# 1 Enantiomerically pure biologically active substances: a new frontier for pharmacology

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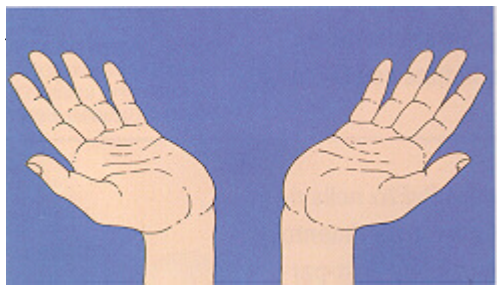
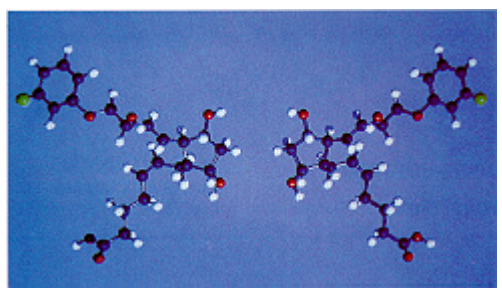
We tend to use the two-dimensional plane to render the natural world with its three dimensions. As a result, certain phenomena are made more difficult to understand. Chirality or asymmetry is one of these. The classic example, (and the simplest one) is our hands (which are endowed with chirality) - they differ, but in a special way: one is the mirror image of the other and they cannot be superimposed. This concept might become clearer if we consider the fact that we can do all kinds of things with our left hand but we can't turn it into a right hand, or vice versa! (see Figure 1).

**FIGURE 1** - *Hands. One is the mirror image of the other - they are not identical*
*(Source: W.B. Wood, J.H. Wilson, R.M. Benbow, L.E. Hood "Biochemistry: A Problem Approach", Benjamin/Cummings Publishing Co., Menlo Park, CA, 1981, modified)*



*Like hands, cloprostenol has two enantiomeric forms: D-cloprostenol and L-cloprostenol*



The vast majority of molecules are chiral - i.e. they are like hands in that they have two possible structures (known as enantiomers, enantiomeric forms or optic enantiomers). Every synthesis of an asymmetric molecule carried out using non-chiral substances as starting material or reagents will produce a 1:1 mixture of enantiomers (racemate, or racemic mixture).

These mixtures have physical and chemical properties which are identical in all respects except with regard to:

**A** *their capacity to interact with polarized light;*

**B** *their capacity to interact with other enantiomers - i.e. with one of the two possible forms of other chiral substances.*

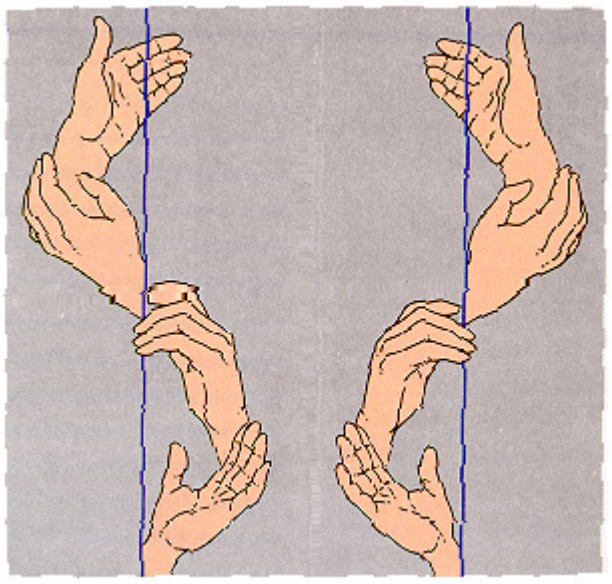
Interaction between an enantiomeric form and polarized light permits determination of the optic rotatory power of the enantiomer in question (expressed by means of a numerical value and a plus or minus sign for dextro- or laevorotatory enantiomers, respectively).

One enantiomer of a given substance, when examined under the same conditions as its counterpart, will show the same numerical value as that counterpart. A plus sign will be used instead of a minus, or vice versa. This indicates differences in reactions with polar light (same numerical value, and positive or negative value). The great scientist, Louis Pasteur, discovered that optic activity is a result of molecular asymmetry. He was also the first scientists to break a racemate down into its enantiomers.

The two enantiomers will differ among themselves terms of their capacity to interact with other asymmetric structures, in much the same way as we find with hands and with "handedness": it is easier to shake a right hand with a right hand than it is with a left hand. This is a highly significant point of departure - one which continues to arouse great interest in the field of the study of the biological activity of "enantiomerically pure" substances. It has constituted the occasion for renewed efforts in the search for valid processes of synthesis for the production of "enantiomerically pure" substances at reasonable prices (1, 2).

With regard to the various naturally occurring processes of synthesis, it is known that enzymes are capable of total control of the enantiomeric purity of the biomolecules they produce. Enzymes can exert such control because they are made up of a series of chiral proteinogenic amino acids which have a single enantiomeric form (see Figure 2).

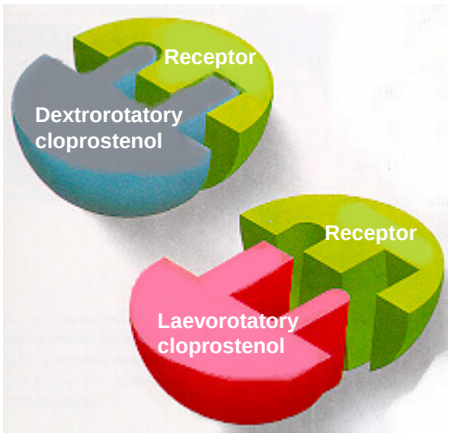
**FIGURE 2** - *Hands as asymmetric objects forming asymmetric spirals. Superimposing these dextrorotatory and laevorotatory spirals is not possible.*
*(Source: W.B. Wood, J.H. Wilson, R.M. Benbow, L.E. Hood "Biochemistry: A Problem Approach", Benjamin/Cummings Publishing Co., Menlo Park, CA, 1981, modified)*



The resultant enzyme is itself a single enantiomeric form and therefore serves as an asymmetric "mould". It is therefore capable of catalysing the substrate through a mechanism of discrimination whereby it can asymmetrically transform the substrate, or, in other words, synthesize only (or at least mainly) one of the enantiomers of the product in question, should this product display asymmetry.

The interactions of an enzyme with the two enantiomers of a substrate molecule must be **different** from each other - in other words, the activity of biologically active asymmetric molecules must often be ascribed to just one of the two enantiomeric forms (i.e. the eutomer). This also means that the other form (i.e. the dystomer), if present, will either be inactive (a "wallflower", so to speak, a "medicinal pollutant" or "isomeric ballast"), or adversely active (3) (Figure 3).

**FIGURE 3** - *Only the dextrorotatory enantiomer of cloprostenol is capable of binding with the ovarian and uterine prostaglandin receptors*



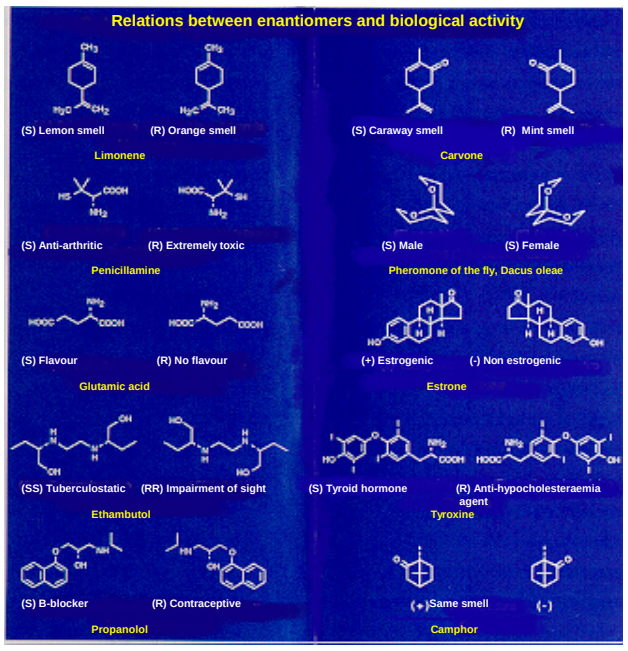

In some cases, the undesired enantiomer may disturb other biological processes with disastrous consequences.

It practically goes without saying that the metabolism of the two enantiomers is characterised by a specific kinetics for each. In most cases, the progress of a racemate within living organisms will lead to modification of the original enantiomeric 1:1 relation.

On the basis of considerations such as the above, Professor Ariens (Nijmegen, Holland) has harshly rebuked the clinical and pharmacological community for not carrying out measurement of the varying relations between enantiomers in organic liquids on a routine basis. He has also criticised many publications on the pharmacodynamics and pharmacokinetics of racemic mixtures. He referred to them as “sophisticated nonsense” (4).

There are many evident cases of activities which differ on the basis of enantiomer status. This point is very clearly illustrated in Table 1, containing some of the most significant and well known differences of this kind.

**TABLE 1**




One of the enantiomers of limonene, S-limonene, smells like lemon, yet the R-enantiomer has an orangey smell. S-carvone smells like caraway seeds and the R-enantiomer like spearmint. These differences are obviously significant

as far as the production of perfumes and aromas is concerned. Another significant example is saccharose, the enantiomers of which are equally sweet. However, only the D-enantiomer is metabolized (which means that the L-enantiomer has potential as a diet sweetening agent).

S-Penicillamine is endowed with anti-arthritic properties, yet the other enantiomer is highly toxic. To avoid R-enantiomer toxicity, the anti-arthritic Penicillamine to be administered as part of the treatment of arthritis must of course be enantiomerically pure (1, 5).

The study of the biological activity of pheromones for the induction of specific social bevhaviour patterns among insects has opened up new vistas in our knowledge of the mechanisms governing the relations between molecular structures and receptors.

The discovery that the R-enantiomer of the pheromone of the fly, *Dacus oleae*, is a sexual lure for males and that the S-enantiomer acts in the same way on females provides indications as to the relation between chirality and the behavioural responses of the society of insects. This discovery has, in turn, led to the production of much valid information over the last decade, during which there has been close collaboration between chemists and entomologists (6).

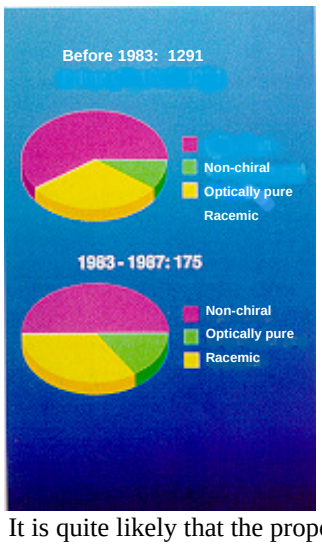
For reasons of space, we cannot go into the other instances provided in Table 1, but it must be pointed out that the teratogenic effects of thalidomide are to be ascribed to an enantiomer while the counterpart enantiomer is an anti-nausea agent. The tragic consequences of the use of thalidomide might have been avoided (at least in theory) had it been laid down, by 1963, that separate tests should be carried out on both enantiomers in the pure state (1); we now know, on the basis of the most recent evidence, that enantiomerically pure thalidomide, in physiological conditions, undergoes racemization, thus generating the undesired enantiomer. On the basis of the brief notes above, it should come as no surprise to readers that the development of enantiomerically pure drugs is one of the great challenges for the pharmaceutical industry today (1, 2, 7, 8); nor should it surprise that the FDA (Food and Drug Administration) has brought about a virtual revolution in the field of the regulatory affairs of the pharmaceutical industry by allowing racemate (mixed enantiomer) drugs to be produced only on condition that it is shown that these mixtures be demonstrably "safe and effective".

These criteria will be applied to each enantiomer (a.k.a. racemic substance, or racemate) prior to marketing. This means that, in many cases, enantiomerically pure substances will be required instead of the racemates marketed at present (7, 9).

It is believed that racemic drugs will be reviewed in Europe along the lines of the procedures already adopted in the USA.

It is indicative that Ariens and Wuis (10), by using the "Pharmazeutische Wirkstoffe" database, should discover that, in 1987, 40% of 1200 synthetic agents contained at least one asymmetric centre but that only 58 were marketed as single enantiomers. Adopting the same criteria, Kooreman (11) examined the NCE's (new chemical entities) launched between 1983 and 1987. In Figure 4, we may note that the proportion of synthetic agents marketed in enantiomerically pure form is increasing and that non-chiral agents are decreasing.

**FIGURE 4** - *Presence within market of new synthetic drugs*

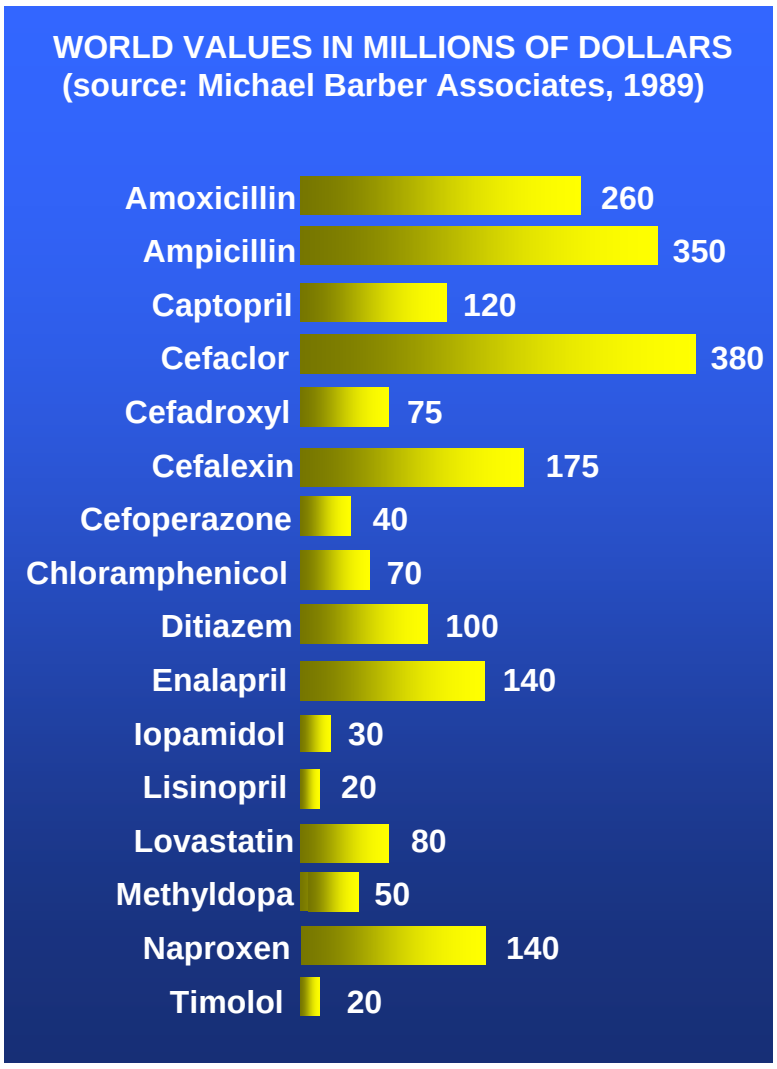



It is quite likely that the proportion of racemates will go down in the future.

See Table 2 for the results of an enquiry carried out by Michael Barber Associates into the market for the main drugs commercially distributed in enantiomerically pure form in 1989 (9). Enantioselectivity with regard to the biological activities exerted by substances does not relate to drugs alone. The agrochemicals sector is also about to undergo a similar process of regulatory revision. It is well known, for example, that the herbicidal activity of phenoxy-propionic acid herbicides is practically entirely ascribed to the R-enantiomer and that there is growing pressure that, in order to significantly reduce the environmental impact of such products, compounds of this kind should only be marketed in enantiomerically pure form.

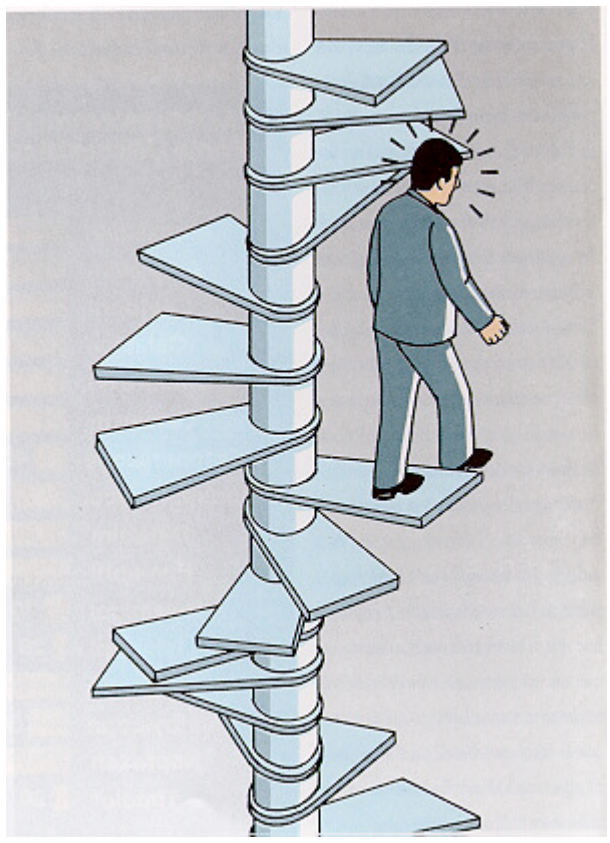
In drug design and manufacturing, as well as in the agrochemicals sector, chirality will undoubtedly play a bigger role in the future. Chirality will also significantly change attitudes towards research, especially among those who are willing to take up a challenge such as this. It is not enough to be “quick off the mark”. Expertise and competence are also required.

**TABLE 2** - *Main medicinal products sold in chiral form*




By way of conclusion, please observe the following illustration (Figure 5). Here, we see what happens when we effect chiral changes. The stairway has its own way of rotating around the pole. In this illustration, a reversal takes place at a given point. When enantiomeric turnabout takes place in this way, the "man on the spiral staircase" is at a loss. That is what happens when a molecule, an enantiomeric form, has dealings with an enzyme system which, at a certain stage, undergoes a change of the kind described here (loss of chiral characterization, or a chiral turnabout).

**FIGURE 5** - *A spiral staircase with chiral change ... and what comes out of it...*
*(Source: L. E. Orgel "The Origins of Life: Molecules and Natural Selection", John Wiley & Sons, New York, 1973 modified)*



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