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Novel lipophilic analogues from 2,4-D and Propanil herbicides: Biological activity and kinetic studies

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Graphical Abstract



HIGHLIGHTS

- Synthesis of new lipophilic amides and esters analogues of classical organochlorides herbicides.
- Lipophilic compounds synthesized showed superior *in vitro* activity than commercial herbicides.
- The kinetic and NMR studies showed a decrease in half-life time of new herbicides compounds compared to 2,4-D.

ABSTRACT

This work describes the synthesis of new lipophilic amides and esters analogues of classical organochlorides herbicides by incorporation of long-chains from fatty acids and derivatives. The new fatty esters and amides were synthesized in 96-99% and 80-89% yields, respectively. In general, all compounds tested showed superior *in vitro* activity than commercial herbicides against growth *L. sativa* and *A. cepa*, in ranges 86-100% of germinative inhibition. The target compounds showed, significantly more susceptible towards acid hydrolysis than 2,4-dichlorophenoxyacetic acid (2,4-D). The kinetic and NMR studies showed that the incorporation of lipophilic chains resulted in a decrease in half-life time of new herbicides compounds (1.5 h) than 2,4-D (3 h). These findings suggest the synthesis of new lipophilic herbicides as potential alternative to traditional formulations, by incorporation of long fatty alkyl chains in the molecular structure of 2,4-D, resulting in superior *in vitro* herbicidal activity, best degradation behavior and more hydrophobic derivatives.

KEYWORDS: Organochlorides herbicides, 2,4-D, renewable resources, fatty acids, propanil.

1. Introduction

About 30 to 40% of losses in food production are related to the presence of weeds in crops (Safdar et al. 2015). Competitiveness, adaptation, and stress tolerance are the characteristics by which weed species secure their survival in a variety of environmental conditions (Korres et al. 2016). Increasing the production of food with environmental responsibility is a challenge for the

research. Annually, around 2.5 million tons of agrochemicals are used worldwide, it's estimated that only 1% reaches the target pests leaving their bulk as a residue. This problem causes an impact for the environment such as water supplier and soil (Ayoub et al. 2018; Horrigan et al. 2016).

The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D, **1**, Figure 1) was the first commercial herbicide to be introduced in the market for the control of broadleaf weeds in the 1940s. This herbicide regulates plant growth and acts like a mimicker of natural auxin, promoting cell division and elongation, increasing shelf-life of fruits at low concentrations (Islam et al. 2018). In addition, the analogues, N-(3,4-dichlorophenyl)propanamide (**2**), 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea (**3**) 3-(3,4-dichlorophenyl)-1,1-dimethylurea (**4**) are used as post-emergent herbicides since 1957 for the control of grasses and broadleaf weeds (Figure 1). This family belongs to the acetanilide class and it has been found to disrupt the electron transport chain by inhibiting the photosystem II, thus impacting in the plant growth (Kanawi et al. 2016).



Figure 1. Classical agrochemicals 2,4-D (1), Propanil (2), Linuron (3) and Diuron (4).

Compounds from the phenoxy acid group, such 2,4-dichlorophenoxyacetic acid (2,4-D, 1), are among the most commonly used herbicides in the world, applied in herbicidal formulations as both ester or salt form (ammonium, sodium or potassium) and recently as choline salt (Marcinkowska et al. 2017). One of the biggest disadvantages of these salts is the high hydro solubility, in association with mobility in the soil, which causes pollution in underground water resources through lixiviation, whereas esters are characterized by high vapor pressure (Pernak et

al. 2016; Peterson et al. 2016). Most herbicides commonly used as active ingredients also pose a threat to the atmospheric environment via either physical drift or volatilization. Recent works has been described the research for ester and amides derivatives with high-activity and low-volatility from 2,4-D as lead compound (Ding et al. 2019).

In order to reduce the volatility of these compounds and increase the herbicide efficacy on weeds, the herbicides are often used in combination with adjuvants (Gitsopoulos et al. 2018). Adjuvants are classified as those that modify the physical characteristics of the spray solution and those that enhance the biological efficacy of a herbicide (Hazen 2000). The biological efficacy of water-soluble, systemic active ingredients is markedly affected by the type of surfactant. Moreover, the spray retention mainly depends on droplet size, droplet velocity and the intrinsic physicochemical properties of both droplet and leaf surface (Haefs et al. 2002). In this sense, the use of vegetable oils as adjuvant's sources had showed environmental advantages as ecotoxicologically compatible, since are neither toxic nor phytotoxic and are quickly degraded by microorganisms in the soil (Stagnari et al. 2006; Izadi-Darbandi et al. 2013).

The most significant contribution of fatty acid insertion on the structure of traditional herbicides in the recent literature, is based on physicochemical properties modifications, mainly volatility, solubility and surface-active properties, which contribute to the increase of the contact surface between the leaves and active ingredient, contributing in the enhancement of the herbicide adsorption into the plant (Niemezak et al. 2018). Seminal works were introduced in the literature (Pernak et al. 2011) by the transformation of herbicides into ionic liquids and the selection of appropriate counter ions in herbicides ionic liquids (HILs), opening access to more eco-friendly, hydrophobic and non-volatile substances (Niemezak et al. 2019). The HILs tested demonstrated 4-8 times higher efficacy compared to of 2,4-D and this phenomenon was suggested by

physicochemical properties of HILs, as decrease in their density, refractive index and solubility in water. (Marcinkowska et al. 2017; Niemezak et al. 2017). In recent literature, the production of bio-ionic liquids from triglycerides present in vegetable oils pointed to the renewable source of chemicals targeted in the synthesis of actives and environmental-friendly compounds applied in agricultural practices (Pernak et al. 2018).

Encouraged by the beneficial properties described to the incorporation of lipophilic alkyl chains in traditional herbicides from recent literature, the objective of this work was to prepare new lipophilic derivatives which could act as effective and eco-friendly herbicides. The purpose was to investigate the synthesis of new fatty esters and amides analogues of classical organochlorides herbicides 2,4-D and Propanil agrochemicals family's by incorporation of long-chains, derived from fatty acids derivatives. The new synthesized compounds had their herbicidal activity investigated towards the growth inhibition of mono and dicotyledonous seeds as studies models. Besides, the degradation's profile was studied by kinetic UV-vis and ¹H NMR experiments.

2. Materials and Methods

Unless otherwise stated, all reactions were carried out under an air atmosphere, and all commercially available reagents were used without further purification. Starting materials were obtained from Merck (Germany), Fluka (Switzerland) and Sigma- Aldrich (USA) and were used without further purification. The progress of the reactions was monitored by thin-layer

chromatography (TLC) plates and all compounds were purified by column chromatography on silica gel (60-230 mesh; Sigma Aldrich). Melting points were determined on Fisatom 430D microscope melting point apparatus and were uncorrected. Infrared (IR) spectra were acquired on a Shimadzu IR PRESTIGIE-21.

2.1 NMR experiments

NMR experiments were performed on a Bruker AVANCE 400 NMR spectrometer operating at 9.4T, observing ¹H and ¹³C at 400.13 MHz and 100.50 MHz, respectively, equipped with a 5 mm direct detection probe (BBO) with gradient along the *z*-axis in CDCl₃ or DMSO-*d6* solution with TMS as the internal standard. For qNMR ¹H experiments, pulse was calculated by *pulsecal*. The relaxation delay for use in the acquisition of the quantitative ¹H NMR spectra was determined by T1 measurements with the aid of the pulse sequence inversion recovery, with same parameters as for ¹H spectra changing the τ values from 0.01 to 15 s. ¹H spectra were acquired by using a 30° pulse sequence (*zg*) with the following parameters: 30 s of relaxation delay (D1), 16 transients, a spectral width (SW) of 4789.27Hz (~ 12.0 ppm), 64 K numbers of data (TD), and 6.84 s of acquisition time (AQ). The experiments were performed at 298 K. FIDs were Fourier transformed with line broadening (LB) = 0.3 Hz. The resulting spectra were manually phased and baseline corrected, and referenced to the TMS at δ 0.0 ppm.

2.2 Kinetic studies

The kinetic studies were carried by UV-Vis spectroscopy (Agilent Cary) monitoring in the region of 190-800 nm under pseudo-first order conditions. An aliquot of 20 μ L stock solution of the target compounds (**6c**, **8c** and **11c**; 0.01 mol.L⁻¹ in acetonitrile) was added to a quartz cuvette (10 mm optical path) containing 3 mL of the reaction medium: acid solution (HCl 0.1 mol.L⁻¹ –

acid hydrolysis) or basic solution (NaOH 0.1 mol.L⁻¹ – alkaline hydrolysis). The reactions were monitored for at least five half-life times, by following the reactant consumption and product formation. The kinetic profiles (absorbance vs time) were fitted with equations (see supplementary information), using iterative least-squares software.

2.3 Herbicidal activities

The pre-emergent herbicidal activities of compounds 6a-d, 8a-c and 11a-c were evaluated against seeds of onion (Allium cepa, 'Anasac Jardin') and lettuce (Lactuca sativa, Vilmorin Jardin') as mono and dicotyledonous models, respectively. Emulsions of target compounds were prepared by dissolving a solution at 30 µM of target compounds in water with 1% of Chloroform (v/v). The dosages employed of all compounds in g/L in the bioassays were: **6a**, 13.33 g/L; **6b**, 14.17 g/L; 6c, 14.10 g/L; 6d, 7.02 g/L; 8a, 13.30 g/L; 8b, 14.14 g/L; 8c, 14.08 g/L; 11a, 11.98 g/L; 11b, 12.82 g/L; 11c, 12.76 g/L. A mixture of the same amount of water and Chloroform was used as negative control. An aqueous solution of the commercial herbicides MCPA (Anasac Chile, MCPA dimethyl ammonium, 750 SL, 750 g/L, 0.8 L/ha), Glyphosate (Roundup, Anasac Chile, Rango 480 SL, 480 g/L, 6 L/ha) and 2,4-D (Anasac Chile, Arco 2,4-D 480 SL, 578 g/L, 1.4 L/ha) were used as a positive control in the dosage indicated by providers. In 78-mm-diameter Petri dishes containing cotton, 15 onion or lettuce seeds were distributed and 10 ml of the test solution was added to each plate. The dishes were sealed and kept in germination chamber in the absence of light for 45 days at 30 °C. The percentage of inhibition was used to describe the efficiency of the compounds, based on growth control, calculated according to the following equation:

$$(G\%) = \frac{(S-C)}{C}.100$$

Where C corresponding to the average growth of the negative control and S is an average of the germinated roots. Each treatment was performed in triplicate.

2.4 Synthesis

2.4.1 General procedure for synthesis of the esters 6a-c

In a round bottom flask, were added the fatty acid alcohols (**5a-c**; 3 mmol), 2,4-D (**1**; 1 mmol) and 10% mol of Sulfamic Acid as catalyst, in acetonitrile (3 mL) as a solvent. The mixture was stirred at reflux by 12 hours. After, the reactional crude was filtered to remove the catalyst, the volatiles were evaporated under vacuum and the residue was submitted to purification by column chromatography with silica-gel as stationary phase and a mixture of hexane and ethyl acetate (95:5 v/v) as eluent.

Hexadecyl 2-(2,4-*dichlorophenoxy*)*acetate* (*6a*)*:* Yield 84%; White solid, m.p. 40 °C; IR υ/cm⁻¹: 3092, 2916, 2849, 1753, 1300, 1229; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.26 (s, 21H), 1.63 (m, 2H), 4.19 (t, *J*= 6.60 Hz, 2H), 4.68 (s, 2H), 6.78 (d, *J*= 8.80 Hz), 7.16 (dd, *J*= 8.80, 2.45 Hz), 7.39 (d, *J*= 2.45 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 25.7, 29.7, 31.9, 65.7, 66.4, 114.7, 124.3, 127.5, 130.3, 152.4, 168.2.

Octadecyl 2-(2,4-*dichlorophenoxy*) *acetate* (**6***b*): Yield 92%; White solid, m.p. 45 °C; IR υ/cm⁻¹: 3092, 2916, 2849, 1753, 1300, 1229; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.26 (s, 20H), 1.63 (m, 2H), 4.19 (t, *J*= 6.60 Hz, 2H), 4.68 (s, 2H), 6.79 (d, *J*= 8.80 Hz), 7.17 (dd, *J*= 8.80, 2.45 Hz), 7.39 (d, *J*= 2.45 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 14.1, 22.7, 26.8, 29.7, 31.9, 68.3, 114.6, 123.7, 127.4, 128.0, 130.2, 151.6, 166.9.

(*Z*)-octadec-9-en-1-yl 2-(2,4-dichlorophenoxy)acetate (**6***c*): Yield 96%; White paste; IR υ/cm⁻¹: 3003, 2924, 2853, 1738, 1759, 1585, 1574, 1475, 1238, 1198; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.27 (s, 17H), 1.61 (m, 2H), 2.02 (m, 4H), 4.19 (t, *J*= 6.72 Hz, 2H), 4.68 (s, 2H), 5.35 (m, 2H), 6.79 (d, *J*= 8.80 Hz), 7.17 (dd, *J*= 8.80, 2.69 Hz), 7.38 (d, *J*= 2.69 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 27.2, 29.3, 31.9, 65.7, 66.4, 114.7, 124.3, 127.5, 129.7, 130.3, 152.4, 168.1.

2.4.2 General procedure for the synthesis of the methyl esters **6d**.

In a round bottom flask, were added 2,4-D (1; 1 mmol), 10% mol of Sulfamic Acid as catalyst and methanol (3 mL). The mixture was stirred at reflux by 12 hours. After, the reactional crude was filtered to remove the catalyst, the volatiles were evaporated under vacuum and the residue was submitted to purification by column chromatography with silica-gel as stationary phase and a mixture of hexane and ethyl acetate (95:5 v/v) as eluent.

Methyl 2-(2,4-*dichlorophenoxy*)*acetate* (*6d*): Yield 99%; White solid, m.p. 32 °C; IR υ/cm⁻¹: 3075, 2955, 1763, 1391; ¹H NMR (CDCl₃, 400 MHz) δ 3.82 (s, 3H), 4.72 (s, 2H), 6.80 (d, *J*= 8.80 Hz), 7.18 (dd, *J*= 8.80, 2.45 Hz), 7.41 (d, *J*= 2.45 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 52.4, 66.3, 114.7, 124.9, 127.5, 130.3, 152.4, 168.5.

2.4.3 General procedure for the synthesis of the amides **8a-c**.

In a round bottom flask were added the methyl ester **6d** (1 mmol) and the fatty acid amine (**7a-c**, 2 mmol), in acetonitrile (3 mL) as a solvent. The mixture was stirred at reflux by 24 hours. After, the volatiles were removed under vacuum and the residue was submitted to purification by

column chromatography with silica-gel as stationary phase and a mixture of hexane and ethyl acetate (80:20 v/v) as eluent.

2-(2,4-dichlorophenoxy)-N-hexadecylacetamide (**8***a*): Yield 80%; White solid, m.p. 78 °C; IR υ/cm⁻¹: 3422, 3084, 2920, 2847, 1686, 1261; ¹H NMR (CDCl₃, 400 MHz) δ 0.90 (t, *J*= 8.0 Hz, 3H), 1.27 (s, 26H), 1.57 (m, 2H), 3.39 (t, *J*= 8.0 Hz, 2H), 4.52 (s, 2H), 6.86 (d, *J*= 8.80 Hz, 2H), 7.24 (dd, *J*= 8.80, 2.69 Hz, 2H), 7.44 (d, *J*= 2.69 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 26.8, 29.7, 31.9, 39.1, 68.2, 114.5, 123.7, 128.0, 130.2, 151.6, 166.4.

2-(2,4-*dichlorophenoxy*)-*N*-*octadecylacetamide* (**8b**): Yield 84%; White solid, m.p. 84 °C; IR υ/cm⁻¹: 3422, 3084, 2920, 2847, 1686, 1258; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.25 (s, 23H), 1.56 (m, 2H), 3.37 (d, *J*= 6.4 Hz, 2H), 4.50 (s, 2H), 6.83 (d, *J*= 8.80 Hz), 7.23 (dd, *J*= 8.80, 2.45 Hz), 7.42 (d, *J*= 2.45 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 25.7, 29.7, 31.9, 65.7, 66.4, 114.7, 127.5, 130.3, 152.4, 168.2.

(*Z*)-2-(2,4-dichlorophenoxy)-*N*- (octadec-9-en-1-yl)acetamide (8c): Yield 72%; White paste; IR υ/cm⁻¹: 3422, 3103, 3007, 2922, 2851, 1686, 1261; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.25 (m, 22H), 1.56 (m, 2H), 1.62 (s, 2H), 2.02 (m, 4H), 3.37 (d, *J*= 6.93 Hz, 3H), 4.50 (s, 2H), 5.35 (m, 2H), 6.82 (d, *J*= 8.80 Hz), 7.22 (dd, *J*= 8.68, 2.57 Hz), 7.42 (d, *J*= 2.45 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.6, 26.8, 29.4, 31.9, 39.1, 68.3, 114.6, 123.7, 128.0, 130.2, 151.6, 166.9.

2.4.4 General procedure for the synthesis of the amides 11a-c

In a round bottom flask were added the fatty acid (**9a-c**, 1 mmol), 3,4-dichloroaniline (**10**, 2 mmol), triethylamine (3 mmol) and 10 mol% of 4-(Dimethyl amino) pyridine (DMAP). Then, a

solution of cyclohexyl carbodiimide (DCC, 1 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at ambient temperature by 24 hours. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was submitted to purification by column chromatography with silica-gel as stationary phase and a mixture of hexane and ethyl acetate (90:10 v/v) as eluent.

N-(3,4-dichlorophenyl)palmitamide (11a): Yield 57%; pale yellow solid, m.p. 65 °C; IR υ/cm⁻¹: 3287, 3094, 2914, 2847, 1663; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.25 (m, 25H), 1.67 (m, 2H), 2.35 (t, *J*= 7.46 Hz, 2H), 7.34 (s, 1H), 7.39 (s, 1H), 7.77 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 25.5, 29.6, 31.9, 37.7, 118.9, 121.5, 127.3, 130.4, 132.7, 137.4, 171.6.

N-(3,4-dichlorophenyl)stereamide (11b): Yield 62%; pale yellow solid, m.p. 71 °C; IR υ/cm⁻¹: 3287, 3094, 2914, 2847, 1663; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (t, *J*= 8.0 Hz, 3H), 1.25 (m, 25H), 1.67 (m, 2H), 2.35 (t, *J*= 7.46 Hz, 2H), 7.34 (s, 1H), 7.39 (s, 1H), 7.77 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 25.5, 29.6, 31.9, 37.7, 118.9, 121.5, 127.3, 130.4, 132.7, 137.4, 171.7.

N-(*3*,*4*-*dichlorophenyl*)*oleamide* (*11c*): Yield 68%; brown oil; IR υ/cm⁻¹: 3414, 3003, 3212, 2926, 2851, 1676; ¹H NMR (CDCl₃, 400 MHz) δ 0.87 (t, *J*= 8.0 Hz, 3H), 1.28 (m, 21H), 1.69 (m, 2H), 2.01 (m, 4H), 2.35 (t, *J*= 7.46 Hz, 2H), 5.33 (m, 2H), 7.33 (s, 1H), 7.76 (s,1H), 7.95 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.1, 22.7, 25.5, 27.2, 29.3, 31.9, 37.6, 119.2, 121.6, 127.3, 129.6, 130.0, 130.4, 132.6, 137.4, 172.0.

3. Results and discussion

3.1 Synthesis of new lipophilic herbicides

The synthesis of new lipophilic esters **6a-c** was realized from esterification reaction of herbicide 2,4-D (1) with palmitic (C16:0, **5a**), stearic (C18:0, **5b**) and oleic (C18:1, **5c**) fatty alcohols (Scheme 1). The initial experiments were performed according to previous work (D'Oca et al. 2012) with 10% sulfamic acid (H₂NSO₃H) catalyst at different times and a molar ratio of fatty alcohol to herbicide 2,4-D (1) to synthesis of **6c**. To compare the esterification process, the reaction catalyzed by sulfuric acid was performed. However, H₂NSO₃H has emerged as a substitute for conventional Bronsted- and Lewis acid catalysts. It is a relatively stable, white crystalline solid that is odorless, non-volatile, non-hygroscopic, non-corrosive, and low-cost, and it is a highly efficient green catalyst in organic synthesis (D'Oca et al. 2020; Heravi et al. 2009).

The experimental conditions were optimized from oleic alcohol (5c) as template in a set of reactions. Afterwards, the palmitic (5a) and stearic (5b) alcohols were utilized to obtain the fatty acid esters **6a** and **6b**, respectively. The results are described in Table 1.



Scheme 1. New lipophilic esters 6a-c from herbicide 2,4-D (1).

Ent.	Stoichiometric ratio (1:5a-c)	Catalyst ^a	Time (h)	Fatty ester	Yield ^b (%)
1	1:1	H ₂ NSO ₃ H	24	6c	65
2	1:2	H_2NSO_3H	24	6c	94
3	1:3	H ₂ NSO ₃ H	24	6c	96

Table 1. Optimization of the experimental conditions for the fatty esters 6a-c synthesis.

4	1:3	H_2NSO_3H	12	6c	94
5	1:3	H_2NSO_3H	8	6c	79
6	1:3	H_2NSO_3H	24	6a	99
7	1:3	H_2NSO_3H	24	6b	98
8	1:1	H_2SO_4	24	6c	91
9	1:2	H_2SO_4	24	6c	88
10	1:3	H_2SO_4	24	6c	94
11	1:3	H_2SO_4	12	6c	89
12	1:3	H_2SO_4	8	6c	78

Reaction conditions: MeCN as solvent, reflux; "Loading 10 mol%; "Isolated from chromatographic column;

According to the results, it was possible to observe the successful synthesis of the fatty esters 6a-c under all tested experimental conditions in reasonable to good yields (65-96%). Firstly, the synthesis of **6c** was tested from stoichiometric ratios 1:1 of **1** and **5c**, in the presence of sulfamic acid as catalysts and MeCN as solvent under reflux for 24 hours and the product 6c was isolated with only 65% yield (Table 1, entry 1). Based in this result, the synthesis of **6c** was investigated in the presence of excess fatty alcohol 5c and different reactional times, using the same catalysts (Table 1, entries 2-5). Progressive increase of yield was observed when excess of fatty alcohol was employed, yielded 6c in 94% and 96% from 1:2 and 1:3 stoichiometric ratios, respectively (entries 2,3). From these findings, the decrease of reaction time to 12 h and 8 h was evaluated and the shorter reactional times resulted in good yields, 94 and 79%, respectively (Table 1, entries 4 and 5). Thus, sulfamic acid was chosen as catalyst and the fatty acid esters **6a** and **6b** were isolated with yields 99% and 98% (Table 1, entries 6 and 7), respectively. Aiming to compare the classical catalytic system used in esterification reactions to the results observed with sulfamic acid, the employment of sulfuric acid as catalyst was tested, and very similar results were observed (Table 1, entries 8-12). According to the results showed in the Table 1, it was possible to observe the successful synthesis of the new lipophilic esters 6a-c from herbicide 2,4-D (1) with 10% sulfamic acid (H₂NSO₃H), a highly efficient green catalyst.

After synthesis of the fatty esters, the synthesis of lipophilic amides **8a-c** (Scheme 2) from 2,4-D was investigated from different methodologies. The results are described in the Table 2. Initially, the synthesis of fatty amide **8c** from **1** was investigated using thionyl chloride from two procedures described in the literature (Wei et al. 2000). In the first, triethylamine and 10 mol% 4-dimethylaminopyridine (DMAP) (Method A) were added in the reaction medium and was possible to observe an inefficient formation of the product, despite the increase of stoichiometric ratios of **7c** (Table 2, entries 1-3).

From the results, these findings were considered inconsistent to typical behavior of reactions promoted by acyl chlorides, witch could be associated with lability of phenoxy group under reactional conditions. Alternatively, an experimental procedure based on the use of benzyltriethylammonium chloride salt (BTEAC) was realized (Method B) (Eubanks and Pacifici 1986). Indeed, treatment of **1** with 3 equiv of SOCl₂ in the presence of catalytic amounts of BTEAC (3 mol%) afforded higher results of **8c**, promoting an increase of yields (Table 2, entries 4-6). From the poor yields, another classical methodology to amide synthesis based on the use of carbodiimide coupling agents was investigated (Dunetz et al. 2016). This procedure employs N,N-dicyclohexylcarbodiimide (DCC) and DMAP (Method C), in the presence of Et₃N and CH₂Cl₂ as solvent at ambient temperature. Again, despite the use of one, two or three equivalents of amine **7c**, poor results were obtained (Table 2, entries 7-9).

Finally, the synthesis of fatty acid amide **8c** was investigated by aminolysis of methyl ester **6d** (methyl 2-(2,4-dichlorophenoxy) acetate), synthesized in yield 95% used directly without previous purification in the procedure (Method D). The aminolysis methyl ester **6d** in the presence of 1-3 equivalents of oleyl amine **7c** was carried out under reflux in the presence of acetonitrile as solvent for 24 hours (Table 1, entries 10-12). The use of 2 equivalents of amine provided 80%

yield of fatty amide **8c** (entry 11), and was extended to the other fatty amines **8a** and **8b** (Table 2, entries 13-14).



Scheme 2. Synthesis of new lipophilic amides 8a-c derived from herbicide 2,4-D (1).

Ent.	Experimental Conditions	Stoichiometric ratio	Fatty amides	Yield (%) ^e
1		1:7c (1:1)		34
2	Method A ^a	1:7c (1:2)	8c	37
3		1:7c (1:3)		48
4		1:7c (1:1)		58
5	Method B ^b	1:7c (1:2)	8c	59
6		1:7c (1:3)		69
7		1:7c (1:1)		23
8	Method C ^c	1:7c (1:2)	8c	27
9		1:7c (1:3)		30
10		6d:7c (1:1)		40
11		6d:7c (1:2)	8c	80
12	Method D ^d	6d:7c (1:3)		72
13		6d:7a (1:2)	8a	85
14		6d:7b (1:2)	8b	89

Table 2. Experimental conditions and yields of fatty acid amides 8a-c from 2,4-D.

Reactional conditions: ^a 2,4-D (1, 1mmol), SOCl₂ (3 mmol), Et₃N (3 mmol), DMAP (10 mol%), DCM (5 mL), 25 °C, 24 h; ^b 2,4-D (1, 1mmol), SOCl₂ (3 mmol), benzyltriethylammonium chloride (3 mol%), CH₂Cl₂, reflux, 24 h; ^c 2,4-D (1, 1mmol), DCC (1 mmol), DMAP (10 mol%), Et₃N (3 mmol), DCM (5 mL), 25 °C, 24 h; ^d Reflux, 24 h; ^e Isolated.

After synthesis of the fatty esters **6a-c** and amides **8a-c** from 2,4-D and fatty amines **11ac** derived from 3,4-dichloroaniline (**10**) and from free palmitic (C16:0, **9a**), stearic (C18:0, **9b**) and oleic (C18:1, **9c**) acids was investigated. The 3,4-dichloroaniline (**10**) is common structure present in Propanil (**2**), Linuron (**3**) and Diuron (**4**) agrochemicals.

Thus, the new fatty acid derivatives were proposed by synthesis of the amide **11c**, via acyl chloride (Method A) or carbodiimide activation methodologies (Method C), using oleic acid (**9c**) and 3,4-dichloroaniline (**10**) as template (Scheme 3).

The acyl chloride methodology was investigated from amine **10** by Method A. Under these conditions, the product **11c** was isolated with poor yields (Table 3, entries 1-2). However, the activation of a fatty acid **9c** using DCC (Method C) and **10** was realized and using two equivalents of **10** was possible to observe better results to synthesis of **11c** (Table 3, entries 3-5). Therefore, this condition was extended to palmitic and stearic fatty acids **9a** and **9b**, respectively (Table 3, Entry 6-7).



Scheme 3. Fatty acid amide synthesis from 3,4-dichloro aniline 10.

Table 3. Experimental evaluation for the synthesis of the fatty acid amides 9a-c.

Ent.	Experimental Conditions	Stoichiometric ratio	Fatty amides	Yield (%) ^c
1	Method A ^a	9c:10 (1:1)	11c	40
2		9c:10 (1:2)	11c	42

					_
3		9c:10 (1:1)	11c	51	
4		9c:10 (1:2)	11c	68	
5	Method C ^b	9c:10 (1:3)	11c	26	
6		9a:10 (1:2)	11a	57	
7		9b:10 (1:2)	11b	62	

Reactional conditions: ^a **9c** (1mmol), SOCl₂ (3 mmol), Et₃N (3 mmol), DMAP (10 mol%), DCM (5 mL), 25 °C, 24 h; ^b **9a-c** (1mmol), DCC (1 mmol), DMAP (10 mol%), Et₃N (3 mmol), DCM (5 mL), 25 °C, 24 h. ^c Isolated.

The lipophilic esters and amides synthesized from 2,4-D (1) and 3,4-dichloroaniline (10) were characterized by ¹H and ¹³C NMR, Infrared spectroscopy and were submitted to studies of herbicidal activity and kinetic behavior in aqueous medium, under basic and acid conditions.

3.2 Biological activity of the new lipophilic herbicides

The pre-emergent herbicidal activities of lipophilic esters **6a-d** and amides **8a-c** and **11a-c** were evaluated against seeds of onion (*Allium Cepa, 'Anasac Jardin'*) and lettuce (*Lactuva Sativa, 'Vilmorin Jardin'*), using monocotyledonous and dicotyledonous models, respectively. The results are shown in Figure 2.

All tested compounds had growth inhibition activity against *A. cepa* and *L. sativa* seeds. For dicotyledonous model, all new derivatives fatty esters **6a-c** and methyl ester **6d** presented the same efficiency that 2,4-D. The same behavior was observed with the fatty acid amides **8a-c**. For monocotyledonous template, a lower response in germination inhibition was observed with 2,4-D. In this case, the fatty esters **6a-b**, the methyl ester **6d** and fatty amides **8a-b** showed superior activities to the original herbicide, while for oleyl derivatives, inferior results were obtained.

The fatty acid amides **11a-c**, derived from 3,4-dichloroaniline, showed germinative inhibition activity towards both dicot and monocots seeds, with similar results to 2,4-D, Glyphosate[®] or 2-methyl-4-chlorophenoxyaceticacid (MCPA) used as control.

According to the literature (Peterson et al. 2016) the metabolites formed during the 2,4-D metabolism between sensitive dicots and tolerant monocots are similar, but in different amounts, resulting in lower concentrations of 2,4-D in biosystem of monocotyledons compared to dicotyledons. In agreement with this, in our work it is possible to observe that the results for the inhibition of the growth were in general better, for all compounds tested, for the dicotyledonous species.



Figure 2. Growth inhibition activity of the new derivatives esters **6a-d** and amides **8a-c** and **11ac** against *L*. *sativa* and *A*. *cepa* seeds. Average of three values with standard deviation; same letter in the line indicates that there were no significant differences between the means according to Tukey's test (p < 0.05).

3.3 Kinetic studies and NMR studies

Motivated by positives germinative inhibition results obtained from new esters and amide derivatives, the next question could be the influence of the fatty alkyl chains about the environmental behavior of new target compounds, incorporated by covalent bond. According to the literature, in the presence of water and light, the bond of phenoxy acetic acid in 2,4-D is broken and 2,4-dichlorophenol (2,4-DCP, **12**) and glycolic acid are formed. At same time, the polyhydroxylated species formed in the medium would subsequently lead to the opening of aromatic rings to form a variety of carboxylic acids, including acetic acid (Wei et al. 2000). However, no kinetic study of the degradation in aqueous medium is reported.

In this regard, a ¹H NMR and kinetic studies were carried out from selected oleyl derivatives **6c**, **8c** and **11c**. The reason of this choice was based in the differentiation of unsaturated fatty alkyl chain present in the starting material and possible sub-products formed in the medium, under acid or basic conditions that was submitted in the degradation's study.

The acid hydrolysis of **1** followed by UV-Vis showed the formation of a product that absorbed at 225 and 250 nm (see Data in Brief). The kinetic profile at 250 nm obeyed a pseudo-first order kinetic, giving an acid rate constant (k_{H3O}) of 3.62 x 10⁻¹ mol L⁻¹ min⁻¹. This means that at pH 2 the acid hydrolysis reaction has a half-life ($t_{1/2}$) of approximately 3 h. The basic hydrolysis showed to be very slow and the rate constant could not be calculated. The monitoring of 2,4-D hydrolysis under acidic conditions at 60 °C by ¹H NMR spectroscopy, showed the immediate formation of byproduct **12** (Figure 3, t = 0 h). In the spectra, it was possible to observe the presence of a signal in 5.15 ppm, attributed to phenol, from phenoxy's group bond cleavage. The emergence of aromatic hydrogens distinct of standard material after 12 hours of experiment is concomitant to

observation of signal at 2.08 ppm, attributed to acetic acid (AA) formation, from polyhydroxylated species (Wei et al. 2000).



Figure 3. ¹H NMR (400 MHz, DMSO-*d6*) experiments accomplishment of chemical behavior of 2,4-D (**1**, 6.67 x 10^{-5} mol.L⁻¹) in HCl (0.1 mol.L⁻¹) and temperature (60 °C).

The influence of fatty ester and amides linkages in the chemical behavior of 2,4-D derivatives (**6c**, **8c** and **11c**), under the same conditions above were also investigated by ¹H NMR and UV-vis experiments. Firstly, the hydrolysis of the fatty acid ester **6c** and amide **8c** were investigated, which showed distinct behaviors under acid or basic conditions.

In the case of the basic hydrolysis, both ester (**6c**) and amide (**8c**) consecutive spectra shows a decrease in the absorbance around 300 nm, attributed to the consumption of **6c** (Figure 4A) or **8c** (Figure 4C). Concomitantly, an increase in the absorbance around 230 nm is observed, assigned

to the product **1** after basic hydrolysis (Figure 6) and no side-reactions. The kinetic profiles for the product formation are shown in Figure 4B and 4D. The reactant profile presented a similar behavior, although noisier that could be due to its lower molar absorptivity and/or overlapping of the bands of **6c** or **8c** and **1** (see Data in Brief).

The rate constant for the basic hydrolysis of **6c** and **8c** obtained from the pseudo-first order fit (k_{OH}) of the kinetic profile are 2.95 x 10⁻² and 3.22 x 10⁻² mol L⁻¹ min⁻¹, respectively. Hence, the $t_{1/2}$ for the basic hydrolysis of ester and amide fatty derivatives are similar, **6c** at pH 12 reaches nearly 40 hours, and for **8c** is 36 hours, clearly more susceptible towards basic hydrolysis than observed for **1**.

For the acid hydrolysis of **6c** and **8c**, the consecutive spectra in Figure 5A and 5C shows a similar behavior of that observed for the alkaline hydrolysis: reactant consumption at 300 nm and product formation at 230 nm. Surprisingly, the kinetic profile at 230 nm (Figures 5B and 5D) did not obey first order kinetic, indicating a more complicated pathway, which was also seen by NMR analysis.



Figure 4. Typical consecutive spectra for the basic hydrolysis of **6c** (A) and **8c** (C); Kinetic profile at 230 nm for the basic hydrolysis of **6c** (B) and **8c** (D); Solid line corresponds to the fits according to a pseudo-first order equation (Silva et al. 2019). Conditions: $[6c] = 6.67 \times 10^{-5} \text{ mol } \text{L}^{-1}$; $[8c] = 6.67 \times 10^{-5} \text{ mol } \text{L}^{-1}$; $[NaOH] = 0.1 \text{ mol } \text{L}^{-1}$; $60 \,^{\circ}\text{C}$.



Figure 5. Typical consecutive spectra for the acid hydrolysis of **6c** (A) and **8c** (C); Kinetic profile at 230 nm for the acid hydrolysis of **6c** (**B**) and **8c** (**D**); Solid line corresponds to the fits according to equation 1. Conditions: $[6c] = 6.67 \times 10^{-5} \text{ mol } \text{L}^{-1}$; $[8c] = 6.67 \times 10^{-5} \text{ mol } \text{L}^{-1}$; $[HC1] = 0.1 \text{ mol } \text{L}^{-1}$; $60 \,^{\circ}\text{C}$.

Based on the NMR results and the kinetic observed herein, we propose that the acid hydrolysis of **6c** preferably lead to the product **12** (k_{H3O}^{1}) (Figure 6). Moreover, **6c** can also form **1** (k_{H3O}^{2}), by a less favorable reaction (*i.e.* slower) and consecutively, **1** can also lead to **12** (k_{H3O}^{3}). Based on these reactions, Equation 1 was deduced, which upon considering the Lambert-Beer relationship for the concentration of the product/reactant and absorbance, fitted adequately with

the experimental results (solid line in Figure 5B). Rate constants of 7.79 x 10^{-1} , 9.93 x 10^{-3} and 3.9 x 10^{-1} mol L⁻¹ min⁻¹ were obtained for k_{H30}¹, k_{H30}², and k_{H30}³, respectively. Indeed, this agrees with NMR results (see Data in Brief) where the formation of **12** is more favorable (higher rate constant, k_{H30}¹), whereas **1** is formed at a slower rate (k_{H30}²). The rate constant calculated for k_{H30}³ is similar to the value obtained previously for the acid hydrolysis of **1** (*vide supra*), indicating that the proposed reaction pathways given in Figure 5 are consistent. These kinetics observations also are supported by ¹H NMR spectroscopy, whose spectra from acid hydrolysis of **6c** showed the presence of 2,4-D (4.83 ppm) only after 48 h of experiment, while **12** it's observed in first hour of monitoring (available in Data in Brief). Overall, the kinetic results show that **6c** is significantly more susceptible towards acid hydrolysis than **1**, with a t_{1/2} of approximately 1.5 h at pH 2 (for the most preferential reaction *i.e.*, direct formation of **12**).



Figure 6. Kinetic profile after acid and alkaline hydrolysis of 6c and 8c derived from 2,4-D (1).

$$[12]_{t} = k_{H30}^{1} \quad [6c]_{0} \left(\frac{1 - e^{-\left(k_{H30}^{2} - k_{H30}^{1}\right)t}}{k_{H30}^{2} + k_{H30}^{1}} \right) + \frac{k_{H30}^{3}[6c]_{0}(k_{H30}^{2} + k_{H30}^{3})}{k_{H30}^{3} - k_{H30}^{2} - k_{H30}^{1}} \left(\frac{1 - e^{-\left(k_{H30}^{2} + k_{H30}^{1}\right)t}}{k_{H30}^{2} + k_{H30}^{1}} + \frac{e^{-k_{H30}^{3}t} - 1}{k_{H30}^{3}} \right)$$

Equation 1. Where k_{H3O^1} , k_{H3O^2} and k_{H3O^3} refer to the pathways shown in Figure 5; [12]_t is the concentration of **12** at a given time (t) and [6c]₀ is the initial concentration of **6c**.

Similar behavior was observed for the acid hydrolysis of **8c**, where the consecutive spectra are shown in Figure 5C and the kinetic profile at 230 nm (Figure 5B) indicates the presence of parallel reactions, as observed with **6c**. In this case, Equation 1 (consider **8c** instead of **6c** in the equation) fitted very well with the experimental results (solid line in Figure 5B), resulting in rate constants of 3.53×10^{-1} , 2.84×10^{-1} and 2.27×10^{-1} mol L⁻¹ min⁻¹ for k_{H30}^{-1} , k_{H30}^{-2} , and k_{H30}^{-3} , respectively. This indicates that the formation of **12** directly from **8c** is slightly faster the formation of **1**, but they are formed almost at the same rate. Compared to the analogous hydrolysis of **1** and **6c**, the reaction of **8c** is similar to **1** and slightly slower than **6c** (considering an overall sum of the rate constants k_{H30}^{-1} and k_{H30}^{-2} of 6.37×10^{-1} mol L⁻¹ min⁻¹ for **8c**). Thereby, the $t_{1/2}$ at pH 2 is approximately 1.8 h. These kinetics observations also are supported by ¹H NMR spectroscopy, whose spectra from acid hydrolysis of **8c** showed the concomitant presence of 2,4-D (**1**) and **12** already in the first hours of experiment (available in Data in Brief).

To hydrolysis reactions with the fatty oleyl amide **11c**, derived from 3,4-dichloroaniline present in the Linuron, Diuron and Propanil herbicide's family, both acid and basic hydrolysis resulted in just one aromatic product (3,4-dichloroaniline), monitored at 230 nm. The reactant was followed at 300 nm. In this case, the only reactional degradation observed was the hydrolysis of amide group produced oleic acid and 3,4-dichloroaniline. Pseudo first order fits gave $k_{\rm H30}$ and $k_{\rm OH}$ of 1.05 x 10⁻¹ and 4.92 x 10⁻² mol L⁻¹ min⁻¹, respectively. Likewise, the t_{1/2} at pH 2 and 12 is approximately 11 and 24 h, respectively.

In general, all new lipophilic derivatives amides e esters demonstrated herbicides activity *in vitro*, with growth inhibition capacity similar or superior to classical agrochemicals tested as control. In addition, the kinetics and NMR experiment showed that new lipophilic herbicides were significantly more susceptible towards acid degradations than 2,4-D (1), with a $t_{1/2}$ of approximately 1.5 h and 1.8 h at pH 2, respectively. In addition, the formation of DCP **12** from fatty acid ester **6c** is slightly faster than **8c**, with rate constants 7.79 x 10⁻¹ and 3.53 x 10⁻¹ mol L⁻¹ min⁻¹, respectively, both faster than 2,4-D (1.90 x 10⁻¹ mol L⁻¹ min⁻¹). These finding suggest that the modifications realized, in agreement with literature, could add interesting properties to new fatty herbicides compounds, such as solubility, volatility and surface-active properties, from renewable resources as vegetable oils, in substitution to mineral oils used in commercial formulations. Besides, the kinetic and NMR experiments show the acceleration of degradation behavior, from incorporation of fatty acid chains by ester or amide linkage.

4. Conclusions

This study presents, for the first time, the synthesis of new fatty acid derivatives of classical organochlorines herbicides. The new fatty esters and amides were synthesized in good yields, from herbicides 2,4-D and 3,4-dichloroaniline present core in Linuron, Propanil and Diuron herbicide's family. The compounds tested showed herbicidal activity against growth *L. sativa* and *A. cepa* as monocotyledonous and dicotyledonous study model seeds, respectively, with similar or superior performance to controls. Moreover, the kinetic and NMR studies showed that the incorporation of lipophilic chains resulted in a decrease in half-life time of new herbicides compounds compared to 2,4-D (from 3 h to 1.5 h). Besides, the fatty derivatives from 3,4-dichloroaniline, demonstrated fast decomposition, under acid or basic conditions. These findings suggest that incorporation of fatty acid alkyl chains, derived from renewable resources as vegetable oils, could add interesting

properties to new fatty herbicides, as low volatility, low solubility in aqueous medium, and surfaceactive properties, in substitution to mineral oils used in commercial formulations.

Conflict of interest

There are no conflicts to declare.

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