ADVANCED PARTNERSHIP PLATFORM FOR EARLY DRUG DISCOVERY
FRAMEWORK OF PRODUCTS AND SERVICES

Fully Integrated Resources For Drug Discovery

**HTS Compounds**
- HTS compound collection
- Pre-plated diversity sets
- Fragment Libraries
- Targeted & Focused Libraries

**Contract research services**
- Custom Synthesis
- Computational Chemistry
- GLP Primary Drug Trials – Key Preclinical

**Advanced Building Blocks**
- *Off-the-shelf Building Blocks*
- *Tangible Building Blocks*
- *Cutting-edge Design of Building Blocks*
- *Custom Synthesis of Building Blocks and Intermediates*

**Fine Chemicals in Multigram Scale**
- *IR-Dyes*
- *APIs*
- *Fine Reagents for Organic Synthesis*
- *Scale-up Synthesis (up to 100kg)*
- *Process Optimization*
OUR FIELDS OF EXPERTISE

✓ Strong position in organic synthesis and medicinal chemistry
✓ Successful experience in custom synthesis projects of high complexity, including multistep procedures
✓ Co-design with customers
✓ Synthesis of reference compounds
✓ Synthesis of impurities
✓ Broadest range of compounds and chemical transformations
✓ Scale-up from grams to kilograms
✓ Recognized scientific portfolio
✓ Cutting-edge techniques and approaches
✓ Primary drug trial services
✓ Qualified and experienced staff
✓ Customer-tailored terms and conditions
✓ IP protection
✓ Timely and efficient data transfer
CUSTOM SYNTHESIS

OUR CUSTOM SYNTHESIS SERVICES

**Synthetic Chemistry**
- Discovery chemistry
- Synthesis of building blocks and scaffolds
- Synthesis of reference compounds and contaminants
- Synthesis of metabolites
- Synthesis of new chemicals or analogs for hit-to-lead development
- Parallel synthesis of compound libraries (10-1000 members)

**Medicinal Chemistry**
- Design and synthesis of drug-like compounds
- Synthesis of peptidomimetics
- Hit-to-lead projects
- Lead optimization
- Characterization of physical and chemical properties

**Process Optimization**
- Route scouting
- Reaction and process optimization
- Catalyst screening
- Material supply (GMP and non-GMP)
CUSTOM SYNTHESIS PROJECTS

General Procedure:
• For each project a research team is assigned for each project
• Both FTE and FFS business models can be offered
• Regular reporting as agreed with the customer
• Regular communication by means of telephone and Skype conferences
• Confidential Disclosure Agreements
• “Need to know” principle
• Hard copies data locked and data on server protected
• IP rights can be transferred to the customer
CUSTOM SYNTHESIS PROJECTS

Some Figures Under FTE Conditions:

USD 90,000 / year for PhD

USD 75,000 / year for Master degree

MSc Under FFS Conditions:

per project

per compound

per chemical step
CATALYTIC HYDROGENATION

- A dedicated laboratory facility (“key” laboratory)
- Know-how in use and optional employment of Ni, Pd, Pt, Rh catalysts
- Selective reduction of functional groups
- Selective hydrogenation of aromatic and heteroaromatic systems

Up to 100 g from 1 run
Synthesis of fluorinated amines

1. \( \text{HCl} \) addition to \( \text{SF}_4 / \text{HF} \) reaction gives \( 92\% \) yield.

2. Reaction of \( \text{BH}_3 \cdot \text{Me}_2\text{S} \) with \( 2 \) yields \( 82\% \) yield.

3. Reaction of \( \text{Br} \) with \( \text{CH}_3\text{NO}_2 \) in DMSO gives \( 54\% \) yield.

4. Reaction of \( \text{NO}_2 \) with \( \text{EtO}_2\text{C} \) in the presence of \( \text{K}_2\text{CO}_3 \) gives \( 87\% \) yield.

5. Reaction of \( \text{SF}_4 \) with \( \text{NO}_2 \) in the presence of \( \text{Zn} / \text{HCl} \) gives \( 67\% \) yield.

6. Reaction of \( \text{HCl} \) with \( \text{SF}_4 \) gives \( 91\% \) yield.

7. Reaction of \( \text{Zn} / \text{HCl} \) with \( \text{SF}_4 \) gives \( 67\% \) yield.

8. Reaction of \( \text{HCl} \) with \( \text{SF}_4 \) gives \( 8\% \) yield.
CHEMISTRY WITH GASEOUS DIAZOCOMPOUNDS

Safety of the process involving the use of highly explosive and toxic CH₂H₂ is achieved by:

• The use of a procedure in which diazomethane is generated in low concentration in octane solution (generator) and then is blown out by argon to the reactors; therefore, dangerous concentration of CH₂N₂ is not possible

• Neutralization of unreacted diazomethane by acetic acid (trap)

• Strict monitoring of the reaction in order to avoid accumulation of diazomethane in the reactors

Trifluoromethyl diazomethane:

• The reagent is synthesized in free state and reacts as a gas

• Know-how in use and optional employment of Cu, Rh catalysts
## FLAMMABLE REDUCING AGENTS

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Source</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAH</td>
<td>Rockwood Lithium (sieved, tablets and solution)</td>
<td>Up to 200g in 1 run</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Aldrich (Sure-Pac™, 1kg reagent grade) in-house generation</td>
<td>Up to 100g in 1 run</td>
</tr>
<tr>
<td>AlH₃</td>
<td>Aldrich (Sure/Seal™, 65% solution in toluene)</td>
<td>Up to 60g in 1 run</td>
</tr>
<tr>
<td>Vitride®</td>
<td>Aldrich (Sure-Pac™, 1M in THF)</td>
<td>Up to 100g in 1 run</td>
</tr>
<tr>
<td>L-Selectride®</td>
<td>Aldrich (Kilo-Lab™, 1M in THF)</td>
<td>Up to 1.8L of solution in 1 run</td>
</tr>
<tr>
<td>Super-Hydride®</td>
<td>BH₃·Me₂S, BH₃·THF, BH₃·py, BH₃·Me₃N, in-house generation</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>“BH₃”</td>
<td></td>
<td>Up to 50g of “BH₃” equivalent in 1 run</td>
</tr>
</tbody>
</table>

**Equation:**

\[
\text{LiAlH}_4 + \text{AlCl}_3 \rightarrow \text{ethylene-glycol, H}^+ \rightarrow \text{100 g of 2 was introduced into reaction in 1 run}
\]

\[
\text{1} \xrightarrow{\text{ethylene-glycol, H}^+} \text{2} \xrightarrow{\text{AlH}_3} \text{3}
\]
## FLAMMABLE STRONG BASES

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Source</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiHMDS</td>
<td>Aldrich (Kilo-Lab™, 1M in THF of hexane), in-house preparation in pure form</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>Rockwood Lithium (2.5M solution in hexane)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>Rockwood Lithium (1.9M in hexane)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>s-BuLi</td>
<td>Aldrich (1.4M in cyclohexane)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>MeLi</td>
<td>Rockwood Lithium (3M in DME)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>LDA</td>
<td>In-house generation in solutions or in-house synthesis in pure form</td>
<td>Up to 30g of pure reagent in 1 run</td>
</tr>
<tr>
<td>LTMP</td>
<td>In-house generation in solutions or in-house synthesis in pure form</td>
<td>Up to 30g of pure reagent in 1 run</td>
</tr>
</tbody>
</table>

Optimization of reaction conditions by varying base, solvent, concentration, temperature, etc.

```
O       O
\( \text{S}^{+} \text{I}^{-} \), NaH
\text{DMSO, r.t.} 92.5\%  \rightarrow \begin{array}{c} \text{5eq s-BuLi} \\ \text{TMEDA} \\ \text{-78 \degree C, 3.5h} \end{array} 20\% \\
\begin{array}{c} \text{OH} \\ \text{Boc} \end{array} \rightarrow \begin{array}{c} \text{O} \\ \text{Boc} \end{array} \rightarrow \begin{array}{c} \text{OH} \\ \text{Boc} \end{array} \rightarrow \begin{array}{c} \text{O} \\ \text{Boc} \end{array}
```
**MG, AL, ZN ORGANODERIVATIVES**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Source</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeMgCl</td>
<td>Rockwood Lithium (3M solution in THF)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>EtMgCl</td>
<td>Rockwood Lithium (2.8M solution in THF)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>c-HexMgCl</td>
<td>Rockwood Lithium (1.3M solution in THF)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>CH₂=CH-CH₂MgBr</td>
<td>Aldrich (0.5M solution in THF)</td>
<td>Up to 1L of solution in 1 run</td>
</tr>
<tr>
<td>PhMgCl</td>
<td>Aldrich, in-house generation</td>
<td>Up to 1L of solution in 1 run</td>
</tr>
<tr>
<td>t-BuMgCl</td>
<td>Rockwood Lithium (1.7M solution in THF)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>CH₂=CHMgBr</td>
<td>Aldrich (Kilo-Lab™, 1M solution in THF)</td>
<td>Up to 2L of solution in 1 run</td>
</tr>
<tr>
<td>i-PrMgCl</td>
<td>Aldrich (2M solution in THF)</td>
<td>Up to 1L of solution in 1 run</td>
</tr>
<tr>
<td>AlMe₃</td>
<td>Aldrich (2M solution in toluene)</td>
<td>Up to 1L of solution in 1 run</td>
</tr>
<tr>
<td>EtAlCl₂</td>
<td>Aldrich (Sure/Seal™, 1M solution in toluene or in heptane)</td>
<td>Up to 200ml of solution in 1 run</td>
</tr>
<tr>
<td>Me₂AlCl</td>
<td>Aldrich (Sure/Pac™)</td>
<td>Up to 50g in 1 run</td>
</tr>
<tr>
<td>Et₂Al</td>
<td>Aldrich (Sure/Pac™)</td>
<td>Up to 1L of solution in 1 run</td>
</tr>
<tr>
<td>Et₂Zn</td>
<td>Rockwood Lithium (0.1M solution in hexane)</td>
<td>Up to 1L of solution in 1 run</td>
</tr>
</tbody>
</table>

**Kulinkovich-de Meijere reaction in multi-gram scale**

120g of 3 was synthesized in 1 run
# TOXIC ORGANOTIN DERIVATIVES

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Source</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu$_3$SnCl</td>
<td>Avokado</td>
<td>Up to 500g in 1 run</td>
</tr>
<tr>
<td>Tributyl(1-ethoxyvinyl)tin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$SnCH=CH$_2$</td>
<td>Aldrich, in-house synthesis</td>
<td>Up to 20g in 1 run</td>
</tr>
<tr>
<td>Bu$_3$SnC≡CH</td>
<td>Advanced Tec</td>
<td>Up to 100g in 1 run</td>
</tr>
<tr>
<td>Bu$_3$SnH</td>
<td>Rintec, in-house synthesis</td>
<td>Up to 20g in 1 run</td>
</tr>
</tbody>
</table>

![Chemical Structures and Reactions](image)
The photoreactor designed to carry out medium-scale synthesis (10 – 50 g)
It is important to use the highly purified argon for the inert atmosphere (trap)
MICROVAWE-ASSISTED CHEMISTRY

Biotage® Initiator
Microwave Synthesizer with Accessories
for Automated Sample Processing

R1 = Alk
R2 = Alk, Ar, Het
R3 = H

MeCN, MW
KAl(SO$_4$)$_2$•6H$_2$O

in situ generated

R1
N
R2
R3
O
O
O
N
O
R2
R1
CO$_2$H
O
O
O
R4
N
R1
R2
R4
O
OH
MeCN, MW

R1 = Alk
R2 = Alk, Ar, Het
R3 = H
R4 = EWG

LIFE CHEMICALS
COMPUTATIONAL CHEMISTRY SERVICES

• Computer-aided rational design of small organic molecules against any biological target
• Drug-likeness and lead-likeness prediction, diversity calculations, 2D/3D similarity and substructure search, compound filtering by any physicochemical properties, compound clustering
• Target profiling: given a molecule, perform an *in silico* target profiling against more than 2,800 protein targets
• Scaffold hopping and fragment linking
• ADME/Tox prediction
• Design of custom target-focused libraries
• Receptor-based virtual screening (molecular docking)
• Ligand-based virtual screening (QSAR, shape similarity, pharmacophore search)
• Molecular dynamics simulation of macromolecules including their complexes with natural or synthetic ligands
• Protein structure modeling, *de novo* or by homology
COMPUTATIONAL CHEMISTRY SERVICES

Software

Molecular modeling/docking/virtual screening
  • Schrödinger
  • GOLD
  • MOE
  • SYBYL
  • DOCK
  • ICM

Cheminformatics
  • E-dragon
  • Datawarrior
  • Canvas

Homology Modeling
  • Swiss-Model server, Moldeller - homology modeling web servers
  • Orchestrar, Fugue from SYBYLX
  • Prime from Scrödinger
  • BLAST

Molecular Dynamics, Geometry Optimization
  • GROMACS MD simulation and protein structure optimization
The Key Preclinical laboratory for primary drug trials provides an advanced highly-efficient and solid framework of services to companies and academic institutions involved in pharmaceutical and biotech research. Available among our products is a variety of *in vitro* and *in vivo* tests, including:

**DRUG SAFETY**
- General toxicology
- Safety pharmacology (ICH S7A and S7B)

**SPECIFIC PHARMACOLOGICAL ACTIVITY**
- Antihypertensive
- Anti-inflammatory
- Anti-ischaemic
- Antiarrhythmic

**DRUG BIOAVAILABILITY STUDIES**

**IN VITRO AND IN VIVO ADMET TESTS**

Today Key Preclinical can expertly carry out short term oral toxicity studies and short term intramuscular toxicity studies in compliance with the **Principles of GLP** and according to the Directive 2004/9/EC and Directive 2004/10/EC, that is equivalent to the OECD Principles of Good Laboratory Practice ENV/MC/Chem (98)17. The Laboratory also meets requirements of GSTU ISO 9001: 2009 (ISO 9001: 2008, IDT). There are about 60 people on the staff of Key Preclinical, with 34 of them directly involved in preclinical drug testing.
**In vitro and in vivo ADMET tests**

It is generally known that the early stage of drug discovery involves ADMET screening to investigate such characteristics as solubility, permeability, microcomal stability and CYP inhibition that enable identifying metabolically stable and potent substances for further analysis.

At Key Preclinicals, we offer the following spectrum of *in vitro* and *in vivo* ADMET tests:

- **In Vitro Metabolism:**
  - Metabolic stability
  - Stability in plasma and buffer

- **In Vivo DMPK:**
  - Animal Pharmacokinetics

- **Drug Interaction**
  - CYP induction/inhibition

- **Permeability and transporters:**
  - Caco-2 permeability
  - Uptake and influx transporters

- **Physicopchemistry and binding:**
  - Solubility
  - Lipophilicity (logD/P)
  - Plasma protein binding
  - Red blood cells binding
  - Tissue binding
  - Microsome/hepatocyte binding

- **In Vitro Toxicology:**
  - Cytotoxicity screening
  - Genotoxicity screening (Ames test, chromatin aberration)
  - Cardiotoxicoty screening (hERG testing, Q-T interval measurement in perfused isolated Langendorff heart, drug’s anti- or proarrhythmic activity using maximal follow frequency (MFF) method which refers to the sequence of consecutive contractions of the papillary muscle following each electrical stimulus)
KEY PRECLINICALS

Additionally, a range of microbiological studies can also be provided:

• screening of potentially active antibacterial and antifungal drugs

• investigation of susceptibility/resistance of microorganisms to antibiotics and antifungal drugs

• studies of antibiofilm activity of drugs on different surfaces

• evaluation of potential drug activity on animal model of sepsis, cutaneous surgical and burn wounds, subcutaneous abscesses and conjunctivitis
Life Chemicals guarantees high quality service and flexibility

**Inquiry:** quotation within 0-3 business days

**Order:** the process is launched immediately after the order

**Synthesis (for non-stock compounds):** normally 2-6 weeks, progress reports are provided upon request

**Quality control:** high quality standards (purity of 90 – 95 % confirmed with NMR and/or LCMS)

**Delivery:** 3-7 days by FedEx to any destination (customer’s FedEx account can be used)

**Payment:** by cheque, credit card or wire transfer to the account in Germany or in Canada, payment terms are NET 30 days.

For small stock orders you can go directly to our shop at [https://shop.lifechemicals.com/](https://shop.lifechemicals.com/)
QUALITY ASSURANCE AND ORDER PROCESSING

- Structure of compounds is validated by analytical data, 400 MHz NMR and/or LCMS analysis. Analytical data is readily available upon the customer’s request.

- ISIS .db or .sdf files are enclosed with every shipment.

- Sample weights: 1 mg - 0.5 g with 0.1 mg weighing precision, mg, micromole amounts.

- Compounds forms:
  - dry powders
  - frozen DMSO solutions

- Formatting:
  - Standard 4mL, 15mm*45mm, amber borosilicate glass vials with rubber-lined plastic screw caps.
  - 96 well PP-masterblocks, Greiner bio-one ref: 780215, U-bottom 1.0ml.
  - 96 well plates, Matrix cat.# 4247, racked round-bottom tubes, 1,4 ml.

- Each plate/box of vials is barcoded and labeled to meet the customer’s requirements.
LIFE CHEMICALS GEOGRAPHY

Head office in Niagara-on-the-Lake, Canada

Life Chemicals Europe in Munich, Germany

Production site in Kiev, Ukraine

Life Chemicals USA in Orange, CT

Life Chemicals China in Tianjin

Production space: 2,500 m²

Total number of employees: Over 110, including 61 chemists (1 Prof, 11 PhDs, 35 MSc, 14 BSc)
WHY LIFE CHEMICALS?

The Company has strong and recognized position in organic synthesis and medicinal chemistry.

- Novel chemistry and highest quality
- Our product catalogue includes over 460,000 screening compounds and 12,000 in-house synthesized building blocks
- Hit resupply
- Experienced project management
- Experience in creating of discovery products (targeted libraries, FBDD)
- Developed platform (analytic labs, logistics, etc.)
- Access to literature (Reaxys, SciFinder, DiscoveryGate)
- Chemical Informatics support
- Our chemists can tackle tasks of highest complexity
- We work as a fully integrated platform to offer best products and services.
Some Facts on our Resources:

- Up to 50 synthetic chemists can be involved
- Up to 1000m² production facilities are available

Renovated building – 2000m² space

- Over 20 years’ experience in parallel synthesis, library design and medicinal chemistry
- Purification techniques:
  - TLC, NP LC (CombiFlash)
  - RP HPLC (Shimadzu)
SYNTHESIS FACILITIES

Chemistry labs are supplied with high-end equipment for organic synthesis:

- Biotage Microwave station
- Paar autoclaves
- Photochemistry lab
- Specialized facility for handling highly toxic reagents
PREPARATIVE CHROMATOGRAPHY LAB

• CombiFlash Rf (SiO2 phase) devices
• Shimadzu HPLC machines (direct phase and reverse phase columns): semi-preparative scale 0.5g/run
• Preparative Thin Layer Chromatography
ANALYTICAL LAB
Certified by ISO/IEC 17025:2005

NMR lab
Capacity: 200 $^1$H NMR spectra daily
• Varian Gemini 2000 400 MHz with an Oxford Instruments superconducting magnet
• Varian VXR-300 300 MHz
• Varian Gemini 200 MHz
  Ready for $^1$H, $^{13}$C, $^{19}$F, $^{29}$Si, $^{31}$P measurements and advanced 2D NMR techniques (COSY, NOESY, HMQC, HSQC, INADEQUATE)

LCMS lab
Capacity: 200 samples per day
• Agilent 1100
• Agilent 1200
• over 10 columns of various types

GCMS
• Agilent 7820A GC/MSD
ANALYTICAL LAB

Certified by ISO/IEC 17025:2005

- Water determination by Karl Fischer Titration
- Qualitative and quantitative determination of functional groups in organic compounds
- Qualitative and quantitative determination of salt form of organic compounds
- QC control of solvents and inorganic compounds
- Measuring Optical Activity (POLAX – 2L, ATAGO polarimeter)
- Melting Point verification
X-RAY DIFFRACTOMETER

Bruker SMART APEX II
2 Enraf-Nonius CAD-4 four-circle diffractometers
CASE STUDIES
CASE STUDIES (IN-HOUSE)

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{NH}_2 \\
\text{N} & \quad \text{F}_3\text{C} \\
\text{Ph} & \\
\text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{N} & \quad \text{F}_3\text{C} \\
\text{H} & \\
\text{CO}_2\text{H} & \quad \text{F}_3\text{C} \\
\text{CF}_3 & \\
\text{H} & \\
\text{N} & \quad \text{F}_3\text{C} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{N} & \quad \text{F}_3\text{C} \\
\end{align*}
\]
CASE STUDIES 2

Advanced building blocks synthesis project
Customer – US Big Pharma

Starting point:
• 500 novel building blocks were designed as per customer’s requirements
• A set of 100 advanced building blocks was selected by the customer

Team task (3.5 months):
• Development/validation of synthetic schemes for the 100 most challenging building blocks
• Synthesis of these building blocks weighing 25 g, with their purity being over 95%

Result:
• 86 of 100 building blocks were delivered
Starting point:
• A library to comply with rigorous criteria for lead-likeness, diversity and novelty was needed for compound collection enhancement

Team task (8 months):
• Design of the library (non-exclusive basis)
• Synthesis of key intermediates
• Synthesis of the library (10 umol, > 90 % by LCMS)

Results:
• 3,500-member library based on 15 templates was synthesized
The synthetic scheme was designed and optimized for multi-gram scale-up:

16 steps

15 steps

16 steps

31 steps

12 steps
FP 7 PROJECT

Combined Highly Active Anti-Retroviral Microbicides

EC Contribution: 12,000,000 Euros
Duration: 60 month
Starting date: 01.01.2010

Spoluka/Life Chemicals objective: to develop new CCR5 inhibitors