two columns with a self-complementary curvature by fitting the bumps of one column into hollows of the other. However, placing a third column at the indentation between the two touching columns to achieve a closed-packing structure is not allowed, because the third column cannot be offset by one-half of a unit with respect to both the first and the second columns. Instead, the offset relationship of one-half of a unit between the neighboring columns and the threefold cross-sectional symmetry of the column result in a preferred Y-shaped arrangement of columns, which eventually turns into the hexagonal open-framework structure (Scheme 1 b).[15] This structure not only demonstrates that the shape and symmetry of a building block can induce a specific crystal structure, but also provides a new strategy to open frameworks with linear hexagonal channels. This novel structure and building principle may provide further insight into designing new porous materials as well as other supramolecular architectures.

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[10] Cucurbituril decahydrate (0.390 g) was added to a saturated solution of Rb_2SO_4 (10 mL). After the mixture was stirred for 1 h, the undissolved cucurbituril was filtered. Methanol vapor was allowed to diffuse into the filtrate at room temperature for a week before the crystalline product **1** was collected, washed with water, and dried in the air. Elemental analysis was performed on the air-dried sample. Elemental analysis (%) calcd for $[(C_{36}H_{36}N_{24}O_{12})Rb_2(OH)_2(CH_3OH)_2]\cdot 3H_2O$: C 34.58, H 3.97, N 25.47; found: C 34.36, H 4.28, N 25.71.

[11] Crystal data of **1**: $[(C_{36}H_{36}N_{24}O_{12})Rb_2(OH)_2(H_2O)_2\cdot(CH_3OH)_2]\cdot 17H_2O$, $M_r = 1608.23$, hexagonal, space group $P6_3/mmc$, $a = 19.628(6)$, $c = 10.544(3)$ Å, $V = 3518(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.518$ g cm^{-3}, $T = 188$ K, Siemens SMART CCD diffractometer, $Mo_{K\alpha}$ ($\lambda = 0.71073$ Å), $\mu = 14.95$ cm^{-1}. The structure was solved by Patterson methods (SHELXS-86). All non-hydrogen atoms were refined anisotropically (SHELXL-93). Final full-matrix least-squares refinement on F^2 with all 1049 reflections and 117 variables converged to $R1 = 0.092$ ($I > 2\sigma(I)$), $wR2 = 0.30$ (all data), and GOF = 1.12. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-103350. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[12] The void volume of the channels was estimated by the method described in reference [3b].

[13] Upon loss of the solvate molecules (water) the open-framework structure collapses to become a denser amorphous material.

[14] Diffusion of THF into the solution of cucurbituril/Rb_2SO_4 produces needle-shaped crystals first, which have the same honeycomb structure as **1**. However, the crystals change their morphology slowly to block-shaped crystals which have different cell parameters: monoclinic, space group $C2/m$, $a = 22.8361(4)$, $b = 10.4759(2)$, $c = 19.8560(4)$ Å, $\beta = 113.483(1)$, $V = 4356.7(1)$ Å^3. X-ray structural analysis on this crystal is in progress.

[15] In another way to look at the structure one may consider cucurbituril as a "pseudosphere". The pseudospheres are forced to line up vertically upon formation of the coordination polymer with the rubidium ions. This vertical lineup prevents the classical hexagonal or cubic closed packing, but leads to the "hexagonal open packing" observed here.

Statistical Investigation into the Structural Complementarity of Natural Products and Synthetic Compounds

Thomas Henkel,* Roger M. Brunne, Hartwig Müller, and Felix Reichel

Natural products represent a rich source of biologically active compounds. They have played a considerable part in the exploration and development of new drugs and crop protection products, which can be informally derived from the retrospective analysis of important commercial products.[1, 2] This historical point of view does not give any information in regard to the question as to how far the structural properties of natural products differ from the easily accessible synthetic substances. With the entrance of high-throughput-screening (HTS) as well as combinatorial chemistry in the lead-finding process this question however becomes of central importance in defining the future role of natural products in this research area. There is a need to evaluate whether natural products

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represent a structurally unique pool of test substances that can not simply be replaced by synthetic efforts. In this context it is also of interest to determine the specific characteristics of individual natural product sources to provide a possible way of focussing and increasing the efficiency of sample selection.

Herein is a first effort to describe statistically the differences between the structural properties of natural products and synthetic substances so as to derive statements into the complementarity of these pools of structures; therefore two data bases, *DNP* and *BNPD*, which describe the bulk of the published natural products, two chemical data bases, which include available chemicals (*ACD*), and a representative pool of test substances (*Synthetics*), as well as a data base that covers pharmaceutical products/compounds in development (*Drugs*) were used (description in the methods section).

An evaluation of the molecular weight as well as the distribution of heteroatoms from the considered data bases was initially undertaken (see Figures 1 – 4). On average, natural products have higher molecular weights than the synthetic compounds; the distribution of the *Drugs* and *DNP* pool appear comparable. A lower number of nitrogen, halogen, or sulphur atoms was evident for natural products whereas the content of oxygen is rather increased. *Synthetics* have about 90% of the average highest content of nitrogen.

With regard to topological parameters the natural products (*DNP*) contain a relatively larger fraction of compounds with sp^3-hybridized bridgehead atoms. Also the average number of rings and chiral centers per molecule is larger (Table 1). As a result natural products can statistically be described as sterically more complex structures.

In regard to the average number of different pharmacophoric groups, for example, amide groups, per molecule natural products (*DNP*, ca. 3.2 pharmacophors/molecule) together with *Synthetics* (ca. 3.3) are positioned between *Drugs* (ca. 3.7) and available chemicals (*ACD*, ca. 2.9). The abundance of certain pharmacophoric groups, however, differs strongly in natural products from those of *Drugs* and *Synthetics* (Figure 5). More distinctly the compounds in the data bases differ in regard to the abundancy of combinations of pharmacophoric groups (Table 2).

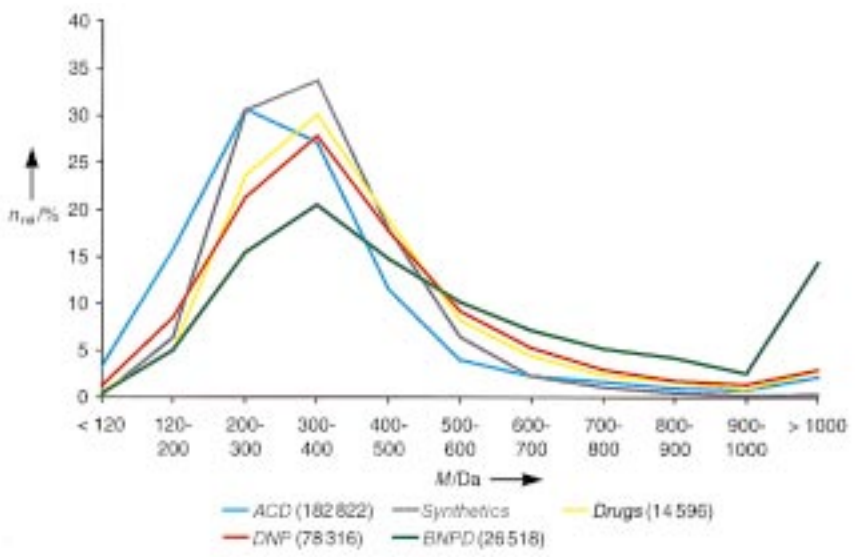

Figure 1. Distribution *n* of the molecular weights in the five data bases investigated. The numbers in brackets represent the total number of entries processed from the data bases.

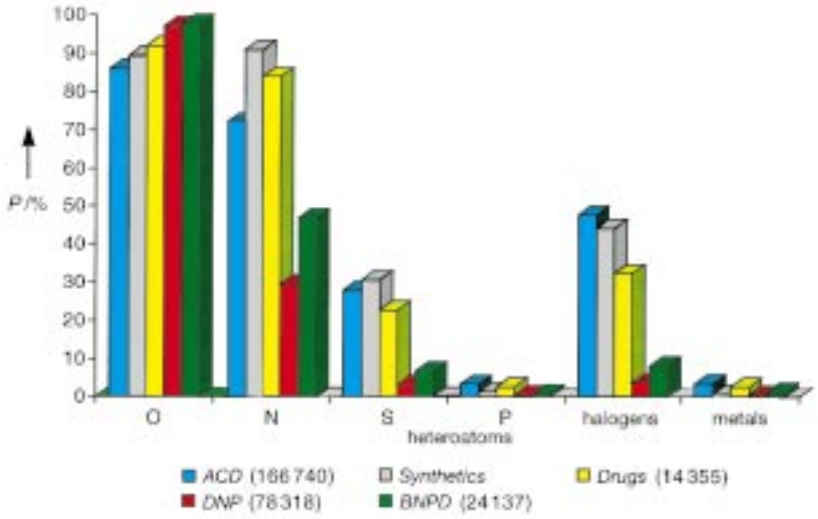

Figure 2. Population *P* of heteroatoms in the five data bases investigated.

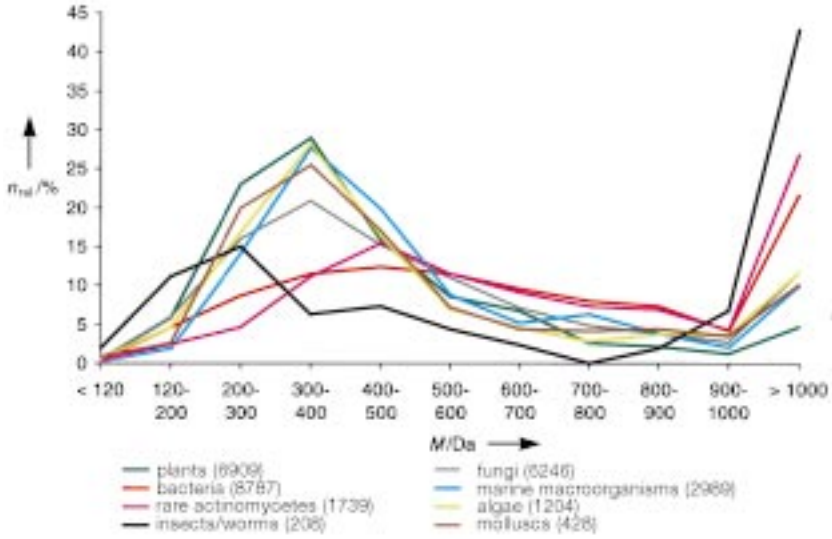

Figure 3. Distribution of the molecular weights of natural products according to producer organism (source: *BNPD*).

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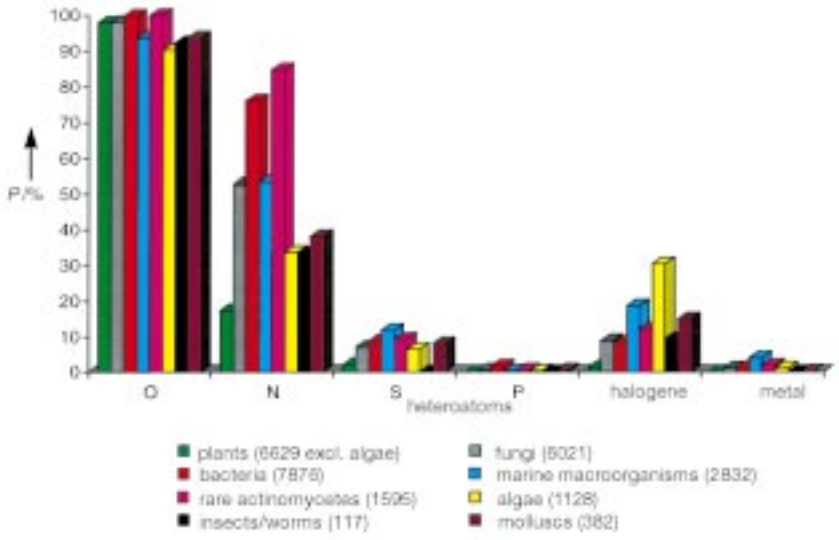

Figure 4. Population *P* of the heteroatoms in the natural products according to producer organisms (source: *BNPD*).

Table 1. Abundance of selected structural properties from all the individual entries of three representative data bases as well as the average number of structural properties per molecule.

Properties	*Drugs*	*Synthetics*	*DNP*
bridgehead atoms with three ring bonds	25 %	9 %	49 %
bridgehead atoms with four ring bonds	4 %	1.4 %	13 %
rotatable C–C bonds	74 %	58 %	66 %
rings per molecule	3.0	2.6	3.3
chiral centers per molecule	1.2	0.1	3.2
rotatable bonds per molecule	10.7	8.0	11.1

Table 2. Combinations of pharmacophoric groups and their abundance.

Pharmacophoric groups	*Drugs* [%]	*Synthetics* [%]	*DNP* [%]
alcohol/ether	19	5	41
alcohol/ester	10	3	30
arene/alcohol	24	13	40
arene/alcohol/ether	12	5	27
amine/arene	50	40	15
arene/amide	31	43	12
amine/arene/amide	20	15	5

The generally known high internal redundancy of natural products—thus the abundance with which at least one structural relative is discoverable for every type of molecule—was determined statistically as 85 % by a computer-based similarity analysis. The *DNP* pool can be reduced from about 80000 substances to 11500 structurally diverse types of molecules by excluding this redundancy. By comparison of the structural similarity between compounds in *DNP with those of Synthetics* it is evident that about 40 % of the natural products are not represented by synthetic compounds.

The potential of individual natural sources with regard to the structural properties was evaluated initially through comparison of the molecular weight and heteroatom distribution of compounds derived from single producer organisms extracted from *BNPD* (Figures 3 and 4). Significant differences of distribution become evident, for example, the significantly higher molecular weights of natural products from rare actinomycetes and the lower average content of nitrogen in plant substances. A large fraction of terpenes (ca. 35 %) and alkaloids (ca. 20 %) in the *DNP* as well as peptides (ca. 17 %) and alicycles (ca. 19 %) in the *BNPD* pool are found from an analysis of the distribution of the types of structures in the natural product data bases (Figure 6). Significant differences in population can likewise be discovered by dividing these

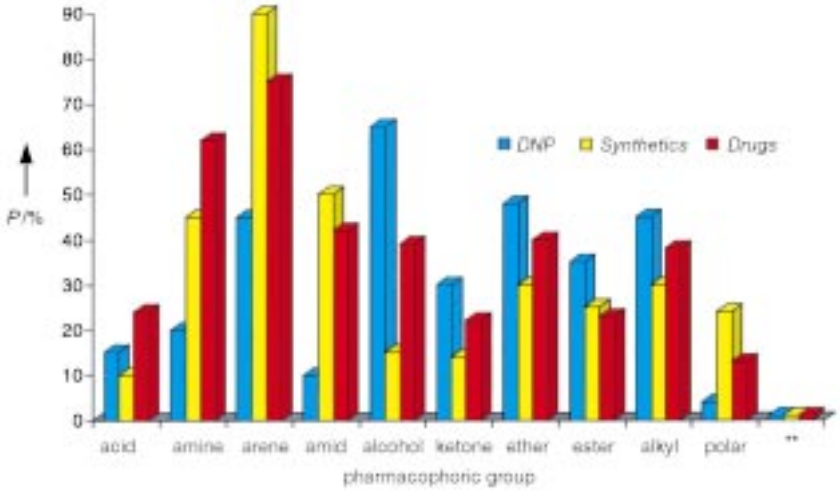

Figure 5. Population *P* of pharmacophore groups analyzed for the *DNP*, *Synthetics*, and *Drugs* data bases, ** = not classified, polar = F, CN, NO_2.

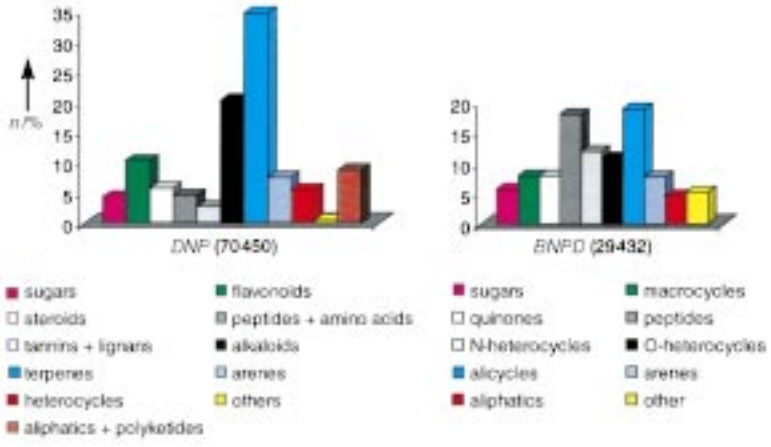

Figure 6. Distribution of structural types in the natural products for the data bases *DNP* and *BNPD* following their assignment in each data base; the data bases are based on different classifications and are listed separately.

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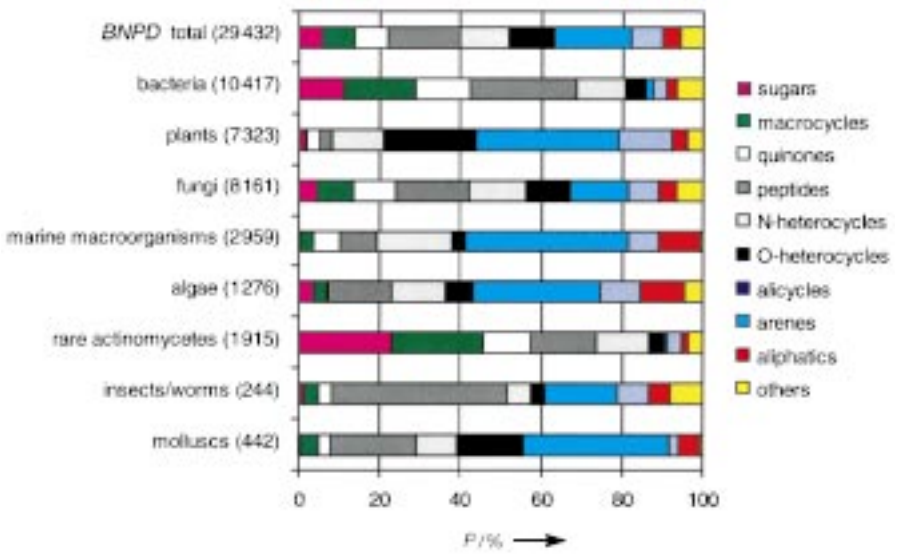

Figure 7. Populations P of the types of structures in the natural products produced by different organisms (source *BNPD*)

distributions in *BNPD* according to producer organisms (Figure 7). In comparison to the total distribution of all bioactive natural products in *BNPD* those of bacteria show an above-average share of macrocycles, which is on the contrary very low in plants. Clearly, a natural product pool that is representative of the types of structures can only be created by consideration of all natural sources. Conversely a supply of individual combinations of preferred types of structures can be obtained.

It can be derived from the number of natural products that have been sorted according to individual sources (Figure 3, 4, 7) that these sources vary in productivity and/or the degree of scientific investigation. More than 10000 bioactive substances from bacteria have been determined as opposed to less than 450 from molluscs. Collectively the origin of approximately 30000 bioactive natural products (*BNPD*) are divided into the four large sources: plants, bacteria, fungi, and animals in 27, 33, 26, and 13%, respectively. The number of bioactive natural products (*BNPD*) described against this background was examined according to year and source (Figure 8). It becomes evident that their number has increased continuously from about 800 between 1960–1965 to more than 5000 between 1990–1995. All the investigated sources contributed, but the numbers for fungi and marine metabolites have increased at a higher rate.

It follows that all the statistical evaluations show a distinct difference in the considered structural properties of natural products relative to the investigated synthetic compounds. They highlight typical structural elements, which up to now have not been routine targets of synthesis for randomized substance pools. The structural variability of natural products between individual natural sources is conspicuous and should be considered according to certain demands. The potential for new natural products is not exhausted and natural products still represent an important source for the lead-finding process. Hence, the occasionally voiced prepossession that natural products have already been sufficiently examined and therefore no more innovations are to be expected can definitely be rejected for that reason.

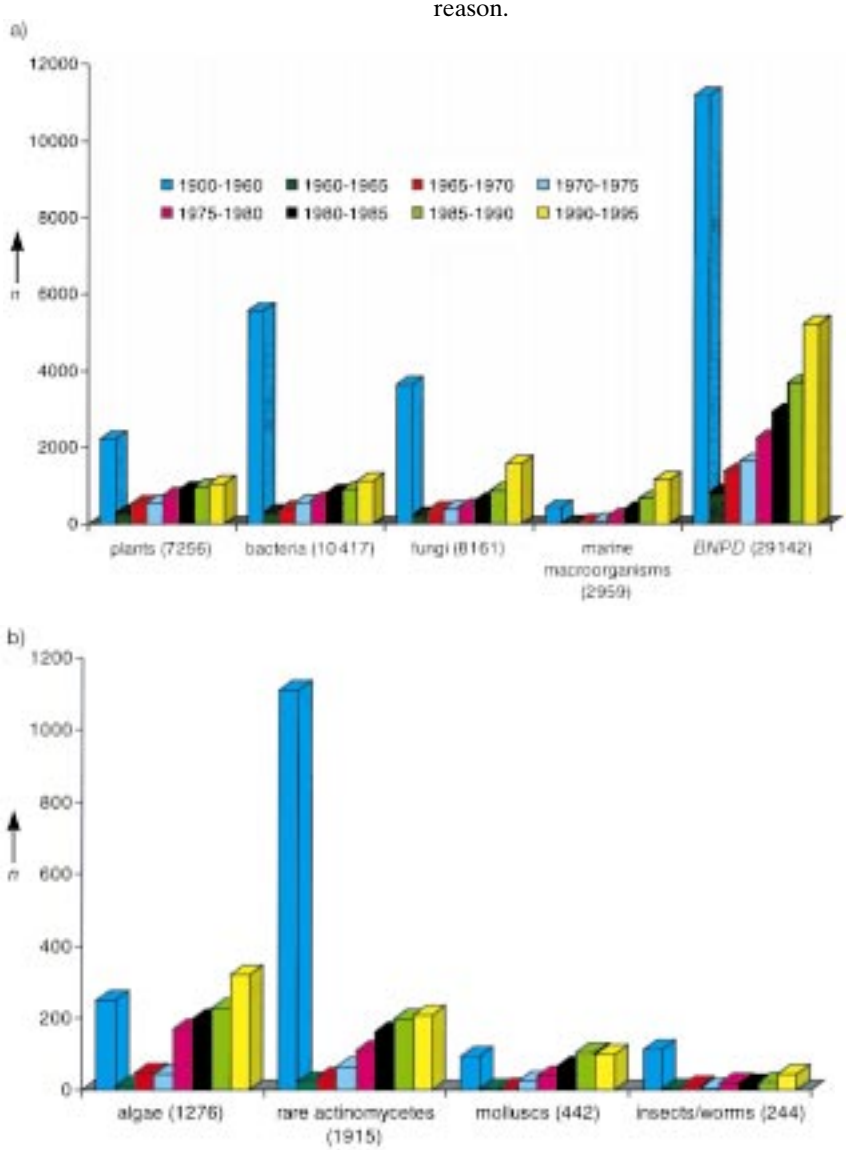

Figure 8. a), b) Time dependency of new entries in *BNPD* according to their biological source.

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Method Section:

The data bases taken as the basis were:

- *DNP*: Dictionary of Natural Products on CD-ROM (Chapman&Hall), 78318 structural entries (status: June 96)
- *BNPD*: Bioactive Natural Product Database, Szenzor Management Consulting Company, Budapest, (Hungary) (by Berdy), 29432 entries of natural products with described biological activity (status: July 96)
- *Drugs*: Pharmaceutical products/compounds in development recorded in Pharmaprojects, RDFocus and in the active compounds pool of Bayer AG, 14596 entries (status: June 96)
- *ACD*: Available Chemicals Directory, Version 93.2, from Molecular Design Ltd. Information Systems Inc., San Leardo, CA (USA), 182822 entries
- *Synthetics:* Representative pool of synthetic test compounds from Bayer AG.

The construction of the data bases unavoidably resulted in some peculiarities in the data evaluation, which should be noticed in the detailed inspection of the determined results: *DNP* contains 78318 compounds from which however only 70450 appear as authentic natural products. In some cases it became necessary to use both data sets as a consequence of the restraints applied. *DNP* does not include any identifier for natural product sources, so that an evaluation of producer organisms was limited on *BNPD*. The numbers of investigated compounds in the figures are lower than the total numbers given in the data bases as the data sets are partly incomplete. For a clearer and simplified description only parts of selected data bases are compared in the tables and figures. The data bases were converted in MACCS-[3] and UNITY[4]-format and analyzed with the available default methods for the evaluations related to structures. The structural similarity analysis between molecules was obtained from the 2D-fingerprint descriptors in the standard definition of UNITY.[4] The similarity/dissimilarity between pairs of molecules was calculated according to Tanimoto[5] and discussed in reference to a limiting value of 0.75. The analysis of pharmacophoric groups, predefined from a general chemical understanding, was carried out with software developed by Bayer AG. Full details can be found in the supporting information.

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Surface-Initiated Polymerization for Amplification of Self-Assembled Monolayers Patterned by Microcontact Printing**

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The generation of complex patterns in polymer films is traditionally achieved by combining spin-casting and photolithographic techniques.[1] Polymer films patterned by this procedure are widely used for the fabrication of microelectronic devices[2] or as selective barriers to etchants[3] and redox-active probes.[4] While successful, the usefulness of these patterned polymer films is restricted by their limited stability with respect to solvents and their tendency to undergo subsequent chemical reactions[5] as well as by difficulties in their preparation over large areas and complicated topographies.[6] To address these latter challenges, Whitesides and co-workers have introduced the concept of microcontact printing (μCP)[7] for the preparation of patterned self-assembled monolayers (SAMs) on both planar and curved surfaces.[8] Self-assembled monolayers formed from alkanethiols on gold and silver have been used as barriers to wet chemical etchants.[9] In this approach, however, the usefulness of SAMs as barriers to etchants is compromised by the susceptibility of monolayer films to formation of defects,[10] their lack of barrier properties when using dry etchants such as reactive ions, and the conflicting time scales necessary for complete formation of SAMs and for high-resolution patterning.[11] To address these limitations, we report a first step in a program of research aimed at using polymerization as a tool for chemically amplifying surfaces patterned with organic molecules by microcontact printing into patterned polymer brushes.[12] The preparation of a macromolecular barrier instead of a molecular one provides a means to mask defects within monolayers and to introduce resistance to a wide range of etchants. We also believe it can provide an avenue to high-resolution patterning of polymers through surface-initiated polymerization to mask incomplete regions of SAMs formed rapidly so as to minimize lateral transport of thiols. The work we report here also represents a general methodology for patterning polymeric films on surfaces.

The basic strategy of this novel process is depicted in Figure 1. Initially a nonreactive SAM formed from CH_3-

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