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Synthesis and Characterization of 5-Substituted Hydantoins as Potential Antimicrobial Inhibitor: A Review Article

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Abstract: ***This work presents the synthesis, characterization and evaluation of a series of new multifunctional N-substituted hydantoin derivative for their antibacterial and antifungal activity. Elemental analysis, ^{1}H NMR, IR and mass spectroscopy were used to confirm the newly synthesized compound structure. The antibacterial and antifungal properties of each synthesized molecule were examined. The examined compound showed significant to moderate antimicrobial activity against the tested Gram-positive, Gram-negative, and fungal strains. The antimicrobial activities were influenced by the structure and concentration of the tested compounds as well as the type of test microorganisms. The examined hydantoin derivatives seem as drug-like candidate for further evaluation of biological activities examined.***

Keywords: Hydantoin, Drugs, Antimicrobial properties, Pharmacophores, Heterocycles

1. Introduction

The important heterocyclic moiety hydantoin has two nitrogen atoms organized in a five-membered ring and contains nitrogen. Researchers have examined the properties and chemistry of hydantoins and their derivatives for more than 140 years. Many physiologically active compounds contain the hydantoin moiety, which has important medical applications [1]. The synthesis and characterization of hydantoin derivatives, a noteworthy family of heterocyclic compounds, have garnered a great deal of interest [2]. Hydantoin derivatives have been found to have fascinating effects on a range of biological targets [3,4]. Hydantoins have been extensively researched because of their many applications in both medicine and commerce as necessary pharmacophoric moieties or skeletal components. Despite its small size, hydantoin offers four derivatizable areas and four hydrogen donors and acceptors. The activity of hydantoin derivatives is dependent on the location and kind of substitution of hydantoin rings. By altering the hydantoin core at N-1 or N-3, the molecule's properties are changed [5].

Edward and Nielsen looked into the effects of various alkyl and aryl groups on these locations on the hydantoin ring under different circumstances [6]. Furthermore, hydantoins are essential components in the chemical production of artificial and natural amino acids. Derivatives of hydantoin are considered preferred structures in medicinal chemistry and have been used widely. Hydantoins, for instance, are helpful as nonsteroidal antiandrogens (enzalutamide and nilutamide), antibiotics (nitrofurantoin), and anticonvulsants (phenytoin and mephenytoin). the chemical structure of the above-mentioned drugs having hydantoin ring that have received clinical approval.

One of the main components in lowering the burden of infectious diseases worldwide is the use of antimicrobial medications. The consistent rise in antimicrobial resistance is a major global public health concern [7]. The development of novel molecules to combat bacteria and fungi has become one of the most important areas of antibacterial and antifungal research today, as the resistance of dangerous bacteria and fungi to currently available antimicrobial drugs is rapidly becoming a major concern worldwide. For this reason, chemists nowadays face more challenges and demands in their quest to discover novel, potent antibacterial and antifungal drugs. By lowering excessive sPLA2 release, hydantoin derivatives may be able to alleviate symptoms. They have shown strong antibacterial and anti-inflammatory properties [8], [9], and [10].In light of this, and as part of our ongoing research into potential therapeutic compounds [11,12,13,14,15,16].At the same time, some hydantoin derivatives also have applications in the agrochemical area as bactericides, fungicides, and herbicides [17,18,19,20,21].

2. Need of the Study

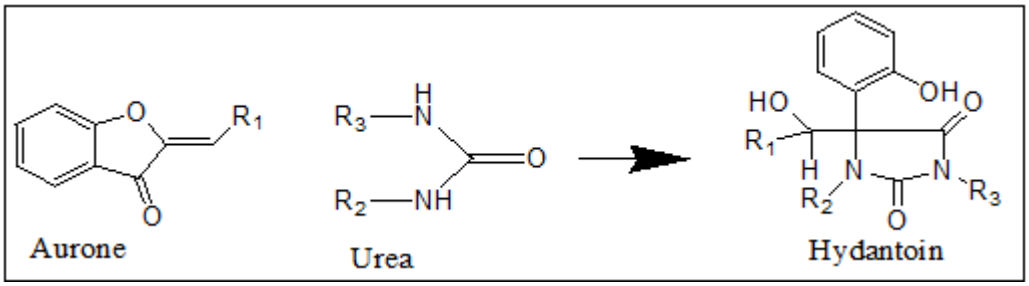
Even with the emergence of new infectious diseases and the growth of multi-drug resistant strains of microbial pathogens, infectious diseases continue to be a leading cause of death, particularly in underdeveloped nations. Antibiotic resistance is now a significant public health issue. The demand to create novel antibacterial and antifungal medicines with improved activity profiles and reduced toxicity is growing due to the quick emergence of resistance to the current antimicrobial medication portfolio [22].
Bacterial antibiotic resistance has emerged, making many antimicrobial drugs used to treat or prevent illnesses less effective [22]. New antimicrobial agents with broad-spectrum activity and a lower risk for the emergence of antibiotic resistance are desperately needed as a result. The major medical problem of bacterial and fungal resistance and the rapid rate at which it develops has therefore made the discovery and development of effective antibacterial and antifungal medications with novel mechanisms of action critical goals for infectious disease research programmers [23, 24]. The current generation of antimicrobial drugs has a number of disadvantages, including toxicity, drug resistance in microorganisms, and limited spectrum of action. The

emergence of novel bacterial pathogens and the development of increasingly effective antimicrobial medications have been the two main areas of research for the creation of new antimicrobial agents. The primary factors in the synthesis of efficacious medications are their rate of activity and structural characteristics. To create the potent antibacterial medication, a heterocyclic molecule has first been considered as a parent compound. Analyzing the extensive body of research on antibacterial literature reveals that heterocyclic compounds have been essential to the area of medicine. The fascinating biological significance of antibacterial pathogens has led to the urgency of drug discovery and the synthesis of new antimicrobial compounds; consequently, the design of new compounds to deal with these problems has become one of the most challenging targets in antibacterial and antifungal research today [25]. As a result, heterocycles are very popular in the field of pharmacology for their unique controlling properties within a drug, such as a solubility, lipophilicity, and polarity, and are also being investigated twice for the discovery of desired active drugs.

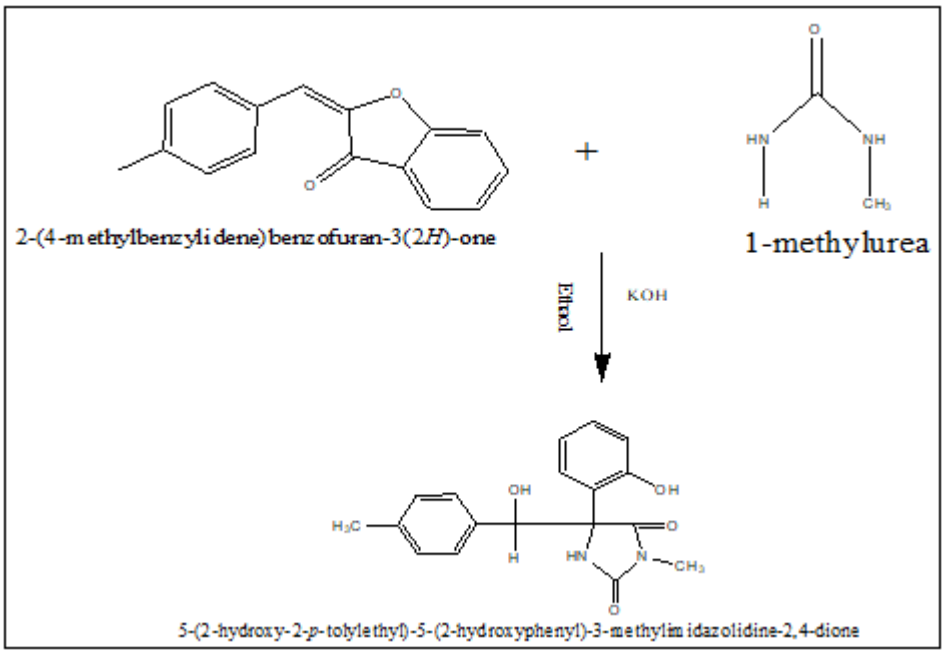
3. Material and methods

All chemicals and reagents used in this research were commercially sourced and of analytical grade. The purity of resultant compound was check by using TLC. The IR spectra were recorded in KBr by using FT-(IR Perkin Elmer-Spectrum RX-FTIR). Mass spectra were recorded on mass spectrometer while 1 HNMR were recorded on FT NMR Spectrometer (BrukerAvance Neo 500 MHz).

General Procedure for synthesis of hydantoin derivatives: - Equimolar Aurone and N-substituted urea were taking in round bottom flask along with KOH and Ethanol as a solvent. Areaction mixture was reflux for few hours. After this period, the mixture was poured in to ice cold water and filters it by using Buchner funnel and suction pump. The final product recrystallized with Ethanol



Synthesis of 5-(2-hydroxy-2-p-tolylethyl)-5-(2-hydroxyphenyl)-3-methylimidazolidine-2,4-dione (3a) :2-(4-methylbenzylidene) benzofuran- 3(2H)-one reflux withN-methyl urea in presence of KOH and appropriate ethanol solvent up to few hours. After completion ofreaction, cooled the mixture and poured in to ice coldwater. The solid product obtained which was filterand washed with dilute HCl and water. The productwas crystallized by using ethanol.



Mol. Formula: $C_{19}H_{20}N_2O_4$: Yellowish Crystalline solid. **m. p.** 244°C **yield** 72%, **Elemental analysis** (%): C, 67.05; H, 5.92; N, 8.23; O,18.80; **IR** (KBr cm-1) 3635.5 (OH), 3018 (=CH), 1629(C=N), 1436 (Ar C=C), **ESI-MS[M+H]** + Calculated for$C_{19}H_{20}O_5N_2$: m/z 340.14, 341.15, 342.15; **1 H-NMR**(500 MHz, DMSO) 2.20-2.30 (s, 3H), 2.25 (s, 1H), 3.03 (m, J=8.4,1.1 Hz, 11H), 3.62-4.65(m, 6H).

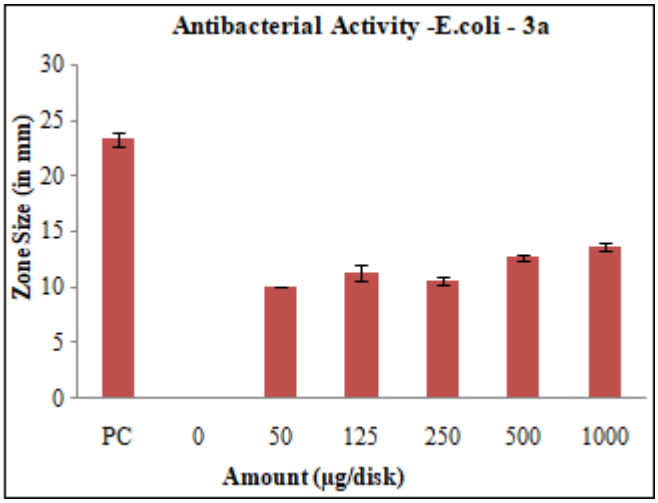
Antimicrobial activity

The disc diffusion technique was used to test for antimicrobial activity against various Gram-positive and Gram-negative bacterial and fungus strains in the newly synthesized compounds. The broth dilution method was used to determine the MIC of these molecules. A careful review revealed that two compounds had antimicrobial activity that was equivalent to that of the reference medications which are broad-spectrum antifungal and antibiotic agents, respectively. Additionally, these two compounds demonstrate lower MIC values against bacterial and fungal strains than reference drugs. Nearly both the drugs showed greater MIC values against Gram-negative bacterial strains than they did against Gram-positive bacterial strains when comparing the two groups of bacteria.

4. Result and Discussion

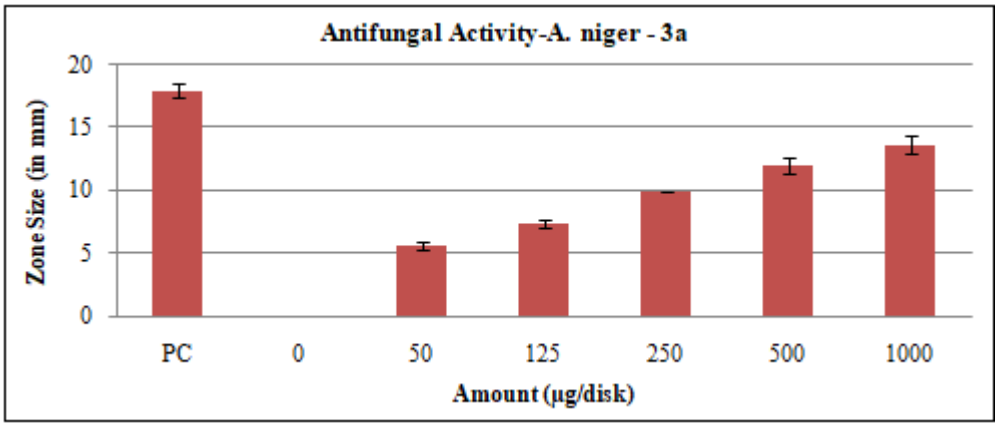
Bioassay	Antibacterial Activity
Test Organism	***E. Coli***
X Axis	Amount (µg/disk)
Y Axis	*Zone Size (in mm)*
Sample code	3a
Title	Antibacterial Activity-E.Coli–3a

Amount (µg/disk)	Plate A	Plate B	Plate C	Average	SD	SEM
PC	24	24	22	23.3333	1.1547	0.6666
0	0	0	0	0	0	0
50	10	10	10	10	0	0
125	10	12	12	11.3333	1.1547	0.6666667
250	11	10	11	10.6667	0.57735	0.3333333
500	13	12	13	12.6667	0.57735	0.3333333
1000	14	13	14	13.6667	0.57735	0.3333333



Bioassay	Antifungal Activity
Test Organism	***A. niger***
X Axis	Amount (µg/disk)
Y Axis	*Zone Size (in mm)*
Sample code	3a
Title	Antifungal Activity-A. niger –3a

Amount (µg/disk)	Plate A	Plate B	Plate C	Average	SD	SEM
PC	18	19	17	18	1	0.57735
0	0	0	0	0	0	0
50	5	6	6	5.66667	0.57735	0.33333
125	7	8	7	7.33333	0.57735	0.33333
250	10	10	10	10	0	0
500	11	13	12	12	1	0.57735
1000	13	15	13	13.6667	1.1547	0.66667



5. Conclusions

To sum up, we created and synthesized hydantoin derivatives in order to find novel substances that inhibit microbes. When these compounds were tested against strains of bacteria and fungi, both of them shown excellent efficacy. Broad-spectrum antibacterial action was demonstrated by the MIC ranges of the compounds against the gram-positive, gram-negative, and fungal pathogens under study.

Aim of the Study

To studies the antimicrobial activities of new hydantoin derivatives which may influenced to be used as chemotherapeutic means.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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