

## Abstract

In this PhD Thesis work, bile acid and indole scaffolds were employed to synthesize new biologically relevant compounds in three different projects.

The first project is focused on the synthesis and biological evaluation of novel deoxyadenosine-bile acid conjugates linked through a 1,2,3-triazole ring. A 'click' chemistry reaction, namely the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), was employed to achieve the new conjugates, starting from 3-azidobile acid derivatives and 8-alkynylated deoxyadenosines. All novel molecules were evaluated *in vitro* for their anti-proliferative activity against four human cell lines and for their cytotoxicity toward human fibroblast cells. Several conjugates exhibited strong anti-proliferative activity against human leukemia T cells. The best cytotoxicity was observed for a chenodeoxycholic acid-based derivative on both leukemia cell lines with IC<sub>50</sub> up to 8.51  $\mu$ M. Furthermore, the apoptotic activity of several conjugates was established. This work resulted in a scientific publication.

The second project is focused on the synthesis of four orthogonally functionalized bile acid scaffolds displaying an azido group at C-3 and a thiol moiety at C-24 through a cysteamine linker. The chenodeoxycholic-based modified scaffold was employed in 'click' chemistry orthogonal reactions to synthesize a collection of chenodeoxycholic acid-bisphosphonate tetraethyl esters. Notably, Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), thiol-ene coupling (TEC) and thiol-yne (TYC) were used and their effectiveness and flexibility were demonstrated. Moreover, a series of fluorescently-labelled analogues of these new bile acid-bisphosphonate derivatives was accomplished with the same methodology. Deprotection of bisphosphonate esters was studied under McKenna conditions and a new bile acid-bisphosphonic acid analogue was achieved. On the last note, a fluororous tag strategy was successfully employed to overcome the purification and separation issues that limited the isolated yields of all the new bile acid-bisphosphonate derivatives synthesized.

The third project, developed in the laboratory of Professor Matteo Zanda at the University of Aberdeen (UK), is focused on the use of the indole scaffold for the synthesis of new positive allosteric modulators (PAMs) of cannabinoid receptors CB<sub>1</sub> for the treatment of pain. Targeting the allosteric binding site on the CB<sub>1</sub> receptors using positive allosteric modulators (PAMs) is a very promising approach because it would cause activation of the endocannabinoid system without causing the unwanted psychotropic effects, thus providing the potential of side-effect-free pain relief where required. In particular, the

structure-activity relationship for ZCZ011, an indole-based new PAM, was investigated replacing substituents at 2-position, 5-position and 6- position of the indole scaffold as well as the thienyl side chain. Hence, in order to easily access a good number of analogues for ZCZ011, a general synthetic strategy was developed. All the new analogues synthesized were evaluated *in vitro* for their ability to potentiate the maximum level of stimulation on CB<sub>1</sub> receptors caused by the endogenous agonist anandamide and some interesting results have been highlighted: five new compounds exhibited higher potency than the lead compound and one in particular could open the possibility to further development, in order to achieve a peripherally restricted positive allosteric modulator of CB<sub>1</sub> receptors.

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