# Identification of Microbial-based Natural Products as Potential CYP51 Inhibitors for Eumycetoma Treatment: Insights from Molecular Docking, MM-GBSA Calculations, ADMET Analysis, and Molecular Dynamics Simulations

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**Table S1**: XP molecular docking interactions between the top-ranked microbial-based natural products and itraconazole (ionized and unionized forms) with the in-house homology model of *Madurella mycetomatis* CYP51. The interactions of the heme group are retrieved from the apo form of the model.

| Compound | Interactions |
|---|---|
| NPA020764<br>(Octacosamicin A) | H-Bond:<br>Gly69 (2.16 Å), Tyr136 (1.88 Å), Asp507 (2.47 Å) and HEM530 (2.43 Å)<br>Salt bridge:<br>Lys235 (3.31 Å) and HEM530 (4.8 Å)<br>Pi-cation:<br>HEM530 (4.42 Å)<br>Hydrophobic:<br>Ile66, Tyr68, Met70, Leu91, Leu92, Ile121, Tyr122, Leu125, Tyr136, Phe229, Ile232, Pro231, Phe234, Ile372, Met376, Tyr508, Ala509, Leu511 and Phe512 |
| NPA029353<br>(Monacyclinone H) | Pi-cation:<br>Tyr122 (5.89 Å) and HEM530 (5.86 Å and 6.43 Å)<br>Pi-Pi stacking:<br>Phe234 (4.38 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Val135, Tyr136, Phe229, Phe234, Met305, Ala306, Ile372, Met376, Val397, Leu511 and Phe512 |
| NPA029354<br>(Monacyclinone I) | Pi-cation:<br>HEM530 (6.31 Å and 6.56 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Tyr136, Phe229, Phe234, Met305, Ala306, Ile372, Met376, Val397, Leu511 and Phe512 |
| NPA017021<br>(Monacyclinone E) | H-Bond:<br>Leu91 (2.11 Å) and Lys94 (2.24 Å)<br>Salt bridge:<br>Lys94 (3.42 Å)<br>Pi-cation:<br>Tyr122 (5.74 Å) and HEM530 (6.0 Å and 6.47 Å)<br>Hydrophobic:<br>Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Val135, Tyr136, Phe229, Met305, Ala306, Ile372, Met376, Val397, Phe234, Leu511 and Phe512 |
| NPA026108<br>(3'-N-methyl-medermycin) | H-Bond:<br>Lys94 (2.48 Å)<br>Pi-cation:<br>HEM530 (6.23 Å)<br>Hydrophobic:<br>Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Tyr136, Phe229, Phe234, Met305, Ile372, Ile375, Met376, Val397, Leu511 and Phe512 |
| NPA029352<br>(Monacyclinone G) | H-Bond:<br>Ser510 (2.17 Å)<br>Pi-cation:<br>HEM530 (4.56 Å and 5.27 Å)<br>Pi-Pi stacking:<br>Phe234 (3.66 Å and 4.06 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Tyr136, Phe229, Phe234, Met305, Ala306, Ile372, Met376, Val397, Leu511 and Phe512 |
| NPA020514<br>(gamma-iso-Rubromycin) | H-Bond:<br>Ile121 (1.76 Å)<br>Pi-Pi stacking: |

| | |
|---|---|
| | HEM530 (4.69 Å and 5.36 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Val135, Tyr136, Phe229, Phe234, Ala306, Ile372, Met376 and Leu511 |
| NPA023185 (2,2'-bis-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione)) | Pi-Pi stacking:<br>HEM530 (5.16 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Val124, Leu125, Phe130, Val135, Tyr136, Phe229, Phe234, Ala302, Leu303, Ala306, Ile372, Ile375, Met376, Leu511 and Phe512 |
| NPA018887 (Roseobacticide K) | H-Bond:<br>Leu91 (2.14 Å)<br>Pi-Pi stacking:<br>HEM530 (5.43 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Phe130, Val135, Tyr136, Phe234, Ala302, Met305, Ala306, Ile372, Met376, Val397, Leu511 and Phe512 |
| Itraconazole-ionized | Halogen bond:<br>Ser374 (3.19 Å)<br>Pi-cation:<br>Tyr122 (5.87 Å)<br>Pi-Pi stacking:<br>Phe229 (4.74 Å), Phe234 (4.23 Å) and HEM530 (4.27 Å and 4.76 Å)<br>Hydrophobic:<br>Leu91, Leu92, Ile121, Tyr122, Va124, Leu125, Val129, Phe130, Val135, Tyr136, Phe229, Phe234, Ala302, Met305, Ala306, Ile372, Ile375, Met376, Val397, Leu511 and Phe512 |
| Itraconazole-unionized | Halogen bond:<br>Ser374 (3.21 Å)<br>Pi-Pi stacking:<br>Phe229 (4.87 Å), Phe234 (3.88 Å) and HEM530 (4.28 Å and 4.77 Å)<br>Hydrophobic:<br>Tyr68, Leu91, Leu92, Ile121, Tyr122, Leu125, Phe130, Val135, Tyr136, Phe229, Phe234, Ala302, Met305, Ala306, Ile372, Ile375, Met376, Val397, Leu511 and Phe512 |
| Heme group (in the apo form) | H-bond:<br>Tyr122 (2.30 Å), Tyr136 (1.90 Å), Lys147 (2.25 Å), Arg377 (2.23 Å) and His469 (2.15 Å)<br>Ionic bond:<br>Cys471 (2.52 Å)<br>Hydrophobic:<br>Leu154, Leu205, Leu303, Ala306, Gly307, Ser310, Thr314, Leu366, Pro371, Ile372, Ile375, Pro463, Phe464, Ile472, Gly473, Phe476, Ala477 and Leu481 |

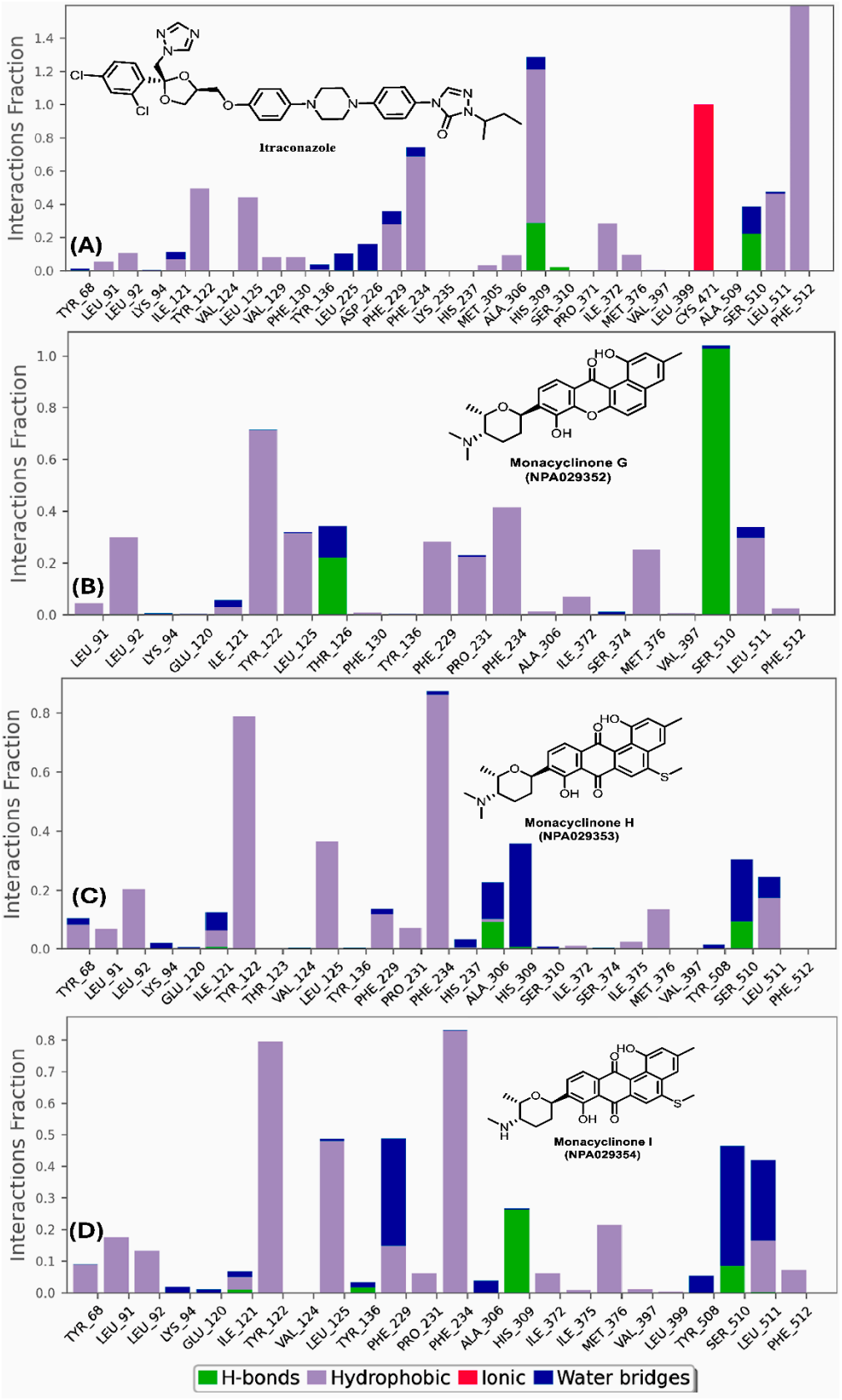



**Figure S1**: Interactions of the in-house homology model of *Madurella mycetomatis* CYP51 residues with itraconazole (**A**), NPA029352 (**B**), NPA029353 (**C**) and NPA029354 (**D**) throughout the entire MD simulations run.