

NEURAMINIDASE INHIBITORS AS-PROMISING H₁N₁ ANTIVIRAL AGENT

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Summary

The neuraminidase inhibitors act by blocking activity of viral neuraminidase enzyme & prevent particles released from infected cells. Various neuraminidase inhibitors are used for antiviral activity & also these agents are used in the treatment of influenza & swine flu.

The present review deals with study of pharmacology, pharmacokinetics, efficacy, and safety of Zanamivir and Oseltamivir for the prophylaxis and treatment of influenza.

Key Words: Swine flu, Zanamivir, Oseltamivir, Laninamivir.

Introduction

SWINE FLU Influenza-like illness (ILI) is defined as fever (temperature of 100°F [37.8°C] or greater) with cough or sore throat in the absence of a known cause other than influenza.

A confirmed case of pandemic H1N1 influenza A is defined as an individual with an ILI with laboratory-confirmed H1N1 influenza A virus detected by real-time reverse transcriptase (rRT)-PCR or culture.

Pandemic H1N1 influenza A may be suspected in an individual who does not meet the definition of confirmed pandemic H1N1 influenza A, but has an ILI and an epidemiologic link

CLASSIFICATION OF SWINE FLU VIRUS.^{2,3}

Of the three genera of influenza viruses that cause human flu two also cause influenza in pigs, with influenza A being common in pigs and influenza C being rare. Influenza B has not been reported in pigs. Within influenza A and influenza C, the strain found in pigs and humans are largely distinct, although due to reassortment there have been transfers of genes among strain crossing swine, avian, and human species boundaries.

INFLUENZA A

Swine influenza is known to be caused by influenza A subtypes H1N1, H1N2, H2N3, H3N1, and H3N2. In pigs, three influenza A virus subtypes (H1N1, H1N2, and H3N2) are the most common strains worldwide. In the United States, the H1N1 subtype was exclusively prevalent among swine population before 1998; however, since late August 1998, H3N2 subtypes have been isolated from pigs. As of 2004, H3N2 virus isolated in US swine and turkey stocks were triple reassortants, containing genes from human (HA, NA, PB1), swine (NS, NP, and M), and avian (PB2, PA) lineages.

INFLUENZA B

In 2007, Japanese investigators detected neuraminidase-resistant Influenza B virus strains in individuals who had not been treated with these drugs. The prevalence was 1.7%. According to the CDC, as of October 3, 2009 no influenza B strains tested have shown any resistance to oseltamivir.

INFLUENZA C

Influenza C viruses infect both humans and pigs but do not infect birds. Transmission between pigs and humans have occurred in past. For example, influenza C caused small outbreaks of mild form of influenza amongst children in Japan and California. Due to its limited host range and the lack of genetic diversity in influenza C, this form of influenza does not cause pandemic in humans.

SYMPTOMS OF SWINE FLU

Below mentioned are some of the common symptoms of swine flu. Make a proper note of such symptoms so that you can take proper action to prevent such disorder.

Headaches, Fever, Breathlessness, Aching body, Feeling of weakness, Throat pain, Coughs, General sickness, Vomiting

TREATMENT

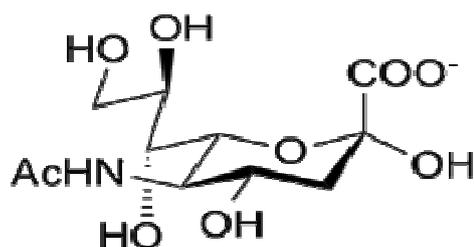
The vast majority of strains of pandemic H1N1 influenza A virus circulating in 2009 appear sensitive in vitro to the neuraminidase inhibitors, oseltamivir and zanamivir, but all strains tested have been resistant to amantadine and rimantadine.

Two antiviral agents have been reported to help prevent or reduce the effects of swine flu. They are zanamivir (Relenza) and oseltamivir (Tamiflu), both of which are also used to prevent or reduce influenza A and B symptoms. These drugs should not be used indiscriminately, because viral resistance to them can and has occurred. Also, they are not recommended if the flu symptoms already have been present for 48 hours or more, although hospitalized patients may still be treated past the 48-hour guideline. Severe infections in some patients may require additional supportive measures such as ventilation support and treatment of other infections like pneumonia that can occur in patients with a severe flu infection

Peramivir, an investigational neuraminidase inhibitor that is administered intravenously, is recommended for the treatment of certain hospitalized and critically ill patients with suspected or confirmed pandemic H1N1 influenza A infection. Limited quantities of intravenous zanamivir are also available for compassionate use from its manufacturer through an emergency investigational new drug application to the FDA.

NEURAMINIDASE

Neuraminidase enzymes are glycoside hydrolase enzymes which cleave the glycosidic linkages of neuraminic acid. The most commonly known neuraminidase is the viral neuraminidase, a drug target for the prevention of influenza infection. Neuraminidases, also called sialidases, catalyze the hydrolysis of terminal Sialic acid residues from the newly formed virions and from the host cell receptors.

STRUCTURE :

SUB TYPES:

Swiss Port lists 137 types of neuraminidase from various species as on October 18, 2006. Nine subtypes of influenza neuraminidase are known; many occur only in various species of duck and chicken.

The following is a list of major classes of neuraminidase enzymes:

- Viral neuraminidase
- Bacterial neuraminidase
- Mammalian neuraminidases

TAMIFLU

Tamiflu is a medication comprised of Oseltamivir phosphate and belongs under the neuraminidase inhibitor class of drugs. The medication works by inhibiting the release of replicated flu virus cells to prevent the infection from spreading. That is because the flu spreads by replicating the virus cells, then infecting other cells. Vaccination is still the best course to prevent flu.

Tamiflu is used to stop flu from spreading. If given within two days of exposure to a flu patient, this medication can prevent the illness from affecting the person; however, when the illness had already started, the medication can only control the infection, not to stop it immediately. That means that the medication can shorten the course of sickness by at least one day. The medication must be taken for at least 10 consecutive days to ensure full recovery and to minimize viral mutations.

Side effects from Tamiflu include bronchitis, asthma, cough, diarrhea, abdominal pain, nausea, vomiting, headache, vertigo, insomnia, nosebleed, and fatigue. Vomiting and nausea are usually experienced as the patient adjusts to the medication but if these last for more than 2 days then the patient must inform the prescribing doctor. The patient should seek medical attention immediately after an allergic reaction starts – hives, rashes, breathing difficulties, and swollen face, throat, or lips.

The patient must inform the physician of any allergies to medication and kidney disorder or any medical condition. Intake of other medications must be with doctor's approval. Also, the patient must limit intake of alcoholic beverages. Patients who are pregnant or breastfeeding should not take this medication as its effects on the unborn or lactating baby are not yet known.

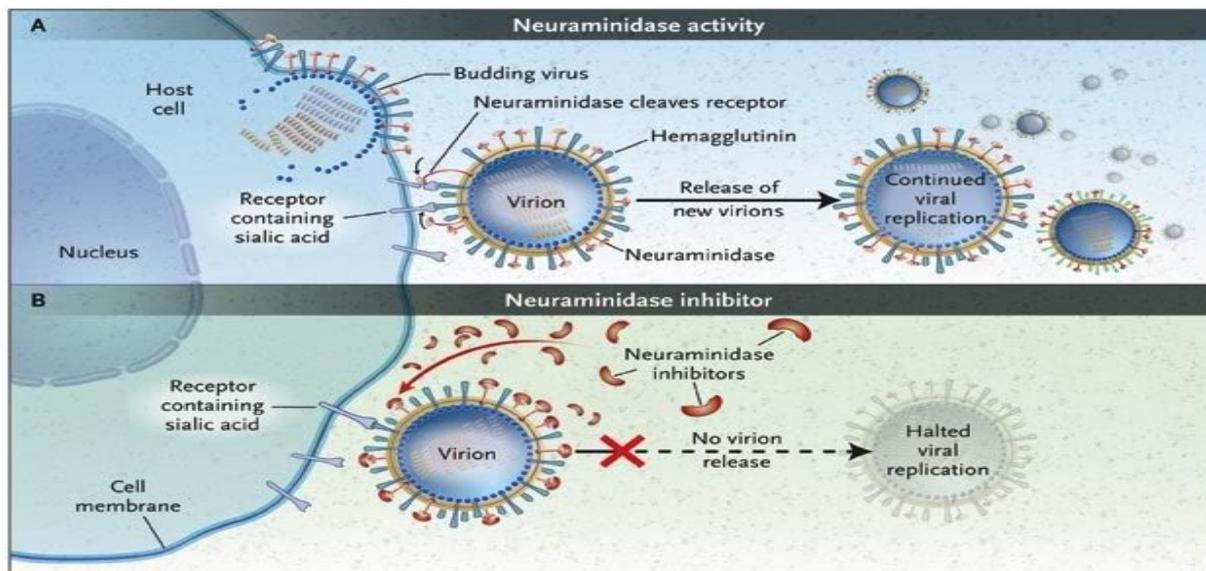
NEURAMINIDASE INHIBITORS

Neuraminidase inhibitors are useful for combating influenza infection: zanamivir administered by inhalation; oseltamivir, administered orally; and under research is peramivir administered parenterally, that is through intravenous or intramuscular injection.

The unsaturated sialic acid (N-acetylneuraminic acid) derivative 2-deoxy-2, 3-didehydro-D-N-acetylneuraminic acid (Neu5Ac2en), a sialosyl cation transition-state analogue, is believed the most potent inhibitor core template. To prepare structurally modified Neu5Ac2en derivatives may give more effective inhibitors.

Many Neu5Ac2en-based compounds have been synthesized and tested for their influenza virus sialidase inhibitory potential. For example: The 4-substituted Neu5Ac2en derivatives 4-amino-Neu5Ac2en which showed two orders of magnitude better inhibition of influenza virus sialidase than Neu5Ac2en5 and 4-guanidino-Neu5Ac2en known as Zanamivir, which is now marketed for treatment of influenza virus as a drug, have been designed by von Itzstein and coworkers.

MECHANISM OF ACTION OF NEURAMINIDASE INHIBITORS.



Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

SAFETY AND DOSAGE OF NEURAMINIDASE INHIBITORS

In general, zanamivir is well tolerated; studies to date suggest that adverse effects, primarily minor transient upper respiratory and gastrointestinal symptoms, develop in equal numbers of patients in drug and placebo groups. However, post-licensure reports indicated that zanamivir may cause cough, bronchospasm, and a reversible decrease in pulmonary function in some patients. On the other hand, a well-controlled trial demonstrated that the recommended dosages of zanamivir did not adversely affect pulmonary function in patients with respiratory disorders. If patients with pulmonary dysfunction do receive zanamivir, it is recommended that they have a fast-acting bronchodilator available and discontinue zanamivir if respiratory difficulty develops. Oseltamivir has few adverse effects when administered for either treatment or prophylaxis. The most frequent side effects are transient nausea, vomiting, and abdominal pain, which occur in approximately 5 to 10 percent of patients. Most adverse events occur only once, close to the initiation of therapy, and resolve spontaneously within one to two days. The consumption of food does not interfere with the absorption of oseltamivir and may reduce nausea and vomiting. The safety profile among elderly persons is similar to that in persons younger than 65.

RESISTANCE TO THE NEURAMINIDASE INHIBITORS

A key advantage of the neuraminidase inhibitors, and a major difference from the adamantanes, is that development of resistance is very rare. The global neuraminidase inhibitor susceptibility network (NISN), which coordinates the analysis of clinical isolates collected through the World Health Organization's surveillance network, found no influenza isolates with spontaneous resistance to neuraminidase inhibitors. Until recently, there was little emergence of resistance during treatment and no resistant viruses isolated from immunocompetent persons who received zanamivir. For oseltamivir, the published frequency of viruses that were isolated after treatment and were resistant to the drug is somewhat higher. About 0.4 percent of treated adults harbored viruses with resistant neuraminidases.

However, more resistant isolates emerged during treatment of children. One study identified resistant isolates in 4 percent of treated children, and in a recent study of children treated with oseltamivir in Japan, 9 of 50 treated children harbored viruses with mutations in the neuraminidase gene that encoded drug-resistant neuraminidase proteins. If this frequent emergence of resistant mutants is found to be a general occurrence in children, it is a serious concern, especially since children are an important source of the spread of influenza in the community. The most clinically relevant question is whether the oseltamivir-resistant viruses are transmissible and pathogenic. To date, no documented transmission of an oseltamivir-resistant virus has occurred between people. Generally, neuraminidase mutations lead to a functionally defective enzyme, which reduces the fitness of the virus and causes decreased pathogenicity, at least in animal models. However, in the ferret model, resistant variants with the same mutation that is found in some children grew well in both the index ferret and in contact animals and were readily transmitted, raising concern that some oseltamivir-resistant mutant viruses might be transmissible during an epidemic.

STRATEGIES FOR TREATMENT

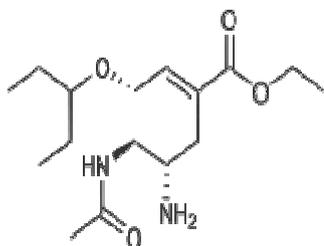
Either zanamivir or oseltamivir may be used for treatment of infection with influenza A or influenza B. Current policy issues will inform recommendations for the future use of neuraminidase inhibitors (and the availability of zanamivir, currently in short supply). When surveillance data indicate the presence of an epidemic in the community, either rapid laboratory confirmation of influenza infection or the typical constellation of influenza symptoms can signal the need for the initiation of treatment in adults; of clinical symptoms, the combination of fever and cough had the highest predictive value. Rapid diagnostic tests, only recently readily available for use in physicians' offices, use antigen, enzyme, or nucleic acid detection methods. Some assays detect only influenza A, whereas others detect both influenza A and influenza B. Results are often available in less than an hour, though the sensitivities vary considerably depending on the specific test. Improved diagnostic tests are needed, particularly for elderly people with atypical presentations who may shed little virus in their secretions. Meanwhile, the results from rapid assays should be interpreted in light of the sensitivity of the particular test along with influenza surveillance data from the community.

The neuraminidase inhibitors should be used only when symptoms have occurred within the previous 48 hours and, as discussed above, should ideally be initiated within 12 hours after the start of illness. An exception may be made for critically ill, hospitalized patients with influenza, in whom therapy can be considered even when more time has elapsed, though no controlled data are available to support this practice. Treatment that is based on clinical grounds alone, even in the absence of diagnostic tests, is particularly valuable for high-risk patients. Limiting the use of antiviral treatment to severely ill patients is illogical, since at the earliest stages, when therapy should be started, it cannot be predicted whether influenza in a patient will progress to severe illness. In the case of children, fever, cough, and other respiratory symptoms have little predictive value, since the important pediatric respiratory viral pathogens can cocirculate with influenza; thus, the focus needs to be on rapid access to laboratory diagnosis and initiation of therapy.

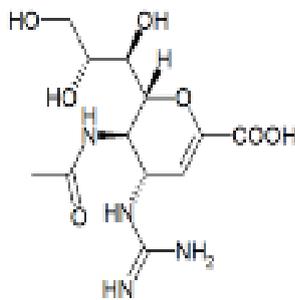
TYPES OF NEURAMINIDASE INHIBITORS

Four drugs are currently available for the treatment or prophylaxis of influenza infections: the types are (amantadine and rimantadine) and the newer class of neuraminidase

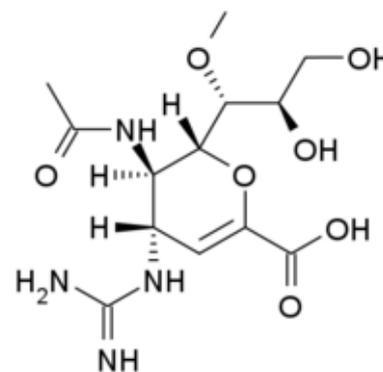
inhibitors(zanamivir[Relenza],oseltamivir[Tamiflu],andlaninamivir)



Oseltamivir



Zanamivir



Laninamivir

FLU -Influenza, commonly known as the flu, is caused by a virus which targets the body's respiratory cells and damages the lining of the respiratory tract, leading to swelling and inflammation of the tract. Influenza spreads rapidly by replicating itself inside the host cell, producing hundreds of copies of the virus in a short period. In approximately an hour the virus can destroy the host cell and propel its replications out into the body to find new host cells. For some people, the flu and its complications can be very serious, even fatal. Influenza is a viral infection more commonly known as 'the flu'. It can be a serious illness, especially in frail and elderly people. The types of flu vary from year to year but the strains of flu this year seem particular nasty with many people being affected for a week or more. As it is viral infection antibiotics are of no value in treatment unless the flu is accompanied by a bacterial infection. Until recently there have been no effective products to treat the underlying infection. Treatment has been focussed on the symptoms, leaving the body to deal with the infection. Relenza is a new product from Glaxo Wellcome which has been clinically proven to shorten the length of time flu symptoms last. It needs to be taken as soon as possible after the symptoms are noticed to get the best results (within 48hrs). It is only available on the prescription of a doctor.

(For the technically minded here's just how Relenza works;..)

Zanamivir inhibits the flu virus neuraminidase enzyme which normally cleaves the bond holding new virus particles to infected cells. Inhibiting the cleavage process stops the release of new virus particles, which lessens the spread of flu in the body. Zanamivir is effective against influenza A and B viruses. It is given as a powder inhaled via a special device and deposited on to the surface of the lungs where the flu virus replicates.

Another product in the same family as Relenza, but in tablet form has been developed by Roche and could be on the market next year.

2009 PANDEMIC H1N1 (SWINE) FLU

As of March 2010, the World Health Organization (WHO) reported 264 out of over 15,000 samples of the prevalent 2009 pandemic H1N1 (swine) flu tested worldwide have shown resistance to oseltamivir.

SEASONAL H1N1

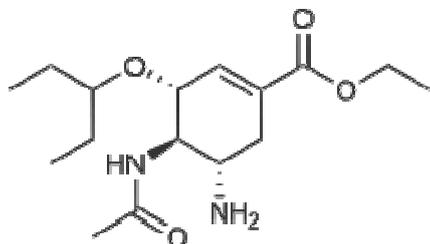
According to the CDC, oseltamivir is not very effective in the 2008 seasonal H1N1 virus anymore due to acquired resistance in 99.6% of all 2008 seasonal H1N1 strains, up from 12% in 2007-2008 flu season.

H3N2

Mutant H3N2 influenza A virus isolates resistant to oseltamivir were found in 18% of a group of 50 Japanese children treated with oseltamivir. Several explanations were proposed by the authors of the studies for the higher-than-expected resistance rate detected. First, children typically have a longer infection period, giving a

longer time for resistance to develop. Second, Kiso et al. claim to have used more rigorous detection techniques than previous studies.

OSELTAMIVIR



IUPAC NAME : ethyl (3R,4R,5S)-5-amino-4-acetamido-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate

Formula - $C_{16}H_{28}N_2O_4$

Mol. mass - 312.4 g/mol

Osetamivir is a prodrug, a (relatively) inactive chemical which is converted into its active form by metabolic process after it is taken into the body. It was the first orally active neuraminidase inhibitor commercially developed.

MECHANISM OF ACTION

The prodrug Osetamivir is itself not virally effective; however, once in the liver, it is converted by natural chemical processes, hydrolysed hepatically to its active metabolite, the free carboxylate of osetamivir. Osetamivir is a neuraminidase inhibitors serving as a competitive inhibitor towards sialic acid, found on the surface proteins of normal host cells. By blocking the activity of the viral neuraminidase enzyme, osetamivir prevents new viral particles from being released by infected cells.

ANTIVIRAL ACTIVITY

The antiviral activity of osetamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of osetamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) were in the range of 0.0008 μ M to > 35 μ M and 0.004 μ M to > 100 μ M, respectively (1 μ M=0.284 μ g/mL). The relationship between the antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

PHARMACOKINETICS

Absorption and Bioavailability Osetamivir is readily absorbed from the gastrointestinal tract after oral administration of osetamivir phosphate and is extensively converted predominantly by hepatic esterases to osetamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as osetamivir carboxylate. Exposure to osetamivir is less than 5% of the total exposure after oral dosing (see Table 1).
Table 1: Mean (% CV) Pharmacokinetic Parameters of Osetamivir and Osetamivir Carboxylate After a Multiple 75 mg Capsule Twice Daily Oral Dose (n=20)

Parameter	Osetamivir	Osetamivir Carboxylate
C max (ng/mL)	65.2 (26)	348 (18)
AUC _{0-12h} (ng·h/mL)	112 (25)	2719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily. Coadministration with food has no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

DISTRIBUTION

The volume of distribution (V_{ss}) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 and 26 liters.

The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

METABOLISM

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms.

ELIMINATION

Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration, indicating that tubular secretion occurs, in addition to glomerular filtration. Less than 20% of an oral radiolabeled dose is eliminated in feces.

VETERINARY USE

There have been anecdotal reports of oseltamivir reducing disease severity and hospitalization time in canine parovirus infection. The drug may limit the ability of the virus to invade the crypt cells of the small intestine and decrease gastrointestinal bacteria colonization and toxin production.

USES:

Oseltamivir is used to treat symptoms caused by the flu virus (influenza). It helps make the symptoms (e.g., stuffy nose, cough, sore throat, fever/chills, aches, tiredness) less severe and shortens the recovery time by 1-2 days. This medication is also used to prevent the flu if you have been exposed to someone who already has the flu (e.g., sick household member).

This medication works by stopping the flu virus from growing. It is not a substitute for the flu vaccine. Oseltamivir should not be used in infants younger than 1 year of age.

POSSIBLE SIDE EFFECTS

Common Adverse drug reaction (ADRs) associated with oseltamivir therapy (occurring in over 1% of clinical trial participants) include: nausea, vomiting, diarrhea, abdominal pain, and headache. Rare ADRs include: hepatitis and elevated liver enzyme, rash, allergic reactions including anaphylaxis.

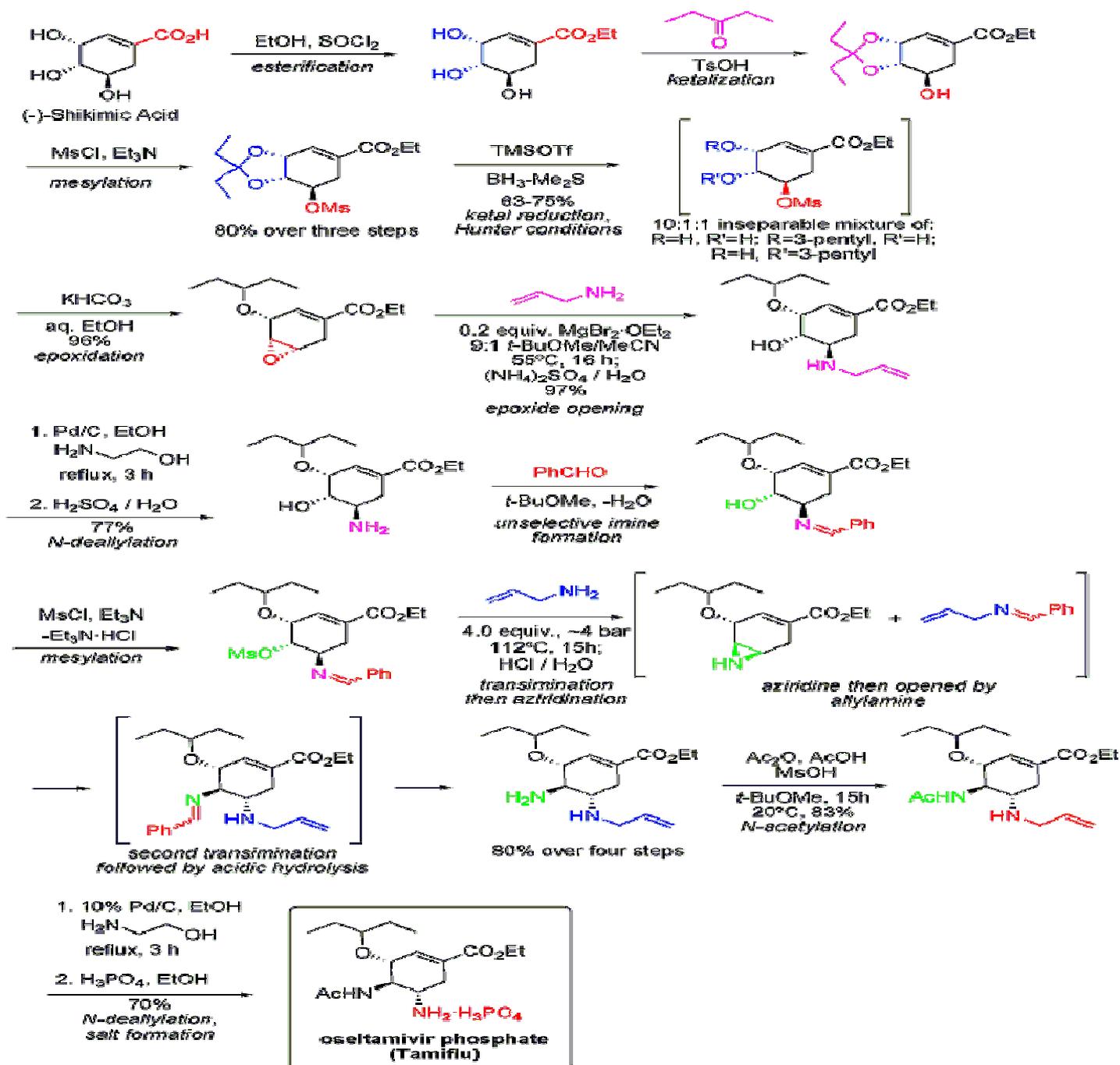
Various other ADRs have been reported in postmarketing surveillance including: toxic epidermal necrosis, cardiac arrhythmia, seizure, confusion, aggravation of diabetes, and haemorrhagic colitis. There are concerns that oseltamivir may cause dangerous psychological, neuropsychiatric side effects including self-harm in some users. Nausea and vomiting may occur as your body adjusts to this medication and usually go away after 1-2 days. Dizziness may also occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly.

RESISTANCE

Mutations conferring resistance are single amino acid residue substitutions (His274Tyr) in the neuraminidase enzyme

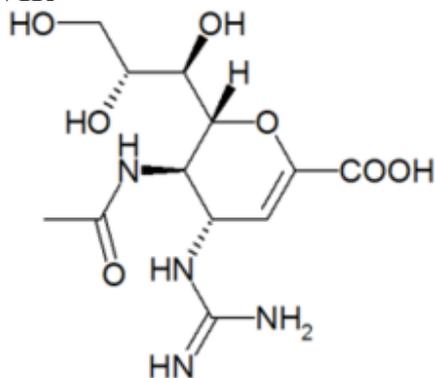
SYNTHESIS

Aqueous solubility of oseltamivir in form of phosphate salt is 588 mg/ml at 25°C. The current production method features a number of reaction steps, two of which involve potentially hazardous azides. A reported azide-free Roche synthesis of tamiflu is summarised graphically below:



The synthesis commences from naturally available (–)-shikimic acid. The 3,4-pentylidene acetal mesylate is prepared in three steps: esterification with ethanol and thionyl chloride; ketalization with p-toluenesulfonic acid and 3-pentanone; and mesylation with triethylamine and methanesulfonyl chloride. Reductive opening of the ketal under modified Hunter conditions^[5] in dichloromethane yields an inseparable mixture of isomeric mesylates. The corresponding epoxide is formed under basic conditions with potassium bicarbonate. Using the inexpensive Lewis acid magnesium bromide diethyl etherate (commonly prepared fresh by the addition of magnesium turnings to 1,2-dibromoethane in benzene:diethyl ether), the epoxide is opened with allyl amine to yield the corresponding 1,2-amino alcohol. The water-immiscible solvents methyl tert-butyl ether and acetonitrile are used to simplify the workup procedure, which involved stirring with 1 M aqueous ammonium sulfate. Reduction on palladium, promoted by ethanolamine, followed by acidic workup yielded the deprotected 1,2-aminoalcohol. The aminoalcohol was converted directly to the corresponding allyl-diamine in an interesting cascade sequence that commences with the unselective imination of benzaldehyde with azeotropic water removal in methyl tert-butyl ether. Mesylation, followed by removal of the solid byproduct triethylamine hydrochloride, results in an intermediate that was poised to undergo aziridination upon transimination with another equivalent of allylamine. With the liberated methanesulfonic acid, the aziridine opens cleanly to yield a diamine that immediately undergoes a second transimination. Acidic hydrolysis then removed the imine. Selective acylation with acetic anhydride (under buffered conditions, the 5-amino group is protonated owing to a considerable difference in pK_a, 4.2 vs 7.9, preventing acetylation) yields the desired N-acetylated product in crystalline form upon extractive workup. Finally, deallylation as above, yielded the freebase of oseltamivir, which was converted to the desired oseltamivir phosphate by treatment with phosphoric acid. The final product is obtained in high purity (99.7%) and an overall yield of 17-22% from (–)-shikimic acid. It is noted that the synthesis avoids the use of potentially explosive azide reagents and intermediates; however, the synthesis actually used by Roche uses azides. Roche has other routes to oseltamivir that do not involve the use of (–)-shikimic acid as a chiral pool starting material, such as a Diels-Alder route involving furan and ethyl acrylate or an isophthalic acid route, which involves catalytic hydrogenation and enzymatic desymmetrization

ZANAMIVIR



IUPAC NAME : (2R,3R,4S)- 4-[(diaminomethylidene)amino]- 3-acetamido- 2-[(1R,2R)- 1,2,3-trihydroxypropyl]- 3,4-dihydro- 2H-pyran- 6-carboxylic acid.

Formula : C₁₂H₂₀N₄O₇

Mol. mass : 332.31 g/mol

Zanamivir was discovered in 1989 by scientists led by Mark von Itzstein, at the Victorian College of Pharmacy, Monash University, in collaboration with the CSIRO and scientists at Glaxo, UK. Zanamivir was the first of the neuraminidase inhibitor. Zanamivir (INN) is a neuraminidase inhibitor used in the treatment and prophylaxis of Influenza virus A and Influenza virus B. It is currently marketed by GlaxoSmithKline under the trade name

Relenza It was also known, as far back as 1974, that 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA), a sialic acid analogue, was an inhibitor of neuraminidase. Sialic acid (N-acetyl neuraminic acid, NANA), the substrate of neuraminidase, is itself a mild inhibitor of the enzyme, but the dehydrated derivative DANA, a transition-state analogue, is a better inhibitor.

MECHANISM OF ACTION

Zanamivir is a potent and highly selective inhibitor of neuraminidase, the influenza virus surface enzyme. Viral neuraminidase aids the release of newly formed virus particles from infected cells, and may facilitate access of virus through mucus to epithelial cell surfaces, to allow viral infection of other cells. The inhibition of this enzyme is reflected in both in vitro and in vivo activity against influenza A and B virus replication, and encompasses all of the known neuraminidase subtypes of influenza A viruses.

The activity of zanamivir is extracellular. It reduces the propagation of both influenza A and B viruses by inhibiting the release of infectious influenza virions from the epithelial cells of the respiratory tract. Influenza viral replication is confined to the superficial epithelium of the respiratory tract. The efficacy of topical administration of zanamivir to this site has been confirmed in clinical studies. Clinical trial data have shown that treatment of acute influenza infections with zanamivir produces reductions in virus shedding from the respiratory tract compared to placebo without any detectable emergence of virus with reduced susceptibility to zanamivir.

BIOLOGICAL ACTIVITY

Zanamivir is specifically for the treatment of infections caused by Influenzavirus A and Influenzavirus B. Zanamivir works by binding to the active site of the neuraminidase protein, rendering the influenza virus unable to escape its host cell and infect others. It is also an inhibitor of influenza virus replication in vitro and in vivo. In clinical trials it was found that zanamivir was able to reduce the time to symptom resolution by 1.5 days if therapy was started within 48 hours of the onset of symptoms

PHARMACOKINETICS

Zanamivir is not bioavailable orally and is marketed as a dry powder for inhalation. It is delivered directly to the respiratory tract through an inhaler (Diskhaler, Glaxo Wellcome) that holds small pouches of the drug. Zanamivir is highly concentrated in the respiratory tract; 10 to 20 percent of the active compound reaches the lungs, and the rest is deposited in the oropharynx. Five to 15 percent of the total dose is absorbed and excreted in the urine, resulting in a bioavailability of 2 percent, a feature that is potentially advantageous in situations in which a systemic drug is undesirable. The concentration of the drug in the respiratory tract has been estimated to be more than 1000 times as high as the 50 percent inhibitory concentration (IC₅₀) for neuraminidase; in addition, the inhibitory effect starts within 10 seconds — two favorable features in terms of reducing the likelihood of emergence of drug-resistant variant viruses.

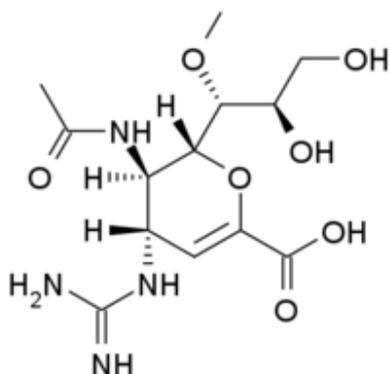
SIDE EFFECTS

The bioavailability of zanamivir is 2%. After inhalation, zanamivir is concentrated in the lungs and oropharynx, where up to 15% of the dose is absorbed and excreted in urine.

Dosing is limited to the inhaled route. This restricts its usage, as treating asthmatics could induce bronchospasm. The U.S. Food and Drug Administration (FDA) has issued a Public Health Advisory warning that it has received some reports of respiratory problems following inhalation of zanamivir by patients with underlying asthma or chronic obstructive pulmonary disease. The zanamivir package insert contains precautionary information regarding risk of bronchospasm in patients with respiratory disease.

MARKETED DRUG: RELENZA

LANINAMIVIR



IUPAC NAME : (4S,5R,6R)-5-acetamido-4-carbamimidamido-6-[(1R,2R)-3-hydroxy-2-methoxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid.

Formula : C₁₃H₂₂N₄O₇

Mol. Mass : 346.33638 g/mol

Laninamivir (CS-8958) is a neuraminidase inhibitor which is being researched for the treatment and prophylaxis of Influenza virus A & Influenza virus B. It is currently in phase III trials.

Conclusion

The neuraminidase inhibitors act by blocking activity of viral neuraminidase enzyme & prevent particles released from infected cells. Various neuraminidase inhibitors are used for antiviral activity & also these agents are used in the treatment of influenza & swine flu.

The agents which are used are oseltamivir, zanamivir & the other agents like laninamivir, peramivir are under clinical research. Many attempts are in progress to find out effective antiviral agents for Swine Flu.

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