Chirality – A New Era of Therapeutics

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Abstract: To develop the newer pharmaceuticals and to spur the strong growth, being a general property of 'handedness', chirality plays a major role. The Easson-Stedman principle shows the differences in the biological activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor. It helps to improve the pharmacokinetic properties and to remove undesirable side effects by virtue of the unique activity of enantiomers. Racemic switching and marketing drug combinations are used as tools for drug life-cycle management and to redevelop racemic mixtures as single enantiomers.

Key Words: Chirality, enantiomers, stereoselectivity, racemic switching, drug combination, pharmacokinetics.

1. INTRODUCTION

In the recent era, chirality plays a major role in the development of newer pharmaceuticals. World wide sales of chiral drugs in single enantiomer dosage forms continued growing at a more than 13% annual rate to $133 billion in 2000, according to the consulting firm Technology Catalysts International (TCI). At a future growth rate estimated by TCI (Tables **2** and **3**), the figure could hit $200 billion in 2008. In a second growth trend, according to the firm, 40% of all dosage-form drug sales in 2000 were of single enantiomers. In 1999, the share was one-third [1]. The drug industry will continue to spur strong growth in chiral compounds, because of efforts to improve drug efficacy and to cut development cost in the face of regulatory pressures. A second reason for the sector's growth arises from the continuing concern of the Food and Drug Administration (FDA) that companies make appropriate choices about whether to develop inherently chiral drug molecules in their single isomer or racemate forms. The logistics of testing are simpler for a single isomer because the FDA (1992) requires that both enantiomers of a racemate be studied in detail (Fig. (**1**)) [2, 3]. Drug regulatory agencies are increasingly concerned with the issue, long recognized scientifically, that the stereoisomers of drugs differ, almost without exception, in their biological activities. Accordingly, a racemic drug may contain two distinct biological entities that should be analysed and evaluated separately for their pharmacodynamic, pharmacokinetic and toxicological properties. Palytoxin, derived from a Hawaiian coral has 64 centres of asymmetry that define more than 10^{21} isomers [4]. Fortunately, neither the issues nor the molecules facing the FDA and other regulatory agencies are typically at this level of complexity, and most synthetic drugs contain a single centre of asymmetry. Nonetheless, even this elementary level of stereochemical complexity presents plenty of scientific, developmental and regulatory challenges.

In conceiving new enantioselective technology, the search going on among the usual alternatives: **use of the chiral pool, resolution of racemates and asymmetric synthesis** [5].

2. WHAT IS EXACTLY MEANT BY CHIRALITY?

The word 'Chiral' (Greek word '*Chier*', means hand) is used for those objects, which have right handed and left handed forms, i.e. molecules which have "handedness" and the general property of "handedness", is termed chirality. Objects, which are not superimposable upon its mirror image and have no plane of symmetry are known to be 'chiral'. An enantiomer occurs only with those compounds whose molecules are chiral and are defined as stereoisomers whose three dimensional arrangement of atoms result in non superimposable mirror images and have identical physical properties except for their ability to rotate the plane of polarized light in an opposite direction with equal magnitude. If a plane of polarized light is passed through a sample of each enantiomer, one will rotate light to the right, or a clockwise direction, are designated as dextrorotatory and this is indicated by a (+) sign before the chemical name. The opposite designation, a levorotatory or (-) sign is given to compounds, which rotate the plane of polarized light to the left or counterclockwise. The letters 'd' and 'l' were formerly used to indicate (+) and (-) respectively. Simple example of enantiomeric drug is Epinephrine (**1**, **2**).

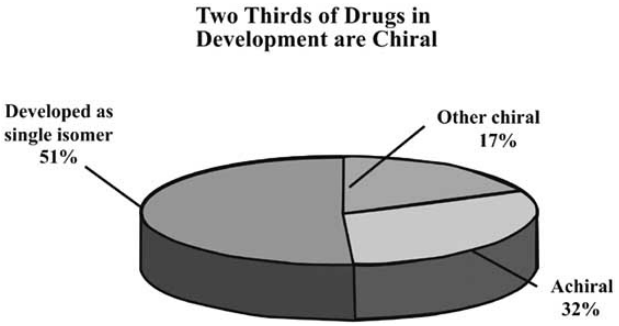

Fig. (1). Developmental drugs worldwide (1200).

This method of nomenclature is based upon physical properties of the molecule and does not provide any information concerning the *absolute configuration* or three-dimen-sional arrangement of atoms around the chiral center. Since the rotation of plane polarized light is a physical property, both the magnitude and direction of rotation can vary depending upon the conditions use. Thus, temperature, solvent and concentration of the substance are only three factors that need to be considered. A good example of this is the antibiotic chloramphenicol (**3**). There are two chiral centers in this molecule resulting in four possible stereoisomers. The isomer shown is dextrorotatory when its optical rotation is measured in ethanol, but levorotatory in ethyl acetate.

It is obvious that simple measurement of a physical property such as rotation of the plane polarized light is not sufficient for the assignment of the absolute configuration of a molecule. Therefore, In 1956 Cahn, Ingold and Prelog devised a system of nomenclature for stereoisomers referred to as the 'Sequence Rule System' (or CIP system). With this system, atoms attached to chiral center are ranked accordingly to their atomic number. Highest priority is given to the atom with highest atomic number and subsequent atoms are ranked accordingly from highest to lowest. When a decision cannot be made regarding priority, e.g., two atoms with the same atomic number attached to the chiral center, the process continues to the next atom until a decision can be made. The molecule

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is then viewed from the side opposite the lowest priority atom and the priority sequence is to the right, or clockwise, the chiral center is designated as the (*R*) (Rectus) absolute configuration. When the priority sequence is to the left or counterclockwise, the designation is (*S*) (Sinister). An example of this is seen in the neurotransmitter norepinephrine (**4**, **5**).

The light passes through a 50:50 mixture of enantiomers, no rotation is observed, this mixture is racemic and optically inactive and is indicated by (±) before the compound name. Confusingly, the rotation of the plane of polarized light does not always equate to the absolute configuration of the molecule, so the terms (*R*) and (*S*) are not necessarily equivalent to (+) and (-) respectively. For further explanation, take a simple example of enantiomeric drug like naproxen sodium (**6**, **7**) (Non-steroidal anti-inflammatory drug) [6-9].

3. DRUG ACTION-A STEREOSELECTIVE PROPERTY

Regardless of the origin, chirality is an integral part of biological process that derived their inherent asymmetry from the chirality of the fundamental building blocks of receptors – the L-amino acids. It would thus be expected that a receptor protein derived from the enantiomeric D-amino acids would have the same fundamental properties, but exhibit opposing chirality of interaction. This is exactly what happens for example; HIV-1 protease in its D and L forms exhibits opposing chiral substrate selectivity [10]. Nature has, on occasion, taken advantage of its own homochirality through the use of post-translational reactions to convert L-amino acid residues to the corresponding D-enantiomers. The resultant peptides and proteins exhibit enhanced stability towards enzymatic degradation. Thus, antibiotic families such as the gramicidins contain D-residues [11, 12] and the naturally occurring dermorphin peptide from the south american tree frog, *Phyllomedusa sauvagei*, contains D-alanine, as do several other peptides from this species [13, 14]. More recently, the Ca^{+2} channel toxins from the funnel-web spider, *Agelenopsis aperta*, have been shown to contain a D-serine residue that is important both for their biological activity and for channel selectivity [15, 16].

Drugs work by reacting with receptors in the body that have a specific physical shape. Going back to the hand analogy, these receptors can be viewed as gloves, and one 'hand' will fit better into this 'glove', or active site [6].

In 1886, Pruitti reported different physiological actions for the enantiomers of aspargine, with (+) aspargine having a sweet taste and (-) aspargine bland. This is one of the earliest observations that enantiomers can exhibit differences in biological action [17].

In 1933, Easson and Stedman reasoned that differences in the biological activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor. They postulated that such interaction requires a minimum of a three point fit to the receptor, which is known as 'Easson-Stedman Principle' of three-point attachment for stereoselective drug-receptor interactions [18].

Easson-Stedman Principle [8, 19] - "If binding is specific for enantiomeric pairs, then a three point attachment must occur between the enantiomer and the dissymmetric surface."

Model of Three-Point Attachment (Fig. 2)

Compound **A** and **B**: Enantiomers, where **B** will bind better than **A** due to the points A, B and G aligning with α, β and γ on the receptor. This shows 3 point binding. If **A** and **B** bond equally, then only interactions with α and β are important, which is 2 point binding.

Compound **C**: no chiral center; no interaction with G on the receptor will occur.

Evidence of specificity of biological systems: relative binding of enantiomers may be used to judge the specificity of an interaction.

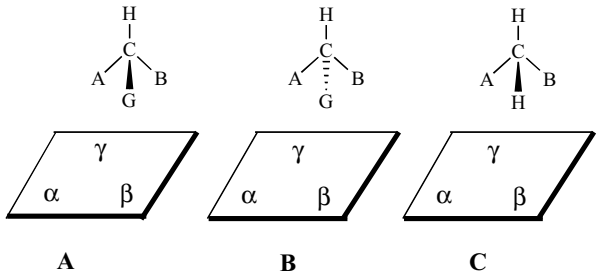


Fig. (2). Model of three-point attachment.

Explanation of Easson-Stedman Principle

A Incorrect enantiomer, **B** Correct enantiomer, **C** Achiral analogue interacting with three points on a hypothetical receptor.

Three point and B bond binding allows for differential binding of the compounds in parts **A** and **B** of Fig. **2**, which are enantiomers, to the hypothetical receptor. In **A**, only A and B line up with α and β, leading to lowered binding, while in **B** all three points, A, B and G align with α, β and γ on the receptor surface, respectively. Note that if γ on the receptor surface is NOT important for binding (i.e. 2 point binding) then the enantiomers in parts **A** and **B** would have similar binding affinities. Lack of a point G on the compound in part **C** yields an achiral compound, which will be less specific due to lack of interactions with the γ site on the receptor.

Example of Easson-Stedman Principle: Binding of catecholamine to an α-adrenergic receptor (Pharmacological (ligand based) classification) specific for l-epinephrine or l-norepinephrine (Fig. **3**)

(R) (-) Epinephrine (R = CH_3) or (R) (-) Nor-Epinephrine (R=H)

The three points of interaction with the receptor site are the substituted aromatic ring, *β* hydroxyl group and the protonated secondary ammonium group. All three functional groups interact with their complementary binding sites on the receptor surface producing necessary interactions that stimulate the receptor (Strongest acting).

(S) (+) Epinephrine (R = CH_3) or (S) (+) Norepinephrine (R=H)

Here, only two interactions are possible which include, the substituted aromatic ring and the protonated secondary ammonium group. The *β*-hydroxyl group occupies the wrong region of space and therefore cannot interact properly with the receptor (Weak acting).

N-methyl Dopamine (R = CH_3, no Benzylic Hydroxyl Group)

It can achieve the same interactions with the receptor as (*S*) (+) epinephrine and it is therefore not surprising that its vasopressor response is the same as (*S*) (+) epinephrine and less than (*R*) (-) epinephrine (Intermediate acting).

4. THE DIMENSIONS OF DRUG STEREOSELECTIVITY

A survey of the chirality of natural/semi-synthetic and totally synthetic drugs reveal, not surprisingly, that the majority of the former are available in a single stereoisomeric form. However, the extent of availability of synthetic single enantiomer chiral drugs is higher [20]. In 1982, some 15% of synthetic racemic drugs were available as single enantiomers, by 1991; this had increased to approximately 40%. It is likely that this increased availability of single enantiomer drugs will continue, fuelled both by decision to pursue single enantiomers rather than racemates and by a decision to switch existing racemic drugs to single enantiomeric forms.

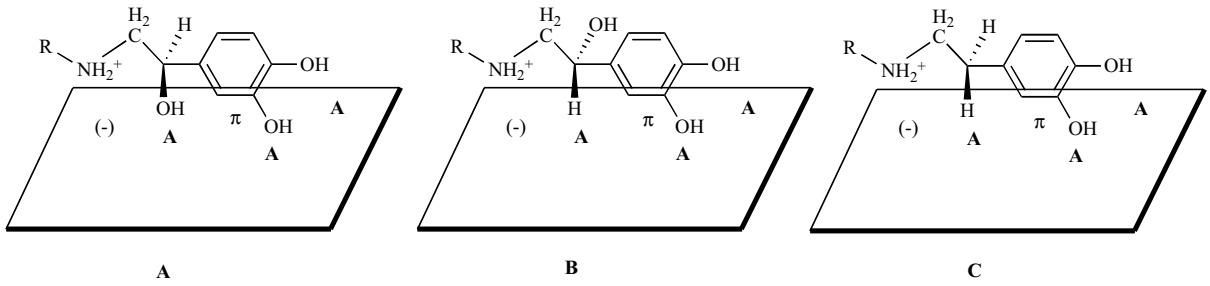


Fig. (3). Example of Easson-Stedman Principle showing the binding of **A** (*R*) (-) epinephrine, **B** (*S*) (+) epinephrine, **C** N-methyl dopamine to a hypothetical receptor.

[A: acceptors, (-): negative charge and π: Sites for π bonding interactions (Charge transfer)].

These numbers of drugs also translate to large numbers in terms of sales [21-23].

Some of the examples of biologically important single enantiomer of racemic drugs from a particular class are shown in Table (**1**) [21].

5. IMPORTANCE OF CHIRAL DRUGS

5.1. The Biological Importance of Chiral Drugs

Enantiomers may differ both quantitatively and qualitatively in their biological activities. At one extreme, one enantiomer may be devoid of any biological activity, at the other extreme, both enantiomers may have qualitatively different biological activities. These stereoselective differences may arise not only from drug interactions at the pharmacological receptors, but also from pharmacokinetic events [20-27].

5.1.1. Pharmacokinetic Importance

With the advent of chiral assays for both drugs and their metabolites, there is increasing interest in the pharmacokinetic processes like absorption, protein binding, metabolism, transport and excretion and to determine their contribution to the observed overall stereoselectivity of drug action [28, 29]. Enantiospecificity in pharmacokinetics is generally quite low and the contribution of such factors to their eudismic ratios (activities of the more active enantiomer, the eutomer, to the less active enantiomer, the distomer) is usually quite small; however, the clinical implications with respect to dosages and routes of administration may very important. This contribution of pharmacokinetic events to the overall stereoselectivity profile of drugs is usefully illustrated with following examples.

(S) (+) Disopyramide

Disopyramide (**8**) is class-I antiarrhythmic drug that exhibit concentration-dependent binding to plasma protein, principally α_1-glycoprotein, in the therapeutic concentration range [30, 31]. The enantiomers are believed to exhibit qualitatively different pharmacological effects, the (*S*) (+) enantiomer being significantly more potent than the (*R*) (-) enantiomer as an antiarrhythmic and with less difference, as an anticholinergic agent at muscarinic receptors [32, 33]. When administered separately, the enantiomers showed no difference in plasma clearance, renal clearance or volume of distribution in human subjects, however, when the pseudoracemate disopyramide is given, the (*S*) (+) enantiomer have a lower plasma clearance and renal clearance, a longer half-life and a smaller apparent volume of distribution than the (*R*) (-) enantiomer [34]. This difference reveals an important pharmacokinetic interaction between the enantiomers of disopyramide, which is explained by their stereoselective binding to plasma proteins and the resultant enantiomer competition.

(S) (-) Verapamil

Verapamil (**9**) is marketed as the racemate and is used for its antianginal, antihypertensive actions as an L-type Ca^{+2} channel antagonist [35-37]. The (*S*) (-) enantiomer has more potent vasodilation and cardiac depressant properties, whereas the (*R*) (+) enantiomer is a predominantly vasodilating drug [38-40]. The stereoselectivity of verapamil derives from both pharmacokinetic and pharmacodynamic factors. The profile of verapamil is thus dependent upon the interplay of these factors [35, 36, 41]. The plasma clearance of (*S*) (-) verapamil in humans (1400 ml/min) is approximately twice that of (*R*) (+) verapamil, and therefore the bioavailability of the pharmacodynamically more active (*S*) enantiomer is correspondingly lower. The enantiomers of verapamil interact stereoselectively with serum proteins, purified albumin and α_1-glycoprotein [42, 43]. The stereoselectivity is modest, with an (*R*)/(*S*) ratio between 1.5 and 2.0. The free fraction of the more active (*S*) enantiomer is always higher over the entire concentration range and, unlike the situation with disopyramide, no evidence for enantiomer-enantiomer interaction in protein binding is observed. Some evidence exists that the dissolution of verapamil from modified-release formulations of verapamil may also be stereoselective [44].

Table 1. Biologically Important Single Enantiomer of Racemic Drugs

• Cardiovascular system (approximately 30 drugs) Acebutol Disopyramide Dobutamine Nicardipine Verapamil • Central nervous system (approximately 12 drugs) Fluoxetine Lorazepam	• Respiratory system (approximately 3 drugs) Albuterol Terbutaline • Anti-inflammatory (approximately 16 drugs) Cicloprofen Ibuprofen Ketoprofen • Antihistamines Terfinadine Cetrizine

(S) (+) Ibuprofen

Ibuprofen (**10**) is non steroidal anti-inflammatory drug and (*S*) (+) isomer reaches therapeutic concentrations in blood in 12 minutes versus 30 minutes for the racemic mixture and can be marketed as fast acting drug [9].

5.1.2. Unique Activity of Enantiomer

Biologically active chiral compounds, such as a drug, interact with its receptor site, which is chiral. It should come as no surprise that the two enantiomers of the drug interact differently and may lead to different pharmacological effects [6].

Ketoprofen

Two isomeric forms of ketoprofen (**11**) are known. (*S*) Ketoprofen is analgesic (NSAID (Non-steroidal anti-inflam-matory drug)), while (*R*) ketoprofen is a toothpaste additive to prevent periodontal disease [9].

Ritalin (methylphenidate)

(*R*, *R*) Ritalin (**12**) is used as anti ADHD (Attention Deficit Hyperactivity Disorder), while (*S*, *S*) ritalin (**13**) is used as antidepressant [45].

(-) Levorphanol & (+) Dextrorphan

The synthetic morphinan (-) Levorphanol (**14**) is a powerful narcotic analgesic with an activity 5-6 times stronger than morphine. It's enantiomer, (+) Dextrorphan (**15**), is totally devoid of this activity, but is active as a cough suppressant and is marketed for this purpose as its methyl ether (Dextromethorphan) [6].

5.1.3. Removal of Undesirable Side Effects

Clinical significance is attached to drugs in which one enantiomer may contribute side effect rather than desired biological effect [6].

Thalidomide

Thalidomide (**16**) is a sedative and was first appeared in Germany on 1st October 1957 for prescribed to pregnant women. It was present in at least 46 countries under different brand names. When taken during the first trimester of pregnancy, children began to be born with shocking disabilities. It was not immediately observed what the cause of this was. Probably the most renowned is Pharcomelia, the name given to the flipper-like limbs, which appeared on the children of women who took thalidomide. Babies affected by this tragedy were given the name 'Thalidomide Babies' (Fig. (**4**)). There is history of an estimated 10,000 deformed infants born to mothers using this drug during pregnancy [9, 46]. Therefore, thalidomide was withdrawn as a sedative in 1961 because of its human teratogenic (fetal deformities) effects. The thalidomide molecule contains one chiral center. It has been speculated than only the (*S*) (-) enantiomer is teratogenic and that the (*R*) (+) enantiomer lacks this effect [47, 48].

Fig. (4). Above picture shows some of the babies born with the flipper-like limbs.

Given the potential utility of thalidomide in such diseases as leprosy, this conclusion would be of great significance. Unfortunately, the enantiomers of thalidomide rapidly racemize in solution, making the determination of enantioselective effects almost impossible. However, configuration stable analogs (α-methyl substitution) of thalidomide show clear-cut congruent S-enantioselectivity for sedation, teratogenicity and inhibition of tumor necrosis factor α-release [49]. Recently, racemic thalidomide has been approved by the FDA in case of leprosy, the condition referred to as ENL (erythrema nodosum leprosum) [50, 51].

Ethambutol

Ethambutol (**17**), an ethylenediiminobutanol (EMB) is administered as its (+) enantiomer, which is 200-500 times more active as a bacteriostatic agent than (-) enantiomer. The large difference in activity between the two isomers suggests a specific receptor for its site of action [52]. (*S*, *S*) Ethambutol having tuberculostatic action through blocking both the synthesis of AG (arabinofuranose and galactose) and LAM (lipoarabinomannan) of mycobacterium [53-55], while (*R*, *R*) ethambutol produces optical neuritis side effects [6].

Levodopa (L-dopa)

The Parkinson's disease drug levodopa (L-dopa) (**18**) is marketed in an enantiomerically pure form because the D-form causes serious side effects such as granulocytopenia - a loss of white blood cells that leaves patients prone to infections [6].

(R) Fluoxetine

(*R*) Fluoxetine (**19**) is a pure isomer of the commercial product Prozac and has been used in the treatment of depression with improved efficacy and minimizing adverse effects of racemic version. (Anxiety and sexual dysfunction) [19].

Levocetrizine

Levocetrizine (**20**) (Xyzal/Xusal) was developed for the treatment of allergic rhinitis (hay fever) and is less sedating than the racemate cetrizine (Zyrtec) [1, 19].

Eszopiclone

Eszopiclone (**21**) is the (*S*) enantiomer of zopiclone (Imovane). The bitter after taste associated with Imovane is absent in eszopiclone [1].

5.2. Pharmaceutical Importance of Chiral Drugs

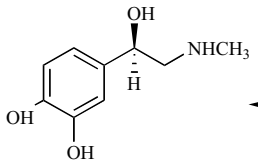
For any new drug whose chiral molecule is likely to be developed and marketed as a single enantiomer; there are more chances of winning than losing; however, exceptions are likely but few [56].

Drug companies are also using chirality as a tool either to extend the patent lives of their blockbuster drugs or to increases their "status". Blockbuster drugs are the drugs with more than $1 billion per year in sales [2].

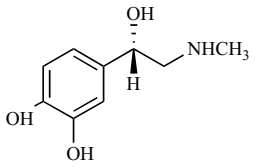
5.2.1. Racemic Switching

The drug companies continue to develop chiral drugs as single enantiomers, to use chirality as a tool for drug life-cycle management, and to redevelop racemic mixtures as single enantiomers. These operations are encompassed under the term racemic switching [2].

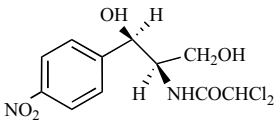
One of the prime examples is AstraZeneca's antiulcerant, omeprazole (*Prilosec/Losec*). Omeprazole (**22**) was the world's top selling pharmaceutical in around 1998, but it has come to the end of its exclusivity, with its European patent expiring in 1999 and its US patent in 2001. Fortunately for AstraZeneca, the company holds a specific patent on the (*S*) isomer, esomeprazole (**23**). This has been launched as *Nexium*, and is protected until 2014. In a series of trials, more patients with erosive esophagitis are healed with esomepra-



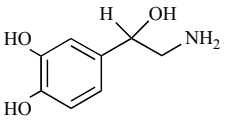
Enantiomers



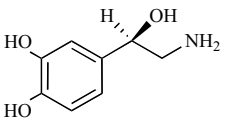
(-) Epinephrine (**1**) (+) Epinephrine (**2**)



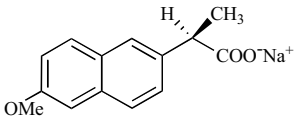
Chloramphenicol (**3**)



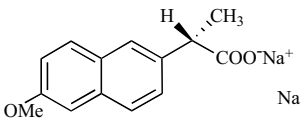
Norepinephrine (**4**)



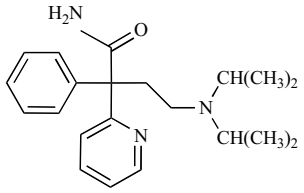
(R) Norepinephrine (**5**)



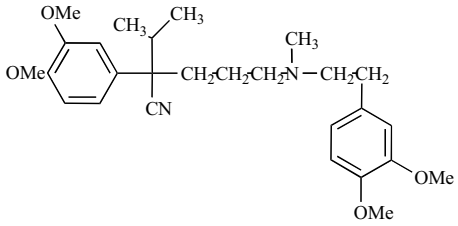
(*R*) (-) Naproxen sodium (**6**)



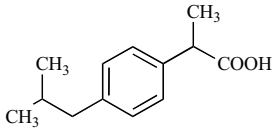
(*S*) (+) Naproxen sodium (**7**)



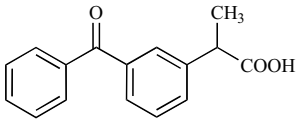
Disopyramide (**8**)



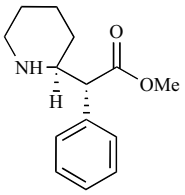
Verapamil **(9)**



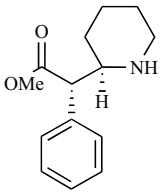
Ibuprofen (**10**)



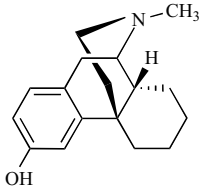
Ketoprofen (**11**)



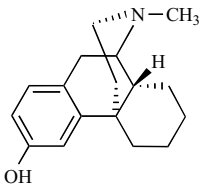
(R, R) Ritalin (**12**)



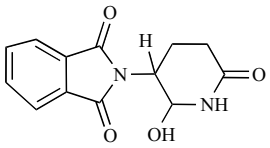
(S, S) Ritalin (**13**)



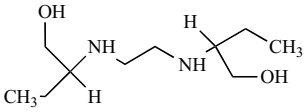
(-) Levorphanol (**14**)



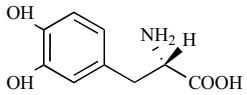
(+) Dextrorphan (**15**)



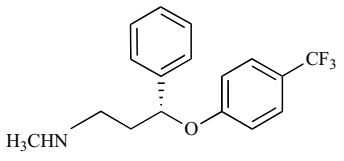
Thalidomide (**16**)



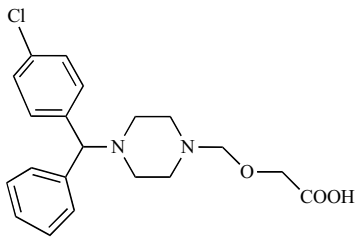
Ethambutol (**17**)



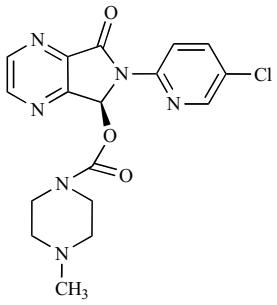
Levodopa (L-dopa) (**18**)



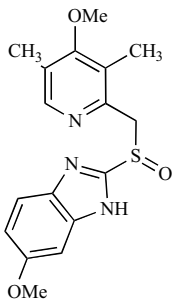
(R) Fluoxetine (**19**)



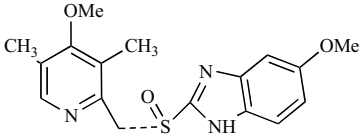
Levpcetrizine (**20**)



Eszopiclone (**21**)



Omeprazole (**22**)



Esomeprazole (**23**)

Table 2. Sales of Enantiomeric Intermediates and Single-Enantiomer Drugs

CHIRAL COMPONENTS	SALES OF ENANTIOMERIC INTERMEDIATES ($ MILLIONS) IN A YEAR			SALES OF BULK ENANTIOMERIC DRUGS ($ MILLIONS) IN A YEAR		
DRUG CATEGORY	1999	2000	2005	1999	2000	2005
ANTIINFLAMMATORY/ANALGESIC	150	156	168	200	223	241
ANTIVIRAL	794	830	1,643	983	1,180	2,054
CANCER	892	1,073	1,297	1,783	2,146	2,593
CARDIOVASCULAR	1,133	2,281	3,269	1,889	3,802	5,449
CENTRAL NERVOUS SYSTEM	1,038	1,142	1,821	1,483	1,632	2,602
DERMATOLOGY	82	85	106	164	170	212
GASTROINTESTINAL	251	331	649	413	567	1,082
OPHTHALMIC	238	284	401	340	405	573
RESPIRATORY	576	656	914	1,151	1,511	2,287
OTHER	140	170	356	315	426	891
TOTAL	5,294	7,008	10,624	8,721	12,062	17,984

Source: Technology Catalysts International Corp.

Table 3. Worldwide Chiral Drug Sales

CHIRAL COMPONENTS	SALES OF ALL DRUGS ($ MILLIONS) IN A YEAR		SALES OF SINGLE ENANTIOMERIC DRUGS ($ MILLIONS) IN A YEAR		
DRUG CATEGORY	1999	2000	1999	2000	2005
ANALGESICS	21,500	23,000	1,173	1,291	1,395
ANTIBIOTIC/ANTIFUNGAL	29,300	31,700	24,918	26,140	29,747
ANTIVIRAL	17,700	19,100	6,717	8,820	12,201
CANCER	13,700	15,600	8,891	10,690	13,605
CARDIOVASCULAR	42,700	46,600	24,895	27,650	34,627
CENTRAL NERVOUS SYSTEM	47,700	53,900	8,439	9,094	14,700
DERMATOLOGY	17,900	18,400	16,202	1,272	1,540
GASTROINTESTINAL	43,900	47,200	1,970	4,033	6,590
HEMATOLOGY	16,500	15,400	7,405	8,879	11,295
HORMONE/ENDOCRINOLOGY	20,000	22,000	14,510	15,384	19,790
OPHTHALMIC	7,100	7,400	1,270	2,265	2,705
RESPIRATORY	36,500	40,500	5,696	6,615	9,620
VACCINES	6,500	7,300	2,503	3,349	4,320
OTHER	39,000	41,900	6,248	7,032	9,730
TOTAL	360,000	390,000	117,763	132,514	171,865

Source: Technology Catalysts International Corp.

NOTE: Figures are for dosage formulations.

zole than with omeprazole, and it has also been found that heartburn symptoms are relieved more frequently, and that it led to greater acid control [2]. According to studies by *Lindberg et. al*. 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, inter individual variability with esomeprazole is reduced [57].

In another review, *Lindberg* and AstraZeneca colleagues *Olbe L* and *Carlsson E* 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 ulcers caused by bacteria *Helicobacter pylori* [58].

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 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. The *prilosec-nexium* chiral switch is considered as ideal because: "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 patent of racemates, and before the incursion of the respective generic drugs. This is the case with esomeprazole" (Table **4**) [56].

In the matter of racemic switching, drug companies like Forest Laboratories of New York City manage the life cycles of their own drugs by patenting the individual enantiomers and then switching the drugs as a means of prolonging total patent life [1].

Forest Labs licensed both the racemic antidepressant citalopram (**24**) and active (*S*) isomer escitalopram (**25**) from the drug firm H. Lundbeck of Copenhagen. Escitalopram is one of the advanced selective serotonin reuptake inhibitors used to treat depression. The Food & Drug Administration approved sale of the racemate in July 1998. Forest filed a New-Drug Application (NDA) for the (*S*) isomer [1].

In August 2000, Forest licensed single enantiomer (*R*) Loxiglumide (**26**) for irritable bowel syndrome from the Italian drug firm Rotta. The compound is a selective cholecystokinin A receptor antagonist [1].

Also in November 2000, Forest licensed the Calcium channel blocker lercanidipine to treat high blood pressure from Recordati of Milan, Italy. The activity of the compound is in the (*S*) isomer (**27**), with the (*R*) isomer reported as having only 1% of its racemate's activity [1].

5.2.2. Sepracor – The Racemic Switching Expert [1]

Perhaps Sepracor's greatest success to date has been (*R*) albuterol, whose assigned generic name is levalbuterol (**28**). The compound is a β_2 adrenergic agonist aerosol inhalant for the treatment of asthmatic bronchospasm.

The discoverer of racemic albuterol was a subsidiary of Glaxo Wellcome in U.K., which markets the drug in the U.S. under the trade name Ventolin. Glaxo Wellcome, now part of GlaxoSmith-Kline-licensed Schering Corp. to market it in the US under the trade name Proventil. Sepracor itself got FDA approval of levalbuterol in 1999.

Sepracor is in partnership with the drug company UCB of Brussels to develop (*S*) cetrizine (**29**) for allergic rhinitis (hay fever); Pfizer markets the racemate. UCB got approval to market the (*S*) isomer in Germany, with Sepracor retaining U.S. rights.

Another Sepracor-sponsored drug is (*S*) zopiclone (**30**), now named espopiclone, for insomnia. The original discoverer of racemic zopiclone was Rhone-Poulenc, now a part of Aventis, which markets the drug in many countries but never has done so in the U.S. Sepracor is finishing Phase III clinical studies on the single-enantiomer compound; the next step will be filing of an NDA with FDA.

In a related development, Sepracor began Phase III studies of (*R*,*R*) Formoterol (**31**) as a long-acting β_2 adrenergic agonist inhalant for once-daily use against asthma, emphysema, and chronic obstructive pulmonary disease. Phase III studies use large numbers of patients to determine the efficacy and long-term safety and are the last step before filing an NDA. The compound has two asymmetric atoms, and Novartis obtained FDA approval to market one diastereomeric racemic mixture in the US in February 2000.

In addition, Sepracor has a slow-release formulation of (*S*) Oxybutynin (**32**) in Phase III studies for urinary incontinence. The racemate is marketed by Alza. Sepracor representatives say the combination of the single enantiomer with slow-release action may give more constant blood levels of the drug at lower oral doses, avoiding such side effects as dry mouth.

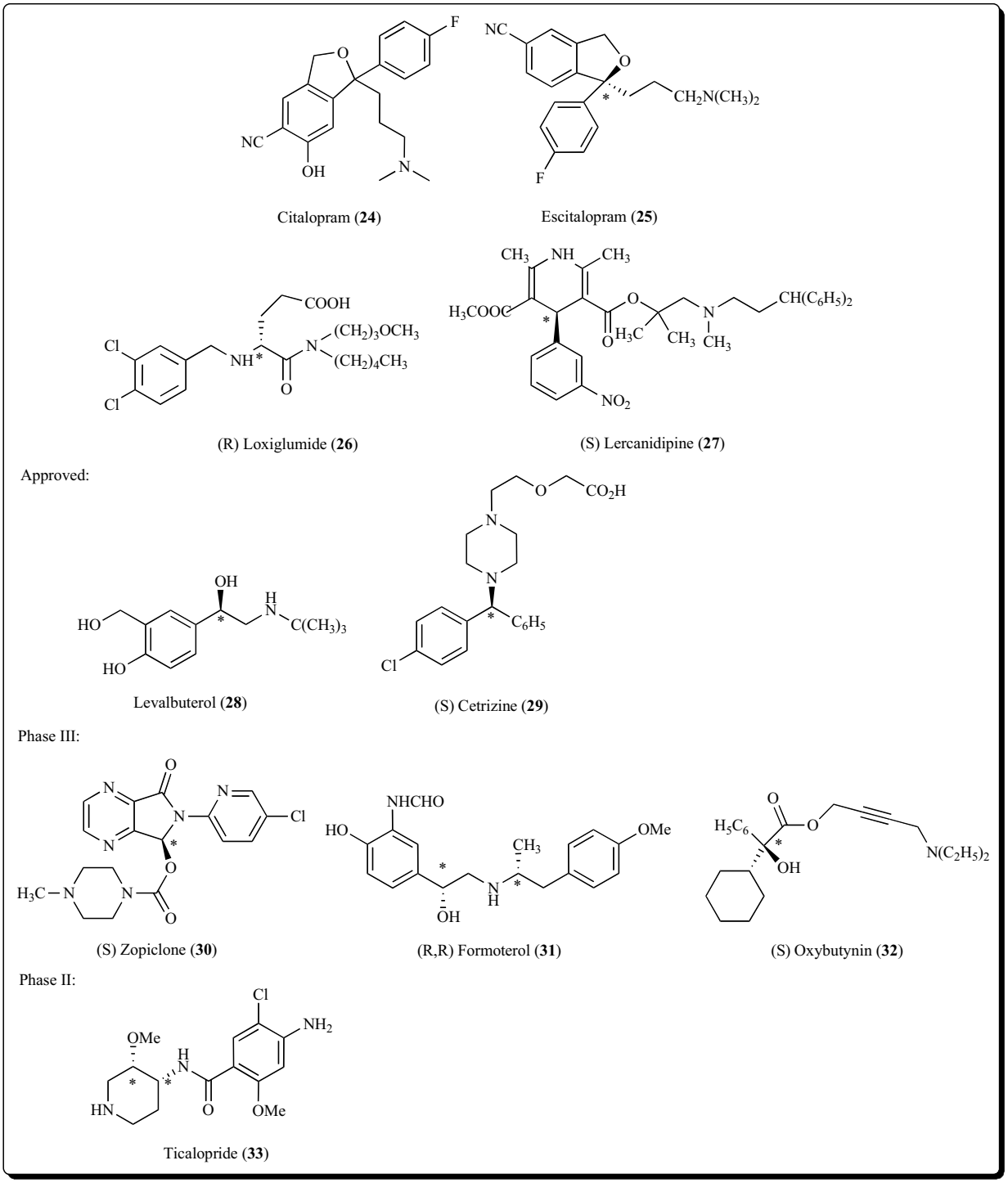
Yet another Sepracor partnership is with Janssen Pharmaceutica Products, Titusville, NJ, to develop Ticalopride (**33**), which is the generic name of a 3*S*, 4*R*-substituted piperidine metabolite of cisapride. Janssen marketed racemic cisapride to improve gastric motility in diabetes patients. The drug is withdrawn in July 2000 because of an adverse interaction with other drugs that compete for the $3A_4$ isozyme of the cytochrome P_{450} metabolic complex. The current aim is treatment of gastroesophageal reflux disorder (heartburn) (GERD).

Another Sepracor candidate for urinary tract problems is (*S*) Doxazosin (**34**) for benign hyperplasia (excessive growth) of the prostate gland. The compound is a α_1 adrenergic blocking agent that relaxes the smooth muscle of the gland and prevents it from constricting and blocking flow from the bladder. Pfizer markets the racemate. Sepracor has the single enantiomer in Phase I, which is a small-scale study in healthy volunteers.

Additional chiral metabolites from Sepracor are those of both (*R*) and (*S*) sibutramine (**35**). Knoll Pharmaceutical, Mount Olive,

Table 4. Top 10 Single-Enantiomer Products Belong to Billion-Dollar Club

BRAND NAME	GENERIC NAME	MARKETER	THERAPEUTIC USE	2002 SALES ($ BILLIONS)
LIPITOR	ATROVASTATIN CALCIUM	PFIZER	CARDIOVASCULAR	8.0
ZOCOR	SIMVASTATIN	MERCK	CARDIOVASCULAR	5.6
PRAVACHOL, MEVALOTIN	PRAVASTATIN SODIUM	BRISTOL-MYER SQUIBB AND SANKYO	CARDIOVASCULAR	4.0
PAXIL	PAROXETINE HYDROCHLORIDE	GLAXOSMITHKLINE	CENTRAL NERVOUS SYSTEM	3.1
PLAVIX	CLOPIDOGREL BISULFATE	SANOFI SYNTHELABO. AND BRISTOL-MYER SQUIBB	HEMATOLOGY	2.9
ZOLOFT	SERTRALINE HYDROCHLORIDE	PFIZER	CENTRAL NERVOUS SYSTEM	2.7
ADVAIR, SERETIDE	FLUTICASONE PROPIONATE & SALMETEROL XINAFOATE	GLAXOSMITHKLINE	RESPIRATORY	2.4
NEXIUM	ESOMEPRAZOLE MAGNESIUM	ASTRAZENECA	GASTROINTESTINAL	2.0
AUGMENTIN	AMOXICILLIN & POTASSIUM CLAVULANATE	GLAXOSMITHKLINE	ANTIBIOTIC	1.8
DIOVAN	VALSARTAN	NOVARTIS	CARDIOVASCULAR	1.7
TOTAL				34.2

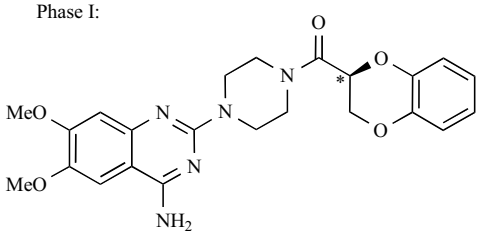


N.J., markets racemic sibutramine, which inhibits reuptake of the neurotransmitters norepinephrine, serotonin, and dopamine at nerve synapses to treat obesity. Sepracor is carrying out Phase I studies of the (*R*) metabolite for treatment of depression and attention deficit disorder, while (*S*) metabolite for treatment of erectile and ejaculatory dysfunction.

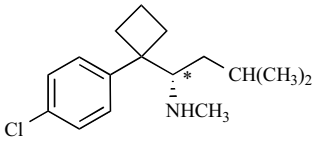
Yet another Sepracor compound is the (*S*) enantiomer of the desmethyl metabolite of zopiclone. The company has assigned the compound code number, SEP-174559 (**36**), and is beginning clinical studies for the treatment of anxiety.

Sepracor has begun preliminary work with several other single-enantiomer compounds that may lead to partnerships or to Sepracor's own marketing of the resulting drugs. These agents include (*S*) amlodipine (**37**), a calcium channel blocker for high blood pressure, whose racemate is marketed by Novartis and Pfizer; and (*R*) ondansetron (**38**), a serotonin blocker to prevent nausea and vomiting

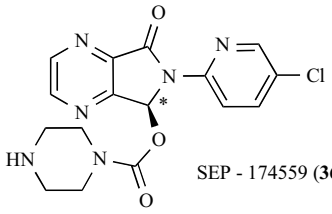
Phase I:



(S) Doxazosin (**34**)

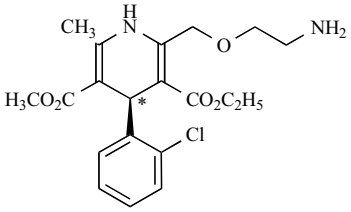


(S) Sibutramine metabolite (**35**)

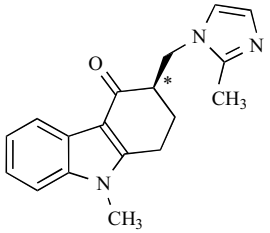


SEP - 174559 (**36**)

Entering Development:



(S) Amlodipine (**37**)



(R) Ondansetron (**38**)

Note: Asterisks indicate chiral centers. Compounds entering development may be developed by Sepracor or licensed to a partner.

during cancer chemotherapy, whose racemate is marketed by GlaxoSmithKline.

5.3. Marketing Drug Combination [2]

In addition to extending patent protection on a racemic drug by later patenting its single active enantiomer, the companies can also "enhance its status", by combining any old drug with a newer, patented one that treats the same disease condition but by a different mechanism. For example,

1. Marketing a combination of Merk's simvastatin and Schering's ezetimibe, both are single enantiomers, to lower serum cholesterol. Simvastatin inhibits the enzyme HMG-Co Enzyme A reductase, which are the mediator steps in the biosynthesis of cholesterol, while ezetimibe inhibits the absorption of dietary cholesterol.
2. Combination of Merck's montelukast and Schering's loratidine for asthma. Both are single enantiomer compounds. Loratidine is a nonsedating antihistaminic, while montelukast is a selective Leukotrienes D_4 receptor antagonist. Both histamines and leukotrienes are mediators of inflammation.

One advantage for marketing such combinations is that a newer agent with a longer patent life adds its independent effectiveness to a drug whose patent is closer to expiration. Ezetimibe is newer than simvastatin, while the patent on montelukast expires after the patent on loratidine.

Marketing such combinations can also send off competition from newer agents. For example, AstraZeneca is bringing along enantiomeric rosuvastatin as a cholesterol-lowering drug. The industry has dubbed this as a "superstatin" because it is more effective than simvastatin. Schering is hoping that the combination of simvastatin plus ezetimibe will trump a superstatin.

6. THE FUTURE: CHIRAL DRUGS OR NON-CHIRAL DRUGS?

By the mid 1980s, people really hit on the idea that they could do better with single enantiomer than with racemate. Until very recently, the issue of chirality in drugs occupied almost exclusively a scientific arena. Within the past decade, this issue has moved to center stage in the development and regulatory arena for several reasons [59].

Development in chemistry, notably in chiral synthesis, has made it much easier to obtain the required stereoisomers. Thus, production and marketing of chiral compounds is no longer a major problem.

In the next decade, some 50-80 racemate drugs will lose their patent protection and there will be a significant impetus to extend their protected lifetime by marketing single-enantiomer versions. The existence of a number of scientific and clinical reasons why single enantiomers of chiral drugs may well be the preferred-marketed entity and these include:

- The absence of undesired or toxic effects in one enantiomer.
- The reduction / elimination of pharmacokinetic complexities that may arise from differential metabolism, protein binding, transport or excretion of one enantiomer.
- The simplification of drug monitoring.

The existing guidelines indicating that regardless of whether a racemate or a single enantiomer is the ultimate critical candidate, the chemical, analytical, pharmacological, pharmacokinetic and

toxicological properties of both racemate and the enantiomer should be documented.

REFERENCES

[1] Stinson, S.C. *Chem. Eng. News*, **2001**, *79*(40), 79.
[2] Stinson, S.C. *Chem. Eng. News*, **2000**, *78*(43), 55.
[3] http://www.acdlabs.com/publish/publ03/eum03_chirbase.html
[4] Armstrong, R.W.; Beau, J.M.; Cheon, S.H.; Christ, W.J.; Fujioka, H.; Ham, W.H.; Hawkins, L.D.; Jin, H.; Kang, S.H.; Kishi, Y.; Martinelli, M.J.; McWhorter, W.W., Jr.; Mizuno, M.; Nakata, M,; Stutz, A.E.; Talamas, F.X.; Taniguchi, J.A.; Tino, J.A.; Ueda, K.; Uenishi, J.I.; White, J.B.; Yonaga, M. *J. Am. Chem. Soc.*, **1989**, *111*, 7525.
[5] Stinson, S.C. *Chem. Eng. News*, **2001**, *79(*20), 45.
[6] Aitken, R.A.; Kilenyi, S.N. Source and strategy for formation of chiral compounds. In *Asymmetric Synthesis*, 1st ed., Blackie Academic & Professional, **1995**; pp. 64-82.
[7] Kalsi, P.S. Chirality In *Stereochemistry Conformation and Mechanism*, 6th ed., New Age International (p) Limited Publishers, **2005**; pp. 15-16.
[8] Williams, D.A.; Lemke, T.L. Drug Design and Relationship of Functional Groups to Pharmacological Activity In *Foye's Principles of Medicinal Chemistry*, 5th ed., Indian edition , Distributed by B.I. Publications Pvt. Ltd., **2005**; pp. 50-53.
[9] http://www.chirality.ouvaton.org/research.htm
[10] Milton, R.C.; Milton, S.C.; Kent, S.B. *Science*, **1992**, *256*, 1445.
[11] Lipmann, E.; Hotchkiss, R.D.; Dubois, R.J. *J. Biol. Chem.*, **1941**, *141*, 163.
[12] Gross, E.; Morell, J.I. *J. Am. Chem. Soc.*, **1971**, *93*(18), 4634.
[13] Montecucchi, P.C.; de Castiglione, R.; Erspamer, V. *Int. J. Pept. Protein Res.*, **1981**, *10*, 316.
[14] Kreil, G. *J. Biol. Chem.*, **1994**, *269*, 10967.
[15] Heck, S.D.; Siok, C.J.; Krapcho, K.J.; Kelbaugh, P.R.; Thadeio, P.F.; Welch, M.J.; Williams, R.D.; Ganong, A.H.; Kelly M.E.; Lanzetti, A.J. *Science*, **1994**, *266*, 1065.
[16] Kuwada, M.; Teramoto, T.; Kumagaye, K.Y.; Nakajima, K.; Watanabe, T.; Kawai, T.; Kawakami Y.; Niidome, T.; Sawada, K.; Nishizawa, Y. *Mol. Pharmacol.*, **1994**, *46*, 587.
[17] Pruitti A. *Compt. Red.*, **1886**, *103*, 134.
[18] Easson L.H.; Stedman, E. *Biochem. J.,* **1933**, *27*, 1257.
[19] http://www..pharmacy.umaryland.edu/courses/PHAR531/lectures_old/chiral _drugs.html .
[20] Millership, J.S.; Fitzpatrick, A. *Chirality,* **1993**, *5*(8), 573.
[21] Stinson, S.C. *Chem. Eng. News,* **1993**, *71*, 38.
[22] Stinson, S.C. *Chem. Eng. News,* **1994**, *72*, 38.
[23] Stinson, S. C. *Chem. Eng. News,* **1995**, *73*, 44.
[24] Vermeulen, N.P.E.; Breimer, D.D. Stereoselectivity in drug and xenobiotic metabolism. In *Stereochemistry and Biological Activity of Drugs;* Ariens, E.J.; Soudijn, W.; Timmermans, P.B.M.W.M. Eds.; Blackwell Scientific Publications, Oxford, **1983**; pp. 33-53.
[25] Wainer, I.W.; Drayer, D.E. In *Drug Stereochemistry, Analytical Methods and Pharmacology*, 2nd ed. Marcel Dekker. **1993**.
[26] Ariens, E.J. *Trends Pharmacal. Sci.*, **1993**, *14*, 68.
[27] Triggle, D.J. In *The Practice of Medicinal Chemistry*; Wermuth, C. Ed., Academic Press, **1996**; pp. 547-570.
[28] Tucker, G.T.; Lennard, M.S. *Pharmacol. Ther.,* **1990**, *45*, 309.
[29] Levy, R.H.; Boddy, A.V. *Pharm. Res*., **1991**, *8*, 551.
[30] Giacomini, K.M.; Swezey S.E.; Turner-tamiyasu K.; Blaschke T.F. *J. Pharmacokinet. Biopharm*., **1982**, *10*, 1.
[31] Lima, J.J.; Boudoulas, H.; Blanford, M. *J. Pharmacol. Exp. Ther.*, **1981**, *219*, 741.
[32] Giacomini, K.M.; Cox, B.M.; Blashke, T.F. *Life Sci.*, **1980**, *27*(13), 1191.
[33] Vanhoutte, F.; Vereecke, J.; Carmeliet, E.; Verbeke, N. Naunyn-Schimiedeberg's *Arch. Pharmacol.*, **1991**, *344*(6), 662.
[34] Giacomini, K.M.; Nelson, W.L.; Pershe, R.A.; Valdivieso, L.; Turner-Tamiyasu, K.; Blaschke, T.F. *J. Pharmacokinet. Biopharm.*, **1986**, *14*(4), 335.
[35] Eichelbaum, M.; Gross, A.S. *Adv. Drug Res.*, **1996**, *28*, 2.
[36] Tiggle, D.J. In *Cardiovascular Pharmacology*; Antonaccio, M. Ed.; Raven Press, **1990**; pp. 107-160.
[37] Physicians' Desk Reference, 50th Edition, Medical Economics Co. **1996**.
[38] Know, Y.K.; Triggle, D.J. *Chirality*, **1991**, *3*, 393.
[39] Van Amsterdam, F.T.M.; Zaagsma, *J. Naunyn Schimiedebergs Arch. Pharmacol.,* **1988**, *337*, 213.
[40] Jim. K.; Harris, A.; Rosenberger, L.B.; Triggle, D.J. *Eur. J. Pharmacol.*, **1981**, *76*, 67.
[41] Van Amsterdam, F.T.M.; Punt, N.C.; Hass, M.; Zaagsma, J. *J. Cardiovasc. Pharmacol.,* **1990**, *15*, 198.
[42] Gross, A.S.; Heuer, B.; Eichelbaum, M. *Biochem. Pharmacol.,* **1988**, *37*, 4623.
[43] Gross, A.S.; Eser, C.; Mikus, G.; Eichelbaum, M. *Chirality*, **1993**, *5*, 414.
[44] Carr, R.A.; Pasutto, F.M.; Longstreth, J.A.; Foster, R.T. *Chirality*, **1993**, *5*, 443.
[45] Hubbard, J.W.; Srinivas, N.R.; Quinn, D.; Midha, K.K. *J. Pharm. Sci.*, **1989**, *78*, 944.
[46] http://www.chm.bris.ac.uk/motm/thalidomide/start.html
[47] Blaschke, G.; Kratt, H.P.; F-ckentscher, K.; Kohler, F. *Arzneim.-Forsch.*, **1979**, *29*, 1640.
[48] http://www.chm.bris.ac.uk/motm/thalidomide/first.html
[49] Wnendt, S.; Finkam, M.; Winter, W.; Ossig, J.; Raabe, G.; Zwingenberger, K. *Chirality*, **1996**, *8*, 390.
[50] Stirling, D.; Sherman, M.; Strauss, S. *J. Am. Pharm. Assoc.*, **1997**, *37*, 306.
[51] Thalidomide-The Medical Letter, 40, The Medical Leter, Inc., New Rochelle, NY, **1998**; 103.
[52] Williams, D.A.; Lemke, T.L. Antimycobacterial Agents In *Foye's Principles of Medicinal Chemistry*, 5th ed., Indian edition, Distributed by B.I. Publications Pvt. Ltd., **2005**; pp. 904-2489.
[53] Mikusova, K.; Slayden R.A.; Besra, G.S.; Brennan, P.J. *Antimicrob. Agents Chemother.*, **1995**, *39*, 2484.
[54] Lee, R.E.; Mikusova, K.; Brennan, P.J.; Bersra, G.S. *J. Am. Chem. Soc.*, **1995**, *117*, 11829.
[55] Khoo, K.H.; Douglas, E.; Azadi, P.; Inamine, J.M.; Besra, G.S.; Mikusova, K.; Berennan, P.J.; Chatterjee, D. *J. Biol. Chem.*, **1996**, *271*, 28628.
[56] Rauhi, A.M. *Chem. Eng. News*, **2003**, *81*(18), 56.
[57] Lindberg, P.; Keeling, D.; Fryklund, J.; Andersson, T.; Lundborg, P.; Carlsson, E. *Aliment. Pharmacol. Ther.*, **2003**, *17*, 481.
[58] Olbe, L.; Carlsson, E.; Lindberg, P. *Nat. Rev. Drug Discov.*, **2003**, *2*, 132.
[59] Heydorn, W.E. *Pharm. News.,* **1995**, *2*, 19.

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