INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
DOI:10.22192/ijcrcps Coden: IJCROO(USA) Volume 4, Issue 4 - 2017

Research Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2017.04.04.003

Molecular docking studies on the DNA binding interactions, thioredoxinreductase and glutathione reductase of Alkynyl(triphenylphosphine) gold(I) complexes

Arsalan Alamdarloo*[1], Elaheh Lotfi[1], Motahareh Fakhri[1], Masood Fereidoonnezhad[1]

Department of Medicinal Chemistry, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

*Corresponding author. Tel.: +98 61 32425305; Fax: +98 61 32424126;
E-mail: arsalanalamdarloo@gmail.com

Abstract

Gold complexes as a new class of non-platinum antitumor drugs with prominent cytotoxic activities are presently being evaluated as potential anticancer agents.It was observed that the gold anticancer mechanism of action are through different pathways such as inhibition of the thioredoxinreductase (TrxR), selenium-glutathione peroxidase and gluthationereductase (GR) enzymes as well as intercalation with the DNA base pairs. Here, Molecular docking studies of Alkynyl(triphenylphosphine)gold(I) complexes, as novel anticancer gold(I) compounds were performed on three targets including TrxR, GR and DNA by means of AutoDock 4.2 to acquire the detailed molecular binding modes and binding sites for these compounds tothe above targets. The docking results indicated that the important amino acids inside the active site of the cavity that are responsible for essential interactions are Ile A52, Glu A54 and Arg B25 for TrxR andArg37, and Asn117 for GR receptors. A5, G4, G10 and C11 are among the most base pairs that involved in the interaction of these compounds to the DNA.

Keywords: Gold complexes, cytotoxic activities, Molecular docking.

Introduction

Platinum-based drugs have become a mainstay of cancer therapy(1-3). However, the platinum based treatment of tumoral diseases is immensely impeded by severe side effects and resistance development(4, 5). Among the non-platinum antitumor drugs, gold complexes are emerging as a new class of metal complexes with outstanding cytotoxic properties and are presently being evaluated as potential antitumor agents(6-8).

The antiproliferative mechanism of action of gold complexes had been under investigation for a long time. It was observed that many of the gold complexes inhibit the thioredoxinreductase (TrxR) enzyme with high specificity and potency and this target is the biological main target of gold complexes(9, 10).

The thioredoxin/thioredoxinreductase system (Trx/TrxR) which comprised of Trx, TrxR and NADPH, is an attractive drug target because of its involvement in various important physiological processes, containing DNA synthesis, antioxidant properties, redox homeostasis and regulating cellular viability and function. Hence, due to great relevance of TrxR for the

proliferation of tumor tissues, its inhibition is great importance in developing anticancer agents(10-12).

It should be mentioned that some gold complexes such as the gold phosphole complex GoPI or several gold(III) complexes interact with the DNA as their targets(13, 14).

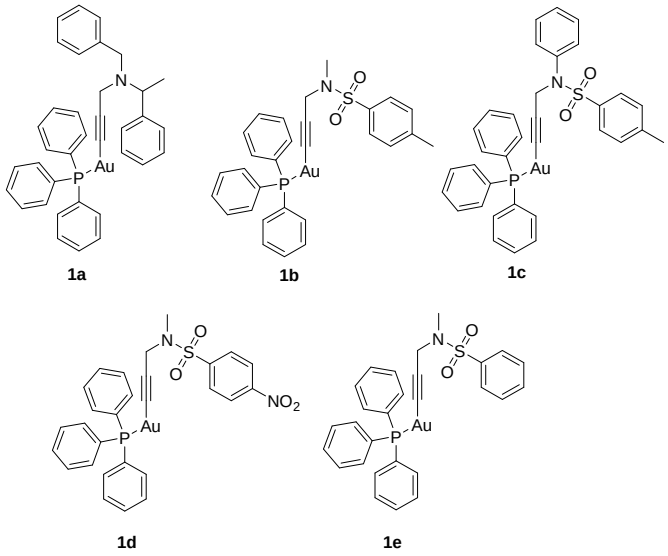
The inhibition of selenium-glutathione peroxidase and gluthationereductase (GR)was also reported for some gold complexes such asauranofin, and aurothioglucose(7, 15). However these targets are more important for gold agents in the treatment of rheumatoid arthritis.

Recently, a class of Alkynyl(triphenylphosphine)gold(I) complexes has been synthesized and fully characterized by De Nisi, Assunta, et al. (16). Anticancer activity of these compounds were also investigated and it was concluded that their antiproliferative activity of them could be related to distinct mechanisms of action through different biological targets.

In the present paper, Molecular docking studies of Alkynyl(triphenylphosphine)gold(I) complexes, were performed on three targets including TrxRs, GR and DNA by means of AutoDock 4.2 to find out the detailed molecular binding modes and binding sites for these compounds interacting with the key residues of their targets.

Materials and Methods

Data set: A data set consisting of five Alkynyl(triphenylphosphine)gold(I) complexes as a series of potent antiproliferative agents were selected for the molecular docking study. The structural features of these compounds are shown in Scheme 1.



Scheme 1. Chemical structure of Alkynyl(triphenylphosphine) gold(I) complexes used in molecular docking study

Docking procedure: Two dimensional structures of all complexes were constructed using ChemBioDraw12.0 software(17). Each complexes was optimized by molecular mechanic methods (MM^+) using HyperChem 8(Version 8, Hypercube Inc., Gainesville, FL, USA), and then energy minimization calculations at Hartree-Fock (HF) level, using Gaussian 09. The output structures were thereafter converted to PDBQT using MGLtools 1.5.6.

The three dimensional crystal structure of DNA (PDB ID: 1BNA), TrxR(PDB ID: 4CBQ) and gluthationereductase (PDB ID: 1BWC) were retrieved from protein data bank (http://www.rcsb.org/pdb/home/home.do). All water molecules were removed, missing hydrogens were added and after determining the Kollman united atom charges non-polar hydrogens were merged into their corresponding carbons using AutoDock Tools(18). As the final part of this process, desolvation parameters were assigned to each protein atom. Among the three different search algorithms performed by AutoDock 4.2 the commonly used Lamarckian Genetic Algorithm (LGA) was applied(19, 20). Subsequently, the enzymes and DNA were converted to PDBQT using MGLTOOLS 1.5.6.

The docking studies were carried out by means of an *in house* batch script (DOCKFACE)(21, 22)of AutoDock 4.2.For Lamarckian GA, a maximum number of 2,500,000 energy evaluations, 27000 maximum generations; 150 population size, a gene mutation rate of 0.02; and a crossover rate of 0.8 were applied. The grid maps of the receptors were calculated using AutoGrid tools of AutoDock 4.2. The size of grid was set in a way to include not only the active site but also considerable portions of the encircling surface. A grid box of 54×56×100,

50×50×50 and 50×50×50 points in x, y, and z directions was built and centered on the center of the ligand in the complex with a spacing of 0.375 Å for 1BNA, 4CBQ and 1BWC, respectively. Number of points for 1BNA in x, y and z was 14.719, 20.979 and 8.824, and for 4CBQ was 1.212, 0.263 and -0.383, and for 1BWC was 23.221, 63.866 and 20.642, consequently. AutoDock Tools was employed to produce both grid and docking parameter files i.e. gpf and dpf. Parameters for docking with metal ions such as gold, used in the docking calculation were added to gpf and dpf files.

Cluster analysis was performed on the docked results using a root mean square deviation (RMSD) tolerance of 2 Å. For the internal validation phase, co-crystal ligand (auranofin) inside the pdb file of TrxR (4CBQ) was extracted using a viewer and treated the same as other ligands. All the docking protocols were done on validated structures with RMSD values below 2 Å.

Ligand-receptor interactions were all detected on the basis of docking results using Autodock tools program (ADT, Version 1.5.6), VMD software(23), and PyMOL molecular graphics program(24).

All calculations were run on a core i7 personal computer (CPU at 8 MB) with Windows 7 operating system. With respect to the AutoDock scoring function, the lowest docking binding energy conformation was chosen as the best binding mode.

Results and Discussion

Here, molecular docking studies were performed on the Au(I) complexes to find their binding site, binding modes and the best direction on the base of their binding energy to DNA, TrxR and GR. The results obtained from this part of study including the estimated free binding energy values (ΔG_{bind}) for the best position of the docked compounds, expressed in $kcalmol^{-1}$(Top ranked binding energies (kcal/mol) in AutoDockdlg output file were considered as response in each run), along with the corresponding favorable interactions with the key amino acid residues at the active site of enzymes and the base pairs of DNA are summarized in Table 1 and figures 1-3.

Table 1. Thedocking binding energies of compounds **1a-e** on DNA, TrxR and GR as well as their biological activities.

Name	ΔE[a] (kcal/mol)			Exp. IC_{50} (μM)[b]		%TrxRinhibition[b,c]
	DNA	TrxR	GR[d]	IGROV1[e]	HL60[f]	
1a	-7.14	-7.49	-7.34	20	19	33
1b	-9.97	-6.86	-9.16	5.3	3.3	-
1c	-9.42	-7.12	-8.97	5.5	2.7	ND[g]
1d	-8.69	-8.31	-8.13	6.5	6.3	55
1e	-8.21	-8.62	-7.86	10	9	52

[a] docking binding energy
[b]Data was extracted from De Nisi , et al. article (16).
[c]The inhibitory effect on TrxR is expressed as % of inhibition taking as reference the auranofin maximal inhibition (100%)
[d]Gluthationereductase
[e] human ovarian adenocarcinoma line
[f] human Caucasian promyelocytic leukemia
[g] Not determined

The ΔG_{bind} values of the best docked poses of compounds **1a-1e**are within the range of -7.14 to -9.97 $kcal.mol^{-1}$ for DNA, -6.86 to -8.62 $kcal.mol^{-1}$ for TrxR and -7.34 to -9.16 $kcal.mol^{-1}$ forglutathione reductase.

As it was shown in table 1, complex **1b**has the greatest binding energy on DNA andglutathione reductase, whereasit has the lowest binding energy on TrxR.These data is in good accordance with biological activity which showed that **1b**couldn't be considered as an inhibitor of this class of enzymes.

The results of molecular docking simulations on DNA and GR targets were highly in accordance with experimental cytotoxic data on cancerous cell lines (Table 1).

Docking validation step was done by re-docking of the co-crystallized conformation of ligands into 3D structure of TrxR ((auranofin is the co-crystal ligand inside the pdb file of TrxR (4CBQ)). Generally, if the root mean square deviation (RMSD) is below 2 A°, it is considered a successful prediction. All the docking protocols were done on validated structures with RMSD values below 2 Å. With respect to the negativity values of the binding free energy, it can be deduced that these complexes reasonably bind to the these targets.

The docked model suggests that the most desirable conformation of the docked pose of **1b**from energetically point of viewinteracts with the minor groove of 1BNA (figure. 1). It interacts via one of the phenyl group of its triphenylphosphine (PPh_3) moiety with G10 through arene-H binding interaction. thiol group with G4 and phenylpyridine moiety with C3 base pairs in the minor groove of DNA.The oxygen atoms of its sulfonamide moiety are involved in acceptor-type hydrogen bond with G4 and A5 base pairs. A weak interaction between methyl attached to the nitrogen with C11 was also observed (figure. 1).

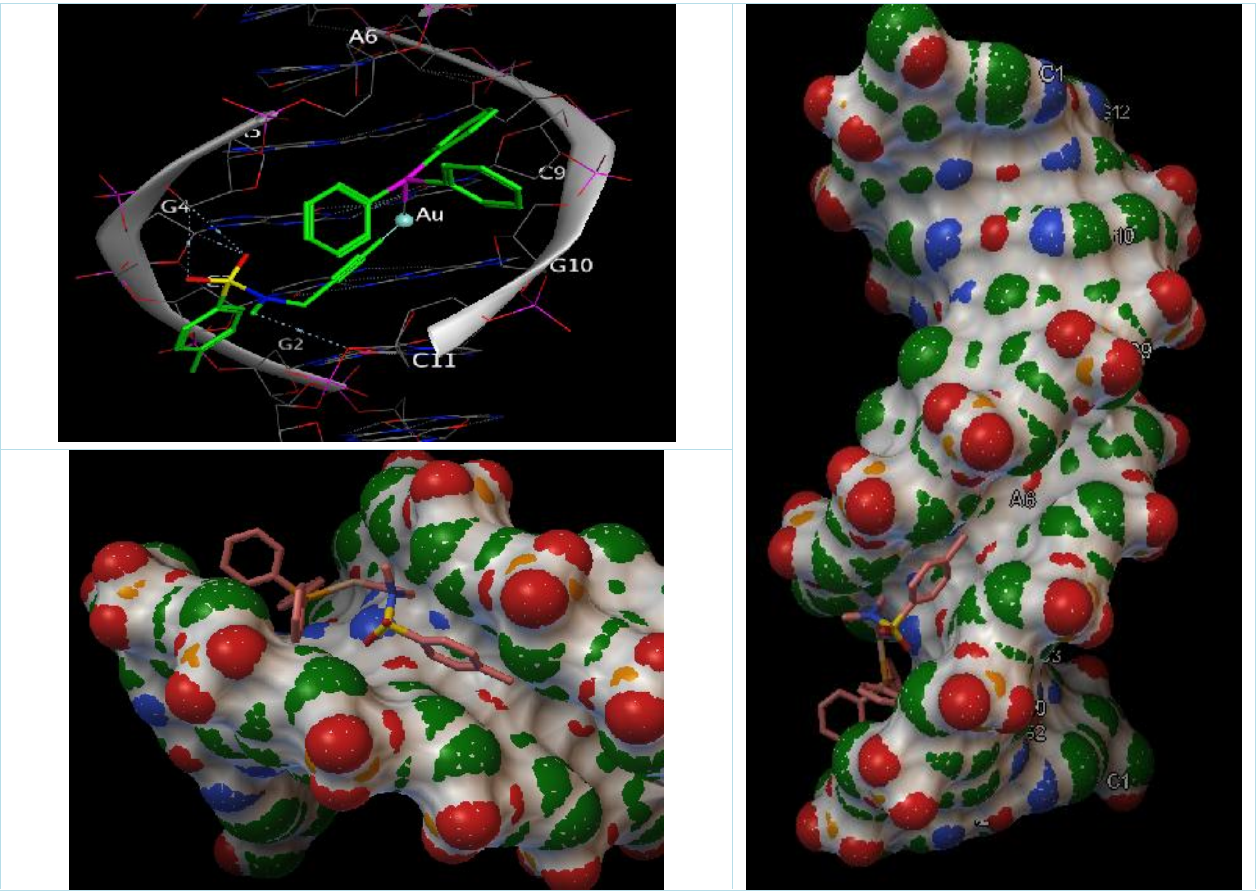


Figure 1. Molecular docking simulation studies of the interaction between **1b** and DNA (PDB ID: 1BNA)

Binding mode of compound **1b** with TrxR (figure 2) shows that oxygen group of its sulfonamideare involved in acceptor hydrogen bond with Glu A54 amino acid. An arene-hydrogen interaction between the phenyl of phenylsulfonamide moiety and residue Ile A52 was observed. It is also interact via its sulfonamide nitrogen with residue Arg B25. The methyl attached to the nitrogen is in the interaction with Glu A54.

As indicated in figure 3, the oxygen atomsofsulfonamide are involved in hydrogen bond interactions with Arg37. The phenylring attached to the sulfonamide group, is involved in interactions with Asn117 amino acid.

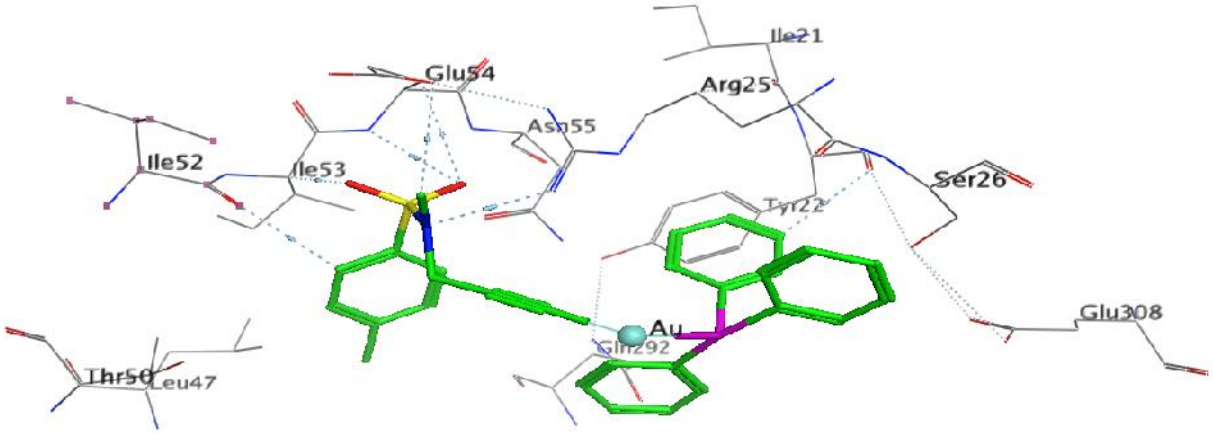


Figure 2. The structure of **1b** surrounded by the key residues in the active site of TrxR enzyme (PDB ID: 4CBQ).

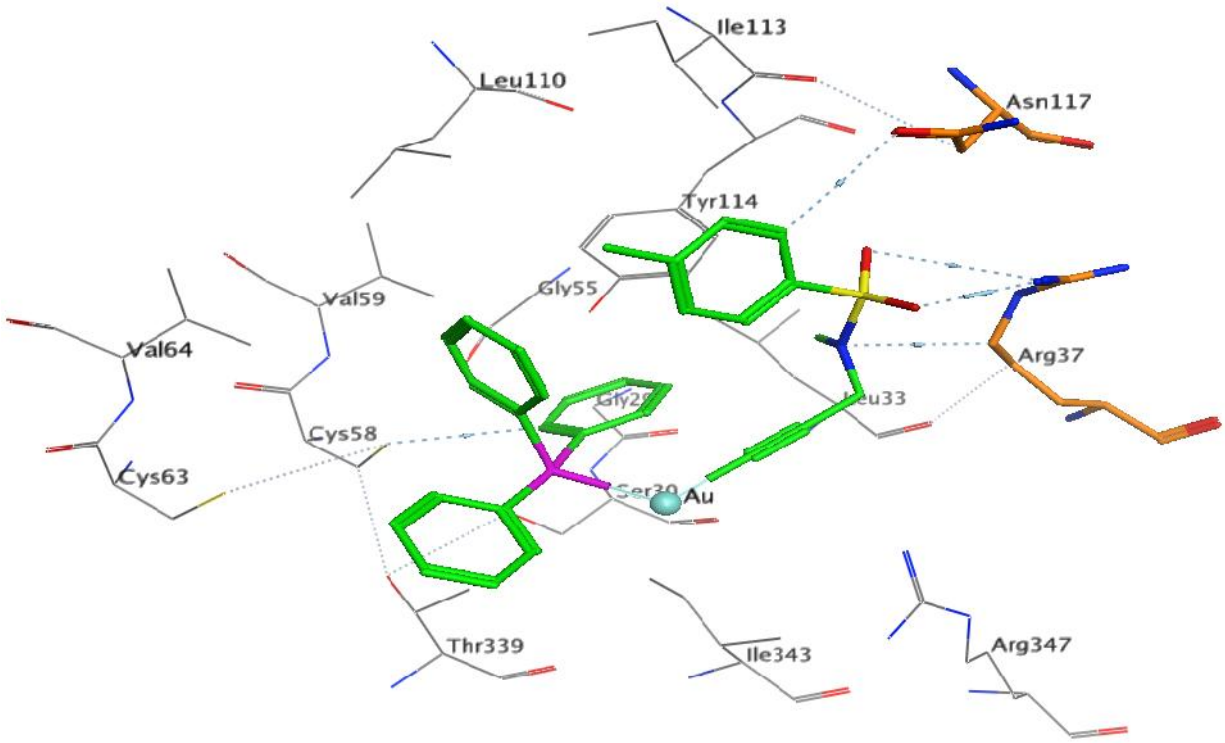


Figure 3. The structure of **1b** surrounded by the key residues in the active site of TrxR enzyme (PDB ID: 4CBQ).

Conclusion

Gold complexes are a new class of non-platinum anticancer agents with outstanding cytotoxic activities. Inhibition of the thioredoxinreductase (TrxR), selenium-glutathione peroxidase and gluthatione reductase (GR) enzymes as well as intercalation with the DNA base pairs are among the most accepted mechanism of action of gold anticancer agents.

In this paper, to obtain the detailed molecular binding modes and binding sites for goldanticancer agents, novel anticancer gold(I) compounds, Alkynyl(triphenylphosphine)gold(I) complexes,were subjected to molecular docking studies on three targets including TrxR, GR and DNA by means of AutoDock 4.2. The docking results indicated that the important amino acids inside the active site of the cavity that are responsible for essential interactions are Ile A52, Glu A54 and Arg B25 for TrxR andArg37, and Asn117 for GR receptors. A5, G4, G10 and C11 are among the most base pairs that involved in the interaction of these compounds to the DNA.

As an overall result these studies suggest that in addition to inhibition of TrxR and GR, the interaction with various biomolecules such as DNA seems to be important for the pharmacology of anticancer gold complexes.

Acknowledgments

The authors would like to thank research deputy Ahvaz Jundishapur University of medical sciences who support this work. Collaboration of medicinal chemistry, faculty of pharmacy, Ahvaz Jundishapur University of Medical Sciences, in providing the required facilities for this work is greatly acknowledged.

References

1. Alexander C, Nithyakumar A, Samy NA. Platinum (II) complexes of imidazophenanthroline-based polypyridine ligands as potential anticancer agents: Syntheses, characterization, and in vitro cytotoxicity studies. Inorganic Chemistry Communications. 2017;78:17-20.
2. Fereidoonnezhad M, Niazi M, Shahmohammadi Beni M, Mohammadi S, Faghih Z, Faghih Z, et al. Synthesis, Biological Evaluation, and Molecular Docking Studies on the DNA Binding Interactions of Platinum (II) Rollover Complexes Containing Phosphorus Donor Ligands. ChemMedChem. 2017;12(6):456-65.
3. Pollak D, Goddard R, Pörschke K-R. Synthesis and Structures of 9-Oxabispidine Analogues of Cisplatin, Carboplatin, and Oxaliplatin. Inorganic Chemistry. 2016;55(18):9424-35.
4. Fong CW. Molecular Mechanisms of Cellular Transport, Resistance and Cytotoxic Side Effects of Platinum and Adjuvant Anti-cancer Drugs–A Molecular Orbital Study. Frontiers in Computational Chemistry: Volume: 3. 2017;3:185.
5. Santabarbara G, Maione P, Rossi A, Gridelli C. Pharmacotherapeutic options for treating adverse effects of Cisplatin chemotherapy. Expert Opinion on Pharmacotherapy. 2016;17(4):561-70.
6. Messori L, Marcon G, Orioli P. Gold(III) Compounds as New Family of Anticancer Drugs. Bioinorganic Chemistry and Applications. 2003;1(2):177-87.
7. Ott I. On the medicinal chemistry of gold complexes as anticancer drugs. Coordination Chemistry Reviews. 2009;253(11):1670-81.
8. Varol M. The importance of metal-based drugs in medicinal inorganic chemistry to improve life quality of patients. Journal of Applied Pharmacy. 2016;8(1):1-2.
9. Casini A, Gabbiani C, Sorrentino F, Rigobello MP, Bindoli A, Geldbach TJ, et al. Emerging protein targets for anticancer metallodrugs: inhibition of thioredoxin reductase and cathepsin B by antitumor ruthenium (II)-arene compounds. J Med Chem. 2008;51(21):6773-81.
10. Schmidt EE, Arnér ES. Thioredoxin Reductase 1 as an Anticancer Drug Target. Selenium: Springer; 2016. p. 199-209.
11. Garcia A, Machado RC, Grazul RM, Lopes MTP, Corrêa CC, Dos Santos HF, et al. Novel antitumor adamantane–azole gold (I) complexes as potential inhibitors of thioredoxin reductase. JBIC Journal of Biological Inorganic Chemistry. 2016;21(2):275-92.
12. Sweeney NL, Lipker L, Hanson AM, Bohl CJ, Engel KE, Kalous KS, et al. Docking into Mycobacterium tuberculosis Thioredoxin Reductase Protein Yields Pyrazolone Lead Molecules for Methicillin-Resistant Staphylococcus aureus. Antibiotics. 2017;6(1):4.
13. Messori L, Orioli P, Tempi C, Marcon G. Interactions of selected gold (III) complexes with calf thymus DNA. Biochemical and biophysical research communications. 2001;281(2):352-60.
14. Urig S, Fritz-Wolf K, Réau R, Herold-Mende C, Tóth K, Davioud-Charvet E, et al. Undressing of phosphine gold (I) complexes as irreversible inhibitors of human disulfide reductases. Angewandte Chemie International Edition. 2006;45(12):1881-6.
15. Roberts JR, Shaw CF. Inhibition of erythrocyte selenium-glutathione peroxidase by auranofin analogues and metabolites. Biochemical pharmacology. 1998;55(8):1291-9.
16. De Nisi A, Bergamini C, Leonzio M, Sartor G, Fato R, Naldi M, et al. Synthesis, cytotoxicity and anti-cancer activity of new alkynyl-gold (I) complexes. Dalton Transactions. 2016;45(4):1546-53.
17. Ultra C. 12.0, Cambridge Soft, Cambridge, MA 2010. Received: May. 2013;10.
18. Weiner SJ, Kollman PA, Case DA, Singh UC, Ghio C, Alagona G, et al. A new force field for molecular mechanical simulation of nucleic acids and proteins. Journal of the American Chemical Society. 1984;106(3):765-84.
19. Morris GM, Goodsell DS, Halliday RS, Huey R, Hart WE, Belew RK, et al. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of computational chemistry. 1998;19(14):1639-62.
20. Hamedi A, Khoshnoud MJ, Tanideh N, Abbasi F, Fereidoonnezhad M, Mehrabani D. Reproductive toxicity of Cassia absus seeds in female rats: possible progesteronic properties of chaksine and b-sitosterol. Pharmaceutical Chemistry Journal. 2015;49(4):268-74.
21. Fereidoonnezhad M, Faghih Z, Mojaddami A, Sakhteman A, Rezaei Z. A Comparative Docking Studies of Dichloroacetate Analogues on Four Isozymes of Pyruvate Dehydrogenase Kinase in Humans. Indian J Pharm Edu Res. 2016;50(2s):S32-S8.
22. Zare S, Fereidoonnezhad M, Afshar D, Ramezani Z. A comparative QSAR analysis and molecular docking studies of phenyl piperidine derivatives as potent dual NK 1 R antagonists/serotonin transporter (SERT) inhibitors. Computational Biology and Chemistry. 2017;67:22-37.

23. Humphrey W, Dalke A, Schulten K. VMD: visual molecular dynamics. Journal of molecular graphics. 1996;14(1):33-8, 27-8.
24.. DeLano WL. PyMOL. DeLano Scientific, San Carlos, CA. 2002; 700.

Access this Article in Online

Website: www.ijcrcps.com

Subject: Medicinal Chemistry

Quick Response Code

DOI: 10.22192/ijcrcps.2017.04.04.003

How to cite this article:
Arsalan Alamdarloo, Elaheh Lotfi, Motahareh Fakhri, Masood Fereidoonnezhad. (2017). Molecular docking studies on the DNA binding interactions, thioredoxinreductase and glutathione reductase of Alkynyl(triphenylphosphine) gold(I) complexes.. Int. J. Curr. Res. Chem. Pharm. Sci. 4(4): 12-18.
DOI: http://dx.doi.org/10.22192/ijcrcps.2017.04.04.003