Potent and Selective Inhibitors of Platelet-Derived Growth Factor Receptor Phosphorylation. 3. Replacement of Quinazoline Moiety and Improvement of Metabolic Polymorphism of 4-[4-(*N*-Substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline Derivatives

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We have previously reported that a series of 4-[4-(*N*-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives were potent and selective inhibitors of platelet-derived growth factor receptor (PDGFR) phosphorylation and demonstrated several biological effects such as suppression of neointima formation following balloon injury in rat carotid artery by oral administration. Here, we investigated structure−activity relationships of the 6,7-dimethoxyquinazolinyl moiety. In regard to 6,7-dimethoxy groups, ethoxy analogues showed potent activity (IC_{50} of **16b** is 0.04 μM; IC_{50} of **17a** is 0.01 μM) and further extension of the alkyl group reduced activity. Interestingly, methoxyethoxy (IC_{50} of **16j** is 0.02 μM; IC_{50} of **17h** is 0.01 μM) and ethoxyethoxy (IC_{50} of **17j** is 0.02 μM) analogues showed the most potent activity, suggesting that the inserted oxygen atom significantly interacts with β-PDGFR. Among tricyclic quinazoline derivatives, the 2-oxoimidazo[4,5-*e*]quinazoline derivative **21a** showed potent activity ($IC_{50} = 0.10$ μM). Regarding replacements of quinazoline by other heterocyclic rings, pyrazolo[3,4-*d*]pyrimidine (**39a**, $IC_{50} = 0.17$ μM) and quinoline (IC_{50} of **40a** is 0.18 μM; IC_{50} of **40b** is 0.09 μM) derivatives showed potent activity. Isoquinoline and some pyridopyrimidine derivatives were completely inactive; therefore, 1-aza has an important role. Also 7-aza and 8-aza substitution on the parent quinazoline ring has a detrimental effect on the interaction with β-PDGFR. We also demonstrated that the substituents on the quinazoline ring possess major consequences for metabolic polymorphism. Although there existed extensive metabolizers and poor metabolizers in Sprague−Dawley rats administrated 6,7-dimethoxyquinazoline derivatives (**1b** and **1c**), 6-(2-methoxy)ethoxy-7-methoxyquinazoline analogue **16k** showed no metabolic polymorphism.

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 PTCA, glomerulonephritis, glomerulosclerosis, liver cirrhosis, pulmonary fibrosis, and cancer.[5−15] Additionally, PDGF and its receptor (PDGFR) are also up-regulated in these proliferative disorders. For example, PDGF plays a major role in the vascular response to injury within restenosis lesions.[16−20] 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 represent a therapeutic benefit for these proliferative disorders.

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In our previous publications, a series of 4-[4-(*N*-substituted (thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives such as KN1022, KN734, and related analogues (**1a**−**d**, Table 1) were found to be selective inhibitors of the PDGFR phosphorylation, initial structure−activity relationships (SARs) focused on the 4-(4-nitrophenylcarbamoyl)piparazinyl moiety and substituents on the quinazolinyl moiety, and several biological effects have been reported.[21−27] Bulky substitution at the 4-position of the phenyl ring was optimal for the urea analogues, especially the 4-isopropyl, 4-*tert*-butyl, or 4-phenoxyphenyl group. Additionally, the benzylthiourea analogues with a small substituent at the 4-position or a 3,4-methylenedioxy group were also found to be optimal. Furthermore, the *N*-(thio)carbamoylpiperazinyl moiety was essential for activity and 6,7-bis substitutions on the quinazoline ring were optimal. These analogues inhibited smooth muscle cell proliferation and migration induced by PDGF-BB and showed several in vivo effects, i.e., suppression of neointima formation following balloon injury in rat carotid artery by oral administration,[21,22,28] reduction of tumor growth of NIH/3T3 cells transformed by PDGF in nude mouse,[29] and improvement of survival due to a delay in disease

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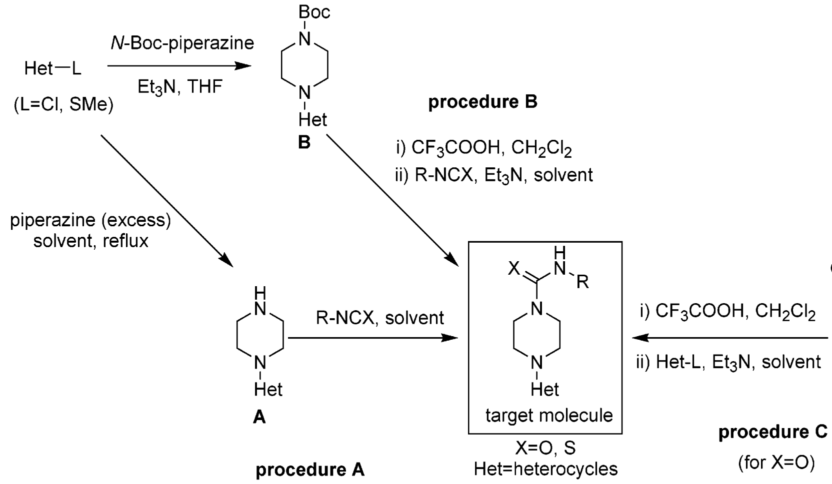
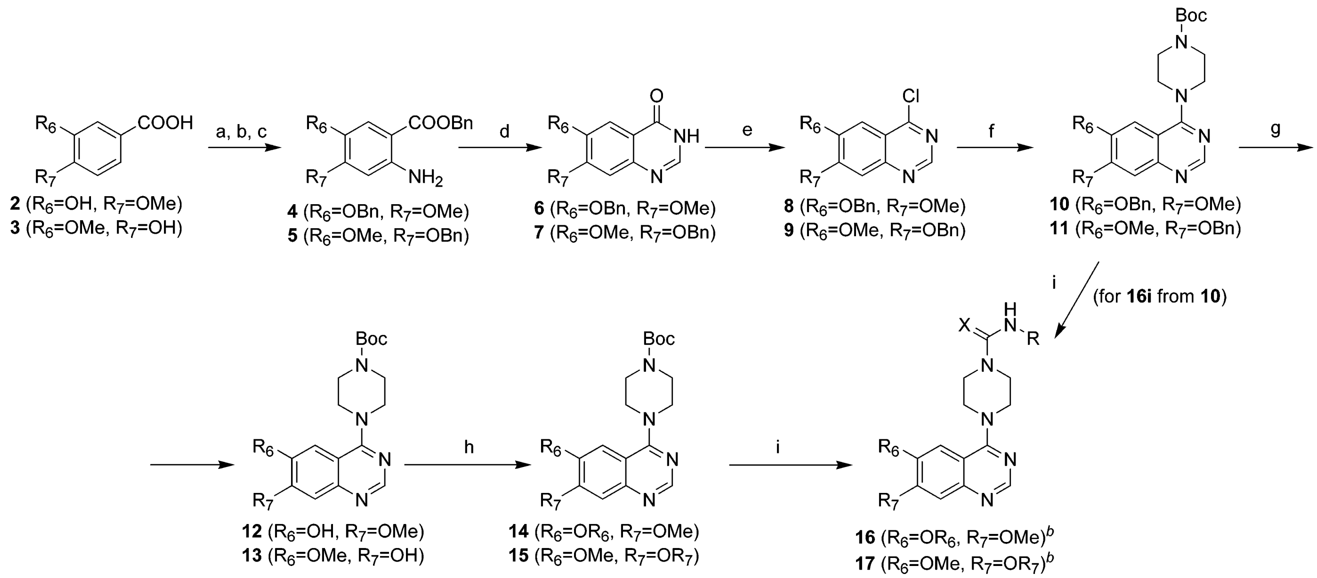
Scheme 1. General Synthetic Procedures



Scheme 2[a]



[a] (a) BnBr, K_2CO_3, DMF; (b) fuming HNO_3, Ac_2O; (c) Zn, AcOH; (d) H_2NCHO, 190 °C; (e) $POCl_3$, reflux; (f) *N*-Boc-piperazine, Et_3N, THF, reflux; (g) H_2, 10% Pd/C, EtOH, H_2O, 40 °C; (h) R_6−Hal or R_7−Hal, K_2CO_3 or NaH or Et_3N or pyridine (KI), DMF or CH_2Cl_2; (i) CF_3COOH, CH_2Cl_2, 0 °C, then R−NCX, Et_3N, CH_2Cl_2. [b] X = O or S.

progression of a mouse model of chronic myelomonocytic leukemia.[30]

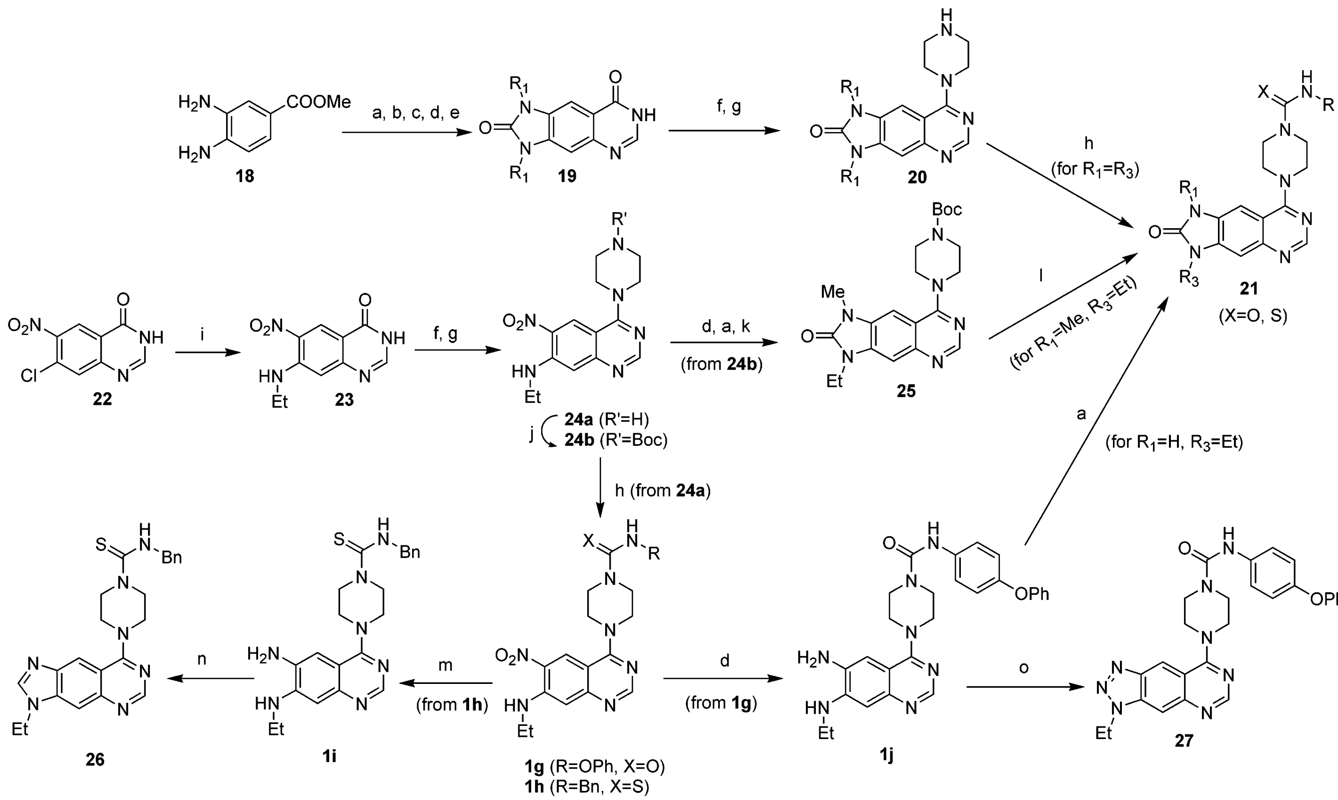
In this paper, we report the synthesis and SARs for inhibition of β-PDGFR phosphorylation by analogues exchanging the 6,7-dimethoxyquinazolinyl moiety. We examine the effect of a series of 6,7-substituents on the quinazoline ring, the effect of further substitution of the 6,7-dimethoxyquinazoline ring, and the possibility of finding a bioisosteric replacement for the quinazoline ring. We also report the metabolic polymorphism of 6,7-dimethoxyquinazoline analogues in Sprague−Dawley rats (SD rats) and the solution by replacing the 6-methoxy group with a 6-(2-methoxyethoxy) group on the quinazoline ring.

Chemistry

To further explore the SAR of KN1022 derivatives, we prepared a series of analogues to examine the effects of the position and nature of substituents on the quinazoline ring and replacements by other heterocyclic ring systems. General synthetic procedures are outlined in Scheme 1. There are three approaches for obtaining target molecules. Condensation of heterocyclic chlorides or methyl sulfide analogues with excess piperazine followed by treatment with iso(thio)cyanates provided the target molecules (procedure A). The target molecules were also obtained from compound **B**, which were synthesized from Het-L and *N*-Boc-piperazine, by deprotection with trifluoroacetic acid and condensation with iso(thio)cyanates (procedure B). Additionally, compound **C**, which was synthesized from *N*-Boc-piperazine and isocyanate, was treated with trifluoroacetic acid followed by condensation with heterocyclic chloride to provide the target molecule (procedure C). The synthetic procedures for all compounds that were evaluated for inhibition of β-PDGFR phosphorylation are described in Tables 1−3.

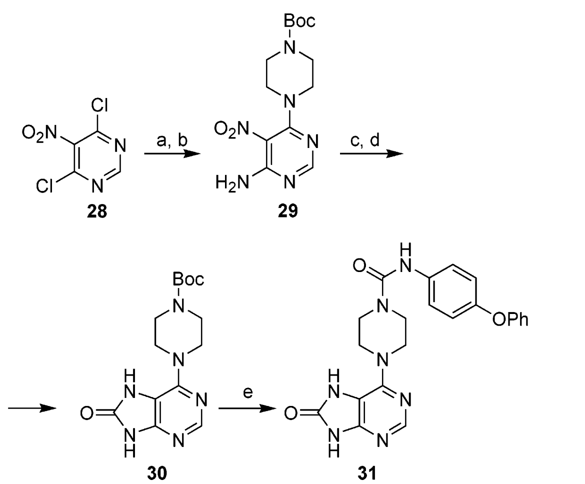
The 6-alkoxy-7-methoxyquinazolines **16** and 6-methoxy-7-alkoxyquinazolines **17** were synthesized from isovanilic acid **2** and vanilic acid **3**, respectively (Scheme 2). Benzylation of **2** and **3**, followed by regiospecific nitration and reduction, yielded anthranilic esters **4** and

Scheme 3[a]



[a] (a) CDI, DMF, 80 °C; (b) fuming HNO_3, Ac_2O; (c) R_1−I, NaH, DMF; (d) H_2, 10% Pd/C, EtOH; (e) H_2NCHO, heat; (f) $POCl_3$, reflux; (g) piperazine (excess), ^{i}PrOH, reflux; (h) R−NCX, solvent; (i) $EtNH_2$, DMSO, 180 °C; (j) Boc_2O, Et_3N, CH_2Cl_2; (k) MeI, NaH, DMF; (l) CF_3COOH, CH_2Cl_2, then R−NCX, solvent, Et_3N; (m) Fe, $FeCl_3$·$6H_2O$, EtOH, H_2O, reflux; (n) $(COCl)_2$, pyridine, DMF, heat; (o) $NaNO_2$, concentrated HCl, AcOH, 0 °C.

Scheme 4[a]

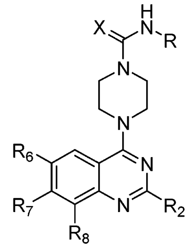


[a] (a) NH_3 (gas), CH_2Cl_2, 0 °C; (b) *N*-Boc-piperazine, Et_3N, DMF, 80 °C; (c) H_2, 10% Pd/C, EtOH; (d) CDI, Et_3N, DMF, 80 °C; (e) CF_3COOH, CH_2Cl_2, 0 °C, then 4-PhOPh-NCO, CH_2Cl_2.

5, respectively. Cyclization by heating in formamide, chlorination, and condensation with *N*-Boc-piperazine afforded the 4-(*N*-Boc-1-piperazinyl)quinazolines (**10** and **11**). Deprotection of the benzyl group by hydrogenation, alkylation, and (thio)urea formation provided the target compounds **16** and **17**, respectively. The 6-OBn-7-OMe analogue **16i** was prepared from **10** by deprotection of the Boc group and condensation with 4-phenoxyphenyl isocyanate. Several analogues were synthesized by modification of the substituents, and the synthetic methods are described in Table 1.

The synthesis of tricyclic quinazolines (**21**, **26**, and **27**) is outlined in Scheme 3. There are three procedures for preparing the 2-oxoimidazo[4,5-*g*]quinazoline analogue **21**. For analogues possessing the same substituents at R_1 and R_3, commercially available **18** was cyclized with *N*,*N′*-carbonyldiimidazole (CDI), followed by regioselective nitration, alkylation at R_1 and R_3, hydrogenation, and cyclization with formamide to afford the imidazo[4,5-*g*]quinazoline-2,8-diones **19**. Chlorination of **19**, followed by condensation with piperazine and treatment with isocyanate, provided the target molecule **21**. The 2-oxoimidazo[4,5-*g*]quinazolines possessing different substituents at R_1 and R_3 were prepared from **22**.[31] Compounds **21b** and **21c** (R_1 = Me, R_3 = Et) were synthesized via 6-NH_2-7-NHEt (**1j**) analogues. Introduction of an ethylamino group for **22**, followed by chlorination[32] and condensation with piperazine, afforded **24a**. Protection of **24a** with Boc group, reduction of nitro group, cyclization by CDI, methylation, deprotection, and treatment with corresponding iso(thio)cyanate provided target molecules. Compound **21g** (R_1 = H, R_3 = Et) was synthesized from 6-NO_2-7-NHEt (**1g**) via 6-NH_2-7-NHEt (**1j**) analogues. Treatment of **24a** with 4-phenoxyphenyl isocyanate, reduction of nitro group, cyclization by CDI yielded the target molecule. 6-NO_2-7-NHEt analogues (**1g**, **1h**) were also key intermediates for preparation of imidazo[4,5-*g*]quinazoline **26** and triazolo[4,5-*g*]quinazoline **27**, respectively. Cyclization of **1i**, which was obtained by reduction of **1h** with Fe dust, was accomplished by treatment with oxalyl chloride in pyridine and *N*,*N′*-dimethylformamide solution under heating

Table 1. Inhibitory Activity on β-PDGFR Phosphorylation by Quinazoline Derivatives



compd	R_2	R_6	R_7	R_8	R	X	procedure	IC_{50} [a] (μM)
KN1022[b]	H	OMe	OMe	H	4-NO_2Ph	O		0.70
1a[b]	H	OMe	OMe	H	4-PhOPh	O		0.08
1b[b]	H	OMe	OMe	H	4-CNPh	O		0.85
1c[b]	H	OMe	OMe	H	4-ClPh	O		1.10
1d[c]	H	OMe	OMe	H	$PhCH_2$	S		0.55
KN734[c]	H	OMe	OMe	H	3,4-(−OCH_2O−)$PhCH_2$	S		0.09
1e	H	H	H	H	4-PhOPh	O		0.38
1f	H	H	H	H	$PhCH_2$	S		>30
1g	H	NO_2	NHEt	H	4-PhOPh	O		0.20
1h	H	NO_2	NHEt	H	$PhCH_2$	S		>30
1i	H	NH_2	NHEt	H	$PhCH_2$	S		1.44
16a	H	OH	OMe	H	4-CNPh	O	hydrogenation of **16i**	4.59
16b	H	OEt	OMe	H	4-PhOPh	O	procedure B	0.04
16c	H	OEt	OMe	H	$PhCH_2$	S	procedure B	0.62
16d	H	OPr	OMe	H	4-PhOPh	O	procedure B	0.19
16e	H	$OCH_2CH{=}CH_2$	OMe	H	4-PhOPh	O	procedure B	0.10
16f	H	$OCH_2C{\equiv}CH$	OMe	H	4-PhOPh	O	procedure B	0.06
16g	H	OCH_2CN	OMe	H	4-PhOPh	O	procedure B	0.09
16h	H	OBu	OMe	H	4-PhOPh	O	procedure B	1.39
16i	H	OCH_2Ph	OMe	H	4-CNPh	O	procedure B	>30
16j	H	$O(CH_2)_2OMe$	OMe	H	4-PhOPh	O	procedure B	0.02
16k	H	$O(CH_2)_2OMe$	OMe	H	4-CNPh	O	procedure B	0.51
16l	H	$O(CH_2)_2OMe$	OMe	H	3,4-(−OCH_2O−)$PhCH_2$	S	procedure B	0.08
16m	H	OCH_2COCH_3	OMe	H	4-PhOPh	O	procedure B	0.30
16n	H	OCH_2COOMe	OMe	H	4-CNPh	O	procedure B	6.08
16o	H	OCH_2COOH	OMe	H	4-CNPh	O	hydrolysis of **16n**	>30
16p	H	OSO_2Me	OMe	H	4-PhOPh	O	procedure B	0.07
16q	H	OSO_2Me	OMe	H	$PhCH_2$	S	procedure B	10.2
17a	H	OMe	OEt	H	4-PhOPh	O	procedure B	0.01
17b	H	OMe	OEt	H	$PhCH_2$	S	procedure B	0.15
17c	H	OMe	OPr	H	4-PhOPh	O	procedure B	0.29
17d	H	OMe	O^iPr	H	4-PhOPh	O	procedure B	0.64
17e	H	OMe	$OCH_2CH{=}CH_2$	H	4-PhOPh	O	procedure B	0.05
17f	H	OMe	$OCH_2C{\equiv}CH$	H	4-PhOPh	O	procedure B	0.07
17g	H	OMe	OBu	H	4-PhOPh	O	procedure B	0.65
17h	H	OMe	$O(CH_2)_2OMe$	H	4-PhOPh	O	procedure B	0.01
17i	H	OMe	$O(CH_2)_2OMe$	H	3,4-(−OCH_2O−)$PhCH_2$	S	procedure B	0.08
17j	H	OMe	$O(CH_2)_2OEt$	H	4-PhOPh	O	procedure B	0.02
17k	H	OMe	Me	H	4-PhOPh	O	procedure A	0.18
17l	H	OMe	Me	H	$PhCH_2$	S	procedure A	1.54
32a	H	OEt	OEt	H	4-PhOPh	O	procedure A	0.08
32b	H	OEt	OEt	H	$PhCH_2$	S	procedure A	0.31
32c	H	OCH_2Ph	OCH_2Ph	H	4-PhOPh	O	procedure A	>30
33a	H	OMe	H	OMe	4-PhOPh	O	procedure A	10.9
33b	H	H	OMe	OMe	4-PhOPh	O	procedure A	>30
34a	H	OMe	OMe	OMe	4-PhOPh	O	procedure A	>30
34b	Me	OMe	OMe	H	4-PhOPh	O	procedure A	>30
34c	Cl	OMe	OMe	H	4-PhOPh	O	procedure B	>30
34d	morphorino	OMe	OMe	H	4-PhOPh	O	procedure B	>30

[a] IC_{50} (μM) of β-PDGFR phosphorylation. Autophosphorylation was measured in intact cells using a two-site enzyme linked immunosorbent assay (ELISA).[28] [b] Previously described in ref 21. [c] Previously described in ref 22.

conditions accompanied by decarboxylation to afford imidazo[4,5-*g*]quinazoline **26**. This method is a new one to synthesize benzimidazole-type compounds. Hydrogenation of **1g** followed by treatment with sodium nitrite under acidic conditions resulted in spontaneous cyclization to afford triazolo[4,5-*g*]quinazoline **27**.

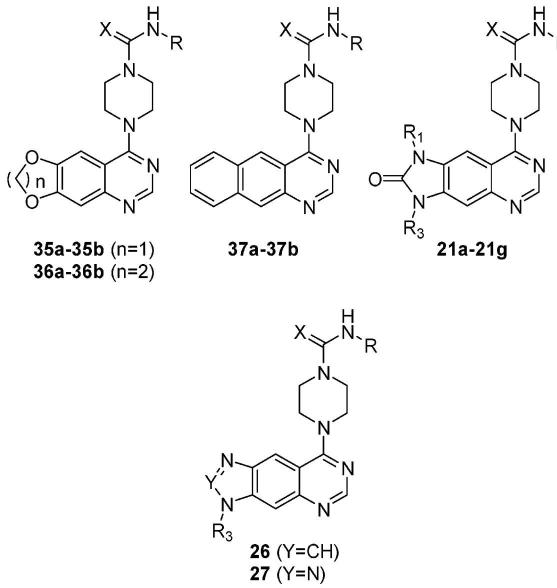
2-Oxoimidazo[4,5-*d*]pyrimidine **31** was synthesized from commercially available **28** (Scheme 4). Introduction of an amino group and *N*-Boc piperazine, followed by hydrogenation and cyclization with CDI, afforded **30**. Application of procedure B for **30** provided the target molecule **31**.

Results and Discussions

SAR for Inhibition of β-PDGFR Phosphorylation. All the analogues prepared were evaluated for their inhibition of β-PDGFR phosphorylation in accordance with known whole-cell assay,[28] and the resulting IC_{50} values are listed in Tables 1−3.

Substituents on Quinazoline Ring. Table 1 shows the results of exchanging substituents on the quinazo-

Table 2. Inhibitory Activity on β-PDGFR Phosphorylation by Tricyclic Quinazoline Derivatives



35a-35b (n=1) **36a-36b** (n=2) **37a-37b** **21a-21g** **26** (Y=CH) **27** (Y=N)

compd	R_1	R_3	R	X	procedure	IC_{50} [a] (μM)
6,7-Alkylenedioxyquinazolines						
35a			4-PhOPh	O	procedure A	0.09
35b			$PhCH_2$	S	procedure A	>30
36a			4-PhOPh	O	procedure B	0.07
36b			$PhCH_2$	S	procedure B	>30
Benzo[*g*]quinazolines						
37a			4-PhOPh	O	procedure B	0.39
37b			$PhCH_2$	S	procedure B	1.30
1,3-Dihydro-2-oxo-2*H*-imidazo[4,5-*g*]quinazolines						
21a	Me	Me	4-PhOPh	O	procedure A[b]	0.10
21b	Me	Et	4-PhOPh	O	procedure B[b]	0.33
21c	Me	Et	$PhCH_2$	S	procedure B[b]	1.14
21d	Et	Et	4-PhOPh	O	procedure A[b]	0.78
21e	Pr	Pr	4-PhOPh	O	procedure A[b]	21.0
21f	Bu	Bu	4-PhOPh	O	procedure A[b]	>30
21g	H	Et	4-PhOPh	O	Scheme 3	>30
3*H*-Imidazo[4,5-*g*]quinazoline						
26		Et	$PhCH_2$	S	Scheme 3	2.70
3*H*-1,2,3-Triazolo[4,5-*g*]quinazoline						
27		Et	4-PhOPh	O	Scheme 3	0.29

[a] IC_{50} (μM) of β-PDGFR phosphorylation. Autophosphorylation was measured in intact cells using a two-site ELISA.[28] [b] Described in Scheme 3.

line ring. In the unsubstituted quinazolines, 4-phenoxyphenylurea analogue **1e** showed moderate activity, whereas the benzylthiourea analogue **1f** was devoid of any activity ($\geq$100-fold), even though the difference of activity for the corresponding 6,7-dimethoxy analogues (**1a** and **1d**) was approximately 10-fold.[23] This discrepancy of activity indicates a distinct SAR and is unsuitable for finding an optimal replacement for the 6,7-dimethoxyquinazolinyl moiety; therefore, we investigated the effect of a combination of substituents on the quinazoline ring and an *N*-substituted (thio)carbamoyl moiety for several potent analogues.

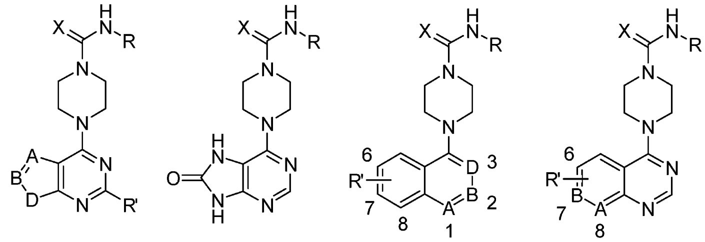
In the 6-exchanged 7-OMe derivatives (**16a**−**q**), 6-OEt analogues (**16b**, **16c**) were equipotent to the initial 6,7-$(OMe)_2$ analogues (**1a**, **1d**) without the discrepancy of activity between 4-phenoxyphenylurea and benzylthiourea. The 6-OPr analogue (**16d**) was slightly less potent, and 6-$OCH_2CH{=}CH_2$ (**16e**) and 6-$OCH_2C{\equiv}CH$ (**16f**) analogues were equipotent to 6-OEt (**16b**) and 6,7-$(OMe)_2$ (**1a**) analogues, suggesting that unsaturation of the alkyl group seems to have a beneficial effect. This effect was clearly observed for 7-(OMe)-exchanged derivatives (discussed below). Since the 6-OCH_2CN analogue (**16g**) also showed a potency similar to that for the 6-$OCH_2C{\equiv}CH$ analogue (**16f**), replacement of the terminal CH with a nitrogen atom on the alkynyl moiety of the propargyl group was acceptable. Further extension to 6-OBu (**16h**) and 6-OCH_2Ph (**16i**) and deletion of the methyl group (**16a**) decreased activity, thus showing that some bulkiness is required but there is also limited bulk tolerance for the alkyl group at this position. However, 6-$O(CH_2)_2OMe$ analogues (**16j**−**l**) revealed the most potent activity among the **16** series, which were more potent than 6-OBu (**16h**) and even the initial 6,7-$(OMe)_2$ analogues (**1a**, **1b**, KN734). Additionally, 6-OCH_2COMe analogue **16m** showed somewhat moderate activity and 6-OCH_2COOMe analogue **16n** was a weak inhibitor compared with 6-$O(CH_2)_2OMe$ analogue **16k**. 6-OCH_2COOH analogue **16o** was completely inactive. These results suggest that insertion of an oxygen atom (not oxo group) into the alkyl chain markedly enhances the activity, and this oxygen atom was speculated to have a significant interaction with β-PDGFR. For the 6-OSO_2Me analogues, 4-phenoxyphenylurea analogue **16p** showed potent activity; however, a distinct SAR for benzylthiourea (**16q**) was observed.

In the 6-OMe-7-exchanged derivatives (**17a**−**l**), similar SARs of 6-exchanged derivatives (**16** series) were observed. The 7-OEt analogues (**17a**, **17b**) were potent inhibitors without discrepancy of activity, and further extension of the alkyl chain reduced activity (**17c**, **17g**). Also, 7-O^iPr analogue **17d** was less potent than 7-OPr analogue **17c**, indicating that bulkiness is unfavorable for the interaction with β-PDGFR. Unsaturation of the alkyl group (**17e**, **17f**) clearly enhanced the activity, compared with **17c** as discussed above. The 7-$O(CH_2)_2$-OMe analogues (**17h**, **17i**) also displayed the most potent activity, similar to the 6-exchanged analogues (**16j**, **16l**), and extension to the 7-$O(CH_2)_2OEt$ group (**17j**) was tolerated, suggesting that there is a significant bulk tolerance available for such substituents in the region of the 6- and 7-position on the quinazoline ring for further design.[33] The 6-OMe-7-Me analogues (**17k**, **17l**) were slightly less potent without the discrepancy of activity than the initial 6,7-$(OMe)_2$ analogue (**1a**, **1d**), suggesting that 7-methylation to 6-methoxyquinazoline[23] is advantageous but less effective than a methoxy group.

Additionally, the 6,7-$(OEt)_2$ analogues (**32a**, **32b**) had potency similar to that of the 6,7-$(OMe)_2$ analogues (**1a**, **1d**); however, bulky 6,7-$(OBn)_2$ analogue **32c** was inactive. Also, the marked decrease in activity was observed with the 6,8-$(OMe)_2$ (**33a**) and 7,8-$(OMe)_2$ (**33b**) analogues, compared with the initial 6,7-$(OMe)_2$ analogues (**1a**). Further addition of a substituent on 6,7-dimethoxyquinazoline resulted in no activity. Placing an additional 8-OMe (**34a**), and 2-substitution by Me (**34b**), Cl (**34c**), and morpholine (**34d**), onto 6,7-dimethoxyquinazoline also completely eliminated activity. These results reveal that the 6,7-dialkoxy subtitution on the quinazoline ring is optimal for potent activity.

Tricyclic Quinazoline Derivatives. The results of tricyclic quinazoline derivatives, which are combined with 6,7-dimethoxy groups on the quinazoline ring, are described in Table 2. Among these derivatives,

Table 3. Inhibitory Activity on β-PDGFR Phosphorylation by Other Heterocyclic Derivatives



38a-38d
39a-39b

31

40a-40l
41a-41b
42
43a-43c

44
45

compd	A	B	D	R′	R	X	procedure	IC_{50} [a] (μM)
Purines								
38a	N	CH	NH	H	4-PhOPh	O	procedure C	0.49
38b	N	CH	NH	H	$PhCH_2$	S	procedure B	>30
38c	N	CH	NH	NH_2	4-PhOPh	O	procedure B	1.50
38d	N	CH	NMe	H	4-PhOPh	O	procedure B	>30
Pyrazolo[3,4-*d*]pyrimidines								
39a	CH	N	NH	H	4-PhOPh	O	procedure B	0.17
39b	CH	N	NMe	H	4-PhOPh	O	procedure A	>30
1,3-Dihydro-2-oxo-2*H*-imidazo[4,5-*d*]pyrimidine								
31					4-PhOPh	O	procedure B[b]	>10
Quinolines								
40a	N	CH	CH	6,7-$(OMe)_2$	4-PhOPh	O	procedure B	0.18
40b	N	CH	C−COOEt	6,7-$(OMe)_2$	4-PhOPh	O	procedure B	0.09
40c	N	CH	C−COOEt	6,7-$(OMe)_2$	$PhCH_2$	S	procedure B	3.26
40d	N	CH	CH	6-Cl	4-PhOPh	O	procedure A	0.13
40e	N	CH	CH	6-Cl	$PhCH_2$	S	procedure A	>30
40f	N	CH	CH	7-Cl	4-PhOPh	O	procedure A	0.10
40g	N	CH	CH	7-Cl	$PhCH_2$	S	procedure A	>30
40h	N	CH	CH	8-Cl	4-PhOPh	O	procedure A	>10
40i	N	C−CF_3	CH		4-PhOPh	O	procedure A	>30
40j	N	CH	CH	7-CF_3	4-PhOPh	O	procedure A	0.55
40k	N	CH	CH		4-PhOPh	O	procedure A	0.27
40l	N	CH	CH		$PhCH_2$	S	procedure A	>30
Isoquinolines								
41a	CH	N	CH	6,7-$(OMe)_2$	4-PhOPh	O	procedure B	>30
41b	CH	N	CH		4-PhOPh	O	procedure B	>30
Cinnoline								
42	N	N	CH	6,7-$(OMe)_2$	4-PhOPh	O	procedure A	0.81
Phthalazines								
43a	CH	N	N		4-PhOPh	O	procedure B	10.3
43b	C−Cl	N	N		4-PhOPh	O	procedure B	>30
43c	C−CH_2Ph	N	N		4-PhOPh	O	procedure A	>30
Pyrido[3,4-*d*]pyrimidine								
44	CH	N		6-F	4-PhOPh	O	procedure B	13.3
Pyrido[2,3-*d*]pyrimidine								
45	N	CH			4-PhOPh	O	procedure B	>30

[a] IC_{50} (μM) of β-PDGFR phosphorylation. Autophosphorylation was measured in intact cells using a two-site ELISA.[28] [b] Described in Scheme 4.

2-oxoimidazo[4,5-*g*]quinazoline analogue **21a** showed potent activity, and extension of alkyl chains at the 1 and 3 positions reduced activity (compare **21a,b,d−f**). The discrepancy of activity between 4-phenoxyphenylurea (**21b**) and benzyl thiourea (**21c**) was not observed. Additionally, **21g** was devoid of activity, indicating that a hydrogen atom on the imidazoline ring has an enormous detrimental effect on activity.

For 6,7-alkylenedioxyquinazoline derivatives, the 4-phenoxyphenylureas (**35a**, **36a**) were equipotent to the corresponding 6,7-$(OMe)_2$ analogue (**1a**); however, a distinct SAR for the benzylthiourea analogues (**35b**, **36b**) was observed. Benzo[*g*]quinazolines (**37a**, **37b**), imidazo[4,5-*g*]quinazoline (**26**), and triazolo[4,5-*g*]quinazoline (**27**) showed only moderate activity. These were weaker than the corresponding initial 6,7-$(OMe)_2$ analogues (**1a**, **1d**).

Exchange of Quinazoline Ring. Finally, the results of exchanging the quinazoline ring with other heterocycles are listed in Table 3. In the purine series, the 4-phenoxyphenylurea **38a** displayed moderate activity with a distinct SAR for benzylthiourea (**38b**). 2-Amination (**38c**) reduced activity. Furthermore, 9-methylation (**38d**) completely abolished activity; therefore, the hydrogen atom at the 9-position was critical for activity. Pyrazolo[3,4-*d*]pyrimidine derivatives showed similar SAR for the purine derivatives, so **39a** showed potent activity and 1-methylation (**39b**) completely abolished activity. 2-Oxoimidazo[4,5-*d*]pyrimidine **31** was also completely inactive, indicating that carbonylation at the 2-position is disadvantageous for interacting with β-PDGFR.

For 6,6-bicyclic heterocycles, 6,7-dimethoxyquinoline **40a** showed potent activity, like the corresponding quinazoline derivatives **1a**. Introduction of a 3-COOEt group (**40b**) retained the potent activity without the discrepancy of activity for benzylthiourea **40c**, suggesting that further modifications at the 3-position could be possible. The 4-phenoxyphenylureas with 6-Cl (**40d**) and 7-Cl (**40f**) and unsubstituted (**40k**) quinoline showed potent activity; however, the distinct SARs for benzylthioureas (**40e**, **40g**, **40l**) were observed. Additionally, 2-substitution (comparing **40i** with **40j** and **40k**) and 8-substitution (comparing **40h** with **40d**, **40f**, and **40k**) resulted in no activity, like the quinazoline derivatives. These results suggest that 6,7-bis substitution is optimal for the quinoline ring and possibly 3-substitution is tolerated for potent activity, and also, bioisosteric replacement of quinazoline by quinoline ring is possible. In contrast, isoquinolines (**41a** and **41b**) were completely inactive. Replacement by a cinnoline nucleus (**42**) was tolerated but led to a 10-fold reduction in potency. Phthalazine derivative **43a** showed weak activity, and the modifications at the 1-position (**43b** and **43c**) had no beneficial effect on activity. These results suggest that the arrangement of the nitrogen atom is crucial, indicating an essential role for the nitrogen atom at the 1-position and a subtly important role for the nitrogen atom at the 3-position on quinazoline ring. It is speculated that these nitrogen atoms might act as hydrogen bond acceptors for interacting with β-PDGFR.

Furthermore, pyrido[2,3-*d*]pyrimidine (**44**) was completely inactive and pyrido[3,4-*d*]pyrimidine (**45**) was appreciably weaker than the corresponding 6-fluoroquinazoline.[23] These results indicate that nitrogen atoms at the 7- and 8-position on the parent quinazoline ring have enormous detrimental effects on the interaction with β-PDGFR.

The 4-anilino-6,7-dimethoxyquinazolines are well-known as potent EGF receptor (EGFR) tyrosine kinase inhibitors reported by several groups.[34−40] The observed SARs for quinazolinyl moiety with β-PDGFR and EGFR are almost similar, both receptors preferring 6,7-dimethoxy and 6,7-diethoxy substitution and disfavoring 2-substitution and 8-substitution on the quinazoline ring. Additionally, phthalazine and isoquinoline were not preferable for both receptors. On the other hand, quinolines were potent β-PDGFR inhibitors but were weak EGFR inhibitors. Also, benzo[*g*]quinazolines were potent EGFR inhibitors but modest β-PDGFR inhibitors. Previously, we reported that the position of substituent on the phenyl ring also had great influence on the activity for each inhibitor whose basic skeleton contains the same 6,7-dimethoxyquinazoline ring system.[21,22] Although we evaluated the inhibitory activity for β-PDGFR phosphorylation using whole-cell assay, in contrast to assay using naked EGFR, these results will reveal some clues to understanding the dimensional differences of each interaction between β-PDGFR and EGFR with inhibitors.

Metabolic Polymorphism and the Solution by Exchanging the Methoxy Group on the Quinazoline Ring. We have already observed the pharmacokinetic polymorphism for 6,7-dimethoxyquinazoline derivatives such as KN1022, **1b**, and **1c**. For instance, with plasma concentration−time profiles and pharmacokinetic parameters of **1b** after intravenous and oral administration to male SD rats delineated in Figures 1 and 2 and Tables 4 and 5, the extensive metabolizers (EMs) and poor metabolizers (PMs) were identified in both administration pathways. In intravenous administration (Figure 1 and Table 4), rat nos. 1−3 were EMs and rat no. 4 was PM with almost a 10-fold difference for $T_{1/2\beta}$, MRT, AUC, and CL and with a similarity for V_{dss}. In oral administration (Figure 2 and Table 5), rat no. 6 was EM and rat nos. 5 and 7 were PMs, with almost a 10-fold higher value of C_{max} and with more than a 10-fold higher value of AUC for PMs.

These observations might be due to the metabolic polymorphism,[41] and we assumed that this metabolic polymorphism was attributed to the major metabolic enzyme for the 6,7-dimethoxyquinazolines because the corresponding desmethyl form was identified as the major metabolite for EMs (data not shown). Therefore,

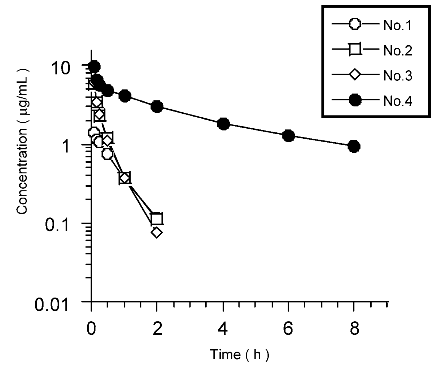


Figure 1. Plasma concentrations of **1b** after intravenous administration to male SD rats (1 mg/kg).

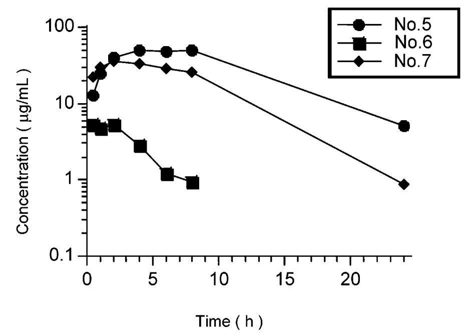


Figure 2. Plasma concentrations of **1b** after oral administration to male SD rats (30 mg/kg).

Table 4. Pharmacokinetic Parameters after Intravenous Administration of **1b** to Male SD Rats (1 mg/kg)

rat no.	$T_{1/2\beta}$ (h)	MRT (h)	AUC (μg·h/mL)	CL (L/(h·kg))	V_{dss} (L/kg)
Extensive Metabolizer					
1	0.97	0.650	2.87	0.349	0.22
2	0.45	0.390	2.48	0.404	0.16
3	0.39	0.350	2.42	0.413	0.15
Poor Metabolizer					
4	3.1	4.20	23.6	0.0424	0.18

Table 5. Pharmacokinetic Parameters after Oral Administration of **1b** to Male SD Rats (30 mg/kg)

rat no.	T_{max} (h)	$T_{1/2}$ (h)	MRT (h)	C_{max} (μg/mL)	AUC (μg·h/mL)
Extensive Metabolizer					
6	2	2.54	3.92	5.22	26.3
Poor Metabolizer					
5	8	5.25	8.56	50.7	815
7	2	3.4	6.36	35.2	455

Table 6. Pharmacokinetic Parameters after Intravenous Administration of **16k** to EM and PM of Male SD Rats (1 mg/kg)[a]

rat no.	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	AUC (μg·h/mL)	CL (L/(h·kg))	V_{dss} (L/kg)
8 (EM)	0.0449	0.230	1.16	0.866	0.215
9 (EM)	0.0498	0.261	1.26	0.791	0.252
10 (PM)	0.0316	0.259	1.28	0.784	0.232
11 (PM)	0.0597	0.219	0.950	1.05	0.286

[a] EM: extensive metabolizer. PM: poor metabolizer.

the 6,7-dimethoxy moiety exchanged analogues prompted us to evaluate the pharmacokinetic profiles and we selected a potent 6-O$(CH_2)_2$OMe-7-OMe analogue **16k** for evaluation. We divided SD rats into EMs and PMs, predosing them with 4-chlorophenyl analogue **1c**. After washout of **1c** for each rat, **16k** was intravenously administrated to each group. The results are displayed in Table 6. There were no differences between EMs and PMs for $T_{1/2}$, AUC, CL, and V_{dss}. These results indicate that the 6-methoxy group might cause the metabolic polymorphism and that exchange of 6,7-dimethoxy groups could prevent the metabolic polymorphism for 6,7-dimethoxyquinazoline derivatives.

Conclusions

The SARs in the 6,7-dimethoxyquinazoline moiety were investigated. Regarding the position and variety of substituents on the quinazoline ring, 6,7-dialkoxy substitution was optimal. Among the alkoxy groups, ethoxy analogues showed potent activity and further extension of the alkyl group reduced activity. Interestingly, 2-methoxyethoxy and 2-ethoxyethoxy analogues displayed the most potent activity. These results indicate that the inserted oxygen atom significantly interacts with β-PDGFR. Among tricyclic quinazoline derivatives, 2-oxoimidazo[4,5-*g*]quinazoline derivatives showed potent activity. Regarding exchanges of quinazoline by other heterocyclic rings, pyrazolo[3,4-*d*]pyrimidine and quinoline derivatives showed potent activity. Isoquinoline and some pyridopyrimidine derivatives were completely inactive; therefore, the N-1 atom has an important role and replacement by N-7 and N-8 atoms in the parent quinazoline ring has detrimental effects on the interaction with β-PDGFR. Several compounds such as unsubstituted quinazolines and quinolines, 6,7-alkylenedioxyquinazolines, and purines showed the distinct SARs between the 4-phenoxyphenylureas and the benzylthioureas with more than a 100-fold difference, in contrast to 6,7-dimethoxyquinazoline derivatives with an almost 10-fold difference.

We also demonstrated that the substituents on the quinazoline ring possess major consequences for metabolic polymorphism. Although there exist extensive metabolizers and poor metabolizers in SD rats administered the 6,7-dimethoxyquinazoline derivatives, 6-(2-methoxy)ethoxy-7-methoxyquinazoline analogue **16k** showed no metabolic polymorphism. These results reveal that replacement of a metabolizable moiety is a significant choice for the prevention of metabolic polymorphism.

Experimental Section

Melting points were determined on a Büchi 535 melting point apparatus or a Yanaco model MP apparatus (Micro Melting Point Apparatus) for 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 a JEOL JNM-EX270 (270 MHz) FT NMR spectrometer or a JEOL JNM-GX270 (270 MHz) FT NMR 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 a JEOL JMS-DX303 mass spectrometer. Low-resolution EI mass spectra were recorded with a JEOL GC-Mate mass spectrometer. The IR spectra were recorded with a JASCO IR-810 IR spectrometer or a HORIBA FT-200 IR spectrometer. Combustion analyses (CHN) were performed with a Perkin-Elmer series II CHNS/O 2400 analyzer, and the results agreed with theoretical values to within ±0.4%.

The typical synthetic methods are described as follows.

General Synthetic Procedure. Reaction for Target Molecules via Compound A (Procedure A). (1) Commercially available 4-hydroxyquinazoline (1.00 g, 6.85 mmol) was chlorinated with phosphorus oxychloride (20 mL) by a known procedure.[42] (2) A mixture of 4-chloroquinazoline and anhydrous piperazine (5.89 g, 68.4 mmol) in 2-propanol (20 mL) was refluxed for 4 h. The reaction mixture was evaporated, and the resulting residue was dissolved in brine, extracted with chloroform, washed with brine, dried over anhydrous sodium sulfate, and evaporated to provide 4-(1-piperazinyl)quinazoline (0.82 g, 3.83 mmol) in 56% yield from 4-hydroxyquinazoline. (3) Condensation of 4-(1-piperazinyl)quinazoline with 4-phenoxyphenyl isocyanate[21,22] provided **1e** in 42% yield. The thioureas were obtained from the corresponding isothiocyanate instead of 4-phenoxyphenyl isocyanate.

Reaction for Target Molecules via Compound B (Procedure B). (1) A mixture of commercially available 2,4-dichloro-6,7-dimethoxyquinazoline (4.62 g, 17.8 mmol) and *N*-*tert*-butoxycarbonylpiperazine (3.65 g, 19.6 mmol) in triethylamine (12.4 mL, 89.1 mmol) and THF (50 mL) was stirred overnight at room temperature. The reaction mixture was evaporated, and then water and NaCl were added. The resulting precipitate was collected, washed with water, and dried to provide 4-(2-chloro-6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (7.15 g, 17.5 mmol) in 98% yield. (2) To an ice-cooled solution of 4-(2-chloro-6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (2.40 g, 5.88 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 1.5 h at the same temperature, evaporated, and azeotroped with toluene. After the residue was dissolved in DMF (30 mL) and triethylamine (4.09 mL, 29.3 mmol), 4-phenoxyphenyl isocyanate (1.24 mL, 5.88 mmol) was added. The reaction mixture was stirred overnight under argon atmosphere at room temperature and poured into water, and then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography to provide **34c** (2.23 g, 4.29 mmol) in 73% yield. The thioureas were obtained by using the corresponding isothiocyanate instead of 4-phenoxyphenyl isocyanate.

Reaction for Target Molecules via Compound C (Procedure C). (1) To a methylene chloride solution (25 mL), *N*-*tert*-butoxycarbonylpiperazine (2.50 g, 13.4 mmol) and 4-phenoxyphenyl isocyanate (2.83 mL, 13.4 mmol) were added. The reaction mixture was stirred overnight at room temperature, followed by addition of methanol, evaporation, and purification by silica gel column chromatography to provide 4-[*N*-(4-phenoxyphenyl)carbamoyl]-1-piperazinecarboxylic acid *tert*-butyl ester (4.25 g, 10.7 mmol) in 80% yield. (2) To an ice-cooled solution of 4-[*N*-(4-phenoxyphenyl)carbamoyl]-1-piperazinecarboxylic acid *tert*-butyl ester (4.57 g, 11.51 mmol) in methylene chloride (50 mL) was added trifluoroacetic acid (60 mL). The mixture was stirred for 2.5 h at the same temperature and evaporated, and the residue was dissolved in dimethylformamide (24 mL) and triethylamine (8 mL). 6-Chloropurine (2.58 g, 16.69 mmol) was added. The reaction mixture was stirred overnight under argon atmosphere at room temperature and poured into water, and then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography to provide **38a** (3.41 g, 8.22 mmol) in 71% yield.

***N*-(4-Phenoxyphenyl)-4-(4-quinazolinyl)-1-piperazinecarboxamide (1e).** 42% yield from 4-(1-piperazinyl)quinazoline and 4-phenoxyphenyl isocyanate as described in general synthetic procedure A; mp 74−75 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{25}H_{23}N_5O_2$·$0.5H_2O$) C, H, N.

***N*-Benzyl-4-(4-quinazolinyl)-1-piperazinethiocarboxamide (1f).** 52% yield from 4-(1-piperazinyl)quinazoline and benzyl isothiocyanate by procedure A; mp 68−70 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS. Anal. ($C_{20}H_{21}N_5S$·$0.25H_2O$) C, H, N.

4-(7-Ethylamino-6-nitro-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (1g). 67% yield from 7-(ethylamino)-6-nitro-4-(1-piperazinyl)quinazoline (**24a**, ^{1}H NMR, EIMS, IR), which was synthesized from 7-(ethylamino)-6-nitroquinazoline-4(3*H*)-one (**23**)[32] in 94% yield and 4-phenoxyphenyl isocyanate by procedure A; mp 242−244 °C (EtOAc−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{27}N_7O_4$) C, H, N.

***N*-Benzyl-4-(7-(ethylamino)-6-nitro-4-quinazolinyl)-1-piperazinethiocarboxamide (1h).** 77% yield from **24a** and benzyl isothiocyanate by procedure A; mp 135−136 °C (EtOAc−$CHCl_3$−MeOH); ^{1}H NMR, FABMS, IR. Anal. ($C_{22}H_{25}N_7O_2S$·$0.5H_2O$) C, H, N.

4-(6-Amino-7-(ethylamino)-4-quinazolinyl)-*N*-benzyl-1-piperazinethiocarboxamide (1i). A mixture of **1h** (4.26 g, 9.44 mmol), iron dust (4.26 g, 76.3 mmol), and $FeCl_3$ $6H_2O$ (430 mg, 1.59 mmol) in ethanol (100 mL) and water (10 mL) was refluxed for 4 h under an argon atmosphere. Removal of iron dust by filtration followed by evaporation and purification by silica gel column chromatography provided the amorphous title compound in 92% yield: ^{1}H NMR, FABMS, IR.

***N*-(4-Cyanophenyl)-4-(6-hydroxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxamide (16a).** A suspension of **16i** (0.40 g, 0.81 mmol) and 10% Pd/C (0.10 g, containing 50% water) in ethanol (30 mL) and water (1 mL) was hydrogenated for 4 h under a stream of hydrogen at 50 °C. Addition of chloroform, filtration through Celite, and evaporation provided the title compound (0.28 g, 0.69 mmol) in 86% yield: mp 199−202 °C ($CHCl_3$); ^{1}H NMR, FABMS, IR. Anal. ($C_{21}H_{20}N_6O_3$·$1.5H_2O$) C, H, N.

4-(6-Ethoxy-7-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16b). (1) To an ice-cooled solution of isovanillic acid (**2**) (4.3 g, 25.6 mmol) in DMF (50 mL) was slowly added potassium carbonate (10.6 g, 76.7 mmol) and then benzyl bromide (6.01 mL, 50.5 mmol). The reaction mixture was stirred overnight under argon atmosphere at room temperature and poured into water. Then NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 3-benzyloxy-4-methoxybenzoic acid benzyl ester (8.06 g, 23.2 mmol) in 91% yield. (2) To a −15 °C solution of 3-benzyloxy-4-methoxybenzoic acid benzyl ester (42.2 g, 121 mmol) in acetic anhydride (400 mL) was added fuming nitric acid (9.71 mL, 243 mmol). After the reaction mixture was stirred for 3 h at room temperature, it was poured into ice−water and neutralized with sodium hydroxide solution. The resulting precipitate was collected, washed with water, and dried to provide 5-benzyloxy-4-methoxy-2-nitrobenzoic acid benzyl ester (49.5 g, 126 mmol) in quantitative yield: ^{1}H NMR, FABMS. (3) A mixture of 5-benzyloxy-4-methoxy-2-nitrobenzoic acid benzyl ester (49.5 g, 126 mmol), iron dust (39.7 g, 711 mmol), and $FeCl_3$ (1.00 g) in ethanol (100 mL), acetic acid (400 mL), and water (20 mL) was heated at 80 °C for 4 h under argon atmosphere. Removal of iron dust by filtration, evaporation, and addition of ethanol provided 2-amino-5-benzyloxy-4-methoxybenzoic acid benzyl ester (**4**) (21.2 g, 58.4 mmol). Purification of the filtrate by silica gel column chromatography also provided **4** (12.3 g, 33.9 mmol). The combined yield of **4** was 73%: ^{1}H NMR, FABMS. (4) A solution of **4** (20.2 g, 55.6 mmol) in formamide (120 mL) was heated at 190 °C for 5 h. The reaction mixture was cooled to room temperature and poured into water. Then NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 6-benzyloxy-7-methoxy-4(3*H*)-quinazolone (**6**) (19.4 g, 68.8 mmol) in quantitative yield. (5) A solution of **6** (18.4 g, 65.2 mmol) in phosphorus trichloride (180 mL) was refluxed for 3 h. The reaction mixture was evaporated and twice azeotroped with toluene. The resulting residue was dissolved in dichloromethane, washed with brine, dried over anhydrous sodium sulfate, and evaporated to provide 6-benzyloxy-4-chloro-7-methoxyquinazoline (**8**) (17.4 g, 57.9 mmol) in 89% yield. (6) The mixture of **8** (17.4 g, 57.8 mmol) and *N*-*tert*-butoxycarbonylpiperazine (16.1 g, 86.4 mmol) in tetrahydrofuran (250 mL), chloroform (50 mL), and triethylamine (36.3 mL, 260 mmol) was stirred overnight at room temperature. After further addition of *N*-*tert*-butoxycarbonylpiperazine (5.4 g, 28.9 mmol) followed by stirring overnight, the reaction mixture was evaporated and suspended in water, and then NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 4-(6-benzyloxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (**10**) (22.8 g, 50.6 mmol) in 88% yield: ^{1}H NMR, FABMS, IR. (7) A suspension of **10** (14.6 g, 32.4 mmol) and 10% Pd/C (3.00 g, containing 50% water) in ethanol (400 mL) was hydrogenated for 5 h at 50 °C under hydrogen stream. After removal of catalyst by filtration through Celite and evaporation, the resulting residue was recrystallized from methanol to provide 4-(6-hydroxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (**12**) (9.24 g, 25.7 mmol) in 79% yield: mp 243−244 °C (MeOH); ^{1}H NMR, FABMS, IR. Anal. ($C_{18}H_{24}N_4O_4$) C, H, N. (8) To a mixture of **12** (8.00 g, 22.2 mmol) and potassium carbonate (1.72 g, 12.4 mmol) in DMF (30 mL) was added iodoethane (1.24 mL, 12.4 mmol). The reaction mixture was stirred overnight under argon atmosphere at room temperature and poured into water. Then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified with silica gel column chromatography to provide 4-(6-ethoxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (3.28 g, 18.2 mmol) in 82% yield: ^{1}H NMR, FABMS, IR. (9) The title compound was obtained from 4-(6-ethoxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and 4-phenoxyphenyl isocyanate by procedure B in 100% yield: mp 213-214 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{29}N_5O_4$·$0.25H_2O$) C, H, N.

***N*-Benzyl-4-(6-ethoxy-7-methoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (16c).** 86% yield from 4-(6-ethoxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and benzyl isothiocyanate by procedure B; mp 170−171 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{23}H_{27}N_5O_2S$) C, H, N.

4-(7-Methoxy-6-propoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16d). 95% yield from 4-(7-methoxy-6-propoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **12** and 1-iodopropane by the same procedure as that of **16b** (step 8) in 82% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 195−196 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{31}N_5O_4$) C, H, N.

4-(6-Allyloxy-7-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16e). 84% yield from 4-(6-allyloxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **12** and allylbromide by the same procedure as that of **16b** (step 8) in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 172−173 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{29}N_5O_4$) C, H, N.

4-(7-Methoxy-6-propargyloxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16f). 53% yield from 4-(7-methoxy-6-propargyloxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, Anal.), which was synthesized from **12** and propargylbromide by the same procedure as that of **16b** (step 8) in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 224–225 °C ($CHCl_3$–$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{27}N_5O_4$) C, H, N.

4-(6-Cyanomethoxy-7-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16g). 41% yield from 4-(6-cyanomethoxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, Anal.), which was synthesized from **12** and bromoacetonitrile by the same procedure as that of **16b** (step 8) in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 167–168 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{26}N_6O_4$) C, H, N.

4-(6-Butoxy-7-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16h). 96% yield from 4-(6-butoxy-7-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, Anal.), which was synthesized from **12** and 1-iodobutane by the same procedure as that of **16b** (step 8) in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 190–191 °C ($CHCl_3$–$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{30}H_{33}N_5O_4 \cdot 0.25H_2O$) C, H, N.

4-(6-Benzyloxy-7-methoxy-4-quinazolinyl)-*N*-(4-cyanophenyl)-1-piperazinecarboxamide (16i). Quantitative yield from **10** and 4-cyanophenyl isocyanate by procedure B; mp 120–121 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{26}N_6O_3 \cdot H_2O$) C, H, N.

4-[7-Methoxy-6-(2-methoxyethoxy)-4-quinazolinyl]-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16j). 69% yield from 4-[7-methoxy-6-(2-methoxyethoxy)-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, Anal.), which was synthesized from **12** and bromoethylmethyl ether by the same procedure as that of **16b** (step 8) in 63% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 197–198 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{31}N_5O_5$) C, H, N.

***N*-(4-Cyanophenyl)-4-[7-methoxy-6-(2-methoxyethoxy)-4-quinazolinyl]-1-piperazinecarboxamide (16k).** 46% yield from 4-[7-methoxy-6-(2-methoxyethoxy)-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester and 4-cyanophenyl isocyanate by procedure B; mp 188–189 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{24}H_{26}N_6O_4 \cdot 0.5H_2O$) C, H, N.

4-[7-Methoxy-6-(2-methoxyethoxy)-4-quinazolinyl]-*N*-(3,4-methylenedioxybenzyl)-1-piperazinethiocarboxamide (16l). 69% yield from 4-[7-methoxy-6-(2-methoxyethoxy)-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester and 3,4-methylenedioxybenzyl isothiocyanate by procedure B; mp 85–86 °C ($CHCl_3$–$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{25}H_{29}N_5O_5S \cdot 0.5H_2O$) C, H, N.

4-[7-Methoxy-6-(2-oxopropoxy)-4-quinazolinyl]-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16m). 13% yield from 4-[7-methoxy-6-(2-oxopropoxy)-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester, which was synthesized from **12** and chloroacetone in the presence of potassium iodide by the same procedure as that of **16b** (step 8) in 83% yield, and 4-phenoxyphenyl isocyanate by procedure B; ^{1}H NMR, FABMS.

***N*-(4-Cyanophenyl)-4-(7-methoxy-6-methoxycarbonylmethoxy-4-quinazolinyl)-1-piperazinecarboxamide (16n).** 87% yield from 4-(7-methoxy-6-methoxycarbonyloxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **12** and methyl bromoacetate by the same procedure as that of **16b** (step 8) in 77% yield, and 4-cyanophenyl isocyanate by procedure B; mp 206–207 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{24}H_{24}N_6O_5 \cdot 0.25H_2O$) C, H, N.

***N*-(4-Cyanophenyl)-4-(7-methoxy-6-carboxymethoxy-4-quinazolinyl)-1-piperazinecarboxamide (16o).** Hydrolysis of **16n** with lithium hydroxide monohydrate in THF and water provided the title compound in quantitative yield: ^{1}H NMR.

4-(6-Methanesulfonyloxy-7-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (16p): 100% yield from 4-(7-methoxy-6-methanesulfonyloxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, IR), which was synthesized from **12** and methanesulfonyl chloride by the same procedure as that of **16b** (step 8) in 65% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 228–229 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{27}N_5O_6S$) C, H, N.

***N*-Benzyl-4-(6-methanesulfonyloxy-7-methoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (16q).** 97% yield from 4-(7-methoxy-6-methanesulfonyloxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and benzyl isothiocyanate by procedure B; mp 76–80 °C ($CHCl_3$–$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{22}H_{25}N_5O_4S_2 \cdot 0.5H_2O \cdot 0.25{}^{i}Pr_2O$) C, H, N.

4-(7-Ethoxy-6-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17a). (1) 4-Benzyloxy-3-methoxybenzoic acid benzyl ester was obtained by the same procedure as that of **16b** (step 1) from vanillic acid in 96% yield. (2) 4-Benzyloxy-5-methoxy-2-nitrobenzoic acid benzyl ester was obtained by the same procedure as that of **16b** (step 2) from 4-benzyloxy-3-methoxybenzoic acid benzyl ester in quantitative yield. (3) 2-Amino-4-benzyloxy-5-methoxybenzoic acid benzyl ester (**5**) was obtained by the reduction of 4-benzyloxy-5-methoxy-2-nitrobenzoic acid benzyl ester with zinc dust in acetic acid at room temperature in 97% yield. (4) 7-Benzyloxy-6-methoxy-4(3*H*)-quinazolone (**7**) was obtained by the same procedure as that of **16b** (step 4) from **5** in 87% yield. (5) 7-Benzyloxy-4-chloro-6-methoxyquinazoline (**9**) was obtained by the same procedure as that of **16b** (step 5) from **7** in 92% yield. (6) 4-(7-Benzyloxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (**11**) was obtained by the same procedure as that of **16b** (step 6) from **9** in 93% yield: IR. (7) 4-(7-Hydroxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (**13**) was obtained from **11** by the same procedure as that of **16b** (step 7) in 90% yield: mp, ^{1}H NMR, FABMS, IR, Anal. (8) The title compound was obtained in 100% yield from 4-(7-ethoxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, IR), which was synthesized from **13** and iodoethane by the same procedure as that of **16b** (step 8) in 91% yield, and 4-phenoxyphenyl isocyanate by procedure B: mp 174–175 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{29}N_5O_4$) C, H, N.

***N*-Benzyl-4-(7-ethoxy-6-methoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (17b).** 97% yield from 4-(7-ethoxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and benzyl isothiocyanate by procedure B; mp 168–169 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{23}H_{27}N_5O_2S$) C, H, N.

4-(6-Methoxy-7-propoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17c). 76% yield from 4-(6-methoxy-7-propoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, Anal.), which was synthesized from **13** and 1-iodopropane by the same procedure as that of **16b** (step 8) in 87% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 162–163 °C ($CHCl_3$–MeOH–$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{31}N_5O_4$) C, H, N.

4-(7-Isopropoxy-6-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17d). 100% yield from 4-(7-isopropoxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, IR), which was synthesized from **13** and 2-iodopropane by the same procedure as that of **16b** (step 8) in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 157–160 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{31}N_5O_4$) C, H, N.

4-(7-Allyloxy-6-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17e). 48% yield from 4-(7-allyloxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **13** and allyl bromide by the same procedure as that of **16b** (step 8) in 50% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 140–141 °C ($CHCl_3$–$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{29}N_5O_4$) C, H, N.

4-(6-Methoxy-7-propargyloxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17f). 39% yield from 4-(6-methoxy-7-propargyloxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **13** and propargyl bromide by the same procedure as that of **16b** (step 8) in 46% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 202−204 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{27}N_5O_4$·0.25H_2O) C, H, N.

4-(7-Butoxy-6-methoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17g). 77% yield from 4-(7-butoxy-6-methoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, Anal.), which was synthesized from **13** and 1-iodobutane by the same procedure as that of **16b** (step 8) in 91% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 197−198 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{30}H_{33}N_5O_4$) C, H, N.

4-[6-Methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17h). Quantitative yield from 4-[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **13** and bromoethylmethyl ether by a procedure similar to that of **16b** (step 8) using sodium hydride instead of potassium carbonate in 57% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 168−169 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{31}N_5O_5$) C, H, N.

4-[6-Methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]-*N*-(3,4-methylenedioxybenzyl)-1-piperazinethiocarboxamide (17i). 78% yield from 4-[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester and 3,4-methylenedioxybenzyl isothiocyanate by procedure B; mp 153−156 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{25}H_{29}N_5O_5S$·0.5H_2O) C, H, N.

4-[7-(2-Ethoxyethoxy)-6-methoxy-4-quinazolinyl]-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17j). 67% yield from 4-[7-(2-ethoxyethoxy)-6-methoxy-4-quinazolinyl]-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from **13** and 2-bromoethylethyl ether by a procedure similar to that of **16b** (step 8) in the presence of potassium iodide in 74% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 182−183 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{30}H_{33}N_5O_5$) C, H, N.

4-(6-Methoxy-7-methyl-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (17k). 31% yield from 6-methoxy-7-methyl-4-(1-piperazinyl)quinazoline (TOFMS), which was synthesized from 4-chloro-6-methoxy-7-methylquinazoline[43] in 77% yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 188−189 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{27}N_5O_3$) C, H, N.

***N*-Benzyl-4-(6-methoxy-7-methyl-4-quinazolinyl)-1-piperazinethiocarboxamide (17l).** 37% yield from 6-methoxy-7-methyl-4-(1-piperazinyl)quinazoline and benzyl isothiocyanate by procedure A; mp 185−186 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{22}H_{25}N_5OS$·0.25H_2O·0.25EtOAc) C, H, N.

4-(6,7-Diethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (32a). 21% yield from 6,7-diethoxy-4-(1-piperazinyl)quinazoline, which was synthesized from 4-chloro-6,7-diethoxyquinazoline[44] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 187−190 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{31}N_5O_4$) C, H, N.

***N*-Benzyl-4-(6,7-diethoxy-4-quinazolinyl)-1-piperazinethiocarboxamide (32b).** 97% yield from 6,7-diethoxy-4-(1-piperazinyl)quinazoline and benzyl isothiocyanate by procedure A; mp 134−136 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{24}H_{29}N_5O_2S$) C, H, N.

4-(6,7-Dibenzyloxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (32c). 65% yield from 6,7-dibenzyloxy-4-(1-piperazinyl)quinazoline (TOFMS), which was synthesized from 6,7-dibenzyloxy-4-chloroquinazoline[44] in 74% yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 137−138 °C ($CHCl_3$−MeOH−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{39}H_{35}N_5O_4$) C, H, N.

4-(6,8-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (33a). 86% yield from 6,8-dimethoxy-4-(1-piperazinyl)quinazoline, which was synthesized from 4-chloro-6,8-dimethoxyquinazoline[45] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 109−110 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{27}N_5O_4$) C, H, N.

4-(7,8-Dimethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (33b). 65% yield from 7,8-dimethoxy-4-(1-piperazinyl)quinazoline, which was synthesized from 4-chloro-7,8-dimethoxyquinazoline[43] in 77% yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 189−190 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{27}N_5O_4$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(6,7,8-trimethoxy-4-quinazolinyl)-1-piperazinecarboxamide (34a).** 55% yield from 6,7,8-trimethoxy-4-(1-piperazinyl)quinazoline, which was synthesized from 4-chloro-6,7,8-trimethoxyquinazoline[45] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 83−84 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{29}N_5O_5$·0.25H_2O) C, H, N.

4-(6,7-Dimethoxy-2-methyl-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (34b). 93% yield from 6,7-dimethoxy-2-methyl-4-(1-piperazinyl)quinazoline (TOFMS), which was synthesized from 4-chloro-6,7-dimethoxy-2-methylquinazoline[44] in 87% yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 146−147 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{29}N_5O_4$·0.5H_2O) C, H, N.

4-(2-Chloro-6,7-dimethoxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (34c). The title compound was synthesized from 4-(2-chloro-6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS) in 73% yield as described in general synthetic procedure B; mp 178−179 °C ($CHCl_3$−MeOH−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{26}ClN_5O_4$·0.5H_2O) C, H, N.

4-(6,7-Dimethoxy-2-morpholino-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (34d). (1) A mixture of 4-(2-chloro-6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (1.22 g, 2.99 mmol) and morphorine (1.30 mL, 4.90 mmol) in *N*-methylpyrrolidone (15 mL) was heated at 140 °C for 3 h. After the reaction mixture was cooled to room temperature and poured into water, NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 4-(6,7-dimethoxy-2-morpholino-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (851 mg, 1.85 mmol) in 62% yield. (2) The title compound was obtained from 4-(6,7-dimethoxy-2-morpholino-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester by procedure B in 79% yield; mp 114−116 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{31}H_{34}N_6O_5$·0.25H_2O) C, H, N.

4-(6,7-Methylenedioxy-4-quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (35a). 85% yield from 6,7-methylenedioxy-4-(1-piperazinyl)quinazoline (TOFMS), which was synthesized from 4-chloro-6,7-methylenedioxyquinazoline[44] in 91% yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 206−207 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{23}N_5O_4$·0.25H_2O) C, H, N.

***N*-Benzyl-4-(6,7-methylenedioxy-4-quinazolinyl)-1-piperazinethiocarboxamide (35b).** 99% yield from 6,7-methylenedioxy-4-(1-piperazinyl)quinazoline and benzyl isothiocyanate by procedure A; mp 176−177 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{21}H_{21}N_5O_2S$·0.25H_2O) C, H, N.

4-(6,7-Ethylenedioxy-4-quinazolinyl)-*N*-(4-phenoxyphen-yl)-1-piperazinecarboxamide (36a). 91% yield from 4-(6,7-ethylenedioxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, IR), which was synthesized from 4-chloro-6,7-ethylenedioxyquinazoline[46] in 49% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 227−228 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{25}N_5O_4$) C, H, N.

***N*-Benzyl-4-(6,7-ethylenedioxy-4-quinazolinyl)-1-piperazinethiocarboxamide (36b).** 88% yield from 4-(6,7-ethylenedioxy-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and benzyl isothiocyanate by procedure B; mp 103−105 °C ($CHCl_3$−$^{i}Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{22}H_{23}N_5O_2S$·1.25H_2O) C, H, N.

4-(4-Benzo[*g*]quinazolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (37a). 24% yield from 4-(4-benzo[*g*]quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR), which was synthesized from 4-chlorobenzo[*g*]quinazoline[47] in 43% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 105−108 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{25}N_5O_2$·$0.5H_2O$) C, H, N.

4-(4-Benzo[*g*]quinazolinyl)-*N*-benzyl-1-piperazinethiocarboxamide (37b). 42% yield from 4-(4-benzo[*g*]quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and benzyl isothiocyanate by procedure B; mp 187−188 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{24}H_{23}N_5S$·$0.25H_2O$) C, H, N.

4-(1,3-Dihydro-1,3-dimethyl-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21a). (1) To a −15 °C solution of 1,3-dihydro-2-oxo-1*H*-benzimidazole-5-carboxylic acid methyl ester[48] (7.86 g, 40.9 mmol) in acetic anhydride (100 mL) was slowly added fuming nitric acid (3.46 mL, 86.4 mmol). The mixture was stirred for 3.5 h at 0 °C and poured into ice−water. The resulting precipitate was collected, washed with water, and dried to provide 1,3-dihydro-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester (7.78 g, 32.7 mmol) in 80% yield: ^{1}H NMR, FABMS. (2) To an ice-cooled solution of 1,3-dihydro-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester (7.78 g, 32.8 mmol) in DMF (100 mL) was added 60% sodium hydride (3.94 g, 98.5 mmol). The mixture was stirred for 15 min at the same temperature, and iodomethane (6.13 mL, 98.5 mmol) was added. Then the reaction mixture was stirred for 1.5 h at room temperature and poured into water. The resulting precipitate was collected, washed with water, and dried to provide 1,3-dihydro-1,3-dimethyl-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester (8.58 g, 32.5 mmol) in 99% yield. (3) A suspension of 1,3-dihydro-1,3-dimethyl-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester (8.58 g, 32.4 mmol) and 10% Pd/C (1.60 g, containing 50% water) in ethanol (100 mL) was hydrogenated for 5.5 h under hydrogen stream at room temperature. After removal of catalyst by filtration through Celite, the filtrate was evaporated to provide 6-amino-1,3-dihydro-1,3-dimethyl-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester. This compound was used for the next reaction without further purification. (4) A solution of 6-amino-1,3-dihydro-1,3-dimethyl-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester in formamide (100 mL) was heated for 2 h at 190 °C. The reaction mixture was cooled to room temperature and poured into water, and then NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 1,3-dihydro-1,3-dimethyl-2*H*,7*H*-imidazo[4,5-*g*]quinazoline-2,8-dione (4.73 g, 20.7 mmol) in 64% yield in two steps. (5) The title compound was synthesized from 1,3-dihydro-1,3-dimethyl-2*H*,7*H*-imidazo[4,5-*g*]quinazoline-2,8-dione by procedure A in 73% yield via 8-chloro-1,3-dihydro-1,3-dimethyl-2-oxo-2*H*-imidazo[4,5-*g*]-quinazoline and 1,3-dihydro-1,3-dimethyl-2-oxo-8-(1-piperazinyl)-2*H*-imidazo[4,5-*g*]quinazoline: mp 250−255 °C ($CHCl_3$−MeOH−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{27}N_7O_3$) C, H, N.

4-(1,3-Dihydro-3-ethyl-1-methyl-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21b). (1) To an ice-cooled solution of **24a** (1.08 g, 3.75 mmol) in dichloromethane (20 mL) were added di-*tert*-butyl dicarbonate (1.33 mL, 5.79 mmol) and triethylamine (2.61 mL, 18.7 mmol). The reaction mixture was stirred overnight at room temperature, evaporated, and purified by silica gel column chromatography to provide 4-(7-(ethylamino)-6-nitro-4-quinazolinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (**24b**) (1.39 g, 3.45 mmol) in 92% yield: ^{1}H NMR, IR. (2) A suspension of **24b** (1.29 g, 3.22 mmol) and 10% Pd/C (0.13 g, containing 50% water) was hydrogenated for 6 h under hydrogen stream at room temperature. After removal of catalyst by filtration through Celite and evaporation, the residue was dissolved in DMF (20 mL) followed by addition of CDI (1.05 g, 6.48 mmol) and triethylamine (2.25 mL, 16.1 mmol). The mixture was heated at 80 °C for 4.5 h under argon atmosphere, cooled to room temperature, and poured into water. Then NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 4-(1,3-dihydro-3-ethyl-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-1-piperazinecarboxylic acid *tert*-butyl ester (1.30 g, 3.27 mmol) in quantitative yield: ^{1}H NMR, FABMS, IR. (3) To an ice-cooled solution of 4-(1,3-dihydro-3-ethyl-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-1-piperazinecarboxylic acid *tert*-butyl ester (1.42 g, 3.57 mmol) in DMF (15 mL) was added 60% sodium hydride (214 mg, 14.8 mmol). After the mixture was stirred for 30 min at room temperature, iodomethane (0.44 mL, 7.07 mmol) was added. The reaction mixture was stirred overnight at room temperature and poured into water. Then NaCl was added. The resulting precipitate was collected, washed with water, and dried to provide 4-(1,3-dihydro-3-ethyl-1-methyl-2-oxo-2*H*-imidazo[4,5-*g*]-quinazolin-8-yl)-1-piperazinecarboxylic acid *tert*-butyl ester (**25**) (749 mg, 1.82 mmol) in 51% yield: ^{1}H NMR, FABMS, IR. (4) The title compound was synthesized from **25** by procedure B in 96% yield: mp 250−251 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{29}H_{29}N_7O_3$·$0.5H_2O$) C, H, N.

***N*-Benzyl-4-(1,3-dihydro-3-ethyl-1-methyl-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-1-piperazinethiocarboxamide (21c).** 57% yield from **25** and benzyl isothiocyanate by procedure B; mp 207−208 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{24}H_{27}N_7OS$·$0.5H_2O$) C, H, N.

4-(1,3-Diethyl-1,3-dihydro-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21d). 66% yield from 1,3-diethyl-1,3-dihydro-2-oxo-8-(1-piperazinyl)-2*H*-imidazo[4,5-*g*]quinazoline, which was synthesized from 1,3-dihydro-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester and iodoethane in 90% yield by a similar reaction of **21a**, and 4-phenoxyphenyl isocyanate by procedure A; mp 168−169 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{30}H_{31}N_7O_3$·$0.25H_2O$) C, H, N.

4-(1,3-Dihydro-1,3-dipropyl-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21e). 62% yield from 1,3-dihydro-1,3-dipropyl-2-oxo-8-(1-piperazinyl)-2*H*-imidazo[4,5-*g*]quinazoline (FABMS), which was synthesized from 1,3-dihydro-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester and 1-iodopropane in quantitative yield by a similar reaction of **21a**, and 4-phenoxyphenyl isocyanate by procedure A; mp 179−180 °C ($CHCl_3$−MeOH-$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{32}H_{35}N_7O_3$·$0.25H_2O$) C, H, N.

4-(1,3-Dibutyl-1,3-dihydro-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21f). 50% yield from 1,3-dibutyl-1,3-dihydro-2-oxo-8-(1-piperazinyl)-2*H*-imidazo[4,5-*g*]quinazoline (TOFMS), which was synthesized from 1,3-dihydro-6-nitro-2-oxo-2*H*-benzimidazole-5-carboxylic acid methyl ester and 1-iodobutane in quantitative yield by a similar reaction of **21a**, and 4-phenoxyphenyl isocyanate by procedure A; mp 134−136 °C ($CHCl_3$−MeOH−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{34}H_{39}N_7O_3$) C, H, N.

4-(3-Ethyl-1,3-dihydro-2-oxo-2*H*-imidazo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (21g). A suspension of **1g** (198 mg, 0.38 mmol) and 10% Pd/C (30 mg, containing 50% water) in ethanol (4 mL) was hydrogenated for 7.5 h under a stream of hydrogen at room temperature. After removal of catalyst by filtration through Celite and evaporation, the residue was dissolved in DMF (10 mL) followed by addition of CDI (187 mg, 1.15 mmol). The mixture was heated at 80 °C for 2 h under argon atmosphere and poured into water, and the resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography to provide the title compound (66 mg, 0.13 mmol) in 34% yield: mp 248−251 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{27}N_7O_3$·H_2O) C, H, N.

***N*-Benzyl-4-(3-ethyl-3*H*-imidazo[4,5-*g*]quinazolin-8-yl)-1-piperazinethiocarboxamide (26).** A mixture of **1i** (504 mg, 1.20 mmol) and oxalyl chloride (0.13 mL, 1.49 mmol) in DMF (10 mL) and pyridine (0.29 mL, 3.60 mmol) was stirred overnight at room temperature under argon atmosphere. The reaction mixture was heated at 80 °C for 5 h, cooled to room temperature, and poured into water. Then NaCl was added. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography to provide the title compound (284 mg, 0.66 mmol) in 55% yield: ^{1}H NMR, FABMS, IR. Anal. ($C_{23}H_{25}N_7S{\cdot}0.7H_2O{\cdot}0.1{}^iPr_2O$) C, H, N.

4-(3-Ethyl-3*H*-1,2,3-triazolo[4,5-*g*]quinazolin-8-yl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (27). A suspension of **1g** (395 mg, 0.77 mmol) and 10% Pd/C (40 mg, containing 50% water) was hydrogenated for 7.5 h under hydrogen stream. After removal of catalyst by filtration through Celite and evaporation, the residue was dissolved in acetic acid (10 mL), water (10 mL), and concentrated hydrochloric acid (1 mL). Sodium nitrite (106 mg, 1.54 mmol) was added to the solution under ice cooling, and then the mixture was stirred for 4 h at the same temperature and poured into saturated aqueous sodium hydrogen carbonate. The resulting precipitate was collected, washed with water, dried, and purified by silica gel column chromatography to provide the title compound (119 mg, 0.24 mmol) in 31% yield: mp 167−168 °C (EtOAc); ^{1}H NMR, FABMS, IR.

***N*-(4-Phenoxyphenyl)-4-(6-purinyl)-1-piperazinecarboxamide (38a).** The title compound was synthesized from 4-[*N*-(4-phenoxyphenyl)carbamoyl]-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS) in 71% yield as described in general synthetic procedure C: mp 250−251 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{22}H_{21}N_7O_2$) C, H, N.

***N*-Benzyl-4-(6-purinyl)-1-piperazinethiocarboxamide (38b).** 70% yield from 4-(6-purinyl)-1-piperazinecarboxylic acid *tert*-butyl ester[49] and benzyl isothiocyanate by procedure B; mp 255−260 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{17}H_{19}N_7S{\cdot}0.25H_2O$) C, H, N.

4-(2-Amino-6-purinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (38c). 95% yield from 4-(2-amino-6-purinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, IR), which was synthesized from commercially available 2-amino-6-chloropurine in 44% yield, and benzyl isothiocyanate by procedure B; mp 244−258 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{22}H_{22}N_8O_2{\cdot}0.25H_2O$) C, H, N.

4-(9-Methyl-6-purinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (38d). 91% yield from 4-(9-methyl-6-purinyl)-1-piperazinecarboxylic acid *tert*-butyl ester[50] and 4-phenoxyphenyl isocyanate by procedure B; mp 168−169 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{23}H_{23}N_7O_2$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(4-pyrazolo[3,4-*d*]pyrimidinyl)-1-piperazinecarboxamide (39a).** (1) To a refluxing suspension of commercially available 4-aminopyrazolo[3,4-*d*]pyrimidine (420.8 mg, 3.11 mmol) in dibromomethane (5 mL) was added isoamyl nitrite (0.43 mL, 3.20 mmol). The mixture was refluxed for 3 h. After further addition of isoamyl nitrite (0.43 mL, 3.20 mmol) followed by refluxing for 3.5 h, the insoluble material was removed by filtration. The filtrate was evaporated, the resulting residue was dissolved in DMF (5 mL), and then triethylamine (2.00 mL, 14.3 mmol) and *N*-*tert*-butoxycarbonylpiperazine (1.00 g, 5.37 mmol) were added, followed by stirring overnight at room temperature. After the reaction mixture was evaporated, the resulting residue was purified by silica gel column chromatography to provide 4-(4-pyrazolo-[3,4-*d*]pyrimidinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (20.4 mg, 0.07 mmol) in 2% yield: ^{1}H NMR, FABMS. (2) The title compound was synthesized from 4-(4-pyrazolo[3,4-*d*]-pyrimidinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and 4-phenoxyphenyl isocyanate by procedure B in 48% yield: ^{1}H NMR, FABMS.

4-(1-Methyl-4-1*H*-pyrazolo[3,4-*d*]pyrimidinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (39b). 81% yield from 1-methyl-4-(1-piperazinyl)-*1H*-pyrazolo[3,4-*d*]pyrimidine, which was synthesized from 4-hydroxy-1-methyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine[50] in 83% yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 155−156 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{23}H_{23}N_7O_2{\cdot}0.25H_2O$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(1,3-dihydro-2-oxo-2*H*-imidazo-[4,5-*d*]pyrimidine-4-yl)-1-piperazinecarboxamide (31).** (1) A mixture of commercially available 4,6-dichloro-5-nitropyrimidine (**28**) (1.00 g, 5.44 mmol) and dichloromethane saturated with ammonia gas (50 mL) was stirred for 1 h at room temperature and evaporated. The resulting residue was dissolved in DMF (10 mL), and then *N*-*tert*-butoxycarbonylpiperazine (1.15 g, 6.17 mmol) and triethylamine (3.59 mL, 25.8 mmol) were added, followed by heating at 80 °C for 4 h. The reaction mixture was cooled to room temperature and poured into water. Then NaCl was added. The resulting precipitate was collected by filtration, washed with water, and dried to provide 4-(6-amino-5-nitro-4-pyrimidinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (**29**) (888 mg, 2.74 mmol) in 50% yield: ^{1}H NMR, FABMS, IR. (2) A suspension of **29** (888 mg, 2.74 mmol) and 10% Pd/C (200 mg, containing 50% water) was hydrogenated for 2 h at room temperature under hydrogen stream. After addition of chloroform and removal of catalyst by filtration through Celite, the filtrate was evaporated. The resulting residue was dissolved in DMF (10 mL) and triethylamine (1.91 mL, 13.7 mmol). CDI (888 mg, 5.48 mmol) was added, followed by heating of the mixture at 80 °C for 4.5 h. After the reaction mixture was cooled to room temperature and poured into water, NaCl was added. The resulting precipitate was collected by filtration, washed with water, and dried to provide 4-(1,3-dihydro-2-oxo-2*H*-imidazo[4,5-*d*]pyrimidine-4-yl)-1-piperazinecarboxylic acid *tert*-butyl ester (**30**) (161 mg, 0.50 mmol) in 18% yield: ^{1}H NMR, FABMS, IR. (3) The title compound was synthesized from **30** and 4-phenoxyphenyl isocyanate by procedure B in 52% yield: ^{1}H NMR, FABMS.

***N*-(4-Phenoxyphenyl)-4-(6,7-dimethoxy-4-quinolyl)-1-piperazinecarboxamide (40a).** 57% yield from 4-(6,7-dimethoxy-4-quinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester, which was synthesized from 4-hydroxy-6,7-dimethoxyquinoline[51] in 10% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 204−206 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{28}N_4O_4{\cdot}0.25H_2O$) C, H, N.

4-(6,7-Dimethoxy-3-ethoxycarbonyl-4-quinolyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (40b). 100% yield from 4-(6,7-dimethoxy-3-ethoxycarbonyl-4-quinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester (mp, ^{1}H NMR, FABMS, IR, Anal.), which was synthesized from 4-chloro-6,7-dimethoxy-3-ethoxycarbonylquinoline[52] in 91% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 163−164 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{31}H_{32}N_4O_6{\cdot}H_2O$) C, H, N.

***N*-Benzyl-4-(6,7-dimethoxy-3-ethoxycarbonyl-4-quinolyl)-1-piperazinethiocarboxamide (40c).** 100% yield from 4-(6,7-dimethoxy-3-ethoxycarbonyl-4-quinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester and benzyl isothiocyanate by procedure B; mp 174−175 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{30}N_4O_4S$) C, H, N.

4-(6-Chloro-4-quinolyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (40d). 83% yield from 6-chloro-4-(1-piperazinyl)quinoline (FABMS), which was synthesized from 4,6-dichloroquinoline[51] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 188−189 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{23}ClN_4O_2{\cdot}0.25H_2O$) C, H, N.

***N*-Benzyl-4-(6-chloro-4-quinolyl)-1-piperazinethiocarboxamide (40e).** 91% yield from 6-chloro-4-(1-piperazinyl)-quinoline and 4-phenoxyphenyl isocyanate by procedure A; mp 173−174 °C ($CHCl_3$−$^iPr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{21}H_{21}ClN_4S{\cdot}0.25H_2O$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(7-chloro-4-quinolyl)-1-piperazinecarboxamide (40f).** 100% yield from 7-chloro-4-(1-piperazinyl)quinoline[53] and 4-phenoxyphenyl isocyanate by procedure A; mp 159−161 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{23}ClN_4O_2$) C, H, N.

***N*-Benzyl-4-(7-chloro-4-quinolyl)-1-piperazinethiocarboxamide (40g).** 89% yield from 7-chloro-4-(1-piperazinyl)-quinoline and benzyl isothiocyanate by procedure A; mp 84−86 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{21}H_{21}ClN_4S{\cdot}0.25H_2O$) C, H, N.

4-(8-Chloro-4-quinolyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (40h). 99% yield from 8-chloro-4-(1-piperazinyl)quinoline (TOFMS), which was synthesized from 4,8-dichloroquinoline[54] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 174−175 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{23}ClN_4O_2{\cdot}0.25{}^iPr_2O$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(2-trifluoromethyl-4-quinolyl)-1-piperazinecarboxamide (40i).** 41% yield from commercially available 2-trifluoromethyl-4-(1-piperazinyl)quinoline and 4-phenoxyphenyl isocyanate by procedure A; mp 203−204 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{23}F_3N_4O_2$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(7-trifluoromethyl-4-quinolyl)-1-piperazinecarboxamide (40j).** 100% yield from 7-trifluoromethyl-4-(1-piperazinyl)quinoline (TOFMS), which was synthesized from commercially available 4-chloro-7-trifluoroquinoline in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 163−164 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{23}F_3N_4O_2$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(4-quinolyl)-1-piperazinecarboxamide (40k).** 93% yield from 4-(1-piperazinyl)quinoline, which was synthesized from 4-chloroquinoline[51] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 145−146 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{24}N_4O_2 \cdot 0.25H_2O$) C, H, N.

***N*-Benzyl-4-(4-quinolyl)-1-piperazinethiocarboxamide (40l).** 96% yield from 4-(1-piperazinyl)quinoline and benzyl isothiocyanate by procedure A; mp 75−79 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{21}H_{22}N_4S \cdot 0.25H_2O \cdot 0.25^i Pr_2O$) C, H, N.

4-(6,7-Dimethoxy-1-isoquinolyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (41a). 87% yield from 4-(6,7-dimethoxy-1-isoquinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester (IR), which was synthesized from 1,3-dichloro-6,7-dimethoxyisoquinoline[55] in quantitative yield via 4-(3-chloro-6,7-dimethoxy-1-isoquinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, IR) by a similar reaction of **43a** (steps 1 and 2), and 4-phenoxyphenyl isocyanate by procedure B; mp 178−179 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{28}H_{28}N_4O_4$) C, H, N.

4-(1-Isoquinolyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (41b). 100% yield from 4-(1-isoquinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, IR), which was synthesized from commercially available 1,3-dichloroisoquinoline in 77% yield via 4-(3-chloro-1-isoquinolyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS, IR) by similar reaction of **43a** (steps 1 and 2), and 4-phenoxyphenyl isocyanate by procedure B; mp 122−123 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{26}H_{24}N_4O_2$) C, H, N.

4-(6,7-Dimethoxy-4-cinnolinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (42). 73% yield from 6,7-dimethoxy-4-(1-piperazinyl)cinnoline, which was synthesized from 4-chloro-6,7-dimethoxycinnoline[56] in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 165−167 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{27}H_{27}N_5O_4 \cdot H_2O$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(1-phthalazinyl)-1-piperazinecarboxamide (43a).** (1) A mixture of commercially available 1,4-dichlorophthalazine (2.09 g, 10.5 mmol), *N-tert*-butoxycarbonylpiperazine (2.35 g, 12.6 mmol), and triethylamine (7.32 mL, 52.5 mmol) in NMP (20 mL) was heated at 70 °C for 2 h under argon atmosphere. The reaction mixture was cooled to room temperature and poured into water. Then NaCl was added. The resulting precipitate was collected by filtration, washed with water, dried, and purified by silica gel column chromatography to provide 4-(4-chloro-1-phthalazinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (2.77 g, 7.95 mmol) in 76% yield: ^{1}H NMR, FABMS, IR. (2) A suspension of 4-(4-chloro-1-phthalazinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (2.30 g, 6.59 mmol) and 10% Pd/C (500 mg, containing 50% water) in acetic acid (30 mL) was hydrogenated at 50 °C for 3 h under hydrogen stream. After removal of catalyst by filtration through Celite and evaporation, the residue was purified by silica gel column chromatography to provide 4-(1-phthalazinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (801.6 mg, 2.55 mmol) in 39% yield: ^{1}H NMR, FABMS, IR. (3) The title compound was synthesized from 4-(1-phthalazinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and 4-phenoxyphenyl isocyanate by procedure B in 98% yield: mp 202−203 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{25}H_{23}N_5O_2$) C, H, N.

4-(4-Chloro-1-phthalazinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (43b). 100% yield from 4-(4-chloro-1-phthalazinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and 4-phenoxyphenyl isocyanate by procedure B; mp 196−197 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{25}H_{22}ClN_5O_2$) C, H, N.

4-(4-Benzyl-1-phthalazinyl)-*N*-(4-phenoxyphenyl)-1-piperazinecarboxamide (43c). 75% yield from 1-benzyl-4-(1-piperazinyl)phthalazine, which was synthesized from commercially available 1-benzyl-4-chlorophthalazine in quantitative yield, and 4-phenoxyphenyl isocyanate by procedure A; mp 100−101 °C ($CHCl_3$−$^i Pr_2O$); ^{1}H NMR, FABMS, IR. Anal. ($C_{32}H_{29}N_5O_2 \cdot H_2O$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(6-fluoro-4-pyrido[3,4-*d*]pyrimidinyl)-1-piperazinecarboxamide (44).** 86% yield from 4-(6-fluoro-4-pyrido[3,4-*d*]pyrimidinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (^{1}H NMR, FABMS), which was synthesized from 6-fluoropyrido[3,4-*d*]pyrimidine-4(3*H*)-one[41] in 58% yield, and 4-phenoxyphenyl isocyanate by procedure B; mp 185−186 °C (EtOAc); ^{1}H NMR, FABMS. Anal. ($C_{24}H_{21}FN_6O_2$) C, H, N.

***N*-(4-Phenoxyphenyl)-4-(4-pyrido[2,3-*d*]pyrimidinyl)-1-piperazinecarboxamide (45).** (1) A mixture of 4-mercaptopyrido[2,3-*d*]pyrimidine[57] (742 mg, 4.55 mmol), potassium carbonate (755 mg, 5.47 mmol), and iodomethane (0.34 mL, 5.47 mmol) in DMF (10 mL) was stirred overnight at room temperature under argon atmosphere. Triethylamine (3.17 mL, 22.7 mmol) and *N-tert*-butoxycarbonylpiperazine (1.67 g, 8.97 mmol) were added, followed by stirring overnight at room temperature. *N-tert*-Butoxycarbonylpiperazine (0.90 g, 4.83 mmol) was further added, followed by heating at 110 °C for 3.5 h. The reaction mixture was cooled to room temperature and poured into water, and the resulting mixture was extracted with dichloromethane. The extract was washed with brine, dried over anhydrous sodium sulfate, evaporated, and purified by silica gel column chromatography to provide 4-(4-pyrido[2,3-*d*]pyrimidinyl)-1-piperazinecarboxylic acid *tert*-butyl ester (1.05 g, 3.33 mmol) in 73% yield: ^{1}H NMR, FABMS, IR. (2) The title compound was synthesized from 4-(4-pyrido[2,3-*d*]pyrimidinyl)-1-piperazinecarboxylic acid *tert*-butyl ester and 4-phenoxyphenyl isocyanate by procedure B in 76% yield: mp 104−106 °C (EtOAc); ^{1}H NMR, FABMS, IR. Anal. ($C_{24}H_{22}N_6O_2 \cdot 2H_2O$) C, H, N.

Pharmacokinetic Studies. Pharmacokinetic Study of 1b. 1b was intravenously (1 mg/kg, rat nos. 1-4) and orally (30 mg/kg, rat nos. 5−7) administered to male Sprague−Dawly (SD) rats, and the plasma concentration was determined by an HPLC method. Pharmacokinetic parameters were obtained by model-independent analysis.

Pharmacokinetic Study of 16k. which was observed to have different pharmacokinetic profiles in two phenotypes (extensive metabolizers (EMs) and poor metabolizers (PMs)), was orally administered to male SD rats (3 mg/kg, $n = 4$). The plasma samples withdrawn 30 min after dosing were analyzed by an HPLC method. EMs and PMs were discriminated by the presence and absence, respectively, of a characteristic peak of the metabolite observed only in EMs in HPLC. After a 1-week washout period, **16k** was intravenously administered to each phenotype (1 mg/kg, $n = 2$) and the plasma concentration was determined by an HPLC method. The pharmacokinetic parameters were obtained by model-independent analysis.

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Supporting Information Available: A listing of the NMR, MS, combustion analysis (CHN), and IR data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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