DESIGN, SYNTHESIS AND PHARMACOLOGICAL CHARACTERIZATION OF NEW CHEMICAL ENTITIES TARGETING NLRP3 INFLAMMASOME ACTIVATION AND RELATED SIGNALING PATHWAYS

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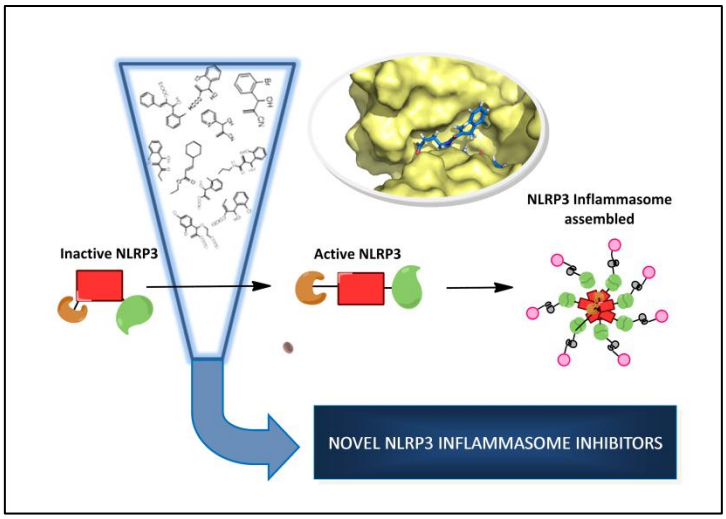
NLRP3 inflammasome is a multiprotein complex that plays a crucial role in activating caspase-1, processing the pro-inflammatory interleukin-1β (IL-1β), and triggering pyroptotic cell death cascade.[1] Gain of function mutations in NLRP3 determine its abnormal activation which is a key factor in the pathogenesis of autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS). The progression of other diseases, such as atherosclerosis, Inflammatory Bowel Disease (IBD), type-2 diabetes, Alzheimer's disease, and gout is also dependent on NLRP3 inflammasome activation.[2] So far, several strategies have been proposed to dampen NLRP3 activity, among them covalent drug development seems to be a promising one.[3]

In this project we designed and synthesized lead compounds acting either as direct NLRP3 inhibitors or as multi-target agents acting multiple stages of NLRP3 signaling pathway. Synthesis of "*ad hoc*" designed chemical probes was also considered to investigate mechanism of NLRP3 activation. The work was articulated in three steps: synthesis of covalent drugs directly targeting NLRP3 (first year)[3]; modulation of cytotoxic properties of electrophilic warheads towards safer compounds (second year)[4]; increase of specificity towards NLRP3 ATPase pocket, investigation of mechanism of action and exploration of other key players of the pathway (third year).

In this work, we successfully identified new candidates for NLRP3 inflammasome inhibition characterized by good in vitro anti-pyroptotic activity, optimized toxicological profile, direct NLRP3 ATPase inhibition, high ability to decrease in vitro and in vivo IL-1β production. Selected compounds showed promising activities in pharmacological models of CAPS,[4] ischemia,[5] and IBD[6].



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