http://dx.doi.org/10.5012/bkcs.2013.34.8.2480

Synthesis and Preliminary Cytotoxicity Evaluation of New Diarylamides and Diarylureas Possessing 2,3-Dihydropyrrolo[3,2-*b*]quinoline Scaffold

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Received May 8, 2013, Accepted May 31, 2013

A new series of diarylamides and diarylureas having 2,3-dihydropyrrolo[3,2-*b*]quinoline scaffold was synthesized. Their *in vitro* antiproliferative activities were tested over NCI-60 cancer cell lines of nine different cancer types. Some target compounds showed good inhibition percentages over different cell lines. Among all the target compounds, compound **1f** possessing 6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinoline nucleus, amide linker, and 4-chloro-3-(trifluoromethyl)phenyl terminal ring showed high selectivity against MCF7 and MDA-MB-468 breast cancer cell lines more than the other tested cell lines. Its inhibition percentages at 10 μM concentration over those two cell lines were 84.97% and 87.13%, respectively.

Key Words : 2,3-Dihydropyrrolo[3,2-*b*]quinoline, Urea, Amide, Antiproliferative activity, Breast cancer

Introduction

Cancer is a major leading cause of death worldwide. 577,190 cancer patients died, and more than 1.6 million new cancer cases were identified in 2012 only in USA according to the American Cancer Society report.[1] More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to exceed 13 million in 2030 according to the World Health Organization (WHO) report.[2] Despite of the extensive efforts and investment in research, the management of human malignancies still constitutes a major challenge for contemporary medicinal chemistry. There has been an urgent need for development of more efficient anticancer agents with minimal side effects.

Diarylamidess and diarylureas have been highlighted as potential antiproliferative agents against a variety of cancer cell lines.[3-18] Sorafenib (Nexavar®, Fig. 1) is an example of anticancer diarylureas that has been approved by the U. S. Food and Drug Administration (FDA) for treatment of advanced renal cancer.[19] It has also been approved in Europe for treatment of hepatocellular carcinoma (HCC).[20] Sorafenib

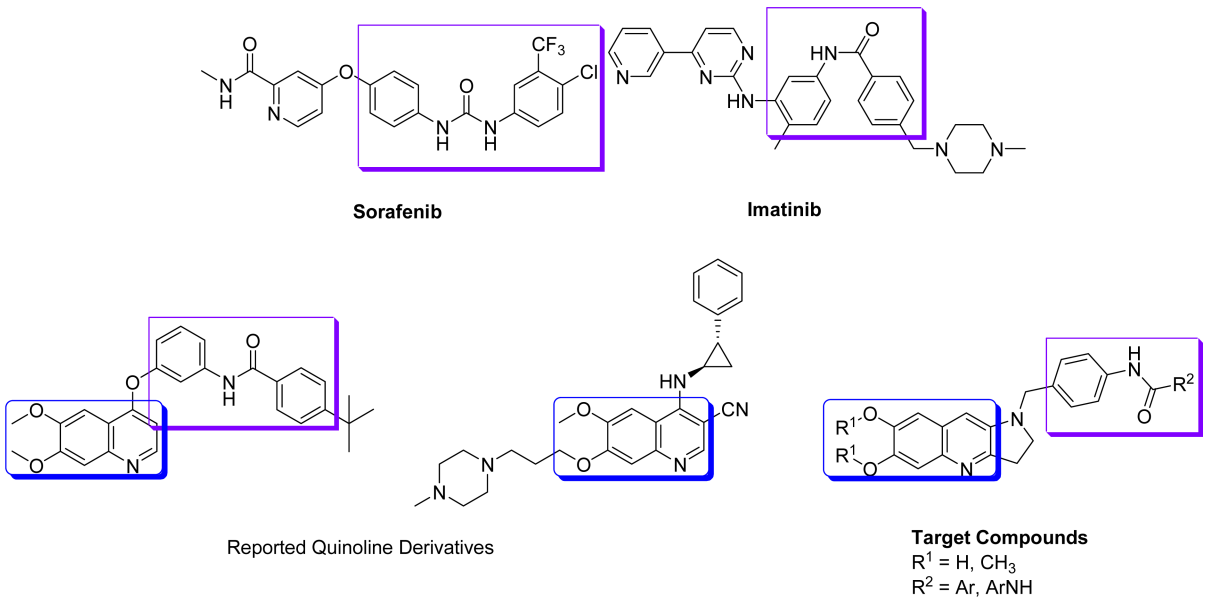
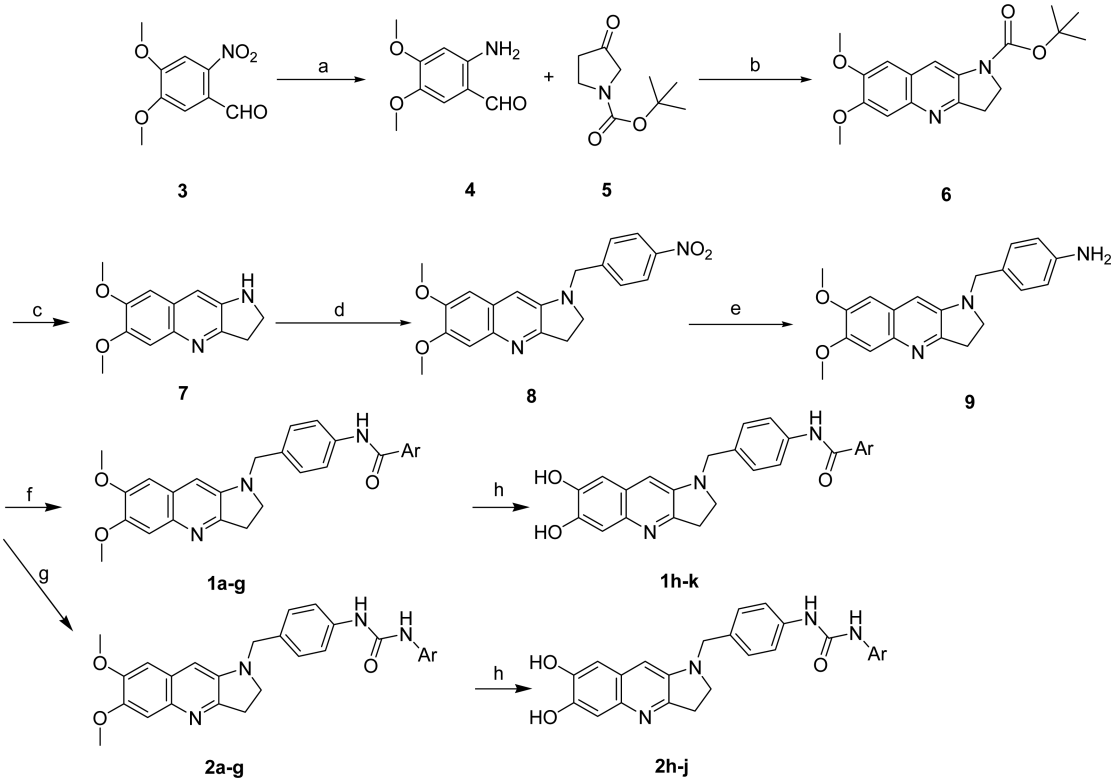


Figure 1. Structures of Sorafenib, Imatinib, reported quinoline derivatives, and the target compounds.



Scheme 1. Reagents and conditions: (a) Pd/C, THF, H_2 gas, 50 psi, 15 min; (b) NaOH, EtOH, rt, 24 h; (c) HCl gas, DCM, 1,4-dioxane, 4 h; (d) 1-(bromomethyl)-4-nitrobenzene, K_2CO_3, DMF, 80 °C, 16 h; (e) $SnCl_2$, EtOH, reflux; (f) ArCOOH, HOBt, EDCI, Cs_2CO_3, DMF, 80 °C, 24 h; (g) ArNCO, Cs_2CO_3, THF rt, 24 h. (h) BBr_3, DCM, −78 °C, 1 h; rt, overnight.

is currently subjected to clinical trials for other types of cancer. Imatinib (Gleevec®, Fig. 1) is an example of diarylamides which is used for treatment of chronic myeloid leukemia (CML) with diminished side effects.[21] In addition, different quinoline analogues have been reported as potent EGFR tyrosine kinase inhibitors (Fig. 1).[22,23] In the present investigation, synthesis and preliminary cytotoxicity evaluation of new diarylamides and diarylureas possessing 2,3-dihydropyrrolo[3,2-*b*]quinoline scaffold are reported. The results are explained in details.

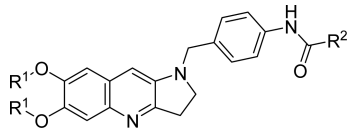
Results and Discussion

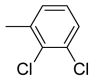
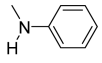
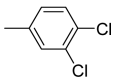
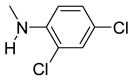
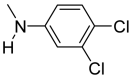
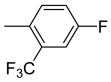
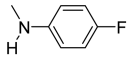
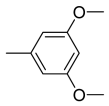
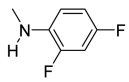
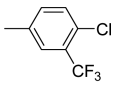
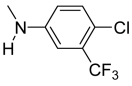
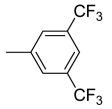
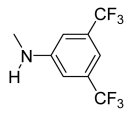
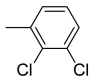
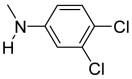
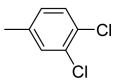
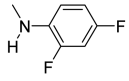
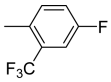
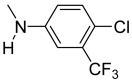
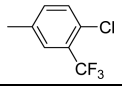
Chemistry. The synthetic strategy to obtain the target compounds **1a-k** and **2a-j** is illustrated in Scheme 1. The pathway started with reduction of 6-nitroveratraldehyde (**3**) using palladium over carbon in hydrogen atmosphere under pressure to obtain 6-aminoveratraldehyde (**4**).[24] Friedländer's cyclization of the *o*-aminoaldehyde compound **4** with *N*-Boc protected pyrrolidine-3-one **5** using sodium hydroxide produced the *N*-Boc protected dihydropyrrolo[3,2-*b*]quinoline derivative **6**. Boc deprotection of compound **6** using HCl gas afforded 6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinoline (**7**). *N*-alkylation of compound **7** using 1-(bromomethyl)-4-nitrobenzene in the presence of anhydrous potassium carbonate gave the corresponding *N*-(4-nitrobenzyl) compound **8**. Reduction of the nitro group of **8** was carried out by reaction with tin(II) chloride in refluxing ethanol produced the corresponding amino compound **9**. The use of Pd/C in hydrogen atmosphere in this step was unsuitable to avoid *N*-debenzylation. Condensation of the amino compound **9** with the appropriate aryl carboxylic acids in the presence of HOBt/EDCI/Ce_2CO_3 gave the target diarylamides **1a-g**. Reaction of the amino derivative **9** with the appropriate aryl isocyanate in the presence of cesium carbonate yielded the target diarylureas **2a-g**. Demethylation of the methoxy groups of some selected dimethoxy target compounds using boron tribromide produced the corresponding dihydroxyl compounds **1h-k** and **2h-j**. Structures of the target compounds and their yield percentages are illustrated in Table 1.

Biological Evaluation. The target compounds were tested for *in vitro* anticancer activity at the National Cancer Institute (NCI), Bethesda, Maryland, USA,[25] against tumor cells in a full panel of 60 cell lines taken from nine different tissues (blood, lung, colon, CNS, skin, ovary, kidney, prostate, and breast). The compounds were tested at a single-dose concentration of 10 μM. And the best results (percentages of growth inhibition) are illustrated in Table 2.

The highest % inhibitions were expressed by compounds **1f**, **1g**, **2a**, **2b**, and **2e-g** (Table 2). All of them are dimethoxy analogues. None of the dihydroxyl derivatives **1h-k** and **2h-j** showed promising activity. And the dimethoxy compounds **1f**, **2e**, and **2f** were more active than the corresponding dihydroxyl analogues. So it can be concluded that dimethoxy groups are more optimum for antiproliferative activity of this series of compounds. This may be attributed to the steric

Table 1. Structures of the target compounds and their yield percentages



Compd. No.	R^1	R^2	Yield %	Compd. No.	R^1	R^2	Yield %
1a	CH_3		23	**2a**	CH_3		48
1b	CH_3		34	**2b**	CH_3		34
1c	CH_3		33	**2c**	CH_3		42
1d	CH_3		38	**2d**	CH_3		53
1e	CH_3		44	**2e**	CH_3		61
1f	CH_3		34	**2f**	CH_3		43
1g	CH_3		52	**2g**	CH_3		43
1h	H		46	**2h**	H		38
1i	H		50	**2i**	H		36
1j	H		38	**2j**	H		32
1k	H		30				

and/or electronic differences between methoxy and hydroxyl groups.

Upon comparing the activities of compounds **1g** and **2g** on MOLT-4 leukemia cell line, we found that the urea derivative **2g** than the corresponding analogue **1g** possessing amide linker. This may be attributed to that the longer spacer, urea moiety, may geometrically permit appropriate fitting of compound **2g** molecule at the receptor site in MOLT-4 cells. Or the terminal NH group of the urea moiety may form additional hydrogen bond(s) at the receptor site. Any or both of these effects would enable optimal drug-receptor interaction, and hence higher antiproliferative activity.

Table 2. % Growth inhibition of selected compounds over the most sensitive cell lines

Compd. No.	Cell Line	Cancer Type	% Inhibition
1f	MCF7	Breast	**84.97**
	MDA-MB-468	Breast	**87.13**
1g	CCRF-CEM	Leukemia	50.05
	MOLT-4	Leukemia	53.36
2a	HOP-92	Non-Small Cell Lung	52.11
2b	UACC-62	Melanoma	56.43
	MCF7	Breast	62.64
	MDA-MB-231/ATCC	Breast	60.47
	MDA-MB-468	Breast	69.81
2e	A498	Renal	50.62
	MDA-MB-468	Breast	54.43
2f	NCI-H460	Non-Small Cell Lung	57.04
	T-47D	Breast	51.87
2g	K-562	Leukemia	50.24
	MOLT-4	Leukemia	63.12
	PC-3	Prostate	60.37
	MCF7	Breast	50.67

The effect of substituents on the terminal aryl ring on activity was also investigated. Compound **2b** with 2,4-dichlorophenyl moiety showed higher activity than the corresponding 2,4-difluorophenyl analogue **2e** against MDA-MB-468 breast cancer cell line. In addition, compound **2b** was more active against MCF7 breast cancer cell line than compound **2g** possessing 3,5-bis(trifluoromethyl)phenyl terminal ring.

Among all the target compounds, compound **1f** with 6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinoline nucleus, amide linker, and 4-chloro-3-(trifluoromethyl)phenyl terminal ring exerted the most promising results with the highest % inhibition values. At the test concentration, it inhibited the growth of MCF7 and MDA-MB-468 breast cancer cell lines by 84.97% and 87.13%, respectively. Its % growth inhibition values over all the tested cell lines are summarized in Figure 2. Interestingly, compound **1f** showed high selectivity against those two cell lines more than all the other tested cell lines. It inhibited the growth of MOLT-4 leukemia cell line by 43.19%, while all the other tested cell lines were inhibited only less than 40%. So the selectivity index of compound **1f** towards MCF7 and MDA-MB-468 breast cancer cell lines is about 2.

It is noteworthy that compounds **1f**, **2b**, and **2e** showed good results against MDA-MB-468 breast cancer cell line. Compound **2b** also inhibited the growth of MDA-MB-231/ATCC breast cancer cell line by 60.47%. In both MDA-MB-468 and MDA-MB-231/ATCC, EGFR tyrosine kinase is overexpressed.[26-28] So EGFR kinase may be a possible target molecule for this series of compounds. This assumption can be reinforced with the higher % inhibition expressed by compound **2b** against MDA-MB-468 cell line (69.81%) than

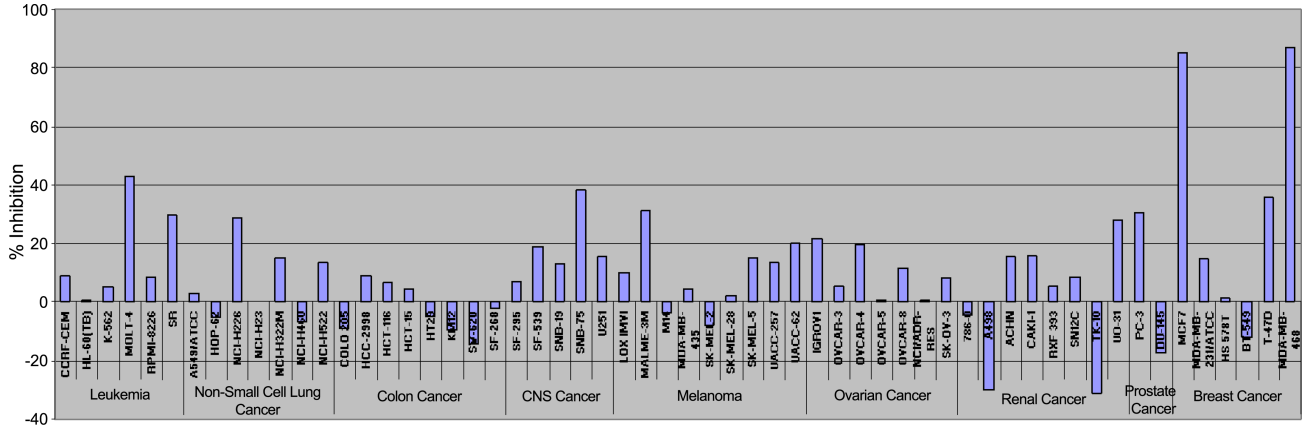


Figure 2. % Inhibition expressed by compound **1f** at a single-dose concentration of 10 μM over the NCI-60 cancer cell lines.

against MDA-MB-231/ATCC (60.47%) which expresses lower level of EGFR.[29]

Conclusions

A series of new diarylamides and diarylureas possessing 2,3-dihydropyrrolo[3,2-*b*]quinoline scaffold was synthesized based on our previous literature studies, and as a continuation of our ongoing anticancer agent development program. Their *in vitro* antiproliferative activities were screened over NCI-60 cancer cell line panel of nine different cancer types. It was found that dimethoxy compounds were generally more active than the corresponding dihydroxyl analogues. Compound **1f** with 6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinoline nucleus, amide linker, and 4-chloro-3-(trifluoromethyl)phenyl terminal ring showed the highest inhibition percentages with selectivity towards MCF7 and MDA-MB-468 breast cancer cell lines. Due to its high activity and selectivity towards those two breast cancer cell lines, compound **1f** can be considered as a promising lead for future development of selective anticancer agents for treatment of breast cancer. In addition to compound **1f**, compounds **2b** and **2e** showed potential activity against MDA-MB-468 cell line at which EGFR tyrosine kinase is highly overexpressed. So EGFR kinase inhibition may be a possible mechanism of anticancer activity of our target compounds. This finding will be considered in the future evaluation of our target compounds at molecular level.

Experimental

General. Nuclear magnetic resonance (NMR) spectroscopy was performed using a Bruker ARX-300, 300 MHz (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Purities of the target compounds (> 95%) were determined by HPLC analysis. Unless otherwise noted, all solvents and reagents were commercially available and used without further purification.

2-Amino-4,5-dimethoxybenzaldehyde (4). Pd/C (5%, 0.5 g) was suspended in a solution of 4,5-dimethoxy-2-nitrobenzaldehyde (**3**, 1.0 g, 4.74 mmol) in dry THF (10 mL), and the reaction mixture was stirred at room temperature for 15 min in hydrogen atmosphere under 50 psi pressure. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to obtain the title compound (0.85 g, 99%). ^{1}H-NMR ($CDCl_3$) δ 9.74 (s, 1H), 6.92 (s, 1H), 6.16 (brs, 3H), 3.94 (s, 3H), 3.90 (s, 3H).

***tert*-Butyl 6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinoline-1-carboxylate (6).** A mixture of compound **4** (1.0 g, 55.19 mmol) and *tert*-butyl 3-oxopyrrolidine-1-carboxylate (**5**, 1.2 g, 6.48 mmol) in ethanol (50 mL) was stirred at room temperature for 10 min. NaOH (80% solution, 3 mL) was slowly added at 0 ºC, and then stirred room temperature for 24 h. Ethanol was concentrated under reduced pressure, distilled water (20 mL) and CH_2Cl_2 (50 mL) were added, and the organic layer was separated. Water (20 mL) was added to the organic layer, and Conc. HCl was added dropwise to adjust the pH to 7-8. The mixture was stirred for 30 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain the title compound (0.8 g, 44%). ^{1}H-NMR ($CDCl_3$) δ 7.14 (s, 1H), 6.92 (s, 1H), 6.65 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.28 (t, 2H, J = 8.2 Hz), 3.10 (t, 2H, J = 8.0 Hz), 1.48 (s, 9H).

6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinoline (7). To a solution of compound **6** (1.0 g, 3.03 mmol) in CH_2Cl_2 (20 mL), HCl solution in dioxane was added dropwise. The reaction mixture was stirred at room temperature for 4 h. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layer extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain the title compound (0.6 g, 86%). ^{1}H-NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.37 (s, 1H), 7.04-7.01 (m, 2H), 4.25 (t, 2H, J = 8.1 Hz), 4.03 (s, 3H), 3.99 (s, 3H), 3.34

(t, 2H, J = 8.3 Hz).

6,7-Dimethoxy-1-(4-nitrobenzyl)-2,3-dihydropyrrolo[3,2-*b*]quinoline (8). To a solution of compound **7** (1.0 g, 4.34 mmol) in dry DMF (10 mL), anhydrous potassium carbonate (1.12 g, 8.68 mmol) was added. The mixture was stirred at room temperature for 30 min. After that, 1-(bromomethyl)-4-nitrobenzene (1.03 g, 4.77 mmol) was added dropwise, and the reaction mixture was stirred at 80 ºC for 16 h. The reaction mixture was cooled to room temperature, and it was partitioned between water (25 mL) and ethyl acetate (25 mL). The organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain the title compound (0.8 g, 50% yield).

4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]benzenamine (9). A mixture of compound **9** (1.0 g, 2.98 mmol) and stannous chloride dihydrate (3.2 g, 14.9 mmol) in ethanol (25 mL) was heated under reflux for 6 h. The mixture was concentrated under reduced pressure, and standard aqueous $NaHCO_3$ solution (20 mL) and CH_2Cl_2 (50 mL) were added thereto. The mixture was stirred for 30 min, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer extracts were dried over anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to obtain the title compound (0.8 g, 87% yield).

General Method for Synthesis of the Target Amide Derivatives 1a-g. A mixture of compound **9** (34 mg, 0.1 mmol), the appropriate carboxylic acid derivative (0.2 mmol), HOBt (36 mg, 0.3 mmol), EDCI (38 mg, 0.2 mmol), and cesium carbonate (65 mg, 0.2 mmol) in dry DMF (1.0 mL) under nitrogen atmosphere was then stirred at 80 °C for 24 h. The reaction mixture was cooled and then partitioned between saturated aqueous sodium carbonate and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layer extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography using the appropriate proportion of ethyl acetate and hexane as mobile phase.

2,3-Dichloro-*N*-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo-[3,2-*b*]quinolin-1-yl)methyl]phenyl}benzamide (1a): ^{1}H-NMR ($CDCl_3$) δ 7.98 (d, 2H, J = 7.9 Hz), 7.94 (d, 2H, J = 8.0 Hz), 7.70 (s, 1H), 7.62-7.49 (m, 4H), 7.30 (s, 1H), 4.30 (s, 2H), 4.25 (t, 2H, J = 8.1 Hz), 3.99 (s, 6H), 3.11 (t, 2H, J = 8.0 Hz).

3,4-Dichloro-*N*-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo-[3,2-*b*]quinolin-1-yl)methyl]phenyl}benzamide (1b): ^{1}H-NMR ($CDCl_3$) δ 8.13 (brs, 1H), 7.67-7.58 (m, 2H), 7.47 (d, 1H, J = 8.4 Hz), 7.38 (d, 2H, J = 7.4 Hz), 7.30 (d, 1H, J = 8.2 Hz), 7.10-7.08 (m, 2H), 7.02 (s, 2H), 4.32 (s, 2H), 3.83 (s, 6H), 3.42 (t, 2H, J = 8.0 Hz), 3.09 (t, 2H, J = 8.0 Hz).

***N*-{4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-2-iodobenzamide (1c):** ^{1}H-NMR ($CDCl_3$) δ 7.82-7.78 (m, 3H), 7.61 (d, 2H, J = 8.2 Hz), 7.53 (d, 2H, J = 8.3 Hz), 7.02 (d, 2H, J = 7.5 Hz), 6.82 (s, 2H), 4.30 (s, 2H), 3.87 (s, 6H), 3.25 (t, 2H, J = 8.0 Hz), 3.11 (t, 2H, J = 8.1 Hz).

***N*-{4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-4-fluoro-2-(trifluoromethyl)benzamide (1d):** ^{1}H-NMR ($CDCl_3$) δ 7.49-7.46 (m, 3H), 7.15-7.13 (m, 2H), 7.10 (d, 2H, J = 7.8 Hz), 7.02 (d, 2H, J = 7.9 Hz), 6.75 (s, 1H), 4.31 (s, 2H), 3.92 (s, 6H), 3.21 (t, 2H, J = 8.1 Hz), 3.10 (t, 2H, J = 8.2 Hz).

***N*-{4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-3,5-dimethoxybenzamide (1e):** ^{1}H-NMR ($CDCl_3$) δ 8.14-8.11 (m, 2H), 7.87 (s, 1H), 7.53-7.50 (m, 2H), 7.02 (d, 1H, J = 8.0 Hz), 7.13-7.09 (m, 3H), 6.01 (d, 1H, J = 7.9 Hz), 4.30 (s, 2H), 3.87-3.85 (m, 12H), 3.29 (t, 2H, J = 8.1 Hz), 3.11 (t, 2H, J = 8.0 Hz).

4-Chloro-*N*-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-3-(trifluoromethyl)benzamide (1f): ^{1}H-NMR ($CDCl_3$) δ 7.98 (d, 2H, J = 7.8 Hz), 7.94 (d, 2H, J = 8.0 Hz), 7.70 (s, 1H), 7.62 (d, 2H, J = 7.6 Hz), 7.49 (d, 2H, J = 7.8 Hz), 7.30 (s, 1H), 4.30 (s, 2H), 3.99 (s, 6H), 3.32 (t, 2H, J = 8.1 Hz), 3.11 (t, 2H, J = 8.0 Hz).

***N*-{4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-3,5-bis(trifluoromethyl)benzamide (1g):** ^{1}H-NMR ($CDCl_3$) δ 8.14-8.11 (m, 2H), 7.87 (s, 1H), 7.52-7.50 (m, 2H), 7.02 (s, 1H), 7.14-7.10 (m, 3H), 6.01 (d, 1H, J = 8.0 Hz), 4.29 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.21 (t, 2H, J = 8.0 Hz), 3.01 (t, 2H, J = 7.8 Hz).

General Method for Synthesis of the Target Urea Derivatives 2a-g. To a mixture of compound **9** (34 mg, 0.1 mmol) and cesium carbonate (33 mg, 0.1 mmol) in anhydrous THF (3 mL), a solution of the appropriate aryl isocyanate (0.1 mmol) in anhydrous THF (3 mL) was added dropwise at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure, and purification was carried out by flash column chromatography using the appropriate proportion of ethyl acetate and hexane as mobile phase.

1-{4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-3-phenylurea (2a): ^{1}H-NMR ($CDCl_3$) δ 7.79-7.77 (m, 2H), 7.52 (d, 2H, J = 7.7 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.14 (d, 2H, J = 7.9 Hz), 7.14-7.10 (m, 3H), 7.02 (d, 1H, J = 6.7 Hz), 4.32 (s, 2H), 3.92 (s, 6H), 3.23 (t, 2H, J = 8.0 Hz), 3.11 (t, 2H, J = 8.1 Hz).

1-(2,4-Dichlorophenyl)-3-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo[3,2-b]quinolin-1-yl)methyl]phenyl}urea (2b): ^{1}H-NMR ($CDCl_3$) δ 7.52 (d, 2H, J = 7.6 Hz), 7.48 (s, 1H), 7.16-7.14 (m, 2H), 7.10 (d, 2H, J = 8.0 Hz), 7.02 (d, 2H, J = 7.3 Hz), 6.75 (s, 1H), 4.31 (s, 2H), 3.97 (s, 6H), 3.21 (t, 2H, J = 8.0 Hz), 3.09 (t, 2H, J = 8.1 Hz).

1-(3,4-Dichlorophenyl)-3-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}urea (2c): ^{1}H-NMR ($CDCl_3$) δ 7.92-7.90 (m, 4H), 7.50 (d, 2H, J = 7.7 Hz), 7.49 (d, 2H, J = 7.9 Hz), 7.01 (d, 2H, J = 8.0 Hz), 4.40 (s, 2H), 3.97 (s, 6H), 3.24 (t, 2H, J = 8.0 Hz), 3.02 (t, 2H, J =

8.0 Hz).

1-{4-[(6,7-Dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-3-(4-fluorophenyl)urea (2d): ^{1}H-NMR ($CDCl_3$) δ 7.95-7.91 (m, 3H), 7.60 (d, 2H, *J* = 7.7 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 7.6 Hz), 6.83 (d, 2H, *J* = 7.8 Hz), 4.34 (s, 2H), 3.97 (s, 6H), 3.20 (t, 2H, *J* = 7.6 Hz), 3.05 (t, 2H, *J* = 7.7 Hz).

1-(2,4-Difluorophenyl)-3-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}urea (2e): ^{1}H-NMR ($CDCl_3$) δ 7.53-7.49 (m, 3H), 7.48-7.46 (m, 2H), 7.15-7.12 (m, 2H), 7.10 (d, 2H, *J* = 7.6 Hz), 7.02-7.00 (m, 2H), 6.75 (s, 1H), 4.31 (s, 2H), 3.95 (s, 6H), 3.25 (t, 2H, *J* = 7.7 Hz), 3.09 (t, 2H, *J* = 7.9 Hz).

1-[4-Chloro-3-(trifluoromethyl)phenyl]-3-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo[3,2-b]quinolin-1-yl)methyl]phenyl}urea (2f): ^{1}H-NMR ($CDCl_3$) δ 7.92-7.89 (m, 3H), 7.51 (d, 2H, *J* = 8.2 Hz), 7.40 (d, 2H, *J* = 8.1 Hz), 7.01-6.98 (m, 3H), 4.40 (s, 2H), 3.92 (s, 6H), 3.32 (t, 2H, *J* = 7.6 Hz), 3.07 (t, 2H, *J* = 7.7 Hz).

1-[3,5-Bis(trifluoromethyl)phenyl]-3-{4-[(6,7-dimethoxy-2,3-dihydropyrrolo[3,2-b]quinolin-1-yl)methyl]phenyl})-urea (2g): ^{1}H-NMR ($CDCl_3$) δ 8.14-8.11 (m, 3H), 7.87 (s, 1H), 7.53-7.51 (m, 2H), 7.02 (s, 1H), 7.13-7.09 (m, 3H), 7.01 (s, 1H), 4.30 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.22 (t, 2H, *J* = 7.7 Hz), 3.01 (t, 2H, *J* = 7.8 Hz).

General Method for Synthesis of the Target Dihdroxyl Derivatives 1h-k and 2h-j. To a solution of the appropriate dimethoxy compound (0.1 mmol) in methylene chloride (1 mL), BBr_3 (0.5 mL of a 1M solution in methylene chloride, 1.2 mmol) was added dropwise at −78 °C under N_2 and the reaction mixture was stirred at the same temperature for 1 h. The mixture was allowed to warm to room temperature and stirred overnight at the same temperature. The mixture was quenched with saturated aqueous $NaHCO_3$. Ethyl acetate was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer extracts were washed with brine, dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by short column chromatography.

2,3-Dichloro-*N*-{4-[(6,7-dihydroxy-2,3-dihydropyrrolo-[3,2-*b*]quinolin-1-yl)methyl]phenyl}benzamide (1h): ^{1}H-NMR ($CDCl_3$) δ 7.81-7.77 (m, 4H), 7.50-7.49 (m, 4H), 7.03-7.01 (m, 2H), 6.89 (d, 2H, *J* = 7.8 Hz), 4.30 (s, 2H), 3.22 (t, 2H, *J* = 7.7 Hz), 3.01 (t, 2H, *J* = 7.6 Hz).

3,4-Dichloro-*N*-{4-[(6,7-dihydroxy-2,3-dihydropyrrolo-[3,2-*b*]quinolin-1-yl)methyl]phenyl}benzamide (1i): ^{1}H-NMR ($CDCl_3$) δ 7.98-7.96 (m, 4H), 7.94 (d, 2H, *J* = 7.8 Hz), 7.70 (s, 1H), 7.62 (d, 2H, *J* = 8.0 Hz), 7.49-7.47 (m, 2H), 7.30 (s, 1H), 4.30 (s, 2H), 3.24 (t, 2H, *J* = 7.7 Hz), 3.01 (t, 2H, *J* = 7.6 Hz).

***N*-{4-[(6,7-Dihydroxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-4-fluoro-2-methylbenzamide (1j):** ^{1}H-NMR ($CDCl_3$) δ 7.92-7.88 (m, 3H), 7.68 (s, 1H), 7.57 (d, 2H, *J* = 8.1 Hz), 7.53 (d, 2H, *J* = 8.2 Hz), 7.47-7.45 (m, 2H), 7.02-7.00 (m, 2H), 4.30 (s, 2H), 3.23 (t, 2H, *J* = 7.6 Hz), 3.01 (t, 2H, *J* = 7.7 Hz).

4-Chloro-*N*-{4-[(6,7-dihydroxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-3-(trifluoromethyl)benzamide (1k): ^{1}H-NMR ($CDCl_3$) δ 7.98-7.94 (m, 4H), 7.70 (s, 1H), 7.62 (d, 2H, *J* = 8.2 Hz), 7.49 (d, 2H, *J* = 8.2 Hz), 7.30 (s, 1H), 7.04-7.01 (m, 2H), 4.30 (s, 2H), 3.21 (t, 2H, *J* = 7.6 Hz), 3.01 (t, 2H, *J* = 7.6 Hz).

1-(3,4-Dichlorophenyl)-3-{4-[(6,7-dihydroxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}urea (2h): ^{1}H-NMR ($CDCl_3$) δ 7.90-7.87 (m, 4H), 7.72-7.62 (m, 4H), 7.49 (d, 2H, *J* = 8.1 Hz), 7.30 (s, 1H), 6.89 (s, 1H), 6.82 (s, 1H), 4.35 (s, 2H), 3.39 (t, 2H, *J* = 7.8 Hz), 3.06 (t, 2H, *J* = 7.7 Hz).

1-(2,4-Difluorophenyl)-3-{4-[(6,7-dihydroxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}urea (2i): ^{1}H-NMR ($CDCl_3$) δ 8.12-8.09 (m, 4H), 7.67 (s, 1H), 7.53-7.51 (m, 3H), 7.02 (d, 1H, *J* = 8.0 Hz), 7.13-7.09 (m, 3H), 7.01 (s, 1H), 4.31 (s, 2H), 3.36 (t, 2H, *J* = 7.9 Hz), 3.08 (t, 2H, *J* = 7.8 Hz).

1-[4-Chloro-3-(trifluoromethyl)phenyl]-3-{4-[(6,7-dihydroxy-2,3-dihydropyrrolo[3,2-*b*]quinolin-1-yl)methyl]phenyl}-urea (2j): ^{1}H-NMR ($CDCl_3$) δ 7.98-7.94 (m, 4H), 7.70 (s, 1H), 7.62 (d, 2H, *J* = 7.9 Hz), 7.49-7.46 (m, 2H), 7.30 (s, 1H), 7.15-7.11 (m, 3H), 4.30 (s, 2H), 3.39 (t, 2H, *J* = 7.8 Hz), 3.09 (t, 2H, *J* = 8.0 Hz).

60 Cancer Cell Line Screening at the NCI. Screening against a panel of 60 cancer cell lines was carried out at the National Cancer Institute (NCI), Bethesda, Maryland, USA,[25] applying the standard protocol of the NCI.[30]

Acknowledgments. This work was supported by Korea Institute of Science and Technology (KIST), KIST Project (2E22360). We would like to thank the National Cancer Institute (NCI), Bethesda, Maryland, USA, for performing the anticancer testing of the target compounds over 60 cancer cell lines.

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