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Short Communication

Asymmetry Synthesis: Powerful Tool for The Pharmaceutical Industry

Gabrielle Pedroso da Silva[1], Leonardo Pizol Ferreira[1], Gustavo Elias Arten Isaac[2] and Renan Marcel Bonilha Dezena[3,4]*

[1]University Center of the Octávio Bastos Teaching Foundation (UNIFEOB), Department of Pharmaceutical Science, Brazil

[2]University Center of the Octávio Bastos Teaching Foundation (UNIFEOB), Faculty of Pharmacy, Professor, Brazil

[3]University Center of the Octávio Bastos Teaching Foundation (UNIFEOB), Faculty of Pharmacy, Expert Collaborator, Brazil

[4]Preformulation Specialist in The Pharmaceutical Industry, Brazil

***Corresponding Author:** Renan Marcel Bonilha Dezena, University Center of the Octávio Bastos Teaching Foundation (UNIFEOB), Faculty of Pharmacy, Expert Collaborator and Preformulation Specialist in The Pharmaceutical Industry, Brazil.

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Background

The understanding of how a chemical substance, used as a drug, exerts its activity within the body, it must be taken into account that the three-dimensional structure of this drug has fundamental importance in the biological receptor, because the format of a drug molecule must be complementary to its receptor site, just as a key is complementary to the lock, so that, through chemical bonds, they bind properly and generate the expected biological response [1,2].

Many of the drugs available on the market are molecules that exhibit optical isomerism, that is, a molecule that cannot be superimposed on its mirror image is called a chiral, and each of these images is called an enantiomer, that is, isomers that are mirror images of each other [3].

As the drug must fit perfectly to its receptor site to cause its effect, the orientation of the molecule is extremely important for this fit to occur correctly, given that the most active enantiomer in one site may not be the most active in another, or induce a biological response opposite to or less than expected [4]. This happens because the enzymes are chiral in nature, resulting in high stereoselectivity, therefore the enantiomer of a drug is often more susceptible than another to metabolizing enzymes and this also happens with drug transporters, which even changes the duration of action of the drug in the body [4].

Although it is known that only one of the enantiomers has the expected biological activity, it is very common for organic drugs synthesized in the laboratory to be commercialized in the form of a racemic mixture, that is, a mixture of enantiomers in equal proportions in some cases, the result of the commercialization of these racemic mixtures is the fact that the patient receives doses of drugs that are 50% less active, inactive or actively toxic [5].

The toxicity of one of the molecules can be so high that the synthesis of only one of the enantiomers is paramount. As an example, one can mention Thalidomide, a drug developed in 1954 and initially used as a sedative and to treat nausea in pregnant women. However, since its commercialization in 1957, there have been many cases of fetal malformation and these cases led to the study of this drug, discovering its teratogenic effects. Research has highlighted the importance of optical isomers, formed from the presence of a chiral carbon, of which one isomer, (R)-Thalidomide has a sedative effect and the other, (S)-Thalidomide has a teratogenic effect [6].

Asymmetric synthesis

The organic synthesis of molecules that have an asymmetric center can be classified as racemic or asymmetric: the racemic synthesis produces a mixture of the two possible enantiomers in equal amounts; while the asymmetric synthesis has a product

of high optical purity, that is, if it is contaminated with the other stereoisomer it will be in proportions below 5%. Currently, drugs marketed as a racemic mixture must have one of the enantiomers inactive, that is, not present biological activity, which does not eliminate the problem of racemic syntheses. From a pharmaceutical point of view, the patient is ingesting a chemical substance that is unnecessary for the body, and therefore, the dose to be administered has to be higher, since that only 50% of the drug administered has the expected biological effect.

Thus, drugs produced from asymmetric synthesis have many advantages: lower doses, more active products and less undesirable effects due to the non-administration of an unnecessary chemical substance (Table 1).

Drug	Enantinomers	
Etodolac	R-enantiomer (Wnt signaling) [7]	S-enantiomer (Cox-2 inhibition) [7]
Ibuprofen	R-enantiomer (gastrointestinal injuries) [8]	S-enantiomer (anti-inflammatory action) [8]
Amlodipine	R-enantiomer [9]	S-enantiomer (Improved affinity with the receptor site - 1000 x) [9]
Naproxen	R-enantiomer (hepatotoxicity) [10]	S-enantiomer (higher Cox inhibition) [10]
Ketoprofen	R-enantiomer (gastrointestinal injuries) [11]	S-enantiomer (Improved anti-inflammatory action - 160 x) [11]
Atenolol	R-enantiomer (inactive or toxic) [12]	S-enantiomer(affinity with β-receptors) [12]
Metoprolol	R-enantiomer (inactive or toxic) [12]	S-enantiomer (affinity with β-receptors) [12]
Propranolol	R-enantiomer (inactive or toxic) [12]	S-enantiomer (affinity with β-receptors) [12]
Warfarin	R-enantiomer [13]	S-enantiomer (greater anticoagulant effect) [13]
Ketamine	R-enantiomer [14]	S-enantiomer (greater anesthetic effect) [14]

Table 1: Pharmacological activities of chiral drugs.

Summary

There are many drugs that are marketed optically pure by asymmetry synthesis, such as Naproxen, Escitalopram and Levosalbutamol [3]. The organic synthesis process allows the production of drugs on an industrial scale, which represented a great advance in chemistry and directly impacted the improvement of human health.

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