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Expanding the medicinal chemistry synthetic toolbox

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A small number of synthetic reactions comprise a large percentage of the reactions used in medicinal chemistry programs.[1] Expanding the medicinal chemistry synthetic toolbox with new synthetic methodologies facilitates the production of structurally diverse and functionalized compounds, and encourages a mind-set change from "what one can make" to efficiently making the right compound at the right time.It also improves scalability from milligrams to hundreds of kilograms for production purposes.

What are robust reactions?

In drug discovery "robust reactions" are reproducible chemical transformations with the following characteristics:

- Provide structures relevant for drug discovery
- Technically straightforward (no special equipment needed)
- Moderately sensitive to reaction parameters
- Broad applicability (also with polar substrates)
- Broad availability of starting materials and reagents
- Broad functional group tolerance including polar functionalities
- Time for delivery of the target compounds is reasonably short
- Simple operational procedure (minimal training and support)
- Low-risk reagents to comply with often onerous local safety rules.

Cost, environmental impact and ready scalability can also influence a chemist's choice of reactions.
The eight most frequently used[1] robust reactions[2] are shown to the right. The relative abundancies of each reaction are shown in numbers, accordingly (from the right up to left down): GVK bioactive products,[3] 2014 medicinal chemistry literature,[1] pharma patents,[4] array syntheses,[5] lead optimization[6] and process chemistry applications[7]

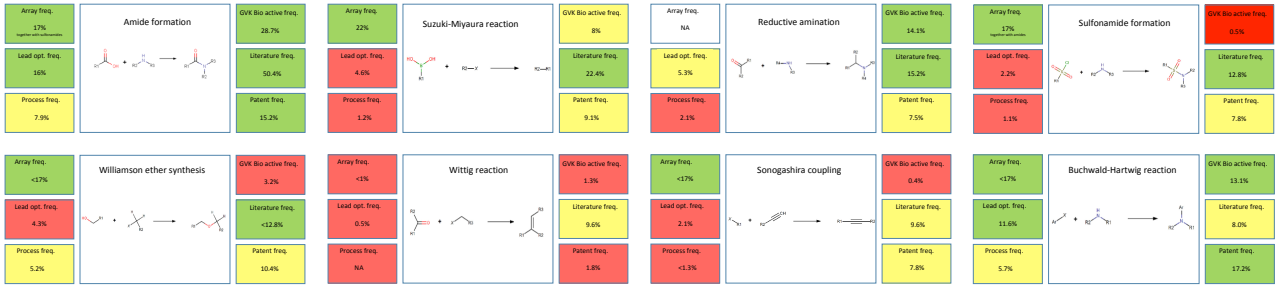
Diversification strategies

Robust late stage functionalization (LSF) can be a very useful drug design strategy. Although similar molecules often show similar properties, small changes can lead to profound influence on activity and properties.[8,9] Strategic hydroxylation,[10] fluorination,[11] methylation[12] and introduction of "necessary nitrogens" [13,14] are examples where further synthetic innovation can be highly impactful.

The poster is available for download as part of the following publication: Boström, J, Brown, D. G, Young, R. J., Keseru, G. M. "Expanding the medicinal chemistry synthetic toolbox", Nature Reviews Drug Discovery, 2018. https://www.nature.com/articles/nrd.2018.116

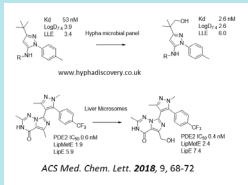
Boxes are colored by the frequency of the reaction:

<5% is red, between 5-10% is yellow and larger than 10% is green. Patterns suggests discordance between drug discovery stages.



Tactic 1: Hydroxylation

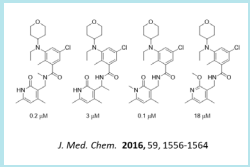
Hydroxylation can for example provide improved activity, selectivity, solubility and lipophilicity. Reduction in lipophilicity can improve metabolic clearance, although increased rates of Phase II metabolism (e.g. glucuronidation) can occur. Quite a few chemical and biochemical and hydroxylation methods are emerging.



ACS Med. Chem. Lett. **2018**, 9, 68-72

Tactic 2: Methylation

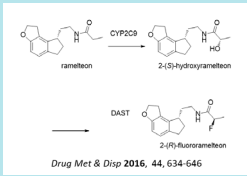
Strategic methylation can produce compounds with pronounced improvements in activity, safety and DMPK properties.
New late stage methylation methods with regio- or stereochemical control could have great utility for this purpose.



J. Med. Chem. **2016**, 59, 1556-1564

Tactic 3: Fluorination

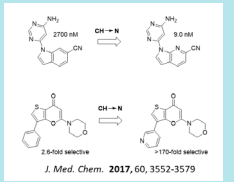
Aromatic fluorination is a common strategy to reduce metabolic liabilities and improve biological activity. The fluorine can serve to blocks C-H "hot-spots" susceptible to P450 oxidation. Aliphatic fluorines can reduce lipophilicity, modulate the pKa of ionisable centers and add conformational rigidity to structures.



Drug Met & Disp **2016**, 44, 634-646

Tactic 4: Necessary nitrogens

The ubiquity of nitrogen heterocycles in drug molecules reflects their importance in molecular recognition and property modulation.[5]
New methods compatible with the presence of aromatic nitrogens in intermediates, enables the production of diverse and functionalized hydrophilic compounds.



J. Med. Chem. **2017**, 60, 3552-3579

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