Drugs from the sea: complex structures to fight a complex problem of resistance in cancer

It is well known that incidence of cancer cases figures among the leading causes of morbidity and mortality. Most of disseminated cancers share the common feature of not responding to anticancer drugs. This phenomenon is known as multidrug resistance (MDR), being characterized by cancer cells developing broad resistance to a wide variety of structurally and functionally unrelated drugs that may arise from several mechanisms. One of the most prominent is associated with the overproduction of membrane protein transporters on tumor cells leading to an increase in drug efflux. Almost 40 years ago, it was proposed that the coadministration of anticancer drugs with compounds that could either block or inactivate these transporters belonging to the ATP-binding cassette (ABC) family of proteins would circumvent MDR. Three generations of inhibitors were developed and entered clinical trials; however, these inhibitors failed in translating to therapy due to toxicity issues. As consequence, scientists focus on searching news molecules from natural products. While the traditional source of terrestrial plants will undoubtedly continue to yield valuable new agents, it is important to explore all available pools of molecular diversity seeking out for new ecosystems. Marine natural products are particular interesting targets for global drug discovery since they not only possess structural and chemical uniqueness but also disclose novel scaffolds for drug development. In the field of chemotherapics, marine natural products are reveling an interesting potential not only as promising anticancer drugs but also for their ability to inhibit ABC transporters.

Our work, “Marine Natural Products as Models to Circumvent Multidrug Resistance”, summarizes the research findings on marine natural products and their effect on ABC transporters highlighting the chemical classes of alkaloids, polyoxygenated sterols, polyketides, terpenoids, diketopiperazines, and peptides (Fig. 1). The synthetic pathways for the total synthesis of the most promising members and analogs are also presented.

Fig. 1. Some examples of marine natural products to circumvent MDR.

The major sources of marine MDR reversal agents and mechanisms have been scarcely studied, and very little is known about their molecular mechanism of action. The most promising marine compounds that have shown to be potent and selective MDR activity against cancer cell belong to alkaloids; however, they present some toxicity. Among marine natural products, trabectedin proved to be the most promising against MDR. Most of the marine natural derivatives are highly lipophilic and contain fused rings and multiple chiral centers, which in turn reflect their complex total synthesis. Among the synthetic analogs, eriburin has been shown to be the most effective against MDR.

These discoveries open new challenges for medicinal chemists to accomplish viable synthetic routes in the design of analogs with suitable properties that would render potential drug candidates. Therefore, we can anticipate more effective chemotherapies based on molecules from the sea.

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