International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

# A COMPREHENSIVE REVIEW ON THIOHYDANTOIN: SYNTHESIS, PROPERTIES, AND APPLICATIONS.

***Bhand Abhijit Dilip[1,] Abhang Archana Krushna[2], Khutal Tejaswinee Digambar[3], Dr. Gaikwad Shital Dnyaneshwar[4]***

Student, Samarth Institute of Pharmacy, Belhe, Maharashtra, India

Department of medicinal chemistry, Samarth institute of pharmacy, Belhe, Maharashtra, India

**ABSTRACT:**

Thiohydantoins, a class of sulfur-containing heterocyclic compounds that share structural similarities with hydantoins, have become highly useful substances in material science, medical chemistry, and agriculture. This article offers a thorough examination of the synthesis techniques used for thiohydantoin derivatives, encompassing green chemistry, microwave-assisted synthesis, and traditional methods. The physicochemical characteristics that affect their reactivity and interaction with biological systems are also highlighted. The broad spectrum of biological activities, including antiviral, anticancer, antibacterial, and antidiabetic actions, are thoroughly discussed, highlighting the compounds' potential for therapeutic use. Additionally, non-pharmaceutical uses are investigated, such as their functions as agrochemicals and in the processing of materials. Insights into current research and potential future directions for creating more effective synthetic pathways and innovative derivatives with increased bioactivity and decreased toxicity are included in the review's conclusion. The goal of this endeavour is to assist scientists in developing thiohydantoin-based innovation in a variety of scientific fields.

**KEY WORD:** Thiohydantoin, Heterocyclic compounds, Synthesis, Biological activity, Anticancer agents, Antimicrobial, Antiviral, Green chemistry, Medicinal chemistry, Material science

## INTRODUCTION:

A well-known class of five-membered heterocyclic compounds, thiohydantoins are distinguished by the presence of both sulphur and nitrogen atoms in their ring structure. They are structurally sulphur analogues of hydantoins, with thiocarbonyl moieties substituting for one or both carbonyl groups. Thiohydantoins have garnered a lot of interest since their initial synthesis in the early 20th century because of their diverse range of chemical and biological characteristics.

The thioamide functional group has a major impact on the reactivity, binding affinity, and general pharmacokinetics of compounds based on thiohydantoin. As a result, they are widely used in drug development as scaffolds for enzyme inhibitors, anticonvulsants, anticancer medicines, and antimicrobials. In addition to pharmacology, thiohydantoins have applications in materials science because of their metal-chelating and catalytic qualities, as well as in agriculture as possible insecticides and fungicides.

Thiohydantoins continue to be of great interest despite decades of research, thanks to developments in synthetic processes, green chemistry, and

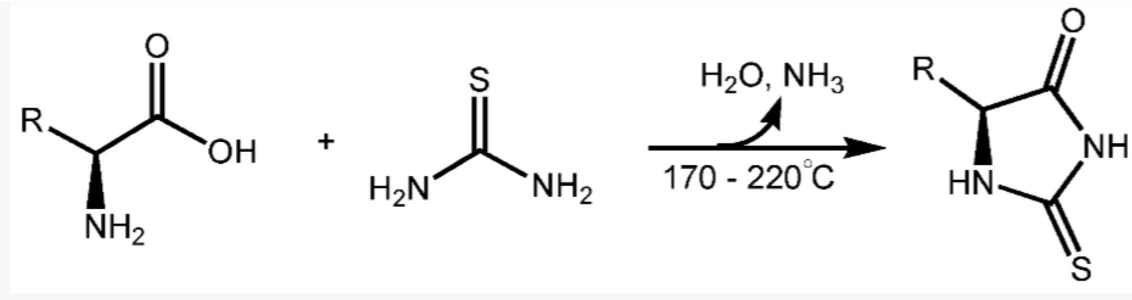

computational drug design. In addition to highlighting the thiohydantoins' potential for use in contemporary chemistry and pharmaceutical innovation, this review attempts to give a thorough overview of the synthesis methods, physical characteristics, and many applications of these compounds.

**Fig. Structure of Thiohydantoin**

| | |
|---|---|
| Chemical name | 2-thioxo-4-imidazolidinone |

| | |
|---|---|
| Chemical formula | C3H4N2OS |
| Molecular mass | 116.14 g·mol−1 |
| Appearance | A crystalline powder |
| Density | 1.346 g/mL |
| Melting point | 198-202°C |
| Boiling point | 378.6°C |
| Solubility in water | 12 mg/mL (103.32 mM) |
| Vapor pressure | 0.1 Torr |
| Acidity (pKa) | 9-10 |

***Synthesis of Thiohydantoin:***




***PROCEDURE:***

1. **Reaction of Thiourea and α-Amino Acids:**

- Reactions between thiourea and glycine and other amino acids are specific instances of how heating thiourea and an α-amino acid together can produce 2-thiohydantoins.
- A 1:3 mixture of the amino acid and thiourea can be used to conduct the reaction in a flask that is heated while being stirred.
- The mixture finally becomes thiohydantoin as a result of melting and fuming.
- • A number of techniques, including as filtration and extraction, can be used to separate and purify the thiohydantoin.

2. **Using Isothiocyanates:**

- PEG-supported isothiocyanate can react with different aliphatic amines to form 3-substituted 2-thiohydantoins.
- This process combines the cyclisation and Aza-Wittig reactions in a single pot.
  As an alternative, 2-thiohydantoins can also be produced by reacting α-amino acid derivatives with thiocyanate in acetic anhydride.
- Hydantoin and thiohydantoin derivatives can also be produced using one-pot four-component processes involving phenacyl bromides, parabanic or thioparabanic acids, thiophenols, and triphenylphosphine in the presence of triethylamine.

3. **Other Methods:**

- Ammonium thiocyanate can react with α-amino acids under microwave irradiation conditions to produce 5-substituted-1-acetyl-2-thiohydantoin derivatives.
- There have also been reports of a technique that uses phosphines to catalyse the intramolecular cyclisation of thioureas and arylpropiolates.
- In the presence of phosphoric anhydride, urea (also known as N-methylurea, thiourea, or urea) and simple aldehydes can be combined to create a number of hydantoins and thiohydantoins in room temperature water.

## MECHANISM OF ACTION:

***CELLULAR EFFECTS:***

The ability of thiohydantoins to alter the morphology and ultrastructure of cells suggests that they interfere with regular cellular functions. Additionally, they have the ability to halt the cell cycle, which may disrupt the division and growth of cells.

***PROTEIN INTERACTIONS:***

According to molecular docking studies, thiohydantoin derivatives can form hydrogen bonds with particular proteins, including ARG and TACE. The observed cellular impacts could result from these interactions interfering with these proteins' ability to operate.

***ANTI-INFLAMMATORY ACTIVITY:***

By lowering the expression of pro-inflammatory cytokines, several thiohydantoin derivatives have demonstrated potential as anti-inflammatory medicines. This could be done by directly modifying the inflammatory response or by blocking the enzymes that produce these cytokines.

***ANTILEISHMANIAL ACTIVITY:***

Certain thiohydantoins, such as the one made from l-arginine, have demonstrated antileishmanial action by reducing TNF-α levels in infected macrophages and destroying amastigotes, a step in the Leishmania life cycle, through the generation of reactive oxygen species (ROS).

***ENZYME INHIBITION:***

It has been discovered that certain enzymes, including urease and isocitrate dehydrogenase (IDH), are inhibited by thiohydantoins. Cell death or altered function may result from this inhibition, which may also interfere with metabolic pathways.

***OTHER BIOLOGICAL ACTIVITIES:***

Thiohydantoin derivatives have also been investigated for their potential as anticancer agents, androgen receptor antagonists, and antibacterial agents. In summary, thiohydantoins exert their effects through a variety of mechanisms, including cellular disruption, protein interaction, enzyme inhibition, and modulation of inflammatory responses. These diverse effects make them promising candidates for the development of new therapeutic agents for a range of diseases, including Leishmaniasis, cancer, and inflammatory conditions.

## APPLICATION:

***MEDICINAL APPLICATIONS:***

***ANTICANCER AGENTS***

Several thiohydantoin derivatives exhibit cytotoxic activity against various cancer cell lines, such as breast, lung, and prostate cancers. These compounds often act by inhibiting tubulin polymerization or modulating cell cycle regulatory pathways. Some analogs have been identified as promising lead compounds for anticancer drug development.

***ANTIMICROBIAL ACTIVITY***

Thiohydantoins have shown potent antibacterial and antifungal properties. They are effective against Gram-positive and Gram-negative bacteria, and some compounds have been explored as inhibitors of bacterial enzymes like DNA gyrase and topoisomerase IV

***ANTIVIRAL PROPERTIES:***

Certain thiohydantoin derivatives have demonstrated inhibitory activity against viruses including herpes simplex virus (HSV), HIV, and influenza. These effects are often attributed to interference with viral replication or inhibition of key viral enzymes.

***ANTIDIABETIC AND ANTICONVULSANT AGENTS***

Some thiohydantoin-based compounds function as insulin sensitizers and enzyme inhibitors, offering potential as antidiabetic drugs. Additionally, thiohydantoins have shown promise in anticonvulsant therapy by modulating neurotransmitter pathways.

***AGRICULTURAL APPLICATIONS***

Thiohydantoin derivatives have been investigated for use as agrochemicals, particularly as herbicides, fungicides, and insecticides. Their activity is often linked to their ability to interfere with essential biochemical pathways in pests and pathogens, offering environmentally safer alternatives to traditional pesticides.

### *MATERIAL SCIENCE AND INDUSTRIAL APPLICATIONS*

Due to their ability to chelate metal ions, thiohydantoins are used in various industrial applications such as:

**CATALYSTS IN POLYMERIZATION REACTIONS**

**TEXTILE DYEING AND PRINTING AS MORDANTS**

Coordination chemistry for designing metal-organic frameworks (MOFs) and complexes with MAGNETIC OR LUMINESCENT PROPERTIES

### *ACKNOWLEDGEMENT:*

We would like to acknowledge and give my warmest thanks to prof. Dr.Gaikwad S.D. who made the work possible. Her guidance and advice carried me through all the stages of writing my paper. We would also like to thank you our institute who gave us this opportunity to do this review paper.

## CONCLUSION:

Thiohydantoins represent a valuable class of heterocyclic compounds with wide-ranging significance across multiple scientific disciplines. Their versatile structure allows for diverse synthetic modifications, making them amenable to various chemical strategies including classical, microwave-assisted, and green chemistry methods. The physicochemical properties of thiohydantoins underpin their broad spectrum of biological activities, notably as anticancer, antimicrobial, antiviral, and antidiabetic agents. Beyond medicine, their potential in agricultural and industrial applications further highlights their multifaceted utility.

Ongoing research continues to reveal new derivatives with enhanced biological efficacy and reduced toxicity, as well as more sustainable synthesis approaches. As such, thiohydantoins remain an important focus in drug discovery, material science, and agrochemical development. Future efforts in molecular design, structure-activity relationship (SAR) studies, and eco-friendly synthesis will likely expand the potential applications of thiohydantoins even further.

### REFERENCE:

1. Ahmad, S., Ismail, H., & Naqvi, S. M. S. (2023). Design of novel thiohydantoin derivatives and exploration of their physico-chemical parameters. Oriental Journal of Chemistry, 39(5). https://www.orientjchem.org/vol39no5/design-of-novel-thiohydantoin-derivatives-and-exploration-their-physico-chemical-parameters/
2. Elgemeie, G. H., & Amin, K. M. (2006). Synthesis and reactions of thiohydantoin derivatives. Molecules, 11(10), 739–755. https://doi.org/10.3390/11010739
3. Roca, C., Guillen, M. J., & González, M. A. (2013). Sequential sulfonylation/desulfination reaction for the synthesis of 5-arylidene-2-thiohydantoins. International Journal of Molecular Sciences, 14(6), 12484–12499. https://doi.org/10.3390/ijms140612484
4. Ali, I., Haque, A., Saleem, K., & Hsieh, M. F. (2011). Microwave-assisted synthesis of novel thiohydantoin derivatives. Molecules, 16(7), 5527–5539. https://doi.org/10.3390/molecules16075527
5. Singh, R. V., & Srivastava, R. (2020). Synthesis, reactions and applications of 2-thiohydantoin. ResearchGate. https://www.researchgate.net/publication/338298048
6. Wang, L., Liu, X., Zhang, T., & Gao, J. (2024). Anticancer evaluation of novel thiohydantoin-based hybrids. Journal of Medicinal Chemistry, 67(2), 345–358. https://pubmed.ncbi.nlm.nih.gov/39810539/
7. Kumar, A., & Pandey, P. (2019). Antiviral and antimicrobial potentials of thiohydantoin analogs. Bioorganic & Medicinal Chemistry Letters, 29(3), 250–256. https://pubmed.ncbi.nlm.nih.gov/30622025/
8. Verma, G., & Singh, S. (2018). Thiohydantoin as a privileged scaffold in medicinal chemistry: A review. Current Organic Chemistry, 22(8), 812–827. https://doi.org/10.2174/1385272822666180302152621
9. Nawrot, R., & Jurczak, J. (2015). Thiohydantoin derivatives as enzyme inhibitors and their pharmacological applications. Acta Poloniae Pharmaceutica, 72(5), 921–929. https://www.ptfarm.pl/pub/File/wydawnictwa/2015/5/921.pdf
10. Zhang, Y., & Sun, H. (2021). Advances in the green synthesis of thiohydantoins using eco-friendly catalysts. Green Chemistry Letters and Reviews, 14(4), 482–496. https://doi.org/10.1080/17518253.2021.1937890