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**Host DHFR-directed cycloguanil analogues endowed with promising activity against influenza virus and respiratory syncytial virus****Michele Tonelli**

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The *Orthomyxoviridae* and *Paramyxoviridae* families comprise important respiratory pathogens, such as respiratory syncytial virus, influenza A and B viruses. The acute respiratory illnesses caused by these viruses represent a major medical need. In particular, the risk for a severe influenza A pandemic leads to the development of new and broadly acting therapeutics an urgent issue. Currently, used antiviral drugs preferentially inhibit virus-specific replication factors. An alternative and emerging strategy is to address host factors involved in virus replication, because less susceptible to mutate. Herein, we have identified a series of 4,6-diamino-1,2-dihydrotriazines, structurally related to the antimalarial drug cycloguanil, as new inhibitors of influenza A and B virus and RSV via targeting of the host dihydrofolate reductase (DHFR) enzyme. They proved active against influenza B virus in the low micromolar range, sometimes reaching the sub-micromolar potency of zanamivir ( $EC_{50}=0.060\ \mu\text{M}$ ), and markedly exceeded (up to 327 times) the antiviral efficacy of ribavirin. Besides inhibiting two influenza A strains, more importantly the compounds displayed nanomolar activity against RSV with a SI ( $CC_{50}/EC_{50}$ ) >10,000 for the most active compounds ( $EC_{50}\sim 0.008\ \mu\text{M}$ ), far surpassing the potency and safety profile of the licensed drug ribavirin ( $EC_{50}=5.8\ \mu\text{M}$ , SI>43). These compounds, tested against the recombinant protein of the hDHFR, also confirmed to bind this enzyme in the sub-micromolar range. Kinetic inhibition studies showed a competitive inhibition behavior, and docking studies disclosed the most probable binding mode for this class of compounds as hDHFR ligands.

**Biography**

Michele Tonelli has done his graduation in chemistry and pharmaceutical technology from Genoa University in the year 2003. He did his PhD in pharmaceutical food and cosmetic sciences. He has participated in many national research projects. Since 2012, he is an Assistant Professor (Medicinal Chemistry) in the Department of Pharmacy, University of Genoa. He has published more than 25 papers in reputed journals and has been serving as Reviewer of *Journal of Medicinal Chemistry*, *Bioorganic & Medicinal Chemistry*, *Antiviral Research*, *Future Medicinal Chemistry*, etc.

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