Compound Quality in Medicinal Chemistry: Considerations Beyond Molecular Properties

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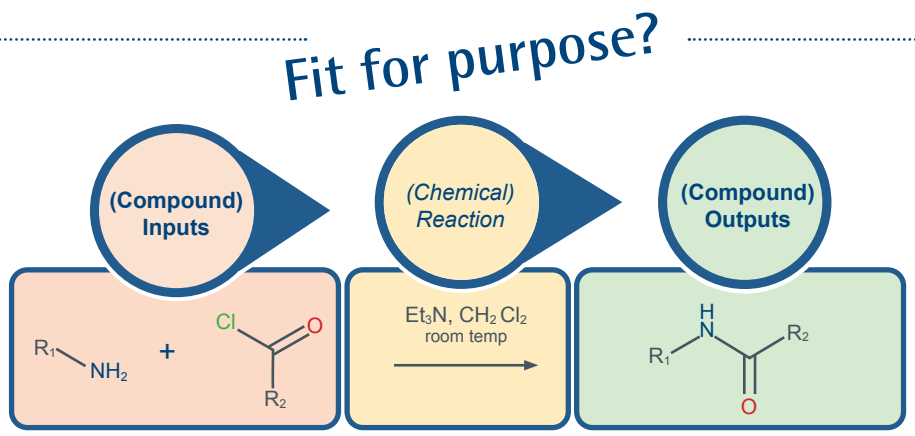
Monitoring and improving the quality of the compounds screened in drug discovery projects is a concept familiar to all medicinal chemists. The term 'quality' usually refers to an assessment of the molecular properties of the compound, and how they relate to enhancing the likelihood of the compound becoming a drug (e.g. by application of Lipinski's rules or related analyses). We propose that there is a more fundamental and important consideration; the concept of 'quality' also refers to the *provenance of the compound*, i.e. how it was selected for synthesis, how that process was carried out, and how a successful outcome was verified. We suggest that these simple-sounding operations, although apparently obvious to any chemist, can potentially be overlooked, and that it is fundamentally important to both consider them, and evidence that, for ALL compounds prepared, irrespective of the modality or discovery strategy.

1. CONTEXT:

Compounds tested in biological assays are usually the products of a chemical reaction. By definition, each reaction has inputs (reagents, starting materials) and outputs (desired products, side products, reagent by-products) along with solvents, catalysts, reaction vessels etc., which facilitate the desired transformation, but are intended (or expected) to remain unchanged. Process chemists are well accustomed to consideration of these aspects, but chemists working on earlier stage projects (Hit-to-Lead, Lead Optimisation) may pay less attention to apparently obvious (but potentially problematic) variables.



2. DATA OVERLOAD:

Chemists have access to many tools to facilitate compound design and synthesis. They select what in their opinion are the best starting materials (e.g. most cost / time effective) along with the reaction conditions which seem likely to effectively deliver the desired product(s). Huge repositories of publicly available analytical and characterisation data exist to facilitate comparisons for identification purposes (e.g. CAS references > 190 million organic & inorganic substances, ZINC15: > 230 million compounds, e-Molecules: 24.6 million screening compounds and 9 million building blocks). Selecting the best compound inputs (I) and suitable chemical reactions (R) to give a particular compound output (O), and ensuring that all information, individual data points and parameters used are fit-for-purpose is critical. However, the huge size of this data set may present an 'information overload' challenge for chemists, encourage assumptions to be made, hinder effective decision making, and influence the outcome.

3. SELECTION BIAS:

The assumptions (or bias) made may be correct, or ignoring them may have no significant consequence. However this may not always be the case. For example, the wrong building block (input) may be selected, or the chemical reaction used may be sub-optimal, for reasons which are not immediately obvious. Chemists usually anticipate this type of random error occurring from time-to-time; it's put down to experience, and they use one of several possible back-up options to ensure success in obtaining the desired compound output. However, the situation is potentially more complex than this, and all the potential assumptions may not always be factored into the decision-making process. Negative consequences can result e.g. wasted time, financial loss and potential pursuit of the wrong direction or lead series for a project. Worst case scenarios could include problems with late-stage compounds, issues with data reproducibility or retractions of papers.

	Variable	Potential consequence(s)	Possible solution(s)
Input	Is the reagent supplied as stated on the bottle label? Could it have been labelled wrongly, or become contaminated by a previous user?	• Failed reaction • Wrong product prepared / isolated • Safety issue	• Check data sheet • Independent analysis at point of receipt / use
	Isomers (regio, geometric, chirality etc) of the reagent are as stated on the bottle / vial [1]	• Failed reaction • Wrong product prepared / isolated	• Independent analysis at point of receipt / use
	How long has the bottle of reagent sat on the shelf in the storeroom, and under what conditions?	• Failed reaction • Unexpected low yield	• Stock room logs • Independent analysis pre-use
Reactions	**Are the reaction conditions described in a paper as producing 85% yield of product correct**, or was it a 'one-off' best case? [2]	• Lower yield than stated • Loss of starting material • Failed reaction	• Adopt same approach as biology with 'n=3' technical replicates
	Are the **components stable** under stated conditions? [3,4]	• Failed reaction • Failure to isolate desired product	• Careful monitoring
Output	Has structure been assigned **accurately** by paper / patent authors and/ or has all **necessary analytical data been used and interpreted correctly?** [5]	• Wrong compound tested • Inaccurate SAR • Project direction changed	• Independent confirmation of structure / regiochemistry using in-house data with no inherent assumptions
	Is the isolated product a free base, salt, hydrate or combination thereof (despite what may be stated in a procedure)	• Unexpected physicochemical properties • Incorrect stoichiometry calculations	• Enhanced analysis, (e.g.) elemental / combustion
	How sure can one be that **there are no undesired, low-level and potentially problem-causing impurities in any 'purified' and isolated sample(s)?** [6]	• Failed reaction • 'Surprise' reaction(s) • Unexpected or erroneous screening results	• Use enhanced purification and more stringent / targeted analysis

4. SOLUTION:

We propose that generating data (evidence) to confirm an assumption (or bias) should be undertaken more frequently and we should rely on 'data not dogma', even if the answer may seem obvious. The potential impact of being wrong may have detrimental consequences for a project. A wide range of variables and associated assumptions exist – each with multiple potential pitfalls, but usually having simple solutions to mitigate them. A non-exhaustive selection of these variables, common assumptions made, potential consequences and possible solutions are provided in the Table, categorised into Input / Reaction / Output, along with publications of relevance to each.

This list is intended to provide some food for thought and illustrate common assumptions that can be made, or where bias can arise during the synthetic process.

AVOID ASSUMPTIONS! Key variables to actively consider before, during and after any synthetic procedure:

INPUT: verify reagent ID and quality

REACTION: verify procedure suitability and information quality

OUTPUT: verify product ID and quality

References:
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