Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Biology

Natural product derived privileged scaffolds in drug discovery

Emma K Davison[a] and Margaret A Brimble[a,b]

The biological activity and structural diversity of natural products are unsurpassed by any available synthetic screening libraries. As such, these privileged scaffolds serve as important, biologically prevalidated platforms for the design of compound libraries in the search for new drug candidates. Recent progress has focussed on improving the potency, selectivity and pharmacokinetics of bioactive natural products through structural modification, leading to the emergence of a number of drug-like lead compounds. Here, we review recent advances in the exploitation of terpenoid, polyketide, phenylpropanoid and alkaloid natural product scaffolds for inspiration in the design and development of important new drug candidates.

Addresses
[a] School of Chemical Sciences, University of Auckland, 23 Symonds St., Auckland, New Zealand
[b] The Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland, Private Bag 92019, Auckland 1010, New Zealand

Corresponding author: Brimble, Margaret A (m.brimble@auckland.ac.nz)

Current Opinion in Chemical Biology 2019, **52**:1–8

This review comes from a themed issue on **Synthetic biomolecules**

Edited by **Johan Winne** and **Annemieke Madder**

For a complete overview see the Issue and the Editorial

Available online 22nd January 2019

https://doi.org/10.1016/j.cbpa.2018.12.007

Introduction

Natural products (NPs) are an invaluable source of inspiration in drug design and development. Having evolved over several millennia to acquire specific ligand–protein binding motifs, NP structures cover a wide range of biologically relevant chemical space that cannot be efficiently explored by synthetic compounds in commercially available screening libraries [1,2]. Several studies in the early 2000s revealed NPs favour inclusion of aliphatic over aromatic rings, as well as more sp^3-hybridised bridgehead atoms and chiral centres than synthetic small molecules [3,4]. As the clinical success of drug candidates is directly correlated to the molecules three-dimensionality [5], NPs clearly possess an advantageous structural foundation over synthetic small molecules in the development of drug candidates. However, the structural complexity, toxicity and unfavourable pharmacokinetics (PKs) often associated with NPs can limit their clinical potential, and as such, structural modification is often required [2]. To this end, many leading chemists are not only targeting bioactive NPs, but also libraries of structurally related compounds for biological evaluation. The core scaffold of NPs and their analogue libraries may, therefore, be considered 'privileged' since contemporary use of the term typically refers to multiple compounds with the same core scaffold possessing bioactivity [6]. Here, we review important advances in the use of small molecule NP-derived privileged scaffolds in drug discovery over the past two years, with focus on the biological activity, structure–activity relationships (SARs), PKs and clinical potential of the resulting lead compounds.

Terpenoid natural product scaffolds

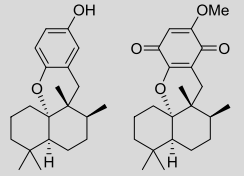
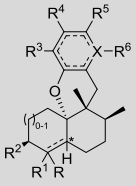
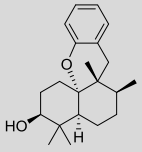
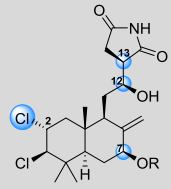
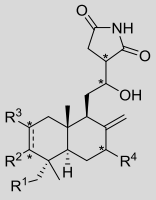
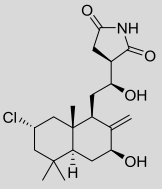
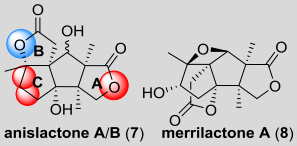
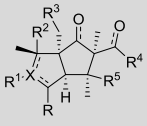
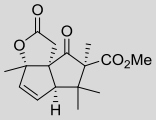
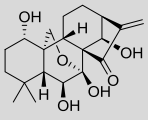
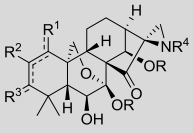
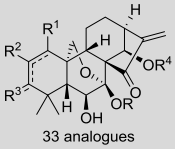
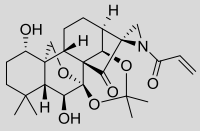
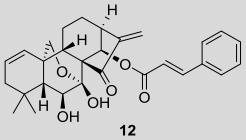
Terpenoids are the largest class of NPs, with about 60% of NP diversity originating from the terpenoid pathway of NP biosynthesis [7]. As such, extensive research has been conducted on terpenoid NP scaffolds in recent years.

The meroterpenoid NP family [represented by aureol (**1**) and smenoqualone (**2**), Table 1] have been found to exhibit antiviral, anticancer and cytotoxic activities [8•]. Thorough antibacterial and antiproliferative assays of six natural meroterpenoids and 15 synthetic analogues identified **3** as a promising lead compound [8•]. Synthetic meroterpenoid **3** exhibited potent activity against two methicillin-resistant *Staphylococcus aureus* (MRSA) strains (EC_{50} 0.2–0.6 μM), as well as antiproliferative activity against four mammalian cancer cell lines (EC_{50} 7–14 μM) [8•].

The lissoclimides and haterumaimides [represented by dichlorolissoclimide (**4**) and haterumaimide A (**5**)] are a large family of structurally related NPs isolated from ascidians of the genus *Lissoclinium*. The cytotoxic potencies of these NPs were found to range from subnanomolar (against the P388 murine leukaemia cell line) to completely inactive [9]. Vanderwal and co-workers recently prepared a library of 10 analogues by *de novo* synthesis in order to further probe the SARs of the NP scaffold [9,10•]. Perturbation of the stereochemistry at C7, C12 or C13, or removal of the C2 chlorine substituent leads to reduced cytotoxicity (**4** and **5**, blue circles) [10•], and identified natural chlorolissoclimide (**6**) as the most potent compound tested. Moreover, **6** was found to exert translational-inhibition by binding to the eukaryotic 80S ribosome (IC_{50} 0.5 μM); activity which exceeds that of the commercially available chronic myeloid leukaemia drug, Synribo [10•]. Although the natural scaffold of

Table 1

Recent advances in the use of terpenoid NPs in drug discovery [8•,10•,13,15,16]

Natural product(s)	Library scaffold	Lead compound
 **aureol** (**1**) **smenoqualone** (**2**) Source: *Smenospongia* sp. Therapeutic activity: antiviral, antibiotic and cytotoxic	 15 analogues	 **3** EC_{50} 0.2-0.6 μM (MRSA DSM 11822/RKI 11-02670)
 **dichlorolissoclimide** (**4**)[a] R = H **haterumaimide A** (**5**)[a] R = Ac Source: *Lissoclinum* sp. Therapeutic activity: cytotoxic	 10 analogues	 **chlorolissoclimide** (**6**) IC_{50} 0.06-0.49 μM (P388, A2058, DU145)
 **anislactone A/B** (**7**) **merrilactone A** (**8**) Source: *Illicium anisatum* and *I. merrillanium* Therapeutic activity: neurotropic	 15 analogues	 **9** 138% neurite outgrowth (N2a cells)
 **oridonin** (**10**) Source: *Isodon rubescens* Therapeutic activity: antineoplastic	 14 analogues  33 analogues	 **11** IC_{50} of 8-9 μM (MDA-MB-231 and MCF-7)  **12** IC_{50} of 0.08-1.0 μM (four human cancer cell lines), 70% TGI *in vivo*

[a]SARs indicated by blue (essential for bioactivity) and red (alteration enhances bioactivity) circles.

chlorolissoclimide (**6**) thus appears optimised for potent bioactivity, PK studies have yet to be conducted to investigate the clinical utility of this NP in chemotherapy.

The neurotropic sesquiterpenes anislactone A/B (**7**) and merrilactone A (**8**) were isolated from the pericarps of the trees *Illicium anisatum* and *Illicium merrillanium*, respectively [11,12]. Despite the important neuronal outgrowth capabilities of these NPs, there had been no SAR studies conducted until recently, possibly due to the lengths of the reported syntheses. Recent *de novo* synthesis and biological profiling of 15 analogues identified several compounds that were capable of exerting neurotropic activity comparable to that of the NPs, despite being significantly structurally simplified [13]. SAR analysis of the library showed that ring opening of lactone A or olefin

insertion in ring C enhanced neurite outgrowth (**7**, red circles), while ring opening of lactone B leads to reduced bioactivity (**7**, blue circles) [13]. Lactone **9** exhibited the most potent activity, causing 138% relative neurite outgrowth of N2a cells, making it a promising, synthetically accessible lead in the development of drugs for the treatment of Parkinson's and Alzheimer's diseases [13].

Oridonin (**10**), an *ent*-kaurene diterpenoid, was isolated from the herb *Isodon rubescens* which is commonly used in Chinese traditional medicine. With an impressive biological profile (anticancer, anti-inflammatory, antimicrobial and neuroprotective activities) [14], oridononin (**10**) has attracted a great deal of attention in recent years. Although unfavourable toxicity and PKs have hampered the advancement of natural **10** into clinical trials [14], the alanine ester prodrug of oridonin was advanced to Phase I clinical trials in 2014 for the treatment of acute myeloid leukemia [14], and numerous recent studies have identified potent drug-like oridonin analogues targeting various diseases [15–23]. Notably, oridonin-derived aziridine **11** was recently identified as potential anticancer drug candidate due to *in vivo* suppression of triple-negative breast cancer xenograft growth and development of lung metastasis, in conjunction with significantly reduced toxicity to normal human mammary epithelial cells as compared to oridonin (**10**) [15,24]. Trans-cinnamic acid derivative **12** was also recently identified as a potent cytotoxin in a screen of 33 oridonin-derived analogues, and displayed pronounced *in vivo* efficacy [70% tumour growth inhibition (TGI)] in an MCF-7 breast cancer xenograft mice model, with no notable toxicity [16].

Polyketide natural product scaffolds

The polyketide class of NPs has great pharmaceutical value, with sales totalling about $10 billion annually [7]. In recent years, K. C. Nicolaou has made remarkable strides in the design of several polyketide NP-derived payloads for antibody drug conjugates (ADCs).

The trioxacarcins [represented by trioxacarcin A (**13**), Table 2] are a family of naturally occurring DNA alkylating agents that possess potent antitumour, antibiotic and antimalarial activity [25]. The impressive biological profiles of the trioxacarcins inspired the *de novo* syntheses of a range of structurally simplified cytotoxic analogues, of which, **14** exhibited the most potent activity against all three cancer lines tested (IC_{50} 0.4–0.6 nM) [26••]. The cytotoxic activity of **14** surpassed that of all five NPs tested, especially against the multi-drug-resistant cell line MES SA DX, making it a valuable lead compound for further optimisation or as a payload for ADCs [26••].

Uncialamycin (**15**) is a natural enediyne antibiotic, possessing extremely high potency against a wide array of both Gram-positive and Gram-negative bacteria, as well as equally impressive picomolar cytotoxic activities against an array of human cancer cell lines [27]. A number of analogues of **15** were prepared by *de novo* synthesis, with masked amino groups acting as handles for the attachment of antibodies (via a linker), so they could be investigated as payloads for ADCs [28••]. Methylamine analogue **16** was found to be 100-fold more potent than uncialamycin (**15**), exhibiting low picomolar activity against four tumour cell lines [28••]. The remarkable potency of **16** was attributed to the aminomethyl group enhancing the rate of Bergman cycloaromatisation and hence DNA cleavage [28••]. As envisaged, several of these analogues were advanced into ADCs which are under further investigation as targeted cancer therapies [29].

The thailanstatins and spliceostatins [represented by thailanstatin A (**17**)] are a family of spliceosome modulating NPs with powerful antiproliferative activities [30]. An impressive article by Nicolaou *et al.* recently detailed the total syntheses of four of these NPs along with the *de novo* syntheses of 48 analogues [31••]. The cytotoxic evaluation of this library, and the resulting SARs were also reported [31••]. A number of these analogues exhibited extremely potent cytotoxicity, with **18** demonstrating the highest average potency across all three cancer cell lines (IC_{50} 0.003–0.14 nM) [31••]. SAR studies indicated that the epoxide motif, a saturated C12–C13 bond and the (1*S*)-configuration, (3*S*)-configuration and (12*S*)-configuration of thailanstatin A were essential for maintaining potent cytotoxicity (**17**, blue circles). Esterification of the carboxylic acid or replacement with a lipophilic group leads to enhanced potencies, and replacement of the C4′ acetate with carbamate, urea or amide functionalities were either tolerated or enhanced bioactivity (**17**, red circles) [31••]. These findings indicate that further refinement of the leading thailanstatin analogues could provide potent clinical anticancer drug candidates and/or payloads for ADCs.

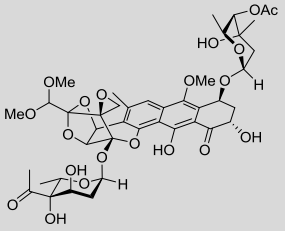
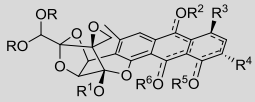
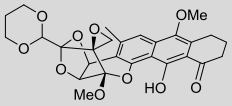
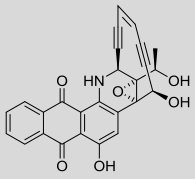
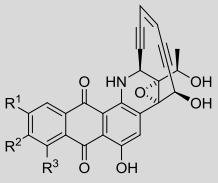
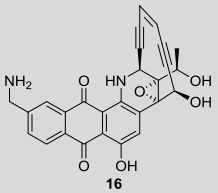
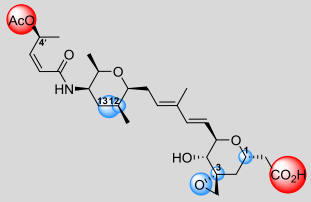
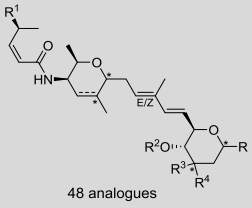
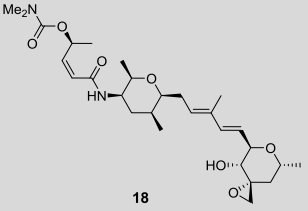
Phenylpropanoid natural product scaffolds

The phenylpropanoids are a diverse class of plant-derived NPs [7]. Isodaphnetin (**19**, Table 3), a phenylpropanoid NP inhibitor of dipeptidyl peptidase-4 (DDP-4) enzyme (IC_{50} 14 μM), recently served as inspiration for the rational *in silico* design of a library of 27 analogues [32•]. *De novo* synthesis and biological testing of this analogue library identified **20** as a lead compound, with ~7400-fold improvement in potency [32•]. The good oral bioavailability of analogue **20**, combined with sustained pharmacodynamic effect (>80% plasma DPP-4 inhibition over 24 hours) and excellent performance in the oral glucose tolerance test [32•] suggest **20** is an outstanding candidate as a long-acting oral-hypoglycemic antidiabetic agent.

Bifidenone (**21**), a tubulin polymerisation inhibitor, was recently isolated from the leaves of *Beilschmiedia* sp. and

Table 2

Recent advances in the use of polyketide NPs in drug discovery [26••,28••,31••]

Natural product(s)	Library scaffold	Lead compound
 **trioxacarcin A (13)** Source: *Streptomyces* sp. Therapeutic activity: antitumour	 33 analogues	 **14** IC_{50} 0.4-0.6 nM (MES SA, MES SA DX and HEK 293T)
 **uncialamycin (15)** Source: Streptomycete Therapeutic activity: antitumour, antibiotic	 18 analogues	 **16** IC_{50} 12-66 pM (H226, N87, OVCAR3, Adr)
 **thailanstatin A (17)**[a] Source: *Burkholderia thailandensis* Therapeutic activity: antiproliferative	 48 analogues	 **18** IC_{50} 0.003-0.14 nM (MES SA, MES SA DX, HEK 293T)

[a]SARs indicated by blue (essential for bioactivity) and red (alteration enhances bioactivity) circles.

exhibited submicromolar antiproliferative activity against a panel of human tumour cell lines [33]. A library of 42 analogues were synthesised *de novo* in an attempt to improve the potency and PKs of bifidenone (**21**) [34•]. SAR analysis of the analogues indicated the C9 methyl group and the C6 stereochemistry were important for activity (**21**, blue circles) [34•]. The C14 methoxy substituent was found to be critical for potency (**21**, blue circle); however, replacement of the C13 methoxy group leads to enhanced bioactivities (**21**, red circle) [34•]. Fluorine substitution on the aromatic ring successfully enhanced both potency and bioavailability of several analogues [34•]. Analogue **22** was selected as a lead compound after it was found to demonstrate superior PK activities, as well as potent *in vitro* activity (IC_{50} 5–60 nM) against a panel of 50 human cancer lines, including 7 taxane-resistant cell lines [34•]. Significant TGI (>60%) was also effected by **22** *in vivo*, indicating **22** has potential as a clinical candidate for taxane-resistant cancer [34•].

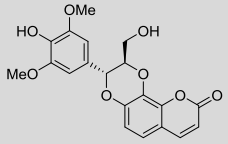
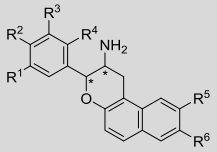
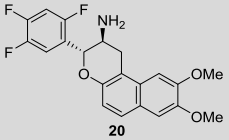
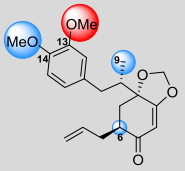
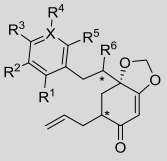
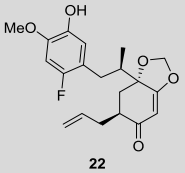
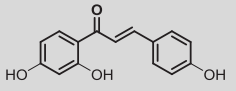
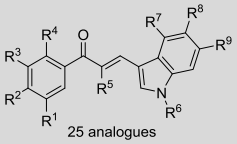
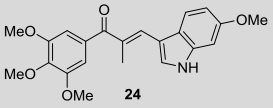
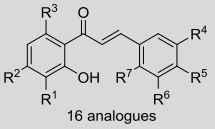
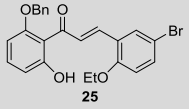
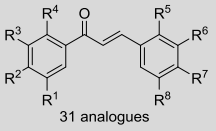
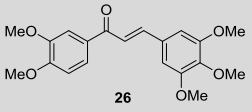
Chalcone is the privileged scaffold of a vast number of NPs, such as isoliquiritigenin (**23**, chalcone scaffold in bold), with an extensive range of biological properties, including anticancer, anti-inflammatory, antibacterial, antidiabetic, antioxidant, antiviral and antimicrobial activities [35]. This privileged scaffold has been used in the recent development of several lead compounds with impressive biological activities, such as anticancer indole-chalcone **24** [36], anti-HIV chalcone **25** [37], and anti-inflammatory pentamethoxychalcone **26** [38].

Alkaloid natural product scaffolds

Despite being the smallest NP class, the alkaloids are of great interest in drug discovery due to the importance of several commercially available alkaloids such as morphine, vincristine, codeine, atropine and quinine [7]. Quinine (**27**, Table 4) belongs to a family of cinchona alkaloids which collectively possess a diverse range of biological activities. A library of ring-distorted cinchonine derivatives were recently prepared from several cinchona

Table 3

Recent advances in the use of phenylpropanoid NPs in drug discovery [32•,34•,36–38]

Natural product(s)	Library scaffold	Lead compound
 **isodaphnetin** (**19**) Source: *Daphne odora* Thunb. var. *marginata* Therapeutic activity: DPP-4 inhibitor	 27 analogues	 **20** IC_{50} 2 nM (DPP-4), *in vivo* hypoglycemic activity
 **bifidenone** (**21**)[a] Source: *Beilschmiedia* sp. Therapeutic activity: antiproliferative	 42 analogues	 **22** IC_{50} 5-60 nM (50 human cancer cell lines), >60% TGI *in vivo*
 **isoliquiritigenin** (**23**) (a chalcone) Source: *Glycyrrhiza glabra* Therapeutic activity: anticancer, antioxidant, anti-inflammation	 25 analogues	 **24** IC_{50} 3-9 nM (13 human cancer cell lines), >66% TGI *in vivo*
	 16 analogues	 **25** 92% inhibition of HIV[b] propagation by host PM1 cells
	 31 analogues	 **26** IC_{50} 2-4 μM (inhibition of TNF-α and IL-6 production *in vitro*), *in vivo* protection against ALI[c]

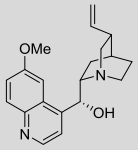
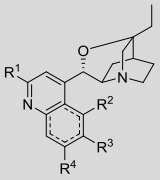
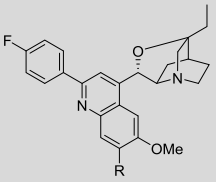
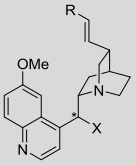
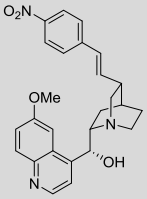
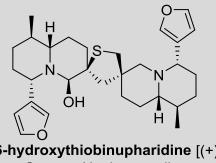
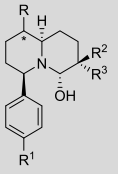
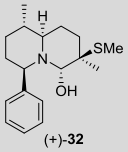
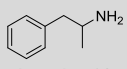
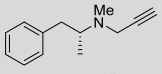
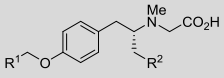
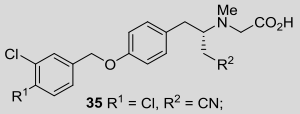
[a]SARs indicated by blue (essential for bioactivity) and red (alteration enhances bioactivity) circles.
[b]Human immunodeficiency virus-1.
[c]Acute lung injury.

alkaloids, and were investigated for their ability to inhibit autophagy induced by amino acid starvation [39]. Oxazatwistanes **28** and **29** both exhibited submicromolar activity by inhibiting both autophagosome biogenesis and maturation; bioactivity which was not shared by the parent NPs [39]. A number of phenyl substituted quinine derivatives were also recently found to exert trypanocidal activity against *Trypanosoma cruzi*, the protozoan responsible for Chagas disease [40]. The most potent derivative, **30**, exhibited an 83-fold increase in potency against intracellular *T. cruzi* amastigotes compared to quinine (**27**), and a threefold increase compared to benznidazole, the current treatment for Chagas disease [40]. Although **30** appears to hold valuable potential for treatment of this neglected tropical disease, the scaffold will likely require further modification to reduce cytotoxicity against host cells.

The dimeric nuphar alkaloids, such as (+)-**31**, were isolated from the yellow water lily, *Nuphar pumilum* and possess a broad biological profile, exhibiting antifungal, antibacterial, immunosuppressant and cytotoxic activities [41,42]. The recent *de novo* synthesis of a collection of truncated monomeric analogues showed that the rapid and potent apoptotic activity of naturally occurring (+)-**31** could be enhanced up to eightfold [for (+)-**32**] despite the

Table 4

Recent advances in the use of alkaloid NPs in drug discovery [39,40,42,43,46•]

Natural product(s)	Library scaffold	Lead compound(s)
 **quinine (27)** Source: *Cinchona officinalis* Therapeutic activity: antimalarial agent	 42 analogues	 **28** R = H; **29** R = CF_3 IC_{50} 0.5-0.7 μM (autophagy inhibition in MCF7-LC3 cells)
	 10 analogues	 **30** IC_{50} 1 μM (*T. cruzi* amastigote)
 **(+)-6-hydroxythiobinupharidine [(+)-31]** Source: *Nuphar pumilum* Therapeutic activity: cytotoxic	 29 analogues	 (+)-**32** Rapid apoptosis of human U937 cells (50% PARP[a] cleavage at 1.25 μM within 2 h)
 **amphetamine (34)** Source: *Vachellia rigidula* Therapeutic activity: CNS stimulant  [deprenyl (**33**)] Source: synthetic drug Therapeutic activity: MAO-B inhibitor	 25 analogues	 **35** R^1 = Cl, R^2 = CN; **36** R^1 = H, R^2 = H IC_{50} 0.21-0.26 μM (MAO-B selective *in vivo*), low BBB permeability

[a]Poly(ADP-ribose) polymerase.

drastic structural simplification [42,43]. Synthetically accessible monomeric quinolizidine (+)-**32** thus appears to be an excellent platform for further investigation as a potential cancer chemotherapeutic agent.

Deprenyl (**33**), a clinically available monoamine oxidase-B (MAO-B) selective inhibitor, is a synthetic analogue of the naturally occurring central nervous system (CNS) stimulant, amphetamine (**34**) [44,45]. Recently, the scaffold of **33** and **34** was employed in the *in silico* design and synthesis of a number of polar derivatives, with the aim of minimising blood–brain barrier (BBB) penetration to target MAO-B inhibition in peripheral tissues [46•]. *In vitro* testing identified four potent and selective MAO-B inhibitors (IC_{50} 0.20–0.26 μM), which all performed well in stability assays, and demonstrated good *in vivo* bioavailability and significantly reduced BBB permeability [46•]. Of these, two lead compounds, **35** and **36**, were chosen (based on selectivity for MAO-B over MAO-A, and lowest maximum brain concentrations *in vivo*) for future evaluation in the management of non-CNS inflammatory diseases [46•].

Conclusions and outlook

NPs and their privileged scaffolds continue to serve as valuable sources of inspiration in the design of novel drugs. The structural complexity of NPs makes their syntheses inherently challenging, and as such, NP analogue libraries are significantly smaller than commercial libraries. However, as NPs are structurally fine-tuned by nature for optimum bioactivity, often only minor structural perturbations are necessary to optimise drugability; thus, commercial sized libraries of NP derivatives are somewhat superfluous.

NP libraries are more frequently prepared by *de novo* synthesis (as opposed to semisynthesis), owing to the greater efficiency of divergent syntheses, and, therefore, greater structural variation allowed for using this method. Functionalisation of key late-stage synthetic intermediates, assembly line synthesis and protecting group-free strategies are becoming crucial in strategising concise synthetic routes to complex organic molecules. However, these methodologies, along with the associated time and funding investments largely constrain this research area to academia, which is unlikely to change in the foreseeable future. As such, considerable development in the efficiency, scalability and even automation of synthetic routes to NPs is needed before these undervalued drug leads can be fully exploited. Nevertheless, many leading research groups are increasingly choosing to prepare NP analogues alongside the NP target, which is pivotal in the development of new NP-derived drugs, and is expected to be the new gold standard of NP chemistry.

Recent focus has primarily been on the development of anticancer drug leads (>50% of lead compounds discussed herein), with the development of several polyketide NP-derived payloads for ADCs holding particular promise in cancer therapy [26••,28••,31••]. However, NPs also hold historical importance as lead scaffolds for novel antibiotics, and as such, these platforms are expected to become increasingly important with the decline of industrial antibiotic development and the growth of antibiotic resistance. The diversity of NP bioactivity has also offered unique groundwork for the design of drugs targeting other important diseases, as exemplified by the recent development of structurally simplified, potent and drug-like lead compounds derived from terpenoid, phenylpropanoid and alkaloid NPs.

Conflict of interest statement

Nothing declared.

Acknowledgement

We sincerely thank the Maurice Wilkins Centre for Molecular Biodiscovery for financial support.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Lachance H, Wetzel S, Kumar K, Waldmann H: **Charting, navigating, and populating natural product chemical space for drug discovery**. *J Med Chem* 2012, **55**:5989-6001.

2. Gerry CJ, Schreiber SL: **Chemical probes and drug leads from advances in synthetic planning and methodology**. *Nat Rev Drug Discov* 2018, **17**:333-352.

3. Henkel T, Brunne RM, Müller H, Reichel F: **Statistical investigation into the structural complementarity of natural products and synthetic compounds**. *Angew Chem Int Ed* 1999, **38**:643-647.

4. Lee ML, Schneider G: **Scaffold architecture and pharmacophoric properties of natural products and trade drugs: application in the design of natural product-based combinatorial libraries**. *J Comb Chem* 2001, **3**:284-289.

5. Lovering F, Bikker J, Humblet C: **Escape from flatland: increasing saturation as an approach to improving clinical success**. *J Med Chem* 2009, **52**:6752-6756.

6. Welsch ME, Snyder SA, Stockwell BR: **Privileged scaffolds for library design and drug discovery**. *Curr Opin Chem Biol* 2010, **14**:347-361.

7. Firn R: *Nature's Chemicals: The Natural Products That Shaped Our World*. Oxford University Press; 2009.

8. • Wildermuth R, Speck K, Haut FL, Mayer P, Karge B, Brönstrup M, Magauer T: **A modular synthesis of tetracyclic meroterpenoid antibiotics**. *Nat Commun* 2017, **8**:2083.
The authors developed a robust modular synthetic route to the meroterpenoids thus enabling the first comprehensive biological profiling of the natural products along with a number of synthetic analogues. This culminated in the identification of a simplified synthetic analogue with enhanced potency against MRSA.

9. Uddin J, Ueda K, Siwu ERO, Kita M, Uemura D: **Cytotoxic labdane alkaloids from an ascidian *Lissoclinum* sp.: isolation, structure elucidation, and structure–activity relationship**. *Bioorg Med Chem* 2006, **14**:6954-6961.

10. • Könst ZA, Szklarski AR, Pellegrino S, Michalak SE, Meyer M, Zanette C, Cencic R, Nam S, Voora VK, Horne DA *et al.*: **Synthesis facilitates an understanding of the structural basis for translation inhibition by the lissoclimides**. *Nat Chem* 2017, **9**:1140-1149.
Synthesis of natural and synthetic lissoclimides enabled greater understanding of the SARs for this family of translation inhibitors. The structural basis for inhibition of protein synthesis was also uncovered by co-crystallisation of synthetic chlorolissoclimide bound to the eukaryotic 80S ribosome.

11. Kouno I, Mori K, Kawano N, Sato S: **Structure of anislactone A, a new skeletal type of sesquiterpene from the pericarps of *Illicium anisatum***. *Tetrahedron Lett* 1989, **30**:7451-7452.

12. Huang J, Yokoyama R, Yang C, Fukuyama Y: **Merrilactone A, a novel neurotrophic sesquiterpene dilactone from *Illicium merrillianum***. *Tetrahedron Lett* 2000, **41**:6111-6114.

13. Richers J, Pöthig A, Herdtweck E, Sippel C, Hausch F, Tiefenbacher K: **Synthesis and neurotrophic activity studies of *Illicium* sesquiterpene natural product analogues**. *Chem—Eur J* 2017, **23**:3178-3183.

14. Xu J, Wold EA, Ding Y, Shen Q, Zhou J: **Therapeutic potential of oridonin and its analogs: from anticancer and antiinflammation to neuroprotection**. *Molecules* 2018, **23**:474.

15. Ding Y, Li D, Ding C, Wang P, Liu Z, Wold EA, Ye N, Chen H, White MA, Shen Q, Zhou J: **Regio- and stereospecific synthesis of oridonin D-ring aziridinated analogues for the treatment of triple-negative breast cancer via mediated irreversible covalent warheads**. *J Med Chem* 2018, **61**:2737-2752.

16. Xu S, Yao H, Luo S, Zhang YK, Yang DH, Li D, Wang G, Hu M, Qiu Y, Wu X *et al.*: **A novel potent anticancer compound optimized from a natural oridonin scaffold induces apoptosis and cell cycle arrest through the mitochondrial pathway**. *J Med Chem* 2017, **60**:1449-1468.

17. Wu J, Ding Y, Chen CH, Zhou Z, Ding C, Chen H, Zhou J, Chen C: **A new oridonin analog suppresses triple-negative breast cancer cells and tumor growth via the induction of death receptor 5**. *Cancer Lett* 2016, **380**:393-402.

18. Chen W, Zhou J, Wu K, Huang J, Ding Y, Yun EJ, Wang B, Ding C, Hernandez E, Santoyo J *et al.*: **Targeting XBP1-mediated β-catenin expression associated with bladder cancer with newly synthetic oridonin analogues**. *Oncotarget* 2016, **7**:56842-56854.

19. Xu S, Wang G, Lin Y, Zhang Y, Pei L, Yao H, Hu M, Qiu Y, Huang Z, Zhang Y, Zu J: **Novel anticancer oridonin derivatives possessing a diazen-1-ium-1,2-diolate nitric oxide donor moiety: design, synthesis, biological evaluation**

and nitric oxide release studies. *Bioorg Med Chem Lett* 2016, **26**:2795-2800.

20. Li D, Han T, Xu S, Zhou T, Tian K, Hu X, Cheng K, Li Z, Hua H, Xu J *et al.*: **Antitumor and antibacterial derivatives of oridonin: a main composition of Dong-Ling-Cao**. *Molecules* 2016, **21**:575.

21. Xu S, Yao H, Pei L, Hu M, Li D, Qiu Y, Wang G, Wu L, Yao H, Zhu Z, Xu J: **Design, synthesis, and biological evaluation of NAD(P)H: quinone oxidoreductase (NQO1)-targeted oridonin prodrugs possessing indolequinone moiety for hypoxia-selective activation**. *Eur J Med Chem* 2017, **132**:310-321.

22. Shen QK, Chen ZA, Zhang HJ, Li JL, Liu CF, Gong GH, Quan ZS: **Design and synthesis of novel oridonin analogues as potent anticancer agents**. *J Enzyme Inhib Med Chem* 2018, **33**:324-333.

23. Cummins CB, Wang X, Xu J, Hughes BD, Ding Y, Chen H, Zhou J, Radhakrishnan RS: **Antifibrosis effect of novel oridonin analog CYD0618 via suppression of the NF-κB pathway**. *J Surg Res* 2018, **232**:283-292.

24. Li D, Wang H, Ding Y, Zhang Z, Zheng Z, Dong J, Kim H, Meng X, Zhou Q, Zhou J, Fang L, Shen Q: **Targeting the NRF-2/RHOA/ROCK signaling pathway with a novel aziridonin, YD0514, to suppress breast cancer progression and lung metastasis**. *Cancer Lett* 2018, **424**:97-108.

25. Pfoh R, Laatsch H, Sheldrick GM: **Crystal structure of trioxacarcin A covalently bound to DNA**. *Nucleic Acids Res* 2008, **36**:3508-3514.

26. •• Nicolaou KC, Chen P, Zhu S, Cai Q, Erande RD, Li R, Sun H, Pulukuri KK, Rigol S, Aujay M, Sandoval J, Gavrilyuk J: **Streamlined total synthesis of trioxacarcins and its application to the design, synthesis, and biological evaluation of analogues thereof. Discovery of simpler designed and potent trioxacarcin analogues**. *J Am Chem Soc* 2017, **139**:15467-15478.

An array of structurally simplified trioxacarcin analogues were prepared in a streamlined synthesis, leading to the identification of a lead compound with potent cytotoxicity as a potential payload for ADCs.

27. Nicolaou KC, Chen JS, Zhang H, Montero A: **Asymmetric synthesis and biological properties of uncialamycin and 26-epi-uncialamycin**. *Angew Chem* 2008, **120**:191-195.

28. •• Nicolaou KC, Wang Y, Lu M, Mandal D, Pattanayak MR, Yu R, Shah AA, Chen JS, Zhang H, Crawford JJ *et al.*: **Streamlined total synthesis of uncialamycin and its application to the synthesis of designed analogues for biological investigations**. *J Am Chem Soc* 2016, **138**:8235-8246.

The uncialamycin analogues prepared in this paper exhibited impressive potencies (low picomolar) against several cancer cell lines. Subsequent preparation and development of ADCs using these devised payloads [29] lends evidence to support the value of these compounds in the design of novel cancer chemotherapies.

29. Nicolaou KC, Lu M, Gangwar S, Chowdari NS, Poudel YB: *Derivatives of Uncialamycin, Methods of Synthesis and their use as Antitumor Agents*. . US20180065976, March 8 2018.

30. Liu X, Biswas S, Berg MG, Antapli CM, Xie F, Wang Q, Tang M-C, Tang G-L, Zhang L, Dreyfuss G, Cheng YQ: **Genomics-guided discovery of thailanstatins A, B, and C as pre-mRNA splicing inhibitors and antiproliferative agents from *Burkholderia thailandensis* MSMB43**. *J Nat Prod* 2013, **76**:685-693.

31. •• Nicolaou KC, Rhoades D, Kumar SM: **Total syntheses of thailanstatins A–C, spliceostatin D, and analogues thereof. Stereodivergent synthesis of tetrasubstituted dihydro- and tetrahydropyrans and design, synthesis, biological evaluation, and discovery of potent antitumor agents**. *J Am Chem Soc* 2018, **140**:8303-8320.

This impressive article detailed a thorough SAR study of 48 synthetic thailanstatin analogues. Biological evaluation of the synthetic library identified several compounds with potent, subnanomolar cytotoxicity, making them important leads as payloads for ADCs or as stand-alone cancer chemotherapies.

32. • Li S, Xu H, Cui S, Wu F, Zhang Y, Su M, Gong Y, Qiu S, Jiao Q, Qin C *et al.*: **Discovery and rational design of natural-product-derived 2-phenyl-3,4-dihydro-2*H*-benzo[*f*]chromen-3-amine analogs as novel and potent dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes**. *J Med Chem* 2016, **59**:6772-6790.

Rational*in silico* design of isodaphnetin analogues leads to a 7400-fold increase in DPP-4 inhibition. The identified lead compound exhibited excellent pharmacokinetic and *in vivo* activity, making it a valuable antidiabetic candidate.

33. Williams RB, Martin SM, Lawrence JA, Norman VL, O'Neil-Johnson M, Eldridge GR, Starks CM: **Isolation and Identification of the novel tubulin polymerization inhibitor bifidenone**. *J Nat Prod* 2017, **80**:616-624.

34. • Huang Z, Williams RB, Martin SM, Lawrence JA, Norman VL, O'Neil-Johnson M, Harding J, Mangette JE, Liu S, Guzzo PR *et al.*: **Bifidenone: structure–activity relationship and advanced preclinical candidate**. *J Med Chem* 2018, **61**:6736-6747.

A library of synthetic analogues of the important new tubulin polymerisation inhibitor, bifidenone, were subjected to SAR and biological studies. This resulted in the identification of a lead tubulin polymerisation inhibitor with enhanced potencies, and excellent pharmacokinetics and*in vivo* activity.

35. Zhuang C, Zhang W, Sheng C, Zhang W, Xing C, Miao Z: **Chalcone: a privileged structure in medicinal chemistry**. *Chem Rev* 2017, **117**:7762-7810.

36. Yan J, Chen J, Zhang S, Hu J, Huang L, Li X: **Synthesis, evaluation, and mechanism study of novel indole-chalcone derivatives exerting effective antitumor activity through microtubule destabilization in vitro and in vivo**. *J Med Chem* 2016, **59**:5264-5283.

37. Cole AL, Hossain S, Cole AM, Phanstiel O: **Synthesis and bioevaluation of substituted chalcones, coumaranones and other flavonoids as anti-HIV agents**. *Bioorg Med Chem* 2016, **24**:2768-2776.

38. Zhang Y, Wu J, Ying S, Chen G, Wu B, Xu T, Liu Z, Liu X, Huang L, Shan X, Dai Y, Liang G: **Discovery of new MD2 inhibitor from chalcone derivatives with anti-inflammatory effects in LPS-induced acute lung injury**. *Sci Rep* 2016, **6**:25130.

39. Laraia L, Ohsawa K, Konstantinidis G, Robke L, Wu Y-W, Kumar K, Waldmann H: **Discovery of novel cinchona-alkaloid-inspired oxazatwistane autophagy inhibitors**. *Angew Chem Int Ed* 2017, **56**:2145-2150.

40. Ceole LF, Gandhi H, Villamizar LH, Soares MJ, O'Sullivan TP: **Synthesis of novel quinine analogs and evaluation of their effects on *Trypanosoma cruzi***. *Future Med Chem* 2018, **10**:391-408.

41. Matsuda H, Yoshida K, Miyagawa K, Nemoto Y, Asao Y, Yoshikawa M: **Nuphar alkaloids with immediately apoptosis-inducing activity from *Nuphar pumilum* and their structural requirements for the activity**. *Bioorg Med Chem Lett* 2006, **16**:1567-1573.

42. Li H, Korotkov A, Chapman CW, Eastman A, Wu J: **Enantioselective formal syntheses of 11 nuphar alkaloids and discovery of potent apoptotic monomeric analogues**. *Angew Chem Int Ed* 2016, **55**:3509-3513.

43. Li H, Cooke TJ, Korotkov A, Chapman CW, Eastman A, Wu J: **Stereoselective synthesis and biological evaluation of C1-epimeric and desmethyl monomeric nuphar analogues**. *J Org Chem* 2017, **82**:2648-2655.

44. Bharate SS, Mignani S, Vishwakarma RA: **Why are the majority of active compounds in the CNS domain natural products? A critical analysis**. *J Med Chem* 2018, **61**:10345-10374.

45. Knull J: **(-)Deprenyl (selegiline), a catecholaminergic activity enhancer (CAE) substance acting in the brain**. *Pharmacol Toxicol* 1998, **82**:57-66.

46. • Gealageas R, Devineau A, So PPL, Kim CMJ, Surendradoss J, Buchwalder C, Heller M, Goebeler V, Dullaghan EM, Grierson DS, Putnins EE: **Development of novel monoamine oxidase-B (MAO-B) inhibitors with reduced blood–brain barrier permeability for the potential management of noncentral nervous system (CNS) diseases**. *J Med Chem* 2018, **61**:7043-7064.

The authors used*in silico* prediction to design a number of polar derivatives of the MAO-B inhibitor deprenyl. Several of these synthetic derivatives displayed excellent pharmacokinetics and reduced blood brain barrier permeability making them valuable leads in the development of drugs to treat non-CNS inflammatory diseases.