

# *In silico* prediction of telomerase reverse transcriptase inhibitors using modified retinol for the treatment of arsenical cancer

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## Article Info

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## Abstract

Telomerase activity is expressed in the cancerous conditions which can be the target for anticancer activity by inhibiting telomerase reverse transcriptase enzyme. In this *in silico* study, retinol molecule was modified to predict the inhibitors of telomerase reverse transcriptase for the treatment of arsenical cancer. The inhibitors were predicted through molecular docking of modified retinol with telomerase reverse transcriptase. Taking into account of low binding energy and high binding affinity, two new compounds (#606 and #609) were predicted as the inhibitors of telomerase reverse transcriptase. The prediction of these two compounds was further supported by drug-likeness test through administration, distribution, metabolism, excretion and toxicity evaluation. The compounds were also compared with some of the known inhibitors of telomerase reverse transcriptase.

## Introduction

Arsenicosis develops following chronic consumption of high concentration of arsenic through drinking water.<sup>1</sup> Consumption of water contaminated with arsenic for a longer period can result in cancer of skin and other internal organs like liver, kidney, bladder, lungs, etc.<sup>2</sup> In Bangladesh, it is estimated that nearly 80 million people are affected by arsenic poisoning and one in ten has probability of developing cancer from the poisoning.<sup>3</sup>

Unfortunately, till today, there is no specific treatment for arsenical cancer. Telomerase activity is expressed in cancerous conditions including arsenical cancer.<sup>4</sup> Inhibitors of telomerase reverse transcriptase enzyme may be presumed to be effective in arsenical cancer. Identification of such a molecule can be predicted from molecular docking since docking process is used to understand the drug-receptor interaction and now-a-days plays an important role in modern drug designing.

This study was aimed for the prediction of inhibitors of telomerase reverse transcriptase as specific molecules for the treatment of arsenical cancer through computer simulation. Inhibitors of telomerase reverse transcriptase enzyme were predicted from modified retinol molecule through molecular docking and virtual screening.

## Materials and Methods

This *in silico* study was done using different software like AutoDock 4, AutoDock Vina, Discovery Studio,<sup>5</sup> Marvin Sketch and FAF-Drug3. The main work consists of the molecular docking of modified retinol molecule with telomerase reverse transcriptase and analyzing the docking results in terms of binding energy.

### Downloading the structures of retinol and telomerase reverse transcriptase

Both the retinol molecule and telomerase reverse transcriptase were downloaded from the worldwide protein data bank website (<http://www.rcsb.org/pdb/home/home.do>) and purified from other heterogeneous structures to get the pure structure of retinol and telomerase reverse transcriptase. Discovery Studio software was used for the purification of the structures.

### Modification of retinol molecule as new ligand

Retinol molecule was modified in its structure by adding, deleting and substituting different atoms in its structure and by adding different functional groups to its structure for the molecular docking of modified retinol with telomerase reverse transcriptase. The modification of retinol structure was done in Discovery Studio.



### Molecular Docking

Docking process was done in AutoDock<sup>6</sup> and AutoDock Vina.<sup>7</sup> Modified retinol molecules were docked with the telomerase reverse transcriptase structure in AutoDock Vina and the binding energies were recorded. The modified compound with least binding energy was further docked in AutoDock 4 to view the molecular interaction.

### Naming of modified compounds

All the new compounds from retinol were named as per International Union of Pure and Applied Chemistry (IUPAC) naming system. MarvinSketch, a Java based chemical drawing tool, was used for naming of the molecules.

### Drug-likeness evaluation

The selected compounds with least binding energy after molecular docking were evaluated for ADMETox (Absorption, Distribution, Metabolism, Excretion and Toxicity) concerning the drug-likeness properties through FAF-Drug3 web server.<sup>8</sup>

### Comparison with known telomerase reverse transcriptase inhibitors

Molecular docking of some known inhibitors of telomerase reverse transcriptase was done with the telomerase reverse transcriptase and the binding

energies were compared with the binding energy of predicted new compounds from this study.

## Results

Retinol molecule was structurally modified into 400 different structures by deleting/shortening side chain and adding ethyl, methyl, imidazolyl, acetyl, amino, thiol group. Fourteen chemical compounds showed binding energy of less than -5.0 kcal/mol with telomerase reverse transcriptase. Further modification of these 14 compounds by adding different functional groups resulted in the formation of another 420 compounds. Analyzing the binding energy of 420 new compounds with telomerase reverse transcriptase, two compounds (#606 and #609) were found to have the minimum binding energy (-7.8 kcal/mol). The chemical structure of these two compounds is shown in Figure 1.

IUPAC name was assigned to all the compounds. Compound #606 with IUPAC name 21,22,23,24-tetraazapentacyclo[16.2.1.1<sup>3,6</sup>.1<sup>8,11</sup>.1<sup>13,16</sup>]tetracos-1,3,5,7,9,11(23),12,14,16,18(21),19-undecaene; 3,4,5-trihydroxybenzaldehyde; 3,7-dimethyl-9-(2,6,6-trimethylcyclohexa-1,4-dien-1-yl)nonan-1-ol and compound #609 with IUPAC name 21,22,23,24-tetraazapentacyclo[16.2.1.1<sup>3,6</sup>.1<sup>8,11</sup>.1<sup>13,16</sup>]tetracos-1,3,5,7,9,11(23),12,14,16,18(21),19-undecaene; 3,7-dimethyl-9-(2,6,6-trimethylcyclohexa-1,4-dien-1-yl)nonan-1-ol; 3-hydroxybenzaldehyde were predicted as the inhibitors of telomerase reverse transcriptase since both the compounds had less binding energy of -7.8 kcal/mol each.

Molecular interaction between the selected compounds and telomerase reverse transcriptase was viewed in AutoDock4. Compound 606 and 609

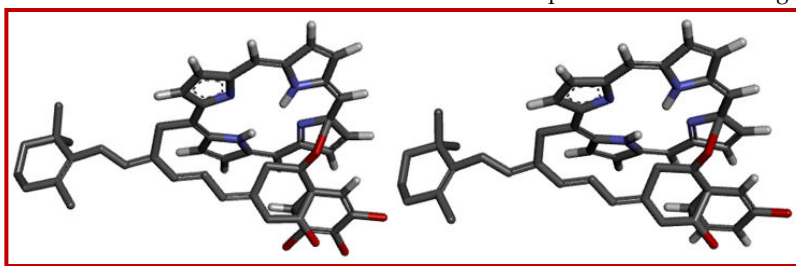


Figure 1: Chemical structure of compound 606 (left) and compound 609 (right)

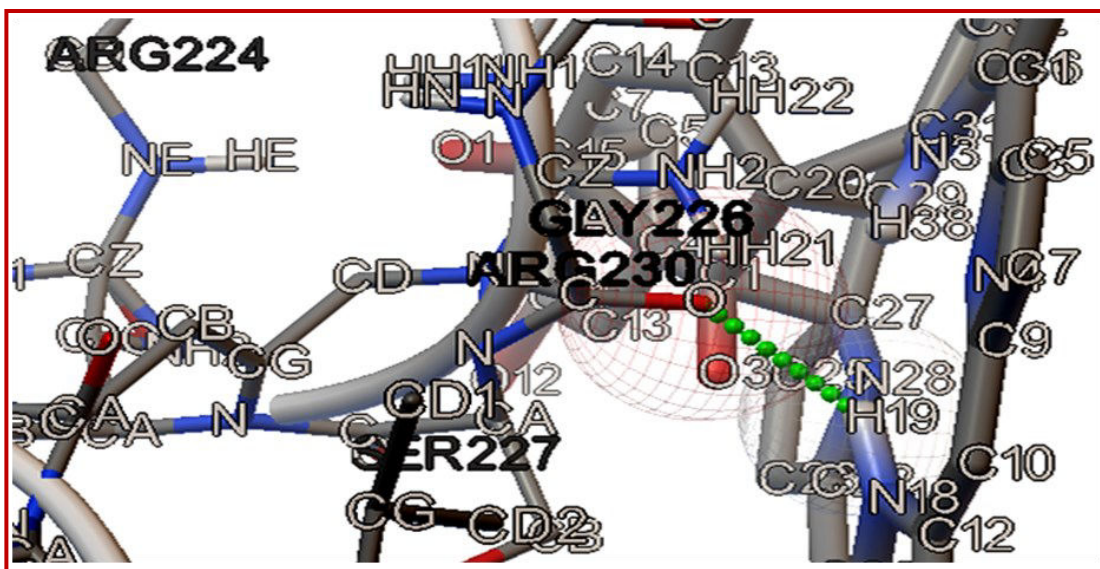


Figure 2: Interaction of compound 606 with telomerase reverse transcriptase (H-bond shown by green spheres)

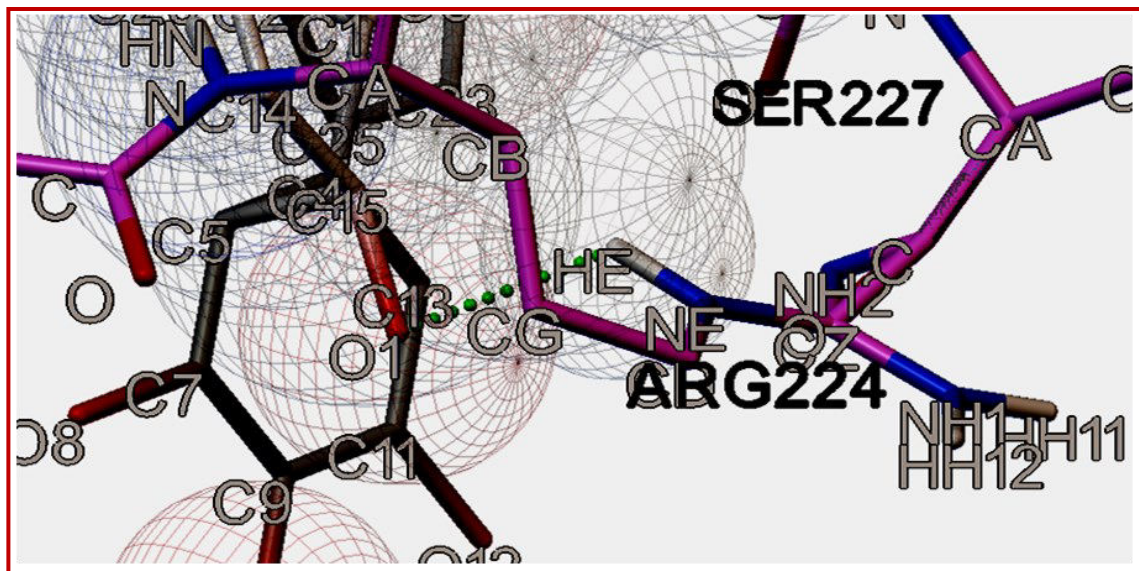


Figure 3: Interaction of compound 609 with telomerase reverse transcriptase (H-bond shown by green spheres)

Table I	
Binding energy of some known inhibitors, compound #606 and #609 with telomerase reverse transcriptase protein	
Compounds	Binding energy (kcal/mol)
Alterperyleneol	-5.0
Boldine	-5.7
Crocin	-5.3
Curcumin	-4.6
Dideoxyguanosine triphosphate	-3.7
Dimethyl sulfoxide	-2.1
Epigallocatechin	-4.7
Genistein	-4.5
Harmine	-4.8
Helenalin	-5.5
Helenin	-4.9
Isoprenoid	-4.0
Levofloxacin	-4.8
Ofloxacin	-4.7
Pristimerin	-0.7
Tanshinone	-6.1
Tretinoin	-4.7
Tocotrienol	-3.4
Triethylene tetraamine	-2.6
Zidovudine	-4.1
Compound 214	-7.5
Compound 606	-7.8
Compound 609	-7.8

interacted with telomerase reverse transcriptase protein by forming hydrogen bond between the atoms of the compounds and the atoms of the amino acids in telomerase reverse transcriptase protein. Compound 606 interacted with the enzyme by hydrogen bond between the H19 (hydrogen number 19) atom in porphyrin ring and O (oxygen) atom of the amino acid ARG230 (arginine number 230) of telomerase reverse transcriptase (Figure 2). The amino acids sequence number in telomerase reverse transcriptase was labeled as per the sequence number in that of the downloaded 4B18 protein, the crystal structure of human importin alpha 5 with telomerase reverse transcriptase NLS peptide.

Compound 609 interacted with the telomerase reverse transcriptase protein by hydrogen bond between O1 (oxygen number 1) atom and HE (epsilon hydrogen) atom of the amino acid ARG224 (arginine number 224) of telomerase reverse transcriptase (Figure 3). The amino acid sequence number mentioned here was as per the sequence number in the downloaded 4B18 protein, the crystal structure of human importin alpha 5 with telomerase reverse transcriptase NLS peptide.

These two compounds were selected and predicted as the potential inhibitors which were further supported by the accepting the drug-

likeness test through ADMETox evaluation and by having the minimum binding energy with telomerase reverse transcriptase when compared with some of the known inhibitors of telomerase reverse transcriptase (Table I).

## Discussion

In this study, two compounds were synthesized from retinol *in silico* using different software those have inhibitory function on telomerase reverse transcriptase. These compounds were accepted through ADMETox evaluation. Compound 606 and 609 chemically composed of modified retinol molecule with added side chains of porphyrin and benzoyl rings with five oxygen atoms in compound 606 and three oxygen atoms in compound 609.

No study has been done to predict new compounds as the inhibitors of telomerase reverse transcriptase for use in the treatment of arsenical cancer by modification of retinol molecule through molecular docking.

Retinol was used as a lead compound. Retinol, like  $\alpha$ -tocopherol, is usually suggested with other antioxidant vitamins and minerals for the treatment of arsenical keratosis (non-malignant skin lesion). Previous study from this department had used  $\alpha$ -tocopherol as lead compound and identified one compound (#214).<sup>2</sup>

Acyclic retinoid induces partial differentiation, down-regulates telomerase reverse transcriptase mRNA expression and telomerase activity, and induces apoptosis in human hepatoma-derived cell lines.<sup>10</sup>

Studies were done for different inhibitors of telomerase reverse transcriptase in other disease



conditions like boldine,<sup>11</sup> crocin,<sup>12</sup> dimethyl sulfoxide,<sup>13</sup> harmine,<sup>14</sup> helenalin,<sup>15</sup> pristimerin,<sup>16</sup> tanshinone,<sup>17</sup> triethylene tetraamine,<sup>18</sup> and tocotrienol.<sup>19</sup> Regarding the use of vitamin A in cancer, vitamin A has shown to prevent squamous cell carcinoma of skin significantly<sup>20</sup> and all-trans retinoic acid has shown complete remission of acute promyelocytic leukemia with daily supplementation of 25,000 IU in 95% of patients in study group.<sup>21</sup>

The present authors compare the inhibitory effects of compound #606, #609 with 21 other inhibitors of telomerase reverse transcriptase using molecular docking. It is apparent that compound #606 and #609 are the most effective drugs. Even these are more potent than compound #214 as inhibitor of telomerase reverse transcriptase. These three compounds have similarities in having the porphyrin ring in their chemical structure. It can be assumed that porphyrin ring can be the functional group which facilitates the interaction of the new compounds with telomerase reverse transcriptase protein in regard to higher binding affinity and lower binding energy.

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## Conclusion

Two compounds (#606 and #609) are identified from retinol using *in silico* study which have potent inhibitor effect against telomerase reverse transcriptase. Future studies on the synthesis of these compound and their effectiveness in wet lab will confirm the present findings.

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