ACCELERATING SYNTHETIC CHEMISTRY: REMOVING THE PURIFICATION BOTTLENECK

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ABSTRACT

High quality purification is at the heart of any successful synthetic protocol and has always been a rate limiting step in the new molecular entity discovery process. Typical technologies employed have either limited resolving power (Flash Chromatography, TLC) or excessive complexity (Mass-directed HPLC). Rilas Technologies' scientists have developed a universal purification process for compound library purification. This process draws on the years of experience of our staff and has been utilized to purify thousands of compounds. It harnesses the purification power of Mass-directed HPLC in a simple, easy to use format enabling medicinal chemists to quickly obtain pure compounds for further testing. The process starts with a set of standard analytical runs from which the user can derive an effective preparative method. This poster describes the protocols used and discusses recent results obtained with one project's samples.

OUTLINE

Successful drug optimization processes minimize the time between idea generation and biological testing.
At the present time synthetic steps and purification steps are optimized independently. Post-synthetic purification is not part of the synthetic route planning and low performance purification techniques are frequently employed.
The Rilas process uses a simple collection of exploratory analytical methods to guide the selection of an appropriate preparative method. These general methods can be used independent of instrument platform and are applicable regardless of synthetic route selection.
The Rilas process has been used on thousands of samples to date in each case eliminating purification as a bottleneck and boosting medicinal chemist's productivity.

PURIFICATION AND THE DRUG OPTIMIZATION PROCESS

- Fully optimized synthetic processes are often times combined with low to medium performance work-up procedures. Time consuming and hard to apply techniques limit opportunities for parallel compound creation.
- Sub-optimal synthetic routes can create mixtures which fail testing due to lack of purity from low performance purification techniques.
- High performance purification techniques are not routinely employed due to perceived complexity.
- Expensive automated purification platforms sit idle due to this perception.
- A clear opportunity exists to adapt these platforms for non-expert users.

THE R&D CHEMIST'S CHALLENGE

- Reduced staffing and investment with increased demand on productivity
- Reliance on low to medium performance techniques for purification
  - Flash
  - TLC
- Access to "experts" when high-performance techniques are needed

MODERN SYNTHETIC PROCESS

- Incorporates the latest advances in synthesis
- 100s of compounds can be synthesized in parallel and purified within days
- Allows the chemist to make all the compounds he/she wants
- Outcome and quality of compounds are less dependent on the chemists' individual talent and experience

Dramatically increases the burden on post-synthesis purification techniques

CONCLUSIONS

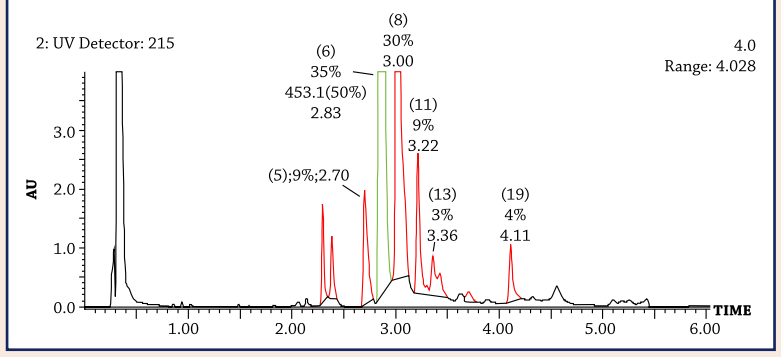
- Mass directed high-performance chromatography should be the routine choice for purification of organic compounds
- This requires close collaboration between purification scientists and organic chemists - before the synthesis starts
- Purification should be considered as a key synthetic step
- The productivity of chemistry R&D will not improve significantly until there is a widespread acceptance and use of HPLC/MS and SFC/MS by organic chemists

REMOVING THE BOTTLENECK: THE RILAS PURIFICATION METHOD

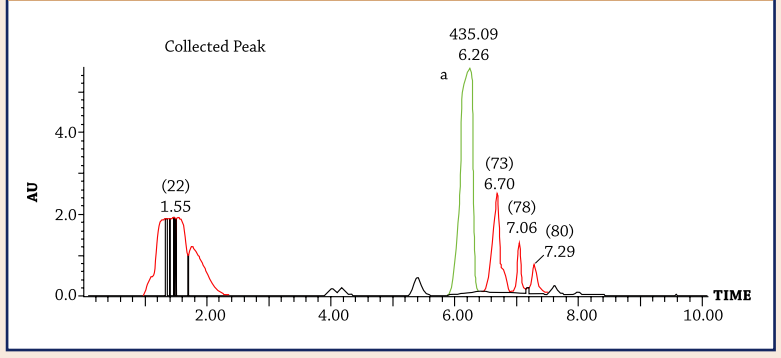
- Samples dissolved in DMSO
- Pre-purification Analysis: 6 minutes
- Selection of focused prep gradient: 2 minutes
- Run preparative method: 10 minutes
- Post purification QC of fractions (2 to 4 per sample): 6 minutes per fraction
- Drying of fractions: 4-6 hours
- Final QC of dried compound: 6 minutes

24 compound library can be purified and ready for biology in under one day

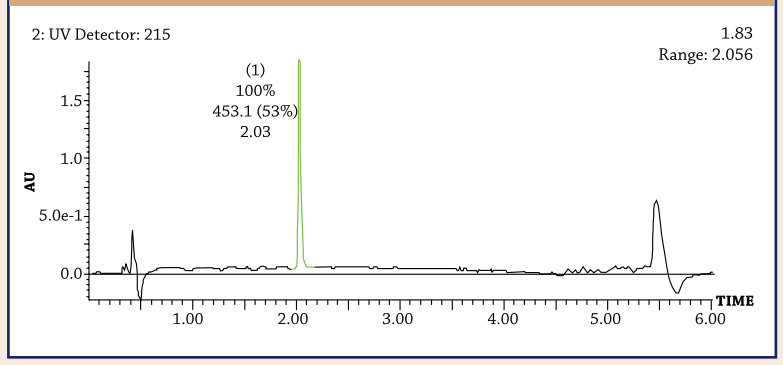
PRE-PURIFICATION QC



MASS-DIRECTED PURIFICATION



FINAL QC



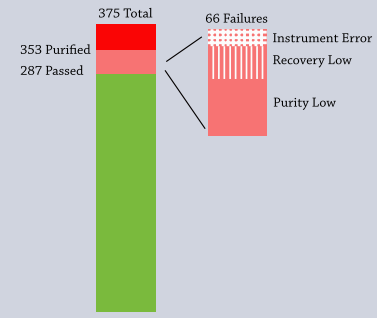
CASE STUDY

Case 1

375 randomly selected final compounds were purified according to the methods above. The passing criteria for each compound were:

- >10umole recovered
- Purity >95%

>75% success rate even though in each case, no structural information was available on the individual compounds



Case 2

In a more recent example, a 240 compound library to a particular target was synthesized and delivered to Rilas personnel for purification. Within three weeks each compound in this library was purified, final QC performed and compounds formatted according to the project specifications. In total, 204 of the 240 compounds passes quality criteria and have been registered. This was all accomplished – from library design to registration – in a five week period. Such a process could take as long as 6 months without employing these advanced purification tools.

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