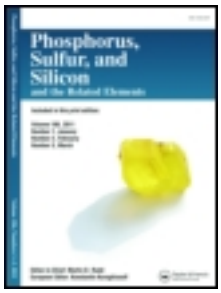

Phosphorus, Sulfur, and Silicon and the Related Elements

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NEW 3H-QUINAZOLIN-4-ONE DERIVATIVES DERIVED FROM 3-PHENYLAMINO- 2-THIOXO-3H-QUINAZOLIN-4-ONE

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME NEW 3H-QUINAZOLIN-4-ONE DERIVATIVES DERIVED FROM 3-PHENYLAMINO-2-THIOXO-3H-QUINAZOLIN-4-ONE

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*Reaction of 3-phenylamino-2-thioxo-3H-quinazolin-4-one (**1**) with methyl iodide, α-chloroethylacetate, and α-bromobenzoylacetophenone in methanol in the presence of KOH with heating resulted in alkylation on the sulfur atom to 2-alkyl thio derivatives **2–4**, respectively. Treatment of **1** with α-bromo-α-cyanoethylacetate afforded 3-hydroxy-10-oxo-4-phenyl-4H,10H-1-thia-4,4a,9-triaza-anthrancene-2-carbonitrile (**5**). Reaction of the ester **3** with hydrazine hydrate afforded hydrazide **6**. The hydrazide **6** on reaction with benzoylacetone, dibenzoylmethane, and ethyl acetoacetate furnished the corresponding pyrazoles **7** and **8** and pyrazolone **9** respectively. Treatment of **6** with methanolic KOH and carbon disulphide afforded 1,3,4-oxadiazole-2-thione derivative **10**. Compound **1** reacted namely with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosylbromide, 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide, or with 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide to yield S-glycoside derivatives **11–13**, respectively. Oxidation of S-glucoside **11** with H_2O_2 afforded the corresponding sulphone; 2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylsulphonyl)-3-phenlyamino-3H-quinazolin-4-one (**14**). The synthesized compounds have been screened for their antimicrobial activity.*

Keywords: 3-Phenylamino-2-thioxo-3H-quinazolin-4-one; alkylation; antimicrobial activity; hydrazide; pyrazole, pyrazolone and oxadiazole derivatives; S-glycosides

A variety of substituents have been introduced into many positions of quinazolinone as means of structural modifications and potentiation

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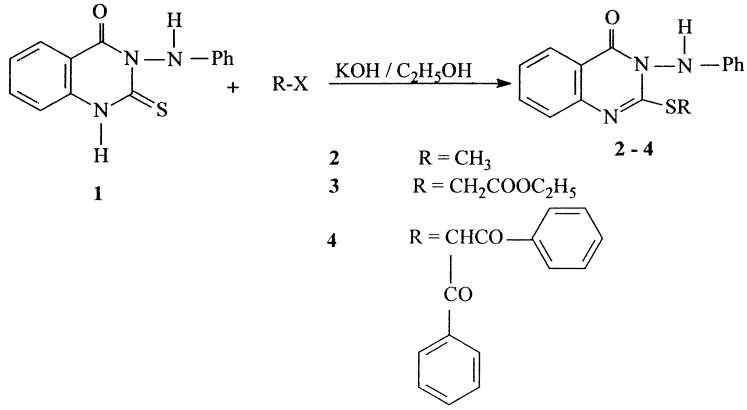
of biological activities. 3H-Quinazolin-4-ones are considered to be very interesting heterocyclic ring systems because of their therapeutic importance. For example, derivatives of 3H-quinazolin-4-one have been found to exhibit interesting biological activities.[1] These include antimicorbial,[2,3] antimalarial,[4] anticonvulsive,[5] antifungal,[6,7] and antiviral[8] activities. Additionally, several of S-substituted thioheterocyclices also exhibit various biological activities.[9–11] Thioamide group is an interesting for heterocyclic chemists because it can used as a useful synthetic building block and its regioselectivity toward different electrophiles has great importance. Data in the literature show that in most cases of nucleophilic substitution of an alkyl halide on a thioamide system the sulfur atom attack is favored.[12–16] In this article we report a study on the regioselectivity of the reaction of several of electrophilic reagents (alkyl and per-O-acetylglycopyranosyl bromides) with thioamide moiety of model compound 3-phenylamino-2-thioxo-3H-quinazolin-4-one (**1**).

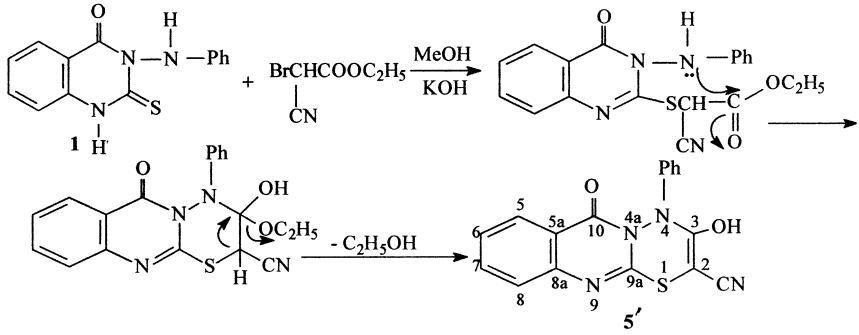
RESULTS AND DISCUSSION

Reaction of **1** with methyl iodide, α-chloroethylacetate and α-bromobenzoylacetophenone in methanol in the presence of KOH with heating resulted in alkylation on the sulfur atom to afford 2-methylthio-3-phenylamino-3H-quinazolin-4-one (**2**), (4-oxo-3-phenylamino-3,4-dihydroquinazolin-2-ylthio) acetic acid ethyl ester (**3**), and 2-(4-oxo-3-phenylamino-3,4-dihydroquinazolin-2-ylthio)-1,3-diphenyl propane-1,3 dione (**4**) (Scheme 1). The structure of the S-substituted derivatives **2–4** was confirmed by analytical data, IR, ^{1}H NMR, and ^{13}C NMR. The IR spectra of **2–4** revealed the absence of the absorption band at 1220 cm^{-1} (C=S) stretching vibration observed in **1**, thus conforming the S-alkylation. The IR spectrum of **3** showed absorption bands at 3427 (NH), 1735 (C=O of carboxylic ester), 1694 (C=O quinazolinone), and 1605 (C=N) cm^{-1}. The ^{1}H NMR spectrum of **3** showed signals at 9.48 (s 1H, NH), 8.07 (d), 7.86 (t), 7.57 (d), 7.27 (t) (4H, quinazolinone moiety), 6.66–7.20 (m, 4H, Ph), 4.00 (s, 2H, SCH_2), 3.67 (q, 2H OCH_2), 2.51 (t, 3H, CH_3). The mass spectrum of **3** showed molecular ion M^+ at m/z 355 and further peaks at 310 and 236 due to sequential expulsion of fragments $-OC_2H_5$ and, $-S-CH_2CO$, respectively (see Experimental for details). The ^{13}C NMR spectrum of **2** was characterized by the presence of a signal at δ 13.9 corresponding to the $S-CH_3$ and the absence of signal at δ 176.2 due to (C=S) band observed in compound **1**. The phenyl and quinazolinone signals appeared at the expected field[17] (see Experimental).



SCHEME 1

On the other hand treatment of **1** with α-bromo- α-cyano ethylacetate afforded the unexpected new heterocyclic 3-hydroxy-10-oxo-4-phenyl-4H,10H-1-thia-4,4a,9-triaza-anthracene-2-carbonitrile (**5**). Formation of compound **5** may be explained by the formation of S-alkyl derivative in the first and then internal nucleophilic attack by the NH group on the C=O takes place with loss of C_2H_5OH molecule to give the cyclized compound **5** (Scheme 2).

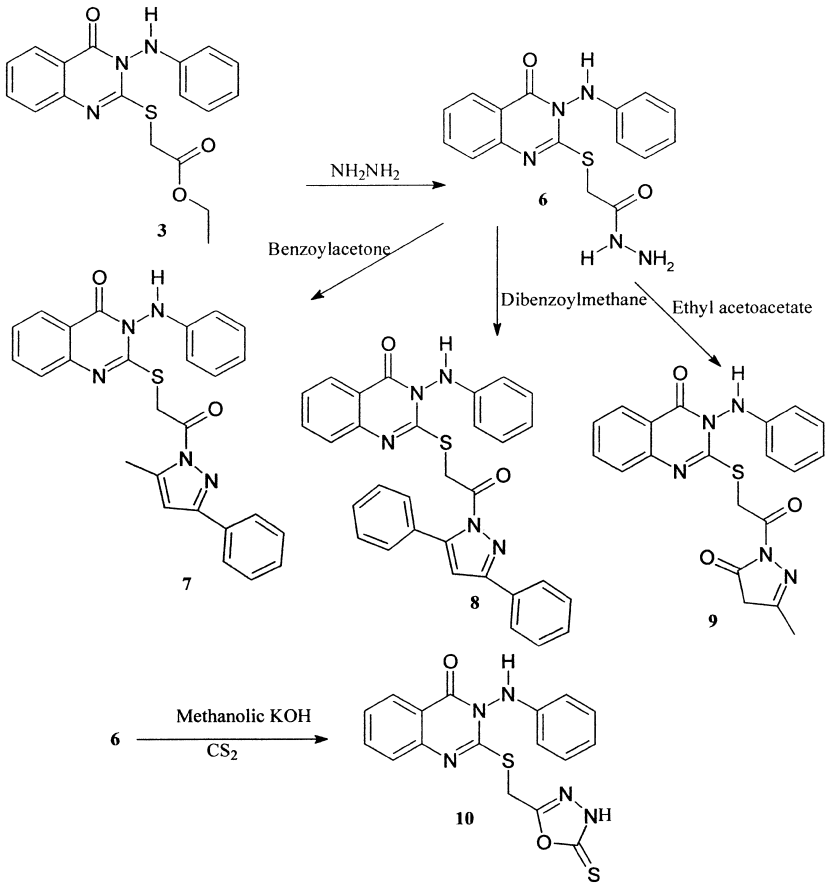


SCHEME 2

The structure of **5** was confirmed on the basis of elemental analysis and spectral data. Its mass was compatible with molecular formula $C_{17}H_{10}N_4O_2S$ (M^+: 334). The IR spectrum of **5** had no C=S band but displayed bands at 3425 (OH), 2225 (CN), 1687 (C=O quinazolinone), 1563 (C=N) cm^{-1}. The ^1H NMR spectrum of **5** showed a signal band

at δ 9.75 ppm, assigned to the OH proton. Ester and NH protons were missing as well as (see Experimental). Structure **5** was indicated by the ^{13}C NMR spectra, which gave conclusive evidence for thiadiazine structure. The spectrum reveals low-field signals at 157.3 (thiadiazine C-2), 157.2 (thiadiazine C-3) and 145.5 ppm (thiadiazine C-9a) in addition to a signal at 114.9 for cyano group (see Experimental). The ^{13}C NMR of **5** showed the absence of ester and thione signals provided strong evidence that cyclization had occurred as depicted (see Experimental).

The ester **3** reacted with hydrazine hydrate in refluxing ethanol (7 h) to yield (4-oxo-3-phenylamino-3,4-dihydro-quinazolin-2-ylthio) acetic acid hydrazide (**6**) in 85% yield (Scheme 3). The IR spectrum of **6** displayed bands at 3435 (NH), 3245, 3160 (NH/NH_2), 1687 (C=O



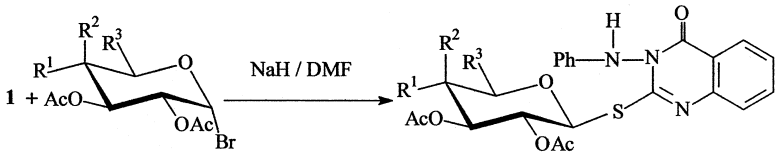
SCHEME 3

quinazolinone), 1670 (C=O amide carbonyl), and 1610 (C=N) cm^{-1}. The ^1H NMR spectrum of **6** showed three singlet signals at δ 11.20, 9.52, and 4.54 ppm related respectively to NH hydrazide, NH attached to phenyl, and NH_2 function. Also, the structure of **6** was confirmed by its mass spectrum which shows a molecular ion peak M^+ at m/z 341 (see Experimental for details).

The hydrazide **6** reacted with benzoyl acetone, dibenzoyl methane, and ethyl acetoacetate in ethanol containing a catalytic amount of concentrated HCl to give 2-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-2-oxo-ethylthio]-3-phenylamino-3H-quinazolin-4-one (**7**), 2-[2-(3,5-diphenyl-pyrazol-1-yl)-2-oxo-ethylthio]-3-phenylamino-3H-quinazolin-4-one (**8**), and 2-[2-(3-methyl-5-oxo-4,5-dihydro-pyrazol-1yl)-2-oxo-ethylthio]-3-phenylamino-3H-quinazolin-4-one (**9**) respectively (Scheme 3). The structures **7–9** were supported by elemental analysis, IR, ^1H NMR, ^{13}C NMR and mass spectroscopic data (see Experimental). The IR spectra of **7–9** showed disappearance of absorption peaks at 3245, 3160 cm^{-1} due to NH/NH_2 and 1670 cm^{-1} due to amide carbonyl function provided strong evidence that cyclization had occurred as depicted. The mass spectrum of **7** was compatibic with molecular formula $C_{26}H_{21}N_5O_2S$ (M^+ 467) and ^1H NMR contained three singlet signals at δ 9.78, 6.15 and 2.19 assigned to NH, pyrazole H-4 and CH_3 and showed a doblet-doublet signal at δ 4.65 ppm, assignable to methylene protons ($-SCH_2$). Structure **7** was indicated by ^{13}C NMR spectra which conclusive evidence for pyrazole structure. The spectrum reveals low-field signals at δ 150.2 (pyrazole C-3), 103.4 (pyrazole C-4) and 147.6 ppm (pyrazole C-5) in addition to signals at δ 162.7 and 168.4 ppm for C=O group. The aromatic, methylene and methyl also appeared at the expected field (see Experimental).

Reaction of hydrazide **6** with methanolic KOH and CS_2 under reflux condition gave 3-phenylamino-2-(5-thioxo-4,5-dihydro[1,3,4]-oxadiazole-2-ylmethylthio)-3H-quinazolin-4-one (**10**) (Scheme 3). Structure of **10** was established with basis of elemental analysis and spectral data (see Experimental). Compound **10** displayed bands in the IR spectrum at 3248 (NH), 3177 (NH—C=S), 1685 (C=O quinazolinone), and 1185 (C=S) cm^{-1} and the absence of bands at 3245, 3160 cm^{-1} due to NH/NH_2 and 1670 cm^{-1} due to amide carbonyl function stretching vibrations observed in **6**, thus confirming that heterocyclization occurred. The ^1H NMR spectrum showed two singlet signals at δ 11.72 and 9.64 ppm assignable to NH (oxadiazole) and NH group at position 3 of quinazolinone, respectively, in addition a doublet-doublet at δ 3.24 ppm corresponding to $-SCH_2$ group, where as the mass spectrum showed the molecular ion peak (M^+) at m/z 383 (see Expermental).

Compound **1** reacted namely with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide, 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide and 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide in the presence of sodium hydride in dry dimethyl formamide to yield 3-phenylamino-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-3H-quinazolin-4-one (**11**), 3-phenylamino-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosylthio)-3H-quinazolin-4-one (**12**), and 3-phenylamino-2-(2′,3′,4′-tri-O-acetyl-β-D-xylopyranosylthio)-3H-quinazolin-4-one (**13**) respectively (Scheme 4).



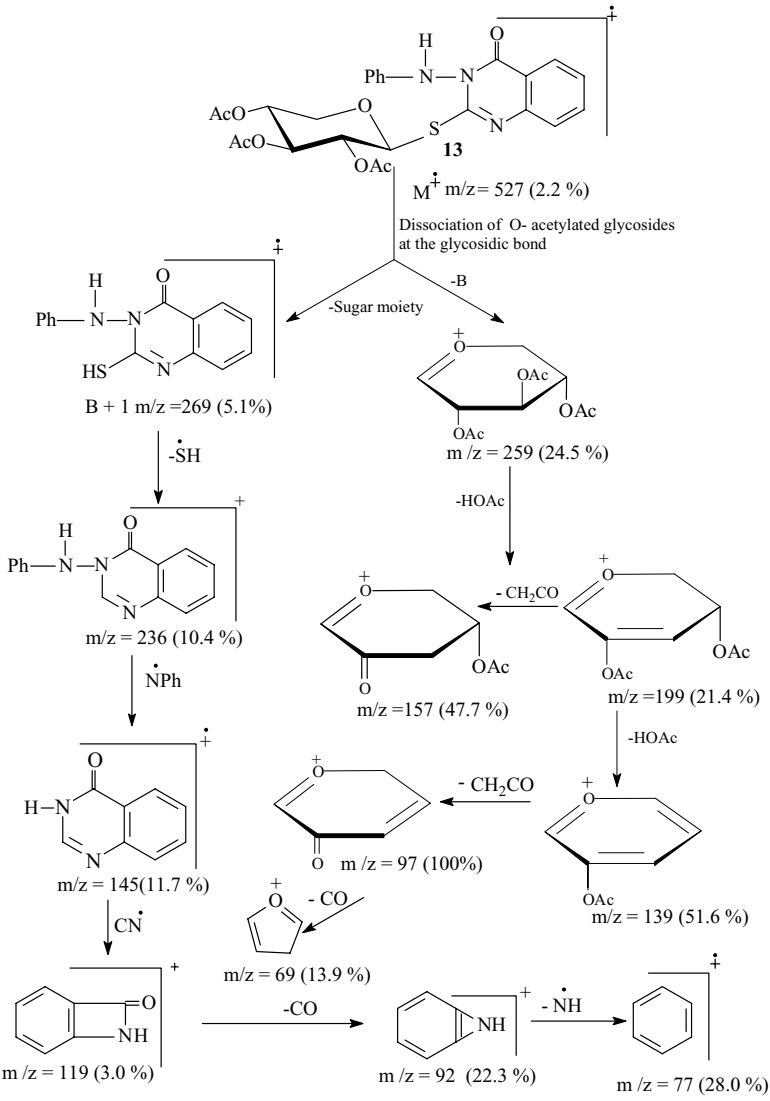
Compound No.	R^1	R^2	R^3
11	OAc	H	CH_2OAc
12	H	OAc	CH_2OAc
13	OAc	H	H

SCHEME 4

The IR spectra of **11–13** were characterized by the absence of absorption band at 3242 (NH—C=S) and absorption band at 1220 (C=S) cm^{-1} and the presence of acetoxy carbonyl stretching bands at 1747–1742 cm^{-1} that is associated with *S*-glycosylation. The ^1H NMR spectrum of **11** showed the signal for the anomeric proton (H-1′) of the carbohydrate moiety in the form of a doublet at δ 5.78 ppm in spin-spin coupling constant $J_{1',2'} = 10.6$ Hz corresponds to the diaxial orientation of H-1′ and H-2′ protons which indicates the β-configuration for **11** (see Experimental).

The structure of S-glycosides **11–13** was further confirmed by close inspection of mass spectral analysis (see Experimental). Fragmentation pathway for **13** can be represented as in Scheme 5.

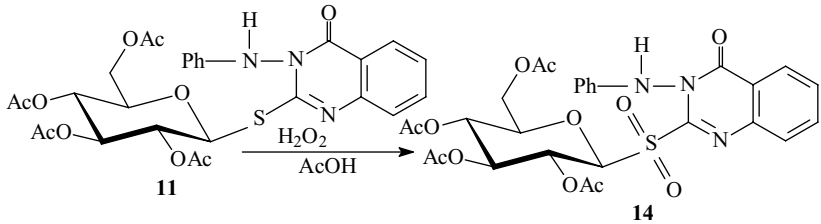
Oxidation of **11** with hydrogen peroxide in acetic acid afforded the corresponding sulphone **14** confirms that glycosylation occurred on sulfur rather than nitrogen (Scheme 6). The IR spectrum of **14** showed appearance of bands at 1185 and 1370 $cm^{-1}(SO_2)$. The ^1H NMR spectrum **14** showed signal at δ 5.93 for anomeric proton H-1′. The spin-spin coupling constant at C1′ and C2′ of the carbohydrate residue ($J_{1',2'} =$ 8.5 Hz), indicates the β configuration of **14** (see Experimental).



SCHEME 5 Proposed cleavage pathway of compound **13**.

BIOLOGICAL RESULTS

All products were in vitro evaluated for antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and for antifungal activity



SCHEME 6

against *Candida albicans*, using the cup-diffusion method.[18] Each cup (8 mm in diameter) was filled with two drops of 1% solution of the test compound in dimethylsulfoxide. The results obtained indicated compounds **1**, **5**, **7**, **8**, **9**, **10**, **13**, and **14** are the only compounds that showed antimicrobial activity. Compound **14** showed the most pronounced inhibitory effect when tested against *S. aureus*. Compound **13** came in the second rank according to its inhibitory effect to *S. aureus*. Compounds **1**, **5**, **7**, **8**, **9**, and **10** inhibited *C. albicans* while no compounds was found to be posses marked activity against *E. coli*.

EXPERIMENTAL

All melting points are uncorrected. They were performed by open capillary method using electrothermal melting MEL-TEMP II apparatus. The IR spectra were recorded with Unicam SP 1200 spectrophotometer using pellet technique KBr discs (υ in cm^{-1}). The ^1H NMR spectra were recorded with Bruker AC 250 FT spectrometer (250 MHz). The ^{13}C NMR spectra were recorded with Bruker AC-250 FT spectrometer (62.9 MHz). TMS was used as an internal standard and chemical shifts are expressed in δ ppm values. The mass spectral data were obtained with micro mass spectrometer model 7070 at energy of 70 eV and inlet temperature 90°C. Elemental analyses (C, H, N) were performed by the Microanalysis Centre, Cairo University and Central Laboratory Service of Microanalysis Tanta University, Egypt.

3-Phenylamino-2-thioxo-3H-quinazolin-4-one (1)

This compound was in 72% yield as previously described,[19] m.p. 250–252°C (lit.[19] 248–250°C); additional data, ^1H NMR ([D_6] DMSO): δ_H = 6.26–7.12 (m, 5H, Ph), 7.33 (t, 1H, J = 7.8 Hz, H-6), 7.42 (d, J = 7.8 Hz, 1H, H-8), 7.76 (t, J = 7.8 Hz, 1H, H-7), 7.97 (d, J = 7.8 Hz, 1H, H-5), 8.72 (br s, 1H, exchangeable with D_2O, NH), 10.00 (s, 1H, exchangeable with D_2O, NH). ^{13}C NMR ([D_6] DMSO): δ_C = 122.7 (2C, C-2 and C-6

of phenyl), 116.4 (C-8), 116.6 (C-4 of phenyl), 119.5 (C-5), 120.4 (C-4a), 128.4 (C-6), 128.6 (2C, C-3 and C-5 of phenyl), 136.7 (C-7), 139.1 (C-1 of phenyl), 146.2 (C8a), 158.7 (C-4), 176.2 (C=S).

2-Methylthio-3-phenylamino-3H-quinazolin-4-one (2).

To a solution of **1** (2.69 g, 10 mmol) in methanolic KOH (30 ml), methyl iodide (0.56 g, 10 mmol) was slowly added with stirring at room temperature. The reaction mixture was heated under reflux for 2 h and it was allowed to stand at room temperature for 1 h. Then it was poured into 300 ml ice/water, whereby a precipitate was formed which was filtered off, washed with water, dried, and recrystallized from methanol/water (30%) to give **2**. Yield, 1.98 g (70%); m.p., 164–165°C. IR (KBr): 3425 (NH), 2849 (Ar-H), 1687 (C=O quinazolinone), 1604, 1540, 1461 cm^{-1} (C=N, C=C). ^1H NMR ([D_6] DMSO): $\delta_H = 2.05$ (s, 3H, CH_3, J = 7.1 Hz), 6.65-7.16 (m, 5H, Ph), 7.42 (t, J = 7.8 Hz, 1H, H-6), 7.63 (d, J = 7.8 Hz, 1H, H-8), 7.81 (t, J = 7.8 Hz, 1H, H-7), 8.05 (d, J = 7.8 Hz, 1H, H-5), 9.31 (s, 1H, exchangeable with D_2O, NH). ^{13}C NMR ([D_6] DMSO): $\delta_C = 13.9$ (CH_3), 112.6 (3C, C-8 and C-2, C-6 of phenyl), 119.4 (C-4 phenyl), 120.6 (C-6), 125.4 (C-5), 125.7 (C-4a), 129.0 (2C, C-3 and C-5 of phenyl), 132.0 (C-7), 145.1 (C-1 of phenyl), 145.9 (C-8a), 147.0 (C-2), 167.2 (C-4).

Anal. Calcd. for $C_{15}H_{13}N_3OS$ (283.34): C, 63.58; H, 4.62; N, 14.83. Found: C, 63.78; H, 4.43; N, 14.48.

(4-Oxo-3-phenylamino-3H-quinazolin-2-ylthio) Acetic Acid Ethyl Ester (3)

Compound **3** was prepared in the same manner as described for **2** using **1** (10 mmol) and α-chloroethylacetae (1.22 g, 10 mmol) and it was recrystallized from methanol.

Yield, 2.31 g (65%); m.p., 138–140°C. IR (KBr): 3427 (NH), 2923 (Ar-H), 1735 (C=O ester), 1694 (C=O quinazolinone), 1605, 1542, 1467, 1402 cm^{-1} (C=N, C=C). ^1H NMR ([D_6] DMSO): $\delta_H = 2.51$ (t, 3H, CH_3, J = 7.0 Hz), 3.67 (q, 2H, OCH_2), 4.00 (s, 2H, SCH_2), 6.66–7.20 (m, 5H, Ph), 7.27 (t, 1H, H-6), 7.57 (d, 1H H-8), 7.86 (t, 1H, H-7), 8.07(d, 1H, H-5), 9.48 (s, 1H, exchangeable with D_2O, NH).^{13}C NMR ([D_6] DMSO): $\delta_C = 14.4$ (CH_3), 38.2 (SCH_2), 61.6 (OCH_2), 117.3 (C-8), 114.0 (2C, C-2 and C-6 of phenyl), 119.7 (C-4 of phenyl), 121.6 (C-6), 125.3 (C-5), 125.8 (C-4a), 129.4 (2C, C-3 and C-5 of phenyl), 131.5 (C-7), 145.7 (C-1 of phenyl), 146.1 (C-8a), 147.4 (C-2), 167.2 (C-4), 167.8 (C=O ester).

EI MS, m/z (%) = 355 (M^+, 28.4), 310 ($M^+ - OC_2H_5$, 16.8), 236 (310-SCH_2CO, 12.2), 145 (18.6), 119 (5.3), 77 (100).

Anal. Calcd. for $C_{18}H_{17}N_3O_3S$ (355.41): C, 60.83; H, 4.82; N, 11.82. Found: C, 61.00; H, 4.54; N, 12.10.

2-(4-Oxo-3-phenylamino-3,4-dihydroquinazolin-2-ylthio)-1,3-diphenyl-propane-1,3-dione (4)

It was prepared by reacting **1** (2.69 g, 10 mmol) with α-bromobenzoylacetophenone (3.3 g, 11 mmol) under the same condition. The product was recrystallized from ethanol to give compound **4**.

Yield, 3.34 g (68%); m.p., 220–221°C. IR (KBr): 3425(NH), 3058, 2919 (Ar-H), 1683 (C=O quinazolinone), 1602, 1543, 1505, 1459 cm^{-1} (C=N, C=C). ^1H NMR ([D_6] DMSO): δ_H = 4.52 (s, 1H, CH), 6.68–7.18 (m, 5H, Ph), 7.37–7.86 (m, 10H, 2Ph), 7.42 (t, 1H, H-6), 7.52 (d, 1H H-8), 7.68 (t, 1H, H-7), 8.26(d, 1H, H-5), 9.48 (s, 1H, exchangeable with D_2O, NH).

^{13}C NMR ([D_6] DMSO): δ_C = 38.2 (CH), 113.8 (Ph), 119.0 (Ph), 120.8 (C-6), 120.9 (C-8), 125.8 (Ph), 125.9 (Ph), 126.3 (C-4a), 128.2 (Ph), 128.6 (C-5 and Ph), 129.0 (Ph), 133.3 (C-7), 135.0 (Ph), 136.5 (Ph), 145.8 (Ph), 146.4 (C-8a), 159.3 (C-2), 160.3 (C-4), 194.3 (2C, C=O aliphatic).

Anal. Calcd. for $C_{29}H_{21}N_3O_3S$ (491.56): C, 70.86; H, 4.31; N, 8.55. Found: C, 70.52; H, 4.23; N, 8.21.

3-Hydroxy-10-oxo-4-phenyl-4H,10H-1-thia-4,4a,9-triaza-anthracene-2-carbonitrile (5)

α-Bromo-α-cyano ethylacetate (1.92 g, 10 mmol) was added dropwise to a stirred suspension compound **1** (2.69 g, 10 mmol) and KOH (10 mmol) in 50% aqueous ethanol (30 ml) at room temperature and stirring is continued for 1 h. The reaction mixture was refluxed for 3 h then was cooled to room temperature. The precipitate was filtered, washed with cold water, dried, and crystallized from methanol to give **5**.

Yield, 2.0 g (60%); m.p., 273–274°C. IR (KBr): 3425 (OH), 3053 (Ar-H), 2225 (CN), 1687 (C=O quinazolinone), 1608, 1563, 1461 cm^{-1} (C=N, C=C). ^1H NMR ([D_6] DMSO): δ_H = 6.96–7.44 (m, 5H, Ph), 7.38 (t, J = 8.0 Hz, 1H, H-6), 7.48 (d, J = 8.0 Hz, 1H, H-8), 7.96 (t, J = 8.0 Hz, 1H, H-7), 8.26 (d, J = 8.0 Hz, 1H, H-5), 9.75 (s, 1H, exchangeable with D_2O, OH).

^{13}C NMR ([D_6] DMSO): δ_C = 114.9 (CN), 120.1 (2C, C-2 and C-6 of phenyl), 121.6 (C-5), 121.7 (C-4 of phenyl), 126.3 (C-7), 126.6 (C-10a), 128.3 (C-8), 129.1 (2C, C-3 and C-5 of phenyl), 135.4 (C-6), 145.5 (C-9a), 145.7 (C-1 of phenyl), 146.7 (C-8a), 157.2 (C-3), 157.3 (C-2), 159.1 (C-10).

MS, m/z (%) = 334 (M^+, 27.24), 257 (M^+-Ph, 14.40), 178 ($C_8H_6N_2SO^+$, 100).

Anal. Calcd. for $C_{17}H_{10}N_4O_2S$ (334.35): C, 61.07; H, 3.01; N, 16.76. Found: C, 61.30; H, 3.10; N, 16.83.

(4-Oxo-3-phenylamino-3,4-dihydroquinazolin-2-ylthio)acetic Acid Hydrazide (6)

To a suspension of **3** (1.8 g, 5 mmol) in ethanol (20 ml), hydrazine hydrate 1.5 ml (30 mmol) was added and the reaction mixture was refluxed for 7 h. After cooling, the resulting crystalline product was filtered, washed with little ethanol, dried, and recrystallized from ethanol to give **6**.

Yield, 1.45 g (85%); m.p., 192–194°C. IR (KBr): υ = 3435 (NH), 3245, 3160 (NH / NH_2), 1687 (C=O), 1670 (C=O), 1600, 1556, 1511, 1465 cm^{-1} (C=N, C=C), 695 (C-S-C); ^1H NMR ([D_6] DMSO): δ_H = 4.25 (br s, 2H, exchangeable with D_2O, NH_2), 4.70 (s, 2H, SCH_2), 6.63–7.13 (m, 5H, Ph), 7.24 (t, 1H, H-6), 7.46 (d, 1H, H-8), 7.72 (t, 1H, H-7), 7.92 (d, 1H, H-5), 8.72 (s, 1H, exchangeable with D_2O, NH), 9.85 (s, 1H, exchangeable with D_2O, NH).

EI MS, m/z (%) = 341 (M^+, 54.21), 310 (M^+-NH-NH_2, 23.54), 282 (310-CO, 18.60), 268 (310-CH_2CO, 100), 236 (310-SCH_2CO, 22.40), 145 (9.21), 119 (6.00), 92 (18.52), 77 (38.62).

Anal. Calcd. for $C_{16}H_{15}N_5O_2S$ (341.39): C, 56.29; H, 4.43; N, 20.51. Found: C, 56.57; H, 4.22; N, 20.34.

2-[2-(5-Methyl-3-phenyl-pyrazol-1-yl)-2-oxo-ethylthio]-3-phenylamino-3H-quinazolin-4-one (7) and 2-[2-(3,5-Diphenyl-pyrazol-1-yl)-2-oxo-ethylthio]-3-phenylamino-3H-quinazolin-4-one (8)

The hydrazide **6** (3.41 g, 10 mmol) was dissolved in ethanol (20 ml), then benzoyl acetone or dibenzoyl methane (10 mmol) was added, followed by the addition 2–4 drops perchloric. The mixture was heated under reflux for 8 h and cooled to room temperature. The product was collected by filtration, washed with little ethanol, dried, and crystallized from a mixture ethanol and ethyl acetate (3: 1) to give **7** or **8**.

Compound 7

Yield, 3.36 g (72%); m.p., 214–216°C. IR (KBr): υ = 3442 (NH), 1730 (C=O), 1678 (C=O quinazolinone), 1607, 1595, 1511, 1462 (C=N, C=C),

691 cm^{-1} (C-S-C). ^1H NMR ([D_6] DMSO): $\delta_H = 2.19$ (s, 3H, CH_3, J = 7.1 Hz), 4.65 (dd, 2H, SCH_2), 6.15 (s, 1H, pyrazole H-4), 6.69–8.32 (m, 14H, 2Ph and quinazolinone), 8.78 (s, 1H, exchangeable with D_2O, NH). ^{13}C NMR ([D_6] DMSO): $\delta_C = 13.4$ (CH_3), 37.6 (SCH_2), 102.9 (pyrazole C-4) 112.8 (2C, C-2, C-6 of Ph), 118.3 (C-8), 120.7 (C-4 Ph), 121.4 (C-6), 125.2 (2C, C-2 and C-6 of Ph), 125.5 (C-5), 126.0 (C-4a), 127.5 (C-4 of Ph), 128.4 (2C, C-3 and C-5 of Ph), 129.2 (2C, C-3 and C-5 of Ph), 132.0 (C-7), 134.4 (C-1 of Ph), 142.4 (C-1 of Ph), 145.9 (C-8a), 147.4 (pyrazole C-5), 149.0 (C-2), 150.3 (pyrazole C-3), 164.7 (C-4), 168.4 (C=O). EI MS, m/z (%) = 467 (M^+, 38.75).

Anal. Calcd. for $C_{26}H_{21}N_5O_2S$ (467.55): C, 66.79; H, 4.53; N, 14.98. Found: C, 67.02; H, 4.42; N, 14.67.

Compound 8

Yield, 4.23 g (80%); m.p., 242–244°C. IR (KBr): $\upsilon = 3438$ (NH), 1725 (C=O), 1685 (C=O quinazolinone), 1605, 1592, 1536, 1490 (C=N, C=C), 695 cm^{-1} (C-S-C). ^1H NMR ([D_6] DMSO): $\delta_H = 4.60$ (dd, 2H, SCH_2), 6.25 (s, 1H, pyrazole H-4), 7.12–8.40 (m, 19H, 3Ph and quinazolinone), 9.21 (s, 1H, exchangeable with D_2O, NH).

Anal. Calcd. for $C_{31}H_{23}N_5O_2S$ (529.63): C, 70.30; H, 4.38; N, 13.22. Found: C, 70.08; H, 4.57; N, 13.49.

2-[2-(3-Methyl-5-oxo-4,5-dihydropyrazol-1-yl)-2-oxo-ethylthio]-3-phenylamino-3H-quinazolin-4-one (9)

A mixture of hydrazide **6** (3.41 g, 10 mmol) and ethyl acetoacetate (1.30 g, 10 mmol) was refluxed in methanol (25 ml) containing 3–4 drops perchloric acid for 5 h. The reaction mixture was cooled to room temperature and separated solid filtered off, washed with little methanol, dried, and crystallized from methanol to give **9**.

Yield, 2.65 g (65%); m.p., 287–288°C. IR (KBr): $\upsilon = 3452$ (NH), 1732 (C=O), 1682 (C=O quinazolinone), 1665 (C=O pyrazolone), 1604, 1598, 1532, 1485(C=N, C=C), 698 cm^{-1} (C-S-C). ^1H NMR ([D_6] DMSO): $\delta_H = 2.25$ (s, 3H, CH_3), 4.63 (dd, 2H, SCH_2), 5.02 (s, 2H, pyrazole H-4), 6.75–8.16 (m, 9H, Ph and quinazolinone), 8.82 (s, 1H, exchangeable with D_2O, NH). ^{13}C NMR ([D_6] DMSO): $\delta_C = 14.6$ (CH_3), 38.2 (SCH_2), 41.8 (pyrazole C-4), 118.7 (C-8), 116.3 (2C, C-2 and C-6 of Ph), 120.4 (C-4 of Ph), 123.0 (C-6), 126.0 (C-5), 127.2 (C-4a), 129.8 (2C, C-3 and C-5 of Ph), 134.4 (C-7), 144.3 (C-1 of Phl), 145.6 (C-8a), 147.4 (pyrazole C-4), 149.4 (C-2), 164.5 (C-4), 167.6 (C=O), 170.2 (C=O pyrazole C-5).

Anal. Calcd. for $C_{20}H_{17}N_5O_3S$ (407.45): C, 58.96; H, 4.21; N, 17.19. Found: C, 58.75; H, 3.94; N, 17.35.

3-Phenylamino-2-(5-thioxo-4,5-dihydro[1,3,4]oxadiazol-2-ylmethylthio)-3H-quinazolin-4-one (10)

A mixture of hydrazide **6** (3.41 g, 10 mmol), potassium hydroxide (10 mmol), and carbon disulphide (3 ml) in ethanol (25 ml) was heated under reflux for 12 h. The solvent was evaporated to dryness and the residue dissolved in cold water. The resulting clear solution filtered and the filtrate was acidified with dilute hydrochloric acid. The separated solid was filtered, dried, and crystallized from ethanol to give **10**.

Yield, 2.83 g (74%); m.p., 172–174°C. IR (KBr): $\upsilon = 3436$ (NH), 3177 (NH-C=S), 1685(C=O quinazolinone), 1608, 1590, 1530, 1482 (C=N, C=C), 1185 (C=S), 697 cm^{-1} (C-S-C). ^1H NMR ([D_6] DMSO): $\delta_H = 3.24$ (dd, 2H, SCH_2), 5.02 (s, 2H, pyrazole H-4), 6.62–8.25 (m, 9H, Ph and quinazolinone), 11.72 (s, 1H, exchangeable with D_2O, pyrazole NH), 9.52 (s, 1H, exchangeable with D_2O, NH).

EI MS, m/z (%) = 383 (M^+, 45.21), 269 (26.41), 145 (14.95), 119 (5.94), 116 ($C_3H_4N_2SO^+$, 38.45), 102 ($C_2H_2N_2SO^+$, 100).

Anal. Calcd. for $C_{17}H_{13}N_5O_2S_2$ (383.45): C, 53.25; H, 3.42; N, 18.26. Found: C, 53.54; H, 3.28; N, 18.29.

3-Phenylamino-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-3H-quinazolin-4-one (11)

To a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (4.1 g, 10 mmol) in DMF (15 ml) was added a solution of compound **1** (2.69 g, 10 mmol) in DMF (5 ml) and a suspension of sodium hydride (0.24 g, 10 mmol) in DMF (15 ml). The reaction mixture was stirred for 3 h and left to stand at room temperature over night. TLC detected completion of the reaction (system: petroleum ether/ethylacetate, 3: 1, V: V). The reaction mixture was poured onto crushed ice and the precipitate that formed, was filtered, washed with cold water, dried, and crystallized from ethanol to afford **11** in 64% yield (3.83 g); m.p., 169–170°C.

IR (KBr): $\upsilon = 3427$ (NH), 2925 (Ar-H), 1744 (C=O acetoxy), 1697(C=O quinazolinone), 1584, 1562, 1460 (C=N, C=C), 915 cm^{-1} (β pyranoside). ^1H NMR ($CDCl_3$): $\delta_H = 1.96$, 2.02, 2.06, 2.12 (4 s, 12H, each CH_3), 3.99 (m, 1H, H-5′), 4.15 (q, 1H, H-6″), 4.24 (q, 1H, H-6′), 4.28 (t, 1H, H-2′), 5.12 (t, 1H, H-4′), 5.40 (t, 1H, H-3′), 5.78 (d, 1H, H-1′, $J_{1',2'} = 10.6$ Hz)), 6.74–7.18 (m, 5H, Ph), 7.39 (t, 1H, H-6), 7.61 (d, 1H, H-8), 7.74 (t, 1H, H-7), 8.15 (d, 1H, H-5), 8.93 (s, 1H, exchangeable with D_2O, NH).

EI MS, m/z (%) = 599 (M^+, 6.4), 331 (sugar$^+$, 17.9), 268 (B, 21.4), 270 (B+2,17.5) 236 (15.5), 229 (4.7), 211 (6.0), 187 (5.3), 169 (32.1), 145 (13.7), 119 (2.6), 109 (25.0), 93 (100).

Anal. Calcd. for $C_{28}H_{29}N_3O_{10}S$ (599.61): C, 56.09; H, 4.87; N, 7.01. Found: C, 56.40; H, 4.64; N, 7.36.

3-Phenylamino-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)-3H-quinazolin-4-one (12)

Compound **12** was prepared in the same manner as described for **11**, using compound **1** (2.69 g, 10 mmol) and 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide (4.1 g, 10 mmol). The product was crystallized from aqueous ethanol (30%) to afford **12** in 58% yield (3.47 g); m.p., 157–159°C.

IR (KBr): υ = 3462 (NH), 2927 (Ar-H), 1747 (C=O acetoxy), 1695(C=O quinazolinone), 1592, 1525, 1438 (C=N, C=C), 860 cm^{-1} (β pyranoside). ^{1}H NMR ($CDCl_3$): δ_H = 1.87, 1.94, 2.04, 2.16 (4 s, 12H, each CH_3), 4.11 (m, 1H, H-5′), 4.15 (q, 1H, H-6″), 4.20 (q, 1H, H-6′), 4.21 (t, 1H, H-2′), 5.26 (t, 1H, H-4′), 5.37 (t, 1H, H-3′), 5.77(d, 1H, H-1′, $J_{1',2'}$ = 9.5 Hz)), 6.74–7.26 (m, 5H, Ph), 7.38 (t, 1H, H-6), 7.63 (d, 1H, H-8), 7.74 (t, 1H, H-7), 8.14 (d, 1H, H-5), 8.90 (s, 1H, exchangeable with D_2O, NH).

EI MS, m/z(%) = 599 (M^+, 3.9), 331 (sugar$^+$, 70.5), 271 (2.9), 269 (B+1, 8.9), 236 (10.4), 229 (6.0), 211 (3.4), 187 (3.1), 169 (100), 145 (11.7), 119 (3.0), 109 (87.3), 92 (22.3), 81 (19.5), 77 (23.0).

Anal. Calcd. for $C_{28}H_{29}N_3O_{10}S$ (599.61): C, 56.09; H, 4.87; N, 7.01. Found: C, 56.30; H, 4.70; N, 7.32.

3-Phenylamino-2-(2′,3′,4′-tri-O-acetyl-β-D-xylopyranosylthio)-3H-quinazolin-4-one (13)

Compound **1** (2.69 g, 10 mmol) was reacted with 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide (3.9 g, 10 mmol) to give compound **13** as described for **11**. The product was crystallized from chloroform / petroleum ether to give **13** in 60% yield (3.16 g); m.p., 180–181°C.

IR (KBr): υ = 3422 (NH), 2923 (Ar-H), 1742 (C=O acetoxy), 1681 (C=O quinazolinone), 1596, 1528, 1482 (C=N, C=C), 928 cm^{-1} (β pyranoside). ^{1}H NMR ($CDCl_3$): δ_H = 1.95, 2.03, 2.08 (3 s, 9H, each CH_3), 3.64 (q, 1H, H-5′), 4.25 (m, 1H, H-5″), 4.97 (t, 1H, H-4′), 5.03 (t, 1H, H-2′), 5.27 (t, 1H, H-3′), 5.95 (d, 1H, H-1′, $J_{1',2'}$ = 7.5 Hz)), 6.73–7.21 (m, 5H, Ph), 7.36 (t, 1H, H-6), 7.44 (d, 1H, H-8), 7.64 (t, 1H, H-7), 8.13 (d, 1H, H-5), 8.86 (s, 1H, exchangeable with D_2O, NH).

EI MS, m/z (%) = 527 (M^+, 2.2), 259 (sugar$^+$, 24.5), 269 (B+1, 5.1), 236 (10.4), 199 (21.4), 157 (47.7), 145 (11.7), 139 (51.6), 119 (3.0), 97 (100), 92 (22.3), 77 (23.0), 69 (13.9).

Anal. Calcd. for $C_{25}H_{25}N_3O_8S$ (527.54): C, 56.92; H, 4.78; N, 7.97. Found: C, 57.10; H, 4.90; N, 8.20.

3-Phenylamino-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylsulphonyl)-3H-quinazolin-4-one (14)

To a solution of the S-glucoside **11** (1.0 g) in glacial acetic acid (7.5 ml), an excess of hydrogen peroxide 30% (1.4 g) was added with stirring for about 6 h at room temperature and poured onto an ice-water (200 ml). The separated solid was collected by filtration, washed with cold water, dried, and crystallized from methanol to afford **14** in 65% yield (0.68 g); m.p., 90–91°C.

IR (KBr): $\upsilon = 3433$ (NH), 2942 (Ar-H), 1749 (C=O acetoxy),1694 (C=O quinazolinone), 1586, 1563, 1473 (C=N, C=C), 1370, 1185 (SO_2), 922 cm^{-1} (β pyranoside). ^1H NMR ($CDCl_3$): $\delta_H = 1.85, 1.91, 1.97, 2.00$ (4 s, 12H, each CH_3), 4.09 (m, 1H, H-5′), 4.10 (q, 1H, H-6″), 4.27 (q, 1H, H-6′), 5.01 (t, 1H, H-2′), 5.06 (t, 1H, H-4′), 5.52 (t, 1H, H-3′), 5.93 (d, 1H, H-1′, $J_{1',2'} = 8.5$ Hz)), 6.67–7.24 (m, 5H, Ph), 7.37 (t, 1H, H-6), 7.63 (d, 1H, H-8), 7.74 (t, 1H, H-7), 8.15 (d, 1H, H-5), 9.38 (s, 1H, exchangeable with D_2O, NH).

Anal. Calcd. for $C_{28}H_{29}N_3O_{12}S$ (631.61): C, 53.25; H, 4.63; N, 6.65. Found: C, 53.63; H, 4.50; N, 6.95.

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