ABSTRACT

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Title of thesis: Isolation and semi-synthesis of germacranolide derivatives: onopordopicrin

This work is focused on onopordopicrin (ONO) as a potent molecule with antiprotozoal activity. ONO is a sesquiterpene lactone of germacranolide structure. Sesquiterpene lactones are typical secondary metabolites of family *Asteraceae*. As a source of ONO *Centaurea ornata* Willd. (*Asteraceae*) was used. It is a thistle-like endemic plant of the Iberian Peninsula. The plant was collected in July 2022, in Zamora region.

First, an ether extract from the aerial flowering part of the plant was obtained (0.26 % of the dried plant weight). The crude plant extract was dissolved in methanolic solution and fractionated by liquid/liquid separation with hexane. Then the methanolic part was concentrated, dissolved in water and fractionated with solvents of increasing polarity (chloroform, ethyl acetate and n-butanol). The chloroform fraction containing ONO was purified by column chromatography to obtain the major compound ONO, which represented 54.8 % of crude extract.

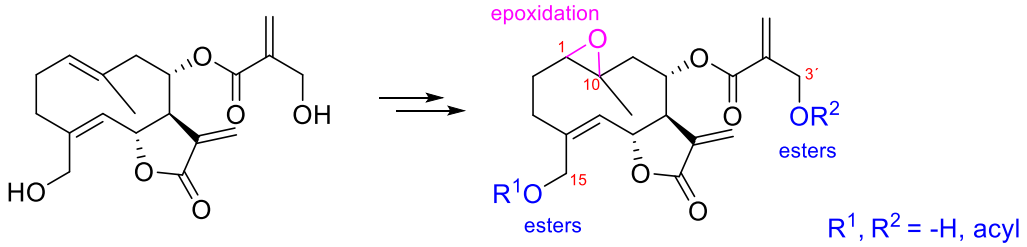

Figure 1. Modifications of onopordopicrin

The aim of this work was the synthesis of novel derivatives of ONO – esters and epoxides (Figure 1). The modifications were proposed to enhance pharmacological properties and selectivity of the molecule for an antiprotozoal treatment. For the esterification of ONO, five different methods were used: Steglich esterification, Yamaguchi esterification, Mukaiyama esterification, and treatment with acyl chlorides and anhydrides. The most convenient methods for the preparation of esters were Mukaiyama esterification and treatment with acyl chlorides and anhydrides. The second synthetic part was focused on the epoxidation of the double bond (1,10) of ONO, followed by treatment with Lewis acids. The epoxidation was performed via reaction of ONO with *meta*-chloroperoxybenzoic acid (*m*CPBA) in order to gain the 1,10-epoxide. The epoxide (1,10) is more reactive and can provide the closure of the cycle in positions 5,10 in presence of Lewis acid.

The obtained compounds were sent to bioassays to set the antiprotozoal activity against *Leishmania donovani*, *Trypanosoma cruzi* and *Plasmodium falciparum*.

Key words: *Centaurea ornata* Willd., onopordopicrin, antiprotozoal activity.