

COVER STORY

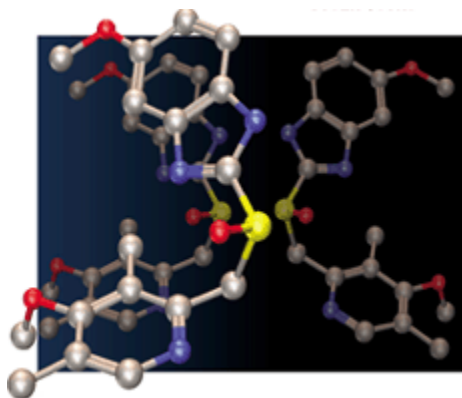
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CHIRALITY AT WORK

Drug developers can learn much from recent successful and failed chiral switches

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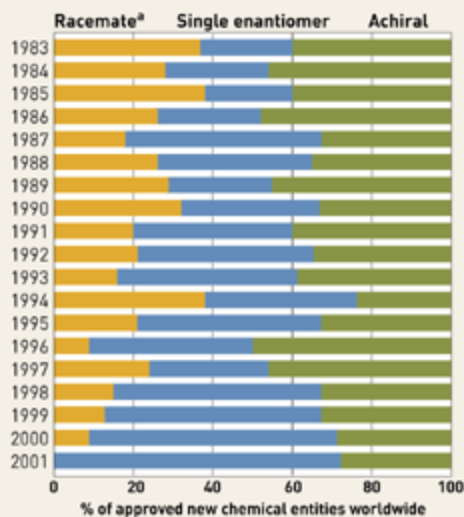


PARAGON The chiral switch of omeprazole (Prilosec) has been called ideal.

CHEMICAL COMPUTING GROUP IMAGE

WINNING STREAK

Single enantiomers have dominated racemates since 1990



^a Data include diastereomeric mixtures. SOURCE: Data for 1989-2000 were reported in *Nature Reviews Drug Discovery* [1, 753 (2002)]. Additional data provided by Israel Agranat and Hava Caner.

In Patricia D. Cornwell's 1991 murder mystery "Body of Evidence," one clue to a woman's death is Robitussin, an over-the-counter cough medicine with the active drug dextromethorphan.

Investigators are puzzled because the amount the woman had ingested was much less than what would normally cause a fatal overdose. Later, polarimetric analysis of extracts of the gastric content reveals the presence of levomethorphan, the enantiomer of dextromethorphan and a powerful narcotic. Because the enantiomers cannot be distinguished by routine toxicological tests, the dead woman almost succeeds in concealing her suicide, were it not for a chief medical examiner who knew of the handedness of some drug molecules.

Awareness of the stereoselectivity of drug action has intensified since the thalidomide tragedies of the 1960s as differences in the pharmacology and

pharmacokinetics of enantiomers have become better understood. By the mid-1980s, people "really hit on the idea that we would do better with single enantiomers than with racemates," says John Caldwell, dean of the faculty of medicine at the University of Liverpool, England. A recent review by Caldwell and organic and medicinal chemists Israel Agranat and Hava Caner at the Hebrew University of Jerusalem indicates that since 1990, the proportion of single-enantiomer drugs among approved new chemical entities worldwide has been consistently greater than that of racemates [*Nat. Rev. Drug Discovery*, **1**, 753 (2002)].

Caldwell has been instrumental in highlighting chiral issues in drug development. Racemic drugs can cause problems because of the differences not only in the biological effects but also in the pharmacokinetics of the enantiomers, he says. Perhexiline, a drug used to treat abnormal heart rhythms, is an example.

According to Caldwell, in the 1980s, the racemate killed a number of people who had accumulated gram quantities of the enantiomer that was more slowly metabolized. If researchers had realized that one enantiomer had a much longer half-life, they might have come up with a drug with just the fast-clearing enantiomer, he says. "It was one of the very early examples of why you need to understand more about what's going on with chiral drugs."

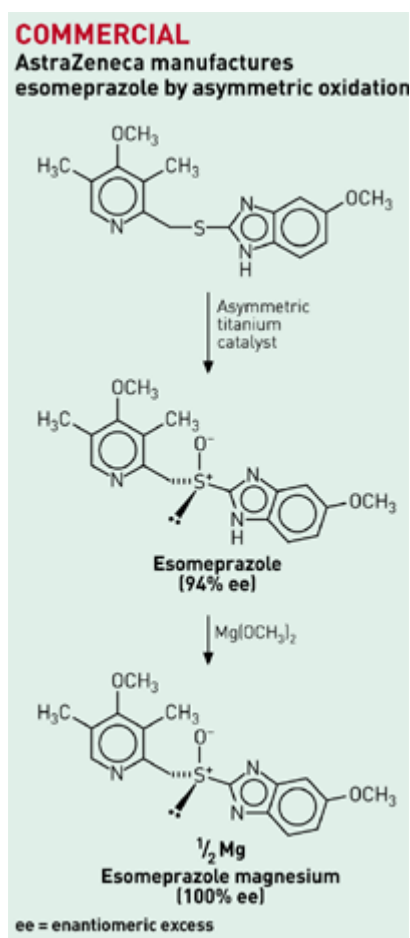
Contrary to popular belief, according to Agranat, Caner, and Caldwell, the thalidomide tragedies could not have been avoided by use of single enantiomers, because both enantiomers have equal teratogenic potency in the rabbit. In addition, the enantiomers rapidly racemize in the body, so even if they had differed in teratogenicity, use of single enantiomers would have been precluded.

In addition to raising the profile of single-enantiomer chiral drugs--a trend fueling growth in chiral technologies--chiral effects in therapeutics are being exploited in two other ways: by developing better single-enantiomer versions of already approved racemic drugs, known as chiral switching, and by discovering distinct therapeutic uses for enantiomers of chiral drugs. The record of success for chiral switches is uneven, and the intellectual-property status of single enantiomers is ambiguous. Drug discoverers and patent attorneys must examine the examples of the past to shape the development and intellectual-property protection of the chiral drugs of the future.

THE POSTER DRUG for chiral switching may as well be the "purple pill." Nexium, or esomeprazole, is the S enantiomer of omeprazole, the active ingredient of AstraZeneca's

heartburn drug, Prilosec. The basic patent for Prilosec, which posted sales of \$5.6 billion in 2001, expired in 2002. Generic omeprazole would have eroded the market share of Prilosec by up to 85%, but tour-de-force development and marketing of Nexium has kept AstraZeneca's share of the market intact. Combined sales of Nexium and Prilosec were almost \$6.2 billion in 2001 and \$6.6 billion in 2002.

Many have hailed the Prilosec-Nexium chiral switch as ideal, including Agranat, Caner, and Caldwell, who wrote in their review: "When the chiral switch is developed by the proprietor of the racemate, it is advantageous for the single enantiomer to reach the market before the expirations of the patents of the racemates, and before the incursion of the respective generic drugs. This was the case with esomeprazole."



Esomeprazole traces its roots to page 68 of lab book 168 maintained by Ylva Örtengren, a chemist working in a research unit called Hässle, belonging to the Swedish company Astra, now AstraZeneca. There, on Jan. 4, 1979, Örtengren described the synthesis of omeprazole, then code-named H168/68. It was the first of so-called proton pump inhibitors, a new class of drugs for controlling gastric acidity.

Although a bright star in the pharmaceutical galaxy, omeprazole had a problem: significant interindividual variability. Some patients rapidly metabolized the drug and needed higher or multiple doses to achieve relief. Others metabolized the drug slowly and their exposure to the drug was greater than what was needed. In 1987, a program was launched to find a better omeprazole, one with higher bioavailability and lower clearance through the liver, according to Per Lindberg, AstraZeneca senior scientific adviser for gastrointestinal therapeutics and coinventor of esomeprazole.

"During the 1980s, we had many reasons not to be interested in omeprazole enantiomers," Lindberg says. One was the belief, on the basis of the drug's mechanism of action and in vitro tests, that the individual enantiomers would have the same effect. Another was the

result of a study by researchers at Merck in the late 1980s, which concluded that concentrations of the enantiomers in plasma after administration of omeprazole are essentially equal [*J. Chromatog. B*, **666**, 323 (1995)]. Still another was the absence of sufficient amounts of single enantiomers to test in vivo.

Lindberg and coworkers took a straight medicinal chemistry approach: work with the omeprazole framework, generate derivatives, and screen compounds on the basis of bioavailability. But in 1990, Lindberg recalls, "we decided to try to get omeprazole enantiomers so we could at least check whether they were metabolized differently." When after much effort from coinventor Sverker von Unge enough material became available, the salts of the enantiomers were tested in rats.



Agranat

Caner

Caldwell

"Any new drug that's chiral is likely to be developed and marketed as a single enantiomer. You win more than you lose with single enantiomers."

THE TESTS SHOWED that the R enantiomer was significantly more active than the S enantiomer or the racemate in the rat, justifying clinical trials. "We were lucky to test in rats," Lindberg says. "Later tests showed that the enantiomers have equal activity in dogs. If we had tested in dogs to start with, we wouldn't have continued." Human testing of both enantiomers brought another surprise: the S enantiomer is more active. Thus did (*S*)-omeprazole find itself vying with three omeprazole derivatives from the medicinal chemistry effort for the title "improved omeprazole." Esomeprazole won.

According to studies by Lindberg and others, the superior clinical efficacy of esomeprazole is due to its higher and more consistent bioavailability compared with omeprazole. And because of the more consistent pharmacokinetics of esomeprazole, interindividual variability with esomeprazole is reduced [*Aliment. Pharmacol. Ther.*, **17**, 481 (2003)].

In another review, Lindberg and AstraZeneca colleagues Lars Olbe and Enar Carlsson summarize other results with esomeprazole that bolster the claim of an improved omeprazole: higher availability and oral potency, higher symptom relief, and higher healing rates in patients with esophagitis. In combination with antibiotics, esomeprazole is also highly effective in healing duodenal ulcers and eradicating the peptic-ulcer-causing bacteria *Helicobacter pylori* [*Nat. Rev. Drug Discovery*, **2**, 132 (2003)].

Esomeprazole manifests inventiveness because its better performance compared with the racemate is not obvious, Agranat says. If the only advantage of a single enantiomer is to lower the dosage by a factor of two, that is not inventive, he explains. "Esomeprazole is way beyond the racemate therapeutically. It is a beautiful example of a chiral switch and the success of medicinal chemistry."

A more recent success story is the citalopram-escitalopram switch. Citalopram (Celexa) is a racemic antidepressant marketed in the U.S. by Forest Laboratories. The basic patent had expired by the time it was approved in 1998. But as a new chemical entity, Forest received five years of marketing exclusivity, which expires in July 2003. By filing pediatric studies, Forest gained six months more, extending the exclusivity to January 2004. By law, the [Food & Drug Administration](#) cannot entertain applications for generic citalopram during the exclusivity period.

Meanwhile, various studies were showing not only that the S enantiomer is the therapeutically active isomer but also that it has a more rapid onset of action and a more favorable benefit/risk ratio than the racemate. FDA approved escitalopram (Lexapro) last August. Because FDA does not consider single enantiomers of already approved drugs as new chemical entities, the marketing exclusivity for escitalopram--as well as esomeprazole--is only three years, plus six months if pediatric studies are filed.

Lexapro became available at a time when sales of Celexa were still growing. At the end of Forest's fiscal 2002, sales of Celexa were almost \$1.1 billion, up 52% from the previous year. In the quarter ending on Dec. 31, 2002, Lexapro sales reached almost \$81 million.

Contrast those scenarios to the aborted chiral switch of fluoxetine (Prozac), Eli Lilly's blockbuster antidepressant. Sales reached \$2.6 billion in 2000, dropped to \$2 billion in 2001 as generic versions entered the market, and plunged to \$734 million in 2002.

Eli Lilly believed that the enantiomers were not significantly different and did not actively pursue a chiral switch, Agranat says. But in the mid-1990s, the drug company Sepracor obtained separate patents for

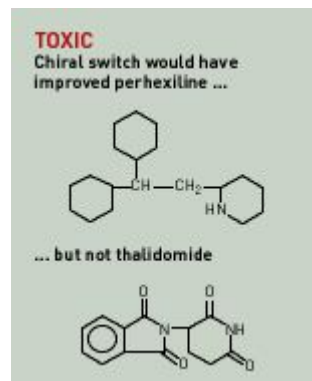
use of (*S*)- and (*R*)-fluoxetine to treat migraine and depression, respectively. In 1998, Eli Lilly and Sepracor agreed to codevelop (*R*)-fluoxetine as the single-isomer, side-effect-free version of Prozac.

"Prozac was a big prize," says Richard D. Kelly, an intellectual-property expert and senior partner at the law firm Oblon, Spivak, McClelland, Maier & Neustadt in Alexandria, Va. "If a safer version came to market, no doctor in his right mind would prescribe Prozac." Generic versions would be irrelevant.

But in October 2000, Eli Lilly called off the deal. Clinical studies showed side effects at high doses not observed with the racemate. Furthermore, Eli Lilly had hoped patients could be switched to (*R*)-fluoxetine before a key patent expired in December 2003, but in August 2000 a court ruled that patent invalid. The ruling was upheld by an appeals court in May 2001. By then, the only other patent protecting Prozac had expired. Moreover, says Agranat, Eli Lilly was developing another antidepressant believed to be better than Prozac, duloxetine hydrochloride (Cymbalta). FDA issued an "approvable" letter for this drug last September.

Lilly took the chiral-switch path "way too late," Kelly says. "Lilly's chief executive last year announced that life-cycle management will now start right at the beginning of projects and not at the end, as happened with Prozac," he adds.

NEVERTHELESS, even a timely and successful chiral switch can be a disaster, as exemplified by the fenfluramine fiasco. Fenfluramine is a racemic drug used as an appetite suppressant. "Fen-phen," the combination of fenfluramine and the achiral antiobesity drug phentermine, became widely used for weight loss. When dexfenfluramine, the *S* enantiomer, came to the U.S. market in 1996, fen-phen also came to mean the combination of dexfenfluramine and phentermine. According to Agranat, Caner, and Caldwell, in 1996 and 1997, about 18 million prescriptions were written in the U.S. for fenfluramine and phentermine and more than 2 million for dexfenfluramine. Fatal side effects soon became clear, and fenfluramine and dexfenfluramine were withdrawn from the market in 1997.



"From the point of view of chiral switching

and intellectual property, dexfenfluramine was a success story," Caner says. "I don't know if the drug companies could have known about the terrible side effects. Because so many people used dexfenfluramine, the side effects came out so clearly, so fast."

According to Agranat, Caner, and Caldwell, litigation related to this fiasco cost American Home Products (now Wyeth), which marketed dexfenfluramine in the U.S., \$13.2 billion.

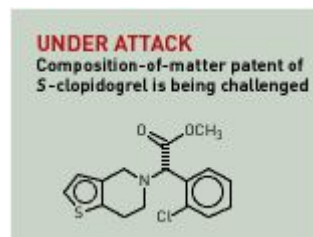
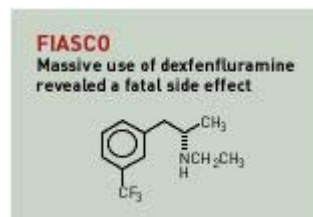
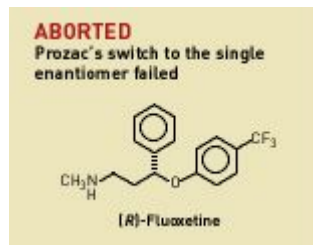
Regarding the chiral-switch poster drug, however, Lindberg says that esomeprazole is not so much about life-cycle management as it is about inventing a better drug. "People misunderstand. Esomeprazole is the achievement of 15 years of research, not simply a trick."

Although Lindberg dislikes references to esomeprazole as a chiral switch, it fits the definition coined by Agranat, Caner, and Caldwell--a change in the status of chirality. And indeed, esomeprazole has been key in extending the life cycle of omeprazole. As Kelly points out, "The patents for Nexium give AstraZeneca more than 20 years of protection on the same molecule, omeprazole."

Sepracor was a pioneer in the use of chiral switching for life-cycle management. By outlicensing its use patents for single enantiomers of racemic drugs, the company tapped a vein of royalty income, usually from the inventors of the racemates, such as Eli Lilly in the case of (*R*)-fluoxetine and UCB Pharma for levocetirizine, the single-enantiomer form of the allergy drug Zyrtec. (Sepracor's strategy also includes filing use patents for active metabolites of approved drugs. For example, the company receives royalties from Schering-Plough for desloratadine, the active metabolite of the allergy drug Claritin and the active ingredient in Clarinex.)

CONFLICTING RULINGS have created confusion about the patentability of single enantiomers. In an earlier review, Agranat and Caner point out precedents [*Drug Discovery Today*, **4**, 313 (1999)]:

- The U.S. Court of Customs & Patent Appeals (CCPA) ruled in



1960 that a claim that the specific therapeutic activity of the (–)-isomers of two spasmolytic compounds is better than that of the (+)-isomers or racemates is unpatentable because the superior activity is obvious in light of a statement in an organic chemistry textbook that the biological effects of enantiomers can differ significantly.

- A claim that a mixture of the (–)-isomers of certain methylbenzomorphans exhibits unique therapeutic activity as well as advantages over similar drugs such as morphine--initially rejected with other claims in the patent application on the basis of obviousness--was upheld by CCPA in 1978, along with other claims, on the basis that the combination of properties "was totally unexpected." According to CCPA, properties expected from prior art must be differentiated from those not obvious from prior art.
- The European Technical Board of Appeal ruled in 1988 against a claim that the (d) enantiomers of α -phenoxypropionic acid derivatives have better biological activity than the racemate because discovery of the effect is not an inventive step; it is obvious from prior art.

According to these precedents, patentability of single enantiomers is based on inventiveness not obvious from prior art. This standard will be tested again in litigation related to patents protecting the blood-thinning drug (*S*)-clopidogrel (Plavix). Plavix was developed by Sanofi Synthelabo and is marketed in the U.S. by Bristol-Myers Squibb. Sales in 2002 were \$2.5 billion.

The composition-of-matter patent covering the racemate, filed in 1983, will expire in 2003. In 1989, a composition-of-matter patent on the *S* isomer was granted; that patent will expire in 2008. When Plavix was approved by FDA in 1997, protection based on this later patent was extended because of delays during regulatory review. It will now expire in 2011.

Both patents are being challenged by generic companies. Because the litigation is still in the discovery phase, the basis of the challenges has not yet been made public. However, consideration of the legal precedents would suggest that the composition-of-matter patent for the single isomer may not hold.

Speaking generally and not about this particular case, Kelly says: "A patent on the racemate is a patent on the chemical formula without specifying stereochemistry. It covers the racemate and the individual isomers." Applied to Plavix, this suggests the single-isomer patent might be invalid because it embodies prior art.

Inventiveness not obvious from prior art is a clear, reasonable, and

consistent criterion for patentability. But the situation is muddled by certain Sepracor patents that triggered Agranat's interest in delving into the scientific basis of intellectual property claims for chiral switches.

U.S. Patents 5,114,714 and 5,114,715 are a case in point. The first claims that using the R enantiomers of the anesthetics isoflurane and desflurane is better than using the racemate. The second claims that using the S enantiomers of the same anesthetics is better than using the racemate. The patents--which Agranat, Caner, and Caldwell call "enantiomeric pairs of patents"--are worded almost identically, except for R and S descriptors.

"You can say that one enantiomer is better than the other or a specific enantiomer is better than the racemate. But something is not right when you say both enantiomers are better than the racemate for the same specific action," Caner says.

Caner has been studying chiral switches, including chiral switch patents, as part of her Ph.D. research in drug discovery under Agranat's direction. When she read these patents, she was studying, also as part of her Ph.D. thesis, the diastereomeric interactions of quinine. "I immediately thought that diastereomeric interactions might be involved here," she says.

"You can explain the claims in these patents scientifically only by invoking diastereomeric interactions," Agranat says. He explains: Consider a pair of enantiomers R and S or a racemic drug RS. R and S may each give rise to homochiral diastereomeric interactions RR and SS, respectively. By contrast, RS may give rise to both homo- (RR and SS) and heterochiral (RS) diastereomeric interactions. Only when both homochiral interactions RR and SS are pharmaceutically superior to the heterochiral interaction RS would Sepracor's patent claims be true.

But when Agranat and Caner examined the chemistry of isoflurane and desflurane, they found no evidence of such interactions. "It was just a matter of covering all the bases," Caner says.

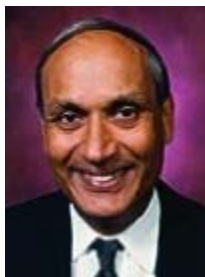
"The patents provoked me," Agranat says. "Sepracor probably didn't know which of the enantiomers was better than the racemate and the other enantiomer. The patents did not even characterize the enantiomers by optical rotations."

Sepracor has many such pairs of patents for various racemic drugs, including UCB Pharma's cetirizine (Zyrtec), for allergy, and Aventis' zopiclone (Imovane), for sleep and convulsive disorder.



Lindberg

The single-enantiomer drugs are better in certain ways than the racemates. For example, levocetirizine, now on the market as Xyzal or Xusal, is less sedating than the racemate Zyrtec, according to a recent Sepracor profile by Datamonitor, a business information company. However, the expectation that levocetirizine will help UCB Pharma retain a good portion of the Zyrtec market lost to generic cetirizine has not been met, the report says.



Midha

Sepracor itself is developing eszopiclone, the S-enantiomer-only version of Imovane, and submitted a New Drug Application early this year. According to Datamonitor's report, the bitter aftertaste associated with Imovane is absent in eszopiclone. However, eszopiclone faces competition from other products, and Sepracor may need a marketing partner to fulfill the drug's potential, the report says.

Sepracor may be at the end of the chiral-switch rope. According to the Datamonitor report, pharmaceutical companies have caught on to its strategy and are themselves filing patents on single isomers very early in drug development.

"Any new drug that's chiral is likely to be developed and marketed as a single enantiomer," Caldwell says. "You win more than you lose with single enantiomers," he adds, allowing that exceptions are likely but few.

By the mid-1980s, people "really hit on the idea that we would do better with single enantiomers than with racemates."

AT PRESENT, a number of chiral switches are still in the pipeline. Moving forward, the number of racemic drugs amenable to chiral switching will diminish, observers say. What is likely to increase is the development of single enantiomers of a chiral compound for different therapeutic uses, as exemplified by the dextromethorpan/levomethorpan dichotomy.

Examples include the work of Kamal K. Midha on methylphenidate (Ritalin), a drug to treat attention deficit hyperactivity disorder (ADHD). Midha is currently an adjunct professor of pharmacy and

associate member of psychiatry at the University of Saskatchewan, Saskatoon.

Methylphenidate has two chiral centers, and the drug is a racemate of the S,S and R,R isomers. During the 1980s, a research program at Saskatchewan, run jointly by Midha and pharmacy professor John W. Hubbard, established that the anti-ADHD activity resides in the R,R isomer [*J. Pharm. Sci.*, **78**, 944 (1989)]. On the basis of this and other studies, in 1995, Midha suggested to a Canton, Mass.-based company called Copley Pharmaceuticals that the single-isomer drug would be better than the racemate.

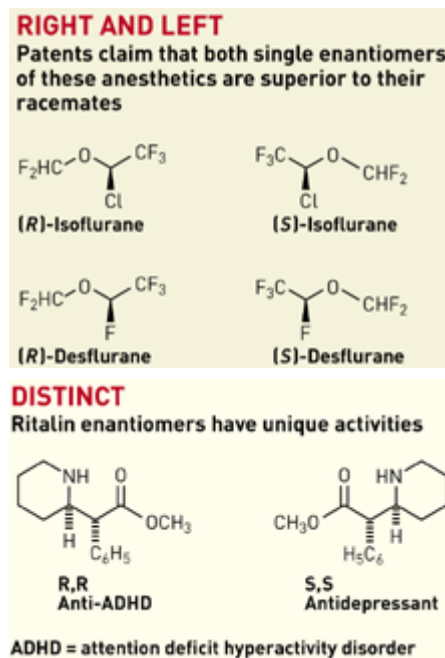
Midha says he was told by a patent attorney that the idea was brilliant but had become prior art because it had been published. Thus, he was stunned when he found a patent for use of the R,R isomer as he had envisioned. The patent was issued to Celgene in 1998, which licensed it to Novartis. In 2001, Novartis launched the single-isomer dexamethylphenidate (Focalin) and has exclusive marketing rights until November 2004.

Focalin is an immediate-release drug, but ADHD is better treated by controlled-release dosing. For that reason, Midha suggests, sales of Focalin have lagged those of controlled-release methylphenidate products.

Although he was disappointed, Midha continued to pursue better ways of treating ADHD with dexamethylphenidate.

Patients with ADHD are treated with a range of drugs. Some respond to methylphenidate, while others respond to other types of analeptics, a class of drugs that stimulate the central nervous system (CNS). "It occurred to me that rather than trying out which one works, the best way is to combine dexamethylphenidate with a second CNS stimulant," Midha says. A patent for such use of dexamethylphenidate was issued in 2001 to Pharmaquest, a Bermuda-based company Midha founded to commercialize these inventions.

Another of Midha's inventions is a once-a-day dexamethylphenidate that delivers pulses of the drug so that control of attention is maintained



from morning until about 9 PM. With pulsatile delivery, one dosage form releases an initial dose followed by a release-free interval, after which a second dose is released, followed by one or more release-free intervals and drug-release pulses. Midha says clinical studies at McLean Hospital in Boston show that such a dosage form allows control of ADHD while also allowing children to sleep at night. The patent for this invention was issued in 2002.

AT THE SAME TIME, Midha and coworkers turned their attention to the S,S-isomer, called *l*-methylphenidate. "I was surprised that it reduces dysphoria, the feeling of depression and dejection," he tells C&EN. Its use to treat depression has been patented. Midha now has two agents with different therapeutic actions: dexamethylphenidate for ADHD and *l*-methylphenidate for depression.

The activity of *l*-methylphenidate can be used to "rescue" patients suffering from depression. Selective serotonin reuptake inhibitors like citalopram, Midha explains, take between three and six weeks to take full effect. "In the meantime, these patients can be very depressed, very suicidal. What do you do then?" he says. *l*-Methylphenidate can help during the period of adjustment to the other drug. A patent for this invention was issued to Pharmaquest in 2000.

For all these studies, Midha and coworkers could get only small amounts of pure enantiomers with much effort. Midha pitched the idea of synthesizing the pure enantiomers to Takasago Chemical. "Takasago said they will experiment. They sent samples and we tested them," he says. Takasago now has an asymmetric chemical route ([C&EN, Feb. 17, page 73](#)).

Pharmaquest and Takasago are in active discussions to license the single-enantiomer patents. A generic company specializing in drug delivery would be the ideal partner for challenging Focalin in 2004.

Natural products present another fertile field for discovering therapeutic properties of single enantiomers. According to Agranat, Caner, and Caldwell, recent studies of the enantiomers of natural products or semisynthetic drugs derived from natural products indicate that they could have distinct therapeutic value. For example, (–)-quinine is an antimalarial, whereas its quasienantiomer (+)-quinidine is an antiarrhythmic compound. Similarly, the (–)-enantiomer of the predominant natural (+)-gossypol has male-contraceptive and anticancer activities. Development of unnatural ent steroids--ent-19-nortestosterone by the Dutch drug company Organon is an example--is further evidence of interest in this type of chiral switch, Agranat adds.

The intellectual property issues related to chiral switches aren't going away soon. Indeed, they may be compounded by formulations

involving mixtures of enantiomers not in a 1:1 ratio. An example is Adderall, which is made up of various salts of amphetamine and dextroamphetamine in a nonracemic ratio. The drug was approved for treatment of ADHD in October 2001.

"Adderall qualifies for a chiral switch," Agranat says. "Maybe the technologies of discovery and evaluation of pharmacological effects may become so good that the starting point could be a single enantiomer, and in a few years, nonracemic mixtures could be developed that are better."

COVER STORY

CHIRAL BUSINESS

Fine chemicals companies are jockeying for position to deliver the increasingly complicated chiral small molecules of the future

CONTEST

Vying For Chiral Hydroformylation Advantage

NICHE PLAYER

Chiral Quest Sees Advantages In Independence

STEADY SHARE

Worldwide sales of single-enantiomer pharmaceutical products approach \$160 billion

BLOCKBUSTERS

Top 10 single-enantiomer products belong to billion-dollar club

CHIRALITY AT WORK

Drug developers can learn much from recent successful and failed chiral switches



ONLINE EXCLUSIVE

REALITY CHECK

When Chemistry Bows To Economics

HARVEST

Research in Chiral Fine Chemicals Reaps Recognition

CONSTANT

Chiral separations are enduring items in the toolbox

CASE HISTORIES

History and choice shape portfolios

CALENDAR



Events Of Interest

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