Synthesis and Biological Evaluation of Olanzapine-based PROTACs Targeting Human D-Aspartate Oxidase (hDASPO)

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D-Aspartate oxidase (DASPO) is one of the most relevant enzymes involved in the degradation of D-amino acids, especially D-aspartate (D-Asp), which has the potential to activate *N*-methyl-D-aspartate (NMDA) receptors. Dysfunction of NMDA receptor-mediated neurotransmission is associated with various mental disorders, such as schizophrenia. Therefore, developing inhibitors for DASPO could increase brain levels of D-Asp, potentially enhancing NMDA receptor function and offering therapeutic benefits. Recently, the antipsychotic drug olanzapine was reported acting as a potent binder of DASPO (IC_{50} = 23.4 μM) increasing extracellular levels of D-Asp in prefrontal cortex (previously published in Sacchi *et al.* (2017) Sci. Rep. 7(1), 46288). Aware of this result, we have decided to employ Proteolysis Targeting Chimeras technology (PROTAC) to target DASPO with bifunctional compounds based on olanzapine structure (previously published in Wang *et al.* (2022) Eur. J. Med. Chem. 235, 114290). The primary goal of PROTACs is to trigger the degradation of enzymes within cells via the proteasomal pathway, consequently enhancing cellular levels of D-Asp. This innovative strategy could offer a potential treatment for diseases connected to a deficiency of D-Asp.
A panel of new bifunctional molecules were designed starting from the olanzapine core structure using aliphatic, amide, or PEGylated linkers, with lenalidomide and VHL ligand serving as E3 ligase binders. Straightforward “click” chemistry strategies were employed to efficiently synthesize the compounds and a preliminary biological assessment showed that the first PROTAC MGA26 exhibited significant DASPO inhibition (IC50 = 4.13 μM) and affected the cellular DASPO level.