El-Zemity *et al. Chem. Biol. Technol. Agric.* (2024) 11:124
https://doi.org/10.1186/s40538-024-00646-1

Chemical and Biological Technologies in Agriculture

RESEARCH

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Design, synthesis, pharmacophore modeling, and molecular docking of some novel chloroacetamide derivatives as herbicidal agents

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Abstract

Background The discovery of new lead compounds with desired properties and biological activity is an excellent challenge in pesticide chemistry. Chloroacetamide are an important class of synthetic herbicides.

Results To explore the herbicidal activity of chloroacetamides, several new chloroacetamide derivatives have been designed, and synthesized. The compounds have been described by forming Schiff bases followed by chloroacetylation of imines. The herbicidal activity as a chlorophyll inhibition was evaluated against two broadleaf weeds (*Chenopodium album* and *Anagallis arvensis*) and two grass weeds (*Lolium temulentum* and *Echinochloa crus-galli*) in comparison with acetochlor as a standard herbicide. ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic analyses confirmed the chemical structures of the synthesized compounds. Several compounds have demonstrated highly potent herbicidal activity compared to the standard herbicide acetochlor. Some of them have been described as the most effective against weeds tested, such as compounds **5b** and **18b**. Molecular docking to the active sites of Very Long Chain Fatty Acid Synthase (VLCFAS) has indicated that most compounds are low-energy binding agents and show high affinity for the active pocket.

Conclusion Novel herbicides may be discovered by combining chloroacetamide derivatives with these existing lead structures.

Keywords Chloroacetamide derivatives, Herbicidal activity, 3D-pharmacophore modeling, Docking, Virtual screening, VLCFAs

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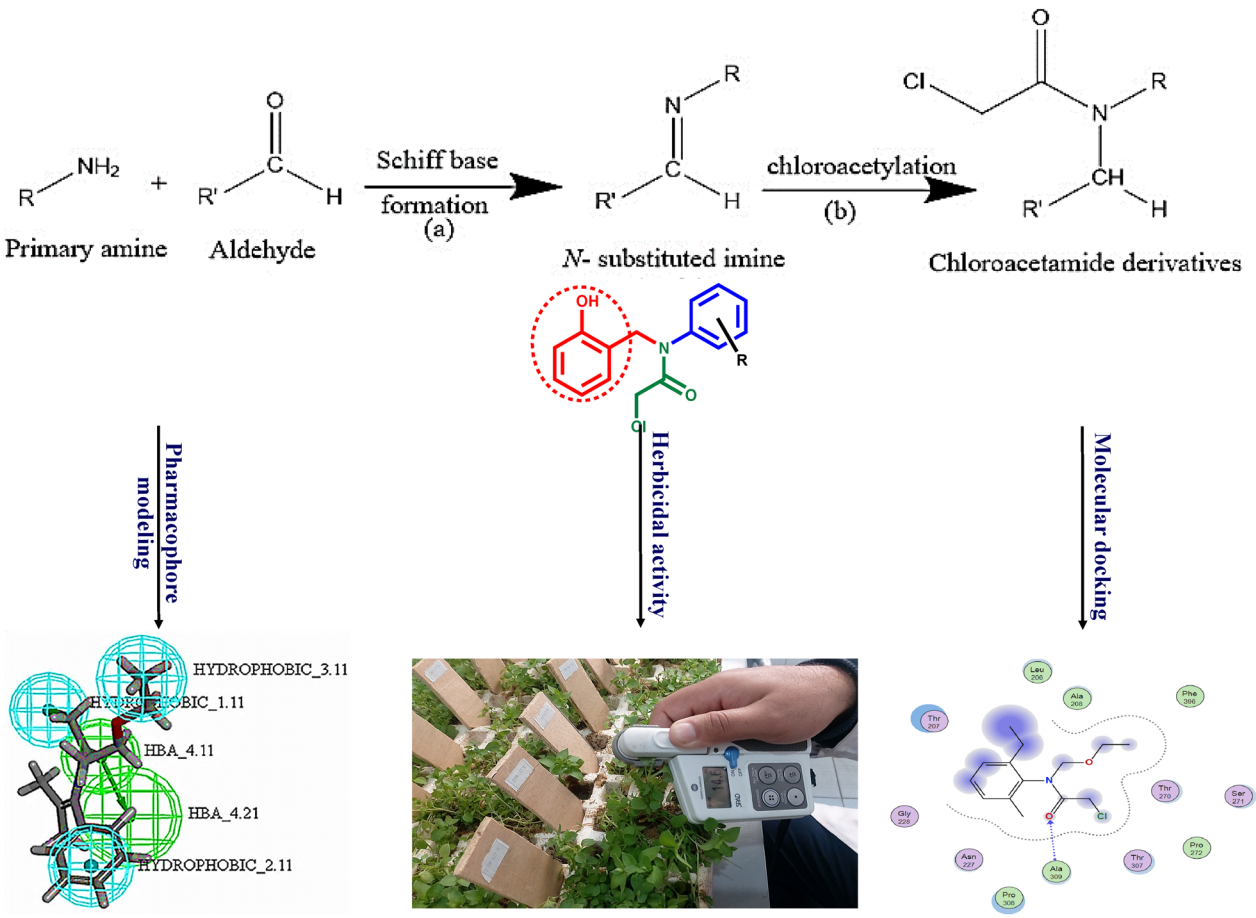
Graphical Abstract



Introduction

Weeds continuously threaten the farming industry by competing with cultivated plants for nutrition resources and dramatically decreasing crop productivity [1, 2]. Despite recent technological advances, there are still diverse challenges for developing effective targeted herbicides. A significant challenge is to create herbicides that are selective to the crops [3]. The significant symmetry between crops and weeds, especially for sites of herbicide action, complicates the discovery process. Moreover, resistance issues need extensive research because there are no herbicides with a new mode of action that have been on the market for decades [4–6]. Most studies of herbicide resistance have focused on the biochemical mechanisms of target and non-target proteins. Little attention has been paid to the effects of the chemical structure properties of the inhibitor molecule on the development of resistance [7, 8].

The successful design of new herbicides depends on the careful consideration of several factors, including the choice of the target enzyme, the design of the inhibitor, the delivery of the inhibitor to the target, and its metabolic fate [9–11]. In herbicide development, synthetic chemistry plays an important role in the chemical modification of active products already known as herbicides [12]. Amide products are deterministic organic compounds with many biological activities. The amide bond stability derives from synthetic chemicals to prepare such compounds based on this function. Some derivatives of amides are known to illustrate specific biological properties, including herbicidal, antimicrobial, anticancer, and antihistamine activities [13, 14]. Reacting chloroacetyl chloride with various amines produces chloroacetamide derivatives with potential herbicidal properties. The

substitution of the aromatic ring of an aromatic amine or aldehyde affects the yield and nature of the final product [15]. Overall, binding and affinity, physical and chemical properties, and synthetic costs for designing novel active compounds based on the binding sites of the target are the primary concerns in the discovery of a target-based herbicide [6].

A group of successful herbicides, classified as group-specific reagents, is the chloroacetamide herbicides. These herbicides contain reactive chlorine, which is a common feature of many known protein modification agents. The main target of such compounds is the inhibition elongation of Very Long Chain Fatty Acid Synthesis (VLCFAs) located in the endoplasmic reticulum. The absence of this protein in the cell and lack of the cuticle waxes consequently loss of membrane stability and leakage, leading to the death of the herbicide-treated plants [16]. Before emergence, chloroacetamide compounds typically affect susceptible weeds (annual grasses and some small-seeded broadleaf weeds) but do not prevent seed germination. The primary absorption and action site of these herbicides on broadleaf species is the roots, while that on grass species is the emerging shoot [17]. In the last few years, the introduction of new chloroacetamide and oxyacetamide herbicides, such as dimethenamid, defense, and flufenacet, has shown that this herbicide class is still going strong in agricultural applications in maize and rice [18–21]. Therefore, challenges remain for the development of new chloroacetamide herbicides.

In silico studies include pharmacophore mapping, virtual screening, and docking, which are the rational methods for identifying novel hits or leads with diverse chemical scaffolds [22, 23]. As mentioned before, the pharmacophore combines steric and electrostatic characteristics of different compounds that are necessary to ensure optimal supramolecular interactions with a specific structure and trigger or block its biological effects. Molecular docking is widely used to suggest the binding modes of protein inhibitors.

Therefore, the present study is based on synthesizing new chloroacetamide derivatives containing important biological moieties and screening them to evaluate their potential activity against some economic weeds. Herein, the skeleton structure was obtained by replacing the aliphatic oxygenated bridge in chloroacetamide herbicides such as acetochlor, alachlor, and *s*-metolachlor with aromatic part of commercial herbicides such as phenol moiety of bromoxynil, methoxyphenyl of anisuron, and 2,4-dichlorophenyl of 2,4-D (Fig. 1). The chloroacetamides are done by forming the Schiff base mechanism followed by chloroacetylation. The spectroscopic characterizations of the synthesized derivatives were examined. The synthetic products were compared to acetochlor as a standard herbicide for evaluating their herbicidal activity against two broadleaf weeds and two grass weeds. The computational studies included pharmacophore modeling, and molecular docking. The achieved pharmacophore model can deliver a rational default hypothetical of the primary chemical properties accountable for biological activity and is expected to afford practical information to develop potential new candidates. The results obtained were further supported by molecular docking studies using enzyme VLCFAs to explore the potential binding methods.

Materials and methods

General methods

Melting points were determined in open glass capillaries using a Griffin melting point apparatus. All spectra of the synthetic compounds were identified and confirmed by ^{1}H-NMR and ^{13}C-NMR spectra using a Bruker NMR 400 MHz (Bruker Biospin, Germany). Deuterated DMSO was used as a solvent. The data were reported as chemical shifts (δ, ppm) relative to tetramethylsilane (TMS) as an internal standard. Molecular weight was determined using an electron impact mass spectrometer (EIMS) at Al-Azhar University, Cairo, Egypt. The relative intensity (%) corresponding to the most characteristic fragments was recorded.

Synthesis of chloroacetamide derivatives

The same strategy for the synthetic method of the typical commercial herbicides (acetochlor, metolachlor, and *s*-metolachlor) was used for the synthesis of chloroacetamide derivatives based on the formation of Schiff bases followed by chloroacetylation of imines (Fig. 2) [24]. Twenty two Schiff bases (**1a**–**22a**, Fig. 2) were synthesized according to Zhu et al. [25] To each amine product dissolved in 20 mL ethyl or methyl alcohol in the 50 mL dry flask, 0.01 mol of the corresponding aldehyde (salicylaldehyde, anisaldehyde, 2,4-dichlorobenzaldehyde) was added dropwise. After the complete addition of aldehyde, 1 mL of glacial acetic acid was added to the reaction mixture and stirred using a magnetic stirrer at room temperature (25 °C) for 10–20 min. The solvent was removed under reduced pressure. The crude product was washed by ether, affording the Schiff base derivative. Afterwards, the imine product (0.01 mol) was dissolved in dichloromethane and cooled at 0–5 °C using ice-water bath. 0.02 mol of chloroacetyl chloride prepared in dichloromethane was added dropwise to the above mixture. The mixtures were stirred for 6 h in water ice mixture and for a further 3 h at room temperature. The

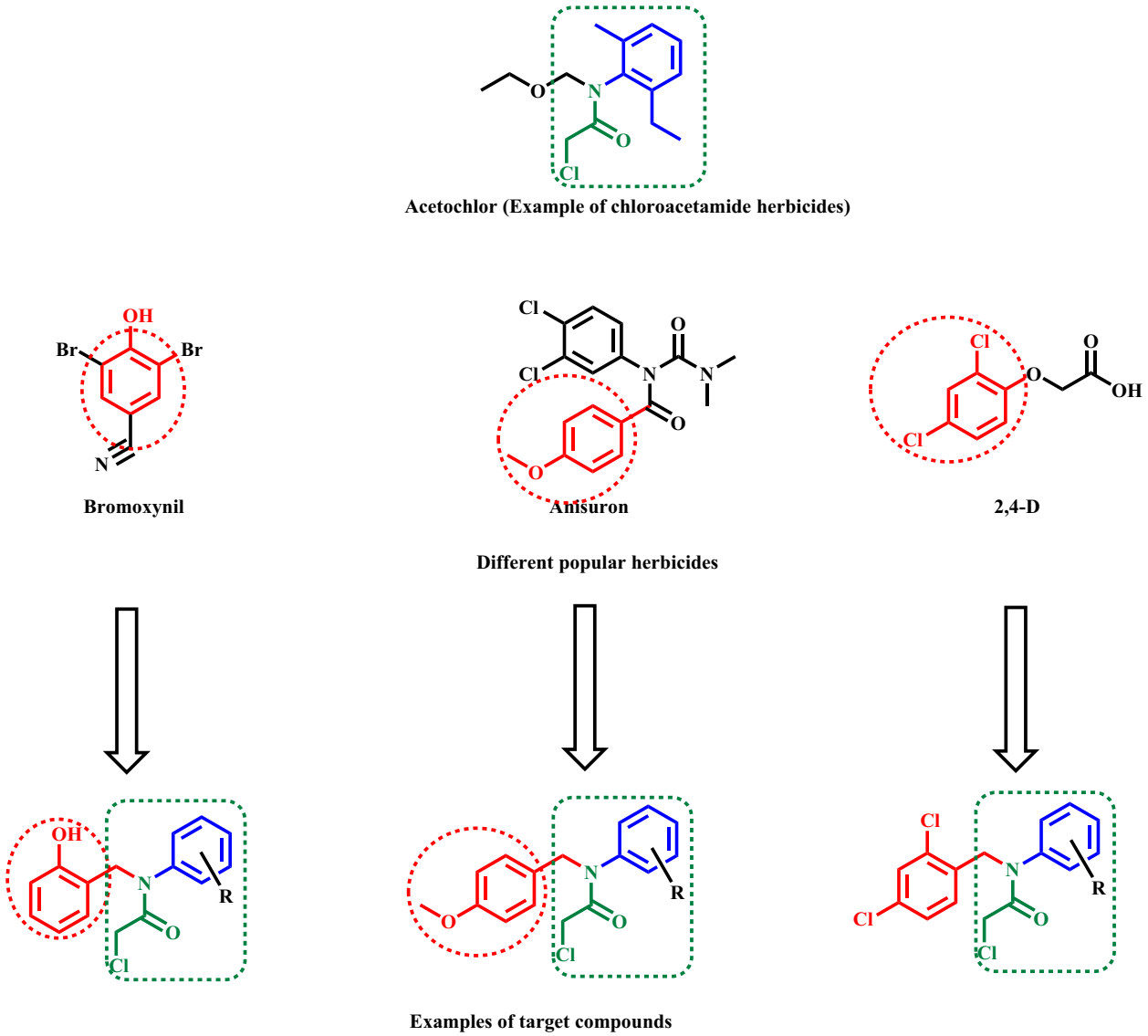


Fig. 1 The design strategy of novel chloroacetamide derivatives (**1b-22b**) containing different aromatic moieties

solvent was evaporated under reduced pressure to obtain the product. The products were washed with water and crystallized in ethanol or methanol [26].

2-chloro-N-(2-hydroxybenzyl)-N-(2-hydroxyphenyl)acetamide (1b)

A yellow powder; yield 30%; mp 235–236 °C. ^{1}H-NMR (DMSO, δ/ppm): 4.33 (*s*, 2H, chloroacetyl), 4.71 (*s*, 2H, NC$\underline{H}_2$), 7.25 (*m*, 2H, hydroxybenzyl, and 2H, hydroxyphenyl), 7.28–7.32 (*d*, 1H, hydroxyphenyl and 1H, hydroxybenzyl), 7.86–7.88 (*d*, 1H, hydroxyphenyl and 1H, hydroxybenzyl), and 9.85 (*s*, 2H, O$\underline{H}$ of phenyl and O$\underline{H}$ of benzyl). ^{13}C-NMR (DMSO, δ/ppm): 42.2 (N$\underline{C}H_2$), 43.7 ($\underline{C}H_2$, chloroacetyl), 119.42 (C3, hydroxybenzyl), 122.1 (C3, hydroxyphenyl), 123.5 (C5, hydroxybenzyl), 124.5 (C5, hydroxyphenyl), 125.9 (C4, hydroxyphenyl), 126.1 (C4 and C6, hydroxybenzyl), 126.9 (C6, hydroxyphenyl), 130.1 (C1, hydroxyphenyl), 141.9 (C2, hydroxyphenyl), 148.1 (C2, hydroxybenzyl) and 165.5 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 45.30 (22.47); 48.73 (100.00); 162.35 (80.95); 163.06 (59.62); 185.36 (67.33); 275.54 (39.60); 286.14 (13.08); 289.54 (32.28); 291.75. ($M^{+\cdot}$) (22.22); Anal. Calc. for $C_{15}H_{14}ClNO_3$ was 291.73 and found 291.75.

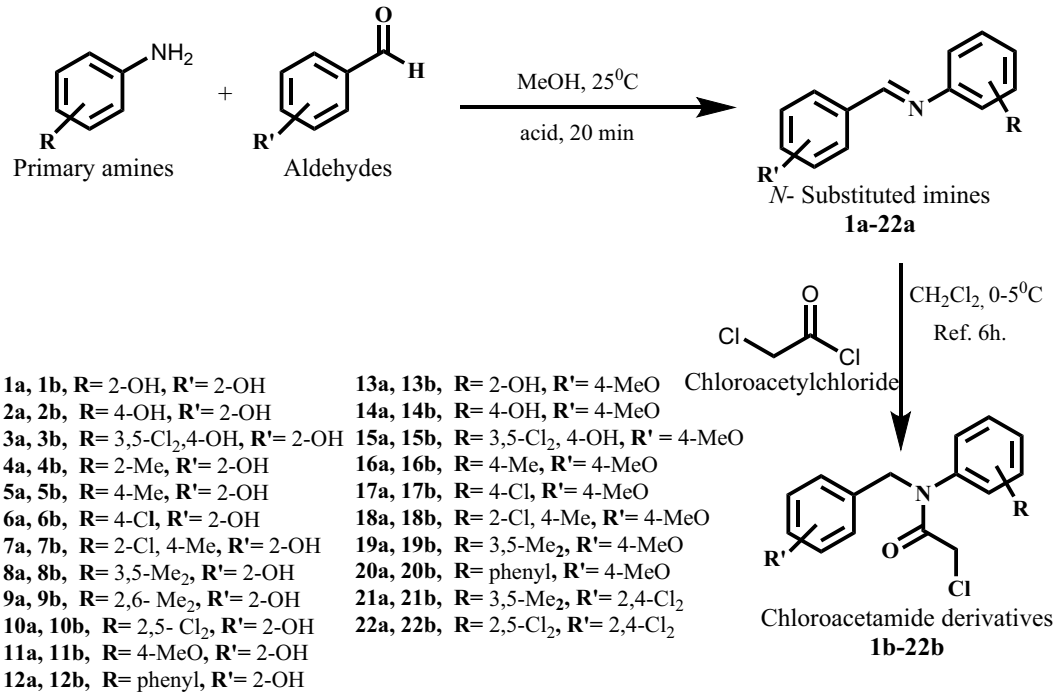


Fig. 2 Synthetic route of synthesized chloroacetamide derivatives (**1**–**22**)

2-chloro-N-(2-hydroxybenzyl)-N-(4-hydroxyphenyl)acetamide (2b)

A pale-yellow powder, yield 54%; mp 176–177 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 4.12 (*s*, 2H, chloroacetyl), 4.28 (*s*, 2H, NC$\underline{H}_2$), 6.855–6.860 (*d*, 2H, hydroxyphenyl), 6.872–6.877 (*d*, 3H, hydroxybenzyl), 7.169–7.174 (*m*, 2H, hydroxybenzyl), 7.186–7.190 (*d*, 2H, hydroxyphenyl), and 9.67 (*s*, 2H, O$\underline{H}$ of phenyl and O$\underline{H}$ of benzyl). ^{13}C-NMR (DMSO, *δ*/ppm): 41.9 (N$\underline{C}H_2$), 43.3 ($\underline{C}H_2$, chloroacetyl), 116.6 (C3 and C5, hydroxybenzyl), 122.5 (C3 and C5, hydroxyphenyl), 124.8 (C2 and C6 of hydroxyphenyl and C1, C4, and C5 of hydroxybenzyl), 129.1 (C1, hydroxyphenyl), 157.7 (C2 of hydroxyphenyl and C2 of hydroxybenzyl) and 169.2 ($\underline{C}$=O). EIMS, m\z (relative abundance, %):211.84 (43.49), 212.96 (100.00), 281.47 (24.80), 286.74 (6.53), 291.42 ($M^{+\cdot}$) (15.49); Anal. Calc. for $C_{15}H_{14}ClNO_3$ was 291.73 and found 291.42.

2-chloro-N-(2-hydroxybenzyl)-N-(3,5-dichloro-4 hydroxyphenyl)acetamide (3b)

A pale brown crystal, yield 20%; mp 284–285 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 4.38 (*s*, 4H, chloroacetyl and NC$\underline{H}_2$), 6.956–6.976 (*d*, 1H, hydroxybenzyl), 6.990–7.117 (*m*, 2H, hydroxybenzyl), 7.23 (*s*, 2H, hydroxyphenyl), 7.35–7.37 (*d*, 1H, hydroxybenzyl), and 8.28 (*s*, 2H, O$\underline{H}$ of phenyl and O$\underline{H}$ of benzyl). ^{13}C-NMR (DMSO, *δ*/ppm): 41.9 (N$\underline{C}H_2$), 42.18 ($\underline{C}H_2$, chloroacetyl), 119.4 (C3, hydroxybenzyl), 122.1 (C5, hydroxybenzyl), 123.5 (C2 and C6, hydroxyphenyl), 125.9 (C3 and C5, hydroxybenzyl), 126.1 (C4 and C6, hydroxybenzyl), 126.9 (C1, hydroxybenzyl), 130.1 (C1, hydroxyphenyl), 141.9 (C2, hydroxyphenyl), 148.1 (C2, hydroxybenzyl) and 165.5 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 99.65 (96.52), 164.56 (100.00), 299.71 (64.81), 358.04 (50.35), 360.22 ($M^{+\cdot}$) (43.43); Anal. Calc. for $C_{15}H_{12}Cl_3NO_3$ was 360.62 found 360.22.

2-chloro-N-(2-hydroxybenzyl)-N-(o-tolyl)acetamide (4b)

A dark brownish to red powder, yield 85%; mp 192–193 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 2.36 (*s*, 3H, –C$\underline{H}_3$), 4.47 (*s*, 2H, chloroacetyl), 5.22 (*s*, 2H, NC$\underline{H}_2$), 7.02–7.06 (*d*, 1H, hydroxybenzyl), 7.35–7.38 (*m*, 2H, hydroxybenzyl), 7.44–7.47 (*d*, 1H, phenyl), 7.49–7.55 (*m*, 2H, phenyl), 7.65–7.68 (*d*, 1H, hydroxybenzyl), 7.74–7.76 (*d*, 1H, phenyl), and 10.27 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 17.2 ($\underline{C}H_3$), 41.38 (N$\underline{C}H_2$), 49.1 ($\underline{C}H_2$, chloroacetyl), 117.4 (C3, hydroxybenzyl), 120 (C6, phenyl), 122.7 (C5, hydroxybenzyl), 123.8 (C5, phenyl), 127.7 (C4, hydroxybenzyl), 129.1 (C6, hydroxybenzyl), 129.8 (C1, hydroxybenzyl), 130.5 (C4, phenyl), 131.9 (C3, phenyl), 132.3 (C2, phenyl), 136.9 (C1, phenyl), 161.2 (C2, hydroxybenzyl) and 164 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 209.55 (56.38), 210.34 (100.00), 211.19 (96.10), 285.96 (2.13), 289.77 ($M^{+\cdot}$) (12.07); Anal. Calc. for $C_{16}H_{16}ClNO_2$ was 289.76 found 289.77.

2-chloro-N-(2-hydroxybenzyl)-N-(p-tolyl)acetamide (5b)

A yellow crystal, yield 46%; mp 165–166 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 2.36 (*s*, 3H, –C$\underline{H}_3$), 4.22 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.12–7.15 (*m*, 2H, hydroxybenzyl), 7.27–7.29 (*d*, 2H, hydroxybenzyl), 7.45–7.47 (*d*, 2H, phenyl), 7.64–7.66 (*d*, 2H, phenyl), and 10.26 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 20.8 ($\underline{C}H_3$), 41.9 (N$\underline{C}H_2$), 43.9 ($\underline{C}H_2$, chloroacetyl), 120 (C3 and C5, hydroxybenzyl), 129.7 (C1, C4, and C6 of hydroxybenzyl and C3 and C5 of hydroxyphenyl), 133.6 (C1, C2, C4, and C6 of hydroxyphenyl), 136.2 (C2, hydroxybenzyl) and 165.1 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 209.55 (56.38), 210.34 (100.00), 211.19 (96.10), 285.96 (2.13), 289.77 (93.68), 65.90 (86.95), 255.92 (100.00), 289.92 ($M^{+\cdot}$) (49.47), 292.08 ($M^{+2\cdot}$) (33.81); Anal. Calc. for $C_{16}H_{16}ClNO_2$ was 289.76 found 289.92.

2-chloro-N-(4-chlorophenyl)-N-(2-hydroxybenzyl)acetamide (6b)

A white crystal, yield 45%; mp 294–295 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 4.63 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.39–7.51 (*m*, 2H, hydroxybenzyl), 7.51–7.64 (*d*, 4H, phenyl), 7.64–7.66 (*d*, 2H, hydroxybenzyl), and 9.01 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 41.9 (N$\underline{C}H_2$), 43.3 ($\underline{C}H_2$, chloroacetyl), 119.7 (C3 and C5, hydroxybenzyl), 128.4 (C2 and C6 of hydroxyphenyl and C1, C4, and C6 of hydroxybenzyl), 133.1 (C1, C3, C4, and C5 of hydroxyphenyl), 134.2 (C2, hydroxybenzyl) and 164.2 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 80.17 (70.77), 92.31 (62.48), 120.07 (100.00), 226.72 (59.94), 270.15 (28.24), 295.01 (70.75), 305.13 (50.10), 310.80 ($M^{+\cdot}$) (26.50); Anal. Calc. for $C_{15}H_{13}Cl_2NO_2$ was 310.17 found 310.80.

2-chloro-N-(2-chloro-4-methylphenyl)-N-(2-hydroxybenzyl)acetamide (7b)

A white crystal, yield 55%; mp 118–119 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 2.30 (*s*, 3H, C$\underline{H}_3$), 4.22 (*s*, 2H, chloroacetyl), 4.36 (*s*, 2H, NC$\underline{H}_2$), 7.16–7.18 (*m*, 2H, hydroxybenzyl), 7.36 (*s*, 1H, phenyl), 7.56–7.58 (*d*, 4H, hydroxybenzyl and phenyl), and 9.83 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 20.6 ($\underline{C}H_3$), 41.9 (N$\underline{C}H_2$), 43.4 ($\underline{C}H_2$, chloroacetyl), 126.5 (C3 and C5, hydroxybenzyl), 127.1 (C5 and C6, phenyl), 128.6 (C1, C4, and C6, hydroxybenzyl), 130.2 (C2 and C3, phenyl), 132 (C1 and C4, phenyl), 137.6 (C2, hydroxybenzyl) and 165.6 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 77.19 (100.00), 191.30 (90.04), 317.26 (81.49), 319.24 (88.99), 321.05 (49.40), 324.20 ($M^{+\cdot}$) (88.99); Anal. Calc. for $C_{16}H_{15}Cl_2NO_2$ was 324.20 found 324.20.

2-chloro-N-(2-hydroxybenzyl)-N-(3,5-dimethylphenyl) acetamide (8b)

A pale brown crystal, yield 60%; mp 144–145 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 2.25 (*s*, 6H, –C$\underline{H}_3$, –C$\underline{H}_3$), 4.23 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 6.42–6.46 (*m*, 2H, hydroxybenzyl), 6.48–6.50 (*d*, 2H, hydroxybenzyl), 6.74 (*s*, 1H, phenyl), 7.21 (*s*, 2H, phenyl), and 10.16 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 21.5 ($\underline{C}H_3$ and $\underline{C}H_3$); 44.1 (N$\underline{C}H_2$), 62.29 ($\underline{C}H_2$, chloroacetyl), 117.5 (C3 and C5 of hydroxybenzyl and C2 and C6 of phenyl), 117.7 (C4, phenyl), 125.42 (C4 and C6, hydroxybenzyl), 125.8 (C1, hydroxybenzyl), 138.1 (C3 and C5, phenyl), 138.3 (C1, phenyl), 138.8 (C2, hydroxybenzyl) and 164.9 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 67.93 (84.76), 101.17 (100.00), 263.62 (87.56), 301.31 (27.76), 302.23 (77.11), 303.50 ($M^{+\cdot}$) (38.47); Anal. Calc. for $C_{17}H_{18}ClNO_2$ was 303.79 found 303.50.

2-chloro-N-(2,6-dimethylphenyl)-N-(2-hydroxybenzyl) acetamide (9b)

A golden to black crystal, yield 85%; mp 104–105 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 2.15 (*s*, 6H, –C$\underline{H}_3$, –C$\underline{H}_3$), 4.31 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.08–7.10 (*m*, 2H, hydroxybenzyl), 7.15–7.16 (*d*, 2H, hydroxybenzyl), 7.47–7.54 (*m*, 1H, phenyl), 7.65–7.67 (*d*, 1H, phenyl), 8.68–8.70 (*d*, 1H, phenyl), and 9.79 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 16.2 ($\underline{C}H_3$ and $\underline{C}H_3$), 42.4 (N$\underline{C}H_2$), 44.8 ($\underline{C}H_2$, chloroacetyl), 114.1 (C3, hydroxybenzyl), 123.5 (C5 of hydroxybenzyl and C4 of phenyl), 124.5 (C3 and C5, phenyl), 125.9 (C1, hydroxybenzyl), 126.9 (C4 and C6, hydroxybenzyl), 130.1 (C2 and C6, phenyl), 136.1 (C1, phenyl), 147.2(C2, hydroxybenzyl) and 166 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 55.23 (43.44), 56.25 (100.00), 77.31 (67.17), 132.24 (26.86), 160.19 (34.39), 303.06 ($M^{+\cdot}$) (11.36); Anal. Calc. for $C_{17}H_{18}ClNO_2$ was 303.79 found 303.06.

2-chloro-N-(2,5-dichlorophenyl)-N-(2-hydroxybenzyl) acetamide (10b)

An off-white crystal, yield 40%; mp 111–112 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 4.42 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.31–7.33 (*m*, 2H, hydroxybenzyl), 7.57–7.59 (*d*, 2H, hydroxybenzyl), 7.70–7.72 (*d*, 2H, phenyl), 7.90 (*s*, 1H, phenyl), and 10.01 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 42 (N$\underline{C}H_2$), 55.9 ($\underline{C}H_2$, chloroacetyl), 115.2 (C3, hydroxybenzyl), 120.2 (C5, hydroxybenzyl), 122.8 (C6, phenyl), 123.2 (C4, phenyl), 125 (C4 and C6, hydroxybenzyl), 129 (C1, hydroxybenzyl), 132.9 (C5, phenyl), 135.6 (C2, phenyl), 136.8 (C1, phenyl), 160 (C2, hydroxybenzyl) and 166 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 90.94 (85.99), 184.55 (100.00), 264.16 (58.75), 300.92 (76.29), 324.03 (38.93), 344.62 ($M^{+\cdot}$) (55.59); Anal. Calc. for $C_{15}H_{12}Cl_3NO_2$ was 344.62 found 344.20.

2-chloro-N-(2-hydroxybenzyl)-N-(4-methoxyphenyl)acetamide (11b)

A darkish brown to black powder, yield 80%; mp 129–130 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 3.75 (*s*, 3H, OC$\underline{H}_3$), 4.40 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.01–7.03 (*d*, 2H, methoxyphenyl), 7.33–7.36 (*m*, 2H, hydroxybenzyl), 7.45–7.47 (*d*, 2H, hydroxybenzyl), 7.58–7.62 (*d*, 2H, methoxyphenyl), and 10.27 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 42 (N$\underline{C}H_2$), 55.9 ($\underline{C}H_2$, chloroacetyl), 56.1 (–O$\underline{C}H_3$), 115.3 (C3 and C5, methoxyphenyl), 117.8 (C3, hydroxybenzyl), 119.8 (C5, hydroxybenzyl), 123 (C2, methoxyphenyl), 123.4 (C6, methoxyphenyl), 124.7 (C4, hydroxybenzyl), 125 (C1 and C6, hydroxybenzyl), 129.2 (C1, methoxyphenyl), 159.2 (C2, hydroxybenzyl), 161.9 (C4, methoxyphenyl) and 165.8 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 71.76 (58.47), 153.45 (100.00), 221.66 (51.53), 302.27 (11.81), 305.95 ($M^{+\cdot}$) (24.93); Anal. Calc. for $C_{16}H_{16}ClNO_3$ was 305.76 found 305.95.

2-chloro-N-(2-hydroxybenzyl)-N-(naphthalen-1-yl)acetamide (12b)

White to grey flakes, yield 80%; mp 160–161 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 4.47 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.51–7.55 (*m*, 1H, hydroxybenzyl), 7.57–7.60 (*m*, 3H, hydroxybenzyl and naphthyl), 7.69–7.70 (*d*, 2H, hydroxybenzyl), 7.82–7.84 (*d*, 2H, naphthyl), 7.97–7.99 (*m*, 1H, naphthyl), 8.06–8.08 (*d*, 2H, naphthyl), and 10.31 (*s*, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 43.8 (N$\underline{C}H_2$ and $\underline{C}H_2$ of chloroacetyl), 122.4 (C2, naphthyl), 123 (C3, hydroxybenzyl), 126.1 (C4, naphthyl), 126.4 (C5 of hydroxybenzyl and C8 of naphthyl), 125.5 (C8a, naphthyl), 126.6 (C3, C6, and C7, naphthyl), 128.2 (C4 and C6, hydroxybenzyl), 128.7 (C5 of naphthyl and C1 of hydroxybenzyl), 133.3 (C4a, naphthyl), 134.2 (C1 of naphthyl and C2 of hydroxybenzyl) and 166.1 ($\underline{C}$=O). EIMS, m\z (relative abundance, %):146.31 (87.02), 210.0 (100.00), 239.16 (86.37), 324.66 (40.51), 325.87 ($M^{+\cdot}$) (2.27); Anal. Calc. for $C_{19}H_{16}ClNO_2$ was 325.79 found 325.87.

2-chloro-N-(2-hydroxyphenyl)-N-(4-methoxybenzyl)acetamide (13b)

A pale yellow powder, yield 60%; mp 172–174 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 1.76 (*s*, 3H, –OC$\underline{H}_3$), 1.91 (*s*, 2H, chloroacetyl), 3.87 (*s*, 2H, NC$\underline{H}_2$), 6.73–6.75 (*d*, 1H, hydroxyphenyl)), 7.27–7.40 (*d*, 5H, methoxyphenyl and hydroxyphenyl), 7.40–7.52 (*m*, 2H, hydroxyphenyl), and 10.76 (*s*, 1H, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 44.1 ($\underline{C}H_2$ of chloroacetyl and N$\underline{C}H_2$), 62.2 (–O$\underline{C}H_3$), 117.5 (C3 and C5, methoxyphenyl), 117.7 (C3, C5, and C6, hydroxyphenyl), 125.4 (C4, hydroxyphenyl), 125.8 (C1 of methoxyphenyl and C1 of hydroxyphenyl), 138.1 (C2 and C6, methoxyphenyl), 138.3 (C2, hydroxyphenyl), 138.8 (C4, methoxyphenyl) and 165.1 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 51.37 (65.16), 134.14 (68.26), 139.66 (52.51), 153.43 (77.16), 175.13 (100.00), 218.82 (64.77), 301.73 (38.45), 305.87 ($M^{+\cdot}$) (5.43); Anal. Calc. for $C_{16}H_{16}ClNO_3$ was 305.76 found 305.87.

2-chloro-N-(4-hydroxyphenyl)-N-(4-methoxybenzyl)acetamide (14b)

A darkish brown powder, yield 75%; mp 202–204 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 3.69 (*s*, 2H, chloroacetyl), 3.87 (*s*, 2H, NC$\underline{H}_2$), 3.94 (*s*, 3H, –OC$\underline{H}_3$), 6.85–6.88 (*d*, 2H, methoxyphenyl), 6.94–7.97 (*d*, 2H, hydroxyphenyl), 7.13–7.15 (*d*, 2H, methoxyphenyl), 7.19–7.21 (*d*, 2H, hydroxyphenyl), and 9.17 (*s*, 1H, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 41.6 ($\underline{C}H_2$, chloroacetyl), 56.2 (N$\underline{C}H_2$), 56.4 (–O$\underline{C}H_3$); 115.4 (C3 and C5, methoxyphenyl), 116.5 (C3 and C5, hydroxyphenyl), 122.8 (C2 and C6, hydroxyphenyl), 123.0–124.8 (C1, methoxyphenyl), 130.1 (C2 and C6, methoxyphenyl), 132.3 (C1, hydroxyphenyl), 157.6 (C4 of hydroxyphenyl and C4 of methoxyphenyl) and 164.7 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 49.90 (57.88), 101.17 (100.00), 210.19 (51.84), 252.39 (58.07), 272.96 (41.90), 275.72 (31.50), 301.31 (26.56), 303.32(76.13); 305.50 ($M^{+\cdot}$) (37.43); Anal. Calc. for $C_{16}H_{16}ClNO_3$ was 305.76 found 305.50.

2-chloro-N-(3,5-dichloro-4-hydroxyphenyl)-N-(4 methoxybenzyl)acetamide (15b)

A pale yellow to brown crystal, yield 20%; mp 65–66 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 1.80 (*s*, 3H, –OC$\underline{H}_3$), 4.17 (*s*, 2H, chloroacetyl), 4.30 (*s*, 2H, NC$\underline{H}_2$), 6.92–6.93 (*d*, 4H, methoxyphenyl), 7.27 (*s*, 1H, hydroxyphenyl), 7.39 (*s*, 1H, hydroxyphenyl), and 10.68 (*s*, 1H, O$\underline{H}$). ^{13}C-NMR (DMSO, *δ*/ppm): 41.8 ($\underline{C}H_2$, chloroacetyl), 43.6 (N$\underline{C}H_2$), 56.2 (–O$\underline{C}H_3$), 115.1 (C3 and C5, methoxyphenyl), 122.8 (C2 and C6, hydroxyphenyl), 126.1 (C3 and C5, hydroxyphenyl), 128.7 (C1, methoxyphenyl), 130.1 (C2 and C6, methoxyphenyl), 132.4 (C1, hydroxyphenyl), 133.1 (C4, hydroxyphenyl), 134.2 (C4, methoxyphenyl) and 169 ($\underline{C}$=O). EIMS, m\z (relative abundance, %):146.04 (100.00), 154.18 (68.17), 187.93 (66.11), 336.41 (86.12), 343.44 (56.32), 374.70 ($M^{+\cdot}$) (64.20), 375.74 ($M^{+1\cdot}$) (23.09); Anal. Calc. for $C_{16}H_{14}Cl_3NO_3$ was 374.64 found 374.70.

2-chloro-N-(4-methoxybenzyl)-N-(p-tolyl)acetamide (16b)

A yellow powder, yield 80%; mp 103–104 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 2.32 (*s*, 3H, –OC$\underline{H}_3$), 3.93 (*s*, 2H, chloroacetyl), 4.29 (*s*, 2H, NC$\underline{H}_2$), 7.12–7.14 (*d*, 3H, methoxyphenyl and tolyl), 7.51–7.53 (*d*, 1H, tolyl), 7.76–7.78 (*d*, 1H, tolyl), 7.87–7.89 (*d*, 2H, methoxyphenyl), and 8.49–8.51 (*d*, 1H, tolyl). ^{13}C-NMR (DMSO, *δ*/ppm): 21 ($\underline{C}H_3$),

44 ($\underline{C}H_2$, chloroacetyl), 56.2 ($N\underline{C}H_2$), 56.6 ($-O\underline{C}H_3$), 115.7 (C3 and C5, methoxyphenyl), 119.7 (C1, methoxyphenyl), 121.4 (C3 and C5, tolyl), 130.5 (C2 and C6, methoxyphenyl), 135.7 (C2 and C6, tolyl), 136.6 (C4, tolyl), 138.1 (C1, tolyl), 139.1 (C4, methoxyphenyl) and 164.7 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 50.70 (70.29), 156.80 (75.23), 197.02 (100.00), 285.26 (70.99), 301.57 (50.17), 303.87 ($M^{+\cdot}$) (45.64); Anal. Calc. for $C_{17}H_{18}ClNO_2$ was 303.79 found 303.87.

2-chloro-N-(4-chlorophenyl)-N-(4-methoxybenzyl)acetamide (17b)

A yellow powder, yield 82%; mp 182–183 °C. ^{1}H-NMR (DMSO, δ/ppm): 3.87 (*s*, 3H, $-OC\underline{H}_3$), 3.90 (*s*, 2H, chloroacetyl), 4.29 (*s*, 2H, $NC\underline{H}_2$), 7.13–7.15 (*d*, 2H, methoxyphenyl), 7.39–7.41 (*d*, 2H, methoxyphenyl), 7.54–7.56 (*d*, 2H, phenyl), and 7.87–7.89 (*d*, 2H, methoxyphenyl). ^{13}C-NMR (DMSO, δ/ppm): 26.6 ($N\underline{C}H_2$), 42 ($\underline{C}H_2$, chloroacetyl), 43.8 ($-O\underline{C}H_3$), 120.9 (C3 and C5, methoxyphenyl), 124.4 (C2 and C6, phenyl), 127.3 (C2 and C6, methoxyphenyl), 129 (C3 and C5, phenyl), 130.6 (C1, methoxyphenyl), 136.1 (C4, phenyl), 137 (C1, phenyl), 141.1 (C4, methoxyphenyl) and 165.2 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 62.24 (91.23), 77.29 (98.33), 100.44 (100.00), 233.13 (64.86), 323.88 (20.77), 324.88 ($M^{+\cdot}$) (21.19); Anal. Calc. for $C_{16}H_{15}Cl_2NO_2$ was 324.20 found 324.88.

2-chloro-N-(2-chloro-4-methylphenyl)-N-(4-methoxybenzyl)acetamide (18b)

A white crystal, yield 50%; mp 115–116 °C. ^{1}H-NMR (DMSO, δ/ppm): 2.3 (*s*, 6H, $-C\underline{H}_3$, $-OC\underline{H}_3$), 4.36 (*s*, 4H, $C\underline{H}_2$ of chloroacetyl and $NC\underline{H}_2$), 7.16–7.18 (*d*, 2H, methoxyphenyl), 7.36–7.38 (*d*, 2H, methoxyphenyl), 7.56–7.58 (*d*, 2H, tolyl), and 9.81 (*s*, 1H, tolyl). ^{13}C-NMR (DMSO, δ/ppm): 20.6 ($-\underline{C}H_3$ and $-O\underline{C}H_3$), 43.5 ($N\underline{C}H_2$ and $\underline{C}H_2$ of chloroacetyl), 126.5 (C3 and C5, methoxyphenyl), 127.1 (C5 and C6, tolyl), 128.6 (C3 of tolyl and C1, C2, and C6 of methoxyphenyl), 130.1 (C2, tolyl), 130.2 (C4, tolyl), 132 (C1, tolyl), 137.2 (C4, methoxyphenyl) and 165.6 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 118.11 (59.20), 170.74 (73.52), 326.93 (98.63), 335.24 (100.00), 336.91 (19.24), 338.48 ($M^{+\cdot}$) (37.24); Anal. Calc. for $C_{16}H_{15}Cl_2NO_2$ was 338.23 found 338.48.

2-chloro-N-(3,5-dimethylphenyl)-N-(4-methoxybenzyl) acetamide (19b)

A white to pale greenish powder, yield 57%; mp 137–138 °C. ^{1}H-NMR (DMSO, δ/ppm): 2.25 (*s*, 9H, $-C\underline{H}_3$, $-C\underline{H}_3$, $-OC\underline{H}_3$), 4.23 (*s*, 4H, $C\underline{H}_2$ of chloroacetyl and $NC\underline{H}_2$), 6.74 (*s*, 1H, tolyl), 7.21 (*s*, 2H, tolyl), 7.32–7.34 (*d*, 2H, methoxyphenyl), and 7.36–7.38 (*d*, 2H, methoxyphenyl). ^{13}C-NMR (DMSO, δ/ppm): 21.6 ($\underline{C}H_3$, $\underline{C}H_3$, $-O\underline{C}H_3$), 44.1 ($N\underline{C}H_2$, and $\underline{C}H_2$, chloroacetyl), 117.5 (C3 and C5 of methoxyphenyl and C2 and C6 of tolyl), 125.8 (C4 of tolyl and C1 of methoxyphenyl), 138.3 (C2 and C6 of methoxyphenyl and C3 and C5 of tolyl), 138.8 (C1 of tolyl and C4 of methoxyphenyl) and 165 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 63.24 (91.23), 77.29 (98.33), 100.44 (100.00), 233.13 (64.86), 264.48 (59.89), 308.72 (25.24); 319.08 ($M^{+\cdot}$) (32.69); 323.88 ($M^{+4\cdot}$) (20.77); 324.88 ($M^{+5\cdot}$) (21.19); Anal. Calc. for $C_{18}H_{20}ClNO_2$ was 317.81 found 319.08.

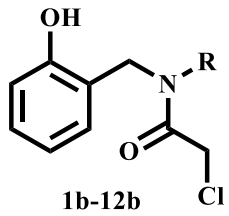
2-chloro-N-(4-methoxybenzyl)-N-(naphthalen-1-yl)acetamide (20b)

A darkish brown powder, yield 30%; mp 110–111 °C. ^{1}H-NMR (DMSO, δ/ppm): 3.88 (*s*, 2H, chloroacetyl), 4.29 (*s*, 3H, $-OC\underline{H}_3$), 4.44 (*s*, 1H, $NC\underline{H}_2$), 7.13–7.16 (*d*, 1H, methoxyphenyl), 7.55–7.57 (*d*, 1H, methoxyphenyl), 7.58–7.61 (*m*, 2H, naphthyl), 7.68–7.70 (*d*, 2H, methoxyphenyl), 7.82–7.84 (*d*, 1H, naphthyl), 7.88–7.90 (*d*, 1H, naphthyl), 7.96–7.99 (*m*, 1H, naphthyl), and 8.08–8.10 (*d*, 2H, naphthyl). ^{13}C-NMR (DMSO, δ/ppm): 41.9 ($\underline{C}H_2$, chloroacetyl), 43.7 ($N\underline{C}H_2$), 55.43 ($-O\underline{C}H_3$), 113.9 (C2, naphthyl), 115 (C3 and C5, methoxyphenyl), 122.8 (C4 and C8, naphthyl), 122.9 (C7 and C8a, naphthyl), 126.1 (C6, naphthyl), 126.60 (C3, naphthyl), 126.7 (C1 of methoxyphenyl and C5 of naphthyl), 128.4 (C2 and C6, methoxyphenyl), 132.4 (C4a, naphthyl), 133.1 (C1, naphthyl), 134.1 (C4, methoxyphenyl) and 169.2 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 76.52 (38.88), 114.03 (28.36), 115.08 (100.00), 142.40 (40.31), 143.23 (73.45), 338.21 (4.25); 339.79 ($M^{+\cdot}$) (16.61); Anal. Calc. for $C_{20}H_{18}ClNO_2$ was 339.82 found 339.79.

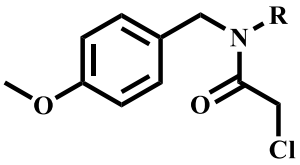
2-chloro-N-(2,4-dichlorobenzyl)-N-(3,5-dimethylphenyl) acetamide (21b)

A white crystal, yield 77%; mp 141–142 °C. ^{1}H-NMR (DMSO, δ/ppm): 2.25 (*s*, 6H, $-C\underline{H}_3$, $-C\underline{H}_3$), 4.23 (*s*, 4H, $C\underline{H}_2$ of chloroacetyl and $NC\underline{H}_2$), 6.74 (*s*, 1H, phenyl), 7.21 (*s*, 2H, phenyl), 7.63–7.66 (*d*, 1H, benzyl), 7.87–7.90 (*d*, 1H, benzyl) and 10.16 (*s*, 1H, benzyl). ^{13}C-NMR (DMSO, δ/ppm): 21.5 ($\underline{C}H_3$ and $\underline{C}H_3$), 44.1 ($N\underline{C}H_2$ and $\underline{C}H_2$ of chloroacetyl), 117.6 (C2 and C6, phenyl), 125.8 (C3, C5, and C6 of benzyl and C4 of phenyl), 138.3 (C2 and C4 of benzyl and C3 and C5 of phenyl), 138.8 (C1 of benzyl and C1 of phenyl) and 164.9 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 210.58 (72.67), 217.97 (69.54), 227.81 (67.25), 264.53 (100.00), 356.06 ($M^{+\cdot}$) (28.24), 358.25 ($M^{+2\cdot}$) (21.98); Anal. Cal. for $C_{20}H_{18}Cl_2NO_2$ was 356.67 found 356.06.

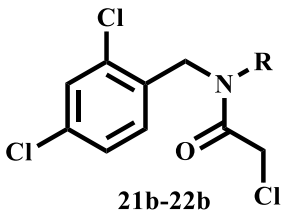
Table 1 The physicochemical properties of synthesized chloroacetamide derivatives (**1b**–**22b**)



1b-12b



13b-20b



21b-22b

Code	R	mp (°C)	Yield (%)	MW	AlogP	HBA	HBD	RB	PSA (Å^2)	Log S	Lipinski violation
Rule		–	–	≤ 500	≤ 5	≤ 10	≤ 5	≤ 10	≤ 140	–	
1b	2-OH-Ph	235–236	30	292	2.79	4	2	4	60.77	− 3.14	0
2b	4-OH-Ph	176–177	54	292	2.79	4	2	4	60.77	− 3.16	0
3b	3,5-Cl_2,4-OH-Ph	284–285	20	326	3.94	3	1	4	40.54	− 4.53	0
4b	2-Me-Ph	192–193	85	290	3.52	3	1	4	40.54	− 3.73	0
5b	4-Me-Ph	165–166	46	290	3.52	3	1	4	40.54	− 3.88	0
6b	4-Cl-Ph	294–295	45	310	3.69	3	1	4	40.54	− 4.23	0
7b	2-Cl,4-Me-Ph	118–119	55	324	4.18	3	1	4	40.54	− 4.58	0
8b	3,5-Me_2-Ph	144–145	60	304	4.00	3	1	4	40.54	− 4.25	0
9b	2,6- Me_2-Ph	104–105	85	304	4.00	3	1	4	40.54	− 3.93	0
10b	2,5- Cl_2-Ph	111–112	40	345	4.36	3	1	4	40.54	− 4.92	0
11b	4-MeO-Ph	129–130	80	306	3.01	4	1	5	49.77	− 3.58	0
12b	Naphthyl	160–161	80	361	4.12	4	2	4	60.77	− 4.92	0
13b	2-OH-Ph	172–174	60	306	3.01	4	1	5	49.77	− 3.56	0
14b	4-OH-Ph	202–204	75	306	3.01	4	1	5	49.77	− 3.58	0
15b	3,5-Cl_2,4-OH-Ph	65–66	20	375	4.34	4	1	5	49.77	− 4.95	0
16b	4-Me-Ph	103–104	80	304	3.74	3	0	5	29.54	− 4.26	0
17b	4-Cl-Ph	182–183	82	324	3.92	3	0	5	29.54	− 4.62	0
18b	2-Cl,4-Me-Ph	115–116	50	338	4.41	3	0	5	29.54	− 4.96	0
19b	3,5-Me_2-Ph	137–138	57	318	4.23	3	0	5	29.54	− 4.64	0
20b	Naphthyl	110–111	30	340	4.16	3	0	5	29.54	− 5.30	0
21b	3,5-Me_2-Ph	141–142	77	357	5.57	2	0	4	20.31	− 5.96	1
22b	2,5-Cl_2-Ph	118–119	72	398	5.93	2	0	4	20.31	− 6.62	1

ALogP: Hydrophobicity factor (octanol/water partition coefficient). HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, RB: Freely rotating bonds, PSA: Polar surface area. Log S: log of solubility in water (Log S scale: insoluble < − 10, poorly − 10 to − 6, moderately − 6 to − 4, soluble − 4 to − 2, very − 2 to 0 and highly soluble > 0)

2-chloro-N-(2,4-dichlorobenzyl)-N-(2,5-dichlorophenyl) acetamide (22b)

A beige crystal, yield 72%; mp 118–119 °C. ^{1}H-NMR (DMSO, *δ*/ppm): 4.42 (*s*, 4H, C$\underline{H}_2$ of chloroacetyl and NC$\underline{H}_2$), 7.31–7.33 (*d*, 2H, benzyl), 7.57–7.59 (*d*, 2H, phenyl) and 7.90 (*s*, 2H, phenyl and benzyl). ^{13}C-NMR (DMSO, *δ*/ppm): 41.1 ($\underline{C}H_2$, chloroacetyl), 43.6 (N$\underline{C}H_2$), 120.84 (C6, chlorophenyl), 124.4 (C4, chlorophenyl), 127.3 (C5, chlorobenzyl), 127.8 (C3, chlorophenyl), 128.8 (C6, chlorobenzyl), 129 (C3, chlorobenzyl), 129.3 (C5, chlorophenyl), 130.7 (2C, C2, and C4, chlorobenzyl), 131.5 (C2, chlorophenyl), 136.1 (C1, chlorobenzyl), 141.2 (C1, chlorophenyl) and 167 ($\underline{C}$=O). EIMS, m\z (relative abundance, %): 156.42 (45.05), 220.73 (100.00), 247.23 (93.03), 264.23 (88.56), 380.27 (61.44), 397.98 ($M^{+\cdot}$) (50.97), 399.82 ($M^{+2\cdot}$) (29.22); Anal. Calc. for $C_{15}H_{10}Cl_5NO$ was 397.50 found 397.98.

Herbicidal activity evaluation

An evaluation of herbicidal activity was conducted using the foliar application method for spraying the four weed species; *Chenopodium album* and *Anagallis arvensis* as broadleaf weeds, *Lolium temulentum* and *Echinochloa crus-galli* as grass weeds. Commercial herbicide acetochlor was obtained from Egyptchem International for Agrochemicals, Egypt, under the trade name of Host

Table 2 Ten top-scored 3D hypothetical pharmacophores generation from the synthesized chloroacetamide derivatives (**1b**–**22b**) with information of predictive power

Hypothesis	Features	Rank	Max fit value
Hypo 1	RA, RA, Hyd, Hyd, HBA, HBA	184.39	4.00
Hypo 2	RA, RA, Hyd, Hyd, HBA, HBA	183.87	3.99
Hypo 3	RA, RA, Hyd, Hyd, HBA, HBA	183.11	3.99
Hypo 4	RA, RA, Hyd, Hyd, HBA, HBA	183.11	3.99
Hypo 5	RA, RA, Hyd, Hyd, HBA, HBA	182.20	3.99
Hypo 6	RA, RA, Hyd, Hyd, HBA, HBA	181.79	3.99
Hypo 7	RA, RA, Hyd, Hyd, HBA, HBA	181.34	3.99
Hypo 8	RA, RA, Hyd, Hyd, HBA, HBA	181.15	3.99
Hypo 9	RA, RA, Hyd, Hyd, HBA, HBA	181.15	3.99
Hypo 10	Hyd, Hyd, HBA, HBA	180.28	3.99

Core 90% EC, with an application rate of 2.6 L/hectare. Plants were grown in seedling-growing peat moss trays in (19×11 cm^2) pots for 7–21 days in a greenhouse with a 15 h at 22–29 °C. Plants were grown to 3 to 5 leaf stages before applications [27]. Stock solutions were prepared by weighing an amount (determined by the highest rate to be tested that calculated as acetochlor rate) of each compound in a 25 mL glass vial and dissolved in 4 mL of acetone/DMSO as a general solution (GS, 97:3, v/v). Each stock solution (5000 mg/L) was diluted with 20 mL of an aqueous mixture composed of containing H_2O, GS, isopropanol, Tensiofix D33, and Tween 80 at a ratio of 45:43:11:2.0:0.03 (v/v) to form the spray mixture associated with the highest application rate. Serial dilutions of 12 and 6 mL of the stock solution were used to prepare the low application rates (2500 and 1250 mg/L). Formulated compounds were applied to the weeds with an atomizer nozzle adjusted to deliver 2.6 L/hectare over an application area of 0.5 cm^2. The control was sprayed with a mixture of solvent blank. The treated and controlled weeds were kept in a greenhouse and irrigated for 21 days. The chlorophyll content of the treated and the control plants was measured by the chlorophyll meter (SPAD 502). This technique is more suitable than the extraction method, where the total chlorophyll (mg/mg plant tissue) is assessed on the same leaf over time with five replicates [28]. The data were subjected to the probit regression analysis [29] in IBM SPSS software version 25.0 (SPSS, Chicago, IL, USA) [30] for calculation of the EC_{50} values.

Computational methods

Generation of 3D-pharmacophore models

3D pharmacophore models of the synthesized chloroacetamide derivatives (**1b**–**22b**) were generated and compared using Discovery Studio (DS) software [31] after drawing chemical structures of all compounds were drawn by ChemDraw professional 18.2 software and saved in Standard Delay Format (SDF) file to submitted to the DS [32]. Properties such as HBA (hydrogen bond acceptor), HBD (hydrogen bond donor), and AR (aromatic ring) were used to establish reliable pharmacophoric sites. Ten models have been obtained, and the

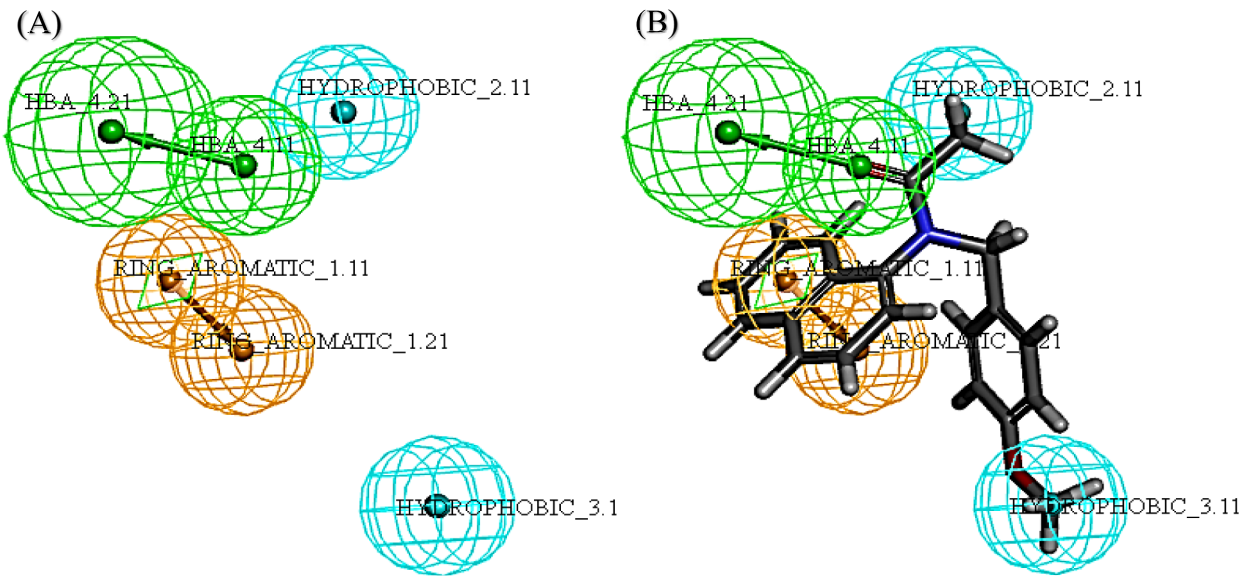


Fig. 3 **A** The best pharmacophore model for the synthesized chloroacetamide derivatives (**1b–22b**). **B** Mapping of the highest fit compound (**20b**) on this model of synthesized chloroacetamide derivatives

Table 3 Mapping of synthesized chloroacetamide derivatives (**1b**–**22b**) on Hypo 1 model of the synthesized chloroacetamide derivatives

Code	Absolute energy	Conformal number	Fit value
1b	43.76	36	1.77
2b	49.53	47	1.16
3b	50.69	47	2.44
4b	54.24	87	1.58
5b	51.27	44	2.38
6b	46.07	49	2.64
7b	56.25	110	2.27
8b	58.73	104	1.95
9b	49.36	6	1.26
10b	45.05	27	2.08
11b	49.46	9	2.86
12b	54.49	21	2.21
13b	55.16	46	3.75
14b	54.96	18	2.83
15b	57.43	60	3.68
16b	58.12	46	3.68
17b	53.44	39	3.26
18b	53.74	38	2.92
19b	62.14	185	3.73
20b	67.36	4	4.00
21b	49.29	82	3.31
22b	48.16	46	3.29

best hypothesis contains a high score of the site points. Finally, the best pharmacophore model was used to map all tested molecules.

Molecular docking

The crystal structure of VLCFAs was obtained from the Protein Data Bank (PDB ID: 1oxh) (http://www.rcsb.org) at 1.54 Å [33] and imported onto the Molecular Operating Environment (MOE) 2014.13 software (Chemical Computing Group Inc, Montreal, Quebec, Canada). The structure of each enzyme was visualized by the MOE [34]. The protein was prepared by removing heteroatoms and crystallographic water molecules. After the protein preparation, the active site was defined based on the volume occupied by the known ligand pose already in an active site [35]. The compounds were converted to the 3D structure and the Merck Molecular Force Field (MMFF94) power was reduced with a 200-iteration limit and the power threshold value of 15 kcal/mol [36]. The triangle-matching algorithm from MOE was used to dock the compounds into the active site of the enzyme. The free energy of binding of the compounds was calculated based on hydrophobic, ionic and hydrogen bond interactions. An enzyme-ligand complex is considered to have an acceptable ligand if its docking score (or interaction energy) is greater than a certain value.

Results and discussion

Chemistry

The target compounds (**1b**–**22b**) were synthesized via acylation of imine derivatives (**1a**–**22a**) (Fig. 2). The effect of substituent patterns on the yields was investigated. It was found that the different aromatic substituents displayed diverse yields (20–85%) (Table 1). The presence of methyl group on the phenyl ring as shown in compounds **4b**, **7b**, **8b**, **9b**, **11b**, **16b**, **18b**, **19b**, and **21b** gave a high yield (50–85%) except compound **5b** (46%) but slowly reaction (≈ 6 h) on the other hand. In contrast, the presence of chlorine substituent on the phenyl ring (**3b**, **6b**, **10b**, **15b**, and **18b**) gave a little yield (20–50%) except compounds **17b** and **22b** (82% and 72% respectively) with rapid reaction (≈ 1 h). All synthesized compounds were compatible with Lipinski rules (MW, ALogP, HBA, HBD, RB, and PSA) except compounds **21b** and **22b** with an ALogP value higher than 5 as presented in Table 1. These characteristics proved that the synthesized compounds have adequate hydrophobic to penetrate the biological membranes, as determined by the Lipinski rule-of-five [37, 38]. According to Lipinski's rules, most of these compounds should be readily bioavailable, allowing them to be used as herbicides. Moreover, the Log S values for all derivatives are between -3.14 and -6.62, which indicate moderately to highly soluble in water [39].

The chemical structures of the synthesized compounds were confirmed by ^{1}H-NMR (Supplementary data Figures S1a–S22a), ^{13}C-NMR (Supplementary data Figures S1b–S22b), and MS (Supplementary data Figures S1c–S22c). All ^{1}H-NMR spectra of the derivatives (**1b**–**22b**) showed peaks at a chemical shift from 4 to 5 ppm, which corresponded to the hydrogen of –NC$\underline{H}_2$ and –C$\underline{H}_2$ of chloroacetyl. In addition, the presence of new peaks by ^{13}C-NMR at a chemical shift from 41 to 43 ppm for the carbon of –N$\underline{C}$H$_2$ and from 48 to 58 ppm for –$\underline{C}$H$_2$ of chloroacetyl also confirmed the chemical structures of these compounds. The peak at 160 to 170 ppm represents the carbonyl group $\underline{C}$=O of synthesized compounds.

Explanation of 3D-pharmacophore models

Table 2 shows the ten top-scored 3D hypothetical pharmacophores generated from the synthesized chloroacetamide derivatives (**1b**–**22b**) with information on predictive power. The model of Hypo 1 for this group was the highest score (fit value = 4). The features of this model include two RA, two Hyd, and two HBA with differences in composition, orientation, and sectorial directions

Table 4 Herbicidal activity of the synthesized chloroacetamide derivatives (**1**–**22b**) against *C. album* compared with acetochlor as a standard herbicide

Code	Substituent	EC_{50}[a] (mg/L)	95% confidence limits (mg/L)		Slope[b] ± SE	Intercept[c] ± SE	(X^2)[d]
			Lower	Upper			
1b	2-OH-Ph	6749	4046	10,135	0.84 ± 0.30	− 3.23 ± 1.05	0.04
2b	4-OH-Ph	7121	4120	8795	0.80 ± 0.31	− 3.09 ± 1.04	0.28
3b	3,5-Cl_2,4-OH-Ph	5412	3509	6174	0.88 ± 0.30	− 3.30 ± 1.04	0.30
4b	2-Me-Ph	3365	2196	10,135	0.80 ± 0.30	− 2.81 ± 1.02	0.04
5b	4-Me-Ph	2903	1836	6174	0.82 ± 0.30	− 2.85 ± 1.02	0.05
6b	4-Cl-Ph	3419	2416	6963	0.96 ± 0.30	− 3.38 ± 1.02	0.57
7b	2-Cl,4-Me-Ph	3564	2598	6669	1.05 ± 0.30	− 3.73 ± 1.03	1.24
8b	3,5-Me_2-Ph	3269	2315	6215	0.97 ± 0.30	− 3.41 ± 1.02	0.30
9b	2,6- Me_2-Ph	3861	2505	5554	0.76 ± 0.30	− 2.74 ± 1.02	0.01
10b	2,5- Cl_2-Ph	4457	3479	6953	1.55 ± 0.31	− 5.64 ± 1.08	1.08
11b	4-MeO-Ph	8208	4735	7859	0.91 ± 0.31	− 3.55 ± 1.06	1.05
12b	Naphthyl	4835	3306	6479	0.97 ± 0.30	− 3.55 ± 1.04	0.19
13b	2-OH-Ph	4107	3009	8129	1.12 ± 0.30	− 4.04 ± 1.04	0.09
14b	4-OH-Ph	3371	2584	5165	1.26 ± 0.30	− 4.43 ± 1.04	0.05
15b	3,5-Cl_2,4-OH-Ph	3765	2728	7581	1.04 ± 0.31	− 3.71 ± 1.03	0.77
16b	4-Me-Ph	3304	2491	5226	1.18 ± 0.30	− 4.15 ± 1.03	0.82
17b	4-Cl-Ph	4663	2830	7658	0.67 ± 0.30	− 2.47 ± 1.02	0.05
18b	2-Cl,4-Me-Ph	2482	1830	3351	1.25 ± 0.30	− 4.24 ± 1.03	0.51
19b	3,5-Me_2-Ph	3561	2644	6218	1.12 ± 0.30	− 3.98 ± 1.03	0.02
20b	Naphthyl	3149	2445	4520	1.32 ± 0.30	− 4.63 ± 1.04	0.06
21b	3,5-Me_2-Ph	3079	2197	5290	1.01 ± 0.30	− 3.52 ± 1.02	0.01
22b	2,5-Cl_2-Ph	3805	2592	11,284	0.91 ± 0.30	− 3.32 ± 1.03	0.03
Acetochlor	-	3717	2841	6009	1.27 ± 0.31	− 4.52 ± 1.04	0.01

[a] The concentration value for a compound that required inhibiting 50% of the chlorophyll content of *C. album* a specified test duration

[b] Slope of the concentration-inhibition regression line ± SE

[c] The y-intercept of the regression line ± SE

[d] Chi-square goodness of fit test

(Fig. 3A). These features indicate different numbers of pharmacological properties. Table 3 shows the mapping of compounds **1b**–**22b** on this model. The results proved that the fit values of the compounds ranged from 1.16 to 4. Compound **20b** exhibited the highest fit value 4, and the 3D orientation on the best model is shown in Fig. 3B.

Herbicidal activity

The herbicidal activity of the synthesized compounds against four weed species including two broadleaf weeds (*C. album* and *A. arvensis*) and two grass weeds (*L. temulentum* and *E. crus-galli*) in comparison with acetochlor as a standard herbicide are shown in Tables 4, 5, 6, 7. The data are presented as EC_{50} values in mg/L and their statistical parameters. The results revealed that most of the tested compounds exhibited remarkable inhibition against the chlorophyll content of four weeds. In addition, the herbicidal activity differed according to the substituents on the molecular structure. In general, most of the compounds exhibited higher activity against grass weeds than broadleaf weeds.

Table 4 shows the herbicidal activity of the derivatives against broadleaf weed *C. album*. Eleven compounds exhibited higher herbicidal activity than the standard acetochlor, with EC_{50} ranging between 2482 to 3564 mg/L. Compounds **5b** and **18b** were the most active with EC_{50} = 2903 and 2482 mg/L, respectively, and superior to the standard (acetochlor). Comparing the results of compound **5b** with **6b** indicates that the presence of the methyl group at position **4** was much more effective than the presence of chlorine at the same position. Similarly, compound **21b** versus compound **22b** showed that the presence of methyl groups increased the herbicidal activity more than the chlorine atoms. Fortunately, all the results are in parallel with the standard acetochlor, which contains methyl and ethyl groups, reflecting that the effective substituent has to be alkyl groups (methyl

Table 5 Herbicidal activity of the synthesized chloroacetamide derivatives (**1**–**22b**) against *A. arvensis* compared with acetochlor as a standard herbicide

Code	EC_{50}[a] (mg/L)	95% Confidence limits (mg/L)		Slope[b] ± SE	Intercept[c] ± SE	(X^2)[d]
		Lower	Upper			
1b	3975	2848	5735	0.72 ± 0.30	− 2.72 ± 1.03	0.09
2b	5173	3579	14,547	1.06 ± 0.31	− 3.92 ± 1.05	1.17
3b	4762	3593	8419	1.39 ± 0.31	− 5.10 ± 1.08	1.08
4b	4380	3285	7918	1.27 ± 0.31	− 4.63 ± 1.06	1.27
5b	2661	1494	5560	0.77 ± 0.30	− 2.65 ± 1.01	0.03
6b	3179	2137	7023	0.86 ± 0.30	− 3.03 ± 1.02	1.11
7b	3429	2576	5622	1.16 ± 0.30	− 4.11 ± 1.04	1.04
8b	3525	2688	5610	1.24 ± 0.30	− 4.39 ± 1.04	0.05
9b	3305	2590	4754	1.38 ± 0.31	− 4.84 ± 1.04	0.01
10b	3152	2439	4555	0.70 ± 0.30	− 2.49 ± 1.02	0.05
11b	3370	2517	5556	1.14 ± 0.30	− 4.02 ± 1.03	0.21
12b	3220	2544	4505	1.42 ± 0.31	− 4.99 ± 1.04	0.16
13b	3887	3013	6089	1.37 ± 0.31	− 4.92 ± 1.06	0.39
14b	3743	2962	5472	1.49 ± 0.31	− 5.31 ± 1.06	0.07
15b	3356	2621	4902	1.35 ± 0.31	− 4.78 ± 1.04	0.11
16b	2998	2304	4276	1.28 ± 0.30	− 4.46 ± 1.04	0.11
17b	3263	2481	5019	1.22 ± 0.30	− 4.27 ± 1.03	0.04
18b	2614	1880	3746	1.13 ± 0.30	− 3.86 ± 1.03	0.61
19b	2977	2265	4305	1.24 ± 0.30	− 4.31 ± 1.03	0.21
20b	3320	2537	5091	1.24 ± 0.30	− 4.36 ± 1.04	0.00
21b	3247	2450	5071	1.18 ± 0.30	− 4.16 ± 1.03	0.04
22b	3654	2721	6419	1.14 ± 0.30	− 4.05 ± 1.04	0.75
Acetochlor	3890	2903	6975	1.17 ± 0.30	− 4.20 ± 1.04	0.18l

[a] The concentration value for a compound that required inhibiting 50% of the chlorophyll content of *A. arvensis* a specified test duration

[b] Slope of the concentration-inhibition regression line ± SE

[c] The y-intercept of the regression line ± SE

[d] Chi-square goodness of fit test

or ethyl) rather than hydroxyl or chlorine atoms. Interestingly, compound **16b** versus **17b** shows that substituting the methyl group at position **4** is more critical than the chlorine atom. Furthermore, compound **1b** versus **4b** proves that the alkyl group has the most significant influence on herbicidal activity. However, the hydroxyl group at the same position **4** as shown in compound **2b** dramatically reduced the herbicidal activity. Additionally, substitution with chlorine atom at position **2** in the presence of methyl group at position **4** significantly increased the herbicidal activity (**16b** versus **18b**). Compounds **9b**, **15b**, and **22b** presented similar herbicidal activity as obtained by acetochlor with EC_{50} = 3861, 3765, and 3805 mg/L, respectively. On the other hand, compounds **1b**–**3b**, **10b**–**13b**, and **17b** showed lower herbicidal activity than acetochlor. Therefore, it could be concluded that compounds with a hydroxyl group at position 2 or 4 on the phenyl ring (compounds **1b** and **2b**) or methoxy group at position 4 on the phenyl ring (**11b**) were less active than the standard.

Table 5 shows the herbicidal activity of the tested derivatives against broadleaf weed, *A. arvensis*. Seventeen compounds showed higher herbicidal activity than the standard herbicide acetochlor, EC_{50} = 3890 mg/L, with EC_{50} ranging from 2614 to 3654 mg/L. Most of these derivatives contain one or two methyl groups such as **5b**, **16b**, **18b**, and **19b** with EC_{50} = 2661, 2998, 2614, and 2977 mg/L, respectively. In addition, all these potent compounds contain one or two methyl groups. For example, compounds **1b** and **13b** exhibited similar herbicidal activity to acetochlor with EC_{50} = 3975 and 3887 mg/L, respectively. However, compounds **2b** and **3b** containing hydroxyl group in their chemical structure showed lower herbicidal activity than the standard herbicide (acetochlor) with EC_{50} = 5173, 4762, and 4380 mg/L, respectively.

Table 6 Herbicidal activity of the synthesized chloroacetamide derivatives (**1**–**22b**) against *L. temulentum* compared with acetochlor as a standard herbicide

Code	EC_{50}[a] (mg/L)	95% confidence limits (mg/L)		Slope[b] ± SE	Intercept[c] ± SE	(X^2)[d]
		Lower	Upper			
1b	7172	4300	8475	0.89 ± 0.31	− 3.44 ± 1.05	0.19
2b	5485	3605	5987	0.93 ± 0.30	− 3.49 ± 1.04	0.25
3b	4316	2930	6387	0.88 ± 0.30	− 3.21 ± 1.04	0.01
4b	4217	2992	10,078	1.00 ± 0.30	− 3.65 ± 1.03	0.07
5b	4070	2794	12,207	0.89 ± 0.30	− 3.22 ± 1.03	0.17
6b	3809	2603	11,026	0.87 ± 0.30	− 3.11 ± 1.02	0.13
7b	4538	2948	6574	0.79 ± 0.30	− 2.91 ± 1.02	0.02
8b	3240	2131	8285	0.82 ± 0.30	− 2.88 ± 1.02	0.04
9b	3794	3111	5095	1.81 ± 0.32	− 6.48 ± 1.09	0.62
10b	7467	4222	8211	0.79 ± 0.31	− 3.05 ± 1.04	0.02
11b	4403	2716	6543	0.69 ± 0.30	− 2.51 ± 1.02	0.09
12b	4084	2992	8096	1.11 ± 0.30	− 4.02 ± 1.04	1.20
13b	5218	3496	19,278	0.95 ± 0.30	− 3.54 ± 1.04	0.07
14b	4810	3446	10,923	1.13 ± 0.31	− 4.17 ± 1.05	0.46
15b	5542	3887	13,696	1.18 ± 0.31	− 4.40 ± 1.07	0.01
16b	4393	3459	6668	1.60 ± 0.32	− 5.81 ± 1.09	0.27
17b	3909	3186	5345	1.78 ± 0.32	− 6.37 ± 1.09	0.34
18b	2213	1633	2849	1.36 ± 0.30	− 4.56 ± 1.03	1.20
19b	3886	3181	5257	1.81 ± 0.32	− 6.50 ± 1.09	0.02
20b	2503	1868	3355	1.28 ± 0.30	− 4.36 ± 1.03	0.00
21b	2948	2304	4050	1.37 ± 0.30	− 4.76 ± 1.04	0.07
22b	3321	2799	4144	2.03 ± 0.32	− 7.14 ± 1.09	1.14
Acetochlor	4141	3100	7472	1.22 ± 0.31	− 4.41 ± 1.05	0.02

[a] The concentration value for a compound that required inhibiting 50% of the chlorophyll content of *L. temulentum* a specified test duration

[b] Slope of the concentration-inhibition regression line ± SE

[c] The y-intercept of the regression line ± SE

[d] Chi-square goodness of fit test

The result of the herbicidal activity against grass weeds (*L. temulentum*) is shown in Table 6, representing that nine compounds are more effective than the standard. The EC_{50} values of the test compounds were between 2213 and 3909 mg/L, which are lower than acetochlor (EC_{50} = 4141 mg/L). However, compounds **4b**, **5b**, and **12b** exhibited herbicidal activity similar to the standard acetochlor with EC_{50} = 4217, 4070, and 4084 mg/L, respectively. Some compounds e.g. **1b**–**3b**, **7b**, **10b**–**11b,** and **13b**–**16b** presented lower activity than acetochlor.

Table 7 shows the herbicidal activity of the tested derivatives against grass weeds (*E. crus-galli*) compared to the acetochlor (standard). Sixteen compounds exhibited higher herbicidal activity than the standard herbicide acetochlor, with EC_{50} ranging from 1472 to 2592 mg/L. The most potent compounds were **1b**, **4b**, **5b**, **6b**, **8b**, **17b**, **18b**, and **20b**. Interestingly, all the compounds showing high herbicidal activity contain methyl groups in their chemical structure. However, compounds **3b**, **7b**, and **10b**–**13b** showed lower herbicidal activity with a range of EC_{50} 2988–3670 mg/L than acetochlor.

Generally, the results indicated that one or two methyl groups on the phenyl ring increased the inhibition of chlorophyll content. However, more than one hydroxyl group or chlorine atom on the phenyl ring decreased the inhibition. Changing the phenyl ring to a naphthyl moiety significantly increased herbicidal activity, as shown by compound **20b**, the fourth compound exhibiting herbicidal activity with an EC_{50} value of 1896 mg/L. Probably, if the naphthyl moiety is substituted with an alkyl group (methyl or ethyl group) will increase the herbicidal activity. According to the post-emergence herbicidal activity, the main structure-activity relationships (SARs) of the compounds **1b**–**22b** can be revealed. The categories of substituents such as hydroxyphenyl, methoxyphenyl, and 2,4-dichlorophenyl rings significantly decreased the herbicidal activity.

Table 7 Herbicidal activity of the synthesized chloroacetamide derivatives (**1**–**22b**) against *E. crus-galli* compared with acetochlor as a standard herbicide

Code	EC_{50}[a] (mg/L)	95% confidence limits (mg/L)		Slope[b] ± SE	Intercept[c] ± SE	(X^2)[d]
		Lower	Upper			
1b	1779	945	2451	1.04 ± 0.30	− 3.37 ± 1.02	0.38
2b	2592	2139	3170	1.83 ± 0.31	− 6.25 ± 1.06	1.31
3b	3156	2384	4826	1.19 ± 0.30	− 4.17 ± 1.03	0.15
4b	1928	1573	2269	2.13 ± 0.32	− 6.99 ± 1.08	0.04
5b	1611	1274	1906	2.21 ± 0.33	− 7.09 ± 1.11	0.22
6b	1797	1166	2335	1.28 ± 0.30	− 4.17 ± 1.03	0.34
7b	3591	2677	6221	1.14 ± 0.30	− 4.04 ± 1.03	0.25
8b	1618	933	2151	1.20 ± 0.31	− 3.86 ± 1.03	0.01
9b	2295	1486	3278	1.03 ± 0.30	− 3.47 ± 1.02	0.03
10b	3036	2411	4105	1.46 ± 0.31	− 5.09 ± 1.04	0.21
11b	3022	1986	6413	0.85 ± 0.30	− 2.96 ± 1.01	0.52
12b	2988	2370	4028	1.46 ± 0.31	− 5.06 ± 1.04	0.91
13b	3670	2874	5497	1.04 ± 0.31	− 5.00 ± 1.04	0.91
14b	2574	2017	3317	1.47 ± 0.31	− 5.02 ± 1.04	0.16
15b	2120	1599	2655	1.51 ± 0.31	− 5.01 ± 1.04	1.09
16b	2162	1366	3017	1.05 ± 0.30	− 3.51 ± 1.02	0.07
17b	1920	1203	2565	1.15 ± 0.30	− 3.78 ± 1.03	0.17
18b	1472	994	1855	1.62 ± 0.32	− 5.12 ± 1.07	0.40
19b	2460	1774	3376	1.19 ± 0.30	− 4.03 ± 1.03	0.24
20b	1992	1338	2612	1.24 ± 0.30	− 4.08 ± 1.03	0.33
21b	2414	1812	3164	1.34 ± 0.30	− 4.52 ± 1.03	0.29
22b	1896	1045	2634	1.02 ± 0.30	− 3.33 ± 1.02	0.18
Acetochlor	2756	1786	4894	0.89 ± 0.30	− 3.06 ± 1.02	1.94

[a] The concentration value for a compound that required inhibiting 50% of the chlorophyll content of *E. crus-galli* a specified test duration

[b] Slope of the concentration-inhibition regression line ± SE

[c] The y-intercept of the regression line ± SE

[d] Chi-square goodness of fit test

The mode of action of the chloroacetamide group is the inhibition biosynthesis of Very Long Chain Fatty Acid Synthesis (VLCFAs) leading to the herbicidal action [16, 19, 21]. Chloroacetamide herbicides act systemically through the lipophilic walls of the phloem tubes [40]. Our obtained results showed that the compounds which contain one or two methyl groups at the phenyl ring exhibited high herbicidal action reflecting a similar effect to the well-known 2-chloroacetamide herbicides [41, 42]. Methoxy benzyl derivatives (**13b**–**20b**) showed good herbicidal action, suggesting that the hydrophilicity of the methoxy group may have contributed to the herbicidal activity. These results indicate that the steric factor around the nitrogen atom of 2-chloroacetamide may have played an essential role in the activity of this type of compound [43]. Several derivatives of the tested compounds proved to be more or equally effective herbicides based on comparisons with acetochlor. Consequently, finding one or more of the tested candidates possible can offer good herbicidal efficacy against the tested weed.

Molecular docking

The docking of the synthesized molecules **1b**–**22b** on the main target protein (VLCFAs) was performed using MOE software. The data were analyzed based on the docking score (ΔG, kcal/mol), hydrogen bonds, and van der Waals connections nearby. Table 8 shows the binding scores and binding interactions of the synthesized derivatives. The results showed that the synthesized derivatives have a well binding convergence with the active sites of the target enzyme with docking energy ranging from − 5.57 to − 7.38 kcal/mol compared to -5.11 kcal/mol for acetochlor. Compounds **5b**, **6b**, **8b**, **13b**, and **17b** showed HBD and hydrophobic interactions together. Compound

Table 8 Molecular docking, binding scores, and binding interactions of synthesized chloroacetamide derivatives (**1b**–**22b**) within the active sites of VLCFAs (PDB ID: 1OXH)

Comp.	Docking score (S) ΔG (kcal/mol)	van der Waals	H-Bond			Hydrophobic interactions (π-interactions)			RMSD
			(Amino acid-ligand atom)	Interaction	Distance (Å)	(Amino acid-ligand atom)	Interaction	Distance (Å)	
1b	− 5.92	Ala 208, His 268, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	N-Ala 309-6-ring CB-Asn 310-6-ring	π–H π–H	4.61 4.61	0.90
2b	− 5.92	Ala 208, Ala 309, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	CB-Asn 310-6ring	π–H	4.62	1.22
3b	− 6.37	Ala 208, Ala 309, Asn 227, Asn 310, Gly 228, His 303, His 337, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Ser 271, Thr 207, Thr 270, and Thr 305	–	–	–	CG2-Thr 307-6-ring CD-Pro 308- 6-ring	π–H π–H	3.61 3.63	0.90
4b	− 6.05	Ala 208, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	N-Ala 309-6-ring CB-Asn 310-6-ring	π–H π–H	4.62 4.65	1.20
5b	− 5.89	Ala 208, Ala 309, His 303, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Thr 207, Thr 270, Thr 305, and Thr 307	O-Leu 206-Cl36	HBD	3.41	CB-Asn 310-6-ing	π–H	4.58	1.75
6b	− 5.91	Ala 208, Ala 309, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Thr 207, Thr 270, Thr 305, and Thr 307	OG-Ser 271-Cl33	HBD	3.46	CB-Asn 310-6-ing	π–H	4.67	1.13
7b	− 6.04	Ala 208, Ala 309, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	CB-Asn 310- 6-ing	π–H	4.62	1.09
8b	− 6.57	Ala 208, Ala 309, His 303, His 337, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305 and Thr 307	O-Leu 206-Cl39	HBD	3.37	CB-Asn 310-6-ing	π–H	4.68	1.44
9b	− 5.57	Ala 208, Ala 309, His 303, Leu 206, Phe 229, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	CB-Asn 310-6-ing	π–H	4.76	1.24
10b	− 6.09	Ala 208, Ala 309, Asn 227, Gly 228, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	CB-Asn 310-6-ing	π–H	4.66	0.92
11b	− 6.34	Ala 208, Ala 309, Asn 310, His 303, Leu 206, Phe 229, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, and Thr 305	–	–	–	CG-Thr 307-6-ing	π–H	3.69	1.40

Table 8 (continued)

Comp.	Docking score (S) ΔG (kcal/mol)	van der Waals	H-Bond			Hydrophobic interactions (π-interactions)			RMSD
			(Amino acid-ligand atom)	Interaction	Distance (Å)	(Amino acid-ligand atom)	Interaction	Distance (Å)	
12b	− 6.25	Ala 208, Ala 309, Gly 228, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	–	–	–	CB-Asn 310-6-ing	π–H	4.54	2.21
13b	− 6.55	Ala 208, Ala 309, Asn 310, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Thr 207, Thr 270,and Thr 305	OG- Ser 271-Cl37	HBD	3.30	CG2-Thr 307-6-ing	π–H	3.74	0.81
14b	− 6.10	Ala 208, Ala 309, Asn 227, Asn 310, Gly 228, His 303, Leu 206, Phe 394, Phe 396, Pro 272, Pro 308, Thr 207, Thr 270, and Thr 305	–	–	–	CG2-Thr 307- 6-ing	π–H	3.66	1.46
15b	− 6.73	Ala 208, Ala 309, Asn 227, Asn 310, Gly 228, His 303, His 337, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, and Thr 305	–	–	–	CG2-Thr 307- 6-ing	π–H	3.72	1.16
16b	− 6.30	Ala 208, Ala 309, Asn 227, Asn 310, Gly 228, His 303, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, and Thr 305	–	–	–	CG2-Thr 307- 6-ing	π–H	3.69	1.21
17b	− 6.63	Ala 208, Ala 309, Asn 310, His 268, His 303, Leu 206, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Thr 207, Thr 270, and Thr 305	OG-Ser 271-Cl36	HBD	3.38	CG2-Thr 307- 6-ing	π–H	3.75	1.18
18b	− 6.65	Ala 208, Ala 309, Asn 310, His 268, His 303, Leu 206, Phe 227 Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, and Thr 305	–	–	–	CG2-Thr 307-6-ing	π–H	3.75	1.65
19b	− 6.68	Ala 208, Ala 309, Asn 227, Asn 310, Gly 228, His 303, Phe 229, Phe 394, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, Thr 305, and Thr 307	O-Leu 206-Cl42	HBD	3.33	-	-	-	1.06
20b	− 7.38	Ala 180, Glu 462, Gly 179, Gly 222, Ile 176, Ile 184, Ile 250, Ile 460, Leu 216, Leu 248, Met 344, Phe 214, Ser 223, Ser 251, Thr 464, and Trp 249	N-Thr 217-Cl41	HBA	3.55	CB-Phe 461-Ring N-Gly 463-Ring	π–H π–H	3.98 4.12	0.79
21b	− 6.68	Ala 180, Glu 462, Gly 179, Gly 463, Ile 176, Ile 184, Ile 250, Leu 248, Leu 337, Phe 214, Phe 461, Thr 217, and Trp 249	N-Ser 251-O33	HBA	3.25	–	–	–	0.83
22b	− 6.60	Ala 180, Gly 179, Gly 463 Ile 176, Ile 184, Ile 250, Leu 337, Met 344, Phe 214, Phe 461, Ser 251, Thr 217, and Trp 249	–	–	–	N-Glu 462-Ring	π-H	3.52	1.26

Table 8 (continued)

Comp.	Docking score (S) ΔG (kcal/mol)	van der Waals	H-Bond			Hydrophobic interactions (π-interactions)			RMSD
			(Amino acid-ligand atom)	Interaction	Distance (Å)	(Amino acid-ligand atom)	Interaction	Distance (Å)	
Acetochlor	− 5.11	Ala 208, Asn 227, Gly 228, Leu 206, Phe 396, Pro 272, Pro 308, Ser 271, Thr 207, Thr 270, and Thr 307	N-Ala 309-O5	HBA	3.36	–	–	–	2.15

RMSD: The root means square deviation of the pose in Å, from the original ligand. This field is present if the site definition was identical to the ligand definition. Residues/water molecules are participation in hydrogen bonds and close van der Waals contacts (1.54 Å) with the ligand

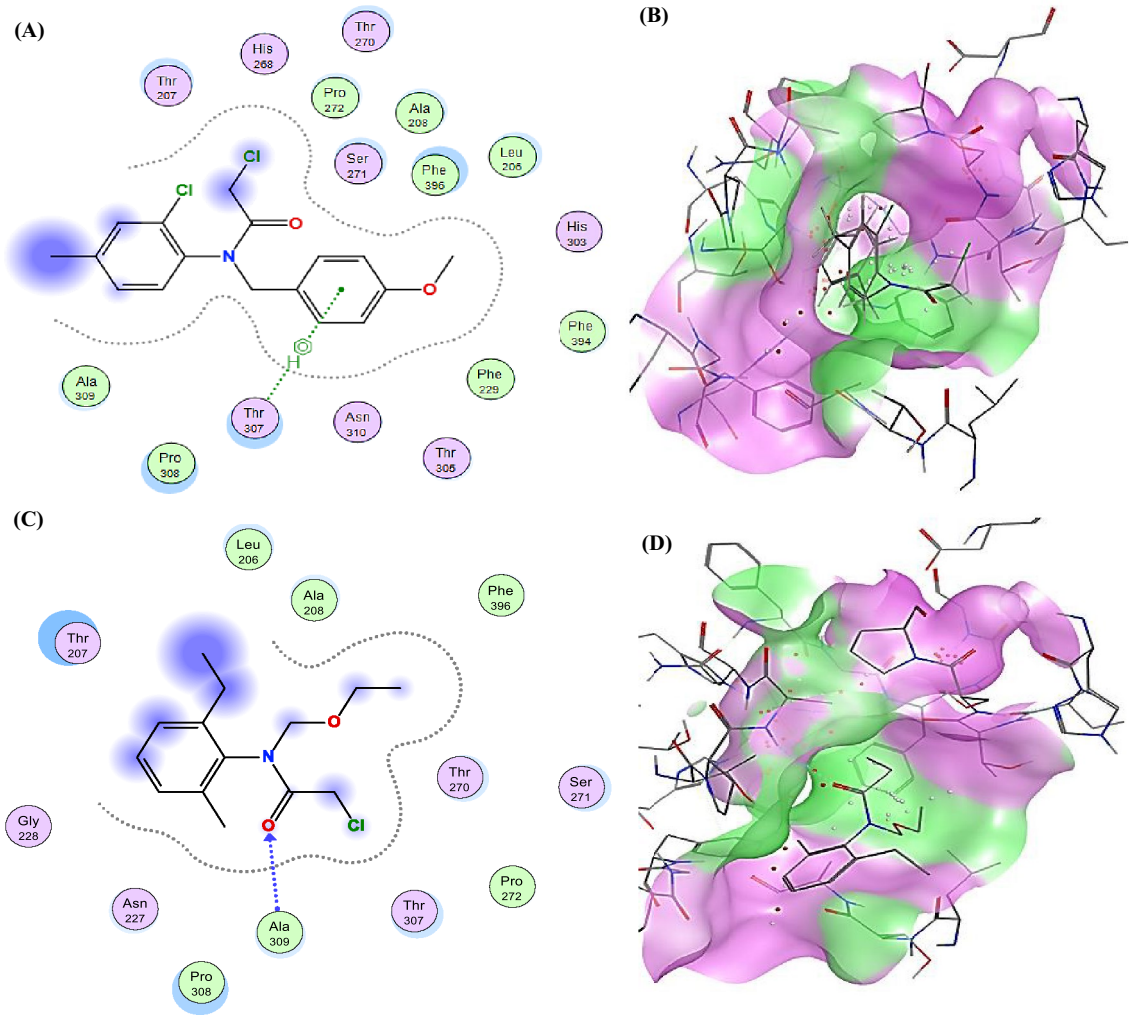


Fig. 4 Docking of the most herbicidal active compound **18b** ($\Delta G = -6.65$ kcal/mol) (**A** and **B**) and the most popular standard herbicide acetochlor ($\Delta G = -5.11$ kcal/mol) (**C** and **D**) in the binding site of VLCFAs (PDB ID 1OXH). Left: 2D interaction diagrams of compounds with 1OXH complex and right are the complex structures in 3D

20b showed HBA and hydrophobic interactions. However, compounds **19b** and **21b** showed only HBD and HBA, respectively, without hydrophobic interaction. The other fourteen derivatives exhibited van der Waals and hydrophobic interactions. All compounds have a distance of 2.88- 3.46 between atoms that bind and hydrogens in amino acid residues. However, the distance of the hydrophobic was in the range of 3.61–4.76 Å. No hydrophobic interaction was found in the case of acetochlor. It can be seen that the amino acids Asn 310, Ala 309, and Thr 307 were bound to most of the derivatives.

Figure 4A and B show the optimal 2D and 3D binding interaction diagrams of the most active compound **18b** ($\Delta G = -6.65$ kcal/mol) compared with the standard herbicide acetochlor (Fig. 4C and D). The interactions of compound **18b** with the enzyme show that the phenyl ring interacted through a hydrophobic with a gamma-2 carbon atom of the amino acid threonine (CG2-Thr 307-6-ing, 3.75 Å). In addition, the compound interacted with 15 amino acids of the enzyme by van der Waals. Therefore, according to the molecular docking results, this compound showed the highest herbicidal activity, and it may be considered a promising inhibitor of the VLCFAs enzyme. On the other hand, acetochlor docked into the enzyme through van der Waals (11 amino acids). Also, the oxygen of the carbonyl group has one H-bonding interaction (HBA) with the nitrogen of alanine (N-Ala 309- O5, 3.36 Å) (Fig. 4C).

It is well known that molecular docking is a powerful tool to explore the mechanisms of enzyme-herbicide interactions. This technique is often applied to enantioselectivity studies [44–46]. Moreover, it was widely applied

to screening novel compounds [47]. The bond interactions were helpful for the elucidation of several biological activities of the tested compounds as herbicides [44]. Sartori et al. indicated that histone deacetylase was the target enzyme in plants for the 18 anilide derivatives compared to *s*-metolachlor [48]. The authors found that through molecular docking, the affinities of the most active anilide compounds for the binding sites of this enzyme were equal to or higher than those calculated for its inhibitors. Filimon et al.[49] added that *s*-metolachlor as a chloroacetamide herbicide was able to bind to the active sites of dehydrogenase, phosphatase, and protease.

Conclusion

A series of novel chloroacetamide derivatives was synthesized through a facile and practical protocol optimized in the current study. The molecular structures of these compounds were confirmed by spectroscopic methods. A study of pharmacophore modeling revealed that these compounds displayed the highest effect and were able to meet the planned common characteristics locates by aligning them onto the pharmacophore model. The compounds were evaluated for in vitro herbicidal activity against four weed species; *C. album* and *A. arvensis* as broadleaf weeds, *L. temulentum* and *E. crus-galli* as grass weeds using the determination of chlorophyll content as an indication of the inhibition. A structure–activity relationship (SAR) study identified that the presence of a methyl group on the phenyl ring led to the highest herbicidal activity. Other compounds exhibited moderate activity. The in silico molecular docking of the synthesized compounds proved that the compounds showed an excellent affinity to bind with the active sites of the main target protein (VLCFAs), and the docking energy ranged from − 5.57 to − 7.38 kcal/mol compared to − 5.11 kcal/mol for acetochlor as a standard herbicide. More importantly, this research identified a new class of lead compounds with potential for herbicide development. In addition, the mode of herbicidal action, selectivity, and quantitative structure–activity relationship (QSAR) study for this type of chemical is now being conducted in our laboratory. At present, we are focusing our efforts on optimizing the herbicidal activity of the most promising compounds, and some structure modifications are being investigated that will be described in a future publication.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40538-024-00646-1.

Supplementary Material 1.

Acknowledgements
Not applicable.

Author contributions
All authors contributed to the study's conception and design. K.E.E performed synthesis, bioassays, data collection, and spectroscopic analysis. S.R.E and M.E.I.B revised the spectroscopic data, in silico studies, and statistical analysis of the bioassay results. All authors participated in manuscript writing, proofreading, sentence correction, and approved the final manuscript.

Funding
Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB). This research did not receive any grant or specific funding from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
All data generated or analyzed during this study are included in this article. Also, the related datasets are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 24 April 2024 Accepted: 6 August 2024
Published online: 28 August 2024

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