Original Articles

SYNTHESIS AND BIOLOGICAL SCREENING OF SOME NEW SUBSTITUTED-3*H*-QUINAZOLIN-4-ONE ANALOGS AS ANTIMICROBIAL AGENTS

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تم تحضير سلسلة جديدة من مماثلات 3-بنزايل-H3-كينازولين-4-أون المستبدلة واختبار فاعليتها المضادة للجراثيم. وقد أظهر المركب 2-(3-نيترو-2-بيريديل) ثيو-3-بنزايل-6-ميثيل-H3-كينازولين-4-أون **(17)** فاعلية واضحة واسعة المدى ضد الجراثيم، بينما أظهر المركب 2-أسيتيل ميثيل ثيو-3-بنزايل-6-نيترو-H3-كينازولين-4-أون **(35)** فاعلية نوعية (اختيارية) ضد الفطريات. ويتضمن المقال الطريقة التفصيلية لتشييد هذه المركبات الجديدة والاختبارات التي أجريب عليها لمعرفة الفاعلية المضادة للميكروبات.

A new series of substituted 3-benzyl-3*H*-quinazolin-4-one analogs was prepared and screened for their antimicrobial activity. Compound 2-(3-nitro-2-pyridyl)thio-3-benzyl-6-methyl-3*H*-quinazolin-4-one (**17**) showed a remarkable broad spectrum antimicrobial activity, while compound 2-acetylmethylthio-3-benzyl-6-nitro-3*H*-quinazolin-4-one (**35**) expressed a selective antifungal activity. The detailed synthesis and the antimicrobial screening of the new compounds are reported.

Key words: Synthesis, 3*H*-quinazolin-4-one, antimicrobial screening.

Introduction

Quinazoline, a nitrogenous heterocycle, proved to possess a multitude of biological potency including antimicrobial activity (1–8). Certain quinazoline analogs also showed a remarkable activity against the opportunistic infections of *Pneumocystis carinii* and *Toxoplasma gondii*. Those microorganisms proved to be the principal cause of death in patients with immunocompromised diseases such as acquired immune deficiency syndrome (AIDS) (9–12). As a continuation of our previous efforts (6, 13) aiming to locate new active quinazoline exhibiting antimicrobial agent(s) with enhanced potency, a new series of 2-substituted-mercapto-quinazolin-4-one analogs was synthesized and screened. In the present study, the quinazoline analogs were designed to contain a 2-substituted-thio functional group, this thioether moiety believed to bound to an electron-deficient carbon atom which identified as a possible pharmacophore of the antimicrobial activity (14). The quinazoline ring was substituted at various locations with methyl, methoxy and nitro groups to correlate the electronic effect of such substituents on the magnitude of the antimicrobial activity. The new synthesized compounds were screened against Gram negative bacteria (*E. coli*), Gram positive bacteria (*S. aureus, B. subtilis*) and fungi (*S. cerevisiae, C. albicans*).

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Experimental

Melting points were determined on a Mettler FP80 melting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer, all of the new compounds were analyzed for C, H, and N and agreed with the proposed structures within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Varian XL 400 MHz FT spectrometer, chemical shifts are expressed in δ ppm with reference to TMS. Mass spectral data were obtained on a Shimadzu GC/MS QP 5000 apparatus. Thin layer chromatography was performed on Merck 5×10 cm precoated (0.25 mm)

silica gel GF_{254} plates (E. Merck, Germany); compounds were detected with a 254-nm UV lamp. Silica gel (60–320 mesh) was employed for routine column chromatography separations. The following organisms were used in the antimicrobial screening. *Escherichia coli* ATCC 10536, *Staphylococcus aureus* ATCC 06538, *bacillus subtilis* ATCC 6633, *Saccharamycess cerevisiae* ATCC 97633, and *Candida albicans* ATCC 1023.

*Substituted 2-Thioxo-3-benzyl-3H-quinazolin-4-ones (**6–10**).*

A mixture of substituted antharanilic acid derivatives **1–5** (0.01 mol) and benzyl isothiocyanate (1.8 g, 0.012 mol) in ethanol (50 ml) was heated under reflux for 4 h. The reaction mixture was then cooled and solvent was evaporated under vacuum. The obtained residue was washed with petroleum ether 40:60, filtered, dried, and recrystallized to give **6–10** (Table 1). ^{1}H NMR (DMSO-d_6) **6**: δ 2.63 (s, 3H, CH_3Ar), 5.62 (s, 2H, CH_2Ph), 7.10 (d, 1H, J=7.5 Hz, ArH), 7.23 (t, 1H, J=7.5 Hz, ArH), 7.28–7.34 (m, 5H, ArH), 7.58 (t, 1H, J=7.5 Hz, ArH), 12.90 (brs, 1H, NH). **7**: δ 2.34 (s, 3H, CH_3Ar), 5.67 (s, 2H, CH_2Ph), 7.22 (t, 1H, J=7.5 Hz, ArH), 7.27–7.33 (m, 5H, ArH), 7.54–7.56 (m, 1H, ArH), 7.73 (s, 1H, ArH), 12.98 (brs, 1H, NH). **8**: δ 2.51 (s, 3H, CH_3Ar), 5.71 (s, 2H, CH_2Ph), 7.20–7.34 (m, 6H, ArH), 7.54 (d, 1H, J=7.0 Hz, ArH), 7.81 (d, 1H, J=7.0 Hz, ArH), 11.75 (brs, 1H, NH). **9**: δ 3.94 (s, 3H, OCH_3), 5.70 (s, 2H, CH_2Ph), 7.21–7.23 (m, 1H, ArH), 7.28–7.32 (m, 6H, ArH&NH), 7.39 (d, 1H, J=7.0 Hz, ArH), 7.52–7.54 (m, 1H, ArH). **10**: δ 5.67 (s, 2H, CH_2Ph), 7.22–7.32 (m, 6H, ArH&NH), 7.53 (d, 1H, J=9.0 Hz, ArH), 8.50–8.52 (dd, 1H, J=9.0 & 3.0 Hz, ArH), 8.63 (d, 1H, J=3.0 Hz, ArH).

*Substituted 2,4-Dithioxo-3-benzyl-3H-quinazolines (**11–15**).*

A mixture of 2-thioxo-3-benzyl-3*H*-quinazolin-4-one derivatives **6–10** (0.015 mol) and phosphorous pentasulfide (8 g, 0.018 mol) in xylene (50 ml) was heated under reflux for 6 h. The reaction mixture was filtered while hot, the filtrate was cooled and the separated solid was filtered, dried and recrystallized to give **11–15** (Table 1). ^{1}H NMR (DMSO-d_6) **11**: δ 2.52 (s, 3H, CH_3Ar), 5.41 (s, 2H, CH_2Ph), 7.15 (m, 1H, ArH), 7.25 (m, 1H, ArH), 7.28–7.36 (m, 5H, ArH), 7.46 (m, 1H, ArH), 11.72 (brs, 1H, NH). **12**: δ 2.31 (s, 3H, CH_3Ar), 5.62 (s, 2H, CH_2Ph), 7.19 (m, 1H, ArH), 7.22–7.31 (m, 5H, ArH), 7.49–7.54 (m, 1H, ArH), 7.69 (m, 1H, ArH), 12.62 (brs, 1H, NH). **13**: δ 2.23 (s, 3H, CH_3Ar), 5.81 (s, 2H, CH_2Ph), 7.21–7.38 (m, 5H, ArH), 7.48–7.59 (m, 3H, ArH), 9.18 (brs, 1H, NH). **14**: δ 3.98 (s, 3H, OCH_3), 5.61 (s, 2H, CH_2Ph), 7.19–7.24 (m, 1H, ArH), 7.30–7.32 (m, 5H, ArH), 7.37 (m, 1H, ArH), 7.48–7.52 (m, 1H, ArH), 10.62 (brs, 1H, NH). **15**: δ 5.62 (s, 2H, CH_2Ph), 7.19–7.28 (m, 6H, ArH&NH), 7.46 (m, 1H, ArH), 8.49–8.53 (m, 1H, ArH), 8.59 (m, 1H, ArH).

*Substituted 2-(3-Nitro-2-pyridyl)thio-3-benzyl-3H-quinazolin-4-ones (**16–20**).*

A mixture of 2-thioxo analogs **6–10** (0.01 mol), 2-chloro-3-nitropyridine (1.6 g, 0.01 mol) and anhydrous potassium carbonate (2.0 g) in dimethylformamide (30 ml) was heated under reflux for 12 h. Solvent was evaporated *in vacuo* and the obtained residue was washed with water, dried and recrystallized from the appropriate solvent to give **16–20** (Table 1). ^{1}H NMR ($CDCl_3$), **16**: δ 2.59 (s, 3H, CH_3Ar), 5.58 (s, 2H, CH_2Ph), 7.12–7.24 (m, 2H, ArH), 7.26–7.49 (m, 6H, ArH), 8.60–8.72 (m, 2H, pyridine-H), 8.95 (s, 1H, pyridine-H). **17**: δ 2.37 (s, 3H, CH_3Ar), 5.59 (s, 2H, CH_2Ph), 7.20–7.33 (m, 6H, ArH), 7.56–7.71 (m, 2H, ArH), 8.58–8.69 (m, 2H, pyridine-H), 8.92 (s, 1H, pyridine-H). **18**: δ 2.49 (s, 3H, CH_3Ar), 5.69 (s, 2H, CH_2Ph), 7.19–7.32 (m, 6H, ArH), 7.52–7.79 (m, 2H, ArH), 8.54–8.68 (m, 2H, pyridine-H), 8.89 (s, 1H, pyridine-H). **19**: δ 3.99 (s, 3H, OCH_3), 5.71 (s, 2H, CH_2Ph), 7.19–7.33 (m, 6H, ArH), 7.42–7.53 (m, 2H, ArH), 8.59–8.71 (m, 2H, pyridine-H), 8.91 (m, 1H, pyridine-H). **20**: δ 5.65 (s, 2H, CH_2Ph), 7.21–7.51 (m, 6H, ArH), 8.49–8.72 (m, 4H, ArH), 9.01 (m, 1H, pyridine-H).

*Substituted 2-Methylthio-3-benzyl-3H-quinazolin-4-ones (**21–25**).*

A mixture of the 2-thioxo analogs **6–10** (0.01 mol), excess methyl iodide (5 ml) and anhydrous potassium carbonate (2.0 g) in acetone (50 ml) was heated under reflux for 5 h. The mixture was filtered while hot and the filtrate was evaporated *in vacuo*. The obtained residue was recrystallized from the appropriate solvent to give **21–25** (Table 1). ^{1}H NMR ($CDCl_3$), **21**: 2.62 (s, 3H, CH_3Ar), 2.64 (s, 3H, SCH_3), 5.64 (s, 2H, CH_2Ph), 7.12–7.24 (m, 2H, ArH), 7.30–7.36 (m, 5H, ArH), 7.60 (t, 1H, J=7.5 Hz, ArH). **22**: δ 2.35 (s, 3H, CH_3Ar), 2.61 (s, 3H, SCH_3), 5.65 (s, 2H, CH_2Ph), 7.20–7.35 (m, 6H, ArH), 7.57–7.70 (m, 2H, ArH). **23**: δ 2.49 (s, 3H, CH_3Ar), 2.63 (s, 3H, SCH_3), 5.69 (s, 2H, CH_2Ph),

7.18–7.52 (m, 7H, ArH), 7.79 (d, 1H, J=7.0 Hz, ArH). **24**: δ 2.59 (s, 3H, SCH_3), 4.01 (s, 3H, OCH_3), 5.72 (s, 2H, CH_2Ph), 7.20–7.32 (m, 6H, ArH), 7.40–7.52 (m, 2H, ArH). **25**: δ 2.64 (s, 3H, SCH_3), 5.36 (s, 2H, CH_2Ph), 7.28–7.76 (m, 6H, ArH), 8.53 (d, 1H, J=8.0 Hz, ArH), 8.79 (s, 1H, ArH).

*Substituted 2-Benzylthio-3-benzyl-3H-quinazolin-4-ones (**26–30**).*

A mixture of the 2-thioxo analogs **6–10** (0.01 mol), benzyl bromide (1.7 g, 0.01 mol) and anhydrous potassium carbonate (2.0 g) in dimethylformaide (30 ml) was heated under reflux for 10 h. Solvent was evaporated *in vacuo* and the obtained residue was washed with water, dried and recrystallized (Table 1). ^{1}H NMR (DMSO-d_6), **26**: δ 2.62 (s, 3H, CH_3Ar), 5.21 (s, 2H, SCH_2Ph), 5.61 (s, 2H, CH_2Ph), 7.09–7.36 (m, 12H, ArH), 7.59 (m, 1H, ArH). **27**: δ 2.35 (s, 3H, CH_3Ar), 5.10 (s, 2H, SCH_2Ph), 5.67 (s, 2H, CH_2Ph), 7.21–7.35 (m, 11H, ArH), 7.53–7.57 (m, 1H, ArH), 7.74 (s, 1H, ArH). **28**: δ 2.52 (s, 3H, CH_3Ar), 5.23 (s, 2H, SCH_2Ph), 5.69 (s, 2H, CH_2Ph), 7.22–7.52 (m, 12H, ArH), 7.79 (d, 1H, J=7.0 Hz, ArH). **29**: δ 3.98 (s, 3H, OCH_3), 5.20 (s, 2H, SCH_2Ph), 5.64 (s, 2H, CH_2Ph), 7.22–7.25 (m, 1H, ArH), 7.26–7.39 (m, 11H, ArH), 7.51–7.54 (m, 1H, ArH). **30**: δ 5.15 (s, 2H, SCH_2Ph), 5.68 (s, 2H, CH_2Ph), 7.22–7.34 (m, 10H, ArH), 7.54 (d, 1H, J=9.0 Hz, ArH), 8.49–8.53 (dd, 1H, J=9.0&3.2 Hz, ArH), 8.65 (d, 1H, J=3.2 Hz, ArH).

*Substituted 2-Acetylmethylthio-3-benzyl-3H-quinazolin-4-ones (**31–35**).*

To a mixture of the 2-thioxo analogs **6–10** (0.01 mol), and anhydrous potassium carbonate (2.0 g) in dry acetone (50 ml), chloroacetone (1.4 g, 0.015 mol) was added dropwise. The reaction mixture was stirred and heated under reflux for 10 h, then filtered while hot and the filtrate was concentrated *in vacuo*. The obtained crude product was recrystallized from the appropriate solvent to give **31–35** (Table 1). ^{1}H NMR (DMSO-d_6), **31**: δ 2.10 (s, 3H, CH_3CO), 2.61 (s, 3H, CH_3Ar), 4.31 (s, 2H, CH_2CO), 5.61 (s, 2H, CH_2Ph), 7.11–7.24 (m, 2H, ArH), 7.30–7.36 (m, 5H, ArH), 7.61 (t, 1H, J=7.5 Hz, ArH). **32**: δ 2.12 (s, 3H, CH_3CO), 2.36 (s, 3H, CH_3Ar), 4.28 (s, 2H, CH_2CO), 5.65 (s, 2H, CH_2Ph), 7.20–7.34 (m, 6H, ArH), 7.51–7.55 (m, 1H, ArH), 7.71 (s, 1H, ArH). **33**: δ 2.10 (s, 3H, CH_3CO), 2.25 (s, 3H, CH_3Ar), 4.35 (s, 2H, CH_3CO), 5.83 (s, 2H, CH_2Ph), 7.22–7.39 (m, 6H, ArH), 7.50 (m, 1H, ArH), 7.83 (s, 1H, ArH). **34**: δ 2.10 (s, 3H, CH_3CO), 3.90 (s, 3H, OCH_3), 4.32 (s, 2H, CH_2CO), 5.70 (s, 2H, CH_2PH), 7.21–7.32 (m, 6H, ArH), 7.40–7.54 (m, 2H, ArH). **35**: δ 2.13 (s, 3H, CH_3CO), 4.30 (s, 2H, CH_2CO), 5.67 (s, 2H, CH_2Ph), 7.23–7.33 (m, 5H, ArH), 7.53 (s, 1H, ArH), 8.51–8.54 (m, 1H, ArH), 8.63 (s, 1H, ArH).

*Substituted 2-(Phenylcarbonylmethylthio)-3-benzyl-3H-quinazolin-4-ones (**36–40**).*

A mixture of the 2-thioxo analogs **6–10** (0.01 mol), phenacyl bromide (2.0 g, 0.01 mol) and anhydrous potassium carbonate (2.0 g) in dimethylformamide (50 ml) was heated under reflux for 12 h. the reaction mixture was filtered while hot and the filtrate was concentrated under reduced pressure, then cooled. The obtained solid was recrystallized from the suitable solvent to give **36–40** (Table 1). ^{1}H NMR (DMSO-d_6), **36**: δ 2.62 (s, 3H, CH_3Ar), 4.62 (s, 2H, CH_2CO), 5.60 (s, 2H, CH_2Ph), 7.15–7.22 (m, 2H, ArH), 7.24–7.65 (m, 11H, ArH). **37**: δ 2.35 (s, 3H, CH_3Ar), 4.65 (s, 2H, CH_2CO), 5.66 (s, 2H, CH_2Ph), 7.23–7.35 (m, 6H, ArH), 7.49–7.68 (m, 6H, ArH), 7.72 (s, 1H, ArH). **38**: δ 2.51 (s, 3H, CH_3Ar), 4.64 (s, 2H, CH_2CO), 5.69 (s, 2H, CH_2Ph), 7.20–7.32 (m, 6H, ArH), 7.39–7.55 (m, 6H, ArH), 7.82 (d, 1H, J=7.5 Hz, ArH). **39**: δ 3.89 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2CO), 5.71 (s, 2H, CH_2Ph), 7.21–7.33 (m, 6H, ArH), 7.39–7.50 (m, 6H, ArH), 7.53 (s, 1H, ArH). **40**: δ 4.69 (s, 2H, CH_2CO), 5.71 (s, 2H, CH_2Ph), 7.23–7.32 (m, 5H, ArH), 7.40–7.54 (m, 6H, ArH), 8.49–8.52 (m, 1H, ArH), 8.64 (d, 1H, J=3.1 Hz, ArH).

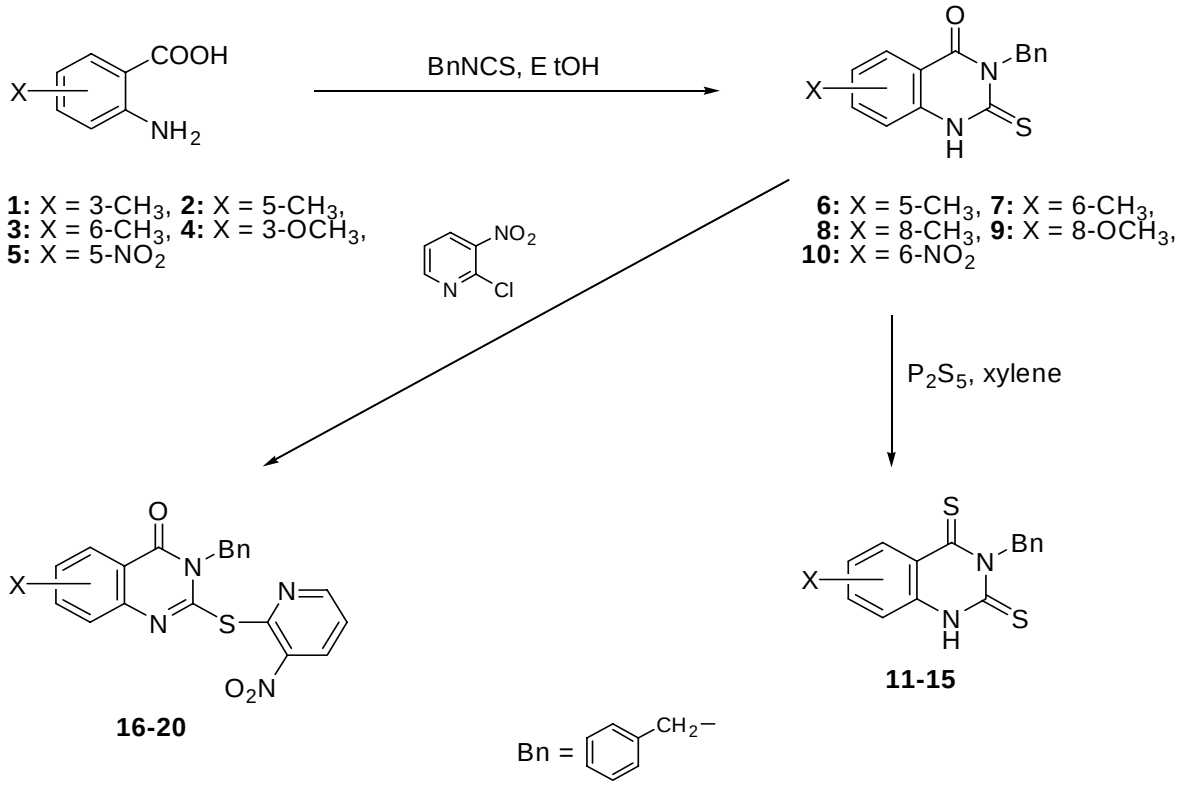
Antimicrobial Testing:

Nutrient agar plates were seeded using 0.1 ml of the diluted organisms overnight cultures. Cylindrical plugs were removed from the agar plate using a sterile cork borer, 100 µl of the test compounds (75–300 µg/ml in DMSO) and blank DMSO were added to each well in triplicates. Plates inoculated with the tested bacteria were incubated at 37°C, while those of fungi were incubated at 30°C. Results were taken after 24 h of incubation and were recorded as average diameter of the inhibition zone in mm (6, 15–17).

Results and Discussion

The strategy to synthesize the target compounds **6–40**, is shown in schemes 1 and 2. The starting materials, 2-mercapto-3-benzyl-5-methyl-3*H*-quinazolin-4-one (**6**), and its 6-methyl (**7**), 8-methyl (**8**), 8-methoxy (**9**), and 6-nitro (**10**) analogs were prepared, adopting a reported procedure (18), by treating the appropriate anthranilic acid derivatives (**1–5**) with benzyl isothiocyanate in boiling ethanol. Thiation of such analogs proved to contribute to the antimicrobial activity (6, 13). Accordingly compounds **6–10** were treated with P_2S_5 to afford the 2,4-dithioxo derivatives **11–15** in reasonable yields. The 2-mercapto function of **6–10** was alkylated using a variety of alkyl and aryl halides. Treatment using a variety of alkyl and aryl halides. Treatment of **6–10** with 2-chloro-3-nitropyridine gave the 2-pyridylthio compounds **16–20**, (Scheme 1, Table 1). Meanwhile, the 2-mercapto function was also methylated or benzylated using either methyl iodide or benzyl bromide to produce the 2-methylthio- analogs **21–25** and the 2-benzylthio- derivatives **26–30**, respectively. Reacting **6–10** with chloroacetone or phenacyl bromide afforded the targets 2-oxo-propylthio- **31–35**, and the 2-phenylcarbonylmethylthio- **36–40**, respectively (Scheme 2, Table 1). All of the synthesized compounds were subjected to structure elucidation processes including IR, MS and ^{1}H NMR spectral analysis.

Scheme 1:



Scheme 2:

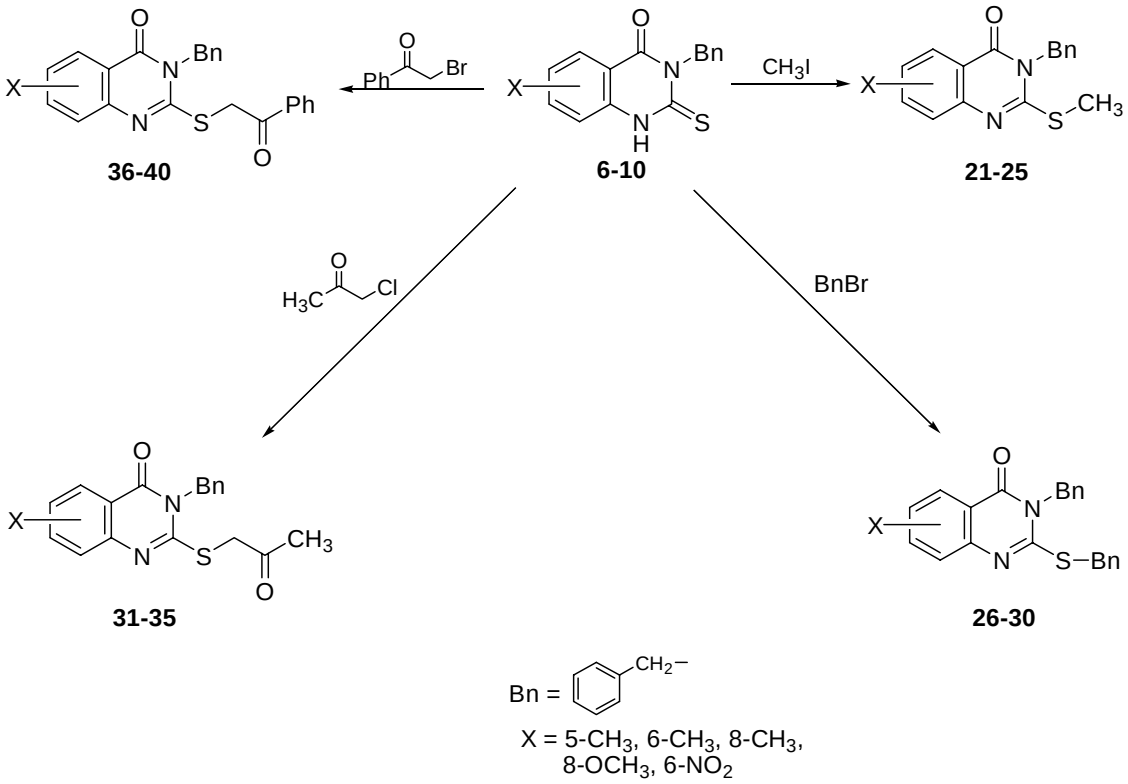


Chart 1:

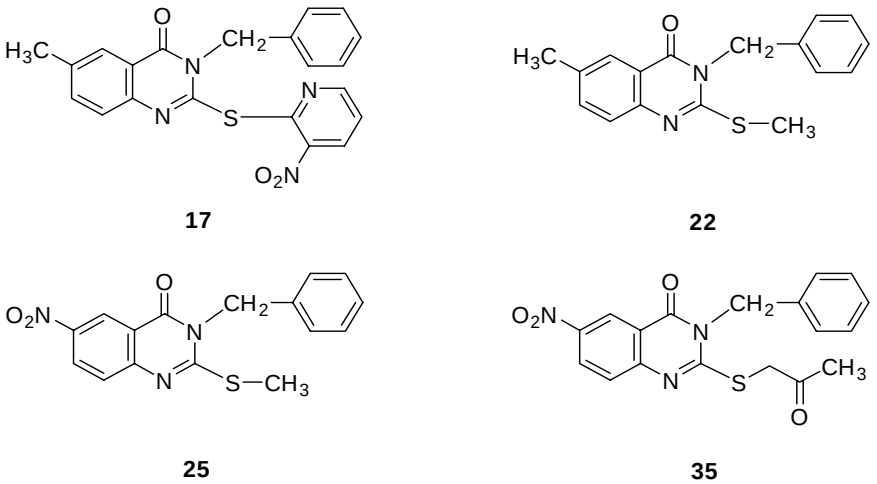


Table 1: Physicochemical properties of the synthesized compounds.

Compd.	X	Solvent	Yield (%)	MP (°C)	Molecular Formulae	MS m/e, (%)
6	5–CH_3	EtOH, benzene	70	230–2	$C_{16}H_{14}N_2OS$	282, (12)
7	6–CH_3	EtOH, benzene	65	225–6	$C_{16}H_{14}N_2OS$	282, (21)
8	8–CH_3	EtOH, benzene	75	180–1	$C_{16}H_{14}N_2OS$	282, (26)
9	8–OCH_3	EtOH, benzene	75	194–6	$C_{16}H_{14}N_2O_2S$	298, (24)
10	6–NO_2	EtOH	55	260–2	$C_{15}H_{11}N_3O_3S$	313, (57)
11	5–CH_3	EtOH	60	207–9	$C_{16}H_{14}N_2S_2$	298, (18)
12	6–CH_3	EtOH	65	211–3	$C_{16}H_{14}N_2S_2$	298, (32)
13	8–CH_3	Dioxane	50	160–2	$C_{16}H_{14}N_2S_2$	298, (51)
14	8–OCH_3	EtOH	50	160–2	$C_{16}H_{14}N_2OS_2$	314, (38)
15	6–NO_2	EtOH	60	235–7	$C_{16}H_{11}N_3O_2S_2$	329, (63)
16	5–CH_3	EtOH	55	150–2	$C_{21}H_{16}N_4O_3S$	404, (45)
17	6–CH_3	EtOH	60	216–8	$C_{21}H_{16}N_4O_3S$	404, (39)
18	8–CH_3	Dioxane	70	270–1	$C_{21}H_{16}N_4O_3S$	404, (47)
19	8–OCH_3	EtOH	70	260–2	$C_{21}H_{16}N_4O_4S$	420, (22)
20	6–NO_2	Dioxane	60	250–2	$C_{20}H_{13}N_5O_5S$	435, (68)
21	5–CH_3	EtOH	75	85–7	$C_{17}H_{16}N_2OS$	296, (10)
22	6–CH_3	EtOH	70	110–2	$C_{17}H_{16}N_2OS$	296, (8)
23	8–CH_3	EtOH	75	118–0	$C_{17}H_{16}N_2OS$	296, (13)
24	8–OCH_3	Dioxane	65	120–2	$C_{17}H_{16}N_2O_2S$	312, (19)
25	6–NO_2	EtOH	70	140–2	$C_{16}H_{13}N_3O_3S$	327, (46)
26	5–CH_3	EtOH	70	73–5	$C_{23}H_{20}N_2OS$	372, (28)
27	6–CH_3	EtOH	65	113–5	$C_{23}H_{20}N_2OS$	372, (19)
28	8–CH_3	EtOH	75	90–2	$C_{23}H_{20}N_2OS$	372, (32)
29	8–OCH_3	EtOH	70	107–9	$C_{23}H_{20}N_2O_2S$	388, (6)
30	6–NO_2	Dioxane	65	160–2	$C_{22}H_{17}N_3O_3S$	403, (72)
31	5–CH_3	EtOH	55	110–2	$C_{19}H_{18}N_2O_2S$	338, (9)
32	6–CH_3	Dioxane	60	135–7	$C_{19}H_{18}N_2O_2S$	338, (21)
33	8–CH_3	Dioxane	55	120–2	$C_{19}H_{18}N_2O_2S$	338, (30)
34	8–OCH_3	EtOH	55	182–4	$C_{19}H_{18}N_2O_3S$	354, (26)
35	6–NO_2	EtOH	60	118–20	$C_{18}H_{15}N_3O_4S$	369, (45)
36	5-CH_3	EtOH	60	158–60	$C_{24}H_{20}N_2O_2S$	400, (7)
37	6-CH_3	Dioxane	55	210–2	$C_{24}H_{20}N_2O_2S$	400, (15)
38	8-CH_3	EtOH	65	150–2	$C_{24}H_{20}N_2O_2S$	400, (19)
39	8-OCH_3	EtOH	50	170–2	$C_{24}H_{20}N_2O_3S$	416, (27)
40	6-NO_2	Dioxane	55	285–7	$C_{23}H_{17}N_3O_4S$	431, (49)

Table 2: Antimicrobial screening results of the 75–300 μg/ml concentration.[a]

Compd	*E. coli*	*S. aureus*	*B. subtilis*	*S. cerevisiae*	*C. albicans*
6	–	+	–	–	+
7	+	–	+	–	–
8	–	–	–	–	+
9	–	–	–	–	–
10	+	–	+	–	+
11	–	–	–	–	+
12	+	–	++	–	+
13	–	–	–	–	+
14	+	–	+	+	+
15	++	+	++	+	++
16	–	+	+	–	+
17	++	+++	+++	+	+++
18	+	–	–	+	+
19	+	–	–	–	+
20	+++	+++	+++	–	+
21	+	+	–	+	+
22	+	–	–	++	+++
23	–	–	–	–	–
24	–	–	–	–	–
25	+	–	+	++	+++
26	–	–	–	–	+
27	+++	+	+	+	+
28	+	–	–	–	–
29	–	–	+	–	+
30	+++	+	+	+	+
31	+	–	–	–	+
32	+	–	–	++	++
33	–	–	–	–	+
34	–	–	–	+	–
35	+	–	+	+++	+++
36	–	+	–	–	+
37	+	++	+++	–	–
38	–	–	+	–	+
39	–	–	–	+	+
40	+	++	++	–	–
Ampicillin	+++	+++	+++	NT	NT
Streptomycin	+++	++	+++	NT	NT
Nystatin	NT	NT	NT	++	+++

[a] –, Inactive (inhibition zone < 10 mm); +, moderate activity (inhibition zone 10–15 mm); ++ active (inhibition zone 15–20 min); +++ remarkable activity (inhibition zone > 20 mm), NT = not tested.

Antimicrobial Screening

All of the new synthesized compounds were subjected to antimicrobial screening by the *in vitro* cup-plate technique (15–17), using ampicillin, streptomycin and nystatin as positive controls. Compounds **20, 27** and **30** showed remarkable activity toward the Gram negative bacteria *E. coli.* The gram positive bacteria *S. aureus* and *B. subtilis* proved to be sensitive toward compounds **17, 20** and **37**. Compounds **17, 22, 25** and **35** showed remarkable activity towards the used fungi *S. cerevisiae* and *C. albicans*. All of the aforementioned compounds showed antimicrobial activity comparable to the used positive control drugs. Compound **17** proved to be the most active broad spectrum antimicrobial agent in this study. In addition, compound **20** exerts selectivity against the pathogenic bacteria rather than the used fungi. Compounds **27** and **30** also showed a preferential activity toward the Gram negative bacteria *E. coli*. Compounds **22, 25** and **35** showed a remarkable selectivity towards the used fungi (Chart 1).

A close examination of the structures of the active compounds revealed that the antimicrobial activity was confined mainly to compounds substituted at position-6 of the quinazoline ring rather than the other substitution positions -5 and -8. Structure activity correlation of those new compounds showed that substitution at position -6 with either electron donating or electron withdrawing functions did not affect the type of activity, but in general the existence of a nitro group increased the magnitude of activity as in case of compound **15** compared with **11–14** and in a similar fashion compounds **20, 25, 30, 35** and **40**. Replacing the 6-CH_3 function of **17** by a 6-nitro group as in **20** preserved the antibacterial activity and dramatically decreased the antifungal potency. Replacing the aromatic 2-pyridylthio function of **17** either by 2-methylthio (as in **22** or **25**) or by 2-oxo-propylthio (as in **32** or **35**) potentiated the antifungal activity and diminished the antibacterial potency. On the other hand, replacing the 2-oxo-propylthio function of **31–35** with 2-phenylcarbonylmethylthio **36–40** restored the antibacterial activity.

In conclusion, the present study showed that compound 2-(3-nitro-2-pyridyl)thio-3-benzyl-6-methyl-3*H*-quinazolin-4-one (**17**) and 2-acetylmethylthio-3-benzyl-6-nitro-3*H*-quinazolin-4-one (**35**) could be used as a template for future development through modification or derivatization to design more potent and selective antimicrobial agents.

Acknowledgement

The authors would like to express their special thanks to the staff members of the Department of Microbiology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt, for performing the antimicrobial testing of the synthesized compounds. The technical assistance of Mr. T. Butt is also acknowledged.

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