Natural Product Reports

ROYAL SOCIETY OF CHEMISTRY

HIGHLIGHT

View Article Online
View Journal

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

Check for updates

Cite this: DOI: 10.1039/d0np00059k

Re-engineering natural products to engage new biological targets

Stephen E. Motika and Paul J. Hergenrother *

Covering: up to 2020

Natural products have a long history in drug discovery, with their inherent biological activity often tailored by medicinal chemists to arrive at the final drug product. This process is illustrated by numerous examples, including the conversion of epothilone to ixabepilone, erythromycin to azithromycin, and lovastatin to simvastatin. However, natural products are also fruitful starting points for the creation of complex and diverse compounds, especially those that are markedly different from the parent natural product and accordingly do not retain the biological activity of the parent. The resulting products have physiochemical properties that differ considerably when compared to traditional screening collections, thus affording an opportunity to discover novel biological activity. The synthesis of new structural frameworks from natural products thus yields value-added compounds, as demonstrated in the last several years with multiple biological discoveries emerging from these collections. This Highlight details a handful of these studies, describing new compounds derived from natural products that have biological activity and cellular targets different from those evoked/engaged by the parent. Such re-engineering of natural products offers the potential for discovering compounds with interesting and unexpected biological activity.

Received 7th August 2020

DOI: 10.1039/d0np00059k

rsc.li/npr

1. Introduction

1.1 Natural product platforms for drug discovery and compound library design

With high-throughput screening (HTS) now commonplace in drug discovery,[1–3] a pre-requisite is access to suitable collections of compounds. Natural products (NPs) have long been a fruitful source for drug discovery, from early examples of screening NP mixtures derived from Actinomycetes[4] to modern times where NP-based therapeutics are now used to treat a range of human diseases.[5] However, with hundreds of abundant NPs now discovered,[6] there are bottlenecks associated with isolating and identifying new NPs. While there are many creative technologies that can assist in the removal of these bottlenecks, in practice these challenges have limited the routine use of NPs in modern drug discovery. As a result, screening collections are largely populated with synthetic small molecules that can be considered structurally 'simpler' than NPs by many metrics; for example, possessing fewer stereogenic centers and a lower fraction of sp^3-hybridized carbons (Fsp^3, a measure of the proportion of carbons in a compound that are sp^3-hybridized).[7] While dozens of drug leads have been identified from screening such compound collections (particularly drugs targeting GPCRs, kinases, and ion channels),[5] some targets and processes have proven challenging to engage or perturb. As such, new paradigms in compound library generation have surfaced, particularly those aimed at delivering more complex compounds that may have the possibility of engaging different types of biological targets.

1.2 Natural product-inspired compound generation and re-engineering

With the goal of generating screening collections of compounds whose physicochemical properties align with those of NPs, it is useful to categorize the various approaches as "bottom up" and "top down" (Fig. 1A). Diversity oriented synthesis (DOS, Fig. 1A)[8–26] is the prototype bottom-up approach, creating complexity through a build/couple/pair strategy,[27] with simpler acyclic and cyclic precursors possessing useful functionality for cyclization and coupling (Fig. 1B). Complex ring scaffolds and connectivity are subsequently achieved through strategic and atom economical reaction sequences. Related strategies, such as biology oriented synthesis (BiOS, Fig. 1A)[28–33] and fragment based designs,[34–37] employ larger NP-inspired synthetic precursors (Fig. 1B) that are coupled or structurally elaborated using chemistry that leverages the rich reactivity within NP-like fragments. Function oriented synthesis[37–40] (FOS) abides by similar synthetic

Department of Chemistry, Institute for Genomic Biology, Cancer Center at Illinois, University of Illinois, Urbana-Champaign, USA. E-mail: hergenro@illinois.edu

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

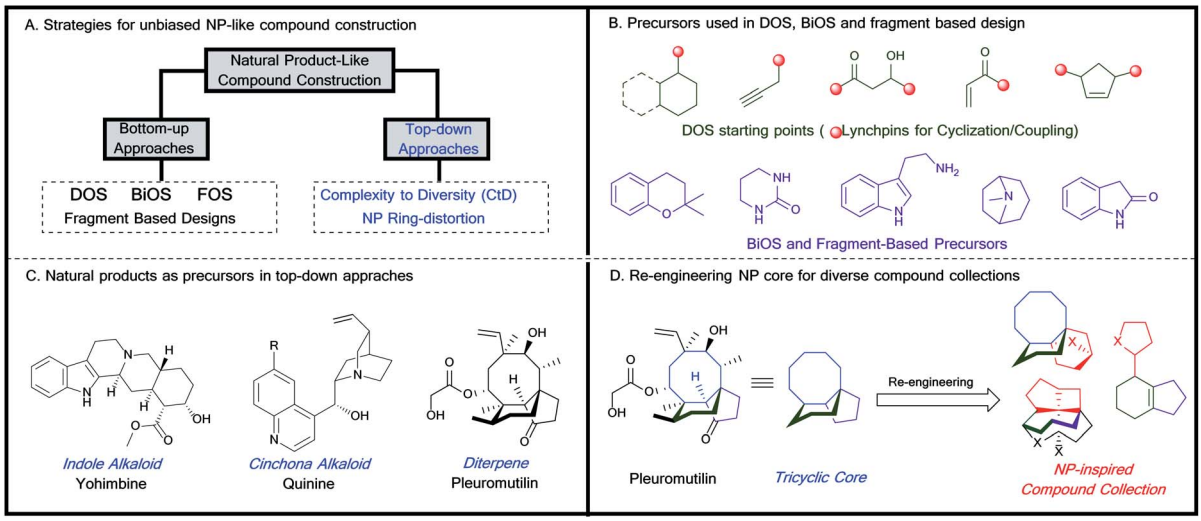

Fig. 1 Strategies for construction of collections of complex, NP-like compounds. (A) Bottom-up strategies build complexity from simpler starting materials, whereas top-down approaches are premised on making dramatic structural alterations to an already complex NP. (B) Some simpler precursors used in bottom-up approaches. (C) NPs that are suitable for top-down diversification through the Complexity-to-Diversity (CtD) strategy. (D) Using a complex NP as a starting material for the generation of compounds with a variety of different scaffolds/ring systems, exemplified here with pleuromutilin.

paradigms as DOS and BiOS but aims to identify new compound collections for specific biological functions. These highly impactful bottom-up approaches are outside the scope of this highlight and have been comprehensively reviewed elsewhere.[11,12,41–46]

Herein, we overview biologically active compounds discovered from a complementary synthetic approach. In this top-down strategy, termed as "Complexity-to-Diversity" (CtD, Fig. 1A),[47] complex and abundant NPs are utilized as synthetic starting points (some examples in Fig. 1C). Through core modifications of these NPs, particularly by way of reactions that alter the ring systems, final products with diverse structural landscapes are produced (Fig. 1D).

1.3 Optimization of NPs for use as medicines

Of course, NPs are often used as synthetic starting points in drug design, primarily in the context of semi-synthesis; that is, NPs with well-established biological activity are structurally altered for greater potency or enhanced pharmacological properties.[48–53] Often times, these modifications are constrained so that the pre-existing skeletal features of the NP remain intact, as is the case with ixabepilone,[37] azithromycin[54] and simvastatin[55] (Fig. 2A). As such, these compounds engage the same target as the parent/progenitor NP; indeed, this feature is a key hallmark of semi-synthesis, and is a major point of distinction from CtD. In CtD, NPs are instead utilized as synthetic precursors for more dramatic forms of

Dr Stephen Motika earned his B.S. in chemistry at Elizabethtown college in 2012 and his Ph.D. in chemistry from the University of South Florida in 2017. Stephen then joined Professor Paul J. Hergenrother's group as a postdoctoral researcher at the University of Illinois Urbana-Champaign, where he eagerly worked at identifying small molecule therapies to combat multi-drug resistant Gram-negative bacteria. To overcome the historical challenge of getting small molecules into Gram-negative bacteria, Stephen enlisted a set of structural guidelines developed in the Hergenrother group, thus enabling the conversion of narrow spectrum antibiotics into broad-spectrum versions.

Prof. Paul J. Hergenrother is the Kenneth L. Rinehart Endowed Chair in Natural Products Chemistry and Professor of Chemistry. He received his B.S. in chemistry from the University of Notre Dame in 1994 and his PhD from the University of Texas at Austin in 1999; after an American Cancer Society postdoctoral fellowship at Harvard University, he joined the faculty at the University of Illinois in 2001. His research group develops novel anticancer and antibacterial drugs, and four anticancer compounds discovered in his lab have been licensed to companies, including Vanquish Oncology which he founded to advance the anticancer compound PAC-1.

This journal is © The Royal Society of Chemistry 2020

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

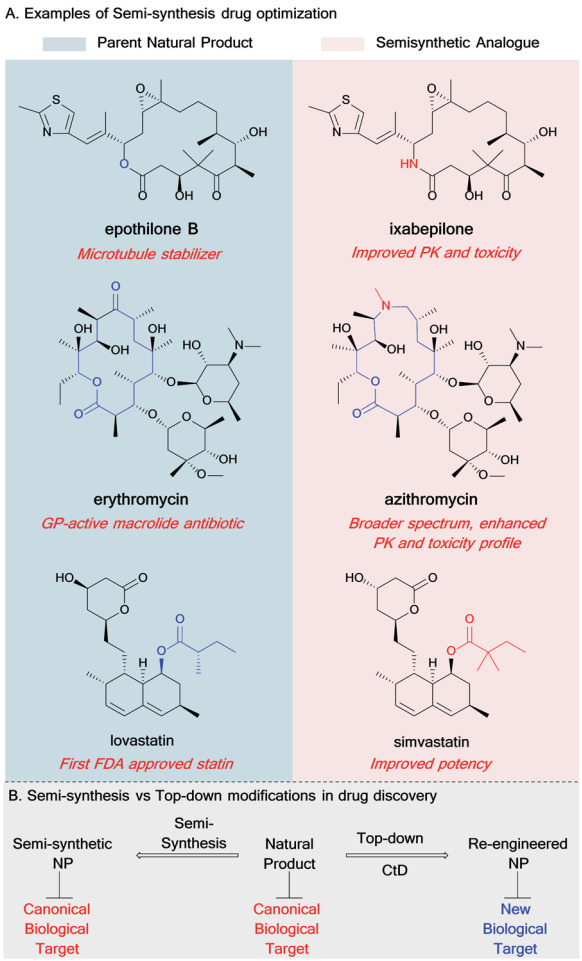

Fig. 2 Semi-synthesis of NPs, and how it differs from CtD. (A) Examples of NPs being tailored through synthesis, resulting in impactful therapeutics. (B) The semi-synthesis approach results in compounds that have only modest structural differences and that engage the same target of the parent NP. In contrast, CtD provides compounds where the skeleton has been radically altered, resulting in compounds that can engage new biological targets.

synthetic alteration, with the explicit goal of identifying compounds with different biological activity from the parent NP (Fig. 2B).

The inherent biological activity of many NPs has been instrumental in discovering new therapeutics, and semi-synthesis campaigns show that modifying the periphery of NPs can often preserve their canonical biological function. With the goal of developing functionally- and structurally-unbiased compound collections, top-down discovery platforms instead revolve around reconfiguring the rigid and spatially defined ring systems found in many NPs (as highlighted in Fig. 1D). In doing so, novel compounds that are NP-like in their physicochemical properties can be accessed. As NPs inherently possess a combination of physicochemical properties making them different from compounds in traditional screening libraries (for example, high Fsp^3, greater number of stereogenic centers, ring scaffold-diversity, *etc.*), use of NPs as synthetic starting points can result in a unique collection of compounds with NP-like structural complexity.

1.4 NP diversification through CtD

CtD studies have shown that pre-organized functionality and ring systems within many NPs are conducive to executing classic ring system distorting transformations such as the Beckmann rearrangement, Baeyer–Villiger oxidation, Diels–Alder reaction, and cationic ring expansion/contraction reactions. The pre-requisites for NP selection and the governing synthetic blueprints underlying CtD have been reviewed[47] and documented in manuscripts on CtD.[56–67] These strategies have been employed to construct compound collections from various NPs, with the explicit goal of identifying new pharmacophores with biological activity that diverges from the parent NP. The works discussed below are recent examples of the successful execution of CtD-guided NP re-engineering to identify interesting new biologically active molecules.

2. Complex molecules with novel biological activity identified from compounds created through the CtD strategy

2.1 Repurposing yohimbine through ring-distortion yields a compound with HIF-dependent anticancer and anti-inflammatory activity

Yohimbine (**1**, Fig. 3) is a complex indole alkaloid isolated from the bark of *Pausinystalia* trees and the *Rauwolfia* root. Indole alkaloids are a distinguished class of NPs, as many constituents of this class are approved therapeutics (such as vincristine,[68] pericine,[69] and zofran[70]) used to treat various human ailments. Yohimbine possesses a tryptoline core, an additional fused ring system, and five stereogenic centers, and itself has modest therapeutic value, primarily utilized as an over-the-counter stimulant. As such, large quantities of high purity yohimbine

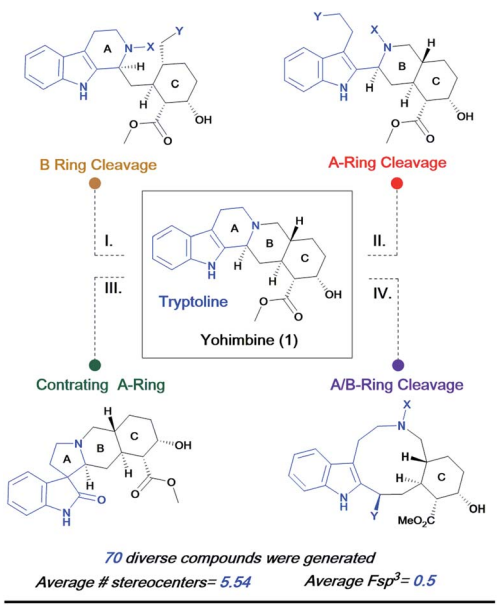

Fig. 3 Ring distortion strategies for diversification of yohimbine.

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

can be purchased from various commercial vendors. The Huigens group leveraged the unique structural features of yohimbine in developing a strategy for construction of novel complex compounds from this NP.[65]

Yohimbine has been utilized in previous studies involving modifications of various functional groups without major modification of the core ring system. These efforts include oxidation of the secondary alcohol,[71] allylation of the indole 3-position,[72] alkylation[73] and hydroxylation of the indole nitrogen,[74,75] reduction of the 2,3-positions of the indole heterocycle,[74,75] and ethylene glycol protection of the 2,3-positions of the indole nucleus.[76] While these products do not possess structural features that significantly diverge from those present in yohimbine, these studies were helpful in understanding the basic reactivity patterns of this NP. Accordingly, the authors focused on tryptoline ring distortion pathways,[71,77] which could provide novel structural features. Employing three orthogonal C–N cleavage strategies and a C–C cleavage (I–IV, Fig. 3), and subsequent modifications of the ring-distorted intermediates, a broad and structurally diverse set of compounds was created. Overall, these synthetic excursions provided 70 complex compounds that share little structural resemblance to yohimbine.[65]

CtD-based library construction designs can rapidly produce compounds with skeletal and functional group diversity, as evidenced here with this library possessing an average of 5.54 stereogenic centers and an average value of 0.5 for Fsp^3 (Fig. 3). The authors noted that the average number of stereogenic centers for FDA approved drugs (100 top selling drugs of 2013) is only 2.58. Additionally, the number of stereocenters and Fsp^3 for the ChemBridge commercial screening collection is only 0.24 and 0.24 respectively.[65]

Screening the collection in several phenotypic assays (anticancer, anti-inflammatory and antibacterial activity) and subsequent validation studies revealed that compound **2** (Fig. 4) exhibited HIF-dependent anticancer activity, while five other analogues (not shown herein) demonstrated either activation or inhibition of the Nrf2-antioxidant response element (ARE) at concentrations below 100 μM.

Compound **2** stands out as the most selective antiproliferative agent from this collection and exhibits a Hypoxia-Inducible Factor (HIF) dependent cancer-cell death phenotype (IC_{50} = 10–32 μM in HIF-positive colorectal cancer cell line (HCT116); $IC_{50} \geq 100$ μM in $HCT116^{HIF\text{-}1\alpha^{-/-}HIF\text{-}2\alpha^{-/-}}$). Hypoxia is an environmental hallmark of most solid tumour types, and cancers cells have keenly adapted to these conditions through HIF pathways. Consequently, cancer cells that enlist these transcriptional programs exhibit more aggressive biological behaviours.[78] To date, no HIF inhibitors have reached clinical approval.[79,80] Although its biological target remains to be elucidated, compound **2** may offer promise as a member of a new class of HIF-dependent anticancer agents. As described in Fig. 4, compound **2** is synthesized in only four steps from yohimbine, starting with a key oxidative contraction of ring A, yielding the oxindole core in **IA**. Subsequent di-alkylation of intermediate **IA** provided lead compound **2**. With this robust synthetic route, along with the dense functionality of this current lead and opportunities for late-stage diversification, extended SAR studies can now be used to identify more potent analogues and facilitate identification of the biological target of **2**. In accordance with CtD design principles, the compounds accessed from yohimbine do not appear to have retained the biological activity of the NP.

2.2 Discovery of autophagy inhibitors *via* ring-fusion of cinchona-alkaloids

Cinchona-alkaloids are well-studied NPs within synthetic organic chemistry and drug discovery. Of the more than 30 cinchona alkaloids isolated from the *Cinchona* genus, quinine (**4**) and quinidine (**5**) (Fig. 5A) are the only variants commonly employed as therapeutics (anthelmintic and arrhythmia, respectively),[81] and are isolated on industrial scales. While cinchonidine (**6**) and cinchonine (**7**) have limited current-day medicinal value,[81,82] they are also commonly isolated on large scale, making any of these four alkaloids (Fig. 5A) viable starting

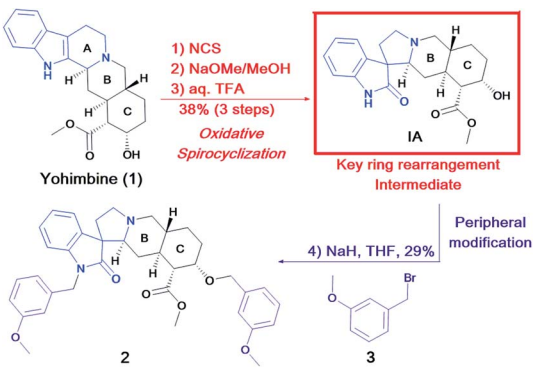

Fig. 4 Synthesis of **2**, a compound with HIF-dependent anticancer activity.

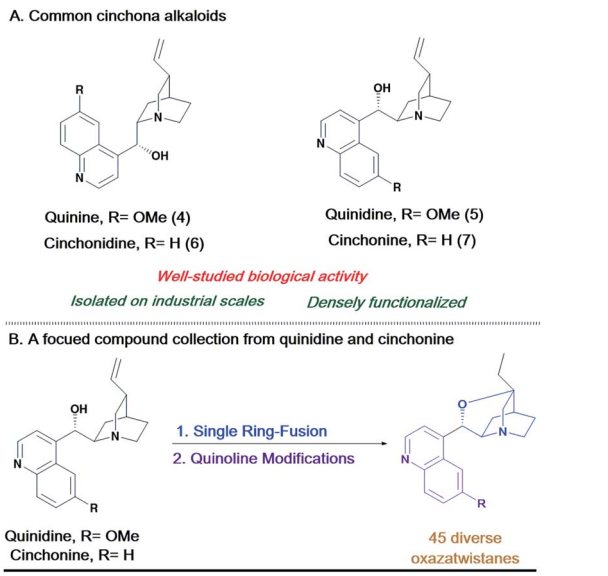

Fig. 5 Cinchona alkaloids as starting points for the construction of complex and diverse compounds.

This journal is © The Royal Society of Chemistry 2020

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

points for CtD studies. The rich reactivity of cinchona-alkaloids endowed with pre-existing functionality (an aromatic quinoline ring, a quinuclidine moiety, vinyl substituent, and a central hydroxyl group) offers an empowering linchpin for rapid structural elaboration, and indeed several groups have utilized these compounds as starting points for CtD syntheses.[58,62,64]

Waldmann and co-workers have reported such efforts, first converting quinidine and cinchonidine into their oxazatricyclo [4.4.0.0]decane (oxazatwistane) counterparts (Fig. 5B).[62] While oxazatwistanes have been studied as organocatalysts,[83,84] comprehensive assessment of their biological activity has not been reported. These compounds can be accessed quickly from quinidine or cinchonidine under exposure to catalytic amounts of acid (Fig. 5B). Using this key methodology in conjunction with quinoline ring modifications, the authors generated a focused compound collection containing 45 oxazatwistane members (Fig. 5B), with subsequent evaluation of these novel compounds as inhibitors of the Wnt and Hedgehog pathways, as well as their ability to inhibit autophagy induced by amino acid starvation (starvation induced autophagy (SIA) as described in Fig. 6).[62]

Although none of the compounds in this collection inhibited the Wnt and Hedgehog pathways, two novel derivatives, coined oxautin-1 (**8**) and -2 (**9**) (Fig. 6), demonstrate potent autophagy inhibition and appear to inhibit both autophagosome biogenesis and autophagosome maturation.[62] Autophagy inhibition has emerged as a potentially fruitful anticancer therapeutic strategy.[85,86] Among the promising preclinical and clinical studies are those that have demonstrated that MAPK targeted therapies (such as MEK inhibition) could be potently combined with autophagy inhibitors, such as chloroquine and hydroxychloroquine.[87,88]

Consistent with the CtD paradigm, none of the four common cinchona-alkaloid NPs in Fig. 5A demonstrate any ability to inhibit autophagy at 30 μM, highlighting CtD's ability to engineer new biological function beyond that endowed in the progenitor natural product. The quinoline modifications in the two lead compounds were also critical to activity, as demonstrated by the lack of autophagy inhibition of related oxazatwistanes (such as compounds **10–12**, Fig. 6). The authors also tested various functionalized quinolines lacking the quinuclidine or oxazatwistane motif, none of which showed activity below 30 μM. Importantly, the oxautins add to the growing body of chemical tools useful for autophagy inhibition.

2.3 Complex compounds from pleuromutilin yields ferroptocide, a pro-ferroptotic anticancer agent

Pleuromutilin (**13**, Fig. 7) is a diterpene NP produced by multiple species of fungi that possesses antibacterial activity through binding to the 50s ribosomal subunit.[89] This novel mechanism of action has inspired intensive semi-synthetic efforts,[89–91] ultimately leading to analogues that are approved as treatments for infections caused by Gram-positive bacteria in humans[92] (retapamulin (**14**)) and *Mycoplasma* spp., *Brachyspira* spp., and *L. intracellularis* infections in farm animals and pets (valnemulin (**15**), tiamulin (**16**)).[89] Pleuromutilin's unique tricyclic core and complex stereochemical landscape has also piqued the interest of organic chemists, resulting in several elegant total syntheses of this diterpene.[93–97] These structural features, as well as its various functional handles, positions pleuromutilin as an intriguing starting point for library development and synthetic diversification through CtD. To this end, Hergenrother and co-workers constructed a diverse compound collection from pleuromutilin using the CtD platform, with a focus on altering the tricyclic core of this NP.[57,59] This work ultimately enabled the identification of a unique covalent modifying agent that induces cancer cell death through ferroptosis.

The construction of complex-and-diverse compounds starting from pleuromutilin was carried out through five different synthetic pathways, each involving one to three ring system distortions (fusion, cleavage, rearrangement, contraction or expansion, as described in Fig. 8). Each sequence resulted in a unique subclass of compounds and intermediates, 27 novel compounds in total. Notably, each member retained the high levels of stereochemical complexity and ring density present

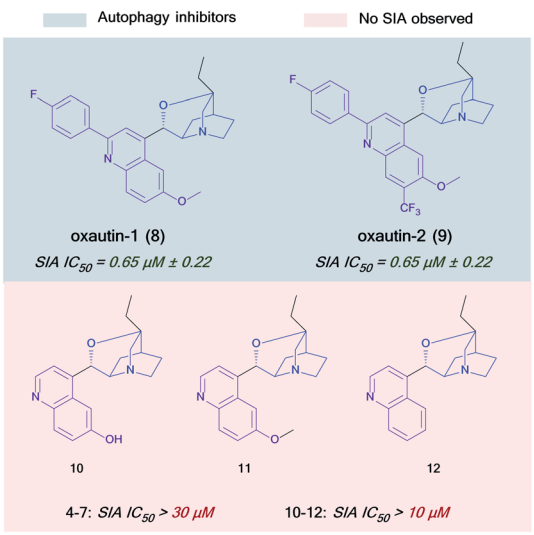

Fig. 6 Autophagy inhibition by oxautin-1 and -2. SIA: starvation induced autophagy.

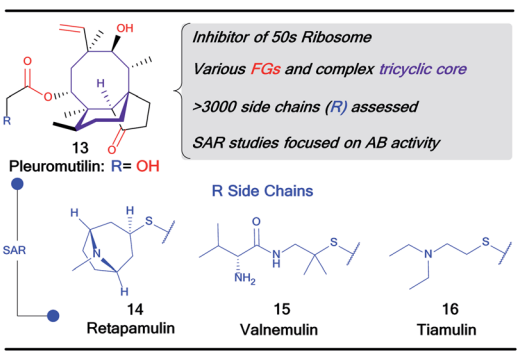

Fig. 7 Pleuromutilin and its derivatives are potent antibiotics with significant clinical utility.

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

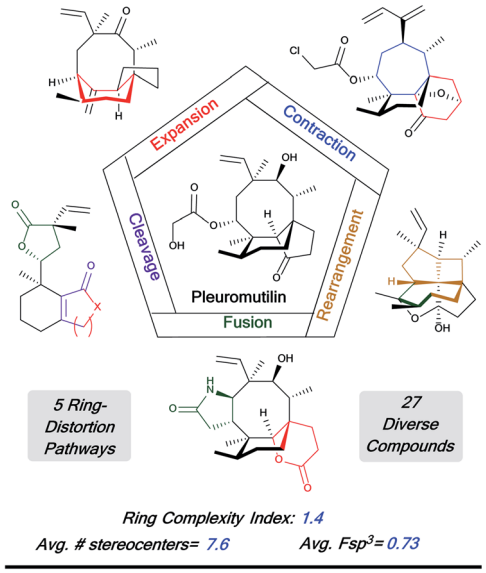

Fig. 8 Pleuromutilin as a starting point for creation of a collection of complex and diverse compounds.

within the parent NP. This collection also possessed compounds with physicochemical features different from FDA approved drugs and virtual and commercial screening libraries as measured by comparison to FDA approved oncology drugs, FDA approved antibiotics, Drugbank, Chembridge-CL, Chembridge-EXP, Microformat, MLSMR-NP and PNAS CC collections.[59] In all cases, the pleuromutilin derived collection possesses at least twice the number of stereogenic centers and two-fold greater Fsp^3 and ring complexity.

The compounds in this collection were assessed for their ability to kill a broad panel of cancer cell lines, with the goal of identifying compounds that induce cancer cell death *via* an unusual mechanism. From these studies emerged ferroptocide (**17**, Fig. 9). A notable and defining trait for ferroptocide is the significant cell death observed in <1 hour in the ES-2 (ovarian cancer) cell line; this activity is notably faster than a host of other cell death inducing agents. Ferroptotic cell death was determined through cytoprotective studies (*i.e.* using ferroptosis inhibitors or lipophilic antioxidants in the presence of ferroptocide) and by monitoring lipid peroxide levels (*i.e.* dose dependent increases observed with ferroptocide).

Importantly, through detailed proteomic studies the authors were able to determine the cellular target of ferroptocide. The α-chloroester electrophile was found to be critical to activity (as evidenced by the activity of ferroptocide *vs.* **18** in Fig. 9), and protein pull-down experiments revealed that ferroptocide inhibits thioredoxin by covalently modifying its reactive cysteines, thereby inducing ferroptosis. Currently, this is the only pro-ferroptotic agent known that operates through this mode-of-action.

Ferroptocide was constructed in 1 step from **19** (5 steps from pleuromutilin) as part of a derivative synthesis campaign that followed the initial phenotypic screen. This screen identified **19** (Fig. 9, product of a ring contraction of pleuromutilin) as being an inducer of cancer cell death, and the introduction of the triazolidine-3,5-dione ring system in ferroptocide afforded an approximately 5-fold increase in potency against the ES-2 cancer cell line (Fig. 9, ferroptocide *vs.* **19**). Five different electrophilic

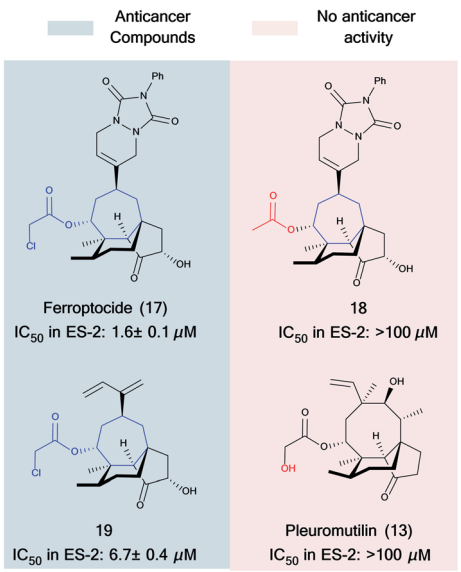

Fig. 9 Anticancer activity of ferroptocide and related compounds, as shown by their ability to kill ES-2 (ovarian cancer) cell.

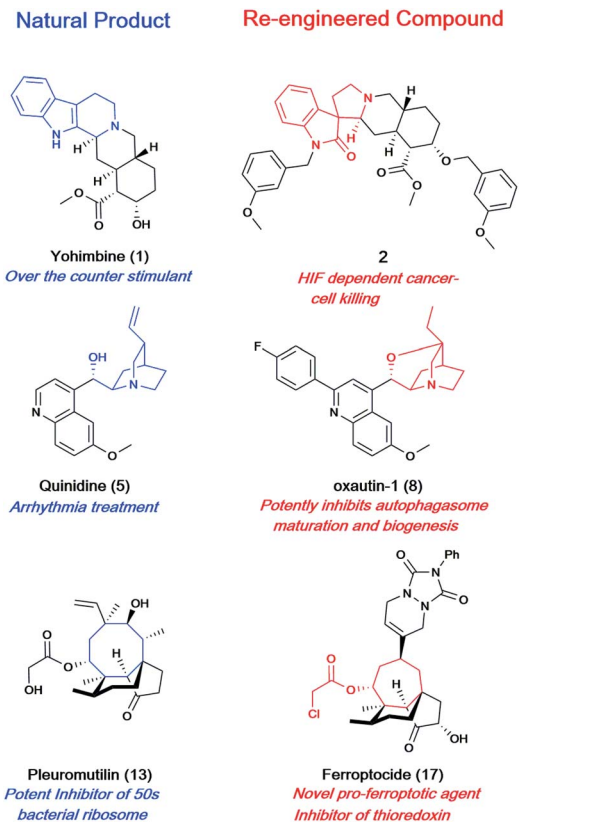

Fig. 10 Compound leads identified by applying the CtD strategy to yohimbine, quinidine, and pleuromutilin.

This journal is © The Royal Society of Chemistry 2020

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

side chains were also incorporated during these investigations, with the α-chloroester offering the most promising potency and selectivity. Pleuromutilin exhibits none of the anticancer activity displayed by either ferroptocide or **19**, and likewise, while pleuromutilin is effective in inhibiting the growth of Gram-positive bacteria, ferroptocide possesses no such antibacterial activity.[59]

2.4 Summary

Application of the CtD strategy to yohimbine, two different cinchona alkaloids, and pleuromutilin, followed by subsequent biological evaluation, led to the discovery of novel compounds possessing biological activity significantly different from the parent NP (Fig. 10). All of these NP starting points contain diverse functionality that enable the CtD strategy, and all can be accessed from commercial sources on decagram scale. Through strategic implementation of ring-distortion pathways, each parent NP was rapidly deconstructed/rearranged, leading to compound collections with structural features that diverge significantly from the parent NP. The physicochemical features of each collection also differ greatly from traditional drug screening libraries, and each CtD campaign yielded a promising probe with interesting and useful biological activity, while the progenitor NPs exhibited none of the re-engineered biological activity. Remarkably, these ventures revealed three new biologically active compound classes from only 142 different screening compounds, highlighting the promise of compounds derived from CtD for biological discovery.

3. Outlook on the field

Natural products (NPs) have been a rich source for the development of novel therapeutics over the past century. Their diverse structural architectures and stereochemical landscapes often confer a specific biological function; if necessary, the chemical features of NPs can be tailored for optimal medicinal value *via* semi-synthesis. While the discovery of new NPs will continue to fuel this mode of drug discovery, there are bottlenecks preventing rapid identification of scores of novel NP-classes. To generate a complementary set of compounds, bottom up synthetic paradigms have been implemented to construct compounds with NP-like features using strategies such as DOS, BiOS, FOS, and NP-fragment based designs. As presented throughout this Highlight, complexity-to-diversity (CtD) provides a top-down alternative, complementing these powerful techniques and utilizing complex natural products as synthetic starting points.

The selection of NPs to initiate a CtD campaign requires some consideration. Dozens of densely functionalized NPs can be purchased from a host of vendors on decagram scale. These compounds should possess pre-existing functional-groups, and ideally several contiguous/overlapping ring systems that can be differentially modified, enabling creation of a broad and diverse compound collection. As described in reports enlisting yohimbine, quinidine, and pleuromutilin, only 3–5 chemical steps were needed to arrive at distinct compound classes. While many classic synthetic reactions have been integral to these CtD successes, the continued development of more selective and functional group tolerant synthetic methodologies will expand the scope and utility of CtD as a drug discovery platform.

4. Conflicts of interest

The University of Illinois has filed patents on some compounds constructed through the CtD strategy.

5. Acknowledgements

We are grateful to the NIH (R01GM118575) for support of this work and for a postdoctoral fellowship (F32AI143207) to S. E. M.

6. Notes and references

1 A. Carnero, *Clin. Transl. Oncol.*, 2006, **8**, 482–490.
2 S. Fox, S. Farr-Jones and M. A. Yund, *J. Biomol. Screening*, 1999, **4**, 183–186.
3 L. M. Mayr and P. Fuerst, *J. Biomol. Screening*, 2008, **13**, 443–448.
4 D. A. Pereira and J. A. Williams, *Br. J. Pharmacol.*, 2007, **152**, 53–61.
5 K. H. Bleicher, H.-J. Böhm, K. Müller and A. I. Alanine, *Nat. Rev. Drug Discovery*, 2003, **2**, 369–378.
6 C. R. Pye, M. J. Bertin, R. S. Lokey, W. H. Gerwick and R. G. Linington, *Proc. Natl. Acad. Sci. U. S. A.*, 2017, **114**, 5601–5606.
7 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
8 C. J. O'Connor, H. S. Beckmann and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 4444–4456.
9 P. A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler and S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 18787–18792.
10 J. Cui, J. Hao, O. A. Ulanovskaya, J. Dundas, J. Liang and S. A. Kozmin, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6763–6768.
11 W. R. Galloway, A. Isidro-Llobet and D. R. Spring, *Nat. Commun.*, 2010, **1**, 80–93.
12 S. L. Schreiber, *Science*, 2000, **287**, 1964–1969.
13 M. R. Spaller, M. T. Burger, M. Fardis and P. A. Bartlett, *Curr. Opin. Chem. Biol.*, 1997, **1**, 47–53.
14 B. Z. Stanton and L. F. Peng, *Mol. BioSyst.*, 2010, **6**, 44–54.
15 M. D. Burke and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2004, **43**, 46–58.
16 C. Chen, X. Li, C. S. Neumann, M. M. Lo and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2005, **44**, 2249–2252.
17 C. Chen, X. Li and S. L. Schreiber, *J. Am. Chem. Soc.*, 2003, **125**, 10174–10175.
18 S. Dandapani, A. R. Germain, I. Jewett, S. le Quement, J. C. Marie, G. Muncipinto, J. R. Duvall, L. C. Carmody, J. R. Perez, J. C. Engel, J. Gut, D. Kellar, J. L. Siqueira-Neto, J. H. McKerrow, M. Kaiser, A. Rodriguez, M. A. Palmer,

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

M. Foley, S. L. Schreiber and B. Munoz, *ACS Med. Chem. Lett.*, 2014, **5**, 149–153.

19 N. Kato, E. Comer, T. Sakata-Kato, A. Sharma, M. Sharma, M. Maetani, J. Bastien, N. M. Brancucci, J. A. Bittker, V. Corey, D. Clarke, E. R. Derbyshire, G. L. Dornan, S. Duffy, S. Eckley, M. A. Itoe, K. M. Koolen, T. A. Lewis, P. S. Lui, A. K. Lukens, E. Lund, S. March, E. Meibalan, B. C. Meier, J. A. McPhail, B. Mitasev, E. L. Moss, M. Sayes, Y. Van Gessel, M. J. Wawer, T. Yoshinaga, A. M. Zeeman, V. M. Avery, S. N. Bhatia, J. E. Burke, F. Catteruccia, J. C. Clardy, P. A. Clemons, K. J. Dechering, J. R. Duvall, M. A. Foley, F. Gusovsky, C. H. Kocken, M. Marti, M. L. Morningstar, B. Munoz, D. E. Neafsey, A. Sharma, E. A. Winzeler, D. F. Wirth, C. A. Scherer and S. L. Schreiber, *Nature*, 2016, **538**, 344–349.

20 F. G. Kuruvilla, A. F. Shamji, S. M. Sternson, P. J. Hergenrother and S. L. Schreiber, *Nature*, 2002, **416**, 653–657.

21 O. Kwon, S. B. Park and S. L. Schreiber, *J. Am. Chem. Soc.*, 2002, **124**, 13402–13404.

22 D. Lee, J. K. Sello and S. L. Schreiber, *Org. Lett.*, 2000, **2**, 709–712.

23 D. R. Schmidt, O. Kwon and S. L. Schreiber, *J. Comb. Chem.*, 2004, **6**, 286–292.

24 D. R. Spring, S. Krishnan, H. E. Blackwell and S. L. Schreiber, *J. Am. Chem. Soc.*, 2002, **124**, 1354–1363.

25 S. M. Sternson, J. B. Louca, J. C. Wong and S. L. Schreiber, *J. Am. Chem. Soc.*, 2001, **123**, 1740–1747.

26 A. M. Taylor and S. L. Schreiber, *Tetrahedron Lett.*, 2009, **50**, 3230–3233.

27 T. E. Nielsen and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2008, **47**, 48–56.

28 S. Basu, B. Ellinger, S. Rizzo, C. Deraeve, M. Schürmann, H. Preut, H. D. Arndt and H. Waldmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6805–6810.

29 M. Potowski, C. Golz, C. Strohmann, A. P. Antonchick and H. Waldmann, *Bioorg. Med. Chem.*, 2015, **23**, 2895–2903.

30 J. Švenda, M. Sheremet, L. Kremer, L. Maier, J. O. Bauer, C. Strohmann, S. Ziegler, K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2015, **54**, 5596–5602.

31 H. van Hattum and H. Waldmann, *J. Am. Chem. Soc.*, 2014, **136**, 11853–11859.

32 S. Wetzel, R. S. Bon, K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 10800–10826.

33 T. J. Zimmermann, S. Roy, N. E. Martinez, S. Ziegler, C. Hedberg and H. Waldmann, *ChemBioChem*, 2013, **14**, 295–300.

34 D. A. Erlanson, S. W. Fesik, R. E. Hubbard, W. Jahnke and H. Jhoti, *Nat. Rev. Drug Discovery*, 2016, **15**, 605–619.

35 B. Over, S. Wetzel, C. Grütter, Y. Nakai, S. Renner, D. Rauh and H. Waldmann, *Nat. Chem.*, 2013, **5**, 21–28.

36 H. Vu, L. Pedro, T. Mak, B. McCormick, J. Rowley, M. Liu, A. Di Capua, B. Williams-Noonan, N. B. Pham, R. Pouwer, B. Nguyen, K. T. Andrews, T. Skinner-Adams, J. Kim, W. G. J. Hol, R. Hui, G. J. Crowther, W. C. Van Voorhis and R. J. Quinn, *ACS Infect. Dis.*, 2018, **4**, 431–444.

37 J. A. Howe, H. Wang, T. O. Fischmann, C. J. Balibar, L. Xiao, A. M. Galgoci, J. C. Malinverni, T. Mayhood, A. Villafania, A. Nahvi, N. Murgolo, C. M. Barbieri, P. A. Mann, D. Carr, E. Xia, P. Zuck, D. Riley, R. E. Painter, S. S. Walker, B. Sherborne, R. de Jesus, W. Pan, M. A. Plotkin, J. Wu, D. Rindgen, J. Cummings, C. G. Garlisi, R. Zhang, P. R. Sheth, C. J. Gill, H. Tang and T. Roemer, *Nature*, 2015, **526**, 672–677.

38 S. Ichikawa, *Chem. Rec.*, 2016, **16**, 1106–1115.

39 J. Liu, Y. Chen, J. Y. Li, C. Luo, J. Li, K. X. Chen, X. W. Li and Y. W. Guo, *Mar. Drugs*, 2018, **16**, 97–111.

40 Y. Nakai, W. H. Tepp, T. J. Dickerson, E. A. Johnson and K. D. Janda, *Bioorg. Med. Chem.*, 2009, **17**, 1152–1157.

41 G. Karageorgis, D. J. Foley, L. Laraia and H. Waldmann, *Nat. Chem.*, 2020, **12**, 227–235.

42 P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Res.*, 2008, **41**, 40–49.

43 G. C. Micalizio and S. B. Hale, *Acc. Chem. Res.*, 2015, **48**, 663–673.

44 P. A. Wender, R. V. Quiroz and M. C. Stevens, *Acc. Chem. Res.*, 2015, **48**, 752–760.

45 A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons and D. W. Young, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6799–6804.

46 S. L. Kidd, T. J. Osberger, N. Mateu, H. F. Sore and D. R. Spring, *Front. Chem.*, 2018, **6**, 460–468.

47 K. C. Morrison and P. J. Hergenrother, *Nat. Prod. Rep.*, 2014, **31**, 6–14.

48 A. Bauer and M. Brönstrup, *Nat. Prod. Rep.*, 2014, **31**, 35–60.

49 J. Chen, W. Li, H. Yao and J. Xu, *Fitoterapia*, 2015, **103**, 231–241.

50 A. M. Lourenço, L. M. Ferreira and P. S. Branco, *Curr. Pharm. Des.*, 2012, **18**, 3979–4046.

51 J. Szychowski, J. F. Truchon and Y. L. Bennani, *J. Med. Chem.*, 2014, **57**, 9292–9308.

52 Z. Xiao, S. L. Morris-Natschke and K. H. Lee, *Med. Res. Rev.*, 2016, **36**, 32–91.

53 H. Yao, J. Liu, S. Xu, Z. Zhu and J. Xu, *Expert Opin. Drug Discovery*, 2017, **12**, 121–140.

54 D. Jelić and R. Antolović, *Antibiotics*, 2016, **5**, 29–42.

55 R. Hajar, *Heart Views*, 2011, **12**, 121–127.

56 A. Garcia, B. S. Drown and P. J. Hergenrother, *Org. Lett.*, 2016, **18**, 4852–4855.

57 R. W. Hicklin, T. L. López Silva and P. J. Hergenrother, *Angew. Chem., Int. Ed.*, 2014, **53**, 9880–9883.

58 R. W. Huigens 3rd, K. C. Morrison, R. W. Hicklin, T. A. Flood Jr, M. F. Richter and P. J. Hergenrother, *Nat. Chem.*, 2013, **5**, 195–202.

59 E. Llabani, R. W. Hicklin, H. Y. Lee, S. E. Motika, L. A. Crawford, E. Weerapana and P. J. Hergenrother, *Nat. Chem.*, 2019, **11**, 521–532.

60 R. J. Rafferty, R. W. Hicklin, K. A. Maloof and P. J. Hergenrother, *Angew. Chem., Int. Ed.*, 2014, **53**, 220–224.

61 S. Z. Tasker, A. E. Cowfer and P. J. Hergenrother, *Org. Lett.*, 2018, **20**, 5894–5898.

62 L. Laraia, K. Ohsawa, G. Konstantinidis, L. Robke, Y. W. Wu, K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 2145–2150.

 This journal is © The Royal Society of Chemistry 2020

Published on 09 October 2020. Downloaded by University of Illinois - Urbana on 10/9/2020 10:25:18 PM.

63 N. G. Paciaroni, D. L. Perry 2nd, V. M. t. Norwood, C. Murillo-Solano, J. Collins, S. Tenneti, D. Chakrabarti and R. W. Huigens 3rd, *ACS Infect. Dis.*, 2020, **6**, 159–167.
64 J. J. Ciardiello, H. L. Stewart, H. F. Sore, W. Galloway and D. R. Spring, *Bioorg. Med. Chem.*, 2017, **25**, 2825–2843.
65 N. G. Paciaroni, R. Ratnayake, J. H. Matthews, V. M. t. Norwood, A. C. Arnold, L. H. Dang, H. Luesch and R. W. Huigens 3rd, *Chem.–Eur. J.*, 2017, **23**, 4327–4335.
66 V. M. t. Norwood, A. C. Brice-Tutt, S. O. Eans, H. M. Stacy, G. Shi, R. Ratnayake, J. R. Rocca, K. A. Abboud, C. Li, H. Luesch, J. P. McLaughlin and R. W. Huigens 3rd, *J. Med. Chem.*, 2020, **63**, 5119–5138.
67 N. G. Paciaroni, V. M. t. Norwood, R. Ratnayake, H. Luesch and R. W. Huigens 3rd, *Bioorg. Med. Chem.*, 2020, **28**, 115546–115551.
68 M. Moudi, R. Go, C. Y. S. Yien and M. Nazre, *Int. J. Prev. Med.*, 2013, **4**, 1231–1235.
69 H. Arens, H. O. Borbe, B. Ulbrich and J. Stöckigt, *Planta Med.*, 1982, **46**, 210–214.
70 A. Markham and E. M. Sorkin, *Drugs*, 1993, **45**, 931–952.
71 J. D. Albright and L. Goldman, *J. Org. Chem.*, 1965, **30**, 1107–1110.
72 N. Kagawa, J. P. Malerich and V. H. Rawal, *Org. Lett.*, 2008, **10**, 2381–2384.
73 U. G. Bhat, M. A. Winter, H. L. Pearce and W. T. Beck, *Mol. Pharmacol.*, 1995, **48**, 682–689.
74 K. N. M. Somei and F. Yamada, *Heterocycles*, 2001, **55**, 1237–1240.
75 M. Somei, K. Noguchi, K. Yoshino, K. Mori, M. Asada, F. Yamada, Y. Tanaka, K. Shigenobu and K. Koike, *Heterocycles*, 2006, **69**, 259–269.
76 H. Takayama, K. Misawa, N. Okada, H. Ishikawa, M. Kitajima, Y. Hatori, T. Murayama, S. Wongseripipatana, K. Tashima, K. Matsumoto and S. Horie, *Org. Lett.*, 2006, **8**, 5705–5708.
77 R. Stahl, H.-J. Borschberg and P. Acklin, *Helv. Chim. Acta*, 1996, **79**, 1361–1378.
78 W. R. Wilson and M. P. Hay, *Nat. Rev. Cancer*, 2011, **11**, 393–410.
79 T. Yu, B. Tang and X. Sun, *Yonsei Med. J.*, 2017, **58**, 489–496.
80 J. Fallah and B. I. Rini, *Curr. Oncol. Rep.*, 2019, **21**, 6–16.
81 K. M. Kacprzak, in *Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes*, ed. K. G. Ramawat and J.-M. Mérillon, Springer Berlin Heidelberg, Berlin, Heidelberg, 2013, pp. 605–641, DOI: 10.1007/978-3-642-22144-6_22.
82 P. J. Boratyński, M. Zielińska-Błajet and J. Skarżewski, in *The Alkaloids: Chemistry and Biology*, ed. H.-J. Knölker, Academic Press, 2019, vol. 82, pp. 29–145.
83 T. Marcelli, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 7496–7504.
84 H. Waldmann, V. Khedkar, H. Dückert, M. Schürmann, I. M. Oppel and K. Kumar, *Angew. Chem., Int. Ed.*, 2008, **47**, 6869–6872.
85 E. Dolgin, *Nat. Rev. Drug Discovery*, 2019, **18**, 408–410.
86 M. Pérez-Hernández, A. Arias, D. Martínez-García, R. Pérez-Tomás, R. Quesada and V. Soto-Cerrato, *Cancers*, 2019, **11**, 1599–1646.
87 C. I. Chude and R. K. Amaravadi, *Int. J. Mol. Sci.*, 2017, **18**, 1279–1290.
88 T. T. Shi, X. X. Yu, L. J. Yan and H. T. Xiao, *Cancer Chemother. Pharmacol.*, 2017, **79**, 287–294.
89 S. Paukner and R. Riedl, *Cold Spring Harbor Perspect. Med.*, 2017, **7**, 1–15.
90 O. Goethe, A. Heuer, X. Ma, Z. Wang and S. B. Herzon, *Nat. Prod. Rep.*, 2019, **36**, 220–247.
91 R. Shang, J. Wang, W. Guo and J. Liang, *Curr. Top. Med. Chem.*, 2013, **13**, 3013–3025.
92 S. Rittenhouse, S. Biswas, J. Broskey, L. McCloskey, T. Moore, S. Vasey, J. West, M. Zalacain, R. Zonis and D. Payne, *Antimicrob. Agents Chemother.*, 2006, **50**, 3882–3885.
93 E. P. Farney, S. S. Feng, F. Schäfers and S. E. Reisman, *J. Am. Chem. Soc.*, 2018, **140**, 1267–1270.
94 N. J. Fazakerley, M. D. Helm and D. J. Procter, *Chem.–Eur. J.*, 2013, **19**, 6509.
95 E. G. Gibbons, *J. Am. Chem. Soc.*, 1982, **104**, 1767–1769.
96 S. K. Murphy, M. Zeng and S. B. Herzon, *Science*, 2017, **356**, 956–959.
97 M. Zeng, S. K. Murphy and S. B. Herzon, *J. Am. Chem. Soc.*, 2017, **139**, 16377–16388.