Chirality & Bioactivity I.: Pharmacology

John C. Leffingwell
Leffingwell & Associates, 4699 Arbor Hill Road, Canton, Georgia 30115, USA, Tel. 770-889-5111, e-mail: leffingwell@mindspring.com, web page: www.leffingwell.com

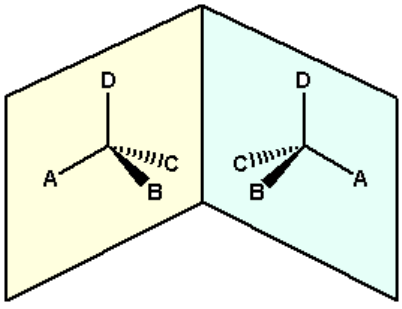
Abstract: This review provides a history of the first important chiral drugs used in treating disease and a basis for understanding the importance of chirality on the bioactivity of pharmacologically active drugs.

Keywords: Chirality, bioactivity, pharmacology, drug, metabolism

Introduction to Chirality

The concept of "chirality" has been known in chemistry since the 1870's although it would be nearly a hundred years before chemists began using this term. In fact, in the first edition of Eliel's "Stereochemistry of Carbon Compounds" in 1962 [1], the word chiral is not mentioned, although it would be prominent in later editions [2]. In extremely simple terms, chirality is "handedness," - that is, the existence of left/right opposition. For example, your left hand and right hand are mirror images and therefore "chiral". The term Chiral is derived from the Greek name kheir meaning "hand" and apparently was coined by Lord Kelvin in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light [3] in which he stated ...*"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."*

While the concepts of "asymmetry" were developed by J.H. van't Hoff [4] and J.A. Le Bel [5] in 1874 following the resolution by Louis Pastuer of a mixture of tartaric acid salt isomers during the period 1848-1853, in which he picked out the differing crystal types by hand - doing so on the basis of the differing physical appearance of the salt crystals [6]. Pastuer recognized that two of the isomers polarized light differently (one to the left and the other to the right) and that this must be due to an asymmetric grouping of atoms in the optically active molecules.



Two "chiral" forms (enantiomers)

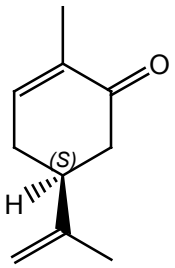
Following Kekule's recognition in 1858 that carbon has a valence of 4 [7], vant' Hoff and Le Bel independently recognized that when four different groups are attached to a carbon atom, arrayed at the corners of a tetrahedron, then the arrangements can be in two different forms, as depicted schematically above

.As the number of carbons with asymmetry (chirality) increase in a molecule the number of possible optical isomer pairs (enantiomers) also increases. With one asymmetric carbon, 2 isomers (one pair of enantiomers)...with two asymmetric carbons, 4 isomers (two pairs of enantiomers), with three asymmetric carbons, 8 isomers (four pairs of enantiomers) ...that is, the number of stereoisomers is 2^n, where n = number of asymmetric atoms. Note that in recent years the term asymmetric is sometimes referred to as "stereogenic".

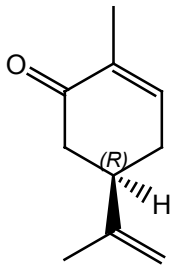
In the early days, chemists often assigned trivial names to differentiate isomers, and enantiomers generally were specified by d- = dextrorotary and l- = leavorotary based on which direction the molecules polarized light (not to be confused with the "capital" L- and D- prefixes used for carbohydrates and amino acids, i.e. Fischer Projection Formulas). But Cahn, Ingold and Prelog [8] devised a system based on assigning sequence rules based on decreasing atomic number (and respective rate of substitution for atoms of the same atomic number) for projection formulas that allows the **absolute configuration** assignments of **R** (for rectus, Latin for right) and **S** (for sinister, Latin for left). These rules are incorporated in the chirality monitor of Accelrys DS Viewer and DS ViewerLite software (the latter being freeware). Very occasionally, DS Viewer provides incorrect assignments (for example, with the enantiomers of gamma-dihydroionone, gamma-damascone & gamma-ionone). However, Cambridgesoft's ChemDraw Ultra appears to provide essentially 100% correct C-I-P (R-, S-) assignments. Thus, even without knowing the Cahn, Ingold and Prelog sequence rules, chemist's today can rapidly establish the R/S configuration at each asymmetric atom for a given molecular structure (of known absolute configuration) in just a few minutes.

Chirality & Bioactivity

Most chemists are familiar with the role of chirality on odorants such as (4S)-(+)-carvone, which has a distinct caraway odor, as compared to (4R)-(-)-carvone which has a characteristically sweet spearmint odor [9].



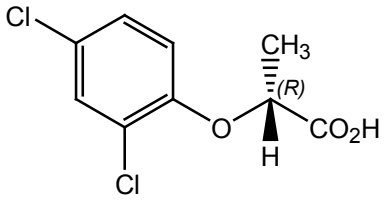
(4S)-(+)-carvone
Caraway odor



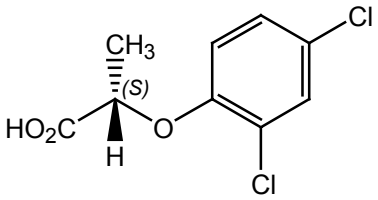
(4R)-(-)-carvone
Spearmint odor

These two odorants possess different odors due to the role of chirality on bioactivity, in this case a different 3-D fit on an odor receptor and/or on different odor receptors. Although the role of chirality in odor perception is still a rather modern area of interest, it should be noted that more than 285 enantiomeric pairs (570 enantiomers) are known to exhibit either differing odors or odor intensities [10].

While the subject of this paper is about the enantioselective bioactivity of pharmacologically active enantiomers it should be recognized that the same principals are important for herbicides and pesticides containing chiral stereogenic centers.



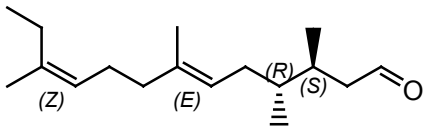
(R)-(+)-dichlorprop
(Active)



(S)-(-)-dichlorprop
(Inactive)

For example, the (R)-(+)-enantiomer of the herbicide dichlorprop (as well as the (R)-(+)-enantiomers of all the phenoxypropionic acid herbicides) is the active enantiomer in killing the weeds, while the (S)-(-)-enantiomer is inactive as an herbicide. In order to reduce the amount of herbicides used and avoid the possibility of the unnecessary enantiomer causing possible adverse impact, several European countries have recently decreed that only the (R)-enantiomers will be used for phenoxypropionic acid herbicides [11].

Similarly, in the case of insect pheromones chirality can influence the degree of attractiveness of the semiochemical.



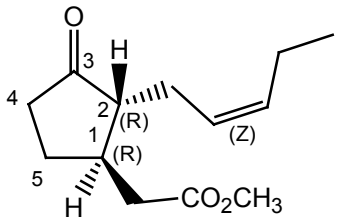
(3S,4R)-Faranal

Thus, (3*S*,4*R*)-Faranal is the only bioactive enantiomer (of four stereoisomers) of the trail following pheromone of the pharaoh's ant *(Monomorium pharaonis)* [12].

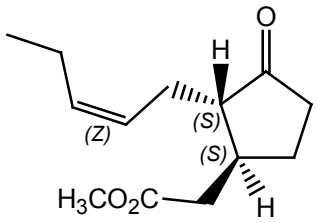
Further, chirality can effect plant growth regulation. In the case of Methyl jasmonate we find a unique example of a chiral compound that is (1.) a plant growth regulator, (2.) a valuable fragrance material (whose stereoisomers have remarkably different odor intensities), (3.) an insect semiochemical that has pheromone activity in certain species and induces plant stress volatiles in plants for defence against

herbivores and (4.) has recently been found to possess promising pharmaceutical activity against cancer cells.

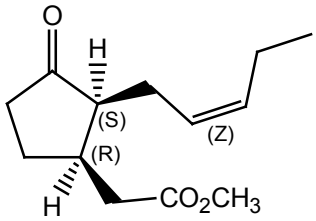
As an odorant, methyl jasmonate and its dihydro derivative (methyl dihydrojasmonate) are important components in fine fragrances. The following table provides the odor descriptions and threshold values [13].



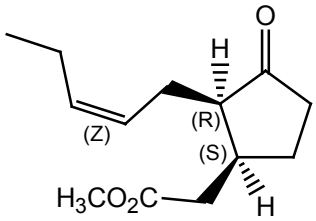
1R,2R-(-)-Z-methyl jasmonate



1S,2S-(+)-Z-methyl jasmonate



1R,2S-(+)-Z-methyl epijasmonate



1S,2R-(-)-Z-methyl epijasmonate

Configuration	Odor Description	Odor Threshold (in PPB)
Methyl jasmonates		
1R,2R-(-)-	Weak odor	>70*
1S,2S-(+)-	Odorless	Odorless
1S,2R-(-)-epi-	Odorless	Odorless
1R,2S-(+)-epi-	Strong odor; floral, true jasmin-like	3*
Methyl dihydrojasmonates		
1R,2R-(-)-	Floral, sweet, jasminelike	240**
1S,2S-(+)-	Floral, fatty, cis-jasmone, hay character, tea note, slightly lemon peellike (weak)	15,360**
1S,2R-(-)-epi-	Herbal, fatty, tea-like, tobacco, β-damascone, *cis*-jasmone	12,500**
1R,2S-(+)-epi-	Intensely floral, jasminelike, bright, cis-jasmone, slightly fatty, woody, β-iononelike, extremely long lasting	15**

* detection threshold

**recognition threshold

Methyl jasmonate (and jasmonic acid) also act as regulators of important biological functions in many plants. For example, they induce the growth of potatoes (*Solanum tuberosum*) [14], control the synthesis of certain proteins (jasmonate-induced proteins) [15] as well as the emission of ethylene and act as growth regulators (phytohormones) [16]. Furthermore, methyl jasmonate and jasmonic acid take part in producing stress signals in the defense of plants against herbivores [17]. Methyl jasmonate has also been identified as a component of the sexual pheromone of the male oriental fruit moth (*Grapholitha molesta*) [18]. In all these cases, the stereoisomers of methyl jasmonate exhibit different activities, with *cis*-(1*R*,2*S*)-methyl epijasmonate generally being considered the most active one [19]. Recently, Holbrook, et. al. have shown that the 1R stereocenter is critical to enhanced bioactivity [20]. Similarly, the 1R configuration has been shown to have importance in the production of anti-cancer drug taxol from cell cultures from the yew tree [21].

Methyl jasmonate (and jasmonic acid) have also been found to induce death in lymphoblastic leukemia cells and cause suppression of cell proliferation in other human cancer cells [22].

Chirality in Pharmacology

In pharmacology, chirality is an important factor in drug efficacy. About 56% of the drugs currently in use are chiral compounds, and about 88% of these chiral synthetic drugs are used therapeutically as racemates. Unfortunately, there are many racemic drugs where the stereospecificity of the metabolism and/or the pharmacodynamic effects of the enantiomers is not known [23].

Prior to Ariens' critical review of "sophisticated nonsense in pharmacokinetics and clinical pharmacology", published in 1984, neglect of stereochemistry in drug development was widespread and only in the last decade or so has it achieved a prominent place in drug design [24].

Quinine & Other Cinchona Alkaloids

One of the earliest known uses of a chiral compound to cure a disease is the case of Quinine (vis-à-vis Cinchona alkaloids).

The use of Cinchona alkaloids is often attributed to the Countess Anna of Chinchón, wife of the Viceroy of Peru; who reputedly was cured of an ague (malarial fever) by Cinchona bark sometime in the late 1620's or early 1630's [25]. More likely it was her husband, the Viceroy, who suffered from the fever and the cure was based on a Peruvian Indian folk medicine that used the bark as a remedy to suppress shivering and fever conditions.

During the 1630's, cinchona bark was introduced into Europe by returning missionary Jesuits. An important ecclesiastical figure, Cardinal de Lugo, who taught at the Collegium Romanum in Rome was impressed by his preliminary trials of its efficacy and reportedly purchased large amounts of it at his own expense. The bark was distributed to patients at the Hospital of Santo Spirito by the Cardinal and

Pietro Paolo Puccerini, keeper of the apothecary's shop at the Collegium Romanum, and they treated hundreds of patients a year and reported the bark to be very successful, in particular for malaria [26].

In 1735, the French Government sent an expedition to South America led by Condamine, ostensibly for geographical exploration, but, in fact, a major purpose was to find the miraculous "fever tree". Condamine found the tree in Peru and on his return to France wrote a treatise "Sur l'arbre du Quinquina" and he provided illustrations and plant samples to Linnaeus, who in 1742 renamed the plant as "Cinchona" (a slight misspelling of Chinchón) [26].

By 1790 the Spanish, realizing the barks importance, set up a monopoly to improve quality and, perhaps more importantly, to control supplies. For the next hundred years, South America would be the main source of supply.

In 1820, the French chemist's, Pierre Pelletier and Joseph Caventou successfully isolated two of the active alkaloids, quinine and cinchonine, and production of a number of the pure alkaloids from Cinchona species soon followed (including quinidine and cinchonidine). Commercial production of Quinine began in 1821. Of course, at the time, the chemical structures of the Cinchona alkaloids had not been determined. Nevertheless, numerous attempts to synthesize quinine would consume chemists for many years. It was not until 1944, that a "formal" synthesis of quinine would be realized by Robert Woodward and William Doering [27]. And it would not be until 2001 that a complete stereoselective synthesis would be achieved by Gilbert Stork, et. al. [28].

By the 1800's the French, British and Dutch all had colonies in malaria infested areas. The lack of sufficient quinine (or cinchona bark) prompted all of these powers to attempt to develop cinchona plantations in areas other than South America. While the French had little success, the efforts of the English, in a strange twist of fate, would eventually lead to the Dutch controlling the Cinchona trade. Clements Markham and Robert Cross were sent to the Eastern Andes by the British in 1860 to obtain plants and seeds with the purpose of transplanting them and developing Cinchona plantations in India and Ceylon. By 1866, these plantations had been established and were able to supply Britain with adequate amounts of bark (and hence quinine) for a period of time [26].

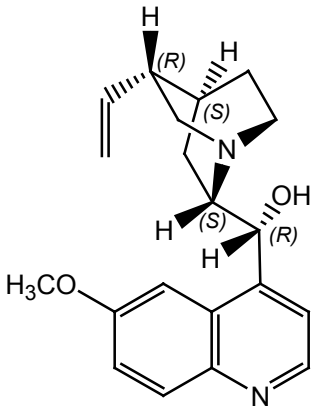
Between 1844 to 1865, Charles Ledger and Manuel Incra Mamani collected bark and seeds in the Andes on the Peruvian/Bolivian border. Eventually (in 1865) they identified a species (subsequently named *Cinchona ledgeriana*) that was found to contain as much as ten per cent of the alkaloids by weight (which was almost double that of other species). While the British Government showed little interest, the Dutch bought a pound of the seeds for 100 guilders (about £20). When planted in Java by the Dutch, and by careful cultivation and experimentation, the yield from the bark of C. ledgeriana was doubled when compared with the wild variety in Peru and Bolivia. This has since been the basis of the world's supply of quinine [26].

The story does not end here. During World War II, allied troops no longer had access to Cinchona supplies and an immense effort was undertaken to develop alternatives to quinine for treatment of malaria. Chloroquine (N^4-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine) is a synthetic

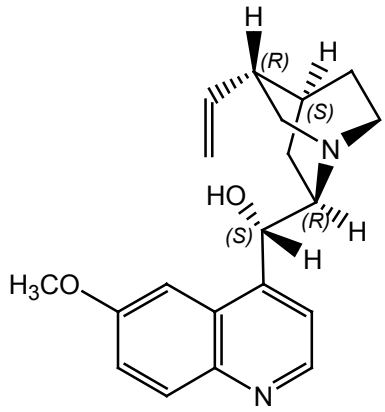
anti-malarial introduced in the 1940's. In conjunction with the use of DDT, chloroquine nearly eradicated malaria in some parts of the world by the mid 1950's. But, with increasing use, the *Plasmodium* protozoa's responsible for malaria developed resistance to this and a number of other antimalarials (includine quinine) and since 1960 malaria has been on the rise. Another synthetic antimalarial, mepacrine (or Atebrin), developed in the 1930s, was one of the main prophylactic agents used by the Allied forces during the World War II [29].

Of recent interest as an anti-malarial is *Artemesia annua*, called qinghao in Chinese, which is a widely growing weed in South China. For centuries the dried plant had been used for treating fevers, including malarial fever. In the 1970s, Chinese chemists extracted the active principle from *Artemesia annua*, which is now called artemisinin and found it to be an excellent anti-malarial drug. Subsequent small changes in the chemical structure have produced several other highly effective anti-malarial drugs [30].

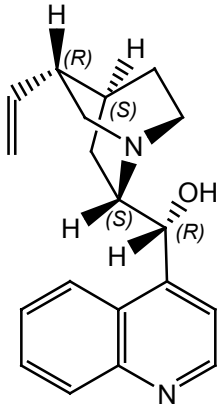
The following chemical structures are the four major alkaloids of Cinchona:



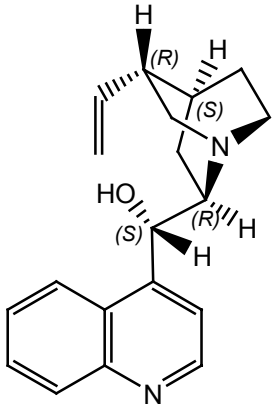
(3R,4S,8S,9R)-(-)-Quinine



(3R,4S,8R,9S)-(+)-Quinidine



(3R,4S,8S,9R)-(-)-cinchonidine



(3R,4S,8R,9S)-(+)-cinchonine

While (-)-Quinine and (+)-Quinidine are diastereomers, they are not enantiomers, as is also the case with (-)-cinchonidine and (+)-cinchonine. Of these four alkaloids, (-)-Quinine, (-)-cinchonidine and

(+)-cinchonine are all antimalarials. While (+)-Quinidine also possesses anti-malarial properties, it is normally prescribed as an antiarrhythmic to regulate heartbeat. As to the pharmacological properties of the enantiomers of these important chiral pharmaceuticals…these are presently unknown due to the difficulty in synthesis.

Enjoy!! Cinchona extracts and quinine are also used in tonic waters, which were popularized in the British colonies as both a malaria prophylactic and for enjoyment in the form of a "Gin & Tonic". With a twist of lime this also prevented scurvy (see Vitamin C below). Tonic water is now one of the largest industrial uses of quinine [31].

As a last comment**,** (+)-Quinidine is sometimes referred to in the scientific literature as a quasi-enantiomer of (-)-quinine. This is popular semantics that should be rejected as having absolutely no scientific basis. There is no such entity as a quasi-enantiomer! It can be called a stereoisomer or diastereomer but never the "non-entity" quasi-enantiomer.

Vitamin C (Ascorbic acid)

Another early use of a chiral compound to cure a disease is the case of Vitamin C (albeit from foodstuffs).

In 1746, James Lind, a British naval surgeon on the H.M.S. Salisbury, conducted a controlled test on 12 seamen suffering the debilitating effects of scurvy. He divided them into six pairs giving each group different supplements to their basic diet. Two men received a quart of cider a day, and two others were given an Elixir of vitriol (made by combining 3 3/4 fluid ounces of sulphuric acid, 1 5/8 fluid ounces of tincture of ginger, and alcohol in sufficient quantity to. make 33 3/4 fluid ounces [32]) three times a day. One pair was treated with seawater, and another was fed with a combination of garlic, mustard and horseradish. Two men were given spoonfuls of vinegar, and the last two were given two oranges and one lemon every day. Four out of the six groups reported no change, the men given cider reported only a slight improvement, but the two seamen fed citrus fruits experienced a remarkable recovery. While there was nothing new about his discovery (the benefits of lime juice had been known for centuries), Lind had established the benefit of citrus fruits in combating scurvy [33]. By 1795, the Royal navy had mandated the use of lime juice or other citrus fruits as a scurvy preventative.

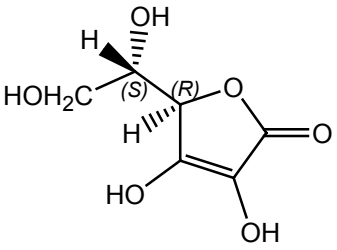
In 1928**,** Albert Szent-Györgyi isolated a reducing substance from the adrenal gland (and various plants) of molecular formula $C_6H_8O_6$ which he named hexuronic acid. In the autumn of 1931 experiments showed unmistakably that hexuronic acid was powerfully anti-scorbutic, and that the anti-scorbutic acitvity of plant juices corresponded to their hexuronic acid content. At about the same time King and Waugh [34] also reported crystals obtained from lemon juice, which were actively anti-scorbutic and resembled hexuronic acid. Szent-Györgyi and Norman Haworth subsequently renamed hexuronic acid as Ascorbic acid [35]. The main features of the constitution of ascorbic acid and its

formula as a lactone of 2-keto-*l*-gulonic acid, capable of reacting in various tautomeric forms, was first announced from the University of Birmingham, early in 1933 by Norman Haworth [36].

Tadeus Reichstein, in Switzerland, as well as Haworth's group independently at about the same time achieved syntheses of Vitamin C [37].

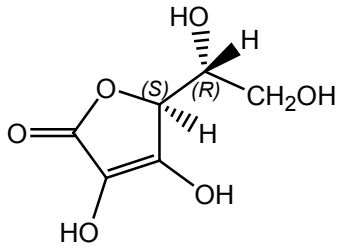
Of the four possible stereoisomeric forms of ascorbic acid only the form identical to natural Vitamin C, (+)-ascorbic acid, has the same anti-ascorbutic activity [38], although all of the diastereomers show the same strong anti-oxidant properties.

Differing biological effects of ascorbic acid enantiomers and diastereomers have also been shown on the growth of human leukemia cells [39].



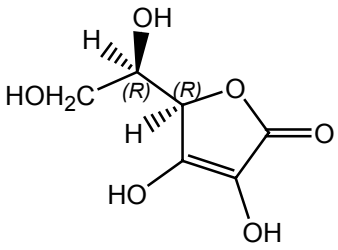
(+)-Ascorbic acid

= (+)-Threoascorbic acid



(-)-Ascorbic acid

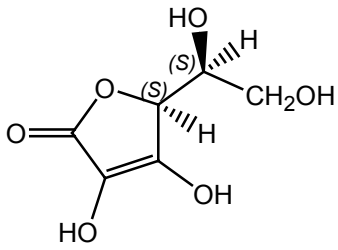
The enantiomer of (+)-Ascorbic acid



(-)-Isoascorbic acid

= Erythorbic acid

A diastereomer of (+)-Ascorbic acid

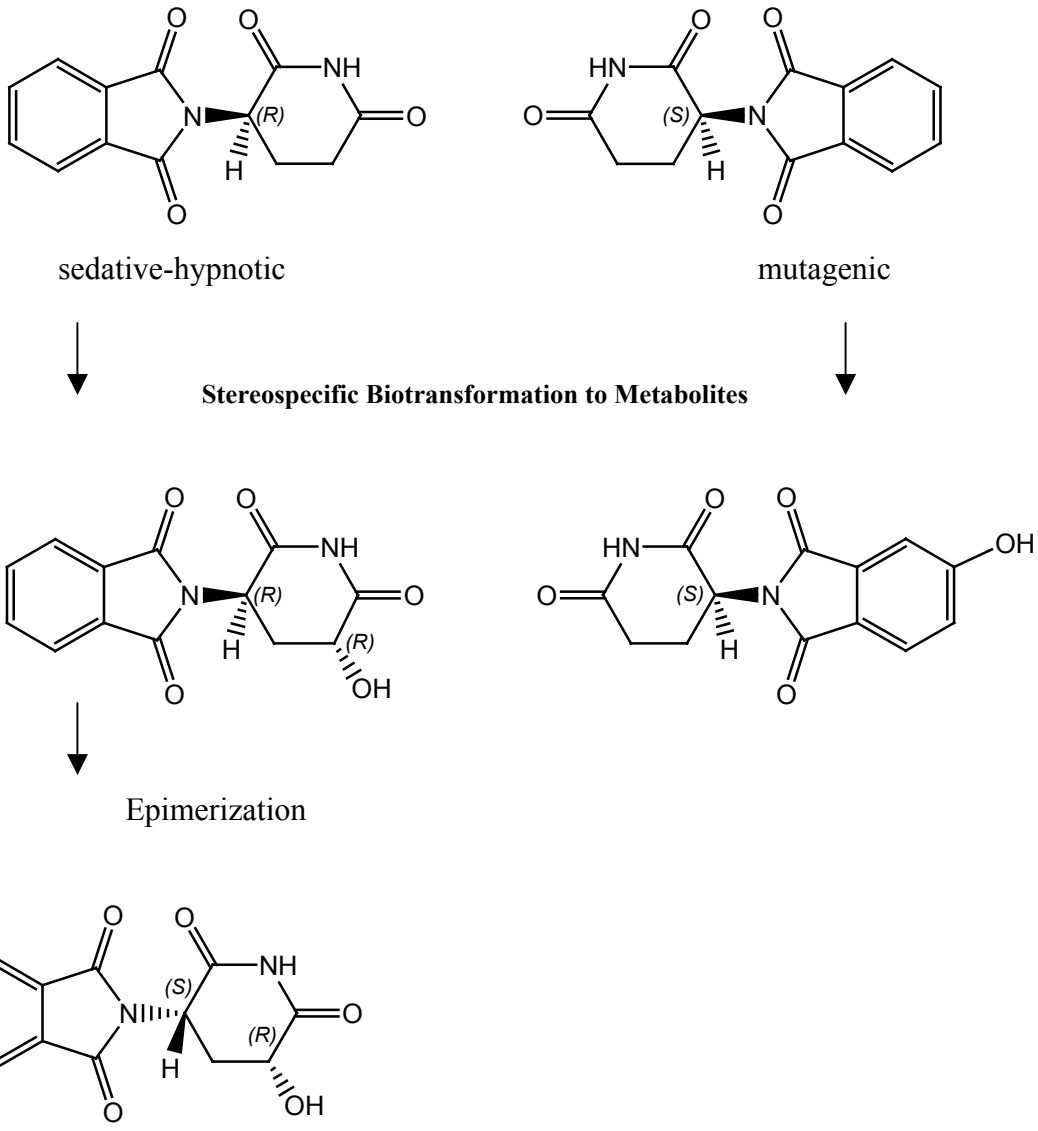


(+)-Isoascorbic acid

As (+)-Ascorbic acid and (-)-Erythorbic acid are often labeled as L-ascorbic acid and D-erythorbic acid, respectively, there is often a misconception that these two items are enantiomers. These are not enantiomers, but are diastereomers as the structures are not mirror images.

While (+)-Ascorbic acid is utilized as a bioactive vitamin nutrient, both (+)-Ascorbic acid and (-)-Erythorbic acid are also commercially important as antioxidant preservatives (e.g., to protect the flavor profile of citrus soft drinks such as orange soda). (-)-Erythorbic acid exhibits only 5% of the anti-ascorbutic activity compared to (+)-Ascorbic acid.

Thalidomide

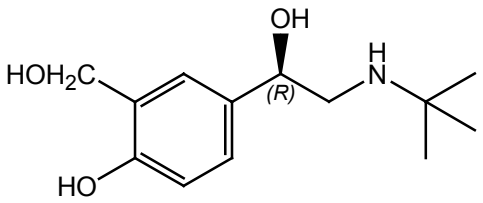


The use of thalidomide (which was marketed as the racemate) led to a tragedy in the 1960s in Europe. The sedative-hypnotic drug thalidomide exhibited irreversible neurotoxicity and teratological (mutagenic) effects in which babies were born deformed. The drug was prescribed to pregnant women to counter morning sickness. Studies later suggested that these effects were caused by the S-enantiomer and that the R-enantiomer contained the desired therapeutic activity. More recently, studies have concluded that both enantiomers of thalidomide are unstable and spontaneously epimerize to form the racemate in-vivo in humans [40]**.** Metabolic elimination of thalidomide is mainly by pH-

dependent spontaneous hydrolysis in all body fluids with an apparent mean clearance of 10 l/h for the (R)- and 21 l/h for the (S)-enantiomer in adult subjects. Blood concentrations of the (R)-enantiomer are consequently higher than those of the (S)-enantiomer at pseudoequilibrium. The metabolites in humans has been studied both from incubation of thalidomide with human liver homogenates and in-vivo in healthy volunteers. The in-vitro studies demonstrated the hydrolysis products 5-hydroxy-thalidomide and 5'-hydroxy-thalidomide while in-vivo only the 5'-hydroxy metabolite was found, in low concentrations, in plasma samples from eight healthy male volunteers who had received thalidomide orally. The hydrolysis of the two thalidomide enantiomers by in-vitro incubation was shown by Meyring, et. al., to be stereospecific. The chiral center of the thalidomide enatiomers is unaffected by the stereoselective biotransformation process. (3'R,5'R)-trans-5'-hydroxythalidomide is the main metabolite of (R)-thalidomide, which epimerizes spontaneously to give the more stable (3'S,5'R)-cis isomer. On the contrary, (S)-thalidomide is preferentially metabolized by hydroxylation in the phthalimide moiety, resulting in the formation of (S)-5-hydroxythalidomide [41].

Although Thalidomide is tainted from its past history, it (and analogs) have recently been a subject of numerous studies. In 1998 the U.S. Food and Drug Administration approved thalidomide for use in treating leprosy symptoms and studies indicate some promising results for use in treating symptoms associated with AIDS, Behchet disease, lupus, Sjogren syndrome, rheumatoid arthritis, inflammatory bowel disease, macular degeneration, and some cancers [42].

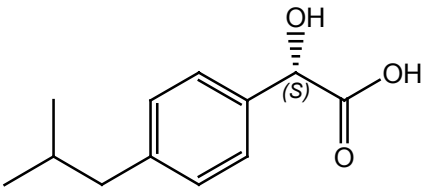
Albuterol



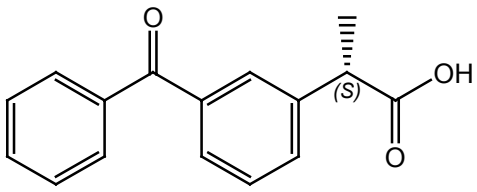
(R)-albuterol

Albuterol is the racemate of 4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol. and is the leading bronchodilator, an adrenoceptor agonist that can increase bronchial airway diameter without increasing heart rate. The bronchodilator activity resides in (R)-albuterol. (S)-Albuterol, however, is not inert, as it indirectly antagonizes the benefits of (R)-albuterol and may have proinflammatory effects. There are pharmacokinetic differences between the enantiomers with (S)-albuterol being cleared more slowly. The (S)-enantiomer tends to accumulate in preference to the therapeutically effective (R)-enantiomer. These pharmacokinetic and pharmacodynamic differences provided the basis for the chiral switch patent of albuterol to levalbuterol, (R)-albuterol), which has the same bronchodilator activity as racemic albuterol, but has a superior side-effect profile [43,44].

Profens



(S)-Ibuprofen



(S)-Ketoprofen

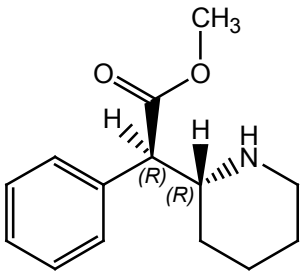
Both (S)-Ibruprofen and (S)-Ketoprofen are the chiral switch drugs of the popular racemates.

The most numerous class of non-steroidal anti-inflammatory drugs that are in use currently is the 2-arylpropionic acids or 'profens'. These are used widely for the treatment of inflammatory diseases, such as rheumatoid arthritis, as both analgesics and antipyretics. However the racemates are responsible for many adverse reactions reported each year. These adverse reactions affect a range of organs, including the gastrointestinal tract, kidney, bone marrow, respiratory system and liver systems. However, the activities of the two enantiomers of Ibuprofen and ketoprofen are essentially indistinguishable *in vivo*, owing to a unidirectional metabolic bioconversion of the (R)-enantiomers to the (*S*)-enantiomers. The combination of the stereospecificity of action, together with the configurational inversion reaction provided drug companies a rationale for the use of the (*S*)-enantiomers of these drugs in therapy, as this reduces the total dose and reduces the toxicity that is associated with the (R)-enantiomer by removing the rate (and extent) of inversion as a source of variation in metabolism and pharmacological effects.

In the ketoprofen case, (S)-(+)-ketoprofen (dexketoprofen) is several times more potent than the racemate. The presentation of dexketoprofen as the tromethamine salt provides three advantages: effective analgesia at lower doses, rapid onset, and reduced gastric irritation and improved tolerability (due to the novel salt form)

Similarly, racemic ibuprofen undergoes rapid and substantial epimeric inversion (about 50-60%), so that the metabolic exposure is principally to (*S*)-ibuprofen (dexibuprofen), with little (*R*)-ibuprofen being present. The (*S*)-ibuprofen that is present is derived from both the 50% of the racemate that is in that form and chiral epimerization of the (R)-enantiomer. While Racemic ibuprofen and (*S*)-ibuprofen are often viewed as being bioequivalent', the use of (*S*)-ibuprofen gives faster onset of action and reduces variability in epimeric inversion as a source of variability in pharmacological response [43].

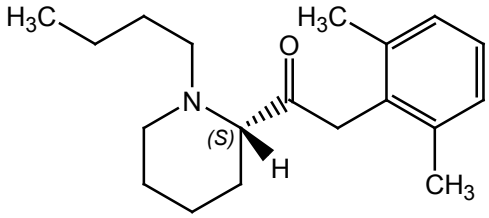
Ritalin



(2R,2'R)-(+)-threo-methylphenidate

The racemic threo-diastereoisomer of methylphenidate is marketed under the tradename Ritalin in the U.S. by Novartis Pharmaceuticals Corp and is widely prescribed, although with considerable controversy, for ADD (attention deficit disorder) and ADHD (attention deficit hyperactivity disorder) in children. Studies of the threo diastereomer have revealed that the preferred therapeutic activity resides in the d-threo (or 2R,2'R enantiomer) [45]. Furthermore, it has been observed that the beneficial effects of administration of the 2R,2'R-enantiomer alone, when measured by both objective and subjective tests, persisted for a significantly longer time than when the same patients were treated with the racemic mixture. More particularly, it has been found that the d-threo enantiomer is between five and thirty-eight times more active then the corresponding l-threo enantiomer. In addition, it has been shown that there are significant metabolic differences between the two enantiomers [46].

Bupivacaine

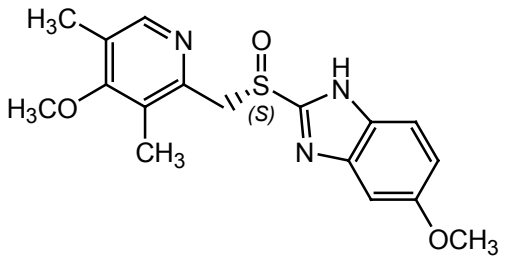


(S)-(-)-Bupivacaine

Racemic Bupivacaine currently is the most widely used long-acting local anaesthetic. Its uses include surgery and obstetrics; however, it has been associated with potentially fatal cardiotoxicity, particularly when given intravascularly by accident. (S)-(-)-Bupivacaine (Levobupivacaine), The S-enantiomer of bupivacaine, has recently been introduced by Purdue Pharma LP under the tradename Chirocaine® as a new long-acting local anaesthetic with a potentially reduced toxicity compared with bupivacaine. Numerous studies have compared levobupivacaine with bupivacaine and in most (but not all) studies there is evidence that levobupivacaine is less toxic [47].

Studies have also shown that, following i.v. administration, levobupivacaine produces significantly less effects on cardiovascular function than does racemic bupivacaine [48].

Omeprazole

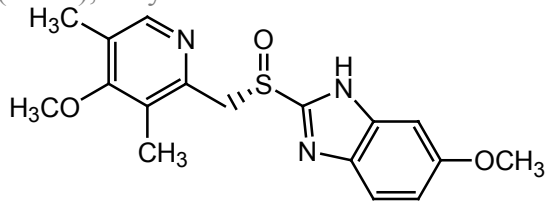


(*S*)-(–)-Omeprazole = Osomeprazole

Omeprazole presents one of the most interesting cases in drug development. "Racemic" Omeprazole is a very potent inhibitor of gastric acid secretion, with a long-lasting duration of action. In clinical studies, it proved superior to previous treatments for gastroesophageal reflux disease and peptic ulcers. Omeprazole is a gastric anti-secretory proton pump inhibitor [49] marketed under the tradenames Losec® and Prilosec® by AstraZeneca. Launched in 1988 by Astra AB (in 1999, Astra AB merged with Zeneca PLC to create AstraZeneca PLC), Omeprazole was a blockbuster commercial success and became the world's best-selling drug with sales of US $6.2 billion in 2000. The first patents on omeprazole expired in the European Union in 1999 and in the United States in 2001. Based partly on the fact that omeprazole exhibits polymorphic metabolism, i.e. a few individuals (3% among the Caucasian populations and 15-20% among Orientals) metabolize omeprazole slowly (slow metabolizers) compared to the rest of the population (rapid metabolizers), AstraZeneca developed the chiral switch drug esomeprazole (which is the (S)-(-)-enantiomer of omeprazole) based on the premise that therapeutic benefit would be achieved by less inter-individual variation, (slow versus rapid metabolizers), and that average higher plasma levels would provide higher dose efficiency in patients [50].

Esomeprazole was introduced as the magnesium trihydrate salt first in Europe (in 2000) and later in the US (in 2001) under the now famous trade name Nexium®. Healing of reflux oesophagitis with a 40 mg per day dose of esomeprazole magnesium occurred in ~78% of patients after four weeks of treatment and in 93% of patients after eight weeks, compared with 65% and 87% of patients, respectively, treated with 20 mg per day of omeprazole. The benefits of esomeprazole have been extensively studied [51].

From inception, Omeprazole has been described and claimed in its patents as 5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1H-benzimidazole. **But..."surprise"…**

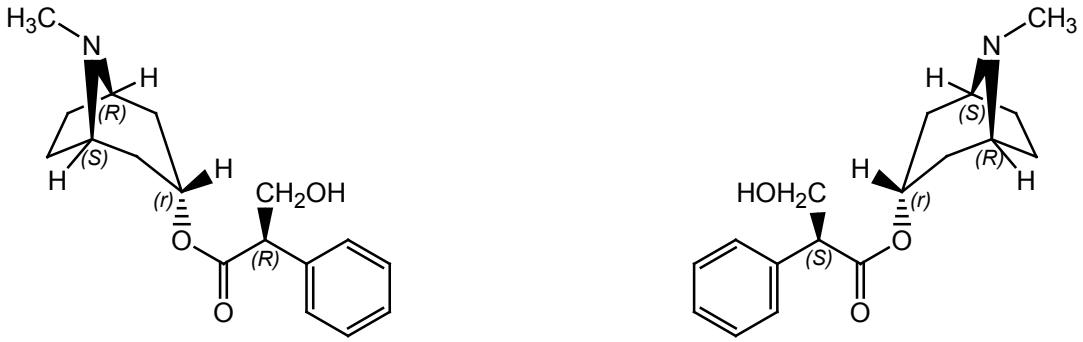


6-Omeprazole

Jenkins et. al. [52] have confirmed that the synthetic methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously thought, nor do all of the methods of the prior art yield consistent results. "In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions".

This discovery is being explored by aaiPharma Inc. which has the 6-methoxy isomer (6-Omeprazole) in pre-clinical studies [53].

Hyoscyamine



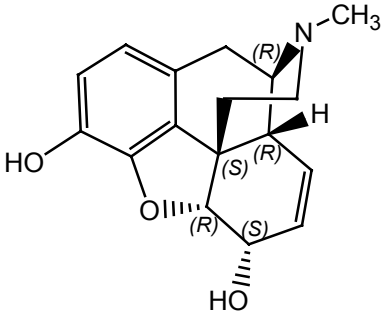
Atropine, the racemic form of hyoscyamine, was first isolated from *Atropa belladonna* in 1833. (-)-Hyoscyamine was also isolated in 1833 from *Hyoscyamus niger*. This tropane alkaloid is a muscarinic receptor antagonist. Muscarinic receptors are involved in vasodilation, moderating the heartbeat, and stimulating secretions.

Atropine is commonly used as an ophthalmic solution to dilate the pupils of the eye and as an antispasmodic for treatment of duodenal or stomach ulcers and intestinal problems. S-(-)-hyoscyamine is also used in medicine and it has historically been accepted that the affinity of muscarinic receptors for S-(-)-hyoscyamine is higher than that for the R-(+) enantiomer. In functional experiments on guinea-pig ileum, Barlow, et al. [54] found a 300 fold difference in affinities, whereas Ghelardini, et. al. [55] discovered a 50 fold difference in the rat atrium and on genetically engineered Chinese hamster ovary cells, the affinity of the M2 muscarinic receptors for S-(-)-hyoscyamine was 36 times higher than that for the R-(+) enantiomer. More recently it has been observed that

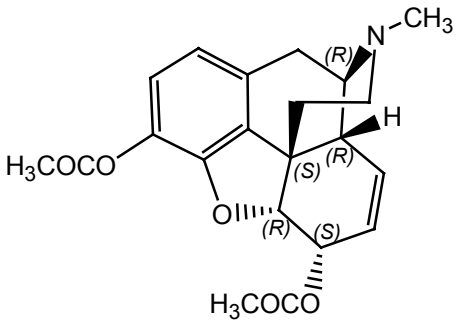
synthesis of cyclic AMP in cardiac ventricular membranes becomes enhanced in the presence of atropine or S-(-)-hyoscyamine, and that the effect of hyoscyamine is stereospecific (enantioselective). The potency of R-(+)-hyoscyamine was 30 fold lower than that of the S-(-) enantiomer, confirming that the action of hyoscyamine is stereospecific and receptor-mediated [56].

The role of chirality also plays an important role in the effect of psychoactive recreational drugs.

Opiates



(-)- Morphine

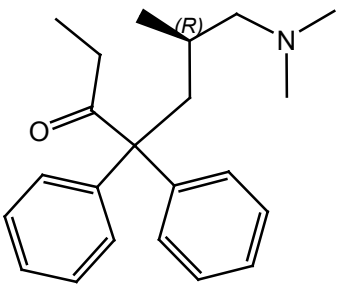


(-)-Heroin

3,6-Diactylmorphine

The opium poppy is cultivated in many countries such as Iran, Turkey, Canada, and Asia primarily for the pharmaceutical alkaloids morphine and codeine, as well as for the illicit production of heroin. Opium poppy alkaloids have been used to treat pain since antiquity. Both morphine and heroin have long been abused and are considered addictive drugs. The opiate receptors are stereospecific and pharmacological activity is dramatically dependent on absolute configuration. For example, unnatural (+)-morphine has extremely weak affinity for opiate receptors [57]. Metabolically, the formation of morphine glucuronides is enantio- and regioselective in rats and humans. In rat liver microsomes, natural (-)-morphine formed only the 3-O-glucuronide, whereas the unnatural (+)-morphine formed glucuronides at both the 3-OH and 6-OH positions, with the 6-O-glucuronide being the principal product. In human liver microsomes, both the 3-OH-and 6-OH positions were glucuronidated with each of the enantiomers, with the 3-O-glucuronide being the major product with (-)-morphine, and the 6-OH position being preferred with the (+)-enantiomer [58].

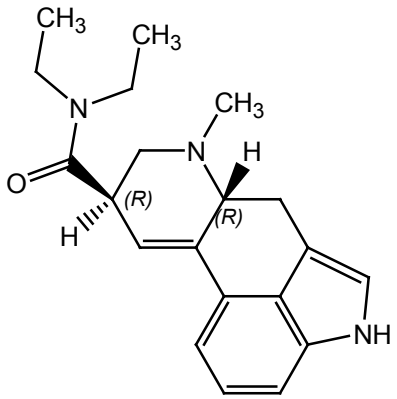
Methadone



(R)-(-)-Methadone

Methadone is a synthetic opioid developed during World War II by the german chemists Bockmuhl and Erhart working for the Hoechst Laboratories of IG Farben [59]. Methadone has been used to assist heroin users in withdrawal since the 1960's and is very effective in helping individuals addicted to heroin or other opiates stabilize their lives and reduce their illicit drug use [60]. Not surprisingly, the opioid agonist properties of racemic-methadone are ascribed almost entirely to only one enantiomer, (R)-(-)-Methadone [61].

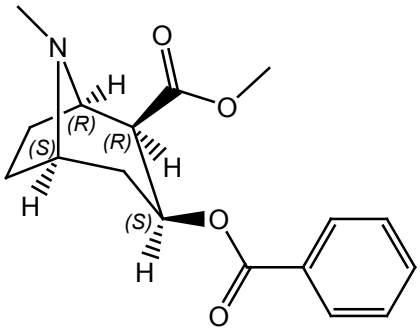
Lysergic acid diethyl amide



LSD

In the case of LSD (lysergic acid diethylamide), the (R,R)-(+)-LSD is >20X more phychoactive than its enantiomer [62]. The stereochemistry is critical for the lysergic acid molecule. The R stereochemistry at both the C(5) and C(8) positions are essential. Inversion of either stereocenter abolishes the hallucinogenic activity [63].

Cocaine

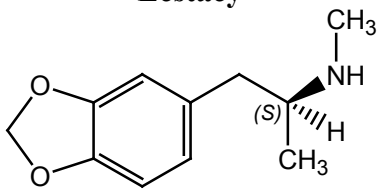


(1R,2R,3S,5S)-(-)-cocaine

Similarly, the naturally occurring (1R,2R,3S,5S)-(-)-cocaine is psychoactive whereas its enantiomer is inactive. Metabolically, the behaviorally inactive (+)-cocaine was found to hydrolyze at least 1,000

times faster in baboon plasma than (–)-cocaine. Positron emission tomography shows that (-)-cocaine is rapidly taken up in the striata of both the human and baboon brain. No brain uptake was seen for (+)-cocaine, although transport of cocaine into the brain was not expected to be stereoselective. The explanation for the lack of uptake was determined to be very rapid metabolism of (+)-cocaine in the blood. 30 seconds after administration of labeled (+)-cocaine, it was undetectable in plasma [64].

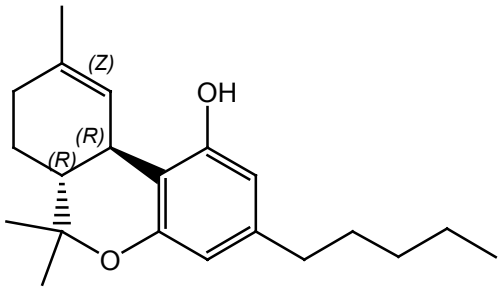
Ecstacy



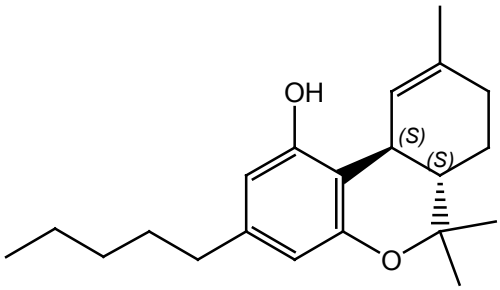
(S)-(+)-Ecstacy

The designer drug "Ecstacy", also known as MDMA is normally used as the racemate. However, (S)-(+)-MDMA appears to be far more active than the R-enantiomer and moderately more active than the racemate. , (S)-(+)-MDMA has a lower effective dose than the R-enantiomer and seems to produce most or all of the effects associated with racemic MDMA, including psychological effects and side effects. (R)-(-)-MDMA was found to have a much higher effective dose range, and did not produce an intoxication comparable to racemic MDMA even at high dosages. With the possible exception of altered perception of color, (S)-(+)-MDMA appeared to possess most of the effects of the racemate. Nevertheless, volunteers preferred the effects of the racemate to either (R)-(-)-MDMA or (S)-(+)-MDMA, and the investigators concluded that racemic MDMA produces effects that are not simply the sum of the effects produced by each enantiomer alone [62]. Studies in animals have indicated that the drug also undergoes stereoselective disposition, with the (+)-S-enantiomer having a shorter half-life than the (-)-R-enantiomer in the rat [65].

Cannabinoids



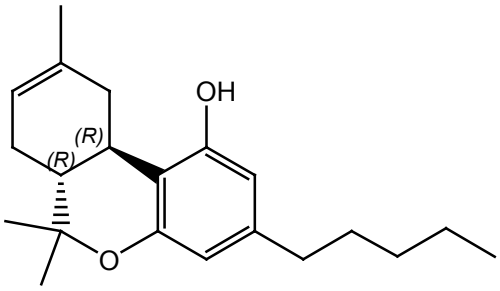
(3R,4R)-(-)- delta-1-THC



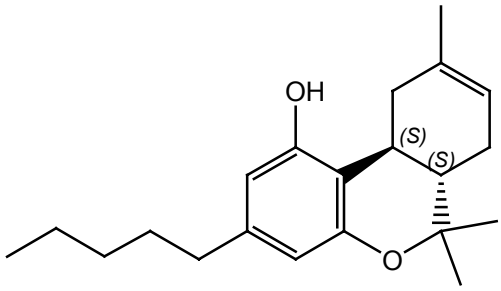
(3S,4S)-(+)- delta-1-THC

In the Cannabinoids, (3R,4R)-(-)-trans-delta-1-tetrahydrocannabinol, the major cannabinoid in *Cannabis sativa L.*, is more potent than the unnatural (3S,4S)-(+)-enantiomer in a variety of tests for

cannabimimetic activity. (-)-delta-1-THC was 13 to 230 times more active than the (+)-isomer [66]. These results indicate an enantiomeric pharmacologic bioactivity preference.

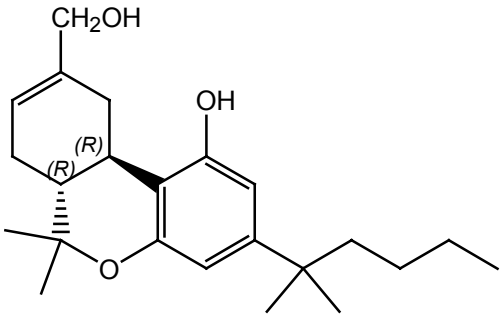


(3R,4R)-(-)- delta-6-THC

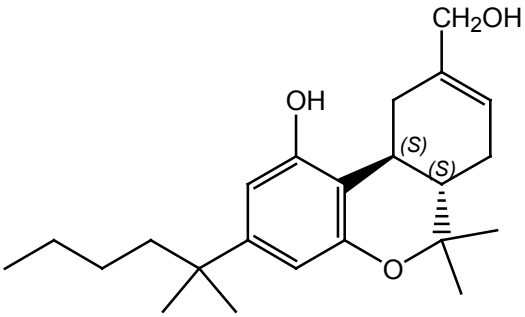


(3S,4S)-(+)- delta-6-THC

Similarly, 3R,4R)-(-)- delta-6-THC shows more cannabimimetic activity than (3S,4S)-(+)-delta-6-THC [66].



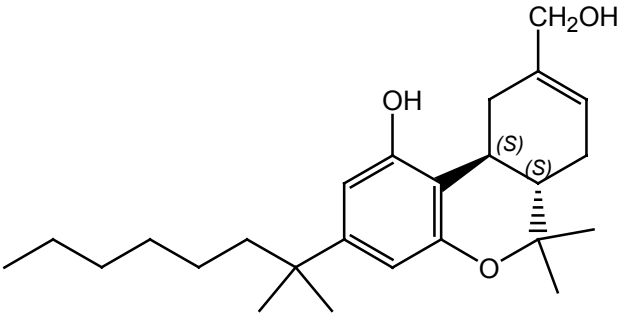
(3R,4R)-(-)- 7-hydroxy-delta-6-THC DMH



(3S,4S)-(+)- 7-hydroxy-delta-6-THC DMH

In the case of the synthetic Dimethyl-7-hydroxy-delta-6-THC (7-OH-delta-6-THC DMH) enanantiomers, the (3R,4R)-(-)- enantiomer is as much as 260 times more potent than natural (-)-delta-6-THC in cannabimimetic tests while the (3S,4S)-(+)- showed no cannabimimetic activity. However, while (3S,4S)-(+)- 7-hydroxy-delta-6-THC DMH does not cause cannabimimetic effects, it is a potent analgesic particularly in the presence of cupric ions. In all tests, it showed activity at (or above) the potency level of morphine [66,67].

Dexanabinol



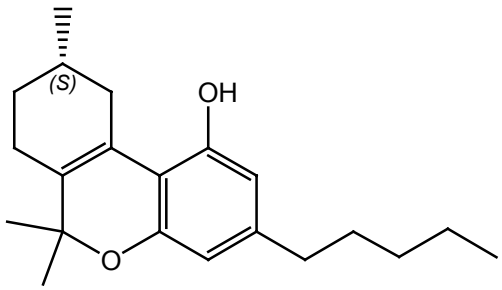
(3S,4S)-(+)-Dexanabinol

The synthetic analog of (3S,4S)-(+)- 7-hydroxy-delta-6-THC DMH, (3S,4S)-(+)- Dexanabinol, is in Phase 3 clinical trials in Europe for treatment of Traumatic Brain Injury (TBI) by Pharmos. In February 2003 the FDA completed its review of Pharmos' Investigational New Drug application allowing the Company to expand the study into the U.S. [68]**.** Pharmos is developing two families of proprietary synthetic cannabinoid compounds as therapeutics to treat neurological, cardiovascular, and autoimmune disorders. Dexanabinol and derivatives are also being studied for neurodegenerative disorders such as Parkinson's disease; and autoimmune disorders such as multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis.

The (3S,4S)-(+)- enantiomer of Dexanabinol, in contrast to the (3R,4R)-enantiomer, does not have affinity toward cannabinoid receptors and is devoid of cannabimimetic activity [69]. The (3R,4R)-(-)-enantiomer is a highly potent cannabimimetic compound (nearly 100 times more active than (3R,4R)-(-)- delta-1-THC, the major active component of hashish) [70].

It should be clear from the above examples that for THC compounds possessing the trans-configuration at the 3 & 4 positions that the (3R,4R)-enantiomers are cannabimimetic while the (3S,4S)-enantiomers are inactive or only weakly cannabimimetic.

delta-3-THC

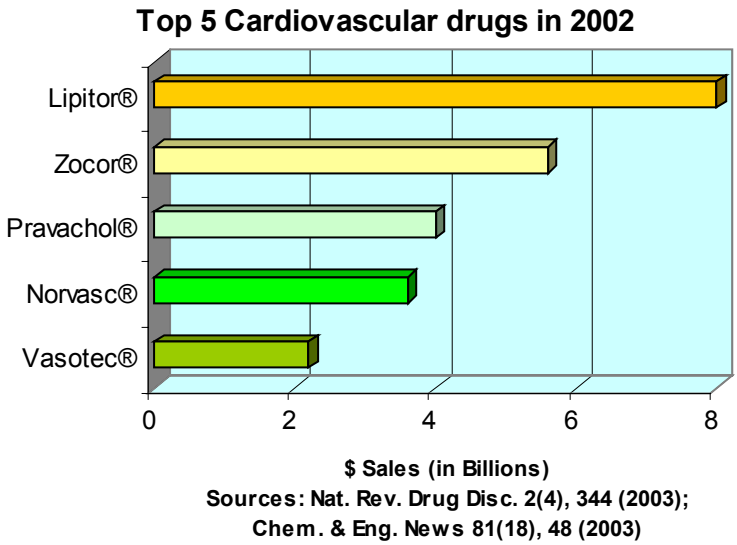


(1S)-(-)-delta-3-THC

In the case of (1S)-(-)-delta-3-tetrahydrocannabinol, cannabimimetic effects with the (1S)-enantiomer were noted at doses of 8 mg or higher. The (1R)- enantiomer was inactive. (1S)-delta-3-THC is estimated to have a potency from one-third to one-sixth that of delta-1-THC [66].

Other chiral Drugs

Nowhere is the importance of chirality more important than in the best selling cardiovascular drugs. Of the top five selling cardiovasculars, 4 are sold as single enantiomers (Lipitor®, Zocor®, Pravacol® and Vasotec®) while the 5th (Norvasc®) is a racemate which potentially may be important as the single (R)-(+)-enantiomer [71].



Summary: We have attempted to provide an insight into a number of chiral chemicals with important pharmacological activity in order to demonstrate that chirality often determines bioactivity. But this review is not all-inclusive. Among some other chiral drugs of interest are L-Dopa, Amoxycillin, Levofloxacin, Levobupivacaine, Escitalopram, Levocetirizine, Dexfenfluramine, Cisapride, Lansoprazole, Pantoprazole, Rabeprazole, Oxybutynin, Formoterol, Acetorphan, Flurbiprofen, Sotalol, Fluoxetine, Sibutramine, and Doxazosin (which have been reviewed elsewhere) [43,72].

Although the use of chiral drugs predates modern medicine, only since the 1980's has there been a significant increase in the development of chiral pharmaceutical drugs, primarily due to recognition that enantiomers often have different bioactivity and metabolic fates. A second and important commercial reason is that as patents on racemic drugs expire, pharmaceutical companies may have the opportunity to extend patent coverage though development of the chiral switch enantiomers with desired bioactivity.

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