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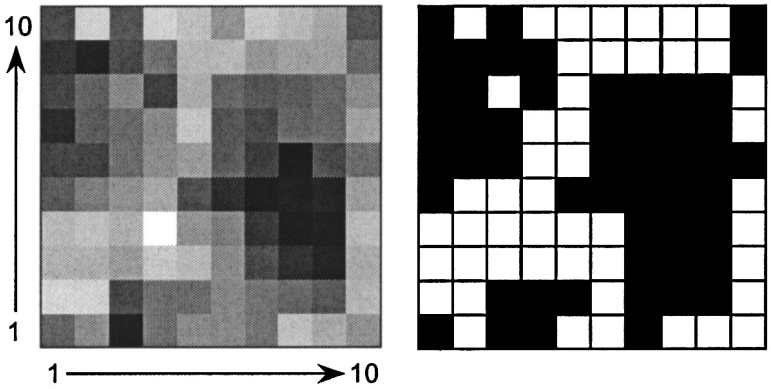

Scaffold Architecture and Pharmacophoric Properties of Natural Products and Trade Drugs: Application in the Design of Natural Product-Based Combinatorial Libraries

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Natural products were analyzed to determine whether they contain appealing novel scaffold architectures for potential use in combinatorial chemistry. Ring systems were extracted and clustered on the basis of structural similarity. Several such potential scaffolds for combinatorial chemistry were identified that are not present in current trade drugs. For one of these scaffolds a virtual combinatorial library was generated. Pharmacophoric properties of natural products, trade drugs, and the virtual combinatorial library were assessed using a self-organizing map. Obviously, current trade drugs and natural products have several topological pharmacophore patterns in common. These features can be systematically explored with selected combinatorial libraries based on a combination of natural product-derived and synthetic molecular building blocks.

Collections of natural compounds are generally considered as a rich source of valuable biologically active substances.[1] Many current drugs either mimic naturally occurring molecules or have structures that are fully or in part taken from such natural motifs.[2−4] It is evident that natural substances offer a wealth of biostructural information that can be used to guide drug discovery and molecular design projects.[5,6] In this work, we have analyzed and compared collections of natural substances against trade drugs in order to reveal novel scaffold architectures for potential use in combinatorial chemistry.

Two data sets were compiled from commercially available databases. Trade drugs were taken from the Derwent World Drug Index (WDI),[7] where all structures with a trade name entry were selected. Molecules with a calculated molecular weight (MW_c) below 100 were omitted. This resulted in a total number of 5757 compounds ("trade drugs"). A total of 10 495 natural products were compiled from the BioscreenNP database.[8] A total of 60−65% of this library are compounds of plant origin, and 5−10% were isolated from microorganisms, with about 5% stem from marine species and the rest from other natural sources. The Daylight program toolkit was used for calculation of molecular weight and numbers of heteroatoms and hydrogen-bond donors.[9] Estimation of the octanol−water partition coefficient ($\log P_c$) was done using the routine of Meylan and Howard.[10]

To get an overview, we compared the two data sets using complete molecules (Table 1). The average calculated molecular weight is almost identical for trade drugs ($MW_c = 356$) and for natural products ($MW_c = 360$), where the trade drugs show a broader distribution (std dev = 261, compared to std dev = 166). The average $\log P_c$ values are slightly higher for the natural product collection ($\log P_c = 2.9$) than for trade drugs ($\log P_c = 2.5$). The most obvious difference between the two data sets is, however, the average number of nitrogen atoms per molecule. This finding is also supported by other investigations.[11] A drug molecule contains approximately twice the number of nitrogens (2.3) than a natural product (1.4). This ratio is also reflected in the average number of potential hydrogen-bond donor sites. In contrast, the average number of oxygen atoms per molecule is almost identical (approximately four per molecule) in both collections. A surprising observation is that the fraction of structures leading to at least two "rule-of-5" violations is low in both compound sets (approximately 10%). A violation was recorded if $MW_c > 500$, or $\log P_c > 5$, or if the sum of nitrogen and oxygen atoms present in a molecule exceeded 10, or if the total number of potential hydrogen-bond donors was greater than 5.[12] We had expected that natural products lead to a higher fraction of alerts. To check whether this is a consequence of a biased data set, we performed the same analysis with a Roche in-house compilation of natural substances (not shown). With only minor deviations the qualitative result was identical to the numbers given in Table 1.

Table 1. Comparison of Whole Molecule Properties

parameter	trade drugs[a]	natural products[a]
total no. of molecules	5757	10495
MW_c	356(261)	360(166)
$\log P_c$	2.1(3.0)	2.9(2.9)
⟨H donors/molecule⟩	2.5	1.8
⟨N/molecule⟩	2.3	1.4
⟨O/molecule⟩	4.1	4.3
"rule-of-5" alerts	10%	12%

[a] Numbers in parentheses are standard deviations.

Comparison of Scaffold Structures

For identification of ring systems that may form drug scaffolds, a two-step scheme was applied.[13] First, cyclic

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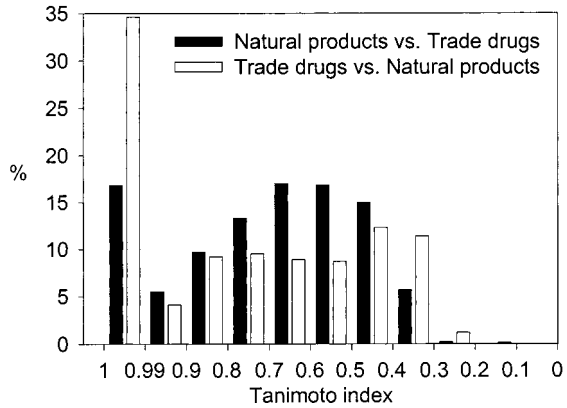

Figure 1. Distribution of nearest-neighbor Tanimoto similarity values obtained from a comparison between ring systems derived from trade drugs and natural products. The two bars on the left give the fraction of identical scaffolds found by pairwise comparison (Tanimoto index is greater than 0.99).

molecular subgraphs were identified. In the second step cleavage rules were applied to remove side chains and linkers connecting different ring systems belonging to the same molecule. Any single bond connecting a ring atom to a side chain was cleaved. Double and triple bonds connecting a ring atom to a side chain were left unchanged (not removed) to protect the existing conjugated systems. These rules were exhaustively applied to a molecule—to the resulting fragment sets—until all susceptible bonds were cleaved. Finally, the remaining fragments (ring systems) were loaded into a Daylight database for further analysis. The algorithms for ring extraction and the cleavage rules were implemented in the C programming language using the Daylight Reaction Toolkit.[9]

We found 1748 different ring systems in the BioscreenNP natural products collection and 807 different ring systems in WDI trade drugs. Approximately 35% of the trade drug ring systems are also present in the natural product collection, but only 17% of the ring systems found in natural products have an identical counterpart in the WDI trade drugs (Figure 1, most left bars). This finding demonstrates a relatively larger diversity of ring systems present in natural substances.[5,11] A more detailed comparison of structural similarity using the Tanimoto similarity coefficient based on Daylight's structural fingerprints indicates that today's trade drugs contain many structural features that are also found in natural products.[14] Again, significantly more (sub)structure similarities are observed comparing natural products to the trade drug collection (black bars in Figure 1) than vice versa (white bars in Figure 1). From this analysis we conclude that there is a clear structural overlap between the two data collections, but natural products contain many additional central ring systems that could be explored in drug discovery projects.

On average, the trade drugs' ring systems are smaller than the ring systems in natural products. This finding is valid for both the numbers of atoms involved and the numbers of rings connected. A total of 27% of the central ring systems consist of a single five- or six-member ring in the trade drug collection, compared to only 16% for the natural products. Most structures contain two rings forming the "scaffold" (approximately 30% of both data sets), and in approximately

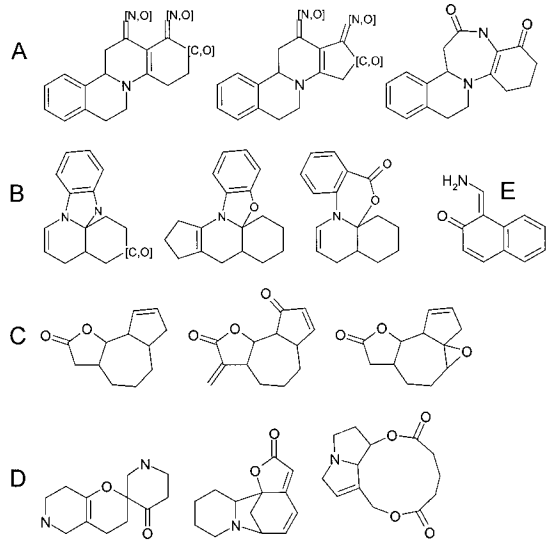

Figure 2. Ring systems found in natural products but not in the trade drug collection. Parts A−E form separate structural clusters.

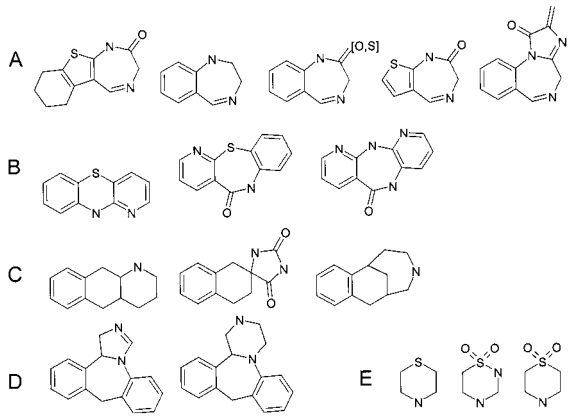

Figure 3. Ring systems found in trade drugs but not in the collection of natural products. Parts A−E form separate structural clusters.

9% of all structures the scaffold ring system contains exactly 10 atoms (e.g., six- plus five-membered rings annealed).

A selection of ring systems found only in the natural product collection is shown in Figure 2. Some ring systems present only in the trade drug collection are shown in Figure 3. These structures were identified by a Jarvis−Patrick clustering procedure of the pooled data sets.[15] Classification was again based on Daylight's structural fingerprints and the Tanimoto index as a similarity criterion. Two structures clustered together if they had at least eight out of their 14 nearest neighbors in common. The ring systems shown in Figures 2 and 3 form five individual structural classes each (pure clusters), denoted by A−E.

Comparison of Topological Pharmacophore Patterns

To compare the collections of trade drugs and natural compounds in a "pharamcophore space" rather than in a purely structure-oriented fashion like the Tanimoto approach with structural fingerprints, we trained a self-organizing map (SOM).[16−18] All molecules were represented by a simple topological pharmacophore descriptor, which is based on a topological correlation of generalized atom types (lipophilic, hydrogen-bond donors and acceptors, positive and negative

charge centers); for the five atom types there are 15 possible pairs. Distance between pairs of atoms was defined as the shortest topological path connecting the two nodes in the molecular graph. Distances between 1 and 10 bonds were considered in the present study. This led to a $15 \times 10 =$ 150-dimensional vector description of a molecule, giving a relative frequency of atom type pairs over bonds in the molecular graph. Since the raw counts were scaled by the number of non-hydrogen atoms present in a molecule, one might regard the descriptor as giving the potential "interaction pair load" of a structure. This molecular representation is rotation- and translation-invariant, and thus, the problem of pairwise structural alignment was avoided. This has been shown to be suited for database similarity searching and de novo design in the absence of three-dimensional conformer models.[19−21] Further details about the topological pharmacophore descriptor and SOM can be found elsewhere.[17−21] The idea of the topological pharmacophore space consequently follows Carhart's concept of atom-pair descriptors.[22,23]

For graphical display the molecule distributions in this 150-dimensional bond-count pharmacophore space were projected onto a toroidal map consisting of $(20 \times 20) =$ 400 neurons (clusters) using Kohonen's SOM algorithm,[16] as implemented in the NEUROMAP package.[18] As a result of this mapping procedure, each neuron represents a cluster of molecules having certain features in common; i.e., the molecules are more similar to each other than to any other molecule in the data set. SOM development is comparable to Voronoi tesselation of the high-dimensional data space, reflecting a vector quantization process.[16] The mapping error can be defined by the mean quantization error, mqe,[24]

$$\mathrm{mqe} = \frac{1}{N}\sum_{c}\sum_{\mathbf{x}\in R_c} ||\mathbf{x} - \mathbf{w}_c||^2 \qquad (1)$$

where N is the total number of molecules used for SOM training, R_c is the "receptive field" (Voronoi region) of a neuron c, $\mathbf{x}$ is the 150-dimensional molecular descriptor, and $\mathbf{w}$ is the 150-dimensional cluster centroid (neuron vector).

To determine the classification accuracy of an SOM, the correlation coefficient, cc, according to Matthews was calculated (vide infra for details):[25]

$$\mathrm{cc} = \frac{PN - OU}{\sqrt{(N+U)(N+O)(P+U)(P+O)}} \qquad (2)$$

In eq 2, P is the number of positive correct predictions, N is the number of negative correct predictions, O is the number of false-positive predictions (overprediction), and U is the number of false-positive predictions (underprediction).

Both natural products and trade drugs exhibit pharmacological activity. To see whether the topological pharmacophore descriptor is able to separate "drugs" from "nondrugs"—and thus may be used to analyze "drug-relevant" pharmacophoric space—we first developed an SOM using Sadowski's collection of drugs and nondrugs (Figure 4).[26] This data set was compiled from the WDI (4998 drugs) and the Available Chemicals Directory (ACD;[27] 4282 nondrugs). For details about this data set and its limitations, see the original publication.[26] The SOM projection reveals a separation between drugs and nondrugs in topological pharmacophore space, as indicated by the light and dark areas in Figure 4a. Neuron (4/4) represents a pure nondrug cluster (white color). Neurons (7/5), (8/4), and (8/6) contain only drug molecules (black color). All other clusters are mixed. The mean quantization error indicating how well the SOM clusters represent the molecule data was mqe = 0.6. To estimate the classification ability of this SOM, a binary pattern class assignment was introduced (Figure 4b): A cluster was regarded as "druglike" (black color) if it contained more than 50% of drug molecules; otherwise, it was regarded as belonging to the "non-drug-like" class (white color). In contrast to U-matrix methods for class assignment, no borderline clusters (no assignment of data to any of the pattern classes) were considered here.[28] The resulting binary class distribution clearly shows a drug and a nondrug region. Note that the map forms a torus. On the basis of this binary classification, 3447 WDI drugs (69%) and 2708 ACD nondrugs (64%) were correctly classified, yielding a Matthews correlation coefficient of cc = 0.33. From the observation of distinct preferred drug and nondrug regions we concluded that the topological pharmacophore vector was suited for the analysis of "drug-relevant" pharmacophore space. The binary prediction accuracy obtained (cc = 0.33) is low compared to the much higher accuracy that can be yielded by supervised techniques and more problem-specific molecular descriptors.[26,29,30] It must be stressed that in the present study the SOM was not intended to form a prediction system. The aim was to visualize the distributions of compound libraries in a high-dimensional space. The projection shown in Figure 4a is a topology-preserving map of the 150-dimensional pharmacophore space containing drugs and nondrugs.

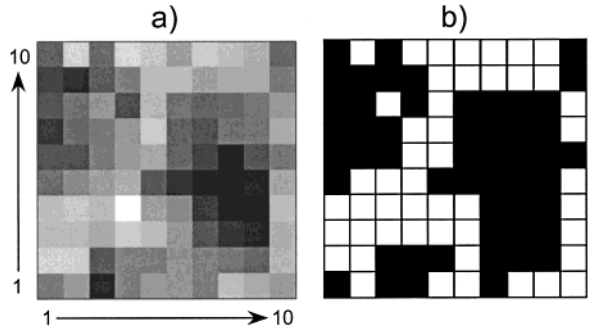

Figure 4. Self-organizing map (SOM) projection of a topological pharmacophore space filled with 4998 "drugs" and 4282 "nondrugs", where each square represents a cluster of molecules (Voronoi region): (a) ratio of drugs and nondrugs clustered shown by gray-scale shading (white is 100% nondrugs, black is 100% drugs); (b) binary classification of the clusters shown in (a), where black clusters contain more drugs than nondrugs and white clusters contain more nondrugs than drugs (50% threshold). Note that the (10×10) map forms a torus.

After the applicability of the topological pharmacophore descriptor to analyzing "drug-relevant" space was demonstrated, the next step was to map the space filled with the natural products and trade drugs. Figure 5a shows the distribution of trade drugs, and Figure 5b shows the natural products map. In Figure 5c the binary classification based on the clustering of natural products and trade drugs is given.

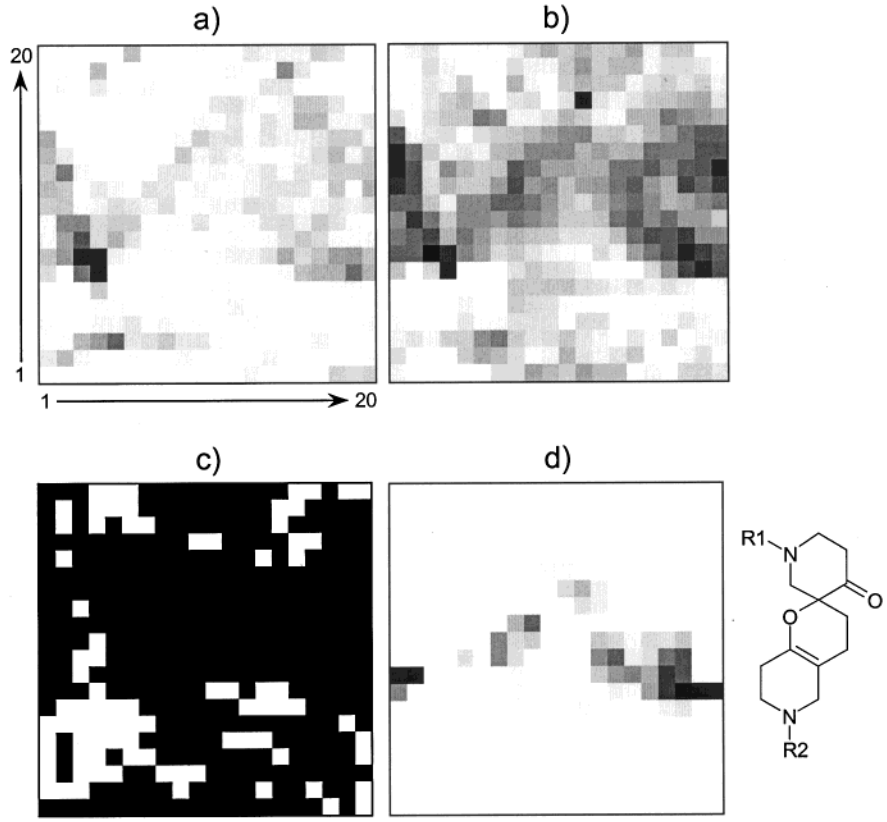

Figure 5. Self-organizing map (SOM) projections of the distributions of different compound libraries in a topological pharmacophore space: (a) WDI trade drugs; (b) a natural product collection; (c) binary classification of the distribution of trade drugs and natural compounds (black is natural products, white is trade drugs, 50% threshold, cf. Figure 4); (d) a virtual combinatorial library generated from a natural product scaffold, where the gray shading indicates the occupancy of the neurons (clusters). Note that the (20 × 20) map forms a torus. The four depictions are based on a single SOM and have corresponding neuron indices.

The SOM's mean quantization error was mqe = 2.8, and the binary classification accuracy based on the cluster assignment shown in Figure 5c was cc = 0.29 (correct predictions: 32% of the trade drugs, 91% of the natural compounds). Despite the higher resolution of the map, the cc is lower and the mqe is higher than the values obtained for the drug/nondrug data (Figure 4), indicating less pronounced separation of natural products and trade drugs in topological pharmacophore space. Both trade drugs and natural products fill the whole space in the (20 × 20) map shown in Figure 5, with peaks in neurons (4/7) and (3/8). These clusters contain many natural steroids. Almost identical coverage of pharmacophore space by trade drugs and natural products is found in lower resolution maps containing (8 × 8) or (10 × 10) neurons (not shown). Trade drugs have a slightly more pronounced density in the lower-left corner of the map and a lower density in the remaining part (Figure 5c). At the given resolution of the map, several small "druglike" and "natural productlike" islands can be found and no clear separation of the two classes is observed. For comparison, we performed the SOM projection with an older version of the WDI from the year 1997 containing only 4429 trade drugs. This older set of compounds revealed some more "holes" in pharmacophore space compared to the natural product collection (not shown). We also found a more conspicuous enrichment of small, nitrogen-rich structures in the older WDI version. One reason for this observation might be that many natural products and mimetics entered the drug market during the past years.[2,5]

The SOM-based comparison of topological pharmacophores suggests that natural compounds and current trade drugs have many similar constellations of generalized atom types. Thus, it appears reasonable to build on scaffold structures derived from natural compounds. One particular advantage can be to obtain novel templates with side chain attachment sites ("exit vectors") that are appropriate for obtaining some desired biological activity.[13] In Figure 5d the distribution of such a virtual combinatorial library in topological pharmacophore space is displayed. On the basis of the natural template shown in Figure 2D (left-hand side molecule), a virtual library was enumerated containing (38 × 38) = 1444 molecules. A total of 38 generic side chains were attached to each nitrogen atom of the scaffold by full permutation. The side chains represent a collection of various lipophilic and polar groups connected via one- or two-atom spacers to the scaffold nitrogens. In the SOM projection the library is not uniformly distributed. Pronounced density is observed in neurons (1/9), (2/9), (18/8), (18/9), and (20/9). Note that these neurons are direct neighbors due to the toroidal architecture of the SOM. The original natural compound leading to the library scaffold was assigned to neuron (18/8). Our virtual combinatorial library can therefore be regarded as a systematic variation of this scheme. Several trade drugs clustered in neuron (18/8) and adjacent clusters have an

antibiotic or antiseptic activity. It might be worthwhile to test the designed combinatorial structures in respective assays. This result clearly shows that a single scaffold can be used to explore a significant portion of "drug-relevant" pharmacophore space.

One must be very careful about generalizing some of the findings because of the biased data sets. Some structural classes are over-represented in either one of the two data collections used in the present analysis, e.g., the many natural and synthetic steroids, lactam structures, and tetracyclins. The BioscreenNP data collection includes many substances of plant origin, including several thousand alkaloids, terpenoids, flavonoids, and coumarins; approximately 1000 peptides, glycosides, and nucleosides; and several hundred phenol compounds. This database is also rich in secondary metabolites.[8] Other collections of natural products (e.g., from marine species) and different, more elaborated pharmacophore concepts will probably lead to different results and hence give rise to miscellaneous interpretations.[31] Furthermore, the set of natural products used in the present study unquestionably represents only a tiny fraction of what is realized by the many different living organisms.[1] It has been estimated that less than 10% of the world's biodiversity has been tested for biological activity.[4]

Keeping these concerns in mind, what can we learn from the present analysis? Certainly natural compounds provide interesting novel scaffold architectures, which can be used in combinatorial drug design approaches. In most cases the scaffolds will have to be modified to provide synthetic feasibility and stability and prevent adverse pharmacokinetic effects. Synthetic drug design emphasized "nitrogen chemistry" in the past. It might be worthwhile to explore molecules that are based on a "natural" scaffold aimed at lowering the overall nitrogen count. Taking such a natural scaffold in combination with synthetic side chains might become a typical strategy in future drug design.[5] Extraction of central ring systems is a straightforward method to explore the diversity of natural product architectures and provides a basis for scaffold selection in combinatorial synthesis approaches. A challenging application will be the use of natural-product-derived molecular building blocks for computer-assisted de novo design. We expect many attractive novel structures from the amalgamation of such building blocks, with a collection of building blocks that was obtained from retrosynthetic fragmentation of the WDI.[20,32,33]

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