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Synthesis, Spectral Characteristics, and Molecular Docking Studies of 2-(2,4-Dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)acetamide †

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Abstract: 2-(2,4-Dichlorophenoxy)acetic acid and its derivatives are promising anti-inflammatory agents capable of selectively inhibiting the COX-2 enzyme. In this paper, we report on the synthesis of a series of new derivatives of 2-(2,4-dichlorophenoxy)acetic acid-2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)acetamides. The method for the synthesis of these compounds is based on the addition of aromatic amines to 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)acetamide. Target products were obtained in 58–72% yield. The structure of the obtained compounds was reliably proven through ^{1}H and ^{13}C NMR spectroscopy data. In order to establish the prospects of the synthesized compounds as potential anti-inflammatory agents, we carried out molecular docking studies with COX-2. Molecular docking was carried out using the AutoDock Vina program based on the PyRx 0.8 platform. The preparation of the enzyme structure (PDB ID: 4M11, *Mus musculus*) and the structures of potential inhibitors was carried out using the Chimera 1.14 and ArgusLab 4.0.1 programs, respectively. The conformation corresponding to the lowest energy was chosen as the most likely binding position. According to the results of molecular docking, the structures of the synthesized compounds effectively interact with the active site of COX-2 and surpass 2-(2,4-dichlorophenoxy)acetic acid in terms of the strength of the complex formed with this enzyme.

Keywords: 2-(2,4-dichlorophenoxy)acetic acid; synthesis; anti-inflammatory; molecular docking; COX-2; thiourea

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1. Introduction

2,4-Dichlorophenoxyacetic acid and its derivatives are widely used as biologically active substances. This acid is one of the most widely used herbicides in the world, known by the abbreviation 2,4-D [1]. 2,4-Dichlorophenoxyacetic acid is also of interest to medicine and pharmacy as a COX-2 inhibitor and, as a result, is a potential anti-inflammatory agent [2]. Several other substances are also known to have anti-inflammatory activity and contain a 2,4-dichlorophenoxy group as a pharmacophore [3–5]. Alkylamide [6–9] and thiourea [10–12] fragments can also be distinguished among the pharmacophore groups with potential anti-inflammatory activity.

This study has combined all three pharmacophore groups in one molecule to create new and effective anti-inflammatory agents. We have obtained a series of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)acetamides (Figure 1), which differ from each other by an aryl substituent in the thiourea fragment. The structures of the obtained compounds have been tested in silico for their ability to inhibit the COX-2 enzyme.

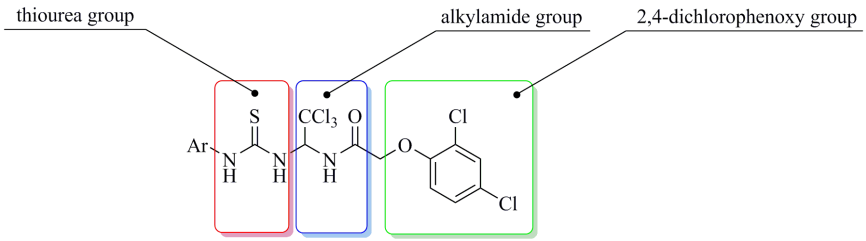


Figure 1. Structure of the obtained potential COX-2 inhibitors simultaneously containing 2,4-dichlorophenoxy, alkylamide, and thiourea pharmacophore groups.

The resulting compounds may also be promising for other areas of pharmacology and toxicology. For example, effective inhibitors of the GADD34:PP1 holoenzyme complex, such as Salubrinal and Sal003 [13–16], as well as moderate inhibitors of some enzymes of the P450 family [17] and the hERG ion channel [18] are known among their structural analogs. In addition, these compounds are of interest for synthetic organic chemistry as substrates for the preparation of 4*H*-1,3,5-oxadiazine derivatives [19–22].

2. Materials and Methods

2.1. Chemistry

Synthesis of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide (**3**) [23]. Hydroxy derivative **3** was obtained through condensation of chloral hydrate (**1**) with 2,4-dichlorophenoxyacetic acid amide (**2**) according to the procedure described in [24]. White crystals; yield 90%; mp 123–125 °C (MeCN); R_f = 0.67. Anal. Calcd (%) for $C_{10}H_8Cl_5NO_3$ (367.43): C, 32.69; H, 2.19; N, 3.81. Found: C, 32.65; H, 2.17; N, 3.85.

Synthesis of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)acetamide (**5**). Isothiocyanate (**5**) was obtained through the stage of formation of the intermediate chlorine derivative (**4**) according to the procedure described in [25]. The product could not be isolated from the reaction mixture. Further transformations involving isothiocyanate (**5**) were carried out using its solution.

Synthesis of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl) acetamides (**7a**–**h**). A solution of 10 mmol of one of the amines **6a**–**h** in 10 mL of acetonitrile was added to a mother solution of 10 mmol (4.09 g, theoretical yield) of isothiocyanate **5** in 10 mL of acetonitrile. The mixture was brought to a boil and left for 24 h. The precipitate formed was filtered, washed with 10 mL of acetonitrile, and purified through recrystallization from acetonitrile or ethanol.

2-(2,4-Dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2,4-dimethylphenyl)thioureido)ethyl) acetamide (**7a**). Pale yellow crystals; yield 72% (3.92 g); mp 191–193 °C (MeCN); R_f = 0.71. ^{1}H NMR: δ 9.89 (s, 1H, NH), 8.89 (d, J = 7.8 Hz, 1H, NH), 8.02 (br. s, 1H, NH), 7.57 (s, 1H, $H_{arom.}$), 7.41 (t, J = 8.8 Hz, 1H, $H_{arom.}$), 7.33 (d, J = 8.3 Hz, 1H, $H_{arom.}$), 7.11–7.00 (m, 4H, $3H_{arom.}$ + CH), 4.77 (dd, ^2J = 15.2, 15.2 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). ^{13}C NMR: δ 182.0 (C=S), 166.7 (C=O), 152.3, 136.2, 134.5, 134.1, 131.1, 129.4, 128.0, 127.7, 126.9, 125.4, 122.7, 115.8 ($C_{arom.}$), 101.6 (CCl_3), 69.7 (CH), 67.8 (CH_2), 20.6 (CH_3), 17.6 (CH_3). Anal. Calcd (%) for $C_{19}H_{18}Cl_5N_3O_2S$ (529.68): C, 43.08; H, 3.43; N, 7.93. Found: C, 43.05; H, 3.39; N, 7.98.

2-(2,4-Dichlorophenoxy)-N-(2,2,2-trichloro-1-(3-(2,5-dimethylphenyl)thioureido)ethyl) acetamide (**7b**). Pale yellow crystals; yield 68% (3.60 g); mp 188–190 °C (MeCN); R_f = 0.77. ^{1}H NMR: δ 9.87 (s, 1H, NH), 8.91 (br. s, 1H, NH), 8.06 (br. s, 1H, NH), 7.61 (s, 1H, $H_{arom.}$), 7.42–7.34 (m, 2H, $H_{arom.}$), 7.15 (d, J = 7.8 Hz, 1H, $H_{arom.}$), 7.04–7.00 (m, 3H, $2H_{arom.}$ + CH), 4.77 (dd, ^2J = 15.2, 15.7 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.14 (s, 3H, CH_3). ^{13}C NMR: δ 181.9 (C=S), 166.7 (C=O), 152.3, 136.5, 135.4, 131.4, 130.4, 129.4, 128.1, 128.0, 127.6, 125.4, 122.6, 115.8 ($C_{arom.}$), 101.6 (CCl_3), 69.7 (CH), 67.8 (CH_2), 20.5 (CH_3), 17.2 (CH_3). Anal. Calcd (%) for $C_{19}H_{18}Cl_5N_3O_2S$ (529.68): C, 43.08; H, 3.43; N, 7.93. Found: C, 43.12; H, 3.40; N, 7.97.

2-(2,4-Dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2-methoxyphenyl)thioureido)ethyl) acetamide (**7c**). Pale yellow crystals; yield 70% (3.72 g); mp 193–195 °C (EtOH); R_f = 0.68.

^{1}H NMR: δ 9.77 (s, 1H, NH), 8.92 (d, J = 8.8 Hz, 1H, NH), 8.47 (br. s, 1H, NH), 7.85 (br. s, 1H, $H_{arom.}$), 7.61 (d, J = 2.9 Hz, 1H, $H_{arom.}$), 7.40–7.34 (m, 2H, $H_{arom.}$), 7.18 (t, J = 7.3 Hz, 1H, $H_{arom.}$), 7.07 (d, J = 7.8 Hz, 1H, $H_{arom.}$), 7.02 (d, J = 9.3 Hz, 1H, $H_{arom.}$), 6.93 (dd, J = 8.8, 6.9 Hz, 1H, CH), 4.79 (dd, ^2J = 15.7, 15.2 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3). ^{13}C NMR: δ 181.1 (C=S), 166.6 (C=O), 152.3, 151.8, 129.4, 128.0, 127.0, 126.3, 125.9, 125.3, 122.5, 119.9, 115.6, 111.5 ($C_{arom.}$), 101.3 (CCl_3), 69.5 (CH), 67.5 (CH_2), 55.7 (OCH_3). Anal. Calcd (%) for $C_{18}H_{16}Cl_5N_3O_3S$ (531.65): C, 40.67; H, 3.03; N, 7.90. Found: C, 40.63; H, 2.99; N, 7.94.

N-(1-(3-(4-Acetamidophenyl)thioureido)-2,2,2-trichloroethyl)-2-(2,4-dichlorophenoxy) acetamide (**7d**). Pale yellow crystals; yield 58% (3.41 g); mp 171–173 °C (MeCN); R_f = 0.28. ^{1}H NMR: δ 9.98 (s, 1H, NH), 9.68 (s, 1H, NH), 8.73 (d, J = 8.8 Hz, 1H, NH), 8.12 (br. s, 1H, NH), 7.60 (s, 1H, $H_{arom.}$), 7.56 (d, J = 8.3 Hz, 1H, $H_{arom.}$), 7.37–7.34 (m, 3H, $H_{arom.}$), 6.76 (d, J = 8.3 Hz, 2H, $H_{arom.}$), 5.98 (dd, J = 9.3, 8.8 Hz, 1H, CH), 4.77 (dd, ^2J = 15.2, 15.7 Hz, 2H, CH_2), 1.98 (s, 3H, CH_3). ^{13}C NMR: δ 180.7 (C=S), 167.6 (C=O), 166.7 (C=O), 152.2, 141.1, 131.3, 129.4, 127.9, 125.3, 124.2, 120.6, 119.3, 114.2 ($C_{arom.}$), 101.6 (CCl_3), 70.7 (CH), 67.1 (CH_2), 23.8 (CH_3). Anal. Calcd (%) for $C_{19}H_{17}Cl_5N_4O_3S$ (558.68): C, 40.85; H, 3.07; N, 10.03. Found: C, 40.81; H, 3.05; N, 10.06.

Ethyl 4-(3-(2,2,2-trichloro-1-(2-(2,4-dichlorophenoxy)acetamido)ethyl)thioureido)benzoate (**7e**). Pale yellow crystals; yield 67% (3.84 g); mp 195–197 °C (MeCN); R_f = 0.60. ^{1}H NMR: δ 10.65 (s, 1H, NH), 8.91 (d, J = 8.8 Hz, 1H, NH), 8.53 (d, J = 9.3 Hz, 1H, NH), 7.94 (d, J = 8.8 Hz, 2H, $H_{arom.}$), 7.77 (d, J = 8.8 Hz, 2H, $H_{arom.}$), 7.61 (d, J = 2.9 Hz, 1H, $H_{arom.}$), 7.37–7.33 (m, 2H, $H_{arom.}$), 7.03 (d, J = 9.3 Hz, 1H, CH), 4.80 (dd, ^2J = 15.7, 15.7 Hz, 2H, CH_2), 4.30 (q, J = 7.3 Hz, 2H, CH_2), 1.31 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR: δ 180.5 (C=S), 166.8 (C=O, amide), 165.2 (C=O, ester), 152.3, 143.4, 129.9, 129.4, 128.0, 125.4, 125.3, 122.5, 121.6, 115.6 ($C_{arom.}$), 101.0 (CCl_3), 69.1 (CH), 67.5 (CH_2), 60.6, 14.2 (ethyl). Anal. Calcd (%) for $C_{20}H_{18}Cl_5N_3O_4S$ (573.69): C, 41.87; H, 3.16; N, 7.32. Found: C, 41.85; H, 3.12; N, 7.37.

2-(2,4-Dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2-chlorophenyl)thioureido)ethyl) acetamide (**7f**). Pale yellow crystals; yield 69% (3.70 g); mp 196–198 °C (MeCN); R_f = 0.63. ^{1}H NMR: δ 9.69 (s, 1H, NH), 8.98 (d, J = 8.8 Hz, 1H, NH), 8.60 (d, J = 9.3 Hz, 1H, NH), 7.68 (d, J = 7.8 Hz, 1H, $H_{arom.}$), 7.61 (d, J = 2.5 Hz, 1H, $H_{arom.}$), 7.53 (d, J = 8.3 Hz, 1H, $H_{arom.}$), 7.37–7.34 (m, 3H, $H_{arom.}$), 7.29–7.25 (m, 1H, $H_{arom.}$), 7.03 (d, J = 8.8 Hz, 1H, CH), 4.81 (dd, ^2J = 15.7, 15.7 Hz, 2H, CH_2). ^{13}C NMR: δ 182.4 (C=S), 166.7 (C=O), 152.3, 135.8, 129.5, 129.4, 129.3, 129.2, 128.0, 127.7, 127.2, 125.3, 122.5, 115.6 ($C_{arom.}$), 101.2 (CCl_3), 69.6 (CH), 67.5 (CH_2). Anal. Calcd (%) for $C_{17}H_{13}Cl_6N_3O_2S$ (536.07): C, 38.09; H, 2.44; N, 7.84. Found: C, 38.12; H, 2.40; N, 7.88.

N-(1-(3-(4-Bromophenyl)thioureido)-2,2,2-trichloroethyl)-2-(2,4-dichlorophenoxy) acetamide (**7g**). Pale yellow crystals; yield 72% (4.30 g); mp 186–188 °C (MeCN); R_f = 0.75 ^{1}H NMR: δ 10.36 (s, 1H, NH), 8.86 (d, J = 8.3 Hz, 1H, NH), 8.34 (d, J = 9.3 Hz, 1H, NH), 7.61 (d, J = 2.4 Hz, 1H, $H_{arom.}$), 7.55 (d, J = 8.8 Hz, 2H, $H_{arom.}$), 7.50 (d, J = 8.8 Hz, 2H, $H_{arom.}$), 7.37–7.32 (m, 2H, $H_{arom.}$), 7.03 (d, J = 8.3 Hz, 1H, CH), 4.80 (dd, ^2J = 15.2, 15.2 Hz, 2H, CH_2). ^{13}C NMR: δ 180.8 (C=S), 166.7 (C=O), 152.3, 138.2, 131.5, 129.4, 128.0, 125.4, 125.1, 122.6, 116.9, 115.7 ($C_{arom.}$), 101.2 (CCl_3), 69.3 (CH), 67.6 (CH_2). Anal. Calcd (%) for $C_{17}H_{13}BrCl_5N_3O_2S$ (580.52): C, 35.17; H, 2.26; N, 7.24. Found: C, 35.13; H, 2.24; N, 7.28.

2-(2,4-Dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(naphthalen-1-yl)thioureido)ethyl) acetamide (**7h**). Pale yellow crystals; yield 64% (3.53 g); mp 205–207 °C (MeCN); R_f = 0.69. ^{1}H NMR: δ 10.44 (s, 1H, NH), 8.89 (d, J = 8.3 Hz, 1H, NH), 8.28 (br. s, 1H, NH), 7.99–7.97 (m, 1H, $H_{arom.}$), 7.92–7.88 (m, 2H, $H_{arom.}$), 7.60–7.54 (m, 5H, $H_{arom.}$), 7.42 (t, J = 9.0 Hz, 1H, $H_{arom.}$), 7.35 (dd, J = 2.5 Hz, 1H, $H_{arom.}$), 7.03 (d, J = 8.3 Hz, 1H, CH), 4.79 (dd, ^2J = 15.7, 15.2 Hz, 2H, CH_2). ^{13}C NMR: δ 182.8 (C=S), 166.7 (C=O), 152.3, 134.2, 133.9, 129.5, 129.4, 128.2, 128.0, 127.0, 126.4, 126.3, 125.6, 125.4, 125.1, 122.8, 122.6, 115.8 ($C_{arom.}$), 101.5 (CCl_3), 69.7 (CH), 67.7 (CH_2). Anal. Calcd (%) for $C_{21}H_{16}Cl_5N_3O_2S$ (551.69): C, 45.72; H, 2.92; N, 7.62. Found: C, 45.70; H, 2.89; N, 7.65.

2.2. Molecular Docking Studies

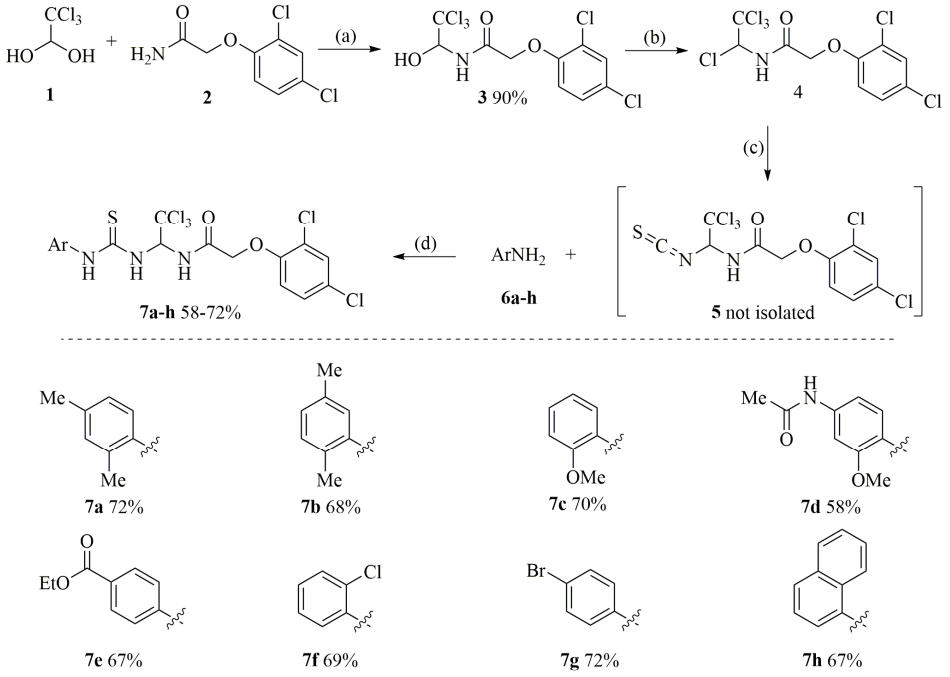
Before molecular docking, the structures of the resulting thioureas **9a**–**h** and 2,4-dichlorophenoxyacetic acid were optimized. We used the semiempirical PM3 method [26] implemented in the ArgusLab 4.0.1 software package [27–31] for optimization.

The 3D structure of the COX-2 enzyme (PDB ID: 4M11, *Mus musculus*) was downloaded in PDB format from the Protein Data Bank [32]. The protein structure was prepared for docking using the Chimera 1.14 program [33]. Before docking, we removed the water molecules and all the non-amino acid components from the protein structure, except for the hemes.

Molecular docking was carried out using AutoDock Vina [34], implemented on the PyRx 0.8 platform. The position of the inhibitor molecule in the active site of the enzyme with the lowest ΔG was taken as the most probable binding position. The docking area was centered on the amino acids Arg 120, Ser 353, Tyr 355, Tyr 385, Val 523, and Ser 530 [35]. The grid size was X: 25.0 Y: 25.0 Z: 25.0 Å, and the coordinates of its center were X: 17.1 Y: 43.2 Z: 32.6. To visualize the results, we used the PyMOL 0.99rc6 program [36].

3. Results and Discussion

The starting materials for obtaining the target 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)acetamides (**7a**–**h**) were synthesized according to previously developed procedures. 2-(2,4-Dichlorophenoxy)-*N*-(2,2,2-trichloro-1-hydroxyethyl)acetamide (**3**) was obtained through the condensation of chloral hydrate (**1**) with 2,4-dichlorophenoxyacetic acid amide (**2**) in the melt [24]. Next, the resulting compound **3** was chlorinated at the hydroxyl group, followed by the chlorine atom substitution in compound **4** for the isothiocyanate group according to the procedure described in [25]. Thioureas (**7a**–**h**) were obtained through the amines **6a**–**h** addition to 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-isothiocyanatoethyl)acetamide (**5**) in acetonitrile medium (Scheme 1).

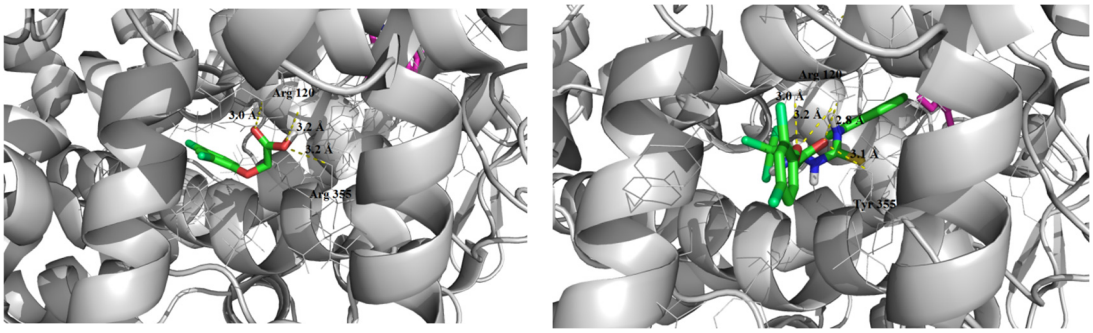


Scheme 1. Synthesis of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)acetamides (**7a**–**h**). Reagents and conditions: (a) heating, solvent-free; (b) $SOCl_2$, CCl_4, reflux 1.5 h; (c) KSCN, MeCN, r.t., 24 h; (d) MeCN, reflux 1 min then left at r.t. 24 h.

The structures of thioureas **7a**–**h** were proved through ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectra, the signals of three NH protons were characteristic, which appeared in the region of 10.65–8.02 ppm. The CH signal of the proton located near the

trichloromethyl group appeared as a doublet or doublet of doublets at 7.03–5.98 ppm. The signal of the methylene group of the 2,4-dichlorophenoxyacetic acid residue was also characteristic, which appeared in the region of 4.81–4.77 ppm in the form of a doublet of doublets with a spin-spin interaction constant of about 15.5 Hz. In the ^{13}C NMR spectra, the signals of the carbons C=S, C=O, CCl_3, CH, and CH_2 groups were characteristic. The C=S signal of the carbon of the thiourea fragment was in the low-field region at 182.8–180.5 ppm. In turn, the carbon signal of the amide group appeared at about 166.7 ppm. The CCl_3, CH, and CH_2 group signals appeared at 101.6–101.0, 70.7–69.1, and 67.8–67.1 ppm, respectively.

The structures of all the studied compounds effectively interacted with the COX-2 active site according to the results of molecular docking. The energy value of the COX-2:Ligand complex ranged from −10.4 to −8.9 kcal/mol. According to this parameter, thioureas **7a**–**h** were significantly superior to 2,4-dichlorophenoxyacetic acid, which we used as a reference compound. The energy value of the complex was −6.7 kcal/mol for 2,4-D. At the same time, the 2,4-dichlorophenoxyacetic acid molecule was effectively fixed in the COX-2 active site (Figure 2a) through the formation of two intermolecular hydrogen bonds, 3.0 and 3.2 Å long, with the amino acid Arg 120, and one hydrogen bond, 3.2 Å long, with Tyr 155 (for comparison, see [2]). Among the studied compounds, thiourea **7h** interacted most effectively with the COX-2 active site. This compound formed four intermolecular hydrogen bonds with the amino acids of the active site, three of which, ranging from 2.8 to 3.2 Å long, were observed with Arg 120, and one, 3.1 Å long, was formed with Tyr 355 (Figure 2b). The value of ΔG was −10.4 kcal/mol.



(**a**) (**b**)

Figure 2. Molecule position of 2,4-dichlorophenoxyacetic acid (**a**) and 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(naphthalen-1-yl)thioureido) ethyl)acetamide (**7h**) (**b**) in the active site of COX-2 according to the results of molecular docking.

4. Conclusions

In this study, we have obtained a series of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)acetamides simultaneously containing 2,4-dichlorophenoxy, alkylamide and thiourea pharmacophore groups. The structures of the obtained compounds were tested for the ability to inhibit the COX-2 enzyme using molecular docking. It was shown that the test compounds are significantly superior to 2,4-dichlorophenoxyacetic acid in terms of the strength of the complex formed with this enzyme.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/ASEC2023-15324/s1, Figure S1. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2,4-dimethylphenyl)thioureido)ethyl)acetamide (**7a**); Figure S2. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2,4-dimethylphenyl)thioureido)ethyl)acetamide (**7a**); Figure S3. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2,5-dimethylphenyl)thioureido)ethyl)acetamide (**7b**); Figure S4. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2,5-dimethylphenyl)thioureido)ethyl)acetamide (**7b**); Figure S5. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2-methoxyphenyl)thioureido)ethyl)acetamide (**7c**);

Figure S6. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2-methoxyphenyl)thioureido)ethyl)acetamide (**7c**); Figure S7. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *N*-(1-(3-(4-acetamidophenyl)thioureido)-2,2,2-trichloroethyl)-2-(2,4-dichlorophenoxy)acetamide (**7d**); Figure S8. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of *N*-(1-(3-(4-acetamidophenyl)thioureido)-2,2,2-trichloroethyl)-2-(2,4-dichlorophenoxy)acetamide (**7d**); Figure S9. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of ethyl 4-(3-(2,2,2-trichloro-1-(2-(2,4-dichlorophenoxy)acetamido)ethyl)thioureido)benzoate (**7e**); Figure S10. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of ethyl 4-(3-(2,2,2-trichloro-1-(2-(2,4-dichlorophenoxy) acetamido)ethyl)thioureido)benzoate (**7e**); Figure S11. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2-chlorophenyl)thioureido)ethyl)acetamide (**7f**); Figure S12. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(2-chlorophenyl) thioureido)ethyl)acetamide (**7f**); Figure S13. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of *N*-(1-(3-(4-bromophenyl)thioureido)-2,2,2-trichloroethyl)-2-(2,4-dichlorophenoxy)acetamide (**7g**); Figure S14. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of *N*-(1-(3-(4-bromophenyl)thioureido)-2,2,2-trichloroethyl)-2-(2,4-dichlorophenoxy)acetamide (**7g**); Figure S15. ^{1}H NMR (400 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(naphthalen-1-yl)thioureido)ethyl)acetamide (**7h**); Figure S16. ^{13}C NMR (100 MHz, DMSO-d_6) spectra of 2-(2,4-dichlorophenoxy)-*N*-(2,2,2-trichloro-1-(3-(naphthalen-1-yl)thioureido)ethyl)acetamide (**7h**).

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