Review

Synthetic approaches to the 2010 new drugs

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Abstract

New drugs are introduced to the market every year and each represents a privileged structure for its biological target. These new chemical entities (NCEs) provide insights into molecular recognition and also serve as leads for designing future new drugs. This review covers the synthesis of 15 NCEs that were launched anywhere in the world in 2010.

1. 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 or medicine.1

This annual review was inaugurated nine years ago2–9 and presents synthetic methods for molecular entities that were launched in various countries during 2010.10 Given that drugs tend to have
Figure 1. Structures of 15 new drugs marketed in 2010.
structural homology across similar biological targets, it is widely
believed that the knowledge of new chemical entities and their
syntheses will greatly accelerate drug design. In 2010, 29 new
products, including new chemical entities, biological drugs, and
diagnostic agents reached the market. This review focuses on
the syntheses of 15 new chemical entities that were launched any-
where in the world for the first time in 2010 (Fig. 1) and excludes
the syntheses of 15 new chemical entities that were launched any-
other major developments in new chemical entities.

2. Alogliptin benzoate (Nesina®)

Alogliptin benzoate is a dipeptidyl peptidase IV (DPP IV) inhibi-
tor discovered by Takeda Pharmaceuticals and approved in Japan
in 2010 for the treatment of type II diabetes mellitus. Alogliptin
is an oral drug for once a day dosing to complement diet and exer-
cise. Alogliptin is the most selective marketed DPP IV inhibition
and has similar PK and PD properties compared to previous entries. The discovery, structure–activity relationship of related analogs,
and synthesis of this compound have been recently published. The
most convenient synthesis for scale-up will be highlighted from several published routes (Scheme 1). Commercially available 2-cycanobenzyl amine 1 was reacted with methylisocy-
anate in DCM at ambient temperature to provide N-methyl urea 2 in
85% yield. Reaction of the urea 2 with dimethyl malonate in reflux-
ing ethanol with sodium ethoxide as base gave the cyclized trione 3 in 78–85% yield. The trione 3 was then refluxed in neat POCl₃ to
provide the penultimate chloride crude 4 in 95% yield which was reac-
ted with Boc-protected diamine 5 in the presence of potassium carbonate in DMF to furnish alogliptin I in 93–96% yield. Treatment
of alogliptin with benzoic acid in ethanol at 60–70 °C followed by
crystallization delivered the desired alogliptin benzoate (I).

3. Bazedoxifene acetate (Conbriza®)

The selective estrogen receptor modulator bazedoxifene acetate
was approved in Spain for the treatment of osteoporosis in
postmenopausal women. The drug was discovered by Wyeth (now Pfizer) and licensed to Almirall. Clinical trials with baze-
doxifene along with conjugated estrogens demonstrated signifi-
cant improvement in bone mineral density and prevented bone
loss in postmenopausal women without osteoporosis. It also
reduces fracture risks among women with postmenopausal oste-
porosis. Among many syntheses reported for this drug, the most recent process scale synthesis (multi-kg scale) is high-
ned (2) and involves the union of azepane ether (9) and indole (12). 4-Hydroxybenzyl alcohol (6) was converted in two steps to chloride (9) (Scheme 2). The reaction of 6 with 2-chloroethyl azepane hydrochloride (7) in a biphasic mixture of sodium hydroxide and toluene in the presence of tetraethylammonium bromide (TBAB) gave the desired intermediate alcohol 8 in 61% yield. Treatment of 8 with thionyl chloride (SOCl₂) gave the requisite chloride 9 in 61% yield. The reaction of 2-bromopropiophenone (10) with an excess of 4-benzoxy aniline hydrochloride (11) in the presence of triethylamine (TEA) in N,N-dimethylformamide (DMF) at elevated temperatures resulted in indole 12 in 65% yield. Alkylation of 12 with benzylchloride 9 in the presence of sodium hydride (NaH) afforded N-alkylated compound 13. The benzyl ether functional-

4. Cabazitaxel (Jevtana®)

Cabazitaxel was developed by Sanofi-Aventis as an intravenous
injectable drug for the treatment of hormone-refractory metastatic prostate cancer. As a microtubule inhibitor, cabazitaxel differs from docetaxel because it exhibits a much weaker affinity for P-glycoprotein (P-gp), an adenosine triphosphate (ATP)-dependent drug efflux pump. Cancer cells that express P-gp become resis-
tant to taxanes, and the effectiveness of docetaxel can be limited
by its high substrate affinity for P-gp. Clinical studies confirmed that cabazitaxel retains activity in docetaxel-resistant tumors. Common adverse events with cabazitaxel include diarrhea and neutropenia. Cabazitaxel in combination with prednisone is an important new treatment option for men with docetaxel-refrac-
tory metastatic CRPC (castration-resistant prostate cancer). The semi-synthesis of cabazitaxel started from 10-deacetylbaclactin III (15) which can be prepared from 7-xylosyl-10-deacetylbaclactin natural product mixture according to a literature process procedure (Scheme 3). 10-Deacetylbaclactin III was protected with tri-
ethylphosphoryl chloride (TSECl) in pyridine to afford the corresponding 7,13-bis-silyl ether in 51% yield, which was methylated with Me

Scheme 1. Synthesis of alogliptin benzoate (I).
and NaH in DMF to give 10-methoxy-7,13-bis silyl ether 16 in 76% yield. After de-silylation of 16 with triethylamine trihydrofluoride complex at room temperature, triol 17 was obtained in 77% yield. Selective methylation of 17 with MeI and NaH in DMF at 0 °C provided 7,10-dimethyl ether 18 in 74% yield. Compound 18 was condensed with commercially available oxazolidinecarboxylic acid 19 in the presence of dicyclohexylcarbodiimide/dimethylaminopyridine (DCC/DMAP) in ethyl acetate at room temperature to generate the oxazolidinone moiety of compound 20 was selectively hydrolyzed under mild acidic conditions to yield the hydroxy Boc-amino ester derivative cabazitaxel (III) in 32% yield.

5. Diquafosol tetrasodium (Diquas®)

Diquafosol tetrasodium was approved in April 2010 as Diquas® ophthalmic solution 3% for the treatment of dry eye syndrome and launched in Japan by Santen Pharmaceuticals.10 Diquafosol tetrasodium was originally discovered by Inspire Pharmaceuticals. In 2001, it was licensed to Santen for co-development and commercialization in Asian countries, and co-developed in collaboration with Allergan for the countries outside of Asia. In the US, diquafosol tetrasodium was submitted for a New Drug Application (NDA) as Prolacria® (2% ophthalmic formulation) in June 2003. However, it is still in Phase III clinical development for dry eye syndrome. Diquafosol tetrasodium, also known as INS-365, is a P2Y2 receptor agonist, which activates P2Y2 receptor on the ocular surface, leading to rehydration through activation of the fluid pump mechanism of the accessory lacrimal glands on the conjunctival surface.27 The large-scale synthesis route of diquafosol tetrasodium is described in Scheme 4.28,29 Commercially available uridine 5'-diphosphate disodium salt (21) was transformed into the corresponding tributylamine salt by ion exchange chromatography on Dowex 50 using Bu3NH+ phase, and then dimerized by means of CDI in DMF at 50 °C. The crude product was purified by Sephadex DEAE column followed by ion exchange using a Dowex 50W resin in Na+ mode. The one-pot process provided diquafosol tetrasodium (IV) in 25% yield.29

6. Eribulin mesylate (Halaven®)

Eribulin is a highly potent cytotoxic agent approved in the US for the treatment of metastatic breast cancer for patients who have received at least two previous chemotherapeutic regimens.30 Eribulin was discovered and developed by Eisai and it is currently undergoing clinical evaluation for the treatment of sarcoma (PhIII) and non-small cell lung cancer which shows progression after platinum-based chemotherapy and for the treatment of prostate cancer (PhII). Early stage clinical trials are also underway to evaluate eribulin’s efficacy against a number of additional cancers. Eribulin is a structural analog of the marine natural product halichondrin B. Its mechanism of action involves the disruption of mitotic spindle formation and inhibition of tubulin polymerization which results in the induction of cell cycle blockade in the G2/M phase and apoptosis.31 Several synthetic routes for the preparation of eribulin have been disclosed,32–35 each of which utilizes the same strategy described by Kishi and co-workers for the total synthesis of halichondrin B.36 Although the scales of these routes were not disclosed in all cases, this review attempts to highlight what appears to be the production-scale route based on patent literature.37,38 Nonetheless, the synthesis of eribulin represents a significant accomplishment in the field of total synthesis and brings a novel chemotherapeutic option to cancer patients.

The strategy to prepare eribulin mesylate (V) employs a convergent synthesis featuring the following: the late stage coupling of sulfone 22 and aldehyde 23 followed by macrocyclization under Nozaki–Hiyama–Kishi coupling conditions, formation of a challenging cyclic ketal, and installation of the primary amine (Scheme 5). Sulfone 22 was further simplified to aldehyde 24 and vinyl triflate

![Scheme 2. Synthesis of bazedoxifene acetate (II).](image-url)
which were coupled through a Nozaki–Hiyami–Kishi reaction. The schemes that follow will describe the preparation of fragments 23, 24 and 25 along with how the entire molecule was assembled.

The synthesis of the C1–C13 aldehyde fragment 23 is described in Scheme 6. L-Mannonic acid-lactone 26 was reacted with cyclohexanone in p-toluene sulfonic acid (p-TSA) to give the biscyclohexylidene ketal 27 in 84% yield. Lactone 27 was reduced with diisobutylaluminum hydride (DIBAL-H) to give lactol 28 followed by condensation with the ylide generated from the reaction of methoxymethylene triphenylphosphorane with potassium tert-butoxide to give a mixture of E and Z vinyl ethers 29 in 81% yield. Dihydroxylation of the vinyl ether of 29 using catalytic osmium tetroxide and N-methylmorpholine-N-oxide (NMO) with concomitant cyclization produced diol 30 in 52% yield. Bis-acetonide 30 was then reacted with acetic anhydride in acetic acid in the presence of ZnCl₂ which resulted in selective removal of the pendant ketal protecting group. These conditions also affected peracylation, giving rise to tetraacetate 31 in 84% yield. Condensation of 31 with methyl 3-[(trimethylsilyl)pent-4-enoate in the presence of boron trifluoride etherate in acetonitrile provided alkene 32. Saponification conditions using Triton B(OH) removed the acetate protecting groups within 32 and presumably induced isomerization of the alkene into conjugation with the terminal ester, triggering an intramolecular Michael attack of the 2-hydroxyl group, ultimately resulting in the bicyclic-bispyranyl diol methyl ester 33 as a crystalline solid in 38% yield over two steps. Oxidative cleavage of the vicinal diol of 33 with sodium periodate gave aldehyde 34 which was coupled to (2-bromovinyl)trimethylsilane under Nozaki–Hiyami–Kishi conditions to give an 8.3:1 mixture of allyl alcohols 35 in 65% yield over two steps. Hydrolysis of the cyclohexylidene ketal 35 with aqueous acetic acid followed by recrystallization gave diastereomerically pure triol 36 which was reacted with tert-butyldimethylsilyl triflate (TBSOTf) to afford the tris-TBS ether 37 in 90% yield. Reduction of the ester with DIBAL-H produced the key C1–C14 fragment 23 in 93% yield.

The preparation of the tetra-substituted tetrahydrofuran intermediate 24 is described in Scheme 7. d-Glucurono-6,3-lactone 39 was reacted with acetone and sulfuric acid to give the diquafosol tetrasodium (IV).
Scheme 5. Synthesis strategy of eribulin mesylate (V).

corresponding acetonide and the 5-hydroxyl group was then removed by converting it to its corresponding chloride through reaction with sulfuryl chloride (SO$_2$Cl$_2$) followed by hydrogenolysis to give lactone 40 in good overall yield. Reduction of the lactone 40 with DIBAL-H gave the corresponding lactol which was condensed with (trimethylsilyl)methylmagnesium chloride to afford silane 41. Elimination of the silyl alcohol of 41 was accomplished under Peterson conditions with potassium hexamethyldisilazide (KHMDS) to afford the corresponding terminal alkene in 94% yield. The secondary alcohol of this intermediate was alkylated with benzyl chloride to afford ether 42 in 95% yield. Asymmetric dihydroxylation of the alkene of 42 under modified Sharpless conditions using potassium osmate (VI) dehydrate (K$_2$OsO$_4$), potassium ferricyanide (K$_3$Fe(CN)$_6$), and the (DHQ)$_2$AQN ligand produced the vicinal diol which was then reacted with benzyl chloride, N-methylmorpholine, and DMAP to give di-benzoate 43 in excellent yield as a 3:1 mixture of diastereomeric alcohols. Allyl trimethylsilane was added to the acetal of 43 in 95% yield. Re-crystallization of 43 affording 44 in >99.5% de in 71% yield. Oxidation of the secondary alcohol of 44 under the modified Swern conditions generated the corresponding ketone which was condensed with the lithium anion of methyl phenyl sulfone to give a mixture of E and Z vinyl sulfones 45. Debenzylation of 45 using iodomethylsilyl (TMSI) followed by chelation-controlled reduction of the vinyl sulfone through reaction with NaBH(OAc)$_3$, and then basic hydrolysis of the benzoate esters using K$_2$CO$_3$ in MeOH resulted in triol 46 as a white crystalline solid in 57% yield over the five steps after re-crystallization. The vicinal diol of 46 was protected as the corresponding acetonide through reaction with 2,2-dimethoxypropane and sulfuric acid and this was followed by methyl iodide-mediated methylation of the remaining hydroxyl group to give methyl ether 47. The protecting groups within acetonide 47 were then converted to the corresponding bis-tert-butyldimethylsilyl ether by first acidic removal of the acetonide with aqueous HCl and reaction with TBSCI in the presence of imidazole to give bis-TBS ether 48. Then, ozonolysis of the olefin of 48 followed by hydrogenolysis in the presence of Lindlar catalyst afforded the key aldehyde intermediate 24 in 68% yield over the previous five steps after re-crystallization from heptane.

Two routes to the C14–C26 fragment 25 will be described as both are potentially used to prepare clinical supplies of eribulin. The first route features a convergent and relatively efficient synthesis of 25, however it is limited by the need to separate enantiomers and mixture of diastereomers via chromatographic methods throughout the synthesis. The second route to 25 is a much lengthier synthesis from a step-counting perspective; however it takes full advantage of the chiral pool of starting materials and requires no chromatographic separations and all of the products were carried on as crude oils until they could be isolated as crystalline solids.

The first route to fragment 25 is described in Scheme 8 and was initiated by the hydration of 2,3-dihydrofuran (49) using an aqueous suspension of Amberlyst 15 to generate the intermediate tetrahydro-2-furanol (50) which was then immediately reacted with 2,3-dibromopropene in the presence of tin and catalytic HBr to

Scheme 7. Synthesis of fragment 24 of eribulin mesylate (V).
afford diol 51 in 45% for the two steps. The primary alcohol of 51 was selectively protected as its tert-butyl diphenylsilyl ether using TBDPSCI and imidazole and the racemate was then separated using simulated moving bed (SMB) chromatography to give enantiopure 52 in 45% yield over the two steps. The secondary alcohol of 52 was reacted with p-toluensulfonyl chloride and DMAP to give tosylate 53 in 78% yield which was used as a coupling partner later in the synthesis of this fragment. The synthesis of the appropriate coupling partner was initiated by condensing diethylmalonate with (R)-2-(3-butenyl)oxirane (54), followed by decarboxylation to give lactone 55 in 71% yield for the two step process. Methylation of the lactone with LHMDS and MeI provided 56 in 68% yield as a 6:1 mixture of diastereomers. The lactone 56 was reacted with the aluminum amide generated by the reaction of AlMe3 and NHOMe, to give the corresponding Weinreb amide which was protected as its tert-butyldimethylsilyl ether upon reaction with TBSCl and imidazole to give 57 in 91% yield over the two steps. Dihydroxylation of the olefin of 57 by reaction with OsO4 and NMO followed by oxidative cleavage with NaIO4 gave the desired coupling partner aldehyde 58 in 93% yield. Aldehyde 58 was coupled with vinyl bromide 53 using an asymmetric Nozaki–Hiyama–Kishi reaction using CrCl2, NiCl2, Et3N and chiral ligand 66 (described in Scheme 9 below). The reaction mixture was treated with ethylene diamine to remove the heavy metals and give the secondary alcohol 59. This alcohol was stirred with silica gel in isopropanol to affect intramolecular cyclization to give the tetrahydrofuran 60 in 48% yield over the three step process. The Weinreb amide of 60 was reacted with methyl magnesium chloride to generate the corresponding methyl ketone which was converted to vinyl triflate 61 upon reaction with KHMDS and Tf2NPh. De-silylation of the primary and secondary silyl ethers with methanolic HCl gave the corresponding diol in 85% yield over two steps and the resulting mixture of diastereomers was separated using preparative HPLC to provide the desired diastereomer in 56% yield. The primary

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\text{Scheme 8. First synthesis route of fragment 25 of eribulin mesylate (V).}
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\text{Scheme 9. Synthesis of intermediates 66 and 67 of eribulin mesylate (V).}
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Scheme 10. Second synthesis route of fragment 25 of eribulin mesylate (V).

Scheme 11. Synthesis of fragment 22 of eribulin mesylate (V).
alcohol was protected as its pivalate ester with the use of pivaloyl chloride, DMAP and collidine; the secondary alcohol was converted to a mesylate upon treatment with methanesulfonyl chloride (MsCl) and Et3N to give the C15–C27 fragment 25 in high yield.

The preparations of the chiral ligand 66 used in the coupling reaction in Scheme 8 along with the chiral ligand 67 utilized later in the synthesis are described in Scheme 9. 2-Amino-3-methylbenzoic acid (62) was reacted with triphosgene to give benzoxazine dione 63 in 97% yield, which then was reacted with either D- or L-valinol in DMF followed by aqueous LiOH to give alcohols 64 and 65, respectively in 65–75% yield for the two steps. Reaction of alcohol 64 or 65 with MsCl in the presence of DMAP effected formation of the dihydrooxazole ring and mesylation of the aniline to give the corresponding (R)-ligand 66 derived from d-valinol or the (S)-ligand 67 derived from l-valinol, respectively in high yield.

An alternative route to intermediate 25 is described in Scheme 10 and although much lengthier than the route described in Scheme 8, it avoids chromatographic purifications as all of the products are carried on crude until a crystalline intermediate was isolated and purified by re-crystallization. Quinic acid (68) was reacted with cyclohexanone in sulfuric acid to generate a protected bicyclic lactone in 73% yield and the resulting tertiary alcohol was protected as its trimethylsilyl ether 69. Reduction of the lactone 69 was accomplished with DIBAL-H and the resulting lactol

Scheme 12. Synthesis of eribulin mesylate (V).
was treated with acetic acid to remove the TMS group and the resulting compound was reacted with acetic anhydride, DMAP and Et3N to give bis-acetate 70 in 65% yield for the three steps after re-crystallization. Methyl 3-(trimethylsilyl)pent-4-enoate was coupled to the acetylated lactol 70 in the presence of boron trifluoride etherate and trifluoroacetic anhydride to give adduct 71 in 62% yield. The acetate of 71 was removed upon reaction with sodium methoxide in methanol and the resulting tertiary alcohol cyclized on to the isomerized enone alkene to give the fused pyran ring. Reduction of the methyl ester with lithium aluminum hydride provided pyranyl alcohol 72. Mesylation of the primary alcohol was followed by displacement with cyanide anion to give nitrite 73. The nitrile was methylated upon reaction with KHMDS and Mel and the resulting product was purified by re-crystallization to provide nitrile 74 in 66% over the previous five steps in a 34:1 diastereomeric ratio. Acid hydrolysis of the ketal of 74 liberated the corresponding diol in 72% yield and this was reacted with 2-acetoxy-2-methylpropionyl bromide to give bromo acetate 75. Elimination of the bromide was accomplished upon treatment with 1,8-diazabicycloundec-7-ene (DBU) to give alkene 76 in 63% yield for two steps. Ozonolysis of the cyclohexene ring followed by reductive work-up with NaNH4 and basic hydrolysis of the acetate produced a triol which upon reaction with NaIO4 underwent oxidative cleavage to give cyclic hemiacetal 77 in 75% yield over the previous four steps. Wittig condensation with carboxylmethoxytrimethylphosphorane gave the homologated unsaturated ester 78. Catalytic hydrogenation of the alkene using PtO2 as the catalyst was followed by converting the primary alcohol to the corresponding triflate prior to displacement with sodium iodide to provide iodide 79 in 75% yield over four steps. The ester of 79 was reduced to the corresponding primary alcohol upon reaction with LiAlH4, THF, −78°C to give diol 80 in 90% yield. This diol was treated with methanolic potassium hydroxide to affect an intramolecular Pinner reaction and this was followed by protection of the primary alcohol as its tert-butyldiphenyldisilyl ether to give lactone 81. The lactone was reacted with the aluminum amide generated from AlMe3 and N,O-dimethylhydroxylamine and the resulting secondary alcohol was protected as its tert-butyldimethylsilyl ether to give Weinreb amide 82 in 99% crude yield over four steps. Compound 82 is the diastereomerically pure version of compound 60 and can be converted to compound 25 by the methods described in Scheme 8 absent the required HPLC separation of diastereomers.

With the three key fragments completed, the next step was to assemble them and complete the synthesis of eribulin. Aldehyde 24 was coupled to vinyl triflate 25 using an asymmetric Nozaki–Hiyami–Kishi reaction using CrCl2, NiCl2, Et3N and chiral ligand 67 (Scheme 9) to give alcohol 83 (Scheme 11). Formation of the THP ring was accomplished by reaction with KHMDS which allowed for displacement of the mesylate with the secondary alcohol and provided the THP containing product in 72% yield for the three steps. The pivalate ester group was removed with DIBAL-H to give the western fragment 22 in 92% yield.

The completion of the synthesis of eribulin is illustrated in Scheme 12. The lithium anion of sulfone 22 generated upon reaction with nBuLi was coupled to aldehyde 23 to give diol 84 in 84% yield. Both of the alcohol functional groups of 84 were oxidized using a Dess–Martin oxidation in 90% yield and the resulting sulfone was removed via a reductive cleavage upon reaction with SmI2 to give keto-aldehyde 85 in 85% yield. Macrocyclization of 85 was accomplished via an asymmetric Nozaki–Hiyami–Kishi reaction using CrCl2, NiCl2, Et3N and chiral ligand 67 to give alcohol 86 in 70% yield. Modified Swern oxidation of the alcohol provided the corresponding ketone in 91% yield and this was followed by removal of the five silyl ether protecting groups upon reaction with TBAF and subsequent cyclization to provide ketone 87. Compound 87 was treated with PPTS to provide the ‘caged’ cyclic ketal 88 in 79% over two steps. The vicinal diol of 88 was reacted with Ts2O in collidine to affect selective tosylation of the primary alcohol and this crude product was reacted with ammonium hydroxide to install the primary amine to give eribulin which was treated with methanesulfonylic acid in aqueous ammonium hydroxide to give eribulin mesylate (V) in 84% yield over the final three steps.

7. Fingolimod hydrochloride (Gilenya®)

Fingolimod hydrochloride is an immunosuppressive drug developed by Novartis and approved in the US, Europe, and Australia in 2010 for the treatment of multiple sclerosis. The structure of fingolimod derives from the naturally-occurring myriocin (ISP-1) metabolite of the fungus I. sinclairii and the aminoalcohol functionality within the drug possesses structural similarity to the sphingosine family of natural products. Although several convenient preparations of fingolimod (FTY720) have been reported in the literature, the route most closely resembling the process-scale approach is described in Scheme 13. Friedel–Crafts acylation of commercial toluene derivative 89 with bromoacetyl chloride followed by ethoxide-mediated N-acylated aminoalcohol (91) attack onto the resulting α-bromoketone 90 gave rise to ketoamide 92 in good overall yield. Next, separate hydride reduction protocols were employed to furnish diol 93. Presumably, triethylsilyl hydride reduced the ketone and both ethyl esters within 92 to the corresponding diacid, which then underwent lithium aluminum hydride treatment to arrive at diol 93. Careful attention to stoichiometry was required to avoid over reduction of amide 93, which was critical to achieve high-yielding (76%) salt formation of fingolimod HCl (VI) through the use of 6 N ethanolic hydrochloric acid.

![Scheme 13. Synthesis of fingolimod hydrochloride (VI).](image-url)
8. Iloperidone (Fanapt®)

Acting as an antagonist on serotonin (5-HT2) and dopamine receptor subtypes, iloperidone is an antipsychotic indicated for the treatment of acute schizophrenia in adults. Based on its in vitro and in vivo binding properties against both serotonin and dopamine receptors, it is expected that iloperidone will show fewer extrapyramidal symptoms than currently marketed...
antipsychotics such as haloperidol and clozapine. The original discovery was made by Hoechst-Roussel Pharmaceuticals who passed the developing rights to Vanda Pharmaceuticals and subsequently Novartis for marketing in the US and Canada. While this drug was originally approved in the US in 2009, the marketing was only initiated in the US in 2010. Although a number of syntheses are reported in the literature, the process enabled route from a key intermediate 98 is described in Scheme 14. The key intermediate 98 was synthesized from isonipecotic acid (94) in four steps. Formylation of isonipecotic acid (76% yield) followed by conversion of the acid to the acyl chloride gave 95 in 100% yield. Friedel–Crafts acylation of 1,3-difluorobenzene (96) with the acid chloride 95 provided ketone 97 in 32% yield. Treatment of ketone 97 with hydroxylamine hydrochloride in the presence of potassium hydroxide gave the corresponding oxime, which upon refluxing in 2-ethoxyethanol and water cyclized to piperidine benzisoxazole 98 with concomitant loss of the N-formyl group. Alkylation of piperidine 98 with 1-chloro-3-bromo propane in DMF in the presence of potassium carbonate provided the chloride intermediate 99 in 80% yield. Subsequent reaction with phenol 100 under basic conditions gave the desired product iloperidone (VII) in 81% yield.

9. Laminamivir octanoate (Inavir®)

Laminamivir octanate, a prodrug of a potent neuraminidase inhibitor (LANI), was approved and launched in 2010 in Japan for the treatment of influenza A and influenza B. This ester prodrug of a potent neuraminidase inhibitor was designed to permeate from the lung tissue to the plasma and then hydrolyze at such a rate to reveal the active form (laminamivir) as a long-acting therapeutic agent. Neuraminidase cleaves the glycosidic linkages of neuraminic acids which are responsible for binding new viruses to infected cells, thereby allowing viruses to release and infect other cells. Neuraminidase is essential for the replication of all influenza viruses. Like other neuraminidase inhibitors, laminamivir octanoate is a sialic acid analogue which is structurally similar to zanamivir, differing only by changing one of the hydroxy groups with a methyl ether substitution on the triol side chain. Laminamivir is administered via an inhalable formulation (20 mg, dry powder inhaler) and results from clinical trials of the drug have demonstrated that a single inhaled dose is as effective as a 5-day course of oseltamivir for treatment of influenza.

The synthesis of laminamivir octanoate began with the well-documented sugar intermediate 101 (Scheme 15). Alcohol 101 was alkylated with dimethyl sulfate in the presence of NaH in DMF to give methyl ether 102 in 80% yield. Acetonide 102 was then de-protected and subsequently acylated with Ac2O, AcOH, and H2SO4 (10:10:1, v/v) which resulted in oxazoline formation along with elimination of the methoxy functionality to furnish α,β-unsaturated ester 103. Exposure of oxazoline 103 to NaN3 in the presence of Dowex 50W/ H+ produced the trans-amidoazide 104 in 70% yield over two steps. Azide 104 was then subjected to guanidine formation conditions utilizing N,N-bis(tertbutyloxycarbonyl)-1H-pyrazole-1-carboxyamide (106), which was prepared from pyrazole-1-carboxamidine (105) by consecutive protection of the amidine nitrogens, first by treatment with Boc anhydride and disopropylethyl amine (DIEA) in DMF, and then subsequent treatment to Boc anhydride in the presence of NaH in THF to give 107 in 80% yield. The protected guanidine 107 was hydrolyzed under basic conditions to give the corresponding acid 108 in good yield. Acid 108 was esterified with diphenyl diazomethane in THF to provide 109 in 85% yield. Finally, the primary alcohol within diol 109 was selectively acylated with octanoyl chloride in the presence of TEA, followed by de-protection with TFA in CH2Cl2 to give laminamivir octanate (VIII) in 70% yield.

![Scheme 16. Synthesis of mifamurtide (IX).](image-url)
10. Mifamurtide (Mepact®)

Mifamurtide is an anticancer agent for the treatment of osteosarcoma, the most common primary malignancy of bone tissue mainly affecting children and adolescents. The drug was invented by Ciba-Geigy (now Novartis) in the early 1980s and the agent was subsequently licensed to Jenner Biotherapies in the 1990s. IDM Pharma bought the rights to the drug from Jenner in April 2003. In March 2009, mifamurtide was approved in the 27 European Union member states plus Iceland, Liechtenstein and Norway via a centralized marketing authorization. After the approval, IDM Pharma was acquired by Takeda, which began launching mifamurtide, as Mepact®, in February 2010. Mifamurtide, a fully synthetic liposomal infusion, is amenable route. Commercially available 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (MTP-PE), which is formulated as a liposomal infusion. Being a phospholipid, mifamurtide accumulates in the lipid bilayer of the liposomes upon infusion. After application of the liposomal infusion, the drug is cleared from the plasma within minutes. However, it is concentrated in lung, liver, spleen, nasopharynx and thyroid, and the terminal half-life is 18 h, which is longer than the natural substance. Two synthetic routes have been reported, and Scheme 16 describes the more processable route. Commercially available 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (110) was coupled with N-Boc-$\text{L}$-ala-nine (111) by means of N-hydroxysuccinimide (112), DCC in DMF to give amide 113, which was followed by hydrogenolysis of the CBZ group to give the corresponding L-alanyl-phosphoric acid (114). Next, commercially available N-acetylmuramyl-$\text{L}$-alanine-$\text{N}$-isoglutamine (115) was subjected to hydroxybenzotriazole (HOBT) and DIC in DMF to provide the corresponding succinimide ester 116, which was condensed with compound 114 to provide mifamurtide (IX). No yields were provided for these transformations.

11. Peramivir (Rapiacta®)

The second drug added to the influenza treatment armamentarium last year was peramivir, a novel neuraminidase inhibitor acting as a transition-state analogue inhibitor of influenza neuraminidase and thereby preventing new viruses from emerging from infected cells. It was first discovered and developed by BioCryst Pharmaceuticals, and Johnson and Johnson licensed the global marketing and development rights in 1998. However, in early 2001, its development was discontinued due to low bioavailability of the oral formulation and failure in clinical trials, and all the rights were returned to BioCryst. The low bioavailability of oral formulation resulted in BioCryst developing an intramuscular and intravenous formulation of peramivir. Fortunately, as part of the US government’s effort to prepare against the threat of the influenza pandemic, peramivir received strong support, including “Fast Track” designation from the FDA and a grant of $180 million from NIH, which accelerated the development of peramivir. Moreover, BioCryst entered into two agreements with Green Cross Pharmaceuticals and with Shionogi Pharmaceuticals in 2006–2007, for the development and marketing peramivir in South Korea and Japan, respectively. In October 2009, the FDA approved the use of intravenous peramivir for the treatment of 2009 H1N1 hospitalized patients under the Emergency Use Act (EUA) which expired on June 23th, 2010. Finally, the intravenous form of peramivir received approval in Japan in early of 2010 and launched for the first time with the commercial name Rapiacta®. Several syntheses of this drug have been reported and the improved route disclosed in a recent patent is described (Scheme 17). Ring opening of commercially available (+)-2-azabicyclo[2.2.1]hept-5-en-3-one (117) with methanolic HCl followed by classical resolution with L-tartaric acid gave the (1S,4R)-methyl ester 118 in 85% yield. Protection of 118 with Boc anhydride and TEA in CH$_2$Cl$_2$ afforded carbamate 119 in 90% yield. Alkene 119 was then subjected to nitrone cycloaddition conditions involving 2-ethyl-N-hydroxybutan-2-imidoyl chloride 120 and triethylamine, followed by the basic workup and then treatment with methanolic HCl, ultimately resulting in dihydroxosazole 121. Interestingly, the nitrone generated from 120 approached alkene 119 from the less hindered face and proceeded with remarkable regioselectivity to provide azacycle 121 in 76% yield for the three step sequence. Treatment of 121 with 1.5 equiv lithium aluminum hydride resulted in rupture of the N-O bond within this system, which afforded the amino alcohol 122 in 81% yield. It should be noted that neither the Boc group or the methyl ester were reduced under these reaction conditions.

**Scheme 17. Synthesis of peramivir (X).**
conditions. Then, a one-pot three step sequence involving acetylation of the amino group, removal of the Boc group, and hydrolysis of the carboxylic ester followed by guanylation with pyrazolecarboxamidine hydrochloride (123) provided peramivir (X) in 82% yield over the final four steps.

12. Prucalopride succinate (Resolor®)

Prucalopride succinate, a first-in-class dihydrobenzofuran-carboxamide, is a selective serotonin (5-HT4) receptor agonist. The drug, marketed under the brand name Resolor®, possesses enterokinetic activity and was developed by the Belgian-based pharmaceutical firm Movetis. Prucalopride alters colonic motility patterns via serotonin 5-HT4 receptor stimulation, triggering the central propulsive force for defecation. An unique set of conditions involving sodium tosylchloramide (chloramine T) trihydrate and sodium iodide were then employed to convert 125 to o-phenolic iodide 126, which then underwent sequential Sonogashira/cyclization reaction utilizing TMS-acetylene with tetramethylguanidine (TMG) in the presence of silica gel to furnish the benzofuran progenitor of 127. Hydrogenation of this intermediate benzofuran Sonagashira product saturated the 2,3-benzofuranyl bond while leaving the chlorine atom intact, ultimately delivering dihydrobenzofuran 127 in excellent yield for the two step sequence. Base-induced saponification and acetamide removal gave rise to acid 128. This acid was activated as the corresponding mixed anhydride and treated with commercial piperidine 129 to construct prucalopride which was stirred at room temperature for 24 h in ethanolic succinic acid to provide prucalopride succinate (XI). The yield for the formation of the salt was not provided.

13. Roflumilast (Daxas®)

Roflumilast is a selective, long-acting PDE-4 inhibitor approved in 2010 for the treatment of inflammatory conditions of the lungs such as asthma and chronic obstructive pulmonary disorder. Marketed under the trade name Daxas®, roflumilast was developed by researchers at the University of Liverpool in partnership with
1. Fmoc-L-Threonine, BOP, DIEA, 95%
2. Et₂NH, CH₂Cl₂, RT
3. N-AlloC-δ-Th-D-cysteine, EDCI, HOBT, DMF, CH₂Cl₂, 67% for 2 steps

1. PdCl₂(PPh₃)₂, Bu₃SnH, HOAc, CH₂Cl₂
2. N-Fmoc-D-valine, EDCI, HOBT, DMF, CH₂Cl₂, 83% for 2 steps

1. LiBF₄, CH₃CN, H₂O, RT
2. NaClO₂, Na₂HPO₄, 2-methyl-2-butene, ᵃBuOH

1. iPrMgCl, NHMe(OMe)
2. HSCPh₃, KOtBu, THF, 0 °C

1. Ts₂O, pyridine, 0 °C
2. DABCO, CH₃CN, RT

1. Ts₂O, pyridine, 0 °C
2. DIAD, PPh₃, TsOH, THF, 0 °C

Nycomed. Although the dose-limiting side effects of the drug are mild nausea, diarrhea, and weight loss, these symptoms subsided after a few weeks of treatment. The straightforward preparation of rofumilast begins with commercially available methyl 3,4-dihydroxybenzoate (130) (Scheme 19). Alkylation of the more reactive 3-hydroxyl group with (bromomethyl)cyclopropane (131) preceded a second alkylation of the remaining p-phenol with chlorodifluoromethane in aqueous sodium hydroxide. These phase-transfer conditions saponified the ester within 130 and after acid quench, carboxylic acid 132 was ultimately furnished in excellent yield (97%) over the three step protocol. Activation of 132 as the corresponding acyl halide through use of thionyl chloride (SOCl2) and subsequent exposure to commercial aminopyridine 133 provided rofumilast (XII) in 81% yield.

14. Romidepsin (Istodax®)

Romidepsin, a histone deacetylase inhibitor, originally developed by Fujisawa (now Astellas Pharma), causes cell cycle arrest, differentiation, and apoptosis in various cancer cells. In 2004, the FDA granted fast-track designation for romidepsin as monotherapy for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have relapsed following, or become refractory to, other systemic therapies. The FDA designated romidepsin as an orphan drug and it was approved in 2009 for this indication and it was commercialized in 2010. In 2007, another fast-track designation was granted for the product as monotherapy of previously treated peripheral T-cell lymphoma. Romidepsin (FR901228) was originally discovered and isolated from the fermentation broth of Chromobacterium violaceum No. 968. It was identified through efforts in the search for novel agents which selectively reverse the morphological phenotype of Ras oncogene-transformed cells since the Ras signaling pathway plays a critical role in cancer development. Therefore, the drug could also have multiple molecular targets for its anticancer activity besides HDAC. FR901228 is a bicyclic depsipeptide which is structurally unrelated to any known class of cyclic peptides with an unusual disulfide bond connecting a thiol and D-cysteine. This drug is commercially produced by fermentation; however its interesting and novel structure warrants examination of its synthesis within the context of this review.

The synthesis of romidepsin described is based on the total synthesis reported by the Williams and Simon groups (Scheme 20). L-Valine methyl ester (134) was coupled to N-Fmoc-D-threonine in the presence of the BOP reagent in 95% yield. The N-Fmoc protecting group was removed with Et2NH and the corresponding free amine was coupled to N-alloc-(S-triphenylmethyl)-D-cysteine with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and HOBT in DMF and CH2Cl2 to yield the tripeptide 135 in good yield. The threonine residue of tripeptide 135 was then subjected to dehydration conditions to give alkene 136 in 95% yield. The N-alloc protecting group of the dehydrated tripeptide 136 was removed with palladium and tin reagents and the corresponding free amine was subsequently coupled with N-Fmoc-D-valine to give tetrapeptide 137 in 83% yield. After removal of the N-Fmoc protecting group of compound 137 with Et2NH amine 138 was obtained in quantitative yield. The acid coupling partner 145 for amine 138 was prepared as follows: methyl 3,3-dimethoxycoproponate (139) was converted to its corresponding Weinreb amide by standard conditions and reacted with lithium acetylide 140 to give propargylic ketone 141 in 75% yield. Noyori’s asymmetric reduction of ketone 141 using ruthenium catalyst 142 gave the (R)-propargylic alcohol in 98% ee. This was followed by Red-Al reduction of the alkyne to selectively yield (E)-alkene 143 in 58% yield for the two steps. Liberation of the primary alcohol with tetrabutylammonium fluoride (TBAF) followed by selective tosylation gave 144 in 70% yield in two steps. Hydrolysis of the dimethyl acetal of 144 with LiBF4 was followed by a Pinnick oxidation to give the corresponding carboxylic acid. The tosylate was displaced with trityl mercapta in the presence of tert-butyl alcohol to give allylic alcohol 145 in 65% yield for the three steps. Aminoamide 138 was then coupled to acid 145 using BOP to give peptide 146 in quantitative yield. The methyl ester of compound 146 was hydrolyzed with lithium hydroxide to provide the free carboxylic acid which underwent macrocyclonization under Mitsunobu conditions in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine to give macrocycle 147 in 24% yield. Finally, the disulfide linkage was formed by treating bis-tritylsulfane 147 with iodine in methanol at room temperature to give romidepsin (XIII) in 81% yield.

Scheme 21. Synthesis of vernakalant hydrochloride (XIV).
15. Vernakalant hydrochloride (*Brinavess*® or *Kynapid*®)

Vernakalant is an investigational drug under regulatory review for the acute conversion of atrial fibrillation. The drug was initially developed by Cardiome Pharma under the trade names Kynapid® and Brinavess® and its intravenous formulation was further developed by Merck in April 2009. Like other class III antiarrhythmics, vernakalant blocks atrial potassium channels, thereby prolonging repolarization. It differs from typical class III agents by blocking the cardiac transient outward potassium current, with increased potency as the heart rate increases. It also slightly blocks the hERG potassium channel, leading to a prolonged QT interval, which may theoretically increase the risk of ventricular tachycardia. The preparation of vernakalant entails the union of a prolinol derivative with a 3,4-dimethoxyphenethyl alcohol through the use of superacid chemistry (Scheme 22). Reaction of 155 with antimony pentafluoride in hydrofluoric acid and N-bromosuccinimide followed by treatment with two equivalents of tartaric acid produced vinflunine ditartrate (XV) in 25% yield. An alternative synthesis of vinylubine was realized through reaction of vinblastine or 3,4-dihydrovinblastine (156) with antimony pentafluoride and hydrofluoric acid in chloroform to give the difluoro alkaloid 157 in 40% yield. Ring contraction was effected by reaction with trifluoroacetic acid and N-bromosuccinimide followed by aqueous sodium bicarbonate and silver tetrafluoroborate to give vinflunine in 88% yield. Vinflunine ditartrate (XV) was prepared by treating a solution of vinflunine in toluene with 2 equiv of tartaric acid.

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**References and notes**

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