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Review

Synthetic approaches to the 2011 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 26 NCEs that were launched in the world in 2011.

Contents

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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 medicine.[1]

This annual review was inaugurated 10 years ago[2–10] and presents synthetic methods for molecular entities that were launched in various countries during 2011. It was a productive year for the pharmaceutical industry in 2011, a total of 38 NCEs and biologics for therapeutic use reached the market for the first time.[11–13] This review focuses on the syntheses of 26 small molecule NCEs that were launched in 2011 (Fig. 1), including the first novel antibody drug conjugate that utilizes a linker/payload prepared by total synthesis. New indications for previously launched medications, new combinations, new formulations of existing drugs, and drugs synthesized purely via bio-processes or peptide synthesizers have been excluded from this review. Although the scale of the synthetic routes was not disclosed in most cases, this review attempts to highlight the most scalable routes based on published or patent literature, and is arranged in alphabetical order by the drug's generic name. The synthesis of new products that were approved for the first time in 2011 but were not launched before the year's end will be covered in our next review.

2. Abiraterone acetate (Zytiga®)

Abiraterone acetate was approved by the U.S. Food and Drug Administration (FDA) in April 2011 for the treatment of castration-resistant prostate cancer.[14] The drug, marketed under the trade name Zytiga®, was originally discovered by researchers at the Cancer Research UK Centre for Cancer Therapeutics in 1990, developed by Cougar Biotechnology, and ultimately commercialized by Johnson & Johnson after its acquisition of Cougar in 2009. Abiraterone acetate inhibits CYP17A1—an enzyme expressed in testicular, adrenal, and prostatic tumor tissues—which has been implied in the production of testosterone and the proliferation of such tumor cell lines.[15]

The most convenient synthesis for scale-up will be highlighted from two published syntheses (Scheme 1).[16–22] Commercially available androstenolone **1** was acylated with acetic anhydride in the presence of boron trifluoride-diethyl etherate to give a near quantitative yield of acetate **2**.[19] The conversion of ketone **2** to vinyl triflate **3** involved careful selection of base to prevent elimination of the acetate group.[19] To this extent, subjection of **2** to triflic anhydride in dichloromethane at ambient temperature followed by slow addition of triethylamine minimized undesired side products and delivered triflate **3** in 60% isolated yield. Subsequent Suzuki coupling with diethylborane **4** under standard conditions ultimately furnished abiraterone acetate (**I**) in 75% yield.

3. Alcaftadine (Lastacaft®)

Alcaftadine, an ophthalmic histamine H_1 receptor antagonist, was approved by the FDA for the prevention of itching associated with allergic conjunctivitis and was launched under the trade name Lastacaft® in early 2011.[11,23] Alcaftadine was discovered by Janssen Pharmaceuticals and marketed by Vistakon Pharmaceuticals, both subsidiaries of Johnson & Johnson. However, unlike other marketed drugs, the synthesis of alcaftadine was only mentioned in the patents filed by Janssen's scientists approximately twenty years ago. The synthetic route described in Scheme 2 is based on the discovery route disclosed in those patents.[24,25] 1-(2-Phenylethyl)-1*H*-imidazole **7** is now commercially available, otherwise it could be prepared by reacting imidazole (**5**) with 2-phenylethyl bromide (**6**).[24–26] With pyridine and triethylamine as base, imidazole **7** was reacted with acyl chloride **8** to provide piperidinecarboxylate **9** in 34% yield, followed by acid hydrolysis with 48% HBr aqueous solution to obtain piperidine dihydrobromide **10** in 98% yield. The N-methylation of **10** was acheived by Leuckart reaction with formaldehyde and formic acid to give 4-methylpiperidine **11** in 82% yield. Treatment of **11** with trifluoromethanesulfonic acid followed by subsequent basification triggered an intramolecular alkylation–dehydration reaction to generate benzazepine **12**. Next, alcohol **13** was obtained by prolonged exposure (7 days) of **12** to hydroxymethylation conditions using 40% aqueous formaldehyde. Oxidation of **13** with manganese (IV) oxide provided alcaftadine (**II**).[24,25] The yields of last three steps from compound **11** to alcaftadine (**II**) were not provided in the patent.

4. Apixaban (Eliquis®)

Apixaban is an oral anticoagulant with highly selective inhibition of factor Xa. It was approved by the European Medicines Agency (EMA) for the treatment of venous thromboembolic events and first marketed in Germany under the brand name Eliquis® in June 2011.[11] Apixaban was co-developed by Bristol-Myers Squibb and Pfizer and represents the first approved drug for this indication since warfarin over 50 years ago. Although several convenient preparations of apixaban (BMS-562247) have been reported,[27–30] the most likely process-scale route is described in Scheme 3. The starting material 4-iodoaniline (**14**) was acylated with 5-bromovaleryl chloride (**15**) and triethylamine followed by cyclization under basic conditions to give lactam **16** in 49% yield. Intermediate **16** was then reacted with phosphorus pentachloride to provide the α,α-dichlorinated lactam **17** in 87% yield.[30] This dichloride was reacted with excess morpholine to affect an alkylation–elimination sequence to afford enaminolactam **18** in 86% yield. N-Arylation of this iodide with valerolactam **19** using a copper (I) catalyst resulted in a 77% yield of the desired *p*-bispiperidone **20**. Interestingly, sequential exposure of **20** to a nitrile imine generated from the treatment of ethyl 2-chloro-2-(2,4-methoxyphenyl)-hydrazono)acetate **21** with base resulted in a [3+2] dipolarcycloadditon reaction. Upon acidification with 4 N HCl, pyrazole **22** was furnished in 67% over two steps. Conversion of the ester within **22** to the corresponding amide was achieved via a mixture of formamide and sodium methoxide to give apixaban (**III**) in 71% yield.[29] It is important to note that intermediate **21** was prepared from commercially available 4-methoxyaniline (**23**) by sequential diazotization and condensation with ethyl 2-chloroacetoacetate (**24**).[27]

5. Avanafil (Zepeed®, Stendra®)

Avanafil was originally discovered at Tanabe Seiyaku (now Mitsubishi Tanabe). JW Pharmaceutical (previously Choongwae