SULFONIMIDAMIDE COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of Chinese Priority Application PCT/CN2021/107085, filed July 19, 2021; and Chinese Priority Application PCT/CN2022/077518, filed February 23, 2022; the disclosures of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

[0002] The present disclosure relates to sulfonimidamide compounds as described herein, and their use in treating a disorder responsive to modulation of cytokines (such as IL-1β and IL-18), modulation of NLRP3, or inhibition of the activation of NLRP3 or related components of the inflammatory process.

BACKGROUND

[0003] The NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) inflammasome is a component of the inflammatory process, and its aberrant activation is pathogenic in inherited disorders such as cryopyrin-associated periodic syndromes (CAPS) and complex diseases such as multiple sclerosis, type 2 diabetes, Alzheimer's disease, and atherosclerosis.

[0004] NLRP3 is an intracellular receptor protein that senses certain inflammatory signals. Upon activation, NLRP3 binds to apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC). The NLRP3-ASC complex then polymerizes to form a large aggregate known as an ASC speck. Polymerized NLRP3-ASC in turn interacts with the cysteine protease caspase-1 to form a complex termed the inflammasome. This results in the activation of caspase-1, which cleaves the proinflammatory cytokines IL-1β and IL-18 to their active forms and mediates a type of inflammatory cell death known as pyroptosis. The ASC speck can also recruit and activate caspase-8, which can process pro-IL-1β and pro-IL-18 and trigger apoptotic cell death.

[0005] Caspase-1 cleaves pro-IL-1β and pro-IL-18 to their active forms, which are secreted from the cell. Active caspase-1 also cleaves gasdermin-D to trigger pyroptosis. Through its control of the pyroptotic cell death pathway, caspase-1 also mediates the release of alarmin molecules such as IL-33 and high mobility group box 1 protein (HMGB1). Caspase-1 also