Natural Products as Leads to Potential Drugs: An Old Process or the New Hope for Drug Discovery?

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I. Introduction

From approximately the early 1980s, the "influence of natural products" upon drug discovery in all therapeutic areas apparently has been on the wane because of the advent of combinatorial chemistry technology and the "associated expectation" that these techniques would be the future source of massive numbers of novel skeletons and drug leads/new chemical entities (NCE[a]) where the intellectual property aspects would be very simple. As a result, natural product work in the pharmaceutical industry, except for less than a handful of large pharmaceutical companies, effectively ceased from the end of the 1980s.

What has now transpired (cf. evidence shown in Newman and Cragg, 2007[1] and Figures 1 and 2 below showing the continued influence of natural products as leads to or sources of drugs over the past 26 years (1981–2006)) is that, to date, there has only been one de novo combinatorial NCE approved anywhere in the world by the U.S. Food and Drug Administration (FDA) or its equivalent in other nations for any human disease, and that is the kinase inhibitor sorafenib (**1**, Chart 1), which was approved by the FDA in late 2005 for renal carcinoma.

However, the techniques of combinatorial chemistry have revolutionized the *development* of active chemical leads where currently, instead of medicinal chemists making derivatives from scratch, a procedure is used whereby syntheses are based on combinatorial processes so that modifications can be made in an iterative fashion. An example of such a process would be the methods underlying the ultimate synthesis of the antibiotic linezolid (Zyvox, **2**) by the Pharmacia (now Pfizer) chemists starting from the base molecules developed in the late 1980s by DuPont Pharmaceutical, who reported the underlying antibiotic activity and mechanism of action of this novel class of molecules, the oxazolidinones.[2–6]

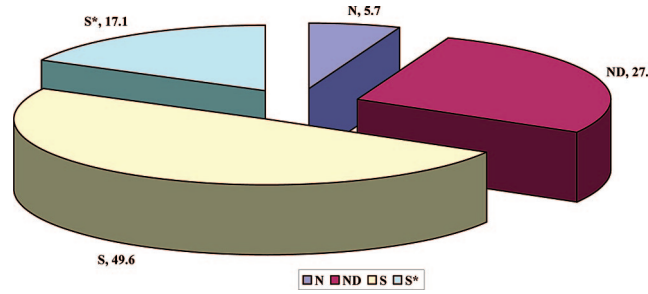

Figure 1. Source of small molecule drugs, 1981–2006: major categories, $N = 983$ (in percentages). Codes are as in ref 1. Major categories are as follows: "N", natural product; "ND", derived from a natural product and usually a semisynthetic modification; "S", totally synthetic drug often found by random screening/modification of an existing agent; "S*", made by total synthesis, but the pharmacophore is/was from a natural product.

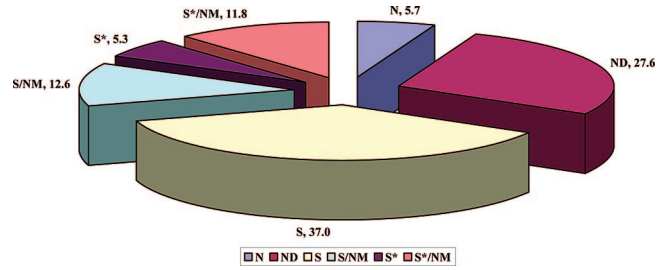

Figure 2. Sources of small molecule drugs, 1981–2006: all categories, $N = 983$ (in percentages). Codes are as in ref 1. Major categories are as follows: "N", natural product; "ND", derived from a natural product and usually a semisynthetic modification; "S", totally synthetic drug often found by random screening/modification of an existing agent; "S*", made by total synthesis, but the pharmacophore is/was from a natural product. The subcategory is as follows: "NM", natural product mimic.

Although the early (late 1980s to late 1990s) combinatorial chemical literature is replete with examples of libraries containing hundreds of thousands to millions of new compounds, as stated rather aptly by Lipinski in the early 2000s, if the early libraries had been disposed of, the productivity of pharmaceutical drug discovery would have materially improved in the prior decade.[7] However, in the late 1990s, synthetic chemists realized that the combinatorial libraries that had been synthesized up to that time (with the exception of those based on intrinsically bioactive compounds such as nucleosides, peptides, and to some extent carbohydrates) lacked the "complexity" normally associated with bioactive natural products, items such as multiple chiral centers, heterocyclic substituents, and polycyclic structures.

Although chemists had probably accepted that as a "basic rule", natural products were different from synthetic compounds; the 1999 analysis by Henkel et al.[8] was perhaps the first of the

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[a] Abbreviations: β-AST-IV, β-arylsulfotransferase-IV; BIOS, biology-oriented synthesis; Cdks, cyclin dependent kinases; DOS, diversity-oriented synthesis; E-FABP, epidermal fatty acid binding protein; EGFR, epidermal growth factor receptor; FKBP-12, FK binding proteins; FXR agonists, farnesoid X receptor agonist; GPCR, G-protein-coupled receptor; hERG, human ether-a-go-go-related-gene K^+ channel; HIF-1α, hypoxia-inducible factor-1α; IGF1R, insulin-like growth factor 1 receptor; LTA4H, leukotriene A4 hydrolase/aminopeptidase; mEST, murine estrogen sulfotransferase; M6p-IGFR2, insulin-like growth factor II/mannose 6-phosphate receptor; NCE, new chemical entity; NMDA, *N*-methyl-D-aspartate; *NodH* sulfotransferase (gene product from *Rhizobium NodH*); PAPS, 3′-phosphoadenosine 5′-phosphosulfate; PFT, protein fold topology; PI3K, phosphoinositol-3-kinase; PKC, protein kinase C, exists in multiple isoforms; PSSC, protein structure similarity clustering; SCONP, structural classification of natural products; SEA, similarity ensemble approach; *Shp-2*, Src homology 2 domain containing tyrosine phosphatase 2; TOR, target of rapamycin; VEGFR-2, vascular endothelial growth-factor receptor-2.

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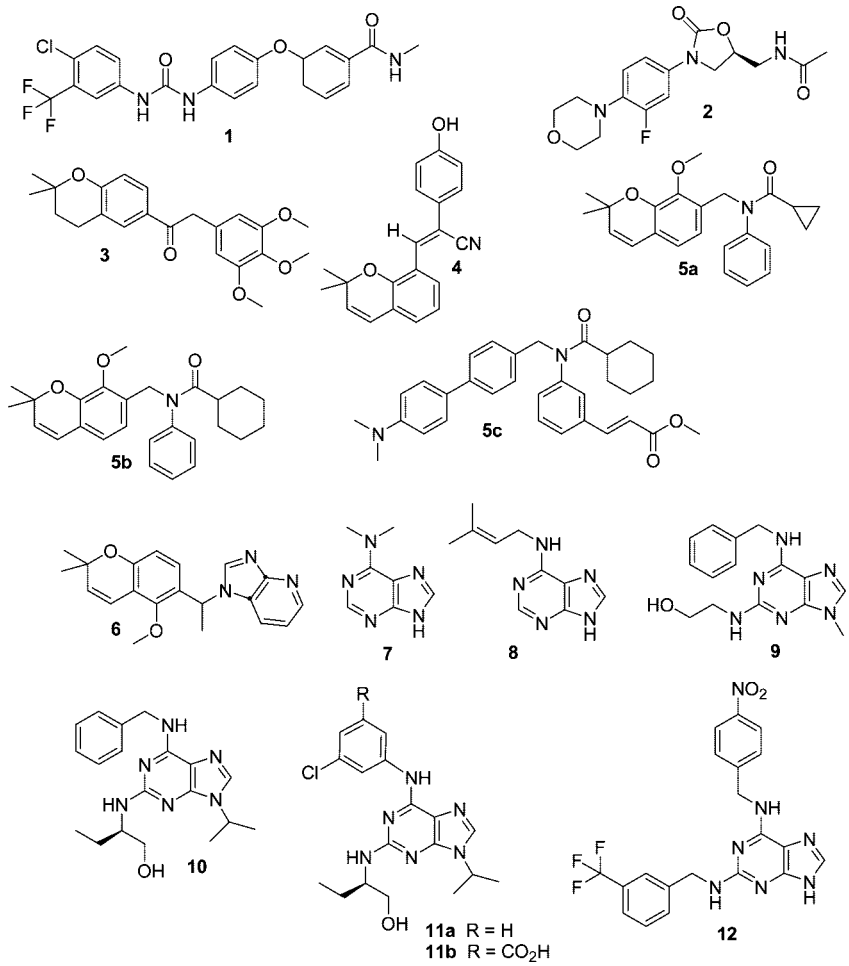
Chart 1



modern treatments demonstrating the intrinsic structural differences between synthetic libraries, in this case those of Bayer AG, and the natural product structures shown in the Chapman and Hall Dictionary of Natural Products, made available to the nonspecialists in the field.

Thus, the concept of diversity-oriented synthesis (DOS) has now come into vogue, where compounds resembling natural products in terms of their complexity (as defined above), or that are based on natural product topologies, have been made by a significant number of synthetic chemists. The "absolute origin of the term" is a trifle difficult to discern. Certainly it was used in Schreiber's group[9,10] in the late 1990s, and the concept was used by Nicolaou in the same time frame as exemplified by the reports on the benzopyran libraries.[11–13] DOS-sourced molecules have been or are being tested in a large number and variety of biological screens in order to determine their role(s) as leads to novel drug entities and/or biological probes. To give an idea of the vast amount of work reported in the literature in the time frame from 2000 to date, over 300 articles have been published in the chemical literature, with 60 plus being reviews, when the term "diversity oriented synthesis" is used as the search parameter in the "Web of Science".

II. Discussion of Specific Topics

II.1. Syntheses around Privileged Structures, aka the Intrinsic Differences of Natural Products. The concept of "privileged structures", among which I personally include natural products with known bioactivities and would also extend this definition to the majority of secondary metabolites, was first suggested by Evans et al. in relation to the benzdiazepines[14] and then extended to natural product structures such as indoles and other partial structural motifs by Mason et al. and references therein.[15]

One can argue fairly successfully that peptides are possibly the best recognized of privileged structures, though purine and pyrimidine bases and their corresponding nucleosides may well be a very close second. Following on from this comment, one of the seminal reviews in the history of use of peptidomimetics derived from natural products is that by Wiley and Rich.[16] This paper gives an excellent history of what might be considered to be *"precombinatorial discoveries from natural product scaffolds"* and should be read by those who wish to see where a significant number of earlier leads in a large variety of biological screens have come from.

The current use of natural product-based privileged structures as leads to novel bioactive compounds is, as mentioned above, probably best demonstrated by the work of Nicolaou's group formally reported in a series of papers in *Journal of the American Chemical Society* in 2000.[11–13] By use as the base structure, a benzopyran or a partially reduced benzopyran (from data showing over 10 000 structures with these base structures in the natural products literature), a series of iterative molecules based on combinatorial syntheses were tested against a wide series of biological assays. To date, four distinct, previously unrecognized biological activities have been reported from this relatively small series of compounds.

These currently include an inhibitor (**3**) of NADH/ubiquinone oxidoreductase with cytostatic activity against specific cell

lines,[17] a compound (**4**) with antibacterial activity against methicillin-resistant *Staphylococcus aureus*,[18] nonsteroidal FXR agonists (**5a–c**) which have helped define the interactions within this receptor for the first time,[19,20] and an inhibitor (**6**) of hypoxia-inducible factor-1α (HIF-1α).[21] These are probably the most diverse activities yet shown from a single base natural product structure, and it will be very interesting to see how many more biological results will be reported from these series in due course.

The potential for such synthetic strategies is further exemplified by another review from the same group that, although covering the benzopyrans, expands the natural products to polysaccharides, the eleutherobin/sarcodictyin derivatives, glycopeptide antibiotics such as vancomycin and epothilones.[22] All of these can be considered to be part of the collection of privileged structures.

Both earlier and then in a similar time frame to the work above, synthetic and natural products chemists were investigating the potential of the simple analogues of adenine, 6-dimethylaminoadenine (**7**), and from a *Castanea* sp., isopentenyl adenine (**8**), as inhibitors of the mitotic histone Hi kinase (better known as cyclin-dependent kinase 1/cyclin B).[23,24] Further investigation with other purine-based compounds showed that the plant secondary metabolite olomucine (**9**), originally isolated from the cotyledons of the radish and that had been synthesized in 1986 by Parker et al.,[25] inhibited cyclin dependent kinases (Cdks) with IC_{50} values in the low micromolar range. This finding disproved the then existing dogma that no "specific" kinase inhibitors could be found for ATP-binding sites because they would be swamped by the normal cellular levels of ATP (which are in the 1−5 mM range).

Further development of the olomucine structure led to roscovitine (**10**), with an IC_{50} against Cdks of 450 nM and then from a focused combinatorial library, the purvalanols (**11a**,**b**) with IC_{50} values in the 4–40 nM range.[26] Currently, roscovitine (**10**) is in phase II clinical trials for cancer under the names CYC202 and seliciclib, with a recent full publication giving details of the phase I trial.[27]

Since there are basic similarities between the enzymic mechanisms of kinases and sulfotransferases, both performing a transfer reaction of anionic groups and both binding adenosine-based substrates, with kinases using ATP as the phosphoryl donor and sulfotransferases using 3′-phosphoadenosine 5′-phosphosulfate (PAPS), it was a logical extension of this work to look at the interactions of purine scaffold libraries utilized for roscovitine and olomucine with suitable target enzymes. Thus, by use of inositol 1,4,5-trisphosphate 3-kinase (IP3K) as the target of a suitable library, compound **12** was found with an IC_{50} value of 10.2 μM, compared to >100 μM against Cdk1/cyclin B.[28]

Variations in the same library had been tested earlier against the *NodH* sulfotransferase from *Rhizobium melioti* giving a new compound (**13**, Chart 2) with equipotent activity ($IC_{50} \approx 20$ μM) against this enzyme and Cdk2/cyclin A.[29] Following from these studies, the use of a similar library protocol, but with a slight variation in the substituents, yielded two further nanomolar purine based inhibitors, one (**14**) demonstrating activity against a murine estrogen sulfotransferase (mEST) but with low activities against kinase targets while another compound in the same series (15) demonstrated a K_i of 96 nM against β-aryl-sulfotransferase-IV (β-AST-IV),[30] with no other inhibitory effects against sulfotransferases/kinases at 10 μM.

The value of this natural product-based approach can be seen in the comments on inhibitor discovery with sulfatases in a 2004 review by Rath et al.[31] where, using synthetic inhibitors not based on natural products, the IC_{50} values are in the 50+ μM range for *Est* and *NodH* in comparison to the 1000 times more potent inhibitors from the purine libraries. Thus, by utilizing a simple "biologically active motif" and then using the techniques of combinatorial chemistry to produce focused libraries, Meijer and Schultz demonstrated very effectively that potent inhibitors of a variety of relatively closely related enzymes could be devised.

Contemporaneously with these results, Waldmann's group at the Max Planck Institute in Dortmund, Germany, began to publish some very interesting data on their work with solid-phase syntheses around indolactam V (**16**), the core structure of the teleocidins (an example of which, teleocidin B, is shown in Chart 2 (**17**)). Indolactam V (**16**) was a known PKC modulator of both PKCα and PKCδ, whereas one of the 31 analogues made (**18**) only modulated PKCδ.[32–34] Also referred to in the above review by Breinbauer et al.[34] is the work on the syntheses around the marine-sourced Cdc25 phosphatase inhibitor dysidiolide (**19**) and the only known inhibitors from nature of the *her/neu* tyrosine kinase, the nakijiquinones A-D (**20a–d**), also isolated from marine sources. The influence of these two very small focused libraries will be dealt with in section II.2 below.

II.2. Syntheses around Privileged Structures Leading to Current Clinical Candidates and Approved Drugs. In addition to the compounds referred to above in section II.1 and those discussed below in section III, there are currently agents in clinical use and in advanced clinical trials that further exemplify the utility of "compounds based on natural product structures be they partially or totally synthetic".

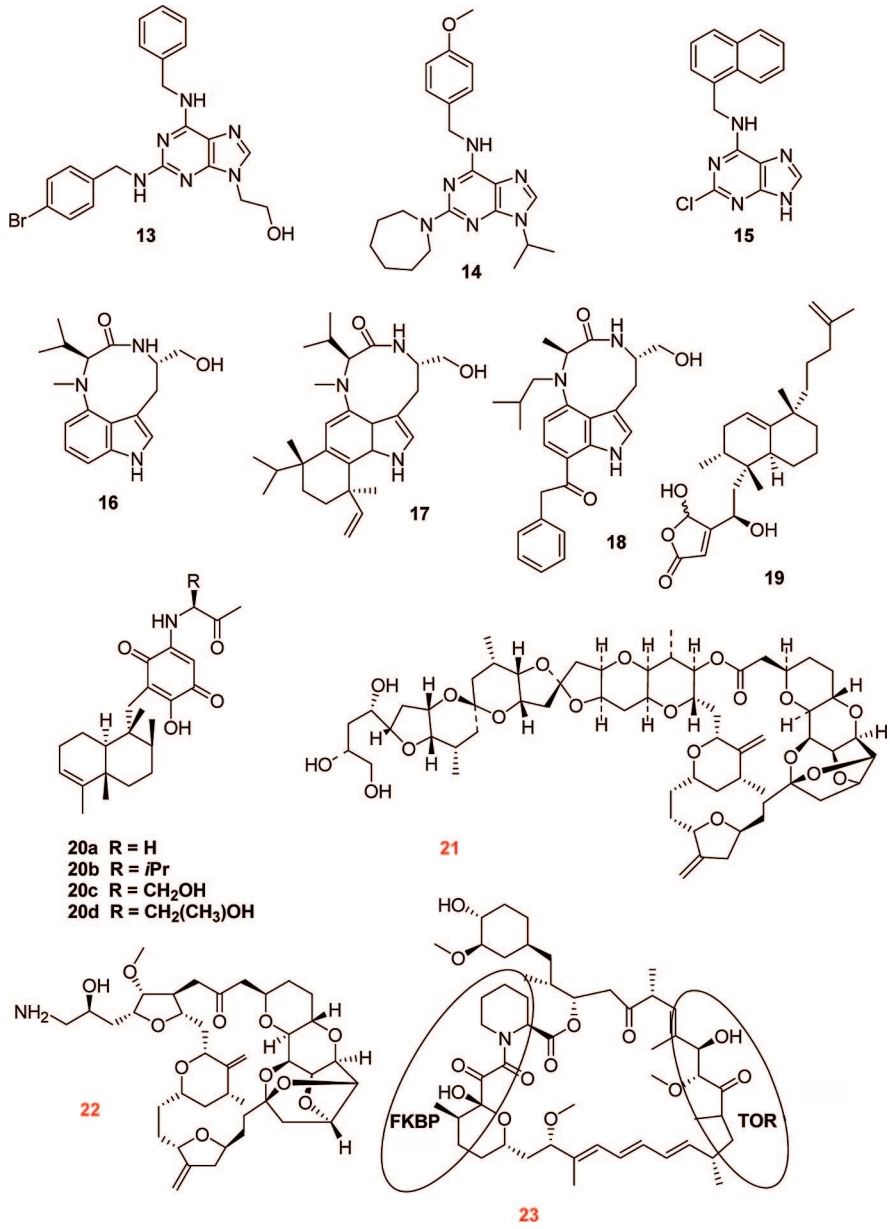
Perhaps the best examplar in the current crop of novel antitumor agents in clinical trials would be the work done by chemists at the Eisai Research Institute utilizing the original work by Kishi's group on the synthesis of halichondrin B (**21**), which led after 200 modifications/molecules to the compound currently known as E7389 (eribulin, **22**), which is a novel tubulin inhibitor now in phase III clinical trials against breast cancer in the U.S. and the EU.[35] Though totally synthetic, the basic halichondrin scaffold can be seen quite clearly on comparison of the two compounds.

A further series of examples are those based on modification of the well-known natural product rapamycin (**23**) (effectively by modification at one site), which has led to three clinical drugs (sirolimus **24**, everolimus **25**, and temsirolimus (CCI-779) **26**) and to one in phase II clinical trials (deforolimus (A23573) **27**) (Chart 3). In all cases, modifications were made in the one area, the C-43 alcoholic hydroxyl group that avoids both the FKBP-12 and the target of rapamycin (TOR) binding sites, since modifications in other areas would negate the basic biological activity of this molecule.[36] For a further discussion on modification of molecules from a similar biosynthetic source (polyketide immunophilin ligands) one should consult the recent review by Koehn.[37]

III. Inter- and Intramolecular Interactions of Compounds and Proteins

III.1. Introduction. The interactions of small molecules with proteins leading to a change in tertiary structure, and in the case of complexes of protein subunits, quaternary structure, were probably first recognized as a result of the 1960s X-ray crystallographic work of the Perutz group on the hemoglobin molecule on binding of oxygen, which was reported in 1970.[38] The shift in the contact faces between the heterodimeric αβ

Chart 2



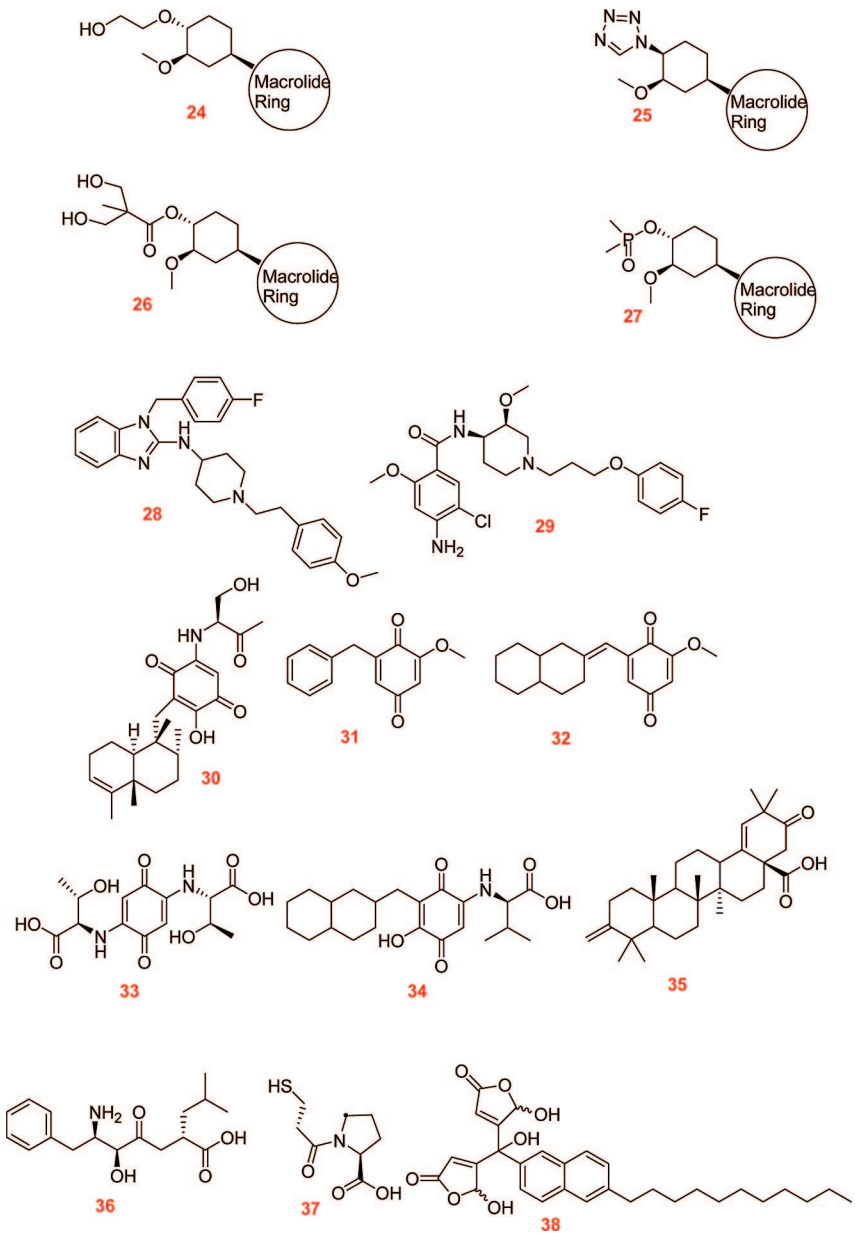
hemoglobin dimers that occurred on initial binding of oxygen and the increase in binding strength/rate of addition of further oxygen molecules to the individual heme units were shown to be directly related to the interaction between the oxygen and the heme prosthetic group, with the subsequent structural perturbation(s) transmitted through the whole complex.

For many years, substrate interactions at the "active/binding site" of an enzyme were thought to be (relatively) specific to a given compound/enzyme/receptor set, though there were some examples of where a given ligand might interact with different "enzymes/proteins". Such an example is the interaction of the opioid methadone with both the μ-opioid receptor, a G-protein-coupled receptor (GPCR), and the *N*-methyl-D-aspartate receptor (NMDA),[39] with the possibility that both may be necessary for the full action of the drug.[40] Similarly, the classical privileged structures, the benzodiazepines, bind to ion channels which is their usually recognized mode of action, but also affect mitochondrial proteins.[41] Then from a potentially significant medical aspect, two compounds with formally quite dissimilar activities, astemizole, an H_1 receptor inhibitor (**28**), and cisapride, a 5-HT_4 agonist (**29**), may both lead to unexpected cardiac events because of their unexpected inhibition of the hERG ion channel.[42]

There are two groups of investigators (one in Germany and the other in Australia) who over the past few years have used such "unexpected protein−ligand interactions" as the basis to discover and develop drug candidates and biological probes based on natural products or on synthesized compounds based on such molecules. Each will be discussed in turn, and very recently, a third group (in the U.S.) has used the ligand (or pharmacophore) to investigate/discover relationships among proteins but have not limited themselves to the use of only natural products or their related structures. As will become apparent, the third iteration is reminiscent of a melding of the first two processes.

III.2. Waldmann's Methods. The earliest reported and currently best described process was based on the realization by Waldmann that "natural products were biologically validated starting points for library design".[34] In a series of elegant combinatorial syntheses around natural product structures, he

Chart 3



and his group have demonstrated that agents with increased biological activities, and in a significant number of cases, activities against targets that had not previously had inhibitors identified, could be produced relatively easily.

In the initial series of experiments as mentioned above, the structures built around the marine-derived putative phosphatase inhibitor dysidiolide **19** led to activity against a variety of cancer tumor lines and activity against phosphatase Cdc25c, though the in vitro and in vivo activities did not track completely.[43]

Nakijiquinone C **20c** was demonstrated to be an inhibitor of epidermal growth factor receptor (EGFR: *her2/neu* is a proto-oncogene from this class of receptors), in addition to having activity against *c-ErbB2* and PKC, and cytotoxic to L1210 and KB cell lines.[44] Waldmann's group tested the compounds that they had synthesized, where they had made sequential changes to the terpene moiety and the aminoacids while keeping the quinone moiety relatively constant (specific details given in the original paper)[45] against *her2/neu* and also against a suite of tyrosine kinases.[46]

From this initial library, the Waldmann group discovered not only inhibitors of the vascular endothelial growth-factor receptor-2 (VEGFR-2) (**30**) and insulin-like growth factor 1 receptor (IGF1R), albeit at micromolar levels, but also four inhibitors of the Tie-2 kinase, (**31**−**34**) a protein involved in angiogenesis and for which, at the beginning of their studies, no inhibitors were known. However, during the studies, the first natural product inhibitor (**35**) was reported from the plant *Acacia aulacocarpa*.[47] This report was followed by three related papers reporting synthetic pyrrolopyrimidines[48–50] and substituted pyrazolopyrimidines[51] demonstrating this activity.

Using his data, Waldmann applied the following logic. Proteins may be regarded as biomolecules built up from individual building blocks (domains) that are parts of the overall protein that fold "independently" from the rest of the structure to give compact arrangements of secondary structures such as α-helices, β-sheets, and β-turns.[46] These individual domains are interconnected by relatively short peptide linkers.

From genomic data, it is possible to suggest the evolutionary relationships between specific sequences in different proteins, and those that are identified in this manner can be considered to be "*domains that are structurally conserved but can be genetically mobile*".[46] By use of published sequence data, it is possible to estimate the number of different proteins in humans to be between 100 000 and less than 500 000, but if one restricts the question to the number of protein "folds and families", then the figures reduce to be somewhere between 600 and 8000 for folds and 4000−60000 sequence families.[52]

Waldmann then postulated that similar folds binding similar ligands, irrespective of the formal primary sequence patterns, may well appear to catalyze entirely different reactions in the formal sense. By use of these concepts, a very interesting example was based on the report in the literature that indicated that leukotriene A4 hydrolase/aminopeptidase (LTA4H) catalyzed two different reactions from the same Zn-containing active site. This led to investigations of relationships to metallopeptidases due to some conserved sequences.

In retrospect, if, from X-ray structure determinations in 1991, the importance of the "folds" had been recognized at that time, then it would probably have led to the investigation of peptidase inhibitors as potential ligands. The recognition that bestatin (**36**) and captopril (**37**) also inhibited LTA_4H had previously led to the syntheses of molecules that inhibited LTA_4H at a nanomolar level.[53,54] When the structure of LTA_4H was ultimately determined, comparison with the metallopeptidase thermolysin showed that they had similar catalytic folds, a feature that they also shared with other peptidases such as aureolysin, elastase, and neprilysin.[46] In the next 2 or so years, Waldmann and his group published much fuller details of the chemistry and "domain" characteristics of the inhibitors that they built around these privileged structures, and the interested reader should consult these papers for the chemistry and genomic aspects of their studies.[55,56]

In late 2004, Waldmann's group published a paper in the *Proceedings of the National Academy of Sciences* that "formalized" the process to date as "protein structure similarity clustering (PSSC)".[57] They expressed their process as follows:

"In this approach, the ligand-sensing cores of individual protein domains are grouped on the basis of structural similarity and *irrespective of sequence similarity* (author's emphasis) to generate a protein structure similarity cluster (PSSC). The structures of ligands that bind to one member of this cluster may be used for the development of novel ligands for other members of the cluster."

They also pointed out that "super sites" may well exist where within a protein fold substrates will bind at similar locations within the fold in a spatial sense, irrespective of the actual amino acid sequences, and similar comments were also made by Quinn (see below in section III.2) .

For the initial "protein seed" to be used in a series of structural protein databases, they used Cdc25A phosphatase. This enzyme (family) was chosen because they had previously synthesized a small series of potential inhibitors based on dysidiolide (as mentioned above), reported initially in significant detail by Brohm et al.[55] These compounds were then compared with other natural product-based phosphatase inhibitors, with the results being reported by Bialy and Waldmann.[58] Inspection of the databases in a sequential manner led to the identification of a member of the superfamily of α/β-hydrolases from which they chose acetylcholinesterase (AChE) as a representative.

Comparison of the structural information of the catalytic cores of these two proteins (Cdc25a and AChE) was then performed, demonstrating significant 3D similarities (cf. Figure 3 in Koch et al.[57]). The third protein was chosen by using AChE as the "second seed" and searching for proteins that displayed the NAD(P)-binding Rossmann fold (this characteristic had also been seen in the Cdc25A search), which suggested the *Datura stramonium* tropinone reductase as a candidate.

Since the tropinone reductase is a member of the short-chain dehydrogenases, for a pharmaceutically relevant third protein, they chose the 11β-hydroxysteroid dehydrogenase (11βHSD), an enzyme that exists in two isoforms. Because a crystal structure was not available, homology models were constructed. Thus, these three proteins were considered to be a similarity cluster (cf Figures 4 and 5 in Koch et al.[57]).

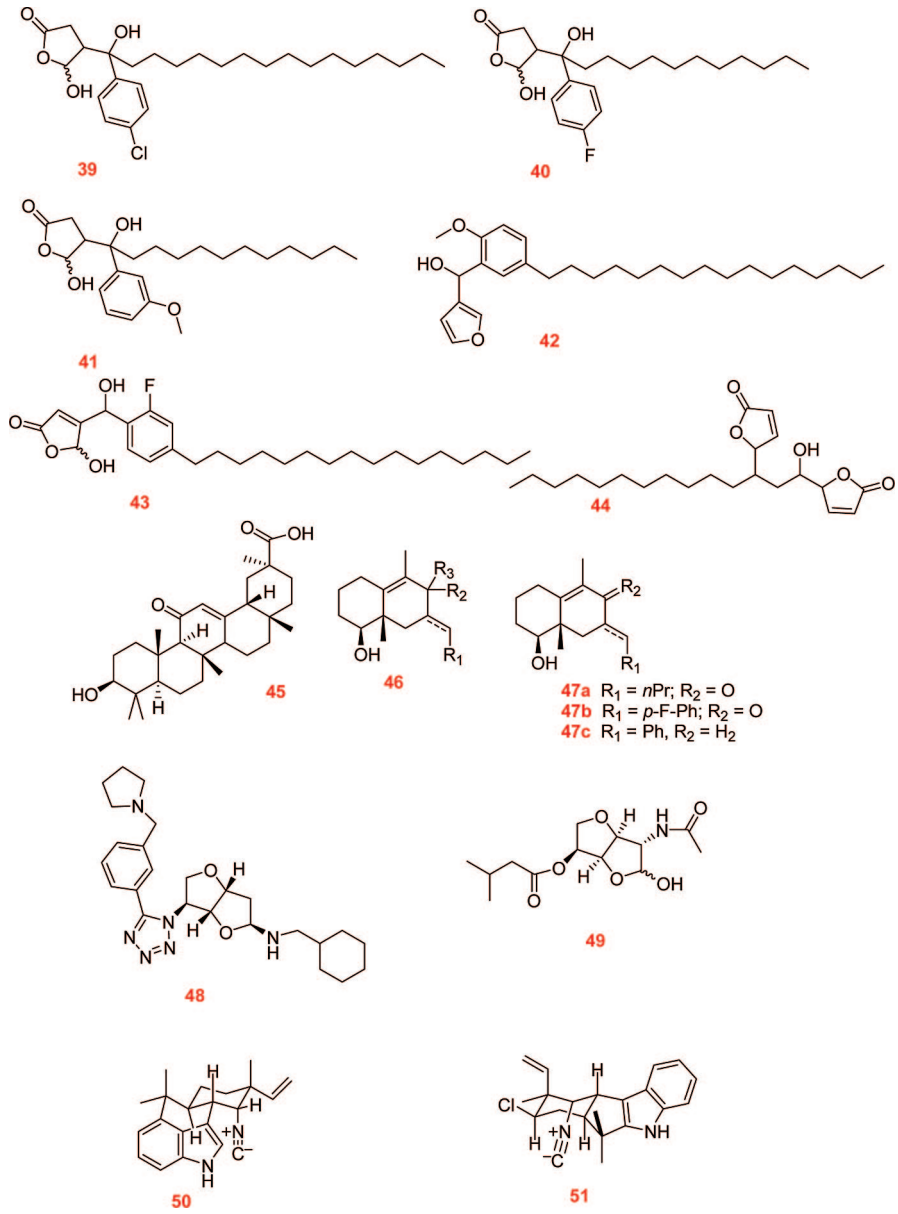
By assaying the 147-member dysidiolide-based library incorporating the γ-hydroxybutenolide side chain against the four enzymes (Cdc25a, AChE, and the two isoforms of 11βHSD) and when a cutoff value of $IC_{50} = 10\ \mu M$ was selected as the upper limit for "hits", seven compounds from this small library demonstrated both initial potency and some selectivity against Cdc25a and isoforms of 11β-HSD at micromolar or submicromolar levels (viz. compounds **39**−**42**, Chart 4). The remaining two compounds, however (**43** and **44**), demonstrated selectivity for the other isoform,11β-HSD. No selectivity was seen at these levels against AChE, though micromolar inhibitors were identified. No previous reports of inhibitors based on γ-hydroxybutenolides (**38**–**42**) or α,β-unsaturated five-membered lactones (**43**, **44**) have been made, thus demonstrating that this process will yield previously unrecognized scaffolds around which to optimize candidates. A fuller record of the compounds and methods mentioned above was published 5 months later by Koch and Waldmann[59] and should be consulted by interested readers for more complete details, particularly with respect to ribbon structures of the proteins.

Quite recently, a dynamic aspect was added to this clustering technique, perhaps removing the need to perform serial structure retrieval and inspection steps used in the approach described above. By use of this molecular dynamics approach, another series of proteins were identified that were related to the large (300 kDa transmembrane receptor) insulin-like growth factor II/mannose 6-phosphate receptor (M6p-IGFR2),[60,61] leading to a link to the epidermal fatty acid binding protein (E-FABP).[62] Thus, by a modification to the original process, the "protein space" opened up considerably, leading to clusters that would not have been discovered using the earlier technique.[63]

Waldmann et al. (including collaborators from both Novartis and the University of Berne) extended their concepts from protein "superstructures' to the "organization" of base structures of natural products. In a paper at the end of 2005, they explained their concept of "SCONP" (structural classification of natural products),[64] the product of an informatic analysis of the CRC Dictionary of Natural Products. In this analysis, they first performed an in silico deglycosylation based on substructure patterns followed by removal of all side chains to derive a base scaffold. This was followed by the derivation of an hierarchical parent−child relationship between scaffolds whereby the parent represents a substructure of the child, using rules that they deposited as Supporting Information with the journal.

The data sets were extended to include taxonomic and biological information, though later analyses demonstrated that because of the lack of specificity in the biological information (i.e., "cytotoxicity" as a term without definition), this was not a currently useable criterion. However, their earlier PSSC concept (see above) could be coupled rather successfully to the hierarchical arrangements of ring sizes or topography. Recently,

Chart 4



an extension of the scaffolding processes has been published using examples from the PubChem database covering both kinase inhibitors and insecticides, thus demonstrating that the process can cover both natural products and synthetic compounds.[65]

This concept was nicely demonstrated by showing the structural underpinnings of the design of 11β-hydroxysteroid dehydrogenase inhibitors descended from glycyrretinic acid (GA, **45**). This compound is a known inhibitor of this class of enzymes, and by use of their "structure tree" (see Figure 2 in Koch et al.[64]), they were able to move from the five-ring system for GA to a dehydrodecalin system (**46**) isomeric with the base ring structure of dysidiolide **19**, a compound that from their earlier PSSC work had led to a series of 11βSHD inhibitors with butenolide structures (**38**−**42**). By use of their new approach, starting with scaffold **46**, they were able to derive nanomolar inhibitors (**47a**−**c**) that had more than a 100-fold selectivity for the 1-isoform. In contrast, the original dysidiolide-based inhibitors (**43**, **44**) were less potent and not significantly isoform-selective.[57]

As the authors rightly emphasize, this coupling of their two processes is not the only way that these concepts can be used nor is it a generally applicable process, but it is a potential starting "thought process for identification of hypotheses as to library scaffolds"[65] and is an iterative process that will be improved as specific biological data can be derived.

Six months later, in a short review article they demonstrated the similarities/subtle differences in the two processes, and it is probably best expressed in their own words: viz. "Fusing PSSC and SCONP means matching proteomic space with biologically prevalidated chemical space. This approach could prove to be a most valuable tool in chemical genomics and the development of small-molecule modulators of protein function."[66] There is an excellent graphical representation of the two processes and their inter-relationships in this review, which should be consulted by interested readers.

Extending the processes, in a later paper from the Waldmann group,[67] this combination has now been given its own acronym, BIOS (biology-oriented synthesis). In this paper, fuller details are given on the variations in designing and synthesizing specific

phosphatase inhibitors, including structures derived from a variety of natural products, that led to novel inhibitors such as the furofuran (**48**) derived from furanodictin A (**49**) that has activity against *Shp-2*.

III.3. Quinn's Methods. McArdle et al., initially in an oral presentation at the 2005 Pacifichem Meeting in Hawaii and then in a paper published soon afterward,[68] approached the interactions of proteins and ligands from a biosynthetic perspective, hypothesizing that the protein-fold characteristics of biosynthetic enzymes should mimic those of the target protein(s) that the secondary metabolite was "designed to interact with by Mother Nature". Or as expressed by the authors in their paper, "If a relationship between natural product recognition of biosynthetic enzyme and therapeutic targets could be established, then this would open up a new approach to drug design.[68]"

By use of structural data on protein kinases (PKs) where all 200 plus structures so far resolved have the "protein-kinase-like fold", from inspection of the compounds that are known to inhibit PKs, a majority of them, including flavanoids, chalcones, and stilbenes, are direct inhibitors of the natural substrate ATP and interact at the ATP-binding site.

By use of published structural details for the various biosynthetic enzymes in the pathways leading from chalcone/stilbene synthases through the various interactions to give flavanones, flavones, or flavanols (see Figure 1 in McArdle et al.[68]), and then by performance of docking experiments, certain structural interactions became apparent between conserved positions within the biosynthetic site and the individual biosynthetic metabolites. Thus, the conserved interactions are always with the 1/2 or 5/6 positions of the compound being synthesized. This specificity implies that the individual biosynthetic protein can only recognize one particular orientation, whereas data from crystallographic analyses of PKs with these classes of molecules indicate that directional specificity is not carried over into some of the potential target proteins.

These specificities are shown in Figure 2 of McArdle et al.,[68] which should be consulted for more thorough analyses of the specific interaction points between these molecules, their biosynthetic enzymes, and the target, phosphoinositol-3-kinase (PI3K). These data demonstrate that the flavanoid/kinase "shared" protein fold topologies define a cavity in both that is equally recognizable to these natural products. This is a telling point also emphasized by Waldmann et al.[57] and discussed earlier in this article.

Obviously these correlations may be of utility in at least two somewhat dissimilar aspects of drug design. In the first, definition of the biosynthetic protein fold topologies (PFTs) would permit putative identification of targets by comparison of potential target proteins against the biosynthetic enzyme(s) data. Or, in what to some extent can be considered a reversal of the process, knowing the PFT of a target and then searching among the published data for biosynthetic enzymes with similar PFTs could give ideas for possible leads/sources of initial inhibitors of that target grouping. Both of these are complementary to the BIOS system described earlier.

III.4. Shoichet's Method. In early 2007 a group led by Shoichet[69] published a very interesting review linking protein pharmacology by the type(s) of ligand chemistry observed. The results were from statistical analyses of a large collection of both synthetic and natural product-based compounds, quantitatively relating their biological receptors to each other by the chemical similarity of their ligands. This method they called the similarity ensemble approach (SEA). Their analyses demonstrated significant recognizable clusters of biologically related proteins from these statistical techniques (which basically resemble BLAST search methods).

Conceptually this type of analysis is not dissimilar from Waldmann's techniques (the overarching methods listed under the acronym BIOS mentioned above in section III.2), as they demonstrate in one of their tables, the "novel target selectivity predictions" for three particular ligands. Of particular interest is that one of these ligands, methadone, is a direct opiod receptor inhibitor and would nowadays be considered as an S/NM using the criteria of Newman and Cragg,[1] and one of the other two is emetine, the natural product that is the principal alkaloid in ipecac (*Uragoga ipecacuanha*). This compound, which though used as an amoebicide since 1912, as a crude extract (syrup of ipecac) was used as an emetic in poisonings in man. Shoichet found that emetine was linked to anti α2-adrenergic blockade when using his informatic technique and confirmed it by direct experimentation. It would be of interest to further analyze the data given in the supplementary tables in this publication for the sources of the ligands identified as "of interest".

It should be emphasized that their analyses of interactions at the protein level rely on comparison of the sequence similarities of receptors and of their relationships to ligands. However, as recently discussed by Beiner[70] in a paper relating protein folding to a very rapid assembling of heterogeneous mobile elements (partial sequences) in proteins, rapid folding is hypothesized to rely on initial specific interactions among certain specific aminoacids. Such a preordained assembly process could overcome Levinthal's paradox[71] because mobility differences along a peptide chain may control the folding processes of proteins, and these intrinsic processes could control the "fold patterning" inherent in protein domains. If this is in fact the case, the use of sequence similarities in specific areas without knowledge of their relationship(s) to such putative fold patterns may lead to correlations that at times could simply be due to happenstance.

III.5. Other Recent Reports. In addition, the following recent papers and reviews covering not only natural products but also synthetic agents that interact with proteins (often because of previously unrecognized topographical relationships) should also be consulted.

Costantino and Barlocco cover a number of both natural product-based and formally synthetic compounds, particularly isosteres that mimic carbohydrates and α-helices and that can be considered to be privileged structures as leads to compounds with medicinal potential.[72] By using the well-known (potentially privileged) bicyclic acetal framework, Milroy et al. synthesized structures based on this structural class and derived relatively simple compounds with cytotoxic activity demonstrating how relatively simple changes could give different responses.[73]

Yin and Hamilton[74] in a review in 2005 covered methods of targeting protein–protein interactions from a more synthetic perspective. However, inspection of their structures showed that they had used a large number of isosteres of natural products as models. A valid approach, but perhaps more recognition of the source of the inspiration to make the compounds, was warranted in their discussions.

Finally, in an analysis that is quite similar to this particular review but that was published after the majority of the data referred to in this review were presented at the 2006 Spring Meeting of the American Chemical Society in Atlanta, GA, by the author,[75] Haustedt et al. have presented similar results and conclusions in that Mother Nature still provides the scaffolds around which to design biologically active molecules.[76]

IV. Conclusion

Hopefully, as has been demonstrated in this Miniperspective, the use of information from nature and from compounds that though formally "synthetic" are derived from natural products, or mimic natural product topographies, can be used in a variety of ways to lead to novel structures with (hopefully) therapeutic potential.

In addition to the work presented above, the prior and present (and hopefully future) publications of synthetic chemistry groups led by Blagg, Boger, Danishefsky, De Brabender, Fuchs, Fürstner, Ganesan, Georg, Holton, Kingston, Kishi, Nicolaou, Patterson, Porco, Schreiber, Shair, Smith, Wender, and Wipf (to name but a few) on the synthesis of natural products and then modifications around the structures, often in a combinatorial sense, are continuing to show the "value" of these scaffolds as leads to significant amounts of the original molecules and to variations on the initial scaffolds with optimized biological activities in manifold therapeutic areas.

To demonstrate how the synthetic approaches might also be changing, a recent paper shows how some natural product syntheses may be materially improved by utilizing methods based on biosynthetic precursors rather than by use of routes based on the customary retrosynthetic schemes.[77] Using such a biosynthetic approach, Baran et al. avoided the use of protecting groups during the synthesis in gram quantities of cyanobacterial alkaloids such as hapalindole U (**50**) and 11-*epi*-fischerindole G (**51**). The other alkaloids in the series could then be synthesized by simple modifications. Such a method eliminates the necessity to use complex synthetic routes to avoid the undesired removal of protecting groups at the wrong stage of a synthetic sequence. The original paper should be consulted for the full details and the complex structures involved.

In closing, a fuller discussion of all of the variations on the methods discussed could well be the subject of a relatively large book on the subject. Hopefully, the necessarily brief details given in this Miniperspective will prompt enough inquisitiveness on the part of the reader to consult the major papers noted in the sections above.

Biography

David J. Newman trained originally as an industrial analytical chemist, then received his M.Sc. (1963) in synthetic Organic Chemistry (University of Liverpool, U.K.), and after some years in the U.K. chemical industry, he received his D.Phil. (1968) in Microbial Chemistry (University of Sussex, U.K.). Following postdoctoral studies (Biochemistry Department at the University of Georgia), he joined SK&F Laboratories in Philadelphia, PA, and spent 15 years in biological and antibiotic discovery chemistry. After 6 years in various biotechnology and pharmaceutical companies working mainly in marine natural products, he joined the NPB in 1991 as a chemist responsible for the marine and microbial collection programs and was appointed Chief in 2006. Has published over 100 research papers, reviews, and book chapters and holds 18 patents.

Note Added after ASAP Publication. This manuscript was released ASAP on April 5, 2008 with an error in Chart 2. The correct version was posted to the web on April 10, 2008.

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