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SYNTHESIS OF NEW 4(3H)-QUINAZOLINONE DERIVATIVES OF POTENTIAL ANTIMICROBIAL ACTIVITY

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تم تحضير سلسله من مشتقات كينازولينون تحتوى على مجموعات هيدرازون وثيوسميكاربازيد وحلقة بيرازول و٤،٢،١ترايزولو[٤،٣ أ]كينازولين ٥ (٤ ه) اون وذلك لدراسة تأثير هذه المجموعات علي الفاعليه المتوقعه ضد الميكروبات. تم تخليق المركبات المستهدفه ٣ ٨ عن طريق تفاعل المركب الابتدائى ٢أ ، ٢ب مع الكيل أو اريل ايزوثيوسيانات. تفاعل ٢أ ، ٢ب مع الدهيد أو كيتون أروماتى نتج عنه هيدرازون مقابل ٩ ١٢. ٤ (٤ بيردينيل) ١و٢ دايهيدرو ٤ فنيل(الليل) ٤،٢،١ ترايزولو[٣،٤ أ]كينازولين ٥ (٤ه) اون ١٣ و ١٤ تم تحضيرهم عن طريق غليان ٩ او ١٠ في حمض خليك. أما ٤ (٣ مشتق ٤،٣ دايهدرو ٤ كينازولينون ٢ وايل) ٣ (٤ كلوروفنيل)بيرازول ٤ كاربالدهيد ١٥ أو ١٦ تم تحضيرهم بواسطة تفاعل ١١ أو ١٢ مع معامل فيلسمير هاك. وقد تم التأكد من التراكيب البنائيه للنواتج النهائيه اعتمادا علي نتائج التحاليل الطيفيه المختلفه الي جانب التحاليل الدقيقه لعناصرها المكونه هذا وقد تم اختبار تاثيرالمشتقات المذكوره علي تثبيط نمو بعض الكائنات البكتيريه و الفطريه وقد أشارت نتائج هذه الدراسه الي أن فاعلية المركبات المختلفه كمثبطات للبكتريا متوسطة بينما لم تظهر فاعليه تذكر ضد الفطريات.

*A new series of quinazoline-4(3H)-one derivatives containing hydrazone, thiosemicarbazide, pyrazole moiety and 1,2,4-triazolo[4,3-a]quinazolin-5-(4H)-one derivatives, were prepared in order to study the effect of such combinations on the expected antimicrobial activity. Synthesis of target compounds (**3-8**) has been achieved through an interaction of the starting **2a** or **2b** with different alkyl or aryl isothiocyanate. Condensation of **2a** or **2b** with various aromatic aldehydes or ketones afforded the corresponding hydrazones **9-12**. 1-(4-Pyridinyl)-1,2-dihydro-4-phenyl(allyl)-1,2,4-triazolo[4,3-a]quinazolin-5-(4H)-one deriva-*

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*tives **13**, **14** have been synthesized through reflux of compound **9** or **10** in glacial acetic acid. On the other hand, 1-(3-substituted-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde **15** or **16** has also been synthesized through interaction of compounds **11** or **12** with Vilsmeier-Haack reagent*[1].

The structures of the new compounds were assigned by spectral and elemental methods of analyses. The synthesized compounds were tested for their in vitro antibacterial and antifungal activities. The tested compounds showed moderate antibacterial activity and weak or no antifungal activity.

INTRODUCTION

Quinazolinone derivatives are important compounds in chemistry and pharmacology. They have drawn much attention due to their broad range of pharmacological properties[2&3], which include anticancer[4], anti-inflammatory[5], anticonvulsant[2] and diuretic[6] activities. Meanwhile, the quinazoline nucleus, as isostere for naphthalene, offers a convenient starting point in the search for new therapeutic agents, since several of its derivatives have been reported to possess antifungal activity as selective DHF-reductase inhibitors[7]. The scientific literature also states that the antiviral[8] and antibacterial[9&10] activities of thiourea derivatives are due to the presence of the -NH-C(=S)-NH- function in the molecule and the changes in this activity depend on the nature of its substituents. These observations prompted us to synthesize some new thiosemicarbazides, hydrazones and triazoloquinazolinones derived from 2-hydrazino-3-phenyl-4(3H)-quinazolinone **2a** and 2-hydrazino-3-allyl-4(3H)-quinazolinone **2b** to investigate their antibacterial and antifungal activities.

EXPERIMENTAL

Materials and equipments

Melting points were uncorrected and determined on an electrothermal melting point apparatus [Stuart Scientific, UK]. Precoated silica gel plates (kiesel gel 0.25 mm, 60G F254, Merck) were used for thin layer chromatography. Developing solvent system of chloroform/methanol (10:3) was used and the spots were detected by ultraviolet light. IR spectra (KBr disc) were recorded on IR-470 Shimadzu spectrometer, Japan. ^{1}H-NMR Spectra were scanned on a Varian EM-360 L NMR spectrometer (60 MHz) USA at Faculty of Pharmacy Assiut University. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard, using either $CDCl_3$ or DMSO-d_6 as a solvent. Elemental analyses were performed at the Department of Chemistry, Faculty of Science, Assiut

University, Assiut, and at micro analytical center, Faculty of Science, Cairo University, Cairo, Egypt. Antimicrobial activity was performed at Department of Botany and Microbiology, Faculty of Science, Al-Azhar University, Assiut, Egypt.

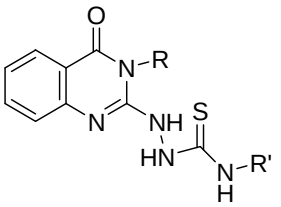
Preparation of 3-substituted-2-substituted-thiocarbamoylhydra-zino-3,4-dihydro-4-quinazolinones 3-8

A hot solution of **2a** or **2b** (0.01 mol) in abs. ethanol (25 mL) was treated with the equimolar amount of substituted isothiocyanate (0.01 mol). The clear solution was allowed to cool to room temperature while stirring. The product started to deposit after 30 min. Stirring was continued for 3 hrs and the separated product were filtered, washed with ethanol, dried and crystallized from methanol; **IR,** υ cm^{-1} (KBr): 3450-3230 (NH), 1683-1645 (C=O), 1646-1615 (C=N), 1600-1593 (C=C), 1531-1522, 1339-1329, 1077-1062, 896-812 (NCS I, mixed vibration bands); elemental analysis data are listed in Table 1 while ^{1}H-NMR data are presented in Table 2.

Table 1: Physicochemical data of the newly synthesized derivatives **3-8**.

Compd. No.	R	R`	Yield %	Formula	M.p. °C	Elemental analysis (Calc/found)		
						C	H	N
3	Ph	C_2H_5	90	$C_{17}H_{17}N_5OS$ (339.42)	136-8	60.16 59.69	5.05 4.35	20.63 20.86
4	Ph		85	$C_{18}H_{17}N_5OS$ (351.43)	144-6	61.52 60.41	4.88 4.66	19.93 19.37
5	allyl		70	$C_{15}H_{17}N_5OS$ (315.39)	150-2	57.12 56.96	5.43 5.29	22.21 21.73
6	allyl	C_6H_5-	82	$C_{18}H_{17}N_5OS$ (351.43)	164-6	61.52 61.28	4.88 5.13	19.93 19.57
7	allyl	p-CH_3-C_6H_5-	80	$C_{19}H_{19}N_5OS$ (365.45)	156-8	62.44 61.77	5.24 4.88	19.16 18.85
8	allyl	m-CH_3-C_6H_5-	74	$C_{19}H_{19}N_5OS$ (365.45)	150-2	62.44 62.40	5.24 4.54	19.16 19.29

Table 2: ^1H NMR data ($CDCl_3$) (60 MHz) of 3-substituted-2-substituted-thiocarbamoylhydrazino-3,4-dihydro-4-quinazolinone **3-8**.



Compd. No.	R	R`	
3	Ph	C_2H_5	1.3 (t, 3H, CH_3), 3.9 (m, 2H, CH2 and –NH-NHCS-), 5.7 (br.s, -NH-Et), 7.5-8.9 (m, 9H, aromatic Hs), 9.3 (br.s., 1H, NH-NH-CS-)
4	Ph	$H_2C=\overset{H}{C}-CH_2$	4 (br. s, 1H, -NH-NH-CS-), 4.5 (d, 2H, -CH_2-CH=CH_2), 5-5.7 (m, 3H, -CH_2-CH=CH_2), 9.6 (br.s, 1H, -HN-Allyl), 10.7 (br.s, 1H, -NH-NH-CS-)
5	allyl	$H_2C=\overset{H}{C}-CH_2$	2.2 (br.s, 1H, -NH-NH-CS-), 4.7 (d, 2H, -NH-CH_2-CH=CH_2), 5.1 (d, 2H, >N^3-CH_2-CH=CH_2), 5.5(d, 2H, ->N^3-CH_2-CH=CH_2), 5.7 (d, 2H, -CS-NH-CH_2-CH=CH_2), 6.0-6.8 (m, 2H, two -CH=CH_2), 7.5-9.0 (m, 4H, aromatic Hs), 10.3 (br. s, 1H, -NH-allyl), 10.8 (-NH-NH-CS-)
6	allyl	C_6H_5-	5.2 (d, 2H, -CS-NH-CH_2-Ph), 5.7 (d, 2H, ->N^3-CH_2-CH=CH_2), 6.4 (m, 1H, -CH=CH_2), 7.5-8.9 (m, 9H, aromatic Hs), 9.8 (-NH-NH-CS-), 10.6 (br. s, 1H, -CS-NH-Ph), 11.4 (br.s, 1H, -NH-NH-CS-)
7	allyl	*p*-CH_3-C_6H_5-	2.5 (s, 3H, CH_3), 5.1 (d, 2H, -CS-NH-CH_2-p-tolyl), 5.6 (d, 2H, ->N^3-CH_2-CH=CH_2), 6.4 (m, 1H, -CH=CH_2), 7.3-8.7 (m, 8H, aromatic Hs), 9.6 (br. s, 1H, -NH-NH-CS-), 10.5 (br. s, 1H, -CS-NH-Ph), 11.1 (br.s, 1H, -NH-NH-CS-)
8	allyl	*m*-CH_3-C_6H_5-	2.4 (s, 3H, CH3), 5.1 (d, 2H, -CS-NH-CH_2-p-tolyl), 5.5 (d, 2H, ->N^3-CH_2-CH=$_{CH2}$), 6.3 (m, 1H, -CH=CH_2), 7.1-8.5 (m, 8H, aromatic Hs), 9.5 (br. s, 1H, -NH-NH-CS-), 10.5 (br. s, 1H, -CS-NH-Ph), 11.0 (br.s, 1H, -NH-NH-CS-)

Synthesis of the hydrazones 9-12

A solution of compound **2a** or **2b** (0.01 mol) and concentrated acetic acid (1 mL) in absolute ethanol (25 mL) was treated with the equimolar amount of the appropriate aldehyde or acetophenone and heated under reflux for 2 h. The separated product was filtered, washed with ethanol, dried and crystallized from dioxane-water; **IR,** υ cm^{-1} (KBr): 3202-3118 (NH), 1673-1677 (C=O), 1602-1609 (hydrazone C=N), 1548-1554 (pyrimidine C=N); MS: m/z (rel. abund. %): for compound **9** M^+ at 341 (30.6), 262 (96.3), 235 (29.2), 220 (13.1), 119 (28.0), 76 (100). MS: m/z (rel. abund. %): for compound **11** M^+ at 388 (13.4), M^++2 at 390 (4.0), 373 (20.8), 276 (10.1), 235 (16.1), 138 (14.6), 118 (13.4), 102 (45.3), 77 (83.1), 76 (100). Elemental analysis data are listed in Table 3 while ^{1}H-NMR data in Table 4.

Synthesis of 1-(4-pyridinyl)-1,2-dihydro-4-substituted-[1,2,4]triazolo[4,3-a]quinazolin-5-(4H)-one (13, 14)

A solution of compound **9** or **10** (0.01 mol) in gl. acetic acid (6 ml) was heated under reflux for 8 hr. The reaction mixture was allowed to cool to room temperature. and poured onto ice-cold water. The separated product was filtered, washed with water, dried and crystallized from DMF-water. Yield 85% (4.7 g) of **13** or 80% (4.17 g) of **14**.

1-(4-pyridinyl)-1,2-dihydro-4-phenyl[1,2,4]triazolo[4,3-a]quinazolin-5-(4H)-one (13)

Yellowish crystals, m.p. 328-30°. **IR,** υ cm^{-1} (KBr): 1696 (C=O), 1616 (C=N), 1595 (C=C); ^{1}H-NMR (DMSO-d_6): δ 7.6-8.5 (m, 11H, NH, N-Ph-Hs, Ar-Hs at C-1, C-6, C-7, C-8, C-9), 8.7 (d, 2H, pyridine C-3-H and C-5-H), 9.1 (d, 2H, pyridine C-2-H and C-6-H). ; MS : m/z (rel. abund. %): M^+ at 341 (2.6), 338 (100), 76 (75.1). Anal. Calc. for $C_{20}H_{15}N_5O$ (M.Wt 341.37): C, 70.37; H, 4.43; N, 20.52. Found: C, 70.07; H, 4.18; N, 21.25.

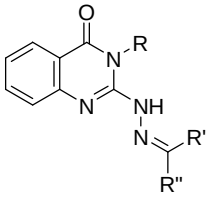
1-(4-pyridinyl)-1,2-dihydro-4-Allyl-[1,2,4]triazolo[4,3-a]quinazolin-5-(4H)-one 14

Orange crystals**,** m.p. 126-8°. **IR,** υ cm^{-1} (KBr): 1681 (C=O), 1602 (C=N), 1538 (C=C); ^{1}H-NMR (DMSO-d_6): δ 4.5 (d, 2H, -$\underline{CH_2}$-$CH=CH_2$), 5.2 (d, 2H, -$CH=\underline{CH_2}$), 5.4-5.9 (m, 1H, -$\underline{CH}=CH_2$), 7.5-8.4 (m, 6H, NH, Ar-Hs at C-1, C-6, C-7, C-8, C-9), 8.4-8.8 (d, 2H, pyridine C-3-H and C-5-H), 9.2-9.7 (d, 2H, pyridine C-2-H and C-6-H). MS : m/z (rel. abund. %): M^+ at 305 (0.8), 290 (1.6), 232 (41.0), 190 (12.1), 161 (11.9), 144 (44.9), 118 (16.6), 106 (100), 90 (71.2), 76 (37.4). Anal. Calc. for $C_{17}H_{15}N_5O$ (M.Wt 305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 67.11; H, 4.80; N, 22.98.

Table 3: Physicochemical data of the newly synthesized derivatives **9-12**.

No.	R	R`	R"	Yield %	Formula	M.p. °C	Elemental analysis (Calc/found)		
							C	H	N
9	Ph	H	4'-pyridinyl	85	$C_{20}H_{15}N_5O$ (341.37)	246-8	70.37 70.22	4.43 3.70	20.52 21.11
10	Allyl	H	4'-pyridinyl	81	$C_{17}H_{15}N_5O$ (305.33)		66.87 66.95	4.95 4.76	22.94 22.94
11	Ph	CH_3	*4*'-Cl-phenyl	80	$C_{22}H_{17}ClN_4O$ (388.85)	160-2	67.95 67.77	4.41 4.60	14.41 14.81
12	Allyl	CH_3	*4*'-Cl-phenyl	76	$C_{19}H_{17}ClN_4O$ (352.82)		64.68 64.92	4.86 4.51	15.88 15.97

Table 4: ^{1}H NMR data ($CDCl_3$ / DMSO-d_6) (60 MHz) hydrazone derivatives **9-12**.



Compd. No.	R	R`	R"	
9*	Ph	H	4'-pyridinyl	7.1-8.9 (m, 12H, quinazolinone Ar-Hs, N-Ph-Hs, N=CH pyridinyl C-3 and C-5-Hs), 9.3 (d, 2H, pyridinyl C-2 and C-6-Hs), 11.6 (br.s., 1H, NH).
10	Allyl	H	4'-pyridinyl	5.2 (d, 2H, -$\underline{CH_2}$-CH=CH_2), 5.7 (d, 2H, -CH_2-CH=$\underline{CH_2}$), 6.1-6.8 (m, 1H, -CH_2-$\underline{CH}$=CH_2), 7.5-8.4 (m, 4H, quinazolinone Ar-Hs), 8.8 (d, 2H, pyridine C-3-H and C-5-H), 9.0 (s, 1H, -N=CH), 9.3 (d, 2H, pyridine C-2-H and C-6-H), 10 (br.s, 1H, NH).
11	Ph	CH_3	*4*'-Cl-phenyl	2.3 (s, 3H, CH_3), 7.5-8.9 (m, 13H, Ar-Hs), 10.1 (br.s., 1H, NH)
12	Allyl	CH_3	*4*'-Cl-phenyl	2.7 (s, 3H, CH_3), 5.2 (d, 2H, -$\underline{CH_2}$-CH=CH_2), 5.6 (d, 2H, -CH_2-CH=$\underline{CH_2}$), 6.1-7.0 (m, 1H, -CH_2-$\underline{CH}$=CH_2), 7.4-8.9 (m, 8H, Ar-Hs), 9.8 (br.s., 1H, NH)

* Deuterated solvent is DMSO-d_6

Vilsmeier-Haack reaction

Dimethylformamide (2.56 g, 0.035 mol) and $POCl_3$ (5.35 g 0.035 mol) were separately cooled at 0 °C before being mixed and stirred at such temperature. A solution of compounds **11** or **12** (0.0116 mol) in DMF (3 mL) was added drop wise to the reaction mixture, which was warmed at room temperature then heated at 70-80°C for 5 h. After cooling at room temperature, the mixture was basified with a cold saturated K_2CO_3 solution. The precipitate was filtered, strongly washed with water and crystallized from ethanol, yielding 95% (4.7 g) of **15** or 92% (4.17 g) of **16**.

1-(3-Phenyl-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde 15

Yellow crystals, m.p. 230-2°. **IR,** υ cm^{-1} (KBr): 1709 (aldehyde C=O), 1666 (quinazoline C=O), 1645 and 1597 (C=N) ^{1}H-NMR (DMSO-d_6) δ 7.7-9.0 (m, 14H, Ar-Hs and pyrazole-C_5-H), 10.3 (s, 1H, CHO). Anal. Calc. for $C_{24}H_{15}ClN_4O_2$ (M.Wt 426.85): C, 67.53; H, 3.54; N, 13.13. Found: C, 67.50; H, 3.41; N, 13.37.

1-(3-Allyl-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chlorophenyl) pyrazole-4-carbaldehyde 16

Yellow needles, m.p. 146-8°. ^{1}H-NMR (DMSO-d_6) δ 5.2 (d, 2H, -$\underline{CH_2}$-CH=CH_2), 5.7 (d, 2H, -CH=$\underline{CH_2}$), 6.1-6.6 (m, 1H, -$\underline{CH}$=CH_2), 7.5-8.8 (m, 9H, aromatic Hs and pyrazole-C_5-H), 10.5 (s, 1H, CHO). Anal. Calc. for $C_{21}H_{15}ClN_4O_2$ (M.Wt 390.82): C, 64.54; H, 3.87; N, 14.34. Found: C, 64.80; H, 3.89; N,14.53.

Antimicrobial screening

Bacterial and Fungal cultures were obtained from Department of Botany and Microbiology, Faculty of science, Al-Azhar University, Assiut, Egypt

Antibacterial activity

Organisms and culture conditions

Four bacterial species represent both Gram-positive and Gram-negative strains were used to test the antibacterial activities of the target compounds: *Staphylococcus aureus*, and *Bacillus subtilis* as representatives for the Gram-positive strains, while the Gram-negative strains were represented by *Klepsilla pneumoniae, and Escherichia coli.*

Materials and method[11]

Cell suspension of bacterial strains was prepared from 48 h old cultures, grown on Nutrient Agar (NA) in sterilized water. The nutrient agar plates (15 cm in diameter) were seeded using 0.1 mL of diluted organism. Cylindrical plugs were removed from the agar using a sterile cork bore. 100 µL of the tested compounds **3-16** (100 µmol/mL in DMSO) and the blank solvent were added to each well in triplicate. The seeded plates were incubated at 35±2° for 24 h. After 24 h incubation the average diameter of inhibition zones was measured in millimeters, Table 5. A solution of chloramphenicol (100 µmol/mL in DMSO) was used as the standard[12] antibacterial agent.

Table 5: Antimicrobial activity of the tested compounds (expressed as the diameter of the inhibition zone[a]).

No.	Rhizupus nigrecans	Aspergillus flavuss	Aspergillus parasiticus	Penicillum italicum	Staphylococcus aureus	Bacillus subtilis	Escherichia coli	Klepsilla pneumonia
3	-	-	9	13	11	15	12	15
4	-	-	-	-	18	18	19	20
5	-	-	7	-	20	11	22	15
6	-	8	-	12	12	10	20	17
7	-	-	-	13	10	16	19	10
8	-	-	-	12	21	15	-	-
9	-	-	10	-	19	15	-	18
10	-	-	-	-	22	14	-	-
11	-	-	-	-	16	13	14	11
12	-	-	-	-	14	11	12	12
13	-	-	-	-	18	-	-	-
14	-	-	-	-	17	-	-	-
15	-	-	-	-	12	-	-	-
16	-	-	-	-	12	-	-	-
Chlor	-	-	-	-	24	32	30	20
Mycost	23	22	20	25	-	-	-	-

[a)]Average of three observations.
Inhibition zone in mm.
"-" no inhibition zone.

Antifungal activity

Organisms and culture conditions

Four fungal species were used in the present study: *Rhizupus nigrecans, Aspergillus flavus, Aspergillus parasiticus, and Penicillum italicum.*

Materials and method[10]

Spore suspension in sterile malt extract broth media was prepared from 2-5 days old culture of the test fungi growing on malt extract agar (MEB). The final spore concentration was 5 x 10^4 spores/mL. About 15 mL of growth medium was introduced on sterilized Petri dishes of 9 cm diameter and inoculated with 1 mL spore suspension. Plates were shaken gently to homogenize the inoculum. Antifungal activity of the tested compounds **3-16** was performed by the standard agar cup diffusion method as follow: Cylindrical plugs were removed from the agar using a sterile cork bore. 100 µL of the tested

compounds (100 µmol/mL in DMSO) and the blank solvent were added to each well in triplicate. The seeded plates were incubated at 28±2° for 3-7 days. After the specified time for incubation the average diameter of inhibition zones was measured in millimeters, Table 5. In addition to a solution of mycostatin (100 µmol/mL in DMSO) was used as standard[11] antifungal agent.

RESULTS AND DISCUSSION

Chemistry

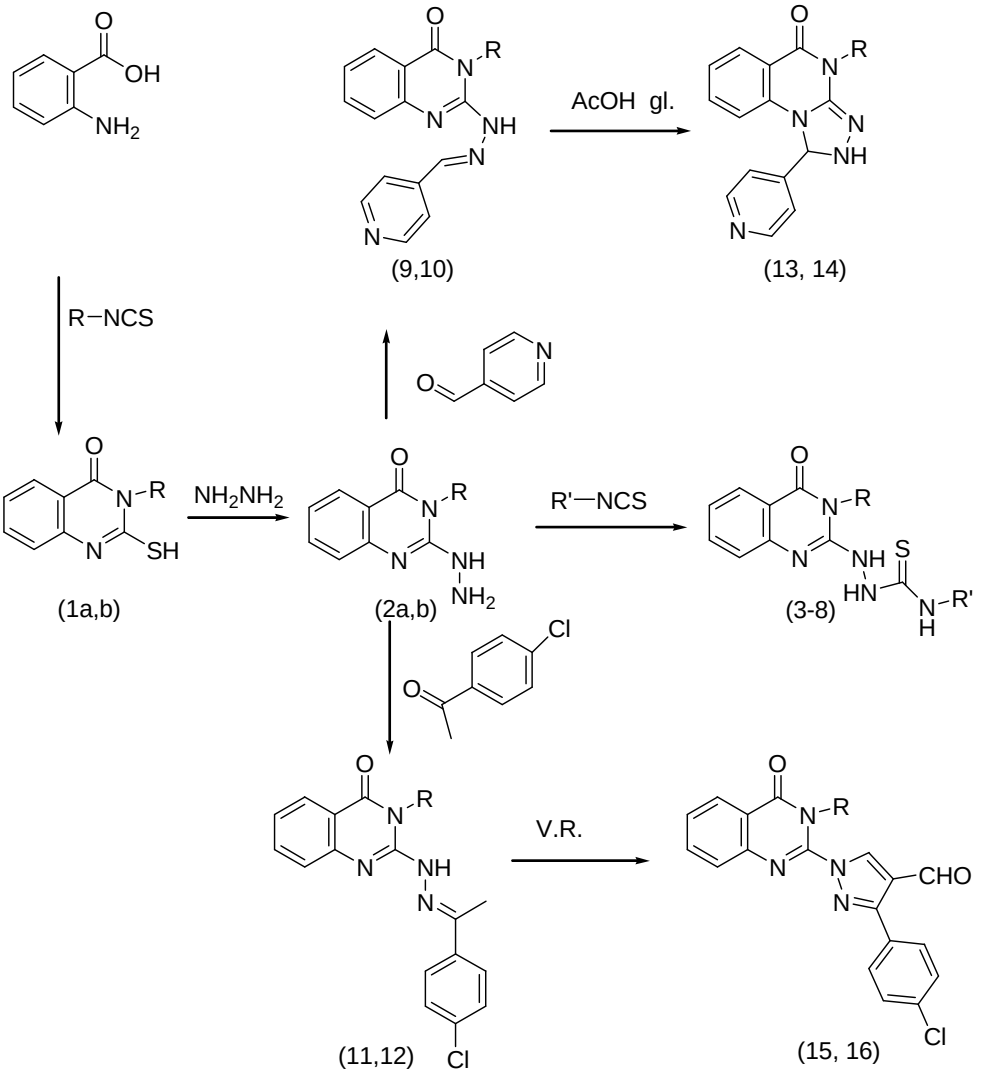
In this study we have prepared new 4(3H)-quinazolinone derivatives from 2-hydrazino-3-allyl(phenyl)-4(3H)-quinazolinone **2a** or **2b** as shown in the following scheme. The initial step in the synthetic method involved the synthesis of 2-mercapto-3-allyl(phenyl)-4(3H)-quinazolinone **1a** or **1b** through a reported method[13]. In the second step, **1a** or **1b** was refluxed with hydrazine hydrate to give 2-hydrazino-3-allyl(phenyl)-4(3H)-quinazolinone[14] **2a** or **2b** which was reacted with equimolar amount of substituted isothiocyanate, isonicotinaldehye and *p*-chloroacetophenone to give the required new compounds 3-substituted-2-substituted-thiocarbamoylhydrazino-3,4-dihydro-4-quinazolinone **3-8**, 3-substituted-2-(4-pyridinyl)methylidene-hydrazino-3,4-dihydro-4-quinazolinone **9, 10,** 3-substituted-2-[1-(4-chlorophenyl)]ethylidenehydrazino-3,4-dihydro-4-quinazolinone **11, 12**, respectively. 1-(3-Substituted-3,4-dihydro-4-quinazolinone-2-yl)-3-(4-chloro phenyl)pyrazole-4-carbaldehydes (**15, 16**) were prepared by the reaction of compounds **11** or **12** with Vilsmeier-Haack reagent. While heating compounds **9** or **10** in acetic acid under reflux gave the corresponding derivatives 1-(4-pyridinyl)-1,2-dihydro-4-substituted-[1,2,4]triazolo[4,3-a]quinazolin-4-(3H)-one **13** or **14**.

Structures of the synthesized compounds were verified on the bases of microanalysis, IR, ^{1}H NMR and MS spectral data. The IR of the quinazolinone derivatives **3-8** showed 3442-3192 (NH), 1690-1645 (C=O), 1646-1615 (C=N), 1550-1520, 1340-1310, 1073-1050, and 870-830 cm^{-1} (NCS I, mixed vibration bands).

Tables 1 and 3 show the physicochemical constants of compounds **3-8** and **9-12** respectively**.** The spectral data of compounds **3-8** and **9-12** are shown in Tables 2 and 4 respectively. All spectral data are in accordance with the expected structures.

Antimicrobial activity

The synthesized compounds 3-16 were tested for their antifungal activity in vitro against (*Rhizupus nigrecans, Aspergillus flavus, Aspergillus parasiticus, and Penicillum italicum)* fungi using agar cup diffusion method[11] and mycostatin[12] as standard. The same compounds were tested, in vitro for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Klepsilla pneumoniae*, and



R= Ph, allyl; R'= C_2H_5, CH_2=CH-CH_2, C_6H_5, p-CH_3-C_6H_4, m-CH_3-C_6H_4

Scheme

Escherichia coli using chloramphenicol as standard[12] Table 5.

The antimicrobial study explored variable activities for variation at position 2 and 3 of 4(3H)-quinazolinone nucleus. Results clearly indicate that 4(3H)-quinazolinone nucleus has good antibacterial activity while showed weak antifungal activity against *Aspergillus parasiticus, and Penicillum italicum* and no antifungal activity against *Rhizupus nigrecans, Aspergillus flavus.*

Against *Staphylococcus aureus,* all the tested 4(3H)-quinazolinone compounds **3-16** showed good antibacterial activity.

While against *Bacillus subtilis, Klepsilla pneumoniae,* and *Escherichia coli* good antibacterial results obtained with thiosemicarbazide and hydrazone compounds **3-12** and no antibacterial activity found for the 1-(4-pyridinyl)-1,2-dihydro-4-substituted-[1,2,4]triazolo-[4,3-a]quinazolin-4-(3H)-one **13** or **14** and 1-(3-Substituted-3,4-dihydro-4-quinazolinon-2-yl)-3-(4-chloro-phenyl)pyrazole-4-carbaldehyde **15, 16**. In other words cyclization of the hydrazones into pyrazolecarbaldehyde or into triazole ring abolished the antibacterial activity of the compounds.

Conclusions

In this work a series of quinazoline-4(3H)-one derivatives was synthesized and tested for antimicrobial activity. The study showed that these compounds have antibacterial activity and have weak or no antifungal activity.

The thiosemicarbazide, hydrazone derivatives of quinazoline-4(3H)-one showed antibacterial activity against all the tested bacterial organisms. However, 4-quinazolinon-2-yl pyrazole-4-carbaldehyde derivatives and [1,2,4]triazolo[4,3-a]quinazolin-4-(3H)-one derivatives showed antibacterial activity only against *Staphylococcus aureus.*

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