ACCESSING NEW CHEMICAL SPACE THROUGH FLOW CHEMISTRY

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http://www.cominnex.com
ComInnex Overview

• 25 years experience (as ComGenex/AMRI/ComInnex) in working with top pharma companies from USA-Europe-Japan

• A drug discovery service provider for the Pharma, biotech and agrochemical industries:
  - Screening compound libraries
  - Novel scaffold design
  - FTE based custom chemistry and medchem
  - Fixed fee custom synthesis

• Unique combination of technologies and know-how
  - Technology-enabled chemistries
  - Integrated production IT system
  - High throughput chemistry and purification

• Mutually beneficial partnership with ThalesNano

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Novel Technologies and Applications

- R&D award winning proprietary technology
- Wide range in terms of temperature and pressure (-70 to +1000 °C and from vacuum to 400 bar)
- Lithiation, hydrogenation, C-C and C-N cross coupling, oxidation, pyrolysis, cyclization, ozonolysis etc.

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I. Ring saturation

Escape from Flatland\textsuperscript{1} – Synthesis of Molecules with High fsp3 Skeletons

• Too many aromatic rings cause higher attrition rate in development $\rightarrow$ significant interest in molecules with lower aromaticity
• Higher fsp3 $\rightarrow$ better physical chemical properties $\rightarrow$ better chance in development
• ComInnex has the integrated technology, design platform and chemical know-how to perform these transformations

\textsuperscript{1} J. Med. Chem. \textbf{2009}, 52, 6752-6756.
H-Cube® vs. Autoclave

- **Continuous**
- Automation is easy
- High throughput rate
- \( H_2 \) is generated inside the apparatus, in situ

- **Batch**
- Automation is difficult
- Low throughput rate
- Safety issues

1. Chemo- and regioselectivity

**BATCH:** 100% conversion, low yield, side products

**H-CUBE:** 100% conversion, 100% selectivity; desired product

**BATCH:** >90% conversion, selective, but B is the main product

**H-CUBE:** 100% conversion; selective; A is the main product
2. Diastereoselectivity

- Several test reactions completed – large expertise
- Successful FTE project covering different types of disubstituted pyridines
- Several libraries designed with different $R_1$ and $R_2$ – cca 1000 piperidines produced

Pd/C: reaction is trans selective or major isomer is the trans isomer
Ru/C: reaction is cis selective or major isomer is the cis isomer
PtO$_2$: reaction is cis selective or major isomer is the cis isomer
Pd/C: reaction is cis selective or major isomer is the cis isomer
PtO$_2$, Rh/alumina,Ru/C, and Ru/alumina: similar selectivity
3. Fluorous Fragments

CF₃ on the pyridine ring

distant F and CF₃

F on the pyridine ring

Parameter optimization: catalyst, temperature ↑, contact time ↓
Selectivity 1:1 → 9:1
II. Cyclization in Phoenix Reactor

- Up to 450 °C temperature capacity
- Perform reactions in a loop homogeneously or use different cartridges for heterogeneous systems
- Perform chemistries not possible in a standard lab circumstances
- Slow reactions in seconds

Novel Heterocycle Synthesis

\[
\text{NHNH}_2 + \text{C}_8\text{H}_8\text{O} \xrightarrow{\text{AcOH/2-propanol (3:1) (0.5M)}} 200 \, ^\circ\text{C}, 75 \text{ bar}, 5 \text{ mL/min} \rightarrow \text{Product}\n\]

Isolated yield: 51 %
NMR purity: >95 %
Production of Imidazopyridine, -pyrazine and -pyrimididine Derivatives

\[ \text{Production of Imidazopyridine, -pyrazine and -pyrimididine Derivatives} \]

A: C, N
R₁: H, X, CO₂Me
R₂: Ph, CO₂Et

\[ \text{Chemical structures and reaction scheme} \]

Batch

Phoenix reactor

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III. Cyclization in Flash Reactor Plus

- The reaction stopped at the first elementary step in the Phoenix reactor
- Compound 3 is an insoluble precipitate → instrument blocked
- Decomposition above 250 °C

**VFP conditions are suitable for thermal cyclisation**
- Extreme high temperature (1000 °C)
- Low pressure (10^{-3} bar)
- Short contact time (1 s)
- First result → promising: over 30% conversion
Conclusions

Flow
- Wide parameter space, effective convection
- Quick optimization and short reaction time
- Higher conversion (for product)
- Clean reaction mixtures
- Acceptable yields
- Easy to scale up
- Clean and safe practice

Batch
- Limitations in temperature
- Long reaction time
- Heat transfer and stirring difficulties
- Lower conversion (sometimes 0)
- Complex mixture, difficult purification
- Lower yields
- Safety issues

Key Intermediate Synthesis
- Traditional chemistry steps

„Know-how“
- Technology-enabled step

Parallel Chemistry
- Library synthesis with proprietary scaffold
• The implementation of the flow technology (provided by ThalesNano) and our cheminformatics knowledge allows us to explore new chemical space

• Diverse chemical problems in batch → resolved in flow

• Flow-enabled compound design and synthesis platform promotes the diversity of our products

Do not hesitate to contact us either online or at our booth: 1321
Thank you for your kind attention!