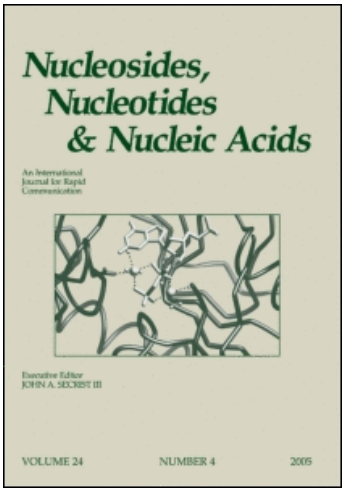

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SYNTHESIS AND ANTIVIRAL EVALUATION OF SOME NEW GLYCOSYLTHIOUREAS CONTAINING A QUINAZOLINONE NUCLEUS

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SYNTHESIS AND ANTIVIRAL EVALUATION OF SOME NEW GLYCOSYLTHIOUREAS CONTAINING A QUINAZOLINONE NUCLEUS

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ABSTRACT

A new synthesis of glycosylthioureas containing a quinazolinone nucleus is described utilizing per-*O*-acetylglycopyranosylisothiocyanates and several aminoquinazolinones as starting compounds. Structural proofs of these compounds are provided from elemental analyses, IR, ^{1}H and ^{13}C NMR spectra and mass spectra. The biological activity of these compounds has been studied.

INTRODUCTION

Sugar isothiocyanates are versatile synthetic intermediates which have been used as precursors of different sugar derivatives such as glycosylthioureas[1–3], glcosyl-aminoheterocycles,[4–6] nucleosides[7–9] and glycosyl derivatives of β-cyclodextrines which have potential pharmacological properties[10–12]. In addition several glcosyl-isothiocyanates are specific enzyme inhibitors[13,14]. As a part of our program directed towards new, simple and efficient procedures for synthesis of antimetabolites[15–21]. We report here synthesis of some new *N*-glycosyl- *N*′-(4-oxoquinazolinyl)

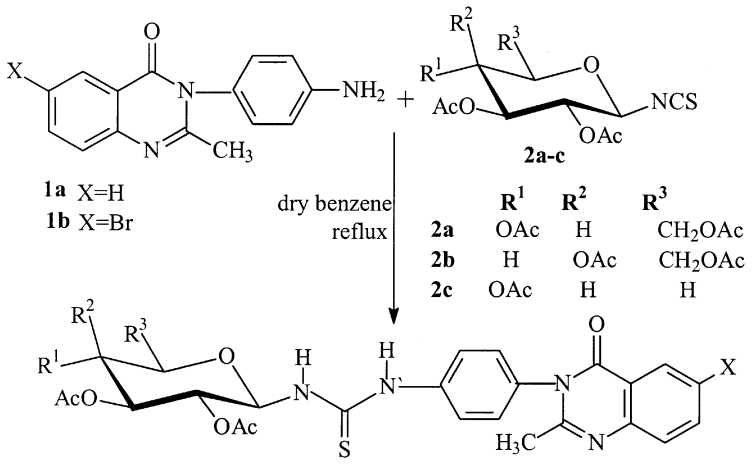
*Corresponding author.

thiourea derivatives and attempts to cause the ring closure of these compounds with methyl cyanoacetate under acidic conditions.

RESULTS AND DISCUSSION

Treatment of 3-(4-aminophenyl)- 2-methyl- 4(3 *H*)- quinazolinone **(1a)**[22] and its 6-bromo derivative **1b** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **(2a)**,[23] 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl isothiocyanate **(2b)** [24] or 2,3,4-tri-O-acetyl-β-D-xylopyranosyl isothiocyanate **(2c)**[24] gave glycosyl thiourea derivatives **3a**–**d** (Sch. 1), whose analytical and spectroscopic data (see experimental) are in agreement with the proposed structures. IR spectra of compounds **3a**–**d** showed absorptions at 3440–3433 (NH), 1753–1751 cm^{-1} (C=O ester) and the absence of the characteristic isothiocyanate band (NCS) at 2100–2000 cm^{-1}.

Proton assignments in ^1H NMR spectra of compounds **3a**–**d**, which are listed in the experimental section, were made by ^1H-^1H homonuclear shift correlated (COSY) 2D NMR, D_2O exchange and double resonance experiments. The spin-spin coupling constant value (J) are indicative of a preponderance of the $^4C_1$ (D) conformation in solution. The chemical shifts

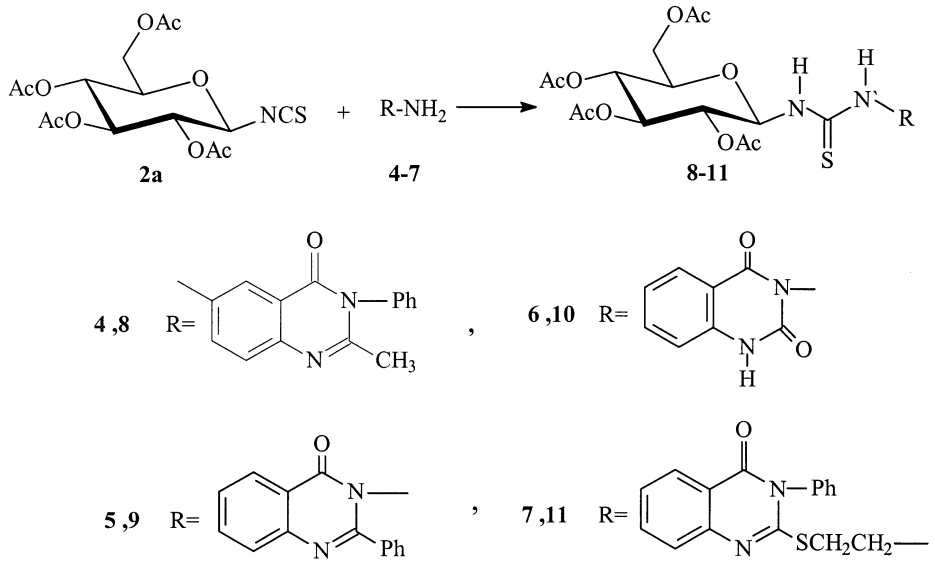


Scheme 1.

(5.78–5.88) of H-1′ and the large values (8.6–9.3 Hz) of $J_{1',2'}$ for compounds **3a–d** are in accord with β-configuration. The ^{13}C NMR spectrum of **3c** revealed a signal at δ 83.1 corresponding to C-1′ of the β-anomer and a signal at δ 182.2 corresponding to C=S of the thiourea moiety. The ^{13}C NMR data listed in the experimental section were assigned on the basis of comparing the data obtained for **3c** and **3d** with those reported in the literature for 2-methyl-3-aryl-4(*3 H*)-quinazolinone[25] and per-O-acetylglycopyranose.[26] The FAB mass spectrum of **3c** showed its M + 23 and M + 1 peaks at m/z 743 (for Br^{81}) and at m/z 721 (for Br^{81}) and at m/z 741 (for Br^{79}) and at m/z 719 (for Br^{79}), respectively. In addition to the fragment ions corresponding to the loss of thiourea moiety ($M^+ - 388$) and the characteristic loss of AcOH in poly-O-acetylated sugars were observed [27] (see experimental). The base peak appeared at m/z 105 (100%) and corresponds to relative stable $C_7H_7N^+$, yet revealed the characteristic fragments depicted in Sch. 5.

The reaction of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate **(2a)** with 6-amino-2-methyl-4(3H)-quinazolinone **(4)**,[28] 3-amino-2-phenyl-4(3 *H*)-quinazolinone**(5)**,[29] 3-amino-2,4(1*H*,3*H*)-quinazolinedione **(6)**[30]or 2-(β-aminoethylthio)-3-phenyl-4(3 *H*)-quinazolinone (7),[31] gave the corresponding *N*′-substituted *N*-glucopyranosylthiourea derivatives **8–11**, respectively (Sch. 2).

The structures **8–11** were supported by **IR**, ^1H and ^{13}C NMR and mass spectral data (see experimental). In the IR spectra of **8–11**, the absorption bands at 3356–3276 cm^{-1} are characteristic for NH groups of thiourea derivatives. The strong bands at 1687–1660 and 1778–1740 cm^{-1} are

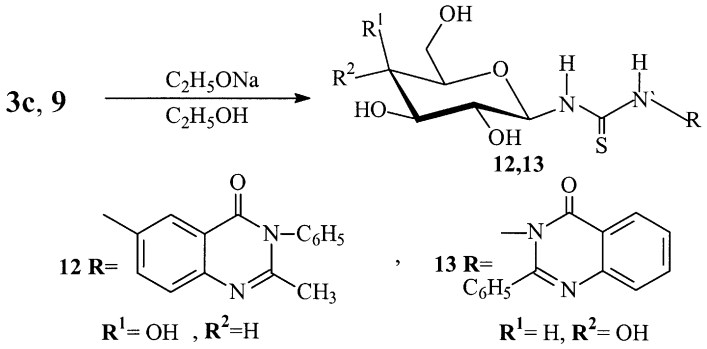


Scheme 2.

attributed to the quinazolinone and ester C=O stretching vibrations, respectively. The ^{1}H NMR spectra of **8**–**11** shows triplets for the anomeric protons at δ 5.65–5.76 which were converted to the doublets upon addition of D_2O. The doublets exhibit a large $J_{1',2'}$ (8.5–9.5 Hz), which is in the range for antiperiplanar protons and indicates that the new glucosidic bond has the β-configuration in a $^4C_1$(D) conformation (see experimental). The chemical shifts of the acetoxy protons in the glucosyl residue provided further verification of the favored $^4C_1$(D) conformation and β-configuration of **8**–**11**, since these signals fell within the range expected for equatorial secondary acetoxy groups[32] (see experimental). The ^{13}C NMR spectrum of **11** is characterized by a signal at δ 82.4 corresponding to C-1′ (anomeric carbon atom), which is also in agreement with the β-configuration of glucosyl residue[33]. The FAB mass spectrum of **11** (Sch. 6) showed ($M^+ + 1$) at m/z 687 and 709 ($M^+ + Na$). Fragmentation of the molecular ion gave peaks at 356, 297, 281and 253 due to sequential expulsion of sugar moiety, NHCS, NH_2 and C_2H_4 fragments. Peaks were observed at m/z 331, 271 and 229 due to loss of thiourea derivatives, HOAc and CH_2CO (see experimental). The base peak appears at m/z 433 (100%) and corresponds to *N*-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-N′-ethylthiourea ($C_{17}H_{25}N_2O_9S^+$).

Deacetylation of **3c** and **9** by Zemplen's method[34] in the presence of a catalytic amount of sodium ethoxide in absolute ethanol gave compounds **12** and **13** (Sch. 3). IR spectra of **12** and **13** show absorption bands at 3380–3345 (NH,OH) and 1665–1687 cm^{-1} (C=O of quinazolinone moiety) and the absence of ester carbonyls at 1753 and 1749 cm^{-1}. Because **3c** and **9** have the $^4C_1$(D) conformation and the β-configuration, deacetylated compounds 12 and 13 were expected to exist with the same conformation and configuration, which was verified by their ^{1}H NMR spectra.

The ^{13}C NMR spectrum of **12** is characterized by a signal at δ 87.1 corresponding to **C-1′**of the β-anomer and a signal at δ 182.0 corresponding to C=S of the thiourea.

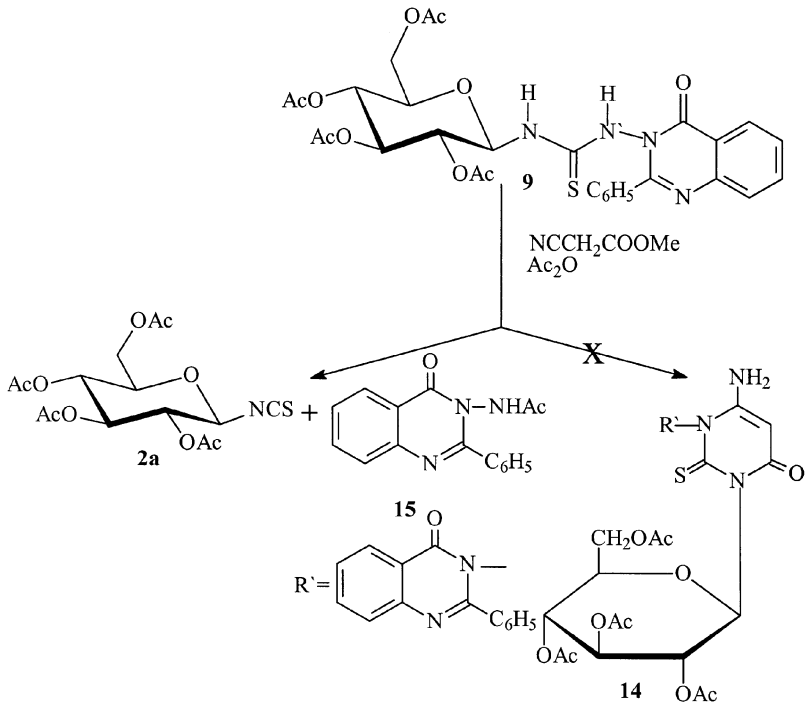


Scheme 3.

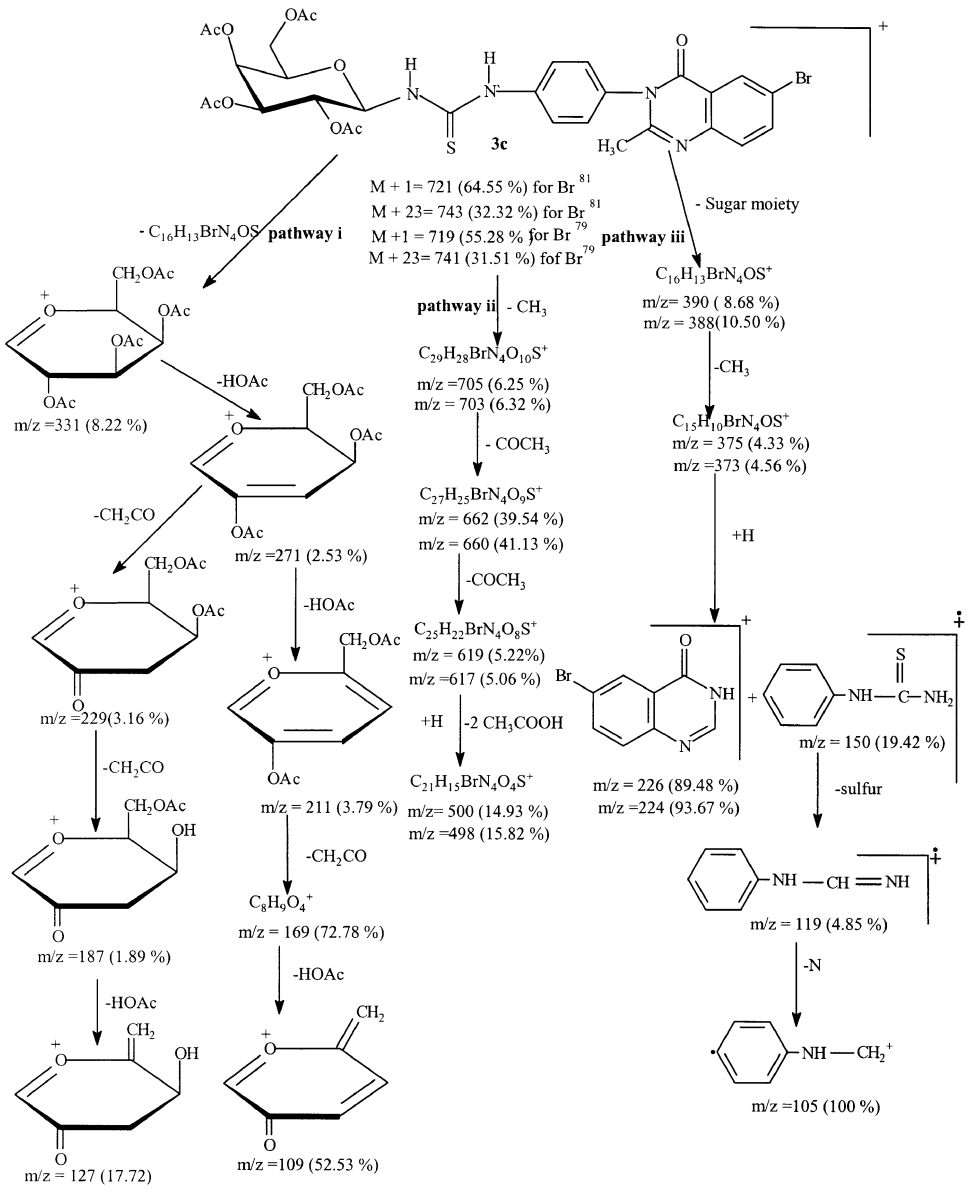
Attempts to induce ring closure of glycosyl thiourea derivatives **3a–d** and **8–11** with methyl cyanoacetate to give compound **14,** under either thermal or acidic conditions were unsuccessful. Heating **9** with methyl cyanoacetate in Ac_2O under reflux gave N^3-acetylamino-2-phenyl-4(*3 H*)-quinazolinone **(15)** in 77% yield and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate **(2a),** as shown in Scheme 4.

The IR spectrum of compound **15** shows a characteristic band at 3462 cm^{-1}, corresponding to the stretching vibration of NH group, and bands at 1716 and 1675 cm^{-1} which correspond to the stretching vibrations for the acetyl and quinazolinone carbonyl groups, respectively. The ^{1}H-NMR spectrum of **15**, shows a singlet peak at δ 2.01 due to the *N*-acetyl group and a singlet at δ 10.45 due to the NH group, which is disappears upon addition of D_2O. The protons of the quinazolinone moiety appear as multiplets in the δ 8.35–7.63 region. Sugar isothiocyanate **2a** was identified by comparing its melting point with that of an authentic sample [22] and from the IR spectrum, which shows a band at 2101 cm^{-1} for the NCS group.

The compounds described in this manuscript showed no activity against Human Immunodeficiency Virus (HIV). They were also devoid of any activity against different types of tumor virus.



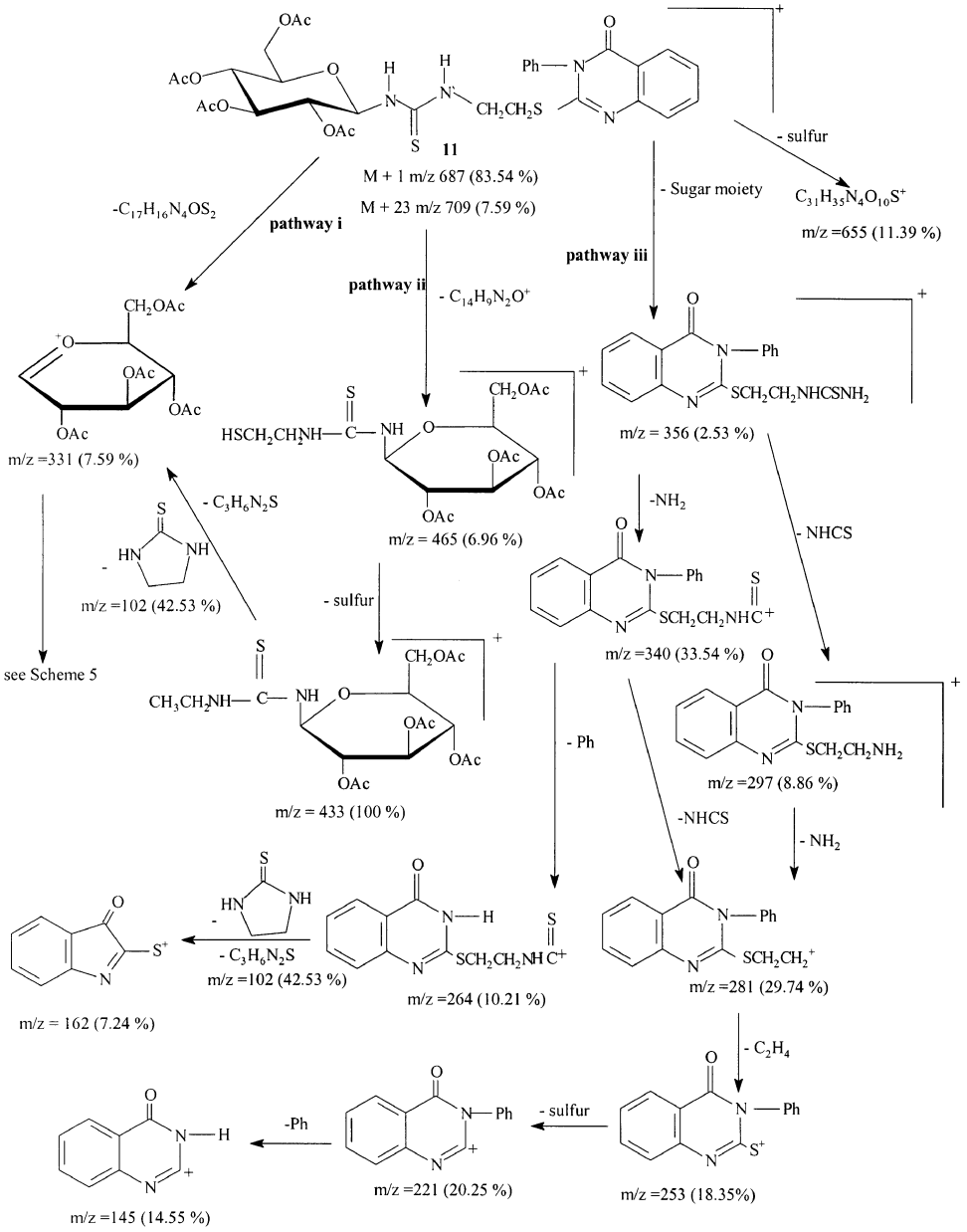
Scheme 4.



Scheme 5. Cleavage pathway of compound **3c**.

EXPERIMENTAL

Melting points were determined on an electro- thermal melting MEL-TEMP II apparatus and are reported uncorrected. IR spectra were recorded on a UNICAM SP1200 spectrophotometer using pellet technique KBr discs. Microanalyses were performed in Tanta University, Tanta, Egypt and



Scheme 6. Cleavage pathway of compound **11**.

National Research Center (NRC) service of microanalysis, Cairo, Egypt. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AC spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR measurement at Department of Chemistry, Georgia State University, University Plaza, Atlanta, USA. Chemical shifts are reported in parts per million relatives to

tetramethylsilane. Low resolution mass spectra data were obtained with a micromass spectrometer model 7070 at 70 ev and an inlet temperature 90°C. FAB (LSIMS) spectra were recorded on a VG- Autospec instrument at University of Wales, Swansea, England. All analytical samples were homogeneous by thin layer chromatography, which was performed on EM silica gel 60 F_{254} sheet (0.2 mm) with chloroform/acetone (5:2 V:V), benzene/acetone (5:2 V:V) and isopropyl alcohol/benzene/ammonia solution (10:5:2 V:V:V) as developing eluents A, B and C, respectively. The spots were detected with UV lamp model UVGL-58. National Cancer Institute, Bethesda, Maryland, U.S.A. did the biological evaluation studies. Anti- HIV tests were determined according to the reported method literature.[35]

General Procedure for the Preparation of 3a–d

A mixture of D-glycosyl isothiocyanates **2a–c** (0.005 mole) and 3-(4-aminophenyl)-2-methyl-4(*3H*)-quinazolinone **(1a)** or its bromo derivative **1b** (0.005 mole) in dry benzene (150 mL) was heated at reflux for 8–24 h. The solvent was evaporated under diminished pressure. The residue was triturated several times with chloroform to remove impurities and was then crystallized from ethanol. The following compounds were prepared in this manner.

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N*′-[4-(2-methyl-4-oxoquinazolin-3-yl) phenyl]thiourea (3a)

After 16 h at reflux, 1.19 g (60%) of **3a** was isolated as fine, colorless needles, m.p. 140-141°C; IR(KBr): 3450–3440 (NH), 1752 (C=O ester), 1654 (C=O quinaz.), 122(C=S), 1225 (C-O-C) and 911 cm^{-1} (glucopyranosyl); ^1H NMR ($CDCl_3$): δ 5.88 (t, 1H, H-1′, $J_{1',2'} = 9.0$ Hz), 4.79 (t, 1H, H-2′, $J_{2',3'} = 9.2$ Hz), 5.33 (t, 1H, H-3′, $J_{3',4'} = 9.2$ Hz), 4.71(t, 1H, H-4′), 4.18 (m, 1H, H-5′), 4.27–3.86 (m, 2H, H-6′,H-6′′), 1.97, 1.98, 2.02 and 2.05 (4 s, each 3H, 4 Ac), 7.44 (d, 1H, exchangeable, *NH*, $J_{1'}$,NH = 8.2 Hz), 8.65(br s., 1H, N′H), 8.40(d, 1H, H-5 of quinaz.), 7.91 (t, 1H, H-6 of quinaz.), 7.67 (t, 1H,H-7 of quinaz.), 7.87 (d, 1H, H-8 of quinaz.), 7.28-7.14 (m, 4H, Ph), and 2.11 (s, 3H, CH_3).

Anal. Calcd for $C_{30}H_{32}N_4O_{10}S$: C, 56.25; H, 5.00; N, 8.75. Found: C, 56.61; H, 4.71; N, 9.01.

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N*′-[4-(6-bromo-2-methyl-4-oxoquinazolin-3-yl) phenyl]thiourea (3b)

After 24 h at reflux, 2.53 g (70%) of **3b** was isolated as an amorphous and hydroscopic solid, m.p. 158–160°C; IR (KBr): 3445–3330 (NH), 1742

(C=O ester), 1652 (C=O quinaz.), and 1228(C=S) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.85 (t, 1H, H-1′, $J_{1',2'} = 8.7$ Hz), 4.96 (t, 1H, H-2′, $J_{2',3'} = 8.5$ Hz), 5.34 (t, 1H, H-3′, $J_{3',4'} = 8.3$ Hz), 4.90−3.82 (m, 4H, H-4′, H-5′, H-6′, H-6″), 1,97, 1.98, 2.04 and 2.06 (4s, each 3H, 4Ac), 8.23 (d, 1H, NH, $J_{1'}$, NH = 8.5 Hz), 9.20 (br s., 1H, N′H), 8.41 (s, 1H, H-5 of quinaz.), 8.21 (d, 1H, H-7 of quinaz.), 7.82(d, 1H, H-8 of quinaz.), 8.21-7.02 (m, 4H, Ph) and 2.13 (s, 3H, CH_3).

Anal Calcd. For $C_{30}H_{31}N_4BrO_{10}S$: C, 50.10; H, 4.30; N, 7.79. Found: C, 49.98; H, 4.14; N, 7.52.

N-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-*N*′-[4-(6-bromo-2-methy-4-oxoquinazolin-3-yl) phenyl]thiourea (3c)

After 10 h at reflux, 2.35 g (65%) of 3c was isolated as colorless crystals, m.p. 128-130-130°C; IR(KBr):3445-3350 (NH), 1753(C=O ester), 1229 (C=S), 1654(C=O quinaz.), 1225(C-O-C) and 912 cm^{-1} (galactopyranose). ^1H NMR(CDCl3): δ 5.78 (t, 1H, H-1′, $J_{1',2'} = 8.6$ Hz), 5.22 (t, 1H, H-2′), 5.49 (t, 1H, H-3′), 4.91(m, 1H, H-4′), 4.24-3.99 (m, 3H, H-5′, H-6′,H-6″), 2.04, 2.06, 2.07 and 2.13(4s, each 3H, 4Ac), 7.92(d, 1H, NH, $J_{1'}$,NH = 8.5 Hz), 8.95(br s., 1H, N′H), 8.56(s, 1H, H-5 of quinaz.), 8.15(d, 1H, H-7 of quinaz.), 7.85 (d, 1H, H-8, of quinaz.), 7.85-6.75(m, 4H, Ph) and 2.16(s, 3H, CH_3). ^{13}C NMR($CDCl_3$):δ 83.1(β C-1′), 72.7, 73.7, 68.8, 70.5 and 61.7(C-2′, C-3′, C-4′, C-5′and C-6′ of sugar moiety),170.9, 170.8, 169.9 and 169.7(4CO ester), 20.5, 20.6, 20.6 and 20.7(4 CH_3), 182.2 (C=S), 166.4, 167.6, 121.6, 129.0, 127.3, 132.4, 122.1 and 138.4 (C-2, C-4, C-5, C-6, C-7, C-8 and C-8a of quinaz. moiety), 23.1(CH_3 at position 2), 126.3(2C, C-2,6 of Ph), 127.8(2C, C-3,5 of Ph), 132.2(C-1 of Ph) and 137.5(C-4 of Ph). FAB Mass spectrum: m/z 743 (32.32, M + Na, for Br^{81}), 721(64.55, M + 1, for Br^{81}), 741 (31.51, M + Na, for Br^{79}), 719 (55.28, M + 1, for Br^{79}), 705 (6.25, 720 - CH_3) 703(6.32, 718 - CH_3), 688(10.65, 721-SH), 390(8.68, thiourea moiety, $C_{16}H_{13}Br^{81}N_4OS^+$), 388 (10.50, thiourea moiety, $C_{16}H_{13}Br^{79}N_4OS^+$), 331(8.22, galactosyl moiety), 271(2.53, 331-AcOH), 229(3.16, 271-CH2O), 211(3.79, 271-AcOH), 169 (72.78, 211-CH_2O), 127 (17.72, 169-AcOH) and 105 (100, $C_7H_7N^+$).

Anal. Calcd. for $C_{30}H_{31}BrN_4O_{10}S$: C, 50.10; H, 4.30; N, 7.79. Found: C, 50.31; H, 4.50; N, 7.51.

N-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)-*N*′-[4-(6-bromo-2-methyl-4-oxoquinazolin-3-yl) phenyl]thiourea (3d)

After 8 h at reflux, 2.43 g (75%) of **3d** was isolated as an amorphous and hydroscopic solid, m.p. 140-142°C. IR (KBr): 3446-3350 (NH), 1752 (C=O ester), 1654 (C=O quinaz.) 1228 (C=S) and 1223 cm^{-1} (C-O-C). ^1H NMR ($CDCl_3$): δ 5.84 (t, 1H, H-1′, $J_{1',2'} = 9.2$ Hz), 5.35(t, 1H , H- 2′), 5.64 (t, 1H,

H-3′), 4.97-3.47 (m, 3H, H-4′, H-5′ and H-5″), 8.20 (d, 1H, NH, $J_{1'}$,NH = 8.3 Hz), 9.05 (br s, 1H, N′H), 8.42 (d, 1H, H-5 of quinaz.), 8.02 (d, 1H, H-7 of quinaz.) 7.89 (d, 1H, H-8 of quinaz.), 7.88−6.75 (m, 4H, ph) and 2.16(s, 3H, 3H). ^{13}C NMR ($CDCl_3$): δ 84.9 (β C-1′), 167.3, 169.7 and 170.1(3 C=O ester), 20.6, 20.7 and 20.8 (each CH_3, 3 Ac), 72.5, 71.3, 69.3 and 63.5(C-2′, C-3′, C-4′ and C-5′ of xylosyl moiety, respectively), 143.9, 166.0, 121.9, 130.2, 128.9 138.9. 122.7 and 141.9(C-2, C-4, C-4a, C-5, C-6, C-7, C-8 and C-8a of quinaz. residue, respectively), 23.9 (CH_3 at position 2), 126.3 (2C, C2,6 of Ph), 127.8 (2C, C3,5 of Ph), 132.2(C-1 of Ph) and 137.5 (C-4 of Ph).

Anal. Calcd for $C_{27}H_{27}BrN_4O_8S$: C, 50.07; H, 4.17; N, 8.65. Found: C, 50.06; H, 4.21; N, 8.31.

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N*′-[(2-methyl-3-phenyl-4-oxoquinazolin-6-yl)]thiourea (8)

Compound **8** was obtained similarly to compound **3b** from 6-amino-2-methyl-4(*3H*)-quinazolinone **(4)** (0.251 g, 0.001 mole) and **2a** (0.390 g, 0.001 mole). Yield (0.38 g, 60%) , m.p. 135°C. IR(KBr): 3356 (NH), 1745 (C=O ester), 1660 (C=O, quinaz.), 1229 (C=S) and 1224 cm^{-1} (C-O-C). ^{1}H NMR($CDCl_3$): 5.47 (t, 1H, H-1′, $J_{1',2'} = 9.5$ Hz), 5.02 (t, 1H, H-2′, $J_{2',3'} = 9.2$ Hz), 5.29 (t, 1H, H-3′, $J_{3',4'} = 9.2$ Hz), 4.76 (t, 1H, H-4′), 4.07 (m, 1H, H-5′), 4.31 (q, 1H, H-6′), 3.80 (m, 1H, H-6″), 1.98, 2.00, 4.04 and 2.06 (4s, each 3H, 4 Ac), 6.84 (d, 1H, NH, $J_{1'}$, NH = 8.5 Hz), 8.49 (br s, 1H, N′H), 7.79 (s, 1H, H-5 of quinaz.), 7.69(d, 1H, H-7 of quinaz.), 7.54 (d, 1H, H-8 of quinaz.), 7.23−7.50 (m, 5H of Ph) and 2.22 (s, 3H, of CH_3 at position 2).

Anal. Calcd. for $C_{30}H_{32}N_4O_{10}S$: C, 56.25; H, 5.00; N, 8.75. Found: C, 56.41; H, 4.78; N, 8.32.

N-(2, 3, 4, 6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N*′-[(2-phenyl-4-oxoquinazolin-3-yl)]thiourea (9)

Thiourea **9** was obtained similarly to compound **3d** from 3-amino-2-phenyl-4(*3H*)-quinazolinone **(5)** (0.24 g, 0.001 mole) and **2a** (0.39 g, 0.001 mole). Yield (0.28 g, 45%), m.p. 119−120°C. IR (KBr): 3297 (NH), 1749 (C=O ester), 1608 (C=O quinaz.), 1229 (C=S) and 1225 cm^{-1} (C-O-C). ^{1}H-NMR ($CDCl_3$): δ 5.69 (t, 1H, H-1′, $J_{1',2'} = 8.5$ Hz), 5.04 (t, 1H, H-2′, $J_{2',3'} = 8.3$ Hz), 5.23 (t, 1H, H-3′, $J_{3',4'} = 9.0$ Hz), 4.92 (t, 1H, H-4′), 3.80−4.82 (m, 3H, H-5′, H-6′ and H-6″), 1.97, 1.99, 2.04 and 2.06 (4s, each CH_3, 4 Ac), 6.97(d, 1H, NH), 8.26(br s, 1H, N′H), 7.80 (d, 1H, H-5 of quinaz.), 7.75 (t, 1H, H-6 of quinaz.) and 7.41−7.53 (m, 7H, H-7, H-8 of quinaz and of Ph). FAB Mass spetrum: m/z 649 (< 1, M^ + Na), 627 (1.57, M + 1), 331 (12.06, glucosyl moiety, S^+), 296 (14.34, thiourea moiety, $C_{15}H_{12}N_4OS^+$), 271

(16.64, 331-AcOH), 229 (1.52, 271-CH_2CO), 169 (99.52, 229-AcOH), 109 (61.79, 169-AcOH), 81 (8.53, 109-CO) and 60 (62.02, AcOH).

Anal. Calcd. For $C_{29}H_{30}N_4O_{10}S$: C, 55.59; H, 4.79; N, 8.94. Found: C, 55.81; H, 4.38; N, 8.81.

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N*′-[2,4-dioxo-(*1H,3H*)-quinazolin-3-yl]thiourea (10)

Compound **10** was obtained similarly to compound **3b** from 3-amino-2,4(*1H, 3H*)quinazolinedione **(6)** (0.18 g, 0.001 mole) and **2a** (0.39 g, 0.001 mole). Yield (0.28 g, 50%), m.p. 128−130°C; IR (KBr): 32769 (NH), 1778 (C=O ester), 1676 (C=O quinaz.), 1229 (C=S) and 1224 cm^{-1} (C-O-C). ^1H NMR ($CDCl_3$): δ 5.76 (t, 1H, H-1′, $J_{1',2'} = 9.0$ Hz), 4.93 (t, 1H, H-2′), 5.15 (t, 1H, H-3′, $J_{3',4'} = 9.0$ Hz), 3.24−4.21 (m, 4H, H-4′, H-5′, H-6′ and H-6″), 1.87, 1,89, 1.94 and 1.96 (4s, 3H, each 3H, 4 Ac), 11.15(br s, 1H , CONH), 6.41 (d, 1H, NH, $J_{1'}$,NH = 8.3 Hz),9.75 (br s., 1H, N′H), 8.32 (d, 1H, H-5 of quinaz.), 7.89 (t, 1H, H-6 of quinaz.), 7.45(t, 1H, H-7 of quinaz.) and 7.24(d, 1H, H-8 of quinaz.).

Anal. Calcd. for $C_{23}H_{26}N_4O_{11}S$: C, 48.76; H, 4.59; N, 9.89. Found: C, 48.36; H, 4.71; N, 9.61.

N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N*′-2-[β-(3-phenyl-4-oxoquinazolin-2-yl)thioethyl]thiourea (11)

A mixture of **2a** (0.39 g, 0.001 mole) and 2-(β-aminoethyl)-3-phenyl-4(*3H*)quinazolinone (7) (0.297 g, 0.001 mole) in dry xylene (100 mL) was heated on a water bath (at 60−70°C) for 8 h and allowed to stand at room temperature for 2 h. After collection of the separated crystals by filtration, the product was crystallized from benzene. Yield (0.52 g, 75%), m.p. 140−141°C. IR (KBr): 3354 (NH), 1752 (C=O, ester), 1687 (C=O of quinaz.), 1228 (C=S), 1223(C-O-C) and 2927 (CH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.65 (t, 1H, H-1′, $J_{1',2'} = 9.2$ Hz), 5.05 (t, 1H, H-2′), 5.21(t, 1H, H-3′), 3.82−4.80(m, 4H, H-4′, H-5′, H-6′ and H-6″) 2.00, 2,04, 2.06 and 2.07(4s, each 3H, 4 Ac), 6.49(d, 1H, NH, $J_{1'}$,NH = 8.7 Hz), 7.29 (br s., 1H, N′H), 8.33 (d, 1H, H-5 of quinaz.), 7.73(t, 1H, H-6 of quinaz.), 7.56(t, 1H, H-7 of quinaz.), 7.31-7.41(m, 6 H, H-8 and of Ph), 4.17(q, 2H, N-CH_2) and 3.25(q, 2H, -SCH_2). ^{13}C NMR (DMSO-d_6): δ 82.4(β C-1′), 170.8, 169.8, 167.5 and 165.8 (4 C=O), 20.5, 20.6, 20,6 and 20.8 (4 CH_3), 183.5 (C=S), 70.7, 72.8, 68.3, 72.3 and 61.8 (C-2′, C-3′, C-4′, C-5′ and C-6′ of glucosyl residue, respectively), 157.5, 161.8, 119.8, 129.7, 130.1, 135.2, 126.1 and 147.4 (C-2, C-4, C-4a, C-5, C-6, C-7, C-8 and C-8a of quinaz., respectively), 129.8 (2C, C-2,6 of Ph), 126.4(2C,C-3,5 of Ph), 128.9 (C-4 of Ph), 135.2(C-1 of ph), 31.1 (-SCH_2) and 40.6 (-$NHCH_2$). FAB mass spectrum: m/z 709 (7.59, M + Na), 687 (83.54, M + 1), 655

(11.39, 687-S), 433 (100, $C_{17}H_{25}N_2O_9S^+$), 356 (2.53, thiourea moiety, $C_{17}H_{16}N_4OS_2^+$), 340 (33.54, 356-NH2), 297 (8.86, 356-NHCS), 281 (29.74, 297-NH_2), 253 (18.35, 281 - C_2H_4), 221 (20.25, 253 -S), 145 (14.55, 221-Ph), 331 (7.59, glucosyl moiety), 271 (3.79, 331-AcOH), 229 (4.43, 271-CH_2CO), 169 (62.02, 229-AcOH), 109 (72.15, 169-AcOH), 187 (4.40, 229-CH2CO), 127 (29.74, 187-AcOH) and 60 (45.80, AcOH).

Anal. Calcd for $C_{31}H_{34}N_4O_{10}S_2$: C, 54.23; H, 4.96; N, 8.16. Found: C, 54.31; H, 5.32;N, 8.51

N-(β-D-Galactopyranosyl)-*N*′-[4-(6-bromo-2-methyl-4-oxoquinazolin-3-yl) phenyl] thiourea(12)

To a suspension of **3c** (1.14 g, 0.002 mole) in absolute methanol (25 mL), 0.6 mL of 1 M sodium methoxide was added, and the reaction mixture stirred over night. The clear solution was neutralized with Dowex 50 (H^+) filtered, concentrated to dryness, and freeze-dried. The solid foam obtained was crystallized from ethanol to give 0.44 g (40% Yield) of deacetylated product **12,** m.p. 172−173°C. IR (KBr): 3300−3060 (NH, OH), 1665 (C=O quinaz.) and 1226 (C=S) cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.25 (t, 1H, H-1′, $J_{1',2'} = 8.3$ Hz), 3.30−5.22 (m, 6H, galactosyl protons), 10.56 (d, 1H, NH), 11.81(br s, 1H, N′H), 8.52 (d, 1H, H-5 of quinaz.), 7.25−8.21 (m, 6H, H-7, H-8 of quinaz. and Ph) and 2.18 (s, 3H, CH_3). ^{13}C NMR(DMSO-d_6): δ 84.1(β C-1′), 72.6, 77.5, 69.8, 78.1 and 60.8 (C-2′, C-3′, C-4′, C-5′ and C-6′, respectively), 182.0 (C=S), 145.5, 167.4, 128.9, 120,9, 134.1,122.9, 128.9 and 135.49 (C-2, C-4, C-4a, C-5, C-6, C-7, C-8 and C-8a of quinaz., respectively), 134.5 (C-1, of Ph), 126.9 (C-2,6 of Ph), 129.8 (C-3 of Ph), 139.1(C-4 of Ph) and 22.8 (CH_3).

Anal. Calcd. for $C_{22}H_{23}BrN_4O_6S$: C, 47.91; H, 4.17; N, 10.16. Found: C, 47.61; H, 4.31; N, 10.61.

N-(β-D-Glucopyranosyl)-*N*′-[3-(2-phenyl-4-oxoquinazolin-3-yl)] thiourea (13)

Compound **13** was obtained similarly to compound **12** from compound **10** (1.25 g, 0.002 mole) and sodium methoxide in methanol to give 0.48 g (52% yield) of compound 13, m.p. 119−120°C. IR(KBr): 3061−3268 (NH,OH), 1687 (C=O quinaz.) and 1228 (C=S) cm^{-1}. ^1H HNMR (DMSO-d_6): δ 5.46 (t,1H, H-1′, $J_{1',2'} = 7.5$ Hz), 3.18−5.15 (m, 6H, glucosyl protons), 6.77 (d, 1H, NH), 9.23 (brs, 1H, N′H) and 7.47−8.30 (m, 9 H, quinaz. and Ph protons).

Anal.Calcd. for $C_{21}H_{22}N_4O_6S$: C, 55.02; H, 4.80; N, 12.22. Found: C, 55.12; H, 4.79; N, 12.02.

Attempted Ring of Closure of Compound 9

A mixture of compound **9** (0.63 g, 0.001 mole) and methyl cyanoacetate (0.099 g, 0.001 mole) in acetic anhydride (10 mL) was heated at reflux for 3 h and poured onto ice water (100 mL). The reaction mixture was extracted with chloroform (50 mL). The organic layer was washed with saturated solution of sodium bicarbonate and dried over anhydrous $MgSO_4$. Removal of the solvent by evaporation left a brown residue. Ether was added to the residue and the separated crystals were collected by filtration. They were identified with starting material **2a.** The filtrate was concentrated under reduced pressure to give 0.11 g (77%) yield of N^3-acetylamino-2-phenyl-4(*3H*)-quinazolinone **15,** m.p. 112−113°C (lit.[36] m.p 112−113°C).

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