J. Appl. Environ. Biol. Sci., 4(8S)101-105, 2014

ISSN: 2090-4274
Journal of Applied Environmental and Biological Sciences
www.textroad.com

Prediction of Binding Mode of Bisphenol-A (A Carcinogen) in Estrogen and Testosterone Receptors by Applying Computational Docking Approach

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Received: September 1, 2014
Accepted: November 13, 2014

ABSTRACT

Background: Bisphenol A (BPA) displays weak estrogenic properties and could be a weak carcinogen. BPA exposure during the perinatal period has been reported to alter both prostate and mammary gland development in ways that may render these organs more susceptible to the development of neoplasia or preneoplastic conditions with subsequent exposures to strong tumour-initiating or tumour-promoting regimens.
Methods: Molecular Operating Environment (MOE-2012) software was used to perform docking calculations. This software returned affinity energy values for several ligand conformations. Subsequently, we used PyMole 1.4 and Ligand Scout 3.1 to check the stereochemistry of chiral carbons, substructure, superstructure, number of rotatable bonds, number of rings, number of donor groups, and hydrogen bond receptors.
Results: some compounds involved in cancer, here computationally we predict the distortion behavior of Bis-Phenol A in equilibration in estrogen and testosterone receptors, and then GROMACS was used to simulate the behavior of the Bis-Phenol A in complex (estrogen -testosterone receptors) after a set of 500 PS and up to 300 K in water. This calculation returned a graph of potential energy against simulation time and showed that the ligand (bis-phenol A) are might be involved in destroying the equilibration of both the receptors.
Conclusions: The results indicate that Bis-Phenol A could be a competitor for steroids which defect the equilibrium of estrogen – Androgen effect, but the binding with testosterone receptor was stronger than binding with estrogen receptor.
KEYWORDS: bisphenol A (BPA), Docking, carcinogen

INTRODUCTION

Bisphenol A (BPA) is a chemical used to make a kind of plastic called polycarbonate. Also BPA is used to make the linings in almost all canned food and drinks, including cans of liquid infant formula (U.S. Environmental Protection Agency, 2010). The important note on BPA that it exhibits hormone-like properties that raise concern about its suitability in some consumer products and food containers (U.S. Food and Drug Administration, 2013). A 2010 report from the US Food and Drug Administration (FDA) identified possible hazards to fetuses, infants, and young children. However, an FDA assessment released in March 2013 said that BPA is safe at the very low levels that occur in some foods (U.S. Food and Drug Administration, 2010).

Endocrine-disrupting chemicals (EDC), including phthalates, bisphenol A (BPA), and phytoestrogens such as genistein and daidzein, are associated with a variety of adverse health effects in organisms or progeny by altering the endocrine system (Yoon K, &Kwack SJ, 2014) which make focusing of researcher to characterize the whole effect of these compounds accurately considering the priorities of hormone system. The widespread exposure of individuals to BPA is suspected to affect a variety of physiological functions, including reproduction, development, and metabolism (Delfosse V, &Grimaldi M, 2014). Recently, Bisphenol A consider as one of the highest volume chemicals produced worldwide.

the previous studies showed that BPA has estrogen like effect and it has binding ability to estrogen receptor (Richard M., 2014). Basically, BPA binds to steroid receptors but it is unclear whether it binds to Estrogen receptor and take role like estrogen agonist or binds to androgen receptor to be antagonist which leading to disrupt the estrogen – androgen equilibrium in breast tissue. Consequently, in this study we try to explain the binding of BPA to

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the two types of receptor using Molecular docking and Docking calculation. Molecular docking is a computational method that can be used to explain the interactions of ligands with the receptor.

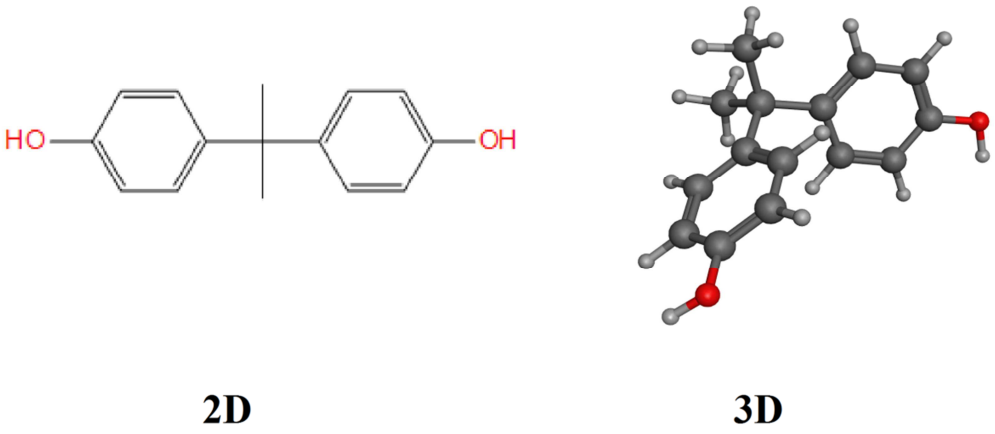
METHODS

In this study an effort was made to carry out the docking of the Bis-Phenol-Ainto the binding pocket of Estrogen (**PDB Code 1a52**) and Testosterone receptor (**PDB Code 2am9**) by means of MOE 2008.10 (Molecular Operating Environment) software package. LigPlot implemented in MOE software was used to envision the interactions between Estrogen and Testosterone receptor and compound Bis-Phenol-A.

RETRIEVAL OF LIGANDS

The compound Bis-Phenol-A, which is a carcinogen and cause breast cancer, was collected from the previous literature (John Bucher, 2010). The structure of the compound was constructed using MOE-Builder tool. The 2D structure of the retrieved Ligand is shown in (**Figure 1**). The related 3D structures were also obtained and the energies of the identified molecules were minimized using the default parameters of MOE energy minimization algorithm [gradient: 0.05, Force Field: MMFF94X].

Figure 12-Dimensional and 3-Dimensional minimized Structure of compound Bis-Phenol-A



Preparation of Receptor Protein

The protein molecules included in our study, Estrogen and Testosterone receptors was downloaded from Protein Data Bank [PDB Codes**1a52 & 2am9**]. Water molecules were removed and the 3D protonation of the receptor molecules was carried out. The energies of the retrieved receptors were minimized using the default parameters of MOE energy minimization algorithm [gradient: 0.05, Force Field: MMFF94X].

Molecular Docking

The default parameters of MOE-Dock program were used for the molecular docking of the compound Bis-Phenol-A. To find the correct conformations of the Ligand and to obtain minimum energy structure, ligands were allowed to be flexible. At the end of docking, the best conformations of the Ligand were analyzed for their binding interactions.

RESULTS AND DISCUSSION

Validation of the docking procedure

In order to evaluate the accuracy of MOE-Dock program the co-crystallized Ligands were removed from the active sites of both of receptors and re-docked within the binding cavity of both receptors (Estrogen and Testosterone receptor). In this study, RMSD value was found as 1.809Å for Estrogen receptor and 1.09 Å for Testosterone receptor, showing that our docking method is valid for the studied (Bostrom J et al. 2003) and MOE-Dock method, therefore, is reliable for docking of the compound Bis-Phenol-A in the cavity of both receptors.

Docking Analysis

Binding interactions of ligands and Protein

From the MOE-docking studies it was observed that the compound Bis-Phenol-Aindicate good agreement of docking score to testosterone receptor (S= -11.7486), as compared to estrogen receptor which has-11.0623 docking score as show in (Table No. 01).

It was observed from the docking conformation of compound Bis-Phenol-A for Testosterone receptor with resolution of 1.64Å that the compound was bound into the binding cavity of Testosterone receptor making interactions with the residues **Arg**752 (basic, side chain donor), **Asn**705and **Thr**877. **Arg**752interacts with the oxygen (hydroxyl group) single bonded to the one side of Benzene ring while **Asn**705 and **Thr**877 were found in polar interaction with the H (of hydroxyl group) of the compound as shown in **Figure 2B**(2-D pose)and 3-D in **Figure 3.**

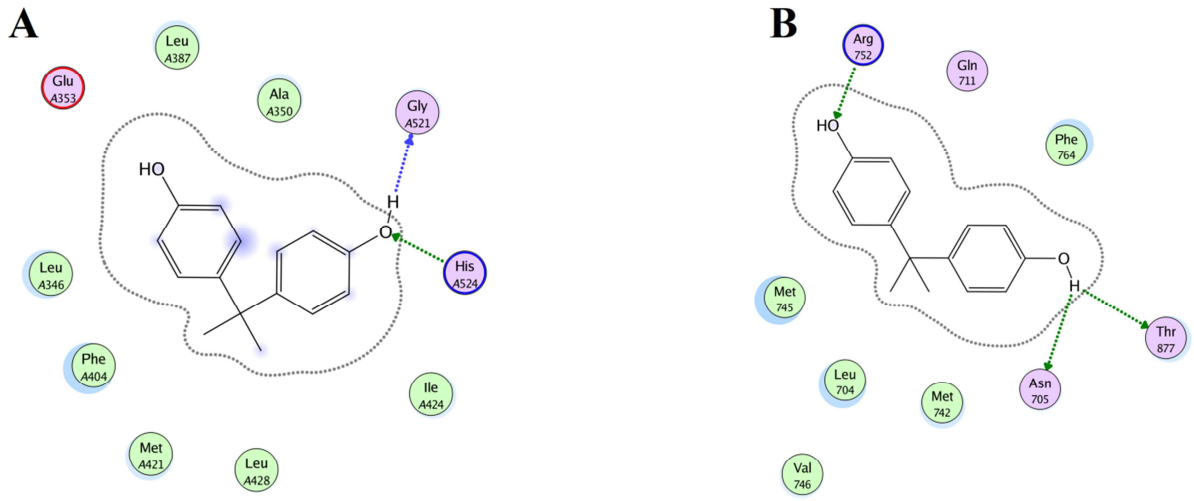


Figure 3. Docked conformation of compound Bis-Phenol-A (**A**) Estrogen Receptor [PDB Code1a52 and Docking Score (S)-11.0623] (**B**) Testosterone Receptor [PDB Code2am9 and Docking Score (S) -11.7486]

Table No. 01 MOE-Dock scoring and Binding Affinity of Testosterone and Estrogen Receptor.

Receptor	MOE-Dock Score (S)	Binding Affinity (pKi)
Testosterone	-11.7486	9.297
Estrogen	-10.0623	8.678

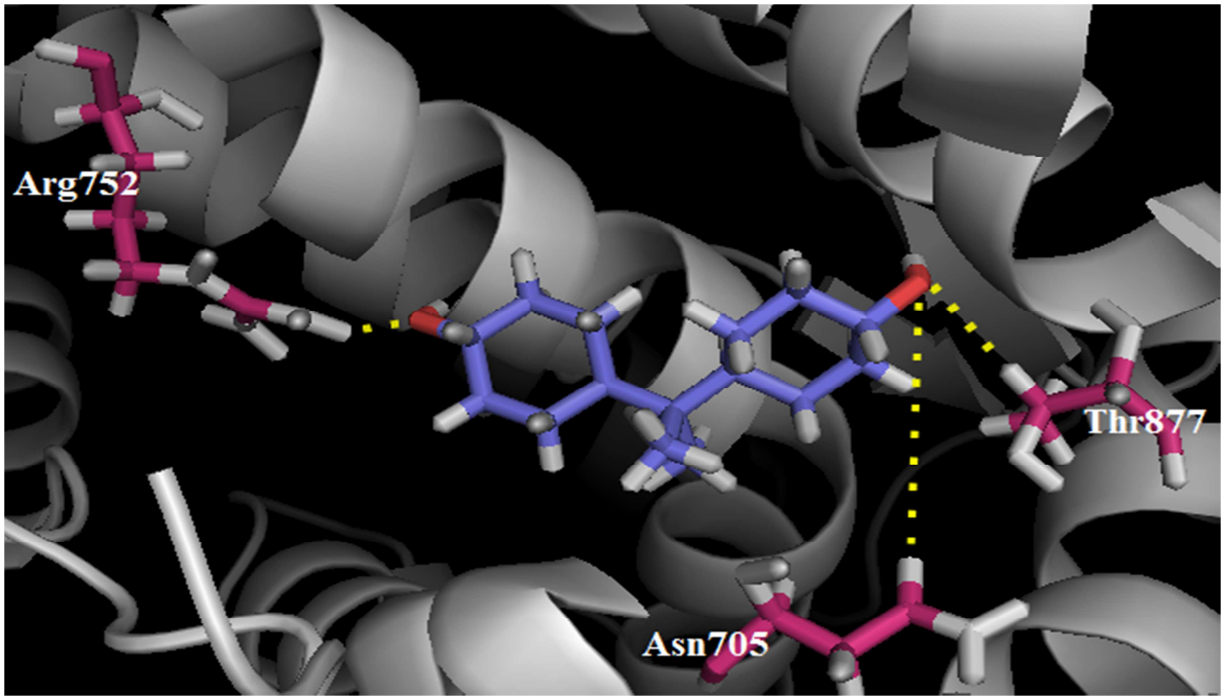


Figure 4:3-Dimensional pose of compound Bis-Phenol-A and Testosterone Receptor

Similarly the same docking conformation of compound Bis-Phenol-A for Estrogen receptor with resolution of 2.80Å, it was observed that the compound established two interactions with the pocketresidues, **Gly**521 and **His**524 of estrogen receptor (PDB Code **1a52**), **Gly**521 established an interaction with the Hydrogen of OH group of benzene ring and to same Benzene ring **His**524 established interaction with the oxygen, as shown in **Figure 2A (**2-Dimensional) and 3-Dimensional in **Figure 4.**

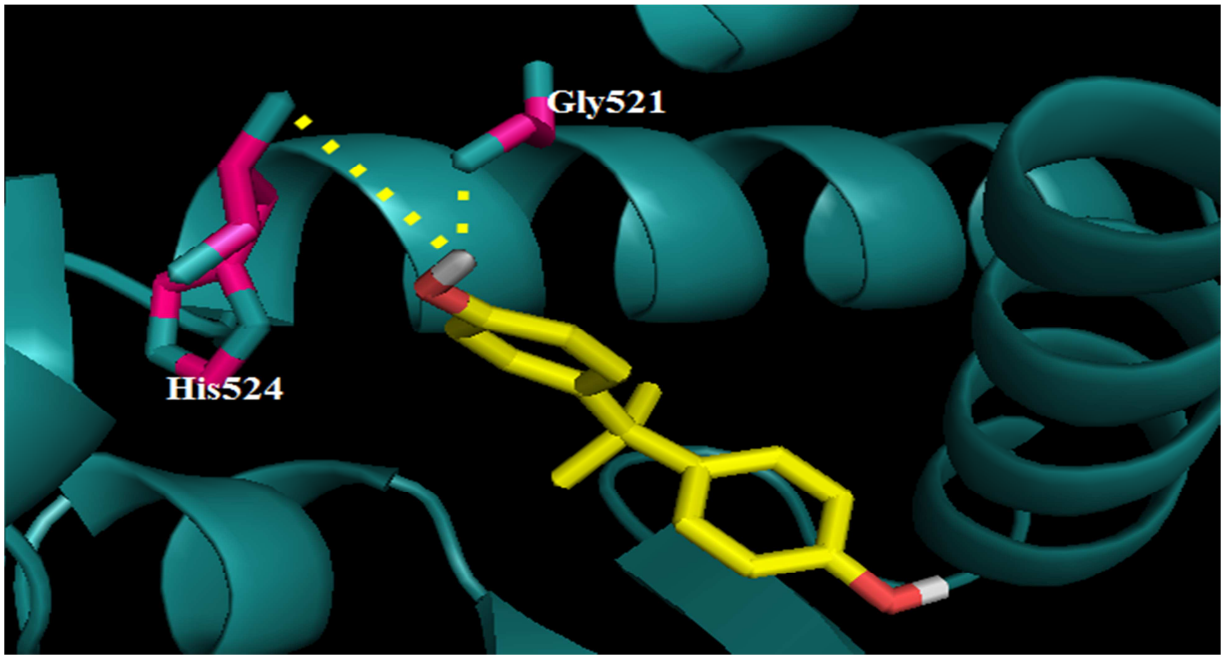


Figure 5:3-Dimensional pose of compound Bis-Phenol-A (magenta color) and Estrogen Receptor (sienna and navy blue color)

It was observed that compound Bis-Phenol-A is an active again Testosterone receptor, because compound was bound side by side into the binding cavity of Testosterone receptor.

CONCLUSION

The docking analysis resulted in the detection of key Ligand interactions with respect to binding site of targeted receptors. As a result of this study we concluded that the compound (B-P-A) computationally studied here have shown good relationship among, docking score and binding interactions. The compound distinctly showed interactions with most important active site residues, **Arg**752, **Asn**705, **Thr**877 and **His**524 (according to the crystal structure of Estrogen and Testosterone receptors [PDB Codes **1a52 & 2am9**]) of the target receptors. So this compound may be active ingredient again Testosterone receptor as compared to the receptor estrogen.

In summary, our findings demonstrate that BPA, which is one of the most prevalent chemicals for daily use materials, can bind to Testosterone receptor more tightly than Estrogen receptor. That means BPA probably behaves as testosterone antagonist and lead to interrupt the equilibrium and finally increase the activity of estrogen which is one of breast tumor cause.

REFERENCES

"Bisphenol A Action Plan". U.S. Environmental Protection Agency. 29 March 2010. Retrieved 12 April 2010.

"FDA Regulations No Longer Authorize the Use of BPA in Infant Formula Packaging Based on Abandonment; Decision Not Based on Safety". Fda.gov. 2013-07-12, Retrieved 2014-02-01.

"Update on Bisphenol A for Use in Food Contact Applications: January 2010". U.S. Food and Drug Administration. 15 January 2010.

Bostrom J et al. J Mol Graph Model. 2003 21: 449 [PMID: 12543140]

Delfosse V, Grimaldi M, le Maire A, Bourguet W, Balaguer P. Nuclear receptor profiling of bisphenol-A and its halogenated analogues. *Vitam Horm. 2014;94:229-51.*

John Bucher, FAO/WHO Expert meeting on Bisphenol A (BPA), Ottawa, Canada, 2010.

Richard M. Sharpe, Is It Time to End Concerns over the Estrogenic Effects of Bisphenol A, *Toxicol. Sci. (2010) 114 (1): 1-4.*

Yoon K, Kwack SJ, Kim HS and Lee BM. Estrogenic endocrine-disrupting chemicals: molecular mechanisms of actions on putative human diseases. *J Toxicol Environ Health B Crit Rev.* 2014;17(3):127-74.