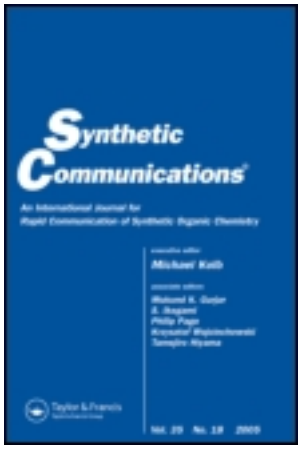

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Novel Benzoxazinone Compounds as Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors

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Accepted author version posted online: 02 Jan 2012.Published online: 29 May 2012.

To cite this article: Shaopeng Chen , Xuemin Li , Shengbiao Wan & Tao Jiang (2012) Synthesis of Novel Benzoxazinone Compounds as Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:19, 2937-2946, DOI: 10.1080/00397911.2011.573169

To link to this article: http://dx.doi.org/10.1080/00397911.2011.573169

Synthetic Communications®, 42: 2937–2946, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.573169

SYNTHESIS OF NOVEL BENZOXAZINONE COMPOUNDS AS EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) TYROSINE KINASE INHIBITORS

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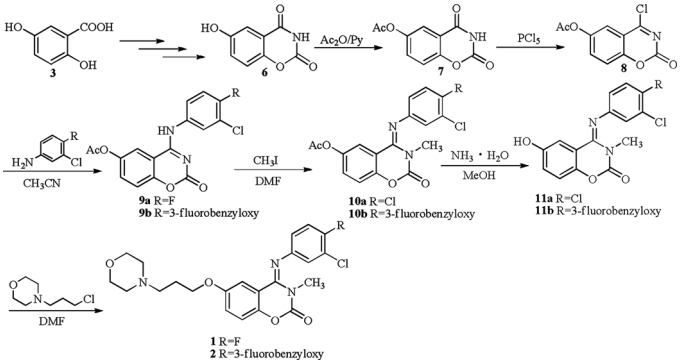
GRAPHICAL ABSTRACT



Abstract *Two benzoxazinone compounds as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors were synthesized and characterized by NMR and high-resolution mass spectrometry (HRMS). An efficient chlorination method was introduced in the synthesis of 4-chloro-2-oxo-2H-benzoxazinone-6-yl acetate. The inhibition activities of the target compounds and the important intermediates for EGFR tyrosine kinase activity* in vitro *were determined.*

Keywords Benzoxazinone; EGFR; inhibitor; synthesis

INTRODUCTION

It is well known that epidermal growth factor receptor (EGFR) tyrosine kinase plays an important role in a wide range of cancers.[1,2] Compounds that inhibit the kinase activity of EGFR are of potential interest as new therapeutic antitumor

Received December 30, 2010.

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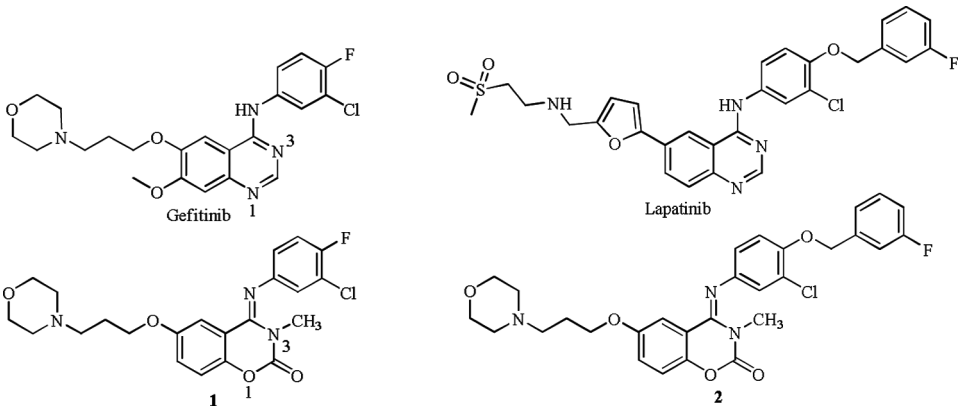


Figure 1. Structures of gefitinib, lapatinib, and the target compounds.

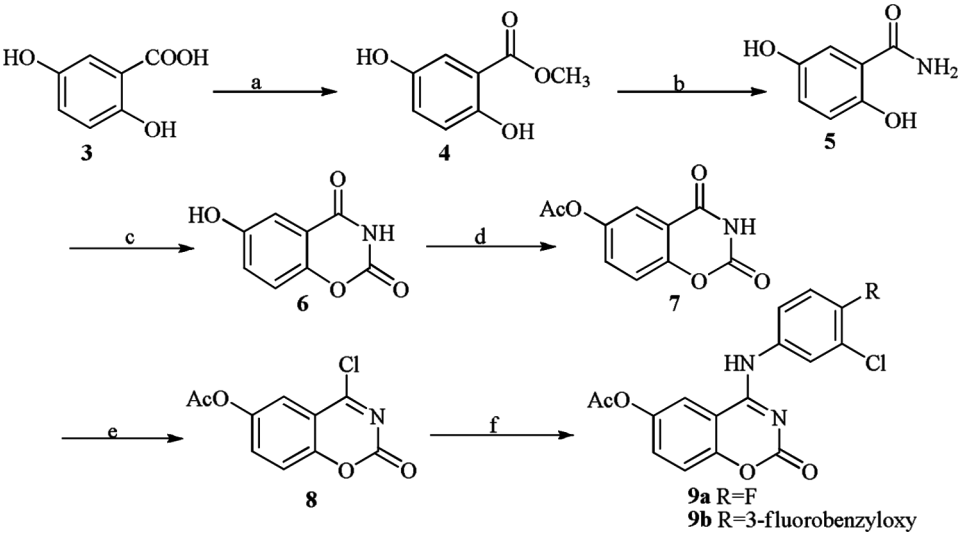
agents.[3,4] A well-studied class of these inhibitors is represented by 4-anilinoquinazolines.[5] Further development in this class led to the discovery of several drugs, such as gefitinib and lapatinib (Fig. 1), which have been used for the treatment of non-small-cell lung cancer and breast cancer.[6,7]

The main modifications of 4-anilinoquinazoline focused on introducing different substituents on the C-6 or C-7 positions and a variety of anilines on the C-4 position of the quinazoline ring.[8] Structure–activity and molecular modeling studies demonstrated that the N-1 and N-3 atoms could interact with the kinase domain by hydrogen bonds.[9] Benzoxazinone compounds with potential anticancer activity have some similarities with the quinazoline ring.[10,11] In this study, two analogs of gefitinib and lapatinib were designed by replacing the quinazoline ring with a 3, 4-dihydro-2H-benzoxazinone-2-one scaffold using the strategy of bioisosterism to develop new EGFR tyrosine kinase inhibitors (Fig. 1).[12]

RESULTS AND DISCUSSION

The synthetic route of the target compounds is outlined in Scheme 1. 2,5-Dihydroxybenzoic acid was refluxed in methanol catalyzed by H_2SO_4 to give methyl 2,5-dihydroxybenzoate, which was then treated with concentrated ammonia liquor (28%) to give 2,5-dihydroxybenzamide. 2,5-Dihydroxybenzamide was subsequently reacted with ethyl chloroformate at 122 °C and treated with hydrochloric acid to give compound **6** following a reported procedure.[13] After acetylation of the hydroxyl group, compound **7** was obtained in 72% yield.

No reaction happened when compound **7** was refluxed in $SOCl_2$ or $POCl_3$ following the conventional procedures.[14,15] To accomplish this reaction, compound 7 was treated with PCl_5 at 165 °C under a nitrogen atmosphere, and then compound **8** was obtained as a yellow solid, which was used for the next step without further purification. With a similar procedure as reported,[11] amination of compound **8** by 3-chloro-4-fluoroaniline or 3-chloro-4-(3-fluorobenzyloxy) aniline in CH_3CN using N-ethyl-N-isopropylpropan-2-amine (DIPEA) as an acid scavenger afforded **9a** and **9b** respectively.



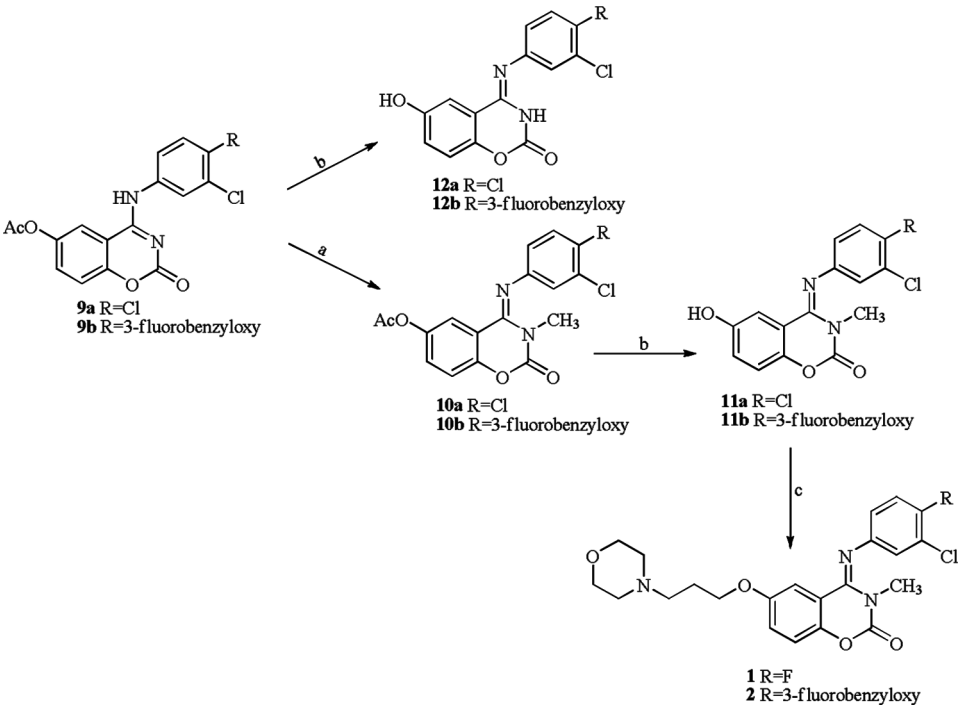
Scheme 1. Reagents and conditions: (a) H_2SO_4, MeOH, reflux, 48 h, 92%%; (b) concentrated ammonia liquor, 50 °C, 13 h, 70%; (c) ethyl chloroformate, 5 to 122 °C, 1 h, 85%; (d) pyridine/Ac_2O, rt to 100 °C, 3 h, 72%; (e) PCl_5, 165 °C, 20 min; and (f) 3-chloro-4-fluoroaniline or 3-chloro-4-(3-fluorobenzyloxy)-aniline, CH_3CN, DIPEA, rt, 12 h, 19–34%.

As shown in Scheme 2, compounds **9a** and **9b** could be deacetylated by concentrated ammonia liquor (28%) in methanol to obtain **12a** and **12b**. However, when **12a** and **12b** were treated with 4-(3-chloropropyl)morpholine, the hydroxy group and the imine group in the N-3 position both might be alkylated simultaneously. Thus, methylation was carried out through the reaction of compounds **9a** and **9b** with CH_3I in dimethylformamide (DMF) to afford **10a** and **10b** respectively before deprotection of the acetyl groups.

After deacetylation of **10a** and **10b** with concentrated ammonia liquor (28%) in methanol, compounds **11a** and **11b** were obtained in 93% and 96% yields. Finally, **11a** and **11b** were reacted with 4-(3-chloropropyl)morpholine in DMF to provide the target compounds **1** and **2** respectively in 65% and 74% yields. The structures of the target compounds and the new intermediates were characterized by ^1H NMR, ^{13}C NMR, and high-resoultion mass spectrometry (HRMS).

The inhibition activity of the target compounds and the important intermediates toward EGFR tyrosine kinase activity in vitro was determined by an enzyme-linked-immunosorbent assay (ELISA).[16] Preliminary evaluation demonstrated that most synthesized benzoxazinone compounds showed low or moderate inhibition effect against EGFR in vitro at the concentration of 10.0 μM. Among the synthesized compounds, **1** and **11a** showed relatively great inhibition effect against the isolated EGFR enzyme (49.3% and 44.6%). The inhibition rates of target compounds **1** and **2** against EGFR in vitro are 49.3% and 38.0% at the concentration of 10.0 μM (Table 1). Comparing with lapatinib, the two analogs exhibited lower EGFR inhibition activity.

In conclusion, two target benzoxazinone compounds and eight novel intermediates were synthesized and characterized by NMR and HRMS spectrometry.



Scheme 2. Reagents and conditions: (a) CH_3I, K_2CO_3, DMF, 70 °C, 3 h, 69–78%; (b) concentrated ammonia liquor/MeOH, 91–96%; and (c) 4-(3-chloropropyl)morpholine, DMF, 80 °C, 3 h, 65–74%.

An efficient chlorination method was introduced to synthesize compound **8** using PCl_5 at melting temperature and we hope it will be useful for the synthesis of other similar compounds. Preliminary evaluation demonstrated that compounds **1** and **11b** showed moderate inhibition effect against EGFR in vitro. The reason for moderate inhibition activity of the target compounds toward EGFR may be the existence of

Table 1. Inhibition effect of compounds **9a–12b** and the target compounds toward EGFR *in vitro*

Compounds	Concentration (μM)	Inhibition (%)
9a	10.0	23.8
9b	10.0	38.5
10a	10.0	31.2
10b	10.0	24.0
11a	10.0	29.5
11b	10.0	44.6
12a	10.0	3.85
12b	10.0	19.3
1	10.0	49.3
2	10.0	38.0
Lapatinib	10.0	76.1

the methyl in the N-3 position, which could block the interaction between N-3 atom and the kinase domain. Further modification and bioactivity investigation of this kind of benzoxazinone compounds are in progress.

EXPERIMENTAL

All reagents used in the experiments were obtained from commercial sources and purified in a conventional manner. Thin-layer chromatography (TLC) was performed on Merck silica-gel 60 F_{254} plates. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Melting points were measured on a WRX-1S melting-point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on Jnm-Ecp-600 spectrometer (Jeol Ltd. Tokyo, Japan) with tetramethylsilane (Me_4Si) as the internal standard. Mass spectra were recorded on a Q-TOF Global mass spectrometer (Waters Co., Milford, MA, USA).

Compounds 4–6

Literature procedures were used for preparation of compounds **4** to **6**.[12,17,18]

Methyl 2,5-dihydroxybenzoate (4). White powder; yield 92%; mp: 85–86 °C (lit.[19] 84–86 °C).

2,5-Dihydroxybenzamide (5). Yellow needles; yield 70%; mp: 216–219 °C (lit.[12] 218–220 °C).

6-Hydroxy-1,3-benzoxazine-2,4(3H)-dione (6). White solid; yield 85%; mp: 301–303 °C (lit.[18] 303–305 °C).

2,4-Dioxo-3,4-dihydro-1,3-benzoxazine-6-yl Acetate (7)

A suspension of 6-hydroxy-1,3-benzoxazine-2,4(3H)-dione **6** (7.0 g, 39.1 mmol) in acetic anhydride (60 mL) and pyridine (18 mL) was stirred and heated to 100 °C under a N_2 atmosphere for 3 h. The solvent was removed under reduced pressure. Crushed ice/water solution (100 mL) was added to the reaction mixture, and the resulting white deposit was filtered, washed with water, and dried under reduced pressure to afford **7** (0.22 g, 91% yield) as a white powder. Mp: 204–206 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 12.14 (br, s, 1H, NH), 7.68–7.67 (d, $J = 2.8$ Hz, 1H, ArH), 7.57–7.55 (dd, $J = 8.8$, 2.7 Hz, 1H, ArH), 7.47-7.45 (d, $J = 8.8$ Hz, 1H, ArH), 2.30 (s, 3H, -OAc); ^{13}C NMR (DMSO-d_6 150 MHz): δ 169.8, 161.5, 151.7, 147.8, 147.4, 130.4, 120.0, 118.5, 115.9, 21.4; ESI-MS 244.2 $(M + Na)^+$; HRMS (ESI): calcd. for $C_{10}H_8NO_5^+$ 222.0402; found 222.0411.

4-Chloro-2-oxo-1,3-benzoxazine-6-yl Acetate (8)

A mixture of 2,4-dioxo-3,4-dihydro-1,3-benzoxazine-6-yl acetate **7** and PCl_5 was stirred and heated to the melting temperature under N_2 atmosphere. The reaction mixture was stirred for a further 20 min. After completion, the solvent was

removed under reduced pressure to give product **8** as a yellow solid which was used for the next step without further purification.

4-(3-Chloro-4-fluorophenylamino)-2-oxo-1,3-benzoxazine-6-yl Acetate (9a)

4-Chloro-2-oxo-1,3-benzoxazine-6-yl acetate **8** (2.62 g, 11.0 mmol) and 3-chloro-4-fluoroaniline (1.6 g, 11.0 mmol) were dissolved in CH_3CN (100 mL). To this solution, N,N-Diisopropylethylamine (3.5 mL) was added dropwise until the solution became alkaline and stirred for a further 12 hours. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the solvent was evaporated under reduced pressure, and the residue was purified through column chromatography on silica gel (eluent, dichloromethane) to give **9a** (1.0 g, 19.2% yield) as a yellow powder. Mp: 213–217 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 10.43 (br, s, 1H, NH), 8.19–8.18 (d, $J = 1.9$ Hz, 1H, ArH), 8.10–8.09 (dd, $J = 6.9$, 2.3 Hz, 1H, ArH), 7.76–7.75 (m, 1H, ArH), 7.62–7.60 (dd, $J = 9.2$, 2.8 Hz, 1H, ArH), 7.53–7.51 (t, $J = 9.2$ Hz, 1H, ArH), 7.45–7.43 (d, $J = 8.7$ Hz, 1H, ArH), 2.35 (s, 3H, -OAc); ^{13}C NMR (DMSO-d_6 150 MHz): δ 169.9, 161.0, 156.1, 154.5, 154.0, 151.9, 146.4, 134.9, 130.4, 126.3, 124.9, 118.5, 117.5, 117.3, 110.8, 21.2; ESI-MS 349.0 $(M + H)^+$. HRMS (ESI): calcd. for $C_{16}H_{11}N_2O_4FCl^+$ 349.0391; found 349.0374.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-2-oxo-1,3-benzoxazine-6-yl Acetate (9b)

Following the procedure used for the preparation of **9a**, but with 3-chloro-4-(3-fluorobenzyloxy)aniline as starting material, product **9b** was obtained as a yellow powder (34% yield). Mp 101–103 °C. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 10.34 (br, s, 1H, NH), 8.19–8.18 (d, $J = 2.3$ Hz, 1H, ArH), 7.95–7.94 (d, $J = 2.8$ Hz, 1H, ArH), 7.68–7.66 (dd, $J = 8.7$, 2.7 Hz, 1H, ArH), 7.60–7.58 (dd, $J = 9.2$, 2.8 Hz, 1H, ArH), 7.50–7.48 (m, 1H, ArH), 7.44–7.42 (d, $J = 9.2$ Hz, 1H, ArH), 7.34–7.32 (dd, $J = 8.8$, 2.8 Hz, 2H, ArH), 7.31 (s, 1H, ArH), 7.20–7.18 (t, $J = 8.8$ Hz, 1H, ArH), 5.28 (s, 2H), 2.35 (s, 3H, -OAc); ^{13}C NMR (DMSO-d_6 150 MHz): δ 169.9, 163.6, 162.0, 160.7, 153.9, 152.0, 151.7, 146.3, 140.0, 131.4, 131.3, 130.0, 126.1, 124.4, 123.9, 120.9, 118.5, 117.5, 115.4, 114.7, 110.9, 69.9, 21.2; ESI-MS 455.0 $(M + H)^+$. HRMS (ESI): calcd. for $C_{23}H_{17}N_2O_5FCl^+$ 455.0810; found 455.0830.

4-(3-Chloro-4-fluorophenylimino)-3-methyl-2-oxo-3,4-dihydro-1,3-benzoxazine-6-yl Acetate (10a)

A suspension of **9a** (450 mg, 1.29 mmol) and anhydrous potassium carbonate (330 mg, 2.39 mmol) in dry DMF (30 mL) was stirred at 40 °C for 20 min, then CH_3I (2.39 mmol) was added, and the mixture was stirred at 70 °C for 8 h under a N_2 atmosphere. After completion, the solvent was removed under reduced pressure and then purified by chromatography on silica gel (eluent, ethyl acetate/petroleum ether 2/5) to give **10a** (364 mg, 69% yield) as a yellow powder. Mp: 149–152 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 7.43–7.39 (m, 3H, ArH), 7.10–7.09 (d, $J = 4.4$ Hz,

1H, ArH), 6.90–6.88 (m, 1H, ArH), 6.70 (br, s, 1H, ArH), 3.30 (s, 3H), 2.16 (s, 3H, -OAc); ^{13}C NMR (DMSO-d_6 150 MHz): δ 169.3, 154.9, 153.3, 149.1, 148.2, 146.1, 146.0, 128.2, 121.2, 120.5, 120.1, 120.0, 118.9, 118.4, 118.3, 56.6, 21.2; ESI-MS 363.1 $(M+H)^+$. HRMS (ESI): calcd. for $C_{17}H_{13}N_2O_4FCl^+$ 363.0548; found 363.0551.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylimino)-3-methyl-2-oxo-3,4-dihydro-1,3-benzoxazine-6-yl Acetate (10b)

Following the procedure used for the preparation of **10a**, but with **9b** as starting material, product **10b** was obtained as a yellow powder (78% yield). Mp 145–147 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.48–7.45 (t, $J=6.0$ Hz, 1H, ArH), 7.40–7.39 (t, $J=2.8$ Hz, 2H, ArH), 7.33–7.30 (m, 2H, ArH), 7.23–7.21 (d, $J=8.8$ Hz, 1H, ArH), 7.20-7.17 (dt, $J=8.2$, 2.2 Hz, 1H, ArH), 7.01 (s, 1H, ArH), 6.83–6.82 (d, $J=8.3$ Hz, 1H, ArH), 6.66 (s, 1H, ArH), 5.22 (s, 2H), 3.34 (s, 3H), 2.19 (s, 3H, -OAc); ^{13}C NMR (DMSO-d_6 150 MHz): δ 169.3, 163.6, 161.9, 150.0, 149.1, 143.0, 140.3, 140.2, 131.1, 131.0, 128.2, 123.8, 121.1, 120.5, 119.2, 118.9, 116.5, 115.3, 115.2, 114.5, 114.4, 70.3, 56.6, 21.1; ESI-MS 469.1 $(M+H)^+$. HRMS (ESI): calcd. for $C_{24}H_{19}N_2O_5FCl^+$ 469.0967; found 469.0985.

4-(3-Chloro-4-fluorophenylimino)-6-hydroxy-3-methyl-3,4-dihydro-1,3-benzoxazine-2-one (11a)

Compound **10a** (314 mg, 0.87 mmol) was dissolved in methanol (30 mL), and then concentrated ammonia liquor (28%, 0.5 mL) was added. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The yellow precipitate formed was filtered and washed with diethylether (50 mL) to give **11a** (259 mg, 93% yield) as a yellow powder. Mp: 176–178 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 9.78 (br, s, 1H, ArOH), 7.41–7.38 (t, $J=9.4$ Hz, 1H, ArH), 7.20–7.18 (d, $J=8.8$ Hz, 1H, ArH), 7.08–7.06 (m, 1H, ArH), 7.00–6.98 (dd, $J=8.8$, 2.8 Hz, 1H, ArH), 6.85–6.83 (m, 1H, ArH), 6.43 (br, s, 1H, ArH), 3.35 (s, 3H); ^{13}C NMR (DMSO-d_6 150 MHz): δ 154.8, 153.7, 153.2, 148.4, 146.4, 145.1, 144.4, 122.2, 120.9, 119.8, 118.7, 118.5, 118.3, 130.0, 56.6; ESI-MS 321.0 $(M+H)^+$; HRMS (ESI): calcd. for $C_{15}H_{11}N_2O_3FCl^+$ 321.0442; found 321.0433.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylimino)-6-hydroxy-3-methyl-3,4-dihydro-1,3-benzoxazine-2-one (11b)

Following the procedure used for the preparation of **11a**, but with **10b** as starting material, product **11b** was obtained as a yellow powder (96% yield). Mp: 199–201 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 10.05 (br, s, 1H, ArOH), 7.48–7.45 (t, $J=7.7$ Hz, 1H, ArH), 7.35–7.32 (t, $J=11.0$ Hz, 2H, ArH), 7.22–7.15 (m, 3H, ArH), 6.99–6.97 (dd, $J=8.8$, 2.2 Hz, 2H, ArH), 6.79–6.77 (dd, $J=8.8$, 2.7 Hz, 1H, ArH), 6.46 (s, 1H, ArH), 5.22 (s, 2H), 3.34 (s, 3H); ^{13}C NMR (DMSO-d_6 150 MHz): δ 163.6, 162.0, 154.1, 149.8, 148.6, 144.1, 143.3, 140.3, 131.1, 123.9, 123.1, 122.0, 120.9, 119.0, 118.5, 116.2, 115.3, 115.2, 114.6, 114.5, 70.1, 56.6; ESI-MS

427.1 $(M+H)^+$; HRMS (ESI): calcd. for $C_{22}H_{17}N_2O_4FCl^+$ 427.0861; found 427.0847.

4-(3-Chloro-4-fluorophenylamino)-2-oxo-1,3-benzoxazine-6-yl Acetate (12a)

Following the procedure used for the preparation of **11a**, but with **9a** as starting material, product **12a** was obtained as a yellow powder (91% yield). Mp 221–223 °C; ^{1}H NMR (DMSOd_6, 600 MHz): δ 10.35 (br, s, 1H, ArH), 9.97 (s, 1H, NH), 8.12–8.11 (t, $J=2.7$ Hz, 1H, ArH), 7.78–7.77 (m, 1H, ArH), 7.74–7.73 (d, $J=2.3$ Hz, 1H, ArH), 7.52–7.49 (t, $J=9.2$ Hz, 1H, ArH), 7.27–7.25 (dd, $J=9.1$, 2.3 Hz, 1H, ArH), 7.24–7.22 (d, $J=9.2$ Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6 150 MHz): δ 161.6, 154.1, 152.5, 149.5, 133.1, 126.4, 125.1, 124.4, 119.6, 118.1, 117.3, 117.2, 110.7, 109.2; ESI-MS 307.0 $(M+H)^+$; HRMS (ESI): calcd. for $C_{14}H_9ClFN_2O_3^+$ 307.0286; found 307.0284.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-6-hydroxy-1,3-benzoxazine-2-one (12b)

Following the procedure used for the preparation of **11a**, but with **9b** as starting material, product **12b** was obtained as a yellow powder (93% yield). Mp 250–252 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 10.23 (br, s, 1H, ArOH), 9.91 (br, s, 1H, NH), 7.95–7.94 (d, $J=2.3$ Hz, 1H, ArH), 7.71–7.70 (d, $J=2.3$ Hz, 1H, ArH), 7.68–7.67 (dd, $J=9.1$, 2.3 Hz, 1H, ArH), 7.50–7.47 (q, $J=8.8$ Hz, 1H, ArH), 7.34–7.29 (q, $J=9.1$ Hz, 3H, ArH), 7.24–7.19 (m, 3H, ArH), 5.28 (s, 2H); ^{13}C NMR (DMSO-d_6 150 MHz): δ 163.6, 162.0, 161.3, 154.0, 152.6, 151.6, 149.5, 140.1, 131.2, 131.1, 126.2, 124.5, 124.2, 123.9, 121.5, 118.1, 115.2, 114.5, 110.8, 109.2, 69.9; ESI-MS 413.1 $(M+H)^+$. HRMS (ESI): calcd. for $C_{21}H_{15}N_2O_4FCl^+$ 413.0704; found 413.0715.

4-(3-Chloro-4-fluorophenylimino)-3-methyl-6-(3-morpholinopropoxy)-3,4-dihydro-1,3-benzoxazine-2-one (1)

A suspension of **11a** (150 mg, 0.47 mmol) and anhydrous potassium carbonate (70 mg, 0.51 mmol) in dry DMF (35 mL) was stirred at 40 °C for 20 min, 4-(3-chloropropyl)morpholine (82 mg, 0.50 mmol) was added, and the reaction mixture was stirred at 80 °C for 8 h under a N_2 atmosphere. After completion of the reaction, the solvent was removed under reduced pressure and then purified by chromatography on silica gel (eluent, ethyl acetate/petroleum ether 2/1) to give product **1** (135 mg, 65% yield) as a yellow solid. Mp: 122–125 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 7.52–7.49 (t, $J=8.8$ Hz, 1H, ArH), 7.36–7.35 (d, $J=8.8$ Hz, 1H, ArH), 7.25–7.23 (dd, $J=8.8$, 2.8 Hz, 1H, ArH), 7.20–7.18 (dd, $J=6.6$, 2.2 Hz, 1H, ArH), 6.98–6.96 (m, 1H, ArH), 6.51 (br, s, 1H, ArH), 3.63–3.58 (m, 6H), 3.43 (br, s, 3H), 2.36–2.31 (m, 6H), 1.74–1.72 (t, $J=6.6$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 154.7, 154.4, 153.1, 148.3, 146.6, 145.6, 122.7, 121.2, 120.2, 120.1, 119.0, 118.4, 118.3, 111.2, 66.8, 66.7, 66.6, 55.0, 54.9, 53.9, 53.8, 25.9; ESI-MS

448.2 $(M+H)^+$; HRMS (ESI): calcd. for $C_{22}H_{24}N_3O_4FCl^+$ 448.1439; found 448.1434.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylimino)-3-methyl-6-(3-morpholinopropoxy)-3,4-dihydro-1,3-benzoxazine-2-one (2)

Following the procedure used for the preparation of **1**, but with **11b** as starting material, product **2** was obtained as a yellow solid (74% yield). Mp: 97–101 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 7.48–7.47 (q, $J=6.1$ Hz, 1H, ArH), 7.34–7.31 (t, $J=7.7$ Hz, 2H, ArH), 7.28 (s, 1H, ArH), 7.27 (s, 1H, ArH), 7.21–7.17 (dd, $J=7.8$, 2.8 Hz, 1H, ArH), 7.16–7.14 (dd, $J=8.8$, 2.8 Hz, 1H, ArH), 7.04–7.03 (d, $J=2.8$ Hz, 1H, ArH), 6.86–6.84 (dd, $J=8.8$, 2.2 Hz, 1H, ArH), 6.49 (s, 1H, ArH), 5.22 (s, 2H), 3.50–3.43 (m, 6H), 3.34 (s, 3H), 2.2 (br, s, 6H), 1.64–1.60 (m, 2H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 163.6, 162.0, 150.0, 148.4, 145.5, 143.6, 140.2, 131.1, 123.6, 123.5, 122.5, 121.1, 119.3, 118.9, 116.3, 115.3, 115.2, 114.4, 114.3, 111.3, 70.1, 66.7, 66.6, 66.4, 56.6, 54.9, 53.8, 53.7, 25.9; ESI-MS 554.2 $(M+H)^+$. HRMS (ESI): calcd. for $C_{29}H_{30}N_3O_5FCl^+$ 554.1858; found 554.185.

ACKNOWLEDGMENTS

We are grateful for the financial support of the Key International S&T Cooperation Projects (No. 2008DFA31040 and No. 2009DFA32080) of the Ministry of Science and Technology of the People's Republic of China. We are also grateful to Meiyu Geng from Shanghai Institute of Materia Medica, Chinese Academy of Sciences, for the biological assay.

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