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TECHNOLOGY OPPORTUNITY

Chemosensitizing Agents for Multidrug Resistance (MDR) & Chemotherapy

Overview:

McGill University is seeking to outlicense intellectual property relating to compounds for reversing multidrug resistance. The invention provides potent first in class flavonoid analogs that reverse resistance of tumors to common chemotherapeutics. Remarkably, the compounds also manifest chemosensitization of pentamidine and sodium stibogluconate resistance in *Leishmania in vitro*. and exhibit intrinsic anti-Leishmanial activity against promastigotes and amastigotes.

Medical need & Opportunity

Multidrug resistance (MDR) is responsible for many forms of resistance in bacteria, fungi and human tumors. The MDR phenotype is a major determinant of clinical outcome in cancer treatment. The resistance of tumor cells is often the result of the enhanced ability of these cells to impair efficacy of cytotoxics through increased drug conjugation and upregulation of drug efflux. The latter is mediated by for instance by P-glycoprotein (MDR1) or multidrug resistance protein 1 (MRP1).

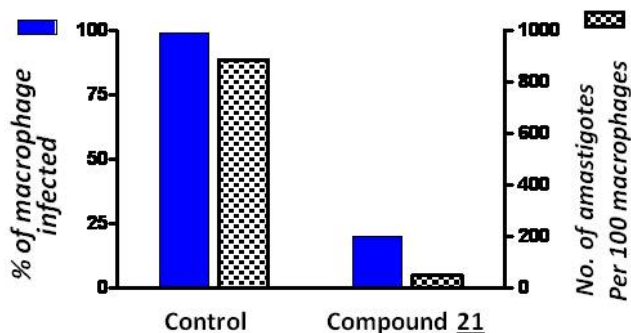
Pentavalent antimonial compounds are the mainstay in the treatment of the various forms of leishmaniasis. Pentamidine and amphotericin B are second-line treatment in cutaneous leishmaniasis. The compounds of the invention present new alternatives indicated as chemosensitizing agents in drug resistant chemotherapy.

Validation

Proof of concept is demonstrated in three drug resistant tumor cell lines: (i) MDA435/LCC6 human breast cancer cells (ii) murine *P388/ADR* leukemic cells and (iii) *2008/MRP1* ovarian carcinoma cells. The chemosensitization of drug resistant tumor cell lines is demonstrated for taxol, doxorubicin, daunomycin, vincristine and vinblastine and others. The compounds are effective in killing parasites resistant to the other current clinically used antileishmanials.

In vitro anti-amastigote activity of compound 21

mouse peritoneal elicited macrophages (PEM) infected with sodium SSG-resistant Ld39 promastigotes, allowed to transform into amastigotes,



Accumulation of Doxorubicin as a function of [compound 18]

