

# D is for

Deuterium modification offers great promise to improve the profiles of drugs and brings opportunities for new uses, report Philip Graham, Julie Liu and Lijun Wu

Poor bioavailability and safety issues have long prevented many drugs and drug candidates from reaching the clinic. To overcome these issues, medicinal chemists have started investigating deuterated compounds as new chemical entities with improved properties. The idea is to selectively incorporate deuterium to alter drug metabolism and absorption properties and thus provide differentiated drugs with improved safety and/or efficacy. Currently, a number of deuterium-substituted drugs are in clinical development.

The size and electronics of a deuterium atom are essentially identical to those of a hydrogen atom. As a result, selective replacement of hydrogen by deuterium results in a molecule with the same size and shape as the original medicine and therefore has very little effect on the chemical and physical properties of the compound. Deuterium-substituted compounds generally retain the full biochemical potency and selectivity of the original chemical entity.

From a drug development perspective, one of the most compelling characteristics of deuterium is that it forms particularly strong bonds compared with hydrogen. A deuterium-carbon bond is from six to 10 times more stable than the corresponding

hydrogen-carbon bond, and so is much harder to break – the primary kinetic isotope effect.

In principle, deuterium modification has the potential to affect the biological fate of certain drugs that are metabolised by pathways involving hydrogen-carbon bond scission. For example, oxidative metabolism by cytochrome P450 enzymes typically involves the cleavage of a hydrogen-carbon bond. However, the deuterium kinetic isotope effect is often masked in whole biological systems by

**A deuterium-carbon bond is six to 10 times more stable than a hydrogen-carbon bond**

competing effects, such as alternate metabolic routes and different rate-limiting steps in enzymatic reactions.

In our drug discovery research at US-based drug company Concert Pharmaceuticals, deuterium modification has been shown to result in altered levels of metabolites in numerous programmes. However, the metabolites we see are identical to those from the non-deuterated molecules, except for the presence of deuterium. We also observe metabolic shunting, where the ratio of metabolites is changed, and in some

# drugs

cases, the rates of overall metabolism are reduced. In several cases, we have also seen, perhaps counter-intuitively, that selective deuteration increases the rate of metabolic clearance *in vitro* and even in humans.

As a result, deuterium incorporation can result in metabolic effects ranging from undetectable to substantial. The magnitude and even direction of deuterium modification effects are unpredictable and depend on a

compound's structure and the specific deuterium substitution pattern.

Our research goal has been to identify instances where a specific deuterium incorporation pattern results in important benefits to the safety, tolerability, and/or efficacy of drugs or drug candidates.

Selective incorporation of deuterium in place of hydrogen at specific sites has the benefit of retaining the pharmacologic activity and selectivity of physiologically active compounds

while, in select instances, modifying metabolic fate. By precisely incorporating deuterium to modify approved drugs and other compounds with well-documented pharmacological activity, Concert is creating new chemical entities that are meaningfully differentiated, patentable and display superior therapeutic properties.

The examples shown in the accompanying boxes illustrate a variety of reasons for pursuing deuterium-

Deuterium modification may resurrect certain failed drugs

## Diabetic nephropathy

Concert's lead drug candidate is CTP-499, a novel potential treatment for diabetic kidney disease or diabetic nephropathy in Type 2 diabetics. Diabetic kidney disease is the leading cause of end-stage renal disease, or kidney failure. Currently, more than 200,000 patients in the US are suffering from kidney failure due to Type 2 diabetes, and that number is expected to grow significantly as the incidence of Type 2 diabetes rapidly increases.

Despite the availability of blood pressure lowering agents such as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE inhibitors), many patients continue to experience a decline in renal function and progress to kidney failure. As a result, there is a critical need for new drugs with untapped mechanisms that can further delay or prevent the decline of kidney

function and eventual need for dialysis or transplant.

CTP-499 is a deuterium-modified analogue of 1-((S)-5-hydroxyhexyl)-3,7-dimethylxanthine (HDX), an active metabolite of *Trental* (pentoxifylline). Concert created CTP-499 by replacing several hydrogen atoms with deuterium at key positions. *Trental*, which is significantly metabolised to HDX, was approved in the US decades ago for the treatment of intermittent claudication, the clinical diagnosis of muscle pain in the leg usually caused by obstructed arteries.

In preclinical studies, CTP-499 was shown to possess anti-inflammatory, anti-oxidative, anti-fibrotic and renoprotective activities, all of which are believed to be important for the treatment of diabetic nephropathy.

In 2012, Concert initiated a Phase 2 efficacy study of CTP-499 in diabetic patients with renal impairment.

## Neuropathic pain, anxiety, spasticity

CTP-354 is a deuterated analogue of a non-benzodiazepine preclinical agent discovered at Merck & Co. The Merck compound, L 838417, was selected by Concert for deuterium substitution because its promising pharmacological profile was extensively characterised in scientific publications, yet it possessed a poor pharmacokinetic profile in preclinical testing and was never progressed into clinical development.

Benzodiazepines, which include well-known drugs such as *Valium* and *Xanax*, exert their effect non-selectively across the GABAA receptor subtypes. Because of this, their use is often limited by undesirable side effects such as sedation and ataxia (lack of muscle coordination). In preclinical models, CTP-354 preserves the desirable pharmacology of benzodiazepines yet exhibits no apparent sedation at therapeutic doses.

Additionally, CTP-354 has demonstrated strong and superior efficacy compared with its hydrogen analogue L-838417 and to the standard-of-care pain drug gabapentin in preclinical animal models of neuropathic pain. Based on this favourable profile, CTP-354 is undergoing further studies with funding support from Fast Forward, the venture division of the US National Multiple Sclerosis Society.

modified drugs. Deuterium modification of a marketed drug offers benefits in terms of drug development costs and reduced technical risks, and can leverage the knowledge gained from the non-deuterated drug to design clinical trials and speed development. It also brings the

**Deuterium modification may affect the biological fates of some drugs**

possibility of advancing a promising drug that failed to enter clinical development due to poor pharmacokinetics. The technical risks are higher for such a drug because there is no hydrogen version that has survived clinical trials with proven safety and efficacy. On the other hand, these drugs might satisfy an unmet need where there is no similar drug in the marketplace. Deuterium incorporation enables unique, potentially first-in-class treatments.

Deuterium modification offers great promise to improve the profiles of drugs and to open opportunities for new uses, creating the potential for improved therapeutic utility. Potential benefits include:

**1. Improved safety, reduced side effects**  
Many drugs are metabolised in complex patterns, forming active, toxic, reactive or innocuous metabolites. Deuterium modification can reduce the formation of toxic or reactive metabolites and/or increase the formation of active metabolites, which can in turn reduce or eliminate unwanted side effects and prevent undesirable interactions with other drugs.

**2. Increased tolerability and efficacy**  
Sometimes the major effect of deuteration is to reduce the rate of clearance by

the body. As a result, the biological half-life of the compound is increased, and it stays in the body longer. Potential drug benefits could include decreased doses and the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels.

This could result in lower side effects and enhanced efficacy, depending on the particular drug's pharmacokinetic/pharmacodynamic relationship.

**3. Lower doses, improved tolerability**  
Reduced rates of first-pass metabolism in the gut wall and/or liver result in a larger percentage of unmetabolised drug reaching the systemic circulation. Deuterated drugs showing this effect may have reduced dosing requirements, produce lower metabolite loads or increase the effect of controlled release formulations. Since gastrointestinal irritation can be related to the amount of dosed compound rather than blood concentration, this effect may improve tolerability and/or the ability to achieve a higher maximum tolerated dose.

### Development strategies

There are several drug development strategies for which deuterium substitution can offer potential benefit. Improvement of an existing marketed drug for the same indication may require substantial differentiation of the deuterated analogue to warrant R&D investment. In other cases, deuterium modification can resurrect a drug that failed due to poor pharmacokinetic properties.

But perhaps the most intriguing use of deuterium is to make improved versions of old drugs for new indications. Concert is pursuing all three strategies with the goal of bringing safer, more effective treatments to patients. ●

**Deuterium modification can improve drug safety**

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## Myelodysplastic syndromes and multiple myeloma

CTP-221 is a deuterium-modified S-enantiomer of the drug lenalidomide containing deuterium atoms at specific positions. Lenalidomide (*Revlimid*), an immunomodulatory drug (IMiD) for the treatment of myelodysplastic syndromes and multiple myeloma, is a mixture of S- and R-enantiomers. Though it is known that the isolated enantiomers of other IMiD compounds, such as thalidomide, have distinct biological activities, isolated enantiomers of IMiDs have not been developed clinically.

Given the therapeutic importance of lenalidomide, we explored a number of deuterium-substituted analogs of lenalidomide either as racemic mixtures or as isolated S- and R-enantiomers. We have demonstrated that deuterated racemic lenalidomide is similar in pharmacological activity to lenalidomide. However, our lead deuterated S-lenalidomide analogue CTP-221 is significantly more potent than lenalidomide in key biological activities believed important for clinical efficacy. In addition, CTP-221 administration in preclinical models resulted in minimal exposure to the R-enantiomer. Dosing of this deuterium-stabilised S-enantiomer reduces exposure to the less potent R enantiomer, and provides the potential for clinical improvements in safety, tolerability, and/or efficacy compared with lenalidomide.