Synthesis of Novel Thioglycoside Derivatives Containing Quinazolinone

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A series of novel thioglycoside derivatives containing 4(3*H*)-quinazolinone was designed and synthesized from 2-chloromethyl-quinazolin-4(3*H*)-ones and 1-thioglycose. Several 2-chloromethyl-quinazolin-4(3*H*)-ones were synthesized on refluxing with 2-(chloroacetylamino)-benzoic acid and arylamines in acetonitrile. All of the novel compounds were characterized by IR, ^{1}H NMR spectra and elemental analysis. The structures of compounds **7b**, **8b** and **8c** have been determined by X-ray diffraction analysis.

Keywords: 4(3*H*)-Quinazolinone; Thioglycoside; 1-Thioglycose; X-ray diffraction.

INTRODUCTION

Thioglycosides have received considerable attention in carbohydrate chemistry and carbohydrate biology, because they are widely employed as biological inhibitors, inducers and ligands for affinity chromatography of carbohydrate-processing enzymes and proteins. [1,2] Among glycosyl donors, thioglycosides are widely used owing to their high degree of stability in many reaction conditions.[3]

Quinazoline compounds are reported to have physiological and pharmacological activities and applications in the treatment of several diseases such as leprosy and mental disorders and also exhibit a wide range of activities, such as antileukemic, anticonvulsant, antitumor, antimicrobial, and anti-inflammatory activities.[4~9] A well known methaquolone[10]-containing quinazoline group are sedative and hypnotic drugs and have been reported to possess anticonvulsant activity. Recently, several scientists elucidated that a quinazoline nucleus possesses variable sites at positions 2 and 3 which can be suitably modified by the introduction of some active groups to yield the quinazolinone compounds in possession of higher activity.[11]

Thus, 2-chloromethyl-quinazolin-4(3*H*)-one was linked with 1-thioglycose generating novel thioglycosides derivatives containing quinazolinone which may possess higher biological activity. The synthetic route of these compounds is shown in Scheme I.

RESULTS AND DISCUSSION

The synthetic route of 2,3-disubstituted quinazolin-4(3*H*)-ones is summarized in Scheme I. The anthranilic acid **3** was linked with chloroaectyl chloride generating **4**, which underwent cyclization by treatment with boiling acetic anhydride to form the intermediate benzoxazin-4-one **5**. In our experiment, the benzoxazinone by treatment with arylamines **6a**-**6d** yielded the benzamide derivatives **7a**-**7d**. But the benzoxazinone reacted with *o*-toluidine (**6e**) produced the quinazolinone **8e** directly. The IR spectra of **7a**-**7d** showed a band at about 3300 cm^{-1} and ^{1}H NMR spectra showed a peak about δ 11.10, exhibiting that a N–H band existed in **7a**-**7d**. Moreover a single crystal of **7b** was obtained; fortunately, furthermore, X-ray diffraction confirmed the structure of *O*-benzamidobenzanilide. Errede reported[12] *O*-benzamidobenzanilide at a fusion temperature of about 250 °C for conversion to the corresponding quinazolones; in order to avoid the various products from competing reactions, we chose the reagents Ac_2O/H_2SO_4 for our investigations, and the expected product quinazolones have been obtained successfully. The benzamide derivatives **7a**-**7d** were converted to quinazolinone products **8a**-**8d** by heating in acetic acid and concentrated sulfuric acid (9:1) at 100 °C for 3 hours. In addition, the cyclization of anthranilic acid **4** with arylamine **6a**-**6e** led to quinazolone **8a**-**8e** in 3 equiv of PCl_3/CH_3CN at 70 °C. Some re-

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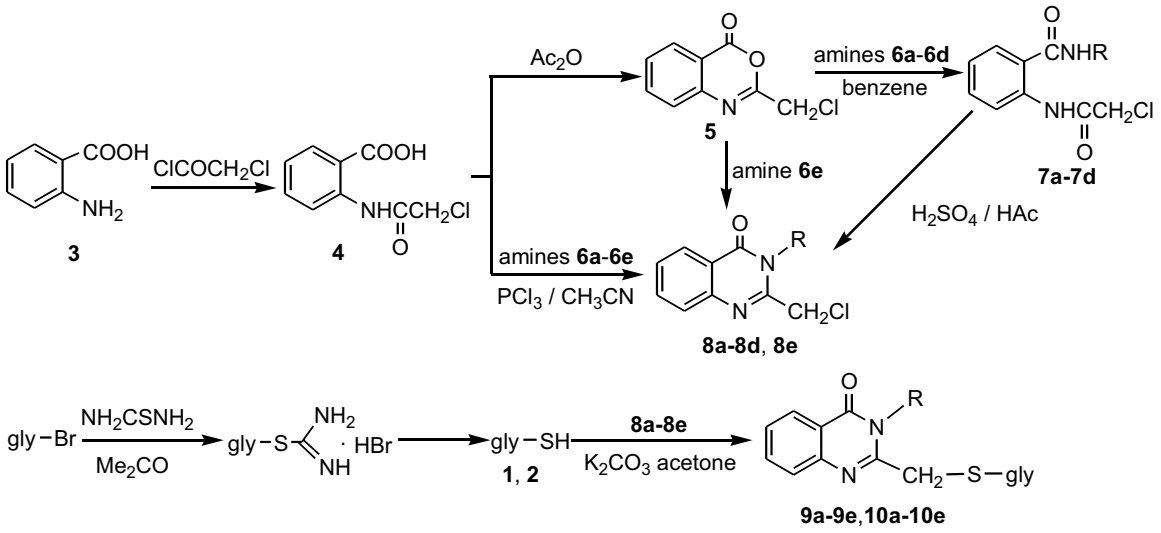
Scheme I



R: **a** C_6H_5; **b** *p*-$C_6H_4CH_3$; **c** *p*-$C_6H_4OCH_3$; **d** *p*-C_6H_4Cl; **e** *o*-$C_6H_4CH_3$

gly: **1**, **9** 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; **2**, **10**: 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl

searchers have reported that benzooxazinones refluxing with amines in toluene gave a mixture of uncyclized diamides and quinazolinones,[13] and when benzooxazinone reacted with primary amine, there were two competitive reactions; at temperatures below 150 °C the major product was *O*-benzamidobenzanilide.[12]

The intermediates **1** and **2** are easily prepared from their corresponding glycosyl bromides, followed by reaction with **8** in the system of K_2CO_3/acetone at room temperature, and the target compounds **9**, **10** were smoothly afforded in mild conditions.

Crystals of the compounds **7b**, **8b** and **8c** suitable for single crystal X-ray analysis were obtained from slow evaporation of an ethanol solution at room temperature. The structures of all the complexes were determined by direct method procedures in SHELXS-97. The structures of **7b**, **8b** and **8c** are shown in Figs. 1~3.

In Fig. 3a, there were intramolecular hydrogen bonds and intermolecular hydrogen bonds in the compound **7b** because of having an N–H bond.

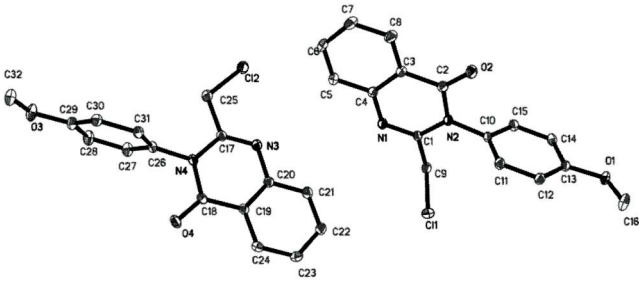


Fig. 1a. Molecular stereo configuration for compound **8b**.

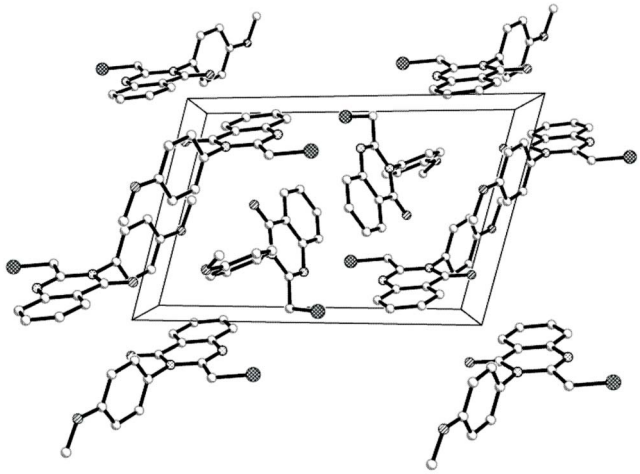


Fig. 1b. A view of the crystal packing down an axis for compound **8b**.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-S3 micro melting point apparatus and are corrected. The IR spectra were recorded as KBr pellets on a Bruker FT-IR Equinox 55 instrument. The ^{1}H NMR spectra were recorded on an Inova 400 (using TMS as the internal stan-

dard, with chemical shifts expressed in δ-units in $CDCl_3$ as solvent). Elemental analyses were performed on a Thermo Flash EA-1112 elemental analyzer. Analytical thin-layer chromatography (TLC) was performed on silica gel GF_{254} (Qingdao, China) with ethyl acetate and light petroleum (fraction boiling in the range of 60~90 ºC) and detection by UV light or iodine vapor. All reagents were commercial products of analytical grade and were used directly without processing unless otherwise specified. X-ray single-crystal diffraction was recorded on a R-AXIS SPIDER X-ray diffractometer.

1. Synthesis of intermediates

1.1 Synthesis of per-*O*-acetyl-thioglycoses 1~2 according to a reported method[14]

1: yield: 54%, m.p. 113~114 °C, lit[14] m.p. 114~115 °C.

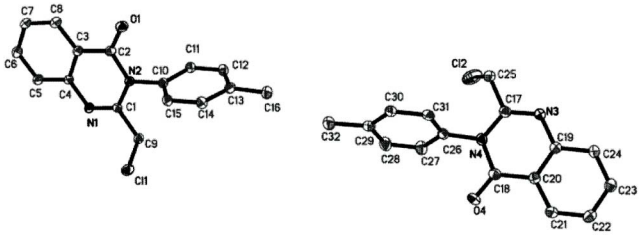


Fig. 2a. Molecular stereo configuration for compound **8c**.

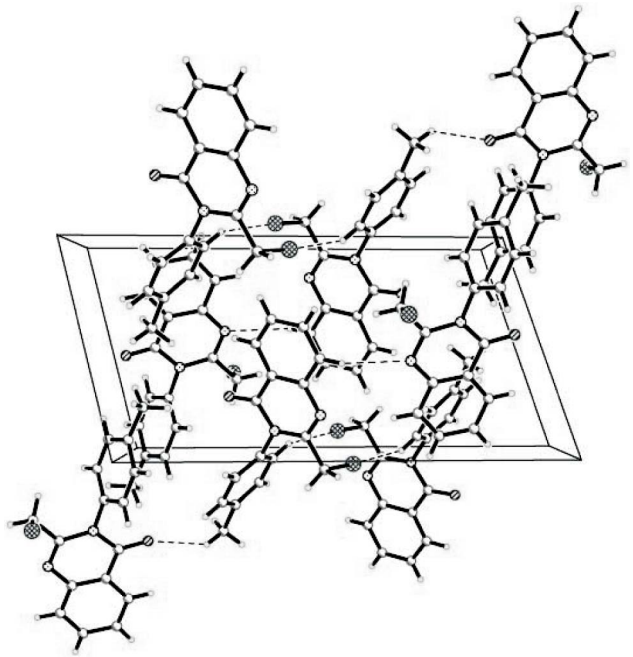


Fig. 2b. A view of the crystal packing down an axis for compound **8c**.

2: yield: 43%, m.p. 131~133 °C.

1.2 Compound 4 was prepared according to a reported method[15]

4: yield 87%, m.p. 183~185 ºC, lit[16] m.p. 186~188 ºC.

1.3 Compound 5 was prepared according to a reported method[16]

5: yield 93%, m.p. 93~94 ºC, lit[16] m.p. 95 ºC.

2. General procedure for the preparation of 2-(cholomethyl)-3-aryl-4(3*H*)-quinazolinone

Method 1

Mixtures of the benzoxazinone **5** (5 mmol), arylamines **6a**-**6d** (5.05 mmol) and dry benzene (30 mL) were stirred for 0.5~4 h at room temperature. Then, the mixtures were refluxed for 0.5~4 h in an apparatus equipped with a water separator. The clear solution obtained in the series was evaporated to dryness at reduced pressure. The residue was crystallized from ethanol.

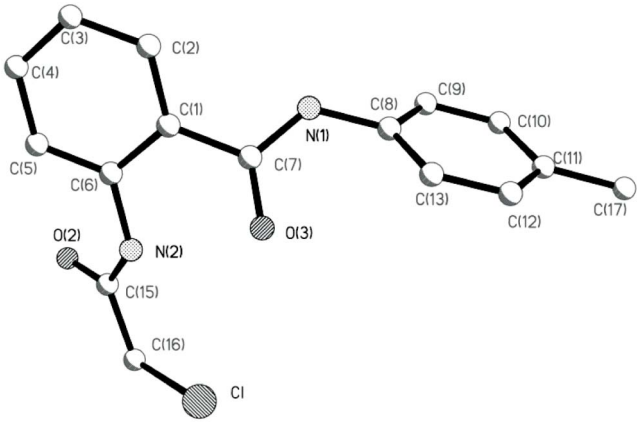


Fig. 3a. Molecular stereo configuration for compound **7b**.

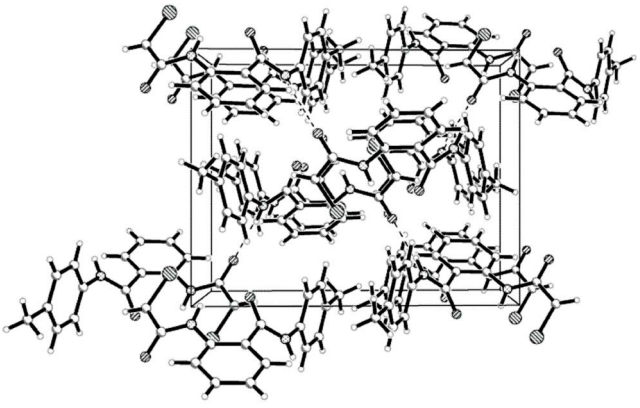


Fig. 3b. A view of the crystal packing down an axis for compound **7b**.

7a: colourless acicular crystal, yield: 54%, m.p. 187~189 ºC;

7b: colourless block crystal, yield: 50%, m.p. 168~170 ºC;

7c: colourless acicular crystal, yield: 43%, m.p. 212~214 ºC;

7d: colourless acicular crystal, yield: 38%, m.p. 182~183 ºC.

To a solution of compounds **7a~7d** in ethanol was added acetic acid and concentrated sulfuric acid (9:1), and the resultant mixture was heated at 100°C for 15 min. The mixture was cooled to room temperature and diluted with ice water. 100 mL $CHCl_3$ was added. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, and evaporated under vacuum to give oily products, which crystallized on standing. The crude products **8a~8d** were recrystallized from ethanol.

Method 2

To a solution of the acetylanthranilic acid (5 mmol) in CH_3CN (15 mL) was added a solution of the aniline (5 mmol) in CH_3CN (15 mL) at room temperature to give a white suspension. 15 mmol PCl_3 was added, and the resultant mixture was heated to 70 °C for 5 h. The mixture was cooled to room temperature and diluted with ice water. 100 mL $CHCl_3$ was added. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, and evaporated under vacuum to give an oil, which crystallized on standing. The crude products were recrystallized from ethanol.[17]

8a: yield: 60%, m.p. 155~156 °C, lit[18] m.p. 152~154 ºC, colourless block crystal.

8b: yield: 40%, m.p. 173~175 °C, colourless block crystal. ^{1}H NMR (400 MHz, $CDCl_3$), 7.23~8.30 (m, 8H), 4.29 (s, 2H, CH_2Cl_2), 2.26 (s, 3H, CH_3). Anal. calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84; found C, 67.63; H, 4.57; N, 9.87.

8c: yield: 43%, m.p. 138~140 °C, colourless block crystal. ^{1}H NMR (400 MHz, $CDCl_3$), 7.10~8.30 (m, 8H), 4.29 (s, 2H, CH_2Cl_2), 3.89 (s, 3H, CH_3). Anal. calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31; found C, 64.01; H, 4.38; N, 9.34.

8d: yield: 41%, m.p. 178~180 °C, colourless crystal. ^{1}H NMR (400 MHz, $CDCl_3$), 7.12~8.30 (m, 8H), 4.32 (s, 2H, CH_2Cl_2). Anal. calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18; found C, 59.16; H, 3.29; N, 9.22.

8e: yield: 61%, m.p. 107~108 °C, lit[18] m.p. 103~105 ºC, colourless acicular crystal.

3. Synthesis of thioglycosides derivatives 9a~9e and 10a~10e

To a well-stirred suspension of K_2CO_3 (0.2 g) in acetone (20 mL) were added sequentially 1-thio-glycose (1 mmol), quinazolinone derivatives (1 mmol) and H_2O (0.1 mL). The resultant mixture was stirred at r.t for 3~4 h, diluted with CH_2Cl_2 (20 mL), filtered, and the solution was evaporated. The expected compound was isolated by crystallization from EtOH/H_2O.

9a: syrup, yield: 75%, R_f = 0.43, ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.97, 1.99, 2.00, 2.03 (3s, 12H, 4 × $COCH_3$), 3.52~3.56 (m, 1H, sugar ring-H-5), 3.57 (d, J = 14 Hz, 1H, SCH_a), 3.68 (d×d, $J_{6,6'}$ = 12.4 Hz, $J_{6,5}$ = 1.2 Hz, 1H, H-6), 3.74 (d, J = 14 Hz, 1H, SCH_b), 3.98 (d×d, $J_{6',6}$ = 12.4 Hz, $J_{6',5}$ = 4.8 Hz, 1H, H-6′), 4.80~5.07 (m, 3H, sugar ring-H), 5.18 (t, J = 9.2 Hz, 1H, C_1-H), 7.00~7.45 (m, 5H, ArH), 7.50~8.28 (m, 4H, quinazolinon-H). Anal. calcd for $C_{29}H_{30}N_2O_{10}S$; C, 58.19; H, 5.05; N, 4.68; found C, 58.29; H, 5.03; N, 4.70.

9b: white solid, yield: 87%, m.p. 170~171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.96, 1.98, 2.00, 2.02 (3s, 12H, 4 × $COCH_3$), 2.43 (s, 3H, CH_3), 3.51~3.58 (m, 1H, sugar ring-H-5), 3.54 (d, J = 14 Hz, SCH_a), 3.65 (d×d, $J_{6,6'}$ = 12.4 Hz, $J_{6,5}$ = 1.2 Hz, 1H, H-6), 3.75 (d, J = 14 Hz, 1H, SCH_b), 3.94 (d×d, $J_{6',6}$ = 12.4 Hz, $J_{6',5}$ = 4.8 Hz, 1H, H-6′), 4.80~5.07 (m, 3H, sugar ring-H), 5.19 (t, J = 9.2 Hz, 1H, C_1-H), 7.05~7.32 (m, 4H, ArH), 7.51~8.28 (m, 4H, quinazolinon-H). Anal. calcd for $C_{30}H_{32}N_2O_{10}S$: C, 58.81; H, 5.26; N, 4.57; found C, 58.70; H, 5.24; N, 4.59.

9c: white solid, yield: 67%, m.p. 182~183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.98, 1.98, 1.99, 2.02 (3s, 12H, 4 × $COCH_3$), 3.53~3.57 (m, 1H, sugar ring-H-5), 3.58 (d, J = 14 Hz, 1H, SCH_a), 3.66 (d×d, $J_{6,6}$ = 12.4 Hz, $J_{6,5}$ = 1.2 Hz, 1H, H-6), 3.73 (d, J = 14 Hz, 1H, SCH_b), 3.88 (s, 3H, OCH_3), 3.96 (d×d, $J_{6',6}$ = 12.4 Hz, $J_{6',5}$ = 4.8 Hz, 1H, H-6′), 4.81~5.05 (m, 3H, sugar ring-H), 5.17 (t, J = 9.2 Hz, 1H, C1-H), 7.02~7.28 (m, 4H, ArH), 7.52~8.29 (m, 4H, quinazolinon-H). Anal. calcd for $C_{30}H_{32}N_2O_{11}S$: C, 57.32; H, 5.13; N, 4.46; found C, 57.43; H, 5.11; N, 4.68.

9d: white solid, yield: 48%, m.p. 184~186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.97, 1.99, 2.01, 2.04 (3s, 12H, 4 × $COCH_3$), 3.50~3.56 (m, 1H, sugar ring-H-5), 3.57 (d, J = 14.0 Hz, 1H, SCH_a), 3.67 (d×d, $J_{6,6'}$ = 12.4 Hz, $J_{6,5}$ = 1.2 Hz, 1H, H-6), 3.74 (d, J = 14.0 Hz, 1H, SCH_b), 3.94 (d×d, $J_{6',6}$ = 12.4 Hz, $J_{6',5}$ = 4.8 Hz, 1H, H-6′), 4.80~5.07 (m, 3H, sugar ring-H), 5.16 (t, J = 9.2 Hz, 1H, C_1-H), 7.21~7.47 (m, 4H, ArH), 7.50~8.27 (m, 4H, quinazo-

linon-H). Anal. calcd for $C_{29}H_{29}ClN_2O_{10}S$: C, 55.02; H, 4.62; N, 4.43; found C, 55.13; H, 4.64; N, 4.45.

9e: white solid, yield: 79%, m.p. 84~86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.97, 1.99, 2.02, 2.04 (3s, 12H, 4 × $COCH_3$), 2.38 (s, 3H, CH_3), 3.51~3.55 (m, 1H, sugar ring-H-5), 3.59 (d, J = 14.0 Hz, 1H, SCH_a), 3.67 (d×d, $J_{6,6'}$ = 12.4 Hz, $J_{6,5}$ = 1.2 Hz, 1H, H-6), 3.72 (d, J = 14.0 Hz, 1H, SCH_b), 3.95 (d×d, $J_{6',6}$ = 12.4 Hz, $J_{6',5}$ = 4.8 Hz, 1H, H-6′), 4.80~5.07 (m, 3H, sugar ring-H), 5.16 (t, J = 9.2 Hz, 1H, C_1-H), 7.03~7.31 (m, 4H, ArH), 7.49~8.28 (m, 4H, quinazolinon-H). Anal. calcd for $C_{30}H_{32}N_2O_{10}S$: C, 58.81; H, 5.26; N, 4.57; found C, 58.70; H, 5.28; N, 4.55.

10a: white solid, yield: 60%, m.p. 194~195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.98, 2.01, 2.02 (3s, 9H, 3 × $COCH_3$), 3.50~3.58 (t, 1H, sugar ring-H-5), 3.60 (d, J = 14.0 Hz, 1H, SCH_a), 3.74 (d, J = 14.0 Hz, 1H, SCH_b), 3.98 (d×d, 1H, sugar ring-H-5′), 4.78~4.90 (m, 3H, sugar ring-H), 5.18 (t, J = 8.0 Hz, 1H, C_1-H), 7.16~7.36 (m, 5H, ArH), 7.50~8.29 (m, 4H, quinazolinon-H). Anal. calcd for $C_{26}H_{26}N_2O_8S$: C, 59.31; H, 4.98; N, 5.32; found C, 59.43; H, 5.00; N, 4.30.

10b: white solid, yield: 49%, m.p. 158~159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 2.00, 2.02, 2.03 (3s, 9H, 3 × $COCH_3$), 2.45 (s, 3H, CH_3), 3.53~3.57 (t, 1H, sugar ring-H-5), 3.59 (d, J = 14.0 Hz, 1H, SCH_a), 3.73 (d, J = 14.0 Hz, 1H, SCH_b), 4.00 (d×d, 1H, sugar ring-H-5′), 4.80~4.91 (m, 3H, sugar ring-H), 5.12 (t, J = 8.0 Hz, 1H, C_1-H), 7.17~7.35 (m, 4H, ArH), 7.51~8.28 (m, 4H, quinazolinon-H). Anal. calcd for $C_{27}H_{28}N_2O_8S$: C, 59.99; H, 5.22; N, 5.18; found C, 59.87; H, 5.24; N, 5.16.

10c: white solid, yield: 61%, m.p. 191~192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00, 2.01, 2.04 (3s, 9H, 3 × $COCH_3$), 3.53~3.57 (t, 1H, sugar ring-H-5), 3.60 (d, J = 14.0 Hz, H, SCH_a), 3.74 (d, J = 14.0 Hz, H, SCH_b), 3.78 (s, 3H, OCH_3), 4.01 (d×d, 1H, sugar ring-H-5′), 4.83~4.91 (m, 3H, sugar ring-H), 5.10 (t, J = 8.0 Hz, 1H, C_1-H), 7.16~7.37 (m, 4H, ArH), 7.50~8.30 (m, 4H, quinazolinon-H). Anal. calcd for $C_{27}H_{28}N_2O_9S$: C, 58.26; H, 5.07; N, 5.03; found C, 58.14; H, 5.09; N, 5.05.

10d: white solid, yield: 57%, m.p. 149~150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.99, 2.01, 2.04 (3s, 9H, 3 × $COCH_3$), 3.50~3.56 (m, 1H, sugar ring-H-5), 3.57 (d, J = 14.0 Hz, 1H, SCH_a), 3.74 (d, J = 14.0 Hz, 1H, SCH_b), 4.02 (d×d, 1H, sugar ring-H-5′), 4.81~5.07 (m, 3H, sugar ring-H), 5.16 (t, J = 8.0 Hz, 1H, C_1-H), 7.21~7.47 (m, 4H, ArH), 7.50~8.27 (m, 4H, quinazolinon-H). Anal. calcd for $C_{26}H_{25}ClN_2O_8S$: C, 55.66; H, 4.49; N, 4.99; found C, 55.55; H, 5.01; N, 5.00.

10e: white solid, yield: 46%, m.p. 148~150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.97, 2.00, 2.03 (3s, 9H, 3 × $COCH_3$), 2.44 (s, 3H, CH_3), 3.53~3.58 (m, 1H, sugar ring-H-5), 3.60 (d, J = 14.0 Hz, 1H, SCH_a), 3.73 (d, J = 14.0 Hz, 1H, SCH_b), 4.01 (d×d, 1H, sugar ring-H-5′), 4.75~4.90 (m, 3H, sugar ring-H), 5.14 (t, J = 8.0 Hz, 1H, C_1-H), 7.14~7.36 (m, 4H, ArH), 7.49~8.30 (m, 4H, quinazolinon-H). Anal. calcd for $C_{27}H_{28}N_2O_8S$: C, 59.99; H, 5.22; N, 5.18; found C, 59.87; H, 5.20; N, 5.16.

ACKNOWLEDGEMENT

This work was supported by the National Natural Science Foundation of China (Grant No. 20462006) and Xinjiang Key Laboratory of Plant Resources & Natural Products Chemistry.

SUPPLEMENTARY DATA

Complete crystallographic data for the structural analysis of compounds **7b**, **8b** and **8c** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 689057, 693620, and 693621, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (telephone: +44-01223-762910, facsimile: +44-01223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). Supplementary data (tables containing selected bond lengths and bond angles for compound 1) associated with this article can be found in the online version, at http://www.ccdc.cam.ac. uk /deposit.

Received November 14, 2008.

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