Enantiopure Drugs - Inspiration from Nature's Innate Chirality or a Futile Mimicry

Aeysha Sultan,[1*] Hira Sultan,[2] Roberto Acevedo[3]

[1]Department of Chemistry, Division of Science & Technology,University of Education, Lahore, Pakistan
[2]EMMG, Physics division, PINSTECH, Nilore, Islamabad, Pakistan
[3]Facultad de Ingeniería y Tecnología, Universidad San, Sebastián, Bellavista 7, 420524 Santiago, Chile
E-mail of Corresponding Author: Blackhawk.aries@gmail.com

Like a pair of human hands, certain organic molecules have mirror-image versions of themselves, a chemical property known as chirality. These so-called "handed" molecules (aka chiral molecules) are essential in biological/physiological and biochemical processes occurring in all living organisms. We smell, taste because of these chiral molecules, the enzymatic actions, binding of various macromolecules and signaling molecules all involve chiral molecules.

Every living thing on Earth uses one, and only one handedness of many types of chiral molecules. This trait, called homochirality, is critical for life and has important implications for many biological structures, including DNA's double helix. Scientists do not yet understand how biology came to rely on one handedness and not the other. The reason why biochemical reactions are highly specific in nature relies on this homochirality.

Selectivity and specificity have always remained of significant importance in not only chemical reactions but also in designing drugs are either selective or specific in their target receptor. For the same reason, chiral drugs are making headlines these days; pharmaceutical industries are providing convincing evidences for marketing of enantiopure drugs. In the early days of the pharmaceutical industry most drugs came from natural sources and hence single enantiomer drugs predominated. As the proportion of synthetic drugs increased, the proportion of achiral and racemic drugs increased.[1] Many of the pure enantiomers sold today are derived from plants or micro-organisms. Only about 10 per cent of the synthetic drugs are sold as chiral molecules while the rest are marketed as mixtures of both enantiomers called 'racemates.[2] It has been well documented that racemic mixtures of pharmaceutical formulations have the potential of severe harmful health effects. That makes it obvious that chirality does have tremendous impact on our health and in the medical industry. But it is important to know why is chirality of that much importance. To answer this question let's start with very basics of chirality.

In simplest terms, an irregularly shaped (asymmetric) object whether macro or microscopic is called a Chiral object when it is non-superimposable on its ***mirror image***. This property of non-super-imposeability of chiral object and its mirror image is called chirality. It is important to note that the "mirror image" being referred to may be just a **theoretical molecule** generated on paper or in using a model. Or the mirror image may actually exist. A chiral molecule with an actual corresponding mirror image, together are referred to as ***enantiomers*** or ***stereoisomers***.

The most unique feature of the chiral objects is that these are identical in each and every aspect and differ only in the sign of optical rotation and their reactivity in chiral envoirnment. In achiral envoirnment, these objects behave as one and the same!

Now when talking about drug design, we mean that we have to administer chemical compounds (synthetic, semisynthetic or derived from nature) in a living system for treating a certain unhealthy condition. It here becomes necessary to point out that the living systems are made up of macromolecules which are highly complex chiral entities. There are chiral proteins interacting with chiral enzymes that produce a desired specific response/ physiological function.[3] It is also crucial to mention here that these macromolecules are high molecular weight highly flexible, highly functionalized molecules with large number of chiral centers. The percentage distribution of the number of chiral centers has been found out to be 6.2 for natural products, 2.3 for drugs and 0.4 for combinatorial molecules. Since natural products are synthesized by enzymes the introduction of a chiral center appears to be effortless, whereas it requires special attention to synthesize chiral compounds in the laboratory.[4]

The chiral drugs being marketed these days contain fewer number of chiral centers than those present in the macromolecules (molecular receptors) with which a drug is supposed to bind. Furthermore, these drugs are rather flat molecules with a number of heteroatoms like nitrogen, sulfur, chlorine, oxygen whereas the macromolecular receptor are rich is oxygen and have a large number of hydrogen bond donors.[5]

A further critical review on the nature of receptor molecules responsible for various biochemical reactions indicates that these molecules are highly flexible molecules with large number of chiral centers which permits them to attain a number of conformations while the signaling molecules (e.g., O_2, CO_2, CO, NO or metal ions etc) that are to bind with receptors tend to be more simpler, flat or linear molecules. Each of the many chiral centers in naturally occurring molecules is associated with a specific configuration. This means that the natural product is only one out of many possible stereoisomer. The configuration of each chiral center has first to be determined, and then a synthesis has to be devised to put each chiral center in place with its correct stereochemistry. When we look at a comparatively simple natural product – for example, oestrone (female hormone) – we can see there are four different chiral centers in the molecule. This means that in theory there are 24 or 16 different stereoisomers, comprising eight pairs of enantiomers. However, only one of theses has hormonal activity. [6] If an active ingredient is chirally correct - meaning it has the right optical activity so as to be recognized and "fit" the chemistry of the human body, it will do the job nature designed it to do.[7]

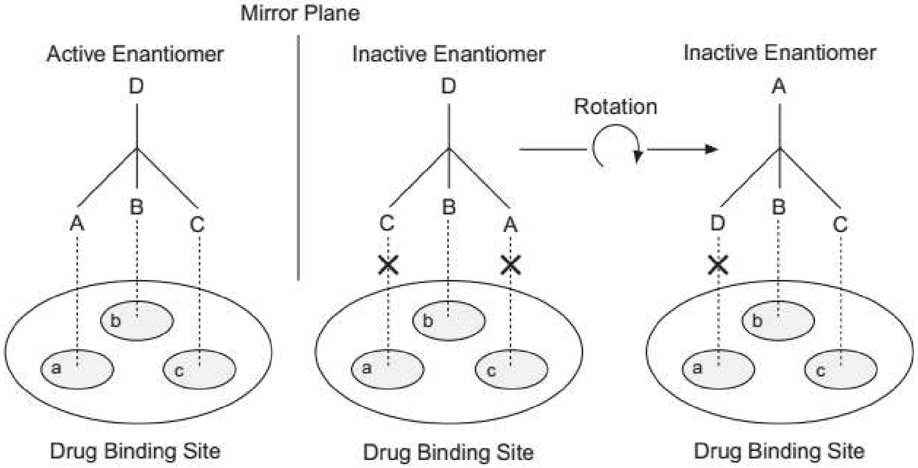

Figure 1: the hypothetical interaction between the two enantiomers of a chiral drug and its binding site. The active enantiomer has a 3D structure that allows drug domain A to interact with binding site domain a, B to interact with b and C to interact with c. In contrast, the inactive enantiomer can't be aligned to bind the same three sites simultaneously. The difference in 3D structure allows the active enantiomer to bind and have a biological effect, whereas the inactive enantiomer cannot.

If we compare these facts with the structural aspects of drugs being synthesized today, we will clearly see that the trends in drug design focus on synthesizing compounds with aromatic system (which makes a system somewhat rigid), include a number of heteroatoms that is supposed to increase the chances of interaction of the drug with a receptor molecule and also the synthesized compounds are often associated with the presence of one or more chiral centers. It is here that the things tend to become more complicated! Since the presence of chiral centers make its quite difficult for the compound/drug to be chirally correct; may be some of the stereogenic centers have the correct configuration to match with the receptor and others may not be compatible. The body with its numerous homochiral compounds being amazingly chiral selector, will interact with each enantiomer of the drug differently and metabolize them by a separate pathway to generate different pharmacological activity. Thus, one isomer may produce the desired therapeutic activities, while the other may be inactive or, in worst cases, produce undesired or toxic effects.[8-13]

Synthesizing a flexible drug with 100% chirally correct drug is far from possible if not possible. The result being that apparent chiral drugs have intense side effects. These drugs are not capable of interacting with the receptor molecules and may reduce a symptom for time being but there are some other interactions that lead to undesired side effects.

A very simple but important example of chiral incorrectness is that of L-glucose. One possible cause of high sugar level in diabetic patients. Our brains need and can only metabolize the right-handed (D) form of sugar (D-glucose). Sugar's enantiomer (L-glucose), though sweet tasting, cannot be metabolized by the body. Manufacturers of artificial sweeteners have taken advantage of this principle by producing left-handed (L) enantiomers of sugar that will taste sweet, but cannot be metabolized and absorbed. Meaning – same great flavor with zero calories, no energy and high glucose in blood and urine (since L-glucose is not metabolized). It’s important to relate here that people who take brown sugar don’t suffer from diabetes while those who take white sugar suffer from diabetes and diseases associated with it including mental fatigue.

The presence of chiral centers in the natural products provides for higher affinity and target specificity and clearly differentiates them from non-natural compounds. The presence of large numbers of chiral centers in natural products compared with de novo man-made synthetic compounds is the biggest and most important difference between the two groups of compounds. Since the biological targets for these drugs are chiral, ligands with correctly constructed chiral centers should provide increased target engagement. Attempts have been made to carry out diversity oriented synthesis (DOS) to synthesize compounds with more chiral centers, thus making them more like natural products. Despite these efforts, natural products still provide most structural and chiral complexity.

It is clear from these analyses that natural products cover much wider and larger chemical space not covered by combinatorial and synthetic compounds. Natural products contain large numbers of chiral centers, ring fusions and a higher density of functional groups allowing for higher ligand affinity and better specificity to biological targets that is generally not achieved by architecturally flat synthetic drugs. Natural products tend to have properties such as unexpected cell penetration, absorption or solubility that are generally not well understood. This may be due to their co-evolution with the proteins in the cells, which are densely populated with biological materials.