# Multitarget Drugs: No-Donor Doxorubicins.

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Doxorubicin (DOXO) is an antibiotic belonging to the class of anthracyclines, used in treating a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas. However, there are some serious limitations on DOXO's efficacy in cancer therapy. One is the ready development of resistance through different mechanisms, the main one being the overexpression of ATP-Binding Cassette (ABC) transporters, such as P-glycoprotein (Pgp), Multidrug Resistance Related Proteins (MRPs) and Breast-Cancer Resistance Related Protein (BCRP), which actively extrude the drug from tumor cells. Resistance to DOXO is often part of a cross-resistance to several anticancer drugs, known as Multidrug Resistance (MDR).[1] The identification of new MDR-reversing agents, selectively targeting drug-resistant cells, is a field of active investigation, but no satisfactory reversing strategies have yet been identified.[2] In previous research our group showed that nitric oxide (NO) can reduce MDR in human cancer cells. Some exogenous NO donors, like S-nitrosopenicillamine, sodium nitroprusside, and S-nitrosoglutathione, were able to reduce the activity of Pgp and MRPs, by nitrating tyrosine residues crucial for protein functions, with consequent increase of intracellular DOXO concentration and toxicity in MDR tumor cells.[3] On this basis, new semisynthetic doxorubicines have been designed, in which the antibiotic is joined through an ester linkage to NO-donor moieties (Fig. 1). These compounds can accumulate in doxorubicin-resistant human colon cancer cells (HT29/dx), inducing cytotoxicity.[4]

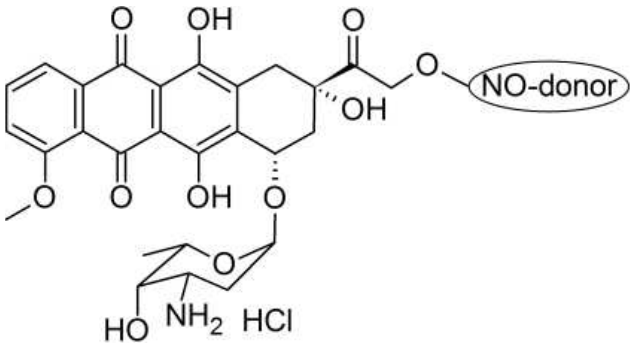


**Figure 1. NO-DOXO chimeras.**

In order to extend this new class of semisynthetic DOXO, a small library of novel chimeras of DOXO were designed, bearing different NO-donor groups at the C-14 position (Fig. 1). Their toxicity against human DOXO-sensitive colon cancer HT29 cells and against DOXO-resistant HT29/dx cells was studied; for the most active compounds, the localization and putative mechanisms of toxicity in DOXO-resistant cells were also investigated.

**References**

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