Isolation and identification of new Daphnane-type diterpenes able to activate PKC and role in the treatment of colorectal cancer.

This thesis project is the continuation of a previous work carried out on the latex of an Amazonian forest tree, *Hura crepitans*. It revealed the presence of more than thirty orthoesterified diterpene derivatives belonging to the daphnane group. Among them, about twenty compounds would be new structures.

In collaboration with Dr Claire Racaud-Sultan from the “Institut de Recherche en Santé Digestive” (IRSD, Hôpital Purpan in Toulouse), a selective in vitro cytotoxic activity of one of these daphnane compounds was demonstrated against colorectal cancer cell lines (Caco-2 cells). It is known that structurally similar diterpenes called phorbol esters and in particular 12-O-Tetradecanoyl-Phorbol-13-Acetate (TPA), exert co-carcinogenic properties via mechanisms involving protein kinases C (PKC).

We were able to demonstrate that a daphnane, huratoxin, had a different effect than TPA on Caco-2 cells and interacted with an atypical isozyme of PKC that could explain its selective cytotoxic effect of this cell type and therefore its potential antitumor activity.

The objective of this thesis work is to isolate, in its pure state, and identify new daphnane structures previously detected by UHPLC-MS in *Hura crepitans* latex in order to evaluate their activities on PKC isozymes involved in the tumor process of colorectal cancer lines and to infer structure/activity relationships.

This thesis work is therefore at the interface between the chemistry of natural products and biology for health. It will involve the extensive use of preparative and analytical chromatographic techniques (LC-MS) as well as spectral techniques, particularly NMR but also UV, CD, X-Ray crystallography and spectral simulation techniques (CD and/or NMR) increasingly necessary to establish absolute configurations. An active participation in bioassays within the IRSD will also be required.


