# The Emergence of Chiral Drugs

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## ABSTRACT

**The emerging market of enantio-pure drugs has provided the general public with some of the most efficacious remedies. The ability to treat ailments effectively has benefited from recent developments in the area of chiral drug technologies. As such, three recently developed commercial drugs which have had marked impact in their respective therapeutic areas will be reviewed.**

As we advance into the next millennium it has become evident by the close of the previous one that chiral drugs have become a major focus of most pharmaceutical companies. Aside from achiral molecules, which represent a fourth of the drugs granted generic and proprietary names in the United States single stereoisomers have proven to be better drugs. As such, new molecules on the market are safer, exhibit fewer side effects, and are more potent than what other drugs have previously been able to afford. Often only one stereoisomer of a racemate drug is able to affect the desired process, and therefore the patients end up absorbing and metabolizing useless quantities of the other stereoisomers of the drug. The fact that pharmaceutical companies can now consider the practicality of marketing chiral drugs is partially due to the ability of synthetic chemists to be able to obtain high enantiomeric excess in asymmetric bond construction. For numerous years this topic has been at the center stage in academic settings. The answer is somewhat obvious in that Nature itself uses chiral molecules. The best way to interact with Nature is by using chiral molecules. It has been only since the early 1980's, and more so since the FDA recognized the importance of single isomer drugs, that pharmaceutical research and development started focusing on this issue. An illustration of the ability of separating racemates and making them into enantiomerically pure drugs is done so by Prozac® ((±)-fluoxetine). At the time of its discovery it was the first selective serotonin reuptake inhibitor, now that its patent is close to expiration, Eli Lilly has both stereoisomers in clinical, one for migrain treatment and the other for depression. Companies such as Sepracor now have numerous patents on such new "optically pure drug". This year Sepracor has two new drug application submissions: Sotara® and the pediatric supplement for Xopenex®. Both of these compounds were originally developed and sold as racemates; now they are being marketed by Sepracor as single isomer drugs. The sale of stereochemical pure chiral drugs has increased 50% from 1999.[1] While companies have focused on the production of combinatorial libraries of compounds for screening purposes, the most poignant lesson in drug development has possibly come from the area of single isomer drugs. As the need becomes increasingly more evident, the demand and market for single isomer drugs becomes the paradigm of the last decade. Since the discovery of cortisone the importance of single isomer drugs has grown at an exponential rate each year. The pharmacological gains in potency, efficacy, and selectivity have become evident with the developments of the past few years.

**Linezolid (*Zyvox*®)**

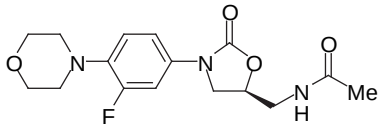
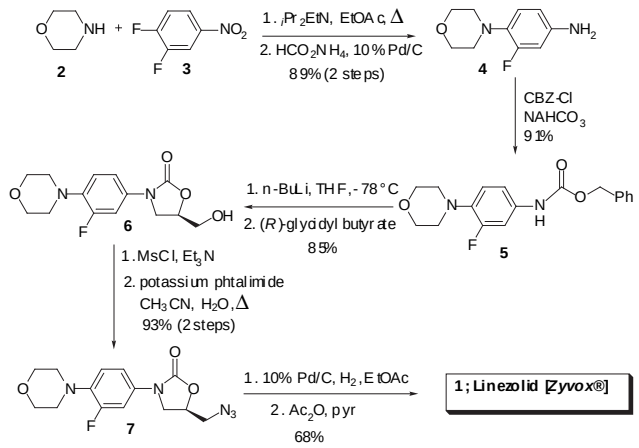



**Figure 1.** Linezolid (*Zyvox*®)

[1] C. & En. News **2000**, *78*, 55-78.

In April 2000, Linezolid (Zyvox® by Pharmacia & Upjohn) is the first member of a new class of antibiotics, the oxazolidinones, to receive FDA approval. This novel bacteriostatic agent is indicated for the treatment of nosocomical (i.e. hospital-acquired) infections involving Gram-positive organisms. These include complicated skin infection due to methicillin-resistant *Straph aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE) infections, and pneumonia caused by multi-resistant strains of *Strep pneumoniae*. The mode of action of Zyvox® is at the ribosomal level. By preventing the formation of the fmet-tRNA:mRNA:20S subunit ternary complex, Zyvox® stops protein formation. Without proteins, the bacteria cease multiplying, and eventually dies.

**Scheme 1.** Synthesis of Linezolid (*Zyvox*®)




The nine step synthesis of Zyvox®[2] commences by formation of the *p*-morpholine substituted nitrobenzene **4** (Scheme 1). Nucleophilic aromatic displacement of 3,4-difluoronitrobenzene with morpholine is followed by reduction of the nitro group to yield **4**. Attachment of a carbobenzoxy group yields 91% of the desired carbamate **5**. Deprotonation followed by treatment with (*R*)-glycidyl butyrate provides in one pot the enantiomerically enriched oxazolidinone **6**. Mesylation of the primary alcohol, followed by displacement provides the azido oxazolidinone **7**. Reduction of the azide to the amine and treatment with acetic acid provides synthetic antibiotic Zyvox®.

Zyvox®, was introduce on the United States market in April 2000. The recorded sales were $23 million in the first quarter, $18 million in the fourth quarter, and $48 million for the full year. [3] Zyvox® is also now in use in the United Kingdom and Japan, as well as in an additional fifteen countries in Europe, Latin America, and Asia.[4] The fact that this drug was able to gain approval around the world in less than a year shows that there is worldwide need to finding treatment for patients with Gram-positive infections, the most frequent cause of hospital infections. Versicor Pharmaceuticals and Pharmacia-Upjohn have a collaboration to develop the next generation of oxazolidinone antibacterial agents. This second generation will posses improved potency and broader pathogen spectrum to include Gram-negative bacteria, such as *H. influenza*.[5]

## Amprenavir (*Agenerase*®; VX-478)

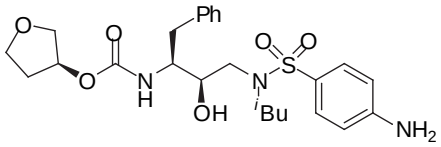


**Figure 2.** Amprenavir (*Agenerase*®)

Amprenavir (Agenerase® discovered by Vertex Pharmaceuticals, licensed by Glaxo Wellcome, Inc.) belongs to the family of antiretroviral drugs. In April 1999 this protease inhibitor was approved by the FDA for the treatment of HIV infection.[6] Agenerase®, like the other five protease inhibitors on the market, work at the final stage of viral replication by interfering with the HIV protease enzyme. This results in the inability of HIV to replicate and affect new cells.

A possible route to the synthesis of Agenerase® is outlined in Scheme 2.[7] Treatment of amino epoxide **8**[8] with chloroformate **9** yields carbamate **10** in 94% yield. Opening of the epoxide with isobutyl amine yields the *syn*-1,2-amino alcohol. Acylation of the amine with nosylchloride to form sulfonamide **12** followed by hydrogenation of the nitro group provide Agenerase®. Additionally, Corey and Zhang reported a stereoselective synthesis of amprenavir employing a selective nitroaldol reaction.[9]

[2] Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673-679.

[3] http://www.pharmacia.com/Investor/1q2001.pdf

[4] Thursday April 5, 1:41 pm Eastern Time Press Release by Pharmacia Corporation "Pharmacia's Zyvox Achieves Regulatory Milestone; Granted Approval in Three Key Global Markets in Less Than One Year"

[5] Versicor 2000 Annual Report

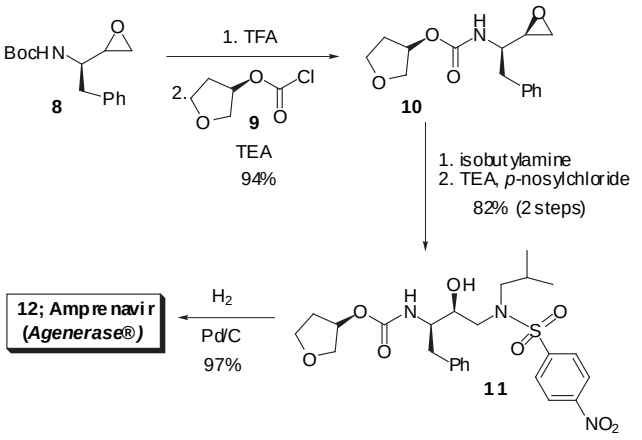
[6] Glaxo Wellcome 04/16/99 Company Press Release: " Twice-Daily Protease Inhibitor Offers Potent New Option for Combination Antiretroviral Therapy"

[7] Karl B. Hansen Harvard University, Ph. D. Thesis 1998.

[8] Reed, Kathryn Lea; Talley, John Jeffrey. (Monsanto Co., USA). PCT Int. Appl. (1992), 175pp. WO 9208699.

[9] Corey, E. J.; Zhang, F.-Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 1931-1934.

**Scheme 2.** Synthesis of Amprenavir (*Agenerase*®)




Since its launch in 1999 in the United States as an HIV protease inhibitor, Agenerase® has been approved in thirty-three countries worldwide, including Canada and Australia. In Japan, Kissei Pharmaceutical Co., Ltd. completed the clinical development of Prozei® (amprenavir). Agenerase®, is the first marketed product of Vertex. For the first quarter of 2001, the estimated worldwide sales of Agenerase® by GlaxoSmithKline is approximately $16.8 million. For the year 2001, the estimated worldwide sales of Agenerase® is $95 million.

## Atorvastatin (*Lipitor*®)

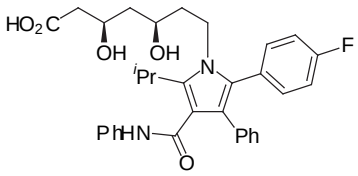
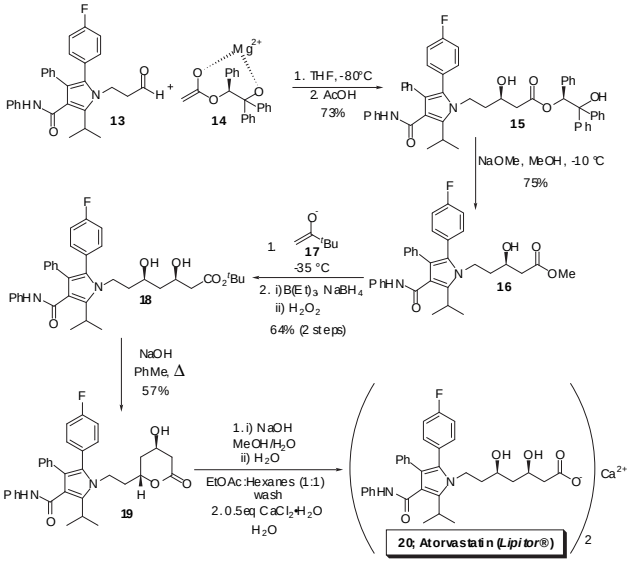



**Figure 3.** Atorvastatin (*Lipitor*®)

Atorvastatin (Lipitor® marked jointly by former Parke Davis and Pfizer) belongs to a class of drugs named statins, which reduce levels of total cholesterol and LDL. Lipitor® is the most potent of the statins. Statins are inhibitors of HMG-CoA reductase, an enzyme that catalyzes the conversion of HMF-CoA to mevalonate. This transformation is one of the early steps in cholesterol biosynthesis. Therefore, inhibition of the production of mevalonate limits the production of cholesterol.

Treatment of aldehyde **13** with enol ether **14** under chelation control affords alcohol **15** in 73% yield. Transesterification with NaOMe in MeOH provides methyl ester **16** in 75% yield (Scheme 3).

**Scheme 3.** Synthesis of Atorvastatin (*Lipitor*®)




Addition of the enolate of *tert*-butyl acetate (**17**) to methyl ester **16** is directly followed by directed reduction to yield the *syn*-1,3-diol **18**. Cyclization to hydroxylactone **19** is accomplished by treatment with NaOH in refluxing toluene. Opening of the hydroxylactone to the corresponding acid and formation of the sodium salt is followed by treament with $CaCl_2 \cdot H_2O$ in water to yield atorvastatin as its calcium salt, Lipitor®.[10]

Since 1996 Lipitor®, co-promoted by Warner-Lambert and Pfizer, has had an enormous growth on the international market. Lipitor®, with sales of $4 billion in 1999, is one of the best selling drugs in the United States (41% of the U. S. market share). This year the sales of this lowering-cholesterol drug should exceed $5 billion in worldwide sales. Lipitor® is the most potent cholesterol-lowering drug and its launch in Japan is eminent.[11]

The importance of chiral drugs in the pharmaceutical market increases with each year. As exemplified with the three drugs discussed in the present review, gains in potency, efficacy, and selectivity obtained by treatment with single isomer drugs are undeniable. As our understanding of molecular recognition and molecular dynamics increases, it follows that our understanding of protein drug interactions will most likely increase. Chiral molecules will certainly play a role in the exploitation of three-dimensional space for the development of new drugs in the future. Access to these potential new drugs will also depend highly on the development of asymmetric methods for the synthesis of chiral building blocks. The fact that pharmaceutical companies can now consider the practicality

[10] Roth, Bruce David Eur. Pat. Appl. (1991),18 pp. EP#: 409281 A1.

[11] Press release: February 7, 2000 "Pfizer and Warner-Lambert Agree to $90 Billion Merger Creating the World's Fastest-Growing Major Pharmaceutical Company"

of marketing chiral drugs is partially due to the ability of synthetic chemists to be able to obtain building blocks in isomerically pure form.