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Medicinal chemistry matters – a call for discipline in our discipline

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Medicinal chemistry makes a vital contribution to small molecule drug discovery, and the quality of it contributes directly to research effectiveness as well as to downstream costs, speed and survival in development. In recent years, the discipline of medicinal chemistry has evolved and witnessed many noteworthy contributions that propose and offer potential improvements to medicinal chemistry practice; however, the impact of these ideas is limited by their acceptance and deployment into everyday activity and, as a result, the quality of medicinal chemistry remains variable. For the good of the industry and the medicinal chemistry discipline, there is a need to move from retrospective learning to prospective control of medicinal chemistry practice to improve cost effectiveness, probability of success and survival rates.

The discipline of medicinal chemistry, deliberately defined broadly here as the design and synthesis of novel molecules for biological knowledge creation and medicinal applications, makes a major contribution to the identification and development of drugs. Medicinal chemists make direct intellectual and experimental contributions during the research phase of drug discovery. Additionally, design and selection decisions made by medicinal chemists in the discovery phase can cast a long shadow downstream onto drug development and can manifest as safety, solid state and formulation challenges (and, therefore, time and cost penalties) many years later.

In recent years, driven by the assembly, availability and analysis of broad data sets, the scientific basis of medicinal chemistry has gained a more firm footing and, based on that platform, greater insights into how to enhance the practice of medicinal chemistry have been gained. As a result, there have been many excellent published ideas, suggestions and proposals to improve the performance of medicinal chemists and to enhance their contribution to drug discovery. Moreover, many of these ideas are similar to, build on, or are compatible with, each other. Indeed, the discipline of medicinal chemistry was recently described as 'mature' and incremental [1].

Therefore, one might imagine that medicinal chemists would respond to these ideas and signposts, and begin to display some convergence in how they go about their scientific endeavours. However, recently published analyses of compounds made by chemists [2–4] from across a range of companies strongly imply that medicinal chemistry directions and approaches remain variable and heavily influenced by company norms. This holds true even after correcting the analyses for the demands of different biological targets [3]. This intriguing finding strongly suggests that local practices have a big impact on medicinal chemistry effectiveness.

In this article, I briefly highlight some of the main recent suggestions and ideas for improving medicinal chemistry practice and, through use of an illustrative example, I suggest that prospective implementation and application of good practices have the potential to improve greatly medicinal chemistry success rates and performance.

Many excellent contributions

A comprehensive review of all proposals for enhancing medicinal chemistry is beyond the scope of this article, but there have been several relatively recent, important contributions that have had the potential to shape how practitioners think about and execute medicinal chemistry. The following highlights are all aspects that, in my own experience, have been beneficial to embrace and

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implement. For example, the whole area of property-based design, propelled to the fore by Lipinski's Rule of 5 for absorption [5], but underpinned by good physicochemical principles, such as the fundamental importance of lipophilicity [6,7] to drug disposition and other properties, including safety [2,8], has become well established. These foundations were built in several directions, such as: (i) the description of ligand efficiency [9], which helped medicinal chemists see the value in low molecular weight (MW), low affinity start points [10], more widely encouraged the practice of deconstructing a larger hit, and introduced phrases such as 'lead-like' [11] and 'molecular budget' to one's vocabulary; (ii) ligand lipophilicity efficiency (LLE, also sometimes referred to as LipE) [2,9,10,12], which steers the practitioner away from one-dimensional optimisation and the pursuit of affinity through increasing lipophilicity [13] and has been exercised in some groups as a strong driver for, and indicator of, medicinal chemistry quality; (iii) escaping 'flat-land' by introducing sp3 centres and chirality [14], the value of which can be directly visualised when tracking LLE because enantiomers often differentiate in LLE analyses owing to differentiated potency for the same lipophilicity [15,16], in effect countering the view that chirality was an unnecessary complication to be avoided; (iv) then, latterly, the combination of these simple concepts into high probability space [17] or a 'Golden triangle' [18] in which low MW and low lipophilicity are combined to create atom-efficient hard-working molecules with higher probability of success.

Such guidelines and probabilistic approaches are helpful in describing where one might wish to end up, but there have also been useful contributions that help the practising medicinal chemist navigate to that destination by design. Structured experimental design [19] and 'sparse arrays' (http://cisrg.shef.ac.uk/shef2010/talks/67.pdf) enable the structured design of sets of molecules to answer hypotheses with the minimum number of molecules, and advances in computational molecular description have enabled rapid identification of matched pairs [20], such that traditional structure–activity relationships (SAR) can now be described on a quantitative, statistical basis [12]. Dramatic improvements in easy-to-use data visualisation [21] and desktop protein modelling (the value of which has been enhanced with more routinely accessible protein structures) have enabled medicinal chemists to explore more thoroughly their data and steer their new ideas [22]. Even medicinal chemistry knowledge has been capitalised on and converted into automated idea generation with the advent of Drug Guru™ [23].

As the scientific discipline of medicinal chemistry has evolved, so too has the organisational approach to the conduct of the science itself. Medicinal chemistry groups were typically organised in the image of the academic research groups from which their members were drawn and, therefore, work was broken down into individually allocated and executed scientific activity. In recent years, such familiar, long-standing organisational models have been scrutinised and, as a result, working practices (such as lean sigma) from non-scientific domains have been adapted and introduced into the lab environment [24,25]. Of course, there has also been a rise in outsourcing of parts of the medicinal chemistry contribution.

If these ideas were genuinely beneficial and generally useful, and if they were integrated together and implemented effectively, on the face of it, more and better ideas could be produced (e.g. Drug Guru, structure-based design), chemical space could be navigated in a more structured manner [e.g. LLE, ligand efficiency (LE) and matched pairs], towards a more clearly defined destination (property-based design), all executed in a more effective organisational model (e.g. Lean). As a result, it might be possible to dramatically improve how effectively the medicinal chemistry contribution to drug discovery is delivered.

Medicinal chemistry philosophy makes a difference

Leeson and St-Gallay's recent comprehensive analysis of patented compounds from several companies [3] is perhaps the most robust illustration that where one works is a major factor in the style and direction (and, more controversially, the quality) of medicinal chemistry. Although this cross-company analysis is unable to detect it, it is probable, and often informally acknowledged, that even more local (such as site-to-site differences within an organisation) drivers and conditions set by local scientific leaders and managers also have a major bearing. Having been part of a multi-site organisation, and having also moved from one organisation to another, I recognise and have witnessed such differences in organisational medicinal chemistry drivers and priorities. These informative retrospective analyses observe differences in compounds made, and the authors speculate that project outcomes could be affected. However, at a recent conference (16th RSC-SCI Medicinal Chemistry Symposium, Cambridge, UK, September 11–14, 2011), a case study was presented by Phil Sanderson from Merck (http://www.merck) that illustrated clearly how the outcome was directly affected by medicinal chemistry strategy and choices, and it is instructive to highlight and examine this case study for this reason.

This single case study describes how different medicinal chemistry drivers, applied to the same start point, resulted in dramatically different destinations and outcomes. No criticism is intended. Instead, the authors of the work deserve credit for sharing their experiences for the benefit of the medicinal chemistry community, and many congratulations on the ultimate identification of two 'beautiful' candidates.

The case study is of the medicinal chemistry efforts of optimising a hit to a candidate allosteric Akt inhibitor for cancer treatment. The two distinct phases of the chemical campaign are laid out schematically in Fig. 1. In the first phase, the random screening hit was weakly active and the initial strategy focused on replacing the primary amine with a diverse collection of functionalised amines, which in turn necessitated the deletion of the gem-dimethyl group [26]. (As we will see, the decision to delete the gem-dimethyl group in pursuit of synthetic ease was pivotal to the resulting medicinal chemistry path and outcome.) Hundreds of compounds were made and potency was improved. However, the series was found to suffer from poor solubility, oral pharmacokinetics and human Ether-à-go-go-Related Gene (hERG) activity [27], presumably because of poor physicochemical properties, such as high log *D* and high MW. After expending considerable effort without resolving the problems, the team went back to the drawing board and re-evaluated the initial hit. This time, the core bicyclic moiety was modified and the synthetically more demanding gem-dimethyl functionality was retained and modified and, once again, potency was dramatically improved. With further small structural changes, two candidates emerged (MK2206 and MK8152), at least one of which is progressing in the clinic. The speaker posed the open question: 'who would have explored the gem-dimethyl earlier?' This inviting question, which was also picked up in the blog 'In the Pipeline' (http://pipeline.corante.com/archives/2011/09/12/from_the_rscsci_symposium_a_medchem_anomaly.php) is, I think, at the heart of the question of medicinal chemistry practice. Is it really true that no-one (or even only a few of us) would have explored the gem-dimethyl earlier? Importantly, even if it was true in 2005, is it still true now? If so, what unseen forces steer people in directions that prove unsuccessful and,

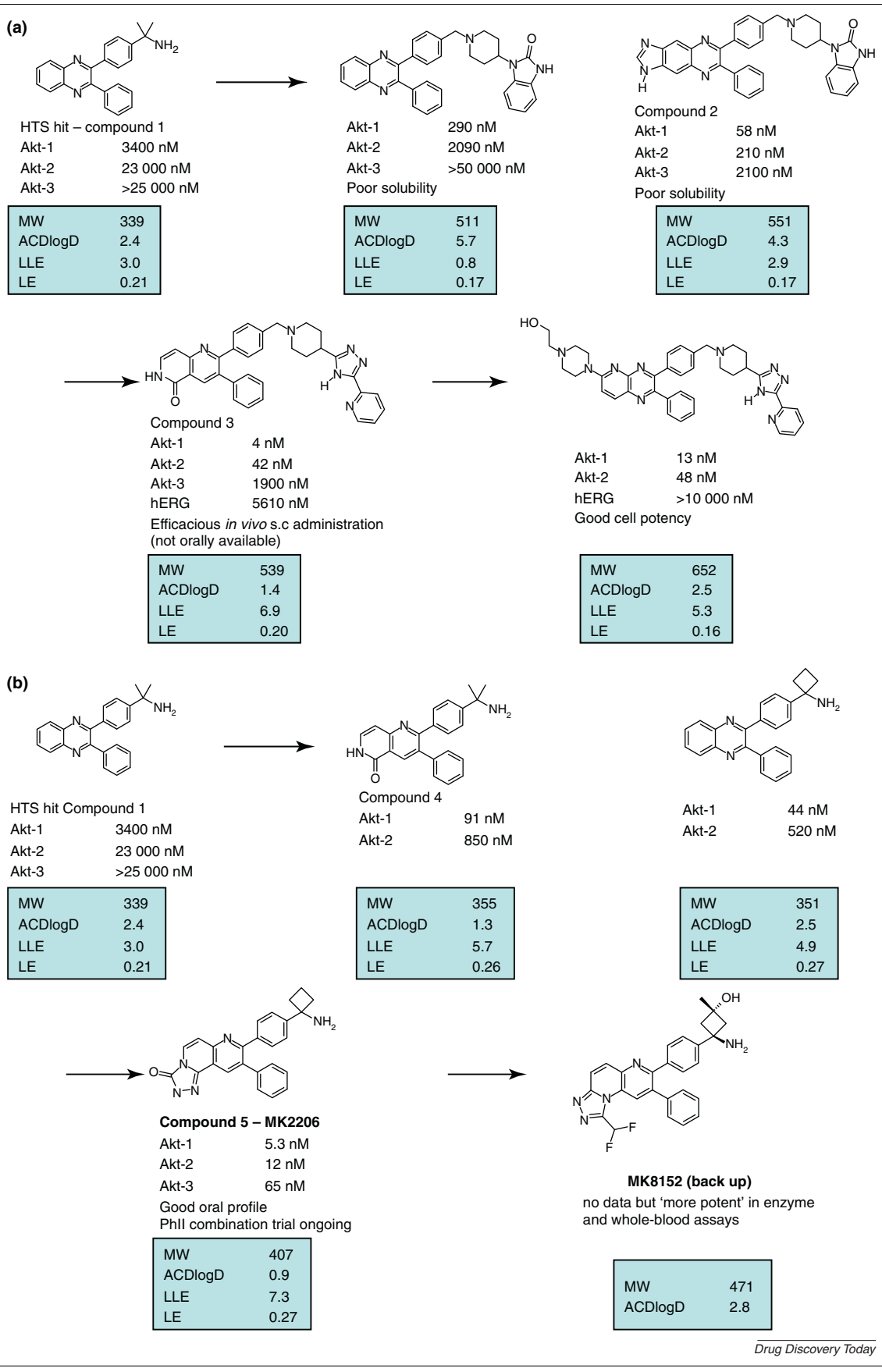

FIGURE 1

Schematic representation of the discovery of allosteric Akt inhibitors. **(a)** First optimisation strategy (illustrated, in part, by white arrows in Fig. 2). **(b)** Second optimisation strategy (illustrated, in part, by red arrows in Fig. 2). The overview of the case study is assembled from published materials [26,27] and the oral

therefore, wasteful of effort? Alternatively, what scientific considerations, steering influences and drivers would make the medicinal chemist more inclined to pursue the second (shorter, less costly and more probable) path towards a low attrition-risk candidate in the first place?

In this example, it is evident from the published articles that the first optimisation strategy put synthetic ease and potency at the forefront of the thinking, and resulted in potent but poorly soluble and poorly bioavailable compounds with hERG activity. These problems were not predictable, but were undoubtedly high probability outcomes for high MW, high lipophilicity bases [17,28]. Alternatively, if one directed the chemistry to control product properties and drive against, for example, LE and LLE, the path would probably have been different. The log *D*, MW, LLE and LE for each molecule have been added to the case study by me to illustrate this. If, in addition, one considered basic scientific aspects, such as conformation (there are only three torsion angles to explore in the hit), one surely would have been more likely to explore alternative conformational constraints much earlier. Illustrated in this way, it becomes clear that medicinal chemistry choices and optimisation practice directly impacted on both the first (unsuccessful) and second successful outcome in this project and, therefore, directly impacted on cost effectiveness overall. How one directs and drives medicinal chemistry strategies, and how medicinal chemists are trained, coached, steered and rewarded all make a difference to outcomes. [Another excellent example of the impact of different medicinal chemistry drivers on outcomes and success can be found in the comparison among the prosecution by four major companies of the same target, chemokine (C–C motif) receptor 5 (CCR5) [2].]

Prospective control of medicinal chemistry practice

Perfect medicinal chemistry practice has not yet been discovered or articulated. The contributions to practice that I have listed and highlighted herein are really nothing more than a reflection of my own experiences, preferences and beliefs of what has worked well in a range of drug project contexts. Some of these ideas might be considered controversial, insufficiently proven, not generally applicable, or perhaps an undesirable attempt to codify the inventive art of medicinal chemistry. It is probable that there is no single 'right' approach. Indeed, variation in practice is essential if the discipline is to evolve and improve. Clearly, in certain circumstances, it will be necessary and desirable for medicinal chemists to design into unusual chemical space [29] (e.g. 'difficult' biological targets, organ-directed therapies, soft drugs, and non-oral routes of administration), and perhaps new guidelines and understanding will emerge as the envelope is pushed with novel molecular frameworks.

However, as illustrated by the Akt case study and in these retrospective reviews [2–4], 'property inflation' or 'molecular obesity' is not an inevitable result of optimisation, but rather is a choice of medicinal chemistry practice. What chemists make is not only driven by the scientific requirements of the biological target, route of administration or other inflexible constraints of biology, but also influenced by knowledge, training, local practices, institutional norms, literature awareness, experience, management guidance, policies and perhaps even the reward systems that surround the practitioner.

As an aside, this observation prompts one to reconsider the definition of 'lead-like', given that small, low lipophilicity start points were originally valued highly in the context that one would inevitably add lipophilicity and MW in optimisation. In a recent elegant analysis by Perola [30], which examines a series of hit-candidate pairs, it is apparent that the medicinal chemistry path taken from hit to candidate (and, therefore, the properties of the compounds made on the journey) might also be influenced by the start point. Whether one can or should add lipophilicity and/or MW will also be influenced by where one starts, even if the high-probability property space destination is unchanged (Fig. 2).

Concluding remarks

Whatever the start point, it is necessary for those who wish to pursue good-quality medicinal chemistry optimisation paths and aspire to improve medicinal chemistry practice further, to avoid repetition of outdated poor practices, adhere to current good practices and build on these high-quality basics further to create forward momentum, better science and enhanced drug discovery performance. Some remarkably similar suggestions for what these basic good practices might be are independently proposed by AstraZeneca (http://www.astrazeneca.co.uk) [3] and Vertex (http://www.vrtx.com) [4] authors and, at least in terms of the desired property space destination and how one might better navigate the path to that destination, have strong overlap with some of the medicinal chemistry literature contributions I have highlighted herein.

However, it is also intriguing and noteworthy that the role of medicinal chemistry leaders in implementing change, enabling the deployment of new tools and encouraging adoption of good practices has not been articulated explicitly in these excellent articles. As a scientist, one tends to adhere to evidence-based and technical recommendations, and avoid conclusions about behavioural, soft aspects of drug discovery and the role of leadership. However, if daily practice is to be improved, one must move from retrospective learning to prospective control of medicinal chemistry practice: one must get better at altering the daily behaviours of practitioners. On the basis of my personal experience (and mistakes made), I offer here some practical suggestions that can aid implementation and successful change towards better practice:

(i) actively encourage taking inspiration from the public domain to reduce 'not invented here' attitudes and negative, defensive responses to new ideas;
(ii) invest in education of all designers to ensure that the retrospective teachings are understood and that the designers are proficient in use of all the tools for prospective control;
(iii) engage and facilitate practitioners in creating their solution within a framework of good practice;
(iv) avoid rules and hard 'cut-offs' (e.g. of MW < 500).These are scientifically weak (given that the risk of a 499-Da and 501-Da molecule are the same, and log *P*/*D* predictors are insufficiently accurate) and, therefore, will provoke derision from scientists. Instead, create the ambition to shift the overall distribution of the property;
(v) monitor and follow up ambitions and intentions with active questioning and review. Request relevant plots of LE and LLE space, and use run charts to check progress over time. Failure to follow up any intervention in this way will signal that it was not very important after all; and
(vi) align performance review and reward systems with the desired practice and activities. Acknowledge and reward early adopters, and communicate good implementations and resultant successes.

presentation given by Phil Sanderson at the 16th RSC-SCI Medicinal Chemistry Symposium, Cambridge, UK, September 11–14, 2011. Lipophilicity is ACD log *D*7.4. Ligand lipophilicity efficiency (LLE) was calculated from Akt-1 inhibition potency as (pIC_{50} − ACD log *D*7.4), and ligand efficiency (LE) was calculated from Akt-1 inhibition potency, as (pIC_{50}/heavy atom count) [2].

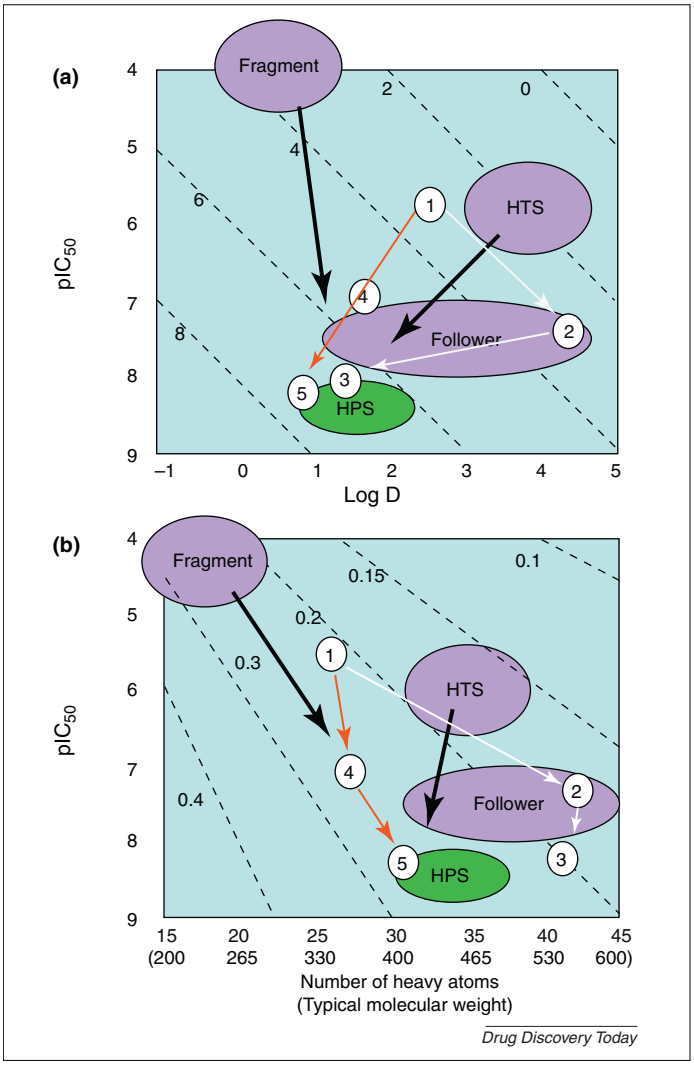

FIGURE 2

Optimisation paths across LE and LLE space. The figure shows optimisation paths from different chemical spaces, which are typified by the hit-finding method. The suggested destination, high probability space (HPS), is a combination of good potency and high probability lipophilicity [7,17,18]. The Akt case study is plotted for interest. Optimisation path 1 (from hit compound 1 to compounds 2 and 3) is shown with white arrows. The second optimisation path from hit compound 1 through compounds 4–5 (MK2206) is shown with red arrows. **(a)** Schematic representation of optimisation paths from different start points across ligand lipophilicity efficiency (LLE) space. Diagonal dotted lines are iso-LLE. This representation might clarify different optimisation drivers and options depending on where one starts. For example, a low lipophilicity, low affinity start point, such as a fragment, might demand modifications that enhance potency in a lipophilicity-neutral manner. Addition of isolipophilic molecular weight (MW) might be a tolerable way to achieve this [30]. By contrast, if the start point is a typical high throughput screening (HTS) hit from a corporate bank, lipophilicity (and MW) might be moderate to high, and potency is often modest. Perhaps especially in this case, the value of driving the medicinal chemistry against LLE improvement to traverse diagonally across the LLE grid becomes apparent. **(b)** Schematic representation of optimisation paths from different start points across ligand efficiency (LE) space. The diagonal dotted lines are iso-LE. Similarly to part (a), this representation might clarify different optimisation drivers and options depending on where one starts. For example, a low MW, low affinity start point, such as a fragment, might demand modifications that enhance potency in a LE neutral manner (i.e. by adding isolipophilic MW). It is noteworthy that only compound 5, MK2206, from the Akt case study falls into HPS on both plots, thus highlighting the value of tracking and optimising all three terms of potency, lipophilicity and MW or composites thereof, such as LE and LLE.

There are many good ideas for how one can improve the execution of medicinal chemistry, and these ideas are available in the public domain. Only by successfully implementing such ideas, and properly pressure-testing them, will it be possible to actually find out what works with generality, and where the exceptions lie. Of course, there are many groups and individuals who have pioneered and ultimately mastered some or all of these techniques (e.g. [31–33]), but the data [2–4] and personal experience at meetings suggest that some of the ideas are not routinely implemented in large sectors of the medicinal chemistry community. It seems that the effective implementation of new ideas into routine practice is constrained by factors that might include one's willingness to change, technical competence and/or capability to deploy change successfully into an organisation. I believe that the time has come for those who are responsible for the leadership and management of medicinal chemistry to apply prospectively firmer guidance and positive pressure on practitioners to make choices towards scientifically sound, shorter, less costly and more probable paths towards low attrition-risk, readily developable candidates. Exerting this kind of pressure might be viewed with concern by some, because it runs counter to the notion of creative, scientific freedom, but surely it is possible to apply some guidance and control of practice while encouraging creativity [34,35] in elegant solutions (such as the Merck Akt candidates). Without some drivers towards good-quality practice, practitioners are left free to repeat past mistakes, and chemical programs follow random-walk paths [13,36], leaving the outcome too much to chance or, worse, to predictable, costly failure; the medicinal chemistry discipline itself, its credibility and its future vigour all suffer as a result. Patients, waiting in need of new innovative medicines, deserve better.

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