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An in-depth review of thalidomide's basic moieties

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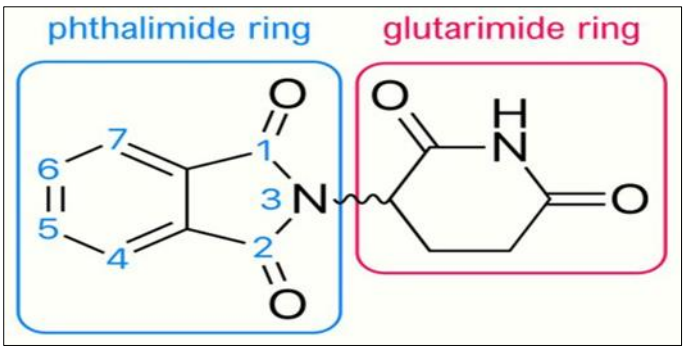
Abstract

Thalidomide, also referred to as N-phthalimido glutarimide, was initially made available as a sedative by Chemie Grunelthal GmbH in West Germany in 1957. Thalidomide's chemical structure primarily consists of two rings: the phthalimide ring and the glutarimide ring. Although small substitutions in one or both rings might be tolerated without a reduction in toxicity, both of these groups were necessary for embryopathic action. A cyclic chemical structure that is a component of thalidomide is the phthalimide ring. The phthalimide ring is thought to contribute to both the teratogenic (causes birth defects) and some therapeutic aspects of the medication. Another cyclic structure seen in the chemical makeup of thalidomide is the Glutarimide Ring. The pharmacological characteristics of thalidomide are also connected to this portion of the molecule. Based on their activities and structural connections, this review study gives an overview of the interaction between phalidimide and the glutarimide ring for teratogenicity of the thalidomide type. Understanding how thalidomide interacts with the human body, both for its intended therapeutic effects and its negative side effects, especially when taken during pregnancy, is important given the combination of these rings in the drug's chemical structure.

Keyword: Thalidomide; Teratogenicity; Therapeutic effect; Interact

1. Introduction



Excellent therapeutic advancements against a wide range of ailments, including infectious, metabolic, and cancerous conditions, have been made possible by pharmaceutical innovation. (Ellis Benjamin, 2017) The two heterocyclic ring structures that make up the thalidomide molecule are the alpha or 3′-position of the glutarimide ring and the N-position of the phthalimide ring. It has two enantiomers, the R and S Forms, which have chemically similar structures. (Xiaoping Wang, 2021) S is in charge of the severe birth defects, whilst R exhibits sedative and anti-nausea effects. One 50 mg tablet of thalidomide was sufficient to induce developmental abnormalities. Although the precise cause of thalidomide's

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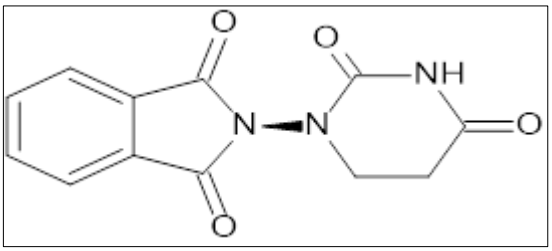
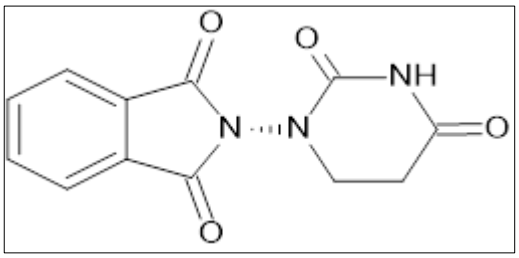
teratogenicity is unknown, it is thought to be connected to the drug's disruption of angiogenesis and embryonic development. (Van Derpoorten K, 1997). The tragic history of thalidomide serves as a sobering reminder of how crucial thorough testing and safety assessment are in pharmaceutical chemistry. Thalidomide is classified as a Multi target medication that impacts multiple cellular processes, including as androgen receptor antagonism, peptidase inhibition, cox inhibition, and glucosidase inhibition.

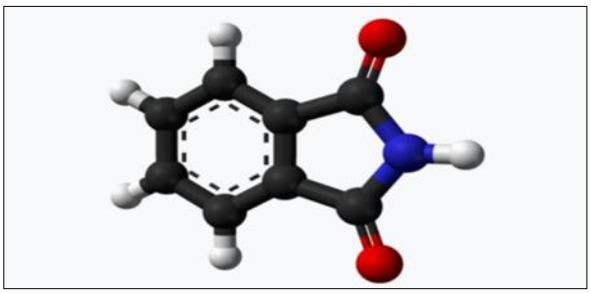


R Thalidomide

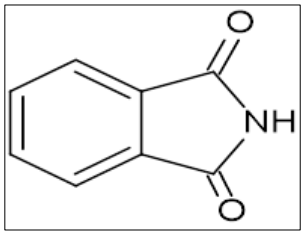


S Thalidomide

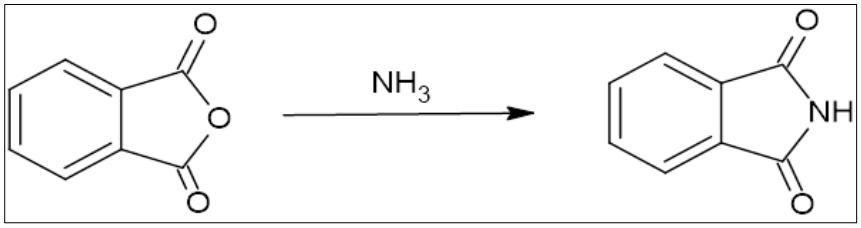
2. Phthalimide Ring



Phthalimides (1H-Isoindole-1,3(2H)-dione) are cyclic imides with the chemical property of having two carbonyl atoms linked to the same nitrogen. (José Guedes da Silva Júnior, 2019) It has the chemical formula C8H5NO2 and is an organic compound. which possesses White Crystalline Solid, which is frequently employed as the first step in the synthesis of organic compounds. (Hayman Sardar Abdulrahman, 2020)The specific uses of the adaptable phthalimide ring can change depending on the intended chemical synthesis or application. (Sanchez E, 2017)

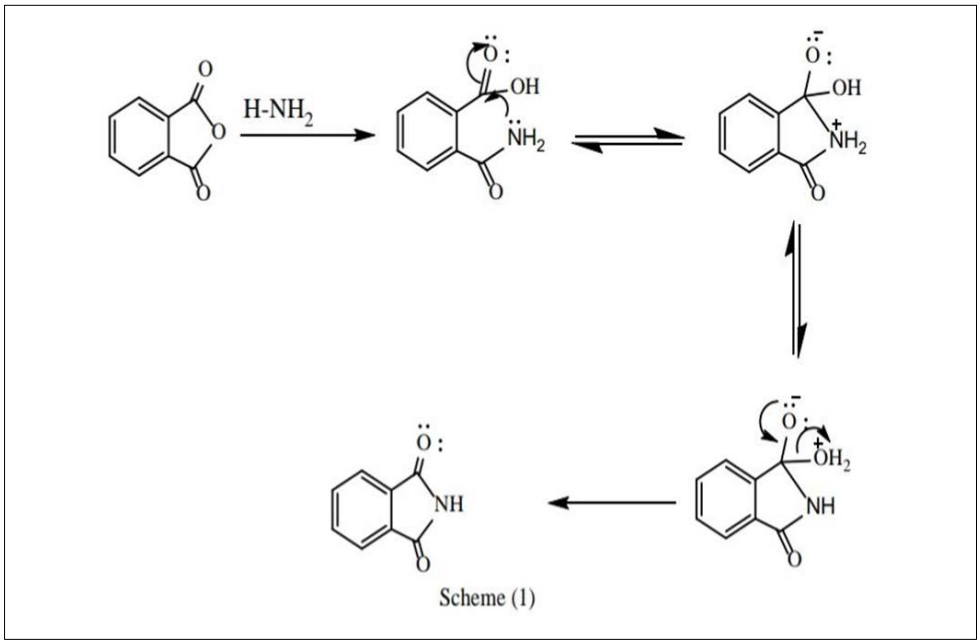


Phalimide ring



There are two ways to make phthalimide. The first approach involves heating phthalic anhydride in the presence of aqueous ammonia to produce phthalimide. The second technique makes use of phthalic anhydride and ammonium

carbonate. Ammonium carbonate has a mildly acidic pH. It produces potassium phthalimide when it is made to interact with KOH.



Mechanism of imide formation , through a nucleophilic attack of amino group to anhydride moiety. (Tomoko Asatsuma-Okumura, 2020)

Gabriel synthesis, which creates primary amines from phthalimide, is a well-known example of organic synthesis. Primary alkyl halides are converted into primary amines by the Gabriel synthesis. (Duong Binh Minh H., 2019) Gabriel synthesis uses the reagent potassium salt. Phthalimide is sufficiently acidic to react with strong potassium hydroxide solution to produce a potassium salt. For the biological effects of being hypolipidemic, analgesic, anticonvulsant, anti-inflammatory, antiviral, antitubercular , and antibacterial, many phthalimide compounds have shown promise. The biological activity of thalidomide, both beneficial and detrimental, is connected to the pthalimide ring. (Benjamin E, 2017) Thalidomide was initially developed as a sedative and anti-nausea drug, but it was later discovered that when used by pregnant women, it causes serious birth abnormalities. Though the precise methods by which thalidomide exerts its effects are complicated and poorly understood, it is thought that the pthalimide ring affects immune system regulation and prevents the release of some inflammatory chemicals. The fact that thalidomide can reduce overactive immune responses makes it effective for treating diseases like leprosy and multiple myeloma. However, thalidomide's teratogenic (birth-defect-causing) effects when taken during pregnancy are also influenced by the same immune-modulating qualities that make it beneficial in some medical diseases. Thalidomide interferes with a fetus' normal growth, resulting in severe defects such limb deformities. Research is still being done to determine the precise interactions that the pthalimide ring in thalidomide has with its biological targets.

3. Defect Caused by pthalimide ring

The phthalimide ring is the main structural element of thalidomide that causes teratogenicity. The phthalimide ring has a flaw in that it can go through racemization under physiological circumstances, forming both the R and S enantiomers of thalidomide. The desirable sedative effects are caused by one enantiomer, whilst the teratogenic effects are caused by the other enantiomer. This means that one enantiomer, which causes birth abnormalities, is exposed to both enantiomers when a pregnant woman takes thalidomide. Babies born to moms who used thalidomide during pregnancy had significant limb and organ malformations as a result of this stereochemical flaw in the phthalimide ring. Teratogenicity of thalidomide is a coupling response. Later, when additional structural analogues are taken into consideration, the significance of the alpha bond and the chiral nature therefore offered will become clear.

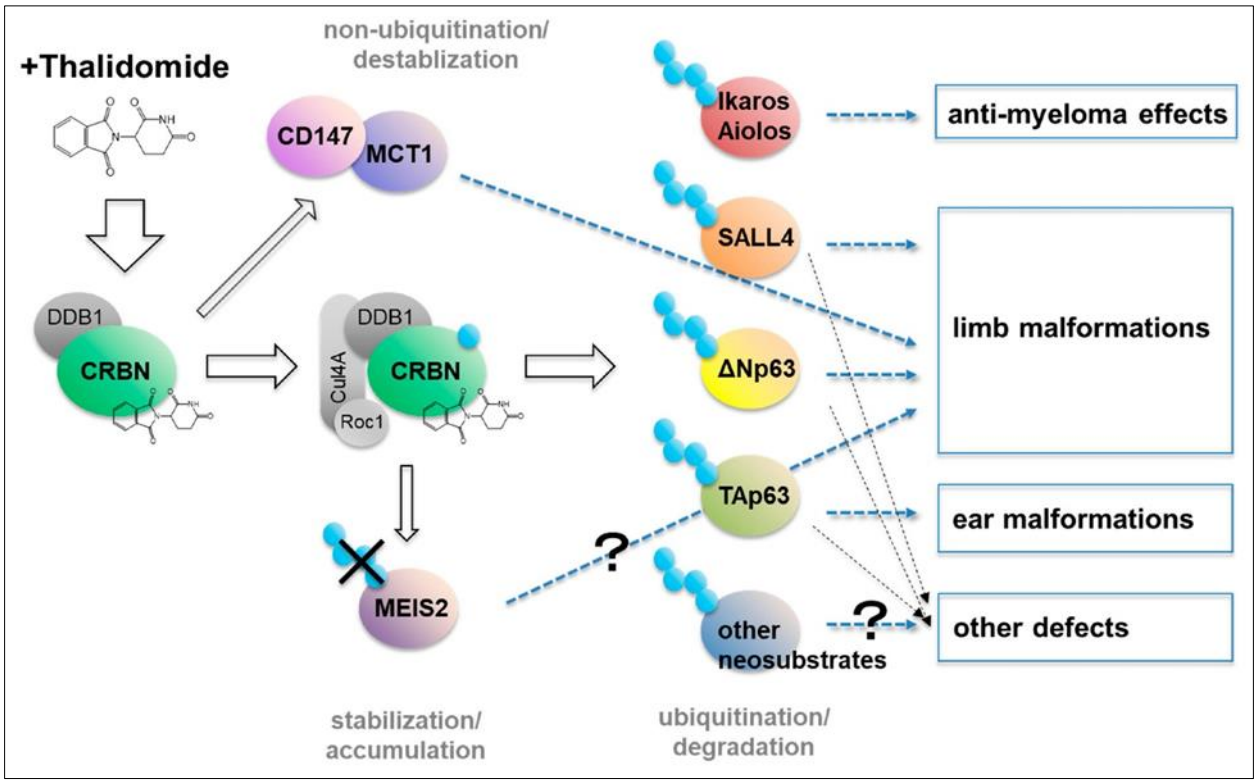
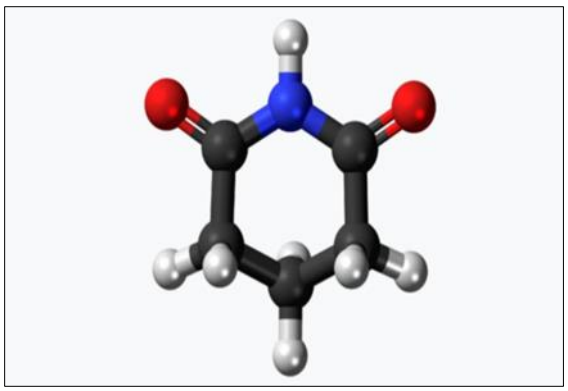
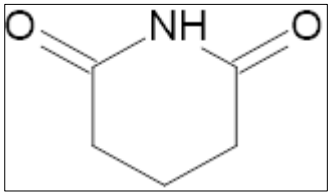


Figure 1 Mechanism of Action of Thalidomide

4. Glutarimide Ring



The Glutarimic ring (Pyrrolidine-2,5-dione) is a cyclic structure having molecular formula(CH2)3(CO)2NH that plays a crucial role in the compound's pharmacological effects and biological activity. (Imran M, 2019)



Glutarimide Ring

It is a cyclic chemical molecule that has two carbonyl groups (diones) linked to the pyrrolidine ring at positions 2 and 5 of the ring.

Here are a few applications and outcomes connected to the glutarimide ring in thalidomide:

- Sedative and Hypnotic: Thalidomide's glutarimide ring contributes to its sedative and hypnotic effects, making it useful for managing sleep disturbances and anxiety.
- Anti-Nausea: Thalidomide was initially prescribed to pregnant women to alleviate morning sickness due to its anti-nausea properties.
- Immuno modulatory Effects: Thalidomide's glutarimide ring is associated with its immuno modulatory properties, which have been explored in the treatment of various immune-related disorders, such as leprosy and certain inflammatory diseases.

5. Basic Comparision Between pthalimide and Glutarimide Ring

Table 1 Comparision of Pthalimide and Glutarimide Ring

	Pthalimide Ring	**Glutarimide Ring**
Chemical Formula	C8h5no2	C5h7no2
Iupac name	1H – Isonindole – 1,3 – dioxoisoindoline Phthalimidoyl	Piperidine-2,6-dione
Other name	1,3 – dioxoisoindoline Phthalimidoyl	2,6-Diketopiperidine
Ph	Strongly acidic	Neutral
Molar mass	147.13g/mol	113.11 g/mol
Density	1.21 gm/cm square	1.2416 gm/cm square
Melting point	238℃.	155-157 ℃
Boiling point	336℃.	288 ℃
Appearance	White solid	White solid
Solubility profile	Soluble in water	Soluble in water, hot ethanol and boiling benzene.
Compound category	Heterocycle	Tetrahydropyridines.
Action in thalidomide	Sedative and hypnotic	Anticonvulsant, and immunomodulatory
Adverse effect	Birth defects , led to severe limb and organ malformations in fetuses phocomelia	Toxicity, allergic reactions, or other health issues
Interaction	With chemical reactions	Specific receptors, enzymes, or biological pathways in the body.

6. Conclusion

In conclusion, a detailed analysis of the fundamental molecules of thalidomide exposes the complexity of this medication. The racemic combination of enantiomers that characterizes thalidomide's chiral characteristics is essential to the drug's biological activity and pharmacokinetics. The substance has phthalimide and glutarimide moieties, which are in charge of its sedative and immuno modulatory properties, respectively. Thalidomide is a fascinating case study in the development and regulation of drugs because its history is characterized by both therapeutic success and catastrophic teratogenicity. Its continued medicinal usage and use as a lesson in drug development depend on our ability to comprehend its basic components. Understanding thalidomide's fundamental components is crucial because of the continuous research into its structure-activity correlations and pharmacological mechanisms.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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