www.chemmedchem.org

CHEMMEDCHEM

CHEMISTRY ENABLING DRUG DISCOVERY

EFMC International Symposium on Medicinal Chemistry

Lisbon, Portugal September 7-11, 2014

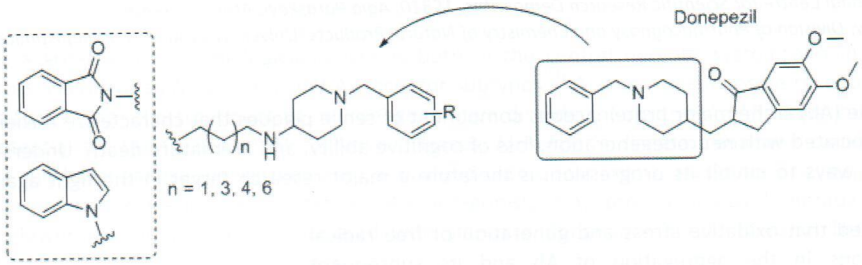
A Journal of ChemPubSoc Europe

BOOK OF ABSTRACTS

WILEY-VCH

Compounds able to bind to the both sites at the same time could not only be more efficient AchE inhibitors but also prevent the formation of the toxic plaques.

The study presents the design, molecular modelling, synthesis, and pharmacological evaluation of novel heterodimeric cholinesterases inhibitors. The structures were designed to combine two pharmacophores: *N*-benzylpiperidine as a fragment interacting with the catalytic site and indole or phthalimide moiety reported as PAS ligands. Among the compounds obtained we found mixed AChE/BuChE inhibitors and selective BuChE inhibitors with sub-micromolar activities. Furthermore, the active compounds significantly prevent the aggregation of Ab in vitro. Given the selectivity towards BuChE and the Aβ-anti-aggregating properties the study described herein is a promising start for the search for new MTDLs as potential drugs against Alzheimer's disease.



References:

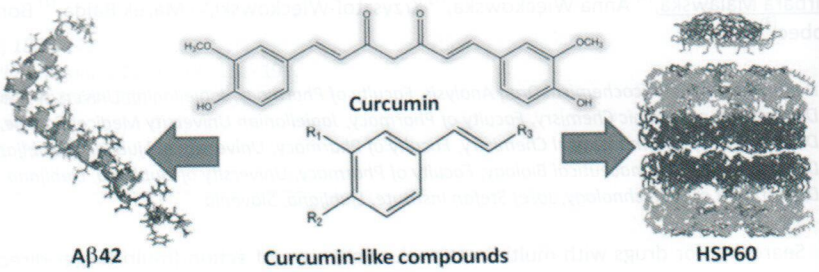
[1] *Multi-target-directed ligands and other therapeutic strategies in the search of a real solution for Alzheimer's disease.* Agis-Torres, A.; Söllhuber, M.; Fernandez, M; Sanchez-Montero, J. M.; *Curr. Neuropharmacol.* **2014**, *12*, 2–36.
[2] *Multi-target-directed ligands in Alzheimer's disease treatment.* Bajda, M.; Ignasik, M.; Guzior, N.; Malawska, B.; *Curr. Med. Chem.* **2011**, *18*, 4949–4975.
[3] *Dual inhiitors of beta-amyloid aggregation and acetylcholinesterase as multi-target anti-Alzheimer drug candidates.* Viayna, E.; Sabate, R.; Muñoz-Torrero, D.; *Curr. Top. Med. Chem.* **2013**, *13*, 1820–1842.

M012 | Curcumin-Like Compounds as Neuroprotective Agents: Interactions with Hsp60 and Amyloid Beta Peptide

Antonio Palumbo Piccionello,[1,2,4] Antonella Marino Gammazza,[1,2] Claudia Campanella,[2,3] Alessio Riccobono,[1] Valentina Giacalone,[1] Silvia Vilasi,[4] Maria Grazia Ortore,[5] Celeste Caruso Bavisotto,[3] Francesco Cappello[2,3,4]

1) University of Palermo, Dpt STEBICEF, Palermo, Italy
2) Euro-Mediterranean Institute of Science and Technology IEMEST, Palermo, Italy
3) University of Palermo, Dpt BIONEC, Palermo, Italy
4) Institute of Biophysics, National Research Council, Palermo, Italy
5) Polytechnic University of Marche, DISVA, Ancona, Italy

Alzheimer's disease (AD) represents a fundamental challenge for public health in the 21st century. Current AD therapies largely focus on symptomatic aspects of the clinical pathology, but they have yet to demonstrate any major impact on the disease progression.[1] The most important role of the research aimed at fighting the AD is the development of neuro-protective agents, able to interfere with the protein aggregation process whose clinical signature is represented by the plaques deposition. An important role in AD's framework could be played by heat shock proteins (HSPs), highly regulated proteins that mediate the proteins proper folding and promote recovery of their native conformations lost due to stress.[2] Recently, it was shown that HSP60 mediates translocation of amyloid precursor protein (APP) and amyloid beta peptide (Aβ) to the mitochondria, leading to dysfunction of the organelle.[3] In the field of potential therapeutic approaches, curcumin, a non-toxic component of the curry spice turmeric, with anti-inflammatory, antioxidant and anti-aggregation properties, is emerging as a lead-compound for the development of neuroprotective drugs.[4] Here we present our recent findings on Curcumin and Curcumin-like drugs obtained by a combination of cellular and in-vitro experiments, such as thioflavine T fluorescence spectroscopy and small angle X-ray scattering.[5] In particular, together with the synthesis of some curcumin-like compounds, we present the results about their effect on a neuronal cell model concerning the cytotoxicity and ability to affect Hsp60 expression, as well as their influence on Aβ aggregation, provided by in vitro experiments.



References:

[1] *The Amyloid Beta Peptide: A Chemist's Perspective. Role in Alzheimer's and Fibrillization.* Hamley, I. W., *Chem. Rev.* **2012**, *112*, 5147–5192.
[2] *Hsp60 chaperonopathies and chaperonotherapy: targets and agents.* Cappello, F., Marino Gammazza, A., Palumbo Piccionello, A., et al., *Expert Opin. Ther. Targets* **2014**, *18*, 185–208.
[3] *Swedish Alzheimer mutation induces mitochondrial dysfunction mediated by HSP60 mislocalization of amyloid precursor protein (APP) and beta-amyloid.* Walls, K.C., Coskun, P., Gallegos-Perez, J. L. et al., *J. Biol. Chem.* **2012**, *31*, 30317–3027.
[4] *A Chemical Analog of Curcumin as an Improved Inhibitor of Amyloid Abeta.* Orlando, R.O., Gonzales, A.M., et al., *PLoS One* **2012**, *7* (3), e31869.
[5] "FIRB-Futuro in Ricerca 2012" Program - Project RBFR12SIPT. Financial support from the Italian MIUR.

M013 | 2-Aminonicotinic Acid-1-oxides Interfere with the Kynurenine Pathway of Tryptophan Metabolism and Inhibit Quinolinic Acid Synthesis in Mammalian Brain

Gabriele Costantino,[1,2] Gianpaolo Vallerini,[1] Elisa Azzali,[1] Marco Pieroni[2] Claudia Beato,[1] Robert Schwarcz[3]

1) Dipartimento di Farmacia. Viale Area delle Scienze 27/A, Università degli Studi di Parma-43124 Parma, Italy
2) Biopharmanet_tec. Viale Area delle Scienze 27/A, Università degli Studi di Parma – 43124 Parm, Italy
3) Department of Psychiatry, Maryland Psychiatric Research Center, PO Box 21247, Baltimore, MD 21228, USA

Both in the periphery and in the brain, mammals degrade most non-proteinogenic L-tryptophan through the so-called kynurenine pathway (KP).[1] This branched metabolic cascade is now recognized as a key component of an intricate network of immune and inflammatory processes. Indeed, several KP metabolites have distinct neuromodulatory properties and may be causally involved in the aetiology of acute and chronic brain diseases. As such, the pathway has attracted substantial attention from investigators in the neurosciences.[2] An imbalance between neuroprotective [kynurenic acid (KYNA)] and neurotoxic [3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN)] KP metabolites has been tentatively linked to the onset and propagation of a number of severe neurological disorders, as those above mentioned.[3] Among the enzymes belonging to this pathway, 3-hydroxyanthranilic acid 3,4-dioxygenase (3-HAO) is the one responsible for the production of the neurotoxic tryptophan metabolite quinolinic acid (QUIN). Elevated brain levels of QUIN are observed in several neurodegenerative diseases, but pharmacological investigation on its role in the pathogenesis of these conditions is difficult because the only class of substrate-analogue 3-HAO inhibitors reported so far suffer of poor chemical stability, resulting in a useless pharmacological tool. Here we report the design, synthesis, and biological evaluation of a novel class of chemically stable inhibitors of 3-HAO based on the 2-aminonicotinic acid 1-oxide nucleus. After the preliminary in vitro evaluation of newly synthesized compounds using brain tissue homogenate, we selected the most active inhibitor and assessed its ability to acutely reduce the production of QUIN in the rat brain in vivo.[4] Along with the innovative clinical relevance, these findings provide a novel pharmacological tool for the study of the mechanisms underlying the onset and propagation of neurodegenerative diseases.

References:

[1] *New promises for manipulation of kynurenine pathway in cancer and neurological diseases.* Costantino, G.; *Expert Opin. Ther. Targets* **2009**, 13, 247–258.
[2] *Kynurenines in the mammalian brain: when physiology meets pathology.* Schwarcz, R.; Bruno, J.; Muchowski, P.; Wu, H.-Q.; *Nature Rev. Neurosci.* **2012**, *13*, 465–477.
[3] *Understanding the roles of the kynurenine pathway in multiple sclerosis progression.* Lim, C.; Brew, B.; Sundaram, G.; Guillemin, G.; Int. J. Tryptophan Res. **2010**, *3*, 157–167.
[4] *Aminonicotinic Acid 1 -Oxides Are Chemically Stable Inhibitors of Quinolinic Acid Synthesis in the Mammalian Brain: A Step toward New Antiexcitotoxic Agents.* Vallerini, G. P., Amori, L., Beato, C., Tararina, M., Wang, X. D., Schwarcz, R., Costantino, G.; *J. Med. Chem.* **2013**, *56*, 9482–9495.

M014 | KMO Inhibitors as Potential Therapeutic Agents for the Treatment of Huntington's Disease

Michael Prime,[1] Dirk Winkler,[2] Maria Beconi,[3] Christopher Brown,[1] Fred Brookfield,[1] Andreas Ebneth,[2] Stephen Courtney,[1] Peter Johnson,[1] William Mitchell,[1] Ladislav Mrzljak,[3] Paula Pena,[1] Laura Reed,[1] Igancio Munoz-Sanjuan,[3] Naomi Went,[1] Leticia Toledo-Sherman,[3] Celia Dominguez[3]

1) Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon, OX14 4SA, UK
2) Evotec AG, Manfred Eigen Campus, Essener Bogen 7, 22419 Hamburg, Germany
3) CHDI Management/CHDI Foundation, 6080 Center Drive, Suite 100, Los Angeles, CA 90045, USA

Huntington's disease (HD) is a rare, fatal, autosomal dominant inherited disease caused by a CAG repeat expansion in the huntingtin (Htt) gene that results in an expanded polyglutamine tract in the mutant huntingtin (mHTT) protein. Clinical manifestations of this disease include motor and cognitive impairment, psychiatric disturbances, as well as metabolic abnormalities, with disease onset typically occurring between the ages of 30 and 50, and death within 15 to 20 years. Kynurenine monooxygenase (KMO) is an enzyme in the Kynurenine Pathway (KP) that catalyses the conversion of kynurenine (KYN) to 3-hydroxykynurenine (3-HK), a precursor of quinolinic acid (QA), a metabolite that has been found to be neurotoxic at supraphysiological concentrations. It has been shown that in