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Study of Some Heterocyclic Compounds Made from a New 4(3*H*)-Quinazolinone and Their Biological and Antioxidant Activities

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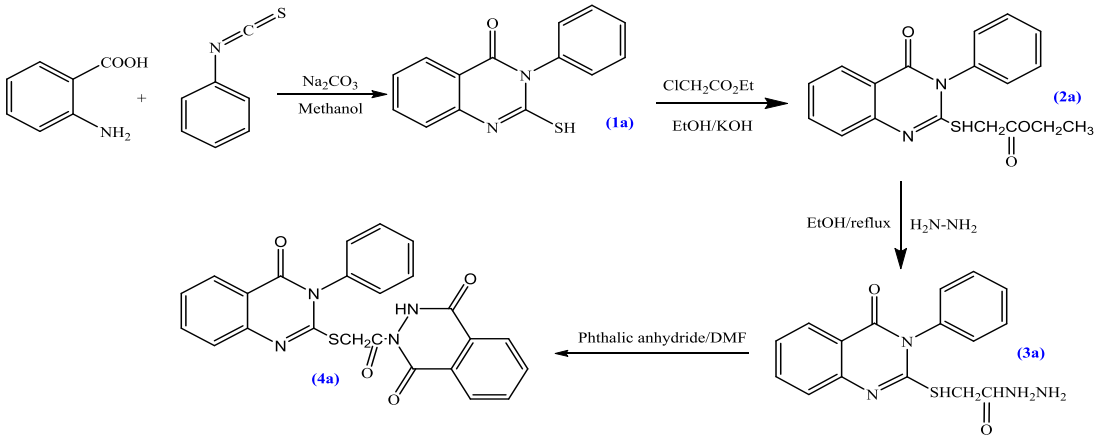
ABSTRACT

The present study aimed at synthesizing new anti-inflammatory quinazolinone derivatives containing heterocyclic moieties by several methods and evaluates their *in vitro* anti-inflammatory, anti-oxidant, and biological activities. The chemical structures of the compounds synthesized were confirmed by spectral analysis, such as FT-IR, UV, GCMS, and ^{1}H-NMR. The anti-inflammatory effect of these compounds was evaluated using the inhibition of denaturation method of bovine serum albumin (BSA) and the results have shown significant *in vitro* activity. The antioxidant activity was evaluated using nitric oxide with a hydroxyl radical scavenging assay, which showed a potential in radical scavenging due to the of electron donating substituent existence on substituted aldehydes. The antifungal and antimicrobial activity of the synthesized compounds against Fungi (*C.albicans* and *A.niger*), gram-positive (*S.aureus* and *S.pyogenes*) and gram-negative (*E.coli* and *P.aeruginosa*) have been studied. The results showed a high activity against gram negative bacteria (*E.coli* and *P.aeragines*) appeared for all compounds except for compound (**1a**) which showed a moderate activity against *E. coli* and weak against (*P.aeragines*). More studies are required to check confirm the antioxidant and biological activities of quinozalinone derivatives.

GRAPHICAL ABSTRACT



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Introduction

Quinazolinones are fused heterocyclic compounds that constitute the building block of numerous natural products and synthetic analogs [1]. Quinazolinones are classified into the five different categories, depending on the patterns of ring system substitution [2]. These are; 2,4-disubstituted-4(3*H*)-quinazolinones, 2,3-disubstituted-4(3*H*)-quinazolinones, 4-substituted-quinazolines, 3-substituted-4(3*H*)-quinazolinones, and 2-substituted-4(3*H*)-quinazolinones. Quinazolinones are also classified into three types depending on the position of the keto or oxo groups [3], namely; 2(1*H*)-quinazolinones, 4(3*H*)-quinazolinones, and 2,4(1*H*, 3*H*)-quinazolinedione. Out of these three types, the 4(3*H*)-quinazolinones structures are most predominant, either as intermediates or as natural products in many proposed biosynthetic pathways [4, 5].

Literature surveys revealed that synthesis of quinazolinones is achieved by the use of anthranilic acid [6-9], 2-aminobenzamide [10], and 2-aminobenzonitril, or their derivatives [6]. Quinazolinone based natural products that demand more structurally complex precursors have been constructed indirectly via thioamide formation, oxidation of dehydro-quinazolinone, and aza-witting condensation [11, 12]. Derivatives of quinazolin-4(3*H*)-ones are heterocyclic compounds with multilateral nitrogen. These compounds are known as promising biologically active compounds [13]. Depending on the nature of substituents in the ring system, the compounds of 4(3*H*)-quinazolinone were reported to possess different biological, anti-fungal, anti-bacterial, anti-tubercular, anti-viral, anti-cancer, and anticonvulsant activities [14-21].

In light of the growing number of applications in recent years, there has been an enormous increase in interest among biologists and chemists in the synthesis and bioactivity of thiazolidinone derivatives. The constant generation of oxygen derivatives free radicals *in vitro* is done by metabolic processes that are specifically occur [22]. The resulted radicals have the ability to react with most molecules including DNA, lipids, lipoproteins, and proteins. A wide range of human illnesses are controlled by these biological molecules such as cancer, cataract, coronary artery diseases, hemorrhagic shock, arthritis, HIV, and degenerative brain diseases that is age-related [23]. Therefore, it is necessary that researchers find an effective and new therapeutic free radical scavenger. Therefore, it was important to synthesize a biologically active new series of 4(3*H*)-quinazolinone derivatives and assessing their biological activities by disc diffusion method and using superoxide radical and free radical scavenging to evaluate the antioxidant properties, with hope to produce new, less toxic, and more active synthetic antibacterial and antioxidant agents.

Materials and Methods

All chemicals and solvents used in this study were of analar grade. They were available with high purity from (Sigma-Aldrich, Alfa-Aesar, and Fluka) suppliers and used without required purification. Melting points of the synthesized compounds were checked using digital apparatus. The compounds purity was further checked on TLC plates using benzene, chloroform, acetone, and water as the eluent. FT-IR measurements were recorded on Shimadzu Model FT-IR 8400 in the range (4000-600) cm^{-1}. UV-Visible 160 spectrophotometer - Shimadzu was utilized using ethanol to obtain the identification spectra of the synthesized compounds. ^{1}H-NMR spectra were obtained using 300 MHz Bruker Ultra Shield in DMSO-d_6 as the solvent.

*Synthesis 2-mercapto-3-phenylquinazolin-4(3H)-one [24] (**1a**)*

A mixture of (0.004 mol, 0.548 g) anthranilic acid and (0.04 mol, 0.424 g) of Na_2CO_3 were dissolved in 35 mL methanol. (0.04 mol) of phenyl isothiocyanate was added dropwise with stirring. The mixture was refluxed for 6 h, and then acidified with dilute HCl until the pH level of solution reached (6). The white precipitate was filtered, washed with distilled water, and

recrystallized from appropriate solvent. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.19-1.24 (t, J=3.2 Hz, 3H), 3.97 (s, 2H), 4.10-4.17 (q, J= 1.6 Hz, 2H), and 7.49-8.09 (m, 9H).

*Synthesis of ethyl 2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio) acetate [25] (**2a**)*

Compound (**2a**) was prepared by dissolving (0.01 mol, 2.5 g) of (**1a**) with (0.01 mol, 0.56 g) of KOH in 25 mL absolute ethanol, and then (0.01 mol, 1.23 g) of ethyl chloroacetate was added to the solution dropwise with stirring and refluxed for 8h. The resulting mixture was cooled and poured into ice water with stirring. The separated solid was filtered, and recrystallized from appropriate solvent. 1.19-1.24 (t, J=3.2 Hz, 3H), 3.97 (s, 2H), 4.10-4.17 (q, J=1.6 Hz, 2H), and 7.49-8.09 (m, 9H).

Synthesis of 2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)

*Acetohydrazide [25] (**3a**)*

The mixture of (0.01 mol, 3.4 g) of (**2a**) and 10 mL of 80% hydrazine hydrate dissolved in 15 mL ethanol absolute was continued to reflux for 10 h, and then the mixture resulted was cooled to room temperature before being poured into ice crushed water with continuous stirring. The final product solid was then filtered and recrystallized using appropriate solvent. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 2H), 5.22 (s, 2H), 7.05-8.23 (m, 9H), and 9.32 (s, 1H).

*Synthesis of 2-(2-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio)acetyl)-2,3-dihydrophthalazine-1,4-dione [26] (**4a**)*

(0.004 mol, 1.3 g) of (3a) was dissolved in 20 mL DMF and (0.004 mol, 0.59 g) of phthalic anhydride which was already dissolved in DMF was added gradually to hydrizide compound. The mixture was refluxed for 6 h, cooled at room temperature, and then filtered to separate the solid for recrystallization from appropriate solvent. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 2H), 7.0-8.32 (m, 13H), and 9.25 (s, 1H).

Antimicrobial activity

Fungi (*C.albicans*, *A.niger)*, gram-positive *(S.aureus* and *S.pyogenes*) and gram-negative (*E.coli* and *P.aeragines)* Microbial strains bacteria panel were tested *in vitro* against synthesized compounds {(**1a**), (**2a**), (**3a**), and (**4a**)} individually to check the antimicrobial screening effects. The previously mentioned bacteria types were cultured at 37 °C overnight in potato dextrose agar medium and nutrient. Microbial strains were collected at Al-Mustansirya University, College of Science, Biology Department, Baghdad, Iraq.

In Vitro Anti-Inflammatory Activity

The activity of anti-inflammatory was screened using albumin denaturation inhibition technique for the synthesized compounds (**1a**), (**2a**), (**3a**), and (**4a**). This test included the dissolution of compounds in dimethyl formamide (DMF)-minimum amount- and the dilution with phosphate buffer (pH 7.4, 0.2 M). The DMF concentration was less than 2.0% in final solutions. Different concentrations (25, 50, 75, and 100) µg/mL test solution (1 mL) of drug were mixed with 1 mL of 1% albumin solution in phosphate buffer before being incubated for 15 min at 27±1 °C. Keeping the reaction mixture at (60±1 °C) has stimulated the denaturation in water bath for 10 min. After cooling down the reaction mixture, Schimadzu 1800 UV-Visible Spectrophotometer was used to measure the turbidity at 660 nm. The control (no-drug added) denaturation inhibition percentage was calculated. All experiments where repeated three times before taking the average of each one.

$$\% \text{ of inhibition} = \frac{V_c - V_t}{V_t} \times 100$$

Where, V_c and V_t are the mean absorbance values of control and test group, respectively [27-29].

Nitric oxide radical scavenging activity

The nitric oxide radical scavenging activity of the synthesized compounds {(**1a**), (**2a**), (**3a**), and (**4a**)} was assayed according to the method of Marcocci *et al.* [30]. Nitric oxide was generated from sodium nitroprusside and nitrite formed

was measured by the Greiss reaction. Sodium nitroprusside in aqueous solution at physiological pH spontaneously generates nitric oxide [30, 31], which interacts with oxygen to produce nitrite ions that can be estimated by the use of Greiss reagent. Scavengers of nitric oxide compete with oxygen leading to reduce production of nitric oxide [32]. About 0.1 mL aqueous sodium nitroprusside and 0.2 mL of 0.2 M Na_2HPO_4 (pH 7.8) were added to 0.4 mL of different concentrations (25, 50, 75, and 100) µg/mL of each compound and the mixture incubated at room temperature for 150 min. About 0.12 Griess reagent was added and the absorbance of pink color was read at 540 nm against blank (distilled water).

$$\frac{A_{control} - A_{sample}}{A_{sample}} \times 100$$

Where,

$A_{control}$=Absorbance of control in the absence of sample, and

A_{sample}=Absorbance of sample.

Hydroxyl radical scavenging assay

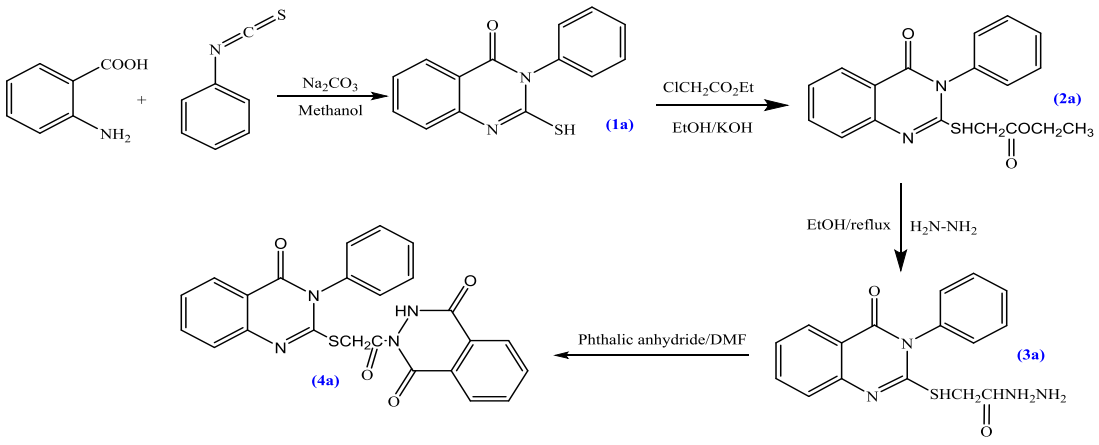
Hydroxyl free radical scavenging was measured using Halliwell *et al.* [33] modified method. All solutions were freshly prepared. 400 µL of $FeCl_3$ (200 µM), 100 µL samples (200 µg/mL), 200 µL of 2-deoxy-D-ribose (2.8 mM), 200 µL of H_2O_2 (1.0 mM), 100 µL EDTA (1.00 Mm) (1:1, V/V) and 200 µL of ascorbic acid (1 mM) were mixed to form a reaction mixture (Fenton Reaction). 1.5 mL of TCA (2.8%) was added to the reaction mixture after 1 hour of incubation at 37 °C to extent the deoxy ribose degradation, and kept for more 30 min at 100° AC taking vitamin C as positive control to develop the pink color. After cooling, the absorbance was measured against an appropriate blank solution at 532 nm. Percentage inhibition was calculated as follows:

$$\text{Inhibition\%} = \frac{\text{Absorbence of control} - \text{Absorence of sample}}{\text{Absorbence of control}} \times 100$$

Results and Discussion

The purpose of the present work was to synthesize new quinazoline derivatives following the reaction sequences, as depicted in Scheme 1. Compound (**1a**) is the key intermediate for the compounds synthesized later in this work. Furthermore, the procedure used commercially available reagents, giving the desired compounds in moderate yields (60-88%). The versatility of this methodology makes it suitable for library synthesis in drug discovery efforts. TLC was run throughout the reaction to optimize the reaction for purity and completion.

All the synthesized compounds were characterized using ^{1}H-NMR, IR, and mass spectral techniques. Both physical and chemical properties of all the synthesized compounds are listed in Table 1.



Scheme 1: Synthesis of target molecule

Table 1: Physicochemical parameters of all synthesized compounds

Compound ID	Molecular formula	Molecular weight	m.p (°C)	Color	Yield (%)	Recovery solvent
1a	$C_{14}H_{22}ON_2S$	266	285-287	White	88	Methanol
2a	$C_{17}H_{28}O_3N_2S$	340	113-115	White	72	Dioxane:H_2O(8:2)
3a	$C_{16}H_{26}O_2N_4S$	338	134-136	White	63	Ethanol:H_2O(6:4)
4a	$C_{24}H_{34}O_4N_4S$	474	223-225	White	60	DMF

**Mobile phase-benzene*

FT-IR spectrum for compound (**1a**) showed the disappearance of the bands (OH) group which present on -COOH group at 3471 cm^{-1}, asymmetrical and symmetrical bands of $-NH_2$ at 3371 cm^{-1}. The appearance of absorption band at 1681 cm^{-1} belong to amide (C=O) group which is produced from the cyclization reaction. A stretching band also appears at 1654 cm^{-1}, which belongs to the C=N group in addition to the basic frequencies, as provided in Table 2.

Spectral results of UV showed transition bands at λ_{max}=297 nm and λ_{max}=249 nm which belong to the transfer of n→π* & π→π*, respectively.

The existence of an absorption peak at 1737 cm^{-1} in compound (**2a**) can be attributed to the ester carbonyl (C=O) bond vibration [34-36] and absorption band at 1653 cm^{-1} is due to vibration of C=N bond for compound (**2a**), Table 2.

The UV spectra of this compound showed λ_{max} bands at 274 nm and 229 nm due to the n→π* and π→π* transitions, respectively, ^{1}H-NMR spectra showed (t , 3H, $-CH_3$) δ_H= 1.19-1.24 ppm , (s, 2H, $-CH_2CO$) δ_H = 3.97 ppm, (q, 2H , $-OCH_2$) δ_H = 4.10-4.17 ppm, and (m, 9H, Ar-H) δ_H = 7.49-8.09 ppm.

The mass spectra results for this compound are displayed in Figure 1.

FT-IR for compound (**3a**) shows the absence of ester carbonyl band at 1735 cm^{-1} and the appearance of asymmetric absorption stretching band belongs to NH_2 group at 3338 cm^{-1} and symmetric band at 3265 cm^{-1} and absorption band at 1664 cm^{-1} belong to amide (C=O) stretch bond (See Table 2). UV spectra represents λ_{max} at 284 nm and 204 nm due to (n→π*) (π→π*) respectively. ^{1}H-NMR spectra of this compound showed (s, 2H, $-CH_2$) δ_H = 3.75 ppm, (s, 2H, NH_2) δ_H = 5.22 ppm, (m, 9H , Ar-H) δ_H = 7.05-8.23 ppm, and (s, 1H, NH) δ_H = 9.32. Mass spectra results are depicted in Figure 2.

Table 2: UV and FT-IR spectra values for the studied compounds

Compound No.	U.V. λ_{max} nm	Characteristic band of I.R spectra (cm^{-1} .KBr disc)					
		ν(C-H) $_{al.}$	ν(C-H)$_{Ar}$	ν(C=O) amide	ν(C=N)	ν(C=C)$_{Ar}$	Others
1a	249 297	2955 2837	3064	1681	1654	1585 1508	ν(C=S)=1249
2a	292 274	2985 2850	3063	1985	1653	1604 1548	ν(C=O)$_{ester}$1737 ν(C-S)=771
3a	204 284	2924	3024	1664	1616	1595 1564	ν(C-S)=750 ν(NH_2)=3338-3265
4a	-	2985 2929	3066	1737 1687 1662	1622	3244 3138	ν(C-S)=756 ν(C=C)$_{Ar}$=1575-1548

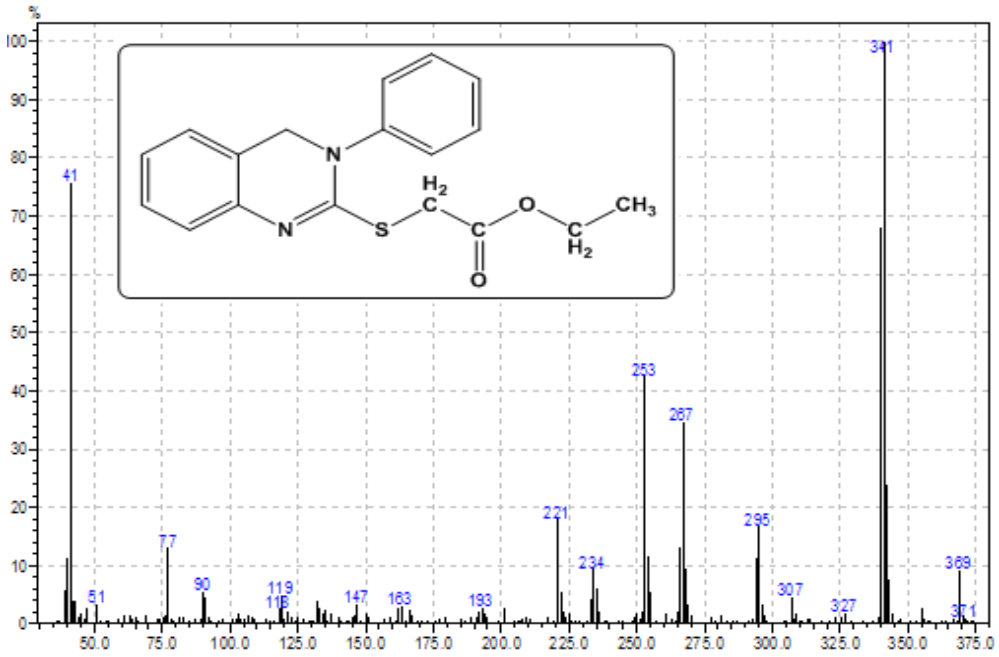


Figure 1. Mass spectroscopy of compound (**2a**)

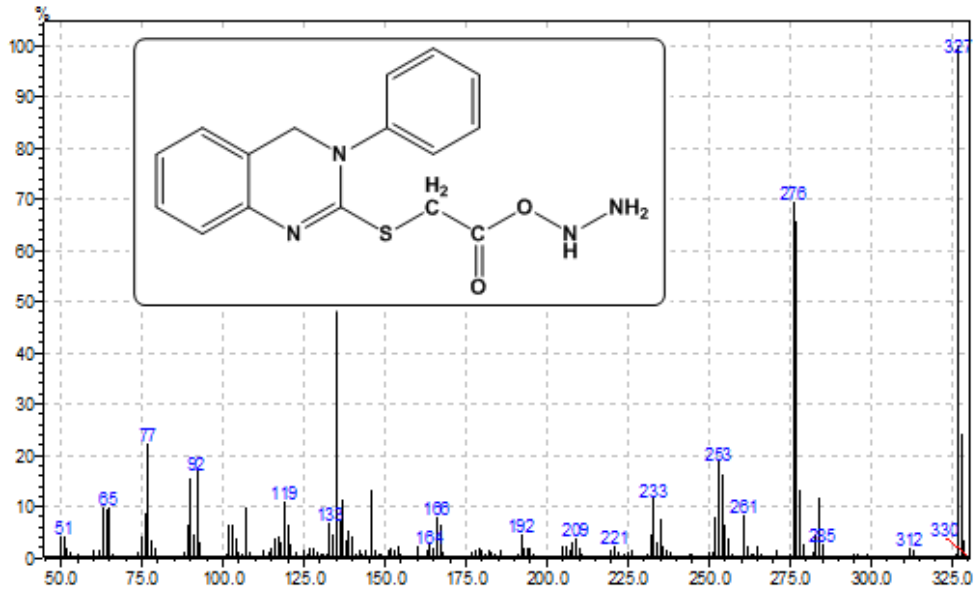


Figure 2: Mass spectroscopy of compound (**3a**)

FT-IR for compound (**4a**) represents the absence of two bands of -NH_2 at 3265-3338 cm^{-1} and the appearance of absorption band at 3244-3138 cm^{-1} due to vibration bond that belong to N-H and appearance of absorption band at 1737, 1687, and 1662 cm^{-1} due to vibration bond of amide (C=O) as presented in Table 2.

^{1}H-NMR spectra of this compound showed (s, 2H, -CH_2) δ_H = 3.75 ppm, (m, 13H, Ar- H) δ_H = 7-8.32 ppm, and (s, 1H, NH) δ_H = 9.25 ppm.

When testing the synthesized compound activity in terms of antifungal and antimicrobial, the increase of the antibiotic detection principles chances was done using organisms (more than one) against the tested compounds. The evaluation has included the antibacterial activity of the novel compounds (**1a**, **2a**, **3a**, and **4a**) against Fungi (*C.albicans* and *A.niger*), gram-positive *(S.aureus* and *S.pyogenes*), and gram-negative (*E.coli* and *P.aeruginosa*). Fluconazole

was used as an antifungal standard. Ampicillin was used as an antibiotic with a comparison between antifungal and antibacterial activities (See Table 3).

Antibacterial assay of the test compounds (**1a**-**4a**) showed a moderate activity against gram positive bacteria (*S. pyogenes*) for compounds (**2a**, **3a**, and **4a**), while a weak activity for compound (**1a**) and a weak activity against (*S. aureus*) for all compounds, a high activity against gram-negative bacteria (*E.coli* and *P. aeragines*) appeared for all compounds except for compound (**1a**) which showed a moderate activity against *E. coli* and weak against *P. aeragines*, as presented in Table 3. Compounds (**1a**, **2a**, and **3a**) represent a high activity against fungi (*C.albicans* and *A. niger*), while compound (**1a**) appeared to have a moderate activity against these fungi (Table 3).

The synthesized compounds are screened for anti-inflammatory activity using inhibition of albumin denaturation technique. Denaturation of proteins is a well-documented cause of inflammation. As part of investigation on the mechanism of anti-inflammation activity, the synthesized compounds are capable to denaturate protein. These compounds have shown highly activity (>50% inhibition) in different concentrations as represented in Table 4.

Table 3: Antibacterial and antifungal activity of the synthesized compounds **(1a**, **2a**, **3a**, and **4a)**

Compounds	*In-vitro* activity zone of inhibition in mm[a]					
	Fungi		Gram-positive		Gram-negative	
	C.albicans	*A.niger*	*S.aureus*	*S.pyogenes*	*E.coli*	*P.aeragines*
1a	6	5	3	4.5	5	3.5
2a	8	6	2	6	9	8
3a	8	7.5	4	5	8	7
4a	8	7	2.5	6.5	9	8.5
Ampicillin	-	-	10	10	10	10
Fluconazole	10	10	-	-	-	-

[a] *Average of three replicates.*

Table 4: *In-vitro* anti-inflammatory activity of compounds **1**, **2**, **3**, and **4**

Compound Code	Inhibition of denaturation%			
	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
1a	84.8	88.9	89.7	95.9
2a	92.3	93.9	96	97
3a	81.4	86.4	87.6	93
4a	88.8	90.6	93.5	96.2

Nitric oxide, as a part of reactive oxygen species (ROS) can be implemented as an anticancer, inflammation agent as well as other pathological conditions. The aqueous solution of sodium nitroprusside at conditions that are similar to *in vivo* pathological conditions is a nitric oxide generator; the latter can produce nitrite ions via the interaction with oxygen. Nitrite ions are evaluated using Griess reagent. A possible competition is observed between oxygen and nitric oxide in scavenging free radicals. This in turn could lead to the reduction of producing nitrite ions. The direct scavenging of NO can partially affect the NO suppression. The generated NO amount which is released from *in vitro* decomposition of SNP has a tendency to be decreased when testing compounds (**1a**, **2a**, **3a**, and **4a**). These compounds can be described as moderate scavengers towards nitric oxide (See Table 5).

Among the reactive oxygen species (ROS), the most reactive radicals are hydroxyl species. These species are capable to form dioxygen and in turn could lead to the initiation of *in vivo* cell damage. This article concerns the application of synthesized compounds in the *in vitro* inhibition that consists of H_2O_2 and Fe^{3+} EDTA ascorbate. The inhibition of hydroxyl radicals were

generated by deoxyribose degradation via the Fenton's reaction, which includes the reaction of thiobarbituric acid (TBA) with deoxyribose fragments at an elevated temperature forming a pink detection color. The antioxidant activity is correlated to the scavenging capacity of hydroxyl radicals. The scavenging activity of the studied compounds is provided in Table 6.

The tested compounds (**1a**, **2a**, and **4a**) showed a moderate hydroxyl scavenging activity, while compound 3 showed a weak activity for all used concentrations except for 100 µg/mL concentration which showed moderate activity, as indicated in Table 6.

Table 5: *In vitro* nitric oxide scavenging activity of the compounds (**1a**, **2a**, **3a**, and **4a**)

Compound Code	Inhibition of Denaturation%			
	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
1a	8.1	13.3	32	56.9
2a	58.1	74.3	75.6	78.3
3a	0.5	8.1	11.5	54.4
4a	12.8	59.2	73.5	71

Table 6: *In vitro* Hydroxyl radical scavenging activity of the compounds (**1a**, **2a**, **3a**, and **4a**)

Compound Code	Inhibition of denaturation%			
	25 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
1	55.2	78.6	78.8	77.4
2	79.3	76.6	77.1	79.6
3	42.3	44.3	43.6	76.6
4	68.4	75.5	78.8	78.4

Conclusion

Our research has introduced novel quinazoline related compound synthesis along with the characterization using different spectral techniques and the implementation of these compounds as antioxidants and antimicrobial agents. The antibacterial evaluation data showed that there was a moderate activity against gram-positive bacteria (*S. pyogenes)* for (**2a**, **3a**, and **4a**) compounds, while a weak activity for compound (**1a**) and a weak activity against (*S. aureus*) for all compounds, high activity against gram-negative bacteria (*E.coli and P. aeragines)* appeared for all compounds except for compound (**1a**) which showed a moderate activity against *E. coli* and weak against *P. aeragines*. Compounds (**1a**, **2a**, and **3a**) represents a high activity against fungi (*C.albicans and A. niger*), while compound (**1a**) appeared to have moderate activity against these fungi. Furthermore, the synthesized compounds are screened for anti-inflammatory activity by using inhibition of albumin denaturation technique. These compounds have shown highly activity (>50% inhibition) in different concentrations. The antioxidant activity was evaluated using nitric oxide with a hydroxyl radical scavenging assay, which showed that scavenging activity assay of both hydroxyl and nitric oxide radicals was in the range between moderate and good for the tested compounds, the tested compounds (**1a**, **2a**, and **4a**) showed a moderate hydroxyl scavenging activity, while compound (**3a**) showed weak activity for all used concentrations except for 100 µg/ml concentration which a showed moderate activity.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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