Identification of Orally Active, Potent, and Selective 4-Piperazinylquinazolines as Antagonists of the Platelet-Derived Growth Factor Receptor Tyrosine Kinase Family

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We have previously found that the 4-[4-(N-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazolines can function as potent and selective inhibitors of platelet-derived growth factor receptor (PDGFR) phosphorylation. A series of highly potent, specific, orally active, small molecule kinase inhibitors directed against members of PDGFR receptor have been developed through modifications of the novel quinazoline template **I**. Systematic modifications in the A-bicyclic ring and D-rings of protype **I** were carried out to afford potent analogues, which display IC_{50} values of <250 nM in cellular βPDGFR phosphorylation assays. An optimized analogue in this series, **75** (CT53518), inhibits Flt-3, βPDGFR, and c-Kit receptor phosphorylation with IC_{50} values of 50−200 nM, whereas 15−20-fold less potent activity against CSF-1R was observed. This analogue also inhibits autophosphorylation of Flt-3 ligand-stimulated wild-type Flt-3 and a constitutively activated Flt-3/internal tandem duplication (ITD) with IC_{50} values of 30−100 nM. Through this optimization process, **75** was found to be metabolically stable and has desirable pharmacokinetic properties in all animal species studied ($F\%$ > 50%, $T_{1/2}$ > 8 h). Oral administration of **75** promotes mice survival and significantly delayed disease progression in a Flt-3/ITD-mediated leukemia mouse model and shows efficacy in a nude mouse model of chronic myelomonocytic leukemia.

Introduction

The platelet-derived growth factor receptor (PDGFR) family belongs to the large family of receptor tyrosine kinases (RTK) that are characterized by an extracellular ligand-binding region, a single transmembrane spanning region, and intracellular tyrosine kinase domains.[1] PDGFRs are contained within the RTK type III subfamily that is distinguished by five immunoglobin-like repeats in the extracellular domain and a split tyrosine kinase in the intracellular domain.[2] Abnormal PDGF-induced cell proliferation has been proposed to lead to proliferative disorders such as atherosclerosis, restenosis following percutaneous coronary intervention, glomerulosclerosis, liver cirrhosis, and certain cancers.[3−7] The members of the PDGFR family include αPDGFR and βPDGFR, colony-stimulating factor 1 receptor (CSF-1R), Flt-3, and c-Kit.[8] Within this kinase subfamily, mutated c-Kit has been identified in mastocytosis, acute myelogenous leukemia (AML), and gastrointestinal stromal tumors.[9−11] Flt-3 is expressed on blasts in most patients with AML.[12] Internal tandem duplication (ITD) mutations of Flt-3 have been found in ∼30% of AML patients.[13] These mutations constitutively activate the receptor and appear to be associated with poor prognosis, making Flt-3 kinase inhibition an attractive therapeutic strategy.[14] Other studies have identified chromosomal translocations involving the βPDGFR in chronic myelomonocyctic leukemia (CMML).[15]

Several adenosine 5′-triphosphate (ATP) competitive inhibitors of PDGFR phosphorylation have been previously reported including 3-arylquinolines,[16] 3-arylquinoxalines,[17] phenylaminopyrimidines,[18] pyrazoles,[19] and phenylbenzimidazoles derivatives[20] (Figure 1). We recently demonstrated that CT52923 (**II**, Figure 1), an analogue within this novel series of 4-[4-(N-substituted thiocarbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazolines, is a potent inhibitor of PDGF receptor phosphorylation.[21] Previous structure−activity studies in this series have identified structural features of these inhibitors that contribute to their specific βPDGFR inhibitory activity including electron-donating substitutions at the 6- and 7-positions in the A-ring of the quinazoline ring and a piperazinylurea or the piperazinylthiourea moiety attached at the 4-position of the quinazoline that is critical for inhibitory potency and PDGFR family specificity.[21b,22] Additionally, one hydrogen atom on the nitrogen of the urea/thiourea moiety, an unsubstituted piperazine B-ring, and bulky hydrophobic functionality at the 4-position on the phenyl D-ring give optimal kinase antagonists. Despite extensive knowledge concerning this pharmacophore, analogues with appropriate pharmaceutical properties have not been identified to date. In this paper, we will present our efforts within the 4-piperazinylquinazoline class of PDGFR family inhibitors involving efforts to increase the potency of analogues in human plasma, obtaining and retaining appropriate kinase specificity of analogues, and achiev-

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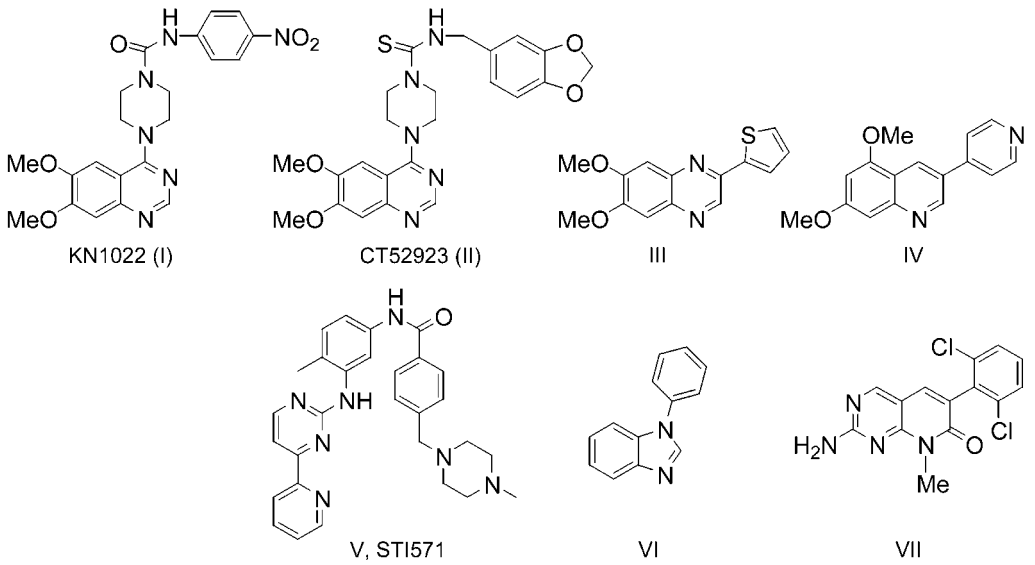
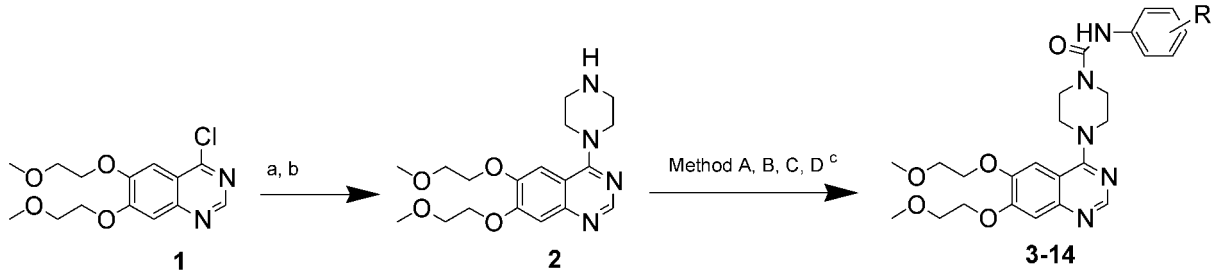


Figure 1. Known class of PDGFR inhibitors.

Scheme 1[a]



[a] Reagents: (a) Boc-piperazine, K_2CO_3, DMF, 65 °C, 6 h. (b) 4 N HCl/dioxane. (c) Method A: R-PhNCO, CH_2Cl_2 or DMF; method B: (i) R-NH_2, DSC, Et_3N, CH_2Cl_2; (ii) Compound **2**, Et_3N, CH_2Cl_2; method C: (i) R-$PhNH_2$, triphosgene, Et_3N, CH_3CN; (ii) Compound **2**, Et_3N, CH_3CN; method D: (i) R-$PhNH_2$, 4-NO_2Ph-OCOCl, Et_3N, CH_2Cl_2; (ii) Compound **2**, heat.

ing desirable pharmacokinetic properties including high oral bioavailability and long plasma half-life.

Chemistry

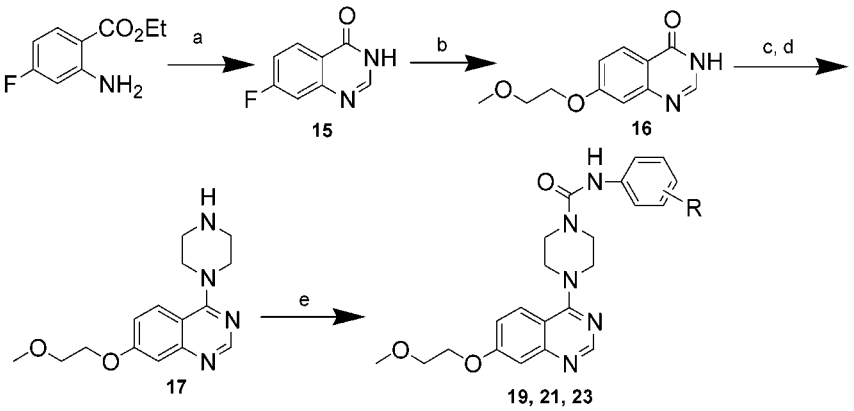
As depicted in Scheme 1, compounds **3**−**14** were prepared by treatment of the known 6,7-bismethoxyethoxy chloroquinazoline **1**[23] with Boc-piperazine followed by removal of the Boc-protecting group to afford **2**, followed by urea formation. Four protocols were used to synthesize urea analogues from various para-substituted anilines (Scheme 1). Condensation of **2** with commercially available isocyanates was carried out in either dichloromethane or dimethylformamide (DMF) (method A). Treatment of various anilines with *N*,*N*′-disuccinimidyl carbonate (DSC) in the presence of triethylamine in dichloromethane, followed by reaction with intermediate **2**, was used to provide the desired ureas (method B). Sequential carbonylation of anilines with triphosgene in the presence of triethylamine, followed by addition of **2** in situ, also gave the desired ureas (method C). Heating **2** with various 4-nitrophenylcarbamates, which were individually prepared by reacting the corresponding anilines with 4-nitrophenylchloroformate in the presence of triethylamine, also provided the ureas (method D).

The synthesis of 6-H,7-methoxyethoxy analogues **19**, **21**, and **23** was achieved via the intermediate **17** (Scheme 2), which was synthesized starting from 7-fluoro-3*H*-quinazolin-4-one (**15**).[24] The 7-fluoro-3*H*-quinazolin-4-one was reacted with methoxyethoxyethanol to afford quinazolin-4-one (**16**), followed by chlorination and piperazine addition to give (**17**) (Scheme 2). The urea linkage formed in the final products was again achieved by reaction of **17** using the methods described in Scheme 1.

The synthesis of 6,7-disubstituted analogues **29**−**32** is shown in Scheme 3, where ethyl 3-hydroxy-4-fluorobenzoate is alkylated with chloroethylpiperidine or chloroethyl morpholine followed by displacement of the fluoro group by the anion of 2-methoxyethanol to provide esters **25a**,**b**. The regiospecific nitration of **25a** or **25b** and subsequent reduction of the nitro groups resulted in amino esters **26a**,**b**. The cyclization of amino esters **26a** or **26b** with formamide yielded the quinazolinone intermediates **27a**,**b**, which were subsequently chlorinated with thionyl chloride in the presence of a catalytic amount of DMF to afford the corresponding 4-chloroquinazolines. These reactive intermediates were subsequently reacted with Boc-piperazine followed by deprotection to give the 4-piperazinylquinazolines **28a**,**b**. The final urea linkage formation was achieved by one of the methods as described in Scheme 1.

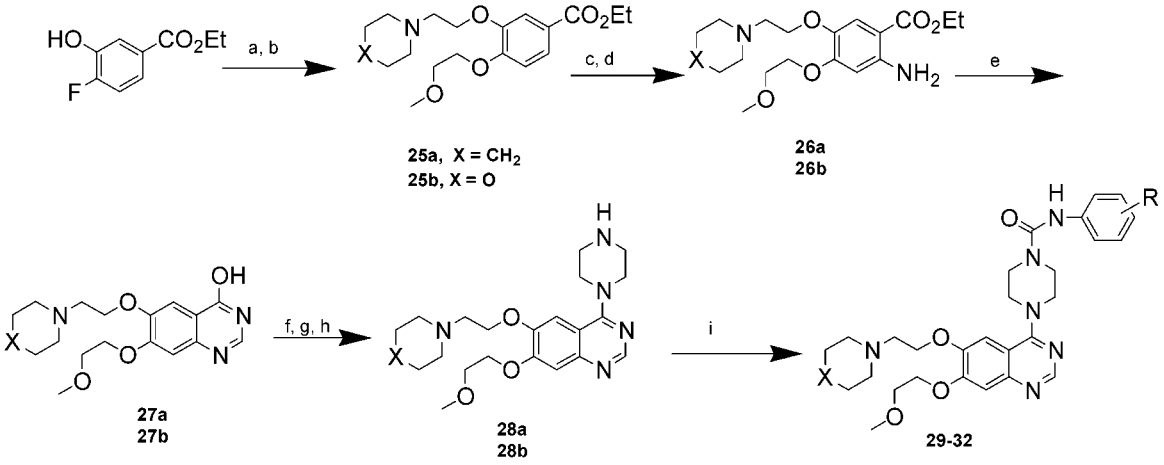
The synthesis of isomeric intermediates with basic groups at the C-7 position of the quinazoline nucleus (analogues **37**−**40**) is shown in Scheme 4. Ethyl 3-hydroxy-4-fluorobenzoate was alkylated with 2-methoxyethyl bromide followed by displacement of the fluorine atom with the anion of 2-piperidin-1-yl or 2-morpholin-

Scheme 2[a]



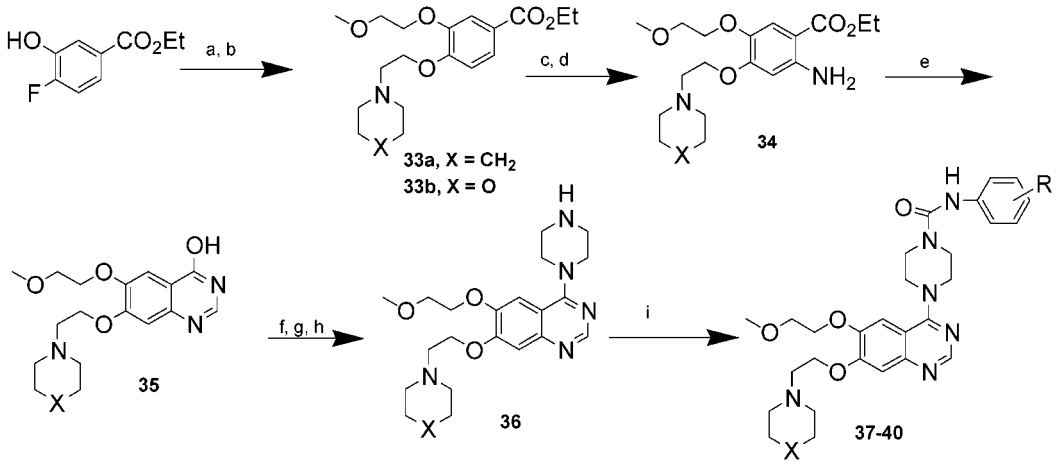
[a] Reagents: (a) $HCONH_2$, HCO_2NH_4, 140 °C, o/n. (b) 2-Methoxy ethanol, NaH, DMF, 90 °C. (c) $POCl_3$, 110 °C. (d) Piperazine, *i*PrOH, reflux, 2 h. (e) See Scheme 1 urea formation.

Scheme 3[a]



[a] Reagents: (a) 1-(2-Chloroethyl)piperidine or 1-(2-chloroethyl)morpholine, K_2CO_3, DMF, 70 °C, 6 h. (b) 2-Methoxy ethanol, NaH, DMF, 90 °C. (c) KNO_3, H_2SO_4, AcOH, −5 °C to room temperature. (d) 10% Pd/C. (e) $HCONH_2$, HCO_2NH, reflux, 12 h. (f) $SOCl_2$, catalytic DMF, 60 °C. (g) Boc-piperazine, isopropanol, reflux. (h) TFA, CH_2Cl_2. (i) See Scheme 1 urea formation.

Scheme 4[a]

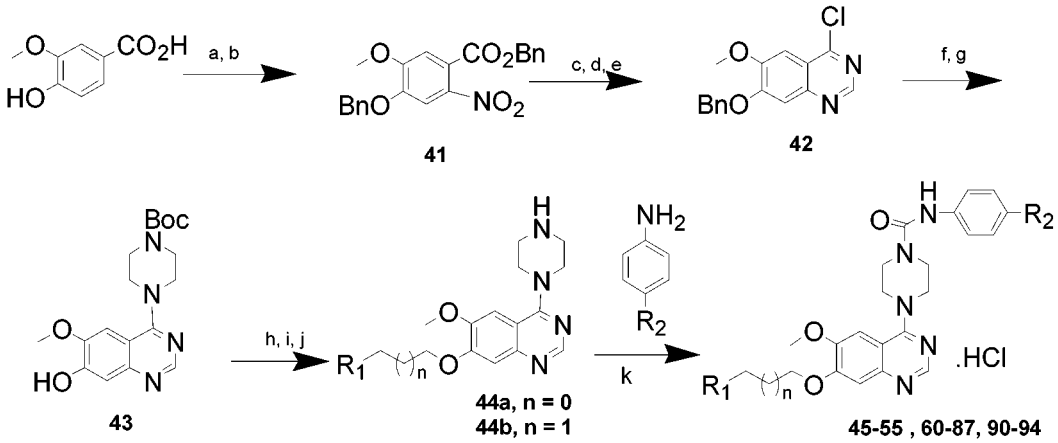


[a] Reagents: (a) Methoxyethoxy bromide, K_2CO_3, DMF, 70 °C, 6 h. (b) 2-Piperidin-1-yl-ethanol or 2-morpholin-1-yl ethanol or 2-pyrrolin-1-yl ethanol, NaH, DMF, 90 °C. (c) KNO_3, H_2SO_4, AcOH, −5 °C to room temperature. (d) 10% Pd/C. (e) $HCONH_2$, HCO_2NH, reflux, 12 h. (f) $SOCl_2$, catalytic DMF, 60 °C. (g) Boc-piperazine, isopropanol, reflux. (h) TFA, CH_2Cl_2. (i) See Scheme 1 urea formation.

1-yl ethanol to give intermediates **33a**,**b**. The same reaction sequence utilized in Scheme 3 was followed to achieve the synthesis of final products.

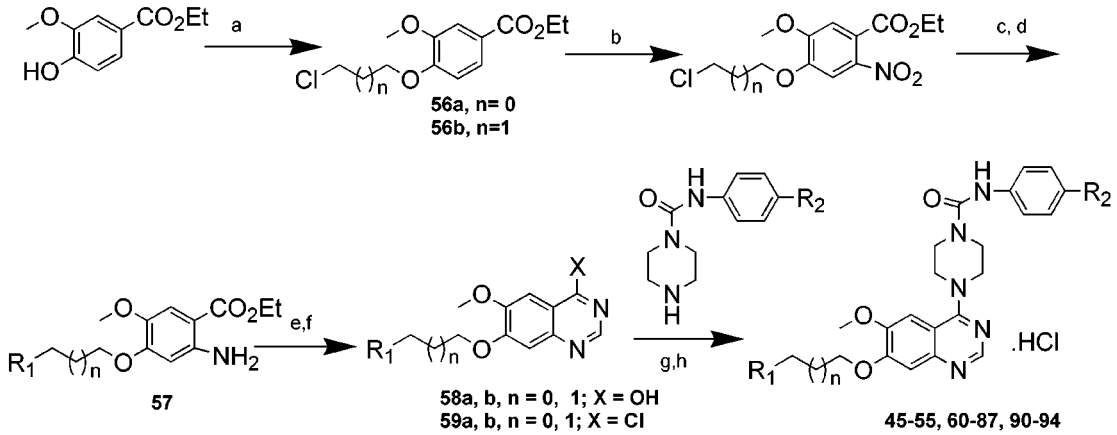
The synthesis of 6-methoxy-7-substituted analogues is represented in Scheme 5. Commercially available vanillic acid was dibenzylated followed by nitration to afford intermediate **41**. The nitroester intermediate **41** was then reduced and cyclized with formamide to form the quinazolinone ring, followed by chlorination to afford intermediate **42**. The chloro group was displaced with

Scheme 5[a]



[a] Reagents: (a) BnBr, K_2CO_3, DMF, room temperature. (b) HNO_3, AcOH, 0−100 °C, o/n. (c) $SnCl_2$, $2H_2O$, EtOAc, 50 °C, o/n. (d) $HCONH_2$, HCO_2NH_4, 145 °C, 12 h. (e) $SOCl_2$, catalytic DMF, toluene, reflux. (f) Boc-piperazine, DIEA, THF, 40 °C, o/n. (g) $Pd(OH)_2$/C, EtOH, 50 psi H_2, o/n. (h) Chloroethyl tosylate for $n = 0$ and chloropropyl tosylate for $n = 1$, Cs_2CO_3, DMF, 80 °C, o/n. (i) R1 = basic moiety such as piperidine etc., DMF, 80 °C. (j) 4 N HCl, dioxane. (k) Substituted anilines; methods A−D as in Scheme 1.

Scheme 6[a]



[a] Reagents: (a) For $n = 0$, chloroethyl tosylate or for $n = 1$, 1-bromo-3-chloropropane, K_2CO_3, DMF, reflux. (b) HNO_3, AcOH, 0−20 °C. (c) R_1 = basic substituent, K_2CO_3, nBu$_4$NBr, toluene, 90 °C. (d) 10% Pd/C, HCO_2K, EtOH, H_2O. (e) $HCONH_2$, HCO_2NH_4, 135 °C, 12 h. (f) $SOCl_2$, catalytic DMF, toluene, reflux. (g) K_2CO_3, DMF, toluene, 45 °C, 8 h. (h) EtOH, AcCl.

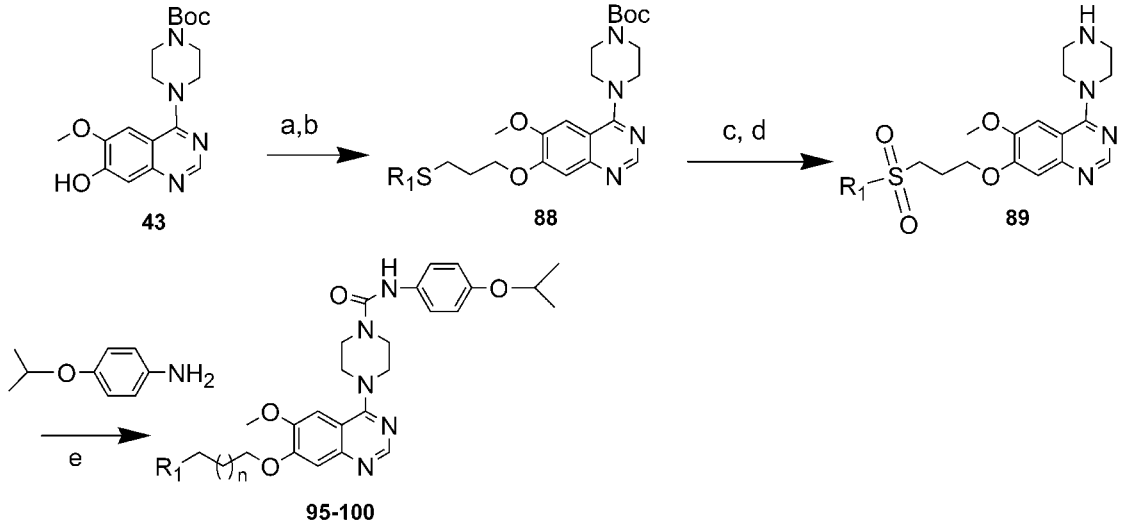
Boc-piperazine followed by debenzylation under hydrogenation conditions to afford intermediate **43**. The intermediate **43** was alkylated with 2-chloroethyl *p*-toluenesulfonate for C-2-linked analogues (Table 4) and with 3-chloropropyl *p*-toluenesulfonate for C-3-linked analogues to afford intermediates **44a**,**b**, respectively (Table 5). The chloroalkyl intermediates **44a**,**b** were condensed with various secondary amines. The final urea-linked analogues **45**−**55** and **60**−**87** were synthesized as described in earlier schemes. These analogues were also synthesized via an alternate route described in Scheme 6. Ethylvanillate was alkylated with 2-chloroethyl *p*-toluenesulfonate for C-2-linked analogues (Table 4) and with 1-bromo-3-chloropropane for C-3-linked analogues (Table 5) to afford intermediates **56a**,**b**, respectively (Scheme 6). The chloroalkyl intermediates were then condensed with various secondary amines, followed by nitration and subsequent reduction to provide intermediate aminoesters **57a**,**b**, respectively. Cyclization with formamide afforded the corresponding quinazolinones **58a**,**b**, which were subsequently chlorinated to give 4-Cl-quinazoline intermediates **59a**,**b**. The 4-chloro group was displaced in the presence of potassium carbonate in DMF with piperazine-1-carboxylic acid(4-cyanophenyl)amide or piperazine-1-carboxylic acid-(4-isopropoxyphenyl)amide to give analogues **45**−**55** and **60**−**87**.

The synthesis of 6-methoxy-7-alkyoxysulfone-substituted analogues (Table 6) is outlined in Scheme 7. The intermediate **43** was alkylated with 3-chloropropyl *p*-toluenesulfonate followed by displacement with various alkylthiolates to afford the thioether intermediate **88**. The thioether **88** was then oxidized with *m*-chloroperbenzoic acid to afford the respective sulfones, followed by deprotection and urea formation as described in earlier schemes.

Results and Discussion

Previous studies have identified a new class of potent and selective inhibitors of PDGFR phosphorylation containing the 4-[4-(N-substituted-carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline nucleus.[21] The quinazoline and pyrimidine nucleus appeared to us to be attractive for lead optimization as this template has been previously exploited to develop orally active EGFR tyrosine kinase inhibitors that are currently in clinical

Scheme 7[a]



[a] Reagents: (a) Chloropropyl tosylate, Cs_2CO_3, DMF, 80 °C, o/n. (b) R_1SH, NaH, or KHMDS, THF, room temperature. (c) *m*CPBA, DCM, room temperature. (d) 4 N HCl, dioxane. (e) DSC, Et_3N, DCM.

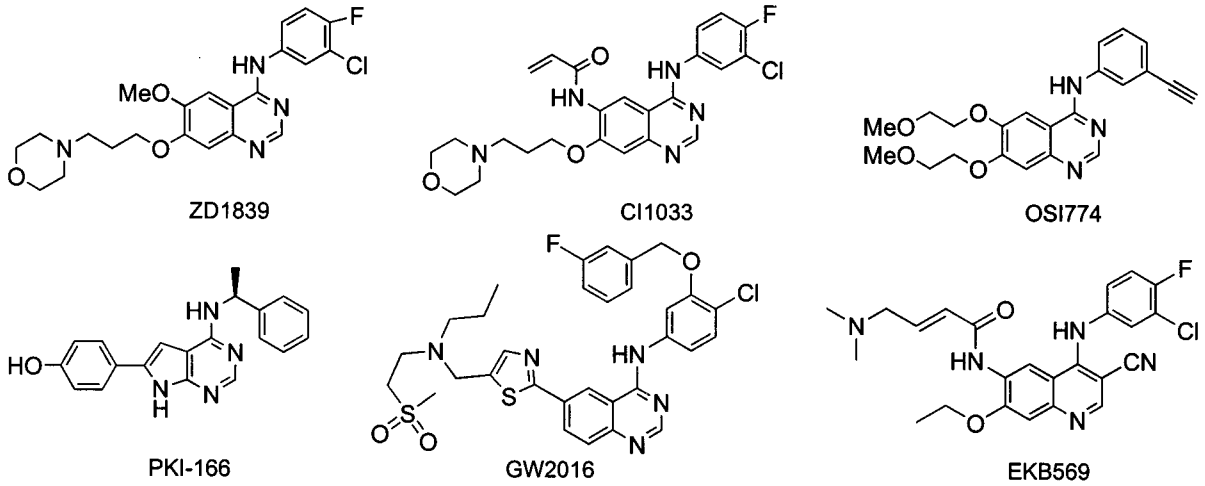


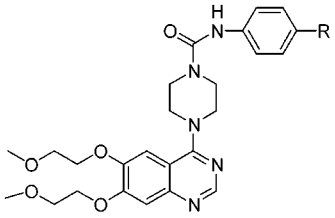
Figure 2. EGFR tyrosine kinase inhibitors in clinic.

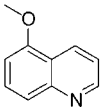
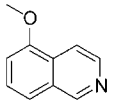
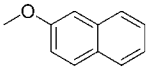
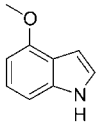
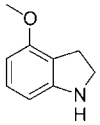
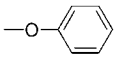
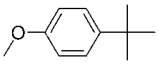
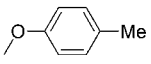
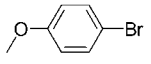
trials (Figure 2).[25−29] Despite the promising biological activity within this novel series of PDGFR inhibitors, the initial 6,7-dimethoxyquinazoline-4-piperazinyl urea series of analogues, in most cases, displayed poor aqueous solubility. We additionally found that many of these analogues were unstable in vitro in human liver microsomes (HLM) and their potency was diminished as much as 50-fold when their cellular activity was measured in the presence of human plasma.

In this paper, we report our efforts toward increasing RTK potency in plasma, achieving good kinase specificity, and achieving desirable pharmacokinetic properties including high oral bioavailability and long plasma half-life. We initiated the structure−activity relationship (SAR) exploration of the A-bicyclic ring, the C-urea linkage, and the D-ring to extensively characterize and optimize the properties of this series. All of the analogues synthesized were evaluated for their inhibition of βPDGFR phosphorylation using the known cell-based assay.[21,30] It should be pointed out from the start that the SAR obtained from such cell-based assays potentially report a combination of intrinsic activity of compounds against the kinase target modulated by the ability of compounds to permeate the cell wall during the assay. Because the ultimate goal of our study was to identify compounds that can effectively inhibit RTK activity intracellularly, the cell-based assay was believed sufficient to develop a robust SAR to guide drug candidate selection.

1. D-Ring Modifications. To improve the kinase inhibitory activity and aqueous solubility characteristics in the series, we initially utilized a strategy of incorporation of methoxyethoxy side chains at the 6,7-positions of the quinazoline nucleus. A similar strategy has previously provided improved physical properties of EGFR inhibitors.[31] As shown in Table 1, substitutions were simultaneously explored in the phenyl D-ring within the 6,7-dimethoxyethoxy quinazoline series. Our previous investigation of various substituents on the D-phenyl ring indicated that bulky hydrophobic substitution at the 4-position increased kinase inhibitory activity.[22] Similar to previous observations, the activity of 4-*tert*-butyl analogue (**3**) was significantly improved as compared with the 4-CN analogue (**4**) in this new series. The bulky 4-phenoxy derivative (**10**) also showed potent activity. Unfortunately, the stability of the 4-*tert*-butyl analogue (**3**) and the 4-phenoxy analogues (**10**) in HLM was not encouraging ($T_{1/2}$ < 10 min). Nevertheless, the high potency shown by bulky substituents at the 4-position of the phenyl group prompted us to

Table 1. Inhibitory Activity in β-PDGFR Phosphorylation Assay

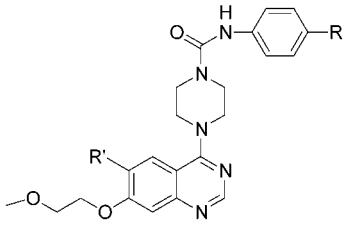


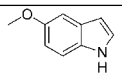
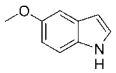
Compound	R	PDGFR Phosphorylation in MG63 cells IC_{50}(uM)[a]		$T_{1/2}$ (min) in HLM[b]
		No Plasma	W/Human plasma	
3	t-Bu	0.0014	0.08	10
4	CN	0.16	0.61	69
5		0.0016	0.50	12
6		0.0004	0.12	15
7		0.0004	0.15	20
8		0.001	0.032	10
9		0.020	0.420	9
10		0.01	0.183	6
11		0.012	0.634	8
12		0.0026	0.206	13
13		0.0024	0.190	20
14		0.050	0.300	86

[a] Autophosphorylation was measured in intact cells using two site ELISA as described elsewhere.[21,29] Assay conditions for PDGFR phosphorylation in the presence and absence of plasma are described in the Experimental Section. IC_{50} values are expressed as the average of at least three determinations. The average error for the determinations was ±15%. [b] HLM assay.

evaluate additional compounds in this series. The addition of small substituents on the 4-phenoxy ring analogue was found to be acceptable, such as *p*-methyl (**12**) and *p*-Br (**13**), since both substituents retained good

Table 2. Inhibitory Activity in β-PDGFR Phosphorylation Assay



Compound	R	R'	PDGFR Phosphorylation in MG63 cells IC_{50} (uM)[a]		$T_{1/2}$ (min) in HLM[b]
			No Plasma	W/Human plasma	
18		-OMe	0.009	0.167	25
19		-H	0.002	0.180	33
20		-OMe	0.040	0.525	35
21		-H	0.040	0.92	
22	-CN	-OMe	1.30	0.80	80
23	-CN	-H	1.25	3.56	
24		-OMe	0.420	0.216	110

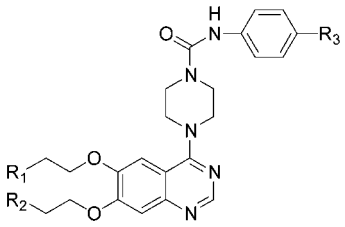
[a,b] See Table 1.

inhibitory activity. However, the *p-tert*-butyl analogue (**11**) showed a 6-fold reduced activity. Even more hydrophobic and bulky substituents such as 5-isoquinolyoxy (**6**), 2-naphthoxy (**7**), and 4-indolyoxy (**8**) retained good potency (IC_{50} < 150 nM). Within the 6,7-dimethoxyethoxy quinazoline series, the general observations were that hydrophobic bulky urea analogues showed absolute increases in potency in cell assays containing human plasma and increased aqueous solubility over the previous 6,7-dimethoxy series. However, there was still a considerable shift in the obtained IC_{50} values depending on whether the assays were run in the presence or absence of plasma (Table 1). This presumably can be attributed to the high plasma protein binding properties of the analogues since the compounds were found to be stable under the assay conditions (Table 1). This series of specific substitutions on the phenyl ring also resulted in derivatives with low stability in rat and HLM ($T_{1/2}$ = 6−20 min), most likely attributable to several sites of potential metabolism. Taking this in vitro data into account, it was not surprising to find that this series of analogues did not display desirable pharmacokinetic properties in the rat, where we were targeting the oral bioavailability of compounds to be greater than 20% and the plasma half-life to be >3 h (data not shown). Of interest in this series was the observation that the 4-CN (**4**) and 4-isopropoxy (**14**) substitutents in the D-ring afford the most metabolically stable analogues ($T_{1/2}$ = 70−90 min).

2. A-Ring Modifications. As shown in Table 2, we also investigated the 6-H,7-methoxyethoxy and 6-OMe,7-methoxyethoxy substitution pattern in the A-ring in order to potentially increase the stability in liver microsomes and attain optimal PK properties since preliminary studies suggested that demethylation within the 6,7-dimethoxy series was a potential liability. Unfortunately, the 6-H,7-methoxyethoxy analogue resulted in a 4.5-fold lower potency (**23** vs **22**). In the case of bulky hydrophobic substituents in the D-ring, the 6-H and 6-methoxy analogues were shown to have similar potency in the phosphorylation assay (**18** vs **19** and **20** vs **21**). The corresponding human liver microsomal half-life of 6-H,7-substituted series of compounds was found to be 25−33 min, which was modestly longer than the 6,7-dimethoxyethoxy series. The 4-cyano analogue **22** and the 4-isopropoxy analogue **24** again displayed greater stability in HLM ($T_{1/2}$ = 80−110 min).

In efforts to improve the aqueous solubility in this series, we also investigated the addition of basic solubilizing functionality at either the C-6 or C-7 side chains of the quinazoline ring system since there have been several reports in the kinase inhibitor literature wherein the addition of a 3-morpholinoalkoxy group at either C-6 or C-7 of various 4-anilinoquinazolines results in not only improved aqueous solubility but also improved cellular activity.[32−34] In our series, various basic groups were introduced into the alkoxy side chains, a versatile way to modify physical properties over a wide range of basicity and lipophilicity. The basic amine side chains were appended to either the C-6 or the C-7 of the methoxyethoxy series (Table 3). Because of early observations that 4-CN and 4-isopropoxy D-ring substitution

Table 3. In Vitro Activity for 6,7-Disubstituted Analogues



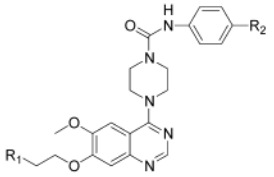
Compound	R_1	R_2	R_3	PDGFR Phosphorylation in MG63 cells IC50 (uM)[a]		$T_{1/2}$ (min) in HLM[b]
				No Plasma	W/Human plasma	
29		-OMe	-CN	1.10	0.582	
30		-OMe		5.0	2.67	
31		-OMe	-CN	0.501	0.335	82
32		-OMe		0.198	0.110	106
37	-OMe		-CN	0.079	0.090	8
38	-OMe			0.099	0.090	36
39	-OMe		-CN	0.168	0.200	70
40	-OMe			0.145	0.175	525

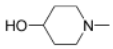
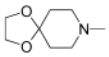
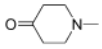
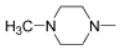
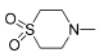
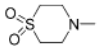
[a,b] See Table 1.

afforded analogues with greatly improved liver microsome stability (analogues **4**, **14**, **22**, and **24**), these D-ring substitutions were kept constant. The morpholine-containing analogues (**29** and **30**) at the C-6 position resulted in equal or lower potency in the phosphorylation assay as compared to **4** and **14**, respectively. The piperidine-substituted analogues (**31** and **32**) at the C-6 side chain significantly improved the potency in comparison to the morpholine analogues (**29** and **30**). The piperidine-containing analogue with the isopropoxy group in the D-ring was 20-fold more potent than the morpholine-containing analogue (**32** vs **30**). Placing the piperidine-containing side chain at the C-7 alkoxy side chain resulted in enhancement of potency by at least 4-fold (**37** vs **31**). The piperidine-containing side chain placed at either the 6- or the 7-position in the D-ring isopropoxy series resulted in similar potent analogues (**38** vs **32**). Because the morpholine-containing side chains in the 6-substituted analogues resulted in decreased potency, we did not synthesize the corresponding analogues with morpholine-containing C-7 side chain in the 6,7-disubstituted series. In this series, the isopropoxy D-ring substitution afforded analogues with greatly improved liver microsome stability (analogues **31**, **32**, and **40**).

In another series, various C-7 basic groups with a fixed ethylene unit were examined with a constant 6-methoxy group and 4-cyanophenyl urea moieties (Table 4). The morpholine-containing analogue in this series resulted in nearly equivalent potency in the plasma-containing cellular assay (**45** vs **22**), whereas the piperidine-containing analogue resulted in a 7-fold increase in potency (**46** vs **22**). The 4-hydroxypiperidine-containing analogue resulted in 33-fold lower potency as compared to the piperidine-containing analogue (**47** vs **46**). The 4-piperidone-containing analogue (**49**) had similar potency as the methoxyethoxy analogue (**22**) and was found to be 6-fold less potent than the piperidine-containing analogue **46**. The pyrrolidine-containing analogue (**53**) was found to be more potent than methoxy analogue **22** but was 3-fold less potent than the corresponding piperidine analogue (**46**). Substitution of the side chain with less basic aromatic amines such as pyrrole and imidazole resulted in 4−9-fold lower potency (**54** and **55** vs **22**). The substitution with piperazine resulted in 12-fold lower potency (**50** vs **22**). Other basic groups studied were found to be detrimental to the activity in this series or not as potent as the piperidine-containing analogues. We also examined the same basic side chains at C-7 in analogues containing a 4-isopro-

Table 4. In Vitro Activity for the C-2-Linked Basic Unit at the C-7 Position



Compound	R_1	R_2	PDGFR Phosphorylation in MG63 cells IC_{50}(uM)[a]		$T_{1/2}$ (min) in HLM[b]
			No Plasma	W/Plasma	
22	-OMe	-CN	1.30	0.800	80
45		-CN	1.41	1.26	
46		-CN	0.424	0.097	40
47		-CN	6.15	3.23	
48		-CN	0.336	0.222	40
49		-CN	1.37	0.601	4
50		-CN	6.50	7.79	
51		-CN	0.750	0.662	88
52		-CN	0.450	0.305	1
53		-CN	0.150	0.206	182
54		-CN	8.18	5.17	
55		-CN	0.715	2.49	
24	OMe		0.420	0.215	110
60			0.198	0.177	53
61			1.25	0.170	85
62			0.335	0.380	>400
63			0.526	0.520	58
64		-CN	2.24	4.69	19
65		-CN	1.20	2.21	
66		-CN	2.13	2.97	
67			0.494	0.680	
68			0.507	1.43	
69			0.216	0.350	119

[a,b] Same as Table 1.

poxyphenylurea D-region. The SAR was found to be subtly different than the 4-cyanophenylurea series. In this series, the piperidine and morpholine-containing analogues are of similar potency (**60** vs **61**). The substitution with the less basic triazole moiety resulted in 3−5-fold lower potency. The substitution with 1-tetrazole (**68**) resulted in 10-fold lower potency, whereas 2-fold lower potency was observed with the 2-tetrazole substitution (**69**). The basic and/or heteroaromatic substituents such as imidazole, pyrrole, triazole, and tetrazole in the C-7 alkoxy side chain resulted in decreases in potency to various degrees (**54**, **55**, **62**−**65**, and **68**). These results are distinct from the observations for a different class of quinazoline VEGFR inhibitors where the heteroaromatic substituents such as imidazole and triazole at the C-7 alkoxy side chain led to very potent submicromolar kinase inhibitors and afforded high plasma levels in mice after oral administration.[34]

Three Carbon-Linked Basic Functionality at C-7. To optimize the potency of this class of compounds further, we explored the methylene unit extension of the C-7 alkoxy side chain (Table 5). The 7-morpholinopropoxy analogue resulted in 10-fold increased potency as compared to the 7-morpholinoethoxy analogue (**71** vs **45**). A similar improvement in kinase inhibitory activity has been reported in a series of anilinoquinazoline VEGF RTK inhibitors where 7-propoxy linkers were found to be more potent than ethoxy or butoxy linkers.[34] The piperidinepropoxy analogue shows a 3-fold increase in potency (**75** vs **61**). In the propoxy series, we also found a lower potency of analogues with aromatic basic functionality in the C-7 position (**73**, **74**, **78**, and **79**). The 4-isopropoxyphenylurea-containing D-ring analogues are in general 3−8-fold more potent than the corresponding 4-cyanophenylurea-containing D-ring analogues. The potency of the analogues in this series was not appreciably affected by the presence of plasma, suggesting that these analogues may have significantly lower plasma protein binding. For example, the IC_{50} values of **75** in MG63 cells are 26 and 36 nM in the absence and in the presence of plasma, respectively. As it is well-documented in the literature, the oral absorption of drugs is often greatly effected by the basicity of the molecule. The predicted pK_a of the basic units in the propoxy-containing side chain is approximately two units higher than the ethoxy-containing side chain analogues. Therefore, to reduce the basicity of the piperidine ring, 3- and 4-difluoropiperidine rings were also explored as the basic side chain units in order to modulate their basicity. The fluoropiperidine-containing analogues (**80**−**82**) were found to retain potency (IC_{50} < 150 nM), but their in vitro liver microsomal stability was surprisingly short ($T_{1/2}$ < 10 min). Interestingly, when we replaced the basic piperidine functionality by a cyclohexyl ring wherein the basic charge has been removed, a very weakly active analogue (**83**) was obtained. This observation strongly suggests that the basic C-7 side chain has requisite interactions with the kinase. The substitution with 4-methylpiperidine (**84** and **85**) and 2-methylpiperidine (**86** and **87**) in the C-7 side chain also results in highly potent analogues (IC_{50} value < 50 nM, Table 5). The 2- and 4-methylpiperidine-containing analogues were also found to be reasonably stable in vitro in HLM ($T_{1/2}$ = 30−106 min). The βPDGFR phosphorylation assay shows that many of the compounds reported in this series are very potent inhibitors (Table 5, IC_{50} < 200 nM).

Additional analogues with other hydrophilic substituents such as hydroxyl, amidine, imidazoline, and proline carboxylic acid substitutions in the C-7 side chain were also prepared and resulted in weakly active analogues, suggesting that introduction of hydrophilic substituents other than tertiary amines is unfavorable at this position (Table 6).

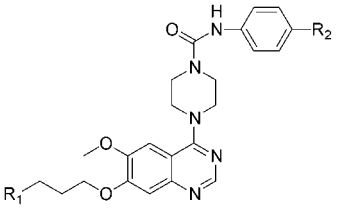
To obtain potent, stable analogues that did not rely on using a basic functionality in the C-7 side chain, various sulfones were also explored as polar, nonbasic C-7 propoxy side chains. The analogues displayed potency in the following order: *iso*-butyl sulfone > *iso*-pentyl = *n*-butyl = *n*-propyl > Et > Me (Table 7). Unfortunately, the sulfone analogues did not approach the potency of the most active amine-containing analogues and did not have the desired in vivo pharmacokinetic properties (F% < 10%, $T_{1/2}$ < 2 h).

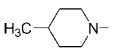
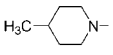
C-Linkage Modifications. In addition to A-ring and D-ring modifications, we also examined the replacement of the urea linkage by the isosteric thiourea unit as has been previously reported.[21] These analogues showed good inhibitory activity for βPDGFR phosphorylation. Most of the benzylthiourea and arylthiourea analogues are highly specific inhibitors of βPDGFR and c-Kit kinases, whereas 30−300-fold higher concentrations were required for these analogues to inhibit Flt-3 and CSF-1R and will be the subject of a separate publication.

In Vitro Characterization for Kinase Selectivity. Some of the more potent compounds prepared were also evaluated for inhibitory activity on related PDGFR kinase family members including c-Kit, Flt-3, and CSF-1R tyrosine kinases using previously reported methods.[21,30] As shown in Table 8, these compounds inhibited Flt-3, βPDGFR, and c-Kit receptor autophosphorylation with IC_{50} values of 50−200 nM and were 15−30-fold less potent against CSF-1R. As shown in Table 8, the IC_{50} value of **75** on PDGFR phosphorylation measured in Chinese hamster ovary (CHO) cells is 200 nM, as compared to that of 26 nM in MG63 cells (Table 5). The difference may in part be due to a 5−10-fold higher level of PDGFR in CHO transfectants than in MG63 cells. To our surprise and gratification, we found that the cyano-substituted D-ring analogues **84** and **86** with 2- and 4-methylpiperidine substitution at the C-7 position inhibited βPDGFR and c-Kit with IC_{50} values of <150 nM, whereas 30−60-fold higher concentration was required to inhibit Flt-3 kinase. By contrast, the 2- and 4-methylpiperidine analogues **85** and **87** with an isopropoxy D-ring inhibited βPDGFR, c-kit, and Flt-3 receptor autophosphorylation with IC_{50} values of 20−200 nM. These observations with kinase specificity suggest that specific substitution in the D-ring has important enzyme interactions that may be influenced by the electronics of this ring. The presence of basic side chains at the C-7 position leads to improved inhibitory activity, good aqueous solubility, improved bioavailability in all species studied, and reduced protein binding.

The kinase specificity profiles of **84** and **86** demonstrate that they are highly specific βPDGFR inhibitors and have similar profiles to STI571 (Gleevec), which inhibits βPDGFR and c-Kit but not Flt-3 or CSF-1R.[35]

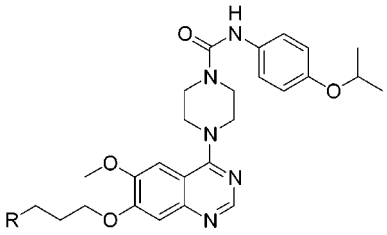
Table 5. In Vitro Activity for the C-3-Linked Basic Unit at the C-7 Position



Compound	R_1	R_2	Phosphorylation in MG63 cells IC_{50}(uM)[a] No Plasma	Phosphorylation in MG63 cells IC_{50}(uM)[a] W/Plasma	$T_{1/2}$ (min) in HLM[b]
70		-CN	0.053	0.06	112
71		-CN	0.145	0.140	14
72		-CN	0.178	0.210	>400
73		-CN	2.81	5.92	
74		-CN	0.943	1.66	
75			0.026	0.036	285
76			0.020	0.060	25
77			0.077	0.100	>400
78			1.45	0.720	>400
79			0.800	0.400	>400
80		-CN	0.110	0.165	6
81			0.040	0.090	9
82			0.029	0.150	4
83			0.813	19.46	31
84		-CN	<0.004	0.022	74
85			<0.004	0.051	106
86		-CN	<0.004	0.029	28
87			<0.004	0.035	102

[a,b] See Table 1.

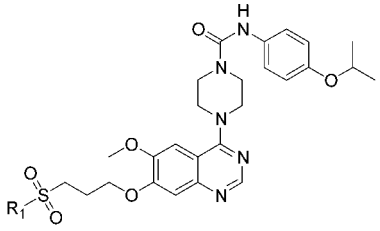
Table 6. In Vitro Activity for 7-Hydrophilic-Substituted Analogues



Compound	R_1	IC_{50}(uM)[a]		$T_{1/2}$ (min)
		W/O Plasma	W/Plasma	in HLM[b]
90		12.25	6.75	
91		0.871	9.10	
92		0.076	0.123	>300
93	—NH_2	3.11	15.42	
94	—OH	5.59	13.97	

[a,b] See Table 1.

Table 7. In Vitro Activity for 7-Substituted Sulfone Analogues



Compound	R_1	IC_{50}(uM)[a]		$T_{1/2}$ (min)
		W/O Plasma	W/Plasma	in HLM[b]
95		0.409	0.530	199
96		0.036	0.121	33
97		0.087	0.265	>300
98		0.112	0.292	59
99		0.050	0.240	31
100	F_3C 	0.564	1.23	

[a,b] See Table 1.

The analogues **23**, **61**, **75** (CT53518), **76**, and **85** were selected for further in vitro and in vivo characterization because of their potent inhibition of Flt-3, their βPDGFR inhibition, and their stability in HLM. Other RTKs, cytoplasmic tyrosine kinases, serine/threonine kinases, or other members of the MAPK pathways were not found to be significantly inhibited at 100−1000-fold higher concentrations of **75** and **76** (Table 9). Analogues **75** (CT53518) and **76** were also found to inhibit autophosphorylation of a constitutively activated Flt3/ITD mutant expressed in hematopoietic cells or AML cell lines with an IC_{50} value of 30−100 nM (data not shown).

Table 8. Specificity Analysis of the Potent Analogues

compd	βPDGFR IC_{50} (μM)[a]	c-Kit IC_{50} (μM)[a]	Flt-3 IC_{50} (μM)[a]	CSF-1R IC_{50} (μM)[a]
24	0.20	0.19	0.45	5.46
61	0.25	0.11	0.07	3.43
75 (CT53518)	0.20	0.17	0.22	3.43
76	0.10	0.06	0.04	1.40
84	0.073	0.004	1.91	
85	0.039	0.021	0.128	
86	0.150	0.006	8.79	
87	0.074	0.016	0.200	
STI571	0.24	0.26	>30	0.96

[a] CHO cell lines expressing wild-type βPDGFR or βPDGFR/c-Kit, βPDGFR/Flt-3, and βPDGFR/CSF-1R chimeric receptors were grown to confluency in 96 well microtiter plates under standard tissue culture conditions. Phosphorylation assays were performed as described for βPDGFR phosphorylation assay in MG63 cells.

In Vivo Characterization. Several of the more potent and metabolically stable analogues (IC_{50} < 300 nM, $T_{1/2}$ (HLM) > 40 min) were also evaluated in vivo. Pharmacokinetic properties of these compounds were obtained from studies in rats, dogs, and monkeys following intravenous and oral administration (Figures 3 and 4 and Table 10). The oral bioavailability of analogues **23**, **61**, **75**, **76**, and **85** following oral dosing ranged from 19 to 100% depending upon the species evaluated. At the oral doses examined, plasma levels

Table 9. IC_{50} Values of **75** and **76** on Various Kinases

	75 (CT53518)	76	staurosporin
	I. RTKs		
KDR	>30	>30	0.08 μM
EFGR	>30	>30	ND
FGFR	>30	>30	0.42
InsR	>30	ND	<0.3
	II. Non-RTKs		
Src	30	>30	0.07
Abl	>30	>30	0.10
	III. Ser/Thr Kinases		
PKC, PKA	>30	ND	0.08
	IV. MAP and MAPK Kinases		
Mek1, Mkk4, Mkk6, Erk2, p38	>30	>30	<1

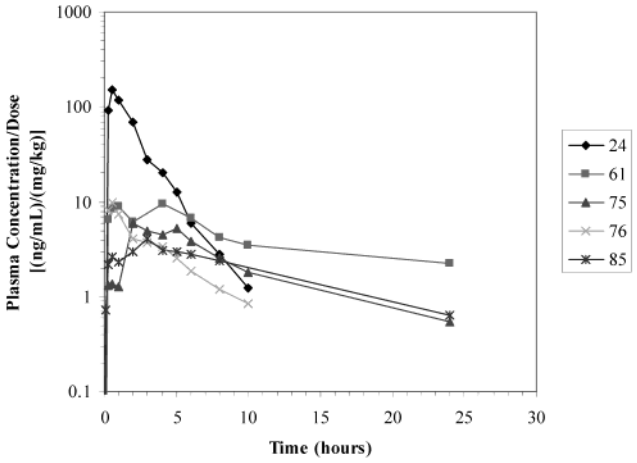


Figure 3. Semilogarithmic plots of dose-normalized plasma concentration−time profiles of selected analogues following oral administration to Lewis rats.

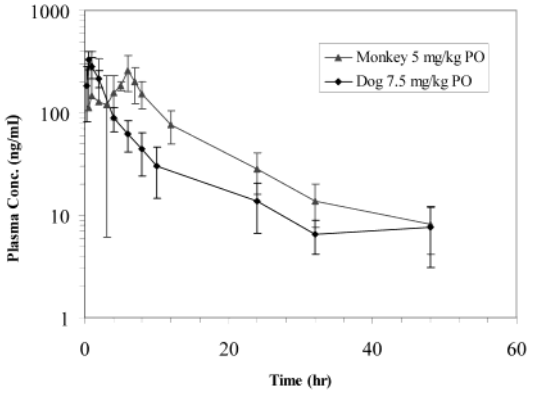


Figure 4. Semilogarithmic plots of mean (±SD) plasma concentration−time profiles of **75** (CT53518) following an oral administration to Cynomolgus monkeys (5 mg/kg) and Beagle dogs (7.5 mg/kg).

of these compounds were maintained well above their IC_{50} values. Maximum plasma concentrations obtained for **23**, **61**, **75**, **76**, and **85** were 762, 414, 256, 49.2, and 82.3 ng/mL, respectively. Apparent terminal half-lives for **61**, **75** (CT53518), and **85** were relatively long (>7 h). Analogue **75** displayed a consistently long half-life in rats, dogs, and monkeys ($T_{1/2}$ > 10 h) and good oral bioavailability (>50%). It also maintained plasma concentrations above its IC_{50} value for 24 h (Figure 4).

On the basis of these data, we chose to demonstrate the in vivo efficacy of **75**, and we have tested it in two

Table 10. Pharmacokinetic Data for Selected Analogues

	24	**61**	**75** (CT53518)	**76**	**85**
		Rat			
dose iv/po (mg/kg)	1.5/5	1/30	10/30	1.5/5	2/20
F (%)	72.1	125	23.8	20.8	24.6
$T_{1/2}$ (h)	1.38	8.32	10.6	2.76	11.2
C_{max} (ng/mL)	762	414	256	49.2	82.3
AUC_{PO} (ng·h/mL)	1580	4412	1700	176	1150
		Dog			
dose iv/po (mg/kg)	0.5/5	0.5/5	2/7.5	0.5/5	2/5
F (%)	73.6	13.5	97.6	63.3	65.1
$T_{1/2}$ (h)	1.36	14.3	14.3	7.16	7.64
C_{max} (ng/mL)	1498	43.0	481	183	113
AUC_{PO} (ng·h/mL)	4250	387	2690	1390	696
		Monkey			
dose iv/po (mg/kg)	0.5/5	0.5/10	0.5/5	0.5/5	1/25
F (%)	26.6	38.8	48.9	18.9	40
$T_{1/2}$ (h)	0.70	6.30	16.6	2.60	14.7
C_{max} (ng/mL)	636	386	317	135	703.2
AUC_{PO} (ng·h/mL)	1250	3080	2920	663	16100
in vitro $T_{1/2}$ (min) in human liver microsomes	110	85	285	25	106

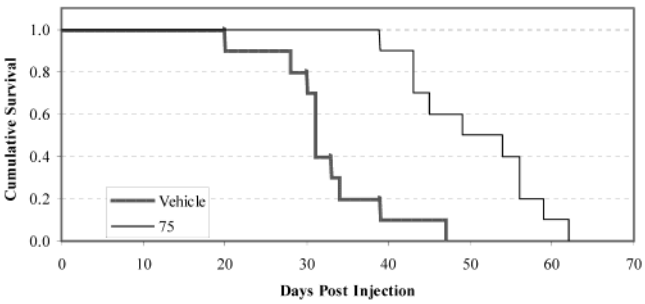


Figure 5. Improved survival in mouse CMML model with oral administration of **75** (CT53518).

different mouse leukemia models by oral dosing. One is a nude mouse CMML model using Baf3 cells expressing Tel/βPDGFR chimera, which had been found in a subset of CMML patients and can confer IL-3-independent cell proliferation in vitro.[36] As shown in Figure 5, injection of 1×10^6 cells into nude mice caused all animals to die within 20−46 days. Oral gavage of **75** (CT53518) at 60 mg/kg, twice daily, from day 7 to day 42 significantly delayed mice death with a $p < 0.0005$. The treated animals did not begin to die until day 40. However, additional deaths occurred in the treated group as late as day 60. These studies provide a "proof of principle" that oral treatment with analogue **75** (CT53518) can provide an effective treatment for CMML-like disease in animals.

Up to 30% of AML patients harbor an ITD within the juxtamembrane domain of the Flt-3 RTK causing constitutive receptor activation. Because **75** and **76** are potent inhibitors of Flt-3, we also analyzed their efficacy in a Flt-3/ITD-mediated leukemia mouse model. We found that oral administration of **75** (CT53518) and **76** significantly delayed disease progression and promoted mice survival in a dose-dependent manner.[37]

Conclusions

Kinase inhibition represents a novel mechanism-based approach to selectively block signaling pathways that are known to mediate disease processes. The highly successful clinical trials employing Gleevec for the treatment of CML have validated kinase inhibition as

a therapeutic strategy in oncology.[38,39] Our synthetic efforts have focused on preparing PDGFR family specific kinase antagonists from an initial series of 4-piperazinyl quinazolines. Our goals were to enhance the intrinsic potency of this series in human plasma, retain the appropriate kinase specificity of analogues, and achieve desirable pharmacokinetic properties including oral bioavailability and long plasma half-life. Novel piperazinylquinazolines possessing 4-phenylurea substituents, a C-6 methoxy, and a wide range of basic C-7 substituents were found to be nanomolar inhibitors of PDGF RTK enzymes. Through this SAR study and compound optimization, we have identified a specific, potent, orally active piperazinylquinazoline class of inhibitors directed against selected members of the PDGFR family. These analogues are equivalent in potency for βPDGFR, c-Kit, and Flt-3. Analogues **84** and **86** are highly specific for βPDGFR and c-Kit, whereas 30−60-fold higher concentrations were required for these analogues to inhibit Flt-3 kinase. Analogues **75** (CT53518) and **85** have desirable pharmacokinetic properties in the animal species studied ($F\% > 50\%$, $T_{1/2} > 8$ h). The oral administration of **75** (CT53518) at 60 mg/kg showed significant delay in murine death in the nude mouse model of CMML. Oral administration of **75** (CT53518) and **76** significantly delayed disease progression and promoted survival in a dose-dependent manner in a Flt-3/ITD-mediated leukemia mouse model. On the basis of the in vitro activity of **75** (CT53518), its microsomal stability, oral bioavailability, and half-life in vivo, we have chosen it as a development candidate for clinical study. Our data support the development of the small molecule RTK inhibitor such as **75** (CT53518), initially as a potential treatment of AML due to its inhibition of Flt-3/ITD mutants. This strategy may be extended to the treatment of other diseases that are mediated by the PDGFR family of RTKs.

Experimental Section

^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity +400 spectrometer unless otherwise noted. Low-resolution mass spectra were recorded with a HP 1100-MSD LC-MS spectrometer. High-resolution mass spectra (HRMS) were recorded with a VG ZAB2-EQ high-resolution mass spectrometer and performed at the University of California, Berkeley. Normal phase silica gel (EM Science, Silica Gel 60) was used for chromatography. Final compounds were purified by reversed phase high-performance liquid chromatography (HPLC) using a Waters 4000Prep, Waters 490E multiwavelength detector, and Vydac 218TP1022 column (10 μm, C_{18}, 22 mm × 250 mm). Purity of the compounds was confirmed by two diverse HPLC systems using Waters 600 controller, Waters 996 photodiode array detector, and Vydac 201HS54 column (5 μm, C_{18}, 4.6 mm × 250 mm). Analytical HPLC run using 214 nm for detection. HPLC no. 1-Gradient method using a Keystone Beta Basic column (C18, 4.6 mm × 50 mm) or HPLC no. 2-Isocratic method using Keystone Beta Basic column (C18, 4.6 mm × 250 mm). K' is the percentage of CH_3CN employed in the H_2O mixture with 0.1% trifluoroacetic acid (TFA). The new compounds synthesized were characterized by mass spectrometry (MS) and NMR, and purity was determined by HRMS and two HPLC systems. We did not obtain melting points and elemental analyses of these compounds as most of the derivatives were amorphous and only small amounts were synthesized.

The typical synthetic methods for urea formation are described as follows.

Method A. A mixture of **2** (1 mmol) and 4-cyanophenylisocyanate (2 mmol) in DMF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into water, and then, saturated sodium chloride solution (100 mL) was added. The aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was dried (Na_2SO_4), filtered, and evaporated to yield the title compound as a crude residue. This was purified by reversed-phase (RP)-HPLC to afford the title compound **4** as an off-white solid (0.112 g, 40%).

Method B. To the tetrahydrofuran (THF)/DCM (1:1.5 mL) solution of 4-(1*H*-indol-4yloxy)phenylamine (2 mmol) was added slowly a DCM solution of *N*,*N*′-disuccinimidyl carbonate (2.1 mmol) and triethylamine. The reaction mixture was stirred at room temperature for 30 min. To this was added rapidly a dichloromethane solution (5 mL) of **2** (2 mmol) and triethylamine (2 mmol), and this reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by RP-HPLC to afford title compound **8**.

Method C. To a solution of triphosgene (0.45 mmol) in acetonitrile (3 mL) at −5 °C was added a acetonitrile (5 mL) solution of 4-(quinolin-5-yloxy)phenylamine (1.35 mmol) and triethylamine (2.25 mmol) over a period of 15 min. The mixture was stirred for an additional 30 min and then was slowly treated with a acetonitrile (5 mL) solution of **2** (1.35 mmol) and triethylamine (2.25 mmol). The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give crude residue. The crude residue was purified by RP-HPLC to afford **5**.

Method D. To a solution of 4-*tert*-butylamine (0.680 mL, 1.5 mmol) in NMP (10 mL) were added 4-nitrophenyl chloroformate (0.44 g, 2.2 mmol) and triethylamine (1.50 mL, 10.95 mmol) under cooling with ice bath. After the reaction mixture was stirred for 2 h, **2** (0.30 g, 1.1 mmol) was added and heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature and then poured into water, extracted with ethyl acetate, and dried over sodium sulfate. The residue after evaporation of solvent was purified by RP-HPLC to give compound **3** (490 mg, 83%).

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-*tert*-Butylphenyl)amide (3). Compound **3** was synthesized using method D as a yellow fluffy solid (0.075 g, 70%). ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.20 (s, 2H), 4.26 (t, 2H, $CH_3OCH_2CH_2O$), 4.22 (t, 2H, $CH_3OCH_2CH_2O$), 3.83 (t, 4H), 3.59 (t, 4H), 3.45 (s, 6H), 3.06 (t, 4H). MS (ES): 538 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 538.3029; found, 538.3015.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (4). Yield 60% using method A. ^{1}H NMR (CD_3OD): δ 8.5 (s, 1H), 7.5 (m, 5H), 7.10 (s, 1H), 4.3 (m, 8H), 3.8 (m, 8H), 3.34 (s, 6H). MS (ES): 507 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 507.2355; found, 507.2351.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(Quinolin-5-yloxy)phenyl]amide (5). (a) 4-(Quinolin-5-yloxy)phenylamine. To a dimethyl sulfoxide (DMSO, 7 mL) solution of 5-hydroxyquinoline (0.519 g, 3.58 mmol) under argon at room temperature was added NaH (0.184 g, 4.61 mmol), and the resultant yellow solution was stirred for 1 h at ambient temperature. 1-Fluoro-4-nitrobenzene (0.50 g, 3.54 mmol) was slowly added to the reaction and was heated at 90 °C under argon for 8 h. No starting material was detected by thin-layer chromatography (TLC) and RP-HPLC. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$), filtered, and evaporated to afford crude residue. The crude residue was purified by silica gel chromatography eluting with 50%EtOAc/Hexane/2%MeOH to afford 5-(4-nitrophenoxy)quinoline as a yellow solid (689 mg, 80%). MS (ES): 267 $(M + H)^+$. The nitro compound (0.67 g, 2.52 mmol) was dissolved in EtOH (5 mL) and EtOAc (5 mL). To this solution was added 10% Pd/C (100 mg), and it was hydrogenated under 1 atm for 2.5 h. This mixture was filtered through Celite, and the filtrate was concentrated to afford the desired

4-(quinolin-5-yloxy)phenylamine as a yellow solid (580 mg, 98.3%). ^{1}H NMR (CD_3OD): δ 8.87−8.81 (m, 1H), 7.75 (d, 1H, J = 8.4 Hz), 7.68−7.48 (m, 3H), 6.92−6.85 (m, 2H), 6.82−6.70 (m, 3H). MS (ES): 625 $(M + H)^+$.

(b) Compound 5. Yield 40% using method C. ^{1}H NMR (CD_3OD): δ 9.41 (d, 1H, J = 8.4 Hz), 9.19 (d, 1H, J = 4.8 Hz), 8.64 (s, 1H), 8.02 (dd, 1H, J = 5, 8.6 Hz), 7.96 (t, 1H, J = 8.2 Hz), 7.85 (d, 1H, J = 8.4 Hz), 7.61 (s, 1H), 7.55 (d, 2H, J = 8.4 Hz), 7.23 (s, 1H), 7.18 (d, 2H, J = 8.8 Hz), 7.10 (d, 1H, J = 7.6 Hz), 4.40−4.36 (m, 8H), 3.88−3.82 (m, 8H), 3.45 (s, 6H). MS (ES): 625 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 625.2774; found, 625.2770.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(Isoquinolin-5-yloxy)phenyl]amide (6). Yield 40% using method C and 4-(isoquinolin-5-yloxy)-phenylamine for the urea formation. ^{1}H NMR (CD_3OD): δ 9.81 (s, 1H), 8.79 (d, 1H, J = 6.6 Hz), 8.62 (s, 1H), 8.61 (d, 1H, J = 6.6 Hz), 8.17 (d, 1H, J = 8.4 Hz), 7.90 (t, 1H, J = 8.0 Hz), 7.85, 7.59 (s, 1H), 7.53 (d, 2H, J = 8.8 Hz), 7.23 (s, 1H), 7.44 (d, 1H, J = 8.0 Hz), 7.30 (s, 1H), 7.15 (d, 2H, J = 8.8 Hz), 4.38−4.32 (m, 8H), 3.87−3.80 (m, 8H), 3.45 (s, 6H). MS (ES): 625.3 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 625.27804; found, 625.2776.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(Naphthalen-2-yloxy)phenyl]amide (7). Compound **7** was synthesized as a white solid (30 mg, 65%) using method C and 4-(naphthalen-2-yloxy)phenylamine instead of 4-(quinolin-5-yloxy)phenylamine. ^{1}H NMR (CD_3OD): δ 8.58 (s, 1H), 7.81−7.75 (m, 2H), 7.63−7.61 (d, 1H, J = 8 Hz), 7.55−7.53 (d, 1H, J = 8 Hz), 7.38−7.32 (m, 4H), 7.18−7.16 (m, 3H), 6.98−6.96 (d, 2H, J = 8 Hz), 4.38−4.31 (m, 8H), 3.85−3.79 (m, 8H), 3.40 (s, 6H). MS (ES): 624.3 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 624.2831; found, 624.2826.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(1*H*-Indol-4-yloxy)phenyl]amide (8). Compound **8** was synthesized as a white solid (25 mg, 30%) using method C employing 4-(1*H*-indol-4-yloxy)phenylamine instead of 4-(quinolin-5-yloxy)phenylamine. ^{1}H NMR (CD_3OD): δ 8.54 (s, 1H), 7.51 (s, 1H), 7.23−7.21 (d, 2H, J = 8 Hz), 7.13 (s, 1H), 7.10−7.08 (d, 1H, J = 8 Hz), 7.06−7.05 (d, 1H, J = 4 Hz), 6.96−6.92 (t, 1H, J = 8 Hz), 6.85−6.83 (d, 2H, J = 8 Hz), 6.46−6.44 (d, 1H, J = 8 Hz), 6.187−6.181 (d, 1H, J = 2.4 Hz), 4.29−4.25 (m, 8H), 3.78−3.73 (m, 8H), 3.37 (s, 6H). MS (ES): 613.3 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 613.2774; found, 613.2779.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(2,3-Dihydro-1*H*-indol-4-yloxy)phenyl]amide (9). Compound **9** was synthesized using method B as a creamy solid (0.050 g, 51%). ^{1}H NMR (CD_3OD): δ 8.54 (s, 1H), 7.52 (s, 1H), 7.37−7.35 (dd, 2H, J = 2, 6.5 Hz), 7.32 (t, 1H, J = 8 Hz), 7.16 (s, 1H), 7.14 (t, 1H, J = 8 Hz), 6.93−6.90 (dd, 2H, J = 2, 6.5 Hz), 6.84−6.82 (d, 1H, J = 1, 8 Hz), 4.28−4.27 (m, 8H), 3.77−3.76 (m, 10H), 3.56 (m, 2H), 3.36 (s, 6H). MS (ES): 615 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 615.2931; found, 615.2930.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Phenoxyphenyl)amide (10). Compound **10** was synthesized as a shiny white solid (132 mg, 88%) using method C employing 4-phenoxyaniline. ^{1}H NMR (CD_3OD): δ 8.61 (s, 1H), 7.58 (s, 1H), 7.35 (d, 2H, J = 8.8 Hz), 7.29 (t, 2H, J = 7.8 Hz), 7.21 (s, 1H), 7.04 (t, 1H, J = 7.2 Hz), 6.92 (d, 2H, J = 7.6 Hz), 6.91 (d, 2H, J = 8.8 Hz), 4.38−4.30 (m, 8H), 3.81−3.78 (m, 8H), 3.43 (s, 6H). MS (ES): 593 $(M + Na)^+$, 574 $(M + H)^+$.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(4-*tert*-Butylphenoxy)phenyl]amide (11). Compound **11** was synthesized as a light yellow solid (34 mg, 80%) using method C. ^{1}H NMR (CD_3OD): δ 8.55 (s, 1H), 7.52 (s, 1H), 7.29−7.25 (m, 4H), 7.15 (s, 1H), 6.84−6.79 (m, 4H), 4.38−4.27 (m, 8H), 3.79−3.73 (m, 8H), 3.37 (s, 6H). MS (ES): 630.3 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 630.3291; found, 630.3289.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-*p*-Tolyloxyphenyl)amide (12). Compound **12** was synthesized as a shiny white solid (50 mg, 28%) using method C and employing 4-(*p*-tolyloxy)phenylamine, which was synthesized by the same method as described for compound **5**. ^{1}H NMR (CD_3OD): δ 8.53 (s, 1H), 7.49 (s, 1H), 7.25−7.23 (d, 2H, J = 8 Hz), 7.15 (s, 1H), 7.04−7.02 (d, 2H, J = 8 Hz), 6.80−6.78 (d, 2H), 6.75−6.73 (d, 2H, J = 8 Hz), 4.26 (m, 8H), 3.76−3.74 (m, 8H), 3.35 (s, 6H), 2.20 (s, 3H). MS (ES): 588.3 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 588.2822; found, 588.2820.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid [4-(4-Bromophenoxy)phenyl]amide (13). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.56 (s, 1H), 7.41−7.38 (m, 2H), 7.231 (s, 1H), 6.93 (d, 2H, J = 8.0 Hz), 6.85 (d, 2H, J = 8.0 Hz), 4.36 (m, 8H), 3.83 (m, 8H), 3.43 (s, 6H). MS (ES): 654.2 $(M + H)^+$.

4-[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (14). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.58 (s, 1H), 7.23−7.21 (d, 2H, J = 8 Hz), 7.21 (s, 1H), 6.83−6.81 (d, 2H, J = 8.8 Hz), 6.80−6.78 (d, 2H, J = 8.8 Hz), 6.75−6.73 (d, 2H, J = 8 Hz), 4.51 (hept, 1H), 4.36−4.31(m, 8H), 3.85−3.78 (m, 8H), 3.43 (s, 6H), 1.27 (d, 6H). MS (ES): 540 $(M + H)^+$. Exact mass (FAB, M + 1)$^+$ calcd, 540.2822; found, 540.2815.

***N*-(4-Indol-5-yloxyphenyl){4-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazinyl}carboxamide (18). (a) *tert*-Butyl-4-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazinecarboxylate.** To a DMF (300 mL) solution of the vanillic acid (25 g, 149 mmol) were added K_2CO_3 (102.7 g, 744 mmol) and BnBr (44.2 g, 372 mmol), and the resulting suspension was stirred at room temperature overnight. The reaction mixture was filtered, EtOAc was added, and the solution was washed with brine, dried, and concentrated. Purification on silica gel chromatography eluting with 10% EtOAc/hexane gave 55 g (96%) of the bis-benzylated product.

To a CH_2Cl_2 solution (100 mL) of the bis-benzyl-protected material (20 g, 57.4 mmol) at −10 °C was slowly added acetic acid (100 mL). To this cold solution was slowly added concentrated HNO_3 (25.8 mL, 574.4 mmol), and the reaction was warmed to room temperature followed by reflux overnight at 100 °C. After it was cooled, it was poured into ice, extracted with EtOAc, washed with brine, and dried with $MgSO_4$. The solvent was removed under vacuum to afford the desired intermediate product as a yellow solid (21.8 g, 96.5%). MS (ES): 416 (M + Na).

To the EtOAc solution (100 mL) of this nitro derivative (10.9 g, 27.7 mmol) was added $SnCl_2 \cdot H_2O$ (18.7 g, 83.1 mmol), and the reaction mixture was heated at 50 °C overnight. After it was cooled, the reaction mixture was filtered through Celite, and the filtrate was washed with 10% $NaHCO_3$ and extracted with EtOAc. The organic layers were dried and evaporated to afford the intermediate amino product as a brown solid (9.5 g, 95%). MS (ES): 364 $(M + H)^+$.

The amino product (3 g, 8.3 mmol) was dissolved in formamide (20 mL), to this was added ammonium formate (0.781 g, 12.4 mmol), and the reaction mixture was heated at 150 °C for 4 h. During this time period, the SM was consumed as evaluated by HPLC. After it was cooled, the reaction was poured into water to afford a creamy precipitate. The precipitate was collected by filtration, which is the desired intermediate, 7-benzyloxy-6-methoxy-4-quinazolinone (1.9 g, 81%). MS (ES): 283$(M + H)^+$.

A mixture of 7-benzyloxy-6-methoxy-4-quinazolinone (1 g, 3.5 mmol), thionyl chloride (5 mL), and DMF (0.5 mL) was heated at reflux for 4 h. After the mixture was cooled, excess thionyl chloride was removed by evaporation and the residue was azeotroped with toluene to afford the intermediate, 4-chloro-6-methoxy-7-benzyloxyquinazoline **42**, as a yellow solid (0.652 g, 62%). MS (ES): 301 $(M + H)^+$.

To a THF solution (20 mL) of 4-chloro-6-methoxy-7-benzyloxyquinazoline (1.8 g, 6 mmol) was added Boc-piperazine (2.2 g, 12 mmol) followed by DIEA (4.2 mL, 24 mmol), and the solution was heated overnight at 50 °C. The solvent was evaporated, and the residue was dissolved in water and

extracted with EtOAc. The EtOAc layer was dried, filtered, and evaporated to give the intermediate *tert*-butyl 4-[6-methoxy-7-phenylmethoxy)quinazolin-4-yl]piperazinecarboxylate as a white solid (2.2 g, 81%). MS (ES): 451 $(M + H)^+$.

The benzyloxy compound (0.500 g, 1.1 mmol) was dissolved in EtOH (5 mL), to this was added $Pd(OH)_2/C$ (0.050 g), and the mixture was placed on a Parr hydrogenator at 50 psi H_2 pressure overnight. The reaction mixture was filtered through Celite, washed with EtOH, and evaporated to dryness to afford the intermediate **43** (0.400 g, 98%). MS (ES): 361 $(M + H)^+$.

To an acetone solution (10 mL) of *tert*-butyl 4-(7-hydroxy-6-methoxyquinazolin-4-yl)piperazinecarboxylate (0.410 g, 1.1 mmol), K_2CO_3 (0.165 g, 1.2 mmol), and $^nBu_4NI$ (0.020 g) was added 2-bromomethylethyl ether (1.4 mL, 1.2 mmol). The mixture was refluxed overnight. The solvent was evaporated, and the crude residue was purified by RP-HPLC to afford the intermediate *tert*-butyl-4-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-yl]piperazinecarboxylate as the desired product (0.180 g, 40%). MS (ES): 419 $(M + H)^+$.

(b) *N*-(4-Indol-5-yloxyphenyl){4-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazinyl}carboxamide (18). To a solution of *tert*-butyl-4-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-yl]piperazinecarboxylate (0.050 g, 0.13 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL), and the reaction was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was resuspended in anhydrous THF/DCM. To a solution of 4-indol-5-yloxyphenylamine (0.046 g, 0.2 mmol) in anhydrous THF/DCM 1:1 (2 mL) at room temperature under argon was added DIEA (0.130 mL, 0.8 mmol) followed by DSC (0.058 g, 0.21 mmol). The resulting solution was stirred at room temperature for 1 h followed by the addition of the solution of [6-methoxy-7-phenylmethoxy)-quinazolin-4-yl]piperazine (0.065 g, 0.185 mmol) in THF/DCM, 1:1 (2 mL). The reaction mixture was stirred at room temperature until no starting material could be detected by RP-HPLC. The solvent was evaporated, and the residue was purified by RP-HPLC to give the title compound **18** (0.090 g, 90%). ^{1}H NMR (CD_3OD): δ 8.6 (s, 1H), 7.48 (s, 1H), 7.34 (d, 1H), 7.30−7.20 (m, 4H), 7.31 (d, 1H), 6.86−6.78 (m, 4H), 6.38 (d, 1H), 4.60 (m, 6H), 4.02 (s, 3H), 3.80−3.60 (m, 6H), 3.48 (s, 3H). MS (ES): 569 $(M + H)^+$.

{4-[7-(2-Methoxyethoxy)quinazolin-4-yl]piperazinyl}-*N*-(4-indol-5-yloxyphenyl (19). (a) 4-Piperazinyl-7-(2-methoxyethoxy)quinazoline (17). To an ethanol solution (15 mL) containing 2-amino-4-fluorobenzoic acid (0.840 g, 5.41 mmol) was added thionyl chloride (1.18 mL, 16.23 mmol), and the resulting suspension was refluxed overnight. The solvent was evaporated followed by addition of EtOAc, washed with 10% NaOH solution, dried, filtered, and evaporated to afford the desired ethylester as a solid (0.811 g, 82%). ^{1}H NMR ($CDCl_3$): δ 7.88−7.86 (d, 1H, H-6), 6.35−6.29 (m, 2H, H-3, H-5), 5.86 (bs, 2H, NH_2), 4.33−4.27 (q, 2H, CH_2), 137 (t, 3H, CH_3). MS (ES): 601 $(M + H)^+$. MS (ES): 184 $(M + H)^+$.

To a formamide (6 mL) solution of ethyl-2-amino-4-fluorobenzoate (0.811 g, 4.43 mmol) was added ammonium formate (0.450 g, 7.14 mmol), and the reaction mixture was heated at 140 °C overnight. After the mixture was cooled, water (50 mL) and ethyl acetate (100 mL) were added. The layers were separated, and the EtOAc layer was dried, filtered, and evaporated to give the desired 7-fluoro-4-quinazolinone **15** (1 g, quantitative). MS (ES): 165 $(M + H)^+$.

To a DMF solution (3 mL) of 2-methoxyethanol (0.962 mL, 12.2 mmol) at 0 °C was added sodium hydride (0.488 g, 12.2 mmol), and the mixture was stirred for 30 min. To this cold solution was added a DMF solution (3 mL) of intermediate 7-fluoroquinazolinone (0.500 g, 3.05 mmol), and the mixture was heated at 95 °C overnight. The solvent was evaporated, and the residue was purified by RP-HPLC to afford desired product **16** as a creamy solid (0.459 g, 75%). MS (ES): 221 $(M + H)^+$.

A mixture of 7-(2-methoxyethoxy)-4-quinazolinone **16** (0.360 g, 1.68 mmol) and $POCl_3$ (5 mL) was heated at 90 °C overnight. After it was cooled, excess $POCl_3$ was removed by evaporation and the residue was azeotroped with toluene to afford crude residue. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ (2 × 50 mL), and the organic layer was dried, filtered, and evaporated to give 4-chloro-7-(2-methoxyethoxy)quinazoline (0.204 g, 54%). MS (ES): 239 $(M + H)^+$.

To a 2-propanol solution (10 mL) of 4-chloroquinazoline (0.204 g, 0.86 mmol) was added piperazine (0.296 g, 3.44 mmol) and heated for 4 h at 90 °C. The solvent was evaporated, and the residue was purified by RP-HPLC to afford 4-piperazinyl-7-(2-methoxyethoxy)quinazoline **17** as a white solid (0.150 g, 60%). MS (ES): 289 $(M + H)^+$.

(b) {4-[7-(2-Methoxyethoxy)quinazolin-4-yl]piperazinyl}-*N*-(4-indol-5-yloxyphenyl (19). Compound **19** (40%) was synthesized by the same method as for **18** using 4-indol-5-yloxyphenylamine and 4-piperazinyl-7-(2-methoxyethoxy)-quinazoline (**17**). ^{1}H NMR (CD_3OD): δ 8.57 (s, 1H), 8.20 (d, 1H), 7.30−7.22 (m, 5H), 7.10 (d, 1H), 6.88−6.85 (m, 6H), 4.31−4.26 (m, 6H), 3.77−3.74 (m, 6H), 3.36 (s, 3H). MS (ES): 499 $(M + H)^+$.

{4-[7-(2-Methoxyethoxy)quinazolin-4-yl]piperazinyl}-*N*-(4-phenoxyphenyl)carboxamide (21). Compound **21** (38%) was synthesized using the same method as for **18** employing 4-phenoxyaniline and 4-piperazinyl-7-(2-methoxyethoxy)quinazoline (**17**). ^{1}H NMR (CD_3OD): δ 8.57 (s, 1H), 8.20 (d, 1H), 7.30−7.22 (m, 5H), 7.10 (d, 1H), 6.88−6.85 (m, 6H), 4.31−4.26 (m, 6H), 3.77−3.74 (m, 6H), 3.36 (s, 3H). MS (ES): 500 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 500.2297; found, 500.2293.

{4-[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazinyl}-*N*-[4-(cyano)phenyl]carboxamide (22). To a solution of *tert*-butyl-4-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazinecarboxylate (0.050 g, 0.13 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL), and the reaction was stirred at room temperature for 1 h. After that, the solvent was evaporated, and the residue was resuspended in anhydrous acetonitrile (1 mL) and added to an acetonitrile (1 mL) solution of cyanophenyl isocyanate (0.042 g, 0.26 mmol). The mixture was heated at 90 °C for 2 h, and during that time, no starting material could be detected by TLC and RP-HPLC. The solvent was evaporated, and the residue was purified by RP-HPLC to yield the title compound **22** as a creamy solid (0.045 g, 76%). ^{1}H NMR ($CDCl_3$): δ 8.40 (s, 1H), 7.80 (s, 1H), 7.38−7.36 (d, 2H), 7.30−7.28 (d, 2H), 7.12 (s, 1H), 4.34 (bs, 2H), 4.24−4.22 (bs, 4H), 3.96 (s, 3H), 3.86−3.80 (m, 6H), 3.40 (s, 3H). MS (ES): 463.50 $(M + H)^+$.

4-[6-Methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (24). The final urea formation was carried out using method C and 4-isopropoxyaniline and 4-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]piperazine to afford desired product **24** as a white solid. ^{1}H NMR (CD_3OD): δ 8.61 (s, 1H), 7.46 (s, 1H), 7.23 (s, 1H), 7.21 (d, 2H, $J = 8.8$ Hz), 6.83 (d, 2H, $J = 8.8$ Hz), 4.51 (hept, 1H), 4.36−4.34 (m, 6H), 4.00 (s, 3H), 3.83−3.78 (m, 6H) 3.42(s, 3H), 1.27 (s, 3H), 1.26 (s, 3H). MS (ES): 496 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 496.2559; found, 496.2563.

4-[7-(2-Methoxyethoxy)-6-(2-morpholin-4-yl-ethoxy)-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (29). (a) 7-(2-Methoxyethoxy)-6-(2-morpholin-4-yl-ethoxy)-4-piperazin-1-yl-quinazoline (28b). To a DMF (10 mL) solution of ethyl 3-hydroxy-4-fluorobenzoate (1.00 g, 5.43 mmol) was added K_2CO_3 (2.63 g, 19.02 mmol) followed by 4-(2-chloroethyl)morpholine (1.02 g, 5.49 mmol), and it was heated to 85 °C for 3.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried **(**$MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure to afford 1.50 g (88%) of the intermediate.

To a THF solution (5 mL) of 2-methoxyethanol (125 μL, 1.58 mmol) at 0 °C was added sodium hydride (22 mg, 0.528 mmol), and the mixture was stirred for 30 min. To this cold solution was added a THF solution (3 mL) of above intermediate (0.159 g, 0.528 mmol), and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by RP-HPLC to afford intermediate as a white solid (0.150 g, 80%). MS (ES): 354 $(M + H)^+$.

This solid (0.810 g, 2.30 mmol) was dissolved in acetic acid (3 mL), and the solution was cooled to −5 °C and treated dropwise with nitric acid (0.300 mL). After 1 h, a solution of sulfuric acid (0.300 mL) and KNO_3 (0.235 g, 2.32 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred overnight. After completion of the reaction, NH_4OH was added to obtain a pH ∼10 and then extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried, filtered, and evaporated to give nitro intermediate as a brown solid (0.83 g, 90.7%). MS (ES): 421 $(M + Na)^+$, 399 $(M + H)^+$.

This nitro derivative (0.133 g) was dissolved in EtOH (10 mL) and ethyl acetate (5 mL) and then treated with 10% Pd/C (60 mg). Hydrogenation was performed under 1 atm of H_2 overnight during which the reduction was determined to be complete. The solution was filtered through Celite, and the filtrate was evaporated to afford the amino intermediate **26b** as an oil (0.085 g, 68%).

To a formamide solution (2 mL) of 2-amino-4-(2-methoxyethoxy)-5-(2-morpholin-4-yl-ethoxy)benzoic acid ethyl ester (0.713 g, 1.94 mmol) was added ammonium formate (0.196 g, 3.10 mmol) followed by heating the mixture to 140 °C for 3 h. After it was cooled, water (50 mL) was added and the solution was washed with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 7-morpholinoethoxy-6-methoxyethoxy-4-quinazolinone formate salt **27b** as a yellow solid (0.800 g). MS (ES): 350 $(M + H)^+$.

A mixture of quinazolinone (0.750 g, 1.79 mmol), thionyl chloride (6 mL), and DMF (300 μL) was heated at reflux for 2 h. After the mixture was cooled, excess thionyl chloride was removed by evaporation and the residue was azeotroped with toluene to afford the intermediate, 4-chloro-quinazoline, as a yellow solid (0.450 g, 80%). MS (ES): 368 $(M+H)^+$.

To a 2-propanol solution (20 mL) of above chloroquinazoline (0.402 g, 1.09 mmol) were added Boc-piperazine (0.31 g, 1.64 mmol) and triethylamine (0.46 mL, 3.28 mmol), and the reaction mixture was heated at 90 °C for 4 h. The solvent was evaporated, and the residue was purified by RP-HPLC to afford the desired intermediate (0.598 g, 86.6%). MS (ES): 518.2 $(M + H)^+$. The deprotection was carried out with 4 N HCl in dioxane at room temperature for 1 h to afford **28b**.

(b) 4-[7-(2-Methoxyethoxy)-6-(2-morpholin-4-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (29). Compound **29** was synthesized using method A as a yellow solid (0.085 g, 65%). ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H), 7.64−7.62 (m, 6H), 7.27 (s, 2H), 4.67−4.63 (m, 3H), 4.40−4.33 (m, 7H), 3.87−3.83 (m, 8H) 3.75−3.71 (m, 4H), 3.42 (bs, 5H). MS (ES): 562.3 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 562.2777; found, 562.2776.

The analogues **30**−**32** were synthesized from the same intermediate using the procedure described for the synthesis of analogue **29**. For the isopropoxy analogues, the urea formation was carried out by method B.

4-[7-(2-Methoxyethoxy)-6-(2-morpholin-4-yl-ethoxy)-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (30). ^{1}H NMR ($CDCl_3$): δ 8.57 (s, 1H), 7.58 (s, 1H), 7.21 (s, 1H), 7.17 (d, 2H, J = 9.2 Hz), 6.77 (d, 2H, J = 9.2 Hz), 4.62−4.57 (m, 1H), 4.36−4.28 (m, 5H), 4.30−3.98 (m, 2H), 3.88−3.72 (m, 6H) 3.72−3.64 (m, 4H), 3.36 (s, 3H), 1.22−1.19 (m, 6H). MS (ES): 617.3 $(M + Na)^+$, 595.3 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 595.3224; found, 595.3233.

4-[7-(2-Methoxyethoxy)-6-(2-piperidin-4-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (31). ^{1}H NMR ($CDCl_3$): δ 8.59 (s, 1H), 7.58 (s, 1H), 7.60−7.52 (m, 5H), 7.20 (s, 1H), 4.58−4.53 (m, 2H), 4.36−4.27 (m, 6H), 3.83−3.73 (m, 6H) 3.74−3.56 (m, 4H), 3.36 (s, 3H), 3.16−3.06 (m, 2H), 1.97−1.74 (m, 5H), 1.57−1.42 (m, 1H). MS (ES): 560 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 560.2985; found, 560.2996.

4-[7-(2-Methoxyethoxy)-6-(2-piperidin-4-yl-ethoxy)-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (32). ^{1}H NMR ($CDCl_3$): δ 8.56 (s, 1H), 7.75 (d, 2H, J = 8.4 Hz), 7.56 (s, 1H), 7.19 (s, 1H), 7.15 (d, 2H, J = 8.4 Hz), 7.20 (s, 1H), 4.56−4.52 (m, 2H), 4.48 (hept, 1H, J = 6.0 Hz), 4.34−4.26 (m, 6H), 3.78−3.64 (m, 8H) 3.60−3.56 (m, 2H), 3.34 (s, 3H), 3.16−3.06 (m, 2H), 1.97−1.74 (m, 5H), 1.54−1.40 (m, 1H), 1.97 (s, 3H), 1.81 (s, 3H). MS (ES): 593 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 593.3451; found, 593.3463.

The regioisomers **37**−**40** were synthesized using similar methods as described for analogue **29** except that in these instances ethyl-3-hydroxy-4-fluorobenzoate was first alkylated with 2-bromoethyl methyl ether followed by displacement of fluorine with the anion of 2-piperidin-1-yl ethanol, 2-morphilin-1-yl ethanol, or pyrrolinyl-1-yl ethanol.

4-[6-(2-Methoxyethoxy)-7-(2-piperidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (37). ^{1}H NMR (CD_3OD): δ 8.65 (s, 1H), 7.63−7.60 (m, 4H), 7.59 (s, 1H), 7.29 (s, 1H), 4.66 (t, 2H, J = 4.6 Hz), 4.38−4.32 (m, 6H), 3.86−3.72 (m, 8H) 3.70 (t, 2H, J = 4.6 Hz), 3.42 (s, 3H), 3.24−3.14 (m, 2H), 2.02−1.78 (m, 5H), 1.62−1.50 (m, 1H). MS (ES): 560 $(M + H)^+$.

4-[6-(2-Methoxyethoxy)-7-(2-piperidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (38). ^{1}H NMR (CD_3OD): δ 8.64 (s, 1H), 7.60 (s, 1H), 7.29 (s, 1H), 7.22 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 9.2 Hz), 4.72−4.62 (m, 2H), 4.53 (hept, 1H, J = 6.0 Hz), 4.39−4.30 (m, 6H), 3.86−3.66 (m, 10H) 3.43 (s, 3H), 2.05−1.78 (m, 5H), 1.62−1.50 (m, 1H), 1.29 (s, 3H), 1.27 (s, 1H). MS (ES): 593 $(M + H)^+$.

4-[6-(2-Methoxyethoxy)-7-(2-pyrrolidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (39). ^{1}H NMR (CD_3OD): δ 8.65 (s, 1H), 7.65−7.55 (m, 6H), 7.30 (s, 1H), 4.64−4.60 (m, 2H), 4.39−4.32 (m, 6H), 3.91−3.78 (m, 12H), 3.42 (s, 3H), 2.27−2.00 (m, 4H). MS (ES): 546 $(M + H)^+$.

4-[6-(2-Methoxyethoxy)-7-(2-pyrrolidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (40). ^{1}H NMR (CD_3OD): δ 8.64 (s, 1H), 7.59 (s, 1H), 7.30 (s, 1H), 7.23 (d, 2H, J = 9.2 Hz), 6.83 (d, 2H, J = 9.2 Hz), 4.51 (hept, 1H, J = 6.4 Hz), 4.38−4.30 (m, 6H), 3.91−3.76 (m, 10H), 3.42 (s, 3H), 2.26−1.98 (m, 4H), 1.27 (s, 3H), 1.26 (s, 3H). MS (ES): 579.3 $(M + H)^+$.

4-[6-Methoxy-7-(2-morpholin-4-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (45). (a) To a DMF solution (2 mL) of 4-(7-hydroxy-6-methoxy-quinazolin-4-yl)piperazine-1-carboxylic acid *tert*-butyl ester **43** (0.040 g, 0.1 mmol) was added Cs_2CO_3 (0.073 g, 0.22 mmol) followed by chloroethyl tosylate (0.045 mL, 0.22 mmol) and stirred overnight at room temperature. The solvent was evaporated, and residue was purified by RP-HPLC to afford the desired intermediate as a viscous oil (0.023 g, 50%). ^{1}H NMR (CD_3OD). MS (ES): 423 $(M + H)^+$.

To a DMF solution (2 mL) of above intermediate (0.015 g, 0.036 mmol) was added morpholine (0.036 mL, 0.036 mmol) for analogue **45** or other respective secondary amines and heterocycles as shown in Table 4 for analogues **46**−**55** and **60**−**69**. The reaction mixture was heated at 80 °C overnight and monitored by HPLC for disappearance of starting material. The solvent was evaporated, and the residue was purified by RP-HPLC to afford basic intermediate as white solid (0.016 g, 92%). MS (ES): 472 $(M + H)^+$.

(b) After deprotection of Boc functionality to afford **44a**, the urea formation was carried out as in method A to afford analogue **45** as a white solid (0.100 g, 66%). ^{1}H NMR (CD_3OD): δ 8.6 (s, 1H), 7.62−7.58 (m, 4H), 7.5 (s, 1H), 7.38 (s, 1H), 4.70 (m, 1H), 4.50 (m, 1H), 4.30 (m, 2H), 3.90 (s, 3H), 3.80−3.40 (m, 6H), 3.60−3.50 (m, 4H), 3.60 (m, 2H), 3.18 (m, 2H), 1.40 (m, 2H). MS (ES): 518 $(M + H)^+$.

4-[6-(2-Methoxy)-7-(2-piperidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (46). ^{1}H NMR (CD_3OD): δ 8.65 (s, 1H), 7.65−7.60 (m, 4H), 7.50 (s, 1H), 7.25 (s, 1H), 4.62−4.60 (m, 2H), 4.39−4.32 (m, 3H), 3.95 (s, 3H), 3.86−3.82 (m, 3H), 3.72−3.68 (m, 3H), 3.18−3.10 (m, 6H), 2.27−2.00 (m, 2H), 1.86−1.79 (m, 3H). MS (ES): 516.3 $(M + H)^+$.

4-{7-[2-(4-Hydroxy-piperidin-1-yl)ethoxy]-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyano-phenyl)amide (47). Yield 30 mg, 63%. ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.65−7.60 (m, 4H), 7.54 (s, 1H), 7.30 (s, 1H), 4.52−4.50 (m, 4H), 4.36−4.32 (m, 4H), 4.01 (s, 3H), 3.91−3.78 (m, 6H), 3.52−3.48 (m, 3H), 2.27−2.00 (m, 4H). MS (ES): 532.6 $(M + H)^+$.

4-{7-[2-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)ethoxy]-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (48). Yield 25 mg, 48%. ^{1}H NMR (CD_3OD): δ 8.64 (s, 1H), 7.62 (s, 4H), 7.50 (s, 1H), 7.34 (s, 1H), 4.62−4.60 (m, 2H), 4.36−4.32 (m, 4H), 4.24−4.01 (m, 6H), 3.95 (s, 3H), 3.84−3.80 (m, 4H), 3.76−3.74 (m, 4H), 2.10−2.00 (m, 4H). MS (ES): 574.64 $(M + H)^+$.

4-{7-[2-(4-Oxo-piperidin-1-yl)ethoxy]-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyano-phenyl)amide (49). Yield 7.8 mg, 38.4%. ^{1}H NMR (CD_3OD): δ 8.61 (s, 1H), 7.58 (s, 4H), 7.48 (s, 1H), 7.28 (s, 1H), 4.60−4.58 (m, 2H), 4.30−4.26 (m, 4H), 4.01 (s, 3H), 3.92−3.90 (m, 2H), 3.84−3.80 (m, 4H), 3.74−3.70 (m, 4H), 2.10−2.00 (m, 4H). MS (ES): 530 $(M + H)^+$.

4-[6-Methoxy-7-(2-piperazin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (50). Yield 37.2 mg, 59.2%. ^{1}H NMR (CD_3OD): δ 8.65 (s, 1H), 7.65−7.55 (m, 6H), 7.30 (s, 1H), 4.64−4.60 (m, 2H), 4.39−4.32 (m, 6H), 3.91−3.78 (m, 12H), 3.42 (s, 3H), 2.27−2.00 (m, 4H). MS (ES): 517 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 517.2675; found, 517.2664.

4-{6-Methoxy-7-[2-(4-methyl-piperazin-1-yl)ethoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyano-phenyl)amide (51). Yield 50 mg, 80.2%. ^{1}H NMR (CD_3OD): δ 8.61 (s, 1H), 7.61 (s, 4H), 7.48 (s, 1H), 7.24 (s, 1H), 4.62−4.60 (m, 2H), 4.36−4.32 (m, 4H), 4.01 (s, 3H), 3.82−3.80 (m, 4H), 3.68−3.20 (m, 7H), 2.98 (s, 3H). MS (ES): 531.6 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 531.2832; found, 531.2819.

4-[6-Methoxy-7-(2-thiomorpholin-4-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (52). Yield 43.9 mg, 75.9%. ^{1}H NMR (CD_3OD): δ 8.40 (s, 1H), 7.62 (d, 2H), 7.58 (d, 2H), 7.50 (s, 1H), 7.30 (s, 1H), 4.70 (m, 2H), 4.40−4.36 (m, 4H), 4.02 (s, 3H), 4.00−3.98 (m, 2H), 3.88−3.86 (m, 4H), 3.78 (m, 2H), 3.50−3.46 (m, 2H), 3.28−3.20 (m, 2H), 2.92−2.88 (m, 2H). MS (ES): 534 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 534.2287; found, 534.2284.

4-[6-Methoxy-7-(2-pyrrolidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (53). Yield 40.9 mg, 58.2%. ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.65 (s, 4H), 7.50 (s, 1H), 7.30 (s, 1H), 4.60 (m, 2H), 4.32−4.30 (m, 4H), 4.0 (s, 3H), 3.84−3.76 (m, 6H), 3.42 (s, 3H), 2.20−2.10 (m, 4H). MS (ES): 502 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 502.2566; found, 502.2570.

4-[7-(2-Imidazol-1-yl-ethoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (54). Yield 34 mg, 47.9%. ^{1}H NMR (CD_3OD): δ 9.1 (s, 1H), 8.62 (s, 1H), 7.8 (s, 1H), 7.62−7.58 (m, 5H), 7.48 (s, 1H), 7.25 (s, 1H), 4.64−4.60 (m, 2H), 4.39−4.32 (m, 4H), 4.06−4.04 (m, 2H), 4.01 (s, 3H), 3.86−3.82 (m, 4H). MS (ES): 499 $(M + H)^+$.

4-[6-Methoxy-7-(2-pyrrol-1-yl-ethoxy)quinazolin-4-yl]-piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (55). Yield 21 mg, 69.8%. ^{1}H NMR (CD_3OD): δ 8.8 (s, 1H), 8.6 (s, 1H), 7.6 (m, 4H), 7.42 (s, 1H), 7.0 (s, 1H), 6.8 (m, 2H), 6.0 (m, 2H), 4.46−4.38 (m, 4H), 4.34−4.30 (m, 4H), 4.0 (s, 3H), 3.84−3.80 (m, 4H). MS (ES): 498 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 498.2253; found, 498.2258.

Analogues **60**−**69** were synthesized using method B for final urea linkage formation.

4-[6-Methoxy-7-(2-morpholin-4-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (60). Yield 29.6 mg, 52.6%. ^{1}H NMR (CD_3OD): δ 8.65 (s, 1H), 7.52 (s, 1H), 7.32 (s, 1H), 7.22 (d, 2H, J = 8.7 Hz), 6.8 (d, 2H, J = 8.7 Hz), 4.70 (m, 2H), 4.5 (hept, 1H, J = 8 Hz), 4.39−4.32 (m, 4H), 4.10−4.04 (m, 2H), 4.01 (s, 3H), 3.91−3.78 (m, 9H), 3.42−3.36 (m, 2H), 1.27 (d, J = 1 Hz, 3H), 1.24 (d, J = 1 Hz, 3H). MS (ES): 551 $(M + H)^+$.

4-[6-Methoxy-7-(2-piperidin-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (61). Yield 338 mg, 93.7%. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.49 (s, 1H), 7.31 (s, 1H), 7.23 (dd, 2H, J = 2.4 and 6.8 Hz), 6.83 (dd, 2H, J = 2.4 and 6.8 Hz), 4.67−4.64 (m, 2H), 4.50 (hept, 1H), 4.36−4.32 (m, 4H), 4.03 (s, 3H), 3.81−3.79 (m, 4H), 3.72−3.66 (m, 4H), 3.18−3.10 (m, 2H), 1.98−1.83 (m, 6H), 1.27−1.25 (d. 6H). MS (ES): 549 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 549.3189; found, 549.3178.

4-[6-Methoxy-7-(2-[1,2,3]triazol-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (62). Yield 147 mg, 36.87%. ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 8.30 (s, 1H), 7.70 (s, 1H), 7.42 (s, 1H), 7.24 (s, 1H), 7.18−7.16 (d, 2H), 6.82−6.80 (d, 2H), 4.98−4.97 (m, 2H), 4.65 (m, 2H), 4.50 (hept, 1H), 4.40 (m, 4H), 4.01 (s, 3H), 3.60−3.50 (m, 4H), 1.30 (d, 6H). MS (ES): 533 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 533.2624; found, 533.2631.

4-[6-Methoxy-7-(2-[1,2,3]triazol-2-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (63). Yield 145 mg, 36.8%. ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.70 (s, 1H), 7.42 (s, 1H), 7.24 (d, 2H), 7.10 (s, 1H), 4.98−4.97 (m, 2H), 4.65 (m, 2H), 4.50 (hept, 1H), 4.40 (m, 4H), 3.90 (s, 3H), 3.70−3.65 (m, 4H), 1.30 (d, 6H). MS (ES): 533 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 533.2624; found, 533.2621.

4-[6-Methoxy-7-(2-[1,2,3]triazol-1-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (64). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 8.30 (s, 1H), 7.72 (s, 1H), 7.60 (s, 4H), 7.46 (s, 1H), 7.14 (s, 1H), 4.66−4.62 (m, 2H), 4.36−4.30 (m, 5H), 3.98 (s, 3H), 3.82−3.80 (m, 5H). MS (ES): 500 $(M + H)^+$.

4-[6-Methoxy-7-(2-[1,2,3]triazol-2-yl-ethoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (65). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.70 (s, 2H), 7.60 (s, 4H), 7.42 (s, 1H), 7.18 (s, 1H), 4.66−4.62 (m, 4H), 4.36−4.30 (m, 4H), 3.94 (s, 3H), 3.82−3.80 (m, 4H). MS (ES): 500 $(M + H)^+$.

4-{7-[2-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)ethoxy]-6-methoxy-quinazolin-4-yl}piperazine-carboxylic Acid (4-Cyanophenyl)amide (66). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.6 (s, 4H), 7.42 (s, 1H), 7.18 (s, 1H), 4.36−4.30 (m, 6H), 4.26−4.22 (m, 2H), 3.98 (s, 3H), 3.96−3.94 (m, 2H), 3.82−3.80 (m, 2H), 3.18−3.12 (m, 4H). MS (ES): 566 $(M + H)^+$.

4-{7-[2-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)ethoxy]-6-methoxy-quinazolin-4-yl}piperazine-carboxylic Acid (4-Isopropoxyphenyl)amide (67). ^{1}H NMR (CD_3OD): δ 8.40 (s, 1H), 7.62 (d, 2H), 7.58 (d, 2H), 7.50 (s, 1H), 7.30 (s, 1H), 4.70 (m, 2H), 4.56 (hept, 1H), 4.40−4.36 (m, 4H), 4.02 (s, 3H), 4.00−3.98 (m, 2H), 3.88−3.86 (m, 4H), 3.78 (m, 2H), 3.50−3.46 (m, 2H), 3.28−3.20 (m, 2H), 2.92−2.88 (m, 2H), 1.27 (d, 6H). MS (ES): 599 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 599.2651; found, 599.2655.

4-[6-Methoxy-7-(2-tetrazol-1-yl-ethoxy)quinazolin-4-yl]-piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (68). ^{1}H NMR (CD_3OD): δ 9.30 (s, 1H), 8.60 (s, 1H), 7.46 (s, 1H), 7.20 (d, 2H), 7.18 (s, 1H), 6.80 (d, 2H), 5.02 (m, 2H), 4.70 (m, 2H), 4.50 (hept, 1H), 4.30 (m, 4H), 4.01 (s, 3H), 3.80 (m, 4H), 1.30 (d, 6H). Exact mass (FAB, $M + 1)^+$ calcd, 534.2577; found, 534.2592.

4-[6-Methoxy-7-(2-tetrazol-2-yl-ethoxy)quinazolin-4-yl]-piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (69). ^{1}H NMR (CD_3OD): δ 8.70 (s, 1H), 8.58 (s, 1H), 7.40 (s, 1H), 7.20 (d, 2H), 7.14 (s, 1H), 6.80 (d, 2H), 5.20 (m, 2H), 4.70 (m, 2H), 4.50 (hept, 1H), 4.30 (m, 4H), 3.90 (s, 3H), 3.75 (m, 4H), 1.20 (d, 6H). Exact mass (FAB, $M + 1)^+$ calcd, 534.2577; found, 534.2587.

Analogues **70**−**87** were synthesized as shown in Scheme 5. The synthesis of representative examples **70** and **75** is described as follows.

4-[6-Methoxy-7-(3-piperidin-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (70). (a) To a DMF solution (3 mL) of 4-(7-hydroxy-6-methoxy-quinazolin-4-yl)piperazine-1-carboxylic acid *tert*-butyl ester **43** (0.100 g, 0.28 mmol) was added Cs_2CO_3 (0.365 g, 1.12

mmol) followed by chloropropyl tosylate (0.103 g, 0.42 mmol) and heated overnight at 65 °C. The reaction was filtered, the filtrate was evaporated, and the residue was purified by RP-HPLC to afford the desired intermediate as a solid (0.100 g, 81.9%). MS (ES): 437 $(M + H)^+$.

To a DMF solution (3 mL) of the above intermediate (0.103 g, 0.236 mmol) was added piperidine (0.376 mL, 2.36 mmol) followed by triethylamine (0.132 mL, 0.944 mmol). The reaction mixture was heated at 70 °C overnight and monitored by HPLC for disappearance of starting material. The solvent was evaporated, and the residue was purified by RP-HPLC to afford intermediate **44b** as a white solid (0.053 g, 46.4%). MS (ES): 486 $(M + H)^+$.

(b) The above intermediate (37 mg) was stirred in 4 N HCl/dioxane (1 mL) for 1 h, and the solvent was evaporated to afford 6-methoxy-4-piperazin-1-yl-7-(3-piperidin-1-yl-propoxy)-quinazoline intermediate. The urea formation was carried out as in method A with 4-cyanophenyl isocyanate to afford analogue **70** as a white solid (0.025 g, 50%). ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.61 (m, 4H), 7.42 (s, 1H), 7.2 (s, 1H), 4.4 (m, 4H), 4.01 (s, 3H), 3.82 (m, 4H), 3.30 (m, 4H), 2.98 (m, 4H), 2.4 (m, 4H), 1.98−1.60 (m, 4H). MS (ES): 530 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 530.2879; found, 530.2877.

4-[6-Methoxy-7-(3-morpholin-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (71). ^{1}H NMR (CD_3OD): δ 8.56 (s, 1H), 7.54 (m, 4H), 7.40 (s, 1H), 7.16 (s, 1H), 4.28−4.25 (m, 6H), 4.08−4.0 (m, 2H), 3.94 (s, 3H), 3.76−3.75 (m, 6H), 3.6−3.5 (m, 2H), 3.38 (m, 4H), 2.3 (m, 2H). MS (ES): 532 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 532.2672; found, 532.2681.

4-[6-Methoxy-7-(3-pyrrolidin-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (72). The final urea formation step was carried out using method A with 6-methoxy-4-piperazin-1-yl-7-(3-pyrrolidin-1-yl-propoxy)quinazoline and 4-cyanophenyl isocyanate to afford **72** as a white solid (65 mg, 69%). ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.61−7.57 (m, 4H), 7.40 (s, 1H), 7.20 (s, 1H), 4.43−4.40(m, 6H), 4.01 (s, 3H), 3.85−3.83 (m, 6H), 3.50−3.45 (m, 2H), 3.19−3.15 (m, 4H), 2.45−1.98 (m, 4H). MS (ES): 516 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 516.2723; found, 516.2728.

4-[6-Methoxy-7-(2-[1,2,3]triazol-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (73). Method A (90 mg, 50%). ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 8.03 (s, 1H), 7.72 (s, 1H), 7.60 (s, 4H), 7.45 (s, 1H), 7.15 (s, 1H), 4.70 (t, 2H), 4.35−4.33 (m, 4H), 4.21 (t, 2H), 4.01 (s, 3H), 3.84−3.81 (m, 4H), 2.50−2.45 (m, 2H). MS (ES): 514 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 514.2315; found, 514.2310.

4-[6-Methoxy-7-(2-[1,2,3]triazol-2-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Cyanophenyl)-amide (74). Method A (100 mg, 50%). ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.66 (s, 1H), 7.61 (s, 4H), 7.60 (s, 1H), 7.45 (s, 1H), 7.13 (s, 1H), 4.70 (t, 2H), 4.34−4.32 (m, 4H), 4.20 (t, 2H), 3.85−3.82 (m, 4H), 3.74 (s, 3H), 2.50−2.45 (m, 2H). MS (ES): 514 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 514.2315; found, 514.2315.

4-[6-Methoxy-7-(3-piperidin-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (75). Method B (55 mg, 59%). ^{1}H NMR (CD_3OD): δ 8.50 (s, 1H), 7.64 (s, 1H), 7.29 (s, 1H), 7.16−7.14 (dd, J = 8,0, 2 Hz, 2H), 6.74−6.72 (dd, J = 8,0, 2 Hz, 2H), 4.43−4.40 (hept, 1H), 4.32−4.28 (t, 2H), 4.16−4.13 (m, 4H), 3.90 (s, 3H), 3.72−3.69 (m, 4H), 3.52−3.50 (m, 2H), 3.19−3.15 (m, 2H), 2.81−2.78 (m, 2H), 2.35−2.25 (m, 2H), 1.85−1.42 (m, 6H), 1.19−1.17 (d, J = 8 Hz, 6H). MS (ES): 563 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 563.3345; found, 563.3341.

4-[6-Methoxy-7-(3-morpholin-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (76). The final urea formation step was carried out using method B to afford **76** as a yellow solid (65 mg, 69%). ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.46 (s, 1H), 7.26 (s, 1H), 7.23−7.21 (dd, 2H), 6.83−6.81 (dd, 2H), 4.53−4.49 (hept, 1H), 4.35−4.31 (m, 4H), 4.01 (s, 3H), 3.80−3.78 (m, 6H), 3.47−3.44 (t, 2H), 3.19−3.15 (m, 2H), 2.39−2.32 (m, 2H), 2.20−2.03 (m, 4H), 1.19−1.17 (d, 6H). MS (ES): 565.3 $(M + H)^+$. Exact mass (FAB, $M + 1)^+$ calcd, 565.3138; found, 565.3127.

4-[6-Methoxy-7-(3-pyrrolidin-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (77). The final urea formation step was carried out using method B to afford **77** as a yellow solid (160 mg, 78%). ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.46 (s, 1H), 7.26 (s, 1H), 7.23−7.21 (dd, 2H), 6.83−6.81 (dd, 2H), 4.53−4.49 (hept, 1H), 4.35−4.31 (m, 4H), 4.01 (s, 3H), 3.80−3.78 (m, 6H), 3.47−3.44 (t, 2H), 3.19−3.15 (m, 2H), 2.39−2.32 (m, 2H), 2.20−2.03 (m, 4H), 1.19−1.17 (d, 6H). MS (ES): 549 $(M + H)^+$.

4-[6-Methoxy-7-(2-[1,2,3]triazol-1-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (78). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 8.03 (d, 1H), 7.73 (d, 1H), 7.46 (s, 1H), 7.23−7.21 (dd, 2H), 7.13 (s, 1H), 6.83−6.81 (dd, 2H), 4.70 (t, 2H), 4.52−4.49 (hept, 1H), 4.35−4.31 (m, 4H), 4.21 (t, 2H), 4.01 (s, 3H), 3.80−3.77 (m, 4H), 2.56−2.48 (m, 2H), 1.27−1.25 (d, 6H). MS (ES): 547 $(M + H)^+$.

4-[6-Methoxy-7-(2-[1,2,3]triazol-2-yl-propoxy)quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (79). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.65 (s, 2H), 7.45 (s, 1H), 7.23−7.20 (dd, 2H), 7.12 (s, 1H), 6.83−6.81 (dd, 2H), 4.69 (t, 2H), 4.52−4.49 (hept, 1H), 4.34−4.32 (m, 4H), 4.19 (t, 2H), 4.01 (s, 3H), 3.80−3.77 (m, 4H), 2.56−2.48 (m, 2H), 1.27−1.25 (d, 6H). MS (ES): 547 $(M + H)^+$.

4-{7-[3-(4,4-Difluoro-piperidin-1-yl)propoxy]-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (80). ^{1}H NMR (CD_3OD): δ 8.56 (s, 1H), 7.53 (s, 4H), 7.39 (s, 1H), 7.16 (s, 1H), 4.30−4.24 (m, 6H), 3.93 (s, 3H), 3.78−3.74 (m, 6H), 3.4 (t, 4H), 2.38−2.30 (m, 6H). MS (ES): 566 $(M + H)^+$.

4-{7-[3-(4,4-Difluoro-piperidin-1-yl)propoxy]-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (81). ^{1}H NMR (CD_3OD): δ 8.55 (s, 1H), 7.40 (s, 1H), 7.16 (s, 1H), 7.15 (dd, J = 8, 2 Hz, 2H), 6.77 (dd, J = 8, 2 Hz, 2H), 4.44 (hept, 1H), 4.29−4.24 (m, 6H), 3.94 (s, 3H), 3.73−3.71 (m, 6H), 3.4 (t, 4H), 2.35−2.30 (m, 6H). MS (ES): 599 $(M + H)^+$.

4-{7-[3-(3,3-Difluoro-piperidin-1-yl)propoxy]-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (82). ^{1}H NMR (CD_3OD): δ 8.55 (s, 1H), 7.40 (s, 1H), 7.16 (s, 1H), 7.15 (dd, J = 8, 2 Hz, 2H), 6.77 (dd, J = 8, 2 Hz, 2H), 4.44 (hept, 1H), 4.29−4.24 (m, 6H), 3.94 (s, 3H), 3.73−3.71 (m, 6H), 3.4 (t, 4H), 2.35−2.30 (m, 6H). MS (ES): 599 $(M + H)^+$.

4-[7-(3-Cyclohexyl-propoxy)-6-methoxy-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (83). ^{1}H NMR (CD_3OD): δ 8.61 (s, 1H), 7.45 (s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.16 (s, 1H), 6.83 (d, J = 8 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.37−4.28 (m, 4H), 4.48−4.20 (m, 4H), 4.00 (s, 3H), 3.82−3.74 (m, 4H), 3.32−3.23 (m, 6H), 1.84−1.50 (m, 6H), 1.27 (s, 3H), 1.26 (s, 3H), 1.80−0.96 (m, 1H). MS (ES): 548.3 $(M + H)^+$.

4-{6-Methoxy-7-[3-(4-methyl-piperidin-1-yl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (84). Compound **84** was synthesized using method A. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.61 (s, 4H), 7.48 (s, 1H), 7.25 (s, 1H), 4.37−4.31 (m, 6H), 4.01 (s, 3H), 3.86−3.80 (m, 4H), 3.66 (d, J = 12.4 Hz, 2H), 3.35 (t, J = 7.4 Hz, 2H), 2.99 (t, J = 12.6 Hz, 2H), 2.41−2.33 (m, 2H), 1.95 (d, J = 13.2 Hz, 2H), 1.78−1.64 (bs, 1H), 1.52−1.40 (m, 2H), 1.02 (d, J = 6.8 Hz, 3H). MS (ES): 544.3 $(M + H)^+$.

4-{6-Methoxy-7-[3-(4-methyl-piperidin-1-yl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (85). Compound **85** was synthesized using method A. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.48 (s, 4H), 7.26 (s, 1H), 7.22 (dd, J = 8.8, 2 Hz, 2H), 6.83 (d, J = 8, 2 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.36−4.30 (m, 6H), 4.01 (s, 3H), 3.82−3.76 (m, 4H), 3.66 (bd, J = 12.4 Hz, 2H), 3.35 (t, J = 7.4 Hz, 2H), 3.03−2.94 (m, 2H), 2.40−2.323 (m, 2H), 1.95 (bd, J = 13.6 Hz, 2H), 1.78−1.64 (bs, 1H), 1.52−1.40 (m, 2H), 1.26 (d, J = 5.6 Hz, 6H), 1.02 (d, J = 6.8 Hz, 3H). MS (ES): 577.3 $(M + H)^+$.

4-{6-Methoxy-7-[3-(2-methyl-piperidin-1-yl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Cyanophenyl)amide (86). Compound **86** was synthesized using method A. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.61 (s, 4H), 7.48 (s, 1H), 7.25 (s, 1H), 4.36−4.30 (m, 6H), 4.01 (s, 3H), 3.86−3.80 (m, 4H), 3.66−3.52 (m, 2H), 3.40−3.30 (m, 2H), 3.12−3.04 (m, 1H), 2.46−2.26 (m, 2H), 2.06−1.72 (m, 4H), 1.72−1.56 (m, 2H), 1.44 (d, J = 6.0 Hz, 3H). MS (ES): 544.3 (M + H)$^+$.

4-{6-Methoxy-7-[3-(2-methyl-piperidin-1-yl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (87). Compound **87** was synthesized using method A. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.47 (s, 4H), 7.28 (s, 1H), 7.22 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.37−4.30 (m, 6H), 4.00 (s, 3H), 3.83−3.75 (m, 4H), 3.67−3.53 (m, 2H), 3.40−3.30 (m, 2H), 3.08 (dt, J = 12.4, 2.8 Hz, 1H), 2.44−2.24 (m, 2H), 2.40−1.70 (m, 4H), 1.70−1.54 (m, 2H), 1.44 and 1.38 (d, J = 6.6 Hz, 3H), 1.26 (d, J = 6.0 Hz, 6H). MS (ES): 577.3 (M + H)$^+$.

4-{6-Methoxy-7-[3-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)propoxy]quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (90). (a) To a DMF solution (5 mL) of 4-[7-(3-chloropropoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic acid *tert*-butyl ester (0.357 g, 0.819 mmol) were added sodium cyanide (0.240 g, 4.92 mmol) and sodium iodide (0.123 g, 0.819 mmol), and the reaction was heated to 65 °C for 36 h. During this time, no starting material was apparent by HPLC. The reaction mixture was diluted after it was cooled with water and ethyl acetate. The ethyl acetate layer was separated, dried, filtered, and concentrated to crude residue. The crude residue was purified by RP-HPLC to afford the desired cyano intermediate. MS (ES): 428.2 (M + H)$^+$.

Into a pyridine/triethylamine (5 mL, 10:1) solution of the above intermediate (0.273 g, 0.639 mmol) was bubbled H_2S(g) at 0 °C for 10 min. The reaction was stirred at room temperature overnight, during which time complete consumption of starting material was observed by RP-HPLC. The solvent was concentrated under vacuum, and the residue obtained was suspended in acetone (dry, 10 mL) followed by addition of methyl iodide (3 equiv) and then stirred at room temperature overnight. The solvent was evaporated to afford thiomethylimidate intermediate as crude residue. MS (ES): 462.1 (M + H)$^+$.

To the methanol solution (10 mL) of thiomethylimidate (0.136 g, 0.286 mmol) was added a premixed solution of *N*-methylethylenediamine (0.020 mL, 0.213 mmol) and acetic acid (0.013 mL) in methanol (1 mL). The mixture was heated to reflux overnight and then, the solvent was evaporated to afford crude residue. The crude residue was purified by RP-HPLC to afford desired *N*-methylimidazoline intermediate. MS (ES): 485.3 (M + H)$^+$.

(b) The above intermediate (0.130 g, 0.284 mmol) was stirred in 4 N HCl/dioxane (2 mL) for 1 h, and the solvent was evaporated to afford 6-methoxy-4-piperazin-1-yl-7-{3-(1-methyl-4,5-dihydro-1*H*-imidazole-2-yl)propoxy}quinazoline intermediate. The urea formation was carried out using method B with 4-isopropoxyphenyl aniline to afford analogue **90** as a white solid (0.020 g, 20%). ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.49 (s, 1H), 7.27 (s, 1H), 7.22 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.51 (hept, J = 6.2 Hz, 1H), 4.36−4.30 (m, 4H), 4.03 (s, 3H), 3.98−3.90 (m, 2H), 3.87−3.77 (m, 4H), 3.14 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 2.32−2.24 (m, 2H), 1.27 (d, J = 6.0 Hz, 6H). MS (ES): 562.3 (M + H)$^+$.

4-[7-(3-Carbamimidoyl-propoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (91). Compound **91** (0.045 g, 45%) was synthesized using the same method for **90** and employing ammonium acetate instead of *N*-methylethylenediamine. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.46 (s, 1H), 7.21 (d, J = 9.2 Hz, 2H), 7.22 (s, 1H), 6.83 (d, J = 9.2 Hz, 2H), 4.50 (hept, J = 6.2 Hz, 1H), 4.33−4.26 (m, 6H), 4.00 (s, 3H), 3.81−3.76 (m, 4H), 2.71 (t, J = 7.6 Hz, 2H), 2.34−2.264 (m, 2H), 1.26 (d, J = 6.0 Hz, 6H). MS (ES): 522.3 (M + H)$^+$.

4-[7-(3-Dimethylamino-propoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (92). Compound **92** (0.045 g, 50%) was synthesized by the same method for **90** using dimethylamine. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.48 (s, 1H), 7.25 (s, 1H), 7.22 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.51 (hept, J = 6.2 Hz, 1H), 4.40−4.28 (m, 6H), 4.02 (s, 3H), 3.84−3.74 (m, 4H), 3.39 (t, J = 7.0 Hz, 2H), 2.97 (s, 6H), 2.40−2.12 (m, 2H), 1.27 (d, J = 6.0 Hz, 6H). MS (ES): 523.2 (M + H)$^+$.

4-[7-(3-Aminopropoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (93). 4-(7-Hydroxy-6-methoxy-quinazolin-4-yl)piperazine-1-carboxylic acid *tert*-butyl ester **43** was alkylated with 3-bromopropylamine hydrobromide in the presence of K_2CO_3 followed by deprotection and urea formation with 4-isopropoxy-aniline to afford **93**. ^{1}H NMR (CD_3OD): δ 8.63 (s, 1H), 7.48 (s, 1H), 7.25 (s, 1H), 7.22 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.51 (hept, J = 6.2 Hz, 1H), 4.40−4.28 (m, 6H), 4.02 (s, 3H), 3.84−3.74 (m, 4H), 3.39 (t, J = 7.0 Hz, 2H), 2.40−2.12 (m, 2H), 1.27 (d, J = 6.0 Hz, 6H). MS (ES): 495 (M + H)$^+$.

4-[7-(3-Hydroxypropoxy)-6-methoxy-quinazolin-4-yl]-piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)-amide (94). ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 7.65 (d, 2H), 7.58 (d, 2H), 7.42 (s, 1H), 7.18 (s, 1H), 4.51 (hept, J = 6.2 Hz, 1H), 4.38−4.26(m, 4H), 4.10−3.94 (m, 7H), 3.84−3.80 (m, 2H), 3.50 (m, 2H), 3.0 (m, 2H), 1.27 (d, J = 6.0 Hz, 6H). MS (ES): 522.2 (M + H)$^+$.

4-[7-(3-Ethanesulfonyl-propoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (95). (a) To an acetone solution (5 mL) of 4-[7-(3-chloropropoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic acid *tert*-butyl ester (0.250 g, 0.573 mmol) was added sodium ethylthiolate, which was stirred at room temperature for 1 h until complete by TLC and RP-HPLC. The reaction mixture was diluted with saturated NH_4Cl and dichloromethane. The layers were separated, and the organic layer was washed with brine, dried (MgSO4), filtered, and concentrated in vacuo to afford intermediate (0.287 g). MS (ES): 463.2 (M + H)$^+$.

To a dichloromethane solution (5 mL) of the above alkylthiol (0.280 g, 0.606 mmol) was added *m*-chloroperbenzoic acid (0.403 g, 1.8 mmol) and stirred at room temperature for 1 h. The RP-HPLC showed consumption of starting material, and a new peak was observed. The solvent was evaporated, and the residue was dissolved in EtOAc washed with saturated $NaHCO_3$ and then 1 N NaOH. The organic layer was then dried ($MgSO_4$), filtered, and concentrated to the desired sulfone intermediate (0.280 g, 95%). MS (ES): 495 (M + H)$^+$.

(b) The above intermediate (0.260 g, 0.526 mmol) was stirred in 4 N HCl/dioxane (2 mL) for 1 h, and the solvent was evaporated to afford 6-methoxy-4-piperazin-1-yl-7-(3-methanesulfonyl-propoxy)quinazoline intermediate. The urea formation was carried out using method B with 4-isopropoxyphenyl aniline to afford analogue **95** as a white solid (0.200 g, 69.8%). ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.47 (s, 1H), 7.23 (s, 1H), 7.20 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.51 (hept, J = 6.2 Hz, 1H), 4.39−4.31 (m, 6H), 4.01 (s, 3H), 3.82−3.77 (m, 4H), 3.34−3.30 (m, 2H), 315 (q, J = 7.2 Hz, 2H), 2.44−2.36 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.27 (d, J = 6.0 Hz, 6H). MS (ES): 594.2 (M + Na), 572.9 (M + H)$^+$.

4-{6-Methoxy-7-[3-(2-methyl-propane-1-sulfonyl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (96). Compound **96** (0.058 g, 50%) was synthesized by the same method used for **95** using isobutyl mercaptan. ^{1}H NMR (CD_3OD): δ 8.54 (s, 1H), 7.39 (s, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.11 (s, 1H), 6.75 (d, J = 8.8 Hz, 2H), 4.43 (hept, J = 6.2 Hz, 1H), 4.31−4.22 (m, 6H), 3.94 (s, 3H), 3.75−3.68 (m, 4H), 3.26−3.22 (m, 2H), 2.97 (d, J = 6.4 Hz, 2H), 2.36−2.28 (m, 2H), 2.25 (hept, J = 6.8 Hz, 1H), 1.19 (d, J = 6.0 Hz, 6H), 1.04 (d, J = 6.8 Hz, 6H). MS (ES): 600.2 (M + H)$^+$.

4-{6-Methoxy-7-[3-(propane-1-sulfonyl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (97). Compound **97** (0.100 g, 90%) was

synthesized by the same method used for **95** using KHMDS to generate anion of propanethiol instead of sodium hydride for methanethiol. ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.47 (s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.39−4.31 (m, 6H), 4.02 (s, 3H), 3.82−3.76 (m, 4H), 3.34−3.30 (m, 2H), 3.14−3.28 (m, 2H), 2.44−2.36 (m, 2H), 1.90−1.80 (m, 2H), 1.26 (d, J = 6.0 Hz, 6H), 1.09 (t, J = 7.6 Hz, 3H). MS (ES): 586.2 $(M + H)^+$.

4-[7-(3-Butane-1-sulfonyl-propoxy)-6-methoxy-quinazolin-4-yl]piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (98). Compound **98** (0.058 g, 50%) was synthesized by the same method used for **95** using KHMDS to generate anion of butanethiol instead of sodium hydride for methanethiol. ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.47 (s, 1H), 7.22 (d, J = 9.2 Hz, 2H), 7.18 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.39−4.30 (m, 6H), 4.01 (s, 3H), 3.82−3.77 (m, 4H), 3.34−3.28 (m, 2H), 3.16−3.10 (m, 2H), 2.44−2.36 (m, 2H), 1.83−1.74 (m, 2H), 1.27 (d, J = 6.0 Hz, 6H). MS (ES): 600.2 $(M + H)^+$.

4-{6-Methoxy-7-[3-(3-methyl-butane-1-sulfonyl)propoxy]-quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (99). Compound **99** (0.045 g, 45%) was synthesized by the same method used for **95** using KHMDS to generate anion of 3-methyl-butane-1-thiol instead of sodium hydride for methanethiol. ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.48 (s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.17 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.40−4.30 (m, 6H), 4.02 (s, 3H), 3.82−3.76 (m, 4H), 3.36−3.30 (m, 2H), 3.16−3.10 (m, 2H), 2.44−2.36 (m, 2H), 1.76−1.66 (m, 3H), 1.27 (d, J = 6.0 Hz, 6H), 0.96 (d, J = 6.4 Hz, 6H). MS (ES): 614.3 $(M + H)^+$.

4-{6-Methoxy-7-[3-(2,2,2-trifluoro-ethanesulfonyl)propoxy]quinazolin-4-yl}piperazine-1-carboxylic Acid (4-Isopropoxyphenyl)amide (100). Compound **100** (0.045 g, 45%) was synthesized by the same method used for **95** using KHMDS to generate anion of 2,2,2-trifluoroethane thiol instead of sodium hydride for methanethiol. ^{1}H NMR (CD_3OD): δ 8.62 (s, 1H), 7.48 (s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.17 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.51 (hept, J = 6.0 Hz, 1H), 4.40−4.30 (m, 6H), 4.01 (s, 3H), 3.82−3.75 (m, 4H), 3.51 (t, J = 7.2 Hz, 2H), 3.19 (q, J = 7.4 Hz, 2H), 2.48−2.40 (m, 2H), 1.27 (d, J = 6.0 Hz, 6H), 0.96 (d, J = 6.4 Hz, 6H). MS (ES): 626.2 $(M + H)^+$.

PDGFR Kinase Phosphorylation Assay in MG63 Cells. Human osteosarcoma MG63 cells expressing endogenous βPDGFR were grown to confluency in 96 well microtiter plates under standard tissue culture conditions, followed by serum starvation for 16 h. Briefly, quiescent cells were incubated at 37 °C with increasing concentrations of the analogues (0.01−30 μM) for 30 min followed by the addition of 8 nM PDGF-BB for 10 min. To measure the effect of plasma on analogue potency, quiescent MG63 cells were incubated with analogues in the presence or absence of 45% human plasma prior to PDGF-BB stimulation. Cells were lysed, and clarified lysates were transferred into a second microtiter plate in which the wells were previously coated with anti-βPDGFR monoclonal antibody and then incubated for 2 h at room temperature. After the cells were washed three times with binding buffer, 250 ng/mL of rabbit polyclonal antiphosphotyrosine antibody (Transduction Laboratory, Lexington, KY) was added and plates were incubated at 37 °C for 60 min. Subsequently, each well was washed three times with binding buffer and incubated with 1 μg/mL of horseradish peroxidase-conjugated antirabbit antibody (Boehringer Mannheim Biochemicals, Indianapolis, IN) at 37 °C for 60 min. Wells were washed prior to adding ABTS (Sigma Chemicals, St. Louis, MO), and the rate of substrate formation was monitored at 650 nm.

Specificity Analysis on PDGFR Family Kinases. PDGFR family kinase assays were cell-based enzyme-linked immunosorbent (ELISA) assays using CHO cells expressing chimeric protein containing the extracellular and transmembrane domains of βPDGFR and the cytoplasmic domain of CSF-1R, c-Kit, and Flt-3, which were grown to confluency in 96 well microtiter plates under standard tissue culture conditions, followed by serum starvation for 16 h. Phosphorylation assays were performed as described for the βPDGFR phosphorylation assay in MG63 cells.

Pharmacokinetic Analysis. Pharmacokinetics analysis of **24**, **61**, **75**, **76**, and **85** was conducted in fasted male Lewis rats, female Beagle dogs, and male Cynomolgus monkeys. The doses studied are summarized in Table 10. Blood samples were collected prior to administration and serially out to 24 or 48 h. The plasma concentration of each compound was analyzed using LC/MS/MS (PE-SCIEX). Pharmacokinetic parameters were calculated by noncompartmental analysis of concentration−time data using Watson program, version 6.1.1.

Metabolic Stability Method. Each compound was incubated with HLM in the presence of cofactors. The experiment was conducted in a shaking waterbath at 37 °C. Incubation mixtures contained a final concentration of 0.1 M phosphate buffer (pH 7.4), 3.3 mM $MgCl_2$, 1 mg/mL liver microsomes, 5 mM of compound, and NADPH-generating system. The NADPH-generating system contained 1.3 mM NADP, 3.3 mM glucose-6-phosphate, and 0.4 U/mL glucose-6-phosphate dehydrogenase. The reaction was started by the addition of the NADPH-generating system. A 0.1 mL aliquot was taken from the incubation at 0, 7, 15, 35, and 60 min into a tube containing 0.1 mL of cold acetonitrile and KN1022, an internal standard. The mixture was vortexed and centrifuged. The supernatant was diluted with water and injected into a SCIEX API-365 LC/MS/MS equipped with an APCI source. The slope of disappearance of each compound in the microsomal incubation was determined by a linear regression analysis of the natural logarithm (ln) of peak area ratio of the compound and internal standard vs time. Half-life values were calculated as ln(2) divided by the disappearance slope.

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