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CHEMICAL & ENGINEERING NEWS

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DEUTERATED DRUGS

Firms try hydrogen isotope to improve medicines P.36

PRELIMINARY PROGRAM

ACS national meeting in Washington, D.C. P.47

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ENGINEERING PLASTICS

On an economic hot seat P.15

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Nylon, polycarbonate, and ABS businesses have all been squeezed by the recession, but some will bounce back better than others. **PAGE 15**



QUOTE OF THE WEEK

"When urgent and important clash, nine out of 10 times urgent wins out."

J. BRIAN FERGUSON,
CHAIRMAN, EASTMAN
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THIS WEEK ONLINE

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REEL SCIENCE

"Moon" is fictional, but its premise could be real—in a decade or two, that is.

PLUS: Feeling green? Don't miss the collection of green chemistry articles on C&EN Online.



MARY TILLE © LUNAR INDUSTRIES / SONY PICTURE CLASSICS

HEAVY-HYDROGEN DRUGS TURN HEADS, AGAIN

Firms seek to improve drug candidates by selective **DEUTERIUM SUBSTITUTION**

AMANDA YARNELL, C&EN BOSTON

IN THE DRUG INDUSTRY, as in fashion, occasionally what's old becomes new again: The latest retro rage in the pharmaceutical world is deuterium substitution, a drug-design strategy that has faded in and out of vogue over the years. Now, firms large and small are banking on its potential to improve existing drugs.

The strategy aims to take advantage of the edge deuterium has on hydrogen in

terms of atomic mass. Carrying a neutron that hydrogen lacks, deuterium forms bonds with carbon that vibrate at a lower frequency and are thus stronger than C-H bonds. If a particular C-H bond in a drug molecule is known to be readily broken during metabolism, swapping that hydrogen for a heavier deuterium can in some instances slow the process down. So, the theory goes, heavy-hydrogen versions of drugs may sometimes last longer in the body and outshine the all-hydrogen originals.

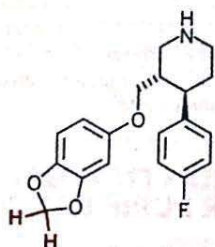
Biochemists have long exploited this phenomenon—dubbed the kinetic isotope effect—to study drug metabolism. Several small start-ups are now aiming to leverage it to improve upon existing medicines.

The idea gained traction in the pharmaceutical world earlier this month, when Glaxo-SmithKline agreed to pay Lexington, Mass.-based Concert Pharmaceuticals \$35 million up front for three compounds

in early stages of development, including a deuterated version of Bristol-Myers Squibb's HIV protease inhibitor Reyataz (C&EN, June 8, page 29). Concert will also make deuterated versions of three lead compounds in GSK's pipeline. As part of the deal, Concert stands to receive up to \$1 billion in milestone payments in addition to double-digit royalty percentages if the deal leads to a marketed product.



CYP2D6



Paroxetine

HEAVY HITTER

The cytochrome P450 enzyme CYP2D6 metabolizes the methylenedioxy portion of the antidepressant paroxetine (Paxil) to a carbene that then irreversibly inhibits the enzyme by binding its heme iron active site. Pharma firm Concert reduced formation of this carbene metabolite by doubly deuterating the methylenedioxy bridge.

"This deal is a sign of industry's validation of our deuteration strategy," says Roger Tung, Concert's chief executive officer. If the partnership leads to new medicines, it should finally solidify deuteration's place in the medicinal chemist's toolbox, he adds.

THE STRATEGY is far from new. Decades ago, chemists at the University of California, Berkeley, attempted to block enzymatic oxidation of morphine by deuterating it (*Science* 1961, 134, 1078). They succeeded—only to find that in doing so

they had significantly reduced the opioid's effectiveness by slowing the formation of its active metabolite. More recently, medicinal chemists at Marlborough, Mass.-based Sepracor tried to extend the half-life of the pain medication tramadol by replacing hydrogen with deuterium at sites in the molecule known to undergo metabolism in vivo (*Bioorg. Med. Chem. Lett.* 2006, 16, 691). Deuteration stymied the formation of several undesirable metabolites in vitro but failed to extend the drug's duration of action in rats, says Liming Shao, the firm's senior director of medicinal chemistry.

"There are a reasonably limited number of cases where this strategy will work," Tung concedes. When hunting for targets, his team looks for drugs that give rise to undesirable metabolites, are cleared from the bloodstream too quickly, are metabolically broken down in the intestines or liver before reaching the bloodstream, or interfere with the clearance of other medications a patient is taking. But Tung notes that the only way to know whether deutera-

tion of those compounds will make a clinically relevant difference is to make the analogs and test them.

Michael Grey, CEO of Vista, Calif.-based Auspex Pharmaceuticals, points to the antidepressant drug venlafaxine as one case in which deuteration has made such a difference. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor bearing a meth-

oxy group that is rapidly converted to a hydroxyl group in the liver. The drug also has a dimethylamine group that is quickly trimmed back to a primary amine. Last October, Auspex announced initial Phase I clinical trial results for its deuterated version of venlafaxine in 16 healthy volunteers. The data showed that the compound, designated as SD-254, was metabolized half as fast as venlafaxine and persisted at effective levels in the body far longer, Grey says.

"We see a significant opportunity for SD-254 in neuropathic pain, an indication for which venlafaxine has shown promis-

RIBBON STRUCTURE COURTESY OF PAUL ROWLAND

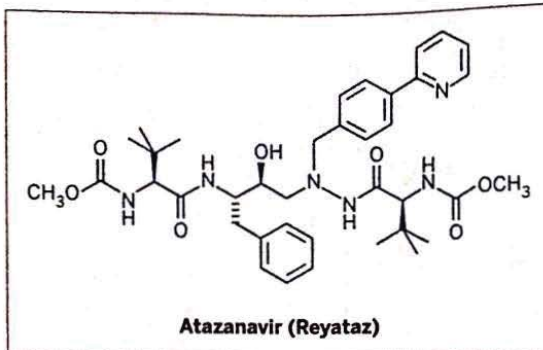
ing activity but was never formally developed," Grey says.

Concert has also demonstrated the clinical potential of deuteration. Concert's CTP-347, a potential nonhormonal treatment for hot flashes, is a doubly deuterated analog of the antidepressant drug paroxetine. Paroxetine also reduces hot flashes, but patients taking certain other drugs can't use it because it irreversibly inactivates the cytochrome P450 enzyme CYP2D6. This liver enzyme is responsible for metabolizing up to a quarter of all medications. So inactivating it with paroxetine can allow other medications a patient is taking to build up to dangerous levels in the bloodstream. Earlier this year, Concert announced encouraging Phase I clinical trial results for CTP-347: The compound substantially preserved the enzyme's activity in patients, "potentially enabling its broader use with other drugs," Tung says.

The peril of paroxetine comes down to the drug's methylenedioxy group. The carbene that's produced when CYP2D6 clips

off the pair of hydrogens on paroxetine's methylenedioxy bridge turns out to be the enzyme's demise. The highly reactive carbene binds to the heme iron in CYP2D6's active site and refuses to let go, inactivating the enzyme. Replacing the pair of hydrogens with a pair of deuteriums dramatically reduces the formation of the carbene and thus lessens the inactivation of the enzyme, Tung says.

Despite CTP-347's encouraging start, Concert recently chose to focus their resources on CTP-518, the deuterated version



of Bristol-Myers Squibb's atazanavir HIV protease inhibitor that's central to the start-up's deal with GSK. Tung notes that deuteration of atazanavir slows the rate at which the HIV drug is eliminated from the body, potentially abolishing the current need to coadminister the drug with ritonavir or another anti-HIV booster agent. CTP-518 is scheduled to enter Phase I clinical trials later this year, he says.

THE SECOND compound named in the GSK deal is a preclinical compound intended for treatment of chronic kidney disease that Tung claims boasts a new mechanism of action and may find use in combination with existing angiotensin modulators. A third deuterated compound from Concert's pipeline will be picked at a later date.

The U.S. Patent & Trademark Office has awarded Auspex a patent on SD-254 and has assigned to Concert patents for deuterated versions of the obesity drug rimonabant and the acid reflux medication

ELEMENTS OF EXCELLENCE ACS VOLUNTEERS

11th Annual ChemLuminary Awards

August 18, 2009 • Capital Hilton Hotel

SOCIAL HOUR/POSTER SESSION – Senate Room & Foyer – 8:00 p.m.

AWARDS CEREMONY – Presidential Ballroom – 9:00 p.m.

DANCING – Congressional Room – 10:00 p.m.



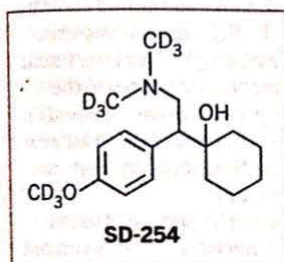
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mosapride. Both companies have more than 100 other patent applications pending for deuterated versions of existing drugs. Meanwhile, Reno, Nev.-based Protia, founded by Anthony W. Czarnik, has filed hundreds of patent applications on "deuterium enriched" versions of all kinds of common medicines. The firm was recently granted the first of those, for deuterium-enriched analogs of the incontinence medication oxybutynin.

All that patenting activity has led some to wonder whether the "Sepracor effect" will take hold: Years ago, Sepracor's success in patenting single isomers of blockbuster racemic drugs led to industry-wide changes in patenting behavior, with companies quickly seeking to claim chiral versions of their compounds. It's too early to tell whether this is happening with deuteration, says patent lawyer Justin J. Hasford of Finnegan, Henderson, Farabow, Garrett & Dunner. "But if a pharmaceutical company thinks this is a good strategy, it definitely will seek to patent deuterated versions of its compounds," he predicts.



Pointing to the subtlety of the chemical changes involved in swapping hydrogen for deuterium, both Tung and Grey predict that the Food & Drug Administration will allow their firms to streamline clinical testing of deuterated drugs, reducing the time and cost of bringing the drugs to market.

Czarnik suggests, however, that the biological consequences might not be as subtle as the chemical change. Because deuterium and hydrogen differ both in size and hydrophobicity, "you should be able to find deuterated drugs that bind more tightly to their biological targets," he says. "The question is whether this effect is large enough to measure and to matter."

AS EVIDENCE for this kind of tighter binding, Czarnik points to data showing that the protease inhibitor gabexate can be separated from tetradeuterated gabexate on columns containing immobilized protease enzymes such as trypsin or thrombin, but not on columns containing immobilized bovine serum albumin or lysozyme, to which gabexate binds only nonspecifically. Emboldened by this data, Czarnik's new company, Deuteria Pharmaceuticals, has built a library of combinatorially deuterated atorvastatins, which they are now screening for the ability to inhibit atorvastatin's biological target, HMG-CoA reductase. Atorvastatin is the active ingredient in Pfizer's Lipitor, the world's biggest-selling drug.

At Concert, "we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it," Tung says. He calls his firm's recent deal with GSK "transformative." In particular, he says, it ensures Concert's financial future in a tough business climate, giving the fledgling firm the kind of resources it typically would only be able to recruit if it had moved compounds into Phase II clinical trials. "That's really unusual," Tung says.

Tung, who helped discover the HIV protease inhibitors fosamprenavir and amprenavir early in his career at Vertex, is quick to point out that it's always been difficult to bring drugs to market, and it's getting harder all the time. "What we're doing is reducing the risk" of failure in drug development, he says. Auspex' Grey agrees, echoing something that Nobel Prize-winning pharmacologist James W. Black once said: "The easiest way to find a drug is to start with one." ■



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