NEWS & VIEWS

ORGANIC CHEMISTRY

Molecular diversity by design

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Many organic syntheses are target-oriented — each multi-step route is designed to make just one compound. But now a diversity-oriented synthesis can make 80 different molecular skeletons in just a few steps.

Genome biology is shining a bright light on the origins of human disease. Unfortunately, the biological targets emerging as ideal points for therapeutic intervention are often viewed as being extremely difficult, if not impossible, to modulate with small molecules — which is a problem, because most drugs are small molecules. But is this view justified? Drug hunters search for candidates for drug-discovery programmes by screening large numbers of compounds in biological assays. Perhaps these collections simply lack compounds from structural classes that would modulate the targets identified by genomics studies[1]. Reporting in *Angewandte Chemie*, Morton *et al.*[2] describe an ingenious synthetic pathway that will help to populate screening collections with structurally diverse compounds.

For many decades, organic chemists have searched for ways of making naturally occurring small molecules (known in the field as natural products). These objects of affection pose strategic challenges: can sequences of reactions be devised that turn simple, readily available compounds into more complex target compounds[3]? In the more-notable successes, the resulting syntheses have provided insights into such fundamental areas as conformational analysis[4,5] (the study of the dynamic shapes of molecules), general principles of reactivity[6], and biosynthesis and life's prebiotic origins[7]. Natural-product syntheses have on several occasions served as starting points for drug development[8], and they have revealed gaps in the methods of organic synthesis, providing motivation to fill them[3].

But in recent years, synthetic targets have changed. Modern biology is gradually discovering how molecules such as transcription factors and regulatory RNAs are involved in disease. Such molecules are considered to be 'undruggable' targets, because they bear little resemblance to the approximately 500 targets of the current pharmacopoeia. In addition, as the functions of disease genes have been uncovered, they have suggested other processes (such as the changing of one type of cell in the body into another) or interactions (such as those between proteins, or between proteins and DNA) that might be targeted and/or disrupted by drugs. But these also fall into the 'undruggable' category. Natural products tend to modulate a limited set of targets that have general functions — cytoskeletal proteins that define the shapes of cells are common examples — but do not seem to modulate these other, more-specialized targets and processes. Chemists are therefore stepping in to make compounds that do.

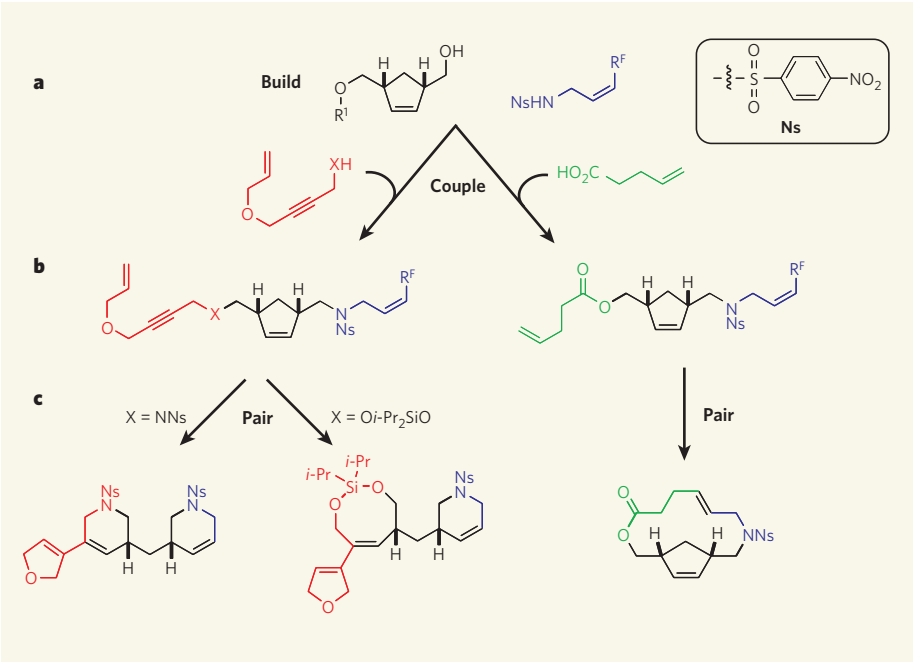

Figure 1 | Diversity-oriented synthesis. Morton *et al.*[2] have devised a general 'build–couple–pair' synthetic strategy, and have used it to make 80 different structural classes of compounds rapidly. **a**, The first step is to build a set of molecular building blocks, of which four are shown here, each in a different colour. R^1 is any hydrocarbon; R^F is a fluorocarbon attached through a linker molecule; and X is a variable structural element. **b**, In the second step, the building blocks are coupled together in various combinations to create intermediate molecules. **c**, Finally, pairs of groups within the intermediates react to form a structurally diverse set of final compounds. *i*-Pr is an isopropyl group, $C(CH_3)_2$.

It is impossible to design such compounds from scratch. Instead, it is best to make a 'super-set' of compounds of such structural diversity that, for any given aspect of a biological process, members can be found that can modulate that aspect. When the super-set is screened in biological assays, compounds would thus be found that modulate even undruggable biological targets. Experience shows that successful programmes for drug discovery, or for finding molecular probes of biological processes, require that many thousands of compounds be available for screening. This makes it impractical to prepare each member of a super-set using its own, target-based synthesis pathway. Instead, flexible, modular syntheses must be devised that allow many structurally diverse compounds to be prepared efficiently. So which compounds should be prepared, and how should such a diversity-oriented synthesis be planned?

The best, but most difficult, strategy is to make compounds in a way that anticipates problems at each step of the drug-discovery process in which organic synthesis is involved. As described above, the first such step involves finding a molecule that modulates a disease

50 & 100 YEARS AGO

50 YEARS AGO

The final stage of a Russian multi-stage rocket, launched at about 17.00 hr. U.T. on January 2, flew past the Moon to become the first artificial planet of the Sun. The final-stage rocket is stated to have weighed 1,472 kgm ... after all its fuel was burnt, and its pay-load of scientific instruments, together with the container, weighed 361.3 kgm ... The instruments were intended to measure the Moon's magnetic field, the intensity and composition of cosmic rays, lunar radioactivity, the impact of meteors and the composition of the Moon's atmosphere ...The programme of scientific measurements is stated to have been successfully accomplished before radio contact was lost on January 5 ... Since the Moon was near last quarter at the time of the launching, the rocket's path was nearly tangential to the Earth's orbit; the rocket's orbit around the Sun, therefore, has almost the same perihelion distance as the Earth's orbit, though the aphelion distance is greater because of the rocket's greater speed at perihelion.

From *Nature* 10 January 1959.

100 YEARS AGO

Never had earthquake taken such toll of human life as that which has just devastated Calabria ... [T]he Yeddo — now Tokio — earthquake of 1703, with its death-roll of 200,000, had stood in a class by itself; yet even this great number seems insufficient to count the deaths on the morning of December 28, 1908, and if to those whose lives were ended by the immediate effects of the earthquake we add the subsequent deaths from injury, exposure, and sickness, the loss will amount to well over a quarter of a million lives ... From Pizzo the band of destruction extends southwards for about 50 miles through ill-starred Monteleone, which no earthquake seems to spare, Palmi, and Bagnara, to Reggio di Calabria.

From *Nature* 7 January 1909.

target or process. This requires thousands of structurally diverse compounds to be made for screening. The next step is to optimize the biological properties of the compounds found during screening. This involves making analogues of the compounds, each containing slightly different structural modifications — ideally, every atom in the compound should be modified, without an overwhelming synthetic effort. The final step involves synthesizing the optimal compound, either for use as a biochemical probe for research or as a drug in medicine, efficiently, at low cost and in large quantities.

Historically, the pharmaceutical industry has dealt with each of these steps in a serial fashion, and the associated problems have been addressed independently. Each step is challenging and can create bottlenecks in the overall process. Diversity-oriented synthesis aims to address, if not overcome, all of these challenges before the first compounds have even been screened.

Morton *et al.*[2] implement a strategy for a diversity-oriented synthesis that might advance each of the above steps of the drug-discovery process. Their approach yields structurally novel and diverse products in high yields and of excellent purity — impressively, the authors made 80 different molecular 'skeletons'. Because the synthetic route is modular, many modifications can in principle be made to each skeleton simply by using different variants of the reactants at the first step. This is ideal for the optimization stage of drug discovery. Finally, the route contains only a small number of steps, which should make it adaptable for large-scale synthesis.

The authors use the 'build–couple–pair' strategy of organic synthesis[9], which entails preparing molecular building blocks that contain several chemical groups (Fig. 1). Some of these groups react in the first step of the synthesis to couple the building blocks together. Once all the different blocks have been coupled, the remaining groups react with others found in the same intermediate molecule. The build–couple–pair strategy precisely mimics that used by nature in the biosynthesis of nearly all natural products, where it also allows structurally diverse products to be formed. Helpfully, Morton *et al.* have designed the protocol of their diversity-oriented synthesis with a particular eye to making it simple to purify the compounds — this is a boon, because purification is usually the most labour-intensive part of any chemical reaction.

The resulting products[2] differ from the compounds found in most small-molecule screening collections. Typically purchased from commercial vendors, the compounds in such collections frequently lack chirality and are structurally simple. This means that they can bind to only a small number of biological targets. The compounds in commercial libraries also tend to be structurally similar — their 'diversity' is limited to variations in appendages attached to a small number of common skeletons. This undesirable combination of properties means that, although enormous numbers of compounds (often more than a million) are frequently tested in screenings, at great expense, in the case of undruggable targets relatively few biologically active 'hits' are found. In principle, a smaller library of compounds that contains a more diverse range of molecular shapes, such as those made by Morton *et al.*, would provide both more hits for less money, and hits for the more challenging biological targets.

The structural complexity of natural products enables them to perform demanding biological tasks, and their structural diversity allows them to perform different tasks. The same is true of non-natural compounds produced using diversity-oriented synthesis and subsequently identified as small-molecule probes of protein–DNA interactions[10], protein–protein interactions[11], transcription-factor activity[12], multi-drug resistance in pathogens[13] and many other processes often imagined to be impervious to modulation by small molecules. These results suggest that Morton and colleagues' synthetic pathway might also yield molecular probes of many aspects of disease.

Diversity-oriented syntheses are growing in number and sophistication, and this study[2] will probably inspire even more advances in the area. The tremendous growth of small-molecule screening for biological research and drug discovery will provide additional clues to the contrasting biological activities of small molecules derived from diversity-oriented syntheses, from commercial libraries, and from nature. There remains an urgent need to understand better both the relationship of structural features of small molecules to screening outcomes and, more generally, the relationship of synthetic strategies to success in discovering probes for biological research and drugs for therapeutic interventions. ■

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