Preparation of Quinoline Hexose Analogs as Novel Chloroquine-Resistant Malaria Treatments (1). Synthesis of 4-Hydroxyquinoline-β-glucosides

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Quinoline hexose analogs are expected to be useful as novel agents for treatment of chloroquine-resistant malaria. Here, we report preparation of 4-hydroxy quinoline-β-glucosides from anilines in 4 steps.

Key words malaria; chloroquine-resistant malaria treatment; quinoline-glucosides

Malaria is one of the most serious infectious diseases in the developing world, with mortality estimated at *ca.* 2.5 million deaths annually, mainly caused by the erythrocytic-stage cells of *Plasmodium falciparum*.[1)] For four decades, malaria has been treated effectively with the 4-aminoquinoline analog chloroquine (CQ). However, CQ-resistant strains of *Plasmodium* spp. have spread and continue to evolve.[1)] Therefore, the development of new chemotherapeutic agents that are effective against CQ-resistant malaria is required.

Malaria parasites are known to take up hemoglobin in their food vacuole as a source of amino acids and release ferriprotoporphyrin IX (FP IX) into the food vacuole and cytoplasm in the erythrocytic stage.[2)] FP IX is very toxic to *Plasmodium* spp., which explains why they have detoxification systems to deal with this complex.[2)] The parasite's food vacuole is acidic, and so CQ accumulates in the vacuole due to its basic quinoline moiety.[2)] CQ is thought to inhibit detoxification of FP IX in the food vacuole by forming a complex between the quinolinic nitrogen of CQ and Fe(II) of FP IX.[2)] Various mechanisms have been proposed to explain CQ resistance, but none have been proven conclusively.[3)] All of the proposed mechanisms of CQ resistance have several points in common: (1) the concentration of CQ in the food vacuole of CQ-resistant strains is lower than that in CQ-sensitive strains, and (2) CQ-resistance is reversible because CQ-resistant strains can recover CQ sensitivity under some conditions.[3)] In this context, quinoline analogs that can be concentrated in the cytoplasm of malaria parasites may be suitable as novel chemotherapeutic candidates against CQ-resistant malaria because they would facilitate maintenance of a high concentration of quinoline in the food vacuole by osmosis, and the detoxification of FP IX in the cytoplasm can be inhibited.

Metabolism and transport of carbohydrates are essential for cell viability. Carbohydrates are transported into the cell through hexose transporters (HTPs), which are membrane proteins expressed on the cell surface.[4)] Furthermore, HTPs transport hexose analogs, such as glycosides.[5)] These molecules can be utilized as novel drug delivery systems (DDS) that can act as carriers and import medicines efficiently into the cell through HTPs.

Malaria parasites have a high demand for carbohydrates in the erythrocytic stage and often cause hypoglycemia.[6)] Accordingly, quinoline hexose analogs can be expected to concentrate quinolines into the cytoplasm of the malaria parasite by the above DDS and serve as novel chemotherapeutic candidates for treatment of CQ-resistant malaria. Here, we report the synthesis of quinoline-β-glucosides in a systematic preparation of quinoline hexose analogs.

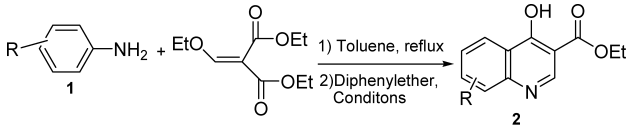
Results and Discussion

The target compounds **5a**—**f** were prepared from the corresponding anilines (**1a**—**f**) in 4 steps shown in Charts 1, 2, 3, and 4.

As shown in Chart 1, 4-hydroxyquinoline-3-ethylesters **2a**—**f** were prepared from the corresponding anilines **1a**—**f** by a modification of the method of Price and co-workers[7)] in the yields shown.

Hydrolysis of **2a**—**f** with 2 N-sodium hydroxide at room temperature for 2 h afforded the corresponding crude quinoline carbonic acids, which were then heated in diphenylether under reflux. The decarboxylation described above gave compounds **3a**—**f** in the yields shown in Chart 2.

The quinoline ring is generally sensitive to reductive conditions. The benzyl group is considered unsuitable as a protecting group in quinoline glucosides, because the deprotection reaction requires reductive conditions. Therefore, the acetyl group was adopted for protection of the hydroxyl group of D-glucose. 1-Bromo-tetraacetyl-α-D-glucose was prepared from pentaacetyl-D-glucose and 30%-hydrobromic acid in acetic acid solution.[8)] The reaction conditions were determined by using 4-hydroxyquinoline (**3g**) and 7-chloro-4-hydoxyquinoline (**3h**), both of which were commercial



		Conditions	Yield (%)
1a R=4-Me-	**1a** R=6-Me-	reflux, 1 h	45
1b R=4-MeO-	**1b** R=6-MeO-	reflux, 1 h	36
1c R=3-MeO-	**1c** R=7-MeO-	230°C, 12 h	14
1d R=4-PhO-	**1d** R=6-PhO-	reflux, 1 h	30
1e R=4-Me_2N-	**1e** R=6-Me_2N-	reflux, 1 h	67
1f R=4-PhNH-	**1f** R=6-PhNH-	reflux, 2 h	35

Chart 1

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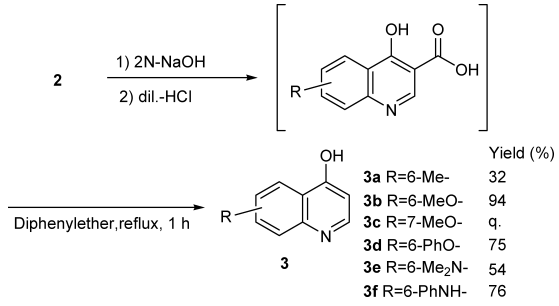

Chart 2

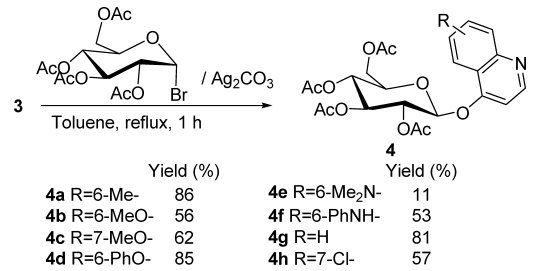

Chart 3

products. A mixture of **3**, 1-bromo-tetraacetyl-α-D-glucose, and 2-fold equiv. silver carbonate in toluene previously dehydrated by passage through molecular sieve 4A was heated under reflux for 1 h under a stream of argon gas. The reaction mixture was subjected to silica gel column chromatography with ethyl acetate as the eluent and afforded quinoline-β-glucoside tetraacetates **4**. Although unreacted **3** was recovered, the formation of α-anomers and glucoside-orthoesters was not confirmed in all cases, as shown in Chart 3. The low yield of **4e** was considered due to insolubility of **3e** in boiling toluene.

Deprotection of acetylated saccharides is generally performed with a strong base, such as sodium methoxide, sodium hydroxide, or potassium hydroxide. Deacetylation of **4** with sodium methoxide was carried out and the reaction mixture was neutralized with sulfuric acid. The workup had some problems: (1) large amounts of mineral salts were produced, and so it was not easy to isolate glucosides **5**, and (2) the reaction showed poor reproducibility. When an acidic ion-exchange resin was employed in the neutralization step, quinolinium salts were obtained. Therefore, deacetylation of **4** with a mineral base, such as sodium methoxide, was not useful. With the use of ammonia gas for deacetylation of **4**, acetamide is produced, which makes it difficult to separate to **5**. Therefore, deprotection of **4** with a basic ion-exchange resin was carried out. A mixture of **4** and a 2- or 3-fold excess of Amberlyst® A-26 (OH) by weight in methanol was stirred at RT. After 1—2 h, the disappearance of acetates **4** was determined by TLC. Use of an ion-exchange resin allowed separation without difficulty using only filtration. The precipitates thus produced were dissolved in methanol and the filtrates were combined. Evaporation of methanol afforded **5** in high yield, as shown in Chart 4.

With regard to anti-malarial activity, **5g** showed an EC_{50} value of 0.15 μg/ml in an *in vitro Plasmodium falciparum* culture system, which was almost the same value obtained with quinine used in commercial anti-malarial preparations.

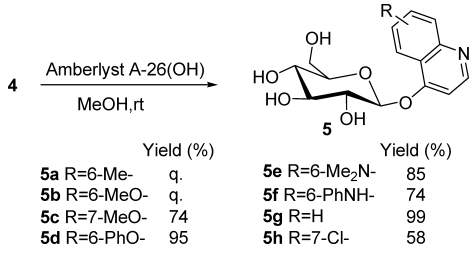

Chart 4

Anti-malarial assays of other **4** and **5** are currently underway and the results will be reported in a subsequent paper.

Experimental

The NMR spectra were obtained using a JEOL JNM-ECA 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded with a PE Biosystems QSTAR spectrometer. IR spectra were performed with a JASCO FT/IR-420 spectrometer.

Preparation of 2 Typical Procedure: A mixture of **1** (10.7 g, 100 mmol) and ethyl ethoxymethylenediethylmalonate (23.3 g, 110 mmol) in toluene (100 ml) was heated under reflux for 1 h and then evaporated *in vacuo*. Diphenylether (150 ml) was added to the residue and the mixture was heated under reflux for 1 h or heated at 130 °C, as shown in Chart 1. After the reaction mixture was cooled to room temperature, *n*-hexane was added and the precipitates thus produced were filtered. The filtrate was washed with ethyl acetate, which yielded **2a** (10.5 g, 45%). Compounds **2** were not subjected to further purification.

Preparation of 3 Typical Procedure: A mixture of **2a** (10.5 g) and 2 N-sodium hydroxide (100 ml) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and 2 N-hydrochloride was added until precipitates were produced. The precipitates were filtered, washed with water, and dried. The obtained quinoline carbonic acid was not purified further. Diphenylether (50 ml) was added to the colorless powder, and the mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and *n*-hexane was added. Compound **3a** (2.3 g, 32%) was obtained by filtration and washing with ethyl acetate.

Preparation of 4 Typical Procedure: A suspension of **3a** (548 mg, 3.44 mmol), 1-bromo-tetraacetyl-α-D-glucose (1.56 g, 3.79 mmol) and silver carbonate (1.24 g, 3.79 mmol) in toluene previously dehydrated by passage through molecular sieve 4A (25 ml) was heated under reflux for 1 h in a stream of argon gas and cooled to room temperature. The insoluble products were filtered off and the filtrate was evaporated *in vacuo*. Ethyl acetate was added to the residue. Compound **4a** (1.48 g, 86%) was obtained by silica gel column chromatography of the solution with ethyl acetate as the eluent.

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-6-methylquinoline (**4a**) as Colorless Needles (Diisopropylether) (86%): mp 175—177 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s), 2.06 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.57 (3H, s), 4.07 (1H, ddd, J=9.8, 5.3, 2.4 Hz), 4.22 (1H, dd, J=12.4, 2.4 Hz), 4.33 (1H, dd, J=12.4, 5.3 Hz), 5.25 (1H, dd, J=9.8, 9.4 Hz), 5.41 (1H, dd, J=9.4, 9.2 Hz), 5.44 (1H, d, J=7.6 Hz), 5.52 (1H, dd, J=9.2, 7.6 Hz), 7.00 (1H, d, J=5.2 Hz), 7.64 (1H, dd, J=8.6, 2.0 Hz), 7.88 (1H, d, J=2.0 Hz), 8.13 (1H, d, J=8.6 Hz), 8.75 (1H, d, J=5.2 Hz). IR (KBr) cm^{-1}: 1749. ESI-MS *m/z*: 512.1551 (Calcd for $C_{24}H_{27}NNaO_{10}$ $(M+Na)^+$: 512.1533).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-6-methoxyquinoline (**4b**) as Colorless Needles (Diisopropylether) (56%): mp 171—173 °C. ^{1}H-NMR (CD_3OD) δ: 2.02 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 3.95 (s, 3H), 4.21 (1H, dd, J=12.2, 2.3 Hz), 4.25 (1H, ddd, J=10.0, 4.9, 2.3 Hz), 4,35 (1H, dd, J=12.2, 4.9 Hz), 5.19 (1H, dd, J=10.0, 9.4 Hz), 5.41 (1H, dd, J=9.5, 7.7 Hz), 5.49 (1H, dd, J=9.5, 9.4 Hz), 5.70 (1H, d, J=7.7 Hz), 7.04 (1H, d, J=5.5 Hz), 7.23 (1H, dd, J=9.2, 2.5 Hz), 7.32 (1H, d, J=2.5 Hz), 7.98 (1H, d, J=9.2 Hz), 8.64 (1H, d, J=5.5 Hz). IR (KBr) cm^{-1}: 1742. ESI-MS *m/z*: 528.1484 (Calcd for $C_{24}H_{27}NNaO_{11}$ $(M+Na)^+$: 528.1482).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-7-methoxyquinoline (**4c**) as Colorless Needles (Diisopropylether) (62%): mp 170—172 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.07 (3H, s), 2.08 (6H, s), 3.96 (s, 3H), 4.08 (1H, ddd, J=10.1, 5.3, 2.3 Hz), 4,23 (1H, dd, J=12.5, 2.3 Hz), 4.36 (1H, dd, J=12.5, 5.3 Hz), 5.24 (1H, dd, J=10.1, 9.5 Hz), 5.43 (1H, d, J=7.6 Hz), 5.43 (1H, dd, J=9.5, 9.5 Hz), 5.54 (1H, dd, J=9.5, 7.6 Hz), 7.03 (1H, d, J=5.3 Hz), 7.39 (1H, d, J=2.8 Hz), 7.47 (1H, dd, J=9.1, 2.8 Hz), 8.22 (1H, d, J=9.1 Hz), 8.68 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 1742. ESI-MS *m/z*: 528.1485 (Calcd for

$C_{24}H_{27}NNaO_{11}$ $(M+Na)^+$: 528.1482).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-6-phenoxyquinoline (**4d**) as Colorless Needles (Diisopropylether) (85%): mp 136—138 °C. ^{1}H-NMR (CD_3OD) δ: 1.90 (3H, s), 2.00 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 4.22 (1H, dd, J=12.4, 2.3 Hz), 4.22 (1H, ddd, J=10.0, 4.9, 2.3 Hz), 4.32 (1H, dd, J=12.4, 4.9 Hz), 5.16 (1H, dd, J=10.0, 9.4 Hz), 5.28 (1H, dd, J=9.6, 7.8 Hz), 5.43 (1H, dd, J=9.6, 9.4 Hz), 5.65 (1H, d, J=7.8 Hz), 7.08 (2H, ddd, J=6.7, 2.0, 1.0 Hz), 7.14 (1H, d, J=5.3 Hz), 7.22 (1H, tt, J=7.4, 1.0 Hz), 7.43 (2H, ddd, J=7.4, 6.7, 2.0 Hz), 7.45 (1H, d, J=2.6 Hz), 7.53 (1H, dd, J=9.1, 2.6 Hz), 7.98 (1H, d, J=9.1 Hz), 8.64 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 1749. ESI-MS m/z: 590.1663 (Calcd for $C_{29}H_{29}NNaO_{11}$ $(M+Na)^+$: 590.1638).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-6-*N*,*N*-dimethylaminoquinoline (**4e**) as Ochre Needles (Diisopropylether) (11%): mp 167—169 °C. ^{1}H-NMR (CD_3OD) δ: 2.03 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 3.09 (6H, s), 4.25 (1H, dd, J=12.6, 2.3 Hz), 4.25 (1H, ddd, J=9.7, 5.2, 2.3 Hz), 4.36 (1H, dd, J=12.6, 5.2 Hz), 5.20 (1H, dd, J=9.7, 9.2 Hz), 5.43 (1H, dd, J=9.7, 7.4 Hz), 5.51 (1H, dd, J=9.7, 9.2 Hz), 5.61 (1H, d, J=7.4 Hz), 7.06 (1H, d, J=5.2 Hz), 7.04 (1H, d, J=2.9 Hz), 7.45 (1H, dd, J=9.7, 2.9 Hz), 7.81 (1H, d, J=9.7 Hz), 8.39 (1H, d, J=5.2 Hz). IR (KBr) cm^{-1}: 1743. ESI-MS m/z: 541.1812 (Calcd for $C_{25}H_{30}N_2NaO_{10}$ $(M+Na)^+$: 541.1798).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-6-*N*-phenylaminoquinoline (**4f**) as Pale Brown Needles (Diisopropylether) (53%): mp 167—169 °C. ^{1}H-NMR (CD_3OD) δ: 1.93 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 4.22 (1H, dd, J=12.4, 2.3 Hz), 4.22 (1H, ddd, J=9.8, 4.9, 2.3 Hz), 4.32 (1H, dd, J=12.4, 4.9 Hz), 5.16 (1H, dd, J=9.8, 9.6 Hz), 5.29 (1H, dd, J=9.5, 7.7 Hz), 5.44 (1H, dd, J=9.6, 9.5 Hz), 5.65 (1H, d, J=7.7 Hz), 6.98 (1H, tt, J=7.4, 1.1 Hz), 7.05 (1H, d, J=5.3 Hz), 7.24 (2H, ddd, J=7.7, 2.0, 1.1 Hz), 7.43 (2H, ddd, J=7.7, 7.4, 2.0 Hz), 7.48 (1H, dd, J=9.1, 2.5 Hz), 7.64 (1H, d, J=2.5 Hz), 7.81 (1H, d, J=9.1 Hz), 8.44 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 1748. ESI-MS m/z: 567.1995 (Calcd for $C_{29}H_{31}N_2O_{10}$ $(M+H)^+$: 567.1979).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-quinoline (**4g**) as Colorless Needles (Diisopropylether) (81%): mp 175—176 °C. ^{1}H-NMR (CD_3OD) δ: 2.02 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 4.22 (1H, dd, J=12.3, 2.3 Hz), 4.27 (1H, ddd, J=10.0, 4.9, 2.3 Hz), 4.36 (1H, dd, J=12.3, 4.9 Hz), 5.21 (1H, dd, J=10.0, 9.2 Hz), 5.44 (1H, dd, J=9.6, 7.7 Hz), 5.51 (1H, d, J=9.6, 9.2 Hz), 5.73 (1H, d, J=7.7 Hz), 7.17 (1H, d, J=5.3 Hz), 7.60 (1H, ddd, J=8.4, 7.0, 1.2 Hz), 7.79 (1H, ddd, J=8.5, 7.0, 1.4 Hz), 7.98 (1H, dd, J=8.5, 1.2 Hz), 8.10 (1H, dd, J=8.4, 1.4 Hz), 8.73 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 1752. ESI-MS m/z: 476.1559 ($C_{23}H_{26}NO_{10}$ $(M+H)^+$: 476.1551).

4-(β-*O*-Tetraacetyl-D-glucosyloxy)-7-chloroquinoline (**4h**) as Colorless Prisms and Colorless Needles (Diisopropylether) (58%): mp 136—138 °C (prisms) and 144—145 °C (needles). ^{1}H-NMR (CD_3OD) (prisms and needles) δ: 2.02 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 4.22 (1H, dd, J=12.3, 2.3 Hz), 4.26 (1H, ddd, J=10.0, 4.9, 2.3 Hz), 4.35 (1H, dd, J=12.3, 4.9 Hz), 5.21 (1H, dd, J=10.0, 9.2 Hz), 5.43 (1H, dd, J=9.6, 7.7 Hz), 5.50 (1H, dd, J=9.6, 9.2 Hz), 5.73 (1H, d, J=7.7 Hz), 7.18 (1H, d, J=5.3 Hz), 7.57 (1H, dd, J=9.0, 2.1 Hz), 7.97 (1H, d, J=2.1 Hz), 8.07 (1H, d, J=9.0 Hz), 8.75 (1H, d, J=5.3 Hz). ($CDCl_3$) (prisms) δ: 2.06 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.10 (3H, s), 4.15 (1H, ddd, J=10.0, 5.2, 2.3 Hz), 4.24 (1H, dd, J=12.6, 2.3 Hz), 4.35 (1H, dd, J=12.6, 5.2 Hz), 5.24 (1H, dd, J=10.0, 9.5 Hz), 5.45 (1H, dd, J=9.5, 9.2 Hz), 5.54 (1H, dd, J=9.2, 7.6 Hz), 5.62 (1H, d, J=7.6 Hz), 7.32 (1H, d, J=6.2 Hz), 7.73 (1H, dd, J=9.0, 1.9 Hz), 8.17 (1H, d, J=9.0 Hz), 8.65 (1H, d, J=1.9 Hz), 8.94 (1H, d, J=6.2 Hz). ($CDCl_3$) (needles) δ: 2.06 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.10 (3H, s), 4.13 (1H, ddd, J=10.0, 5.2, 2.2 Hz), 4.23 (1H, dd, J=12.6, 2.2 Hz), 4.34 (1H, dd, J=12.6, 5.2 Hz), 5.24 (1H, dd, J=10.0, 9.5 Hz), 5.44 (1H, dd, J=9.5, 8.9 Hz), 5.54 (1H, dd, J=8.9, 7.7 Hz), 5.58 (1H, d, J=7.7 Hz), 7.24 (1H, d, J=6.1 Hz), 7.69 (1H, dd, J=9.0, 1.6 Hz), 8.14 (1H, d, J=9.0 Hz), 8.55 (1H, d, J=1.6 Hz), 8.92 (1H, d, J=6.1 Hz). IR (KBr) cm^{-1}: 1746 (prisms), 1752 (needles). ESI-MS m/z: 510.1144 ($C_{23}H_{25}ClNO_{10}$ $(M+H)^+$: 510.1162).

Preparation of 5 Typical Procedure: A suspension of **4a** (500 mg, 1.02 mmol) and Amberlyst® A-26 (OH) (1.50 g) in methanol (50 ml) was stirred for 1 h at room temperature. Insoluble materials were filtered and the colorless powder was extracted with a large excess of methanol. The extract was combined with the filtrate and evaporated *in vacuo* yielding compound **5a** (337 mg, q.).

4-(β-D-Glucosyloxy)-6-methylquinoline (**5a**) as a Colorless Crystalline Powder (Ethanol) (q.): mp 180—182 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 2.55 (3H, s), 3.46 (1H, dd, J=9.5, 9.2 Hz), 3.55 (1H, dd, J=9.2, 9.2 Hz), 3.59 (1H, ddd, J=9.5, 5.7, 2.1 Hz), 3.68 (1H, dd, J=9.2, 7.7 Hz), 3.72 (1H, dd, 12.2, 5.7 Hz), 3.93 (1H, dd, J=12.2, 2.1 Hz), 5.28 (1H, d, J=7.7 Hz), 7.15 (1H, d, J=5.3 Hz), 7.61 (1H, dd, J=8.6, 1.9 Hz), 7.85 (1H, d, J=8.6 Hz), 8.16 (1H, d, J=1.9 Hz), 8.61 (1H, d, J=5.3 Hz). IR (KBr) cm^{-1}: 3357 (br). ESI-MS m/z: 322.1268 (Calcd for $C_{16}H_{20}NO_6$ $(M+H)^+$: 322.1291).

4-(β-D-Glucosyloxy)-6-methoxyquinoline (**5b**) as Colorless Needles (Ethanol) (74%): mp 175—177 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.46 (1H, dd, J=9.2, 9.2 Hz), 3.56 (1H, dd, J=9.2, 9.2 Hz), 3.59 (1H, ddd, J=9.2, 5.7, 2.3 Hz), 3.69 (1H, dd, J=9.2, 7.4 Hz), 3.73 (1H, dd, J=12.6, 5.7 Hz), 3.93 (1H, dd, J=12.6, 2.3 Hz), 3.96 (3H, s), 5.29 (1H, d, J=7.4 Hz), 7.17 (1H, d, J=5.2 Hz), 7.39 (1H, dd, J=9.2, 2.9 Hz), 7.65 (1H, d, J=2.9 Hz), 7.85 (1H, d, J=9.2 Hz), 8.54 (1H, d, J=5.2 Hz). (KBr) cm^{-1}: 3356 (br). ESI-MS m/z: 360.1065 (Calcd for $C_{16}H_{19}NNaO_7$ $(M+Na)^+$: 360.1059).

4-(β-D-Glucosyloxy)-7-methoxyquinoline (**5c**) as Colorless Needles (Ethanol) (q.): mp 177—181 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.45 (1H, dd, J=9.5, 9.1 Hz), 3.54 (1H, dd, J=9.1, 9.1 Hz), 3.57 (1H, ddd, J=9.5, 5.7, 2.1 Hz), 3.65 (1H, dd, J=9.1, 7.8 Hz), 3.72 (1H, dd, J=12.1, 5.7 Hz), 3.92 (1H, dd, J=12.1, 2.1 Hz), 3.95 (3H, s), 5.29 (1H, d, J=7.8 Hz), 7.07 (1H, d, J=5.4 Hz), 7.20 (1H, dd, J=9.2, 2.4 Hz), 7.29 (1H, d, J=2.4 Hz), 8.25 (1H, d, J=9.2 Hz), 8.60 (1H, d, J=5.4 Hz). (KBr) cm^{-1}: 3376 (br). ESI-MS m/z: 360.1066 (Calcd for $C_{16}H_{19}NNaO_7$ $(M+Na)^+$: 360.1059).

4-(β-D-Glucosyloxy)-6-phenoxyquinoline (**5d**) as Colorless Needles (Ethyl Acetate) (74%): mp 170—173 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.43 (1H, dd, J=9.6, 9.0 Hz), 3.52 (1H, dd, J=9.1, 9.0 Hz), 3.57 (1H, ddd, J=9.6, 5.7, 2.2 Hz), 3.58 (1H, dd, J=9.1, 7.7 Hz), 3.71 (1H, dd, J=12.1, 5.7 Hz), 3.91 (1H, dd, J=12.1, 2.2 Hz), 5.29 (1H, d, J=7.7 Hz), 7.06 (2H, ddd, J=8.7, 2.1, 1.1 Hz), 7.16 (1H, tt, J=7.4, 2.1 Hz), 7.19 (1H, d, J=5.4 Hz), 7.39 (2H, ddd, J=8.7, 7.4, 1.1 Hz), 7.48 (1H, dd, J=9.2, 2.8 Hz), 7.87 (1H, d, J=2.8 Hz), 7.97 (1H, d, J=9.2 Hz), 8.63 (1H, d, J=5.4 Hz). (KBr) cm^{-1}: 3255 (br). ESI-MS m/z: 422.1217 (Calcd for $C_{21}H_{21}NNaO_7$ $(M+Na)^+$: 422.1216).

4-(β-D-Glucosyloxy)-6-*N*,*N*-dimethylaminoquinoline (**5e**) as an Ochre Crystalline Powder (Ethyl Acetate) (85%): mp 179—184 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.09 (6H, s), 3.46 (1H, dd, J=9.7, 9.0 Hz), 3.55 (1H, dd, J=9.1, 9.0 Hz), 3.56 (1H, ddd, J=9.7, 5.6, 2.3 Hz), 3.68 (1H, dd, J=9.1, 7.8 Hz), 3.73 (1H, dd, J=12.1, 5.6 Hz), 3.92 (1H, dd, J=12.1, 2.3 Hz), 5.27 (1H, d, J=7.8 Hz), 7.06 (1H, d, J=5.3 Hz), 7.31 (1H, d, J=2.9 Hz), 7.44 (1H, dd, J=9.4, 2.9 Hz), 7.79 (1H, d, J=9.4 Hz), 8.38 (1H, d, J=5.3 Hz). (KBr) cm^{-1}: 3357 (br). ESI-MS m/z: 351.1561 (Calcd for $C_{17}H_{23}N_2O_6$ $(M+H)^+$: 351.1556).

4-(β-D-Glucosyloxy)-6-*N*-phenylaminoquinoline (**5f**) as Brown Needles (Ethyl Acetate) (74%): mp 168—175 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.45 (1H, dd, J=9.6, 9.0 Hz), 3.52 (1H, dd, J=9.0, 9.0 Hz) 3.58 (1H, ddd, J=9.6, 5.6, 2.3 Hz), 3.62 (1H, dd, J=9.0, 7.7 Hz), 3.72 (1H, dd, J=12.2, 5.6 Hz), 3.91 (1H, dd, J=12.2, 2.3 Hz), 5.29 (1H, d, J=7.7 Hz), 6.93 (1H, tt, J=7.3, 1.2 Hz), 7.08 (1H, d, J=5.3 Hz), 7.23 (2H, ddd, J=8.7, 2.0, 1.2 Hz), 7.29 (2H, ddd, J=8.7, 7.3, 2.0 Hz), 7.51 (1H, dd, J=9.1, 2.6 Hz), 7.80 (1H, d, J=9.1 Hz), 7.87 (1H, d, J=2.6 Hz), 8.44 (1H, d, J=5.3 Hz). (KBr) cm^{-1}: 3323 (br). ESI-MS m/z: 421.1356 (Calcd for $C_{21}H_{22}N_2NaO_6$ $(M+Na)^+$: 421.1376).

4-(β-D-Glucosyloxy)-quinoline (**5g**) as a Colorless Crystalline Powder (Ethanol) (99%): mp 178—179 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.46 (1H, dd, J=9.7, 9.1 Hz), 3.56 (1H, dd, J=9.2, 9.1 Hz), 3.60 (1H, ddd, J=9.7, 5.7, 2.2 Hz), 3.69 (1H, dd, J=9.2, 7.8 Hz), 3.73 (1H, dd, J=12.2, 5.7 Hz), 3.93 (1H, dd, J=12.2, 2.2 Hz), 5.31 (1H, d, J=7.8 Hz), 7.20 (1H, d, J=5.4 Hz), 7.58 (1H, ddd, J=8.4, 7.0 1.3 Hz), 7.76 (1H, ddd, J=8.6, 7.0, 1.5 Hz), 7.96 (1H, dd, J=8.6, 1.3 Hz), 8.38 (1H, dd, J=8.4, 1.5 Hz)), 8.70 (1H, d, J=5.4 Hz). (KBr) cm^{-1}: 3348 (br). ESI-MS m/z: 308.1129 (Calcd for $C_{15}H_{18}NO_6$ $(M+H)^+$: 308.1129).

4-(β-D-Glucosyloxy)-7-chloroquinoline (**5h**) as a Colorless Crystalline Powder (Ethyl Acetate) (58%): mp 167—172 °C (decomp.). ^{1}H-NMR (CD_3OD) δ: 3.45 (1H, dd, J=9.7, 9.0 Hz), 3.55 (1H, dd, J=9.2, 9.0 Hz), 3.60 (1H, ddd, J=9.7, 5.7, 2.2 Hz), 3.67 (1H, dd, J=9.2, 7.7 Hz), 3.72 (1H, dd, J=12.2, 5.7 Hz), 3.93 (1H, dd, J=12.2, 2.2 Hz), 5.30 (1H, d, J=7.7 Hz), 7.21 (1H, d, J=5.5 Hz), 7.56 (1H, dd, J=9.0, 2.1 Hz), 7.95 (1H, d, J=2.1 Hz), 8.36 (1H, d, J=9.0 Hz), 8.72 (1H, d, J=5.5 Hz). (KBr) cm^{-1}: 3347 (br). ESI-MS m/z: 342.0715 (Calcd for $C_{15}H_{17}ClNO_6$ $(M+H)^+$: 342.0739).

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