proceedings

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Extended Abstract

4,4-Disubstituted *N*-benzylpiperidines: A Novel Class of Fusion Inhibitors of Influenza Virus H1N1 Targeting a New Binding Site in Hemagglutinin †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 14 November 2019

Influenza epidemics are estimated to result in 3–5 million cases of severe illness and 290.000–650.000 deaths per year. Due to the limited anti-influenza drugs available and the emergence of drug-resistant viral strains, innovative influenza therapeutics directed at new targets and/or with novel mechanisms of action are urgently needed.

In an effort to discover novel anti-influenza agents, several molecules of our diverse in-house library were screened against a panel of different influenza virus strains. Following this approach, we identified structurally novel 4,4-disubstituted *N*-benzylpiperidine compounds as interesting hit compounds that display antiviral activity against influenza virus A/H1N1 in the low micromolar range. To investigate the structure–activity relationships, several analogues were easily synthesized, by a one-step Ugi four-component reaction, from commercially available amines, isocyanides, *N*-substituted piperidones, and a variety of amino acids as carboxylic acid components. The mechanism of action of the most active compounds was examined, taking into account time-of-addition, resistance selection, and functional assays for HA-mediated binding or membrane fusion, suggesting that the compounds inhibit HA-mediated fusion. Mutational and computational simulations proposed an unexplored new cavity near the fusion peptide as the putative binding site for these *N*-benzylpiperidine analogues. Interestingly, a pi-stacking interaction between the *N*-benzylpiperidine moiety with a Phe residue of the fusion peptide represents one of the most relevant ligand–protein interactions. These compounds may be considered useful research tools to explore a new cavity at HA for the design of novel small-molecule fusion influenza inhibitors.

The synthesis, biological evaluation, mechanism of action, and computational studies of these *N*-benzylpiperidine derivatives will be reported in this communication.