the analogs of which are in the clinic today. However, random HTS (screening all compounds against all targets) might not be the correct approach for the current and future requirements. With a constantly increasing chemical library size as well as screenable targets, a more rationalized HTS is necessary. It is apparent from many of the recent conferences that I have attended that such approaches are beginning to be implemented.

By contrast to HTS, virtual screening and other computational methods are relatively new technologies in drug discovery. All virtual screening methods rely on a subjective model based on a set (or sets) of calculated and/or perceived data derived from primary information such as protein sequences, homology, 3D-structures and biological (including HTS) activities. Therefore, the accuracy of this calculation or perception is the greatest limiting factor in virtual screening. Only when the calculations and presumptions are accurate will the subjective model become objective. For virtual screening to be successful, the model should be built using as many data sets as possible, and using all the information present in the data sets (there is nothing called improper information). Unfortunately, current data sets are very limited and, more importantly, the tools available to extract the information content (data mining) from the data are too primitive.

There is a tremendous effort to develop more valuable and 'right' tools. Without the correct tools, the correct information cannot be extracted (and so remains mostly unknown) and, without the correct information, the correct tools cannot be developed. This is not to say that a dead-end has been reached, but to emphasize the fact that the process of developing the right tools is an evolving process. This involves many reiterating cycles of presumption, testing (mainly biologically) and refinement until it develops into the 'right' tools. It is only then that true objective calculations can begin and the 'right' models can be developed. This process has only just begun. Considering the complexity of the information content in biological and chemical data, and considering how little of the biological and chemical data are known today, it is my view that the quantity of knowledge in knowledge-based computational methods is only at a minimum.

The point that I am trying to emphasize is that, at the present time, virtual screening has not evolved enough or acquired enough sophistication to be successful by itself. It does not, however, mean that virtual screening and other computational methods should be ignored. The limited knowledge acquired by computational methods has to be used in combination with other non-computational technologies (such as HTS, CC and MC). This is how computational methods can make a significant impact on the rationalization of HTS, CC, MC and alike and, in doing so, can increase the knowledge-base of these screening methods. This is the only objective method of carrying out lead discovery. In my opinion, the screening technologies (such as HTS, CC and computational methods) are only the tools. Provided these tools are used intelligently, they can increase speed and reduce costs. It is only then that there will be a significant impact on drug discovery.

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Dimeric malarial drugs for enhanced activity

US chemists have synthesized new dimeric derivatives of an extract from an ancient Chinese herbal remedy that have high activity against malaria. Herbal extracts of the Chinese wormwood, *Artemesia annua*, have been used for centuries to treat fever, including malaria-related fever. The active compound, qinghaosu (known in the West as artemisini) is a natural trioxane containing an unusual seven-membered C–O ring bridged by an O–O peroxide unit, thought to be central to its biological activity. The compound has shown great promise in continuing trials against malaria in China and elsewhere.

Mechanism of action of artemisinin

Gary Posner's team at the Department of Chemistry (Johns Hopkins University, Baltimore, MD, USA) has been studying the mode of action of artemisinin (Fig. 1) against the malarial parasite, *Plasmodium falciparum*, to find a simpler compound with similar or improved activity but without the chemical complexity, hence reducing manufacturing costs. In 1996, Posner's team, working with colleagues at the Weizmann Institute (Rehovot, Israel), found that the essential structure of the artemisinin molecule required for activity is an oxygen triad (trioxane)[1,2].

Malarial parasites obtain their nutrients from the human host's haemoglobin and

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concentrate it in haematin storage sites. The abundance of the haem iron in the parasitic cells means they can chemically reduce molecules containing O–O linkages. However, the reduction of the artemisinin trioxane forms a highly reactive Fe(IV)=O species. The molecular machinery of parasitic cells is damaged by oxidative chain reactions triggered by the radical iron-oxo species. On the basis of their earlier studies, the researchers have designed several lead compounds that are much simpler than the parent compound. While these compounds are still being studied, Posner confesses that the results using these simplified artemisinins are, so far, not very encouraging.

Posner and his team, however, considered that doubling up the antimalarial compound might produce a more effective drug, albeit with greater complexity than the parent. This idea was based on the greater effectiveness of bis-mustard cross-linked lexitropsins, the dimeric steroid-pyrazine marine alkaloids, and the DNA cross-linking dimeric benzodiazepines and bis-enediynes, all of which have enhanced biological activity compared with their respective monomeric forms. The researchers have reported nine such dimeric versions of artemisinin, prepared using the novel synthetic technique of coupling the α,β-unsaturated aldehyde derivatives of artemisinin using the bis-Wittig reaction[3]. This involved connecting two trioxanes through an aromatic linker group, such as a furan or a benzene ring. This technique produced high yields of stable products, boding well for their use as putative drugs.

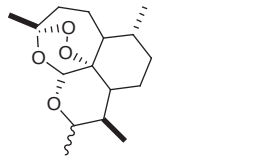

Figure 1. *The structure of artemisinin.*

The team tested the series of compounds against their standard assay for chloroquine-sensitive *Plasmodium falciparum* (NF54) parasites. They found that the benzoylmethylene-linked dimers, the aryl dimer and the furan dimer were considerably more potent antimalarial agents than artemisinin itself, using tritiated hypoxanthine to follow the mortality of the parasite (IC_{50} values for their compounds was 1.3–3.2 nM, compared with 9.7 nM for artemisinin). 'The high antimalarial potency of some of the dimers would indeed be offset by the high cost of producing such dimers from two valuable trioxane units,' says Posner.

Hence, the team has begun looking at an alternative use for these biologically active compounds. They have also tested their dimeric compounds against the National Cancer Institute's 60-tumour cell line assay and found that their derivatives are active against numerous cancers including some colon and leukaemic cancers. They also tested the compounds against the mouse hollow fibre assay for anticancer activity and found them to be potent cell antiproliferative agents. The benzoylmethylene dimer, in particular, can significantly reduce cancer cell mass and is as effective *in vivo* at remote subcutaneous implant sites as at intraperitoneal implant sites. '*In vivo* testing data show that a trioxane dimer is potent and safe as an antitumour agent in one rodent model for human cancer', adds Posner. Further clinical testing is therefore planned for the future.

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