Activating checkpoints to selectively kill cancer cells

Designing test plates with maximal information content and diversity for the development of library protocols
Jean E. Patterson, Ying Zhang, Andrew Smellie, Daming Li, David S. Hartsough, Libing Yu, and Carmen M. Baldino.
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Development Workflow for High-Throughput Chemistry Libraries

- Library Design
- Explore Chemistry
- Test Plate
- Qualify Reagents
- Pilot Runs
- High Throughput Synthesis & Purification
The Challenge

Library Design  Explore Chemistry  Test Plate  Qualify Reagents  Pilot Runs  High Throughput Synthesis & Purification

Property Y

Which test compounds predict?

Property Y

Initial Virtual Library

Production Library
How do I design a test plate?

Need to predict how final library will behave
- Production library overlaps with virtual library, but exact compound set is not yet known
- Best estimate is a small, diverse set that represents large virtual library
- Represents behavior of multiple, unrelated properties
  - Product LogD or LogP
  - Product Molecular Weight
  - Reagent Reactivity
  - Reagent and Product Solubility
  - Reagent Availability
- Prior to complete procedure optimization
Reagent reactivity can be described by “binning”

Assumption: Reagents with similar structural features will have similar reactivity

Many approaches
Med chemists’ “eye”
Tanimoto coefficients
Daylight fingerprints
Many others…
Automated Binning Tool

- Pipeline Pilot Interface
- Common reactivity bins defined by chemists (SMARTS pattern matching)

  *Primary, secondary, aromatic, heteroaromatic, aliphatic, benzylic, cyclic, EDG, EWG, hindered, tertiary N, aminoalcohols, aminoacids, salts, racemic*

- Sorts reagents in structural order (minimum spanning tree algorithm)
- Excel output of structures, bins, and summary histogram

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User-Friendly Interface in Pipeline Pilot

Chemist inputs list of reagent smiles and identifiers
Flexible Excel output

- Sorted in structural order
- Can resort by bin of interest
- Summary gives concatenation of all bins
Histogram output focuses development efforts
Visualization of Bins

Bins can be merged with other library design data for powerful, interactive visualizations.

- Simple Pipeline Pilot protocol
- Merge library design data (automatically generated from MapMaker™) and data from automated bin tool
• Ability to interactively deselect reagent bins facilitates development
• Reagent reactivity, logP, and MW data – how to get others?
Many properties considered in design criteria

- Product LogP – library design (MapMaker™)
- Product Molecular Weight – library design (MapMaker™)
- Reagent Reactivity – bin (automated PP tool)
- Product LogD
  - Related to logP, but varies with pH
  - Correlates to retention time in high-throughput purification
  - Calculated property
- Reagent and Product Solubility - experimental
- Reagent Availability – what’s on the chemists’ bench (Reactor™)
Design Strategy

- Automate diversity with respect to calculated properties
  - LogP and Molecular Weight
  - LogD – should be diverse if logP is diverse
- Let chemists influence design with respect to non-calculated properties
  - Reagent Reactivity (guided by bins)
  - Reagent and Product Solubility
  - Reagent Availability
- Display design diversity and allow for easy modifications by users
To use the Diverse Design with Preferred Reagents with a Pop-Up selector:
1) Export a csv file from your Spotfire file
2) Input your csv file in "Spotfire CSV file" below
3) Change the # of molecules below, if you want
4) Hit the green Go arrow (above in menu bar)
5) Choose the reagents you are willing to use in your design when menu pops up
6) After Spotfire opens up, close the Details on Demand window, and apply template
   (K/PK/functional/ATP Spotfire Template/New ATP template)
7) Manually edit selections in Spotfire, if you want

For more help, contact Jean Patterson

Test Plate Design Tool

Diverse Design with Preferred Reagents (Pop-up Selector)
This protocol will choose a diverse set of reagents based on user input (via pop-up menu) of which reagents are preferred. User can input combi or non-combi crosses exported out of Spotfire files. This protocol supports up to 4 reagent lists. User can change # of molecules selected in parameter window.
Selection Window allows users to influence design

- Users eliminate reagents unwilling to use in design
- Next, diverse set chosen wrt logP and MW
Diversity can be viewed in Spotfire

- Selected test compounds are triangles against all virtual library
- Scatter plot toggles between properties – logD, logP, MW
- Color by reagent bins

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Design can be modified easily in Spotfire

- User can mark new records in the appropriate space
- Reagent/product structures viewable in Details-on-Demand window
Test Plate Design Workflow

1. Library Design
2. Explore Chemistry
3. Test Plate
4. Qualify Reagents
5. Pilot Runs
6. High Throughput Synthesis & Purification

- Reactor™ & MapMaker™
  - Enumerated product SMILES
  - LogP, MW, calculated properties
  - Automated Spotfire output

- Automated Bin Tool (PP) & Merge Bins (PP)

- Test Plate Design Tool (PP) & Spotfire visualization/edit
Conclusion

- Test plate design is crucial to the successful development of production-friendly high-throughput chemistry.
- Test plate design is a challenging balance of many, non-orthogonal design constraints.
- A flexible design process has been developed that involves library design data, reagent binning, Pipeline Pilot protocols, and Spotfire visualizations.
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Abstract

Designing test plates with maximal information content and diversity for the development of library protocols Jean E. Patterson1, Ying Zhang1, Andrew Smellie2, Daming Li, David S. Hartsough3, Libing Yu2, and Carmen M. Baldino4. (1) Department of Chemistry, ArQule, Inc, 19 Presidential Way, Woburn, MA 01801, (2) ArQule Inc, 19 Presidential Way, Woburn, MA 01801, (3) Informatics and Modeling, ArQule, Inc, 19 Presidential Way, Woburn, MA 08101, (4) Chemistry Department, ArQule Inc, 19 presidential way, woburn, MA 01801

The design of test plates used to develop a parallel synthesis library often has multiple, competing constraints such as a wide range of physico-chemical properties (molecular weights, logP, logD, solubility, HPLC retention times, etc.), structural diversity, and practical limitations such as reagent availability or reactivity that need to be taken into account. At ArQule, we have developed a test plate design process that involves reagent binning, automated Pipeline Pilot protocols that allow chemists maximum flexibility in choosing preferred reagents, and standardized Spotfire visualization tools that enable chemists to interactively view the design diversity and other information with respect to the virtual library.

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