Chirality and Drug Activity*

Bireddy Srinivasa Reddy and Pramod Kumar Dubey

Certain biological 'receptors' are known to generate disease conditions in the animal/human body. Small molecules, determined by the nature of their groups and shape in three dimensions, fit into the cavities of these receptors and deactivate them, thereby acting as 'drugs'. Several factors, such as pharmacokinetics, pharmacodynamics, metabolism, toxicology and clinical trials, play a crucial role in evaluating any drug. Drugs may be chiral, achiral or racemic in nature. These may be obtained either by extraction from a natural source or by semi-synthetic or synthetic methods.

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1. Introduction

Stereochemistry is a very important branch of chemistry that deeply influences the areas of organic, inorganic, biological, physical and supramolecular chemistries. Stereochemistry deals with the structure and shape of molecules in space and how these influence their behaviour/reactivities. Some authors [1] also prefer to call it 3D chemistry because the prefix '*stereo*' means space, that is, 'three-dimensionality'.

The differences in the biological activities of enantiomers or diastereomers—a type of stereoisomers—have been known for over 100 years. In 1886, Piutti described [2] the isolation of isomers from asparagine which were found to possess different tastes. Ever since this discovery, many examples of such differences in the biological activities of stereoisomers have been recorded. For example, in the chemistry of terpenes, *R*-limonene (I) (found in oranges) has the smell of oranges, whereas its optical isomer, *S*-limonene (II) (found in lemons) has a lemonoidal smell

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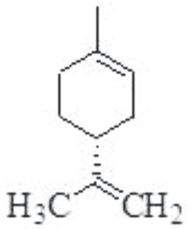
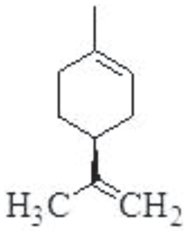
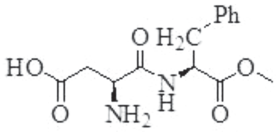


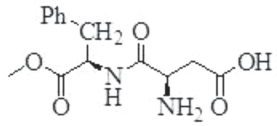
R-Limonene (I)
(Found in oranges)



S-Limonene (II)
(Found in lemons)



(*S,S*-Aspartame)(III)
(200 Times sweeter than sugar)



(*R,R*-Aspartame)(IV)
(Strong bitter taste)

[3]. Similarly, in peptide chemistry, S,S-aspartame (III) (the methyl ester of the dipeptide of essential amino acids, *L*-aspartic acid and *L*-phenylalanine) is 200 times sweeter than sugar, whereas its optical isomer, R,R-aspartame (IV) (the methyl ester of the dipeptide of amino acids *D*-aspartic acid and *D*-phenylalanine) has a strong bitter taste [4].

It may be mentioned here that S,S-aspartame or simply called aspartame, has been approved as a sugar substitute in food products by the US FDA, commercially sold under the trade names NutraSweet, Equal and Candere, whereas R,R-aspartame has no commercial use.

Again, naturally occurring (+)-ascorbic acid (V), commonly known as vitamin C, has strong anti-scurvy activity, whereas its synthetic isomer (-)-ascorbic acid (VI) has no such activity [5].

Marked differences in activity have also been found among the synthetic derivatives in pesticide/herbicide chemistry. For example, among dichlorophenoxypropionic acids, the enantiomer

Keywords
Chirality, optical activity, enantiomers, stereochemistry, sign of rotation, configuration, drug activity, non-therapeutic activities of enantiomers.

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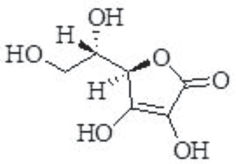
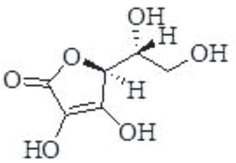
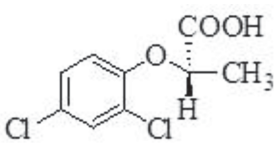


(+)-Ascorbic acid (V)
(Naturally occurring) (active)

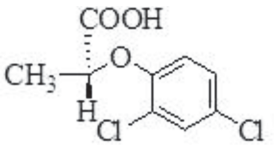


(-)-Ascorbic acid (VI)
(Synthetic) (inactive)

known as *R*(+)-dichloroprop (VII) has high pesticidal/herbicidal activity, whereas *S*(-)dichloroprop (VIII) is devoid of any pesticidal/herbicidal activity [6].



(*R*)(+)Dichloroprop (VII)
(Active)



(*S*)(-)Dichloroprop (VIII)
(Inactive)

Biological activity differences may also arise due to geometrical isomerism in compounds. For example, the all-trans-conjugated-double-bond configuration is responsible for the biological activity of vitamin A (IX), which plays an essential part in the chemistry of vision [7].

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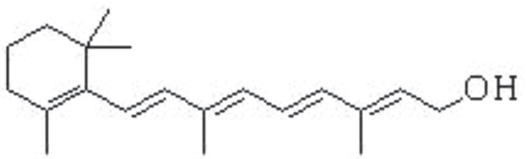

(Vitamin A) (IX)

Even if one double bond were to change its configuration to cis, all the biological activity would be lost. This is what happens when '*ghee*' (clarified butter) is made, traditionally from butter by heat treatment. Due to excessive heating, some of the double bonds change from trans to cis configuration. This decreases the

vitamin-A content, thereby reducing the nutritional value of butter on converting it into *ghee*. However, since butter is not stable for long storage, its thermally stable end product, i.e., *ghee*, is made by judicious heat treatment of the former.

In hormone chemistry, trans-dihydroxystilbene (X) has very good estrogenic properties, whereas its cis-isomer (XI) is non-estrogenic in nature.

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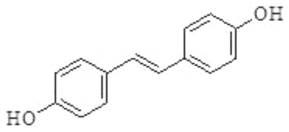
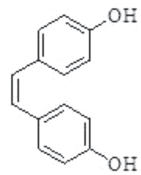
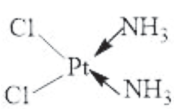


(Trans-Dihydroxystilbene)(X)
(Estrogenic)

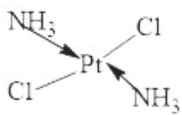


(Cis-Dihydroxystilbene)(XI)
(Non-Estrogenic)

Differences in biological activity have been found in inorganic metal complexes too. For example, cisplatin (XII) is a very good anti-cancer agent, unlike the trans isomer, i.e., transplatin (XIII), which has no anti-cancer activity [7]. These are just a few examples to mention.



Cisplatin(XII)
(Anti-cancer agent)



Transplatin(XIII)
(No Anti-cancer activity).

2. Chirality [8]

An object is said to be chiral if the object and its mirror image are non-superimposable.

The word chirality is derived from the Greek word '*Cheir*', meaning hand. An object is said to be chiral (*Figure* 1) if the object and its mirror image are non-superimposable, just like our right and left hands. When the mirror image of an object is placed over the original object, and the two do not overlap, then the object and its image are said to be non-superimposable. By logic, 'achiral' objects are those whose mirror images are superimposable on their

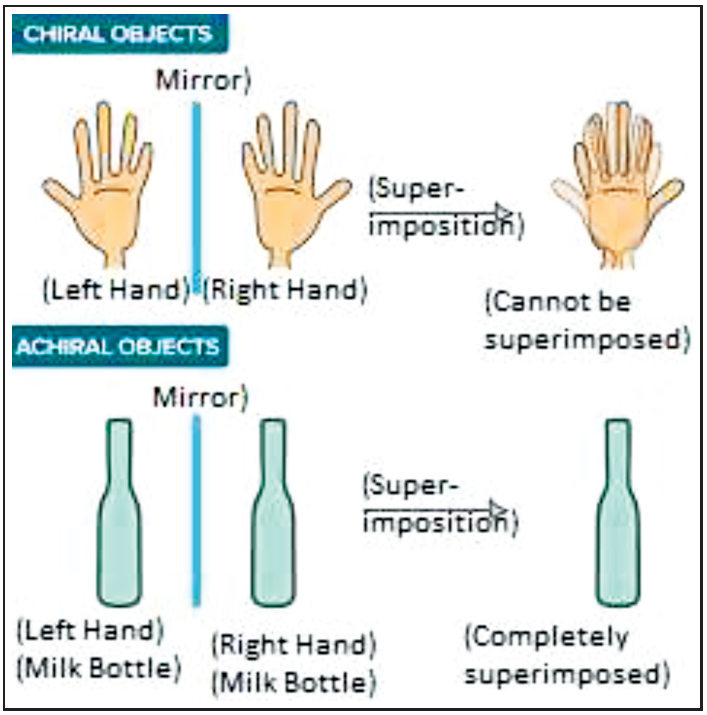


Figure 1. Difference between chiral and non-chiral objects.

originals—for example, a water bottle, tennis ball, etc.

Just like any object, a molecule and its mirror image may also be non-superimposable. Such a molecule is said to be chiral. It has been found from the study of a large number of organic compounds that those molecules which contain a carbon atom bonded to four different atoms/groups of atoms give rise to chiral molecules. The carbon centres in such molecules are referred to as 'asymmetric' carbon atoms (in old terminology) or chiral carbons/stereogenic centres (in new terminology). Since a pair of chiral molecules—the original and its look-alike (i.e., its mirror-image)—contains the same atoms/groups of atoms, they have identical physical, chemical and spectral properties except for their effect on plane-polarized light. The latter property can be measured by putting the solution of one of the chiral molecules and measuring its optical rotation in a polarimeter instrument. Such a pair of chiral molecules are referred to as 'enantiomers', 'mirror-image isomers', 'optical isomers', or 'optical antipodes'.

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If an enantiomer rotates the plane of polarized light (as observed by a polarimeter instrument) to the right or in a clockwise direction, it is said to be (+) or a dextrorotatory isomer. On the other hand, if the plane of polarized light is rotated to the left or in an anti-clockwise direction by the solution containing the molecules, the enantiomer is called (-) or levorotatory isomer.

3. Configuration

The manner in which the four atoms/groups of atoms are bonded to a chiral carbon/stereogenic centre is known as 'configuration'. Although configurations of molecules at the chiral centre have been proposed by several scientists, with varying degrees of success, the best method is the one given by Cahn, Ingold and Prelog. Using a set of assignment rules based on atomic or group masses, their relative orientations projected in 2-dimensions, the configurations of enantiomers (original and their mirror-images) have been assigned as '*R*' (Latin: *Rectus*) or '*S*' (Latin: *Sinister*). A detailed description of the rules for Configurational Designation of molecules as *R* and *S* is commonly available in most of the general textbooks [8] in organic chemistry. The reader is advised to look into them.

4. Chirality and Drug Action

In biology, the cells in the animal body are made of macromolecules manifesting as enzymes (which catalyse various biochemical reactions), proteins (which are built from L-amino acids) and carbohydrates (which are built from D-sugars). Under conditions of external impact or internal malfunctioning of the animal body, these macromolecules undergo folding/conformational flip or configurational changes to become 'receptors' that cause disease conditions.

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It was Paul Ehrlich, the German scientist, who, in 1906, first suggested [7] the idea of using chemicals to treat diseases, calling it 'chemotherapy'. An organic molecule used as a drug would reach

the receptor like a bullet reaching its target; Ehrlich called it a 'magic bullet'. According to Emil Fischer [9], a drug molecule would fit into the cavity of the receptor, exactly like a key fitting into the lock, thereby deactivating the receptor leading to a cure from the disease or preventing further propagation/progression of the disease.

A large number of drugs currently used in the market are chiral organic molecules. The enantiomers of a chiral drug have the same connectivity of atoms and exhibit identical physicochemical properties under achiral conditions. However, they have different biological properties. This is because biological receptors are made of enzymes, proteins, and carbohydrates (sometimes combining three or two of them) thereby generating a highly chiral environment.

A large number of drugs currently used in the market are chiral organic molecules.

Binding of chiral drugs to specific drug receptors is explained by a three-point interaction of the drug with the receptor site, as proposed by Easson and Stedman [10]. The difference between the interactions of the two enantiomers of a chiral drug with its receptor is shown in *Figure* 2.

Using the illustration in *Figure* 2, Easson and Stedman hypothesized that the three substituents—A, B and C—of the active enantiomer on the left can interact very efficiently with three binding sites—a, b and c, respectively—of the receptor by forming three contacts Aa, Bb and Cc. In contrast, the inactive enantiomer on the right will have insufficient interaction by forming contacts Ca, Bb and Ac, respectively.

A proper fit of the substituents (A, B and C, i.e., three of them) of the first enantiomer into the cavities of the receptor (a, b and c, i.e., three of them), similar to the lock and key mechanism proposed by Emil Fischer, produces an active biological response. In comparison, an improper fit (only one, i.e., B) of the substituents of the other enantiomer produces no biological effect. The attachment of an enantiomer to the biological receptor is analogous to a hand fitting into a glove. Thus, a right hand can fit only and properly into a right-hand glove, whereas a left hand will never

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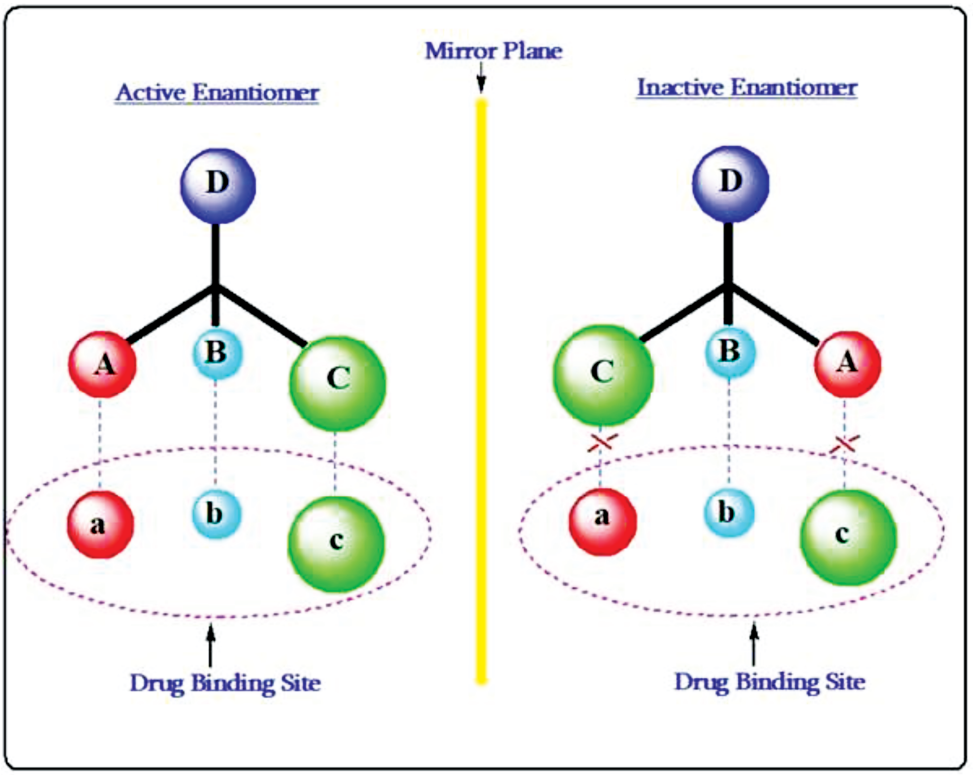

Figure 2. Drug-receptor bindings.

fit into a right-hand glove (one can also give a similar example of shoes!).

Some drugs are marketed as single enantiomers, while others are marketed as racemic mixtures. In general, most drugs obtained from natural sources (plants or animals) or from semi-synthetic methods are optically pure and are marketed as such. However, drugs obtained from synthetic sources (by and large) are racemic mixtures. The latter are marketed as such or after separation (called resolution) as pure enantiomeric drugs depending on the requirements.

Some drugs are marketed as single enantiomers, while others are marketed as racemic mixtures.

The chart shows, as per the *Indian Pharmacopia–2018* [11], the number of drugs currently sold in the market from natural, semi-synthetic and synthetic sources and also the number of synthetic drugs sold in racemic and enantiomerically pure forms.

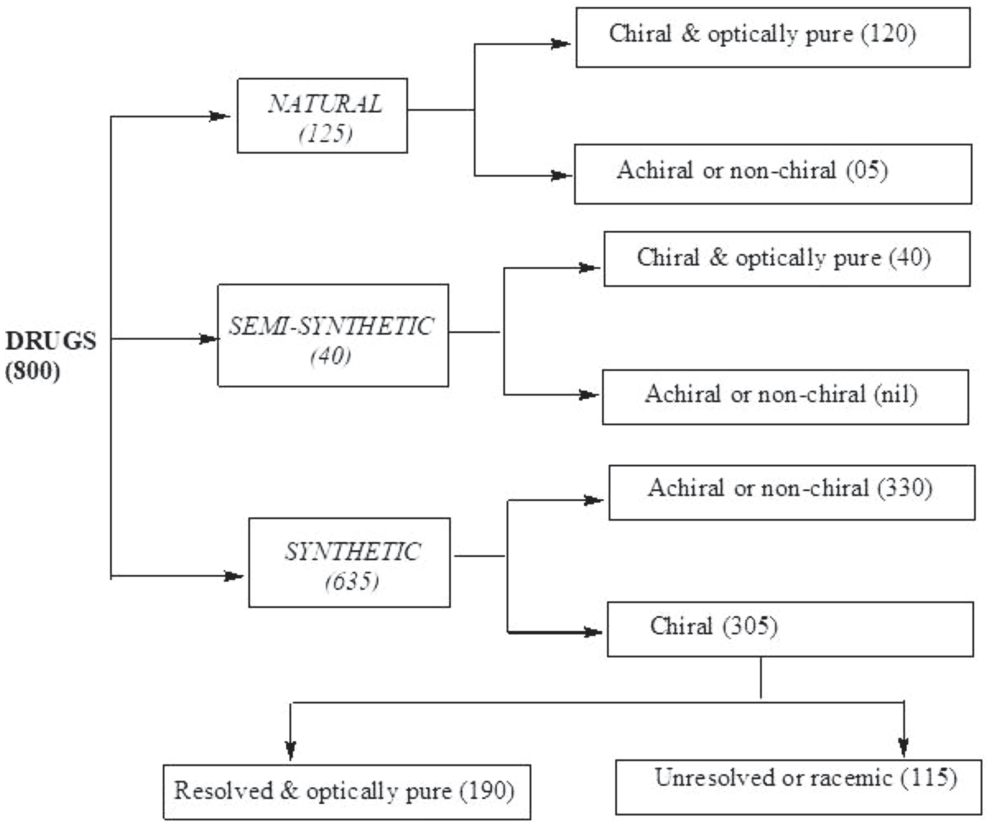

Chart: Different categories of drugs in approximate numbers.

5. Purity of Chiral Drugs

The purity of a commercial drug sample (if it is achiral) is measured by its physicochemical properties, spectral properties and assay analysis. The purity of any chiral drug sample is measured, in addition to these properties, by its optical properties determined by its specific optical rotation as measured experimentally with a polarimeter instrument [10]. Chiral drug samples, which are racemic, will have a 50:50 mixture of the two enantiomers, normal physicochemical and spectral properties, and assay analysis but 'zero' optical rotation. Only when the racemic mixture is separated into individual isomers, i.e., when the mixture is resolved, the two isomers will have equal but opposite optical rota-

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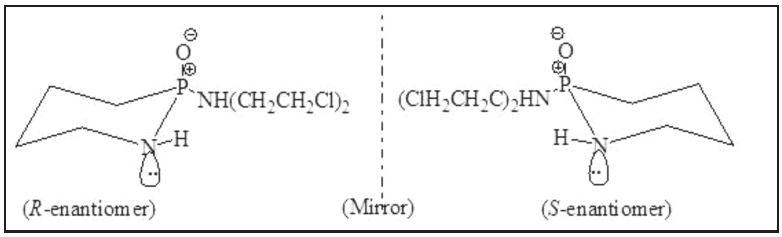


Figure 3. Non-superimposable mirror-images of cyclophosphamide.

tions [8].

6. Different Therapeutic Effects of Drug Enantiomers

The two enantiomers administered as a racemic mixture into the animal/human body will operate in a highly chiral environment.

The two enantiomers administered as a racemic mixture into the animal/human body will operate in a highly chiral environment. So, they will have different efficacies and/or therapeutic effects. In such a situation, the following scenarios may be observed regarding their drug effects (although there are many drugs in each class, only representative examples have been provided):

(i) Both Forms Equally Active

While this is a very desirable situation, it is one of the rarest of rare cases. The drug is usually administered as a 50:50 or ± or racemic mixture. An example of this class is cyclophosphamide (*Figure* 3) [12], used in the treatment of certain types of blood cancer, especially in children. Cyclophosphamide is a unique molecule in that the stereogenic centre is on the tetrahedral phosphorus atom, and it is part of the six-membered ring system.

(ii) One Form More Active Than the Other

An example of this class is propranolol [12] (*Figure* 4), used as a β-blocker and anti-hypertensive drug.

It has been found that the *S*-form/enantiomer/isomer of propranolol is ~ 100 times more active than the *R*-form/enantiomer/isomer. Obviously, in a case like this, it is imperative to separate the racemic mixture/racemate into individual isomers and then sell

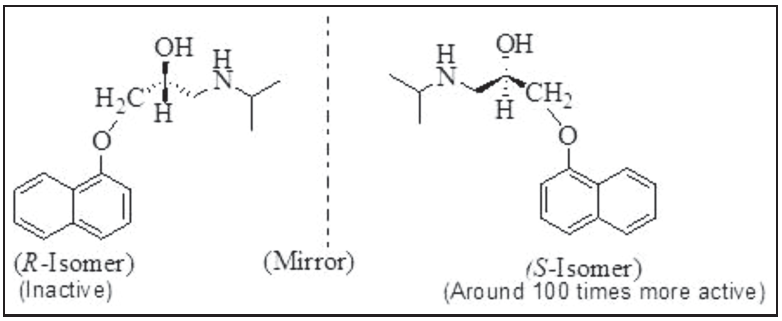


Figure 4. Non-superimposable mirror-images of propranolol.

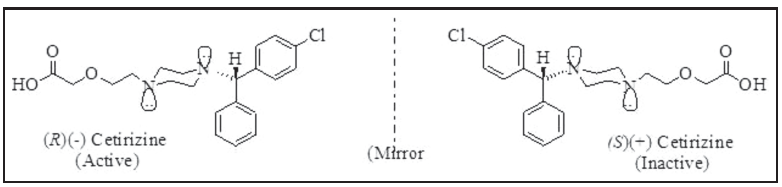


Figure 5. Mirror-image isomers of cetirizine.

the active enantiomer (i.e., *S*-form) alone as the actual drug in the market.

(iii) Only One Form Active, Other Inactive

An example of this class of drugs is the well-known cetirizine (*Figure* 5) [12], commonly used as an anti-histaminic, especially for allergic colds.

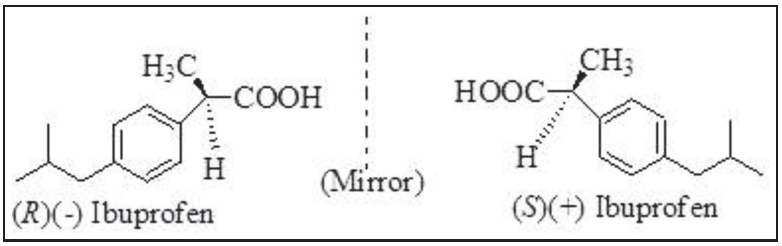
It has been found that the (-) isomer, having *R* configuration, is 100% active anti-histaminic compound, whereas the (+) isomer having *S* configuration, is totally inactive as an anti-histamine.

Each 10 mg tablet of (racemic) cetirizine costs ~ Rs 2.00 whereas each 5 mg tablet of (-) cetirizine, which is the actual efficacious drug, commonly known as levocetirizine, costs ~ Rs 4.00. This is because the resolution of the ±/racemic mixture leads to obtaining only the (-) isomer, wherein the unwanted (+) isomer is drained out, thereby doubling the cost (of the same drug).

Furthermore, it has been found that levocetirizine, originally marketed by Sepracor company of USA under the brand name Xyzal

Levocetirizine, originally marketed by Sepracor company of USA under the brand name Xyzal is non-sedating compared to the racemate (which has sedation as the side effect), previously sold under the brand name Zyrtec by the same company.

Figure 6. Mirror-image forms of ibuprofen.



is non-sedating compared to the racemate (which has sedation as the side effect), previously sold under the brand name Zyrtec by the same company. In other words, the inactive isomer (part of racemate) also has an undesirable side effect.

Several such examples can be found in the literature. A notable example is the commonly used antibacterial drug ofloxacin (which is the racemic drug) and its efficacious enantiomeric half 'levofloxacin' [12]. Another example is the blockbuster psychotic drug citalopram (the ±, RS, racemic drug) being sold after resolution as *S*-isomer called escitalopram [12], in which rests the entire anti-depressant activity.

(iv) One Form Active, Other Inactive but Convertible Into the Active Form in the Human Body

A well-known drug belonging to this class is ibuprofen (*Figure* 6) [12]. The latter comes under the category of 'profens', which are anti-inflammatory agents popularly known as non-steroidal anti-inflammatory drugs (NSAIDs). These profen drugs have the general formula of Ar-*CH(CH_3)-COOH with a chiral centre (marked as *) at the α-carbon of the propionic acid moiety. Other notable examples of this class of drugs are *S*-naproxen, ketoprofen, indoprofen, etc.

It has been found from animal studies that the *S*-form of ibuprofen is active as an anti-inflammatory agent, whereas the *R*-form is inactive.

It has been found from animal studies that the *S*-form of ibuprofen is active as an anti-inflammatory agent, whereas the *R*-form is inactive. However, the *R*-form is converted into the *S*-form in the human body, which then, together with the *S*-form, acts as an effective anti-inflammatory agent. As such, ibuprofen is prepared

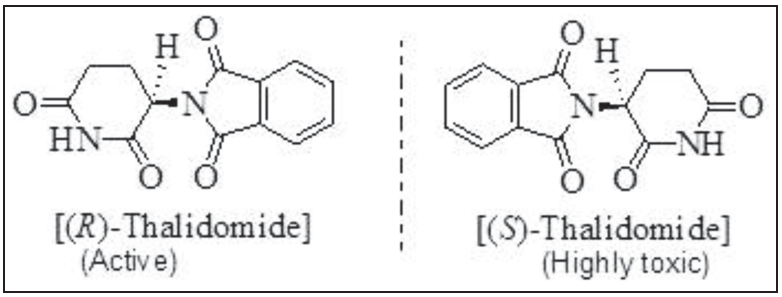


Figure 7. Enantiomers of thalidomide.

and sold largely as the racemate only.

(v) One Form Active, Other Highly Toxic

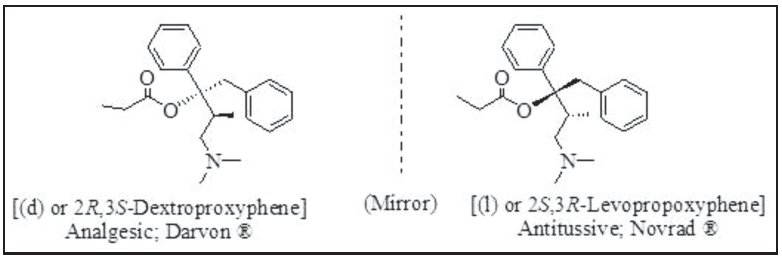
An example of this class of drugs is the most famous 'thalidomide' (*Figure* 7) [12]. The latter was synthesized by a German company—Chemie Grunenthal—in 1954, for which it was granted a patent in 1957. The drug was sold in the European market as a racemic mixture to overcome morning sickness (nausea, anxiety and drowsiness) in pregnant women.

The *R*-enantiomer of 'thalidomide' is hypnotic and effective drug, while the *S*-enantiomer is found to cause teratogenic birth defects.

Subsequent toxicological and animal studies showed that while the *R*-enantiomer was the hypnotic and effective drug, the *S*-enantiomer was found to cause teratogenic birth defects. A teratogenic fetus is one with deficient, redundant, misplaced or grossly miss-happened parts. In fact, *S*-thalidomide was shown to be responsible for over 10,000 cases of serious birth defects in children born to women who took the racemic drug during pregnancy. This came to be known [1] as the 'thalidomide tragedy' in medical history, leading to a ban on the drug in 1961, but not long before great damage was done to humankind.

Later experiments involving clinical trials in male human volunteers and post-menopausal women showed that even if enantiomerically pure *R*-thalidomide was administered, there was a slow and partial in-vivo conversion (due to inversion of configuration at the chiral centre) leading to an equilibrium between the *R* and *S* enantiomers. Thus, the hypothesis, "Had the pure *R*-enantiomer been used to treat morning sickness in pregnant

Figure 8. Enantiomers of propoxyphene.



women, the thalidomide tragedy would have been averted", might not have worked. Nevertheless, the thalidomide tragedy acted as a great precedent cum trend-setter, bringing out strong awakening among chemists, pharmacists, pharmacologists and doctors about the role of chirality in drugs.

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Another example of this type of compound is 'naproxen'. Presently, it is commonly used to relieve pain in treating rheumatoid arthritis, osteoarthritis, juvenile arthritis and acute gout. First launched in 1976 by the Syntex Company, naproxen was one of the top 15 prescription drugs in the late 70s and early 80s. While the *S*(+) enantiomer is the actual pain reliever, the *R*(-) enantiomer is highly toxic to the lever. So, the synthesised racemic mixture is resolved before the *S*-isomer (i.e., *S*-naproxen) is administered as the efficacious drug.

(vi) One Form Active Against One Ailment, Other Form Against Another Ailment

Examples of this type of chiral drugs are not many but are highly desirable, especially from the point of view of pharma companies since the racemate, which is synthesised, may profitably be separated into its constituent enantiomers, which may be marketed and sold separately. An example of this type is 'propoxyphene' (*Figure* 8) [13].

Both enantiomers of propoxyphene are commercially available. The dextro isomer, called dextropropoxyphene, marketed by the Eli Lilly company (of USA) under the trade name of Darvon, is used as an analgesic. The levo isomer, called levopropoxyphene,

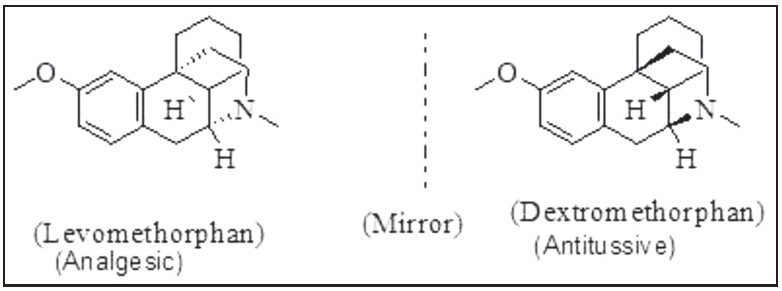

Figure 9. Mirror-image isomers of methorphan.

marketed by Eli Lilly company under the trade name of Novrad, is used as an antitussive agent. It may be noted that not only the drugs, even their trade names are mirror images of each other.

Another drug of this type is methorphan (*Figure* 9), relating to the opiate category. Among the latter types, most of them naturally occurring, are narcotic analgesics and are levorotatory, while their synthetic analogues are dextrorotatory and of the non-opiatic types. Thus, levomethorphan is an analgesic drug, whereas dextromethorphan is an antitussive agent.

7. Chiral Switches

It is obvious from the above discussion that for any racemic drug, one enantiomer (say *R*) may be active while its mirror image (say *S*) will, in all probabilities, be inactive or vice-versa. At any given time, it is very difficult to say or predict, a priori, which one will be active and which one will be inactive. This has been referred [1] to by some authors as a situation akin to a coin toss. Furthermore, when administered to a body, the two enantiomers will have different pharmacokinetic, pharmacodynamic, toxicological and metabolic pathways. When an enantiomer is administered to a body, say through the oral route, it will have a certain dissolution pattern (due to binders, excipients etc., present in the formulation such as cyclodextrins, sugars etc., which are chiral substances in addition to gastric juices in the stomach) different from its antipode. So will be its absorption by intestines and subsequent diffusion into and/or transfer through the blood to the site

When administered to a body, two enantiomers will have different pharmacokinetic, pharmacodynamic, toxicological and metabolic pathways.

of action, thereby making a characteristic pharmacokinetic profile. On reaching the site of action, the stereoisomer will bind to the receptor with a force or binding energy. It will remain attached until appropriate drug action takes place, thus making a pharmacodynamic profile. Once detached, it may find its hepatic/renal/metabolic routes of excretion.

It is difficult to predict the toxicological activity/metabolic route of any chemical inside the body.

Furthermore, it is difficult to predict the toxicological activity/metabolic route of any chemical inside the body. For these reasons, the inactive/harmless enantiomer in a racemate is regarded as a 'biological load' on the body. Some authors [1] call a racemic mixture a 50:50 mixture of two compounds or even the unwanted enantiomer as a 50% impurity in the drug. Take the case of paracetamol, an over-the-counter (OTC) drug used to treat mild body pain, fever and inflammation. The *Indian Pharmacopia–2018* [11] mandates commercial paracetamol to have an assay of $100 \pm 2\%$. In contrast, its next-door neighbour, ibuprofen (also an OTC drug), used as an analgesic and anti-inflammatory agent, is a racemic drug with a 50:50 mixture of *R* (inactive) and *S* (active) isomers even though the assay of commercial ibuprofen is also mandated to be $100 \pm 2\%$! This problem arises because an 'assay' is performed based on chemical composition and not based on biological activity, the latter depending on the chiral purity of drugs.

Given the above facts, most pharma companies which have originally manufactured and marketed the racemic drugs try to switch over to the active enantiomers by resolution of the racemic drugs or by direct manufacture of the active isomers—a process known as 'chiral switch' [14] (i.e., switch over to the chirally pure, active drug component). Thus, it may look as if racemates of chiral drugs have reached a dead end and that they may not be marketed in future. However, this is not always true, as shown by the following two case studies as representative examples.

Fluoxetine hydrochloride, a blockbuster psychotic drug, was developed in the early nineties as a racemate and marketed under the trade name Prozac by Eli Lilly.

Fluoxetine hydrochloride, a blockbuster psychotic drug, was developed in the early nineties as a racemate and marketed under the trade name Prozac by Eli Lilly company for treating depression. Fluoxetine is a racemate of two enantiomers, *R*(-) fluoxe-

tine and $S(+)$ fluoxetine. Eli Lilly believed that the enantiomers were not significantly different and did not actively pursue a chiral switch programme. However, in the mid-nineties, another company Sepracor, which specializes in the chiral switch programmes (of other companies' racemic drugs), obtained separate patents for R(-) fluoxetine and $S(+)$ fluoxetine for the treatment of depression and migraine headaches respectively. In 1998, Eli Lilly and Sepracor agreed to jointly develop R(-) fluoxetine as the single isomer, side-effect–free version of Prozac (i.e., the chiral switch) for depression. Subsequently, in Phase II clinical trials, it was found that R(-) fluoxetine causes severe cardiac problems. So the development of this drug was halted. As of now, 50:50 racemic fluoxetine has been used as a safe and effective antidepressant for over 15 years without any problems, whereas the R-enantiomer could not make it to the market due to safety concerns. It is believed (not knowing how) that the S-enantiomer nullifies the toxic effects of the R-enantiomer in the racemate [15].

Another example is labetalol [15], an antihypertensive agent that works as both α- and β-blocker. The drug has two chiral centres in its structure, and accordingly, there are $2^n = 2^2 = 4$ optical isomers or two pairs of enantiomers. Labetalol is marketed as a mixture of all four stereoisomers! Any attempt to market the drug as individual isomers led to severe liver toxicity. Several other such examples can be found in the literature.

Stereochemistry is an important branch of chemistry that determines the chirality of drugs.

8. Conclusion

Stereochemistry is an important branch of chemistry that determines the chirality of drugs. The biological activity of drugs depends on either of the chemical entity's two enantiomers/other diastereomers on a case-to-case basis. It so happens, in most cases, that one of the enantiomers/diastereomers has the requisite drug activity. So the race for obtaining it in pure form goes on, although, in certain situations, racemic mixtures or mixtures of diastereomers are still used.

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