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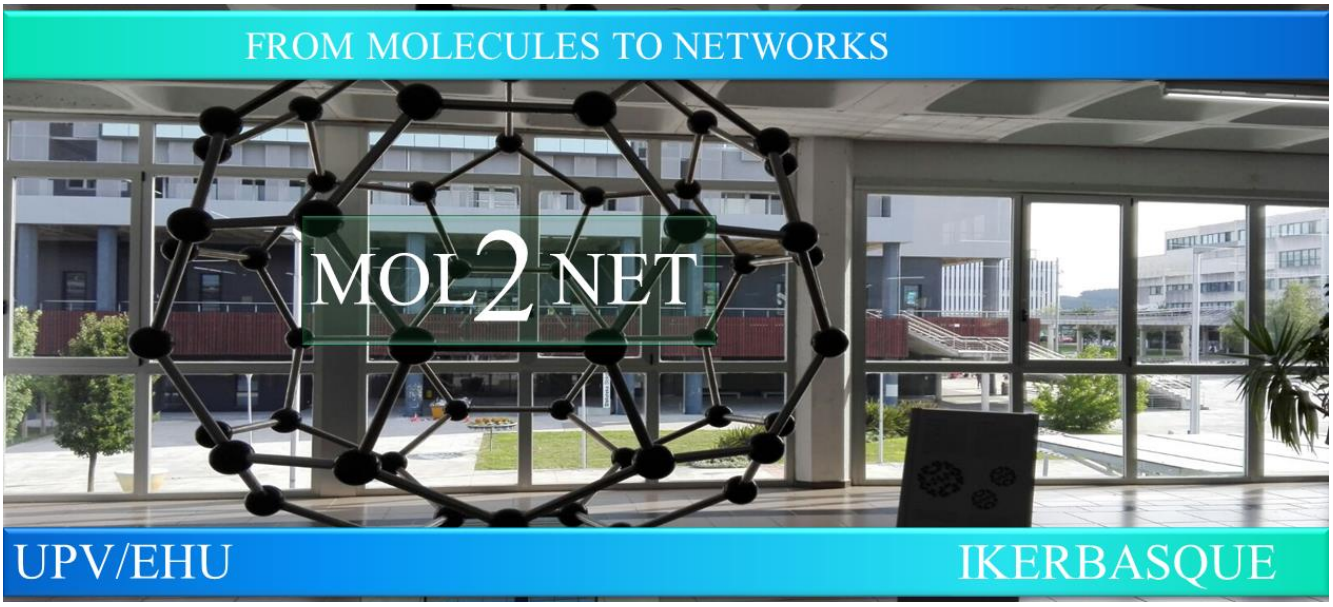

Anti-HIV Isomers Drugs: Critical Review

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Graphical Abstract	Abstract. *HIV-human immunodeficiency virus is an infection caused by a virus that causes the progressive destruction of some white blood cells present in the blood, causing AIDS-acquired immunodeficiency syndrome. Calanolide A is a drug indicated for people with the AIDS-AIDS acquired immunodeficiency syndrome, in which it enables the inhibition of the HIV-protase of the virus in order to prevent the initial development of the virus until its maturation.*

Calanolide B is a compound present in C. cerasiferum, used as other agents in the therapy of the human immunodeficiency virus (HIV). In this study, the main objective was the study of spatial dispositions and their effects and activities based on the position in which Calanolides A and B are presented in the context of stereochemistry.

Introduction

The human immunodeficiency virus (HIV) is an infection caused by a virus that causes the progressive destruction of some white blood cells present in the blood, causing AIDS - acquired immunodeficiency syndrome, it is the last stage of HIV infection, this retrovirus belongs to the family Retroviridae and subfamily Lentivirinae [1].

According to the World Health Organization (WHO) and the Joint United Nations Program on HIV/AIDS (UNAIDS) in 2021, there were 38.4 million [33.9 million – 43.8 million] people in the world living with HIV in 2021 and 650,000 [510,000 – 860,000] people died from AIDS-related illnesses in 2021[2].

The stereochemistry of drugs is extremely important to be studied, especially in relation to therapeutic importance. Its studies can be carried out through its spatial arrangement, as the presence of two enantiomers allows a drug to antagonize the action of its stereoisomer. the two enantiomers the same performance in terms of activity. Based on the data presented above, it is possible to affirm that the stereoisomers enable different therapeutic effects of different profiles [3].

Conceptually, isomers are classified as two or more compounds that have the same molecular formula, but are structurally different [4]. In this study, Calanolide A and Calanolide B, two optical isomeric compounds and their pharmacological stereochemistry, were addressed, aiming at the study of their spatial dispositions and their effects and activities based on the position in which they are presented in the stereochemistry context.

Critical Review

The first article discusses Calanolide A, a drug indicated for people with the AIDS-AIDS acquired immunodeficiency syndrome, in which it enables the inhibition of the HIV-protase of the virus in order to prevent the initial development of the virus until its maturation. Calanolide A is an isomeric drug that has antiviral properties characteristically and is an inhibitor of several proteins that make it possible to hinder the reproduction of the virus. Regarding the structure of saquinavir, according to studies previously carried out by several researchers, it is considered an active optical isomer compound [5]. The chemical structure of Calanolide A is shown in Figure 1.

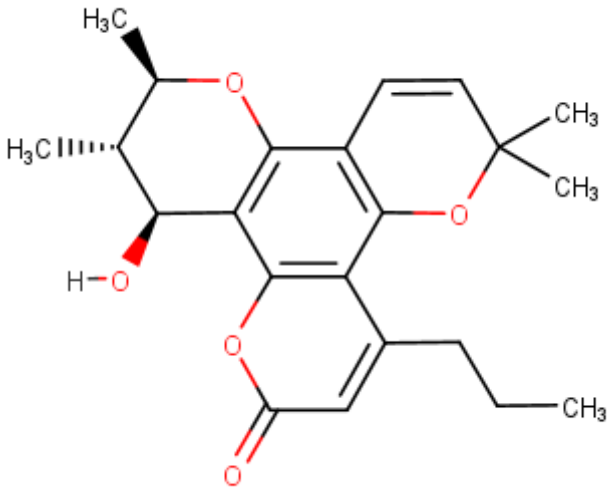

Figure 1. 2D Structure of Calanolide A

Calanolide A is classified as an organic heterotetracyclic compound, presented with the structure 11,12-dihydro-2H,6H,10H-dipyrano[2,3-f:2',3'-h]chromen-2-one substituted , in which there is substitution by a hydroxyl group at position 12, in addition to methyl groups at position 6, 6, 10 and 11 and a propyl group and space isomerism at position 4, (10R,11S,12S) also called stereoisomer. This compound is isolated from a natural product of the species *Calophyllum lanigerum* var. and has great potential against the transcriptase enzymes present in HIV-causing retroviruses [5].

Molecularly, calanolides A and B are considered 4-substituted tetracyclic dipyranocoumarins, and their C ring contains a *gem*-dimethyl group. Chemically, calanolide A is a heterotetracyclic organic compound, a delta-lactone, a cyclic ether and a secondary alcohol [6]. This compound presents hydrogen bonds that have great relevance in biological studies, these non-covalent interactions have as main function the conformations of noble macromolecules, such interactions are composed of oxygen, nitrogen, hydrogen of O-H, N-H bonds, classified as electronegative heteroatoms. The hydrogen bonds with amino acid residues of the active site allow the recognition of the enzymatic inhibitor in certain studies directly or through the water molecule [7].

The stereochemistry of Calanolide A consists of the *trans* configurations (10R, 11S, 12S), the anti-HIV activities, are mainly present in the chiral centers C-10, C-11 and C-12, these three one chiral carbons has four different ligands in the structure of this compound under study. In studies carried out by several authors, it was shown that, of the diastereoisomers, compounds containing 10,11-*trans*-methylation and 12-(S)-OH chirality showed excellent efficacy against HIV, on the other hand, other compounds of this class showed no activity for this pathology [8]. Another observation to be made is that the functionality of methyl on carbon 11 in calanolide A is not a fundamental structural characteristic for effective activity for this pathology, requiring further study of this chiral carbon, through synthetic studies of this compound.

Based on this analysis, it is possible to conclude that the stereochemistry of Calanolide A, related to the chiral carbons C-10 and C-11, are structurally essential for the potentiality of the activity against HIV, simultaneously the S configurations at the chiral carbon 12, as well as the presence of the

heteroatom in the chemical structure of the compound, such as oxygen (O) at C-12, are fundamental support for effects against the virus that causes HIV.

The second article addressed Calanolide B, a compound present in *C. cerasiferum*, used as other agents in the therapy of the human immunodeficiency virus (HIV). This compound is considered a potent inhibitor of reverse transcriptase [9]. Regarding the structure of Calanolide B, according to studies previously carried out by several researchers, it is considered an active optical isomer compound. The chemical structure of Calanolide B is shown in Figure 2.

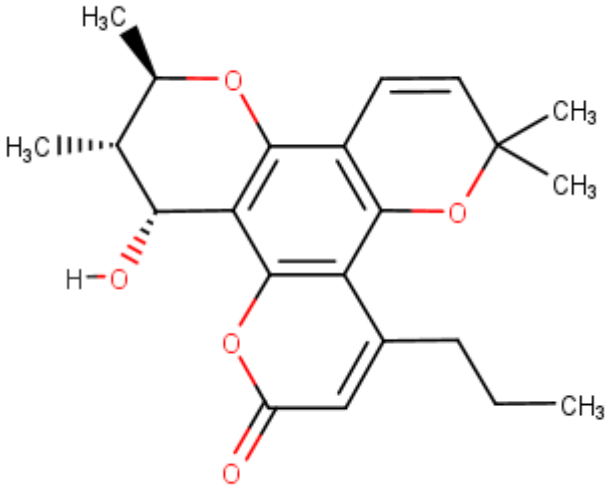

Figure 2. 2D Structure of Calanolide B

Molecularly Calanolide B is similar to Calanolide A, both have three different rings, coumarin, chromene and chromane, built around a phloroglucinol nucleus, the difference of the two is found in stereochemistry at asymmetric carbon or chiral centers. Characteristically the chiral carbon according to the concepts of optical isomerism, the carbon atom binds to four different ligands. In the case of calanolides, it is considered a chiral molecule because it has a bond with a hydrogen, a cyclic amine, with an oxygen and another with a methyl group [10].

The stereochemistry of Calanolide B consists of the presence of chiral centers, in which the C-12 hydroxyl group in Calanolide B in previous studies investigated the relevance of this substituent in the activity against HIV. Several studies report that it has a cis relationship between the 11-methyl and 12-hydroxyl groups, however it has little biological activity compared to Calanolide A. More studies have shown that this compound shows that the cis relationship between the 10- and 11-portions -alkyl were completely devoid of activity, whereas the 12-hydroxyl group exhibited activity against HIV. However, Calanolide has a lower coupling constant between cis-11,12 protons, which leads to its lower effectiveness compared to anti-HIV Calanolide A.

Conclusions

Based on the study carried out, it is possible to verify the importance of the chirality of the isomers, as they can result in a better biological activity of the drugs. In this context, it is essential to highlight that the optically active spatial isomers called enantiomers, such as Calanolide A and B addressed in this study, must be analyzed as different chemical compounds, because in the biological aspect they present

themselves in different ways. It is thus concluded that the anti-HIV activity of calanolide B is less potent than that of calanolide A, probably due to the difference in the stereochemistry of the chiral centers. Currently, there are several studies in progress that aim at the comparison and safety of enantiomers, both individual and racemic mixtures. These are studies that aim at a promising future in the pharmaceutical market.

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