Data Article

Data on molecular docking of tautomers and enantiomers of ATTAF-1 and ATTAF-2 selectivity to the human/fungal lanosterol-14α-demethylase

Hamid Irannejad\textsuperscript{a,b}, Saeed Emami\textsuperscript{a,b}, Hassan Mirzaei\textsuperscript{c}, Seyedeh Mahdieh Hashemi\textsuperscript{a,b,*}

\textsuperscript{a} Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
\textsuperscript{b} Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran
\textsuperscript{c} Ischemic Disorders Research Center, Golestan University of Medical Sciences, Gorgan, Iran

\textbf{ARTICLE INFO}

Article history:
Received 13 June 2020
Accepted 24 June 2020
Available online xxx

Keywords:
Molecular docking
Lanosterol-14α-demethylase
Selectivity
Antifungal

\textbf{ABSTRACT}

The data have been obtained for tautomers and enantiomers of ATTAF-1 and ATTAF-2 that were developed based on antifungal standard drugs with triazole scaffold. These compounds were docked into the human and fungal lanosterol-14α-demethylase. In order to validate the data, 8 standard triazole antifungal drugs (Fluconazole, Itraconazole, Posaconazole, Ravuconazole, Albconazole, Voriconazole, Isavuconazole and Efinaconazole) were also docked into the human and fungal lanosterol-14α-demethylase. The binding conformations of these molecules and their interactions with lanosterol-14α-demethylase may inform the development of further small molecule lanosterol-14α-demethylase inhibitors with significant selectivity toward this enzyme. The analysis has done on the basis of type of interactions (bond type and distance). The length of the Fe-N coordination bond for (R)-N2-ATTAF-1 and (S)-N1-ATTAF-2 complexes is obtained 6.36 and 4.19 Å, respectively and about 2 Å in the other tautomer and enantiomer complexes, reflecting the lower basicity of the N-4 atom in the 1,2,4-
The lanosterol 14α-demethylase has been identified as a molecular target for the treatment of fungal diseases.

The modeling data was produced to rationalize the structural necessities for lanosterol 14α-demethylase inhibition.

The binding conformations of the ATTAF-1 and ATTAF-2, their interactions with human and fungal lanosterol 14α-demethylase and coordination bond distance may inform further studies focused on the development of lanosterol 14α-demethylase inhibitors.

Novel synthetic analogues with improved bioactivity and minimized side effects can be expanded against this target by using this in silico docking data and research time can be minimized significantly.
Table 1
List of targets.

| Entry | PDB ID  | Resolution (Å) | Description                                      | RMSD (Å) |
|-------|---------|----------------|--------------------------------------------------|----------|
| 1     | 5V5Z    | 2.9            | Structure of CYP51 from the pathogen Candida albicans [7] | 1.71     |
| 2     | 5JLC    | 2.4            | Structure of CYP51 from the pathogen Candida glabrata [7] | 1.58     |
| 3     | 3LD6    | 2.8            | Crystal structure of human lanosterol 14alpha-demethylase (CYP51) in complex with ketoconazole [8] | 1.04     |

Table 2
Coordinates of the cubic box used to dock ATTAF-1 and ATTAF-2 to the fungal and human CYP51.

| Entry | Side | Coordinate CACYP51 | Coordinate CGCYP51 | Coordinate hCYP51 |
|-------|------|--------------------|--------------------|-------------------|
| 1     | X    | −42.490            | −40.056            | 42.287            |
| 2     | Y    | −13.523            | 74.850             | 4.969             |
| 3     | Z    | 26.334             | −23.564            | 1.219             |

- This dataset can be useful to model other potent antifungal agents in future and researchers in pharmaceutical chemistry can gain from the data.

1. Data description

Lanosterol-14α-demethylase (CYP51) is found in mycobacteria, fungi, plants, animals and humans. This enzyme is required for biosynthesis of sterol in eukaryotes and is the major target forazole antifungal agents [1,2]. In mammals, lanosterol-14α-demethylase is the enzyme that catalyzes lanosterol to cholesterol conversion, which is necessary to maintain a variety of metabolic functions [3]. An ideal antifungal agent should have minimal effect on human CYP51 enzymes while keeping potent inhibition of fungal enzyme to reduce the side effects [4]. Lanosterol-14α-demethylase consists of an iron protoporphyrin unit in its active site. At the molecular level, N-4 in the 1,2,4-triazole ring selectively coordinates to the lanosterol-14α-demethylase heme iron and cause the prevention of the fungal ergosterol biosynthesis pathway [5]. In order support a medicinal chemistry campaign to develop potentazole antifungal agents with high CYP51 affinity, we have previously synthesized and reported a series of novel fluconazole analogues, with the most promising ones introduced as ATTAF-1 and ATTAF-2 [6] and provided the computational-based docking and MD simulation outputs for all tautomeric and enantiomeric forms of ATTAF-1 and ATTAF-2 plus 8 antifungal standard drugs were docked into the human and fungal lanosterol-14α-demethylase [9]. Here, our studies provide important protein-ligand interaction information for the further development of lanosterol-14α-demethylase inhibitors. In this article Table 1 provides the details about the targets and their description. Table 2 gives the coordinates of the cubic box used to dock ATTAF-1 and ATTAF-2 to the fungal and human CYP51. Table 3 gives the length of the Fe-N coordination bond. Table 4 provides tautomers and enantiomers of ATTAF-1 and ATTAF-2 interactions with fungal and human CYP51. To point to the N-4 coordination with heme iron, 3D interactions of all tautomeric and enantiomeric forms of ATTAF-1 and ATTAF-2 with the target enzymes are shown in the Figs. 1–3. 2D interactions of all tautomeric and enantiomeric forms of ATTAF-1, ATTAF-2 and 8 standard triazole antifungal drugs with the target enzymes are shown in the supplemental file.

2. Experimental design, materials and methods

2.1. Protein selection and preparation

The crystal structures of the selected proteins were retrieved from protein data bank. (PDB database, www.rcsb.org). Protein preparation was done by preprocessing the structures by re-
Fig. 1. Ligand interaction map of the predicted binding mode of tautomers and enantiomers of ATTAF-1 and ATTAF-2 in the active site Candida albicans CYP51.
Fig. 2. Ligand interaction map of the predicted binding mode of tautomers and enantiomers of ATTA1 and ATTA2 in the active site Candida glabrata CYP51.
Fig. 3. Ligand interaction map of the predicted binding mode of tautomers and enantiomers of ATTAF-1 and ATTAF-2 in the active site human CYP51.
### Table 3
Length of the Fe-N coordination bond.

| Entry | Compound | Coordination Bond Distance (Å) |
|-------|----------|--------------------------------|
|       |          | CACYP51 | CGCYP51 | hCYP51 |
| 1     | (R)-N1-ATTAF-1 | 2.52    | 2.93    | 2.17   |
| 2     | (R)-N2-ATTAF-1 | 2.21    | 2.63    | 6.36   |
| 3     | (R)-N4-ATTAF-1 | 2.91    | 2.25    | 1.92   |
| 4     | (S)-N1-ATTAF-1 | 2.56    | 2.44    | 2.83   |
| 5     | (S)-N2-ATTAF-1 | 2.29    | 2.89    | 2.92   |
| 6     | (S)-N4-ATTAF-1 | 2.53    | 2.80    | 2.70   |
| 7     | (R)-N1-ATTAF-2 | 2.32    | 2.83    | 2.67   |
| 8     | (R)-N2-ATTAF-2 | 2.12    | 2.85    | 2.19   |
| 9     | (R)-N4-ATTAF-2 | 2.20    | 2.26    | 2.03   |
| 10    | (S)-N1-ATTAF-2 | 2.33    | 2.80    | 4.19   |
| 11    | (S)-N2-ATTAF-2 | 2.45    | 2.86    | 2.04   |
| 12    | (S)-N4-ATTAF-2 | 2.74    | 2.74    | 3.12   |

### Table 4
Tautomers and enantiomers of ATTAF-1 and ATTAF-2 interactions with fungal and human CYP51.

| Entry | Target | Ligand | Interaction | Type of interaction | Bond distance (Å) |
|-------|--------|--------|-------------|--------------------|-------------------|
| 1     | 5V5Z   | (R)-N1-ATTAF-1 | Tyr132 | H-Bond | 2.34 |
|       |        |        | Phe233 | Pi-Pi stacking | 5.13 |
|       |        |        | Met508 | Pi-Sulfur | 5.85 |
|       |        |        | Tyr118 | Pi-Sulfur | 3.60 |
|       |        |        | Phe233 | Pi-Sulfur | 5.96 |
|       |        | (R)-N2-ATTAF-1 | Tyr132 | H-Bond | 2.32 |
|       |        |        | Phe380 | Pi-Pi stacking | 4.92 |
|       |        |        | Met508 | Pi-Sulfur | 5.45 |
|       |        |        | Phe228 | Pi-Sulfur | 5.87 |
|       |        | (R)-N4-ATTAF-1 | Phe380 | Pi-Pi stacking | 4.93 |
|       |        |        | Phe233 | Pi-Pi stacking | 5.81 |
|       |        |        | Tyr118 | Pi-Pi stacking | 3.44 |
|       |        |        | Ser378 | Pi-Pi stacking | 4.17 |
|       |        | (S)-N1-ATTAF-1 | Tyr132 | H-Bond | 3.16 |
|       |        |        | Tyr118 | Pi-Pi stacking | 3.54 |
|       |        |        | Phe380 | Pi-Pi stacking | 5.08 |
|       |        | (S)-N2-ATTAF-1 | Tyr132 | H-Bond | 3.21 |
|       |        |        | Tyr118 | Pi-Pi stacking | 3.71 |
|       |        |        | Phe380 | Pi-Pi stacking | 5.91 |
|       |        | (S)-N4-ATTAF-1 | Ser378 | Pi-Pi stacking | 4.14 |
|       |        |        | Phe380 | Pi-Pi stacking | 4.96 |
|       |        |        | Phe233 | Pi-Pi stacking | 5.86 |
|       |        |        | Tyr118 | Pi-Pi stacking | 3.52 |
|       |        | (R)-N1-ATTAF-2 | Phe233 | Pi-Pi stacking | 5.75 |
|       |        |        | Phe228 | Pi-Sulfur | 5.48 |
|       |        | (R)-N2-ATTAF-2 | Tyr118 | Pi-Pi stacking | 5.84 |
|       |        |        | Phe380 | Pi-Pi stacking | 5.31 |
|       |        | (R)-N4-ATTAF-2 | Tyr132 | H-Bond | 2.59 |
|       |        |        | Tyr118 | Pi-Pi stacking | 4.45 |
|       |        |        | Phe228 | Pi-Sulfur | 5.50 |
|       |        |        | Met508 | Pi-Sulfur | 5.41 |
|       |        | (S)-N1-ATTAF-2 | Phe233 | Pi-Pi stacking | 5.01 |
|       |        |        | Tyr118 | Pi-Sulfur | 4.35 |
|       |        |        | Met508 | Pi-Sulfur | 5.62 |
|       |        | (S)-N2-ATTAF-2 | Tyr118 | H-Bond | 2.64 |
|       |        |        | Ser378 | H-Bond | 2.10 |
|       |        | (S)-N4-ATTAF-2 | Tyr132 | H-Bond | 2.94 |
|       |        |        | Phe380 | Pi-Pi stacking | 5.93 |
|       |        |        | Tyr118 | Pi-Pi stacking | 3.72 |

(continued on next page)
| Entry | Target  | Ligand   | Interaction | Type of interaction | Bond distance (Å) |
|-------|---------|----------|-------------|--------------------|-------------------|
| 2.    | **5JLC** | (R)-N1-ATTAF-1 | Tyr127       | H-Bond             | 1.99              |
|       |         |          | Phe237       | Pi-Pi stacking     | 5.01              |
|       |         |          | Tyr127       | Pi-Pi stacking     | 5.89              |
|       |         |          | Phe237       | Pi-Sulfur          | 5.02              |
|       |         |          | Phe135       | Pi-Sulfur          | 5.12              |
|       |         |          | (R)-N4-ATTAF-1 | Pi-Pi stacking | 5.28              |
|       |         |          | Tyr127       | Pi-Pi stacking     | 5.41              |
|       |         |          | Phe135       | Pi-Pi stacking     | 5.44              |
|       |         |          | Tyr141       | Pi-Sulfur          | 5.39              |
|       |         |          | Met512       | Pi-Sulfur          | 4.82              |
|       |         | (S)-N1-ATTAF-1 | Tyr141       | H-Bond             | 2.61              |
|       |         | (S)-N2-ATTAF-1 | His318       | H-Bond             | 2.68              |
|       |         |          | Thr319       | H-Bond             | 3.58              |
|       |         |          | Ser383       | H-Bond             | 1.98              |
|       |         |          | Phe242       | Pi-Pi stacking     | 5.31              |
|       |         |          | Met512       | Pi-Sulfur          | 5.29              |
|       |         |          | Tyr127       | Pi-Sulfur          | 4.20              |
|       |         | (S)-N4-ATTAF-1 | Tyr141       | 2 H-Bond           | 2.60, 3.58        |
|       |         |          | Phe242       | Pi-Pi stacking     | 5.32              |
|       |         |          | Tyr127       | Pi-Pi stacking     | 4.04              |
|       |         |          | Tyr141       | Pi-Sulfur          | 4.86              |
|       |         |          | Tyr127       | Pi-Sulfur          | 3.93              |
|       |         |          | Met512       | Pi-Sulfur          | 4.79              |
|       |         | (R)-N1-ATTAF-2 | Tyr141       | Pi-Pi stacking     | 5.42              |
|       |         | (R)-N2-ATTAF-2 | Ser383       | H-Bond             | 2.09              |
|       |         |          | Phe385       | Pi-Pi stacking     | 5.01              |
|       |         |          | Met512       | Pi-Sulfur          | 4.93              |
|       |         | (R)-N4-ATTAF-2 | Tyr141       | Pi-Sulfur          | 5.10              |
|       |         |          | Phe237       | Pi-Sulfur          | 5.80              |
|       |         | (S)-N1-ATTAF-2 | Phe242       | Pi-Pi stacking     | 5.54              |
|       |         |          | Phe385       | Pi-Pi stacking     | 5.89              |
|       |         |          | His382       | Pi-Pi stacking     | 5.31              |
|       |         |          | Tyr127       | Pi-Sulfur          | 4.16              |
|       |         |          | Met512       | Pi-Sulfur          | 5.46              |
|       |         | (S)-N2-ATTAF-2 | Tyr127       | H-Bond             | 2.86              |
|       |         |          | Ser383       | H-Bond             | 2.32              |
|       |         |          | His382       | Pi-Pi stacking     | 5.36              |
|       |         | (S)-N4-ATTAF-2 | Ser383       | H-Bond             | 2.61              |
|       |         |          | Phe385       | Pi-Pi stacking     | 5.08              |
|       |         |          | Phe242       | Pi-Pi stacking     | 5.59              |
|       |         |          | Tyr141       | Pi-Pi stacking     | 5.45              |
|       |         |          | Met512       | Pi-Sulfur          | 4.83              |
| 3.    | **3LD6** | (R)-N1-ATTAF-1 | Thr135       | H-Bond             | 3.16              |
|       |         |          | Tyr131       | Pi-Pi stacking     | 4.79              |
|       |         |          | Phe234       | Pi-Pi stacking     | 5.11              |
|       |         |          | Tyr145       | Pi-Sulfur          | 4.80              |
|       |         |          | Phe139       | Pi-Sulfur          | 5.51              |
|       |         |          | Phe234       | Pi-Sulfur          | 5.60              |
|       |         | (R)-N2-ATTAF-1 | Met378       | H-Bond             | 2.81              |
|       |         |          | Val130       | H-Bond             | 2.85              |
|       |         |          | Tyr131       | Pi-Pi stacking     | 4.32              |
|       |         |          | Trp239       | Donor-Donor        | 2.09              |
|       |         | (R)-N4-ATTAF-1 | Tyr131       | 2 Pi-Pi stacking   | 4.18, 4.23        |
|       |         |          | Phe139       | Pi-Pi stacking     | 5.14              |
|       |         |          | Tyr145       | Pi-Sulfur          | 5.78              |
|       |         |          | Thr135       | Pi-Sulfur          | 2.94              |
|       |         |          | Phe139       | Pi-Sulfur          | 4.34              |
|       |         |          | Phe234       | Pi-Sulfur          | 4.74              |

(continued on next page)
Table 4 (continued)

| Entry | Target | Ligand       | Interaction | Type of interaction | Bond distance (Å) |
|-------|--------|--------------|-------------|---------------------|-------------------|
| (S)-N1-ATTAF-1 |       | Thr135       | H-Bond      |                     | 1.90              |
|       |        | Tyr145       | H-Bond      |                     | 2.76              |
|       |        | Phe234       | Pi-Pi stacking |                   | 5.23              |
|       |        | Tyr131       | Pi-Sulfur   |                     | 3.97              |
| (S)-N2-ATTAF-1 |       | Tyr145       | 2 H-Bond    |                     | 2.82, 3.54        |
|       |        | Tyr131       | 2 Pi-Pi stacking |               | 4.13, 4.73        |
|       |        | Phe139       | Pi-Pi stacking |                   | 5.09              |
| (S)-N4-ATTAF-1 |       | Thr135       | H-Bond      |                     | 2.91              |
|       |        | Phe234       | Pi-Pi stacking |                   | 5.06              |
|       |        | Phe234       | Pi-Sulfur   |                     | 5.64              |
| (R)-N1-ATTAF-2 |       | Tyr131       | H-Bond      |                     | 2.53              |
|       |        | Thr135       | H-Bond      |                     | 2.64              |
|       |        | Tyr145       | H-Bond      |                     | 3.49              |
|       |        | Phe234       | Pi-Pi stacking |                   | 4.84              |
| (R)-N2-ATTAF-2 |       | Ile379       | H-Bond      |                     | 2.25              |
|       |        | Phe234       | Pi-Sulfur   |                     | 5.89              |
| (R)-N4-ATTAF-2 |       | Tyr131       | Pi-Pi stacking |               | 4.27              |
|       |        | Met381       | Pi-Sulfur   |                     | 4.94              |
|       |        | Phe234       | Pi-Sulfur   |                     | 5.99              |
| (S)-N1-ATTAF-2 |       | Pro379       | H-Bond      |                     | 2.29              |
|       |        | Met378       | Donor-Donor | (Unfavorable)        | 2.51              |
| (S)-N2-ATTAF-2 |       | Ala311       | Pi-Alkyl    |                     | 4.34              |
|       |        | Ile379       | Pi-Alkyl    |                     | 4.45              |
|       |        | Met381       | Pi-Alkyl    |                     | 4.30              |
| (S)-N4-ATTAF-2 |       | Leu310       | H-Bond      |                     | 2.68              |
|       |        | Ala311       | H-Bond      |                     | 2.99              |
|       |        | Phe234       | Pi-Pi stacking |                   | 4.21              |

moving water molecules, ions and cocrystallized ligands, polar hydrogens addition and assigning Gasteiger-Marsili partial charges, adjusting bonds and formal charges for metals, and removing unwanted chains. In order to rmsd validation, the co-crystallized ligand was re-docked. The target input files were converted to PDBQT format for AutoDock by using the AutoDockTools-1.5.4.

2.2. Ligand preparation and molecular docking

Ligands 3D structures were sketched by using ChemDraw Ultra 8.0 and energy minimized using PM3 force field. For all ligands, the nonpolar hydrogen atoms were merged and the Gasteiger charges were assigned. Then set number of torsion with detect root and choose torsion in Autodock program. Later, ligand input files were also saved as PDBQT format utilizing the AutoDock Tools. The minimized structures were docked on the prepared protein.

Discovery Studio Client 2016 and Molegro Molecular Viewer were used for further analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Research reported in this publication was supported by a grant from Research Council of Mazandaran University of Medical Sciences, Sari, Iran (Grant no. 3365).
Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.dib.2020.105942.

References

[1] L. Friggeri, T.Y. Hargrove, Z. Wawrzak, F.P. Guengerich, G.I. Lepesheva, Validation of human sterol 14alpha-demethylase (CYP51) druggability: structure-guided design, synthesis, and evaluation of stoichiometric, functionally irreversible inhibitors. J. Med. Chem. 62 (22) (2019) 10391–10401 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31663733, doi: 10.1021/acs.jmedchem.9b01485.

[2] Pooja, Prasher, P. Singh, K. Pawar, K.S. Vikramdeo, N. Mondal, S.S. Komath, Synthesis of amino acid appended indoles: appreciable anti-fungal activity and inhibition of ergosterol biosynthesis as their probable mode of action, Eur. J. Med. Chem. 80 (2014) 325–339 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24794769, doi: 10.1016/j.ejmech.2014.04.063.

[3] X.L. Chang, L. Liu, N. Wang, Z.J. Chen, C. Zhang, The function of high-density lipoprotein and low-density lipoprotein in the maintenance of mouse ovarian steroid balance, Biol. Reprod. 97 (6) (2017) 862–872 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29092018, doi: 10.1093/biolre/iox134.

[4] B.C. Monk, A.A. Sagatova, P. Hosseini, Y.N. Ruma, R.K. Wilson, M.V. Keniya, Fungal Lanosterol 14alpha-demethylase: a target for next-generation antifungal design, Biochim. Biophys. Acta Proteins Proteom. 1868 (3) (2020) 140206 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30851431, doi: 10.1016/j.bbapap.2019.02.008.

[5] T.Y. Hargrove, L. Friggeri, Z. Wawrzak, A. Qi, W.J. Hoekstra, R.J. Schotzinger, … G.I. Lepesheva, Structural analyses of Candida albicans sterol 14alpha-demethylase complexed withazole drugs address the molecular basis of azole-mediated inhibition of fungal sterol biosynthesis, J. Biol. Chem. 292 (16) (2017) 6728–6743 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28258218, doi: 10.1074/jbc.M117.778308.

[6] S.M. Hashemi, H. Badali, H. Irannejad, M. Shokrzadeh, S. Emami, Synthesis and biological evaluation of fluconazole analogs with triazole-modified scaffold as potent antifungal agents, Bioorg. Med. Chem. 23 (7) (2015) 1481–1491 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25740636, doi: 10.1016/j.bmc.2015.02.011.

[7] M.V. Keniya, M. Sabherwal, R.K. Wilson, M.A. Woods, A.A. Sagatova, J.D.A. Tyndall, B.C. Monk, Crystal structures of full-length Lanosterol 14 alpha-demethylases of prominent fungal pathogens candida albicans and candida glabrata provide tools for antifungal discovery, Antimicrob. Agents Chemother. (2018), doi: 10.1128/AAC.01134–18.

[8] N. Strushkevich, S.A. Usanov, H.W. Park, Structural basis of human CYP51 inhibition by antifungal azoles, J. Mol. Biol. 397 (2010) 1067–1078, doi: 10.1016/j.jmb.2010.01.075.

[9] H. Irannejad, S. Emami, H. Mirzaei, S.M. Hashemi, In silico prediction of ATTAF-1 and ATTAF-2 selectivity towards human/fungal lanosterol 14α-demethylase using molecular dynamic simulation and docking approaches, IMU 20 (2020) 100366, doi: 10.1016/j.imu.2020.100366.