were corrected for by adding distilled water in some cases. The gel was shaken at room temperature for 12 h for homogenization and aging. The multiclave was placed in an oven for 24 h at 160 °C. The products were washed and isolated as an array by a custom-designed centrifuge apparatus. The sample array collected on filter paper was transferred to an X-ray sample holder for X-ray analysis. Automated X-ray diffraction analysis was carried out with a computer-controlled xy stage on either a Scintag XDS 2000 diffractometer equipped with a liquid N_2 cooled germanium solid-state detector using $Cu_{K\alpha}$ radiation, or on a rotating anode diffractometer with a Nonius CCD detector using $Mo_{K\alpha}$ radiation. In both cases, the diffractograms were obtained in the transmission mode. Data collection time varied from 10 to 60 min per spot depending on the detector. The data collection time for the standard powder diffractometer can be significantly reduced by using a more powerful X-ray source within the same setup. Powderize, a program from Nonius, was employed to integrate the CCD images.

Received: April 7, 1999 [Z 13253 IE]
German version: *Angew. Chem.* **1999**, *111*, 3070 – 3073

Keywords: aluminophosphates · combinatorial chemistry · hydrothermal synthesis · molecular sieves · solid-state chemistry

[1] *Acc. Chem. Res.* **1996**, *29*, 112 – 170 (special issue).
[2] G. Lowe, *Chem. Soc. Rev.* **1995**, *24*, 309 – 317.
[3] X. D. Xiang, X. Sun, G. Briceno, Y. Lou, K. A. Wang, H. Chang, W. G. Wallace-Freedman, S. W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738 – 1740; for a review on combinatorial materials science, see: B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648 – 2689; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494 – 2532.
[4] D. E. Akporiaye, I. M. Dahl, A. Karlsson, R. Wendelbo, *Angew. Chem.* **1998**, *110*, 629 – 631; *Angew. Chem. Int. Ed.* **1998**, *37*, 609 – 611.
[5] J. Klein, C. W. Lehmann, H.-W. Schmidt, W. F. Maier, *Angew. Chem.* **1998**, *110*, 3557 – 3561; *Angew. Chem. Int. Ed.* **1998**, *37*, 3369 – 3372.
[6] The custom-built robot is a modified xy chart recorder which has a nozzle head that can hold four to six reagent lines. Each reagent line is made up of a unique reagent reservoir, an independently operable micropump, and a nozzle that has a sapphire tip with an orifice of 0.12 mm in diameter. The entire apparatus is controlled by a personal computer and was programmed using LabView.
[7] The custom-designed centrifuge apparatus consists of two different filter papers (glass microfibre and normal filter paper), a PVC block with a matching hole pattern, a filtrate reservoir, and a PVC cylinder. Two pieces of filter paper were placed between the multiclave and the PVC block that was connected to the filtrate reservoir. For washing, the multiclave and the PVC block were turned upside down, and water was added into the holes of the PVC block and then forced into the multiclave by centrifugation. These steps were repeated several times before isolation of the final library.
[8] K. J. Balkus, A. G. Gabrielov, S. Shepelev, *Microporous Mater.* **1995**, *3*, 489 – 495.
[9] L. Schreyeck, P. Caullet, J. C. Mougenel, J. Patarin, J. L. Paillaud, *Microporous Mater.* **1997**, *11*, 161 – 169.
[10] J. E. Sheats, M. D. Rausch, *J. Org. Chem.* **1970**, *35*, 3245 – 3249.
[11] L. T. Reynolds, G. Wilkinson, *J. Inorg. Nucl. Chem.* **1959**, *9*, 86.

"Scaffold-Hopping" by Topological Pharmacophore Search: A Contribution to Virtual Screening**

Gisbert Schneider,* Werner Neidhart, Thomas Giller, and Gerard Schmid

In the process of drug discovery the crucial step to initiate a medicinal chemistry program is to identify molecular entities that interact with a specific target, namely an enzyme, a receptor, or an ion channel. The usual experiment one carries out to identify these lead structures is the so-called "blind screening". Although today automation has made this process fast for large target families, there are still particular cases for which the set-up of the screen is expensive and time-consuming. This is especially true when a very complex device is used for measuring the interaction of chemical compounds with a protein, as for instance in functional receptor assays. In these latter cases as soon as a few lead structures have been identified a very appealing complementary approach is to derive a pharmacophore model from the known active structure (the "seed" or "query" structure) and perform a computer-based similarity search to speed up the process of lead identification.[1]

Several such "virtual screening" techniques have been invented on the basis of two- or three-dimensional representations of molecular structures and various definitions of biophores/pharmacophores.[2] The underlying idea is to define a measure of molecular similarity and collect the most similar compounds to a given seed from a large collection of prospective candidates. Despite recent advances in predicting three-dimensional molecular structures,[3] current high-throughput similarity searches are primarily based on two-dimensional (2D) topology.[4] Herein we present the successful application of a novel straightforward technique to "scaffold-hopping", that is, identification of isofunctional molecular structures with significantly different molecular backbones.

Topological cross-correlation of generalized atom types is a simple molecular descriptor that leads to a compact, molecular size independent description of potential pharmacophores.[5] The general idea of this representation scheme is to count the distances between atom pairs and then to regard the histogram of counts as a simplifying but exhaustive pharmacophore fingerprint of the molecule. Distances are expressed as the number of bonds along the shortest path connecting two nodes (non-hydrogen atoms) in the molecular graph (Figure 1). Each node is checked as to whether it can be assigned one of the following generalized atom types: hydrogen-bond donor (D), hydrogen-bond acceptor (A), positively

[*] G. Schneider, W. Neidhart, T. Giller, G. Schmid
F. Hoffmann-La Roche Ltd
Pharmaceuticals Division
CH-4070 Basel (Switzerland)
Fax: (+41) 61-6889041
E-mail: gisbert.schneider@roche.com

[**] We wish to thank our colleagues Petra Schneider, Eric Ertel, Hans-Joachim Böhm, Eva-Maria Gutknecht, Christian Hubschwerlen, Man-Ling Lee, Martin Stahl, and Manfred Kansy for helpful discussions and encouragement.

  1433-7851/99/3819-2894 $ 17.50+.50/0

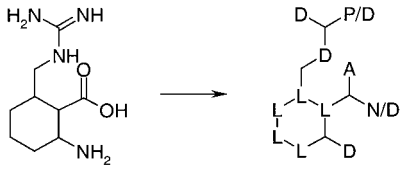


Figure 1. Conversion of a two-dimensional molecular representation (**A**) into the molecular graph (**B**), in which generalized atom types are assigned as implemented in CATS. See text for more information.

charged (P), negatively charged (N), or lipophilic (L). The numbers of all 15 possible pairs of generalized atom types (DD, DA, DP, DN, DL, AA, AP, AN, AL, PP, PN, PL, NN, NL, LL) are determined, and the resulting histogram counts are divided by the total number of non-hydrogen atoms to obtain scaled vectors. Distances of up to ten bonds were considered in the present study, which led to a 150 (15×10) dimensional vector representation of a molecular compound.

Large virtual compound libraries can be searched on the basis of this correlation-vector representation for structures similar to a given molecule with a defined biological activity. Each library molecule is compared to the query vector (derived from the query structure). Here we used the euclidian distance measure D(A,B) [Eq. (1)] to express the similarity between two molecules A and B.

$$D(\mathrm{A,B}) = \sqrt{\sum_{i=1}^{150} (v_i^{\mathrm{A}} - v_i^{\mathrm{B}})} \qquad (1)$$

v^{A} and v^{B} are the correlation vectors derived from molecules A and B, respectively. As a result the library compounds are ordered by their distance-to-seed value, and a ranking list of virtual hits is constructed. This technique is referred to as "CATS" (*c*hemically *a*dvanced *t*emplate *s*earch) herein. Molecules with a low distance-to-seed value are expected to exhibit an overall distribution of pairs of generalized atom types that reflects the characteristics of the query molecule. The in vivo or in vitro activity of potential hits can then be tested for using a biological assay.

Correlation vectors are not new to the field of computer-based similarity searches, for example, they were used as an encoding scheme for molecular surface properties and amino acid sequences.[5, 6] The special attraction of CATS is its exhaustive 2D pharmacophore/biophore model based on the cross-correlation of generalized atom types. As a consequence problems associated with three-dimensional model building and multiple conformers can be avoided.[7] All potential ligand–receptor contact points are described by five interaction types (D, A, P, N, L) and expressed as a scaled histogram of two-point parmacophores. By defining this topological descriptor for a similarity search we minimize the risk of using a misleading three-dimensional pharmacophore model, which can easily happen if, for example, the conformation of the receptor-bound ligand is unknown or several different conformations appear equally possible.[2] We are well aware that ignoring three-dimensional conformation bears the danger of missing essential information required to capture relevant pharmacophores and enantiomers. The heuristic CATS pharmacophore representation can, however, easily be extended to the third dimension.

As a simple retrospective test of CATS we used the thrombin inhibitor PPACK as a query structure to search for other known thrombin inhibitors in the MEDCHEM library (version 1997, as distributed by Daylight Chemical Information Systems Inc., Irvine, CA, USA) containing approximately 33000 molecules.[8] The CATS system was able to rank 15 out of 29 (52%) annotated thrombin inhibitors among the top 100 potential hits. For comparison, the commercially available search tool MERLIN (Daylight Chemical Information Systems Inc., Irvine, CA, USA)—which is based on Daylight's definition of topological fingerprints—retrieved only 12 (41%) known inhibitors among the top 100. In addition, CATS found five inhibitors not reported by MERLIN, whereas MERLIN retrieved only two thrombin inhibitors not found by CATS among the top 100. As a result of this preliminary analysis in which CATS retrieved a larger number of relevant structures than a conventional fingerprint-based search we concluded that CATS seems to be a useful tool for database mining.

In a prospective test CATS was applied to the prediction of novel cardiac T-type Ca^{2+} channel blocking agents by exploring the Roche in-house compound depository. Mibefradil (**1**), a known T-channel blocking agent ($IC_{50} = 1.7\ \mu M$) (Figure 2),[9] was used as the seed structure for CATS. The 12 highest-ranking molecules were tested using a cell culture

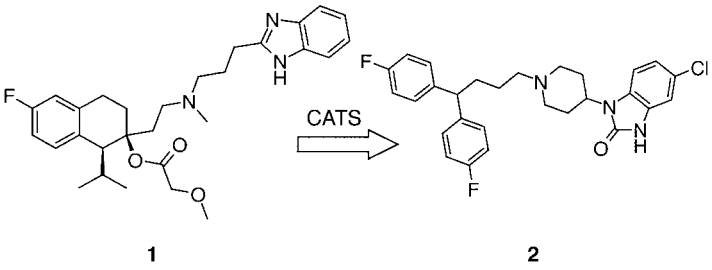


Figure 2. Query structure **1** (mibefradil) and a high-ranking isofunctional structure **2** (clopimozid) derived from **1** by CATS.

assay for their ability to inhibit cellular Ca^{2+} influx.[10] Nine compounds (75%) showed significant activity ($IC_{50} < 10\ \mu M$), of which one compound (**2**, clopimozid[11]) had an $IC_{50} < 1\ \mu M$. The IC_{50} values of the next best structures (not shown) were: 1.7, 2.2, 3.2, and 3.5 μM. These hits have structural scaffolds that differ significantly from the query structure **1**. However, essential function-determining points are preserved, which form the basis of a relevant pharmacophore pattern.

From the experimental results we conclude that CATS can be useful for identifying novel molecular structures with substantial biological activity. The procedure might help to save time and efforts to create targeted libraries and obtain rational molecular designs.[12]

Received: May 17, 1999 [Z13432IE]
German version: *Angew. Chem.* **1999**, *111*, 3068–3070

Keywords: computer chemistry · drug research · structure–activity relationships · virtual screening

  1433-7851/99/3819-2895 $ 17.50+.50/0

[1] a) *Molecular Similarity in Drug Design* (Ed.: P. M. Dean), Chapman & Hall, Glasgow, **1995**; b) G. Schneider, W. Schrödl, G. Wallukat, J. Müller, E. Nissen, W. Rönspeck, P. Wrede, R. Kunze, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12179–12184; c) P. Willett, J. M. Barnard, G. M. Downs, *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 983–996.

[2] a) G. W. Milne, M. C. Nicklaus, S. Wang, *SAR QSAR Environ. Res.* **1998**, *9*, 23–38; b) H. Briem, I. D. Kuntz, *J. Med. Chem.* **1996**, *39*, 3401–3408.

[3] a) J. Sadowski, J. Gasteiger, *Chem. Rev.* **1993**, *93*, 2567–2581; b) R. S. Bohacek, C. McMartin, *Curr. Opin. Chem. Biol.* **1997**, *1*, 157–161.

[4] a) R. D. Brown, Y. C. Martin, *SAR QSAR Environ. Res.* **1998**, *8*, 23–39; b) H. Matter, *J. Med. Chem.* **1997**, *40*, 1219–1229.

[5] G. Schneider, P. Wrede, *Prog. Biophys. Mol. Biol.* **1998**, *70*, 175–222, and references therein.

[6] a) G. Moreau, P. Broto, *Nouv. J. Chim.* **1980**, *4*, 757–764; b) M. Wagener, J. Sadowski, J. Gasteiger, *J. Am. Chem. Soc.* **1995**, *117*, 7769–7775; c) S. Anzali, W. W. K. R. Mederski, M. Osswald, D. Dorsch, *Bioorg. Med. Chem. Lett.* **1997**, *8*, 11–16; d) D. D. Jones, *J. Theor. Biol.* **1975**, *50*, 167–183.

[7] M. Vieth, J. D. Hirst, C. L. Brooks III, *J. Comput. Aided Mol. Des.* **1998**, *12*, 563–72.

[8] a) C. Kettner, E. Shaw, *Methods Enzymol.* **1981**, *80*, 824–826; b) P. D. Grootenhuis, M. Karplus, *J. Comput. Aided Mol. Des.* **1996**, *10*, 1–10.

[9] a) S. I. Ertel, E. A. Ertel, *Trends Pharmacol. Sci.* **1997**, *18*, 37–42; b) D. Sarsero, T. Fujiwara, P. Molenaar, J. A. Angus, *Br. J. Pharmacol.* **1998**, *125*, 109–119.

[10] The cloned T-type Ca^{2+} channel was expressed in HEK293 cells, and the inhibition by the compounds was monitored using a fluorescence assay. T. Giller, unpublished results.

[11] J. Qar, J. P. Galizzi, M. Fosset, M. Lazdunski, *Eur. J. Pharmacol.* **1987**, *141*, 261–268.

[12] D. R. Liu, P. G. Schultz, *Angew. Chem.* **1999**, *111*, 36–56; *Angew. Chem. Int. Ed.* **1999**, *38*, 36–54.

Cascade Reactions in Quantitative Solid-State Syntheses**

Gerd Kaupp,* Jens Schmeyers, Axel Kuse, and Adnan Atfeh*

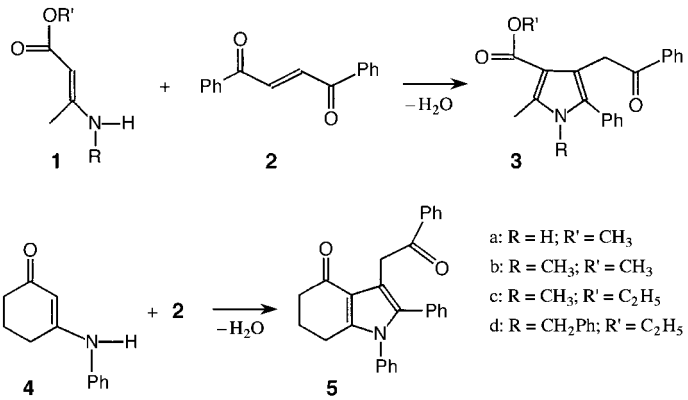
Solvent-free reactions of solids with solids profit from crystal packing effects and are usually highly selective.[1, 2] In contrast to gas–solid reactions[3] no multistep syntheses are known in this field. We report herein on a one-pot synthesis of highly substituted pyrroles (see Scheme 1), which gives moderate yields in solution, but quantitative yields in the solid–solid variant at much lower temperatures, although at least four reaction steps are required in these reactions, not counting proton transfers from N and O. Such reaction cascades[4] have not yet received due recognition in academic teaching, because some particularly elegant examples, which exhibit environmentally friendly and resource-saving behavior due to the lack of workup requirements for intermediates, and which use generally accessible starting materials,[5] were not mentioned in the leading reviews.[6] Rather, the complexity of the starting materials in these reviews require complicated multistep syntheses and thus question both sustainability and broader applications. The execution of the present cascade reactions in the absence of liquid phases avoids product workup because of the 100% yield and is thus truely resource-saving and environmentally friendly.

If the primary or secondary enamine esters **1a–d** or the enamine ketone **4** are treated with *trans*-1,2-dibenzoylethene (**2**) in solution or in a ball-mill without liquid phase, the pyrroles **3** or indole **5** are obtained in moderate or quantitative yields (Table 1), despite the multistep course of reaction (Scheme 1). A thermal after-treatment is only required in the case of **3c** in order to complete the elimination of water (from **8c**, see Scheme 2).

Table 1. Reactions of **1** and **4** with **2** to give **3** and **5**, respectively.

Compound	M.p. [°C] (starting material)	Yield [%] in solution	Yield [%] in crystal	M.p. [°C] (product)	Milling time [h] (T [°C])
1a	81–83	68	100	144–146	3 (25)
1b	67–68	81	100	152	3 (25)
1c	1–2	78[a]	100[a]	122–124	3 (−20)
1d	21	55	100	130–131	3 (0)
4	182	46	100	240–241	3 (25)

[a] After short heating (150 °C) of the 1:1 mixture (78%; solution) or 2:3 mixture (solid) of **3c** and **8c**.



Scheme 1. One-pot synthesis of pyrrole derivatives from easily accessible starting materials.

The complex cascade reactions are remarkable in view of their high selectivity (Table 1) and apparently broad versatility.[7] The constitution of the compounds **3** and **5** is derived from analytical and spectroscopic data.[8] The neighborhood of the phenyl group to the pyrrole-N atom becomes evident from the $\delta(^{13}C)$ values of C4 and C3 in **3b** (C2 and C3 in **5**), which were determined to be 110.1 and 115.1 (114.2 and 119.2). These values correspond much better to the calculated chemical shifts[9] of 112.7 and 117.9 (117.4 and 120.0) than those of the isomeric structure in which the phenyl and benzoylmethyl groups are exchanged: 106.5 and 124.7 (127.5

[*] Prof. Dr. G. Kaupp, Dr. J. Schmeyers, Dipl.-Chem. A. Kuse
Universität Oldenburg, FB9-Organische Chemie I (Germany)
Fax: (+49) 441-798-3409
E-mail: kaupp@kaupp.chemie.uni-oldenburg.de
Dr. A. Atfeh
Daaboul & Aktaa Co.
Damaskus (Syria)

[**] This work was supported by the Fonds der Chemischen Industrie, the Deutscher Akademischer Austauschdienst (1995, for A.A.) and the Daaboul & Aktaa Co., Damaskus.

  1433-7851/99/3819-2896 $ 17.50+.50/0