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SYNTHESIS, CHARACTERIZATION, AND ANTIOXIDANT ACTIVITY OF NOVEL HYDRAZONES OF PURINE

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ABSTRACT. A novel series of purine hydrazones (**1**-**5**) was synthesized in good yield from 6-chloropurine *via* the reaction with the corresponding hydrazone derivatives. All the synthesized compounds were characterized by spectral data, including FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry, thereby confirming their structures. The synthesized compounds were screened for their antioxidant activity by the DPPH method. Compounds **2** and **3** exhibited the highest DPPH radical-scavenging activity among the synthesized derivatives. However, their activities were lower than those of the reference antioxidant ascorbic acid (IC_{50} = 27.91 ± 0.84 μM).

KEY WORDS: Hydrazones, Purines, Antioxidant activity, DPPH, Ascorbic acid

INTRODUCTION

Reactive oxygen species (ROS), including superoxide anion, hydroxyl radical, and hydrogen peroxide, are continuously generated in living organisms as byproducts of normal cellular metabolism. Under physiological conditions, endogenous antioxidant defense systems maintain a delicate balance between the production and elimination of ROS. However, excessive generation of free-radicals or insufficient antioxidant protection results in oxidative stress, which has been implicated in the pathogenesis of numerous diseases, including cancer, diabetes mellitus, cardiovascular disorders, neurodegenerative diseases, and chronic inflammatory conditions [1-3]. Therefore, the development of effective antioxidant agents capable of scavenging free radicals and preventing oxidative damage remains an important objective in medicinal chemistry.

Hydrazones constitute an important class of Schiff base derivatives characterized by the presence of the azomethine (–C=N–NH–) functional group. These compounds have attracted considerable attention owing to their diverse biological activities, including antimicrobial, antitubercular, anticancer, anti-inflammatory, and antioxidant properties [4-6]. The antioxidant potential of hydrazones is generally attributed to their ability to donate electrons or hydrogen atoms to free radicals, thereby interrupting radical chain reactions. Moreover, the conjugated π-electron system and the presence of heteroatoms stabilize radical intermediates through resonance effects, enhancing their free-radical scavenging capacity [7-8].

Among heterocyclic systems, purine derivatives occupy a unique position in medicinal chemistry because they form the structural basis of several biologically essential molecules, including adenine, guanine, ATP, and numerous coenzymes [9-10]. Purine-containing compounds exhibit a broad spectrum of biological activities, including antiviral, anticancer, antimicrobial, anti-inflammatory, and enzyme-inhibitory effects [11-12]. The fused imidazole-pyrimidine ring system of purines provides multiple sites for molecular interactions and contributes significantly to their pharmacological versatility [13-14].

The molecular hybridization approach, which combines two pharmacologically important scaffolds within a single molecular framework, has emerged as an effective strategy for

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developing new bioactive compounds [15]. In this context, incorporating a hydrazone moiety into the purine nucleus is expected to generate compounds with enhanced biological activity due to the synergistic contribution of both pharmacophores. Several studies have demonstrated that heterocyclic hydrazones possessing extended conjugation and multiple heteroatoms exhibit promising antioxidant activity. Therefore, systematic evaluation of structurally diverse purine hydrazones may provide valuable information regarding the relationship between molecular structure and antioxidant activity. Despite the extensive studies on hydrazone derivatives and purine-based compounds independently, reports describing the antioxidant properties of purine hydrazones remain scarce.

Accordingly, the present work describes the synthesis of a series of novel purine hydrazone derivatives bearing 3-nitrophenyl, 1,3-benzodioxol-5-yl, 3-methoxy-4-hydroxyphenyl, 2,4-dichlorophenyl, and 2-bromophenyl substituents. The synthesized compounds were characterized by melting point, FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry spectroscopic techniques, which confirmed the structures of the compounds. The antioxidant activities of the compounds were evaluated using the *in vitro* free-radical-scavenging (DPPH) method [16].

EXPERIMENTAL

All solvents were obtained from Merck, New Jersey, USA. Thin layer chromatography (TLC) was performed on Silica gel 60F_{254} (Merck Millipore, Billerica, MA, USA). A PerkinElmer FT-IR spectrophotometer (PerkinElmer Inc., Waltham, MA, USA) was used for IR spectroscopy. The Gallenkamp (Electronic) melting point apparatus was used for melting point determination. ^{1}H-NMR spectra of the compounds were recorded on a Bruker NMR 700 MHz spectrometer (Bruker Corporation, Billerica, MA, USA). Mass spectrometry was performed using an Agilent 6320 ion trap mass spectrometer (MS) equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA) and a Waters Xevo G2-XS time-of-flight (TOF) MS.

General synthesis of purine hydrazone derivatives

A mixture of 6-chloropurine (1.54 g, 0.01 mol) and the hydrazone derivative (2.84 g, 0.01 mol) in ethanol was refluxed for 4 h. The mixture was concentrated and poured into ice-cooled water. The product was precipitated and filtered. The product was dried under vacuum. The product was recrystallized from ethanol. The purity of the compound was checked by thin-layer chromatography (TLC). The percentage yield was calculated. Melting points, FT-IR, ^{1}H-NMR, ^{13}C-NMR, and MS were determined.

*4-[(5,7-dihydro-4H-purin-6-yl) amino]-N'-[(Z)-(3-nitrophenyl) methylidene] benzohydrazide (**1**).* Yield: 85%; m. p.: 220-222 °C; FT-IR (KBr): ν (cm^{-1}): 2956, 1603, 1500, 1191, 1136, 1065, 946, 851, 790, 641, 550, 502; ^{1}H-NMR (700 MHz, DMSO-d_6) δ: 6.86 (1H, bs, NHPh, D_2O exchg.), 7.77-8.60 (10H, m, Ar-H), 11.0 (1H, s, CONH, D_2O exchg.), 12.10 (1H, s, NH, D_2O exchg.); ^{13}C-NMR (176.0 MHz, DMSO-d_6) δ: 120.2 (C_{12}), 121.2 (C_{16}, C_9), 124.6 (C_{14}), 129.0 (C_{13}), 129.1 (C_{15}), 130.9 (C_{25}, C_{26}), 131.4 (C_{23}), 133.8 (C_{27}), 135.3 (C_{22}), 136.7 (C_{11}), 137.6 (C_{21}), 148.7 (C_2, C_{24}), 150.6 (C_4, C_6), 163.0 (C_{17}), 192.3 (C_8); Mass (ESI) *m/z*: 403.2 $[M-1]^+$; Calc. for $C_{19}H_{16}N_8O_3$, 404.382.

*N'-[(E)-(2H-1,3-benzodioxol-5-yl) methylidene]-4-[(7H-purin-6-yl) amino] benzohydrazide (**2**).* Yield: 82%; m. p.: 210-212 °C; FT-IR (KBr) ν (cm^{-1}): 3431, 3319, 2969, 2354, 1590, 1022, 838, 787, 594, 470; ^{1}H-NMR (700 MHz, DMSO-d_6) δ: 6.10 (2H, s, OCH_2), 6.18 (1H, s, NHPh, D_2O exchg.), 7.00-8.42 (10H, m, Ar-H), 9.81 (1H, s, CONH, D_2O exchg.), 11.70 (1H, s, NH, D_2O exchg.); ^{13}C-NMR (176.0 MHz, DMSO-d_6) δ: 102.0 (C_{28}), 102.8 (C_{12}), 105.5 (C_9, C_{16}), 106.7 (C_{14}), 108.9 (C_{13}), 120.3 (C_{15}), 123.7 (C_{25}), 129.3 (C_{26}), 131.9 (C_{23}), 142.3 (C_{27}), 147.7 (C_{22}), 148.4

(C_{11}), 148.8 (C_{21}), 149.5 (C_2), 150.5 (C_{24}), 150.6 (C_4), 153.2 (C_6), 162.9 (C_{17}), 191.4 (C_8); Mass (ESI) *m/z*: 402.2 $[M+1]^+$; $C_{20}H_{15}N_7O_3$, 401.378.

*N'-[(E)-(4-hydroxy-3-methoxyphenyl) methylidene]-4-[(7H-purin-6-yl) amino] benzohydrazide (**3**).* Yield: 83%; m. p.: 200-202 °C; FT-IR (KBr) ν (cm^{-1}): 2973, 1655, 1443, 1276, 1051, 951, 767, 681, 598, 481; ^{1}H-NMR (700 MHz, DMSO-d_6) δ: 3.84 (3H, s, OCH_3), 6.86 (1H, s, NHPh, D_2O exchg.), 6.97-8.77 (10H, m, Ar-H), 9.77 (1H, s, CONH, D_2O exchg.), 11.77 (1H, s, NH, D_2O exchg.); ^{13}C-NMR (176.0 MHz, DMSO-d_6) δ: 56.0 (C_{29}), 109.4 (C_{12}), 115.8 (C_{16}), 120.5 (C_9), 122.55 (C_{14}), 126.2 (C_{13}), 128.9 (C_{15}), 129.1 (C_{25}, C_{26}), 148.5 (C_{23}, C_{27}), 148.6 (C_{22}), 149.4 (C_{11}), 150.0 (C_{21}), 150.3 (C_2, C_{24}), 153.5 (C_4, C_6), 162.8 (C_{17}), 191.4 (C_8); Mass (ESI): *m/z* = 403.2 $[M]^+$, 404.2 $[M+1]^+$; $C_{20}H_{17}N_7O_3$, 403.394.

*N'-[(E)-(2,4-dichlorophenyl) methylidene]-4-[(7H-purin-6-yl) amino] benzohydrazide (**4**).* Yield: 80%; m. p.: 215-217 °C; FT-IR (KBr) ν (cm^{-1}): 2966, 1669, 1576, 920, 846, 638, 561, 504, 455; ^{1}H-NMR (700 MHz, DMSO-d_6) δ: 6.63 (1H, bs, NHPh, D_2O exchg.), 7.52−8.82 (10 H, m, Ar-H), 10.28 (1H, s, CONH, D_2O exchg.), 12.0 (1H, s, NH, D_2O exchg.); ^{13}C-NMR (176.0 MHz, DMSO-d_6) δ: 115.0 (C_{12}), 118.0 (C_{16}), 119.8 (C_9), 127.0 (C_{14}), 128.4 (C_{13}, C_{15}), 128.9 ($C_{25,}$ C_{26}), 129.8 (C_{23}), 134.2 (C_{27}), 135.4 (C_{22}), 140.0 (C_{11}), 142.6 (C_{21}), 143.0 (C_2, C_{24}), 150.0 (C_4), 151.9 (C_6), 163.3 (C_{17}), 189.4 (C_8); Mass (ESI) *m/z*: 427.1 [M+1], 428 $[M+2]^+$; $C_{19}H_{13}Cl_2N_7O$, 426.258.

*N'-[(E)-(2-bromophenyl) methylidene]-4-[(7H-purin-6-yl) amino] benzohydrazide (**5**).* Yield: 82%; m. p.: 225-227 °C; FT-IR (KBr) ν (cm^{-1}): 3337, 3216, 2972, 1591, 1280, 1187, 1021, 927, 839, 750, 677, 616, 491; ^{1}H-NMR (700 MHz, DMSO-d_6) δ: 6.72 (1H, bs, NHPh, D_2O exchg.), 7.68-8.86 (11H, m, Ar-H), 10.78 (1H, s, CONH, D_2O exchg.), 11.82 (1H, s, NH, D_2O exchg.); ^{13}C-NMR (176.0 MHz, DMSO-d_6) δ: 114.3 (C_{12}), 120.1 (C_{16}, C_9), 123.7 (C_{14}), 127.5 (C_{13}), 128.5 (C_{23}, C_{15}), 129.0 (C_{25}), 131.8 (C_{26}), 133.5 (C_{27}, C_{22}), 133.6 (C_{11}), 142.4 (C_{21}), 146.0 (C_2, C_{24}), 150.8 (C_4), 151.0 (C_6), 163.1 (C_{17}), 192.1(C_8); Mass (ESI) *m/z*: 436.1 $[M]^+$, 437.1 $[M+1]^+$, 438.1 $[M+2]^+$, 439.0 $[M+3]^+$; $C_{19}H_{14}BrN_7O$, 436.264.

DPPH radical scavenging activity assay

The stock solution was made by dissolving 24 mg DPPH in 100 mL methanol (80%). The working solution was obtained by diluting the DPPH solution with methanol to obtain an absorbance of about 0.941 ± 0.01 at 517 nm. The assay was performed in a 96-well plate to screen a series of synthesized compounds. An aliquot of 200 µL of DPPH solution was mixed with 10 µL of the samples. We tested compounds at a concentration of 100 µM. Concentrations were selected based on trial and error to fit the range of concentrations that can fully epitomize the rational change of antioxidant activity with the increasing concentration of the samples. Also, we assumed that such a range of concentrations is suitable for the smooth calculation of $IC_{50.}$ The plate was covered with foil to avoid light and incubated at room temperature in the dark for 10 min. The absorbance of the solution was measured at 517 nm against a blank solution using a microplate reader (ELX 800). Ascorbic acid was used as a reference compound. The decrease in absorbance was correlated with the radical scavenging potential of test samples. The percentage of inhibition was calculated as follows:

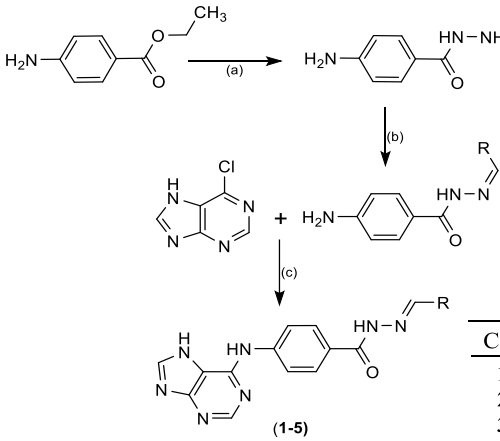
DPPH scavenging (%) =[Ac−As)/Ac] ×100.

Where Ac is the absorbance of the DPPH solution and As is the absorbance of the test compound in the presence of DPPH solution. Each sample was analyzed in triplicate, and all the values were subtracted from the blank absorbance before calculation. Due to a restricted concentration range (four doses), the IC_{50} values were estimated via manual interpolation of the

nonlinear best-fit model on the scatter gradient (R = 0.9928) in GraphPad Prism 10, representing the concentration at exactly 50% inhibition.

RESULTS AND DISCUSSION

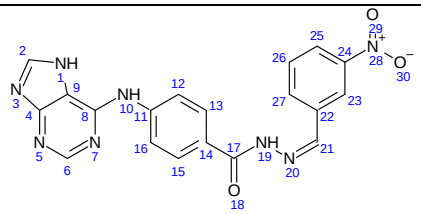
The synthetic route adopted for the preparation of the target purine hydrazones (**1-5**) is outlined in Scheme 1. The desired compounds were obtained through the reaction of 6-chloropurine with the corresponding hydrazone intermediates in ethanol under reflux conditions. The hydrazide was obtained from benzocaine by treating it with hydrazine hydrate 99%. The reaction of the hydrazide with substituted aldehydes in ethanol and glacial acetic acid forms hydrazones. The reaction proceeded smoothly and afforded the target products in good yields of 80-85%. The formation of the desired compounds was attributed to nucleophilic substitution of the chlorine atom at the C-6 position of the purine ring by the amino group of the hydrazone precursor, yielding the corresponding purine-linked hydrazones.

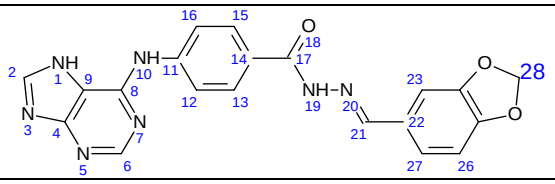
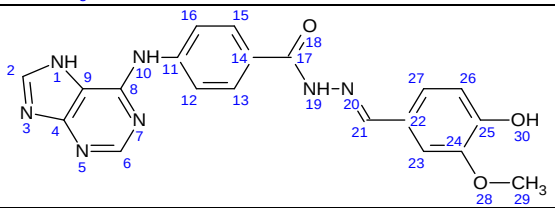
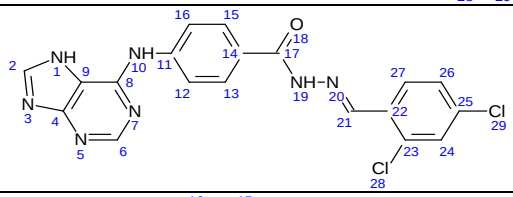
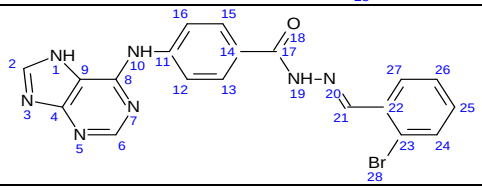


Compd.	R
1	3-Nitrophenyl
2	1,3-Benzodioxol-5-yl
3	3-Methoxy-4-hydroxyphenyl
4	2,4-Dichlorophenyl
5	2-Bromophenyl

Scheme 1. Reaction scheme for the synthesis of compounds (**1-5**). (a): Hydrazine hydrate 99%, Ethanol, reflux 4 hr. (b) RCHO, CH_3COOH, Ethanol, reflux 4 hr.; (c) Ethanol, reflux 1 hr.

Table 1. Structures of the synthesized compounds (**1-5**).

Compound	Structure
1	

2	
3	
4	
5	

The synthesized compounds were isolated as stable solids and purified by recrystallization from ethanol. The structures of the prepared compounds were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. The analytical data were in good agreement with the proposed molecular structures. The FT-IR spectra of compounds **(1-5)** exhibited characteristic absorption bands corresponding to the hydrazone and purine functionalities. The NH stretching vibrations of the hydrazide and purine NH groups appeared as broad bands in the region of 2956-3431 cm^{-1}. The carbonyl group of the hydrazide moiety showed a strong absorption band around 1590-1669 cm^{-1}. The azomethine (C=N) functionality was identified by absorption bands in the range of 1443-1669 cm^{-1}, confirming successful condensation between the aldehydes and hydrazide precursor. Additional characteristic bands were observed depending on the substituent present on the aromatic ring. The ^{1}H-NMR spectra of compounds **(1-5)** provided strong evidence for the formation of the target hydrazones. All compounds displayed signals corresponding to aromatic and heteroaromatic protons in the region δ 6.72–8.86 ppm. The hydrazide NH proton appeared as a singlet in the downfield region between δ 9.77 and 11.00 ppm due to hydrogen bonding effects. The purine NH proton resonated further downfield at δ 11.70–12.10 ppm and disappeared upon D_2O exchange, confirming its assignment. Compound **2** exhibited a characteristic singlet at δ 6.10 ppm corresponding to the methylenedioxy (-OCH_2O-) protons of the piperonal moiety. Similarly, compound **3** showed a singlet at δ 3.84 ppm assigned to the methoxy group. The presence of these characteristic resonances provided additional confirmation of the successful incorporation of the respective aromatic substituents into the hydrazone framework. The ^{13}C-NMR spectra further supported the proposed structures. Signals attributable to the amide carbonyl carbon appeared in the region δ 189.4-192.3 ppm. The purine ring carbons and azomethine carbon resonated within the expected aromatic heterocyclic region. Compounds containing oxygenated aromatic substituents exhibited characteristic resonances between δ 147 and 154 ppm corresponding to oxygen-bearing aromatic carbons. For compound **2**, the

methylenedioxy carbon appeared near δ 102 ppm, while compound **3** showed the methoxy carbon resonance at approximately δ 56 ppm. These observations were consistent with the assigned structures. The mass spectra of compounds **(1-5)** showed molecular ion peaks corresponding to their expected molecular weights. Compound **1** displayed a molecular ion peak at *m/z* 403.2 $[M-1]^+$, while compounds **2** and **3** showed molecular ion peaks at *m/z* 402.2 $[M+1]^+$ and 403.2 $[M]^+$, 404.2 $[M+1]^+$, respectively. The chlorinated derivative **4** exhibited molecular ion peaks at *m/z* 427.1 $[M+1]^+$, 428 $[M+2]^+$. The bromo derivative **5** exhibited molecular ion peaks at *m/z* 436.1 $[M]^+$, 437.1 $[M+1]^+$, 438.1 $[M+2]^+$. These values were in excellent agreement with the calculated molecular masses, confirming the molecular composition of the synthesized compounds.

Antioxidant activity

The antioxidant activities of compounds (**1-5**) were evaluated using the DPPH free-radical scavenging assay, and the results are presented in Table 2.

Table 2. IC_{50} values (half-maximal inhibitory concentration/dose inducing 50% inhibition of radicals) in the DPPH assay. Data are represented as mean ± SEM (n=3).

Compd.	IC_{50} (μM) ± SEM
1	70.05 ± 1.27
2	37.92 ± 1.23
3	35.41 ± 1.27
4	>100
5	67.50 ± 1.91
Ascorbic acid	27.91 ± 0.84

The activity was expressed as IC_{50} values, representing the concentration required to scavenge 50% of DPPH radicals. Among the synthesized compounds, compound **3** showed the highest antioxidant activity (IC_{50} = 35.41 ± 1.27 μM), followed closely by compound **2** (37.92 ± 1.23 μM). Although their activities were lower than the reference antioxidant ascorbic acid (IC_{50} = 27.91 ± 0.84 μM), both compounds showed stronger radical-scavenging activity than the other synthesized compounds. In contrast, compounds **1** and **5** showed only moderate activity with IC_{50} values of 70.05 ± 1.27 μM and 67.50 ± 1.91 μM, respectively, whereas compound **4** displayed the weakest activity with an IC_{50} value exceeding 100 μM. The observed antioxidant activities can be rationalized based on the electronic nature of the substituents attached to the hydrazone framework. Compound **3**, containing a 4-hydroxy-3-methoxyphenyl moiety, exhibited the strongest activity among the synthesized derivatives. Enhanced activity may be attributed to the presence of the phenolic hydroxyl group, which can readily donate a hydrogen atom to neutralize free-radicals. Furthermore, the methoxy substituent increases electron density on the aromatic ring and stabilizes the resulting phenoxy radical through resonance, thereby facilitating radical scavenging. Compound **2**, bearing a methylenedioxy-substituted aromatic ring, also demonstrated potent antioxidant activity. The electron-rich oxygen atoms of the methylenedioxy group contribute to electron delocalization and stabilization of radical intermediates, which may account for its favorable DPPH scavenging activity. The comparable activities of compounds **2** and **3** suggest that oxygen-containing electron-donating substituents play a crucial role in enhancing antioxidant properties. On the other hand, compound **1,** containing a nitro substituent, exhibited only moderate activity. The nitro group is a strong electron-withdrawing substituent that reduces electron density on the aromatic system and consequently diminishes the ability of the molecule to donate electrons or hydrogen atoms to free-radicals. Similarly, compound **5**, possessing a bromine substituent, showed moderate activity, indicating that halogen substitution does not favor efficient radical scavenging. Compound **4**, incorporating two chlorine atoms at the 2 and 4-

positions of the aromatic ring, was the least active derivative. The strong electron-withdrawing effect of the dichloro substituents likely decreases the electron-donating capability of the hydrazone system, thereby reducing its antioxidant efficiency. Additionally, steric effects associated with ortho-substitution may adversely affect molecular planarity and conjugation, further diminishing radical stabilization. The results suggest that electron-donating substituents, particularly hydroxyl and methoxy groups, enhance antioxidant activity, whereas electron-withdrawing halogen and nitro substituents reduce radical scavenging potential. These findings suggest that incorporation of phenolic and oxygen-containing functionalities into the purine hydrazone framework represents a promising strategy for the development of potent antioxidant agents.

CONCLUSION

A new series of novel synthesized compounds **(1-5)** was synthesized, characterized by spectral data, and tested for their antioxidant activities. The DPPH assay was chosen because it allows rapid quantification of the antioxidant capacity of new compounds. All compounds were first screened for their antioxidant activity at a 100 µM concentration. Compounds **2** and **3** exhibited the highest DPPH radical-scavenging activity among the synthesized compounds, with IC_{50} values of 37.92 ± 1.23 µM and 35.41 ± 1.27 µM, respectively. The IC_{50} of the standard drug ascorbic acid (Asc) was 27.91 ± 0.84 µM. Considering these results, it can be suggested that compounds **2** and **3** will be further tested for various antioxidant activities. These compounds warrant further antioxidant evaluation using complementary assays and biological models.

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Data availability

The data supporting this study's findings are available from the corresponding author upon request. Samples of the compounds **(1-5)** in pure form are available from the authors.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

M. A. Bhat: Conceptualization, Data curation, Funding acquisition. M. A. Al-Omar: Project administration, Investigation.

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