Medicinal Chemistry
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Tutorial-14
Combinatorial and Parallel Synthesis, Computers in Medicinal Chemistry and Anti-Bacterial Agents

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Welcome to the tutorial session, so in this week we have looked at a number of concepts including combinatorial and parallel synthesis, computers in medicinal chemistry and antibacterial agents. So today's tutorial session will cover these topics.

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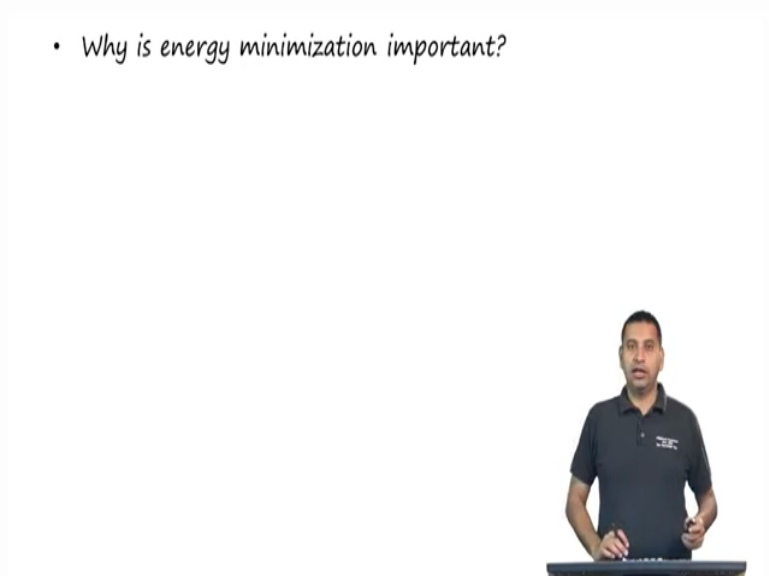

The first question is why is energy minimization important?

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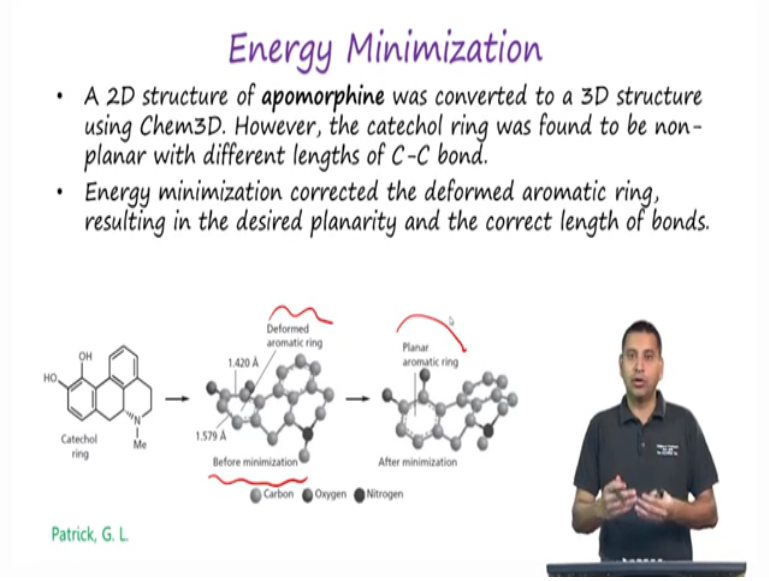

So energy minimization if you draw out a structure in a software such as ChemDraw, then what it does is it gives you an approximate structure based on you know various bond lines that are already you know available, but then these may not be in the optimized form which means that they may not be the thermodynamic minima of the structure. So in order to achieve the thermodynamic minima we would need to do what is known as energy minimization.

So the example here is apomorphine when you convert it to the 3D structure using Chem3D you will find the various aspects of this you know that there is a deformed aromatic ring and then you know the bond lengths or the geometries are quite different. But then when you do the minimization you actually get up a planar aromatic ring which is more reflective of what happens in reality.

So therefore before we get into any further drug discovery efforts, we would need to do what is known as energy minimization this allows us to work with one of the major thermodynamic minima of the structure.

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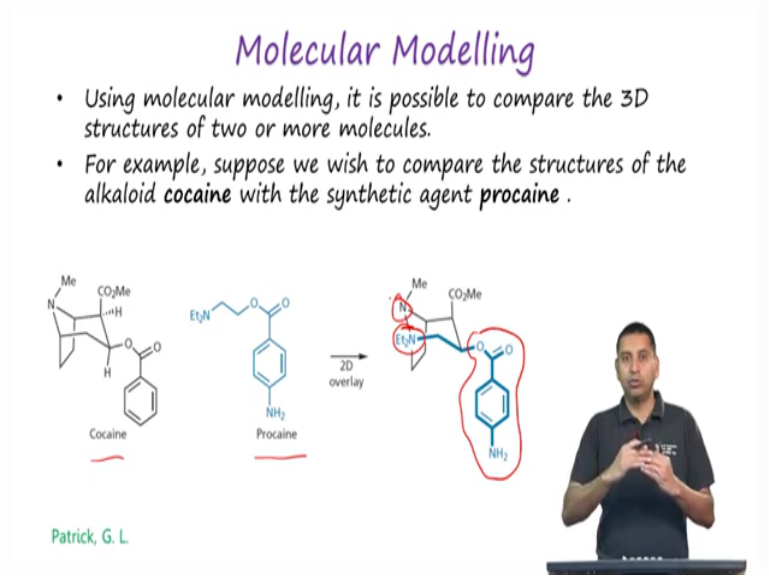

So molecular modelling is it is possible to compare the 3D structures of two or more molecules. So the example that we looked at in class which I will repeat here is that of cocaine and procaine. So this is the structure of procaine and this is the structure of cocaine and if we just do a 3D mapping of the two structures you can overlap the ester and the amine part with this over here and that suggests that the N Me is actually quite far away from the N Et 2 that means that there is very minimal overlap in the between the two nitrogens.

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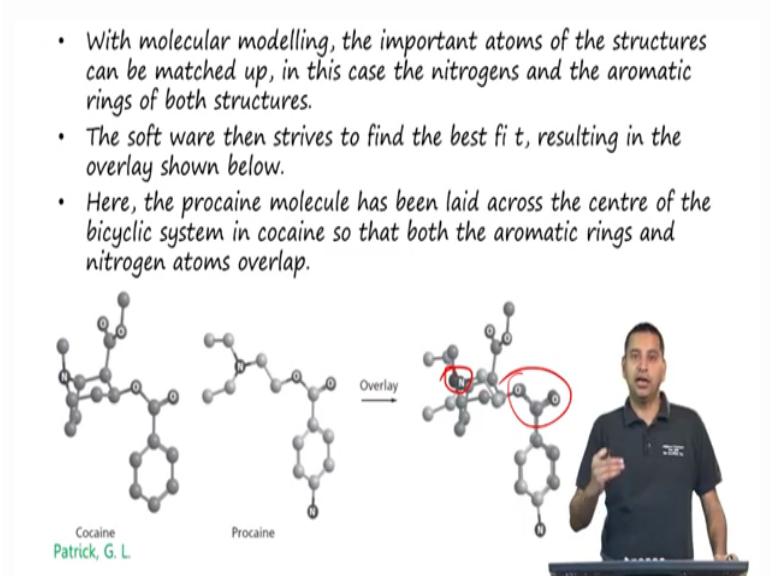

However, when you do the molecular modelling then you achieve the and you actually do sort of overlay these two structures then what happens is that the software will try to find the best fit and once it tries to find the best fit you will see that the two nitrogens are actually overlapping. So you have the ester that is overlapping, as well as the nitrogen which is overlapping. So this kind of information is available by minimization and overlay.

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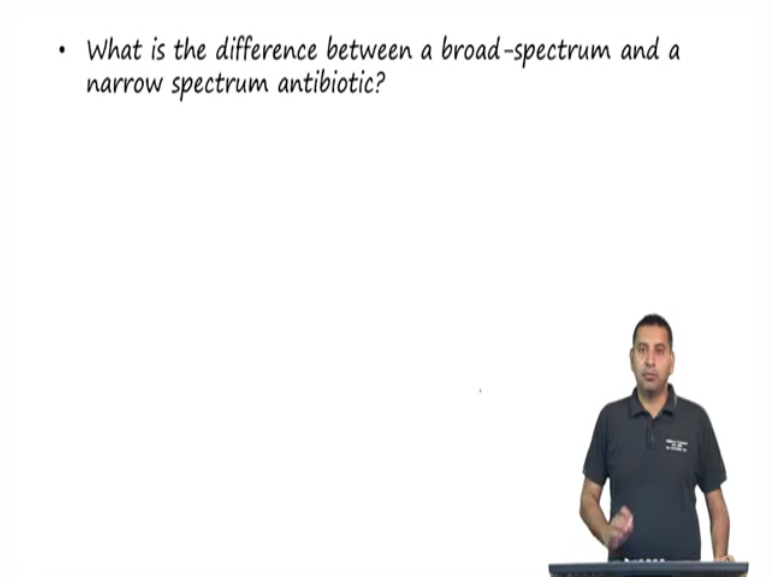

Next question is what is the difference between a broad spectrum and a narrow spectrum antibiotic?

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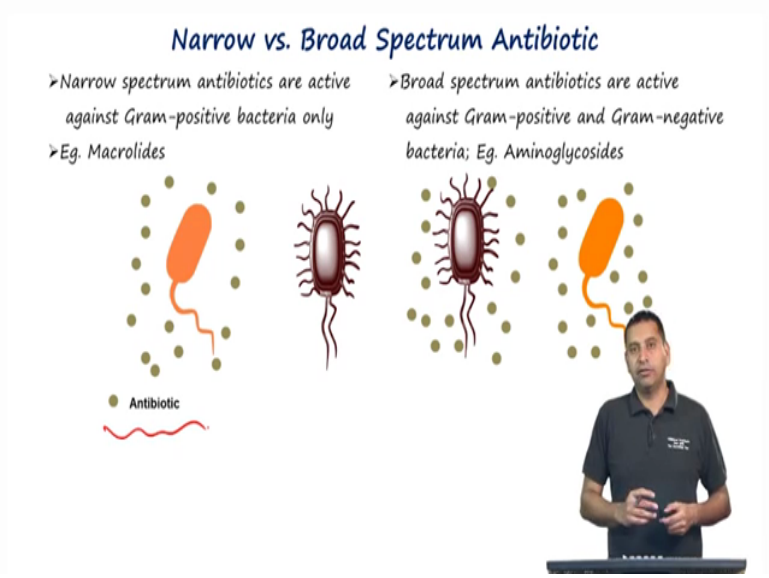

So in order to address this we will look at what are the various kinds of bacteria, so there are gram-positive bacteria which stain positively for the Gram stain and there are gram-negative bacteria which do not stain with the gram stain. So narrow spectrum antibiotics are typically only active against gram-positive bacteria, so if this antibiotic that you have screened and if it is active only against gram-positive bacteria such as staphylococcus aureus, then this is called as a narrow spectrum antibiotic, so one of the examples that we looked at in class is macrolides.

On the other hand broad-spectrum antibiotics are active against both gram-positive as well as gram-negative bacteria. So these are highly potent molecules which can get rid of both gram-positive as well as gram-negative infections. The example that we have looked at is amino glycosides. So that narrow spectrum antibiotics are able to permeate into gram-positive bacteria, whereas the broad spectrum permeates into both gram-positive as well as gram-negative in order to hit the target.

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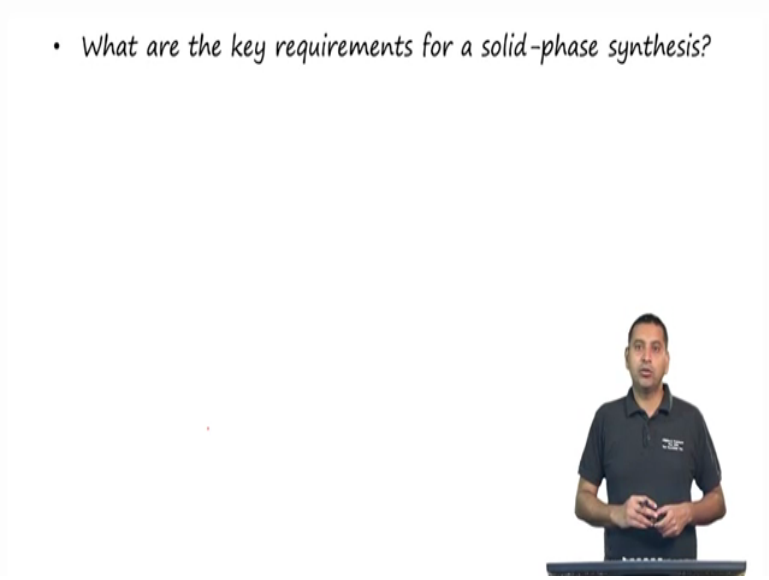

The next question is what are the key requirements for a solid phase synthesis? So we have looked at this concept in class and the idea here is that you want to move from solution phase synthesis to solid phase synthesis because of ease of conduct of the reaction and workup and isolation.

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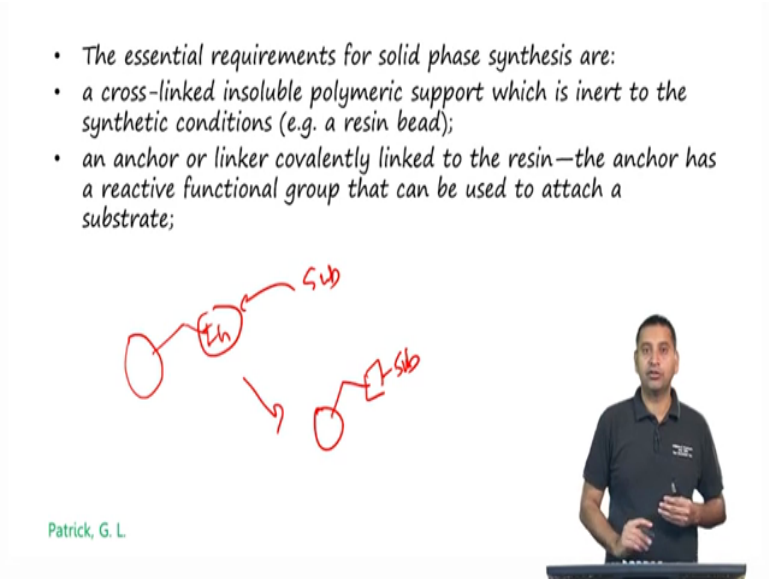

So the essential requirements for solid phase synthesis are you need a cross-linked insoluble inert polymer support and for example you can use a resin bead, you need an anchor or linker that covalently links the resin and has a reactive functional group that can be used to attach the substrate. So you need a something here which has a functional group which can react

with your substrate and anchor it. So you would be looking for a situation where you have the substrate which is immobilized on the surface.

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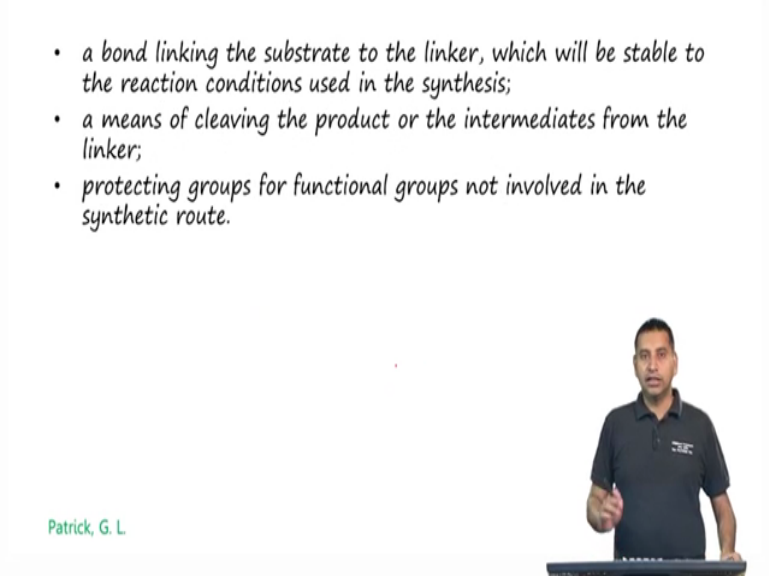

Then you need a bond which links the substrate to the linker which will actually be stable to the reaction conditions used in the synthesis. So if you have a bond that is going to be labile then the substrate will be washed off during the workup, so that bond that you need to construct will have to be inert to the reaction conditions used in the synthesis. Then once the product is formed you would need a way to cleave the product from the linker. So here you need a chemistry which is useful or which is efficient in cleaving the product otherwise the yield of the product is going to be extremely low.

Lastly if there are other functional groups that are available in the substrate those will have to be appropriately protected otherwise they will interfere with the reaction. So in order to develop a solid phase synthetic method you need these above mentioned aspects to be conditions to be fulfilled.

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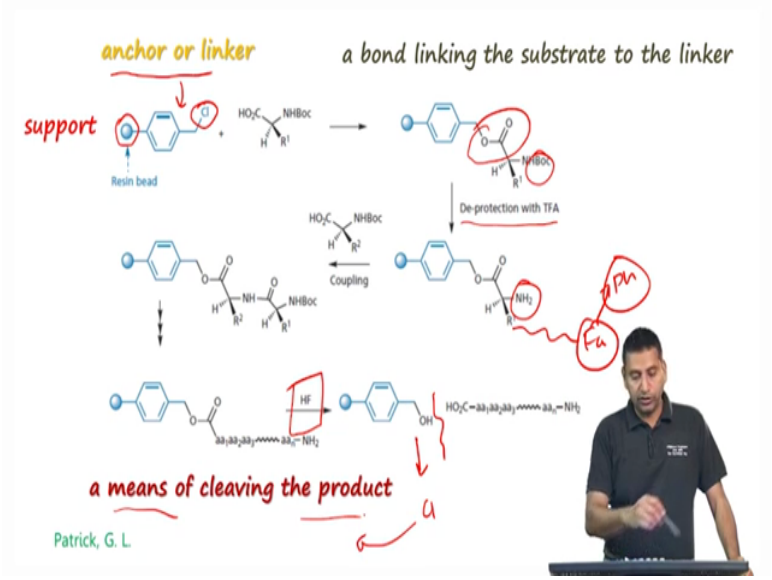

So just to summarize with an example, so here is the resin bead which is the support and you have an anchor or linker which is shown here and then here this is the reactive functional group which is the benzyl chloride which can react with a carboxylic acid to give the ester and this ester would be stable under the conditions of the reaction. So the reaction that we are going to do is a cross coupling reaction and so the ester is stable here not just that we may have to protect the substrate or a functional group in the substrate which we are going to use for the reaction.

So for example here we protect it with BOC and then we de-protect it, not just that we may have some other functional group here which might have to be protected. Then we do the cross coupling reaction and then we repeat this again and again and again with various substrates and then you should have a way to cleave the product. So the way you would cleave the product in this case is to use hydrofluoric acid which then breaks this bond to give you the free carboxylic acid and the alcohol. Of course here you can then subsequently convert this to the chloride and then reuse it for the next reaction.

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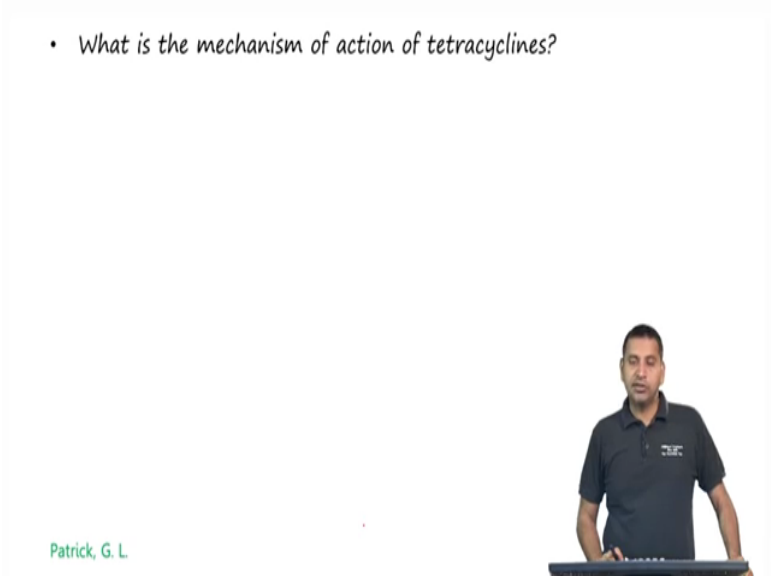

Next question is what is the mechanism of action of tetracyclines?

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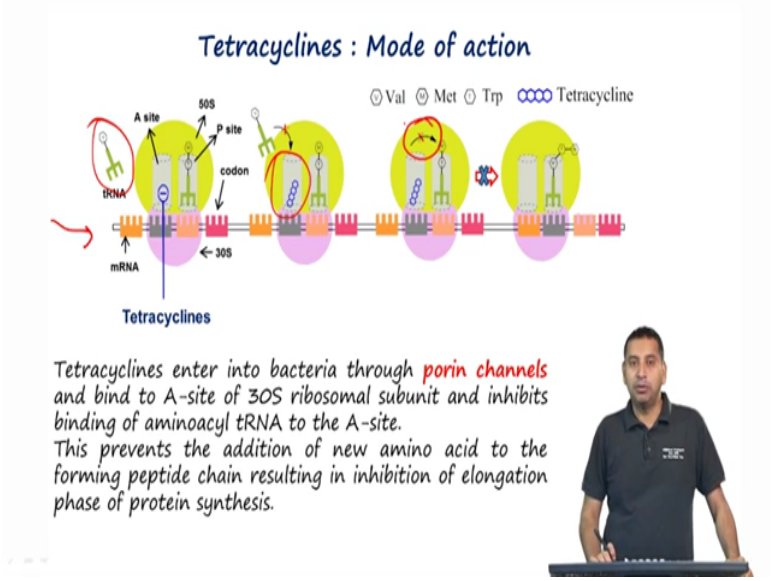

So tetracyclines enter the bacteria through porin channels and they interfere with the action of ribosomes. So the A site of the ribosomes which are important in protein synthesis is where this tetracyclines are going to bind to, so there are as we have discussed earlier there are two sub units of ribosomes the 50S sub unit and the 30S sub unit and here is the mRNA and here is a tRNA which comes which is charged with the amino acid.

So what happens is that we have already discussed this previously there is an A site and there is a B site and there is a codon and the codon is a three nucleotide unit which reads for or

which codes for the amino acid. Now what happens is that once the tetracycline enter and they enter through the porin channels, then they go and bind to the A site. So here is the A site of the ribosome and once it binds to the A site it prevents the binding of the charged tRNA into the A site. So once it prevents this then the next step which is shown here will does not occur and therefore you have incomplete protein synthesis.

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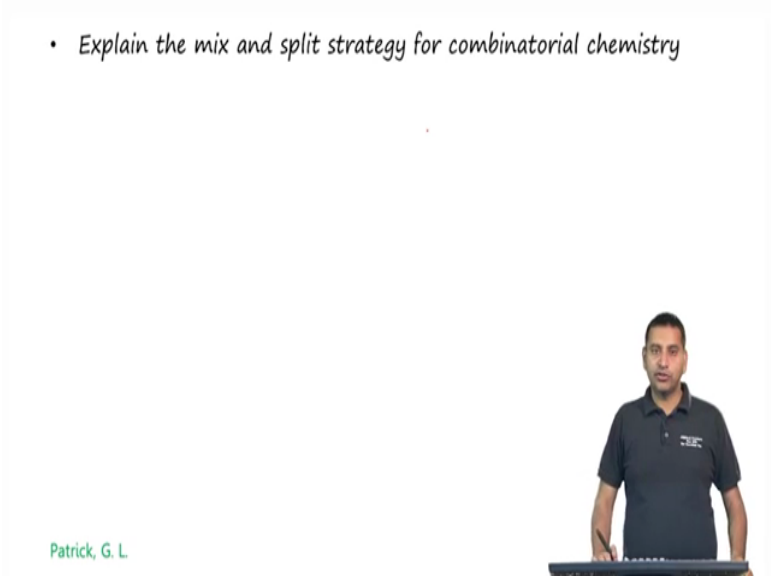

The next question is explain the mix and split strategy for combinatorial chemistry.

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So mix and split strategy as we have discussed before is the way in which you would generate libraries of mixtures of products, but this does not mean that we randomly have

mixtures of molecules but we have a very controlled way of generating a mixture of molecules. And we would have intimate knowledge of what is there in the reaction vessel.

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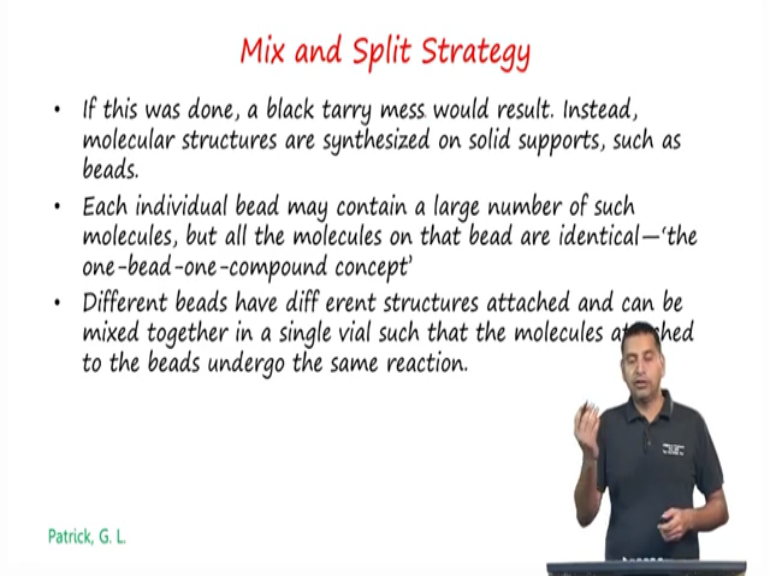

So otherwise what would happen is we would get a black tarry mess. So the way we would do this is to follow the one bead one compound concept.

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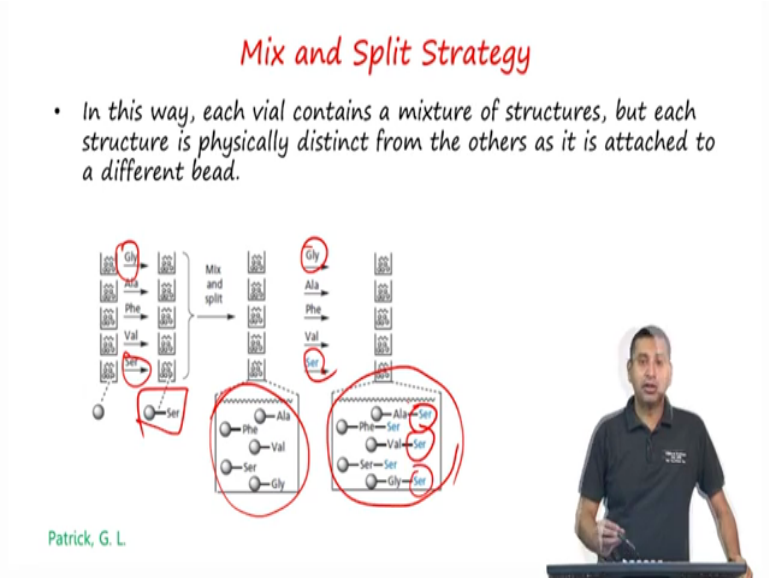

So the example that we have looked at is in again in peptide synthesis. So we would have a set of beads which have which are charged with a single amino acid as shown here, then what you do is you mix these individual components and then divide them among maybe five or

six vessels and to each of them now you add the next amino acid. So for example you have glycine added here or serine added here.

So if I zoom into this vessel it will contain a mixture of all of these mono amino acid residues and then after the reaction these are going to contain a dipeptide which is then going to have a series of structures but they are all very defined. So for example in all of these serine is the terminal amino acid.

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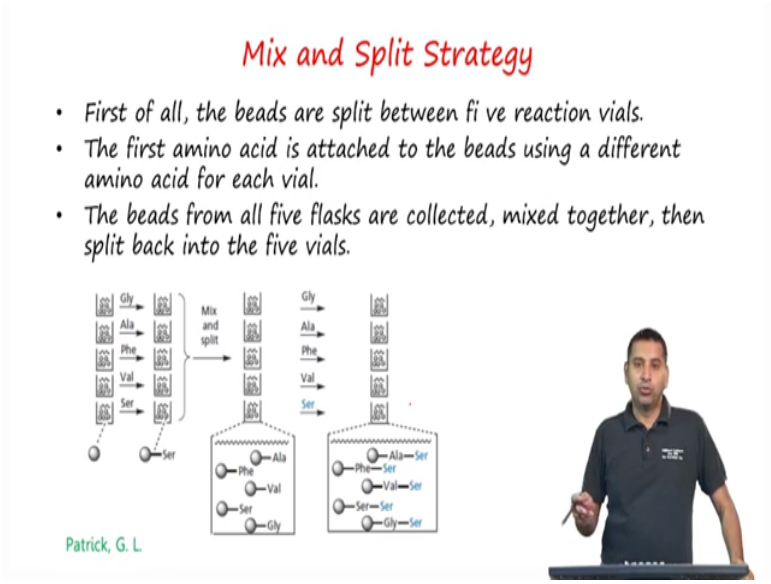

So then what you do is then you can go repeat this process and from all the five flasks so then again split it into five vials and so on.

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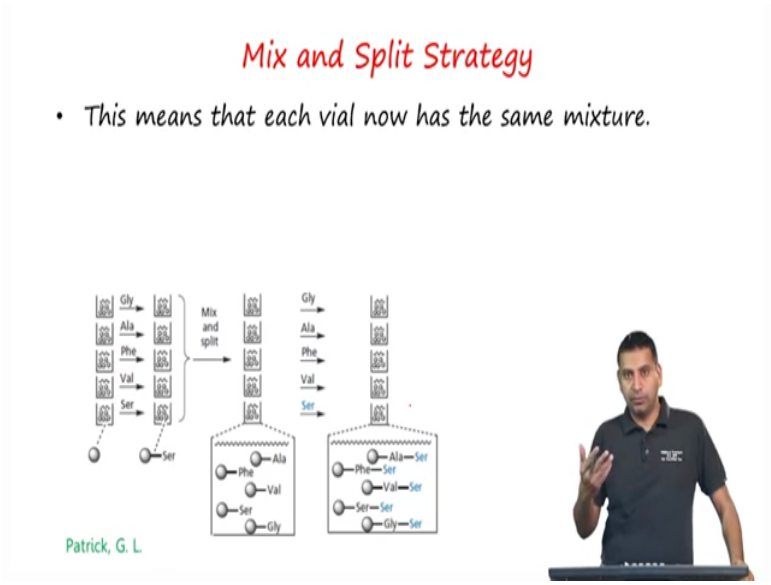

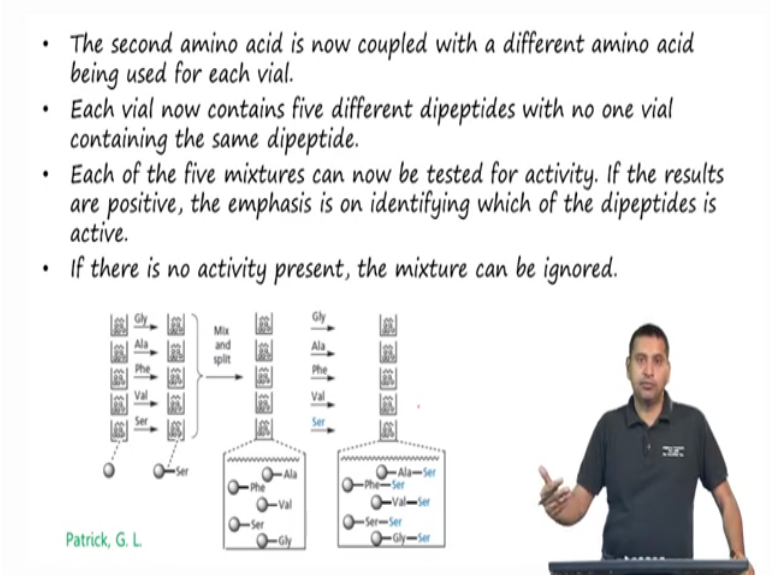

So here if you look at the you know the mixture then we take this mixture and screen for biological activity and if the mixture does not have any significant biological activity it is discarded. But if the mixture has some activity then we go back and since we know exactly what is the component of this mixture we can go back and synthesize each of these molecules and then screen them for the activity.

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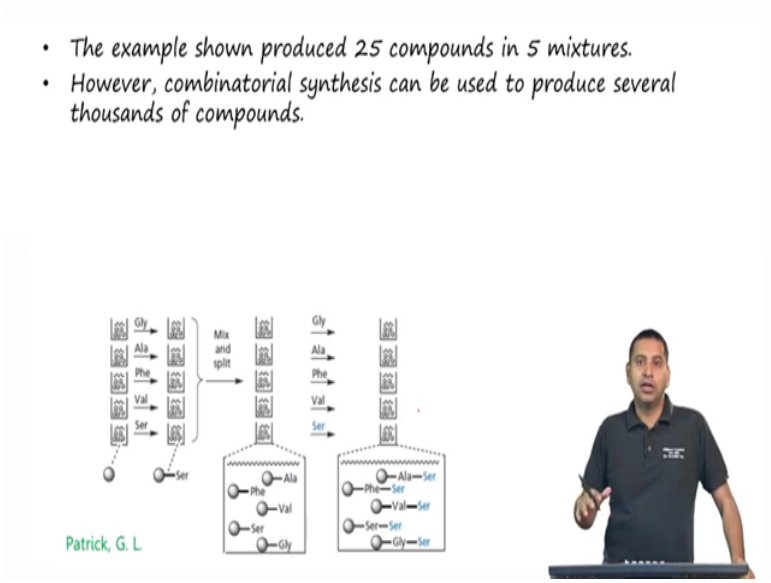

So in the example shown we have been able to generate 25 compounds in 5 mixtures, but what in reality we can do is to actually have thousands of compounds using combinatorial synthesis.

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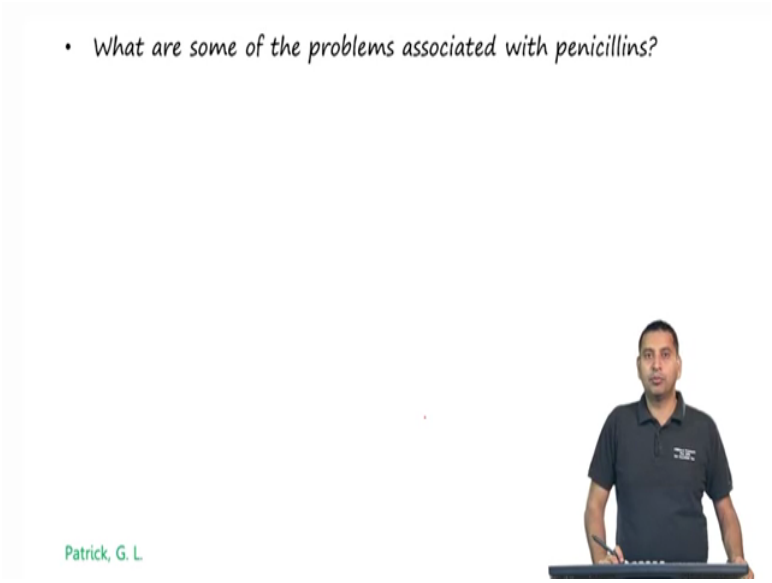

Next question is what are some of the problems associated with penicillins?

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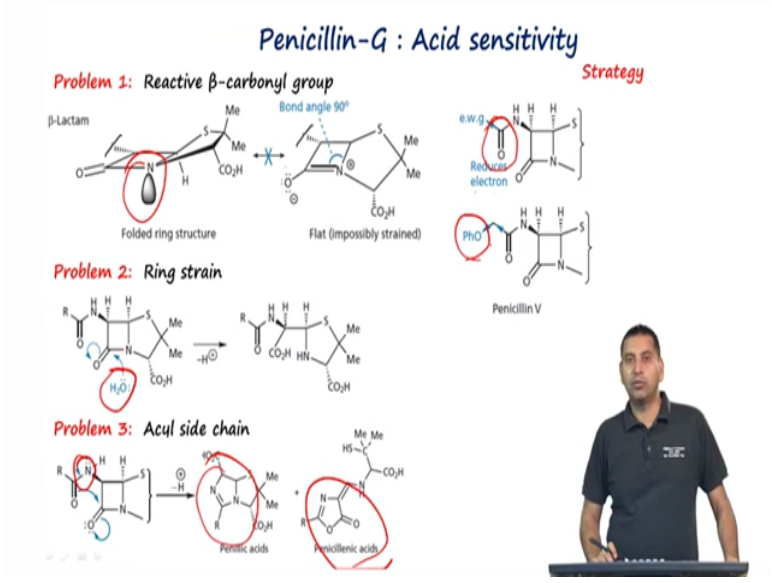

So one of the major problems that we have encountered with penicillins is the lack of oral bioavailability and this is because once it gets into the stomach where the acidic pH in the stomach cleaves it and if you go back and look at the structure of penicillins it has a beta lactam structure, but you know because it is present in a bicyclic system it does not form the amide, so this is not like a traditional amide and therefore it is more susceptible to cleavage.

So you have under acidic conditions you can open up this beta lactam and generate a carboxylic acid and amine, this by-product or product that is formed is actually inactive. So

one of the major problems associated with penicillins is the lack of stability in acids. So therefore penicillins are actually injected.

The next problem is actually the susceptibility to cleavage by the acyl side chain. So here even if you have an electron withdrawing group what happens is that the lone pair on the nitrogen is important and it can move and form a you know intramolecular reaction to give you what are known as penicillic acids or penicillanic acids and both of these are actually inactive.

So the strategy that one would adopt to sort this problem is to actually put in an electron withdrawing group on this carbonyl functional group here and the reason we would do this is then it would reduce the possibility of the attack intramolecular attack. So one of the ways in which to do this is to put a phenoxy ether and because oxygen is electronegative it pulls electrons from the carbonyl and reduces the possibility of the intramolecular reaction.

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The next question is explained de novo drug design.

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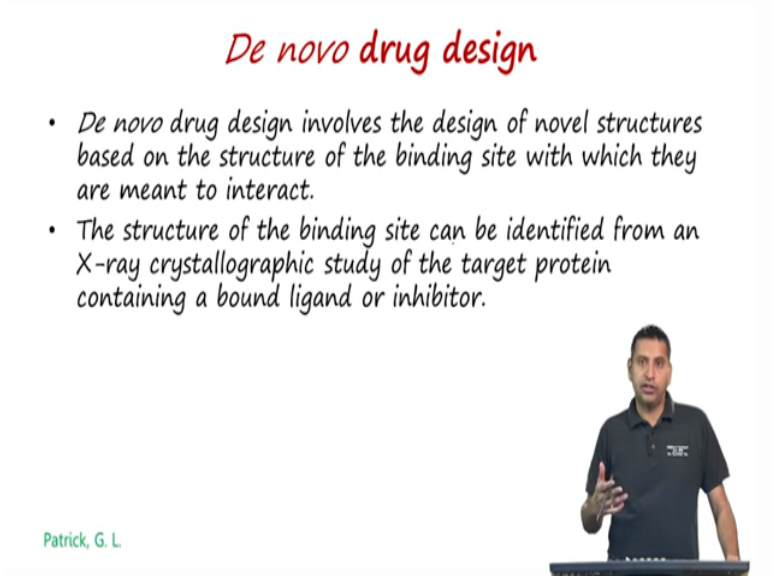

So as the name de novo suggests it is actually from scratch. So the way we would do this is basically by starting from the knowledge of the structure of the binding site and this has to be obtained from x-ray crystallography. Ideally we would want a structure of the protein target protein which is bound to the ligand or inhibitor. So then that gives us intimate knowledge of what the major interactions are.

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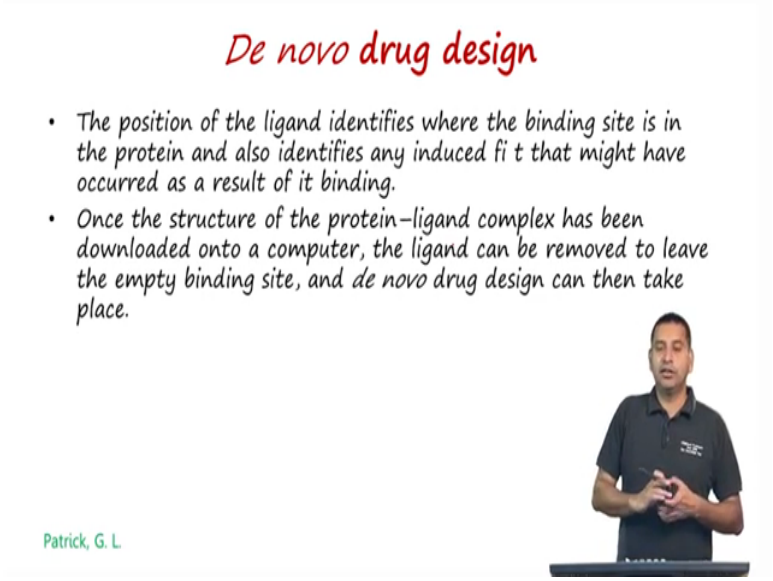

Once we have this then we can download it onto one of our computers and then delete the structure of the ligand and whatever is remaining which is the protein is the starting point for our de novo drug design.

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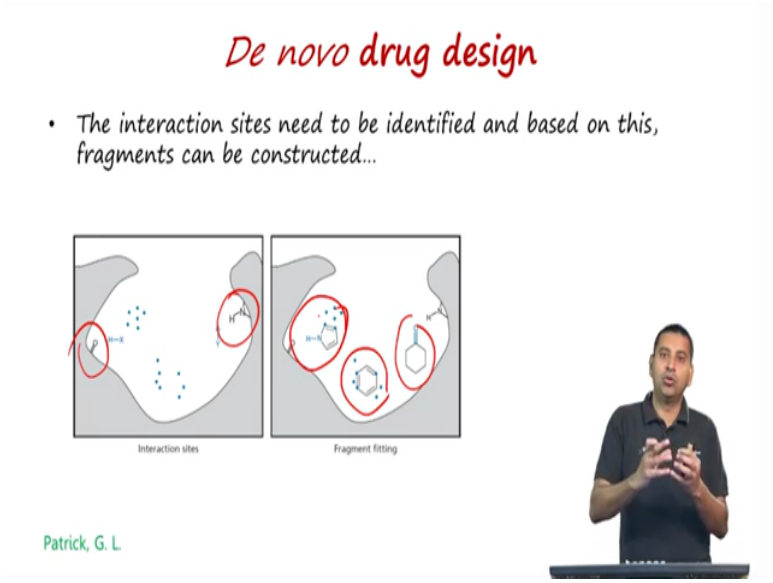

Then what we do is then we systematically start populating these binding areas. So for example here you have an NH, you have a carbonyl and you have some hydrophobic interaction sites and so then you can start putting in fragments and here is the first fragment that you can put in which is a aromatic ring or you can put a carbonyl or a heterocyclic moiety and all of these are designed to go and bind to this active site.

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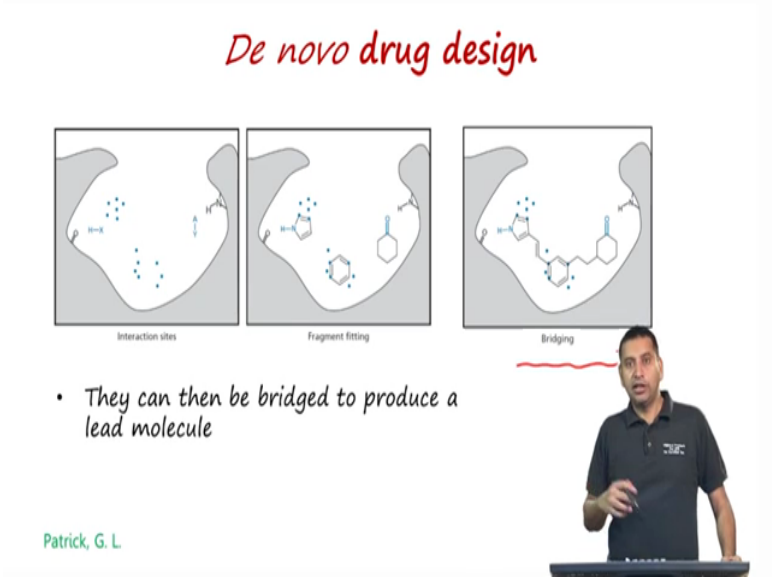

Now what our job would be to start bridging these molecules and this will help us identify this kind of a structure which is going to perhaps I have activity. So of course the way to find this out would be to actually go and synthesize the molecule and test it out.