From Leucettamine B to *leucettine* as emerging drug for potential treatment of Alzheimer's disease (AD) and Down syndrome *via* the 2-amino imidazoline-4-one chemistry

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This presentation is dedicated to the synthetic development of stereocontrolled (5*Z*) 5-arylidene imidazolinones in our laboratory since 1990s. The story begins with the construction of these platforms by 1,3-dipolar cycloaddition reactions based on aminoester imidate ylides[1] (period 1). The presence of an amino group in position C-2 of the imidazolinone platform showed the limits of these 1,3-dipolar cycloadditions. This fact led us to explore completely the thiohydantoin approach[2] to build various marine alkaloids derivatives (leucettamine B[3], dispacamide A[4]) as (5*Z*) 2-amino-5-arylidene-imidazolin-4-ones by using three components reactions[5] and sulphur/nitrogen displacements under microwave irradiation[6] (period 2). The controls of these synthetic methods highlighted that leucettamine B analogues, named leucettines[7](*) present an excellent capacity of inhibition of the protein kinase DYRK1A (period 3) because this protein kinase is connected to Alzheimer's disease (AD) and Down syndrome[8]. For the 3rd period, we shall show that immobilization of one of these leucettines (L41) by affinity chromatography[9] on agarose gel is a relevant approach from cells extracts of mouse brain[10] showing a strong interaction between this linked leucettine L41 and DYRK1A. Finally, the story will end (period 4) with the presentation of the "feuille de route" for the preparation of the next pre- and clinical trials in order to validate (or not) a potential drug for AD.

(*) The leucettine family research program is linked to an Exclusive Operating Licence with *ManRos Therapeutics*. The drug development is currently realized through an Industry-Academic Contract named TRIAD Project "**TRI**somy/**A**lzheimer's **D**isease" (Call 14 FUI Pole of Competitiveness "Mer Bretagne & Alsace Biovalley"): Inhibitors of natural origin for the kinase DYRK1A, to treat the cognitive deficits in trisomy 21 and Alzheimer's disease.

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