Received: 30 November 2018 Revised: 16 January 2019 Accepted article published: 22 January 2019 Published online in Wiley Online Library: 10 March 2019

(wileyonlinelibrary.com) DOI 10.1002/ps.5350

Natural products: a strategic lead generation approach in crop protection discovery

Beth A Lorsbach,* Thomas C Sparks, Robert M Cicchillo, Negar V Garizi, Donald R Hahn and Kevin G Meyer

Abstract

With the anticipated population growth in the coming decades, the changing regulatory environment, and the continued emergence of resistance to commercial pesticides, there is a constant need to discover new lead chemistries with novel modes of action. We have established a portfolio of approaches to accelerate lead generation. One of these approaches capitalizes on the rich bioactivity of natural products (NPs), highlighted by the numerous examples of NP-based crop protection compounds. Within Corteva Agriscience and the affiliated preceding companies, NPs have been a fruitful approach, for nearly three decades, to identifying and bringing to the market crop protection products inspired by or originating from NPs, . Included in these NP-based crop protection products are the spinosyns family of insecticides, and those from more recent areas of NP-based fungicidal chemistry, as highlighted in this perspective.

Keywords: natural products; biologics; crop protection; lead generation; agrochemicals; genomics

1 INTRODUCTION

Natural products (NPs) have a long history as a source of active ingredients and inspiration for a wide range of pharmaceuticals and crop protection compounds. Over the past 35 years NPs, in some form, have accounted for 30–35% of all new FDA approved drugs.[1,2] Likewise, NPs have played a central role in the development of new active ingredients for crop protection for more than six decades.[3–6] Recent sales figures (2016) for the different types (insecticides, fungicides, and herbicides) of crop protection compounds show that NPs have impacted crop protection discovery in each area to varying degrees – a rather modest impact on herbicides, a far larger impact on fungicides, and the most impact on insecticides (Fig. 1). However, and importantly for crop protection compounds, NPs can account for more than 60% of the known modes of action (MoAs).[5] In the case of insecticides, more than 70% of current global sales are based on products that were NPs/NP-derived or could have been (NP synthetic equivalents [NPSE])[6] (Fig. 1). Thus, the potential for NPs to impact crop protection discovery remains high.

Despite the past impact and the future potential of NPs to influence discovery of crop protection compounds, NP-based discovery remains challenging. NP discovery in the pharmaceutical industry declined during the late 1980s and early 1990s,[8,9] coinciding with the rise of combinatorial libraries and high-throughput screening.[8] At the time, NP libraries were viewed as being not very compatible with high-throughput screening.[9,10] These aspects were coupled with an increasing dissatisfaction with the NP discovery process that tended to require a great deal of time and effort for what was seen at the time as a decreasing benefit.[9] Another influence on the shift away from NP discovery on the part of the pharmaceutical industry was the introduction and adoption of the biodiversity treaty, or the Convention on Biological Diversity (CBD), which came into force on December 29, 1993.[11] Our company and most others support the premise of the CBD and incorporate the principles of access, benefit sharing and biodiversity conservation via international collaborations. Unfortunately, compliance with the CBD is complex[11] and could become a barrier to countries being able to benefit from their natural resources.[12] NP-based discovery can be a low-yield venture; very few molecules that have true product potential are discovered. This aspect, coupled with the increasingly high costs of bringing a new crop protection product to market[13,14] can make NP-based discovery very challenging. Investment in any crop protection chemistry or NPs is undertaken only when the molecule has demonstrated robust activity in model or field situations, and instances where there are high up-front fees or long-term obligations concerning bioresources can further limit interest in and evaluation of NPs. Optimally, countries would place a low entry cost on bioresources, with a clear legal definition of benefit sharing for the rare successes.

One substantial issue was and remains the challenge in finding new NPs. As observed in a recent analysis of NPs discovered over the past 45 years,[15] more NPs are being discovered on a yearly basis; however, uncovering a really novel NP is proportionally on the decline. Potential implications from the Pye et al. study[15] are: (i) many NPs have been identified but were not explored in depth for biological utility or new opportunities, and (ii) if new novel NPs are to be discovered, different sources and approaches to NP discovery are required.

* *Correspondence to: BA Lorsbach, Corteva Agriscience™, Agriculture Division of DowDuPont™, Crop Protection Discovery, Dow AgroSciences, 9330 Zionsville Road, Indianapolis, IN 46268, USA. E-mail: beth.lorsbach@corteva.com*

Correction added on 20 March 2019 after first online publication: the Acknowledgement section has been updated in the current version of this article.

Corteva Agriscience™, Agriculture Division of DowDuPont™, Crop Protection Discovery, Dow AgroSciences, Indianapolis, IN, USA

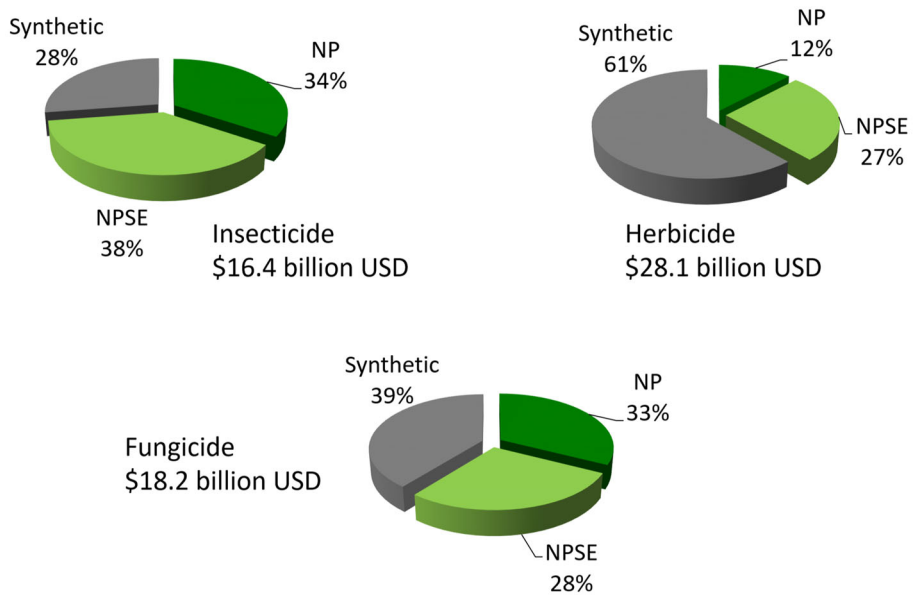

Figure 1. Impact of natural products (NPs), semi-synthetics, NP-inspired products or areas of chemistry that have NP models, but were discovered by other means (NP synthetic equivalents [NPSE]) on 2016 end-user sales.[7]

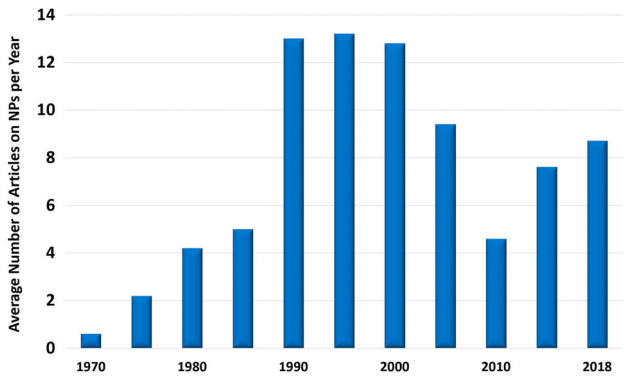

Figure 2. Average number of articles concerning natural products (NPs) per year by crop protection companies involved in the discovery of new agrochemicals. Data were compiled from 50 companies in the USA, Europe and Japan that are, or were, active in agrochemical discovery during the past 30–40 years.

Unlike the pharmaceutical industry, interest in NPs on the part of crop protection companies did not decline in the same way. One measure of interest in NPs as a source for new crop protection compounds is the average number of publications per year concerning NPs by crop protection companies involved in discovery of new herbicides, fungicides, and insecticides. Interestingly, and in some contrast to the pharmaceutical industry, the crop protection (agrochemical) industry has had an interest in NPs for some time, especially beginning in the 1990s (Fig. 2), just as interest on the part of the pharmaceutical industry was declining. However, the data in Fig. 2 may also be an underrepresentation of industry interest and research efforts as publishing in industry is not emphasized to the same extent as it is for academics. The interest in NPs on the part of industry is also supported by the results of a survey conducted in the early 1990s among 20 crop protection companies that details a robust interest in NPs as sources of starting points for products or leads for new agrochemicals.[16]

As discussed in previous and more recent reviews, there are a number of discovery approaches utilized by crop protection research organizations, of which NP-based discovery is only one.[17–22] Moreover, the challenges involved in discovery of a new crop protection product are significant, including a continual increase in the time required to bring a molecule to market, on average, 10–12 years, as well as the cost of discovery and development of a new agrochemical product, last estimated at 286 million US$.[14,23] Therefore, it is critical that agrochemical companies look for ways to increase the probability of success and to accelerate the building of a product (Fig. 3). One tactic that Corteva Agriscience (CAS) has employed is the exploitation of NPs. As noted above, NPs have been, or could have been, involved in the determination of a high proportion of the known MoAs of crop protection compounds. Thus, NP-based discovery programs continue to have the potential to lead to new crop protection compounds with new, unexploited MoAs, a highly prized attribute in the crop protection marketplace. However, in spite of the long-standing interest in NPs on the part of the crop protection industry, NP-based discovery remains a challenging source of inspiration and products for new crop protection compounds. Although a majority (65%) of the companies surveyed in 1993 had some success with NPs as a discovery tool, many of these same companies had abandoned in-house NP discovery, with a higher proportion using external collaborations.[16] Today, far fewer companies have in-house-based NP discovery programs that involve isolation and characterization of NPs. Several factors contributed to the move away from NP-based discovery. First, as noted above, is the fundamental challenge and the difficulties of finding truly new NPs. Second, few NPs have the physicochemical properties suitable for direct use as crop protection products, and some degree of semi-synthesis, to address translation and/or stability limitations, as well as to improve efficacy, may be required. Most commonly, NPs have best served as inspiration for synthetic mimics. However, morphing complex NPs into synthetically accessible chemistry can take longer than other lead generation approaches.[20]

Within CAS (formerly Dow AgroSciences, DAS), NP-based discovery has been a long-standing lead generation approach,[21,24] emerging from the NP research at Eli Lilly (Elanco) that carried

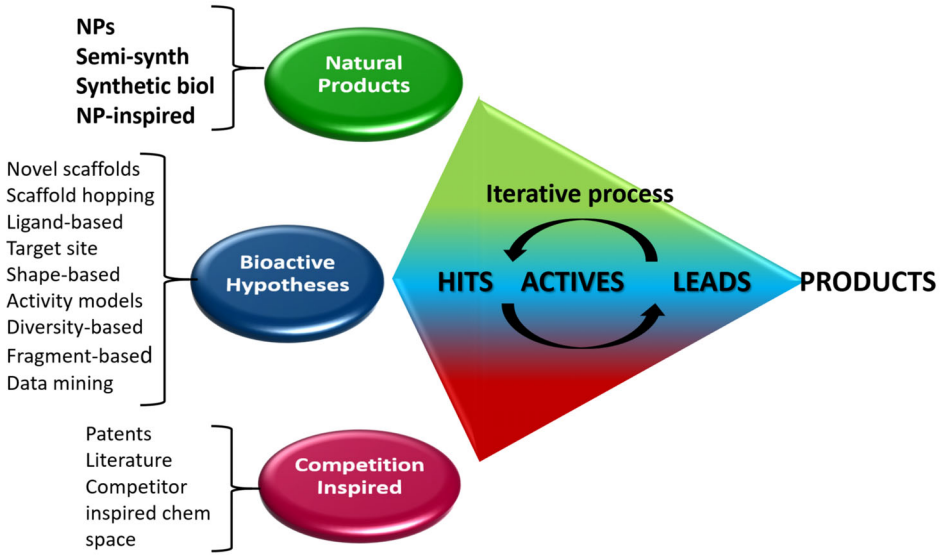

Figure 3. Lead generation using a portfolio of approaches.

over to the joint venture in crop protection between Dow Chemical and Elanco (DowElanco) in 1989. In the 1940s, Eli Lilly and Company was one of the key companies involved in the production of the antibiotic penicillin, followed in the 1950s and 1960s by the discovery and successful marketing of the microbial-based antibiotics erythromycin,[25,26] vancomycin,[27] cephalosporin,[28] and tyosin.[29] Continued interest in NP-based lead generation within DowElanco/DAS/Corteva Agriscience has been fueled, in part, by the discovery and successful development of spinosad, a naturally occurring mixture of the highly insecticidal macrolide spinosyns A and D, NPs produced by a soil microbe.[24] Continued interest in NP-based insecticides stimulated the development of a second spinosyn-based, semi-synthetic insecticide, spinetoram.[30] Along the way, the discovery a new family (21-butenyl) of spinosyns[31] and the genetic engineering of the spinosyn biosynthetic pathway to produce new spinosyn derivatives[32] have also helped maintain interest in NPs. More recently, the NP-based discovery program at Corteva has continued to deliver new crop protection compounds, including the new fungicides fenpicoxamid[33,34] and florylpicoxamid[7] and the new insecticidal synthetic spinosyn mimics.[35,36] As noted above, a key advantage of an NP-based discovery program is the enhanced probability of finding crop protection compounds that possess new MoAs. This outcome is exemplified by both the spinosyns and new fungicidal chemistry, and it has further served to maintain interest in NP-based lead generation within CAS. The following perspective will discuss our approach to NP discovery, including an overview of our strain collection, as well as providing highlights of typical NP discovery projects at our company, and will conclude with a look to the future and the options for accelerating NP discovery with new approaches.

2 LEAD GENERATION APPROACHES

As noted above, lead generation in crop protection discovery can involve a wide range of activities. Within CAS, these activities are grouped into three broad arenas:[2] competitor inspired activities, bioactive hypotheses, and NP discovery (Fig. 3). Competitor-inspired lead generation is a somewhat self-explanatory approach focused on gleaning insights from patents and scientific literature, and is a widely practiced and successful approach to delivering commercial products. Having said that, this approach is implemented slightly differently at CAS, in that the objective is to identify starting points from which to exploit and deliver novel pesticidal motifs and scaffolds rather than to identify gaps in intellectual property and obtain rights to derivative analogs. The second approach to lead generation is bioactive hypotheses; the notion that biological activity leads to biological pesticide activity is the core to this approach. Scientists identified privileged scaffolds, motifs, functional groups, and compounds that have demonstrated a biological response within any system, cell, or whole organism. This supports the notion that incorporation of such scaffolds, motifs, or functional groups in developing new compounds could result in a higher probability of eliciting a biological response. The stronger this evidence and correlation between the cores (e.g. scaffolds) and the biological response are, the greater the chances of observing biological activity in novel compounds. Moreover, this approach relies on ensuring that desirable physical properties are built into compounds at an early stage, to increase translation from *in vitro* cell-based assays to *in vivo* whole *planta* and insect assays.[37] The third lead generation approach centers around NPs. NP-based discovery has been and remains one of the three key pillars for lead generation in our company, influenced, in part, by NP-based products such as the spinosyns (spinosad, spinetoram) which generate more than 400 million US$/year in end-user sales (2014–2016).[6,7,38] For nearly three decades, the NP-discovery program at DowElanco/Dow AgroSciences/Corteva Agriscience, has had a basic interest in the identification and isolation of new, novel NPs. Biodiverse inputs have been examined to maximize the opportunity of discovering novel active molecules.

3 NATURAL PRODUCT COLLECTION

Conventional biology has assumed that biodiversity is distributed unevenly, with an abundance of observable species in tropical and marine environments and in natural, as opposed to urban, landscapes. To sample diversity for NP discovery, approximately 90% of the inputs to the DAS NP program over the past 30 years were the result of collaborations with more than 50 private,

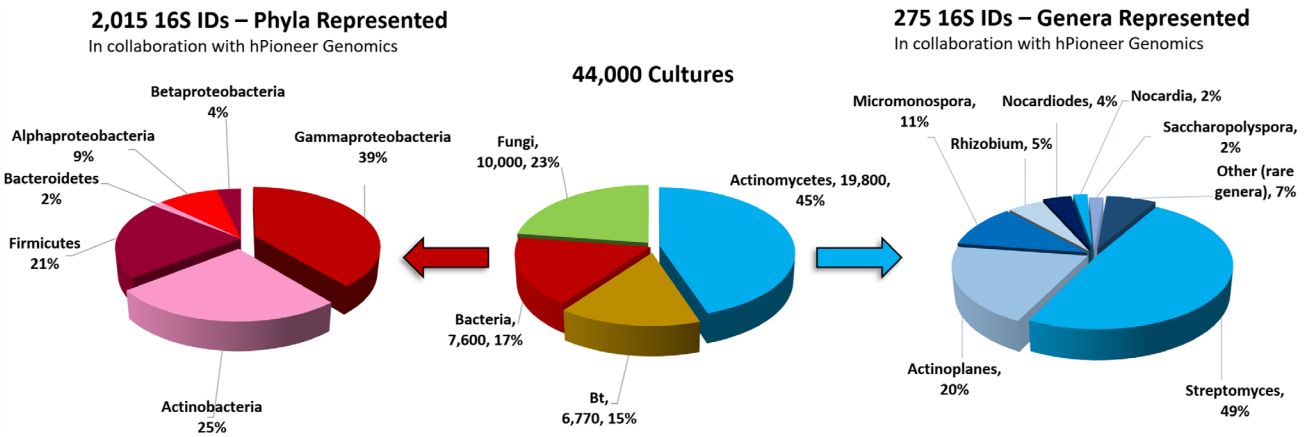

Figure 4. Heritage Dow AgroSciences (now Corteva Agriscience) culture collection.

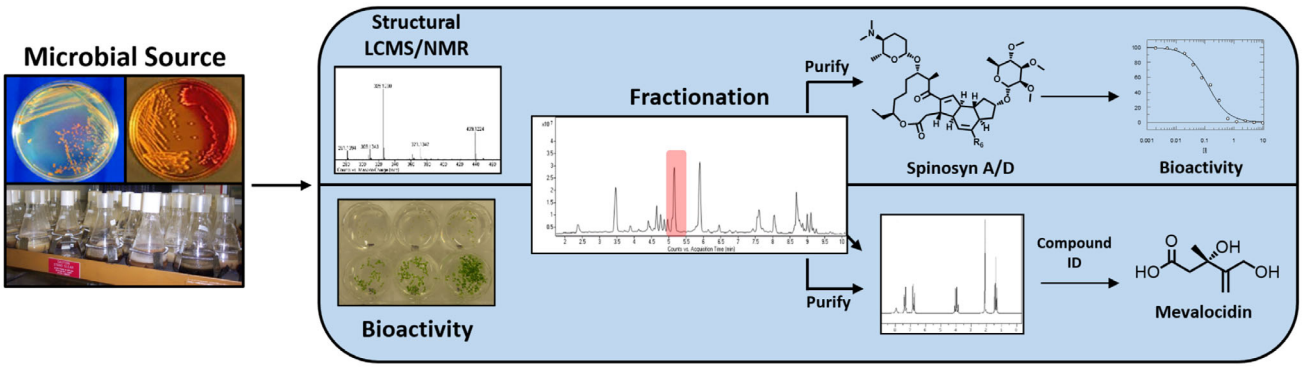

Figure 5. Traditional bioactivity- and structure-based approaches to natural product (NP) discovery.

academic and governmental entities.[39–44] This third-party sourcing enabled sampling of biodiversity from a wide range of geographic, environmental and taxonomic sources. Third-party sources for DAS NP discovery over the past 25 years included more than 850 000 NP extracts and more than 2500 pure NPs. The vast majority of those entities were screened prior to 2013. Since then, our per capita screening numbers are now lower as we have moved to a more targeted approach for NP inputs.

The remainder of the DAS NP discovery effort (*c* 10%) was dedicated to the evaluation of microbes (bacteria, actinomycetes, and fungi) from the DAS culture collection (Fig. 4). This culture collection comprises approximately 44 000 strains, isolated primarily from domestic soil samples by DAS, Lilly and Mycogen scientists over the course of more than 30 years. Approximately 10 000 cultures were purchased from third parties. One third of the organisms were obtained with a focus on discovery of novel insect resistance traits, and the remainder were obtained for NP discovery. The collection is largely taxonomically uncharacterized, as it was assembled in a high through-put fashion under the assumption that diversity of source led to diversity of bioactivity. Recent efforts to characterize the collection using 16S sequencing have revealed a wide taxonomic diversity as detailed in Fig. 4. The collection comprises three groups of organisms: 14 400 bacteria (traits focus), 10 000 fungi (NP focus) and 19 800 actinomycetes (NP focus). The bacterial collection includes 6800 *Bacillus thuringiensis* (*Bt*) isolates and 7600 non-*Bt* bacteria isolates (Fig. 4). A major proportion of the non-*Bt* bacteria isolates are non-filamentous actinomycete genera such as *Micrococcus* and *Curtobacteria*. The 10 000 fungi isolates are primarily unidentified soil fungi, although a significant number of plant, pathogenic and entomopathogenic, fungi are included. The 19 800 actinomycete isolates are mostly filamentous genera including approximately 50% *Streptomyces* and 50% rare actinomycetes such as *Micromonospora, Saccharopolyspora* and *Actinoplanes* (Fig. 4). Recent investigations into microbial genomics have indicated that microbes, particularly actinomycetes and fungi, have a large number of cryptic biosynthetic pathways that are not expressed under normal laboratory conditions.[45] As a result, cultures in the DAS culture collection have a significant potential value for further NP discovery. The actinomycete collection will be our primary focus for the next few years, for further investigation using metabolo-genomics.

4 STRATEGIES TO IDENTIFY NATURAL PRODUCTS

Two strategies are typically used to identify interesting NPs within a broth or extract; (i) bioactivity-based tactic or (ii) structure-based tactic (Fig. 5). The bioactivity-based tactic involves evaluation of the crude extract/broth in a bioassay such as an *in vitro* fungitoxicity assay. Crude extracts/broths that demonstrate biological activity are then fractionated and evaluated again in appropriate bioassays. Fractions that confirm bioactivity are purified and the identities of any isolated compounds are structurally elucidated via NMR and MS. The structure-based tactic begins with analytical assessment for unique structural/physical property attributes in the crude extract/broth. The crude mixture is then fractionated, based on novelty, as compared to the historic DAS

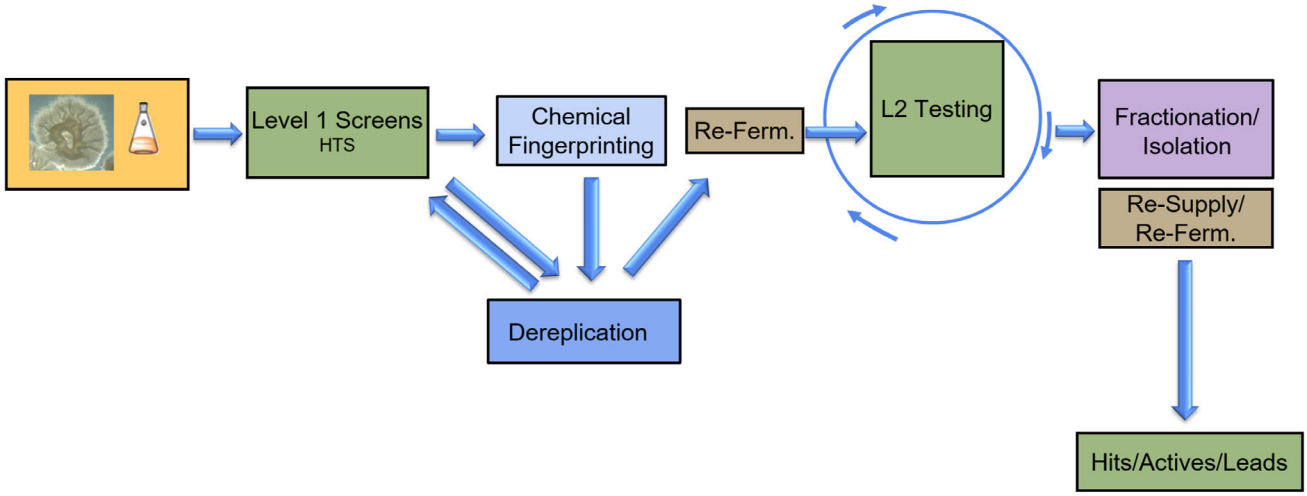

Figure 6. Current approach to natural product (NP) discovery at Corteva Agriscience.

NP collection, according to the analytical evaluation. The fractions are re-assessed for unique structural features, subsequently purified, and tested for bioactivity.[46] At CAS, the focus on a bioactivity-based tactic has proven fruitful, albeit lengthy, in identifying agrochemically relevant NPs of interest.[21,31,40,42,47] The specific workflow and screening cascade utilized currently is illustrated in Fig. 6. Bioactivity-based NP discovery at DAS has resulted in the discovery of more than 50 compounds that were classified as hits, and seven compounds with more interesting features, including higher levels of biological activity, that were classified as actives. It should be noted that CAS has internal efficacy thresholds, which NP hits must meet, that are similar to hits and actives from the other lead generation approaches discussed above. These molecules were derived from 1665 extracts that had activity sufficient to be scaled for further testing. A total of 704 extracts were fractionated for isolation, resulting in the more than 50 hits that had not been discovered previously at DAS. Targeted screening of 2500 pure NPs, obtained from venders or collaborators, resulted in more than 100 hits and four actives. These molecules were selected *a priori* for unique chemistry or bioactivity and, thus, had a higher initial hit rate.

5 CASE STUDIES

At CAS, there has been significant success with insecticidal NPs, specifically the spinosyns spinosad[24] and spinetoram,[30] and most recently, with the development of simplified synthetic mimics of the spinosyns[35,36] These success stories have been discussed in several forums and truly provided the platform for NP research efforts. As such, in this perspective, the cases studies will focus on NP research efforts that were made possible by the legacy and successes of the NP efforts with spinosyn.

One example, where this approach successfully led to a novel NP of interest, is our previous efforts concerning mevalocidin (Fig. 7). In the course of screening a large collection of fungal extracts from *Mycosynthetix,* mevalocidin was discovered at DAS[42] from static cultures of two fungal isolates of *Coniolariella* spp. MSX92917 (DA092917) and MSX56446 (DA056446).[48] Mevalocidin demonstrated broad-spectrum post-emergence activity on grasses and broadleaves.[42] Symptoms of plants treated with mevalocidin suggest a novel MoA and ambi-mobility in grass as well as in broadleaf weeds. While the NP displays good post-emergent activity in high-volume/high-rate applications, a synthetic investigation of mevalocidin demonstrated that the structure–activity relationship is quite narrow, and significant enhancements of potency have not been obtained to date. Mevalocidin is thought to act via disruption of early steps in the mevalonate/isoprenoid biosynthetic pathway in the cytoplasm (Fig. 7). Some preliminary work with *Arabidopsis* suggests that activation and metabolism (a protoxon) may play a role in the overall efficacy of mevalocidin (unpublished data). Additionally, the fungal biosynthetic machinery required for mevalocidin production has not been elucidated. Further work is necessary to understand the biosynthesis, MoA, and *in planta* fate in order to enhance the efficacy of mevalocidin and/or mevalocidin analogs.

Recently, we described some of the biological characteristics of fenpicoxamid (Fig. 8), a novel picolinamide fungicide discovered in collaboration with Meiji Seika Pharma Co. Ltd., which is currently under development by CAS.[33] Fenpicoxamid is a derivative of the natural antifungal compound UK-2A, originally isolated from actinomycete *Streptomyces* sp. 517–02 fermentation broth,[49–52] extracts that demonstrated strong antifungal activity against a broad spectrum of fungi in *in vitro* assays (Fig. 6).[50] The picolinamide class of chemistry acts by inhibiting mitochondrial respiration via binding to the Qi ubiquinone site of the cytochrome bc_1 complex and shows no target site-based cross-resistance with strobilurins acting at the Qo target site.[34]

For these reasons, UK-2A was considered an attractive candidate for semi-synthetic modification, to optimize intrinsic antifungal activity and other key attributes required for *in planta* pathogen control. Synthesized in one step post fermentation from UK-2A, fenpicoxamid provides exceptional control of *Zymoseptoria tritici* (synonym, *Mycosphaerella graminicola,* wheat leaf blotch), the pathogen of greatest concern for winter wheat production in Europe.[55] With its novel biochemical MoA, fenpicoxamid is anticipated to be an important addition to EU resistance management programs for cereals.

UK-2A has other structural features amenable to semi-synthetic modification which provide an opportunity for structure–activity relationship (SAR) studies. The enabling synthetic strategy focuses on three regions of UK-2A for study: alternative 'head' groups, C7 exocyclic esters, and C8 benzyl substituents (Fig. 9). More than 250 analogs were prepared and evaluated for control of *Z. tritici* as well as for synthetic feasibility.[54,56] Typical synthetic routes to these

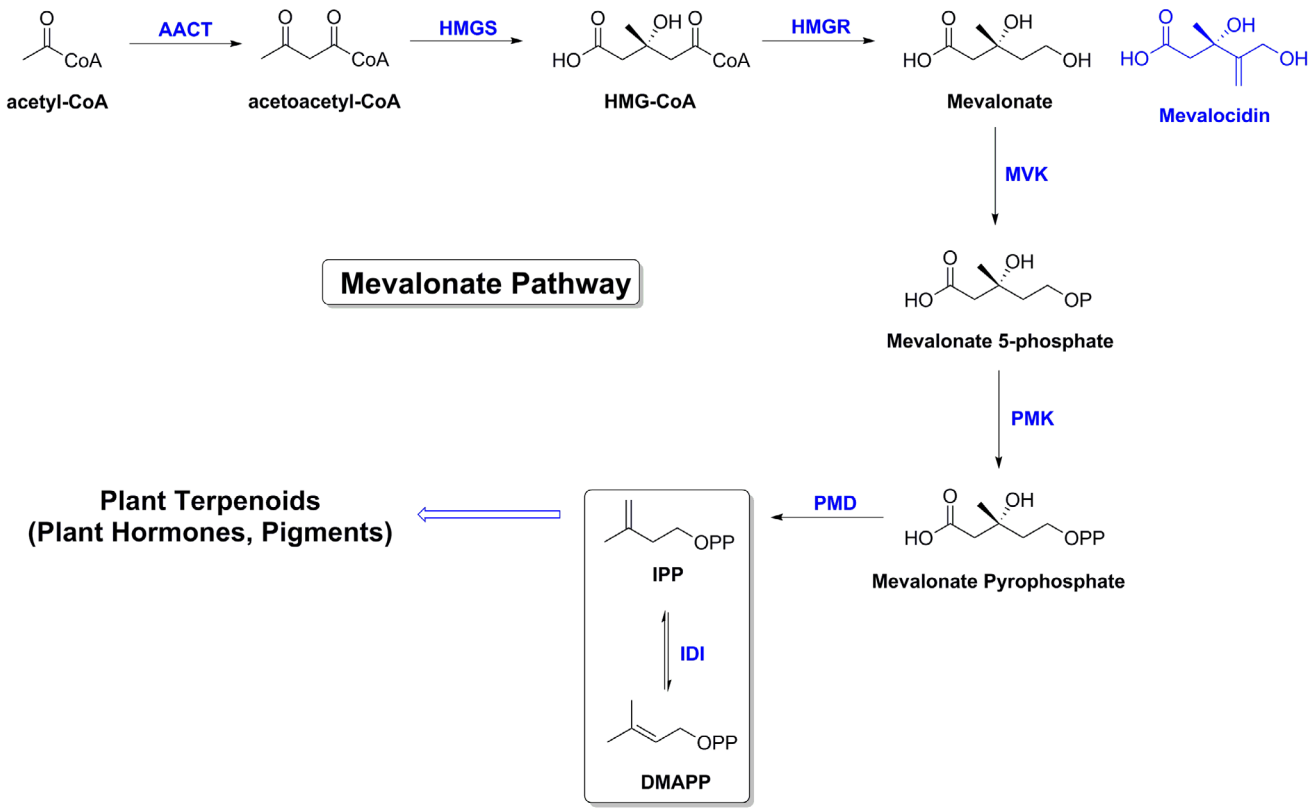

Figure 7. Mevalonate pathway in terpenoid biosynthesis. Structure of mevalocidin in blue. Abbreviations: AACT, acetoacetyl-CoA thiolase; HMGR, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; HMGS, 3-hydroxy-3-methyl-glutaryl coenzyme A synthase; IDI, isopentenyl diphosphate isomerase; MVK, mevalonate kinase; PMD, diphosphomevalonate decarboxylase; PMK, phosphomevalonate kinase.

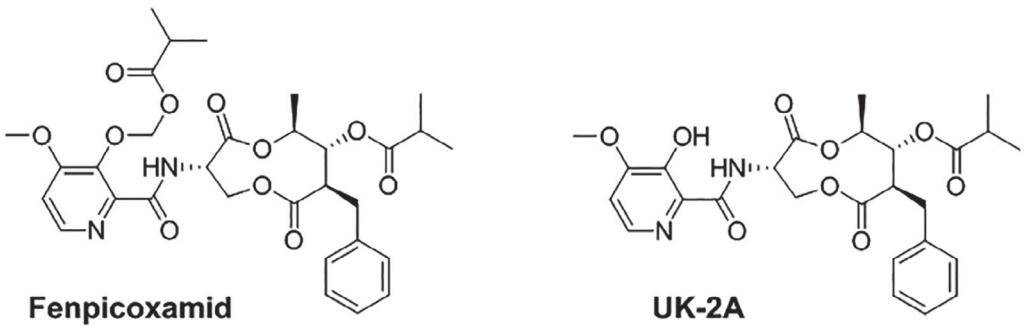

Figure 8. Structures of fenpicoxamide and UK-2A.

analogs are illustrated in Fig. 10 and, although some structural replacements resulted in analogs with comparable or even slightly better *in vitro* potency relative to fenpicoxamid, the efficacy gains were not sufficient for consideration of development.

6 POTENTIAL FUTURE DIRECTIONS FOR NP DISCOVERY

Despite successful efforts in the context of NPs, historic reliance on sampling a broad range of NP extracts from geographically diverse sources is no longer considered a viable path forward, because of high levels of re-discoveries, an absence of novelty in scaffolds that are readily accessible, and the aforementioned difficulty in obtaining large number of samples as the result of the CBD.[15] Following extensive analysis (see also References 5 and 6), the current NP strategy has shifted to include other avenues such as more targeted sources of NPs.

Recent advances in whole genome sequencing, metagenomics, and synthetic biology, coupled with more sensitive mass and NMR spectroscopy capabilities, have ushered in what has been coined as the "New Golden Age"[57] or 'Renaissance'[58] of NP discovery. Researchers have successfully demonstrated that genome-guided NP discovery via direct capture of gene clusters from gDNA and subsequent expression in heterologous hosts can lead to novel NP scaffolds.[59] But the full potential of this approach has not yet been fulfilled because of the bioinformatic challenges in identifying novel biosynthetic gene clusters (BGC) and in subsequently predicting chemical structures.[60] A more actionable approach is the combination of genomic analyses and metabolomics data to more accurately allow the linkage of BGC to known and unknown NP families.[61] The success of this approach is directly linked to

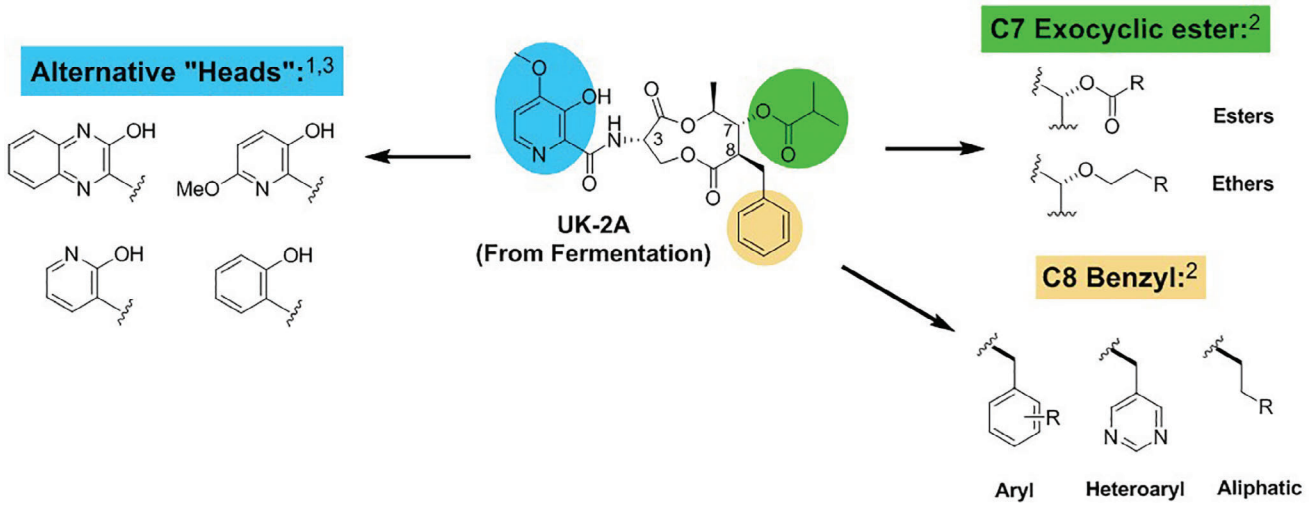

Figure 9. Synthetic derivatization strategy. 'Head', Usuki *et al.*[53] and C7 exocyclic ester and C8 benzyl, Meyer *et al.*[54]

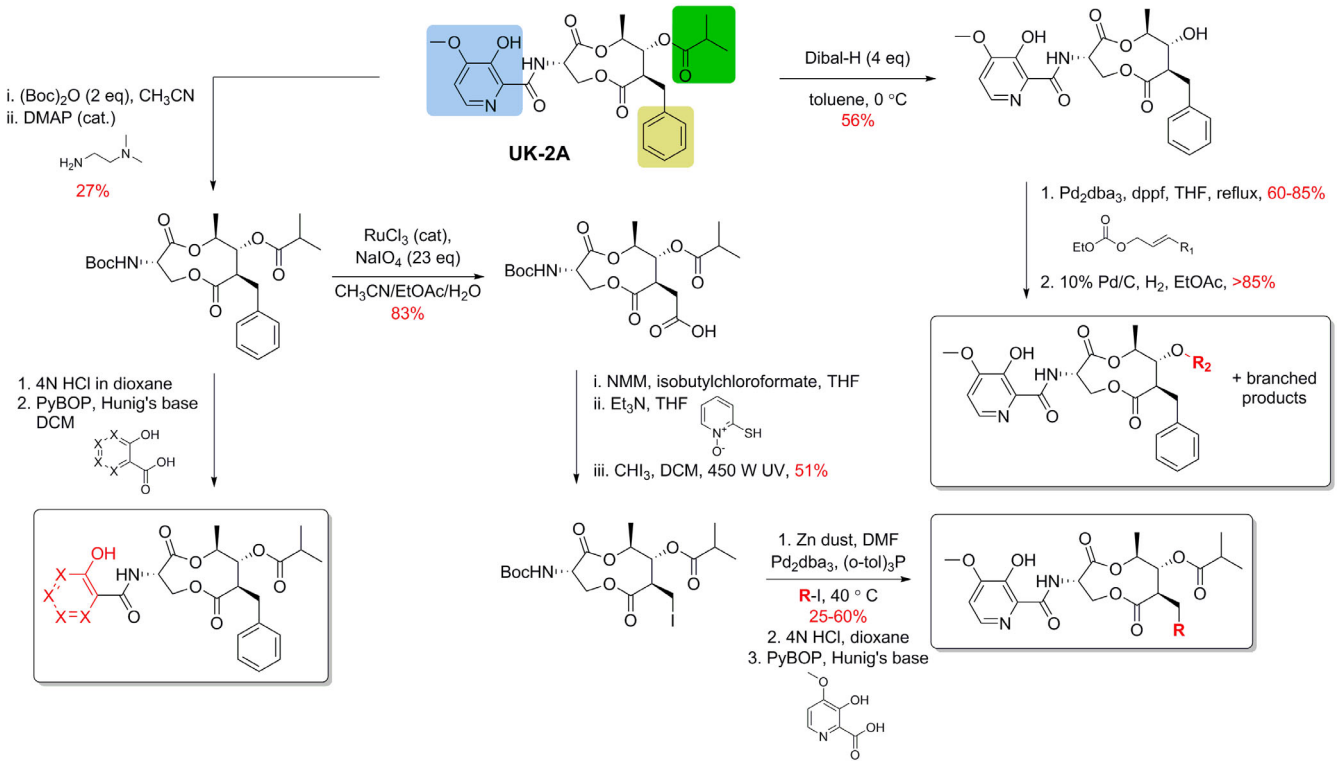

Figure 10. Derivatization of three accessible regions of UK-2A.

the scale of generated data sets, as well as to a diverse strain collection, as there is a strong connection between phylogeny and NP BGCs. The data presented by Metcalf and co-workers[61] shows that two strains separated by a ribosomal protein distance of 0.5% probably share almost all of their NP gene clusters, whereas strains separated by 7% share almost none. While this approach is promising for the discovery of novel NP scaffolds, it is crucial to enabling access to large quantities of these novel scaffolds for SAR exploration and, ultimately, for large scale production. In cases where traditional synthetic chemistry approaches may not be adequate or economical, the use of synthetic biology could allow access to NP analogs and synthetically useful intermediates. One remarkably successful example of the use of synthetic biology to create a key precursor on a large scale is the production of artemisinic acid, a precursor to artimisinin. The incorporation of the gene cluster from *Artemisia annua* into a recombinant yeast host has yielded artemesinic acid in a 25 g/L fermentation titre.[62]

7 NATURAL PRODUCT DISCOVERY GAPS

Strengthening the ties between industry and academic institutions is a must, to fully tap into and take advantage of the opportunities presented by NPs and to better explore the evolving technologies. Many academic groups have isolated novel NPs, but they do not have the means to fully evaluate the compounds for crop protection bioactivity/utility. This link between NPs

and relevant crop protection assay systems is recognized by speakers this conference on "Natural Products in Pest Management: Innovative approaches for increasing their use" which took place in Bellagio, Italy on 25–29 September 2018., by academic institutions, and by potential industry partners such as CAS who aim to increase the means and lower the barriers to testing these NPs. Participating in a collaboration would be welcomed by CAS, as it is line with our long history with NPs and our track record of delivering innovative solutions based on NPs.

8 SUMMARY

NPs are sources of great chemical diversity, biological function and novel modes of action. Both crop protection companies and pharmaceutical companies are continuing and increasing investment into NP research. Despite the challenges of NP-based discovery, the advantages of identifying new modes of action and new chemistry starting points makes this a worthy pursuit. Looking toward the future, the advent of genomics and its application to NP-based discovery could accelerate the identification and development of agrochemical solutions that are directly based on, or inspired by, NPs.

ACKNOWLEDGEMENT

We thank Dr James Hunter for useful comments and discussion during the writing of this perspective. We also thank Drs Stephen Duke, Maurizio Vurro, and Antonio Evidente for the invitation to participate to a conference sponsored by the OECD's Co-operative Research Programme on Biological Resource Management for Sustainable Agricultural Systems, and all of the participants at the conference for their stimulating discussions and feedback regarding NP research at Corteva Agriscience.

This paper was presented at the workshop on Natural Products in Pest Management: Innovative approaches for increasing their use which took place in Bellagio, Italy on 25–29 September 2018, which was sponsored by the OECD Co-operative Research Programme: Biological Resource Management for Sustainable Agricultural Systems and whose financial support made it possible for Beth Lorsbach to participate in the workshop.

The opinions expressed and arguments made in this paper are the sole responsibility of the authors and do not necessarily reflect those of the OECD or of the governments of its member countries.

REFERENCES

1 Patridge E, Gareiss P, Kinch MS and Hoyer D, An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discov Today* **21**:204–207 (2015).
2 Newman DJ and Cragg GM, Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* **79**:629–661 (2016).
3 Dayan FE, Cantrell CL and Duke SO, Natural products in crop protection. *Bioorg Med Chem* **17**:4022–4034 (2009).
4 Cantrell CL, Dayan FE and Duke SO, Natural products as source for new pesticides. *J Nat Prod* **75**:1231–1242 (2012).
5 Gerwick BC and Sparks TC, Natural products for pest control: an analysis of their role, value and future. *Pest Manag Sci* **70**:1169–1185 (2014).
6 Sparks TC, Hahn DR and Garizi NV, Natural products, their derivatives, mimics and synthetic equivalents: role in agrochemical discovery. *Pest Manag Sci* **73**:1169–1185 (2017).
7 Agranova Alliance, Crop Protection Actives. Available: http://www.agranova.co.uk [20 September 2018].
8 Ortholand J-Y and Ganesan A, Natural products and combinatorial chemistry: back to the future. *Curr Opinion Chem Biol* **8**:271–280 (2004).
9 Lam KS, New aspects of natural products in drug discovery. *Trends Microbiol* **15**:279–289 (2007).
10 Li JW-H and Vederas JC, Drug discovery and natural products: end or an era or an endless frontier? *Science* **325**:161–165 (2009).
11 Kingston DGI, Modern natural products drug discovery and its relevance to biodiversity conservation. *J Nat Prod* **74**:496–511 (2011).
12 McKluskey K, Barker KB, Barton HA, Boundy-Mills K, Brown DR, Coddington JA *et al.*, The U.S. culture collection network responding to the requirements of the Nagoya Protocol on access and benefit sharing. *MBio* **8**:1–10 (2017).
13 Maienfisch P and Stevenson TM, Modern agribusiness – markets, companies, benefits and challenges, in *Discovery and Synthesis of Crop Protection Products*, ed. by Maienfisch P and Stevenson TM. ACS, Washington, DC, pp. 1–13 (2015).
14 Sparks TC and Lorsbach BA, Perspectives on the agrochemical industry and agrochemical discovery. *Pest Manag Sci* **73**:762–677 (2017).
15 Pye CR, Bertin MJ, Lokey RS, Gerwick WH and Linington RG, Retrospective analysis of natural products provides insights for future discovery trends. *Proc Natl Acad Sci U S A* **114**:5601–5606 (2017).
16 Pllimoor JR, Wright K and Terry AS, Natural products as a source of agrochemicals and leads for chemical synthesis. *Pestic Sci* **39**:131–140 (1993).
17 Menn JJ, Contemporary frontiers in chemical pesticide research. *J Agric Food Chem* **28**:2–8 (1980).
18 Morrod RS, Lead generation: designing the right approach. *Phil Trans R Soc London B* **295**:35–44 (1981).
19 Hummel HE, Insecticides and their design. *J Nematol* **15**:615–639 (1983).
20 Sparks TC, Insecticide discovery: an evaluation and analysis. *Pestic Biochem Physiol* **107**:8–17 (2013).
21 Loso MR, Garizi N, Hegde VB, Hunter JE and Sparks TC, Lead generation in crop protection research: a portfolio approach to agrochemical discovery. *Pest Manag Sci* **73**:678–685 (2017).
22 Sparks TC and Lorsbach BA, Agrochemical discovery – building the next generation of insect control agents, in *Advances in Agrochemicals: Ion Channels and G Protein-Coupled Receptors (GPCRs) as Targets for Pest Control*, ed. by Gross AD, Ozoe Y and Coats JR. American Chemical Society, Washington, DC, pp. 1–17 (2017).
23 Phillips M, The cost of new agrochemical product discovery, development and registration in 1995, 2000, 2005–8 and 2010 to 2014, in *R&D Expenditure in 2014 and Expectations for 2019*. A Consultancy Study for CropLife International, CropLife America and the European Crop Protection Association, London, p. 41 (2016).
24 Thompson GD, Dutton R and Sparks TC, Spinosad – a case study: an example from a natural products discovery programme. *Pest Manag Sci* **56**:696–702 (2000).
25 McGuire JM, Bunch RL, Anderson RC, Boaz HE, Flynn EH, Powell HM *et al.*, Ilotycin, a new antibiotic. *Antibiot Chemother* **2**:281–284 (1952).
26 Forfar JO and Maccabe AF, Erythromycin – a review. *Antibiot Chemother* **4**:115–157 (1957).
27 McCormick MH, McGuire JM, Pittenger GE, Pittenger RC and Stark WM, Vancomycin, a new antibiotic. I. chemical and biologic properties. *Antibiot Ann* **3**:606–611 (1956).
28 Morin RB, Jackson BG, Flynn EH and Roeske RW, Chemistry of cephalosporin antibiotics. I. 7-aminocephalosporanic acid from cephalosporin C. *J Am Chem Soc* **84**:3400–3401 (1962).
29 McGuire JM, Boniece WS, Higgens CE, Hoehn MN, Stark WM, Westhead J *et al.*, Tylosin, a new antibiotic: I. microbiological studies. *Antibiot Chemother* **11**:320–327 (1961).
30 Sparks TC, Crouse DG, Dripps JE, Anzeveno P, Martynow J and Gifford J, Artificial neural network-based QSAR and the discovery of spinetoram. *J Comput Aided Mol Des* **22**:393–401 (2008).
31 Lewer P, Graupner PR, Hahn DR, Karr LL, Duebelbeis DO, Gilbert JR *et al.*, Discovery of the butenyl-spinosyn insecticides: novel macrolides from the new bacterial strain, *Saccharopolyspora pogona*. *Bioorg Med Chem* **17**:4185–4196 (2009).
32 Sheehan LS, Lill RE, Wilkinson B, Sheridan RM, Vousden WA, Kaja AL *et al.*, Engineering the spinosyn PKS: directing starter unit incorporation. *J Nat Prod* **69**:1702–1710 (2006).
33 Owen WJ, Yao C, Myung K, Kemmitt G, Leader A, Meyer KG *et al.*, Biological characterization of fenpicoxamid, a new fungicide with utility in cereals and other crops. *Pest Manag Sci* **73**:2005–2016 (2017).

34 Young DH, Wang NX, Meyer ST and Avila-Adame C, Characterization of the mechanism of action of the fungicide fenpicoxamid and its metabolite UK-2A. *Pest Manag Sci* **74**:489–498 (2018).
35 Crouse GD, Demeter DA, Samaritoni G, McLeod CL and Sparks TC, *De novo* design of potent insecticidal synthetic mimics of spinosyn macrolide natural products. *Sci Rep* **8**:4861 (2018).
36 Sparks TC, Crouse GD, Demeter D, Samaritoni G and McLeod CL, Discovery of highly insecticidal synthetic spinosyn mimics – CAMD enabled de novo design simplifying a complex natural product. *Pest Manag Sci* **75**:309–313 (2019).
37 Zhang Y, Lorsbach BA, Castetter S, Lambert WT, Kister J, Wang NX *et al.*, Physicochemical property guidelines for modern agrochemicals. *Pest Manag Sci* **74**:1979–1991 (2018).
38 Sparks TC, Hunter JE, Lorsbach BA, Hanger G, Gast RE, Kemmitt G *et al.*, Crop protection discovery: is being first best? *J Agric Food Chem* **66**:10337–10346 (2018).
39 Brennen NJ, Larsen L, Lorimer SD, Perry NB, Chapin EL, Werk TL *et al.*, Fungicidal sesquiterpene dialdehyde cinnamates from *Pseudowintera axillaris*. *J Agric Food Chem* **54**:468–473 (2006).
40 Irvine NM, Yerkes CN, Graupner PR, Roberts RE, Hahn DR, Pearce C *et al.*, Synthesis and characterization of synthetic analogs of cinnacidin, a novel phytotoxin from *Nectria* sp. *Pest Manag Sci* **64**:891–899 (2008).
41 Cao S and Kingston DGI, Biodiversity conservation and drug discovery: can they be combined? The Suriname and Madagascar experiences. *Pharm Biol* **47**:809–823 (2009).
42 Gerwick BC, Brewster WK, deBoer GJ, Fields SC, Graupner PR, Hahn DR *et al.*, Mevalocidin: a novel, phloem mobile phytotoxin from *Fusarium* DA056446 and *Rosellinia* DA092917. *J Chem Ecol* **39**:253–261 (2013).
43 Radkotonodraibe LH, Graupner P, Xiong Q, Olson M, Wiley JD, Krai P *et al.*, Neolignans and other metabolites from *Ocotea cymosa* from the Madagascar rain forest and their biological activities. *J Nat Prod* **78**:431–440 (2015).
44 Fotso S, Graupner P, Xiong Q, Gilbert JR, Hahn DR, Avila-Adame C *et al.*, Alveolaride A-C three antifungal peptides from *Microascus alveolaris* and their biological activities. *J Nat Prod* **18**:10–15 (2017).
45 Nett M, Ikeda H and Moore BS, Genomic basis for natural product biosynthetic diversity in the actinomycetes. *Nat Prod Rep* **26**:1353–1508 (2009).
46 Henkea MT and Kelleher NL, Modern mass spectrometry for synthetic biology and structure-based discovery of natural products. *Nat Prod Rep* **33**:942–950 (2016).
47 Hahn DR, Graupner PR, Chapin E, Gray J, Heim D, Gilbert JR *et al.*, Albucidin: a novel bleaching herbicide from *Streptomyces albus* subsp. *clorinus* NRRL B-24108. *J Antibiot* **62**:191–194 (2009).
48 Sica VP, Figueroa M, Raja HA, El-Elimat T, Darveaux BA, Pearce CJ *et al.*, Optimizing production and evaluating biosynthesis in situ of a herbicidal compound, mevalocidin, from *Coniolariella* sp. *J Ind Microbiol Biotechnol* **43**:1149–1157 (2016).
49 Hanafi M, Shibata K, Ueki M and Taniguchi M, UK-2A, B, C and D, novel antifungal antibiotics from *Streptomyces* sp. 517–02. II. Structural elucidation. *J Antibiot* **49**:1226–1231 (1996).
50 Ueki M, Abe K, Hanafi M, Shibata K, Tanaka T and Taniguchi M, UK-2A, B, C and D, novel antifungal antibiotics from *Streptomyces* sp. 517–02. I. Fermentation, isolation, and biological properties. *J Antibiot* **49**:639–643 (1996).
51 Shibata K, Hanafi M, Fujii J, Sakanaka O, Iinuma K, Ueki M *et al.*, UK-2A, B, C and D, novel antifungal antibiotics from *Streptomyces* sp. 517–02 III. Absolute configuration of an antifungal antibiotic, UK-2A, and consideration of its conformation. *J Antibiot* **51**:1113–1116 (1998).
52 Shimano M, Shibata T and Kamei N, Enantioselective total synthesis of the antifungal dilactone, UK-2A: the determination of the relative and absolute configurations. *Tetrahedron Lett* **39**:4363–4366 (1998).
53 Usuki Y, Mitomo K, Adachi N, Ping X, Fujita K-L, Sakanaka O *et al.*, Semi-synthesis and biological evaluation of analogs of UK-2A, a novel antifungal antibiotic from *Steptomyces* sp. 517-02. *Bioorg Med Chem Lett* **15**:2011–2014 (2005).
54 Meyer KG, Owen WJ, Niyaz NM, Rogers RB, Fitzpatrick GM, Li F, Nugent J, Ricks MJ, Slanec TJ, Yao C, Structure-activity relationship studies on the natural product UK-2A. *Proceedings of the 252nd National ACS meeting AGRO* 197. (2016).
55 Torriani SFF, Sierotzki H, Melichar JPE, Mills C, Pain N and Courbot M, *Zymoseptoria tritici*: a major threat to wheat production, integrated approaches to control. *Fungal Genet Biol* **79**:8–12 (2015).
56 Owen WJ, Meyer KG, Slanec TJ, Wang NX, Meyer ST, Niyaz NM *et al.*, Synthesis and biological activity of analogs of the antibiotic UK-2A. I. Impact of picolinamide ring replacement. *Pest Manag Sci* **75**:413–426 (2019).
57 Shen B, A new golden age of natural products drug discovery. *Cell* **163**:1297–1300 (2015).
58 Maison W, Natural products research: renaissance with strengthened integration of biology and chemistry. *Angew Chem Int Ed Engl* **45**:3000–3002 (2006).
59 Chan AN, Santa Maria KC and Li B, Direct capture technologies for genomics-guided discovery of natural products. *Curr Top Med Chem* **16**:1695–1704 (2016).
60 van der Lee TAJ and Medema MH, Computational strategies for genome-based natural product discovery and engineering in fungi. *Fungal Genet Biol* **89**:29–36 (2016).
61 Doroghazi JR, Albright JC, Goering AW, Ju KS, Haines RR, Tchalukov KA *et al.*, A Roadmap for natural product discovery based on large-scale genomics and metabolomics. *Nat Chem Biol* **10**:963–968 (2014).
62 Paddon CJ, Westfall PJ, Pitera DJ, Benjamin K, Fisher K, McPhee D *et al.*, High-level semi-synthetic production of the potent antimalarial artemisinin. *Nature* **496**:528–536 (2013).

