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MCRs: changing the chemists' mindset ▼

In an excellent Drug Discovery Today article [1], Weber puts a convincing case for the combined use of multi-component reactions (MCRs) and *in silico* evolutionary selection in drug discovery. This appears to be a marriage of complementary approaches, with the efficiency of MCR enabling synthesis to be conducted on a comparable timescale to the computational assessment. As the author states, MCRs are not new but the systematic use of this chemistry in a directed manner for drug discovery is only just emerging. However, although the word 'multi-component' now frequently appears in combinatorial literature, the actual chemistry involved is remarkably limited, not extending much beyond the Ugi and related reactions and cyclo-addition chemistries. Thus, for all the potential, this paucity of available chemistries places considerable limitations on the structures that are currently accessible by the MCR approach.

This is not an inherent flaw in the MCR concept but rather a result of the lack of basic science that lies behind MCRs. There are still comparatively few researchers working on the understanding and development of new MCR processes, which might not be simply a result of the inherent chemical challenges of MCRs (which are considerable), but a result of the chemists' mindset that synthesis must be performed in a step-wise manner. The main difficulty with MCRs is obtaining a predictable outcome from the combination of several reactive species. To date, this is most easily achieved by selecting MCRs with a mechanism that enables all reagents to be added simultaneously, but a more general approach will be by physical segregation or the introduction of each reagent at the appropriate time.

Several new technologies, including the use of solid-supported reagents [2] and micro-reactor chemistry [3], appear to offer exciting potential to address this problem. In addition, other under-used techniques, such as microwave-assisted [4] and enzymatic synthesis, could enable access to reaction conditions that are not available to standard chemistry, from which new or controllable MCR processes might emerge. However, all these approaches need rigorous fundamental examination, probably best conducted from outside a drug discovery environment and on an academic basis. Not until the repertoire of basic MCR understanding reaches a level similar to that of standard organic chemistry will MCR be raised beyond a niche synthesis strategy.

A particularly exciting prospect is the development of a continuous synthesis and screening process in contrast to the disconnected approach that is universally employed at present. If MCR synthesis were placed in an environment that enabled screening to be conducted on the same platform, and possibly concurrently, a genuine evolutionary approach might arise [5]. Thus, from the huge diversity pool that MCRs in theory can generate, only those compounds of biological interest could be selected for enrichment, identification and progression. Such a 'chemical SELEX' (Systematic evolution of ligands by exponential enrichment) concept, might seem far-fetched, but it is almost impossible to imagine without using one-pot MCR to perform synthesis.

If classical organic synthesis is considered as travelling by car, MCR chemistry could be thought of as travelling by plane – it is much faster but, although you can get close, it does not often take you to your final destination. More fundamental science is required to both increase the genuine diversity of the pool that MCRs can generate and to enable practical access to that pool.

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