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Design and semisynthesis of new herbicide as 1,2,3-triazole derivatives of the natural maslinic acid

Aymen Ben Nejma[a,b], Mansour Znati[b], Adam Daich[a], Mohamed Othman[a], Ata Martin Lawson[a,*], Hichem Ben Jannet[b,*]

[a] Normandie Univ, France; UNILEHAVRE, URCOM, EA 3221, INC3M, FR 3038 CNRS, F-76600 Le Havre, France
[b] Laboratory of Heterocyclic Chemistry, Natural Products and Reactivity (LR11ES39), Team: Medicinal Chemistry and Natural Products, Faculty of Science of Monastir, University of Monastir, Avenue of Environment, 5019 Monastir, Tunisia

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ABSTRACT

Interesting biological activities (anti-inflammatory, anticancer, antiviral, antioxidant, antidiabetic…) have been reported for maslinic acid (MA) and MA-based compounds. In continuation of our previous work on MA, herbicide potential of Tunisian plant extracts and 1,4-triazolyl derivatives of MA, we now wish to report semisynthesis of new MA-based triazole hybrid compounds with herbicide potential. These compounds were synthesized through Cu-catalyzed azide-alkyne cycloaddition (CuAAC) under microwave irradiation conditions between propargylated MA and a series of phthalimide azides. Here, the first partner of CuAAC reaction (propargylated MA) resulted from propargylation of C-28 carboxylic acid group of isolated MA from the well-known Mediterranean plant *Olea europaea* L. (Oleaceae). So far, phthalimide azide derivatives were achieved by trapping of *N*-acyliminium ion, *in-situ* generated under catalytic condition of $Bi(OTf)_3$, by aromatic nucleophiles. The cycloaddition reaction afforded regiospecifically 1,4-disubstituted triazoles in good yields. The latter hybrid compounds were shown to exhibit a high inhibition potential of seed germination. This constitutes the first step in development of potent herbicides since one of the final semisynthesized structures can serve as a promising lead candidate for further studies.

1. Introduction

The use of insecticides, pesticides and herbicides [1] in the agricultural sector remains one of the solutions to drastically reduce economic losses in terms of crop yields. Nevertheless, these products, particularly herbicides have also negative effects on the environment and the health of living organisms, including humans [2]. Natural herbicides and allelochemicals are increasingly used by farmers for weeds management in intensive farming, organic agriculture, sustainable and family agriculture. In the light of these considerations, many efforts are more and more devoted to the research in natural herbicides, allelochemicals or natural products-based herbicides areas [3]. Most of allelochemicals are secondary metabolites and belong, among others, to phenolic compounds, long-chain fatty acids, organic cyanides and terpenoids [4]. Indeed, in the latter terpenoids class, pentacyclic skeletons such as lupane, oleanane, and ursane triterpenes were reported for their plant growth modulation potential [5–7]. As hydroxy pentacyclic triterpene acids (HPTAs) are found in higher concentration (MA: 73.25% and oleanolic acid: 25.75% (Fig. 1)) in the skin of olive fruit extracts [8], we decided to take advantage of this high content of triterpenoids in olive tree (*Olea europaea*). So far, since *N*-phenylphthalimide and triazole derivatives were two different classes of herbicides such as Flumioxazin Pestanal® and Amitrol Pestanal® (Fig. 2) [9], it was envisioned through this work to connect these entities to a natural product to design a new class of herbicides (Fig. 3). Based on our previous work on MA [10], allelopathic potential of Tunisian plant extracts [11], 1,4-triazolyl derivatives of MA [12] and oleanolic acid (OA) [13], the present study aims to access novel modulators of plant growth based on natural products such as MA (Fig. 3). This triterpene is mainly isolated from *Olea europaea* L. under ultrasonic conditions in a large amount [10]. Classified under Oleaceae family, *Olea europaea* plays a pivotal role in Mediterranean diet and is considered to be a high economic value plant that has accompanied the development of Mediterranean civilization [14]. So far, olive tree, the major oil-producing crop in Tunisia and the Mediterranean basin is used in traditional medicine over the world. Decoctions of dried fruits and leaves are used to treat diarrhea as well as respiratory and urinary tract infections whereas fresh leaves infusion was reported for anti-inflammatory use [15]. As

* Corresponding authors at: Normandie University, UNILEHAVRE, URCOM, EA 3221, INC3M, FR 3038 CNRS, F-76600 Le Havre, France (A.M. Lawson).
E-mail address: lawsona@univ-lehavre.fr (A.M. Lawson).

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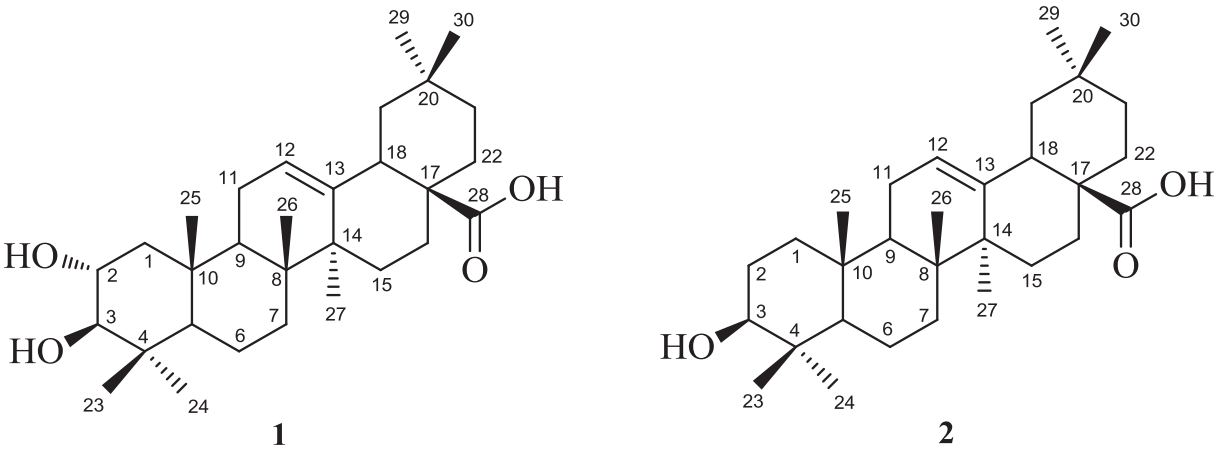


Fig. 1. Major compounds from *Olea europaea*: maslinic acid (MA) **1** and oleanolic acid (OA) **2**.

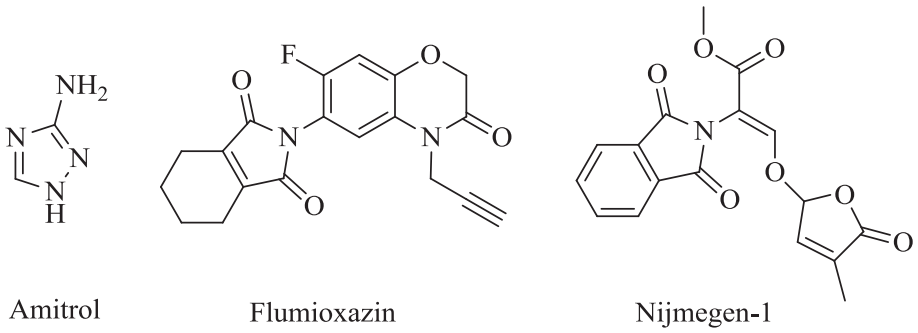


Fig. 2. Herbicide marketed (Amitrol, Flumioxazin, Nijmegen-1).

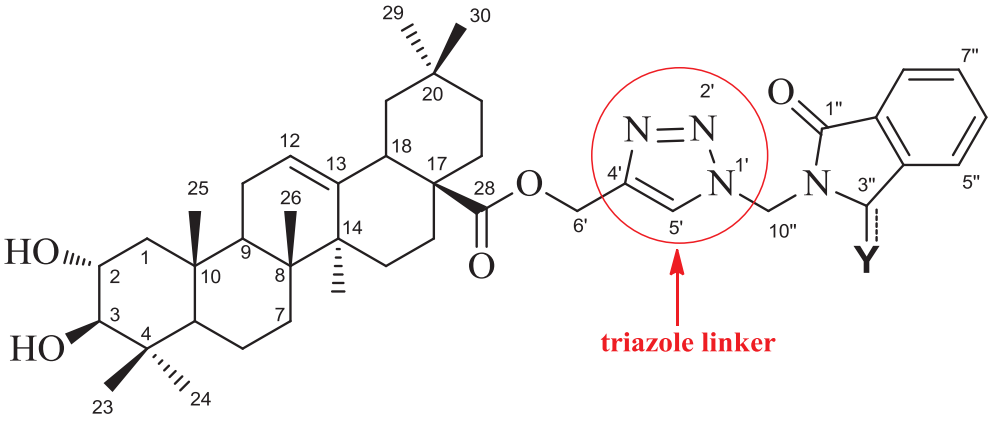


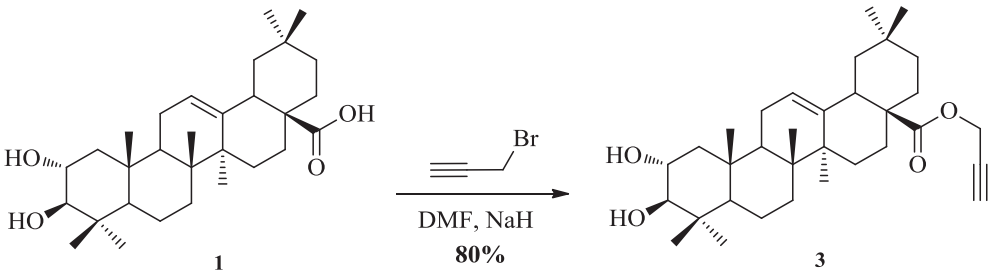
Fig. 3. Triazole core as a linker in the design of a new class of herbicides.

described in literature, MA displayed several biological activities, such as antioxidant [16], anti-inflammatory [17], antitumoral [18], anti-diabetic [19], anti-allodynic [20] and anticancer activities [21]. Nevertheless, MA-based compounds have never been reported as powerful herbicidal agents. Herein, is described the design and the preparation of a series of novel MA linked to phthalimide derivatives through 1,2,3-triazolo moiety as a spacer (Fig. 3). These compounds are semisynthesized in moderate to good yields via Huisgen [3 + 2] cycloaddition ("click reaction") between a terminal alkyne and phthalimide-based azides. This copper-catalyzed 1,3-dipolar cycloaddition reaction was regioselectively controlled and led to a series of novel MA-based hybrid molecules that connect two distinct entities. The first moiety has natural origin (MA) while the second part was synthesized trough "*N*-acyliminium ion chemistry" (phthalimide derivatives) [22]. Since lupane triterpenes are known as *Lactuca sativa* L. growth promoters [5,6], we expected through this work to shift this property into inhibitory activity by adding a potential active moiety (triazolo-methyl phtalimide part).

2. Materials and methods

2.1. Materials and reagents

Unless otherwise specified, reagents and starting materials were purchased from traditional suppliers and were used without further purification. Reactions were carried out in standard glassware. Solvents were purified and dried using standard methods before their use. Commercial TLC plates (Silica gel 60, F254, 0.2 mm-thick) were used to monitor the progress of the reaction. Column chromatography was performed with silica gel 60 (particle size 40–63 μm). HRMS were



Scheme 1. Synthesis of propargylated MA 3.

acquired with a LCT Premier XE mass spectrometer. For ESI experiments, Leucine-enkephaline peptide was employed as a lock mass for the LockSpray. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded at room temperature (rt) on a Bruker AM-300 Fourier Transform spectrometer equipped with a 10 mm probe. Deuterated chloroform ($CDCl_3$) was used as solvent with all chemical shifts (δ), reported in ppm, referred to residual non deuterated signal. Coupling constants were measured in Hz and following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet, etc., were used for ^{1}H NMR signals.

2.2. Extraction and isolation of compound 1

The pomace of *Olea europaea* L. was collected from the factory of soap located in Sousse (Tunisia) and kept at room temperature in the dark until its use. 2.5 kg of pomace was extracted once with Acetone-Water (1:1) at room temperature for five days. Then the oil phase was obtained after solvent evaporation under vacuum and a series of decantation and separation. A white solid (10.5 g, yield 0.42%) has been obtained after treatment of the oil phase with hexane under ultrasonic agitation (30 min, bath at 25 °C). Compound **1** (6.0 g of MA, yield 0.24%) was purified by column chromatography (L: 100 cm, d: 2.5 cm) over silica gel (elution: 100% pentane to pentane/ethyl acetate (1/1)).

2.3. Bioassay (Herbicide potential)

Samples were dissolved in chloroform in order to test their herbicide potential. 5 mL of each sample was dissolved at a concentration range of 500 µg/mL. The solution was then put on a sheet of filter paper in a Petri dish and evaporated to dryness for 24 h at 25 °C. The filter paper was moistened with 5 mL of sterile distilled water. Then, 20 imbibed seeds of *Lactuca sativa* were arranged in each Petri dish and were allowed to grow in growth chamber in the dark at 25 ± 2 °C for 7 days. The same operation has been done for the control without adding the sample. The germination and root length percentages of the targeted species were measured for all seedlings in each Petri dish on day 7. The data were transformed to inhibitory percent using the following equation.

Inhibition percentage % = [(control − sample)/control] × 100, where sample represents the parameter measured in the presence of the sample and control is the parameter measured in the presence of distilled water. Experiments were performed in triplicates.

2.4. Statistical analysis

The data from the experiments were subjected to analysis of variance (ANOVA) using SPSS 13.0 for Windows. The percentage data were transformed using arcsine-square root (arcsine $\sqrt{x}$) before ANOVA analysis. Mean was calculated as 5% significance level by the least significant difference test (Student's *t*-test).

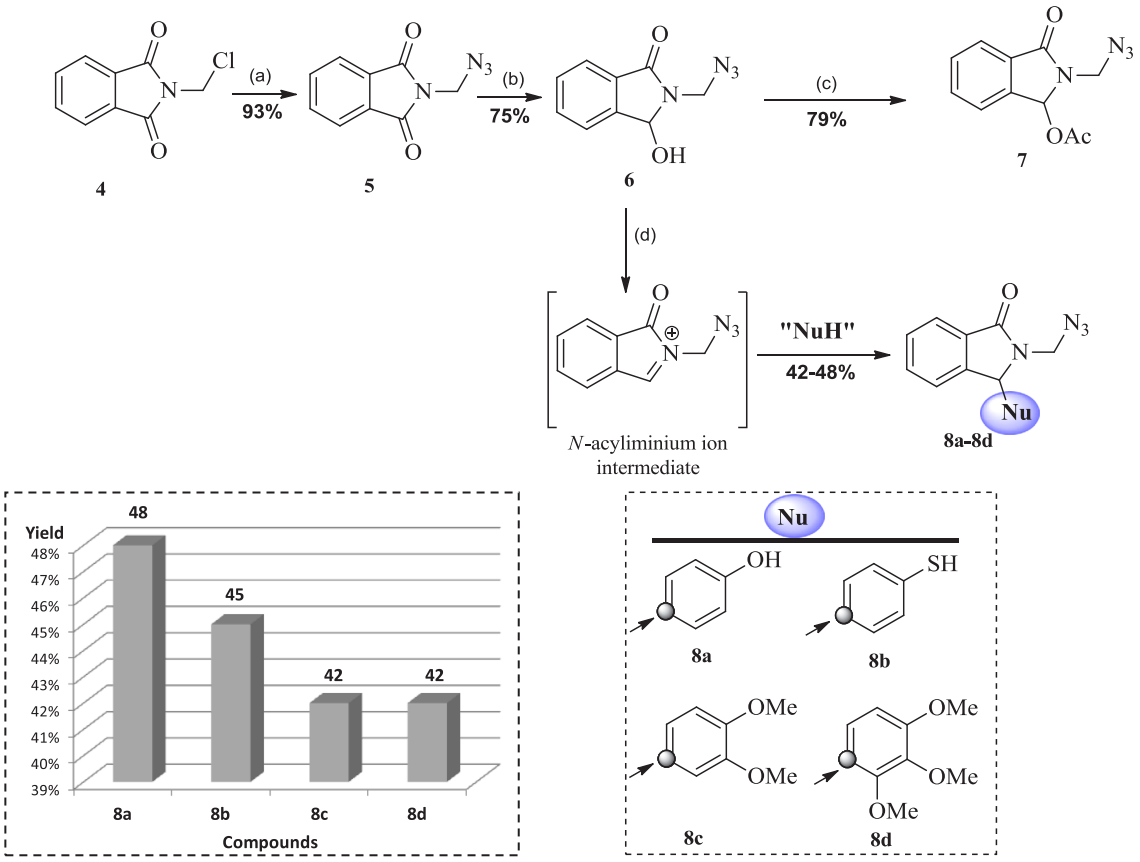
3. Results and discussion

MA (Fig. 1) was isolated from the pomace of *Olea europaea* by using a solid-liquid extraction (maceration in a mixture of Acetone/Water: 1/1) followed by ultrasonic agitation. Under these conditions, large amount of MA (6.0 g) was selectively obtained.

The structural analysis of compound **1** using spectroscopic methods including 1D-NMR (^{1}H, ^{13}C and DEPT 135) showed the presence of seven methyl groups in the higher field region (δ_H 0.46–1.04), an ethylenic group at δ_H 5.20, two oxygenated carbons at δ_C 68.6 and 84.5 and acid function at δ_C 177.5 corresponding to the digital fingerprint signals of MA. Moreover, this structural elucidation was confirmed by the literature [23] and the presence of a pseudo molecular ion peak $[M+H]^+$ at *m/z* 473.3625 in ESI-HRMS analysis.

3.1. Semisynthesis

After MA isolation, we turned our attention to the synthesis of the Cu alkyne-azide cycloaddition (CuAAC) partners (propargylated MA and *N*-(azidomethyl)phthalimide derivatives). Firstly, the propargylated MA synthesis was conducted by engaging the isolated MA in the propargylation of the carboxyl at C-28 position. The reaction was performed in dry DMF by using NaH as base catalyst and provided the desired alkyne **3** in 80% yield (Scheme 1). The comparison of spectral data of compounds **1** and **3** showed the appearance of new signals such as methylene at δ_H 4.69; 4.57 (dd, 2H, J = 15.6; 2.4 Hz, $H_{1'}$) and methylidyne group at δ_H 2.41 (d, J = 2.4 Hz, 1H, $H_{3'}$) corresponding to the added propargyl moiety. Also, the structure of dipolarophile **3** was supported by its ESI-HRMS which showed a pseudo molecular ion peak $[M+H]^+$ at *m/z* 511.3778. On another hand, *N*-(azidomethyl)phthalimide derivatives (**8a–8d**) were synthesized in three steps starting from commercially available *N*-chloromethylphthalimide (**4**) (Scheme 2). The first step of the reaction sequence led to azide derivative **5** in excellent yield (93%) through nucleophilic substitution of the halogen (Cl) by using NaN_3 in DMSO at room temperature for 24 h. The latter reaction was followed by one of the two carbonyl groups reduction by using $LiEt_3BH$ in anhydrous dichloromethane (DCM) at −80 °C that resulted in the *N*-acyliminium precursor hydroxy lactam **6** in 75% of isolated yield. The ^{1}H NMR spectrum of compound **6** revealed new signals at δ_H 5.89 (*s*, 1H), 5.03 (d, J = 12.6 *Hz*, H_{10a}) and 4.57 (d, J = 12.6 *Hz*, H_{10b}) corresponding respectively to an hydroxyl methine and a methylene beside an asymmetric center. From this *N*-acyliminium precursor, the acetoxy lactam **7** can be easily achieved by simple acetylation (Scheme 2) under classical conditions [24]. The added acetyl group was confirmed by observation of two new signals in the ^{13}C NMR spectrum of compound **7** at δ_C 170.8 and 21.0 attributable to carbonyl and methyl group, respectively, compared to ^{13}C spectrum of azide **6**. Finally, the synthesized hydroxy lactams **5** were involved in π-cyclisation of Friedel-Crafts type under bismuth (III) trifluoromethanesulfonate-mediated conditions. This cyclization led to different azides partners (**8a–8d**) required for the "click reaction" in modest yields (42–48%), through the electron-rich aromatic ring attack of the *in situ* formed *N*-acyliminium ion by mono-, di-, and tri-substituted aromatic nucleus. Additionally, this last step required only 5 mol% of $Bi(OTf)_3$ which makes the latter more environmentally and economically benign process. The structures of these azides partners



Reagents and conditions: (a) NaN_3, DMSO, 24 h, RT, (b) $LiEt_3BH$, DCM, 30 min, -80 °C, (c) Ac_2O, Pyr, 24 h, RT, (d) DCM, RT, $Bi(OTf)_3$

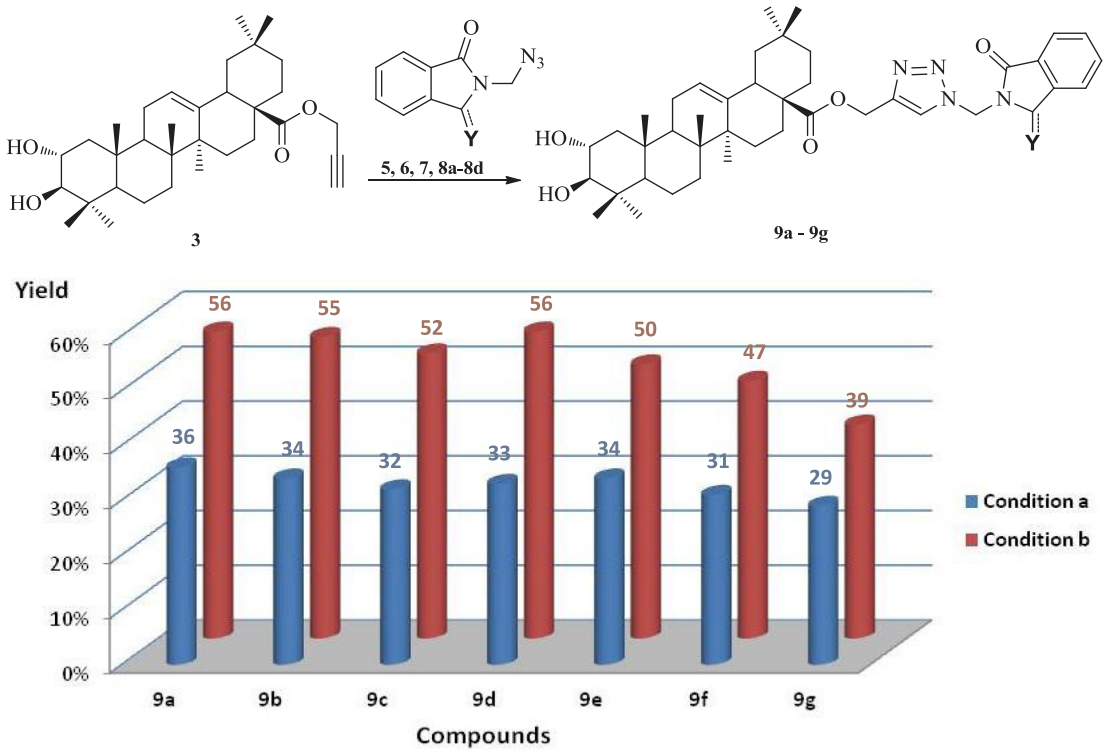
Scheme 2. Synthesis of azides **5–7**, **8a–8d**.

were confirmed according to their spectral data since the comparison of their ^1H and ^{13}C NMR spectra with those of compound **6** shows the appearance of new signals in aromatic region corresponding to the inserted aromatic ring. In the other hand, the ESI-HRMS analysis revealed the presence of a pseudo molecular ion peak $[M+H]^+$ for each azide formed. In the ^1H NMR spectrum of azide **8a** as an example, we observed two new doublets at δ_H 7.00 (2H, $J = 7.8\,Hz$) and 7.19 (2H, $J = 7.8\,Hz$) compared to ^1H spectrum of compound **6**. Indeed, these protons corresponded satisfactorily to the added aromatic group. The mass spectrometry of compound (**8a**) also confirmed this observation by exhibiting a pseudo molecular ion peak for $(C_{15}H_{13}N_4O_2)^+$ at *m/z* 281.1033.

Once the two partners were prepared, we were embarked in the synthesis of 1,2,3-triazole moiety through ligation of azides and propargylated-MA terminal alkyne. In this perspective, two conditions of Cu alkyne-azide cycloaddition (CuAAC) were used. Both conditions are based on Cu(I) species as commonly used for "click reaction" (Scheme 3, conditions (a) and (b)). Nevertheless, in condition (a) the Cu(I) was *in-situ* generated by the reduction of $CuSO_4$ (Cu(II) salt) in organo-aqueous (DCM/H_2O) media. From the two tested conditions, we could observe that condition (b) was more efficient and shorter in terms of reaction time than condition (a) (Scheme 3). Indeed, under condition (a) ($CuSO_4{\cdot}5H_2O$, sodium ascorbate, DCM/H_2O, 25 °C) the targeted compounds were synthesized in modest yields ranged from 29% for **9g** to 36% for **9a**. Concerning condition (b) that uses a 250 W microwave irradiation (CuI, Et_3N, DMF, MW-220 °C, 3–5 min) yields were 10–20% higher than those of the previous conditions. Ranged from 39% for **9g** to 56% for **9a**, the lowest yields (< 50%) for **9f** (47%) and **9g** (39%) were probably due to steric hindrance of azide heterocycles through dimethoxy or trimethoxyphenyl moieties. The synthesis of triazoles **9a–g** was confirmed by 1D, 2D-NMR. The comparison ^1H NMR spectra of compounds **9a–g** with propargylated-MA (**3**) showed the appearance of new signals in aromatic region 6.83–7.90 ppm relative to aromatic protons introduced by the azides used. It can be also noticed the disappearance of the methylidyne signal in compound **3** and the appearance of new singlet (1H) located in the region 7.80–7.95 ppm attributable to the sole proton of triazole moiety. It is worth mentioning that the reaction was regiospecific leading to 1,4-substituted triazolyl derivatives **9a–9g** (Scheme 3). The resulting 1,4-regioisomers were evidenced from the **NOE** $H_{5'(triazole)}/H_{6'(methylene)}$, $H_{5'(triazole)}/H_{10''(methylene)}$ and the absence of **NOE** between $H_{5'(triazole)}/H_{(methylene\text{-}MA)}$. High Resolution Mass spectrometry (HRMS) data of all the formed derivatives were also in agreement with the proposed structures.

3.2. Herbicide potential

After MA-based hybrid compounds being synthesized, their regulatory effects were evaluated on seed germination and on early growth stages of *Lactuca sativa* L. used as a target plant. The results displayed in Table 1 showed interesting herbicide potential (up to 100% of inhibition). At a first sight, using chloroform as solvent did not affect the germination process of *Lactuca sativa* L. Therefore, the growth inhibitory effects could be really attributed to synthesized compounds. Satisfactorily, the results indicated that targeted compounds have different degree of inhibitory effect on germination and seedling growth. The latter fluctuation in the plant germination inhibition was closely related to the nature and the structure of compounds. At the seventh day, the maximum toxicity of these compounds was registered. Concerning azide series **5–7** and **8a–8d**, the percentage of inhibition varied from 34.55 to 69.99%. This activity of the azide series (**5–7**) seems



Reaction conditions: **Condition (a)** $CuSO_4.5H_2O$, sodium ascorbate, DCM/H_2O, 25 °C; **Condition (b)** CuI, Et_3N, DMF, MW-250 W, 3-5 min, 39-56%.

Scheme 3. Synthesis of triazoles **9a–9g**.

Table 1
Effects of compounds on total inhibition (G^T), root length (R^L) and shoot length (S^L) of *Lactuca sativa* L. Different letters in columns indicate significant differences among fractions at $P < 0.05$ (LSD test).

compound	G^T	R^L	S^L
1	5.56 ± 0.10^g	97.81 ± 0.20^i	95.70 ± 0.21^i
3	0.00 ± 0.00^h	100 ± 0.00^j	100 ± 0.00^j
4	46.70 ± 0.27^f	15.55 ± 0.29^d	13.98 ± 0.10^d
5	58.89 ± 0.27^e	42.75 ± 0.25^g	42.65 ± 0.10^g
6	49.15 ± 0.32^f	61.00 ± 0.38^h	51.56 ± 0.15^h
7	34.55 ± 0.20	66.50 ± 0.10^h	58.64 ± 0.11^h
8a	64.20 ± 0.01^d	20.50 ± 0.30^e	31.12 ± 0.10^f
8b	69.99 ± 0.12^d	19.70 ± 0.60^d	20.01 ± 0.15^e
8c	57.88 ± 0.37^e	32.13 ± 0.19^f	43.85 ± 0.05^g
8d	59.75 ± 0.32^e	30.24 ± 0.22^f	40.03 ± 0.10^g
9a	91.79 ± 0.09^c	09.0 ± 0.05^c	10.00 ± 0.10^c
9b	96.00 ± 0.05^b	03.85 ± 0.06^a	04.50 ± 0.07^b
9c	92.44 ± 0.10^c	06.85 ± 0.09^b	09.08 ± 0.08^c
9d	94.85 ± 0.10^b	05.09 ± 0.10^b	05.66 ± 0.05^b
9e	100.00 ± 0.0^a	00.0 ± 0.0^a	00.0 ± 0.0^a
9f	95.79 ± 0.05^b	03.0 ± 0.04^a	02.78 ± 0.10^a
9g	98.21 ± 0.08 ^{a}	02.23 ± 0.11^a	03.02 ± 0.12^a
Control	01.89 ± 0.07 ^{h}	98.57 ± 0.14^i	98.94 ± 0.25^i

The different letters (a–j) indicate a significant difference between the compounds ($p < 0.05$).

mainly due to the presence of phthalimide group. Moreover, the phthalimide-based azido adduct **5** (58.89%) increased the activity of *N*-(chloromethyl)phthalimide **4** (46.70%), underlining the positive effect of azide group in the germination inhibition. However, hydroxy lactam **6** (49.15%) and acetoxy lactam **7** (34.55%) did not provide higher activity when compared to compound **5** (58.89%). Considering the latter compound **5** as a reference, the replacement of one of its carbonyl group by substituted aromatic groups through *N*-acyliminium chemistry, generally increased the inhibition percentage of azides (59.75–69.99%) except for **8c** (57.88%). The compound **8b** showed in this series, the highest percentage of inhibition with 69.99% and the herbicide potential was probably due to the presence of the thiol group.

In MA-based series, firstly we noticed that free maslinic acid (**1**) exhibited a very weak percentage of inhibition of 5.56%. On the other hand, the propargylation of MA displayed a reverse effect, since compound **3** lacked the phytotoxic effect and even slightly promoted the germination and seedling growth of Lettuce (*Lactuca sativa*). This compound can thus serves as reference in MA-based triazolophthalimide hybrid compounds. The phytotoxic effects of synthesized triazoles **9a–9g** (Table 1) showed higher activities compared to the propargylated MA (**3**) and azides (**4–7**, **8a–8d**). Indeed, these hybrid compounds displayed an important inhibition of total germination ranged from 91.79 to 100%. According to the literature and activities of the propargylated MA (**3**) and azides taken separately, the herbicide potential of compounds **9a–9g** as expected was mainly due to the added triazolomethyl phtalimide part [9]. Interestingly, it's important to underline that seed germination was completely inhibited in presence of compound **9e** (100%). As already hypothesized in phthalimide series, here also the highest inhibitory activity of germination was probably due to presence of the thiol group in the hybrid compound structure. Finally, free MA (**1**) seems to have negligible inhibitory effect on *Lactuca sativa* L. seeds germination while propargylated MA (**3**) tends to boost their growth. Overall, it can be also noticed that phthalimide and methyltriazolo moieties are certainly responsible of this switch in the activity of propargylated MA (**3**) into inhibitory activity observed for synthesized hybrid compounds.

4. Conclusion

In summary, maslinic acid (MA) was isolated from pomace olive (6.0 g of MA, yield 0.24%) under ultra-sonication conditions. After identification and characterization, this well-known natural product was employed as building block in the semisynthesis of new hybrid molecules through a 1,3-dipolar cycloaddition involving propargylated MA and phthalimide-based azides. The Cu alkyne-azide cycloaddition (CuAAC) conditions used under microwave irradiation led regiospecifically to diverse 1,4-disubtituted triazole derivatives in modest to good yieds in maximum 5 min of reaction time. The ability of these hybrid 1,4-disubtituted triazole molecules to disrupt seed germination and therefore plant growth were evaluated and showed interesting activities that can serve as models in potent and valuable herbicide development. The herbicide activity of triazole-bridged compounds was very high and ranged from 91.79 to 100%. The high activities of these novel hybrid molecules are mainly due to the triazole bridge connecting both MA and phthalimide parts. Finally, this is the first description of MA and phthalimide-based 1,4-disubstituted triazole hybrid molecules as agrochemicals that may be of great help in improving crop production and weeds management. The interesting herbicide activity displayed by synthesized hybrid compounds in preliminary assays can serve as a starting point of design of potent natural herbicides.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.steroids.2018.07.004.

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