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Identification of a new molecular target to prevent metastatic dissemination of breast cancer cells exposed to cl-CD95L

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Breast cancers represent a heterogeneous pathology, which can be classified as Triple-negative breast cancers (TNBC), non-TNBC and HER2+. TNBCsare characterized by a negative immunohistochemical staining for estrogen (ER) and progesterone (PR) receptors and human epidermal growth factor-2 (HER2). Metastases and relapsesremain more frequent in TNBC patients than in Non-TNBC women due to the aggressiveness of these tumors and the lack of tailor-made therapeutic treatment options.Therefore, identification of new therapeutic targets for TNBCs is ofcrucial interest. Our group works on the so-called death receptor CD95 known to initiate apoptosis by interacting with its ligand CD95L. CD95L is a transmembrane ligand (m-CD95L) that can be cleaved by metalloproteases. We recently showed that unlike m-CD95L, the naturally-processed CD95L (cl-CD95L) is a potent prognostic marker of metastatic dissemination in TNBC women. Furthermore, we demonstratedthat cl-CD95L promotes TNBC cellmigrationthrough induction of an "unconventional"PI3K/Akt/mTOR signaling pathway. To block this non-apoptotic signaling pathway, we attempted to generate in collaboration with modelers and chemists, an inhibitor of the PI3K/mTOR pathway. From a chromene backbone and multiple rounds of *in silico/in vitro* and *in cellulo* drug screening, we identified a molecular lead designated DHM25 that showed a strong anti-tumor activity against breast tumor cells. A large-scale kinase assay against the human kinome revealed that DHM25 turnedout to be a selective and potent mTOR inhibitor. In summary, we have designed and synthesized a potent and covalentmTOR inhibitor that represents a very attractive therapeutic agent to impair CD95-mediated cell motility in TNBC cells and, by doing this, to reduce the risk of metastatic dissemination in these women.

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Broad spectrum anticancer activity of pistagremic acid

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Pistagremic acid was isolated from the chloroform fraction of *Pistacia integerrima* by anticancer activity guidance, and the chemical structure was identified as 3-methyl-7-(4,4,10,13,14-pentamethyl-3-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthr-en-17-yl)-oct-3-enoic acid by NMR and X-ray crystallography analysis. Cytotoxic evaluation against NCI-60 DTP human tumor cell line was performed which showed broad spectrum antiproliferative activity with an average GI_{50}, and TGI, values 0.103 μM and 0.259 μM, respectively. It also showed significant LC_{50} value at the average 0.634 μM against all cell lines excluding K-562, RPMI-8226, NCI-H226, and NCI-H460 cell-lines and pistagremic acid may serve as a potential structure lead for the development of new anticancer drugs.