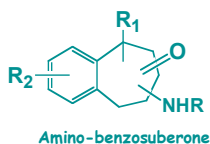


## New family of aminopeptidase-N (AP-N) inhibitors

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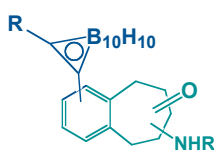
Aminopeptidase N (APN)/CD13 (EC 3.4.11.2) is a transmembrane protease present in a wide variety of human tissues and cell types. This enzyme expression is dysregulated and overexpressed in diseases such as cancer, and known to play a key role in tumor invasion and angiogenesis. Therefore APN inhibition lead to the development of new anti-cancer drug. New compounds as APN inhibitors have been synthesized, and tested on the CD13 in our laboratory. These compounds are derivatives of benzosuberone, and most of them showed  $K_i$  activity in the nanomolar range, the best of them even inhibits this enzyme with a really low  $K_i$  -60 pM-. All structures have been applied in a patent ("INHIBITEUR D'APN" 3 nov 2006 - FR 06.09615).



All of these inhibitors prevent the endothelial cells types organisation in capillaries tubes when they are on Matrigel. The concentrations used to do these experiments are below the cytotoxic dose ( $CD_{50}$ ). In this models capillaries tubes are nearly non existent when cell are treated with CD13 inhibitors, and the ones who exist are really narrow.

To prove the therapeutics interests of theses molecules, test on the animal (in-vivo) are going to be started.

Beside this work, we hope used our CD13 inhibitors in Boron Neutron Capture Therapy (BNCT). For this, the structures of our inhibitors are going to be slightly modified in introducing carbaboranyl groups.



Boron-10 in or adjacent to the tumor cells (thanks the inhibition of CD13) disintegrates after capturing a neutron and the high energy heavy charged particles produced destroy only the cells in close proximity to it, primarily cancer cells, leaving adjacent normal cells largely unaffected.