

# **An *in silico* Investigation of Dichlorodiphenyltrichloroethane (DDT) as a Potential Endocrine Disrupting Chemical**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

This study aimed at investigating the endocrine disruption tendency of the isomers and derivatives of DDTs *in silico* through the methodology and instrumentality of molecular docking and online softwares, appropriate ligands and receptors were selected from online bioinformatics database. The result shows that the derivatives of Estrogen receptor beta (1QKM) such as Dichlorodiphenyldichloroethylene (o,p'-DDE) (-8.1077), Dichlorodiphenyldichloroethane (m,p'-DDD) (-7.5605), Dichlorodiphenyldichloroethane (p,p'-DDD or Rhothane) (-7.4761) had higher binding energy relative to the parent molecule Dichlorodiphenyltrichloroethane (o, o'-DDT) (-5.9572) and also as compared to the control, Genistein (-8.0746) and Bisphenol A (-6.5464), Methoxychlor (-7.8910). For its derivatives of Estrogen receptor alpha (17xR); Dichlorodiphenyltrichloroethane (o,o'-DDT) (-7.76949), Dichlorodiphenyldichloroethylene (o,p'-DDE) (-7.2949) had higher binding energy relative to the parent molecule Dichlorodiphenyltrichloroethane (o, o'-DDT) (-7.7649) and also as compared to the control Dihydrotestosterone (-8.2092), Genistein (-7.1892) and Bisphenol A (-6.8010). For its derivatives of Androgen receptor alpha (2AMA), Dichlorodiphenyldichloroethane (m,p"-DDD) (-7.76949), had higher binding energy relative to the parent molecule DDT and also as compared to the control Dihydrotestosterone (-6.7349). Since the derivatives had high binding energy which also translates to high affinity, it suggests that they can be potential endocrine disrupting chemicals.

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## 1. INTRODUCTION

“The endocrine system is a messenger system comprising feedback loops of the hormones and hormonal signals released by internal glands of an organism directly into the blood circulatory system, regulating distant target organs. In vertebrates, the hypothalamus is the neural control center for all endocrine systems. In human beings, the major endocrine glands are the thyroid gland and the adrenal glands. The study of the endocrine system and its disorders is known as endocrinology” [1]. “Glands that signal each other in sequence are often referred to as an axis, such as the hypothalamic-pituitary-adrenal axis. In addition to the specialized endocrine organs mentioned above, many other organs that are part of other body systems have secondary endocrine functions, including bone, kidneys, liver, heart and gonads. For example, the kidney secretes the endocrine hormone erythropoietin. Hormones can be amino acid complexes, steroids, eicosanoids, leukotrienes, or prostaglandins” [2].

Diseases of the endocrine system are common, [3] “including conditions such as Cancer (ovarian cancer, prostate cancer, lung cancer, breast cancer), diabetes mellitus, thyroid disease, and obesity”. “Endocrine disease is characterized by misregulated hormone release (a productive pituitary adenoma), inappropriate response to signaling (hypothyroidism), lack of a gland (diabetes mellitus type 1, diminished erythropoiesis in chronic kidney failure), or structural enlargement in a critical site such as the thyroid (toxic multinodular goitre)” [4].

“In 2002, the International Programme on Chemical Safety (IPCS), a joint programme of the World Health Organization (WHO), the United Nations Environment Programme (UNEP) and the International Labour Organization, published a document entitled Global Assessment of the State-of-the-Science of Endocrine Disruptors [5] which x-rayed the effects of a number of chemical substances with potentials of causing various levels of destructions on the endocrine system after exposure to them”.

The effects are endocrine system related and not necessarily species dependent. Effects shown in

wildlife or experimental animals may also occur in humans if they are exposed to EDCs at a vulnerable time and at concentrations leading to alterations of endocrine regulation. Of special concern are effects on early development of both humans and wildlife, as these effects are often irreversible and may not become evident until later in life.

“Molecular docking is an attractive scaffold to understand drug-biomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity” [6,7]. The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complexes. At present, docking technique is utilized to predict the tentative binding parameters of ligand-receptor complex beforehand.

**Dichlorodiphenyltrichloroethane**, “commonly known as **DDT**, is a colorless, tasteless, and almost odorless crystalline chemical compound” [8] “an organochloride. Originally developed as an insecticide, it became infamous for its environmental impacts. DDT was first synthesized in 1874 by the Austrian chemist Othmar Zeidler. DDT's insecticidal action was discovered by the Swiss chemist” [9]. DDT was used in the second half of World War II to limit the spread of the insect-borne diseases malaria and typhus among civilians and troops. Müller was awarded the Nobel Prize in Physiology or Medicine in 1948 “for his discovery of the high efficiency of DDT as a contact poison against several arthropods”.

Probing the molecular recognition of DDT analogs at the atomic level is critical for deciphering the mechanism of endocrine disruption toward ER $\alpha$  and ER $\beta$ , which is essential for full evaluation of underlying diseases related to the exposure of DDT analogs. In this study, molecular docking techniques were used to determine the binding of DDT analogs to the endocrine system *in vitro* which is predictive of its ability to disrupt the endocrine system, a model that would suggest what would happen in *in vivo* analysis.

## 2. MATERIALS AND METHODS

### 2.1 Materials

**Receptors;** A number of receptors were employed such as Crystal structure of estrogen receptor alpha complex with Genistein (PDB ID:17xR), Human estrogen receptor Beta with partial agonist Genistein (PDB ID:1QKM), Crystal structure of human androgen receptor ligand binding domain in complex with dihydrotestosterone (PDB ID: 2AMA).

**Ligands:** Literature guided and ligand download from pubchem, African Natural/product Database (ANPDB) select using a pharmacophore model.

**Stand-alone offline softwares such as;** Molecular Operating Environment (MOE) Complete Package, 2015 Version and Discovery Studio Full Package.

**Others include online links such as;** **Chemsketch:**<http://chemsketch.en.softonic.com>, **Chemspider:** <http://www.chemspider.com> and **online database such as;** Pubchem URL: <http://pubchem.ncbi.gov>. RSCB PDB URL: <http://www.rcsd.org/pdb> ANPDB: [http://african\\_compounds.org.anpdb](http://african_compounds.org.anpdb) and Pubmed

### 2.2 Methods

**Ligand selection and preparation:** The selection of the ligands (compounds) used in this study were largely informed by available literatures. The 3D - structural data of most of the query compound/some controls were downloaded from Pubchem <https://pubchem.ncbi.nlm.nih.gov/> in SDF format and converted to *moe* format in Molecular Operating Environment (MOE). Others were drawn with builder in Molecular Operating Environment (MOE), chemsketch or chemspider. Control ligands, co-crystallized with receptors were isolated from the 3D structure of the ligand-protein complex (in *pdb* format from RSCB PDB database) in MOE using the Seq tool. A database of all the query ligands/controls was created in MOE and saved for docking. The database of ligand structures was prepared for docking as follows in MOE: protonation at a temperature of 300 °C and pH 7 and energy minimization, using default parameters - Amber10-EHT force field was used with no

periodicity and the constraints were maintained at the rigid water molecule level. Partial charges were applied [10,11].

**Protein target preparation:** X-ray crystallography structural data in *pdb* format were downloaded with its co-crystallized ligand (were available) from the RCSB database (<http://www.rcsb.org/pdb>). The preparation and minimization of all target proteins were performed using tools and protocols in the MOE. The preparatory process included removal of water molecules and other co-crystallized molecules, Protonation, partial charges and energy minimization were implemented as described above in ligand preparation. The fully prepared and optimized 3D structure was saved in *moe* format for docking [10,11].

**Binding/docking site prediction:** The co-crystallized ligand bound to the target protein was used to define the binding site for molecular docking.

**Docking Simulation:** Docking simulation was performed in MOE. The ligand was selected, the ligands were docking using Triangular matcher/rigid receptor method and scored using London dG and GBVI/WSA dG options, on an Intel core i7 CPU @ 2.0Ghz, 2.60Ghz. Protein-ligand docking poses and scores were saved in *db* format and ligand interaction with protein visualized (2D and 3D using MOE or Discovery studio ligand interaction options. The results were presented in tables and figures [10,11].

## 3. RESULTS AND DISCUSSION

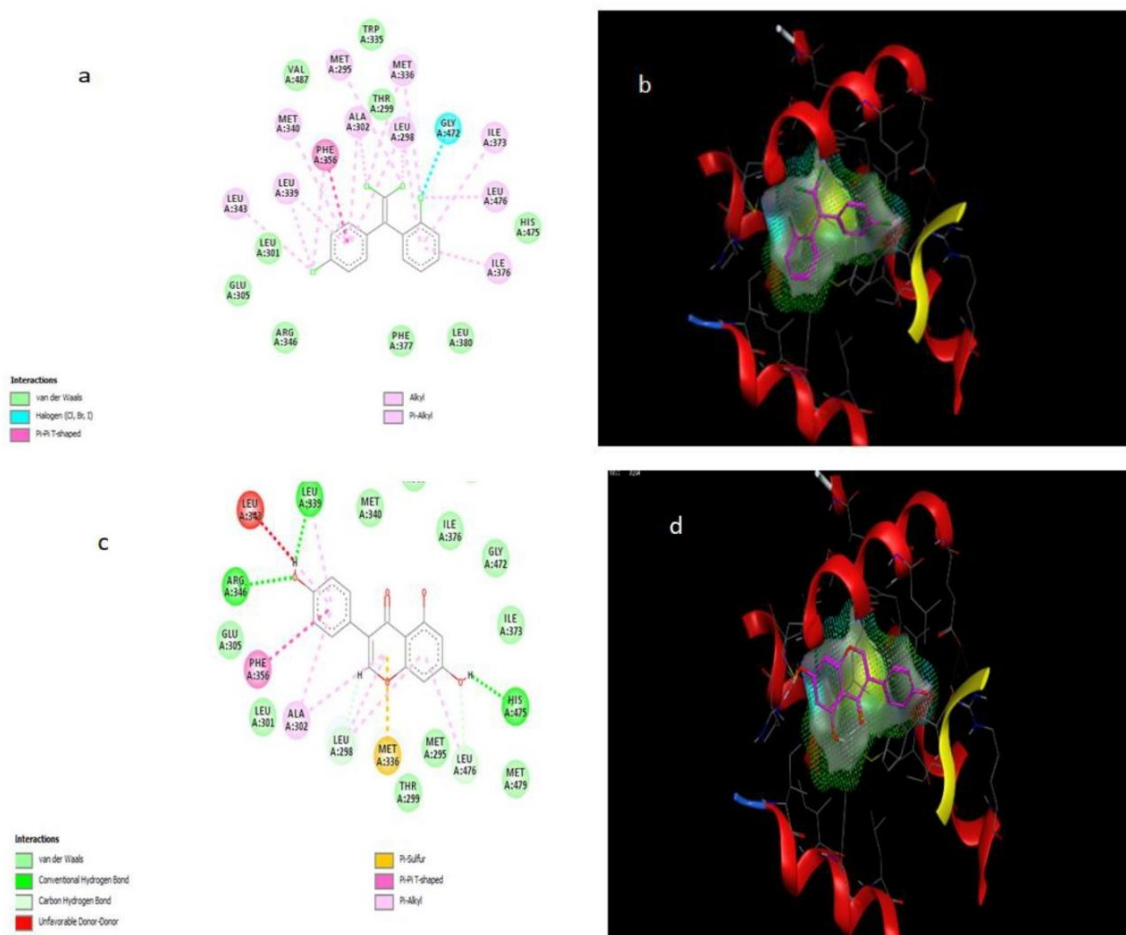
### 3.1 Results

The result of the molecular docking of Dichlorodiphenyltrichloroethane (DDT) and its derivatives of Estrogen receptor beta (1QKM) are presented in Table 1: The result shows that the derivatives such as Dichlorodiphenyldichloroethylene (*o,p'*\_DDE) (-8.1077), Dichlorodiphenyldichloroethane (*m,p'*\_DDD) (-7.5605), Dichlorodiphenyldichloroethane (*p,p'*\_DDD or Rhothane) (-7.4761) have higher binding energy relative to the parent molecule Dichlorodiphenyltrichloroethane (*o, o'*-DDT) (-5.9572) and also as compared to the control, Genistein (-8.0746) and Bisphenol A (-6.5464).

**Table 1. Molecular docking result Dichlorodiphenyltrichloroethane (o, o'-DDT)/derivatives, on human Estrogen receptor beta (1QKM)**

S/N	Compound	Binding Energy	RMSD	Interacting Amino Acid Residue(s)
1.	Dichlorodiphenyldichloroethylene (o, p'-DDE)	-8.1077	0.8366	<sup>a1</sup> (Gly 472), <sup>c</sup> (Leu 343, Leu 339, Phe 356, Ala 302, Met 336, Met 295, Leu 298, Leu 476)
2.	Genistein		1.1016	<sup>a</sup> (Arg 346, Leu 339, His 475,), <sup>b</sup> (Leu 298, Leu 476)
3.	Beta-Estradiol	-8.0564	1.0156	<sup>a</sup> (Glu 305), <sup>b</sup> (Gly 472), <sup>c</sup> (Ile 373, Leu 298)
4.	Dichlorodiphenyldichloroethane (m, p'-DDD) - 8.0746	-7.5605	0.7977	<sup>c</sup> (Leu 343, Leu 339, Ile 373, His 475, Ala 302, Val 487, Trp 335, Met 336, Leu 476, Leu 298)
5.	Dichlorodiphenyldichloroethane (p, p'-DDD or Rhothane)	-7.4761	1.8024	<sup>c</sup> (Leu 343, Leu 339, Met 336, Trp 335, Val 487, Ala 302, Leu 476, Leu 298, Phe 377, Ile 373, Ile 376)
6.	Dichlorodiphenyldichloroethylene (p, p'-DDE)	-7.4159	0.8865	<sup>c</sup> (Leu 343, Leu 339, Met 336, Trp 335, Val 487, Ala 302, Leu 476, Phe 377, Ile 373)
7.	Bisphenol A	-6.5464	1.9206	<sup>a</sup> (Leu 339, Arg 346), <sup>c</sup> (Phe 356, Leu 298, Ala 302, Met 336)
8.	Dichlorodiphenyltrichloroethane (o, o'-DDT)	-5.9572	1.5624	-----
9.	Clofenotane (p,p'-DDT)	-5.9173	1.7529	-----
10.	Methoxychlor	-5.7645	2.7858	-----
11.	Dicofol	-5.0868	0.9949	-----

*Superscripts a: Hydrogen bond, a1: Halogen, b: Carbon-hydrogen bond, c: Alkyl linkages*



**Fig. 1. Docked pose of Dichlorodiphenyldichloroethylene (o, p'-DDE) and Genistein (control) in Estrogen receptor beta (1QKM); (a): 2D view of interaction of Dichlorodiphenyldichloroethylene (o, p'-DDE) with surrounding amino acids of 1QKM, (b): 3D view of Dichlorodiphenyldichloroethylene (o, p'-DDE) within the binding pocket of Estrogen receptor beta (c): 2D view of interaction of Genistein with surrounding amino acids of 1QKM, (d): 3D view of Genistein within the binding pocket of Estrogen receptor beta**

The result of the molecular docking of Dichlorodiphenyltrichloroethane (DDT) and its derivatives of Estrogen receptor alpha (17xR) are presented in Table 2. The result shows that the derivatives such as Methoxychlor (-7.8910), Dichlorodiphenyltrichloroethane (o,o'-DDT) (-7.76949), Dichlorodiphenyldichloroethylene (o,p'-DDE) (-7.2949) have higher binding energy relative to the parent molecule Dichlorodiphenyltrichloroethane (o, o'-DDT) (-7.7649) and also as compared to the control Dihydrotestosterone (-8.2092), Genistein (-7.1892) and Bisphenol A (-6.8010).

The result of the molecular docking of Dichlorodiphenyltrichloroethane (DDT) and its derivatives of Androgen receptor alpha (2AMA)

are presented in Table 3. The result shows that the derivatives such as Dichlorodiphenyldichloroethane (m,p''\_DDD) (-7.76949), have higher binding energy relative to the parent molecule DDT and also as compared to the control Dihydrotestosterone (-6.7349).

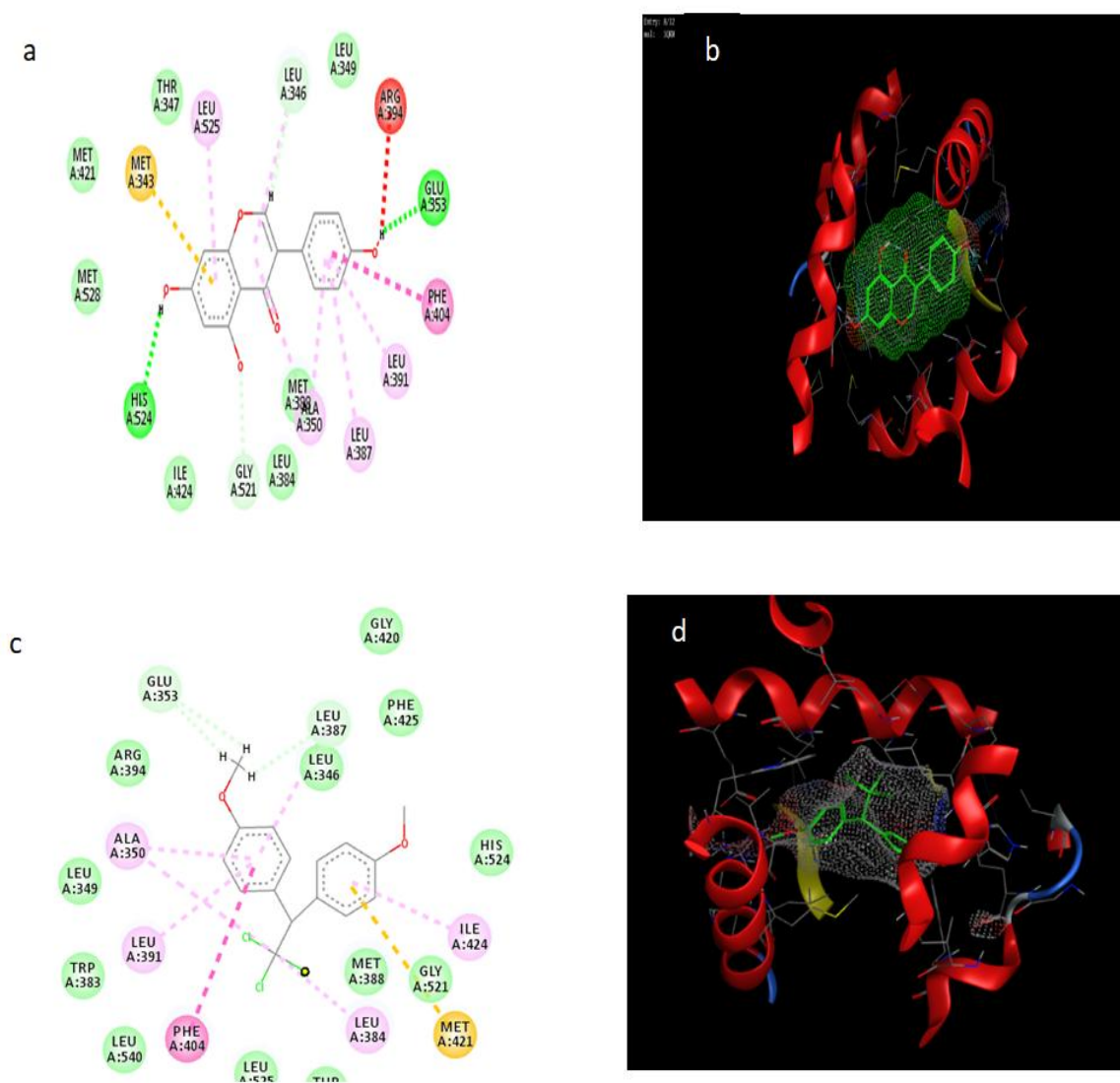
### 3.2 Discussion

The exposure of DDT-related pesticides has long been linked to endocrine disruption from animal studies and epidemiological data, however, their mechanism of endocrine disruption remains unclear. Dichlorodiphenyltrichloroethane analogs (DDE, DDD, MXC) were reported to bind targeted receptors [12,13] such as estrogen receptors (ERs) [14]. This could be an evolving

target in diseases such as cancer as well as other metabolic disorders and behaves as an activator of transcription process. Scrutinizing the molecular recognition of DDT analogs at the atomic level is critical for understanding the mechanism of endocrine disruption toward ERA and ERR $\alpha$ , which is essential for full evaluation of underlying diseases related to the exposure of DDT analog.

In Table 1, the result shows that the derivatives of Dichlorodiphenyldichloroethylene have higher binding energy than the control (genistein) in the

Estrogen receptor beta. This is probably because DDE and the parent DDT, are shown to be reproductive toxicants to human and certain species. DDE are more potent than DDT. This also implies that the high binding affinity of the receptor may exact that DDE is particularly dangerous because it is fat soluble like other organochlorines; thus it is rarely excreted from the body and the concentrations tend to increase throughout life and becomes toxic just like other organophochlorides [15].



**Fig. 2. Docked pose of Methoxychlor and Genistein (control) in Estrogen receptor alpha (17XR); (a): 2D view of interaction of Methoxychlor with surrounding amino acids of 17XR, (b): 3D view of Methoxychlor within the binding pocket of Estrogen receptor alpha (c): 2D view of interaction of Genistein with surrounding amino acids of 17XR, (d): 3D view of Genistein within the binding pocket of Estrogen receptor alpha**

**Table 2. Molecular docking result Dichlorodiphenyltrichloroethane (o, o'-DDT)/derivatives, on human Estrogen receptor alpha (17XR)**

S/N	Compounds	Binding Energy (Kcal)	RSMD	Interacting Amino Acid Residue(s)
1.	Beta-Estradiol	-8.2832	1.3013	<sup>a</sup> (His 524, Leu 387), <sup>c</sup> (Leu 525, Ile 424, Leu 384)
2.	Methoxychlor	-7.8910	0.9214	<sup>b</sup> (Glu 353, Leu 387), <sup>c</sup> (Ala 350, Leu 384)
3.	Dichlorodiphenyltrichloroethane (o, o'-DDT)	-7.7649	0.9628	<sup>c</sup> (Met 388, Leu 387, Leu 391, Leu 346)
4.	Dichlorodiphenyldichloroethylene (o, p'-DDE)	-7.2949	1.0076	<sup>a1</sup> (Glu 353), <sup>c</sup> (Leu 391, Leu 387, Phe 404, Met 388, Leu 428, Ile 424, Met 421, Leu 346)
5.	Dichlorodiphenyldichloroethane (m, p'-DDD)	-7.2486	1.4124	<sup>c</sup> (Leu 428, Met 388, Phe 404, Leu 391, Leu 346, Met 421, Trp 383, Leu 540, Leu 525, Ala 350, Leu 387)
6.	Dichlorodiphenyldichloroethane (p, p'-DDD or Rhothane)	-7.2149	1.0608	<sup>a1</sup> (Glu 353), <sup>c</sup> (Leu 391, His 524, Phe 404, Met 421, Leu 346, Ile 424, Ala 350, Leu 525, Leu 540, Leu 349)
7.	Genistein	-7.1892	0.7605	<sup>a</sup> (His 524, Glu 353), <sup>b</sup> (Gly 521)
8.	Dicofol	-7.0452	1.0000	-----
9.	Clofenotane (p,p'_DDT)	-7.0291	1.2973	-----
10.	Dichlorodiphenyldichloroethylene (p, p'-DDE)	-6.8866	1.3559	-----
11.	Bisphenol A	-6.8010	0.7756	<sup>a</sup> (Leu 387), <sup>c</sup> (Leu 346, Phe 404, Met 388)

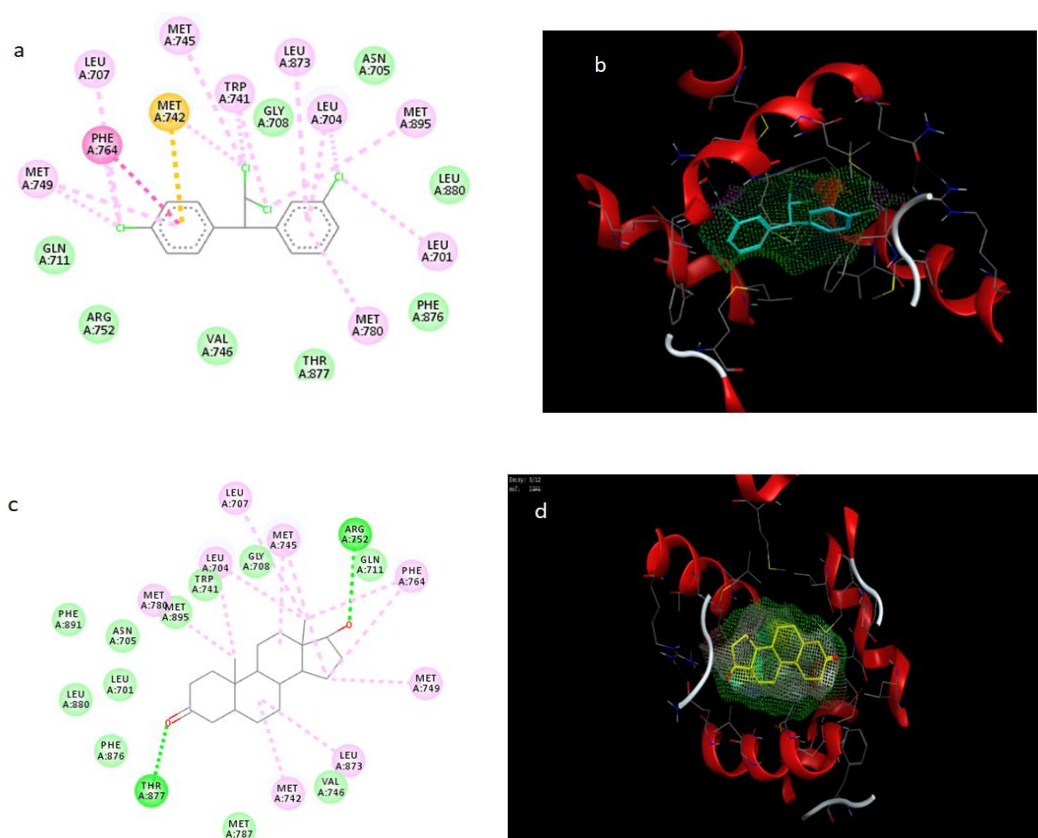
Superscripts a: Hydrogen bond, a1: Halogen, b: Carbon-hydrogen bond, c: Alkyl linkages

**Table 3. Molecular docking result Dichlorodiphenyltrichloroethane (o, o'-DDT)/derivatives, on human androgen receptor alpha (2AMA)**

S/N	Compounds	Binding Energy (Kcal)	RSMD	Interacting Amino Acid Residue(s)
1.	Dichlorodiphenyldichloroethane (m, p'-DDD)	-6.7349	1.2069	<sup>c</sup> (Phe 764, Leu 707, Met 749, Trp 741, Met 742, Met 745, Trp 741, Met 895, Leu 704, Leu 701)
2.	Dihydrotestosterone	-6.6578	1.6905	<sup>a</sup> (Arg 752, Thr 877), <sup>c</sup> (Met 749, Phe 764, Met 745, Leu 707, Leu 704, Met 780)
3.	Methoxychlor	-6.5520	1.4561	<sup>a</sup> (Thr 877), <sup>b</sup> (Phe 764), <sup>c</sup> (Met 742)
4.	Dichlorodiphenyldichloroethylene (o, p'-DDE)	-6.2806	1.4867	<sup>a1</sup> (Met 742), <sup>c</sup> (Leu 701, Leu 880, Phe 876, Met 745, Leu 873, Val 746, Met 749, Phe 764, Trp 741, Met 787)
5.	Dichlorodiphenyltrichloroethane (o, o'-DDT)	-6.1850	1.2332	<sup>c</sup> (Val 746, Trp 741, Met 742, Leu 873, Met 780, Met 787)
6.	Dichlorodiphenyldichloroethane (p, p'-DDD or Rhothane)	-6.0975	0.8034	-----
7.	8268	-5.9900	1.3199	-----
8.	3036	-5.9491	1.1734	-----
9.	Dichlorodiphenyldichloroethylene (p, p'-DDE)	-5.6402	1.3125	-----

Superscripts a: Hydrogen bond, a1: Halogen, b: Carbon-hydrogen bond, c: Alkyl linkages





**Fig. 3. SDocked pose of Dichlorodiphenyldichloroethane (m, p'-DDD) and Dihydrotestosterone (control) in Androgen receptor (2AMA). (a): 2D view of interaction of Dichlorodiphenyldichloroethane (m, p'-DDD) with surrounding amino acids of Androgen receptor (2AMA) (b): 3D view of Dichlorodiphenyldichloroethane (m, p'-DDD) within the binding pocket of Androgen receptor (2AMA) (c): 2D view of interaction of Dihydrotestosterone with surrounding amino acids of 17XR, (d): 3D view of Dihydrotestosterone within the binding pocket of Androgen receptor (2AMA)**

In Table 2, the result shows that the derivatives (Methoxychlor, DDT, DDE) have higher binding energy in the estrogen receptor alpha compare to the control. Methoxychlor can be toxic because high doses can lead to neurotoxicity [16]. Some methoxychlor's metabolites have estrogenic effects in adult and developing animals before and after birth [16]. Such effects may adversely affect both the male and female reproductive systems because they are linked to the endocrine systems through the glands of the male and female hormones. While in Table 3 above, the result of the DDT analog (m,p' DDD) of androgen receptor alpha shows high binding affinity as compared to the control (dihydrotestosterone). This means that the high binding energy may exact it is an organochlorines insecticides that is slightly irritating to the skin which is a metabolite of DDT (Environmental Protection Agency, 2007).

#### 4. CONCLUSION

The result shows that these chemicals have high binding affinity to the receptors than the parent molecules and this implies that, they have higher potential of exerting carcinogenic characteristics in the system of the living organism.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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