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Introduction

The NLR family protein NLRP3 is an intracellular signalling molecule activated by many pathogen-derived, environmental and host-derived factors. Upon activation, NLRP3 controls the formation of the catalytically active protease, caspase-1, leading to cleavage of proinflammatory cytokines interleukin-1β (IL-1β) and IL-18 to their active forms and to a type of inflammatory cell death known as pyroptosis. NLRP3 plays a critical role in the inflammatory process and it has been implicated in the pathogenesis of metabolic disorders such as type 2 diabetes, atherosclerosis and obesity. NLRP3 has also been involved in diseases of the central nervous system and lung, liver, kidney diseases and aging (Coll et al. *Nat Med.* 2015, 21(3):248; Mathur et al. *J Leukoc Biol*. 2018, 103:233).

Materials and methods

Several series of NLRP3 inhibitory compounds has been synthetized by SynBioMed group of the Department of Drug Science and Technology of Turin through the chemical modulation of a benzo[d]imidazol-1-one sub-moiety, which was identified as a weak inhibitor of ATPase activity. Their protective effect on pyroptosis was evaluated on THP-1 cell lines, after stimulation with LPS/ATP, comparing their activity to that of known inhibitors, such as MCC950 (Coll et al., *Nat Med*. 2015, 21(3):248); to evaluate this effect, LDH levels was measured using LDH cytotox 96 non radio cytotoxicity assay (Promega). We also evaluated the cytotoxicity of these compounds and the release of Il-1beta.

Results

Compounds with a N-piperidin acrylamide moiety showed a greater antipyroptotic effect than propanamide derivates; no compounds showed a significant cytotoxicity.

Discussion and conclusion

Several non-cytotoxic acrylamide and propanamide derivatives able to target the activation of the NLRP3 inflammasome were obtained. Among the acrylamide derivates, we can find promising compounds able to reduce LDH release induced by LPS/ATP. Further studies will be performed in order to better characterize the antipyroptotic activity of these new compounds and to chemically modulate their structure to increase their ability to inhibit NLRP3 inflammasome.