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Design and synthesis of nitric oxide releasing acridone carboxamide derivatives as reverters of doxorubicin resistance in MCF7/dx cells

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Objective: In the present investigation, based on our earlier observations we have designed new NO donating acridones as MDR modulators, capable of releasing NO in controlled manner into P-gp and/or BCRP that could reverse the doxorubicin resistance in cancer.

Methods: We prepared an essentially complete set of N10- substituted acridone-4-carboxamides whose amide fragments were formed by the alkyl groups or aryl ring systems bearing exocyclic groups at different ring positions. The in vitro cytotoxic effects against Drug sensitive and resistant human cancer cell lines [MCF7, (P-gp and BCRP), MCF7/dx (P-gp expressed) and MCF7/mr (BCRP expressed)] are studied by using SRB assay. Selected molecules were also screened for their cytotoxic properties against SW1398, WIDR and LS174T cell lines. Doxorubicin accumulation and efflux studies were performed and in vitro levels of formed nitrate/nitrite were determined by the colorimetric assay.

Results and Conclusion: NO releasing acridones showed activity against MCF-7/wt (0.7 – 3.1 μM), MCF7/mr proved to be sensitive towards the compounds 1, 2, 3, 7, 10, 11 and 16 with IC50 ranges of 0.7-2.3 μM. MCF7/dx sensitivity was observed with compounds 1, 10 and 11 with IC50 range of 1.9-2.9 μM. Compounds 1, 10 and 11 showed significant cytotoxic activity against SW1398, WIDR and LS174T cell line. The results indicate NO-acridones are potent against both the sensitive and resistant cells and significantly correlated with rate of in vitro nitric oxide release. The results of accumulation studies showed that intracellular accumulation of doxorubicin is significantly dependent on the rate of nitric oxide release.

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