

CHAPTER 1

OPEN-CHAIN COMPOUNDS

Carbocyclic or heterocyclic ring systems comprise the core of chemical structures of the vast majority of therapeutic agents. This finding results in the majority of drugs exerting their effect by their actions at receptor or receptor-like sites on cells, enzymes, or related entities. These interactions depend on the receiving site being presented with a molecule that has a well-defined shape, distribution of electron density, and array of ionic or ionizable sites, which complement features on the receptor. These requirements are readily met by the relatively rigid carbocyclic or heterocyclic molecules. A number of important drugs cannot, however, be assigned to one of those structural categories. Most of these agents act as false substrates for enzymes that handle peptides. The central structural feature of these compounds is an open-chain sequence that mimics a corresponding feature in the normal peptide. Although these drugs often contain carbocyclic or heterocyclic rings in their structures, these features are peripheral to their mode of action. Chapter 1 concludes with a few compounds that act by miscellany and mechanisms and whose structures do not fit other classifications.

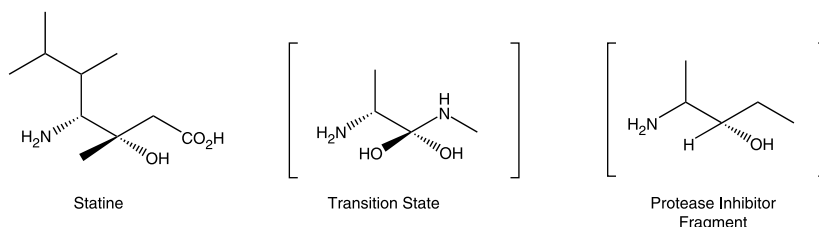
1. PEPTIDOMIMETIC COMPOUNDS

A. Antiviral Protease Inhibitors

1. Human Immunodeficiency Virus. The recognition of acquired immune deficiency syndrome (AIDS) in the early 1980s and the subsequent explosion of what had seemed at first to be a relatively rare disease into a major worldwide epidemic, lent renewed emphasis to the study of virus-caused disease. Treatment of viral disease is made particularly difficult by the fact that the causative organism, the virion, does not in the exact meaning of the word, replicate. Instead, it captures the reproductive mechanism of infected cells and causes those to produce more virions. Antiviral therapy thus relies on seeking out processes that are vital for producing those new infective particles. The first drugs for treating human immunodeficiency virus (HIV) infection comprised heterocyclic bases that interfered with viral replication by interrupting the transcription of viral ribonucleic acid (RNA) into the deoxyribonucleic acid (DNA) required by the host cell for production of new virions. The relatively fast development of viral strains resistant to these compounds has proven to be a major drawback to the use of these reverse transcriptase inhibitors. The drugs do, however, still form an important constituent in the so-called cocktails used to treat AIDS patients. Some current reverse transcriptase inhibitors are described in Chapters 4 and 6. The intense focus on the HIV virus revealed yet another point at which the disease may be tackled. Like most viruses, HIV comprises a packet of genetic material, in this case RNA, encased in a protein coat. This protein coat provides not only protection from the environment, but also includes peptides that recognize features on host cells that cause the virion to bind to the cell and a few enzymes crucial for replication. Many normal physiological peptides are often elaborated as a part of a much larger protein. Specialized peptidase enzymes are required to cut out the relevant protein. This proved to be the case with the peptides required for forming the envelopes for newly generated virions. Compounds that inhibit the scission of the protein elaborated by the infected host, the HIV protease inhibitors, have provided a valuable set of drugs for treatment of infected patients. The synthesis of four of those drugs were outlined in Volume 6 of this series. Work on compounds in this class has continued apace as evidenced by the half dozen new protease inhibitors that have been granted nonproprietary names since then.

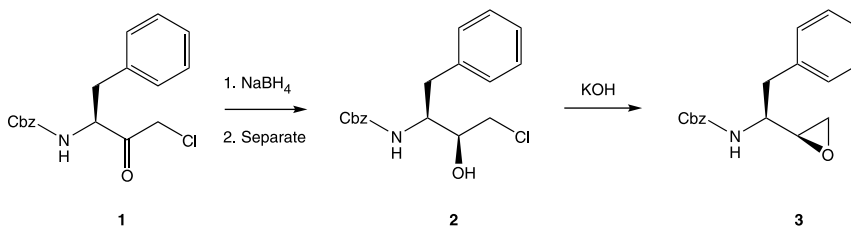
As noted in Volume 6, the development of these agents was greatly facilitated by a discovery in a seemingly unrelated area. Research aimed

at development of renin inhibitors as potential antihypertensive agents had led to the discovery of compounds that blocked the action of this peptide cleaving enzyme. The amino acid sequence cleaved by renin was found to be fortuitously the same as that required to produce the HIV peptide coat. Structure–activity studies on renin inhibitors proved to be of great value for developing HIV protease inhibitors. Incorporation of an amino alcohol moiety proved crucial to inhibitory activity for many of these agents. This unit is closely related to the one found in the statine, an unusual amino acid that forms part of the pepstatin, a fermentation product that inhibits protease enzymes.



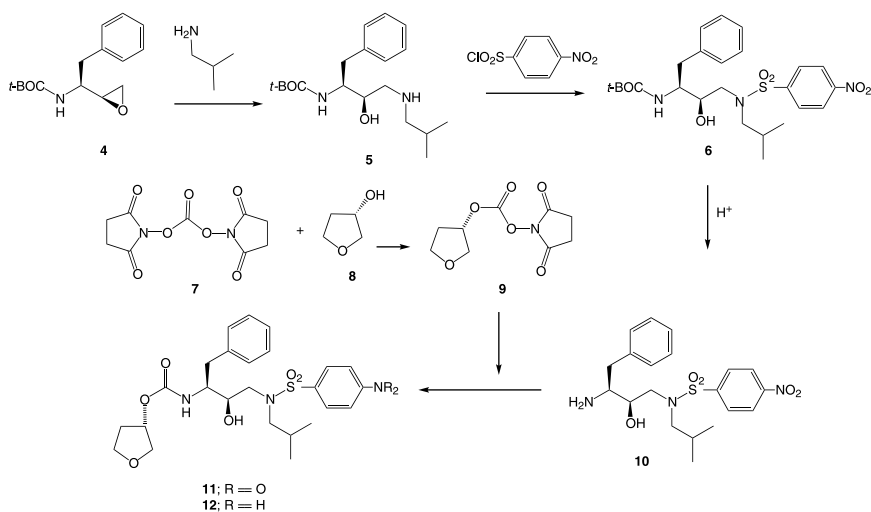
This moiety may be viewed as a carbon analogue of the transition state in peptide cleavage. The fragment is apparently close enough in structure to such an intermediate as to fit the cleavage site in peptidase enzymes. Once bound, this inactivates the enzyme as it lacks the scissile carbon–nitrogen bond. All five newer HIV protease inhibitors incorporate this structural unit.

One scheme for preparing a key intermediate for incorporating that fragment begins with the chloromethyl ketone (**1**) derived from phenylalanine, in which the amine is protected as a carbobenzyloxy (Cbz) group. Reduction of the carbonyl group by means of borohydride affords a mixture of aminoalcohols. The major syn isomer **2** is then isolated. Treatment of **2** with base leads to internal displacement of halogen and formation of the epoxide (**3**).¹



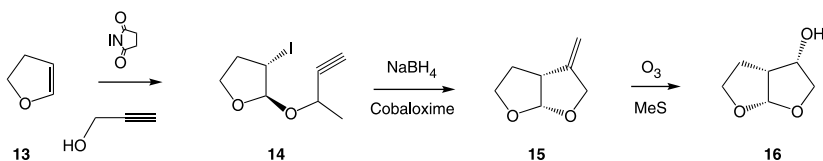
4 OPEN-CHAIN COMPOUNDS

The corresponding analogue (**4**) in which the amine is protected as a *tert*-butyloxycarbonyl function (*t*-BOC) comprises the starting material for the HIV protease inhibitor **amprenavir** (**12**). Reaction of **4** with isobutyl amine leads to ring opening of the oxirane and formation of the aminoalcohol (**5**). The thus-formed secondary amine in the product is converted to the sulfonamide (**6**) by exposure to *p*-nitrobenzenesulfonyl chloride. The *t*-BOC protecting group is then removed by exposure to acid leading to the primary amine (**10**). In a convergent scheme, chiral 3-hydroxytetrahydrofuran (**8**) is allowed to react with bis(*N*-succinimidooxy)carbonate (**7**). The hydroxyl displaces one of the *N*-hydroxysuccinimide groups to afford the tetrahydrofuran (THF) derivative (**9**) equipped with a highly activated leaving group. Reaction of this intermediate with amine **10** leads to displacement of the remaining *N*-hydroxysuccinimide and incorporation of the tetrahydrofuryl moiety as a urethane (**11**). Reduction of the nitro group then affords the protease inhibitor (**12**).²

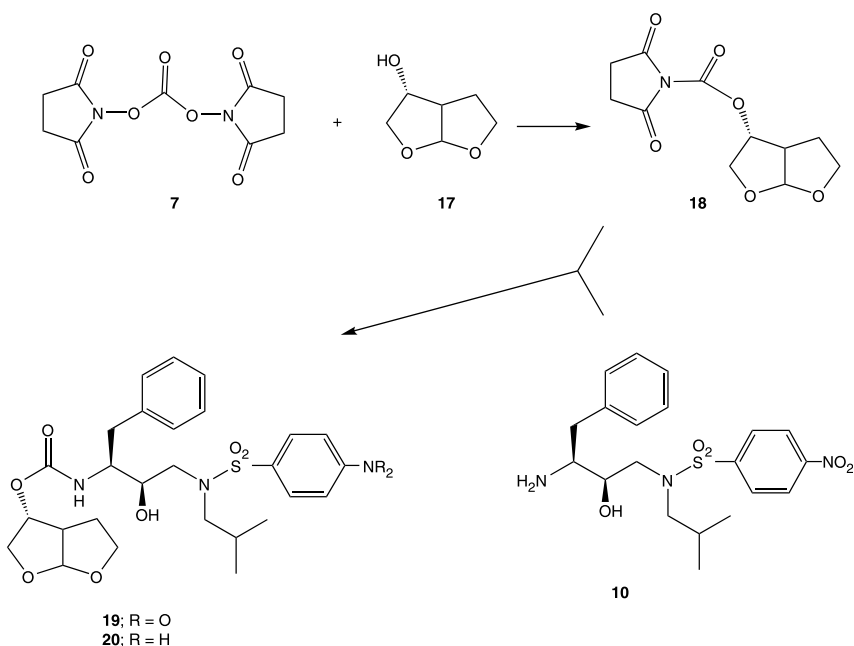


Much the same sequence leads to a protease inhibitor that incorporates a somewhat more complex furyl function-linked oxygen heterocyclic. This fused bis(tetrahydrofuryl) alcohol (**16**) was designed to better interact with a pocket on the viral protease. The first step in preparing this intermediate consists of reaction of dihydrofuran (**13**) with propargyl alcohol and iodosuccinimide to afford the iodoether (**14**). Free radical displacement of the iodine catalyzed by cobaloxime leads to the fused

perhydrofuranofuran (**15**). The exomethylene group in the product is then cleaved by means of ozone; reductive workup of the ozonide leads to racemic **16**. The optically pure single entity (**17**) is then obtained by resolution of the initial mixture of isomers with immobilized lipase.³

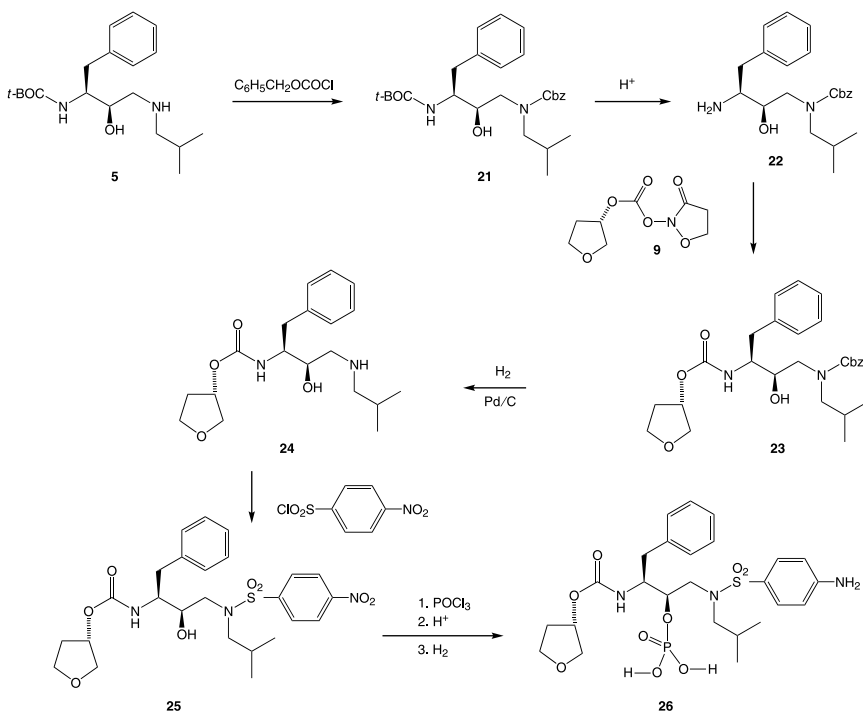


That product (**17**) is then converted to the activated *N*-hydroxysuccinimide derivative **18** as in the case of the monocyclic furan. Reaction with the primary amine **10** used to prepare amprenavir then leads to the urethane (**19**). Reduction of the nitro group then affords **darunavir**⁴ (**20**).



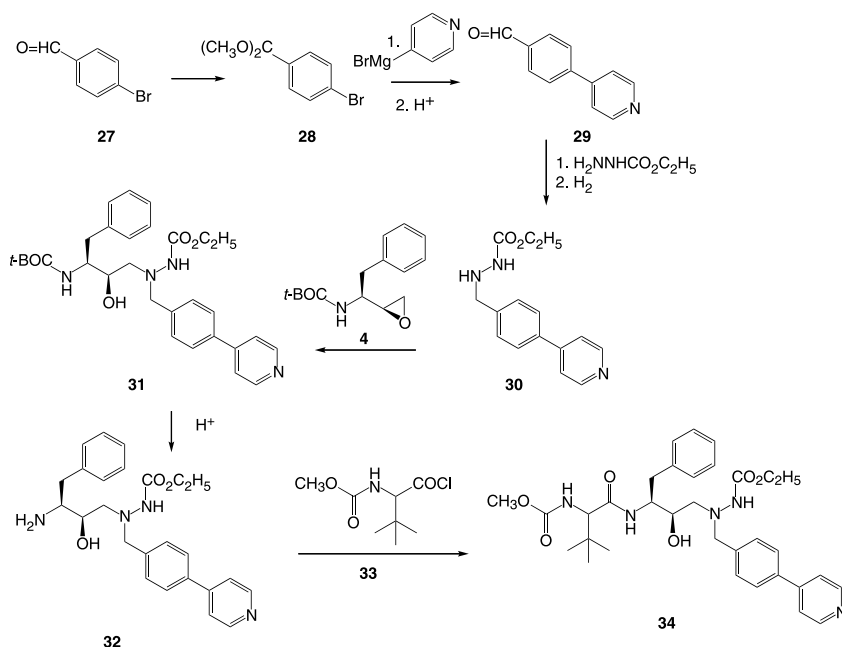
The synthesis of the amprenavir derivative, which is equipped with a solubilizing phosphate group, takes a slightly different course from that used for the prototype. The protected intermediate **5** used in the synthesis of **12** is allowed to react with benzyloxycarbonyl chloride to provide the

doubly protected derivative **21**, a compound that bears a *t*-BOC group on one nitrogen and a Cbz grouping on the other. Exposure to acid serves to remove the *t*-BOC group, affording the primary amine **22**. This compound is then condensed with the activated intermediate **9** used in the preparation of the prototype to yield the urethane **23**. Catalytic hydrogenation then removes the remaining protecting group to give the secondary amine **24**. Reaction as before with *p*-nitrobenzenesulfonyl chloride gives the sulfonamide **25**. This intermediate is allowed to react with phosphorus oxychloride under carefully controlled conditions. Treatment with aqueous acid followed by a second catalytic hydrogenation affords the water soluble protease inhibitor **fosamprenavir (26)**.⁵



The preceding three antiviral agents tend to differ from each other by only relatively small structural details. The next protease inhibitor includes some significant structural differences though it shares a similar central aminoalcohol sequence that is presumably responsible for its activity. Construction of one end of the molecule begins with protection of the carbonyl function in *p*-bromobenzaldehyde (**27**) as its methyl acetal (**28**) by treatment with methanol in the presence of acid. Reaction of that intermediate with the Grignard reagent from 4-bromopyridine leads to unusual

displacement of bromine from the protected benzaldehyde and formation of the coupling product. Mild aqueous acid restores the aldehyde function to afford **29**. This compound is then condensed with carboethoxy hydrazine to form the respective hydrazone; reduction of the imine function leads to the substituted hydrazine (**30**). Reaction of **30** with the by-now familiar amino-epoxide (**4**) results in oxirane opening by attack of the basic nitrogen in the hydrazine (**30**) and consequent formation of the addition product **31**. The *t*-BOC protecting group is then removed by treatment with acid. The final step comprises acylation of the free primary amine in **32** with the acid chloride from the *O*-methyl urethane (**33**). This last compound (**32**) is a protected version of an unnatural α -amino acid that can be viewed as valine in with an additional methyl group on what had been the side-chain secondary carbon atom. Thus, the protease inhibitor **atazanavir** (**34**) is obtained.⁶

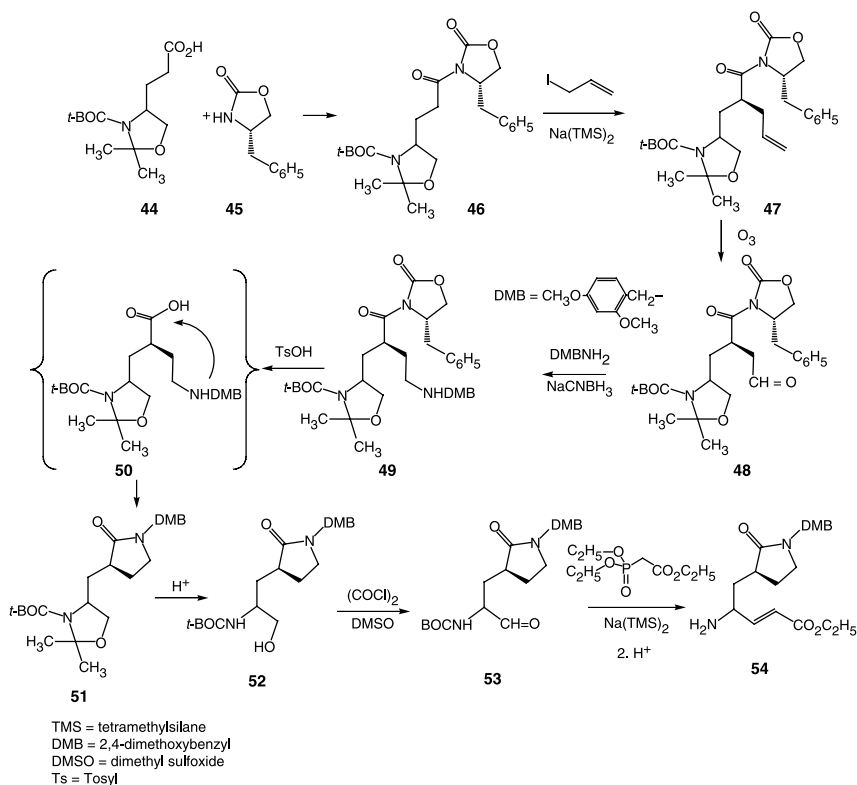


A terminal cyclic urea derivative of valine is present at one terminus in **lopinavir** (**43**). Preparation of this heterocyclic moiety begins with conversion of valine (**35**) to its phenoxycarbonyl derivative by reaction with the corresponding acid chloride. Alkylation of the amide nitrogen with 3-chloropropylamine in the presence of base under very carefully controlled pH results in displacement of the phenoxide group to give the

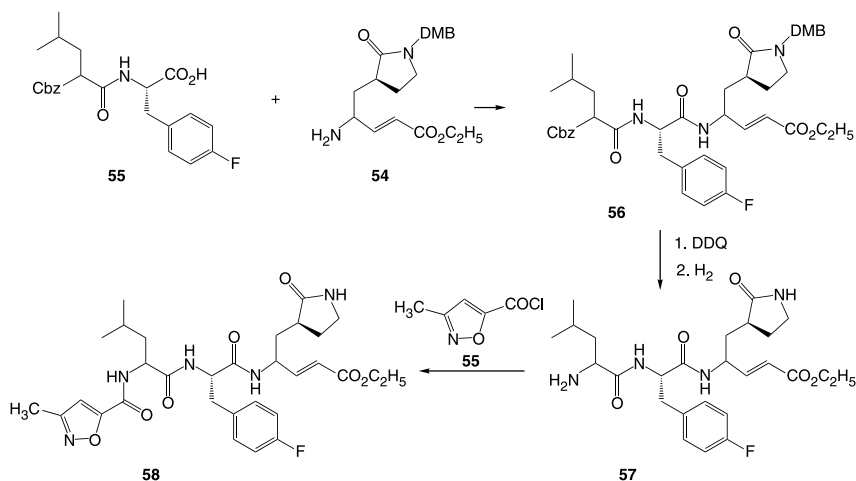
2. Human Rhinovirus. Human rhinoviruses are one of the most frequent causes of that affliction that accompanies cooling weather, the common cold. This virus also consists of a small strand of RNA enveloped in a peptide coat. Expression of fresh virions in this case depends on provision of the proper peptide by the infected host cell. That in turn hinges on excision of that peptide from the larger initially produced protein. Protease inhibitors have thus been investigated as drugs for treating rhinovirus infections. The statine-based HIV drugs act by occupying the scission site of the protease enzyme and consequently preventing access by the HIV-related substrate. That binding is, however, reversible in the absence of the formation of a covalent bond between drug and enzyme. A different strategy was employed in the research that led to the rhinovirus protease inhibitor **rupinavir (58)**. The molecule as a whole is again designed to fit the protease enzyme, as in the case of the anti-HIV compounds. In contrast to the latter compound, however, this agent incorporates a moiety that will form a covalent bond with the enzyme, in effect inactivating it with finality. The evocative term “suicide inhibitor” has sometimes been used for this approach since both the substrate and drug are destroyed.

The main part of the somewhat lengthy convergent synthesis consists of the construction of the fragment that will form the covalent bond with the enzyme. The unsaturated ester in this moiety was designed to act as a Michael acceptor for a thiol group on a cysteine residue known to be present at the active site. The preparation of that key fragment starts with the protected form of chiral 3-amino-4-hydroxybutyric acid (**44**); note that the oxazolidine protecting group simply comprises a cyclic hemiaminal of the aminoalcohol with acetone. The first step involves incorporation of a chiral auxiliary to guide introduction of an additional carbon atom. The carboxylic acid is thus converted to the corresponding acid chloride and that reacted with the (*S*)-isomer of the by-now classic oxazolidinone (**45**) to give derivative **46**. Alkylation of the enolate from **46** with allyl iodide gives the corresponding allyl derivative (**47**) as a single enantiomer. The double bond is then cleaved with ozone; reductive workup of the ozonide affords the aldehyde (**48**). Reductive amination of the carbonyl group with 2,6-dimethoxybenzylamine in the presence of cyanoborohydride proceeds to the corresponding amine **49**. This last step in effect introduced a protected primary amino group at that position. The chiral auxiliary grouping is next removed by mild hydrolysis. The initially formed amino acid (**50**) then cyclizes to give the five-membered lactam (**51**). Treatment under stronger hydrolytic conditions subsequently serves to open the cyclic hemiaminal grouping to reveal the free aminoalcohol

(52). Swern-type oxidation of the terminal hydroxyl group in this last intermediate affords an intermediate (53) that now incorporates the aldehyde group required for building the Michael acceptor function. Thus reaction of that compound with the ylide from ethyl 2-diethoxyphosphonoacetate adds two carbon atoms and yields the acrylic ester (54).



The remaining portion of the molecule is prepared by the condensation of *N*-carbobenzyloxyleucine with *p*-fluorophenylalanine to yield the protected dipeptide (55). Condensation of that intermediate with the Michael acceptor fragment (54) under standard peptide-forming conditions leads to the tripeptide-like compound (53). Reaction of 53 with dichloro-dicyanoquinone (DDQ) leads to unmasking of the primary amino group at the end of the chain by oxidative loss of the DMB protecting group. Acylation of that function with isoxazole (55) finally affords the rhinovirus protease inhibitor rupinavir (58).⁹

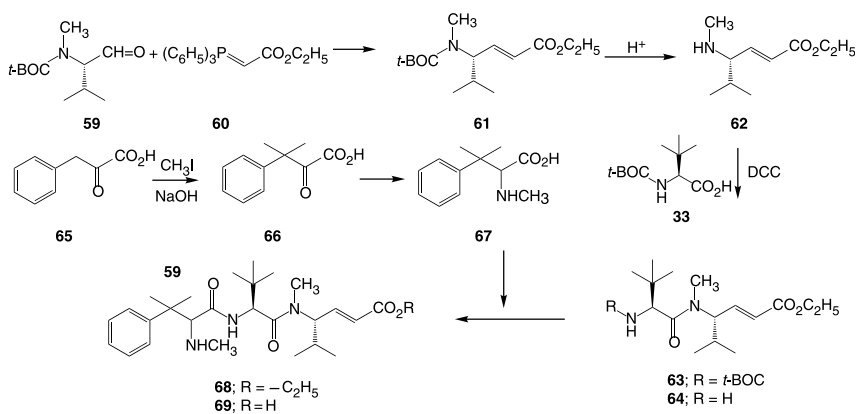


2. MISCELLANEOUS PEPTIDOMIMETIC COMPOUNDS

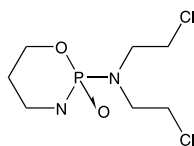
Polymers of the peptide tubulin make up the microtubules that form the microskelton of cells. Additionally, during cell division these filaments pull apart the nascent newly formed pair of nuclei. Compounds that interfere with tubulin function and thus block this process have provided some valuable antitumor compounds. The vinca alkaloid drugs vincristine and vinblastine, for example, block the self-assembly of tubulin into those filaments. Paclitaxel, more familiarly known as Taxol, interestingly stabilizes tubulin and in effect freezes cells into mid-division. Screening of marine natural products uncovered the cytotoxic tripeptide-like compound hemiasterlin, which owed its activity to inhibition of tubulin. A synthetic program based on that lead led to the identification of **taltobulin (69)**, an antitumor compound composed, like its model, of sterically crowded aminoacid analogues. The presence of the nucleophile-accepting acrylate moiety recalls **58**.

One arm of the convergent synthesis begins with the construction of that acrylate-containing moiety. Thus, condensation of the *t*-BOC protected α -aminoaldehyde derived from valine with the carbethoxymethylene phosphorane (**60**) gives the corresponding chain extended amino ester (**61**). Exposure to acid serves to remove the protecting group to reveal the primary amine (**62**). Condensation of that intermediate with the tertiary butyl-substituted aminoacid **33**, used in a previous example leads to the protected amide (**63**); the *t*-BOC group in this is again removed with acid unmasking the primary amino group in **64**. Construction of the other major fragment first involves addition of a pair of methyl groups

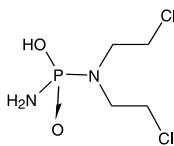
to the benzylic position of pyruvate (**65**). This transform is accomplished under surprisingly mild conditions by simply treating the ketoacid with methyl iodide in the presence of hydroxide. Treatment of product **66** with methylamine and diborane results in reductive amination of the carbonyl group, and thus formation of α -aminoacid **67** as a mixture of the two isomers. Condensation of that with the dipeptide-like moiety **64** under standard peptide-forming conditions gives the amide **68** as a mixture of diastereomers. The isomers are then separated by chromatography; saponification of the terminal ester function of the desired (*SSS*)-isomer affords the antitumor agent taltobulin (**69**).¹⁰



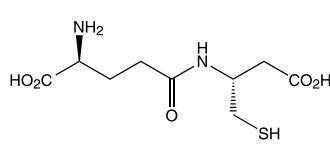
The alkylating agent cyclophosphamide is one of the oldest U.S. Food and Drug Administration (FDA)-approved antitumor agents, having been in use in the clinic for well over four decades. Though this chemotherapeutic agent is reasonably effective, it is not very selective. The drug affects many sites and is thus very poorly tolerated. Over the years, there has been much research devoted to devising more site-selective related compounds. It was established that a heterocyclic ring in this compound is opened metabolically and then discarded. The active alkylating metabolite comprises the relatively small molecule commonly known as the “phosphoramidate mustard”.



Cyclophosphamide

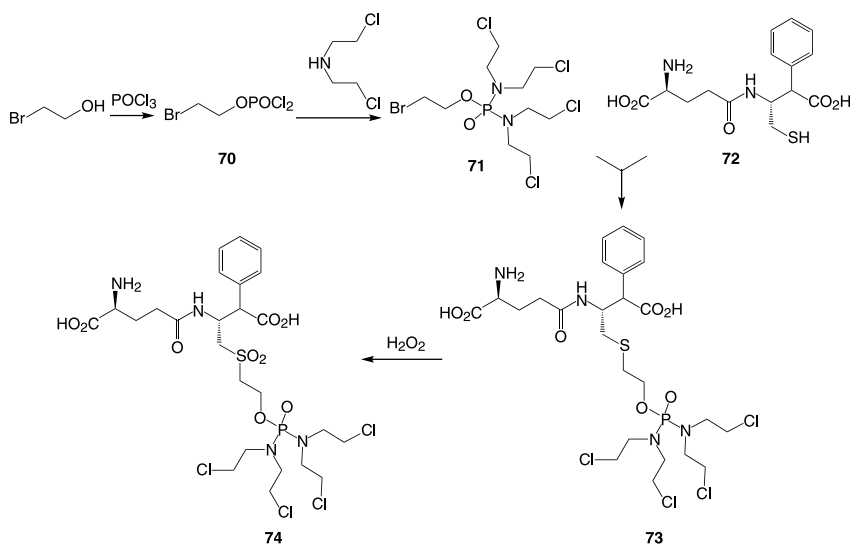


Phosphoramidate Mustard



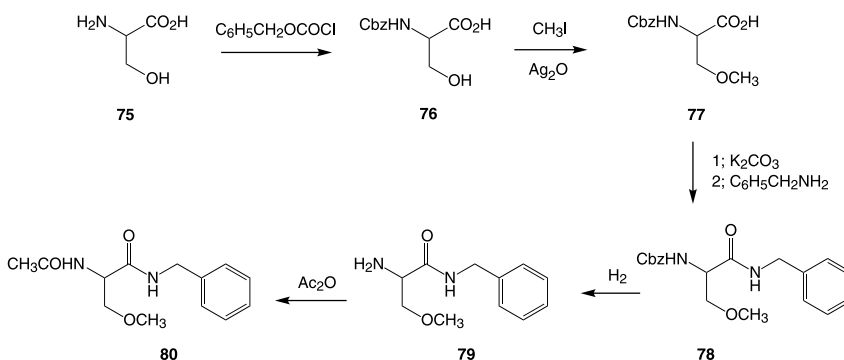
Glutathione

This result opens the possibility of delivering this active fragment or a related alkylating function in a large molecule that would itself be recognized by an enzyme involved in cancer progression. As an example, it was observed that many types of cancer tissues often have elevated levels of glutathione transferase, the agent that removes glutathione. A version of the modified natural substrate, glutathione, which carries a phosphoramidate alkylating function, has shown activity on various cancers. Reaction of bromoethanol with phosphorus oxychloride affords intermediate **70**. This compound reacts without purification with bis-2-chloroethylamine to give the phosphoramidate (**71**), which is equipped with two sets of alkylating groups. Compound **71** is then reacted with the glutathione analogue **72**, in which phenylglycine replaces the glycine residue normally at that position. The bromine atom in intermediate **71** is apparently sufficiently more reactive than the chlorines in the mustards so that displacement by sulfur preferentially proceeds to **73**. Oxidation of the sulfide with hydrogen peroxide affords **canfosamide (74)**.^{11,12}

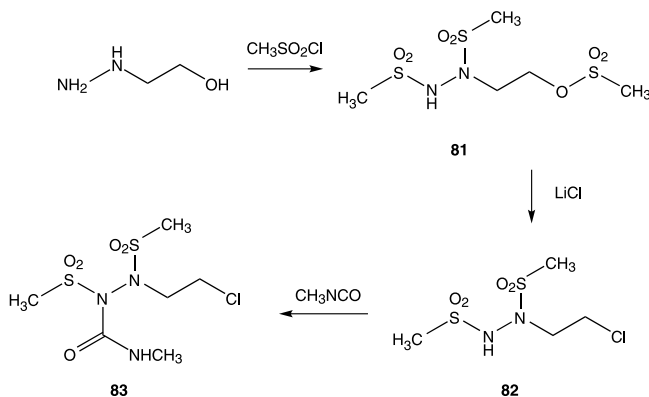


The D(*R*) isomer of the amino acid *N*-methyl-D-aspartate, more commonly known as NMDA serves as the endogenous agonist at a number of central nervous system (CNS) receptor sites. This agent is not only involved in neurotransmission, but also modulates responses elicited by other neurochemicals. A relatively simple peptide-like molecule has been found to act as an antagonist at NMDA receptors. This activity is manifested *in vivo* as antiepileptic activity. This agent in addition blocks the nerve pain suffered by many diabetics, which is often called neuropathic pain. The synthesis begins by protecting the unnatural D-serine

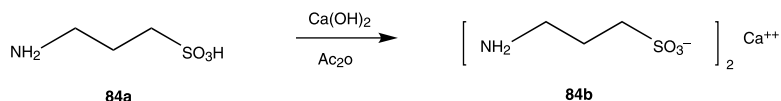
(75) as its carbobenzyloxy derivative 76. This is accomplished by reacting 75 with the corresponding acid chloride. Reaction of the product with methyl iodide in the presence of silver oxide alkylates both the free hydroxyl and the carboxylic acid to give the ether ester (77). Saponification followed by coupling with benzylamine leads to the benzylamide (78). Hydrogenolysis of the Cbz protecting group (79) followed by acylation with acetic anhydride affords **lacosamide** (80).¹³



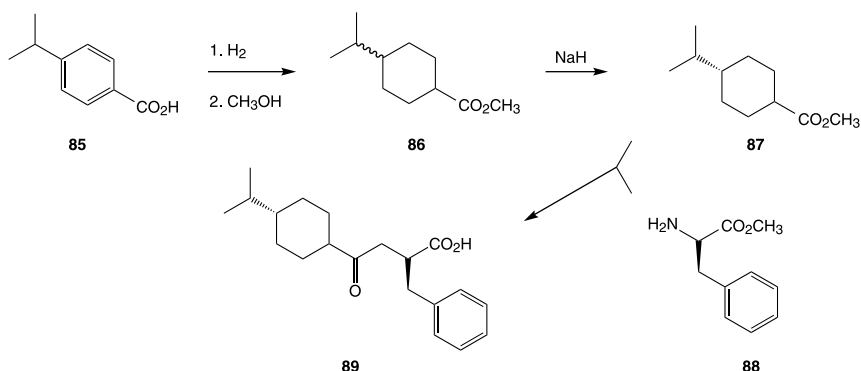
As noted in the discussion of canfosamide, alkylating agents have a long history as a class of compounds used in chemotherapy. The trend is to attach the active electrophilic groups to molecules that will deliver them to specific sites. A simple alkylating agent, **cloretazine** (83), is being actively pursued because of its promising antitumor activity. Exhaustive methanesulfonylation of hydroxyethyl hydrazine with methanesulfonyl chloride yields the *N,N,O*-trimesylate (81). Reaction of this intermediate with lithium chloride leads to displacement of the *O*-mesylate by chlorine and formation of the alkylating group in 82. Treatment of 82 with the notorious methylisocyanate (MCI) yields the antitumor agent cloretazine (83).^{14,15}



The relatively simple homologue of taurine, 3-aminosulfonic acid (**84a**), also known as homotaurine, is an antagonist of the neurochemical gamma-aminobutyric acid (GABA). Homotaurine has been found to suppress alcoholism in various animal models. Speculation is that this occurs because of its activity against GABA to which it bears a some resemblance. The calcium salt (**84b**) of the *N*-acetyl derivative has been used to help alcoholics maintain abstinence from alcohol by preventing relapse. The compound is prepared straightforwardly by acylation of homotaurine in the presence of calcium hydroxide and acetic anhydride.¹⁶ The product, **acamprosate calcium (84b)**, was approved by FDA for use in the United States in 2004.

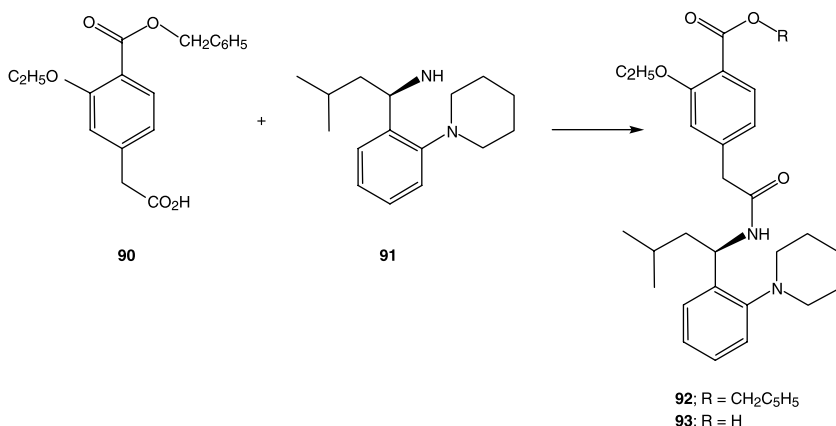


A relatively simple derivative of phenylalanine shows hypoglycemic activity. This compound, **nateglinide**, is usually prescribed for use as an adjunct to either metformin, or one of the thiazolidine hypoglycemic agents. Catalytic reduction of the benzoic acid (**85**) leads to the corresponding substituted cyclohexane as a mixture of isomers. This compound is then esterified with methanol to give the methyl esters (**86**). Treatment with sodium hydride leads **86** to equilibrate to the more stable *trans* isomer **87** via its enolate. Condensation of **87** with the ester of phenylalanine (**88**) yields nateglinide (**89**) after saponifications.¹⁷



The hypoglycemic agent **repaglinide** may loosely be classed as a peptidomimetic agent, because it essentially shows the same activity as nateglinide. The actual synthetic route is difficult to decipher from the patent in which it

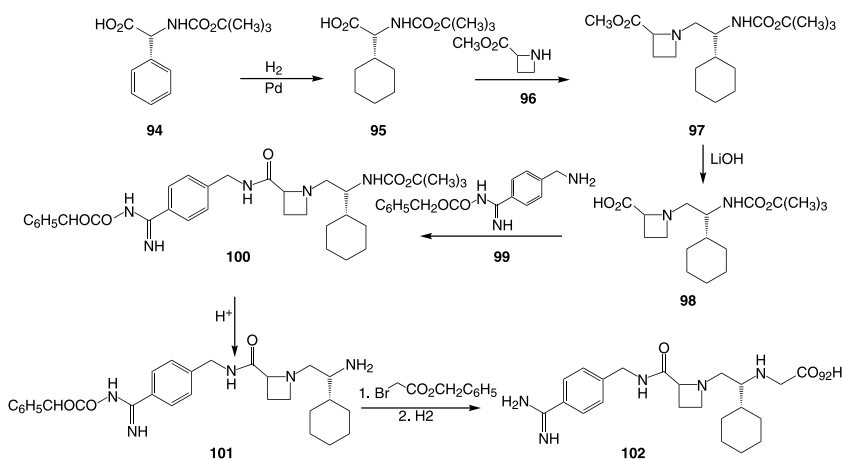
is described. No description is provided for the origin of the starting materials. It is speculated that condensation of the protected monobenzyl ester (**90**) with diamine **91** would lead to the amide (**92**). Hydrogenolysis of the benzyl ester in the product would afford the free acid. Thus, repaglinide (**93**) would be obtained.¹⁸



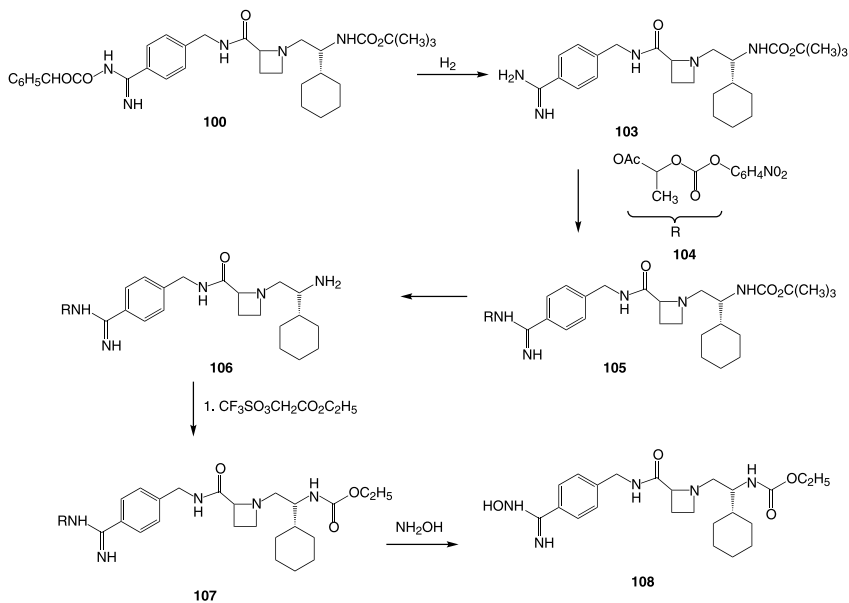
Formation of blood clots is the natural process that preserves the integrity of the circulatory system. Damage to the vasculature sets off an intricate cascade of reactions. These reactions culminate in the formation of a fibrin clot that seals the damaged area preventing the further loss of blood. Surgery, heart attacks, and other traumatic events lead to inappropriate formation of clots that can result in injury by blocking the blood supply to organs and other vital centers. The drugs that have traditionally been used to prevent formation of clots, coumadin and heparin have a very narrow therapeutic ratio, necessitating close monitoring of blood levels of these drugs in patients. One of the first steps in the formation of a clot involves the binding of fibrinogen to specific receptors on the platelets that start the process. A number of fibrinogen inhibitors have recently been developed whose structure is based on the sequence of amino acids in the natural product. Two more recent compounds, **melagartan**, and **xymelagartan**, both contain the amidine (or guanidine) groups that are intended to mimic the similar function in fibrinogen and that characterize this class of drugs.¹⁹

The synthesis of these agents begins with the hydrogenation of phenylglycine *t*-BOC amide (**94**) to the corresponding cyclohexyl derivative **95**. The free carboxyl group is then coupled with the azetidine (**96**) to afford

the amide (**97**). Saponification with lithium hydroxide yields the free acid (**98**). The carboxyl group in that product is then coupled with the benzylamine (**99**), where the amidine group at the para position is protected as the benzoyloxycarbonyl derivative to give intermediate **100**. The protecting group on the terminal amino group is then removed by hydrolysis with acid (**101**). The primary amine in this last intermediate is then alkylated with benzyl bromoacetate. Hydrogenolysis removes the protecting groups on the terminal functions in this molecule to afford melagartan (**102**).²⁰

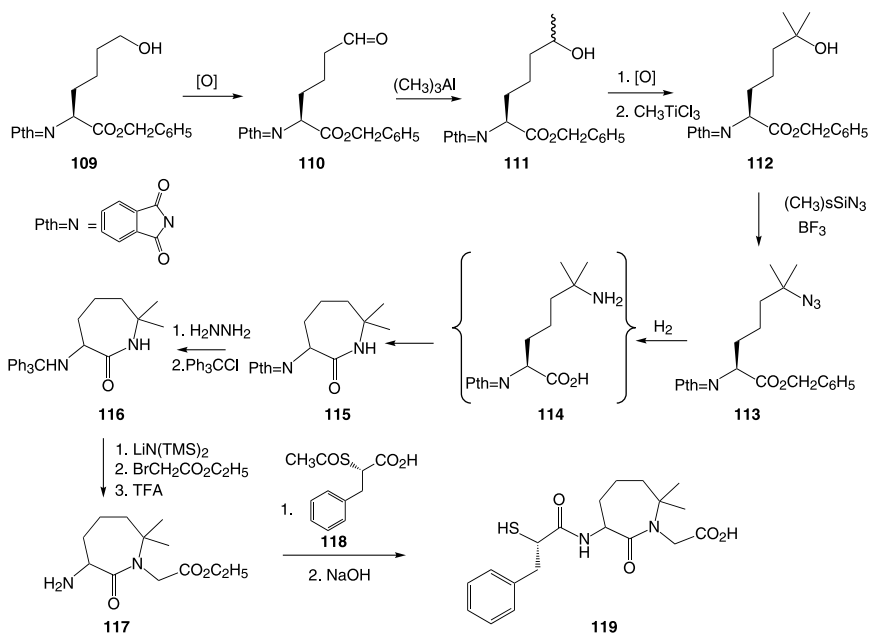


Intermediate **100** serves as the starting material for the structurally closely related fibrinogen inhibitor xymelagartan. Hydrogenation over palladium on charcoal removes the protecting group on the amidine function (**103**). This compound is then allowed to react with what is in effect and unusual complex ester of carbonic acid (**104**). The basic nitrogen on the amidine displaces nitrophenol, a good leaving group to afford **106**. Regiochemistry is probably dictated by the greater basicity of the amidine group compared to the primary amine at the other end of the molecule. The amine is then alkylated with the trifluoromethylsulfonyl derivative of ethyl hydroxyacetate. Reaction of this last intermediate (**107**) with hydroxylamine result in an exchange of the substituent on the amidine nitrogen to form an *N*-hydroxyamidine. Thus, **xymelagartan** (**108**) is obtained.²⁰ This drug is interestingly rapidly converted to **102** soon after ingestion and is in effect simply a prodrug for the latter.



Drugs that inhibit the conversion of angiotensin 1 to the vasoconstricting angiotensin 2, the so-called angiotensin converting enzyme (ACE) inhibitors, block the action of angiotensin converting enzyme, one of a series of zinc metalloproteases. A closely related enzyme causes the degradation of the vasodilating atrial natriuretic peptide. A compound that blocks both metalloproteases should in principle lower vascular resistance and thus blood pressure by complementary mechanisms. A drug that combines those actions, based on a fused two-ring heterocyclic nucleus, omapatrilat, is described in Chapter 10. A related compound that incorporates a single azepinone ring shows much the same activity. The synthesis begins by Swern oxidation of the terminal alcohol in the heptanoic ester **109**. Reaction of the product **110** with trimethylaluminum proceeds exclusively at the aldehyde to afford the methyl addition product (**111**). A second Swern oxidation, flowed this time by methyl titanium chloride, adds a second methyl group to afford the *gem*-dimethyl derivative (**112**). Construction of the azepinone ring begins by replacement of the tertiary carbinol in **112** with an azide group by reaction with trimethylsilyl azide and boron trifluoride. Hydrogenation of the product (**113**) reduces the azide to a primary amine and at the same time cleaves the benzyl ester to the corresponding acid (**114**). Treatment of this intermediate with a diimide leads to formation of an amide, and thus the desired azepinone ring (**115**). The

phthalimido function, which has remained intact through the preceding sequence, is now cleaved in the usual way by reaction with hydrazine. The newly freed amine is again protected, this time as triphenylmethyl derivative. The anion on the amide nitrogen from treatment of **116** with lithium hexamethyl disilazane is then alkylated with ethylbromoacetate; exposure to trifluoroacetic acid (TFA) then cleaves the protecting group on the other nitrogen to afford **117**. The primary amino group is acylated with (*S*)acetylthiocinnamic acid (**118**). Saponification cleaves both the acetyl protection group on sulfur and the side-chain ethyl ester to afford **gemopatrilat (119)**.²¹



REFERENCES

1. D.P. Getman et al., *J. Med. Chem.* **36**, 288 (1993).
2. R.D. Tung, M.A. Murcko, G.R. Bhisetti, U.S. Patent 5,558,397 (1996). The scheme shown here is partly based on that used to prepare darunavir and phosamprenavir due to difficulty in deciphering the patent.
3. A.K. Ghosh, Y. Chen, *Tetrahedron Lett.* **36**, 505 (1995).
4. D.L.N.G. Surleraux et al., *J. Med. Chem.* **48**, 1813 (2005).
5. L.A. Sobrera, L. Martin, J. Castaner, *Drugs Future*, **23**, 22 (2001).

6. G. Bold et al., *J. Med. Chem.* **41**, 3387 (1998).
7. For a scheme for this intermediate see D. Lednicer, "The Organic Chemistry of Drug Synthesis", Vol. 6, John Wiley & Sons, Inc., NY 1999, pp. 12,13.
8. E.J. Stoner et al., *Org. Process Res. Dev.* **4**, 264 (2000).
9. P.S. Dragovich et al., *J. Med. Chem.* **42**, 1213 (1999).
10. A. Zask et al., *J. Med. Chem.* **47**, 4774 (2004).
11. L.M. Kauvar, M.H. Lyttle, A. Satyam, U.S. Patent 5,556,942 (1996).
12. A. Satyam, M.D. Hocker, K.A. Kane-Maguire, A.S. Morgan, H.O. Villar, M.H. Lyttle, *J. Med. Chem.* **39**, 1736 (1996).
13. J.A. McIntyre, J. Castaner, *Drugs Future* **29**, 992 (2004).
14. A. Sartorelli, K. Shyam, U.S. Patent 4,684,747 (1987).
15. A. Sartorelli, K. Shyam, P.G. Penketh, U.S. Patent 5,637,619 (1997).
16. J.P. Durlach, U.S. Patent 4,355,043 (1982).
17. S. Toyoshima, Y. Seto, U.S. Patent, 4,816,484 (1989).
18. W. Grell, R. Hurnaus, G. Griss, R. Sauter, M. Reiffen, E. Rupprecht, U.S. Patent, 5,216,167 (1993).
19. See Ref. 7, pp. 15–18.
20. L.A. Sobrera, J. Castaner, *Drugs Future*, **27**, 201 (2002).
21. J.A. Robl et al., *J. Med. Chem.* **42**, 305 (1999).