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ISSN: 2329-6798
Modern Chemistry & Applications

Perspective

Racemisation of Thalidomide Drug Involving in Stereoisomers

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DESCRIPTION

The branch of chemistry which involves in the study of the different spatial arrangements of atoms and molecules is known as "Stereochemistry". The Cis and Trans isomers are the forms of stereoisomers, differing structurally only in the location of the atoms and molecule in three-dimensional space. In drugs, the shape of a molecule is an important factor which determines how it interacts with various biological molecules (enzymes, receptors, etc.) that encounters in the body.

Stereochemistry has become a significant issue for both the pharmaceutical industry and the regulatory authorities. Racemization of optically pure pharmaceuticals may occur in vivo, negating single enantiomer benefits or causing unexpected side effects. The evolution of the role of stereochemistry in drug development has depended on accumulating knowledge of the synthesis and analysis of chiral molecules and the stereo-selective nature of the interaction.

Enantioselectivity

The Enzymes, receptors, and other binding molecules involved in biological processes can recognize enantiomers as different molecular entities, due to their different dissociation constants, leading to diverse responses in the biological processes. Enantioselectivity can be observed in drugs pharmacodynamics and pharmacokinetic (absorption, distribution, metabolism, and excretion), especially in metabolic profile and in toxicity mechanisms.

The drug in stereoisomers can undergo different metabolic pathways due to different enzyme systems, resulting in different types and/or number of metabolites. The configuration of enantiomers can cause unexpected effects, due to related changes in unidirectional or bidirectional inversion that can occur during pharmacokinetic processes.

Thalidomide

One of the most infamous demonstrations for the significance of stereochemistry was the thalidomide disaster. As thalidomide possesses two optical isomers which have been reported to exhibit different pharmacological and toxicological activities. In the human body, the thalidomide undergoes racemization even if only one of two stereoisomers is ingested, the other one is produced.

For the approval of new drugs, separation and characterization it has to be carried out for each stereoisomer and also evaluation of the bioactivity, pharmacodynamics, pharmacokinetics, and toxicology of each isomer. A relevant rational also has to be provided for the stereoisomer selected for development and marketing. Stereo-chemical identity tests and assay a method has to be established for the active ingredient (the drug substance) and for the final formulation (drug product).

Psychotropic drugs are either achiral (fluvoxamine, nefazodone) and are already marketed as single enantiomers (e.g., sertraline, paroxetine, escitalopram), a number of antidepressants are currently marketed racemates, including bupropion, citalopram, fluoxetine, tranylcypromine, trimipramine, and venlafaxine. Other drugs often used in the psychiatric practice includes zopiclone, methylphenidate, and some phenothiazines are also available as racemates. Of these, the single-enantiomer formulations are being developed for bupropion and zopiclone.

Since interconversion of thalidomide enantiomers could occur under physiological conditions, special precautions are required inorder to delineate any enantiomer-specific differences in the biological activity of thalidomide. To this end, each thalidomide is synthesized to enantiomer with deuterium substitution of the hydrogen atom bonded to the chiral carbon atom. Racemic thalidomide was purchased from "Tocris Biosciences" which includes S and R-thalidomides and the deuterated D-thalidomide to the enantiomers was synthesized.

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Received: 24-May-2022, Manuscript No. MCA-22-17393; **Editor assigned:** 27-May-2022, PreQC No. MCA-22-17393 (PQ); **Reviewed:** 17-Jun-2022, QCNo. MCA-22-17393; **Revised:** 23-Jun-2022,Manuscript No.MCA-22-17393(R); **Published:** 29-Jun-2022, DOI: 10.35248/2329-6798.22.10.360.

Citation: Cravotto C (2022) Racemisation of Thalidomide Drug Involving in Stereoisomers. Modern Chem Appl.10:360.

CONCLUSION

Based on the complex structures, the CRBN-binding affinity is a thalidomide derivative. The glutarimide ring is a relaxed six-membered ring conformation which is important for CRBN binding with the imide group, serving as both a hydrogen donor and acceptor. Based on the chemical nature of the glutarimide ring, the five carbon atoms $C_{1\text{-}3}$,C_5 and C_6 of the ring are in-plane arrangement because of the sp^2 configuration of two carbonyl carbon atoms (C_2 and C_6) with the amido (CONHCO) π electron resonance. Thus, ring puckering usually occurs at C_4 carbon atoms. In the isolated state, the C_4-endo conformation of the S-thalidomide glutarimide ring minimizes the conformational energy by allowing the N-C bond at the chiral C_3 atom to be oriented in a stable equatorial conformation.