ANNELATED MEDIUM-SIZED AZAHETEROCYCLES AS ATTRACTIVE SCAFFOLDS FOR CNS TARGETED LEADS

Altomare, C. D.;[a] de Candia, M.;[a] Purgatorio, R.;[a] Pisani, L.;[a] Catto, M.;[a] Cellamare, S.;[a] Titov, A. A.;[b] Voskressensky, L. G.[b]

[a]Dipartimento di Farmacia-Scienze del Farmaco, Università degli Sudi di Bari Aldo Moro, Via E. Orabona 4, 70125 Bari, Italy [b]Department of Organic Chemistry, Faculty of Science, RUDN University, 6 Miklukh-Maklaya St., Moscow 117198, Russia.

E-mail of the presenting author: cosimodamiano.altomare@uniba.it

Medium-sized nitrogen heterocycles (7-to-15-membered) have widespread interest in organic synthesis and medicinal chemistry. Indeed, such heterocyclic rings are found as subunits or core structures in natural and bioactive molecules, including pharmaceutical products, whereas on the other hand they often can serve as key intermediates in the synthesis of bicyclic compounds by selective transformations (e.g., transannular ring-contractions, cycloadditions). These molecular frameworks, particularly annelated 7-to-10-membered aza-heterocycles, have long drawn our attention as potential scaffolds for developing new multitarget-directed ligands (MTDLs) for treating Alzheimer's disease (AD) and other neurodegenerative syndromes.

AD, the most common form of dementia affecting people worldwide, is a progressive neurodegenerative disorder, whose multifactorial pathogenesis is still not completely understood. The main histopathological changes include synaptic dysfunction and neuronal loss resulting from intracellular and extracellular fibrillar aggregates of β-amyloid (Aβ), hyperphosphorylated and β-folded tau proteins, cholinergic impairment, oxidative stress, neuroinflammation, metal dys-homeostasis and mitochondrial damage. Among others, *N*-methyl-D-aspartate receptors (NMDARs) play a major role in learning and memory, and their overactivation causes excessive calcium influx and consequent excitotoxicity, which is associated with CNS diseases, including Parkinson's disease.

Starting from our old[1,2] and recent[3] findings on the suitability of partially hydrogenated benzo-, chromane-4-one- and indole-fused azepine and azocine derivatives targeted at enzymes, receptors and biochemical pathways involved in the pathogenesis of AD, we extended the investigation to novel derivatives of annelated azonines and azecines.

Herein, our recent advances of benzo- and indol-fused 7-to-10-membered nitrogen heterocycles as molecular tools for AD-associated targets (e.g., butyryl- and acetylcholinesterase, monoamine oxidases A and B, Aβ aggregation, ROS insult, NMDAR antagonism), along with the results from investigation on cell and ex vivo/in vivo animal models, will be presented and discussed in an effort of rationalizing structure-activity relationships and progressing drug optimization of the examined CNS-targeted lead compounds.

References

1. Carotti, A.; de Candia, M.; Catto, M.; Borisova, T. N.; Varlamov, A. V.; Méndez-Álvarez, E.; Soto-Otero, R.; Voskressensky, L. G.; Altomare, C. *Bioorg Med. Chem.* **2006**, *14*, 7205-7212.
2. Soto-Otero, R.; Méndez-Álvarez, E.; Sánchez-Iglesias, S.; Labandeira-García, J. L.; Rodríguez-Pallares, J.; Zubkov, F. I.; Zaytsev, V. P.; Voskressensky, L. G.; Varlamov, A. V.; de Candia, M.; Fiorella, F.; Altomare, C. D. *Arch. Pharm. (Weinheim)* **2012**, *345*, 598-609.
3. de Candia, M.; Zaetta, G.; Denora, N.; Tricarico, D.; Majellaro, M.; Cellamare, S.; Altomare, C. D. *Eur. J. Med. Chem.* **2017**, *125*, 288-298.