Natural products to drugs: natural product-derived compounds in clinical trials

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Covering: 2005 to 2007

Natural product and natural product-derived compounds that are being evaluated in clinical trials or are in registration (as at 31st December 2007) have been reviewed, as well as natural product-derived compounds for which clinical trials have been halted or discontinued since 2005. Also discussed are natural product-derived drugs launched since 2005, new natural product templates and late-stage development candidates.

1 Introduction
2 NP-derived drugs approved from 2005 to 2007
3 Compounds undergoing evaluation in infectious diseases
3.1 Antibacterial
3.2 Antifungal
3.3 Antiparasitic
3.4 Antiviral
3.5 Halted or discontinued compounds in infectious diseases
4 Neurological disease
4.1 Compounds undergoing evaluation in neurological diseases
4.2 Halted or discontinued compounds in neurological diseases
5 Cardiovascular and metabolic disease
5.1 Compounds undergoing evaluation in cardiovascular and metabolic diseases
5.2 Halted or discontinued compounds in cardiovascular and metabolic diseases
6 Immunological, inflammatory and related disease
6.1 Compounds undergoing evaluation in immunological, inflammatory and related diseases
6.2 Halted or discontinued compounds in immunological, inflammatory and related diseases
7 Oncological disease
7.1 Small-molecule anticancer agents
7.2 NP-antibody anticancer conjugates
8 New natural product templates
9 Conclusions
10 Acknowledgements
11 References

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1 Introduction

This review describes natural products (NPs), semi-synthetic NPs and NP-derived compounds that are undergoing clinical evaluation or registration at the end of December 2007 by disease area and follows a similar format to the previous review in this series.[1] NP-derived drugs launched since 2005 are discussed in Section 2, while compounds undergoing clinical evaluation or compounds that have been halted or discontinued since 2005 are listed by disease area: Infectious disease (Section 3), Neurological disease (Section 4), Cardiovascular and metabolic disease (Section 5), Immunological, inflammatory and related diseases (Section 6) and Oncology (Section 7). Clinical candidates with new structural templates are discussed in Section 8, while late-stage development compounds are summarised in Section 9.

Compounds are classified into 3 groups: NPs, semi-synthetic NPs or NP-derived. NPs are classified as a NP in this review even if they are produced synthetically for clinical studies or for the market. Semi-synthetic NPs are compounds that were derived from a NP template using semi-synthesis, while NP-derived compounds are synthetically derived or in some cases inspired from a NP template. These definitions are simpler compared to those used in Newman, Cragg and Snader's reviews[2,3] and Newman and Cragg's 2007 update.[4] No number has been assigned to a compound if it does not have a publicly disclosed structure. Compounds derived from primary metabolites (*e.g.* steroids, nucleosides, prostaglandins, sialic acid[5] and tyrosine), vitamins (*e.g.* vitamin D and retinoids[6]), hormones and protein fragments, herbal mixtures,[7,8] polyamines,[9,10] porphyrin[11] derivatives and new uses of existing drugs have not been listed exhaustively. In addition, the background description for compounds in this review that were also discussed in the previous review[1] may not be as detailed.

A brief description of terms used during the drug approval process: an Investigational New Drug Application (IND) (or equivalent elsewhere in the world) must be made to the United States of America (US) Food and Drug Administration (FDA), European Medicines Agency (EMEA) or equivalent agency before clinical trials can commence. Once clinical trials have been completed successfully, the applicant files a New Drug

Table 1 NP-derived drugs launched since 2005 by year with reference to their lead compound, classification and therapeutic area[23–28,a]

Year	Generic name (trade name)	Lead compound	Classification	Disease area
2005	dronabinol **1**/cannabidol **2** (Sativex®)	dronabinol **1**/cannabidol **2**	NPs	pain
2005	fumagillin **3** (Flisint®)	fumagillin **3**	NP	antiparasitic
2005	doripenem **4** (Finibax®/Doribax™)	thienamycin **5**	NP-derived[b]	antibacterial
2005	tigecycline **6** (Tygacil®)	tetracycline **7**	semi-synthetic NP	antibacterial
2005	ziconotide **8** (Prialt®)	ziconotide **8**	NP[b]	pain
2005	zotarolimus **9** (Endeavor™ stent)	sirolimus **10**	semi-synthetic NP	cardiovascular surgery
2006	anidulafungin **11** (Eraxis™/Ecalta™)	echinocandin B **12**	semi-synthetic NP	antifungal
2006	exenatide **13** (Byetta™)	exenatide-4 **13**	NP[b]	diabetes
2007	lisdexamfetamine **14** (Vyvanse™)	amphetamine **15**	NP-derived[b]	ADHD
2007	retapamulin **16** (Altabax™/Altargo™)	pleuromutilin **17**	semi-synthetic NP	antibacterial (topical)
2007	temsirolimus **18** (Torisel™)	sirolimus **10**	semi-synthetic NP	oncology
2007	trabectedin **19** (Yondelis™)	trabectedin **19**	NP[c]	oncology
2007	ixabepilone **20** (Ixempra™)	epothilone B **21**	semi-synthetic NP	oncology

[a] In October 2006, Merck gained FDA approval for the use of vorinostat (Zolinza™, suberoylanilide hydroxamic acid, SAHA) **22** for the treatment of advanced, refractory cutaneous T-cell lymphoma. In the previous review in this series,[1] vorinostat **22** was classified as "NP-derived" due to its chemical and biological similarity to trichostatin **23**,[30] an actinomycete-derived HDAC inhibitor.[31,32] However, Marks and Breslow have since published a review[33] indicating that vorinostat **22** was developed independently of trichostatin **23** but later recognition of their structural similarities helped elucidate the mechanism of action of **22**.[34] [b] These drugs are manufactured by total synthesis. [c] Trabectedin is produced semi-synthetically from cyanosafracin B **24**.[35]

Application (NDA) with the FDA or a Marketing Authorization Application (MAA) with the EMEA to seek the drug's approval for marketing in the US and Europe respectively. The agency will then reply with an "approval letter", "non-approval letter" or "approvable letter". An "approval letter" allows the applicant to begin marketing the product, while a "non-approval letter" rejects the application. An "approvable letter" informs the applicants that the agency have completed their scientific review and determined that the application can be approved pending resolution of minor deficiencies identified in the letter or during an inspection of the manufacturing facilities.

Kinghorn and co-workers published a related review "Drug discovery from natural sources" in 2006, which lists NP and NP-derived drugs in clinical trials and on the market.[12] Also of general interest are the 2005 reviews "The search for novel drug leads for predominately antitumor therapies by utilizing mother nature's pharmacophoric libraries",[13] "The evolving role of natural products in drug discovery",[14] "The renaissance of natural products as drug candidates',[15] and "Natural products as drug leads: an old process or the new hope for drug discovery?",[16] the 2006 reviews "Drug discovery from natural products",[17] "Small molecule natural products in the discovery of therapeutic agents: the synthesis connection",[18] and "The role of pharmacognosy in modern medicine and pharmacy",[19] and finally the 2007 reviews "New aspects of natural products in drug discovery",[20] "The value of natural products to future pharmaceutical discovery",[21] and "Natural products as a screening resource".[22] Reviews that are specific to the therapeutic area are listed in the appropriate sections.

Although this review represents a thorough evaluation of publicly available data, there may be some NP-derived compounds that have been excluded. The status of compounds undergoing clinical investigation and the companies involved can change rapidly and readers are encouraged to consult the recent literature, company web pages and clinical trial registers such as the US National Institutes of Health's (NIH) website (http://www.clinicaltrials.gov) for the latest information.

2 NP-derived drugs approved from 2005 to 2007

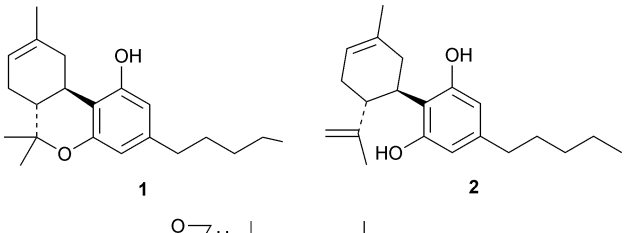
A total of 13 NP and NP-derived drugs were approved for marketing worldwide (Table 1) from 2005 to 2007 (see ref. 1 for

Mark Butler received a PhD from The University of Melbourne for his research on novel metabolites from Southern Australian marine sponges in 1992. After postdoctoral work with Prof. Pettit at the Arizona State University, he joined the newly established Queensland Pharmaceutical Research Institute (now part of the Eskitis Institute for Cell and Molecular Therapies), a joint venture between Griffith University and AstraZeneca. In 1999, he moved to Singapore to lead the Natural Product Chemistry group at the Centre of Natural Product Research (CNPR), which was part of the Institute of Molecular and Cell Biology and affiliated with GlaxoSmithKline. In 2002, CNPR privatized to become MerLion Pharmaceuticals where his present position is Director of Natural Product Chemistry. He has over 40 papers on various aspects of natural product chemistry and in 2002 was awarded the Matt Suffness (Young Investigator) Award by the American Society of Pharmacognosy. Since 2006, he has been an Adjunct Associate Professor in the Department of Chemistry at the National University of Singapore.

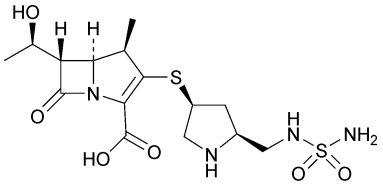
a similar table from 1998 to 2004), with 5 being classified as NPs, 6 semi-synthetic NPs and 2 NP-derived drugs. In addition, ziconotide **8**, exenatide **13**, retapamulin **16**, trabectedin **19** and ixabepilone **20** are the first members of new human drug classes. To further support the importance of NPs in drug discovery, it should be noted that 6 of 27 small molecule drug launches in 2005 (22%), 2 of 21 in 2006 (9%) and 5 of 21 (24%) in 2007 were NPs or derived from NPs,[23–28] and the numbers are greater if you consider drugs inspired from other naturally occurring molecules such as steroids, nucleosides, prostaglandins, hormones and vitamins. Lisdexamfetamine **14** was classed as NP-derived due to the structural relationship between amphetamine **15** and ephedrine.[29]

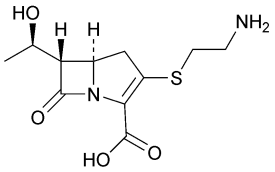
Sativex® (GW Pharmaceuticals) is a mixture of the cannabinoids, dronabinol (Δ^9-THC) **1** and cannabidol **2**, which was first launched in Canada in April 2005 as an adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis (MS) patients.[36–38] In August 2007, Health Canada also approved Sativex® as adjunctive analgesic for patients with advanced cancer who experience moderate to severe pain with the highest tolerated dose of strong opioid therapy. Sativex® is undergoing a Phase II/III cancer pain trial in the US and late-stage clinical development in Europe, but is already prescribed in the UK on a named patient basis for both pain indications.[39]

In September 2005, fumagillin (Flisint®, Sanofi-Aventis) **3** was approved for use in the treatment of intestinal microsporidiosis in France. Microsporidiosis is a disease caused by the spore-forming unicellular parasite *Enterocytozoon bieneusi*, which is of major concern to immunocompromised patients as it can cause chronic diarrhoea.[40,41] Fumagillin **3** was first isolated in 1949 from *Aspergillus fumigatus* and used shortly thereafter to treat intestinal amoebiasis.[42,43] In addition, semi-synthetic derivatives of fumagillin **3** with antiangiogenic activity have undergone clinical evaluation for the treatment of cancer (Section 7.2).



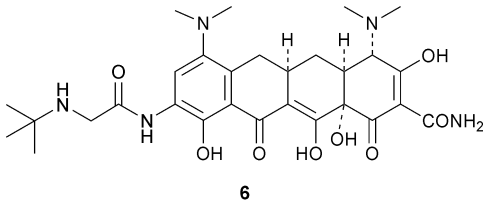
Doripenem (Finibax®, Doribax™) **4** is a synthetic carbapenem-type β-lactam that was launched in 2005 in Japan by Shionogi & Co. as a broad-spectrum antibiotic.[44–46] The first carbapenem to be identified was the actinomycete-derived NP thienamycin **5**.[47,48] Johnson & Johnson (J&J) (formerly Peninsula Pharmaceuticals) obtained formal FDA approval in October 2007 for use of doripenem **4** in the treatment of complicated intra-abdominal and complicated urinary tract infections, including pyelonephritis. The use of doripenem **4** for treatment of hospital-acquired (nosocomial) pneumonia (HAP) is under FDA review, while in Europe treatment of HAP and complicated urinary tract infections are under review. Other carbapenems undergoing clinical evaluation are described in Section 3.1.

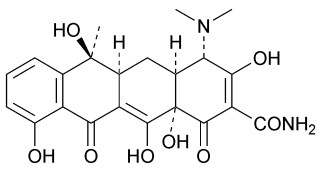


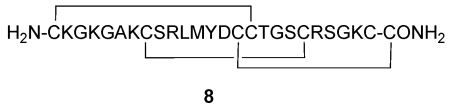


Tigecycline (Tygacil®) **6** is the first member of a new generation of tetracyclines **7** called glycylcyclines that was developed by Wyeth to have more potent antibacterial activity and reduced bacterial efflux.[49–51] Tigecycline **6** was approved by the FDA in June 2005 for use in the treatment of complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infections. In addition, a supplemental NDA was submitted to the FDA in October 2007 for the treatment of patients with community-acquired pneumonia (CAP). Tigecycline **6** was approved for use in Europe in May 2006 for cSSSIs and complicated intra-abdominal infections.

Ziconotide (Prialt™) **8** is a synthetic version of the *N*-type calcium channel blocker ω-conotoxin MVIIA, a peptide first isolated from the venom of *Conus magus*.[52] Ziconotide **8** was launched by Elan in both the US and Europe in 2005 for the treatment of patients suffering from chronic pain.[53] In March 2006, Eisai obtained the rights to market Prialt™ in Europe. Further information on conotoxin-derived development candidates can be found in Section 4.







In July 2005, Medtronic received European approval for the sale of the Endeavor™ drug eluting coronary stent that consists

of a cobalt-based alloy integrated with a biomimetic phosphorylcholine polymer.[54–56] Endeavor™ delivers the active principle zotarolimus (ABT-578) **9**,[57] a semi-synthetic derivative of sirolimus (rapamycin) **10**, into surrounding vascular structures, inhibiting cell proliferation, preventing scar tissue formation and minimizing restenosis in angioplasty patients. Sirolimus **10** was first isolated from a soil sample of *Streptomyces hygroscopicus*[58] and is marketed as an immunosuppressant by Wyeth under the trade name Rapamune®. The Endeavor™ stent is currently used in more than 100 countries worldwide and is moving closer to US registration after a positive recommendation by an FDA Advisory Committee in October 2007.

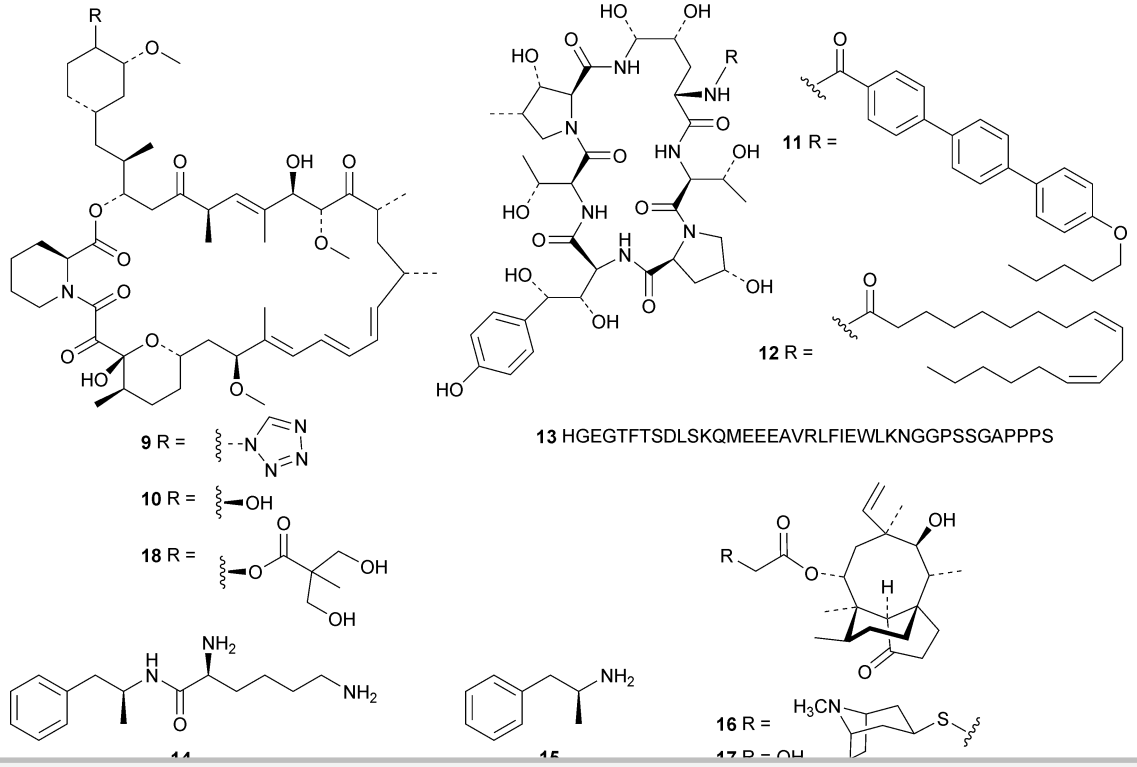
Pfizer obtained FDA approval in February 2006 (Eraxis™ in the US) and EMEA approval in July 2007 (Ecalta™ in Europe) for the use of anidulafungin **11** in the treatment of invasive and oesophageal candidiasis and candidemia.[59,60] Anidulafungin **11** is a semi-synthetic derivative of the fungal metabolite echinocandin B **12** originally developed by Eli Lilly[61] and licensed to Vicuron Pharmaceuticals, who were purchased by Pfizer in June 2005. Further information on echinocandin antifungal drugs can be found in Section 3.

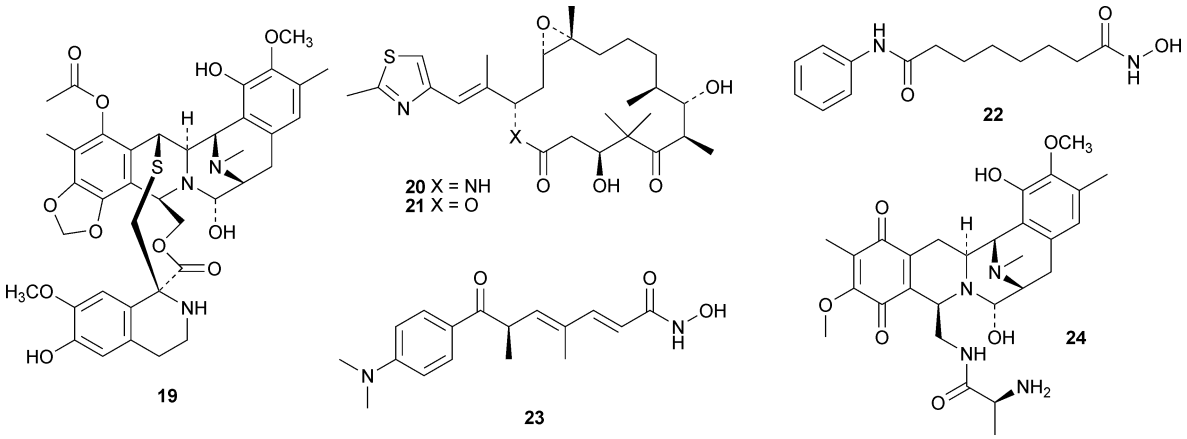
Eli Lilly and Amylin Pharmaceuticals obtained FDA and EMEA approval in April 2005 and November 2006 respectively for the use of exenatide (Byetta™) **13** as an adjunctive therapy to improve blood sugar control in patients with type 2 diabetes.[62,63] Exenatide **13**, originally named exenatide-4, is a 39 amino acid peptide isolated from the oral secretions of the Gila monster (*Heloderma suspectum*), a poisonous lizard found in the southwestern US and northern Mexico.[64,65] Exenatide **13** has a structure similar to glucagon-like peptide-1 (GLP-1), a human hormone that helps the pancreas to regulate glucose-induced insulin secretion when the blood glucose levels are elevated, and is the first compound in a new class of drugs called "incretin mimetics". Other incretin mimetics in clinical evaluation are not described in this review but further information can be obtained in these references.[62,66–68]

Although the underlying causes of Attention-Deficit Hyperactivity Disorder (ADHD) are not well understood, there is evidence suggesting that dopaminergic and noradrenergic neurotransmission are dysregulated in ADHD. Methylphenidate and amphetamines have been used to treat ADHD for many years but these drugs are controlled substances due to their abuse potential.[69] New River Pharmaceuticals designed an amphetamine prodrug, lisdexamfetamine (Vyvanse™, NRP104) **14**, which is converted to D-amphetamine **15** in the gastrointestinal tract after oral administration and, as a consequence, has reduced abuse potential.[69–71] In February 2007, New River and Shire Pharmaceuticals obtained FDA approval for the use of lisdexamfetamine **14** to help treat ADHD, and in April 2007 Shire bought New River.

Retapamulin (SB-275833) **16** is a semi-synthetic derivative of the fungal metabolite pleuromutilin **17**, which exerts its antimicrobial activity by binding to the 50*S* bacterial ribosome.[72–74] A 1% retapamulin ointment (called Altabax™ in the US and Altargo™ in Europe) developed by GlaxoSmithKline (GSK) was approved by the FDA in April 2007 and the EMEA in June 2007 for the topical treatment of impetigo caused by *Staphylococcus aureus* or *Streptococcus pyogenes*.[75–77] Further information on other pleuromutilin derivatives undergoing clinical evaluation can be found in Section 3.

Temsirolimus (Torisel™, CCI-779) **18** is a semi-synthetic derivative of sirolimus **10** that was approved in the US in May 2007 and Europe in November 2007 for the treatment of advanced renal cell carcinoma.[78–81] Temsirolimus **18** is the first mTOR inhibitor approved for use in oncology, and other semi-synthetic sirolimus **10** derivatives are discussed in Sections 6 and 7.





Trabectedin (Yondelis™, ecteinascidin-743, ET-743) **19**, a tetrahydroisoquinoline alkaloid produced by the ascidian *Ecteinascidia turbinata*,[82–84] was approved by the EMEA in September 2007 for the treatment of advanced soft tissue sarcoma.[85,86] Trabectedin **19** is in Phase III clinical trials for the treatment of ovarian cancer (with J&J in the US) and other ongoing Phase II trials include paediatric sarcomas, breast and prostate cancers. Trabectedin **19** binds to the minor groove of DNA and disrupts the cell cycle, causing cell proliferation inhibition, and is produced commercially semi-synthetically from the eubacterium-derived cyanosafracin B **24**.[35]

Ixabepilone (Ixempra™, BMS-247550) **20** is a semi-synthetic derivative of epothilone B **21** developed by Bristol-Myers Squibb (BMS) that was approved in October 2007 by the FDA for the treatment of breast cancer, either as a monotherapy or in combination with capecitabine.[87–90] Ixabepilone **20**, like other epothilones, binds directly to β-tubulin subunits on microtubules, leading to suppression of microtubule dynamics, blocking of cells in the mitotic phase and ultimately leading to cell death. The status of other epothilone derivatives in clinical evaluation is discussed in Section 7.

Finally, it is worth noting that Veregen™ (Polyphenon® E ointment), a defined mixture of catechins extracted from green tea leaves,[91–93] became the first herbal medicine to receive FDA approval in 2006. Veregen™ was developed by MediGene AG and launched in the US by Bradley Pharmaceuticals in December 2007 for the treatment of genital warts.[94]

3 Compounds undergoing evaluation in infectious diseases

3.1 Antibacterial

As with immunosuppression and to a lesser extent oncology, NP-derived drugs have played a pivotal role in anti-infective drug development.[48,95–99] With the notable exception of quinolones, the majority of antibacterial drugs currently in clinical use are NPs or were designed using NP templates. The ability of an organism to produce effective antibacterial compounds gives it an evolutionary advantage over other organisms and it is not surprising that many different NPs have evolved to interact with specific antibiotic protein targets. Also, the intrinsic ability of NP-derived drugs to penetrate bacterial cell membranes despite often having complex structures is a desirable and often privileged property.[100] Worries about shrinking development pipelines, economics, clinical trial design and eventual resistance has placed increasing pressure on antibacterial research. This, coupled with the increased difficulty identifying of new druggable templates, especially with novel mechanisms of action, has made many pharmaceutical companies reduce or completely cease their antimicrobial research and development efforts. Nowhere is this situation better demonstrated than Payne and co-workers review describing GSK's limited success using a genomics-based platform for antibacterial drug discovery.[101] Despite the difficulties,[101–107] there still are a significant number of NP-derived antibacterial compounds undergoing clinical evaluations but most are based on well known antibacterial templates.[108,109]

β-Lactams inhibit the formation of peptidoglycan cross links in the bacterial cell wall, leading to bacterial death, and have been the mainstay for treating community-acquired infections since the commercialization of penicillins in the 1940s. There are presently 9 β-lactams (2 cephalosporins, 6 carbapenems and 1 penem) in clinical trials or undergoing drug registration.[110,111] As discussed in Section 2, the carbapenem doripenem **4** was launched in Japan in 2005 and obtained FDA approval in October 2007. In addition to these compounds, Gilead are evaluating an inhaled lysine salt formulation of the monobactam aztreonam (Cayston™) **25** in Phase III clinical trials as a treatment for cystic fibrosis sufferers who have a pulmonary infection of the Gram-negative bacteria *Pseudomonas aeruginosa*.[112,113] Aztreonam **25** is an existing intravenous (IV) antibiotic first launched in 1984.

Ceftobiprole medocaril (BAL-5788) **26** is a fourth-generation cephalosporin that has potent bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP).[114–116] Basilea Pharmaceutica and the J&J affiliate Cilag GmbH International filed an MAA on 18 June 2007 and an NDA on 21 May 2007 for the treatment of cSSSIs. In March 2008, Basilea received an Approvable Letter indicating that **26** was approvable subject to completion and assessment of clinical study site inspections, assessment of clinical and microbiological data provided but not yet reviewed, and further characterization of patients with diabetic foot infections. In addition, various Phase III trials are underway for hospital- and community-acquired pneumonia (HAP/CAP). Ceftaroline acetate (PPI-0903, TAK-599) **27**, which

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