Medicinal Chemistry
Professor Dr. Harinath Chakrapani
Department of Chemistry
Indian Institutes of Science Education and Research Pune
Tutorial 13
Optimizing Access - Prodrugs

So in today's tutorial session we will be discussing problems with respect to how to optimise the drug target interaction as well as prodrugs.

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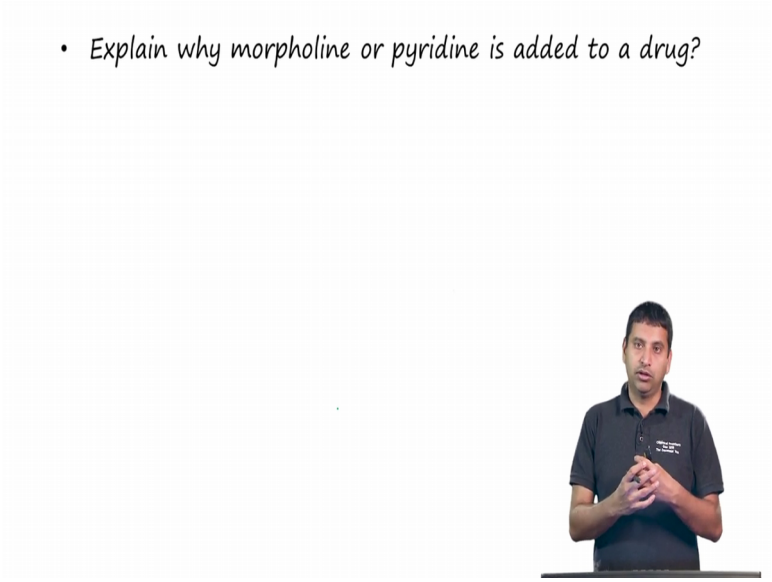

So first questioners explain why morphine or pyridine is added to a drug molecule? So in many times what we find is that the drug molecule is actually quite poorly soluble, so in order to improve the solubility one needs to add groups which can be hydrofolic in nature but they are not going to dramatically alter the properties of the drug.

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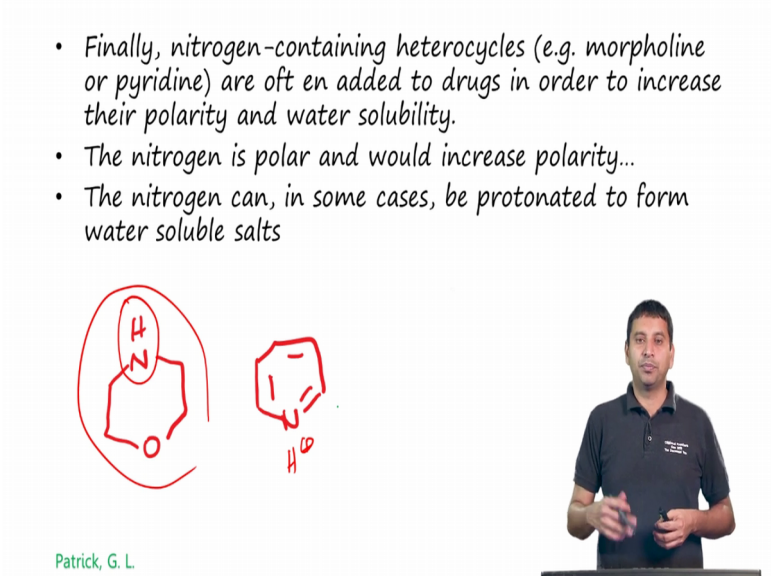

So here nitrogen containing heterocycles such as morpholine or pyridine are quite often used, so the nitrogen is polar and definitely increases the polarity and in some cases the protonated form can also be isolated as water-soluble salts, so here for example if you connect it through this nitrogen then you can sort of this whole molecule morpholine is quite polar and here in the case of pyridine you can make the pyridinium salt and actually isolated as a pyridinium salt.

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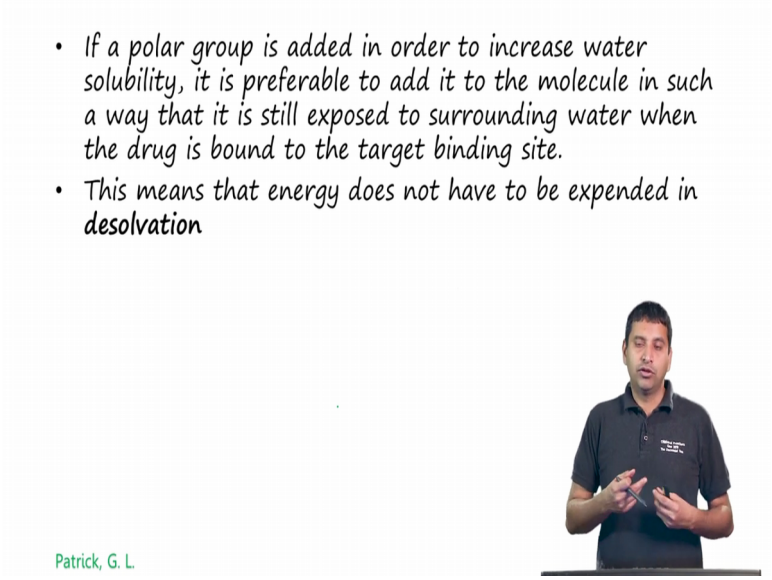

So if a polar group is added in order to increase the solubility, it is preferable to added to the molecule in such a way that it is still exposed to surrounding water okay, so therefore because it is exposed to the surrounding water, the drug when it is bound to the target site does have to

sort of desolvate before binding to the active site, so this is an important criterion when we are trying to add more functional group to the drug.

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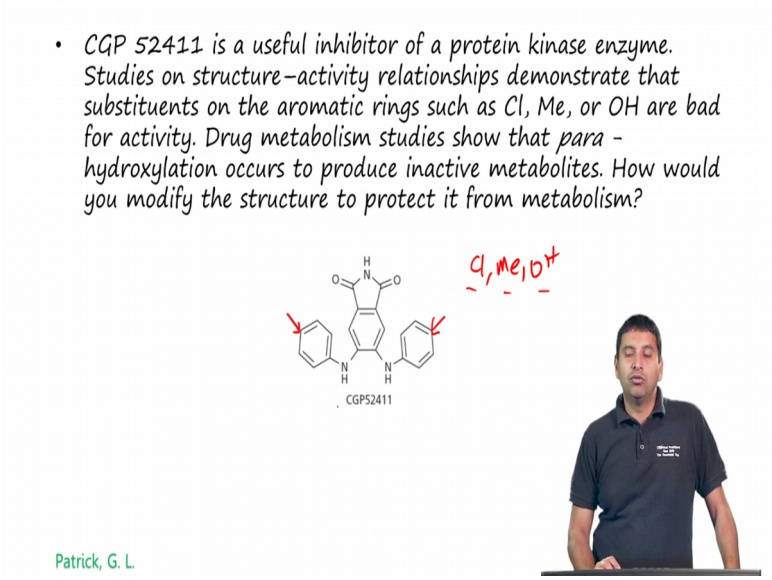

The next question his CGP 52411 is a useful inhibitor of protein kinase enzyme. Studies on structure activity relationship demonstrate that subsequence on the aromatic rings such as Cl, Me or OH, so Cl, Me or OH are bad for activity okay. Drug metabolism studies show that Para-hydroxylation occurs to produce in active metabolites, so how would you modify the structure to protect it from metabolism? So here is a question is that none of these molecules are useful and this side is actually susceptible to metabolism, so we can follow couple of strategies.

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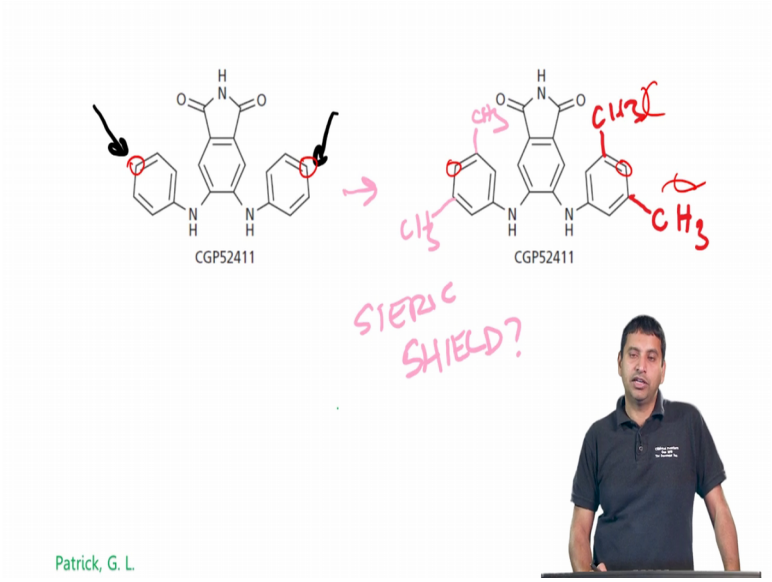

The first one is to use a steric shield strategy, so because this is the position of attack, what we could do is we could add 1 or 2 methyl groups around the this carbon and this presents a steric shield for it to oxidise okay. Of course the problem with this approach is that you are increasing the hydrophobicity of the molecule by adding methyl group, so what we could do this you could first add one methyl group in the meta position and see how susceptible it is to oxidation and then follow it up with a second one if necessary.

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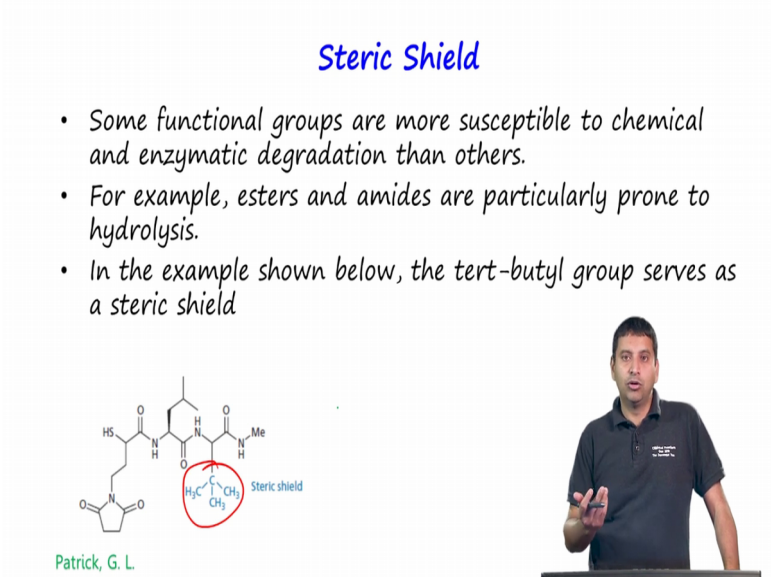

So just to recap steric shield is very useful concept because it helps in preventing chemical and enzymatic degradation, so for example esters and amides are particularly prone to hydrolysis, so by adding a tertiary butyl group here we can prevent this hydrolysis from occurring, so here the tert-butyl group serve as a steric shield.

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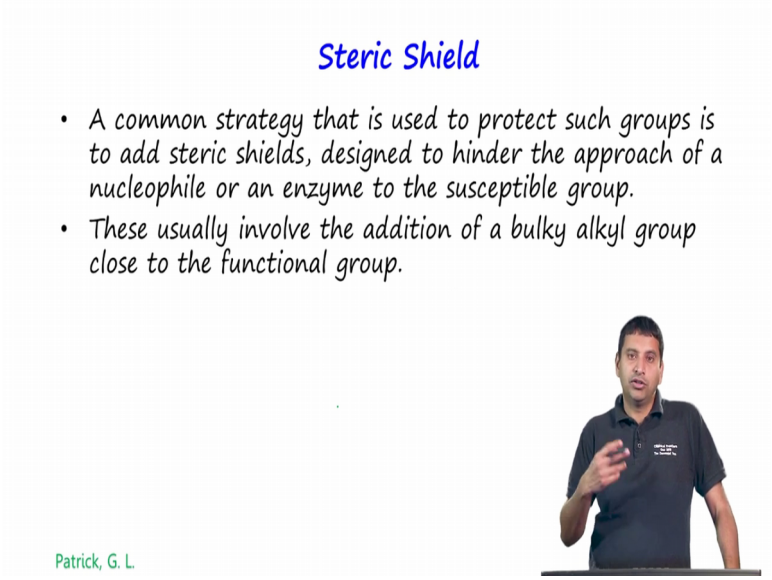

A common strategies that is used to protect such groups is to add steric shields to hinder the approach of nucleophile, so these involve addition of bulky groups closed the functional groups.

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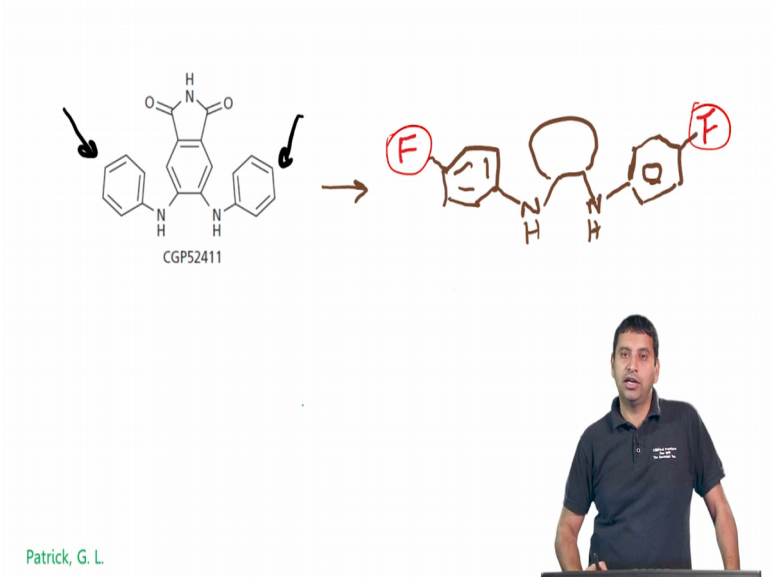

The next way to do it would be to replace the hydrogen with a fluorine atom okay, so fluorine is again something that is fairly similar in size to hydrogen so it may not affect the size of the molecule by (())(3:50).

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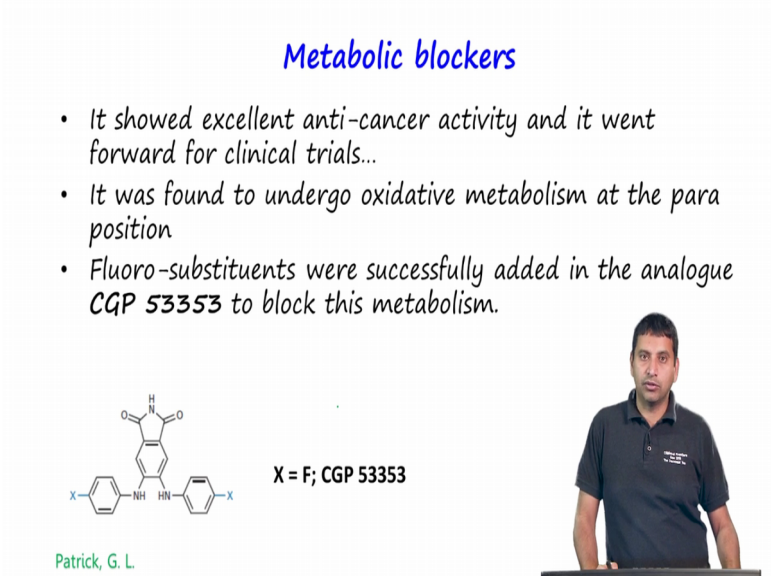

So this concept is known as metabolic blocker, so one of the ways to prevent metabolism or to inhibit metabolism is to use what is known as the metabolic blocker. This we have studied in class, so the para position here which X can be replaced by fluorine, so this molecule which is shown here which is x equal hydrogen was actually had excellent anti-cancer activity but it underwent oxidative metabolism at the para position, so when the fluoro-substituents was successfully added this molecule actually was quite resistant to metabolism.

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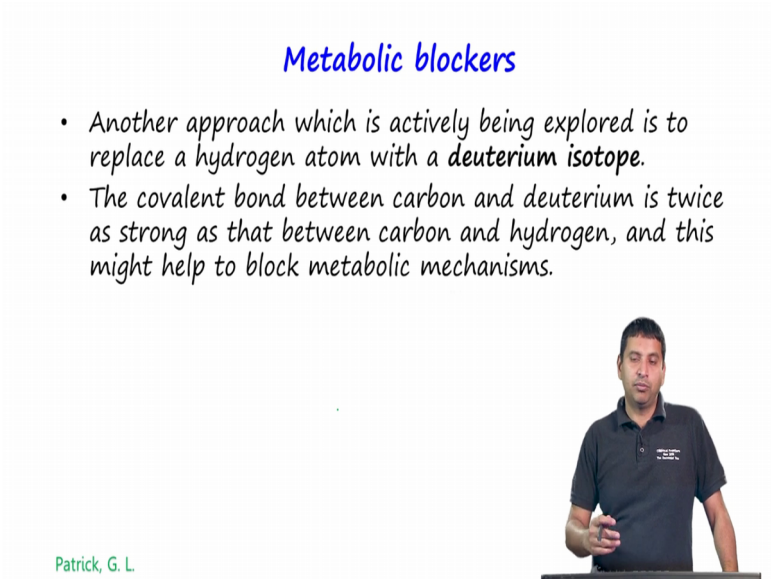

Another approach is to replace the hydrogen with a deuterium isotope, so as we know that the deuterium isotope effect may be operational and that is the carbon deuterium bond it is more

difficult to break compared to carbon hydrogen bond and this may help slow down the metabolism at that position.

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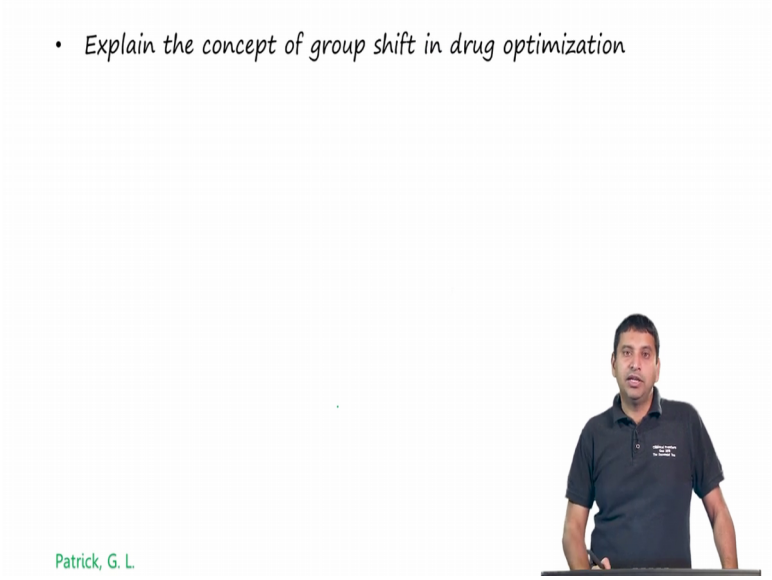

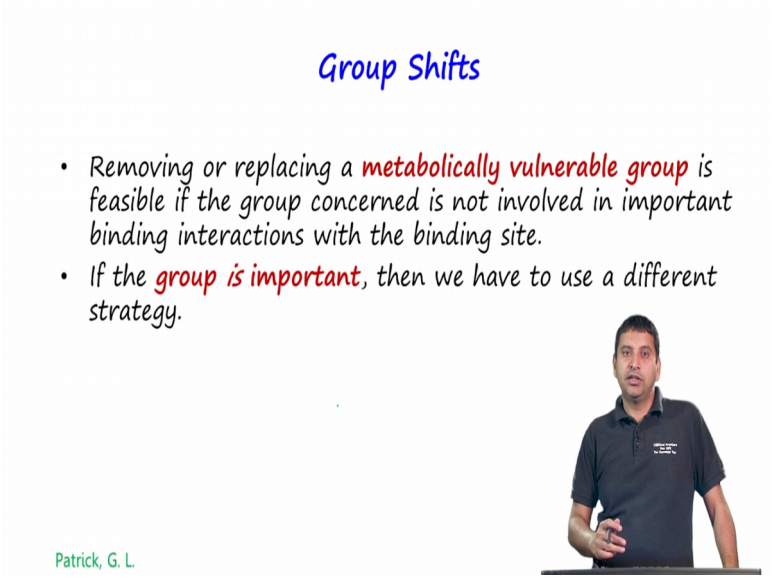

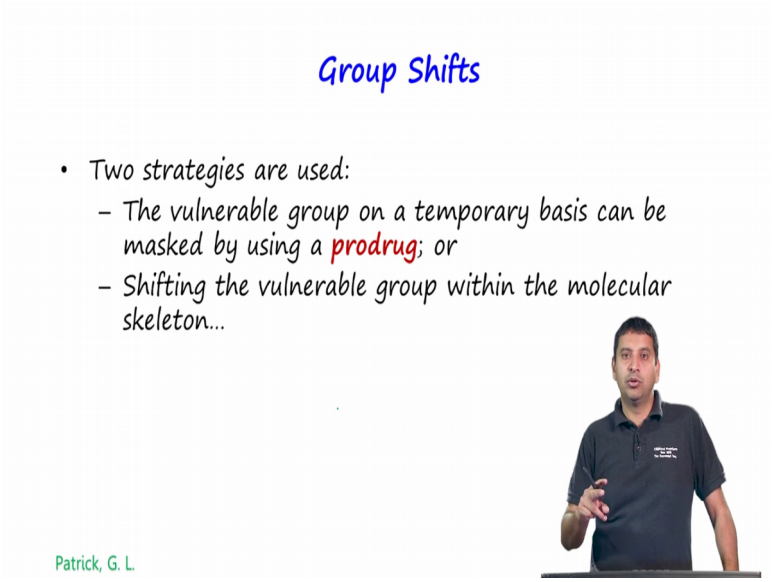

Next question is explain the concept of groups shift in drug optimisation, so group shift is nothing but replacing or moving a metabolically vulnerable group if it is possible and this group concern is not involved in important binding interaction with the binding site but if the group is important then we will have to use different strategy. So first one is to use prodrugs strategy where you can mask it with a temporary group and then remove it during metabolism. The second one is to shift the vulnerable group within the molecule skeleton.

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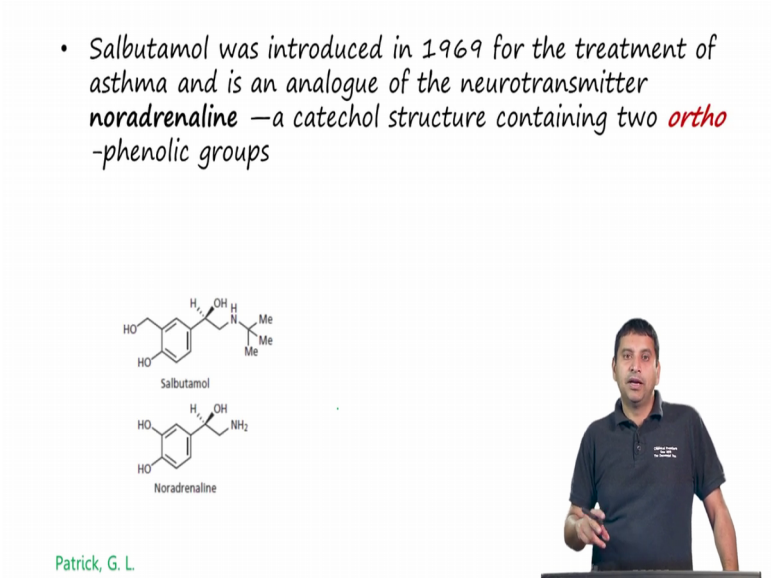

So here is an example so Salbutamol which was introduced in 1969 for the treatment of asthma is an analogue of the neurotransmitter noradrenaline, so this is salbutamol and this is noradrenaline. Noradrenaline contains a catechol structure which contains 2 auto phenolic groups.

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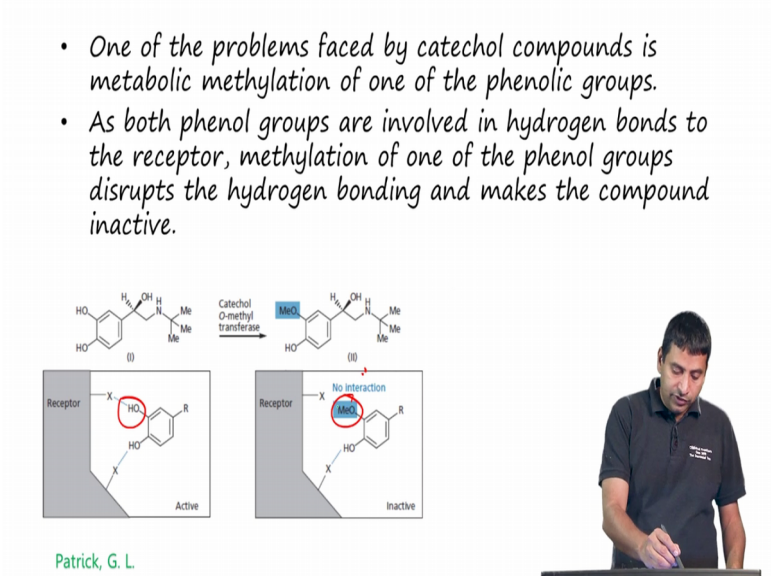

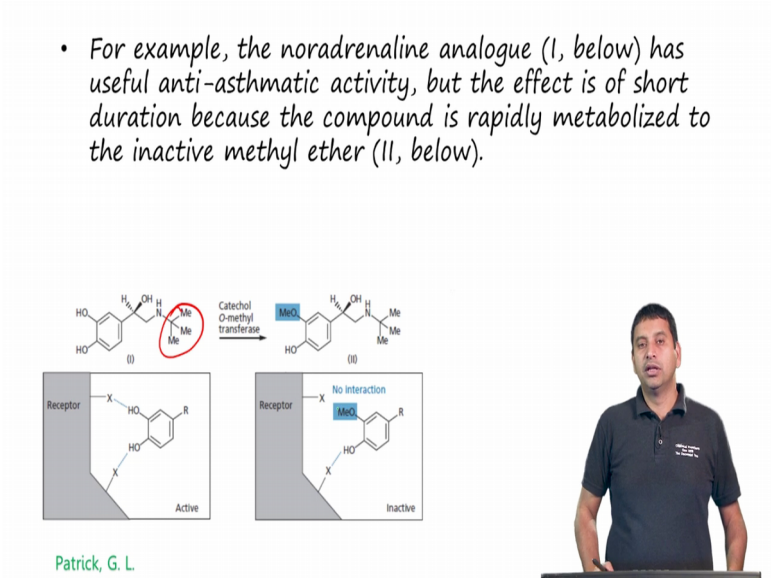

So one of the problems with this catechol compound is that it is metabolically susceptible to methylation of one of the phenol groups, so as both the phenol groups are involved in hydrogen bonds and the receptor side methylation of one of the phenol groups actually disrupts the hydrogen bonding and makes the molecule inactive. So here is the hydrogen OH which then undergoes methylation and since this has no interaction then the problem is that this becomes inactive okay, so this reaction is catalysed by catechol o-methyl transferase. So for example if you now use an analogue you know this OME compound it is been found to have… as useful anti-asthmatic activity, but the effect is of short duration because the compound is rapidly metabolised to the methyl ether, so if you use this analogue For example it is quite good but it is going to be a rapidly metabolised okay.

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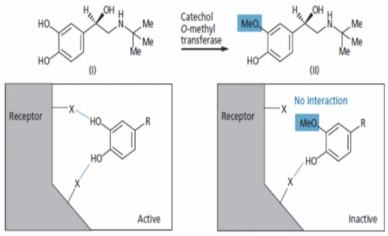
- Removing the OH or replacing it with a methyl group prevents metabolism, but also prevents the important hydrogen bonding interactions with the binding site.



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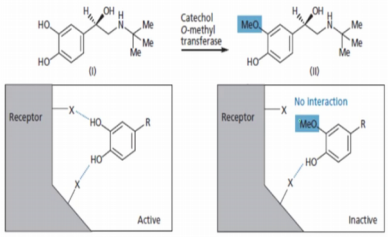
- So how can this problem be solved?



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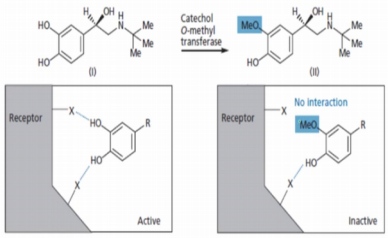
- The answer was to move the vulnerable hydroxyl group out from the ring by one carbon unit.
- This was enough to make the compound unrecognizable to the metabolic enzyme, but not to the receptor binding site.



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So removing the OH or replacing it with the methyl group was also were found to be inactive because of the important hydrogen bonding interactions, so therefore they are situation wherein we need the hydrogen bonding capability but we cannot sort of put a phenol ring there because it is going to get methylated. So this problem can be solved by shifting the group, so what we do is we shift one of the phenol group to make it a benzoyl alcohol okay, so once you do this then you are making the molecule… If you convert a phenol to a benzoyl alcohol then you are making the molecule less susceptible to the metabolic enzyme but the receptor binding site may still have activity.

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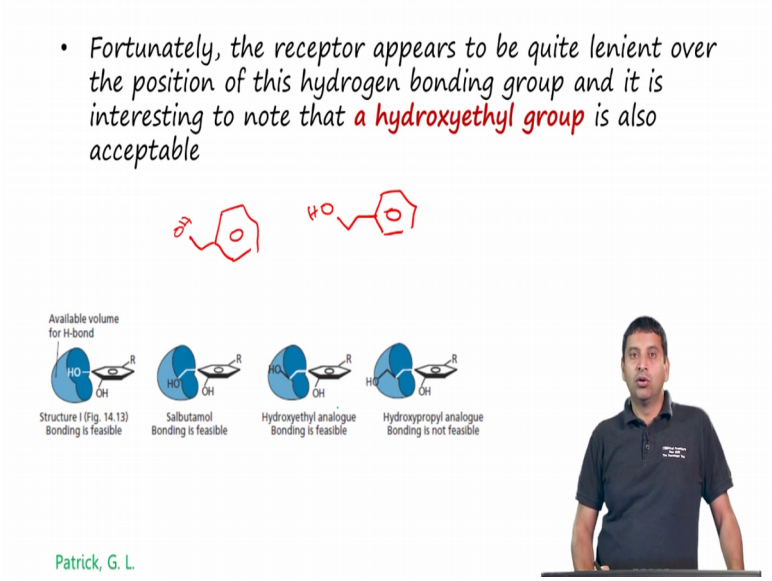

And thankfully the receptor appears to be quite lenient over the position of hydrogen bonding and of course it is interesting to note that the hydroxyethyl group is also acceptable, so you have you know CH2 CH2 OH or CH2 OH both of these are acceptable to the molecule to the receptor binding site okay but if you add one more carbon then it does not work okay.

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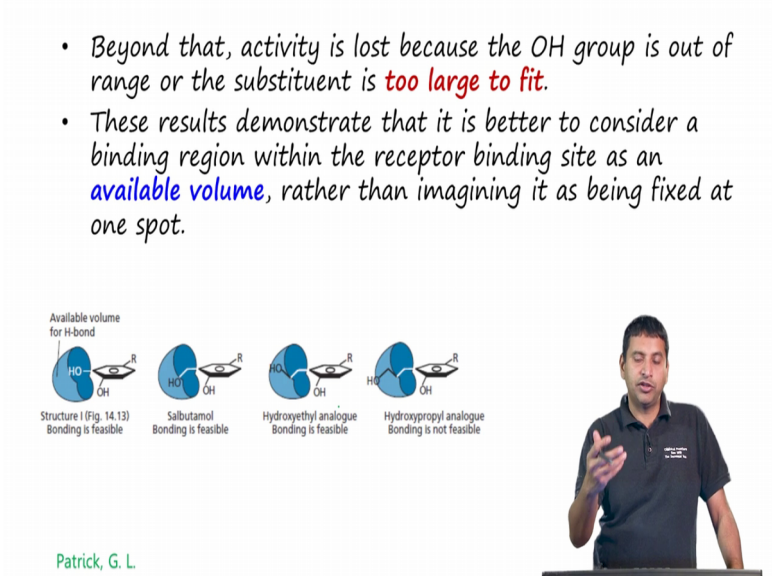

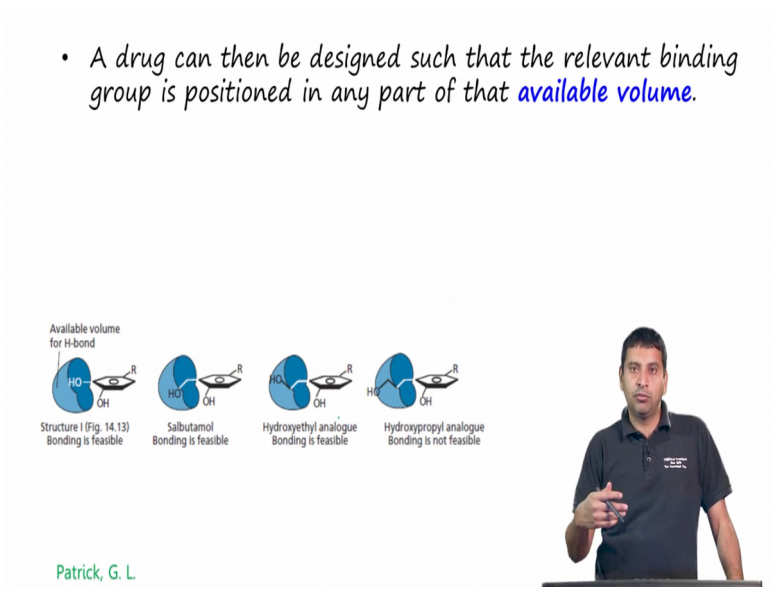

So beyond this if you add 3 carbons between the benzene ring and the alcohol then it is too large to fit, so this also suggest to us that there is a binding region within the receptor binding site which has an available volume and then a volume is what we need to sort of workaround, so if you are able to find the right molecule or the right functional group which can fit in this volume then it is possible to develop the metabolically more stable molecule. So this is an example of group shift, so identifying this volume becomes very important and knowledge of this volume helps us in making the molecule more metabolically stable okay.

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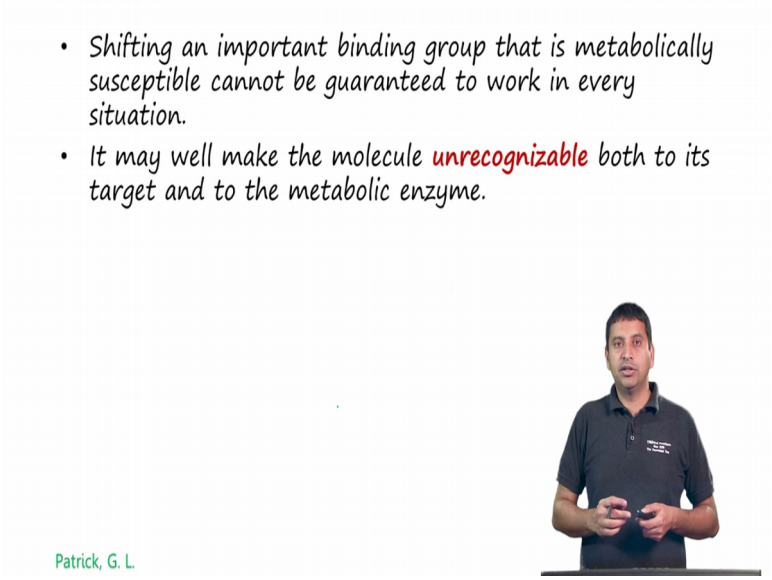

So of course by doing this you know we may make the molecule unrecognisable both to the target as well as the metabolic enzyme, so the key balance that we need to work with is the fact that we should not allow the molecule to be metabolised. At the same time it should continue to be recognised by the receptor.

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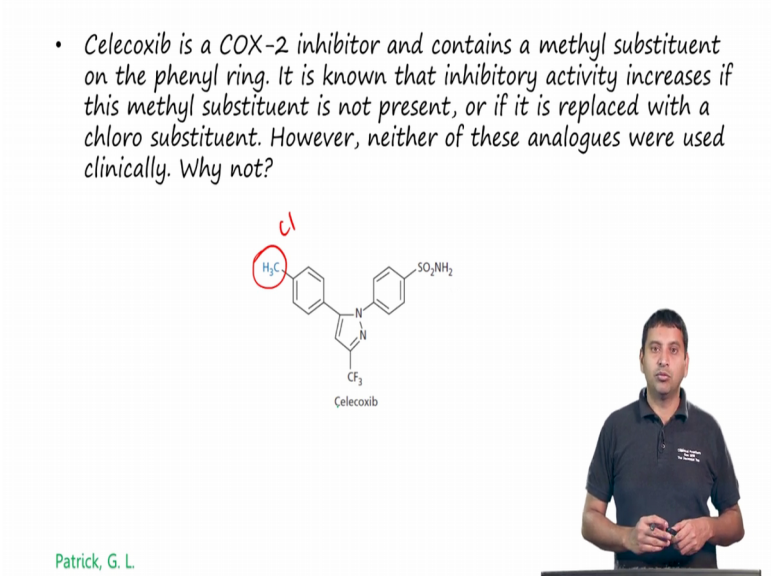

Next question Celecoxib is a Cox-2 inhibitor and contains a methyl subsequent on the phenyl ring. It is known that inhibitory activity increases if the methyl subsequent is not present, so if you have this metal substituents here you should remove it and it increases the activity, right or it is replaced by a chloro. However, neither of these analogues were used clinically. Why not?

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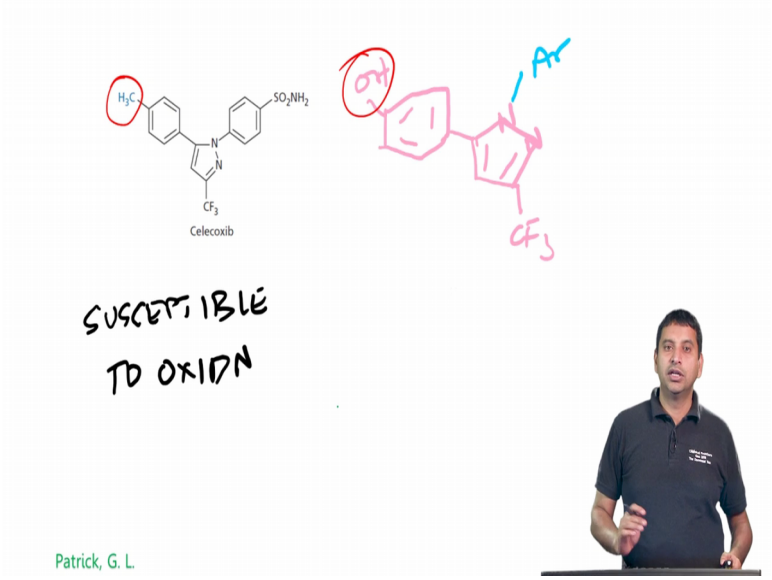

So in order to address this question we can think about what happens if you remove the methyl group, so if you remove the methyl group then the compound itself might be active in the real system but it is actually susceptible to oxidation, so once you form the hydroxyl group here then this compound perhaps is not active.

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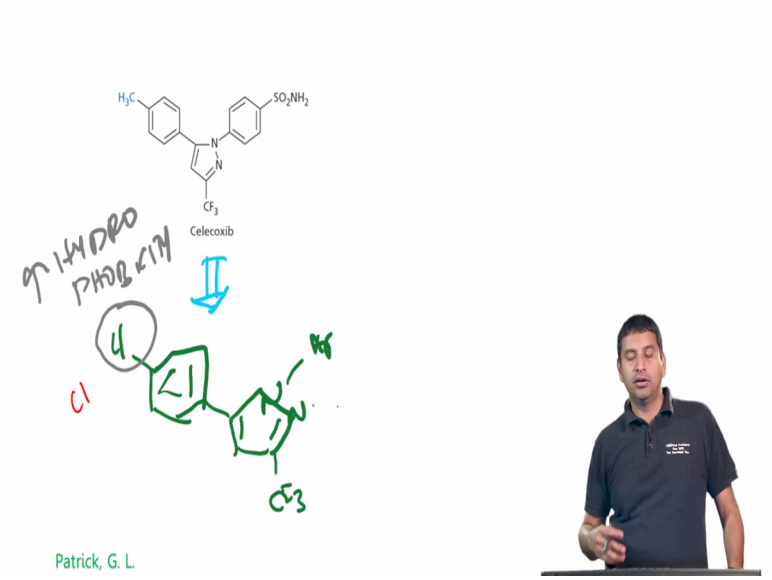

Now if you replace the hydrogen with chloride in then what we may actually end up doing is we may be increasing the hydrophobicity at that centre and this may actually result in poor (())(9:56).

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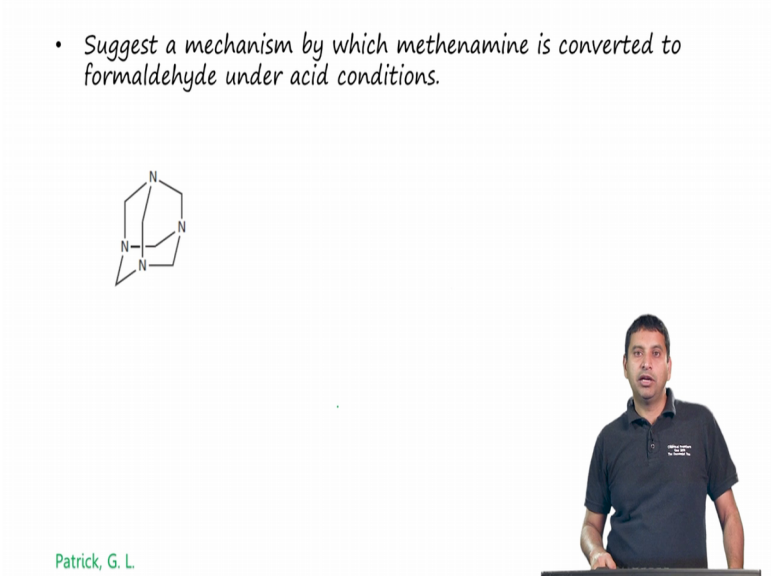

Suggest a mechanism by which methenamine is converted to formaldehyde under acidic conditions.

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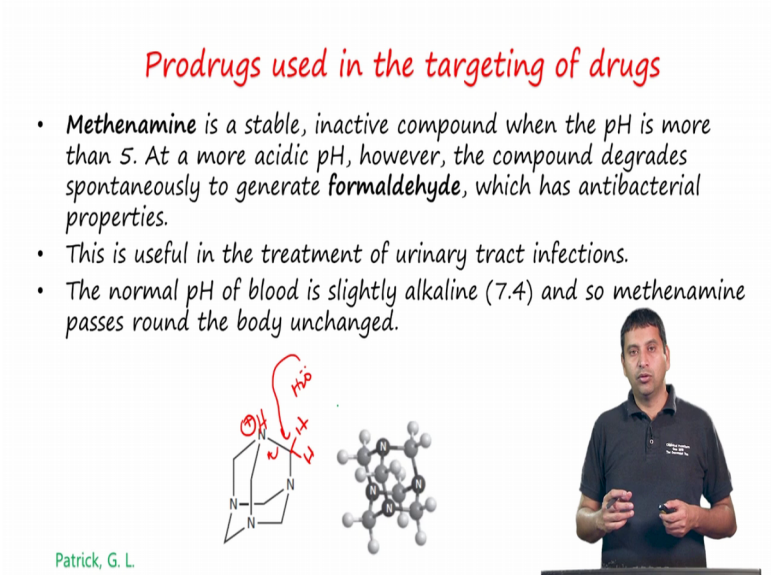

In order to address this let us go back and look at how this molecule works, so methenamine is a stable inactive compound when the pH is more than 5 okay but in acidic pH the compound and integrates spontaneously to generate formaldehyde, so the first step perhaps is that it gets protonated over here and then probably water attacks her and kicks it out, so this may be 1 mechanism by which you generate a formaldehyde like molecule which then undergo further decomposition to produce formaldehyde but the beauty of this molecule is that in the normal pH of the blood which is 7.4 this passes around pretty much unchanged.

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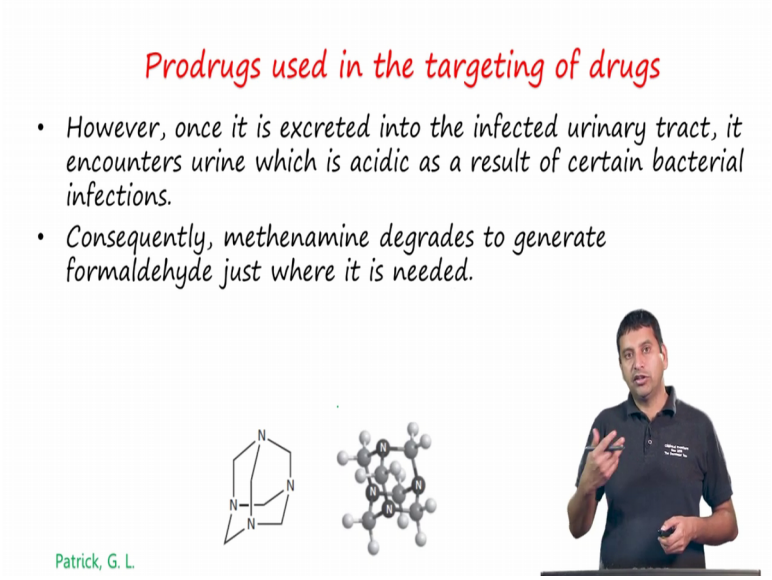

But once it reaches the urinary tract… where the pH is quite low that it degrades to generate formaldehyde which has antibacterial properties.

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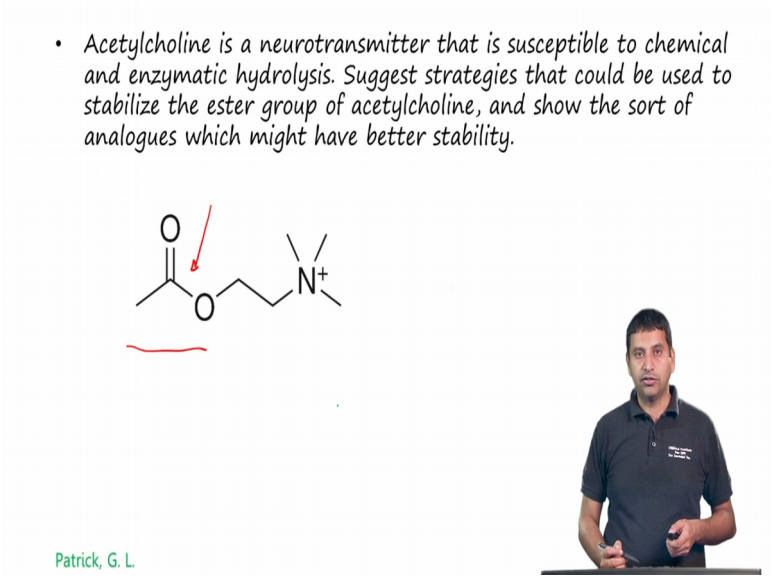

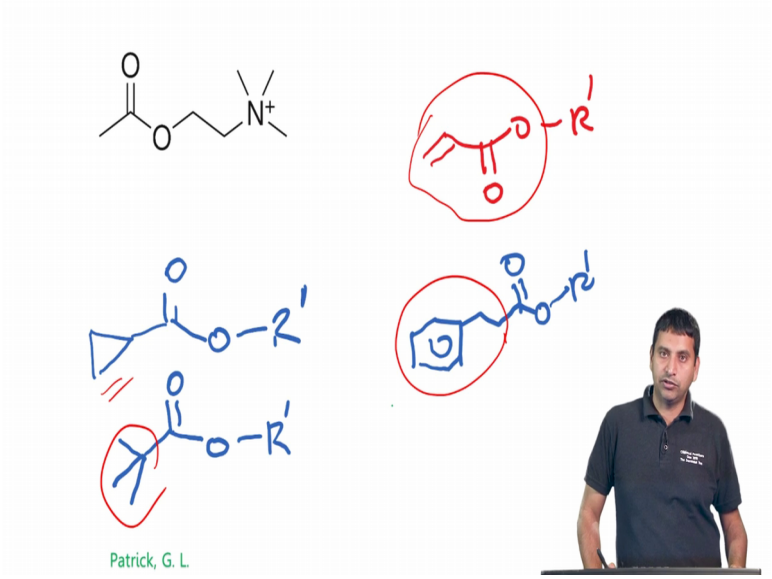

The next question acetylcholine is a neurotransmitter that is susceptible to chemical and enzymatic hydrolysis. Suggest strategies that could be used to stabilise the ester group of acetylcholine and show the sort of analogues which might have better stability okay. So here this acetylcholine and this is the bond that is going to be cleaved by ester (())(11:16). So in order to improve the stability of this molecule what we could do is we could make a cyclopropyl ester we have already looked at it previously or we can use a tert butyl molecule which is called pivaloyl group or we could also introduced may be a slightly longer chain aliphatic molecule with either an aromatic side change or just aliphatic side change. In the last strategy that might be used is to use alpha beta unsaturated ester.