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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