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Synthesis and In Vitro Antibacterial Evaluation of Some Novel Annulated Quinazolinone Derivatives[1]

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Abstract—A series of novel substituted quinazoline derivatives are synthesized. Antibacterial tests demonstrate their high activity against Gram-positive and Gram-negative bacteria. 3-[4-(2-Bromoacetyl)-phenyl]-2-phenylquinazolin-4(3*H*)-one **2** and 3-oxo-3-{[4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}propane-nitrile **3** are used as intermediates in the synthesis of functionalized heterocyclic derivatives such as 3-[4-(2-amino-thiazol-5-yl)phenyl]-2-phenylquinazolin-4(3*H*)-one **4**, Schiff base **5**, 3-{5-(4-[4-oxo-2-phenylquina-zolin-3(4*H*)-yl]phenyl)thiazol-2-yl}-2-phenylthiazolidin-4-one **6,** and *N*-phenyl acetohydrazonoyl derivatives **7a, 7b**. The latter react with ethyl cyanoacetate with formation of **9a, 9b**. Chalcone **10** is the key intermediate in the synthesis of *N*-acetylpyrazole derivative **11** and 1-thiocaramoyl pyrazole derivative **12**. Treatment of **12** with chloroacetyl chloride and compound **2** leads to formation of compounds **13** and **14**, respectively. Treatment of compound **3** with phenyl isothiocyanate affords the corresponding quinazolin-3(4*H*)-yl acrylonitrile derivative **15**, which reacts with phenyl hydrazine to give the corresponding product **16**. The synthesized compounds are characterized by IR, MS and ^{1}H NMR spectra.

Keywords: quinazolin-4(3*H*)-one, pyrazolecarbonitrile, nitrogen nucleophile, antibacterial actiyity

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INTRODUCTION

Many quinazolinones derivatives demonstrated antibacterial, antifungal, antiviral, antitumor, anti-malarial, and some other types of biological activities [1–8]. Common anticancer compounds that are currently present on the market contain quinazolinone ring [9]. Enhancement of this type of activity could be achieved by combining quinazolinone moiety and thiazole ring in one molecule. For this reason we synthesized a corresponding series of novel annulated quinazoline derivatives with potential biological responses.

EXPERIMENTAL

Melting points were measured on an electro-thermal digital apparatus. IR spectra were recorded as KBr pellets on a Buck scientific model 500 IR spectrophotometer. ^{1}H NMR spectra were measured in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a Shimadzu GCMS-QP 2010 plus Ex mass spectrometer at 70 eV. Micro-analyses was carried out at the Micro-analytical center, Cairo University.

3-[4-(2-Bromoacetyl)phenyl]-2-phenylquinazolin-4(3*H*)-one (2). A mixture of 3-(4-acetylphenyl)-2-phenylquinazolin-4(3*H*)-one **1** (1 mmol) with *N*-bromo succinimide (1 mmol) in dioxane was refluxed for 4 h. The reaction mixture was filtered off while hot and concentrated. The precipitated solid was washed with petroleum ether (40 : 60) and recrystallized from ethanol to give compound **2**. Yield 72%, mp 190–192°C. IR spectrum, ν, cm^{-1}: 1705–1695 (CO), 1595 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.3 s (2H, CH_2), 7.7–7.75 m (13H, ArH). Found, %: C 63.04; H 3.49; Br 19.01; N 6.62. $C_{22}H_{15}BrN_2O_2$. Calculated, %: C 63.01; H 3.58; Br 19.07; N 6.68.

3-Oxo-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]-phenyl}propanenitrile (3). A mixture of compound **2** (1 mmol) with KCN (1 mmol) was refluxed in ethanol for 3 h. The precipitated solid was filtered off, dried and crystallized from benzene affording compound **3.** Yield 76%, mp 202–204°C. IR spectrum, ν, cm^{-1}: 2230 (CN), 1700–1690 (CO). ^{1}H NMR spectrum, δ, ppm: 3.7 s (2H, CH_2), 7.13–7.80 m (13H, ArH).

[1] The text was submitted by the author in English.

Found, %: C 75.53; H 4.10; N 11. 45. $C_{23}H_{15}N_3O_2$. Calculated, %: C 75.60; H 4.14; N 11.50.

3-[4-(2-Aminothiazol-5-yl)phenyl]-2-phenylquinazolin-4(3*H*)-one (4). Equimolar amounts of compound **2** and thiourea were refluxed in ethanolic piperidine solution for 6 h. The reaction mixture was poured onto ice HCl. The precipitated solid was filtered off and crystallized from butanol to give compound **4**. Yield 65%, mp 221–223°C. IR spectrum, ν, cm^{-1}: 3300–3200 (NH2), 1690 (CO). ^1H NMR spectrum, δ, ppm: 5.8–6.0 br.s (2H, NH_2), 6.99–7.51 m (14H, olefinic and ArH). Found, %: C 69. 63; H 4.02; N 14. 08. $C_{23}H_{16}N_4OS$. Calculated, %: C 69.68; H 4.07; N 14.13.

(*E*)-3-{4-[2-(Benzylideneamino)thiazol-5-yl]phenyl}-2-phenylquinazolin-4(3*H*)-one (5). A mixture of compound **4** (1 mmol) with benzaldehyde (1 mmol) was refluxed in ethanol containing piperidine for 3 h. The precipitated solid was separated, dried and recrystallized from ethanol to give compound **5**. Yield 80%, mp 170–172°C. IR spectrum, ν, cm^{-1}: 1695 (CO), 1600–1590 (C=N). Found, %: C 74. 29; H 4.09; N 11.49. $C_{30}H_{20}N_4OS$. Calculated, %: C 74.36; H 4.16; N 11.56.

3-{5-(4-[4-Oxo-2-phenylquinazolin-3(4*H*)-yl]-phenyl)thiazol-2-yl}-2- henylthiazolidin-4-one (6). A mixture of compound **5** (1 mmol) with thioglycolic acid (1 mmol) was refluxed in benzene for 10 h. The excess solvent was distilled off, and the precipitated solid was recrystallized from AcOH to give compound **6.** Yield 60%, mp 230–232°C. IR spectrum, ν, cm^{-1}: 1690–1680, (CO), 1605–1595 (CN). ^1H NMR spectrum, δ, ppm: 3.2 s (2H, CH_2), 5.2 s (1H, CH), 7.21–7.81 m (19H, olefinic and ArH). Found, %: C 68. 73; H 3.89; N 9.97. $C_{32}H_{22}N_4O_2S_2$. Calculated, %: C 68.80; H 3.97; N 10.03.

Synthesis of compounds 7a, 7b *(general procedure).* Aniline (1 mmol) solution in 10 mL of ethanol was mixed with 3 mL of concentrated hydrochloric acid and sodium nitrite dissolved in 15 mL of cold water and stirred for 1 h. Then it was added to a compound **2** or **3** in the presence of anhydrous sodium acetate. Upon completion, the reaction mixture was concentrated, the precipitated solid was filtered off, washed with petroleum ether (40 : 60) and recrystallized from butanol to give a compound **7a** or **7b**, respectively.

(*Z*)-2-Oxo-2-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-*N*-phenylacetohydrazonoylbromide (7a). Yield 51%, mp 246–248°C. IR spectrum, ν, cm^{-1}: 3260 (NH), 1695-1690 (CO). ^1H NMR spectrum, δ ppm: 7.30–7.85 m (18H, ArH), 9.3 s (1H, NH). Found, %: C 64.19; H 3.57; Br 15. 23; N 10.64. $C_{28}H_{19}BrN_4O_2$. Calculated, %: C 64.26; H 3.66; Br 15.27; N 10.70.

(*E*)-2-Oxo-2-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-*N*-phenylacetohydrazonoylcyanide (7b). Yield 58%, mp 261–263°C. IR spectrum, ν, cm^{-1}: 3250 (NH), 2230 (CN), 1690–1685 (CO). Found, %: C 74.05; H 4.01; N 14.86. $C_{29}H_{19}N_5O_2$. Calculated, %: C 74.19; H 4.08; N 14.92.

Synthesis of compounds 9a, 9b *(general procedure).* A mixture of compound **7** (1 mmol) with ethyl cyanoacetate was refluxed in boiling ethanol containing few drops of piperidine for 6 h. The precipitated solid was dried and recrystallized from AcOH to give a compound **9a** or **9b,** respectively.

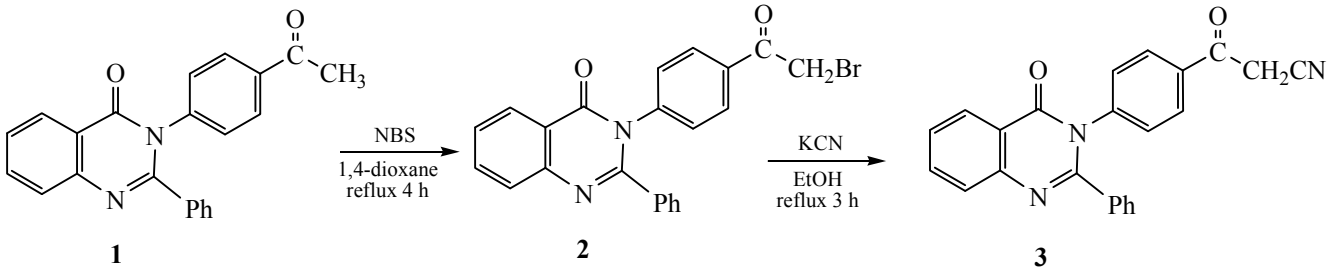
6-Bromo-3-oxo-5-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (9a). Yield 65%, mp 227–229°C. IR spectrum, ν, cm^{-1}: 2237 (CN), 1690–1689 (CO). Found, %: C 64. 97; H 3.08; Br 13.91; N 12.16. $C_{31}H_{18}BrN_5O_2$. Calculated, %: C 65.05; H 3.17; Br 13.96; N 12.23. MS: *m/z*: 572 $[M]^+$ 0.6.

6-Oxo-4-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]-phenyl}-1-phenyl-1,6-dihydro-pyridazine-3,5-dicarbonitrile (9b). Yield 61%, mp 251–253°C. IR spectrum, ν, cm^{-1}: 2235– 2230 (CN), 1695–1690 (CO). ^1H NMR spectrum, δ, ppm: 7.20–7.85 m (18H, ArH). Found, %: C 74.06; H 3.45; N 16.14. $C_{32}H_{18}N_6O_2$. Calculated, %: C 74.12; H 3.50; N 16.21.

(*E*)-2-{4[(4-Oxo-2-phenylquinazolin-3(4*H*)-yl]-benzoyl}-3-phenyl crylonitrile (10). A mixture of compound **3** (1 mmol) with benzaldehyde (1 mmol) was refluxed in ethanol for 4 h. The precipitated solid was dried and recrystallized from benzene to give compound **10**. Yield 53%, mp 217–219°C. IR spectrum, ν, cm^{-1}: 2230 (CN), 1693–1685 (CO). ^1H NMR spectrum, δ, ppm: 7.25–7.88 m (19H, olefinic and ArH). Found, %: C 79.38: H 4.16; N 9.23. $C_{30}H_{19}N_3O_2$. Calculated, %: C 79.46; H 4.22; N 9.27.

1-Acetyl-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-5-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile (11). A mixture of compound **10** (1 mmol) with hydrazine hydrate (1 mmol) was refluxed in AcOH for 4 h. The precipitated solid was dried and recrystallized from AcOH to give compound

Scheme 1.



1 **2** **3**

11. Yield 67%, mp 266–268°C. IR spectrum, ν, cm^{-1}: 2235 (CN), 1695-1685 (CO). ^1H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 4.85 s (1H, CH), 5.02 s (1H, CH), 7.11–7.56 m (18H, ArH). Found, %: C 75. 34; H 4.47; N 13. 45. $C_{32}H_{23}N_5O_2$. Calculated, %: C 75.43; H 4.55; N 13.74.

4-Cyano-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (12). A mixture of compound **10** (1 mmol) with thiosemicarbazide (1 mmol) was refluxed in acetic acid (30 mL) for 4 h. The reaction mixture was cooled down and treated with ice-cold hydrochloric acid. The precipitated solid was filtered off, washed with water, dried, and crystallized from benzene to give compound **12.** Yield 60%, mp 271–273°C. IR spectrum, ν, cm^{-1}: 3320-3300 (NH_2), 2230 (CN), 1390 (CS). Found, %: C 70.66; H 4.16; N 15.90. $C_{31}H_{22}N_6OS$. Calculated, %: C 70.70; H 4.21; N 15.96.

3-{4-[4-Oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-1-(4-oxo-4,5-dihydrothiazol-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile (13). A mixture of compound **12** with chloroacetyl chloride was refluxed in ethanolic trimethylamine for 3 h. The precipitated solid product was dried and recrystallized from EtOH to give compound **13**. Yield 57%, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2225(CN), 1690–1685 (CO). Found, %: C 69. 87; H; 3.84; N 14. 76. $C_{33}H_{22}N_6O_2S$. Calculated, %: C 69.95; H 3.91; N 14.83.

3-{4-[4-Oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-1-{5-(4-[4-oxo-2- phenylquinazolin-3(4*H*)-yl]phenyl) thiazol-2-yl}-5-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile (14). An equimolar mixture of compounds **12** and **2** was refluxed in ethanol containing few drops of piperidine for 5 h. The precipitated solid was dried and recrystallized from AcOH to give compound **14.** Yield 56%, mp 270–272°C. IR spectrum, ν, cm^{-1}: 2235 (CN), 1695-1680 (CO). Found, %: C 75.09; H 4.01; N 13.17. $C_{53}H_{34}N_8O_2S$. Calculated, %: C 75.16; H 4.05; N 13.23. MS: *m/z*: 846 $[M]^+$ 0.4.

(*E*)-3-(Methylthio)-2-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoyl}-3-(phenylamino)acrylonitrile (15). A mixture of KOH in DMF with the compound **3** was stirred for 4 h, then phenyl isothiocyanate was added. The precipitated solid was filtered off, washed with water, dried, and crystallized from xylene to give compound **15.** Yield 63%, mp 236–238°C. IR spectrum, ν, cm^{-1}: 3290 (NH), 2225 (CN), 1695–1685 (CO). Found, %: C 72.31; H 4.26; N 10.83. $C_{31}H_{22}N_4O_2S$. Calculated, %: C 72.35; H 4.31; N 10.89. MS: *m/z*: 514 $[M]^+$ 0.6.

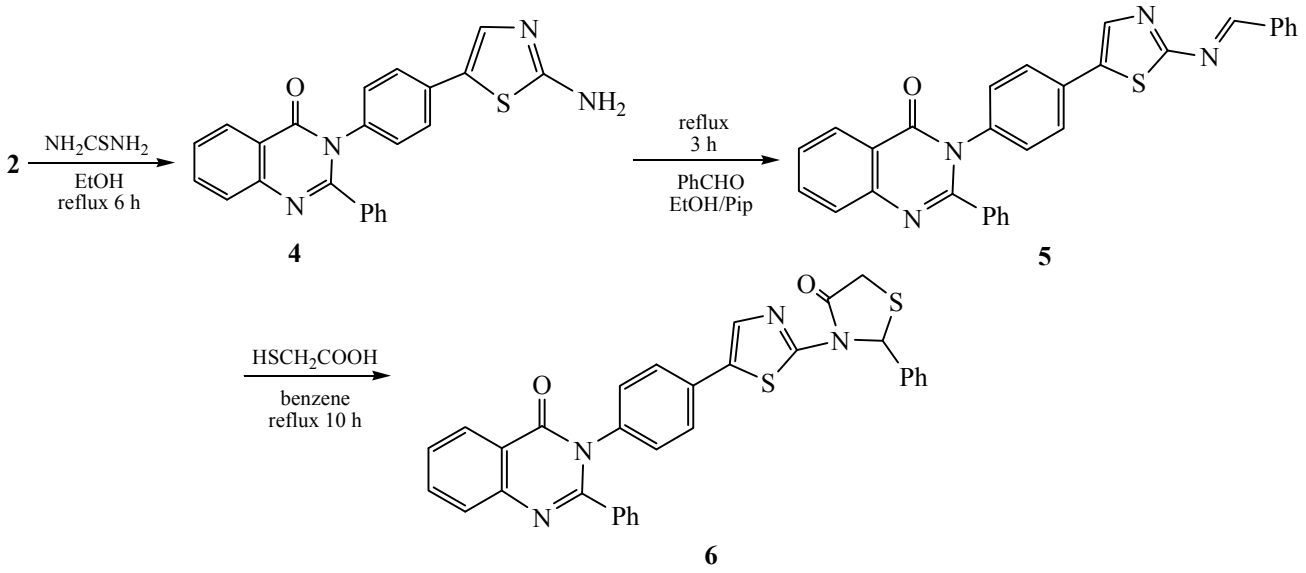
3-{4-[3-Amino-5-(phenylamino)-1*H*-pyrazole-4-carbonyl]phenyl}-2-phenylquinazolin-4(3*H*)-one (16). A mixture of compound **15** (1 mmol) with hydrazine hydrate (1 mmol) was refluxed in AcOH for 8 h. The precipitated solid product was dried and recrystallized from toluene to give compound **16**. Yield 60%, mp 273–275°C. IR spectrum, ν, cm^{-1}: 3360–3200 (NH, NH_2), 1690-1685 (CO). Found, %: C 72. 22; H 4.38; N 16. 82. $C_{30}H_{22}N_6O_2$. Calculated, %: C 72.28; H 4.45; N 16.86. MS: *m/z*: 498 $[M]^+$ 0.7.

RESULTS AND DISCUSSION

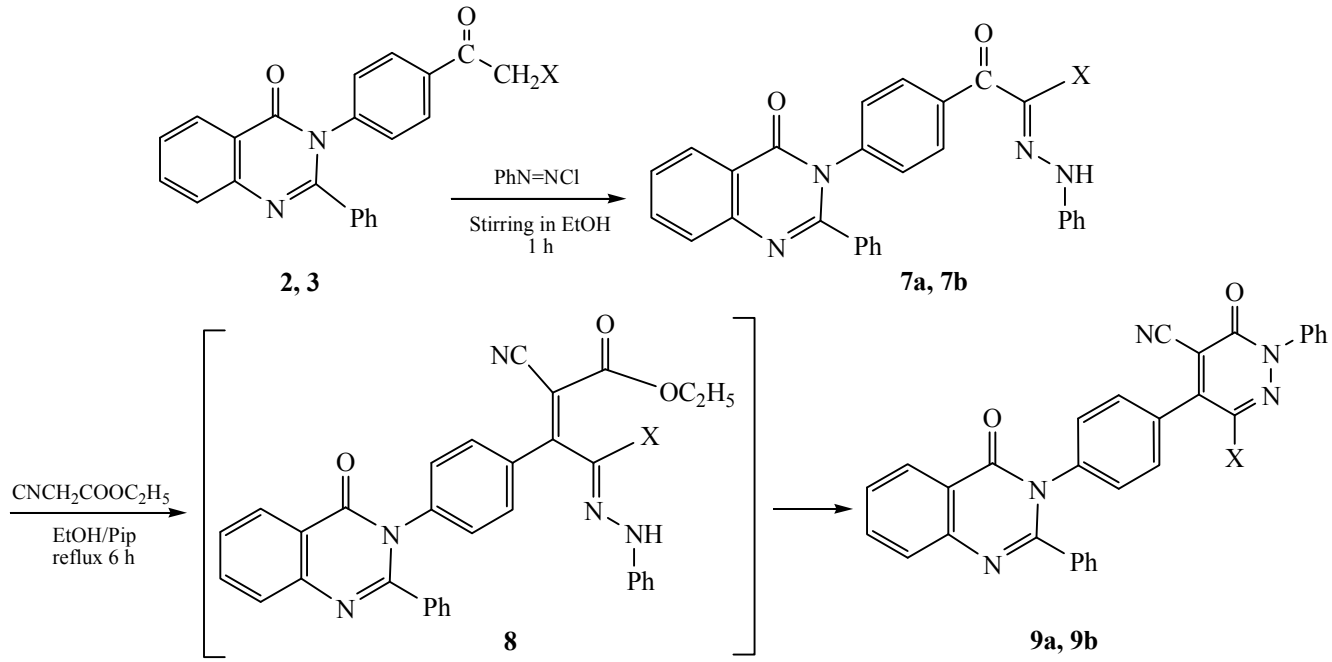
In continuation our earlier studies [10–14], we considered possible application of 3-(4-acetylphenyl)-2-phenylquinazolin-4(3*H*)-one **1** in the synthesis of different, otherwise not readily accessible, heterocyclic compounds containing quinazoline moiety with antimicrobial activity [15,16]. 3-[4-(2-Bromoacetyl)-phenyl]-2-phenylquinazolin-4(3*H*)-one **2** was prepared in quantitative yield by heating 3-(4-acetylphenyl)-2-phenylquinazolin-4(3*H*)-one **1** in dioxane with *N*-bromosuccinimide as a bromating agent. Treatment of 3-[4-(2-bromoacetyl)pheny])-2-phenyl-quinazolin-4(3*H*)-one **2** with KCN gave 3-oxo-3-{4-[4-oxo-2-phenyl quinazolin-3(4*H*)-yl]phenyl}propane nitrile **3** in high yield. The latter was used as a precursor in the synthesis of some heterocyclic compounds (Scheme 1).

Compound **2** reacted with thiourea [17] upon refluxing in ethanol–piperidine solution to give the

Scheme 2.



Scheme 3.

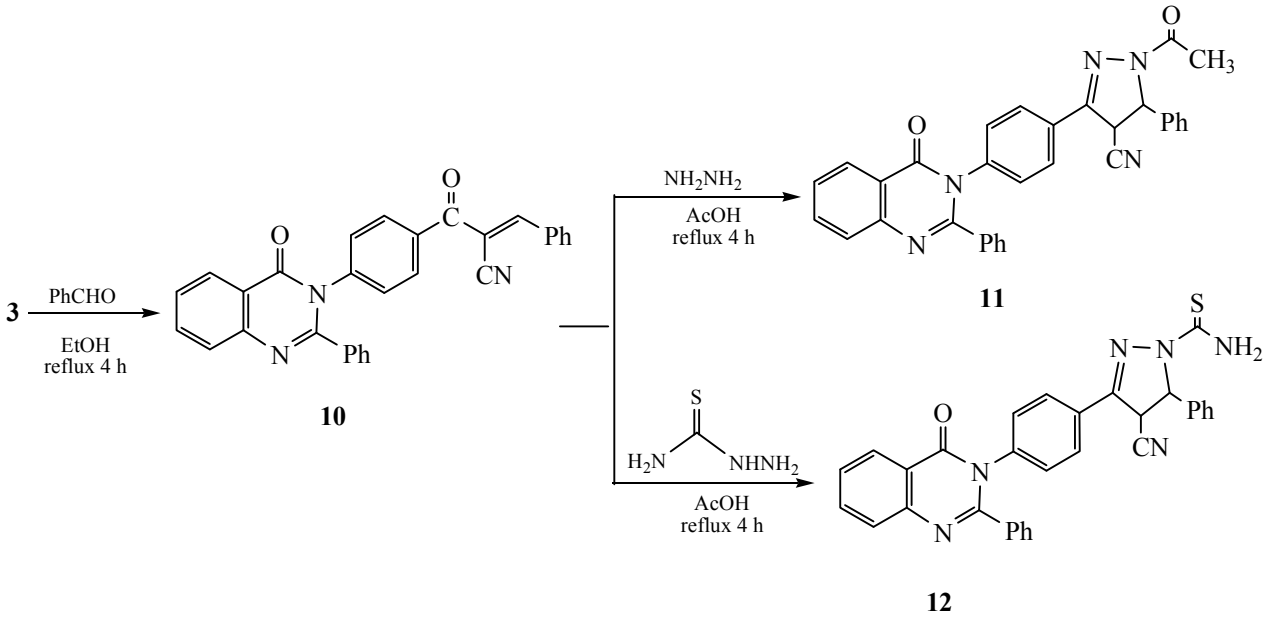


X = Br (**2, 7a, 9a**), CN (**3, 7b, 9b**).

corresponding 3-{4-(2-aminothiazol-5-yl)phenyl]-2-phenylquinazolin-4(3*H*)-one **4**. The latter was condensed with benzaldehyde in ethanol containing piperidine upon refluxing and led to the corresponding Schiff base **5.** 3-{5-(4-[4-Oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl)thiazol-2-yl}-2-phenylthiazolidin-4-one **6** was formed upon nucleophilic addition of the thiol function to the imino carbon of Schiff base.

Direct coupling of 3-[4-(2-bromoacetyl)phenyl]-2-phenylquinazolin-4(3*H*)-one **2** and/or 3-oxo-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}propane-

Scheme 4.



nitrile **3** with benzene diazonium chloride gave the corresponding (*Z*)-2-oxo-2-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-*N*-phenylacetohydrazonoyl bromide **7a** and (*E*)-2-oxo-2-{4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]phenyl}-*N*-phenylaceto-hydrazonoyl cyanide **7b,** respectively, in high yields (Scheme 3). Three reactive centers of compounds **7a, 7b** allowed to explore their application in preparing new heterocyclic derivatives. Thus, treatment of it with ethyl cyanoacetate in boiling ethanol in presence of few drops of piperidine afforded the corresponding 6-bromo-3-oxo-5-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-2-phenyl-2,3-dihydropyridazine-4-carbo-nitrile **9a** and 6-oxo-4-{4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]phenyl}-1-phenyl-1,6-dihydro-pyridazine-3,5-dicarbonitrile **9b**, respectively, via the intermediate **8,** which formed upon condensation of a compound **7a** or **7b** with ethyl-cyanoacetate and subsequent cyclization accompanied by elimination of ethanol (Scheme 3). The above assumption was based on the spectral data.

The key chalcone intermediate **10** was synthesized via condensation of equimolar amounts of 3-oxo-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}propane nitrile **3** with benzaldehyde in ethanol containing piperidine upon refluxing (Scheme 4).

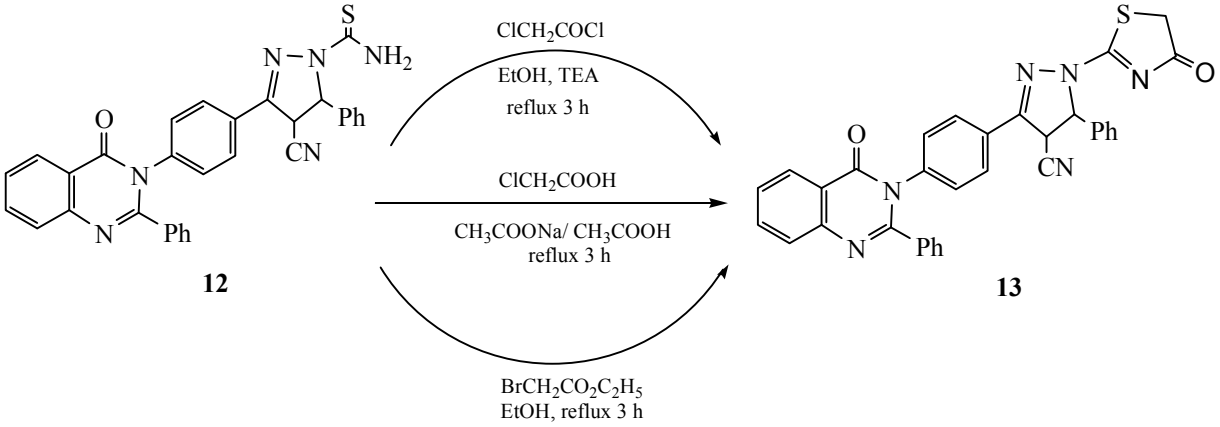
In the present study, two types of pyrazole derivatives were synthesized utilizing different reaction conditions [18, 19]. In acidic media the novel 1-acetyl-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-5-phen-yl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile **11** was synthesized by refluxing the corresponding (*E*)-2-{4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]benzoyl}-3-phenyl acrylonitrile **10** with hydrazine hydrate in acetic acid (Scheme 4).

The novel 4-cyano-3-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]phenyl}-5-phen-yl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **12** was obtained upon refluxing equimolar amounts of thiosemicarbazide and the corresponding α,β-unsaturated ketone **10** in acetic acid for 4 h (Scheme 4).

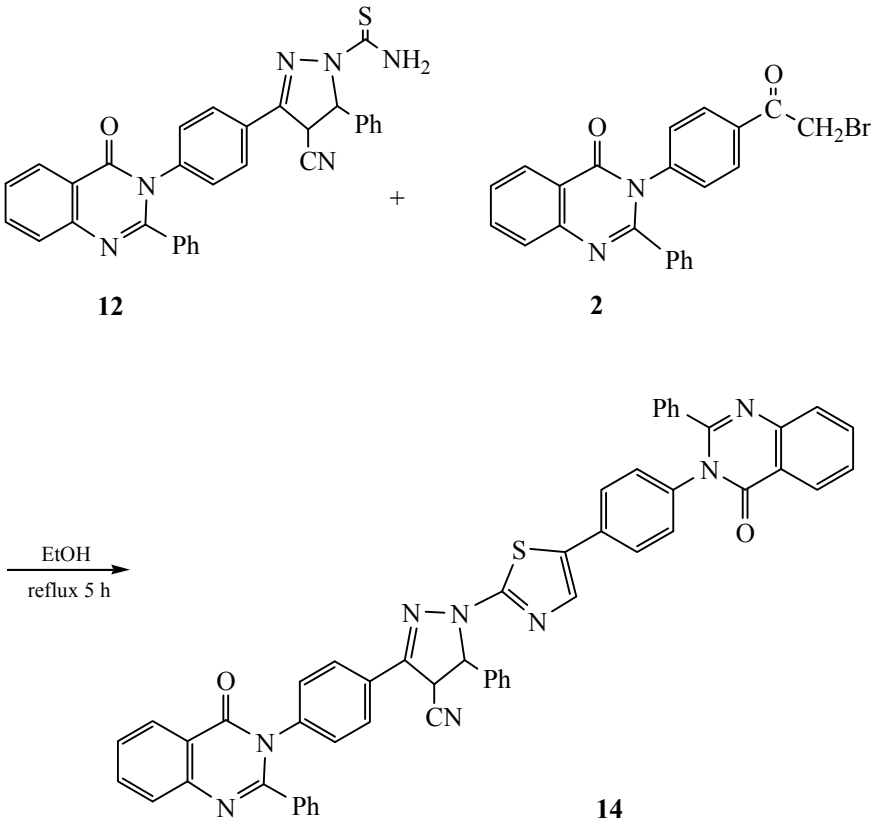
Treatment of compound **12** with chloroacetyl chloride in ethanolic TEA [20] led to 3-{4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]phenyl}-1-(4-oxo-4,5-dihydrothiazol-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile **13**. The same product was formed in the reaction of compound **12** with chloroacetic acid in glacial acetic acid in the presence of catalytic amount of sodium acetate. The third route to the product **13** involved reaction of compound **12** with ethyl bromoacetate in ethanol (Scheme 5).

Reaction of compound **12** with compound **2** upon refluxing in ethanol yielded 3-{4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]phenyl}-1-{5-(4-[4-oxo-2-phenyl-quinazolin-3(4*H*)-yl]phenyl)thiazol-2-yl}-5-phenyl-4,5-dihydro-1*H*-pyrazole-4-carbonitrile **14** (Scheme 6).

Scheme 5.



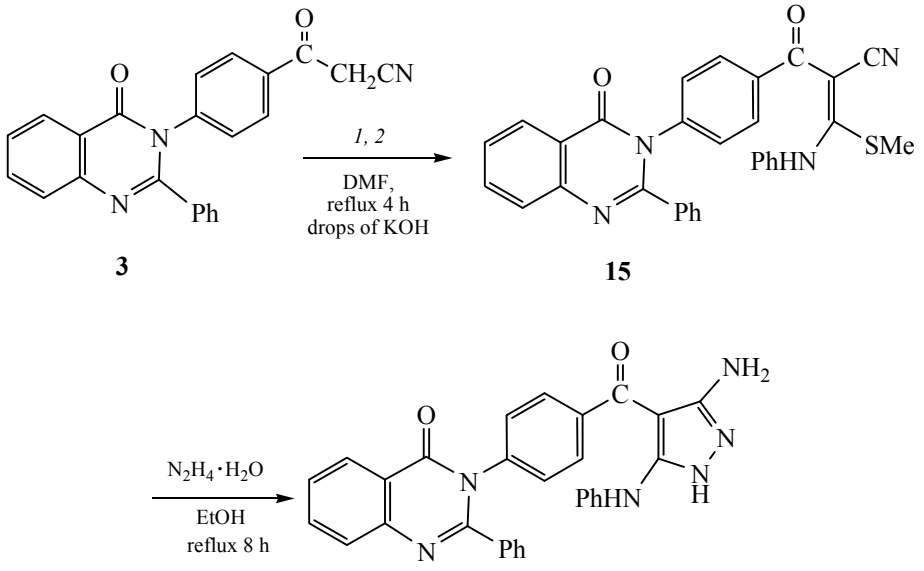
Scheme 6.



Treatment of compound **3** by phenyl isothiocyanate in DMF in the presence of KOH at room temperature, followed by addition of CH_3I led to (*E*)-3-(methylthio)-2-{4-[4-oxo-2-phenylquinazolin-3(4*H*)-yl]benzoyl}-3-(phenylamino)acrylonitrile **15** (Scheme 7).

Reaction of compound **15** with hydrazine upon refluxing in ethanol gave the corresponding pyrazole derivative **16** (Scheme 7). The structures of newly synthesized derivatives were confirmed by elemental analysis and spectroscopic data.

Scheme 7.



(*1*) PhNCS/KOH/DMF, (*2*) MeI.

Antimicrobial activity. Antibacterial activity of the newly synthesized compounds was tested by the agar well diffusion method [21] against Gram positive microorganisms *Staphylococcus aureus* (MTCC 96) and *Staphylococcus epidermis* (MTCC 435), and two kinds of Gram negative *Pseudomonas aeruginosa* (MTCC 741) and *Escherichia coli* (MTCC443) at concentration of 100 μg/mL using DMSO as a solvent. The bacteria were subcultured on Mueller Hinton agar medium. Streptomycin was used as a standard

Antibacterial activity of the synthesized compounds[a]

Comp. no.	Inhibitore zone diameter, mm				Compound	Inhibitore zone diameter, mm			
	gram negative strains		gram positive strains			gram negative strains		gram positive strains	
	Pseudomonas aeruginosa	*Staphylococcus epidermis*	*Staphylococcus aureus*	*Escherichia coli*		*Pseudomonas aeruginosa*	*Staphylococcus epidermis*	*Staphylococcus aureus*	*Escherichia coli*
2	22	18	21	20	**11**	22	19	19	18
3	20	20	19	17	**12**	19	15	17	13
4	17	14	18	14	**13**	20	16	19	17
5	20	15	20	18	**14**	17	13	20	15
6	19	21	17	19	**15**	18	16	17	19
7	16	21	16	15	**16**	15	13	18	16
9	19	21	18	19	Streptomycin (standard)	29	24	23	21
10	20	22	16	14					

[a] Concentration of standard 59 μg/mL, compounds 100 μg/mL.

antibacterial drug under similar conditions. The results of antibacterial screening are outlined in the table.

Antibacterial assay of all tested compounds demonstrated their high activity, with MIC values ranging from 100–0.2 μg/mL against both of Gram positive and Gram negative bacteria.

CONCLUSIONS

We have synthesized some novel 3-[4-(2-bromoacetyl)phenyl]-2-phenyl-quinazolin-4(3*H*)-one derivatives. All synthesized products demonstrated significant antibacterial activity.

ACKNOWLEDGEMENTS

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CONFLICT OF INTERESTS

No conflict of interest was declared by the author.

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