Rapid Chemical Space Exploration – Applications from Discovery to Manufacturing

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Contents

- An Introduction to Reaction Optimization Workflows
- Reaction Optimization in Process Chemistry
- Adapting to Discovery Chemistry
- Case Examples
Solving Chemistry Across the Portfolio

- Discover Drugable Molecules
- Supply Drug Substance
- Develop Commercial Processes
- Transfer Technology to Production

How we do this in less time and at a lower cost?
Adapting to Industry Pressures

Technology must ‘fill the gap’

Workload

Resources

199X

20XX
The First Reaction Optimization Tool

- In 1998 a Process Research Technology Group was created with the aim of speeding Process Development
- The SK233 was the first tool of its kind, 10 simultaneous reactions with integrated analytics
- 1g per reaction, 10 reactions, 10-50ml volume
Despite a few successes, the general adoption of the SK233 and reaction optimization technologies was slow...

...but that was to change...

UK-427,387 was nominated as a follow up PDE5 inhibitor to Sildenafil (Viagra)
UK-427,387 Pyrazole Alkylation

- 25kg Required for Phase 1
- Parallel Synthesis Robot (PSR)
- 250mg per reaction, 50 reactions, 5-25ml volume

Issues (where to start?!)
- 30% overall yield
- 2:1 undesired : desired pyrazole
- 7 days reaction time, complex conditions (4 solids, 2 solvents)
- 5-14% undesired alkylated isolated
UK-427,387 Pyrazole Alkylation

- **New Conditions**
  
  - \( \text{Na}_2\text{CO}_3(1.1\text{eq.}) \)
  
  - \( \text{NaI} (1.1\text{eq.}) \)

  - THF / Water
  
  - LiOtBu / MeCN

  - 80°C / 6hrs

- **Before**
  
  - 1:2 \( \text{N1:N2} \)

- **After**
  
  - 30:1 \( \text{N1:N2} \)

- **Results**
  
  - 30:1 selectivity achieved
  
  - 12hrs vs. 6 days reaction time

  - Scaled to 32kg, 71% isolated yield of 99% purity

  - MeCN solvent found to be key

Q. Would this obscure hit have been found in the short time frame allowed without reaction screening technology?
Development of High Throughput Experimentation (HTE) Workflows 2002-2005

Statistical Methods

Solids Dispensing

Data Analysis

Rational Design

Reaction Platform

Fast Conclusions

Chemists

Liquids Dispensing

Data Mining

2002-2005 Investment in Technology

- By 2005 the HTE group in Process had expanded to 5 FTE’s with state of the art equipment at their disposal
- 25mg per reaction, 50 reactions, 1-2ml volume

One 2 Many

Gaseous Chemistry

Many 2 Many Weighing

2ml Reaction
Volume

2-4 minute HPLC cycle-time per sample

Fast HPLC Analysis Platform

High-throughput analytics and generic methods are critical to HTE Modular Workflows
# Application of High Throughput Chemistry Workflows Across the Portfolio

<table>
<thead>
<tr>
<th>Applications</th>
<th>Discovery</th>
<th>Process Development</th>
<th>Supply Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility Profiling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid Form Identification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution Screening</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Diagram shows workflows integrated across the portfolio, with start points indicated.
Example Workflow - Resolution Screening

- Scalable access to chiral molecules via diastereoisomeric salt formation

Resolution Coupling Protocol:
- 96 Chiral Acids or Bases
- 1 Solvent
- 10-20mg per reaction: 2g Total
- 0.5 FTE Days
- 1 Day Start to Finish per Solvent
RESOLUTION SCREENING

Resolution screening is successful in 80% of cases

Zhou, Ru; Bi, Chris; He, Mingying; Hoffman, Robert; Jalaie, Mehran; Keth, John; Kupchinsky, Stan; Ling, Tony; Lu, Jihong; Marx, Matthew; Richardson, Paul; Sach, Neal; Tran, Khanh; Barbour, Nicole; Cho-Schultz, Su. Asymmetric synthesis of Pyrrolodino-pyridine based CXCR4. Abstracts of Papers, 240th ACS National Meeting, Boston, MA, United States, August 22-26, 2010 (2010)
Example Workflow - Solubility Screening

- Isolating good quality material can be as difficult as forming the covalent bonds.
- Problematic isolations may result in large quantities of organic and aqueous waste streams and loss of product.
- Traditional Reaction Sequence:
  1. Design Reaction
  2. Run Reaction
  3. Analyse Reaction
  4. Design Work-up
  5. Work-up Reaction

- Bottom-up approach to Reaction Design:
  1. Design Reaction
  2. Run Reaction
  3. Analyse Reaction
  4. Design Work-up
  5. Work-up Reaction

- Driven by solubility screening.
Example Results of Solubility Screens

- **Objective:**
  - Map solubility of all synthetic intermediates in range of process solvents
- **HTE Workflow:**
  - 20 solvents screened as standard chosen by chemist
  - Solution saturated and liquors analysed
  - Quantitative LC

- Typically applied to entire synthesis
- 250mg-1g per screen in 0.5 Day

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility of Impurity @ RT mg/ml</th>
<th>Solubility of product @ RT mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>&lt;1</td>
<td>34</td>
</tr>
<tr>
<td>Methanol</td>
<td>14.00</td>
<td>86</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>61.00</td>
<td>15</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10.00</td>
<td>74</td>
</tr>
<tr>
<td>Acetone</td>
<td>&gt;100</td>
<td>78</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<tr>
<td>2-Propanol</td>
<td>7.00</td>
<td>15</td>
</tr>
<tr>
<td>2-Butanone</td>
<td>85.00</td>
<td>65</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>&gt;100</td>
<td>34</td>
</tr>
<tr>
<td>Ethylacetate</td>
<td>43.00</td>
<td>16</td>
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<tr>
<td>Butyl Acetate</td>
<td>40.00</td>
<td>14</td>
</tr>
<tr>
<td>t-amyl OH</td>
<td>4.00</td>
<td>17</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>&gt;100</td>
<td>36</td>
</tr>
<tr>
<td>Diisopropylether</td>
<td>5.00</td>
<td>12</td>
</tr>
<tr>
<td>Toluene</td>
<td>22.00</td>
<td>8</td>
</tr>
<tr>
<td>Heptane</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>1M HCl</td>
<td>&gt;100</td>
<td>&gt;20</td>
</tr>
<tr>
<td>1M NaOH</td>
<td>&lt;1</td>
<td>&gt;20</td>
</tr>
<tr>
<td>1M NaHCO3</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
2007 - Bringing HTE to Discovery

Reaction Optimization Projects 2002-2007

Discovery 2007
1 FTE!!

Process Projects
2002-2006
5 FTE’s

...the workflow was not designed for this throughput and was too slow...
Reaction Optimization in Process

Project Team Problem

Experiment Design

Experimental Set-Up

Reaction Analysis

Results Interpretation

Answer

Cycle 2 = 4 days
Discovery chemists want answers…

…faster and using less material compared with process development

…and they have no product markers!

Discovery
Speed
Diversity
Yield
Isolation
Scalable

Process Development
Scalable
Yield
Isolation
Speed
Diversity
Challenge over the past three years has been to speed the workflow by removing the bottle necks.

Where is the time spent?

- **Manual and slow** 50%
  - Reaction
  - Design
- **Semi-Automated and fast** 20%
  - Reaction
  - Execution
- **Semi-automated and slow** 30%
  - Analysis
  - Visualisation

These steps needed addressing.
Designing a Reaction Screen in Process

Statistical Methods

Literature Surveillance

Intelligent Reaction Design

Green Chemistry Principals

Chemists and CeN

Monodentate Phosphine PCA map

333 monodentate ligands with 28 descriptors

Transformations > Amide Couplings (Arhiral)
Wide Utility
Scalability

“Greenness”
...searching the literature on a per screen basis helps us move into the “correct” chemical space but if the chemistry doesn’t work in this initial screen we spend a lot of time searching or settling at local maxima...

...what if we moved to a more generic one-size fits all type template... that would save time but...the chemical space covered increases dramatically...

Unchartered territory

Unchartered territory

Literature Says
Start Here

Literature Says
Start Here

Catalyst

Catalyst

Base

Base

Solvent

Solvent

Large Reaction Template

Cycle 2 = 8 days

Cycle 2 = 8 days

...besides...was we ever really comfortable excluding this space?

will you ever find something new?
Sonogashira Reaction

- 161/161 references utilize \( \text{Pd}(\text{Ph})_4 \) or \( \text{Pd}(\text{P}(\text{Ph})_3)\text{Cl}_2 \)

- What have we really learnt?
  - Precedent (we knew that)

Project team report poor yields using standard conditions

Literature Search

Un-precendented
Increasing Chemical Screening Space vs. Material Demands

...discovery project teams can’t afford >500mg of material for each screen, in-fact they would like to reduce the amount required...

WE NEED TO MINATURIZE (but without diluting)

1.2ml Reaction Volume

2007 to 2011

120uL Reaction Volume

20 Reactions=100mg

200 Reactions=100mg
Reducing Scale – Air/Moisture Sensitivity

With just 0.04mg of catalyst present the workflow had to be moved into a glove box with a controlled O₂ (<10 ppm) and H₂O atmosphere (<20 ppm).
Projects by Reaction Type

- **Templated**: Buchwald Couplings, Amide Couplings, Heck Couplings, Carbynylations, Classical Resol., Alkylations, Hydrogenation, Sonogashira, Ullman Couplings, Halogenations, etc...

- **Other**: 26%

- **Flow Chemistry**: 9%

- **Library Validation**: 3%

- **Oxidation**: 1%

- **Biotransformation**: 2%

- **Buchwald Couplings**: 12%

- **Sonogashira Couplings**: 17%

- **Amide Couplings**: 13%

- **Templated**: 60%

- **Flow Chemistry**: 9%

- **Hydrogenation**: 8%
For templated chemistry (60%) the workflow is significantly faster...

...but analytical samples have increased by a magnitude...
Data Analysis, Capture and Visualisation

- Capturing data, identifying products, analysing trends and reaching quick conclusions

Rapid Resolution 1200 LC/MSD

Per sample cycle time dropped from 4 to 0.8 mins

50-500 data points per reaction screen.
100 reactions take 1.5 hrs

Spotfire Visualization with Data Display

Email report and then capture in CeN as well as in-house reaction screening database

Data to knowledge in 1 hour

combining reaction templates with miniaturization and glove box technologies has enabled a reduction in material demands and reduced screen cycle times leading to an increased applicability to Discovery Chemistry.
Examples

- Amide Bond Formations
- Carboamidation Technology
- C-N Couplings
- 25% of all reactions in discovery involve amide couplings

- Large numbers of coupling agents are commercially available
Difficult Amide Bond Formations - Discovery

60%
1. Cyanuric Fluoride
2. 2C-DMI-TFB

Selectivity

70%
1. T3P
2. 1G2MB

Electron poor amine

Amide Coupling Protocol:
36 Coupling Agents
2 Solvents, 2 Temperatures, 1 Additive
150 reactions = 90mg total (300MW)
0.5 FTE Days
2 Days Start to Finish

50%
1. (COCl)₂
2. CDMT
3. iBuCOCl
4. HATU
The amide bond remains a popular connection in drug discovery to explore SAR...

- But there are other ways of making an amide bond and a monomer analysis reveals the advantages...
Carboamidation – Accessing New Chemical Space

- **Carbonylation Screen**

- **Details**
  - Method required for primary, secondary and non-nucleophilic amines
  - 78 Conditions (0.005mmol, 1mg per reaction)
    - 12 catalyst/ligand combinations (all monomers)
    - 56 catalyst/ligand combinations (one monomer)
    - DMAC (0.03M), DIPEA (5eq.), 100C, 8Bar CO

- **Technology**
Carbonylation Library Validation

- **Carbonylation Screen**
  - CO Pressure
  - Catalyst
  - Base
  - Solvent

- **Details**
  - Take top eight ligands from initial screen and run under actual library conditions
  - 78 Conditions (0.05mmol=10mg per reaction)
    - 8 catalyst/ligand combinations
    - 3 monomers (3eq.)
    - DMAc (0.1M), DIPEA (5eq.), 100C, 4Bar CO

- **Comments**
  - SM is not soluble at this concentration at 25C. Solids weighing robot is used to weigh 80 x 10mg

- **Conclusions**
  - Ligand system works across all demonstration monomers
  - Library 1 = 88 designed products
  - 82 / 88 achieved = 93% success rate @ 0.05mmol scale. How would acid compare?
  - 500 products have since been prepared using these conditions (2 weeks)
Suzuki Optimization

%Area UV 80%

MeOH / CsF(aq.) / Pd-132 / 80°C / 18hrs

Original Conditions

Product

Des Bromo

Screen Design

1/96 conditions gave >80% in-situ yield
MeOH, CsF and Pd-132 are critical. Three factor interactions are hard to find. One factor at a time optimizations won't work here.

Request to Results Cycle Time = 1 day
Scaled to 200 mg, 90% isolated yield

Request to Registration Time = 2 days

Issue
- Team tried DME / H₂O / Pd(dppf)₂Cl₂ / 80°C but gave only 50% conversion after 2 days.

Results
- 1/96 conditions gave >80% in-situ yield
- MeOH, CsF and Pd-132 are critical. Three factor interactions are hard to find. One factor at a time optimizations won’t work here.
- Request to Results Cycle Time = 1 day
- Scaled to 200 mg, 90% isolated yield
- Request to Registration Time = 2 days
Conclusions

* KNOWLEDGE PER GRAM PER UNIT TIME *

- Maximize information per reaction
- Minimize material consumption
- Minimize time to explore any given chemical space

* Using HTE Workflows, optima within a given parameter space can be quickly identified to focus resource at any stage across the portfolio*
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