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Synthesis and characterization of new (E)-N'-(substituted benzylidene)-2-(3-(2-methyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazides

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Abstract: A small library of new azomethine derivatives of 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones was synthesized. The key intermediates 2-thioxo-quinazolinones **(3a–e)**, obtained in 2 steps from the corresponding anilines, were treated with methyl chloroacetate to afford S-substituted esters (**4a**,**d**), which were then converted into corresponding acetohydrazides (**5a**,**d**). Further, acetohydrazide (**5d**) was converted to the azomethines derivatives (**6a**–**k**) by reacting with a number of suitably substituted benzaldehydes. FTIR, ^{1}H NMR, ^{13}C NMR, GC-MS, and elemental analyses were used to confirm the assigned structures of the synthesized compounds. Further, compounds **3a**, **5**, and **6j** were also confirmed by X-ray diffraction data.

Key words: Synthesis, crystal structures, 3,4-dihydroquinazolines, acetohydrazides, azomethines

1. Introduction

Quinazolinone is one of the leading and flourishing structures in medicinal chemistry. Quinazolinone derivatives display a wide range of biological and pharmacological activities such as anticonvulsant, anti-inflammatory, antitumor, analgesic, anticancer, cytotoxic, anticoccidial, antibacterial, and antifungal.[1–10] Moreover, quinazolinone derivatives are effectively used as inhibitors of human microsomal prostaglandin synthase 1 (mPGES 1)[11] and a potential PET tracer for growth hormone secretagogue receptor (GHSR).[12] 3-Aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones are a very important subclass of quinazolinones having a diversity of pharmacological and biological activities like anticonvulsant,[13] 5-HT$_{2A}$ receptor antagonistic,[14] antitumor,[15] antimicrobial,[16] anticancer,[17,18] antimicrobial,[19] analgesic, and anti-inflammatory.[20] On the other hand, hydrazides, hydrazones, or azomethines are of wide interest because of their diverse synthetic, biological, and clinical applications,[21–28] e.g., antimalarial, antiparasitic, antimicrobial, anticonvulsant, and antituberculosis activity.

Herein, we report the synthesis of new hydrazone derivatives of S-linked quinozolines with a number of substituted benzaldehydes in an attempt to obtain compounds with enhanced bioactivities.

2. Results and discussion

The synthesis of 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**3a**–**e**) was carried out according the synthetic route shown in Scheme 1 involving treatment of substituted anilines with carbon disulfide and sodium hydroxide in dimethyl sulfoxide to afford sodium dithiocarbamates (**2**). Quinazolin-4(1*H*)-ones (**3a**–**e**) were

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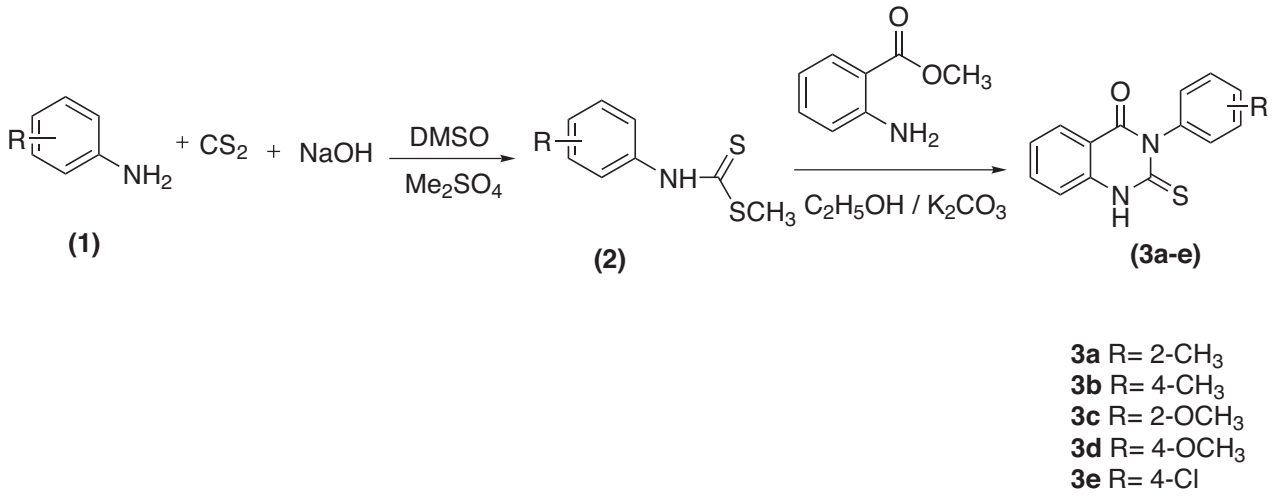
obtained by adding methyl anthranilate to the solution of the latter in ethanol using anhydrous potassium carbonate as a weak base.



Scheme 1. Synthetic route to 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones (**3a**–**e**).

The FTIR spectra of **3a**–**e** showed stretching vibrations at 3186–3189 cm^{-1} for NH, at 1702–1706 cm^{-1} for C=O, and at 1220–1225 cm^{-1} for C=S. In ^{1}H NMR the characteristic NH proton of the ring appeared in the range of 13.02–11.80 ppm and the aromatic protons at 8.10–6.99 ppm.

Figure 1 shows the molecular structure of 3-o-tolyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (**3a**), while the crystal packing is shown in Figure 2. The crystal packing of **3a** with 2 crystallographically independent molecules A and B shows N12–H...O1(–x + 1, y + 0.5, –z + 1.5) with H...O 2.35 Å and N22–H...O2(–x, y – 0.5, –z + 0.5) with H...O 1.95 Å interactions that link molecules into endless chains extended along the b-axis (Figure 2). The aromatic planes of the molecules are twisted along the N–C axes and make dihedral angles of 77.1(2)° for molecule A and 79.0(2)° for B. In general, there are no unexpected geometric parameters.

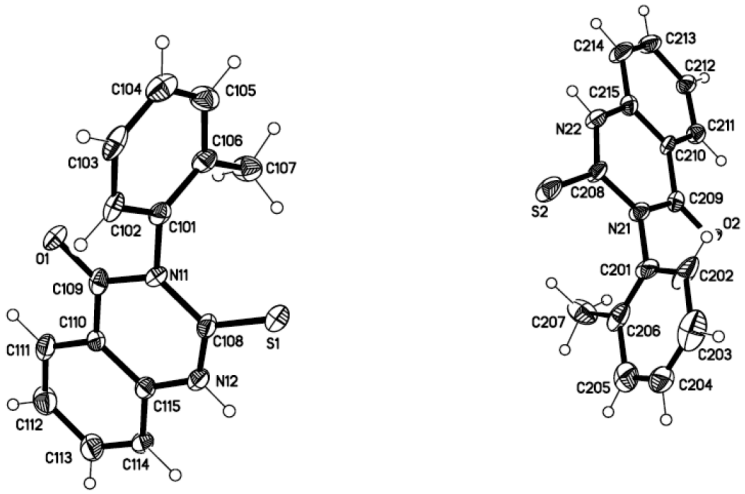


Figure 1. Molecular structure of **3a** (both molecules A and B) with displacement ellipsoids plotted at 50% probability level.

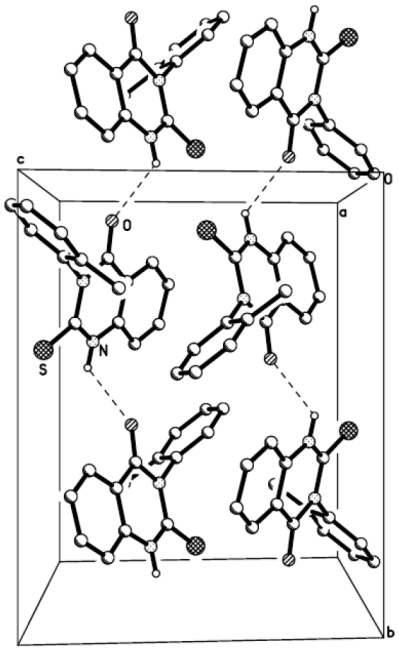


Figure 2. Crystal packing pattern of **3a** with hydrogen bonds as dotted lines. H-atoms not involved are omitted.

The quinazolinones (**3a**–**e**) were converted to corresponding esters (**4a**,**d**) by treating with methyl chloroacetate in ethanol using a catalytic amount of anhydrous potassium carbonate. In the case of **4a**, the NH absorption disappeared and ester carbonyl stretching in the range of 1730–1733 cm^{-1} in the FTIR spectrum indicated ester formation. ^{1}H NMR confirmed the formation of quinazolinyl esters by the appearance of methylene protons at 4.05–3.67 ppm as 2 separate doublets due to their diastereotopic nature. In ^{13}C NMR the appearance of a signal in the range of 168.76–169.35 ppm for the C=O of ester, disappearance of the signal for C=S, and the appearance of methylenic carbons in the range of 34.73–34.35 ppm were observed.

The acetohydrazides (**5a**,**d**) were obtained by treating the esters (**4a**,**d**) with hydrazine hydrate in ethanol. In the case of **5a**, characteristic absorption for primary NH_2, along with a shoulder at 3420–3402 cm^{-1} and an absorption peak for secondary NH in the range 3239–3230 cm^{-1}, was observed in the FTIR. In ^{1}H NMR characteristic signals for N–H and NH_2 protons appeared in the regions 9.80–9.40 and 9.05–8.35 ppm, respectively. In ^{13}C NMR the disappearance of methoxy protons of ester and the methoxy carbon signal was noted. Figure 3 shows the molecular structure of **5a**, while the crystal packing is shown in Figure 4.

The dihedral angle between the 2 aromatic ring planes is 85.51(6)°, while the N4–C3–S1–C1 torsion angle measures 176.9(1)°. Prominent D–H...A bonds are N1–H...O2(x – 1, y, z) with H...O 2.00 Å and N2–H2B...O1(–x, –y + 1, –z) with H...O 2.15 Å that link molecules into centro-symmetric dimers connected along the a-axis (Figure 4).

Finally, the hydrazones (**6a**–**k**) were prepared for only the acetohydrazide (**5d**) by treating an ethanolic solution of the latter with different substituted aromatic aldehydes using a catalytic amount of sulfuric acid. In a typical case of **6a**, disappearance of NH_2 stretching of hydrazides and appearance of stretching around (Scheme 2) 1608–1602 cm^{-1} for C=N in FTIR indicated the formation of azomethine linkage. Appearance of the azomethine protons in the range of 8.90–8.20 ppm in ^{1}H NMR and the signal around 158–156 ppm for C=N in ^{13}C NMR spectra further confirmed the formation of the final compounds.

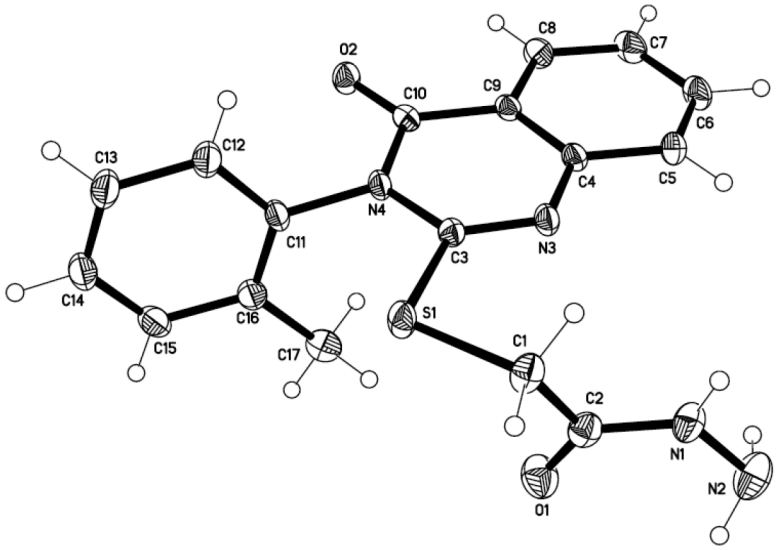


Figure 3. Molecular structure of **5a** with displacement ellipsoids plotted at 50% probability level.

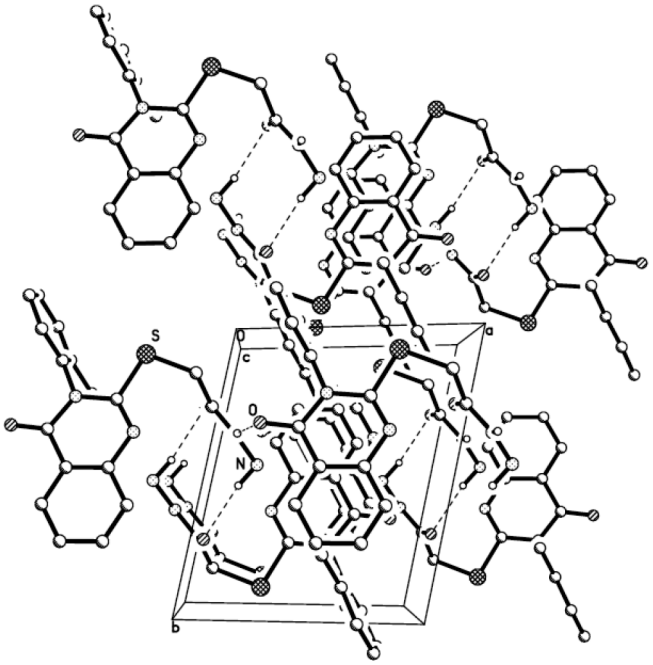
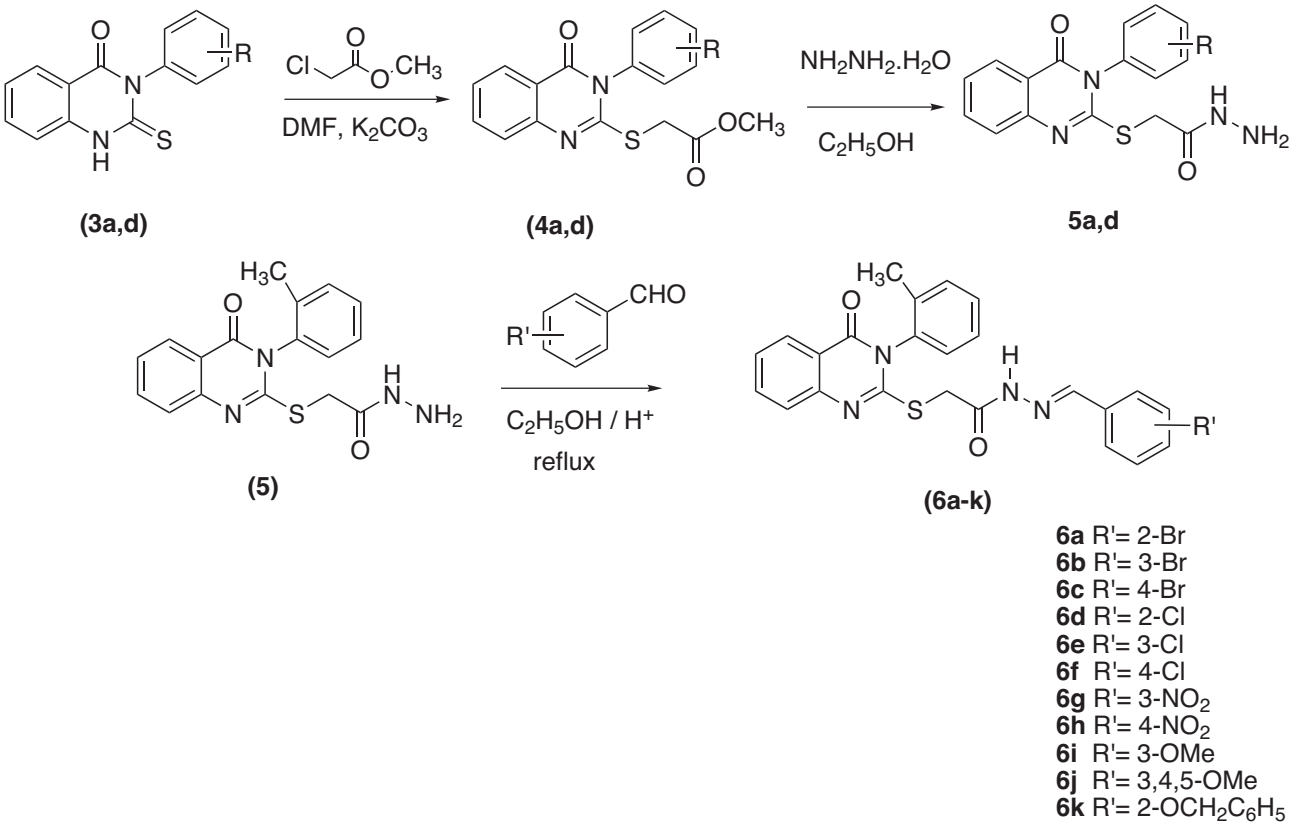


Figure 4. Crystal packing pattern of **5a** with hydrogen bonds as dotted lines. H-atoms not involved are omitted.

Figure 5 shows the molecular structure of the (E)-N'-(3,4,5-trimethoxybenzylidene)-2-(3-o-tolyl-4-oxo-3,4-dihydroquinazo lin-2-yl thio)acetohydrazide (**6j**), while the crystal packing is shown in Figure 6.

In **6j**, the dihedral angle between the 2 aromatic ring planes is 71.94(6)° and the N4–C13–S1–C1 torsion angle is 169.5(1)°. Intermolecular hydrogen bond interactions N1–H...O100(x – 1, y, z) with H...O 1.97 Å, O100–H100...O200(–x + 3, –y, –z) with 1.86 Å, O200–H210...O1 with 1.98 Å, and O200–H202...O3(x, –y – 0.5, z + 0.5) with 2.11 Å link the water and the ethanol solvent moieties to the main molecule (Figure 6).



Scheme 2. Synthesis of (*E*)-N'-(substituted benzylidene)-2-(3-o-tolyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazides.

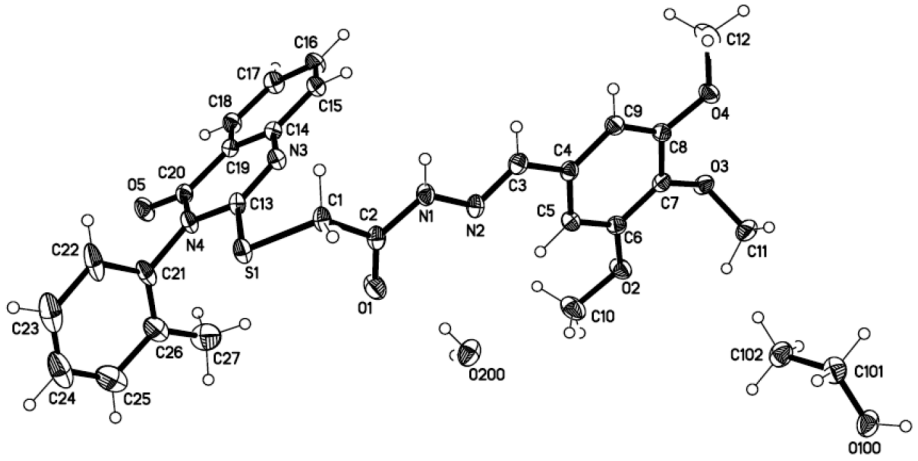


Figure 5. Molecular structure of **6j** with displacement ellipsoids plotted at 50% probability level.

3. Experimental

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined at 300 MHz using a Bruker AM-300 spectrophotometer. FTIR spectra were recorded on a Bio-Rad-Excalibur Series Mode FTS 3000 MX spectrophotometer.

Mass spectra (EI, 70 eV) were obtained on a GC-MS (Agilent Technologies 6890N) and an inert mass selective detector (5973 mass spectrometer, Agilent Technologies) and elemental analyses were conducted using a LECO-183 CHNS analyzer. Thin layer chromatography (TLC) was conducted on 0.25-mm silica gel plates (60 F254, Merck). Visualization of chromatograms was done with UV at 365 and 254 nm.

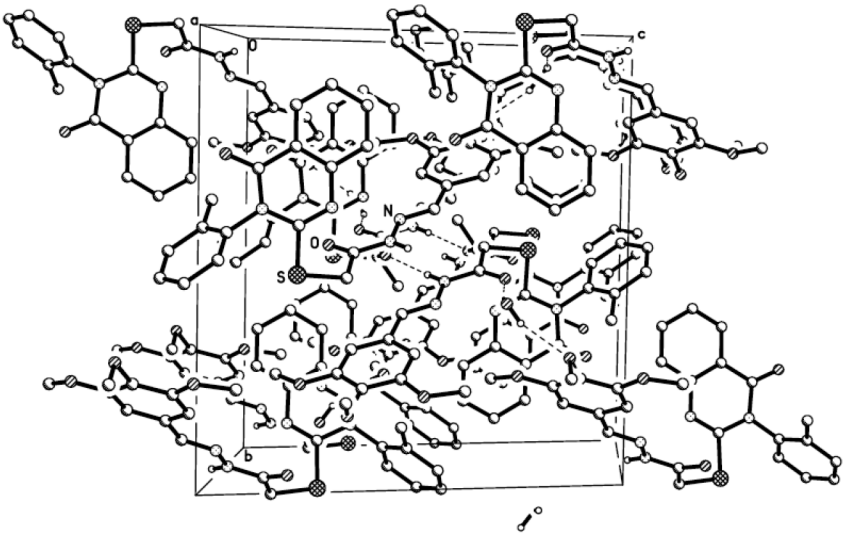


Figure 6. Crystal packing pattern of **6j** with hydrogen bonds as dotted lines. H-atoms not involved are omitted.

General procedure for the synthesis of 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*) ones (3a–e)

To a solution of substituted aniline (**1**) (0.02 mol) in DMSO (10 mL) was added carbon disulfide (1.6 mL, 0.026 mol) followed by an aqueous solution of sodium hydroxide (1.2 mL, 20 M) dropwise with stirring. After 2 h dimethyl sulfate (0.02 mol) was added gradually and the reaction mixture was stirred in a freezing mixture for 5 h. After completion, the reaction mixture was poured into ice water. The solid obtained was filtered, washed, and recrystallized from ethanol to give methyl substituted phenylcarbamodithioate (**2**). To the solution of **2** (0.01 mol) in ethanol (20 mL) methyl anthranilate (0.01 mol) and anhydrous potassium carbonate (100 mg) were added and the reaction mixture was refluxed for 25 h. The reaction mixture was added to ice cold water and a solid product was obtained. The solid obtained was filtered off and purified by dissolving in 10% alcoholic sodium hydroxide solution followed by further refluxing. After cooling at room temperature it was re-precipitated by treating with dilute hydrochloric acid. The solid was obtained, washed with water, and recrystallized from ethanol to give 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones (**3a**–**e**).

3-*o*-Tolyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3a):

(80%): mp 245 °C; $R_{f.}$ 0.20 (Petroleum ether:ethyl acetate 4:1); IR (Pure) υ: 3185–3189 (N–H), 1702–1706 (C=O), 1583–1586 (Ar–C=C), 1220–1225 (C=S), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.81 (s, 1H, NH), 8.09 (d, 1H, Ar–H, J =8.1 Hz), 7.90 (m, 1H, Ar–H), 7.74–7.05 (m, 6H, Ar–H), 2.07 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 176.3 (C=S), 159.4 (C=O), 139.9 (Ar), 138.7 (Ar), 136.0 (Ar), 135.7 (Ar), 132.4 (Ar), 130.4 (Ar), 128.8 (Ar), 128.4 (Ar), 127.8 (Ar), 126.6 (Ar), 116.1 (Ar), 115.3 (Ar), 16.6 (C–H); Anal. Calcd. For $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; O, 5.96; S, 11.95; Found: C, 67.10; H, 4.48; N, 10.40; S, 11.90; GC-MS m/z: 268.07 ($M^{\cdot}+$, 100).

3-*p*-Tolyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3b):

(75%): mp 230 °C; R_f: 0.19 (Petroleum ether:ethyl acetate 4:1); IR (Pure) υ: 3185–3189 (N–H), 1705–1710 (C=O), 1586–1590 (Ar–C=C), 1223–1237 (C=S), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 12.10 (s, 1H, NH), 8.10 (d, 1H, Ar–H, J =8.2 Hz), 7.80 (m, 1H, Ar–H), 7.76–6.99 (m, 6H, Ar–H), 2.07 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 175.3 (C=S), 159.4 (C=O), 139.8 (Ar), 138.7 (Ar), 136.0 (Ar), 135.7 (Ar), 132.4 (Ar), 130.4 (Ar), 128.8 (Ar), 128.8 (Ar), 127.8 (Ar), 127.8 (Ar), 116.1 (Ar), 115.3 (Ar), 16.6 (C–H); Anal. Calcd. For $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95; Found: C, 67.11; H, 4.49; N, 10.41; S, 11.91; GC-MS m/z: 268.07 (M·+, 100).

3-(2-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3c):

(79%): mp 250 °C; R_f: 0.17 (Petroleum ether:ethyl acetate 4:1); IR (Pure) υ: 3186–3191 (N–H), 1703–1707 (C=O), 1584–1589 (Ar–C=C), 122–1225 (C=S), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.80 (s, 1H, NH), 7.99 (d, 1H, Ar–H, J =8.1 Hz), 7.80 (m, 1H, Ar–H), 7.75–7.10 (m, 6H, Ar–H), 3.7 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 178.3 (C=S), 160.4 (C=O), 159.0 (Ar), 139.8 (Ar), 138.7 (Ar), 136.1 (Ar), 135.7 (Ar), 132.4 (Ar), 130.4 (Ar), 128.8 (Ar), 127.2 (Ar), 126.3 (Ar), 125.2 (Ar), 116.1 (Ar), 115.3 (Ar), 55.7 (C–O); Anal. Calcd. For $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28; Found: C, 63.33; H, 4.22; N, 9.86; S, 11.24; GC-MS m/z: 284.06 (M·+, 100).

3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3d):

(80%): mp 280 °C; R_f: 0.15 (Petroleum ether:ethyl acetate 4:1); IR (Pure) υ: 3187–3191 (N–H), 1704–1708 (C=O), 1585–1590 (Ar–C=C), 1224–1227 (C=S), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 13.02 (s, 1H, NH), 7.95 (d, 1H, Ar–H, J =8.3 Hz), 7.75 (m, 1H, Ar–H), 7.54–7.00 (m, 6H, Ar–H), 3.8 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 176.8 (C=S), 160.4 (C=O), 159.1 (C–O, Ar), 139.9 (Ar), 136.0 (Ar), 132.4 (Ar), 130.4 (Ar), 127 (Ar), 124.7 (Ar), 116.6 (Ar), 116.1 (Ar), 114.5 (Ar), 55.7 (O–C); Anal. Calcd. For $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; O, 11.25; S, 11.28; Found: C, 63.31; H, 4.21; N, 9.83; S, 11.25; GC-MS m/z: 284.06 (M·+, 100).

3-(4-Chlorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (3e):

(75%): mp 270 °C; R_f: 0.20 (Petroleum ether:ethyl acetate,4:1); IR (Pure) υ: 3189–3193 (N–H), 1705–1710 (C=O), 1586–1590 (Ar-C=C), 1225–1230 (C=S), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.80 (s, 1H, NH), 8.10 (d, 1H, Ar–H, J =8.1 Hz), 7.80 (m, 1H, Ar–H), 7.78–6.98 (m, 6H, Ar–H); ^{13}C NMR (75 MHz) δ: 173.2 (C=S), 161.2 (C=O), 139.8 (Ar), 138.7 (Ar), 136.1 (Ar), 135.7 (Ar), 132.0 (Ar), 132.0 (Ar), 128.0 (Ar), 128.0 (Ar), 126.1 (Ar), 125.0 (Ar), 116.0 (Ar), 115.2 (Ar); Anal. Calcd. For $C_{14}H_9ClN_2OS$: C, 58.23; H, 3.14; N, 9.70; S, 11.10; Found: C, 58.20; H, 3.11; N, 9.67; S, 11.12; GC-MS m/z: 288.01 (M·+, 100).

General procedure for the synthesis of quinazolinyl esters (4a,d)

To a solution of quinazolinone (**4a**,**d**) (0.01 mol) in 15 mL of dimethylformamide were added methyl chloroacetate (0.014 mol) and 5 g of K_2CO_3. The reaction mixture was heated on an oil bath for 2 h keeping the temperature at 50 to 60 °C, poured into ice-water, and allowed to stand overnight. The precipitate was filtered and recrystallized from ethanol to get quinazolinyl esters (**4a**,**d**).

Methyl 2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetate (4a):

(87%): mp 99 °C; R_f: 0.28 (Petroleum ether:ethyl acetate, 4:1); IR (Pure) υ: 1730–1735 (C=O, ester), 1680–1685 (C=O, lactam), 1606–1610 (C=N), 1580–1583 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ:

8.11 (d, 1H, Ar–H, J =8.2 Hz), 7.85 (m, 1H, Ar–H), 7.54–7.38 (m, 6H, Ar–H), 4.05 (d, 1H, CH_2, J = 15.7 Hz), 3.97 (d, 1H, CH_2, J = 15.7 Hz), 3.67 (s, 3H, C–H), 2.09 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.3 (C=O), 160.5 (C=O), 156.8 (C–S), 147.6 (Ar), 136.8 (Ar), 135.6 (Ar), 135.1 (Ar), 131.6 (Ar), 130.9 (Ar), 129.9 (Ar), 127.8 (Ar), 127.1 (Ar), 126.7 (Ar), 126.4 (Ar), 119.7 (Ar), 52.8 (C–O), 34.3 (C–H), 17.2 (C–H); Anal. Calcd. For $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23; S, 9.42; Found: C, 63.48; H, 4.71; N, 8.25; S, 9.39; GC-MS m/z: 340.09 (M·+, 100).

Methyl 2-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetate (4d):

(85%): mp 120 °C; R_f: 0.35 (Petroleum ether:ethyl acetate, 4:1) IR (Pure) υ: 1733–1735 (C=O, ester), 1682–1685 (C=O, lactam), 1606–1610, (C=N), 1572–1577 (Ar–C=C) cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 8.25 (d, 1H, Ar–H, J =8.2 Hz), 7.73 (m, 6H, Ar–H), 7.58–7.03 (m, 6H, Ar–H), 4.01 (d, 1H, CH_2, J= 15.4 Hz), 3.94 (d, 1H, CH_2, J = 15.4 Hz), 3.8 (s, 3H, C–H), 3.70 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 168.7 (C=O), 160.5 (C=O), 159.6 (C–O), 156.5 (C–S), 147.5 (Ar), 135.2 (Ar), 134.6 (Ar), 130.2 (2Ar), 129.4 (Ar), 127.9 (Ar), 126.4 (Ar), 119.8 (Ar), 115.0 (2Ar), 55.5 (C–O), 52.8 (C–O), 34.7 (C–H); Anal. Calcd. For $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86; S, 9.00; Found: C, 60.60; H, 4.50; N, 7.83; S, 9.03; GC-MS m/z: 356.08 (M·+, 100).

General procedure for the synthesis of quinazolinyl hydrazides (5a,d)

To a solution of quinazolinyl ester (**4a**,**d**) (0.01 mol) in 50 mL of absolute ethanol was added hydrazine hydrate (0.02 mol). The reaction mixture was refluxed in an oil bath for 4 h and allowed to stand overnight. The solid obtained was filtered, washed, and recrystallized from ethanol to afford quinazolinyl hydrazides (**5a**,**d**).

2-(3-*o*-Tolyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (5a):

(87%): mp 130 °C; R_f: 0.57 (Chloroform:methanol 9:1); IR (Pure) υ: 3402–3406 (NH_2), 3230–3235 (NH), 1660–1664 (C=O), 1608–1612 (C=N), 1575–1580 (Ar–C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.40 (s, 1H, NH), 8.35 (s, 2H, NH_2), 8.30 (d, 1H, Ar–H, J =8.2 Hz), 7.81 (m, 1H, Ar–H), 7.66–7.23 (m, 6H, Ar–H), 3.85 (d, 1H, CH_2, J = 15.5 Hz), 3.73 (d, 1H, CH_2, J = 15.5 Hz), 2.17 (s, 3H, CH_3); ^{13}C NMR (75 MHz) δ: 169.5 (C=O), 160.7 (C=O), 157.3 (C–S), 147.2 (Ar), 136.7 (Ar), 135.1 (Ar), 134.2 (Ar), 131.6 (Ar), 130.8 (Ar), 129.1 (Ar), 127.6 (Ar), 127.6 (Ar), 126.6 (Ar), 125.8 (Ar), 119.7 (Ar), 33.5 (CH_2), 17.5 (CH_3); Anal. Calcd. For $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46; S, 9.42; Found: C, 59.94; H, 4.70; N, 16.41; S, 9.44; GC-MS m/z: 340.10 (M·$^+$, 100).

2-(3-(4-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (5d):

(90%): mp 160 °C; R_f: 0.50 (Chloroform:methanol 9:1); IR (Pure) υ: 3420–3423 (N–H_2), 3239–3243 (N–H), 1662–1665 (C=O), 1608–1612 (C=N), 1585–1590 (Ar–C=C), cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.82 (s, 1H, NH), 9.35 (s, 2H, NH), 8.15 (d, 1H, Ar–H, J =8.1 Hz), 7.83 (m, 1H, Ar–H), 7.55–7.9 (m, 6H, Ar–H), 4.05 (d, 1H, CH_2, J= 15.5 Hz), 3.85 (d, 1H, CH_2, J = 15.5 Hz), 3.75 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 168.7 (C=O), 160.5 (C=O), 159.6 (C=O), 156.5 (C=S), 147.5 (Ar), 135.2 (Ar), 134.6 (Ar), 130.2 (2Ar), 129.4 (Ar), 127.9 (Ar), 126.4 (Ar), 119.8 (Ar), 115.0 (2Ar), 55.5 (C–O), 34.8 (C–H); Anal. Calcd. For $C_{17}H_{16}N_4O_3S$: C, 57.29; H, 4.52; N, 15.72; S, 9.00; Found: C, 57.24; H, 4.49; N, 15.75; S, 9.03; GC-MS m/z: 356.09 (M·$^+$, 100).

General procedure for the synthesis of (E)-N'-(substituted benzylidene)-2-(3-o-tolyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazides (6a–k)

The quinazolinyl hydrazide (**5a**) (1.0 mmol) was added to a solution of suitably substituted benzaldehyde (1.0 mmol) in absolute ethanol (10 mL). The reaction mixture was refluxed for 3–6 h and completion was monitored by TLC. The reaction mixture was concentrated and the resulting solid product was separated and recrystallized from ethanol to afford compounds **7a**–**k**.

(E)-N'-(2-Bromobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6a):

(58%): mp 205 °C; R_f: 0.35 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3187–3191 (N–H), 1678–1682 (C=O), 1601–1604 (C=N), 1574–1579 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.4 (s, 1H, NH), 8.2 (s, 1H, CH=N), 8.30 (d, 1H, Ar–H, J =8.1 Hz), 7.8 (m, 1H, Ar–H), 7.63–6.98 (m, 10H, Ar–H), 4.56 (d, 1H, CH_2, J= 15.9 Hz), 4.38 (d, 1H, CH_2, J = 15.9 Hz), 2.1 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.0 (C=O), 165 (C=O), 160 (C–S), 157 (C=N), 147 (Ar), 136.7 (Ar), 135.8 (Ar), 135.6 (Ar), 135.4 (Ar), 132.2 (Ar), 131.5 (Ar), 130.7 (Ar), 130.3 (Ar), 129.9 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.1 (Ar), 126.3 (Ar), 125.3 (Ar), 121.2 (Ar), 119.6 (Ar), 34.9 (C–H), 17.2 (C–H); Anal. Calcd. For $C_{24}H_{19}BrN_4O_2S$: C, 56.81; H, 3.77; N, 11.04; S, 6.32; Found: C, 56.78; H, 3.73; N, 11.0, S, 6.29; GC-MS m/z: 506.04 ($M^{\cdot+}$, 100).

(E)-N'-(3-Bromobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6b):

(66%): mp 203 °C; R_f: 0.37 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3186–3190 (N–H), 1676–1680 (C=O), 1604–1610 (C=N), 1575–1580 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.2 (s, 1H, NH), 8.3 (s, 1H, CH=N), 8.25 (d, 1H, Ar–H, J =8.1 Hz), 7.85 (m, 1H, Ar–H), 7.70–6.99 (m, 10H, Ar–H), 4.58 (d, 1H, CH_2, J = 15.8 Hz), 4.42 (d, 1H, CH_2, J = 15.8 Hz), 2.0 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.2 (C=O), 166.3 (C=O), 160.4 (C–S), 157.1 (C=N, Ar), 147.2 (Ar), 136.4 (Ar), 135.8 (Ar), 135.7 (Ar), 135.5 (Ar), 132.2 (Ar), 131.3 (Ar), 130.2 (Ar), 130.2 (Ar), 129.0 (Ar), 128.2 (Ar), 127.1 (Ar), 127.1 (Ar), 127.2 (Ar), 126.1 (Ar), 126.5 (Ar), 122.1 (Ar), 119.0 (Ar), 35.1 (C–H), 18.0 (C–H); Anal. Calcd. For $C_{24}H_{19}BrN_4O_2S$: C, 56.81; H, 3.77; N, 11.04; S, 6.32; Found: C, 56.79; H, 3.74; N, 11.02; S, 6.30; GC-MS m/z: 506.04 ($M^{\cdot+}$, 100).

(E)-N'-(4-Bromobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6c):

(60%): mp 170 °C; R_f: 0.48 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3187–3192 (N–H), 1674–1680 (C=O), 1606–1611 (C=N), 1545–1550 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.4 (s, 1H, NH), 8.4 (s, 1H, CH=N), 8.25 (d, 1H, Ar–H, J =8.1 Hz), 7.77 (m, 1H, Ar–H), 7.70–7.00 (m, 10H, Ar–H), 4.59 (d, 1H, CH_2, J= 15.8 Hz), 4.64 (d, 1H, CH_2, J = 15.8 Hz), 2.1 (s, 3H, C-H); ^{13}C NMR (75 MHz) δ: 169.5 (C=O), 166.2 (C=O), 159.2 (C–S), 158.1 (C=N), 147.2 (Ar), 136.8 (Ar), 135.8 (Ar), 135.7 (Ar), 135.5 (Ar), 132.2 (Ar), 131 (Ar), 131 (Ar), 130.1 (Ar), 129.2 (Ar), 128.2 (Ar), 128.2 (Ar), 127 (Ar), 127 (Ar), 126 (Ar), 125.2 (Ar), 125.1 (Ar), 119.1 (Ar), 34.7 (C–H), 17.1 (C–H); Anal. Calcd. For $C_{24}H_{19}BrN_4O_2S$: C, 56.81; H, 3.77; N, 11.04; S, 6.32; Found: C, 56.82; H, 3.75; N, 11.05; S, 6.33; GC-MS m/z: 506.04 ($M^{\cdot+}$, 100).

(E)-N'-(2-Chlorobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6d):

(50%): mp 190 °C; R_f: 0.48 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3189–3192 (N–H), 1678–1682 (C=O), 1602–1610 (C=N), 1574–1580 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.2 (s, 1H,

NH), 8.32 (s, 1H, CH=N), 8.19 (d, 1H, Ar–H, J =8.1 Hz), 7.80 (m, 1H, Ar–H), 7.69–7.02 (m, 10H, Ar–H), 4.84 (d, 1H, CH_2, J = 15.9 Hz), 4.60 (d, 1H, CH_2, J= 15.9 Hz), 2.25 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 168.5 (C=O), 165.6 (C=O), 158.2 (C–S), 157 (C=N), 147 (Ar), 136.8 (Ar), 135.8 (Ar), 135.6 (Ar), 134.2 (Ar), 133.1 (Ar), 132.2 (Ar), 131 (Ar), 130.1 (Ar), 130 (Ar), 129.2 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 127.3 (Ar), 126.5 (Ar), 125.2 (Ar), 120 (Ar), 34.8 (C–H), 18.7 (C–H); Anal. Calcd. For $C_{24}H_{19}ClN_4O_2S$: C, 62.27; H, 4.14; N, 12.10; S, 6.93; Found: C, 62.29; H, 4.1; N, 12.06; O, 6.88; S, 6.90; GC-MS m/z: 462.09 ($M^{\cdot+}$, 100).

(E)-N'-(3-Chlorobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6e):

(60%): mp 187 °C; R_f: 0.21 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3182–3185 (N-H), 1677–1680 (C=O), 1604–1610 (C=N), 1551–1555 (Ar-C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.42 (s, 1H, NH), 8.45 (s, 1H, CH=N), 8.21 (d, 1H, Ar–H, J =8.1 Hz), 7.74 (m, 1H, Ar–H), 7.73–6.95 (m, 10H, Ar–H), 4.86 (d, 1H, CH_2, J= 15.8 Hz), 4.54 (d, 1H, CH_2, J = 15.8 Hz), 2.1 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.2 (C=O), 166.5 (C=O), 159.5 (C–S), 157 (C=N), 147 (Ar), 136.5 (Ar), 135.6 (Ar), 135.4 (Ar), 135.2 (Ar), 134.5 (Ar), 131.8 (Ar), 131.6 (Ar), 130.7 (Ar), 130.5 (Ar), 129.8 (Ar), 127.9 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 126.5 (Ar), 125.2 (Ar), 119 (Ar), 35.1 (C–H), 19.2 (C–H); Anal. Calcd. For $C_{24}H_{19}ClN_4O_2S$: C, 62.27; H, 4.14; N, 12.10; S, 6.93; Found: C, 62.25; H, 4.10; N, 12.07; S, 6.95; GC-MS m/z: 462.09 ($M^{\cdot+}$, 100).

(E)-N'-(4-Chlorobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6f):

(50%): mp 173 °C; R_f: 0.38 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3187–3191 (N–H), 1674–1680 (C=O), 1606–1610 (C=N), 1545–1551 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.3 (s, 1H, NH), 8.5 (s, 1H, CH=N), 8.11 (d, 1H, Ar–H, J =8.1 Hz), 7.79 (m, 1H, Ar–H), 7.70–6.99 (m, 10H, Ar–H), 4.59 (d, 1H, CH_2, J= 15.8 Hz), 4.41 (d, 1H, CH_2, J = 15.8 Hz), 2.09 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 170.1 (C=O), 165.9 (C=O), 158.3 (C–S), 157.2 (C=N), 146.9 (Ar), 136.5 (Ar), 135.8 (Ar), 135.7 (Ar), 135.6 (Ar), 132.5 (Ar), 131.6 (Ar), 130.5 (Ar), 130.5 (Ar), 130.2 (Ar), 129.5 (Ar), 128.2 (Ar), 128.2 (Ar), 127.2 (Ar), 127 (Ar), 126.1 (Ar), 125.2 (Ar), 120 (Ar), 34.5 (C–H), 20.1 (C–H); Anal. Calcd. For $C_{24}H_{19}ClN_4O_2S$: C, 62.27; H, 4.14; Cl, 7.66; N, 12.10; S, 6.93; Found: C, 62.26; H, 4.11; Cl, 7.64; N, 12.08; S, 6.94; GC-MS m/z: 462.09 ($M^{\cdot+}$, 100).

(E)-N'-(3-Nitrobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6g):

(66%): mp 211 °C; R_f: 0.31 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3188–3192 (N–H), 1673–1675 (C=O), 1605–1610 (C=N), 1550–1560 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.5 (s, 1H, NH), 8.6 (s, 1H, CH=N), 8.30–7.40 (m, 12H, Ar–H), 4.61 (d, 1H, CH_2, J = 15.9 Hz), 4.43 (d, 1H, CH_2, J = 15.9 Hz), 2.10 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169 (C=O), 166.3 (C=O), 158.5 (C–S), 157 (C=N), 148.3 (Ar), 147.0 (Ar), 136.6 (Ar), 135.9 (Ar), 135.8 (Ar), 135.5 (Ar), 132.8 (Ar), 131.7 (Ar), 130.7 (Ar), 130.6 (Ar), 130.7 (Ar), 129.9 (Ar), 128.8 (Ar), 128.7 (Ar), 127.6 (Ar), 127.2 (Ar), 126.2 (Ar), 120 (Ar), 34.1 (C–H), 20.1 (C–H); Anal. Calcd. For $C_{24}H_{19}N_5O_4S$: C, 60.88; H, 4.04; N, 14.79; S, 6.77; Found: C, 60.85; H, 4.01; N, 14.74; S, 6.74; GC-MS m/z: 473.12 ($M^{\cdot+}$, 100).

(E)-N'-(4-Nitrobenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6h):

(65%): mp 245 °C; R_f: 0.35 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3192–3195 (N–H), 1677–1680 (C=O), 1606–1610 (C=N), 1575–1580 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.95 (s, 1H, NH), 8.50 (s, 1H, CH=N), 8.32–7.38 (m, 12H, Ar–H), 4.59 (d, 1H, CH_2, J = 15.8 Hz), 4.48 (d, 1H, CH_2, J = 15.8 Hz), 2.12 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 170 (C=O), 167.2 (C=O), 158 (C–S), 156.9 (C=N), 149 (Ar), 147.2 (Ar), 136.8 (Ar), 135.9 (Ar), 135.7 (Ar), 135.6 (Ar), 132.8 (Ar), 131.8 (Ar), 130.7 (Ar), 130.6 (Ar), 130.7 (Ar), 129.9 (Ar), 128.8 (Ar), 128.8 (Ar), 127.6 (Ar), 127.6 (Ar), 126.1 (Ar), 119.7 (Ar), 34.3 (C–H), 20.2 (C–H); Anal. Calcd. For $C_{24}H_{19}N_5O_4S$: C, 60.88; H, 4.04; N, 14.79; S, 6.77; Found: C, 60.84; H, 4.02; N, 14.75; S, 6.75; GC-MS m/z: 473.12 ($M^{\cdot+}$, 100).

(E)-N'-(2-Methoxybenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-yl thio)acetohydrazide (6i):

(73%): mp 193 °C; R_f: 0.35 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3185–3190 (N–H), 1675–1681 (C=O), 1602–1608 (C=N), 1565–1570 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.83 (s, 1H, NH), 8.20 (s, 1H, CH=N), 8.11 (d, 1H, Ar–H, J =8.1 Hz), 7.80 (m, 1H, Ar–H), 7.70–6.98 (m, 10H, Ar–H), 4.59 (d, 1H, CH_2, J = 15.9 Hz), 4.41 (d, 1H, CH_2, J = 15.9 Hz), 3.77 (s, 3H, C–H), 2.09 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.2 (C=O), 164 (C=O), 160.6 (C–S), 159.9 (C–O), 157.4 (C=N), 147.7 (Ar), 136.9 (Ar), 135.9 (Ar), 135.5 (Ar), 135.3 (Ar), 131.6 (Ar), 130.8 (Ar), 130.4 (Ar), 129.9 (Ar), 127.8 (Ar), 127.1 (Ar), 126.5 (Ar), 120.4 (Ar), 119.9 (Ar), 119.7 (Ar), 116.7 (Ar), 111.9 (Ar), 55.5 (C–O), 35.4 (C–H), 17.3 (C–H); Anal. Calcd. For $C_{25}H_{22}N_4O_3S$: C, 65.48; H, 4.84; N, 12.22; S, 6.99; Found: C, 65.44; H, 4.81; N, 12.24; S, 6.95; GC-MS m/z: 458.14 ($M^{\cdot+}$, 100).

(E)-N'-(3,4,5-Trimethoxybenzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazo lin-2-yl thio) acetohydrazide (6j):

(60%): mp 166 °C; R_f: 0.24 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3187–3190 (N–H), 1675–1680 (C=O), 1602–1610 (C=N), 1575–1580 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.01 (s, 1H, NH), 8.90 (s, 1H, CH=N), 8.21 (d, 1H, Ar–H, J =8.1 Hz), 7.90 (m, 1H, Ar–H), 7.80–6.98 (m, 8H, Ar–H), 4.58 (d, 1H, CH_2, J = 15.7 Hz), 4.40 (d, 1H, CH_2, J = 15.7 Hz), 4.41 (s, 9H, C–H), 2.19 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.7 (C=O), 165.1 (C=O), 161.2 (C–S), 156.5 (C=N), 153.5 (Ar), 153.4 (Ar), 148.6 (Ar), 147.7 (Ar), 136.8 (Ar), 135.9 (Ar), 135.5 (Ar), 134.3 (Ar), 131.5 (Ar), 130.8 (Ar), 130.4 (Ar), 129.9 (Ar), 127.8 (Ar), 127.2 (Ar), 126.5 (Ar), 119.9 (Ar), 104.9 (Ar), 104.4 (Ar), 60.9 (C–O), 55.6 (C–O), 34.5 (C–H), 17.5 (C–H); Anal. Calcd. For $C_{27}H_{26}N_4O_5S$: C, 62.53; H, 5.05; N, 10.80; S, 6.18; Found: C, 62.50; H, 5.01; N, 10.76; S, 6.14; GC-MS m/z: 518.16 ($M^{\cdot+}$, 100).

(E)-N'-(2-(Benzyloxy)benzylidene)-2-(3-*o*-tolyl-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (6k):

(60%): mp 186 °C; R_f: 0.33 (Petroleum ether:ethyl acetate 1:1); IR (Pure) υ: 3187–3192 (N–H), 1665–1670 (C=O), 1607–1610 (C=N), 1573–1575 (Ar–C=C), cm^{-1}; ^{1}H NMR (DMSO, 300 MHz) δ: 11.12 (s, 1H, NH), 8.50 (s, 1H, CH=N), 8.19 (d, 1H, Ar–H, J =8.1 Hz), 7.80 (m, 1H, Ar–H), 7.70–6.98 (m, 15H, Ar–H), 5.16 (s, 2H, CH_2), 4.56 (d, 1H, CH_2, J = 15.8 Hz), 4.43 (d, 1H, CH_2, J = 15.8 Hz), 2.09 (s, 3H, C–H); ^{13}C NMR (75 MHz) δ: 169.2 (C=O), 164.1 (C=O), 160.6 (C–S), 159.9 (C–O), 157.2 (C=N), 147.7 (Ar), 136.8 (Ar), 135.9 (Ar), 135.5 (Ar), 135.3 (Ar), 131.5 (Ar), 130.8 (Ar), 130.4 (Ar), 129.9 (Ar),128.5 (Ar), 128.5 (Ar), 128.3 (Ar),

127.9 (Ar), 127.8 (Ar), 127.6 (Ar), 127.1 (Ar), 127 (Ar), 126.5 (Ar), 120.5 (Ar), 119.9 (Ar), 119.7 (Ar), 116.7 (Ar), 111.9 (Ar), 70.6 (C–O), 35.5 (C–H), 17.3 (C-H); Anal. Calcd. For $C_{31}H_{26}N_4O_3S$: C, 69.64; H, 4.90; N, 10.48; S, 6.00; Found: C, 69.62; H, 4.92; N, 10.45; S, 6.02; GC-MS m/z: 534.17 ($M^{\cdot+}$, 100).

X-ray data collection and structure refinement for 3a, 5, and 6j

Data were collected at 120(2) K on a Bruker AXS SMART APEX CCD diffractometer using MoKα radiation. Structures were solved by direct methods,[29] full-matrix least-squares refinement[29] on F^2. 346/6176 parameters/unique intensities for **3a**, 226/3881 for **5** and 384/6986 for **6j**, respectively. All atoms but H atoms were refined anisotropically; all H atoms were derived from difference Fourier maps and refined on idealized positions with $U_{iso} = 1.2\ U_{eq}$(C/N) or $1.5U_{eq}$(C methyl) and C–H distances of 0.95–0.98 Å, O(water)–H for **6j** with 0.84(1) Å; H(N2)-positions for **5** were refined freely. H(C_{methyl}) were allowed to rotate but not to tip. For **3a** there are 2 crystallographically independent molecules, A and B, per asymmetric unit with numbering schemes 1xx for A and 2xx for B, resp. **6j** contains 1 EtOH and 1 H_2O solvent molecule per asymmetric unit. Experimental data are listed in the Table, while Figures 1, 3, and 5 show the molecular structures.

Table. Crystal data and structure refinement for compounds **3a**, **5**, and **6j**.[a]

Compound	**3a**	**5a**	**6j**
Formula weight	268.3	340.4	582.7
Crystal system	monoclinic	triclinic	monoclinic
Space group	P 2_1/c	P -1	P 2_1/c
a/Å	18.956(11)	8.556(2)	11.7195(12)
b/Å	13.269(8)	9.848(3)	16.4891(16)
c/Å	10.385(6)	10.590(3)	15.8773(15)
α/°		94.591(5)	
β/°	97.006(10)	109.259(5)	107.597(2)
λ/°		99.802(5)	
V/Å^3	2593(3)	821.1(4)	2924.6(5)
Z	8	2	4
Dc/Mgm^{-3}	1.375	1.377	1.323
Absorp. coeff./mm^{-1}	0.242	0.215	0.163
F(000)	1120	356	1232
Crystal size/mm^3	0.28 × 0.05 × 0.04	0.43 × 0.35 × 0.22	0.49 × 0.42 × 0.30
Data collection			
H	–24/24	–11/10	–15/15
K	–17/17	–12/12	–21/20
L	–12/13	–13/13	–20/20
Data collected	23,851	7680	27,413
Max./min. transm.	0.99/0.93	0.95/0.91	0.95/0.92
Parameters	346	226	384
GooF	0.922	1.021	0.998
R1[I>2sigma(I)]	0.089	0.047	0.052
wR2 (all data)	0.208	0.121	0.137
max/min ΔF/e.Å^{-3}	0.74/–0.33	0.49/–0.22	0.94/–0.33
CCDC deposition numbers	820987	915651	915652

[a] Further conditions and refinement comments: Temperature 120(2) K, Wavelength 0.71073 Å, Absorption correction: Semi-empirical from equivalents, Refinement method: Full-matrix least-squares on F^2.

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