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Natural product and natural product derived drugs in clinical trials

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There are a significant number of natural product (NP) drugs in development. We review the 100 NP and NP-derived compounds and 33 Antibody Drug Conjugates (ADCs) with a NP-derived cytotoxic component being evaluated in clinical trials or in registration at the end of 2013. 38 of these compounds and 33 ADCs are being investigated as potential oncology treatments, 26 as anti-infectives, 19 for the treatment of cardiovascular and metabolic diseases, 11 for inflammatory and related diseases and 6 for neurology. There was a spread of the NP and NP-derived compounds through the different development phases (17 in phase I, 52 in phase II, 23 in phase III and 8 NDA and/or MAA filed), while there were 23 ADCs in phase I and 10 in phase II. 50 of these 100 compounds were either NPs or semi-synthetic (SS) NPs, which indicated the original NP still plays an important role. NP and NP-derived compounds for which clinical trials have been halted or discontinued since 2008 are listed in the Supplementary Information. The 25 NP and NP-derived drugs launched since 2008 are also reviewed, and late stage development candidates and new NP drug pharmacophores analysed. The short term prospect for new NP and NP-derived drug approvals is bright, with 31 compounds in phase III or in registration, which should ensure a steady stream of approvals for at least the next five years. However, there could be future issues for new drug types as only five new drug pharmacophores discovered in the last 15 years are currently being evaluated in clinical trials. The next few years will be critical for NP-driven lead discovery, and a concerted effort is required to identify new biologically active pharmacophores and to progress these and existing compounds through pre-clinical drug development into clinical trials.

1 Introduction

The last 5-10 years have seen massive changes in the pharmaceutical industry with a narrowing of therapeutic focus, continued mergers, a large number of redundancies and a massive increase in outsourcing. However, the number of new small molecule drug approvals has remained relatively constant at around 20-30 per year despite increased expenditure.[1-3] Identifying novel lead compounds is a difficult task with companies now predominantly relying upon the use of high throughput screening and fragment-based discovery. Natural product (NP) screening is rarely used for lead identification, which is somewhat counterintuitive as natural products have traditionally played an important role in drug development[4-8] with a considerable number of marketed drugs being derived from naturally occurring compounds.[9-12] In addition, NPs often also occupy chemical space not usually found in synthetically based corporate screening libraries[13-15] and can be excellent leads for drug development despite sometimes having complex structures and limited oral bioavailability.[16,17]

This review describes NPs, semi-synthetic (SS) NPs and NP-derived compounds that are undergoing clinical evaluation or registration by disease area at the end of December 2013 and follows a similar format to the previous reviews in this series.[10-12] The structures in the Figures of the NPs are blue in colour, while the NP-derived compounds are in black. NP-derived drugs launched since 2008 are discussed in Section 2, while

compounds currently undergoing clinical evaluation are listed by the following disease areas: Infectious Disease (Section 3), Neurological Disease (Section 4), Cardiovascular and Metabolic Disease (Section 5), Immunological, Inflammatory and Related Diseases (Section 6), and Oncology (Section 7.1). Antibody drug conjugates (ADCs) with NP-derived cytotoxic components are listed in Section 7.2. In this review the route of administration and original lead NP structures have been detailed. Clinical candidates with new drug pharmacophores are discussed in Section 8, while late stage development compounds are summarised in Section 9. NP-derived compounds that have been halted or discontinued from clinical development since 2008 are listed in the Supplementary Information Tables S2 to S7.

The compounds classifications, NPs, SS NPs or NP-derived, are defined in the same way as previous reviews in this series.[10-12] NPs are naturally occurring metabolites that are still classified as NPs even if they are produced synthetically for clinical studies or for the market. SS NPs are compounds that were derived from a NP template using semi-synthesis, while NP-derived compounds are synthetically derived or in some cases inspired from a NP template. These definitions are simpler compared to those used in Newman, Cragg and Snader's 1997 review[18] and updates.[9,19,20] No compound number has been assigned if there is no publicly disclosed structure. Although compounds derived from primary metabolites (*e.g.* steroids, nucleosides, prostaglandins, sialic acid and tyrosine), vitamins (e.g. vitamin D and retinoids),[21-26] hormones and protein fragments, herbal mixtures, polyamines, porphyrin derivatives and new uses of existing drugs have not been listed exhaustively, launched drugs since 2008 that fall into these categories are listed at the end of Section 2. PEGylated compounds in clinical trials[27] have not been included except for naloxegol **1** (Section 6).

In order to get a full understanding of the drug development process, the associated terms need to be understood and a brief description used during the drug approval process are as follows:[11] an Investigational New Drug Application (IND) (or equivalent elsewhere in the world) must be made to the United States of America (US) Food and Drug Administration (FDA), European Medicines Agency (EMA) or equivalent agency before clinical trials can commence. Once clinical trials have been completed successfully, the applicant files a New Drug Application (NDA) or a Biologics License Application (BLA) with the FDA or a Marketing Authorisation Application (MAA) with the EMA to seek the drug's approval for marketing in the US and Europe respectively. New drugs approved from an NDA are New Chemical Entities (NCEs) and from a BLA are New Biological Entities (NBEs). NCEs are regarded as small molecules, while NBEs are biological products such as proteins, antibodies, viruses and vaccines. NPs are playing a major role as the "warheads" for antibody drug conjugates (ADCs) and have featured as key components in two recent ADC NBEs (Section 2 and 7.2).

Although this review was based on a thorough evaluation of publicly available data, there are bound to be some NP-derived compounds that have been overlooked. In addition, the status of compounds undergoing clinical investigation and the companies involved can change rapidly and readers are encouraged to consult the recent literature, company web pages and clinical trial registers (*e.g.* US National Institutes of Health's (NIH) http://www.clinicaltrials.gov/, EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ and JAPIC Clinical Trials Information http://www.clinicaltrials.jp/) for the latest information.

2 NP-Derived Drugs Approved from 2008 to 2013

2.1 NP-derived drugs

A total of 25 NP and NP-derived drugs were approved for marketing (Table 1) from January 2008 to December 2013 with 5 being classified as NPs, 10 as SS NPs, and 10 as NP-derived drugs, which include 2 NP-containing ADCs.[28-40] Previous reviews in this series have detailed NP-derived drugs launched from 1998 to 2004[10] and 2005 to 2007.[11] Of these 25 new drug launches, there are 12 new human drug classes: romidepsin **14**, fingolimod **20** (lead: myricocin **21**), eribulin **23** (halichondrin B **24**), mifamurtide **25** (muramyl dipeptide **26**), fidaxomicin **29**, spinosad (spinosyn **30** and **31**), brentuximab vedotin **32** (dolatsatin 10 **33**), ingenol mebutate **34**, dapagliflozin **35** (phlorizin **36**), omacetaxine mepesuccinate **37**, carfilzomib **38** (epoxomicin **39**) and ado-trastuzumab emtansine **44** (maytansine **45**). New NP drug pharmacophores will be discussed in detail in Section 9. Varenicline **2**, which was launched in 2006 but was omitted from the previous review,[11] will also be discussed, along with selected new drugs that just fall outside of NP, SS-NP and NP-derived definitions.

NP-derived drugs accounted for a meaningful number of the small molecule drug and ADC launches: 3 of 19 in 2008 (14%), 5 of 24 in 2009 (17%), 6 of 19 (32%) in 2010, 3 of 21 (14%) in 2011, 6 of 28 (21%) in 2012 and 2 of 25 (8%) in 2013 (Fig. 1, Supplementary Information Table S1). From 2000-2013, there were 375 worldwide drug approvals,[28-40] which could be classified as 317 NCEs (54 NP-derived, 17%), 56 NBEs and 2 ADCs (2 NP-derived, 100%). On average, 24.4 new NCEs were approved each year with 4.1 being NP-derived. There are also a surprising number of unmodified NPs (14, 25%) of the 56 NP-derived drugs launched from 2000-2013 (Fig. 2, Supplementary Information). A majority were SS-NPs (24, 43%) with 16 NP-derived (29%) and 2 ADCs (3%).

Table 1 NP-derived drugs launched since 2008 by year with reference to their lead compound, classification and disease area[28-40]

Year	Generic name (trade name)	Lead compound (source)	Classification	Disease area
2006	varenicline **2** (Chantix®/Champix®)[a]	(–)-cytisine **3** (plant)	NP-derived	nicotine dependence
2008	ceftobiprole medocaril **4** (Zeftera®, Zevtera™)	cephalosporin C **5** (fungus)	SS NP	antibacterial
2008	umirolimus **6** (Biomatrix™)	sirolimus **7** (actino)[b]	SS NP	cardiovascular surgery
2008	methylnaltrexone **8** (Relistor®)	morphine **9** (plant)	NP derived	opioid-induced constipation
2009	tebipenem pivoxil **10** (Orapenem®)	thienamycin **11** (actino)	SS NP	antibacterial
2009	telavancin **12** (Vibativ®)	vancomycin **13** (actino)	SS NP	antibacterial
2009	romidepsin **14** (Istodax®)	romidepsin **14** (bacteria)	NP	cancer
2009	vinflunine **15** (Javlor®)	vinorelbine **16** (vinblastine) (plant)	SS NP	cancer
2009	nalfurafine **17** (Remitch®)	morphine **9** (plant)	SS NP	pruritus
2010	cabazitaxel **18** (Jevtana®)	paclitaxel **19** (plant)	SS NP	cancer
2010	fingolimod **20** (Gilenya®)	myricocin **21** (fungus)	NP-derived	multiple sclerosis
2010	ceftaroline fosamil **22** (Teflaro®)	cephalosporin C **5** (fungus)	SS NP	antibacterial
2010	eribulin **23** (Halaven®)	halichondrin B **24** (sponge)	NP-derived	cancer
2010	mifamurtide **25** (Mepact®)	muramyl dipeptide **26** (bacteria)	NP-derived	cancer
2010	zucapsaicin **27** (Zuacta®)	capsaicin **28** (plant)	NP-derived	pain
2011	fidaxomicin **29** (Dificid®)	fidaxomicin **29** (actino)	NP	antibacterial
2011	spinosad **30**/**31** (Natroba™)	spinosyn A : D 5:1 **30**:**31** (actino)	NP	antiparasitic
2011	brentuximab vedotin **32** (Adcetris®)	dolastatin 10 **33** (sea hare / cyanobacteria)[41]	ADC	cancer
2012	ingenol mebutate **34** (Picato®)	ingenol mebutate **34** (plant)	NP	actinic keratosis
2012	dapagliflozin **35** (Forxiga®)	phlorizin **36** (plant)	NP-derived	Type 2 Diabetes
2012	omacetaxine mepesuccinate **37** (Synribo®)	omacetaxine mepesuccinate **37** (plant)	NP	oncology
2012	carfilzomib **38** (Kyprolis®)	epoxomicin **39** (actino)	NP-derived	oncology
2012	arterolane **40**/ piperaquine (Synriam™)	artemisinin **41** (plant)	NP-derived	antiparasitic
2012	novolimus **42** (DESyne™)	sirolimus **7** (actino)	SS NP	cardiovascular surgery
2013	canagliflozin **43** (Invokana®)	phlorizin **36** (plant)	NP-derived	Type 2 Diabetes
2013	ado-trastuzumab emtansine **44** (Kadcyla®)	maytansine **45** (bacteria / plant)[42]	ADC	cancer

[a] Varenicline was not included in the previous review.[11] [b] actino = actinomycetes

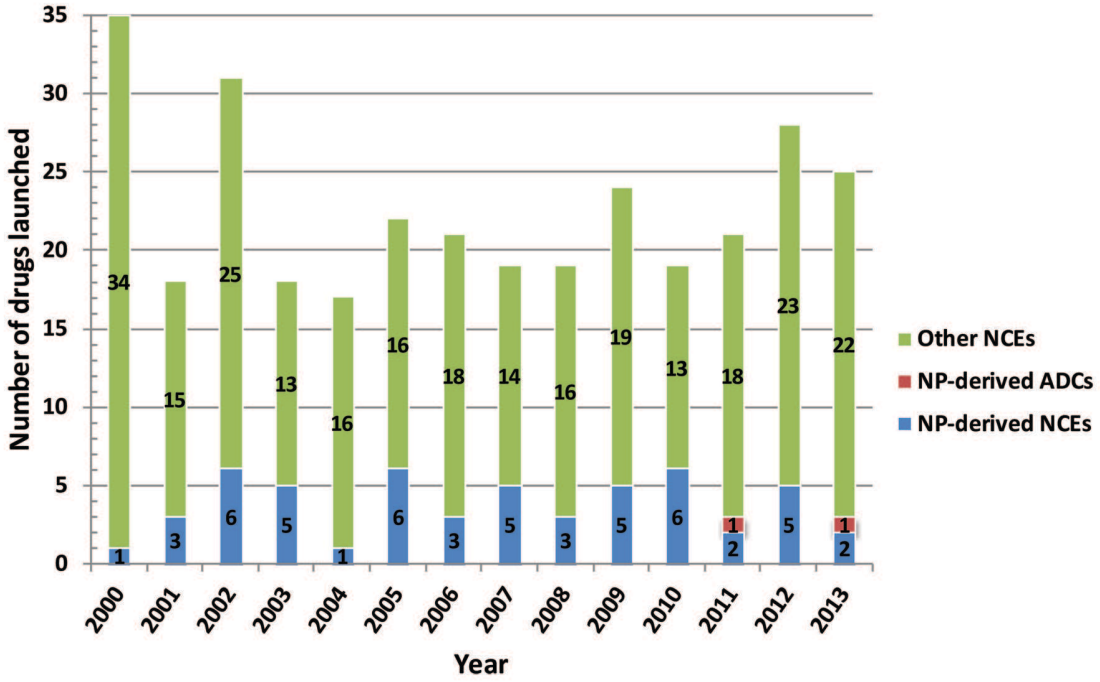


Fig. 1 Worldwide NCEs approved from 2000-2013 divided into NP-derived NCEs, NP-derived ADCs and other NCEs.

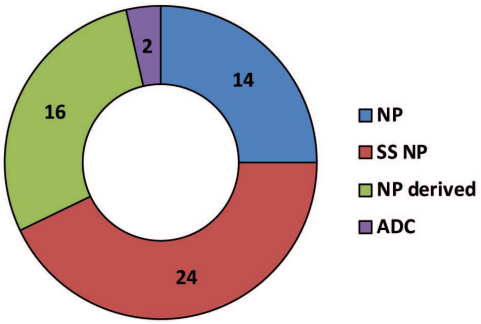


Fig. 2 Classification of the 54 NP-derived NCEs and 2 ADCs approved from 2000-2013.

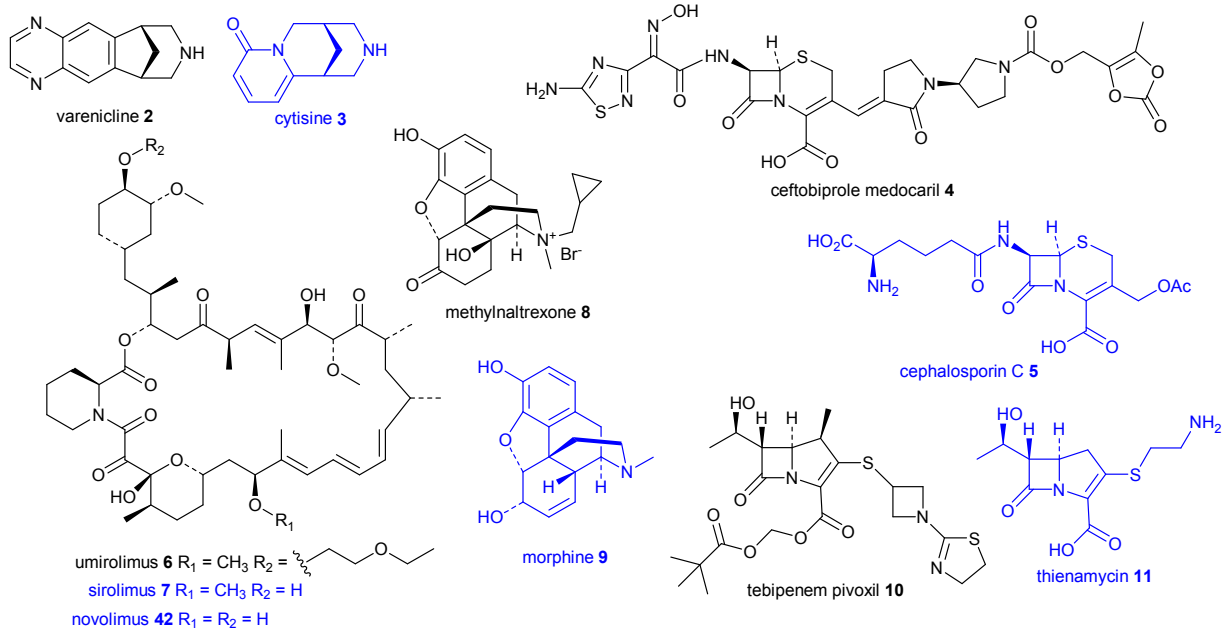
Varenicline **2** (CP 526555) is a partial agonist of the nicotinic acetylcholine receptor subtype $\alpha_4\beta_2$ developed by Pfizer that was approved in 2006 for the treatment of tobacco dependence.[43-45] The structure of varenicline **2** is based[43,45] upon the plant quinolizidine alkaloid (–)-cytisine **3**, which is found in various members of the Leguminosae/Fabaceae family.[46,47] Cytisine **3** itself has been used since the 1960s to aid with smoking cessation and it is available today in Eastern Europe as Tabex® (Sopharma AD).[47]

Ceftobiprole medocaril **4** (BAL5788) is cephalosporin **5**-type antibiotic developed by Basilea Pharmaceutica, which has potent activity against the Gram-positive bacteria such as methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* (MRSA and VRSA), penicillin- and ceftriaxone-resistant *Streptococcus pneumoniae*, and Gram-negative bacteria including strains of Enterobacteriaceae and *Pseudomonas* species.[48-50] Ceftobiprole medocaril **4** was approved for the treatment of complicated skin and skin structure infections (cSSSIs) first in Canada in 2008 and subsequently in Switzerland, Russia, Ukraine and Azerbaijan in partnership with Cilag GmbH International. The FDA and EMA had issues with Cilag's NDA and MAA submissions, which resulted in Cilag discontinued sales of **4** in 2010 and returning rights to Basilea in 2011. Ceftobiprole medocaril **4** will once again be used in the clinic as Basilea obtained EU approval in October 2013 to treat hospital- and community-acquired pneumonia (HAP/CAP) in adults (excluding ventilator-associated pneumonia, VAP).

Umirolimus **6** (biolimus A9™, Biomatrix™) is a sirolimus **7** (rapamycin)-derivative is incorporated into a biodegradable polymer that slowly releases **6** to decrease restenosis.[51,52] Sirolimus **7** is a macrocyclic lactone originally isolated from *Streptomyces hydroscopicus*[53] that is used as an immunosuppressant with analogues also used in cancer treatment.[54] The lipophilicity of umirolimus **6** compared to sirolimus **7** leads to increased vessel targeting improving its pharmacological properties.[51]

Methylnaltrexone bromide **8** (MRZ 2663) is a μ-opioid receptor antagonist clinically developed by Wyeth and Progenics that was approved for the treatment of opioid-induced constipation in Canada and US in April 2008 and in Europe in July 2008.[55] Ono Pharmaceutical Co. is evaluating **8** in Japan (coded as ONO-3849) in phase II trials.[56] Methylnaltrexone **8** is the *N*-methyl derivative of naltrexone, a morphine **9**-derived drug used in management of alcohol and opioid dependence.[57] Methylnaltrexone **8** blocks peripheral opioid receptors activated by opioids administered for pain relief but does not have pain-relieving properties and does not penetrate the blood brain barrier.[58,59]

Tebipenem pivoxil **10** (ME-1211, L-084) is an orally delivered carbapenem antibiotic prodrug that was approved in Japan in April 2009 for the treatment of otolaryngologic (ear, nose, and throat) and respiratory infections such as persistent otitis media, upper respiratory infection and bacterial pneumonia in paediatric patients.[60-63] Thienamycin **11**, isolated from *Streptomyces cattleya*,[64] was the first reported carbapenem



and next generation carbapenems such as tebipenem pivoxil **10** are produced synthetically and incorporate an additional β-Me for extra stability. An X-ray crystal structure of tebipenem bound to Penicillin-Binding Protein (PBP) 2X and PBP 1A from *S. pneumoniae* has been reported.[65]

Telavancin **12** (TD-6424) is a semi-synthetic vancomycin **13** derivative[66-68] developed by Theravance that was first approved by the FDA September 2009 for the treatment of cSSSI. Telavancin **12** has a dual mode of action though membrane disruption in addition to the inhibition of cell wall synthesis.[69,70] Telavancin **12** was approved for use in Europe in September 2011, for the treatment of MRSA nosocomial and ventilator-associated pneumonia, but its MAA was suspended in May 2012 due to manufacturing concerns. Recently, Clinigen Group announced that this suspension had been lifted.[71] The FDA approved the use of **12** in June 2013 for the treatment of nosocomial-acquired and ventilator-associated bacterial pneumonia when other alternatives are not suitable. The development of telavancin **12** in Japan was halted by Astellas in early 2012 and the rights returned to Theravance.[72]

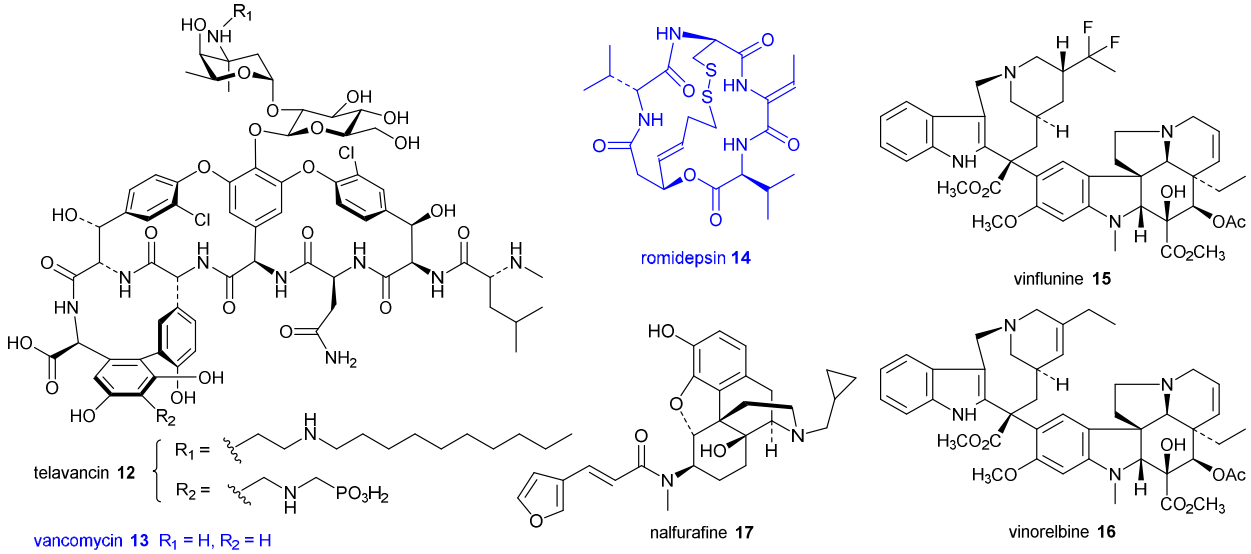
Romidepsin **14** (FR-901228, FK-228) is a cyclic depsipeptide isolated from *Chromobacterium violaceum*[73,74] with potent histone deacetylase (HDAC) inhibitory activity.[75,76] The clinical development of romidepsin **14** was sponsored by the NCI and Gloucester Pharmaceuticals (now part of Celgene Corporation) and approval by FDA for cutaneous T-cell lymphoma (CTCL)[77] was obtained in November 2009 and for peripheral T-cell lymphoma (PTCL) in June 2011.[78]

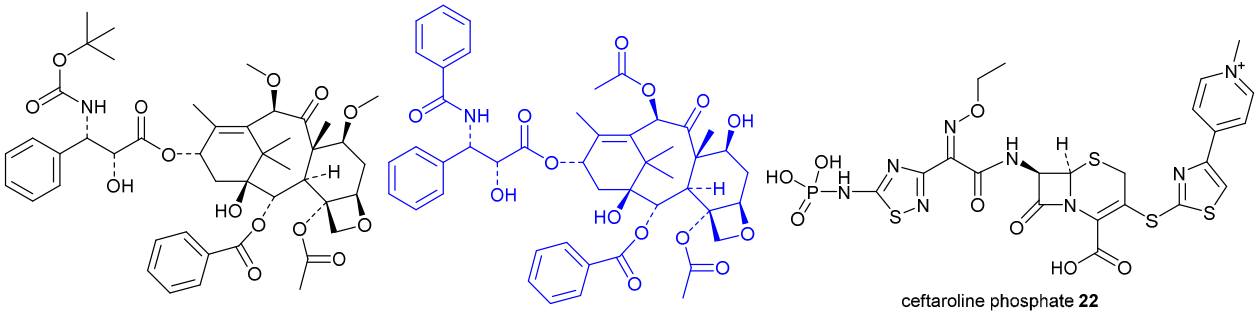
Vinflunine **15** is a fluorine containing derivative of the semi-synthetic vinca alkaloid vinorelbine **16** that was discovered by the Poitiers University and Pierre Fabre Médicament.[79-81] Vinflunine **15** was approved in September 2009 by the EMA for the treatment of patients with advanced urothelial cancer who have failed a prior platinum-containing regimen and is currently being investigated to treat other cancers.[82,83]

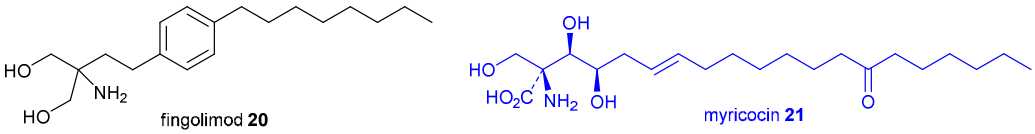
Nalfurafine **17** (MT-9938, AC-820, TRK-820), which is a morphine **9**-type opioid jointly developed by Toray International, Japan Tobacco and Torii Pharmaceutical, is a κ-opioid receptor agonist that was approved in Japan in January 2009 as a treatment for uraemic pruritus (severe itching) in people undergoing haemodialysis.[84-86] Although Toray International withdrew its MAA for Europe in January 2014 after a negative EMA opinion in December 2013,[87] Mitsubishi Tanabe Pharma are still evaluating nalfurafine **17** in trials in the US and Canada (NCT01660243).[88]

Cabazitaxel **18** (XRP-6258, TXD-258, RPR-116258A) is a paclitaxel **19**-derivative that was developed by Sanofi Aventis and approved for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen in combination with prednisone by the FDA in 2010 and EMA in March 2011.[89-92] Cabazitaxel **18** has poorer affinity for the efflux pump P-glycoprotein (P-gp) compared with the taxol drugs paclitaxel **19** and docetaxel, which leads to improved activity against resistant cancers.[93]

Fingolimod **20** (FTY720) was developed by Mitsubishi Tanabe and Novartis and was first approved by the FDA in September 2010 for reducing relapses and delaying disability progression in patients with relapsing forms of multiple sclerosis (MS).[94-96] Fingolimod **20** has also been approved in Europe in March 2011 and Japan in September 2011. The design of fingolimod **20** (FTY720) was based on the structure of the fungal metabolite myriocin **21** and later identified as an immunosuppressant.[94,97-99] Fingolimod **20** is a prodrug that is phosphorylated by sphingosine kinase *in vivo* to give a potent agonist of sphingosine-1-phosphate (S1P) receptors.[100,101]





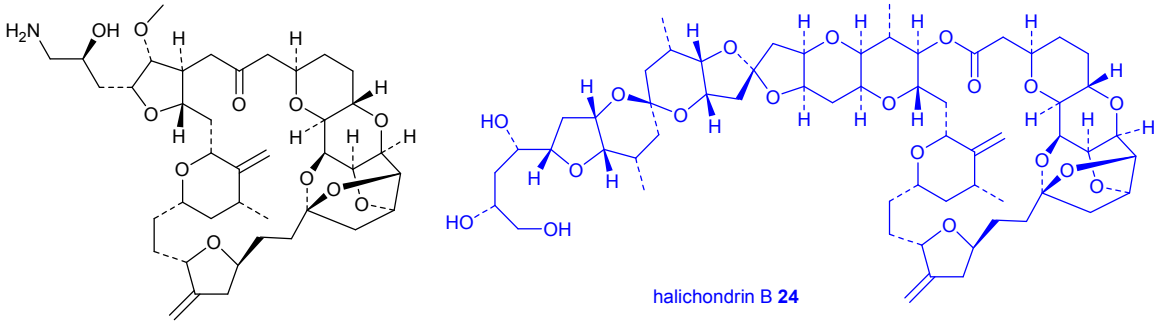


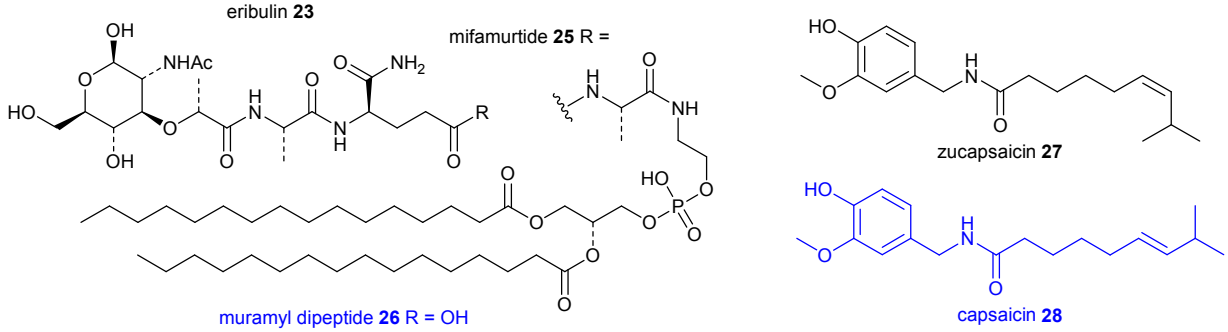
Ceftaroline fosamil **22** (PPI-0903, TAK-599) is a cephalosporin **5**-type β-lactam approved by the FDA in October 2010 for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) and is marketed by AstraZeneca. Ceftaroline fosamil **22** was originally developed by Takeda and is a prodrug that is rapidly converted by plasma phosphases to its active metabolite T-91825.[102-104] Ceftaroline fosamil **22** has broad-spectrum antibacterial activity against Gram-positive bacteria, including MRSA and multidrug resistant *S. pneumoniae* and selected Gram-negative bacteria.[105,106]

Eribulin **23** (E7389, NSC-707389) is a simplified, synthetic analogue of the sponge-derived tubulin inhibitor halichondrin B **24** developed by Eisai.[107-109] The tubulin inhibiting activity of the fragment was identified during Kishi's synthesis of halichondrin B.[110] Eribulin **23** was approved in November 2010 in US, March 2011 in Europe and April 2011 in Japan for the treatment of patients with metastatic breast cancer.[111] A review on the scale up synthesis has been recently published.[112]

Mifamurtide **25** (MTP-PE, Takeda Pharmaceutical) was approved in the Europe in March 2009 for the treatment of osteosarcoma as an adjunct to combination chemotherapy after complete excision of the cancer.[113-115] Osteosarcoma is a rare and often fatal disease, with approximately 1,200 new cases diagnosed in Europe each year; which are primarily children and young adults.[115,116] Mifamurtide **25** is a liposomal formulation of L-alanyl-phosphoethanolamine derivative of muramyl dipeptide **26**, which is the smallest immunogenic component of the bacterial cell wall,[117] synthesised by Ciba-Geigy (now Novartis) in the early 1980s.[118-121] Miramurtide **26** is not available in the US after IDM Pharma (later acquired by Takeda) received a Non-Approvable Letter from the FDA in August 2007.[122]

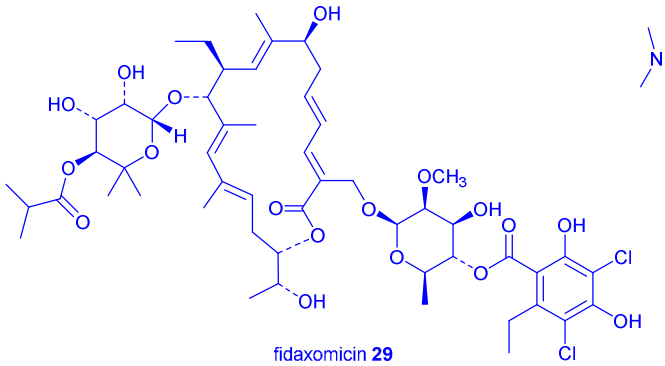
Zucapsaicin **27** (civamide, (*Z*)-capsaicin) was developed by Winston Pharmaceuticals and approved in Canada in July 2010 for the treatment of severe pain in adults with osteoarthritis of

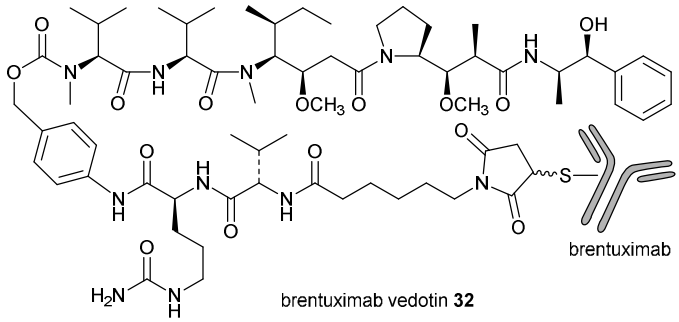




the knee.[123] Capsaicin **28** and zucapsaicin **27** both bind to a transient receptor potential vanilloid type 1 (TRPV1) receptor.[124] NeurogesX also launched capsaicin **28** containing transdermal patches (Qutenza®) in 2009 in the US to treat pain along a nerve associated with shingles.[125]

Fidaxomicin **29** (tiacumicin B, difimicin, OPT-80, PAR-101), which was developed by Optimer Pharmaceuticals, was approved by the FDA in May 2011 for the treatment *C. difficile* associated diarrhoea (CDAD).[126] In October 2013 Cubist Pharmaceutical acquired Optimer.[127] Fidaxomicin **29** is an actinomycete-derived macrolactone first reported by Abbott Laboratories as the major component of the tiacumicin antibiotic complex[128] and is identical in structure to lipiarmycin A3 and clostomicin B1.[129-131] Fidaxomicin **29** inhibits bacterial RNA synthesis by stopping DNA fitting into the RNA polymerase catalytic site.[126,132,133]

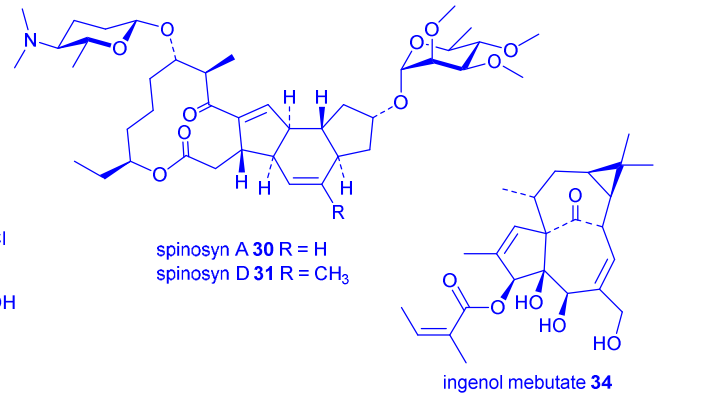


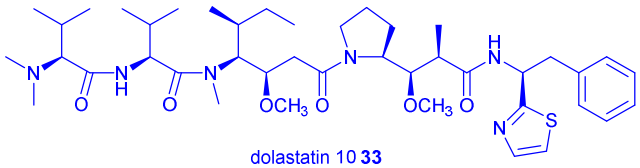


Spinosad®, which is a 5:1 mixture of spinosyn A **30**: spinosyn D **31**, was approved by the FDA in January 2011 for the treatment of head lice infestations in patients four years of age and older marketed by ParaPRO.[134,135] The spinosyns were originally isolated from the actinomycetes *Saccharopolyspora spinosa*[136] and Spinosad® was registered for use as an insecticide in 1997.[137,138] The insecticidal activity spinosyns is due to a novel mechanism of nicotinic acetylcholine receptor activation.[137,139]

Brentuximab vedotin **32** (SGN-35) is an ADC approved by the FDA in August 2011 and the EMA in October 2012 for Hodgkin's lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL).[140,141] Brentuximab vedotin **32** was developed by Seattle Genetics and consists of chimeric monoclonal antibody (mAb) brentuximab (cAC10), which targets the cell-membrane protein CD30, linked to monomethyl auristatin E (MMAE) via a valine-citrulline linker cleavable by cathepsin with a *p*-aminobenzylcarbamate spacer.[142-144] MMAE is an analogue of dolastatin 10 **33**, which is a tubulin inhibitor isolated in 1987 from the sea hare *Dolabella aurlcularia*.[145] It was later shown that dolastatin 10 **33** was produced by marine cyanobacteria, which were consumed by the sea hare.[41]

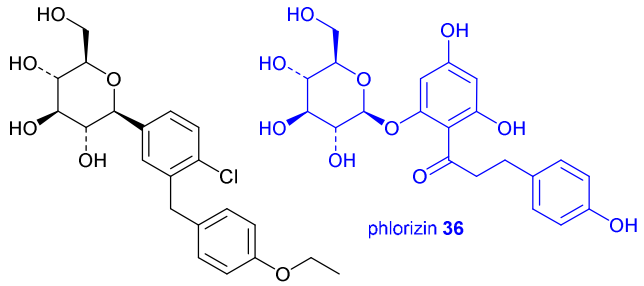
Ingenol mebutate **34** (PEP005, ingenol-3-angelate; Leo Pharma) was approved by the FDA in January 2012 and EMA in November as a topical treatment of actinic keratosis.[146,147] Ingenol mebutate **34** was first reported from an Egyptian collection of *Euphorbia paralias* in 1980[148] and was later identified as one of the active principles of *E. peplus*,[149,150] which had been used a home remedy in Australia for the treatment of basal cell carcinoma,[151] skin cancer and solar keratoses.[152] *E. peplus* was also listed in Hartwell's 1969 compendium[153] of plants used against cancer and in a 1770 monograph that describes the use of the milky sap for the treatment of warts.[154] Ingenol mebutate **34** is substrate for the Epidermal Multidrug Transporter (ABCB1), targets tumour vasculature,[155] reduces lesions and removes mutant p53 patches.[156]





Dapagliflozin **35** (BMS 512148) is a first in class selective Sodium-D-glucose cotransporter-2 (SGLT2) inhibitor developed as an adjunct therapy for diet and exercise for treatment of Type 2 Diabetes developed by AstraZeneca and Bristol Myers Squibb. In April 2012 the EMA recommended grant of marketing authorisation for dapagliflozin **35** indicating quality, safety and efficacy data showed a favourable risk to benefit profile[157] and in January 2014 the EMA also granted marketing authorisation for the combination of dapagliflozin **35** and metformin (Xigduo™).[157] Also in January 2014, the FDA approved dapagliflozin **35** tablets to improve glycaemic control

in Type 2 Diabetes patients but treatment was not recommended for patients with active bladder cancer.[158] The FDA has recommended six post marketing studies and had previously declined approval based on safety concerns surrounding breast and bladder cancer and drug-induced liver injury in July 2011.[159] Dapagliflozin **35** was recently also approved in Japan[160] and is derived from phlorizin **36**, which



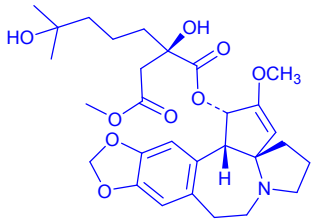
was first isolated from the bark of apple trees in 1835[161,162] and inhibits both SGLT1 and SGLT2 (Section 5).

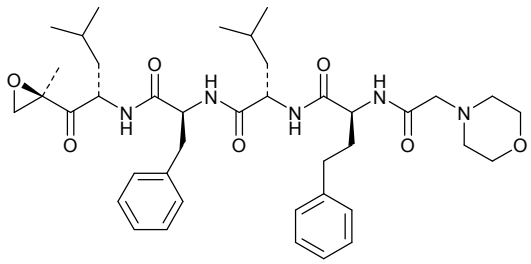
Omacetaxine mepesuccinate **37** (homoharringtonine; Teva) was approved by the FDA in October 2012 for the treatment of chronic myelogenous leukaemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors.[163-165] Omacetaxine mepesuccinate **37** is also being evaluated in a phase I trial for the treatment of solid tumours (NCT01844869) and a phase II trial for acute myelogenous leukaemia (AML) (NCT02029417). The anticancer effects of **37** is via its protein translation inhibitors protein activity.[166] Omacetaxine mepesuccinate **37** was isolated from *Cephalotaxus harringtonia*[167] and has been used in China since 1970s for the treatment of AML.[163] Omacetaxine mepesuccinate **37** is present in the leaves of *C. harringtonia* along with other closely related cephalotaxine esters and the drug used to treat patients is a semi-synthetic product derived from hydrolysis of the mixture and re-esterification.[168]

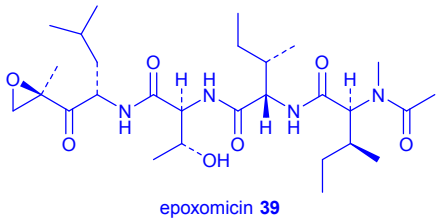
Carfilzomib **38** (PX-171-007) is a selective proteasome inhibitor that was approved by the FDA in July 2012 for the treatment of patients with multiple myeloma who have received at least two prior therapies.[169,170] The lead compound for carfilzomib **38** was the *Streptomyces* metabolite epoxomicin **39**, which was first reported by Bristol-Myers Squibb in Japan as an anticancer agent in 1992.[171] The mode of action of epoxomicin **39** was determined to be proteasome inhibition by Crews using biotin-tagged epoxomicin.[172] Insights into the epoxomicin **39** binding site on the proteasome led to the synthesis of the epoxomicin derivative YU-101 by Proteolix, which was made more water soluble by the addition of the morpholine group to give carfilzomib **38**.[170] Proteolix were acquired by Onyx Pharmaceuticals in October 2009, who in turn were acquired by Amgen in August 2013.

Arterolane **40** (RBx11160, OZ-277) in combination with piperaquine, which is a bisquinoline antimalarial drug, was launched by Ranbaxy in India in 2012 for the treatment of uncomplicated malaria in adults caused by *Plasmodium vivax* parasite. The drug will be administered as a tablet with 150 mg of arterolane maleate **40** and 750 mg of piperaquine phosphate.[173] Ranbaxy have also received permission to conduct phase III clinical trials for the treatment of uncomplicated *P. falciparum* malaria in paediatric patients.[173] Arterolane **40** is a synthetic trioxolane modelled on the artemisinin **41** pharmacophore[174-176] that was jointly developed by the Medicines for Malaria Venture and Ranbaxy until 2007.

Novolimus **42** (DESyne™, 16-*O*-demethylsirolimus) is the 16-*O*-demethyl derivative of sirolimus **7** that is the active component of the DESyne™ stents and DESolve® stents developed by Elixir Medical Corporation used in the treatment of coronary artery disease.[177,178] The DESyne™ and DESolve®

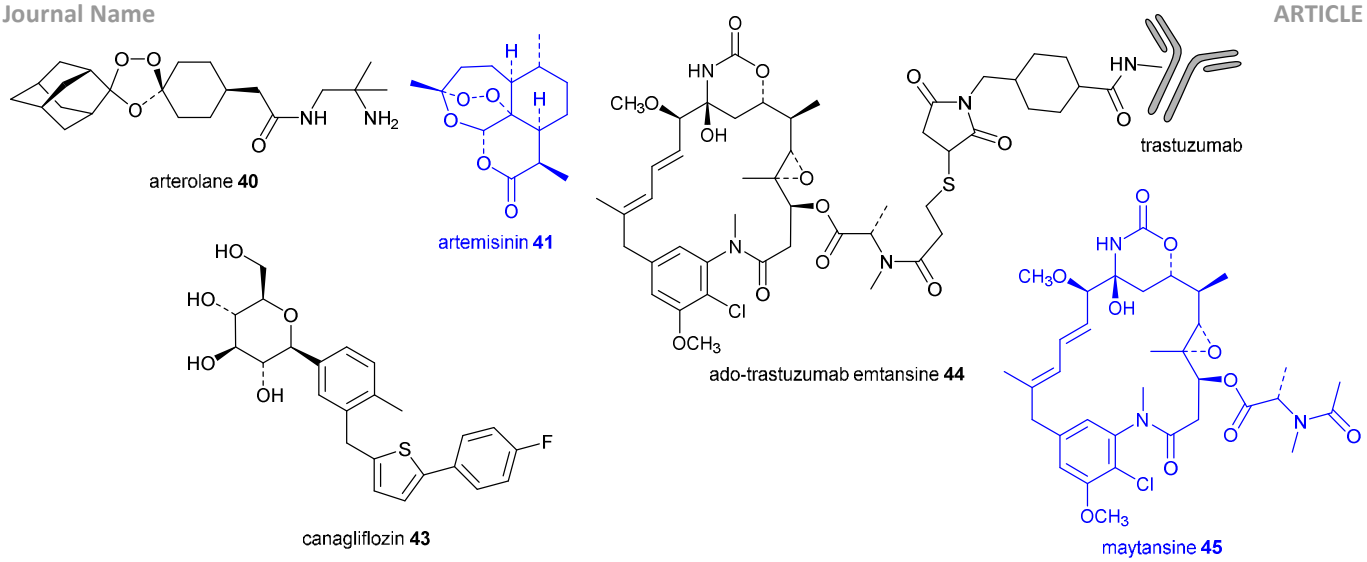






stents received CE Mark approval in August 2012 and March 2013 respectively.[179,180] Novolimus **42** was first reported as biotransformation product[181] but is also a human metabolism product.[182,183]

Canagliflozin **43** (JNJ 28431754, TA 7284), which was developed by Mitsubishi Tanabe Pharma and marketed under license by Janssen, was the first selective SGLT2 inhibitor to be approved by the FDA in March 2013 for use in the treatment of Type 2 Diabetes as adjunct to diet and exercise.[184] In November 2013 the EMA also approved canagliflozin **43** for Type 2 Diabetes. Canagliflozin **43**, like dapagliflozin **35**, is derived from phlorizin **36**.



Ado-trastuzumab emtansine **44** (T-DM1) is an ADC was developed by Genentech and ImmunoGen approved in February 2013 by the FDA for the treatment of HER2-positive metastatic breast cancer in patients that have received prior treatment with the mAb trastuzumab (Herceptin®) and a taxane chemotherapy.[185-187] Ado-trastuzumab emtansine **44** consists of trastuzumab linked to the tubulin inhibitor maytansine **45**-derivative DM1 via a succinimidyl *trans*-4-(maleimidylmethyl)cyclohexane-1-carboxylate.[188,189] Maytansinoids are potent tubulin-binding cytotoxic agents that have been isolated from both plants and mosses but their likely source are microorganisms.[42,190]

2.2 Other NP-related botanicals and compounds of interest

Also of interest is the botanical product Crofelemer (Fulyzaq®, SP-303; Napo Pharmaceuticals) that was approved by the FDA in December 2012 to relieve symptoms of diarrhoea in HIV/AIDS patients taking antiretroviral therapy.[191,192] The drug is a purified proanthocyanidin oligomer extracted from the red bark latex of *Croton lechleri*,[193] which was first investiagated by Shaman Pharmaceuticals in the 1990's.[194] Veregen™ (Polyphenon® E ointment), a defined mixture of catechins extracted from green tea leaves used to treat genital warts, was the first botanical product approved in October 2006.[195,196]

There have also been other drugs approved that just fall out of the NP and NP-derived definitions (Section 1) and these are summarised below.[28-40] In 2010, the two silaic acid analogues, laninamivir octanoate (Inavir®) and peramivir (Rapiacta®) were approved in Japan for the treatment of influenza. The FDA approved the use of the ethyl ester of eicosapentaenoic acid (EPA), icosapent ethyl (Vascepa®), for the treatment of hypertriglyceridemia in 2012. A prostaglandin analogue, tafluprost (Taflotan®, Zioptan®) was approved in 2008 as an anti-glaucoma drug, while a vitamin D analogue, eldecalcitol (Edirol®) was approved for the treatment of osteoporosis in 2011. There were two steroid derivatives, ulipristal acetate (EllaOne®, Ella®, and Esmya®, 2009, contraceptive) and abiraterone acetate (Zytiga®, 2011, anticancer), and three nucleosides, diquafosol (Diquas®, 2010, dry eye), ticagrelor (Brilinta®, Brilique® and Possia® 2011, antithrombotic), and sofosbuvir (Sovaldi®, 2013, antiviral), approved. There were two glucagon-like peptide-1 (GLP-1) agonists, liraglutide (Victoza®, 2009) and albiglutide (Tanzeum®, 2014) approved for the treatment of Type 2 Diabetes.

3 Compounds Undergoing Evaluation in Infectious Diseases

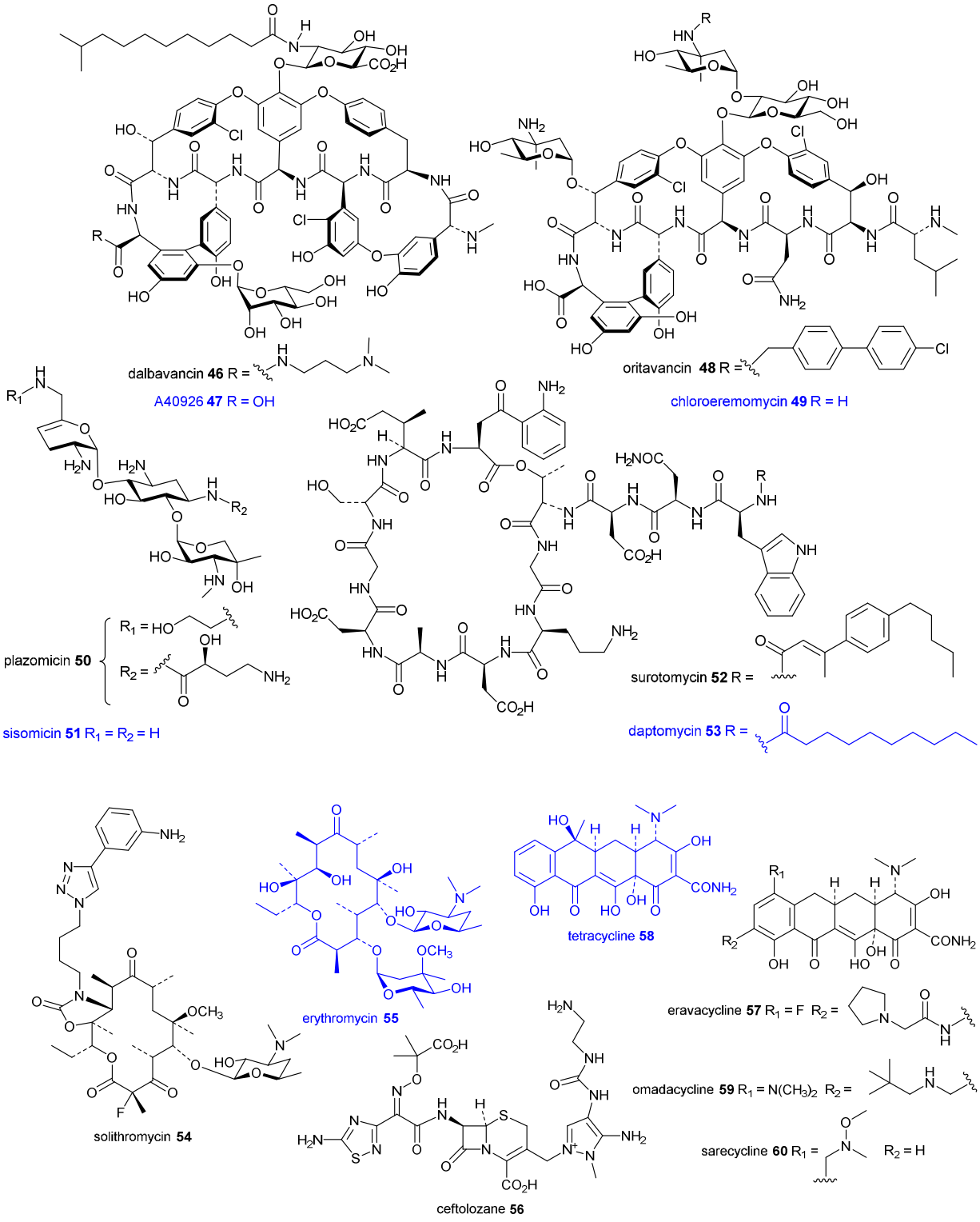
3.1 Antibacterial

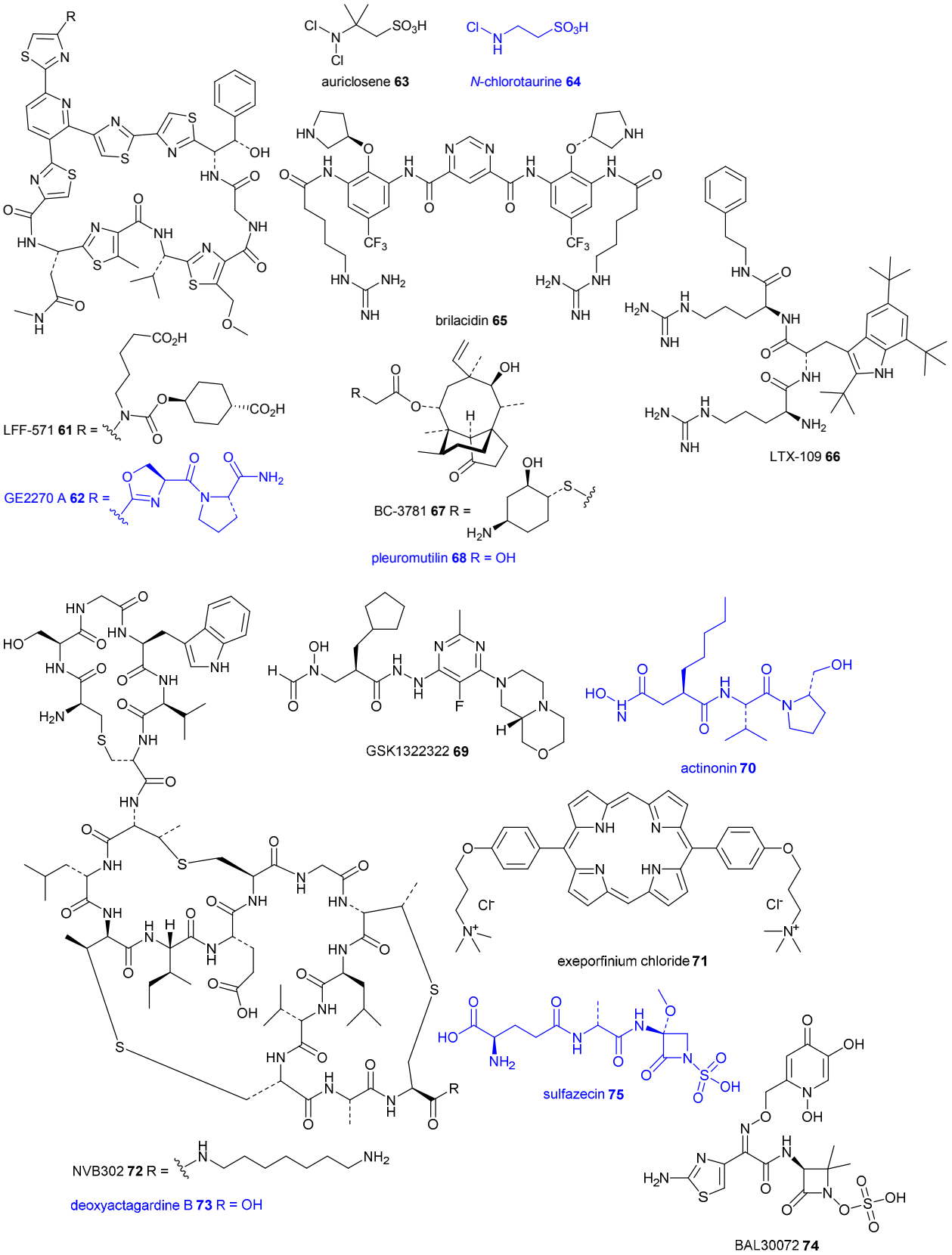
The NP-derived compounds in clinical trials are summarised in Table 2 with further details on each compound in the recently published review "Antibiotics in the pipeline in 2013"[197] and other reviews.[198-200] Since this review was published The Medicines Co. announced on 19 February 2014 that the FDA had accepted an NDA for oritavancin **48**,[201] while an FDA Advisory Committee recently recommended the approval of dalbavancin **46** for the treatment of skin infections.[202] In November 2013, it was announced that Roche had licensed the *Pseudomonas*-specific antibiotic RG7929 (POL7080) from Polyphor Ltd.[203] RG7929 affects the membrane of *P. aeruginosa* by targeting lipopolysaccharide-assembly protein (LptD) and is currently in phase II.[204,205]

Table 2 NP and NP-derived compounds in antibacterial clinical trials

Compound (synonym) and references	Lead compound (class,[a] source)	Derivation	Mode of action	Development status (administration)	Developer
dalbavancin **46** (Zeven™; BI-397; MDL-62476)[202,206-209]	A40926 **47** (glycopeptide, actino)	SS-NP	cell wall synthesis	MAA/ NDA (IV)[b]	Durata Therapeutics
oritavancin **48** (LY333328)[208-211]	chloroeremomycin **49** (glycopeptide, actino)	SS-NP	cell wall synthesis	NDA (IV)	The Medicines Company
plazomicin **50** (ACHN-490)[212-215]	sisomicin **51** (aminoglycoside, actino)	SS-NP	protein synthesis	phase III (IV)	Achaogen
surotomycin **52** (CB-183,315)[216-219]	daptomycin **53** (actino)	SS-NP	membrane	phase III (topical CDI)[c]	Cubist
solithromycin **54** (CEM-101, OP-1068)[220-223]	erythromycin **55** (macrolide, actino)	SS-NP	protein synthesis	phase III (oral/IV)	Cempra
ceftolozane **56** (CXA-201, FR264205)[224-227] / tazobactam[d]	cephalosporin C **5** (β-lactam, fungi)/ clavulanic acid (β-lactam, actino)	SS-NP	cell wall synthesis	phase III (IV)	Cubist
eravacycline **57** (TP-434)[228-231]	tetracycline **58** (actino)	NP-derived	protein synthesis	phase III (IV)	Tetraphase
omadacycline **59** (amadacycline, PTK-0796)[232-235]	tetracycline **58** (actino)	NP-derived	protein synthesis	phase II (phase III) (oral / IV)	Paratek
sarecycline **60** (P005672)[236,237]	tetracycline **58** (actino)	NP-derived	protein synthesis	phase II (completed) (topical)	Warner Chilcott
LFF-571 **61**[238-242]	GE2270 A **62** (thiazole peptide, actino)	SS-NP	protein synthesis	phase II (topical CDI)	Novartis
auriclosene **63** (NVC-422)[243-249]	*N*-chlorotaurine **64** (human)	NP-derived	oxidation	phase II (topical)	Novabay / Galderma
RG7929 (POL7080)[e,203-205]	protegrin I (pig)	NP-derived	β-barrel protein LptD (Imp/OstA)	phase II (*unknown*)	Roche (Polyphor)
brilacidin **65** (PMX-30063)[250-253]	defensin (human)	NP-derived	cell membrane lysis	phase II (IV)	CellCeutix
LTX-109 **66**[254-256]	cationic peptide	NP-derived	membrane	phase II (topical)	Lytix Biopharma
BC-3781 **67**[257-261]	pleuromutilin **68** (fungus)	SS-NP	protein synthesis	phase II (completed) (IV)	Nabriva
GSK1322322 **69**[262-265]	actinonin **70** (actino)	NP-derived	peptide deformylase	phase I (oral)	GSK
exeporfinium chloride **71** (XF-73)[266-269]	porphyrin (plant)	NP-derived	membrane perturbation	phase I /II (topical)	Destiny Pharma
S-649266 (GSK-2696266)[e,199,270]	β-lactam (actino)	*unknown*	cell wall synthesis	phase I (IV)	GSK/Shionogi
NVB302 **72**[271-273]	deoxyactagardine B **73** (lantibiotic, actino)	SS-NP	cell wall synthesis	phase I (completed) (topical CDI)	Novacta
BAL30072 **74**[274-276]	sulfazecin **75** (monobactam, bacteria)	NP-derived	cell wall synthesis	phase I (IV)	Basilea

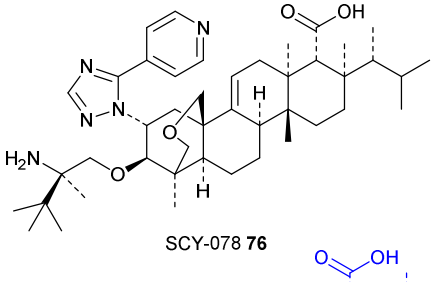
[a] Antibiotic class if different from the lead compound [b] Dalbavancin **46** was approved in May 2014 by the FDA for the treatment of ABSSSI [c] Topical CDI is oral administration to the gut for the treatment of *Clostridium difficile* infections [d] Tazobactam is NP-derived derivative of the actinomycetes metabolite clavulanic acid that was launched in combination with piperacillin in 1992[277] [e] Structure not publically available.


dalbavancin 46 R =
A40926 47 R = OH
oritavancin 48 R =
chloroeremomycin 49 R = H
plazomicin 50
sisomicin 51 R1 = R2 = H
surotomycin 52 R =
daptomycin 53 R =
solithromycin 54
erythromycin 55
tetracycline 58
eravacycline 57 R1 = F R2 =
omadacycline 59 R1 = N(CH3)2 R2 =
sarecycline 60 R1 = R2 = H
ceftolozane 56

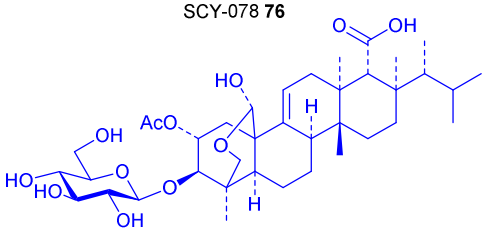


3.2 Antifungal

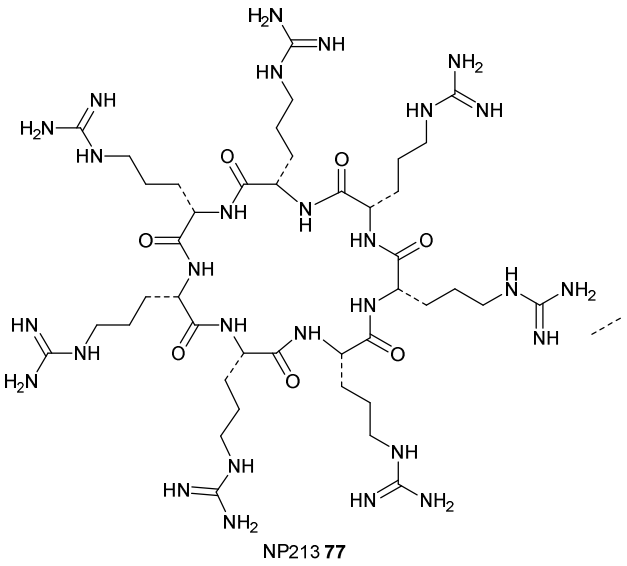
There are only two NP-derived compounds, SCY-078 **76** and NP213 **77**, in clinical trials to treat fungal infections. Reviews discussing antifungal leads and clinical candidates have been recently published.[278-282] SCY-078 **76** (MK-3118) is a semi-synthetic derivative[283] of enfumafungin **78**, which is an acidic triterpenoid β-1,3-D-glucan synthase inhibitor first isolated from the fungus *Hormonema* sp. in 2000 by workers at Merck & Co.[284-286] Other naturally occurring β-1,3-D-glucan synthase inhibitors include the papulacandins, FR901469 and enchinocandins.[281,287] Although enfumafungin **78** has promising *in vitro* activity against *Candida* spp. and *Aspergillus* spp., the presence of the glucose led to sub-optimal pharmacokinetics that rendered **78** unsuitable for clinical development. Synexis and Merck were successful in identifying an orally active, semi-synthetic derivative, SCY-078 **76**,[283] which had excellent *in vitro* against echinocandin-resistant *Candida* sp. and *Aspergillus* sp.[288-290] Merck successfully completed multiple phase I trials of **76** but in May 2013 returned the rights to Synexis due to a reorganisation of their infectious disease portfolio.[291] Synexis has plans for a phase IIa trial but no starting date has been confirmed.[292] In September 2013, R-Pharm licensed the rights to develop and market SCY-078 **76** in Turkey, Russia and its territories.[292]



SCY-078 **76**



enfumafungin **78**



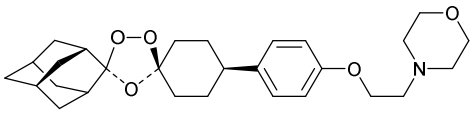
NP213 **77**

NP213 **77** (Novexatin®) is a cyclic cationic peptide based on naturally occurring cationic peptides with seven arginine residues[293,294] being developed by NovaBiotics Ltd. that has completed a phase IIa for the treatment of onychomycosis (nail infections). In August 2013 NovaBiotics entered in an agreement with Taro Pharmaceuticals North America, Inc. to undertake a phase IIb study for mild-to-moderate onychomycosis.[295]

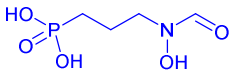
3.3 Antiparasitic

OZ439 **79** (artefenomel) is a synthetic, artemisinin **41**-inspired peroxide containing antimalarial that is being developed by the Medicines for Malaria Venture in phase II trials (NCT01213966, NCT01713621 and NCT02083380) for the treatment of malaria. OZ439 **79** is an analogue of arterolane **40** (OZ277), which was launched by Ranbaxy in 2012 (Section 2), with an increase *in vivo* half-life and blood exposure profile compared to arterolane **40** and artemsisinin-based drugs.[296-299] A recent study has reported that OZ439 **79** was a strong inhibitor of gametocyte maturation and gamete formation.[300]

Fosmidomycin **80** (FR-31564) is an antibiotic first reported in 1980 from *Streptomyces lavendulae*.[301,302] The mode of action of fosmidomycin **80** was determined in 1998 to be via inhibition of DXP reductoisomerase, a key enzyme in the non-mevalonate pathway of isoprenoid biosynthesis.[303] This discovery explained the specificity of fosmidomycin **80** for microorganisms that use non-mevalonate pathway and the lack of activity against *S. aureus*.[303] It was later shown that **80** was a



OZ439 **79**



fosmidomycin **80**

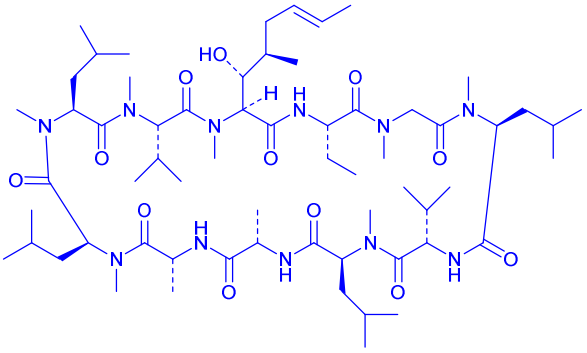
potent inhibitor of *P. falciparum* DXP reductoisomerase and displayed *in vivo* efficacy in a rodent malaria parasite model.[304] Recently cellular metabolic profiling was used to identify methylerythritol phosphate cytidyltransferase (IspD) as a secondary target for fosmidomycin **80** in malaria.[305] Jomaa Pharma first evaluated **80** in combination with clindamycin, which is a protein synthesis inhibitor active against bacteria and malaria, in a phase II trial (NCT01464138) but inadequate efficacy was obtained.[306,307] Jomaa Pharma GmbH recently started a phase IIa trial of a combination of fosmidomycin **80** and piperaquine, which is a bisquinoline antimalarial drug, to treat adults and older children with acute uncomplicated *P. falciparum* malaria.

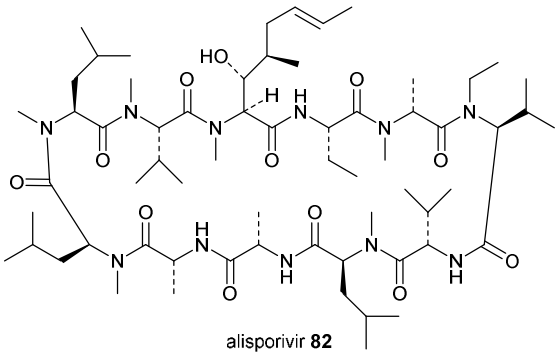
3.4 Antiviral

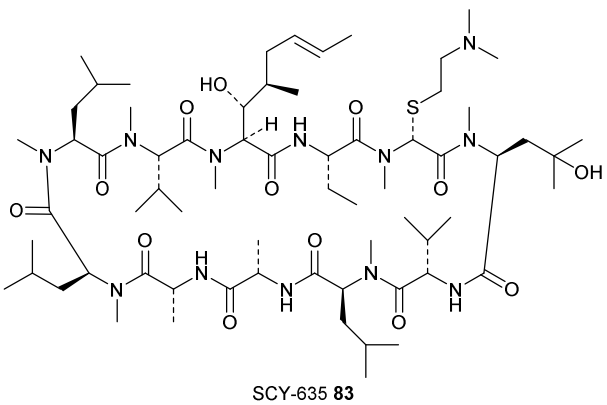
Cyclosporin A **81** is a fungal peptide discovered in 1976[308,309] and used as an immunosuppressive agent since 1982. Cyclosporin **81** exerts its biological activity through the formation of a complex with cyclophilin, which is a peptidyl-prolyl isomerase that mediates *cis-trans* amide isomerisation of *N*-terminal proline residues and plays an important role in protein folding. Cyclophilins are also critical for HCV replication[310] and have been an important target for antiviral therapy.[311] As cyclosporin **81** is not suitable for use as an antiviral drug due to its immunosuppressive and calcineurin-related side effects, cyclosporin derivatives alisporivir **82** and SCY-635 **83**, were identified that strongly inhibited cyclophilin but had minimal immunosuppressive activity.

Alisporivir **82** (DEB025, debio-025, UNIL025, MeAla3EtVal4-cyclosporin) has amino acids 2 and 3 changed on the calcineurin binding site that leads to 7,000 times less immunosuppressive activity and a better toxicity profile than cyclosporin **81**.[312,313] Novartis has evaluated alisporivir **82** in combination with PEGylated interferon-alfa 2a and ribavirin in a phase III trial for the treatment of Hepatitis C Virus (HCV) (NCT01500772) and **82** is currently being evaluated in combination with ribavirin in a phase II trial for the treatment of patients infected with chronic HCV genotype 2 and 3 (NCT01970904).[314] This new focus on the treatment of genotypes 2 and 3 is because a number of drugs have been recently launched that treat genotype 1 and genotype 3 is not sensitive interferon-alfa. The alisporivir **82** and ribavirin combination has already been reported to show positive results in trials.[315]

SCY-635 **83** completed a phase II trial in combination with peginterferon-alfa 2a and ribavirin for the treatment of HCV genotype 1 in 2012 (NCT01265511).[316-318] SCY-635 **84** was originally synthesised by Rhone-Poulenc Rorer SA (now Sanofi Aventis)[319] and later patented by Scynexis for the treatment of HCV.[320] Scynexis have a second generation analogue SCY-575 **83** in late stage clinical development with activity against a number of viruses.







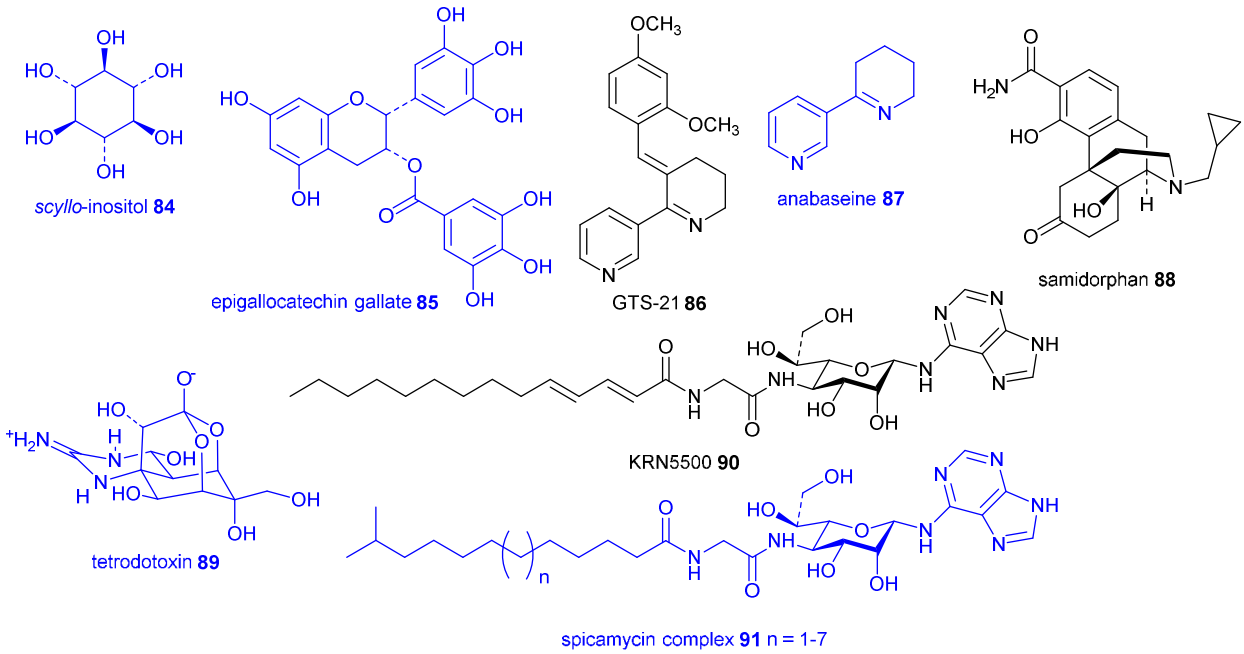
4 Compounds Undergoing Evaluation in Neurological Diseases

ELND005 **84** (*scyllo*-inositol, AZD-103) is a naturally occurring inositol that can stabilise a small conformer of the Aβ42 amyloid *in vitro*, neutralise cell derived Aβ trimers and promote low molecular weight Aβ species *in vivo*.[321-323] ELND005 **84** is being evaluated by Perrigo Company plc, who acquired Elan Pharmaceuticals in 2013, for the treatment of Down syndrome patients without dementia (phase IIa, NCT01791725), the treatment of agitation/aggression in patients with moderate to severe Alzheimer's disease (phase II, NCT01735630) and as an adjunctive maintenance treatment in patients with Bipolar I Disorder to delay mood episode occurrences (phase II, NCT01674010).

Epigallocatechin gallate **85**, which has also been shown to bind to amyloids,[323,324] is a plant-derived polyphenol that is being evaluated as a highly enriched Green tea extract (>90% with less than <0.1% caffeine) that is in clinical development by Charite University, Germany, for Alzheimer's disease (phase II/III, NCT00951834), Duchenne Muscular Dystrophy (phase II, NCT01183767) and Huntington's Disease (phase II, NCT01357681). Epigallocatechin gallate **85** is also being investigated in phase II for Cardiac Amyloid Light-chain Amyloidosis by the University Hospital Heidelberg, Germany (NCT02015312).

GTS-21 **86** (DMXBA) is being evaluated as a sustained release formulation by the University of Colorado in a phase II trial for the treatment of patients with schizophrenia who also smoke cigarettes (NCT01400477). GTS-21 **86**,[325] which is a potent agonist of the α7 nACh receptor, is derived from anabaseine **87**, an alkaloid isolated intertidal Pacific nemertine worm *Paranemertes peregrina*.[326]

Samidorphan **88** (ALKS 33) is a μ-opioid receptor antagonist designed from naltrexone,[327] which is an approved drug used in management of alcohol and opioid dependence that was based on morphine **9**. Samidorphan **88** is being investigated in a combination with olanzapine, which for the



treatment of schizophrenia and bipolar disorder, called ALKS 3831 in a phase II trial by Alkermes plc for the treatment of schizophrenia (NCT01903837). Samidorphan **88** also recently completed a phase II trial in combination with buprenorphine, a κ-opioid receptor antagonist and a μ-opioid receptor agonist approved for the treatment of pain and opioid addiction, called ALKS 5461 for the treatment of Major Depressive Disorder (MDD) and inadequate response to antidepressant therapy (NCT01500200).[328]

Tetrodotoxin **89** is being evaluated in phase II and phase III trials by WEX Pharmaceuticals to relive pain in patients resulting from chemotherapy treatment (NCT01655823 and NCT00725114 respectively).[329] Tetrodotoxin **89**-mediated pain relief is due to either a decrease in the propagation of action potentials by Na^+ ion channels and/or by blocking of ectopic discharges associated with chronic pain.[330,331] The tetrodotoxin **89** used in these clinical trials is extracted directly from puffer fish. Interestingly, a 1% solution was used clinically in Japan in the 1930s[332] based on an extraction method detailed in a 1913 Patent.[333]

KRN-5500 **90** is a semi-synthetic spicamycin derivative that has been evaluated in a phase II trial by DARA BioSciences for the treatment of neuropathic pain (NCT00474916).[334] The spicamycin complex **91** was first isolated from *Streptomyces alanosinicus*[335,336] by Kirin Breweries.[334,335] KRN-5500 **90** was originally evaluated in oncology clinical trials and displayed no anti-cancer activity but was instead found to provide pain relief.[337] DARA BioSciences recently announced that KRN5500 **90** had received an Orphan Drug Designation from the FDA.[338]

5 Cardiovascular and Metabolic Disease

5.1 Compounds Undergoing Evaluation in Cardiovascular and Metabolic Diseases

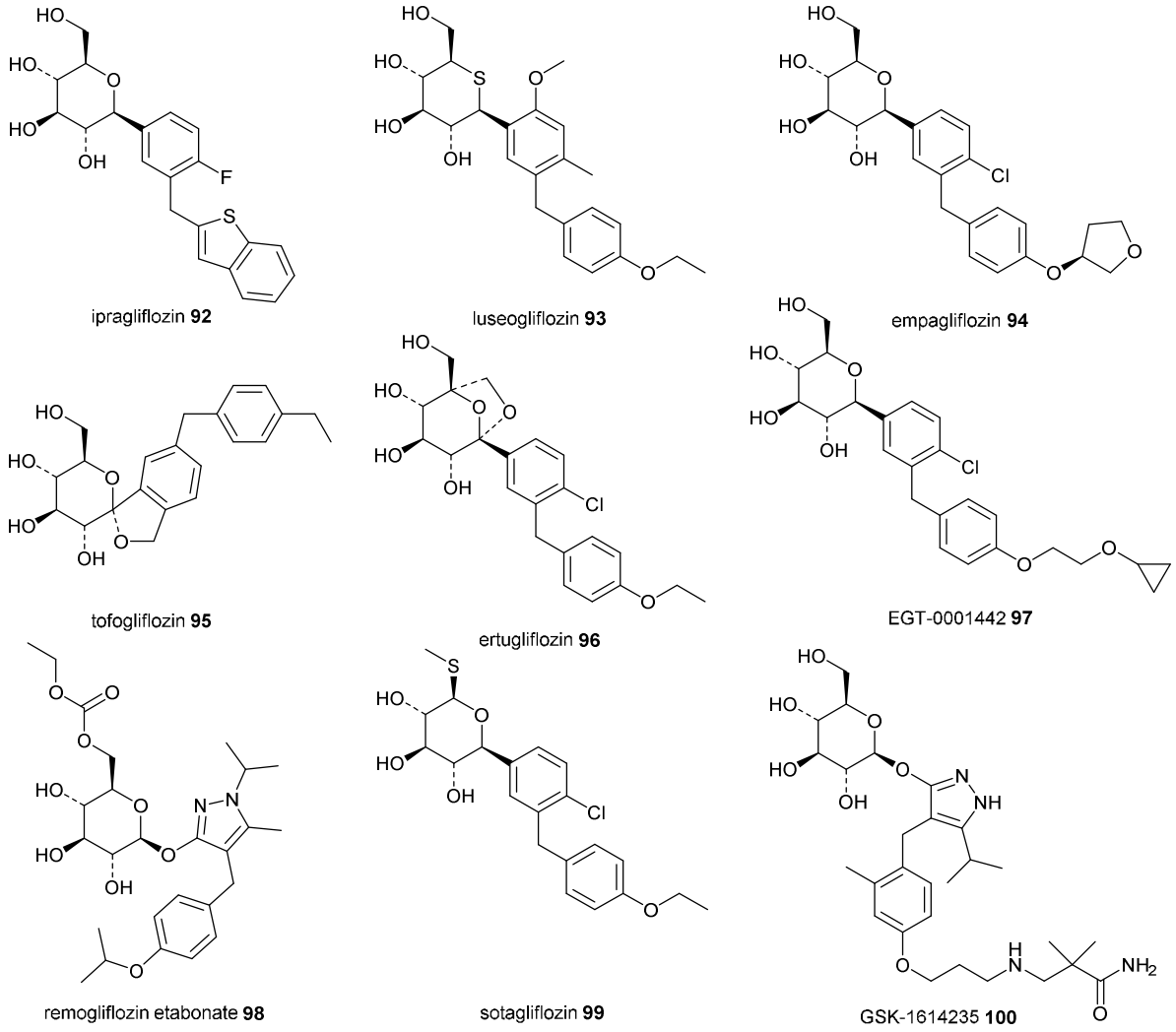
SGLT2 inhibitors are becoming a major new treatment class in diabetes and many of these inhibitors are based on the plant NP phlorizin **36** (Table 3).[339-342] SGLT2 is almost exclusively expressed in the proximal tubule of the nephron and facilitates glucose re-uptake and when SGLT2 is inhibited glucose is excreted in the urine. As a consequence, blood glucose levels are reduced, which can lead to a beneficial reduction in weight and blood pressure. This class of therapeutics has however been also associated with an increased incidence of genitourinary infections.[343] The recent phlorizin **36**-derived selective inhibitors of SGLT2, dapagliflozin **35**[344] first launched in 2012[157] and canagliflozin **43** [345,346] first launched in 2013[184] (Section 2), are proving efficacious in treatment of Type 2 Diabetes mellitus both as monotherapy and also in combination with other antidiabetic agents such as metformin.[347]

More recently ipragliflozin **92** [348] became the first SGLT2 inhibitor to be approved in Japan (January 2014)[358] just ahead of dapagliflozin **35**[160] and luseogliflozin **93**[359] (March 2014) with canagliflozin **43** likely to follow in the near future.[360] These analogues are all β-*C*-aryl glucosides where different aglycone moieties or, in the case of luseogliflozin **93**, a modified sugar moiety with pyranose oxygen replaced by sulfur, have provided proprietary chemical space for the companies involved. All of these derivatives overcome the liabilities of the original phlorizin **36** *O*-aryl glucoside class which suffered from side effects due to lack of selectivity over SGLT1, poor intestinal absorption and degradation by glucosidase enzymes.[161] NDA approval of empagliflozin **94**,[350,351] a further β-*C*-aryl glucoside aglycone variant, jointly developed by Boehringer Ingelheim and Eli Lilly, has recently been delayed by the FDA until deficiencies in manufacturing have been addressed.[361] However, the EMA has recommended approval in the EU market.[362] An NDA filing for combination therapy of empagliflozin **94** and linagliptin, a DPP-4 inhibitor, has been accepted by the FDA.[363] Tofogliflozin **95**[352] is a conformationally constrained *O*-spiroketal β-*C*-aryl glucoside.

Table 3 Phlorizin **36**-derived, orally administered SGLT inhibitors approved for the treatment of diabetes or in clinical trials

Name (synonym) and references	Development status 2013 (2014 update)	Developer
dapagliflozin **35** (Farxiga®, Forxiga®)[a,344]	Launched 2012	AstraZeneca, BMS, Ono
canagliflozin **43** (Invokana®)[a,346]	Launched 2013	Janssen (Mitsubishi)
ipragliflozin **92** (ASP1941, Suglat®)[a,348]	NDA (JP) (Approved Jan 2014)	Kotobuki, Astellas
luseogliflozin **93** (TS-071, Lusefi®)[a,349]	NDA (JP) (Approved Mar 2014)	Taisho
empagliflozin **94** (BI10773)[a,350,351]	NDA (USA), MAA (EU)	Boehringer Ingelheim, Lilly
tofogliflozin **95** (CSG452, RG7201)[a,352]	NDA (Japan)	Kowa (Chugai / Sanofi KK)
ertugliflozin **96** (MK-8835/PF-04971729)[a,353]	phase III	Merck / Pfizer
EGT-0001442 **97** (THR1442)[a,354]	phase II completed July 2013	Theracos Inc (Egret Pharma)
remogliflozin etabonate **98** (BHV091009, GSK189075)[a,355]	phase II	Islet Sciences (BHV Pharma, GSK)
sotagliflozin **99** (LX4211)[b,356]	phase II completed 3 trials, last February 2014	Lexicon
GSK-1614235 **100** (DSP-3235, KGA-3235)[c,357]	phase I	GSK, Kissei, Dainippon Sumitomo

[a] Selective SGLT2 inhibitor [b] Dual SGLT1 and SGLT2 inhibitor c SGLT1 inhibitor.



This SLGT2 inhibitor was submitted for NDA approval in Japan in April 2013 by Sanofi K.K. and Kowa Company.[364]

Ertugliflozin **96**[353] is being developed in partnership between Merck and Pfizer as monotherapy and also as a fixed dose combination with metformin and sitagliptin.[365] Ertugliflozin **96** comprises a novel sugar moiety, dioxabicyclo[3.2.1]octane, developed at Pfizer and an aglycone moiety identical to that used for dapagliflozin **35**. Phase II clinical trials (NCT01059825 and NCT01096667) were successfully completed with average reductions in blood glucose (A1c) by 0.8%, weight by 5.5 lbs and blood pressure by 4 mmHg based on a once daily oral dose.[366] Recruitment of

patients for phase III clinical trials is now underway (NCT02036515, NCT01999218, NCT01986855, NCT01958671 and NCT01986881).

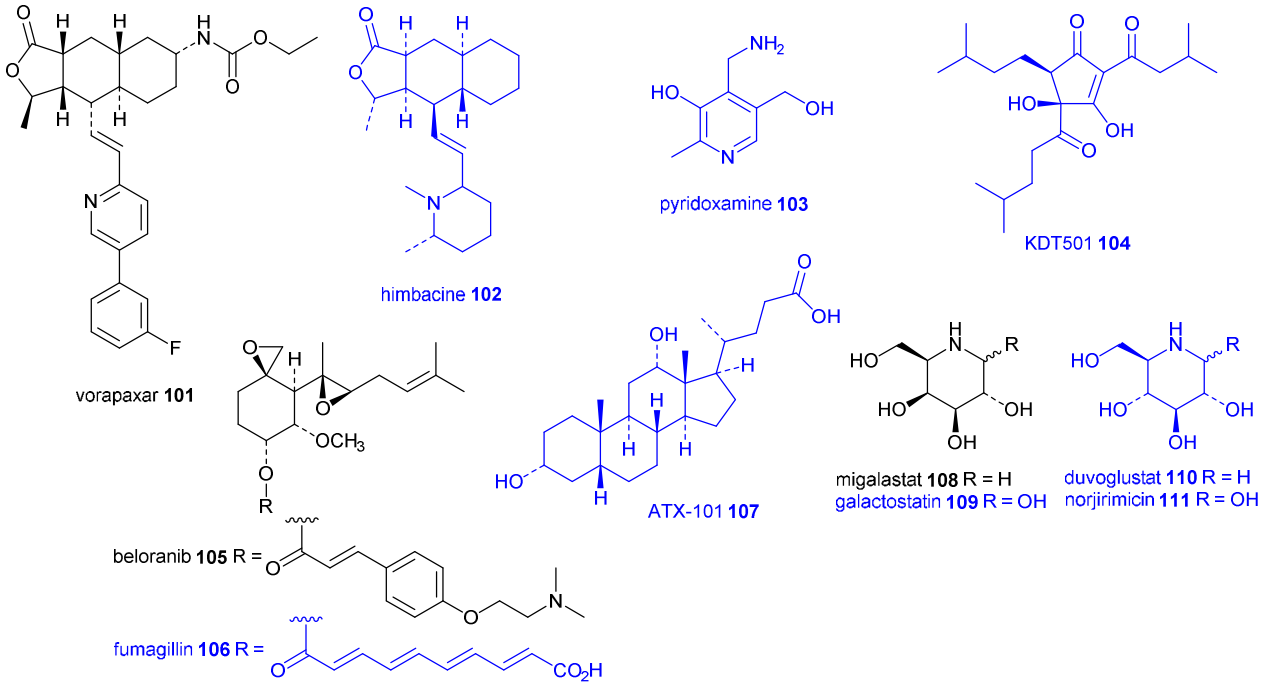
EGT-0001442 **97** (THR1442),[354] developed by Theracos, has been successfully evaluated in a double-blinded, placebo-controlled phase II study with 288 Type 2 Diabetes patients over a 96 week period (NCT01029704). The study showed EGT-0001442 **97** monotherapy to be highly efficacious and void of the classical genitourinary side effects commonly associated with this class of inhibitor[367] thereby differentiating the compound from its competitors. A second phase II clinical trial (NCT01377844) is underway to evaluate lowering of glycosylated haemoglobin at 24 weeks from baseline.

Remogliflozin etabonate **98**[355] (Islet Sciences, BHV Pharma[368]), which is in phase II trials, marks an interesting return to the *O*-aryl glucoside structural class. Remogliflozin etabonate **98** is a pro-drug that forms remogliflozin, which is further metabolised to an active metabolite GSK279782.[369] Sixteen phase I trials have been completed and show remogliflozin etabonate **98** is safe and well tolerated both as monotherapy[370] and also in combination with metformin (NCT00519480 and NCT189075).[371] Phase II studies (NCT00500331, NCT00291356 and NCT00495469) are reporting best in class reductions in HbA1c, plasma glucose and body weight over a 12 week treatment period with Type 2 Diabetes patients.[372] Remogliflozin etabonate **98** also completed a phase II study in Type 1 diabetic patients (NCT00575159) and is in preclinical evaluation as a future therapeutic for non-alcoholic steatohepatitis.

Sotagliflozin **99** (LX-4211), developed by Lexicon Pharmaceuticals,[342,356,373] is the most promising dual SGLT1/SGLT2 inhibitor thus far and is currently in phase II trials. Inhibition of SGLT1 in the small intestine has historically been associated with adverse gastrointestinal effects. However, phase I and II trials with sotagliflozin **99** have proven that partial inhibition of SGLT1 could be beneficial leading to increased secretion of hormones GLP-1 and PYY, involved in glycaemic control and appetite. Moreover, contrary to expectation, there were no additional gastrointestinal effects by comparison to placebo and an improvement when compared to metformin. Of particular note sotagliflozin **99** has successfully completed phase IIb trials with patients who have poorly-controlled Type 2 Diabetes (NCT01376557) and phase I trials in patients with additional renal impairment (NCT01555008). Lexicon have moved into treatment of Type 1 Diabetes where sotagliflozin **99** successfully complemented insulin therapy in phase II trials (NCT01742808).[374]

GSK-1614235 **100**,[357] is the first SGLT1 inhibitor to be evaluated in phase I trials (NCT00976261, NCT01607385) for Type 2 Diabetes but further information is not yet available. The same structure has also been the subject of a patent for prevention and treatment of constipation.[375]

Vorapaxar **101** (SCH 530348) has completed two phase III trials (NCT00526474 and NCT00617123) that aimed to help reduce atherothrombotic events in patients with a history of heart attack and no history of stroke or transient ischemic attack. The NDA for vorapaxar **101** was accepted by the FDA in July 2013,[376] a recommendation for approval by the FDA Advisory Panel was announced in January 2014[377] and approval granted in May 2014.[378] Vorapaxar **101** is a protease-activated receptor-1 (PAR-1) antagonist derived from a research programme at Schering Plough that was investigating himbacine **102** analogues for M2 subtype antimuscarinic activity.[379] One of the synthesised himabacine **102** derivatives displayed no antimuscarinic activity but later was found to be a PAR-1 antagonist and structure optimisation led to the identification of vorapaxar **101**.[379,380] Himabcine **102** was originally isolated from Queensland collections of the trees



Galbulimima baccata and *G. belgraveana*.[381-383]

Pyridoxamine **103** (Pyridorin™) is a vitamin B6 analogue originally developed by Biostratum to retard progression of diabetic nephropathy. Biostratum successfully completed two phase II clinical trials before licensing the program to NephroGenex in 2006.[384] NephroGenex worked together with a collaborative study group to complete a phase IIb trial to evaluate the efficacy of two different doses of **103** in Type 2 Diabetes patients with nephropathy (NCT00734253).[385] In this study the expected loss of renal function was not ameliorated by pyridoxamine **103**. However, on closer examination of patient subgroups those with less renal damage showed significant response. NephroGenex are now collaborating with both Collaborative Study Group and Medspace to conduct the first of two phase III trials known as the PIONEER (PyrIdOriN in DiabEtic NEphRopathy) study expected to commence in the first half of 2014.[386] The patient population has been accepted by the FDA through a Special Protocol Assessment with an end point of 50% serum creatinine increase rather than 100% moreover patients who previously had >50% effect in phase II studies can be included.

Reduced hops extracts are used in brewing as a preservative and contribute to a classical bitter taste. These extracts also have reported anti-inflammatory, weight loss, anti-diabetic and anticancer effects. KinDex Pharmaceuticals have worked together with Professor Kaminsky from The University of Washington to study a number of bitter hops derived acids of the humulone class and determine their absolute structures using X-ray crystallography.[387] KDT501 **104** proved particularly interesting in preclinical murine studies of Type 2 Diabetes however the mode of action has not yet been elucidated.[388] A phase I safety, tolerability and PK study (NCT) has been completed successfully and KinDex hope to initiate phase IIa studies in 2014.[389] KDT501 **104** is also under preclinical evaluation for inflammatory disease.

Obesity is a particularly challenging therapeutic area with high failure rate and expectations of risk to benefit profiles for weight loss drugs are exceptional;[390] however, the lucrative rewards of success in this area maintains commercial interest. Beloranib **105** (CKD-732, ZGN-440, ZGN-440) was designed and synthesised by CKD research institute[391] and is being developed by the start-up company Zafgen. Beloranib **105**, an unlikely looking drug with two epoxides and a Michael acceptor, was synthesised from fumagillol, which is the hydrolysis product of fungal metabolite fumagillin **106**. Fumagillin **106** binds covalently to the active site of methionine aminopeptidase type 2 (MetAP-2).[392-394] CKD used homology modelling to develop highly potent fumagillin analogues resulting in their optimal compound beloranib **105**.[391] Beloranib **105** was initially designed and evaluated as an injectable angiogenesis inhibitor in treatment of cancer where phase I clinical trials were conducted in combination with capecitabine and oxaliplatin.[395] Significant antitumour activity was not observed and dose limiting toxicity was identified at 10 mg/m^2/day including insomnia, nausea and fatigue.[396,397] However, beloranib **105** did prove effective as an intravenously administered weight loss therapeutic in a phase I trial (NCT01507077).[398] Low doses could be used that were generally well tolerated and efficacious but had the common side effects of insomnia, nausea and vomiting. A subsequent phase II trial (NCT01666691) examined doses ranging from 0.3 to 3.2 mg twice per week to evaluate pharmacokinetics, safety and weight loss in obese patients. The trial was successful resulting in reduced body weight, improved cardiometabolic risk markers and lower blood pressure.[399] A further proof of concept phase II study (NCT01818921) examined beloranib **105** in obese patients with the additional complications of Prader-Willi syndrome.[400] Prader-Willi syndrome is a particularly debilitating genetic condition where one symptom is chronic hunger leading to severe obesity. Zafgen reported remarkable success where, despite a 50% increased calorie intake, an 8.1% reduction in body fat was achieved over a four week period; moreover, hunger was reduced and weight improved. A further phase II study is planned for 2014 but with obese patients who have hypothalamic injury (NCT02063295).

ATX-101 **107**[401,402] is a first in class injectable therapy for submental contouring by Kythera Biopharmaceuticals, Inc. and Bayer which has completed six phase III clinical trials with one further phase III trial active (NCT02007434) and two in recruitment. ATX-101 **107** is derived from bile acid and functions as a selective adipolytic agent leaving surrounding non-fat tissues unaffected. An NDA application is anticipated to be filed in the second quarter of 2014. Bayer have rights to ATX-101 **107** within the US and Canada but Kythera hold all rights outside this region.[403]

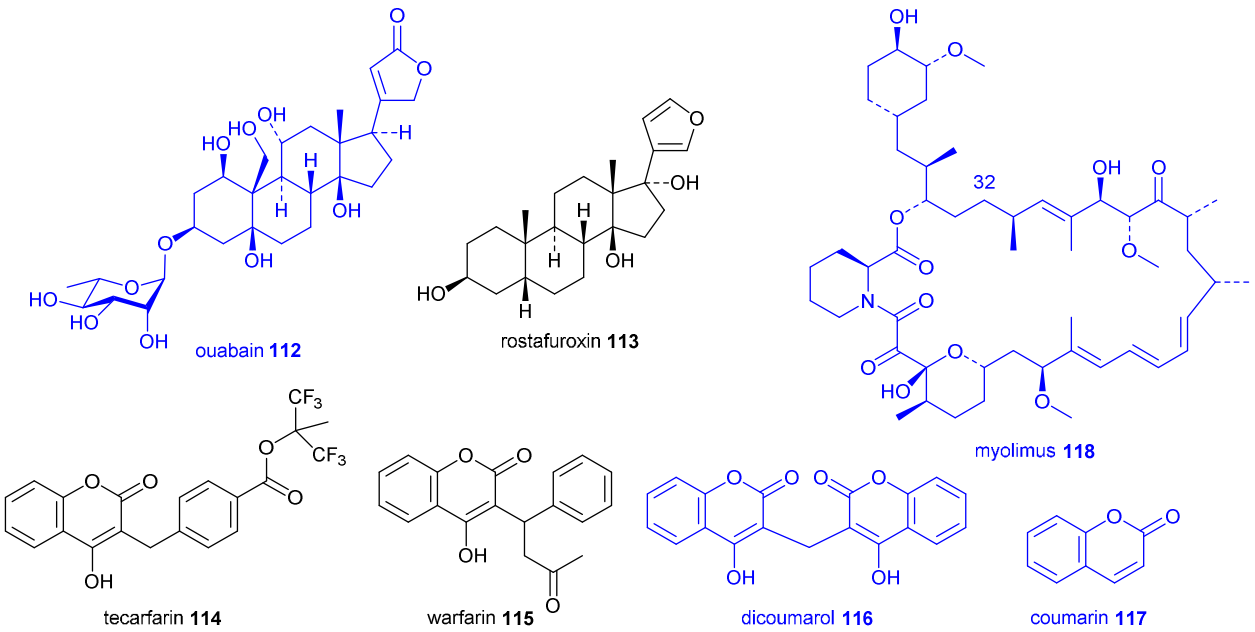
Migalastat **108** (AT1001, Amigal™), which is derived from the *Streptomyces* metabolite galactostatin **109** (galactonojirimicin),[404-406] is being developed by Amicus Therapeutics as an oral drug for treatment of Fabry disease. Amicus had been developing migalastat **108** in partnership with GlaxoSmithKline but all rights were returned to Amicus in November 2013.[407] Fabry disease is a rare inherited genetic disease caused by deficiency of α-galactosidase A (α-gal), an enzyme involved in degradation of lysosomal lipids particularly globotriasosylceramide (GL-3). Accumulation of GL-3 ultimately causes disease to the CNS, heart, kidneys and skin. However, it is estimated up to half of the patients with Fabry disease can produce limited amounts of α-gal, migalastat **108** acts as a chaperone which binds to and stabilises α-gal increasing trafficking to the lysosome to degrade GL-3.[408,409] The first double-blind phase III clinical trial (NCT00925301) treated 67 patients, who had genetically susceptible Fabry disease, with either oral migalastat **109** or placebo every second day over a 6 month period. In late 2012 this trial failed to reach statistical significance in the primary end point.[410] A 6 month open-label period followed[411] where all patients were treated with migalastat **108** but this trial is ongoing and results of the 12 and 24 month data are anticipated in the second quarter of 2014.[412] A second phase III clinical trial (NCT01218659), the ATTRACT study, is ongoing to compare migalastat **108** to standard enzyme replacement therapy, Amicus are due to announce these results in the second half of 2014.[412] A phase II

trial (NCT01196871) to examine drug-drug interactions between a single oral dose of migalastat **108** in combination with enzyme replacement therapy (ERT) agalsidase in Fabry disease patents was successfully completed. A phase I trial to investigate pharmacokinetics of migalastat **108** as a co-formulation with ERT for intravenous administration is also planned. This is part of Amicus chaperone-advanced replacement therapy (CHART™) program[413] where the standard enzyme replacement therapy is used in combination with a molecular chaperone in treatment of lysosomal storage disorders. The enzymes used can be unstable and lose activity furthermore the patient can illicit an immune response to ERT which inactivates the enzyme.[414] The use of a molecular chaperone can stabilise the enzyme in an active conformation and increase overall efficacy.[415]

Duvoglustat **110** (1-deoxynojirimycin, AT2200, moranoline) is also part of Amicus's The CHART™ program that focusses on Pompe disease (glycogen storage disease type II), which is a rare neuromuscular and lysosomal storage disorder caused by genetic mutation in the gene responsible for expression of the lysosome associated enzyme α-glucosidase (GAA).[416] Deficiency of α-glucosidase leads to accumulation of glycogen in lysosomes. Amicus had investigated duvoglustat **110** as chaperone based monotherapy to treat Pompe disease in both phase I and II trials. However serious adverse events and poor pharmacokinetics led to use in combination with ERT.[417] Phase II clinical trial results (NCT1380743) were positive where single dose of **110** prior to treatment with recombinant human GAA was well tolerated and led to a 1.5 to 2.8 % increase in GAA plasma levels.[418,419] Nojirimycin **111** was first reported from *Streptomyces* in 1966 by workers at Meiji Seika Kaisha[420] and **110** was obtained using catalytic hydrogenation or borohydride reduction.[421] Naturally occurring **110**, which was called moranoline, was later reported in 1976 from the root bark of mulberry trees (*Morus* sp.)[422-424] and from other plants, silk worms and microorganisms.[425-427]

Ouabain **112** is derived from plants but is also an endogenous human hormone playing an important role in sodium homeostasis and blood pressure regulation through modulation of the sodium pump, Na^+/K^+-ATPase. High concentrations of ouabain **112** have an inhibitory effect while low concentrations, typically found endogenously, have a stimulatory effect. Activation of Na^+/K^+-ATPase leads to downstream c-Src kinase activation, oxidative stress, reduced nitric oxide bioavailability and endothelial dysfunction.[428] High levels of ouabain **112** have been found in patients with hypertension and this has been associated with increased mortality. In 1997 a selective ouabain **112** antagonist, rostafuroxin **113** (PST2238)[429-432] was synthesised by chemists at Sigma-Tau i.f.r. S.p.A. This digitoxigenin derivative was synthesised in a single step where the furan-2(5*H*)-one moiety was reduced to the corresponding furan and found to act as an antihypertensive agent. CVie (Lee's Pharmaceutical holdings) have licensed rostafuroxin **113** and patients are now being recruited for comparator (Losartan®) controlled phase IIb trial (NCT01320397) involving 320 patients (including both Caucasian and Chinese) in which a pharmacogenomics approach will be used for the first time to evaluate an antihypertensive agent.[433] Rostafuroxin **113** is targeted at newly diagnosed hypertension patients with genetic profiles consistent with adducing and EO-hypertensive mechanisms.

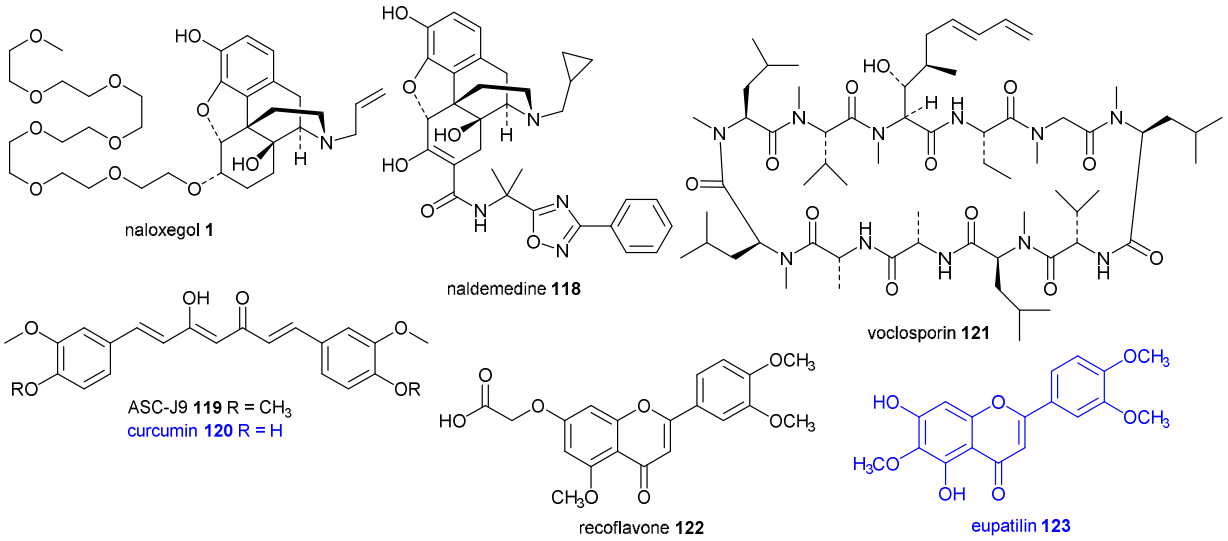
Tecarfarin **114** (ATI-5923) is a warfarin **115** analogue designed by the former ARYx Therapeutics Inc[434] to avoid the warfarin's cytochrome P450 mediated metabolism that considerably improved drug-drug interaction liabilities. A phase III trial (NCT00431782) showed tecafarin **115** was more effective than warfarin **115** in patients with a CYP2C9 genetic variant and was likely to have application where current oral



anti-coagulants cannot be used or are ineffective.[435] In March

2013 Armetheon Inc. announced a plan to develop tecafarin **114** in patient populations with CYP2C9 genetic variant prosthetic heart valves or chronic renal dysfunction but there has been no subsequent update. Warfarin **115** and tecafarin **114** are designed from the anticoagulant dicoumarol **116**, which is produced by fungal biotransformation of coumarin **117** in sweet clover,[436] and are both inhibitors of vitamin K epoxide reductase.[437]

Myolimus **118** (olcorolimus, SAR943, 32-deoxorapamycin)[438-440] is an immunosuppressant derived from sirolimus **7**. It is likely that chemical modification of sirolimus **7** to give myolimus **118** was conducted by Novartis Pharma AG in order to give analogues with improved chemical stability.[440] These compounds act through binding to FK506-binding protein 1A followed by inhibition of the mammalian target of rapamycin (mTOR) giving an antiproliferative effect. Myolimus **118** is under investigation by Elixir Medical Corporation in a phase I trial as part of a drug eluting coronary stent (NCT02086006).[441,442]



6 Compounds Undergoing Evaluation in Immunological, Inflammatory and Related Diseases

Naloxegol **1** (NKTR-118) is a morphine **9**-type pegylated-naloxol derivative co-developed by Nektar Therapeutics and AstraZeneca that has completed multiple phase III trials for the treatment of opioid-induced constipation. An NDA for naloxegol **1** was accepted in the US in November 2013[443] and an MAA in the Europe in September 2013.[444] The hepta-glycerol linkage on the naloxol limits its capacity to cross the blood–brain barrier, which minimises the pain relieving properties.[445] A comprehensive review describing pegylated drugs and drug candidates has been recently published.[446]

Naldemedine **118** (S-297,995) is a μ-opioid receptor antagonist being developed by Shionogi and is in three phase III trials for the treatment of opioid-induced constipation (NCT01965652, NCT01993940 and NCT01965158).[447,448] There is no further information available about this compound.

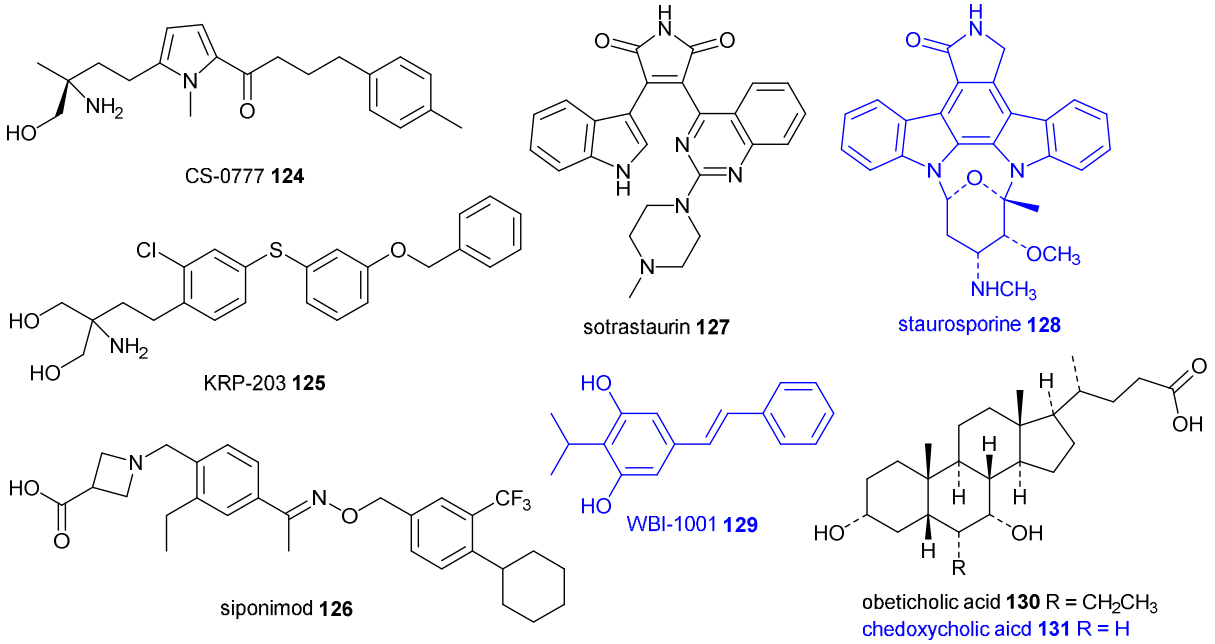
ASC-J9 **119** is a curcumin **120** derivative being developed by AndroScience Corp that successfully completed a phase IIb trial (NCT01289574) for the treatment of acne.[449] Curcumin **120** is isolated from the spice turmeric and has a variety of biological activities.[450,451] ASC-J9 **119** is an androgen receptor antagonist[452-454] that regulates the transcription of target genes that are involved in numerous physiological functions and pathological disorders, such as acne vulgaris, androgenetic alopecia, benign prostate hyperplasia and prostate cancers.[455]

Voclosporin **121** (ISA-247, R1524) is a semi-synthetic cyclosporin **81** derivative that has completed various clinical trials for renal transplantation (phase II: NCT01586845, Aurinia/Isotechnika), psoriasis (phase III: NCT00244842, NCT00258713 and NCT00408187, Aurinia/Isotechnika) and non-infectious uveitis (phase III: NCT01243983, Lux Biosciences). Aurinia Pharmaceuticals is now focusing the clinical development of voclosporin **121** towards the treatment of active lupus nephritis and a phase IIb trial is planned. An X-ray structure of voclosporin **121** binding to cyclophilin A was published in 2011.[456]

Recoflavone **122** (DA-6034) is being developed by the Dong-A Socio Holding and recently completed a phase III trial (NCT01813812) in Korea for the treatment of gastritis. Recoflavone **122** has also completed a phase II trial (NCT01670357) for the treatment of dry eye syndrome with a phase III trial in the planning stage. It has been recently proposed that **122** enhances the migration of gastric epithelial cells that could activate mTOR and S6K1 downstream of PI3K.[457] Recoflavone **122** is derived from the plant flavonoid eupatilin **123**,[458] which is the major component of a Korean traditional medicine sold since 2002 by Dong-A called Stillen®.

CS-0777 **124** is a S1P agonist being developed by Daiichi Sankyo that has completed a phase I trial (NCT00616733) for the treatment of MS.[459,460] CS-0777 **124** is an analogue of the NP-derived fingolimod **20** (Section 2), which is a prodrug that is phosphorylated *in vivo*.[461]

KRP-203 **125** is also a fingolimod **20** analogue that is being investigated in a phase I trial (NCT01830010) by Novartis Pharmaceuticals for the treatment of MS and a phase II trial (JapicCTI-132108) by Kyorin Pharmaceutical for transplantation, autoimmune diseases and inflammatory bowel disease (IBD).[462]



Siponimod **126** (BAF312) is another S1P derived from fingolimod **20** developed by Novartis that is in phase III trials (NCT01665144) for the treatment of secondary progressive MS.[463] Other S1P modulators are also in clinical development.[464,465]

Sotrastaurin **127** (AEB071) was developed by Novartis and has completed phase II trials for kidney transplantation (NCT00504543, NCT00403416 and NCT00820911), renal transplantation (NCT01064791), liver transplantation (NCT01128335), psoriasis (NCT00885196) and uveitis (NCT00615693). Sotrastaurin **127** is also being evaluated in phase I/II oncology trials for the treatment of uveal melanoma (NCT01801358) and B-Cell lymphoma (NCT01854606). Sotrastaurin **127** is a staurosporine **128**-inspired selective inhibitor PKC isotypes and displays highly efficient immunomodulator through inhibition of early T cell activation.[466-468]

WBI-1001 **129** (benvitimod) completed a phase II trial (NCT01098721) in December 2012 for the treatment of psoriasis.[469,470] WBI-1001 **129** has been shown to decrease the production of proinflammatory cytokines and migration of T cells[470] and is being developed by Stiefel (part of GSK) after being licensed from Welichem Biotech in July 2012.[471] WBI-1001 **129** was originally isolated from an insect-symbiotic bacteria *Xenorhabdus* sp.[472] and later from other bacteria including *Photorhabdus luminescens*.[473]

Obeticholic acid **130** (INT-747, 6-ECDCA) is currently being evaluated by Intercept Pharmaceuticals in a phase III trial (NCT01473524) for the treatment of primary biliary cirrhosis,[474] which is a liver autoimmune disease that causes slow and progressive destruction of the small bile ducts. Obeticholic acid **130** is an antagonist of the farnesoid X receptor (FXR)[475,476] that is derived semi-synthetically from chenodeoxycholic acid **131**, which is a naturally occurring human bile acid. Bile acids acid are endogenous ligands for the nuclear receptor FXR, which form a heterodimer with the retinoid X receptor (RXR) to regulate bile acid synthesis, transport, conjugation and excretion.[476,477]

7 Oncological Disease

7.1 Small Molecule Anticancer Agents

NPs and NP-derived compounds in clinical development for oncology are listed according to their lead compound source, plant (Table 4), microorganism (Table 5) and marine (Table 6), while ADCs are listed in Table 7. Compounds and ADCs for which clinical trials have been halted or discontinued since 2008 are listed in Supplementary Information Tables S6 and S7.

7.2 NP-Antibody Anticancer Conjugates (ADCs)

Anticancer ADCs are a combination of an antibody and a cytotoxic "warhead" that is joined via a linker with all three components very important for *in vivo* efficacy. ADCs are one of the hottest areas of cancer research and there are currently over 30 ADCs in clinical development (Table 7) with multiple recent reviews published.[586-593]

The first clinically approved ADC, gemtuzumab ozogamicin (Mylotarg®), which is a N-acetyl-γ-calicheamicin dimethyl hydrazide derivative linked through a pH-labile hydrazone moiety to a recombinant humanized IgG4 κ antibody co-developed by Wyeth and UCB Pharma, was launched in 2000 for the treatment of refractory acute myeloid leukaemia.[594] Gemtuzumab ozogamicin was withdrawn by Pfizer from the

US market in June 2010 when a clinical trial showed the drug increased patient death and added no benefit over conventional cancer therapies but is still available in Japan.[595] There is debate about whether of gemtuzumab ozogamicin should be re-introduced for a subset of patients.[596,597] More recently, two ADCs brentuximab vedotin **32** and ado-trastuzumab emtansine **43** were approved in 2011 and 2013 respectively (Section 2).

There are currently at least 33 ADCs with NP-derived "warheads" in clinical trials with ten in phase II and 23 in phase I (Table 7). The NP-derived cytotoxic "warheads" are derivatives of calicheamicin, dolastatin 10 **33** (MMAE and MMAF), maytansine **45** (DM1 and DM4), doxorubicin **159**, SN-38 (camptothecin **132**-type, irinotecan metabolite) and anthramycin **155** (SGD-1882) (Fig. 3).

8 Analysis of Natural Product-Derived Compounds in Clinical Trials

There are 100 NP-derived compounds defined in Section 1 that were undergoing clinical trials at the end of 2013, with a majority being in oncology (38, 38%, Section 7.1) and anti-infectives (26, 26%, Section 3) (Fig. 4). There were also an additional 33 ADCs that contained NP-derived cytotoxic warheads in oncology clinical trials (Section 7.2). The next largest category was Cardiovascular and Metabolic Diseases with 19 (19%, Section 5), which is largely fuelled by the phlorizin **36**-derived SGLT1 and SGLT 2 inhibitors (Table 3), Immunological, Inflammatory and Related Diseases with 11 (11%, Section 6), and Neurological 6 (6%, Section 3). Of the 100 NP-derived compounds in clinical development, 17 were in phase I, 52 in phase II, 23 in phase III and 8 were has NDA and/or MAA filed (Fig. 5). Of the 100 compounds in clinical trials, 50 (50%) are classed as NP-derived, while 19 (19%) are NPs and 31 (31%) are SS NPs (Fig. 6). The late-stage development candidates in phase III and NDA/MAA are listed in Table 8.

Table 8 NP-derived drugs in late stage clinical development (NDA or equivalent and phase III) on 31 December 2013

Compound	Classification	Disease area (Therapeutic area)
NDA or equivalent		
dalbavancin **46**	SS-NP	antibacterial (anti-infective)
oritavancin **48**	SS NP	antibacterial (anti-infective)
ipragliflozin **92**	NP-derived	Type 2 Diabetes (cardiovascular and metabolic)
luseogliflozin **93**	NP-derived	Type 2 Diabetes (cardiovascular and metabolic)
empagliflozin **94**	NP-derived	Type 2 Diabetes (cardiovascular and metabolic)
tofogliflozin **95**	NP-derived	Type 2 Diabetes (cardiovascular and metabolic)
vorapaxar **101**	NP-derived	anti-thrombotic (cardiovascular and metabolic)
naloxegol **1**	SS-NP	opioid-induced constipation (immunological, inflammatory)
Phase III		
plazomicin **50**	SS NP	antibacterial (anti-infective)
surotomycin **52**	SS NP	antibacterial (anti-infective)
solithromycin **54**	SS NP	antibacterial (anti-infective)
ceftolozane **56** / tazobactam	SS NP	antibacterial (anti-infective)
eravacycline **57**	NP-derived	antibacterial (anti-infective)
epigallocatechin gallate **85**	NP	Alzheimer's disease (neurological)
tetrodotoxin **89**	NP	pain (neurological)
ertugliflozin **96**	NP-derived	Type 2 Diabetes (cardiovascular and metabolic)
ATX-101 **107**	bile acid	submental fat reduction (cardiovascular and metabolic)
migalastat **108**	SS-NP	Fabry disease (cardiovascular and metabolic)
naldemedine **118**	NP-derived	opioid-induced constipation (immunological, inflammatory)
recoflavone **122**	NP-derived	gastritis / dye eye (immunological, inflammatory)
obeticholic acid **130**	SS-NP	biliary cirrhosis (immunological, inflammatory)
siponimod **126**	NP-derived	multiple sclerosis (immunological, inflammatory)
karenitecin **134**	SS NP	oncology
fosbretabulin **139**	SS NP	oncology
vintafolide **154**	NP-derived	oncology
zoptarelin doxorubicin **160**	SS-NP	oncology
lestaurtinib **164**	NP derived	oncology
midostaurin **165**	NP derived	oncology
tivantinib **166**	NP	oncology
plitidepsin **171**	NP	oncology
panobinostat **178**	NP-derived	oncology

Table 4 Plant-derived compounds in oncology clinical trials

Lead compound/s	Name (synonym) and references	Derivation	Mode of action	Development status (administration)	Developer
camptothecin **132**	gimatecan **133** (ST-1481)[478-481]	NP-derived	topoisomerase I	phase I (phase II completed) (oral)	Novartis/Sigma-Tau
camptothecin **132**	Karenitecin® **134** (BNP-1350)[482-484]	NP-derived	topoisomerase I	phase III (IV)	BioNumerik
camptothecin **132**	CZ48 **135**[485-487]	NP-derived	topoisomerase I	phase I (oral)	CHRISTUS Stehlin Foundation for Cancer Research
combretastatin A-1 **136**	OXi4503 **137** (combretastatin A-1 diphosphate)[488-491]	SS NP	tubulin binding	phase I/II (IV)	OXiGENE
combretastatin A-4 **138**	fosbretabulin **139** (combretastatin A-4 phosphate, Zybrestat™)[492-494]	SS NP	tubulin binding	phase II/III (IV)	OXiGENE
combretastatin-A-4 **138**	BNC105P **140**[495-497]	NP-derived	tubulin binding	phase I/II (IV)	Bionomics
curcumin **120**	curcumin **120**[450,451,498]	NP	anti-inflammatory and anti-oxidative properties	phase I/II (oral)	Various (see clinicaltrials.gov)
gossypol **141**	(-)-gossypol **141** (AT-101)[499-501]	NP	Bcl-2 inhibitor	phase I/II (oral)	Ascenta Therapeutics
genistein **142**	ME-143 (NV-143) [502]	NP-derived	NADH oxidase	phase I (completed) (IV)	MEI Pharma
genistein **142**	ME-344 (metabolite of NV-128)[502]	NP-derived		phase I (IV)	MEI Pharma
genistein **142**	genistein **142**[503]	NP	protein-tyrosine kinase inhibitor, antioxidant	phase I/II (oral)	Various (see clinicaltrials.gov)
ARQ 761	β-lapachone **143**[504]	NP-derived	NAD(P)H:quinone oxidoreductase 1	phase I (IV)	ArQule
paclitaxel **19**	ortataxel **144** (IDN-5109, BAY-59-8862) [505,506]	SS NP	tubulin stabilisation	phase II (IV)	Mario Negri Institute for Pharmacological Research (Spectrum)
paclitaxel **19**	TPI-287 **145** (ARC 100) [507,508]	SS NP	tubulin stabilisation	phase II (IV)	Cortice Biosciences (Archer Biosciences)
picropodophyllotoxin **146**	AXL1717 **146** (picropodophyllotoxin)[509,510]	NP	tubulin binding/IGF-1R inhibitor	phase I/II (oral)	Axelar AB
resveratrol **147**	resveratrol **147**[511,512]	NP	various biological activities	phase I/II (oral)	Various (see clinicaltrials.gov)
rohitukine **148**	alvocidib **149** (flavopiridol, HMR 1275) [513-516]	NP-derived	cyclin-dependent kinase inhibition	phase II (IV)	NCI (Sanofi-Aventis)
rohitukine **148**	riviciclib **150** (P276-00) [515,517,518]	NP-derived	cyclin-dependent kinase inhibition	phase I/II (IV)	Piramal Enterprises
rohitukine **148**	voruciblib **151** (P1446A) [519]	NP-derived	cyclin-dependent kinase inhibition	phase I/II (oral)	Piramal Enterprises
triptolide **152**	Minnelide™ 001 **153**[520-522]	SS NP	unknown (prodrug released by phosphatases)	phase I (IV)	Minneamrita Therapeutics
vinblastine **16** / folate	vintafolide **154** (EC145, MK-8109) [523-526]	NP-derived	transcription inhibitor	phase II/III (IV) [a]	Merck (Endocyte)

[a] In March 2014 the EMA Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for a Conditional Marketing Authorisations of vintafolide **154** for the treatment of adult patients with folate receptor-positive, platinum-resistant, ovarian cancer, in combination with pegylated liposomal doxorubicin **159**;[527]however, in May 2014 development of **154** was halte due to a lack of efficacy.

Table 5 Microorganism-derived compounds in oncology clinical trials

Lead compound/s	Name (synonym) and references	Derivation	Mode of action	Development status (administration)	Developer
Actinomycete					
anthramycin **155**	SG2000 **156** (SJG136, NSC694501)[528-530]	NP-derived	DNA minor groove binder	phase I/II (IV)	Spirogen
distamycin A **157**	brostallicin **158** (PNU-166196)[531-534]	NP-derived	DNA minor groove binder	phase II (IV)	Cell Therapeutics
doxorubicin **159**	zoptarelin doxorubicin **160** (AEZS-108)[535-538]	SS NP	topoisomerase II inhibition	phase II/III (IV)	Æterna Zentaris Inc.
doxorubicin **159**	aldoxorubicin **161** (INNO-206) [539-541]	SS NP	topoisomerase II inhibition	phase II (IV)	CytRx
epoxomicin **39**	oprozomib **162** (ONX 0912, PR-047)[542-544]	NP-derived	proteasome inhibition	phase I/II (IV)	Onyx Therapeutics
K252a **163**	lestaurtinib **164** (CEP-701, KT-5555)[545-548]	SS NP	JAK2, FLT3 and TrkA kinase inhibition	phase II/III (oral)	NCI (Teva, Cephalon)
staurosporine **128**	midostaurin **165** (PKC-412, CGP 41251, 4'-N-Benzoyl-staurosporine) [549-551]	NP-derived	FLT3 kinase inhibition	phase II/III (oral)	Novartis
staurosporine **128**	tivantinib **166** (ARQ 197) [552-555]	NP-derived	cMet kinase inhibition	phase III (oral)	Kyowa Hakko Kirin (ArQule)
marizomib **167** (salinosporamide A)	marizomib **167** (NPI-0052, salinosporamide A) [556-559]	NP	proteasome inhibition	phase I (IV)	Triphase Research and Development I Corporation (Nereus)
Myxobacteria					
tubulysin **168**/folate	EC1456 (tubulysin B hydrazide)[560]	NP-derived	tubulin polymerization inhibition	phase I (IV)	Endocyte
Fungus					
wortmannin **169**	sonolisib **170** (PX-866)[561,562]	NP-derived	PI3 kinase	phase I/II (oral)	Oncothyreon Inc.

Table 6 Marine invertebrate derived compounds in oncology clinical trials

Lead compound/s	Name (synonym) and references	Derivation	Mode of action	Development status (administration)	Developer
Ascidian					
plitidepsin **171**	plitidepsin **171** (Aplidin®)[563-566]	NP	VEGF and VEGFR1 inhibitor, G1/G2 phase cell cycle inhibitor	phase III (IV)	PharmaMar
trabectedin **172**	lurbinectedin **173** (PM-01183)[567-569]	SS NP	DNA binding	phase I/II (IV)	PharmaMar
Sponge					
PM060184 **174**	PM060184 **174**[570-572]	NP	bind to unassembled αβ-tubulin dimers	phase I (IV)	PharmaMar
psammaplin A **175** (sponge) / trichostatin A **176** (actino) / trapoxin B **177** (fungus)	panobinostat **178** (LBH-589)[a,573-576]	NP-derived	HDAC inhibition	phase II/III (oral)	Novartis
Bryozoan symbiont					
bryostatin 1 **179**	bryostatin 1 **179**[577-581]	NP	Protein kinase C inhibition	phase I/II (IV)	NCI
Nudibranch (various)					
jorumycin **180**	Zalypsis® (PM00104) **181**[569,582-584]	SS NP	DNA binding and transcriptional activity	phase II (IV)	PharmaMar

[a] The derivation of the HDAC inhibitor dacinostat **182** (LAQ-824, NVP-LAQ824)[585] was based in part on the psammaplin A **175**, trichostatin A **176** and trapoxin B **177** pharmacophores[573] and the structures of dacinostat **182** and panobinostat **178** were reported in the same publication.[574]

Table 7 Antibody-drug conjugates (ADCs) in oncology clinical trials[586-593] (part 1)

Lead compound[a] / antibody target	Name (synonym)	Development status (cancer)[b]	Developer
calicheamicin / CD22	inotuzumab ozogamicin (CMC-544)	phase II (DLBCL, aggressive NHL; ALL); was in phase III for NHL but terminated due to inadequate enrolment numbers	Pfizer
MMAE / CD79b	RG-7596 (DCDS4501A) with rituximab	phase II (DLBCL, follicular NHL)	Genentech
MMAE / CD22	pinatuzumab vedotin (RG-7593, DCDT2980S)	phase II (DLBCL, follicular NHL)	Genentech
MMAE / GPNMB	glembatumumab vedotin (CDX-011)	phase II (breast)	Celldex
DM4 (plant) / CD19	SAR-3419	phase II (DLBCL; ALL)	Sanofi
DM1 / CD56	lorvotuzumab mertansine (IMGN-901)	phase II (small-cell lung cancer, multiple myeloma)	ImmunoGen
DM4 / CD138	BT-062	phase II (multiple myeloma)	BioTest
MMAE / PSMA	PSMA-ADC	phase II (prostate, glioblastoma)	Progenics
MMAF / EGFR	ABT-414	phase I/II (glioblastoma; squamous cell tumours)	AbbVie
doxorubicin **159** / CD74	milatuzumab doxorubicin (hLL1-DOX)	phase I/II (multiple myeloma)	Immunomedics
SN-38 / TACSTD2	IMMU-132	phase I (multiple cancers)	Immunomedics
SN-38 / CEA	IMMU-130 (labetuzumab-SN-38)	phase I (colorectal)	Immunomedics
DM4 / folate receptor 1	IMGN-853	phase I (solid tumour)	ImmunoGen
DM1 / CD37	IMGN-529	phase I (NHL)	ImmunoGen
MMAE / mucin 16	RG-7458 (DMUC5754A)	phase I (ovarian, pancreatic)	Genentech
MMAE / endothelin receptor ETB	RG-7636 (DEDN6526A)	phase I (melanoma)	Genentech
MMAE /STEAP1	RG-7450 (DSTP3086S)	phase I (prostate)	Genentech
undisclosed / undisclosed	RG-7600	phase I (ovarian, pancreatic)	Genentech
undisclosed / undisclosed	RG-7598	phase I (multiple myeloma)	Genentech
undisclosed / undisclosed	RG-7599 (DNIB0600A)	phase I (non-small-cell lung, ovarian)	Genentech
MMAE / CD19	SGN-CD19A	phase I (ALL, aggressive NHL)	Seattle Genetics
MMAE / LIV-1	SGN-LIV1A	phase I (breast)	Seattle Genetics
SGD-1882 / CD33A	SGN-CD33A	phase I (acute myeloid leukaemia)	Seattle Genetics
undisclosed / tissue factor	HuMax®-TF-ADC	phase I (solid tumour)	Genmab
MMAE / SLC44A4 (AGS-5)	ASG-15ME	phase I (pancreatic, stomach)	Agensys (Astellas)

Continued on next page

Table 7 Antibody-drug conjugates (ADCs) in oncology clinical trials[586-593] (part 2)

Lead compound[a] / antibody target	Name (synonym)	Development status (cancer)[b]	Developer
MMAE / nectin 4	ASG-22ME (enfortumab vedotin)	phase I (solid tumour)	Agensys (Astellas)
MMAF / AGS-16	AGS-16C3F (AGS-16M8F)	phase I (renal cell carcinoma)	Agensys (Astellas)
MMAE / guanylyl cyclase C	MLN-0264	phase I (gastrointestinal, solid tumour)	Millennium
MMAF / 5T4	PF-06263507 (A1-mcMMAF)	phase I (neoplasms)	Pfizer
DM4 / Mucin 1	SAR-566658	phase I (solid tumour)	Sanofi
DM1/ CD70	AMG-172	phase I (renal cell carcinoma)	Amgen
DM1 / EGFRvIII	AMG-595	phase I (glioma)	Amgen
DM4 / Mesothelin	BAY-94-9343	phase I (mesothelioma)	Bayer

[a] Calicheamicin is an actinomycetes-derived, enediyne-type that binds to the minor groove of DNA causing double strand DNA breakage; MMAE (monomethylaurisatin E) and MMAF (monomethylaurisatin F) are dolastatin 10 **33** derivatives. Dolastatin 10 **33** was originally isolated form a sea hare but it is a cyanobacteria product;[41] DM1 and DM4 are maytansine **45** derivatives. Maytansine **45** was originally derived from plants but it is likely to be bacterially-derived;[42] Doxorubicin **159** is an actinomycetes-derived, clinically used anticancer agent; SN-38 is the active metabolite of irinotecan, which is an camptothecin **132**-derived anticancer drug that acts via topoisomerase I inhibition; SGD-1882 is a pyrrolobenzodiazepine (PBD) dimer structurally related to the actinomycetes-derived anthramycin **155**, which is a DNA minor groove binder.[598] [b] Diffuse large B-cell lymphoma (DLBCL), non-Hodgkin's lymphoma (NHL), Acute lymphoblastic leukaemia (ALL); chronic lymphocytic leukaemia (CLL).

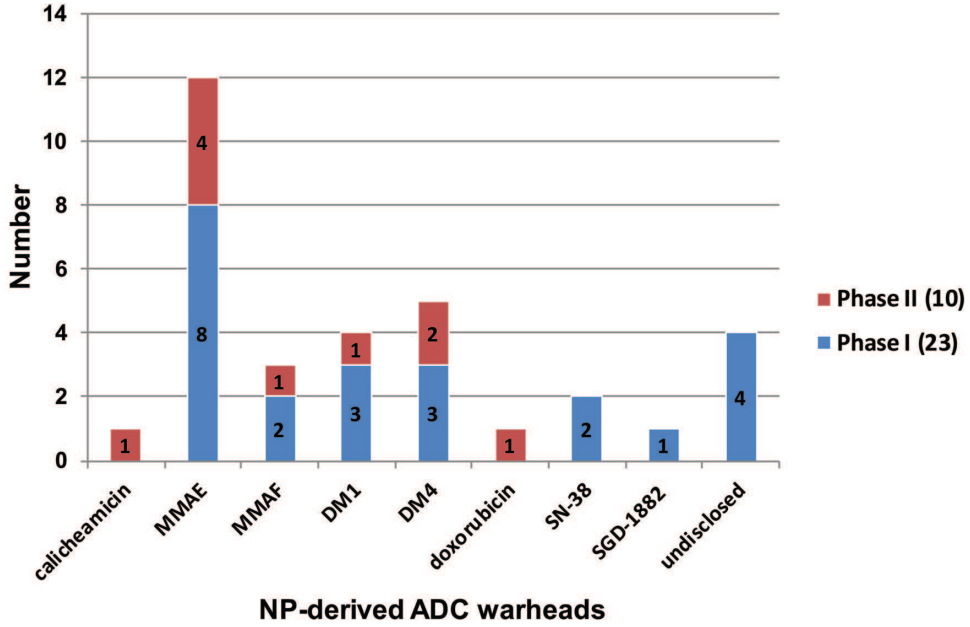
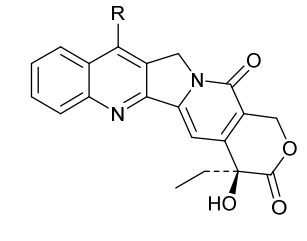
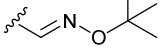
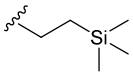
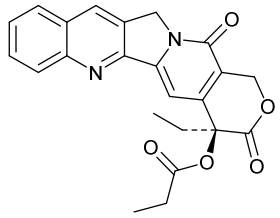


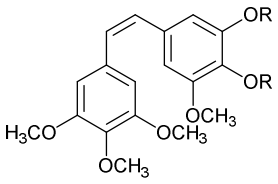
Fig. 3 NP-derived ADC cytotoxic warheads classified into NP-lead and clinical phase.

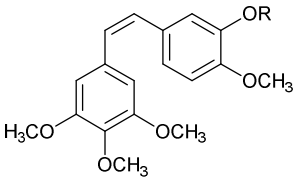

camptothecin **132** R = H

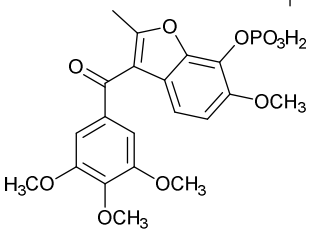
gimatecan **133** R = 

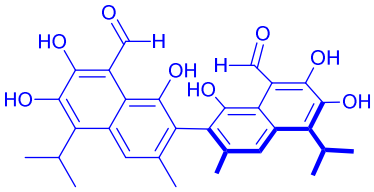
karenitecan **134** R = 

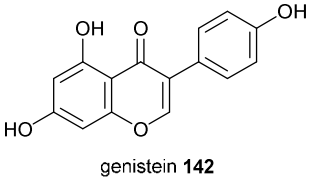

CZ48 **135**

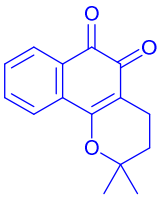

combretastatin A-1 **136** R = H
OXi4503 **137** R = PO_3Na_2

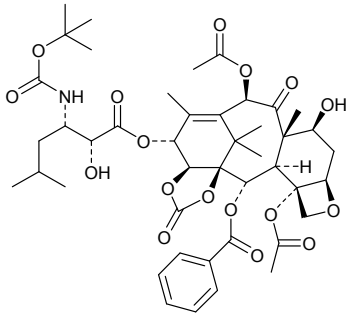

combretastatin A-4 **138** R = H
fosbretastatin **139** R = PO_3Na_2

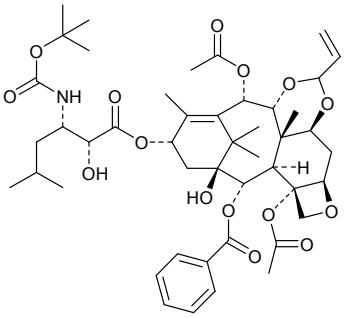

BNC105P **138**

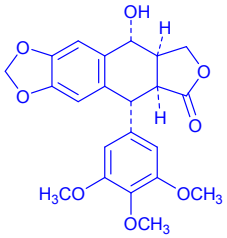

(-)-gossypol **141**

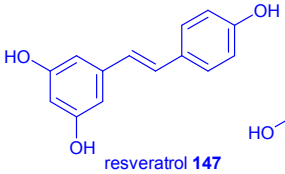

genistein **142**

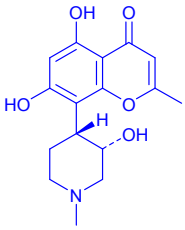

β-lapachone **143**

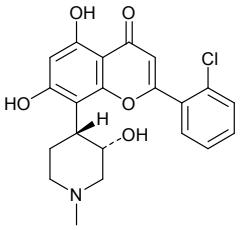

ortataxel **144**

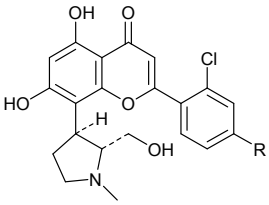

TPI-287 **145**

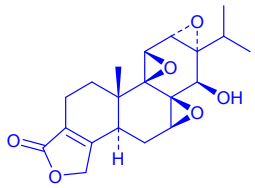

picropodophyllotoxin **146**

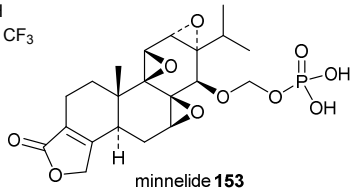

resveratrol **147**


rohitukine **148**

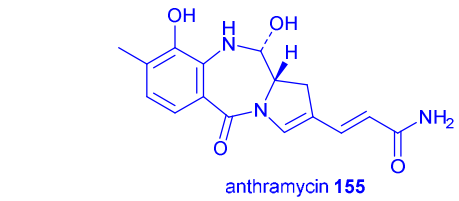

alvocidib **149**

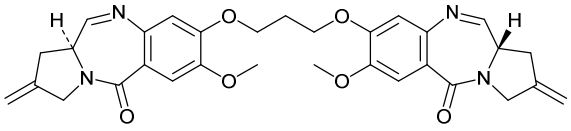

riviciclib **150** R = H
voruciblib **151** R = CF_3

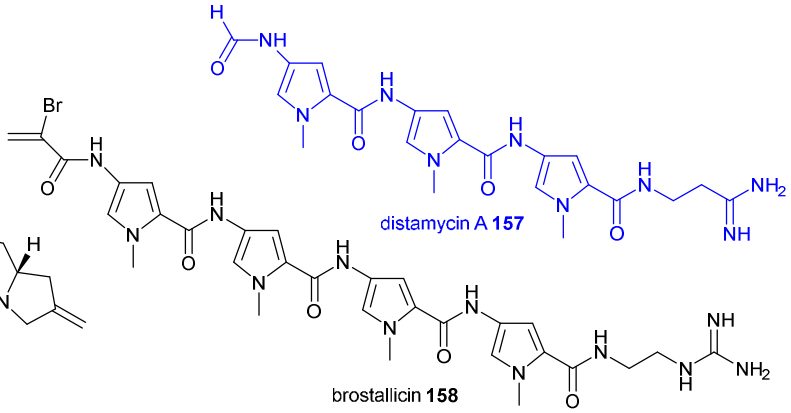

triptolide **152**


minnelide **153**

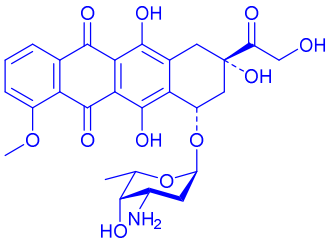
vintafolide **154**

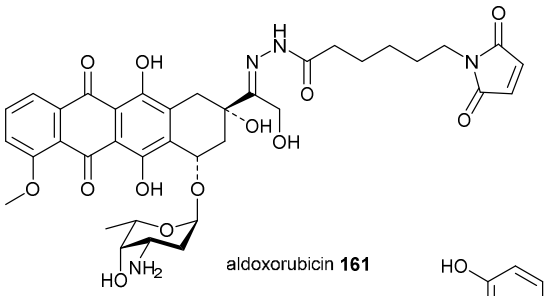

anthramycin **155**


SJG-136 **156**


distamycin A **157**

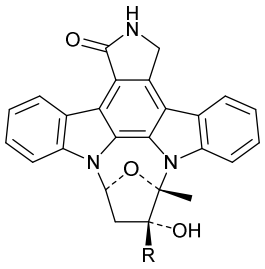
brostallicin **158**


doxorubicin **159**

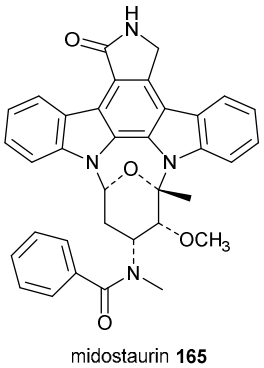

aldoxorubicin **161**

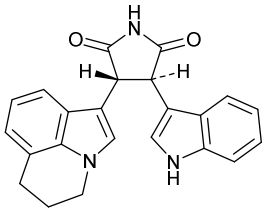
zoptarelin doxorubicin **160**

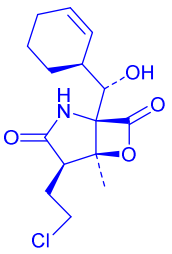
oprozomib **162**

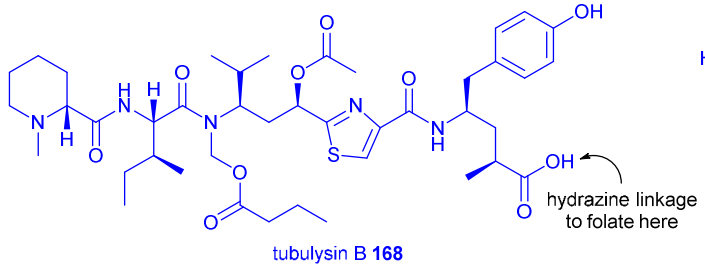

K252a **163** R = CO_2CH_3

lestaurtinib **164** R = CH_2OH

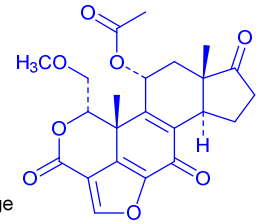

midostaurin **165**

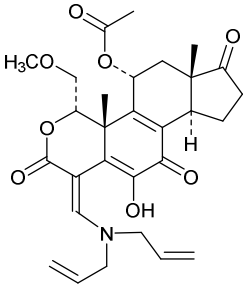

tivantinib **166**

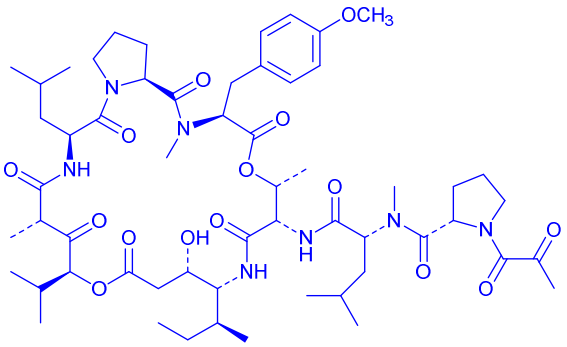

marizomib **167**


tubulysin B **168**

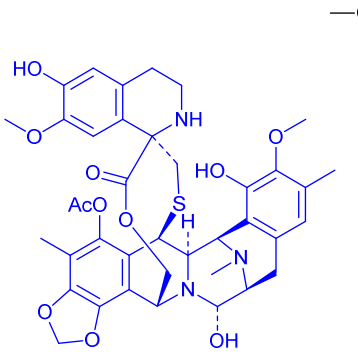
hydrazine linkage to folate here


wortmannin **169**

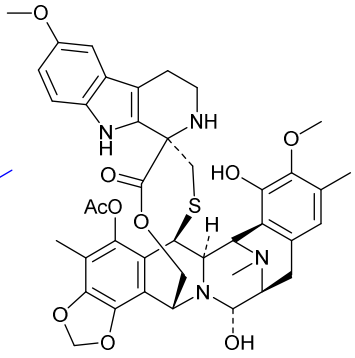

sonolisib **170**



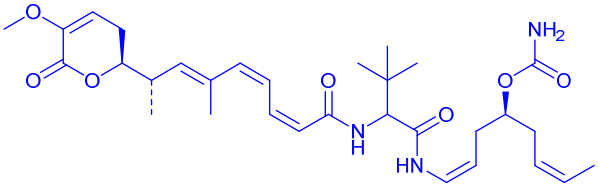
plitidepsin **171**



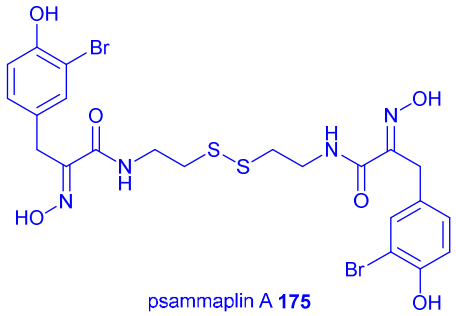
trabectedin **172**



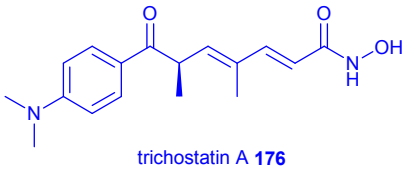
lurbinectedin **173**



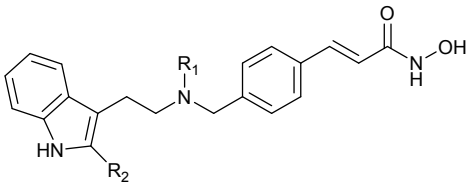
PM060184 **174**



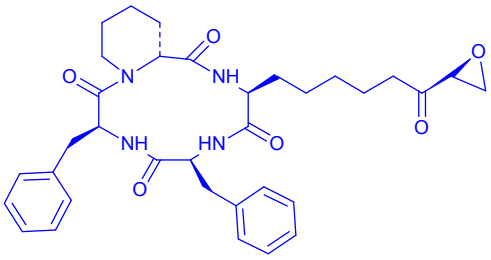
psammaplin A **175**



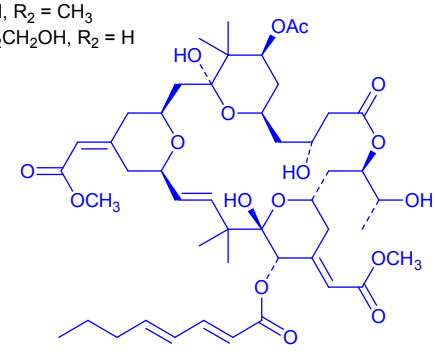
trichostatin A **176**



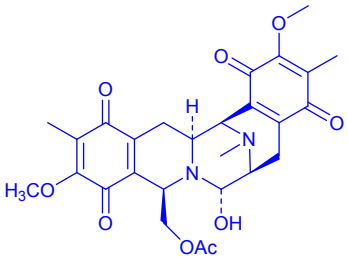
panobinostat **178** R_1 = H, R_2 = CH_3
dacinostat **182** R_1 = CH_2CH_2OH, R_2 = H



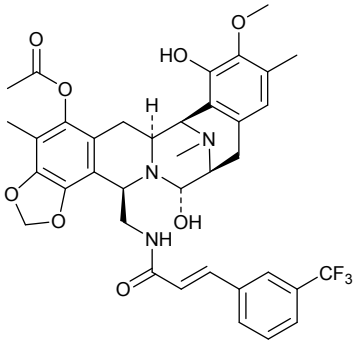
trapoxin A **177**



bryostatin 1 **179**



jorumycin **180**



PM00104 **181**

9 New Natural Product Drug Pharmacophores

In Table 9 the NP-derived drugs launched from 2000 to 2013 (Section 2, Table 1 and Supplementary Information) have been listed chronologically from the date the lead compound correct structure was first published in a journal. As expected there was a cluster of 13 lead compounds whose structures were determined from 1986 until 1995, which is quite reasonable given the usual 8-15 year timeline from lead discovery to approval. The other 11 lead compounds are from 1929 until 1980 and the drugs derived from recognition of a new biological activity or improvement of physiochemical properties required for bioavailability.

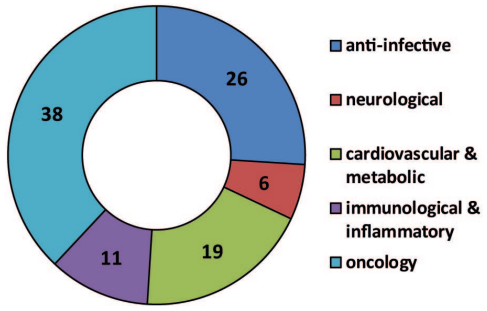


Fig. 4 Classification of the 100 NP-derived compounds in clinical development by therapeutic area.

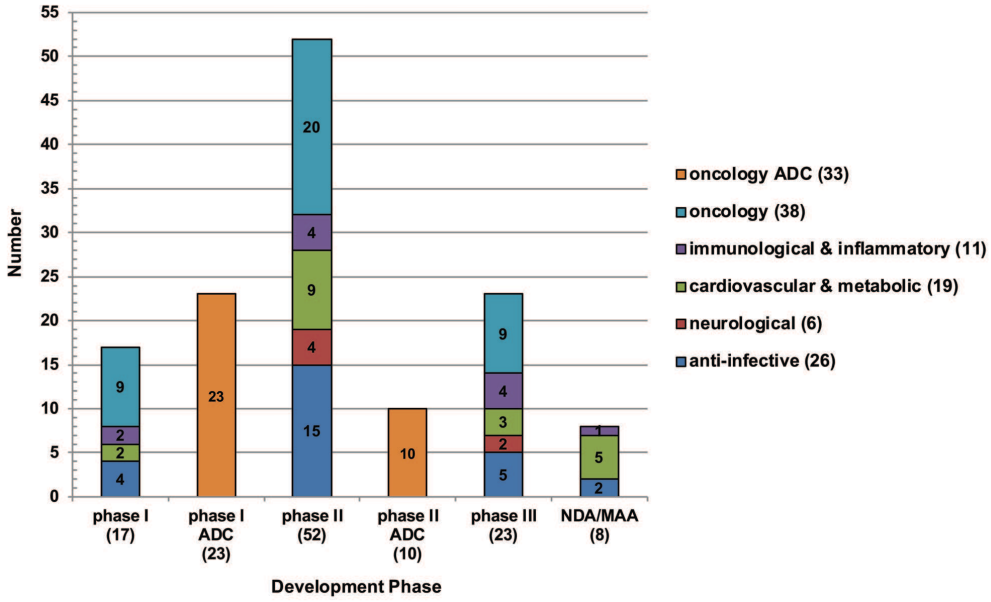


Fig. 5 NP-derived compounds and ADCs in clinical development by clinical trial development phase and therapeutic area.

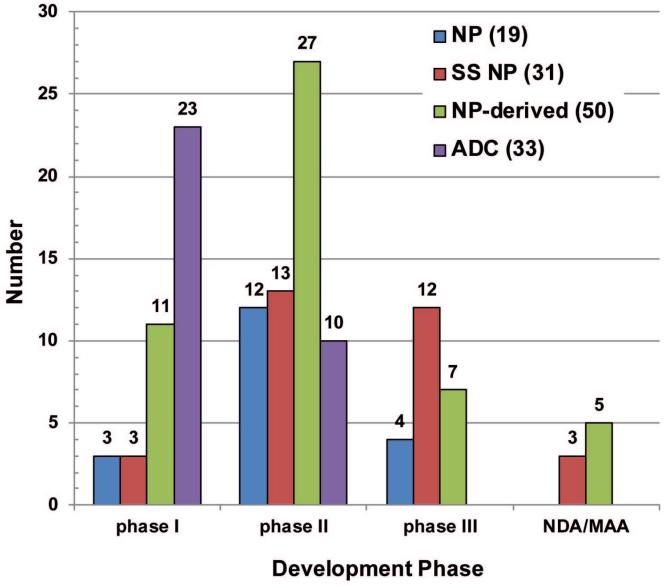


Fig. 6 NP-derived compounds and ADCs in clinical development by NP, SS NP, NP-derived and ADC classes and development phase.

The same analysis was undertaken for the NP-derived compounds with new drug pharmacophores undergoing clinical development that are not present in existing human medicines (Table 10). Alarmingly, in the last 15 years are only been five new NP- drug pharmacophores that were discovered: enfumafungin **78** (2000), tubulysin **168** (2000), marizomib **167** (2003), deoxyactagardine B **73** (2010) and PM060184 **174** (2013). Since the previous review,[11] the following new pharmacophores have been discontinued from clinical development: WAP-8294A$_2$ (antibiotic), friulimicin B (amphomycin, antibiotic), eritoran (lipid A, sepsis), E7107 (pladienolide/FD-895, oncology) and obatoclax (prodigiosin, oncology).

10 Conclusions

This review describes the 100 NP and NP-derived compounds (as defined in Section 1) and 33 ADCs with a NP warhead and their corresponding lead compounds that were being evaluated

Table 9 New human drug pharmacophores from NP-derived drugs launched from 2000-2013 by year and laboratory that the structure was first published, the lead compound and its source, the compound(s) in clinical trials and disease area

Year structure determined (Laboratory) and reference(s)	Lead (source)	Launched drugs / Compounds in clinical trials	Disease area
1929 (University of Vienna)[481,482]	phlorizin **36** (plant)	dapagliflozin **35** (2012), canagliflozin **43** (2013), ipragliflozin **92** (2014), luseogliflozin **93** (2014) / 7 others (Table 3)	Type 2 Diabetes
1938 (Auckland University College)[599]	leptospermone (plant)	nitisinone (2002)	anti-tyrosinaemia
1961 (University of Rochester)[600]	fumagillin **106** (fungus)	fumagillin **106** (2005) / beloranib **105**	anti-parasitic
1964 (Weizmann Institute of Science)[601]	dronabinol and cannabidiol (plant)	Sativex® (dronabinol and cannabidiol) (2005)	pain
1966 (Meiji Seika Kaisha)[420]	nojirimycin **111** (actino)	miglustat (2003) / migalastat **108**, duvoglustat **110**	Type 1 Gaucher disease
1970 (Northern Regional Research Laboratory, Peoria, Illinois)[167]	omacetaxine mepesuccinate **37** (plant)	omacetaxine mepesuccinate **37** (2012)	oncology
1972 (University of Virginia)[602]	maytansine **45** (bacteria/plant)[42]	ado-trastuzumab emtansine **44** (2013) / 9 ADCs (**Table 8**)	oncology
1973 (Ayest Research Laboratories)[97]	myriocin **21** (fungus)	fingolimod **20** (2010)	multiple sclerosis
1974 (Ciba-Geigy Ltd)[117]	muramyl dipeptide **26** (bacteria)	mifamurtide **25** (2010)	oncology
1980 (Pharmaceutical Science Laboratory, National Research Centre, Cairo)[148]	ingenol mebutate **34** (plant)	ingenol mebutate **34** (2012)	actinic keratosis
1986 (Keio University)[603]	halichondrin B **24** (sponge)	eribulin **23** (2010)	oncology
1987 (Arizona State University)[145]	dolastatin 10 **33** (sea hare / cyanobacteria)[41]	brentuximab vedotin **32** (2011) / 15 ADCs (Table 8)	oncology
1987 (Abbott Laboratories)[128]	fidaxomicin **29** (actino)	fidaxomicin **29** (2011)	antibacterial
1987 (Lilly Research Laboratories)[604]	daptomycin **53** (actino)	daptomycin **53** (2003) / surotomycin **52**	antibacterial
1987 (University of Utah)[605]	zirconotide (cone shell)	zirconotide (2005)	pain
1988 (Fujisawa)[606]	ascomycin (actino)	pimecrolimus (2001)	atopic dermatitis
1990 (University of Illinois)[607]	trabectedin **172** (ascidian)	trabectedin **172** (2007) / lurbinectedin **173**	oncology
1991 (Lilly and DowElanco)[136]	spinosyn (actino)	Natroba™ (spinosyn A : D 5:1 **30**:**31**) (2011)	antiparasitic
1992 (Bristol Myers Squibb)[171]	epoxomicin (actino)	carfilzomib **38** (2012) / oprozomib **162**	oncology
1992 (Solomon A. Berson Research Laboratory, New York)[608]	exenatide-4 (lizard)	exenatide (2006)	Type 2 Diabetes
1992 (Merck & Co)[609]	pneumocandin B_0 (fungus)	caspofungin (2001), micafungin (2002), anidulafungin (2006)	antifungal
1994 (Fujisawa)[73]	romidepsin **14** (bacteria)	romidepsin **14** (2009)	oncology
1995 (German Research Centre for Biotechnology (GBF))[610]	epothilone (myxo)	ixabepilone (2007)	oncology

in clinical trials at the end of 2013. 50 (50%) of the 100 compounds were classed as NP-derived, 19 (19%) were NPs and 31 (31%) were SS NPs (Fig. 6). Therefore, 50% of the compounds were the original NP or were a semi-synthetic derivative, while the remaining 50% were NP-derived. There was a spread of small molecule NP and NP-derived compounds through the different development phases (17 in phase I, 52 in phase II, 23 in phase III and 8 NDA and/or MAA filed) and 23 ADCs in phase I and 10 ADCs in phase II (Fig. 5). There were 33 compounds in last stage clinical development at the end of 2013 (Table 8) and already ipragliflozin **93** (Suglat®) and luseogliflozin **94** (Lusefi®) have been approved in Japan in January and March of 2014 respectively.[358,359] In addition, the FDA approved vorapaxar **101** (Zontivity™) for the reduction of thrombotic cardiovascular events in patients with a history of heart attack or with peripheral arterial disease in May 2014. In addition, an FDA Advisory Committee recommended the approval of dalbavancin **46** for the treatment of skin infections in March 2014.[202] Also in March 2014, the EMA CHMP issued a positive opinion for a Conditional Marketing Authorisations of vintafolide **154** for the treatment of adult patients with folate receptor-positive, platinum-resistant, ovarian cancer, in combination with pegylated liposomal doxorubicin **159**.[527]

38 of 100 NP and NP-derived compounds (Fig. 4) were being investigated as potential oncology treatments (38%, Section 7.1) with an additional 33 ADCs that contained NP-derived cytotoxic warheads in oncology clinical trials (Section 7.2). The remaining compounds were in the following therapeutic areas: 26 anti-infectives (overall 26%, 20 antibacterial, 2 antifungal, 2 antimalarial and 2 antiviral, Section 3), 19 cardiovascular and metabolic diseases (19%, Section 5), 11 inflammatory and related diseases (11%, Section 6) and 6 neurological (6%, Section 3). The increase in numbers in the metabolic diseases area is predominantly due to the phlorizin **36**-derived SGLT1 and SGLT 2 inhibitors (Table 3). These percentages reflect the traditional strength of NPs in the oncology and anti-infective therapeutic areas.

Table 10 Potentially new human drug pharmacophores from compounds currently in clinical trials listed by year and laboratory that the structure was first published, the lead compound and its source, the compound(s) in clinical trials and disease area

Year structure determined (Laboratory) and reference(s)	Lead (source)	Compound(s) in clinical trials	Disease area
1910 (Universitätslaboratorium, Bern)[611]	curcumin **120** (plant)	ASC-J9 **119**, curcumin **120**	acne, oncology
1938 (University of Illinois)[508,509]	gossypol **141** (plant)[612,613]	gossypol **141**	oncology
1942 (University of Lausanne)[510,511]	*scyllo*-inositol **84** (plant)[614,615]	*scyllo*-inositol **84**	Down syndrome
1961 (University of Sydney)[381]	himbacine **102** (plant)	vorapaxar **101**	cardiovascular
1962 (Medical Research Council, Antibiotics Research Station)[153,512]	actinonin **70** (actino)[262,616]	GSK1322322 **69**	antibacterial
1964 (Harvard University)[617]	tetrodotoxin **89** (fish, bacteria)	tetrodotoxin **89**	pain
1964 (Laboratori di Ricerche Farmitalia, Milano)[618]	distamycin A **157** (actino)	brostallicin **158**	oncology
1965 (Hoffmann-La Roche)[619]	anthramycin **155** (actino)	SG2000 **156**, SGN-CD33A (ADC)	oncology
1969 (University of Virginia)[620]	eupatilin **123** (plant)	recoflavone **122**	gastritis
1971 (Medical Academy, Krakōw)[243]	*N*-chlorotaurine **64** (human)	auriclosene **63**	antibacterial
1971 (University of Illinois)[326]	anabaseine **87** (worm)	GTS-21 **86**	schizophrenia
1972 (University of Virginia)[621]	triptolide **152** (plant)	minnelide **153**	oncology
1972 (University of Bristol)[622]	wortmannin **169**(fungus)	sonolisib **170**	oncology
1978 (Kitasato University and The Kitasato Institute)[623]	staurosporine **128** (actino)	sotrastaurin **127**, midostaurin **165**, tivantinib **166**	oncology, immunosuppression
1979 (National Institute of Arthritis and National Heart, Lung, and Blood Institute, Maryland)[513]	rohitukine **148** (plant)	alvocidib **149**, riviciclib **150**, voruciblib **151**	oncology
1980 (Fujisawa)[301]	fosmidomycin **80** (actino)	fosmidomycin **80**	antimalarial
1981 (Scripps Institution of Oceanography)[472]	WBI-1001 **129** (bacteria)	WBI-1001 **129**	psoriasis
1982 (Arizona State University)[577]	bryostatin **179** (bryozoan/ bacteria)[624]	bryostatin **179**	oncology
1983 (Kirin Breweries)[335]	spicamycin **91** (actino)	KRN5500 **90**	pain
1986 (Kyowa Hakko Kogyo Co)[545]	K252a **163** (actino)	lestaurtinib **164**	oncology
1987 (Arizona State University)[625]	combretastatin A-1 **136** (plant)	OXi4503 **137**	oncology
1989 (Arizona State University)[626]	combretastatin A-4 **138** (plant)	fosbretabulin **139**, BNC105P **140**	oncology
1991 (Lepetit Research Center)[238]	GE2270 A **62** (actino)	LFF 571 **61**	antibacterial
1996 (University of Illinois)[564]	plitidepsin **171** (ascidian, bacteria)[627]	plitidepsin **171**	oncology
2000 (Merck & Co)[175,176]	enfumafungin **78** (fungus)[285,286]	SCY-078 **76**	antifungal
2000 (German Research Centre for Biotechnology (GBF))[628]	tubulysin **168** (myxo)	EC1456	oncology
2003 (Scripps Institution of Oceanography/ UCSD)[556]	marizomib **167** (actino)	marizomib **167**	oncology
2010 (Novacta Biosystems)[271]	deoxyactagardine B **73** (actino)	NVB302 **72**	antibacterial
2013 (Pharmamar)[570]	PM060184 **174** (sponge)	PM060184 **174**	oncology

The year that the structure was first correctly assigned in the literature was used as a guide to chronological discovery of each new NP drug pharmacophores for both the drugs launched from 2000-2013 (Table 9) and the NP and NP-derived compounds in clinical trials (Table 10). 13 of the 24 lead compounds of the launched drugs with new pharmacophores has their structures first reported from 1986 until 1995, which is a reasonable timeframe given the usual 8-15 year timeline from lead discovery to approval (Table 9). The structures of the remaining 11 were first reported from 1929 until 1980 and most of these drugs arose from the identification of a new mode of action or a significant improvement of the physiochemical properties. There were 29 NP and NP-derived compounds with new drug pharmacophores and the years that structures were first published were 1910-1980 (16), 1981-1989 (6), 1991-1999 (2) and 2000-2103 (5) (Table 10). The fact there have only been five NP-drug pharmacophores, enfumafungin **78** (2000), tubulysin **168** (2000), marizomib **167** (2003), deoxyactagardine B **73** (2010) and PM060184 **174** (2013), in the last 15 years is worrying.

The short term prospect of NP and NP-derived drugs is bright with 23 in phase III trials and 8 with an NDA and/or MAA filed, which should ensure the average of 4.1 NP-derived drugs each year since 2000 is maintained at least for the next five years. The fact that 50% of 100 NP and NP-derived compounds in clinical trials are either the native NPs or SS NPs is also promising, as there is common misconception that most NP-derived drugs have only distant links to their original lead NPs. However, the lack of the discovery of NP drug pharmacophores in recent years is worrying, with only deoxyactagardine B **73** (2010) and PM060184 **174** (2013) having had their structures first reported since 2004 (Table 10). The next few years are critical for NP lead discovery and a concerted effort is required to identify new biologically active pharmacophores and bring these and existing compounds through pre-clinical drug development.

Acknowledgements

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Notes and references

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Electronic Supplementary Information (ESI) available: Table S1 NP and NP-derived launched since 2000 by year with reference to their lead compound, classification, disease area, developer, first launch company and route of administration; Tables S1 to S7 Halted or Discontinued NP-derived Compounds. See DOI: 10.1039/b000000x/

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