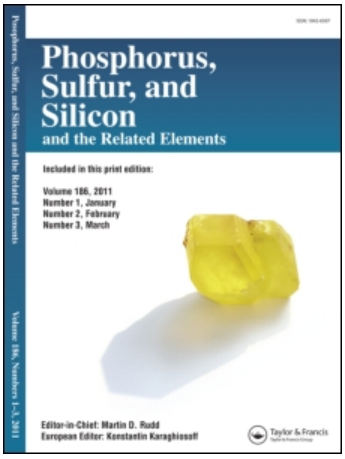

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SYNTHESIS OF SOME FUNCTIONALIZED 3-(4-THIOXO-3,4-DIHYDROQUINAZOLIN-2-YL) ACRYLIC ACID OF PHARMACEUTICAL INTEREST

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3-(4-Thioxo-3,4-dihydroquinazolin-2-yl)acrylic acid ***1*** *proved to be a convenient precursor for the synthesis of novel polyfunctional quinazoline derivatives of pharmaceutical interest via its treatment with some* π*-deficient compounds such as phenyl isocyanate and phenyl isothiocyanate. Also, S- and N-glucosidation of quinazoline has been achieved by treatment of* ***1*** *with glucopyranosyl bromide in alkaline medium. The behavior of* ***1*** *toward acrylonitrile (under Michael reaction condition), paraformaldehyde in the presence of secondary amines (under Mannich reaction condition) and sodium azide were investigated. Moreover, the peptidyl derivatives of quinazoline have been synthesized by condensation of* ***1*** *with* α*-amino acids via different routes. Some of the newly synthesized products were tested for their antimicrobial activities. The structure assignments are based on the analytical and spectroscopic results.*

Keywords: Antimicrobial activities; peptidyl derivatives; quinazolinylacrylic acid; quinazolinylacryloyl azide, S- and N-glucosides

Quinazoline derivatives and heterocyclic annelated quinazoline continue to attract great interest due to their diverse pharmacological activities. The syntheses and utility of many quinazoline derivatives as analgesic, antimalarial, diuretic, antitumor, and muscle relaxant have been reported.[1–6] Encouraged by all these facts, and as a continuation of the investigation on biologically active derivatives among six membered heterocycles,[7–9] I report herein the synthesis of novel heterocyclic compounds containing a quinazoline moiety of anticipated biological and medicinal importance.

I am grateful to Dr. M. M. Amer, Department of Botany, Faculty of Science, Benha University for biological screening.

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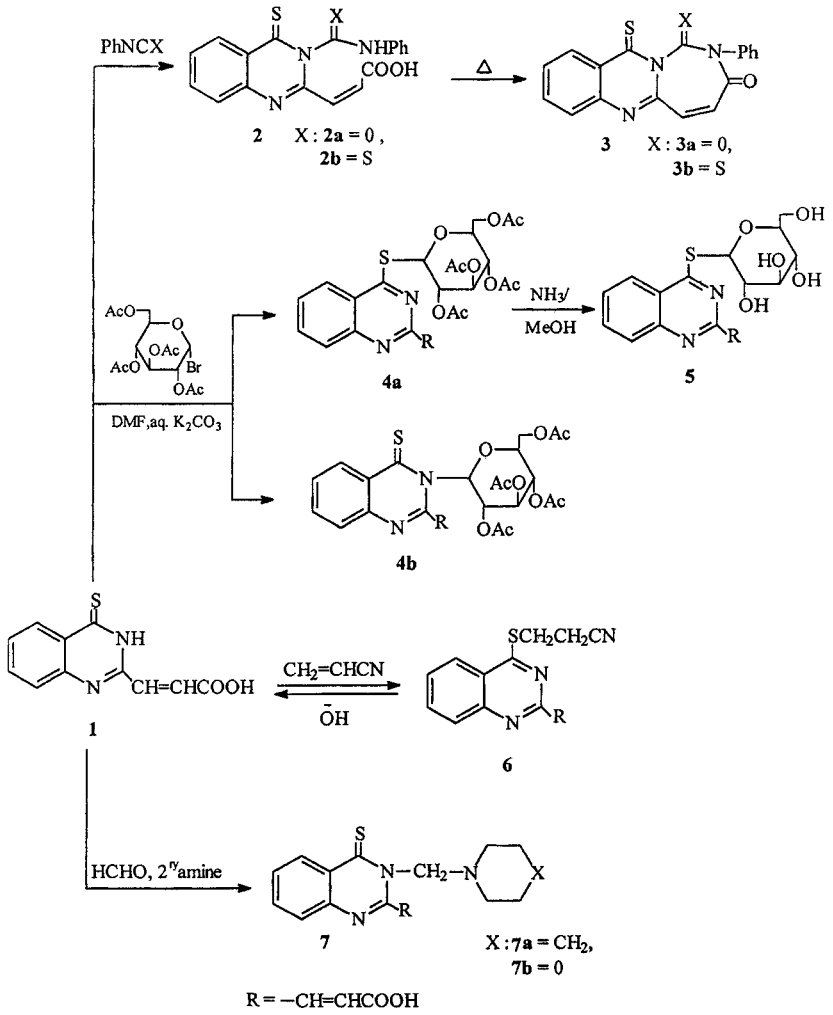
RESULTS AND DISCUSSION

The requisite starting compound 3-(4-thioxo-3,4-dihydroquinazolin-2-yl)acrylic acid (**1**) was prepared by reaction of phosphorus pentasulphide with 3-(4-oxo-3,4-dihydroquinazolin-2-yl)acrylic acid.[9] Treatment of the quinazolinethione **1** with either phenyl isocyanate or phenyl isothiocyanate in boiling benzene afforded 3-(3-phenylcarbamoyl/thiocarbamoyl-4-thioxo-3,4-dihydroquinazolin-2-yl) acrylicacid (**2a,b**). The readily available **2a,b** could be easily dehydrated by fusion above its melting point to give the diazepinone derivatives **3a,b**.

Recently, significant progress has been made in the development of antiviral chemotherapy due to the discovery of nucleoside analogues with potent antiviral activities.[10,11] Accordingly, the glucosidation of quinazolinethione **1** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in alkaline medium affords 3-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)quinazolin-2-yl]acrylic acid (**4a**) in high yield and 3-[4-thioxo-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3,4-dihydroquinazolin-2-yl]acrylic acid (**4b**) in low yield. The ^{1}H NMR spectra of compounds **4a** and **4b** showed the presence of two doublets at δ 6.26, 6.11 ppm with spin-spin coupling constants 10.89, 10.83 Hz, respectively, that were assigned to H-1′ for **4a** and **4b**, which corresponds to a diaxial orientation of H-1′ and H-2′ indicating the presence of only β-configuration[12,13] for compounds **4a,b**.

Deprotection of the glucoside **4a** with methanolic ammonia at room temperature gave 3-[4-(β-D-glucopyranosylsulfanyl)quinazolin-2-yl]acrylic acid (**5**). The ^{1}H NMR spectrum of compound **5** revealed the presence of a doublet at δ 5.20 ppm with spin-spin a coupling constant 10.13 Hz due to H-1′ corresponding to diaxial orientation of H-1′ and H-2′ which indicated the presence of only β-D-glucopyranose moiety.[12,13]

When the quinazolinethione **1** was allowed to react with acrylonitrile in dry pyridine, it underwent a Michael-type addition to the activated double bond of the nitrile to give 3-[4-(2-cyanoethylsulfanyl)quinazolin-2-yl]acrylic acid (**6**). Interestingly, the attempted alkaline hydrolysis of **6** failed to provide the corresponding acid, but resulted in the cleavage of the cyanoethyl group giving back the starting compound **1.** Obviously, a retro Michael reaction had occurred owing to the presence of a bulky substituted quinazolinyl moiety at the β-carbon and the use of high temperature under which the reaction was carried out.[14] Moreover, the reaction of quinazolinethione **1** with paraformaldehyde in the presence of secondary amines (viz piperidine and morpholine) proceeded smoothly to give the Mannich bases **7a,b**, (Scheme 1).

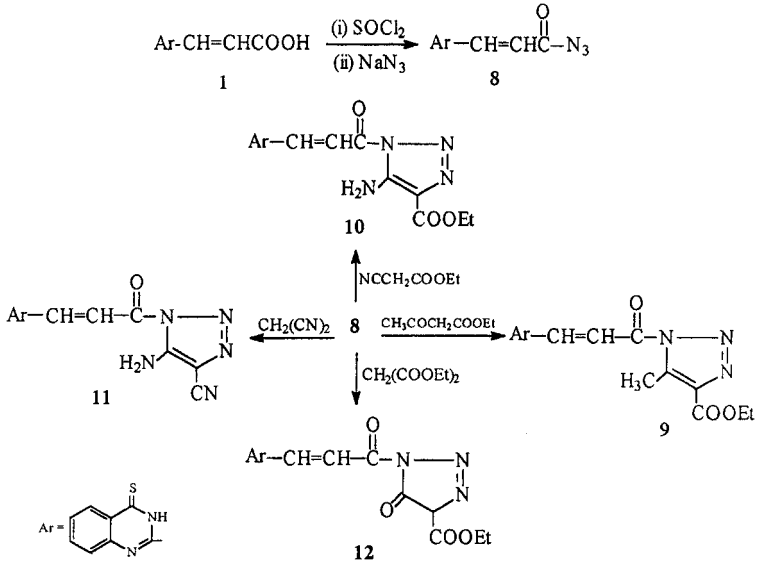


SCHEME 1

Recently there has been a growing interest in the area of application of azides in organic synthesis which could be attributed to the broad spectrum of reactivity of this versatile reagents.[15] Because of this, 3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloyl azide (**8**) was synthesized following the standard method available in the literature.[16] Thus, stirring equimolar amounts of the acid chloride and aqueous NaN_3 in dry acetone at 0–5°C afforded the acid azide **8**.

The acid azide **8** was used to add a triazole moiety which is known to be associated with a broad spectrum of biological action[17]

to quinazoline. Thus, the 1,3-dipolar cycloaddition reaction of acryloyl azide **8** with active methylene compounds[18] (viz ethyl acetoacetate, ethyl cyanoacetate, malononitrile and diethyl malonate) in the presence of sodium ethoxide afforded the corresponding triazoles **9–12**, (Scheme 2).



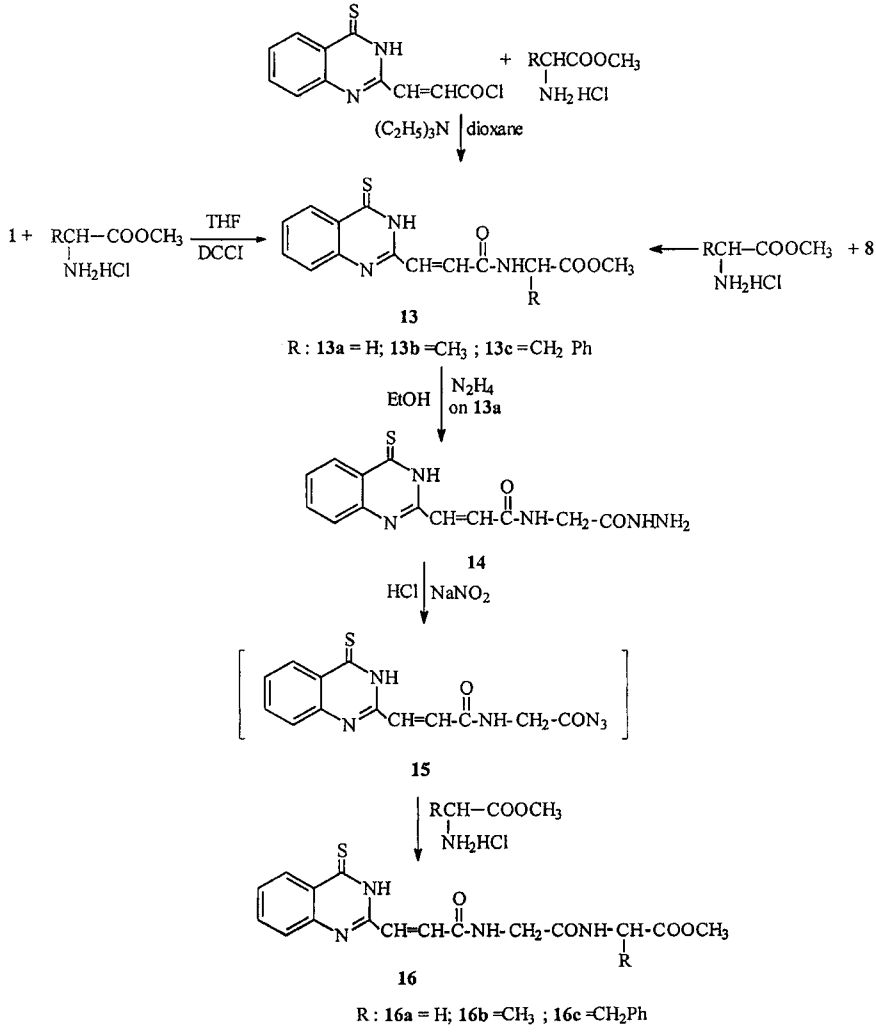
SCHEME 2

Finally, the main goal of this study was the utility of the quinazolinylacrylic acid **1** as a building block for the construction of novel quinazolines containing different amino acid residues incorporated in an amide linkage to form peptidyl derivatives of interesting pharmacological activities.[19–21] Thus, the condensation of **1** with α-amino acid methyl ester hydrochlorides (viz glycine, DL-alanine and DL-phenylalanine methyl ester hydrochloride) in tetrahydrofuran containing triethyl amine and dicyclohexyl carbodiimide[22] afforded quinazolinylacryloyl amino acid methyl esters **13a–c**.

The compounds **13a–c** were also obtained independently by two other routes:

(1) Condensation of quinazolinylacryloyl chloride with α-amino acid methyl ester hydrochlorides in dioxane-Et_3N medium.
(2) Coupling of quinazolinylacryloyl azide **8** with α-amino acid methyl ester hydrochlorides.[23]

Hydrazinolysis of methyl [3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloyl-amino]acetate (**13a**) in absolute ethanol gave N-hydrazino-carbonylmethyl-3-(4-thioxo-3,4-dihydroquinazolin-2-yl)acryl amide (**14**). The diazotization of **14** in acidic medium gave the corresponding acid azide **15** which proved to be a versatile building block for new peptides of biological interest via its reaction with α-amino acid methyl ester hydrochlorides (viz glycine, DL-alanine and DL-phenylalanine methyl ester hydrochloride) to give the dipeptides **16a–c** (Scheme 3).



SCHEME 3

Antimicrobial Activity

The antimicrobial activities of some synthesized compounds were tested in *vitro* by the filter paper and hole plate method[24] against various pathogenic bacteria, such as Gram +ve bacteria as *Bacillus subtilis, staphlococcus aureus*, and Gram −ve bacteria as *Escherichia coli, Pseudomonas aerginosa* in addition to fungi as *Aspergillus niger* using sulphadiazine as a reference standard. The culture medium was normal nutrient agar (NA) supplemented with 1 g yeast cm^3. According to the solubility of the tested compounds, different polar and nonpolar solvent were used, a good solubility was shown in 15% acetone (V/V) for all test compounds. Preliminary tests were carried out to estimate the minimum inhibitory concentration (MIC) of the test compounds. Based on the previous preliminary test, closely spaced test concentration were selected, they are (500, 250, 125 μg/ml).

Sulphadiazine was dissolved in filter sterilized 10 ml of 15% acetone (V/V) and employed in similar concentration as control. The zones of inhibition were measured in mm and the results are shown in Table I.

The results obtained from the antimicrobial tests showed that compound 1 exhibits a moderate activity against bacteria but is inactive against fungi. Also, compound **3b,** has promising bactericidal activity but is inactive against *Aspergillus niger*. But, compounds **4a, 6b, 8, 10**, and **13a** showed higher activity against bacteria and fungi. Also, compounds **16a,b** have higher activity than the other tested compounds when compared with the standard drug. These data indicate that the incorporation of a carbohydrate moiety, a basic mannich side and a peptidyl moiety into quinazolinethione **1** enhances its activity towards the bacteria and fungi.

TABLE I Antimicrobial Activity

Tested samples/organisms	B. subtilis	S. aureus	E. coli	P. aerginosa	A. higer
1	8	10	10	12	—
3b	10	12	10	15	—
4a	18	22	18	14	13
6b	13	18	16	21	16
8	10	8	12	15	8
10	12	—	12	14	—
13a	10	12	—	12	—
16a	15	23	18	16	18
16b	14	12	21	18	16
Sulphadiazine	10	12	—	12	—

Diameter of inhibition zones is measured in nm; (—) = no inhibition.

In conclusion, the readily obtainable quinazolinylacrylic acid are valuable precursors for the synthesis a variety of, otherwise not readably obtainable, heteroaromatics and modified peptides of biological interest.

The structural formulas of all newly synthesized compounds were elucidated and confirmed by elemental and spectroscopic analysis (cf. Table II; Experimental).

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Shimadzu 470 spectrophotmeter and ^{1}H NMR spectra ($CDCl_3$, DMSO-d_6) were recorded on a Varian Gemini, 200 MHz using TMS as internal reference (Chemical shifts are expressed as δ, ppm). Mass spectra were obtained on a Shimadzu, GCMS QP 1000EX mass spectrometer (70 ev EI mode).

TABLE II Physical Data of Compounds **(1–7)**

Cpd. No.	Yield (%)	m.p. (°C)	Molecular formula (mol. wt.)	Analysis % Calcd./(Found) C	H	N
1	68	>300	$C_{11}H_8N_2O_2S$ (232.26)	56.88 (56.75	3.47 3.53	12.06 12.19)
2a	75	238–9	$C_{18}H_{13}N_3O_3S$ (351.38)	61.53 61.63	3.73 3.60	11.96 11.83)
2b	62	261–3	$C_{18}H_{13}N_3O_2S_2$ (367.45)	58.84 (58.71	3.57 3.69	11.44 11.58)
3a	41	201–3	$C_{18}H_{11}N_3O_2S$ (333.36)	64.85 (64.93	3.33 3.41	12.60 12.69)
3b	46	210–12	$C_{18}H_{11}N_3OS_2$ (349.43)	61.87 (61.75	3.17 3.11	12.03 12.09)
4a	57	261–3	$C_{25}H_{26}N_2O_{11}S$ (562.55)	53.38 (53.61	4.66 4.48	4.98 4.79)
4b	7	236–8	$C_{25}H_{26}N_2O_{11}S$ (562.55)	53.38 (53.49	4.66 4.77	4.98 4.83)
5	62	261–3	$C_{17}H_{18}N_2O_7S$ (394.40)	51.77 (51.56	4.60 4.71	7.10 7.19)
6	67	197–9	$C_{14}H_{11}N_3O_2S$ (285.32)	58.93 (58.81	3.89 3.80	14.73 14.61)
7a	60	190–2	$C_{17}H_{19}N_3O_2S$ (329.42)	61.98 (61.82	5.81 5.76	12.76 12.83
7b	62	176–8	$C_{16}H_{17}N_3O_3S$ (331.39)	57.99 (57.85	5.17 5.23	12.68 12.75)

3-(4-Thioxo-3,4-dihydroquinazolin-2-yl)acrylic Acid (1)

To a solution of 3-(4-oxo-3,4-dihydroquinazolin-2-yl)acrylic acid[9] (10 mmol) in xylene (40 ml), phosphorus pentasulphide (10 mmol) was added and the reaction mixture was heated under reflux for 1h. The solid formed after cooling was filtered off and crystallized from ethanol to give **1**. IR: ν = 3450–3260 (OH, NH), 1690 (CO), 1605 (C=N) and 1285 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta = 6.99$ (d, 1H, $J = 13.67$ Hz, β-olefinic-H), 7.00–7.13 (m, 5H, ArH and α-olefinic-H), 9.10 (s, 1H, NH exchangeable), 11.93 (s, 1H, OH, exchangeable).

3-(3-Phenylcarbamoyl/thiocarbamoyl-4-thioxo-3, 4-dihydroquinazolin-2-yl)acrylic Acid (2a,b)

General Procedure

A mixture of quinazolinethione **1** (5 mmol) and phenyl isocyanate or phenyl isothiocyanate (5 mmol) in dry benzene (30 ml) was refluxed for 3 h. The excess of benzene was distilled under reduced pressure, the separated product was filtered and crystallized from ethanol to afford **2a,b**. IR: ν = 3450–3200 (OH, NH) 1690, 1675–1670 (CO) and 1289 cm^{-1} (CS); ^1H NMR of **2b** (DMSO-d_6): $\delta = 6.97$ (d, 1H, $J = 13.66$ Hz, β-olefinic-H) 6.99–7.48 (m, 10H, ArH and α-olefinic-H), 10.22 (s, 1H, NH exchangeable), 12.1 (s, 1H, OH exchangable).

9-Phenyl-8,9,10,11-tetrahydro-11-thioxo-5,9,10a-triazacyclohepta[b]naphthalene-8,10-dione (3a) and 9-Phenyl-8,9,10,11-tetrahydro-10,11-dithioxo-5,9,10a-triaza-cyclohepta[b]naphthalen-8-one (3b)

The quinazoline derivatives **2a** or **2b** (4 mmol) were heated in a fusion tube provided with an air condenser above their melting points on a sand bath for 2 h. The solid product which formed after cooling crystallized from ethanol to give **3a,b**. IR: ν = 1670–1660 (CO), 1296 (CS of **3b**). The absence of any absorption bands due to OH or NH, confirmed the cyclization process; ^1H NMR ($CDCl_3$) of **3a**: $\delta = 6.88$ (d, 1H, J = 13.68 Hz, β-olefinic-H) 6.90–7.35 (m, 10H, ArH and α-olefinic-H); MS of **3a** m/z (%) 333 (56.6) and MS of **3b:** m/z (%) 349 (79.8).

3-[4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylsulfanyl)-quinazolin-2-yl]acrylic acid (4a) and 3-[4-Thioxo-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3,4-dihydroquinazolin-2-yl]acrylic Acid (4b)

To a solution of **1** (5 mmol) in a mixture of (20 ml) DMF and aq. K_2CO_3 (5 mmol) in (15 ml) H_2O, was added 2,3,4,6-tetra-*O*-acetyl-α-D-

glucopyranosyl bromide (9 mmol) in (15 ml) DMF dropwise with stirring at room temperature for 30 min. Stirring was continued overnight until the starting material was consumed (TLC). The reaction mixture was cooled and poured on ice/cold water. The solids obtained was filtered off and chromatographed on a column of silica gel (petroleum ether/ethyl acetate, 3:1, v/v) to give **4a,b**. IR: ν = 3405 (OH), 1735–1730 (CO of acetyl), 1690 (CO of acid); ^{1}H NMR of **4a** ($CDCl_3$): δ = 1.80, 1.91, 1.97, 2.08 (4 s, 12H, 4Ac), 3.97–4.21 (m, 2H, H-6′, H-5′), 4.81–5.36 (m, 3H, H-4′, H-2′, H-3′), 6.26 (d, 1H, J = 10.89 Hz, H-1′), 6.99 (d, 1H, J = 13.65 Hz, β-olefinic-H), 7.01–7.75 (m, 5H, ArH and α-olefinic-H), 11.98 (s, 1H, OH, exchangeable); MS of **4a**: m/z (%) 562 (81.51); ^{1}H NMR of **4b** ($CDCl_3$): δ = 1.83, 1.95, 2.06, 2.11 (4 s, 12H, 4Ac), 3.91–4.29 (m, 2H, H-6′, H-5′), 5.10–5.32 (m, 3H, H-4′, H-2′, H-3′), 6.11 (d, 1H, J = 10.83 Hz, H-1′), 6.97 (d, 1H, J = 13.66 Hz, β-olefinic-H), 7.11-8.21 (m, 5H, ArH and β-olefinic-H).

3-[4-(β-D-glucopyranosylsulfanyl)quinazolin-2-yl]acrylic Acid (5)

To a suspension of compound **4a** (4 mmol) in absolute methanol (20 ml), a saturated solution of ammonia in absolute methanol (20 ml) was added. The reaction mixture was stirred at room temperature for 1 h. and left overnight in refrigerator until the starting material was consumed (TLC). The solvent was evaporated under reduced pressure and the residue was purified over a column of silica gel (chloroform/methanol, 5:1, v/v) to afford **5.** IR: ν = 3450–3210 (OH), 1691 (CO); ^{1}H NMR ($CDCl_3$) δ = 3.26 (m, 3H, H-6′, H-6′, H-5′), 3.36 (m, 1H, H-4′), 3.52 (m, 2H, H-3′, H-2′), 4.11 (t, 1H, J = 6.16 Hz, HO-6′), 4.82 (d, 1H, J = 6.11 Hz, HO-4′), 5.14 (d, 1H, J = 6.10 Hz, HO-3′), 5.20 (d, 1H, J = 10.13 Hz, H-1′), 5.31 (d, 1H, J = 5.88 Hz, HO-2′), 6.96 (d, 1H, J = 13.65 Hz, β-olefinic-H) 6.98–7.81 (m, 5H, ArH and α-olefinic-H), 11.87 (s, 1H, OH, exchangeable); MS: m/z (%) 394 (28.66).

3-[4-(2-Cyanoethylsulfanyl)quinazolin-2-yl]acrylic Acid (6)

Compound **6** was prepared according to the published procedure,[25] and was crystallized from benzene. IR: ν = 3490–3300 (OH), 2225 (C≡N), 1690 (CO), 1290 cm^{-1} (CS); ^{1}H NMR ($CDCl_3$): δ = 2.96 (t, 2H, J = 7.34 Hz, CH_2CN), 3.79 (t, 2H, J = 7.45 Hz, CH_2S), 6.89 (d, 1H, J = 13.66 Hz, β-olefinic-H) 6.92-7.84 (5H, ArH and α-olefinic-H), 12.12 (s, 1H, OH exchangeable).

3-[(3-Piperidin-1-yl/morpholin-4-yl)methyl-4-thioxo-3,4-dihydroquinazolin-2-yl]acrylic acid (7a,b)

A mixture of **1** (5 mmol), formaldehyde solution in water (5 ml) and secondary amines (10 mmol) in ethanol (25 ml) was refluxed for 6 h. The reaction mixture was concentrated and the solid formed after cooling was filtered and crystallized from methanol to give **7a,b**. IR: $\nu = 3480$–3320 (OH), 1690–1685 (CO), 1295 (CS); ^{1}H NMR of **7a** ($CDCl_3$): $\delta = 1.46$ (m, 6H, 3 CH_2), 2.62 (m, 4H, CH_2NCH_2), 5.09 (s, 2H, CH_2), 6.88 (d, 1H, $J = 13.66$ Hz, β-olefinic-H) 6.91–7.89 (m, 5H, ArH and α-olefinic-H), 12.3 (s, 1H, OH, exchangeable), ^{1}H NMR of **7b** ($CDCl_3$) $\delta = 2.77$ (m, 4H, CH_2NCH_2), 3.63 (m, 4H, CH_2OCH_2), 5.21 (s, 2H, CH_2), 6.92 (d, 1H, $J =$ 13.66 Hz, β-olefinic-H) 6.94–7.98 (m, 5H, ArH and α-olefinic-H), 11.86 (s, 1H, OH, exchangeable).

3-(4-Thioxo-3,4-dihydroquinazolin-2-yl)acryloyl azide (8)

A saturated solution of sodium azide in water[16] (8 mmol) was added dropwise to a stirred solution of 3-(4-thioxo-3,4-dihydroquinazolin-2-yl)acryloyl chloride (4 mmol) in dry acetone (20 ml) at 0–5°C. The mixture was stirred for further 30 min. The reaction mixture was added to crushed ice and the precipitated product was filtered to give the azide **8**, yield (73%), m.p: 120–3°C (with decomposition). IR: $\nu = 2170$ (CON_3), 1295 cm^{-1} (CS).

Reaction of acryloyl azide 8 with active methylene compounds: Formation of compounds 9–12

General Procedure

A solution of Na (0.15 g) in absolute ethanol (20 ml) is added in one portion to an ice-cold solution of compound **8** (5 mmol) in absolute ethanol (20 ml) and the active methylene compounds (10 mmol). The mixture was stirred overnight. Then the solvent was evaporated in vacuo, the concentrated ethanol solution was poured into ice-cold water and the corresponding product was collected by filtration and crystallized from ethanol to give the compounds **9–12**.

Ethyl 5-methyl-1-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)acryloyl]-1H-1,2,3-triazole-4-carboxylate (9)

Prepared from **8** and ethyl acetoacetate; yield: 81% m.p: 151–153°C; Anal. Calcd. for $C_{17}H_{15}N_5O_3S$ (369.40):C, 55.27; H, 4.09; N, 18.96%; Found: C, 55.20; H, 4.18; N, 18.83; IR: $\nu = 3290$ (NH), 1730, 1670 (CO),

1610 (CN), 1297 cm^{-1} (CS); ^1H NMR (DMSO-d_6) : $\delta = 1.27$ (t, 3H, $J =$ 8.11 Hz, CH_3), 2.11 (s, 3H, CH_3), 3.96 (q, 2H, $J = 8.11$ Hz, CH_2), 6.99 (d, 1H, $J = 13.67$ Hz, β-olefinic-H) 7.00–7.38 (m, 5H, ArH and α-olefinic-H), 9.21 (s, 1H, NH, exchangeable); MS: m/z (%) 369 (83.2).

Ethyl 5-amino-1-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloyl]-1H-1,2,3-triazole-4-carboxylate (10)

Prepared from **8** and ethyl cyanoacetate; yield: 65%; m.p.: 163–165°C; Anal. Calcd. for $C_{16}H_{14}N_6O_3S$ (370.39): C, 51.88; H, 3.81; N, 22.69%; Found: C, 51.97; H, 3.70; N, 22.60; IR: $\nu =$ 3350–3260 (NH), 1731, 1675 (CO), 1291 cm^{-1} (CS); ^1H NMR (DMSO-d_6): $\delta = 1.31$ (t, 3H, $J = 8.12$ Hz, CH_3), 4.13 (q, 2H, $J = 8.12$ Hz, CH_2), 4.97 (br, 2H, NH_2), 7.02 (d, 1H, J = 13.65 Hz, β-olefinic-H) 7.04–8.11 (m, 5H, ArH and α-olefinic-H), 9.32 (s, 1H, NH, exchangeable); MS: m/z (%) 370 (78.5).

5-Amino-1-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloyl]-1H-1,2,3-triazole-4-carbonitrile (11)

Prepared from **8** and malononitrile; yield: 86%, m.p.: 140–142°C; Anal. Calcd. for $C_{14}H_9N_7OS$ (323.33): C, 52.01, H, 2.81; N, 30.33%; Found: C, 52.17; H, 2.68; N, 30.47; IR: $\nu =$ 3380–3250 (NH); 2226 (C≡N), 1671 (CO), 1290 cm^{-1} (CS); ^1H NMR (DMSO-d_6): $\delta = 5.1$ (br, 2H, NH_2), 6.88 (d, 1H, $J = 13.65$ Hz, β-olefinic-H) 6.90–7.93 (m, 5H, ArH and α-olefinic-H), 9.25 (s, 1H, NH, exchangeable).

Ethyl 5-oxo-1-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloyl]-4,5-dihydro-1H-1,2,3-triazole-4-carboxylate (12)

Prepared from **8** and diethyl malonate, yield: 71%; m.p.: 170–172°C; Anal. Calcd. for $C_{16}H_{13}N_5O_4S$ (371.37): C, 51.75; H, 3.53; N, 18.86%; Found: C, 51.82; H, 3.65; N, 18.72; IR: $\nu =$ 3210 (NH), 1732, 1710, 1670 (CO), 1293 cm^{-1} (CS); MS: m/z (%) 371 (97.1).

General Procedure for Preparation of Acryloyl Amino Acid Methyl Esters 13a–c

Method A

To a solution of the α-amino acid methyl ester hydrochlorides (7 mmol) in tetrahydrofuran (50 ml) was added triethylamine (3 ml). The solution was kept for 25 min at 0–5°C and the precipitated triethylamine hydrochloride was filtered off. To the filtrate at −5°C was added the quinazolinylacrylic acid **1** (5 mmol) and dicylohexyl-carbodiimide

(5 mmol). The reaction was allowed to proceed for 3 h at 0°C; for 3 h at 5°C and for 24 h at room temperature. The dicyclohexylurea was removed by filteration and the solvent evaporated to dryness under reduced pressure. The residual solid was recrystallized from ethanol to give **13 a–c**

Method B

Quinazolinylacryloyl chloride (5 mmol) was dissolved in dioxane (40 ml) containing (3 ml) triethylamine and added to a solution of the α-amino acid methyl ester hydrochlorides (7 mmol). The reaction mixture was stirred at room temperature for 30 min followed by refluxing for (2–3 h) until completion of the reaction (TLC). After cooling of the reaction mixture, the $Et_3N{\cdot}HCl$ was filtered off and a benzeneether mixture (1:1) (100 ml) was added. The reaction mixture washed with 10% $NaHCO_3$ and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the solid products **13a–c**.

Method C

To a solution of acryloyl azide **8** (5 mmol) in ethyl acetate was added α-amino acid methyl ester hydrochlorides (7 mmol) and triethylamine (3 ml). The reaction mixture was stirred for 6 h at 4°C and for 12 h at room temperature. Then the reaction mixture was washed with 0.5 N HCl, $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solution was evaporated under vacuum to dryness and the residual material was recrystallized to give compounds **13a–c**.

Methyl [3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloylamino]acetate (13a)

Yield: 67%; m.p.: 173–175°C; Anal. Calcd. for $C_{14}H_{13}N_3O_3S$ (303.34): C, 55.43; H, 4.32; N, 13.85%; Found C, 55.51; H, 4.45; N, 13.93; IR: ν = 3320–3290 (NH), 1730 (CO of ester), 1680–1675 (CO of amide), 1290 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta = 2.82$ (s, 3H, CH_3), 3.51 (d, 2H, CH_2), 6.98 (d, 1H, $J = 13.68$ Hz, β-olefinic-H) 6.99–7.39 (m, 5H, ArH and α-olefinic-H), 9.20, 9.31 (2s, 2H, 2NH, exchangeable); MS: m/z (%) 303 (81).

Methyl 2-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloylamino]propanoate (13b)

Yield 63%; m.p.: 186–188°C; Anal. Calcd. for $C_{15}H_{15}N_3O_3S$ (317.36): C, 56.77; H, 4.76; N, 13.24%; Found : C, 56.82; H, 4.89; N, 13.35; IR: ν = 3295–3200 (NH), 1732 (CO of ester), 1675–1670 (CO of amide),

1301 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta = 1.23$ (d, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.11–4.16 (m, 1H, CH), 6.92 (d, 1H, $J = 13.67$ Hz, β-olefinic-H) 6.91–7.41 (m, 5H, ArH and α-olefinic-H), 9.24, 9.35 (2s, 2H, 2NH, exchangeable).

Methyl 2-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloylamino]-3-phenylpropanoate (13c)

Yield: 71%; m.p. 161–163°C; Anal. Calcd. for $C_{21}H_{19}N_3O_3S$ (393.46): C, 64.10; H, 4.87; N, 10.68%; Found: C, 64.20; H, 4.75; N, 10.52; IR: $\nu =$ 3350–3260 (NH), 1728 (CO of ester), 1680–1670 (CO of amide), 1286 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta = 2.81$ (s, 3H, CH_3), 2.99 (d, 2H, CH_2), 4.03–4.15 (m, 1H, CH), 6.89 (d, 1H, $J = 13.66$ Hz, β-olefinic-H) 6.90–7.39 (m, 5H, ArH and α-olefinic-H), 9.12, 9.26, (2s, 2H, 2NH, exchangeable); MS : m/z (%) 393 (76).

N-Hydrazinocarbonylmethyl-3-(4-thioxo-3,4-dihydroquinazolin-2-yl)acryl Amide (14)

To a solution of **13a** (5 mmol) in ethanol (30 ml) was added hydrazine hydrate (2 ml). The reaction mixture was kept for 24 h at 0–5°C. The solid which separated was crystallized from ethanol to give the hydrazide **14**. Yield: 60; m.p.: 216–268°C; Anal. Calcd. for $C_{13}H_{13}N_5O_2S$ (303.34): C, 51.47; H, 4.32; N, 23.09%; Found: C, 51.31; H, 4.41; N, 23.18%; IR: $\nu =$ 3210–3195 (NH), 1680–1670 (CO), 1615 (CN), 1287 cm^{-1} (CS), ^1H NMR ($CDCl_3$) $\delta = 3.31$ (d, 2H, CH_2), 4.91 (br, 2H, NH_2), 7.02 (d, 1H, $J =$ 13.65 Hz, β-olefinic-H) 7.03–7.85 (m, 5H, ArH and α-olefinic-H), 9.21, 9.29, 9.32, (3s, 3H, 3NH, exchangeable).

General Procedure for the Preparation of the Dipeptide Derivatives 16a–c

The hydrazide **14** (7 mmol) was dissolved in a mixture of 8 ml acetic acid, 4 ml 5N HCl and 10 ml water, the solution was cooled to 0°C, and the solution of 0.5 g of sodium nitrite in (4 ml) water was added dropwise over 10 min and the reaction was allowed to proceed for 10 min at 0°C. The acid azide **15** was precipitated as a syrup which was taken up in (50 ml) cold ethyl acetate. The ethyl acetate layer was washed with cold 3% $NaHCO_3$ and briefly dried over anhydrous Na_2SO_4. The solution of azide **15** was added to 8 mmol of α-amino acid methyl ester hydrochlorides in (20 ml) ethyl acetate containing (4 ml) Et_3N and the reaction mixture was stirred for 6 h at 4°C and for another 12 h at room temperature. The reaction mixture washed with 0.5N HCl, $NaHCO_3$

and dried over anhydrous Na_2SO_4. The solution was evaporated under vacuum to dryness and the residual material crystallized from benzene to give the dipeptide derivatives **16a–c**.

Methyl 2-{2-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloylamino]acetylamino}-acetate (16a)

Yield: 55%; m.p.: 164–166°C; Anal. Calcd. for $C_{16}H_{16}N_4O_4S$ (360.39): C, 53.32; H, 4.47; N, 15.55%; Found: C, 53.41; H, 4.56; N, 15.67; IR: ν = 3310–3200 (NH), 1730 (CO of ester), 1679–1670 (CO of amides), 1296 cm^{-1} (CS); ^1H NMR (DMSO-d_6) $\delta = 2.82$ (s, 3H, CH_3), 3.12 (d, 2H, CH_2), 3.46 (d, 2H, CH_2), 7.00 (d, 1H, $J = 13.63$ Hz, β-olefinic-H) 7.01–7.52 (m, 5H, ArH and α-olefinic-H), 9.19, 9.22, 9.32 (3s, 3H, 3NH, exchangeable); MS: m/z (%) 360 (78.2).

Methyl 2-{2-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloylamino]acetylamino}-propanoate (16b)

Yield: 51%; m.p.: 183–185°C; Anal. Caled. for $C_{17}H_{15}N_4O_4S$ (374.42): C, 54.53; H, 4.85; N, 14.96%; Found: C, 54.66; H, 4.98; N, 14.81; IR: ν = 3290–3200 (NH), 1731 (CO of ester), 1675–1670 (CO of amides), 1290 cm^{-1} (CS); MS: m/z (%) 374 (83.22).

Methyl 2-{2-[3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acryloylamino]acetylamino}-3-phenylpropanoate (16c)

Yield: 56%; m.p.: 190–192°C; Anal. Calcd. for $C_{23}H_{22}N_4O_4S$ (450.51): C, 61.32; H, 4.92; N, 12.44%; Found: C, 61.41; H, 4.85; N, 12.51; IR: ν = 3285–3195 (NH), 1729 (CO of ester), 1680–1670 (CO of amides), 1294 cm^{-1} (CS); ^1H NMR (DMSO-d_6) $\delta = 2.82$ (s, 3H, CH_3), 2.91 (d, 2H, CH_2), 4.10–4.17 (m, 1H, CH), 6.96 (d, 1H, $J = 13.64$ Hz, β-olefinic-H) 6.98–7.41 (m, 5H, ArH and α-olefinic-H), 9.20, 9.24, 9.34 (3s, 3H, 3NH, exchangeable); MS: m/z (%) 450 (65.32).

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