Diterpenes as Multidrug Resistance (MDRs) Modulating Agents in Tumors

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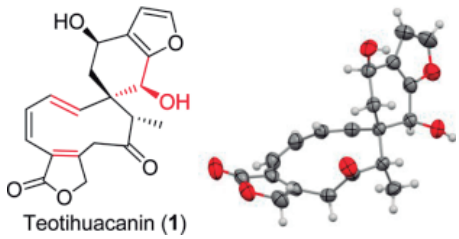
(Status: patent pending)

Abstract

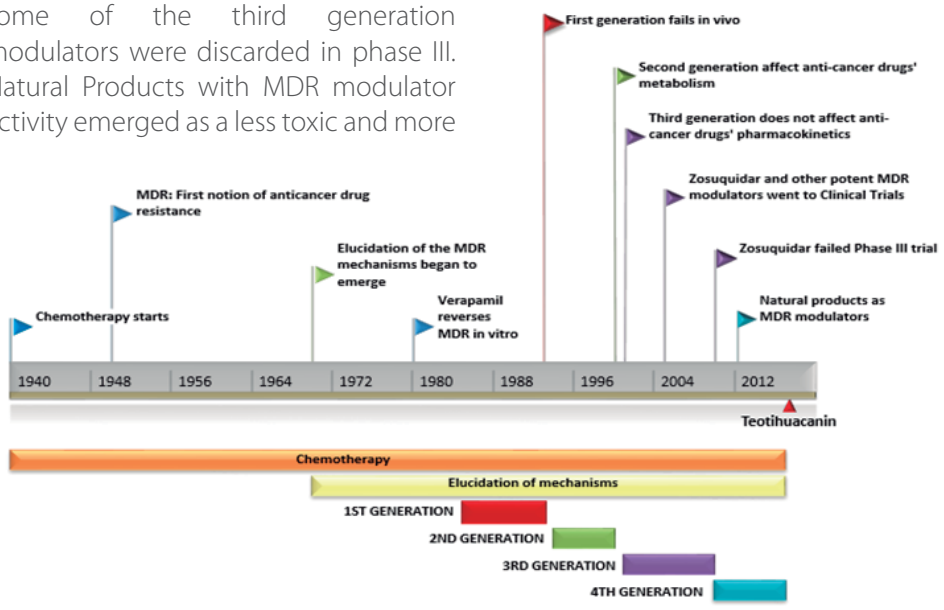
Unusual rearranged clerodane diterpenes with a new carbon skeleton have been isolated from the plant *Salvia amarissima*. These compounds have shown to be potent cytotoxic agents and modulators of multidrug resistance (MDR) against cancer cell lines of the human breast, colon and cervix. These diterpenes have a great potential to enhance the chemotherapy medication when the cancer cells have acquired multidrug resistance (MDR), through the resensitization of these cells. It is highly probable that these compounds show less toxicity and more potent MDR modulator activity, but further research needs to be done.



Teotihuacanin (**1**)

Background and Importance

The multidrug resistance (MDR) phenotype is one of the major barriers to successful chemotherapies in cancer patients. With the exposure to the treatment, the cancer cells become immune through several molecular mechanisms. In the last decades, research groups have been looking for new strategies to resensitate the tumor cells testing compounds with MDR modulator activity. There have been encouraging and disappointed results, going into four generations of MDR modulators. The first generation raised hope for many researchers, but unfortunately the high doses required caused side effects in patients. Second generation modulators were more potent in vitro but when tried in vivo showed interference with anti-cancer drugs metabolism. The third generation did not have this problem and were very potent. Until 2008, there were high hopes on the third generation when several of these compounds, like Zosuquidar, were in clinical trials. Later, some of the third generation modulators were discarded in phase III. Natural Products with MDR modulator activity emerged as a less toxic and more potent option. Since then, several natural compounds have been studied. Teotihuacanin and the diterpenes isolated from *Salvia amarissima* have shown great *in vitro* results.



Applications

- These diterpenes may be used to enhance the chemotherapy medication through the resensitization of these cells.
- Reversal MDR activity has been seen (*in vitro*), but not limited, in Breast, Colon and Cervix Cancer Vinblastine resistant cell lines.
- Their new carbon skeleton might be used as a scaffold to develop new MDR modulators.
- Their further development might bring advantages in the treatment of cancer, together with new MDR modulators and other alternatives to face crossed resistance.

Market

Multidrug resistance affects patients with a variety of hematologic cancers and in solid tumors, including breast, ovarian, lung, and lower gastrointestinal cancers. MDR modulators give these patients a second chance to respond to chemotherapy.

Expectations

Given the good and unexpected results of these compounds *in vitro*, the Institute of Chemistry in collaboration with other research centers are currently investigating and developing on its molecular mechanism, proving its safety and efficacy *in vivo*, for the generation of new and better MDR modulators using Teotihuacanin's carbon skeleton as scaffold.

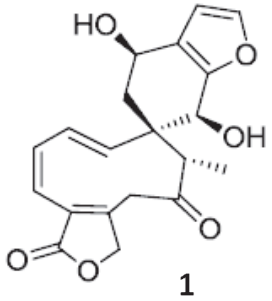
Benefits and competitive advantages regarding existing technologies

The most remarkable characteristic of these compounds is that they have been isolated from a natural source (*S. amarissima*), purified through specialized techniques, characterized and proved against MDR cell lines by the IQ researchers. Fortunately, all this effort has shown anticancer and MDR modulator activity potential. These compound's MDR activity tested *in vitro* seems to be greater than the average showed by other natural products and drug controls (Reserpine). Their physical and chemical properties confer them an adequate size and lipophilicity to cross cell membranes, which allows them to better interact with therapeutic targets. The molecular target is unknown, but it has been proposed to be the P-gp protein. It could be possible that their molecular mechanism involves more than one ABC transporter.

It is also possible to use these compounds, especially Teotihuacanin, as a chemical platform or scaffold to develop novel MDR modulators.

Other natural compounds that have had also good *in vitro* results as MDR modulators and have been taken into clinical trials. It is possible that some of them do not approve these trials, so it is important to keep developing new alternatives. Teotihuacanin and the diterpenes isolated from *S. amarissima* have a completely new carbon structure, which could give them a different behavior from the results seen until today.

If these compounds (or their derivates) prove efficacy and security in vivo, they would be a very useful weapon to face the MDR cancer. These would be excellent news for both, patients and industry.



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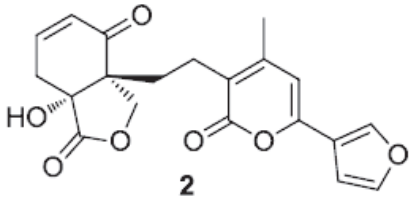

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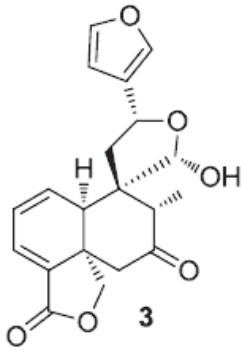

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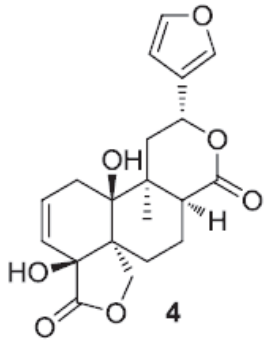

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