



IMPORTANCE OF CHIRALITY IN DRUG DEVELOPMENT: - CASE OF TERATOGENIC COMPOUND THALIDOMIDE AND IT'S EFFECTS

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ABSTRACT

We have been taught chirality in chemistry in school textbooks as- “a molecule is called to be a chiral if it cannot be superimposed on its mirror image by any combination of rotation, translation, and some conformational change”. So basically a compound is said to be chiral if it contains a asymmetric centre (chiral atom or chiral centre) and thus can occur in two non-superimposable mirror image forms enantiomers. (Pair of molecules that exist in two forms that are mirror images of one another also are chemically identical). Now what they don't teach us is the importance of these chiral compounds in biological system. Chirality has become a major part for the synthesis and development of drugs. Most of the drugs discovered are chiral. The pharmacology activity of drugs depends mainly on its interaction with biological

targets such as proteins, nucleic acids, bio membranes. One enantiomer of a chiral drug may be of medicinal importance for a particular disease whereas; another enantiomer of the molecule may be not only inactive but can also be toxic. Hence chirality plays an essential role in drugs. Therefore synthesizing compound as single enantiomer is crucial in the design and synthesis of drugs. Now talking about teratogenic compounds and its relation to chirality, basically teratogens are refer broadly to any agent capable of eliciting directly or indirectly deleterious effects on developing embryos or fetues to an extend that permanent or semi-permanent defects are manifested subsequently to the fetal development period. Defects include not only dysmorphic phenomena but also permanent or semi-permanent growth, retardation, neoplasm and functional deficit involving the nervous system e.g. behavioral, mental or motor deficits, the reproductive system, the immunologic system, metabolic

systems or any of the individual organs comprising the organism i.e. kidney heart or lungs. Such permanent or semi-permanent deleterious squeals are referred to as terata or simply as birth defects.

The physiochemical and biochemical properties of racemic mixtures and individual stereo isomers can differ significantly, for the living system in the environment where specific structure activity relationships may be required for the proper working effect of enzymes, receptors, transporters and DNA. In drug development, enantiomeric selections are done to maximize clinical effects or to reduce drug toxicity sometimes these attempts turn into failures. Optically active pure organic compounds or molecules used for drug synthesis may undergo racemization in vivo, nullifying single enantiomer benefit or it can also induce unexpected adverse effects. Appropriate chiral antidotes must be selected for therapeutic benefit and to minimize adverse events since enantiomers may possess different carcinogenicity and teratogenicity. There are several examples seen in which compounds bio-accumulation, persistence and toxicity show chiral dependency.

Therefore chirality plays a very important role in drug development, from the selection of enantiomers to devising a drug in such a way that one enantiomer which might be inactive or toxic should be tackled in such a way that its capability of producing adverse effect can be stopped or producing an antidote for it. In this article we will be talking about the teratogenic compounds its adverse effects how chemically they affect our biochemical functions what reaction takes place resulting in tragic results taking thalidomide as our special case.

KEYWORDS: Chirality, Teratogenic compounds, Enantiomers, Dysmorphic, Racemic mixtures, Stereo isomers, Drug toxicity.

INTRODUCTION

We know the concept of chirality theoretically as science students, but the concepts applications unfolds a great importance in drug development. We know that all living organism have L configuration of amino acids that means our all biological system is made of L configuration α amino acids now the relation with chirality lies in drug development. Suppose we have a drug which is a chiral and if we take a mixture of L & D configuration that means its racemic mixture then there will be some different types of interactions with the drug molecule in our body. Sometimes these interactions are extremely dangerous. Therefore stereochemistry plays a major role in drug development.

FDA initial guidance on chiral drugs was set forth in 1992, as more and more evidences of toxic enantiomers came in sight with chiral drug development and detection advanced. According to the guidelines, composition of a chiral drug had to be known when applied in pharmacology, toxicological and clinical studies. Single enantiomers or achiral drugs now dominate newly approved drugs. Usually it is stated that therapeutic activity would reside in one enantiomer and adverse or toxic effects in the other, unfortunately there is a range of possibilities. As discussed above biological systems are chiral entities. Humans are primarily composed of L- amino acids and D- carbohydrates. The secondary proteins structures include right handed alpha helixes, and most DNA are BDNA (the one studied by Watson and Crick having 10 base pairs and the most common DNA found) rather than ZDNA (unusual DNA form which are left handed double helixes). Unique three- dimensional binding, catalytic and stabilizing domains are created by tertiary structures. Thus, a unique structural-activity relationship proceeds from specific architecture. Therefore, in a chiral environment, stereoisomers might experience selective absorption, protein binding, enzyme interaction and metabolism receptor interaction, and DNA binding. Thus each stereoisomer or isomeric mixtures (racemic mixtures) can have different pharmacokinetics, pharmacodynamic, therapeutic, adverse effect profiles. Given structure's capacity to accommodate different chirals will influence the magnitude and type of different effects if any present.

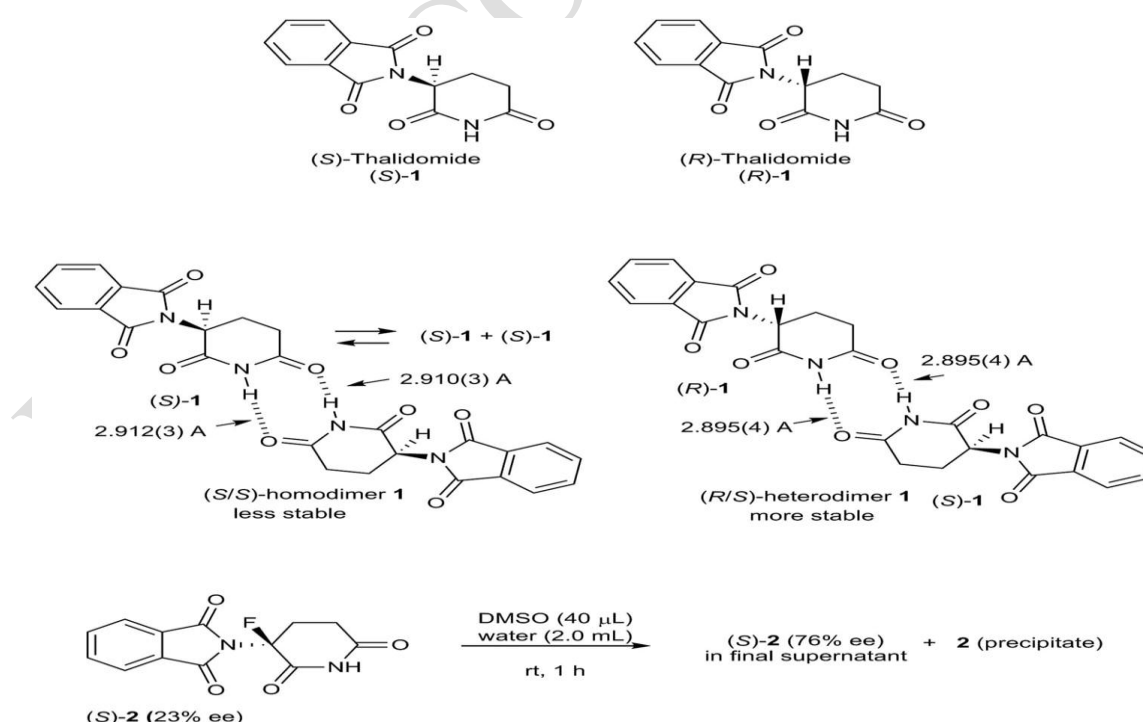


Figure 1: Understanding the thalidomide chirality in biological processes by the Self-disproportionation of enantiomers.

Now talking about chiral toxicity in drugs chemically a racemic drug is not a single compound, but a 50: 50 mixture of two stereoisomers. As we know enantiomers can be distinguished by experiments because they have different ability to rotate a beam of plane polarized light to the clockwise direction (+) dextrorotatory, and to the counterclockwise direction (-) laevorotatory. The mixture of equal proportion 50-50 of +ve & -ve enantiomer is called racemic mixture, when these racemic mixtures are administered by our body which is made of L- α -amino acid (configuration amino acid) one stereoisomer out of two might react with body to create an adverse effect and one of those compounds are teratogenic compounds, causing birth defects thus stereoisomers may produce unique mutations. It has been chemically found that chiral factors are involved in the actual teratogenic mechanism of several compounds. Stereospecific maternal or fetal enzymes, fetal receptors, or placental transport mechanism might all contribute to toxicity. Several teratogen compounds are present which follow stereospecific mechanism of human teratogenicity, e.g.:- thalidomide, valproic acid, retinoic acid out of which thalidomide will be our main concern in

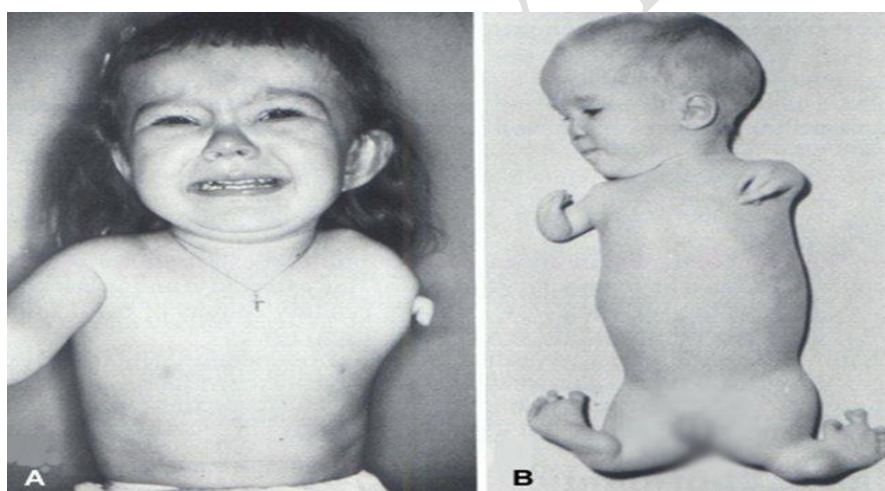


Figure 2: Anomalies in infants caused due to thalidomide.

Thalidomide: The teratogenic compound

Thalidomide is a known teratogenic compound which shook the drug development industry, its aftermath made a history. In 1957, a pharmaceutical company in West Germany Chemie Grünenthal GmbH introduced a new drug to the market called thalidomide. It was originally intended as a sedative or tranquilizer and soon was used for treating other symptoms including morning sickness in pregnant women, and it was used by pregnant women due to the **drugs ability to alleviate morning sickness**. The drug soon was sold in 46 countries under at least 37 brand names.

This sedative hypnotic drug with inherent anti-inflammatory properties was independently identified as a human teratogen by McBride and Lenz as the observations followed an alarming increase in incidence of rare, severe limb anomalies in infant exposed to the drug in uterus between 23rd and 38th days of pregnancy. Some babies were born with hands and feet protruding directly from torsos a condition known as phocomelia while other had libless trunks with toes extending from their hips others were born with just a head with a torso and some other abnormalities in internal organs these tragic abnormalities were due to the tragic drug thalidomide. It was estimated that around 8,000-80,000 deformed babies were born in Europe and thalidomide was withdrawn from German market but the drug was not banned worldwide until 1962.

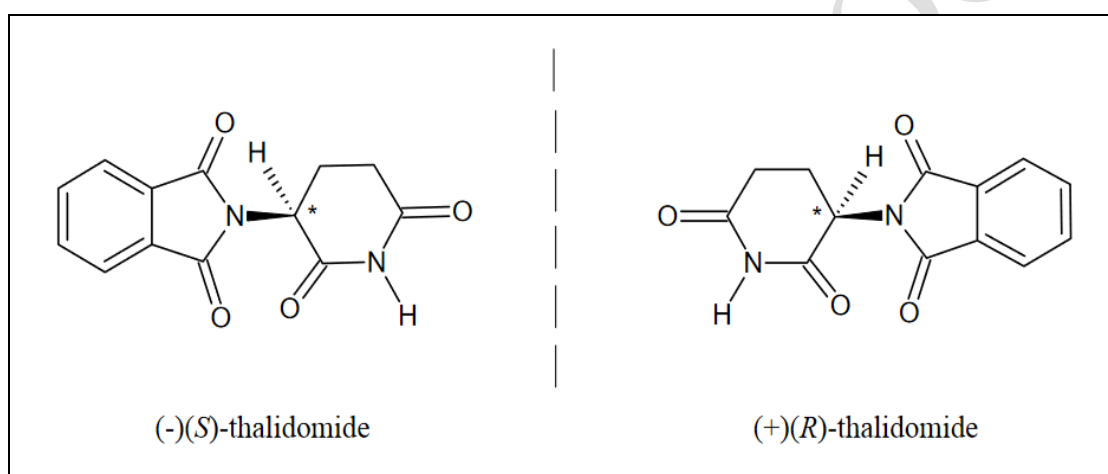


Figure 3: Enantiomers of thalidomide.

Chemistry of this compound

Thalidomide molecular weight on average is 258.2295 and monoisotopic weight 258.064056818 with the molecular formula $C_{13}H_{10}N_2O_4$. Thalidomide is a synthetic derivative of glutamic acid (α -phthalimido-glutarimide) with teratogenic immunomodulatory, anti-inflammatory, anti-angiogenic properties. Thalidomide acts primarily by inhibiting both the production of tumor necrosis factor α (TNF α) in stimulated peripheral monocytes and the activities of interleukins and interferons. Thalidomide is racemic- it contains both left and right handed isomers in equal amounts one enantiomer is effective against morning sickness, and the other is teratogenic. The enantiomers are converted to each other in-vivo, which means if a human is given D-Thalidomide or L-Thalidomide both isomers can be found in serum, hence administering only one enantiomer will not prevent the teratogenic effect of the drug in human. Its protein binding is 55% for the (+) R and 66% for (-) S enantiomers.

Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. Thalidomide may be metabolized hepatically by enzymes of the cytochrome P450 enzyme system. The end product of the metabolism is phthalic acid is excreted as a glycine conjugate. The (R)-configuration enantiomer is an effective sedative medication and the (S)-enantiomer may be the teratogenic one. (S)-thalidomide was shown to be responsible for over 2000 cases of birth defects in the children born to women who took the drug during pregnancy.

Thalidomide [Thalidomide, ($\pm$)-phthalimidoglutarimide], undergoes bioactivation by peroxidases including cyclooxygenases which oxidizes DNA(deoxyribonucleic acid) and GSH (tripeptide, γ -l-glutamyl-l-cysteinyl-glycine called Glutathione antioxidant synthesized in the cells, GSH is the reduced form because it's an electron donor) indicating free radical mediated oxidative stress as a likely cause of its toxic side-effects. Similar to other imides, the mechanism of peroxidase mediated bioactivation of thalidomide involves the single electron oxidation of the glutarimide moiety to the nitrogen centered free radical. The thalidomide free radical may generate highly reactive oxygen species such as $\text{HO}^\cdot$ or superoxide anion radical $\text{O}_2^\cdot$, this is the hypothesis consistent with the in vivo oxidation of GSH by thalidomide.

An alternate bioactivation pathway of thalidomide involve the P450 (cytochrome P450 are superfamily of enzymes containing heme as a cofactor that functions as monooxygenases, these proteins oxidizes steroids, fatty acids and xenobiotics) mediated bioactivation of thalidomide to reactive arene oxides intermediate has also been reported. The isolation of phenolic metabolites from the urine of animals treated with thalidomide provides some evidences for the existence for the existence of this pathway. Further evidence for the existence of the arene oxides intermediate in the teratogenic effect of thalidomide, as opposed to the free radical theory is provided by the findings that ring opened thalidomide metabolites retain the teratogenic effect of thalidomide. The evidence against the arene oxide pathway are provided by the SAR studies on thalidomide analogs that states that it retain the teratogenic effect of the parent drug even though they lack the ability to form arene oxides in hepatic tissue.

The mechanism of Thalidomide is given by a lot of scientist more than 30 mechanisms have been proposed to explain the teratogenic action of (-)S-Thalidomide, some scientist have proposed that the S configuration enantiomer of thalidomide might exerts its teratogenic

effect by blocking the gene coding for some essential proteins. Thus (-) S -Thalidomide is the unwanted enantiomer. Also we might think of an idea that drug companies could have simply purified the racemic mixture and give to the patients only the (+)R-Thalidomide. Unfortunately we can't do that as human liver contains an enzyme that can convert (+) R-Thalidomide to (-) S-Thalidomide. Therefore, even administration of enantiomeric pure (+) R-Thalidomide results in racemic mixture.

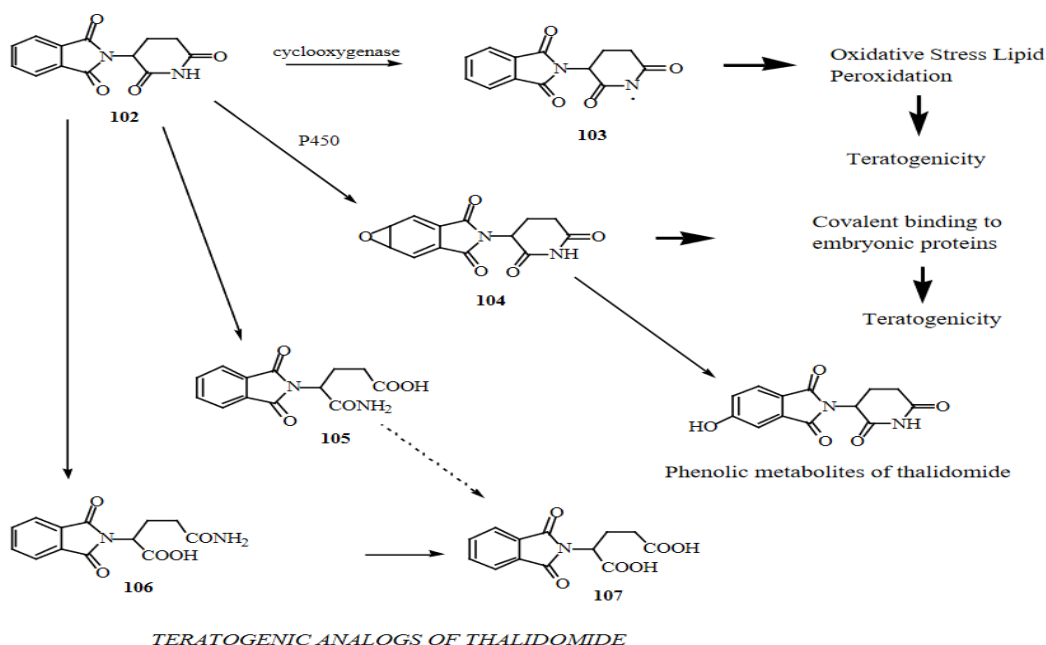


Figure 4: Showing teratogenic chemical mechanism of thalidomide where 102- Thalidomide, 103- thalidomide free radical, 104- arene oxide intermediate, and 105,106,107- Ring opened thalidomide metabolites.

One class of thalidomide analogues is called immunomodulatory drugs. Examples are lenalidomide and CC-4047. In 1999, scientists found that lenalidomide and CC-4047 can inhibit $\text{TNF-}\alpha$ and are 2,000 and 20,000 times more potent than thalidomide respectively. Lenalidomide and CC4047 also stimulate T cells, which are a type of white blood cells involved in a variety of immune reactions. In 2000, analogues of thalidomide were found to have the ability to kill myeloma cells.

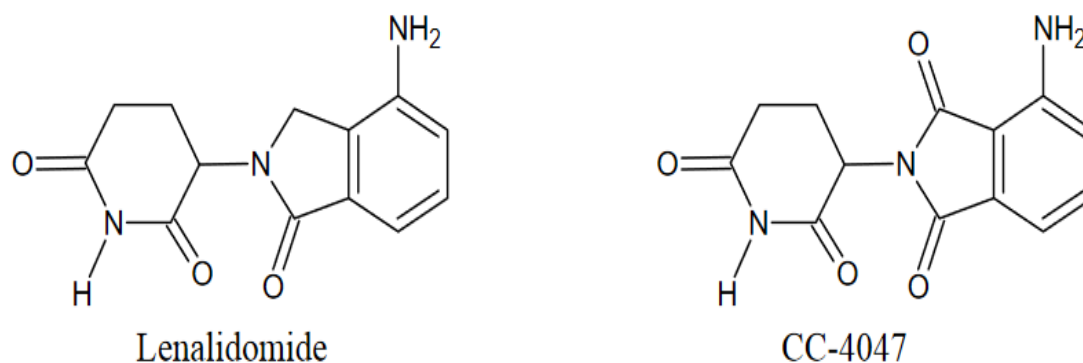


Figure 5: Structures of Lenalidomide and CC-4047.

CONCLUSION

“Chirals” a property of asymmetric carbon, as simple as it seems it holds a way more important application in real world. For an enthusiast of chemical science knowing chirality theoretically makes it quite a topic which is often taken for granted sometimes but after knowing its application in drug development makes it a topic that can't be ignored. Thalidomide incident shook the entire nation of Germany as well the world, showed us how much powers a single enantiomer of a chiral hold. Imagining the condition of the newborns with such anomalies can shake ones soul. One enantiomer of a chiral drug may be a medicine and other enantiomer can be inactive or toxic. Thus chirality plays a very important role in drug industries. Synthesizing a drug compound as a single enantiomer or with an antidote for the toxic enantiomer is very important. Before developing a drug chemically we should know the compound is chiral does its enantiomers are toxic? And if it is does it have any negative impact on the body or not, as it is seen in case of thalidomide the chiral toxicity was not taken into consideration and it impacted in infants being born with unimaginable anomalies. While physically and chemically, enantiomers may seem identical; in a biological environment the outcomes of their reactivity can be dramatically different. Within the past two decades chirality has become a focus in regulatory guidelines for drug development.

Since there has been a lot of mechanism been proposed by scientist for thalidomide (a teratogenic compound) for its teratogenic activity in our body out of which bioactivation of thalidomide involving cytochrome P450 is the most accepted one but even after knowing its mechanism. The evidence against the arene oxide pathway are provided by the SAR(structure activity relationship) studies on thalidomide analogs that states that it retain the teratogenic effect of the parent drug even though they lack the ability to form arene oxides in hepatic

tissue. Only if there would have been a way to inhibit this mechanism and make thalidomide lose its teratogenicity it wouldn't have affected so many lives. Recently it was found that it again showed its teratogenic effects in Africa leaving its trace. Thalidomide is also regarded as the medicine that makes monsters justifying its tag being amongst the notorious drugs of all time.

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