Identification of Potent and Selective Inhibitors of PDGF Receptor Autophosphorylation

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We report the structure−activity relationship of quinoline and quinazoline derivatives, which include urea, thiourea, urethane, and acylthiourea groups, as inhibitors of the platelet-derived growth factor (PDGF) receptor autophosphorylation. Our previous studies showed that the quinoline and quinazoline derivatives including urea, thiourea, and carbamate groups were highly potent compounds as the PDGF receptor autophosphorylation inhibitor, but these compounds did not exhibit receptor selectivity between the PDGF receptor and the c-kit receptor. As a result of further synthesis and biological evaluation, we have found that the quinoline and quinazoline-acylthiourea derivatives showed not only good inhibitory activity for the PDGF receptor but also receptor selectivity between the PDGF receptor and the c-kit receptor. Furthermore *N*-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-*N*′-(2-methylbenzoyl)thiourea exhibited potent oral efficacy in in vivo assay using the rat carotid balloon injury model. Therefore, the quinoline and quinazoline-acylthiourea derivatives may be expected to have potential as therapeutic agents for the treatment of restenosis.

Introduction

Platelet-derived growth factor (PDGF) is known as a potent mitogen and chemotactic factor for various mesenchymal cells such as fibroblasts and vascular smooth muscle cells. PDGF stimulates the tyrosine kinase activity of its receptor, the PDGF receptor, and induces the autophosphorylation of the PDGF receptor that is followed by the stimulation of various intracellular signalings. Because the PDGF/PDGF receptor is proposed to be correlated with various cell-proliferative diseases such as vascular restenosis, liver cirrhosis, and cancer,[1−3] a selective inhibitor of the autophosphorylation of the PDGF receptor may have a therapeutic potential. Furthermore, recent success in the clinical evaluation of tyrosine kinase inhibitors, for example **1** (STI571),[4−5] strongly suggests that these targets represent drug intervention opportunities. Several adenosine 5′-triphosphate (ATP) competitive inhibitors of the PDGF receptor autophosphorylation have been reported. Recently, several series of compounds, 3-substituted quinolines,[6,7] 3-substituted quinoxalines,[8,9] 2-phenylaminopyrimidines,[10−12] 3-substituted indolinones,[13] and piperazinyl quinazolines,[14] were reported as small molecule PDGF receptor inhibitors. Even though several compounds[15,16] are known as potent inhibitors of the PDGF receptor autophosphorylation, receptor selectivity, especially against the c-kit receptor[17] that belongs to the PDGF receptor family, is still low. In our previous screening of in-house compounds,[18−20] we have found a novel series of *N*-substituted-*N*′-{4-(4-quinolyloxy)phenyl}urea derivatives as potent inhibitors for the PDGF receptor autophosphorylation. Especially **2**, shown in Figure 1, strongly inhibited the PDGF receptor autophosphorylation with an IC_{50} value of 12 nM. Therefore, we designed and synthesized 6,7-dimethoxyquinoline and 6,7-dimethoxyquinazoline derivatives to increase receptor selectivity. In this paper, we present our effort to improve the inhibitory activities for the PDGF receptor autophosphorylation and receptor selectivity, in particular, against the c-kit receptor by a SAR study focusing on the urea, thiourea, carbamate, and acylthiourea moieties. The result of a biological evaluation including an in vivo study is also described.

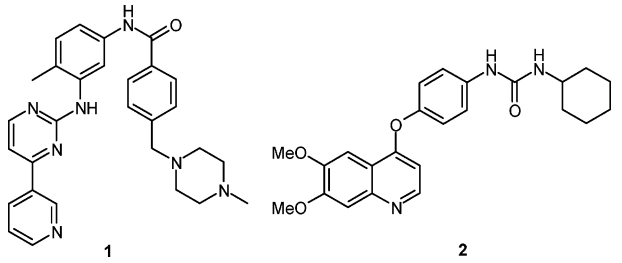
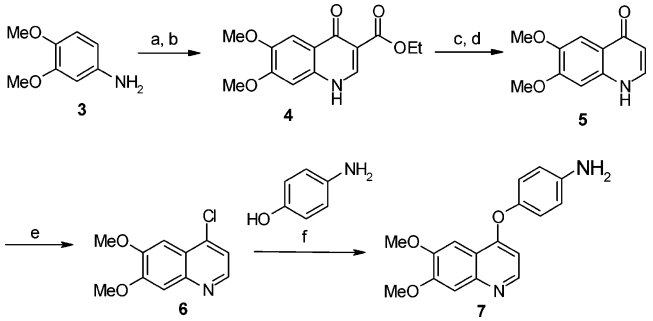


Figure 1. Structure of **1** and novel quinoline−urea derivative **2**.

Scheme 1[a]



[a] Reagents and conditions: (a) diethyl ethoxymethylenemalonate, 120 °C; (b) diphenyl ether, 280 °C (66% for 2 steps); (c) 10% aqueous NaOH/MeOH, reflux; (d) diphenyl ether, 280 °C (99% for 2 steps); (e) $POCl_3$, reflux (85%); (f) NaH, DMSO, 100 °C (92%).

Results and Discussion

The general synthetic route of the 4-phenoxyquinoline derivatives is summarized in Scheme 1. 3,4-Dimethoxyaniline **3** was reacted with diethyl ethoxymethylmalonate, and then cyclization to form the quinolone structure was carried out in diphenyl ether at 280 °C. After hydrolysis of the ethyl ester, removal of carbon dioxide and chlorination provided the intermediate 4-chloro-6,7-dimethoxyquinoline **6** in good yield. 4-Aminophenol was then reacted with the quinoline derivative **6** to provide the key intermediate **7**.

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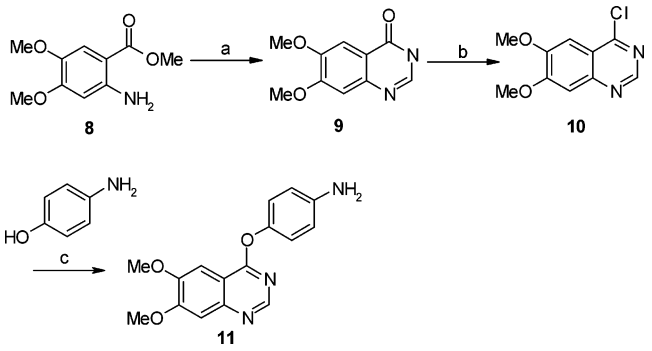
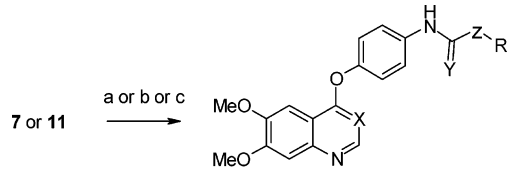
Scheme 2[a]



[a] Reagents and conditions: (a) H_2NCOH, NaOMe, 150 °C 10 h (90%); (b) $POCl_3$, reflux, 1 h (70%); (c) $^nBu_4NBr$, 2-butanone, 20% NaOH, reflux, 10 min (80%).

Scheme 3[a]



12 X = CH or N, Y = O, Z = NH
13 X = CH or N, Y = S, Z = NH
14 X = CH or N, Y = O, Z = O

[a] Reagents and conditions: (a) RNH_2, triphosgene, Et_3N, $CHCl_3$, rt, 1 h; (b) RNH_2, thiophosgene, Et_3N, $CHCl_3$, rt, 1 h; (c) ROH, triphosgene, Et_3N, toluene−$CHCl_3$, reflux 1 h.

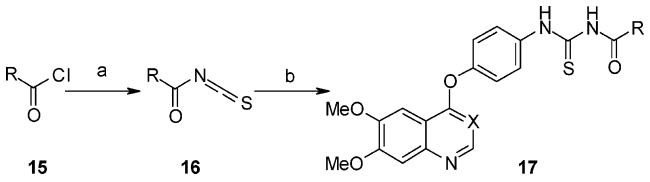
The synthesis of the quinazoline scaffold substituted by the 4-aminophenoxy groups at the C-4 position is illustrated in Scheme 2. Cyclization of methyl 2-amino-4,5-dimethoxybenzoate **8** using formamide as a solvent provided the quinazolone derivative **9** in high yield. The chlorination of the quinazolone derivative with phosphoryl chloride provided **10** in good yield. The chloroquinazoline derivative **10** was coupled with 4-aminophenol in the presence of the phase-transfer catalyst *n*-Bu_4NBr in 20% NaOH aqueous and 2-butanone to give the aminophenoxyquinazoline derivative **11** in good yield. The total yield of this synthetic route was over 50%, and the compounds were purified by filtration without column chromatography in each step.

The syntheses of several quinoline and quinazoline derivatives were carried out using quinoline and quinazoline scaffold **7** and **11**. The treatment of **7** and **11** with triphosgene and several primary amines in chloroform afforded the urea derivatives **12** in high yields (>80%). In the case of using thiophosgene instead of triphosgene, the thiourea derivatives **13** were obtained in moderate yields. The treatment of **7** and **11** with triphosgene and several primary or secondary alcohols in toluene−chloroform under reflux conditions provided the carbamate derivative **14** in high yields. The amino groups of **7** and **11** were modified into functionalized bonds using commercially available amines or alcohols (Scheme 3).

The synthesis of quinoline and quinazoline acylthiourea derivatives substituted by aliphatic or aromatic groups is illustrated in Scheme 4. Several commercially available acyl chlorides **15** were reacted with potassium thiocyanate in CH_3CN to give the thioisocyanate derivative **16**. The desired products **17** were obtained in moderate yield from quinoline and quinazoline key intermediates **7** and **11**.

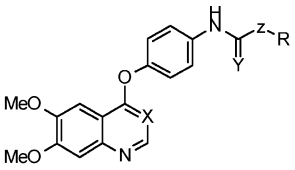
The inhibitory activities to the autophosphorylation of the PDGF receptor and the c-kit receptor by quinoline and quinazoline derivatives substituted by 4′-urea, thiourea, and carbamates

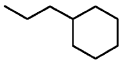
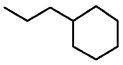
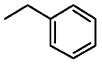
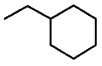
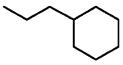
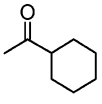
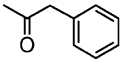
Scheme 4[a]



[a] Reagents and conditions: (a) NCSK, CH_3CN, 50 °C 1 h; (b) **7** (X = CH) or **11** (X = N), toluene:EtOH = 5:1, rt 2−10 h.

Table 1. Inhibitory Activity of PDGF Receptor and c-kit Receptor Phosphorylation

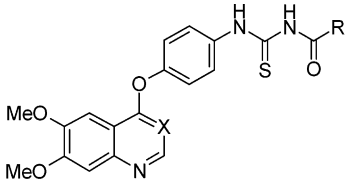


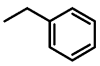
Compound	X	Y	Z	R	in vitro IC_{50} (nM) [a] PDGF-R	c-kit
1	-	-	-	-	96	219
2	CH	O	NH		12	22
12a	N	O	NH		7	27
12b	CH	O	NH		6	<30
12c	N	O	NH		9	<30
13a	CH	S	NH		40	69
13b	N	S	NH		46	303
13c	N	S	NH		37	153
14a	CH	O	O		5	19
14b	CH	O	O		18	80
17a	CH	S	NH		15	233
17b	CH	S	NH		28	202

[a] IC_{50} values were measured in intact cell, G292 cell for PDGF receptor and M07e cell for c-kit receptor, using an ELISA kit. IC_{50} values were determined by two separate tests and reported as mean values.

on the phenoxy ring are summarized in Table 1. The inhibitory activities to the kinase phosphorylation were measured in intact cells, G292 cells, and M07e cells using an ELISA kit. The urea derivatives attached to the cyclohexyl group and the 2-cyclo-

Table 2. Inhibitory Activity in PDGF Receptor and c-kit Receptor Phosphorylation Assay of Acylthiourea Derivatives



Compound	X	R	in vitro IC_{50} (nM)[a] PDGR-R	c-kit
17a	CH		15	233
17b	CH		28	202
17c	CH		8	938
17d	CH		5	637
17e	CH		4	434
17f	N		6	623

[a] See Table 1.

hexylethyl group exhibited comparable inhibitory activities compared to **2**. However, the selectivity between PDGF receptor and c-kit receptor were still very low in these compounds. There were no significant differences of in vitro activity between the quinoline and the quinazoline derivatives. The replacement of the urea group by a thiourea group decreased inhibitory activity for the PDGF receptor autophosphorylation. The selectivity of thiourea derivatives was still low. As for the carbamate derivatives, results very similar to those for the urea derivatives were obtained. Compounds substituted by phenyl or 2-cyclohexylethyl groups showed good inhibitory activity for the PDGF receptor, but the selectivity was still low. Even though these compounds had a good in vitro activity, the receptor selectivity was not satisfactory. On the other hand, using synthetic methods for the acylthiourea bond shown in Scheme 4, compounds **17a** and **17b** were synthesized and assayed. It is noted that these compounds exhibited good inhibitory activity for the PDGF receptor autophosphorylation; furthermore, the receptor selectivity was also increased. These results indicated that the acylthiourea bond was particularly effective in the receptor selectivity between the PDGF receptor and the c-kit receptor.

As shown in Table 2, the acylthiourea derivatives exhibited good inhibitory activity for the PDGF receptor, and the selectivity was increased compared to that of urea, thiourea, and carbamate derivatives. There was no significant difference in in vitro activity between the quinoline and the quinazoline derivatives. Furthermore replacement of the cyclohexyl or benzyl group by an aromatic ring produced more favorable results. It indicated that the aromatic ring attached to the acylthiourea moiety was important for the inhibitory activity

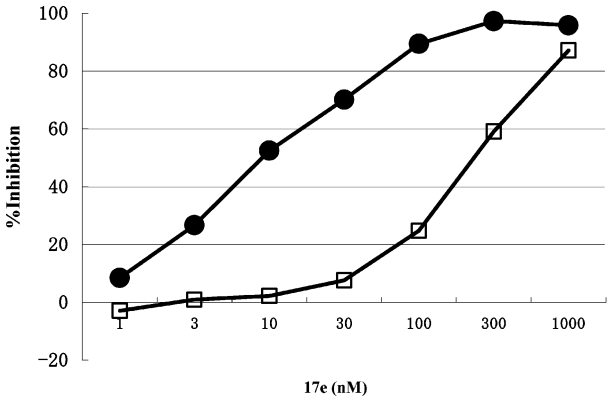


Figure 2. Inhibitory activities of **17e** on PDGF-Rα and c-kit (transactivation enzyme assays): (●) PDGF-Rα; (□) c-kit.

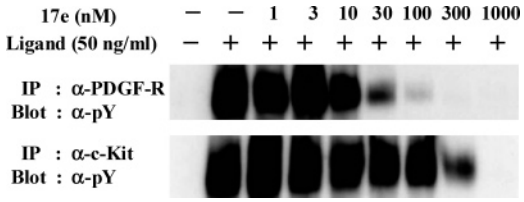


Figure 3. Effects of **17e** on the tyrosine phosphorylation of PDGF-Rα (G292 cells) and c-kit (M07e cells).

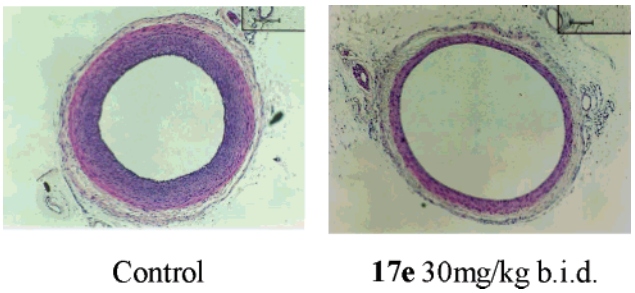


Figure 4. Cutaway of the rat carotid artery: (left) control; (right) oral administration of **17e** for 2 weeks.

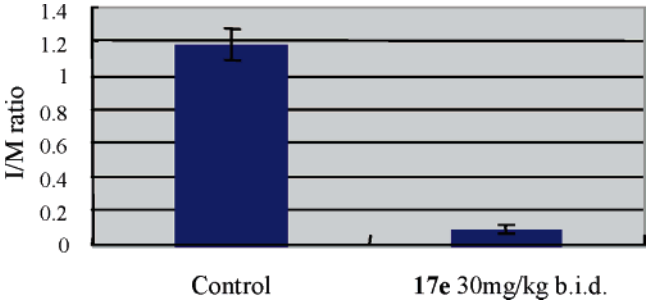


Figure 5. Inhibition of neointima formation, determined from intima/media ratio, of the rat carotid artery by oral administration of **17e** (30 mg/kg) twice daily for 2 weeks.

and high selectivity in these two receptors. Compounds **17c**−**f** showed good inhibitory activity and excellent receptor selectivity. Recently structural analysis of c-kit receptor was reported.[21] Computational analysis on the relationship between the conformational difference of these receptors and the high selectivity of **17c**−**f** will be discussed separately.

In enzyme assays, **17e** showed potent and selective inhibition on PDGF-Rα kinase compared to that on c-kit kinase (Figure 2). IC_{50} values were 7.6 nM for PDGF-Rα and 234 nM for c-kit. Figure 3 shows the inhibitory activities of **17e** on the tyrosine phosphorylation of PDGF-Rα in G292 cells and of c-kit in M07e cells. In these immunoprecipitation assays, **17e** showed

comparable results in the activities and the kinase selectivity with the data in ELISA assays.

The in vivo efficacy of **17e** was tested in the rat carotid balloon injury model. The compound was suspended in methylcellulose and was orally administrated (30 mg/kg) to Sprague Dawley rats ($n = 6$) twice daily for a period of 14 days starting on the day after the balloon injury. As shown in Figures 4 and 5, the oral administration of **17e** potently inhibited the formation of neointima in the injured carotid compared to vehicle treated controls. The reduction of the intima/media (I/M) ratio was 92%, with no abnormalities in the body weights of the treated animals. These results suggest that the acylthiourea derivative **17e** is a promising compound as an inhibitor for certain types of cell-proliferative disorders.

Conclusions

We prepared quinoline and quinazoline scaffolds to synthesize modified compounds including urea, thiourea, carbamate, and acylthiourea bonds, and evaluated their inhibitory activity for the PDGF receptor and the c-kit receptor phosphorylation in intact cells. These studies showed that the quinoline and quinazoline derivatives including urea, thiourea, and carbamate bonds were highly potent inhibitors of the PDGF receptor autophosphorylation, but these compounds did not exhibit receptor selectivity between the PDGF receptor and the c-kit receptor. On the other hand, the quinoline and quinazoline-acylthiourea derivatives showed not only good inhibitory activity for the PDGF receptor but also receptor selectivity. Especially **17c**−**f**, which have the aromatic ring directly to the acylthiourea moiety, exhibited an excellent selectivity between the PDGF receptor and the c-kit receptor. Additionally, **17e** exhibited potent oral efficacy in the rat balloon injury model. These results suggest that the quinoline and quinazoline-acylthiourea derivatives are promising therapeutic compounds for certain types of cell-proliferative diseases.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a JEOL JNM-LA400 (400 MHz) or JEOL JNM-A500 (500 MHz). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as the internal standard. MS spectra were collected with a PLATFORM-LC (micromass). High-resolution mass spectra were performed by TORAY Research Center, Inc. Column chromatography was carried out on silica gel 60 (70−230 mesh, KANTO Chemical) or preparative thin-layer chromatography (PLC plates; Merck). The purity of compounds was checked using a Shimazu CLASS-VP V5.032 HPLC equipped with XTerra RP18 (150 × 4.6 mm, s-3.5 μm) for methods A−D or INERTSIL ODS-3 (150 × 4.6 mm, s-5 μm) for methods E−I. The solvent system of CH_3CN/H_2O (100 mM NH_4OAc) was 45/55 (method A), 50/50 (method B), 55/45 (method C), 60/40 (method D), 55/45 (method E), 60/40 (method F), 65/35 (method G), 70/30 (method H), and 75/25 (method I) in 20 min; flow rate of 1 mL/min. The purity of all compounds used by biological assay was >95%. Compound **1** was purified from Gleevec (Novartis).

Measurement of Kinase Inhibitory Activities. Cell-Based ELISA Assays. G292 cells for PDGF-Rα assays and M07e cells for c-kit assays were cultured in 96-well microtiter plates and quiesced in the medium containing 0.1% FBS. The serial concentrations of test compounds were added and incubated at 37 °C for 1 h, followed by activating the receptors by adding the 50 ng/mL of PDGF-AA (01−309, Upstate Biotechnology) or SCF (Kirin CMC R&D Laboratories). Cells were solubilized by adding lysis buffer, and the solutions were transferred to the 96-well plates coated with an anti-phosphotyrosine antibody PY-20 (610000, BD Biosciences Pharmingen), and incubated the overnight at 4 °C. An anti-PDGF-Rα antibody (c-20, Santa Cruz Biotechnology Inc.) or an anti-c-kit antibody (c-19, Santa Cruz Biotechnology Inc.) was added to plates as a primary antibody, incubated for 1 h, followed by incubating with an anti-rabbit IgG conjugated with HRP (NA9340V, Amersham Biosciences) for 1 h. Color development was carried out using a color development kit for peroxidase (SUMIRON, Sumitomo Bakelite Co., Ltd.), and the absorbance was measured at 450 nm. The phosphorylation levels of kinase proteins were measured by presuming a phosphorylation degree of the receptor in the presence of a ligand to be 100% and in the absence of a ligand to be 0%, and IC_{50} values were then determined.

Enzyme Assays. PDGF-Rα (14-467, Upstate Biotechnology) or c-kit (P3081, Invitrogen) and the serial concentrations of test compound were incubated with ATP (10 μM) at rt for 30 min for PDGF-Rα and at 37 °C for 60 min for c-kit in the 96-well plates precoated with poly-Glu,Tyr (4:1). Reactions in plates were stopped by washing with PBS containing 0.05% Tween 20, and then an anti-phosphotyrosine antibody PY-20 (610000, BD Biosciences Pharmingen) was added and incubated for 1 h, followed by the incubation with an anti-mouse IgG conjugated with HRP (NA9310V, Amersham Biosciences) for 1 h. Color development was carried out using a color development kit for peroxidase (SUMIRON, Sumitomo Bakelite Co., Ltd.), and the absorbance was measured at 450 nm. The phosphorylation level of poly-Glu, Tyr (4:1) was measured by presuming the phosphorylation degree in the presence of ATP to be 100% and in the absence of ATP to be 0%, and IC_{50} values of test compound were then determined.

Immunoprecipitation Assay. The serial concentrations of test compound were added to G292 cells or M07e cells cultured in 6-well plates and incubated at 37 °C for 90 min. PDGF-Rα in G292 cells and c-kit in M07e cells were activated by the 50 ng/mL of PDGF-AA (01-309, Upstate Biotechnology) or SCF (Kirin CMC R&D Laboratories). Cells were solubilized by adding the lysis buffer, and equivalent amounts of proteins from each well were immunoprecipitated overnight at 4 °C with anti-PDGF-Rα antibody (c-20, Santa Cruz Biotechnology Inc.) or anti-c-kit antibody (c-19, Santa Cruz Biotechnology Inc.). SDS−PAGE was carried out, and proteins were transferred to nitrocellulose membranes. Tyrosine phosphorylation of PDGF-Rα proteins or c-kit proteins were blotted with an anti-phosphotyrosine antibody PY-20 (610000, BD Biosciences Pharmingen) for 1 h and then with an anti-mouse IgG conjugated with HRP (NA9310V, Amersham Biosciences) for 1 h, followed by development by using ECL Western blotting detection reagents (RPN2106, Amersham Biosciences).

Rat Carotid Balloon Injury Model. Wistar male rats (330 to 370 g) were anesthetized, a Fogaty 2F catheter was inserted through the right femoral artery to the left carotid artery, and abrasion was made three times with an expansion diameter of 2.5 mm. The test compound suspended in 1% cremophore EL (C-5135, SOGMA) was orally administered at 0.4 mL/100 g body weight twice a day for 2 weeks from the day before surgery. Fourteen days after the surgery, rats were euthanized and the left carotid artery was removed and fixed in buffered formalin. Sliced preparations embedded in paraffin were stained with HE and were subjected to image analysis for the measurement of the neointima area (I) and medial area (M) in the section of injured arteries. The I/M area ratio was calculated as an index for the evaluation of drug efficacy.

Ethyl 6,7-Dimethoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylate (4). A mixture of 3,4-dimethoxyaniline (3.00 g, 19.6 mmol) and diethyl ethoxymethylenemalonate (5.08 g, 23.50 mmol) was stirred at 120 °C for 1 h. Diphenyl ether (30 mL) was then added and stirred at 280 °C for 1 h. The reaction mixture was purified by column chromatography eluting with $CHCl_3$/MeOH (100/1 to 10/1) to obtain 3.58 g of **4** (66%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.28 (t, $J = 7.1$ Hz, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.20 (q, $J = 7.1$ Hz, 2H), 7.05 (s, 1H), 7.52 (s, 1H), 8.43 (d, $J = 6.6$ Hz, 1H), 12.06 (d, $J = 6.6$ Hz, 1H). MS (ESI): m/z 278 ($M^+ + 1$).

6,7-Dimethoxy-4-quinolone (5). To a solution of **4** (3.28 g, 11.84 mmol) in MeOH (30 mL) was added 10% aqueous NaOH (45 mL), and the mixture was heated under reflux for 1 h. The reaction mixture was acidified with 10% aqueous HCl. The resulting solid was collected by filtration and washed with $CHCl_3$/MeOH (200

mL/40 mL) to obtain 2.85 g of crude 6,7-dimethoxy-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid. Then, a mixture of the acid (2.85 g) and diphenyl ether (90 mL) was stirred at 280 °C for 1 h. The reaction mixture was purified by column chromatography eluting with $CHCl_3$/MeOH (100/1 to 10/1) to obtain 2.3 g of **5** (99%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.82 (s, 3H), 3.86 (s, 3H), 5.95 (d, J = 4.6 Hz, 1H), 6.69 (s, 1H), 7.43 (s, 1H), 7.78 (d, J = 4.6 Hz, 1H), 8.13 (s, 1H). MS (ESI): m/z 206 ($M^+ + 1$).

4-Chloro-6,7-Dimethoxyquinoline (6). A mixture of **5** (2.13 g, 10.39 mmol) and $POCl_3$ (1.45 mL, 15.59 mmol) was heated under reflux for 0.5 h. The reaction mixture was concentrated and extracted with $CHCl_3$/MeOH (40 mL/10 mL). The organic layer was washed with 5% aqueous NaOH and brine. The solution was dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography eluting with $CHCl_3$/MeOH (50/1) to obtain 1.98 g of **6** (85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.07 (s, 3H), 7.36 (d, J = 4.9 Hz, 1H), 7.42 (s, 1H), 7.43 (s, 1H), 8.59 (d, J = 4.6 Hz, 1H). MS (ESI): m/z 224 ($M^+ + 1$).

4-[(6,7-Dimethoxy-4-quinolyl)oxy]aniline (7). Sodium hydride (60 wt %, 3.2 g) was added to dimethyl sulfoxide (50 mL), and the mixture was stirred at room temperature for 20 min. 4-Aminophenol (8.7 g) was added thereto, and the mixture was stirred at room temperature for 10 min. Next, **6** (18.2 g) was added thereto, and the mixture was stirred at 100 °C for 3 h. Water was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogen carbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. Methanol was added to the residue, and the precipitated crystal was collected by suction filtration to give **7** (21.8 g, yield 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.3.82 (s, 2H), 4.09 (s, 3H), 4.13 (s, 3H), 6.64 (d, J = 6.3 Hz, 1H), 6.64 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.62 (s, 1H), 7.95 (s, 1H), 8.45 (d, J = 6.3 Hz, 1H). MS (ESI): m/z 297 ($M^+ + 1$).

6,7-Dimethoxy-4-quinazolone (9). To a solution of **8** (200 g) in DMF (1.6 L) and methanol (400 mL), formamide (180 g) and sodium methoxide (146 g) were added. The reaction mixture was stirred for 10 h under reflux conditions. After quench by cold water, the mixture was neutralized by 1 N hydrochloride solution. Precipitated solid was collected by filtration and washed with water, ethyl acetate, and hexane to give **9** (190 g, yield 97%).

4-Chloro-6,7-dimethoxyquinazoline (10). A mixture of **9** (100 g) and phosphoryl chloride (120 mL) was refluxed for 1 h. After concentration, $CHCl_3$ (400 mL) and cold water (200 mL) were added carefully. The mixture was basified by 20% sodium hydroxide solution and extracted with chloroform. The extract was washed with saturated $NaHCO_3$ aq., water, and brine and then dried over sodium sulfate. The residue was concentrated to give **10** (94 g, yield 86%).

4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]aniline (11). A solution of **10** (30.3 g), aminophenol (17.7 g), and tetra-*n*-butylammonium bromide (18.7 g) in methyl ethyl ketone (300 mL) and 20% sodium hydroxide solution (150 mL) was refluxed for 30 min. After dilution by chloroform (500 mL) and water (200 mL), the mixture was extracted with chloroform. The extract was washed with water and brine and then dried over sodium sulfate. The residue was concentrated, and then precipitated solid was collected by filtration and washed with methanol to give **11** (36.5 g, yield 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.4.06 (s, 3H), 4.07 (s, 3H), 6.77 (d, J = 8.78 Hz, 2H), 7.04 (d, J = 8.78 Hz, 2H), 7.31 (s, 1H), 7.56 (s, 1H), 8.63 (s, 1H). MS (ESI): m/z 298 ($M^+ + 1$).

***N*-Cyclohexyl-*N*′-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea (2). 7** (100 mg) was dissolved in chloroform (10 mL) and triethylamine (1 mL) to prepare a solution. A solution of triphosgene (151 mg) in chloroform (2 mL) was then added to the solution, and the mixture was stirred at room temperature for 10 min. Next, a solution of cyclohexylamine (49 mg) in chloroform (2 mL) was added thereto, and the mixture was further stirred at room temperature for 1 h. Water was added to stop the reaction, and the reaction solution was then extracted with chloroform, followed by concentration. The residue was purified on a column using chloroform/methanol to give **2** (121 mg, yield 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.1.10−1.41 (m, 5H), 1.58−1.71 (m, 3H), 1.95−1.98 (m, 2H), 3.68−3.74 (m, 1H), 4.03 (s, 6H), 5.24 (d, J = 8.05 Hz, 1H), 6.42 (d, J = 5.37 Hz, 1H), 7.08 (d, J = 9.03 Hz, 2H), 7.27−7.45 (m, 4H), 7.55 (s, 1H), 8.44 (d, J = 5.37 Hz, 1H). MS (ESI): m/z 422 ($M^+ + 1$). Purity: 99% (method A; t_R = 10.58 min), 100% (method E; t_R = 9.94 min).

***N*-Cyclohexyl-*N*′-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea (12a). 11** (100 mg) was dissolved in chloroform (10 mL) and triethylamine (1 mL) to prepare a solution. A solution of triphosgene (151 mg) in chloroform (2 mL) was then added to the solution, and the mixture was stirred at room temperature for 10 min. Next, the solution of cyclohexylamine (49 mg) in chloroform (2 mL) was added thereto, and the mixture was further stirred at room temperature for 1 h. Water was added to stop the reaction, and the reaction solution was then extracted with chloroform, followed by concentration. The residue was purified on a column using chloroform/methanol to give **12a** (116 mg, yield 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.1.10−1.20 (m, 2H), 1.26−1.43 (m, 2H), 1.59−1.77 (m, 4H), 1.96−1.99 (m, 2H), 3.64−3.71 (m, 1H), 4.06 (s, 6H), 4.99 (d, J = 7.81 Hz, 1H), 6.90 (s, 1H), 7.18 (d, J = 8.78 Hz, 2H), 7.31 (s, 1H), 7.41 (d, J = 8.78 Hz, 2H), 7.54 (s, 1H), 8.61 (s, 1H). MS (ESI): m/z 423 ($M^+ + 1$). Purity: 99% (method A; t_R = 7.78 min), 99% (method E; t_R = 8.10 min).

***N*-(2-Cyclohexyl)ethyl-*N*′-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}urea (12b). 7** (100 mg) was dissolved in chloroform (10 mL) and triethylamine (1 mL) to prepare a solution. A solution of triphosgene (151 mg) in chloroform (2 mL) was then added to the solution, and the mixture was stirred at room temperature for 10 min. Next, the solution of 2-cyclohexylethylamine (65 mg) in chloroform (2 mL) was added thereto, and the mixture was further stirred at room temperature for 1 h. Water was added to stop the reaction, and the reaction solution was then extracted with chloroform, followed by concentration. The residue was purified on a column using chloroform/methanol to give **12b** (63 mg, yield 41%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.0.88−0.93 (m, 2H), 1.13−1.29 (m, 4H), 1.38−1.44 (m, 2H), 1.61−1.69 (m, 5H), 3.26−3.31 (m, 2H), 4.03 (s, 6H), 5.36−5.38 (m, 1H), 6.42 (d, J = 5.37 Hz, 1H), 7.08 (d, J = 8.79 Hz, 2H), 7.40 (s, 1H), 7.45 (d, J = 9.03 Hz, 2H), 7.55 (s, 1H), 7.57 (s, 1H), 8.44 (d, J = 5.12 Hz, 1H). MS (ESI): m/z 450 ($M^+ + 1$). Purity: 98% (method C; t_R = 8.65 min), 98% (method G; t_R = 9.76 min).

***N*-(2-Cyclohexyl)ethyl-*N*′-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea (12c). 11** (100 mg) was dissolved in chloroform (10 mL), and triethylamine (1 mL) to prepare a solution. A solution of triphosgene (151 mg) in chloroform (2 mL) was then added to the solution, and the mixture was stirred at room temperature for 10 min. Next, the solution of 2-cyclohexylethylamine (65 mg) in chloroform (2 mL) was added thereto, and the mixture was further stirred at room temperature for 1 h. Water was added to stop the reaction, and the reaction solution was then extracted with chloroform, followed by concentration. The residue was purified on a column using chloroform/methanol to give **12c** (109 mg, yield 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.0.84−0.93 (m, 2H), 1.10−1.42 (m, 6H), 1.60−1.70 (m, 5H), 3.24−3.29 (m, 2H), 4.046 (s, 3H), 4.049 (s, 3H), 5.45−5.46 (m, 1H), 7.15 (d, J = 9.03 Hz, 2H), 7.29 (d, J = 0.73 Hz, 1H), 7.42 (d, J = 9.03 Hz, 2H), 7.52 (s, 1H), 8.58 (d, J = 0.73 Hz, 1H). MS (ESI): m/z 451 ($M^+ + 1$). Purity: 98% (method B; t_R = 10.02 min), 98% (method G; t_R = 8.20 min).

***N*-Cyclohexyl-*N*′-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-thiourea (13a). 7** (50 mg) was dissolved in toluene (4 mL) and ethanol (6 mL) to prepare a solution. Cyclohexyl isothiocyanate (42 mg) was added to the solution, and the mixture was stirred at 80 °C for 6 h. The reaction solution was concentrated, and ether and hexane were added to the residue. The resultant crystals were collected by filtration to give the title compound (52 mg, yield 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.1.20−1.28 (m, 3H), 1.39−1.48 (m, 2H), 1.64−1.76 (m, 3H), 2.07−2.10 (m, 2H), 3.35−3.36 (m, 1H), 4.05 (s, 3H), 4.06 (s, 3H), 6.58−6.60 (m, 1H), 7.20−7.23 (m, 2H), 7.37−7.38 (m, 1H), 7.46−7.51 (m, 2H), 7.57−7.58 (m,

1H), 8.42−8.44 (m, 1H). MS (ESI): *m*/*z* 438 ($M^+ + 1$). Purity: 98% (method B; $t_R = 7.95$ min), 99% (method F; $t_R = 9.59$ min).

***N*-Benzyl-*N*′-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}-thiourea (13b). 11** (50 mg) was dissolved in toluene (4 mL) and ethanol (6 mL) to prepare a solution. Benzyl isothiocyanate (44 mg) was added to the solution, and the mixture was stirred at 80 °C for 6 h. The reaction solution was concentrated, and ether and hexane were added to the residue. The resultant crystals were collected by filtration to give the title compound (74 mg, yield 98%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ.3.97 (s, 3H), 3.99 (s, 3H), 4.73−4.79 (bs, 2H), 7.24−7.56 (m, 11H), 8.18−8.25 (bs, 1H), 8.55 (s, 1H), 9.63−9.67 (bs, 1H). MS (ESI): *m*/*z* 447 ($M^+ + 1$). Purity: 97% (method A; $t_R = 8.25$ min), 98% (method E; $t_R = 8.70$ min).

***N*-Cyclohexylmethyl-*N*′-{4-[(6,7-dimethoxy-4-quinazolinyl)-oxy]phenyl}thiourea (13c). 11** (50 mg) was dissolved in toluene (4 mL) and ethanol (6 mL) to prepare a solution. Cyclohexylmethyl isothiocyanate (53 mg) was added to the solution, and the mixture was stirred at 80 °C for 6 h. The reaction solution was concentrated, and ether and hexane were added to the residue. The resultant crystals were collected by filtration to give the title compound (52 mg, yield 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ.0.92−1.00 (m, 2H), 1.11−1.30 (m, 3H), 1.65−1.74 (m, 5H), 3.50−3.53 (m, 2H), 4.07 (s, 3H), 4.08 (s, 3H), 6.21 (s, 1H), 7.27 (s, 1H), 7.35−7.36 (m, 4H), 7.53 (s, 1H), 7.87 (s, 1H), 8.63 (s, 1H). MS (ESI): *m*/*z* 453 ($M^+ + 1$). Purity: 95% (method B; $t_R = 8.53$ min), 96% (method G; $t_R = 7.97$ min).

Phenyl *N*-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}carbamate (14a). 7 (100 mg) was added to toluene (10 mL) and triethylamine (1 mL), and the mixture was heated under reflux to prepare a solution. The solution of triphosgene (151 mg) in methylene chloride (2 mL) was then added thereto, and the mixture was heated under reflux for 10 min. Next, phenol (46 mg) was added thereto, and the mixture was further stirred with heating under reflux for 3 h. A saturated aqueous sodium bicarbonate solution was added to stop the reaction, and the reaction solution was then extracted with chloroform, followed by washing with water and brine in that order. The extract was dried over sodium sulfate and was then concentrated. The residue was purified on a column using chloroform/methanol to give **14a** (100 mg, yield 63%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ.4.03 (s, 3H), 4.04 (s, 3H), 6.83 (d, $J = 6.3$ Hz, 1H), 7.24−7.30 (m, 3H), 7.38−7.47 (m, 3H), 7.57 (s, 1H), 7.72−7.74 (m, 3H), 8.79 (d, $J = 6.6$ Hz, 1H), 10.50 (s, 1H). MS (ESI): *m*/*z* 417 ($M^+ + 1$). Purity: 95% (method B; $t_R = 8.08$ min), 95% (method F; $t_R = 9.15$ min).

2-Cyclohexylethyl *N*-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]-phenyl}carbamate (14b). Compound **14b** was prepared in 76% yield from **7** and 2-cyclohexyl-1-ethanol by a method similar to that described for **14a**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ.0.95−1.01 (m, 2H), 1.15−1.27 (m, 3H), 1.40−1.43 (m, 1H), 1.57−1.77 (m, 7H), 4.10 (s, 3H), 4.17 (s, 3H), 4.24 (t, $J = 6.8$ Hz, 2H), 6.70 (d, $J = 6.3$ Hz, 1H), 6.82 (s, 1H), 7.18 (d, $J = 8.8$ Hz, 2H), 7.61 (d, $J = 8.8$ Hz, 2H), 7.64 (s, 1H), 8.15 (s, 1H), 8.48 (t, $J = 6.6$ Hz, 1H). MS (ESI): *m*/*z* 452 ($M^+ + 1$). Purity: 97% (method D; $t_R = 10.73$ min), 97% (method I; $t_R = 11.16$ min).

***N*-Cyclohexylcarbonyl-*N*′-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}thiourea (17a).** 1-Cyclohexanecarbonyl isothiocyanate **16** was prepared from 1-cyclohexanecarbonyl chloride as a starting compound **15** and potassium thiocyanate. 1-Cyclohexanecarbonyl chloride (80 mg) and potassium thiocyanate (53 mg) were dissolved in acetonitrile (3 mL). After stirring at 50 °C for 1 h, the reaction mixture was concentrated. The residue was diluted with AcOEt and saturated $NaHCO_3$ aq. and then extracted with AcOEt. The extract was concentrated to give crude 1-cyclohexanecarbonyl isothiocyanate. This crude compound was dissolved in ethanol (1 mL). **7** (50 mg) in toluene (5 mL) and ethanol (1 mL) were added to the solution, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated, and the residue was purified by chromatography on silica gel using chloroform/acetone to give **17a** (60 mg, yield 76%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ.1.21−1.38 (m, 6H), 1.66−1.85 (m, 5H), 3.92 (s, 3H), 3.95 (s, 3H), 6.54 (d, $J = 5.12$ Hz, 1H), 7.28 (d, $J = 9.03$ Hz, 3H), 7.39 (s, 1H), 7.49 (s, 1H), 7.76 (d, $J = 8.78$ Hz, 1H), 8.50 (d, $J = 5.12$ Hz, 1H), 11.41 (bs, 1H), 12.56 (bs, 1H). MS (ESI): *m*/*z* 466 ($M^+ + 1$). Purity: 98% (method D; $t_R = 7.62$ min), 100% (method I; $t_R = 8.22$ min).

***N*-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}-*N*′-(2-phenylacetyl)thiourea (17b).** Compound **17b** was prepared in 80% yield from **7** and 2-phenylethanoyl isothiocyanate by a method similar to that described for **17a**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ.3.82 (s, 2H), 3.96 (s, 3H), 3.98 (s, 3H), 6.51 (d, $J = 6.01$ Hz, 1H), 7.25−7.35 (m, 7H), 7.44 (s, 1H), 7.48 (d, $J = 8.78$ Hz, 1H), 7.51 (s, 1H), 7.69 (m, 1H), 8.14−8.16 (m, 1H), 8.57 (bs, 1H), 11.81 (s, 1H). MS (ESI): *m*/*z* 474 ($M^+ + 1$). Purity: 98% (method C; $t_R = 7.32$ min), 98% (method G; $t_R = 8.91$ min).

***N*-Benzoyl-*N*′-{4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-thiourea (17c).** Compound **17c** was prepared in 94% yield from **7** and 1-benzenecarbonyl isothiocyanate by a method similar to that described for **17a**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ.4.02 (s, 6H), 6.54 (d, $J = 5.12$ Hz, 1H), 7.22 (d, $J = 8.78$ Hz, 2H), 7.33−7.77 (m, 5H), 7.81 (t, $J = 3.42$ Hz, 1H), 7.83−7.95 (m, 3H), 8.02 (d, $J = 8.76$ Hz, 1H), 8.49 (d, $J = 5.12$ Hz, 1H), 9.42 (bs, 1H). MS (ESI): *m*/*z* 460 ($M^+ + 1$). Purity: 100% (method B; $t_R = 10.92$ min), 99% (method G; $t_R = 9.76$ min).

***N*-(2-Chlorobenzoyl)-*N*′-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-phenyl}thiourea (17d).** Compound **17d** was prepared in 100% yield from **7** and 2-chloro-1-benzenecarbonyl isothiocyanate by a method similar to that described for **17a**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ.4.07 (s, 6H), 6.57 (d, $J = 5.37$ Hz, 1H), 7.23−7.29 (m, 3H), 7.44−7.47 (m, 2H), 7.53−7.54 (m, 3H), 7.79−7.86 (m, 3H), 8.53 (d, $J = 5.37$ Hz, 1H), 9.23 (s, 1H). MS (ESI): *m*/*z* 494 ($M^+ + 1$). Purity: 98% (method C; $t_R = 8.02$ min), 99% (method H; $t_R = 8.26$ min).

***N*-{4-[(6,7-Dimethoxy-4-quinolyl)oxy]phenyl}-*N*′-(2-methylbenzoyl)thiourea (17e).** Compound **17e** was prepared in 97% yield from **7** and 2-methyl-1-benzenecarbonyl isothiocyanate by a method similar to that described for **17a**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ.2.17 (s, 3H), 4.09 (s, 3H), 4.13 (s, 3H), 6.69 (d, $J = 5.86$ Hz, 1H), 7.26−7.36 (m, 5H), 7.47−7.49 (m, 1H), 7.58 (d, $J = 8.05$ Hz, 1H), 7.61 (s, 1H), 7.88 (bs, 1H), 7.94 (d, $J = 9.03$ Hz, 2H), 8.52 (d, $J = 5.86$ Hz, 1H), 8.89 (s, 1H): HRMS, (ESI): calcd for $C_{26}H_{22}N_3O_4S$ $[M-H]^-$ 472.1331; found: 472.1357. Purity: 97% (method C; $t_R = 7.70$ min), 97% (method G; $t_R = 9.95$ min).

***N*-{4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl}-*N*′-(2-methylbenzoyl)thiourea (17f).** Compound **17f** was prepared in 90% yield from **11** and 2-methyl-1-benzenecarbonyl isothiocyanate by a method similar to that described for **17a**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ.2.50 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 7.29−7.38 (m, 7H), 7.42−7.46 (m, 1H), 7.52 (d, $J = 7.81$ Hz, 1H), 7.57 (s, 1H), 7.80−7.82 (m, 2H), 8.56 (s, 1H). MS (ESI): *m*/*z* 475 ($M^+ + 1$). Purity: 98% (method B; $t_R = 10.45$ min), 99% (method G; $t_R = 9.11$ min).

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