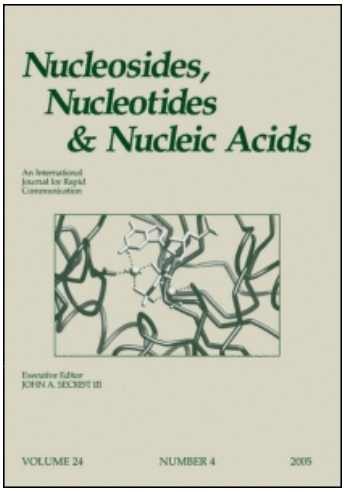

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Combinatorial Generation of Nucleobase Libraries by MCR

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COMBINATORIAL GENERATION OF NUCLEOBASE LIBRARIES BY MCR

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Abstract: Multi component reactions (MCR) together with a suitable set of nucleobase building blocks provide a valuable tool for the fast generation of combinatorial libraries. These arrays of compounds are of high interest as anticancer and antiviral drugs. The preparation of small libraries and their analytics is described.

Many therapeutics in the field of virus-based diseases and of cancer are nucleoside mimics, that inhibit transcription and translation. Out of 8 by the FDA approved anti-AIDS drugs, 5 are nucleoside analoga. Since most of these drugs in use suffer from high mitochondrial toxicity[1], and furthermore cancer cells and viruses[2] are getting resistant with prolonged therapy, the discovery of new and improved nucleobase or nucleoside analoga is a great challenge in medicinal chemistry.

Synthesizing and screening combinatorial libraries of novel low molecular weight organic compounds is emerging as an important new technology for drug discovery[3]. Numerous techniques for combinatorial chemistry are available, ranging from solid-phase chemistry to liquid-phase chemistry, from "one pot one compound" to mixtures of compounds. None of these methods can be judged as the best one and every problem has to be solved by its intrinsic best method.

In principal all kinds of chemical reactions are suitable for combinatorial chemistry. However, the major goal is the fast and time-

saving synthesis of huge arrays of diverse compounds by using either commercially available or easy to prepare starting material.

Whereas a 2-component reaction of 2 sets of 4 starting materials yields a maximum of 16 products, a 4-component reaction of 4 sets of 4 starting materials can yield up to 256 products. Therefore MCRs are superior to conventional two component reactions[4]. The most versatile MCR today is the Ugi reaction[5].

Herein we show the fast generation of nucleobase libraries by using MCR of the Ugi type. Other MCRs are also appropriate for this purpose[6]. The Ugi reaction starting materials are carboxylic acids, aldehydes, amines and isocyanides. The formation of uniform products from four different reactants is accounted for the fact that most of the potential side reactions are reversible, while the main reaction is not.

As nucleobase building blocks we used compounds containing the suitable functional group for MCR. The nucleoside library was generated in a 96 mtp "one compound per well" format. A selection of 16 compounds generated by the MCR approach is shown in Fig.1.

The identity and purity of the library products was ensured by tlc, nmr, ms and hplc. The purity and yield is generally very high (>90%). With the MCR approach of the starting materials used two diastereoisomers were generated with a ratio of 1:1 in most of the cases. These iminodicarboxylic acid derivatives are enantiopure compounds if an optically active α-amino acid is used as starting material.

Obviously the fine tuning of drug properties such as hydro-/lipophilicity, cellular uptake, cell specific uptake, nucleobase content, functional groups (hydroxy, phosphoesters, etc.) and toxicity is particularly easy to achieve by the MCR approach.

Since huge nucleoside type libraries with almost every physical property by using the appropriate starting material can be provided solutions to the well known problems of nucleoside analoga, such as high mitochondrial toxicity, poor tissue selectivity, poor cellular uptake, etc. can be proposed. Therefore our MCR approach with modular target directed building blocks will certainly speed up drug discovery not only in the field of nucleoside analoga.

EXPERIMENTAL

For all new compounds generated by the MCR approach were obtained the correct ^{1}H-NMR spectra by a Bruker AC 250 in $CDCl_3$ or d^6-DMSO with

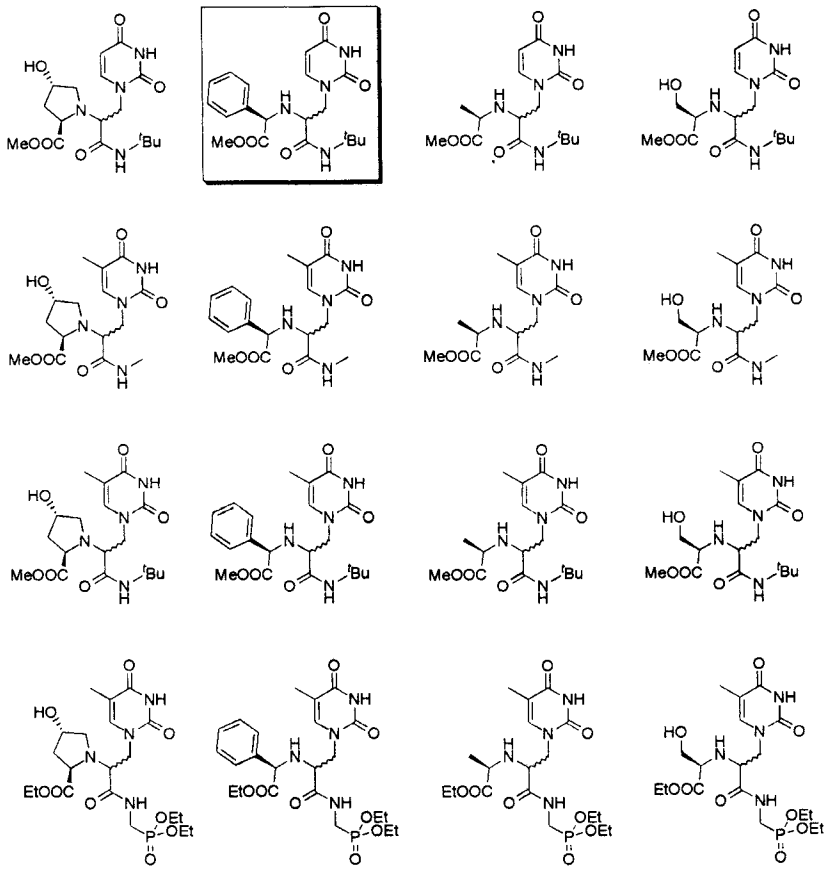

Fig.1: Selection of compounds generated by the MCR approach.

TMS as internal standard at 250.13 MHz. The purity was confirmed by tlc on Silica gel 60 F_{254} plates (Merck) with $CHCl_3$/MeOH (9:1, v/v) as developing solution and by HPLC using water/methanol as eluent.

A typical procedure is as follows: To a suspension of an α-amino acid in methanol were added an equimolar amount of the appropriate aldehyde followed by an equimolar amount of isonitrile. When the suspension became clear the solvent was removed to obtain the desired products either as crystalline solids or oils which gave a stable foam by drying in high vacuum. Further purification if necessary can be achieved

by adding chloroform and washing with water. Drying the organic phase with $MgSO_4$ and evaporation of the solvent furnished the products in a very pure state.

Analytical data are presented for the compound framed in Fig.1.
^{1}H-NMR ($CDCl_3$): 1.24, 1.33 (s, 9H); 3.15, 3.23 (dd, 1H); 3.65, 3.67 (s, 3H); 3.81-4.21 (m, 3H); 4.27 (s, 1H); 5.08, 5.36, 6.04 (d, J=5.2Hz, 1H); 5.64 (d, J=7.9Hz, 1H); 7.20-7.33 (m, 6H); 9.26 (br s, 1H).
MS (EI-mode, 70eV): 402(M^+), 343, 302, 242, 149, 121.
HPLC: 2 peaks (10.5min, 10.9min; ratio 40:60), eluent H_2O/MeOH (80:20 -> 0:100).

REFERENCES

1. W.Lewis, M.C.Dalakas, *Nature Medicine*, **1**, 417 (1995).
2. M.J.Kozal, *Nature Medicine*, **2**, 755 (1996).
3. The possibility of generating large libraries of low molecular weight compounds was proposed the first time by one of us: I.Ugi, C.Steinbrückner, *Chem. Ber.*, **94**, 734 (1961).
   I.Ugi, A.Dömling, B.Gruber, M.Heilingbrunner, C.Heiß, W.Hörl, in: Softwareentwicklung in der Chemie (R.Moll, Ed.), Frankfurt: Gesellschaft Deutscher Chemiker, 1995, p.113 (Volume of the GDCh-workschop 16.-18.11.1994.
4. A.Dömling, W.Hörl, I.Ugi.,*Endeavour*, **18**, 115 (1994).
5. G.Gokel, G.Lüdke, I.Ugi: "*Four-Component Condensations and Realated Reactions* " in: Isonitrile Chemistry, Ed. I.Ugi, Academic Press, New York, 1971.
6. A.Dömling, W.Richter unpublished results.