DEUTERATED DRUGS

Relief from racemization

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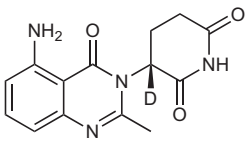

A single enantiomer of a drug is often more active than a racemic mixture. Indeed, the opposite enantiomer may lead to harmful side effects, and because of this, synthesis and testing of a stereochemically pure compound is now preferred when possible. Since the 1990s several drugs have been the subject of so-called chiral switching — the substitution of previously developed racemic mixtures with enantiopure formulations. Although the well-known teratogenic effects of thalidomide have been attributed to the *S*-enantiomer, a chiral switch cannot be applied in this case as it is known to racemize in the body. But, there remains wide interest in the drug and related analogues due to their antitumour and anti-inflammatory properties. Now, Sheila DeWitt and co-workers from DeuteRx and Kalexsyn have investigated deuterated versions of two thalidomide analogues.

The racemization half-life for thalidomide analogues is known to be significantly shorter than the half-life for elimination from the body making it difficult to dose and study the effect of a single enantiomer. DeWitt and co-workers resolve this issue by replacing the acidic proton at their stereocentres with deuterium. Racemization occurs by exchange at this stereocentre and deuteration slows the process — as would be expected from a primary kinetic isotope effect. The retarded racemization is essentially independent of metabolism, however, meaning that there is little change in the pharmacokinetic properties of the drugs.

The laevorotatory enantiomers of the deuterated drugs were shown to have a significantly better activity against tumour growth than the protonated racemate (even at two times the dose to account for presence of the inactive enantiomer). This is attributed to an improved absorption of the individual enantiomers into the bloodstream. The smaller dose of the undesired component may also help to avoid detrimental side effects. Further synthetic work to reduce the amount of protonated impurities in the deuterated formulation will be essential to better understand the effects of the individual deuterated enantiomers. *SD*

MOLECULAR LOGIC

Detection on the edge

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Though it may not seem like it, edge detection — which involves visualizing the contours of dark and light areas rather than the areas themselves — is a rather

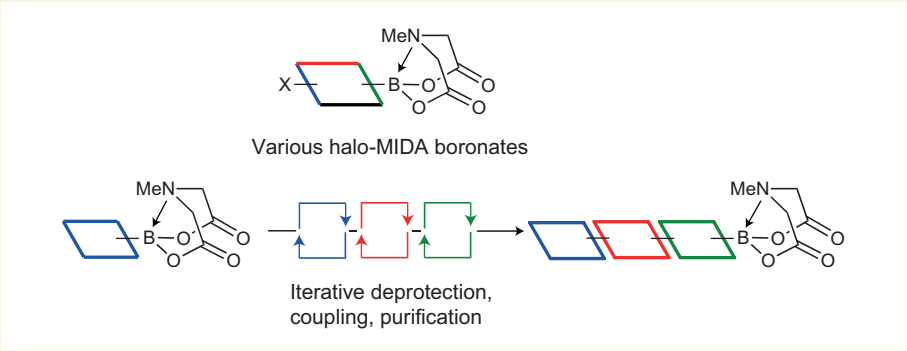
ORGANIC SYNTHESIS

Made by machine

Science http://doi.org/3cc (2015)

The idea of automating the synthesis of small complex molecules, while appealing, is certainly a massive task, but it is one that can be made significantly easier with a building-block-based iterative synthesis strategy. In previous research, Martin Burke and co-workers, from the University of Illinois at Urbana-Champaign, developed such a synthesis strategy using *N*-methyliminodiacetic acid (MIDA)-protected boronic acids. They showed that a molecule featuring a halogen and a MIDA-protected boronate could be used in a Suzuki reaction, with no fear of the protected boronate reacting. Then, a simple hydrolysis could deprotect the product, opening up a new reactive boronic acid site for the next Suzuki reaction.

Burke and co-workers have now used this chemistry to form the basis of an automated synthesis machine. The key to this was to address the issue of intermediate purification. They realized that MIDA-containing compounds showed a high affinity for silica gel with typical polar solvents (for example methanol or ether), but eluted rapidly when tetrahydrofuran (THF) was used. This allowed the purification procedure to be automated — undesired compounds can be washed away before isolating the MIDA-containing product simply by switching the chromatography solvent. The MIDA boronate thus acts as a purification tag and, importantly, because it is also the reactive handle no additional functional group is necessary to automate the purification.



With these results in hand, the group built a machine that could automate the deprotection–coupling–purification sequence and repeat it as many times as needed. It uses computer-controlled syringe pumps to transfer solutions of the required reactants to modules that carry out different tasks. The first deprotects a MIDA-protected boronate with base. This solution is then added to a solution of the next building block in the coupling reaction module. Once the reaction is complete, the mixture is loaded onto a module containing silica gel to remove by-products and excess reagents before the purified product is washed-off with THF, priming it for the next iteration in the synthesis. Multiple natural products and related molecules were made with the machine, including complex macrocyclic and polycyclic molecules. *EB*