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Aniline-based inhibitors of influenza H1N1 virus acting on hemagglutinin-mediated fusion

Content

The influenza virus hemagglutinin (HA) is responsible for fusion between the viral and endosomal membranes during influenza virus entry. This fusion process can be blocked by compounds interfering with the acid-induced conformational change of HA.
After identifying two series of easily accessible anilines as inhibitors of influenza A/H1N1 virus, extensive chemical synthesis and analysis of the structure-activity relationship were performed. In Madin-Darby canine kidney cells infected with A/H1N1 viruses, the lead compound, **9d**, displayed a 50% effective concentration of 1.5 to 5.5 μM and an antiviral selectivity index of 30. Inhibition of polykaryon formation in HA-expressing cells indicated that **9d** and its analogue **14a** interfere with low pH-induced membrane fusion mediated by the H1 and H5 (group 1) HA subtypes. Virus resistance as well as NMR experiments with the lead molecule **9d** demonstrated that it interferes with HA-mediated f1usion by binding to the HA stem and preventing its refolding at low pH. Molecular dynamics simulations suggest that ligand **9d** is able to fill the "TBHQ pocket" (1) in the HAs of A/PR/8/34 and A/Virginia/ATCC3/2009. This implies that the "TBHQ pocket" represents a common and particularly relevant site for small-molecule HA fusion inhibitors, although distinct chemotypes are required to address the different polarity of this cavity in group-1 versus group-2 HA subtypes.
1) Russell et al., Proc. Natl. Acad. Sci. U. S. A. **2008**, 105, 17736-17741.

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