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Editorial

There is a story of a young organic chemist taking the structure of his latest creation to his supervisor, who declared that this would be an excellent drug. Impressed that the experienced chemist could be able to deduce this from the structure alone, and prepared to be further impressed by subtle scientific insights, the young man enquired how he could tell. "Bags of nitrogen, lad" was the reply. "Bags of nitrogen."

Considering one of the most successful drugs of recent times, cimetidine, is approximately one-third nitrogen by weight, the old-timer might well have had a point!

Nevertheless, most people believe that structure-activity studies have progressed since this tale was first told. Chemists now design the structure of their candidate drug compounds well in advance of the laboratory work, making use of sophisticated software and extremely powerful computers. There are indeed several descriptions of the successful development of new chemical entities based on computer-aided design, and although the neatness of some of these descriptions may owe something to selective hindsight, it is fair to say that molecules binding to specific receptors can now be designed by the molecular modellers.

It is argued by some that the main advantage of this approach is that the chemist makes fewer compounds, but there is greater chance of success, and more effort can be spent on the more difficult syntheses that will be demanded for such molecules.

With this optimism, why is it that the real rate of success of the designed molecule is not more spectacular? Is it because the molecule, even though exquisitely active at the proposed site of action, still has to run the gauntlet of absorption, distribution and elimination—processes that pay no heed to the compound's ability to bind to its receptor—as well as the hazards of toxicity?

There have been notable studies to correlate structures with toxic effects and advances in this area could well further reduce the number of compounds considered worth synthesis and testing. Of the other factors mentioned above, absorption from the gastrointestinal tract would appear the simplest to predict from the physicochemical properties of the molecule. After all, standard text-books on biopharmaceutics are quite clear on the main factors effecting absorption (molecular size, lipophilicity, pK_a).

Distribution is a little more uncertain, with protein-binding—both to the carrier protein in the blood and to the proteins of target and non-target tissues—playing a significant role. Presumably such protein binding is as amenable to molecular modelling prediction as is receptor binding. Should the molecular modellers be equally concerned with this binding as with the binding to target receptors?

Elimination may be by excretion or by metabolism. Excretion into the bile and excretion with the urine are processes that are to a large degree controlled by physicochemical factors (pH, pK_a, molecular size, lipophilicity) and thus would be predictable, although active transport processes may cloud the picture somewhat. Metabolism would appear to be one of the most unpredictable factors in determining the pharmacokinetic profile of a new molecule. Yet, paradoxically, it was consideration of metabolic features that was one of the earliest subjects of structure-activity relationships for drugs in the whole animal; one thinks of the protection of vulnerable functional groups to retard metabolism and prolong the life of an active compound. There appears to be little current study on the prediction of metabolism from structure using molecular modelling techniques, although it is well recognized that slight changes in structure can have dramatic effects on the metabolic pathways as well as on the extent of metabolism. Should the molecular modeller also be considering how structural changes will affect metabolism?

Organic chemists can now prepare a wider variety of compounds with new reagents and synthetic methods. The rationale for preparing specific compounds has also improved. The problems in the conversion of new chemical entities to successful drugs remain the same; activity in the test-tube is no guarantee of activity in the patient. Rather like Rubic's Cube, improvement of the drug's property in one area may completely disrupt one of its other properties. As with Rubic's Cube, there may be a perfect solution, but in the meantime it is more likely that the best drug will not be the best bound to its receptor, or best absorbed following oral dosing, but the optimum may be found more quickly if all the appropriate factors are considered in the discovery phase.

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