Title	**New agents for multifaceted targeting of neurodegenerative diseases**
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Project description:

The prevalence of neurodegenerative diseases, in particular of the most common Alzheimer's disease (AD) and Parkinson's disease (PD), is expected to rise with the increasing life expectancy in most countries and the disabling features and cognitive decline associated to these disorders is particularly relevant owing to its great influence on health span and quality of life. AD is an age-related chronic and progressive neurodegenerative disease, characterized by a substantial cognition loss, including intellectual, language, visual-spatial disturbances as well as memory damage. Several pathophysiological factors have been revealed to be the main factors for leading to the progression of AD, including amyloid beta deposits, low levels of acetylcholine, hyperphosphorylated tau protein, oxidative stress and dyshomeostasis of biometals. PD is a common and complex neurological disorder with early prominent death of dopaminergic neurons in the substantia nigra. The resultant dopamine deficiency leads to a movement disorder characterized by classical parkinsonian motor symptoms. Lewy bodies and Lewy neuritis, consisting of abnormal aggregates of α-synuclein protein, are also features associated with PD. The mainstay of PD management is symptomatic treatment with drugs that increase dopamine concentrations or directly stimulate dopamine receptors. Even if different, AD and PD share some common pathogenic mechanisms, that seem to be closely related to the evolution and progression of neurodegeneration, such as protein misfolding, phosphorylation impairment, increase of monoamine oxidase activity (mainly MAO-B isoform) in brain, which may contribute both to a depletion of amine neurotransmitters and to an overproduction of reactive oxygen species. Conventional drug design approaches that embrace the "one molecule-one one-target" failed to provide successful ways of treating disorders showing multifactorial aetiologies as AD and PD. Indeed, despite advances in drug discovery, all current therapeutic interventions are symptomatic, none halt or retard neuronal cell loss. Otherwise, disease-modifying treatments that reduce the rate of neurodegeneration or stop the disease process, have remained elusive and represent the greatest unmet therapeutic need in these disorders. Based on these knowledge the aim of our research is to identify novel chemical scaffolds able to hit validate hubs, namely monoamino oxidases (MAO-B) and protein kinases (GSK-3β and DIRK1A), involved in the pathogenic phosphorylation process of α-synuclein and tau proteins.

Publications:

L. G. Iacovino, L. Pinzi, G. Facchetti, B. Bortolini, M. S. Christodoulou, C. Binda, G. Rastelli, I. Rimoldi, D. Passarella, M. L. Di Paolo, **L. Dalla Via*** Promising non-cytotoxic monosubstituted chalcones to target monoamine oxidase-B *ACS Med. Chem. Lett.* (2021) 12, 1151-1158 DOI: 10.1021/acsmedchemlett.1c00238

M. L. Di Paolo, M. S. Christodoulou, A. M. Calogero, L. Pinzi, G. Rastelli, D. Passarella, G. Cappelletti, **L. Dalla Via*** 2-Phenyloxazole-4-carboxamide as a Scaffold for Selective Inhibition of Human Monoamine Oxidase B *ChemMedChem* 14, 1641-1652 (2019) DOI: 10.1002/cmdc.201900261