Processes for the Preparation of Tamiflu and Analogs

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Technology description

This technology provides a short synthesis of Tamiflu that would be amenable to producing this important antiviral agent on a commercial scale.

Description

The technology relates to a process for the manufacture of novel intermediate useful for the preparation of Oseltamivir, and Oseltamivir Phosphate (Tamiflu) from readily available precursors and processes to prepare Oseltamivir and Oseltamivir Phosphate.

Background

World Health Organizations officials have recently warned that the risk of a human influenza pandemic remains real and is probably growing as the bird flu virus becomes entrenched in poultry in more countries. [1] The current estimated market size for Tamiflu is in excess of $2.2 billion. [2] By full-year 2007, Roche was on target to produce 400 million doses of Tamiflu.

The key market opportunity stems from the fact that there is much concern over an impending global outbreak of avian influenza. The highly pathogenic Influenza A virus subtype H5N1 virus is an emerging avian influenza virus that has been causing global concern as a potential pandemic threat. There is widespread doubt that manufacturers can supply enough doses of key antiviral medication (in particular, Tamiflu). The combination of a threat of a global-level infection, along with a compromised supply of required medication and a complex manufacturing process, creates an opportunity for a cheaper, faster and better manufacturing process

The key problem that the proposed technology overcomes is that in the current manufacturing process, shikimic acid is used in the manufacturing of Tamiflu. Shikimic acid is expensive and in limited supply, since it is obtained almost exclusively from the pods of the star anise, a fruit that is found mainly in China and whose availability has dwindled due to high demand for the flu drug. Thus, process to avoid the use of shikimic acid, and reduce the overall complexity of the manufacturing process will have commercial potential.

Tamiflu is one of the few compounds effective against H5N1 influenza virus. World governments have undertaken stockpiling the material as an insurance against a major breakout of avian flu or other forms of influenza. The amounts required for Canada and USA are estimated at 25 tons of the raw drug substance.

The current commercial syntheses, as well as several academic efforts, produce Tamiflu in sequences ranging form 8 to 21 steps. Almost all syntheses originate in either natural products or chiral pool

reagents. The technology has the potential to provide an 8-step first-generation synthesis. The synthesis will be optimized to a scale of 100 grams of Tamiflu with the provision of detailed experimental procedures to make it possible for a large-scale process group to further increase the scale to kilogram level and beyond. All intermediates from the synthetic operation resembling Tamiflu in structure or functionality will be screened for antiviral activity. Any active compound will be subjected to lead optimization and structure-activity relationships would be investigated in collaboration with an industrial partner. This novel syntheses of Tamiflu hold a great potential as means of large-scale supply of this medicinal agent.

Application area

For the large scale manufacture of Tamiflu.

Advantages

Shorter synthesis (i.e. fewer chemical operations) can currently used systems.
The novel processes uses readily available starting materials.

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