Synthetic Approaches to the 2006 New Drugs

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Abstract: New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biological target. In addition, these new chemical entities (NCEs) not only provide insights into molecular recognition, but also serve as drug-like leads for designing future new drugs. To these ends, this review covers the syntheses of 16 NCEs marketed in 2006.

Key Words: Synthesis, new drug, new chemical entities, medicine, therapeutic agents.

INTRODUCTION

"*The most fruitful basis for the discovery of a new drug is to start with an old drug*." ─ Sir James Whyte Black, winner of the 1988 Nobel prize in physiology and medicine [1].

Inaugurated five years ago, this annual review presents synthetic methods for molecular entities that were launched in various countries for the first time during the past year. The motivation to write such a review is the same as stated in the previous articles [2-5]. Briefly, drugs that are approved worldwide tend to have structural similarity across similar biological targets. We strongly believe that knowledge of new chemical entities and their syntheses will greatly enhance our abilities to design new drug molecules in shorter period of time. With this hope, we continue to profile these NCEs that were approved in 2006.

In 2006, 41 new products including new chemical entities, biological drugs, and diagnostic agents [6] reached the market. Another nine new products were approved for the first time in 2006 but were not launched before year end. Syntheses of those drugs will be covered in 2007's review. The current article will focus on the syntheses of 16 new drugs marketed last year (Fig. **1**), while excluding new indications for known drugs, new combinations and new formulations. Drugs synthesized *via* bio-process and peptide synthesizers will also be excluded as well. The syntheses of these new drugs were published sporadically in different journals and patents. The synthetic routes cited here represent the most suitable methods based on the author's judgment and appear in alphabetical order by generic names.

Anecortave Acetate (*Retaane*®)

Anecortave acetate, an angiogenesis inhibitor, was launched in Australia by Alcon for the treatment of age-related macular degeneration (AMD). AMD is the leading cause of untreatable blindness among people aged 65 to 74 years in the U.S. Worldwide, approximately 20 to 25 million people suffer from AMD, a disease that until recently was untreatable. Anecortave, an angiostatic steroid, down-regulates the expression MMP-2 and -9 to exert its antiangiogenic effects [7]. Anecortave has been synthesized by several different routes, and Pharmacia process patents are cited here [8,9]. The synthesis is depicted in Scheme **1**. Compound **1** was condensed with 2-chlorovinyl ethyl ether with *n*-BuLi in THF at low temperature to give a mixture of two isomeric aldehydes **2** in 91% yield [8]. The mixture **2** was treated with acetic anhydride and anhydrous potassium acetate in DMF at 106°C to give acetate **3** which was reacted with $RhCl(PPh_3)_3$ and triethylsilane in methylene chloride at 45°C for 4 hours to yield the corresponding triethylsilane ether **4** as a solid after crystallization in hexane. Finally, compound **4** was oxidized with 40% peracetic acid in toluene at low temperature, and the reaction was quenched with SO_2 in methanol (2M), and treated with TEA to give anecortave acetate [9].

Darunavir (*Prezista*™)

Darunavir (TM-114) is a potent HIV protease inhibitor that has been shown to be efficacious in both wild type and resistant forms of HIV with low toxicity. With increased use of both protease inhibitors and reverse transcriptase inhibitors, there has been an increased level of resistance to most commonly used anti-HIV agents. Darunavir, developed and marketed by Tibotec, has so far shown excellent efficacy against the HIV-1 strains that show resistance to other approved protease inhibitors [6,10]. Several routes to the synthesis of darunavir have been reported utilizing the chiral hexahydro-furo[2,3-*b*]furan-3-ol carbonate **12** [11-13] and several chiral syntheses of bisfuranol **12** have been disclosed as well [12-15]. One route that has been performed on kilogram scale is highlighted in Scheme **2** [13]. Thus 2,3-*O*-isopropylidene-glyceraldehyde **5** was stirred with dimethyl malonate at RT for 3 h in tetrahydrofuran followed by addition of pyridine and heating to 45ºC. Then acetic anhydride was added at 45ºC over 4h and stirred at that temperature for 12 h. Concentration of the reaction followed by basic workup and extraction with toluene and solvent swap to methanol gave the products as a 23.6% solution in methanol. Nitromethane was added to this methanol solution followed by the addition of DBU over 30 min keeping the reaction temperature below 25ºC. Stirring the reaction for an additional 3 h afforded intermediate **7**. The reaction was cooled

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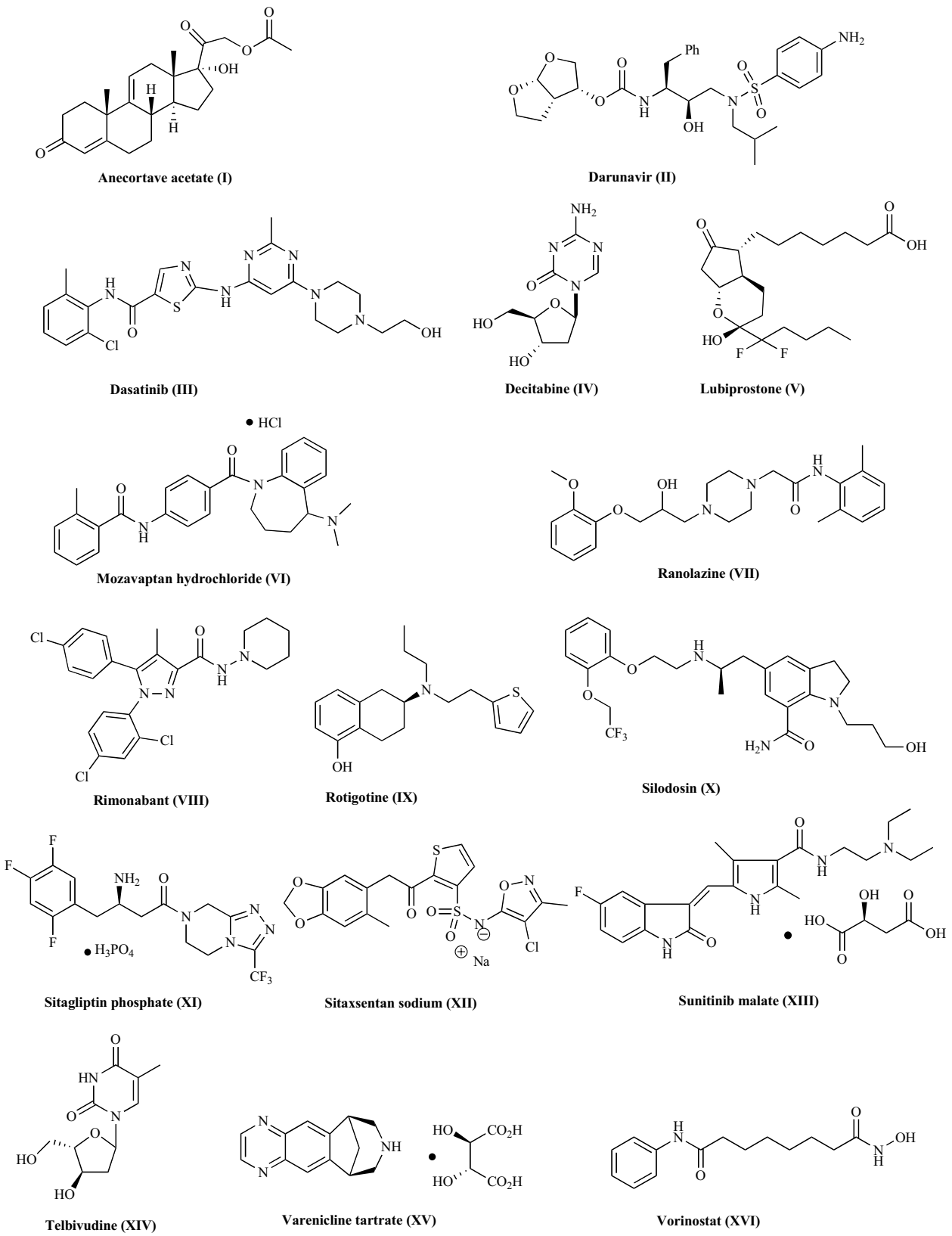
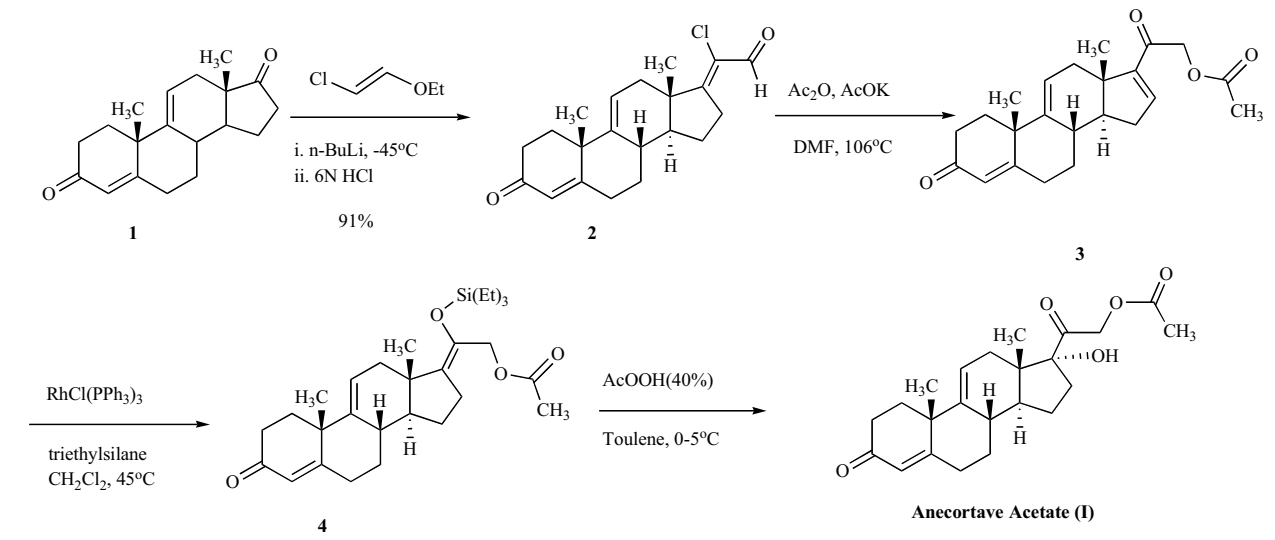
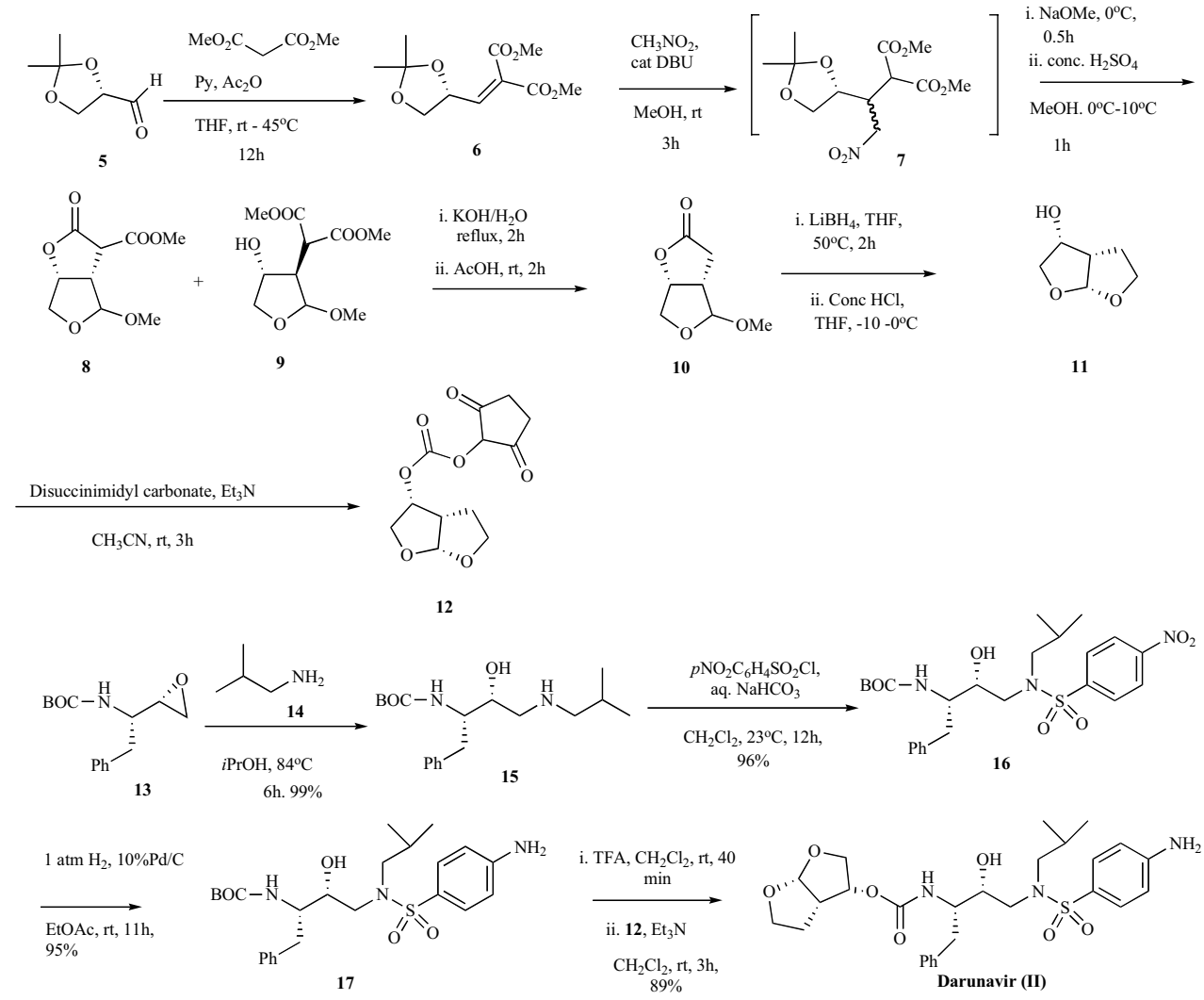


Fig. (1). Structures of 16 new drugs marketed in 2006.



Scheme 1. Synthesis of Anecortave Acetae.



Scheme 2. Preparation of Darunavir.

to 0ºC and sodium methoxide was added dropwise over 30 min After stirring the reaction for 30 min, the reaction was added slowly over 1h to conc. H_2SO_4 in methanol at 0°C while ensuring the temperature did not exceed 10°C. This cooled reaction mixture (0ºC) was then added to a vigorously stirred mixture of ethyl acetate and 1N sodium hydrogen carbonate at 0°C. The organic layer was separated, washed with brine and concentrated to give the residue containing a mixture of **8** and **9**. This mixture was dissolved in methanol then water and potassium hydroxide were added and the resulting mixture was heated at reflux for 2 h. The reaction was cooled to 35ºC and acetic acid was added and the resulting mixture concentrated. Additional acetic acid was added and stirred at room temperature for 2 h. The mixture was concentrated, diluted with water and extracted with ethylacetate. The ethylacetate layer was washed with 1N sodium bicarbonate three times and the organic layer was concentrated and diluted with isopropanol. The isopropanol mixture was then heated to 60-70ºC and further evaporation of isopropanol under reduced pressure to a concentrated volume with cooling to 0ºC over 4-5 h, allowed for the crystallization of product **10**. After filtration and drying, the intermediate lactone **10** was dissolved in THF and treated over 30 min with a solution of lithium borohydride in THF. The reaction was warmed to 50ºC over 1 h and stirred at that temperature for 2h. The resulting suspension was cooled to -10ºC and conc. HCl was added slowly over 4h, while maintaining the temperature below 0ºC. Solvent swap was done by concentrating to a small volume and addition of ethyl acetate and further concentration of the solvent with continuous addition of ethylacetate. Following this procedure, when the final ratio of THF:ethylacetate reached 4:1 ratio, the mixture was cooled to 0ºC and filtered off while washing the filter cake with more ethylacetate. Concentration of the filtrate to dryness gave the hexahydro-furo [2,3-*b*]furan-3-ol **11** which was confirmed by NMR and chiral gas chromatography. Carbonate intermediate **12** was prepared in 66% yield by treating **11** with disuccinimidyl carbonate at RT for 3h in the presence of triethylamine [13]. Since the process scale synthesis of darunavir has not been disclosed, the latest reported synthesis is highlighted [13]. The commercially available epoxide **13** was mixed with isobutyl amine in isopropanol at RT and refluxed for 6h. The reaction was concentrated and purified by chromatography to provide amine **15** (99%). *p*-Nitrophenyl sulfonyl chloride was added to a mixture of the amine **15** in dichloromethane and saturated aqueous bicarbonate at RT and stirred for 12 h to give sulfonamide **16** in 96% yield after purification. Hydrogenation of **16** with 10% Pd/C under 1 atm hydrogen for 11h at room temperature gave aniline **17** in 95% yield. The BOC group was removed by treating **17** with TFA in dichloromethane and the resulting amine was reacted with carbonate **12** in the presence of triethylamine for 3h to provide the desired darunavir (II) in 89% yield.

Dasatinib (*Sprycel*™)

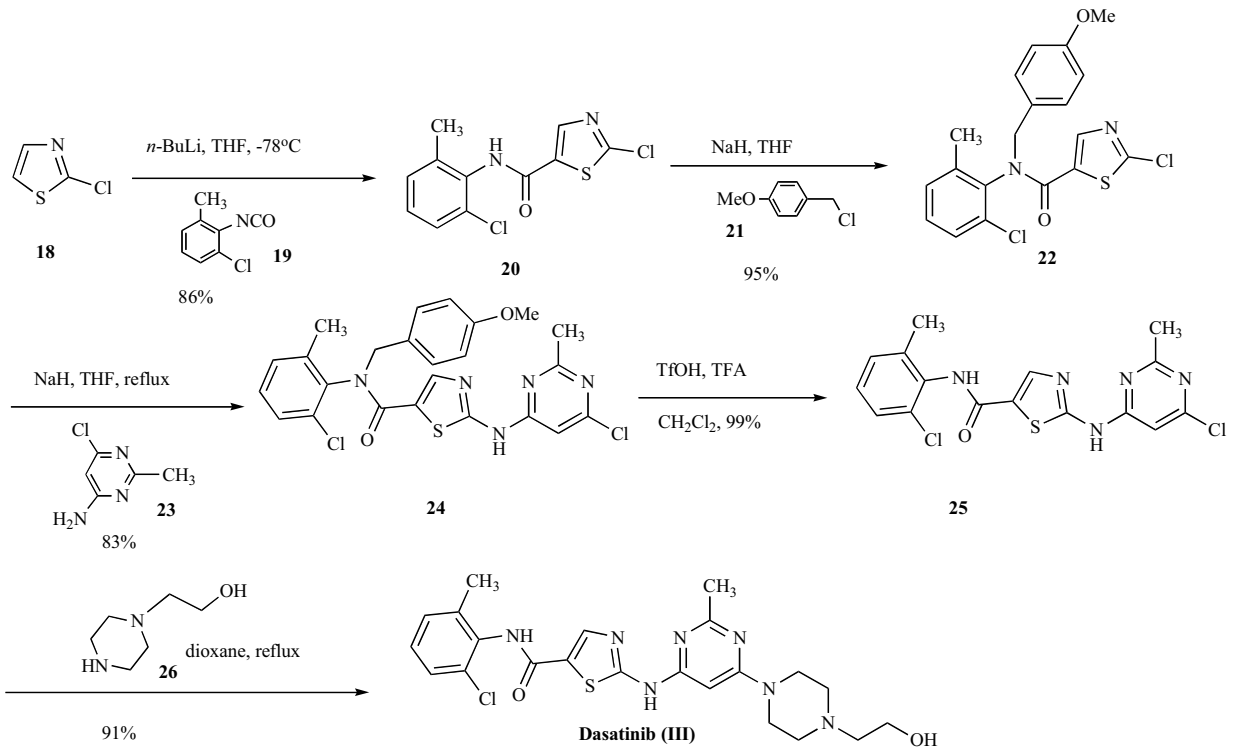
Dasatinib, developed and marketed by Bristol Myers, is the first approved oral tyrosine kinase inhibitor which binds to multiple conformations of ABL kinase for the treatment of two leukemia indications: chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) [16]. Dasatinib is a highly potent, ATP-competitive kinase inhibitor which, at nanomolar concentrations, inhibits BCR-ABL, SRC family, c-KIT, EPHA2 and PDGFR-B. A concise and efficient route (Scheme **3**) was developed for the synthesis of dasatinib [17,18]. Reaction of 2-chlorothioa-zole (**18**) with *n*-butyllithium at low temperature followed by addition of 2-chloro-6-methylphenyl isocyanate (**19**) gave anilide **20** in 86% yield. The amide **20** was protected as corresponding 4-methoxy benzyl (PMB) anilide **22** in 95% yield which was subsequently reacted with 4-amino-6-chloro-2-methylpyrimidine (**23**) in the presence of sodium hydride in hot THF to give compound **24** in 83% yield. The PMB protecting group was then removed with triflic acid to give compound **25** in 99% yield. Compound **25** was reacted with 1-(2-hydroxyethyl)piperazine (**26**) in refluxing dioxane to give dasatinib (**III**) in 91% yield.

Decitabine (*Dacogen*™)

SuperGen's decitabine was approved for the treatment of myelodysplastic syndromes (MDS) and exerts its antineoplastic effects by incorporation into DNA and inhibition of DNA methyltransferase in rapidly dividing cells. However, non-proliferating cells are relatively insensitive to this agent [19]. Silylated 5-aza-cytosine (**28**) was condensed with 9-fluorenylmethoxycarbonyl (Fmoc) protected 2-deoxy-1-chlororibose (**27**) with tin chloride (IV) in dichloroethane (Scheme **4**). The coupled product **29** was de-protected with excess triethylamine in dry pyridine to give decitabine (**IV**) in 36% yield after separation from its corresponding α isomer [20].

Lubiprostone (*Amitiza*™)

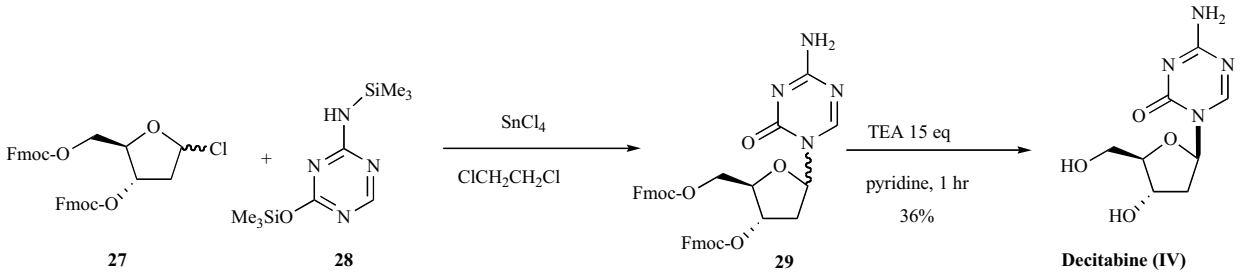
Lubiprostone, developed by Sucampo Pharmaceuticals and jointly marketed with Takeda, represents a novel pharmacotherapy for the treatment of chronic idiopathic constipation which is a form of constipation characterized by difficult passage of stools for a period of at least 3 months. It is the first selective chloride channel (ClC-2) activator on the market and works by exerting its effects through increasing fluid secretion and motility in the intestine to alleviate symptoms associated with chronic idiopathic constipation [21]. Synthesis of lupiprostone started with the tetrahydropyran (THP) protected (-)Corey lactone **30** [22] (Scheme **5**). Desilylation of **30** with TBAF in THF gave free carbinol in 82% yield which was oxidized with oxalyl chloride and DMSO to give corresponding crude aldehyde **31**. Aldehyde **31** was condensed with dimethyl 3,3,-difluoro-2-oxoheptylphosphonate (**32**) in the presence of thallium ethoxide to give unsaturated difluoroketone **33** which was hydrogenated with H_2 over Pd/C in ethyl acetate and the resulting ketone was subsequently reduced with sodium borohydride in methanol to give lactone **34** in excellent yield. The lactone **34** was reduced to lactol **35** with DIBAL at -78°C in toluene and the crude lactol **35** was condensed with 4-carboxybutyl triphenylphosphonium bromide (**36**) in the presence of *t*-BuOK in THF to yield compound **37**. Crude **37** was reacted with benzyl bromide and DBU in dichloromethane (DCM) to give the benzyl ester in 96% yield. Oxidation of the alcohol with Collins reagent and removal of the THP protecting group under acidic conditions gave corresponding prostaglandin E2 benzyl ester **38**. Finally, compound **38** was submitted to simultaneous benzyl ester group cleavage and double bond hydrogenation with H_2 over Pd/C in ethyl acetate to give lubiprostone (**V**) in 94% yield.



Scheme 3. Synthesis of Dasatinib.

Mozavaptan (*Physuline*®)

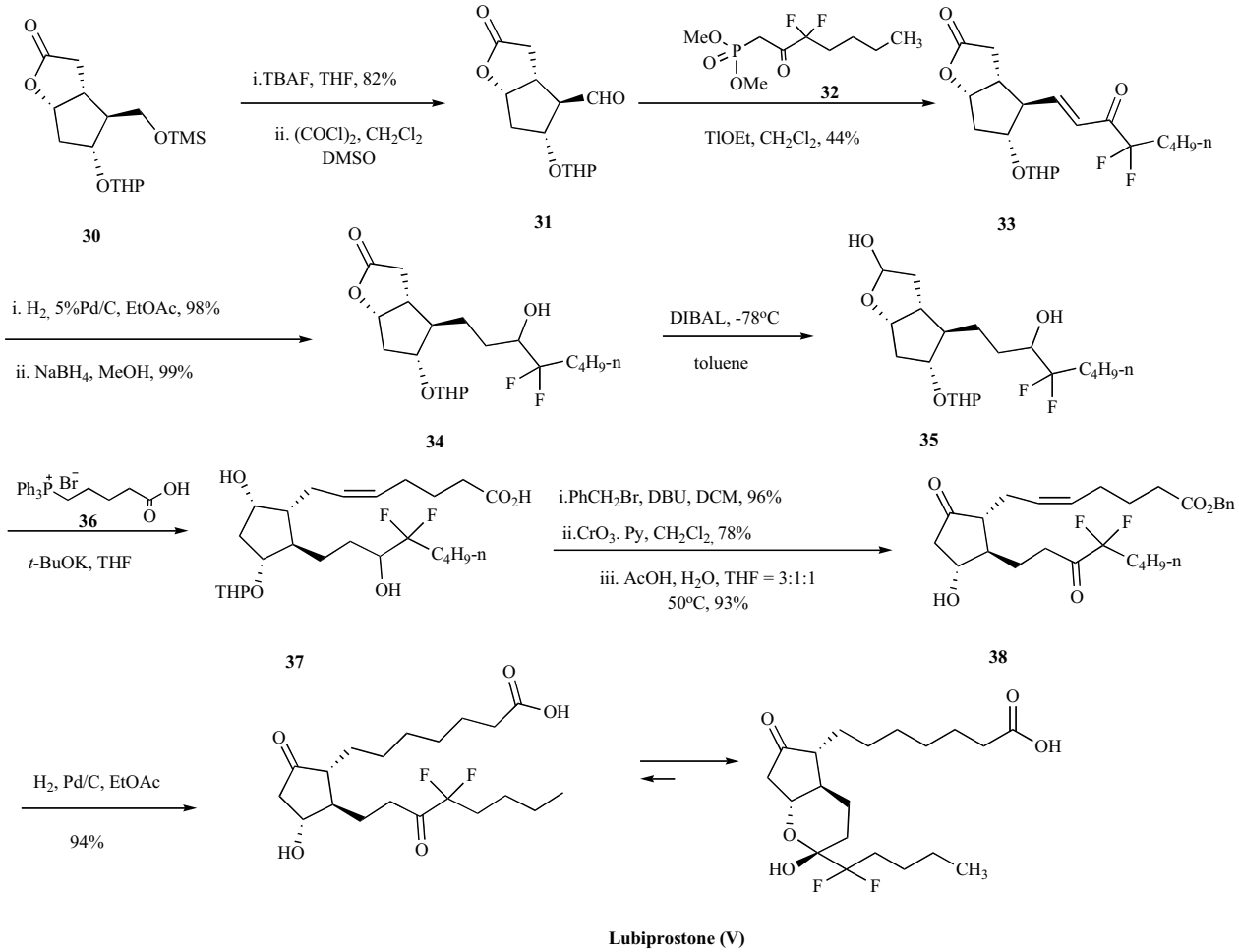
Mozavaptan is a vasopressin V2 antagonist developed by Otsuka Pharmaceutical Co. in Japan for the treatment of hyponatremia in patients with inappropriate anti-diuretic hormone (ADH) secretion syndrome. This tends to occur in patients with tumors with ectopic ADH production and others with liver failure, cardiac failure and volume contraction [6,23]. The reported synthesis of mozavaptan is shown in Scheme **6** [24,25]. Readily available benzazepin-5-one **39** [26] was refluxed with 40% methyl amine methanol solution in the presence of molecular sieves for 5h followed by the reduction of the resulting imine with sodium borohydride to give the monomethyl amine. Reductive alkylation of the monomethyl amine with formaldehyde in the presence of sodium cyanoborohydride gave the dimethyl amino benzazepine **40**. Removal of the tosyl group was facilitated by heating **40** in polyphosphoric acid at 150°C for 2 h to give **41** in 97% yield. Reaction of the resulting benzazepine **41** with *p*-nitrobenzoyl chloride (**42**) in the presence of triethylamine provided amide **43** which was hydrogenated in the presence of 10% Pd/C in ethanol at room temperature to give aniline **44**. Acylation of aniline **44** with 2-methylbenzoylchloride (**45**) in the presence of triethylamine gave mozavaptan (**VI**) in 54% yield.



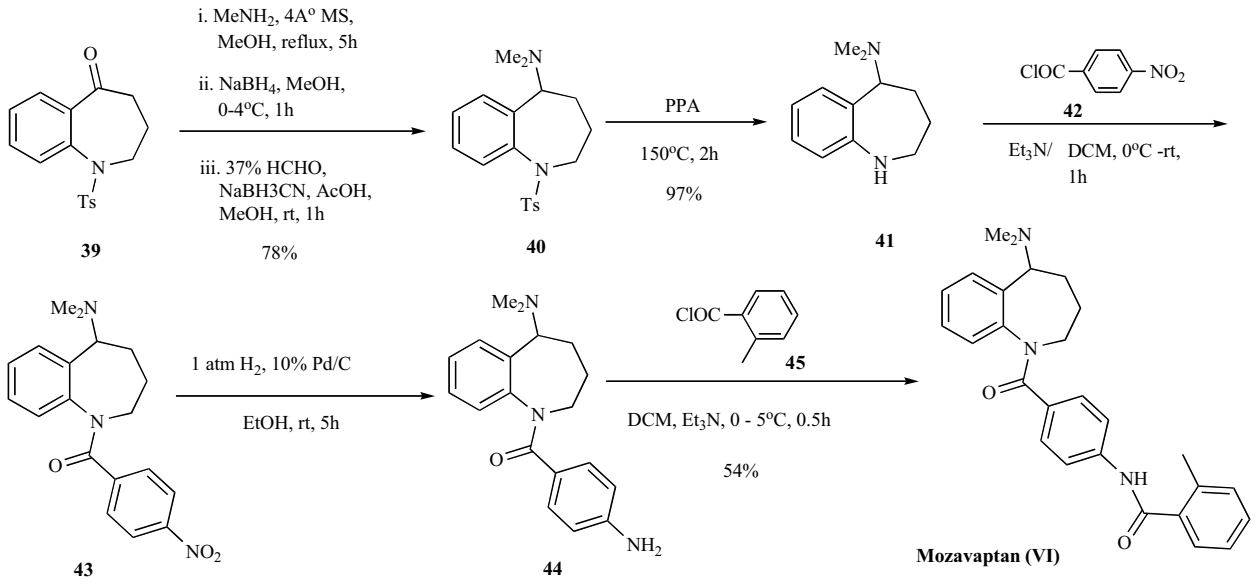
Scheme 4. Synthesis of Decitabine.

Ranolazine (*Ranexa*™)

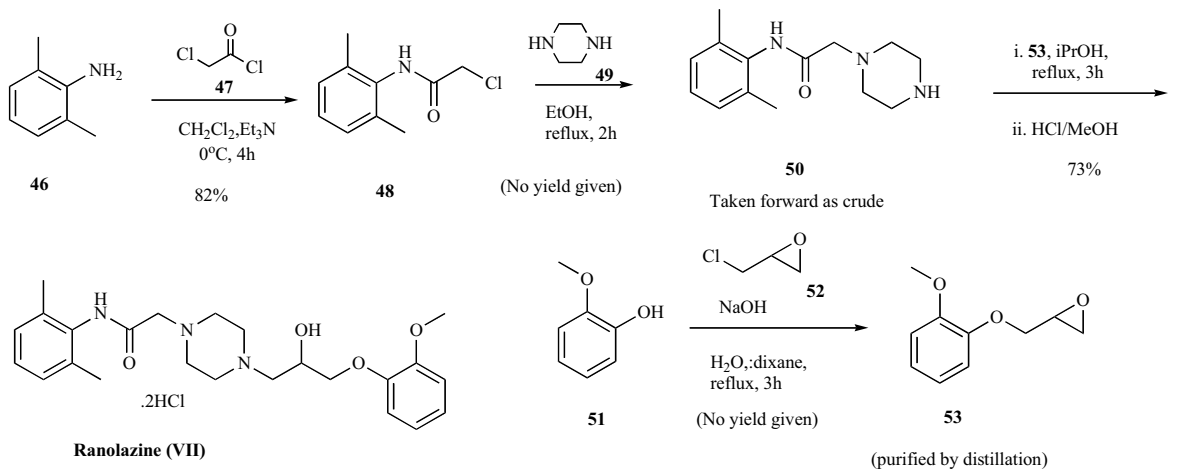
Ranolazine, developed by CV therapeutics after licensing it from Roche (Syntex), is a late stage sodium channel blocker approved in March 2006 for the treatment of chronic angina. The compounds anti-angina and anti-ischemic affects do not depend on reductions in heart rate or blood pressure. Because of the potential for QT prolongation, the drug is indicated for treating patients that do not get adequate response with other anti-anginal drugs [6,27]. Two syntheses, one from the inventors at Roche [28] and other from a group



Scheme 5. Synthesis of Lubiprostone.



Scheme 6. Synthesis of Mozavaptan.

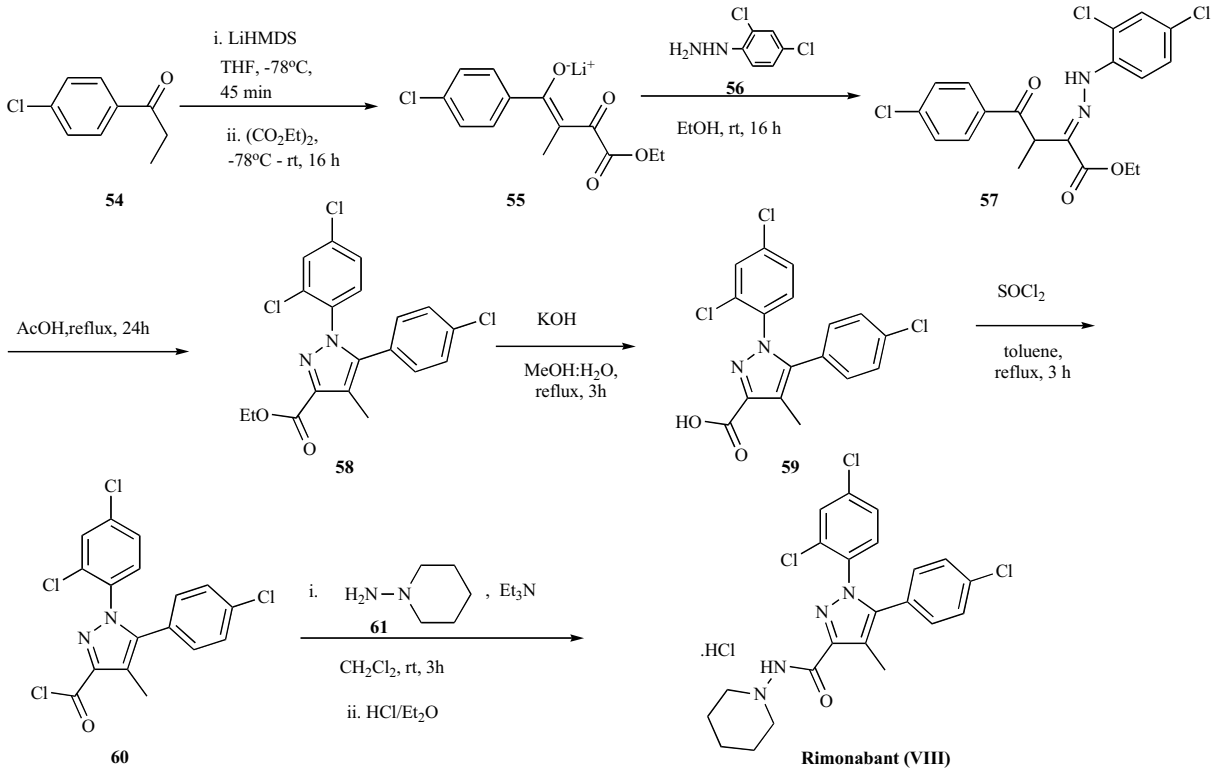


Scheme 7. Synthesis of Ranolazine.

in Hungary [29], of Ranolazine have been described in the patent literature. The original synthesis is highlighted in Scheme **7**. Reaction of 2,6-dimethylaniline **46** with chloroacetyl chloride (**47**) in the presence of triethylamine for 4h at 0ºC gave amide **48** in 82% yield. This chloro amide **48** was reacted with piperazine in refluxing ethanol for 2 h to give piperazinyl amide **50**. Reaction of amide **50** with epoxide intermediate **53**, prepared by reacting 2-methoxy phenol **51** with epichlorohydrin, in refluxing isopropanol for 3 h followed by treatment with HCl/methanol gave ranolazine dihydrochloride (**VII**) in 73% yield.

Rimonabant (*Acomplia*®)

Rimonabant is a central cannabinoid receptor 1 (CB-1) antagonist developed by Sanofi-Aventis and approved for the treatment of obesity in Europe. It's currently under review in the US. The inhibition of the endocannabinoid pathway, which is believed to play an important role in the control of appetite signals, reduces food intake and thus may aid in obesity control [6,30,31]. The reported preparation of rimonabant, both in small and large scale, is shown in Scheme **8** [32]. Lithium enolate formation of *p*-chlorophenyl ethyl



Scheme 8. Synthesis of Rimonabant.

ketone **54** with LiHMDS in THF at -78ºC for 45 min followed by reaction with diethyl oxalate at -78ºC and warming to room temperature over 16 h provided the lithium enolate salt of the diketoester **55**. Reaction of diketoester salt **55** with 2,4-dichlorophenyl hydrazine (**56**) in ethanol at room temperature gave intermediate hydrazone **57** which is then cyclized in refluxing acetic acid for 24 h to obtain pyrazole ester **58**. Hydrolysis of ester **58** with KOH in refluxing methanol:water mixture gave acid **59** which was then converted to the acid chloride **60** with thionyl chloride in refluxing toluene in very good yield. On scale, the synthesis of the acid chloride was performed in cyclohexane at 83ºC. Reaction of acid chloride **60** with 1-aminopiperidine (**61**) in the presence of triethylamine at 0ºC to room temperature over 3h gave rimonabant (**VIII**) which was isolated as the HCl salt by treating it with HCl in ether.

Rotigotine (*Neupro*®)

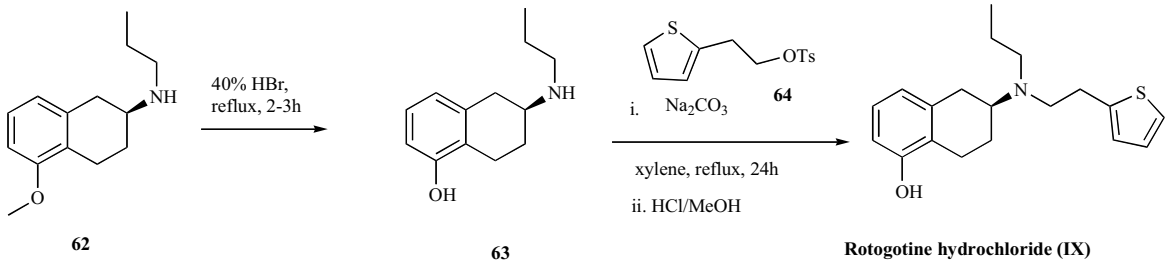
Rotigotine is a nonergolinic dopamine D_2/D_3 receptor agonist that was developed and approved for marketing in Europe for the treatment of Parkinson's disease. It was developed jointly by Aderis Pharmaceuticals and Swartz Pharmaceuticals as a transdermal patch for an once daily application [6]. The synthesis described by the originators at Discovery Therapeutics Inc. (now known as Aderis Pharmaceuticals) is shown in Scheme **9** [33]. The synthesis utilizes the chiral methoxy tetralin **62** as starting precursor which was obtained *via* chiral crystallization procedure described in a patent literature [34]. Demethylation of tetraline **62** with refluxing 40% HBr solution for several hours provided phenol **63** in 96% yield [35]. Reaction of the amine **63** with 2-thiophenylethyl tosylate **64** in refluxing xylene for 24-32 h in the presence of 0.6 equiv sodium carbonate gave the desired rotigotine (**IX**) without requiring chromatographic purification. The ratio of sodium carbonate to the amine was critical to achieving good yields (59-84% yield) without requiring extensive purification. Rotigotine was isolated as the HCl salt.

Silodosin (*Urief*)

Silodosin (KMD 3213) is an α_{1a} receptor subtype inhibitor indicated for the treatment of urinary disturbances due to urethral resistance from enlarged prostate. It was developed by Kissei and jointly marketed with Daiichi in the Japanese market since approval in 2006 [6,36]. The synthesis of silodosin has been disclosed in several patents [37-39]. The latest synthetic route disclosed in the 2006 patent is highlighted in Scheme **10** [38d]. The synthesis started with Grignard generation from readily available bromoindoline **65** by treating it with Mg in the presence of a catalytic dibromoethane in THF. After initiation of the reaction with some heat and refluxing at a steady rate, CBZ protected oxazolidinone **66** [39b] was added over 1 h, refluxed for 4 h and then stirred at room temperature for 2 days. The reaction was quenched with 6 M aqueous HCl and stirred for 12 h after which time the reaction was worked up to provide product **67** in 53% yield. Ketone **67** was then treated with triethylsilane in TFA at 0ºC and stirred at room temperature for 10 h to provide amine **68** in 61% yield. Bromination of the indoline **68** with bromine in warm acetic acid furnished bromide **69** in 53% yield which was reacted with copper cyanide in DMF at 130ºC to give the cyano indoline **70** in 82% yield. Selective deprotection of the benzyloxycarbonyl over the benzyl group was accomplished by reacting indoline **70** with 1 atm hydrogen in the presence of 5% Pd/C in ethanol at room temperature. The resulting free amine **71** was then reacted with mesylate **72** [37] in *t*-butanol with sodium carbonate as base at 80-90ºC for 46 h to provide **73** in 67% yield. Removal of the benzyl ether was accomplished by reacting **73** with 1 atm hydrogen in the presence of 10%Pd/C to give alcohol **74,** which upon hydrolysis provided the desired silodosin (**X**). No yield for the final reaction was given.

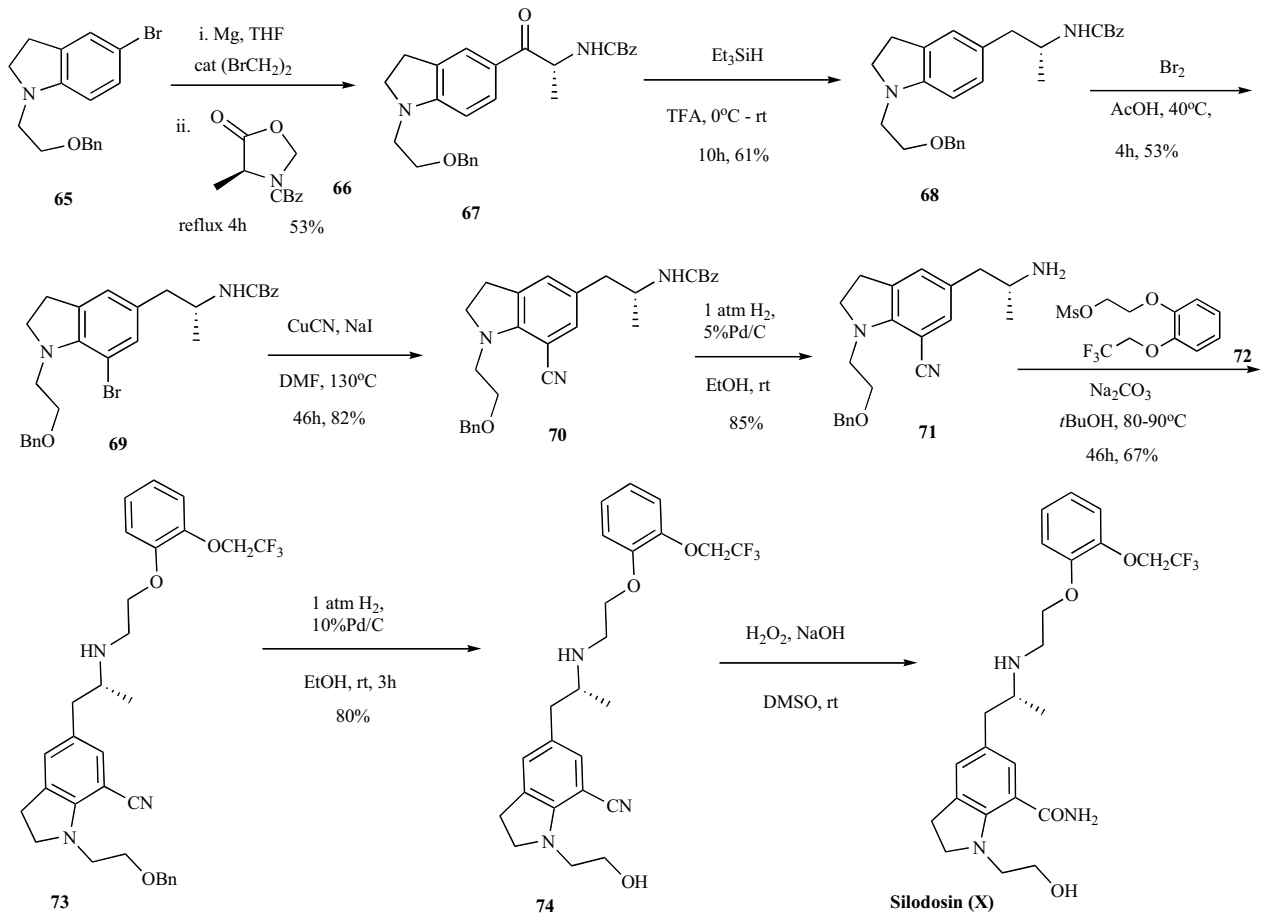
Sitagliptin Phosphate (*Januvia*™)

Sitagliptin is the first novel dipeptidyl peptidase IV inhibitor from Merck for the treatment of type 2 diabetes without weight gain and the incidence of hypoglycemia was similar to placebo. Sitagliptin acts by enhancing the body's incretin system, which helps to regulate glucose by affecting β and α cells in the pancreas [40]. Synthesis of sitagliptin [41,42] started with the slow addition of chloropyrazine (**75**) to 35% aqueous hydrazine at 60-65°C, controlling this exothermic reaction and making it process-friendly, and the resulting crude pyrazinyl hydrazine was acetylated with trifluoroacetic anhydride to afford bis-trifluoromethylhydrazide **76** in 49% yield from the chloropyrazine (Scheme **11**). Compound **76** was treated with superphosphoric acid, a diluted form of polyphosphoric acid, to give cyclized compound **77** which was hydrogenated with Pd/C and the resulting product was treated with HCl in IPA to afford compound **78** as its HCl salt in 51% yield from **76**. Compound **78** was used later on in a coupling reaction to generate sitagliptin. Compound **79**, a beta-ketoester, was subjected to asymmetric reduction with (*S*)-BinapRuCl$_2$-triethylamine complex in methanol at 80°C, catalytic amount of hydrogen bromide, and 90 psi of hydrogen atmosphere to give the desired beta-hydroxy ester



62 **63** **Rotogotine hydrochloride (IX)**

Scheme 9. Synthesis of Rotigotine.

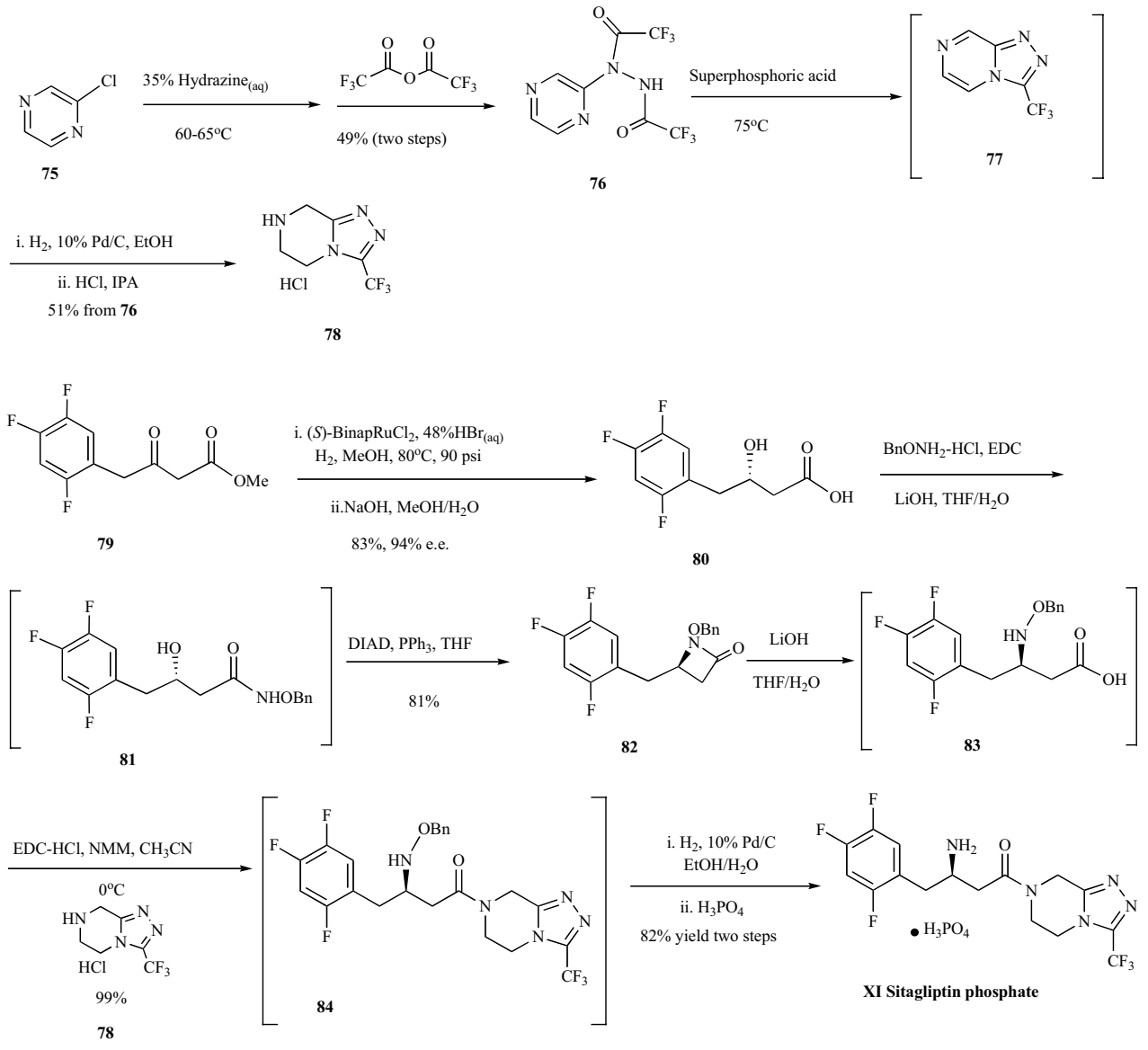


Scheme 10. Synthesis of Silodosin.

which was hydrolyzed to give carboxylic acid **80** in 94% e.e. and 83% yield. The carboxylic acid **80** was coupled with $BnONH_2$-HCl in the presence of EDC and lithium hydroxide in THF/H_2O to give coupled compound **81** which was cyclized to compound **82** with DIAD and triphenylphosphine in THF in 81% yield from compound **80**. Compound **82** was then hydrolyzed to β-amino acid **83** with lithium hydroxide, and the acid was coupled with compound **78** at 0°C with EDC-HCl and NMM as base to give compound **84** in excellent yield. Compound **84** was hydrogenated with 10% Pd/C in an ethanol/H_2O mix solvent system. The water was crucial to complete the reaction and restore catalyst activity. Finally, the ethanol solution of the hydrogenated product was treated with phosphoric acid, and sitagliptin (**XI**) was crystallized as its anhydrous phosphoric acid salt from aqueous ethanol solution.

Sitaxsentan Sodium (*Thelin*®)

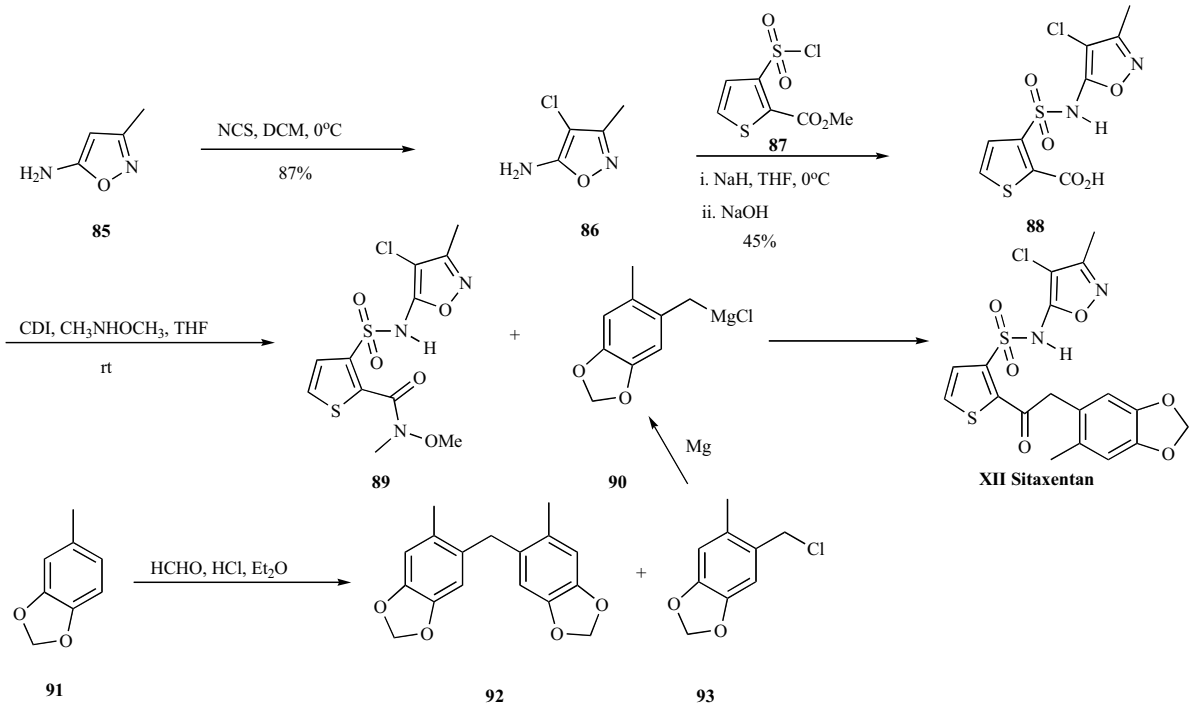
In November Encysive Pharmaceuticals launched *Thelin*® (sitaxsentan sodium) in the U.K. for the treatment of pulmonary arterial hypertension (PAH), following European Commission approval in August 2006. Sitaxsentan is the first selective endothelin A (ETA) receptor antagonist, and the first once-daily oral treatment available for patients with PAH. It is 6,500-fold selective in the targeting of ETA versus ETB receptors. Sitaxsentan is indicated for improving exercise capacity in PAH patients classified as World Health Organization (WHO) functional class III. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. In the U.S., Encysive has submitted a complete response to an approvable letter received from the FDA in July. The synthesis of sitaxentan is depicted in Scheme **12**. 5-amino-3-methylisoxazole **85** was treated with NCS in DCM at 0°C to give chloroisoxazole **86** in 87% yield. The amine was then coupled with the commercially available 2-(methoxycarbonyl)-3-thiophenesulfonyl chloride (**87**) using sodium hydride in THF at 0°C. The resulting ester was directly hydrolyzed in 1N NaOH to furnish acid **88** in 45% yield [43]. The acid **88** was then coupled with *N,O*-dimethylhydroxylamine to give Weinreb amide **89**. The amide **89** was then treated with benzylic Grignard reagent followed by acidic workup to give the sitaxentan **XII** in 50% yield in two steps. The Grignard reagent **90** was prepared through the following sequence. The 5-methylbenzodioxole **91** was treated with aqueous formaldehyde and concentrated HCl in ethyl ether to give the desired benzyl chloride **93** and condensation product **92**. The mixture of **92** and **93** was used to form the Grignard reagent without separation [44].



Scheme 11. Synthesis of Sitagliptin.

Sunitinib Malate (*Sutent*®)

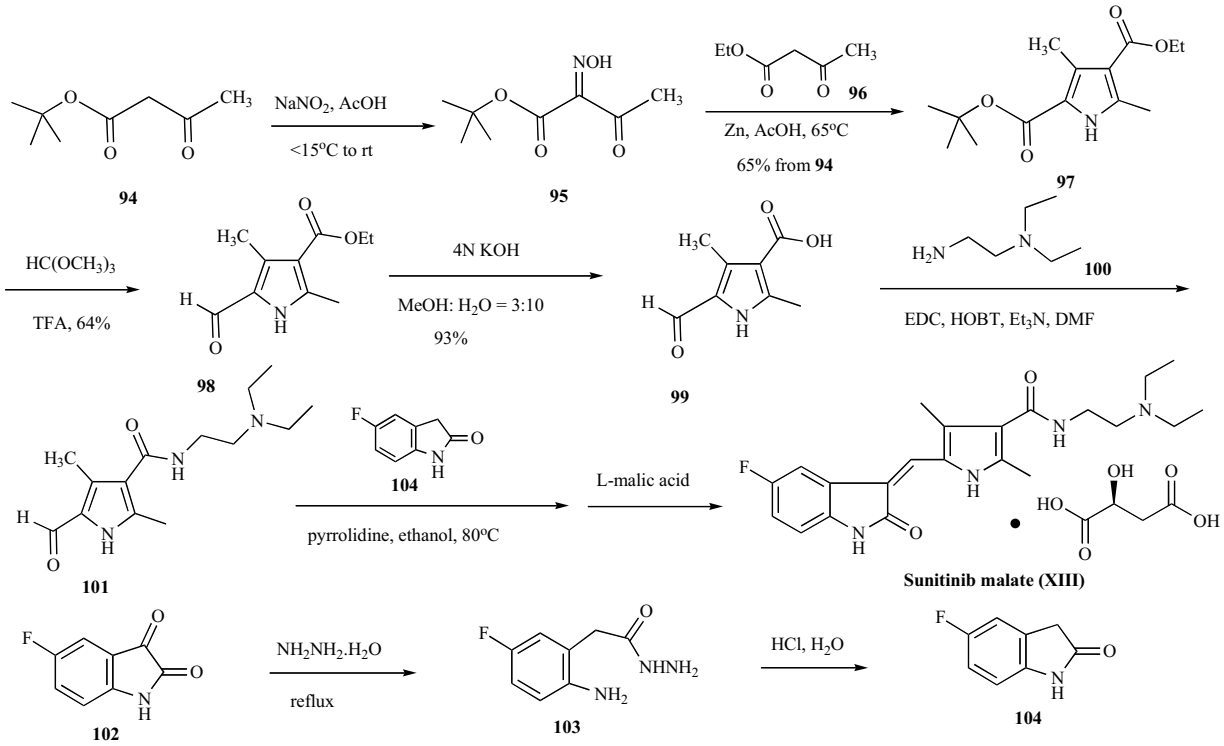
Sunitinib, an orally active multi-tyrosine kinase inhibitor from Pfizer, was approved for the treatment of gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma (RCC). This was the first time that FDA simultaneously granted two indications for a new oncology drug. Sunitinib is a potent inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). [45]. The commercially available 3-oxobuturic acid *tert*-butyl ester (**94**) was condensed with sodium nitrite in acetic acid to give corresponding hydroxyimine **96** which was treated with 3-oxobutyrate ethyl ester in the presence of zinc dust in acetic acid to give cyclized compound **97** in 65% yield from **94** (Scheme **13**). Compound **97** was subjected to hydrolytic decarboxylation and formylation with trifluoroacetic acid and triethylorthoformate to give compound **98** in 64% yield which was hydrolyzed with potassium hydroxide to give corresponding acid **99** in 93% yield. Acid **99** was coupled with 2-(diethylamino)ethylamine (**100**) with EDC, HOBT in DMF to give amide **101**. The oxindole **104** was prepared from 5-fluoroisatin (**102**) by heating **102** with neat hydrazine hydrate to give hydrazide **103** which was cyclized under acid to provide 5-fluorooxindole (**104**). The crude amide **101** was finally condensed with oxindole **104** in the presence of pyrrolidine in ethanol at 80°C and the resulting product (SU011248) was treated with L-malic acid to provide sunitinib malate (**XIII**) [46].



Scheme 12. Synthesis of Sitaxentan.

Telbivudine (Tyzeka™ in US; Sebivo® in Switzerland)

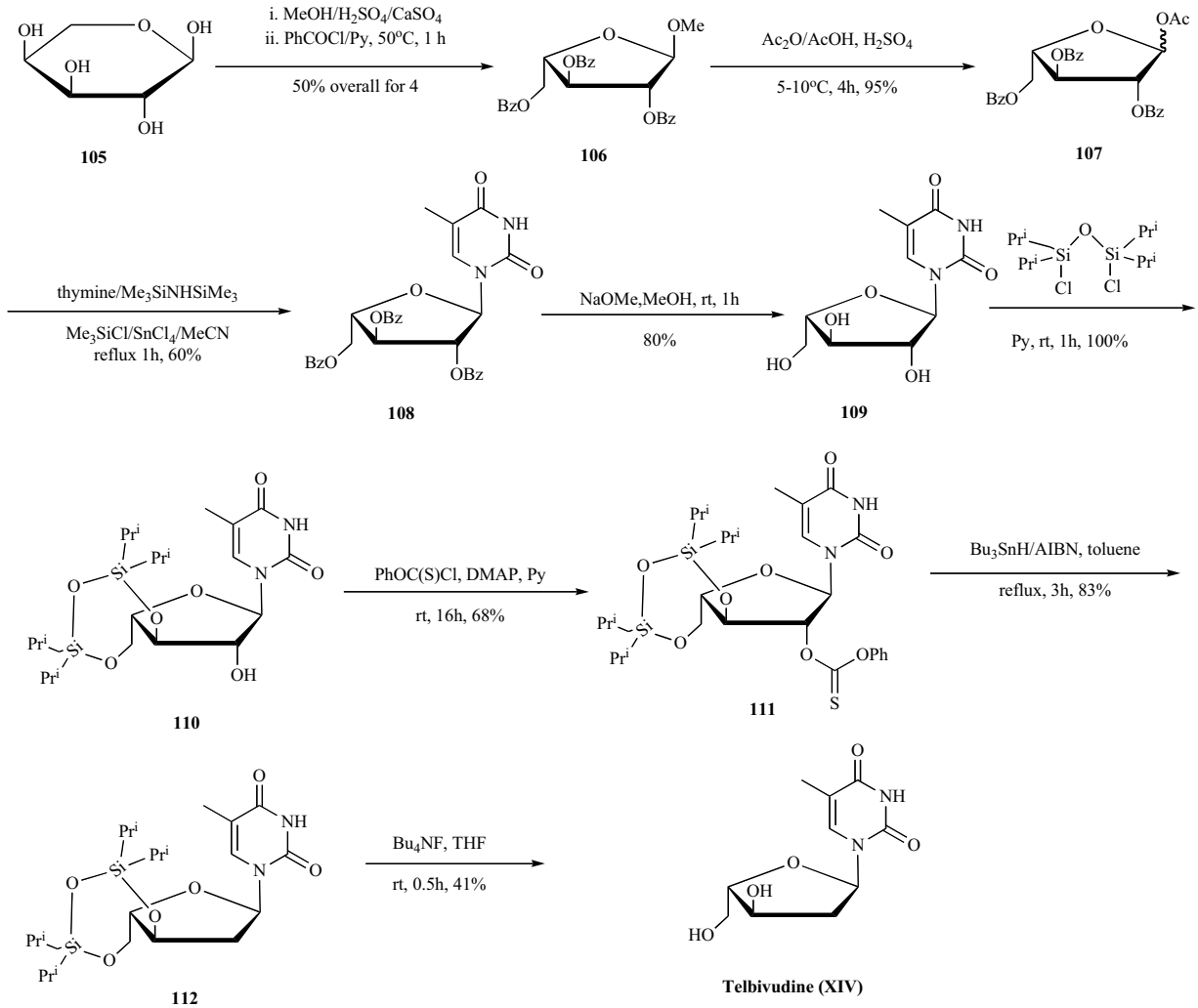
There are approximately 400 million people worldwide with chronic hepatitis B virus (HBV) infection, about one-third of whom have potentially progressive and life-threatening liver disease associated with the infection. Chronic hepatitis B infection can lead to cirrhosis, liver failure and



Scheme 13. Synthesis of Sunitinib Malate.

hepatocellular carcinoma. Globally, HBV infection accounts for over one million deaths annually. At present, lamivudine and adefovir dipivoxil are the only approved nucleoside/ nucleotide analogs for the treatment of HBV infection. However, resistance to lamivudine is now recognized in 16 to 32% of HBV-infected patients after the first year of monotherapy [47,48] and about 50% of patients after two years. With adefovir treatment, the resistance rate is much lower, at about 2.5% after two years of therapy. Experience in treating chronic HIV infections has proven the advantage of therapy with a combination of antiviral compounds. Similarly for HBV, there is a clear need for additional antiviral compounds. Several promising candidates are currently in clinical development. Idenix (then known as Novirio) discovered that the known beta-L-nucleosides, L-dA, L-dC (torcitabine) and L-dT (telbivudine), have highly specific activity against HBV [47]. These L-nucleosides are essentially without activity against any of the other viruses tested and are similarly without effect in cell culture and *in vivo* toxicological tests. However, they are phosphorylated within human cells to their triphosphates which inhibit the HBV DNA polymerase, but not human polymerases [47,48]. Of these three compounds, telbivudine was the only one to combine reasonable oral bioavailability with good anti-HBV activity and so was progressed to development jointly with Novartis with the highest priority.

The synthesis of telbivudeine is depicted in Scheme **14** [49,50]. The L-arabinose (**105**) was treated with acid in methanol to form the semi-acetyl intermediate which was then reacted with benzoyl chloride to provide **106** in 50% yield [51]. Acetolysis of **106** with a mixture of acetic acid and acetic anhydride afforded **107** in 95% yield. The α/β mixture was directly condensed with activated thymine to give **108**. The nucleoside **108** was purified by column chromatography and characterized as the α-anomer. Debenzoylation of **108** with sodium methoxide in methanol afforded **109**. Differentiation of the 2'-OH was achieved by selective protection of the two other hydroxyl groups with 1,3-dichloro-1,1,3,3,-tetraisopropyldisiloxane to form **110**. In order to limit undesired reaction during the deoxygenation step, **110** was transformed into o-phenylthiocarbonate **111**



Scheme 14. Synthesis of Telbivudine.

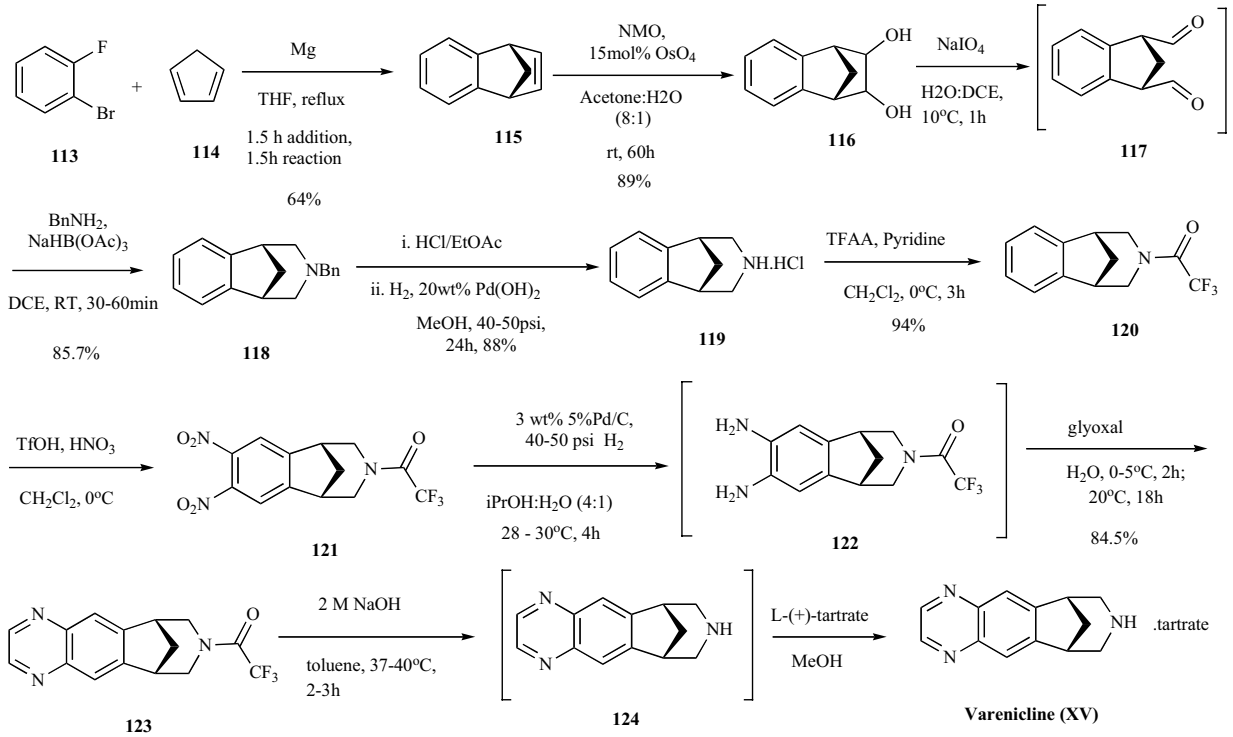
which upon treatment with tributyltin hydride under Barton's conditions afforded **112** in good yield. Desilylation of **112** gave Telbivudine (**XIV**).

Varenicline (*Chantix*™)

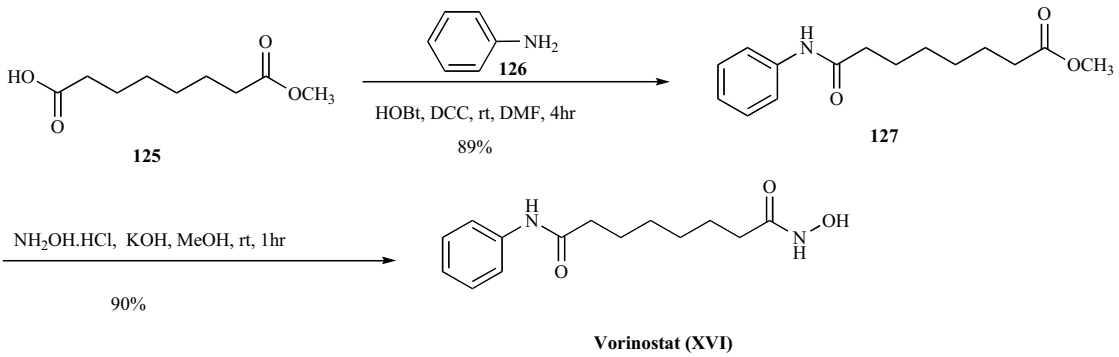
Varenicline, a nicotinic $\alpha_4\beta_2$ partial agonist, was approved in the US for the treatment of smoking cessation in May of 2006. It was developed and marketed by Pfizer as a treatment for cigarette smokers who want to quit. Varenicline partially activates the nicotinic receptors and thus reduces the craving for cigarette that smokers feel when they try to quit smoking. By mitigating this craving and antagonizing nicotine activity without other symptoms, this novel drug helps quitting this dangerous addiction easier on the patients [6,52]. Several modifications [54,55] to the original synthesis [53,56] have been reported in the literature, including an improved process scale synthesis of the last few steps (Scheme **15**) [57]. The Grignard reaction was initiated on a small scale by addition of 2-bromo fluorobenzene **113** to a slurry of Magnesium turnings and catalytic 1,2-dibromoethane in THF and heating the mixture until refluxing in maintained. To this refluxing mixture was added a mixture of the 2-bromo fluorobenzene **113** and cyclopentadiene **114** over a period of 1.5 h. After complete addition, the reaction was allowed to reflux for additional 1.5 h to give the Diels-Alder product **115** in 64% yield. Dihydroxylation of the olefin **115** by reacting with catalytic osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide (NMO) in acetone:water mixture at room temperature provided the diol **116** in 89% yield. Oxidative cleavage of diol **116** with sodium periodate in biphasic mixture of water: DCE at 10ºC provided di-aldehyde **117** which was immediately reacted with benzyl amine in the presence of sodium acetoxyborohydride to give benzyl amine **118** in 85.7% yield. The removal of the benzyl group was effected by hydrogenation of the HCl salt in 40-50 psi hydrogen pressure with 20% $Pd(OH)_2$ in methanol to give amine hydrochloride **119** in 88% yield. Treatment of amine **119** with trifluoroacetic anhydride and pyridine in dichloromethane at 0ºC gave trifluoroacetamide **120** in 94% yield. Dinitro compound **121** was prepared by addition of trifluoroacetamide **120** to a mixture of trifluoromethane sulfonic acid and nitric acid, which was premixed, in dichloromethane at 0ºC. Reduction of the dinitro compound **121** by hydrogenation at 40-50 psi hydrogen in the presence of catalytic 5%Pd/C in isopropanol:water mixture provided the diamine intermediate **122** which was quickly reacted with glyoxal in water at room temperature for 18h to give compound **123** in 85% overall yield. The trifluoroacetamide **123** was then hydrolyzed with 2 M sodium hydroxide in toluene at 37-40ºC for 2-3h followed by preparation of tartrate salt in methanol to furnish varenicline tartrate (**XV**).

Vorinostat (*Zolinza*™)

Vorinostat, a histone deacetylase (HDAC) inhibitor from Merck, was approved for the treatment of cutaneous T-cell lymphoma (CTCL), a type of non-Hodgkin's lymphoma. Vorinostat was shown to inhibit HDAC1, HDAC2, HDAC3 and HDAC6 at nanomolar concentrations. HDAC inhibitors are potent differentiating agents toward a variety of neoplasms, including leukemia and breast and prostate cancers [58]. Commercially available monomethyl ester **125** was



Scheme 15. Synthesis of Varenicline.



Scheme 16. Synthesis of Vorinostat.

reacted with aniline in the presence of DCC and HOBt in DMF to give amide **127** in 89% yield [59] (Scheme **16**). Methyl ester amide **127** was then reacted with hydroxylamine HCl salt and potassium hydroxide in methanol to give vorinostat (**XVI**) in 90% yield.

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ABBREVIATIONS

AIBN = 2,2'-Azobisisobutyronitrile

CBZ = Benzyloxycarbonyl

CDI = N,N'-carbonyldiimidazole

DCE = Dichloroethane

DCM = Dichloromethane

DIAD = Diisopropyl azodicarboxylate

DIBAL-H = Diisobutylaluminum hydride

DIPEA = Diisopropylethylamine

DMAP = 4-Dimethylaminopyridine

DMF = *N,N*-Dimethylformamide

DMPU = *N,N'*-dimethylpropyleneurea

DMSO = Methyl sulfoxide

DPPC = Diphenylphosphinic chloride

EDC = *N*-(3-Dimethylaminopropal)-N'-ethylcarbodiimide

HOBT = 1-Hydroxybenzotriazole hydrate

IPA = Isopropyl alcohol

IPAC = Isopropyl acetate

LDA = Lithium diisopropylamide

LIHMDS = Lithium bis(trimethylsilyl)amide

MS = Molecular sieves

NBS = *N*-Bromosuccinimide

NCS = *N*-Chlorosuccinimide

NEP = *N*-Ethylpyrrolidinone

NMM = *N*-Methylmorpholine

NMP = 1-Methyl-2-pyrrolidinone

PCC = Pyridinium chlorochromate

PDC = Pyridinium dichromate

PMB = 4-methoxylbenzyl

PPA = Poly phosphoric acid

TBAF = *t*-Butyl ammonium fluoride

TBDMS = *t*-Butyldimethylsilyl

TEA = Triethyl amine

TFA = Trifluoroacetic acid

TFAA = Trifluoroacetic acid anhydride

THF = Tetrahydrofuran

THP = Tetrahydropyran

TIPS = Triisopropyl silyl

TPAP = Tetrapropylammonium perruthenate

TMG = 1,1,3,3-Tetramethylguanidine

p-TSA = *para*-Toluene sulfonic acid

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