THE SECOND EUROPEAN SYMPOSIUM ON
COMBINATORIAL SCIENCES

EUROCOMBI-2

June 29th – July 3rd 2003, Bella Center, Copenhagen, Denmark
Organised by the European Society of Combinatorial Sciences (ESCS)
International Scientific Committee
Arpad Furka
Rob Liskamp
Mark Bradley
Hubert Gstach
Antonello Pessi
Ferenc Darvas
Günther Jung
Kevin Burgess

Local Organising Committee
Morten Meldal (Head of Organising Committee)
John Nielsen
Thomas Hoeg-Jensen
Thomas Groth
Claus Hviid Jacobsen
Ernst Meinjohanns
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Bella Center, Lecture Hall 15
Center Boulevard 5
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Welcome.

Dear Colleague,

It is a pleasure for the organising committee and me as Chairman of ESCS to welcome you all to an exciting week at EUROCOMBI 2 at Bella Centre in Copenhagen. The European Society of Combinatorial Sciences was established upon the initiative of the European Commission seek to nurture and develop Combinatorial Science within the industrial and academic environment. ESCS is a non-profit organisation with the aims:

- To create a fond supporting Combinatorial Sciences
- To arrange the EUROCOMBI meetings
- To publish a general scientific journal: Combinatorial Science
- To support educational activities within Combinatorial Sciences
- To bridge Industry and Academia in the field of Combinatorial Sciences
- To establish standards for Combinatorial methods and results

Combinatorial Science grew out of observation of the mechanism of many processes, essential to life and life’s successful development. Scientists in the fields of genetics, evolution, molecular biology and immunology made these observations simultaneously. The observation was that most successful generation of new traits necessary for survival were occurred through processes composed of 3 steps: i) Random generation of molecular diversity, ii) Survival of features through selective pressure, and iii) Reiteration and refinement.

During the last decade, scientists of all fields adopted this unique aspect of Nature to promote a completely new revolutionary way of thinking and performing scientific research. The new combinatorial mindset recognized that the subtleties of Nature do not allow us to easily design compounds (pharmaceuticals, materials or catalysts) with the perfect properties. Instead we can mimic Nature and use building blocks, accessible through isolation and synthesis to construct large numbers of diverse structures with high probability for activity, then determined by a variety of screening and selection tools.

Although Combinatorial Science is still in its infancy together with genomics and proteomics, it has had a dramatic influence on the drug discovery process, on material science and on development of specific catalyst. Combinatorial Science is an emerging and fast-moving field driven by a continuous need to identify better and more specific mimetics of biomolecules for use in medicine and biotechnology.

The revolutionary concept of Nano-Technology, fuelled by the increasing demand for miniaturization in Combinatorial Science including screening and selection, still has a long way to go before the full potential of the combinatorial process can be realised. Therefore, the initial emphasis on mixtures of very large numbers of compounds has largely given way to a more measured approach based on arrays of fewer, well characterized compounds, albeit still in significant numbers.

The necessary advancement in these fields needs a strong coordination of interdisciplinary activities both in Academia and in Industry. ESCS is the leading Society promoting these combinatorial principles at a high technological level for both parties in Europe and Worldwide. These objectives are realized by focused publication in the field, support of international teaching programs and particularly by arranging the biannual EUROCOMBI meeting of the Society, the only combinatorial meeting, where presentations are selected by an international scientific committee based on innovative merits in a broad spectrum of scientific disciplines.

ESCS would like to thank the meeting sponsors, the exhibitors and the participants for supporting its mission for mutual benefits. The Combinatorial Sciences may be expected have a dramatic effect on the speed with which scientific results can be obtained. The industry already has developed new valuable products with high market values based on this field.

EUROCOMBI 2 in Copenhagen follows the very successful first EUROCOMBI meeting in Budapest 2001. The third EUROCOMBI meeting will be held in England in 2005. The ESCS and the Organising Committee wishes you all a pleasant stay in Copenhagen with plenty of fruitful interdisciplinary scientific discussions.

Morten Meldal, Chairman of ESCS
## Scientific Program

<table>
<thead>
<tr>
<th>Sunday, June 29</th>
<th>Monday, June 30</th>
<th>Tuesday, July 1</th>
<th>Wednesday, July 2</th>
<th>Thursday, July 3</th>
</tr>
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<tbody>
<tr>
<td>08:45: Opening Remarks</td>
<td><strong>Supports and Solid Phase Chemistry</strong></td>
<td><strong>Drug Discovery and Lead Optimisation</strong></td>
<td><strong>Dynamic Libraries and Molecular Recognition</strong></td>
<td></td>
</tr>
<tr>
<td><strong>09:00:</strong> Mark Bradley (IN1)</td>
<td><strong>09:00:</strong> Manfred Auer (IN5)</td>
<td><strong>09:00:</strong> H. Saneii (IN9)</td>
<td><strong>09:00:</strong> Jeremy Sanders (PL3)</td>
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<tr>
<td>09:45: R. Michael</td>
<td>09:45: R. Frank</td>
<td>10:05: L. Meerpoel</td>
<td>10:00: T. Hoeg-Jensen</td>
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<tr>
<td>10:05: J. Rademann</td>
<td><strong>10:05:</strong> Ferenc Darvas (IN6)</td>
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<td>10:20: J. Benito</td>
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**ESCS Tutorial**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>08:50-17:00</td>
<td><strong>Supports and Solid Phase Chemistry</strong></td>
</tr>
<tr>
<td>10:25: Coffee Break</td>
<td><strong>New Scaffolds and Natural Product Synthesis</strong></td>
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<tr>
<td>10:25: Coffee Break</td>
<td><strong>Drug Discovery and Lead Optimisation</strong></td>
</tr>
<tr>
<td>10:40: Coffee Break</td>
<td><strong>Multicomponent Reactions in Combinatorial Chemistry</strong></td>
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**Registration**

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>16:00-18:00</td>
<td><strong>Combinatorial Synthesis and Technology</strong></td>
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<tr>
<td>11:55: Lunch/Poster/Exhibition</td>
<td><strong>Combinatorial Biochemistry and Biology</strong></td>
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<tr>
<td>12:00: Lunch/Poster/Exhibition</td>
<td><strong>Material Science and Catalysts</strong></td>
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<tr>
<td>12:35: Lunch/Poster/Exhibition</td>
<td><strong>Multicomponent Reactions in Combinatorial Chemistry</strong></td>
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**Posters**

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<th>Time</th>
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<tr>
<td>16:10 – 19:00</td>
<td><strong>Posters</strong></td>
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<tr>
<td>16:05: Y. Uozumi</td>
<td>16:25: Eicke Kunst</td>
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**Awards and Closing**

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<thead>
<tr>
<th>Time</th>
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<tr>
<td>15:30:</td>
<td><strong>Awards and Closing</strong></td>
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**Reception**

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<tr>
<th>Time</th>
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<tr>
<td>18:00–20:00</td>
<td><strong>Reception</strong></td>
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<tr>
<td>17:15 – 19:00</td>
<td><strong>Posters</strong></td>
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**Galla Dinner**

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<th>Time</th>
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<tr>
<td>17:05:</td>
<td><strong>Galla Dinner</strong></td>
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IN = Invited Lecture  
PL = Plenary Lecture
### Scientific Program

#### Program for EUROCOMBI-2

Second International Meeting of Combinatorial Sciences  
June 29th –July 3rd, Bella Center, Copenhagen, Denmark  
Organised by the European Society of Combinatorial Sciences (ESCS)

<table>
<thead>
<tr>
<th>Monday, June 30, 2003</th>
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</table>
| **08:45 – 09:00**: Opening Remarks  
Chair: Morten Meldal |
| **09:00 – 09:25 IN1**: Mark Bradley, University of Southampton  
“High-Throughput Methods of Library Synthesis and Screening” |
| **09:25 – 09:45 O1**: Andreas Marzinzik, Novartis Pharma AG  
"Combinatorial Chemistry on Macrobeads: Single Compounds from Individual Carriers" |
| **09:45 – 10:05 O2**: Roice Michael, Carlsberg Biosector  
"Synthesis and characterization of ULTRAMINE: a high capacity polyethyleneamine-based polymer and its application as a scavenger resin" |
| **10:05 – 10:25 O3**: Jörg Rademann, Eberhard-Karls University Tübingen  
“Reagent linkers for diversity-oriented preparation of compound libraries” |
| **10:25**: Coffee Break |
| **10:55 – 11:15 O4**: Morten Meldal, Carlsberg Laboratory, SPOCC Centre  
"Single bead structure analysis, progress in MAS NMR spectroscopy and MS/MS fragmentation analysis by ES-mass spectrometry." |
| **11:15 – 11:35 O5**: Jamart-Gregoire Brigitte, ENSIC-INPL  
"Solid phase synthesis of chiral α-hydrazinoacids" |
| **11:35 – 11:55 O6**: Knud Jensen, Dept. of Chemistry, KVL  
"A highly Acid-Labile Thiophene Backbone Amide Linker: T-BAL" |
| **11:55**: Lunch/Poster/Exhibition |

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**Supports and Solid Phase Chemistry**  
Chair: Mark Bradley

**Combinatorial Synthesis and Technology**  
Chair: Mats Larhed
### Scientific Program

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Title</th>
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<tbody>
<tr>
<td>13:25 – 13:50</td>
<td>IN2:</td>
<td>Oliver Kappe, Karl-Franzens University</td>
<td>&quot;Rapid generation and scaffold decoration of dihydropyrimidine libraries&quot;</td>
</tr>
<tr>
<td>13:50 – 14:10</td>
<td>O7:</td>
<td>Árpád Furka, Eötvös Loránd University</td>
<td>&quot;Application of string synthesis for preparation of cherry-picked combinatorial libraries&quot;</td>
</tr>
<tr>
<td>14:10 – 14:30</td>
<td>O8:</td>
<td>Jin Ku Cho, University of Southampton</td>
<td>&quot;Sensor Beads and in situ Reaction Monitoring&quot;</td>
</tr>
<tr>
<td>14:30 – 14:50</td>
<td>O9:</td>
<td>Pino Pilotti, Personal Chemistry AB</td>
<td>&quot;Solid phase synthesis of aminopropanones and aminopropenoates as efficient and versatile synths for combinatorial synthesis of heterocycles&quot;</td>
</tr>
<tr>
<td>14:50</td>
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<td>Break</td>
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<tr>
<td>15:20 – 15:45</td>
<td>IN3:</td>
<td>Günther Jung, University of Tübingen</td>
<td>&quot;Combinatorial Microelectrochemistry and Fast Capillary Chromatography on Monolithic Silica Coupled to ESI-FTICR-MS&quot;</td>
</tr>
<tr>
<td>15:45 – 16:05</td>
<td>O10:</td>
<td>A. Ganesan, University of Southampton</td>
<td>&quot;New vistas in the Pictet-Spengler reaction&quot;</td>
</tr>
<tr>
<td>16:05 – 16:25</td>
<td>O11:</td>
<td>Thomas E. Nielsen, Carlsberg Laboratory, SPOCC Centre</td>
<td>&quot;Novel Applications of the Pictet-Spengler Reaction to Solid-Phase Combinatorial Chemistry&quot;</td>
</tr>
<tr>
<td>16:25 – 16:45</td>
<td>O12:</td>
<td>Fernando Albericio, University of Barcelona</td>
<td>&quot;Solid-phase and solution strategies for the preparation of α-Amido Ketone-based libraries&quot;</td>
</tr>
<tr>
<td>16:45</td>
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<td>Break</td>
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<tr>
<td>17:05 – 17:30</td>
<td>IN4:</td>
<td>Rob Liskamp, Utrecht University</td>
<td>&quot;From synthetic receptors towards synthetic antibodies using combinatorial chemistry&quot;</td>
</tr>
<tr>
<td>17:30 – 17:50</td>
<td>O13:</td>
<td>Chaim Gilon, The Hebrew University, Jerusalem</td>
<td>&quot;Discovery of SEB superantigen antagonists using backbone cyclic peptide libraries&quot;</td>
</tr>
<tr>
<td>17:50 – 18:10</td>
<td>O14:</td>
<td>Koichi Fukase, University of Osaka</td>
<td>&quot;Synthesis based on affinity separation : rapid synthesis using affinity tag&quot;</td>
</tr>
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## Scientific Program

### Tuesday, July 1st

#### Nanoscale Synthesis, Assays and Analysis

**Chair:** Lars Baltzer

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Presentation Title</th>
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<tbody>
<tr>
<td>09:00 – IN5</td>
<td>Manfred Auer, Novartis, Austria</td>
<td>“CONA-HTS (Confocal Nanoscanning - Bead-Picking - AIDA-Technology), Redefining the lead discovery process by a joint combinatorial chemistry-, confocal fluorescence- and dye chemistry approach”</td>
</tr>
<tr>
<td>09:25 – 09:45 O15</td>
<td>György Dormán, ComGenex, Inc.</td>
<td>&quot;Immobilized surrogate compound libraries for rapid affinity profiling&quot;</td>
</tr>
<tr>
<td>09:45 – 10:05 O16</td>
<td>Ronald Frank, GBF</td>
<td>&quot;Highly parallel micro-scale synthesis of structurally diverse compound repertoires: chemical recombination of natural product fragments&quot;</td>
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<tr>
<th>Time</th>
<th>Coffee Break</th>
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#### New Scaffolds and Natural Product Synthesis

**Chair:** Dennis Hall

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<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Presentation Title</th>
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<tbody>
<tr>
<td>11:00 – 11:25 IN7</td>
<td>Ole Hindsgaul, University of Alberta</td>
<td>&quot;Screening of Mixtures Using Frontal Affinity Chromatography Coupled to Mass Spectrometry (FAC/MS): Emphasis on Oligosaccharide Ligands&quot;</td>
</tr>
<tr>
<td>11:25 – 11:45 O17</td>
<td>Mercedes Alvarez, University of Barcelona</td>
<td>&quot;Solid Phase Synthesis of Lamellarins&quot;</td>
</tr>
<tr>
<td>11:45 – 12:05 O18</td>
<td>Takayuki Doi, Tokyo Inst. Of Technology</td>
<td>&quot;A library synthesis of cyclic depsipeptides Aurilide and its derivatives on solid-support&quot;</td>
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<tr>
<th>Time</th>
<th>Lunch/Poster/Exhibition</th>
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#### Combinatorial Biochemistry and Biology

**Chair:** Arpad Furka

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<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Presentation Title</th>
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<tbody>
<tr>
<td>13:35 – 14:15 PL1</td>
<td>Jim Wells, Sunesis Pharmaceuticals, Inc.</td>
<td>&quot;Drug Discovery at Signaling Interfaces&quot;</td>
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### Scientific Program

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Title</th>
<th>Location</th>
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<tbody>
<tr>
<td>14:15 – 14:35</td>
<td>O19</td>
<td>Phaedria St.Hilaire, Carlsberg Biosector</td>
<td>&quot;Protein Affinity Profiling&quot;</td>
<td></td>
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<tr>
<td>14:35 – 14:55</td>
<td>O20</td>
<td>Lars Baltzer, University of Linköbing</td>
<td>&quot;The combinatorial approach to receptors, screens and sensors in designed folded polypeptides that catalyze their own functionalization site-selectively&quot;</td>
<td></td>
</tr>
<tr>
<td>14:55 – 15:15</td>
<td>O21</td>
<td>Michael Pirrung, Duke University</td>
<td>&quot;Analysis of combinatorial mRNA splicing using Arrayed Primer Extension (APEX)&quot;</td>
<td></td>
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<tr>
<td>15:15 – 15:45</td>
<td>IN8</td>
<td>Renata Pasqualini, The University of Texas</td>
<td>“Mapping Vascular Diversity by Screening Peptide Libraries”</td>
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<tr>
<td>15:45</td>
<td>Break</td>
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<tr>
<td>16:10 – 19:00</td>
<td>Posters</td>
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**Wednesday, July 2**

**Drug Discovery and Lead Optimisation**

Chair: **Steve Maginn**

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<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Title</th>
<th>Location</th>
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<tbody>
<tr>
<td>09:00 – 09:25</td>
<td>IN9</td>
<td>Hossain Saneii, President &amp; CEO, Advanced SynTech</td>
<td>&quot;Ugi-Type Multi-Component Condensation Reactions on Solid Support&quot;</td>
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<tr>
<td>09:25 – 09:45</td>
<td>O22</td>
<td>Hans Emtenas, Umea University</td>
<td>&quot;Design and Synthesis of 2-Pyridiones; Inhibition of Pili Assembly in Pathogenic Bacteria&quot;</td>
<td></td>
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<tr>
<td>09:45 – 10:05</td>
<td>O23</td>
<td>László Ürge, ComGenex, Inc.</td>
<td>&quot;Novel method for calculating the absolute diversity index (ADI) for drug candidate libraries&quot;</td>
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<td>10:25 – 10:55</td>
<td>Break</td>
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**Drug Discovery and Lead Optimisation**

Chair: **Ferenc Darvas**

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<th>Session</th>
<th>Speaker</th>
<th>Title</th>
<th>Location</th>
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<tbody>
<tr>
<td>10:55 – 11:20</td>
<td>IN10</td>
<td>Takashi Takahashi, Tokyo Institute of Technology</td>
<td>&quot;Solution- and solid-phase synthesis for a library of oligosaccharides&quot;</td>
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### Scientific Program

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<th>Session</th>
<th>Speaker/Institution</th>
<th>Title/Abstract</th>
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<tbody>
<tr>
<td>11:20 – 11:40</td>
<td>O25</td>
<td>Mats Larhed, University of Barcelona</td>
<td>&quot;High-Speed Optimization of Malarial Plasmepsin I and II Inhibitors&quot;</td>
</tr>
<tr>
<td>11:40 – 12:00</td>
<td>O26</td>
<td>Rubén Ventura, University of Barcelona</td>
<td>&quot;Functionally diverse purine libraries as Chemical Inductors of dimerization (CID)&quot;</td>
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<tr>
<td>12:00</td>
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<td>Lunch/Poster/Exhibition</td>
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<tr>
<td>13:55 – 14:35</td>
<td>PL2</td>
<td>Manfred Baerns, ACA Institute for Applied Chemistry Berlin-Adlershof</td>
<td>&quot;Combinatorial heterogeneous catalysis - design of experiments and data analysis&quot;</td>
</tr>
<tr>
<td>14:55 – 15:15</td>
<td>O28</td>
<td>Stephen Boppart, Symyx Technologies AG</td>
<td>&quot;High Throughput Exploration of the Physical and Chemical Properties of Materials and Drug Candidates&quot;</td>
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<tr>
<td>15:15 – 15:45</td>
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<td>Break</td>
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<tr>
<td>15:45 – 16:05</td>
<td>O29</td>
<td>Johannes G. de Vries, DSM Research, Life Sciences - Advanced Synthesis &amp; Catalysis</td>
<td>&quot;Use of High Throughput Experimentation in Homogeneous Catalysis for Fine Chemicals&quot;</td>
</tr>
<tr>
<td>16:05 – 16:25</td>
<td>O30</td>
<td>Yasuhiro Uozumi, Institute for Molecular Science, Okazaki</td>
<td>&quot;Development of Amphiphilic Polymer-Supported Palladium-Phosphine Complexes: Catalysts for Green, Safe and High-Throughput Processes&quot;</td>
</tr>
<tr>
<td>16:25 – 17:45</td>
<td>O31</td>
<td>Eicke Kunst, University of Hannover</td>
<td>&quot;Pd-Catalysed transfer hydrogenations and C-C cross coupling reactions in flowthrough reactors&quot;</td>
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<tr>
<td>17:15 – 19:00</td>
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<td>Posters</td>
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<td>19:15</td>
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<td>Galla Dinner</td>
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<tr>
<td>09:00 – 09:40</td>
<td><strong>Dynamic Libraries and Molecular Recognition</strong></td>
<td>Jeremy Sanders, University Chemical Laboratory, Cambridge</td>
<td>&quot;Dynamic combinatorial chemistry: New opportunities for molecular recognition and catalysis&quot;</td>
</tr>
<tr>
<td>09:40 – 10:00</td>
<td><strong>Dynamic Libraries and Molecular Recognition</strong></td>
<td>Christina Chamorro, Utrecht University</td>
<td>&quot;Combinatorial Synthesis and Screening of a CTV-based Tripodal Artificial Receptor Library&quot;</td>
</tr>
<tr>
<td>10:00 – 10:20</td>
<td><strong>Dynamic Libraries and Molecular Recognition</strong></td>
<td>Thomas Hoeg-Jensen, Novo Nordisk A/S</td>
<td>&quot;Preparation and screening of diboronate libraries for identification of new carbohydrate sensors&quot;</td>
</tr>
<tr>
<td>10:20 – 10:40</td>
<td><strong>Dynamic Libraries and Molecular Recognition</strong></td>
<td>Juan M. Benito, Carlsberg Laboratory, SPOCC Centre</td>
<td>&quot;Design and Synthesis of Cyclic Peptides as Small Molecule Receptors: A Solid-Phase Combinatorial Approach&quot;</td>
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<tr>
<td>10:40 – 11:00</td>
<td><strong>Coffee Break</strong></td>
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<tr>
<td>11:10 – 11:35</td>
<td><strong>Multicomponent Reactions in Combinatorial Chemistry</strong></td>
<td>Alexander Dömling, Morphochem</td>
<td>&quot;Three themes in drug discovery using multicomponent reaction chemistry&quot;</td>
</tr>
<tr>
<td>11:55 – 12:15</td>
<td><strong>Multicomponent Reactions in Combinatorial Chemistry</strong></td>
<td>Dennis Hall, University of Alberta</td>
<td>&quot;A three-component reaction for the diversity-oriented combinatorial synthesis of polysubstituted piperidines&quot;</td>
</tr>
<tr>
<td>12:15 – 12:35</td>
<td><strong>Multicomponent Reactions in Combinatorial Chemistry</strong></td>
<td>Gerardo Byk, Bar Ilan University</td>
<td>&quot;Anomalous regioselective MCR4 Biginelli reaction: One pot synthesis of spiro heterobicyclic aliphatic rings&quot;</td>
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<td><strong>Lunch/Poster/Exhibition</strong></td>
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<td>14:05</td>
<td>O38: Jefferson Revell</td>
<td>University of Southampton</td>
<td>&quot;Polymer Bound 9-Borabicyclo[3.3.1]nonane: A Novel and Selective Hydroborating Reagent&quot;</td>
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<td>14:25</td>
<td>O39: Michael Barth</td>
<td>University of Tübingen</td>
<td>&quot;High loaded ULTRA-resins: An evaluation of different supports and their application in polymer-supported chemistry&quot;</td>
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<td>14:45</td>
<td>O40: Birgitte Gundersen</td>
<td>Acadia Pharmaceuticals A/S</td>
<td>&quot;A Combinatorial Scaffold Approach Based Upon a Multicomponent Reaction&quot;</td>
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<td>Break</td>
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<td>Awards and Closing</td>
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PL = Plenary Lecture  
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Abstracts

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O = Oral Presentation
P = Poster Presentation
"Site-Directed Drug Discovery"

James A. Wells  
Sunesis Pharmaceuticals, 341 Oyster Point Blvd., S. San Francisco, CA 94080  

The means by which proteins recognize other proteins and small molecules is fundamental to protein and small molecule design. We have been developing a novel drug discovery technology we call tethering (Erlanson, D.A., Braisted, A.C., Raphael, D.R., Randal, M., Stroud, R.M., Gordon, E.M. and Wells, J.A. (2000) Proc. Natl. Acad. Sci. USA 97, 9367-9372). Tethering is an approach to find weak drug fragments (MW~200 Da) to nucleate the drug discovery process. A native or engineered thiol in a protein is allowed to react reversibly under thiol exchange conditions with a small library of disulfide-containing small molecules at concentrations that are typical for drug screening. The thiol-captured ligands, which are identified by mass spectroscopy, represent the most stable complexes even though in the absence of the covalent tether the most stable ligand may bind very weakly (Kd ~0.1 to 2 mM), compounds that would be undetectable by High Through-put Screening (HTS). Moreover, the method provides binding stoichiometry and site location for the tethered compounds, data that are not immediately available by HTS. These nucleating fragments can be affinity optimized using a combination of structural analysis and medicinal chemistry. Recent advances in this technology for drug discovery will be presented toward protein:protein and enzyme targets.
PL2

Combinatorial heterogeneous catalysis - design of experiments and data analysis –

Manfred Baerns, Dorit Wolf, Martin Holena, Gerd Grubert, Uwe Rodemerck
ACA Institute for Applied Chemistry Berlin-Adlershof, Richard-Willstätter-Strasse 12, D-12489 Berlin, Germany, baerns@aca-berlin.de

The approach comprises preparation of a first generation of materials of randomised composition of elements selected by fundamental knowledge and possibly also serendipity. These materials are tested for catalytic performance. A suitable objective function is used for selecting individual materials compositions. For designing the next generation (reproduction) of materials based on an evolutionary approach applying a genetic algorithm, i.e., allowing cross over and mutation among the selected materials [1]. After several generations an optimum composition of the catalytic material is obtained which may be further optimised by varying additional variables like methods of solids preparation and reaction conditions when carrying out catalytic testing. In this process artificial neural networks are used for the approximation of the dependence of yield on compositions to find a global maximum for the objective function [2]. Elucidation of the basis for good performance may serve as a feedback for further catalyst improvement.

The methodology is explained by two case studies, i.e., the oxidative dehydrogenation of ethane and propane to the respective olefins.

Dynamic combinatorial chemistry: New opportunities for molecular recognition and catalysis

Jeremy K. M. Sanders
University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK

Dynamic combinatorial chemistry (DCC) offers a new approach to finding ligands for biological receptors, and new synthetic receptors for guest templates. And if that guest is designed to be a transition state analogue for a given reaction, the optimum receptor might turn out to be a good catalyst for that reaction. DCC is the synthetic chemists’ equivalent of biology’s evolution and selection approach, and is the solution state equivalent of the molecularly imprinted polymer approach.

In a dynamic combinatorial library \( (M_1 \ldots M_n) \) the connections between building blocks \( (A, B, C \ldots) \) are reversible, continuously being made and broken. The composition of a dynamic library will be dependent on its environment as shown: addition of a template \( T \) that selectively binds one member will bias the equilibrium towards that member.

Covalent synthesis of macrocycles under such thermodynamic control offers proof reading of ‘incorrect’ structures and access to the optimum receptor for any given guest template. We have explored several reactions including exchange of hydrazones and disulfides; our building blocks include peptides and synthetic aromatics.

The templated amplification of receptors and a catalyst from dynamic libraries will be presented, and the potential for drug discovery will be briefly explored.

High-Throughput Methods of Library Synthesis and Screening

Mark Bradley, Iain Linguard, Boon-ek Yingyongnarongkul, Juan Jose Diaz Mochon, Stefan Mittoo, Combinatorial Centre of Excellence, Department of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK.

In my presentation I will illustrate the breadth of combinatorial methodologies being developed at Southampton in the areas of library synthesis, screening and analysis. This will include the use of so-called “dyad” bead libraries that contain both a catalyst and a substrate and that were used successfully in a split and mix catalyst library screening process to identify new Diels-Alder catalysts.

I will also demonstrate a range of micro-array based methods for library analysis in a number of areas. The use of combinatorial methods for the development of supports for chiral chromatography will also be presented to show the power and breadth of combinatorial methodologies and how these technologies can be applied across a broad range of chemistries.


Rapid generation and scaffold decoration of dihydropyrimidine libraries

C. Oliver Kappe
Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria, oliver.kappe@uni-graz.at

Several solution- and solid phase strategies for the assembly of dihydropyrimidine (DHPM) libraries of type I will be presented. A key technology for both the solution and the solid phase approach is the utilization of high-speed microwave-assisted chemistry, which reduces reaction times from many hours to several minutes, and often produces better yields [1]. Libraries of DHPMs were initially constructed employing multicomponent Biginelli chemistry in solution, and on solid phase with one of the components attached to a polymer support [2]. Several different protocols were elaborated employing multidirectional- and cyclative cleavage strategies. In the solution phase procedures, polymer-supported reagents and scavengers were used in order to make these protocols amenable to a high-throughput format. Scaffold decoration focused on the introduction/elaboration of substituents R', R2, and R3 around the DHPM core.

Invited Lectures

**IN 3**

**Combinatorial Microelectrochemistry and Fast Capillary Chromatography on Monolithic Silica Coupled to ESI-FTICR-MS**

Dietmar G. Schmid, Felix C. Leinweber, Dieter Lubda, Karl-Heinz Wiesmüller, Ulrich Tallarek and Günther Jung

1. Institute of Organic Chemistry, Auf der Morgenstelle 18, University of Tübingen, Tübingen, Germany
2. Otto-von-Guericke-Universität Magdeburg, Institut für Verfahrenstechnik, Universitätsplatz 2, 39106 Magdeburg, Germany
3. Meck KGaA, Frankfurter Straße 250, 64271 Darmstadt, Germany
4. EMC microcollections GmbH, Sindelfinger Straße 3, 72070 Tübingen, Germany

Technically advanced and miniaturized separation and detection systems of highest resolution power are prerequisites to meet the analytical requirements for proteomics and complex combinatorial libraries. Appropriate analytically demanding probes for novel hypenfied methods are complex yet defined synthetic peptide libraries mimicking natural peptide mixtures such as protein digests or MHIC ligand isolates. [1]

Silica-based monolithic capillary columns combine the three performance characteristics such as fast, efficient elution and, due to the complexity of samples, a high loading capacity in a unique manner due to a tailored adjustment of both macro- and mesopore sizes in the highly-porous silica structure [2]. On-line coupling of capillary liquid chromatography (cLC) with silica-based monolithic capillary columns to ESI-FTICR-MS allows the separation and sequencing of numerous isobaric peptides present in synthetic peptide libraries. Even libraries containing 1000 peptides were analyzed on monoliths with high separation efficiency within 20 min.


**IN 4**

**From synthetic receptors towards synthetic antibodies using combinatorial chemistry**


Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands, r.m.j.liskamp@pharm.uu.nl

Combinatorial chemistry of synthetic receptor molecules is attractive for gaining insight in processes of biomolecular recognition. In addition, combinatorial approaches can be valuable for applications of artificial receptors as binders of molecular components of pathogenic organisms, catalysts, sensors, chiral selectors, and perhaps ultimately as artificial synthetic antibodies. For these purposes we have developed tweezer-like and tripod synthetic receptors. In order to prepare diverse and sizable libraries of these synthetic receptors we have introduced the cyclotriveratrylene (CTV) and the triazacyclophane scaffold for attachment of peptidic arms [1]. Libraries of tweezer and tripods are used in screening to uncover e.g. synthetic receptor molecules mimicking the action of glycopeptide antibiotics and molecules binding to crucial sequences in proteins also aiming at the mimicry of discontinuous epitopes and antibodies.

CONA-HTS (Confocal Nanoscanning - Bead-Picking - AIDA-Technology), Redefining the lead discovery process by a joint combinatorial chemistry-, confocal fluorescence- and dye chemistry approach

Hubert Gstach and Manfred Auer
Novartis Forschungsinstitut, Innovative Screening Technologies Unit, Lead Discovery Center, Brunnerstrasse 59, A-1235 Vienna, Austria
Email: manfred.auer@pharma.novartis.com

Since years, the drug discovery industry faces ultimate challenges. The increasing number of potential drug targets which became available with the knowledge of the human genome, miniaturized assay and screening technologies processing more than hundred thousand compounds a day, and strongly improved structure based drug design tools have, among many other technological improvements, not reduced the costs to bring a new chemical entity to the market. The process of lead discovery remains a high risk endeavor and this inability to routinely identify multiple high quality lead compounds against drug targets remains a major issue. We took up the challenge to completely redefine the initial phases of the drug discovery process with a combination of new strategies in chemistry, physics and biology. CONA-HTS (confocal nanoscanning – bead scanning picking – AIDA technology) is a high throughput – low hit-rate HTS process based on the following key principles:

- to include flexible use of any target: peptide, protein, domains, DNA, RNA any size,
- to screen with known and functionally undefined new proteins from genomics approaches,
- to make optimal use of combinatorial chemistry in HTS by split-mix&divide synthesis concepts and by shifting the assay process as close as possible to the origin where compounds are produced – namely on the surface of solid supports,
- with that strategy, we (a) leave the "compound archive dogma" in HTS and (b) shift investments largely towards active compounds,
- to use genetics/genomics and cell physiology concepts – an iterative decision process rather than step-wise precision selection. To make this concept successful we included a multilayer process of exclusion of artifacts and false positives,
- to provide a pragmatic alternative to target validation through functional genomics by allowing molecular recognition between LMWCompounds and biological system components to define the target,
- to validate targets through affinity, specificity and biological effect of the identified LMW hit compound. This leads us to the target-compound pair philosophy: Only a target with a compound acting on it in a biologically modifying form is a good target.
- to make the non-tractable target drug able by non restricted chemistry,
- to optimally exploit the serendipic identification of biological understanding through screening.

The CONA hit identification process is based on a series of quantitative selection criteria for the consecutive exclusion of false positives and artifacts. The binding reaction on the solid surface in which on-bead fluorescence (ring) intensity is directly proportional to on-bead affinity can either be specific or unspecific. The binding specificity is therefore checked immediately after selecting a bead by cleavage and determination of a dissociation constant to the unlabelled target protein using the Novartis proprietary AIDA-dye. In parallel, the structure is decoded by MS and after re-synthesis, confirmation on-bead, and off-bead the potential hit compounds are tested with and without AIDA-tag for their in-vitro and cellular activity.

The CONA-HTScreening process is fully established and running on three PickoScreen instruments in 96 well plate format and 2 color excitation/emission. ~ 3 million compounds from AIDA-based libraries are available for screening. With ISE an information system and database was established to follow the information flow of each hit bead and the compounds derived thereof from picking to in-vivo evaluation.
IN 6
Combinatorial Chemistry: Facing the Challenge of Micro- and Nanochemistry
Ferenc Darvas1,2 Tamás Karancsi2, Ágota Bucsai2, Lajos Gödörházy2
1ComGenex, Inc H-1027 Budapest, Bem rkp 33-34 df.cex@comgenex.hu
2Thales Nanotechnology Inc, H-1027 Budapest, Bem rkp 33-34

Combinatorial chemistry is a target-oriented, adaptive science, like QSAR or bioinformatics. As part of the adaptation, combinatorial chemistry is facing the challenge of micro- and nanochemistry, two rapidly emerging important fields, which offer a magnitude of increase both in productivity and performance of combinatorial library synthesis together with unusual chemical and process operational opportunities.

The presentation will give a review of the utilization of microfabricated devices, like microfluidics or pressure-operated microchips for synthesis of general and focused libraries and for lead optimization. A broader perspective of applying the devices in several phases of drug discovery will also be discussed.

The combinatorial use of microfabricated devices is exemplified on reactions performed in glass chip reactors with extended 2D surfaces, and furthermore in metal microtube reactors for a number of single and multicomponent reactions. The purification of the reaction products was performed in the same or in a separate reactor by using two or three phased liquid-liquid extractions, sometimes with fluorochemical solvents.

For rapid library generation, the reactors were operated by an instrument, composed of a biarmed robot, an automatically linked chromatography facility and of an experiment design software. After a few optimization rounds, the instrument was used for production under the optimized conditions. As a general observation, a substantial (more than one magnitude) increase of the reaction rate relative to the batch mg-scale liquid phase reactions was established, allowing a faster synthesis of a larger number of compounds sometimes in high purity.


IN 7
Screening of Mixtures Using Frontal Affinity Chromatography Coupled to Mass Spectrometry (FAC/MS): Emphasis on Oligosaccharide Ligands
Ole Hindsgaul
Department of Chemistry, University of Alberta, Edmonton AB T6G 2G2, Canada

Many methods exist for evaluating the binding of oligosaccharides to proteins. Almost all of these methods involve the measurement of the interaction of a single oligosaccharide species (at a known concentration) with the protein of interest.

The research presented here will demonstrate the use of FAC/MS for characterizing the interactions of mixtures of oligosaccharides competing for the same protein.

FAC/MS (Angew. Chemie 34, 3383, 1998, Anal Biochem 299, 173, 2001, Combi. Chem. H.T.S. 5, 395, 2002) can provide estimates of the dissociation constants for individual compounds present in a mixture while simultaneously confirming the molecular weights of each of the active species. We routinely screen mixtures of 10–30 oligosaccharides against an immobilized protein. The experiment requires at most 0.5 micrograms of each sugar. An extraordinary power of FAC/MS is that the concentration of individual compounds present in a mixture does not affect their order of elution from the column of immobilized protein. This means that even if we have no idea of the relative concentrations of the individual compounds present in a mixture, we can still establish the tightest binding compound. Examples will be given on the use of FAC/MS for screening the binding of mixtures to lectins and glycosyltransferases.
Mapping Vascular Diversity by Screening Peptide Libraries.

Renata Pasqualini Ph.D. and Wadih Arap, M.D., Ph.D. UT M. D. Anderson Cancer Center, The University of Texas, Graduate School of Biomedical Sciences at Houston, Houston, TX 77225-0334

Despite major progress brought about by the Human Genome Project, the molecular diversity of human blood vessels remains largely unexplored. Our research is aimed at targeting diagnostic and therapeutic agents to blood vessels by using probes that can bind to specific vascular addresses. Towards this goal, we developed technologies to identify small peptides that target the endothelium. Different strategies are used to isolate peptides from large libraries displayed in the surface of bacteriophage. Through this platform technology, we have uncovered various tissue-specific and angiogenesis-related vascular addresses. This complex system of ligand-receptor pairs will lead to a better understanding of tumor circulatory microenvironment, changes in blood vessels during tumor progression, and the localization of novel markers in cancer and other diseases with an angiogenesis component. This lecture will review several targeting strategies that may enable the construction of a molecular map outlining vascular diversity in each organ, tissue, or disease.

Ugi-Type Multi-Component Condensation Reactions on Solid Support

Hossain Saneii
President & CEO, Advanced SynTech

The importance of multi-component reactions (MCR) has been received increasing attention due to the emergence of combinatorial chemistry. These reactions enable us to introduce three or more different building blocks, in most cases, in a single chemical process. The Ugi condensation reaction employs four components including a carboxylic acid, an amine, an aldehyde and an isocyanide to construct an α-acylaminoamide which can be transferred into a variety of biologically interesting structures by post Ugi transformations. Our interest in broadening the scope of the known reaction prompted us to investigate into condensation reactions utilizing sulfonamides instead of regular amines or without acid inputs. Several new condensation reactions on solid support and their applications to the syntheses of protease-targeted combinatorial libraries will be presented.
Solution- and solid-phase synthesis for a library of oligosaccharides.

Takashi Takahashi
Department of Applied Chemistry, Tokyo Institute of Technology, Tokyo 152-8552, Japan, ttakashi@o.cc.titech.ac.jp

A library synthesis of oligosaccharides, functionalized trisaccharides 1, phytalexin elicitor active β(1→3)-linked glucoside containing β(1→6)-branch 2, Lewis X (3) will be presented. Toward the library synthesis of various oligosaccharides will be discussed (i) glycosylation on solid-phase with a sulfonate linker on Crowns followed by diversification by displacement with nucleophiles, (ii) orthogonal deprotection glycosylation in solution phase utilizing an automated synthesizer, (iii) one-pot multi-component glycosylation.
Three themes in drug discovery using multicomponent reaction chemistry.

Alexander Dömling
Morphochem AG, Gmünderstr.37-37a, 81379 München, Germany,
alexander.doemling@morphochem.de

Multicomponent reactions (MCR) with isocyanides are especially useful for the discovery process of novel bioactive compounds for several reasons [1]. They allow for the search and synthesis of potentially very large chemical spaces. They are highly economic since they are the prototype of convergent reactions. Many different scaffolds are easily accessible in a one-pot methodology. Thus they are especially suitable for automation. Three projects performed at Morphochem and building on MCR technology are presented.

1. We recently introduced a novel 4-component thiazole synthesis. There β-dimethylaminoisocyanoacylates react with primary amines, aldehydes or ketones and thiocarboxylic acids. Several variations where developed for solid as well as liquid phase synthesis. Moreover we could use this reaction to built-up the central part of the highly cytotoxic natural product Tubulyisin A in one step.

2. Current HIV protease inhibitors suffer from pure bioavailability and several side effects associated with their structure. Moreover they all have to be synthesised by a long and divergent (sequential) type of synthesis, most in more than 20 synthetic steps! Thus the current standard regiment to combat AIDS is far from affordable in third world counties. We herein disclose a novel MCR leading in a convergent 2-5-step synthesis to a novel class of potent HIV-protease inhibitors.

3. Natural product like macrocyclic compounds can be made in a short and convergent synthesis route using a MCR and a RCM. Some resulting compounds showed activity in a phenotypic assay aiming to regenerate growth inhibited nerve cells.

Combinatorial Chemistry on Macrobeads: Single Compounds from Individual Carriers

Andreas L. Marzinzik¹, Rocco A. Falchetto¹, Serge Moss¹, Werner Breitenstein¹, Philipp Grosche¹, Edi Felder, Juerg Zimmermann¹
¹Novartis Pharma AG, Central Technologies, CH-4002 Basel, Switzerland, andreas.marzinzik@pharma.novartis.com

The interest in increasingly efficient, combinatorial chemistry based lead finding approaches led us to the development of methodologies for a closer integration of rapid compound preparation and screening. The perception is that the exploitation of the Split-and-Mix process, invented more than ten years ago by Arpad Furka, could be maximized by directing the technological progress to the use of solid phase beads as carriers of individually distinct chemical entities, while allowing to screen such compounds in solution.

In this presentation, solid phase chemistry on macrobeads [1] and illustrative examples of the analysis of single bead eluates by microanalytical LC/MS in combination with a nitrogen detection system will be discussed.


Synthesis and characterization of ULTRAMINE: a high capacity polyethylenamine-based polymer and its application as a scavenger resin

Michael Roice, Morten Meldal
Department of Chemistry, Carlsberg Laboratory, Gamle Carlsberg Vej 10, DK-2500 Valby, Denmark

The synthesis of a new high loading polyethylenamine resin is presented. The resin was prepared by inverse suspension polymerization of partially acryloylated polyethylenamine. The application of ULTRAMINE beads as a scavenger resin was demonstrated by various organic reactions.
Reagent linkers for diversity-oriented preparation of compound libraries

Jörg Rademann, Steffen Weik, Michael Barth
Eberhard-Karls University Tübingen, Institute for Organic Chemistry, Auf der Morgenstelle 18, 72076 Tübingen. E-Mail: joerg.rademann@uni-tuebingen.de

Recently, we have demonstrated the synthesis of several advanced polymer reagents for important transformations (alkylations, oxidations), in which recyclable, covalently bound reactive groups are generated and employed for the clean conversion of dissolved compounds.\[1\]

Our next step was the combination of novel polymer reagents to the synthesis of biologically relevant products. As an example we show the first solid-supported acylanion equivalents, which are used for the versatile synthesis of \(\alpha\)-hydroxy-\(\beta\)-amino compounds as biologically validated lead structures for protease inhibitors.\[2\]

As new carrier for polymer reagents we have developed the ULTRA-resins.\[3\] These carriers with high loadings up to 23 mmolg\(^{-1}\) could increase the efficiency in solid phase synthesis considerably.


Single bead structure analysis, progress in MAS NMR spectroscopy and MS/MS fragmentation analysis by ES-mass spectrometry.

SPOCC-center, Carlsberg Laboratory, Gamle Carlsberg Vej 10, DK-2500 Valby, Denmark, mpm@crc.dk

The introduction of combinatorial chemistry and the powerful method of solid phase split and combine techniques for generation of compound diversity revolutionized our ways of thinking and of approaching scientific problems in chemistry, biology and material science. However it soon became apparent that the strength of using single beads as containers for synthesis as well as screening, also was the Achilles heel of the method. It was simply difficult to access the structures attached to the bead. Stepwise development of PEG-based resins that are suited for high-resolution solid phase magic angle spinning NMR has allowed structure analysis to be performed on the single bead level. The technique is lengthy and cumbersome and in reality only few active hits can be analysed by this method. This may be enough in many instances, however, mostly screening affords ~0.01- 0.1 % of active structures and the full analysis of these hits can yield valuable statistical structure/activity information.

Only few analytical techniques have the ability to provide structural information rapidly from minute amounts of material. One such method is high resolution MS/MS of compound released from single beads. We will describe how the accurate mass differences uniquely identify fragmentation pathways in a particular scaffold independent of the displayed pharmacophores. The method is also useful for the complete analysis of protease substrate libraries.
Oral Presentations

**O 5**

Solid phase synthesis of chiral $\alpha$-hydrazinoacids.


The recently described liquid synthesis of chiral $\alpha$-hydrazinoacids using Mitsunobu protocol [1] can be easily adapted to solid phase synthesis by the preparation of solid supported N-benzyloxy carbonyl-aminophthalimide. The Mitsunobu condensation of chiral $\alpha$-hydroxy esters followed by a final transprotection step [2] results in an efficient synthesis of $N_{\alpha},N_{\beta}$ orthogonally diprotected $\alpha$-hydrazinoesters. In addition to the excellent purity of these compounds, a large number of aminoacid derivatives can be synthesised with this method because of the presence of three diversity points.


**O 6**

A Highly Acid-Labile Thiophene Backbone Amide Linker: T-BAL

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Handles (linkers) with an aldehyde functionality allow anchoring of substrates by convenient reductive amination and have become widely used tools in solid-phase synthesis. A growing peptide chain can be anchored through a backbone amide, thus providing easy access to C-terminal modified and cyclic peptides. This Backbone Amide Linker (BAL) concept was first implemented in a tris(alkoxy)benzyl system, which allowed release of final products by treatment with conc. trifluoroacetic acid (TFA). However, new BAL-type handles with higher acid-lability would extend the reach of this methodology. Towards this goal, we have designed a new handle, T-BAL. (Thiophene Backbone Amide Linker), which is based on 3,4-ethylenedioxy-thiophene (EDOT). EDOT has found wide use as an electron donating monomer in conducting materials and is relatively inexpensive. The electron-richness of EDOT makes it a promising candidate as carbocation stabilizing core structure in acid-labile linkers. T-BAL was prepared in three steps from EDOT. After peptide chain assembly, peptides were indeed released by mild acidolysis, with acid conc. as low as TFA-DCM (1:99).
O 7
Application of string synthesis for preparation of cherry-picked combinatorial libraries

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String synthesis [1] is an efficient and cheap manual method for preparation of combinatorial libraries using macroscopic solid support units. Sorting the units between two synthetic steps is an important operation of the procedure. The software developed to guide sorting can be used only when complete combinatorial libraries are prepared. Since very often only selected components of the full libraries are needed, a new software was constructed that guides sorting in preparation of non-complete libraries.

The new software analyses the sequences of the input library, then generates the virtual library from which the actual members of the input library can be deduced. The virtual library helps to deduce the position of the products on the final strings. Since the library to be synthesized is not a full combinatorial library, the delivery of the support units from the source strings into the destination ones can not occur in equal groups. The software generates tables that guide the sorting operations in every phase of the process.

In the original string synthesis crowns manufactured by Mimotopes were used as solid support units. Since now Mimotopes offers lanterns instead of crowns, that are even better suited for string synthesis than the crowns, a new manual device was constructed that can be used to sort lanterns.


O 8
Sensor Beads and in situ Reaction Monitoring

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Solid-phase organic synthesis and solution-phase parallel synthesis assisted by polymer-supported reagents and/or scavenger resin enable painstaking purifications to be avoided during synthesis. This concept was applied to reaction monitoring through the development of resin-bound indicators. Here, we wish to introduce resin-bound indicators for the efficient analysis of multiple chemistries. Bromophenol blue was chosen as an indicator and attached to the resin after derivation. The resin was successfully used as a “sensor” for in situ monitoring during the synthesis of a library of ureas. The sensor was also used for monitoring solid-phase peptide synthesis in a high successful manner [Figure].
Oral Presentations

O 9

Solid phase synthesis of aminoproponones andaminoproponoates as efficient and versatile synthons for combinatorial synthesis of heterocycles.

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A novel microwave assisted, solid phase approach to heterocycles have been developed. The new approach is based on the solution phase chemistry using DMF-DEA (dimethyl formamide-diethyl acetal) to synthesise alkylamino proponones and alkyl amino proponoates which subsequently are reacted with di nucleophiles to give a variety of heterocycles. This approach was shown to perform very well under microwave conditions.

Two different approaches were developed for alkylamino proponones and alkylamino proponoates, respectively.

The procedures are generally applicable and give products in moderate to excellent yields with overall excellent purities. Application for combinatorial/ high throughput chemistry will be presented.

O 10

New vistas in the Pictet-Spengler reaction

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The venerable Pictet-Spengler reaction involves the intramolecular capture of an iminium ion by an aromatic system to generate a six-membered ring. For many years, it has been widely used for the preparation of heterocycles such as tetrahydro-β-carbolines and tetrahydroisoquinolines. Nevertheless, the reaction suffers from two key limitations: 1) Reactivity: Many combinations of imines and aromatic systems fail to give the product in acceptable yields. For the same reason, it is difficult to devise truly general reaction conditions that are successful with a broad range of substrates. 2) Stereocontrol: Reliable diastereo- or enantioselective variants of the reaction are currently unavailable. In this talk, I will discuss our recent progress with these two issues. The problem of low reactivity can be ameliorated by the use of N-acyliminium Pictet-Spengler reactions1 (eq 1), which have been developed under both solution and solid-phase conditions. With regards to stereocontrol, I will describe examples of parallel screening for Lewis acid catalyzed Pictet-Spengler reactions2 (eq 2).


Novel Applications of the Pictet-Spengler Reaction to Solid-Phase Combinatorial Chemistry.

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The Pictet-Spengler reaction has been widely used for the synthesis of N-heterocyclic compounds, such as the biologically important tetrahydroisoquinolines and tetrahydro-β-carbolines.1 Traditionally, the reaction has been carried out as an acid-catalyzed two-component reaction, comprising the intermolecular condensation of an aldehyde with an amine, followed by cyclization of the resulting iminium ion. We here wish to report the application of the analogous amide form of this important reaction to solid-phase synthesis.

Our research group have previously reported the use of solid-supported N,O-protected aldehyde building blocks.2 Upon unmasking, the aldehyde may undergo a variety of reactions.3 In the present investigation, such aldehydes undergo intramolecular condensation reactions with the amide N of a solid-supported peptide backbone, thus forming a cyclic N-acyliminium ion, which may append a second ring via a modified Pictet-Spengler reaction with the indole moiety of a neighbouring tryptophan. The methodology has been extended to the formation of larger ring systems. The key points of diversity for the synthesis of combinatorial libraries are provided by the substituents of the aldehyde building block and tryptophan moiety, in addition to the combination of ring sizes being formed, thus both providing a range of templates and pharmacophore substitutions.


O 12
Solid-phase and solution strategies for the preparation of α−α−α−α−Amido Ketones based libraries

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α−Amino ketones are of great interest in many bioactive molecule discovery programs in agrochemical and pharmaceutical research. Although in the literature, there are described several strategies for the preparation of those molecules, this is not always a straightforward process. Herein, several approaches for the preparation of α−amino ketones based libraries will be discussed.

For the preparation of libraries based in the high sterically hindered α,α-disubstituted-α-acylamino ketone (1), a combined solid-phase and solution synthesis has been shown superior to a total solid-phase one. For libraries based in the hydantoin structure (2), Fmoc-protected amino ketones prepared in solution are incorporated onto a solid support through either the β-carboxyl group or the ketone function itself. Further solid-phase manipulation of the Asp derivative leads to the target molecules. The use of different handles, supported reagents, colorimetric tests, and spectroscopic techniques will be presented.

\[
\begin{align*}
\text{(1)} & \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \quad \text{N} \\
\text{(2)} & \quad \text{R}_1 \quad \text{R}_2 \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{OH}
\end{align*}
\]
O 13

Discovery of seb superantigen antagonists using backbone cyclic peptide libraries

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Superantigens trigger excessive cellular immune response, leading to toxic shock. Based on the 3D structure of the conserved sequence 150-161 of the staphylococcal enterotoxin SEB and its linear peptide variant p12 [1], we have designed and synthesized two spatial backbone cyclic peptide libraries [2] that mimic the β sheet-turn-helix motif of this region. The libraries comprising 20 extended backbone cyclic undeca peptides and 14 reverse-extended backbone cyclic deca peptides were screened for their ability to inhibit SEB triggered cytokine gene expression in blood T cells. Two backbone cyclic peptides, SEB 18 from the first library and SEB 32 from the second, tenfold more potent then the linear peptide p12, were found.


O 14

Synthesis based on affinity separation: rapid synthesis using affinity tag

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A new method termed “synthesis based on affinity separation (SAS)” was developed for rapid synthesis. The interaction between crown ether (32-crown-10) and ammonium ion was first found to be useful for this method. After each reaction cycle, the reaction mixture was applied to the aminomethylated polystyrene column (TFA form). The compound possessing the crown ether tag was selectively adsorbed on the column, whereas other impurities without the crown ether were washed off. Subsequent desorption afforded the desired compound in high yield.

The interaction between a barbituric acid derivative and its artificial receptor [= bis(2,6-diaminopyridine)amide of isophthalic acid] was also found to be effective. Both methods were applied to the synthesis of peptides, heterocycles, and oligosaccharides. Application of this method to the synthesis of complex glycoconjugate lipid A [1] and analogs will be also presented.

**Immovilized surrogate compound libraries for rapid affinity profiling**

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Diverse small molecule libraries can be utilized early in the post-genomic discovery process as well as in lead generation and optimization. Large numbers of small molecules attached to a solid surface provide a platform to study rapid affinity profiles of analogue libraries under uniform conditions with minimum requirements for both proteins and small molecules.

The library contains end-products; its relevant building blocks and their bioanalogous replacements constitute a total coverage fragment-based, pharmacophore surrogate library. The compounds are linked through a special tether to appropriate terminal functional groups enabling their attachment to the glass-surface in high yield. Novel surface chemistry enables high-density spotting and results in high sample concentration and good accessibility for the biopolymers.

The rapid affinity profiling results could be used to design strategies for the application of chemical microarrays in drug discovery.

L Hackler Jr., G Dormán, I Novák, Z Kele, L Úrge, F Darvas and L G. Puskás*

Development of chemicaly modified glass surfaces for nucleic acid, protein and small molecule microarrays, Mol. Div. (manuscript in preparation)

**Highly parallel micro-scale synthesis of structurally diverse compound repertoires: chemical recombination of natural product fragments**

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We are exploring a new route towards innovative compound repertoires for drug screening aiming to exploit the particular properties of natural products. Novel and unique chiral building blocks of high structural diversity were obtained by selective chemical fragmentation of a series of natural products isolated from myxobacteria. Subsequent modification/protection provided primary alcohol and carboxylic acid derivatives suitable for the use in solid phase synthesis. The SPOT-synthesis technique when performed on a novel polypropylene membrane support allowed the highly parallel combinatorial chemical reassembly of these rare and precious building blocks on an appropriate 10nmol scale. More than 30,000 structures have been prepared so far. Such type of compound libraries, however, require an adequate miniaturized screening technology which has been developed by EVOTEC, the EVOscreen®-system. This is based on single molecule detection technology and uses assay volumes of only 1µl.
Solid Phase Synthesis of Lamellarins

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The lamellarin alkaloids are a group of approximately 45 compounds isolated from the marine prosobranch mollusc Lamellaria sp., the marine ascidian Didemnum sp. and the sponge Dendrilla cactos. The interesting range of pharmacological activities, including antitumor and anti HIV-1 properties, reversal of multidrug resistance (MDR), and immunomodulatory activity makes them a particularly important target. [1] Two different strategies for the solid phase synthesis of lamellarins of structure 1 and 2 are described.

The synthetic procedures are of general application to a large number of compounds, which differ in the nature, number of substituents of rings A-E and also in the nature of the aromatic rings; being possible its change by polyaromatic rings, heterocyclic rings or polyheterocyclic rings. This versatility together with the facilities of the solid phase approach offers the advantage of its applicability to the synthesis of libraries of compounds and the possibility of a fast production of new compounds for the pharmacological evaluation of a considerable number of new related structures.

A library synthesis of cyclic depsipeptides Aurilide and its derivatives on solid-support

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A solid phase combinatorial synthesis approach towards the cyclic depsipeptide Aurilide (1) and related analogs will be presented. The peptide moiety including N-methyl amino acids was assembled on trityl linker-functionalized SynPhase™ Crowns™ using an Fmoc strategy. Optimization of the tetrapeptide assembly 2 was carried out using parallel multiple synthesis and LC/MS analysis. Coupling of 2 and 3, cleavage of the cyclization precursor, and macrocyclization provided 1 in 11% overall yield. Synthesis of a combinatorial library of its derivatives was accomplished using the TranSort™ technique.
O 19

Protein affinity profiling using solid-phase combinatorial libraries

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In the post-genomic era, focus is shifting from merely analysing an organism’s genome, towards deciphering the functions and signalling pathways of the myriad protein families encoded. Protein and small molecule microarrays are being used to investigate the function of proteins.

We will present the use of the one-bead-one-compound combinatorial library in identifying specific protein-ligand binding pairs. The libraries were synthesised on hydrophilic PEGA resin, and after incubation with a fluorescently labelled protein mixture isolated from cells, beads containing bound protein are sorted by fluorescence activated bead sorting (FABS). Both the ligands and their protein binding partners are identified from single beads using mass spectrometry. The relevance of the identified protein-ligand binding pair(s) was investigated using the appropriate biological assays. By this approach, novel ligand-protein binding pairs are efficiently and rapidly identified, and may provide putative drug leads and targets.

O 20

The combinatorial approach to receptors, screens and sensors in designed folded polypeptides that catalyze their own functionalization site-selectively.

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A designed helix-loop-helix motif has been developed that catalyzes its own functionalization, site-selectively, allowing for the incorporation of a large variety of functionalities in a combinatorial fashion in microtiterplate format1. The order of addition of active esters to a solution of the scaffold in aqueous solution determines the position in which the acyl groups will be incorporated in the folded polypeptide, and the self catalyzed nature of the reaction eliminates the need for protection group strategies. The chemistry is based on His and Lys residues and functional groups will form amides at the side chains of lysine residues. Anything that can be presented in the form of an active ester can be incorporated, examples include compounds from small-molecule libraries, sugars, peptides, nucleotides, PNA and combinations of these. If one or more fluorescent probes are incorporated together with groups that recognize and bind biomolecules multifunctional scaffolds can be produced for screening and biosensing applications, and if many ligands are combined a new class of artificial receptors for biomolecules can be developed. The chemistry will be presented together with applications from screening, biosensing and receptor engineering.

Analysis of combinatorial mRNA splicing using Arrayed Primer EXtension (APEX)

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The analysis of RNA splicing is important to understanding the diversity in protein sequences at specific disease loci, in the immune response, and across the genome. It is now understood that the combinatorial splicing of initial RNA transcripts creates significant protein sequence diversity. The presence of each exon in a mature mRNA formed from a genomic sequence of \( n \) exons can be represented by a Boolean variable, enabling mRNA structure to be encoded by an \( n \)-bit binary number. The CD44 locus has been studied as an example of a variably spliced RNA. Microarray methods can be used to assess RNA splicing provided they exhibit high fidelity. Our previous work showed the APEX (arrayed primer extension; single-nucleotide polymerase extension of microarrays of DNA primers) method gives high-fidelity, digital detection of nucleic acid sequences, and has been used for the solution of Boolean computing problems. APEX was adapted to RNA analysis by the use of reverse transcriptase and arrays of primers specific to each exon in the CD44 locus. “Splicotypes” were readily assigned for a number of variant RNA templates. Because CD44 is known to be aberrantly spliced in a number of cancers, the RNA APEX method with a CD44 microarray was applied to samples from primary tumors of individual patients. Up to four different splicing forms of CD44 were detected, whereas there have been no previous reports of the presence of more than two CD44 isoforms within the same tissue.

Design and Synthesis of 2-Pyridinones; Inhibition of Pili Assembly in Pathogenic Bacteria

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Previously a new stereoselective synthesis of 2-pyridinones in solution from simple building blocks was reported. Now a solid phase strategy to build up libraries of these structures has been developed. A design was made and from \( \frac{1}{2} \times 8 \) building blocks 20 2-pyridinones were chosen for synthesis. \(^{19}F\) NMR was used to optimize the reaction conditions and the 2-pyridinones could thus be synthesized with a total yield of \( \approx 80\% \) and with a purity high enough to ensure accuracy in biological evaluation (\( \approx 90\% \)) without any purification.\(^1\)

Using a Biacore 3000 instrument, the compounds were screened for their ability to bind to periplasmic chaperones that are essential for pili assembly in pathogenic Gram negative bacteria such as \( E.\)\( \text{Coli} \). By interfering with the chaperone, pili assembly can be disrupted and thereby prevent bacteria from causing infection. These classes of substances, named pilicides, were able to depililated bacteria and further biological evaluations of this new class of antibacterial agents will be presented.

Oral Presentations

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Novel method for calculating the absolute diversity index (ADI) for drug candidate libraries

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In today’s drug discovery process, the diversity of drug candidate libraries is crucial. There are several methods to select a diverse subset from a group of compounds, but there is no absolute measure to determine the diversity of combinatorial libraries. For this purpose ComGenex developed a novel method for calculating the Absolute Diversity Index (ADI). The diversity of a library is described with two important properties: structural diversity and structural dissimilarity, which is plotted on a 3D coordinate system. Structural dissimilarity is described as the number of compounds belonging to a core chemical structure. Structural diversity is expressed with the relative average Tanimoto-coefficient, which is the quotient of the average Tanimoto coefficients for a reference database and for a database containing ComGenex or any other types of compounds. We developed a new, shortened algorithm to calculate this value, based on the nearest neighbor theory, because in the case of large datasets, the calculation based on Total Tanimoto Diversity is very time consuming. On the third axis, the values of physico-chemical parameters for drug-like and lead-like properties (e.g. logP, Number of H-Bond Donor and Acceptor Groups, Number of Rotatable Bonds) is represented. The final value of ADI is calculated with the Spectral Mapping Technique [1]. Tanimoto-coefficients are calculated from the Unity 2D Fingerprints of the molecules [2,3].


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Apolipoprotein B (ApoB), the major protein component of triglyceride-rich lipoproteins such as very low density lipoproteins (VLDL) and chylomicrons, is assembled into a lipoprotein particle via a complex, multistep process. Recent studies indicate that the assembly of triglyceride-rich ApoB-containing lipoproteins requires the activity of microsomal triglyceride transfer protein (MTP). Genetic loss of functional MTP is the basis of the human recessive disorder called abetalipoproteinemia. This disease results from an inability of both the liver and the intestine to secrete apoB-containing lipoproteins leading to extremely low plasma lipid levels and malabsorption of dietary fat. In recent studies it has been proven that MTP inhibitors are excellent lipid lowering agents with potential use in hyperlipidemia, obesity and atherosclerosis. Previously, we identified R103757 as a novel inhibitor of MTP (IC50 = 6 nM) and demonstrated that this compound inhibits ApoB secretion of the human hepatoma cell line HepG2 (IC50 = 26 nM).

Recently, we elaborated some novel classes of MTP inhibitors. In this communication we will present the optimization of novel MTP inhibitors using solid-phase parallel synthesis strategies. Exploring several linkers and different synthetic strategies finally resulted in a four to six steps solid-phase synthesis of focused libraries which revealed several highly potent ApoB/MTP inhibitors. The synthesis schemes and structure-activity relationship of the compounds obtained will be presented.

Solid-Phase approach 1

Solid-Phase approach 2

40
High-Speed Optimization of Malarial Plasmepsin I and II Inhibitors

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Reported here are the results of a search for improved antimalarial plasmepsin I and II inhibitors. Four focused libraries targeted for the proteases were designed, synthesized, purified and screened. Selected carboxylic acids and organometallic reactants with diverse physical properties were attached to the hydroxyethylamine scaffold in the P3 and P1' positions to furnish inhibitors with highly improved activity. The concept of controlled and sequential single-mode microwave heating was employed for rapid library generation. Compared to conventional thermal heating, microwave irradiation accelerated the library synthesis step by reducing the reaction times of the Suzuki reactions from hours to minutes. This combinatorial optimization protocol afforded plasmepsin inhibitors with not only Ki values in the low nanomolar range, but also with high selectivity versus the human protease cathepsin D. With this class of inhibitory agents, modifications of the P1' substituents resulted in the largest impact on the plasmepsin / cathepsin D selectivity. New examples of microwave-heated organic transformations will also be discussed.

Functionally diverse purine libraries as Chemical Inductors of dimerization (CID)

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Recently, it has been demonstrated that a number of G-protein coupled receptors (GPCR) are presented as dimers or multidimers. Furthermore it has been also put in evidence that many dopamine and adenosine receptor subtypes exhibit this phenomenon, specially in response to certain agonists/antagonists. The "polymer-linked ligand dimers" (a polymer linking two biomolecules in each end) strategy can be used as a powerful tool to interact simultaneously with multiple active sites proteins and allosteric proteins and induce the dimerization in the last ones. Herein, the application of this principle to obtain a new compound family that promote the heterodimerization between adenosine and dopamine receptors is reported. In these new compounds the length of the linker could be critical, as well as the biomolecule and the linkage group between the biomolecule and the linker. A full integrated combinatorial approach to explore all these aspects is used. Our strategy is based in a new combined solid/solution phase strategy for the synthesis of a library of purine derivatives wherein each molecule incorporates a chemical linkage group (that is one of the diversity points), which allow to attach this molecule to a dimeric ligand. The aim of these libraries is to explore the diversity in the scaffold structure (adenine), as well as the best way to attach it to the linker.


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To drive the discovery of catalysts forward, smart screening methods are needed to test large numbers of different compounds for their catalytic performance in various types of reactions. Here, we present a new general screening method for the discovery of catalysts within split-and-mix libraries.

Our concept for the visualization of catalysts within a one-bead-one-compound library relies on the immobilisation of one reaction partner (A) along with each library member - the potential catalyst - on the same bead. If the reaction partner (B) is labeled with e.g. a dye a reaction between A and B is easily visualized by the covalent attachment of the marker to those beads that carry catalytically active library members.

We will demonstrate the feasibility of the method with the example of the acylation of an alcohol by a dye-marked Pfp-ester using peptidic catalysts.


High Throughput Exploration of the Physical and Chemical Properties of Materials and Drug Candidates

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Application of high-throughput design, parallel synthesis, high-throughput screening and data analysis is now being practiced across a range of pharmaceutical and materials science applications, including drug discovery, catalysts, polymers, and electronic materials. Feedback has come full circle: high-throughput methods that originated in drug discovery that then moved into materials science and are now finding their way back into the later stages of drug development. High-throughput methods and tools are now in practice addressing critical areas of pharmaceutical pre-formulations, including solubility, salt selection and polymorphs.

We will present these workflows and discuss the key factors learned in their implementation. These success factors span the technical, including overall workflow, design, synthesis, sample preparation, properties screening, instrument and software integration, databasing, data management, and data mining functions, as well as economic and cultural components.
Oral Presentations

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Use of High Throughput Experimentation in Homogeneous Catalysis for Fine Chemicals

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Use of homogeneous catalysis in the production of fine chemicals has long been limited because of time-to-market constraints that do not allow sufficient time to develop a robust catalytic process. This picture has radically changed with the advent of High Throughput Experimentation (HTE). Having available robots that allow us to perform up to 96 reactions at the same time has strongly reduced the time necessary to find a catalyst and develop a process.

In addition, HTE also speeds up the development of new catalytic reactions. We have in the recent past used HTE for lead finding and optimisation, scope determination, as a tool in mechanistic research, and for the production of ligand libraries. [1]

In the presentation we will give an example of the scope determination we have performed using HTE on our recent finding that ligandless palladium can be used in Heck and Suzuki reactions on aryl bromides as long as low loadings (0.01-0.1 mol%) are used.[1],[2]

Another area where we have extensively used HTE is based on our recent discovery of the use of monodentate phosphoramidite ligands in asymmetric hydrogenation. Examples will be given of a mechanistic study and a few recent developments.[3]


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Development of Amphiphilic Polymer-Supported Palladium-Phosphine Complexes: Catalysts for Green, Safe and High-Throughput Processes

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Amphiphilic polystyrene-poly(ethylene glycol) copolymer resinsupported palladium-phosphine complexes were designed and prepared with a view to use them for organic transformations in water under heterogeneous conditions which would meet safe, green, and highthroughput requirements. A supported palladium-monophosphine complex catalyzed \( \pi \)-allylic substitution [1], carbonylation [2], Heck reaction [3], and Sonogashira coupling [4] in water smoothly where the catalyst resin was recovered by simple filtration and reused without additional charge of palladium. A palladium complex of chelating bisphosphine was found to be the best catalyst for coupling of aryl (or vinyl) halides and organoboron reagents [5] exhibiting wide range of functional group tolerance. Asymmetric catalysis in water using polymeric chiral palladium complexes [6] will also be presented.

Pd-Catalysed transfer hydrogenations and C-C cross coupling reactions in flowthrough reactors

Andreas Kirschning, Wladimir Solodenko, Hongliang Wen, Eike Kunst, Ulrich Kunz, Stefanie Leue, Friedrich Stuhlmann, and Gerhard Jas

Polymer-supported reagents have seen a dramatic renaissance lately, because this hybrid solid/solution phase technique allows simple purification and the possibility to use reagents in excess to drive reactions in solution to completion. The opportunity to employ this technique in conjunction with continuous flow processes is particularly appealing as this application would create an ideal almost workup-free technique for automated solution phase synthesis.

Recently, we reported on a new reactor system for polymer-assisted solution phase synthesis in the flowthrough mode which we termed the PASSflow technique.[1] A monolithic flowthrough microreactor, which is loaded with polymer-bound reagents or catalysts allows to perform organic transformations in solution associated with low to moderate pressure drop.[2] Regeneration of the reactor can be easily achieved. Here, a flowthrough reactor is presented which is loaded with various Pd(0) catalysts and which performs a wide variety of catalytic transformations including (transfer) hydrogenations, and Suzuki as well as Heck reactions in high yields and very high purity of crude products. Leaching parameters are determined. Depending on the stability of the catalysts the reactions can be repeated more than 10 times.

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Combinatorial Synthesis and Screening of a CTV-based Tripodal Artificial Receptor Library

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Combinatorial synthesis of artificial receptor libraries and parallel screening for their recognition properties have emerged as promising tools for uncovering novel selective interactions with possible biological relevance.

Tweezer-like artificial receptors which have been developed in our group, were capable of selective binding peptide sequences [1]. A more preorganised tweezer structure led to a considerable increase of the binding affinity [2]. We have used TAC (TriAzaCyclophane) and CTV (CycloTriVeratrylene) scaffolds with three identical peptide arms for the preparation of more preorganised tripodal receptor [3,4], that could mimic vancomycin for its ability of binding D-Ala-D-Ala, present in the cell wall precursors of pathogenic bacteria.

Here we describe the solid phase synthesis of the first combinatorial CTV-based receptor library. These CTV-based tripodal artificial receptors contain one peptide arm, which is different from the other two identical peptide arms.

In addition to screening for the binding properties of the library of CTV-based tripodal receptor for D-Ala-D-Ala containing ligands, validation of the binding by the selected library members is described.

**O 3.3**

**Preparation and screening of diboronate libraries for identification of new carbohydrate sensors**

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Boronates, the anionic form of boronic acids, are known to bind reversibly to a number of carbohydrates. This asset has been utilized in development of various carbohydrate sensors with spectroscopic or electrochemical read-out. Unfortunately, simple monoboronates bind relatively weakly to glucose, and considerably stronger to e.g. fructose. This is in contrast to the importance of glucose in among other monitoring of diabetes. Sensor selectivity for glucose can however be obtained by using diboronates of suitable geometry, but diboronates have so far been prepared and tested apparently only on a one-by-one basis. The abstracted paper describes a method for parallel solid-phase preparation of libraries of diboronates and screening of their carbohydrate selectivities under physiologically relevant conditions using an alizarin-based competition assay.

**O 3.4**

**Design and Synthesis of Cyclic Peptides as Small Molecule Receptors: A Solid-phase Combinatorial Approach.**

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Molecular recognition plays a crucial role in many biological processes where guest molecules are selectively bound by their host. Recognition processes can be imitated with synthetic receptors offering possible a wide variety of applications in the medical or pharmaceutical fields. Among others, cyclic peptides are important targets in supramolecular host-guest chemistry due to their reduced flexibility, metabolic stability, or enhanced binding affinity towards their linear counterparts. In this communication we report the design and synthesis of a new type of cyclic peptides with potential capability for the selective binding of small molecules such as monosaccharides. The design of the receptors allows (i) a proper guest inclusion into the cavity, while facilitating its interaction with host side chains and (ii) a strait forward synthetic pathway amenable for the use of solid-phase combinatorial chemistry approaches. Receptor construction has been based on a non-peptidic element responsible for the initial interaction with the guest (an aromatic segment in case of carbohydrates) that trigger secondary interactions with the peptide core.

Synthetic approaches to the cyclic receptors as well as preliminary results on their binding to monosaccharides will be presented.

Novel applications of Biginelli reaction. Solution phase parallel synthesis of dihydropyrimidinone, dihydropyrimidinethione, dihydropyrimidothiazine libraries

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To develop novel biologically active core structures, we exploited the potential of the Biginelli reaction. First we synthesized 1-R1-6-R2-2-(thi)oxo-4-(3 or 4-R4-amino-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid esters. We extended the scope of a previously reported synthetic protocol with a novel substituent pattern around the dihydropyrimidinone and dihydropyrimidothione core that enabled the synthesis of libraries in solution phase. We further exploited the application of the Biginelli reaction to 6-(3 or 4-R4-amino-phenyl)-8-R1-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carboxylic acid ester and amide based compound libraries. In the case of dihydropyrimidothiazines when intermediates were reacted with 1,3-dibromopropane exclusively, the regioisomer A was detected contrary to the literature[1], where the formation of both of the possible regioisomers were reported. Using an amino group linked extension we obtained a >1000 member library. Furthermore, we have studied the above reactions with a 1,2-dielectrophile (1,2-dibromoethane) and we obtained the reported regioisomers (B,C) in various ratios.


A three-component reaction for the diversity-oriented combinatorial synthesis of polysubstituted piperidines

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The piperidine unit is common to several naturally occurring alkaloids and azasugar analogues. This communication describes the design and optimization of the first aza[4+2]/allylboration tandem reaction to access polysubstituted α-hydroxyalkyl piperidines (4) in a highly stereocontrolled fashion from 4-borono-hydrazonobutadienes (1), maleimides (2), and aldehydes (3).

In a single operation, this simple one-pot three-component reaction produces four stereogenic centers, up to four elements of diversity, and allows for a wide scope of compatible substrates. This process is thus particularly well adapted for applications in the diversity-oriented combinatorial synthesis of polysubstituted piperidine derivatives. The optimization of this novel multicomponent reaction towards library generation will be described both in solution-phase and solid-phase chemistry.
O 37

Anomalous regioselective MCR4 Biginelli reaction: One pot synthesis of spiro heterobicyclic aliphatic rings

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In a previous work we have found that a cyclic beta-keto ester reacts with one molecule of urea and 2 of aldehyde to give a new family of spiro heterobicyclic aliphatic rings in good yields. Interestingly, the expected Biginelli product was not detected. After analysis of products using HPLC, $^1$H NMR and $^{13}$C NMR, we have found that the reaction is driven by a regio-specific condensation of 2 molecules of aldehyde with the other reagents to afford only products harboring substituents exclusively in syn configuration. In the present work, we report a large and exciting extension of this new reaction utilizing high throughput organic synthesis arrays as demonstrated by the use of $\beta$-keto-$\gamma$-lactames, derived from natural amino acids, and the potential of the spirobicyclic products to generate libraries from libraries. Interestingly, we note an unusual and important anisotropy effect induced by perpendicular interactions between rigid $\pi$ systems and different substituents on the $\alpha$ position of the obtained spiro-bicyclic system. Stereo-selectivity of the aldehyde condensation is driven by the nature of the substituents on the starting $\beta$-keto-$\gamma$-lactam. Aromatic as well aliphatic aldehydes can be used as starting reagents, the late afford the desired products in poor yields similarly to the classical Biginelli reaction, the reasons for these poor yields are addressed in the discussion and clarify at some extent the complexity of the Biginelli multicomponent reaction mechanism.

O 38

Polymer Supported 9-Borabicyclo[3.3.1]nonane

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Following the first reports by H.C.Brown in 1968 detailing the use of 9-borabicyclo[3.3.1]nonane (9-BBN) in solution, there has been a continual interest in this versatile hydroborating reagent, sustained by the development of many diverse applications of significance. For the first time, a novel immobilised analog of 9-BBN has been prepared via a simple and robust two step procedure, starting from commercially available 1,5-cyclooctadiene (COD).

High loaded ULTRA-resins: An evaluation of different supports and their application in polymer-supported chemistry

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ULTRA-resins are based on the crosslinking of polyethylene imine. The polymers show loadings up to 14 mmol/g of amine [1].

The characterization and evaluation of several ULTRA-resins which differ in the length of the polyethylene imine monomer and in the amount of crosslinker will be presented. Therefore different physical parameters of the supports are investigated and compared to common used resins. Furthermore ULTRA-resins with different linkers are presented. The availability of these high loadings in solid phase peptide synthesis will be shown. As a result of these investigations we will present an optimized ratio of polyethylene imine and crosslinker for the synthesis of ULTRA-resins in relation to chemical and mechanical stability, conversion in chemical reactions and accessibility of the high loadings.

In addition we will present some applications for the use of ULTRA-resins in polymer-supported chemistry.


A Combinatorial Scaffold Approach Based upon a Multicomponent Reaction

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The design of drug-like chemical entities, for non-biased screening, constitutes an enormous challenge. Combinatorial scaffold approaches have mainly been based on the decoration of core structures, e.g. dichloroheterocycles, or by formation of the skeleton during the addition of the diversity generating building blocks, as in diversity-oriented synthesis. We report a conceptually distinct methodology of combinatorial scaffolding built upon first generating the three necessary pharmacophore elements followed by constructing the central core unit as a fourth point of diversity. This fourth point of diversity mainly constitutes the spatial arrangement of the pharmacophore elements.
**P 1**

**Strategy to Constrained Cyclopeptide Libraries**

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Cyclic peptides are interesting tools in medicinal chemistry because they exhibit an improved metabolic stability, facing to their linear precursors. Cyclopeptides are also useful scaffolds for the design of new drugs providing diverse functionalities around a core, whose flexibility depends on the ring size.

Cyclization is the key step in the synthesis of constrained cyclopeptides. A flexible approach to such compounds is represented by on-resin head-to-tail cyclization, performed by SPPS anchoring the side-chain of a trifunctional amino acid to a resin and adopting the three-dimensional protection scheme Fmoc/tBu/OAl. We applied this strategy to the synthesis of a library of 2,5-diketopiperazines, comparing the standard thermal heating ring-closure to the microwave-assisted technique. We also synthesized, as a model, a series of RGD containing cyclopeptides. Finally, we evaluated and optimized all the parameters involved in on-resin head-to-tail cyclization to further synthesize new libraries of constrained cyclopeptides.

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**P 2**

**Synthesis of Spiroimidazolidinone Libraries on Solid Support**

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Spiropiperidines belong to a relevant class of molecules for various G-protein coupled receptor targets and are often referred as “privileged GPCR-structures” [1]. These derivatives which constitute high-functionalized templates could offer a useful structure for the discovery of new active compounds. In this study, we focused our attention on 1,4,8-triazaspiro[4.5]decane-2-one architecture (Figure 1) which can be easily obtained in one step by condensation of N-benzyl-4-piperidone to an amino acid involved in an amide bond.

First, we set up their synthesis on solid support (Synphase™ Lanterns). Then, we optimized the synthetic approach by using the Multipin methodology [2] to ultimately prepare chemical libraries [3].

![Figure 1](image)

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**P 3**

**Polymer-Bound Oxidant : IBX Reagent**

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Hypervalent iodine reagents have been used extensively in organic chemistry owing to their low toxicity, ready availability and ease of handling [1]. 1-Hydroxy-(H)-benzo-1,2-naphthox-3-one-1-oxide (IBX) oxidizes benzyl, allylic and aliphatic alcohols mildly and efficiently to carbonyl compounds in high yields. However, this reagent is poorly soluble in many organic solvents and sometimes can be difficult to remove from the reaction mixture. The polymer-supported version of IBX overcomes these limitations and offers the additional benefits of being environmentally safe and recyclable [2-3].

![Image of IBX]

The reaction kinetics of this supported oxidant were studied to develop optimized procedures. A comparison of different polymer-bound oxidants reagents [4-5] is presented in order to have a complementary approach of reaction conditions in solution phase chemistry.


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**P 4**

**Trimellilitic anhydride linker – A novel tool for highly orthogonal conversions of primary amines with particular potential in carbohydrate chemistry**

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A new linker concept for solid phase synthesis tolerating a broad range of reaction conditions was developed [1]. The TAL-resin (trimellitic anhydride linker) allows for the immobilization of amines as pthalimides and therefore represents a versatile tool especially suitable for diversity-oriented protocols of carbohydrate derivatives.

![Image of TAL-resin]

We present two orthogonal routes for smooth amine immobilization on TAL-resin 1. Several examples for chemical transformations of TAL-bound functionalized amines and the application of FT-ATR-IR for efficient solid-phase reaction monitoring are demonstrated. Product release of modified amines from the polymer support with excellent yields and purities was achieved by three orthogonal cleavage-protocols including a safety-catch protocol. The exceptional value of the novel TAL-resin in polymer-supported synthesis of carbohydrates due to its broad stability range towards harsh acidic, basic and oxidative conditions is demonstrated.

Poster Presentations

**P 5**  
**Speeding up Combinatorial Synthesis: Applications and Automation**  
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Combinatorial Synthesis has become an integral part of the research activities of most pharmaceutical companies and a key technology in the drug discovery process. However, success depends on the quality of the compound collections and the efficiency of the overall workflow.  
At Bayer we have set up a highly productive CombiChem platform implementing new automation technologies, optimising logistic processes and realising novel synthetic concepts. High Throughput approaches deliver thousands of unique drug-like test compounds per year, balancing solid and solution phase combinatorial chemistry according to the specific need. This presentation will highlight applications of solid phase and solution phase CombiChem and illustrate facets of the highly automated and optimised workflow.

Design and profiling criteria are of increasing importance when it comes to improving physicochemical properties and refining biological spectra of compound collections. Currently we witness a trend towards the design of smaller sets of molecules that focus on specific desired qualities. Integrated automated hardware solutions for synthesis, chromatography and compound handling guarantee high standards in purity and weight frames for all test substances. Sample logistics, data handling and documentation are vital factors for overall efficiency especially when dealing with large compound libraries and have to be taken care of.

**P 6**  
**En Route to Multicomponent Synthesis of GBR Analogues**  
**Kathrine Bjerre** and Mikael Bols.  
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It has been shown that the azido group in α-azidobenzylethers can very effectively be substituted with a wide variety of Grignard reagents in a traditional combinatorial fashion. The GBR series of compounds is under serious investigation as a therapeutic agent in the treatment of cocaine abuse. The compounds contain a benzylether functionality, and insertion of an azido group would make the GBR compounds prone to combinatorial chemistry using the Grignard reaction. This has been investigated in the present work.

\[ \text{Ar=Ph, R=Ph GBR 12935} \]


**P 7**  
**Radical azidonation and its use in Solution phase Combinatorial Chemistry**  
**Mikael Bols**, Mukulesh Baruah, Xifu Liang  
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Radical azidonation is a high yielding and convenient way of selectively introducing the azido-group at an activated position.[1] The azido-group can not only act as a nitrogen functionality but also as a pseudohalide and be substituted with carbon nucleophiles.[2] Combined with solution phase combinatorial Grignard reagents[3] libraries can effectively and readily be prepared such as a series of analogues of antihistamines diphenylpyraline and ebastine (see figure)

\[ \text{Diphenylpyraline R = Me} \]
\[ \text{Ebastine R = C}_2\text{H}_5\text{CH}_2\text{NMe}_2 \]


**P 8**  
**Synthesis of cocaine analogues by multicomponent Grignard reactions**  
**Anne Bülow** and Mikael Bols  
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In the search for dopamine transporter ligands thought to be useful in the treatment of cocaine addiction, a variety of cocaine analogues were synthesised in small libraries. This was done by development of a technique involving the use of a multicomponent Grignard reaction.

![Cocaine and analogues](image)

To facilitate identification of a possible hit in the library screening was done in 2 dimensions.
**Poster Presentations**

**P 9**

**Rapid, In-Process QC Method for Binary Library Synthesis using IRORI Directed Sort and Combine Approach.**

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Each library synthesis at ACTC undergoes a production process. The developed synthesis protocol is tested on a set of compounds called a rehearsal library. A software tool (QC Wizard) was designed to pick this set from the full matrix of the virtual library. QC Wizard will choose a representative group of compounds showing all building blocks planned to use. Final library design depends on QC results of the rehearsal library.

The typical size of a library is anywhere between 4,000 to 10,000 compounds and the size of the rehearsal library usually represents 1.5-2% of the full size library. Preparation of rehearsal library for binary libraries of similar size would not be feasible, as the number of building blocks is logically higher than in complex libraries with more than 2 randomization points; typically over 65 members per step. The rehearsal libraries designed by QC Wizard would be representing 10% of the full size library, which is not very efficient.

Thus we are trying to accommodate a new, in process QC method that will be implemented during the synthesis. The directed sort and combine approach allows poor performers to be eliminated during the production process or at the very end. Additional final QC can verdict their removal from library. Using the IRORI equipment and the NanoKan technology easily accommodates this process.

Quick QC for binary library in comparison with the use of QC Wizard and rehearsal library synthesis will be described in a few examples of complex 2 and 3 dimensional libraries.

**P 10**

**Combinatorial solid phase synthesis of fluorogenic peptide libraries to explore site-specific release of a cytotoxic drug**

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Enzymes known to be secreted by tumor cells include matrix metalloproteinases (MMP), among them gelatinase (MMP-2), a target for inhibition in cancer treatment strategies. Our goal is the exploitation of its proteolytic characteristics, for the release of cytotoxic drugs from conjugate carriers. Biochemical (fluorescent resonance energy transfer) FRET assay for detection of short peptides bearing two fluorescent probes is envisaged to evaluate their potential use for site-specific release of a cytotoxic drug (from the conjugate) in tumor cells.

Here we illustrate how a variety of combinatorial tools are exploited for the preparation of the “FRET libraries” Dabcyl-ACA-P2-P1-P1’-P2’. Edans, in order to find sequences specifically cleaved by gelatinase. Combinatorial chemistry technologies were involved in the specific peptide spacer synthesis of dual probe tetrapeptides and dual probe triptides. The solid phase synthesis starts from the “Kenner safety catch” linker, and the peptides are prepared as N-terminal Dabcyl derivatives with C6 spacer. The activation of the linker and nucleophilic displacement with Edans provides the fluorogenic final products. The REC (radio frequency encoded combinatorial chemistry) based IRORI system is integrated in the production process. FT-IR (KBr pellets), 1D and 2D (DQF-COSY, TOCSY, ROESY and HSQC) MAS-NMR analysis, as well as purification by reverse phase SPE, with full characterization of selected final products.

**P 11**

**A Solid-phase Combinatorial Approach to Novel Peptide Based Transition Metal Catalysts for Asymmetric Synthesis**

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Asymmetric synthesis using catalytic organometallic reagents is currently one of the most active areas of organic chemistry. Enzymes, providing highly efficient catalysis for biological processes, benefits from the ability of peptides to form stable three-dimensional structures, creating an environment, in which the active site is situated, offering unique selectivity. Thus, combining the scaffold and chiral topology of folded peptides with the ligating properties of e.g. phosphine moieties should provide new ligands for transition metals, affording complexes with their removal from library. Using the IRORI equipment and the NanoKan technology easily accommodates this process.

Here we report the design and synthesis of novel phosphine containing molecules as well as preliminary results on their transition metal complexes and potential catalytic properties. The strategy used relies on solid-phase peptide synthesis, which offers a number of advantages. The peptides can be easily prepared from readily available chiral building blocks (i.e. Fmoc protected amino acids) and the phosphine moieties may be introduced by the incorporation of premade phosphine building blocks or by solid phase phosphinisation. Hence it should be possible to synthesise libraries of phosphine containing transition metal ligands using well-known solid-phase combinatorial techniques, and secondly screen a vast number of complexes for their catalytic properties. Furthermore, this methodology provides the desired catalysts immobilised on a solid support.

**P 12**

**Design and synthesis of an optimised peptoid library of controlled mixtures and studies on the generation of a sublibrary of cyclic derivatives**

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From the experience acquired in the design and synthesis of a library of peptoids by using the positional scanning format (M. Humet et al., 2003), we have constructed a second peptoid library containing over 5,000 molecules in 52 controlled mixtures. In this new library, drawbacks found in the former one, derived from the use of primary amines bearing additional amino groups, have been adequately circumvented. The library has been evaluated through the corresponding deconvolution processes after screening against different therapeutic targets.

On the other hand, preliminary results on the construction of a library of cyclic peptoid-based molecules will be also presented. In this case, a set of peptoids bearing free carboxylic acid groups have been prepared on solid phase and the conditions for their efficient cyclodehydration (vs. linear condensation) have been studied.

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In the process of achieving fast quantitative structure activity relations from compound libraries designed for optimization of hits into leads, a need was encountered for a high throughput purification system with the ability to estimate the actual amounts of the individual compounds. With the aim to meet this need a system for mass directed preparative HPLC directly coupled to simultaneous evaporation light scattering detector (ELS) quantification was developed. Fraction collection is controlled by the extracted target ion from the full scan data set. The amount of the purified compound in each collected fraction is assessed by on-line ELS detection. The detection is performed directly on a split flow from the preparative LC system. The ELS signal is filtered (by a special device Uni-kvant) allowing data to be collected only when factions are collected. As fraction start and stop are marked, the area for each fraction (not peak) can be translated directly to an amount (mg) by correlation with an external calibration curve. The system which is based on a Gilson LC system and an Agilent MS system will be described in detail. Also the interfacing and coordination of two different software programs controlling the hardware will be described.

A new method for high-speed binding assays

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Since the introduction of the split-mix synthesis strategy [1], combinatorial chemistry has revolutionized the drug discovery process. Practically, the synthesis of libraries of any compounds can be easily realized within a few days. By integrating robotic instrumentation with the plate format, from the middle of 1990s, high throughput screening (HTS) systems were able to test thousands of compounds a day. A considerable portion of screening experiments is based on specific binding of the compound of interest to a target macromolecule. Basically, the target macromolecules are proteins of different origins (e.g. receptors, enzymes, antibodies) or nucleic acids. In the post-genomic era, the number of the pharmacologically important targets obtained from the proteome has been growing at an unprecedented rate. Thus, there is a high demand for faster and more efficient high-throughput screening technologies. An obvious solution is to use high-density plates and to miniaturize the assay format. In spite of all these efforts, HTS is expected to be a bottleneck in the future drug discovery efforts. Facing this challenge, we present a conceptually new approach, which opens a way to fast and efficient screening of tens of thousand of target macromolecules with millions of small-molecule compounds.

A new strategy for the solid phase synthesis of 3,4-biarylisoaxozoles and 3,4-biarylpyrazoles

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A new solid phase synthesis of 3,4-biarylisoaxozoles and 3,4-biarylpyrazoles will be presented leading to products in high yields: Immobilized aliphatic aldehydes 1 are coupled to biarylketones 2 which are easily accessible by solution phase reactions [1]. The products 4 are formed by reaction of the enones 3 with hydroxylamine or hydrazines.

Novel parallel synthesis of 3-imidazo[1,2-a]pyridin-3-yl-propionic acid libraries

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We devised a new method for the synthesis of a novel 3-imidazo[1,2-a]pyridin-3-yl-propionic acid based compound library (1) in order to explore their pharmacological activity. According to the literature the only useful synthetic route for the targets was a condensation of 2-amino-pyridines (2) and 4-acyl-4-bromobutyrates (3) only useful synthetic route for the targets was a condensation of 2-amino- pyridine ring-systems (4). Our 3-step process proved to be a straightforward method leading to the targets with simple work-up, purification and improved yield, which was applicable for parallel synthesis. The presentation will focus on this novel method, and its applicability and limitations will be discussed.

Inverse strategy of amino-acid residue anchoring on solid support affords new chemistry – first examples.

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Conventional C to N terminus solid-phase peptide synthesis is based upon the anchoring of a carboxylic acid to a hydroxy or amino resin to give an ester or amide. However, the need to prepare a wide variety of low molecular weight chemical compounds by solid-phase synthesis encouraged us to develop a different strategy. For this approach, we investigated the anchoring of amino-acids via their amine function, opening by this way all the chemistry reactions on the free carboxylic acid group. In this preliminary report, we will discuss about our results on the Hofmann rearrangement of a single residue anchored to the resin via its amine function, the generation of aldehydes from Weinreb amides, the Arndt-Eistert homologation and use of these moieties in further chemistry. Other potential reactions are actually explored.
**Poster Presentations**

**P 2 1**

Synthesis and characterization of new heterocyclic amino acid derivatives as potential bioavailable antitumor agents

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Recently a great number of heterocyclic tyrosine kinase inhibitor quinazoline derivatives have been developed as potential antitumor agents. Other condensed pyrimidine derivatives like pyrazolopyrimidines are also known tyrosine kinase inhibitors. We have developed and synthesized a focused library of amino acid derivatives of condensed pyrimidines: quinazoline and pyrazolo-pyrimidines. The quinazoline core were substituted directly with the amino acids, the pyrazoles were connected with amino acids through a spacer. The amino acid containing molecules may have better bioavailability and ADME parameters. We used partially solid phase organic chemistry with FMOC synthetic strategy and classical solution phase chemistry. The compounds were tested in EGFR kinase inhibitory and tumor cell proliferation (MTT) assay. We will discuss the structure-activity relationships of the compounds.

**P 2 2**

Synthesis and Screening of a Library of 4-Sulfamoylphenylthioureas for the Development of Carbonic Anhydrase Inhibitors

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Sulfonamides are widely used as inhibitors of the zinc enzyme carbonic anhydrase (CA) for the treatment of important diseases such as glaucoma and macular edema. However, all these compounds are systemic inhibitors showing many undesired side effects due to inhibition of CA isozymes present in other tissues than the eye. Among the different approaches used to reduce such problems, the introduction of a covalently linked hydrophilic tails to aromatic/heterocyclic sulfonamide scaffolds have been proved to be effective. The main role of such moieties is the possibility to formulate the eye drop solutions at pH values close to neutrality. We recently developed new benzenesulfonamides bound by a thiourea linkage to an amino moieties, amino acid or dipeptide [1]. In order to understand the effect of the amino-acid side chain on the biological activity, a library of 4-sulfamoylphenylthiourea derivatives characterized by amino-acid diversity was synthesized. Parallel syntheses were undertaken comparing a solution strategy with a solid-phase one. The esterase activity of several physiologically relevant CA isozymes was tested both on on-resin thioeas and on the isolated components of the library.


**P 2 3**

Design of Focused and Restrained Subsets from Extremely Large Virtual Libraries

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With the current and ever-growing offering of reagents along with the vast palette of organic reactions, virtual libraries accessible to combinatorial chemists can reach sizes of billions of compounds or more. Extracting practical size subsets for experimentation has remained an essential step in the design of combinatorial libraries. A typical approach to computational library design involves enumeration of structures and properties for the entire virtual library, which may be impractical for such large libraries. This study describes a new approach termed On The Fly Optimization (OTFO) where descriptors are computed as needed within the subset optimization cycle and without intermediate enumeration of structures. Results reported herein highlight the advantages of coupling an ultra-fast descriptor calculation engine to subset optimization capabilities. We also show that enumeration of properties for the entire virtual library may not only be impractical but also wasteful. Successful design of focused and restrained subsets can be achieved while sampling only a small fraction of the virtual library. We also investigate the stability of the method and compare results obtained from Simulated Annealing (SA) and Genetic Algorithms (GA).

**P 2 4**

Solid phase Synthesis of Philanthotoxin Analogues with Modified and Elongated Polyamine Chains

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Introduction: Philanthotoxin-433 (PhTX-433) is isolated from the Egyptian digger wasp Philanthus triangulum. PhTXs have an antagonistic action on ionotropic receptors such as nACHr and AMPAR, by blocking the channels, which regulate the flow of cations into neural cells. High flow of cations may result in neuro-degenerating diseases i.e. Alzheimer and Parkinson.

The ion channels are blocked due to an electrostatic interaction between the charges polyamine chain and the ionized carbonyl acid residues in the interior of the channel. Apparently, hydrophobic interactions of the toxin head group (the N-acylated amino acid moiety) with the outer part of the receptor contribute significantly to the binding affinity.

Aim: The aim of this project is to obtain PhTX analogues with conformationally constrained or hydrophobic aromatic head groups as well as novel types of elongated polyamine or diamine chains by solid phase parallel synthesis. The reactions performed on solid phase include pentafluorophenyl ester activation of amino acids, Hoffman rearrangement, guanidinylation reactions, and development of a suitable protective group strategy. The compounds will be tested against the AMPA and the nACH receptors.
**P 25**

**Combinatorial Microelectrosynthesis of 1,2,4-Triazoles in 96-well Plates**

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The first example of parallel microelectrochemical syntheses using newly designed automated instrumentation for the common format of a 96-well plate is presented. The computer-controlled instrument allows to move a bundle of four electrodes (foil and ultramicro disc working electrodes, counter and reference electrodes) whereby cyclic voltammetric measurements or preparative potentiostatic electrolyses are performed.

A representative collection of 1,3,5-triaryl-1,2,4-triazoles has been generated by anodic oxidation of various benzaldehyde phenylhydrazones in the presence of benzonitriles. Special work-up procedures were elaborated and the triazoles were analyzed by HPLC-MS and GC-MS. The selectivity of the combinatorial electrochemical syntheses with respect to the substitution pattern of the triazoles is discussed.

Acknowledgement: This project was supported by the Deutsche Forschungsgemeinschaft.

**P 26**

**Fast Separation of Complex Peptide Libraries by Capillary Liquid Chromatography on Silica-Based Monoliths Coupled to ESI-FTICR-MS**

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Technically advanced and miniaturized separation and detection systems of highest resolution power are prerequisites to meet the analytical requirements for proteomics and complex combinatorial libraries. Appropriate analytically demanding probes for novel hyphenated methods are complex yet defined synthetic peptide libraries mimicking natural peptide mixtures such as protein digests or MHC ligand isolates.

Silica-based monolithic capillary columns combine the three performance characteristics such as fast, efficient elution and, due to the complexity of samples, a high loading capacity in a unique manner due to a tailored adjustment of both macro- and mesopore sizes in the highly-porous silica structure. On-line coupling of capillary liquid chromatography (cLC) with silica-based monolithic capillary columns to ESI-FTICR-MS allows the separation and sequencing of numerous isobaric peptides present in synthetic peptide libraries. Even libraries containing 1000 peptides were analyzed on monoliths with high separation efficiency within 20 min.


**P 27**

**Microwave-Enhanced Solid-Phase Synthesis of 1,2,3-Triazoles**

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The use of microwaves has been established as an important tool for effective and reproducible heating processes in combinatorial solid-phase organic chemistry (SPOS). For our studies on microwave accelerated 1,3-dipolar cycloaddition reactions we use a single-mode microwave-oven (SmithSynthesizer®, Personal Chemistry, Uppsala, Sweden) which allows automated work under heating conditions with temperature and pressure control.

An accelerated protocol was developed for the solid-phase synthesis of 1,4,5-trisubstituted 1,2,3-triazoles on Rink-amide-resin. Polymer-bound azides – with aliphatic as well as aromatic residues X - were reacted with dimethyl-acetylene dicarboxylate (DMAD) under microwave optimized conditions to yield polymer-bound 1,2,3-triazoles (Fig. 1).

Cleavage was afforded by treatment with TFA / CH2Cl2 (1:4). The products were analyzed by HPLC and ES-FTICR-MS. Several postmodifications were carried out to obtain a collection of diverse triazoles.


**P 28**

**Parallel Production of Pure Peptidyl Aldehydes by Using Polymer-bound Oxidation and Resin-capture-release Reagents**

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All methods described for the preparation of peptidyl aldehydes have drawbacks in the parallel production of highly pure peptidyl aldehydes. This is especially true if the C-terminal amino aldehydes contain chemically diverse side chains, including derivatives of trifunctional amino acids. Most procedures give varying yields and product purities, depending on the chemical nature of the peptidic precursor molecule.

We elaborated an oxidative synthesis route via the corresponding peptidyl alcohols, which were prepared by automated solid phase peptide synthesis. Using polymer-supported IBX,[1] we performed the oxidation of peptidyl alcohols in a parallel manner. Still, most of the crude aldehydes contain varying amounts of peptidyl alcohols which usually coelute in RP-HPLC. Therefore, we used a resin-capture-release technique for the rapid parallel purification of the peptidyl aldehydes, which allows the deprotection of most trifunctional sidechains with TFA, leading to collections of highly pure and highly diverse peptidyl aldehydes. While the oxidation itself induces no detectable racemization, the final resin-capture-release procedure leads to epimerization of about 10% C-terminal D-amino aldehyde.

Solid Supported Synthesis of Bicyclic Peptides Containing Three Parallel Peptide Chains

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Conformational rigidity makes cyclic peptides an interesting subject of research. To study the feasibility of building libraries of rigid homodetic bicyclic peptides containing three parallel amino acid chains on a solid support, we have synthesized four such peptides on hydroxyethyl polyurethane. These peptides consist of two different branching units, viz. α₁α₂bis(aminomethyl)β-alanine and N-succinyliminodiacetic acid, used to cap the carboxylic and amino termini of the peptide chains, respectively. The synthesis is initiated by assembling the peptide chains one after another on the three orthogonally protected (Alloc, Boc, Fmoc) amino groups of solid-supported α₁α₂bis(aminomethyl)β-alanine. Allyl protected N-Succinyliminodiacetic acid anhydride is then coupled to one of the chains and cyclizations with the remaining two branches are carried out on the support. Release of the bicyclic peptides from the solid support as free acids makes them suitable for possible further conjugation.


AN ORTHOGONALLY PROTECTED α₁α₂-BIS(AMINOMETHYL)-β-ALANINE BUILDING BLOCK FOR THE CONSTRUCTION OF GLYCOCONJUGATES ON A SOLID SUPPORT.

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A straightforward method for the preparation of triantennary peptide glycolusters by parallel synthesis on a solid support is reported. The key building block is orthogonally protected α₁α₂bis(aminomethyl)-β-alanine (1) that bears conventional Fmoc, Boc and Alloc protective groups on the three amino functions and a free carboxylic acid group for the attachment to a solid support. The assembly of the glycolusters involved removal of the three amino protections of the solid supported branching unit 1 in the order Fmoc, Boc and Alloc, and subsequent coupling of peracetylated O-glycosyl-N-Fmoc-L-serine pentafluorophenyl esters to each amino group exposed.

P 33
A novel oxidizing agent based on the polymer-supported oxoanion of TEMPO
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The controlled oxidation of primary and secondary alcohols to the corresponding carbonyl compounds is an important transformation in organic synthesis. Oxidation is often employed in the synthesis of a diversity of aldehydes and ketones due to the wide availability of alcohols. Particularly important is the synthesis of reactive aldehydes on demand, which are unstable to storage. We have developed MP-TsO-TEMPO as a novel polymer-bound oxoanion sulfonate for the selective oxidation of primary and secondary alcohols. This reagent is derived from TEMPO and a polymer-supported sulfonic acid.

MP-TsO-TEMPO

The major advantage of this reagent is that the products are isolated by simple filtration of the resin without any aqueous workup or chromatography. The ease of purification makes MP-TsO-TEMPO very well suited for parallel synthesis and library applications. The scope and selectivity of MP-TsO-TEMPO will be reported.

P 35
Ultra high-throughput mining of virtual combinatorial libraries
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The process of mining virtual combinatorial libraries for chemicals with desired properties can be very computationally and resource intensive if those libraries contain a very large number of compounds. We have developed a novel approach that allows the evaluation of tens of thousands of virtual compounds / s on a desktop computer. This approach employs neural network techniques and capitalizes on the fact that all structural diversity of a combinatorial library stems from a limited set of building blocks. We will describe the approach and present several examples of rapid selection of combinatorial compounds with pharmaceutically useful property profiles.

P 34
New potential phenazine antibiotics: Small combinatorial libraries and arrays by solution and solid-phase synthesis
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The ocean constitutes a vast source of potentially useful microorganisms; several natural products with antibiotic and antitumor activities isolated from marine habitats contain the heterocyclic phenazine structure. We focus on compounds derived from 6-(1-hydroxyethyl)-1-phenazine-carboxylic acid (saphenic acid) and its isomers, which are synthetically available to us. The total synthesis and determination of the absolute stereoconfiguration of the natural antibiotic saphenicin, an ester of saphenic acid, was recently published and the mode-of-action has been studied. Based on this family of natural products, we present the synthesis of small molecules that could serve as leads in the development of new classes of anti-infective drugs.

P 36
Integration of resin handling in an existing modular parallel chemistry environment
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The Solvay AMAP (Automated Molecular Assembly Plant) at our laboratories was originally set up for parallel solution phase chemistry. The system is modular, i.e. sets of reaction blocks are carried through a series of operations on different robotic systems. The ability to use polymeric supports in this setup has the potential to significantly improve compound diversity, and quality of the delivered materials. This would enable multistep solid phase syntheses, as well as use of polymer-bound reagents and scavenger resins to improve solution-phase reaction protocols.

With parallel powder dispensing still being an issue that sometimes requires special attention, handling of different types and bead-sizes of polystyrene resin could be achieved with only minor adaptations to the existing AMAP components. A key role is played by a special set of needles mounted to a standard multi-channel liquid handler that, in combination with in-house developed software, allows top filtration. Thus, excesses of reagent(s) and/or side-products can be washed from the resins, or liquid product fractions can be transferred to clean containers.

Proof of principle was established with the multistep solid phase synthesis of three compound libraries so far, the largest of 720 compounds. Duplicate experiments with established technology (on single compound level, or on parallel level using the Robbins FlexChem® system) showed that entries failing to pass our QC criteria were the result of chemical rather than technological failures. Studies on the use of scavenger resins and polymer-bound reagents are currently ongoing.
P 37
Solid and solution phase synthesis of jasplakinolide collections

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Due to their modular built, cyclic depsipeptides present interesting lead compounds for the synthesis of natural product like libraries [1,2]. Thus, synthesis of building blocks followed by assembly line manufacturing of the macrocycles leads to analogs that vary in ring size or in the decorating residues. In this presentation, the synthesis of a collection of jasplakinolide analogs is described. This molecule which shows antifungal and antitumor activity consists of four building blocks, among them a hydroxy acid that functions as a conformational lock.

Some of the analogs were assembled on the Wang resin using Fmoc protecting groups. In addition, several smaller ring size analogs were prepared using the hydroxy acid as a molecular workbench. In the course of these studies a novel synthesis for the hydroxy acid was developed that is based on the reductive cleavage of a cyclopropyl ring.


P 38
A combinatorial chemistry approach to HIV entry that results in a potent CD4 mini-protein inhibitor

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We have recently reported that a 27-amino acid mini-protein could be engineered by using structural information to reproduce the core of the CD4 receptor site binding the HIV-1 gp120 glycoprotein, resulting in an inhibitor of viral entry and infection [1]. This molecule was derived from the scyllatoxin scaffold and contains an α/β motif stabilized by three disulfide bonds. Here we report the use of combinatorial chemistry to obtain a new CD4 mini-protein, which binds gp120 with superior affinity. Four critical positions of the mini-protein β-hairpin, which constitutes the gp120 binding site and mimics the CDR2 loop of CD4, have been randomized by using L- and D-amino acids in a split and combine approach. Four libraries were produced by automated solid phase synthesis, tested by circular dichroism, and screened in two independent gp120 binding assays, based on competition ELISA and fluorescence polarisation. The CD4 mini-protein resulting from library deconvolution inhibits CD4+gp120 interaction at picomolar concentrations and, by binding gp120, induces a conformation into the viral protein that exposes epitopes, which are the target of neutralizing antibodies. This new mini-protein can represent a new potent HIV entry inhibitor and a potential component of an immunogen formulation useful in AIDS vaccines. These results demonstrate that a multi-disulfide mini-protein is amenable to combinatorial chemistry and that functional selection can result in a potent receptor ligand, independently of structural information, not always available in biologically relevant protein-receptor systems.


P 39
Identification of bioactive compounds from a library of 3-oxopiperazinium and perhydro-3-oxo-1,4-diazepinium derivatives

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The design and synthesis of a library of novel families of 3-oxopiperazinium and perhydro-3-oxo-1,4-diazepinium derivatives is reported. The library was composed by 44 3-oxopiperazinium derivatives (11 of these compounds had a spiranic skeleton) and 22 perhydro-3-oxo-1,4-diazepinium compounds. The synthetic procedure involved a 6-step sequence carried out in solution phase, the use of solid-phase linked scavengers for the removal of the excess of amine reagents and of microwave activation for accelerating these elimination reactions. Screening of this library on two biological assays identified active compounds that inhibit the activity of the vanilloid receptor TRPV1, and modulators of the multidrug resistance phenomenon.

P 40
Automated UV/MS RP/NP High-Throughput HPLC

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In this communication we like to elaborate on the compound- and data flow in high-throughput chemistry. A key step in this process is the parallel purification of medium to large series of compounds on an automated normal- and reverse phase HPLC system. We will elaborate in more detail about the technical aspects of this purification platform.
A Polymer-Supported Reagent for the Amidination of Amines

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The guanidine moiety is present in many biologically active compounds and plays a key role in the biochemical recognition and catalysis. Synthetic guanidines are widely used in the design of drugs covering a variety of therapeutic areas. However, due to the polarity of the guanidine group and hence excellent water solubility of organic materials that bear the guanidine moiety, workup and separation from by-products including those derived from the reagent are often cumbersome. By attaching the 3,5-dimethyl-1H-pyrazole-1-carboxamidine ring to the Merrifield resin via an intermediate polymer-bound 1,3-diketone[1] we obtained a new polymer-bound reagent which circumvents workup problems and which allows easy workup after amidination of primary and secondary amines.[2] Guanidines are obtained in good yields and with high purity.


Evaluation of a new photolabile Backbone Amide Linkage (BAL) in the synthesis of a cyclic glycopeptide ligand for sia lodhesisin.

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Solid-phase synthesis has been applied successfully in the preparation of peptides, small proteins, oligonucleotides, and small organic molecules. A crucial part of the overall synthesis plan is the choice of an appropriate "handle" (linker) for the attachment to the support. One concept for solid-phase synthesis involves attachment of a backbone amide nitrogen to an appropriate handle. This backbone amide linker (BAL) approach allows for the preparation of C-terminal modified and cyclic peptides, small organic molecules, and modified amino sugars, as well as combinatorial synthesis applications. So far, only acid-labile tris(alkoxy) benzylamidine systems have been exploited as BAL-systems. We report the design and synthesis of a new photolabile BAL, similar in structure to the O-nitrobenzyl photolabile linkers developed by Holmes.[1] The usage of the linker will be presented in the context of a cyclic glycopeptide synthesis. This glycopeptide contains sialic acid acting as a ligand for sialodhesisin. Its structure was modeled to fit the active site of the enzyme, based on crystal structures of the most promising hits of two stialic acid containing glycopeptide libraries attached to sialodhesisin[2].


On-Resin Analysis of Solid-Phase Oligosaccharide Synthesis With 19F NMR Spectroscopy

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A Simple, versatile and nondestructive method for analysing solid-phase oligosaccharide synthesis with gel-phase 19F NMR spectroscopy is described. The method relies on use of fluorinated variants of protective groups commonly used in carbohydrate chemistry.[1,2] It is illustrated by the synthesis of tri saccharide antigen which is responsible for hyperacute rejection in xenotransplantation of porcine organs.


MW-assisted synthesis of 2-substituted-4-bromo-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones

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During the past decade our group has been using pyridones 1, obtained by condensation of an α,β-unsaturated ester and malononitrile in NaOMe/MeOH, as starting materials for the synthesis of pyrazolo[3,4-b]pyridines, 1,6-naphthyridines, and pyrido[2,3-d]pyrimidines. In this later case, treatment of 1 with guanidine or amidines yielded 2,4-diamino (G1=G2=NH2) and 2-substituted-4-amino substituted (G1=H, alkyl, aryl; G2=NH2) pyridopyrimidines 2 and 3, respectively. On the other hand, substitution of the methoxyl group present in the starting material for the synthesis of pyrazolo[3,4-b]pyridines. In this later case, treatment of 1 with 3,5-dimethyl-1H-pyrazole-1-carboxamidine[4] pyrido[2,3-d]pyrimidines 4 and 5 (G1=G2=NH2) and 6 (G1=G2=Br) depending on the thermal level employed. Furthermore, the use of an acyclic strategy consisting in the treatment of the Michael adduct of an α,β-unsaturated ester and methyl cyanoacetate with guanidine or an amidine allowed us to introduce a carbonyl group in position C4 of pyridopyrimidines 6 (G1=G2=NH2, alkyl, aryl; G3=CHO). However, in no case was possible to obtain a 2-alkyl (or aryl) 4-bromo substituted pyridopyrimidine susceptible of a further functionalization in position C4 (G2).

Poster Presentations

P 4.5 Synthesis of 5,5-disubstituted-2-amino-3,5-dihydroimidazol-4-ones via a novel rearrangement

Tamás Nagy, László Varga, J. Jordi Benet-Buchholz, György Dormán, László Urge, Ferenc Darvas

Chalcones have been very attractive starting materials in medicinal chemistry, because they are easy to prepare with large variability at the two aromatic rings, and enone provides a bifunctional site for 1,3-bond formation. In our continuing efforts towards the design and synthesis of novel biologically active core structures, we devised a reaction route to obtain new 6-membered 4,6-diaryl-2-amino-pyrimidine by reacting chalcones with guanidine as 1,3-dinucleophile. Several oxidizing agents with various orders of addition were investigated in order to complete the aromatization that spontaneously follows the cycloaddition reaction. When the oxidizing agent was added together with guanidine (‘one pot’ approach) an unusual rearrangement was discovered leading to 5,5-disubstituted-2-amino-3,5-dihydroimidazol-4-ones (2) instead of the expected 4,6-diaryl-2-amino-pyrimidine (1) derivatives.

In the presentation, the synthetic details and full elucidation of the novel core structure is presented using 1D, 2D NMR and X-ray diffraction. In addition, the mechanism for the rearrangement is also proposed [1].


P 4.7 Parallel Solid-Phase Synthesis of Philanthotoxin-83 Analogues

Christian Adam Olsen, Jerzy W. Jaroszewski, and Henrik Franzén

The natural Philanthotoxin-83 (PhTX-83) has been isolated from the Egyptian digger wasp Philanthus triangulum. PhTX-83 and various synthetic analogues interact with ionotropic receptors including nicotinic acetylcholine receptors (nAChR) and ionotropic glutamate receptors (iGluR). Generally, these toxins consist of three units: (i) a polyamine moiety, (ii) an amino acid residue and, (iii) an acyl group.

Philanthotoxins block ion channels in neural cells in vitro, and are therefore interesting leads in medicinal chemistry research in relation to neurodegenerative diseases (e.g. sclerosis, Alzheimer and Parkinson’s disease).

In this work, we have prepared novel polyamine moieties by simple SN2 reactions on solid supports. These polyamines were employed in small libraries combined with different amino acids and acyl groups by combinatorial parallel solid-phase synthesis. The compounds will be tested against nAChR and iGluR in electrophysiological assays.

P 4.6 Microwave-Assisted High-Speed PCR

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PCR amplification has emerged as a very important tool in biological research. The utility of the PCR is, however, hampered by the fact that it is a slow technique. Faster heating cycles are therefore needed, both to enhance the activity of the enzyme, and to enable shortening of the reaction times. Polymerase chain reactions with focused microwave irradiation as the source of heat is demonstrated for the first time[1]. Thus, it was established that pulsed microwave heating does not terminate the enzymatic function of the polymerase. The results indicate the possibility to shorten the total reaction time. In addition, the technique may give the possibility to perform PCR reactions in millilitre scale.


P 4.8 Pralins: A New Program Code for Combinatorial subLibrary Design

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The strategy of combinatorial chemistry plays a growing demand on efficient combinatorial design and rational selection methods. Their aim is to keep the number of considered compounds at a reasonable size on behalf of the particular synthetic capabilities, without reducing the probability of discovering useful leads[1]. This is achieved by maximizing diversity (the coverage of the chemical-property space) or similarity (for focused libraries), relying on the hypothesis that close compounds in the descriptor space should exhibit similar biological properties[2]. We present a new program code, Pralins, which offers a variety of design strategies. It includes classical non-combinatorial subset selection methodologies, but our goal and success has been to implement effective methods for combinatorial subsets selection based on the properties of the resulting products. Not only direct sampling methods such as Maximin have been adapted, but also clustering and partitioning algorithms[3]. The user can select the cluster or partition level and choose between space or population coverage as optimality criteria. Due to the NP-completeness of the combinatorial problem, heuristic techniques such as Monte Carlo, Simulated Annealing and Local Search have been used for optimization, where a collection of starting reactions can be introduced as a random seed and also for comparison purposes. The enumerative technique has also been included as a baseline for small problems. Furthermore, the program is able not only to include desired reactions in the final selection, but also allows the user to define synthetic steps that share common reagents, and seek a common combinatorial selection that maximizes diversity or similarity. Additionally, the Pralins program offers 3D-visualization and drawing features for SD-files, a library enumeration facility, and an interface to well-known computational chemistry programs to automate the properties calculation process.


**Poster Presentations**

**P 49**

En Route to Multicomponent Synthesis of Benztropin Analogues.

Hanne Pedersen and Mikael Bols.
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In the last decades many hundreds of cocaine analogues have been synthesized in an attempt to develop a drug, which can be used as a cocaine abuse treatment.

Benztropine which is a cocaine analog, was synthesized in 1952 and showed to be a useful anticholinergic drug in the treatment of Parkinson's disease. Like cocaine, benztropine binds potently to the dopamine transporter and it is a dopamine reuptake inhibitor equipotent to cocaine.

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The poster will present a methodology to synthesize combinatorial libraries of benztropine analogues and an attempt to find compounds, which block the dopamine binding site at the dopamine transporter without affecting the dopamine transport.

**P 50**

Multivalent phage probes for targeting bacteria, spores and cancer cells


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Multivalent “landscape” display of random peptides (8-9-mers) on all 4,000 copies of the major coat protein pVIII in phage fd-tet is achieved by splicing of degenerated DNA sequences into the gene VIII of vectors f8-1, f8-5 and f8-6 in various registers. Hundreds of clones from the landscape libraries were sequenced to characterize their diversity, evolution and censoring. Biopanning of the landscape libraries against complex biological systems: bacterium Salmonella typhimurium, Sterne spores of Bacillus anthracis, prostate and glioma cancer cells resulted in selection of unique families of phage-binders specific for the target systems. Targeting the complex biological systems with landscape phage allowed selecting various lead binders for different receptors. Target-specific landscape phage were crosslinked and used as affinity absorbents for isolation and identification of biomarkers.


**P 51**

A high capacity PEG-based amino resin for solid phase combinatorial synthesis

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A new high capacity PEG-based resin for solid phase synthesis is presented. The resin was synthesized from a commercially available low capacity PEGA resin [1] by the exhaustive reduction of amides using borane in THF [2]. The application of the resin was demonstrated by performing peptide and peptido-organic reactions in high yield and purity.

**P 52**

A Polymer-bound 1,3-Diketone – A Highly Efficient Scavenger for Hydrazines, Hydroxylamines and Primary Amines

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Today solid supported reagents and scavengers play an important role in parallel chemistry. In our group a 1,3-diketone resin was developed as the basis for a selective scavenger for hydrazines, hydroxylamines and primary amines[1,2]. In high throughput synthesis the reductive alkylation of primary amines very often is used for the production of secondary amine libraries. We will present data that this new 1,3-diketone resin can be used efficiently for the selective removal of primary amines to deliver secondary amines of high purity. Furthermore examples will be given for the scavenging of hydrazines and hydroxylamines.

**Poster Presentations**

**P 53**

**Preparation of Biphenyltetrazole Hydantoins and Thiohydantoins as Growth Hormone Secretagogues Analogs.**

Rune Severinsen\(^a\), Jesper F. Lau\(^a\), Kent Bondensgaard\(^a\), Birgit S. Hansen\(^a\), Mikael Begtrop\(^b\) and Michael Ankersen\(^a\)*

An efficient solid phase protocol for the synthesis of substituted (5-biphenyltetrazolyl)-hydantoins and thiohydantoins has been developed. Suzuki cross-coupling reaction between resin bound 2-(tetrazol-5-yl) phenylboronane and 4-bromo benzaldehyde gave the corresponding biphenyl aldehyde. Subsequent reductive amination with amino acid esters gave the pivotal intermediate for hydantoins or thiohydantoins formation. The resin bound amino acid esters were transformed to hydantoins or thiohydantoins via two routes. i) treatment with isocyanates or isothiocyanates or ii) treatment with triphosgene followed by primary amines. Using molecular modeling we were able to jump from L-692,429, a well known non-peptidyl GHRH, to biphenyl tetrazolyl hydantoins, obtaining compounds with IC\(_{50}\) values below 500 nM after two iterative cycles only.

![Chemical structures](image)

**P 55**

**Versatile new strategy for the solution phase synthesis of pyrrole libraries**

Bernd Sontheimer\(^1\) and Günther Jung\(^1\)

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The solid phase synthesis of combinatorial libraries leading to pyrrole derivatives provides thousands of compounds in 1 – 100 mg scale with mean purities over 80 % [1 – 2].

![Chemical structures](image)

A new solution phase synthesis strategy will be presented. In contrast to the solid phase synthesis, the 3-carboxamide nitrogen atom may be alkyl substituted. Branched amines (R\(^1\)R\(^2\)CH-NH\(_2\)) can be introduced in 1-position and a variety of alkyl-groups in 2-position. Thus, the new heterocycles have more diversity sites and they are accessible in multigram scale with mean purities over 90 %.

![Chemical structures](image)


**P 54**

**Search for New Red Phosphors for White LED Using an Evolutionary Optimization Process**

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A computational evolutionary optimization process was adopted to screen a Eu\(^{3+}\) - doped alkali earth borosilicate system in an attempt to search for red phosphors with a high luminescent efficiency, when excited by soft ultra violet irradiation. The ultimate goal of our study was to develop oxide red phosphors, which are suitable for three-band white light emitting diodes (LED). To accomplish this, we developed an evolutionary optimization process involving a genetic algorithm and combinatorial chemistry (combi-chem), which was tailored exclusively for the development of LED phosphors. The genetic algorithm is a well known, very efficient heuristic optimization method and combi-chem is also a powerful tool for use in an actual experimental optimization process. Therefore the combination of a genetic algorithm and combi-chem would enhance the searching efficiency when applied to phosphor screening. Vertical simulations and an actual synthesis were carried out in the present investigation and promising red phosphors for three-band white LED applications, such as Eu\(_{1.14}\)Mg\(_{1.16}\)Ca\(_{0.07}\)Ba\(_{0.12}\)B\(_{0.17}\)Si\(_{0.32}\)O\(_{8}\) were obtained.

**P 56**

**Neuroactive natural products: Combinatorial synthesis and pharmacological evaluation**

Kristian Stromgaard

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Nature has provided several tools to study one of the most complex systems - the brain – and its functions. Here we describe how combinatorial approaches are used in the discovery and optimization of two such tools. Polyamine toxins are antagonists of several important ionotropic receptors. We have developed solid-phase synthetic methods, which have greatly facilitated the synthesis, and have been used in various SAR studies [1]. Recently, a combinatorial library was produced, which resulted in very potent, subunit-specific derivatives [2]. Ginkgolides and bilobalide are unique and structurally complex components of *Ginkgo biloba* with a reputation of having neuromodulatory properties. Recently, we have showed that these compounds are potent and selective antagonists of glycine receptors (GlyRs) [3]. This prompted the synthesis of a combinatorial library of ginkgolide derivatives, using solid- and solution-phase methods, as well as pharmacological evaluation on cloned GlyRs.


Poster Presentations

P 57
Synthesis of arylpiperazine library on Synphase™ Lanterns

Pawel Zajdel, Jean Martinez, Maciej Pawlowski and Gilles Subra

Arylpiperazine derivatives represent attractive targets for medicinal chemists. They bind to many classes of G-protein coupled receptors and produce a variety of pharmacological responses [1]. Previous SAR studies showed that affinity and selectivity depend on the 1-aryl substituent, the terminal fragment (amide or imide moiety) and the alkyl spacer linking the amide/imide fragment with the piperazine core [2,3]. We focused our attention on the impact of incorporation of amino acid moieties into the terminal pharmacophoric group (Fig. 1). To obtain a direct and easy access to this class of molecules, we developed a new solid supported synthetic pathway using BAL linker functionalized Mimotopes Lanterns. Each reaction step was optimized using Mimotopes Multipin[4] technology.

![Fig 1:](image)

We applied our optimized conditions to the synthesis of a 100-member focused library using a sort and combine approach. Analytical data and biological results of some compounds of the library will be presented.


P 58
Synthesis of 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-ones using solid-supported reagents.

D. Tourwé1, I. Van den Eynde1, K. Van Rompaey1, F. Lazzaro1
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The 4-amino-1,2,4,5-tetrahydro-2-benzazepine-3-one structure has been developed as a conformationally constrained analogue of phenylalanine and has been used with success in a variety of peptides[1]. This heterocycle, like the frequently used benzodiazepines, allows the attachment of various substituents at the two differentiated nitrogen atoms. We have developed a protocol for the generation of substituted analogues using solid supported reagents.

![A set of analogues has been prepared in solution using aldehydes or amines (R1), carboxylic acids or sulfonamides (R2) and solid-supported cyanoborohydride for reductive amiations and carbodiimide reagents for ring closure.](image)


P 59
Privileged structures asGPCRs chemical inducers of dimerization

Marc Vendrell1, Rubén Ventura1, Ester Angulo2, Vicent Cassadó2, Carme Lluis2, Rafael Franco2, Fernando Albericio3, Miriam Royo3
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There is no doubt that G-protein coupled receptors (GPCRs) dimerization plays a key role in their function [1]. This dimerization could be explored as a new therapeutic tool for neurological diseases, namely Parkinson’s syndrome and schizophrenia. The application of the chemical inducers of dimerization’s (CID) concept [2] in the development of a new type of compounds could provide the guidelines to obtain a lead compound for these diseases. The use of a combinatorial approach could be crucial for that objective. In the present work, the synthesis of a library of 36 compounds based on the ergolene system as a privileged structure owing to its capability of mimetize some neurotransmitters such as dopamine, adenosine and serotonin is regarded. The introduction of 36 different tripeptides as the diversity point in the library has provided some compounds that exhibit high affinity and selectivity for D1 and D2 dopamine receptors as well as for A1 and A2A, adenosine receptors. To the best of our knowledge, never before had ergolene derivatives been described to show high affinity for adenosine receptors.

![A set of analogues has been prepared in solution using aldehydes or amines (R1), carboxylic acids or sulfonamides (R2) and solid-supported cyanoborohydride for reductive amiations and carbodiimide reagents for ring closure.](image)


P 60
Strategies for Combinatorial Libraries Design and Synthesis

Eric Wegrzyniak, Anil Nair, Dasha Cabel, James A Connelly
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Combinatorial chemistry and High Throughput Synthesis are valuable tools for an acceleration of the lead discovery and lead optimization process. Chemo-informatics is commonly used to design combichem libraries and arrays of compounds with optimized biopharmaceutical properties. Strategies and processes developed at Aventis ACTC center to ensure the synthesis of high quality combinatorial libraries using IRORI Nanoka System and other state of the art directed sorting techniques will be presented.

![A set of analogues has been prepared in solution using aldehydes or amines (R1), carboxylic acids or sulfonamides (R2) and solid-supported cyanoborohydride for reductive amiations and carbodiimide reagents for ring closure.](image)
P 61
Application of novel C-C-coupling linker reagents in the synthesis of transition state isosteres for protease inhibition

Steffen Weik1, Jörg Rademann1
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Norstatins represent a family of highly potent protease inhibitors, containing the 3-amino-2-hydroxy-4-substituted butanoic acid as the active, isosteric motif, that mimics the tetrahedral intermediate formed during amide bond cleavage.

[\text{acyl anion addition}]

We present the development of novel linker reagents based on polymer-supported acyl-anion equivalents which expand and supplement the use of polymer reagents recently demonstrated [1]. They are employed in advanced synthetic challenges as in a diversity-oriented approach to norstorn libraries [2]. The reactive intermediates which provide C-C-coupling activity are derived from phosphoranes and N,N-dialkyl-hydrazones.


P 62
Parallel Synthesis of putative β-turn mimetics from amino acid, peptoid, and sulfonamide peptoid building blocks

Bas Wels1, John A.W. Kruijtzer1, Rob M.J. Liskamp1
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The parallel synthesis of cyclic peptidomimetics consisting of amino acid, peptoid and sulfonamide peptoid residues is presented. These have been designed by adapting our putative β-turn mimetics based on cyclic tripeptides [1], thereby improving the stability and ease of synthesis of the latter. The cyclic peptidomimetic trimers are easily accessible through a convenient solid phase synthesis route followed by cyclisation and deprotection in solution. A key feature is the incorporation of peptoid and sulfonamide peptoid residues, which provide easy access to side chain functionality variation while meeting the requirements for cyclisation of the linear precursors.

The synthesis of a library of these cyclic trimers will be presented, together with the results of screening library members for their ability to bind to the MC4 receptor.


P 63
Arylnitro-reduction promoted solid-phase synthesis of heterocycles on SynPhase™ Lanterns

Zemin Wu and Nicholas J. Ede
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Combinatorial solid-phase synthesis of small molecule compounds is now recognized as an essential tool for generating new leads and lead optimization in the pharmaceutical industry and academic research. Particular attention has been paid to the solid-phase synthesis of heterocyclic small molecules primarily due to the nature of existing drugs. Mimotopes’ SynPhase Lanterns are discrete, modular and quantized solid supports optimized for the synthesis of small molecules and peptides. While ensuring the highest level of chemical performance, SynPhase Lanterns offer increased handling convenience compared to conventional liquid phase libraries. These screening compounds are mainly for Herbicide indication [1].

The parallel synthesis of cyclic peptidomimetics consisting of amino acid, peptoid and sulfonamide peptoid residues is presented. These have been designed by adapting our putative β-turn mimetics based on cyclic tripeptides [1], thereby improving the stability and ease of synthesis of the latter. The cyclic peptidomimetic trimers are easily accessible through a convenient solid phase synthesis route followed by cyclisation and deprotection in solution. A key feature is the incorporation of peptoid and sulfonamide peptoid residues, which provide easy access to side chain functionality variation while meeting the requirements for cyclisation of the linear precursors.

The synthesis of a library of these cyclic trimers will be presented, together with the results of screening library members for their ability to bind to the MC4 receptor.


P 64
Automated Synthesis & Purification at Bayer CropScience Chemistry Frankfurt

Jürgen Zindel1
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The Automated Synthesis & Purification Team provides services in the area of synthesis and post synthesis activities for chemists at Frankfurt. Our workflow will be presented showing special robotic systems and software tools. We produce small and medium sized liquid phase libraries. These screening compounds are mainly for Herbicide indication [1].

The synthesis is done on two customized robots designed for parallel automated synthesis. The ISRA robot does 50 reactions, producing up to 1g of product with a liquid-liquid workup. The Scitec robot does 100 reactions, producing up to 150mg of product with a SPE workup. For purification we are using a customized robot from Labman or bench top HPLC equipment combined with fraction collectors.

Our High Throughput Lab Journal is designed for data exchange with the synthesis robots. Barcode labeled containers are monitored during post synthesis activities within our Compound Tracking tool.

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