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MOLECULAR MODELLING STUDIES OF BINDING OF DACA DERIVATIVES INTO G-QUADRUPLEX DNA: COMPARISON OFFORCE FIELD AND QUANTUM POLARIZED LIGAND DOCKING METHODS

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ABSTRACT
The DNA G-quadruplexes are one of the targets being actively explored for anti-cancer therapy by inhibiting them through small molecules. This computational study was conducted to predict the binding strengths and orientations of a set of novel dimethyl-amino-ethyl-acridine (DACA) analogues that are well known to intercalate into the DNA structure. The crystal structure of DNA G-Quadruplex(TGGGGT, PDB ID: 1O0K) was used as target for their binding properties in our studies. We used both the force field (FF) and QM/MM derived energy of receptor-ligand complexes dramatically as a consequence to the change in atomic charges at interface by ignoring the induced polarization effects. To address this problem, several novel attempts have been aimed at using different quantum mechanics techniques for calculating the polarization ligand charges in receptor environment. Accounting for charge polarization of ligands in the receptor environment provides a platform for finding the right drug candidates from a set of putative ligands more accurately through better description of force field energy parameters. But, the usage of these charges in combination with standard force field parameters for the given geometries are expected to result in enhanced quality of drug binding pose predictions and their energies. Applications of such QM/MM combination methods have been reported in the recent literature that aim to capture the polarization effects only on the ligand charges while the receptor charges were kept unaltered. Such methods typically takes the results from molecular mechanics software as inputs for quantum mechanics packages and the results being used again in the molecular mechanics programs in a iterative manner. Such quantum polarization techniques might need intensive computational power, but it can pay off via the enhanced accuracies in predictions.

INTRODUCTION
The Guanine tetrads (G-tetrad or G-Quadruplex) are guanine rich telomeric DNA structures which adapt a locked tetrad conformation in non-dividing phase of the cell. But, these locked conformations are resolved by appropriate resolubles to form single strands of DNA during cell division, such that they could be further processed by the cell replication machinery. Cancers are characterized by uncontrolled cell replication which can be benign or malignant. Hence, the small molecules stabilizing G-Quadruplex DNAs in cancer cells are being developed as potential anti-cancer agents. Acridine-4-carboxamides (DACA) analogues are planar topoisomerase poisons that are well known to intercalate into the DNA structure. The structure of the first parallel DNA Quadruplex – Drug complex (PDB ID: 100K) was resolved by single molecule crystallography, which revealed the binding mode for three daunomycins. The drug daunomycin possesses a planar chromophore similar to that of DACA analogues, and hence a highly similar DNA binding orientation is expected for the latter. The daunomycin layers were packed tightly at one terminus of the G-Quadruplex DNA, while the daunorosine sugar moieties were placed within the negatively charged groove regions. The sugar moieties were found to have hydrophilic interactions via several H-bonds with the backbone oxygen atoms in order to stabilize the complex, while the planar chromophore surfaces had high amount of hydrophobic contacts with terminal the G-quadruplex bases through π-π stacking stabilization. One significant difference between the daunomycin and the studied acridine analogues is that the latter had more flexible and aliphatic side chains/linkers than the former. As the crystals of the acridine derivative-DNA complexes did not diffract in powerful synchrotron light source, we decided to study their binding computationally, in order to understand their molecular mechanisms and possibly improve their binding strengths in future.

The molecular mechanics force field based modeling techniques prove to be invaluable tools in biophysical studies and current drug discovery pipelines. But, their inherent inaccuracies due to high level of approximations lay limitations on their applications.

Keywords: G-Quadruplex DNA, Molecular Docking, Force Field, Quantum Mechanics, Quantum Mechanics/Molecular Mechanics Hybrid Simulations.
We addressed two main questions in this study, which are: i) What would be the possible optimal binding modes of the novel DACA analogues and a phenelene derivative (Fig. 1), which were successfully co-crystallized with G-tetrads but failed to diffract in synchrotron light, ii) Does the inclusion of induced charge polarization scheme in receptor environment lead to betterment of the docking results obtained by using fixed force field charges? In order to accomplish this, we used a uniform grid box for blind docking of drug molecules that enclosed the whole DNA. The docking study was conducted at three levels: a) Glide XP Force Field docking, b) Quantum Polarized Ligand Docking (QPLD) using Jaguar with B3LYP density functional method and LACVP basis sets, c) QPLD docking with B3LYP density function method and LACVP* basis sets. Ultimately, the results from each of these methods were compared and contrasted for obtaining useful insights.

**METHODS**

**Preparation of Receptor and Ligand Molecules for Docking**

The G-quadruplex DNA was extracted from PDB structure 1O0K and the ions and waters were removed manually. The ligand molecules were sketched in Accelrys DS viewer academic version and their structures were cleaned to remove any van der Waals clashes before being used in the docking program Glide. Several different conformations were generated for each ligand by varying the torsional degrees of freedom via Ligprep algorithm in Schrodinger suite and up to 1000 energetically low conformations were stored, which were then converted into individual ligand conformational databases. Initially, each of these conformations in the databases was docked via Glide XP algorithm using fixed point charges and the results were pipelined to single point quantum mechanics optimizations in the Jaguar module. The quantum polarized ligand charges were then obtained by fitting to the QM/MM calculation results via proprietary scripts embedded in the QPLD workflow of Schrodinger suite. The resulting polarized ligand charges were then obtained by fitting to the QM/MM calculation results via proprietary scripts embedded in the QPLD workflow of Schrodinger suite. The predictions were finally ranked based on least docking scores of drug bound DNA complexes and the results were compared.

**The Docking Methodologies**

The Glide module was used for force field docking via the XP algorithm. The Glide XP scoring function, which is a modified version of Chemscore was used to assess the binding of small molecules into DNA. The XP scoring function contains four main components that account for: i) Coulomb energy of the interacting atoms, ii) the van der Waals energy of atoms, iii) A collection of terms that favor binding interactions, and iv) A collection of terms that hinder binding interactions. The supremacy of XP over SP methodology is attributed to the inclusion of more number of terms than the SP scoring function, which leads to more accurate description of ligand binding into the receptor.

\[
\text{XP GlideScore} = E_{\text{coul}} + E_{\text{vdW}} + E_{\text{bind}} + E_{\text{penalty}}
\]

Where:

\[
E_{\text{bind}} = E_{\text{hyd_enclosure}} + E_{\text{hb_nn_motif}} + E_{\text{hb_cc_motif}} + E_{\text{PI}} + E_{\text{hb_pair}} + E_{\text{phobic_pair}}.
\]

\[
E_{\text{penalty}} = E_{\text{desolv}} + E_{\text{ligand_strain}}.
\]
Meanwhile, the quantum polarized ligand docking was performed through the QPLD workflow deployed in the Schrodinger suite, using B3LYP DFT functional with two different basis sets.

**Multi-Ligand Biomolecular Association (EMBRACE) Calculations**

The EMBRACE minimization tool deployed in the Macromodel module is used to study the association of ligands with the receptor, using simple minimizations. The energy difference mode was used to calculate the binding strengths, whereby the differences in total energies between the drug bound DNA complexes and their uncomplexed DNA were studied. The calculation is performed first on the receptor, then on the ligand, and finally on the complex, as described below:

\[
\Delta E = E_{\text{complex}} - E_{\text{ligand}} - E_{\text{protein}}.
\]

These calculations include the full effects of relaxation and solvation through an implicit solvation model.

**RESULTS**

The DNA G-tetrad surface is characterized by presence of negative charges in the central pore region formed between the guanine tetrads and in the groove regions due to backbone oxygens. Typically, the acridines stack with the terminal nucleotides via \(\pi-\pi\) interactions, while the side chains penetrate into the shallow groove regions. Hence there clearly exist high possibilities for polarization of ligand molecules, especially in the functional groups lining chromophore and side chain regions. Although the common trends exhibited by the crystallographic ligand binding poses were present in the binding modes predicted by both techniques, we found that the top ranking poses of XP docking results did not remain the same in most cases when re-docked with induced polarized charges. This is because the polarized charges obtained using quantum mechanics optimization is aimed at capturing the strengths of dipole – dipole, dipole – monopole and monopole – monopole interactions, which should remain standard in ff point charge scheme. Comparing the force field docking and QPLD docking revealed subtle differences in the electrostatic potential maps (Fig. 3) of ligands bound to DNA G-tetrad and several parameters used in Glide XP scoring function highlighted these differences.

**FF Point Charges Vs. QPLD: Comparison of Predicted Binding Orientations**

The molecular docking results revealed that agreement between fixed charges and polarized charges varied to different extents depending on the chemistry of drug molecules. Although there was some overlap in drug 3 chromophores, they did not align completely. Meanwhile, their side chains got placed in different grooves, thus revealing huge differences in their binding predictions when compared to the chromophore placement. Whereas the chromophore of drug 3 aligned nicely between the QPLD1 and QPLD2, highlighting a good consistency between these two methods. On the other hand, the binding orientations of drugs 2, 4 and 5 deviated heavily, which were further analyzed for comparing the efficiencies of different methods used in the study. The stacking interactions of DACA chromophore in ff docking seemed to be quite irrational for drugs 2 and 4, wherein the flat and hydrophobic acridine chromophore was placed away from the tetrad surface, just above the groove regions in drug 2, which led to reduction in the quantity of hydrophobic contacts between acridine and the terminal bases tremendously. Meanwhile, this binding orientation also led to a complete lack of \(\pi-\pi\) stacking interactions. The drug 4 ff docking predictions revealed quite contradicting binding orientation as the less favorable aliphatic side chains/linkers were shown to be placed above the G-tetrad surface while the big and rigid chromophores were docked into the shallow grooves. The phenaline derivative drug 5 binding orientation was also very poorly predicted as it mimicked the ff docking characteristics of drug 4 by placing the rigid hydrophobic chromophores out of the G-tetrad surface, exhibiting only partial stacking interactions.

![Fig. 2: The molecular docking poses of studied drug molecules. Color Code: Blue = XPDock, Red = QM/MM 3-21G/LACVP, Green = QM/MM 6-31G*/LACVP*](image)
FF Point Charges Vs. QPLD: Comparison of Ligand Charges via Electrostatic Potential (ESP) Surfaces

The ligand charge distributions of ff and QPLD are depicted in Fig. 3. The drugs drug 1 and drug 6 revealed few differences in charge polarization (Fig. 3), but only within their chromophores. As the charge differences were low and there were no side chains attached to the chromophore, their binding orientations also remained highly similar between ff and QPLD predicted poses. Also, there were hardly any charge polarization events seen in the ESP surfaces of drug 2 and drug 5. Meanwhile, drug 3 and drug 4 highlighted some polarization in the chromophore, terminal functional groups and linker regions. The drug 4 possesses quite positively charged connecting linker due to the presence of several amino groups. Though the polarized charge surface was not strikingly different than the ff charges, the aliphatic linker was placed across the G-tetrad, which left one of the chromophores to have less interactions at the G-Quad terminus in XP docking. But, this binding mode changed tremendously in QPLD, where the linker was docked into one of the negatively charged shallow groove region. This mode of binding has been reported several times with other similar flexible drug molecules, which is in good agreement with the predicted results of QPLD. Overall, the positive charge distributions were seen to be affected by QPLD compared to the negative charges. This could be because of the prevalent negative charge surfaces present in the central pore and groove regions of the G-tetrad.

Fig. 3: The charge surface maps of studied drug molecules. Left = Surfaces mapped on the standard FF charges, Right = Surfaces mapped on the QPLD derived charges. The differences in charge maps shows the polarization effects at the drug – receptor interfaces.
FF Point Charges Vs. QPLD: Comparison of Parameters in the Scoring Function

In order to analyze the impact of changes in the overall docking score through charge polarization by QPLD, we monitored five different parameters: “Lipo” (lipophilic contact score), “RotB” (penalty for freezing rotatable bonds), “Coul” (Coulombic energy), “CvdW” (Coulombic + van der Waal’s energy), and “Internal” (Internal energy). These parameters are included in the final scoring function of XP algorithm and hence are useful in discriminating the performance of the studied methods. Histograms comparing these values between the FF and QPLD based techniques are depicted in Fig. 4. Two of these terms, “Lipo” and “RotB” revealed relatively high variance for some drug molecules (Table 1), while the differences in other terms were either marginal or non-discriminatory in nature. However, there was a distinct observation by the QPLD charges, wherein the QPLD methods using LACVP and LACVP* basis sets were quite deviating from the FF docking terms, but they generally revealed a high level of agreement between the two QPLD methods. The drug 1 and drug 6 revealed a high “Lipo” value, which were predicted to be in positive range for the phenalinederivative drug 5. This is suggestive of loss of lipophilic interaction mediated stabilization. The drugs drug 2, drug 3, and drug 4 also revealed a similar trend, wherein the “lipo” scores were very poor and hence a poor binding profile is expected for these drug molecules. The 1st ranking binding mode orientations from the QPLD/LACVP* docking simulations were extracted and their ligand binding strengths were evaluated using the EMBRACE minimization method of Macromodel module (Table 2). Thus, the binding profiles of the studied ligands were evaluated based on their difference in potential energies between the drug unbound DNA and drug-DNA complexes. The top 3 best binding acridine derivatives, viz., drug 1, drug 6 and drug 4 were suggested for future development such that a high affinity drug-DNA complex could be formed, which possibly are amenable for X-ray diffraction in the future development programs.

![Histogram plots of various parameters used in the scoring function of the Glide docking algorithm.](image)

**Table 2: Evaluation of the binding strengths of the studied ligands using the EMBRACE biomolecular ligand association tool**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Ligand</th>
<th>$\Delta E_{\text{Total}}$</th>
<th>RMS Deviation</th>
<th>$\text{vdW}$ Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug 1</td>
<td>-182.5</td>
<td>0.05</td>
<td>-149.24</td>
</tr>
<tr>
<td>2</td>
<td>Drug 6</td>
<td>-148.9</td>
<td>0.09</td>
<td>-137.07</td>
</tr>
<tr>
<td>3</td>
<td>Drug 5</td>
<td>-133.74</td>
<td>0.05</td>
<td>-244.57</td>
</tr>
<tr>
<td>4</td>
<td>Drug 4</td>
<td>-118.81</td>
<td>0.04</td>
<td>-189.23</td>
</tr>
<tr>
<td>5</td>
<td>Drug 2</td>
<td>-106.87</td>
<td>0.05</td>
<td>-161.6</td>
</tr>
<tr>
<td>6</td>
<td>Drug 3</td>
<td>-85.25</td>
<td>0.05</td>
<td>-162.11</td>
</tr>
</tbody>
</table>

$\Delta E$ represents the energy change upon association of the drug molecule into the DNA, which is a similar measure to that of the Gibbs free energy, but obtained with a rather simple minimization. The root mean squared (RMS) deviation describes the change in ligand structure before and after EMBRACE minimization, expressed in Å. The drug molecules are finally ranked based on their $\Delta E$ values, expressed in Kcal/mol.
their predicted binding modes agreed between each other. But, the QPLD1/QPLD2 predicted orientations of studied drug molecules, few drug molecules, while they differed in the others. The correlation between the FF and QM/MM docking results were present only for the others. The correlations between the FF and QM/MM docking results were poor when there were no polarization events taking place in receptor-drug interface, and vice versa. The QPLD workflow seems to have captured at least the crucial polarization events in the drug charge surface through QM/MM SP optimization. As expected, there were some polarization events observed in the drug molecules. Especially, drugs drug 1 and drug 6 were found to be the strongest binding drugs via their docking scores and their charge surfaces looked alike. A good agreement was seen between the predicted binding poses of QPLD1 and QPLD2 because their methodological changes were limited only to the choice of basis sets. Though there are no crystal structures available for comparing the QPLD1/QPLD2 predicted orientations of studied drug molecules, their predicted binding modes agreed between each other. But, the correlation between the FF and QPLD results were present only for few drug molecules, while they differed in the others. Our results were able to shortlist three drug molecules for future applications to metalloproteins. 1. Illingworth CJR, Morris GM, Parkes KEB, Snell CR, Reynolds CA Assessing the role of polarization in docking. J PhysChem A2008;112:12157-12163.

Table 1: The values for various parameters used in the scoring function of Glide XP docking algorithm. The different QPLD methods are described as: QPLD with LACVP basis sets = QM Med, QPLD with LACVP* basis sets = QM High

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Method</th>
<th>Lipo</th>
<th>Coul</th>
<th>RotB</th>
<th>CvdW</th>
<th>Intern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1</td>
<td>XP</td>
<td>-7.27</td>
<td>-49.0</td>
<td>-25.0</td>
<td>-119.7</td>
<td>-74.0</td>
</tr>
<tr>
<td></td>
<td>QM Med</td>
<td>-4.81</td>
<td>-50.4</td>
<td>-31.9</td>
<td>-132.7</td>
<td>-82.3</td>
</tr>
<tr>
<td></td>
<td>QM High</td>
<td>-6.62</td>
<td>-47.3</td>
<td>-34.3</td>
<td>-139.9</td>
<td>-81.6</td>
</tr>
<tr>
<td>Drug 2</td>
<td>XP</td>
<td>-0.57</td>
<td>-35.1</td>
<td>-12.4</td>
<td>-69.7</td>
<td>-47.5</td>
</tr>
<tr>
<td></td>
<td>QM Med</td>
<td>-4.9</td>
<td>-45.8</td>
<td>-21.5</td>
<td>-94.1</td>
<td>-67.3</td>
</tr>
<tr>
<td></td>
<td>QM High</td>
<td>-5.63</td>
<td>-45.6</td>
<td>-23.2</td>
<td>-96.5</td>
<td>-68.9</td>
</tr>
<tr>
<td>Drug 3</td>
<td>XP</td>
<td>-2.5</td>
<td>-36.5</td>
<td>-5.0</td>
<td>-54.7</td>
<td>-41.4</td>
</tr>
<tr>
<td></td>
<td>QM Med</td>
<td>-1.28</td>
<td>-32.6</td>
<td>-20.4</td>
<td>-65.5</td>
<td>-53.0</td>
</tr>
<tr>
<td></td>
<td>QM High</td>
<td>-1.07</td>
<td>-35.9</td>
<td>-22.4</td>
<td>-77.0</td>
<td>-57.8</td>
</tr>
<tr>
<td>Drug 4</td>
<td>XP</td>
<td>-4.16</td>
<td>-43.1</td>
<td>-22.8</td>
<td>-94.2</td>
<td>-65.9</td>
</tr>
<tr>
<td></td>
<td>QM Med</td>
<td>0.53</td>
<td>-38.2</td>
<td>-44.8</td>
<td>-125.0</td>
<td>-83.0</td>
</tr>
<tr>
<td></td>
<td>QM High</td>
<td>0.37</td>
<td>-38.6</td>
<td>-44.4</td>
<td>-125.9</td>
<td>-83.0</td>
</tr>
<tr>
<td>Drug 5</td>
<td>XP</td>
<td>-2.54</td>
<td>-39</td>
<td>-4.8</td>
<td>-59.0</td>
<td>-43.9</td>
</tr>
<tr>
<td></td>
<td>QM Med</td>
<td>2.41</td>
<td>-45.3</td>
<td>-11.1</td>
<td>-75.2</td>
<td>-56.4</td>
</tr>
<tr>
<td></td>
<td>QM High</td>
<td>2.43</td>
<td>-42.0</td>
<td>-14.6</td>
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<td>-56.6</td>
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<tr>
<td>Drug 6</td>
<td>XP</td>
<td>-5.64</td>
<td>-27.4</td>
<td>-11.5</td>
<td>-49.9</td>
<td>-38.9</td>
</tr>
<tr>
<td></td>
<td>QM Med</td>
<td>-6.36</td>
<td>-28.4</td>
<td>-22.5</td>
<td>-69.9</td>
<td>-50.9</td>
</tr>
<tr>
<td></td>
<td>QM High</td>
<td>-6.13</td>
<td>-34.7</td>
<td>-16.5</td>
<td>-66.9</td>
<td>-51.3</td>
</tr>
</tbody>
</table>

CONCLUSIONS
Our results were able to shortlist three drug molecules for future optimization and also highlighted that the inclusion of receptor induced charge polarization showed a direct influence on the choice of top ranking binding poses predicted by the XP docking algorithms. As observed in drugs drug 1 and drug 6, the results were well consistent with the theory that there should be no differences in binding pose predictions between FF and QM/MM docking results when there were no polarization events taking place in receptor-drug interface, and vice versa. The QPLD workflow seems to have captured at least the crucial polarization events in the drug charge surface through QM/MM SP optimization. As expected, there were some polarization events observed in the drug molecules. Especially, drugs drug 1 and drug 6 were found to be the strongest binding drugs via their docking scores and their charge surfaces looked alike. A good agreement was seen between the predicted binding poses of QPLD1 and QPLD2 because their methodological changes were limited only to the choice of basis sets. Though there are no crystal structures available for comparing the QPLD1/QPLD2 predicted orientations of studied drug molecules, their predicted binding modes agreed between each other. But, the correlation between the FF and QPLD results were present only for few drug molecules, while they differed in the others.

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