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SYNTHESIS OF P-TOLYLPENTACHLOROPHENOXYACETATE AND ITS MOLECULAR DOCKING ANALYSIS

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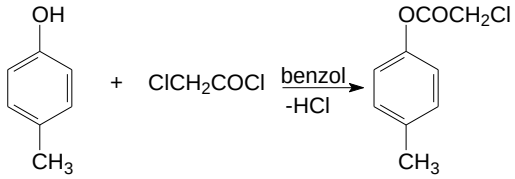
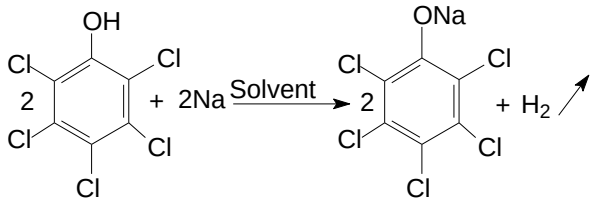
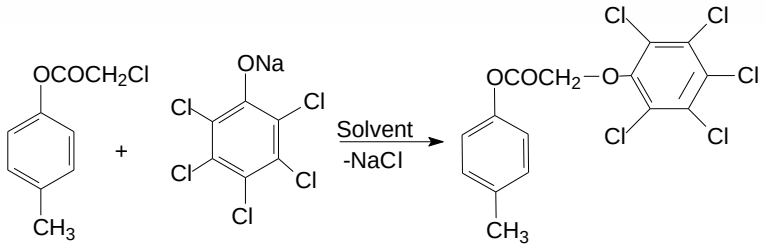
Substances synthesized on the basis of chloroacetylation reactions of phenol and its derivatives have high biological activity and are widely used in pharmaceuticals as antibacterial, analgesic and bactericidal drugs against pathogenic microorganisms [1]. Among these are substances such as adrenaline, noradrenaline, isadrin with high biological activity, which are used in medicine as immunostimulants, anti-diabetic and anti-cancer drugs, as well as in pharmaceuticals as hormonal drugs [2,3,4].
In order to synthesize substances with biological activity, research was conducted and the reaction of p-cresol with chloroacetyl chloride was conducted. The reaction went as follows:



The most convenient way to carry out these reactions was found. The reaction was carried out in absolute benzene solution and pure p-tolyl chloroacetate was isolated. Solvents benzene, acetone, benzodioxane, DMF and DMSO were used to obtain p-Cresol phenolate.



p-Tolylpentachlorophenoxyacetate was synthesized by nucleophilic exchange reaction of sodium salt of p-cresol formed with p-Tolylchloroacetate.



The properties of p-Tolylpentachlorophenoxyacetate were theoretically studied using Gaussian 09 W software.

In molecular docking, the binding energy is calculated as the sum of several energy values, including:

1. Van der Waals energy: this is the energy of attraction or repulsion between the nonpolar atoms in the ligand and the receptor.
2. Electrostatic energy: this is the energy of attraction or repulsion between charged atoms or groups on the ligand and receptor.
3. Hydrogen bond energy: this is the energy of attraction between the hydrogen bond donor and acceptor groups in the ligand and receptor.
4. Solvation energy: this is the energy change that occurs when a molecule is surrounded by a solvent.

In drug discovery, ligands with more negative binding energies are generally considered more potent and more likely to succeed as drug candidates.

Binding energy ($\Delta G_{binding}$) is the main parameter of molecular docking used to determine the strength of interaction between a ligand and a receptor. It represents the energy change that occurs when a ligand binds to a receptor and is usually expressed in units of kilocalories per mole (kcal/mol) or kilojoules (kJ/mol).

Molecular docking analysis of p-Tolylpentachlorophenoxyacetate

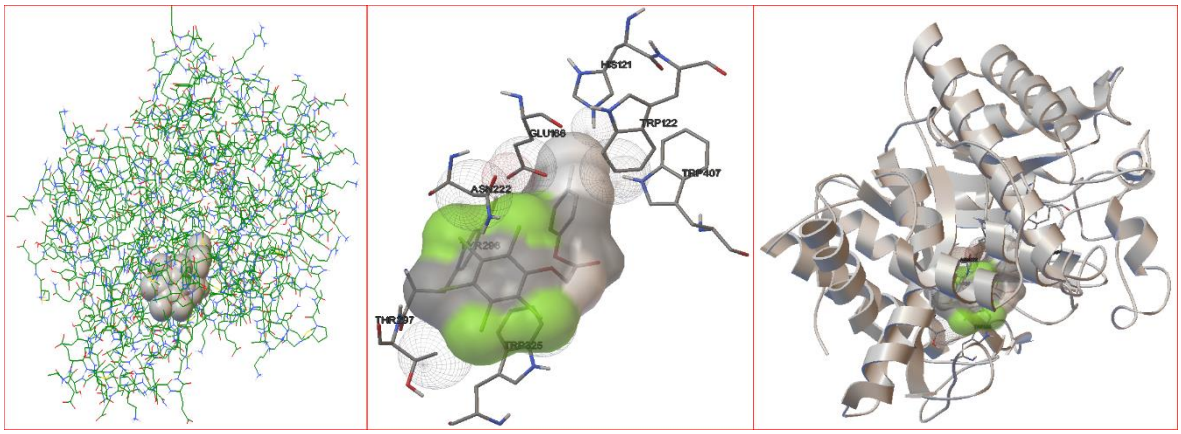


Figure 1. p-Tolylpentachlorophenoxyacetate - binding of p-tolylpentachlor ophenoxyacetate to protein amino acid residues in the protein complex.

Table 1 Interaction of ligand molecules with protein amino acid residues (by H-bond, VdV, etc.) in the complexes obtained as a result of molecular docking studies.

	Active amino acids not involved in binding
p-Tolylpentachlorophenoxyacetate	**ASN222, GLU166, HIS121, TYR296, THR297, TRP325, TRP407, TRP122,**

In molecular docking, a more negative binding energy indicates a stronger interaction between the ligand and the receptor. This is because the binding energy represents the free energy change that occurs when a ligand binds to a receptor. According to the result of the AutoDock program presented in the table, it can be seen that among the above ligands, phenylpentachloroacetate and p-tolyl pentachlorophenoxyacetate have the lowest binding energy with the bacterial protein, and the bond between this ligand and the 3AHX protein is strong. Means The smallest energy value representing the bond strength was $\Delta G_{binding}$ =-7.34 for p-tolylpentachlorophenoxyacetate (Table-2). In drug discovery, ligands with more negative binding energies are generally considered more potent and more likely to succeed as drug candidates.

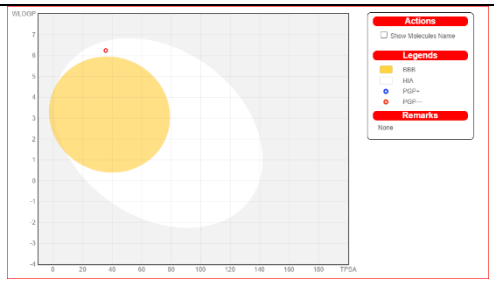
When p-Tolylpentachlorophenoxyacetate docking experiment was carried out 8 times, the following results were obtained. The results are presented in Table 2.

Table 2

№	Dock №1	Dock №2	Dock №3	Dock №4	Dock №5	Dock №6	Dock №7	Dock №8
$\Delta G_{binding}$	-7.34	-6.79	-6.60	-6.25	-6.17	-6.04	-5.27	-5.20

Boiled-egg results of p-Toylylpentachlorophenoxyacetate were determined. Boiled-egg results show that gastrointestinal absorption and brain entry are two pharmacokinetic behaviors that are critical to evaluate at different stages of drug discovery processes. To this end, the Brain Or IntestinaL EstimateD conductance method (BOILED-Egg) is proposed as an accurate predictive model that works by calculating the lipophilicity and polarity of small molecules. BOILED-Egg is used in the early stages of drug discovery to filter chemical libraries and evaluate drug candidates for development.

Table 3 p-Toylylpentachlorophenoxyacetate BOILED-Egg result

№	A synthesized substance	BOILED-Egg results
1.	p-Toylylpentachlorophenoxyacetate	

p-Toylylpentachlorophenoxyacetate was located in the white region, that is, in the physicochemical field of molecules with a high probability of absorption by the gastrointestinal tract.

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