

Take-home Exam 1-31-06 (Due: 2-13-06)

Analyze the structure of the complex of fluconazole with lanosterol 14 α -demethylase (PDB code 1EA1) using RasTop as described in the Take-home Exercises on UBlerns.

Question #1 (40 pts)

Find all the H-bonds the waters make with the ligands (drug and heme) and measure their distances (should be >2.5 Å and <3.5 Å) by clicking on  (monitors) then clicking on the water oxygen (green, if you changed the color), followed by clicking on the other atom close by. You can remove the unwanted distance markings by clicking on the 2 atoms in the reverse order.

Write down these values and identify them by the residue name, numbers and the type of atom [e.g., HOH 300 ---- OOC-GLU 342: 2.78 Å or HOH 400 ---- N-HEM 319: 2.82 Å]

HOH 174 ---- O-TPF 470: 2.81Å
HOH 173 ---- OOC-HEM 460: 2.87Å

HOH 174 ---- OOC-HEM 460: 2.95Å
HOH 175 ---- N-TPF 470: 2.66Å

Question #2 (5 pt)

What is the length of the coordination bond between the triazole-N of fluconazole and the Fe of the heme? This bonding is the primary cause of the inhibition of this enzyme by the drug

2.34Å

Question #3 (20 pt)

Which atom in the drug molecule is in contact with the protein? What amino acid residue is involved and what is the shortest distance between them? Is this a favorable interaction?

Fluorine F2 ---- C-PHE 255: 2.88Å not favorable

Question #4 (10 pt)

What is the average distance of the Fe from the coordinating 4 nitrogens of the heme?

2.01Å

Question #5 (5 pt)

What is the distance between the S-atom of the cysteine and the Fe of the heme?

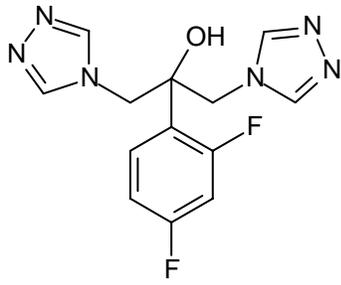
2.31Å

Question #6 (20 pts)

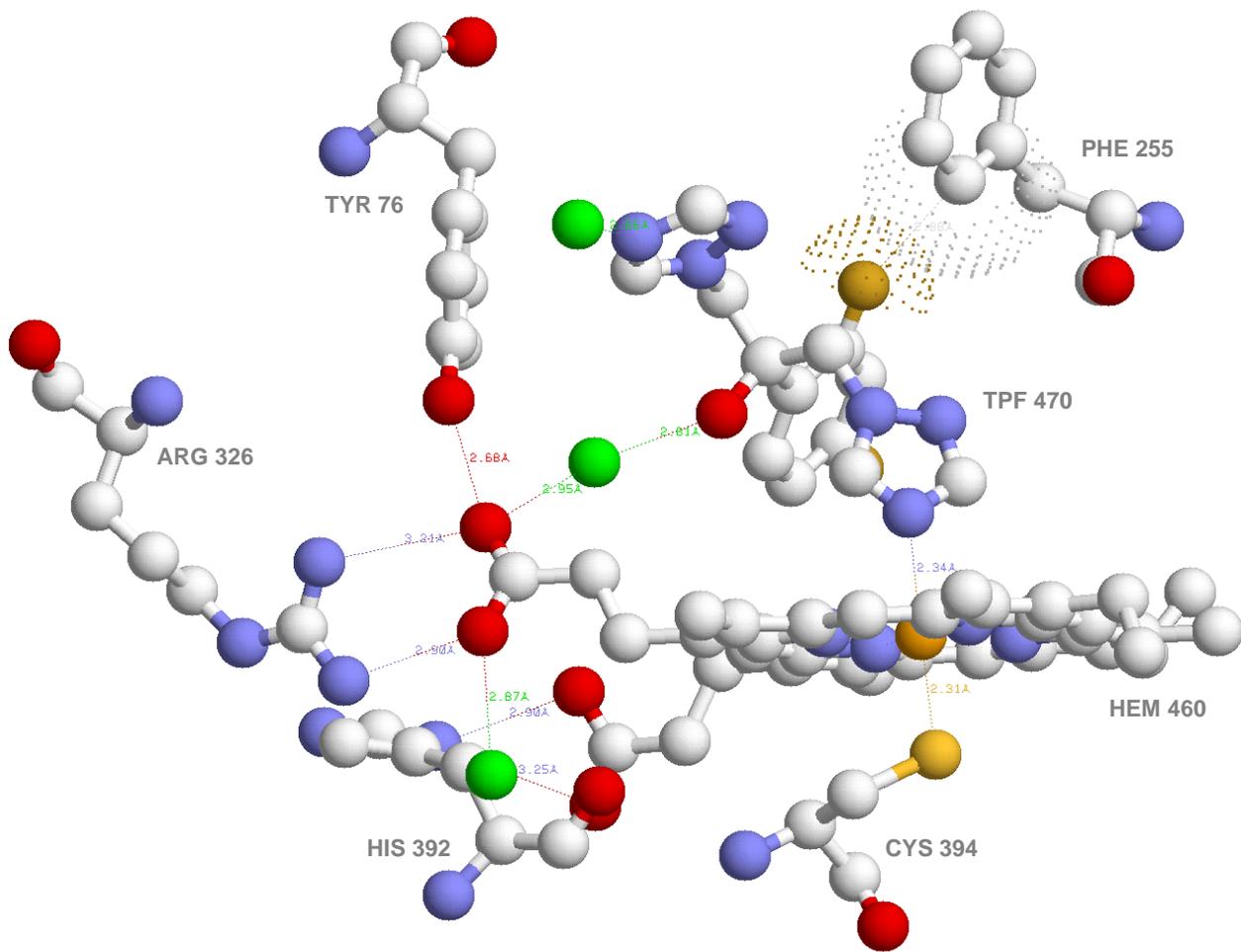
Are there charge-charge interactions between the heme and the protein? If so, identify the functional groups and amino acid residues involved and give the length of the ionic bonds.

N-ARG 326 ---- OOC-HEM 460: 2.90Å; 3.21Å
N-HIS 392 ---- OOC-HEM 460: 2.90Å; 3.25Å

SEE NEXT PAGE!



Fluconazole (TPF 470)



1EA1