Potent and Selective Inhibitors of PDGF Receptor Phosphorylation. 2. Synthesis, Structure Activity Relationship, Improvement of Aqueous Solubility, and Biological Effects of 4-[4-(*N*-Substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Derivatives

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4-[4-(*N*-Substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives such as KN1022 are potent inhibitors of the phosphorylation of platelet derived growth factor receptor (PDGFR). Structure activity relationships in the (thio)urea moiety, the phenyl ring itself, the linker between these two moieties, and the piperazine moiety were investigated. The role of the linker was found to be quite different, where ureas yielded decreasing activity, while thioureas provided increasing activity. Cyanoguanidine as a bioisostere of thiourea and related dicyanovinyl or nitrovinyl groups were not suitable for potent activity. A hydrogen atom on the (thio)urea moiety was essential for activity. Stereochemistry was also important for inhibition of PDGFR phosphorylation. Through the modification of these moieties, benzylthiourea analogues with a small substituent on the 4-position and the 3,4-methylenedioxy group (KN734/CT52923) were found to be optimal for selective and potent activity. Replacement of the phenyl ring by heterocycles improved aqueous solubility without loss of activity and kinase selectivity. Introduction of a methyl group on 5-position of the piperazine ring and replacement by homopiperazine reduced inhibitory activity. An efficient synthetic method was also developed for 2-pyridylurea-containing analogues, via carbonylation of 2-aminopyridine with *N*,*N*′-carbonyldiimidazole. A potent analogue, KN734, inhibited smooth muscle cell proliferation and migration induced by platelet derived growth factor-BB (PDGF-BB) and suppressed neointima formation following balloon injury in rat carotid artery by oral administration. Therefore, 4-[4-(*N*-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives may be expected to have potential as therapeutic agents for the treatment of restenosis.

Introduction

Platelet derived growth factor (PDGF) is known to act as a potent mitogen and chemotactic factor for various cells such as fibroblasts, smooth muscle cells (SMCs), mesenchymal cells, and brain glial cells.[1−4] Abnormal PDGF-induced cell proliferation has been proposed to lead to proliferative disorders such as atherosclerosis, restenosis following percutaneous transluminal coronary angioplasty (PTCA), glomerulonephritis, glomerulosclerosis, liver cirrhosis, pulmonary fibrosis, and cancer.[5−15] 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.[16−20] PDGF receptor (PDGFR) is known to possess a tyrosine kinase activity and is autophosphorylated in the course of receptor activation. Therefore, an inhibitor of PDGFR phosphorylation would be expected to possess a therapeutic potential in the treatment of these proliferative disorders.

Recently, 4-[4-(*N*-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives such as KN1022 or **1a**−**1f** (Table 1) were found to be selective inhibitors for the PDGFR phosphorylation,[21−23] and initial structure activity relationships (SARs) focused on 4-nitrophenylcarbamoyl moiety have been reported.[24] Bulky substitution on the 4-position of the phenyl ring was generally favorable for the urea analogues, especially 4-isopropyl, 4-*tert*-butyl, or 4-phenoxyphenyl. Thioureas also showed inhibitory activity; however, SARs were slightly different from the ureas. Bulky hydrophobic substituents on the 3- or 4-position were found to be suitable for potent activity, and the potency of the thiourea analogues was weaker than that of the corresponding urea analogue.

In this paper, we report further synthesis and the SARs for inhibition of in vitro β-PDGFR phosphorylation focused on the (thio)urea moiety, the phenyl ring itself, the insertion of a linker between these two moieties for the modification of the distance and orientation of a phenyl ring relative to the (thio)urea moiety, and modification of the piperazine moiety. We report at-

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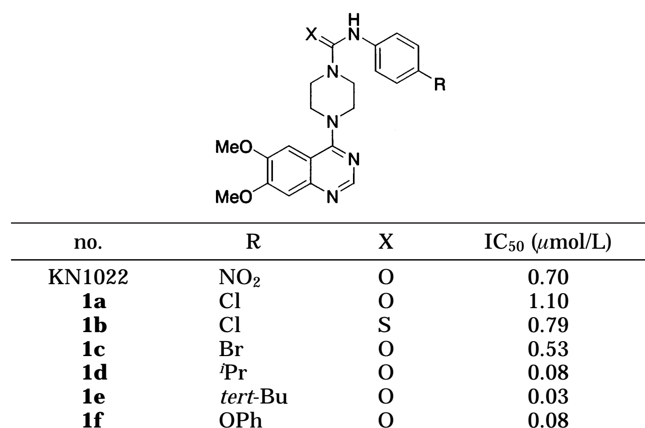
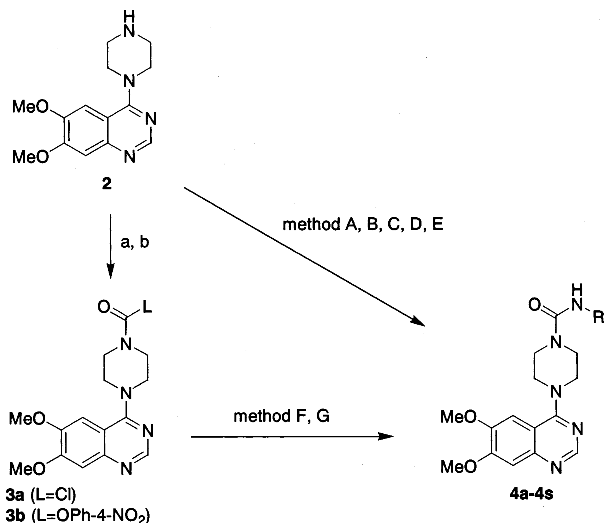
Table 1.



no.	R	X	IC_{50} (μmol/L)
KN1022	NO_2	O	0.70
1a	Cl	O	1.10
1b	Cl	S	0.79
1c	Br	O	0.53
1d	^{i}Pr	O	0.08
1e	*tert*-Bu	O	0.03
1f	OPh	O	0.08

Scheme 1[a]



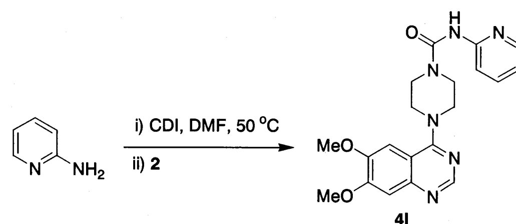
[a] Method A: R-NCO, solvent. Method B: (i) R-NH_2, CDI, solvent, (ii) **2**. Method C: (i) R-COCl, NaN_3, Et_2O, H_2O, 0 °C; (ii) **2**, toluene, 70 °C. Method D: (i) R-COOH, diphenylphosphoryl azide (DPPA), Et_3N, toluene; (ii) 70 °C; (iii) **2**. Method E: (i) R-NH_2, 4-methoxyphenyl 4-nitrophenylcarbonate, MeCN; (ii) **2**, DBU. Method F: **3a**, R-NH_2, Et_3N, DMF. Method G: **3b**, R-NH_2, NMP, 60 °C. (a) For **3a**: triphosgene, Et_3N, CH_2Cl_2, 0 °C, 38%. (b) For **3b**: 4-nitrophenylchloroformate, Et_3N, CH_2Cl_2, 75%.

tempts to improve the solubility of analogues without loss of the inhibitory activity by replacing the phenyl ring with a heterocyclic ring since the initial lead compound KN1022 was quite insoluble (Table 7). An evaluation of kinase selectivity for selected analogues is also reported. Furthermore, we also report the selection of analogues for in vivo evaluation by measurement of plasma drug concentration after oral administration to Sprague–Dawley rats (SD rats) and the inhibitory activity on neointima formation in rat carotid artery.

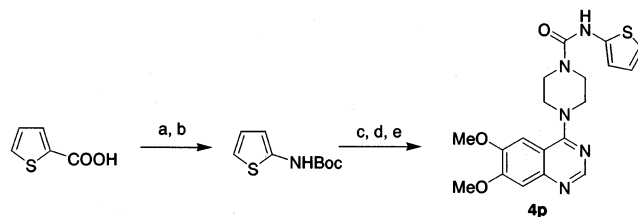
Chemistry

General synthetic methods for the ureas **4** are outlined in Scheme 1. There are seven methods (methods A, B, C, D, E, F, G) to prepare analogues **4a**–**4s** from the known intermediate 4-(1-piperazinyl)-6,7-dimethoxyquinazoline (**2**)[25] or the related compounds **3a** and **3b**. Method A (condensation of **2** and commercially available isocyanate) and method B (carbonylation of amine with *N,N'*-carbonyldiimidazole (CDI), followed by condensation with **2**) was described in our previous publication.[24]

Scheme 2



Scheme 3[a]



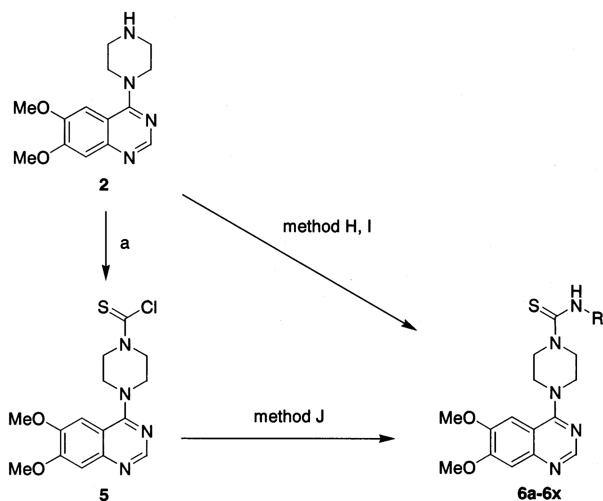
[a] (a) DPPA, Et_3N, dioxane; (b) *tert*-BuOH, 80 °C; (c) hydrochloric acid, aqueous Et_2O; (d) CDI, Et_3N, CH_2Cl_2; (e) **2**.

Curtius rearrangement of the carboxylic azide that was prepared from carboxylic acid analogues with sodium azide (method C) or diphenylphosphoryl azide (method D), or treatment of amines with 4-methoxyphenyl 4-nitrophenyl carbonate in acetonitrile,[26] followed by addition of **2** provided the ureas (method E). Treatment of amines with known carbamoyl chloride **3a**[27] in the presence of triethylamine provided the urea (method F). Heating amines in *N*-methylpyrrolidinone (NMP) with 4-nitrophenylcarbamate **3b**, which was prepared from **2** and 4-nitrophenylchloroformate in the presence of triethylamine, also provided the ureas (method G). Application of method F and G for aniline type amines was inappropriate because of their low nucleophilicity.

Method B was found to be widely applicable for synthesis of the ureas. 2-Pyridylisocyanate could not be prepared by treatment of 2-aminopyridine with phosgene since the resulting isocyanate spontaneously dimerized.[28] On the other hand, a mixture of 2-aminopyridine and CDI was warmed to 50 °C in *N,N*-dimethyformamide (DMF), followed by addition of **2** to provide the desired 2-pyridylurea analogue **4l** as shown in Scheme 2. From this result, we speculate that the reaction species is *N*-(2-pyridyl)-1-imidazolecarboxamide. Since there are limited synthetic procedures to prepare the 2-pyridylureas such as carbamoylation of 2-aminopyridine, this method is quite efficient, especially in the case of the complex 2-pyridylurea derivatives. The 2-thienyl analogue **4p** was also obtained by method B. For 2-thienyl analogue **4p**, since 2-aminothiophene is known to be unstable,[29] deprotection of known 2-*tert*-butoxycarbonylaminothiophene,[29] followed by quickly treating under the condition of method B in the presence of triethylamine, successfully provided the desired compound **4p** as shown in Scheme 3.

The widely used synthetic routes to the thioureas **6** are outlined in Scheme 4. Method H (condensation of **2** and isothiocyanate) and method I (thiocarbonylation of amine with thiophosgene in the presence of triethylamine, followed by condensation with **2**) were described in the previous publication.[24] Treatment of **2** with thiophosgene gave thiocarbamoyl chloride **5**, followed by condensation with an amine provided the thiourea

Scheme 4[a]



[a] Method H: R-NCS, solvent. Method I: (i) R-NH_2, $CSCl_2$, Et_3N, solvent; (ii) **2**. Method J: R-NH_2, Et_3N, DMF. (a) Thiophosgene, Et_3N, CH_2Cl_2, 52%.

(method J). This method was also inappropriate for the anilines like the carbamoyl chloride **3a**.

The cyanoguanidine **10**, whose moiety is a well-known for a bioisostere of thiourea as made famous by cimetidine, and the dicyanovinyl **11** and nitrovinyl **12** analogues were obtained by condensation of **7a** (or **7b**), **8**, **9**, and amine under heating in the appropriate solvent, respectively (Scheme 5). 2-Propanol was especially suitable for this reaction since the substitution of ethoxy group occurred in ethanol. For all amines presented in Schemes 1, 4, and 5 where salt forms such as hydrochloride were used, addition of more than one equivalent triethylamine for the amine in the reaction mixture yielded the desired compounds.

The *N*-methylurea **4t** was successfully obtained by methylation of **1c**[24] (Scheme 6). However, methylation of the thiourea **6a** did not provide the desired *N*-methylthiourea **6y** but the *S*-methylated isothiourea. Therefore, we prepared **6y** via thiocarbamoyl chloride from *N*-methylbenzylamine and thiophosgene under the same conditions of method I as shown in Scheme 7.

The methylated piperazine analogues were obtained as shown in Scheme 8. Condensation of **13**[25] with (*RS*)-2-methylpiperazine, C_2-symmetric (*RS*)-*trans*-2,5-dimethylpiperazine or *cis*-2,6-dimethylpiperazine following treatment with iso(thio)cyanate gave as sole products **17**−**19**, respectively. The homopiperazine analogue **21** was obtained from **20**[25] as shown in Scheme 9.

Results and Discussions

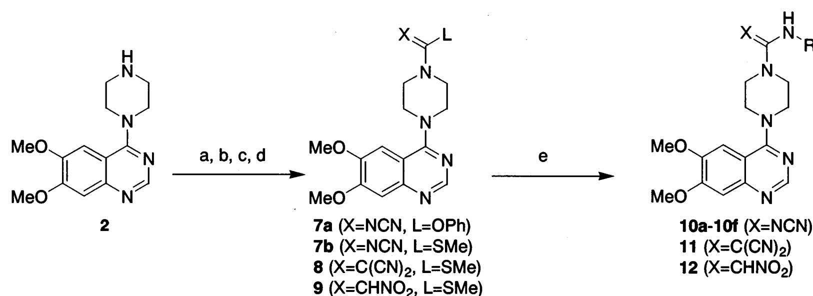
SAR for Inhibition of β-PDGFR Phosphorylation. As further exploration for the SAR of KN1022 derivatives, we prepared a series of analogues examining the effect of the linker between phenyl ring and the (thio)urea moieties, replacement and substitutions of these moieties, and the piperazine moiety on inhibitory activity against the β-PDGFR. We also attempted to improve aqueous solubility by replacing the phenyl ring with heterocyclic rings such as pyridine. All the analogues prepared were evaluated for their inhibition of β-PDGFR phosphorylation in accordance with a previously reported whole cell assay,[30] and the resulting IC_{50} values are listed in Tables 2−4.

Table 2 shows the results that the linker between the phenyl ring and the (thio)urea moiety has a substantially different influence on the inhibitory activity. Regarding urea derivatives, insertion and extension of the methylene chain reduced the activity (**1c** vs **4c**, **1d** vs **4e**, **1e** vs **4f**, **1f** vs **4h**, **4a** vs **4j**). The bulky 4-substituent on the phenyl ring was favorable among the benzylurea series (comparison **4d**, **4e**, and **4f**); however, the IC_{50} values were higher than those of the corresponding phenylurea analogues.[24] Interestingly, phenacyl analogue **4k**, which was carbonylated at benzyl position of the phenethyl group, showed potent activity.

In contrast, for the thiourea derivatives, insertion of one methylene unit between the thiourea moiety and phenyl ring (the benzylthioureas) was found to enhance inhibitory activity with log scale in some substituents. For instance, comparing chloro analogues, the 4-chlorobenzylthiourea (**6b**, IC_{50} = 0.07 μmol/L) showed much more potent activity than 4-chlorophenylthiourea **1b** or 4-chlorobenzylurea **4a**. The most suitable place for substitution was the 4-position by comparison of **6b** with **6c** and **6d**. Further extension of the methylene chain, 4-chlorophenethyl analogue **6m**, resulted in reduced activity. When the linker was cyclopropylmethyl (**6n**), the activity was completely eliminated. Although the bulky 4-bromo analogue **6e** was a potent inhibitor, the 4-methyl analogue (**6f**, IC_{50} = 0.03 μmol/L) and 4-methoxy analogue (**6i**, IC_{50} = 0.10 μmol/L) showed more potent activity than the bulky 4-isopropyl **6g** and 4-phenoxy **6j** analogues among the alkyl and alkoxy-substituted analogues, respectively. From these results, benzylthioureas with relatively small substituents were found to be suitable for the potent activity differing from the phenylthiourea analogues.[24] 3,4-Dimethoxy analogue **6k** was a weak inhibitor; however, bicyclic 3,4-methylenedioxybenzyl analogue (KN734, IC_{50} = 0.09 μmol/L) was found to be more potent than **6k**, unlike the activity of corresponding phenylthioureas described in our previous report.[24] Furthermore, **(*S*)-6l**, which is α-methylated analogue of the benzylthiourea **6a**, retained activity, and the enantiomer **(*R*)-6l** was a considerably weaker inhibitor. As we have already described in a previous biological article,[30] the inhibition mechanism of KN734 was via reversible competition with ATP with a K_i value of 3 nmol/L. These results suggest that the chirality of the molecule was recognized by β-PDGFR and the binding pocket of the inhibitor may be a narrow cleft with the (*R*)-methyl group causing quite unfavorable steric interactions.

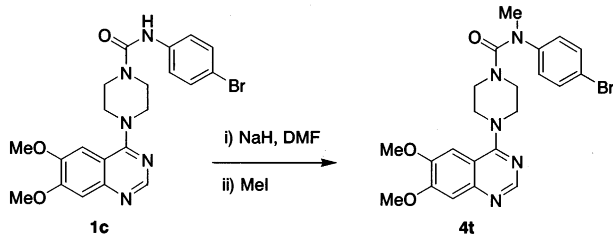
Next, we attempted to replace the phenyl ring with other ring systems, especially with heterocycles in expectation of improvement for the aqueous solubility, and to obtain some SARs as shown in Table 3. Regarding the urea analogues, pyridyl analogues (**4l**, **4m**, and **4o**) were devoid of any activity. Introduction of chlorine atom on 3-pyridine ring at 5-position (i.e., para substitution, **4n**) somewhat enhanced activity but the IC_{50} value was still weak. Thienyl analogues (**4p** and **4q**) showed similar activity with initial KN1022, and insertion of one methylene unit (**4r**) was detrimental. In marked contrast of ureas, several pyridine-containing thiourea analogues showed moderate activity. Among pyridylthioureas (**6o**, **6p**, **6r**), 4-pyridyl (**6r**) and 3-pyridyl (**6p**) analogues showed similar activity with

Scheme 5[a]

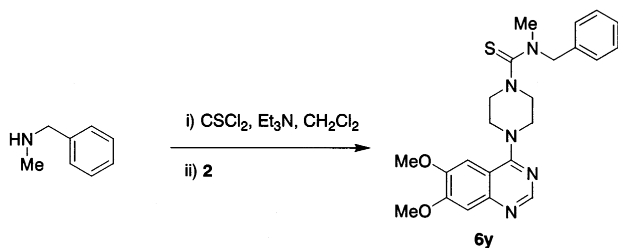


[a] (a) $(PhO)_2NCN$, ^{i}PrOH, reflux, for **7a**, 46%; (b) $(MeS)_2NCN$, EtOH, reflux, for **7b**, 84%; (c) $(MeS)_2C{=}C(CN)_2$, MeCN, reflux, for **8**, 85%; (d) $(MeS)_2C{=}CHNO_2$, EtOH, reflux, for **9**, 31%; (e) R-NH_2, solvent, heat.

Scheme 6



Scheme 7



KN1022; however, 2-pyridyl analogue **6o** was inactive. Substitution on 3-pyridine ring at 5-position (**6q**) had a negligible effect on potency. Insertion of a methylene (**6s**) was acceptable; however, extension of the methylene chain to ethylene (**6t**) abolished the activity. Furthermore, **6v** and **6w**, which are perhydrogenated analogues of the furfuryl analogue **6u** and benzyl analogue **6a**, respectively, showed no activity. These results indicate that the aromaticity in this moiety is essential for the inhibitory activity.

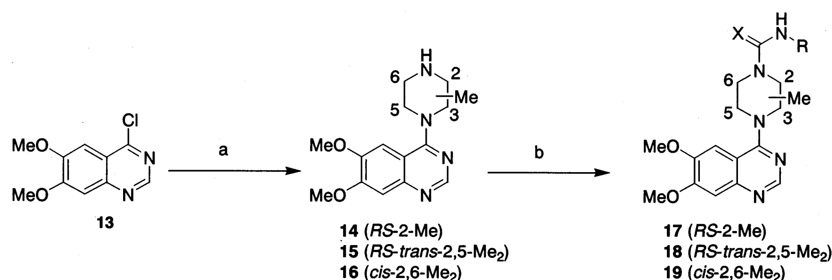
To further optimize the (thio)urea moiety, we prepared several related compounds as listed Table 4. In particular, the high potency shown by the several benzylthiourea analogues prompted us to evaluate the cyanoguanidine **10**, which is a well-known bioisotere of the thiourea, and the related derivatives (**11** and **12**). Cyanoguanidine analogues showed inhibitory activity with almost the same preference of substituents as the thiourea analogues for orientation (comparison **10a**, **10b**, and **10c**) and group (comparison **10d** and **10e**) on the phenyl ring, albeit less potent than the thiourea analogues (comparison **10a** and **6b**). Among the cyanoguanidine analogues, **10f** ($IC_{50} = 0.19$ μmol/L) showed the most potent activity. Additionally, replacement of (thio)urea by dicyanovinyl **11**, nitrovinyl **12**, acylthiourea **6x**, or sulfonylurea **4s** was not tolerated; therefore, benzylthioureas was optimal for their potent activity in this region. Replacement of NH moiety by oxygen (**3b**) and *N*-methylation of (thio)urea moiety (**4t** and **6y**) completely abolished activity. These results indicated that the hydrogen atom is essential for the activity. Since KN734 was found to be competitive with ATP using purified receptor kinase domain expressed in insect cells,[30] we speculated that the acidic hydrogen on the (thio)urea moiety interacts at a site of PDGFR similar to the phosphate moiety of ATP.

Finally, modification of the piperazine ring had no positive influence on the activity (Table 5). Introduction of methyl group on the piperazine ring, 2-methyl (**17**), and *cis*-2,6-dimethyl (**18**) analogues retained activity compared with the parent compounds (**1f**, **6a**); however, the *trans*-2,5-dimethyl analogue **19** showed very poor activity, so introduction of methyl group at 5-position of piperazine ring was detrimental effect on the activity. Furthermore, exchanging with the homopiperazine (**21**) reduced activity. These results suggest that the orientation of quinazoline ring and carbamoyl moiety are important for interaction with PDGFR and/or steric tolerance of piperazine-interacting site is quite limited.

Kinase Selectivity. We also evaluated three potent compounds KN734, **6a**, and **4u** (hydrochloride of **4q**) for inhibitory activity on various kinases, including c-kit and Flt3, which are closely related PDGFR-family tyrosine kinases[31] using previously reported methods.[30,32] As shown in Table 6, all compounds showed similar inhibitory activity for PDGFRs and c-kit. For Flt3, better selectivity with 10 to more than 100-fold was observed. KN734 showed weak inhibitory activity against vascular endothelial growth factor-2 (VEGF-2); however, no significant inhibition was observed on other receptor tyrosine kinases (epidermal growth factor receptor; EGFR, fibroblast growth factor; FGFR, VEGF-2), nonreceptor tyrosine kinases (src, abl), and Ser/Thr kinases (protein kinase A; PKA, protein kinase C; PKC) at 100−1000 higher concentrations. These studies also demonstrate that our synthesized compounds retained good selectivity for the PDGFR-family tyrosine kinases, similar to that in our previous report.[24]

Aqueous Solubility. We obtained many potent inhibitors of PDGFR phosphorylation, and these were expected to possess therapeutic potential; however, aqueous solubility of the parent compound KN1022 was not satisfactory for oral administration (Table 7). We evaluated the solubility in phosphate buffer (pH 7.4) and log *D* values of some potent analogues (**4q**, **6s**, and **6u**) which were expected to improve the solubility by replacement of the phenyl ring with a heterocyclic ring. As listed in Table 7, the log *D* values and the aqueous solubility of these compounds were improved over that of KN1022. Especially, 3-thienyl analogue **4q** and 3-py-

Scheme 8[a]



[a] (a) methylated-piperazine (excess), ^{i}PrOH, reflux; (b) R-NCX, solvent.

Scheme 9

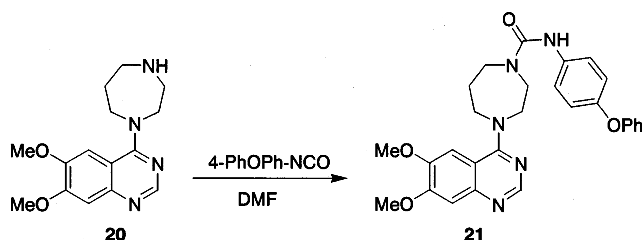


Table 2. Synthetic Method and Inhibitory Activity on β-PDGFR Phosphorylation[a]

no.	R	Y	X	procedure	IC$_{50}$[a,b] (μmol/L)
4a	4-Cl	CH$_2$	O	method G	1.27
4b	4-F	CH$_2$	O	method E	9.59
4c	4-Br	CH$_2$	O	method G	0.74
4d	4-Me	CH$_2$	O	method F	2.94
4e	4-Pr	CH$_2$	O	method G	0.55
4f	4-*tert*-Bu	CH$_2$	O	method F	0.11
4g	4-MeO	CH$_2$	O	method E	3.06
4h	4-PhO	CH$_2$	O	method B	0.38
4i	3,4-(OCH$_2$O)−	CH$_2$	O	method F	1.87
4j	4-Cl	CH$_2$CH$_2$	O	method G	5.84
4k	4-Br	CH$_2$CO	O	method F	0.14
6a	H	CH$_2$	S	method H	0.55
6b	4-Cl	CH$_2$	S	method H	0.07
6c	3-Cl	CH$_2$	S	method H	0.23
6d	2-Cl	CH$_2$	S	method H	0.98
6e	4-Br	CH$_2$	S	method J	0.03
6f	4-Me	CH$_2$	S	method H	0.03
6g	4-^{i}Pr	CH$_2$	S	method I	0.20
6h	4-*tert*-Bu	CH$_2$	S	method I	0.16
6i	4-MeO	CH$_2$	S	method H	0.10
6j	4-PhO	CH$_2$	S	method I	0.96
6k	3,4-(MeO)$_2$	CH$_2$	S	method H	2.41
KN734	3,4-(OCH$_2$O)−	CH$_2$	S	method H	0.09
(*S*)-**6l**	H	(*S*)-(Me)CH	S	method H	0.54
(*R*)-**6l**	H	(*R*)-(Me)CH	S	method H	>30
6m	4-Cl	CH$_2$CH$_2$	S	method H	1.09
6n				method J	>30

[a] IC$_{50}$ (μmol/mL) of β-PDGFR phosphorylation. [b] Autophosphorylation was measured in intact cells using a two-site ELISA.[30]

ridylmethyl analogue dihydrochloride **6s** showed 50-fold higher aqueous solubility than initial parent compound KN1022.

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

no.	R	Y	X	procedure	IC$_{50}$[a,b] (μmol/L)
4l	2-pyridyl	none	O	method B	>10
4m	3-pyridyl	none	O	method C	>30
4n	3-(5-Cl)pyridyl	none	O	method C	8.23
4o	4-pyridyl	none	O	method C	14.1
4p	2-thienyl	none	O	Scheme 3	0.41
4q	3-thienyl	none	O	method D	0.56
4r	3-thienyl	CH$_2$	O	method D	>30
6o	2-pyridyl	none	S	method I	>30
6p	3-pyridyl	none	S	method H	0.41
6q	3-(5-Cl)pyridyl	none	S	method I	0.55
6r	4-pyridyl	none	S	method I	0.98
6s[c]	3-pyridyl	CH$_2$	S	method H	0.28
6t	3-pyridyl	CH$_2$CH$_2$	S	method I	20.1
6u	furfuryl	CH$_2$	S	method H	0.33
6v	(*RS*)-tetrahydro-furfuryl	CH$_2$	S	method H	>30
6w	cyclohexyl	CH$_2$	S	method H	>10

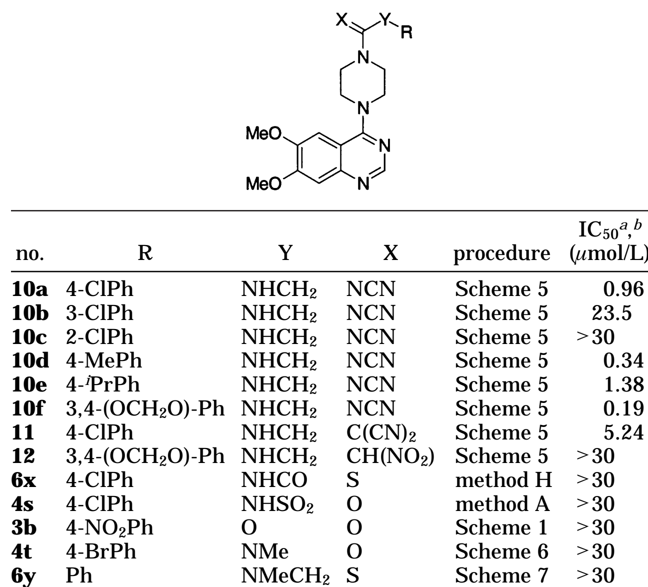
[a] IC$_{50}$(μmol/mL) of β-PDGFR phosphorylation. [b] Autophosphorylation was measured in intact cells using a two-site ELISA.[30] [c] 2HCl salt.

Plasma Drug Concentration after Oral Administration to Rats. To select some oral available analogues which also afford high plasma drug concentration over time for in vivo evaluation, we measured plasma concentration of several KN1022 analogues at 1 and 8 h after oral administration (30 mg/kg) to Sprague−Dawley rats (SD rats, $n = 2$) as shown in Table 8. We observed same relationships between the structure and plasma concentration like in our previous report,[24] i.e., the plasma concentration of the urea **4g** was found to be higher than that of the corresponding thiourea **6i**. The plasma concentration of KN734 was maintained at 2−4 μg/mL up to 8 h. Additionally, the plasma concentrations of **6b** and **4q** in each rats were different. The results indicated that there might be metabolic polymorphism of these analogues in SD rats.

We also evaluated T_{max}, C_{max}, $T_{1/2}$, and AUC$_{0-\infty}$ for several analogues as listed in Table 9. Compounds **4q**, KN734, and **6u** showed longer $T_{1/2}$ and higher AUC$_{0-\infty}$ than **6s**, as easily predicted form the data in Table 8.

Inhibitory Effect on Neointima Formation after Balloon Injury of Rat Carotid Artery and other Biological Effects. We evaluated the effect on neoin-

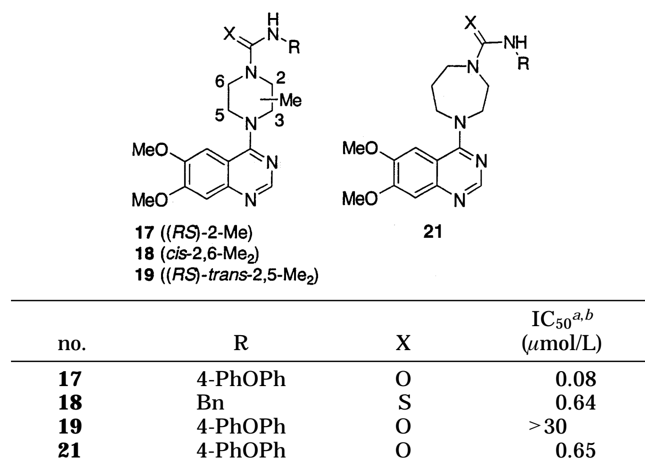
Table 4. Synthetic Method and Inhibitory Activity on β-PDGFR Phosphorylation



no.	R	Y	X	procedure	IC_{50}[a,b] (μmol/L)
10a	4-ClPh	$NHCH_2$	NCN	Scheme 5	0.96
10b	3-ClPh	$NHCH_2$	NCN	Scheme 5	23.5
10c	2-ClPh	$NHCH_2$	NCN	Scheme 5	>30
10d	4-MePh	$NHCH_2$	NCN	Scheme 5	0.34
10e	4-^{i}PrPh	$NHCH_2$	NCN	Scheme 5	1.38
10f	3,4-(OCH_2O)-Ph	$NHCH_2$	NCN	Scheme 5	0.19
11	4-ClPh	$NHCH_2$	$C(CN)_2$	Scheme 5	5.24
12	3,4-(OCH_2O)-Ph	$NHCH_2$	$CH(NO_2)$	Scheme 5	>30
6x	4-ClPh	NHCO	S	method H	>30
4s	4-ClPh	$NHSO_2$	O	method A	>30
3b	4-NO_2Ph	O	O	Scheme 1	>30
4t	4-BrPh	NMe	O	Scheme 6	>30
6y	Ph	$NMeCH_2$	S	Scheme 7	>30

[a] IC_{50} (μmol/mL) of β-PDGFR phosphorylation. [b] Autophosphorylation was measured in intact cells using a two-site ELISA. [30]

Table 5. Inhibitory Activity on β-PDGFR Phosphorylation



no.	R	X	IC_{50}[a,b] (μmol/L)
17	4-PhOPh	O	0.08
18	Bn	S	0.64
19	4-PhOPh	O	>30
21	4-PhOPh	O	0.65

[a] IC_{50} (μmol/mL) of β-PDGFR phosphorylation. [b] Autophosphorylation was measured in intact cells using a two-site ELISA. [30]

tima formation after balloon injury of rat carotid artery by **4q**, KN734, and **6u**, which showed good oral absorption and 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 10, all compounds showed significant inhibition of neointima formation relative to vehicle treated controls ($p < 0.05$, Student's t-test or Aspin-Welch test). The reduction of I/M ratios for **4q**, KN734, and **6u** was 31%, 31%, and 45%, respectively. No obvious affect on rat body weight was observed (data not shown). Based on these data, 4-[4-(*N*-substituted (thio)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. Additionally, the simple and conventional measurement of plasma drug concentration as described in Table 8 was useful method to select the suitable compounds for evaluating in this model.

Table 6. Kinase Specificity[a]

kinase	IC_{50} (μmol/L) 6a	KN734	4u[b]
β-PDGFR	0.55	0.14	0.56
α-PDGFR	0.24	0.21	NT
EGFR	>100	>100	>100
FGFR	>200	160	>30
CSF-1R	>30	>30	NT
VEGFR-2	>100	17.3	NT
Src	>30	>30	NT
Abl	NT	>30	NT
PKA	>30	>30	>30
PKC	>30	>30	>30
Mek 1	>30	>30	NT
Mkk 3	>30	NT	NT
Mkk 6	>30	>30	NT
Erk	>30	>30	NT
Jnk	>30	>30	NT
p38	>30	>30	NT
c-kit	0.36	0.22	0.8
Flt3	>30	14.9	7.02

[a] Autophosphorylation of all receptor tyrosine kinases were measured in intact cells using a two-site ELISA.[30] For all other kinases, substrate phosphorylation was measured in an in vitro assay with purified enzyme.[30] [b] HCl salt of **4q**. NT: not tested.

Table 7. Solubility in Aqueous Phosphate Buffer (pH 7.4)[a]

no.	solubility (μg/mL)	log *D*
KN1022	0.049	3.22
4q	2.0	2.72
6s[b]	2.2	2.49
6u	0.96	2.75

[a] Solubility in aqueous phosphate buffer (pH 7.4) at 20 °C, determined by HPLC. [b] 2HCl salt.

Table 8. Plasma Concentration after Oral Administration to Rats (30mg/kg, $n = 2$)

no.		plasma concentration (μg/mL) 1 h	8h
4g	rat 1	7.3	1.4
	rat 2	11.6	1.9
6a	rat 3	5.4	1.6
	rat 4	8.1	0.9
6b	rat 5	2.4	1.3
	rat 6	<0.1	<0.1
6i	rat 7	2.3	0.4
	rat 8	2.5	0.5
KN734	rat 9	5.1	2.4
	rat 10	5.9	3.6
4q	rat 11	12.4	3.7
	rat 12	7.7	0.7
6s	rat 13	2.6	<0.1
	rat 14	2.6	<0.1
6u	rat 15	3.0	1.2
	rat 16	3.7	1.4

Table 9. PK Parameters after Oral Administration to Rats (30 mg/kg, $n = 3$)

no.	T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	$AUC_{0-\infty}$ (μg h mL^{-1})
4q	3.33	15.9	4.25	145
KN734	3.33	14.5	3.92	89.9
6s	0.67	6.98	2.11	9.84
6u	3.67	7.20	3.33	95.8

We have recently reported that KN734 (CT52923) was a potent inhibitor of the smooth muscle cell proliferation and migration induced by PDGF-BB.[30] KN734 also

Table 10. Inhibitory Activity on Neointima Formation in Rat Cartoid Artery[a]

	no. of animals		I/M ratio	
no.	vehicle	cmpd treated	vehicle	cmpd treated
4q	**10**	**10**	0.99 ± 0.07	0.69 ± 0.06 ($p < 0.05$)
KN734	**9**	**10**	0.95 ± 0.07	0.61 ± 0.07 ($p < 0.05$)
6u	**9**	**9**	0.86 ± 0.10	0.47 ± 0.04 ($p < 0.05$)

[a] All results were mean ± S.E.M.

showed several in vivo effects by oral administration, i.e., suppression of neointima formation following balloon injury in rat carotid artery with various doses,[30] reduction of tumor growth of NIH/3T3 cells transformed by PDGF in nude mouse,[33] and improvement of survival due to a delay in disease progression of mouse model of chronic myelomonocytic leukemia.[34] Therefore, 4-[4-(*N*-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives have a therapeutic potential especially for treating various aspects of atherosclerosis, cancer and leukemia. Glivec (Gleevec), which is a phenylaminopyrimidine inhibitor of bcr/abl kinase and recently launched for indication for chronic myelogenous leukemia, also has the inhibitory activity against c-kit. As recent studies have shown that c-kit plays a central role in the pathogenesis of gastrointestinal stromal tumor (GIST)[35,36] and this agent was demonstrated to have the therapeutic benefit for metastatic GIST,[37] our analogues may also possess therapeutic potential for GIST.

Conclusions

SARs in the (thio)urea moiety, the phenyl ring itself, the linker between these two moieties, and the piperazine moiety were investigated in the 4-(1-piperazinyl)-quinazoline series of PDGFR phosphorylation inhibitors. The effect of the linker was quite different, i.e., for ureas with decreasing activity and for thioureas with increasing activity. Regarding the (thio)urea moiety, cyanoguanidine, which is well-known as bioisostere of thiourea, and related nitrovinyl or dicyanovinyl group were not suitable for potent activity. A hydrogen atom on the (thio)urea moiety was essential for the activity. We also demonstrated that a stereochemistry possess major consequences for inhibition of PDGFR phosphorylation. Through these modifications, benzylthioureas with a relatively small substituent on the 4-position (**6b**, **6e**, **6f**, etc.) and 3,4-methylenedioxy group (KN734) were found to be optimal for selective and potent activity. Replacement of the phenyl ring by heterocycles (**4q**, **6s**) improves the aqueous solubility without activity and loss of selectivity. Introduction of methyl group on 5-position of the piperazine ring and replacement by homopiparazine reduced the activity.

Since KN734 inhibited smooth muscle cell proliferation and migration induced by PDGF-BB and **4q**, KN734, and **6u** suppressed neointima formation following balloon injury in rat carotid artery by oral administration, 4-[4-(*N*-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives may be expected to represent a therapeutic potential for restenosis.

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Experimental Section

Melting points were determined on BÜCHI 535 Melting Point or Yanaco Model MP (Micro Melting Point Apparatus) on compounds isolated as described in the experimental procedures and are uncorrected. 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. ^{1}H NMR spectra were recorded on 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 internal TMS in appropriate organic solutions. FAB-mass spectra were recorded with JEOL JMS-DX303 Mass Spectrometer. Low-resolution EI-mass spectra were recorded with JEOL GC-Mate Mass Spectrometer. TOF-mass spectra were recorded with Micromass Quattro Mass Spectrometer. The IR spectra were recorded with JASCO IR-810 IR spectrometer or HORIBA FT-200 IR spectrometer. Combustion analysis (CHN) were performed by 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 followed except previous reported method A, B, H, and I.[24]

Method C. A solution of nicotinoyl chloride hydrochloride (5.9 g, 33 mmol) in Et_2O (50 mL) was added dropwise with vigorously stirring to an aqueous solution (50 mL) of sodium azide (12.0 g, 185 mmol) at 0 °C. The organic layer was separated, washed with brine, dried over $MgSO_4$, and carefully evaporated under 30 °C. The residue was dissolved in toluene (40 mL). After **2** (548 mg, 2.00 mmol) was added, the mixture was heated at 70 °C for 3 h. The residue after the removal of solvent was purified by silica gel column chromatography and recrystallized from EtOAc to provide **4m** (197 mg, 0.50 mmol).

Method D. After a mixture of 3-thiophenecarboxylic acid (5.46 g, 42.7 mmol), triethylamine (6.25 mL, 44.8 mmol), and diphenylphosphoryl azide (9.67 mL, 44.9 mmol) in toluene (200 mL) solution was heated at 70 °C for 4 h, **2** (6.16 g, 22.5 mmol) was added. The reaction mixture was heated at 80 °C for 3 h, cooled, poured into water, extracted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. The residue after the removal of solvent was purified by silica gel column chromatography eluting with EtOAc/MeOH (100:5 to 100:8) and recrystallized from EtOAc to provide **4q** (11.0 g, 27.6 mmol).

Method E. To a solution of 4-methoxyphenyl 4-nitrophenyl carbonate (954 mg, 3.30 mmol) in acetonitrile (20 mL) was added solution of 4-fluorobenzylamine (375 mg, 3.00 mmol) in acetonitrile (5 mL). After the reaction mixture was stirred for 1 h at room temperature, **2** (548 mg, 2.00 mmol) and DBU (0.33 mL, 2.20 mmol) were added, and then resulting mixture was refluxed for 1.5 h. The residue after the removal of solvent was purified by silica gel column chromatography eluting with EtOAc/$CHCl_3$/MeOH (50:10:2 to 50:10:4) and recrystallization from EtOAc to provide **4b** (480 mg, 1.13 mmol).

Method F. A mixture of **3a** (389 mg, 1.16 mmol), 4-*tert*-butylbenzylamine (0.64 mL, 3.45 mmol), and triethylamine (0.81 mL, 5.81 mmol) in DMF (10 mL) solution was stirred overnight at room temperature under argon atmosphere. The reaction mixture was poured into water, and then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography

eluting with EtOAc/$CHCl_3$/MeOH 50:10:4 to provide **4f** (515 mg, 1.11 mmol).

Method G. A mixture of **3b** (815 mg, 1.86 mmol) and 4-chlorobenzylamine (1.13 mL, 9.29 mmol) in NMP (20 mL) solution was heated at 60 °C for 4.5 h. The reaction mixture was cooled, poured into brine, extracted with $CHCl_3$, and dried over Na_2SO_4. The residue after the removal of solvent was purified by silica gel column chromatography eluting with EtOAc/$CHCl_3$/MeOH 50:10:5 to provide **4a** (621 mg, 1.40 mmol).

Method J. A mixture of **5** (502 mg, 1.42 mmol), 4-bromobenzylamine hydrochloride (950 mg, 4.27 mmol), and triethylamine (1.00 mL, 7.17 mmol) in DMF (10 mL) solution was stirred overnight at room temperature under argon atmosphere. The reaction mixture was poured into water; then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography eluting with EtOAc/$CHCl_3$ 50:10 to provide **6e** (543 mg, 1.08 mmol).

4-(6,7-Dimethoxy-4-quinazolinyl)-1-piperazinecarbonyl Chloride (3a). To a 0 °C solution of triphosgene (5.41 g, 18.2 mmol) in dichloromethane (50 mL) was added slowly a dichloromethane (20 mL) solution of **2** (5.00 g, 18.2 mmol) under argon atmosphere. After triethylamine (7.62 mL, 54.7 mmol) was added slowly, the reaction mixture was stirred for 2 h under the same temperature. The residue after the removal of solvent was purified by silica gel column chromatography eluting with EtOAc/acetone 7:1 to provide 4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarbonyl chloride (**3a**) (2.30 g, 6.84 mmol) in 38% yield.

4-(6,7-Dimethoxy-4-quinazolinyl)-1-piperazinecarboxylic Acid 4-Nitrophenyl Ester (3b). To a 0 °C solution of **2** (1.00 g, 3.65 mmol) in $CHCl_3$ (25 mL) solution were added triethylamine (2.54 mL, 18.2 mmol) and 4-nitrophenyl chloroformate (0.88 g, 4.36 mmol). The reaction mixture was stirred overnight at room temperature, poured into water, extracted with $CHCl_3$, and dried over $MgSO_4$. The residue after the removal of solvent was purified by silica gel column chromatography eluting with EtOAc/acetone 7:1 to provide **3b** (1.16 g, 2.73 mmol) in 75% yield; mp 230−231 °C ($CHCl_3$), ^1H NMR, EIMS, IR, Anal. ($C_{21}H_{21}N_5O_6$ 0.25H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-1-piperazinethiocarbonyl Chloride (5). To a 0 °C solution of thiophosgene (3.06 mL, 40.1 mmol) in dichloromethane (100 mL) was added slowly a dichloromethane (100 mL) solution of **2** (10.0 g, 36.5 mmol) under argon atmosphere. After triethylamine (12.4 mL, 89.1 mmol) was added slowly, the reaction mixture was stirred for 2 h under the same temperature. The residue after the removal of solvent was purified by silica gel column chromatography eluting with EtOAc/acetone (7:1 to 5:1) to provide 4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarbonyl chloride (**5**) (6.65 g, 18.9 mmol) in 52% yield.

***N*-(4-Chlorobenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4a).** 76% by method G; mp 203−204 °C ($CHCl_3$-$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{24}ClN_5O_3$ 0.5H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-fluorobenzyl)-1-piperazinecarboxamide (4b). 53% by method E; mp 200−201 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{24}FN_5O_3$) C, H, N.

***N*-(4-Bromobenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4c).** 55% by method G; mp 211−212 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{24}BrN_5O_3$ 0.25H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methylbenzyl)-1-piperazinecarboxamide (4d). 58% by method F; mp 174−175 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_3$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-isopropylbenzyl)-1-piperazinecarboxamide (4e). 31% by method G; mp 135−136 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{25}H_{31}N_5O_3$) C, H, N.

***N*-(4-*tert*-Butylbenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4f).** 96% by method F; mp 209−210 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{26}H_{33}N_5O_3$ 0.25EtOAc) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methoxybenzyl)-1-piperazinecarboxamide (4 g). 34% by method E; mp 147−148 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_4$ 0.25H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxybenzyl)-1-piperazinecarboxamide (4h). 82% by method B; mp 170−171 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_4$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3,4-methylenedioxybenzyl)-1-piperazinecarboxamide (4i). 75% by method F; mp 172−173 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{25}N_5O_5$ 0.25H_2O) C, H, N.

***N*-[2-(4-Chlorophenyl)ethyl]-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4j).** 70% by method G; mp 177−178 °C (EtOAc), ^1H NMR, FABMS, IR, ($C_{23}H_{26}ClN_5O_3$) C, H, N.

***N*-(4-Bromophenacyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4k).** 72% by method F; mp 198−199 °C (EtOAc) ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{24}BrN_5O_4$) C, H, N.

***N*-Benzyl-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6a).** 61% by method H; mp 187−189 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{25}N_5O_2S$ 0.5H_2O) C, H, N.

***N*-(4-Chlorobenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6b).** 77% by method H; mp 218−220 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{24}ClN_5O_2S$) C, H, N.

***N*-(3-Chlorobenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6c).** 98% by method H; mp 117−119 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{24}ClN_5O_2S$ H_2O) C, H, N.

***N*-(2-Chlorobenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6d).** 89% by method H; mp 175−176 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, HRMS−FAB, IR, Anal. ($C_{22}H_{24}ClN_5O_2S$ 0.5H_2O 0.25$^iPr_2O$) C, H, N.

***N*-(4-Bromobenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6e).** 76% by method J; mp 217−218 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{24}BrN_5O_2S$ 0.25EtOAc) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methylbenzyl)-1-piperazinethiocarboxamide (6f). 89% by method H; mp 202−204 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_2S$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-isopropylbenzyl)-1-piperazinethiocarboxamide (6 g). 86% by method I; mp 178−179 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{25}H_{31}N_5O_2S$) C, H, N.

***N*-(4-*tert*-Butylbenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6h).** 91% by method I; mp 104−105 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{26}H_{33}N_5O_2S$ 0.25H_2O 0.25$^iPr_2O$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-methoxybenzyl)-1-piperazinethiocarboxamide (6i). 72% by method H; mp 201−204 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, HRMS−FAB, IR, Anal. ($C_{23}H_{27}N_5O_3S$ 0.5H_2O 0.25$^iPr_2O$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxybenzyl)-1-piperazinethiocarboxamide (6j). 89% by method I; mp 218−219 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_3S$ H_2O) C, H, N.

***N*-(3,4-Dimethoxybenzyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6k).** 82% by method H; mp 196−197 °C ($CHCl_3$−$^iPr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_4S$ 0.25H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3,4-methylenedioxybenzyl)-1-piperazinethiocarboxamide (KN734). 86% by method H; mp 113−114 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{25}N_5O_4S$ 0.25H_2O) C, H, N.

(*R*)-4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(1-phenylethyl)-1-piperazinethiocarboxamide ((*R*)-6l). 82% by method H,

mp 99−101 °C ($CHCl_3$-MeOH-$^i Pr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_2S$ 0.5H_2O) C, H, N. $[\alpha]_D^{25}$ + 6.09° (*c* 0.49, $CHCl_3$).

(*S*)-4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(1-phenylethyl)-1-piperazinethiocarboxamide ((*S*)-6l). 88% by method H; mp 98−100 °C ($CHCl_3$−$^i Pr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_2S$ 1.5H_2O) C, H, N. $[\alpha]_D^{25}$−6.66° (*c* 0.53, $CHCl_3$).

***N*-[2-(4-Chlorophenyl)ethyl]-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6m).** 74% by method H; mp 106−109 °C ($CHCl_3$−$^i Pr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{23}H_{26}ClN_5O_2S$ 0.5H_2O) C, H, N.

***N*-[1-(4-Chlorophenyl)cyclopropylmethyl]-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6n).** 91% by method J; mp 108−111 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{25}H_{28}ClN_5O_2S$ H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(2-pyridyl)-1-piperazinecarboxamide (4l). 44% by method B; mp 101−102 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{22}N_6O_3$ 1.25H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3-pyridyl)-1-piperazinecarboxamide (4m). 25% by method C; mp 208−209 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{22}N_6O_3$ 0.25H_2O) C, H, N.

***N*-(6-Chloro-3-pyridyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4n).** 53% by method C; mp 238−240 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{21}ClN_6O_3$ 0.5H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-pyridyl)-1-piperazinecarboxamide (4o). 76% by method C; mp 141−143 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{22}N_6O_3$ 0.75H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(2-thienyl)-1-piperazinecarboxamide (4p). (1) To a 0 °C solution of 2-thiophenecarboxylic acid (1.00 g, 7.80 mmol) in 1,4-dioxane (20 mL) were added triethylamine (1.63 mL, 11.7 mmol) and DPPA (1.68 mL, 7.80 mmol). The mixture was stirred for 3 h at room temperature, followed by addition of *tert*-butyl alcohol (1.12 mL, 11.7 mmol), and heated at 80 °C for 4.5 h. After further addition of *tert*-butyl alcohol (1.12 mL, 11.7 mL), heating at 80 °C for 1.5 h, and the removal of solvent, the residue was purified by silica gel column chromatography to provide 2-*tert*-butoxycarbonylaminothiophene[29] (1.05 g, 5.28 mmol) in 68% yield; EIMS (*m*/*z*): 199 $(M)^+$. (2) To a solution of 2-*tert*-butoxycarbonylaminothiophene (500 mg, 2.51 mmol) in Et_2O (20 mL) was added hydrochloric acid (9 mL). The mixture was stirred for 30 min at room temperature, evaporated under 30 °C, and azeotroped with 1,4-dioxane. The residue was suspended in dichloromethane (15 mL). CDI (479 mg, 2.19 mmol), followed by triethylamine (0.76 mL, 5.45 mmol), was added at 0 °C, and the reaction mixture was stirred at the same temperature for 1 h. After **2** (500 mg, 1.82 mmol) was added, the resulting mixture was stirred at room-temperature overnight. The residue after the removal of solvent was purified by silica gel column chromatography to provide **4p** (479 mg, 1.20 mmol) in 67% yield; mp 231−233 °C ($CHCl_3$−$^i Pr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{19}H_{21}N_5O_3S$) C, H, N.

4-(6,7-Dimethoxyquinazolinyl)-*N*-(3-thienyl)-1-piperazinecarboxamide (4q). Quantitative yield by method D. Analytical sample was obtained by recrystallization from toluene; mp 239−241 °C (toluene), ^1H NMR, FABMS, IR, Anal. ($C_{19}H_{21}N_5O_3S$) C, H, N.

Hydrochloride (4u). To a 0 °C suspension of free base **4q** (1.50 g, 3.76 mmol) in EtOAc (50 mL) was added 4 mol/L hydrogen chloride in EtOAc solution (9.40 mL, 37.6 mmol). After the mixture was stirred for 30 min at the same temperature, the resulting precipitate was collected, washed with cold EtOAc, and dried to provide hydrochloride **4u** (1.63 g, 3.74 mmol) in 99% yield. Analytical sample was obtained by recrystallization from water; mp 231−232 °C (H_2O), ^1H NMR, FABMS, IR, Anal. ($C_{19}H_{21}N_5O_3S$ HCl H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3-thienylmethyl)-1-piperazinecarboxamide (4r). 48% by method F; mp 178−179 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{23}N_5O_3S$ 0.25H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(2-pyridyl)-1-piperazinethiocarboxamide (6o). 30% by method I; mp 208−210 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{22}N_6O_2S$ 0.25EtOAc) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3-pyridyl)-1-piperazinethiocarboxamide (6p). 100% by method H; mp 169−171 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{22}N_6O_2S$ 0.25H_2O) C, H, N.

***N*-(6-Chloro-3-pyridyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6q).** 73% by method I; mp 154−156 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{21}ClN_6O_2S$ H_2O 0.25EtOAc) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-pyridyl)-1-piperazinethiocarboxamide (6r). 43% by method I; mp 218−220 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{22}N_6O_2S$ H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(3-picolyl)-1-piperazinethiocarboxamide dihydrochloride (6s). To a 0 °C suspension of free base of **6s** (437 mg, 1.03 mmol) obtained by method H in EtOAc (50 mL) was added 4 mol/L hydrogen chloride in EtOAc solution (2.58 mL, 10.3 mmol). After the mixture was stirred for 15 min at room temperature, the resulting precipitate was collected, washed with EtOAc, and dried to provide hydrochloride **6s** (428 mg, 0.86 mmol) in 83% yield; mp 183−192 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{21}H_{24}N_6O_2S$ 2HCl H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-[2-(3-pyridyl)ethyl]-1-piperazinethiocarboxamide (6t). 97% by method H; mp 124−125 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{26}N_6O_2S$ 0.75H_2O) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-furfuryl-1-piperazinethiocarboxamide (6u). 99% by method H; mp 189−190 °C ($CHCl_3$−$^i Pr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{23}N_5O_3S$ 0.25H_2O) C, H, N.

(*RS*)-4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-tetrahydrofurfuryl-1-piperazinethiocarboxamide (6v). 88% by method H; mp 195−196 °C ($CHCl_3$−$^i Pr_2O$), ^1H NMR, FABMS, IR, Anal. ($C_{20}H_{27}N_5O_3S$ 0.25H_2O) C, H, N.

***N*-Cyclohexylmethyl-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6w).** 73% by method H; mp 170−171 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{22}H_{31}N_5O_2S$) C, H, N.

***N*-Cyano-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboximidic Acid Phenyl Ester (7a).** A mixture of **2** (1.00 g, 3.65 mmol) and commercially available diphenyl cyanocarbonimidate (0.96 g, 4.03 mmol) in 2-propanol (25 mL) solution was refluxed for 12 h. After the reaction mixture was cooled, the resulting precipitate was collected, washed with 2-propanol, and dried to provide **7a** (0.70 g, 1.67 mmol) in 46% yield; mp 204−205 °C (EtOAc), ^1H NMR, FABMS, Anal. ($C_{22}H_{22}N_6O_3$) C, H, N.

***N*-Cyano-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboximidic Thio Acid Methyl Ester (7b).** A mixture of **2** (5.00 g, 18.2 mmol) and commercially available *S*,*S*'-dimethyl-*N*-cyanodithioimide carbonate (3.26 g, purity 90%, 20.1 mmol) in ethanol (30 mL) solution was refluxed for 14.5 h. After the reaction mixture was cooled, the resulting precipitate was collected, washed with ethanol, and dried to provide **7b** (5.69 g, 15.3 mmol) in 84% yield; ^1H NMR, FABMS.

4-[4-(2,2-Dicyano-1-methylthiovinyl)-1-piperazinyl]-6,7-dimethoxyquinazoline (8). A mixture of **2** (5.00 g, 18.2 mmol) and commercially available [bis(methylthio)methylene]-propanedinitrile (3.40 g, 20.0 mmol) in acetonitrile (50 mL) solution was heated at 50 °C for 9 h and then refluxed for 4.5 h. After the reaction mixture was cooled to room temperature, the resulting precipitate was collected, washed with acetonitrile, and dried to provide **8** (6.17 g, 15.6 mmol) in 85% yield; mp 210−211 °C (EtOAc), ^1H NMR, FABMS, IR, Anal. ($C_{19}H_{20}N_6O_2S$) C, H, N.

6,7-Dimethoxy-4-[4-(1-methylthio-2-nitrovinyl)-1-piperazinyl]quinazoline (9). A mixture of 2 (6.00 g, 21.9 mmol) and commercially available 1,1-bis(methylthio)-2-nitroethylene (4.27 g, 25.8 mmol) in ethanol (30 mL) solution was heated at 50 °C for 9 h and then refluxed for 2.5 h. The residue after

the removal of solvent was purified by silica gel column chromatography to provide **9** (2.65 g, 6.78 mmol) in 31% yield; mp 168−172 °C (EtOAc), ^{1}H NMR, FABMS, Anal. ($C_{17}H_{21}N_5O_4S$ H_2O) C, H, N.

***N*-(4-Chlorobenzyl)-*N*′-cyano-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamidine (10a).** A mixture of **7a** (438 mg, 1.05 mmol) and 4-chlorobenzylamine (0.64 mL, 5.26 mmol) in ethanol (10 mL) solution was refluxed for 7.5 h. The residue after the removal of solvent was purified by silica gel column chromatography to provide **10a** (0.39 g, 0.83 mmol) in 79% yield; mp 218−219 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{23}H_{24}ClN_7O_2$) C, H, N.

***N*-Cyano-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboximidic Acid Ethyl Ester** was also obtained (66.7 mg, 0.18 mmol) together with **10a** in 17% yield; ^{1}H NMR, FABMS.

***N*-(3-Chlorobenzyl)-*N*′-cyano-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamidine (10b).** A mixture of **7a** (0.50 g, 1.20 mmol) and 3-chlorobenzylamine (0.44 mL, 3.60 mmol) in 2-propanol (10 mL) solution was refluxed for 6 h. The residue after the removal of solvent was purified by silica gel column chromatography to provide **10b** (0.53 g, 1.14 mmol) in 95% yield; mp 209−211 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{23}H_{24}ClN_7O_2$) C, H, N.

***N*-(2-Chlorobenzyl)-*N*′-cyano-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamidine (10c).** A mixture of **7b** (0.60 g, 1.61 mmol) and 2-chlorobenzylamine (0.97 mL, 8.04 mmol) in ethanol (10 mL) solution was refluxed for 10 h. Followed by further addition of 2-chlorobenzylamine (0.97 mL, 8.04 mmol), the mixture was refluxed for 6.5 h. The residue after the removal of solvent was purified by silica gel column chromatography to provide **10c** (0.73 g, 1.57 mmol) in 98% yield; mp 227−228 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{23}H_{24}ClN_7O_2$ $0.5H_2O$) C, H, N.

***N*′-Cyano-4-(6,7-dimethoxy-4-quinazolinyl)-*N*-(4-methylbenzyl)-1-piperazinecarboxamidine (10d).** From **7a** and 4-methylbenzylamine in 2-propanol reflux in 81% yield; mp 215−216 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{27}N_7O_2$) C, H, N.

***N*′-Cyano-4-(6,7-dimethoxy-4-quinazolinyl)-*N*-(4-isopropylbenzyl)-1-piperazinecarboxamidine (10e).** From **7a** and 4-isopropylbenzylamine in 2-propanol reflux in 69% yield; mp 176−177 °C (^{i}PrOH), ^{1}H NMR, FABMS, IR, Anal. ($C_{26}H_{31}N_7O_2$ 0.5^iPrOH) C, H, N.

***N*′-Cyano-4-(6,7-dimethoxy-4-quinazolinyl)-*N*-(3,4-methylenedioxybenzyl)-1-piperazinecarboxamidine (10f).** From **7b** and piperonylamine in pyridine at 80 °C in 25% yield; mp 217−218 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{25}N_7O_4$) C, H, N.

4-{4-[1-(4-Chlorobenzylamino)-2,2-dicyanovinyl]-1-piperazinyl}-6,7-dimethoxyquinazoline (11). From **7c** and 4-chlorobenzylamine in acetonitrile reflux in 62% yield; mp 242−243 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{25}H_{24}ClN_7O_2$ $0.25H_2O$) C, H, N.

6,7-Dimethoxy-4-{4-[1-(3,4-methylenedioxybenzylamino)-2-nitrovinyl]-1-piperazinyl}quinazoline (12). From **7d** and piperonylamine in pyridine at 80 °C in 8% yield; mp 208−210 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{26}N_6O_6$) C, H, N.

***N*-(4-Chlorobenzoyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (6x).** 15% by method H; mp 166−168 °C ($CHCl_3$-$^iPr_2O$), ^{1}H NMR, FABMS, HRMS−FAB, IR, Anal. ($C_{22}H_{22}ClN_5O_3S$ 0.25^iPr_2O $0.5H_2O$) C, H, N.

***N*-(4-Chlorobenzenesulfonyl)-4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (4s)**. 67% by method A; mp 228−234 °C ($CHCl_3$−MeOH−$^iPr_2O$), ^{1}H NMR, FABMS, HRMS-FAB, IR.

***N*-(4-Bromophenyl)-4-(6,7-dimethoxy-4-quinazolinyl)-*N*-methyl-1-piperazinecarboxamide (4t).** After a mixture of **1c**[24] (1.01 g, 2.15 mmol) and NaH (60% suspension in mineral oil, 171.9 mg, 4.30 mmol) in DMF (15 mL) was stirred for 30 min at room temperature, iodomethane (0.27 mL, 4.34 mmol) was added. The reaction mixture was poured into water; then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography eluting with EtOAc/$CHCl_3$/MeOH 50:10:4 to provide amorphous **4s** (846 mg, 1.74 mmol) in 81% yield; ^{1}H NMR, FABMS, IR.

***N*-Benzyl-4-(6,7-dimethoxy-4-quinazolinyl)-*N*-methyl-1-piperazinethiocarboxamide (6y).** From *N*-methylbenzylamine and **2** by method I in 58% yield; mp 158−159 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{23}H_{27}N_5O_2S$) C, H, N.

(*RS*)-4-(6,7-Dimethoxy-4-quinazolinyl)-2-methyl-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17). (1) A mixture of (*RS*)-2-methylpiperazine (4.46 g, 44.5 mmol) and 4-chloro-6,7-dimethoxyquinazoline (**13**)[25] (2.00 g, 8.91 mmol) in 2-propanol (30 mL) was refluxed for 18 h. The reaction mixture was evaporated, and the residue was dissolved in brine, extracted with dichloromethane, washed with brine, dried over anhydrous sodium sulfate, and evaporated to provide (*RS*)-6,7-dimethoxy-4-(3-methyl-1-piperazinyl)quinazoline (**14**) (1.35 g, 4.69 mmol) in 53% yield. (2) Reaction of **14** (445 mg, 1.55 mmol) and 4-phenoxyphenylisocyanate (0.39 g, 1.85 mmol) in dichloromethane provide **17** (372 mg, 0.75 mmol) in 48% yield; mp 231−232 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{28}H_{29}N_5O_4$ $0.25H_2O$) C, H, N.

(*RS*)-4-(6,7-Dimethoxy-4-quinazolinyl)−(*trans*-2,5-dimethyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (18). (1) Reaction of excess (*RS*)-*trans*-2,5-dimethylpiperazine and **13** in 2-propanol provide (*RS*)-4-(*trans*-2,5-dimethyl-1-piperazinyl)-6,7-dimethoxyquinazoline (**15**) in 95% yield; TOFMS (*m*/*z*): 303 $(M + H)^+$. (2) Reaction of **15** and benzylisothiocyanate provide **18** in 51% yield; mp 182−184 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{29}H_{31}N_5O_4$ $0.25H_2O$) C, H, N.

***N*-Benzyl-4-(6,7-dimethoxy-4-quinazolinyl)−(*cis*-2,6-dimethyl)-1-piperazinethiocarboxamide (19).** (1) Reaction of excess *cis*-2,6-dimethylpiperazine and **13** in 2-propanol provide 4-(*cis*-3,5-dimethyl-1-piperazinyl)-6,7-dimethoxyquinazoline (**16**) in 92% yield; TOFMS (*m*/*z*): 303 $(M + H)^+$. (2) Reaction of **16** and benzylisothiocyanate provide **19** in 90% yield; mp 165−166 °C (EtOAc), ^{1}H NMR, FABMS, IR, Anal. ($C_{24}H_{29}N_5O_2S$) C, H, N.

4-(6,7-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-homopiperazinecarboxamide (21). Reaction of **20**[25] and 4-phenoxyphenylisocyanate provide **21** in 95% yield; mp 93−96 °C ($CHCl_3$-$^iPr_2O$), ^{1}H NMR, FABMS, IR (KBr), Anal. ($C_{28}H_{29}N_5O_4$ $0.5H_2O$) C, H, N.

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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