Design and Synthesis of Phenylphosphonate Derivatives as Potent Anti-Influenza Activity

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Influenza remains an epidemic healthy threat worldwide yearly. Breakout exposure to the highly pathogenic H1N1 influenza a viruses is responsible for the frightened death in Taiwan this year. Safe and effective anti-influenza drugs are clearly needed to treat the segment of the population that suffer from influenza each year.

Oseltamivir (Tamiflu) and zanamivir (Relenza) are two drugs that were approved for the treatment of influenza infections. These two drugs block viral replication by inhibiting the enzymatic activity of the viral neuraminidase (NA). Neuraminidase appears to be required for elution of newly synthesized virus from infected cells and may also have a role in allowing the virus to move through the mucus of the respiratory tract. It plays an important role in the release of virus particles from infected cells. Therefore, neuraminidase was usually regarded as an inhibiting target for treatment of influenza.

In the continuous search of new anti-flu agents, a series of phenylphosphonate derivatives were synthesized on the basis of that phosphonate group as a bioisostere instead of carboxylate in drug design from structural modification of *p*-aminobenzoic acid. Bearing C_3-amino or C_3-guanidinium group, C_4-amide group and C5-amino or long carbon-chain group is modified on the phenylphosphonate core for binding packet of NA similar to the NA-oseltamivir complex.

The ability of the synthetic compounds to interfere with the plaque formation by human influenza viruses was examined on the basis of the maximum non-toxic concentration of the test compounds. Some of our products showed potent activity, in vitro, against H1N1 viruses. Further investigations on the mechanisms of action are in progress.