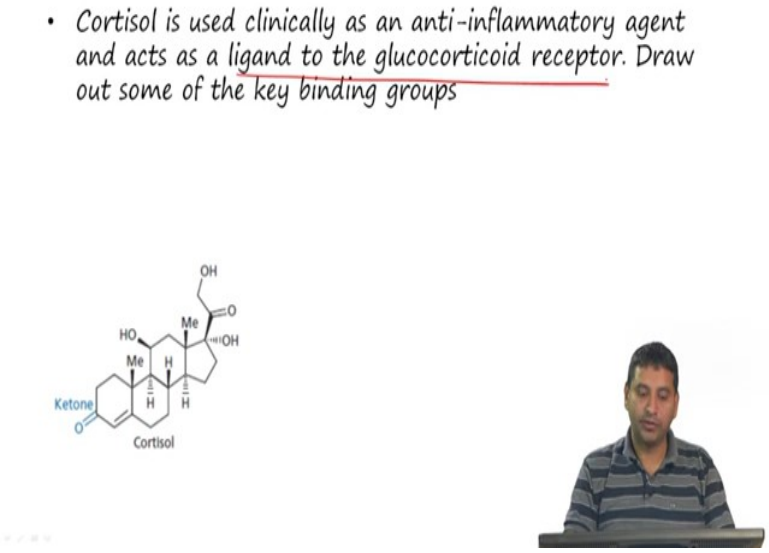
Medicinal Chemistry
Professor Dr. Harinath Chakrapani
Department of Chemistry
Indian Institute of Science Education and Research, Pune
Tutorial-07
Receptor-Drug Interactions, Stereochemistry, Chirality, Nomenclature

(Refer Slide Time: 0:16)

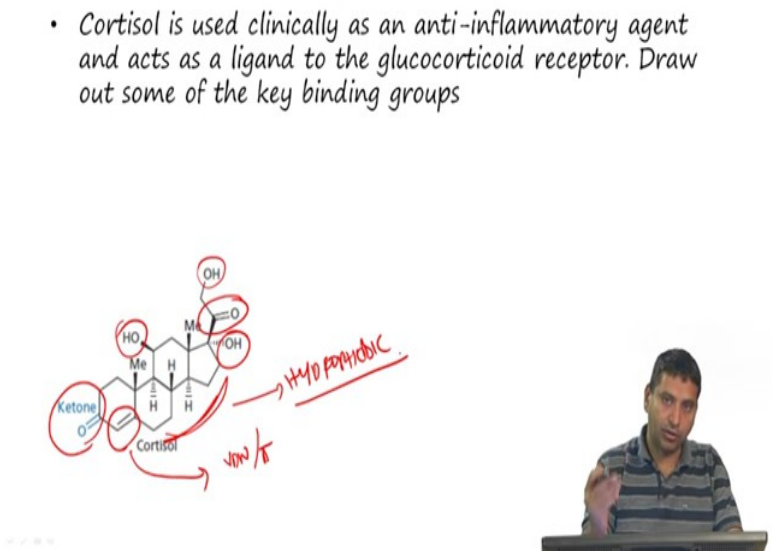
Welcome to the tutorial session.

(Refer Slide Time: 0:20)



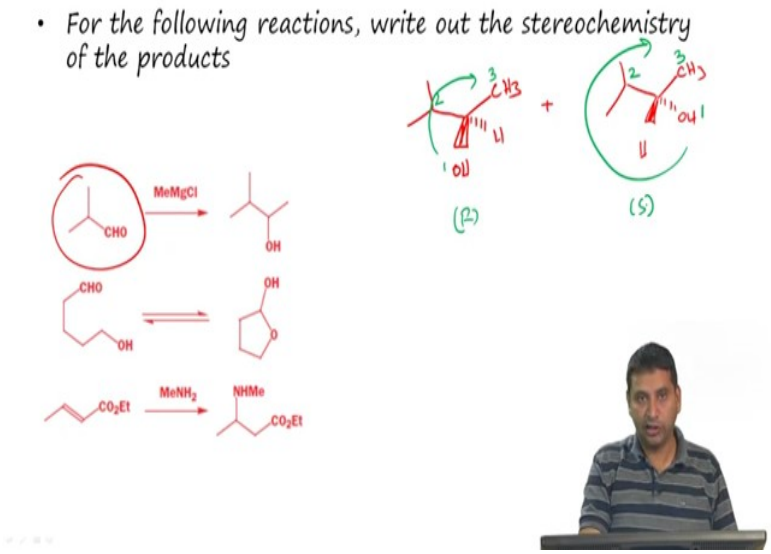
So what we will start out is looking at how a ligand binds to the receptor, so Cortisol used clinically as an anti-inflammatory agent and acts as an agent to the glucocorticoid receptor. So draw out some of the key binding groups.

(Refer Slide Time: 0:35)



The major functional groups that are present in Cortisol are as follows, you have a carbonyl C double bond O here, there is another carbonyl C double bond O, there are hydroxyl groups present here these are the major hydrogen bond donors and acceptors in Cortisol, you also have a olefin which can involve itself in Van der Waals interaction or pi interactions and you have a good significant hydrophobic which can interact with the receptor surface. So these are the major key binding areas that one can identify from the structure. So keep in mind that Cortisol because it is hydrophobic can get across cells quite well.

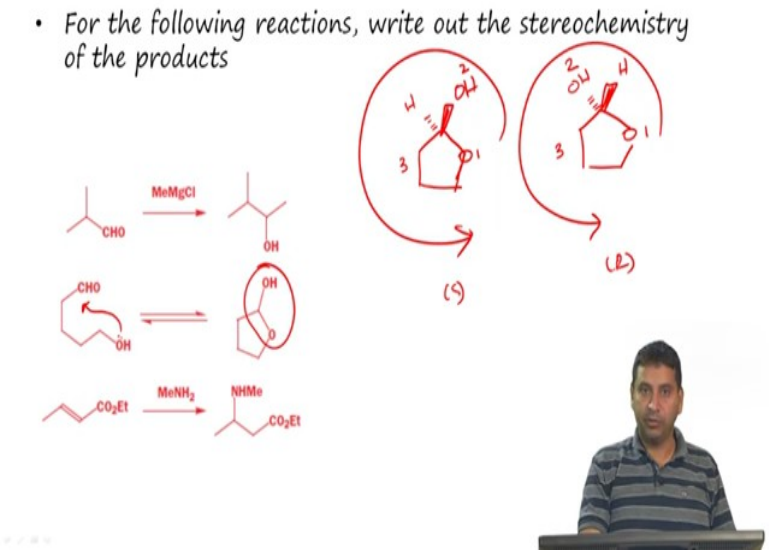
(Refer Slide Time: 1:24)



Now let us look at some revise some concepts on stereochemistry, so if you take this aldehyde and do a reaction with methyl magnesium chloride you get this product. So the question is write out the stereochemistry of the product. So in order to answer this let us first write out the rest of the molecule which is you would expect this product plus hydrogen in the front, hydroxyl group inside and the methyl group over here.

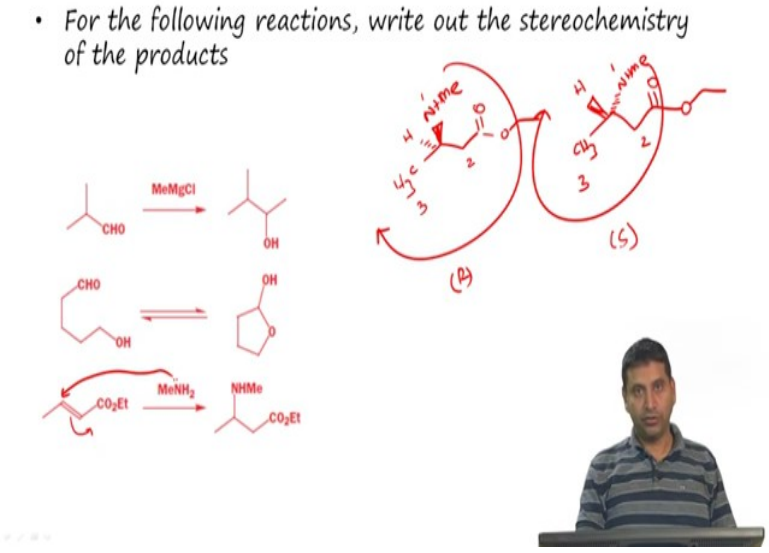
So these two this is a pair of enantiomers that you would get and now let us (look at) assign the absolute stereochemistry, so in order to do that let us look at so this would be priority number 1, this will be priority number 2, this is priority number 3 and so if you do this is clockwise R because this priority is inside of the plane. Here let us do the same assignment, this is priority number 1, this is priority number 2, this is priority number 3 it is clockwise but since hydrogen is coming towards us we would flip the stereochemistry and this would actually be S. So you will end up with a racemic mixture as shown here.

(Refer Slide Time: 2:47)



Now to the second problem where we have the formation of an intermolecular adduct here as shown here which is a hemiacetal. So now let us draw this structure separately as shown here we have an oxygen and this OH can be up or and the hydrogen is going in or in the other possibility you have a hydrogen going up and OH going in. So here if we were to assign the stereochemistry the priority would go number 1 over here, number 2 over here and number 3 over here and so this would be anti-clockwise and so this would be S and in the next case you would have priority number 1 here, priority number 2 here and priority number 3 here and this is again anti clockwise but since the hydrogen is towards us this would become R. so again you get a racemic mixture as shown here.

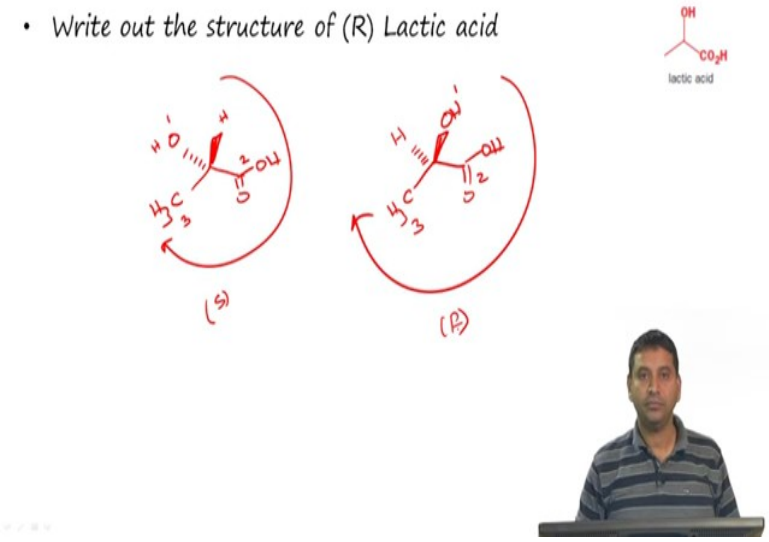
(Refer Slide Time: 3:52)



In the last case let us look at a Michael Addition reaction, so here you have is amine attacking here and then you can push the arrows to give you the final product, we are not going into the details of the mechanism, but I am just going to draw the structure like this you have NHM e like this and the hydrogen can be inside or this methyl group here or NHMe can approach from the bottom and the hydrogen goes to the top and methyl group is here again let us look at the priorities here, so this is priority number 1, number 2, number 3 so this goes like this, so this will be R because hydrogen is going inside.

In the second case you have the same priority 1, 2, 3 and again this is going clockwise but since hydrogen is pointing towards us this is assigned as S, so you get again a racemic mixture as shown here.

(Refer Slide Time: 5:08)

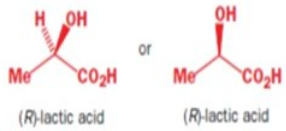


Next question is write out the structure of R lactic acid. So let us see how to systematically approach this, so I do not know what are lactic acid to begin with this so I have to make a choice. So let me first choose let us draw the structure of lactic acid in the following manner and I will just assign this as a stereochemistry chemistry I mean we will put this stereochemistry over here and now let me just start by putting the hydroxyl group inside and hydrogen towards me.

Now let us assign the priorities this is priority number 1, number 2, number 3 so this is going clockwise but since the hydrogen is towards us this becomes S. Now let me repeat this exercise with the other structure which is possible, so here the hydroxyl group is coming

towards me, hydrogen is going inside and now again if we assign stereochemistry priority 1, 2, 3 this is going clockwise and since hydrogen is going inside it is R.

(Refer Slide Time: 6:24)



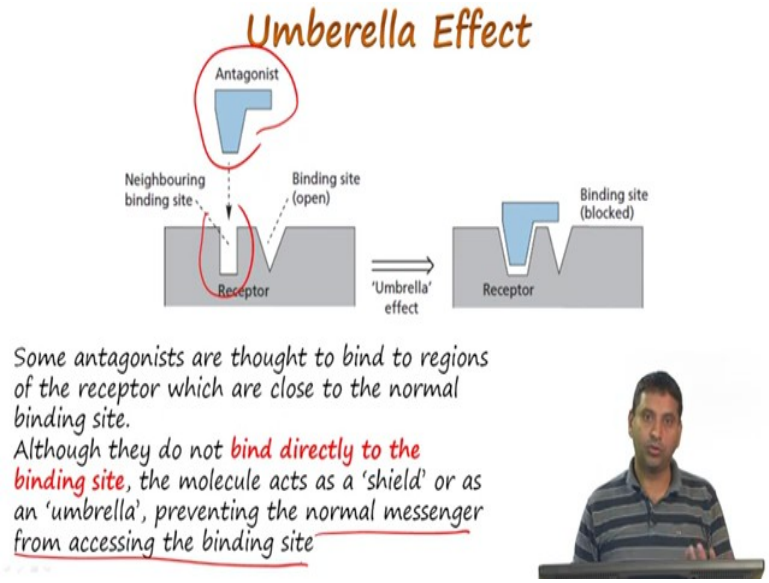
Now let us look at the structure of R lactic acid as shown here which is the correct structure that we drew out so in order to address this problem there is no simple formula to do this so it is better that we draw both the structures that are possible and then assign the correct structure and that would help us give the correct enantiomer.

(Refer Slide Time: 6:45)

- What is the umbrella effect?

Next question is what is the umbrella effect?

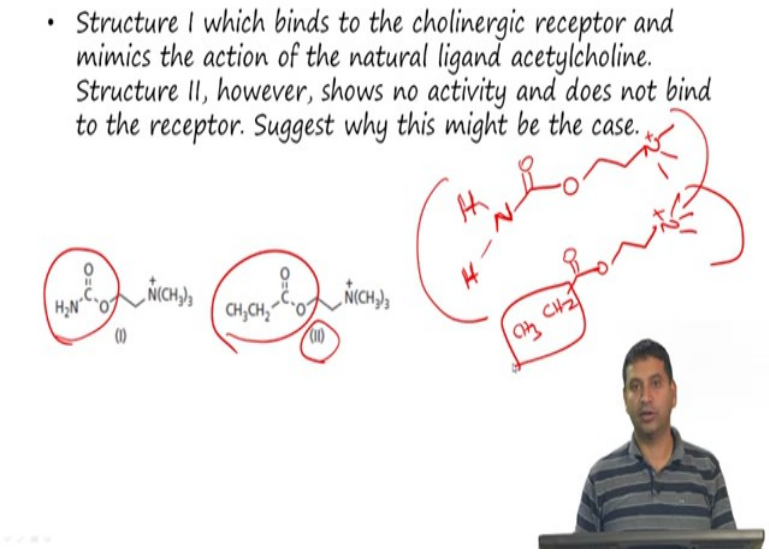
(Refer Slide Time: 6:50)



So umbrella effect we have looked at previously is an effect where a compound can act as an antagonist, but it does not bind to the active site or the binding site of the receptor, but what it does is it binds to a neighbouring binding site and once the antagonist binds to this neighbouring binding site because the structure is fairly large it actually blocks the binding site from functioning normally.

So therefore the normal messenger does not access the binding site and this is called the umbrella effect where you can imagine that there is an umbrella which is providing a shade. So it can provide shade to one individual or it can also provide shade to two individuals.

(Refer Slide Time: 7:34)

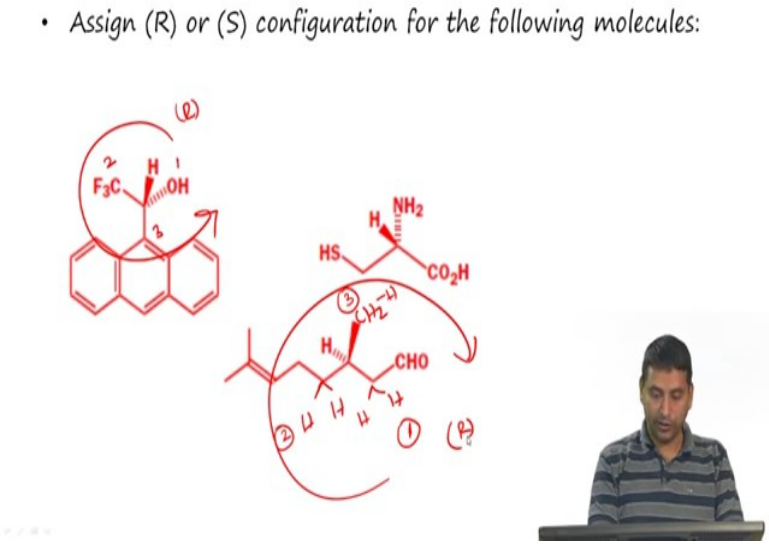


Next question is structure 1 which binds to the cholinergic receptor and mimics the action of natural ligand acetylcholine. Structure 2 as shown here shows no activity and does not bind to the receptor. Suggest why this might be the case. So in order to understand this let us look at the structures .So here you have a carbamate and here you have a ester, so since the second molecule does not bind to the receptor or shows no activity, it is quite likely that the first structure has a structural aspect to it which is very important and that is for the binding activity.

So if you look at the amide, the amide is NH C double bond O O in this case it is a carbamate so it is N the positive charge, so this part of the molecule is identical so there is no change here, so it is quite likely that this hydrogen and this nitrogen NH_2 group is very important. So we know perhaps that there is some hydrogen bonding interaction over here that does not happen in the case of the ethyl. So here you have CH_2, CH_3, C double bond O O and the rest of the molecule is the same.

So it is quite possible that there is an important hydrogen bonding effect that is important for the receptor to bind to the ligand which does not happen in the case of the second molecule.

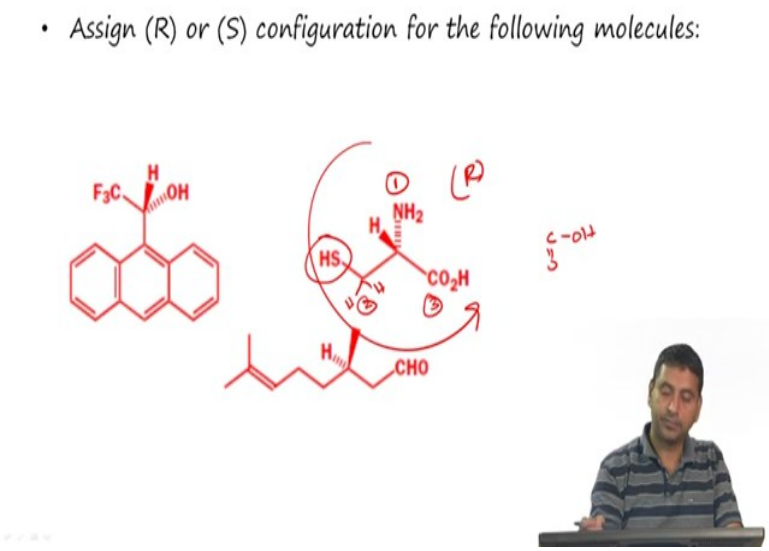
(Refer Slide Time: 9:18)



Now we have another case of assigning R and S configuration. So let us go through this systematically, so you have priority number 1, priority number 2, priority number 3 and so this is going in the anti-clockwise direction but since hydrogen is coming towards us this would be assigned as R, here you have an example of a molecule which has CH_2 and all of them have CH_2's in it, here the CH_2 is bound to hydrogen, here it is bound to an aldehyde and

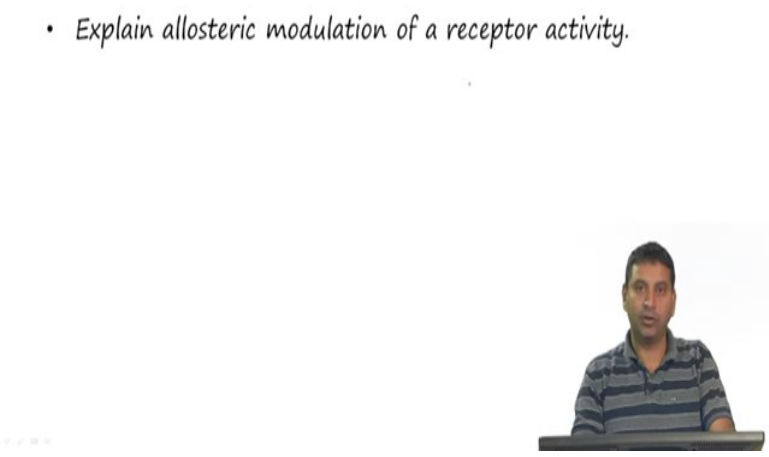
here it is bound to a carbon CH_2 and so this would get priority number 1, this would get priority number 2 and this would get priority number 3 and now if we have to look at the stereochemistry it is going in the clockwise direction and since hydrogen is going inside the board it would still be R.

(Refer Slide Time: 10:15)



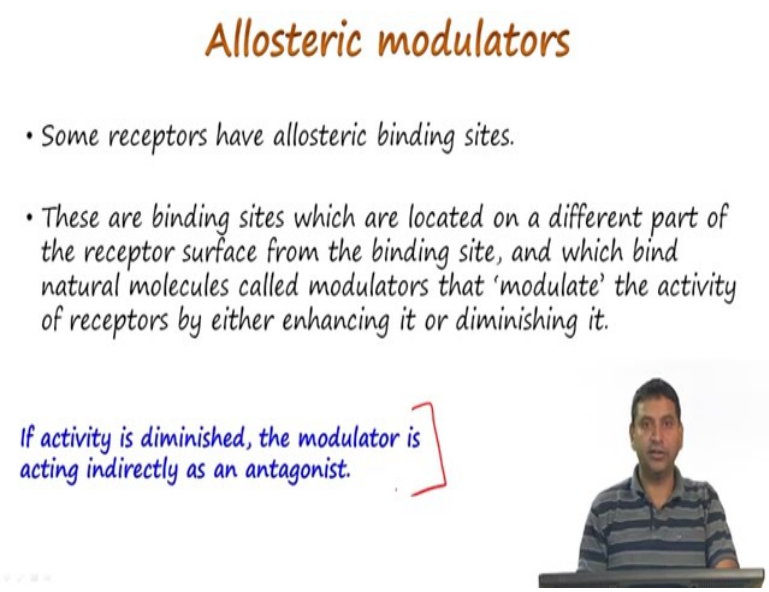
Let us look at the last example of cysteine, so here nitrogen gets priority number 1 and since the carboxylic acid can be drawn as C double bond OOH and the CH_2 is SH so since sulphur has a higher atomic number sulphur get a higher precedence compared to oxygen and so this would be priority number 2 and this would be priority number 3. So it would be in this case anti-clockwise direction since hydrogen is coming towards us this would be this is anti-clockwise and so it would become R.

(Refer Slide Time: 11:02)



Next question is explain allosteric modulation of a receptor activity. So again allosteric modulation is again very important because it is a way which receptors are regulated and regulation of all these biological micro molecules is very important for a normal functioning of a cell.

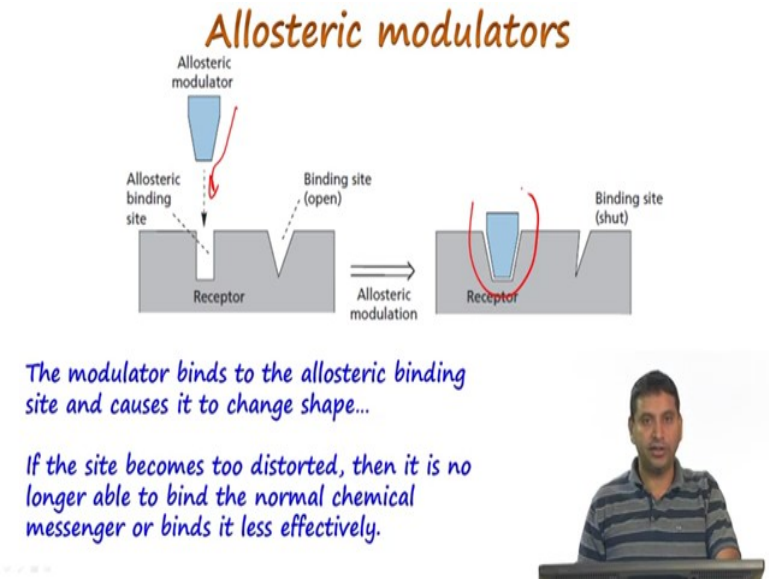
(Refer Slide Time: 11:18)



So allosteric modulators are nothing but molecules which can go and bind to a centre which is not the binding site and it can modulate it. (So these are) if there are binding sites which are located on a different part of a receptor surface from the binding site, but which bind to the natural molecules called as modulators and this because they bind they have an allosteric

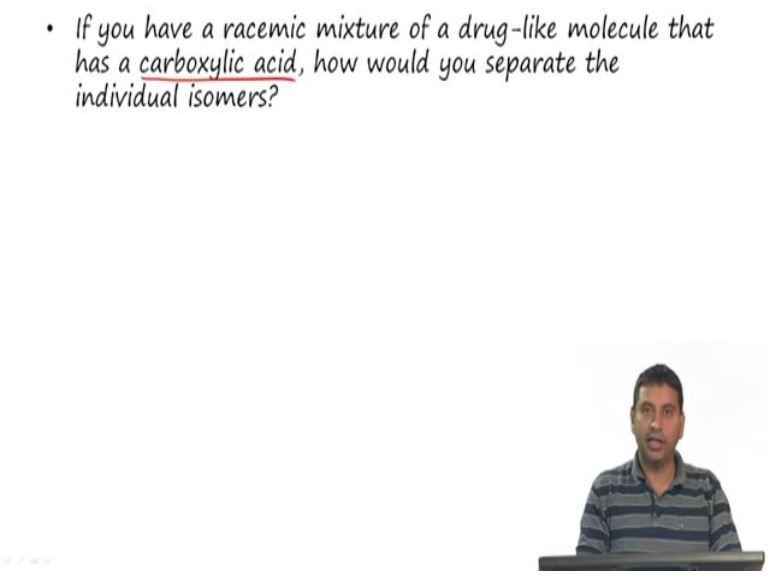
effect which can either increase or decrease the effect of the receptor. So if the activity is diminished then the modulator is indirectly acting as an antagonist.

(Refer Slide Time: 11:55)



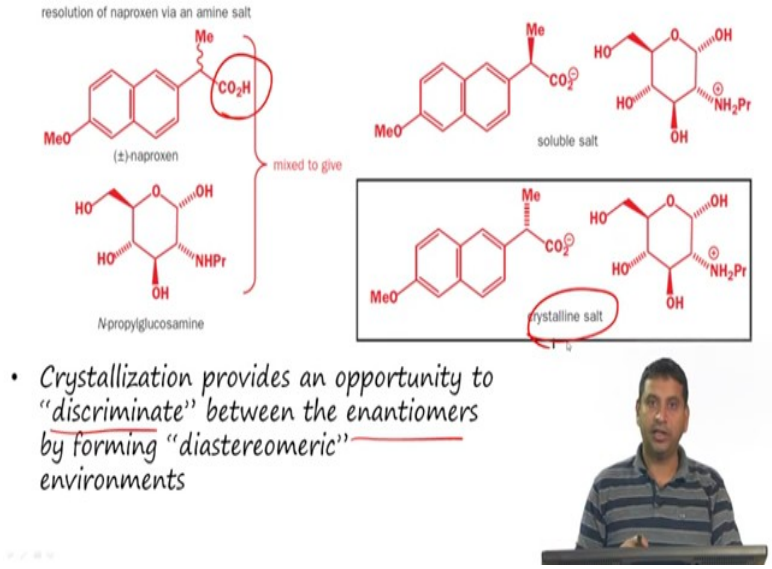
So here is the pictorial representation of this, so the allosteric modulator can come in and bind to a site which is not same as the binding site and once it binds it gives you it results in this particular case it closes the binding site and prevents further activity from happening, but it is also possible that this allosteric binding site can enhance the effect of the binding of the natural ligand and increase the activity.

(Refer Slide Time: 12:22)



The next question is if you have a racemic mixture of a drug like molecule that has a carboxylic acid, how would you separate the individual isomers?

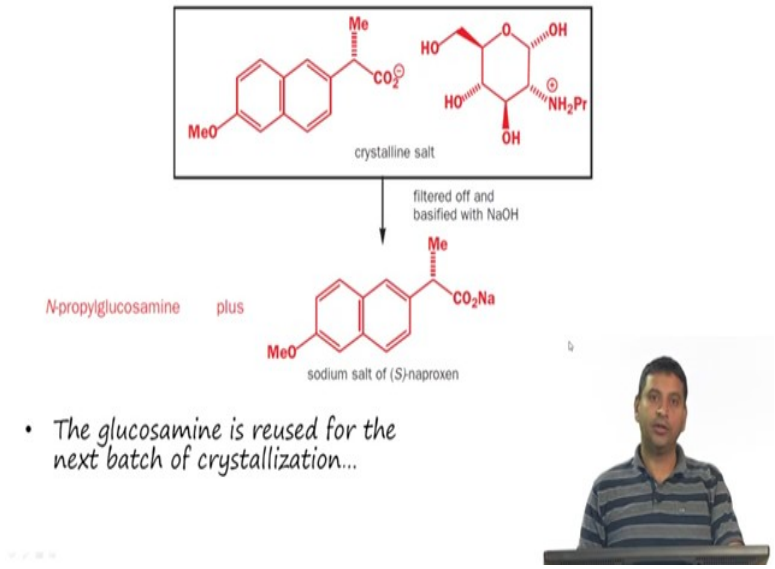
(Refer Slide Time: 12:34)



So we have looked at an example in class so which is basically naproxen, so naproxen has a carboxylic acid and since it is isolated as a racemic mixture what we can do is we can do crystallization. So crystallization provides us an opportunity to discriminate between these two enantiomers by forming a diastereomeric environment crystal. So since diastereomers are going to be different chemically and physically the possibility of this diastereomeric environment inducing different crystallization. So since it is possible there are small fractions of such carboxylic acids which can be re-crystallized as pure enantiomers.

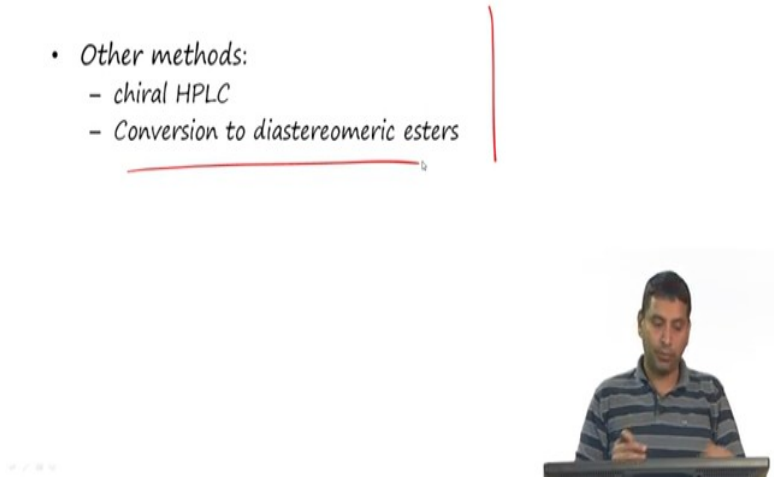
So the way this is done is you can make a crystalline salt of this molecule with *N*-acetyl glucosamine and then once you separate it out the soluble salt is separated out and then the crystalline salt as *N*-acetyl glucosamine can be further processed and now the glucosamine can actually be recycled after this.

(Refer Slide Time: 13:30)



So once you filter it off then you can use the glucose amine for the next batch of crystallization.

(Refer Slide Time: 13:36)



Of course there are other methods that one could use, one is the chiral HPLC where you use a silica which is which is coated with a chiral molecule and since you are going to produce a diastereomeric environment it is possible that they will elute at different rates and you can separate out this racemic mixture, you can also convert it to actual covalently modified and make diastereomeric esters with a chiral alcohol and since these diastereomeric esters are separable you can separate them and then you do a ester hydrolysis to give you the product.