Combined in silico/in vitro strategies for the identification of new highly selective ADP/ATP carrier inhibitors for triggering mitochondrial apoptosis in Cancer Cells.

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The mitochondrial ADP/ATP carriers (AACs) translocate the ATP synthesized within mitochondria to the cytosol in exchange for the cytosolic ADP, playing a key role in energy production, in promoting cell viability and regulating mitochondrial apoptosis through the opening of permeability transition pore. In Homo sapiens four genes code for AACs with different tissue distribution and expression patterns. Since AACs are dysregulated in several cancer types, the employment of known and new AAC inhibitors might be crucial for inducing mitochondrial-mediated apoptosis in cancer cells. Albeit carboxyatractyloside (CATR) and bongkrekic acid (BKA) are known to be powerful and highly selective AAC inhibitors, able to induce mitochondrial dysfunction at molecular level and poisoning at physiological level, we estimated for the first time their affinity for the human recombinant AAC2 through in vitro transport assays as reported in. We found that the inhibition constants (Ki) of CATR and BKA for the human AAC2 are 4 nM and 2.0 μM, respectively. For identifying new AAC inhibitors we also performed a docking-based virtual screening of an in-house developed chemical library and we identified about 100 ligands showing high affinity for the AAC2 binding region according to our validated protocols. By testing 13 commercially available molecules, out of the 100 predicted candidates, we found that 2 of them, namely suramin and chebulinic acid, are competitive AAC2 inhibitors with Ki equal to 0.3 μM and 2.1 μM, respectively. We also demonstrated that chebulinic acid and suramin are “highly selective” AAC2 inhibitors, since they poorly inhibit other human mitochondrial carriers (namely ORC1, APC1 and AGC1).

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