SELECTED OPPORTUNITIES IN NEUROSCIENCES

New molecules for neurodegenerative pathologies : indirect β-secretase inhibitors (CHIM17092)

New molecules for neurodegenerative pathologies : indirect β-secretase inhibitors

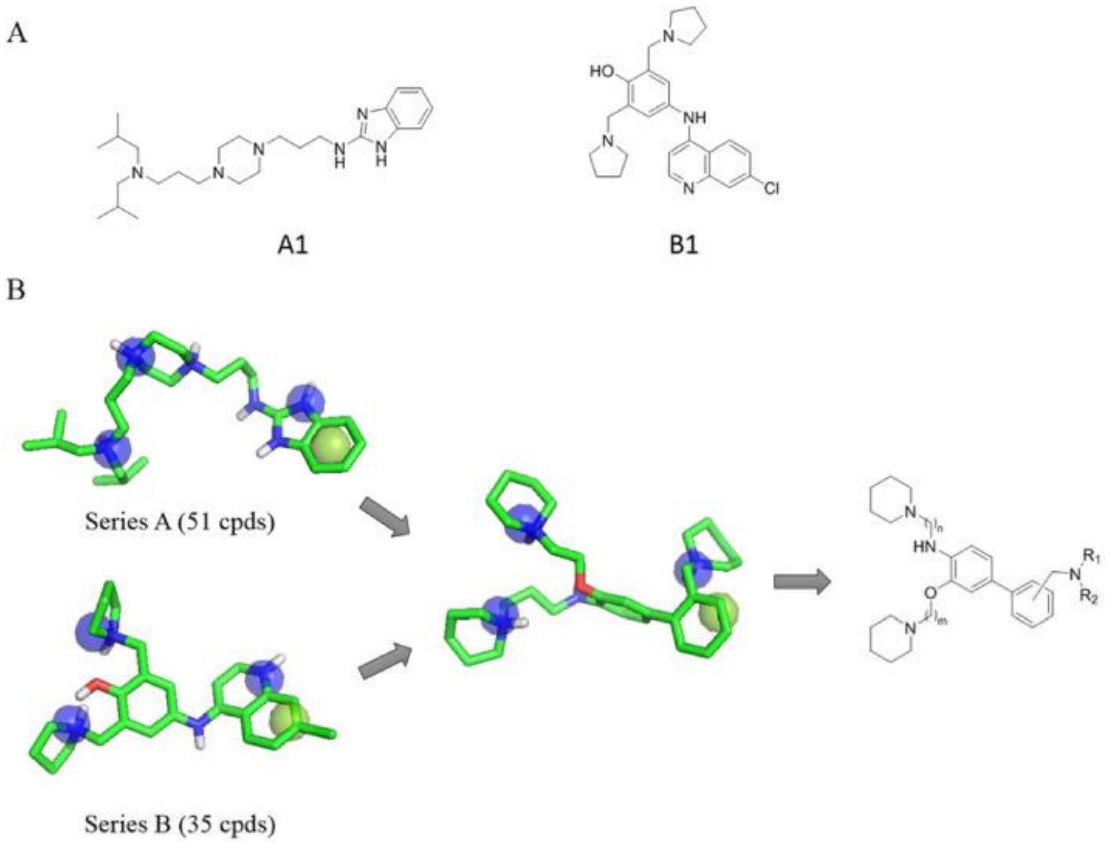
Product factsheet

- **Product :** New chemical entities that promote non-amyloidogenic processing of the amyloid precursor protein
- **Rational / PoC:**
  - Molecules have been designed to maintain inhibition of APP processing into Aβ while loosing inhibition of lysosomal degradation – SAR study was performed
  - All compounds lead to a decrease of the secretion of Aβ peptides responsible of senile plaques in Alzheimer's disease
  - Compounds promote an increase of "good" fragments CTFα and AICD
  - Absence of neurotoxicity
  - *in vivo* evaluation is ongoing
- **Patent :** EP 18305932.8 filed July 2018
- **Publication:**
  - A phenotypic approach to the discovery of compounds that promote non-amyloidogenic processing of the amyloid precursor protein: Toward a new profile of indirect β-secretase inhibitors. Gay et al.. Eur J Med Chem. 2018 Sep 22;159:104-125.
  - Contribution of the Endosomal-Lysosomal and Proteasomal Systems in Amyloid-β Precursor Protein Derived Fragments Processing. Evrard et al.Front Cell Neurosci. 2018 Nov 22;12:435

New molecules for neurodegenerative pathologies : indirect β-secretase inhibitors

Proof of concept

SAR analysis to design the pharmacophore



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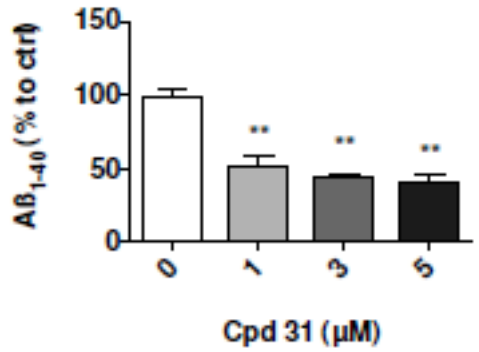
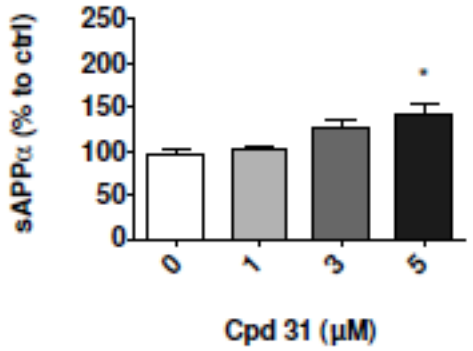
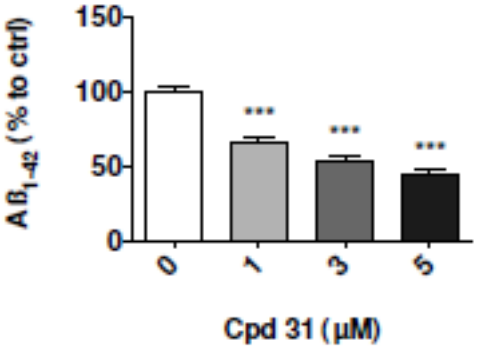
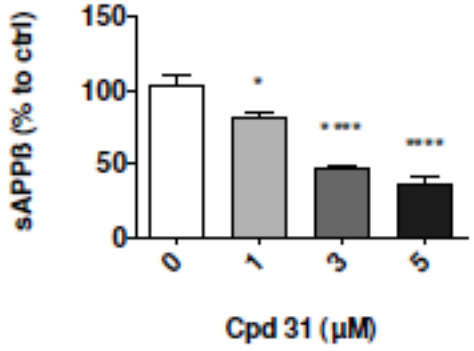
Proof of concept

In vitro effect on mature APP processing in neuronal cell line









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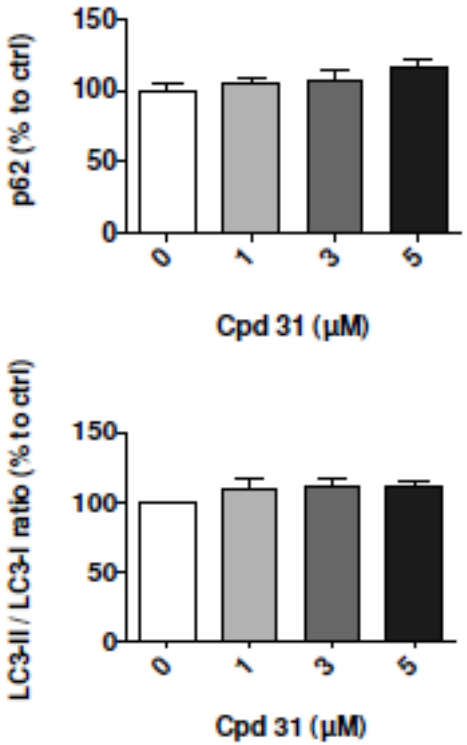
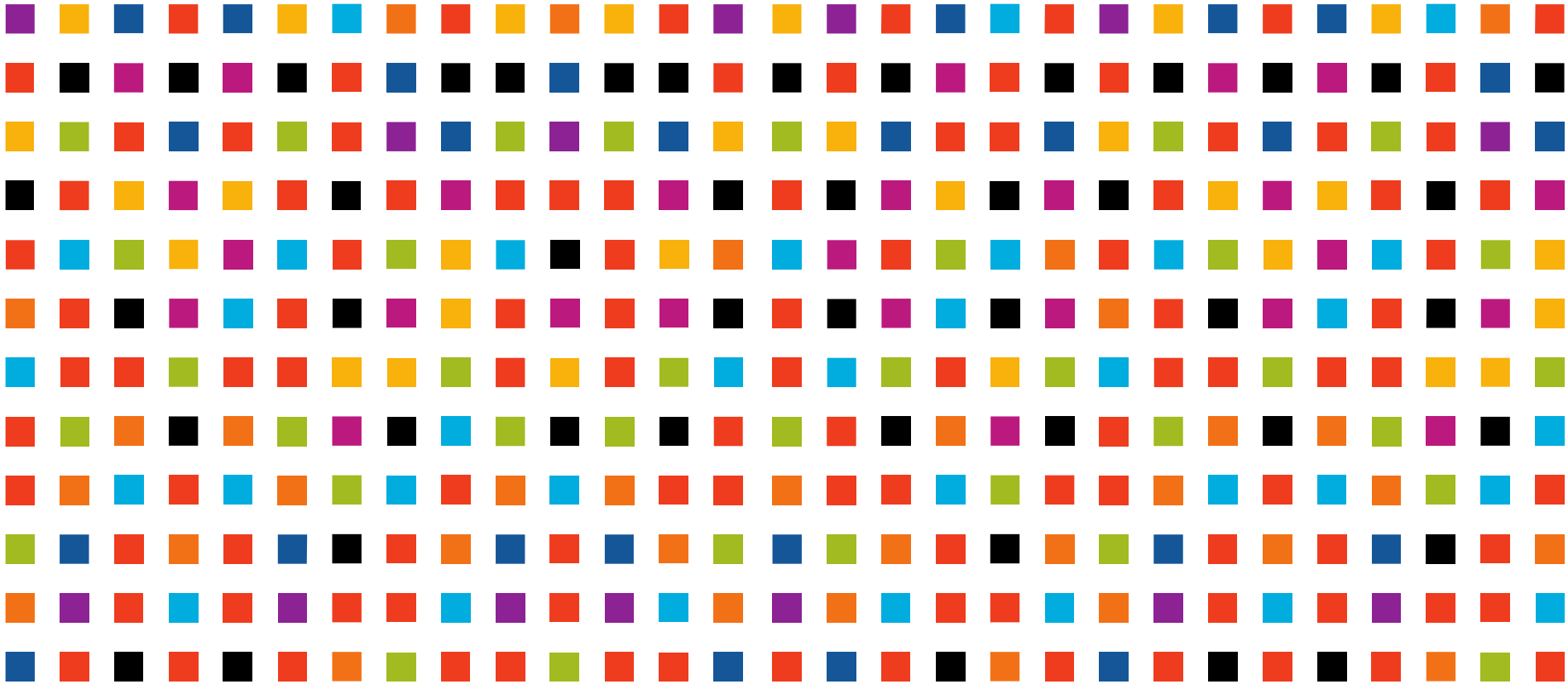
Proof of concept

Absence of autophagy inhibition in neuronal cell line





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