

# Strategies for discovering drugs from previously unexplored natural products

Alan Harvey

Natural products are the most consistently successful source of drug leads. Despite this, their use in drug discovery has fallen out of favour. Natural products continue to provide greater structural diversity than standard combinatorial chemistry and so they offer major opportunities for finding novel low molecular weight lead structures that are active against a wide range of assay targets. As less than 10% of the world's biodiversity has been tested for biological activity, many more useful natural lead compounds are awaiting discovery. The challenge is how to access this natural chemical diversity.

Approximately 60% of the world's population relies almost entirely on plants for medication<sup>1</sup> and natural products have long been recognized as an important source of therapeutically effective medicines. Of the 520 new drugs approved between 1983 and 1994, 39% were natural products or derived from natural products and 60–80% of antibacterials and anti-cancer drugs were derived from natural products<sup>2</sup>.

Current commercial evidence also supports the case for natural products. Of the 20 best-selling non-protein drugs in 1999, nine were either derived from or developed as the result of leads generated by natural products – simvastatin, lovastatin, enalapril (Fig. 1), pravastatin, atorvastatin, augmentin, ciprofloxacin, clarithromycin and cyclosporin –

with combined annual sales of >US\$16 billion. Newer developments based on natural products include the anti-malarial drug artemisinin and the anticancer agents taxol, docetaxel and camptothecin (Fig. 2) (for more examples, see Refs 3–5). Therefore, the use of natural products has been the single most successful strategy for the discovery of new medicines.

In addition to this historical success in drug discovery, natural products are likely to continue to be sources of new commercially viable drug leads. The chemical novelty associated with natural products is higher than that of any other source: 40% of the chemical scaffolds in a published database of natural products (Dictionary of Natural Products, Chapman & Hall) are absent from synthetic chemistry<sup>6</sup>. This is particularly important when searching for lead molecules against newly discovered targets for which there are no known small-molecule leads. Despite the commonly held assumptions, natural products can be a more economical source of chemical diversity than the synthesis of equivalent numbers of diverse chemicals.

Additionally, natural products that are biologically active in assays are generally small molecules with drug-like properties. That is, they are capable of being absorbed and metabolized by the body. Hence, the development costs of producing orally active medicines are likely to be much lower than with biotechnological products or with most compounds produced to date from combinatorial chemistry. Indeed, the value of combinatorial chemistry and HTS as a source of useful lead molecules has been questioned<sup>7,8</sup>. Combinatorial chemistry might enable ligands for well-established, tractable targets to be found more quickly, rather than being suited to the more complex signalling interactions that are associated with the

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majority of targets<sup>8</sup>. For such targets, the chemical diversity of natural products is a major advantage.

However, as highlighted in a recent Editorial in *Drug Discovery Today*<sup>9</sup>, although natural products have inherently greater structural diversity than synthetic compounds, this diversity must be accessed efficiently and effectively. This article reviews the strategies that are emerging for improved access to previously untapped biodiversity (Table 1).

### Access to biodiversity

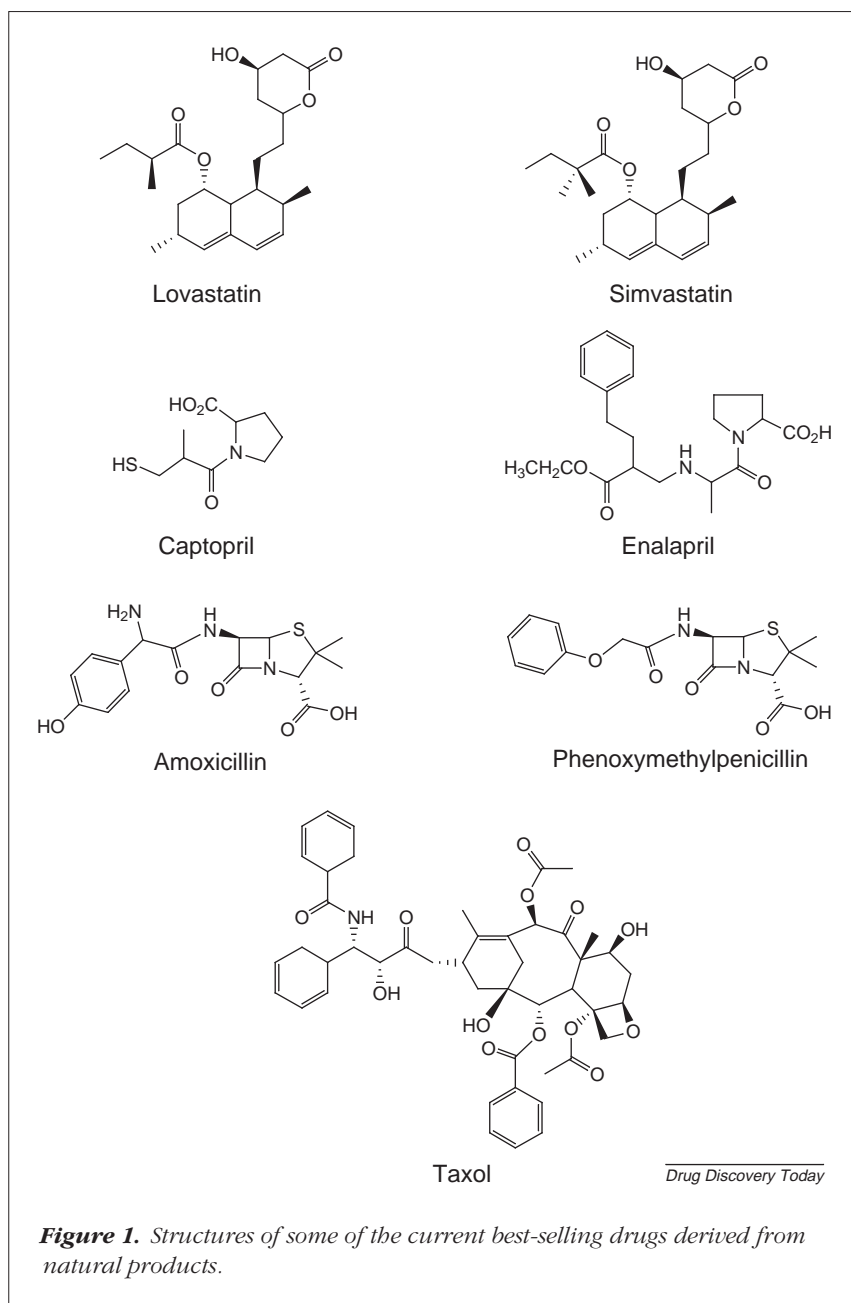
The Earth Summit in Rio de Janeiro (3–14 June 1992) highlighted many political concerns about the environmental changes affecting the world. One of these was the loss of biodiversity, and the Summit saw the introduction of the United Nations Convention on Biological Diversity<sup>10</sup> (CBD). The CBD recognizes that countries have sovereign rights over the biological resources within their boundaries and sets out conditions for the preservation and sustainable use of biodiversity. Biodiversity-rich countries have to facilitate access to the biological resources, but access must be in accordance with appropriate legislation, involving prior informed consent. The source country is expected to be involved in R&D projects relating to its biodiversity and the source country should benefit from technology transfer and share any commercial benefits resulting from the use of its biodiversity.

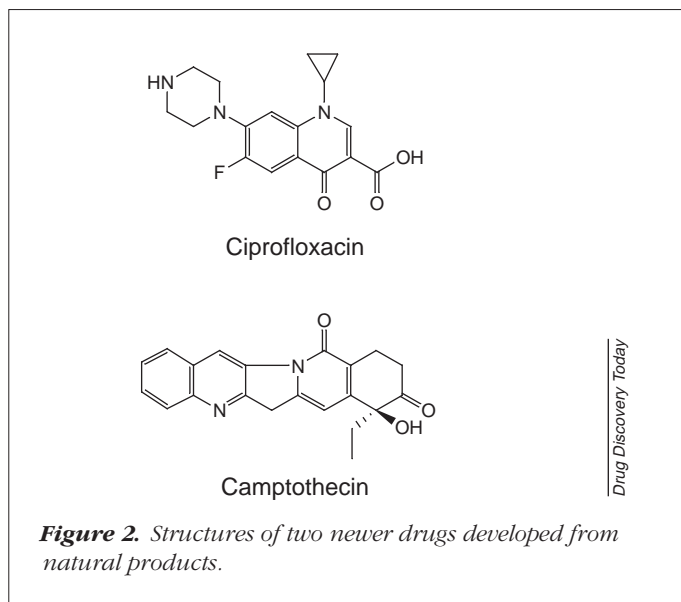
Since 1992, over 180 countries have ratified the CBD but access issues have not been totally resolved<sup>11–13</sup>. Some countries have introduced new regulations that appear to hinder rather than facilitate access, and most countries have still to formulate the appropriate laws. The CBD is not retrospective and so there are plenty of opportunities for the political debate to be coloured by examples of earlier natural-product-led drug discovery that are now producing obvious commercial rewards that are not shared with the source country. Examples include the development of cyclosporin A from a fungus (*Tolypocladium inflatum*) collected in Norway, and the development of rapamycin from an organism (*Streptomyces hygroscopicus*) from Easter Island. Tales of 'biopiracy' will continue for the foreseeable future<sup>14</sup> but the dangers of the inap-

propriate exploitation of fragile environments are very real<sup>15</sup>.

### New places to look for biodiversity

One aspect of concern about biodiversity is the loss of species through environmental changes and other developments. However, the number of species involved is unknown and subject to speculation<sup>16,17</sup>. Although species are becoming extinct, there are many areas of the world and many different habitats in which new and unusual biodiversity is being discovered. It can therefore be predicted





that novel chemicals with potential as drug leads will be discovered if this biodiversity can be accessed.

*The plant kingdom*

Plants supply most of the active ingredients of traditional medicinal products, and plant extracts have long been used in screening programmes in pharmaceutical companies and university institutes. It might be thought that most of the plant kingdom has been thoroughly examined in the search for biologically active molecules. However, this is unlikely to be the case. There are estimated to be

~250,000 species of plant in the world and probably ~10% of these have been tested for some type of biological activity<sup>4</sup>. Even fewer will have gone through extensive HTS programmes.

Why should this be? This is partly because of the difficulties perceived in using complex mixtures (plant extracts) in HTS and partly because many of the most biodiverse regions of the world have been relatively inaccessible to collectors. The first problem is being addressed by several companies that are working on methods to make plant extracts more ‘assay friendly’. Treatment to remove tannins and other protein-precipitating components are routine, although it is not clear whether this is essential<sup>18</sup>. This type of clean-up can be extended to remove other highly reactive chemicals and hence to reduce the incidence of false-positive results<sup>19</sup>.

There are also attempts to create collections of isolated plant chemicals by large-scale purification before any biological testing (e.g. by Analyticon, Berlin, Germany and Molecular Nature, Aberystwyth, UK). In general, extracts are processed by a combination of HPLC and solid-phase extraction techniques. Mass spectroscopy is used to provide a chemical ‘fingerprint’ and to identify and exclude known structures. These methods have been developed as a means to compare extracts and to provide tools for increasing the chemical diversity of the compounds that are eventually isolated<sup>20</sup>. Another approach uses high-performance thin-layer chromatography to separate secondary metabolites in natural product mixtures followed by exposure to a range of staining reagents. Novel components

**Table 1. Strategies to expand the range of natural products available for drug discovery screening**

Strategy	Proponents	Advantages	Disadvantages
Untapped geographical sources	Drug Discovery	Plant-based diversity has been historically successful	Concerns over sustainability of natural collecting
Preparation of libraries of isolated compounds	Analyticon Molecular Nature	More compatible than mixtures for HTS	Cost of production
Marine sources	PharmaMar Australian Institute for Marine Sciences	Unusual chemistry	Identification of source organisms Recollection difficult on large scale
Insects	INBio CSIRO (Entomology)	Little studied	Scale-up potentially difficult
Plant tissue culture	Phytera	Control over genetic pathways	Concerns over access to genetic material sourced from developing countries
Combinatorial genetics	Kosan Biosciences Galilaeus Oy Terragen	Convenient production using fermentor technology	Restricted range of structures

can be found by comparisons with absorbance spectral libraries of known molecules<sup>21</sup>.

Since the introduction of the CBD, there has been little progress in accessing plant material from more diverse geographical areas. The collection programme of the National Cancer Institute (Frederick, MD, USA) continues<sup>22</sup> and there are some regional initiatives, such as the Bioresources Development and Conservation Programme (Silver Spring, MD, USA) in parts of Africa<sup>23</sup> and the Indian Council for Scientific and Industrial Research's Coordinated Programme on Bioactive Molecules from Natural Product Sources (New Delhi, India). These tend to focus on the exploration of plants that have a history of use in systems of traditional medicine. For a broader range of plant biodiversity, Drug Discovery (Glasgow, UK) has established a network of collaborators in 20 different countries to build up a very diverse range of species. Its collection of approximately 5000 species come from 70% of the known plant families in the world.

#### *Microbial diversity*

Microorganisms have been exceptionally rich sources of drugs, including antibiotics, immunosuppressants and the lipid-lowering statins. However, these drugs have been produced from a very small range of the world's microbial diversity<sup>24,25</sup>, and how many species of microorganism there might be is not known. Only approximately 6000 bacterial species have been named (compared with more than a million plants and animals) and estimates of 1.5 million species of fungi and 1.5 million species of algae and prokaryote<sup>17</sup> might have to be revised upwards.

With the availability of techniques to sequence ribosomal RNA genes extracted and cloned from natural environments, it appears that less than 1% of microbial diversity has been cultured and studied experimentally<sup>26,27</sup>. Bacteria are also being found in surprisingly extreme environments: polar ice<sup>28-30</sup>, geothermal vents<sup>31,32</sup>, dark caves<sup>33</sup> and deep-sea sites<sup>34</sup>. One species (*Pyrolobus fumarii*) grows at 90–113°C and makes metabolic energy by oxidizing diatomic hydrogen with nitrate, producing ammonia<sup>31</sup>. With so many organisms with metabolic pathways adapted to such a range of environments, an unusual array of chemicals might be produced that could add to the diversity of any screening library. As described below, techniques are being developed to make use of genes isolated from unusual organisms in more manageable systems<sup>24</sup>.

#### *Beneath the sea*

One of the findings of the new techniques for detecting bacteria was that sea water contains up to a million free-

living cells in each millilitre<sup>30</sup>. However, most drug discovery from marine sources involves much larger organisms – plants or animals. The sea covers 70% of the earth's surface and is home to examples of most types of organism: there could be >10 million species of marine macrofauna<sup>35</sup>. Again, very few species have been used for drug discovery purposes, and the ones that have been used are from a restricted range of phyla, with sponges (Porifera) and seamats (Bryozoa) being most popular<sup>16,36,37</sup>. Despite this, unusual chemical structures have been isolated and several compounds of marine origin (mainly potential anti-cancer agents<sup>37</sup>) are in clinical trials, including aplidine and ecteinascidin 743. There are specialist companies (e.g. PharmaMar, Madrid, Spain) and institutes (e.g. the Australian Institute for Marine Sciences, Townsville, Queensland, Australia) that are amassing large collections of marine samples for drug discovery.

#### **New organisms**

As well as looking in relatively unexplored habitats, drug discovery efforts can be applied to groups of novel organisms. For example, there are thought to be 30 million species of insect<sup>17</sup> but very few of them have ever been available for screening for therapeutically relevant molecules. The collaboration between Merck (Rahway, NJ, USA) and the Instituto Nacional de Biodiversidad (Heredia, Costa Rica) has stimulated the collection of insect samples from Costa Rica<sup>38</sup>, but the outcome of any screening is not yet known. In Australia, the Entomology branch of the Commonwealth Science and Industrial Research Organization (Canberra, ACT, Australia) provides extracts of insects for screening purposes. However, the difficulties of collection, identification and scale-up are formidable. Without positive examples of unique chemical diversity from insects, it is hard to see a major growth in screening of samples from this particular source of biodiversity.

#### *Cone snails*

Another rather inaccessible source of novel chemicals is the *Conus* genus of marine snails. However, cone snail venoms are a particularly rich source of pharmacologically active peptides, acting on a variety of receptors and ion channels<sup>39</sup>. One particular conopeptide,  $\omega$ -conotoxin MVIIA from *Conus magus*, is in Phase III clinical trials for the treatment of intractable pain; it acts as a specific blocker of N-type calcium channels in the pain fibres of the spinal cord<sup>40</sup>. With this successful example of a use for a conopeptide, *Conus* venoms can be expected to be actively searched for novel lead structures<sup>41</sup>. Moreover, of the 500 known species of *Conus*, only about a dozen have

been examined in any detail, and new groups of biologically active peptide continue to be found<sup>42</sup>. Difficulties in collecting the snails and worries about conservation will require a molecular engineering approach to expand access to the peptide constituents of most *Conus* venoms. This is a challenging assignment because many of the more interesting components contain several post-translational modifications<sup>43</sup>.

#### Microalgae

Microalgae are a widespread group of photosynthetic organisms. There are probably >40,000 species but they have not been extensively studied in terms of their secondary metabolites. Although they are best known for the toxins produced by some species (including saxitoxin, maitotoxin, okadaic acid and microcystins), microalgae have provided novel structures with different activities. These include potential anticancer and antifungal compounds<sup>44-47</sup>.

Some species of microalga can be grown conveniently in photobioreactors<sup>48</sup> and they can also be stored by cryopreservation. With the ability to manipulate the yields and diversity of metabolites through changes in culture conditions, microalgae should be examined more closely for their ability to provide novel chemical diversity for drug discovery.

#### Gliding bacteria

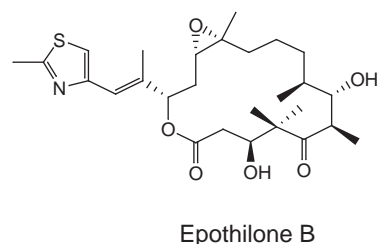
Another example of a previously ignored group of organisms is the myxobacteria<sup>49</sup>. Also known as gliding bacteria, these are common but unusual soil bacteria that can form fruiting bodies. Compounds isolated from myxobacteria include many with unusual structures. They include epothilon (Fig. 3), a macrolide that, although originally discovered in 1987, was more recently shown to have taxol-like effects on tubulin, with the advantage of being active in multi-drug-resistant cells<sup>50</sup>.

#### Taking the nature out of natural products

With the difficulty of gaining access to large tracts of biodiversity in natural habitats, several techniques have been developed to produce natural products in non-natural ways. These range from plant tissue culture to combinatorial genetics. In addition to offering a secure supply of naturally occurring metabolites, such technologies can be used to produce more diverse chemicals.

#### Plants in tissue culture

There has been much interest in using tissue culture to obtain adequate quantities of commercially valuable



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**Figure 3.** Structure of the potential anticancer agent epothilone B.

chemicals, such as taxol, from plants. However, plant tissue cultures can also be used to produce compounds for screening<sup>51</sup>. Undifferentiated cell cultures produce secondary metabolites, and the types of compound produced can be varied by altering the culture conditions or by adding chemicals to elicit the expression of different metabolic pathways. Phytera (Worcester, MA, USA) reported that such manipulations can provide a wider range of chemical diversity from cell cultures than can be extracted directly from plant material<sup>51</sup>. Similar approaches with different elicitors can be applied to more highly differentiated plant cultures, such as root and leaf cultures<sup>52</sup>. Again, different metabolic pathways can be selectively stimulated *in vitro*, providing a wider range of secondary metabolites than in classical extracts from the plant itself.

#### Combinatorial genetics

As mentioned earlier, only a tiny proportion of microbial diversity has been cultured and many microorganisms, particularly the marine microorganisms, are difficult to maintain under laboratory conditions. One potential solution to the problem of accessing the chemical diversity of such inaccessible species is to remove the appropriate genetic material that codes for the secondary metabolic pathways and to incorporate it into more convenient organisms, such as *Streptomyces*<sup>24,53</sup>. This strategy is being applied by Galilaeus Oy (Kaarina, Finland) for novel anthracyclines and by Terragen (Vancouver, BC, Canada) to access secondary metabolites from lichens and marine organisms. It is also being used by Kosan Biosciences (Hayward, CA, USA) in attempts to produce large quantities of epothilone<sup>54</sup>.

Apart from such genetic transfers, the availability of the genes for different biosynthetic enzymes enables a combinatorial genetics approach to be used to create non-natural homologues of natural products. The pioneering work in this area was based on the cluster of microbial genes

involved in the synthesis of polyketide antibiotics such as the tetracyclines<sup>55</sup>; this technology is being developed commercially by Kosan Biosciences. More recently, similar approaches have been applied to macrolides<sup>56</sup>. By introducing combinations of genes not found in nature into a productive strain of *Streptomyces*, a range of novel structures can be produced for screening<sup>57–60</sup>.

Although most of the interest in combinatorial genetics has focused on microbial pathways, there have also been advances in our understanding of the molecular biology behind the production of secondary metabolites in plants<sup>53,61,62</sup>. Molecular cloning has revealed many genes that appear to code for enzymes related to known and characterized synthetic enzymes. The function and specificity of these gene products is still being explored but the families of enzymes will probably have different specificities and stereospecificities in the reactions that they can carry out; combining them will thus produce an even greater range of chemical diversity.

This type of approach, of 'combinatorial biocatalysis', is already being applied with more readily available enzymes and also with whole cells<sup>53,63</sup>. This differs from combinatorial genetics in avoiding the need for genetically engineering biosynthetic pathways into living organisms. Instead, it uses the enzymes and other catalysts *ex vivo*. It has been used to build chemical libraries from various scaffolds such as nucleosides, flavonoids, polyketides and taxanes<sup>63</sup>.

## Conclusions

Little of the world's biodiversity has been tested for biological activity, yet natural products have been the single most productive source of drug leads. Advances in separation and analytical methods mean that active compounds can be isolated and identified rapidly from natural product extracts. High-speed approaches to dereplication and deconvolution remove many of the technical barriers to using libraries of natural products in HTS campaigns. However, political sensitivity concerning access to biodiversity from different source countries still must be dealt with; the international networks such as those of Drug Discovery and the Bioresources Development and Conservation Programme provide frameworks for appropriate access.

Cloning and genetic engineering also offer alternative approaches to the production of suitable quantities of natural chemical diversity. By incorporating the appropriate metabolic pathways from unculturable organisms into convenient species, the range of accessible chemical diversity can be greatly expanded. Similar techniques can be used to 'mix-and-match' enzymes in artificial combinations, leading to even more novel structures.

With the continuing need for novel drug-like lead compounds against an increasing number of ever-more-challenging molecular assay targets, the chemical diversity derived from natural products will be increasingly relevant to the future of drug discovery.

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### Collaboration...

**American Home Products Corporation** (AHP; Madison, NJ, USA) have formed a collaboration with **Elan Corporation** (Dublin, Ireland) to develop a vaccine for the treatment of mild to moderate Alzheimer's disease and possibly also for the prevention of disease onset. The two companies will collaborate in research, development and commercialization of AN1792. In preclinical studies, Elan has shown that this product reduces and prevents the development of amyloid plaques in transgenic mice, and they have commenced Phase I human safety studies in Alzheimer's patients in the US and the UK. The collaboration will include a five-year research program for the discovery and characterization of additional products. AHP will make an initial payment to Elan and additional payments will be made for key development benchmarks and regulatory milestones. Costs and revenues from AN1792 and other products developed will be shared equally by the two companies.