New Single-Isomer Compounds on the Horizon

By Joseph Gal, PhD

ABSTRACT

In 1992, the Food and Drug Administration (FDA) issued new guidelines governing stereoisomerism in new-drug development. The guidelines strongly encourage the development of single isolomers and discourage stereoisomeric (eg, racemic) mixtures. As a result, most new chiral drugs are being developed as single enantiomers (ie, single isolomers). There are three mechanisms for the identification and development of new single-isomer drugs: chiral switches (CS), chiral metashifts (CM), and new single-isomer chemical entities (NSICEs). In a CS, one of the two enantiomers of an established racemate is developed as a new drug, with the expectation that the single-isomer form has advantages over the racemic parent in terms of efficacy and/or adverse effects. Many new CS drugs are in development, eg, (S)-oxybutynin for urinary incontinence and escitalopram for depression. In a CM, a chiral metabolite of a drug is developed, in single-isomer form, as an agent with the advantage of a parent. Among the current CM drugs in development are (+)-norcisapride (safer GI prokinetic agent than the racemic parent cisapride) and (S)-desmethylzopiclone (anxiolytic agent, metabolite of the sedative-hypnotic zopiclone). Many NSICEs are in development, eg, rosuvastatin as an antihypercholesterolemic, posaconazole as an antifungal, sitafloxacin as a fluoroquinolone antibacterial, pregabal in as an anticonvulsant, abarelx as an antineoplastic, etc. As in the development of any new drug, not every single-isomer candidate will reach the clinic, but there is no doubt that the move to single-isomer agents is an important step forward in the search for better and safer drugs.

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INTRODUCTION

Single-isomer drugs—more appropriately termed single-enantiomer drugs—contain only one of the two mirror-image forms of a chiral molecule (see Gal, pp 8-13). Interest in such drugs has intensified greatly during the past quarter-century, and a great deal of research on the basic and clinical aspects of single-isomer drugs has shown that the two mirror-image forms often differ significantly in their effects. As a result, the consensus today is that in most cases a single-isomer form of chiral drugs is advantageous over the corresponding racemic mixture. Many single-isomer compounds are in various stages of development as new therapeutic agents, and many others are being studied in research laboratories for their pharmacological potential.

The purpose of the present article, then, is to survey interesting new single-isomer candidates that are, at the time of this writing, in more advanced stages of development and that have a good probability of reaching the clinic. It is recommended that the companion article on the fundamentals of the phenomenon of single-isomer compounds be reviewed as an aid to the appreciation of the nature and terminology of these agents.

A BRIEF HISTORY OF SINGLE-ISOMER DRUGS

Single-isomer drugs are not new; indeed, some of the oldest drugs in use have been single isolomers. These drugs were first used as crude plant extracts, and subsequently their medicinal properties were discovered by modern medicine. For example, ephedrine has been used in China for 5,000 years as an extract from ephedra species (“Ma Huang”).1 Pure ephedrine substance was isolated in 1887 and introduced into Western medicine in 1925.1 Another example is morphine, the main active alkaloid in opium, an extract of poppy (Papaver somniferum) seed capsules. The first credible reference to opium was in the writings of Theophrastus, the Greek philosopher and pupil of Aristotle, in the third century B.C.,2 but opium may have been used by the ancient Egyptians as early as 3,500 years ago, although this point is a matter of debate.1 Pure morphine substance was isolated in 1805, and by the middle of the 19th century it came into use as the alkaloid instead of the crude extract.3 There are many other centuries-old single-isomer drugs still in use, eg, quinine, cocaine, digoxin, etc.

By the end of the 20th century, about one half of all drugs in use were chiral, and about 50% of such drugs were used in single-isomer form, the other half being racemic. An interesting aspect of the introduction of chiral drugs was pointed out by Ariens and Wuis, who, in 1987, found that 98% of chiral drugs obtained from natural sources (or directly derived from natural compounds) were marketed in single-isomer form, while only 12% of synthetic chiral drugs were single isolomers.4 The interpretation is clear: since nature usually provides chiral substances in single-isomer form, drugs from natural sources were introduced almost always as single isolomers; on the other hand, when chemical synthesis was required to obtain chiral drugs, the more easily accessible and cheaper racemic form was chosen.

In the past 25 years, intensive research efforts have been exerted to elucidate the role of chirality in drug action and disposition.5 In general, it has become abundantly clear that chirality often has an important role in shaping the pharmacodynamic and/or pharmacokinetic behavior of chiral drugs and that the two enantiomers of a racemate often differ.

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significantly, sometimes even drastically, in their pharmacological and/or pharmacokinetic behavior.\textsuperscript{3} As a result, regulatory agencies, academia, and the pharmaceutical industry took up the question of the development of new drugs as single isomers versus racemates.

The debate culminated with the United States Food and Drug Administration (FDA) issuing new guidelines in May 1992 on the role of stereoisomerism in new-drug development.\textsuperscript{4} Similar guidelines were also issued by other drug-regulatory agencies around the world. In essence, the new guidelines strongly encourage the development of single-isomer drugs and discourage new racemates, although the latter are not banned and new racemic drugs can be introduced in certain circumstances. However, the overall effect of the new regulatory climate has been to stimulate the development of single-isomer drugs with a near-complete exclusion of new racemates.

This new regulatory climate is already making itself felt, and the development and marketing of single-isomer drugs has greatly accelerated during the last ca. 10 years, to the point that in 1999 the worldwide sale of single-isomer drugs topped the $100 billion mark, representing approximately one third of total drug sales.\textsuperscript{5}

**SINGLE-ISOMER DRUG CANDIDATES IN DEVELOPMENT**

As discussed above, most new chiral drugs will undoubtedly be developed in single-isomeric form. It is also clear that research activities both in academic and industrial laboratories on the detailed role of chirality in the actions and disposition of chiral drugs will continue unabated. Such research is of fundamental importance for the rational design and development of safe and effective single-isomer drugs. It is important to note, however, that for the foreseeable future many of the established racemic drugs will continue to be used in the racemic form.

The development of new single-isomer drugs relies, in general, on the same scientific and technological foundations necessary for the development of any new drug. However, there are certain branches of biomedical science and technology that are specific underpinnings of the development of single-isomer agents. It goes without saying that understanding the three-dimensional aspects of the interaction of drugs with their target receptors is of paramount importance if we are to design safe and effective single-isomer agents. A variety of approaches are used in studying the three-dimensional details of drug-receptor interactions, but the recent advances in molecular biology and in computational methodologies are providing great power for such investigations.\textsuperscript{6} Access to a large variety of single-isomer drugs has become possible as a result of the considerable advances of recent decades in synthetic organic chemistry and in combinatorial chemistry. Finally, advances in analytical methodology based on enantioselective chromatography permit isomer-specific measurement of drugs in biological fluids, a prerequisite for the development of single-isomer agents.

Pharmacological, pharmacokinetic, and toxicological considerations suggest that, as a generalization, the single enantiomer may possess one or more of the following potential advantages over the racemic mixture: reduced dosage; reduced adverse effects, including fewer drug interactions; improved therapeutic efficacy; better-understood and simpler pharmacology; clearer pharmacokinetics; better-defined relationship between serum drug concentration and therapeutic/toxic effects. Naturally, not every one of these potential benefits is realized in every case, and in this context each new single-isomer drug candidate must be considered on its own merits. Furthermore, and importantly, exceptions to the generalization that a single isomer is better than the racemate do exist (see below).

The survey that follows focuses primarily on single-isomer agents that are not yet approved in the US (at the time of writing) but that are relatively well advanced in the drug-development process. However, a few compounds that are not as far along the process will also be mentioned when such agents are of particular interest or illustrate an important principle. One unavoidable handicap in a survey of new drugs not yet approved is that the information available on their pharmacology, pharmacokinetics, and clinical aspects is at times limited. It should also be pointed out that since the number of single-isomer new-drug candidates is very large, the survey is necessarily not comprehensive. Thus, only a selection of agents can be discussed, and while an effort was made to cover a variety of therapeutic areas and agents, to some extent the choices reflect the author's interests and bias.

In general, the new drug candidates in development may be loosely divided into two types: (1) compounds derived from nature or closely related to natural products, such as steroids, alkaloids, antibiotics, peptides, etc. These are often large molecules containing multiple (>3) chiral centers, and are obtained directly from natural sources or are chemically modified derivatives of compounds from nature; some, however, may be entirely synthetic; and (2) other, typically smaller molecules not directly connected to compounds from nature, often with few (1–3) chiral centers and usually totally synthetic. The borderline between the two groups, however, is not sharp and overlap is not infrequent, eg, some natural products may only have a few chiral centers, while some synthetic drugs may be rather large and have multiple chiral centers.

New single-isomer drugs are created via one of three available mechanisms: (1) the chiral switch; (2) the chiral metashift; or (3) new single-isomer chemical entity.

**The Chiral Switch**

In a chiral switch (CS), one of the two enantiomers from an existing racemic drug is developed as a new drug. The new single-isomer agent may be for the same indication as the parent racemate or for a different indication. The rationale for a CS is, of course, the advantage obtained by using a single isomer instead of the racemate. With the recent and current intense interest in single-isomer drugs a number of
CSs have been implemented and many more CS candidates are in development.24,25

Recently implemented examples include the antibacterial agent levofloxacin (from racemic ofloxacin); levosulpiride (from racemic sulpiride) available in some European countries but not in the US; the anesthetic agent levubupivacaine (from racemic bupivacaine); the analgesic/anti-inflammatory dexketoprofen (from racemic ketoprofen); the bronchodilator levalbuterol (from racemic albuterol); the anesthetic (S)-ketamine (from racemic ketamine) available in Germany; the analgesic and anti-inflammatory dexibuprofen (from racemic ibuprofen) available in several European countries but not in the US, etc. It is noteworthy, however, that CSs were practiced long before the current era of intensive focus on single-isomer therapeutics. For example, several decades ago the introduction of the racemic oral contraceptive norgestrel was followed some years later by the marketing of its active single-isomer form levonorgestrel, and both drugs are still available today. The theoretical advantages of single-isomer drugs are generally accepted and the benefits of many of the implemented CSs are clear; however, confirmation of the advantages of some of the recent CS drugs in clinical practice will have to await more extensive clinical experience.

Not surprisingly, not all CSs are successful. For example, dilevalol (a single isomer from the antihypertensive agent labetalol, a mixture of two racemates, ie, four stereoisomers) was withdrawn because of hepatotoxicity13; the single-isomer antiarrhythmic agent dexsotalol (from racemic sotalol) failed a major clinical trial because of a high mortality rate15; the development of the antidepressant (R)-fluoxetine (from racemic fluoxetine) was halted due to cardiotoxicity at higher doses.19 It is important to note that in all of these cases the racemic parent continues to be available.

There are several potential reasons for such CS failures, but one significant factor, often unappreciated, is the nature of racemic mixtures: when the two isomers are used together they may interact (ie, compete with or inhibit each other) at various critical sites (eg, at receptors, enzyme active sites, on binding proteins), and such interactions render the racemate more complex than a simple linear combination of the two isomers. Recognizing the presence of and predicting such interactions are not straightforward and it is not surprising therefore in some instances the single isomer displays “unexpected” behavior when it is separated from the mixture and used alone.

Another reason for the failure of the single isomer in a CS may be the independent protective effects provided by the other isomer present in the racemate. For example, it has been suggested that the better safety margin of racemic sotalol over dexsotalol may be due to the β-blocking effects of the racemate (provided by levo-sotalol).15 Overall, these phenomena are an expression of the pharmacological complexities of drug mixtures and do not negate the potential advantages of single-isomer agents as a general proposition, but they do emphasize the importance of good basic and clinical research necessary to elucidate such complexities.

An interesting and important fallout of the new climate favoring single isomers merits attention. In the past, the racemate was first developed, and the single isomer came later, if at all. Today, however, the scenario is different: henceforth most new chiral drugs will be developed from the outset in single-isomer form. In practice, then, a new racemic compound will be separated into the two isomers very early in the development process, and the latter will be evaluated individually for a decision on the isomer to be developed as the new single-isomer drug candidate. If the isomer selected eventually shows unacceptable adverse effects, its development will be halted. However, in such a case, ie, after the failure of the single isomer, no pharmaceutical company would even remotely contemplate to undertake the development of the racemate as a potentially safer drug (in what might be called a “reverse CS”). Thus, in reference to the above-mentioned failed CS of the antidepressant (R)-fluoxetine, if the development of fluoxetine were initiated today, it is clear that after the initial finding that the single isomer (R)-fluoxetine is cardiotoxic, racemic fluoxetine would not be brought to the market. Considering that racemic fluoxetine (Prozac) has been an important and successful drug, the conclusion is clear: potentially useful and safe racemic drugs may not be developed today because of the emphasis on single-isomer agents. This loss must, however, be weighed against the potential benefits of single-isomer agents.

**Drugs in Development Via CSs**

Many new CSs, in a variety of therapeutic areas, are in development.24-41 An example is oxybutynin, an antimuscarnic and antispasmodic agent used for the treatment of urinary incontinence. The drug is used as the racemic mixture (Ditran), and the S-enantiomer (Figure 1) is currently in development as a single-isomer agent for the treatment of urinary incontinence.40 It has been suggested that the relatively weak antimuscarnic activity of (S)-oxybutynin may translate into a lower incidence of antimuscarinic side effects,42 eg, dry mouth and blurred vision. (S)-Oxybutynin has completed Phase II clinical studies.

A well-advanced CS drug candidate is escitalopram (Figure 1), the single-isomer version of the racemic antidepressant citalopram (Celexa). Citalopram is a selective serotonin reuptake inhibitor (SSRI), and it has been reported that the SSRI activity resides essentially exclusively in the S-enantiomer of the racemate, ie, escitalopram.40 It would thus appear that the development of the pure active (single-isomer) form as a drug in its own right is indeed a logical step. In addition, in vitro studies of the cytochrome-P450 (CYP) mediated metabolism of escitalopram have led to the conclusion that the drug is unlikely to become involved in CYP-based drug interactions.49 A selection of other CSs reported in progress are shown in the Table. As seen in the table, a variety of therapeutic areas are addressed by these agents. It should be emphasized that not necessarily all the drugs in development in CSs will actually reach the clinic, but clearly many will and the CS sce-
nario is a viable mechanism for the introduction of new single-isomer drugs.

**The Chiral Metashift (CM)**

Many drugs are biotransformed to metabolites whose molecules are chiral. In a CM the chiral metabolite is developed in single-isomer form as a drug in its own right. As in CSs, the rationale is that the new drug has advantages over the parent, in terms of efficacy and/or adverse effects. As in CSs, the new drug may be for the same indication as the parent or for a different indication. The parent drug in a CM may be racemic, single-isomeric, or even non-chiral, but the metabolite is chiral and is developed as a new drug in single-isomer form.

The CM scenario has been little used and is only now beginning to receive significant attention. Active metabolites may represent an unexploited source of new drugs, since in many cases the metabolic fate of drugs and the activity of metabolites have not been determined. Furthermore, in many cases (e.g., the N-demethylated metabolites of N-methylated drugs), the metabolites are likely to have a longer elimination and reduced toxicity.

An early attempt at a CM involved nicotine (a single-isomer drug) and its major metabolite, the single-isomer compound (S)-cotinine. The latter was patented in the mid-1960s as a treatment for depression, but was not developed. In the 1990s, cotinine was patented as an aid in smoking cessation, but subsequent clinical trials demonstrated that it was not effective in that indication. More recently (S)-nicotine, another single-isomer metabolite of nicotine, has been suggested, based on animal studies, to be potentially useful in smoking cessation.

**Drugs in Development via CMs**

Currently, several new single-isomer CM drugs are in development. Racemic cisapride (Propulsid, Figure 2) is a gastrointestinal prokinetic agent associated with potentially life-threatening cardiac arrhythmias in certain situations such as accumulation of the drug (e.g., via drug interactions), the presence of other drugs that prolong the QT interval, or other diseases that may predispose the patient to arrhythmias. Among the metabolites of cisapride are the N-dealkylated compounds (+)- and (-)-nor cisapride (Figure 2). (+)-Nor cisapride, an active metabolite, is reported to be considerably safer than the parent in terms of cardiotoxicity and is in development as a new single-isomer drug.

Zopiclone (Figure 3) is a short-acting non-benzodiazepine sedative-hypnotic agent marketed as the racemate (Imovane). A biotransformation pathway of the drug is via N-demethylation of the (S)-isomer to the corresponding secondary amine (S)-desmethylzopiclone (Figure 3). Company literature from

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**TABLE. NEW SINGLE-ISOMER DRUGS REPORTED IN DEVELOPMENT VIA CHIRAL SWITCHES**

<table>
<thead>
<tr>
<th>Single isomer</th>
<th>Parent</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,R)-Formoterol</td>
<td>rac-formoterol</td>
<td>Asthma</td>
</tr>
<tr>
<td>(R)-Lomefloxacin</td>
<td>rac-lomefloxacin</td>
<td>Bacterial infection</td>
</tr>
<tr>
<td>(2R,4S)-Itraconazole*</td>
<td>mix-itraconazole†</td>
<td>Fungal disease</td>
</tr>
<tr>
<td>(+)-Pantoprazole</td>
<td>rac-pantoprazole</td>
<td>GE reflux</td>
</tr>
<tr>
<td>(S)-Lansoprazole</td>
<td>rac-lansoprazole</td>
<td>GE reflux</td>
</tr>
<tr>
<td>(R,R)-Methylphenidate</td>
<td>rac-methylphenidate</td>
<td>ADHD</td>
</tr>
<tr>
<td>(S)-Fluoxetine</td>
<td>rac-fluoxetine</td>
<td>Migraine</td>
</tr>
<tr>
<td>(S)-Zopiclone</td>
<td>rac-zopiclone</td>
<td>Sedative/hypnotic</td>
</tr>
<tr>
<td>(R)-Ondansetron</td>
<td>rac-ondansetron</td>
<td>Nausea</td>
</tr>
<tr>
<td>(-)-Amiodipine</td>
<td>rac-amiodipine</td>
<td>Hypertension</td>
</tr>
<tr>
<td>(S)-Doxazosin</td>
<td>rac-doxazosin</td>
<td>BPH</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>rac-cetirizine</td>
<td>Allergy</td>
</tr>
<tr>
<td>(S)-Sibutramine</td>
<td>rac-sibutramine</td>
<td>Obesity</td>
</tr>
<tr>
<td>(S)-Bupropion</td>
<td>rac-bupropion</td>
<td>Depression</td>
</tr>
</tbody>
</table>

* Mixture of two isomers (epimers).
† Mixture of two racemates, i.e., four stereoisomers.

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**FIGURE 1. THE CHEMICAL STRUCTURES OF SOME SINGLE-ISOMER DRUGS IN DEVELOPMENT VIA CHIRAL SWITCHES**

Sepracor Inc. (www.sepracor.com) and other information have indicated that this metabolite is in development as an antianxiety agent, i.e., an indication different from that of the parent racemate.

Other CM candidates include the two didesmethylated metabolites of sibutramine (Meridia), an antiobesity agent used clinically as the racemic mixture. Its chemical structure includes a dimethylamino group, -N(CH3)2, and the drug is metabolized via sequential oxidative removal of the two methyl groups, leaving the primary amino group, -NH2, in the molecule. Both isomers of the parent compound are converted to the respective didesmethyl metabolites (R)-(+)-didesmethylsibutramine and (S)-(-)-didesmethylsibutramine. Pharmacological studies of the two isomeric metabolites have found significant differences in their ability to inhibit the reuptake of dopamine, norepinephrine, and serotonin, and the R-enantiomer was suggested to be a potentially advantageous agent for the treatment of obesity and depression. Furthermore, Sepracor company literature indicates that the other metabolite isomer, (S)-(-)-didesmethylsibutramine, is in development for sexual dysfunction and stress urinary incontinence, but few details are available.

FIGURE 2. THE STRUCTURES OF THE TWO ISOMERS IN RACEMIC CISAPRIDE AND OF THE TWO ISOMERS OF THE METABOLITE NORCISAPRIDE

The arrows in the structure of norcisapride indicate the atom from which the metabolic biotransformation removed a group. One of the two isomers of norcisapride, (+)-norcisapride (i.e., dextro-norcisapride), is in development as a new drug via a chiral metathesis, but it is not known which of the two structures it is.

As we have seen, relatively few CM drugs are in development, but it is safe to predict that CM will be increasingly used in the future as a mechanism for the identification and development of new single-isomer drugs.

**THE NEW SINGLE-ISOMER CHEMICAL ENTITY (NSICE)**

In normal drug development, the term new chemical entity (NCE) refers to a new chemical compound for a given indication. For the purposes of the present discussion, new single-isomer chemical entity (NSICE) is defined as a new single-isomer drug candidate that is the result of neither a CS nor a CM. Thus, a NSICE may be an entirely new compound or it may be a known molecule that is being considered for development for a new indication.

A large number of NSICEs are at various stages of drug development, from pre-clinical laboratory studies to late clinical testing phases just prior to application to FDA for approval. Furthermore, a large variety of chemical structures and therapeutic areas are encompassed by these single-isomer drug candidates. Several mechanisms for the identification of new candidates are available, eg, systematic structure-activity-relationship studies; modification of lead compounds obtained from natural sources or identified from other existing agents; combinatorial synthesis; and computer-aided drug design.

The large number of NSICEs precludes a comprehensive review of such drug candidates in the present forum and only a small fraction of the many compounds in development can be discussed here. Nevertheless, it is hoped that this survey of representative NSICEs will provide a flavor of the variety of compounds and therapeutic areas involved.

**DRUGS IN DEVELOPMENT AS NSICEs**

Cardiovascular diseases are a major target area for new drug development, and single-isomer agents are well represented in this field. For example, rosuvastatin (ZD4522, Figure 4) is a new “statin” drug, ie, an inhibitor of HMG-CoA reductase indicated for the treatment of hypercholesterolemia. Results of Phase III clinical trials of rosuvastatin were presented in early 2001.26-27 The clinical trials compared the effectiveness of rosuvastatin to other forms of therapy for elevated cholesterol. It was reported that rosuvastatin was significantly more effective than diet or other statins in reducing

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**FIGURE 3. THE SINGLE-ISOMER DRUG CANDIDATE (5)-DESMEZTHZIPICOLNE, A METABOLITE OF THE S-ISOMER OF ZOPICOLNE, AND THE TWO ISOMERS OF ZOPICOLNE**

The arrow in the structure of the metabolite indicates the site from where the methyl group was removed in the biotransformation. The letters R and S in the structure of zopiclone refer to the three-dimensional configuration.


**FIGURE 4. SOME SINGLE-ISOMER CARDIOVASCULAR DRUGS IN DEVELOPMENT AS NEW SINGLE-ISOMER CHEMICAL ENTITIES**

The letters R and S indicate the configurations in the molecules.

FIGURE 5. SOME SINGLE-ISOMER ANTI-INFECTIVE AGENTS IN DEVELOPMENT AS NEW SINGLE-ISOMER CHEMICAL ENTITIES
The arrows pointing to the amino and hydroxy group in DAPD and diocolane guanine, respectively, indicate the site of biotransformation catalyzed by adenosine deaminase. The letters $R$ and $S$ indicate the configurations in the molecules.

FIGURE 6. ADDITIONAL SINGLE-ISOMER COMPOUNDS IN DEVELOPMENT AS NEW SINGLE-ISOMER CHEMICAL ENTITIES

The letters D, L, R and S indicate the configurations in the molecules.

levels of total and low-density lipoprotein (LDL) cholesterol and increasing levels of high-density lipoprotein (HDL) cholesterol. Rosuvastatin was effective both in patients with heterozygous familial hypercholesterolemia and in patients with primary hypercholesterolemia. A different approach to the reduction of cholesterol levels is taken with another single-isomer drug candidate, ezetimibe (SCH48361, Figure 4). The drug molecule contains the (for cardiovascular drugs) unusual β-lactam ring (the four-membered nitrogen-containing ring in the structure in Figure 4) characteristic of penicillins and cephalosporins. Ezetimibe acts by inhibiting the intestinal absorption of cholesterol, and in Phase II studies more than 50% of patients receiving the drug as monotherapy achieved a >15% reduction in LDL cholesterol, while in 15% of the patients the reduction was at least 25%. Interestingly, in animal models the phenolic glucuronide metabolite of ezetimibe was found to be 400 times more potent than the parent drug as an inhibitor of intestinal cholesterol absorption.

Anti-infective therapy is also a field of intense drug-development activities, and, not surprisingly, a number of single-isomer candidates are in development in this area. For example, posaconazole (SCH56592, Figure 5) is a new antifungal candidate. The compound is a synthetic product, and it is interesting to note that based on its chemical structure (four chiral centers, see Figure 5), it is a single isomer out of 16 possible stereoisomers, attesting to the power of synthetic organic chemistry. Posaconazole is an “azole” type antifungal containing the triazole moiety (Figure 5) that binds to the active-site heme group of a fungal CYP. Such binding results in the inhibition of the enzyme which in turn is the mechanism of antifungal action of azoles. The drug is a broad-spectrum antifungal, with in vitro and in vivo activity against Candida spp., Cryptococcus neoformans, Aspergillus spp., Fusarium solani, Blastomyces dermatitidis, and Coccioides immitis. The presence of a triazole or imidazole group is often the cause of significant drug-drug interactions ofazole antifungal drugs, since the imidazole or triazole group can also bind to and inhibit human CYPs involved in the clearance of many other drugs. It is not clear whether posaconazole is likely to be involved in such drug interactions.

Antibacterial agents are another important group in anti-infective therapy. A number of new single-isomer agents are in development. For example, sitafloxacin (Figure 5) is one of a new generation of quinolone-type antibacterial agents with activity against multi-resistant Gram-positive pathogens and especially against methicillin-resistant Staphylococcus aureus. The pharmacokinetic properties of sitafloxacin allow once-a-day dosing.

The antiviral agent (-)-β-D-2,6-diaminopurine (DAPD, Figure 5) is a nucleoside reverse-trancriptase inhibitor with activity against the human immunodeficiency virus (HIV-1) and against hepatitis B virus. The drug is actually a prodrug and is rapidly converted by adenosine deaminase to (-)-β-dioxolane guanine (DXG, Figure 5). In HIV-infected subjects a majority of the DAPD absorbed is metabolized to DXG and the plasma levels reached by DXG indicate that it is the active anti-HIV compound. Also, in these patients the plasma half-life of DXG is considerably longer that of DAPD.

Many other NSICE drug candidates in a variety of other therapeutic areas are also in development. For example, aprepitant (L-754,030 and MK-0869, Figure 6) is an inhibitor of the substance P-prefering NK1 receptor. Such substance P antagonists have been proposed for the therapy of chronic pain, emesis, and depression. Interestingly, however, while efficacy in depression and emesis is confirmed, their ability to alleviate pain has been recently questioned. At any rate, aprepitant is in development as an intravenous agent for the treatment of migraine and chronic pain and as an antiemetic. Since the drug has insufficient water solubility, a phosphoramidate derivative (L-758,298; Figure 6) was synthesized as a water-soluble prodrug of aprepitant. Interestingly, the prodrug was stable in human blood in vitro, but was rapidly converted to aprepitant in human liver microsomes.

Pregabalin (Figure 6) is a 3-substituted GABA analog related to the anticonvulsant agent gabapentin. As seen in Figure 6, the molecule is a single isomer of very simple structure. The drug was originally developed as an antiepileptic but subsequently it became clear that this agent might be useful in other indications, eg, in pain and in behavioral disorders, and the drug is now in development for pain in diabetic neuropathy, migraine, and social phobias.

It was predicted recently that a boom in peptide drugs is in the making. Among the reasons for this prediction are the many new biological targets being identified, improved manufacturing methods for peptides, and the development of new delivery systems. Indeed, it is already clear that many peptide drug candidates are in development. One example is abarelix (Figure 6), a decapeptide that is a single isomer out of a possible 1024 stereoisomers. Several of the amino acid moieties in the molecule are synthetic rather than naturally occurring, and five of the amino acids are in the unnatural D configuration (Figure 6). Abarelix is a LHRH receptor antagonist in development for prostate cancer and endometriosis. As of this writing, a new-drug application (NDA) for a depot dosage form of abarelix in the treatment of prostate cancer is under review by the FDA.

**CONCLUSION**

Nearly all new drug candidates based on chiral molecules are being developed in single-isomer form rather than the racemate, and basic pharmacological considerations suggest that the single-isomer form is preferable in most cases. The new single-isomer agents now in advanced development encompass a large variety of chemical structures and therapeutic indications. It is clear that a new age of single-isomer therapeutics has dawned.