Synthesis and Antimicrobial Activity of Methyl 2-(2-(2-Arylquinazolin-4-yl)sulfanyl)acetylamino Alkanoates

M. I. Megahed and W. Fathalla*

Physics and Mathematical Engineering Department, Faculty of Engineering, Port Said University, Port Said, Egypt
*E-mail: walid3369@yahoo.com

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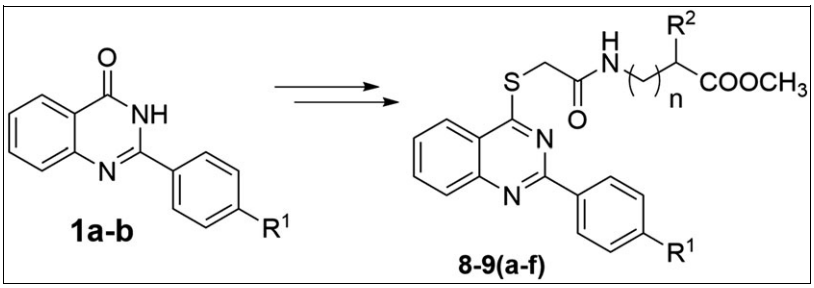

A series of methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl)acetylamino alkanoates have been developed on the basis of the *S*-chemoselective reaction of 2-arylquinazolin-4(3*H*)-thione with ethyl chloroacetate and *N*,*N*′-dicyclohexylcarbodiimide coupling method with amino acid ester hydrochloride. The precursor 2-arylquinazolin-4(3*H*)-thione was prepared by a new thiation method from 2-arylquinazolin-4(3*H*)-one by a two-step reaction that includes chlorination and then the reaction with *N*-cyclohexyldithiocarbamate cyclohexyl ammonium salt. The antimicrobial activity of the synthesized compounds was tested *in vitro* via paper-disc agar-plate method against two bacterial strains Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* and a pathogenic yeast *Candida albicans*. Most synthesized compounds showed remarkable antibacterial activity against *E. coli* overpassing the standard reference antibiotics applied: tetracycline, erythromycin, and novobiocin. On the other hand, most synthesized compounds gave moderate antifungal activity against pathogenic yeast *C. albicans*.

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INTRODUCTION

Quinazolines [1] constitute an important class of heterocyclic compounds especially in medicinal chemistry. These compounds possess a wide range of antimicrobial [2–5], antimalarial [6], analgesic [7], anti-inflammatory [8], antiviral [9], and antitumor activities [10,11].

The chemoselective reactions of heterocyclic thioamides always attracted our research group [12–14]. Earlier we eported the chemoselective *S*-alkylation and *N*-alkylation of the model compound 4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazolin-5-one with different electrophiles. These results were supported by quantum-chemical calculations [12,13].

Non-proteinogenic amino acids are major component in a number of drugs including β-lactam antibiotics, glutamate antagonists, and antiviral [15–17].

The attachment of new quinazoline ring to proteinogenic or non-proteinogenic amino acid esters might provide structures with interesting conformation, stability, and biological activity. A strong need still remains to construct structures of quinazoline derivatives linked to amino acid residues by a spacer using simple, mild, selective, and efficient synthetic methods. In continuation of our interest in the chemistry of heterocyclic thioamides, we found it interesting to prepare a number of methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl)acetylamino alkanoates **7**–**8**(**a**–**f**) and evaluate their antimicrobial activities.

RESULTS AND DISCUSSION

2-Arylquinazolin-4(3*H*)-ones **1a**–**b** are excellent precursors for the preparation of our target substrate 2-arylquinazolin-4(3*H*)-thiones **4a**–**b** by thiation procedures. These quinazolinone derivatives **1a**–**b** were prepared by multistep reactions starting from anthranilic acid [18]. The transformation of heterocyclic amides into thioamides is an important task in organic synthesis. Earlier reports for this type of *O*/*S* conversions were achieved by several thiating reagents such as Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) [19–21], Berzelius reagent [22–24] (P_4S_{10}), and phosphorus pentasulfide [25] in dry toluene, xylene, or pyridine under reflux condition. Thus, the reaction of 2-arylquinazolin-4(3*H*)-one **1a**–**b** with phosphorus pentasulfide in boiling xylene afforded 2-arylquinazolin-4(3*H*)-thione **4a**–**b** in poor yield 14% (method C), with bad smell during the workup procedure. Our alternative method for the preparation of 2-

arylquinazolin-4(3*H*)-thione **4a**–**b** was achieved by a two-step procedure: chlorination of 2-arylquinazolin-4(3*H*)-one **1a**–**b**, followed by thiation via reaction with thiourea in the presence of strong base to afford the thione derivative **5a**–**b** in low yield (35%) and bad smell during workup (method B; Scheme 1) [26].

A number of methods have been applied for the preparation of aryl and alkyl isothiocyanates from dithiocarbamates using the appropriate desulfurylating reagents. Among these desulfurylating reagents of special interest is the use of chloroheterocycles such as 2-chloro-1-methylpyridinium iodide [27], cyanuric chloride [28], and 2,4-dichloro-5-nitropyrimidine [29]. The reaction starts by the reaction of alkyl dithiocarbamate potassium salt or triethyl ammonium salt with the chloroheterocycles to principally give the *in situ* generated heterocyclic substituted carbamodithioate, which was subsequently converted to the mercapto heterocycles as by-products and the desired isothiocyanate derivatives in high yield under strong basic condition (NaOH) [28], weak base (NET_3) [27], or in the absence of a base [29]. We found it interesting to maximize the benefit of these findings in the synthesis of quinazoline-4(3*H*)-thione **5a**,**b** from the corresponding quinazoline-4(3*H*)-one **1a**,**b**.

This method started by a first step chlorination of the corresponding quinazoline-4(3*H*)-one **1a**–**b** to afford chloroquinazolines **2a**–**b**. The second step involves heating the chloroquinazolines **2a**–**b** with *N*-cyclohexyldithiocarbamate cyclohexyl ammonium salt **3** in chloroform for 12 h at 61°C to afford quinazolinethione **4a**–**b** in excellent yields (Scheme 1) [30].

The chemical confirmation of this new thiation procedure was carried out by structure modification of the resultant thione derivatives **4a**–**b** to give a number of biologically promising compounds. Structure modification of the model compounds **4a**–**b** could be simply achieved by chemoselective alkylation reactions with electrophiles. Thus, the reaction of quinazolines **4a**–**b** with ethyl chloroacetate in the presence of triethylamine in ethanol gave the chemoselective *S*-substituted quinazoline ester derivatives **5a**–**b** in good yield (Scheme 1) [12–14].

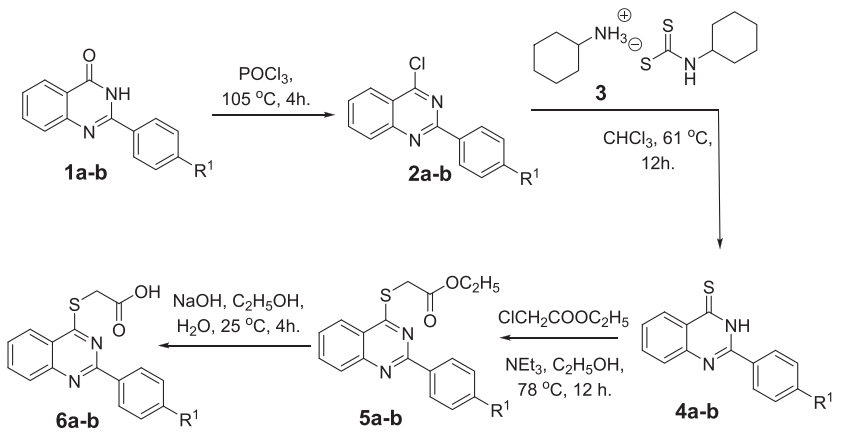
(2-Arylquinazolin-4-ylsulfan-yl)acetic acid **6a**–**b** in pure state and in good yields was successfully achieved by saponification of esters **5a**–**b** with KOH in methanol water mixture with stirring at room temperature for 4 h (Scheme 1).

Our successful method to introduce a peptide bond at the *S*-atom connected to the quinazoline ring moiety was efficiently carried out with the key substrate carboxylic acid derivatives **6a**–**b** via *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling method. The DCC coupling method is one of the major tools employed to introduce peptide bonds by the reaction of carboxylic acid with amino acid methyl ester [31,32]. Hydroxybenzotriazole (HOBt) is widely used as an additive to decrease racemization in the carbodiimide peptide coupling and to enhance the percentage yield [32].

Treatment of carboxylic acid **6a**–**b** with amino acid ester hydrochlorides in the presence of triethylamine and coupling reagents DCC and HOBt afforded *S*-quinazoline amino acid esters **7**–**8**(**a**–**f**) in good yield (Scheme 2 and Table 1).

The ^{1}H NMR spectrum of compound **7a** in $CDCl_3$ showed multiplet signals ranging between 8.63 and 7.54 ppm corresponding to nine aromatic protons, broad singlet signal at 7.41 ppm corresponding to NH proton of the peptide bond, singlet signal at 4.23 ppm for SCH_2 group, doublet signal at 4.02 ppm for NCH_2 group, and singlet signal at 3.57 ppm for three protons of OCH_3. The ^{13}C NMR spectrum of **7a** showed signals for CO group appeared at 171.9 and 169.6 ppm, signals for C–Ar appeared at 168.6, 158.9, 149.2, 137.4, 134.3, 130.9, 129.2, 128.7, 128.5, 127.2, 123.7, and 122.2 ppm, signal at 52.2 ppm for OCH_3 group, signal at 41.6 ppm for $NHCH_2$ group, and signal at 32.6 ppm for SCH_2 group.

Scheme 1. Synthesis of 2-((2-arylquinazolin-4-yl)thio)acetic acid **6a**–**b**.



Scheme 2. Synthesis of methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl)acetylamino alkanoates **7–8(a–f)**.

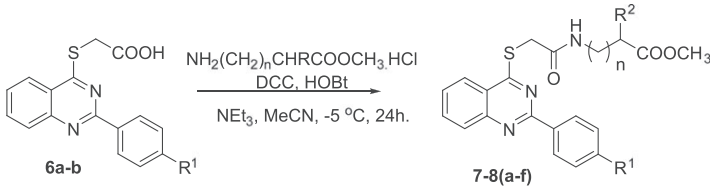


Table 1

Structures of methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl)acetylamino alkanoates **7–8(a–f)**.

No.	R^1	n	R^2	Abr.
7a	H	0	H	Gly
7b	H	1	H	β-Ala
7c	H	2	H	γ-Abu
7d	H	0	CH_3	L-Ala
7e	H	0	CH $(CH_3)_2$	L-Val
7f	H	0	$CH_2CH(CH_3)_2$	L-Leu
8a	OCH_3	0	H	Gly
8b	OCH_3	1	H	β-Ala
8c	OCH_3	2	H	γ-Abu
8d	OCH_3	0	CH_3	L-Ala
8e	OCH_3	0	CH $(CH_3)_2$	L-Val
8f	OCH_3	0	$CH_2CH(CH_3)_2$	L-Leu

Antibacterial and antifungal activities. The compounds quinazolinthione **4a–b**, ester **5a–b**, acid **6a–b**, and methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl)acetylamino alkanoates **7–8(a–f)** in addition to the reference tetracycline, erythromycin, and novobiocin were tested *in vitro* against two reference bacterial strains (*Escherichia coli* NCMB 11943 and *Staphylococcus aureus* NCMB 6571) and a pathogenic yeast *Candida albicans*. The method applied is paper-disc agar-plate method [33], using two concentrations 30 and 15 μg per disc. The plates were incubated at 37°C for 24 h for antibacterial evaluation and at 37°C for 48 h for antifungal evaluation. The antimicrobial activity was evaluated by measuring the diameter of the inhibition zone (IZ) around the disc in millimeter as shown (Tables 2 and 3).

From the results listed in Tables 2 and 3, we can conclude the following:

1. Table 2 shows general screening for all compounds and reference antibiotics: tetracycline and novobiocin with concentrations of 30 μg toward the microorganisms—Gram-positive bacteria *S. aureus*, Gram-negative bacteria *E. coli*, and pathogenic yeast *C. albicans*.
2. Almost all compounds tested showed high activity against Gram-negative bacteria *E. coli* (IZ ranging from 0.6 to 1.9 mm) overpassing the standard reference antibiotics applied—tetracycline (IZ = 0.7 mm) and novobiocin (no IZ). Remarkable antibacterial activity against Gram-negative bacteria *E. coli* was observed for the starting ester derivative **5a** and carboxylic acid derivatives **6a–b** with IZ ranging 1.5–1.9 mm.
3. Best antibacterial activity against Gram-negative bacteria *E. coli* for the amino acid ester derivatives **7–8(a–f)** was observed for **7a–b** and **7d–e** (R^1 = H, amino acid residue Gly, β-Ala, L-Ala, and L-Val, respectively), IZ 1.0–0.9 mm. On the other hand, compounds **9c–d** (R^1 = OCH_3, amino acid residue γ-Aba and L-Ala) showed IZ 0.9 and 0.8 mm, respectively.
4. The starting quinazoline thione **4a–b**, esters **5a–b**, and acids **6a–b** showed maximum activity against Gram-positive bacteria *S. aureus* (IZ ranging from 0.8 to 2.9 mm) overpassing the standard reference antibiotics applied—tetracycline (IZ = 0.6 mm) and novobiocin (no IZ). Exceptionally, amino acid esters **7a**, **7f**, **8a**,

Table 2

Samples (30 μg each) were analyzed using "disc diffusion method."

	Antibacterial activity		Antifungal activity
	Zone of inhibition (mm)		Zone of inhibition (mm)
Code no.	*Escherichia coli*	*Staphylococcus aureus*	*Candida albicans*
Control	-ve	-ve	-ve
4a	0.7	1.0	1.0
4b	0.7	0.8	0.8
5a	1.7	2.5	1.9
5b	0.7	1.1	0.7
6a	1.5	2.9	1.6
6b	1.9	1.9	1.5
7a	0.9	0.8	0.9
7b	0.9	-ve	0.6
7c	0.7	-ve	0.6
7d	1.0	-ve	0.9
7e	0.9	-ve	-ve
7f	0.7	1.2	0.8
8a	0.6	0.8	0.7
8b	0.6	-ve	0.6
8c	0.9	-ve	0.8
8d	0.8	-ve	0.8
8e	-ve	-ve	-ve
8f	0.6	-ve	0.7
Tetracycline	0.7	0.6	1.2
Novobiocin	-ve	-ve	2

-ve, no inhibition zone was observed.

Table 3

Samples (15 μg each) were analyzed using "disc diffusion method."

	Antibacterial activity Zone of inhibition (mm)		Antifungal activity Zone of inhibition (mm)
Code no.	*Escherichia coli*	*Staphylococcus aureus*	*Candida albicans*
Control	-ve	-ve	-ve
5a	2.0	1.9	2.2
6a	1.8	1.5	2.3
6b	1.8	1.5	1.9
Erythromycin	-ve	-ve	2

-ve, no inhibition zone was observed.

and **8f** (R^1 = H, Gly and L-Leu; R^1 = OCH_3, Gly and L-Leu) gave promising activity against Gram-positive bacteria *S. aureus* (IZ 0.8–1.2 mm) overpassing the standard reference tetracycline.

5. Almost all compounds tested showed moderate activity against pathogenic yeast *C. albicans* (IZ ranging from 0.6 to 1.9 mm). The IZ of the standard reference antibiotics applied—tetracycline (IZ = 1.2 mm) and novobiocin (IZ = 2.0 mm)—overpasses the antifungal activity of the tested compounds.
6. Maximum antifungal activity against pathogenic yeast *C. albicans* was observed for the ester derivative **5a** (R^1 = H) and carboxic acids **6a** (R^1 = H) and **6b** (R^1 = OCH_3) showing IZ 1.9, 1.6, and 1.5 mm, respectively.
7. Maximum antimicrobial activity of all screened compounds toward all three microorganisms Gram-negative bacteria *E. coli* and pathogenic yeast *C. albicans* was observed for the starting ester derivative **5a** and carboxylic acid derivatives **6a**–**b**.
8. Table 3 shows antimicrobial testing for compounds ester **5a** and acid derivatives **6a**–**b** and reference antibiotic erythromycin with concentrations of (15 μg) toward the microorganisms—Gram-positive bacteria *S. aureus*, Gram-negative bacteria *E. coli*, and pathogenic yeast *C. albicans*. The starting quinazoline esters **5a** and acids **6a**–**b** showed maximum activity against all three microorganisms Gram-positive bacteria *S. aureus*, Gram-negative bacteria *E. coli*, and pathogenic yeast *C. albicans* overpassing the standard reference antibiotic erythromycin.

CONCLUSIONS

The precursor 2-arylquinazolin-4(3*H*)-thione **4a**–**b** was prepared by a new thiation method designed in our laboratory from 2-arylquinazolin-4(3*H*)-one **1a**–**b** by a two-step reaction that includes chlorination and then the reaction with *N*-cyclohexyldithiocarbamate cyclohexyl ammonium salt **3**. This compound was used to prepare a series of methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl) acetylamino alkanoates **7**–**8**(**a**–**f**) on the basis of chemoselective *S*-alkylation reaction of heterocyclic thioamides. 2-Arylquinazolin-4(3*H*)-thione **4a**–**b** react with ethyl chloroacetate to give the *S*-substituted quinazoline **5a**–**b**, followed by hydrolysis to give the carboxylic acids **6a**–**b**. The carboxylic acid derivatives reacted with a series of amino acid ester hydrochloride in the presence of DCC, HOBt, and triethylamine to give the desired products **7**–**8**(**a**–**f**).

The antimicrobial activity of the synthesized compounds was tested *in vitro* via paper-disc agar-plate method against two bacterial strains Gram-positive bacteria *S. aureus* and Gram-negative bacteria *E. coli* and a pathogenic yeast *C. albicans*. Most synthesized compounds showed remarkable antibacterial activity against *E. coli* overpassing the standard reference antibiotics applied: tetracycline, erythromycin, and novobiocin. On the other hand, most synthesized compounds gave moderate antifungal activity against pathogenic yeast *C. albicans*. Finally, the tested compounds gave an equivocal antibacterial activity toward Gram-positive bacteria *S. aureus* with some few examples exceeding the activity of the standard reference antibiotics.

EXPERIMENTAL

General. The boiling point range of the petroleum ether used was 40–60°C. Thin-layer chromatography was carried out on silica gel 60 F_{254} plastic plates (layer thickness 0.2 mm; E. Merck). The spots on thin-layer plates were detected by UV lamp. Melting points were determined on a Buchi 510 melting point apparatus, and the values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively (Bruker AC 300), in $CDCl_3$ and DMSO-d_6 solution with tetramethylsilane as an internal standard. The NMR analysis was performed at Organic Chemistry Department, Masaryk University,

Brno, Czech Republic. Elemental analyses were performed on a FlashEA 1112 instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Compounds **1a**–**b** and **2a**–**b** were prepared, in our laboratory, according to reported procedures [17,18,34,35].

Preparation of thiating reagent *N-cyclohexyldithiocarbamate cyclohexyl ammonium salt (3)*. To a mixture of freshly distilled cyclohexyl amine (60 mmol) and water (50 mL) was added carbon disulfide (21 mmol) dropwise. The reaction mixture was stirred overnight at room temperature. The white solid obtained was filtered, washed with water, dried, and crystalized from ethanol to provide pure product of *cyclohexylamine cyclohexyl ammonium dithiocarbamate* (**3**). White crystals (98%) **3**, mp: 188–189°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (3H, bs, 3NH), 4.15–3.95 (1H, m, CH), 3.05–2.96 (1H, m, CH), 1.98–0.96 (20H, m, 10CH_2); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 212.4 (C═S), 55.3 (CH), 50.0 (CH), 32.3 (2CH_2), 30.9 (2CH_2), 25.8 (CH_2), 25.5 (2CH_2), 25.1 (CH_2), 24.3 (2CH_2). Found %: C: 56.63; H: 9.28; N: 10.06. For $C_{13}H_{26}N_2S_2$ (274.2), calculated %: C: 56.88; H: 9.55; N: 10.21.

General procedures for preparation of 2-arylquinazolin-4 (3H)-thione (4a–b).

Method A. from chloroquinazoline and the reagent *N*-cyclohexyldithiocarbamate cyclohexyl ammonium salt **3**.

To a solution of chloroquinazoline **2a**–**b** (2.5 mmol) in $CHCl_3$ (25 mL) was added *N*-cyclohexyldithiocarbamate cyclohexyl ammonium salt **3** (0.69 g, 2.5 mmol). The reaction mixture was refluxed at 61°C for 12 h. The reaction mixture was evaporated under reduced pressure, and 25 mL of ethanol was added to the solid residue. The yellowish precipitate was filtered to give the desired product, crystalized from the appropriate solvent.

Method B. from 4-chloro-2-phenylquinazoline (**2a**) and thiourea.

A solution of 4-chloro-2-phenylquinazoline (**2a**) (0.24 g, 1.0 mmol), thiourea (0.15 g, 2.0 mmol), and sodium methoxide (0.15 g, 3.0 mmol) in 100 mL of absolute methyl alcohol was refluxed for 6 h. The solution was concentrated to a small volume and diluted with 250 mL of water. On acidifying with acetic acid, a yellowish product formed was separated by filtration, washed with water, and dried. The yield was 0.08 g or 35%.

Method C. from 2-phenylquinazolin-4(3*H*)-one **1a** and P_2S_5.

2-Phenylquinazolin-4(3*H*)-one **1a** (0.22 g, 1.0 mmol) was boiled with phosphorus pentasulfide (0.44 g, 2.0 mmol) for 2 h in 45 mL of xylene. The mixture was cooled, diluted with $CHCl_3$, washed with $NaHCO_3$ solution, water dried, and finally evaporated under reduced presssure. The residue was recrystallized from ethanol (charcoal).

2-Phenylquinazoline-4(3H)-thione (4a) *[36].*

Method A. (ethanol 95%–DMF) yellowish crystals 1.32 g (92%) **5a**, mp: 220–221°C Lit. 221–223°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.85 (1H, bs, NH), 8.63 (1H, d, *J* = 6.0 Hz, Ar–H), 8.17 (2H, d, *J* = 6.0 Hz, Ar–H), 7.93–7.77 (2H, m, Ar–H), 7.62–7.57 (4H, m, Ar–H); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 188.4 (C═S), 152.0, 144.8, 135.9, 132.7, 131.9, 129.8, 128.9, 128.6, 128.4, 128.2, 128.1 (C–Ar). Found %: C: 70.40; H: 4.11; N: 11.64. For $C_{14}H_{10}N_2S$ (238.06), calculated %: C: 70.56; H: 4.23; N: 11.76.

Method B. 0.08 g or 35%.

Method C. 0.03 g or 14%.

2-(4-Methoxyphenyl)-3H-quinazoline-4-thione (4b) *[36].*

(Ethanol 95%–DMF) yellowish crystals 0.82 g (89%) **5b**, mp: 195–196°C Lit. 200–201°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.71 (1H, bs, NH), 8.60 (1H, d, *J* = 6.0 Hz, Ar–H), 8.19 (2H, d, *J* = 6.0 Hz, Ar–H), 7.88 (1H, t, *J* = 6.0 Hz, Ar–H), 7.75 (1H, d, *J* = 9.0 Hz, Ar–H), 7.56 (1H, t, *J* = 6.0 Hz, Ar–H), 7.11 (2H, d, *J* = 9.0 Hz, Ar–H), 3.87 (3H, s, OCH_3); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 187.9 (C═S), 162.5, 151.5, 135.9, 130.7, 129.8, 128.5, 128.0, 127.8, 124.6, 114.4 (C–Ar), 55.9(OCH_3). Found %: C: 66.92; H: 4.37; N: 10.27. For $C_{15}H_{12}N_2OS$ (268.1), calculated %: C: 67.14; H: 4.51; N: 10.44.

General procedures for preparation of ethyl (2-arylquinazolin-4-ylsulfanyl) acetate (5a–b). To a solution of 2-arylquinazolin-4(3*H*)-thione **4a**–**b** (1.0 mmol) in ethyl alcohol (30 mL) was added ethyl chloroacetate (1.2 mL, 1.0 mmol) and triethyl amine (1.2 mL, 1.2 mmol). The reaction mixture was stirred under reflux for 12 h. The reaction mixture was filtered and poured over ice cooled water 50 mL and gave white precipitate filtered and dried. The resultant solid was crystalized from ethanol 95%–water to give the pure ester **5a**–**b**.

Ethyl (2-phenylquinazolin-4-ylsulfanyl) acetate (5a). White crystals 0.54 g (80%) **5a**, mp: 180–181°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64–8.62 (2H, m, Ar–H), 8.12–8.03 (2H, m, Ar–H), 7.86 (1H, t, *J* = 9.0 Hz, Ar–H), 7.60–7.53 (4H, m, Ar–H), 4.30–4.22 (4H, m, OCH_2, SCH_2), 1.31 (3H, t, *J* = 6.0 Hz, CH_3); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 172.7 (C═O), 168.9, 158.9, 149.0, 137.8, 133.9, 130.6, 129.1, 128.6, 128.4, 126.9, 123.7 (C–Ar), 61.9 (OCH_2), 32.2 (SCH_2), 14.2 (CH_3). Found %: C: 66.35; H: 4.82; N: 8.47. For $C_{18}H_{16}N_2O_2S$ (324.1), calculated %: C: 66.64; H: 4.97; N: 8.64.

Ethyl [2-(4-methoxyphenyl)quinazolin-4-ylsulfanyl] acetate (5b). White crystals 0.65 g (58%) **6b**, mp: 105–106°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.55 (2H, d,

J = 8.0 Hz, Ar–H), 8.04–7.95 (2H, m, Ar–H), 7.82–7.78 (1H, t, J = 8.0 Hz, Ar–H), 7.51–7.47 (1H, t, J = 8.0 Hz, Ar–H), 7.01 (2H, d, J = 8.0 Hz, Ar–H), 4.25–4.18 (4H, m, OCH_2, SCH_2), 3.89 (3H, s, OCH_3) 1.29–1.25 (3H, t, J = 8.0 Hz, CH_3). Found %: C: 64.27; H: 5.01; N: 7.69. For $C_{19}H_{18}N_2O_3S$ (354.10), calculated %: C: 64.39; H: 5.12; N: 7.90.

General procedures for preparation of (2-arylquinazolin-4-ylsulfan-yl)acetic acid (6a–b). To a solution ester **5a–b** (1.0 mmol) in methyl alcohol (30 mL) was added potassium hydroxide (0.11 g, 2.0 mmol) solution in 10 mL H_2O. The reaction mixture was stirred at room temperature for 4 h till complete consumption of the ester (monitored by thin-layer chromatography). The reaction mixture was evaporated under reduced pressure, diluted with water, and acidified by conc. HCl. The separated precipitate was filtered off and washed several times with water and dried. Crystallization from ethanol gave pure crystals from carboxylic acid **6a–b**.

(2-Phenylquinazolin-4-ylsulfanyl)acetic acid (6a). White crystals 0.84 g (75%) **6a**, mp: 160–161°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.60 (1H, bs, OH), 8.58–8.55 (2H, m, Ar–H), 8.14 (1H, d, J = 9.0 Hz, Ar–H), 8.01 (2H, s, Ar–H), 7.73–7.68 (1H, m, Ar–H), 7.57–7.55 (3H, s, Ar–H), 4.29 (2H, s, SCH_2); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 170.7 (C═O), 170.2 (C_q), 158.3 (C_q), 148.2 (C_q), 137.4 (C_q), 135.3 (CHAr), 131.5 (CHAr), 129.1 (CHAr), 128.8 (CHAr), 128.4 (CHAr), 124.1 (CHAr), 121.9 (C_q), 32.6 (SCH_2). Found %: C: 64.73; H: 3.86; N: 9.26. For $C_{16}H_{12}N_2O_2S$ (296.1), calculated %: C: 64.85; H: 4.08; N: 9.45.

[2-(4-Methoxyphenyl)quinazolin-4-ylsulfanyl]acetic acid (6b). White crystals 1.21 g (88%) **6b**, mp: 120–121°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.96 (1H, bs, OH), 8.51 (2H, d, J = 8.0 Hz, Ar–H), 8.09 (1H, d, J = 8.0 Hz, Ar–H), 7.95 (2H, d, J = 8.0 Hz, Ar–H), 7.65 (1H, s, Ar–H), 7.07 (2H, d, J = 8.0 Hz, Ar–H), 4.25 (2H, s, SCH_2), 3.85 (3H, S, OCH_3). Found %: C: 62.35 H: 4.13; N: 8.37. For $C_{17}H_{14}N_2O_3S$ (326.1), calculated%: C: 62.56 H: 4.32; N: 8.58.

General procedures for preparation of methyl 2-(2-(2-arylquinazolin-4-yl)sulfanyl)acetylamino alkanoates 7–8(a–f) by DCC coupling method. To a cold solution (−5°C) of amino acid ester hydrochloride (4.4 mmol) in acetonitrile (40 mL) containing triethyl amine (0.62 mL, 4.4 mmol), 1-hydroxybenzotriazole (HOBt) (0.59 g, 4.4 mmol), dicyclohexylcarbodiimide (DCC) (0.88 g, 4.4 mmol), and the carboxylic compounds (**6a–b**) (1.5 g, 4.4 mmol) were added successively. The solution was stirred at 0°C for 2 h and at room temperature for 8 h. The precipitated dicyclohexylurea was filtered off, and the filtrate was evaporated under reduced pressure. The residue was extracted with ethyl acetate, filtered off evaporated, and extracted once again with ethyl acetate. This workup procedure was repeated several times to ensure the complete removal of dicyclohexylurea. The filtrate was washed successively with saturated NaCl solution, 5% $NaHCO_3$ solution, 1*M* HCl, and water. After drying over anhydrous Na_2SO_4, the solvent was evaporated, and the remaining residue was crystallized from ethyl acetate-petroleum ether and afforded *S*-quinazoline amino acid esters **7–8(a–f)**.

Methyl (2-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetyl) aminoacetate (7a). White crystals 1.54 g (94%) **7a**, mp: 162–163°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63–8.60 (2H, m, Ar–H), 8.12–8.06 (2H, m, Ar–H), 7.90 (1H, t, J = 9.0 Hz, Ar–H), 7.63–7.54 (4H, m, Ar–H), 7.41 (1H, bs, NH), 4.23 (2H, s, SCH_2), 4.02 (2H, d, J = 6.0 Hz, $NHCH_2$), 3.57 (3H, s, OCH_3); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 171.9 (C═O), 169.6 (C═O), 168.6 (C_q), 158.9 (C_q), 149.2 (C_q), 137.4 (C_q), 134.3 (CHAr), 130.9 (CHAr), 129.2 (CHAr), 128.7 (CHAr), 128.5 (CHAr), 127.2 (CHAr), 123.7 (CHAr), 122.2 (C_q), 52.2 (OCH_3), 41.6 ($NHCH_2$), 32.6 (SCH_2). Found %: C: 61.84; H: 4.28; N: 11.36. For $C_{19}H_{17}N_3O_3S$ (367.1), calculated %: C: 62.11; H: 4.66; N: 11.44.

Methyl (3-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetyl) aminopropanoate (7b). White crystals 0.50 g (97%) **7b**, mp: 140–141°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60–8.58 (2H, m, 2Ar–H), 8.09–8.02 (2H, m, Ar–H), 7.90 (1H, t, J = 4.0 Hz, Ar–H), 7.60–7.52 (4H, m, Ar–H), 7.38 (1H, bs, NH), 4.11 (2H, s, SCH_2), 3.42 (2H, q, J = 6.0 Hz, $NHCH_2$), 3.22 (3H, s, OCH_3), 2.34 (2H, t, J = 6.0 Hz, CH_2). Found %: C: 62.84; H: 4.81; N: 10.87 For $C_{20}H_{19}N_3O_3S$ (381.1), calculated %: C: 62.97; H: 5.02; N: 11.02.

Methyl (4-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetyl) aminobutanoate (7c). White crystals 0.35 g (65%) **7c**, mp: 145–146°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58–8.56 (2H, m, 2Ar–H), 8.10–8.03 (2H, m, Ar–H), 7.89 (1H, t, J = 8.0 Hz, Ar–H), 7.60–7.49 (4H, m, Ar–H) 7.13 (1H, bs, NH), 4.13 (2H, s, SCH_2), 3.48 (3H, s, OCH_3), 3.22 (2H, q, J = 6.0 Hz, $NHCH_2$), 2.11 (2H, t, J = 6.0 Hz, CH_2), 1.94–1.63(2H, m, CH_2). Found %: C: 63.63; H: 5.22; N: 10.48. For $C_{21}H_{21}N_3O_3S$ (395.1), calculated %: C: 63.78; H: 5.35; N: 10.63.

Methyl (2-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetyl) aminopropanoate (7d). White crystals 0.74 g (60%) **7d**, mp: 165–166°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59–8.54 (2H, m, Ar–H), 8.08–8.02 (2H, m, Ar–H), 7.89 (1H, t, J = 8.0 Hz, Ar–H), 7.58–7.51 (5H, m, Ar–H, NH), 4.54–4.50 (1H, m, NHC<u>H</u>), 4.16 (2H, dd, J = 28.0, 16.0 Hz, SCH_2), 3.49 (3H, s, OCH_3), 1.16 (3H, d, J = 6.0 Hz, CH_3). Found %: C: 62.75; H: 4.83; N: 10.72. For $C_{20}H_{19}N_3O_3S$ (381.1), calculated %: C: 62.97; H: 5.02; N: 11.02.

Methyl (2-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetyl) amino-3-methylbutanoate (7e). White crystals 0.39 g (52%) **7e**, mp: 142–143°C; ^{1}H NMR (300 MHz, $CDCl_3$):

δ = 8.65–8.50 (2H, m, Ar–H), 8.20–8.17 (2H, m, Ar–H), 7.90 (1H, t, *J* = 8.0 Hz, Ar–H), 7.78–7.50 (5H, m, Ar–H, NH), 4.27 (2H, dd, *J* = 32.0, 15.0 Hz, SCH_2), 3.56 (3H, s, OCH_3), 2.24–2.14 (1H, m, CH), 0.75–0.67 (6H, m, CH_3); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 172.2 (C═O), 170.5 (C═O), 167.4 (C_q), 158.6 (C_q), 148.6 (C_q), 137.5 (C_q), 135.0 (CHAr), 131.3 (CHAr), 129.0 (CHAr), 128.8 (CHAr), 128.5 (CHAr), 128.2 (CHAr), 124.0 (CHAr), 122.0 (C_q), 58.4 (NHCH), 52.1 (OCH_3), 33.5 (SCH_2), 30.6 (CH), 19.3 (CH_3), 18.3 (CH_3). Found %: C: 64.32; H: 5.48; N: 10.14. For $C_{22}H_{23}N_3O_3S$ (409.15), calculated %: C: 64.53; H: 5.66; N: 10.26.

Methyl (2-(2-(2-phenylquinazolin-4-yl)sulfanyl)acetyl) amino-4-methylpentanoate (7f). White crystals 1.13 g (79%) **7f**, mp: 140–141°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61–8.58 (2H, m, Ar–H), 8.12–8.05 (2H, m, Ar–H), 7.90 (1H, t, *J* = 8.0 Hz, Ar–H), 7.62–7.56 (4H, m, Ar–H), 7.35 (1H, d, *J* = 6.0 Hz, NH), 4.60–4.52 (1H, m, NHCH), 4.18 (2H, dd, *J* = 32.0, 15.0 Hz, SCH_2), 3.51 (3H, s, OCH_3), 1.44–1.12 (3H, m, CH_2, CH), 0.70–0.58 (6H, m, CH_3); ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 172.2 (C═O), 170.5 (C═O), 168.2 (C_q), 158.9 (C_q), 149.1 (C_q), 137.4 (C_q), 134.3 (CHAr), 130.9 (CHAr), 129.2 (CHAr), 128.7 (CHAr), 128.5 (CHAr), 127.3 (CHAr), 123.8 (CHAr), 122.1 (C_q), 52.0 (OCH_3), 51.0 (NHCH), 32.7 (SCH_2), 24.6 (CH_2), 22.5 (CH), 21.5 ($2CH_3$). Found %: C: 65.01; H: 5.72; N: 9.76. For $C_{23}H_{25}N_3O_3S$ (423.16), calculated %: C: 65.23; H: 5.95; N: 9.92.

Methyl (2-(2-(2-(4-methoxyphenyl)quinazolin-4-yl)sulfanyl) acetyl) amino acetate (8a). White crystals 1.40 g (96%) **8a**, mp: 150–151°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (2H, d, *J* = 8.0 Hz, Ar–H), 8.05–7.98 (2H, m, Ar–H), 7.86–7.83 (1H, t, *J* = 8.0 Hz, Ar–H), 7.55–7.51 (1H, m, Ar–H), 7.41 (1H, bs, NH), 7.04 (2H, d, *J* = 8.0 Hz, Ar–H), 4.17 (2H, s, SCH_2), 3.98 (2H, d, *J* = 6.0 Hz, $NHCH_2$), 3.89 (3H, s, OCH_3), 3.55 (3H, s, OCH_3). Found %: C: 60.28; H: 4.62; N: 10.42. For $C_{20}H_{19}N_3O_4S$ (397.11), calculated %: C: 60.44; H: 4.82; N: 10.57.

Methyl (3-(2-(2-(4-methoxyphenyl)quinazolin-4-yl)sulfanyl) acetyl) aminopropanoate (8b). White crystals 0.85 g (92%) **8b**, mp: 155–156°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (2H, d, *J* = 8.0 Hz, Ar–H), 8.05–7.97 (2H, m, Ar–H), 7.86–7.82 (1H, t, *J* = 8.0 Hz, Ar–H), 7.55–7.51 (1H, t, *J* = 8.0 Hz, Ar–H), 7.32 (1H, bs, NH), 7.04 (2H, d, *J* = 8.0 Hz, Ar–H), 4.08 (2H, s, SCH_2), 3.90 (3H, s, OCH_3), 3.43 (2H, q, *J* = 6.0 Hz, $NHCH_2$), 3.22 (3H, s, OCH_3), 2.32 (2H, t, *J* = 6.0 Hz, CH_2). Found %: C: 61.08; H: 5.02; N: 10.01. For $C_{21}H_{21}N_3O_4S$ (411.13), calculated %: C: 61.30; H: 5.14; N: 10.21.

Methyl (4-(2-(2-(4-methoxyphenyl)quinazolin-4-yl)sulfanyl) acetyl) aminobutanoate (8c). White crystals 0.54 g (62%) **8c**, mp: 160–161°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (2H, d, *J* = 8.0 Hz, Ar–H), 8.05–7.98 (2H, m, Ar–H), 7.85 (1H, t, *J* = 8.0 Hz, Ar–H), 7.55–7.51 (1H, m, Ar–H), 7.17 (1H, bs, NH), 7.04 (2H, d, *J* = 8.0 Hz, Ar–H), 4.10 (2H, s, SCH_2), 3.89 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.22 (2H, q, *J* = 8.0 Hz, $NHCH_2$), 2.11 (2H, t, *J* = 8.0 Hz, CH_2CO), 1.67–1.62 (2H, m, CH_2). Found %: C: 61.96; H: 5.34; N: 9.67. For $C_{22}H_{23}N_3O_4S$ (425.14), calculated %: C: 62.10; H: 5.45; N: 9.88.

Methyl (2-(2-(2-(4-methoxyphenyl)quinazolin-4-yl)sulfanyl) acetyl) aminopropanoate (8d). White crystals 0.97 g (78%) **8d**, mp: 130–131°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56–8.50 (2H, d, *J* = 8.0 Hz, Ar–H), 8.06–7.98 (2H, m, Ar–H), 7.85 (1H, t, *J* = 8.0 Hz, Ar–H), 7.55–7.49 (2H, m, Ar–H, NH), 7.03 (2H, d, *J* = 8.0 Hz, Ar–H), 4.55–4.51 (1H, m, NHCH), 4.16 (2H, dd, *J* = 32.0, 15.0 Hz, SCH_2), 3.89 (3H, s, OCH_3), 3.51 (3H, s, OCH_3), 1.18 (3H, d, *J* = 6.0 Hz, CH_3). Found %: C: 61.14; H: 5.02; N: 10.05. For $C_{21}H_{21}N_3O_4S$ (411.13), calculated %: C: 61.30; H: 5.14; N: 10.21.

Methyl (2-(2-(2-(4-methoxyphenyl)quinazolin-4-yl)sulfanyl) acetyl) amino-3-methylbutanoate (8e). White crystals 1.11 g (59%) **8e**, mp: 110–111°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (2H, d, *J* = 8.0 Hz, Ar–H), 8.04–7.96 (2H, m, Ar–H), 7.82 (1H, t, *J* = 8.0 Hz, Ar–H), 7.51 (1H, t, *J* = 8.0 Hz, Ar–H), 7.32 (1H, bs, NH), 7.01 (2H, d, *J* = 8.0 Hz, Ar–H), 4.48–4.44 (1H, m, NHCH), 4.14 (2H, dd, *J* = 32.0, 15.0 Hz, SCH_2), 3.87 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 1.97–1.90 (1H, m, CH), 1.08–1.05 (6H, m, CH_3). Found %: C: 62.62; H: 5.52; N: 9.39. For $C_{23}H_{25}N_3O_4S$ (439.16), calculated %: C: 62.85; H: 5.73; N: 9.56.

Methyl (2-(2-(2-(4-methoxyphenyl)quinazolin-4-yl)sulfanyl) acetyl) amino-4-methylpentanoate (8f). White crystals 0.69 g (64%) **8f**, mp: 120–121°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (2H, d, *J* = 8.0 Hz, Ar–H), 8.06–7.98 (2H, m, Ar–H), 7.85 (1H, t, *J* = 8.0 Hz, Ar–H), 7.53 (1H, t, *J* = 8.0 Hz, Ar–H), 7.33 (1H, bs, NH), 7.03 (2H, d, *J* = 8.0 Hz, Ar–H), 4.56–4.51 (1H, m, NHCH), 4.14 (2H, dd, *J* = 32.0, 15.0 Hz, SCH_2), 3.89 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 1.38–1.20 (3H, m, CH_2, CH), 0.82–0.81 (6H, m, CH_3). Found %: C: 63.40; H: 6.87; N: 9.13. For $C_{24}H_{27}N_3O_4S$ (453.17), calculated %: C: 63.56; H: 6.00; N: 9.26.

Biological activity materials and methods.

Bacterial strain: Gram-positive bacteria *S. aureus* and Gram-negative bacteria *E. coli* were used to evaluate the antibacterial activity of the synthesized compounds. **Fungal strain:** Clinical culture (*C. albicans*) was used to evaluate the antifungal activity of the synthesized compounds.

Reference therapeutic drugs: Three antibiotic drugs were used in this work:

1) tetracycline (30 μg),
2) erythromycin (15 μg), and
3) novobiocin (30 μg).

The synthetic compounds dissolved in DMSO were tested by paper-disc agar-plate method [33], using three concentrations 30 and 15 μg per disc against two reference bacterial strains (*E. coli* NCMB 11943 and *S. aureus* NCMB 6571) and one clinical culture (*C. albicans*). Nutrient agar was used for testing the bacterial strains, and potato dextrose agar was used for fungi. The experiment was performed in triplicate; negative controls (DMSO loaded discs) and positive controls (four commercial antibiotic discs, Oxoid) were included. Inhibitory activity was recorded by measuring the clear zone diameter after incubation at 37°C for 24 h for bacteria and at 30°C for 48 h for *Candida*.

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