Phosphonate Congeners of Oseltamivir and Zanamivir as Effective Anti-influenza Drugs: Design and Synthesis

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Oseltamivir (Tamiflu™) and zanamivir (Relenza™) are effective anti-influenza drugs by targeting the viral neuraminidases. These neuraminidase inhibitors are designed to have (oxa)cyclohexene scaffolds to mimic the intermediate of oxonium-like geometry in the enzymatic cleavage of N-acetylneuraminic acid (Neu5Ac, also known as sialic acid), the outmost saccharide on the cell surface glycoprotein for binding with the active site of viral neuraminidase. Oseltamivir is orally available, whereas zanamivir is administered by inhalation. The oseltamivir-resistant strains have emerged due to the extensive use of oseltamivir. Though the resistance to zanamivir is still rare, we may also face the problem in treatment of the zanamivir-resistant viral infection. To cope with the need of new anti-influenza agents that are especially in urgent need for possible global pandemics, we have explored new anti-influenza agents, tamiphosphor and zanaphosphor, which are the phosphonate congeners of oseltamivir and zanamivir. By replacement of the carboxylate group with phosphonate group as a bioisostere, tamiphosphor and zanaphosphor show higher affinity to influenza virus neuraminidases than oseltamivir and zanamivir, presumably due to the stronger electrostatic interactions of the phosphonate group with the three arginine residues (Arg118, Arg292 and Arg371) in the active site of neuraminidase. In this symposium, we shall present the syntheses of tamiphosphor, zanaphosphor and their analogs.
Bio:
Dr. Jim-Min Fang received his B. S. degree in 1974 from the National Taiwan University (Department of Chemistry) and Ph. D. degree in 1980 from Yale University. After finishing postdoctoral research in Columbia University and in the Suntory Institute for Bioorganic Research (Osaka), he joined the Department of Chemistry, National Taiwan University, as Associated Professor in 1982. He was promoted to Professor in 1986, and Distinguished Professor in 2006. He has joint appointment in the Genomics Research Center, Academia Sinica since 2003. His current interests are organic synthesis and chemical biology, including new synthetic methods, asymmetric catalysis, biomolecular recognition, natural.

Representative Publications:

