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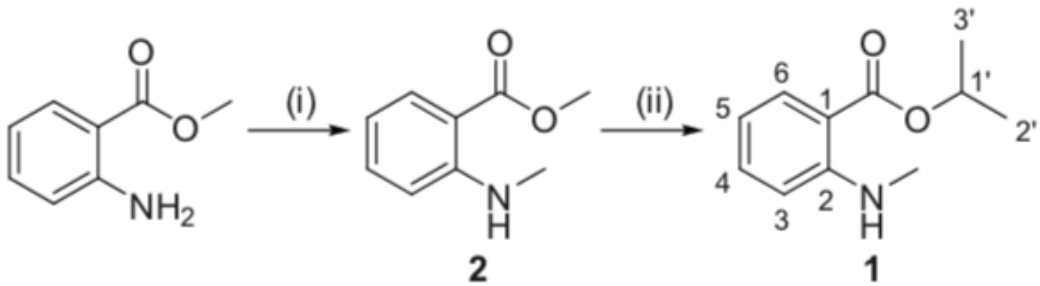
Pharmacological properties of natural volatile derivatives of anthrnanilic acid

This research begun with the evaluation of the volatile composition from a Mexican Rutaceae named Mexican Orange – *Choysia ternata* Kunth. A literature survey showed two previously published papers on the essential oil analysis of this plant, with the identification of 18 and 36 compounds respectively. However we were able to identify 158 compounds, among them Methyl (MMA) and Isopropyl (IMA) esters of N-Methylanthranilic acid (Fig 1) [1]. IMA, named by us ternanthranin, was identified for the first time in the plant kingdom. Volatile anthranilic acid derivatives bear importance in the aroma industry since the 19th century. During the beginning of the 20th century, Schimmel, Van Dyk & Co., W.J. Blush & Co., important industries in the aroma field, were commercializing Methylanthranilate as a flavouring agent but very little was known about its pharmacological/toxicological properties. MMA, a derivative of methylanthranilate, is also the key component of Neroli essential oil and it is also present in other species belonging to the family Rutaceae. After the identification of MMA and IMA in trace quantities in the essential oil of *C. ternata,* we moved on to achieve them in reasonable quantities to proceed with their pharmacological/toxicological evaluations. Our studies showed that both molecules have been proven to possess a variety of pharmacological actions, to include antinociceptive [1,2], anti-inflammatory [3], gastro-, hepato- and neuroprotective [4-6], anxiolytic and antidepressant as well as the ability to prolong the diazepam-induced sleep [7]. Although the toxicity of MMA has been previously investigated [2,8], data is still scarce about IMA's toxicity. We were unable to identify in a previous study [2] signs of acute toxicity for both MMA and IMA in mice (100mg kg^{-1}, *p.o.*, 5-day study). Pharmacokinetic studies were undertaken for MMA and IMA evidencing their distribution pattern in mice's main organs [9] as well as the molecules metabolisation through analogous biotransformation pathways, with MMA predominantly suffering chemical conversions of the ester group and IMA predominantly suffering hydroxylation of the aromatic core [10]. *In silico* studies were used to propose chemical modifications that could enhance the pharmacological action predicted and observed for the two molecules [11].

Keywords: methyl N-methylanthranilate, isopropyl N-methylanthranilate, Rutaceae, essential oil, pharmacology, toxicology



2 **1**

Figure 1- Methyl N-Methylanthanilate (2) and Isopropyl N-Methylanthranilate (1)

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