

Figure S1. Proton (^1H) Nuclear Magnetic Resonance spectrum of STC1

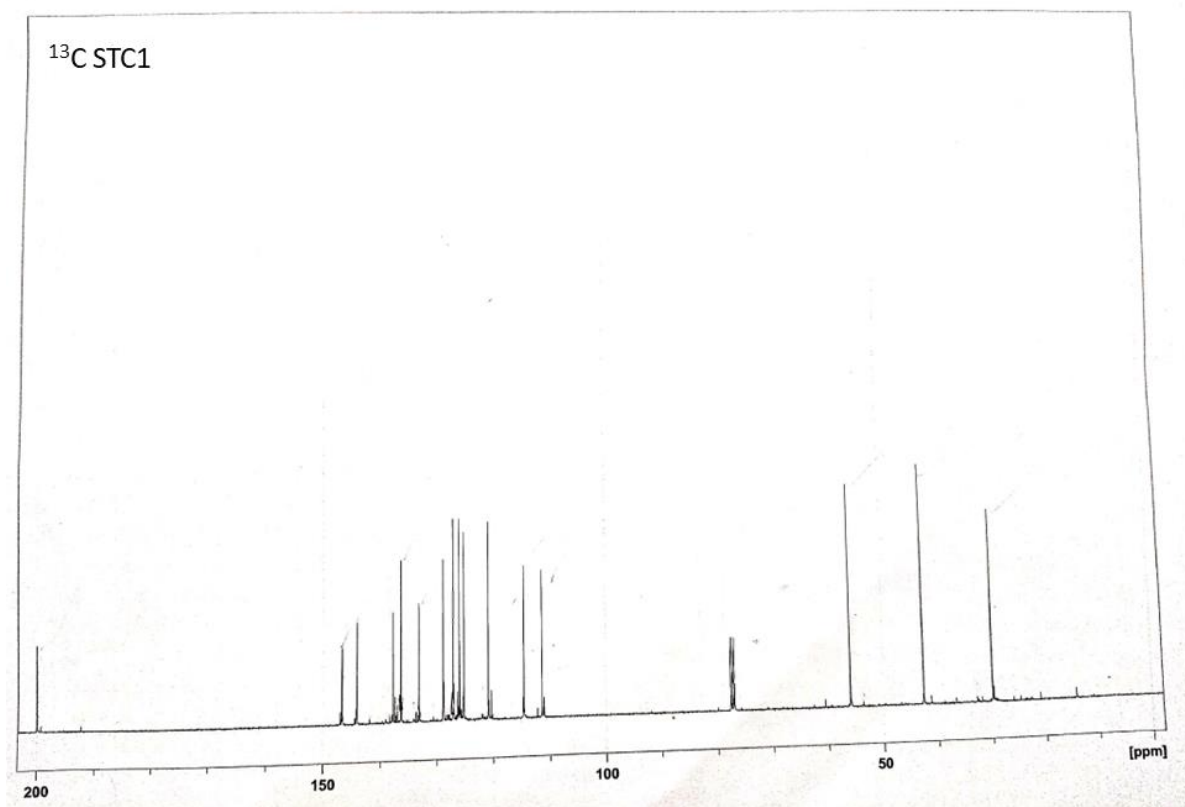


Figure S2. Carbon (^{13}C) Nuclear Magnetic Resonance spectrum of STC1

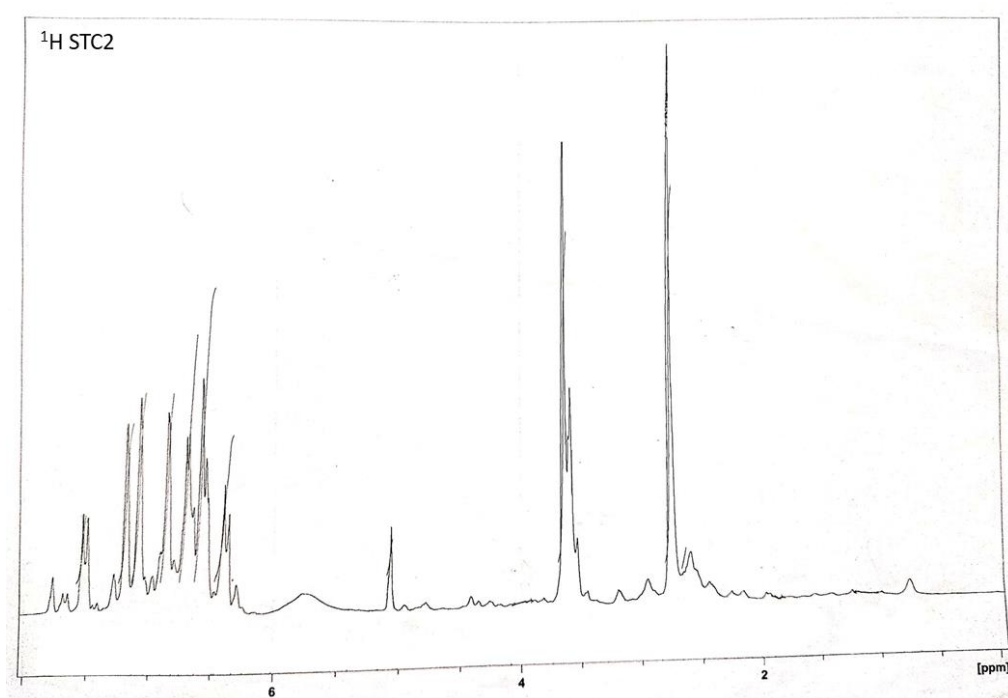


Figure S3. Proton (^1H) Nuclear Magnetic Resonance spectrum of STC2

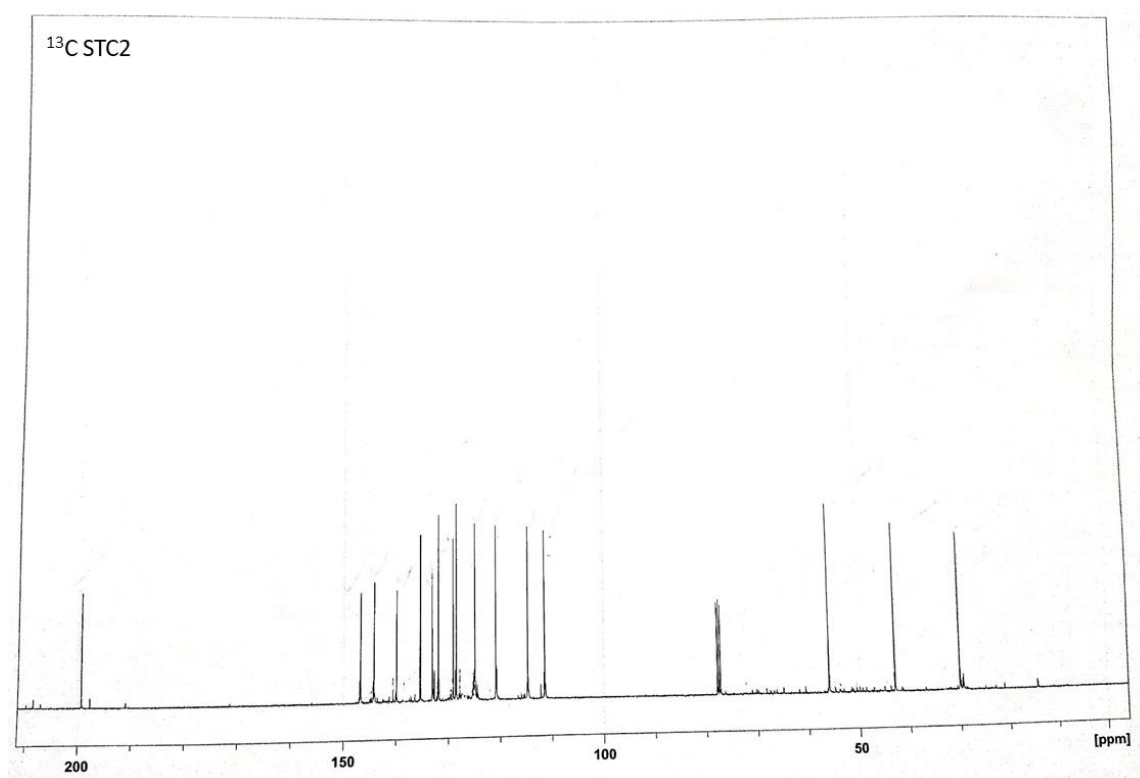


Figure S4. Carbon (^{13}C) Nuclear Magnetic Resonance spectrum of STC2

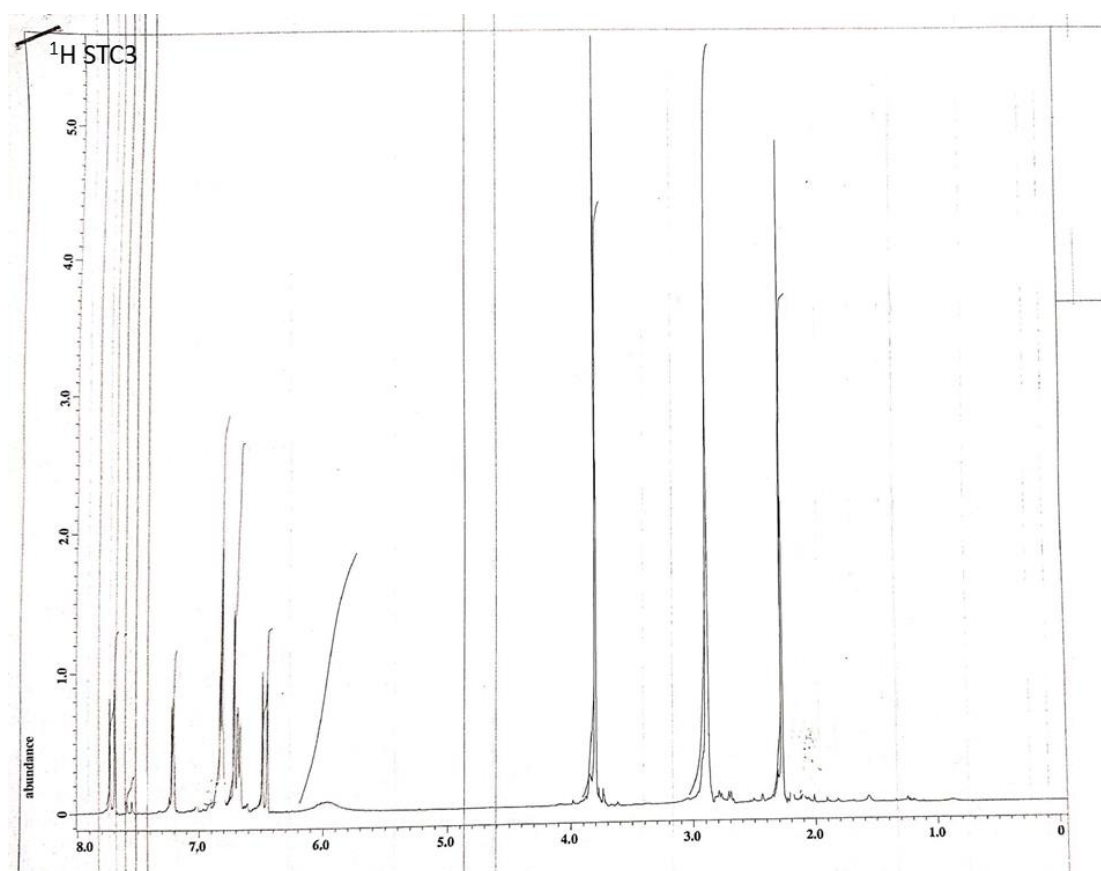


Figure S5. Proton (^1H) Nuclear Magnetic Resonance spectrum of STC3

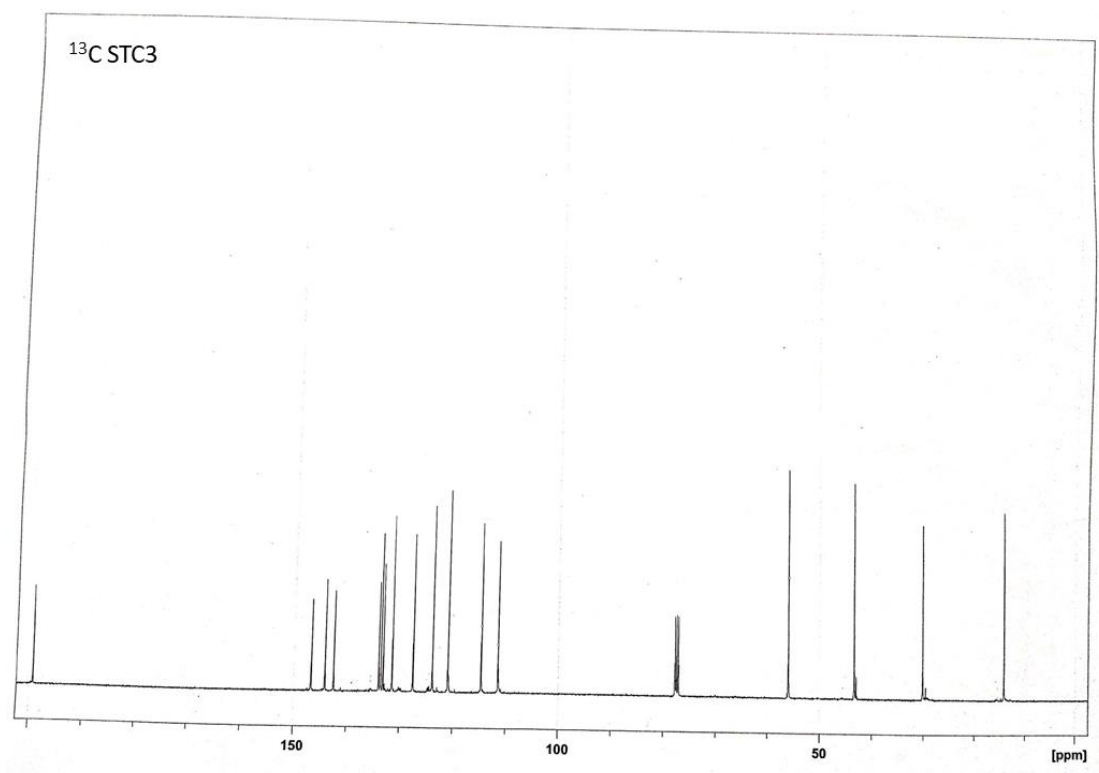


Figure S6. Carbon (¹³C) Nuclear Magnetic Resonance spectrum of STC3

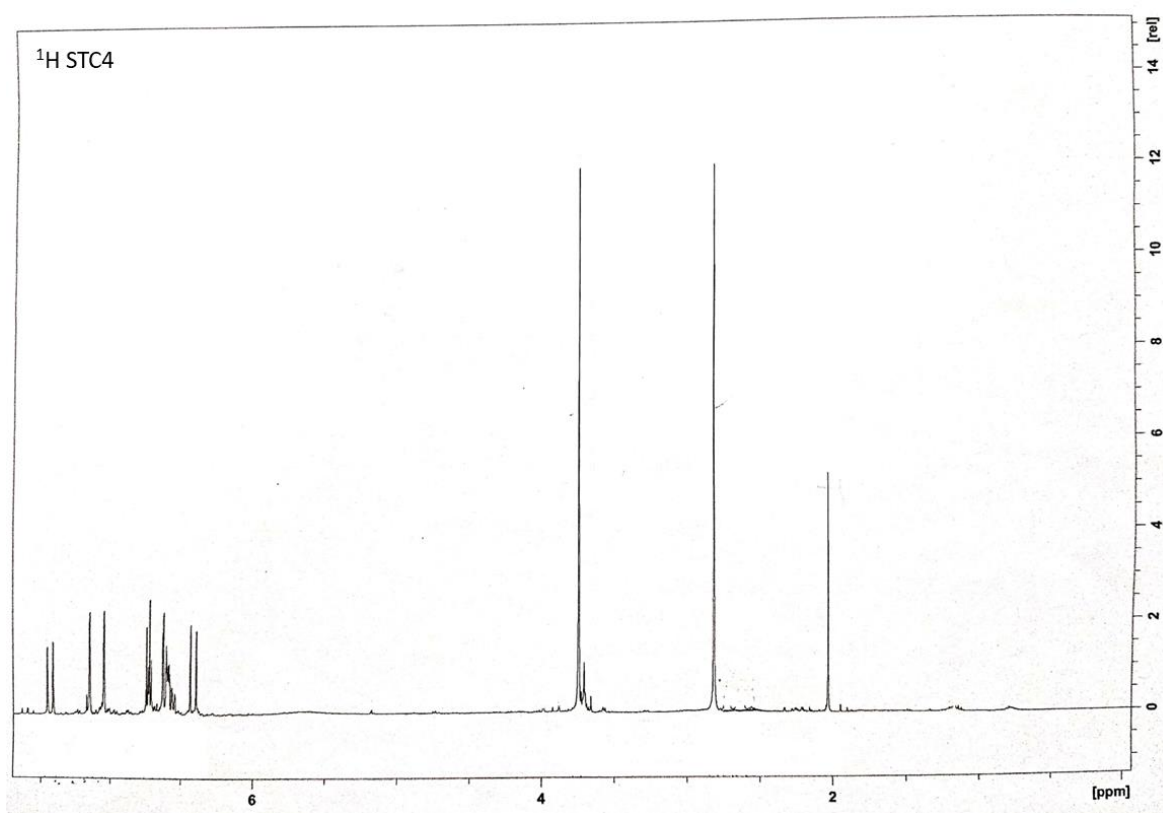


Figure S7. Proton (¹H) Nuclear Magnetic Resonance spectrum of STC4

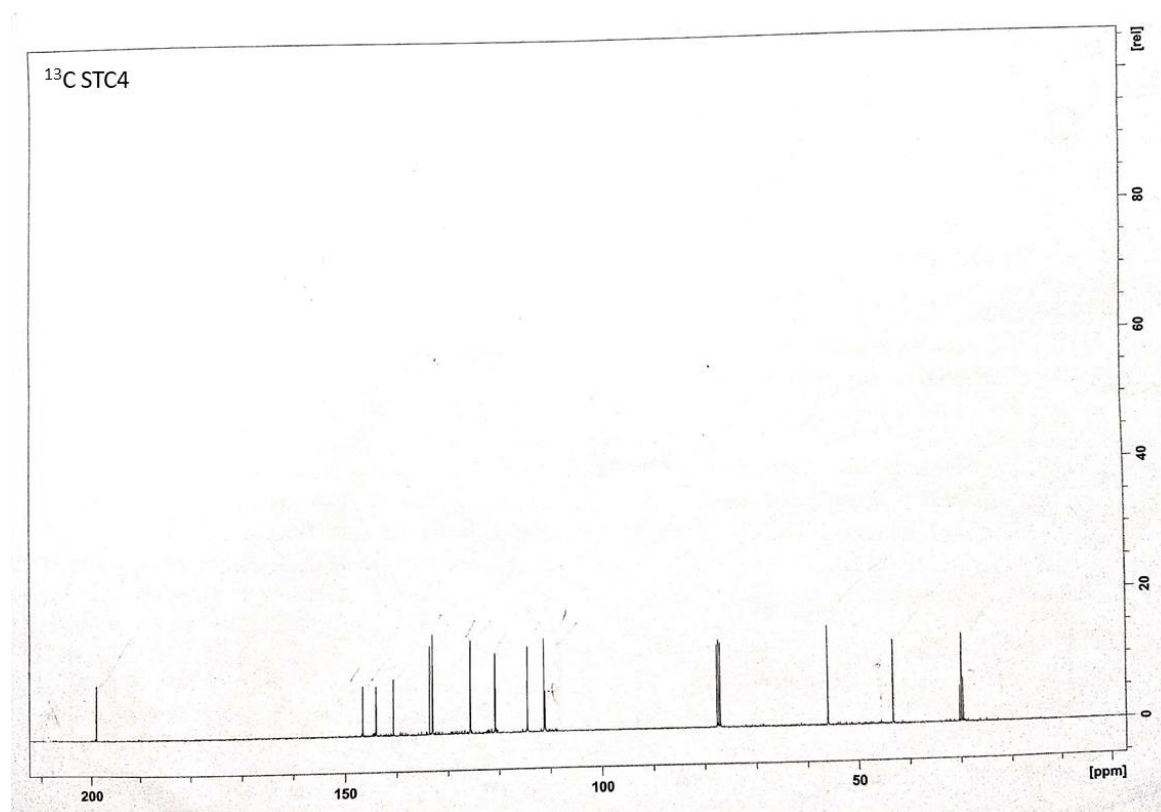


Figure S8. Carbon (¹³C) Nuclear Magnetic Resonance spectrum of STC4

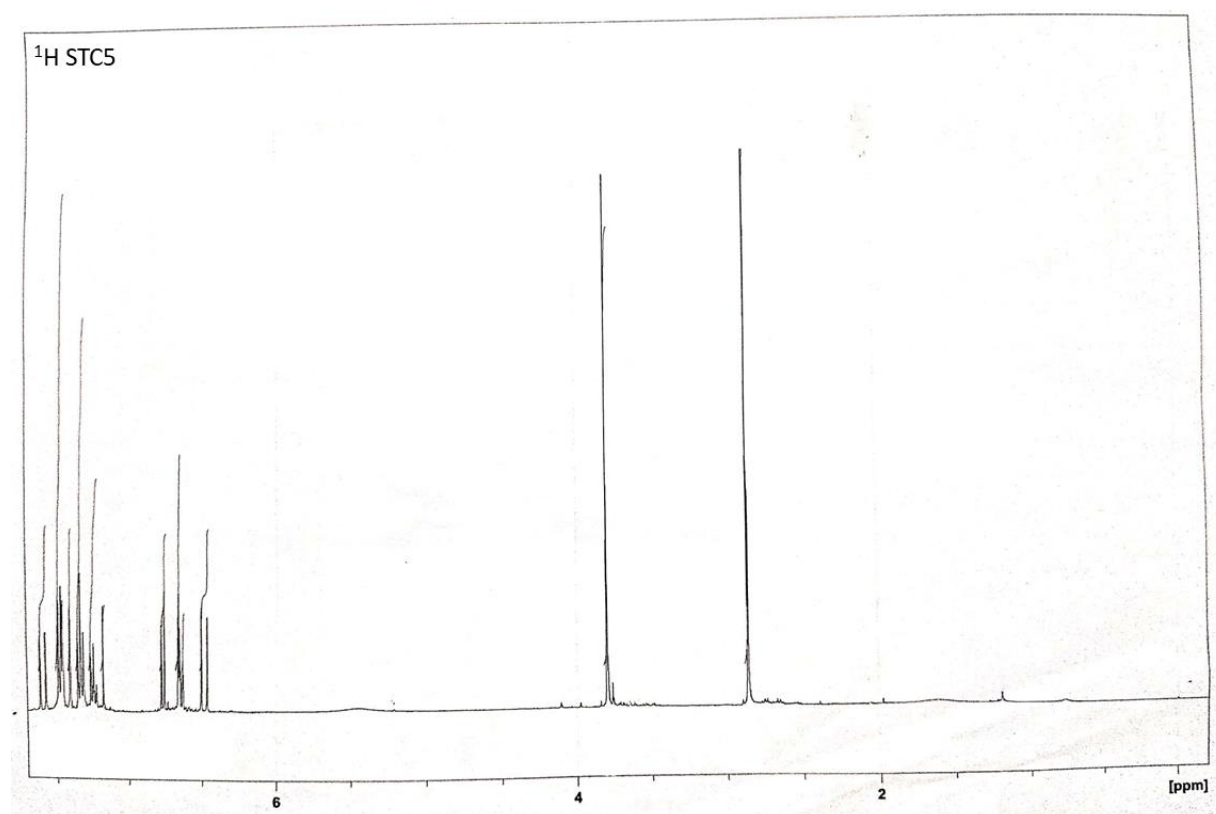


Figure S9. Proton (¹H) Nuclear Magnetic Resonance spectrum of STC5

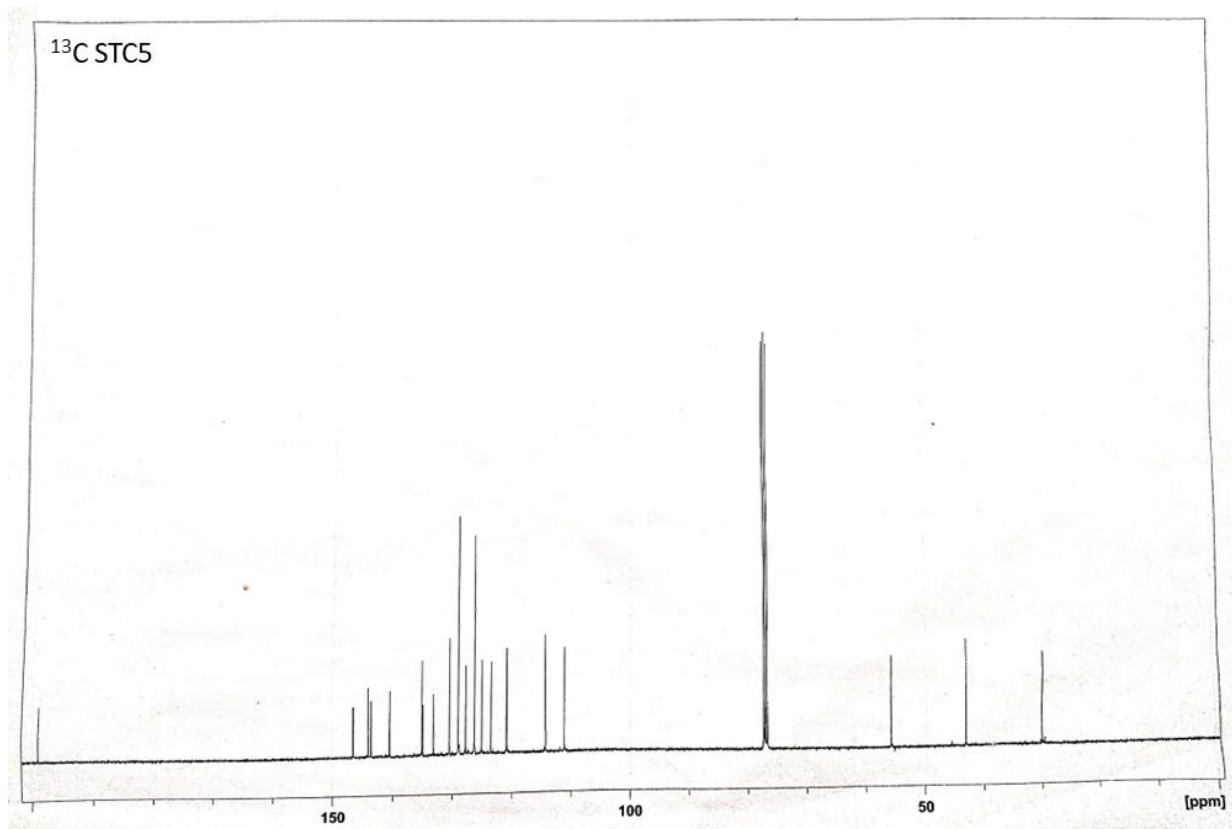


Figure S10. Carbon (¹³C) Nuclear Magnetic Resonance spectrum of STC5

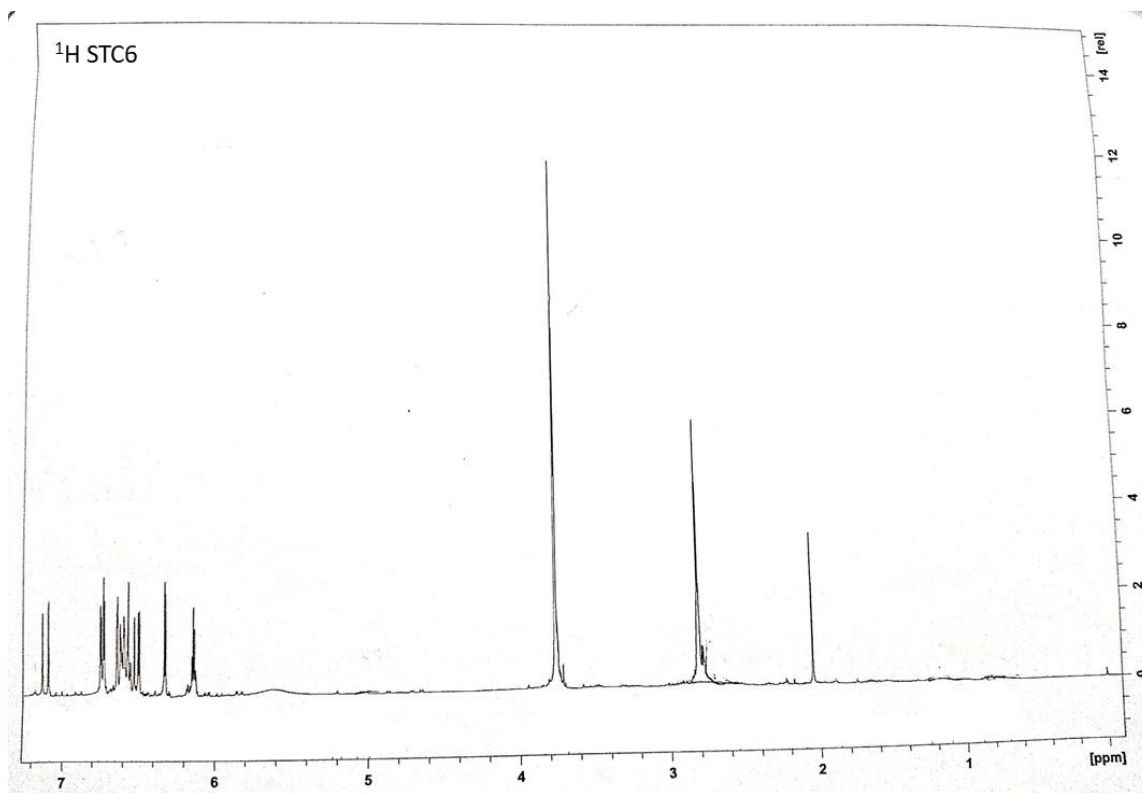


Figure S11. Proton (¹H) Nuclear Magnetic Resonance spectrum of STC6

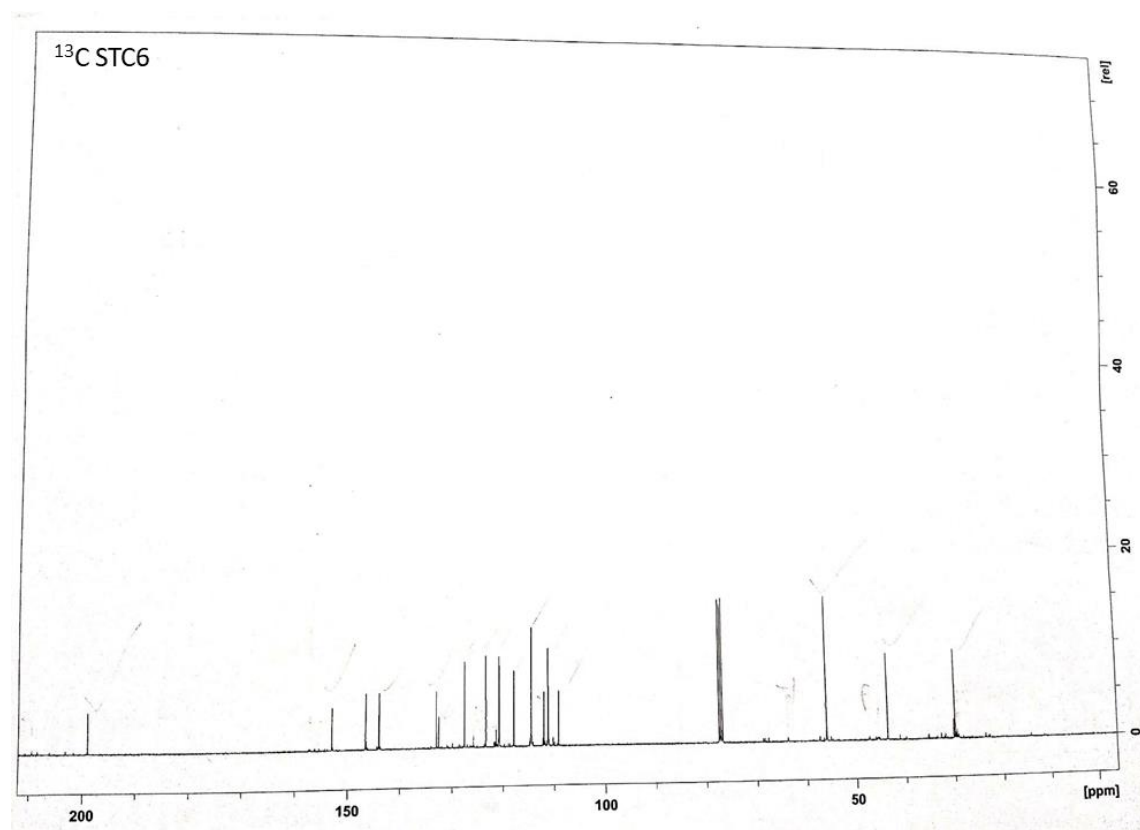


Figure S12. Carbon (^{13}C) Nuclear Magnetic Resonance spectrum of STC6.

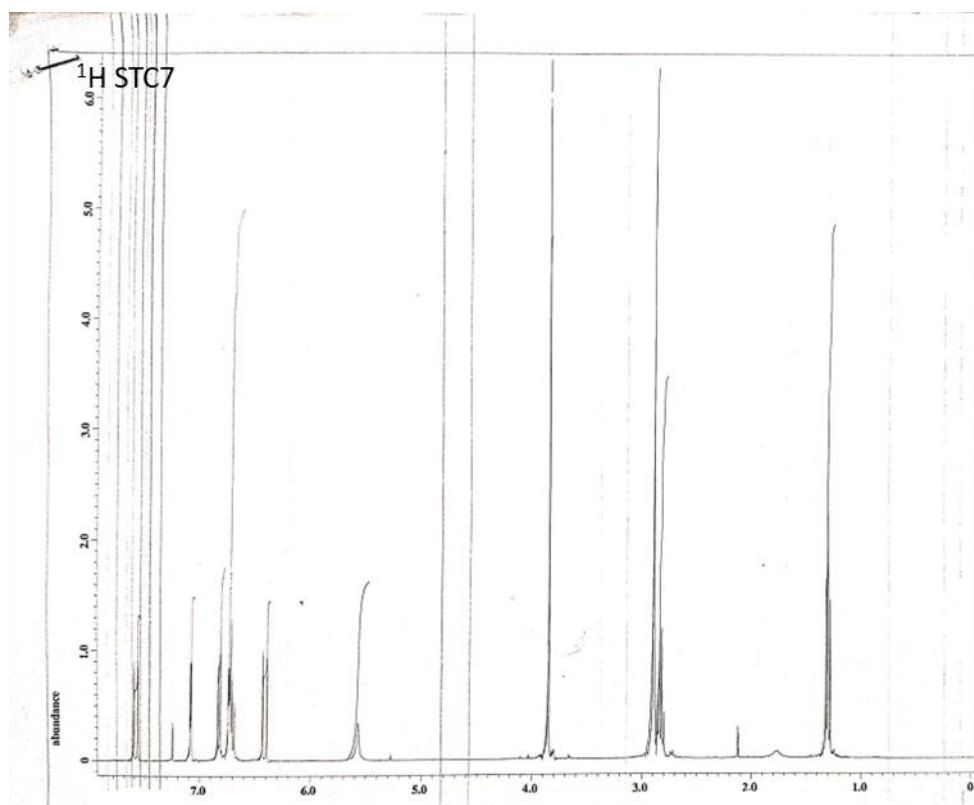


Figure S13. Proton (^1H) Nuclear Magnetic Resonance spectrum of STC7.

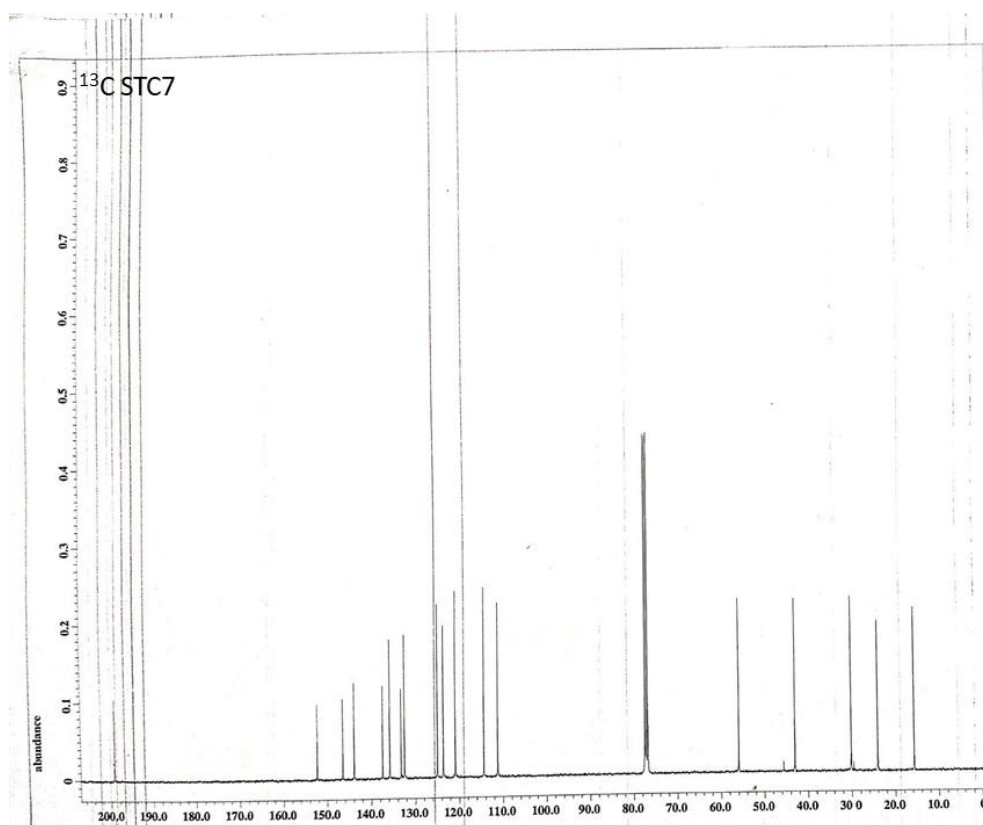


Figure S14. Carbon (^{13}C) Nuclear Magnetic Resonance spectrum of STC7.

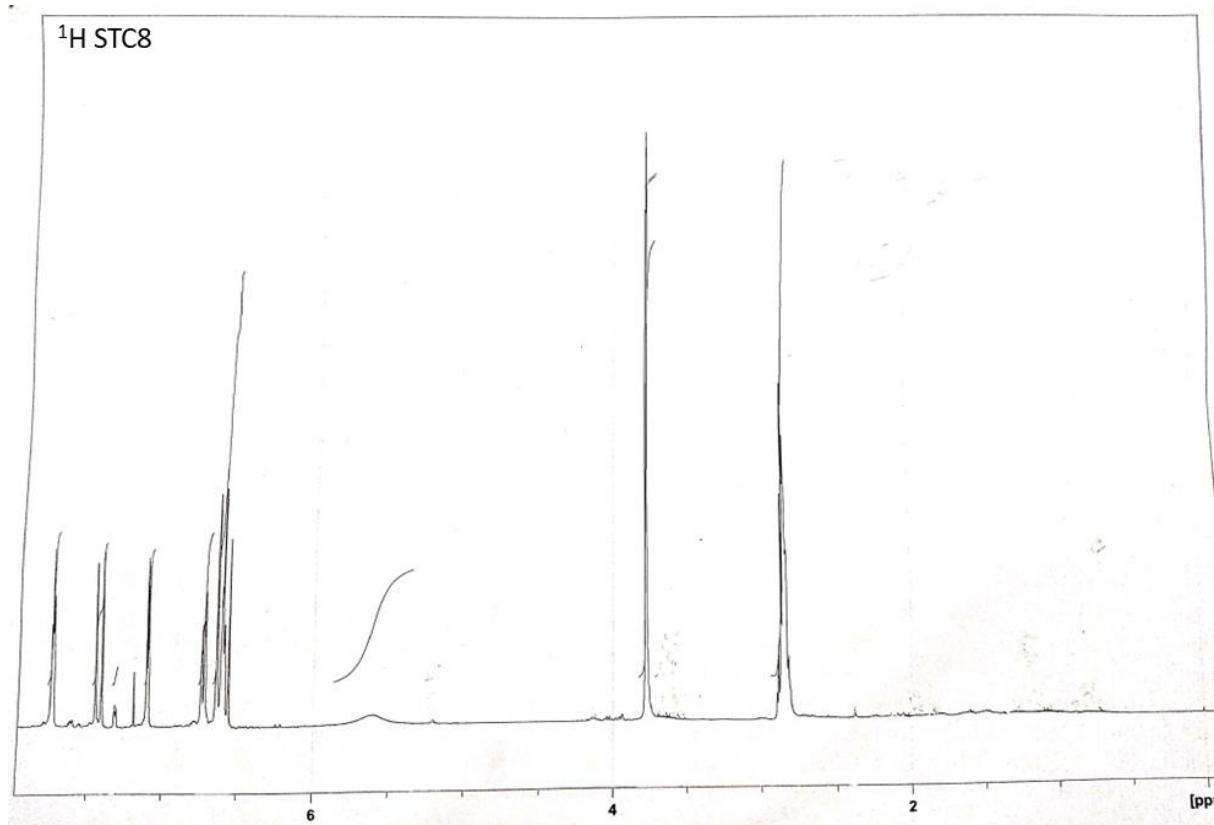


Figure S15. Proton (¹H) Nuclear Magnetic Resonance spectrum of STC8.

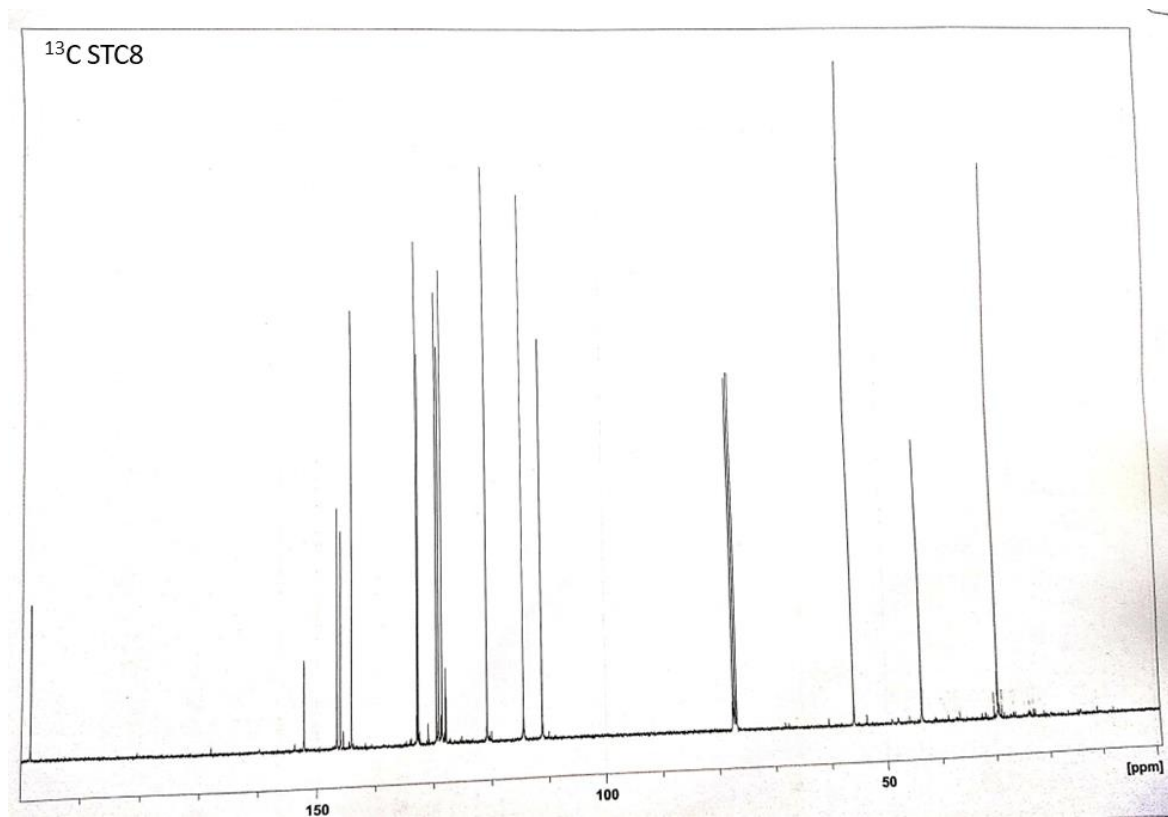


Figure S16. Carbon (¹³C) Nuclear Magnetic Resonance spectrum of STC8.

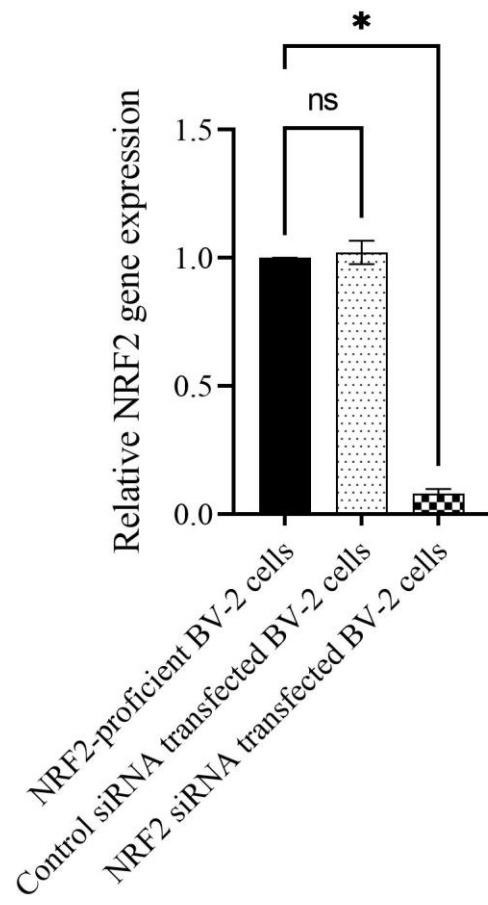


Figure S17. Relative NRF2 gene expression in NRF2-proficient BV-2 cells, control siRNA transfected BV-2 and NRF2 siRNA transfected BV-2 cells.

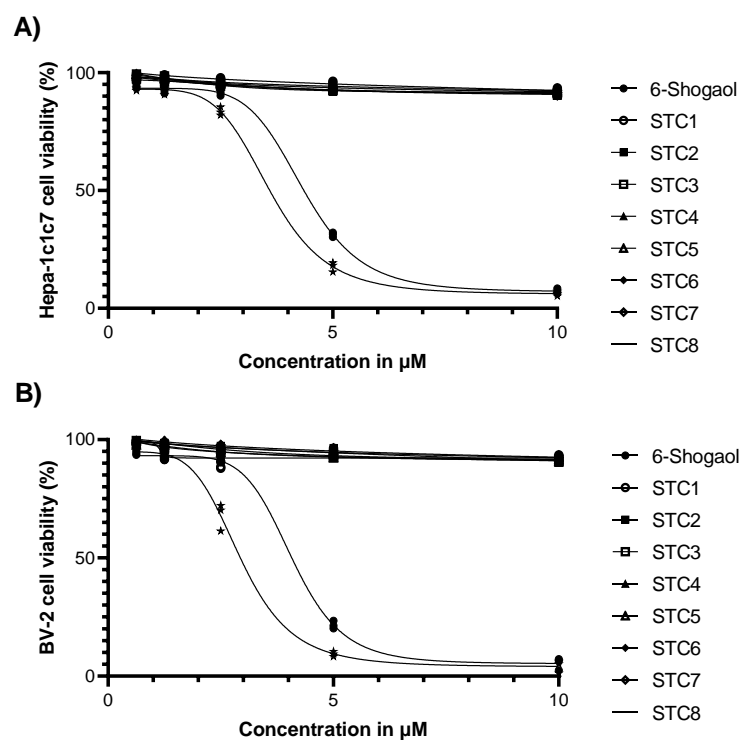


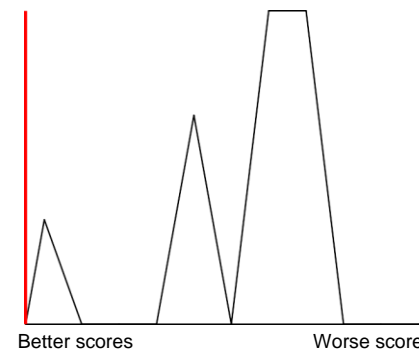
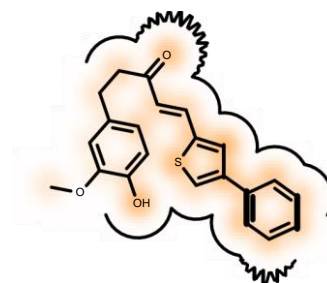
Figure S18. The cytotoxic effect of STCs and 6-Shogaol on Hepa-1c1c7 and BV-3 cells.

Molecule Name STC5.mol_43
Molecular Weight 364.5
XLogP 5.0
PSA 46.5
Heavy Atoms 26
Acceptor Count 3
Donor Count 1
Chelator Count 1

Total Score -14.47

Score compared to other molecules

94%



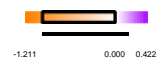
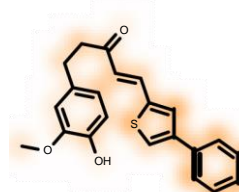
Protein Contact

Protein Cavity

Residue Fingerprint

| | |
|----------------|----------------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

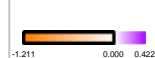
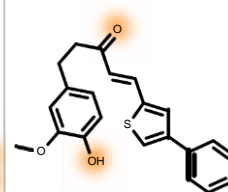
Shape -15.50



89%



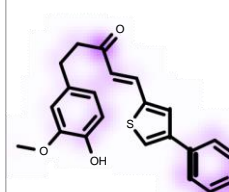
Hydrogen Bond -2.28



94%



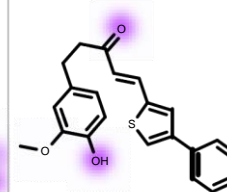
Protein Desolvation 2.49



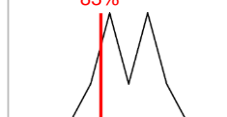
6%



Ligand Desolvation 0.82



83%



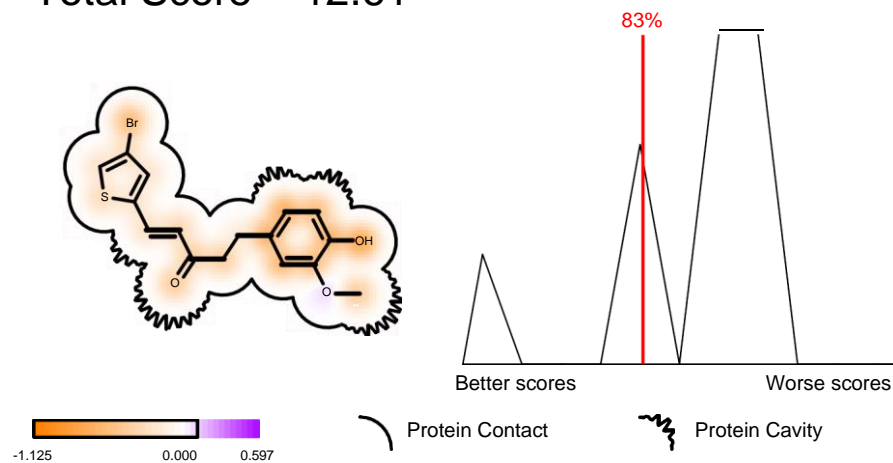
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S19. FRED report of STC5 with 4IQK.

Molecule Name STC4.mol_52
Molecular Weight 367.3
XLogP 3.9
PSA 46.5
Heavy Atoms 21
Acceptor Count 3
Donor Count 1
Chelator Count 1

Total Score -12.61

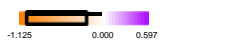
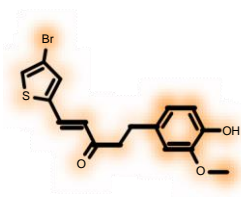
Score compared to other molecules



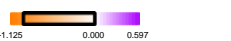
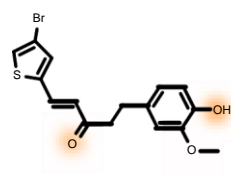
Residue Fingerprint

| | |
|----------------|----------------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

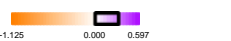
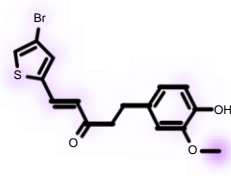
Shape -14.06



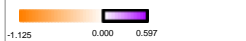
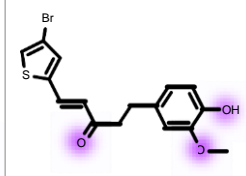
Hydrogen Bond -1.65



Protein Desolvation 1.50



Ligand Desolvation 1.60



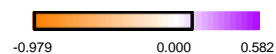
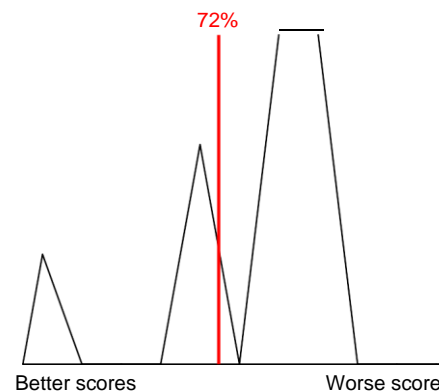
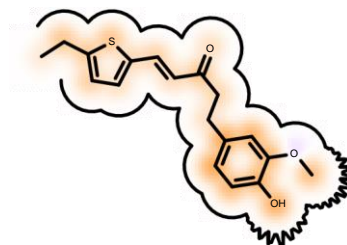
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S20. FRED report of STC4 with 4IQK.

Molecule Name STC7.mol_113
Molecular Weight 316.4
XLogP 3.7
PSA 46.5
Heavy Atoms 22
Acceptor Count 3
Donor Count 1
Chelator Count 1

Total Score -12.50

Score compared to other molecules



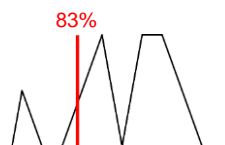
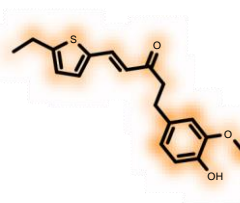
Protein Contact

Protein Cavity

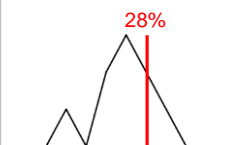
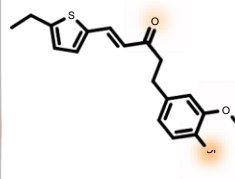
Residue Fingerprint

| | |
|----------------|---------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| 39 VAL463A | VAL604A |

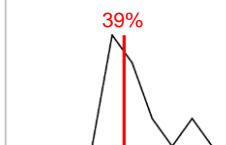
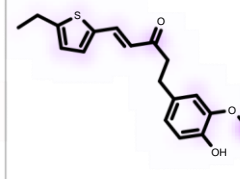
Shape -14.40



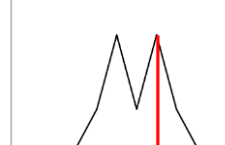
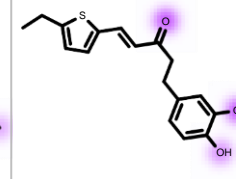
Hydrogen Bond -1.13



Protein Desolvation 1.51



Ligand Desolvation 1.52



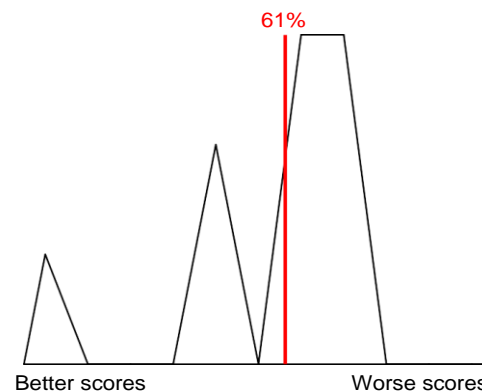
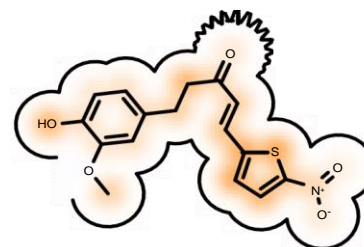
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S21. FRED report of STC7 with 4IQK.

Molecule Name STC8.mol_125
Molecular Weight 333.4
XLogP 1.8
PSA 89.7
Heavy Atoms 23
Acceptor Count 5
Donor Count 1
Chelator Count 1

Total Score -12.18

Score compared to other molecules

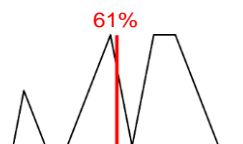
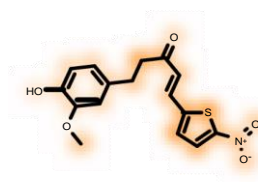


Protein Contact Protein Cavity

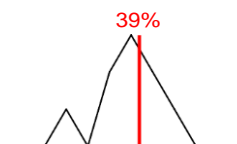
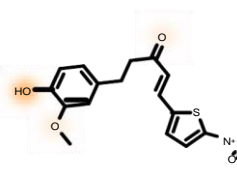
Residue Fingerprint

| | |
|----------------|---------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

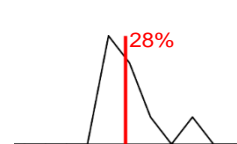
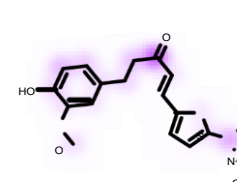
Shape -13.98



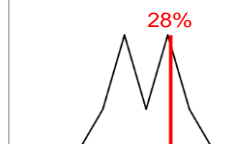
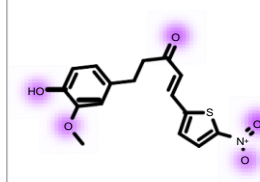
Hydrogen Bond -1.31



Protein Desolvation 1.57



Ligand Desolvation 1.54



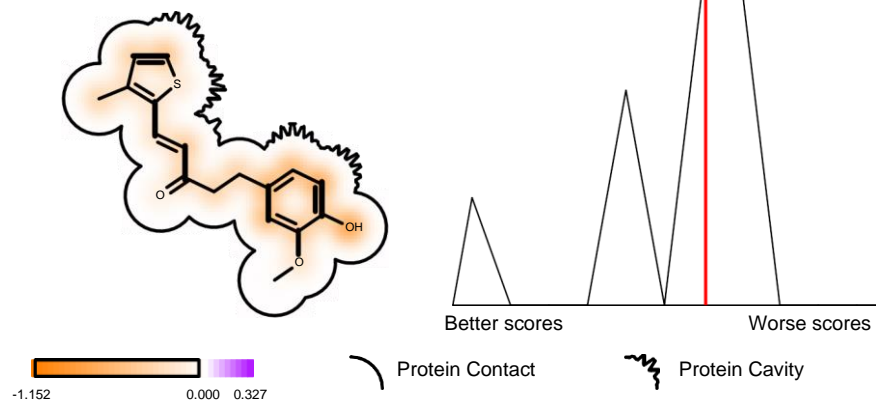
Figure

Figure S22. FRED report of STC8 with 4IQK.

Molecule Name STC3.mol_193
Molecular Weight 302.4
XLogP 3.4
PSA 46.5
Heavy Atoms 21
Acceptor Count 3
Donor Count 1
Chelator Count 1

Total Score -12.06

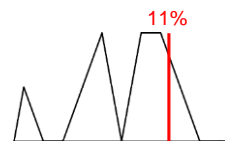
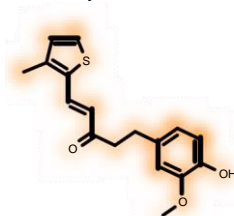
Score compared to other molecules



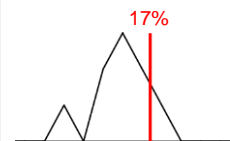
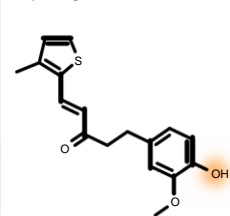
Residue Fingerprint

| | |
|----------------|---------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

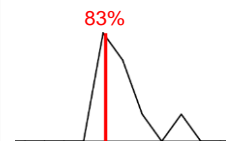
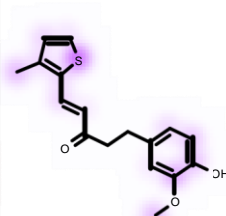
Shape -13.12



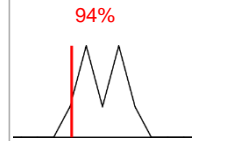
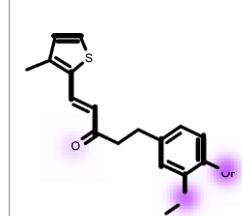
Hydrogen Bond -1.03



Protein Desolvation 1.38



Ligand Desolvation 0.71



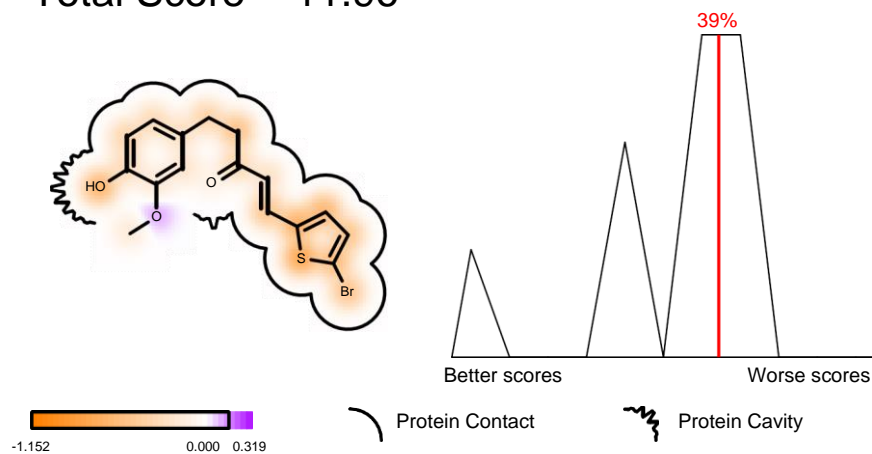
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S23. FRED report of STC3 with 4IQK.

Molecule Name STC6.mol_175
Molecular Weight 367.3
XLogP 4.3
PSA 46.5
Heavy Atoms 21
Acceptor Count 3
Donor Count 1
Chelator Count 1

Total Score -11.96

Score compared to other molecules

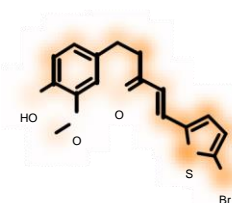


Residue Fingerprint
ALA510A ALA556A
ARG415A GLN530A
GLY364A GLY462A

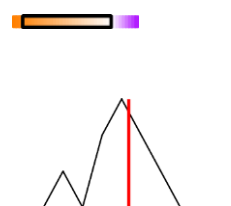
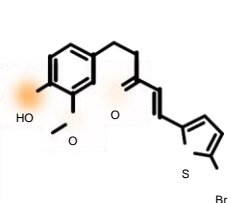
GLY509A GLY603A
ILE416A LEU365A
LEU557A PHE577A
SER363A SER508A

SER555A SER602A
TYR334A TYR572A VAL463A VAL604A

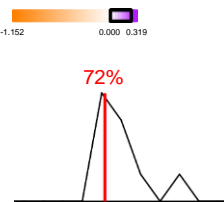
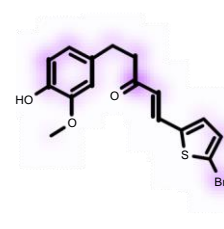
Shape -12.97



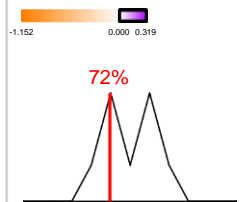
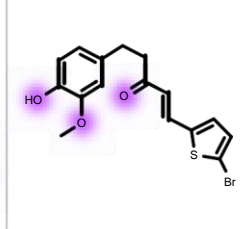
Hydrogen Bond -1.32



Protein Desolvation 1.39



Ligand Desolvation 0.94



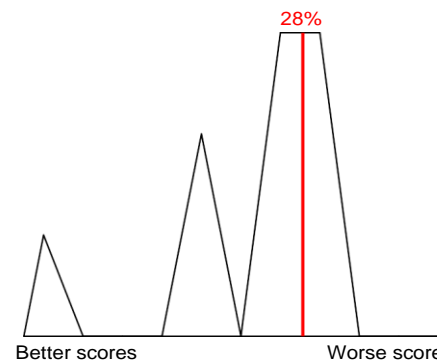
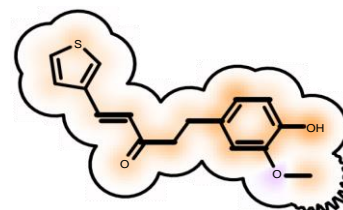
Acceptor Donor
Metal Contact

Figure S24. FRED report of STC6 with 4IQK.

Molecule Name STC1.mol_142
 Molecular Weight 288.4
 XLogP 3.2
 PSA 46.5
 Heavy Atoms 20
 Acceptor Count 3
 Donor Count 1
 Chelator Count 1

Total Score -11.92

Score compared to other molecules



Protein Contact

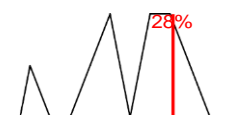
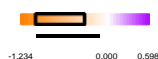
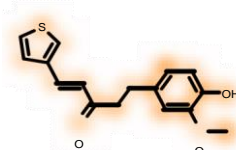


Protein Cavity

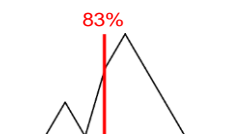
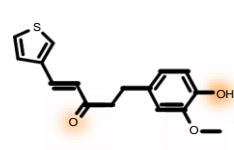
Residue Fingerprint

| | |
|----------------|----------------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

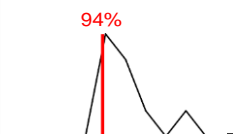
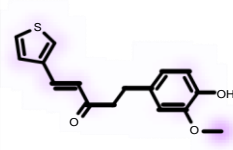
Shape -13.19



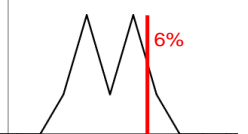
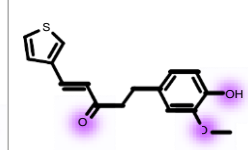
Hydrogen Bond -1.70



Protein Desolvation 1.30



Ligand Desolvation 1.67



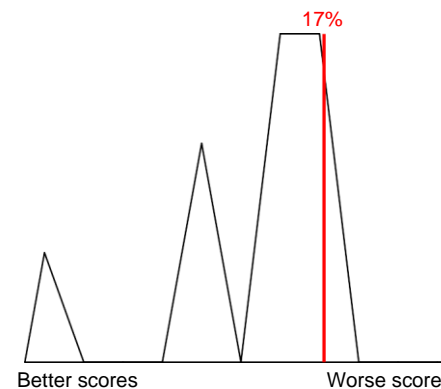
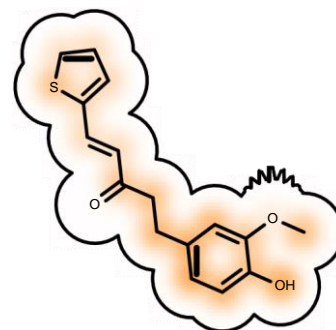
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S25. FRED report of STC1 with 4IQK.

Molecule Name STC2.mol_188
 Molecular Weight 288.4
 XLogP 3.1
 PSA 46.5
 Heavy Atoms 20
 Acceptor Count 3
 Donor Count 1
 Chelator Count 1

Total Score -11.77

Score compared to other molecules



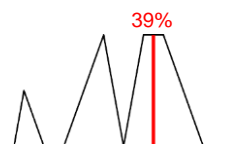
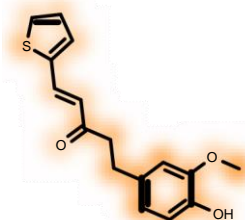
Protein Contact

Protein Cavity

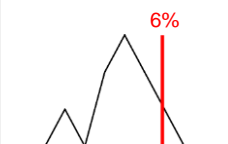
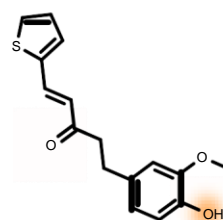
Residue Fingerprint

| | |
|----------------|---------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

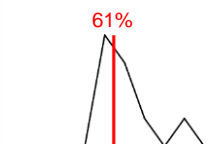
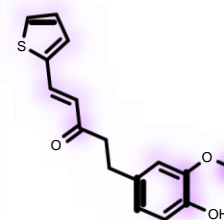
Shape -13.37



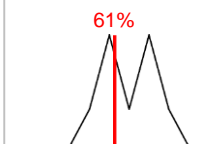
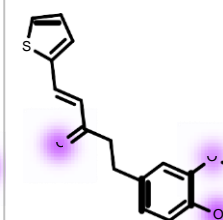
Hydrogen Bond -0.90



Protein Desolvation 1.47



Ligand Desolvation 1.03



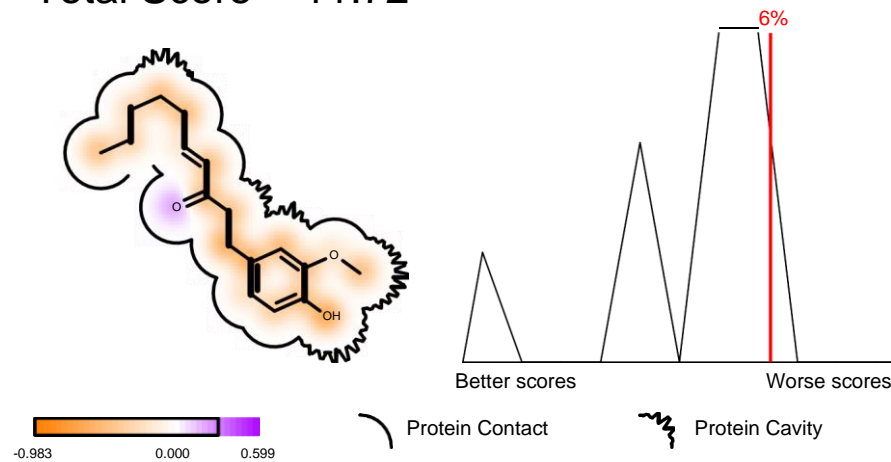
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S26. FRED report of STC2 with 4IQK.

Molecule Name 6-Shogaol.mol_45
Molecular Weight 276.4
XLogP 3.8
PSA 46.5
Heavy Atoms 20
Acceptor Count 3
Donor Count 1
Chelator Count 1

Total Score -11.72

Score compared to other molecules

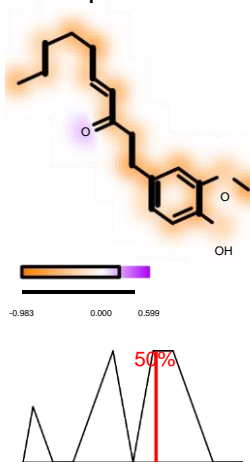


Residue Fingerprint

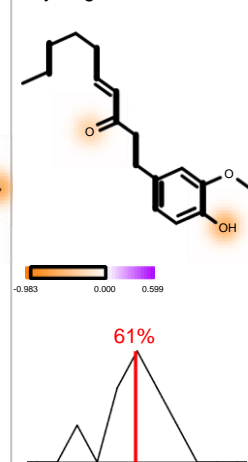
| | |
|----------------|---------|
| ALA510A | ALA556A |
| ARG415A | GLN530A |
| GLY364A | GLY462A |
| GLY509A | GLY603A |
| ILE416A | LEU365A |
| LEU557A | PHE577A |
| SER363A | SER508A |
| SER555A | SER602A |
| TYR334A | TYR572A |
| VAL463A | VAL604A |

| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

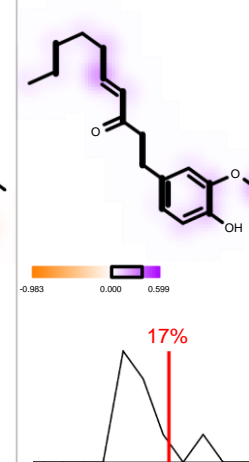
Shape -13.47



Hydrogen Bond -1.44



Protein Desolvation 1.97



Ligand Desolvation 1.21

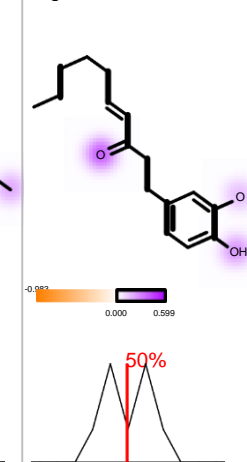


Figure S27. FRED report of 6-Shogaol with 4IQK.

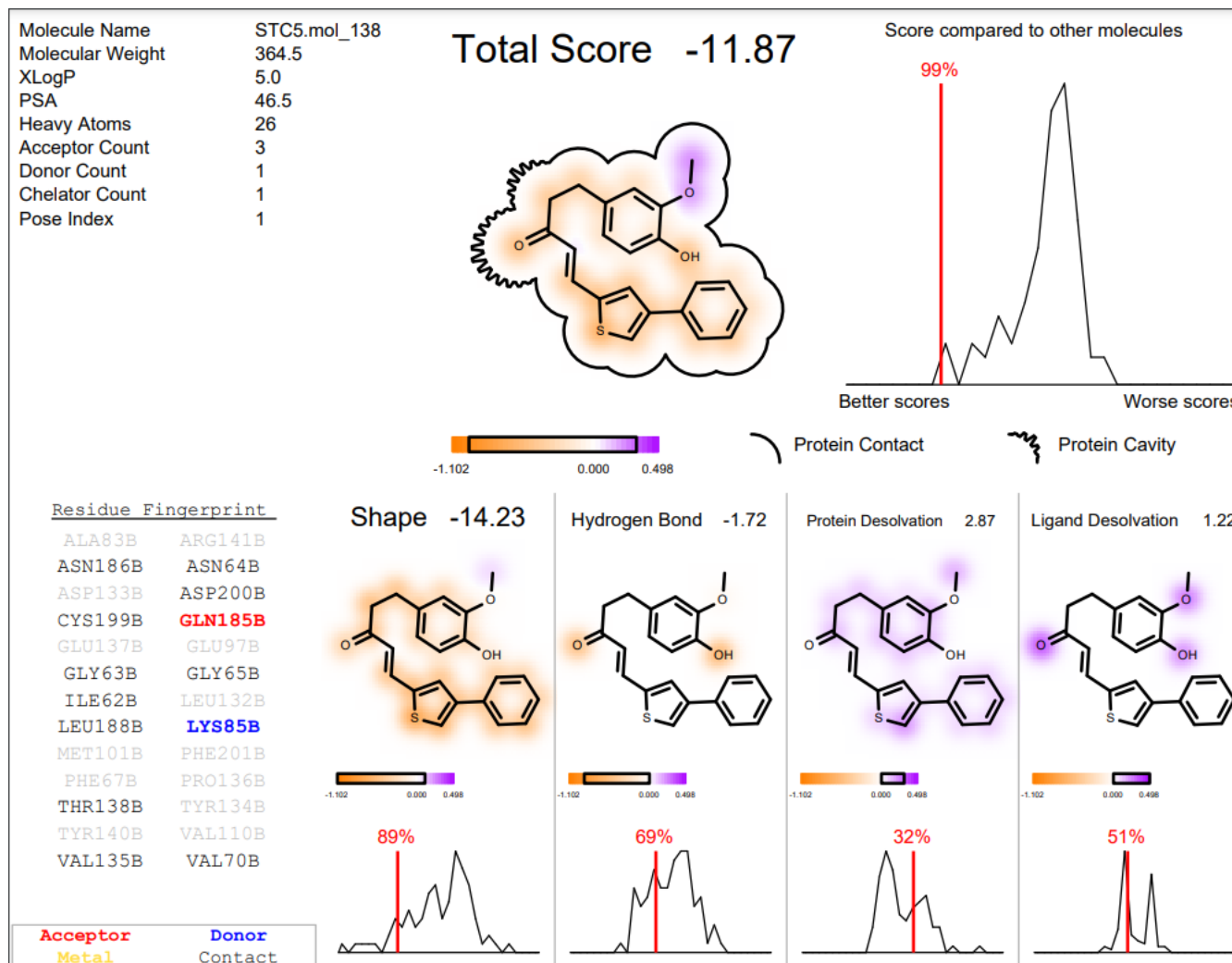


Figure S28. FRED report of STC5 with 1Q41.

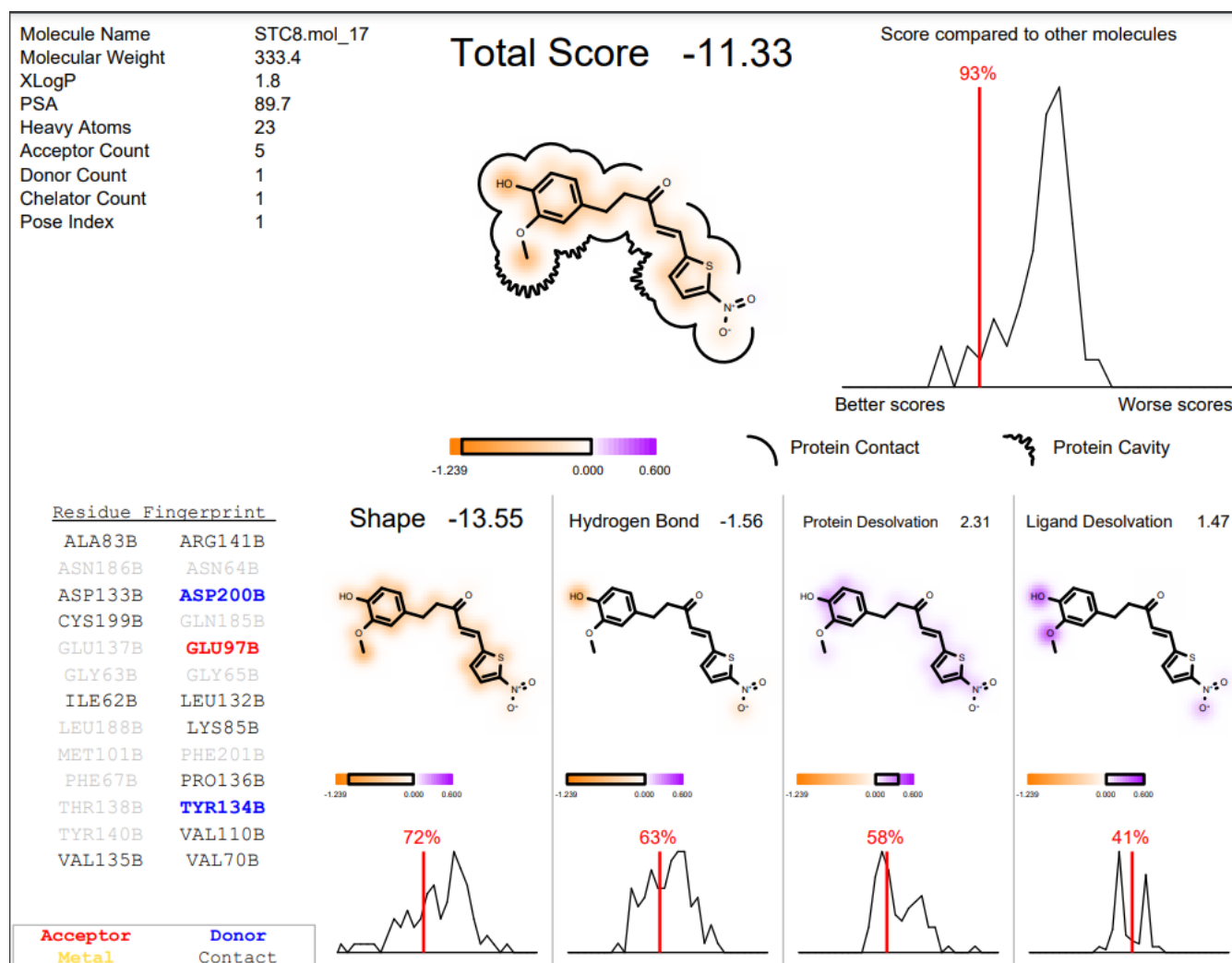
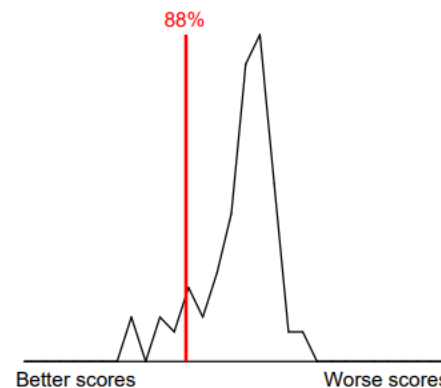
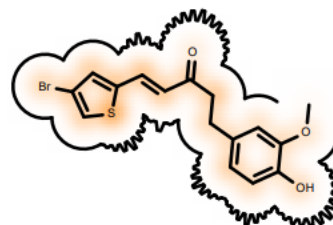


Figure S29. FRED report of STC8 with 1Q41.

Molecule Name STC4.mol_170
Molecular Weight 367.3
XLogP 3.9
PSA 46.5
Heavy Atoms 21
Acceptor Count 3
Donor Count 1
Chelator Count 1
Pose Index 1

Total Score -11.18

Score compared to other molecules



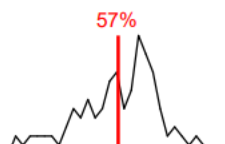
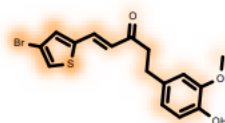
Protein Contact

Protein Cavity

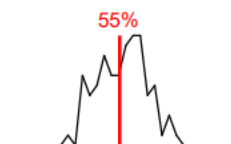
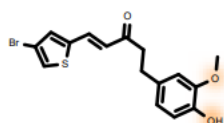
Residue Fingerprint

| | |
|---------|----------------|
| ALA83B | ARG141B |
| ASN186B | ASN64B |
| ASP133B | ASP200B |
| CYS199B | GLN185B |
| GLU137B | GLU97B |
| GLY63B | GLY65B |
| ILE62B | LEU132B |
| LEU188B | LYS85B |
| MET101B | PHE201B |
| PHE67B | PRO136B |
| THR138B | TYR134B |
| TYR140B | VAL110B |
| VAL135B | VAL70B |

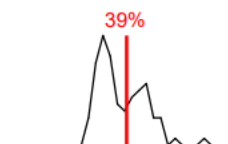
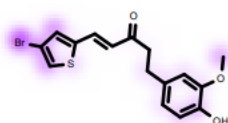
Shape -13.26



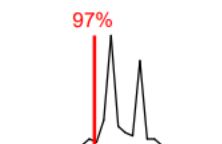
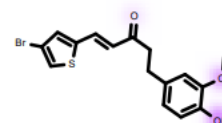
Hydrogen Bond -1.41



Protein Desolvation 2.73



Ligand Desolvation 0.76



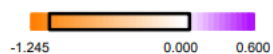
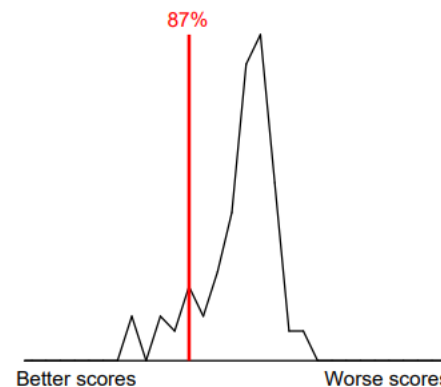
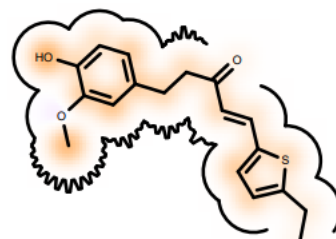
Acceptor Donor
Metal Contact

Figure S30. FRED report of STC4 with 1Q41

Molecule Name STC7.mol_31
Molecular Weight 316.4
XLogP 3.7
PSA 46.5
Heavy Atoms 22
Acceptor Count 3
Donor Count 1
Chelator Count 1
Pose Index 1

Total Score -11.15

Score compared to other molecules



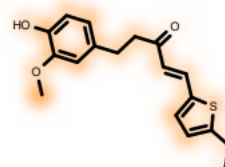
Protein Contact

Protein Cavity

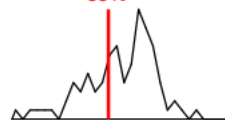
Residue Fingerprint

| | |
|---------|----------------|
| ALA83B | ARG141B |
| ASN186B | ASN64B |
| ASP133B | ASP200B |
| CYS199B | GLN185B |
| GLU137B | GLU97B |
| GLY63B | GLY65B |
| ILE62B | LEU132B |
| LEU188B | LYS85B |
| MET101B | PHE201B |
| PHE67B | PRO136B |
| THR138B | TYR134B |
| TYR140B | VAL110B |
| VAL135B | VAL70B |

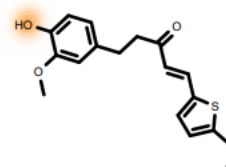
Shape -13.49



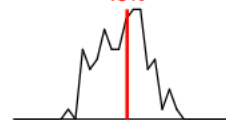
69%



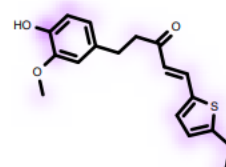
Hydrogen Bond -1.25



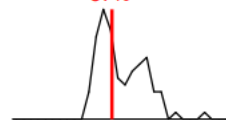
46%



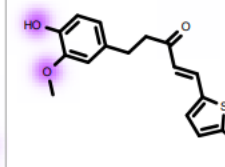
Protein Desolvation 2.38



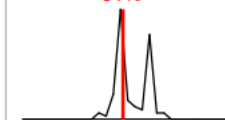
57%



Ligand Desolvation 1.20



61%



Acceptor Donor
Metal Contact

Figure S31. FRED report of STC7 with 1Q41

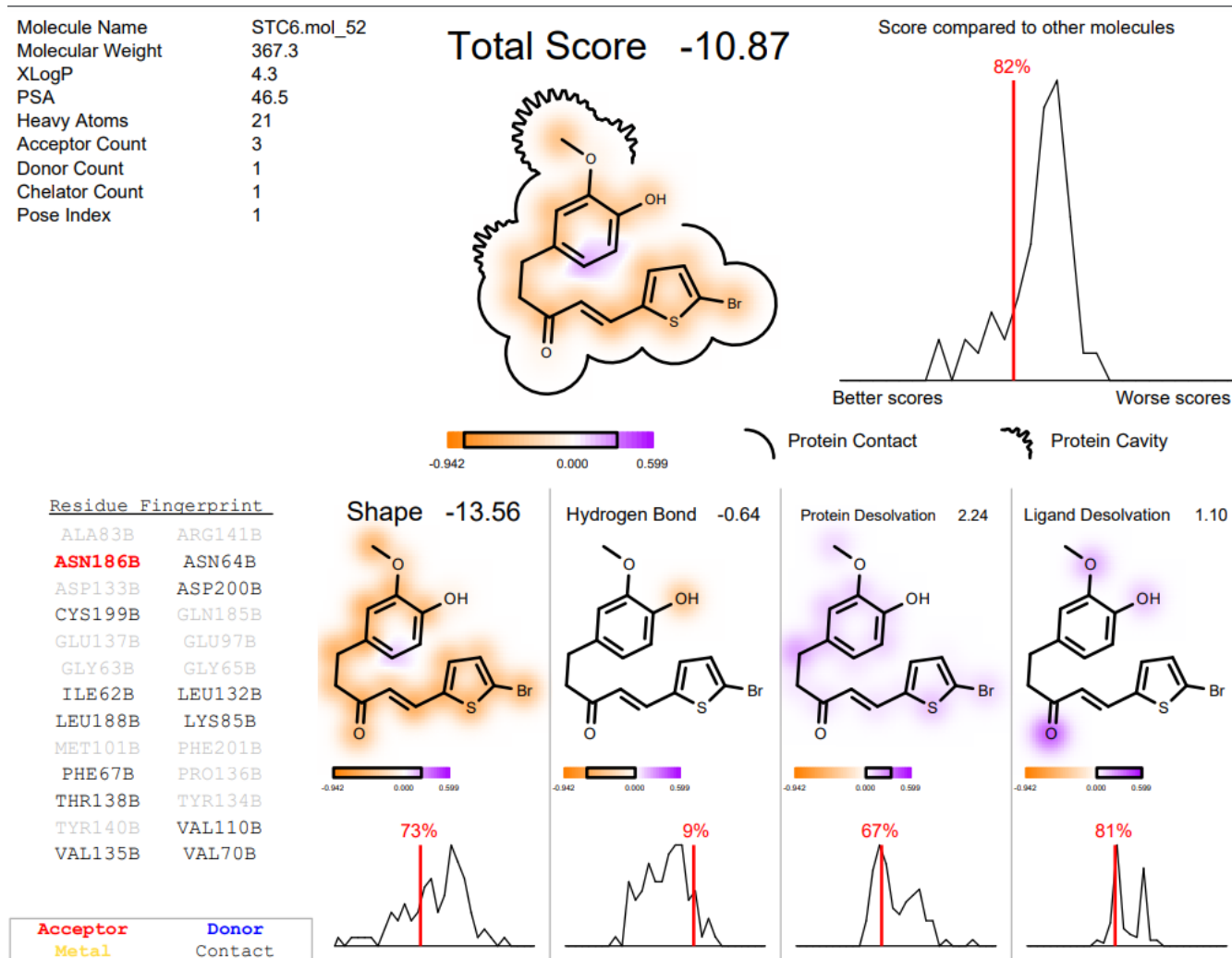
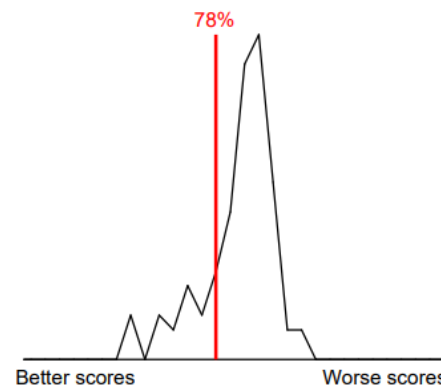
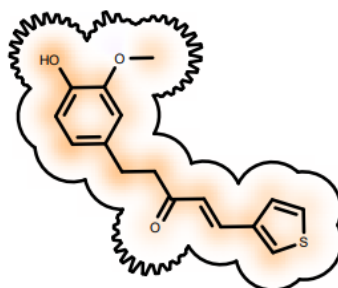


Figure S32.. FRED report of STC6 with 1Q41

Molecule Name STC1.mol_85
Molecular Weight 288.4
XLogP 3.2
PSA 46.5
Heavy Atoms 20
Acceptor Count 3
Donor Count 1
Chelator Count 1
Pose Index 1

Total Score -10.82

Score compared to other molecules



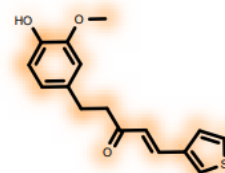
Protein Contact

Protein Cavity

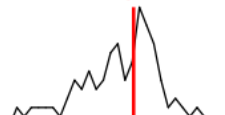
Residue Fingerprint

| | |
|---------|---------------|
| ALA83B | ARG141B |
| ASN186B | ASN64B |
| ASP133B | ASP200B |
| CYS199B | GLN185B |
| GLU137B | GLU97B |
| GLY63B | GLY65B |
| ILE62B | LEU132B |
| LEU188B | LYS85B |
| MET101B | PHE201B |
| PHE67B | PRO136B |
| THR138B | TYR134B |
| TYR140B | VAL110B |
| VAL135B | VAL70B |

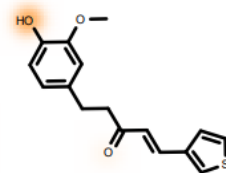
Shape -12.93



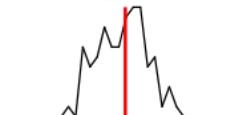
45%



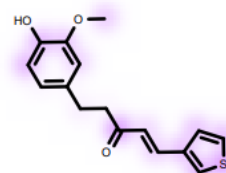
Hydrogen Bond -1.29



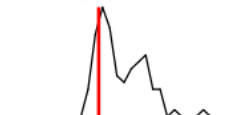
51%



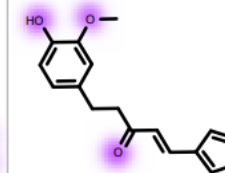
Protein Desolvation 2.10



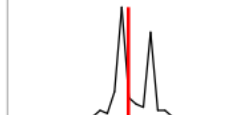
83%



Ligand Desolvation 1.30



44%



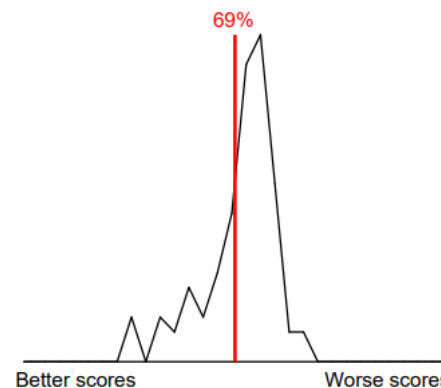
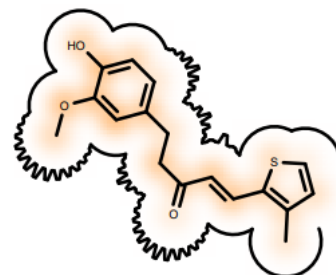
| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S33 FRED report of STC1 with 1Q41

Molecule Name STC3.mol_41
Molecular Weight 302.4
XLogP 3.4
PSA 46.5
Heavy Atoms 21
Acceptor Count 3
Donor Count 1
Chelator Count 1
Pose Index 1

Total Score -10.62

Score compared to other molecules



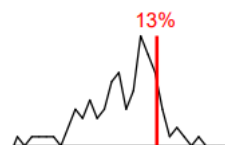
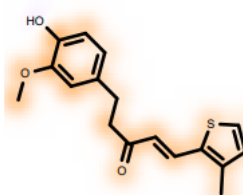
Protein Contact

Protein Cavity

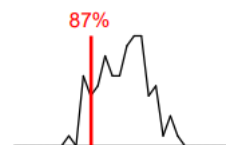
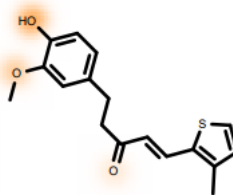
Residue Fingerprint

| | |
|----------------|----------------|
| ALA83B | ARG141B |
| ASN186B | ASN64B |
| ASP133B | ASP200B |
| CYS199B | GLN185B |
| GLU137B | GLU97B |
| GLY63B | GLY65B |
| ILE62B | LEU132B |
| LEU188B | LYS85B |
| MET101B | PHE201B |
| PHE67B | PRO136B |
| THR138B | TYR134B |
| TYR140B | VAL110B |
| VAL135B | VAL70B |

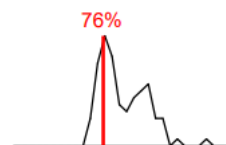
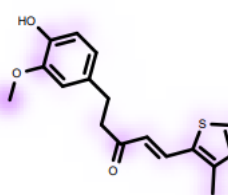
Shape -12.42



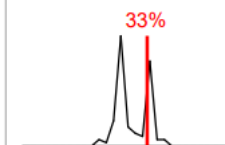
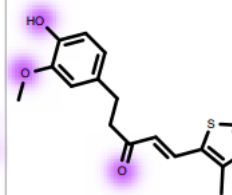
Hydrogen Bond -2.09



Protein Desolvation 2.15



Ligand Desolvation 1.75



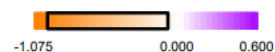
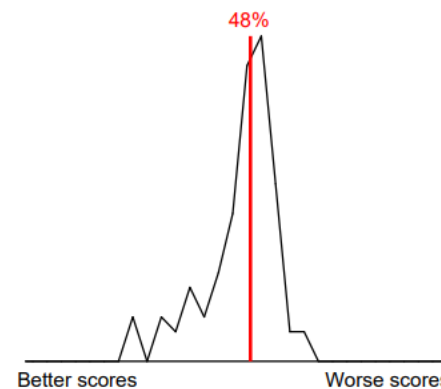
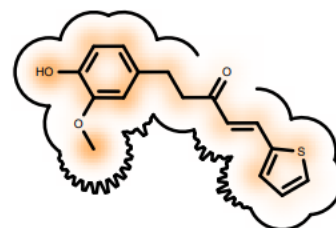
Acceptor Donor
Metal Contact

Figure S34. FRED report of STC3 with 1Q41

Molecule Name STC2.mol_16
Molecular Weight 288.4
XLogP 3.1
PSA 46.5
Heavy Atoms 20
Acceptor Count 3
Donor Count 1
Chelator Count 1
Pose Index 1

Total Score -10.45

Score compared to other molecules



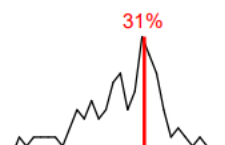
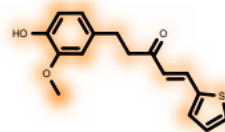
Protein Contact

Protein Cavity

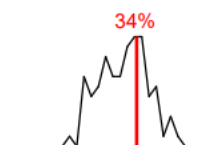
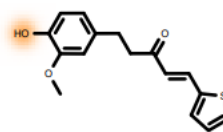
Residue Fingerprint

| | |
|---------|----------------|
| ALA83B | ARG141B |
| ASN186B | ASN64B |
| ASP133B | ASP200B |
| CYS199B | GLN185B |
| GLU137B | GLU97B |
| GLY63B | GLY65B |
| ILE62B | LEU132B |
| LEU188B | LYS85B |
| MET101B | PHE201B |
| PHE67B | PRO136B |
| THR138B | TYR134B |
| TYR140B | VAL110B |
| VAL135B | VAL70B |

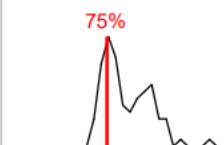
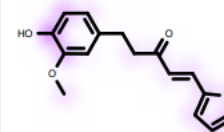
Shape -12.74



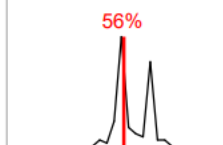
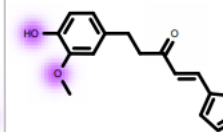
Hydrogen Bond -1.06



Protein Desolvation 2.15



Ligand Desolvation 1.20



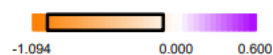
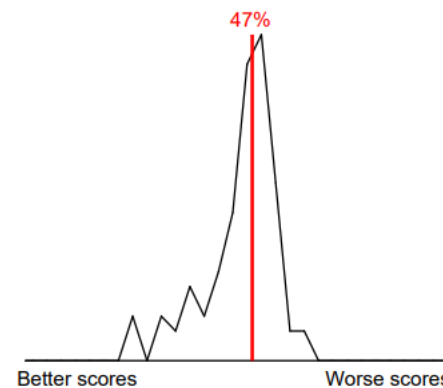
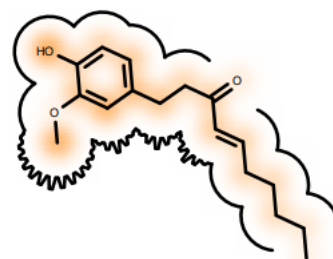
Acceptor Donor
Metal Contact

Figure S35. FRED report of STC2 with 1Q41

Molecule Name 6-Shogaol.mol_40
Molecular Weight 276.4
XLogP 3.8
PSA 46.5
Heavy Atoms 20
Acceptor Count 3
Donor Count 1
Chelator Count 1
Pose Index 1

Total Score -10.43

Score compared to other molecules



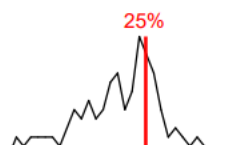
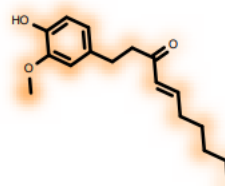
Protein Contact

Protein Cavity

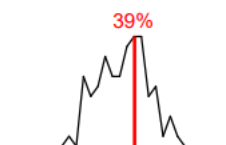
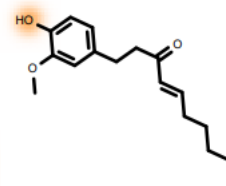
Residue Fingerprint

| | |
|---------|----------------|
| ALA83B | ARG141B |
| ASN186B | ASN64B |
| ASP133B | ASP200B |
| CYS199B | GLN185B |
| GLU137B | GLU97B |
| GLY63B | GLY65B |
| ILE62B | LEU132B |
| LEU188B | LYS85B |
| MET101B | PHE201B |
| PHE67B | PRO136B |
| THR138B | TYR134B |
| TYR140B | VAL110B |
| VAL135B | VAL70B |

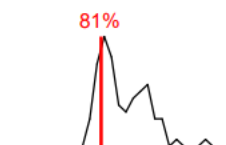
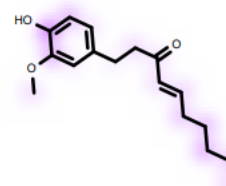
Shape -12.65



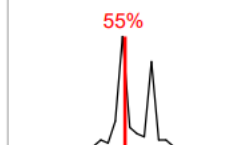
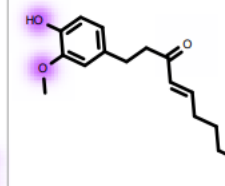
Hydrogen Bond -1.09



Protein Desolvation 2.11



Ligand Desolvation 1.20



| | |
|----------|---------|
| Acceptor | Donor |
| Metal | Contact |

Figure S36. FRED report of 6-Shogaol with 1Q41

Simulation Interactions Diagram Report

Simulation Details

Jobname: desmond_md_job_4IQK_STC5

Entry title: 4IQK - minimized STC5.mol

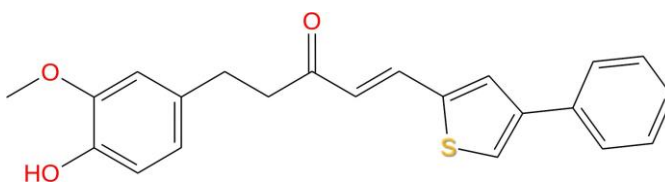
| CPU # | Job Type | Ensemble | Temp. [K] | Sim. Time [ns] | # Atoms | # Waters | Charge |
|-------|----------|----------|-----------|----------------|---------|----------|--------|
| 1 | mdsim | NPT | 300.0 | 100.102 | 30328 | 8669 | 0 |

Protein Information

| | Tot. Residues | Prot. Chain(s) | Res. in Chain(s) | # Atoms | # Heavy Atoms | Charge |
|-----|---------------|----------------|---|---------|---------------|--------|
| | 285 | 'A' | ict_values([285]) | 4272 | 2185 | -3 |
| - A | 325 | SSA | 325 330 335 340 345 350 355 360 365 370 375 380 385 390 394 | | | |
| | | | GRLIYTAGGYFRQSLSYLEAYNPSNGTWLRLADLQVPRSGLAGCVVGGLLYAVGGRNNSPDGNTDSSALD | | | |
| - A | 395 | SSA | 395 400 405 410 415 420 425 430 435 440 445 450 455 460 464 | | | |
| | | | CYNPMTNQWSPCAPMSVPRNRIGVGVIDGHIYAVGGSHGCIHHNSVERYEPERDEWHLVAPMLTRRIGVG | | | |
| - A | 465 | SSA | 465 470 475 480 485 490 495 500 505 510 515 520 525 530 534 | | | |
| | | | VAVLNRLLYAVGGFDGTRNLNSAECYPERNEWMITAMNTIRSGAGVCVLHNCIYAAGGYDGDQLNSV | | | |
| - A | 535 | SSA | 535 540 545 550 555 560 565 570 575 580 585 590 595 600 604 | | | |
| | | | ERYDVATATWTFVAPMKHRRSALGITVHQGRIYVLGGYDGHTFLDSVECYDPDPTDTWSEVTRMTSGRSGV | | | |
| - A | 605 | SSA | 605 609 | | | |
| | | | GVAVT | | | |

Ligand Information

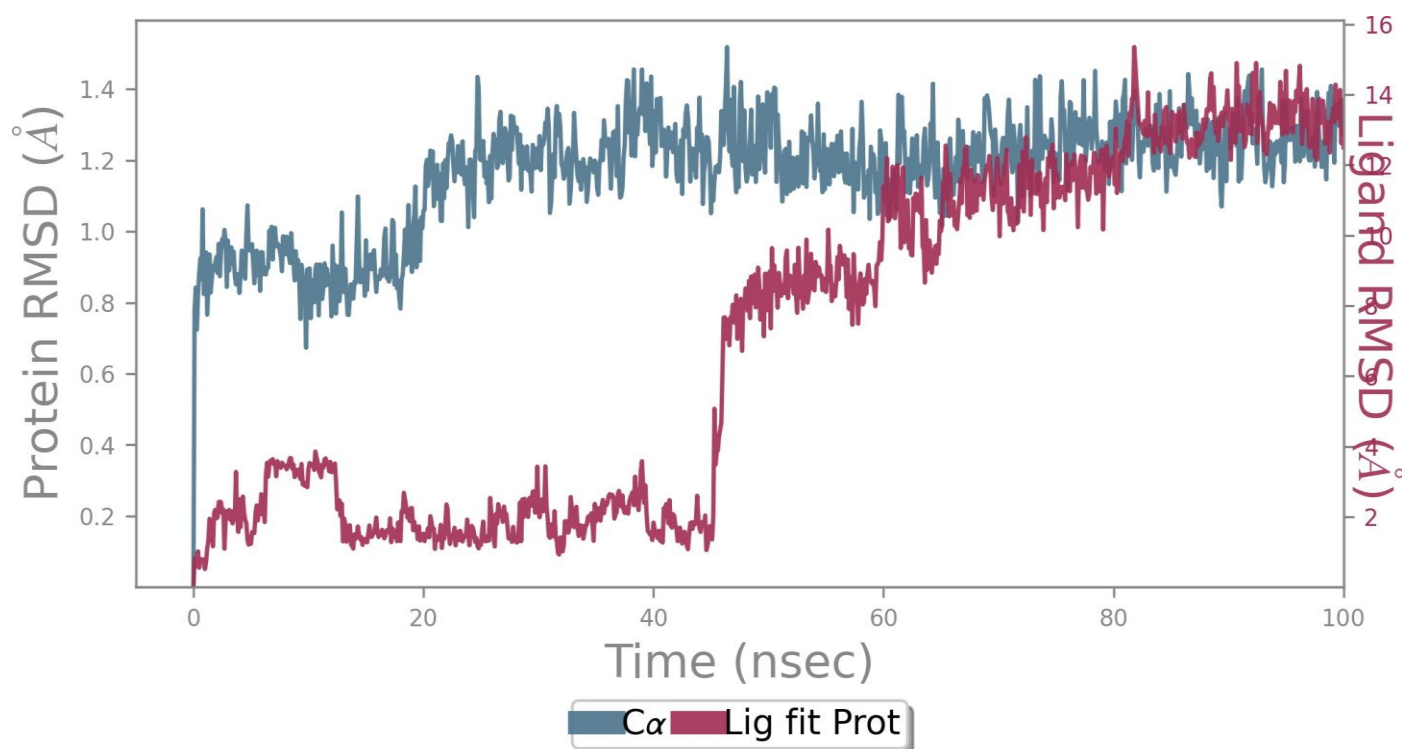
| | |
|--------------------|---|
| SMILES | c1cc(O)c(OC)cc1CCC(=O)/C=C/c2cc(cs2)-c3ccccc3 |
| PDB Name | 'UNK' |
| Num. of Atoms | 46 (total) 26 (heavy) |
| Atomic Mass | 364.467 au |
| Charge | 0 |
| Mol. Formula | C22H20O3S |
| Num. of Fragments | 3 |
| Num. of Rot. Bonds | 8 |



Counter Ion/Salt Information

| Type | Num. | Concentration [mM] | Total Charge |
|------|------|--------------------|--------------|
| Na | 3 | 6.292 | +3 |

Protein-Ligand RMSD



The Root Mean Square Deviation (RMSD) is used to measure the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame. It is calculated for all frames in the trajectory. The RMSD for frame x is:

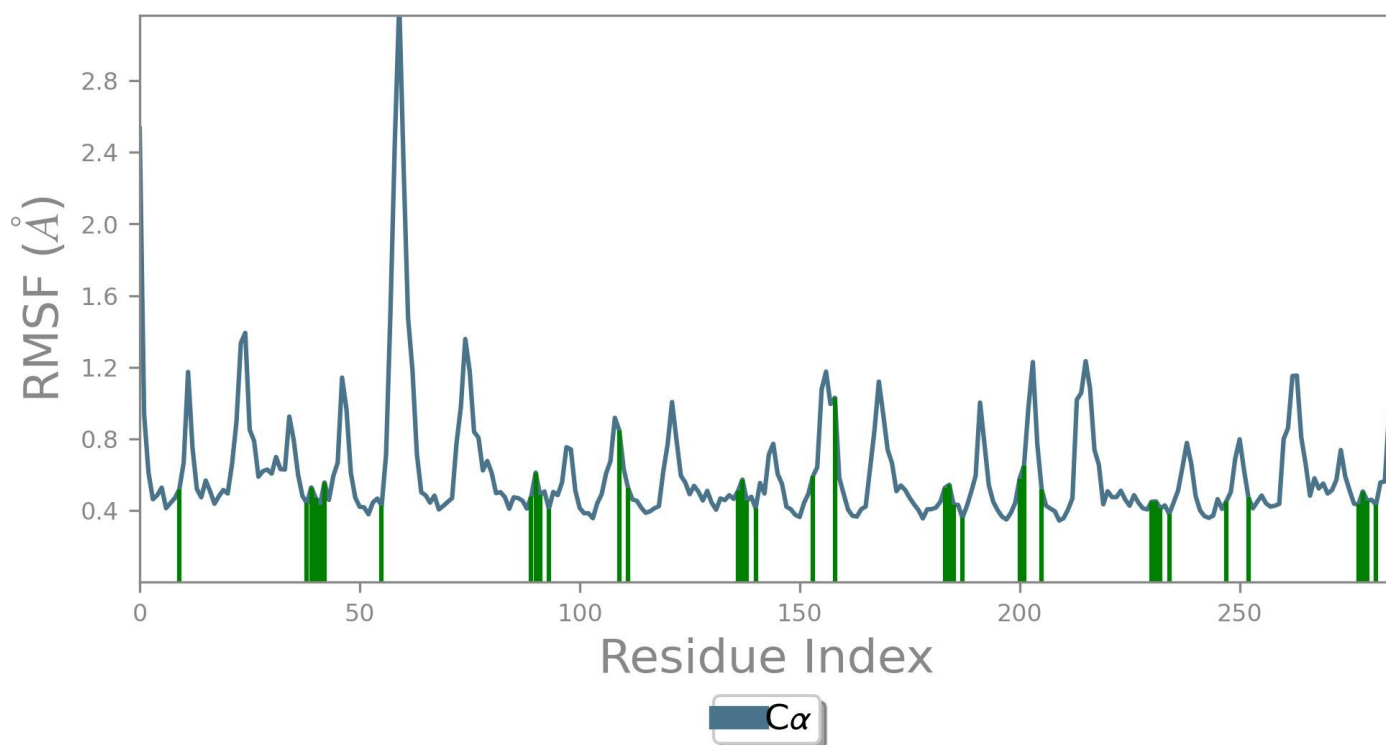
$$RMSD_x = \sqrt{\frac{1}{N} \sum_{i=1}^N (r'_i(t_x) - r_i(t_{ref}))^2}$$

where N is the number of atoms in the atom selection; t_{ref} is the reference time, (typically the first frame is used as the reference and it is regarded as time $t=0$); and r' is the position of the selected atoms in frame x after superimposing on the reference trajectory, where frame x is recorded at time t_x . The procedure is repeated for every frame in the simulation trajectory.

Protein RMSD: The above plot shows the RMSD evolution of a protein (left Y-axis). All protein frames are first aligned on the reference frame backbone, and then the RMSD is calculated based on the atom selection. Monitoring the RMSD of the protein can give insights into its structural conformation throughout the simulation. RMSD analysis can indicate if the simulation has equilibrated — its fluctuations towards the end of the simulation are around some thermal average structure. Changes of the order of 1-3 Å are perfectly acceptable for small, globular proteins. Changes much larger than that, however, indicate that the protein is undergoing a large conformational change during the simulation. It is also important that your simulation converges — the RMSD values stabilize around a fixed value. If the RMSD of the protein is still increasing or decreasing on average at the end of the simulation, then your system has not equilibrated, and your simulation may not be long enough for rigorous analysis.

Ligand RMSD: Ligand RMSD (right Y-axis) indicates how stable the ligand is with respect to the protein and its binding pocket. In the above plot, 'Lig fit Prot' shows the RMSD of a ligand when the protein-ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand heavy atoms is measured. If the values observed are significantly larger than the RMSD of the protein, then it is likely that the ligand has diffused away from its initial binding site.

Protein RMSF



The Root Mean Square Fluctuation (RMSF) is useful for characterizing local changes along the protein chain. The RMSF for residue i is:

$$RMSF_i = \sqrt{\frac{1}{T} \sum_{t=1}^T \langle (r'_i(t)) - r_i(t_{ref})^2 \rangle}$$

where T is the trajectory time over which the RMSF is calculated, t_{ref} is the reference time, r_i is the position of residue i ; r' is the position of atoms in residue i after superposition on the reference, and the angle brackets indicate that the average of the square distance is taken over the selection of atoms in the residue.

On this plot, peaks indicate areas of the protein that fluctuate the most during the simulation. Typically you will observe that the tails (N - and C -terminal) fluctuate more than any other part of the protein. Secondary structure elements like alpha helices and beta strands are usually more rigid than the unstructured part of the protein, and thus fluctuate less than the loop regions.

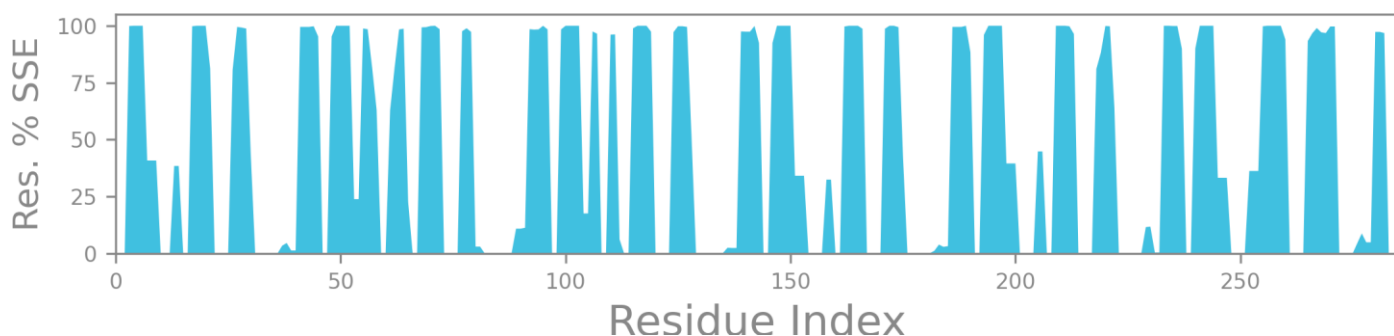
Ligand Contacts: Protein residues that interact with the ligand are marked with green-colored vertical bars.

Protein Secondary Structure

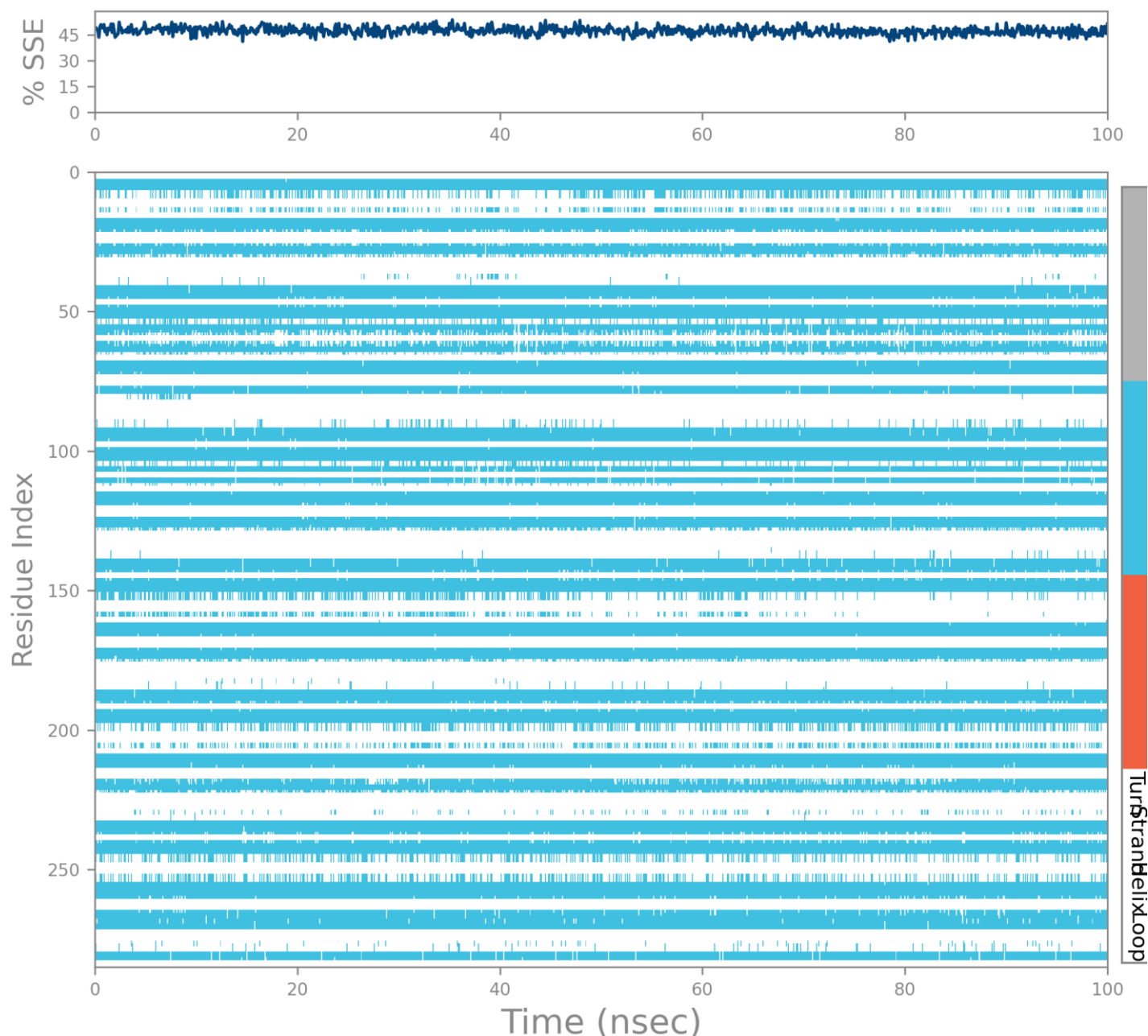
% Helix
0.00

% Strand
47.27

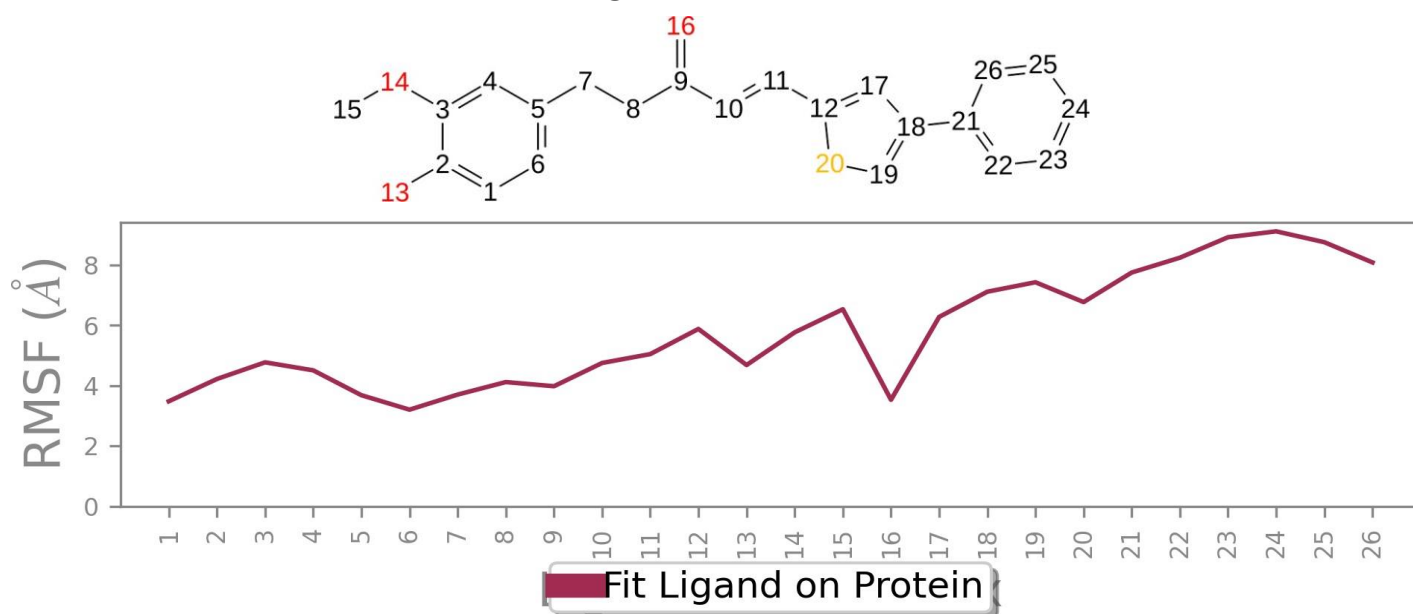
% Total SSE
47.27



Protein secondary structure elements (SSE) like alpha-helices and beta-strands are monitored throughout the simulation. The plot above reports SSE distribution by residue index throughout the protein structure. The plot below summarizes the SSE composition for each trajectory frame over the course of the simulation, and the plot at the bottom monitors each residue and its SSE assignment over time.



Ligand RMSF



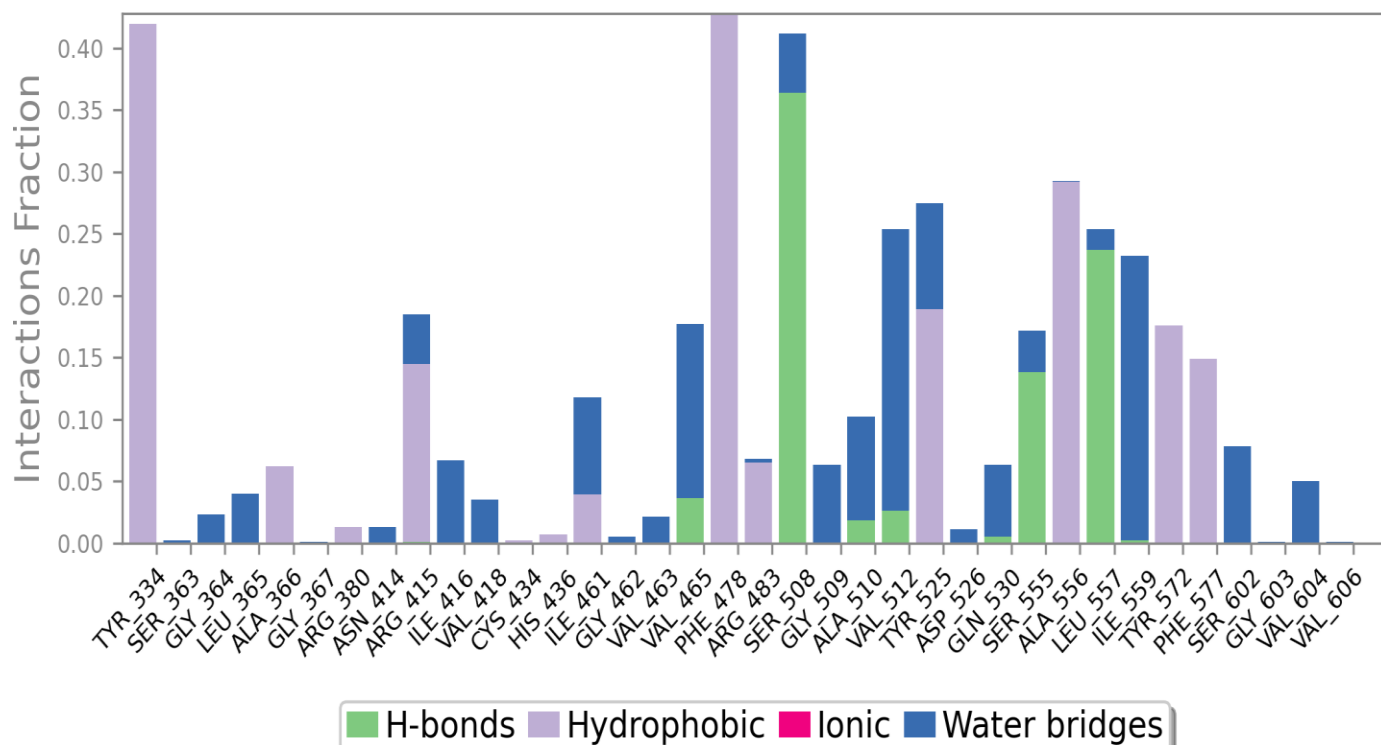
The Ligand Root Mean Square Fluctuation (L-RMSF) is useful for characterizing changes in the ligand atom positions. The RMSF for atom i is:

$$RMSF_i = \sqrt{\frac{1}{T} \sum_{t=1}^T (r'_i(t) - r_i(t_{ref}))^2}$$

where T is the trajectory time over which the RMSF is calculated, t_{ref} is the reference time (usually for the first frame, and is regarded as the zero of time); r is the position of atom i in the reference at time t_{ref} and r' is the position of atom i at time t after superposition on the reference frame.

Ligand RMSF shows the ligand's fluctuations broken down by atom, corresponding to the 2D structure in the top panel. The ligand RMSF may give you insights on how ligand fragments interact with the protein and their entropic role in the binding event. In the bottom panel, the 'Fit Ligand on Protein' line shows the ligand fluctuations, with respect to the protein. The protein-ligand complex is first aligned on the protein backbone and then the ligand RMSF is measured on the ligand heavy atoms.

Protein-Ligand Contacts



Protein interactions with the ligand can be monitored throughout the simulation. These interactions can be categorized by type and summarized, as shown in the plot above. Protein-ligand interactions (or 'contacts') are categorized into four types: Hydrogen Bonds, Hydrophobic, Ionic and Water Bridges. Each interaction type contains more specific subtypes, which can be explored through the 'Simulation Interactions Diagram' panel. The stacked bar charts are normalized over the course of the trajectory: for example, a value of 0.7 suggests that 70% of the simulation time the specific interaction is maintained. Values over 1.0 are possible as some protein residue may make multiple contacts of same subtype with the ligand.

Hydrogen Bonds: (H-bonds) play a significant role in ligand binding. Consideration of hydrogen-bonding properties in drug design is important because of their strong influence on drug specificity, metabolism and adsorption. Hydrogen bonds between a protein and a ligand can be further broken down into four subtypes: backbone acceptor; backbone donor; side-chain acceptor; side-chain donor.

The current geometric criteria for protein-ligand H-bond is: distance of 2.5 Å between the donor and acceptor atoms (D—H···A); a donor angle of $\geq 120^\circ$ between the donor-hydrogen-acceptor atoms (D—H···A); and an acceptor angle of $\geq 90^\circ$ between the hydrogen-acceptor-bonded atom atoms (H···A—X).

Hydrophobic contacts: fall into three subtypes: π -Cation; π - π ; and Other, non-specific interactions. Generally these type of interactions involve a hydrophobic amino acid and an aromatic or aliphatic group on the ligand, but we have extended this category to also include π -Cation interactions.

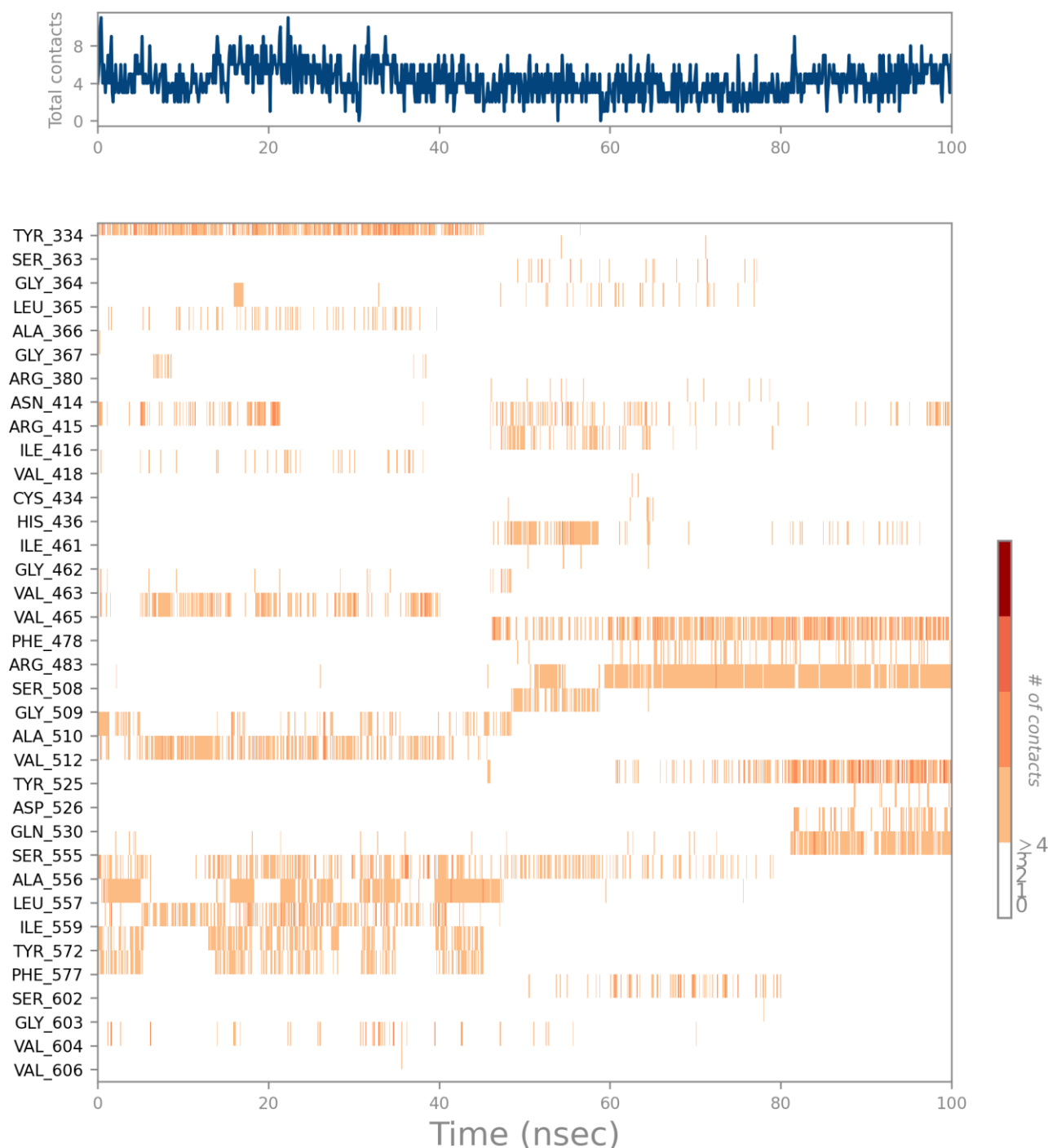
The current geometric criteria for hydrophobic interactions is as follows: π -Cation — Aromatic and charged groups within 4.5 Å; π - π — Two aromatic groups stacked face-to-face or face-to-edge; Other — A non-specific hydrophobic side chain within 3.6 Å of a ligand's aromatic or aliphatic carbons.

Ionic interactions: or polar interactions, are between two oppositely charged atoms that are within 3.7 Å of each other and do not involve a hydrogen bond. We also monitor Protein-Metal-Ligand interactions, which are defined by a metal ion coordinated within 3.4 Å of protein's and ligand's heavy atoms (except carbon). All ionic interactions are broken down into two subtypes: those mediated by a protein backbone or side chains.

Water Bridges: are hydrogen-bonded protein-ligand interactions mediated by a water molecule. The hydrogen-bond geometry is slightly relaxed from the standard H-bond definition.

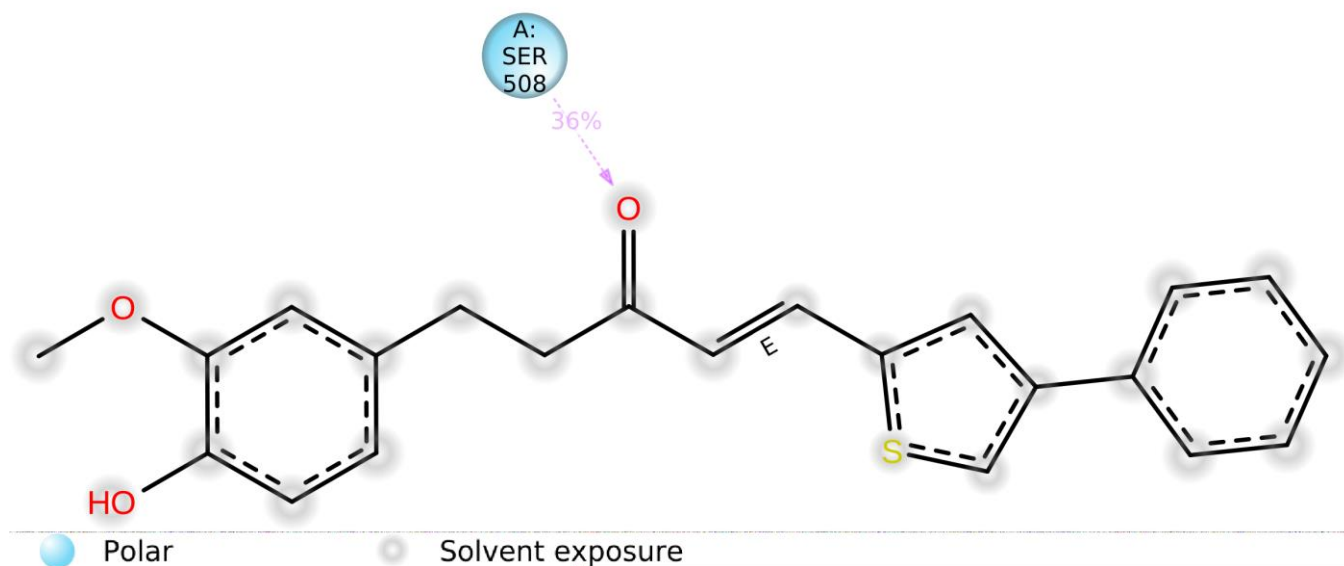
The current geometric criteria for a protein-water or water-ligand H-bond are: a distance of 2.8 Å between the donor and acceptor atoms (D—H···A); a donor angle of $\geq 110^\circ$ between the donor-hydrogen-acceptor atoms (D—H···A); and an acceptor angle of $\geq 90^\circ$ between the hydrogen-acceptor-bonded atom atoms (H···A—X).

Protein-Ligand Contacts (cont.)



A timeline representation of the interactions and contacts (H-bonds, Hydrophobic, Ionic, Water bridges) summarized in the previous page. The top panel shows the total number of specific contacts the protein makes with the ligand over the course of the trajectory. The bottom panel shows which residues interact with the ligand in each trajectory frame. Some residues make more than one specific contact with the ligand, which is represented by a darker shade of orange, according to the scale to the right of the plot.

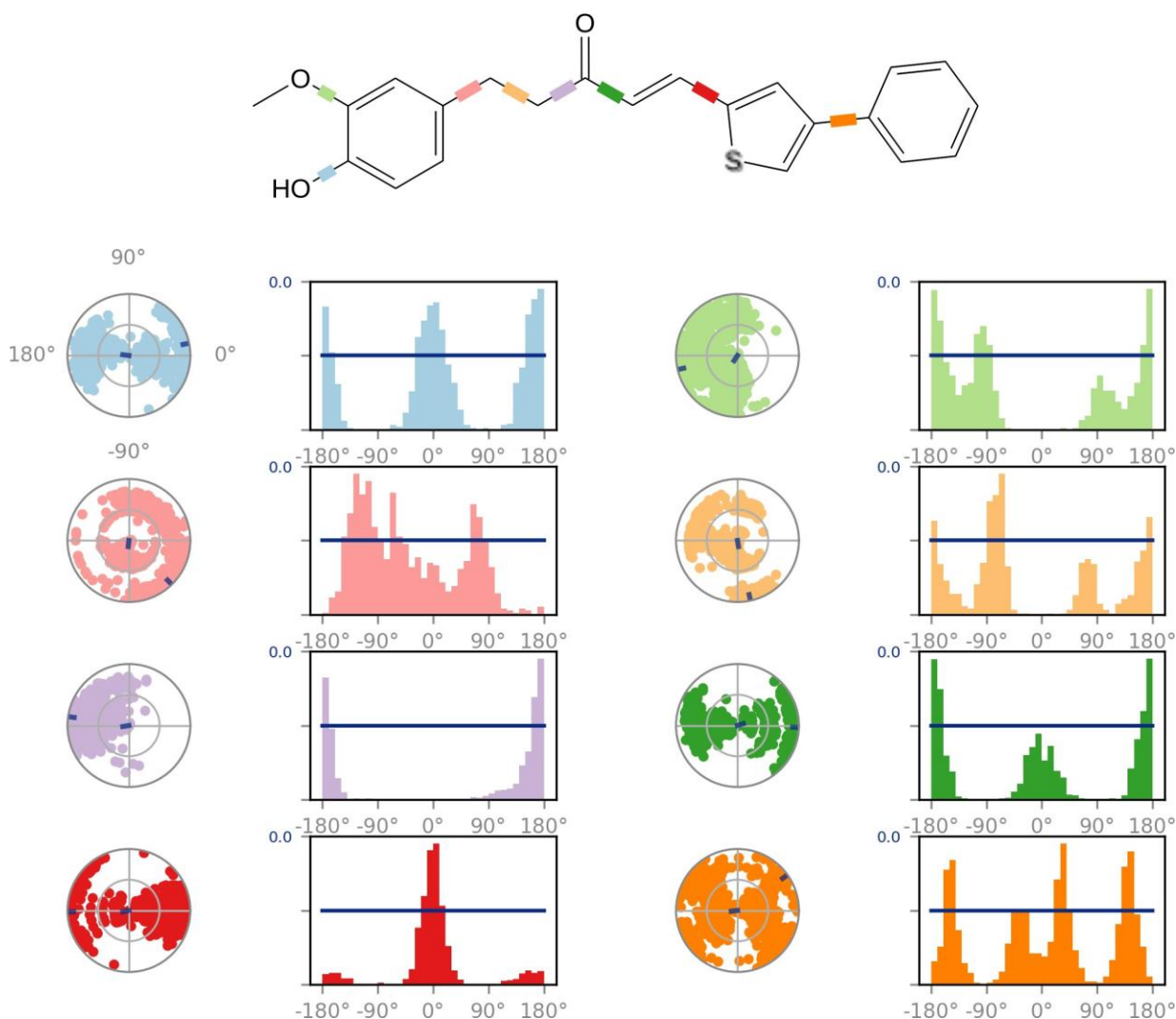
Ligand-Protein Contacts



A schematic of detailed ligand atom interactions with the protein residues. Interactions that occur more than 30.0% of the simulation time in the selected trajectory (0.00 through 100.00 nsec), are shown.

Note: it is possible to have interactions with >100% as some residues may have multiple interactions of a single type with the same ligand atom. For example, the ARG side chain has four H-bond donors that can all hydrogen-bond to a single H-bond acceptor.

Ligand Torsion Profile



The ligand torsions plot summarizes the conformational evolution of every rotatable bond (RB) in the ligand throughout the simulation trajectory (0.00 through 100.00 nsec). The top panel shows the 2d schematic of a ligand with color-coded rotatable bonds. Each rotatable bond torsion is accompanied by a dial plot and bar plots of the same color.

Dial (or radial) plots describe the conformation of the torsion throughout the course of the simulation. The beginning of the simulation is in the center of the radial plot and the time evolution is plotted radially outwards.

The bar plots summarize the data on the dial plots, by showing the probability density of the torsion. If torsional potential information is available, the plot also shows the potential of the rotatable bond (by summing the potential of the related torsions). The values of the potential are on the left Y-axis of the chart, and are expressed in *kcal/mol*. Looking at the histogram and torsion potential relationships may give insights into the conformational strain the ligand undergoes to maintain a protein-bound conformation.



L
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Ligand RMSD: Root mean square deviation of a ligand with respect to the reference conformation (typically the first frame is used as the reference and it is regarded as time $t=0$).

Radius of Gyration (rGyr): Measures the 'extendedness' of a ligand, and is equivalent to its principal moment of inertia.

Intramolecular Hydrogen Bonds (intraHB): Number of internal hydrogen bonds (HB) within a ligand molecule.

Molecular Surface Area (MolSA): Molecular surface calculation with 1.4 Å probe radius. This value is equivalent to a van der Waals surface area.

Solvent Accessible Surface Area (SASA): Surface area of a molecule accessible by a water molecule.

Polar Surface Area (PSA): Solvent accessible surface area in a molecule contributed only by oxygen and nitrogen atoms.

Simulation Interactions Diagram Report

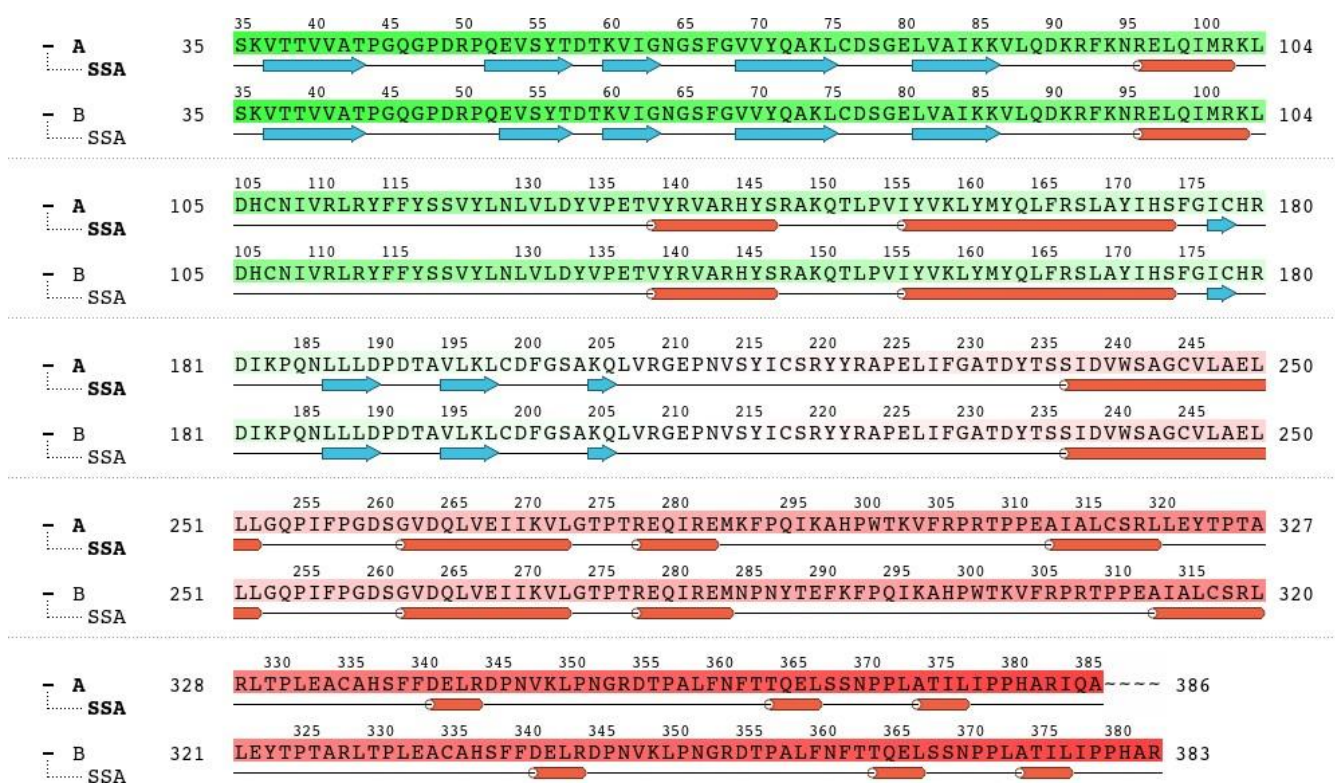
Simulation Details

Jobname: desmond_md_job_1Q41_STC5
Entry title: 1Q41 - minimized_ligandB_removed STC5.mol

| CPU # | Job Type | Ensemble | Temp. [K] | Sim. Time [ns] | # Atoms | # Waters | Charge |
|-------|----------|----------|-----------|----------------|---------|----------|--------|
| 1 | mdsim | NPT | 300.0 | 100.102 | 77172 | 22057 | 0 |

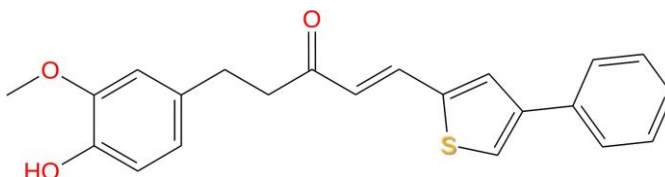
Protein Information

| Tot. Residues | Prot. Chain(s) | Res. in Chain(s) | # Atoms | # Heavy Atoms | Charge |
|---------------|----------------|------------------------|---------|---------------|--------|
| 682 | 'A', 'B' | ict_values([339, 343]) | 10937 | 5428 | +18 |



Ligand Information

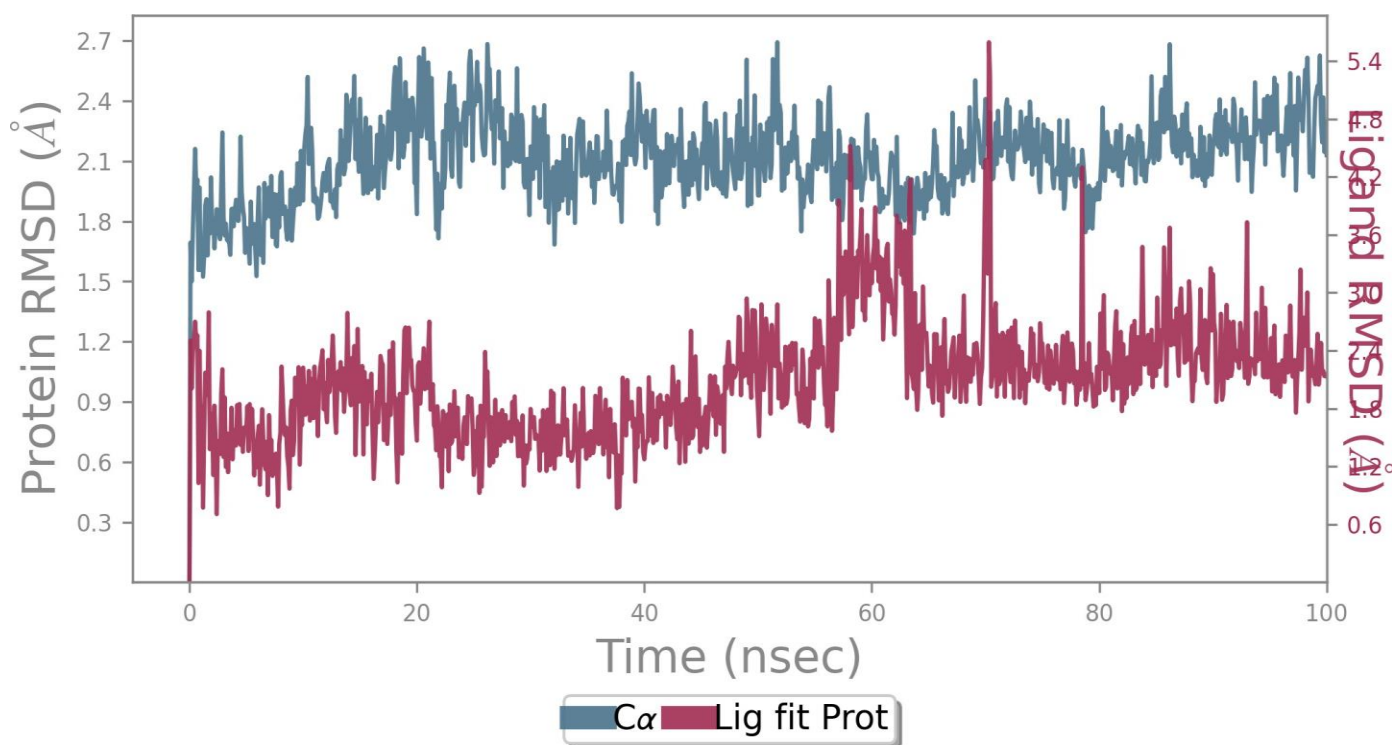
| | |
|--------------------|---|
| SMILES | c1cc(O)c(OC)cc1CCC(=O)/C=C/c2cc(cs2)-c3ccccc3 |
| PDB Name | 'UNK' |
| Num. of Atoms | 46 (total) 26 (heavy) |
| Atomic Mass | 364.467 au |
| Charge | 0 |
| Mol. Formula | C22H20O3S |
| Num. of Fragments | 3 |
| Num. of Rot. Bonds | 8 |



Counter Ion/Salt Information

| Type | Num. | Concentration [mM] | Total | Charge |
|------|------|--------------------|-------|--------|
| Cl | 18 | 14.838 | -18 | |

Protein-Ligand RMSD



The Root Mean Square Deviation (RMSD) is used to measure the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame. It is calculated for all frames in the trajectory. The RMSD for frame x is:

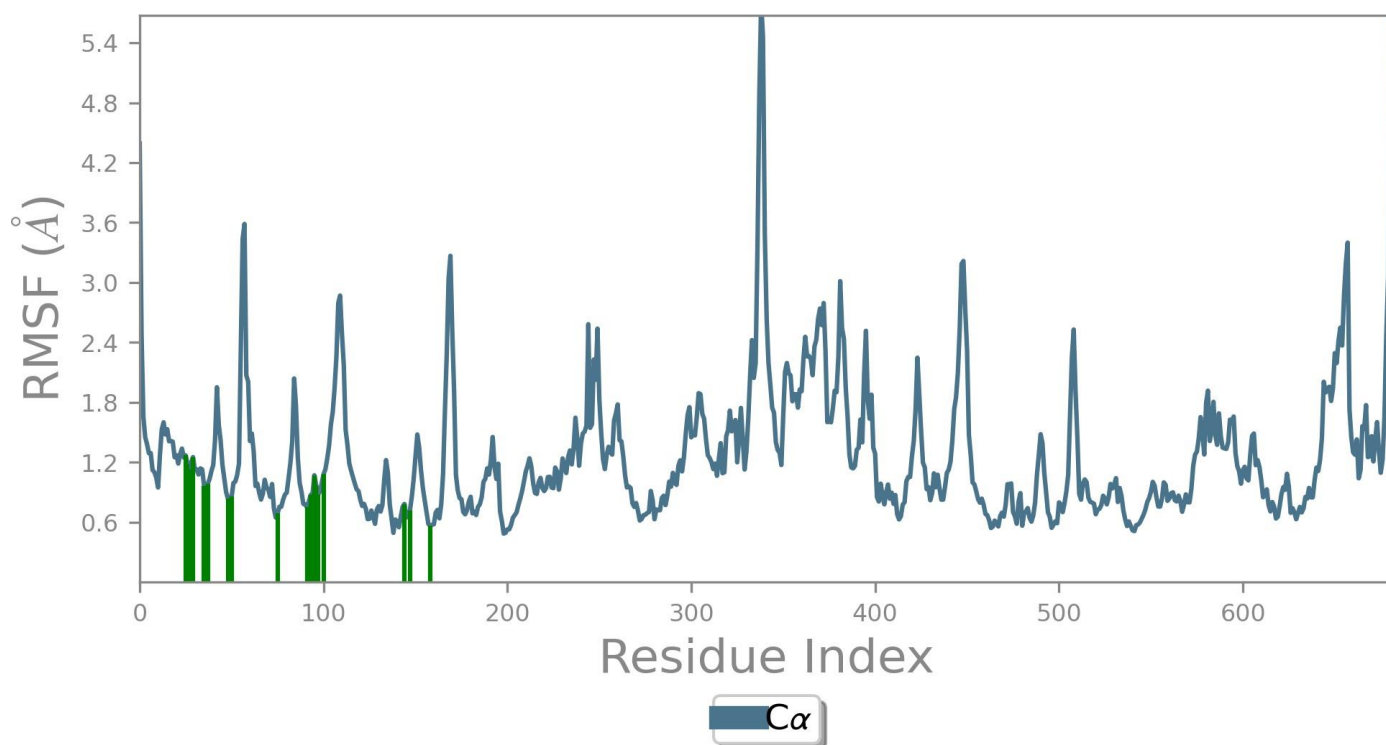
$$RMSD_x = \sqrt{\frac{1}{N} \sum_{i=1}^N (r'_i(t_x) - r_i(t_{ref}))^2}$$

where N is the number of atoms in the atom selection; t_{ref} is the reference time, (typically the first frame is used as the reference and it is regarded as time $t=0$); and r' is the position of the selected atoms in frame x after superimposing on the reference trajectory, where frame x is recorded at time t_x . The procedure is repeated for every frame in the simulation trajectory.

Protein RMSD: The above plot shows the RMSD evolution of a protein (left Y-axis). All protein frames are first aligned on the reference frame backbone, and then the RMSD is calculated based on the atom selection. Monitoring the RMSD of the protein can give insights into its structural conformation throughout the simulation. RMSD analysis can indicate if the simulation has equilibrated — its fluctuations towards the end of the simulation are around some thermal average structure. Changes of the order of 1-3 Å are perfectly acceptable for small, globular proteins. Changes much larger than that, however, indicate that the protein is undergoing a large conformational change during the simulation. It is also important that your simulation converges — the RMSD values stabilize around a fixed value. If the RMSD of the protein is still increasing or decreasing on average at the end of the simulation, then your system has not equilibrated, and your simulation may not be long enough for rigorous analysis.

Ligand RMSD: Ligand RMSD (right Y-axis) indicates how stable the ligand is with respect to the protein and its binding pocket. In the above plot, 'Lig fit Prot' shows the RMSD of a ligand when the protein-ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand heavy atoms is measured. If the values observed are significantly larger than the RMSD of the protein, then it is likely that the ligand has diffused away from its initial binding site.

Protein RMSF



The Root Mean Square Fluctuation (RMSF) is useful for characterizing local changes along the protein chain. The RMSF for residue i is:

$$RMSF_i = \sqrt{\frac{1}{T} \sum_{t=1}^T \langle (r'_i(t)) - r_i(t_{ref})^2 \rangle}$$

where T is the trajectory time over which the RMSF is calculated, t_{ref} is the reference time, r_i is the position of residue i ; r' is the position of atoms in residue i after superposition on the reference, and the angle brackets indicate that the average of the square distance is taken over the selection of atoms in the residue.

On this plot, peaks indicate areas of the protein that fluctuate the most during the simulation. Typically you will observe that the tails (N - and C -terminal) fluctuate more than any other part of the protein. Secondary structure elements like alpha helices and beta strands are usually more rigid than the unstructured part of the protein, and thus fluctuate less than the loop regions.

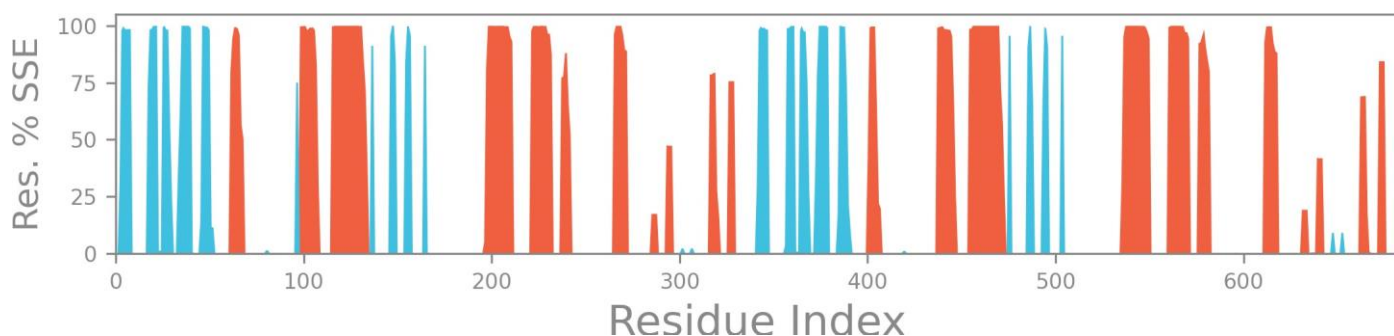
Ligand Contacts: Protein residues that interact with the ligand are marked with green-colored vertical bars.

Protein Secondary Structure

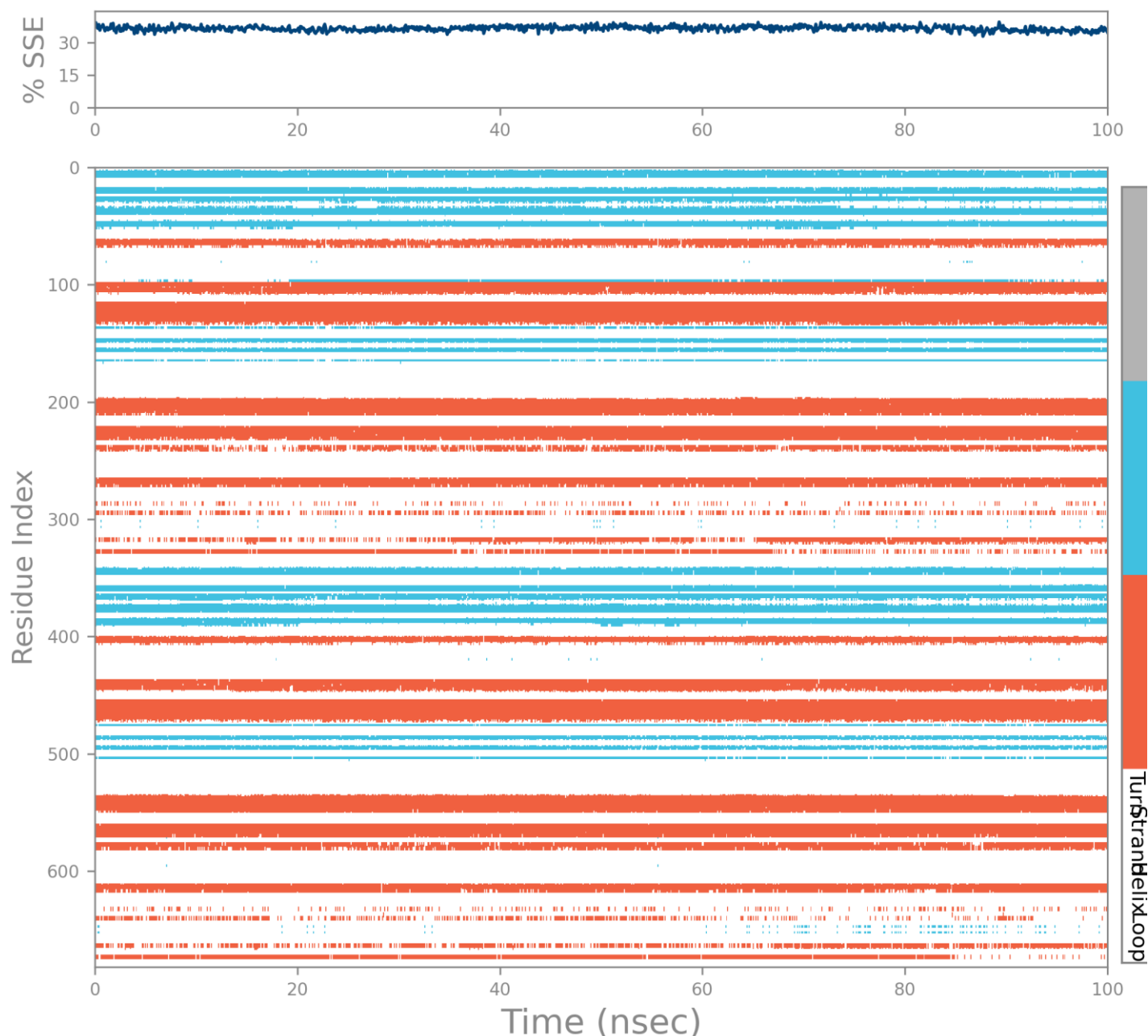
% Helix
24.50

% Strand
11.97

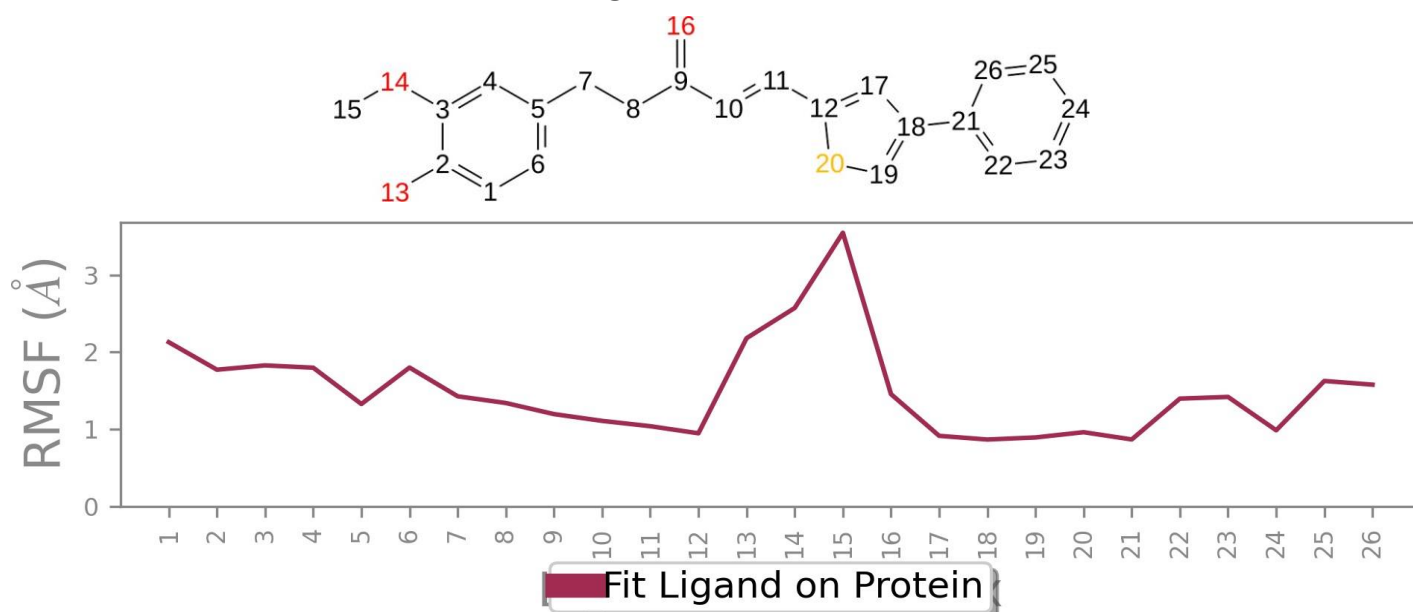
% Total SSE
36.48



Protein secondary structure elements (SSE) like alpha-helices and beta-strands are monitored throughout the simulation. The plot above reports SSE distribution by residue index throughout the protein structure. The plot below summarizes the SSE composition for each trajectory frame over the course of the simulation, and the plot at the bottom monitors each residue and its SSE assignment over time.



Ligand RMSF



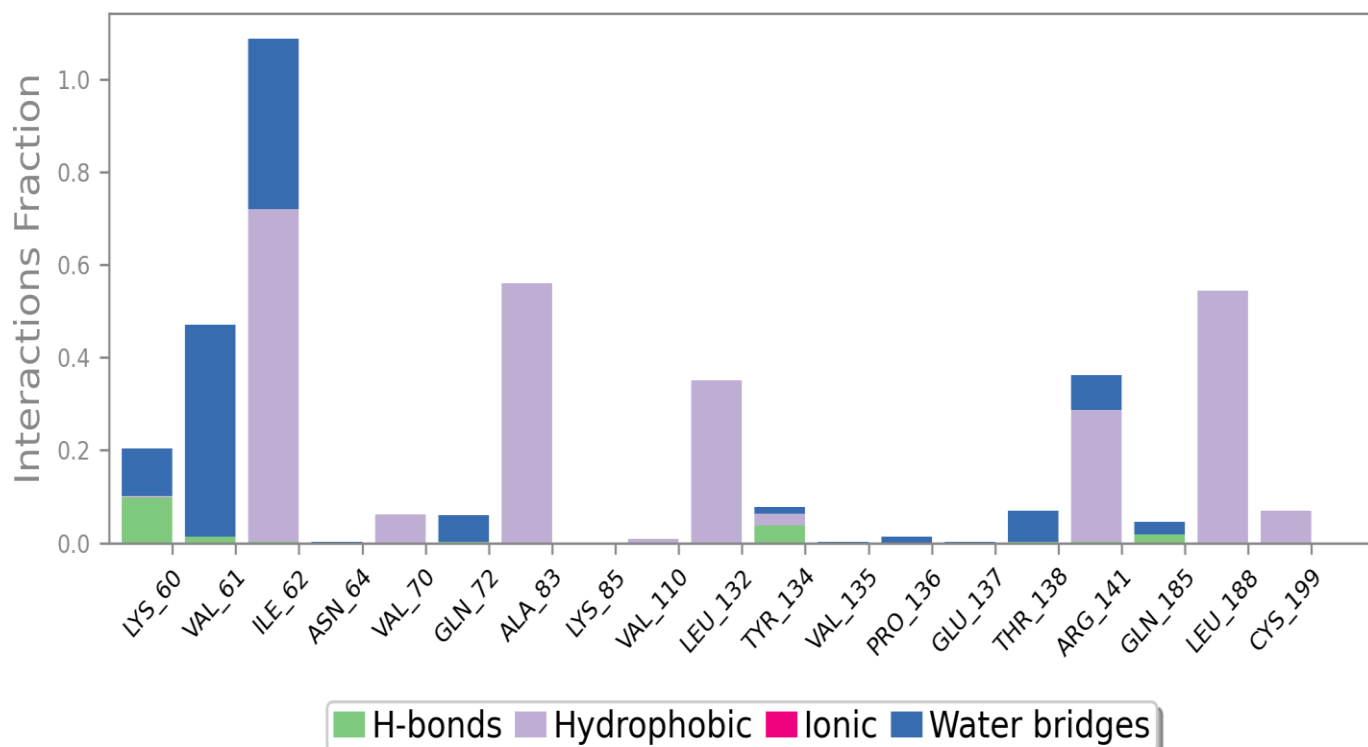
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Protein interactions with the ligand can be monitored throughout the simulation. These interactions can be categorized by type and summarized, as shown in the plot above. Protein-ligand interactions (or 'contacts') are categorized into four types: Hydrogen Bonds, Hydrophobic, Ionic and Water Bridges. Each interaction type contains more specific subtypes, which can be explored through the 'Simulation Interactions Diagram' panel. The stacked bar charts are normalized over the course of the trajectory: for example, a value of 0.7 suggests that 70% of the simulation time the specific interaction is maintained. Values over 1.0 are possible as some protein residue may make multiple contacts of same subtype with the ligand.

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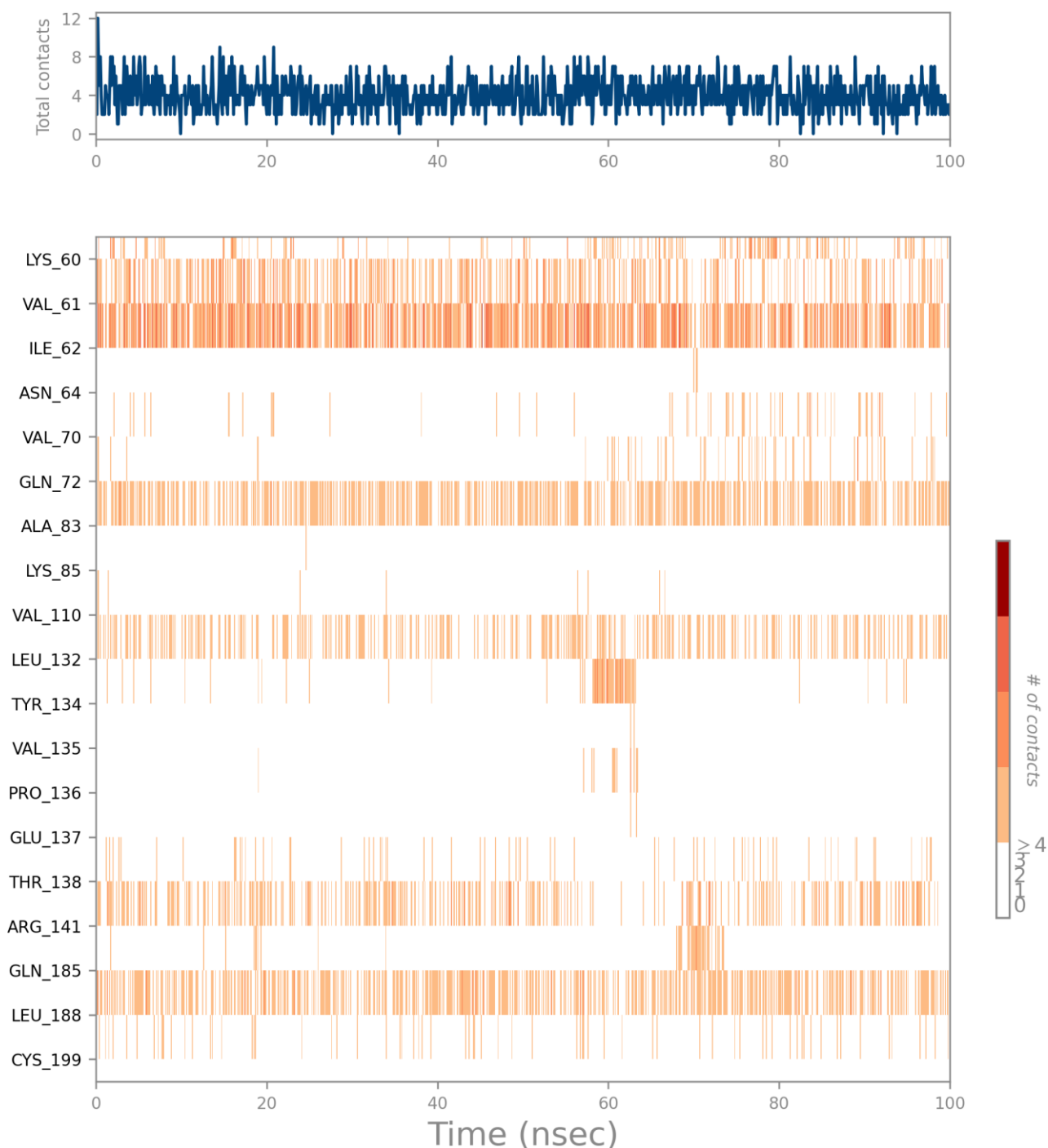
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Water Bridges: are hydrogen-bonded protein-ligand interactions mediated by a water molecule. The hydrogen-bond geometry is slightly relaxed from the standard H-bond definition.

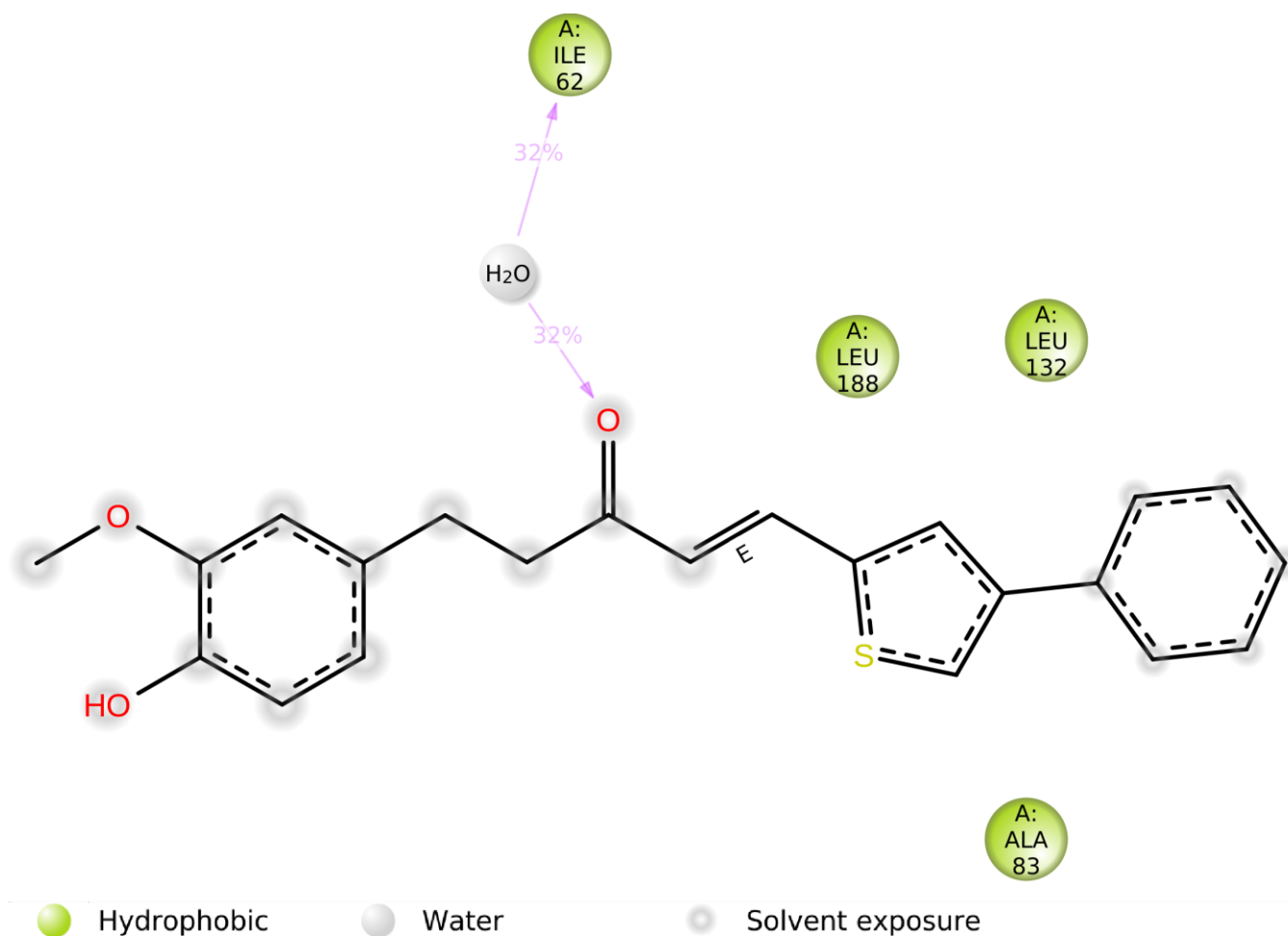
The current geometric criteria for a protein-water or water-ligand H-bond are: a distance of 2.8 Å between the donor and acceptor atoms (D—H···A); a donor angle of $\geq 110^\circ$ between the donor-hydrogen-acceptor atoms (D—H···A); and an acceptor angle of $\geq 90^\circ$ between the hydrogen-acceptor-bonded atom atoms (H···A—X).

Protein-Ligand Contacts (cont.)



A timeline representation of the interactions and contacts (H-bonds, Hydrophobic, Ionic, Water bridges) summarized in the previous page. The top panel shows the total number of specific contacts the protein makes with the ligand over the course of the trajectory. The bottom panel shows which residues interact with the ligand in each trajectory frame. Some residues make more than one specific contact with the ligand, which is represented by a darker shade of orange, according to the scale to the right of the plot.

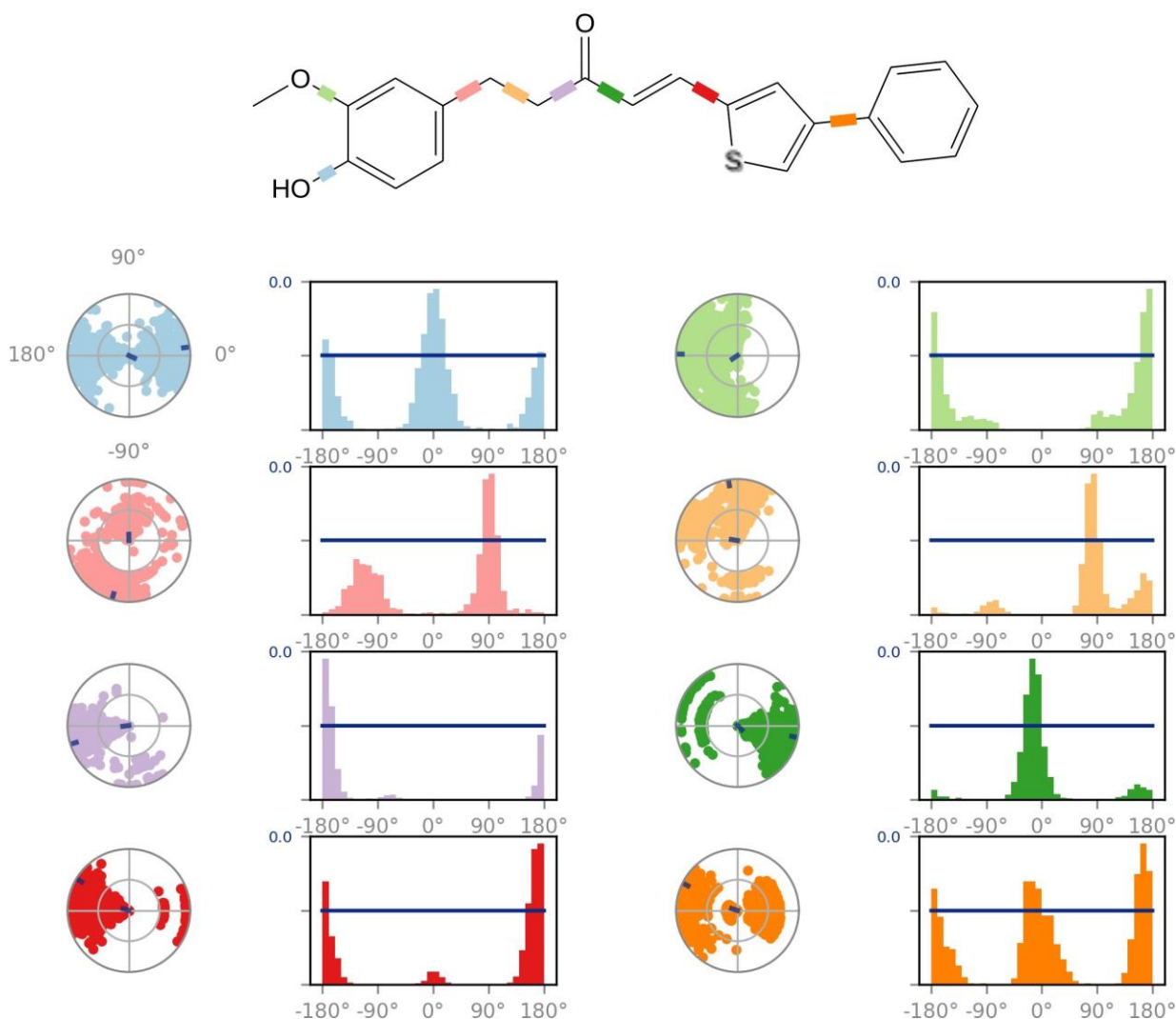
Ligand-Protein Contacts



A schematic of detailed ligand atom interactions with the protein residues. Interactions that occur more than 30.0% of the simulation time in the selected trajectory (0.00 through 100.00 nsec), are shown.

Note: it is possible to have interactions with >100% as some residues may have multiple interactions of a single type with the same ligand atom. For example, the ARG side chain has four H-bond donors that can all hydrogen-bond to a single H-bond acceptor.

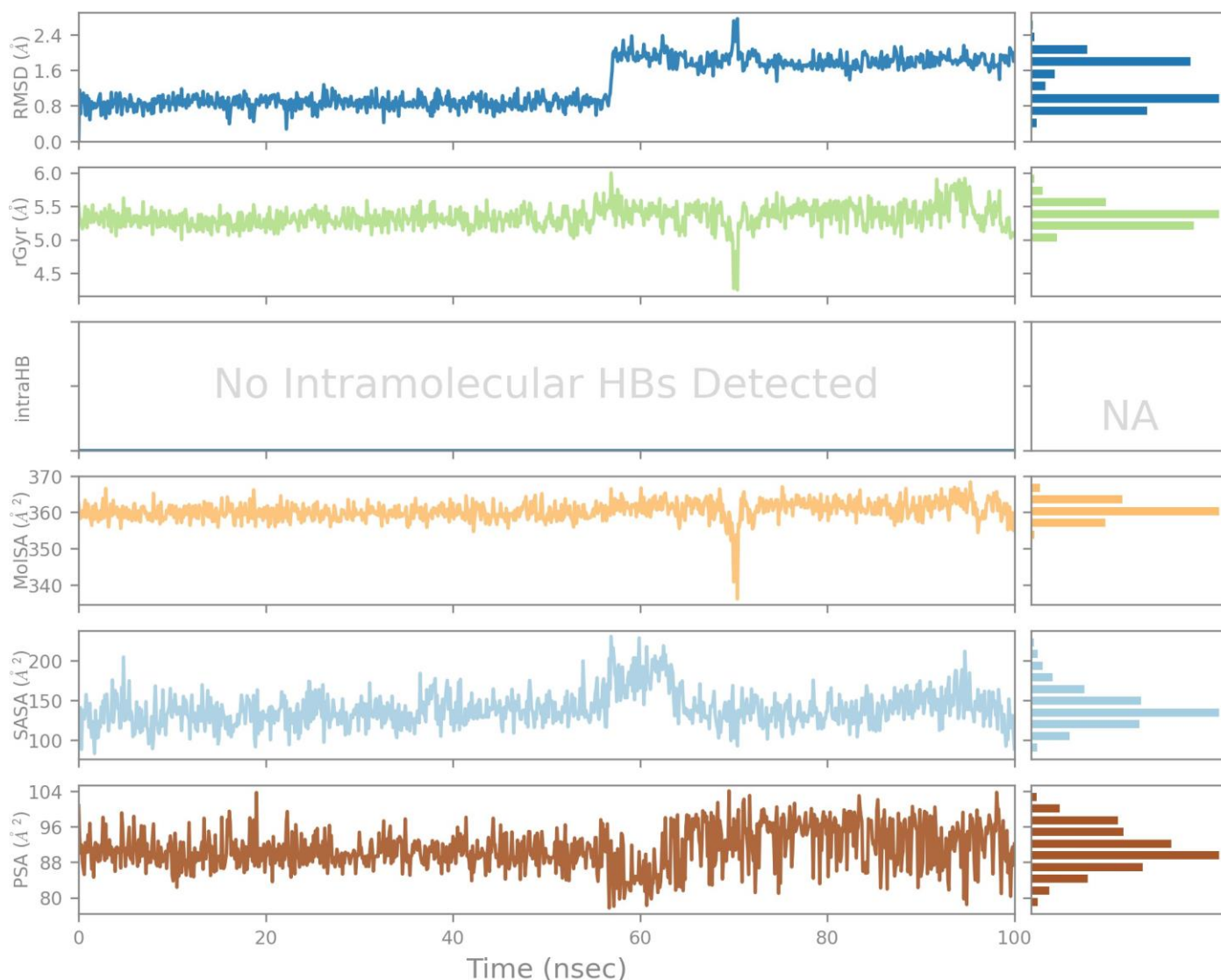
Ligand Torsion Profile



The ligand torsions plot summarizes the conformational evolution of every rotatable bond (RB) in the ligand throughout the simulation trajectory (0.00 through 100.00 nsec). The top panel shows the 2d schematic of a ligand with color-coded rotatable bonds. Each rotatable bond torsion is accompanied by a dial plot and bar plots of the same color.

Dial (or radial) plots describe the conformation of the torsion throughout the course of the simulation. The beginning of the simulation is in the center of the radial plot and the time evolution is plotted radially outwards.

The bar plots summarize the data on the dial plots, by showing the probability density of the torsion. If torsional potential information is available, the plot also shows the potential of the rotatable bond (by summing the potential of the related torsions). The values of the potential are on the left Y-axis of the chart, and are expressed in *kcal/mol*. Looking at the histogram and torsion potential relationships may give insights into the conformational strain the ligand undergoes to maintain a protein-bound conformation.



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Ligand RMSD: Root mean square deviation of a ligand with respect to the reference conformation (typically the first frame is used as the reference and it is regarded as time $t=0$).

Radius of Gyration (rGyr): Measures the 'extendedness' of a ligand, and is equivalent to its principal moment of inertia.

Intramolecular Hydrogen Bonds (intraHB): Number of internal hydrogen bonds (HB) within a ligand molecule.

Molecular Surface Area (MolSA): Molecular surface calculation with 1.4 Å probe radius. This value is equivalent to a van der Waals surface area.

Solvent Accessible Surface Area (SASA): Surface area of a molecule accessible by a water molecule.

Polar Surface Area (PSA): Solvent accessible surface area in a molecule contributed only by oxygen and nitrogen atoms.

Simulation Interactions Diagram Report

Simulation Details

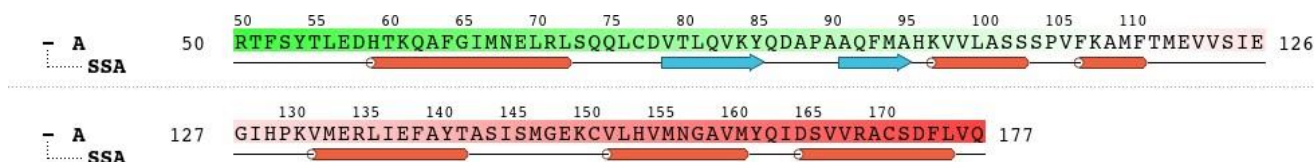
Jobname: desmond_md_job_5DAF_covalent_STC5

Entry title: STC5.mol

| CPU # | Job Type | Ensemble | Temp. [K] | Sim. Time [ns] | # Atoms | # Waters | Charge |
|-------|----------|----------|-----------|----------------|---------|----------|--------|
| 1 | mdsim | NPT | 300.0 | 100.102 | 26135 | 8065 | 0 |

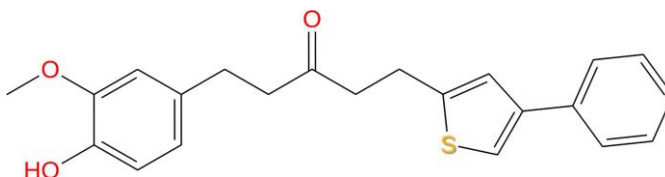
Protein Information

| Tot. Residues | Prot. Chain(s) | Res. in Chain(s) | # Atoms | # Heavy Atoms | Charge |
|---------------|----------------|-------------------|---------|---------------|--------|
| 121 | 'A' | ict_values([121]) | 1890 | 942 | -3 |



Ligand Information

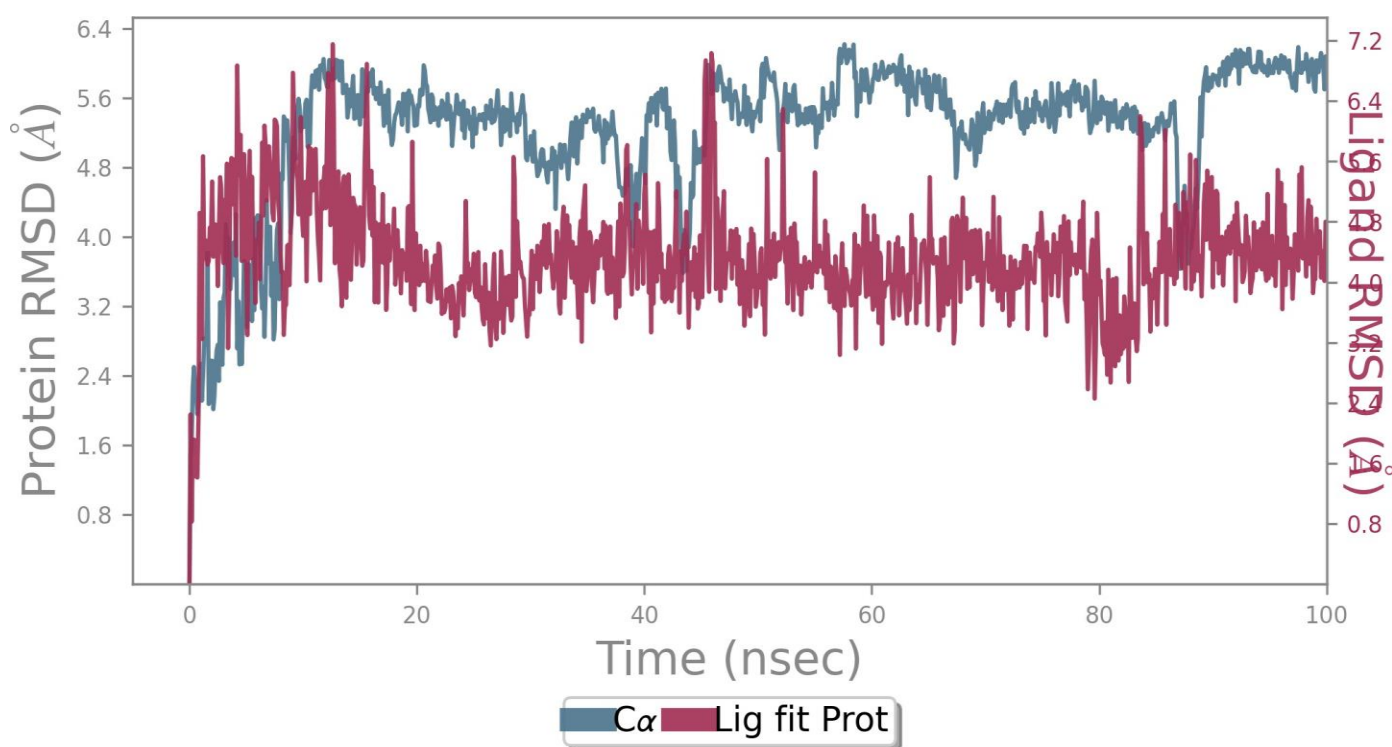
| | |
|--------------------|--|
| SMILES | c1cc(O)c(OC)cc1CCC(=O)CCc2cc(cs2)-c3ccccc3 |
| PDB Name | 'UNK' |
| Num. of Atoms | 47 (total) 26 (heavy) |
| Atomic Mass | 365.475 au |
| Charge | 0 |
| Mol. Formula | C22H21O3S |
| Num. of Fragments | 2 |
| Num. of Rot. Bonds | 9 |



Counter Ion/Salt Information

| Type | Num. | Concentration [mM] | Total | Charge |
|------|------|--------------------|-------|--------|
| Na | 3 | 6.763 | | +3 |

Protein-Ligand RMSD



The Root Mean Square Deviation (RMSD) is used to measure the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame. It is calculated for all frames in the trajectory. The RMSD for frame x is:

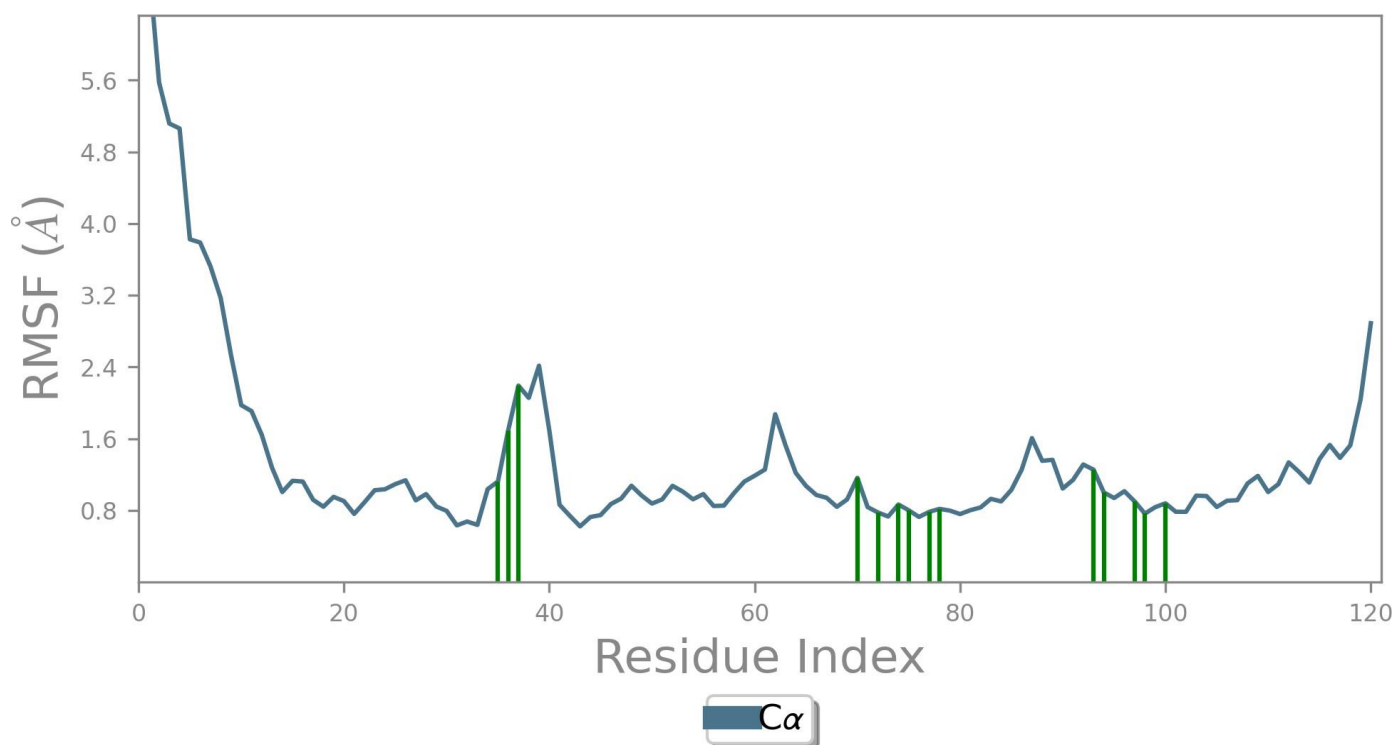
$$RMSD_x = \sqrt{\frac{1}{N} \sum_{i=1}^N (r'_i(t_x) - r_i(t_{ref}))^2}$$

where N is the number of atoms in the atom selection; t_{ref} is the reference time, (typically the first frame is used as the reference and it is regarded as time $t=0$); and r' is the position of the selected atoms in frame x after superimposing on the reference trajectory, where frame x is recorded at time t_x . The procedure is repeated for every frame in the simulation trajectory.

Protein RMSD: The above plot shows the RMSD evolution of a protein (left Y-axis). All protein frames are first aligned on the reference frame backbone, and then the RMSD is calculated based on the atom selection. Monitoring the RMSD of the protein can give insights into its structural conformation throughout the simulation. RMSD analysis can indicate if the simulation has equilibrated — its fluctuations towards the end of the simulation are around some thermal average structure. Changes of the order of 1-3 Å are perfectly acceptable for small, globular proteins. Changes much larger than that, however, indicate that the protein is undergoing a large conformational change during the simulation. It is also important that your simulation converges — the RMSD values stabilize around a fixed value. If the RMSD of the protein is still increasing or decreasing on average at the end of the simulation, then your system has not equilibrated, and your simulation may not be long enough for rigorous analysis.

Ligand RMSD: Ligand RMSD (right Y-axis) indicates how stable the ligand is with respect to the protein and its binding pocket. In the above plot, 'Lig fit Prot' shows the RMSD of a ligand when the protein-ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand heavy atoms is measured. If the values observed are significantly larger than the RMSD of the protein, then it is likely that the ligand has diffused away from its initial binding site.

Protein RMSF



The Root Mean Square Fluctuation (RMSF) is useful for characterizing local changes along the protein chain. The RMSF for residue i is:

$$RMSF_i = \sqrt{\frac{1}{T} \sum_{t=1}^T \langle (r'_i(t)) - r_i(t_{ref})^2 \rangle}$$

where T is the trajectory time over which the RMSF is calculated, t_{ref} is the reference time, r_i is the position of residue i ; r' is the position of atoms in residue i after superposition on the reference, and the angle brackets indicate that the average of the square distance is taken over the selection of atoms in the residue.

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Protein Secondary Structure

% Helix

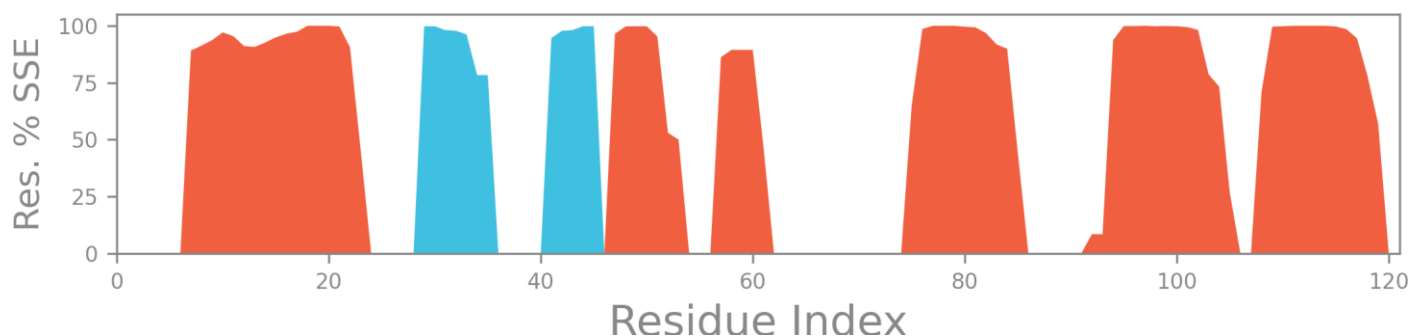
47.36

% Strand

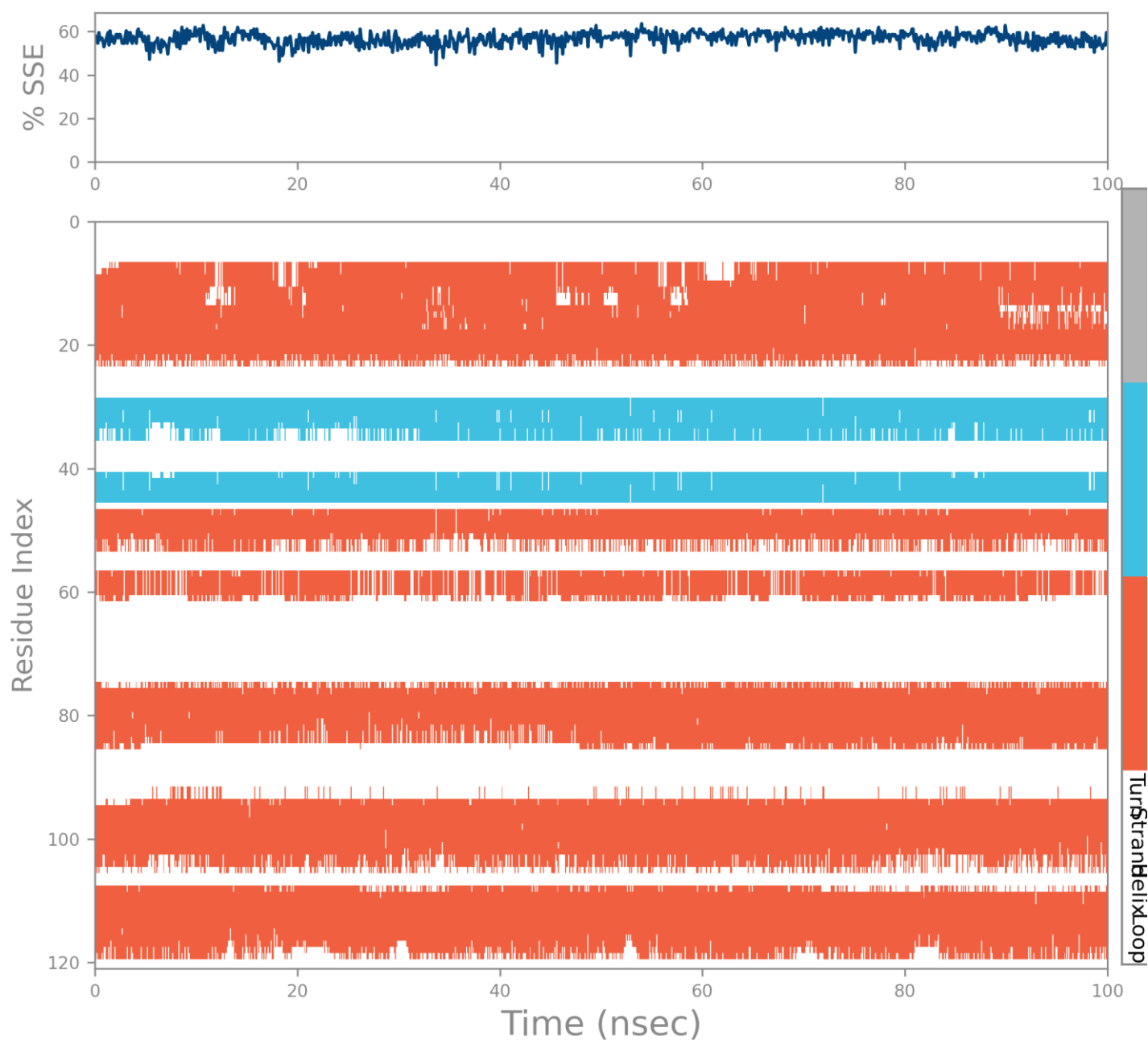
9.41

% Total SSE

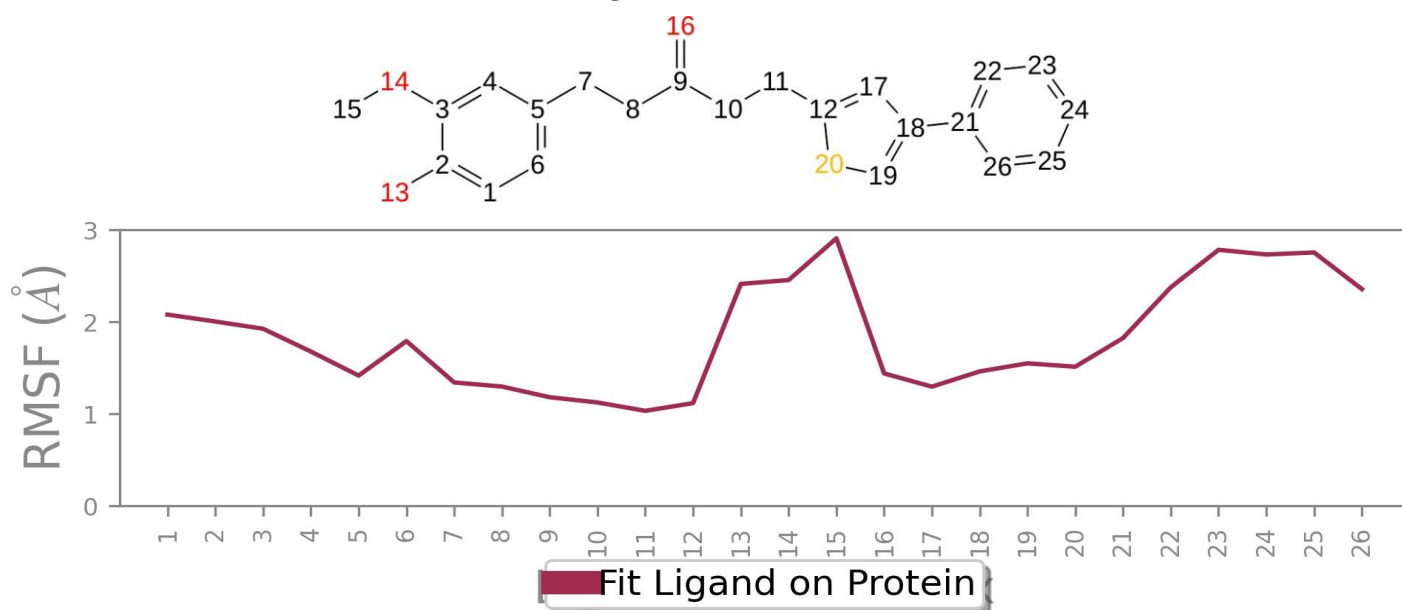
56.77



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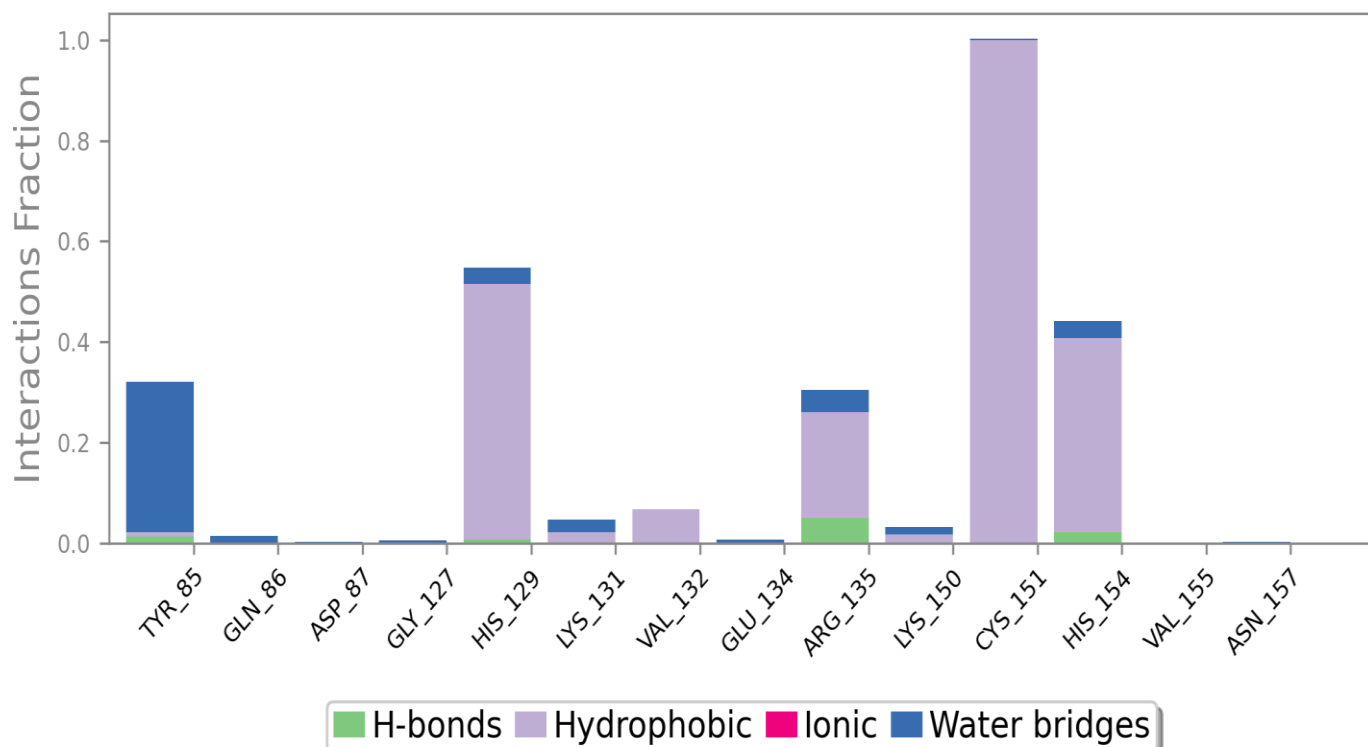
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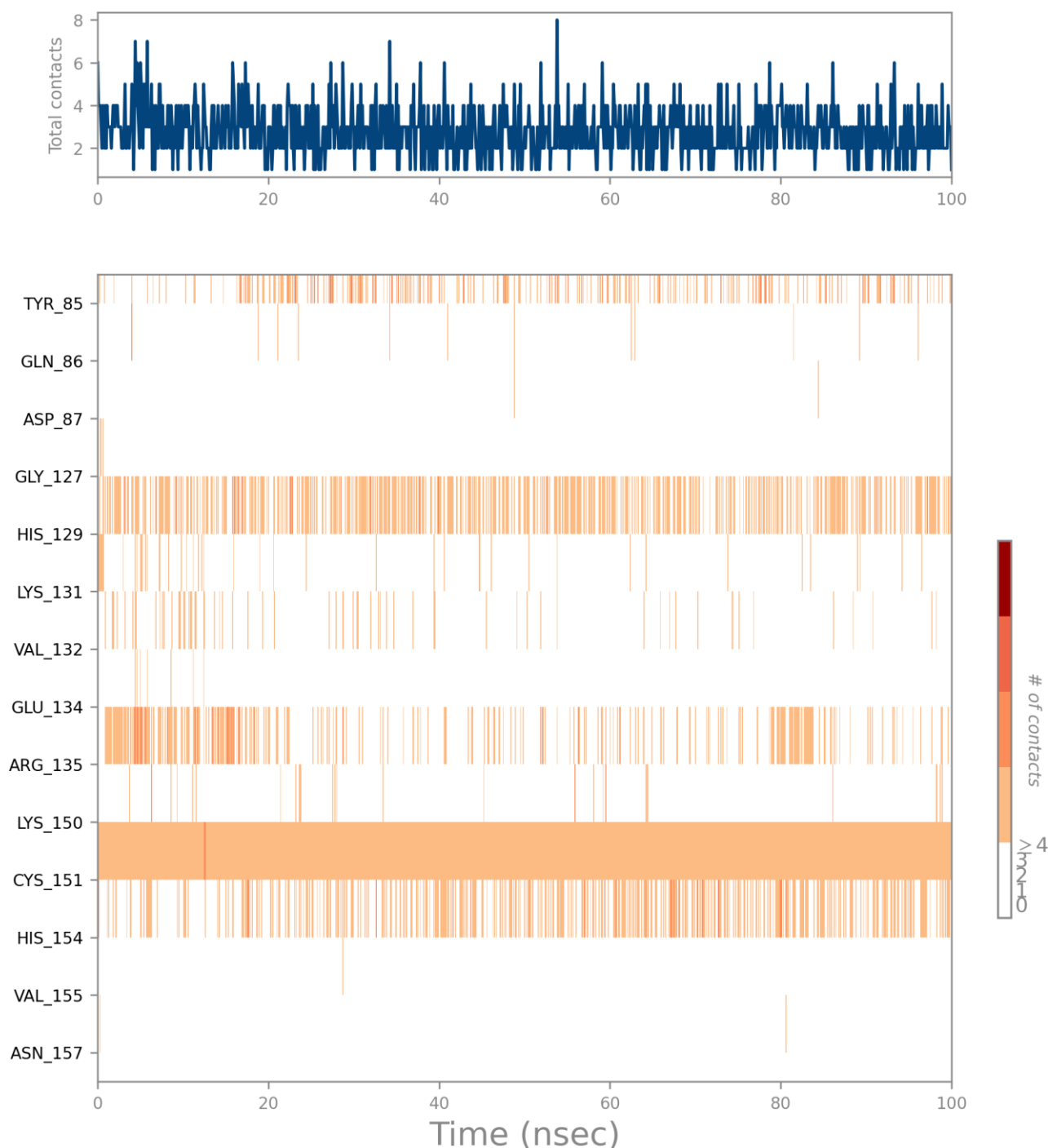
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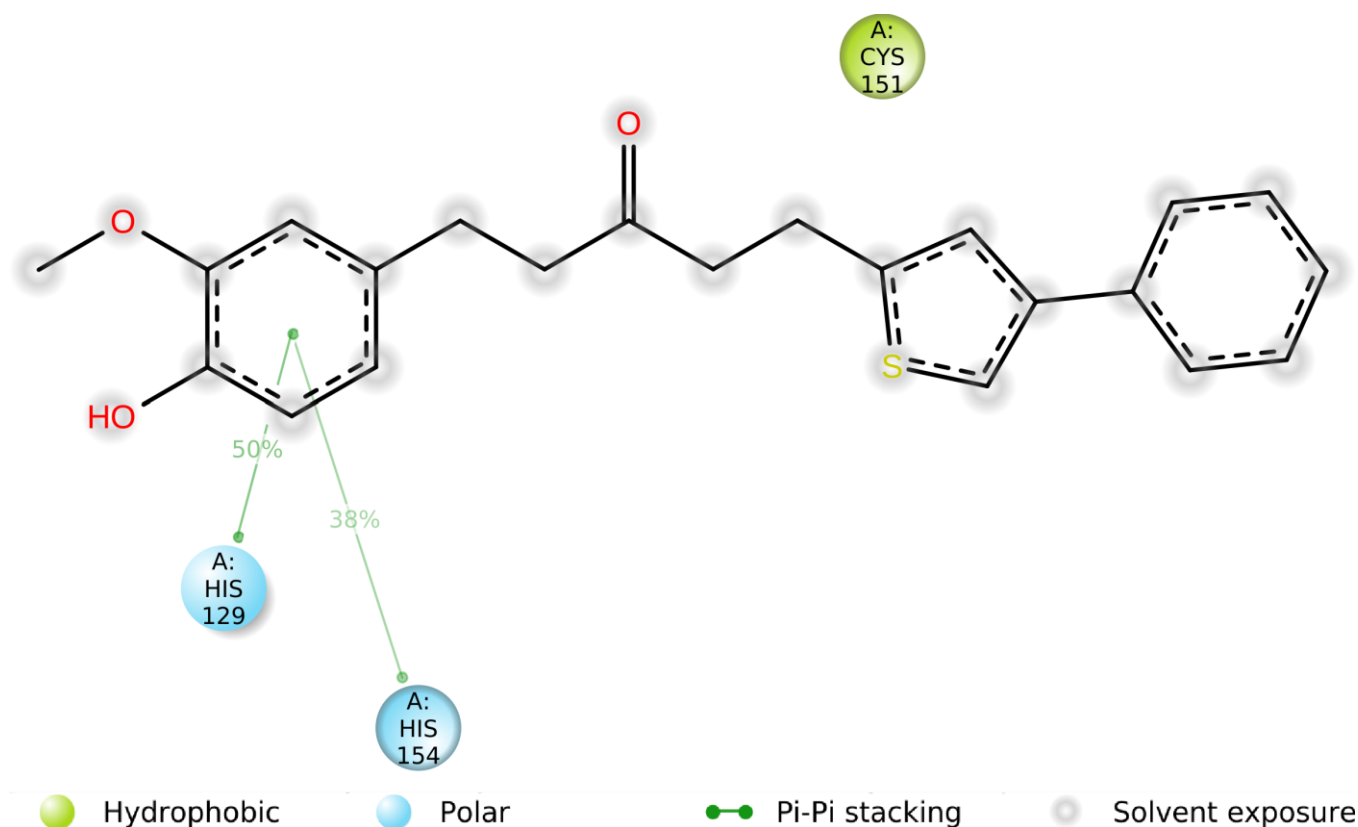
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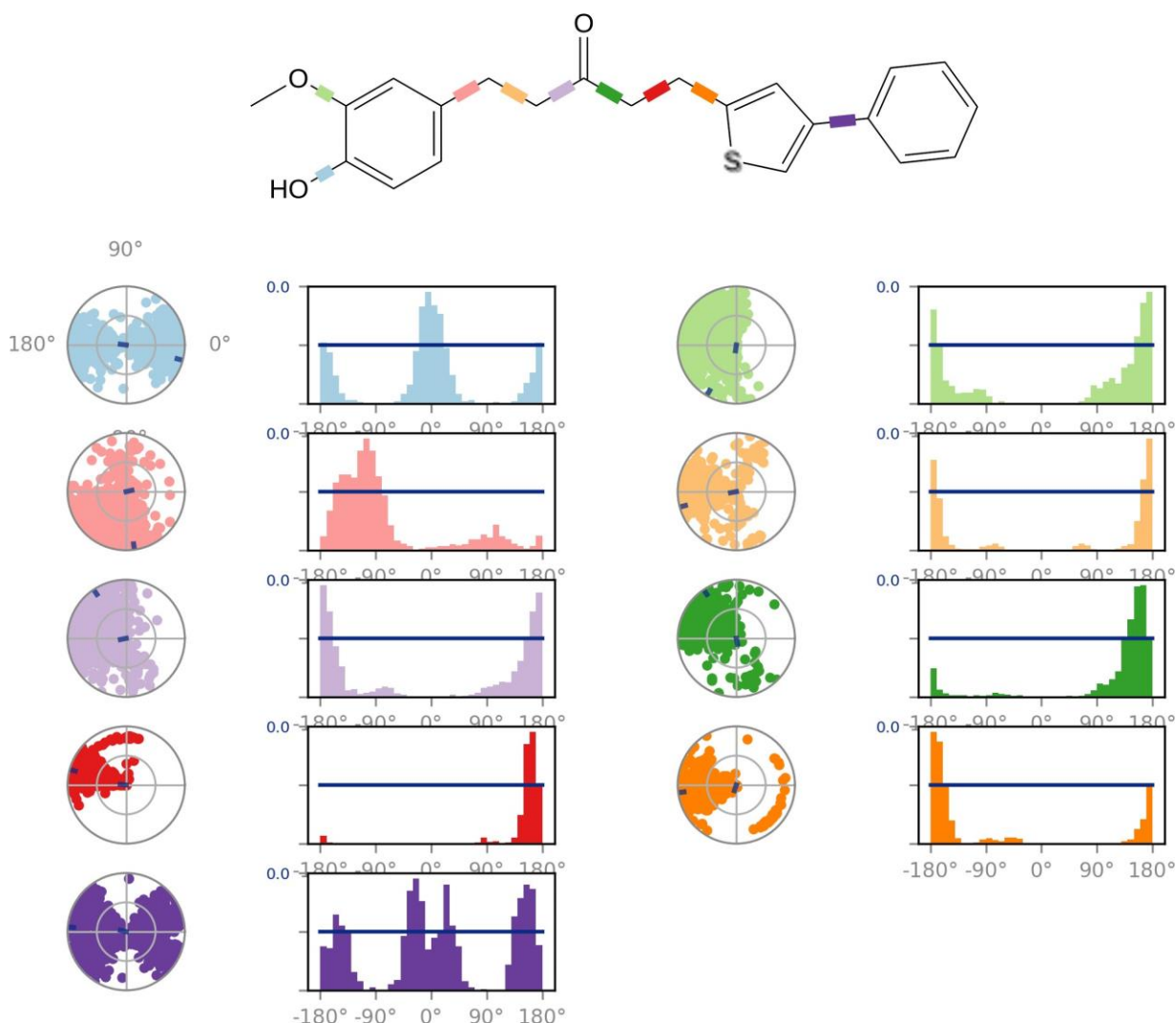
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