METHODS OF TREATING CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/154,699, filed April 29, 2015, U.S. Provisional Application No. 62/155,451, filed April 30, 2015, U.S. Provisional Application No. 62/252,085, filed November 6, 2015, U.S. Provisional Application No. 62/265,696, filed December 10, 2015, U.S. Provisional Application No. 62/158,469, filed May 7, 2015, U.S. Provisional Application No. 62/252,916, filed November 9, 2015, U.S. Provisional Application No. 62/265,774, filed December 10, 2015, U.S. Provisional Application No. 62/192,940, filed July 15, 2015, U.S. Provisional Application No. 62/265,658, filed December 10, 2015, U.S. Provisional Application No. 62/323,572, filed April 15, 2016, U.S. Provisional Application No. 62/192,944, filed July 15, 2015, U.S. Provisional Application No. 62/265,663, filed December 10, 2015, and U.S. Provisional Application No. 62/323,576, filed April 15, 2016, all of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] Breast cancer is divided into three subtypes based on expression of three receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her2). Overexpression of ERs is found in many breast cancer patients. ER-positive (ER+) breast cancers comprise two-thirds of all breast cancers. Other than breast cancer, estrogen and ERs are associated with, for example, ovarian cancer, colon cancer, prostate cancer and endometrial cancer.

[0003] ERs can be activated by estrogen and translocate into the nucleus to bind to DNA, thereby regulating the activity of various genes. See, e.g., Marino et al., "Estrogen Signaling Multiple Pathways to Impact Gene Transcription," *Curr. Genomics* 7(8): 497-508 (2006); and Heldring et al., "Estrogen Receptors: How Do They Signal and What Are Their Targets," *Physiol. Rev.* 87(3): 905-931 (2007).

[0004] Agents that inhibit estrogen production, such as aromatase inhibitors (AIs, e.g., letrozole, anastrozole and aromasin), or those that directly block ER activity, such as selective estrogen receptor modulators (SERMs, e.g., tamoxifen, toremifene, droloxifene, idoxifene, raloxifene, lasofoxifene, arzoxifene, miproxifene, levormeloxifene, and EM-652 (SCH 57068)) and selective estrogen receptor degraders (SERDs, e.g., fulvestrant, TAS-108 (SR16234), ZK191703, RU58668, GDC-0810 (ARN-810), GW5638/DPC974, SRN-927, ICI182782 and

[00257] Figure 24 shows the modeling of RAD1901-1R5K (a) and GW5-1R5K (b). RAD1901 bound with H-bond interactions to E353, R394, and L536; and with p-interaction with F404.

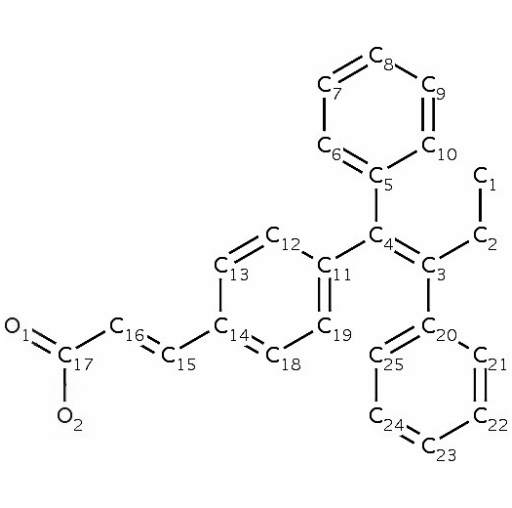
[00258] Figure 25 shows the modeling of RAD1901-1SJ0 (a) and E4D-1SJ0 (b). RAD1901 bound with H-bond interactions to E353, and D351; and with p-interaction with F404.

[00259] Figure 26 shows the modeling of RAD1901-2JFA (a) and RAL-2JFA (b). RAD1901 bound with p-interaction with F404.

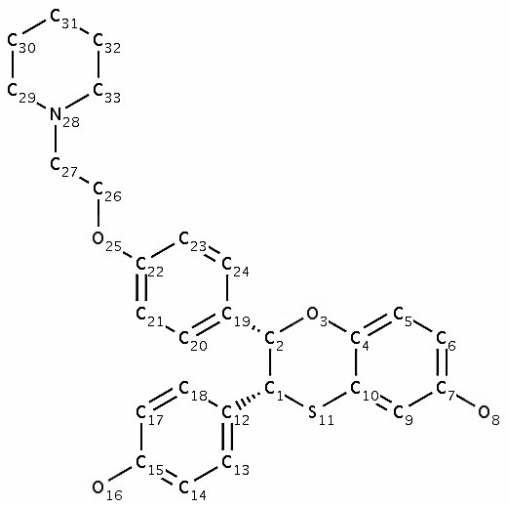
[00260] Figure 27 shows the modeling of RAD1901-2BJ4 (a) and OHT-2BJ4 (b). RAD1901 bound with H-bond interactions with E353 and R394; and p-interaction with F404.

[00261] Figure 28 shows the modeling of RAD1901-2IOK (a) and IOK-2IOK (b). RAD1901 bound with H-bond interactions with E353, R394, and D351; and p-interaction with F404.

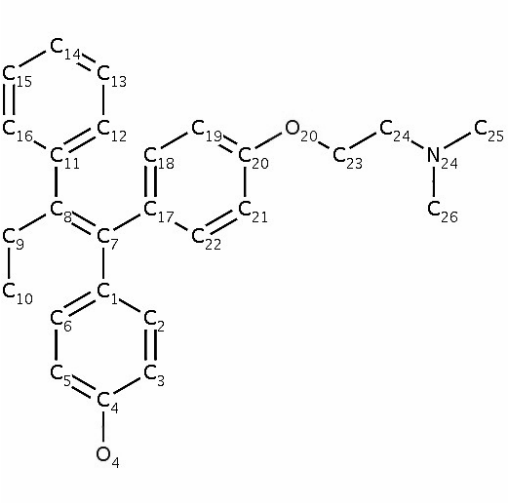
[00262] The published ligands in the models have the following structures:



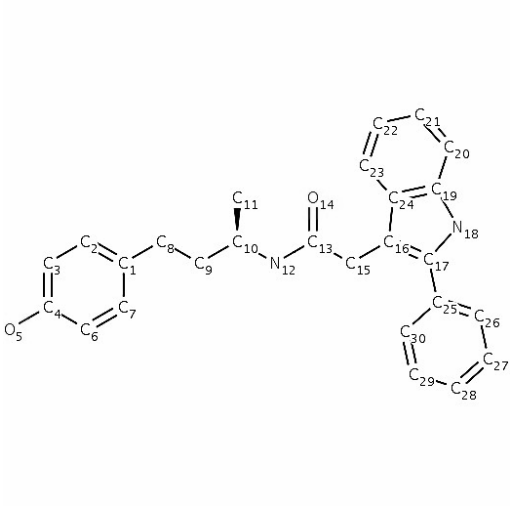
GW5, (2E)-3-{4-[(1E)-1,2-DIPHENYLBUT-1-ENYL]PHENYL}ACRYLIC ACID



E4D, (2S,3R)-2-(4-(2-(PIPERIDIN-1-YL)ETHOXY)PHENYL)-2,3-DIHYDRO-3-(4-HYDROXYPHENYL)BENZO[B][1,4]OXATHIIN-6-OL



OHT, 4-HYDROXYTAMOXIFEN



IOK, N-[(1R)-3-(4-HYDROXYPHENYL)-1-METHYLPROPYL]- 2-(2-PHENYL-1H-INDOL-3-YL)ACETAMIDE

[00263] Example V(A)-2. Induced fit docking (IFD) of ERα with RAD1901 and fulvestrant

[00264] Binding conformation of RAD1901 in ERα was further optimized by IFD analysis of the five ERα crystal structures 1R5K, 1SJ0, 2JFA, 2BJ4, and 2OUZ. IFD analysis accounted for the receptor flexibility (upon ligand binding) to accommodate its correct binding conformation.

[00265] A library of different conformations for each ligand (e.g., RAD1901 and fulvestrant) was generated by looking for a local minima as a function of rotations about rotatable bonds. The library for RAD1901 had 25 different conformations.

[00266] The five ERα crystal structures were prepared and minimized. The corresponding ligand in the published X-ray structures were used to define the ERα binding pocket.

[00267] RAD1901 conformations were docked into the prepared ERα structures wherein they were allowed to induce side-chain or back-bone movements to residues located in the binding pocket. Those movements allowed ERα to alter its binding site so that it was more closely conformed to the shape and binding mode of the RAD1901 conformation. In some examples, small backbone relaxations in the receptor structure and significant side-chain conformation changes were allowed in the IFD analysis.

[00268] An empirical scoring function was used to approximate the ligand binding free energy to provide a docking score or Gscore. Gscore is also known as GlideScore, which may be used interchangeably with docking score in this example. The docking score was an estimate of the