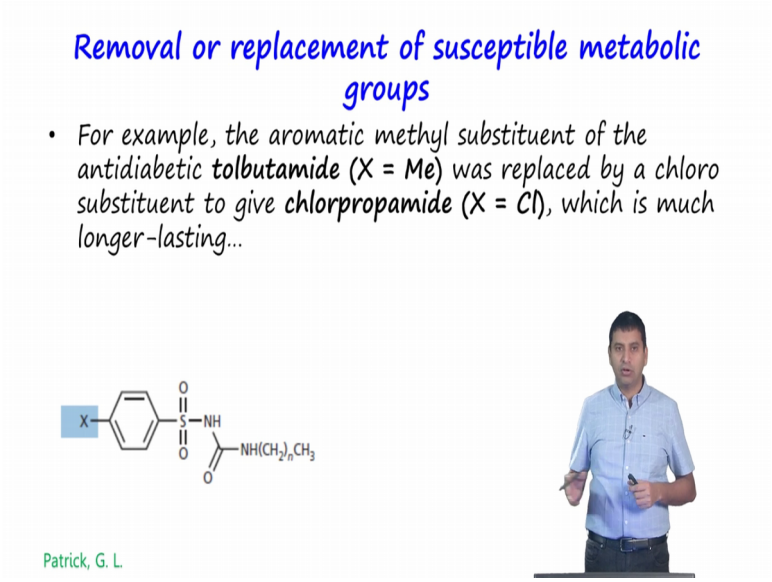

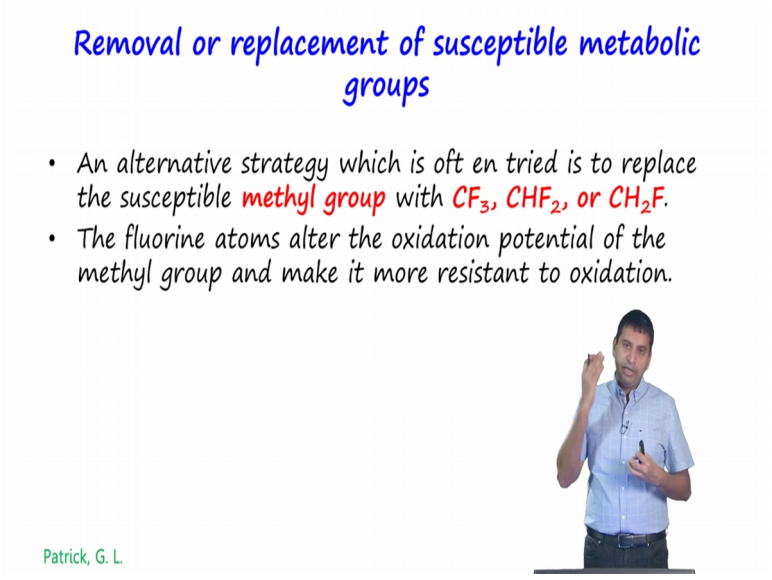

For example, the aromatic methyl substituent of this antidiabetic compound tolbutamide was replaced by a chloro substituent, which gives chlorpropamide, which is much longer lasting.

An alternate strategy which is often tried is to replace the susceptible metal group with a fluoro substituent, so you can have a CH2F or CHF2 or CF3 and this fluorine atoms alter the oxidation potential of the methyl group and made it more resistant to oxidation.

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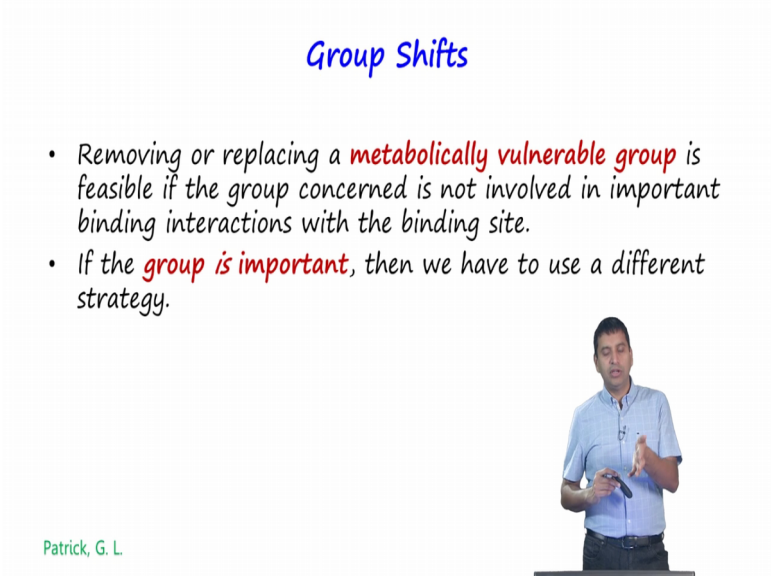

The next strategy that is used is called as group shifts, so removing or replacing a metabolically vulnerable group is feasible if the group concern is not involved in the important binding interaction, but let us assume that in this case that we have encountered that a group important, so what we have to do is we have to use a different strategy.

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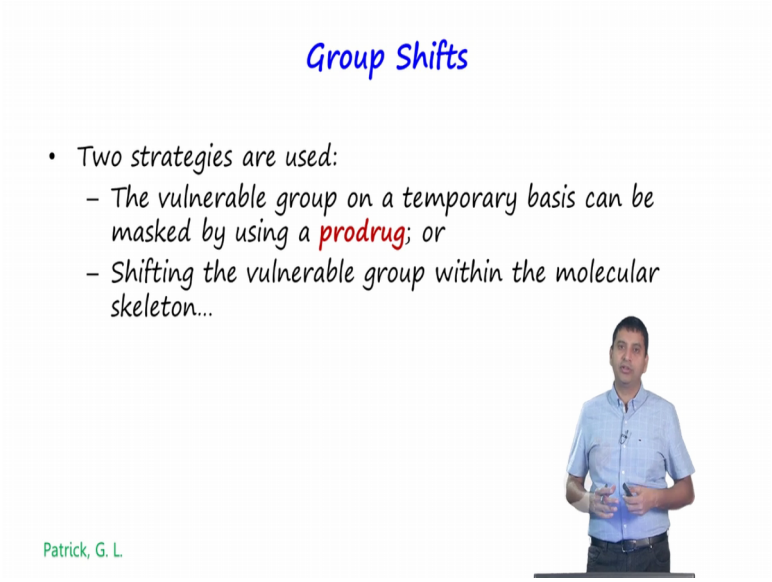

So there are two a broad strategies that are used which we have already discussed the first one, which is to convert into a prodrug, so we will look at in the subsequent lectures, but the next approach is to shift the vulnerable group within the molecule skeleton to reduce its metabolic reaction.

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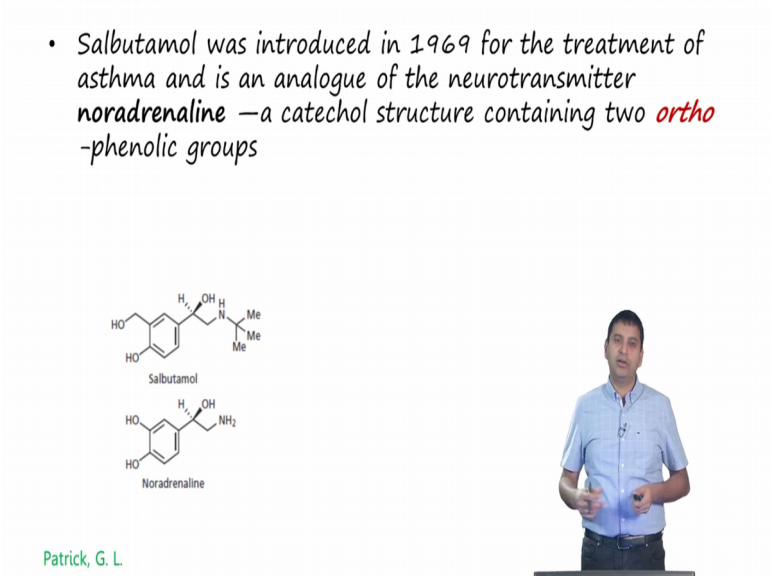

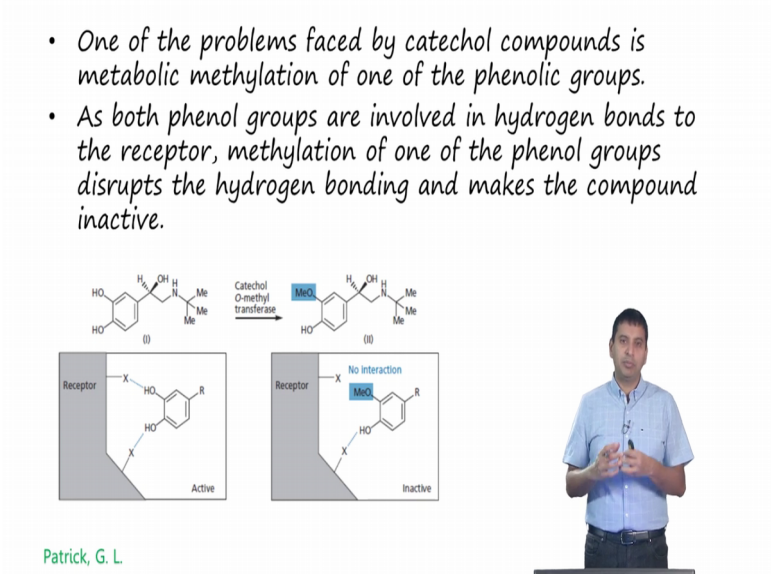

So salbutamol was introduced in 1969 for the treatment of asthma and is an analogue of the neurotransmitter noradrenaline, so noradrenaline catechol structure that means it has two alcohols on the aromatic ring, now because it has this two ortho-phenolic groups, it is quite susceptible to metabolism, so one of the problems that was faced by the catechol compounds is the metabolic methylation of one of the phenolic groups, so as both the phenol groups are involved in hydrogen bonding, the methylation of this group is going to be detrimental.

So what it does is it disrupts this hydrogen bond as shown here and make the compound inactive, so because this interaction is very important we need to be able to keep the interaction but prevent the metabolism.

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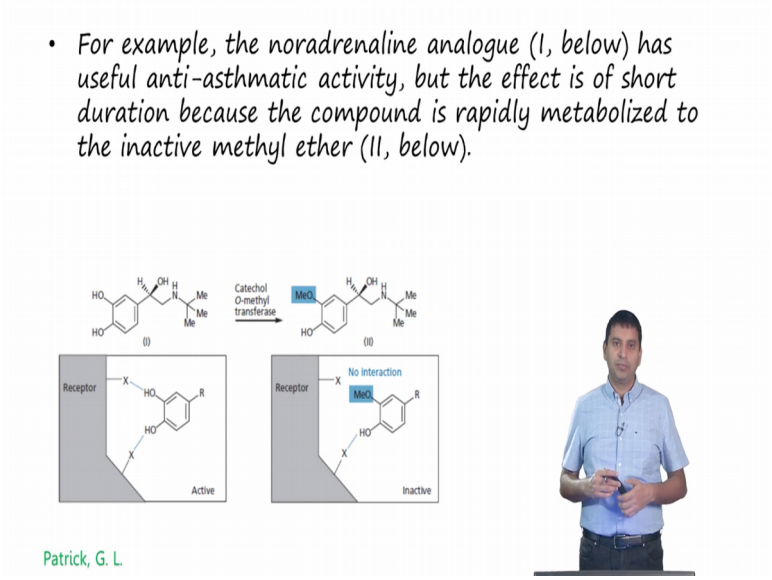

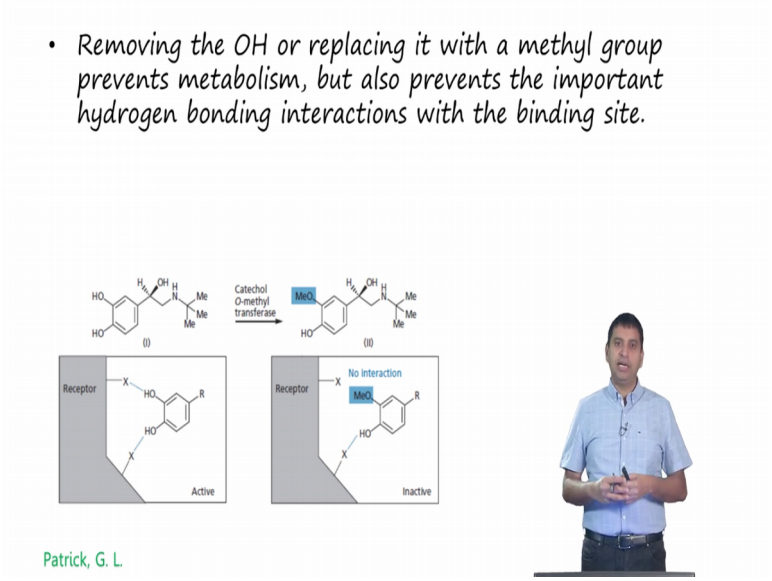

So the way to do is to convert, so for example the noradrenaline analogue below has useful anti-asthmatic activity, but the effect is of short duration because the compound is rapidly metabolized to the inactive methyl ester shown here okay.

So removing the OH group or replacing it with a methyl group prevents metabolism but also, it also prevents the important hydrogen bonding interaction with its binding site.

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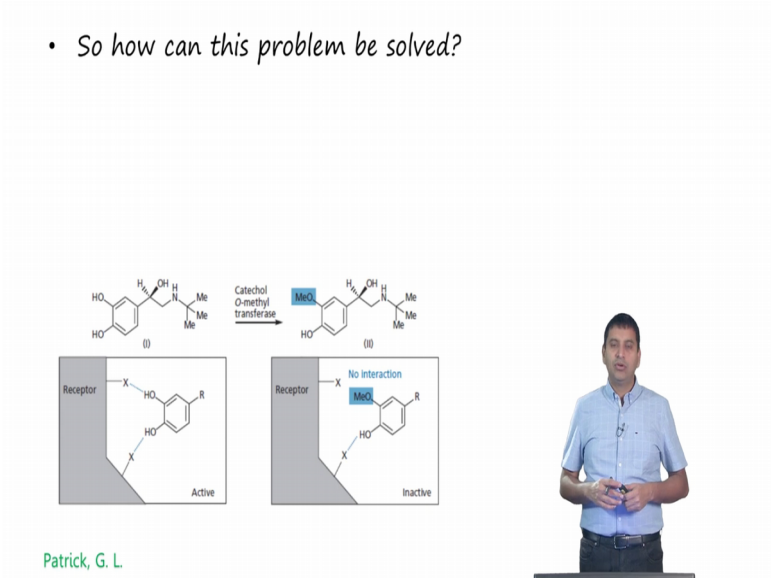

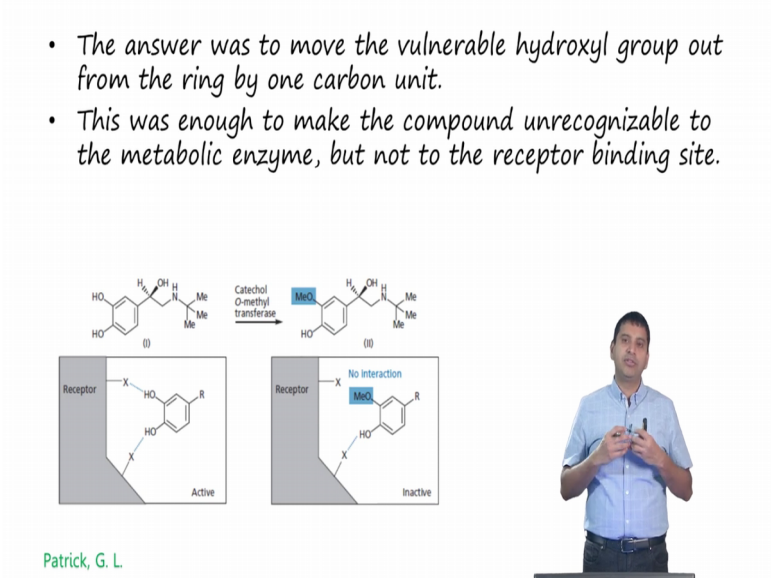

So how can this problem be solved? So the answer was to move the vulnerable group out of the ring by one carbon unit, so now we have converted the phenols to actually a benzyl alcohol, so what this does is that this modification was enough to make the compound unrecognizable to metabolic enzymes but it retained very much the receptor binding activity okay.

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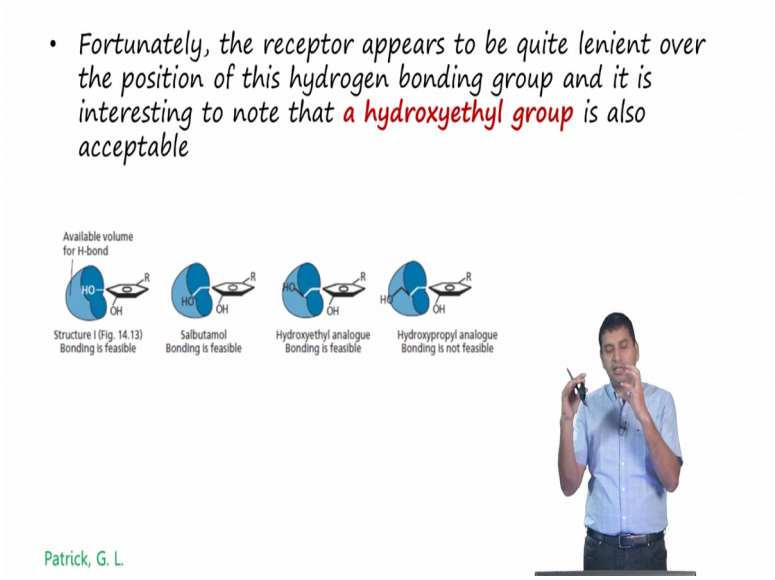

So, fortunately, the receptor appears to be quite lenient over the position of this hydrogen bonding group and so this hydroxyethyl group which we have proposed is also acceptable, so in the cartoon show on here you can see that the initial OH group has a very nice hydrogen bonding interaction and there is some volume available for hydrogen bonding, by changing in salbutamol the OH to CH to OH we are still perhaps accessing this volume and therefore we are able to have some level of hydrogen bonding but when you go one more carbon, which is hydroxyethyl analogue bonding is also feasible, but when you go to the hydroxypropyl compound here because this hydrogen bonding volume is quite restricted it gets out of it and the bonding is not feasible.

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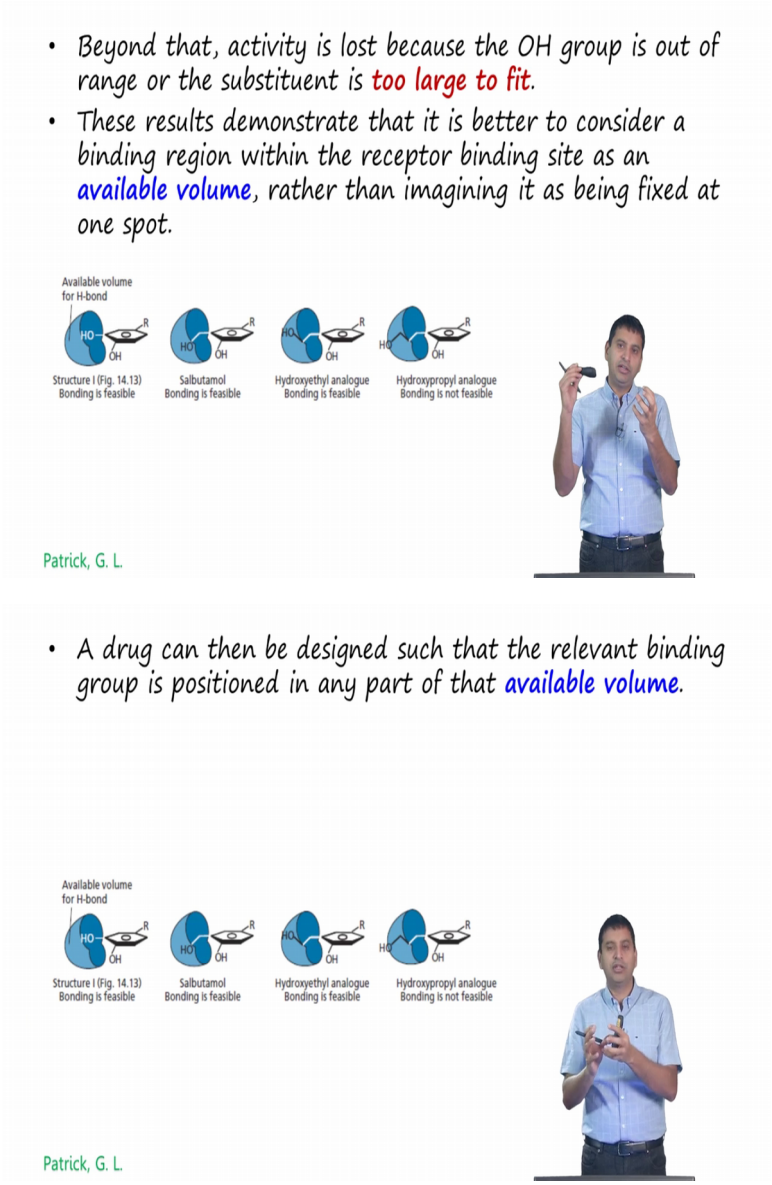

So beyond this, the activity is lost because the OH group is out of the range and it is too large to fit, so these results demonstrate that it is better to consider a binding region within the receptor as an available volume rather than imagining it to be a fixed it one spot.

A drug can then be designed to access this relevant or available volume rather than the binding site.

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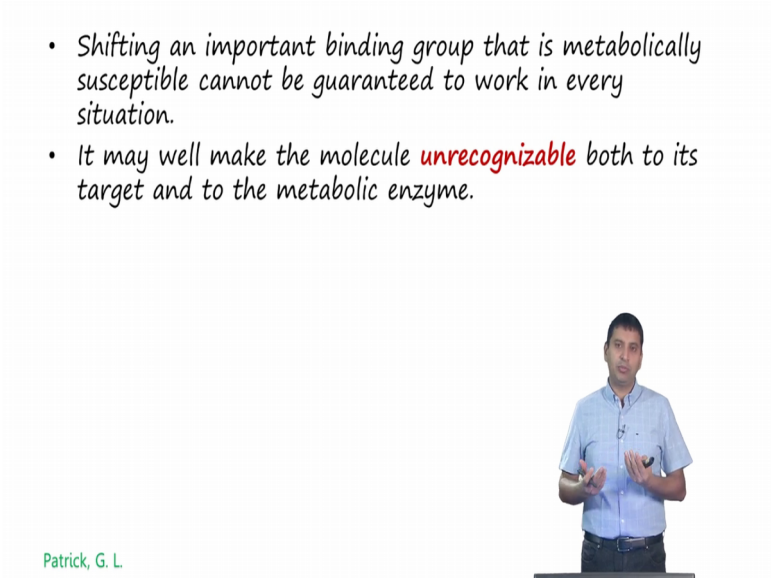

Shifting of an important binding group that is metabolically susceptible is of course not guaranteed to work in every situation, sometimes it may make the molecule unrecognizable to both its target as well as the metabolic enzyme, so we need to able to optimize these properties based on what we wish to achieve.

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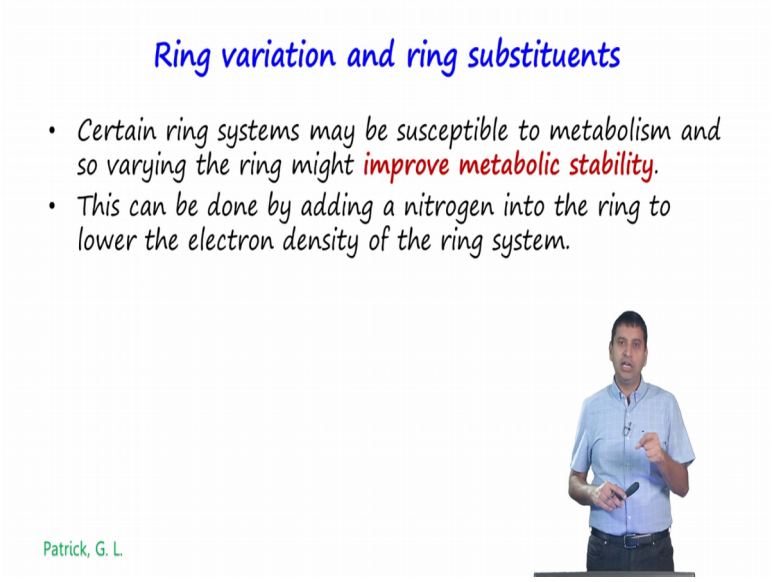

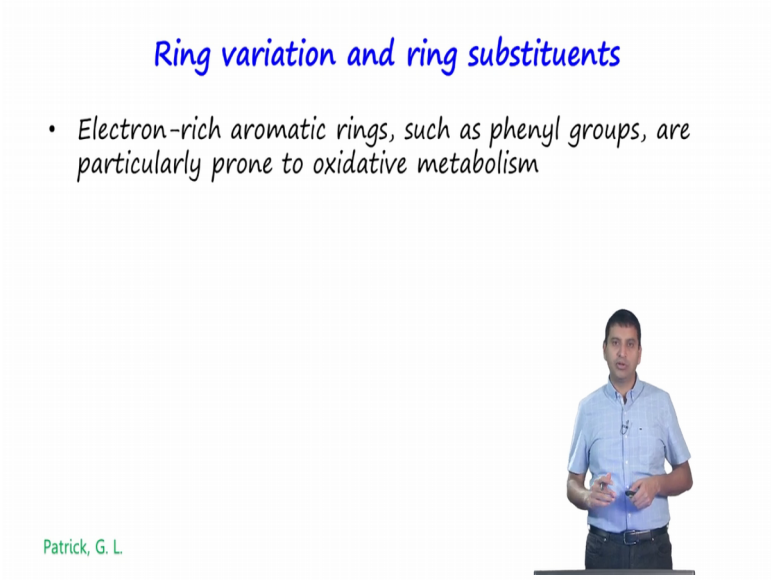

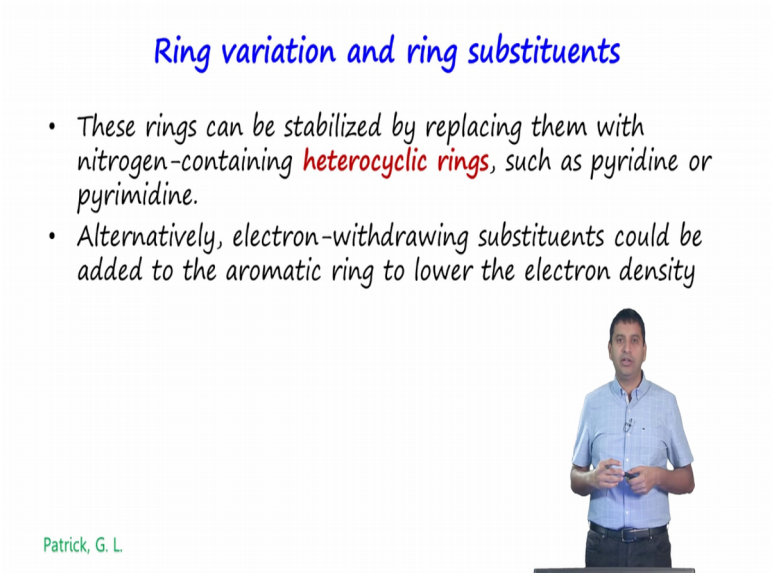

The next major strategy is to vary rings, certain ring systems may be susceptible to metabolism and so varying the ring might improve the metabolic stability, this can be done by adding a nitrogen into the ring to lower the electron density of the ring system.

Electron rich aromatic rings such as phenyl groups are prone to oxidative metabolism.

These rings can be stabilized by replacing them with nitrogen-contain heterocyclic rings such as pyridine or pyrimidine, alternatively you can also have a electron withdrawing groups such as sino or nitro this can reduce the electron density on the aromatic ring.

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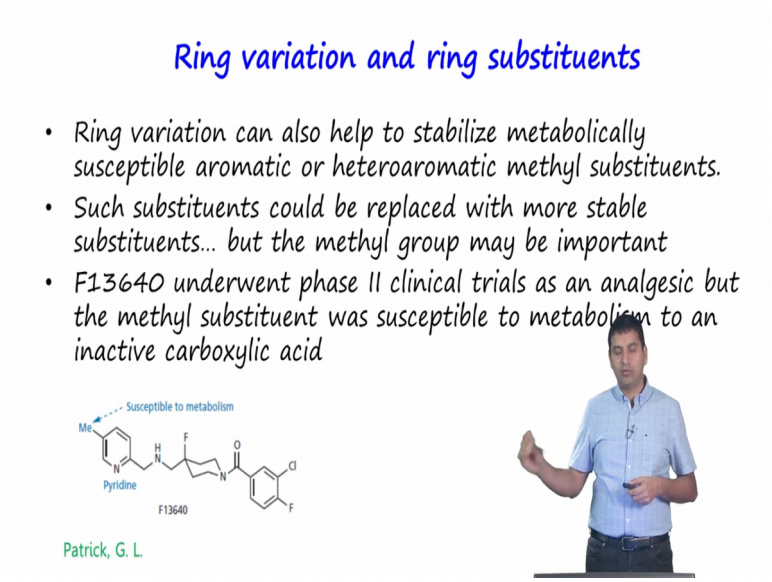

So ring variation can also help stabilize metabolically susceptible aromatic or heteroaromatic methyl groups, so such substituents can be placed with more stable substituents but the methyl group may be important, so this molecule shown below F13640 underwent phase II clinical trials as an analgesic, but the methyl substituent was susceptible to metabolism to form an inactive carboxylic acid.

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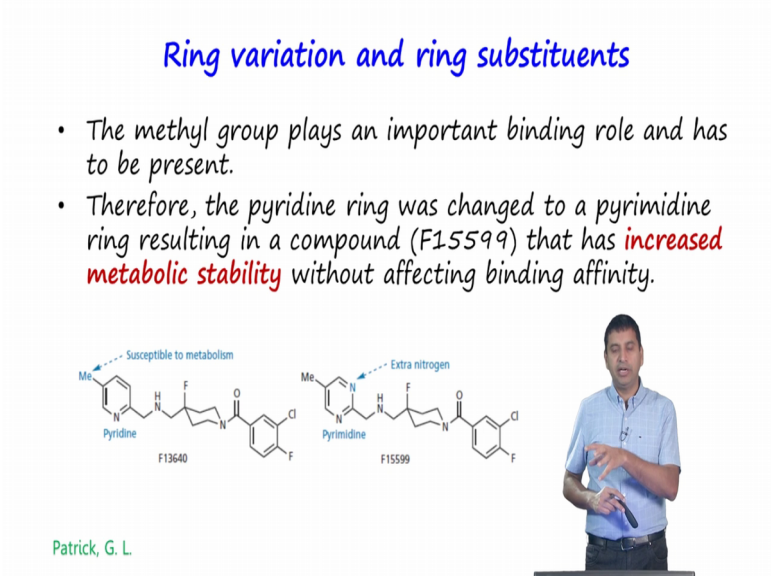

The also plays an important role in binding and has to be present, therefore, the pyridine ring was then changed to pyrimidine ring, so if added another nitrogen into the pyridine ring, what

this did was that this resulted in increased metabolic stability, but the binding affinity remain intact.