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Synthesis, characterisation and antimicrobial activity of n-substituted 2-thiohydantoin derivatives

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Abstract
Novel 2-thiohydantoin derivatives (1a and 1b) were synthesized from aurones with solvent ethanol. The structures of synthetic compounds were characterized using Fourier-transform infrared spectroscopy (FT-IR), 1H-nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry. Synthesized compounds shows good to moderate antibacterial and antifungal activities against Bacterial culture, *Escherichia coli* (MTCC-452), *Pseudomonas aeruginosa* (MTCC-3541), *Mycobacterium tuberculosis* (MTCC-300), *Enterococcus faecalis*, *Aspergillus niger*, (MTCC-281), *Candida*. *Albicans*, (MTCC-854) species.

Keywords: 2-thiohydantoin, antibacterial, antifungal

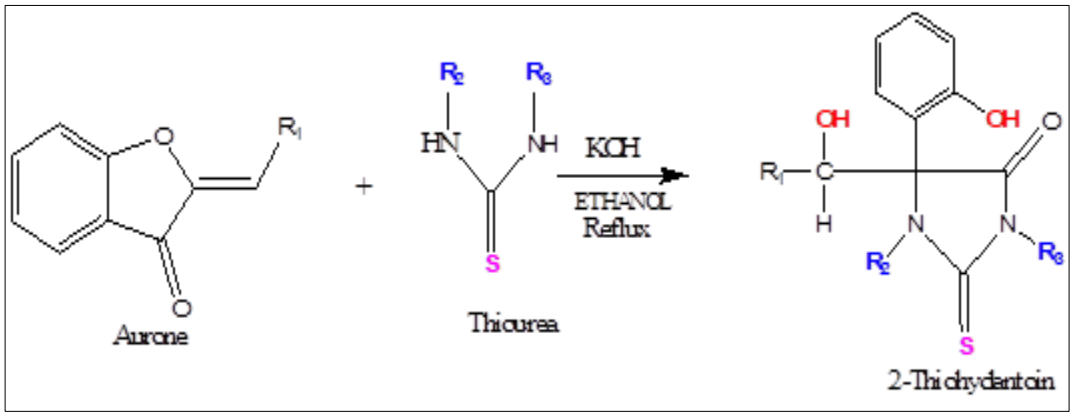
1. Introduction
The chemical substances that stop microorganisms from growing or that eradicate them, is known as an antimicrobial agent. This characteristic is displayed by a variety of substances when utilized at a sufficiently higher focus. Nonetheless, the term is typically limited to substances that exhibit efficacy at concentrations appropriate for real-world use. The substance ought to have a wide range of antibacterial activity at low concentrations.
Hippocrates, a Greek physician who lived in 450 B.C., is credited with introducing the idea of disease as a pathogenic process and organizing the field of medicine through the use of deduction, analysis, and abbreviation. James Gregory (1753-1821) is credited with popularizing heroic symptomatic treatment, which included bloodletting, high dosages of ematic, and drastic purgatives - many of which had disastrous outcomes. This treatment, which lacked any scientific foundation, was dubbed ("allopathy").
The oldest and most revered scripture, the Rigveda, which was composed between 4500 and 1600 B.C., contains the first record of the use of plants for medicinal purposes. Certain drug properties and their applications have been detailed in detail in the Ayurveda, which is regarded as an "Upa-Veda." Actually, the basis of India's traditional medical knowledge is Aryurveda [1].
Several Western scholars have determined that Ayurveda dates back to between 2500 and 600 B.C. Ayurveda is divided into eight branches, which are separated by two later works called Sushruta [2].
Literature survey reveals that chalcones, aurones and 2-thiohydantoin derivatives has antimicrobial, anti-inflammatory, anti-diabetic. Anticancer, analgesic, insecticidal etc. properties.
Kolli *et al*. revealed that, 2-thioxo imidazolidinones derivatives shows moderate to higher antimicrobial activity against *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and Staphylococcus aureus [3].
Joshi *et al*., synthesized thiohydantoin derivative and explored regioselectivity as well as antimicrobial activity [4].
Badiger *et al*., synthesized 5-[6-aryl-2-(4-methoxybenzyl)imidazo[2,l-b][l,3,4] thiadiazol-5-yl]methylene-2-thioxoimidazolidin-4-one derivatives & screened for their antibacterial and antifungal activities [5].
Bhambi *et al*., synthesized 3-Thiazolidin-4-one-2-yl-methylene hydrazido-1H-indole 2 and 3-[2-thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole 3, which were characterized for their antibacterial and antifungal activities, with some showing significant inhibition [6].

2-Thiohydantoins are important class of compounds within pharmaceutical industries and exist in various pharmacologically active molecules that possess important bioactivities like antimicrobial [7], antiviral [8], fungicides [9], anti-parasite, [10] and anticancer [11].
These molecules contribute to drug discovery and the importance of these compounds in bioactive, we have decided to synthesize the thiohydantoin derivatives and investigated its antimicrobial properties because these properties explain the nature and reactivity towards drugs.

2. Methods and Materials

2.1 General

Using TLC, the final compound's purity was assessed. The FT-(IR Perkin Elmer - Spectrum RX-IFTIR) was used to record the IR spectra in KBr. While 1HNMR data was recorded on an FT NMR Spectrometer (Bruker Avance Neo 500 MHz), mass spectra were recorded on a mass spectrometer. The data are presented as chemical shifts in parts per million downfield from TMS, assignment, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), and coupling constant, in that order.
A round bottom flask containing 10% KOH and ethanol as a solvent was filled with aurone (0.01 M) and N-substituted thiourea (0.01 M). For three hours, reflux was a reaction mixture. The mixture was then added to ice-cold water and filtered using a suction pump after this time. Ethanol was used to help the finished product recrystallize.



Compounds	R1	R2	R3
1a	C7H7O	C6H5	C6H5
1b	C6H4Cl	H	C6H5

2.2 Preparation of 5-(hydroxyl (4-methoxyphenyl) methyl)-5-(2-hydroxyphenyl)-1,3-diphenyl-2-thioxoimidazolidin-4-one (Thiohydantoin-1a)

2-(4-methoxybenzylidene) benzofuran-3(2H)-one (0.01 M) and 1,3-diphenylthiourea (0.01 M) were taking in round bottom flask along with 10% KOH and Ethanol as a solvent. A reaction mixture was reflux for 3 hours. After complete the reaction, the mixture was poured in to ice cold water and filter it by using suction pump. The final product recrystallized with Ethanol.

Mol. Formula $C_{29}H_{24}O_4N_2S$

Light yellow amorphous solid, M.P 226 °C, yield 71%, Elemental analysis (%):C,70.14; H,4.87; N,5.64; O,12.89; S,6.46; IR (KBr cm-1) 3548.78 (O-H), 3418.58 (N-H), 1690.05 (C=O), 1632.5 (Ar C-H),ESI-MS[M+H]+ Calculated for $C_{29}H_{24}O_4N_2S$ *m/z* 496.12, 497.15; 1H-NMR (500 MHz, DMSO): δ 3.76 (3H, s), 5.66 (1H, s), 6.85-7.37 (11H, 6.91 (ddd, *J* = 8.4, 1.1, 0.5 Hz), 8.03 (1H, ddd, *J* = 8.0, 1.3, 0.5 Hz).

2.3 Preparation of 5-((4-chlorophenyl)(hydroxy)methyl)-5-(2-hydroxyphenyl)-3-phenyl-2-thioxoimidazolidin-4-one (Thiohydantoin-1b)

2-(4-chlorobenzylidene) benzofuran-3(2H)-one (0.01 M) and 1-phenylthiourea (0.01 M) were taking in round bottom flask along with 10% KOH and Ethanol as a solvent. A reaction mixture was reflux for 3 hours. After complete the reaction, the mixture was poured in to ice cold water and filter it by using suction pump. The final product recrystallized with Ethanol.

Mol. Formula $C_{22}H_{17}O_3N_2SCl$

Faint yellowish crystalline solid, M.P. 228 °C, yield 74%, Elemental analysis (%): C, 62.19; H, 4.03; N, 6.59; O, 11.30; S, 7.55; Cl, 8.34. IR (KBr cm-1) 3616.5 (O-H), 3268.1 (N-H), 1682(Amide C=O), 1436 (Ar C=C), 755.2 (C-Cl); ESI-MS [M+H]+ Calculated for $C_{22}H_{17}O_3N_2SCl$: m/z 424.06, 426.06, 425.07, 427.07. 1H-NMR (500 MHz, DMSO) 5.58 (s, 1H), 7.04 (m, *J*=8.0, 7. 8 Hz, 1H), 7.48 (m, *J*=8.3, 1. 6, 0. 5 Hz, 8H), 8.02(m, *J*=8.0, 1.4 Hz, 1H).

3. Antimicrobial Screening

The Antibacterial activity was checked by following Zone Inhibition Method (Kirby-Bauer method). The MHA plates were inoculated by spreading with 100 µl of Bacterial culture, *Escherichia coli* (MTCC-452), *Pseudomonas aeruginosa* (MTCC-3541), *Mycobacterium tuberculosis* (MTCC-300), *Enterococcus faecalis*, *Aspergillus niger*, (MTCC-281), *Candida*. *Albicans*, (MTCC- 854). (Adjusted to 0.5 McFarland Unit - Approx cell density (1.5 X 108 CFU/mL) and followed by placing the discs containing 10 µl of different concentration (0 to 1000 mg/ml). One disc in each plate was loaded with solvent alone which served as vehicle control and Ciprofloxacin disc (10µg) were taken as positive control. The plates were incubated at 37 °C for 24 hrs. A clear zones created around the disc were measured and recorded.

3.1 Result and Discussion

The antimicrobial activities of synthesized compounds 1a and 1b, have been assayed at the concentration of 1000 µg/disc against some pathogens *viz*. bacteria *Escherichia*

coli (MTCC-452), *Pseudomonas aeruginosa* (MTCC-3541),*Mycobacterium tuberculosis* (MTCC-300), *Enterococcus faecalis*, and some fungi *viz*. *Aspergillus niger*, (MTCC-281), *Candida*. *Albicans*, (MTCC- 854). The efficacy of titled compounds is given in following table.

Table 1: Zone of inhibition (mm)

Compounds	Zone of inhibition (mm)					
	Bacterial pathogens				Fungal pathogens	
	E. coli	***P. aeruginosa***	***M. tuberculosis***	***E. faecalis***	***A. niger***	***C. Albicans***
1a	15.33	20.67	18	16.24	15	21
1b	12.14	12	9.50	11.46	10	13

The results of antimicrobial screening indicate that the titled compound shows good to moderate antimicrobial activity against tested bacteria. Here compound 1a shows highest antimicrobial activity than compound 1b due to electron donating group present at para position as well as phenyl group attached to nitrogen in thiohydantoins. These changes in functional groups cause changes in the biological activities of the compounds. The newly synthesized titled compounds are capable to cramp the growth of fungal and bacterial pathogens.

Conclusion

The presented data showed that the diversity of chemical synthesis of thiohydantoins has benefited many drug discovery projects. The chemical structure of these molecules possesses two main variable positions 3-N and 5-C where most of their derivatives could be synthesized. In present study compound 1a shows higher antimicrobial activity than 1b due to presence of electron donating group directly attached to benzene ring as well as nitrogen atom contains phenyl group.

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Conflicts of Interest

The authors declare no conflicts of interest.

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