

References

Reviews and General Articles

1. Calfee, D.P.; Hayden, F.G. New Approaches to Chemotherapy: Neuraminidase Inhibitors. *Drugs* **1998**, *56*, 537-553.
2. Colman, P.M.; Smith, B.J. Specificity and Promiscuity in Protein-Ligand and Protein-Protein Interactions. *Aust. J. Chem.* **2003**, *56*, 763-767.
3. Dreitlein, W.B.; Maratos, J.; Brocavich, J. Zanamivir and Oseltamivir: Two New Options for the Treatment and Prevention of Influenza. *Clin Ther.* **2001**, *23*, 327-355.
4. Kati, W.M.; Saldivar, A.S.; Mohamadi, F.; Sham, H.L.; Laver, W.G.; Kohlbrenner, W.E. GS4071 is a Slow-Binding Inhibitor of Influenza Neuraminidase from Both A and B Strains. *Biochemical and Biophysical Research Communications* **1998**, *244*, 408-413.
5. Laver, G.; Garman, E. The Origin and Control of Pandemic Influenza. *Science* **2001**, *293*, 1776-1777.
6. Masukawa, K. M.; Kollman, P.A.; Kuntz, I.D. Investigation of Neuraminidase-Substrate Recognition Using Molecular Dynamics and Free Energy Calculations. *J. Med. Chem.* **2003**, *46*, 5628-5637.
7. McNicholl, I.R.; McNicholl, J.J. Neuraminidase Inhibitors: Zanamivir and Oseltamivir. *The Annals of Pharmacotherapy* **2001**, *35*, 57-70.
8. Oxford, J.S.; Lambkin, R. Targeting Influenza Virus Neuraminidase: A New Strategy for Antiviral Therapy. *Drug Design Today* **1998**, *3*, 448-456.
9. Oxford, J.S.; Novelli, P.; Sefton, A.; Lambkin, R. New Millennium Antivirals Against Pandemic and Epidemic Influenza: The Neuraminidase Inhibitors. *Antiviral Chem. Chemother.* **2002**, *13*, 205-217.
10. Roberts, N. A. Anti-influenza Drugs and Neuraminidase Inhibitors. *Progress in Drug Research* **2001**, *56*, 198-237.
11. Steindl, T.; Langer, T. Influenza Virus Neuraminidase Inhibitors: Generation and Comparison of Structure-based and Common Feature Pharmacophore Hypotheses and Their Application in Virtual Screening. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1849-1856.
12. Stoll, V.; Stewart, K.D.; Maring, C.J.; Muchmore, S.; Giranda, V.; Gu, Y.Y.; Wang, G.; Chen, Y.; Sun, M.; Zhao, C.; Kennedy, A.L.; Madigan, D.L.; Xu, Y.; Saldivar, A.; Kati, W.; Laver, G.; Sowin, T.; Sham, H.L.; Greer, J.; Kempf, D. Influenza

Neuraminidase Inhibitors: Structure-Based Design of a Novel Inhibitor Series. *Biochemistry* **2003**, *42*, 718-727.

13. Varghese, J.N.; Smith, P.W.; Sollis, S.L.; Blick, T.J.; Sahasrabudhe, A.; McKimm-Breschkin, J.L.; Colman, P.M. Drug Design Against a Shifting Target: A Structural Basis for the Resistance to Inhibitors in a Variant of Influenza Virus Neuraminidase. *Structure* **1998**, *6*, 735-746.
14. Wade, R.C. "Flu" and Structure-Based Drug Design. *Structure* **1997**, *5*, 1139-1145.
15. Wang, T.; Wade, R.C. Comparative Binding Energy (COMBINE) Analysis of Influenza Neuraminidase-Inhibitor Complexes. *J. Med. Chem.* **2001**, *44*, 961-971.

Neuraminidase Enzyme

16. Blok, J.; Air, G.M. Variation in the Membrane-Insertion and "Stalk" Sequences in Eight Subtypes of Influenza Type A Virus Neuraminidase. *Biochemistry* **1982**, *21*, 4001-4007.
17. Colman, P.M.; Varghese, J.N.; Laver, W.G. Structure of the Catalytic and Antigenic Sites in Influenza Virus Neuraminidase. *Nature (London)* **1983**, *303*, 41-44.
18. Janakiraman, M.N.; White, C.L.; Laver, W.G.; Air, G.M.; Luo, M. Structure of Influenza Virus Neuraminidase B/Lee/40 Complexed with Sialic Acid and a Dehydro Analog at 1.8-Å Resolution: Implications for the Catalytic Mechanism. *Biochemistry* **1994**, *33*, 8172-8179.
19. Lentz, M.R.; Webster, R.G.; Air, G.M. Site-Directed Mutation of the Active Site of Influenza Neuraminidase and Implications for the Catalytic Mechanism. *Biochemistry* **1987**, *26*, 5351-5358.
20. Sivasubramanian, N.; Nayak, D.P. Mutational Analysis of the Signal-Anchor Domain of Influenza Virus Neuraminidase. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 1-5.
21. Varghese, J.N.; Laver, W.G.; Colman, P.M. Structure of the Influenza Virus Glycoprotein Antigen Neuraminidase at 2.9 Å Resolution. *Nature (London)* **1983**, *303*, 35-40.

Zanamivir (Relenza®)

22. Bamford, M.J.; Pichel, J.C.; Husman, W.; Patel, B.; Storer, R.; Weir, N.G. Synthesis of 6-, 7- and 8-carbon Sugar Analogues of Potent Anti-Influenza 2,3-didehydro-2,3-dideoxy-*N*-acetylneuraminic Acid Derivatives. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1181-1187.

23. Chandler, M.; Bamford, M.J.; Conroy, R.; Lamont, B.; Patel, B.; Patel, V.K.; Steeples, I.P.; Storer, R.; Weir, N. G.; Wright, M.; Williamson, C. Synthesis of the Potent Influenza Neuraminidase Inhibitor 4-guanidino Neu5Ac2en. X-ray Molecular Structure of 5-acetamido-4-amino-2,6-anhydro-3,4,5-trideoxy-D-erythro-L-glucononic acid. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1173-1180.
24. GlaxoSmithKline. Relenza[®] (Zanamivir for Inhalation): Prescribing Information. **2003**, 1-13.
25. von Itzstein, M.; Wu, W-Y.; Kok, G.B.; Pegg, M.S.; Dyason, J.C.; Jin, B.; Phan, T.V.; Smythe, M.L.; White, H.F.; Oliver, S.W.; Colman, P.M.; Varghese, J.N.; Ryan, D.M.; Woods, J.M.; Bethell, R.C.; Hotham, V.J.; Cameron, J.M.; Penn, C.R. Rational Design of Potent Sialidase-based Inhibitors of Influenza Virus Replication. *Nature (London)* **1993**, 363, 418-423.
26. von Itzstein, M.; Dyason, J.C.; Oliver, S.W.; White, H.F.; Wu, W-Y.; Kook, G.B.; Pegg, M.S. A Study of the Active Site of Influenza Virus Sialidase: An Approach to the Rational Design of Novel Anti-Influenza Drugs. *J. Med. Chem.* **1996**, 39, 388-391.

Oseltamivir (Tamiflu[®])

27. Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U.; The Synthetic Development of the Anti-Influenza Neuraminidase Inhibitor Oseltamivir Phosphate (Tamiflu[®]): A Challenge for Synthesis & Process Research. *Chimia* **2004**, 58, 621-629.
28. Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffman, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckler-Stäbler, O.; Trussardi, R.; Zwahlen. Industrial Synthesis of the Key Precursor in the Synthesis of the Anti-Influenza Drug Oseltamivir Phosphate (Ro 64-0796/002, GS-4104-02): Ethyl (3R,4S,5S)-4,5-epoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate. *Org. Process. Res. Dev.* **1999**, 3, 266-274.
29. Harrington, P.J.; Brown, J.D.; Foderaro, T.; Hughes, R.C. Research and Development of a Second-Generation Process for Oseltamivir Phosphate, Prodrug for a Neuraminidase Inhibitor. *Org. Process. Res. Dev.* **2004**, 8, 86-91.
30. Kim, C.U.; Lew, W.; Williams, M.A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M.S.; Mendel, D.B.; Tai, C.Y.; Laver, W.G.; Stevens, R.C. Influenza Neuraminidase Inhibitors Possessing a Novel Hydrophobic Interaction in the Enzyme Active Site: Design, Synthesis, and Structural Analysis of Carbocyclic Sialic Acid Analogues with Potent Anti-Influenza Activity. *J. Am. Chem. Soc.* **1997**, 119, 681-690.

31. Kim, C.U.; Lew, W.; Williams, M.A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P.A.; Mendel, D.B.; Laver, W.G.; Stevens, R.C. Structure-Activity Relationship Studies of Novel Carbocyclic Influenza Neuraminidase Inhibitors. *J. Med. Chem.* **1998**, *41*, 2451-2460.
32. Lew, W.; Williams, M.A.; Mendel, D.B.; Escarpe, P.A.; Kim, C.U. C₃-Thia and C₃-Carba Isosteres of a Carbocyclic Influenza Neuraminidase Inhibitor, (3*R*,4*R*,5*S*)-4-Acetamido-5-Amino-3-Propoxy-1-Cyclohexene-1-Carboxylic Acid. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1843-1846.
33. Lew, W.; Escarpe, P.A.; Mendel, D.B.; Sweeny, D.J.; Kim, C.U.; Stereospecific Synthesis of a GS4104 Metabolite: Determination of Absolute Stereochemistry and Influenza Neuraminidase Inhibitory Activity. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2811-2814.
34. Lew, W.; Wu, H.; Mendel, D.B.; Escarpe, P.A.; Chen, X.; Laver, W.G.; Graves, B.J.; Kim, C.U. A New Series of C₃-Aza Carbocyclic Influenza Neuraminidase Inhibitors: Synthesis and Inhibitory Activity. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3321-3324.
35. Roche Pharmaceuticals. Tamiflu® (Oseltamivir Phosphate): Complete Product Information. **2004**, 1-17.
36. Roche Pharmaceuticals. Backgrounder: Tamiflu®. **2005**. 1-3.
37. Roche Pharmaceuticals. Factsheet Tamiflu. **2005**. 1-5.
38. Rohloff, J.C.; Kent, K.M.; Postich, M.J.; Becker, M.W.; Chapman, H.H.; Kelly, D.E.; Lew, W.; Louie, M.S.; McGee, L.R.; Prisbe, E.J.; Schultze, L.M.; Yu, R.H.; Zhang, L. Practical Total Synthesis of the Anti-Influenza Drug GS-4104. *J. Org. Chem.* **1998**, *63*, 4545-4550.
39. Sidwell, R.W.; Huffman, J.H.; Barnard, D.L.; Bailey, K.W.; Wong, M-H.; Morrison, A.; Syndergaard, T.; Kim, C.U. Inhibition of Influenza Virus Infections in Mice by GS4104, an Orally Effective Influenza Virus Neuraminidase Inhibitor. *Antiviral Res.* **1998**, *37*, 107-120.
40. Williams, M.; Bischofberger, N.; Swaminathan, S.; Kim, C.U. Synthesis and Influenza Neuraminidase Inhibitory Activity of Aromatic Analogues of Sialic Acid. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2251-2254.
41. Williams, M.A.; Lew, W.; Mendel, D.B.; Tai, C.Y.; Escarpe, P.A.; Laver, W.G.; Stevens, R.C.; Kim, C.U. Structure-Activity Relationships of Carbocyclic Influenza Neuraminidase Inhibitors. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1837-1842.

42. Zhang, L.; Williams, M.A.; Mendel, D.B.; Escarpe, P.A.; Kim, C.U. Synthesis and Activity of C₂-Substituted Analogs of Influenza Neuraminidase Inhibitor GS 4071. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1847-1850.
43. Zhang, L.; Williams, M.A.; Mendel, D.B.; Escarpe, P.A.; Chen, X.; Wang, K-Y.; Graves, B.J.; Lawton, G.; Kim, C.U. Synthesis and Evaluation of 1,4,5,6-tetrahydropyridazine Derivatives of Neuraminidase Inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1751-1756.

Peramivir (BCX-1812)

44. Babu, Y.S.; Chand, P.; Bantia, S.; Kotian, P.; Dehghani, A.; El-Kattan, Y.; Lin, T-H.; Hutchison, T.L.; Elliott, A.J.; Parker, C.D.; Ananth, S.L.; Horn, L.L.; Laver, G.W.; Montgomery, J.A. BCX-1812 (RWJ-270201): Discovery of a Novel, Highly Potent, Orally Active, and Selective Influenza Neuraminidase Inhibitor through Structure-based Drug Design. *J. Med. Chem.* **2000**, *43*, 3482-3486.
45. Bantia, S.; Ghate, A.A.; Ananth, S.L.; Babu, Y.S.; Air, G.M.; Walsh, G.M. Generation and Characterization of a Mutant of Influenza A Virus Selected with the Neuraminidase Inhibitor BCX-140. *Antimicrob. Chem. Chemother.* **1998**, *42*, 801-807.
46. BioCryst Pharmaceuticals. Company Press Release. **2002**, 1-2.
47. Chand, P.; Kotian, P.L.; Dehghani, A.; El-Kattan, Y.; Lin, T-H.; Hutchison, T.L.; Babu, Y.S.; Bantia, S.; Elliott, A.J.; Montgomery, J.A. Systematic Structure-based Design and Stereoselective Synthesis of Novel Multisubstituted Cyclopentane Derivatives with Potent Antiinfluenza Activity. *J. Med. Chem.* **2001**, *44*, 4379-4392.
48. Chand, P.; Babu, Y.S.; Bantia, S.; Rowland, S.; Dehghani, A.; Kotian, P.L.; Hutchinson, T.L.; Ali, S.; Brouillette, W.; El-Kattan, Y.; Lin, T-H. Syntheses and Neuraminidase Inhibitory Activity of Multisubstituted Cyclopentane Amide Derivatives. *J. Med. Chem.* **2004**, *47*, 1919-1929.

Pandemic Influenza

49. Centers for Disease Control and Prevention. Fact Sheet: Information About Influenza Pandemics. **2005**, 1-4.
50. U.S. Department of Health and Human Services. HHS Pandemic Influenza Plan. **2005**.
51. United States of America Homeland Security Council. National Strategy for Pandemic Influenza. **2005**, 1-12.
52. World Health Organization. Fact Sheet: Influenza. **2003**, 1-3.

53. World Health Organization. Antiviral Drugs: Their Role During a Pandemic. **2005**.

Additional References

ABT-675

54. Barnes, D.M.; McLaughlin, M.A.; Oie, T.; Rasmussen, M.W.; Stewart, K.D.; Wittenberger, S.J. Synthesis of an Influenza Neuraminidase Inhibitor Intermediate via a Highly Diastereoselective Coupling Reaction. *Org. Lett.* **2002**, *4*, 1427-1430.
55. DeGoey, D.A.; Chen, H.-J.; Flosi, W.J.; Grampovnik, D.J.; Yeung, C.M.; Klein, L.L.; Kempf, D.J. Enantioselective Synthesis of Antiinfluenza Compound A-315675. *J. Org. Chem.* **2002**, *67*, 5445-5453.
56. Maring, C.J.; Stoll, V.S.; Zhao, C.; Sun, M.; Krueger, A.C.; Stewart, K.D.; Madigan, D.L.; Kati, W.M.; Xu, Y.; Carrick, R.J.; Montgomery, D.A.; Kempf-Grote, A.; Marsh, K.C.; Molla, A.; Steffy, K.R.; Sham, H.L.; Laver, W.G.; Gu, Y.-G.; Kempf, D.J.; Kohlbrenner, W.E. Structure-Based Characterization and Optimization of Novel Hydrophobic Binding Interactions in a Series of Pyrrolidine Influenza Neuraminidase Inhibitors. *J. Med. Chem.* **2005**, *48*, 3980-3990.
57. Wang, G.T.; Chen, Y.; Wang, S.; Gentles, R.; Sowin, T.; Kati, W.; Muchmore, S.; Giranda, V.; Stewart, K.; Sham, H.; Kempf, D.; Laver, W.G. Design, Synthesis, and Structural Analysis of Influenza Neuraminidase Inhibitors Containing Pyrrolidine Cores. *J. Med. Chem.* **2001**, *44*, 1192-1201.

Benzoic Acid-Derived Inhibitors

58. Atigaada, V.R.; Brouillette, W.J.; Duarte, F.; Ali, S.M.; Babu, Y.S.; Bantia, S.; Chand, P.; Chu, N.; Montgomery, J.A.; Walsh, D.A.; Sudbeck, E.A.; Finley, J.; Luo, M.; Air, G.M.; Laver, G.W. Potent Inhibition of Influenza Sialidase by a Benzoic Acid Containing a 2-Pyrrolidinone Substituent. *J. Med. Chem.* **1999**, *42*, 2332-2343.
59. Brouillette, W.J.; Atigadda, V.R.; Luo, M.; Air, G.M.; Babu, Y.S.; Bantia, S. Design of Benzoic Acid Inhibitors of Influenza Neuraminidase Containing A Cyclic Substitution for the *N*-Acetyl Grouping. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1901-1906.
60. Chand, P.; Babu, Y.S.; Bantia, S.; Chu, N.; Cole, L.B.; Kotian, P.L.; Laver, W.G.; Montgomery, J.A.; Pathak, V.P.; Petty, S.L.; Shrout, D.P.; Walsh, D.A.; Walsh, G.M. Design and Synthesis of Benzoic Acid Derivatives as Influenza Neuraminidase Inhibitors Using Structure-Based Drug Design. *J. Med. Chem.* **1997**, *40*, 4030-4052.

61. Chand, P.; Kotian, P.L.; Morris, P.E.; Bantia, S.; Walsh, D.A.; Babu, Y.S. Synthesis and Inhibitory Activity of Benzoic Acid and Pyridine Derivatives on Influenza Neuraminidase. *Bioorg. Med. Chem.* **2005**, *13*, 2665-2678.

Viral Resistance to Neuraminidase Inhibitors

62. Ives, J.A.L.; Carr, J.A.; Mendel, D.B.; Tai, C.Y.; Lambkin, R.; Kelly, L.; Oxford, J.S.; Hayden, F.G.; Roberts, N.A. The H274Y Mutation in the Influenza A/H1N1 Neuraminidase Active Site Following Oseltamivir Phosphate Treatment Leave Virus Severely Compromised Both in Vitro and In Vivo. *Antiviral Res.* **2002**, *55*, 307-317.

63. Mishin, V.P.; Hayden, F.G.; Gubareva, L.V. Susceptibilities of Antiviral-Resistant Influenza Viruses to Novel Neuraminidase Inhibitors. *Antimicrob. Agents Chemother.* **2005**, *49*, 4515-4520.

64. Smith, B.J.; McKimm-Breshkin, J.L.; McDonald, M.; Fernley, R.T.; Varghese, J.N.; Colman, P.M. Structural Studies of the Resistance of Influenza Virus Neuraminidase to Inhibitors. *J. Med. Chem.* **2002**, *45*, 2207-2212.