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Facile synthesis of a 4-anilinoquinazoline dimer by Suzuki cross-coupling reaction

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Abstract

A novel 4-anilinoquinazoline dimer linked by a carbon–carbon bond in the C-7 position was synthesized *via* a one step Suzuki cross-coupling reaction. All structures of new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. The inhibition rate of the synthetic 4-anilinoquinazoline dimer **8** against epidermal growth factor receptor-tyrosine kinase enzymes (EGFR) *in vitro* was 44.4% at the concentration of 5.5 μmol/L.

Keywords: Quinazoline; Suzuki reaction; Dimer; EGFR; Synthesis

The 4-anilinoquinazoline derivatives, which exhibited a large range of biological activities such as anti-inflammatory, anti-cancer, antiviral and antitubercular activity, have attracted the attention of research groups concerning with chemical modification in recent years [1–5]. Of several candidate compounds synthesized and tested, Gefitinib, Erlotinib and Lapatinib (Fig. 1) which belongs to the category of EGFR inhibitors are being used clinically for the treatment of cancers [6].

Many modifications of 4-anilinoquinazoline have been carried out to develop more potent EGFR inhibitors which bear various substituents on C-6 position or C-7 position and a variety of anilines on C-4 position of the quinazoline [6,7]. However, there have been no reports on the synthesis of quinazoline dimers. As a further research in this field, we developed a facile method for the synthesis of a quinazoline dimer linked by a carbon–carbon bond *via* a one step Suzuki cross-coupling reaction [8]. In addition, most of the 4-anilinoquinazoline derivatives exhibited poor solubility in water which led to considerable difficulty in further research [9]. In this study glucose ring was introduced into the target molecule to improve the water solubility [10].

The synthesis of the target 4-anilinoquinazoline dimer **8** was shown in Scheme 1. 2-Bromoethoxy 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside was reacted with 4-nitrophenol in DMF to give compound **1**, subsequent reduction of compound **1** by hydrogen using Pd/C as catalyst gave the aniline **2**. The important intermediate 4-anilinoquinazoline derivative **6** was synthesized based on methods reported in the literatures [11–13]. 2-Amino-4-bromo-5-chlorobenzoic acid **3** was refluxed with ammonium acetate in triethyl orthoformate to provide 7-bromo-6-chloroquinazolin-4(3*H*)-

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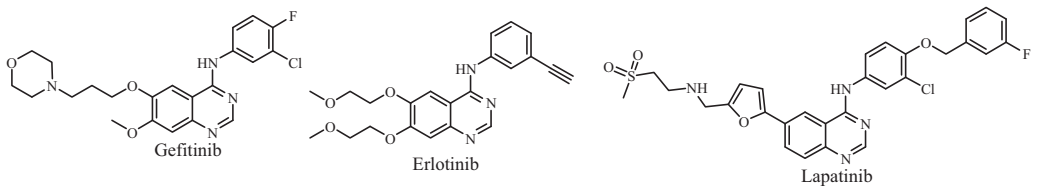
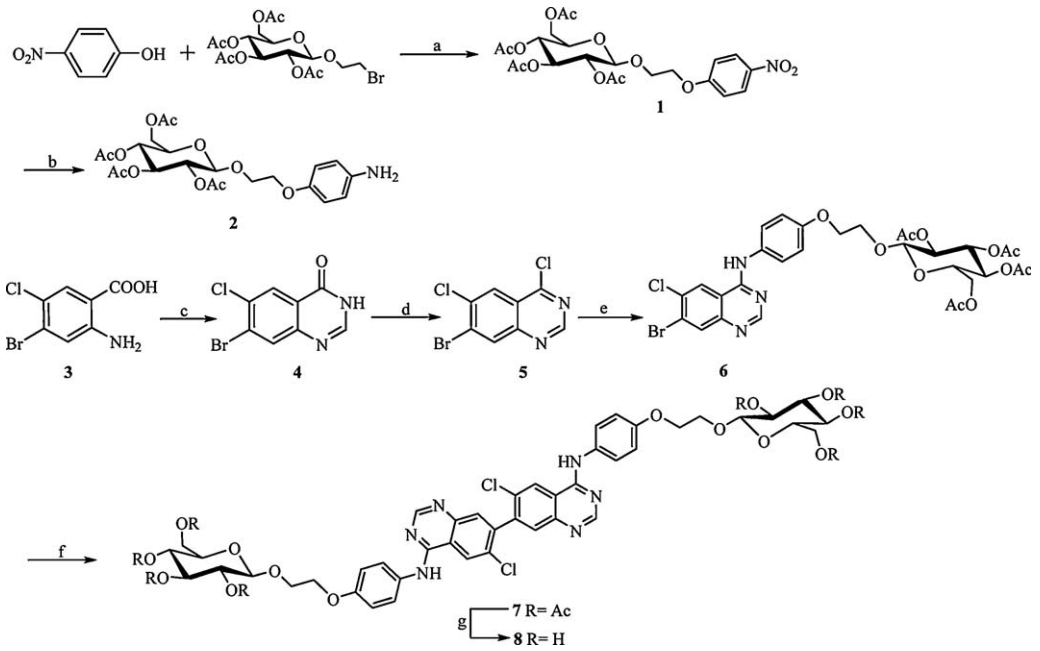


Fig. 1. The structure of compounds.



Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, 80 °C, 6 h, 83%; (b) H_2, Pd/C, MeOH, rt, 10 h, 95%; (c) $CH(OC_2H_5)_3$, MeOH, 120 °C, 3 h, 94%; (d) $POCl_3$, DIPEA, 100 °C, N_2, 1 h, 92%; (e) compound **2**, *i*-PrOH/CH_2Cl_2, reflux, 4 h, 86%; (f) Bis(pinacolato)diboron, $PdCl_2$ (dppf), AcOK, DMSO, 80 °C, 20 h 52%; (g) NaOMe/MeOH, rt, 6 h, 91%.

one **4**. Compound **4** was then subjected to phosphoryl chloride to afford 7-bromo-4, 6-dichloroquinazoline **5** in 92% yield. Compound **5** was refluxed with aniline **2** in isopropanol and dichloromethane to give **6** in 86% yield.

Different from the classical two-step Suzuki reaction [8], the quinazoline dimer **7** was obtained directly in one-step when compound **6** was reacted with bis(pinacolato)diboron using [$PdCl_2$(dppf)] as a catalyst in the presence of KOAc. The reason of smooth homocoupling of compound **6** might be the existence of chloride in the 6-position. Previous research also demonstrated that both electron-withdrawing groups and electron-donating groups on the aryl ring favored the homocouplings in the synthesis of the symmetrical biaryls [15].

After deacetylation of compound **7** by sodium methoxide in methanol [14], the target compound **8** was obtained successfully in 95% yield. The structures of the target compound and novel intermediates were characterized by ^{1}H NMR, ^{13}C NMR and HRMS [17]. The dimer **7** showed satisfactory solubility in chloroform (40 mg/mL) and the target compound **8** exhibited good solubility in water (3.5 mg/mL).

The inhibition activity of compounds **7** and **8** toward EGFR tyrosine kinase activity *in vitro* was determined by an enzyme-linked-immunosorbent assay (ELISA) [16]. The assay was performed in 96-well plates precoated with 20 μg/mL Poly(Glu, Tyr) 4:1. In each well, 85 μL of 8 μmol/L ATP solution and 10 μL of compound were added at varying concentrations. Experiments at each concentration were performed in triplicate. The reaction was initiated by adding 5 μL of EGFR tyrosine kinase. A492 was measured using a multiwell spectrophotometer. The inhibition rate (%) was calculated using the equation: [1 − (A492/A492 control)] × 100%. The inhibition rate of **8** against EGFR *in vitro* was 44.4% at the concentration of 5.5 μmol/L with gefitinib as a standard (Table 1).

Table 1
Inhibition effect of compounds **7** and **8** toward EGFR *in vitro*.

Compounds	Concentration (μmol/L)	Inhibition (%)
7	5.3	2.2
8	5.5	44.4
Gefitinib	10.0	86.1

In conclusion, a novel quinazoline dimer was designed and synthesized with good water solubility. The quinazoline dimer **8** showed moderate inhibition against EGFR *in vitro* and its further bioactivity evaluation is in progress in our laboratory. A facile method was developed for the construction of quinazoline dimers and hoped to be useful in the synthesis of other dimers connected by a carbon–carbon bond.

Acknowledgments

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[17] Spectral data. Compound **7** HRMS(ESI): calcd. for $C_{60}H_{63}N_6O_{22}Cl_2^+$ 1289.3372, found 1289.3395; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.71 (s, 1H, ArH), 8.22 (s, 1H, ArH), 8.15 (s, 1H, ArH), 7.82 (s, 1H, ArH), 7.58–7.57 (d, 2H, J = 7.7 Hz, ArH), 6.93–6.91 (d, 2H, J = 8.8 Hz, ArH), 5.26–5.23 (t, 1H, J = 9.6 Hz), 5.12–5.09 (t, 1H, J = 9.6 Hz), 5.05–5.02 (dd, 1H, J = 9.3, 7.7 Hz), 4.69–4.68 (d, 1H, J = 8.2 Hz), 4.28–4.25 (dd, 1H, J = 12.1, 4.4 Hz), 4.15–4.12 (m, 4H), 3.96–3.94 (m, 1H), 3.75–3.73 (m, 1H), 2.09 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.98 (s, 3H, OAc). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 170.4, 169.7, 169.5, 157.4, 156.3, 155.9, 142.1, 131.2, 131.0, 130.6, 125.1, 124.8, 124.7, 122.1, 116.0, 115.2, 115.1, 101.1, 72.8, 72.0, 71.3, 68.5, 68.4, 67.6, 62.0, 20.9, 20.8, 20.7, 20.6. Compound **8** HRMS(ESI): calcd. for $C_{44}H_{47}N_6O_{14}Cl_2^+$ 953.2527, found 953.2505; ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.96 (s, 1H, NH), 8.90 (s, 1H, ArH), 8.61 (s, 1H, ArH), 7.85 (s, 1H, ArH), 7.75–7.73 (d, 2H, J = 8.8 Hz, ArH), 7.04–7.03 (d, 2H, J = 9.4 Hz, ArH), 5.09 (s, 1H), 4.96 (s, 1H), 4.56 (s, 1H), 4.27–4.26 (d, 1H, J = 7.7 Hz), 4.20–4.17 (m, 2H), 4.14–4.11 (m, 1H), 3.87–3.84 (m, 1H), 3.71–3.69 (d, 1H, J = 11.0 Hz), 3.49–3.46 (m, 1H), 3.19–3.15 (m, 3H), 3.10–3.08 (d, 1H, J = 9.4 Hz), 3.03–3.00 (t, 1H, J = 9.4 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 157.6, 156.2, 155.8, 148.9, 142.0, 132.3, 130.6, 130.2, 124.9, 124.8, 124.0, 116.4, 115.0, 114.9, 103.7, 77.5, 77.3, 74.0, 70.6, 68.0, 67.7, 61.7.