Natural Products as a Source for Novel Antibiotics

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Abstract: Natural products have historically been of critical importance in the identification and development of therapeutically viable antibacterial agents. However, interest in these systems has waned in recent years, but the rapid emergence of resistant bacterial strains has forced their re-evaluation as a route to identify novel chemical skeletons with antibacterial activity for elaboration in drug development. This overview examines the current situation, highlights new natural product systems which have been found, along with re-examination of some old ones, and new technologies for their identification. While natural products certainly have the potential to re-emerge once again as a key start point in antibacterial drug discovery, reports of new or reinvestigated structures need to be supported with sufficient quality chemical (solubility, stability), biochemical (including toxicity in particular, along with target information) and microbiological (MIC and resistance frequency) validation data to assist in the identification of genuinely promising hit structures, and to avoid wasted effort being expended by trawling over already cultivated territory. This is particularly important in a resource limited research environment.

Keywords: natural products; antibiotics; drug discovery

The Need for new antibiotics

The emergence of antimicrobial resistance (AMR), which began very soon after the introduction of antibiotics but has accelerated markedly over the last decade, has focused attention on the sustainability of current modern medical practice in the global arena.[1-3] From the perspective of an individual patient or an institutional health provider, assumptions – which have taken root over the last 70 years or so - about the nature, availability and outcomes of hitherto successful treatment protocols are being challenged, as community and hospital-acquired infections become more problematic.[4] The very success of antimicrobial drug discovery and therapies developed in the modern era has fostered a level of complacency which is likely to require substantial revision of medical practice in the coming decades, if we wish to maintain the standards of health care to which we have become accustomed, or to improve healthcare in underdeveloped countries.[5] Warnings of doomsday scenarios, perhaps dismissed all too readily in recent years, are beginning to look ever

more plausible, especially with the recent emergence of colistin-resistant bacteria in China and even in the United Kingdom.[6, 7] Fortunately, the urgency of the task is now becoming more widely known and accepted, and has attracted the attention of governments and policymakers,[8-18] and led to the establishment of action groups (Antibiotic Action) [19] and charities (Antibacterial Research UK, ANTRUK).[20] That a concerted global approach is required, and that this will need to be an ongoing effort since all cells are capable of developing resistance to xenobiotics, has been recognised.[21, 22] A particular focus of current attention are the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Enterobacter* species) which are both responsible for a wide range of infections and increasingly resistant to common antibacterial drugs.[23] Application of antibiotics in agriculture and farming exacerbates environmental dispersal, and the implication for human use has been considered.[24]

The emergence of AMR has coincided with, or perhaps in part been caused by, an unfortunate series of circumstances. Firstly, the antibacterial drug pipeline is currently very poorly populated.[25-27] Secondly, commercially-driven models for drug development within the pharmaceutical industry, so successful during the last century, are looking very fragile for new antibacterial drug development in the twenty-first century.[12] Thirdly, restructuring within the industry has seen the loss of financial and human resource which translates to a serious diminution of drug–discovery capability.[28-31]. Fourthly, it now appears that there are challenges relating to bacterial cell wall ingress and egress which are unique to antibacterial drug discovery, and which significantly negatively impact on the probability of success.[32-37]. Although changes in the financial structure which supports antibacterial drug development and use are surely needed,[38] it nonetheless remains a productive activity, and antibacterials still comprise the biggest share of the global drug portfolio.[39] However, there is no doubt that high levels of collaboration will be required in order to address this problem, and an interesting case study of an effective academic–industrial partnership leading to antibacterial drug discovery highlights that a combination of chance, determination and adequate funding can generate material outcomes.[40] However, a recent note of caution, highlighting the need for adequate multidisciplinary training, in the way this should be done has been emphasised if academic laboratories are to make a valuable contribution in this endeavour, and not generate misleading outcomes.[41, 42]

An underpinning ethos critical to the success of modern antibacterial therapy has been the concept of the “magic bullet” – that is, a small molecule drug which is both selectively lethal for bacteria, and capable of mammalian administration. Alternative non-compound approaches (such as antibody, probiotic, phage and vaccine therapies) have recently been considered in detail, and their potential assessed.[43] Assuming that we adhere to the small molecule approach, a key

question arises: how do we go forward to identify new drugs? Over the last century, natural products have provided a critical start point in antibacterial therapies and drug discovery[44] and because antibacterially active natural products appear to occupy an unusual chemical property space,[32, 45-47] this strategy still offers excellent opportunities for exploitation in drug development.[48] This realisation has led to a renaissance of interest in natural products for the identification of new members of the 'antibiotic-ome' (defined as natural products with antibiotic activity) and their application in antibacterial drug discovery in the genomics era.[40, 44, 45, 49-64] and that this need not necessarily result from random screening has been demonstrated very recently by the establishment of a relationship between protein-targeted or riboprotein-targeted antibacterial agents and their physicochemical properties.[45] This review attempts to show that recent developments in the natural products arena continue apace, and that reasons to expand work in this area are even greater under the current circumstances. In modern parlance, such an approach is referred to as "forward genetics," "forward pharmacology," "classical pharmacology" or "phenotypic drug discovery"[65] and there is an increasing realisation that it need not rely completely on serendipity, but that design rules may be identified,[66, 67] and some time ago an overview of the various databases listing natural products has appeared.[68] Whilst natural product isolation is often criticised for the fact that it only re-isolates known substances, and indeed this a serious disadvantage of this approach for the discovery of novel antibiotics, novel chemotypes continue to be discovered.[44, 69, 70] Natural sources of new antimicrobials and resistance-modifying agents include land plants,[71-73] fungi,[74] lichens,[75] endophytes,[76] as well as marine plants,[77-80] seaweeds,[81], corals,[82] and other marine microorganisms.[83, 84] A high throughput screening approach for the discovery of natural product antibiotics has recently been reported,[85] while cheminformatic approaches[86] and enhanced methodology for the identification of antibiotics[87] and producing strains[88] have also been developed. Of great significance is the development of novel genomic-type approaches to find small molecules with antibacterial activity, and it is likely that this will become an important avenue for the identification of novel opportunities in the future. [89-92] The particular value of natural products for the disruption of bacterial biofilms has been recognised[93-95] and so to has their antibacterial role in food[96, 97] textiles[98] and caries prevention.[99, 100]

Opportunities for Natural Products in Antibiotic Drug Discovery

This short review exemplifies the status of natural products with antibacterial activity by focusing on reports drawn largely from the last two years; the compound coverage is not meant to be comprehensive but rather illustrative. Noteworthy, though, is the breadth of chemical structures with wide-ranging antibacterial activity. Perhaps the single most important discovery in recent

years has been that of the structurally unusual depsipeptide, teixobactin, which has generated a high degree of excitement, both for its intrinsic antibacterial activity, but also for its method of identification which involved culture of the producing bacterium in its natural soil environment.[101] New analogues have even been synthesised and evaluated in the short time since the original isolation was reported.[102] Importantly, teixobactin was found to inhibit cell wall synthesis by binding at both lipid II and lipid III, to possess MIC activity against a wide panel of Gram-positive organisms, to remain potent in the presence of blood serum, and to exhibit both microsomal stability and low toxicity.[101] Moreover, it was effective *in vivo* (*S. aureus* and *Streptococcus pneumonia* models). Other cyclic depsipeptides have been reported; examples are ulleungamides A and B with limited antibacterial activity (against *S. aureus* and *Salmonella typhimurium*) but no cytotoxicity; [103] salinamide F with significant Gram-positive and -negative activity (and potent activity against bacterial RNAP)[104] and further members of the enniatin class.[105] Copsin, isolated from a co-cultivated fungal source, is an antibiotic peptide which is unusually stabilized by six cysteine bonds, and which exhibits good activity for Gram-positive bacteria (*B. subtilis, Listeria* spp., and *Enterococcus* spp., and including vancomycin resistant *E. faecium*) but not Gram-negative species.[106] Copsin also inhibited cell wall biosynthesis by inhibition at lipid II. The structure of albicidin has been established, and is an unusual polyaromatic oligopeptide mainly composed of substituted *p*-aminobenzoic acids and linked by the nonproteinogenic α-amino acid β-cyano-L-alanine.[107] It is a potent inhibitor of bacterial DNA gyrase (topoisomerase II) with excellent activity against a wide range of Gram-positive and -negative bacteria. Cystobactamids are a similar system, but instead the *p*-aminobenzoamides are linked through an iso-β-methoxyasparagine or a β-methoxyasparagine unit. These too are bacterial DNA gyrase (topoisomerase II) inhibitors, and are effective against *E. coli, A. baumannii, E. faecalis, S aureus and S. pneumonia*.[108]

Development of Small Molecules

Small – and not so small – molecules continue to be found (Figure 1). Tetramate–containing natural products[109] with potent antibacterial activity, include hymenosetin **1**, only recently reported[110] and which has already succumbed to total synthesis.[111] Kibdelomycin **2** has been reported to exhibit broad-spectrum bactericidal activity, including against *C. difficile*, and to act by inhibiting DNA gyrase and topoisomerase IV;[112, 113] kibdelomycin A, a desmethyl analogue, has also been isolated.[114] Interestingly the dietziamides, tetramate dimers, were shown to possess antioxidative activity, but this did not translate into phenotypic antibacterial activity.[115] Hunanamycin A **3**, containing a quinoxaline-2,3-dione core, was isolated from a marine-derived bacterium, *B. hunanensis*, and found to be selectively active against the bacterial

pathogen *Salmonella enterica* and is postulated to be an inhibitor of riboflavin synthase.[70] Penicyclones A–E **4**, antibacterial polyketides with a highly functionalized cyclohexenone core, were isolated from a Deep-Sea *Penicillium* species, and shown to have high levels of antimicrobial activity against the Gram-positive bacterium *S. aureus*, although were not found to be cytotoxic.[116]

Polyenic amides have been increasingly found which exhibit interesting antibacterial activity. Inthomycins A, B, and C **5a-c**, all isomeric in the triene system, are known for their antibacterial activity, and have been prepared using highly efficient metal-catalysed coupling processes[117] which represent significant improvements over earlier work.[118] New simocyclinones (D9, D10, and D11), comprising aminocoumarin, polyketide and sugar sub-units linked by a tetraene, have been identified and this of interest since the parent, simocyclinone D8 **6**, is a DNA gyrase inhibitor with excellent activity against activity against both Gram-positive and -negative bacteria.[119] Oxazolomycins **7a-d**, known to possess limited antibacterial activity, comprise complex polyene lactam-lactone sub-structures and their total synthesis has been a focus of some considerable attention by Ishihara; their efforts open the door to more detailed microbiological examination of this interesting compound.[120] Batumin **8** is a general aminoacyl tRNA synthase inhibitor; it was also found to inhibit bacterial cell motility, although does not kill, and it has been suggested that it is not likely to induce resistance.[121] In that regard, it appears to be superior to the closely related system, mupirocin.

Other structurally unusual examples have been reported. The novel antibiotics, baulamycins A and B **9**, capable of inhibiting growth of a range of both Gram-positive and -negative species, have been reported; these are inhibitors of a siderophore synthetase and their bacterial inhibitory activity against several bacterial species suggests that such targets might be worthy of more detailed investigation. [122, 123] Artonin I **10** has been reported to be an efflux pump inhibitor, to inhibit multidrug resistance in *S. aureus* and, when used in combination with existing antibiotics, to lower their MIC values.[124] Such “helper” systems offer the possibility of extending the lifetime of existing clinically effective drugs.

The realisation of the importance of finding new antibacterial agents, or developing old ones, has re-invigorated total synthesis in the total synthesis of antibacterials. The first total synthesis of tetarimycin A **11** has been reported, and the route been used to generate a small set of analogues, some of which were shown to be MRSA and VRE active; the presence of a critical hydroxyl group was essential for antibacterial activity.[125] Detailed analysis of viridicatumtoxin **12**, the parent of an unusual class of polyketides closely related to the tetracycline antibiotics, indicates excellent inhibitory activity against vancomycin-resistant *Enterococci* and methicillin-resistant *S. aureus*.[126] Of interest is both its higher acid stability and bioactivity over the

corresponding tetracycline antibiotics, although it does show some cytotoxicity. Other new polyketides (e.g. barceloneic acid C) have been isolated from *Phoma* species, but found to have only weak or no activity.[127] The total synthesis of hongoquercin B **13** has been efficiently achieved by a biomimetic cascade tetracyclization.[128]

Alkaloids continue to be identified with antibacterial activity (Figure 2); detailed overviews of their biological (including antibacterial) activity have been reported.[129, 130] The development of a practical synthetic and fully scalable route to the axinellamines **14** has enabled a more detailed assessment of their antibacterial activity, which is favourable against both Gram-positive and -negative bacteria; they appear to function by membrane destabilization.[131] Curvulamine **15**, a structurally highly novel antibacterial alkaloid has been reported to be isolated from the white croaker, a fish observed to be resistant to infections which commonly affect other species,[130] and was found to be both more potent and selective than the positive control, tinidazole.

Combination therapies are a possible way forward, in which the synergistic action of complementary antibiotics is harnessed to achieve a better overall clinical outcome. It has been suggested that polyphenols, an intensively investigated and widely distributed group of natural products often possessing antibacterial activity, possess potential as therapeutic agents alone or in combination with currently available antibiotics[132] and recent developments in antibacterial activities of chalcones has been reviewed.[133] The co-administration of antibiotics, or their chemical conjugation, has been reported to lead to a better therapeutic outcome than their use individually. Synthesis of tridecaptin conjugated with any of several antibiotics (vancomycin, rifampicin, erythromycin A) using Click chemistry provided access to a novel library, and conjugation with the latter particularly gave a hybrid with excellent MIC against *Klebsiella pneumoniae*.[134] The synergistic activity of epigallocatechin gallate and quercetin when used in combination has been shown to be particularly effective against a topical methicillin-resistant *S. aureus* infection.[135]

A Case Study – Antitubercular Agents

A particular area in which natural product isolation and synthesis has remained both popular and productive is in the discovery of antitubercular agents,[136, 137] and while terpenoid[138] and coumarin[139] systems are well known, newer structures continue to be found (Figures 3 and 4). The application of more modern approaches has also proven to be valuable: a virtual screening protocol optimizing physicochemical and pharmacokinetic parameters against rhamnose pathway enzymes has been able to identify compounds with good binding affinity, including butein, diospyrin, indicanine, and rumexneposide A, and antitubercular activity was confirmed for butein.[140] By contrast, a return to whole-cell screening has enabled the identification of

structurally diverse novel antitubercular hits.[141] Natural product isolation has yielded diverse hits with promising activity. These include two new marine diterpenoids **16a,b**, belonging to the unusual isoneoamphilectane-class, isolated from the marine sponge *Svenzea flava*, along with semi-synthetic derivative **16c** and other known amphilectane diterpenes, which exhibited both strong growth inhibition of *Mycobacterium tuberculosis* H37Rv and low mammalian toxicity.[142] Complex tetronates lobophorins A, B and G were isolated from a newly isolated *Actinomycetes* strain using a bioassay-guided isolation protocol, and shown to possess moderate anti-*M. tuberculosis* H37Rv activity but strong inhibition against against *B. subtilis*.[143] Alkaloids, too, continue to be found, and include denigrins A-C **17a-c**, new 3,4-diarylpyrrole alkaloids from the marine sponge *Dendrilla nigra*,[144] again identified by bioactivity guided isolation protocol, with denigrin C offering the most activity against *M. tuberculosis* H37Rv. Phomapyrrolidones A-C **18a-c**, containing both a cyclopenta[b]fluorene and succinimide ring system, were isolated from the endophytic *Phoma sp*. fungus, but exhibited only weak antitubercular activity below their cytotoxic concentrations, with phomapyrrolidone C being the most active.[145] Caulerpin **19** and some closely related analogues **19** (R = F, Cl, Br, I, Me, OMe), all bis-indole alkaloids, were synthesized in a short efficient cyclocondensation sequence, but only the parent natural product exhibited significant anti-tuberculosis activity.[146] Agelasines B, C and D **20a-c**, known antituberculars, were re-isolated from an Indonesian marine sponge of the genus *Agelas*, and agelasine D were found to bind to the target protein BCG3185c (K_D 2.42 μM), and to have the best activity against *M. smegmatis* and *M. bovis* BCG under aerobic and hypoxic conditions.[147] Quinonoid systems regularly crop up: four new pluramycins, heraclemycins A–D **21a-d**, were isolated from an endophytic *Streptomyces sp* which have been used in traditional Chinese medicine, with heraclemycin C in particular showing selective antitubercular activity, while heraclemycin D was active against *S. aureus*, Methicillin-resistant *S. aureus*, and *B. subtilis* but not *Pseudomonas aeruginosa*.[148] New natural products, taiwanensols A, B and C **22a-c**, were isolated using a bioassay-guided protocol and found to possess some antitubercular activity.[149] The known 5-(3-hydroxyphenyl)-penta-2,4-dienamide, ergosterol, ergosterol peroxide and halolitoralin B were all recently isolated from an endophytic *Streptomyces sp*, and all shown to exhibit anti-*M. Tuberculosis* activity.[150]

The synthetic and biological re-evaluation of known natural products is also gaining attention (Figure 4). A wide variety of natural products were screened for activity against *M. tuberculosis*, and of these, vermelhotin **23**, a tetramic acid isolated from fungi, was found to be the most active.[151] Further investigation of the natural products emodin, diospyrin, plumbagin, menadione and thymoquinone were evaluated for antitubercular activity, and shown to be active, with the best compound, plumbagin, reported to be effective at 0.25 μg/mL.[152]

Synthetic and semi-synthetic approaches have also proven to be effective in the identification of new antitubercular actives. For example, a natural product inspired application of Ugi four-component couplings of amines, aldehydes, acids with a diisocyanide to generate antitubercular and antimalarial pharmacophores has been shown to give α-acylamino amides **24** with good anti-infective activity and selectivity, and were found also to inhibit *in vitro* thromboxane B2 (TXB2) and superoxide anion generation.[153] Similarly, mimics of the natural product engelhardione (published structure) **25** and its revised structure (pterocarine) **26** have been prepared using a short sequence, and some were shown to have *Mycobacterium tuberculosis* along with more general Gram-positive and –negative activity.[154] Commercially available oridonin **27** has been modified in a series of transformations to introduce a range of functional groups onto the core tetracyclic skeleton; evaluation of their antimycobacterial activity indicated some activity, and most importantly, against *M. tuberculosis H37Rv*.[155, 156] Modified griselimycins, all cyclic peptides, exhibit excellent MIC values with improved metabolic stability and hydrophobicity, leading to improved cell membrane permeability.[157] In a different approach, biotransformations of monoterpenoids has been used to generate antibacterial actives.[158] Improvements in the total synthesis of a number of natural products has opened the door for their further investigation. This includes the enantioselective total synthesis of thuggacin B **28**[159] (active against *M. tuberculosis* with a novel mode of action) and hirsutellones A,B and C **29** (strongly active against a resistant strain of *M. tuberculosis*).[160] Caprazamycin is a complex nucleoside derivative which incorporates a number of key structural elements, including a diazepanone ring, an amino ribose, a pyranose, a uridine, and a fatty-acid side chain with activity against against *Mycobacterium tuberculosis* (TB), including multidrug-resistant variants. Its first total synthesis, achieved in 23 steps, has been reported and is noteworthy because it is scalable and opens the possibility of more detailed examination of SAR of this class of antibiotics.[161] An effective route to the simpler analogue capuramycin **30**, and its analog UT-01309, using elegantly designed new protecting groups specifically designed for the primary alcohol and uridine ureido nitrogen groups of the target, and which permits the synthesis of gram-quantities of an advanced intermediate suitable for elaboration to capuramycin and its analogs in as few as four steps, has been reported.[162]

Concluding Remarks

Although a recent study has identified the opportunities which might arise from non-small molecule antibacterial therapies,[43] it is clear that there is ample scope for innovation inspired by an understanding of natural product chemistry, and many have argued that this approach should be re-activated as a matter of some urgency.[31, 163-167] Indeed there is still a danger that the importance of serendipitously discovered small molecules will be de-emphasised relative to

"rational" target driven approaches. A recent analysis of drugs approved by the USA FDA drugs has again come to the conclusion both that natural products and their derivatives have both played a key role in the past and are likely to be a productive way forward in the future, and that appropriate investment from private and public sectors is justified.[168] Certainly, small molecules, and many of them related to natural products, offer interesting opportunities for the identification of short term solutions using resistance reversal agents[124, 169] and resistance breakers; an example is artonin **10** (*vide supra*).[170] Notwithstanding the opportunities for the discovery of new natural products (perhaps using new approaches) outlined above, there is nonetheless plenty of life left in these known systems too, if they are examined in detail; this provides a different possible approach to the development of short term solutions by re-invigorating historically effective antibacterial small molecules. Critically, it is wrong to assume that well known and currently clinically used systems have been optimised fully during their development, and in any case historical optimisation was not made against parameters relevant in the modern context. A good example is the recent identification of next-generation polymixin lipopeptides **30** with both superior activity against MDR Gram-negatives and superior pharmacokinetic profiles when compared to colistin; this was achieved by a "classical" SAR study in which three key components of the polymixin framework were systematically modified and evaluated in detail.[171, 172] Other examples include tetarimycin **11** and the viridicatumtoxins **12** (*vide supra*), the latter of which are fungal polyketides which are closely related to the tetracycline antibiotics but which have not found clinical application.[126] Their isolation and detailed structural assignment followed by antibacterial and cytotoxic characterisation identified promising activity, but importantly also that the viridicatumtoxin scaffold was significantly more acid-stable than the tetracycline antibiotics themselves, and opening the door to the development of new next-generation systems in this important class of antibiotics. In a slightly different approach, the well known antibacterial activity of tetramate-containing natural products,[173, 174] exemplified by streptolydigin **31**, has inspired the construction of small molecule analogues which have been found to exhibit promising levels of antibacterial activity.[175-177] The very fact that many antibacterial active natural products are comprised of clearly define structural subunits – arising of course from the metabolic process of cellular biosynthetic machinery – provides an easy opportunity for medicinal chemists to rapidly and effectively create mimics for optimisation for biological parameters.

But if natural products chemistry is to make an impact in the development of new antibacterial drugs, and especially in an academic context, reports of new or reinvestigated structures need to be supported with sufficient quality chemical (solubility, stability), biochemical (including toxicity in particular, along with target information) and microbiological (MIC and resistance frequency) data which permits the scientific community to assess if the system is worthy

of further examination – and many of the reports included here show the value of inclusion of that information. However, natural products are not immune to providing false leads, and the importance of the recognition of, and appropriate response to, pan-assay interference has recently been highlighted, and is something to which academic groups need to pay particular attention.[178, 179] Fortunately, acquiring this data is now much more readily possible with the availability of a world-wide open access phenotypic screening service, CO-ADD,[180, 181] which embraces the crowd sourcing model for drug discovery. Moreover, a greater understanding of the 'antibiotic-ome', its relationship to natural products, and methods for identifying their modes of action, is likely to provide greater predictive power for the identification of worthwhile avenues to explore[52, 182] and this type of approach is finding commercial application.[183] In the race to find new antibacterials, there is good reason to be optimistic, but diverse strategies will need to be adequately resourced and there is no room for complacency!

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