When Drug Molecules Look in the Mirror

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Almost 150 years have elapsed since Louis Pasteur separated the enantiomers of tartaric acid. Derived from the Greek word "enantio" meaning opposite, enantiomers are nonsuperimposable mirror-image structures. Because these "twins" possess identical physical properties, except for the direction of rotation of polarized light, they are often viewed as a single entity–this is especially true among drug regulating agencies throughout the world. But enantiomers can exhibit distinct chemical behavior when subjected to a chiral environment, that is, surroundings consisting of one twin and not the other.

Differences in the biological activities of the individual enantiomers for dozens of racemic drugs have been reported in specialized journals and texts (*1–9*). While therapeutic activity often resides in one twin, the other can lead to undesirable side effects. The thalidomide tragedy offers a noteworthy example. In the 1960's, many pregnant women who had taken racemic thalidomide gave birth to deformed babies. Ensuing investigations (*10*) showed only the right-handed version of the drug to cause the same birth defects in rat embryos. Had the sedative been administered in the form of L-thalidomide, the single-enantiomer that rotates polarized light counterclockwise, the disaster may never have occurred.

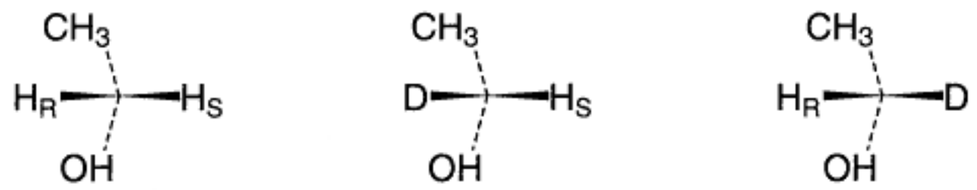
With more and more students in organic chemistry courses pursuing careers in medical-related fields, and with the current trend in the pharmaceutical industry to develop optically pure products, the stereoselectivity of drugs has become a timely subject. This paper aims to convey the uniqueness and the preparation of single-enantiomer drugs. Pertinent information for drugs cited in the article are highlighted in table form. Additional information regarding properties and contraindictions (excluding indacrinone) may be found in the *Physicians Desk Reference* or *Merck Index.*

Chiral Recognition

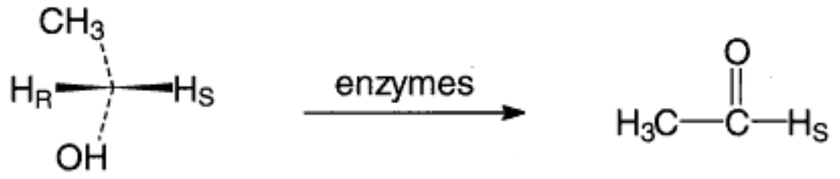
When subjected to a chiral environment such as the human body, how are mirror-image twins differentiated? Discrimination between enantiomers, referred to as chiral recognition, depends on the degree of interaction exhibited between each enantiomer and the chiral bonding site (*11*). In a way, chiral recognition resembles the matching of a right hand with a right-handed glove. The figure represents interactions between chiral bonding site –CXYZ and enantiomers CWXYZ. For one enantiomer, a three-point interaction is possible at X–X, Y–Y, and Z–Z (part a of figure). The other enantiomer (part b of figure) can only accommodate a two-point interaction at X–X and Y–Y with the same chiral binding site. In this instance, chiral recognition relies on the absence of a Z–Z fit in conjunction with the other two interactions.

Chiral recognition may include interactions with certain achiral structures possessing stereochemically nonequivalent (heterotopic) ligands or sides (*12*). The labeled hydrogens in achiral ethanol (**1**) are heterotopic because "imaginary replacement" of the pro-R hydrogen (H_R) or the pro-S hydrogen (H_S) with deuterium gives rise to the *R* (**2**) and *S* (**3**) configurations of 1-deuteroethanol, respectively.

In the enzyme-catalyzed oxidation of ethanol to form acetaldehyde (eq 1) , only H_R is eliminated. In this case, chiral recognition depends on enzymes to discriminate between the two hydrogens.

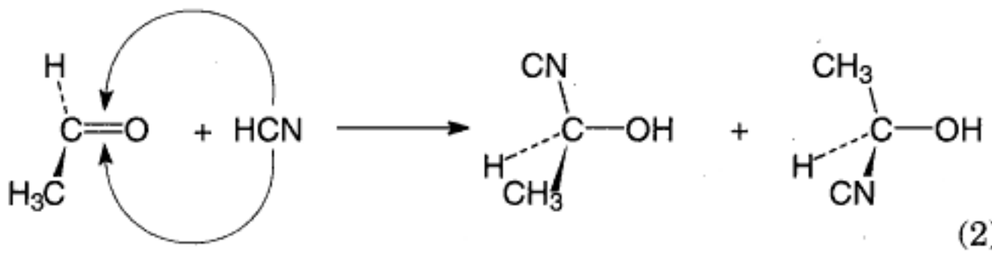


1 **2** **3**



(1)

Flat molecules may possess stereochemically nonequivalent sides called "heterotopic faces". If the heterotopic faces of acetaldehyde are subjected to addition by hydrogen cyanide, cyanide ion equally attacks the top and bottom faces (eq 2) to produce racemic acetaldehyde cyanohydrin. If special chiral catalysts favor attack at one face over the other, the discrimination leads to a single-enantiomer product.

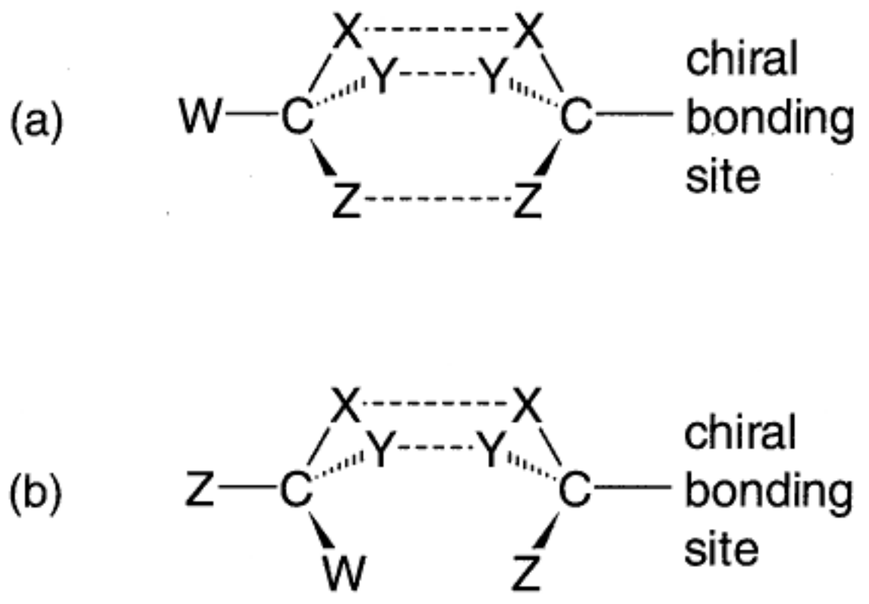


(2)

Enantiomer Uniqueness

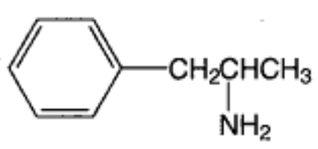
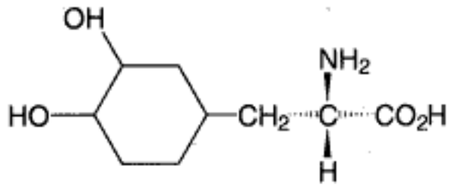
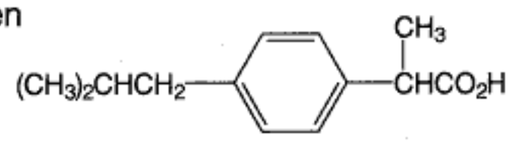
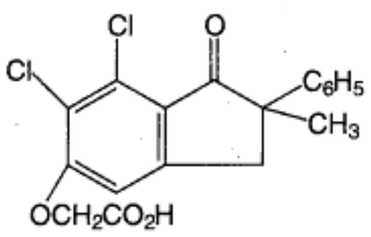
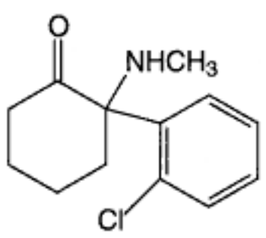
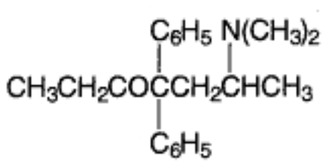
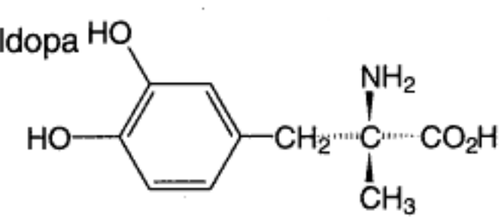
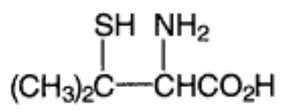
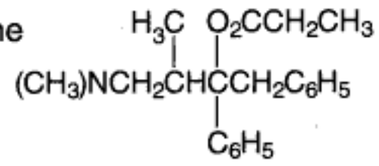
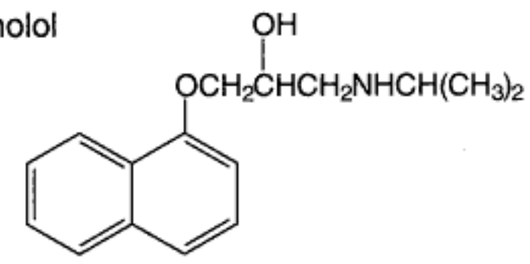
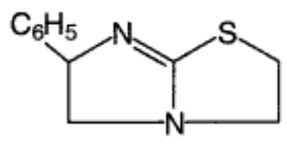
According to the modern receptor-site theory, drugs attach themselves to specific sites by means of three-dimensional bonding capabilities. The fit of a drug onto a receptor site has been compared to the fit of a key into a lock. The right drug is the "key" that can fit the receptor "lock" and turn on the desired biological response. Sometimes two slightly different keys will fit inside the same lock, but only one will open the door.

Racemic drugs often contain therapeutic activity in a



Enantiomers of CWXYZ and chiral bonding site (–CXYZ) displaying (a) three-point and (b) two-point interactions.

Drug Summary

Name/Structure	Desired Enantiomer	Other Enantiomer
Amphetamine 	*S*(+) 3–4 times more potent as stimulant.	*R*(–) produces more adverse cardiovascular effects.
L-Dopa 	Only *S*(–) used to treat Parkinson's disease	*R*(+) contributes to side effects.
Ibuprofen 	Analgesic activity resides primarily in *S*(+).	
Indacrinone 	*R*(–) has diuretic properties.	*S*(+) induces excretion of uric acid.
Ketamine 	*S*(+) 4 times more potent as anesthetic.	*R*(–) produces more side effects.
Methadone 	As narcotic, *R*(–) is 3 times more active than racemate.	
L-Methyldopa 	*S*(–) effective in treating hypertension.	*R*(+) contributes to side effects.
Peniccillamine 	Only *S*(–) used to treat copper poisoning.	*R*(+) is toxic.
Propoxyphene 	2*R*,3*S*(+) is analgesic.	2*S*,3*R*(–) is antitussive.
Propranolol 	Only *S*(–) effective in treating angina.	
Tetramisole 	Anthelmintic activity resides primarily in *S*(–).	*R*(+) produces undesirable side effects.

single enantiomer. The enantiomer that binds to a receptor and triggers the desired response is called the agonist. The antagonist binds to the same receptor but does not elicit the desired response. It may display different therapeutic activities, produce undesirable properties, or simply be pharmacologically inert. A look at enantiomeric differences for some racemic drugs will illustrate this point.

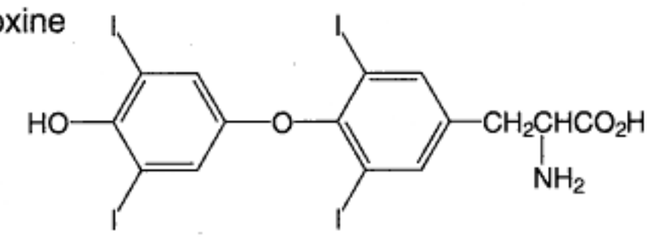
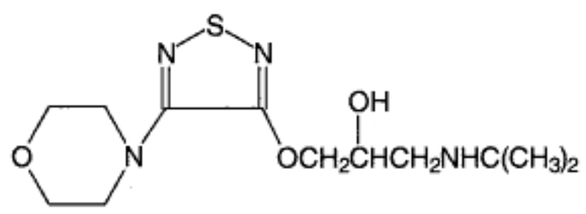
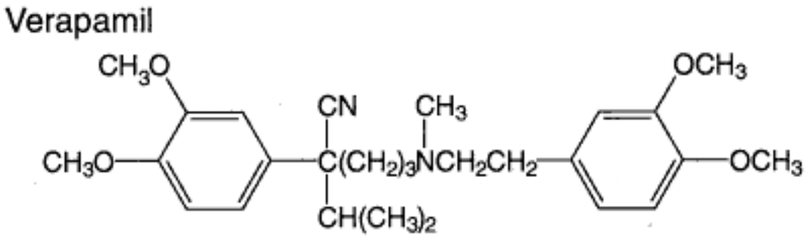
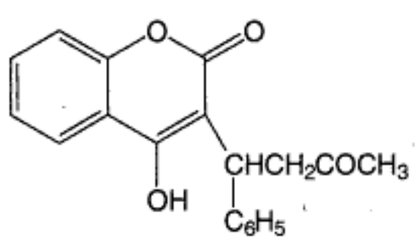
The enantioselectivity of warfarin, the anticoagulant prescribed for over half a century, has been investigated more than any other racemic drug. Warfarin acts by blocking the action of vitamin K, an essential for blood clotting. Studies (*1, 6, 7*) show that while *S*(–)-warfarin is two to five times more potent than the *R*(+) isomer, it also is eliminated two to five times faster. Therefore, the actual activity over time may be similar for the two isomers. But the more interesting warfarin studies have been made in the presence of other drugs. For example, the antiinflammatory agent phenylbutazone inhibits the metabolism of *S*-warfarin while inducing that of *R*-warfarin. These studies demonstrate the importance of knowing drug–drug stereoselective interactions.

The enantiomers of propranolol and verapamil, two antiarrythmic agents introduced in the mid 1960's, also have been studied thoroughly. Propranolol works by reducing heart rate as well as contraction forces of the heart. Investigations (*1, 6, 7*) have shown only *S*(–)-propranolol, about 100 times more potent than the *R*(+) isomer, to be effective in treating patients with angina. For verapamil (*1, 5, 6*), both enantiomers offer similar potency; however, the *R*(+) isomer produces much fewer cardiodepressant side effects.

As a general anesthetic, ketamine causes delirium, excitement, or visual disturbances in 50% of patients (*1, 3, 5, 7*). Tests conducted on surgical patients found the *S*(+) isomer to be four times more potent than the *R*(–) configuration. But even more significant, *S*(+)-ketamine created considerably less disturbing side effects than either the racemate or the *R*(–) isomer alone.

Sold over the counter in a number of pain remedies such as Advil and Nuprin, ibuprofen (*2, 6, 8*) contains therapeutic activity only in the *S*(+) isomer.

Drug Summary, *Continued*

Name/Structure	Desired Enantiomer	Other Enantiomer
Thyroxine 	*S*(–) prescribed for thyroid deficiency.	*R*(+) decreases serum cholesterol.
Timolol 	*S*(–) precribed for angina and high blood pressure.	*R*(+) prescribed for glaucoma.
Verapamil 	Both enantiomers increase coronary flow but *R*(–) produces much less cardiodepressant effect.	
Warfarin 	*S*(–) is 2–5 times more potent as anticoagulent. *S*(–) is eliminated 2–5 times more rapidly.	

When administered in an *S* to *R* ratio of 6:94, the excreted ratio was 80:20. Because enzymes are able to convert *R*(–)-ibuprofen into the active *S*(+) isomer, advantages of preparing ibuprofen in enantiomerically pure form may not be worth the extra manufacturing cost.

The experimental drug indacrinone represents the first attempt to improve efficacy by manipulating the enantiomer ratio (*1–3*). The *R*(–) isomer possesses diuretic properties along with undesirable uric acid retention. In contrast, *S*(+)-indacrinone lacks diuretic properties but works effectively to induce the secretion of uric acid. Although the 1:1 racemic mixture still causes retention of uric acid, an *S* to *R* ratio of 1:9 provides diuretic properties without increasing the uric acid level. The study indicates how variations of enantiomeric proportions may offer therapeutic benefits.

Some drugs are made available in both racemic and optically pure form. Methadone and amphetamine are two examples: Racemic methadone, used to treat patients in drug withdrawal programs, contains the more active component in the *R*(–) isomer. However, *R*(–)-methadone or levadone usually is prescribed in cases involving severe liver damage. While the *S*(+) isomer of amphetamine (*1, 6, 8*) is 3–4 times more potent than its mirror image, both racemic amphetamine and dexedrine, the *S*(+) isomer, are prescribed to suppress appetite.

Preparing Single Enantiomers

Methods for obtaining optically pure drugs not found in nature generally are organized into three categories: Resolution of a racemic mixture, modification of a naturally occurring optically pure substance (chiral pool method), and direct synthesis. While the three approaches for obtaining optically pure drugs vary, they all require a chiral source.

Racemate resolution, the major industrial method, has been used for more than a century to produce pure enantiomers. Enantiomers have virtually identical physical properties and cannot be separated by conventional methods. But diastereomers–stereoisomers that are not mirror images possess different physical properties and are separated readily. To streamline physical separations such as crystallization, distillation, or extraction, chiral stationary phases in liquid chromatography has developed into a popular method (*14*). Advantages include no need to remove resolving agents or further purification of the separated enantiomers.

The chiral pool method starts with inexpensive, readily available natural chiral products such as carbohydrates, amino acids, terpenes, lactic, or tartaric acid. By conventional organic reactions that do not alter specific chiral centers, substrates are converted into enantiomerically pure derivatives.

Direct synthesis of single enantiomers has flourished in the last 30 years from a little studied academic area to an intensely investigated field of commercial importance. Optical activity can be imparted from the reaction of predominantly one of two heterotopic groups or faces.

Fermentation, the oldest industrial process for obtaining optically pure compounds, relies on reproduction of microorganisms and takes place in living cells. This method is generally less attractive to industry due to low productivity and large quantities of biomass. However, fermentation is still used widely to produce certain amino acids, antibiotics, and vitamins.

Optically Pure Drugs

In 1990, of the 521 chiral synthetic drugs marketed worldwide, 61 were optically pure (*4*). On the other hand, out of the 517 chiral drugs derived from natural sources, only eight were marketed as racemates. The numbers indicate that while most drugs derived from natural sources consist of a single enantiomer, only 12% of synthetic chiral drugs are made available in optically pure form. But the data does not reflect current trends in the pharmaceutical industry. In 1990, nine of the 15 leading drugs worldwide by sales were marketed in optically pure form (*9*).

When is it most beneficial to use single-enantiomer drugs? Foremost is when one of the isomers proves toxic or causes undesirable side effects. Penicillamine and tetramisole offer two examples: Administered as the single enantiomer to treat Wilson's disease (*9*), an inherited defect in copper metabolism, *S*(–)-penicillamine serves as a copper chelating agent; the *R*(+) isomer is toxic and can lead to blindness. Racemic tetramisole (*5, 16*), once prescribed to rid intestinal worms, contains most of its anthelmintic activity in the *S*(–) isomer; the *R*(+) isomer causes various side effects including vomiting. Not surprisingly, the *S*(–) isomer, marketed as levamisole, has replaced racemic tetramisole in the treatment of intestinal worms. Levamisole is also administered with fluorouracil in the treatment of colon cancer.

The original clinical work on L-dopa, often prescribed in the treatment of Parkinson's disease, was performed in the mid 1960's with the racemic mixture. Researchers soon recognized that only the *S*(–) isomer was active. Because the drug is administered in large doses, early methods to resolve the racemate could not keep up with demand. Making use of a chiral derivative of the Wilkinson catalyst, Monsanto developed a method for the direct synthesis of L-dopa (*17*). Many of the serious side effects encountered with the racemate, such as granulocytopenia, were not seen with L-dopa and, therefore, can be attributed to the *R*(+) isomer.

The majority of enantiomerically pure drugs are prepared by separating racemic mixtures. The resolution of methyldopa into L-methyldopa, the active isomer in the treatment of hypertension, represents an interesting breakthrough. In a process developed by researchers at Merck to produce L-methyldopa (*18*), a key racemic intermediate was resolved by a "spontaneous crystallization." Rather than using a chiral resolving agent to form diastereomers, the separation was achieved by careful control of supersaturation and seeding.

Timolol has been prescribed since 1974 to treat angina and high blood pressure. While the *S*(–) isomer is more effective in reducing intraocular pressure, the *R*(+) isomer is practically free of 8-adrenergic blocking action. These properties make *R*(+)-timolol ideal for treating glaucoma (*19*). Because of its resistance to resolution through diastereomeric salts, timolol has been prepared from the carbohydrate mannitol (*20*), an optically active substance.

For certain chiral drugs, individual enantiomers are prescribed for different disorders. Thyroxine (*1*) and propoxyphene (*2, 5, 6*) are two examples: *S*(–)-thyroxine or levothroid is a naturally occurring thyroid hormone used to treat thyroid deficiency; *R*(+)-thyroxine or dextroid is prescribed to decrease serum cholesterol. The enantiomers of propoxyphene are sold separately by Eli Lilly— dextropropoxyphene as an analgesic and levopropoxyphene as an antitussive. Interestingly, the reversed trade names of these drugs, Darvon and Novrad, reflect their chemical mirror-image relationship.

Closing Remarks

This paper has focused on the enantioselectivity of pharmaceuticals; however, the phenomenon emerges wherever chiral substances interact with living systems—food additives, perfumes, agricultural chemicals, etc. For example, many D-amino acids are sweet such as D-leucine (L-leucine is bitter). Marketed predominantly as racemates, synthetic agricultural chemicals usually provide the desired response in a single enantiomer. With residues of agricultural chemicals often accumulating in food, wildlife, soil, and water, single-enantiomer products offer the advantage of reducing pollutants by half.

The Federal Drug Administration (FDA) was established in 1906 when Congress passed the first Food and Drugs Act. The original act intended to address two issues: the questionable use of narcotics and the deplorable conditions of the Chicago stockyard described by Upton Sinclair in *The Jungle*. Several amendments to the act now require manufacturers to document properties, safety, performance, and toxicity of a new drug. Armed with a staff of over 9000, the authority of the FDA has expanded to include standards for mammograms and safety of microwave ovens to claims made by vitamin and cigarette manufacturers.

Ariens (*2*) views the current documentation required for racemic drugs on par with knowing the average age, weight, and shoe size of a married couple. Simonyi (*21*) proposes that pharmaceutical companies be compelled to identify optically pure drugs with prefixes of dextro and levo. Has the time arrived for the FDA to adopt new regulations regarding racemic drugs? In a 1989 symposium (*22*) on chiral synthesis, many speakers predicted that the drug industry eventually will be required to generate optically pure products. The advantages are evident: smaller doses, products twice as active, fewer side effects, and superior pharmacological profiles of the active compound.

Literature Cited

1. Wainer, I. W.; Drayer, D. E. *Drug Stereochemistry*; Marcel Dekker: New York, 1988.
2. Ariens, E. J.; van Rensen, J. J. S.; Welling, *W. Stereoselectivity of Pesticides: Biological and Chemical Problems*; Elsevier: Amsterdam, 1988.
3. Ariens, E. J.; Soudijn, W.; Timmermans, P. B. M. W. M. *Stereochemistry and Biological Activity of Drugs*; Blackwell Scientific Publcications: Oxford, 1983.
4. Krogsgaard–Larson, P.; Bundgard, H. *The Textbook of Drug Design and Development*; Harwood Academic Publishers: Switzerland, 1991.
5. Drayer, D. E. *Clin. Phamacol. Ther.* **1986**, *40*, 125.
6. Williams, K.; Lee, E. *Drugs* **1985**, *30*, 333.
7. Simonyi, M. *Med. Res. Rev.* **1984**, *4*, 359.
8. Ariens, E. J. *Med. Res. Rev.* **1984**, *6*, 451.
9. Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optically Active Compounds*; Marcel Dekker: New York, 1993.
10. Brown, J. M.; Davies, S. G. *Nature* **1989**, *342*, 631.
11. Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347.
12. Thall, E. *J. Chem. Educ.* **1994**, *71*, 1034.
13. Sheldon, R. *Chem. & Ind.* **1990**, April 2, 212.
14. Pirkle, W. A.; Prochapsky, T. C. *Advan. Chromatog.* **1987**, *27*, 73.
15. Crawford, T. C.; Crawford, S. A. *Advan. Carbohydrate Chem.* **1980**, *37*, 79–155.
16. Jucker, E. *Progress in Drug Research*; Birkhauser Verlag: Basel, 1976.
17. Knowles, W. S. *J. Chem. Educ.* **1986**, *63*, 222.
18. Stinson, S. C. *Chem. Eng. News* September 27, **1993**, 38.
19. Richards, R.; Tattersfield, A. Br. *J. Clin. Pharmac.* **1984**, *17*, 453.
20. Weinstock, L. M.; Mulvey, D. M.; Tull, R. *J. Org. Chem.* **1976**, *41*, 3121.
21. Simonyi, M.; Gal, J.; Testa, B. *Trends Parmacol. Sci.* **1989**, *10*(9), 349.
22. Laird, T. *Chem. & Ind.* June 19, **1989**, 366.