Computer Aided Drug Design
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Lecture - 32
Pharmacophore modelling

Hello everyone, welcome to the course on computer aided drug design. Today we are going to take up a new topic, it is called pharmacophore modeling. Pharmacophore looks at the ligand, the structural features that are common in a set of ligand. Now, what is a pharmacophore?

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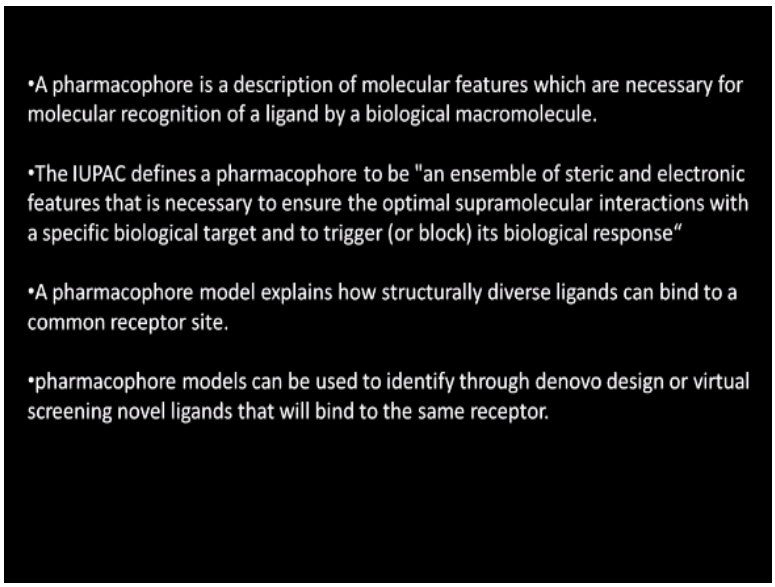

It is a description of molecular features, which are necessary for recognition of ligand by a macromolecule. Because, ultimately if you look at a ligand, it goes and binds to the active site. So, there are certain features in the ligand, which the active site recognize. So, the IUPAC definition is an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with the target okay.

Target is your protein or enzyme or whatever it is okay. Whereas this is the ligand. The pharmacophore model explains how structurally diverse ligands can bind to a common receptor. You might have seen that completely different looking ligands can bind to active site, which is because of certain structural features and in pharmacophore modeling you are trying to identify those structural features and try to see what are those important structural features.

So, they can be used to identify through denovo design or virtual screening novel ligands that will bind to the same receptor. So, if I find out the structural features or pharmacophores of a set of molecules, I can look for similar pharmacophores in the various database zinc database or trial database and so on actually that is the advantage of it. So, what are these pharmacophores features?

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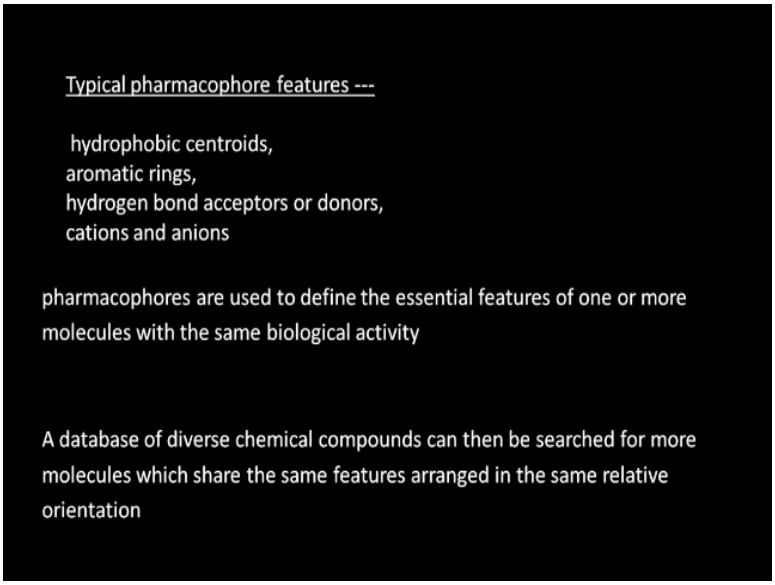

Hydrophobic centroids, hydrophobic means may be cs3 okay c2h5 and so on these are Hydrophobic. Aromatic rings okay lot of array groups. Hydrogen bond acceptors or donors okay acceptors means oxygen or nitrogen, donors could be oh nh. Cations and anions okay so all these are pharmacophores features which a set of molecules can have and they all seem to bind to the same active site and we try to identify those features.

So, these are the essential features of one or more molecules with the same biological activity. Then we can search a diverse set of chemical compound database for more molecules with the same features. That is the advantage of first identifying pharmacophores of a set of molecules and then later on identify new compounds okay.

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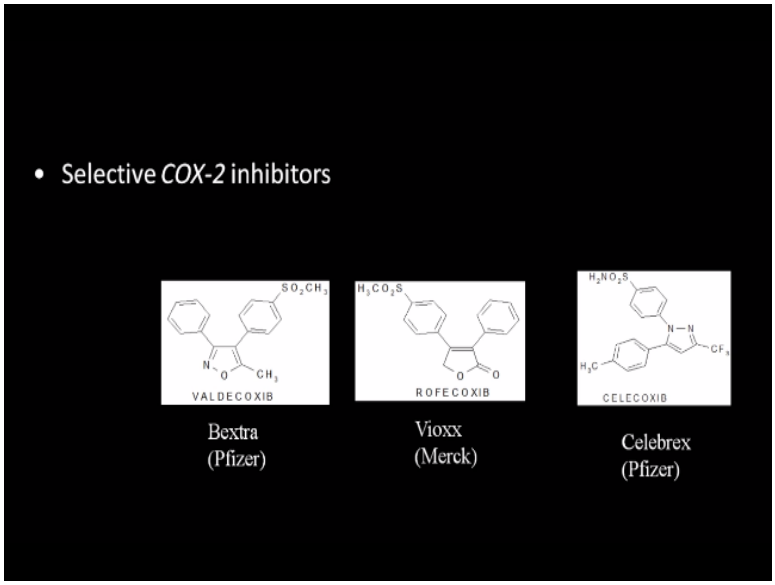

Let us look at some example. Because an example will always help you to understand. These are selective COX-2 inhibitors. COX-2 is an enzyme that is found in the recadonic acid inflammation path way. COX-2 is nothing but cyclooxygen is 2 and there are many inhibitors reported in literature, which are selective. They are marketed by Pfizer, Merck so these are called Bextra, Vioxx, Celebrex and so on.

So, we want to find out what are the special pharmacophore features of this molecule okay. So, we did not use a software called Pharmagist.

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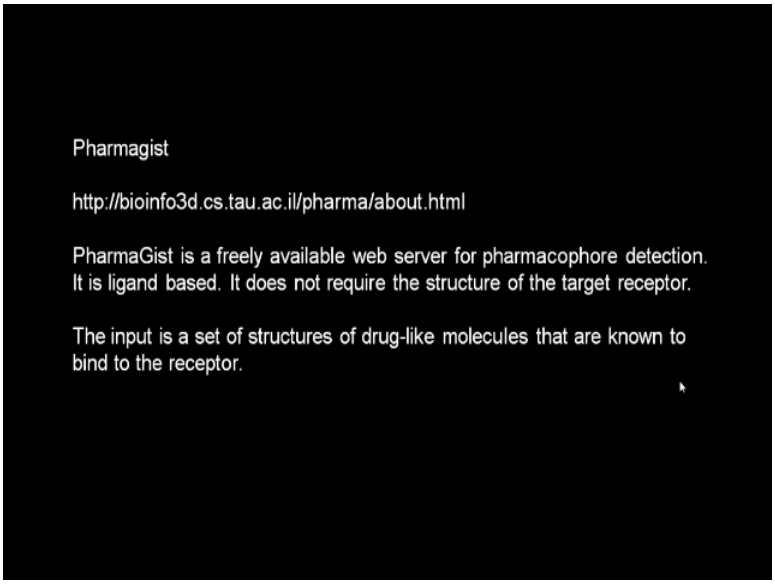

These are very nice software. It is a free available web software for pharmacophore detection. It is ligand based. So, it does not require any idea about your target protein. So, the input is a

set of molecules which are known to bind to the same receptor. For example, I am going to look at these molecules and see whether they have similar pharmacophore features okay.

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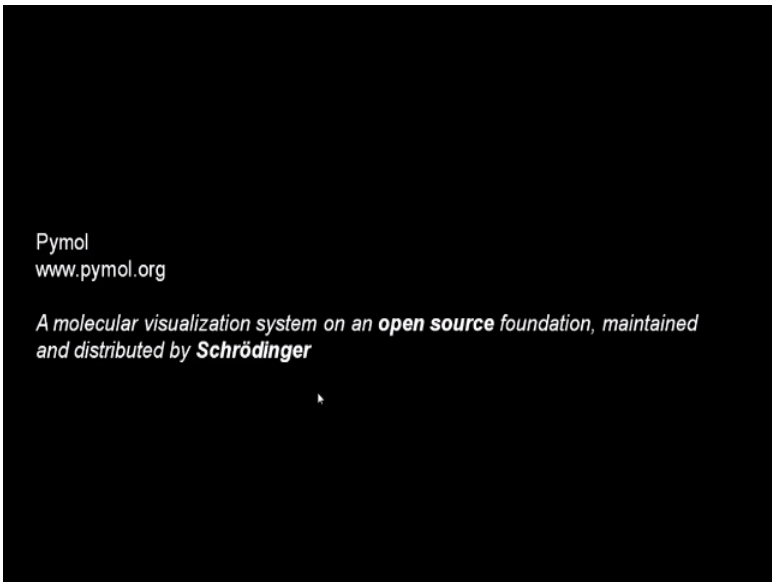

Later on we will use Pymol, which is a molecular visualization system. Again this is free software and distributed by Schrodinger. So, we will be using these 2 softwares okay Pharmagist and Pymol okay. So, how do you go about doing that?

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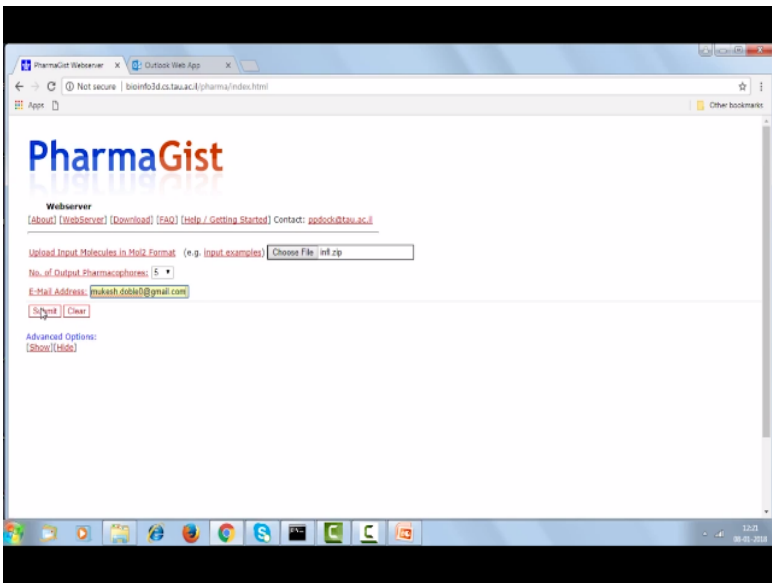

Okay this is the Pharmagist. This is the web address and then we will see web server okay. So, here we input the file. So, the file so I am looking at inflammation selective COX-2 inhibitors. So, if you look at this zip file okay it contains set of molecules okay for which I want to see whether there are any common features. You have to give it in mol 2 format

Bextra, Celebrex, there is another compound called dup 697, Rofecoxib so, I have selected these 4 see please note, they have to be mol 2 format.

So, I have put it into single zip file and then we upload the file okay, then you give your email id and the results come into your emailed okay. You submit it and then the results will come in the emailed okay. Assume I have done that. So, you get output okay like this.

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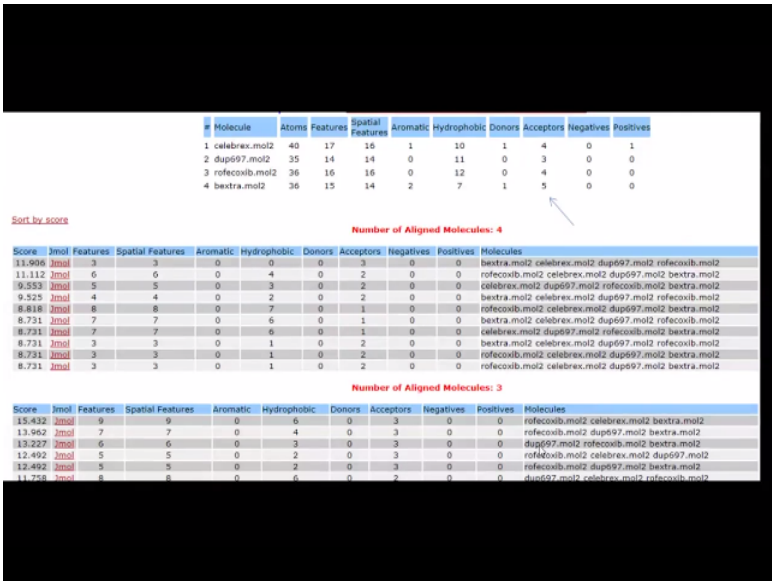

So Celebrex, DUP 697, Rofecoxib, Bextra so, for each molecule you can see this contains an aromatic, 10 hydrophobic, 1 donor, 4 acceptors and so on okay and then DUP 697 has no aromatic but it has got 11 hydrophobic okay. And then Bextra has 2 aromatics then it has got 5 acceptors. So, one thing we can easily see that they all have these acceptors. Acceptors, that means they must be having oxygen and nitrogen okay.

The software now 4 molecules, it aligns all the 4 and comes up with set of results okay. So, this gives the highest score okay. It says 3 acceptors. So, if you take all the 4 molecules and align them it has found 3 acceptors okay. That is the highest score. Here, it aligns 3 molecules at a time okay and then again you can get results so, if you are interested you can look at them also. You can neglect one of the molecules okay.

But, assume that we take this particular system okay. So, there are 3 hydrogen bond acceptors okay. So, the results file coming here so, it goes in to pymol. So, if we double click I have Pymol with me. So, hopefully it should give you Pymol.

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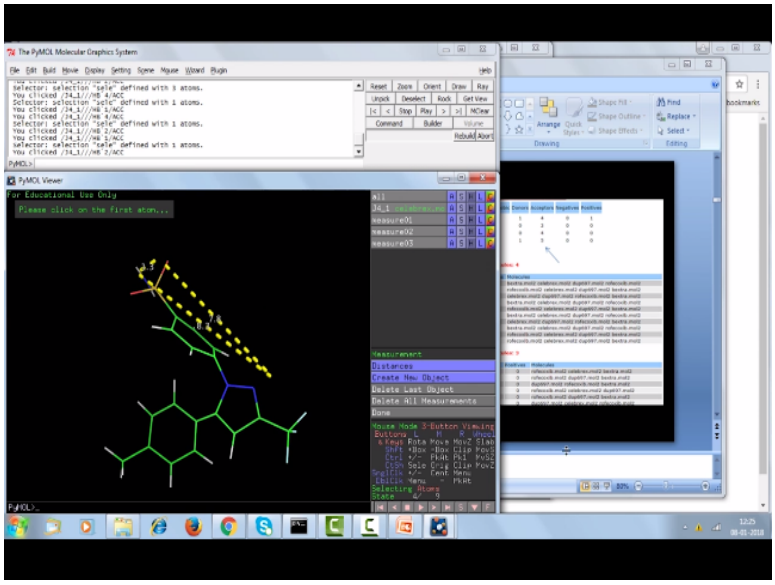

So, this will be the 3 acceptors okay. So, I can say label atom name. see, you can see ACC then again label atom name ACC, label atom name ACC so, it has got 3 acceptors which are common to all these 4 selective cyclooxygen is 2. Now, we can also look at the distances that command is called wizard. If you look a t wizard measurement okay. So, it gives you distance 7.8 so, you can see that. It gives you a 8.3. so, it also gives you the distance between each, this is 1.3.

So, these set of 4 molecules like we have selected Bextra, Rofecoxib, DUP 697, they have 3 acceptors common at this particular distance okay. Now, we can super impose the molecule on this also to see how they look like. So, that command is called movie. So, you can see this, we can look at one at a time also. You can see this so, this is acceptor here, acceptor here, acceptor here as you can see this.

So, again you can see this acceptor here, acceptor here, acceptor here. You can super impose the molecules on top of that, you will see this acceptor oxygen, oxygen one more here okay. Again you can see nitrogen and so on. So, the beauty is, we can also look at.

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Molecule	Atoms	Features	Spatial Features	Aromatic	Hydrophobic	Donors	Acceptors	Negatives	Positives
celebrex.mol2	40	17	16	1	10	1	4	0	1
dup697.mol2	35	14	14	0	11	0	3	0	0
rofecoxib.mol2	36	16	16	0	12	0	4	0	0
bextra.mol2	36	15	14	2	7	1	5	0	0

So, like I said acceptors, they seem to have that is very common and 3 is the minimum number so, the pharmacophore for these 4 molecules is 3 acceptors as I showed you how to measure the distances and so on. So, it has got 3 acceptors okay.

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pharmacophore

Score	Aromatic	Hydrophobic	Donors	Acceptors	Negatives	Positives
11.906	0	0	0	3	0	0
11.112	0	4	0	2	0	0

That gives you score of 11.9 here.

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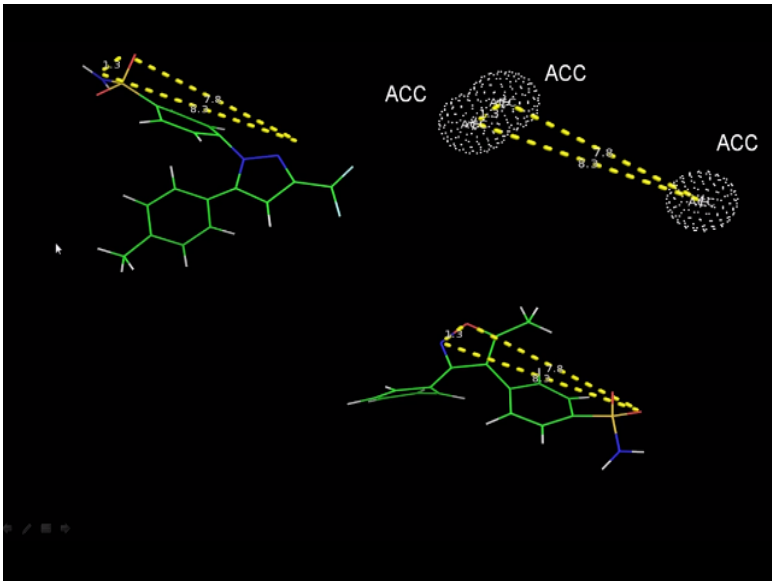

So, 3 acceptors we can see, we can super impose each one of these molecule on this to see which portions actually continue to the acceptor as you can see here there is nitrogen, oxygen, there is an oxygen, there is nitrogen, oxygen, there is nitrogen okay so it is very nice.

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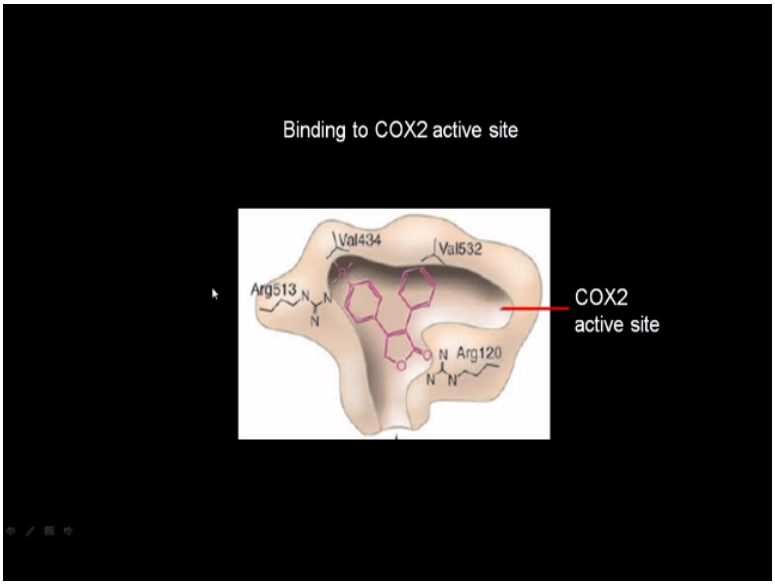

So, if you look at the cyclooxygen is 2 enzymes, it has got an active side pocket like this actually okay. It has got a main active side and there is a secondary active side and as you can see it goes and binds here okay. There is an oxygen acceptor okay so as you can see the importance of these acceptors and binding to the active side okay.

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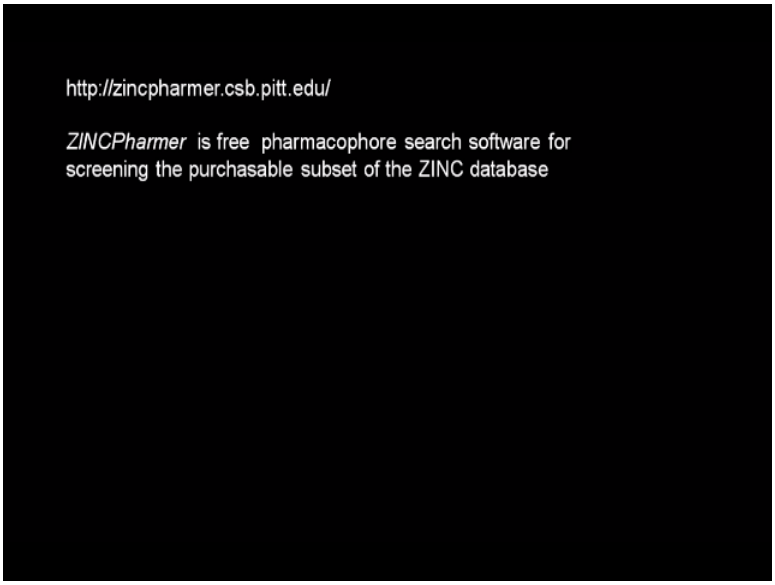

Then, after finding the common pharmacophore, we can go to a software called ZINCPharmer, we can look at which compounds in the zinc database has these type of pharmacophores okay. That is called zincpharmer okay. Say it is a zinc okay now, we need to load features like I said we get from the yes, that is the output which had come okay 3 acceptors.

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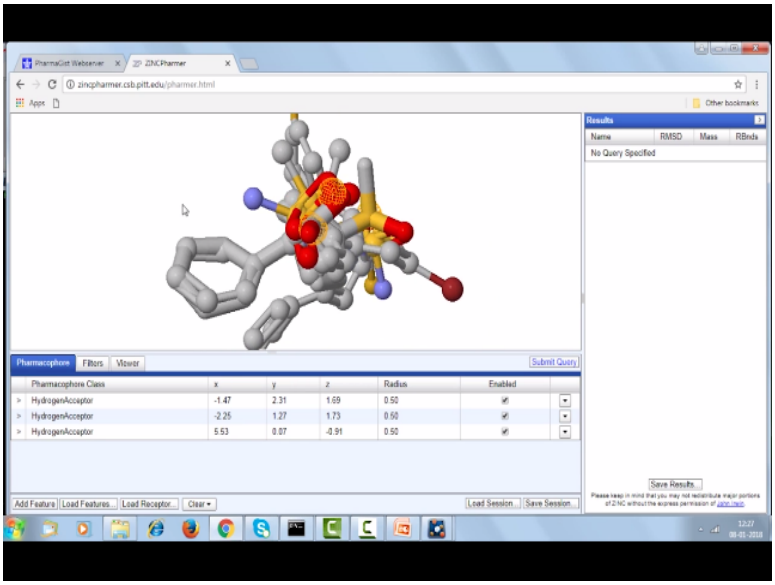

Hydrogenacceptor so, we can look at we can see this and the hydrogenacceptor and this molecule, this is the acceptor, this is acceptor, this is acceptor. Like I showed here right acceptor, we can see through here also okay. Now, we can submit this query and try to search the zinc database for molecules which have this type of features acceptor, acceptor at certain distance. So, that is called submit query so it runs here so it looks at lot of compounds okay.

So, it also gives you RMSD here molecular rate, rotator with bonds so, we can say so, this is the molecule which has got the lowest RMSD with this type of pharmacophore acceptor, acceptor at these distances actually okay acceptor at this is 8.3, 7.8, 1.3 and so on okay. So, what is that molecule? If you go to zinc database and you see the details about the molecules okay.

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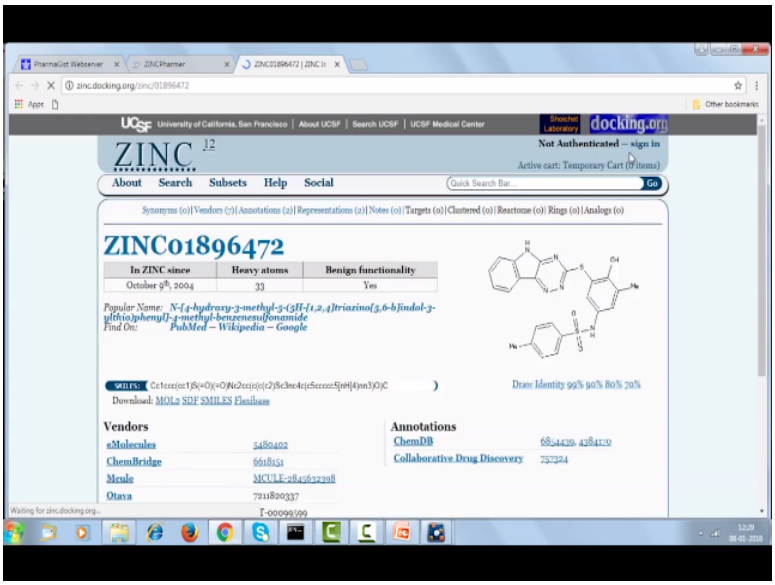

This is the molecule okay which has that particular feature of acceptor acceptor acceptor okay or this may be. This is the molecule N 4 hydroxy 3 methyl 55 H124 triazino Indol, indol is there right okay so, we can look at the second best molecule also from the zinc database and so on actually. So, now, there are lot of molecules, mass is given we can run rule search and find out those which satisfy rule.

We can run barrier rules, we can run opera rule of 3 and so on then shortlist some of those molecules which has got acceptable numbers okay. So, this duty of pharmacophore modeling basically you try to find out the structural features that are common in this set of molecules so, this is 3 and one more. So, you run the Pharmagist, so that is a web server. It gives you a output through email and then you can view it through Pymol.

So, it gives you results like this. So, if you take all the 4 molecules and align, you end up with the 3 acceptor, hydrogen bond acceptor feature, this is the test score so, you can consider that okay. So, you can see this, we can the distance is 7.8, 8.3, 1.3. so, those molecules how they map on to these feature. Then we can run the zincpharmer to see whether there are any molecules in the purchasable zincdatabase which have this particular feature.

So, we can look at those molecules test out the drug likeness property by availability properties and then may be select few and then start testing for activity. So, this is how you use the pharmacophore way to model okay.

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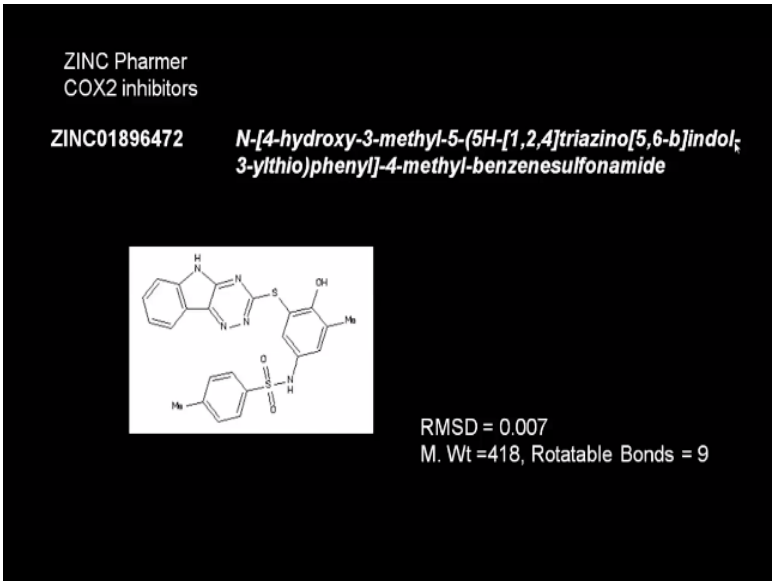

So, this is the molecule which we saw okay. Let us look at another example. This is called angiotensin.

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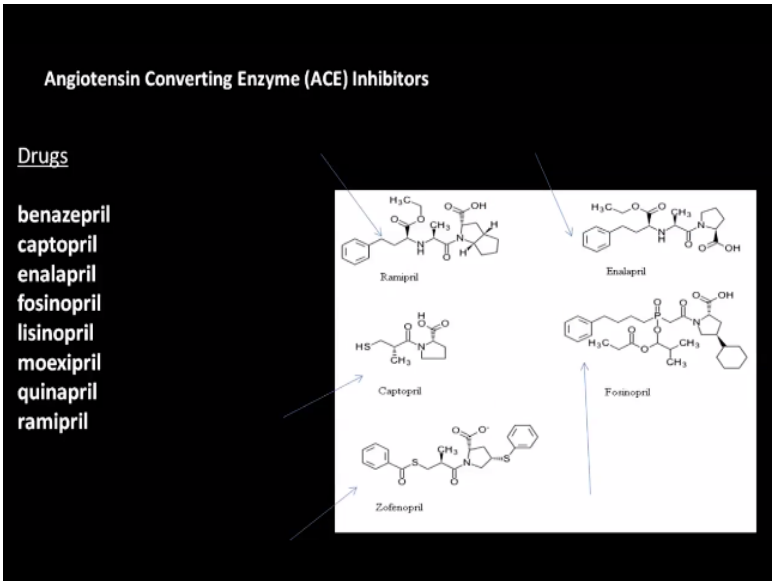

There are drugs which are given to prevent increase blood pressure because, there is an enzyme which converts angiotensin 1 to 2. So, these drugs benazepril, captopril, enalapril, fosinopril, lisinopril and so on are given, which go and inhibit this enzyme. So, prevents the

angiotensin conversion thereby prevent the raise in blood pressure. So, we looked at 4 of these ramipril, captopril, zafenopril, enalapril, fosinopril okay.

These 5 molecules and then I wanted to check out their pharmacophore features okay. When we do that, we find that it has got acceptors and hydrophobic features that seem to be coming okay.

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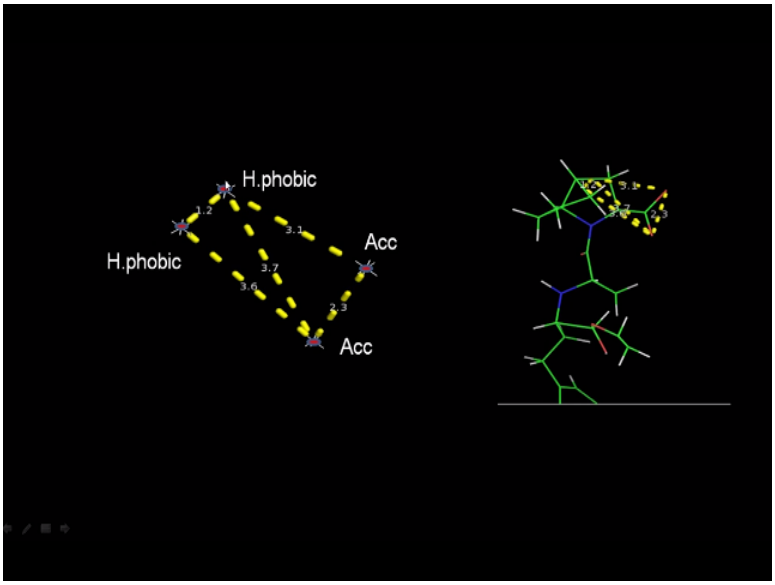

So, it has got 3 hydrophobic features and 2 acceptors that seem to be coming which is common to these molecules. We can also check it out because I had already run that. So, we have these 4 features we can find out what those features are right. We can check the label atom name acceptor 2 acceptors, 2 hydrophobic right. And we can run movie.

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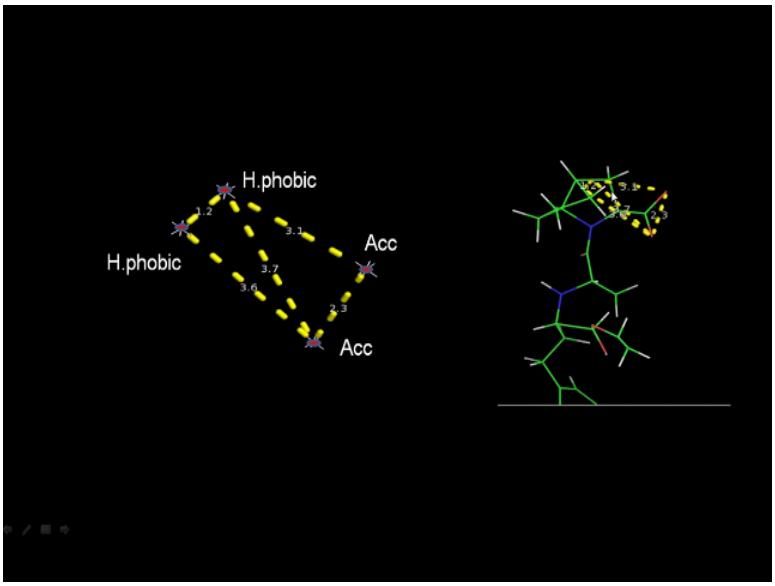

How each of them map we can see? For example, look at the structure it maps with the 2 hydrophobic points and 2 acceptor points okay. Once again we can run the zinc pharmar mode features. It is shown here, you can see these 2 acceptors here and 2 hydrophobic features here. We can see here these 2. We can also search the zinc database. So, if needed we can disable one of the features if you think we want to get more compounds otherwise we can keep all of them 4 and again we can start searching the zinc database.

So, it searches many results and had come up with set of compounds with different values of RMSD so we can look at those which have been RMSD and then see whether they satisfy the rule and other drug likeness property rules okay. So, where the best molecule that came out with minimum RMSD is this Bromopyrimidin-2-yl azepane molecule okay. So, we can look at different molecules. You can see for example let us look at okay.

So, by combining zinc pharmer and pharmagist, Pymol we can do a very good job of doing a pharmacophore search of a certain molecules and we can also look out for molecules with that structural features from the zinc database okay.

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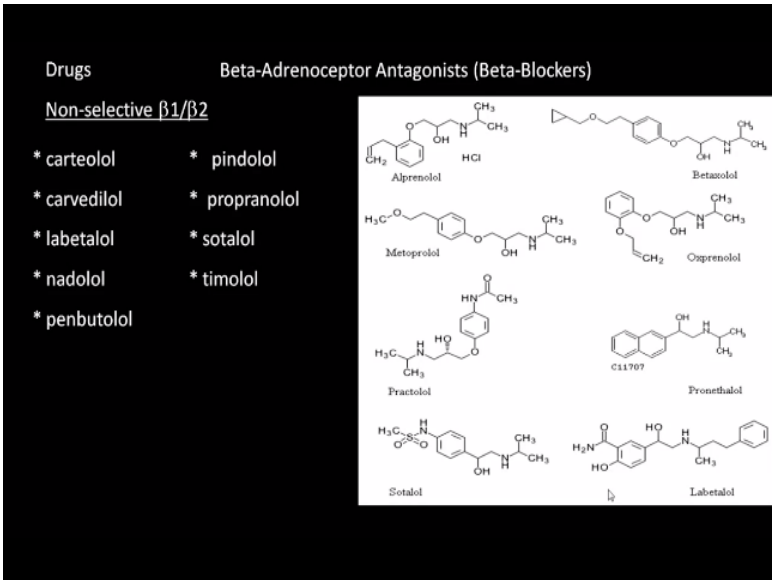

Similarly, these are again beta blockers they are called again involved in blood pressure so these are non selective there are 2 beta blockers beta 1 and beta 2 and here we have beta 1 selective so we have Propranolol, atenolol, acebutolol, Timolol so we looked at these 4 molecules and then we tried to do it.

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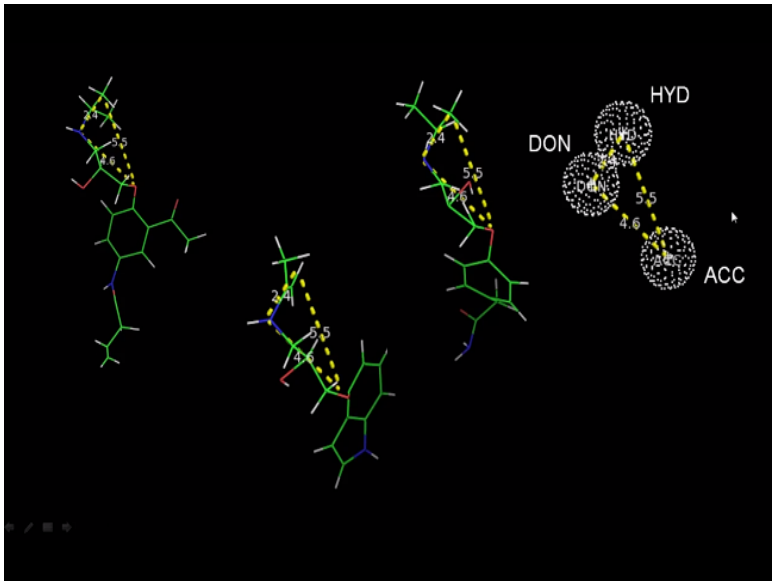

The pharmacophore again you see an acceptor a donor, acceptors and then one hydrophobic. So, when you map the molecules you will see which portions contribute to which. Again we can go to zincpharmer to identify molecules with that particular structural feature okay. So, it is a very powerful tool, this is ligand based drug discovery. So, you should know a set of molecules which are reported to be binding to the same target and then we tried to find out what are the structural features okay.

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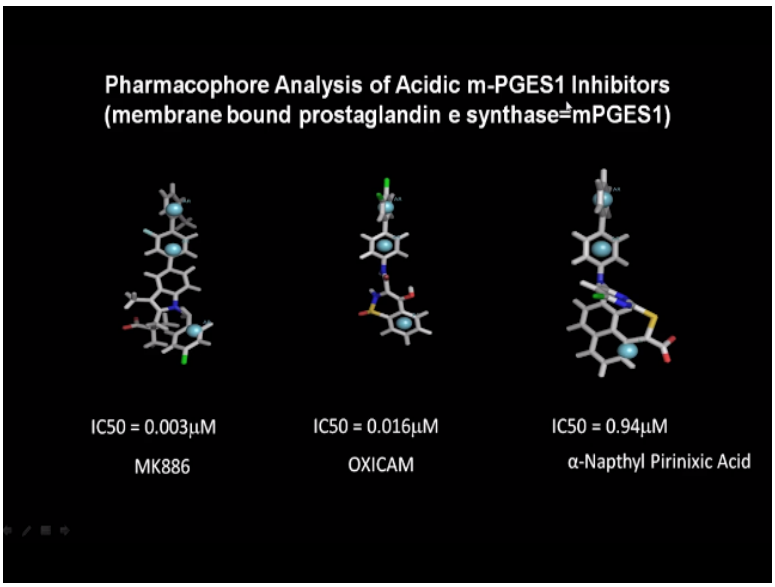

Another enzyme membrane bound prostaglandin e synthase 1 okay, this is enzyme downstream of cyclooxygen is true, which I showed you some time back, which are involved in the arcedonic acid and pathway okay. This is a membrane bound enzyme so there is a compound called MK886, it works in nanaomol IC50, OXICAM again it works in quite a bit

nanomol range then Napthyl Pirinixic acid so, you can see the pharmacophore, these are aromatic features 3, aromatic features at certain distance okay.

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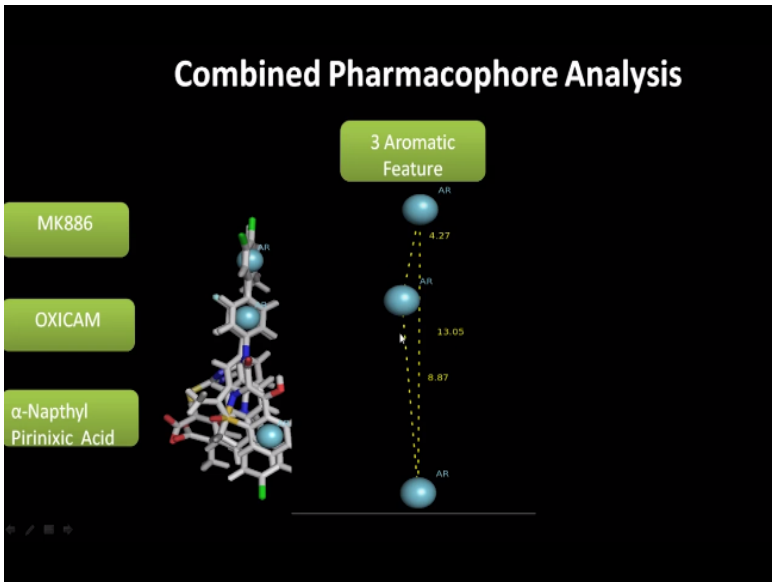

So, if you map all of them together 3 aromatic features comes out here okay at certain distances. So, that is the pharmacophore feature of ligands, which go and bind Acidic m-PGES1 ligands okay, neutral ligands may have a slightly different pharmacophore but acidic ligands.