Molecular docking of potential inhibitors with the mTOR protein

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Abstract:
The mTOR (mammalian or mechanistic Target of Rapamycin) is linked with oral cancer. Therefore, it is of interest to study the molecular docking-based binding of paclitaxel (a FDA approved drug for oral cancer) and its analogues with mTOR. Hence, we report the binding features of 10-Deacetyltaxol, 7-Epi-10-deacetyltaxol, 7-Epi-Taxol and 6alpha-Hydroxy paclitaxel with mTOR for further consideration.

Keywords: mTOR, paclitaxel, analogues, molecular docking, oral cancer.

Background:
The mTOR (mammalian or mechanistic Target of Rapamycin) is linked with oral cancer [1-8]. Therefore, it is of interest to study the molecular docking-based binding of paclitaxel (a FDA approved drug for oral cancer) and its analogues with mTOR.

Materials and Methods
Ligand preparation
Structure of paclitaxel and its 10 analogues were downloaded from PUBCHEM database in SDF format (Table 1).

Protein Preparation
A crystal structure of mTOR (PDB ID: 4JSV) was downloaded from the Protein Data Bank (PDB).

Table 1: List of selected paclitaxel analogues

| S. No | Compound Name          |
|-------|------------------------|
| 1     | 6alpha-Hydroxy paclitaxel |
| 2     | 7-Epi-10-deacetyltaxol  |
| 3     | 7-Epi-Taxol             |
| 4     | 10-Deacetyltaxol        |
| 5     | Cabazitaxel             |
| 6     | docetaxel trihydrate    |
| 7     | Larotaxel               |
| 8     | Paclitaxel-d5          |
| 9     | Taxol C                 |
| 10    | Taxotere                |

Molecular Docking
Molecular docking analysis has been performed using the Autodock module available in PyRx Version 0.8 [9-10] and visualized by PyMOL [11].

Table 2: Molecular docking results of paclitaxel and its analogues

| S. No | Compound Name          | Binding energy kcal/mol | Hydrogen bond interaction | Distance A° |
|-------|------------------------|-------------------------|---------------------------|-------------|
| 1     | Paclitaxel             | -6.8                    | GLY-2203                  | 2           |
|       |                        |                         | ARG-2224                  | 2.3         |
|       |                        |                         | THR-2207                  | 2.5         |
|       | Selected best analogues|                         |                           |             |
| 1     | 10-Deacetyltaxol       | 6.7                     | THR-2207                  | 2.3         |
|       |                        |                         | SER-2221                  | 2.5         |
|       |                        |                         | ARG-2224                  | 2.6         |
| 2     | 7-Epi-10-deacetyltaxol | -6.6                    | SER-2221                  | 2.4         |
|       |                        |                         | ARG-2224                  | 2.1         |
|       |                        |                         | LYS-2352                  | 2.8         |
| 3     | 7-Epi-Taxol            | -5.8                    | ASP-2212                  | 2           |
|       |                        |                         | THR-2214                  | 1.7         |
| 4     | 6alpha-Hydroxy paclitaxel | -5.4                   | SER-2221                  | 2.4         |
|       |                        |                         | ARG-2224                  | 2.2         |
Figure 1: Molecular docking interaction of mTOR with (a) 10-deacetyltaxol; (b) 7-epi-10-deacetyltaxol; (c) 7-epi-taxol; (d) 6-alpha-hydroxyplacttaxel
**Results and Discussion:**

Paclitaxel and its 10 analogues were docked to the active site of mTOR and the desirable conformations of the studied ligands were identified. It is observed that the ligands were appropriately bound to the active site and in some instances has identical orientations and is equivalent to the typical drug used as control. The values of the binding energies are given in Table 2. These analogues were arranged in order based on binding energies; 10-Deacetyltauxol > 7-Epi-10-deacetyltauxol > 7-Epi-Taxol > 6alpha-Hydroxypaclitaxel. GLY-2203, THR-2207, ASP-2212, T HR-2214, SER-2221, ARG-2224, ARG-2234, LYS-2352 were the residues for hydrogen bond interactions with the ligands. This is similar to the interaction with paclitaxel. The binding energy of -6.8 kcal/mol was shown by the docked findings of Paclitaxel with mTOR protein and the three hydrogen bond interaction was formed with GLY-2203, ARG-2224 & THR-2207 amino acid residues. Of the ten analogues, 10-Deacetyltauxol, 7-Epi-10-deacetyltauxol, 7-Epi-Taxol, and 6alpha-Hydroxypaclitaxel showed comparable effects to Paclitaxel as compared with other analogues.

10-Deacetyltauxol was chosen as the best ligand docked on the active mTOR segment with a binding energy of -6.7 kcal/mol (Table 2). This docking showed that 10-Deacetyltauxol was observed to be binding on the protein in the active segment due to the formation of three hydrogen bonds with THR-2207, SER-2221, ARG-2224 at a distance of 2.3Å, 2.5Å, 2.6Å and 2.3Å respectively (Figure 1). The best compound 10-Deacetyltauxol selected also showed the very same interaction of the hydrogen bond with THR-2207, almost equivalent to Paclitaxel with ARG-2224. The results obtained from molecular docking indicate that selected active compound 10-Deacetyltauxol can inhibit the growth of the cancer cell lines by inhibiting the mTOR. Orientation, and interaction of the ligand with the mTOR protein, paclitaxel, the standard FDA-approved drug used for the treatment of oral cancer, was docked. There were some good similarities when comparing the position, orientation, and interaction of the ligand (paclitaxel) with the topmost docked ligand conformation (10-Deacetyltauxol). This study showed that all paclitaxel analogues are more effective in targeting mTOR, particularly 10-Deacetyltauxol with binding energy, than the standard drug paclitaxel.

**Conclusion:**

We report the binding features of 10-Deacetyltauxol, 7-Epi-10-deacetyltauxol, 7-Epi-Taxol and 6alpha-Hydroxypaclitaxel with mTOR for further consideration.

**Conflict of interest:** Nil

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