NEW ANTI-VIRAL DRUGS FOR THE TREATMENT OF COMMON COLD

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Human Rhinovirus (HRV) is the most important etiologic agent of common cold in adults and children. At the present, no antirhinovirus agent exists in the market and the large number of different serotypes (~105) makes unlikely the development of vaccines. HRV is a single-stranded, positive sense RNA virus. Protease 3C is a cysteinyl protease which hydrolises Gln-Gly, Gln-Ser and Gln-Ala pairs and it is an essential protein for viral replication. Also, despite the high level of conservation among different serotypes, sequence allignment of viral protease 3C with mammalian protease reveals no homology. Thus, protease 3C is an optimal target for the development of anti-HRV agents. In the present work we investigated the design, the synthesis and the development of new potential reversible inhibitors against HRV protease 3C. In the past, several peptidic and non-peptidic structures have been formulated in order to act as analogues of the substrate. They all contain groups which can be attacked by the SH of the cysteine present in the active site of the protease, thus generating a reversible analogue of the transition state. Aldehydes, fluoromethylketones, isatines are just examples with excellent in vitro activity. Peptidic lactam AG7088 is now in Phase II clinical trial. Docking studies on the crystallized structure of HRV2 protease 3C, led us to the design and the synthesis of a series of 3,5 disubstituted benzamides, carrying electrophile moieties able to act as analogues of the substrate. Electrophile moieties include amides, esters and aloketones. Different substitutions on the aryl ring led us to investigate the importance of π-π interaction on the stabilization of protease 3C-inhibitor complex. All structures were tested for enzimatic inhibition on HRV14 protease 3C at 10μM and, for the more active compounds, at 100 μM, 10 μM 1 μM and 0.1 μM. Results showed good improvement compared to the reference compound and need to be further investigated.