Potent and Selective Inhibitors of Platelet-Derived Growth Factor Receptor Phosphorylation. 1. Synthesis, Structure−Activity Relationship, and Biological Effects of a New Class of Quinazoline Derivatives

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A new series of 4-[4-(*N*-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives were found to show potent and selective inhibition of platelet-dervied growth factor (PDGF) receptor phosphorylation. In this exploration of the structure−activity relationships (SARs) of the prototype inhibitor KN1022, the 4-nitrophenylurea moiety was probed. We found that 4-substitution on the phenyl ring was optimal and the introduction of more than two substituents on the phenyl ring decreased activities. Bulky substituents on the phenyl ring enhanced activities. Thiourea analogues were also prepared, and the SARs were found to be slightly different from those of the urea derivatives. Through this research, we obtained some potent KN1022 derivatives such as 4-(4-methylphenoxy)phenyl (**36**, IC_{50} 0.02 μmol/L), 4-*tert*-butylphenyl (**16**, IC_{50} 0.03 μmol/L), and 4-phenoxyphenyl (**21**, IC_{50} 0.08 μmol/L) analogues, which had almost a 10-fold increase in activity against KN1022. These potent compounds retained their high selectivity against the PDGF receptor family similar to KN1022. We also observed that these compounds could inhibit the PDGF-BB-induced proliferation of porcine vascular smooth muscle cells without cell toxicity almost at the same IC_{50} values observed for PDGF receptor phosphorylation. To evaluate the biological effects in vivo, we selected some analogues on the basis of the measurement of the plasma drug concentration after oral administration to rats. Oral administration of the 4-chlorophenyl (**6**), 4-bromophenyl (**9**), or 4-isopropoxyphenyl (**20**) analogue to Sprague−Dawley rats (30 mg/kg, twice daily) resulted in significant inhibition (24−38%) of neointima formation in the carotid artery of the balloon catheter deendothelialized vessel in the rats. Therefore, 4-[4-(*N*-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives, which are potent inhibitors of PDGFR phosphorylation, may be expected to represent a new therapeutic approach for the treatment of various aspects of atherosclerosis and other cellar proliferative disorders.

Introduction

Platelet-derived growth factor (PDGF) is known to act as a potent mitogen and chemotactic factor for various mesenchymal cells such as fibroblasts, smooth muscle cells (SMCs), mesangial cells, and brain glial cells. PDGF is a disulfide-linked dimer of two related polypeptide chains, designated A and B, which are assembled as heterodimers (PDGF-AB) or homodimers (PDGF-AA and PDGF-BB).[1−3] PDGF exerts its biological activity by binding to structurally similar α- or β-PDGF receptors, and inducing receptor dimerization.[4,5] The receptor binding specificity for the PDGF isoforms indicates that PDGF-AA induces only α/α receptor dimers, PDGF-AB induces α/α and α/β receptor dimers, and PDGF-BB induces all three receptor dimer combinations.[6−10] Once dimerized, the PDGF receptor (PDGFR) undergoes transphosphorylation on cytoplasmic tyrosine residues, which creates the sites for physical interaction with a number of proteins that contain a Src homology two (SH-2) domain.[11]

Abnormal PDGF-induced cell proliferation has been proposed for various proliferative disorders such as atherosclerosis, restenosis following PTCA, glomerulonephritis, glomerulosclerosis, liver cirrhosis, pulmonary fibrosis, and cancer.[12−22] Additionally, PDGF and its receptor (PDGFR) are also upregulated in these proliferative disorders. Within restenosis lesions, PDGF plays a major role in the vascular response to injury.[23−27] After the vascular injury, PDGF induces migration of SMCs from the media into the intima of the artery wall, and then subsequent excessive and disorderly proliferation of intimal SMCs in concert with additional growth factors. Therefore, an inhibitor of PDGFR phosphorylation would be expected to represent a therapeutic benefit for these proliferative disorders.

Several inhibitors of PDGFR phosphorylation have also been previously reported, 3-arylquinoline,[28] 4-aryloxyquinoline,[29] pyridylpyrimidine,[30] benzimidazole,[31] or pyrazole[32] derivatives, which are illlustrated in Chart 1. Recently we found a new class of potent and selective

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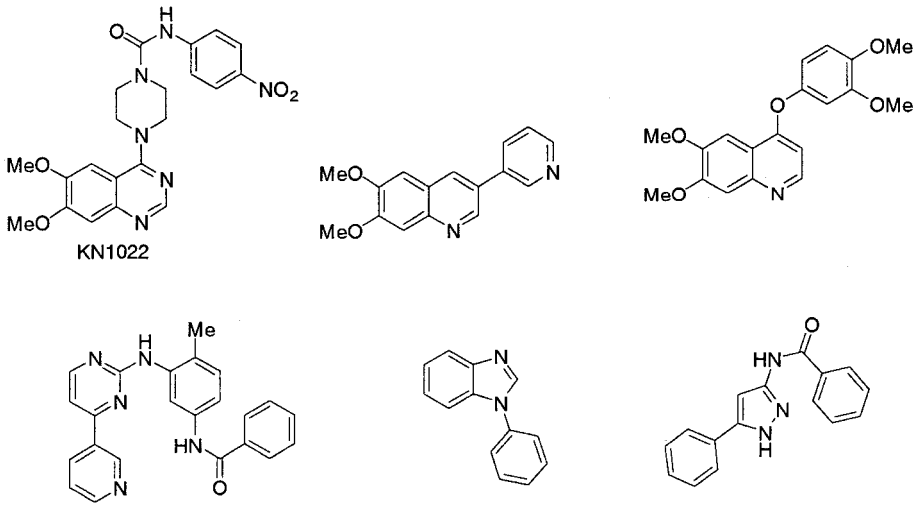
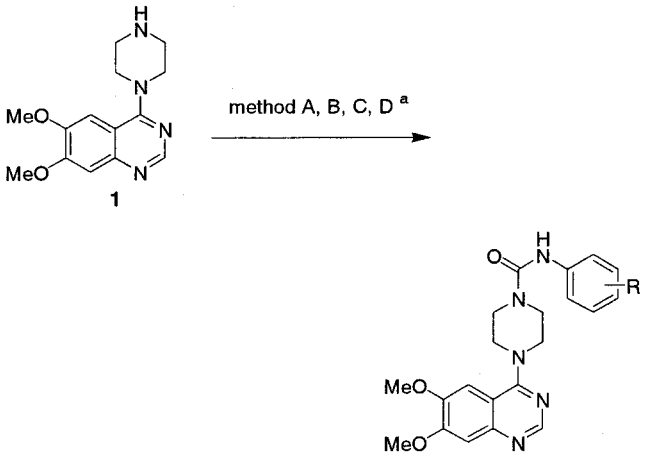
Chart 1

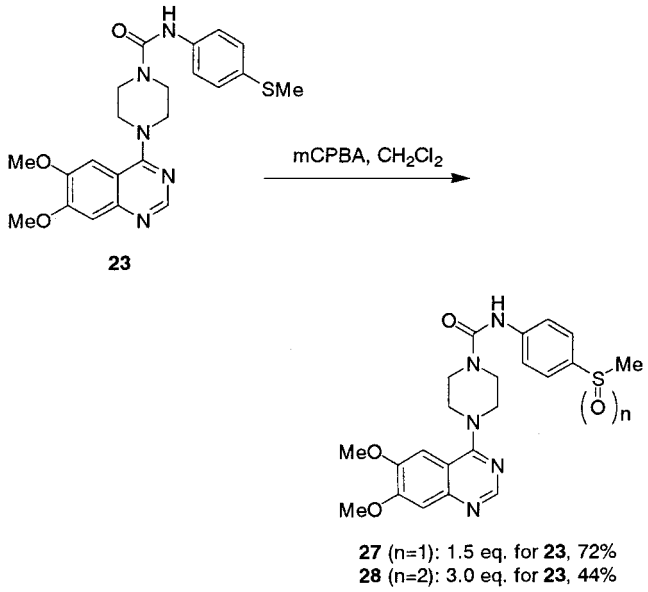


Scheme 1[a]



[a] Method A: RPhNCO, solvent. Method B: (i) $RPhNH_2$, CDI, solvent; (ii) **1**. Method C: (i) $RPhNH_2$, triphosgene, Et_3N, CH_3CN; (ii) **1**, Et_3N, CH_2Cl_2. Method D: (i) $RPhNH_2$, 4-NO_2PhOCOCl, Et_3N, NMP; (ii) **1**, heat.

Scheme 2



inhibitors of PDGFR phosphorylation, the 4-[4-(*N*-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives such as KN1022. In this paper, we report the synthesis of KN1022 analogues, focused on the 4-nitrophenylurea moiety, and discuss the structure−activity relationships (SAR) for inhibition of in vitro β-PDGFR phosphorylation by this new class of compounds. Selected analogues were also evaluated for their kinase selectivity as well as their inhibition of porcine aorta SMC proliferation induced by PDGF-BB. Furthermore, selection of analogues for in vivo evaluation by measurement of the plasma drug concentration after oral administration to Sprague−Dawley rats (SD rats) and inhibitory activity on neointima formation in the rat carotid artery is also reported.

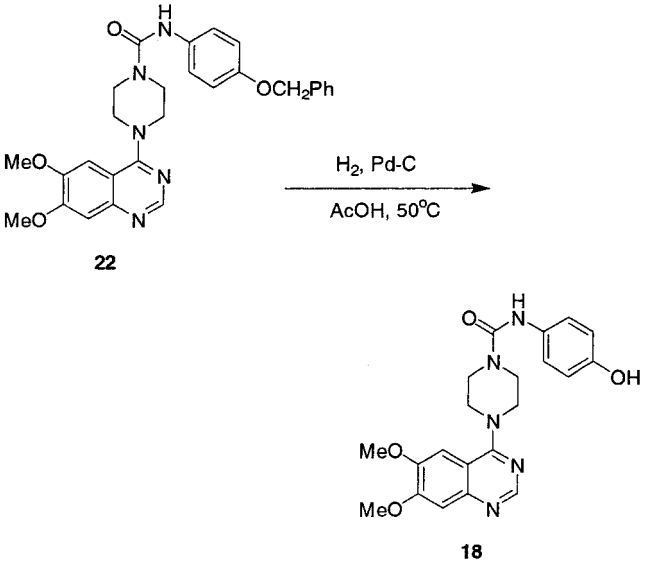
Chemistry

General synthetic methods for the ureas are described in Scheme 1. There are four methods (methods A−D) which we found useful for preparing analogues from the known intermediate 4-(1-piperazinyl)-6,7-dimethoxyquinazoline (**1**).[33] Condensation of **1** with commercially available isocyanates was carried out in appropriate inert solvents such as dichloromethane or dimethylformamide (method A). Treatment of amines with *N*,*N*′-carbonyldiimidazole in dichloromethane, followed by addition of **1** to the reaction mixture in situ, provided the desired ureas (method B). Sequential carbonylation of amines with triphosgene in the presence of triethylamine, followed by addition of **1** in situ, gave the ureas (method C). Heating **1** in *N*-methylpyrrolidinone (NMP) with 4-nitrophenylcarbamate, which was prepared from the corresponding aniline and 4-nitrophenylchloroformate in the presence of triethylamine, also provided the ureas (method D).

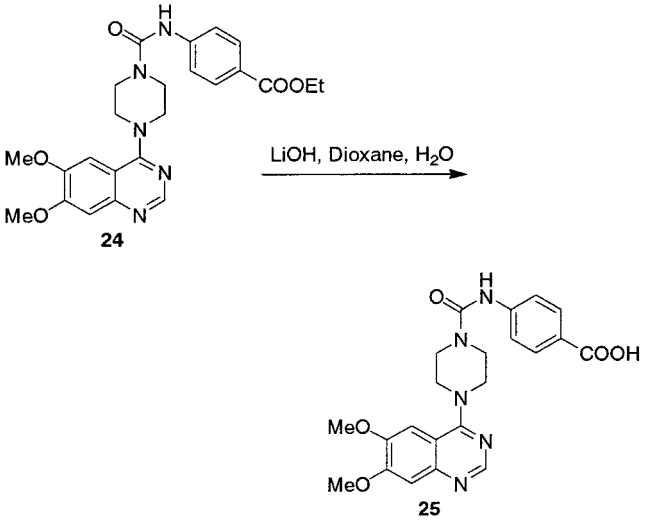
The *dl*-sulfoxide **27** and the sulfone **28** were synthesized by oxidation of the methylthio analogue **23** with differing numbers of equivalents of *m*-chloroperbenzoic acid (Scheme 2). The hydroxy analogue **18** was synthesized by catalytic hydrogenation of the benzyloxy analogue **22** (Scheme 3). The carboxy analogue **25** was obtained by hydrolysis of the ester **24** (Scheme 4).

The widely used synthetic route to the thioureas was condensation of **1** with commercially available isothiocyanates described in Scheme 5 (method E). Additionally, isothiocyanates were also prepared by treatment of the corresponding amines with thiophosgene in inert

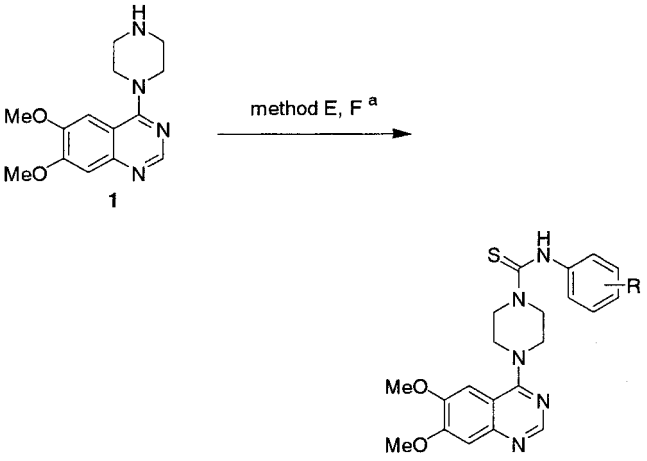
Scheme 3



Scheme 4



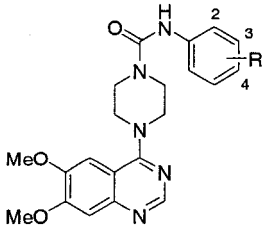
Scheme 5[a]



[a] Method E: RPhNCS, solvent. Method F: (i) $RPhNH_2$, $CSCl_2$, Et_3NA, solvent; (ii) **1**.

solvent in the presence of triethylamine, and then **1** was added to the reaction mixture in situ to provide the desired thioureas (method F, Scheme 5).

Table 1. Synthetic Method and Inhibitory Activity on β-PDGFR Phosphorylation



compd	R	procedure	PDGFP (μmol/L)[a]
KN1022	4-NO_2	method A	0.70
2	3-NO_2	method A	2.57
3	2-NO_2	method A	>30
4	H	method A	11.1
5	4-F	method A	6.72
6	4-Cl	method A	1.10
7	3-Cl	method A	2.06
8	2-Cl	method A	>30
9	4-Br	method A	0.53
10	4-I	method A	0.29
11	4-Me	method A	9.96
12	4-Et	method A	1.21
13	4-^{n}Pr	method B	0.11
14	4-^{i}Pr	method A	0.08
15	4-^{n}Bu	method A	0.21
16	4-^{t}Bu	method D	0.03
17	4-Ph	method D	0.26
18	4-OH	hydrogenation of **22**	>30
19	4-OMe	method A	5.36
20	4-O^{i}Pr	method B	0.23
21	4-OPh	method A	0.08
22	4-OCH_2Ph	method B	0.29
23	4-SMe	method A	0.48
24	4-COOEt	method A	0.74
25	4-COOH	hydrolysis of **24**	>30
26	4-CN	method A	0.85
27	(*dl*)-4-SOMe	oxidation of **23**	>30
28	4-SO_2Me	oxidation of **23**	9.42
29	2,4-Cl_2	method A	21.6
30	3,4-Cl_2	method A	1.20
31	3-NO_2, 4-Cl	method A	1.47
32	3,5-Cl_2	method A	9.21
33	3,4-(OCH_2O)−	method B	>30

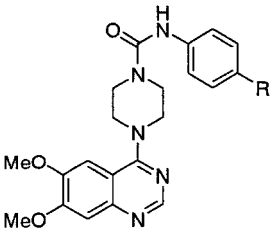
[a] IC_{50} (μmol/L) of β-PDGFR phosphorylation.

Results and Discussion

SAR for Inhibition of β-PDGFR Phosphorylation. As an initial exploration of the SAR of KN1022 we prepared a series of analogues examining the role of the phenyl ring of the urea function and substitutions in this ring on the activity against the PDGFR. All the analogues prepared were evaluated for their inhibition of β-PDGFR phosphorylation in accordance with known whole cell assay,[34] and the resulting IC_{50} values are listed in Tables 1−3.

Table 1 shows the results that the position and nature of the substituents on the phenyl ring attached to the urea moiety have a substantial influence on the inhibitory activity. For urea derivatives, substitution at the 4-position on the phenyl ring was the most favorable and the activity was reduced at the 3- and 2-positions with increasing magnitude, respectively. Regarding the nitrophenyl derivatives, 4-substitution of the nitro group (KN1022) showed the most potent activity and 3-substitution (**2**) yielded moderate activity whereas 2-substitution (**3**) completely abolished activity. Additionally,

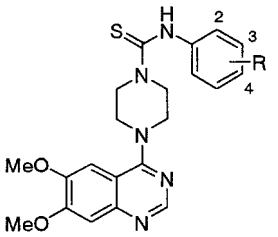
Table 2. Synthetic Method and Inhibitory Activity on β-PDGFR Phosphorylation



compd	R	procedure	PDGFP (μmol/L)[a]
34	2-(MeO)PhO	method B	0.10
35	4-ClPhO	method B	0.02
36	4-MePhO	method B	0.02
37	4-NO_2PhO	method B	>30
38	4-NH_2PhO	hydrogenation of **37**	0.15
39	4-pyridyl-O	method C	2.31
40	1-naphthyl-O	method C	0.05
41	PhNH	method B	0.08
42	$PhCH_2$	method B	0.06
43	4-pyridyl-CH_2	method B	1.04

[a] IC_{50} (μmol/L) of β-PDGFR phosphorylation.

Table 3. Synthetic Method and Inhibitory Activity on β-PDGFR Phosphorylation



compd	R	procedure	PDGFP (μmol/L)[a]
44	4-NO_2	method E	0.33
45	3-NO_2	method E	0.19
46	2-NO_2	method E	1.24
47	H	method E	3.18
48	4-F	method E	2.00
49	4-Cl	method E	0.79
50	3-Cl	method E	0.44
51	2-Cl	method F	>10
52	4-Br	method E	0.22
53	4-I	method E	0.44
54	4-Me	method E	1.26
55	4-^{i}Pr	method E	0.72
56	4-^{n}Bu	method E	0.51
57	4-^{t}Bu	method E	0.29
58	4-O^{i}Pr	method F	1.41
59	4-OPh	method E	0.37
60	4-SMe	method F	0.44
61	3-COOH	method E	>30
62	3-NO_2, 4-Cl	method E	0.16
63	3-Cl, 4-Br	method E	0.10
64	3,4-$(OMe)_2$	method E	1.14
65	3,4-(OCH_2O)−	method E	18.2

[a] IC_{50} (μmol/L) of β-PDGFR phosphorylation.

for the chloro derivatives **6**−**8**, the same order of potency was observed.

Investigation of a variety of substituents on the phenyl ring indicated that bulky hydrophobic substitution at the 4-position increased activity as shown in the halogene (**5**−**10**), alkyl (**11**−**17**), and alkoxy (**19**−**22**) series. The activity of the 4-*tert*-butyl analogue **16** was significantly improved compared with that of the 4-*n*-butyl analogue **15**. The bulky 4-phenoxy analogue **21** also showed potent activity, although the 4-phenyl analogue **17** and 4-benzyloxy analogue **22** displayed reduced activity just by deletion of an oxygen atom and addition of a methylene unit, respectively. The ethoxycarbonyl (**24**) and cyano (**26**) analogues showed similar IC_{50} values of KN1022. The hydroxy (**18**), carboxylic acid (**25**), sulfoxide (**27**), and sulfone (**28**) analogues were inactive, therefore suggesting that introduction of hydrophilic substituents was unfavorable.

Introduction of two substituents on the phenyl ring was found to be unfavorable for increasing activity. The activity of 2,4-dichloro analogue **29** was almost at the same level as that of 2-substituted analogue **8**, which was weaker than the analogue with monosubstitution at the 4-position (**6**). The 3,4-disubstitution almost retained activity in comparison with 4-substitution (**30** vs **6** and **7**, **31** vs **6** and **2**). The 3,5-disubstitution reduced activity (**32** vs **7**). Furthermore, bicyclic derivative **33** was found to be inactive.

The high potency shown by bulky substituents at the 4-position of the phenyl group prompted us to evaluate such compounds in more detail. We focused on **21** and synthesized the related compounds listed in Table 2. Small substituents on the phenoxy group were found to be acceptable, such as in the 4-chlorophenoxy (**35**), 4-methylphenoxy (**36**), 2-methoxyphenoxy (**34**), or 4-aminophenoxy (**38**) analogue; however, 4-nitrophenoxy (**37**) substitution completely abolished the activity. Replacement of the oxygen atom was also investigated. Benzylphenyl (**42**) and anilinophenyl (**41**) analogues retained potent activity. Regarding exchange of the phenoxy group, the 1-naphthoxy analogue **40** showed potent activity; however, 4-pyridyloxy (**39**) and 4-pyridylmethyl (**43**) analogues were only moderate inhibitors.

The thiourea derivatives also showed inhibitory activity on β-PDGFR phosphorylation as listed in Table 3. The SARs were somewhat different from those of the ureas and thioureas regarding the position and type of the substituents on the phenyl ring as follows. 2-Substitution on the phenyl ring showed the weakest activity in the thiourea series, as was observed for the ureas. However, 3-substituted derivatives were potent inhibitors similar to 4-substituted derivatives. Regarding nitrophenyl analogues, the 3-nitro analogue **45** was found to be potent and the activity was similar to the 4-nitro analogue **44**. Although the 2-substituted compound **46** showed the weakest activity among the series, the magnitude of activity decrease was relatively small compared to that observed in the urea series. Additionally, the chlorophenyl analogues **49**−**51** showed similar SARs.

Next, in accordance with investigation of a variety of substituents, bulky hydrophobic substitution was also suitable for potent activity. Among the halogene (**48**−**53**), alkyl (**54**−**57**), and alkoxy (**58**−**59**) series, the 4-phenoxy (**59**) and 4-*tert*-butyl (**57**) analogues showed somewhat potent activity; however, the magnitude of enhancement was not as much and the inhibitory activity was weaker compared with that of the ureas possessing the same substituent (**21** and **16**), respectively. The hydrophilic carboxy analogue **61** was also inactive like the urea. The inhibitory activity of the 3,4-disubstituted compounds was similar or more potent

Table 4. Kinase Specificity[a]

kinase	IC$_{50}$ (μmol/L)				
	KN1022	compd **9**	compd **14**	compd **21**	compd **26**
β-PDGFR	0.24	0.27	0.02	0.13	0.45
α-PDGFR	0.89	0.71	0.09	0.05	0.77
EGFR	>100	>100	>30	>30	>100
FGFR	>200	>200	>30	29.7	>200
CSF-1R	>30	>30	NT	NT	>30
VEGFR-2	>100	>100	NT	NT	>100
Src	>30	>30	>30	>30	>30
PKA	>30	>30	>30	>30	>30
PKC	>30	>30	>30	>30	>30
Mek 1	>30	>30	NT	NT	>30
Mkk 3	>30	>30	NT	NT	>30
Mkk 6	>30	>30	NT	NT	>30
Erk2	>30	>30	NT	NT	>30
Jnk1	>30	>30	NT	NT	>30
p38	>30	>30	NT	NT	>30
c-Kit	0.39	0.13	0.05	0.05	0.48
Flt3	3.3	11.4	0.05	0.23	19.7

[a] NT = not tested.

compared with that of the monosubstituted derivatives at the 3- or 4-position (**62**, **45**, and **49** and **63**, **50**, and **52**). Furthermore, bicyclic 3,4-methylenedioxy analogue **65** was found to be weaker than the 3,4-dimethoxy analogue **64**.

The 4-anilino-6,7-dimethoxyquinazolines were previously reported as potent EGF receptor (EGFR) tyrosine kinase inhibitors by the Parke-Davis and Zeneca groups.[35,36] The EGFR also preferred substitution on the phenyl ring of the anilino moiety; namely, a hydrophobic substitutent at the 3-position such as the 3-bromo was found to be optimal for potent inhibition.[35,36] Although the optimal position for the inhibitory activity of our series was different from that of these inhibitors of EGFR, it is interesting that the position of the substituent on the phenyl ring had great influence on activity for each inhibitor whose basic skeleton contains the same 6,7-dimethoxyquinazoline ring system. Unique to our series is the 4-piperazinyl substitution of the 6,7-dimethoxyquinazoline ring system, which specifically yields inhibitors of the PDGFR family of receptor tyrosine kinases, unlike the 4-anilino substitution, which provides EGFR kinase inhibitors.

Kinase Selectivity. We also evaluated several potent compounds for inhibitory activity on various kinases including c-Kit and Flt3, which are closely related PDGFR family tyrosine kinases,[37] using previously reported methods.[34,38] As shown in Table 4, the analogues **14** and **21** showed similar inhibitory activity on PDGFRs, c-Kit, and Flt3 with IC$_{50}$ values ranging between 0.05 and 0.23 μmol/L, whereas analogues **9** and **26** inhibited Flt3 with 40-fold higher concentration compared with PDGFRs and c-Kit. It seems that a less bulky substituent on the phenyl ring gave specificity for PDGFR and c-Kit. No significant inhibition was observed on Ser/Thr kinases (PKA, PKC), EGFR, FGFR, or VEGFR-2 at 100−1000-fold higher concentrations. Although it was not obvious whether other classes of inhibitors for PDGFR phosphorylation described in Chart 1 had inhibitory activity on c-Kit or Flt3, these studies demonstrate that our synthesized compounds showed good selectivity for the PDGFR family of receptor tyrosine kinases.

Inhibition of SMC Proliferation Induced by PDGF-BB. In the blood vessels of patients with atherosclerosis, the abnormal proliferation of SMCs is observed. We examined several potent compounds against porcine aorta SMC proliferation induced by PDGF-BB in vitro using the XTT method.[39] As shown in Table 5, these compounds inhibited the cell proliferation induced by PDGF-BB at almost the same concentration as observed for inhibition of PDGFR phosphorylation. Obvious toxic cell transformation was not observed in these studies.

Table 5. Inhibitory Activity on the Proliferation of SMCs Induced by PDGF-BB

compd	IC$_{50}$ (μmol/L)	compd	IC$_{50}$ (μmol/L)	compd	IC$_{50}$ (μmol/L)
KN1022	0.10	**14**	0.18	**45**	0.14
6	0.15	**15**	0.08	**46**	0.74
9	0.08	**21**	0.25	**49**	0.24
12	0.36	**24**	0.19		

Table 6. Plasma Concentration after Oral Administration to Rats[a]

compd		plasma concn (μg/mL)	
		1 h	8 h
6	rat 1	15.8	7.9
	rat 2	20.5	20.3
49	rat 3	<0.1	<0.1
	rat 4	2.4	1.3
9	rat 5	63.2	58.6
	rat 6	37.0	62.4
52	rat 7	6.6	0.4
	rat 8	7.1	0.1
12	rat 9	9.3	0.5
	rat 10	5.7	<0.1
20	rat 11	21.3	4.2
	rat 12	37.7	2.5

[a] $n = 2$.

Plasma Drug Concentration after Oral Administration to SD Rats. We initiated an evaluation of the in vivo biological effects of KN1022 analogues, especially the inhibition of neointima formation after balloon injury. We selected the analogues which showed good oral availability and afforded a high plasma drug concentration over time for in vivo evaluation. For this purpose, we measured the plasma drug concentration of several KN1022 analogues 1 and 8 h after oral administration to SD rats ($n = 2$) as shown in Table 6. We observed some relationships between the structure and plasma drug concentration. The plasma drug concentration of the ureas **6** and **9** was found to be higher than that of the corresponding thioureas **49** and **52**, respectively. Additionally, the high plasma drug concentration of **6** and **9** was maintained at 8 h compared with that of **12** and **20**. These results suggested that the urea analogues were suitable for oral absorption and that electron-withdrawing groups on the phenyl ring lead to a high plasma drug concentration for a longer period of time.

Inhibitory Effect on Neointima Formation after Balloon Injury of the Rat Carotid Artery. We evaluated the effect on neointima formation after balloon injury of the rat carotid artery by **6**, **9**, and **20**, which showed good oral absorption and a high plasma drug concentration at 8 h. Compounds were suspended in methylcellulose 400 and were orally administrated (30 mg/kg) to SD rats twice daily for a period of 15 days starting on the day before the balloon injury. As shown in Table 7, all compounds showed significant inhibition

Table 7. Inhibitory Activity on Neointima Formation in the Rat Carotid Artery

	no. of animals		I/M ratio		
compd	vehicle	compd treated	vehicle	compd treated	reduction of I/M ratio (%)
6	8	8	0.93	0.67	38.5 ($p < 0.05$)
9	10	10	1.00	0.65	35.0 ($p < 0.05$)
20	10	10	0.99	0.68	24.0 ($p < 0.05$)

(24−38%) of neointima formation relative to vehicle-treated controls ($p < 0.05$, Student's t test or Aspin−Welch test). No obvious affection for rat body weight was observed (data not shown). On the basis of these data, 4-[4-(*N*-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives, which are inhibitors of PDGFR phosphorylation, may be expected to represent a new approach for treating various aspects of atherosclerosis.

Conclusions

Screening for inhibitors of the PDGFR has led to the discovery of a compound series containing the new 4-piperazinyl-substituted quinazoline nucleus. The position and nature of the substituents on the phenyl ring attached to the (thio)urea moiety were found to be important for activity in this series. These compounds showed good selectivity for the PDGFR family of receptor tyrosine kinases and inhibited the proliferation of porcine aorta smooth muscle cells induced by PDGF-BB. To evaluate the biological effects in vivo, we selected some analogues on the basis of the measurement of the plasma drug concentration after oral administration to rats. Oral administration of **6**, **9**, and **20** (30 mg/kg, twice daily) to SD rats resulted in significant inhibition of neointima formation in the carotid artery of the balloon catheter deendothelialized vessel in the rats. These results indicate that 4-[4-(*N*-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazolines are expected to have therapeutic potential for the treatment of cellar proliferative disorders, especially various aspects of atherosclerosis such as restenosis following PTCA.

Experimental Section

Melting points were determined on a Büchi 535 melting point or Yanaco model MP micro melting point apparatus on compounds isolated as described in the experimental procedures and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz) FT NMR spectrometer, JEOL JNM-GX270 (270 MHz) FT NMR spectrometer, or Varian Unity + 400 spectrometer. Chemical shifts are reported as δ values (parts per million) downfield from that of internal TMS in appropriate organic solutions. FAB-mass spectra were recorded with a JEOL JMS-DX303 mass spectrometer. Low-resolution ES-mass spectra were recorded with an HP 1100-MSD LC−MS spectrometer. High-resolution ES-mass spectra were recorded with a VG ZAB2-EQ high-resolution mass spectrometer. The IR spectra were recorded with a JASCO IR-810 IR spectrometer or HORIBA FT-200 IR spectrometer. Analytical TLC was carried out on E. Merck 0.25 mm silica gel precoated glass plates (60 F-254) with detection by UV light. Normal-phase silica gel (EM Science, silica gel 60) was used for chromatography. Combustion analyses (CHN) were performed on a Perkin-Elmer series II CHNS/O analyzer 2400 and agreed with theoretical values to within ±0.4%. Supporting Information is available.

The typical synthetic methods were described as follows.

Method A. A mixture of **1** (432 mg, 1.57 mmol) and 4-fluorophenylisocyanate (0.27 mL, 2.4 mmol) in DMF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into water, and then NaCl was added. The solid was collected by filtration, washed with water, and dried under vacuum. Purification by silica gel column chromatography eluting with AcOEt/$CHCl_3$/MeOH (50:10:4) gave **5** (630 mg, 1.53 mmol).

Method B. 4-Propylaniline (0.28 mL, 2.25 mmol) was added slowly to a solution of 1,1′-carbonyldiimidazole (0.36 g, 2.2 mmol) in dichloromethane (15 mL) under cooling with an ice bath. After the reaction mixture was stirred for 4 h at room temperature, **1** (0.50 g, 1.8 mmol) was added, and then the resulting mixture was stirred overnight at room temperature. The residue after removal of solvent was purified by silica gel column chromatography eluting with AcOEt/$CHCl_3$/MeOH (50:10:3) to afford **13** (829 mg, 1.91 mmol).

Method C. To a solution of triphosgene (0.20 g, 0.67 mmol) in acetonitrile (3 mL) at −5 °C were added an acetonitrile (8 mL) solution of 4-(4-aminophenoxy)pyridine (0.21 g, 1.1 mmol) and triethylamine (0.2 mL, 1.4 mmol) over a period of 15 min. The mixture was stirred for an additional 30 min, and then a dichloromethane solution (5 mL) of **1** (0.31 g, 1.1 mmol) and triethylamine (0.2 mL, 1.4 mmol) was slowly added. The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and evaporated to give a crude residue as an oil. The crude residue was purified by RP-HPLC to afford **39** (0.06 g, 0.12 mmol).

Method D. To a solution of 4-*tert*-butylamine (1.36 mL, 8.54 mmol) in NMP (20 mL) were added 4-nitrophenyl chloroformate (0.88 g, 4.4 mmol) and triethylamine (3.05 mL, 21.9 mmol) under cooling with an ice bath. After the reaction mixture was stirred for 2.5 h, **1** (0.60 g, 2.2 mmol) was added, and the resulting mixture was heated at 80 °C for 4 h, at 100 °C for a further 3 h, and at 140 °C for a further 9 h. The reaction mixture was cooled to room temperature, poured into water, extracted with chloroform, and dried over sodium sulfate. The residue after removal of solvent was purified by silica gel column chromatography eluting with AcOEt/$CHCl_3$/MeOH (50:10:3) to give **16** (191 mg, 0.43 mmol).

Method E. A mixture of **1** (0.40 g, 1.5 mmol) and 4-chlorophenylisothiocyanate (0.34 g, 2.2 mmol) in DMF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into water, and then NaCl was added. The precipitated solid was collected by filtration, washed with water, and dried under vacuum. Purification by silica gel column chromatography eluting with AcOEt/$CHCl_3$/MeOH (50:10:1) gave **49** (0.62 g, 1.4 mmol).

Method F. To a solution of thiophosgene (0.18 mL, 2.4 mmol) in dichloromethane (10 mL) were slowly added 4-(methylmercapto)aniline (0.29 mL, 2.3 mmol) and then triethylamine (0.76 mL, 5.5 mmol) under cooling with an ice bath. After the reaction mixture was stirred for 4 h, **1** (0.50 g, 1.8 mmol) was added, and then the resulting mixture was stirred overnight at room temperature. Methanol was added for quenching excess isothiocyanate, and the residue after removal of solvent was purified by silica gel column chromatography eluting with AcOEt/$CHCl_3$/MeOH (50:10:3) to give **60** (634 mg, 1.39 mmol).

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-nitrophenyl)-1-piperazinecarboxamide (KN1022): yield 90% by method A; mp 272−274 °C ($CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}N_6O_5$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3-nitrophenyl)-1-piperazinecarboxamide (2): yield 89% by method A; mp 123−125 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}N_6O_5$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(2-nitrophenyl)-1-piperazinecarboxamide (3): yield 13% by method A; mp 217−218 °C ($CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}N_6O_5$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-phenyl-1-piperazinecarboxamide (4): yield 44% by method A; mp 121−123 °C (Et_2O); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{23}N_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-fluorophenyl)-1-piperazinecarboxamide (5): yield 97% by method A; mp 198−202 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}FN_5O_3$) C, H, N.

Data for *N*-(4-Chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (6): yield 100% by method A; mp 217−219 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}ClN_5O_3$) C, H, N.

Data for *N*-(3-Chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (7): yield 86% by method A; mp 223−224 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}ClN_5O_3 \cdot 0.25H_2O$) C, H, N.

Data for *N*-(2-Chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (8): yield 100% by method A; mp 186−187 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, Anal. ($C_{21}H_{22}ClN_5O_3$) C, H, N.

Data for *N*-(4-Bromophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (9): yield 100% by method A; mp 223−228 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}BrN_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-iodophenyl)-1-piperazinecarboxamide (10): yield 86% by method A; mp 238−242 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}IN_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-tolyl)-1-piperazinecarboxamide (11): yield 91% by method A; mp 225−228 °C (AcOEt−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-ethylphenyl)-1-piperazinecarboxamide (12): yield 92% by method A; mp 251−252 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-propylphenyl)-1-piperazinecarboxamide (13): yield 100% by method B; mp 214−215 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-isopropylphenyl)-1-piperazinecarboxamide (14): yield 70% by method A; mp 252−254 °C (AcOEt−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_3 \cdot 0.25H_2O$) C, H, N.

Data for *N*-(4-Butylphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (15): yield 83% by method A; mp 216−222 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{25}H_{31}N_5O_3$) C, H, N.

Data for *N*-(4-*tert*-Butylphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (16): yield 20% by method D; mp 109−111 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, HRMS-FAB, IR, Anal. ($C_{25}H_{31}N_5O_3 \cdot 0.25{}^i Pr_2O \cdot 0.25H_2O$) C, H, N.

Data for *N*-(4-Biphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (17): yield 9% by method D; mp 221−224 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{27}N_5O_3 \cdot H_2O$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-hydroxyphenyl)-1-piperazinecarboxamide (18). To a solution of **22** (4.60 g, 9.22 mmol) in acetic acid (30 mL) was added 10% Pd/C (1.50 g, containing 50% water) in acetic acid (20 mL), and the resulting mixture was hydrogenated at 50 °C. After the removal of the catalyst by filtration and evaporation, methanol was added to the residue to give the title compound (2.99 g, 7.31 mmol, 79% yield): mp 152−154 °C (MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{23}N_5O_4 \cdot 0.25H_2O \cdot$MeOH) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methoxyphenyl)-1-piperazinecarboxamide (19): yield 87% by method A; mp 221−223 °C (Et_2O); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_4$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-isopropoxyphenyl)-1-piperazinecarboxamide (20): yield 67% by method A; mp 220−222 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_4 \cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21): yield 97% by method A; mp 218−219 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{27}N_5O_4$) C, H, N.

Data for *N*-(4-Benzyloxyphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (22): yield 100% by method B in the presence of triethylamine; mp 195−196 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_4$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methylthiophenyl)-1-piperazinecarboxamide (23): yield 84% by method A; mp 231−233 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_3S \cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-ethoxycarbonylphenyl)-1-piperazinecarboxamide (24): yield 96% by method A; mp 242−246 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{27}N_5O_5$) C, H, N.

***N*-(4-Carboxyphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (25).** To a solution of **24** (390 mg, 0.84 mmol) in 1,4-dioxane (10 mL) were added lithium hydroxide monohydrate (141 mg, 3.36 mmol) and water (1 mL). The reaction mixture was stirred overnight and evaporated. The residue was suspended in water and adjusted to pH 4 with 4 mol/L hydrochloric acid, and then the solid was collected by filtration, washed with water, and dried under vacuum. Purification by silica gel column chromatography gave the title compound in 100% yield: ^{1}H NMR, FABMS, IR.

Data for *N*-(4-Cyanophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (26): yield 90% by method A; mp 274−275 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{22}N_6O_3 \cdot 0.25H_2O$) C, H, N.

***(dl)*-4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methylsulfinylphenyl)-1-piperazinecarboxamide (27).** To a solution of **23** (647 mg, 1.47 mmol) in dichloromethane (15 mL) was added *m*-chloroperbenzoic acid (381 mg, 2.21 mmol) at 0 °C, and the resulting mixture was stirred for 6 h under an argon atmosphere. $Na_2S_2O_3$ solution (0.1 mol/L) was added, and the mixture was stirred for 30 min. Following separation of dichloromethane, the mixture was washed with brine, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography to give the title compound (482 mg, 1.06 mmol, 72% yield): mp 241−244 °C ($CHCl_3$−MeOH); ^{1}H NMR, FABMS, HRMS-FAB, IR.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methanesulfonylphenyl)-1-piperazinecarboxamide (28). Similar reaction of **27** except with 3 equiv of *m*-chloroperbenzoic acid gave the title compound: yield 44% yield; mp 266−269 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_5S \cdot 0.25H_2O$) C, H, N.

Data for *N*-(2,4-Dichlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (29): yield 100% by method A; mp 166−167 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{21}Cl_2N_5O_3$) C, H, N.

Data for *N*-(3,4-Dichlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (30): yield 100% by method A; mp 221−222 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{21}Cl_2N_5O_3$) C, H, N.

Data for *N*-(4-Chloro-3-nitrophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (31): yield 64% by method A; mp 253−255 °C (AcOEt−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{21}ClN_6O_5$) C, H, N.

Data for *N*-(3,5-Dichlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (32): yield 93% by method A; mp 139−140 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{21}Cl_2N_5O_3$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3,4-methylenedioxyphenyl)-1-piperazinecarboxamide (33): quantitaive yield by method B; mp 218−219 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{23}N_5O_5$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[4-(2-methoxyphenoxy)phenyl]-1-piperazinecarboxamide (34): yield 52% by method B; mp 186−187 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_5$) C, H, N.

Data for *N*-[4-(4-Chlorophenoxy)phenyl]-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (35): yield 97% by method B; mp 204−205 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{26}ClN_5O_4$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[4-(4-methylphenoxy)phenyl]-1-piperazinecarboxamide (36): yield 97% by method B; mp 201−202 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_4$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[4-(4-nitrophenoxy)phenyl]-1-piperazinecarboxamide (37): yield 87% by method B; mp 261−262 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{26}N_6O_6\cdot 0.25H_2O$) C, H, N.

***N*-[4-(4-Aminophenoxy)phenyl]-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (38).** To a solution of **37** (300 mg, 0.57 mmol) in ethanol (25 mL) was added a suspension of 10% Pd/C (100 mg, containing 50% water) in ethanol (5 mL) and water (1 mL). The mixture was hydrogenated for 5.5 h, then a suspension of 10% Pd/C (50 mg, containing 50% water) was added, and the mixture was further hydrogenated for 7.5 h. The catalyst was removed by filtration, and the residue after removal of solvent was purified by silica gel column chromatography to give the title compound (172 mg, 0.34 mmol, 61% yield): mp 106−108 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{28}N_6O_4\cdot H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxyquinazolinyl)-*N*-[4-(4-pyridyloxy)phenyl]-1-piperazinecarboxamide (39): yield 11% by method C; mp 163−164 °C; ^{1}H NMR, ESMS, HRMS-ES, IR.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[4-(1-naphthyloxy)phenyl]-1-piperazinecarboxamide (40): yield 65% by method C; mp 178−180 °C; ^{1}H NMR, ESMS, HRMS-ES, IR.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[4-phenylaminophenyl]-1-piperazinecarboxamide (41): quantitative yield by method B; mp 219−220 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{28}N_6O_3$) C, H, N.

Data for *N*-(4-Benzylphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (42): quantitative yield by method B; mp 215−216 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_3\cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[4-(4-pyridylmethyl)phenyl]-1-piperazinecarboxamide (43): yield 59% by method B; mp 174−175 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{28}N_6O_3\cdot 0.5H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-nitrophenyl)-1-piperazinethiocarboxamide (44): yield 67% by method E; mp 221−224 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}N_6O_4S\cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3-nitrophenyl)-1-piperazinethiocarboxamide (45): yield 83% by method E; mp 140−143 °C (AcOEt−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}N_6O_4S$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(2-nitrophenyl)-1-piperazinethiocarboxamide (46): yield 100% by method E; mp 177−178 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}N_6O_4S\cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-phenyl-1-piperazinethiocarboxamide (47): yield 97% by method E; mp 230−232 °C (Et_2O); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{23}N_5O_2S\cdot 0.4Et_2O\cdot 0.4H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-fluorophenyl)-1-piperazinethiocarboxamide (48): yield 56% by method E; mp 212−217 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}FN_5O_2S\cdot 1.5H_2O$) C, H, N.

Data for *N*-(4-Chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (49): yield 96% by method E; mp 199−204 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}ClN_5O_2S\cdot 0.75H_2O$) C, H, N.

Data for *N*-(3-Chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (50): yield 79% by method E; mp 222−224 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}ClN_5O_2S\cdot 0.25H_2O$) C, H, N.

Data for *N*-(2-Chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (51): yield 53% by method F; mp 166−167 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}ClN_5O_2S$) C, H, N.

Data for *N*-(4-Bromophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (52): yield 78% by method E; mp 170−171 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}BrN_5O_2S\cdot 0.25$AcOEt) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-iodophenyl)-1-piperazinethiocarboxamide (53): yield 94% by method E; mp 129−132 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{22}IN_5O_2S\cdot H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-tolyl)-1-piperazinethiocarboxamide (54): yield 82% by method E; mp 204−205 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_2S$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-isopropylphenyl)-1-piperazinethiocarboxamide (55): yield 84% by method E; mp 194−195 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_2S$) C, H, N.

Data for *N*-(4-Butylphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (56): yield 80% by method E; mp 171−173 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{25}H_{31}N_5O_2S$) C, H, N.

Data for *N*-(4-*tert*-Butylphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (57): yield 61% by method E; mp 221−224 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{25}H_{31}N_5O_2S\cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-isopropoxyphenyl)-1-piperazinethiocarboxamide (58): yield 74% by method F; mp 208−209 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_3S$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinethiocarboxamide (59): yield 74% by method E; mp 242−243 °C (AcOEt−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR, Anal. ($C_{27}H_{27}N_5O_3S\cdot 0.25H_2O$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methylthiophenyl)-1-piperazinethiocarboxamide (60): yield 77% by method F; mp 214−216 °C (AcOEt); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_2S_2$) C, H, N.

Data for *N*-(3-Carboxyphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (61): yield 96% by method E; ^{1}H NMR, FABMS, HRMS-FAB, IR.

Data for *N*-(4-Chloro-3-nitrophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (62): yield 74% by method E; ^{1}H NMR, FABMS, IR.

Data for *N*-(4-Bromo-3-chlorophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (63): yield 89% by method E; mp 169−172 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{21}H_{21}BrClN_5O_2S$) C, H, N.

Data for *N*-(3,4-Dimethoxyphenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (64): yield 100% by method E; mp 174−176 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_4S$) C, H, N.

Data for 4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3,4-methylenedioxyphenyl)-1-piperazinethiocarboxamide (65): yield 100% by method E; mp 207−211 °C ($CHCl_3$−MeOH−$^i Pr_2O$); ^{1}H NMR, FABMS, IR, Anal. ($C_{22}H_{23}N_5O_4S\cdot 0.5H_2O$) C, H, N.

Plasma Concentration after Oral Administration to SD Rats. A suspension of each compound in methylcellulose (6 mg/mL) was orally administrated to male SD rats (30 mg/kg, $n = 2$), and the plasma was collected via a tail vein by capillary at 1 and 8 h. DMF (10 μL) and acetonitrile (200 μL) were added to the plasma (100 μL). The mixture was well stirred and centrifuged for 5 min. The supernatant was evaporated under centrifugation to dryness, the mobile phase of HPLC (acetonitrile−phosphate buffer containing 5 mmol/L sodium octanesulfonate pH-adjusted by phosphoric acid, 200 μL) was added, and the solution was membrane-filtered. The concentration of the drug was determined by HPLC, using the calibration determined previously.

Inhibitory Effect on Neointima Formation after Balloon Injury of the Rat Carotid Artery. Male SD rats ($n =$

8−10) were anesthetized with sodium pentobarbital (50 mg/kg, ip). A cervical midline incision was made, the left common carotid artery was isolated, and a balloon catheter (2F, Edwards Laboratories) was inserted through the external branch into the carotid artery to the aortic arch. The balloon was inflated with air and passed seven times up and down the common carotid artery. After the above treatment was repeated seven times, the catheter was pulled out, the left external carotid was ligated, and the wound was sutured. A suspension of each compound in methylcellulose 400 was administrated (30 mg/kg) orally twice a day for a period of 15 days starting on the day before the balloon injury. On the 14th day after the balloon injury, the rats were sacrificed and their left common carotid arteries were isolated, fixed with formalin, and embedded in paraffin. Cross-sections of the carotids were mounted on slides and stained with Elastica-Van Gieson. The cross-sectional areas of the intima and media were measured with an image analyzer (Luzex F, NIRECO), and the intimal/medial area ratio (I/M) was the index of neointima formation.

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Supporting Information Available: Spectral and elemental analysis data for the compounds in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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