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

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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

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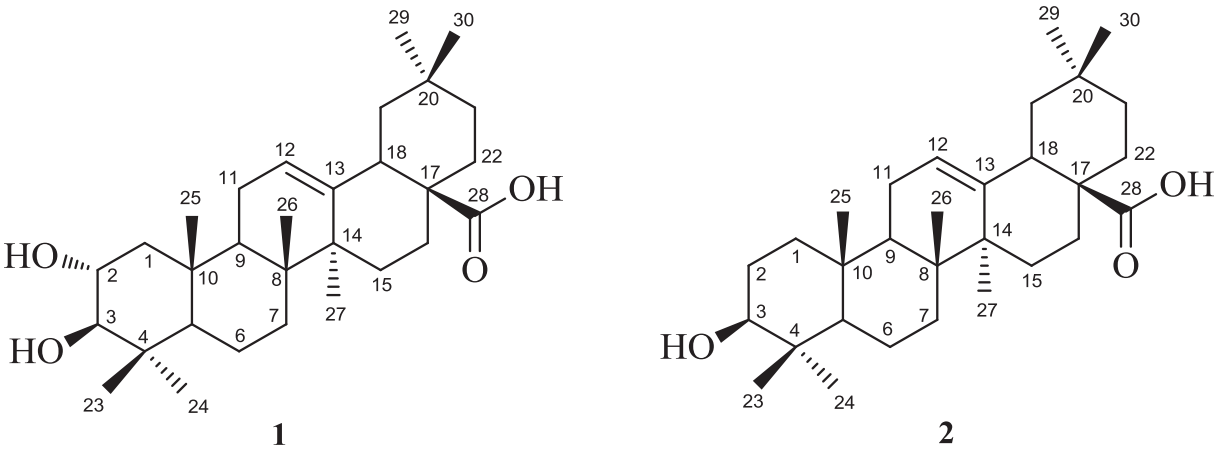

Fig. 1. Major compounds from *Olea europaea*: maslinic acid (MA) **1** and oleanolic acid (OA) **2**.

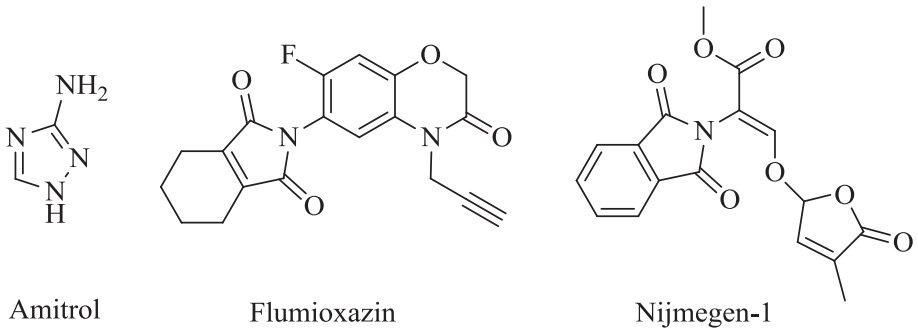

Fig. 2. Herbicide marketed (Amitrol, Flumioxazin, Nijmegen-1).

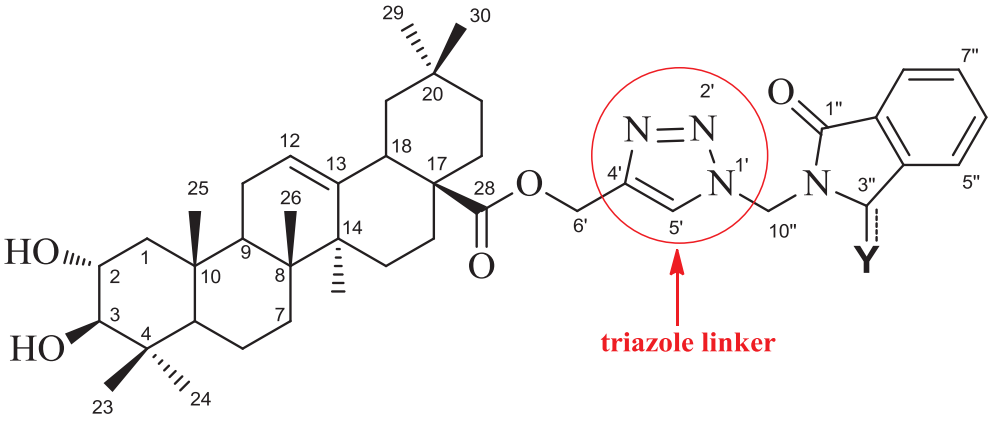

Fig. 3. Triazole core as a linker in the design of a new class of herbicides.

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