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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.

Contents

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 ago[2–9] and presents synthetic methods for molecular entities that were launched in various countries during 2010.[10] Given that drugs tend to have

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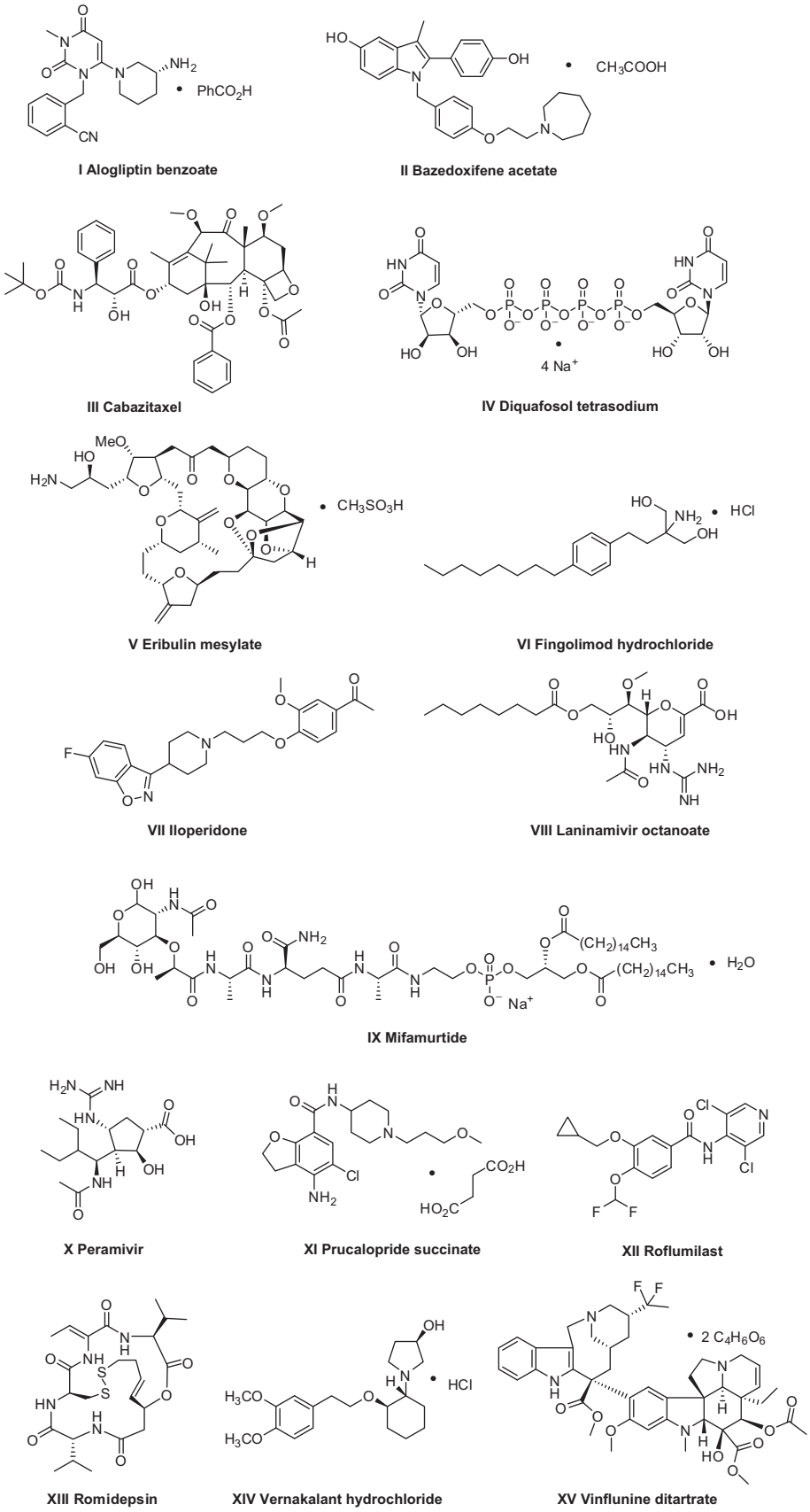


Figure 1. Structures of 15 new drugs marketed in 2010.

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.[10] This review focuses on the syntheses of 15 new chemical entities that were launched anywhere in the world for the first time in 2010 (Fig. 1) and excludes new indications for previously launched medications, new combinations, new formulations and drugs synthesized via bio-processes or peptide synthesizers. Although the scale of the synthetic routes were not disclosed in all cases, this review attempts to highlight the most scalable routes based on the patent or primary literature and appear in alphabetical order by generic name. The syntheses of new products that were approved for the first time in 2010 but not launched before year's end, will be covered in the 2011 review.

2. Alogliptin benzoate (*Nesina*®)

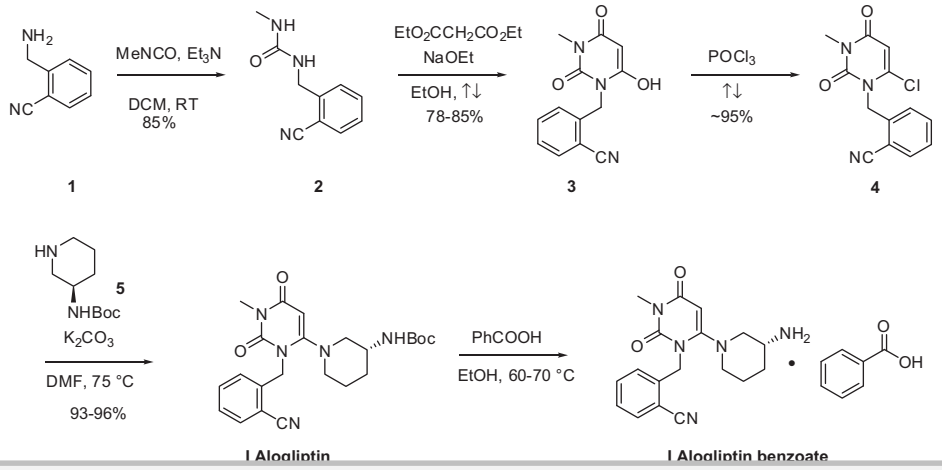
Alogliptin benzoate is a dipeptidyl peptidase IV (DPPIV) inhibitor discovered by Takeda Pharmaceuticals and approved in Japan in 2010 for the treatment of type II diabetes mellitus.[10] Alogliptin is an oral drug for once a day dosing to complement diet and exercise. Alogliptin is the most selective marketed DPPIV inhibition and has similar PK and PD properties compared to previous entries.[11,12] The discovery, structure–activity relationship of related analogs, and synthesis of this compound have been recently published.[13] The most convenient synthesis for scale-up will be highlighted from several published routes (Scheme 1).[13–16] Commercially available 2-cycanobenzyl amine **1** was reacted with methylisocyanate in DCM at ambient temperature to provide *N*-methyl urea **2** in 85% yield. Reaction of the urea **2** with dimethyl malonate in refluxing ethanol with sodium ethoxide as base gave the cyclized trione **3** in 78–85% yield. The trione **3** was then refluxed in neat $POCl_3$ to provide the penultimate chloride crude **4** in 95% yield which was reacted 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**).

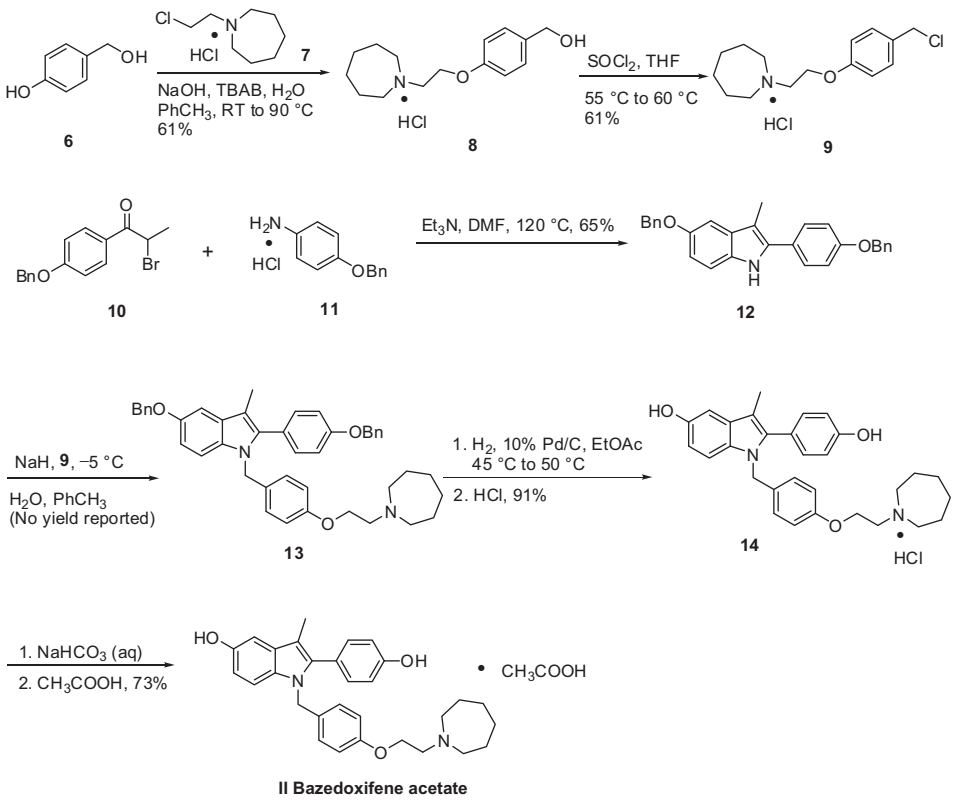
3. Bazedoxifene acetate (*Conbriza*®)

The selective estrogen receptor modulator bazedoxifene acetate was approved in Spain for the treatment of osteoporosis in postmenopausal women.[10] The drug was discovered by Wyeth (now Pfizer) and licensed to Almirall.[10] Clinical trials with bazedoxifene along with conjugated estrogens demonstrated significant improvement in bone mineral density and prevented bone loss in postmenopausal women without osteoporosis. It also reduces fracture risks among women with postmenopausal osteroporosis.[10] Among many syntheses reported for this drug,[17–22] the most recent process scale synthesis (multi-kg scale) is highlighted[22] 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 tetrabutylammonium bromide (TBAB) gave the desired intermediate alcohol **8** in 61% yield. Treatment of **8** with thionyl chloride ($SOCl_2$) gave the requisite chloride **9** in 61% yield. The reaction of 2-bromopropiophenone (**10**) with an excess of 4-benzyloxy 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 functionalities from compound **13** were removed via hydrogenolysis and subsequently subjected to acidic conditions, providing diol **14** as the hydrochloride salt in 91% yield. The hydrochloride was then exchanged for the acetate via free base preparation with 5% sodium bicarbonate or triethylamine, followed by treatment with acetic acid giving bazedoxifene acetate (**II**) in 73–85% yield.

4. Cabazitaxel (*Jevtana*®)

Cabazitaxel was developed by Sanofi-Aventis as an intravenous injectable drug for the treatment of hormone-refractory metastatic prostate cancer.[23] 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.[24] Cancer cells that express P-gp become resistant to taxanes, and the effectiveness of docetaxel can be limited by its high substrate affinity for P-gp.[24] Clinical studies confirmed that cabazitaxel retains activity in docetaxel-resistant tumors.[23] Common adverse events with cabazitaxel include diarrhea and neutropenia. Cabazitaxel in combination with prednisone is an important new treatment option for men with docetaxel-refractory metastatic CRPC (castration-resistant prostate cancer).[23] The semi-synthesis of cabazitaxel[25] started from 10-deacetylbaccatin III (**15**) which can be prepared from 7-xylosyl-10-deacetylbaccatin natural product mixture according to a literature process procedure (Scheme 3).[26] 10-Deacetylbaccatin III was protected with triethylsilyl chloride (TESCl) in pyridine to afford the corresponding 7,13-bis-silyl ether in 51% yield, which was methylated with MeI





Scheme 2. Synthesis of bazedoxifen acetate (**II**).

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 ester **20** in 76% yield. The oxazolidine moiety of compound **20** was selectively hydrolyzed under mild acidic conditions to yield the hydroxy Boc-amino ester derivative cabazitaxel (**III**) in 32% yield.

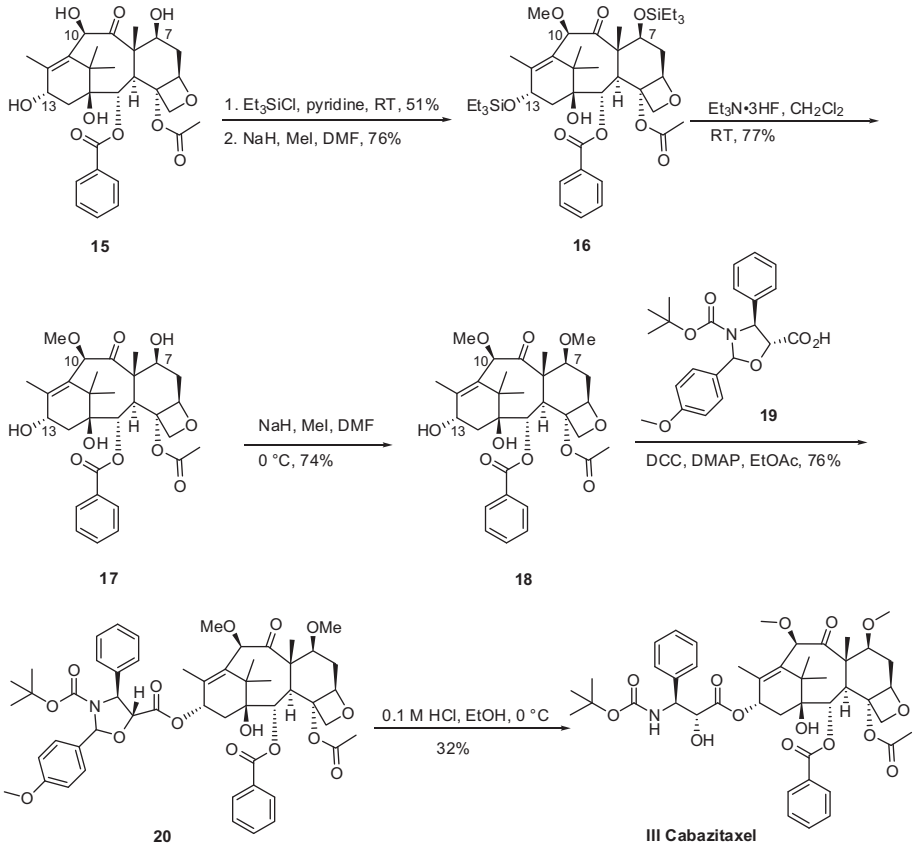
5. Diquafosol tetrasodium (*Diquas*®)

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 $P2Y_2$ receptor agonist, which activates $P2Y_2$ 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 followed by ion exchange using a Dowex 50W resin in Na^+ mode. The one-pot process provided diquafosol tetrasodium (**IV**) in 25% yield.[29]

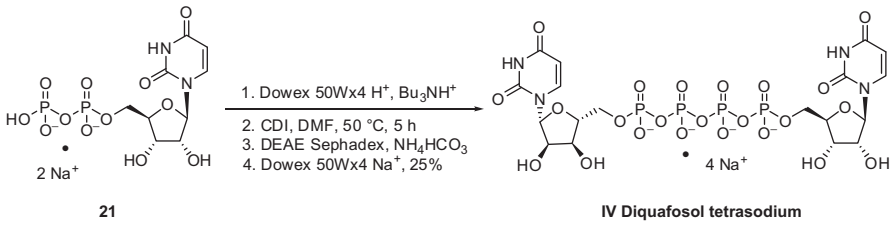
6. Eribulin mesylate (*Halaven*®)

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–Hiyami–Kishi coupling conditions, formation of a challeng-



Scheme 3. Synthesis of cabazitaxel (**III**).



Scheme 4. Synthesis of diquafosol tetrasodium (**IV**).

25 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 teteroxide 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 $ZnCl_2$ 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 tion 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 bicylic-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 cyclohexylidine 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 good yield. Vinyl silane **37** was treated with NIS and catalytic *tert*-butyldimethylsilyl chloride (TBSCl) to give vinyl iodide **38** 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

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