Medicinal Chemistry
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Receptors as Drug Targets Part-1

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Today we will look at how receptors can be targets for new drug development.

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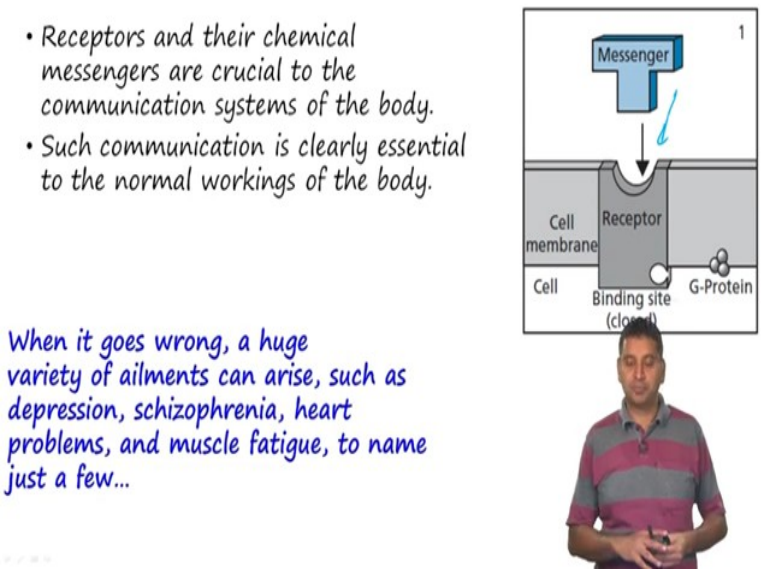

So just to recall we have looked at receptors how they function and so on and typically there is a messenger which comes and binds to the receptor and after the receptor binds to the messenger there is an induced fit which results in amplification of the signal and so here is an

example of a G protein couple receptor which we have looked at previously and of course we also are very well aware that such communication is vital for the normal functioning of the body.

So what goes wrong is that there are either there is an increased functioning of a receptor or diminished functioning of receptor and so this reads to a large number of ailments such as depression, schizophrenia, heart problems, muscle fatigue and just to name a few.

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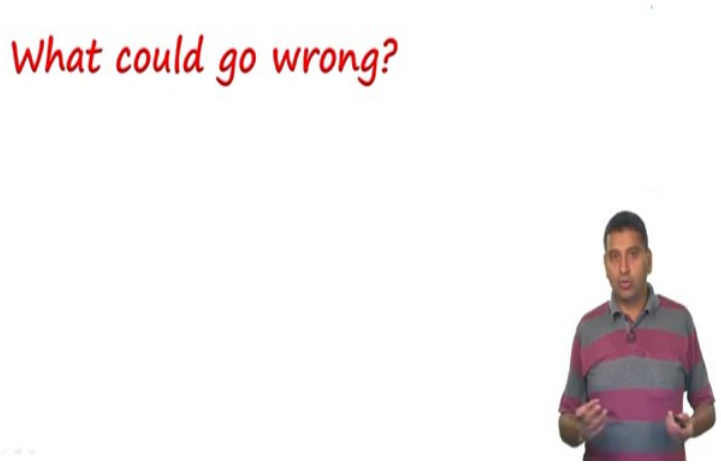

So what could go wrong?

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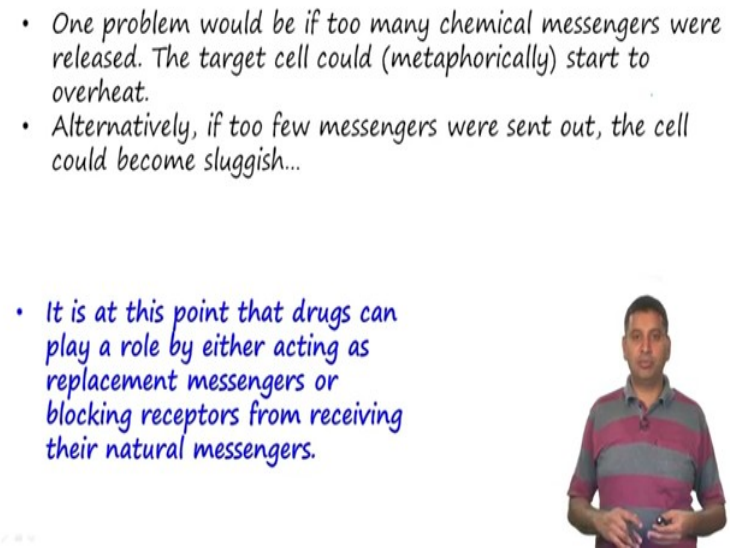

So one problem is that if there are too many chemical messengers which were released and so then the sort of target cell starts to overheat. Alternatively if there are too few messengers that were sent out, then the cell becomes sluggish and so we do not respond as well to stimuli. So both these are actually problematic and so and our approaches towards solving these problems would be opposite that is we would want to decrease the number of chemical messengers in the first case, whereas we would want to increase the receptor function by using or signalling by the second case. So it is at this point that drugs can play a vital role either by acting as replacement messengers or by blocking receptors from receiving their natural messengers.

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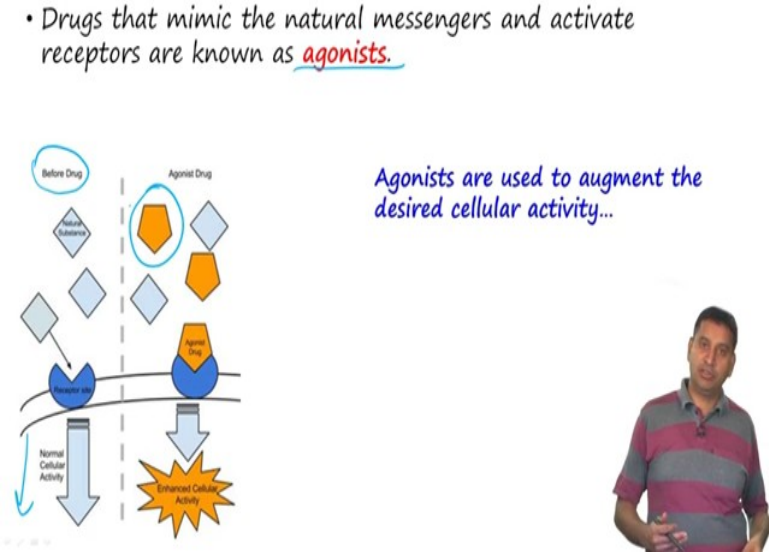

So let us look at the first case now, here what we would introduce this term known as agonists, agonists are nothing but small molecules which mimic the natural messenger and activate the receptors as the natural messenger would do. So here is the cartoon that represents it, so here let us say you have a before drug treatment there is some receptor that is being activated by this ligand and after the receptor is activated there is normal cellular activity, but now let us say we want to augment this the cellular activity then we would add what is known as an agonist drug which were then go and bind to this receptor and since there are more number of these molecules the function of the receptor would or the cellular activity would enhance.

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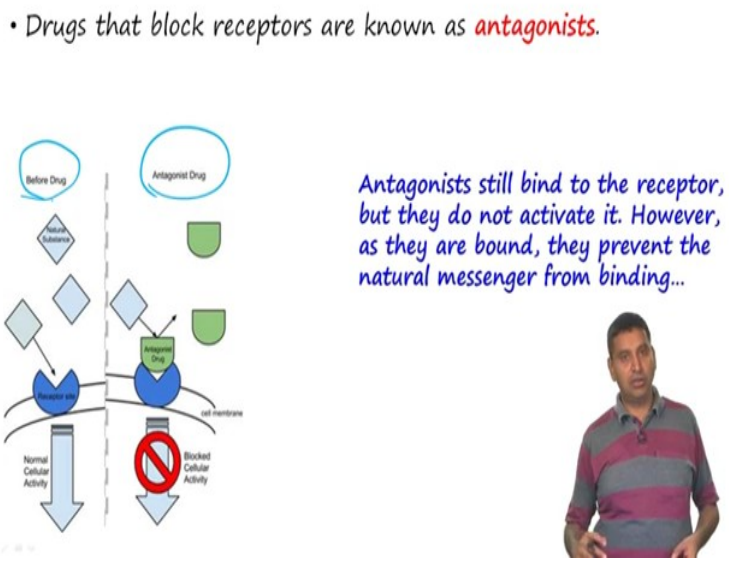

In contrast the drugs that block these receptors are known as antagonists. So antagonists basically what they do is that if there is (on the) on this side you see that before drug there is some functioning of a cell that is happening and now in the presence of an antagonist, the antagonist would go and bind to the receptor but will not activate it that means that the signal is not going to be transmitted.

So therefore an antagonist would bind to the receptor but it would not activate it and therefore the natural messenger (would now) will not have a place for it to bind and so together what this results is in is a diminished cellular activity.

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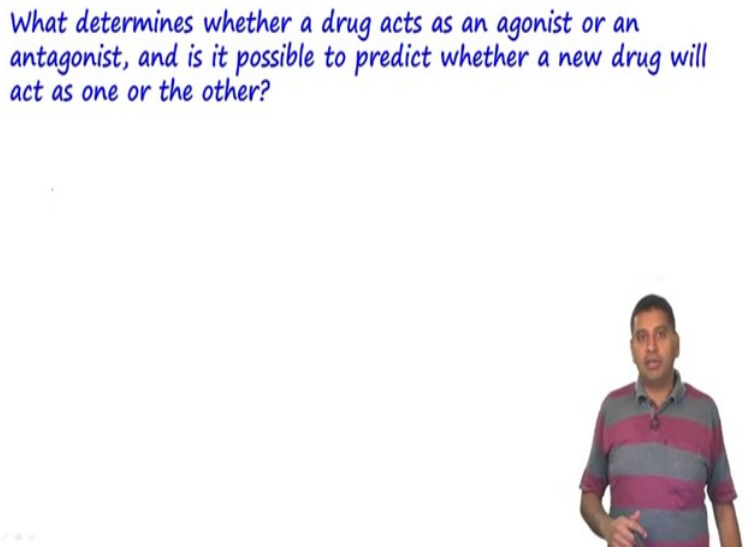

So what determines whether a drug acts as an agonist or an antagonist, is it possible to predict whether a new drug will be one or the other? So these are some of the important questions that we would ask in this lecture.

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And in order to answer this, what we need to do is we need to go into a fundamental molecular level and consider what happens when a small molecule binds to the receptor. So we have looked at previously in detail a broad picture we have looked at is to how various classes of receptors function, but we have not really looked at it from the molecular level. So what we will do now is to look at these types of interactions and see how we can design an antagonist or an agonist as the case maybe or as the application maybe.

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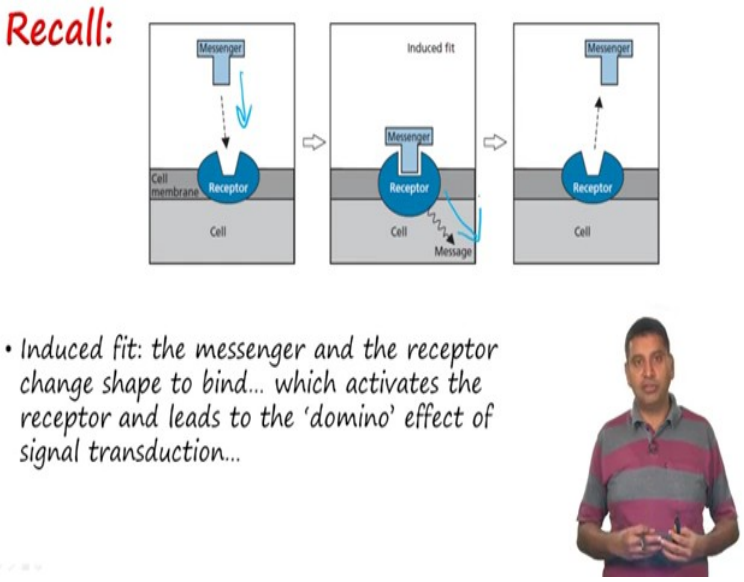

So just to recall the understanding of how a receptor functions is that there is what is known as an induced fit, so there is a natural messenger which then comes in binds to the receptor and the receptor would have to alter its shape in order to bind to this messenger molecule and the messenger molecule would also have some shape changing effect and together it binds and then that results in a message being sent out.

After the message is sent out, we will look at how receptors are regulated later, but then the messenger must dissociate and then the signal transduction stops. So together this induced fit model helps us understand how signals are transmitted by binding of a messenger to receptor.

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In order to design an agonist, we need to know what the binding sites are. So we would have to have the knowledge as to where the receptor binds the ligand, how it binds it and then it would help us understand what is going on in or how the receptor functions? So keeping this in mind there are three major characteristics or major requirements that we would need in order to design an agonist.

The first one, the drug must have the correct binding groups, if it does not have the correct binding groups then it is likely that it may not bind to the major parts of the receptor. The second one is a drug must have these binding groups correctly positioned, so not only must it have the binding groups but they must also be correctly positioned and lastly there must be the right size for the binding site, so if you design a molecule which is too large, then it may not even go and interact with the receptor site and therefore it may not be able to present its binding groups in the proper manner.

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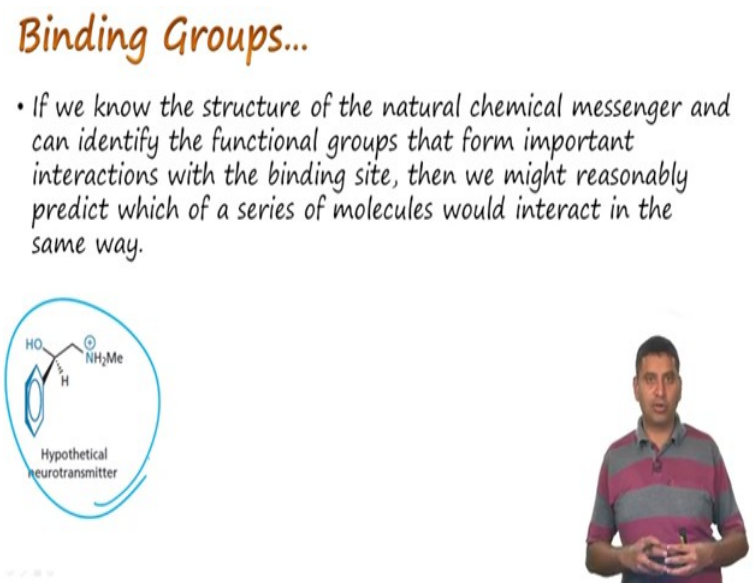

So now let us look at what the binding groups are. So let us say we have a receptor a hypothetical receptor and we know the structure of the natural chemical messenger, so as shown here this is the hypothetical neurotransmitter. Now what we need to do is to understand this molecule from the perspective of how it is going to bind to the receptor. So looking at this group we should be able to reasonably predict what happens in this molecule and what are the major binding groups that are important?

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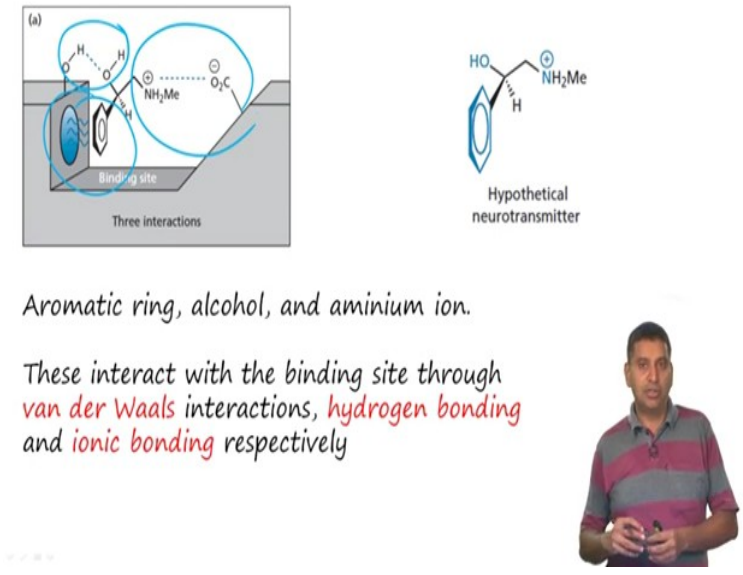

So let us say we look at the receptor site receptor binding site and again being a hypothetical example we could suggest that there could be three major interactions, so the first interaction is this hydrophobic interaction or Vander Waals interaction over here, the second one would

be a hydrogen bonding and the third one would be an ionic bond, okay. So we can reasonably predict that these may be the three major interactions that would occur with this hypothetical neurotransmitter.

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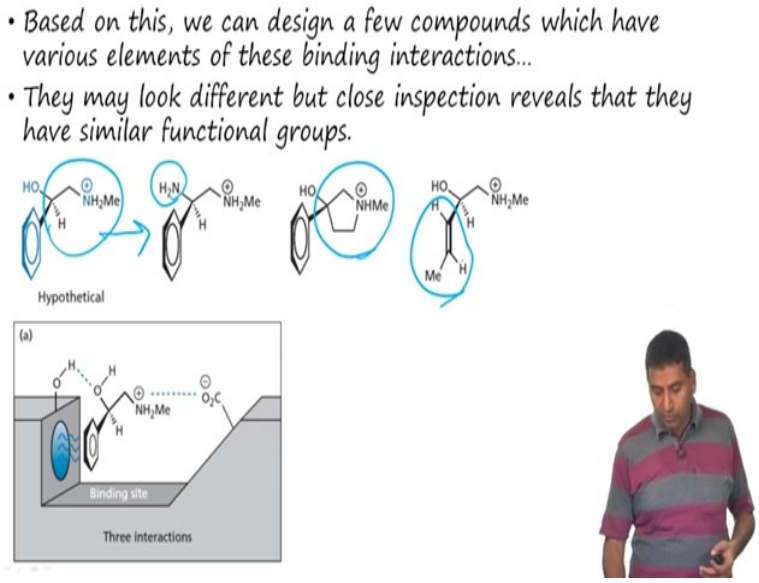

So based on this information we could then design a series of compounds which have similar functional groups. So starting from here let us say what we do here is we replace the hydroxyl group with an anime, so the amine has a hydrogen which can interact in hydrogen bonding, so therefore it may be a good replacement for a hydroxyl group. Alternatively we could close this ring so if you see here this is an open chain compound and we can close this ring and make it into a five membered pyrrolidine.

Alternatively we could replace this benzene ring over here with an olefin. So all these have some small tweaks in the functional group and then what we could reasonably suggest is that these may be compounds that may go and bind to this receptor.

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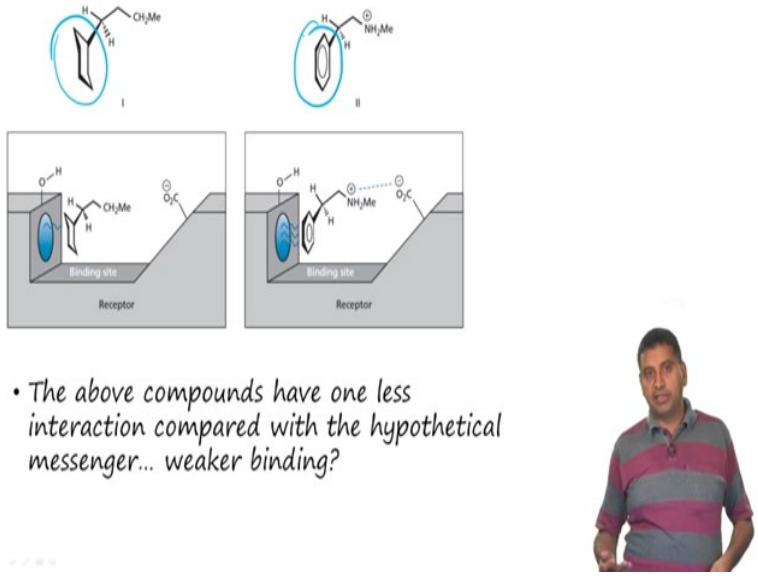

So there could also be situations where we could reduce one of the interactions, so let us say we design this kind of a molecule where you have a lower Vander Waals interaction or here where there is no hydrogen bonding capability. So what ends up happening is that you will have lesser number of interactions with the receptor. So we would predict that it would have weaker binding.

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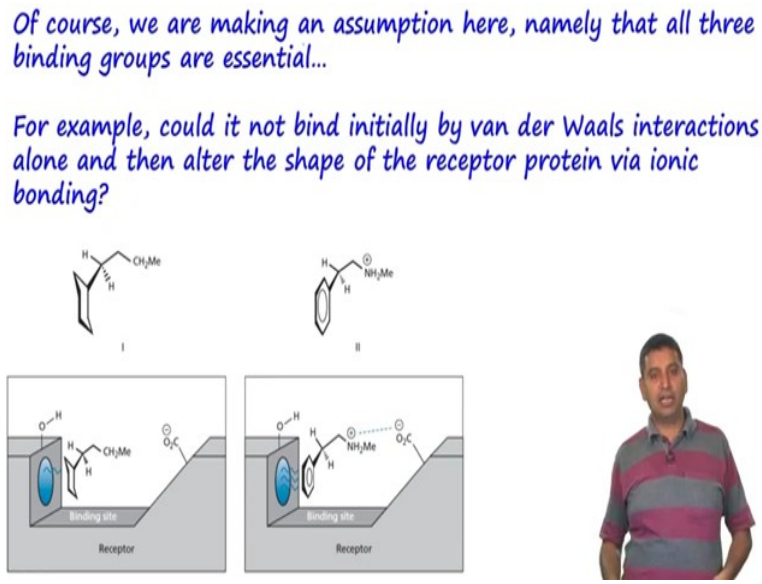

Of course, here in this process we are actually making an assumption we are assuming that all three binding groups are essential. So it may turn out that the Vander Waals interaction may first occur and that may have a major impact on altering the shape of the receptor and with

ionic bonding and Vander Waals interactions alone it is possible that the receptor can function exactly the same way as it would even without the hydrogen bonding interaction.

So what we would need to do as you will figure out the logic that we are trying to apply here is that we would first start out by and trying to predict what the binding interactions would be and then from there we would probably systematically change the group so that we can understand which binding interactions are more important and which binding interactions are not that important. So this is the exercise that we would normally undertake if we want to design a agonist.

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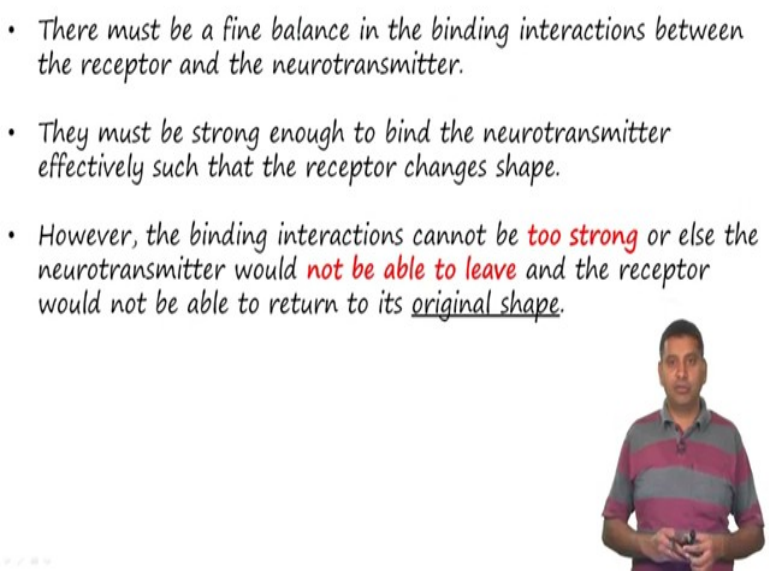

And as we can see here there must be a balance, so if the binding interactions are too strong then it is possible that it is going to bind but it is not going to let go and if that happens then that is not very desirable. Alternatively it is also possible that you will have a very weak binding so that then the conformational change that is required to occur may not happen and so the balance that needs to be achieved is very important.

So if the interactions are too strong then it is possible that it would not leave and it would not return to its original shape. So we will have to figure out what is the optimal number of interactions for us to mimic the natural substrate.

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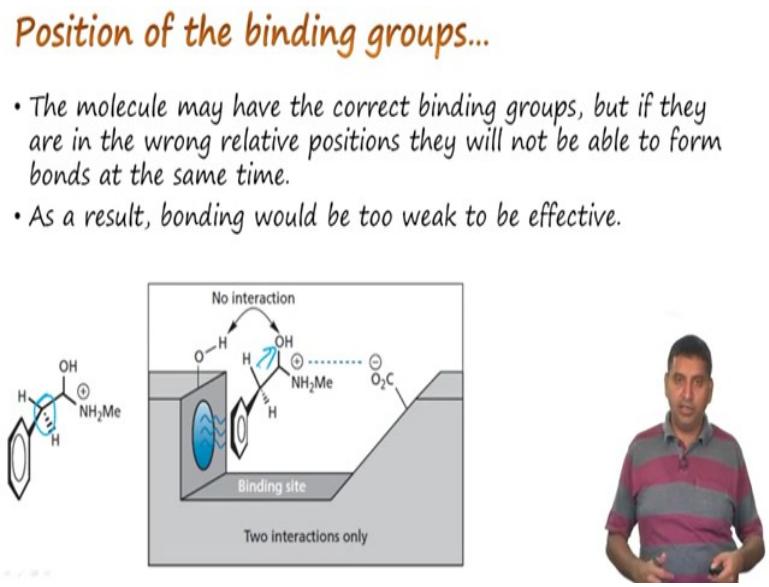

Secondly we need to look at the position of the binding groups, so here (we would) if for example we design this molecule which has an extra CH_2 here compare to the natural messenger then what we have done is we have sort of displaced the hydroxyl group over here, whereas by keeping the rest of the structure the same it is likely that the other two interactions will not be effected as much.

Now it is possible that because we have displaced or we have moved this hydrogen bond a little bit towards the right or hydrogen bonding group towards the right it is possible that you may not have any interaction with the receptor hydroxyl group which would sort of cut one of the hydrogen bonding interaction. So therefore the position of the binding group is very important in how we design the agonist.

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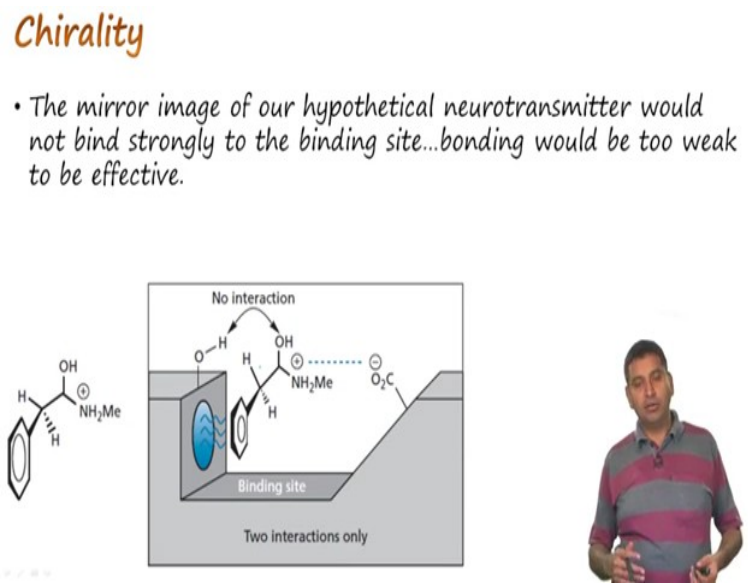

The next part is chirality, so we look at some of the aspects of chirality later in this lecture but suffice to say now that the mirror image of the neurotransmitter may or may not bind to the receptor surface it is possible that the mirror image may not have the same level of interactions as the original molecule.

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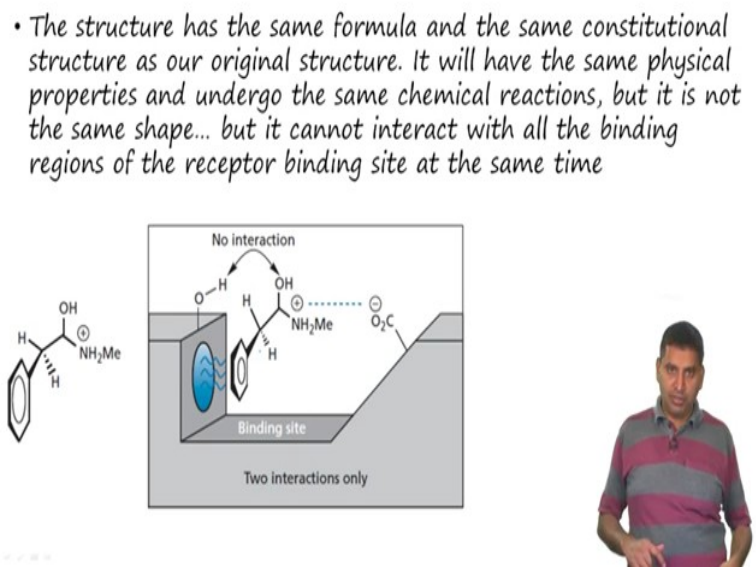

So although the structure has the same formula and the same constitutional structure as our original structure and we will look at later it will have the same physical properties and we will of course undergo the same chemical reactions but it cannot interact with all the binding regions of the receptor at the same time in the same level. So therefore even chiral or the mirror image molecules may not have the appropriate binding regions.

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Now let us take a minute and try to understand what chirality is, I am going to put this picture out here and just take a look at it and then we will come back to this later.

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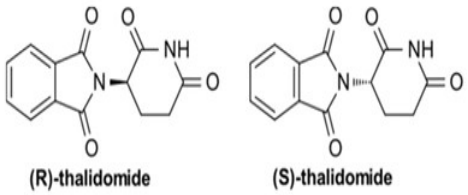

One enantiomer is a drug for morning sickness, nausea etc
The other causes abnormalities in the growing feotus

Thomas Quasthoff, Grammy award winner

So the classic example of why chirality is important in drug discovery comes from this drug called as thalidomide, you will see here this person Thomas Quasthoff, who has won the prestigious Grammy award and he was one of the victims of a drug that has been taken in an incorrect manner. So as you can see his hands are less developed and they are extremely small, so one enantiomer of this drug was used for was able to help with morning sickness during pregnancy, whereas the other enantiomer caused abnormalities in the growing fetus

and at that time people were given this as a racemic mixture. So this is a classic example of how chirality is very important in drug discovery.

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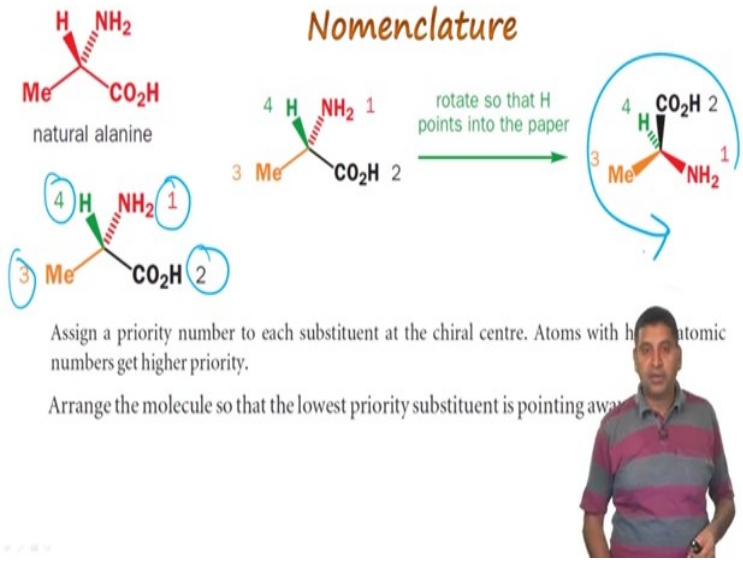

So in order to understand chirality first let us start with nomenclature, so here is a structure of natural alanine and so we will look at the Cahn Ingold Prelog nomenclature priorities and let us assign the priority based on that, I am not going to go over the CIP rules because that is thought in basic organic chemistry, but if we were to assign priority so then this NH would be number 1, COOH would be 2, methyl would be 3 and hydrogen would be 4 and so what we would do is we would rotate so that the hydrogen points into the paper and so now if I were assign the priority I go from here to here and this would be S.

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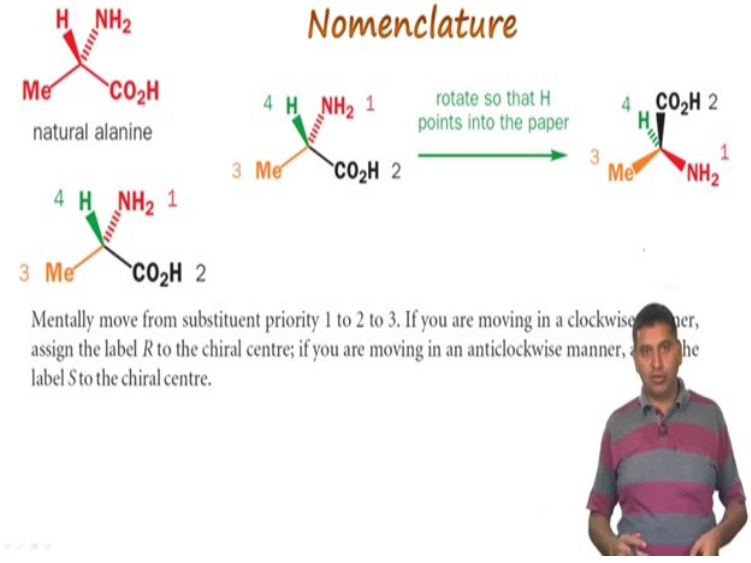

Now if you are not moving in a clock wise manner it is S and if it is a clock wise manner it is R.

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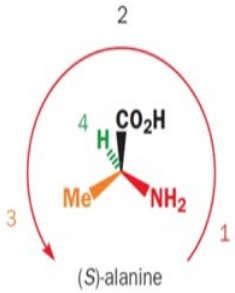

This is the structure of S alanine.

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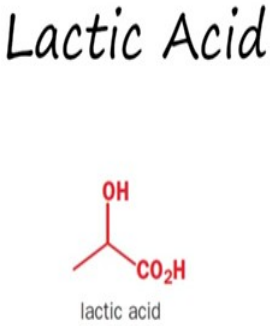

Now let us take a minute and look at how we would assign the R and S lactic acid?

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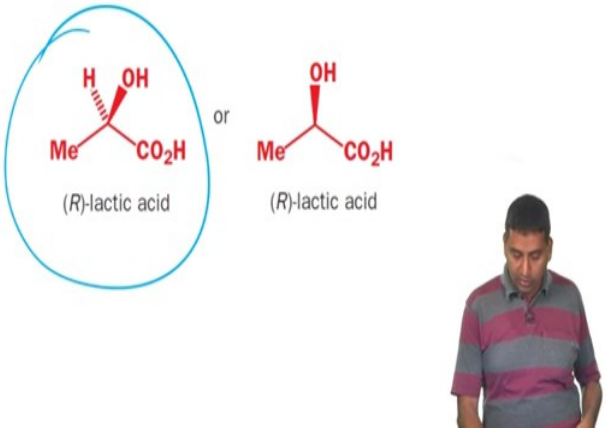

So here you would have figured out by now that this structure over here is R lactic acid and so it can also be represented without the hydrogen in the following manner.

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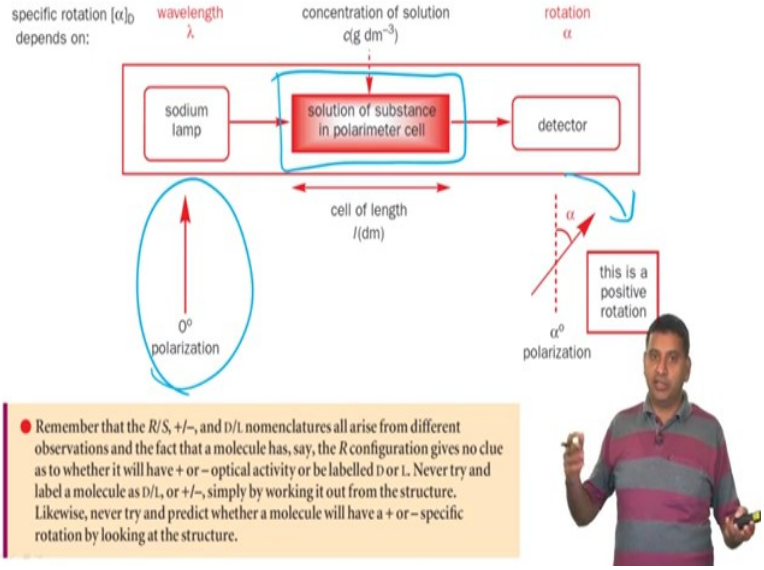

Now if we were to take a bottle of the R enantiomer and the bottle of the S enantiomer one of the features that is really different is the way in which the molecule is able to interact with plane polarised light. So in order to study this we would use what is known as a polarimeter. So here is a polarimeter cell in which we could put in the solution of the substance and it would be exposed to a sodium lamp and then there is a polarizer that would make it into a plane polarised light and then of course there is a detector.

So if there is no rotation then what happens is that there would be 0 degrees there is no rotation either right or left, but if the constituent of the solution is able to rotate the plane polarised light you will see that there is no signal at this angle but once you move it to a slightly different angle then you will see some signal. So what this means is that you can this molecule rotates the plane of plane polarised light and one can measure this angle and we would be able to determine the number and this will help us understand whether it is dextrorotatory or levorotatory.

So using this technique one can distinguish between the R and S isomer and please keep in mind that there is no connection between R and dextrorotatory or S and dextrorotatory either one of them can rotate the plane of plane polarised light in anyway. The only thing that is absolutely right is that R will rotate it in one direction and S will rotate it in the opposite direction.

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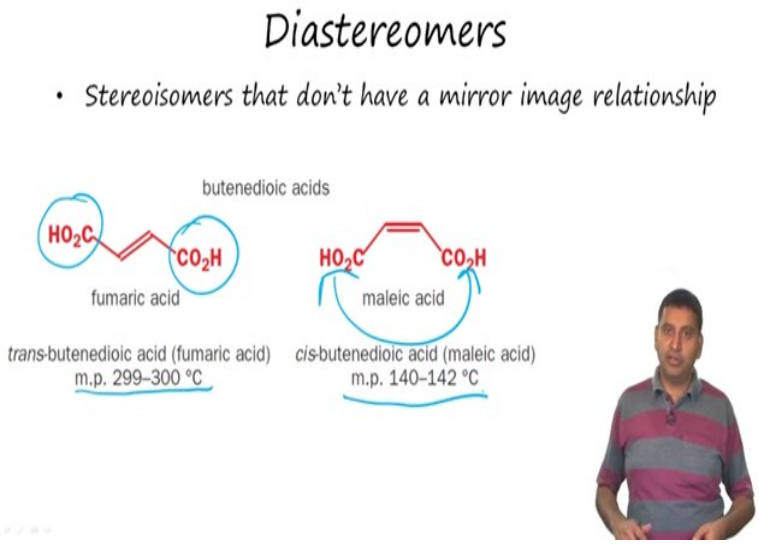

Now let us look at the concept of diastereomers, diastereomers are stereoisomers which do not have a mirror image relationship. So the example here is fumaric acid and maleic acid. As you can see they have the same connectivity that is they have two carboxylic acids and then they have an olefin but in space they have differences. So this the fumaric acid is trans to the two carboxylic acids are trans to one another, whereas in maleic acid they are cis to one another.

So this difference between trans and cis manifest itself in a number of physical and chemical properties. So here for example the melting point of fumaric acid is between 299 and 300

degree centigrade, whereas for maleic acid it is 140 to 142 degree centigrade. So Diastereomers have a number of although the connectivity is identical diastereomers have a number of differences in their physical and chemical properties.

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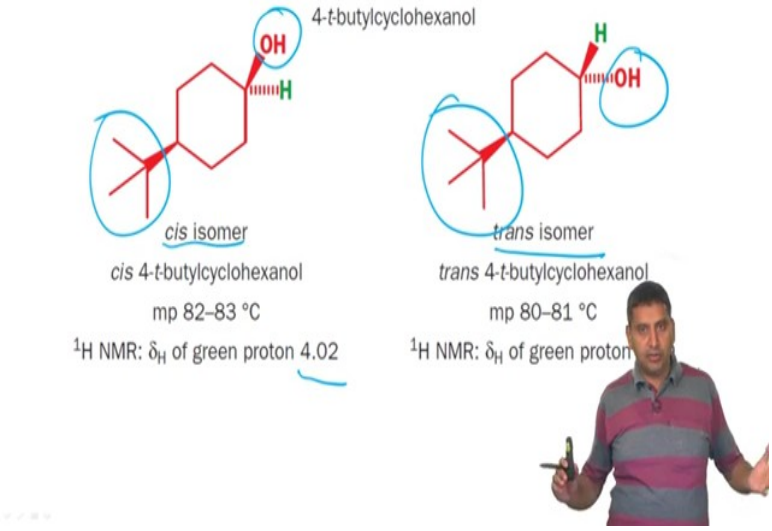

So here is another example where you have a cyclohexane system and so here you can draw this out in the chair conformation at your leisure, but this is cis isomer over here and here is the trans isomer. So the groups that we are looking at are the tertiary butyl group and the hydroxyl group over here and the melting point of the cis isomer is about 82 to 83 degree centigrade and the trans isomer is fairly close but there is a difference but it is close the melting point is 80 to 81 degree centigrade.

However if we record the proton NMR spectrum of the cis isomer and the proton NMR of the trans isomer the differences become quite significant. So using NMR techniques one can actually distinguish between cis and trans isomers, however in the case of chiral compounds that is in the case of R or S the NMR spectrum would look identical.

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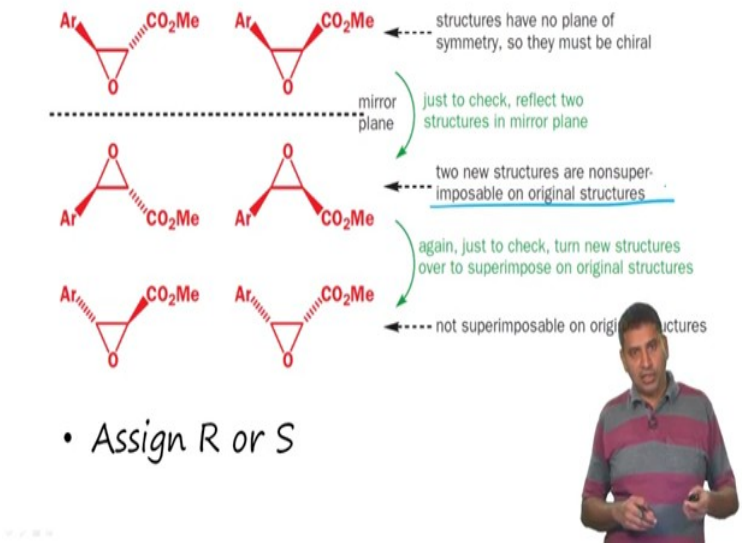

So what we will do now is to look at this epoxide and try to understand how this epoxide you know the various stereoisomers that are presented. So what we need to do is we look at these two structures and we need to identify whether there is a any plane of symmetry in the molecule or any element of symmetry in this molecule. So the structures on the top have no plane of symmetry and so they must be chiral and now we can look at draw a mirror plane and take the and look at the mirror image of these molecules and these two structures are also non superimposable on the original structure and therefore these molecules are enantiomer of each other and now if you just want to check it, you can just do a rotation and just make sure that they are not superimposable. Now the task is to assign R or S nomenclature to these molecules.

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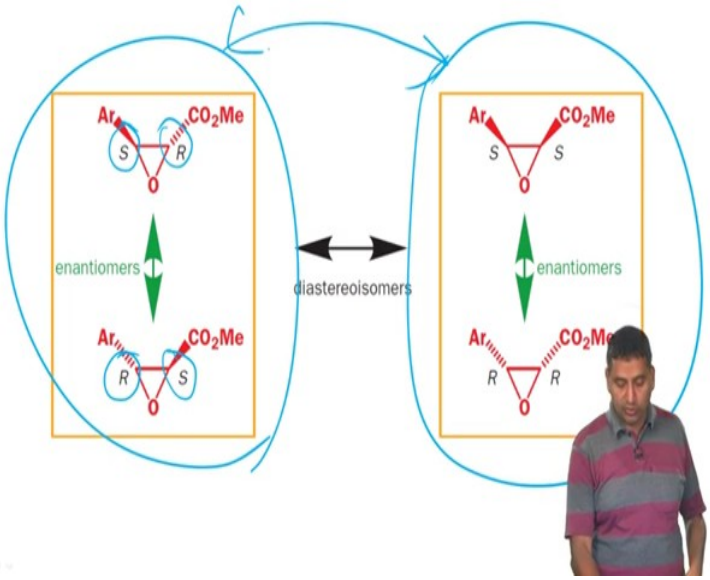

So you must have done it by now and so the answer is S over here and R over here and this enantiomer of this molecule has R and S (in the) of the corresponding carbons and similarly the enantiomers of the other two molecules are shown over here, but this group of molecules has a diastereomeric relationship with the other group of molecules. So just to recall diastereomers are molecules which do not have a mirror image relationship, so therefore there is no mirror image relationship between this set of molecules and this set of molecules.

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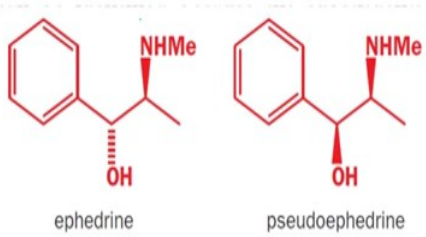

So let us look at this example of ephedrine and pseudoephedrine.

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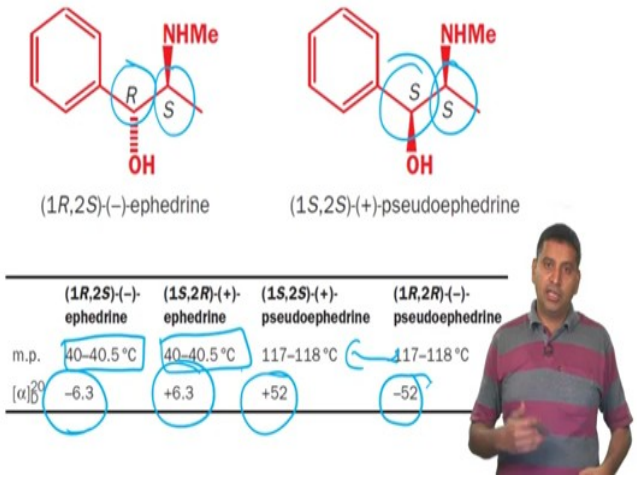

So ephedrine has if you are assigning R and S stereoisomers there are two isomers here R and S the carbon here is R and the carbon here is S and pseudoephedrine has S and S. So between the two isomers between the two enantiomers of ephedrine there is no difference in the melting point so they both are 40 to 40.5 degree centigrade and as we discussed earlier the specific rotation of this one enantiomer is opposite to the other one. So here it is minus 6.3 and plus 6.3, as we would have expected.

In the case of pseudoephedrine the melting points are again identical 117 to 118 degree centigrade and the rotations are exactly opposite that is one is minus 52 and the other one is plus 52. You can take few minutes and figure out the nomenclature of these molecules and that would be a good exercise for you.

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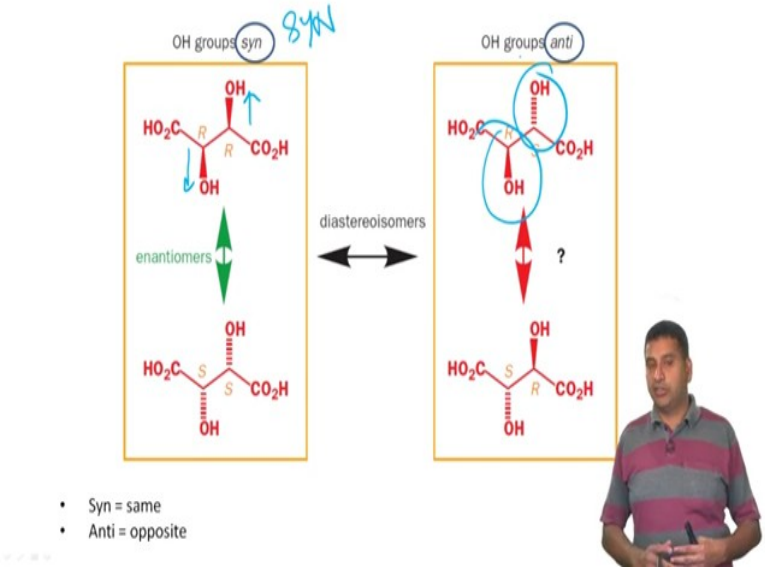

Now there is another important nomenclature that comes in stereochemistry that is called as Syn and Anti, if we were to look at a molecule putted in a draw it in a plane and let us say we are this hydroxyl group is pointing towards us and this other hydroxyl group is pointing again towards us and this kind of molecule would be called Syn that is Syn and if the corresponding diastereomer of this molecule where the (hydroxyl group is pointing) one hydroxyl group is pointing towards us and the other hydroxyl group is pointing away from us this molecule would be called as Anti.

So the Syn compounds are actually enantiomers of each other and the Anti compounds are enantiomers of each other. However these two groups Syn and Anti are actually diastereomers of each other.

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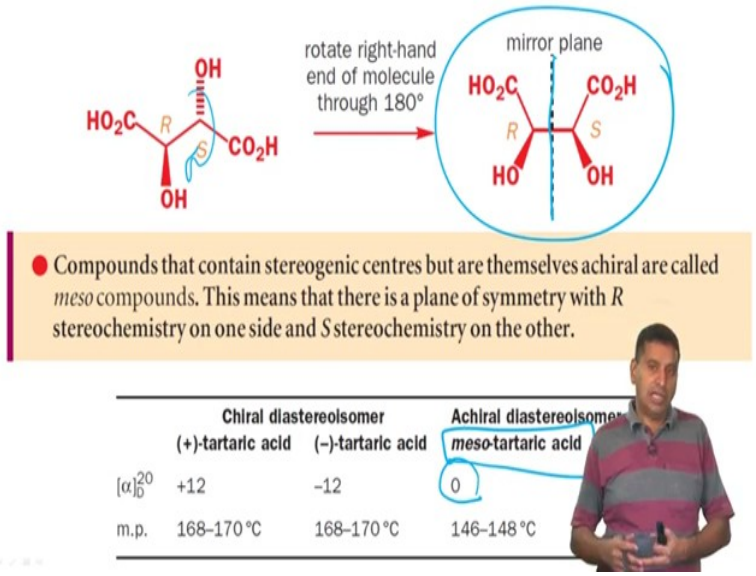

Now there is a small catch once I use this molecule which has the absolute stereochemistry R, S and then if I rotate the right hand side of the molecule like this I end up with a compound as shown here. So this molecule is a special molecule because it has a mirror plane of symmetry, so if I have to draw a plane of symmetry right between this exactly in the centre of this bond then one side of the molecule is identical to the other side.

So the condition for a compound to be chiral is that it must have no elements of symmetry. So this molecule although it has an R and an S has an internal plane of symmetry and therefore this molecule turns out to be achiral and you would find that this molecule has no interaction with the plane polarised light and so the value is 0, whereas the corresponding tartaric acids plus tartaric acid and minus tartaric acid very nicely give a rotation of 12 degrees and of course as we would expect their melting points are identical.

So this achiral diastereomer is called meso. So tartaric acid whose structure is shown above has two enantiomers and one meso molecule and that is achiral and therefore hopefully in this exercise you have found that there can be compounds that are chiral and the molecules which are chiral are going to rotate the plane of plane polarised light and this plane polarised light rotation is going to be opposite to one another.

However, when there is more than one stereo centre that is present it is possible that in certain cases you will have some additional element of symmetry which was not present in the original molecule and once this additional element of symmetry presents itself then the molecule becomes achiral.

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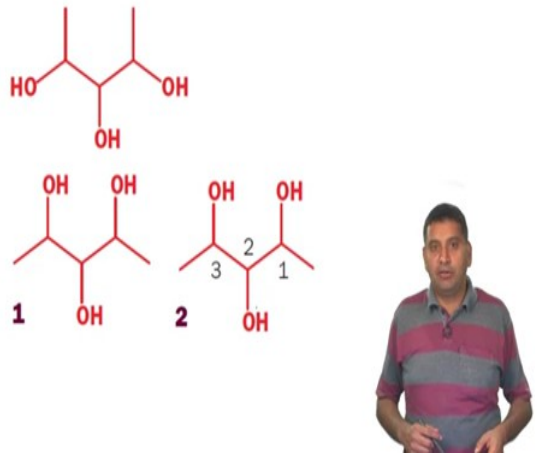

So I will leave you with these structures and we can look at assign the stereochemistry of these molecules.

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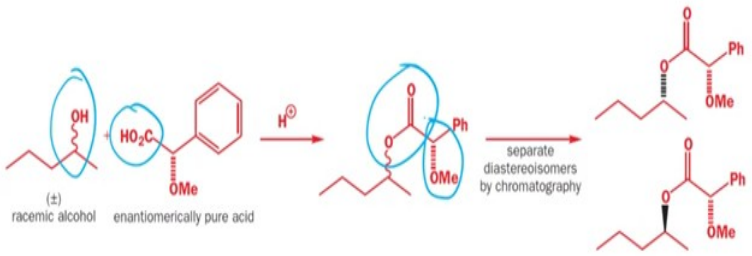

- One commonly used methodology is to separate a racemate to its individual components...

Now since we have figured out that dealing (with the) with single enantiomer is what we would like to do, we need to be able to figure out asymmetric syntheses that means we need to be able to figure out how to make molecules as a single enantiomer, but if that is a separate topic but what normally happens is that we will end up with a racemic mixture. So consider this molecule this alcohol here and this alcohol is chiral and you will find that it is when we let us say we do a reduction of the ketone to give you the alcohol you will end up with a racemic mixture.

One way in which we can actually separate out the two enantiomers is by converting this molecule or this racemic mixture into the corresponding diastereomer. As we have discussed earlier, diastereomers have very different chemical and physical properties or can have very different chemical and physical properties and therefore they are actually separable by simple chromatography techniques.

So what we would do the strategy that we would adopt is to carry out a synthesis where we can make a pair of diastereomers. So here is the acid that we would use and this acid is present as a single enantiomer and now so once it interacts with the racemic alcohol it would form an ester and this ester would have again 50 percent of the R and 50 percent of the S, but since this chiral centre is there is a single chiral centre here you would end up with a mixture of diastereomers and now we can separate out the diastereomers and once we separate it out then we will be able to use one of the enantiomers for further transformations.

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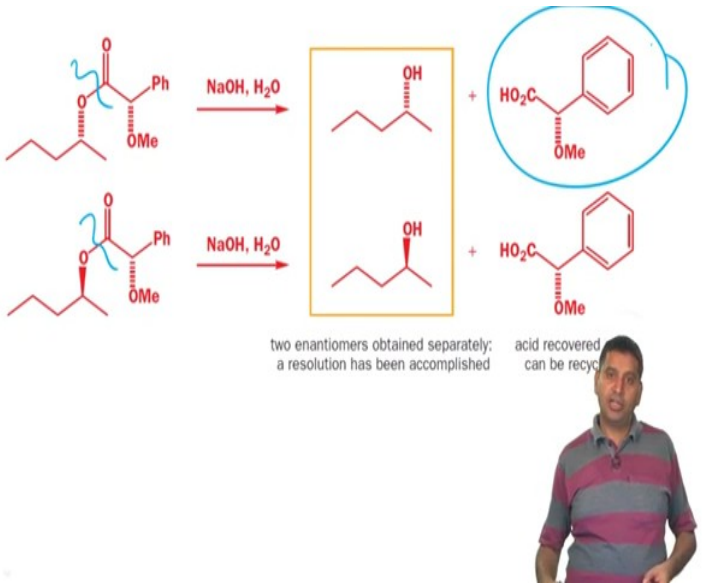

Now after we separate this out we could then hydrolyse of this ester and we would have with us two enantiomers which are separated and this molecule that we used to make the diastereomer can be recovered and recycled.

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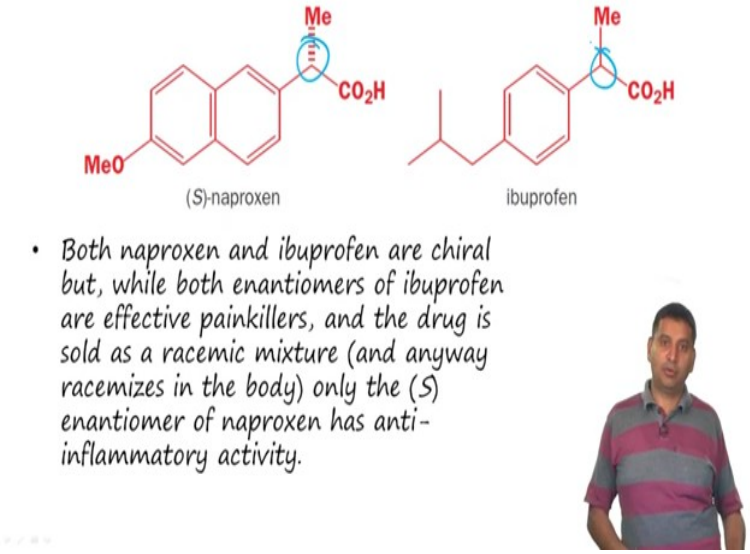

So naproxen and ibuprofen are actually two molecules which are very commonly used as non-steroidal anti-inflammatory drugs or painkillers and so naproxen and ibuprofen they both are chiral and the chiral centre is present over here. Now ibuprofen is sold as a racemic mixture and it anyway racemises in the body whereas naproxen the only the S enantiomer of naproxen has anti-inflammatory activity.

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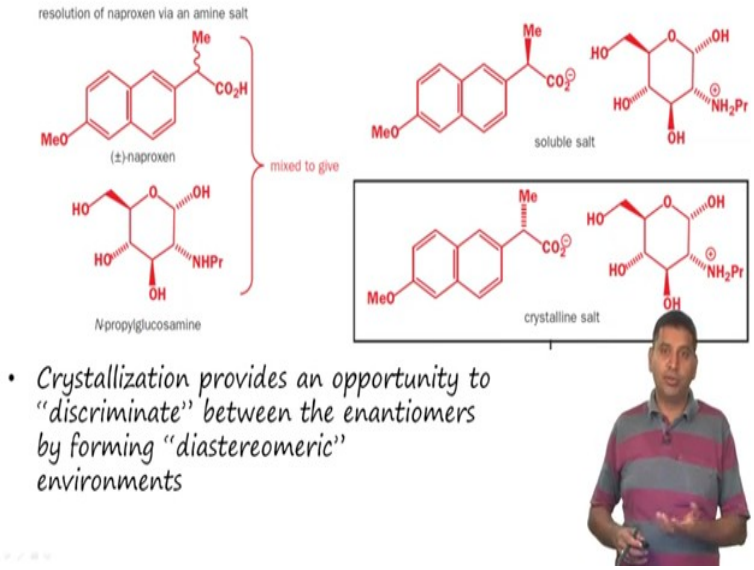

So in order to resolve the naproxen what we would need to do is we do what is known as crystallization. So crystallization is a process by which we can use enantiomerically pure molecule to co crystalize with the desired compound let us say racemic mixture and some

because we are introducing a diastereomeric environment it is possible that one of these enantiomers actually crystalizes out while the other one remains in the solution.

So by doing this what we do is that we set up a crystallization reaction crystallization setup and this allows us to discriminate between the two enantiomers, again it is not necessary that all the enantiomers are going to crystalize out separately but it is a commonly used methodology to be able to separate out one enantiomer from the other and it works very well in the case of naproxen.

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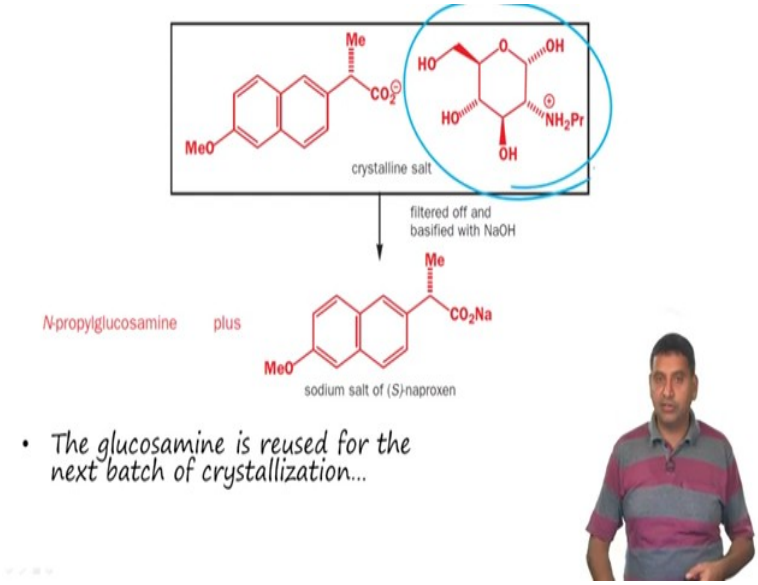

So once the molecule crystalizes then what you can do is just filter it off and then we need to convert it to the sodium salt which can be done with sodium hydroxide and now the glucosamine that is used is now recycled.

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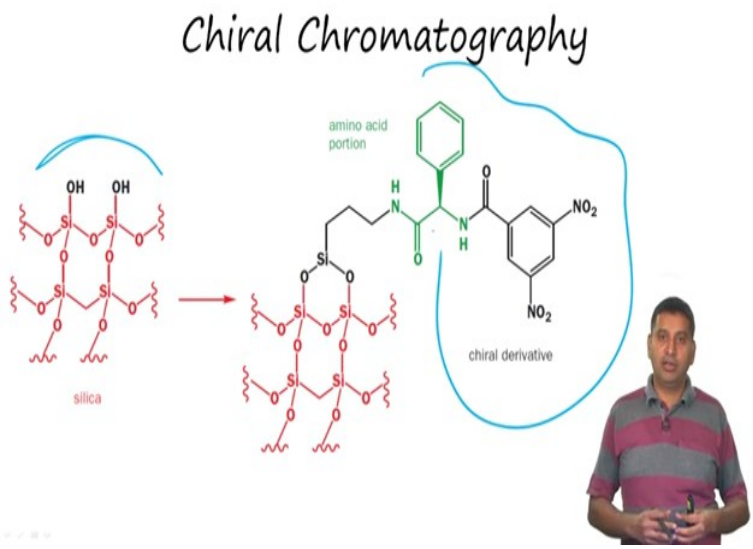

Another important technique by which we can separate out enantiomers is chiral chromatography. So chromatography typically is carried out with silica and silica surface adsorbs the molecule and it is able to because the molecule has some elements of polarity in it, it would bind to the silica surface and once we elute out this silica surface it is possible that the compound that is binding stronger will elute slower, while the molecule that binds weaker would elute faster.

So this is a very commonly used technique to separate out molecules in organic chemistry, but since enantiomers have identical, physical and chemical properties most physical and chemical properties are identical, silica gel will not be useful for separating out enantiomers. However, using the same concept that we looked at before we can convert these enantiomers into diastereomers and now since diastereomers have may have different physical and chemical properties one would be able to separate this out by chromatography.

Alternatively the surface of the silica can actually be derivatized and you can make it chiral. So that is what is done over here if you introduce a chiral molecule on the surface of silica. Now what happens is that you can separate out these molecules because you are introducing a diastereomeric environment.

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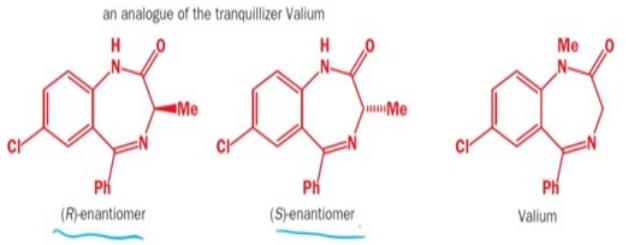

So here is an example of this molecule which is an analogue of valium, so the R enantiomer and S enantiomer need to be separated out.

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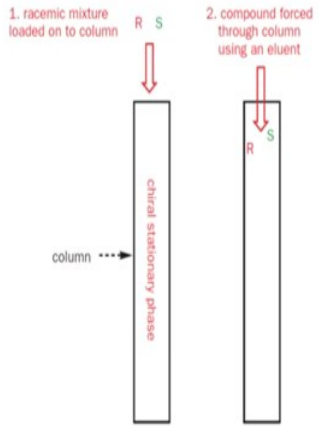

So what we would do is we would take this column, we will have a chiral stationary phase and once we load on the racemic mixture to the column what happens is that they both will go and bind to the surface of the chiral stationary phase.

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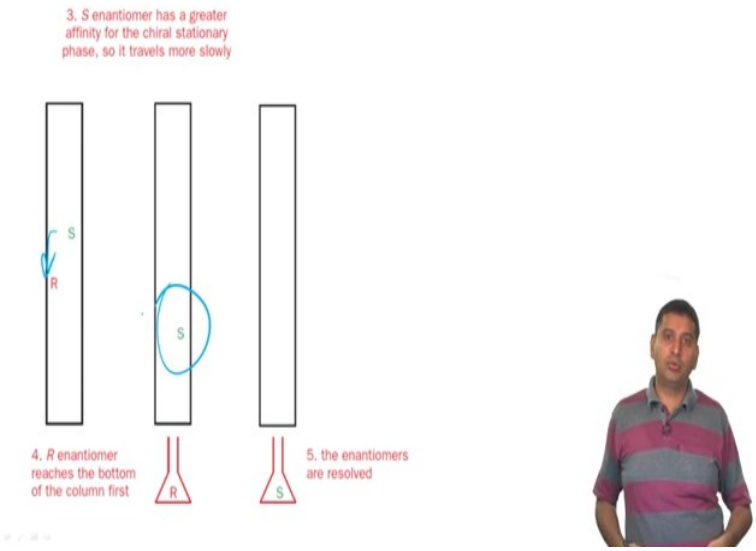

Then we elute it out and since the S isomer binds stronger to the environment that means the diastereomeric environment that is created seems to have a stronger binding for the S isomer over the R isomer and so there is a gap between the S and R isomer in terms of how they elute. So the R isomer elutes faster and reaches the bottom of the column first, so once we collect this portion and we keep it separately and then we start collecting the fractions where the S isomer presents itself and then the S isomer can be separated out.

So again this is a very powerful technique to be able to separate enantiomers. Of course ideally we would like to synthesize molecules which are of single enantiomers and that is the field of asymmetric syntheses that has emerged to be able to do that. So the way they do it is to be using to introduce similarly a diastereomeric environment either as an intermediate or in the transition state and that enables selective synthesis of only one enantiomer over the other.

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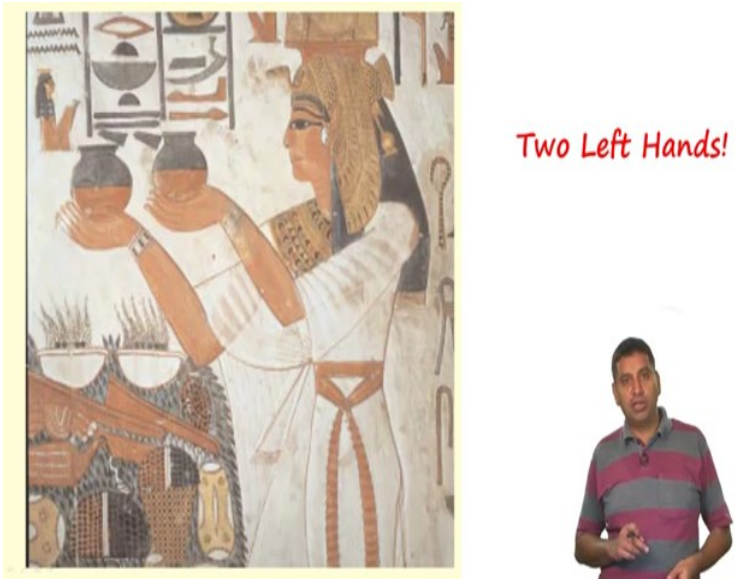

Now coming back to the original picture that we looked at, this picture actually has two left hands.

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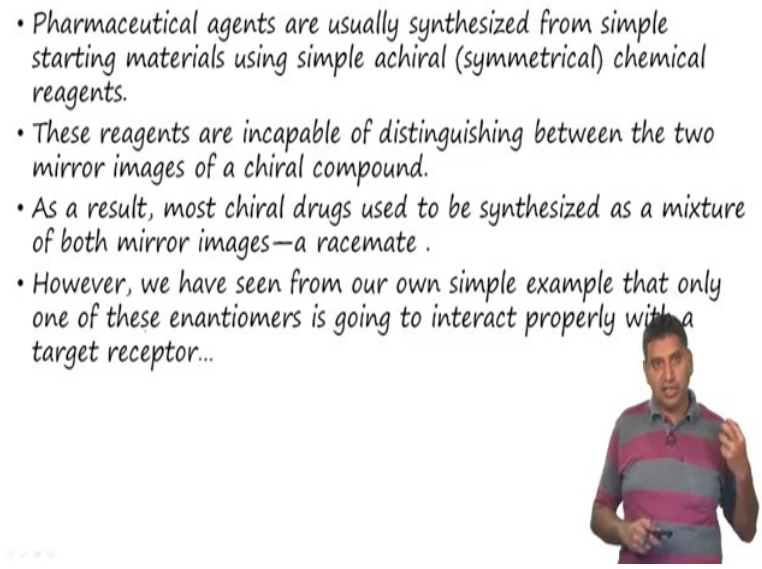

So how do we understand chirality or what is the importance of chirality in medicinal chemistry? So pharmaceutical agents are usually synthesized from simple starting materials because you need to be able to scale it up to kilograms and tons and so on and so they usually use achiral chemical reagents, so these achiral reagents as we looked at earlier are incapable of distinguish between two mirror images of a chiral compound.

So as a result most chiral drugs are synthesized as a mixture, but we looked at previously some problems with this approach because one enantiomer could be quite toxic (to the) or could have very bad effects on human, whereas the other one is going to actually help. So this also the way in which this is going to interact with a target receptor for example is going to be different.

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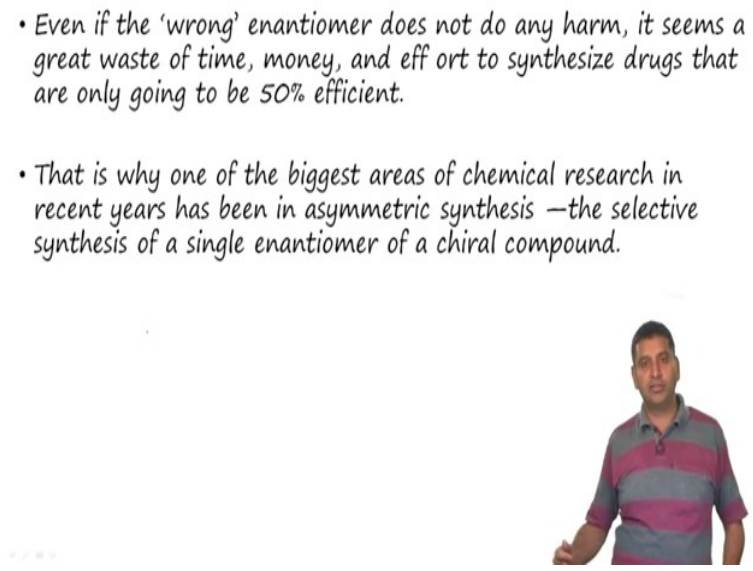

So even if the wrong enantiomer does not do any harm it is a great waste of time, money and effort to synthesize only 50% efficiency, so this is one of the biggest areas as I mentioned earlier where you have to selectively synthesize a single enantiomer of a chiral compound.

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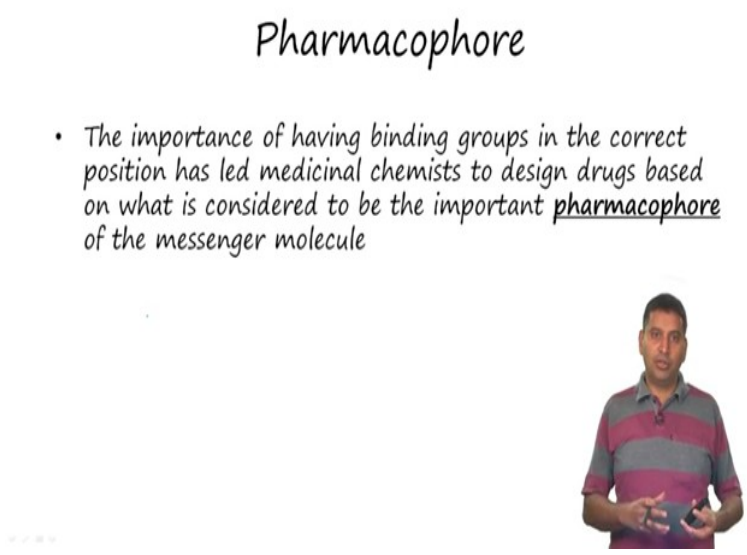

Now let us take a little bit of time and look at what a pharmacophore is? So what we have looked at earlier is that there has to be the binding centre in the receptor and the molecule that we are using or we are designing must go and bind to this area. So the importance of having binding groups in the correct position helps us to design drugs based on what is considered to be important pharmacophore of the messenger molecules. So pharmacophore is basically a concept where we have the important parts of the binding groups for the messenger molecule which we use.

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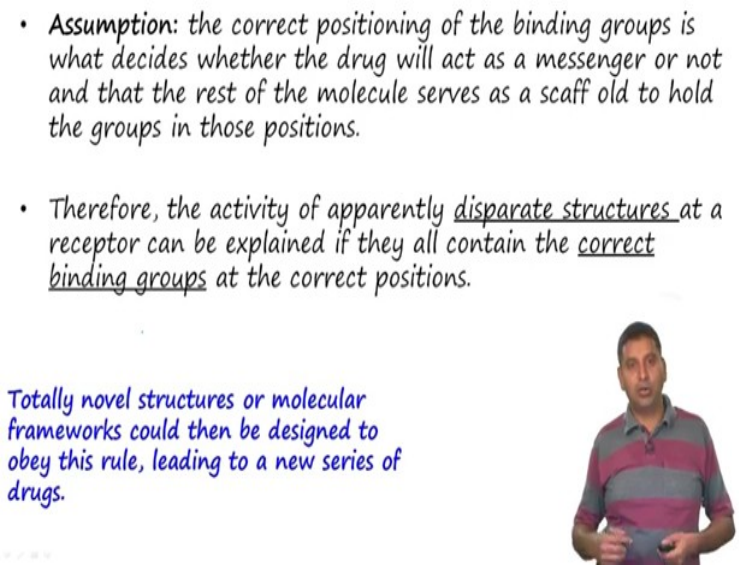

So here of course the assumption is that the correct positioning of the binding groups is what decides whether the drug will act as a messenger or not. So it is possible that the rest of the molecule serves only as the scaffold to hold these groups in position. So these are some assumptions that we need to make. So therefore the activity of apparently disparate or very different structures at a receptor can be explained if they all contain the correct binding groups at the correct position.

So as I mentioned earlier it is possible that a receptor can interact with molecules which are completely different in structure. Now our job is to able to identify the correct binding groups and figure out if they are at the correct positions and that is how we can actually design completely novel structures or molecular frameworks which can bind to this receptor and this would lead to a new series of drugs.

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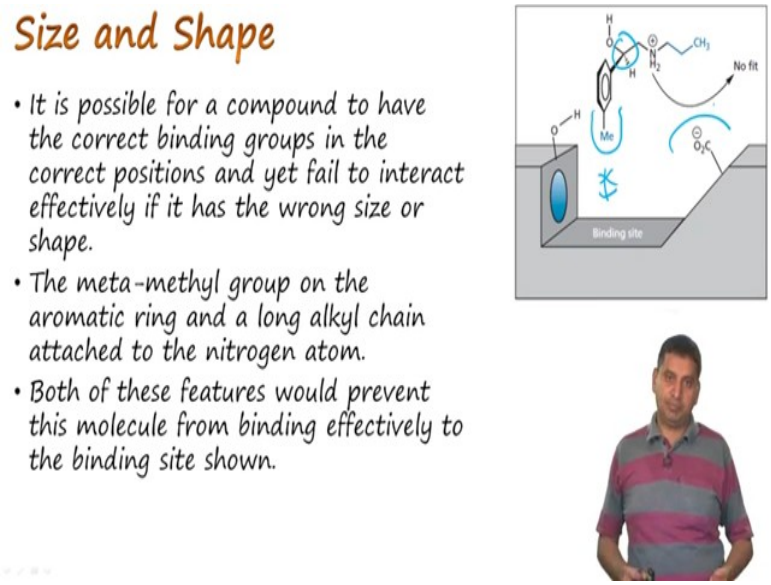

So let us look at the concept of size and shape. So it is possible for a compound to have the correct binding groups in the correct position and yet failed to interact effectively because it has the wrong size or shape. So in this example this is a methyl group which is meta to the functional group over here and what it can do is that when it enters the receptor surface since there is a induce fit going on here, it is possible that the binding site repels and this does not go happen.

Second thing we also have a propyl chain on the amine. Since this amine has the propyl chain it is possible that this carboxylate sterically hindered from interacting with the amine. So therefore not only does it have to have the correct binding groups but it also must have the correct size and shape.

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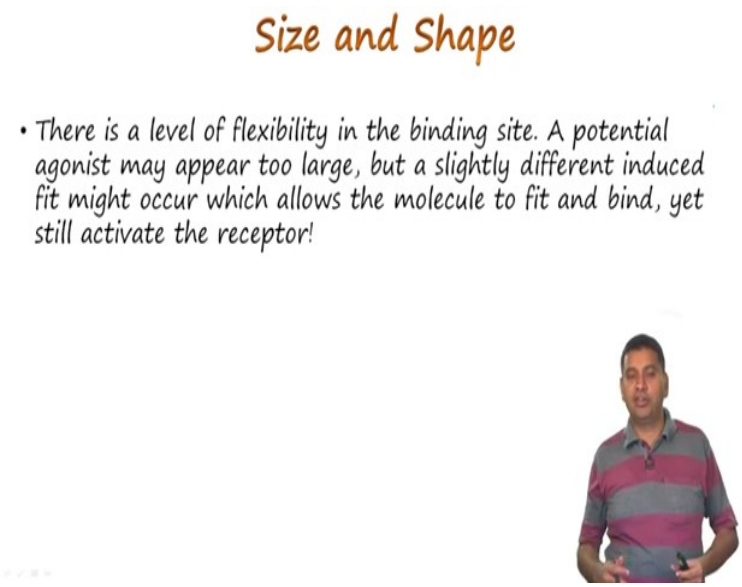

So of course there is a level of flexibility in the binding site and a potential agonist that we have designed may be looking too large, but a slightly different induced fit might occur which allows the molecule to fit and bind and still activate the receptor. So therefore it a fairly complicated situation but yet we need to understand certain key aspects of this functioning and clearly size and shape are important.

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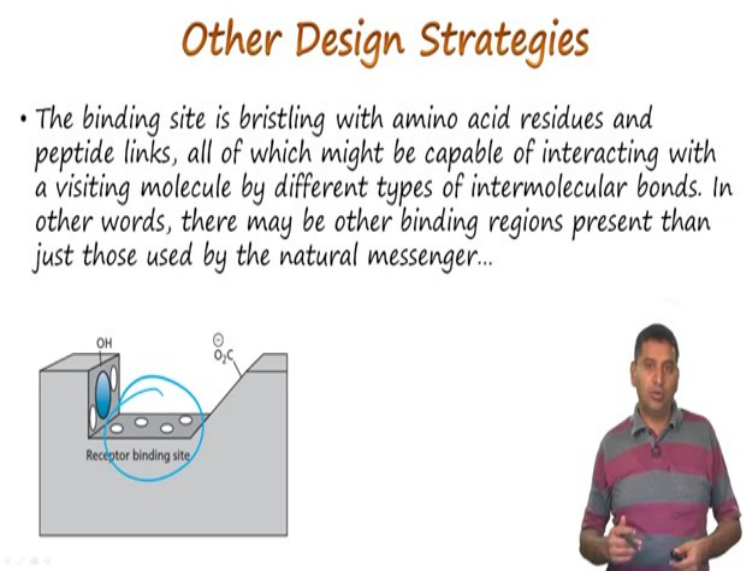

Some of the other design strategies that people employ is that since the receptor is a protein there are a number of other binding regions which may play an important role. Since we are basing our understanding on the natural messenger it is possible that we may be ignoring

some other binding sites. So these binding interactions may be exploited in designing new molecules.

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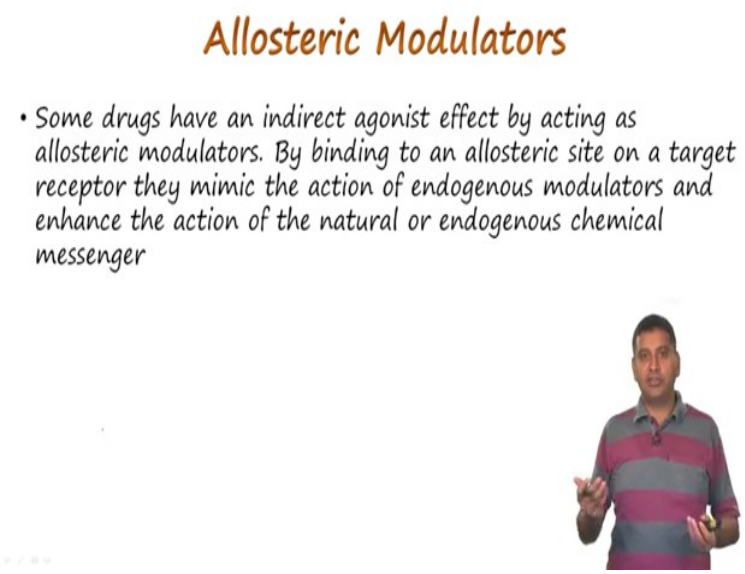

Now much like the allosteric centre in enzyme catalysis which we have looked at earlier, there are also allosteric modulators. So some drugs have an indirect agonist effect by acting as an allosteric modulator. So by binding at an allosteric site on a target receptor what they do is that they mimic action of the endogenous modulator and enhance the action or natural or endogenous chemical messenger.