A Simulated Docking of Abiraterone with Cytochrome P450 17A1

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Abstract

Cytochrome P450 17A1 (also known as CYP17A1) catalyses the biosynthesis of androgens in humans. Because prostate cancer cells proliferate in response to androgen steroids, CYP17A1 inhibition can help to prevent androgen synthesis and treat lethal metastatic prostate cancer. Here I report the results of a computational docking of abiraterone, a steroidal inhibitor of CYP17A1 recently approved by the FDA, with the CYP17A1 active site, based on recent X-ray crystallography of the receptor/ligand complex.

Keywords: cytochrome P450, CYP17A1, abiraterone, computational docking, prostate cancer

1.0 Introduction

Cytochrome P450 17A1 (also known as CYP17A1 and cytochrome P450c17) is a membrane-bound monoxygenase that plays a fundamental role in the synthesis of several human steroid hormones ([5]). The 17α-hydroxylase activity of CYP17A1 is required for the generation of glucocorticoids such as cortisol; the hydroxylase and 17,20-lyase activities of CYP17A1 are required for the production of androgenic and oestrogenic sex steroids. CYP17A1 is thus an important target for the treatment of breast and prostate cancers that proliferate in response to oestrogens and androgens ([6],[7]).

Until recently, steroidal CYP17A1 inhibitors were thought to bind the cytochrome P450 haem iron, more or less parallel to the plane of the haem group in the active site ([8]).

Abiraterone is the active form of a steroidal prodrg recently approved by the US Food and Drug Administration for metastatic prostate cancer ([9],[10]); it is also is under investigation for breast cancer ([11]). Recent X-ray crystallography of abiraterone complexed with the active site of CYP17A1 shows the drug binds the haem iron in the receptor active site, forming a 60° angle above the haem plane and packing against the central I helix with the 3β-OH interacting with asparagine 202 in the F helix ([1],[3]). This conformation differs substantially from those that are predicted by homology models and from steroids in other cytochrome P450 enzymes with known structures; some features of this conformation are more similar to steroid receptors ([1]).
2.0 Method

The general objective of this study is straightforward: to computationally assess the binding energy of the active site of crystallized cytochrome p450 17A1 with abiraterone. Unless otherwise noted, all processing described in this section was performed on a Dell Inspiron 545 with an Intel Core2 Quad CPU Q8200 (clocked @ 2.33 GHz) and 8.00 GB RAM, running under the Windows Vista Home Premium (SP2) operating environment.

Protein Data Bank (PDB) 3RUK is a structural description of a crystallized cytochrome p450 17A1-bound to abiraterone. 3RUK has 4 chains, designated A-D.

3RUK was downloaded from PDB ([6]) on 30 January 2012. The ligand and receptor-active-site portions of 3RUK Chain A were extracted to separate files, one each for the ligand and the receptor, using AutoDock Tools (ADT, [2]). ADT was then used to perform the docking of the ligand to the receptor. More specifically, in ADT, approximately following the rubric documented in [4]

-- all waters, and Chains B-D of 3RUK were deleted

-- the ligand (abiraterone) and Chain A’s active-site were extracted (3RUK identifies the active site of Chain A as 7 residues: ALA113, ASN202, ILE205, ASP298, ALA302, THR306, and HEM600.)

-- the hydrogens, charges, and torsions in the ligand and active site were adjusted using ADT default recommendations and finally, the ligand, assumed to be flexible wherever that assumption is physically possible, was auto-docked to the active site, assumed to be rigid, using the Lamarckian genetic algorithm implemented in ADT.

autodock_parameter_version 4.2       # used by autodock to validate parameter set
outlev 1                             # diagnostic output level
intelec                              # calculate internal electrostatics
seed pid time                        # seeds for random generator
ligand_types A C OA HD N             # atoms types in ligand
fld 3RUK_A_active_receptor.maps.fld  # grid_data_file
map 3RUK_A_active_receptor.A.map     # atom-specific affinity map
map 3RUK_A_active_receptor.C.map     # atom-specific affinity map
map 3RUK_A_active_receptor.OA.map    # atom-specific affinity map
map 3RUK_A_active_receptor.HD.map    # atom-specific affinity map
map 3RUK_A_active_receptor.N.map     # atom-specific affinity map
elecmap 3RUK_A_active_receptor.e.map # electrostatics map
desolvmap 3RUK_A_active_receptor.d.map# desolvation map
move 3RUK_A_ligand.pdbqt             # small molecule
about 27.936 -1.9813 32.3924         # small molecule center
tran0 random                         # initial coordinates/A or random
axisangle0 random                    # initial orientation
dihe0 random                         # initial dihedrals (relative) or random
tstep 2.0                            # translation step/A
qstep 50.0                           # quaternion step/deg
dstep 50.0                           # torsion step/deg
torsdof 2                            # torsional degrees of freedom
rmstol 2.0                           # cluster_tolerance/A
extrnrg 1000.0                        # external grid energy
The minimum-energy configuration among those configurations sampled was saved. Interatomic distances between ligand and receptor in the computed form were compared to those in [3].

### 3.0 Results

The interactive problem setup, which assumes familiarity with the general CYP17A1 "landscape", took about 20 minutes in ADT; the docking proper, about 24 minutes on the platform described in Section 2.0. The platform's performance monitor suggested that the calculation was more or less uniformly distributed across the four processors at ~25% of peak per processor (with occasional bursts to 40% of peak), and required a constant 2.9 GB of memory.

Figure 2 shows the ligand/receptor energy and position summary produced by ADT for the best-fit conformation obtained under the conditions described in Figure 2.0. The estimated free energy of binding is ~6.7 kcal/mol; the estimated inhibition constant, ~13.4 microMolar at 298 K. All distances between receptor and ligand atoms in the computed ligand position lie within 10% of the distances of the corresponding atoms in 3RUK.
Figure 2. Coordinates of abiraterone generated by this study.
Figure 3 is a rendering produced in ADT of the CYP17A1/abiraterone docking described in Section 2.0.

Figure 3. AutoDock Tools (ADT,[2]) rendering of a computational docking of abiraterone (the ligand, shown in stick-and-ball form in darker grey) with molecular surface of the active site of Chain A of cytochrome p450 17A1 (shown in lighter grey), derived from PDB 3RUK ([1],[3]). The lower right end of the ligand lies directly above the center of the haem group in the active site.

4.0 Discussion

The method described in Section 2.0 and the results of Section 3.0 motivate several observations:

1. The inhibition constant computed in this study (~13.4 microMolar at ~298 K) is comparable to the inhibition constant of cancer-therapeutic ligand/receptor interactions that are clinically effective.

2. All distances between receptor and ligand atoms in the computed ligand position lie within 10% of the distances of the corresponding atoms in 3RUK. (For electrostatic forces, a 10% distance difference would correspond to a ~20% difference in electrostatic force and potential energy, in the worst case. One could of course apply other statistics to the coordinate sets and provide a more comprehensive comparison of other forces/energies. Future work will address those issues.)
3. The docking study reported here assumes that the receptor is rigid. This assumption is appropriate for the binding energy computation for PDB 3RUK per se. However, the calculation does not reflect what receptor “flexing” could contribute to the interaction of the ligand with native unliganded receptor.

4. The analysis described in Sections 2.0 and 3.0 assumes receptor is in a crystallized form. In situ, at physiologically normal temperatures (~310 K), the receptor is not in crystallized form. The ligand/receptor conformation in situ, therefore, may not be identical to their conformation in the crystallized form.

5. Minimum-energy search algorithms other than the Lamarckian genetic algorithm used in this work could be applied to this docking problem. Future work will use Monte Carlo/simulated annealing algorithms.

6. A variety of torsion and charge models could be applied to this problem, and future work will do so.

7. 3RUK has four chains, each with its own active site. The work described in this paper was performed on Chain A only. Chains B-D appear to have active sites highly similar to the Chain A active site. Future work will assess the ligand/receptor binding energies of Chains B-D.

8. CYP17A1 is a membrane-bound protein; 3RUK describes a conformation that is not bound to a membrane. The membrane-bound conformation of CYP17A1 may differ from the conformation in 3RUK.

5.0 References


