

**Medicinal Chemistry**  
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**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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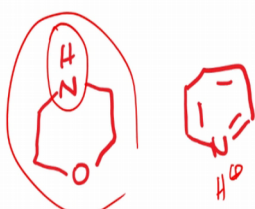
- *Explain why morpholine or pyridine is added to a drug?*



So first questioners explain why morpholine 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 hydrophilic in nature but they are not going to dramatically alter the properties of the drug.

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- Finally, nitrogen-containing heterocycles (e.g. morpholine or pyridine) are often added to drugs in order to increase their polarity and water solubility.
- The nitrogen is polar and would increase polarity...
- The nitrogen can, in some cases, be protonated to form water soluble salts



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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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- If a polar group is added in order to increase water solubility, it is preferable to add it to the molecule in such a way that it is still exposed to surrounding water when the drug is bound to the target binding site.
- This means that energy does not have to be expended in desolvation

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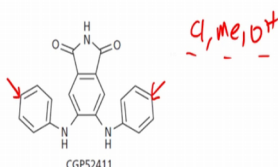


So if a polar group is added in order to increase the solubility, it is preferable to add it to the molecule in such a way that it is still exposed to surrounding water okay, so therefore because it is exposed to the surrounding water, the drug when it is bound to the target site does have to

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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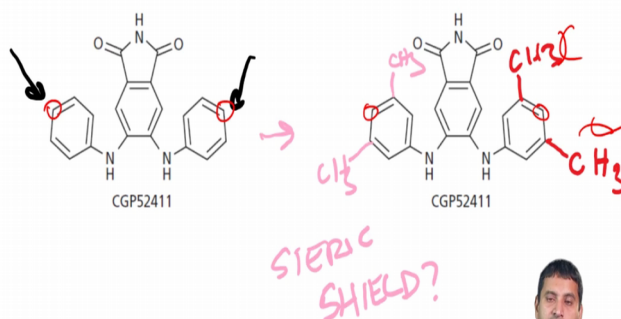
- CGP 52411 is a useful inhibitor of a protein kinase enzyme. Studies on structure-activity relationships demonstrate that substituents on the aromatic rings such as Cl, Me, or OH are bad for activity. Drug metabolism studies show that *para*-hydroxylation occurs to produce inactive metabolites. How would you modify the structure to protect it from metabolism?



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The next question is CGP 52411 is a useful inhibitor of protein kinase enzyme. Studies on structure activity relationship demonstrate that substituents 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 inactive 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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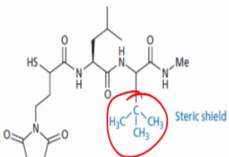
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The first one is to use a steric shield strategy, so because this is the position of attack, what we could do is we could add 1 or 2 methyl groups around the this carbon and this presents a steric shield for it to oxidise okay. Of course the problem 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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**Steric Shield**

- Some functional groups are more susceptible to chemical and enzymatic degradation than others.
- For example, esters and amides are particularly prone to hydrolysis.
- In the example shown below, the tert-butyl group serves as a steric shield



The chemical structure shows a peptide backbone with a tert-butyl group (t-Bu) attached to the alpha-carbon of a residue. The t-Bu group is highlighted with a red circle and labeled "Steric shield". The molecule also contains a thiol group (HS-), an amide group (NH), and a methyl group (Me).

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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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### Steric Shield

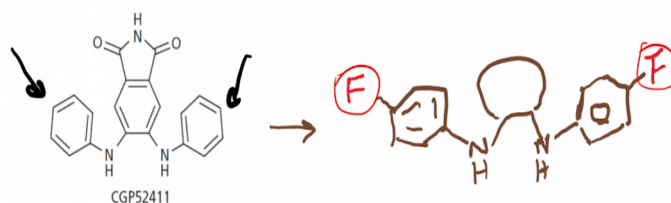
- A common strategy that is used to protect such groups is to add steric shields, designed to hinder the approach of a nucleophile or an enzyme to the susceptible group.
- These usually involve the addition of a bulky alkyl group close to the functional group.

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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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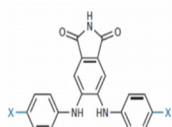


The next way to do it would be to replace the hydrogen with a fluorine atom okay, so fluorine is again something that is fairly similar in size to hydrogen so it may not affect the size of the molecule by ( ) (3:50).

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### Metabolic blockers

- It showed excellent anti-cancer activity and it went forward for clinical trials...
- It was found to undergo oxidative metabolism at the para position
- Fluoro-substituents were successfully added in the analogue **CGP 53353** to block this metabolism.



X = F; CGP 53353

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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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### Metabolic blockers

- Another approach which is actively being explored is to replace a hydrogen atom with a **deuterium isotope**.
- The covalent bond between carbon and deuterium is twice as strong as that between carbon and hydrogen, and this might help to block metabolic mechanisms.

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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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- Explain the concept of group shift in drug optimization

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### Group Shifts

- Removing or replacing a **metabolically vulnerable group** is feasible if the group concerned is not involved in important binding interactions with the binding site.
- If the **group is important**, then we have to use a different strategy.

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## Group Shifts

- Two strategies are used:
  - The vulnerable group on a temporary basis can be masked by using a **prodrug**; or
  - Shifting the vulnerable group within the molecular skeleton...

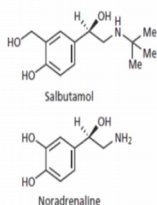
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Next question is explain the concept of groups shift in drug optimisation, so group shift is nothing but replacing or moving a metabolically vulnerable group if it is possible and this group concern is not involved in important binding interaction 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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- Salbutamol was introduced in 1969 for the treatment of asthma and is an analogue of the neurotransmitter **noradrenaline** —a catechol structure containing two **ortho**-phenolic groups



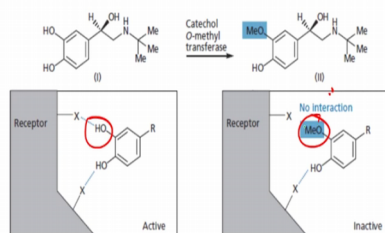
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So here is an example so Salbutamol which was introduced in 1969 for the treatment of asthma is an analogue of the neurotransmitter noradrenaline, so this is salbutamol and this is noradrenaline. Noradrenaline contains a catechol structure which contains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

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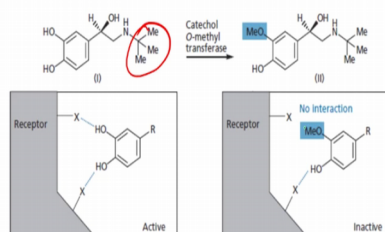
- One of the problems faced by catechol compounds is metabolic methylation of one of the phenolic groups.
- As both phenol groups are involved in hydrogen bonds to the receptor, methylation of one of the phenol groups disrupts the hydrogen bonding and makes the compound inactive.



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- For example, the noradrenaline analogue (I, below) has useful anti-asthmatic activity, but the effect is of short duration because the compound is rapidly metabolized to the inactive methyl ether (II, below).



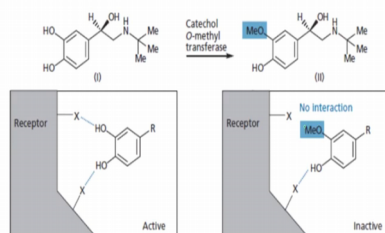
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So one of the problems with this catechol compound is that it is metabolically susceptible to methylation of one of the phenol groups, so as both the phenol groups are involved in hydrogen bonds and the receptor side methylation of one of the phenol 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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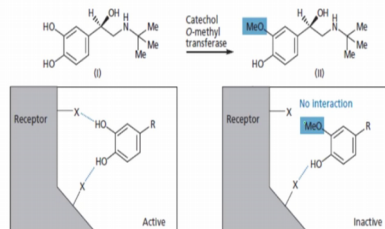
- Removing the OH or replacing it with a methyl group prevents metabolism, but also prevents the important hydrogen bonding interactions with the binding site.



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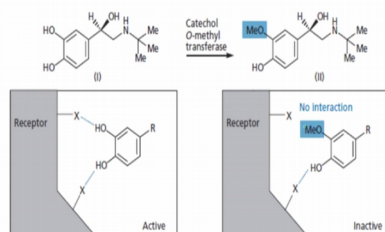
- So how can this problem be solved?



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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.



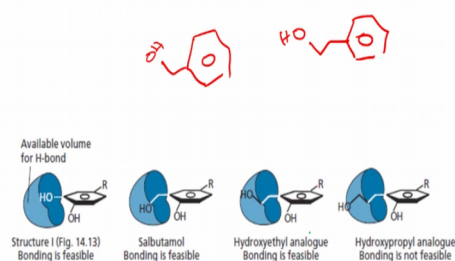
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So removing the OH or replacing it with the methyl group was also found to be inactive because of the important hydrogen bonding interactions, so therefore they are situation wherein we need the hydrogen bonding capability but we cannot sort of put 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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- Fortunately, the receptor appears to be quite lenient over the position of this hydrogen bonding group and it is interesting to note that **a hydroxyethyl group** is also acceptable



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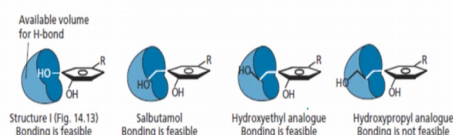


And thankfully the receptor appears to be quite lenient over the position of hydrogen bonding and of course it is interesting to note that the hydroxyethyl group is also acceptable, so you have you know CH<sub>2</sub> CH<sub>2</sub> OH or CH<sub>2</sub> OH both of these are acceptable to the molecule to the receptor binding site okay but if you add one more carbon then it does not work okay.



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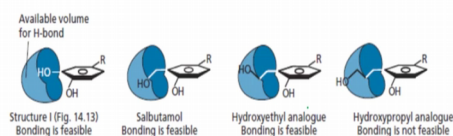
- Beyond that, activity is lost because the OH group is out of range or the substituent is **too large to fit**.
- These results demonstrate that it is better to consider a binding region within the receptor binding site as an **available volume**, rather than imagining it as being fixed at one spot.



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- A drug can then be designed such that the relevant binding group is positioned in any part of that **available volume**.



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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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- Shifting an important binding group that is metabolically susceptible cannot be guaranteed to work in every situation.
- It may well make the molecule **unrecognizable** both to its target and to the metabolic enzyme.

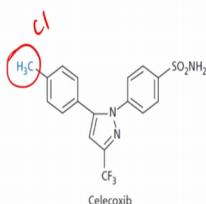
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So of course by doing this you know we may make the molecule unrecognisable both to the target as well as the metabolic enzyme, so the key balance that we need to work with is the fact that we should not allow the molecule to be metabolised. At the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

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- Celecoxib is a COX-2 inhibitor and contains a methyl substituent on the phenyl ring. It is known that inhibitory activity increases if this methyl substituent is not present, or if it is replaced with a chloro substituent. However, neither of these analogues were used clinically. Why not?

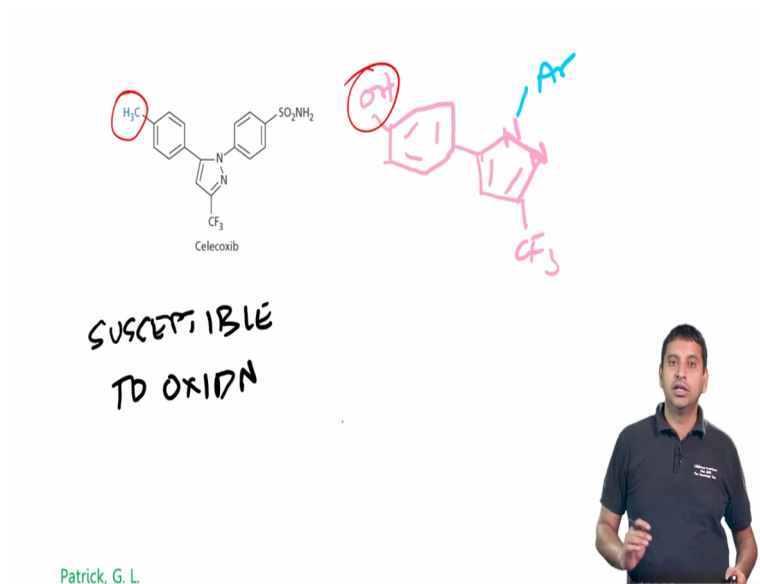


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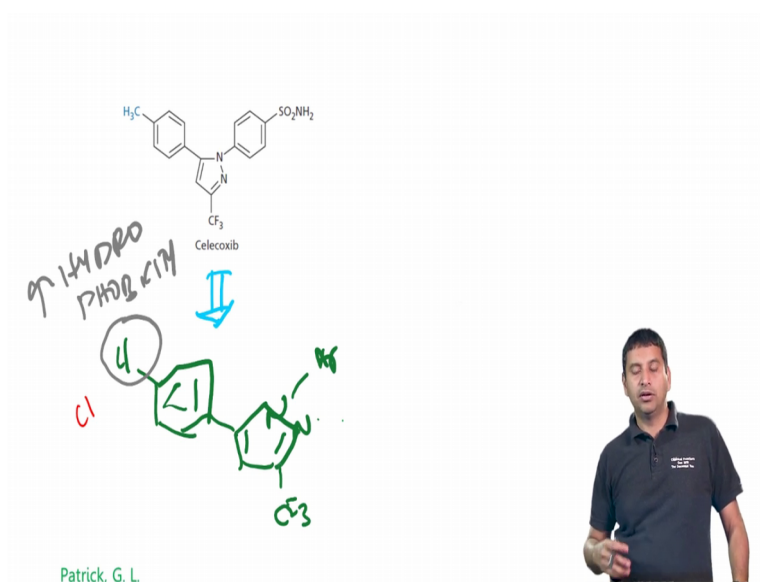
Next question Celecoxib is a Cox-2 inhibitor and contains a methyl subsequent on the phenyl ring. It is known that inhibitory activity increases if the methyl subsequent is not present, so if you have this metal substituents here you should remove it and it increases the activity, right or it is replaced 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.

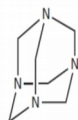
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Now if you replace the hydrogen with chloride in then what we may actually end up doing is we may be increasing the hydrophobicity at that centre and this may actually result in poor ( $\text{O}$ )(9:56).

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



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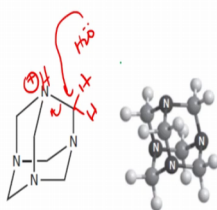


Suggest a mechanism by which methenamine is converted to formaldehyde under acidic conditions.

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### Prodrugs used in the targeting of drugs

- **Methenamine** is a stable, inactive compound when the pH is more than 5. At a more acidic pH, however, the compound degrades spontaneously to generate **formaldehyde**, which has antibacterial properties.
- This is useful in the treatment of urinary tract infections.
- The normal pH of blood is slightly alkaline (7.4) and so methenamine passes round the body unchanged.



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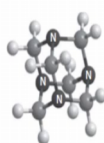
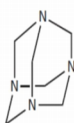


In order to address this let us go back and look at how this molecule works, so methenamine is a stable inactive compound when the pH is more than 5 okay but in acidic pH the compound and integrates spontaneously to generate formaldehyde, so the first step perhaps is that it gets protonated over here 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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### Prodrugs used in the targeting of drugs

- However, once it is excreted into the infected urinary tract, it encounters urine which is acidic as a result of certain bacterial infections.
- Consequently, methenamine degrades to generate formaldehyde just where it is needed.



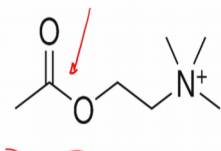
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But once it reaches the urinary tract... where the pH is quite low that it degrades to generate formaldehyde which has antibacterial properties.

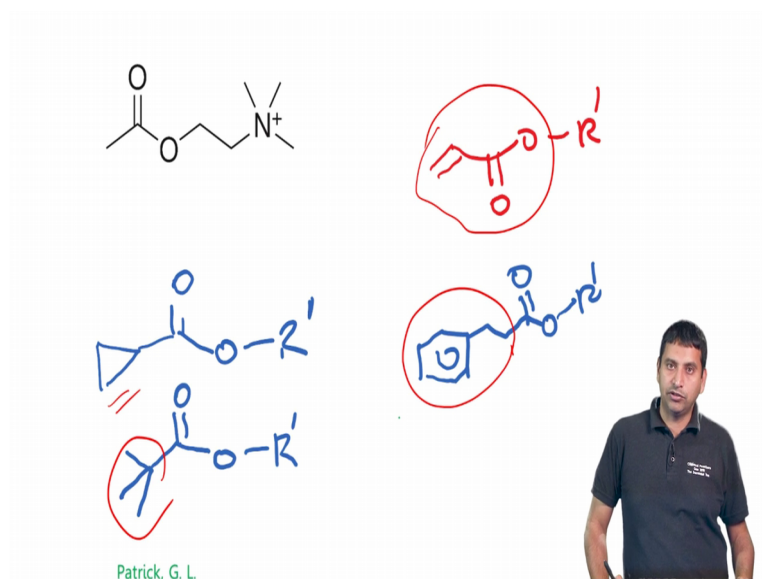
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- Acetylcholine is a neurotransmitter that is susceptible to chemical and enzymatic hydrolysis. Suggest strategies that could be used to stabilize the ester group of acetylcholine, and show the sort of analogues which might have better stability.



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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 (O)(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.