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PATENT HIGHLIGHT

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Influenza RNA-Dependent RNA Polymerase (RdRp) Inhibitors: Potential New Therapy for Influenza Treatment

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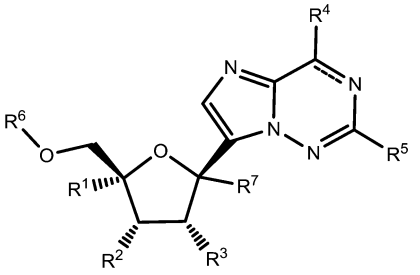
Title:	2′-Substituted Carba-Nucleoside Analogues for Antiviral Treatment		
Patent Application Number:	WO 2013/138236 A1	**Publication date:**	19 September 2013
Priority Application:	US 61/610,411	**Priority date:**	13 March 2012
Inventors:	Clarke, M. O. H.		
Assignee Company:	Gilead Sciences, Inc.; 333 Lakeside Drive, Foster City, CA 94404, USA		
Disease Area:	Influenza (Flu)	**Biological Target:**	Influenza RNA-dependent RNA polymerase (RdRp)

Summary: The invention in this patent application relates to 2′-substituted carba-nucleoside analogues represented generally by formula (I). These compounds are inhibitors of RNA-dependent RNA polymerase (RdRp) of the *Orthomyxoviridae* family of viruses that include influenza A and B viruses and may potentially provide a treatment for influenza infections.

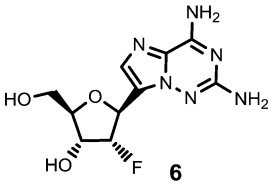
The influenza virus is a single-strand, negative-sense, segmented RNA virus of the *Orthomyxovirus* family that uses RNA-dependent RNA polymerase (RdRp) to synthesize the viral RNAs needed for replication. Some new anti-influenza agents such as the experimental drug favipiravir and the compounds of formula (I) described in this patent application introduce a promising novel mechanism of action for the treatment of influenza infections. These compounds act by inhibiting the action of influenza RdRp and target the virus replication process to stop or slow down its replication. This may potentially provide better alternative treatment for influenza virus infections with low potential for emergence of drug resistance.

Important Compound Classes:



Formula (I)

Key Structures: Representative examples of formula (I) compounds:



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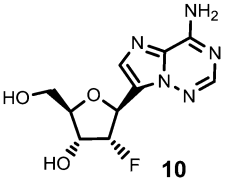

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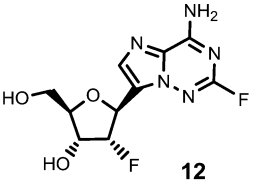

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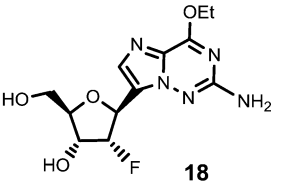

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Biological Assay:

- Influenza RNA Polymerase Inhibition (IC_{50}) Assay
- Normal Human Bronchial/Tracheal Epithelial Cell Influenza Infection Assay (EC_{50})

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Biological Data: Data from normal human bronchial/tracheal epithelial cell influenza infection assay for compounds **6**, **10**, **12**, and **18** (structures above)

Compound	Infl A PC/1/73 EC_{50} (μM)	Infl B Lee/40 EC_{50} (μM)
6	21	51
10	0.9	0.9
12	>100	>100
18	>200	>200

Additional Information: The most severe influenza infections are caused by type A virus. Influenza A virus infects humans and other species such as birds and pigs; it has caused all known pandemics and most epidemics. Type A virus undergoes sudden genetic changes called antigenic shifts associated with changes in the hemagglutinin (H) and neuraminidase (N) proteins, and such changes introduce new strains of the virus. Scientists have identified 15 hemagglutinin (H1 to H15) and 9 neuraminidase (N1 to N9) subtypes on type A influenza virus. The type A virus is named according to the hemagglutinin and neuraminidase subtypes, e.g., H1N1, H1N2, H3N2, etc.

Influenza is a highly contagious acute respiratory infection that infects 10−20% of the population annually. It is associated with significant morbidity and mortality in high-risk patient populations and responsible for >200,000 hospitalizations and 20,000−35,000 deaths annually in the US alone. Globally it results in 250,000−500,000 deaths annually, and it causes major pandemics. The most devastating is the 1918−19 pandemic (Spanish Flu) caused by H1N1 virus and resulted in an estimated 50−100 million deaths.

Available influenza therapy

- Vaccination is the first known influenza therapy developed in the 1940s; it is still the primary method for prophylactic protection from infection with influenza virus. However, the production of vaccines requires 6 to 8 months and the vaccine should be administered about 4 weeks before infection to be effective. Vaccines lose effectiveness quickly due to viral mutations and become ineffective against new pandemic forms.
- The antiviral drugs amantadine and rimantadine block the ion channel M2-protein responsible for uncoating of the virus. They are mostly ineffective drugs that suffer from virus resistance and cause severe side effects.
- Neuraminidase inhibitors (NAIs) are currently the most effective direct acting drugs approved to treat influenza A and B virus infections. NAIs act by blocking the enzyme neuraminidase, which cleaves the connection to sialic acid to free the emerging viruses after replication. Without cleaving the connections to sialic acid, viruses clump together and lose the ability to spread to other cells. Known neuraminidase inhibitors include Relenza, Tamiflu, and Peramivir. Recently, some influenza virus strains have developed resistance with the use of NAIs.

Some experimental influenza treatments

- Combination therapy including the triple-combination antiviral drug (TCAD) regimen containing amantadine, oseltamivir, and ribavirin and the double-combination of favipiravir and oseltamivir.[4]
- Inhibitors of influenza RNA-dependent RNA polymerase (RdRp) such as favipiravir and the compounds of formula (I) described in this patent application.
- Host-targeted approach: the sialidase fusion protein, DAS181 effectively cleaves sialic acid receptors used by both human and influenza viruses in the respiratory epithelial cells. DAS181 has shown potent inhibition of virus replication with EC_{50} in the range of 0.04 to 0.9 nM.[5]

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Notes
The authors declare no competing financial interest.