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Article

Synthesis and Phytotoxic Evaluation of 3-Indolylglycine Derivatives as New Natural-Like Herbicides

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A novel class of potential herbicides, 3-indolylglycines, was synthesized using an effective, green and rapid approach via multicomponent reaction (aza-Friedel-Crafts) between indoles, aldehydes and anilines in a water/sodium dodecyl sulfate system. The main advantages of this methodology are ease of handling, scalable to gram scale and a metal-free approach. The reaction is compatible with a variety of functional groups, obtaining the desired products in moderate to excellent yields. The biological activity of the 3-indolylglycines was evaluated, and it was found that these compounds interfere with the germination and radicle growth of *Lactuca sativa*, mainly the compound **4k**.

Keywords: *Lactuca sativa*, natural-like herbicides, 3-indolylglycines, phytotoxicity, aza-Friedel-Crafts reaction, water/surfactant

Introduction

The advance of Chemistry in the discovery of new herbicides with weed control and crop selectivity is a great challenge to be explored. It is known that the presence of weeds has a great impact on crop productivity, as they compete for the same resources: soil, water, and nutrients. They can also harbor insect and disease pests.[1] The use of synthetic pesticides is the most effective way to control weeds. However, the concern with the environment, the high toxicity that pesticides bring to mammals, and the resistance acquired by weeds are some of the concerns faced by science. Therefore, the search for new pesticides that are more selective to weeds and less toxic to the environment and mammals continues to be a challenge for chemical companies.[2]

A strategy that has been used in a promising way is based on the synthesis of molecules containing the core of natural products as a role model for the preparation of "natural-like" herbicides. In this sense, indolylglycines derivatives are presented as a new class of "bio-inspired" potential herbicides since they are analogues of 3-indolylacetic acid, a plant growth regulator of the auxins family.[3,4]

The biological potential of indolylglycine derivatives has never been reported in the literature, only it is used as an intermediate for the synthesis of biologically active compounds.[5-8] On the other hand, the search for new compounds that are efficient and safe as pesticides has been growing because the excessive use of pesticides is one of the major causes of environmental pollution.[9-16]

Recently, many advances in the synthesis of indolylglycine derivatives have been developed.[17] Jiang *et al.*[7] described a protocol that uses glyoxalate imines without the use of any acid catalyst. However, this methodology required an extended reaction time (days) to obtain the desired products and the prior preparation of the imine precursor (Scheme 1a).[6]

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In 2015, Wu and co-workers[18] demonstrated the functionalization of amino acid derivatives by C–H bond activation using Ru and Co as photosensitizer and catalyst, where a variety of indolylglycine derivatives can be converted into the desired products (Scheme 1b). Feng and co-workers[19] reported a mild and general C–H activation using α-amino carbonyls with indoles catalyzed by $Fe(ClO_4)_3$ with TBHP (*tert*-butyl hydroperoxide) as the oxidant, obtaining the indolylglycines in good yields (Scheme 1c). However, these methodologies require the prior synthesis of the α-amino carbonyls precursors, the use of an oxidant agent and a metal as catalyst.

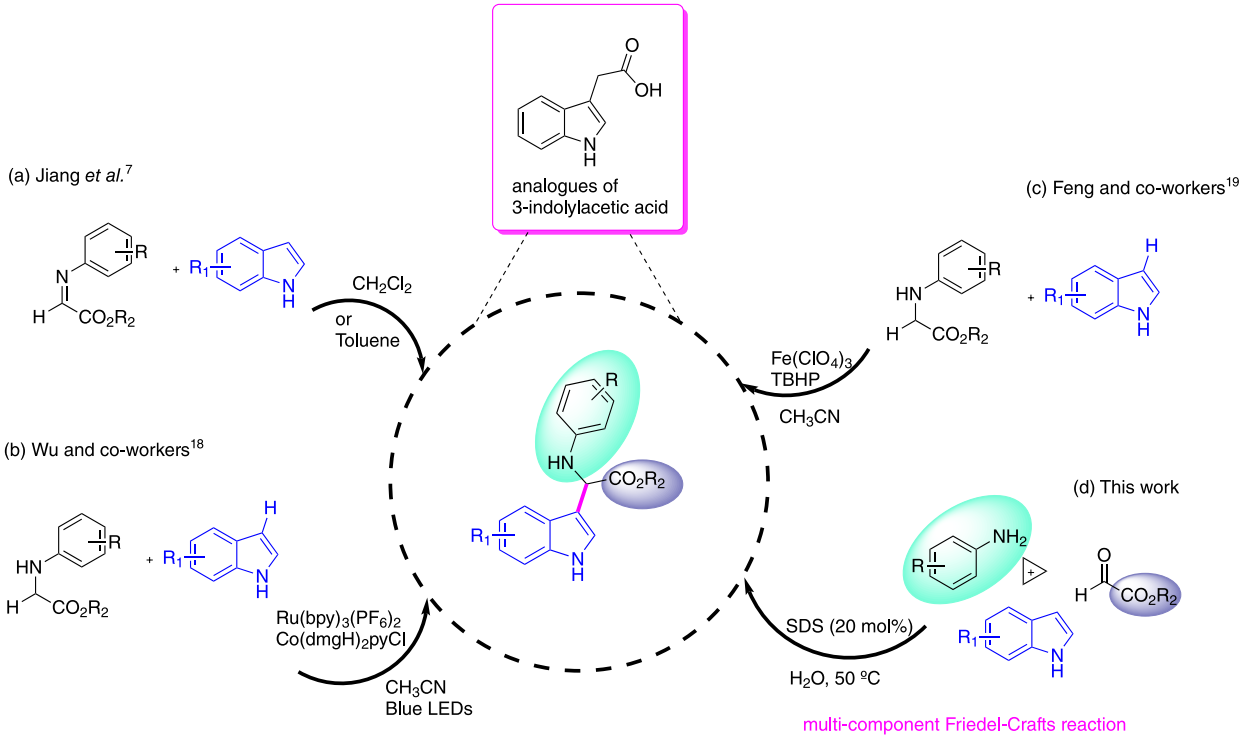
In this context, the synthesis of indolylglicines from three-component Friedel-Crafts reaction, using primary amines as substrate, is rare in the literature.[20,21] For example, the catalyst- and solvent-free approach described by Zhao *et al.*[21] Despite the success of this reaction, this protocol has their limitation regarding the scope of the reaction, since it is applied to a small variety of amines as starting materials.

Thus, in this work, we report the synthesis of indolylglicines by an effective, green, and rapid approach based on the three-component (aldehyde, primary amine and indole) Friedel-Crafts reaction (Scheme 1d). Furthermore, the phytotoxic activity of these compounds was assayed *in vitro* on germination and root growth of *Lactuca sativa* and was compared to commercial herbicides (glyphosate and atrazine), showing significant and very promising potential herbicidal activity.

Experimental

General experimental procedures

All reagents used in the synthesis were purchased from commercial suppliers (Sigma-Aldrich, Steinheim, Germany) and used without further purification. Solvents used in liquid-liquid extraction and as eluents for chromatographic purification, hexane and ethyl acetate, were purchased from commercial suppliers (Quimidrol, Joinvile, Brazil) and were distilled before use. The reactions were monitored by thin-layer chromatography (TLC) using Merck Silica Gel GF254, 0.25 mm thickness and visualized with UV light, iodine tub or stained with vanillin. Flash column chromatography was performed using Merck Silica Gel 60 (230-400 mesh). All compounds were characterized by ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR; the spectra can be found in the Supplementary Information (SI) section. The spectra were obtained using a Bruker DPX 300 (^{1}H at 300 MHz and ^{13}C at 75 MHz), using $CDCl_3$ and acetone-d_6 as solvents. All ^{1}H NMR shifts are reported in δ units, parts *per* million (ppm), and were measured relative to the signal for tetramethylsilane (TMS, 0.00 ppm). Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in hertz and integrated intensity. Abbreviations to denote the multiplicity of a particular signal are as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). All ^{13}C NMR shifts are reported



Scheme 1. Methodologies for synthesis of indolylglycines derivatives.

in ppm relative to deuterated-chloroform (77.23 ppm) or deuterated-acetone (206.0), unless otherwise stated, and all spectra were obtained with ^{1}H decoupling. High-resolution mass spectra (HRMS) were recorded on a Shimadzu ESI-TOF (Kyoto, Japan) mass spectrometer. Infrared spectra were recorded on a PerkinElmer Frontier Optica SD-10 (Vienna, Austria), with attenuated total reflection (ATR) module.

Biological assays

The bioassays of the phytotoxic activities of 3-indolylglycine derivatives were evaluated using an adaptation of the methodology described by Cunico *et al*.[22] The bioassays used Petri dishes (90 mm diameter) with one sheet of Whatman No. 1 filter paper as a substrate. The target plant was *Lactuca sativa* (cv Grand Rapids) seeds purchased from Isla Pak, RS, Brazil. It is noteworthy that seeds of the species *Lactuca sativa* were chosen for these bioassays because of their rapid germination rate, high sensitivity and cultivation practically worldwide.

For the germination test, 25 lettuce seeds were placed *per* dish with 5 mL of solution test (10, 25, 50, 100 and 150 ppm) or a control solution. All solutions of the compound synthetized were prepared dissolving the compound in a mixture of dimethyl sulfoxide (DMSO, 30 µL) and the surfactant Tween 20 (60 µL) and MES (buffered with 10 mM 2-(*N*-morpholino) ethanesulfonic acid) were adjusted to 6.0-6.5 with NaOH solution. The negative control was aqueous solution containing DMSO but no test compound.

The Petri dishes were covered with parafilm to reduce evaporation and incubated at 25 ± 2 ºC, 75% humidity, with light simulating day and night for 5 days. After this time, the number of germinated seeds was counted (a seed was considered to be germinated when the radicle was at least 0.2 mm long). Treatments were carried out in a completely randomized design with four replications.

The percentage of germination was calculated in relation to the germination of the control, using equation 1.

$$\text{Germination}(\%) = \frac{S}{C} \times 100 \quad (1)$$

where S corresponds to the average value of seed germination and C corresponds to the average germination of the control.

To plant growth bioassay, 10 seeds of *Lactuca sativa* previously sprouted (2 mm radicle) in distilled water, were placed in the Petri dishes with 5 mL of the test solution (10, 25, 50, 100 and 150 ppm). After the exposition period, the root and aerial part lengths of each radicle were measured manually to the nearest millimeter, using a ruler. The test was performed in quadruplicate. The percentage of growth inhibition was calculated in relation radicle length of the control, according to equation 2.

$$\text{Growth inhibition}(\%) = \frac{AGs}{AGc} \times 100 \quad (2)$$

where AGs corresponds to the average value of the radicle (root and shoot) length and AGc corresponds to the average growth of the control. The test data were subjected to statistical analysis using Origin® software (version 8.0)[23] and Microsoft Excel® (version 2016).[24]

General procedure for the synthesis of **4a-4o**

In a 10 mL tube, sodium dodecyl sulfate (SDS) (0.2 mmol), aniline **3** (1.2 mmol), aldehyde **2** (1.2 mmol) and 1.0 mL of water were added and stirred at 50 °C. After 5 min, indole **1** (1.0 mmol) and more 1.0 mL of water were added. The reaction was monitored by TLC to determine reaction time and it was indicated in Scheme 2. The organic compounds were then directly extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel using an appropriate mixture of hexane and ethyl acetate as the eluent. The identity and purity of the products were confirmed by ^{1}H NMR, ^{13}C NMR and melting points, all spectral data were in perfect agreement with those reported in the literature (see SI section).

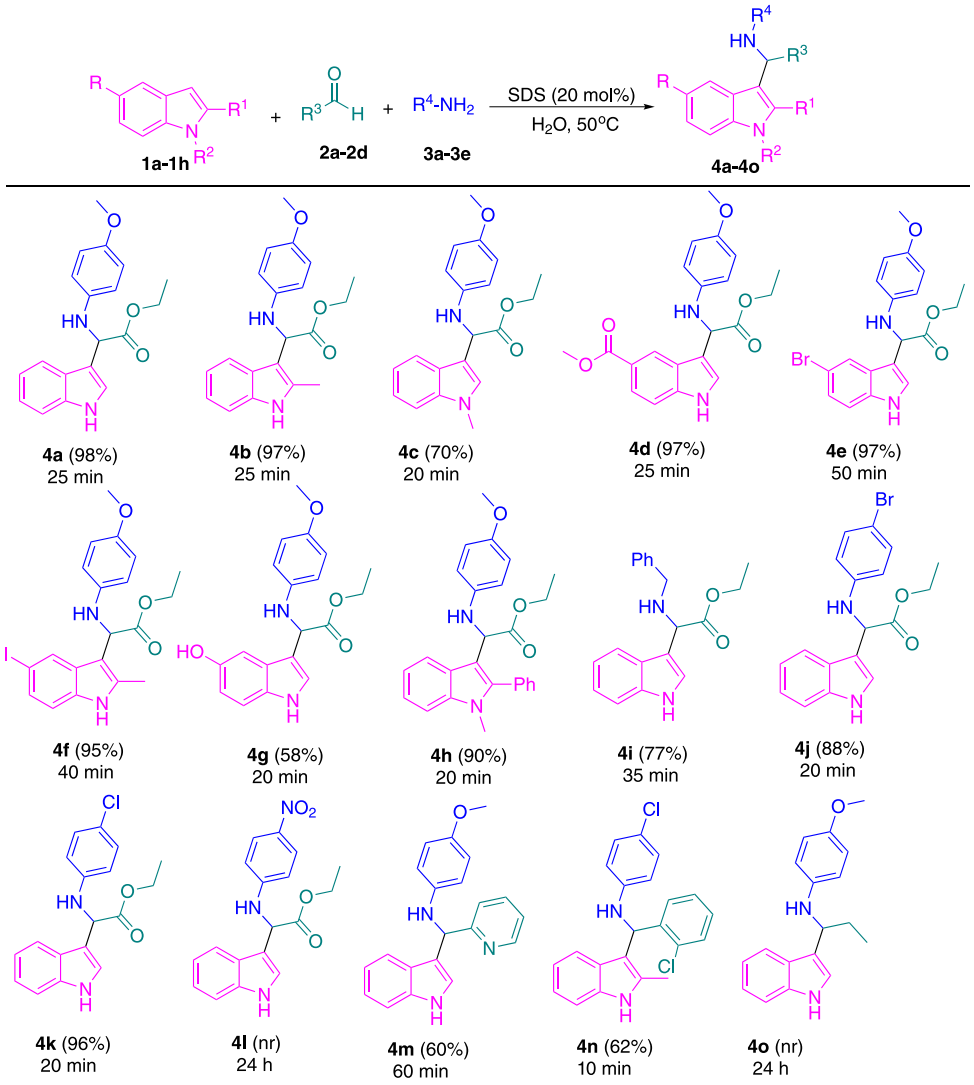
Characterization of the compounds **4a-4o**

Ethyl-2-(1*H*-indol-3-yl)-2((methoxyphenyl)amino)acetate (**4a**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 98% (318 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 10.23 (br, 1H), 7.79 (d, *J* 7.9 Hz, 1H), 7.41 (s, 2H), 7.09-7.02 (m, 2H), 6.73 (s, 4H), 5.36 (s, 1H), 5.06 (s, 1H), 4.13-4.09 (m, 2H), 3.67 (s, 3H), 1.16 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.4, 153.1, 142.6, 137.8, 127.1, 124.6, 122.6, 120.2, 120.0, 115.4 (2C), 115.4 (2C), 113.0, 112.4, 61.4, 55.8, 55.8, 14.5; IR υ_{max} / cm^{-1} 3281, 3263, 1665, 1462, 1152, 1004, 797, 732; HRMS (ESI-TOF) *m/z*, calcd. for $C_{19}H_{19}N_2O_3$ $[M - H]^-$: 323.1390, found: 323.1250.

Ethyl-2-((4-methoxyphenyl)amino)-2-(2-methyl-1*H*-indol-3-yl)acetate (**4b**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 97% (328 mg); ^{1}H NMR



Scheme 2. Scope and generality in the synthesis of indolylglycines. Reaction conditions: indole (1.0 mmol), aldehyde (1.2 mmol), aniline (1.2 mmol), SDS (0.2 mmol), H_2O (2.0 mL). Yield (%) of isolated product.

(300 MHz, CD_3COCD_3) δ 10.04 (br, 1H), 7.74 (d, *J* 7.4 Hz, 1H), 7.27 (d, *J* 7.8 Hz, 1H), 7.08-6.93 (m, 2H), 6.68 (s, 4H), 5.29 (s, 1H), 4.20-4.00 (m, 2H), 3.64 (s, 3H), 2.52 (s, 3H), 1.12 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.1, 153.1, 142.5, 136.4, 134.5, 128.0, 121.5, 119.9, 119.7, 115.4 (2C), 115.2 (2C), 111.3, 108.2, 61.4, 55.8, 55.3, 14.5, 12.0; IR υ_{max} / cm^{-1} 3276, 2833, 1665, 1462, 1411, 1393, 1194, 1141, 989, 793, 719; HRMS (ESI-TOF) *m/z*, calcd. for $C_{20}H_{21}N_2O_3$ $[M - H]^-$: 337.1557, found: 337.1360.

Ethyl-2-((4-methoxyphenyl)amino)-2-(1-methyl-1*H*-indol-3-yl)acetate (**4c**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 70% (237 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.79 (d, *J* 7.8 Hz, 1H), 7.39-7.27 (m, 2H), 7.19 (t, *J* 7.5 Hz, 1H), 7.08 (t, *J* 7.5 Hz, 1H), 6.73 (s, 4H), 5.36 (s, 1H), 4.2-4.03 (m, 2H), 3.94 (s, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 1.15 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.4, 153.3, 142.6, 138.3, 128.9, 127.6, 122.6, 120.5, 120.1, 115.5 (2C), 115.5 (2C), 112.1, 110.5, 61.6, 55.9, 55.7, 33.0, 14.6; IR υ_{max} / cm^{-1} 3248, 2829, 2760, 1669, 1585, 1462, 1413, 1199, 1154, 1048, 981, 719; HRMS (ESI-TOF) *m/z*, calcd. for $C_{20}H_{22}N_2O_3$ $[M]^+$: 338.1630, found: 338.1304.

Methyl-3-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-1*H*-indole-5-carboxylate (**4d**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 97% (371 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 10.59 (br, 1H), 8.59 (s, 1H), 7.84 (d, *J* 8.6 Hz, 1H), 7.54-7.47 (m, 2H), 6.74 (s, 4H), 5.45 (s, 1H), 5.15 (s, 1H) 4.25-4.04 (m, 2H), 3.88 (s, 3H), 3.67 (s, 3H), 1.18 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.2, 168.2, 153.3, 142.4, 140.4, 126.6, 126.4, 123.8,

123.3, 122.4, 115.5 (2C), 115.4 (2C), 114.6, 112.3, 61.6, 55.8, 55.7, 51.9, 14.4; IR υ_{max} / cm^{-1} 3200, 2853, 1665, 1631, 1462, 1391, 1242, 1199, 1147, 985, 747, 726, 661; HRMS (ESI-TOF) *m/z*, calcd. for $C_{21}H_{23}N_2O_5$ $[M + H]^+$: 383.1607, found: 383.1607.

Ethyl-2-(5-bromo-1*H*-indol-3-yl)-2-((4-methoxyphenyl) amino)acetate (**4e**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 97% (390 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 8.00 (s, 1H), 7.48 (s, 1H), 7.38 (d, *J* 8.6 Hz, 1H), 7.23 (d, *J* 8.6 Hz, 1H), 6.74 (s, 4H), 5.37 (s, 1H), 4.22-4.06 (m, 2H), 3.67 (s, 3H), 1.17 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.1, 153.3, 142.4, 136.4, 128.8, 126.2, 125.2, 123.0, 115.6 (2C), 115.4 (2C), 114.2, 113.0, 112.8, 61.6, 55.8, 55.7, 14.5; IR υ_{max} / cm^{-1} 3287, 2883, 1665, 1462, 1188, 985, 795; HRMS (ESI-TOF) *m/z*, calcd. for $C_{19}H_{20}BrN_2O_3$ $[M + H]^+$: 403.0657, found: 403.117.

Ethyl-2-(5-iodo-1*H*-indol-3-yl)-2-((4-methoxyphenyl)amino) acetate (**4f**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 95% (428 mg); ^{1}H NMR (300 MHz, CD_3COCD_3,) δ 10.42 (br, 1H), 8.21 (s, 1H), 7.41 (d, *J* 10.2 Hz, 2H), 7.28 (d, *J* 8.5 Hz, 1H), 6.73 (s, 4H), 5.37 (s, 1H), 4.23-4.03 (m, 2H), 3.66 (s, 3H), 1.17 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.1, 153.3, 142.4, 136.9, 130.8, 129.4, 125.9, 115.5 (2C), 115.4 (2C), 114.8, 114.7, 112.6, 83.2, 61.6, 55.8, 55.7, 14.5; IR υ_{max} / cm^{-1} 3246, 2881, 2833, 2739, 1665, 1462, 1404, 1194, 1141, 1065, 987, 851, 795, 771; HRMS (ESI-TOF) *m/z*, calcd. for $C_{19}H_{18}IN_2O_3$ $[M - H]^-$: 449.0357, found: 449.080.

Ethyl-2-(5-hydroxy-1*H*-indol-3-yl)-2-((4-methoxyphenyl) amino)acetate (**4g**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 58% (197 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 9.44 (br, 1H), 7.30 (s, 1H), 7.26-7.15 (m, 1H), 6.72 (s, 6H), 5.58 (s, 1H), 5.25 (s, 1H), 4.20-4.00 (m, 2H), 3.75 (s, 1H), 3.66 (s, 3H), 1.15 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 173.5, 153.2, 151.8, 142.6, 132.4, 127.8, 125.0, 115.4 (2C), 115.3 (2C), 112.8, 112.8, 112.0, 104.3, 61.4, 55.9, 55.8, 14.5; IR υ_{max} / cm^{-1} 3231, 2829, 2060, 1665, 1460, 1413, 1194, 1140, 991, 795, 775; HRMS (ESI-TOF) *m/z*, calcd. for $C_{19}H_{19}N_2O_4$ $[M - H]^-$: 339.1339, found: 339.1081.

Ethyl-2-((4-methoxyphenyl)amino)-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)acetate (**4h**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 90% (373 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* 7.9 Hz, 1H), 7.51 (s, 5H), 7.39-7.06 (m, 3H), 6.60 (d, *J* 8.8 Hz, 2H), 6.33 (d, *J* 8.8 Hz, 2H), 5.13 (s, 1H), 4.28-4.01 (m, 2H), 3.65 (s, 3H), 3.57 (s, 3H), 1.20 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 154.4, 140.8, 140.1, 137.5, 131.1, 128.9 (2C), 128.6 (3C), 125.7, 122.1, 120.2, 120.1, 115.0 (2C), 114.8 (2C), 109.7, 109.1, 61.5, 55.8, 55.2, 31.0, 14.3; IR υ_{max} / cm^{-1} 3291, 2885, 2836, 1676, 1654, 1462, 1419, 1317, 1182, 1143, 992, 793, 720, 681; HRMS (ESI-TOF) *m/z*, calcd. for $C_{26}H_{27}N_2O_3$ $[M + H]^+$: 415.2022, found: 415.0781.

Ethyl 2-(benzylamino)-2-(1*H*-indol-3-yl)acetate (**4i**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 77% (237 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (br, 1H), 7.60 (d, *J* 7.6 Hz, 1H), 7.25-7.12 (m, 6H), 7.05-7.09 (m, 3H), 4.64 (s, 1H), 4.20-3.93 (m, 2H), 3.75 (s, 2H), 2.97 (s, 1H), 1.09 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4, 139.2, 136.5, 128.6 (2C), 128.5 (2C), 127.3, 126.1, 123.5, 122.2, 119.8, 119.3, 112.3, 111.6, 61.2, 57.5, 51.6, 14.19; HRMS (ESI-TOF) *m/z*, calcd. for $C_{19}H_{21}N_2O_2$ $[M + H]^+$: 309.1603, found: 309.1317.

Ethyl-2-((4-bromophenyl)amino)-2-(1*H*-indol-3-yl)acetate (**4j**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 88% (327 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 10.27 (br, 1H), 7.78 (d, *J* 7.9 Hz, 1H), 7.43 (s, 1H), 7.22 (d, *J* 8.9 Hz, 3H), 7.18-7.01 (m, 2H), 6.73 (d, *J* 8.8 Hz, 2H), 5.59 (s, 1H), 5.43 (s, 1H), 4.23-4.07 (m, 2H), 1.16 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 172.8, 147.7, 137.7, 132.4 (2C), 126.9, 124.7, 122.7, 120.2, 116.6, 115.9, 112.4, 112.2, 109.1, 61.7, 54.9, 14.49; IR υ_{max} / cm^{-1} 3289, 2881, 1665, 1542, 1443, 1411, 1268, 1141, 1039, 979, 788, 719; HRMS (ESI-TOF) *m/z*, calcd. for $C_{18}H_{18}BrN_2O_2$ $[M + H]^+$: 373.0552, found: 373.0266.

Ethyl-2-((4-chlorophenyl)amino)-2-(1*H*-indol-3-yl)acetate (**4k**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 96% (3150 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 10.26 (br, 1H), 7.80 (d, *J* 7.8 Hz, 1H), 7.43 (d, *J* 7.0 Hz, 2H), 7.21-7.00 (m, 4H), 6.78 (d, *J* 8.8 Hz, 2H), 5.63 (s, 1H), 5.45 (s, 1H), 4.24-4.03 (m, 2H), 1.16 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ172.8, 147.2, 137.7, 129.4 (2C), 126.9, 124.8, 122.6, 122.0, 120.1 (2C), 115.3 (2C), 112.4, 112.2, 61.6, 54.9, 14.4; IR υ_{max} / cm^{-1} 3291, 2827, 2760, 1665, 1547, 1445,

1270, 1140, 1056, 979, 789, 719; HRMS (ESI-TOF) *m/z*, calcd. for $C_{18}H_{18}ClN_2O_2$ $[M + H]^+$: 329.1057, found: 329,0746.

N-((1*H*-Indol-3-yl)(pyridin-2-yl)methyl)-4-methoxyaniline (**4m**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 60% (197 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 10.22 (br, 1H), 8.64 (s, 1H), 7.87-7.63 (m, 3H), 7.45 (d, *J* 8.1 Hz, 1H), 7.36-6.99 (m, 4H), 6.79 (s, 4H), 5.99 (s, 1H), 4.13 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 164.0, 152.9, 149.7, 143.4, 338.1, 137.4, 127.4, 124.2, 122.8, 122.5, 122.5, 120.4, 119.9, 118.5, 115.5 (2C), 115.5 (2C), 112.4, 58.5, 55.9; IR υ_{max} / cm^{-1} 3281, 2952, 2833, 2739, 1648, 1540, 1460, 1387, 1194, 1194, 1000, 793, 719; HRMS (ESI-TOF) *m/z*, calcd. for $C_{21}H_{20}N_3O$ $[M + H]^+$: 330.1606, found: 330.1301.

4-Chloro-*N*-((2-chlorophenyl)(2-methyl-1*H*-indol-3-yl) methyl)aniline (**4n**)

Purification by column chromatography, eluent: hexane:ethyl acetate 90:10; yield 62% (236 mg); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 9.72 (br, 1H), 7.54 (d, *J* 6.2 Hz, 1H), 7.01 (m, 5H), 6.75 (d, *J* 8.8 Hz, 2H), 6.66 (t, *J* 7.5 Hz, 1H), 6.52 (t, *J* 7.5 Hz, 1H), 6.30 (d, *J* 8.8 Hz, 2H), 5.70 (s, 1H), 5.33 (s, 1H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, CD_3OCD_3) δ 147.9, 140.6, 136.7, 134.5, 134.4, 130.9, 130.7, 129.6 (2C), 128.5 (2C), 127.8, 121.7, 121.5, 119.8, 119.4, 115.2 (2C), 111.5, 110.7, 53.8, 12.46; IR υ_{max} / cm^{-1} 3289, 2827, 2760, 1648, 1546, 1445, 1413, 1251, 1004, 789, 719; HRMS (ESI-TOF) *m/z*, calcd. for $C_{22}H_{19}Cl_2N_2$ $[M + H]^+$: 380.0847, found: 380.3605

Results and Discussion

Prompted by our recent work[25] on the synthesis of bis(indolyl)methane derivatives under ytterbium triflate catalysis in relation to expanding our interest in the Friedel-Crafts alkylation reaction as well as in the design of eco-friendly processes, we decided to investigate this methodology to obtain 3-indolylglycine derivatives. In this regard, we initially evaluated the use of $Yb(OTf)_3$/SDS in H_2O to obtain 3-indolylglycine derivatives using indole (**1a**), ethyl glyoxylate (**2a**) and *p*-anisidine (**3a**) as model substrates.

Thus, when the reaction was performed with 5 mol% $Yb(OTf)_3$ and 15 mol% SDS at room temperature the product **4a** was obtained in 80% yield (Table 1, entry 1). In order to increase the yield, the catalyst and surfactant loading was increased two-fold, obtaining 90% yield (Table 1, entry 2). To investigate the importance of SDS, the reaction was conducted in the absence of SDS, but the yield decreased to 72% (Table 1, entry 3).

Next, we investigated the influence of other ytterbium sources, such as $YbCl_3.6H_2O$ and $Yb(OAc)_3.4H_2O$. However, the product was obtained in only moderate yield (Table 1, entries 4 and 5). Moreover, the influence of triflate source in the catalysts was also studied, such as $Sc(OTf)_3$, $In(OTf)_3$ and $Cu(OTf)_2$. However, the yields were lower than those obtained with $Yb(OTf)_3$ (Table 1, entries 6-8). Other catalysts were tested (CuCl and $FeCl_3.6H_2O$), but with no increases in yield (Table 1, entries 9 and 10).

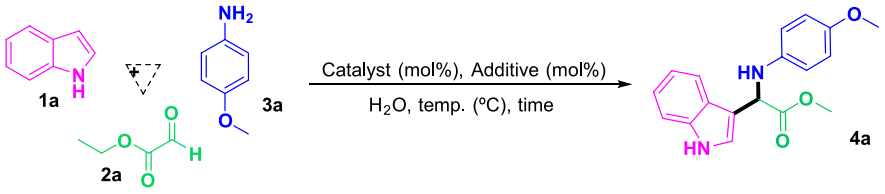
Next, the reaction was carried out in the absence of $Yb(OTf)_3$, and the product **4a** was obtained but in a lower yield even after 24 h (Table 1, entry 11). Thus, we decided to test the effect of temperature on the reaction, based on the article described by Kumar *et al.*[26] for the synthesis of amino alkylated indoles, and to our surprise the product was obtained in a high yield (Table 1, entry 12), using lower temperature and shorter reaction time when compared to the methodology described. However, when the amount of SDS was decreased, the yield also decreased. (Table 1, entry 13).

With the best reaction conditions obtained (Table 1, entry 12), we evaluated the generality and scope of the reaction in order to study reactivity and electronic effects, as shown in Scheme 2. Thus, we explored the reaction of different indoles **1a-1h**. However, no significant differences in reactivity were observed when indoles with electron-withdrawing or electron-donating groups were employed, obtaining the products **4a-4h** in good to excellent yields (58-98%), except when an –OH group was at position 5 of the indole, which resulted in **4g** at a lower yield than the other substrates.

In addition, different substituted anilines were tested (**3a-3e**) and afforded the respective 3-indolylglycines **4i-4k** in 77-96% yields. When *p*-nitroaniline was employed, the reaction did not occur **4l**, whereas the nitro group is strongly electron-withdrawing and influences imine formation. We have also investigated the behavior of different aldehydes on the reaction **2a-2d**, affording the desired 3-indolylmethanamines **4m** and **4n** in satisfactory yields. It is worth to note that product **4n** can act as part of new therapy to reduce prostate cancer cell growth and enables investigations toward the function of vitamin D receptor-coactivator interactions during gene regulation.[27] It is notable that the use of an alkyl aldehyde did not provide the desired product **4o** even after a long reaction time.

Moreover, to demonstrate the synthetic utility of this methodology, a scale-up reaction at 5 mmol was performed between indole **1a**, ethyl glyoxylate **2a** and *p*-anisidine **3a** under optimized conditions (Table 1, entry 12), affording **4a** with no decrease in yield (Scheme 3), indicating that this

Table 1. Optimization of standard reaction parameters for the synthesis of **4a**[a]



entry	Catalyst / mol%	Additive / mol%	time / min	Temperature / ºC	Yield[b] / %
1	$Yb(OTf)_3$ (5)	SDS (15)	60	rt	80
2	$Yb(OTf)_3$ (10)	SDS (30)	60	rt	90
3	$Yb(OTf)_3$ (10)	–	120	rt	72
4	$YbCl_3.6H_2O$ (10)	SDS (30)	60	rt	47
5	$Yb(OAc)_3.4H_2O$ (10)	SDS (30)	60	rt	62
6	$Sc(OTf)_3$ (10)	SDS (30)	60	rt	60
7	$In(OTf)_3$ (10)	SDS (30)	60	rt	53
8	$Cu(OTf)_2$ (10)	SDS (20)	60	rt	35
9	CuCl (10)	SDS (10)	60	rt	70
10	$FeCl_3.6H_2O$ (10)	SDS (30)	60	rt	35
11	–	SDS (15)	1440	rt	29
12	–	SDS (20)	25	50	98
13	–	SDS (10)	50	50	40

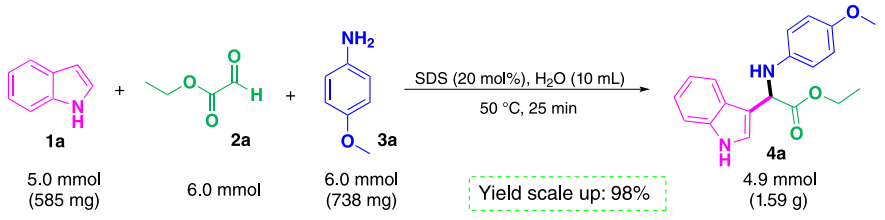
[a]Reaction conditions: indole **1a** (1.0 eq.), ethyl glyoxalate **2a** (1.2 eq.) *p*-anisidine **3a** (1.2 eq.), catalyst, additive, H_2O (2.0 mL). [b]Yield of isolated product. SDS: sodium dodecyl sulfate; rt: room temperature.

protocol could be used as a robust method for the larger scale synthesis of 3-indolylglycine derivative.

The products **4a**, **4b**, **4c**, **4e**, **4g**, **4h**, **4j**, **4k** and **4n** were evaluated for their ability to inhibit the seed germination and radicle growth of the dicotyledonous species *Lactuca sativa*. They were evaluated at five different concentrations (10, 25, 50, 100 and 150 ppm) and the results are shown in Figure 1. As positive control, it was used two herbicides, atrazine (Atra) and glyphosate (Gly). In Figure 1, it can be observed that most of the 3-indolylglycine derivatives had a significant influence on the germination of lettuce seeds. It is interesting to note that the phenyl substituent in C2-indole influences biological activity, since the **4h** derivative (at all concentrations tested) inhibited about 100% seed germination while **4c** did not significantly inhibit even at the highest concentration (3.5 ± 1.5%).

Furthermore, we observed the importance of halogen in the amine precursor, once that, in the compounds **4j**, **4k**, **4n** the inhibition was almost 100% in the highest concentration. In order to prove this effect, the precursors **1a**, **3a** and **3d** were tested and it was noted that the halogen substituted amine (**3d**) at 100 and 150 ppm concentrations, as well as the indole nucleus (**1a**) at 150 ppm concentration had an inhibitory effect, while *p*-anisidine did not show a significant result (**3a**) (Figure 1).

The compounds **4b**, **4h** and **4k** inhibited germination relative to control by almost 100% in the highest concentration, especially compound **4k** (Figure 2). It is noteworthy that the compounds **4h** and **4k** at the lowest concentration showed a significant reduction in germination (73.3 ± 4.64% and 79.1 ± 3.10%, respectively). With these results, to verify which target site of compounds that may influence inhibition, the synthetic precursors **1a**, **3a** and **3d** were tested. These precursors inhibited the germination, but only at the highest concentration. However, the **3a** showed no significant inhibition.



Scheme 3. Scale up reaction in the synthesis of **4a**.

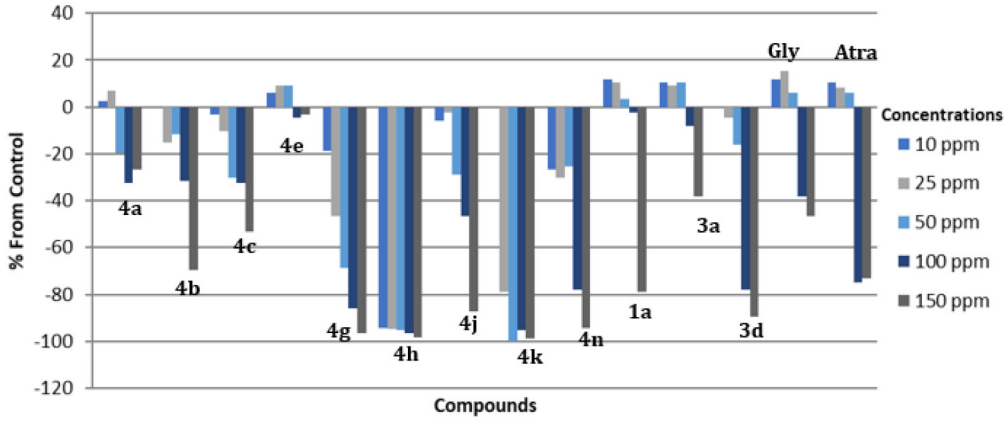


Figure 1. Phytotoxic activities of synthesized indolylglycines derivatives (**4a**, **4b**, **4c**, **4e**, **4g**, **4h**, **4j**, **4k**, **4n**) and commercial compounds on germination of *Lactuca sativa*.

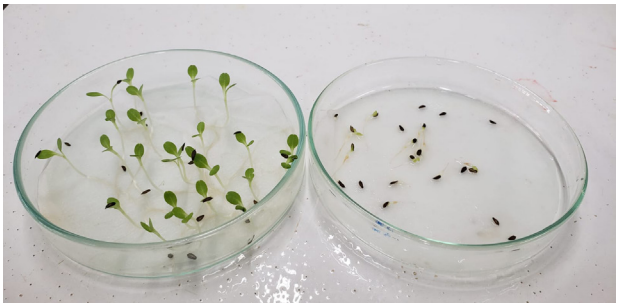


Figure 2. Anomalous germination of *Lactuca sativa* rootlets after 5 days of exposure to 150 ppm solution of compound **4k** (right) in comparison with the control (left).

When we compare the results to compounds **4b**, **4h** and **4k**, especially **4h**, with those obtained from glyphosate and atrazine, we can observe a greater inhibitory effect on the germination of lettuce seeds for synthesized compounds, especially the compound **4h** that was the most significant in all concentrations tested. This is an important result because of the resistance to weed control generated by excessive rotation of herbicides. Thus, it is of fundamental importance the search for new herbicidal chemical agents that act as specific inhibitors for use in pest control.[28]

The phytotoxicity of a compound may interfere with other germinal process variables, such as inhibition of root growth. Considering the results obtained in seed germination, for the growth test, only the 6 compounds that presented the best results (**4a**, **4b**, **4h**, **4j**, **4k** and **4n**) were used. Thus, we study phytotoxic activity in relation to inhibition of root growth, as shown the Figure 3.

Analyzing the results obtained, we observed that the compounds **4b** and **4h** had a growth inhibition of approximately 30% in relation to the control, only in the highest concentrations. The compound **4n** showed growth inhibition at higher concentrations, with 33.5 ± 1.19%.

The compounds **4a**, **4j** and **4k** inhibited the radicle growth in all concentrations tested. It is worth noting that the best result was observed for **4k** (83.8 ± 0.48%) mainly when compared to atrazine (54.9 ± 0.68%) and glyphosate (60.9 ± 0.64%) at 150 ppm. The compounds **4a** and **4j** showed inhibition of approximately 33% at the lowest concentration 82.7 ± 0.41 and 60.9 ± 0.8%, respectively, for the highest concentration. The compound **4k** had the highest inhibition both at the lowest (41.7 ± 0.89%) and highest concentrations (83.8 ± 0.48%). This is easily seen

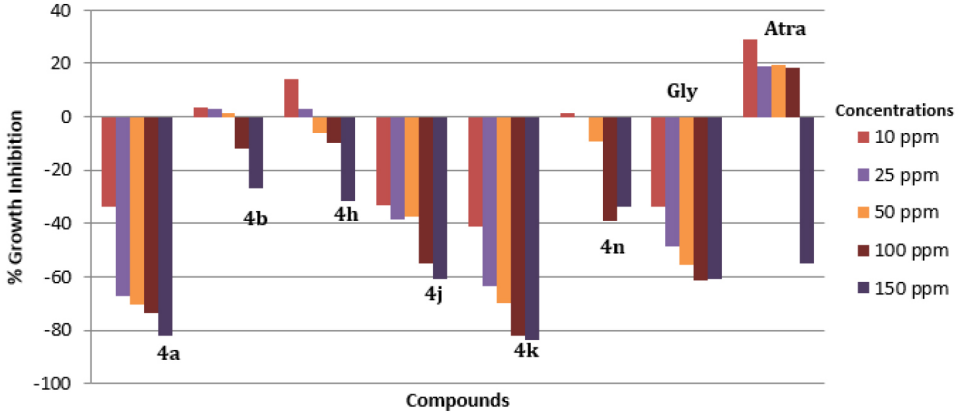


Figure 3. Effect of **4a**, **4b**, **4h**, **4j**, **4k** and **4n** on shoot length of *Lactuca sativa*.

in Figures 3 and 4. In summary, the compounds **4a**, **4j** and **4k** indicated greater inhibition of shoot length in the lettuce species compared to the control, glyphosate and atrazine herbicides.

Figure 4. Anomalous growth of *Lactuca sativa* rootlets after 5 days of exposure to 150 ppm solution of compound **4k** (right) in comparison with the control (left).

Conclusions

The results showed that multicomponent reaction in an SDS/H_2O system was a versatile strategy to obtain 3-indolylglycine derivates, this methodology showed advantages that include: no use of a metallic catalyst, ease of scale-up to gram scale, atom-economy, short reaction time, water as solvent. The phytotoxicity of 3-indolylglycine derivates was investigated against dicotyledonous specie, *Lactuca sativa*. The products exhibited predominantly inhibitory activity on germination and plant growth in the target species, in particular compound **4k**. Many of them were more phytotoxic than the positive control (atrazine and glyphosate). These results suggested that indolylglycines derivatives, especially **4k** could be promising as new natural-like herbicides.

Supplementary Information

Supplementary information (NMR spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

Alexandra A. Amaral was responsible for the organic synthesis work and phytotoxic activity studies; Isadora M. de Oliveira and Helio A. Stefani for the NMR and MS analysis; Conceição F. Alves Olguin for the phytotoxic activity studies; Julia C. M. Willig for the writing-review and editing the article; Giancarlo V. Botteselle and Flavia Manarin for the coordination of organic synthesis and writing the article. All authors contributed by reading, revising, and editing the article.

References

1. Tomlin, C. D. S.; *The Pesticide Manual*, 14th ed.; BCPC: Alton, USA, 2006.
2. Böger, P.; Wakabayashi, K.; Hirai, K.; *Herbicide Classes in Development. Mode of Action, Targets, Genetic Engineering, Chemistry*, 1st ed.; Springer-Verlag: Berlin, Germany, 2002.
3. Da Rosa, F. A. F.; Rebelo, R. A.; Nascimento, M. G.; *J. Braz. Chem. Soc*. **2003**, *14*, 11. [Crossref]
4. Calatayud, J. M.; de Ascenção, J. G.; Albert-García, J. R.; *J. Fluoresc*. **2006**, *16*, 61. [Crossref]
5. Wang, X.-W.; Hua, Y.-Z.; Wang, M.-C.; *J. Org. Chem.* **2016**, *81*, 9227. [Crossref]
6. Xu, Z.; Yu, X.; Feng, X.; Bao, M.; *J. Org. Chem.* **2012**, *77*, 7114. [Crossref]
7. Jiang, B.; Huang, Z. G.; *Synthesis* **2005**, *13*, 2198. [Crossref]
8. Segundo, M. S.; Guerrero, I.; Correa, A.; *Org. Lett.* **2017**, *19*, 5288. [Crossref]
9. Borgati, T. F.; Alves, R. B.; Teixeira, R. R.; de Freitas, R. P.; Perdigão, T. G.; da Silva, S. F.; dos Santos, A. A.; Bastidas, A. J. O.; *J. Braz. Chem. Soc*. **2013**, *24*, 953. [Crossref]
10. Xu, X.; Hu, F.; Shuai, Q.; *New J. Chem*. **2017**, *41*, 13319. [Crossref]
11. Dias, L. C.; Demuner, A. J.; Valente, V. M.; Barbosa, L. C. A.; Martins, F. T.; Doriguetto, A. C.; Ellena, J.; *J. Agric. Food Chem*. **2009**, *57*, 1399. [Crossref]
12. Ma, H.-J.; Li, Y.-H.; Zhao, Q.-F.; Zhang, T.; Xie, R.-L.; Mei, X.-D.; Ning, J.; *J. Agric. Food Chem*. **2010**, *58*, 4356. [Crossref]
13. Zhu, S.; Xu, S.; Jing, W.; Zhao, Z.; Jiang, J.; *J. Agric. Food Chem*. **2016**, *64*, 9702. [Crossref]
14. Cao, Y.-Y.; Mao, D.-J.; Wang, W.-W.; Du, X.-H.; *J. Agric. Food Chem*. **2017**, *65*, 6114. [Crossref]
15. Wang, D.-W.; Zhang, R.-B.; Ismail, I.; Xue, Z.-Y.; Liang, L.; Yu, S.-Y.; Wen, X.; Xi, Z.; *J. Agric. Food Chem*. **2019**, *67*, 9254. [Crossref]
16. Zhao, L.-X.; Jiang, M.-J.; Hu, J.-J.; Zou, Y.-L.; Cheng, Y.; Ren, T.; Gao, S.; Fu, Y.; Ye, F.; *J. Agric. Food Chem*. **2020**, *68*, 3729. [Crossref]
17. Bonandi, E.; Perdicchia, D.; Colombo, E.; Foschi, F.; Marzullo, P.; Passarella, D.; *Org. Biomol. Chem*. **2020**, *18*, 6211 [Crossref]; Ni, C.; Chen, W.; Jiang, C.; Lu, H.; *New J. Chem*. **2020**, *44*, 313. [Crossref]
18. Gao, X.-W.; Meng, Q.-Y.; Li, J.-X.; Zhong, J.-J.; Lei, T.; Li, X.-B.; Tung, C.-H.; Wu, L.-Z.; *ACS Catal.* **2015**, *5*, 2391 [Crossref];

Kumar, G.; Pillai, R. S.; Khan, N. H.; Neogi, S.; *Appl. Catal., B* **2021**, *292*, 120149. [Crossref]
19. Zhang, Y.; Ni, M.; Feng, B.; *Org. Biomol. Chem.* **2016**, *14*, 1550. [Crossref]
20. Desimoni, G.; Faita, G.; Mella, M.; Toscanini, M.; Boiocchi, M.; *Eur. J. Org. Chem.* **2008**, 6232. [Crossref]
21. Zhao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D.; Chen, Y.-J.; *Synlett* **2006**, *1*, 96. [Crossref]
22. Cunico, M. M.; Dias, J. G.; Miguel, M. D.; Miguel, O. G.; Auer, C. G.; Côcco, L. C.; Lopes, A. R.; Yumamoto, C. I.; Monache, F. D.; *Quim. Nova* **2006**, *29*, 746. [Crossref]
23. *Origin*, version 8.0; OriginLab, Northampton, USA, 2016.
24. *Microsoft Excel*, version 2016; Microsoft, Redmond, Washington, D. C., USA, 2007.
25. Tornquist, B. L.; Bueno, G. P.; Willig, J. C. M.; de Oliveira, I. M.; Stefani, H. A.; Rafique, J.; Saba, S.; Almeida, I. B.; Botteselle, G. V.; Manarin, F.; *ChemistrySelect* **2018**, *3*, 6358. [Crossref]
26. Kumar, A.; Gupta, M. K.; Kumar, M.; Saxena, D.; *RSC Adv.* **2013**, *3*, 1673. [Crossref]
27. Nandhikonda, P.; Lynt, W. Z.; McCallum, M. M.; Ara, T.; Baranowski, A. M.; Yuan, N. Y.; Pearson, D.; Bikle, D. D.; Guy, R. K.; Arnold, L. A.; *J. Med. Chem.* **2012**, *55*, 4640. [Crossref]
28. Lein, W.; Börnke, F.; Reindl, A.; Ehrhardt, T.; Stitt, M.; *Curr. Opin. Plant. Biol.* **2004**, *7*, 219. [Crossref]

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