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Antioxidant and Antimicrobial Activities of Some Novel 2-Thiohydantoin Derivatives

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Abstract

Four new 2-thiohydantoin derivatives (4a-d) were synthesized from the reaction of maleimide derivatives (3a-d) with phenylisothiocyanate. The structures of synthetic compounds were characterized using Fourier-transform infrared spectroscopy (FT-IR), ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry. The antioxidant activity of the synthesized compounds showed inactive 4b and 4c compounds, moderately active 4a, and strongly active 4d, compared with vitamin C as positive control (IC_{50} values = 1.380, 1.726, 4.147, 8.085, and 9.826 µM, respectively). Antibacterial and antifungal activities of compounds showed that only compound 4b had an effect on *Pseudomonas aeruginosa*, *Candida albicans, and* Aspergillus niger species.

*Keywords***:** Bioactive heterocyclic compounds; 2-thiohydantoin; Antioxidant; Antibacterial; Antifungal.

Introduction

Bacteria, viruses, fungi, protozoa, and worms are main pathogenic organisms cause diseases such as hepatitis B and C, malaria, dengue, and tuberculosis [1]. The development of antimicrobial drugs based on their modes of mechanism to reduce or prevent resistant pathogens [2]. The problems of medical community could be reduce the risk of diseases caused by pathogenic used effective and low toxic antimicrobials and challenging request a capability of researches to design new antimicrobial drugs [3]. In addition, the increasing of fungal infections with limited therapeutic treatment, leads to discover novel antifungal drugs via set new approaches to target the chemical matter [4].

Recently, efficient methods for the preparation of thiohydantoin derivatives, other than the conventional multi-step methods were investigated [5,6]. The 2-thioxoimidazolidin-4-ones or 2-thiohydantoins are five-member heterocyclic systems with very reactive nuclei and cyclic thiourea cores [7]. The modification of substitution groups on 2-thiohydantoin always generate new biological activities [8], such as antimicrobial [9, 10], anti-neoplastic [11,12], anti-mutagenic [13], anti-ulcer and anti-inflammatory agents [14, 15], antiviral [16], and as pesticides [17], Scheme 1. Fenamidone is an example for 2-thiohydantoin derivatives, used in some fruits and vegetables to act as quinine outside inhibitors [18]. Thus, natural or man-made antioxidant substances play a role in the prevent/delay of cellular damage via the action of scavenging reactive oxygen species (ROS) [19]. Heterocyclic compounds have been approved for their antioxidant activities based on the type of substitutes function groups [20]. 2-Thiohydantoin is heterocyclic compound with important functions in the organic synthesis of new bioactive compounds [21]. A study reported that homo- 2-thiohydantoin derivatives are suitable for designing new 2-thiohydantoin derivatives as

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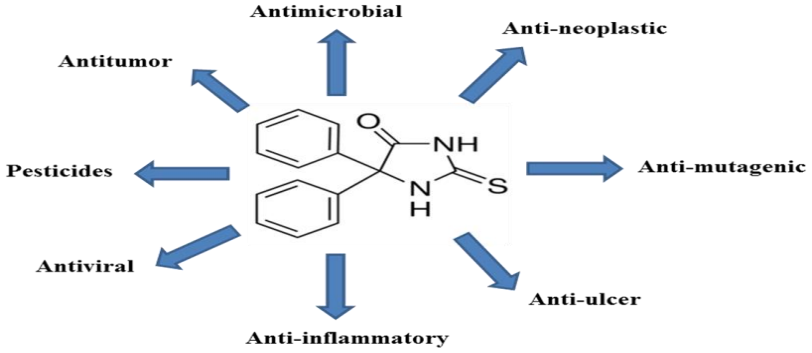
antioxidant agents [22]. Therefore, synthesis of new 2-thiohydantoin derivatives with high antioxidant activity will increase their functions and uses in the medical applications [23]. The current study was designed to synthesize and evaluate antioxidant and antimicrobial activities of new 2-thiohydantoin derivatives.



Scheme 1. Biological activities of 2-Thiohydantoin

EXPERIMENTAL

Chemistry

Gallenkamp apparatus used to measure melting point. The ^{1}H and ^{13}C-NMR spectra were recorded using deuterated solvents and tetramethylsilane (TMS) as an internal standard. Bruker DRX-500 spectrometer operating at 500 MHz and 125 MHz, the chemical shifts were indicated in (δ) ppm. Spectrophotometer FT-IR-1600 Perkin-Elmer was obtained from infrared spectra. Thin layer chromatography (TLC) used with Merck silica gel, and the spots were visualized in UV and I_2. Mass spectra were examined using the method using EI at 70 eV with Agilent Technologies 5975C Spectrometer.

Synthesis of compounds (3a-d): [24]

The preparation of substituted maleimides same as in literature.

Maleimides (0.01mol) mixed with benzohydrazide (0.01mol) in acetonitrile (25 ml), and continuous refluxing and stirring for 6-24 h. The residue was filtered and purified in ethanol.

Synthesis of 2-thiohydantoins (4a-d): [25]

Compound (3a-d) (0.01 mol) mixed in acetonitrile (25 ml) and reflux with phenylisothiocyanate (0.011 mol) for 16-36 h. The white solid was obtained after evaporation of the solvent then purified in ethanol:

N-(4-oxo-5-(2-oxo-2-(phenylamino) ethyl)-3-phenyl-2-thioxoimidazolidin-1-yl)benzamide (4a)

Yield 85 %; White powder; M.p.= 210-212 ^{o}C; FT-IR (KBr, cm^{-1}): 3354 (NH amide), 3138 (NH), 3057 (CH aromatic), 1743 (C=O) Asym.), 1687 (C=O sym.), 1666 (C=O amide), 1600, 1539 (C=C aromatic), 1215 (C=S); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.49 (s, 1H, H_d), 10.18 (s, 1H, H_e), 7.95 (d, J = 7.8 Hz, 2H, H aromatic), 7.71-7.05 (m, 13H, H aromatic), 4.92 (br.t, J = 4.0 Hz, 1H, H_c), 3.19-3.10 (m, 2H, H_a, H_b); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 184.49 C=S), 172.08 (C=O thioimidazole), 167.15 (C=O amide), 166.12 (NNHC=O), [139.37, 134.38, 132.98, 131.94, 129.47, 129.33, 129.22 , 129.05 , 128.99, 128.23, 123.80 , 119.57 (C-aromatic)] , 60.22 (CH_c), 35.46 (CH_aH_b); Ms (m/z): 444 (M^+).

N-(5-(2-((4-chlorophenylamino)-2-oxoethyl)-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)benzamide (4b)

Yield 75 %; White solid; M.p.= 220-223 ^{o}C; FT-IR (KBr, cm^{-1}): 3331 (NH amide), 3265 (NH), 3142 (CH aromatic), 1761 (CO Asym.), 1678 (CO Sym.), 1658 (C=O amide), 1552, 1489 (C=C aromatic), 1244 (C=S); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.46 (s, 1H, H_d), 10.32 (s, 1H, H_e), 7.93 (d, J = 7.9 Hz, 2H, H aromatic), 7.62-7.37 (m, 12H, H aromatic), 4.91 (br.t, J = 3.8 Hz, 1H, H_c), 3.22-3.13 (m, 2H, H_a, H_b); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 184.45 (C=S), 171.99 (C=O thioimidazole), 167.35 (C=O amide), 166.09 (NNHC=O), [138.30, 134.33, 132.98, 131.92, 129.47, 129.34, 129.15, 129.07, 129.05, 128.97, 128.21, 127.34, 121.12 (C-aromatic)], 60.17 (CH_c), 35.44 (CH_aH_b): Ms (m/z): 479 (M^+).

N-(5-(2-((4-bromophenylamino)-2-oxoethyl)-4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)benzamide (4c)

Yield 80 %; Light white solid; M.p.= 261-263 ^{o}C; FT-IR (KBr, cm^{-1}): 3332 (NH amide), 3261 (NH), 3057 (CH aromatic), 1759 (CO Asym.), 1668 (CO sym.), 1658 (CO amide), 1548, 1485 (C=C aromatic), 1244 (C=S); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.46 (s, 1H, H_d), 10.32 (s, 1H, H_e), 7.94-7.92 (m, 2H, H aromatic), 7.58-7.41 (m, 12H, H aromatic), 4.91 (br.t, J = 3.9 Hz, 1H, H_c), 3.18-3.16 (m, 2H, H_a, H_b); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 184.44 (C=S), 171.97 (C=O thioimidazole), 167.38 (C=O amide), 166.07 (NNHC=O), [138.72, 134.32, 132.97, 132.05, 131.93,

129.47, 129.34, 129.05, 128.96, 128.20, 127.04, 121.49, 115.35 (C-aromatic)], 60.15 (CH_c), 35.47 (CH_aH_b); Ms (m/z): 524 (M^+).

N-(4-oxo-5-(2-oxo-2-(p-tolylamino) ethyl)-3-phenyl-2-thioxoimid azolidin-1-yl)benzamide (4d) Yield 87 %; White solid; M.p.= 257-258 ºC; FT-IR (KBr, cm^{-1}): 3329 (NH amide), 3267 (NH), 3142 (CH aromatic), 1759 (CO Asym.), 1660 (C=O sym.), 1606 (amide), 1546, 1508 (C=C aromatic), 1269 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.49 (s, 1H, H_d), 10.08 (s, 1H, H_e), 7.97- 7.93 (m, 2H, H aromatic), 7.59-7.42 (m, 10H, H aromatic), 7.12 (d, J = 8.0 Hz, 2H, H aromatic), 4.89 (br.t, J = 3.9 Hz, 1H, H_c), 3.19-3.12 (m, 2H, H_a, H_b), 2.25 (s, 3H, CH_3); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 184.51(C=S), 172.08 (C=O thioimidazole), 166.87 (C=O amide), 166.09 (NNHC=O), [136.87, 132.97, 132.68, 131.94, 129.58, 129.46, 129.32, 129.04, 128.98, 128.22, 119.57 (C-aromatic)], 60.22 (CH_c) , 35.38 (CH_aH_b) , 20.92 (CH_3); Ms (m/z): 458 (M^+).

Antimicrobial activities

Antioxidant activity According to Al-Shawi et al. [**26**], used DPPH (2,2-Diphenyl1-picrylhydrazyl) method with some modification to examine the scavenger activity of new compounds. Different volumes (10-80) µl of synthesized compounds (4a-d) and vitamin C (1 mg/mL) were added to 200 µl of DPPH (1 mm) in 96 well/plate and left for 30 min in dark place. The absorbance was measured at 570 nm using a micro-plate reader (ELISA, Asyshitech., UK).

Antibacterial test

The method of diffusion was used to estimate the minimum inhibition concentration (MIC) of the compounds against three Gram-positive and Gram-negative pathogens **(***Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa (*ATCC 9027)*)*. Four concentrations (25, 50, 75, and 100) mg/ml of the compounds were applied to each plate. The plates were kept for 24 h at 36 ± 1ºC, under aerobic conditions. Zones of inhibition were in millimeters **[27]**. Cefotaxime (100 µg/ml) used as standard drug.

Antifungal test

To determine MIC of the compounds against two fungal species, *Candida albicans and Aspergillus niger*. Briefly, the fungal suspension in sterile saline solution (0.85%) was standardized to 10^6 conidia/mL. Each Petri dish contains 100 µl of fungal suspension. After a 10 minutes, 6-mm-diameter holes were punched and loaded with four concentrations (25, 50, 75, and 100) mg/ml. Dimethyl sulfoxide (DMSO) was used as control at 70%, and the fungicide tebuconazole (TEB) (Folicur 20EC) was used at 0.1%. The plates were incubated at 28 ± 2 °C, and the experiment was evaluated thrice. The evaluation was carried out after 72 h by measuring the diameter of the inhibition of the mycelial growth (clear zones of inhibition formed around the holes were considered indicative of antifungal activity) **[28]**. Fluconazole (100 µg/ml) used as standard drug.

Statistical analysis IC_{50} values of antioxidant activity to estimate IC_{50} value were performed by plotting dose-response curves vs the concentrations of synthetic compounds using GraphPad Prism version 8.1.

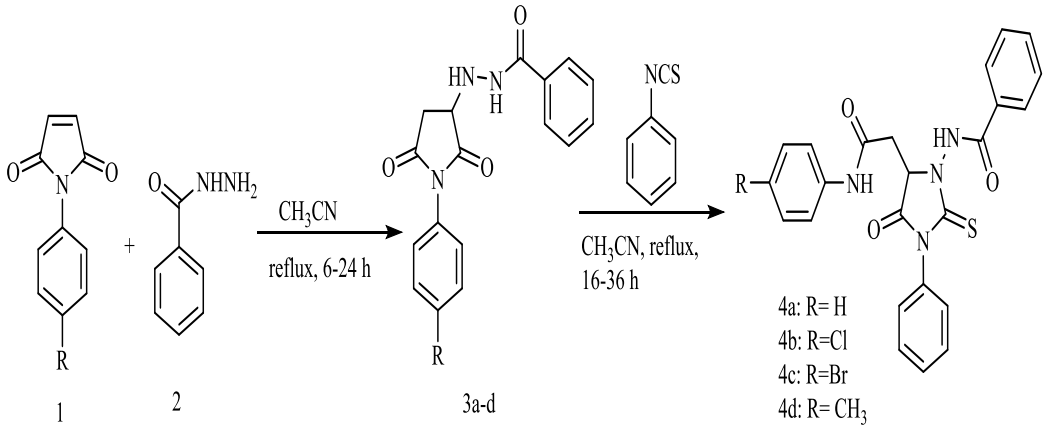
Results and discussions

Synthesis

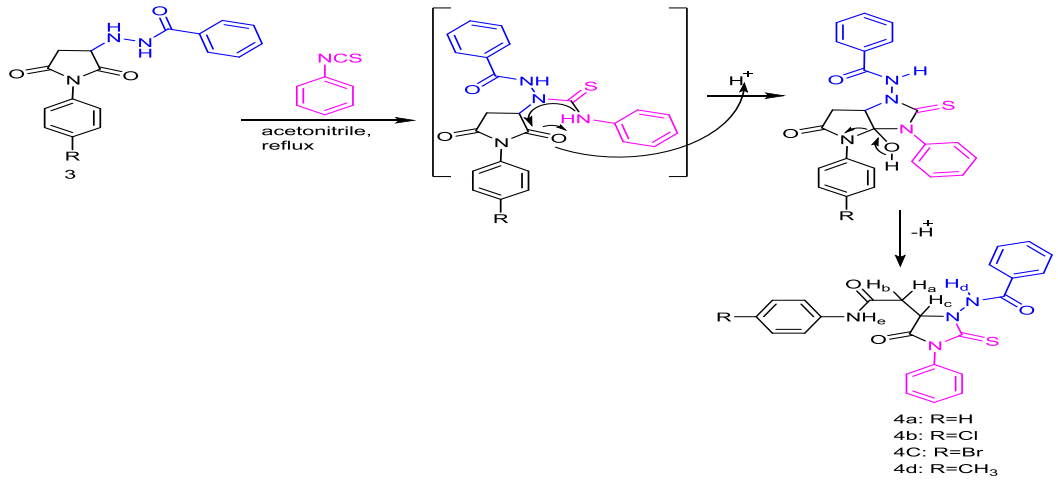
The 2-thiohydantoins (4a-d) were synthesized from substituted N-arylmaleimides (1) and benzohydrazide (2) via the Micheal addition in acetonitrile was followed by heating for 6 to 24 hours to yield a sufficient amount of the product (3a-d) **[29]**. Compounds (3a-d) were reacted with phenylisothiocyanate in acetonitrile with the presence of two drops of glacial acetic acid under reflux for 16 to 36 h, to allow the complete conversion of the starting material to compounds (4a-d) content with good yields, **Scheme 2**. The mechanism of the reaction between compounds 3a-d and phenylisothiocyanate in the presence of catalyst **[30, 31]**, **Scheme 3**.

The FT-IR of 2-thiohydantoins 4a-d showed characteristic frequencies at 1761-1606 for carbonyl group (C=O) and 1269-1215 cm^{-1} for thiocarbonyl (C=S) group. The absorption frequencies shown in the region of 3354 to 3329 and 3267 to 3138 cm^{-1} suggested the presence of -NH amide, and -NHPh groups, respectively.

The ^{1}H-NMR spectrum of compounds 4a-d showed two singlets at 11.49 to 11.6 ppm and 10.32 to 10.08 ppm attributed to the protons H_d and H_e, respectively. The ^{1}H-NMR spectra of compounds 4a-d showed characteristic patterns of an ABX system, because of the presence of two signals as a broad triplet at 4.92 to 4.89 ppm for the H_c and multiplet at 3.19 to 3.10 ppm corresponding to protons H_a and H_b, respectively. The aromatic protons rings showed multiplet signals in the region 7.97-7.37 ppm. The presences of all carbon atoms for compounds 4a-d are confirmed by ^{13}C-NMR spectra. For the compounds (4a-d), carbon signals of all C=O groups appeared in the 172.08-166.07 ppm region. The signals of the C=S group appeared in the 184.51-184.44 ppm region. The mass spectra of the 4a-d groups showed a molecular ion [M^+]: 444, 479, 524, and 458. The target structures of new compounds confirmed by mass spectra.



Scheme 2: Synthesis of 2-thiohydantoins derivatives (4a-d)



Scheme 3: The mechanism of 2-thiohydantoins derivatives synthesis (4a-d)

Antioxidant activity

Synthesis of new heterocyclic compounds with function as antioxidant activity will raise the biological importance. One report exhibited the antioxidant activities of 2-thiohydantoin derivatives, Kiec-Kononowicz et al., synthesized 20 compounds of fused 5,5-diphenyl and 5-arylidene-2-thiohydantoin and found they have weak antioxidant activities **[32]**. In this study, four new 2-thiohydantoin derivatives were synthesized and their antioxidant activities examined using simple and fast DPPH method. The results of estimated IC_{50} values showed lack of an antioxidant effect of compounds 4b and 4c, and moderate action for compound 4a. The 4d compound showed strong antioxidant activity compared with vitamin C (**Table** 2). The substituted function groups were shown to play a role in the scavenger activity of the hetero-bicyclic/tricyclic compounds **[32]**. Thus, stabilization of free radical of nitrogen atom for the aromatic ring linked with electron-donor methyl group in the para position 4d might increase its function as an antioxidant via the elimination of hydrogen atom by double conjugation with the oxygen group, and enhance free radical stability, rather than other subsisted functional electron-withdrawing 4b (Cl), 4c (Br), and 4a (H), **Fig** 1.

Antimicrobial activity

The diseases caused by microbial such as bacteria, archaea, fungi, protozoa, algae, and viruses are harmful to humanity. The studies about these pathogens are continuously presenting discoveries of

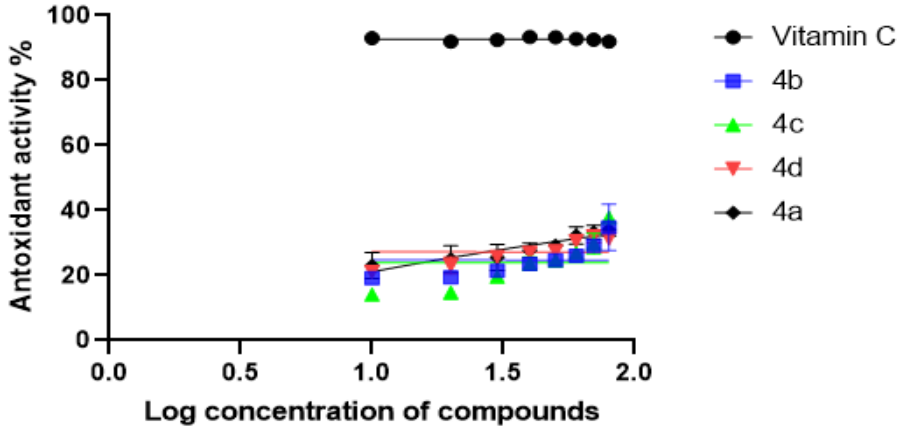


Fig 1. Antioxidant activity of the new compounds compared with vitamin C as positive control. GraphPad Prism 8.1 was used for analysis and estimating IC_{50}

new antimicrobial agents with less toxicity toward normal cells **[33, 34]**. 2-Thiohydantoin derivatives have been proposed as antibacterial **[35]**. In this study, the four new 2-thiohydantoin derivatives were examined against three types of pathogens (*S. aureus*, *E. coli*, and *P. aeruginosa*). The compounds 4b, 4c, and 4d showed zones of inhibition toward *P. aeruginosa (Gram-negative), a pathogen that causes diseases in plants, animals, and human. The MIC was estimated to be (100, 25, and 25) mg/ml, zones of inhibition (18, 12, and 13) mm, respectively, but was negative toward S. aureus and* E. *coli, while compound 4a was inactive. Compound 4b was has inhibition compared with the standard drug (*Cefotaxime, zones of inhibition= 23 mm).

In addition, the antifungal test with *C. albicans and A. niger, showed MIC values of compound 4b (100 and 25) mg/ml, zones of inhibition was 15 mm for on both fungal species, compared with standard drug (*Fluconazole, zones of inhibition = 20 and 18, respectively) mm. Compound 4b has an electron-withdrawing chloro group, compound 4c has an electron-withdrawing bromo group, and compound 4d has an electron-donor chloro group in the para position. These changes in functional groups cause changes in the biological activities of the compounds. Therefore, various MICs for both bacterial and fungal species were observed. Based on the types of functional groups and results, the compound 4b exhibited good effect on *P. aeruginosa*, *C. albicans and A. niger*, **Table** 1.

Table 1: Zones of inhibition of the compounds (4a-d) and standard drugs measured in millimeter (mm) against the selected bacterial and fungal species.

Compounds		***Antibacterial activity*** Zones of inhibition in mm			**Antifungal activity** Zones of inhibition in mm	
Symbol	R group	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albican*	*A. niger*
4a	H	NA	NA	NA	NA	NA
4b	Cl	NA	NA	18	15	15
4c	Br	NA	NA	12	NA	NA
4d	CH_3	NA	NA	13	NA	NA
*Standard	-	NT	NT	23	NT	NT
**Standard	-	NT	NT	NT	20	18

NA: No activity; **NT**: No tested; * Cefotaxime ; ** Fluconazole

Table 2. Antioxidant activity (IC_{50}) and antimicrobial activity (MIC) values of the synthesized compounds.

Symbol	Antioxidant activity (IC_{50}) in µM	*S. aureus*	*E. coli*	*P. aeruginosa* in mg/ml	*C. albicana* in mg/ml	*A. niger* in mg/ml
Vitamin C	9.826±038	-	-	-	-	-
4a	4.147	-	-	-	-	-
4b	1.380±093	-	-	100	100	25
4c	1.726±148	-	-	25	-	-
4d	8.085±086	-	-	25	-	-

Conclusion

Thiohydantoins are important class of heterocyclic compounds in the field of drugs discovery. 2-Thiohydantoins derivatives showed antimicrobial activities based on their functional groups. Thus, compound **4d** exhibited strong antioxidant activity. Compound **4b** inhibited Gram-positive bacteria (*P. aeruginosa*), and the two fungal species (*C. albicans and A. niger*). Therefore, the new compounds **4b** and **4d** could be serving in the development of new antioxidant and antimicrobial agents.

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Conflict of interests: There is no conflict of interest.

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