REVIEW

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

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Natural product and natural product-derived compounds that are being evaluated in clinical trials or in registration (current 31 December 2004) have been reviewed. Natural product derived drugs launched in the United States of America, Europe and Japan since 1998 and new natural product templates discovered since 1990 are discussed.

Mark Butler received a BSc (Hons) and PhD, with a focus on marine sponges, from The University of Melbourne in 1992. After postdoctoral work with Professor Pettit at the Arizona State University, he joined the newly established Queensland Pharmaceutical Research Institute (now Natural Product Research), 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. 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 products chemistry and in 2002 was awarded the Matt Suffness (Young Investigator) Award by the American Society of Pharmacognosy.

Mark S. Butler

1 Introduction

Natural Products (NPs) traditionally have played an important role in drug discovery and were the basis of most early medicines.[1–6] Over the last 10 to 15 years advances in X-ray crystallography[7–9] and NMR,[9–11] and alternative drug discovery methods such as rational drug design[11–14] and combinatorial chemistry[15–18] have placed great pressure upon NP drug discovery programmes and during this period most major pharmaceutical companies have terminated or considerably scaled down their NP operations.[19–24] However, despite the promise of these alternative drug discovery methods, there is still a shortage of lead compounds progressing into clinical trials. This is especially the case in therapeutic areas such as oncology, immunosuppression and metabolic diseases where NPs have played a central role in lead discovery. In a recent review, Newman, Cragg and Snader analysed the number of NP-derived drugs present in the total drug launches from 1981 to 2002 and found that NPs were a significant source of these new drugs, especially in the oncological and antihypertensive therapeutic areas.[25] In addition to providing many new drug leads, NPs and NP-derived drugs were well represented in the top 35 worldwide selling ethical drugs in 2000, 2001 and 2002.[26]

This review describes NPs, semi-synthetic NPs and NP-derived compounds undergoing clinical evaluation or registration by disease area at the end of 2004. The last comprehensive review of NPs in clinical trials, "Recent Natural Products Based Drug Development: A Pharmaceutical Industry Perspective", was published in August 1998 by Shu.[27] Since then, reviews have been published that describe compounds in clinical trials by organism type, compound class and/or therapeutic area. In addition, there have been a number of reviews that detail marine-derived NPs in clinical trials.[28–33]

This review follows a similar format to Shu's publication[27] with compounds 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 Oncological Disease (Section 7). NP-derived drugs launched since 1998 (Section 2) and novel NP-derived templates of clinical candidates discovered since 1990 (Section 8) are also discussed. In this review, compounds have been classified as a NP, semi-synthetic NP or NP-derived. These definitions are simpler than those used in Newman, Cragg and Snader's excellent reviews.[25,34] If a NP is produced synthetically for clinical studies or for the market, it is still defined as a NP for the purposes of this review. Similarly, semi-synthetic NPs are compounds that were originally semi-synthetically derived from a NP template, while NP-derived compounds are synthetically derived from a NP template.

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Table 1 NP-derived drugs launched in the United States, Europe or Japan since 1998 by year with reference to their lead compound, classification and therapeutic area

Year	Generic name (trade name)	Lead compound	Classification	Disease area	References
1998	orlistat (Xenical®)	lipstatin	semi-synthetic NP[a]	antiobesity	35–39
1998	cefoselis (Wincef®)	cephalosporin	NP-derived[a]	antibacterial	35,36
1999	dalfopristin and quinupristin (70 : 30 mixture) (Synercid®)	streptogramin B and streptogramin A	semi-synthetic NP	antibacterial	40–42
1999	valrubicin (Valstar®)	doxorubicin **144**	NP-derived[a]	oncology	40,41
1999	colforsin daropate (Adele, Adehl®)	forskolin	semi-synthetic NP	cardiotonic	40,41
2000	arteether (Artemotil®)	artemisinin **40**	semi-synthetic NP	antimalarial	43–45
2001	ertapenem (Invanz™)	thienamycin	NP-derived[a]	antibacterial	46–49
2001	caspofungin (Cancidas®)	pneumocandin B	semi-synthetic NP	antifungal	46,47,50
2001	telithromycin (Ketek®)	erythromycin **19**	semi-synthetic NP	antibacterial	46,47,51–54
2001	pimecrolimus (Elidel®)	ascomycin	semi-synthetic NP	atopic dermatitis	46,47,55,56
2002[b]	galantamine (Reminyl®)	galantamine	NP[a]	Alzheimer's disease	57–61
2002	micafungin (Funguard®)	FR901379	semi -synthetic NP	antifungal	57–59,62,63
2002	amrubicin hydrochloride (Calsed®)	doxorubicin	NP-derived[a]	oncology	57–59,64
2002	biapenem (Omegacin®)	thienamycin	NP-derived[a]	antibacterial	57–59,65
2002	nitisinone (Orfadin®)	leptospermone	NP-derived[a]	antityrosinaemia	57–59,66,67
2003	miglustat (Zavesca®)	1-deoxynojirimycin	semi-synthetic NP[a]	type 1 Gaucher disease	68–72
2003	mycophenolate sodium (Myfortic®)	mycophenolic acid	NP[a]	immunosuppression	68–70,73,74
2003	rosuvastatin (Crestor®)	mevastatin	NP derived[a]	dyslipidemia	68–70,75,76
2003	pitavastatin (Livalo®)	mevastatin	NP derived[a]	dyslipidemia	68–70,77
2003	daptomycin (Cubicin™)	daptomycin	NP[c]	antibacterial	68–70,78–81
2004	everolimus[d] (Certican™) **92**	sirolimus **91**	semi-synthetic NP[a]	immunosuppression	82–84

[a] These drugs are manufactured by total synthesis. [b] Galantamine was launched in Austria as Nivalin® in 1996 and as Reminyl® in the rest of Europe and the US in 2002. [c] Daptomycin is manufactured by semi-synthesis. [d] Everolimus (RAD-001) is also being evaluated by Novartis in phase II clinical trials for solid tumours (Section 7).

Compounds derived from primary metabolites, hormones and protein fragments have not been included except for some interesting invertebrate-derived peptides. Also, herbal mixtures and new uses of existing drugs have not been listed exhaustively.

Although this review represents a thorough evaluation of publicly available data, there may be some NP-derived compounds that have been overlooked. The status of compounds in clinical investigation and the companies involved can change rapidly and readers are encouraged to consult the recent literature and company web pages for up to date information.

2 NP derived drugs launched since 1998

At least 21 NP and NP-derived drugs have been launched onto the market in the United States, Europe or Japan (Table 1) in the 6 years since Shu's review.[27] In addition, a semi-synthetic camptothecin derivative, belotecan **1**, was launched in Korea in 2004 (Section 7). The 21 drugs in Table 1 can be classified as 3 NPs, 10 semi-synthetic NPs and 8 NP-derived drugs and include the "first in kind" drugs caspofungin (echinocandin antifungal), galantamine (novel anti-Alzheimer's drug), nitisinone (new treatment for the orphan disease hereditary tyrosinemia type I), miglustat (new treatment of Type 1 Gaucher Disease) and daptomycin (novel antibacterial lipopeptide). Although the number of new NP-derived launches in 2004 was low, there are many NP-derived compounds in Phase III or registration that may be launched in 2005 and 2006.

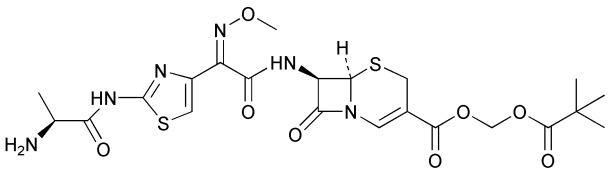
3 Infectious disease area

3.1 Antibacterial

NPs have played a pivotal role in the development of antibacterial drugs as most have been derived from a NP lead: β-lactams (first introduced 1941), aminoglycosides (1944), cephalosporins (1945), chloramphenicol (1949), tetracyclines (1950), macrolides (1952), lincosamides (1952), streptogramins (1952), glycopeptides (1956), rifamycins (1957) and lipopeptides (2003). Only the sulfonamide (1935), nitroimidazole (1959), quinolone (1962), trimethoprim (1968) and oxazolidinone (2000) antibacterials are synthetically derived. Despite the introduction in 2000 and 2003 of the first 2 novel antibacterial classes since 1968, antibacterial research is in crisis as only a few major pharmaceutical companies are actively engaged in the field.[85–95] This crisis has coincided with a pressing need for new and improved antibacterial drugs due to the widespread nature of antibacterial drug resistance. A worry for major pharmaceutical companies is that an acceptable financial return may not be made on the huge investment needed to bring an antibacterial drug through clinical trials to market. Sales of a new antibacterial may be limited due to potential rapid antibacterial resistance and the possibility that a new drug may be quarantined for use only as a last resort. Concerns also have been raised that today's regulatory procedures make approval difficult for new antibacterials as they are compared head to head against established drugs in sensitive strains, while activity against resistant strains is not adequately weighted. Finally, most mechanism based antibacterial screening programmes undertaken to date have not been successful in identifying new *in vivo* active antibacterial drugs. However, despite the bad news, many biotechnology companies have taken up the challenge of anti-infectives research. These issues have been discussed in various articles[85–95] and a recent discussion paper, "Bad Bugs, No Drugs", was released in July 2004 by the Infectious Diseases Society of America.[96] General reviews on antibacterials under clinical development, which include "Taking Inventory: Antibacterial Agents Currently at or Beyond Phase I"[97] and "Bacterial Targets to Antimicrobial Leads and Development Candidates",[98] have been published recently.[97–100]

β-Lactam antibacterial drugs are produced either by semi-synthesis from a NP template or total synthesis and can be divided into the following subclasses: penicillins, cephalosporins, cephamycins, cephems, carbapenems, penems and monobactams.[101–104] Presently, there are 4 cephalosporins (ceftizoxime alapivoxil **2**, ceftobiprole **3**, RWJ-442831 **4** and PPI-0903 **5**), 1 penem (faropenem daloxate **6**) and 3 carbapenems (CS-023 **7**, tebipenem **8** and doripenem **9**) in clinical development.[97,98,105–110]

Ceftizoxime alapivoxil (AS-924) **2**, which is a prodrug of the second generation cephalosporin ceftizoxime, is in preregistration in Japan and was developed by Kyoto Yakuhin and licensed to Asahi Kasei Pharma.[109,111,112] Basilea Pharmaceutica is developing the cephalosporin ceftobiprole (BAL-5788,



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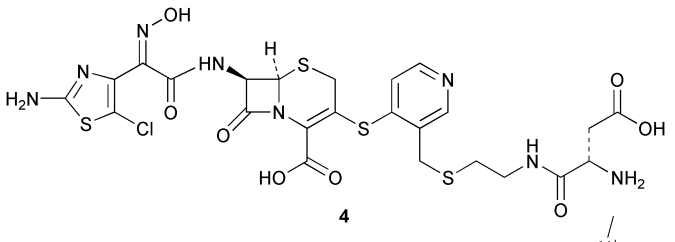

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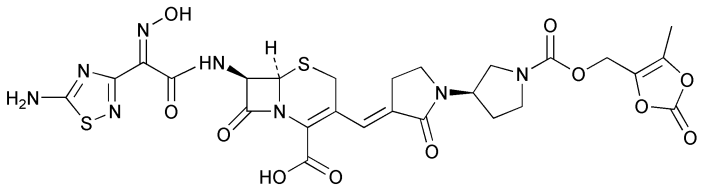

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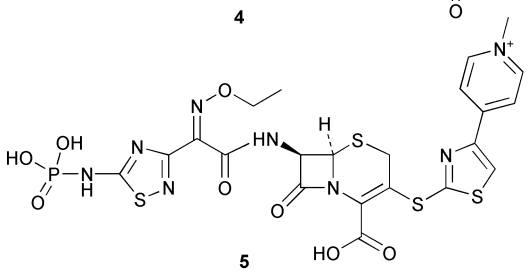

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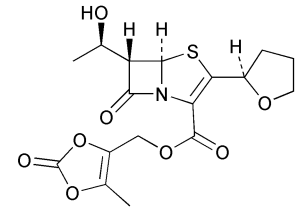
Ro-65-5788) **3**, a prodrug of BAL-9141 (Ro-63-9141), as a broad spectrum antibiotic with activity against both Gram positive and negative bacteria.[109,113–116] Ceftobiprole **3** is in Phase III development and has potent bactericidal activity against methicillin resistant *Staphylococcus aureus* (MRSA) and penicillin resistant *Streptococcus pneumoniae*. Basilea obtained the right to develop **3** from Roche after Basilea spun-off from Roche in October 2000 and gained the global marketing and manufacturing rights following Roche's decision in May 2004 not to exercise its opt-in right. Basilea plan to register ceftobiprole **3** as a New Drug Application (NDA) in 2006.[116] Another cephalosporin, RWJ-442831 **4**, which is a prodrug of RWJ-54428 that was discovered by Microcide Pharmaceuticals and developed by RW Johnson Pharmaceutical Research Institute, has been reported to be undergoing Phase I clinical evaluation.[97,109,117–120] Finally, Peninsula Pharmaceuticals announced in September 2003 that they had secured an exclusive worldwide license (except Japan) from Takeda to develop and commercialise the cephalosporin PPI-0903 (TAK-599) **5**, a prodrug of T-91825. Peninsula completed Phase I clinical trials in October 2004 and are planning to investigate PPI-0903 **5** in a Phase II trial against complicated skin infections and community-acquired and hospital-acquired pneumonias.[109,121–123]

Faropenem daloxate (SUN-208, BAY-56-6824) **6** is an orally active, penem-type β-lactam that was licensed to Replidyne by Daiichi Suntory Pharma in August 2004.[124–126] Faropenem daloxate **6** is a pro-drug of faropenem, an antibiotic which has been available for clinical use in Japan since 1997.[127] Bayer had previously licensed faropenem daloxate **6** from Suntory in 1999 but discontinued further development during Phase III trials in 2002.[128] Replidyne intends to complete the clinical evaluation of **6** for use in community-acquired bacterial infections.[124]

The carbapenem CS-023 **7** was developed by Sankyo and licensed to Roche in November 2003. Sankyo and Roche are co-operatively evaluating CS-023 **7** in Phase I and II clinical trials as a broad spectrum antibiotic.[128–130] Tebipenem (ME-1211, L-084) **8**, which was originally developed by Wyeth in Japan, is being evaluated in late Phase II clinical trials by Meiji Seika.[131–134] Shionogi & Co have submitted a NDA in Japan for doripenem (S-4661) **9** as a broad spectrum antibiotic[135–142] and in March 2003, licensed the development and marketing rights of **9** for North America, South America and Europe to Peninsula Pharmaceuticals.[143] Peninsula started their final Phase III trials of doripenem **9** in July 2004 and in October 2004, was granted fast track status by the US Food and Drug Administration (FDA) for the treatment of nosocomial pneumonia.[144]

The glycopeptide antibiotics vancomycin **10** and teicoplanin **11** are used to treat multi-drug resistant Gram positive infections and exert their antibacterial activity by binding to the D-Ala-D-Ala termini of peptidoglycan precursors, which prevent the



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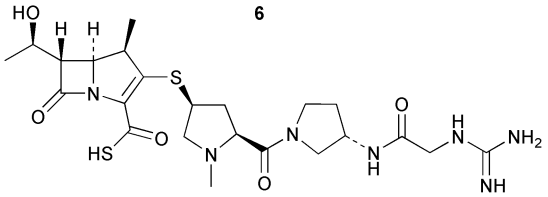

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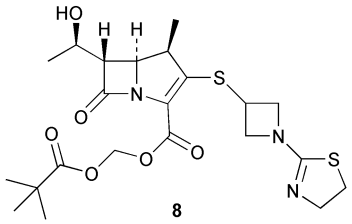

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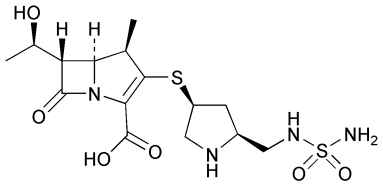

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transglycosylation and transpeptidation reactions essential for cell wall production.[145–147] Vancomycin **10** was discovered in the early 1950s and was used only sparingly until the mid 1970s when MRSA started to become a widespread problem, while teicoplanin **11** was first introduced in 1988 into Europe.[148] Unfortunately, it was not long before some bacteria became resistant to **10** and **11** by substituting either D-Ala-D-Lac or D-Lac-D-Ala in place of D-Ala-D-Ala in their peptidoglycan precursors.[146,147] A search for semi-synthetic glycopeptide derivatives with improved antibacterial properties has led to the discovery of three derivatives, dalbavancin **12**, telavancin **13** and oritavancin **14**, that have been evaluated in clinical trials during the last few years. A detailed account of these semi-synthetic derivatives can be found in the recent reviews "Glycopeptides in Clinical Development: Pharmacological Profile and Clinical Perspectives"[149] and "Glycopeptide Antibiotics: from Conventional Molecules to New Derivatives".[150]

Dalbavancin (BI-397) **12** is a semi-synthetic derivative developed by Biosearch Italia (now part of Vicuron Pharmaceuticals) that uses the teicoplanin-related A40926 glycopeptide complex as a template.[151–153] The A40926 complex was isolated originally from *Nonomuraea* sp. ATCC 39727 and significant work has been undertaken to increase the yield of the desired A40926 factor **15**.[154–157] Vicuron filed a NDA for dalbavancin **12** for the treatment of skin and soft tissue infections in December 2004, while a Phase II trial for the treatment of catheter-related bloodstream infections is ongoing.[158]

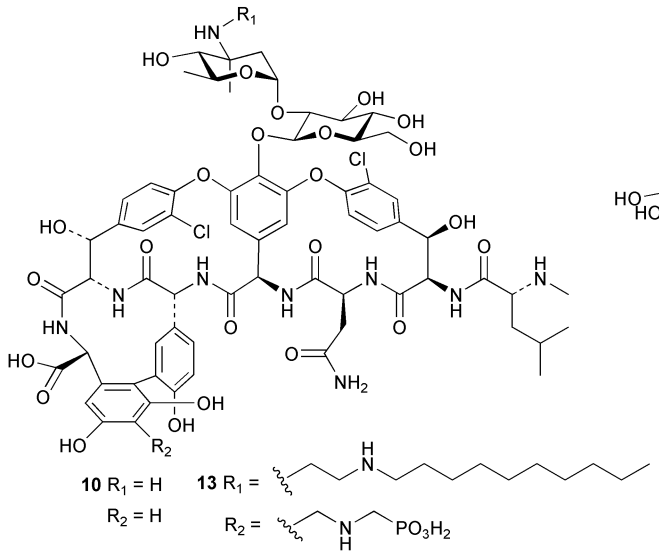
Telavancin (TD-6424) **13** is a semi-synthetic derivative of vancomycin **10** developed by Theravance,[159,160] which is undergoing Phase III clinical evaluation for treatment of patients whose infections are due to MRSA in both complicated Gram positive skin and skin structure infections and hospital-acquired pneumonia.[161–163] Although telavancin **13** and vancomycin **10** both disrupt bacterial cell wall growth, only telavancin **13** disrupts bacterial cell membrane integrity.

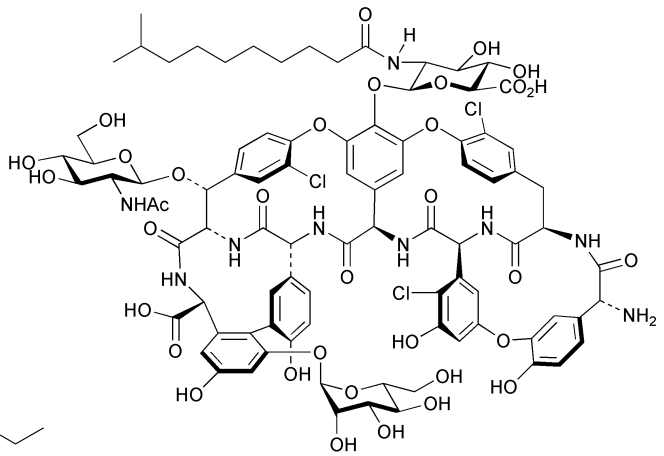
Oritavancin (LY-333328) **14** is a semi-synthetic derivative of the vancomycin **10** related glycopeptide chloroeremomycin (LY-264826) **16**, which was originally isolated from *Nocardia orientalis*.[164–166] Eli Lilly licensed the worldwide development rights for oritavancin **14** to InterMune, but Phase III clinical trials were halted in November 2003 due to manufacturing problems.[167] An additional clinical safety study must be completed prior to the submission of a NDA for oritavancin **14** and InterMune are seeking another company to complete its future development.[167]

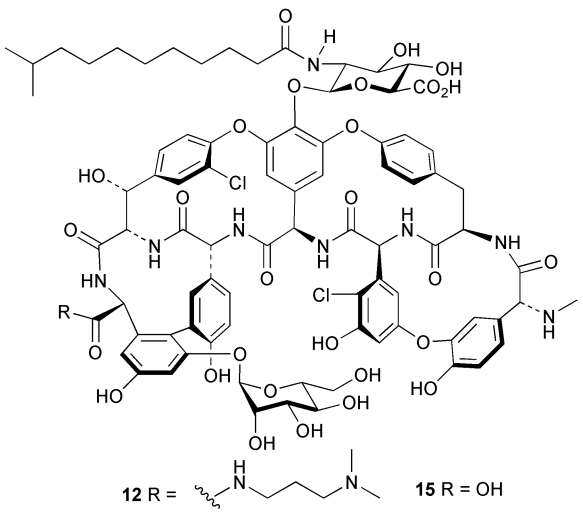
Ramoplanin is an antibacterial complex originally isolated from *Actinoplanes* sp. ATCC 33076 by BioSearch Italia (Vicuron Pharmaceuticals) and consists of three factors A1, A2 **17** and A3 that have similar biological activity.[168–179] Ramoplanin exerts its antibacterial activity by binding to the peptidoglycan intermediate Lipid II and disrupting bacterial cell wall synthesis.[180] Recent work has shown that the lipid side chain is not important for Lipid II binding but is necessary for antibacterial activity.[181] Factor A2 **17** is the major component of the antibacterial complex and its percentage within the complex and overall yield have been increased significantly by strain improvement and media development. Oscient Pharmaceuticals (previously Genome Therapeutics), which licensed ramoplanin **17** from Vicuron, has been evaluating **17** for the treatment of *Clostridium difficile*-associated diarrhoea in Phase II trials and has been granted fast track status by the FDA for this use.[182] A Phase III clinical study for treatment of vancomycin-resistant *Enterococci* (VRE) closed its enrolment prior to completion and Oscient will examine the existing data before making any further decisions.[183]

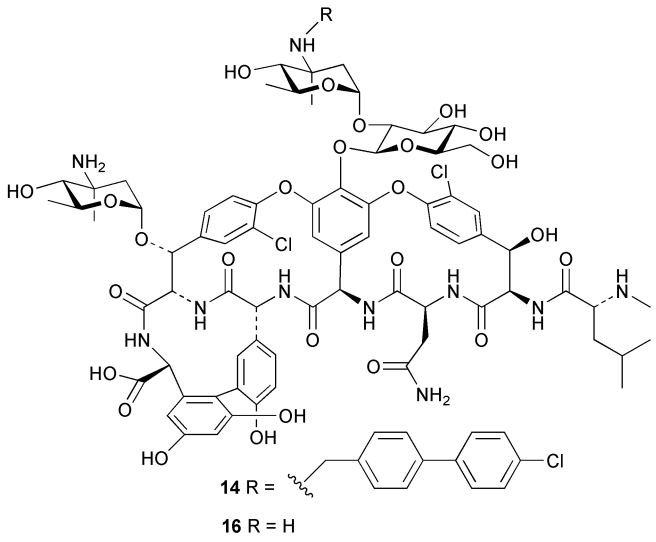
VIC-ACNE (BI-K-0376) (structure not available) is a novel semi-synthetic derivative of the cyclic thiazolyl peptide GE-2270 A **18**[184–187] developed by BioSearch Italia/Vicuron Pharmaceuticals. VIC-ACNE has good selectivity against *Propionibacterium acnes*, the bacterium associated with acne, compared to other bacteria normally associated with skin flora.[187,188] As a consequence, VIC-ACNE is potentially useful as a topical treatment for acne and Vicuron has reported the successful completion of Phase I clinical trials in June 2003 but have indicated a preference to out-license VIC-ACNE for future development.[188]

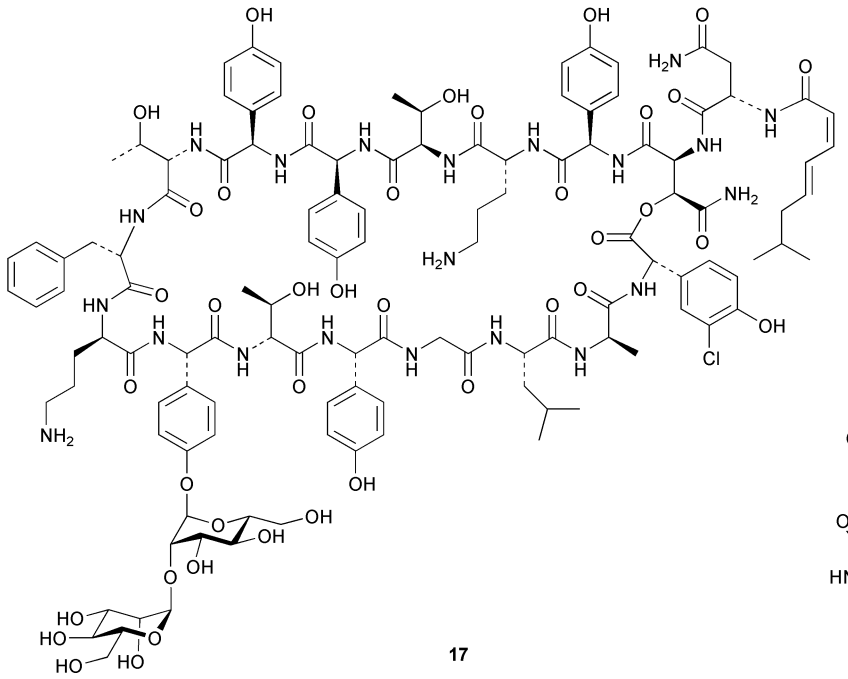
The macrolide antibiotic erythromycin **19** was first isolated from the actinomycete *Saccharopolyspora erythraea* (formally











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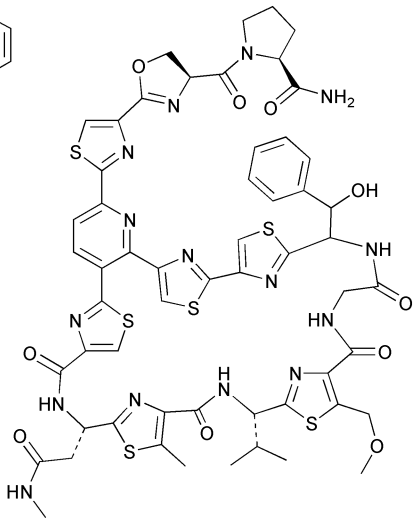

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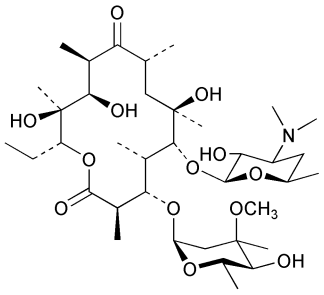

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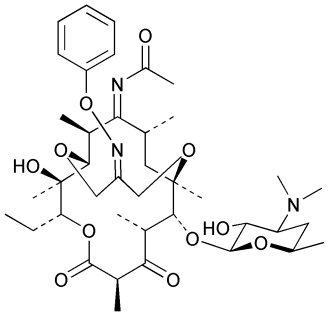

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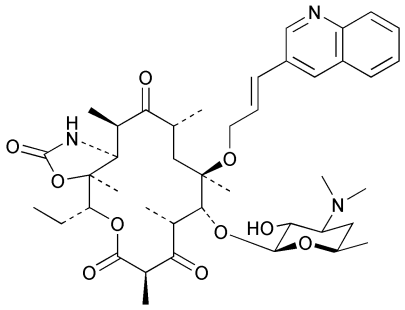

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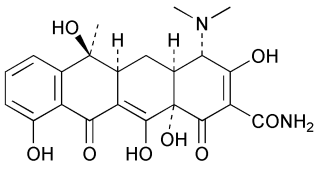
Streptomyces erythreus) and used in the clinic as early as 1952.[189] Since 1982, the naturally occurring macrolide miokamycin (launched 1985),[190] the semi-synthetic miokamycin derivative rokitamycin (1986)[191] and the semi-synthetic erythromycin derivatives roxithromycin (1987),[192] azithromycin (1988),[148] erythromycin acistrate (1988),[148] RV-11 (1989),[193] clarithromycin (1990),[194] dirithromycin (1993),[195] flurithromycin ethylsuccinate (1997)[196] and telithromycin (2001)[46,47,53,54] have been commercialised. The antibacterial activity of both the naturally occurring and semi-synthetic macrolides is due to protein synthesis inhibition through binding to the peptidyl transferase site of the bacterial 50S ribosomal subunit.[197–200] Erythromycin **19** also acts as agonist of the motilin receptor and a semi-synthetic derivative is under development as a potential treatment for gastric motility disorder (Section 5).

EP-013420 **20** is the only semi-synthetic macrolide in active clinical development as an antibacterial. EP-013420 **20** is a novel, bridged bicyclic erythromycin **19** derivative developed by Enanta Pharmaceuticals to have optimal pharmacokinetic properties compared to existing macrolides and ketolides, while retaining broad spectrum antibiotic activity.[201,202] In August 2004, Enanta announced the start of Phase I clinical trials of EP-013420 **20**, 1 month after licensing **20** to the Shionogi & Co for development and commercialization in Japan and East Asian countries.[135,203] Another semi-synthetic erythromycin **19** derivative, cethromycin (ABT-773) **21**,[204,205] that was recently undergoing clinical development had Phase II clinical trials suspended by Taisho in April 2004.[206] Abbott Laboratories had already halted the development of cethromycin **21** during Phase III clinical trials.[206]

The tetracyclines are a group of antibacterial drugs first discovered from various *Streptomyces* species in the late 1940s.[207–211] The marketed tetracycline drugs, chlortetracycline, oxytetracycline and tetracycline **22**, and the semi-synthetic derivatives doxycycline and minocycline **23**, display activity against both Gram positive and negative bacteria by binding reversibly to the 30S bacterial ribosome and effectively halting protein synthesis. The most common causes of tetracycline resistance are bacterial efflux and ribosome protection.[207–211] A new generation of tetracyclines known as glycylcyclines have been developed that generally have more potent antibacterial activity and undergo less bacterial efflux compared to other tetracyclines.[207] Wyeth's tigecycline (Tygacil™, GAR-936) **24** is the only glycylcycline in clinical development and, in December 2004, registration dossiers were submitted simultaneously to European, US, Canadian, Australian and Swiss authorities.[212] Tigecycline **24** is derived from nitration of minocycline **23**, which is in turn semi-synthetically derived from the NP tetracycline **22**.[213]

Rifamycin B **25** is a naturally occurring actinomycete-derived antibiotic which has been used as a template for rifampin, rifaximin, rifapentine and rifabutin.[214,215] Rifalazil (ABI-1648, KRM-1648) **26** is a new derivative of rifamycin B **25** developed by the Japanese company Kaneda Corporation and licensed to ActivBiotics in 2002.[214–218] ActivBiotics are evaluating rifalazil **26** in Phase II clinical trials for the treatment of *Chlamydia trachomatis* in men with non-gonococcal urethritis and for the treatment of gastritis and peptic ulcer disease caused by *Helicobacter pylori*.[219] An additional Phase II trial for rifalazil **26** is planned for the treatment of *Clostridium difficile*-associated disease.[219]



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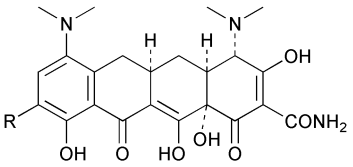

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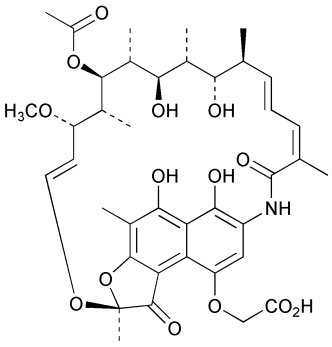

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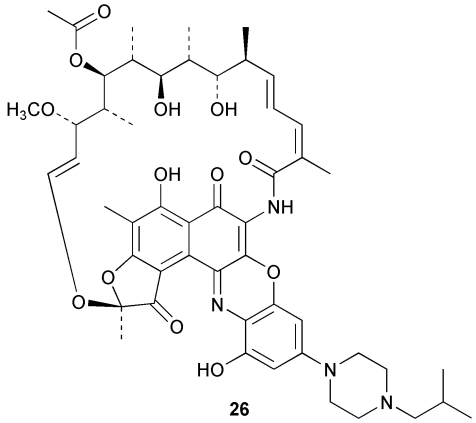
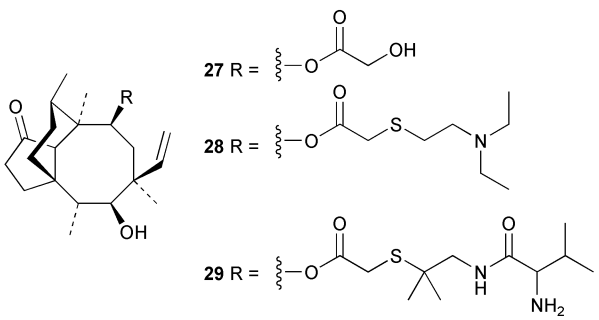


26

The fungal metabolite pleuromutilin (275833) **27**,[220] which exerts its antimicrobial activity by binding to the 50S bacterial ribosome,[221–223] is in Phase III clinical trials for use as a topical antibacterial and GlaxoSmithKline expect **27** to be registered in 2005.[224] Although there are no pleuromutilin **27** derivatives in human clinical use, 2 semi-synthetic derivatives, tiamulin **28** and valnemulin **29**, are widely used as antibiotics for the treatment of swine diseases.[225,226]



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3.2 Antifungal

Most antifungal drugs in use today have some connection to NPs. The polyenes and griseofulvin are NPs, while the echinocandins are semi-synthetically derived from NPs. 5-Fluorocytosine is a nucleoside that interferes with DNA and RNA synthesis and is primarily used in combination with the polyene amphotericin B. Although the azoles generally are considered to be synthetic in origin, Sneader traces their drug prototype pathway back to the *Streptomyces* metabolite azomycin.[227] The antifungal activity of the azoles is due to the inhibition P450 3A-dependant C14-α-methylase, an enzyme that converts lanosterol to ergosterol, which leads to ergosterol depletion and disruption of the fungal cell membrane integrity. The following reviews discussing new antifungal agents have been published: "Microbial Natural Products as a Source of Antifungals",[228] "Emerging Novel Antifungal Agents",[229] "Discovery and Development of Antifungal Compounds"[230] and "New Antifungal Drugs and New Clinical Trials: Interpreting Results may be Difficult".[231]

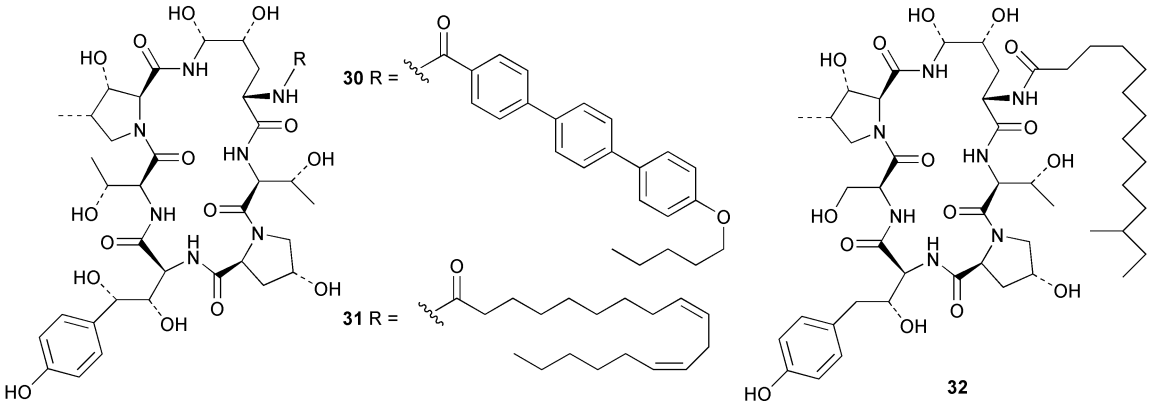
The echinocandins are a group of naturally occurring lipopeptides produced by various fungi that display potent antifungal activity by inhibition of 1,3-β-D-glucan synthesis in the fungal cell wall.[232,233] To date, 2 echinocandin-based drugs have been approved for clinical use. Caspofungin, a semi-synthetic derivative of pneumocandin B, was first launched by Merck in the United States in 2001,[46,47,234,235] while micafungin is a semi-synthetic derivative of FR901379 that was first launched by Fujisawa in Japan in 2002.[57,58,236] There are 2 echinocandins, anidulafungin **30** and aminocandin (structure not available), currently undergoing clinical evaluation.

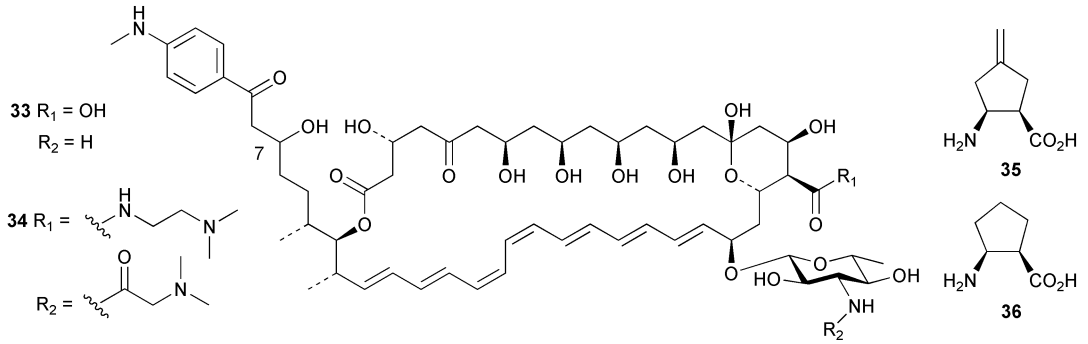
Anidulafungin **30** was developed by Eli Lilly and licensed to Vicuron Pharmaceuticals in May 1999 and is a semi-synthetic derivative of echinocandin B **31**, a fungal metabolite originally isolated from *Aspergillus rugulovalvus* (formerly *Aspergillus rugulosus*).[237–239] Vicuron has completed a Phase III trial of anidulafungin **30** for the treatment of oesophageal candidiasis and Phase III trials are in progress for treatment of invasive aspergillosis and candidiasis/candidemia. In May 2004, Vicuron received an approvable letter†,[240] from the FDA for anidulafungin **30** which has delayed its launch.[241] In consultation with the FDA, Vicuron has decided to further investigate **30** for its potential treatment of oesophageal candidiasis and invasive candidiasis/candidemia. Vicuron plans to submit an amended NDA for oesophageal candidiasis in the second quarter of 2005 and a new NDA for invasive candidiasis/candidemia in the third quarter of 2005.[241]

Indevus licensed the echinocandin, aminocandin (HMR-3270),[233,242,243] from Novexel[244] (originally Sanofi-Aventis anti-infective group) in April 2003 and initiated Phase I clinical trials against systemic fungal infections in February 2004.[245] Although the structure of aminocandin is not yet in the public domain, it is known to be a semi-synthetic derivative of deoxymulundocandin **32**,[233] a NP originally isolated from the fungus *Aspergillus sydowii* by Hoechst India in 1992.[246]

Polyene antibiotics are naturally occurring polyketides isolated from various *Streptomyces* species that display broad spectrum antifungal activity. Their mechanism of action involves complexation with ergosterol and destabilization of the fungal cell membrane, which causes increased membrane permeability and fungal death. Amphotericin B is commonly used to treat fungal infections, but has serious side effects which can be reduced by liposomal preparations. Amphotericin B and the related polyene nystatin also are used to treat topical fungal infections.

† An "approvable letter" informs the applicant that FDA has completed its scientific review and determined that the application can be approved pending resolution of minor deficiencies identified in the letter or during FDA's inspection of the device's manufacturing facilities.



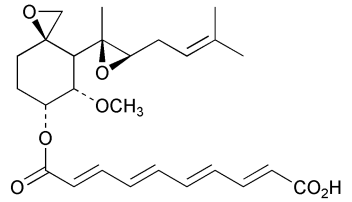


The aureofacin antibiotic complex, which was first described in 1956 from *Streptomyces aureofaciens*,[247] has 2 major components, partricin A (vacidin A) **33** and partricin B (gedamycin).[248] Partricin A **33** is a 38-membered heptaene polyene that exists partially as a 19 → 15 cyclic hemiacetal and its relative stereochemistry, except for C-7, has been determined.[249–251] The diaspartate (SPA-S-753) and diascorbate salts (SPK-843/SPA-S-843) of the semi-synthetic partricin A derivative **34** were developed by Società Prodotti Antibiotici and have showed promise as new antifungal agents.[252] SPA-S-753[253–255] and SPK-843[256–258] have comparable activity but are water soluble unlike amphotericin B. Preliminary reports have suggested these compounds have a longer serum half-life, are less toxic and are at least equipotent compared to amphotericin B. SPK-843 has been chosen for further development because the antioxidant activity of ascorbic acid improves the stability of the formulation.[259] The Japanese company Kaken Pharmaceuticals have completed a successful Phase I evaluation of SPK-843 and have initiated Phase II studies for systemic mycosis.[260] The Dutch company Aparts BV hold the worldwide rights outside Japan for the development of SPA-S-753 and SPK-843.[259]

PLD-118 (BAY-10-8888) **35** is a NP-derived synthetic compound in Phase II clinical trials whose structure is based upon the cyclic β-amino acid cispentacin (also known as FR109615) **36**.[261,262] Cispentacin **36** was isolated from *Bacillus cereus* and reported in December 1989 by workers from Bristol-Myers Research Institute in Japan as an antifungal agent.[263] One month later, workers at Fujisawa reported the isolation and antifungal activity of FR109615 **36** from *Streptomyces setonii*.[264] PLD-118 **35** inhibits fungal growth through intercellular accumulation and the disruption of fungal protein synthesis through the inhibition of isoleucyl-tRNA synthetase.[261,262] The dual mechanism of action exhibited by **35** is entirely different from other antifungal clinical candidates and drugs. Results from the first Phase II study conducted by Pliva Pharmaceutical were promising and suggested that **35** is likely to be safe and effective in human immunodeficiency virus (HIV)-infected patients with oropharyngeal candidiasis and additional dose refinement is being evaluated in a second Phase II study for this indication. Pliva has been looking for a partner interested in co-development and/or a commercialization license of PLD-118 **35**.[265]

3.3 Antiparasitic

Fumagillin (SR-90144) **37** is being evaluated in Phase III clinical trials by Sanofi-Aventis for the treatment of intestinal microsporidiosis and was granted EU orphan drug status for this use in March 2002.[266] Microsporidiosis is caused by the spore-forming unicellular parasite *Enterocytozoon bieneusi* and is of major concern to immunocompromised patients in who it causes chronic diarrhoea.[267,268] Fumagillin **37** was first isolated in 1949 from *Aspergillus fumigatus* and was used shortly after its discovery to treat intestinal amoebiasis.[269,270] Fumagillin **37** was later found to inhibit angiogenesis through binding to methionine aminopeptidase 2 (MetAP2)[271–273] and an X-ray crystal structure of **37** bound to MetAP2 was published in 1998.[274] However, a recent paper has shown that depletion of MetAP2 does not alter cell response to fumagillin **37** and bengamides.[275] Other semi-synthetic derivatives are undergoing clinical evaluation as potential anticancer drugs (Section 7). The antifungal activity of **37** and analogues against *Saccharomyces cerevisiae* is also thought to be due to the inhibition of MetAP2.[276] Fumagillin **37** also plays an important role in the treatment of bees with *Nosema* disease, which is caused by infection with the protozoan organism, *Nosema apis*, and is sold as its bicyclohexylammonium salt (Fumidil B® and Fumagilin B®).[277–279] One the largest manufacturers of **37** is Chinoin, a Hungarian subsidiary of Sanofi-Aventis.[278,280]



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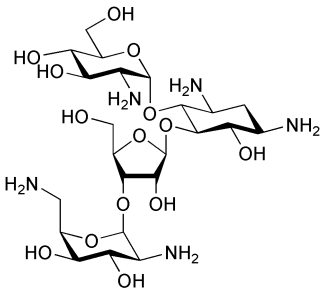
The Institute of OneWorld Health[281] and Drugs for Neglected Diseases Initiative (DNDi)[282] are investigating the broad spectrum aminoglycoside antibiotic paromomycin **38** in Phase III clinical trials for the treatment of visceral leishmaniasis in India and Africa respectively.[283–285] Paromomycin **38** is produced by *Streptomyces rimosus* var. *paromomycinus* and is currently used in an oral formulation to treat intestinal parasites. The Institute of OneWorld Health completed their Phase III trial in November 2004 and will apply for approval in India in 2005,[281] while DNDi expect their trial to end in the first quarter of 2006.[282,286]



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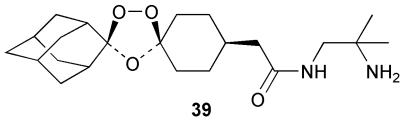
In May 2003, Ranbaxy Laboratories entered into an agreement with Medicines for Malaria Venture (MMV) to develop trioxolane OZ-277 (RBx11160) **39**, an artemisinin **40** inspired orally available compound that can be easily synthesised in large quantities.[287–290] Ranbaxy commenced Phase I clinical trials of OZ-277 **39** in August 2004.[286]



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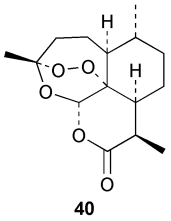

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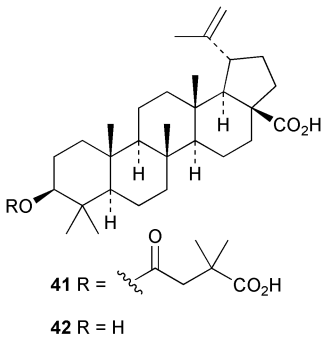
A semi-synthetic derivative of artemisinin **40**, artemisone (BAY 44-9585) (structure not available), which was first synthesised by Richard Haynes' group at Hong Kong University, is being evaluated in Phase I clinical trials by Bayer AG and MMV.[288] The antimalarial mechanism of action of artemisinin **40** has been determined to be due to inhibition of SERCA orthologue PfATP6 outside the food vacuole after activation by iron.[291–294]

3.4 Antiviral

Some of the greatest health risks known to humans are caused by viral diseases such as HIV, hepatitis B and C (HCV), Ebola, influenza, dengue fever and yellow fever.[295] The 2003 outbreak of the new Severe Acute Respiratory Syndrome (SARS) illustrates the potential danger and disruption which can be caused by viral epidemics.[296] As a consequence, there has been considerable effort over the last 20 years invested into antiviral drug discovery, especially in the field of HIV.[297,298] In addition to development of small molecule antiviral drugs, vaccines also are commonly used to try to prevent diseases like influenza, measles, mumps, polio and smallpox.

One of the most promising compounds being evaluated to treat HIV is PA-457 **41**, a semi-synthetic derivative of the plant triterpenoid betulinic acid **42**.[299] Betulinic acid **42** was found to be a weak inhibitor of HIV replication[300] and a concerted medicinal chemistry programme by Lee and co-workers at the University of North Carolina identified a semi-synthetic derivative **41** as the promising candidate for further evaluation.[301–303] Panacos Pharmaceuticals licensed **41** and started antiretroviral Phase I clinical trials in March 2004 and plans for Phase II clinical development were announced in December 2004.[299] Workers at Panacos have reported that the antiretroviral activity of PA-457 **41** was due to a novel mechanism of action: targeting a late step in the Gag processing.[304] This finding has prompted great interest in **41** as it represents a new class of HIV inhibitor.[303,305–307]

In 1992, workers at the National Cancer Institute (NCI), a branch of the US National Institutes for Health, reported the isolation of coumarins, which they named calanolides, with potent activity against HIV-1 from the tree, *Calophyllum lanigerum*, collected in Sarawak, Malaysia.[308,309] The right to develop these compounds was licensed to Sarawak Medichem Pharmaceuticals who have progressed the most promising candidate, (+)-calanolide A **43**, through to Phase II clinical trials in combination with other anti-HIV agents.[310] Calanolide A **43** for use in preclinical and clinical studies was produced by total synthesis as the original plant source was not readily accessible and produced only small quantities of **43**.[311–315] Calanolide A **43** was also found to have activity against all *Mycobacterium tuberculosis* strains tested, including some which are resistant to standard antitubercular drugs.[316] This property is unique amongst antiviral agents and may allow more efficient treatment of patients infected with both HIV and tuberculosis. The related coumarins calanolide B (costatolide), dihydrocalanolide B and oxocalanolide are also under preclinical development by Sarawak Medichem and the NCI.[310]



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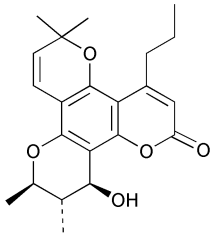

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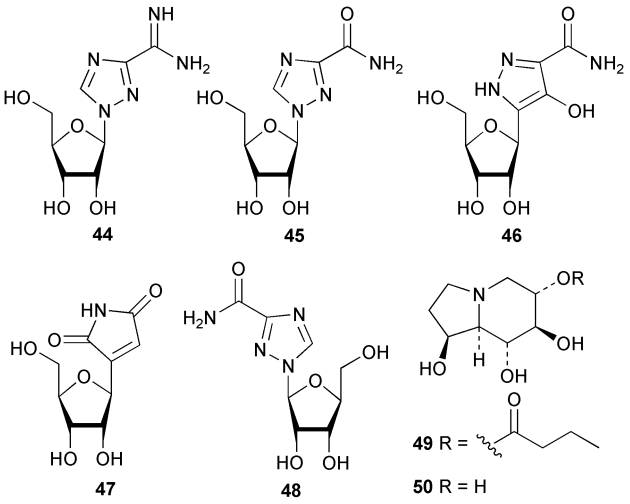
Viramidine (ribamidine) **44** is being evaluated in Phase III clinical trials by Valeant Pharmaceuticals International (previously ICN and Ribpharm Inc) in combination with pegylated interferon α-2b for treatment of chronic HCV.[317] Viramidine **44** is a prodrug that is converted to ribavarin **45** by adenosine deaminase in the liver.[318] A combination of ribavarin **45** and interferon α-2b is the gold standard treatment for HCV and in studies to date, viramidine **44** appears to have a better safety profile than ribavarin **45**.[318–321] Viramidine **44** can be classified as NP-derived as it is related to ribavarin **44**, whose structure was based upon 2 nucleoside antibiotics, pyrazomycin **46** and showdomycin **47**, which were isolated from *Streptomyces* in the 1960s.[318,322,323] Valeant also licensed levovirin **48**, which is the enantiomer of ribavarin **44**, to Roche, but clinical studies were discontinued in October 2003.[324]

The Canadian company MIGENIX, which recently changed its name from Micrologix Biotech, has initiated enrolment in a Phase II clinical trial to evaluate the efficacy of MBI-3253 (celgosivir, 6-*O*-butanoylcastanospermine) **49** for the treatment of patients with chronic HCV.[325–328] MBI-3253 **49** is a semi-synthetic derivative of castanospermine **50**,[329,330] an alkaloid originally isolated from the Australian tree, *Castanospermum australe* (Fabaceae), commonly called the Moreton Bay Chestnut. MBI-3253 **49** was licensed to MIGENIX from Virogen Ltd. (UK), who in turn had licensed **49** from Aventis. Aventis had previously unsuccessfully investigated **49** (coded MDL-28574) for the treatment of HIV. MBI-3253 **49** is an orally active inhibitor of α-glucosidase, a mammalian enzyme that affects

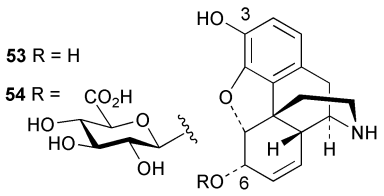
the early stages of glycoprotein processing.[325–329] Glycoprotein processing is essential for HCV and other enveloped viruses as they require proper glycosylation of structural proteins for stability, maturation, assembly and secretion of infective particles.[325] MBI-3253 **49** will be evaluated in combination with ribavarin **45** and interferon and has a potential advantage over existing antiviral agents as it inhibits a mammalian enzyme rather than a viral target, which may be less likely to lead to drug-resistant viral mutants.[325]



4 Neurological disease area

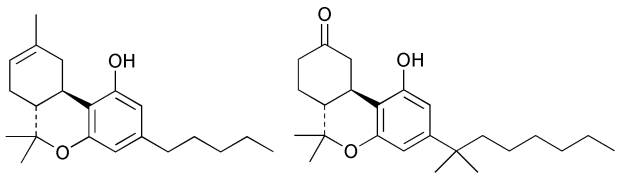
Some of the earliest NP derived drugs used for the treatment of pain and central nervous system (CNS) diseases include the opiate alkaloids from the opium poppy, *Papaver somniferum*, ergot from the fungus, *Claviceps purpurea*, tropane alkaloids like cocaine from the South American plant, *Erythroxylon coca*, and the anticholesterinase agent physostigmine **51** from the Nigerian plant, *Physostigma venenosum*.[3,6,331] More recent examples include huperzine **52** from the club moss, *Huperzia serrata*,[332,333] and galantamine from the plant, *Galanthus nivalis*, used to treat Alzheimer's disease[60] and the nicotinic acetylcholine receptor agonist epibatidine from the Ecuadorian frog, *Epipedobates tricolor*, used as a lead compound for the development of drugs for pain relief.[334–336] Recently published general relevant reviews about CNS related drug discovery include "Natural Products as a Source of CNS-Active Agents",[337] "List of Drugs in Development for Neurodegenerative Diseases",[338] "Drugs in Development for Parkinson's Disease",[339] "Clinical Trials of Neuroprotection for Parkinson's Disease",[340] "Cholinergic Drugs in Pharmacotherapy of Alzheimer's Disease",[341] "New Trends in the Design of Drugs Against Alzheimer's Disease"[342] and "A Review of Neuroprotective Agents".[343]

Morphine **53** is one of the major alkaloids of the opium poppy, *Papaver somniferum*, and has been used as an analgesic and narcotic for thousands of years.[6] In the human body morphine **53** is metabolized into 2 glucuronides, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) **54**, which are then readily eliminated from the body.[344–346] While M6G **54** shows analgesic activity, M3G displays very low affinity for opioid receptors and has no analgesic activity.[344–346] The British company CeNeS acquired the rights for a cost effective synthetic route to **54** and the use of preliminary clinical results from Nycomed Amersham in January 2000.[347] In Phase II clinical trials, CeNeS have demonstrated that M6G **54** produces equivalent post-operative pain relief compared to morphine. In September 2004, CeNeS released promising preliminary results from a Phase III clinical trial which showed that patients suffer less post-operative nausea and vomiting when receiving M6G **54** compared to morphine **53**. This study also confirmed the effective dose of **54** and supported the findings of earlier Phase



I and II studies. Further Phase III studies are underway and results are expected in 2005.[347]

Cannabis sativa preparations have been used for thousands of years for their psychotropic activity and ability to relieve pain but are illegal in many countries.[348–350] However, it was not until 1964 that the structure was determined of one of the most active components, Δ^9-tetrahydrocannabinol (THC) **55**.[350,351] Synthetic THC **55** was introduced in 1986 as dronabinol (Marinol®) to treat nausea and vomiting associated with cancer chemotherapy and later to treat appetite loss in AIDS patients,[191,350] while a synthetic THC analogue, nabilone **56**, first launched in 1982 has been used as an anti-emetic and appetite stimulant.[352] The molecular targets of cannabinoids, the cannabinoid receptors CB_1 and CB_2, have been the focus of extensive research.[353–356]

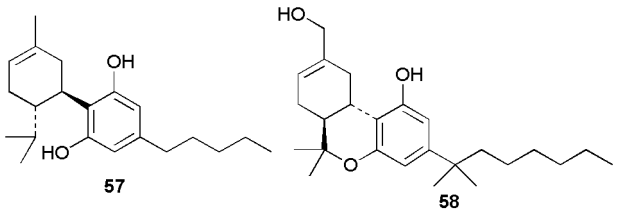


GW Pharmaceuticals have been investigating a cannabis extract called Sativex®, which contains THC **55** and cannabidiol **57** as its principal components in varying amounts, that will be administered using a mouth spray. Sativex® is in Phase II and III clinical trials for various therapeutic uses and in registration phase in the UK and Canada for treatment of multiple sclerosis and neuropathic pain.[357] Health Canada has issued a Qualifying Notice that should enable full approval in early 2005.[357]

Dexanabinol (HU-211) **58** is a synthetic dextrocannabinoid which has neuroprotective properties through inhibition of NMDA glutamate receptors, as well as anti-inflammatory and antioxidant activities.[358–360] Pharmos Corporation have been evaluating dexanabinol **58** in a Phase III clinical trial for the treatment of severe traumatic brain injury (TBI)[360,361] and had been granted orphan drug status by the FDA.[359] However, in December 2004, Pharmos announced that no efficacy was observed as measured by the primary clinical outcome endpoint in Phase III TBI trials.[359] Pharmos plan to continue developing **58** for cognitive impairment in cardiac surgery.[359]

In June 2002, Manhattan Pharmaceuticals (then Atlantic Technology Ventures) licensed IP-751 (ajulemic acid, CT-3) **59** to Indevus Pharmaceuticals who hope to develop as a treatment for both acute and chronic pain.[362–365] IP-751 **59** appears to inhibit COX-2 and other inflammatory cytokines, particularly interleukin-1β and TNF-α, and has significant activity in multiple preclinical models of pain and inflammation. Recent work has indicated that **59** also inhibited peroxisome-proliferative activated receptor-γ (PPAR-γ).[365] A Phase I clinical trial demonstrated that IP-751 **59** was well tolerated and no evidence of psychotropic activity was found. The compound successfully completed a phase II trial in December 2002 and showed a significant reduction in the degree of neuropathic pain but no significant differences were observed between IP-751 **59** and placebo. Indevus plan to undertake additional clinical work with **59** in 2005.[365]

DA-5018 **60** is a synthetic capsaicin **61** analogue that is being developed by the Korean company Dong-A Pharmaceuticals as a non-narcotic analgesic and is in Phase II clinical trials in Korea.[366–369] Capsaicinoids are a group of NPs, of which capsaicin **61** is usually the major component, that cause the



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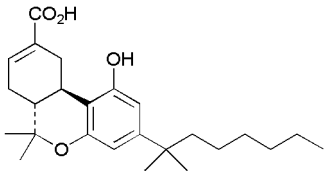

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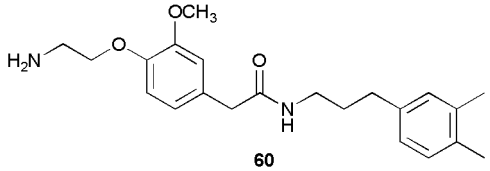
burning sensation associated with eating of chillies by binding to the ion channel receptor vanilloid receptor subtype 1 (VR1).[370,371] Capsaicin-based creams and patches are available for topical use to relieve pain associated with conditions such as osteoarthritis, post-herpetic neuralgias, psoriasis and diabetic neuropathy. In related work, the US based company AlgoRx are developing 2 formulations of capsaicin **61** (ALGRX 4975) for treatment of severe post-surgical pain, post-traumatic neuropathic pain and musculoskeletal diseases in various Phase II clinical trials.[372]



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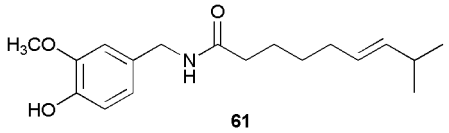

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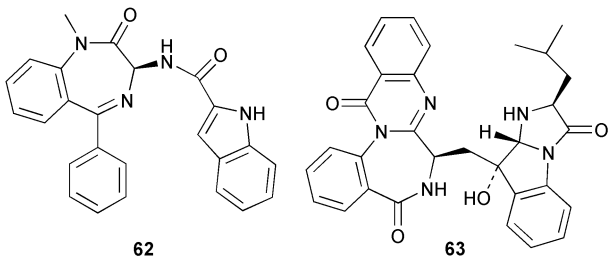
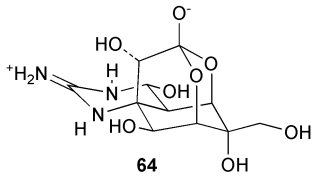
Devacade (devazepide) **62** is an orally active cholecystokinin A (CCK-A) antagonist that ML Laboratories have successfully evaluated in a Phase II clinical trial for patients with severe neuropathic pain.[373–375] In early 2004, ML Labs started a Phase III study that will evaluate the potential of devacade **62** to enhance the pain relieving properties of opioid drugs.[373] Merck originally synthesised **62** (then called devazepide, L-364718 and MK-329) and evaluated it for the treatment of gastric motility disorder but its development was halted in the early 1990s.[27,376] The structure of **62** is based upon the NP lead compound asperlicin **63**, a fungal metabolite isolated from *Aspergillus alliaceus* with CCK-A antagonist activity.[377–380] Panos Therapeutics originally licensed devacade **62** from Merck and later licensed it to ML Laboratories.



62 63

The principle agent responsible for puffer fish poisoning, tetrodotoxin (TTX) **64**, was first isolated as a crude crystalline material by Yokoo in 1950.[381] Since then, TTX **64** has been isolated from various animals including newts, crabs, goby fish, frogs, blue-ringed octopi and bacteria.[382–387] Although it has been proposed that TTX **64** enters the food chain through bacteria, there is evidence that some higher organisms produce **64**.[386,387] TTX **64** exerts its potent biological activity by blocking sodium channels without affecting any other types of voltage- and transmitter-activated ion channels.[388] The Canadian company Wex Pharmaceuticals, in conjunction with Chinese medical institutes, is investigating TTX for its use in the treatment of cancer pain (Tectin™) and the management of opiate withdrawal symptoms (Tetrodin™).[389] Tectin™ has completed a Canadian Phase IIa trial in which it was found to relieve chronic pain in 71% of cancer patients and Wex has a Phase IIb/III clinical trial underway that is expected to finish during 2005. Tectin™ also has been approved for a Phase II clinical trial in China. Tetrodin™ has recently started Phase IIa clinical trials in Canada. Wex are also investigating TTX **64** in preclinical studies for use as a local and topical anaesthetic for patients undergoing surgery or procedures for which general anaesthesia may be impractical or unnecessary (Tocudin™). TTX **64** used in clinical studies is isolated from puffer fish.[389]



64

Conotoxins are a group of peptides produced by cone shells which have a variety of biological actions.[390–396] Ziconotide (Prialt™, SNX-111) **65** is a synthetic version of ω-conotoxin MVIIA, a peptide first isolated from the venom of *Conus magus*.[397,398] Ziconotide **65** is an *N*-type calcium channel blocker that has been evaluated by Elan Pharmaceuticals as a potential treatment for patients suffering from chronic pain and is at the registration stage in both the US and Europe.[398–401]

The Utah based company Cognetix is focused upon the development of conotoxins for use predominantly in the pain and CNS therapeutic areas.[402] Its most advanced candidate is contulakin G (CGX-1160) **66**, which is a 16 amino acid peptide originally isolated from *C. geographus*, that binds to the neurotensin receptor.[402–404] CGX-1160 **66** has completed 2 Phase I clinical trials in spinal cord injury patients and was delivered intravenously (IV) in one study and intrathecally (IT) in the other. No serious adverse events were observed in either study and these results were consistent with the wide therapeutic index observed in preclinical studies. Cognetix plan to start Phase II trials of CGX-1160 **66** in 2005.[402]

Cognetix also have evaluated conantokin-G (CGX-1007) **67**, a selective inhibitor of NR2B sub-type NMDA receptor also isolated from *C. geographus*, in a Phase I clinical trial for neuroprotection and are looking to out-license **67**.[402,405–407]

In July 2004, the Australian company Xenome commenced Phase I clinical trials of Xen-2174 (χ-MrIA) **68** for the treatment of neuropathic pain.[408] Xen-2174 **68** was originally isolated from *C. marmoreus* and is a 13 amino acid peptide with 2 cysteine bridges that has been found to inhibit the norepinephrine transporter (NET), a known CNS drug target that is inhibited by the antidepressant desipramine.[409–411] Norepinephrine is the dominant neurotransmitter in the spinal cord that activates the descending inhibitor pain pathway. In preclinical studies, Xen-2174 **68** was found to provide superior pain relief to morphine when administered IT to rats with neuropathic pain.[412]

ω-Conotoxin CVID (AM336) **69**, which was originally isolated from *C. catus*, has completed a Phase II clinical trial for the treatment of neuropathic pain.[413,414] Although AM336 **69** was reported to have a better therapeutic index than ziconotide **65**, development was halted by Amrad Corporation due to changes in the company's priorities.[415]

Finally, ACV1 (Vcl.1) **70**, an α-conotoxin with neuronal nicotinic acetylcholine receptor (nAChR) antagonist activity, was identified by screening uncharacterised conopeptide sequences from the venom duct of *C. victoriae* using PCR-RACE

(polymerase chain reaction-rapid amplification cDNA ends) to identify cDNA transcripts that encode specific antagonists of neuronal nAChRs.[416,417] ACV1 **70** is undergoing preclinical evaluation by the Australian company Metabolic Pharmaceuticals for neuropathic pain.[418]

H_2N-CKGKGAKCSRLMYDCCTGSCRSGKC-$CONH_2$

65

PSEEGGSNAT$_g$KKPYIIL

66

T_g = *O*-glycosylated threonine

GEγγLQγNQγLIRγKSN

67

γ = γ-carboxyglutamate

NGVCCGYKLCHOC

68

H_2N-CKSKGAKCSKLMYDCCSGSCSGTVGRC-$CONH_2$

69

GCCSDPRCNYDHPEIC

70

Phenserine **71**, which is a third generation derivative of physostigmine **51**, is an acetylcholinesterase (AChE) and beta amyloid precursor protein (β-APP) inhibitor being developed by Axonyx to treat mild to moderate Alzheimer's disease.[419–422] None of the AChE inhibitors presently on the market reduce the levels of β-APP and, as a consequence, phenserine **71** may represent an important new treatment for Alzheimer's disease if approved. Axonyx has concurrent Phase IIb and Phase III clinical trials in progress.[422]

Huperzine **52** is a potent AChE originally isolated from the club moss, *Huperzia serrata*,[423] which shows promise in the treatment of Alzheimer's disease.[331,332] A pro-drug of huperzine **52**, ZT-1 **72**, which was originally synthesised by Zhu and co-workers at the Shanghai Institute of Material Medica,[424,425] is being evaluated by Debiopharm in Phase II clinical trials for the treatment of Alzheimer's disease.[426]

51 R = CH_3

71 R =

52

72

CEP-1347 (KT-8138) **73**[427] is a semi-synthetic derivative of K-252a **74**, a NP related to staurosporine **75** originally isolated from *Nocardiopsis* sp. by Kyowa Hakko Kogyo in 1986.[428,429] CEP-1347 **73** is a potent inhibitor of members of the mixed lineage kinase (MLK) family.[430–434] The MLK kinases are key participants in the activation of c-Jun *N*-terminal kinase (JNK), a kinase which has been proposed to govern neuronal dysfunction and subsequent death. Studies have shown that CEP-1347 **73** enhances the survival of neurons that produce dopamine and Cephalon (US) and H. Lundbeck A/S (Denmark) are evaluating **73** in Phase II and III clinical trials to determine its efficacy in delaying disability caused by the progression of Parkinson's disease.[435,436] If CEP-1347 **73** is found to be effective against the onset of Parkinson's disease, it will revolutionise treatment because existing drugs only offer symptomatic relief.

73 R =

74 R = H

75

The UK company Hunter-Fleming are evaluating HF-0220 (7β-OH-epiandrosterone, 7β-OH-EPIA) **76** in Phase I clinical trials for chronic and acute neurodegenerative diseases.[437] Dehydroepiandrosterone (DHEA) **77** is produced in the brain and is hydroxylated into 7α and β derivatives by a cytochrome P450 enzyme (cyp7b) that is expressed at high levels in the brain.[438–440] Although the role of these 7-hydroxylated steroids is unknown, the 7β **76** and 7α **78** derivatives of EPIA have been found to significantly reduce neurotoxicity at 10 and 100 nM respectively, while DHEA **75**, EPIA **79** and oestradiol **80**, were inactive at 100 nM during and post hypoxia.[440] In addition to neuroprotection, 7β-OH-EPIA **76** has shown promise in *in vitro* preclinical studies for ischemic stroke and cardioprotection models.[437] Interestingly, MitoKor (now MIGENIX) has completed a Phase I study of 17α-oestradiol (MX-4509, MITO-4509) **80** for the treatment of Alzheimer's disease.[339,441]

76 R = OH

78 R = OH

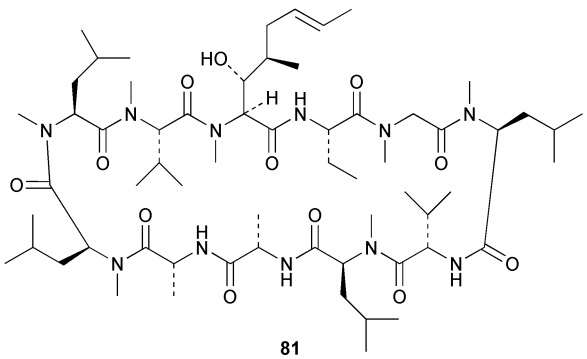
79 R = H

77

80

The Swedish based company Maas BiolAB has demonstrated that the immunosuppressant cyclosporine A **81** has potent neuroprotective properties in stroke, trauma and neurodegeneration by prevention or reduction of neuron cell death by the inhibition of critical enzymes and free radicals and protecting the mitochondria.[442–444] Preclinical studies showed that cyclosporine A **81** is the most powerful known neuroprotectant in stroke and traumatic brain injury and Maas BiolAB is evaluating **81** in Phase IIa clinical trials for stroke and brain injury.[442] Cyclosporine A **81** also shows promise in the treatment of Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS).[442]

Lobeline **82** is a piperidine alkaloid isolated from the North American native plant *Lobelia inflata* (Campanulaceae), which has been used for centuries as an emetic and respiratory stimulant and more recently as a tobacco smoking cessation agent.[445,446] Yaupon Therapeutics and NIH are evaluating lobeline **82** in Phase I clinical trial as a pharmacological treatment for methamphetamine addiction and preclinical studies have suggested that **82** also has utility in helping to treat attention deficit hyperactivity disorder (ADHD).[447]



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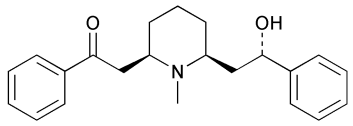


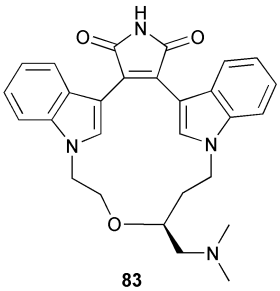
82

New River Pharmaceuticals began Phase I clinical evaluation of NRP104, a prodrug of amphetamine, for the treatment of ADHD soon after an Investigational New Drug (IND) application was filed with the FDA in March 2004.[448] In August 2004, New River announced that NRP104 had been fast tracked by the FDA for treatment of cocaine dependence, which is a second indication for NRP104.[448]

5 Cardiovascular and metabolic disease area

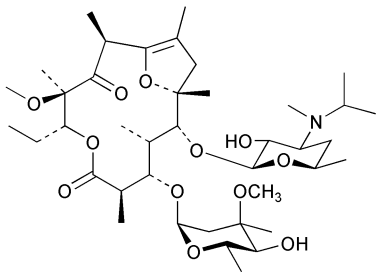
NPs have made a major impact in the treatment of cardiovascular and metabolic diseases. The lipid lowering statin drugs are based on the lead compound mevastatin (also named ML-236B and compactin), which was first isolated from *Penicillium citrinum* by Endo and co-workers at Sankyo using a 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase bioassay.[449–452] The statins are the standard treatment for lipidaemia and generate billions of dollars of yearly drug sales. Other recent NP derived drugs include the lipase inhibitor orlistat, a tetrahydro derivative of the *Streptomyces* metabolite lipstatin,[453–455] which is used to help inhibit the absorption of fats, the α-glucosidase inhibitors acarbose, miglitol and voglibose used to help control type 2 diabetes mellitus[328,456] and angiotensin converting enzyme (ACE) inhibitors like Capropril® and Enalapril® derived from teprotide, a peptide that was originally isolated from the venom of the pit viper, *Bothrops jararaca*.[3,457,458]

Ruboxistaurin (LY333531) **83**, which is synthetic analogue of staurosporine **75**, is a competitive inhibitor of adenosine triphosphate (ATP) binding to protein kinase C β isozyme developed by Eli Lilly for the treatment of microvascular complications in patients with diabetes mellitus.[459–462] The mesylate salt of ruboxistaurin **83** is being evaluated in Phase III clinical trials for diabetic retinopathy and diabetic macular oedema and is undergoing Phase II trials for diabetic peripheral neuropathy.[463,464]



83

Motilin is a 22 amino acid peptide that triggers phase III migration of the myoelectric complex in the stomach.[200,465] In addition to their antibacterial activity, macrolides like erythromycin **19** also display potent motilin agonist activity that increases the amplitude and frequency of antral contractions and initiates gastric contractions. The motilin binding site has been identified as a guanine nucleotide-binding protein (G protein)-coupled receptor. Two types of motilin inhibitors, erythromycin **19** derivatives and motilin peptide mimics,[465] have been evaluated but only Chugai Pharmaceuticals' semi-synthetic erythromycin **19** derivative mitemcinal fumarate (GM-611) **84** is in active development.[466–469] Mitemcinal fumarate **84** is in Phase II clinical trials for the treatment of diabetic reflux oesophagitis and idiopathic gastroparesis.[469] In a recent development, Kosan Biosciences announced that they are evaluating several potent, non-antibiotic motilin agonists in preclinical studies.[470]



84

Exenatide-4 **85** is a 39 amino acid peptide originally isolated from the oral secretions of the Gila monster (*Heloderma suspectum*), a poisonous lizard found in the south-western US and northern Mexico.[471] Exenatide-4 **85** has a structure similar to that of the glucagon-like peptide-1 (GLP-1) **86**,[471] a human hormone which helps the pancreas to regulate glucose induced insulin secretion when blood glucose levels are elevated.[472–474] As a consequence, compounds which mimic GLP-1 **86** have the potential to significantly improve glycaemia control in patients with diabetes.[472–474] A synthetic version of **85** (named exenatide) is being developed jointly by Amylin Pharmaceuticals and Eli Lilly to improve the glucose control in patients with type 2 diabetes who are not using insulin and are not achieving target levels with diet and oral medications.[475] A NDA for exenatide **85** was submitted to the FDA on 29 June 2004 and has been accepted for evaluation.[475]

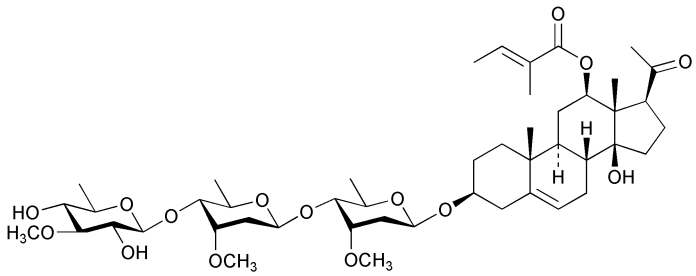
85 HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS

86 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

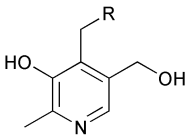
In 1996, the South African Council for Scientific and Industrial Research (CSIR) patented the hunger-suppressing steroidal glycoside P57A3 **87** and related compounds that were isolated from the cactus, *Hoodia gordonii*.[476–478] In 1997, CSIR licensed this discovery to the UK based company Phytopharm, who named the project P57 and, in turn, licensed it to Pfizer in 1998.[479] The licensing of P57 by CSIR to Phytopharm without an agreement with the San indigenous people, who traditionally used the cactus for appetite suppression, caused considerable controversy but a benefit sharing agreement was signed later by CSIR and the South African San Council.[480–482] In July 2003, Pfizer discontinued development of P57 and returned the rights to Phytopharm who, in December 2004, licensed P57 to Unilever for development as an herbal product.[483]

BioStratum is investigating the vitamin B6 (pyridoxol) **88** derivative, pyridoxamine dihydrochloride (Pyridorin™) **89**, for diabetic kidney disease and FDA fast track status was granted in July 2002.[484] In preclinical studies, pyridoxamine **89** prevented hyperglycaemia-induced damage to proteins and tissues and dramatically retarded the progression of kidney disease in animal models of diabetes. No serious adverse events were observed in Phase I studies and Phase II trials are underway for diabetic kidney disease.[484]

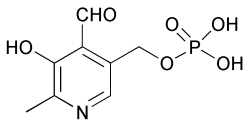
MC-1 **90** is a naturally occurring vitamin B6 derivative[485] with P2X receptor antagonist activity that is under development by



87



88 R=OH
89 R=NH_2



90

Medicure for the treatment of acute coronary syndromes.[486] It is also being evaluated as an adjunct to cardiovascular intervention such as angioplasty and coronary bypass graft surgery (CABG). MC-1 **90** is being evaluated in a Phase II/III clinical trial for its cardioprotective and neuroprotective effects in patients undergoing high-risk CABG surgery.[486,487] MC-1 **90** in combination with an angiotensin blocker (combination coded MC-4232), is also being evaluated in a Phase II trial.[486]

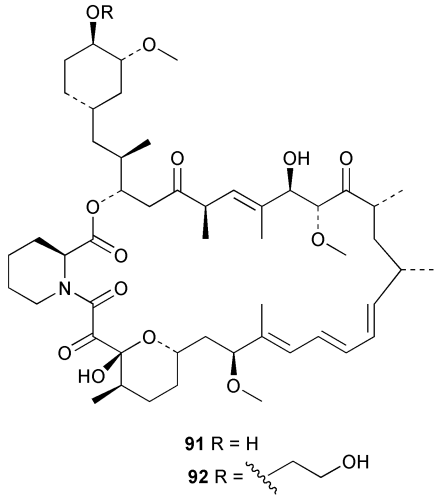
6 Immunological, inflammatory and related disease areas

The discovery that the weak antifungal cyclosporine A **81** was an immunosuppressant revolutionised organ transplantation and since then, NPs have played a pivotal role in the development of most immunosuppressive drugs (Table 2).[488–492] Aspirin (acetylsalicylic acid) is one of the most famous NP-derived drugs that was discovered in the late 1890s and is still used widely as an analgesic and anti-inflammatory.[496] The discovery of the anti-inflammatory mechanism of action of aspirin led to the discovery of the cyclooxygenase isozymes COX-1 and -2,[497,498] which were used in the discovery of novel anti-inflammatory drugs.[499] Other important anti-inflammatory drugs used in controlling asthma are the corticosteroids and salbutamol and salmeterol, beta 2 agonists modelled on adrenaline.[499,500]

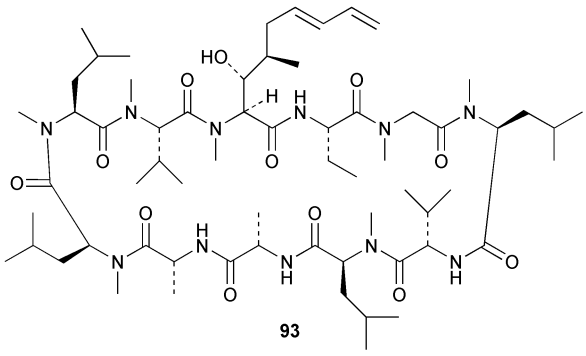
ISA-247 **93** is a semi-synthetic derivative of cyclosporine A **81** that the Canadian company Isotechnika is evaluating in Phase II clinical trials for kidney transplantation and Phase III clinical trials for psoriasis.[501–503] ISA-247 **93** was evaluated originally as a mixture of double bond isomers and like cyclosporine **81**, exerts its biological activity through inhibition of calcineurin.[501,502] The *trans* isomer of ISA-247 **93**, which is now used for all clinical studies, was found to be 1.5 and 5 times more potent than the isomeric mixture and cyclosporine A **81** respectively.[501,502]

Isotechnika have also started Phase I clinical studies on a sirolimus **91** pro-drug, TAFA-93 (structure not available), for the prevention of transplant rejection.[504] Other sirolimus **91** derivatives are in clinical evaluation as anti-cancer agents (Section 7).

FTY720 **94** is a new immunosuppressant which is being evaluated by Novartis in Phase III clinical trials for use in transplantation, autoimmune diseases and multiple sclerosis.[505] Workers at Yoshitomi Pharma (later Mitsubishi Pharma) synthesized FTY720 **94**[506,507] based upon the lead compound myriocin **95**,[508] which originally was isolated from the fungi *Mycelia sterilia* and *Myriococcum albomyces* and later identified as an



91 R = H
92 R =



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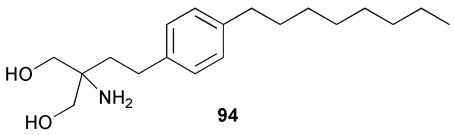

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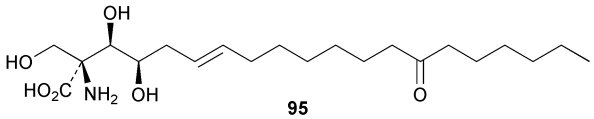

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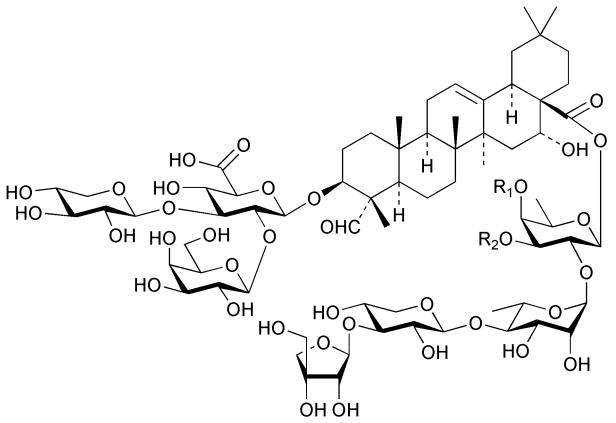
Table 2 Natural product derived immunosuppressant drugs[488–492]

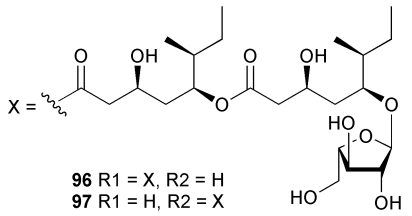
Drug	Year launched	Comment
cyclosporine A **81**	1983	fungal metabolite
mizoribine	1984	fungal metabolite
tacrolimus (FK-506)	1993	actinomycetes metabolite
gusperimus	1994	based on bacterial metabolite spergualin
mycophenolate mofetil	1995	semi-synthetic derivative of mycophenolic acid
sirolimus **91**	1999	actinomycetes metabolite
mycophenolate sodium	2003	fungal metabolite
everolimus **92**[493–495]	2004	semi-synthetic derivative of sirolimus

immunosuppressant from the fungus *Isaria sinclairii*.[509] FTY720 **94** exerts its immunosuppressive activity after phosphorylation *in vivo* by sphingosine kinase to yield an active metabolite, which is an agonist of sphingosine-1-phosphate (S1P) receptors 1, 3, 4 and 5.[510–514] Novartis expect to file a NDA for transplantation in 2005 and multiple sclerosis in 2006. Mitsubishi Pharma retained the Japanese rights for FTY720 **94** and are investigating its potential in Phase II clinical trials for renal transplantation.[515]

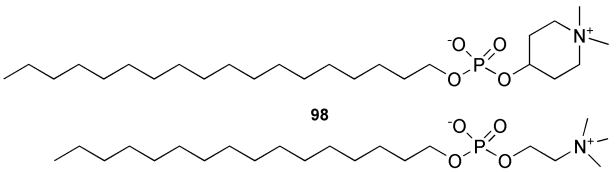
Saponins derived from the South American tree, *Quillaja saponaria* (Rosaceae), have shown great promise as investigational adjuvants,[516–528] substances added to vaccines and other immunotherapies designed to enhance the body's immune response to the antigen contained within the treatment. One of the most well studied adjuvants is Antigenics' QS-21, which is a mixture of 2 saponins, QS-21A **96** and QS-21B **97**,[518,519] isolated by C18 reverse-phase HPLC from *Q. saponaria*.[522–524] QS-21 is integral part of experimental vaccines being examined in Phase II and III trials for melanoma, malaria and HIV and other infectious diseases. The lead product of Galenica Pharmaceuticals, GPI-0100 (SaponImmune™), is a semi-synthetic derivative of a *Q. saponaria* saponin that is also used as an adjuvant in various vaccines.[525–528]

Ancrod (Viprinex™) is a thrombin-like peptide being developed by Neurobiological Technologies that was isolated from the venom of the Malayan pit viper, *Calloselasma rhodostoma* (*Agkistrodon rhodostoma*), which binds with high specificity to fibrinogen, a protein involved in blood clotting.[529,530] Ancrod has been shown to rapidly deplete plasma fibrinogen when administered systemically to stroke patients and its effects include anticoagulation, improved blood viscosity and a secondary fibrinolytic or clot lysing action.[529,531,532] When these effects are combined oxygen flow to the affected area of the brain appears to be restored and enhanced.[529,531,532] Ancrod has completed a positive Phase II programme and a statistically significant Phase III trial in the US, but failed a Phase III trial in Europe.[529]





96 R1 = X, R2 = H
97 R1 = H, R2 = X



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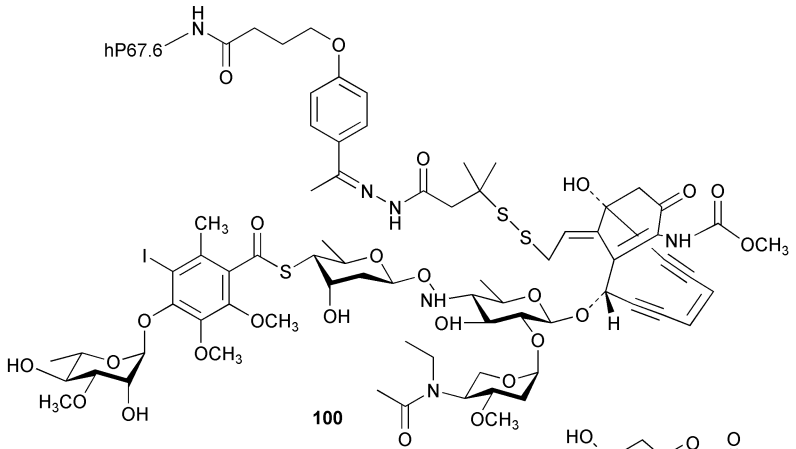

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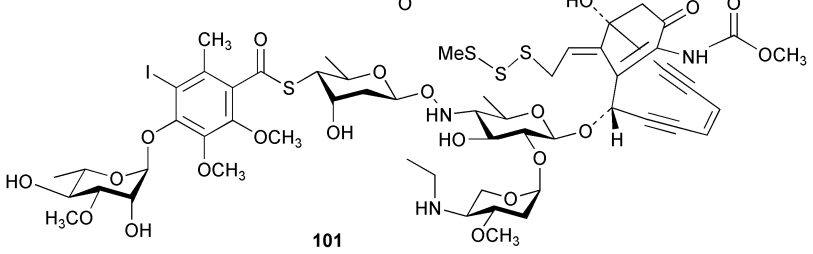

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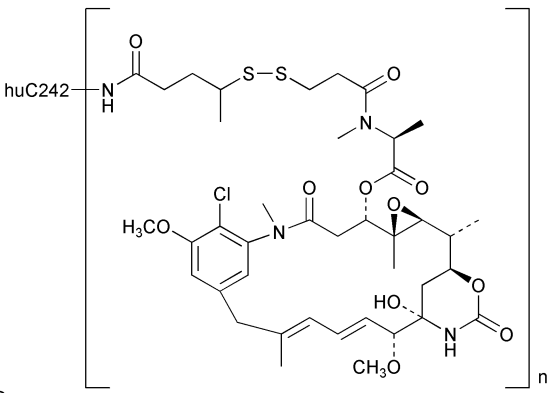
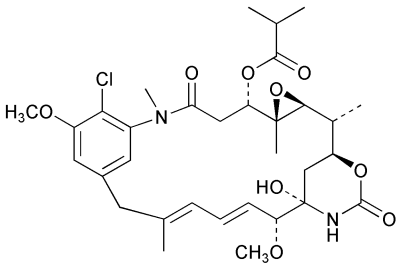


102 n = 3 to 4



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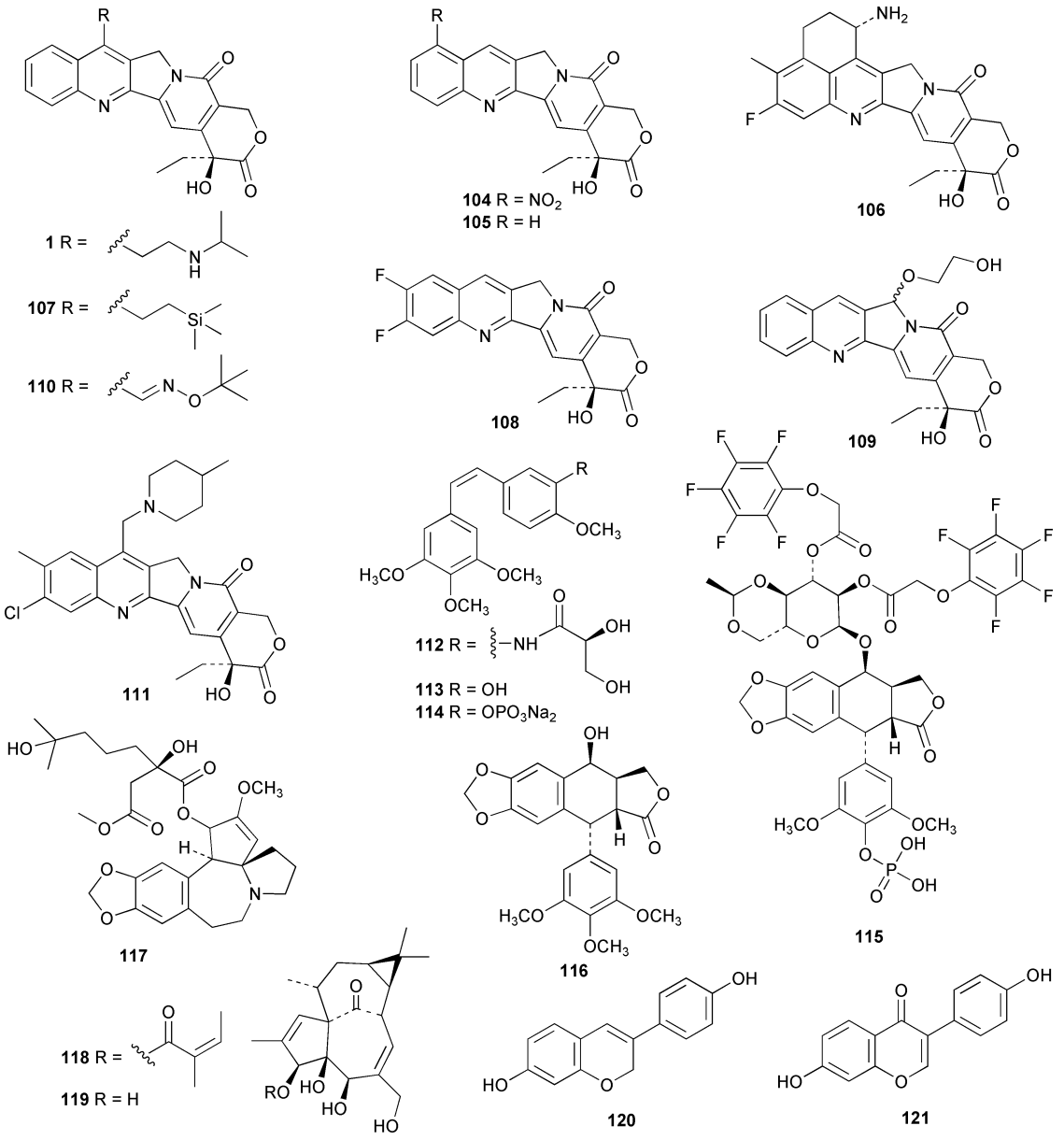


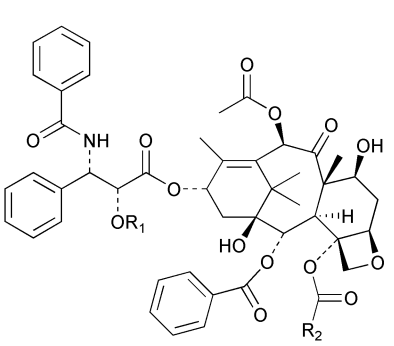
Ancrod will undergo additional Phase III testing in the future with single-administration dosing.[529]

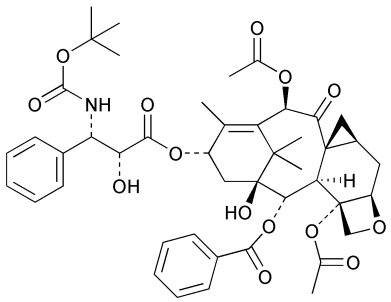
7 Oncological disease area

NPs and NP-derived compounds in clinical development for oncology have been reviewed extensively in the last few years.[533–543] As a consequence, compounds in clinical trials have been tabulated according to their lead compound source: plant (Table 3), microorganism (Table 4) and marine (Table 5).

Although not falling inside the definition of "NP" in this review (Section 1), the alkylphosphocholine derivative perifosine **98** and antibody-anticancer agent conjugates are discussed below. Perifosine (KRX-0401) **98** is a synthetic derivative of alkylphosphocholine[544–547] and is related to miltefosine **99**, a drug used as a topical treatment of cutaneous breast cancer (Miltex®) and as an oral treatment for leishmaniasis (Impavido®).[548–552] Perifosine **98** is an oral AKT kinase inhibitor[553–556] and its activity against a variety of cancers is being evaluated in Phase II trials by Keryx Biopharmaceuticals (North America) and Æterna Zentaris (Europe).[557,558] No other AKT inhibitors are presently in clinical development or marketed.

The launch in 2000 of the first antibody–anticancer agent conjugate,[559–561] gemtuzumab ozogamicin (Mylotarg®) **100**, a recombinant humanized IgG4 kappa antibody and calicheamicin **101** conjugate co-developed by Wyeth and Celltech (now UCB Pharma), was an important breakthrough in the treatment of cancer.[562–564] Wyeth and UCB Pharma are evaluating a related conjugate CMC-544, which has calicheamicin **101** linked to the antibody anti-CD22 Ab, in Phase I clinical trials for non-Hodgkin's lymphoma.[565–567] Cantuzumab mertansine (huC242-DM1) **102** is a conjugate of the huC242 antibody and DM1, a semi-synthetic derivative of ansamitocin P-3 **103**, developed by ImmunoGen for the treatment of CanAg-expressing cancers, which include most colorectal, pancreatic, gastric and other abdominal cancers as well as many non-small-cell lung cancers.[568–570] Cantuzumab mertansine **102** was licensed to SmithKline Beecham in 1999, but ImmunoGen regained the rights in 2003 and plan to initiate Phase II proof of concept testing during the first half of 2005.[570] ImmunoGen have another DM1 antibody conjugate huN901-DM1 in Phase I development for the treatment of cancers that express CD56, which include small-cell lung cancer, certain haematologic malignancies and cancers of neuroendocrine origin.[570] Using technology from ImmunoGen, Millennium have developed





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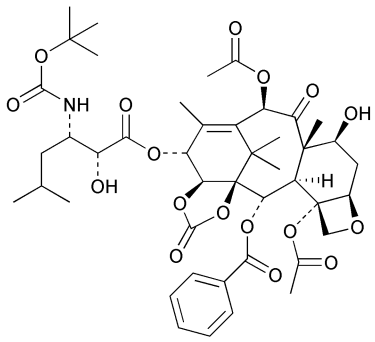
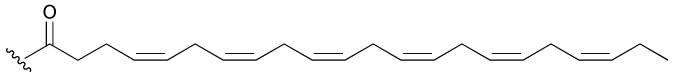


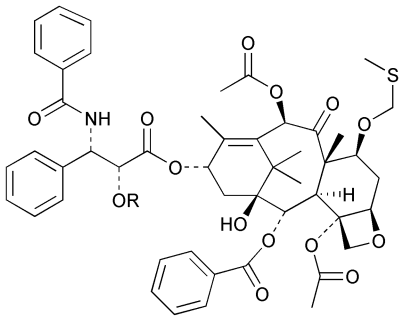
125

122 $R_1 = CH_3$, R_2 =



123 $R_1 = CH_3$, $R_2 = H$

127 $R_1 = OCH_3$, $R_2 = H$



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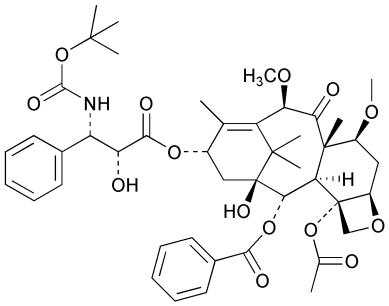

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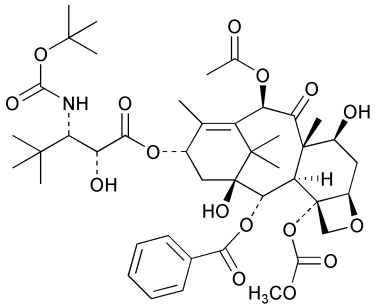

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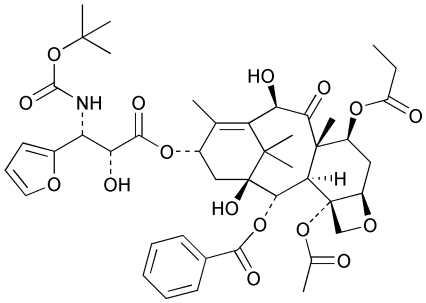

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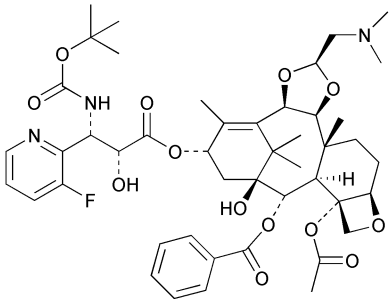

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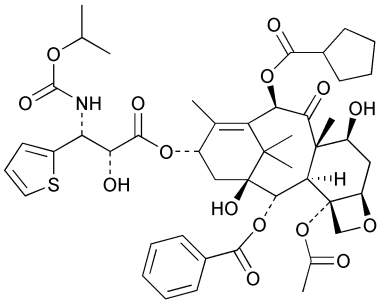

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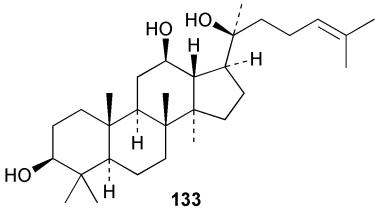

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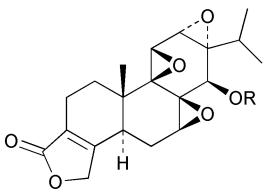
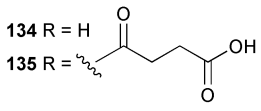
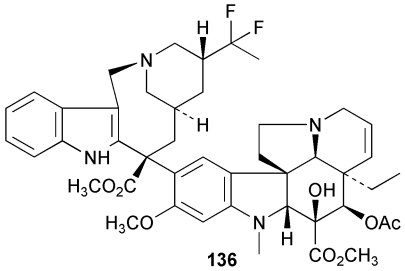


134 R = H

135 R =





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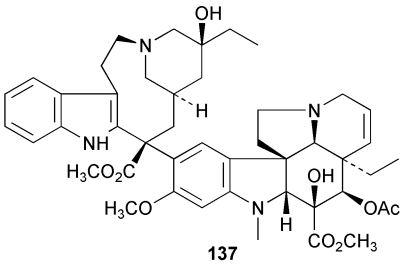

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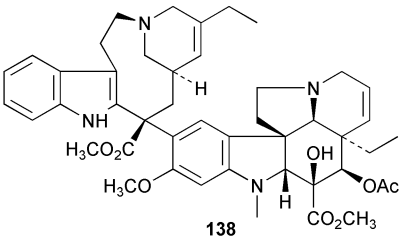

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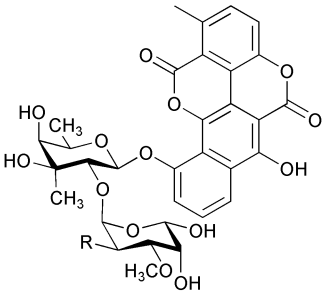
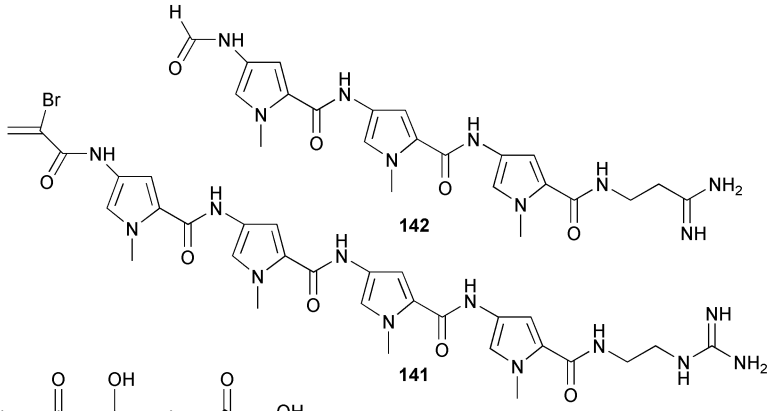


139 R = NH_2
140 R = OH



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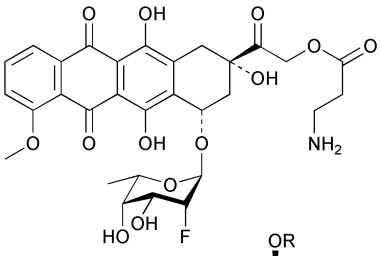

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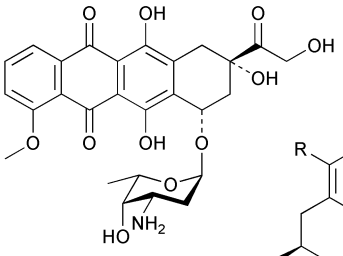

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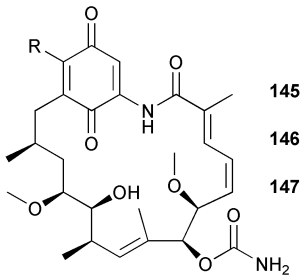
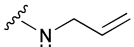
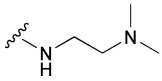
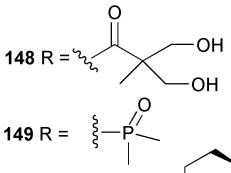
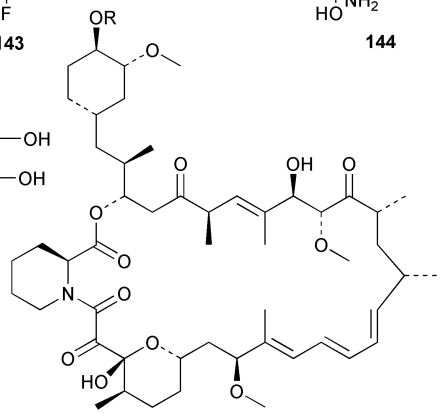
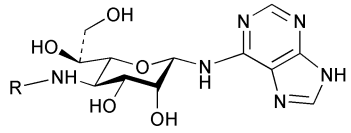


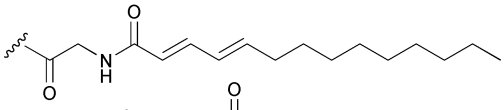
145 R = 
146 R = OCH_3
147 R = 

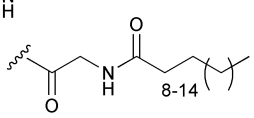


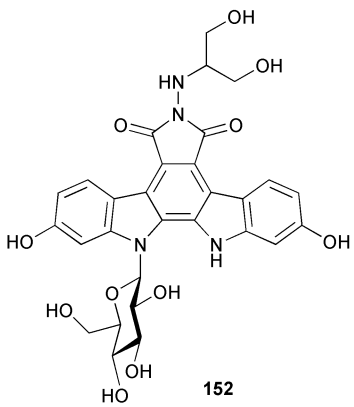
148 R =
149 R =





150 R = 

151 R = 
8-14



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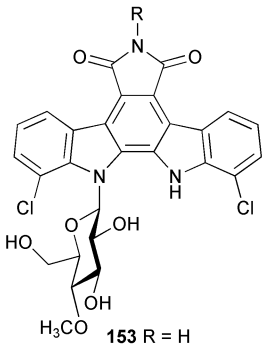
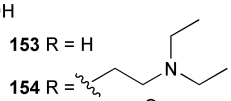
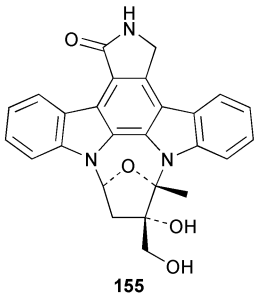


153 R = H
154 R = 



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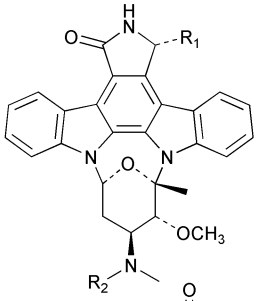
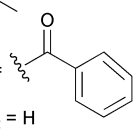
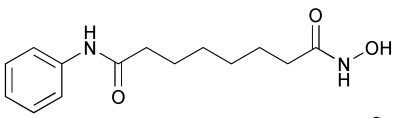


156 R_1 = H, R_2 = 
157 R_1 = OH, R_2 = H



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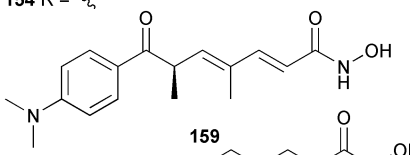

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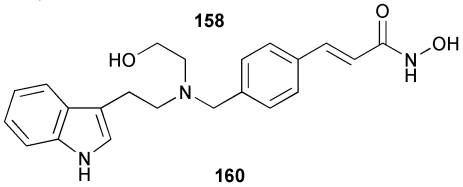

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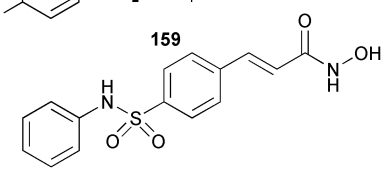

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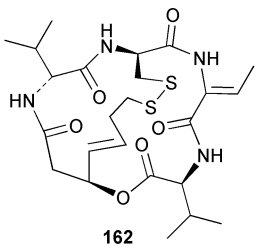

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Table 3 Plant derived compounds in oncology clinical trials

Name (synonym)	Lead compound	Mechanism of action	Development status	Developer	References
belotecan (Camptobell, CDK-602) **1**	camptothecin **104**[577–583]	topoisomerase I	launched in Korea 2004	Chung Kun Dong	584–587
rubitecan (Orathecin™, 9-NC) **105**	camptothecin	topoisomerase I	pre-registration	SuperGen	588–592
exatecan (DX-8951f) **106**	camptothecin	topoisomerase I	phase III	Daiichi	593–596
Karenitecin® (BNP-1350) **107**	camptothecin	topoisomerase I	phase I/II	BioNumerik	597–601
diflomotecan (BN-80915) **108**	camptothecin	topoisomerase I	phase II	Ipsen	602–605
DRF-1042 **109**	camptothecin	topoisomerase I	phase II	Dr Reddy	606,607
gimatecan (ST-1481) **110**	camptothecin	topoisomerase I	phase II	Novartis/Sigma-Tau	608–612
BN-80927 (R-1559) **111**	camptothecin	topoisomerase I	phase I	Ipsen/Roche	605,613
AVE-8062 (AC-7700) **112**	combretastatin A-4 **113**	tubulin binding	phase II	Sanofi-Aventis	614,615
CA4P (combretastatin A-4 phosphate) **114**	combretastatin A-4	tubulin binding	phase I/II	OXiGENE	616–621
tafluposide **115**	epipodophyllotoxin **116**	topoisomerase I and II	phase I	Pierre Fabre	622
homoharringtonine (Ceflatonin®) **117**	homoharrington **117**	protein synthesis inhibition	phase II	ChemGenex	623–626
ingenyl 3-angelate (PEP005) **118**	ingenol **119**	protein kinase C activation	phase I	Peplin	627–631
phenoxodiol **120**	daidzein **121**	NADH oxidase (tNOX) inhibition	phase II	Marshall Edwards	632–635
DHA-paclitaxel (Taxoprexin®) **122**	paclitaxel **123**	tubulin stabilization	phase III	Luitpold	636–639
XRP-9881 (RPR-109881A) **124**	paclitaxel	tubulin stabilization	phase III	Sanofi-Aventis	640–642
ortataxel (IDN-5109, BAY-59-8862) **125**	paclitaxel	tubulin stabilization	phase II	Bayer/Indena	643–647
BMS-184476 **126**	paclitaxel	tubulin stabilization	phase II	Bristol-Myers Squibb	648–651
BMS-188797 **127**	paclitaxel	tubulin stabilization	phase II	Bristol-Myers Squibb	651,652
TXD-258 (XRP-6258, RPR-116258A) **128**	paclitaxel	tubulin stabilization	phase II	Sanofi-Aventis	653,654
BMS-275183 **129**	paclitaxel	tubulin stabilization	phase I	Bristol-Myers Squibb	655–657
MAC-321 (TL-00139) **130**	paclitaxel	tubulin stabilization	phase I/II	Wyeth/Taxolog	658,659
DJ-927 **131**	paclitaxel	tubulin stabilization	phase I	Daiichi	660,661
MST-997 (TL-909) **132**	paclitaxel	tubulin stabilization	phase I	Wyeth/Taxolog	659,662
protopanaxadiol (PBD-2131, Pandimex™) **133**	protopanaxadiol **133**	caspase 3, 8 and 9 stimulant	phase I	PanaGin	663–665
PG490-88Na **134**	triptolide **135**	T-cell proliferation suppression, IL-2 expression and NFκ-B activation	phase I	Pharmagenesis	666–672
vinflunine ditartrate (Javlor®) **136**	vinblastine **137**	tubulin binding	phase III	Pierre Fabre/Bristol-Myers Squibb	673–678
anhydrovinblastine (Hydravin™, KRX-0403) **138**	vinblastine	tubulin binding	phase II	Keryx	679–680

Table 4 Microorganism derived compounds in oncology clinical trials

Name (synonym)	Lead compound and source (compound class)	Mechanism of action[a]	Development status	Developer	References
	Actinomycete				
elsamitrucin (elsamicin A) **139**	elsamicin A (chartreusin **140**)	topoisomerase I and II inhibition	phase II	Spectrum	681–685
brostallicin (PNU-166196) **141**	distamycin A **142**	DNA minor groove binder	phase II	Pfizer	686–690
galarubicin (DA-125) **143**	doxorubicin **144**	topoisomerase II inhibition	phase II	Dong-A	691–694
17-AAG[b](KOS-953, NSC-330507) **145**	geldanamycin **146**	HSP90 inhibitor	phase II	Kosan/NIH	695–699
17-AAG[b] (CNF-1010)	geldanamycin	HSP90 inhibitor	phase I	Conforma	700
17-DMAG (NSC-707545) **147**	geldanamycin	HSP90 inhibitor	phase I	NIH	701–704
temsirolimus (CCI-779) **148**	sirolimus **91**	mTOR	phase III	Wyeth	563,705–710
RAD-001[c] (everolimus) **92**	sirolimus	mTOR	phase II	Novartis	711
AP-23573 **149**	sirolimus	mTOR	phase II	ARIAD	712,713
KRN-5500 (NSC 650426) **150**	spicamycin **151**	DNA synthesis inhibitor	phase I	Kirin Brewery/NCI	714–719
edotecarin (J-107088) **152**	rebeccamycin **153** (staurosporine **75**)	topoisomerase I	phase III	Pfizer/Banyu	720–723
becatecarin (XL-119, NSC 655649, BMY-27557) **154**	rebeccamycin (staurosporine)	topoisomerase II	phase III	Exelixis	724–728
CEP-701 (KT-5555) **155**	K252a **74** (staurosporine)	FLT3 inhibition	phase II	Cephalon	729–732
midostaurin (PKC-412, CGP 41251, 4′-*N*-benzoyl-staurosporine) **156**	staurosporine	FLT3 inhibition	phase II	Novartis	733–735
UCN-01 (KW-2401) **157**	UCN-01 **157** (staurosporine)	CDK1 inhibition	phase I/II	Kyowa Hakko	736–738
suberoylanilide hydroxamic acid (SAHA) **158**	trichostatin **159**	HDAC inhibition[734–738]	phase II	Merck	739–744
LAQ-824 **160**	trichostatin	HDAC inhibition	phase I	Novartis	745–749
PDX101 **161**	trichostatin	HDAC inhibition	phase I	CuraGen	750–752
	Bacteria				
depsipeptide (FR-901228, FK-228) **162**	depsipeptide **162**	HDAC inhibition	phase II	Gloucester	753–757
	Myxobacteria				
ixabepilone (BMS-247550) **163**	epothilone B **164**[758–764]	tubulin stabilization	phase III	Bristol-Myers Squibb	760–768
patupilone (epothilone B, EPO-906) **164**	epothilone B	tubulin stabilization	phase II	Novartis	769–772
epothilone D (KOS-862) **165**	epothilone D **165**	tubulin stabilization	phase II	Kosan Biosciences/ Roche	773–777
ABJ879 **166**	epothilone B	tubulin stabilization	phase I	Novartis	760,778
9,10-didehydroepothilone D (KOS-1584) **167**	epothilone D	tubulin stabilization	phase I	Kosan Biosciences/ Roche	779–781
BMS-310705 (21-aminoepothilone B) **168**	epothilone B	tubulin stabilization	phase I	Bristol-Myers Squibb	782–783
ZK-EPO[d]	epothilone	tubulin stabilization	phase I	Schering AG	784–786
	Fungi				
CKD-732 **169**	fumagillin **37**	MetAP2 inhibition	phase II	Chung Kun Dong	787–789
PPI-2458 **170**	fumagillin	MetAP2 inhibition	phase I	Praecis	790,791
irofulven (MGI-114, HMAF) **171**	illudin S **172**	DNA synthesis inhibition	phase II	MGI Pharma	792–798

[a] HSP90 = heat shock protein 90, mTOR = mammalian target of rapamycin (sirolimus) **91**, FLT3 is a class III tyrosine kinase, CDK = cyclin-dependent kinase, HDAC = histone deacetylase and MetAP2 = methionine aminopeptidase Type 2. [b] 17-AAG (17-allylaminogeldanamycin) **145** is being developed using 2 different formulations. [c] Everolimus **92**, which has been launched as an immunosuppressant (Certican™), is under investigation in oncology as RAD-001. [d] Structure not available.

Table 5 Marine derived compounds in oncology clinical trials

Name (synonym)	Lead compound and source	Mechanism of action	Development status	Developer	References
	Ascidian				
Aplidin® **173**	aplidin **173**	VEGF and VEGFR1 inhibitor, G1/G2 phase cell cycle inhibitor	phase II	PharmaMar	799–804
trabectedin (Yondelis™, ET-743) **174**	trabectedin **174**	transcription-coupled nucleotide excision repair (TC-NER) and p53-independent apoptosis	phase II	PharmaMar	799,800,805–809
	Sponge				
KRN-7000 (α-GalCer, α-galactosylceramide) **175**	agelasphin	immunostimulation through ligand activated Vα14 NKT	phase I/II	Kirin Brewery	810–813
discodermolide **176**	discodermolide **176**	tubulin stabilization	phase I	Novartis	814–824
E-7389 (NSC-707389) **177**	halichondrin B **178**	tubulin assembly inhibition	phase I	Eisai/NIH	825–833
HTI-286 (SPA-110) **179**	hemiasterlin **180**	tubulin assembly inhibition	phase I	Wyeth	834–840
	Others				
dolastatin-10 **181**	dolastatin 10[a] **181**	tubulin assembly inhibition	phase II	NIH	841–846
soblidotin (TZT-1027, auristatin PE) **182**	dolastatin 10[a]	tubulin assembly inhibition	phase II	Daiichi	847–852
synthadotin (ILX-651) **183**	dolastatin 15[a] **184**	tubulin assembly inhibition	phase II	Genzyme	853
kahalalide F **185**	kahalalide F[b] **185**	alters lysosomal membrane function	phase II	PharmaMar	854–858
squalamine lactate **186**	squalamine **186** (shark)	Na^+/H^+ exchanger isoform (NHE-5) inhibition	phase II	Genaera	859–868
spisulosine (ES-285) **187**	spisulosine **187** (clam)	GTP-binding protein Rho	phase I	PharmaMar	869–873

[a] Although first isolated from a sea hare, the dolastatins originate from cyanobacteria. [b] Although first isolated from a mollusc, kahalalide F **185** originates from green algae. [c] Squalamine **186** is also in phase II clinical trials for age-related macular degeneration (AMD) and is present in a standardised shark cartilage extract of <500 Da called Neovastat® (AE-941),[874,875] which is in phase III trials for treatment of non-small cell lung cancer (Æterna Zentaris).

Table 6 Lead compound templates discovered since 1990 with compounds in clinical trials

Year	Lead compound template	Compounds in clinical trial	Therapeutic area
1990	discodermolide[a]	**176**	oncology
1991	GE-2770[a]	VIC-ACNE	antibacterial
1992	calanolide[b]	**43**	antiviral
1993	squalamine[a]	**186**	oncology
1994	depsipeptide[a]	**162**	oncology
1994	hemiasterlin[a]	**179**	oncology
1994	betulinic acid[c]	**41**	antiviral
1994	myriocin[d]	**94**	immuno-supression
1995	epothilone[a]	**163–168**	oncology
1996	P57[a]	**87**	appetite suppression

[a] Novel templates. [b] Calanolide B has the same structure as costatolide (isolated 1964)[886] but no antiviral activity was reported. [c] Antiviral activity of betulinic acid **42** first reported in 1994. [d] Immunosuppressive activity of myriocin **95** first reported in 1994.

MLN2704, a conjugate of DM1 and the antibody T-MAV, which is in Phase I/II trials for the treatment of metastatic androgen-independent prostate cancer and has been granted fast track status by the FDA.[570,571] Seattle Genetics is evaluating SGN-15 (BMS-182248, BR96-DOX), a conjugate of the antibody BR96 and doxorubicin **144**, in combination with docetaxel (Taxotere®) in a phase II clinical trial for the treatment of non-small cell lung cancer.[572,573] Seattle Genetics also has 2 auristatin (synthetic dolastatins) antibody conjugates, SGN-35 and SGN-75, in preclinical development.[572,574–576]

8 New natural product templates

Many NPs have been shown to occupy different and sometimes difficult to access chemical space compared to synthetic compounds.[876,877] The uniqueness of many NP core structures (or templates) makes these compounds of interest for use as starting points for semi-synthesis and total synthesis.[878–881] The Pharmaceutical Research and Manufacturers of America (PhRMA) has calculated that the average time in the 1980s and 1990s from lead discovery to market in the US was 14.2 years and, although the length of preclinical studies has shortened in some cases, the average length of clinical trial studies has not changed.[882–885] Since 1990, which is approximately 1 drug discovery cycle, there have been 10 new NP templates discovered that have compounds in clinical investigation or registration (Table 6). Not surprisingly, the oncology (5) and anti-infective (3) therapeutic areas have provided 8 of the 10 NP templates, while the other 2 are in immunosuppression and appetite suppression. It is interesting to note that no new templates/novel structures have been discovered since 1996 that have resulted in compounds entering clinical trials. As a consequence, most NP and NP-derived drugs currently in clinical trials are derived from relatively old templates. Also, only GE-2770 **18** and depsipeptide **162** were discovered by companies, while the remaining 8 were discovered by universities and public research organisations. The small number of new NP templates discovered over the last 10 years coincides with a significant reduction in the screening of NPs by the pharmaceutical industry. This may be a coincidence, a sign that novel lead compounds are becoming increasing difficult to discover or a combination of both.

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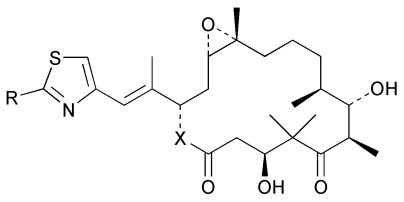
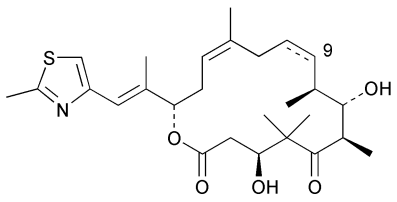
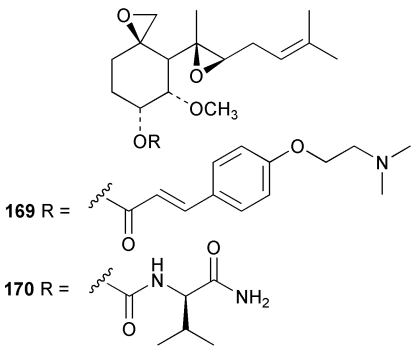


163 X = NH R = CH_3
164 X = O R = CH_3
166 X = O R = SCH_3
168 X = O R = CH_2NH_2

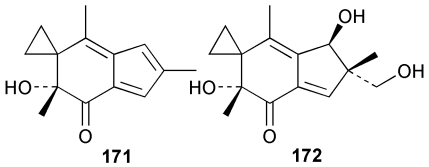


165
167 $\Delta^{9,10}$

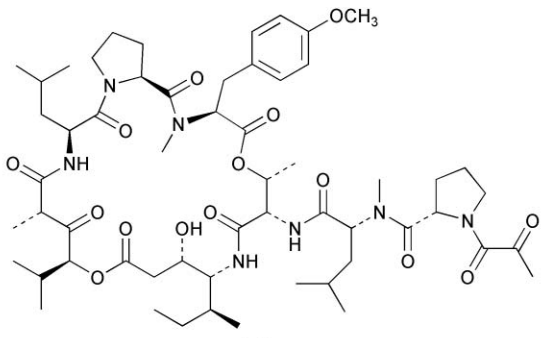


169 R =

170 R =



171 **172**



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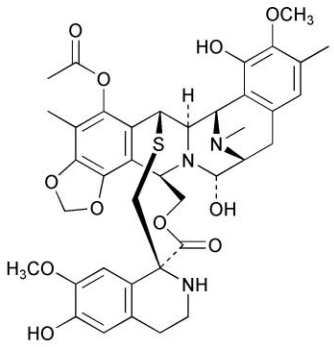

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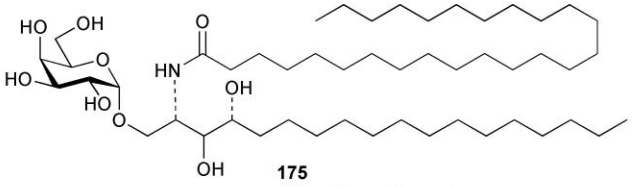

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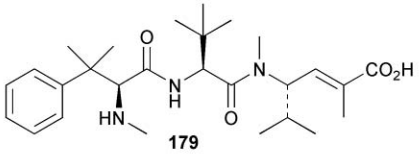

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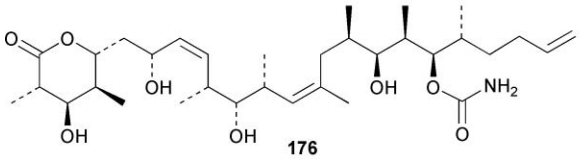

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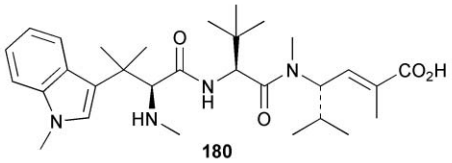

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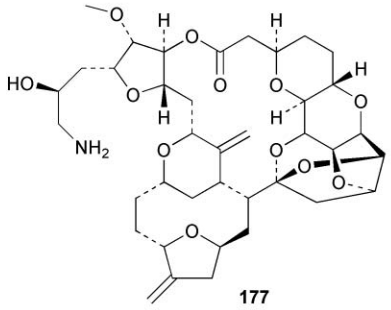

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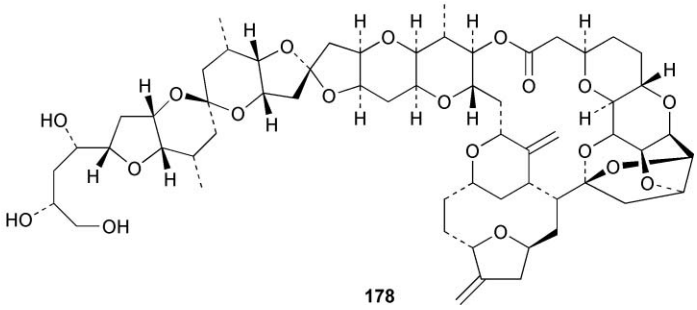

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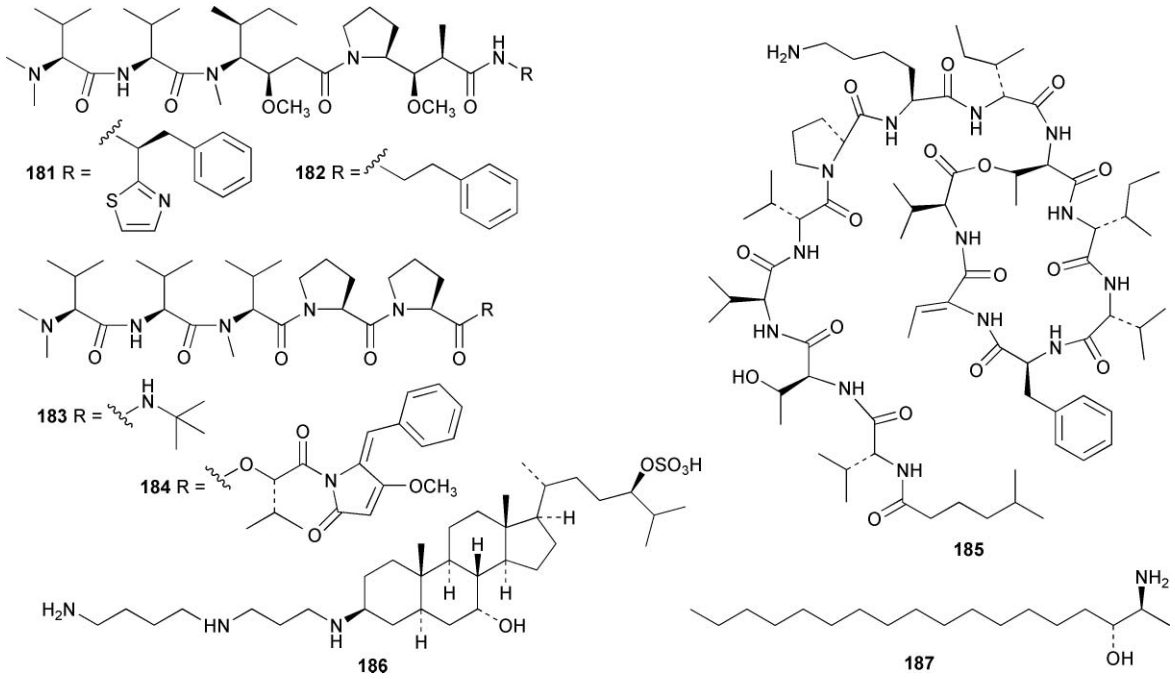

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