# WC1 – Stereospecific Active Sites

Download and then open the file **1h9z_Warfarin_Enantiomers** in PyMOL. This is a model of a human serum albumin protein. This is a protein which travels in the blood plasma and transports drugs around the body through the bloodstream. Attached to the protein are the two enantiomers of the drug warfarin, known as S-warfarin and R-warfarin, which are mirror images of each other. Warfarin is an anti-coagulant drug that preventing blood clots, which if left untreated, can result in deep vein thrombosis, leading to possible strokes and heart attacks (myocardial infarctions). Warfarin is sold as a racemic mixture – a 50:50 mixture of each enantiomer.

One of the enantiomers is more potent, and induces a stronger reaction than the other.

1. Using the command **S-Warfarin>A>orient**, focus in on the molecule. By holding the right mouse button and moving the mouse, zoom in/out to get a clear view of the drug. You can move the position of the camera by holding and panning the left mouse button. Use the command **S-Warfarin>S>as>spheres**, to show a 3D view of S-warfarin. Describe the relationship between the active site and S-warfarin.

2. Deselect S-Warfarin and then select R-Warfarin. Use the command **R-Warfarin>S>as>spheres**, to show a 3D view of R-warfarin. Describe the relationship between the active site and R-warfarin.

3. Now reselect S-Warfarin. Compare the two enantiomers in the active site. Does any either appear to be a better fit than the other?

4. We know that one of the enantiomers is more potent – it has a stronger effect – than the other enantiomer. If the two enantiomers appear to have a complementary shape to the active site, what else may cause the two enantiomers to have different effects in the body?

5. Using the command chain **S>as>sticks**, show both of the enantiomers. This will show both of the enantiomers partially superimposed. On the diagram below, circle the part of the molecule which is arranged differently in each enantiomer. Also, label the chiral centre.
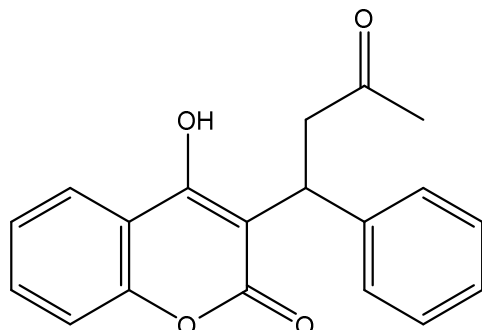
6. Now by selecting **S-Warfarin_polar** and **R-Warfarin_polar**, show the polar interactions between each enantiomer and the protein. Which enantiomer interacts the most with the protein?

7. Use the command **1h9z_Human_Albumin>S>as>sticks**. This will show the amino acid structures around the active site. Two of these residues will be interacting directly with warfarin. Select both of the residues, which should be highlighted as 222R and 242H in the residue bar at the top. Using the command **(sele)>C>by element**, explain why one of the enantiomers can interact more with the active site than the other.

8. S-warfarin is a more potent drug than R-warfarin. Using your previous answers regarding the strength of the interactions between each enantiomer and the transporter protein, predict why S-warfarin is has a greater biological effect than R-warfarin.

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