Conception of Natural-Inspired Small-Molecule Inhibitors of Bcl-2 Family Proteins

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Natural products possess a vast chemical diversity and cover a large chemical space. For these reasons, they are still playing a significant role in the drug discovery and development process. Thus, among the new chemical entities approved as drugs between 1981 and 2016, about 70% were from natural origin or inspired by natural compounds. Screening of plant extracts, marine organisms or microorganisms can provide highly original and functionalized bioactive molecules that are unlikely to be obtained by the screening of synthetic libraries. In fact, chemical complexity is often a criterion of specificity for the target of interest.

Bcl-2 family proteins are important regulators of apoptosis used by multicellular organisms to regulate tissue homeostasis through the elimination of useless or potentially harmful cells. These proteins, divided into anti-apoptotic and pro-apoptotic members, are often over-expressed in many kinds of cancer or involved in the resistance to chemotherapy. Targeting these proteins is a highly promising strategy for anticancer therapy that has emerged over the last decades. Particularly, the development of small molecules that are able to bind the hydrophobic cleft of the anti-apoptotic proteins, liberating the pro-apoptotic ones and restoring apoptosis is an enormous challenge.

Over the past years, our team has been involved in the identification of natural compounds that target the anti-apoptotic proteins of the Bcl-2 family thanks to a large screening of ICSN extract library by polarization assay (FPA). Various original natural molecules, active on Bcl-xL, Bcl-2, and/or Mcl-1 have been isolated, and chemically modified or synthesized. I will present some of the results we have achieved in this field.