*proceedings*

MDPI

*Extended Abstract*

# Novel Dual Ligands Targeting Sigma1 Receptor and Acetylcholinesterase Endowed with Antioxidant Properties †

**Giacomo Rossino [1], Marta Rui [1], Dirk Schepmann [2], Bernard Wünsch [2], Stefania Monteleone [3,4], Klaus Liedl [4], Vittorio Pace [5], Daniela Rossi [1] and Simona Collina [1,*]**

[1] Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Viale Taramelli 6 and 12, 27100 Pavia, Italy
[2] Institute of Pharmaceutical and Medicinal Chemistry, University of Münster, Correnstrasse 48, 48149 Muenster, Germany
[3] Department of Pharmaceutical Chemistry, Philipps-University Marburg, Marbacher Weg 6, 35032 Marburg, Germany
[4] Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innrain 80-82, 6020 Innsbruck, Austria
[5] Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria
* Correspondence: simona.collina@unipv.it
† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 8 August 2019

**Keywords:** neurodegenerative disorders, Sigma1 receptor agonist, RC-33; structure optimization

---

Neurodegenerative disorders represent one of the main therapeutic challenges of our time. An effective strategy to counteract such pathologies may be the multitarget-directed ligand approach, and there is a growing interest in the identification of compounds acting simultaneously on diverse biological targets. Our strategy consists in targeting the Acetylcholinesterase (AChE) enzyme along with Sigma1 Receptor (S1R). Indeed, AChE inhibitors have noteworthy pharmacological application in the treatment of neurological disorders manifestations such as Alzheimer's disease, Parkinson's disease, and myasthenia gravis. Moreover, S1R agonists have emerged as promising pharmacological tools in the fight against neurodegenerative disorders. We prepared a small compound library endowed with both anti-AChE activity and S1R affinity, combined with antioxidant properties. The new compounds series is characterized by a arylalkylaminoketone scaffold, which bears the structural elements of our developed S1R agonist RC-33, the well-known AChE inhibitor Donepezil and the antioxidant molecule Curcumin. Their affinity and selectivity towards S1R, their inhibition of AChE and their antioxidant profile were determined [1–3]. In the present communication we present the structure optimization of *hit* compounds, with the final aim to achieve viable tools for the treatment of neurodegenerative pathologies.

## References

1. Rossi, D.; Urbano, M.; Pedrali, A.; Serra, M.; Zampieri, D.; Mamolo, M.G.; Laggner, C.; Zanette, C.; Florio, C.; Schepmann, D.; et al. Design, synthesis and SAR analysis of novel selective σ1 ligands (Part 2). *Bioorg. Med. Chem.* **2010**, *18*, 1204–1212.
2. Marra, A.; Rossi, D.; Pignataro, L.; Bigogno, C.; Canta, A.; Oggioni, N.; Malacrida, A.; Corbo, M.; Cavaletti, G.; Peviani, M.; et al. Toward the identification of neuroprotective agents: g-scale synthesis, pharmacokinetic evaluation and CNS distribution of (R)-RC-33, a promising Sigma1 receptor. *Future Med. Chem.* **2016**, *8*, 287–295.
3. Rui, M.; Rossino, G.; Coniglio, S.; Monteleone, S.; Scuteri, A.; Malacrida, A.; Rossi, D.; Catenacci, L.; Sorrenti, M.; Paolillo, M.; et al. Identification of dual Sigma1 receptor modulators/acetylcholinesterase inhibitors with antioxidant and neurotrophic properties, as neuroprotective agents. *Eur. J. Med. Chem.* **2018**, *158*, 353–370.