Enhancement of Different Biomedical Activities of Newly Synthesized Quinazoline Derivatives

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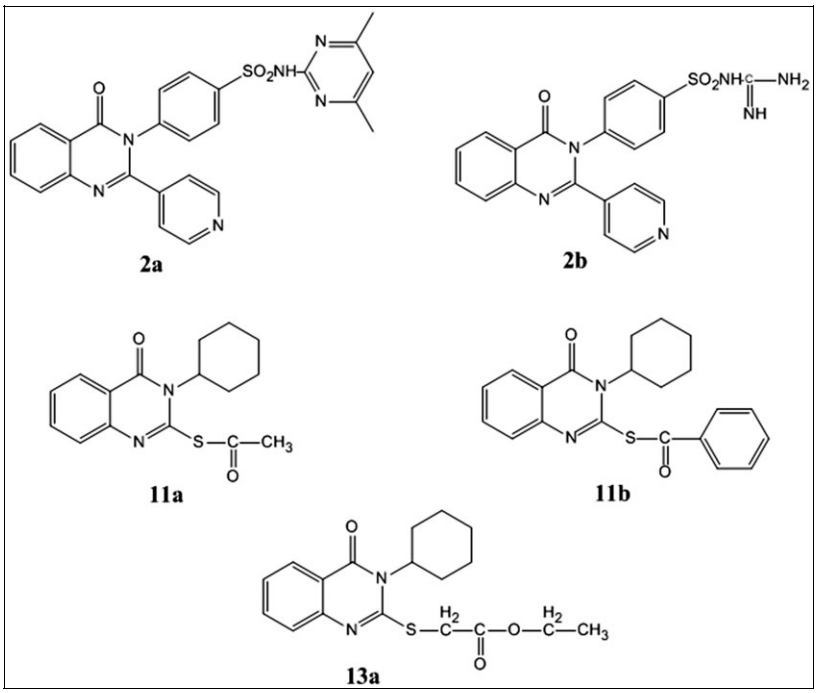

A series of newly synthesized compounds of quinazolinone by various substituents was screened for its pharmacological activities. These included their action as antibacterial agents against pathogenic bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) and as antifungal agents against *Aspergillus niger* and pathogenic yeast (*Candida albicans*). The presently investigated compounds were synthesized in higher yields, and the structure features were elucidated on the basis of IR, ^{1}H-NMR, and mass and elemental analysis data. These compounds were also evaluated as antioxidant agent. The results revealed that six compounds (**2a**, **11b**, **11a**, **2b**, **13a**, and **3c**) exhibited higher antimicrobial activity against the tested pathogenic strains. In addition, it was found that compound **6a** exhibited a radical scavenging activity higher than other studied compounds.

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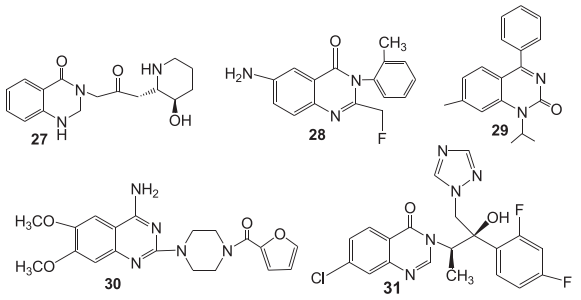
INTRODUCTION

Quinazolines are a fundamental class of *N*-heterocyclic system; it is considered as a base unit in various natural and synthetic compounds with different biological activities [1–4]. Quinazoline ring represents a building block for approximately 150 bioactive naturally occurring alkaloids [5,6]. Quinazoline derivatives have also emerged as integral backbones of over 60 existing drugs [7,8].

The most objective result in many researches showed the effectiveness of quinazolines against various diseases caused by microorganisms. In the last decades, the search for quinazoline compounds has been characterized by significant advances. As on date, about 60 clinically used drugs are quinazoline derivatives, for example, febrifugine 27 [9], a quinazolinone alkaloid, possessing antimalarial potential from the Chinese plant Aseru (*Dichroa febrifuga* Lour), besides the discovery of considerable soporific and sedative action of the synthetic 2-methyl-3aryl-4-quinazolone derivatives as afloqualone 28 [10], proquazone 29 (Biarison®) [11], a nonsteroidal anti-inflammatory drug, prazocin 30 (Minipress®) [8], a sympatholytic with antihypertensive activity, and albaconazole 31 (UR-9825) [12], a triazole antifungal.



Resistance of pathogenic strain against antibiotic still becoming a potential problem for various diseases and infections led to the screening of novel synthetic compounds of quinazoline and its derivatives through substituted groups. Owing to the broad spectrum of quinazoline, which possesses pharmacological activities [13–33], therefore, different biological activities were evaluated for these new synthetic quinazolines. Anticoagulant and antithrombotic activities are among the most widely studied properties of newly synthesized compounds. Thus, the present synthetic quinazoline derivatives were also examined for their anticoagulant and fibrinolytic activities.

The biological activities of quinazoline are related to their structural features such as the position of branching. Therefore, the aim of the present study was to examine the antimicrobial, antioxidant, and fibrinolytic and anticoagulation activities of synthesis of quinazoline and their derivatives by modification on structure.

RESULTS AND DISCUSSION

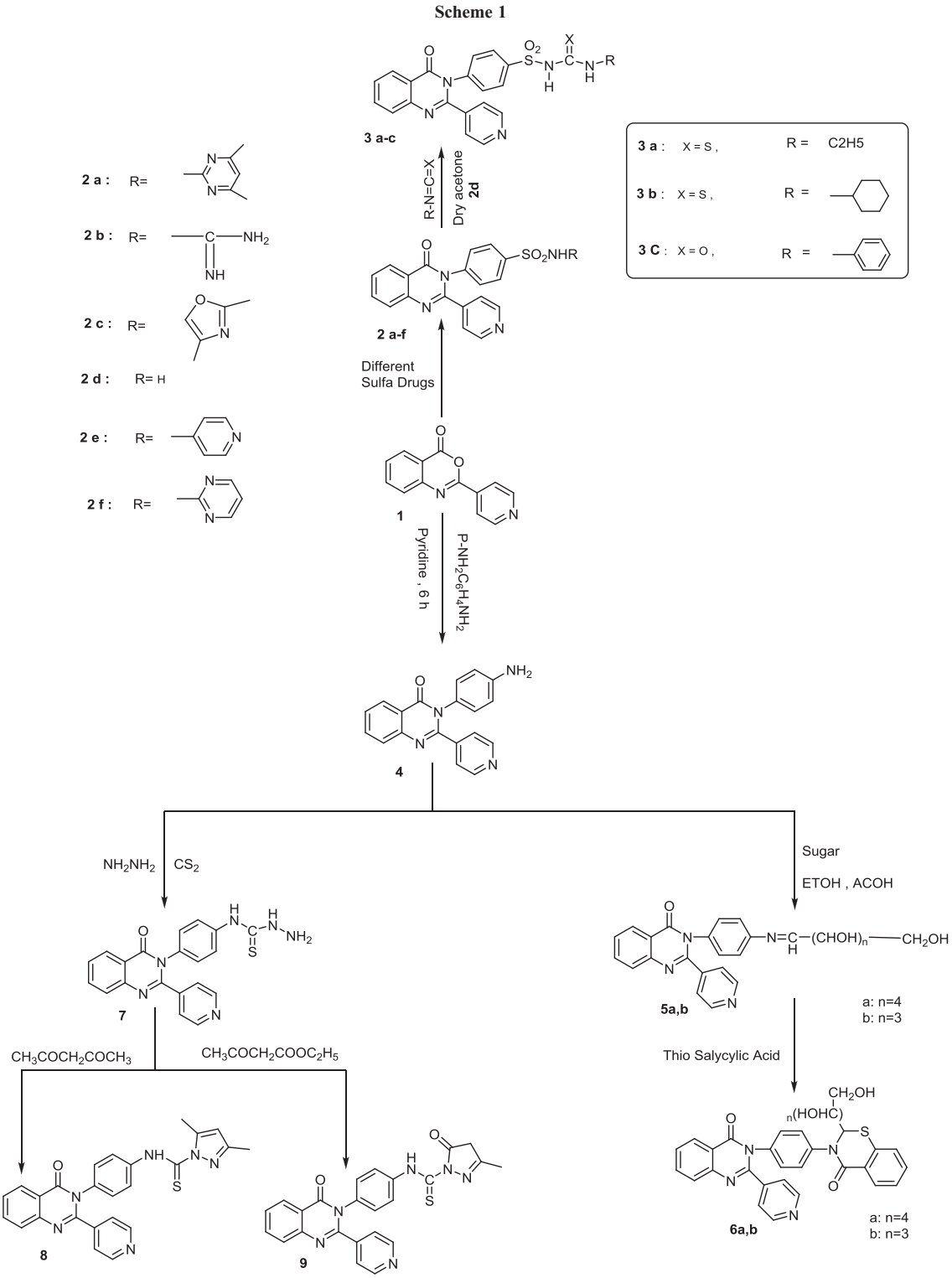
Chemistry. Compound 2-(pyridin-4-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (**1**) reacted with appropriate sulfa drugs, namely, sulfamethazine, sulfaguanidine, sulfamethoxazole, sulfanilamide, sulfapyridine, and sulfadiazine, in the presence of glacial acetic acid and anhydrous sodium acetate via refluxing to produce (**2a**–**f**), respectively (Scheme 1). Compound (**2d**) reacted with cyanate isothiocyanate derivatives, namely, ethyl isothiocyanate, cyclohexyl isothiocyanate, and phenyl isocyanate, in dry acetone via refluxing to give (**3a**–**c**), respectively. Also, compound (**1**) reacted with *p*-phenylenediamine in the presence of pyridine by heating on sand bath to afford 3-(4-aminophenyl)-2-(pyridin-4-yl) quinazolin-4(3*H*)-one (**4**), which was allowed to react with appropriate linear sugar, namely, D-mannose and/or D-arabinose, in absolute ethanol in the presence of drops of glacial acetic acid via heating at 80°C for 6 h to produce compounds (**5a**,**b**), respectively (Scheme 1). The latter was allowed to react with thiosalicylic acid in the presence of dry benzene via refluxing to produce (**6a**,**b**), respectively. Compound (**4**) can be reacted with carbon disulfide in dimethylformamide (DMF) and in the presence of hydrazine hydrate via stirring to produce compound (**7**), which was allowed to react with acetyl acetone/ethyl acetoacetate via heating on water bath to afford compounds (**8**) and (**9**), respectively (Scheme 1).

Compound (**10a**) reacted with acetyl/benzoyl chloride in the presence of pyridine via refluxing to produce compounds (**11a**,**b**), respectively. Compound (**10b**) can be reacted with chloroacetic acid in the presence of absolute ethanol via stirring to afford compound (**12**). Compounds (**10a**,**b**) [34] can be reacted with ethyl chloroacetate in the presence of methanol to give compounds (**13a**,**b**). Compounds (**14a**,**b**) were synthesized by the reaction of compounds (**13a**,**b**) with 4-chloroaniline in ethanol by refluxing. Compounds (**15a**,**b**) were synthesized by the reaction of compounds (**13a**,**b**) with thiosemicarbazide in DMF via refluxing (Scheme 2).

Evaluation of biological activity depending on structure–activity relationship. ***Antimicrobial activity of quinazoline derivatives.*** The antimicrobial activity of the investigated samples was examined against Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pneumoniae*) and Gram-negative bacteria (*Escherichia coli ATCC25922*, *Klebsiella pneumoniae ATCC13883*, and *Pseudomonas aeruginosa ATCC27953*) as pathogenic bacteria, *Candida albicans NRRL Y-477* as pathogenic yeast, and *Aspergillus niger* as pathogenic fungi. Antimicrobial activity was expressed as mean diameter of inhibition zone (IZ) (mm). Table 1 illustrates the diameter of IZ differs according to the compound used against all studied pathogens. As shown from the data, there are eight main compounds appeared more effective than the other. Among all compounds, **11b** has a potent antimicrobial activity on all the tested pathogens forming a maximum value (IZ) of 24.0 ± 0.2, 22.0 ± 0.5, 22.0 ± 0.5, 20 ± 0.3, 18 ± 0.3, 13 ± 0.2, and 10 ± 0.2 mm against *C. albicans*, *A. niger*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. pneumoniae*, and *S. aureus*, respectively. Noteworthy is that activity is arranged in the following order: **11b** > **2a** > **2b** > **11a** > **3c**. Compound **13a** shows the highest antimicrobial activity against *S. aureus*. The other compounds exhibit a weak antimicrobial activity.

Minimum inhibitory concentration of quinazoline derivatives (MIC). According to the data in Table 2, the quinazoline compound as starting compound possesses variable sites at positions **2** and **3**, which improving broad spectrum antimicrobial activity owing to substitution such as most active compound **11b** by adding phenyl group, consequently **2a** compound by interfering sulfadiazine group, also **2b** compound substitution happened by addition of sulfaguanidine group, **11a** compound addition of acetyl group make enhancement in antimicrobial

Scheme 1



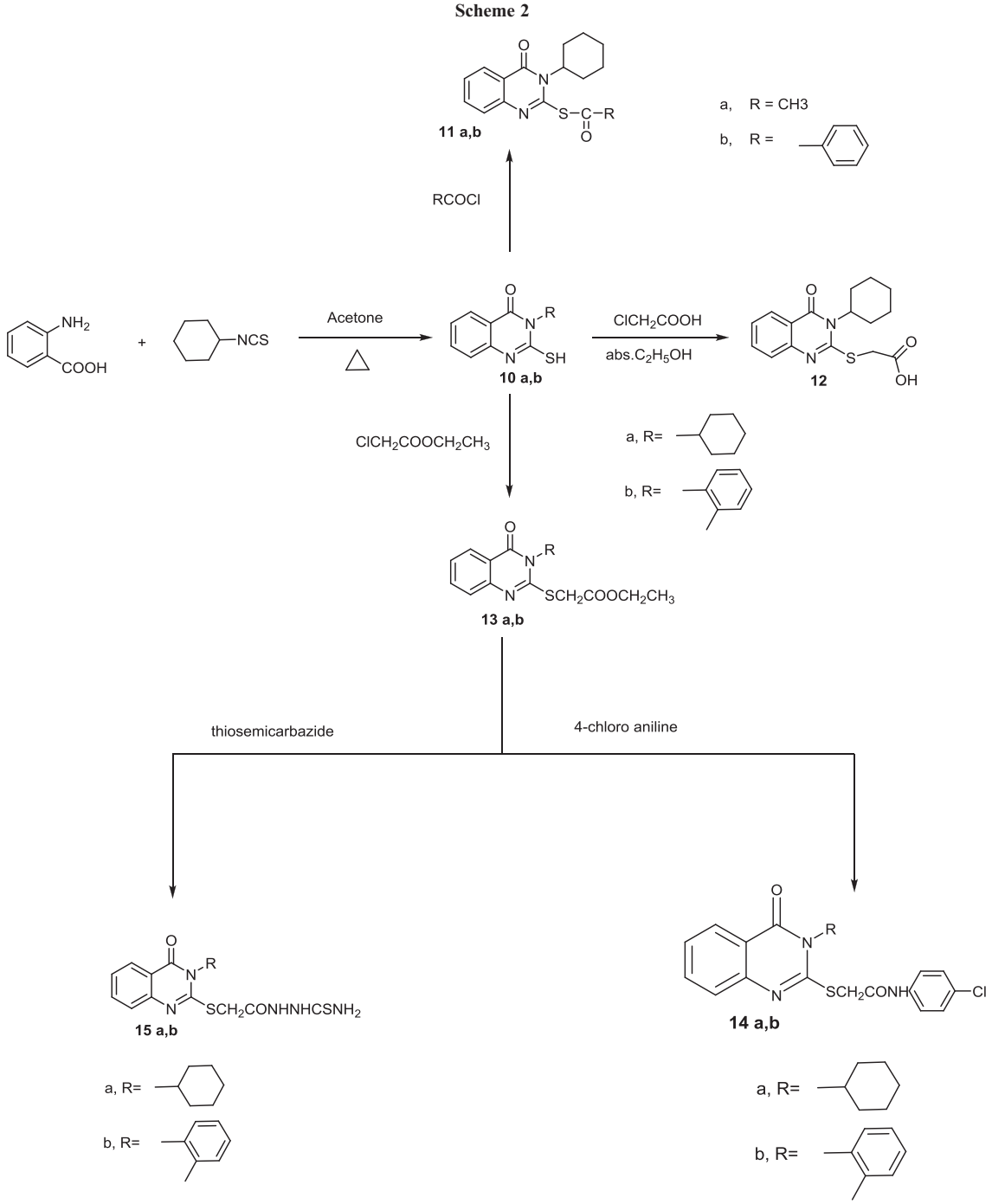
activity, respectively, compound **3c** changed by interfering phenyl group.

Modification to quinazoline moiety in case of **13a** presented by addition of ester group showed that greater antibacterial activity against *S. aureus*.

The results indicated that the list of the newly synthesized compounds have antibacterial and antifungal activities expect **6b**, **5b**, **2e**, and **13b**.

Antioxidant activity of quinazoline derivatives. The free-radical scavenging activity of new derivatives compound of

Scheme 2



quinazoline was evaluated using the DPPH method. Obviously, structural modifications improve the antioxidant activity. According to the results in Table 3, a significant increase concentration of DPPH radical because of the scavenging ability of soluble solids in compound (**6a**) exhibited the highest antioxidant activity of 65%.

Fibrinolytic and anticoagulant activity of quinazoline derivatives. As the newly synthesized compounds of quinazoline exhibited relatively higher antimicrobial and antioxidant action, they were subjected to further biological evaluation by determining their fibrinolytic and anticoagulant activities. The results of Table 4 indicates that the "four compounds (**6b**, **5b**, **2b**, and **4**)" were characterized by their relatively higher fibrinolytic activities (80% lysis of plasma clot) as compared with those of the "remaining compounds" (50–75% lysis of plasma clot) and

Table 1

Antimicrobial activity of newly synthesized quinazoline derivatives that was expressed as mean diameter of inhibition zone (mm).

	Mean diameter of inhibition zone (mm)						
	Gram-positive bacteria		Gram-negative bacteria			Yeast	Fungi
Compound no.	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Candida albicans*	*Aspergillus niger*
2a	15.0 ± 0.1	17.0 ± 0.2	20.0 ± 0.2	18.0 ± 0.5	20.0 ± 0.2	22.0 ± 0.3	18.0 ± 0.2
2b	10.0 ± 0.2	12.0 ± 0.2	20.0 ± 0.5	20.0 ± 0.5	18.0 ± 0.5	12.0 ± 0.2	14.0 ± 0.5
2c	–	–	22.0 ± 0.3	20.0 ± 0.2	18.0 ± 0.2	15.0 ± 0.1	17.0 ± 0.3
2e	–	–	–	–	–	–	10.0 ± 0.2
2f	15.0 ± 0.2	15.0 ± 0.2	15.0 ± 0.2	10.0 ± 0.5	12.0 ± 0.2	–	12.0 ± 0.1
3c	12.0 ± 0.2	10.0 ± 0.5	20.0 ± 0.2	12.0 ± 0.5	14.0 ± 0.5	10.0	12.0 ± 0.5
4	–	–	–	–	–	22.0	18.0 ± 0.3
5a	–	–	–	–	–	–	–
5b	–	–	–	–	–	–	–
6a	–	12.0 ± 0.2	10.0 ± 0.1	12.0 ± 0.2	12.0 ± 0.1	12.0 ± 0.2	12.0 ± 0.3
6b	–	–	–	–	–	–	–
11a	10.0 ± 0.3	15.0 ± 0.2	18.0 ± 0.2	15.0 ± 0.2	20.0 ± 0.5	17.0 ± 0.1	13.0 ± 0.2
11b	10.0 ± 0.2	13.0 ± 0.2	22.0 ± 0.5	18.0 ± 0.3	20.0 ± 0.3	24.0 ± 0.5	22.0 ± 0.5
13a	25.0 ± 0.2	20.0 ± 0.3	12.0 ± 0.2	15.0 ± 0.5	16.0 ± 0.2	18.0 ± 0.2	18.0 ± 0.3
13b	–	–	–	–	–	–	10.0 ± 0.1
14a	–	12	15.0 ± 0.5	10.0 ± 0.2	12.0 ± 0.2	–	12.0 ± 0.1
14b	–	–	25.0 ± 0.3	22.0 ± 0.5	22.0 ± 0.2	–	12.0 ± 0.1
15a	–	–	12.0 ± 0.1	15.0 ± 0.1	15.0 ± 0.2	–	15.0 ± 0.2
15b	–	10.0 ± 0.2	16.0 ± 0.2	10.0 ± 0.2	10.0 ± 0.1	–	–
Control	22.0	20.0	22.0	20.0	20.0	25.0	22.0

Control: Imipenem 10 μg for bacteria and griseofulvin 10 μg for fungi and yeast.

Table 2

MIC of newly synthesized quinazoline on indicator pathogens.

	MIC (μg/mL)						
	Gram-positive bacteria		Gram-negative bacteria			Yeast	Fungi
Compound no.	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	*Candida albicans*	*Aspergillus niger*
2a	100	100	50	100	100	50	100
2b	100	100	100	100	100	100	150
2c	–	–	50	100	100	100	100
2e	–	–	–	–	–	–	10
2f	100	100	100	100	100	–	200
3c	100	100	100	100	100	100	100
4	–	–	–	–	–	200	200
5a	–	–	–	–	–	–	–
5b	–	–	–	–	–	–	–
6a	–	200	200	200	200	200	200
6b	–	–	–	–	–	–	–
11a	100	100	100	100	100	100	100
11b	100	100	50	50	50	50	100
13a	25	50	100	100	100	100	100
13b	–	–	–	–	–	–	100
14a	–	50	150	100	100	–	100
14b	–	–	100	100	100	–	200
15a	–	–	100	100	100	–	200
15b	–	100	100	100	100	–	–
Control	50	50	50	50	50	50	50

The MIC value was expressed as the lowest concentration of the antibacterial and antifungal agents.
MIC, minimum inhibitory concentration.

Table 3

Antioxidant activity of newly synthesized quinazoline.

Compound no.	TAC %
2a	32
2b	46
2c	31
2e	26
2f	34
3c	54
4	58
5a	12
5b	29
6a	65
6b	13
11a	34
11b	36
13a	32.5
13b	26.5
14a	28
14b	24
15a	33
15b	29
Ascorbic acid	96

TAC, total antioxidant activity/content.

Table 4

Fibrinolytic and anticoagulation activities of newly synthesized quinazoline.

Compound no.	Fibrinolytic activity (lysis %)	Anticoagulation activity (clotting time)	
		min	s
2a	75	4	57
2b	>75	7	20
2c	50	30	18
2e	<50	30	18
2f	75	4	12
3c	75	8	45
4	>75	11	12
5a	50	9	53
5b	>75	5	55
6a	75	13	10
6b	>75	5	36
11a	75	3	30
11b	50	30	15
13a	50	7	35
13b	50	6	20
14a	<50	30	15
14b	75	7	49
15a	50	6	55
15b	75	30	18
Blank	—	2	30
Standard (Hemoclar 2 mg)	75	—	—
Standard (heparin 1.4 IU)	—	>30	—

standard "Hemoclar" preparation (75% lysis). Similarly, the "five compounds (**2c**, **11b**, **2e**, **14a**, and **15b**)" exhibited anticoagulant activity higher than that of "other studied compounds" despite it was still lower than that of standard "Heparin" preparation. The variation in fibrinolytic and anticoagulant activities of the synthesized compounds can be attributed to the position of branching and structure differences (structure–activity relationship).

MATERIAL AND METHODS

Chemistry. All melting points are uncorrected and measured by the use of an electrothermal capillary melting point apparatus. Infrared spectra were acquired with a Jasco FT/IR-6100 using KBr discs. ^{1}H-NMR spectra were acquired with Joel 270-MHz and Jeol sx 500-MHz spectrometers, using tetramethylsilane as internal standard. Mass spectra were acquired with a Jeol JMS-AX 500. All reactions were followed and checked by thin-layer chromatography (aluminum-backed plates) with chloroform–methanol 9:1 (v/v) as mobile phase. For detection, the plates were sprayed with iodine.

General procedure for preparation of compounds 2a–f. A mixture solution of **1** (0.01 mol) and (0.01 mol) of the appropriate sulfa drug, namely, sulfamethazine, sulfaguanidine, sulfamethoxazole, sulfanilamide, sulfapyridine, and sulfadiazine, in (20 mL) glacial acetic acid containing (0.02 mol) sodium acetate anhydrous was refluxed for 15 h. Upon pouring on crushed ice/water, white crystals were obtained, filtered, washed with water, and recrystallized from proper solvent.

N-(4,6-Dimethylpyrimidin-2-yl)-4-(4-oxo-2-(pyridin-4-yl) quinazolin-3(4H)-yl)benzene sulfonamide (2a). Crystallized from ethanol/petroleum ether, mp 290°C, yield 70%. Analysis: for $C_{25}H_{20}N_6O_3S$, MW 484.53, calcd: C: 61.97, H: 4.16, N: 17.34. Found: C: 61.86, H: 3.98, N: 17.29. IR (KBr; cm^-): 3377 (NH), 1680 (C═O), 1620 (C═N), 1340 (SO_2NH). H-NMR (DMSO, δ ppm): 2.30 (s, 6H, $2CH_3$), 6.68–7.80 (m, 13H, Ar–H, CH of diazine), 10.25 (s, 1H, NH exchangeable with D_2O). MS: (*m/z*) ~484 (20.61%).

N-Carbamimidoyl-4-(4-oxo-2-(pyridin-4-yl)quinazolin-3(4H)-yl)benzene sulfonamide (2b). Crystallized from ethanol, mp 254°C, yield 71%. Analysis: for $C_{20}H_{16}N_6O_3S$, MW 420.44, calcd: C: 57.13, H: 3.84, N: 19.99. Found: C: 57.22, H: 3.70, N: 20.02. IR (KBr; cm^-): 3467, 3432, 3211 (2NH, NH_2), 1681 (C═O), 1315 (SO_2NH). H-NMR (DMSO, δ ppm): 5.31, 9.80, 10.72 (3s, 2H, 2H, NH_2, 2NH), 7.10–8.0 (m, 12H, Ar–H). MS: (*m/z*) ~420 (13.85%).

N-(2-Methyloxazol-4-yl)-4-(4-oxo-2-(pyridin-4-yl)quinazolin-3(4H)-yl)benzene sulfonamide (2c). Crystallized from isopropanol, mp 246°C, yield 62%. Analysis: for $C_{23}H_{17}N_5O_4S$, MW 459.48, calcd: C: 60.12, H: 3.73, N: 15.24. Found: C: 60.31, H: 3.70, N: 15.14. IR (KBr; cm^-): 3320 (NH), 1692 (C═O), 1316 (SO_2NH). H-NMR (DMSO, δ ppm): 2.34 (s, 3H, CH_3), 7.10–8.00 (m, 13H,

Ar–H, 1H, isoxazole ring), 10.20 (s, 1H, NH exchangeable with D_2O). MS: (*m/z*) ~459 (13.02%).

4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4H)-yl)benzene sulfonamide (2d). Crystallized from isopropanol, mp 263°C, yield 69%. Analysis: for $C_{19}H_{14}N_4O_3S$, MW 378.40, calcd: C: 60.31, H: 3.73, N: 14.81. Found: C: 60.21, H: 3.70, N: 14.86. IR (KBr; cm^-): 3207, 3153 (NH_2), 1690 (C═O), 1391 (SO_2NH). H-NMR (DMSO, δ ppm): 4.90 (s, 2H, NH_2 exchangeable with D_2O), 7.20–8.00 (m, 12H, Ar–H). MS: (*m/z*) ~378 (19.01%).

4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4H)-yl)-N-(pyridin-4-yl)benzene sulfonamide (2e). Crystallized from isopropanol/petroleum ether, mp 207°C, yield 65%. Analysis: for $C_{24}H_{17}N_5O_3S$, MW 455.49, calcd: C: 63.29, H: 3.76, N: 15.38. Found: C: 63.36, H: 3.59, N: 15.45. IR (KBr; cm^-): 3355 (NH), 1695 (C═O), 1327 (SO_2NH). H-NMR (DMSO, δ ppm): 10.23 (s, 1H, NH, exchangeable with D_2O), 7.10–8.02 (m, 16H, Ar–H). MS: (*m/z*) ~455 (11.51%).

4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4H)-yl)-N-(pyrimidin-2-yl)benzene sulfonamide (2f). Crystallized from ethanol/petroleum ether, mp 267°C, yield 73%. Analysis: for $C_{23}H_{16}N_6O_3S$, MW 456.48, calcd: C: 60.52, H: 3.53, N: 18.41. Found: C: 60.47, H: 3.58, N: 18.81. IR (KBr; cm^-): 3320 (NH), 1680 (C═O), 1620 (C═N), 1325 (SO_2NH). H-NMR (DMSO, δ ppm): 10.23 (s, 1H, NH, exchangeable with D_2O), 7.21–8.13 (m, 15H, Ar–H). MS: (*m/z*) ~456 (19.81%).

General procedure for preparation of compounds 3a–c.

A mixture of **2d** (0.005 mol) and anhydrous potassium carbonate (0.01 mol) in dry acetone (50 mL) was refluxed with continuous stirring for 1.5 h. While hot, a solution of the appropriate cyanate/isothiocyanate derivatives, namely, ethyl isothiocyanate, cyclo hexylisothioocyanate, and phenyl isocyanate (0.007 mol), in dry acetone was added dropwisely, and the reflux was continued for further 18 h. The excess acetone was removed under reduced pressure, and the obtained solid residue was washed with water, filtered, and recrystallized from the proper solvent.

N-(Ethylcarbamothioyl)-4-(4-oxo-2-(pyridin-4-yl)quinazolin-3(4H)-yl)benzene sulfonamide (3a). Crystallized from ethanol, mp >300°C, yield 59%. Analysis: for $C_{22}H_{19}N_5O_3S_2$, MW 465.55, calcd: C: 56.76, H: 4.11, N: 15.04. Found: C: 56.59, H: 4.08, N: 15.06. IR (KBr; cm^-): 3340, 3333 (2NH), 1710 (C═O), 1320 (SO_2NH), 1160 (C═S). H-NMR (DMSO, δ ppm): 1.20 (t, 3H, CH_3, ethyl group), 3.62 (q, 2H, CH_2), 7.20–8.0 (m, 12H, Ar–H), 9.80–10.20 (2s, 2H, 2NH exchangeable with D_2O). MS: (*m/z*) ~465 (14.51%).

N-(Cyclohexylcarbamothioyl)-4-(4-oxo-2-(pyridin-4-yl)quinazolin-3(4H)-yl)benzene sulfonamide (3b). Crystallized from ethanol/petroleum ether, mp 250°C, yield 63%. Analysis: for $C_{26}H_{25}N_5O_3S_2$, MW 519.64, calcd: C: 60.10, H: 4.85, N: 13.48. Found: C: 60.20, H: 4.90, N: 13.57. IR (KBr; cm^-): 3423, 3280, (2NH), 1710 (C═O), 1311 (SO_2NH), 1162 (C═S). H-NMR (DMSO, δ ppm): 2.00 (s, 10H, cyclohexane), 4.20 (m, 1H, CH–N), 7.02–7.92 (m, 12H, Ar–H), 9.20, 10.10 (2s, 2H, 2NH, exchangeable with D_2O). MS: (*m/z*) ~519 (17.32%).

4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4H)-yl)-N-(phenylcarbamoyl) benzene sulfonamide (3c). Crystallized from chloroform, mp 210°C, yield 69%. Analysis: for $C_{26}H_{19}N_5O_4S$, MW 497.53, calcd: C: 62.77, H: 3.85, N: 14.08. Found: C: 62.75, H: 3.73, N: 14.13. IR (KBr; cm^-): 3340, 3299 (2NH), 1689, 1665 (2C═O), 1312 (SO_2NH). H-NMR (DMSO, δ ppm): 9.26, 10.35 (2s, 2H, 2NH exchangeable with D_2O), 7.12–8.10 (m, 17H, Ar–H). MS: (*m/z*) ~497 (19.83%).

3-(4-Aminophenyl)-2-(pyridin-4-yl)quinazolin-4(3*H*)-one (4). A mixture of compound **1** (0.01 mol) and *p*-phenylenediamine (0.01 mol) was dissolved in (50 mL) of anhydrous pyridine and heated on sand bath for 6 h. The resulting solution was cooled in ice bath and treated with 100 mL of dilute hydrochloric acid. The product was filtered, washed with water, and crystallized from ethanol.

Crystallized from ethanol, mp >300°C, yield 75%. Analysis: for $C_{19}H_{14}N_4O$, MW 314.34, calcd: C: 72.60, H: 4.49, N: 17.82. Found: C: 72.50, H: 4.51, N: 17.91. IR (KBr; cm^-): 3410, 3390 (NH_2), 1712 (C═O), 1614 (C═N). H-NMR (DMSO, δ ppm): 4.72 (s, 2H, NH_2), 7.03–8.12 (m, 12H, Ar–H). MS: (*m/z*) ~314 (89%).

General procedure for preparation of compounds 5a,b.

A mixture of compound **4** (0.01 mol) and the appropriate linear sugar, namely, D-mannose and/or D-arabinose (0.01 mol), in absolute ethanol (30 mL) in the presence of few drops of glacial acetic acid was heated at 80°C for 6 h. The reaction mixture was cooled, and the formed precipitate was filtered off and recrystallized from isopropanol to obtain the desired Schiff's bases **5a**,**b**.

2,3,4,5,6-Pentahydroxyhexylidene)amino)phenyl)-2-(pyridin-4-yl)quinazolin-4(3H)-one (5a). Crystallized from isopropanol, mp >300°C, yield 64%. Analysis: for $C_{25}H_{24}N_4O_6$, MW 476.48, calcd: C: 63.02, H: 5.08, N: 11.76. Found: C: 63.10, H: 5.05, N: 11.79. IR (KBr; cm^-): 3680–3480 (5OH), 1694 (C═O), 1609 (C═N). H-NMR (DMSO, δ ppm): 2.43–2.92 (m, 5H, 5OH), 3.32–3.83 (m, 6H, 4CH, CH2), 6.92–8.14 (m, 13H, Ar–H, CH═N). MS: (*m/z*) ~476 (43.40%).

2-(Pyridin-4-yl)-2,3,4,5-tetrahydroxypentylidene)amino)phenyl) quinazolin-4(3H)-one (5b). Crystallized from isopropanol, mp >300°C, yield 71%. Analysis: for $C_{24}H_{22}N_4O_5$, MW 446.46, calcd: C: 64.53, H: 4.97. N: 12.55. Found: C: 64.53, H: 4.95, N: 12.60. IR (KBr; cm^-): 3587–3481 (4OH), 1702 (C═O), 1613 (C═N). H-NMR (DMSO, δ ppm): 2.55–2.89 (m, 4H, 4OH), 3.38–3.87 (m, 5H, 3CH, CH_2), 6.90–8.12 (m, 13H, Ar–H, CH═N). MS: (*m/z*) ~446 (86.73%).

General procedure for preparation of compounds 6a,b.

A mixture of compounds **5a**,**b** (0.005 mol) and thiosalicylic acid (0.005 mol) in dry benzene (20 mL) was refluxed for 16 h. The excess solvent was evaporated under reduced

pressure, and the obtained residue was treated with petroleum ether (60–80). The solid product was filtered off, washed with petroleum ether (60–80), and crystallized from isopropanol to obtain the desired products **6a**,**b**, respectively.

3-(4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4H)-yl)phenyl)-2-1,2,3,4,5-pentahydroxypentyl)-2,3-dihydro-4H-benzo[e][1,3] thiazin-4-one (6a). Crystallized from isopropanol, mp >300°C, yield 63%. Analysis: for $C_{32}H_{28}N_4O_7S$, MW 612.65, calcd: C: 62.73, H: 4.61, N: 9.14. Found: C: 62.70, H: 4.63, N: 9.15. IR (KBr; cm^-): 3565–3440 (OH), 1696, (C═O), 1610 (C═N). H-NMR (DMSO, δ ppm): 3.34–3.51 (m, 6H, 4CH, CH_2), 4.07–4.31 (m, 5H, 5OH), 6.51 (s, 1H, CH of benzothiazine ring), 7.01–7.96 (m, 16H, Ar–H). MS: (*m/z*) ~612 (18.41%).

3-(4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4H)-yl)phenyl)-1,2,3,4-tetrahydroxybutyl)-2,3-dihydro-4H-benzo[e][1,3]thiazin-4-one (6b). Crystallized from isopropanol, mp >300°C, yield 71%. Analysis: for $C_{31}H_{26}N_4O_6S$, MW582.63, calcd: C: 63.91, H: 4.50, N: 9.62. Found: C: 63.80, H: 4.61, N: 9.55. IR (KBr; cm^-): 3545–3430 (OH), 1683 (C═O), 1609 (C═N). H-NMR (DMSO, δ ppm): 2.60–2.92 (m, 5H, 3CH, CH_2), 4.11–4.30 (m, 4H, 4OH), 6.54 (s, 1H, CH of benzothiazine ring), 6.69–7.99 (m, 16H, Ar–H). MS: (*m/z*) ~582 (22.13%).

***N*-(4-(4-oxo-2-(Pyridin-4-yl)quinazolin-3(4*H*)-yl)phenyl) hydrazine carbothioamide (7)**. A solution of compound **4** (0.01 mol), sodium hydroxide (0.01 mol), and carbon disulfide (0.01 mol) in dimethyl formamide (30 mL) was stirred at 15–20°C and after 1 h was added with hydrazine hydrate (0.01 mol), and the stirring continued at 60°C for 1 h. The separated solid after adding water was filtered off, washed with water, air dried, and then crystallized from DMF/ethanol to give compound **7**.

Crystallized from DMF/ethanol mp >300°C, yield 61%. Analysis: for $C_{20}H_{16}N_6OS$, MW 388.45, calcd: C: 61.84, H: 4.15, N: 21.63. Found: C: 61.73, H: 4.20, N: 21.55. IR (KBr; cm^-): 3455, 3391, 3287, 3189 (NH_2, 2NH), 1672 (C═O), 1130 (C═S). H-NMR (DMSO, δ ppm): 5.41 (s, 2H, NH_2 exchangeable with D_2O), 6.72–7.41 (m, 12H, Ar–H), 11.01, 11.80 (2s, 2H, 2NH exchangeable with D_2O). MS: (*m/z*) ~388 (28.31%).

3,5-Dimethyl-*N*-(4-(4-oxo-2-(pyridin-4-yl)quinazolin-3(4*H*)-yl)phenyl)-1*H*-pyrazole-1-carbothioamide (8). A mixture of **7** (0.01 mol) and acetyl acetone (0.05 mol) was heated on a water bath for 9 h. The reaction mixture was cooled, and the solid was filtered off, air dried, and crystallized from methanol to give compound **8**.

Crystallized from methanol mp 170°C, yield 65%. Analysis: for $C_{25}H_{20}N_6OS$, MW 452.53, calcd: C: 66.35, H: 4.45, N: 18.57. Found: C: 66.21, H: 4.39, N: 18.62. IR (KBr; cm^-): 3429 (NH), 1698 (C═O), 1614 (C═N), 1131 (C═S). H-NMR (DMSO, δ ppm): 2.37 (s, 6H, 2CH3), 6.82–8.12 (m, 13H, Ar–H, 1H of pyrazole), 10.82 (s, 1H, NH exchangeable with D_2O). MS: (*m/z*) ~452 (35%).

3-Methyl-5-oxo-*N*-(4-(4-oxo-2-(pyridin-4-yl)quinazolin-3(4*H*)-yl)phenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (9). A mixture of compound **7** (0.01 mol) and ethyl acetoacetate (0.05 mol) was heated on a water bath for 8 h. The reaction mixture was cooled, and the solid was filtered off, air dried, and crystallized from methanol to give compound **9**.

Crystallized form methanol mp 160°C, yield 70%. Analysis: for $C_{24}H_{18}N_6O_2S$, MW 454.50, calcd: C: 63.42, H: 3.99, N: 18.49. Found: C: 63.30, H: 4.01, N: 18.51. IR (KBr; cm^-): 3437 (NH), 1690, 1667 (2C═O), 1135 (C═S). H-NMR (DMSO, δ ppm): 1.97 (s, 3H, CH_3), 2.15 (s, 2H, CH_2), 7.11–7.95 (m, 12H, Ar–H), 10.15 (s, 1H, NH exchangeable with D_2O). MS: (*m/z*) ~454 (40%).

General procedure for preparation of compounds 11a,b. A mixture of compound **10a** (0.01 mol) and/or acetyl/benzoyl chloride (0.01 mol) in pyridine (20 mL) was refluxed for 6 h. The reaction mixture was cooled and poured into ice-cold water, and then the formed precipitate was filtered and crystallized from ethanol to give the corresponding compounds **11a**,**b**, respectively.

3-Cyclohexyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethanethioate (11a). Crystallized from ethanol, mp 168°C, yield 77%. Analysis: for $C_{16}H_{18}N_2O_2S$, MW 302.39, calcd: C: 63.55, H: 6.00, N: 9.26. Found: C: 63.57, H: 6.01, N: 9.19. IR (KBr; cm^-): 1714, 1697 (C═O), 1615 (C═N). H-NMR (DMSO, δ ppm): 1.98 (s, 11H, cyclohexane), 2.61 (s, 3H, $COCH_3$), 7.02–7.62 (m, 4H, Ar–H). MS: (*m/z*) ~302 (13.41%).

S-(3-Cyclohexyl-4-oxo-3,4-dihydroquinazolin-2-yl)benzothioate (11b). Crystallized from ethanol, mp 104°C, yield 104%. Analysis: for $C_{21}H_{20}N_2O_2S$, MW 364.46, calcd: C: 69.20, H: 5.53, N: 7.69. Found: C: 69.10, H: 5.62, N: 7.67. IR (KBr; cm^-): 1689 (C═O), 1533 (C═N). H-NMR (DMSO, δ ppm): 2.16 (s, 11H, cyclohexane), 6.96–7.55 (m, 9H, Ar–H). MS: (*m/z*) ~364 (18.53%).

2-((3-Cyclohexyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio) acetic acid (12). Sodium hydroxide (22 mmol) was dissolved in 50 mL of water, and 20 mmol of (**10a**) was added. After stirring for 15 min, a solution of 20 mmol of chloroacetic acid in 5 mL of methanol was added dropwise over 20 min. After the addition was completed, the solution was stirred at room temperature for about 2 h. The solid was filtered and recrystallized from ethanol to give compound **12**.

Crystallized from ethanol, mp 230°C, yield 80%. Analysis: for $C_{16}H_{18}N_2O_3S$, MW 318.39, calcd: C: 60.36, H: 5.70, N: 8.80. Found: C: 60.37, H: 5.67, N: 8.83. IR (KBr; cm^-): 3433 (OH), 1714, 1685 (C═O), 1623 (C═N). H-NMR (DMSO, δ ppm): 2.01 (s, 11H, cyclohexane), 4.52 (s, 2H, CH_2), 7.11–7.90 (m, 4H, Ar–H), 11.33 (s, 1H, OH exchangeable with D_2O). MS: (*m/z*) ~318 (10.7%).

General procedure for preparation of compounds 13a,b. Sodium hydroxide (0.022 mol) was dissolved in 50 mL of

water, and 0.02 mol of compounds **10a**,**b** was added. After stirring for 15 min, a solution of 0.002 mol of ethyl chloroacetate in 5 mL of methanol was added dropwise over 20 min. After addition was completed, the solution was stirred at room temperature for about 2 h. The solid was filtered and recrystallized from ethanol to give compounds **13a**,**b**.

Ethyl 2-((3-cyclohexyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio) acetate (13a). Crystallized from ethanol, mp 133°C, yield 69%. Analysis: for $C_{18}H_{22}N_2O_3S$, MW 346.44, calcd: C: 62.40, H: 6.40, N: 8.09. Found: C: 62.35, H: 6.17, N: 8.10. IR (KBr; cm^{-}): 1710, 1683 (C═O), 1609 (C═N). H-NMR (DMSO, δ ppm): 1.71 (t, 3H, CH_3, ethyl group), 2.01 (s, 11H, cyclohexane), 3.62 (q, 2H, CH_2, ethyl group), 4.07 (s, 2H, S–CH_2), 7.01–7.63 (m, 4H, Ar–H). MS: (*m/z*) ~346 (8.25%).

Ethyl 2-((4-oxo-3-(o-tolyl)-3,4-dihydroquinazolin-2-yl)thio) acetate (13b). Crystallized from ethanol, mp 119°C, yield 72%. Analysis: for $C_{19}H_{18}N_2O_3S$, MW 354.42, calcd: C: 64.39, H: 5.12, N: 7.90. Found: C: 64.20, H: 5.23, N: 7.96. IR (KBr; cm^{-}): 1715, 1686 (C═O), 1611 (C═N). H-NMR (DMSO, δ ppm): 1.51 (t, 3H, CH_3, ethyl group), 2.40 (s, 3H, CH_3), 3.60 (q, 2H, CH_2, ethyl group), 4.82 (s, 2H, S–CH_2), 6.92–7.91 (m, 8H, Ar–H). MS: (*m/z*) ~354 (13.51%).

General procedure for preparation of compounds 14a,**b**. A mixture of compounds **13a**,**b** (0.01 mol) and 4-chloroaniline (0.01 mol) in ethanol (20 mL) was added in flask. Then catalytic amount of concd sulfuric acid (five drops) was added. The mixture was refluxed for 2 h. On cooling, solid was separated out, filtered, and recrystallized from ethanol.

N-(4-Chlorophenyl)-2-((3-cyclohexyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio)acetamide (14a). Crystallized from ethanol, mp 165°C, yield 68%. Analysis: for $C_{22}H_{22}ClN_3O_2S$, MW 427.95, calcd: C: 61.74, H: 5.18, N: 9.82. Found: C: 61.57, H: 5.20, N: 9.80. IR (KBr; cm^{-}): 3225 (NH), 1691, 1672 (C═O), 1603 (C═C). H-NMR (DMSO, δ ppm): 2.10 (s, 11H, cyclohexane), 4.14 (s, 2H, CH_2), 6.98–7.75 (m, 8H, Ar–H), 9.98 (s, 1H, NH exchangeable with D_2O). MS: (*m/z*) ~427 (15.21%).

N-(4-Chlorophenyl)-2-((4-oxo-3-(o-tolyl)-3,4-dihydroquinazolin-2-yl)thio)acetamide (14b). Crystallized from ethanol, mp 120°C, yield 71%. Analysis: for $C_{23}H_{18}ClN_3O_2S$, MW 435.93, calcd: C: 63.37, H: 4.16, N: 9.64. Found: C: 63.35, H: 4.19, N: 9.69. IR (KBr; cm^{-}): 3180 (NH), 1689, 1670 (C═O), 1614 (C═C). H-NMR (DMSO, δ ppm): 2.45 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 6.65–7.40 (m, 12H, Ar–H), 11.20 (s, 1H, NH exchangeable with D_2O). MS: (*m/z*) ~435 (10.11%).

General procedure for preparation of compounds 15a,**b**. To a solution of compounds **13a**,**b** (0.01 mol) in DMF (10 mL), thiosemicarbazide (0.01 mol) was added, and the reaction mixture was refluxed for 6 h. The mixture was then cooled and poured into crushed ice, and the precipitate that formed was filtered off and crystallized from ethanol.

2-(2-((3-Cyclohexyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio) acetyl)hydrazine-1-carbothioamide (15a). Crystallized from ethanol, mp 212°C, yield 70%. Analysis: for $C_{17}H_{21}N_5O_2S_2$, MW 391.51, calcd: C: 52.15, H: 5.41, N: 17.89. Found: C: 52.13, H: 5.42, N: 17.90. IR (KBr; cm^{-}): 3401, 3240 (NH_2, NH), 1695, 1678 (C═O), 1240 (C═S). H-NMR (DMSO, δ ppm): 2.31 (s, 11H, cyclohexane), 4.41 (s, 2H, CH_2), 5.48 (s, 2H, NH_2 exchangeable with D_2O), 6.83–7.52 (m, 4H, Ar–H), 9.87, 10.62 (2s, 2H, 2NH exchangeable with D_2O). MS: (*m/z*) ~391 (19.81%).

2-(2-((4-oxo-3-(o-tolyl)-3,4-Dihydroquinazolin-2-yl)thio) acetyl)hydrazine-1-carbothioamide (15b). Crystallized from ethanol, mp 230°C, yield 78%. Analysis: for $C_{18}H_{17}N_5O_2S_2$, MW 399.49, calcd: C: 54.12, H: 4.29, N: 17.53. Found: C: 63.11, H: 4.29, N9.86. IR (KBr; cm^{-}): 3423, 3188 (NH_2, NH), 1698, 1670 (C═O), 1251 (C═S). H-NMR (DMSO, δ ppm): 2.29 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 5.40 (s, 2H, NH_2 exchangeable with D_2O), 7.51–8.22 (m, 8H, Ar–H), 9.84, 10.65 (2s, 2H, 2NH exchangeable with D_2O). MS: (*m/z*) ~399 (22.41%).

Biological evaluation. ***Antimicrobial activity test.*** The different synthesized compounds were examined for its antimicrobial activity against Gram-negative bacilli bacteria, Gram-positive cocci bacteria, *C. albicans*, and *A. niger* by well diffusion method [35,36]. The experiment was performed using a culture at 37°C for 24 h on 20 mL of nutrient agar for bacteria or PDA for yeast, which was poured into sterile Petri dishes and allowed for solidification. Wells were made in agar plates using sterile cork pore of 4 mm diameter. The cultures were adjusted to approximately 10^6 CFU/mL with sterile saline solution. One hundred and fifty microliters of the suspensions were spread over the agar plates using a sterile glass spreader. Each tested sample was dissolved in 1 mL of DMSO and sterilized by filtration through a 0.22-μm membrane filter (by using Millipore membrane filter apparatus). To the appropriate wells in the Petri dishes, 150 μg/mL of each sample was added separately.

Minimum inhibitory concentration value of quinazoline derivatives. Minimum inhibitory concentration value is performed according to Andrews *et al*. [37] and expressed as the lowest concentration of an antimicrobial compound that inhibits the visible growth of a microorganism after incubation 24 h for bacteria at 37°C and 48 h for fungi at 28°C. Well-cut diffusion technique was used to determine the minimal inhibitory effect of the final concentrations of antibacterial and antifungal agents, which were 25, 50, 100, and 200 μg/mL DMSO against all studied pathogens.

Antioxidant activity (DPPH assay). This assay was performed according to Brand-Williams *et al*. [38]. Stock

solutions from modified synthesized compounds samples will be prepared by dissolving 10 mg of samples in 1 mL DMSO is an organosulfur compound with the formula $(CH_3)_2SO$ and then diluted into several dilutions. A triplicate of 10 µL from each concentration will be prepared; after that, 90 µg/mL of DPPH was added on ELISA plate, and then the plate will be stored in dark cover with aluminum foil for 30 min then measured at 520 nm on ELISA apparatus /reader.

Anticoagulation activity. Adopting the method of the USA, Pharmacopeia [39], for the assay of sodium heparin, the anticoagulation activities, of the different synthesized compounds, were evaluated as follows.

Reagents. The reagents were human plasma, standard heparin sodium preparation, and calcium chloride solution 1% (w/v), and saline solution 0.9% (w/v).

Procedure. Hard-glass test tubes (31 × 100 mm) were cleaned by immersion overnight in chromic acid. To each tube was added 0.8 mL of sample solution (0.01%), 0.8 mL of standard heparin sodium solution (1.4 U.S.P unit/?0.8 mL), or 0.8 mL saline solution as control. To each of the prepared tubes, 1 mL plasma and 0.2 mL calcium chloride solution were added. The tubes were incubated in water bath at 37°C. The time was immediately recorded, and each tube was stoppered. The time required for clotting was then determined as an average of three reading.

Fibrinolytic activity. This was determined by exposing a plasma clot to the effect of an aqueous solution (at suitable concentration) of the investigation. Preparation of the plasma clot was achieved under the same conditions mentioned previously for determination of anticoagulation activity [39].

Procedure. Sets of three hard-glass test tubes (31 × 100 mm) were cleaned by immersion overnight in chromic acid. To each tube, 0.8 mL saline solution (0.89% w/v), 1 mL plasma, and 0.2 mL calcium chloride solution (1% w/v) were added. After mixing, the tubes were incubated in water bath at 37°C, and when clotting was complete, 1 mL of the saline solution, Hemoclar preparation (2 mg per tube), or the tested sample (1 mg per tube) was added individually. The lyses percentages of the plasma clots at 37°C were recorded with each sample and compared with that of standard Hemoclar.

CONCLUSION

Newly synthesized 3-phenyl-2-(pyridin-4-yl)quinazolin-4(3*H*)-one and their modified derivatives were evaluated with different biomedical activities as bactericidal and fungicidal agents. Derivatives of quinazoline compounds exhibited broad spectrum of antibacterial and antifungal activities.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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