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Novel Nonpeptide CCK-B Antagonists: Design and Development of Quinazolinone Derivatives as Potent, Selective, and Orally Active CCK-B Antagonists[1]

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We have designed a novel series of CCK-B receptor antagonists by combining key pharmacophores, an arylurea moiety of **1** and a quinazolinone ring of **3**, from two known series. Our earlier studies showed that compounds with methylene linkers in our "target" produced moderate binding affinity and selectivity for CCK-B receptors, whereas its higher and lower homologues resulted in loss of affinity. Introduction of −NH− as a linker dramatically enhanced binding affinity and selectivity for CCK-B receptors, thus providing several compounds with single-digit nanomolar binding affinity and excellent selectivity. Analogous to the earlier studies of the series of quinazolinone derivatives **3**, we also found 3-isopropoxyphenyl as a preferred substitution on the N-3 quinazolinone. Electron-withdrawing substitutions on the urea terminal phenyl ring enhanced the CCK-B potency. Representative compounds of this series were tested in the functional assay and showed pure antagonist profiles. Compounds **51** and **61** were orally active in the elevated rat X-maze test. These compounds were also evaluated for their pharmacokinetic profile. The absolute oral bioavailability of compound **61** was 22% in rats.

Introduction

Cholecystokinin (CCK), a 33-amino acid polypeptide, is distributed in various molecular forms throughout the peripheral and central nervous system.[2] The receptors for CCK have been classified in two subtypes, CCK-A and CCK-B, by using various radiolabeled probes.[3] CCK-A receptors exist primarily in peripheral tissues, such as the gall bladder and pancreas, whereas CCK-B receptors are mainly located in the central nervous system.[4,5] Discovery of potent and selective ligands for both CCK-A and CCK-B receptors has provided further support for the existence of two receptor subtypes. Recently, cloning and expression of both of the CCK receptors from rat and human have been achieved.[6−8] It has been postulated that CCK-B is involved in a variety of neurological disorders such as anxiety, pain, and panic disorder.[9,10] These findings have led to the development of a variety of CCK-B receptor antagonists with remarkable structural diversity for the treatment of neurological diseases.[11] Earlier, we reported CI-988,[12] a 'peptoid' analogue of CCK-4, as a clinical candidate which showed poor oral bioavailability in both preclinical and clinical studies.[13−16] Further optimization in the 'peptoid' series provided CI-1015 with an improved pharmacokinetic profile;[17] however, we felt the need to develop potent and selective nonpeptide CCK-B antagonists which might possess even better pharmacokinetic properties.

Asperlicin, a weak and nonselective CCK ligand,[18] has been used as a template for designing distinct series of novel nonpeptide CCK ligands by many research groups (Table 1).[19−24] On the basis of earlier studies, we recently outlined our approach to designing a novel series of CCK-B antagonists (Figure 1).[25] The initial results showed that the linker between the two key moieties was critical for CCK-B binding affinity. Compound **7**, with a methylene group as a linker, showed moderate binding affinity and selectivity for CCK-B receptors, whereas its higher and lower homologues (**8** and **12**) resulted in loss of binding affinity (Table 2). We anticipated that the optimal linker between the two key moieties, the quinazolinone ring and the arylurea functionality, would bring the cyclic amide group of the constrained quinazolinone and the urea moieties into a preferred orientation, thus providing more potent and selective CCK-B antagonists. As a part of our continued search for the optimal linker, we decided to explore the effect of a heteroatom as a linker. Thus, we introduced the −NH− group as a linker and observed dramatic improvement in CCK-B binding affinity and selectivity. In this paper, we present the synthesis, structure−activity relationship, functional and in vivo activities, and pharmacokinetic profile of compounds in this new series.

Chemistry

Compounds with methylene and ethylene linkers, **7** and **8**, respectively, were prepared as shown in Scheme 1. Coupling of methyl anthranilate with protected

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Table 1. Binding Affinities of Reference Compounds

			IC_{50} (nM)		
compd	R^1	R^2	CCK-B	CCK-A	A/B
1a	3-Me		8.5[21]	740[21]	87
1b	3-COOMe		8.0[21]	1200[21]	150
2a	3-MeO	3-Me	8.0[22]	140[22]	18
2b	3-MeO	3-COOH	23[22]	925[22]	40
3a	3-iPrO	Br	9.3[23]		
3b	3-NMe_2	Br	16[23]		

amino acids (**4a**,**b**) and subsequent hydrolysis provided the corresponding acid derivatives (**5a**,**b**). Formation of the quinazolinone ring (**6a**,**b**) was achieved in one pot under the coupling condition with CDI. This one-pot cyclization was unique since the reported procedure involved preparation of the corresponding bisamide derivative using CDI and then treatment with a dehydrating agent such as pyridinium *p*-toluenesulfonate or *p*-toluenesulfonic acid to form the quinazolinone ring.[23,24] Deprotection of compounds **6a**,**b** followed by treatment with 4-bromophenyl isocyanate provided the corresponding ureas **7** and **8**. Attempts to prepare the requisite amine precursor (**11**) of compound **12** by the literature procedures were unsuccessful.[26−28] These methods included treatment of the thioxoquinazolinone with ammonia or benzylamine. Amine **11** was successfully prepared by the treatment of the thioxoquinazolinone **9** with an excess of hydrazine in refluxing ethanol to obtain the hydrazino derivative **10**[29] and subsequent cleavage of the N−N bond by hydrogenolysis using 10% palladium on carbon as a catalyst. 2-Aminoquinazolinone **11** was then treated with 4-bromophenyl isocyanate in the presence of sodium hydride to yield compound **12** (Scheme 2). Those thioxoquinazolinones which were not commercially available were prepared by the treatment of anthranilic acid with the requisite isothiocyanate. The isothiocyanates which were not commercially available were prepared by standard methodology reported in the literature. The 3-(3-aminophenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one was prepared by the hydrogenolysis of the corresponding nitro derivative using Raney nickel as a catalyst.

Compound **14** was prepared by the acylation of the 2-hydrazinoquinazolinone with 4-bromobenzoyl chloride. Compounds **13**, **15**−**51**, and **53**−**61** were prepared by the treatment of the 2-hydrazinoquinazolinone with the requisite isocyanate in acetonitrile or a mixture of acetonitrile and 1,4-dioxane (Scheme 3). The carboxylic acid derivative **52** was prepared from its *tert*-butyl ester (**51**) by the treatment with TFA in methylene chloride.

Results and Discussion

Our initial work[25] in this series suggested that the linker between the two key moieties was critical for CCK-B binding affinity (Table 2). Compound **7**, with a methylene group as a linker, showed moderate binding affinity and selectivity for CCK-B receptors, whereas its higher and lower homologues (**8** and **12**) resulted in loss of CCK binding affinity. To further search for the optimal linker, we chose to probe the effect of a heteroatom as a linker. Replacement of the methylene group with nitrogen provided compound **13** with marked improvement in binding affinity and selectivity for CCK-B receptors. The significant improvements in binding affinity and selectivity of compound **13** suggest that the −NH− group may play an important role in interactions with the CCK-B receptor. The corresponding amide analogue **14** was less active, suggesting the requirement of the *N*-arylurea functionality for CCK-B potency.

Having identified the −NH− linker as critical for CCK-B binding affinity and selectivity, we then chose to search for the optimal substitution on the N-3 position of quinazolinone with −NH− as a linker. We selected two preferred substitutions, 3-methyl and 3-carbethoxy, on to the *N*-phenyl ring of the urea moiety from our previous study.[30] Compounds shown in Tables 3 and 4 were prepared simultaneously and are segregated only for the purpose of clarity. The binding data for the compounds shown in Table 3 suggested that the compounds with one chloro substitution on the urea terminus phenyl ring (**18** and **19**) showed no significant improvement in binding affinities, whereas compounds **20** and **21**, with dichloro substitution, showed moderate improvement in the CCK-B binding affinity. In the case of alkoxy group substitution at the meta position of the phenyl ring, an increase in the size of the alkoxy side chain at the group (methoxy **22**, ethoxy **24**, and isopropoxy **25**) showed improved CCK-B binding. Thus, compound **25**, with 3-isopropoxyphenyl substitution, showed 11 nM binding affinity for the CCK-B receptor with 582-fold selectivity. Compound **26**, with 3-amino substitution, showed better binding affinity (107 nM) for CCK-A receptors with 2-fold selectivity. However, no further effort was made to improve the CCK-A binding affinity. Interestingly, the *N*,*N*-dimethylamino analogue **27** reverted back to CCK-B selectivity. Replacement of the phenyl ring with a heterocycle (pyridyl **28** and 1-naphthyl **29**) proved detrimental to CCK receptor binding affinity.

Binding affinities for a similar series of compounds with the above set of substitutions on the N-3 position of the quinazolinone ring, having 3-carbethoxy substitution on the *N*-phenyl ring of the urea moiety, are shown in Table 4. It is evident from Table 4 that all the compounds showed consistent improvement in the CCK-B binding affinity over their corresponding 3-methyl derivatives. In particular, compound **40**, with 3-isopropoxy substitution, showed 1.5 nM binding affinity and 2313-fold selectivity for CCK-B receptors. Thus, analogous with earlier studies related to compound **3a**,[23] we also found that 3-isopropoxyphenyl and 3-(*N*,*N*-dimethylamino)phenyl were preferred substitutions on to the N-3 position of the quinazolinone.

Having established that 3-isopropoxyphenyl substitution is a preferred substitution on the N-3 position of quinazolinone, we then examined a structure−activity relationship (SAR) at the urea terminus. Binding data (Table 5) suggest that a planar hydrophobic ring was preferred over a nonplanar lipophilic moiety (phenyl **45** vs cyclohexyl **44**). Unsubstituted phenyl derivative **45** and its 3-methyl analogue **25** were equipotent. The substitution of the electron-donating methoxy group at any position showed no dramatic effect in binding affinities (**46**−**48**), whereas the substitution of the electron-withdrawing carbethoxy group showed significant effects (**49**, **40**, and **50**). Carbethoxy substitution at the meta position was preferred over that at the para

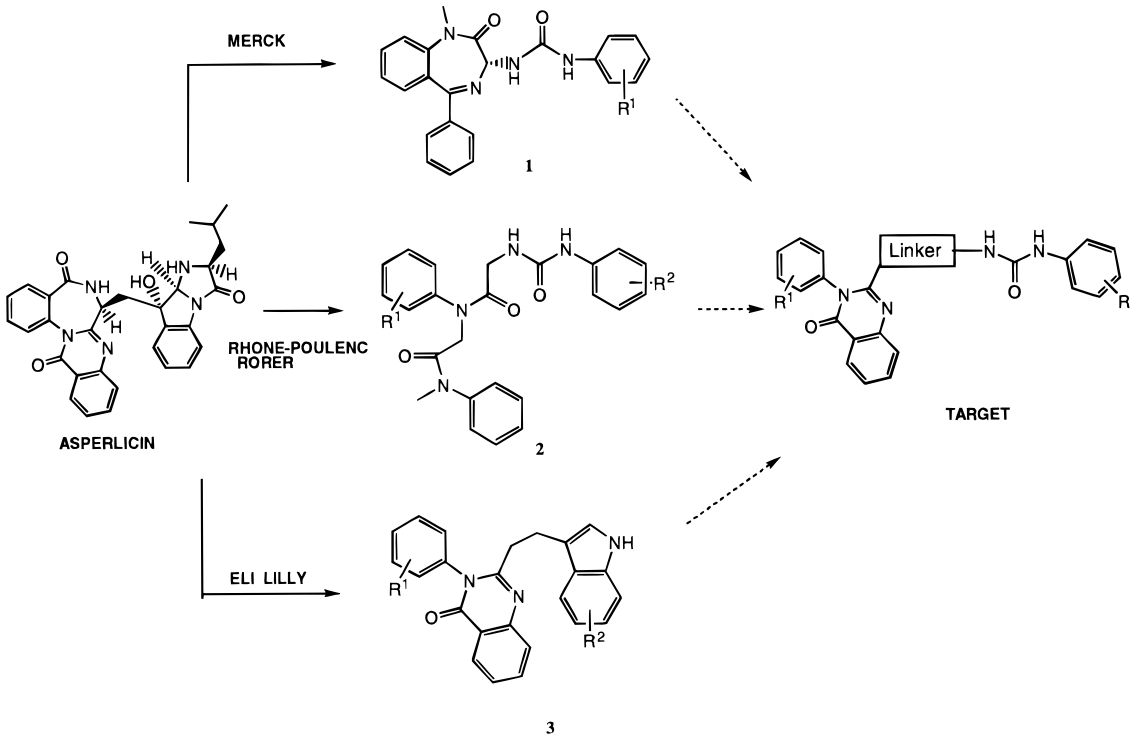
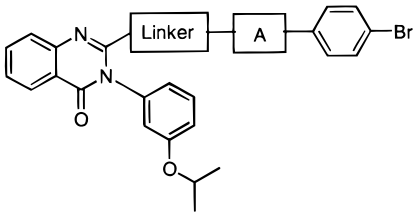


Figure 1. Design of novel target.

Table 2. Linker SAR[a]



			IC_{50} (nM)		
compd	linker	A	CCK-B	CCK-A	A/B
7	CH_2	NHCONH	140	980	7
8	CH_2CH_2	NHCONH	585	1630	2.8
12	–	NHCONH	>1000	>1000	
13	NH	NHCONH	14	3430	245
14	NH	NHCO	88	5560	63

[a] IC_{50} represents the concentration (nM) producing half-maximal inhibition of specific binding of [^{125}I]Bolton Hunter CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) or the rat pancreas (CCK-A). The values given are the geometrical mean of at least three separate experiments. Statistical errors were 15% of the mean values.

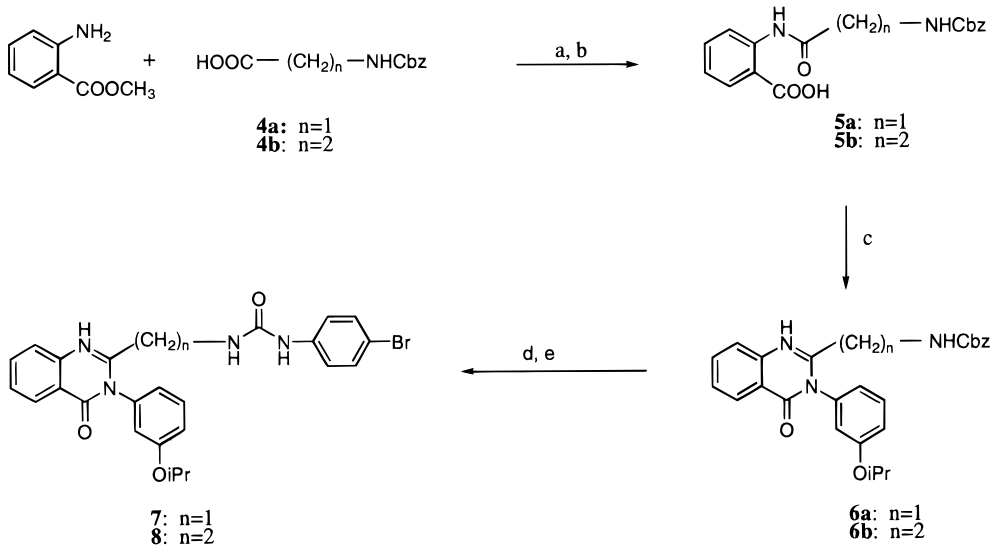
position (**40** vs **50**). However, carbethoxy substitution at the ortho position was detrimental to CCK binding affinities. The bulky *tert*-butylcarbonyl group (**51**) was well-tolerated at the meta position, but the corresponding acid derivative (**52**) lost some CCK-B binding affinity. Compounds with electron-withdrawing halogen substitutions in the para position (bromo **13** and chloro **53**) showed no improvement in potency over the unsubstituted phenyl analogue, but chlorine substitution at the meta position was preferred over that at the para position (**54** vs **53**). A similar trend was also observed for trifluoro derivatives (**55** and **56**). On the basis of these observations, additional compounds with other electron-withdrawing groups at the meta position (nitro **57** and cyano **58**) were prepared, and as expected, they exhibited excellent potency and selectivity for CCK-B receptors.

Since compound **58**, with the 3-cyano group on the phenyl ring at the urea terminus, showed 1.2 nM binding affinity and 4458-fold selectivity for CCK-B receptors, we prepared compounds **59**−**61** (Table 6) to probe the effect of the combination of a 3-cyanophenyl moiety at the urea terminus with other key substitutions at the N-3 position of the quinazolinone ring that were identified earlier. Binding data suggested that most of the compounds maintained their potency for CCK-B receptors.

While the synthesis and SAR study were ongoing, we chose to establish functional activity of this novel series of ligands. Thus, we examined selected compounds in in vitro functional assay which utilizes CCK-B receptors (Table 7). Compounds **13**, **40**, and **33** were evaluated in the guinea pig stomach strip assay.[30] All the compounds reversibly antagonized pentagastrin-evoked increase in intracellular calcium levels and showed no agonist activity.

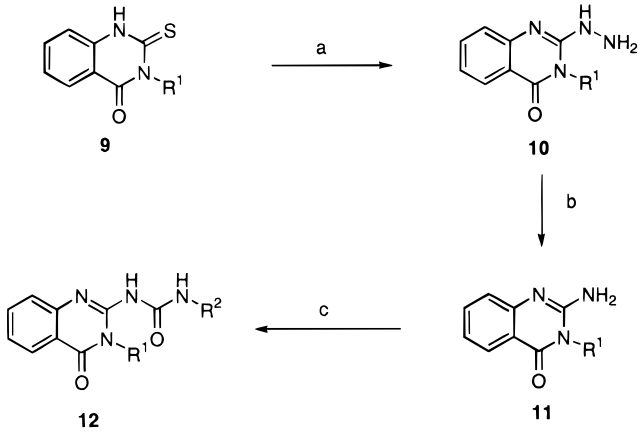
To further establish the ability of these novel ligands to antagonize CCK-induced behavioral response in an animal model in vivo, compounds **51** and **61** were evaluated in the elevated rat X-maze test.[31] Compound **51** was selected because of its excellent CCK-B binding affinity, whereas compound **61** was selected because of its basic functionality. These compounds were compared with the reference compound **3a**. Oral administration of **3a**, **51**, and **61** (0.01−1.0 mg/kg dissolved in poly(ethylene glycol)-200) 40 min before the test increased time spent by rats on the end sections of the X-maze with respective minimum effective doses of 0.1, 1.0, and 1.0 mg/kg (Figure 3). The increase in the percentage time spent on the end sections of the X-maze suggests that these compounds possess anxiolytic-like

Scheme 1[a]



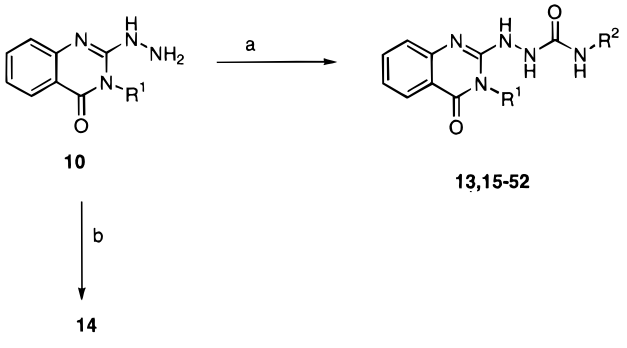
[a] (a) CDI; (b) LiOH; (c) CDI, 3-iPrO-PhNH$_2$; (d) Pd−C/H$_2$; (e) 4-Br-PhNCO.

Scheme 2[a]



[a] (a) Hydrazine, ethanol; (b) Raney Ni, H$_2$; (c) NaH/DMF, R^{2}NCO.

Scheme 3[a]

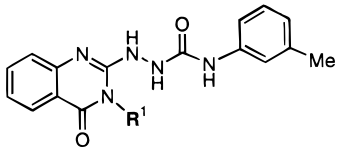


[a] (a) R^{2}NCO; (b) R^1 = 3-iPrO-Ph, 4-bromobenzoyl chloride, TEA.

action. None of the compounds altered the total number of entries, suggesting a lack of sedative action.

Compounds **51** and **61** were also examined for their pharmacokinetic profile (Table 8).[32] Both compounds were administered orally at 10 mg/kg, and different vehicles were used for the administration because of aqueous solubility limitation. Compound **51** was delivered as a solution in 25:40:35 ethanol/PEG400/5% dextrose water (v/v/v) at a nominal concentration of 1.5 mg/mL, whereas compound **61** was dosed as a solution

Table 3. Binding Affinities of (3-Methylphenyl)urea Derivatives[a]



		IC$_{50}$ (nM)		
compd	R^1	CCK-B	CCK-A	A/B
15[b]	Ph	1244	7330	6
16	Ph	1083	39% @ 10 μM	
17	3-F-Ph	915	26% @ 10 μM	
18	3-Cl-Ph	225	20% @ 10 μM	
19	4-Cl-Ph	1170	10% @ 10 μM	
20	2,3-Cl$_2$-Ph	73	3010	41
21	3,4-Cl$_2$-Ph	97[c]	10% @ 10 μM	
22	3-MeO-Ph	200	5100	26
23	3,4-(MeO)$_2$-Ph	2110	34% @ 10 μM	
24	3-EtO-Ph	45	2568	57
25	3-^{i}PrO	11	6400	582
26	3-NH$_2$-Ph	219	107	0.5
27	3-NMe$_2$-Ph	63	4900	78
28	3-pyridyl	4280	12500	3
29	1-naphthyl	3562	7% @ 10 μM	

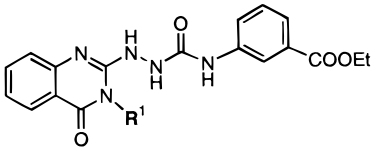
[a] See footnote a of Table 2. [b] Unsubstituted phenylurea derivative. [c] The value from a single experiment.

in 10:40:50 dimethylacetamide/PEG400/5% dextrose water (v/v/v) at 3.3 mL/kg. After po administration, there were no notable clinical observations. Plasma concentrations of compound **51** were below the limit of quantitation (<0.25 μg/mL) for all samples from all po-dosed animals. In addition, there was no evidence of the corresponding carboxylic acid derivative **52** in the samples. Estimation of best case oral bioavailability for compound **51** was <5%. After po administration of compound **61**, maximum observed plasma concentration (C_{max}) was 0.91 mg/mL and time to reach C_{max} (t_{max}) was 25.0 min. Estimate of absolute oral bioavailability of compound **61**, based on the ratio of normalized po AUC to iv AUC, was 22%.

Conclusion

Our original strategy of designing a novel target by combining key pharmacophores of two known series has

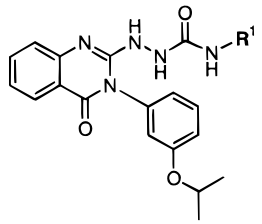
Table 4. Binding Affinities of (3-Carbethoxyphenyl)urea Derivatives[a]



compd	R^1	IC_{50} (nM) CCK-B	CCK-A	A/B
30	Ph	152	37% @ 10 μM	
31	3-F-Ph	26	30% @ 10 μM	
32	3-Cl-Ph	33	4980	151
33	4-Cl-Ph	14	15% @ 10 μM	
34	2,3-Cl_2-Ph	50	1660	33
35	3,4-Cl_2-Ph	2.4	16% @ 10 μM	
36	3-MeO-Ph	15	2330	155
37	4-MeO-Ph	592	20%	
38	3,4-$(MeO)_2$-Ph	611	20% @ 10 μM	
39	3-EtO-Ph	5.0	1210	242
40	3-iPrO	1.5	3470	2313
41	3-NMe_2-Ph	5.0	2650	530
42	3-pyridyl	319	11200	35
43	1-naphthyl	35% @ 10 μM	5% @ 10 μM	

[a] See footnote a of Table 2.

Table 5. Binding Affinities of *N*-3-(3-Isopropoxyphenyl)-quinazolinone Derivatives[a]

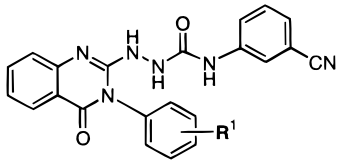


compd	R^1	IC_{50} (nM) CCK-B	CCK-A	A/B
44	cyclohexyl	108	17300	160
45	Ph	15	4580	305
25	3-Me-Ph	11	6400	582
46	2-MeO-Ph	10	4200	420
47	3-MeO-Ph	22	7470	340
48	4-MeO-Ph	25	15490	620
49	2-COOEt-Ph	7670	22%	
40	3-COOEt-Ph	1.5	3470	2313
50	4-COOEt-Ph	57	3160	55
51	3-COOtBu-Ph	1.9	2960	1557
52	3-COOH-Ph	29	8110	280
13	4-Br-Ph	14	3430	245
53	4-Cl-Ph	14	3590	256
54	3-Cl-Ph	5.9	2420	410
55	4-CF_3-Ph	38	2780	73
56	3-CF_3-Ph	8.0	2240	280
57	3-NO_2-Ph	1.0	2560	2560
58	3-CN-Ph	1.2	5350	4458

[a] See footnote a of Table 2.

resulted in the identification of more potent series of CCK-B receptor antagonists. The spatial arrangement of these two moieties was critical for potency and selectivity (Figure 2). The introduction of −NH− as a linker significantly enhanced CCK-B binding affinity and selectivity, thus providing compounds with single-digit nanomolar binding affinity and excellent selectivity. Analogous to the earlier studies of the series of quinazolinone derivatives **3**, we also found 3-isopropoxyphenyl as a preferred substitution on to the N-3 quinazolinone. Electron-withdrawing substitutions on the urea terminal phenyl ring enhanced CCK-B potency. The representative compounds from this series showed

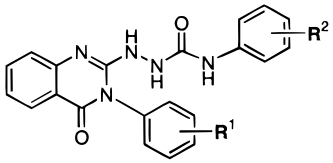
Table 6. Binding Affinities of (3-Cyanophenyl)urea Derivatives[a]



compd	R^1	IC_{50} (nM) CCK-B	CCK-A	A/B
59	H	262	37% @ 10 μM	
60	3-EtO	5.8	4450	767
58	3-iPrO	1.2	5350	4458
61	3-NMe_2	14	7100	507

[a] See footnote a of Table 2.

Table 7. Functional Activity of Selected CCK-B Receptor Antagonists[a]



compd	R^1	R^2	IC_{50} (nM)
13	3-iPrO	4-Br	54
40	3-iPrO	3-COOEt	22
33	4-Cl	3-COOEt	33

[a] Functional assays were carried out on guinea pig stomach strip cells.

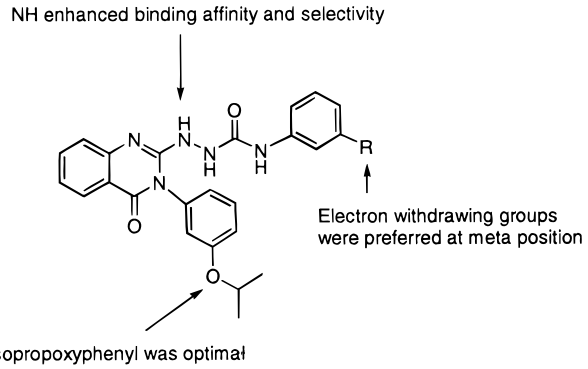


Figure 2. Summary of the SAR.

full antagonist profiles in the in vitro assay. Compounds **51** and **61** were orally active in the elevated rat X-maze test and showed dose-dependent anxiolytic-like action. These compounds were also evaluated for their pharmacokinetic profile, and absolute oral bioavailability of compound **61** in rats was estimated at 22%.

Experimental Section

Materials used were obtained from commercial suppliers and were used without purification, unless otherwise noted. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were determined on a Varian Unity 400 spectrometer with tetramethylsilane as an internal standard. Elemental analyses were determined on a Perkin-Elmer model 240C instrument or were determined by Robertson Labs. All new compounds yielded spectral data consistent with the proposed structure and microanalyses within 0.4% of the theoretical values unless indicated otherwise. Physical data for compounds are given in Table 9.

***N*-(4-Bromophenyl)-*N*-[[3,4-dihydro-3-[3-(1-methylethoxy)phenyl]-4-oxo-2-quinazolinyl]methyl]urea (7). (a)**

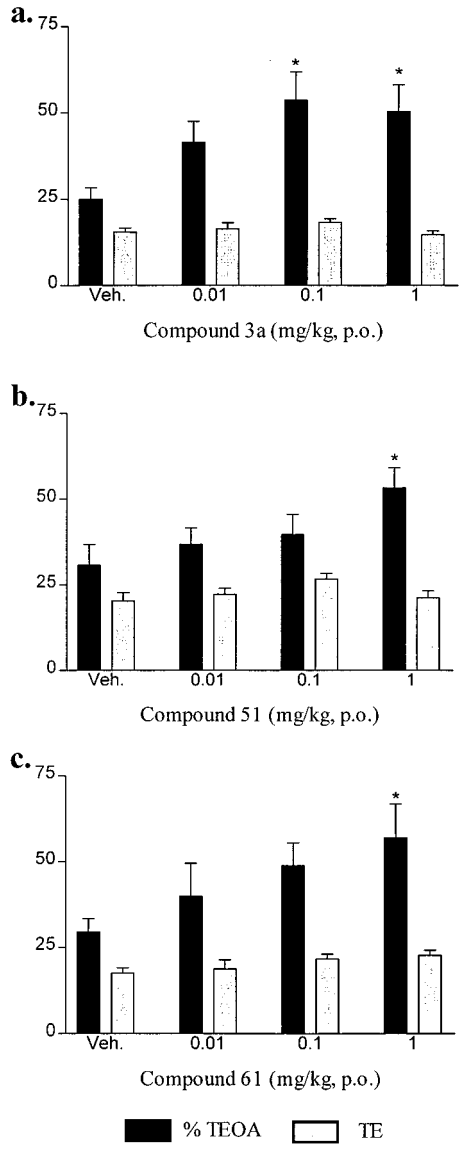
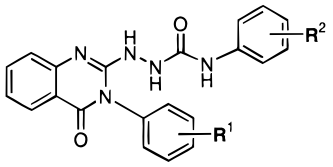


Figure 3. Effects of compounds **3a**, **51**, and **61** in the elevated X-maze. Compounds **3a**, **51**, and **61** were administered po in PEG200 40 min before the test. The percent time spent (% TOEA) and the total number of entries (TE) were measured for each animal during the 5-min test. Results are shown as the mean (verticle bars represent ±SEM) of 10 animals/per group. *Significantly different from vehicle-treated controls; *P*, 0.05 (ANOVA followed by Dunnett's *t*-test).

2-[[[[(Phenylmethoxy)carbonyl]amino]acetyl]amino]-benzoic Acid Methyl Ester. To a solution of [(carbobenzyl)-oxy]glycine (9.8 g, 4.7 mmol) in THF (100 mL) was added 1,1-carbonyldiimidazole (8.1 g, 5.0 mmol) at room temperature. After the mixture stirred under nitrogen for 1 h, methyl anthranilate (6.3 g, 4.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature and then concentrated. The residue was dissolved in ethyl acetate (100 mL) and washed with water, 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated. The resulting product was crystallized from ethyl acetate to yield 7.6 g (55%) of the title compound as a white solid, mp 121−122 °C. ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 3H), 4.1 (d, J = 5.8 Hz, 2H), 5.19 (s, 2H), 5.5 (br s, 1H), 7.1 (dt, J = 1.0, 7.1 Hz, 1H), 7.15−7.45 (m, 5H), 7.55 (dt, J = 1.5, 7.1 Hz, 1H), 8.69 (dd, J = 1.5, 7.5 Hz, 1H), 11.52 (br s, 1H). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

(b) 2-[[[[(Phenylmethoxy)carbonyl]amino]acetyl]-amino]benzoic Acid. To a solution of 2-[[[[(phenylmethoxy)-carbonyl]amino]acetyl]amino]benzoic acid methyl ester (7.6 g, 2.2 mmol) in dioxane (100 mL) was added lithium hydroxide (1.4 g, 3.3 mmol) in water (20 mL). The reaction mixture was stirred for 24 h, concentrated, and acidified with 10% HCl. The solid that separated was filtered and washed with water. Drying in a vacuum at 60% C provided 7.0 g (95%) of the title compound as a white solid, mp 155−156 °C. ^{1}H NMR (DMSO): δ 3.8 (d, J = 6.0 Hz, 2H), 5.08 (s, 2H), 7.1−7−45 (m, 6H), 7.61 (dt, J = 1.7, 7.0 Hz, 1H), 8.02 (m, 2H), 8.61 (d, J = 7.9 Hz, 1H), 11.7 (br s, 1H), 13.68 (br s, 1H). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

Table 8. Summary of Pharmacokinetic Profile of Selected CCK-B Receptor Antagonists[a]



compd	R^1	R^2	vehicle	C_{max}	t_{max}	CL	% F (% RSD)
51	3-iPrO	3-COOtBu	A	<0.25	NA	18	<5 (10)
61	3-NMe_2	3-CN	B	0.91	25	29.5	22 (8)

[a] A, 25:40:35 ethanol/PEG400/5% dextrose water (v/v/v); B, 10:40:50 DMA/PEG400/5% dextrose water (v/v/v); C_{max}, maximum observed plasma concentration (μg/mL); t_{max}, time to reach C_{max} (min); CL, systemic plasma clearance (mL/min/kg); % F, percent absolute oral bioavailability; % RSD, percent relative standard deviation.

(c) *N*-[[3,4-Dihydro-3-[3-(methylethoxy)phenyl]-4-oxo-2-quinazolinyl]methyl]benzeneacetamide. To a solution of 2-[[[[(phenylmethoxy)carbonyl]amino]acetyl]amino]benzoic acid (3.35 g, 10 mmol) in 100 mL of THF at room temperature was added 1,1-carbonyldiimidazole (1.8 g, 11 mmol). After the mixture stirred under nitrogen for 1 h, a solution of 3-isopropoxyaniline (1.51 g, 10 mmol) in 25 mL of THF was added and the mixture was heated to reflux for 24 h. The reaction mixture was cooled, and solvent was removed under reduced pressure. The resulting product was dissolved in ethyl acetate and washed with water, 1 N HCl, saturated aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and concentration, it was chromatographed over silica gel (1:1, v/v, ethyl acetate−hexane) to provide 3.0 g (65%) of the title compound as a white solid, mp 155 °C. ^{1}H NMR ($CDCl_3$): δ 1.3 (m, 6H), 4.13 (m, 2H), 4.55 (s, 1H), 5.16 (s, 2H), 6.75 (s, 1H), 6.78 (dd, J = 2.0, 7.7 Hz, 1H), 7.0 (dd, J = 1.9, 6.5 Hz, 1H), 7.7 (d, J = 8.0 Hz, 1H), 7.8 (m, 1H), 7.5−7.1 (m, 8H), 8.3 (dd, J = 1.2, 3.4 Hz, 1H). Anal. ($C_{26}H_{25}N_3O_4$) C, H, N.

(d) 2-(Aminomethyl)-3-[3-(methylethoxy)phenyl]- 4(3*H*)-quinazolinone. A solution of *N*-[[3,4-dihydro-3-[3-(methylethoxy)phenyl]-4-oxo-2-quinazolinyl]methyl]benzeneacetamide (1.47 g, 3.3 mmol) in 100 mL of methanol was treated with 20% palladium on carbon (100 mg), and the resulting suspension was subjected to 1 atm of hydrogen at 51.9 psi for 4 h with agitation at 30 °C. This mixture was then filtered through Celite, and the solvent was removed under reduced pressure to give 1.0 g (92%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.33 (dd, J = 2.7, 6.3 Hz, 6H), 2.15 (br s, 2H), 3.56 (s, 2H), 4.55 (m, 1H), 6.7 (m, 1H), 6.77 (m, 1H), 7.0 (m, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.48 (dt, J = 1.2, 5.53 Hz, 1H), 7.73−7.82 (m, 2H), 8.29 (dd, J = 1.2, 7.5 Hz, 1H). Anal. ($C_{18}H_{19}N_3O_2 \cdot 0.5CH_3OH$) C, H, N.

(e) *N*-(4-Bromophenyl)-*N*-[[3,4-dihydro-3-[3-(1-methylethoxy)phenyl]-4-oxo-2-quinazolinyl]methyl]urea. To a solution of 2-(aminomethyl)-3-[3-(methylethoxy)phenyl]-4(3*H*)-quinazolinone (0.1 g, 0.33 mmol) in 15 mLof ethyl acetate was added at room temperature 4-bromophenyl isocyanate (0.047 g, 0.35 mmol). The mixture was stirred for 2 h, and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel (1:1, v/v, ethyl acetate−hexane) to give 70 mg (50%) of the title compound as a white solid, mp 125−130 °C. ^{1}H NMR ($CDCl_3$): δ 1.33 (m, 6H), 4.16 (m, 2H), 4.53 (m, 1H), 6.35 (br t, 1H), 6.76 (t, J = 1.1 Hz, 1H),

Table 9. Physical Data for Compounds of Tables 2−6

compd	mol formula	mp (°C)	anal.
7	$C_{25}H_{23}BrN_4O_3 \cdot 0.1C_4H_8O_2$	125−130	C, H, N, Br
8	$C_{26}H_{25}BrN_4O_3$	191−192	C, H, N, Br
12	$C_{24}H_{21}BrN_4O_3 \cdot 0.92H_2O$	230−233	C, H, N
13	$C_{24}H_{22}BrN_4O_3$	212	C, H, N, Br
14	$C_{24}H_{21}BrN_4O_3$	120−122	C, H, N, Br
15	$C_{21}H_{17}N_5O_2$	>280	C, H, N
16	$C_{22}H_{19}N_5O_2$	277−279	C, H, N
17	$C_{21}H_{19}FN_5O_2$	>280	C, H, N, F
18	$C_{22}H_{19}ClN_5O_2$	>280	C, H, N, Cl
19	$C_{22}H_{19}ClN_5O_2$	>280	C, H, N, Cl
20	$C_{22}H_{17}Cl_2N_5O_2 \cdot 0.65H_2O$	217	C, H, N, Cl
21	$C_{22}H_{17}Cl_2N_5O_2$	>280	C, H, N, Cl
22	$C_{23}H_{21}N_5O_3$	193−195	C, H, N
23	$C_{24}H_{23}N_5O_4$	230−235	C, H, N
24	$C_{24}H_{23}N_5O_3$	209−210	C, H, N
25	$C_{25}H_{25}N_5O_3$	204	C, H, N
26	$C_{22}H_{20}N_6O_2$	205−207	C, H, N
27	$C_{24}H_{24}N_6O_2$	205−207	C, H, N
28	$C_{26}H_{21}N_5O_2$	225−227	C, H, N
29	$C_{21}H_{18}N_6O_2 \cdot 0.1H_2O$	>280	C, H, N
30	$C_{24}H_{21}N_5O_4 \cdot 0.2H_2O$	235−236	C, H, N
31	$C_{24}H_{20}FN_5O_4$	217−218	C, H, N, F
32	$C_{24}H_{20}ClN_5O_4$	214−215	C, H, N, Cl
33	$C_{24}H_{20}ClN_5O_4$	215−216	C, H, N, Cl
34	$C_{24}H_{19}Cl_2N_5O_4$	228−229	C, H, N, Cl
35	$C_{24}H_{19}Cl_2N_5O_4$	236−237	C, H, N, Cl
36	$C_{25}H_{23}N_5O_5$	195−196	C, H, N
37	$C_{25}H_{23}N_5O_5$	211−213	C, H, N
38	$C_{26}H_{25}N_5O_6$	>280	C, H, N
39	$C_{26}H_{25}N_5O_5$	186−187	C, H, N
40	$C_{27}H_{27}N_5O_5$	190−191	C, H, N
41	$C_{26}H_{26}N_6O_4$	207−209	C, H, N
42	$C_{23}H_{20}N_6O_4 \cdot 0.34C_4H_8O_2$	212−213	C, H, N
43	$C_{28}H_{23}N_5O_4 \cdot 0.38H_2O$	258−259	C, H, N
44	$C_{24}H_{29}N_5O_3$	205−207	C, H, N
45	$C_{24}H_{23}N_5O_3$	197−198	C, H, N
46	$C_{25}H_{25}N_5O_4$	209−211	C, H, N
47	$C_{25}H_{25}N_5O_4$	204−205	C, H, N
48	$C_{25}H_{25}N_5O_4$	190−191	C, H, N
49	$C_{27}H_{27}N_5O_5$	194−195	C, H, N
50	$C_{27}H_{27}N_5O_5 \cdot 0.32C_4H_8O_2$	194−195	C, H, N
51	$C_{29}H_{31}N_5O_5$	185−186	C, H, N
52	$C_{25}H_{23}N_5O_5 \cdot 0.28H_2O$	207	C, H, N
53	$C_{24}H_{22}ClN_5O_3$	204−206	C, H, N, Cl
54	$C_{24}H_{22}ClN_5O_3 \cdot 3H_2O$	200−201	C, H, N, Cl
55	$C_{25}H_{22}F_3N_5O_3$	201−202	C, H, N, F
56	$C_{25}H_{22}F_3N_5O_3$	113−120	C, H, N, F
57	$C_{24}H_{22}N_6O_5 \cdot 3H_2O$	195−196	C, H, N
58	$C_{25}H_{22}N_6O_3$	195	C, H, N
59	$C_{22}H_{16}N6O_2 \cdot 0.25H_2O$	222−223	C, H, N
60	$C_{24}H_{20}N_6O_3$	218−220	C, H, N
61	$C_{24}H_{21}N_7O_2$	204−205	C, H, N

6.78 (m, 1H), 7.01 (d, J = 8.6 Hz, 1H), 7.06 (br s, 1H), 7.22 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.75 (m, 1H), 8.30 (dd, J = 1.2, 6.7 Hz, 1H). Anal. ($C_{25}H_{23}N_4O_3Br_1 \cdot 0.1C_4H_8O_2$) C, H, N.

***N*-(4-Bromophenyl)-*N′*-[2-[3,4-dihydro-3-[3-(1-methylethoxy)phenyl]-4-oxo-2-quinazolinyl]ethyl]urea (8).** Compound **8** was synthesized according to the procedure described for compound **7**, mp 191−192 °C. ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 5.25 Hz, 6H), 2.67 (t, J = 5.25 Hz, 2H), 3.66 (m, 2H), 4.55 (m, 1H), 6.10 (br s, 1H), 6.50 (br s, 1H), 6.76 (m, 2H), 7.0 (m, 1H), 7.00 (m, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.33 (m, 2H), 7.41 (m, 2H), 7.49 (m, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.75 (dt, J = 1.44, 7.0 Hz, 1H), 8.26 (dd, J = 2.12, 6.75 Hz, 1H). Anal. ($C_{26}H_{25}N_4O_3Br_1$) C, H, N.

***N*-(4-Bromophenyl)-*N*-[3-(3-isopropoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]urea (12). (a) 3-(3-Isopropoxyphenyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one.** To a mixture of 3-isopropoxyaniline (6.0 g, 40 mmol) and triethylamine (4.85 g, 48 mmol) was slowly added thiophosgene (5.06 g, 44 mmol) at 0 °C in an ice bath. The reaction mixture was warmed to room temperature, stirred for 2 additional hours, and concentrated under reduced pressure. The residue was diluted with ethyl acetate, and solid triethylamine hydrochloride salt was removed by filtration. The filtrate was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to yield 9.0 g of crude 3-isopropoxyphenyl isothiocyanate.

The mixture of the above crude 3-isopropoxyphenyl isothiocyanate and anthranilic acid (6.04 g, 44 mmol) in 150 mL of acetic acid was refluxed for 16 h. The reaction mixture then was cooled to room temperature, and the white solid was separated which was filtered to yield 9.0 g of the title compound (72.1%), mp 288−290 °C. ^{1}H NMR (DMSO): δ 1.27 (dd, J = 1.8, 3.9 Hz, 6H), 4.58 (m, 1H), 6.8 (d, J = 8.7 Hz, 1H), 6.87 (dd, J = 1.9, 2.2 Hz, 1H), 6.93 (m, 1H), 7.4 (m, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 1.5, 7.0 Hz, 1H), 7.92 (d, J = 1.1, 6.75 Hz, 1H), 13.0 (br s, 1H). Anal. ($C_{17}H_{16}N_2O_2S_1$) C, H, N, S.

(b) 2-Hydrazino-3-(3-isopropoxyphenyl)-3*H*-quinazolin-4-one. A mixture of the above product (3.12 g, 10 mmol) and anhydrous hydrazine (3.2 g, 100 mmol) in 100 mL of ethanol was refluxed for 18 h. The reaction mixture was then cooled to room temperature, and a white solid was separated which was filtered and washed with 10 mL of ethanol to obtain 1.2 g (38%) of the title compound as a white solid. The filtrate was concentrated, and an additional 1.6 g (50.4%) of the title compound was isolated by crystallization from ethyl acetate, mp 158−160 °C. ^{1}H NMR (DMSO-d_6): δ 1.28 (d, J = 5.55 Hz, 6H), 4.36 (br s, 2H), 4.64 (m, 1H), 6.83 (d, J = 7.71 Hz, 1H), 6.89 (br s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.15 (m, 1H), 7.35−7.45 (m, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H). Anal. ($C_{17}H_{18}N_4O_2$) C, H, N.

(c) 2-Amino-3-(3-isopropoxyphenyl)-3*H*-quinazolin-4-one. A solution of 2-hydrazino-3-(3-isopropoxyphenyl)-3*H*-quinazolin-4-one (2.5 g, 8.0 mmol) in 100 mL of methanol−THF (1:1) was treated with Raney Ni (2.0), and the resulting suspension was subjected to 1 atm of hydrogen at 52.0 psi for 30 h with agitation at a temperature of 50 °C. An additional 1.0 g of Raney Ni was added, and reaction was continued for an additional 40 h at 50 °C. The mixture was then filtered through Celite, and the solvent was removed under reduced pressure to give the title compound as a reddish-yellow solid. This crude product was then triturated with ethyl acetate and hexane to isolate product as a light-yellow solid, mp 130−133 °C. ^{1}H NMR (DMSO-d_6): δ 1.28 (d, J = 5.8 Hz, 6H), 4.65 (m, 1H), 6.29 (br s, 2H), 7.04 (m, 1H), 6.93 (m, 1H), 7.04 (m, 1H), 7.11 (dt, J = 0.9, 6.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H), 7.6 (m, 1H), 7.88 (dd, J = 1.2, 6.8 Hz, 1H). Anal. ($C_{17}H_{17}N_3O_2$) C, H, N.

(d) 1-(4-Bromophenyl)-3-[3-(3-isopropoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]urea. To a solution of 2-amino-3-(3-isopropoxyphenyl)-3*H*-quinazolin-4-one (295 mg, 1.0 mmol) in DMF (10 mL) was added 50% NaH (48 mg, 1 mmol) at room temperature, and the mixture stirred for 30 min. To this mixture was added 4-bromophenyl isocyanate (198 mg, 1.0 mmol), and the mixture stirred for 2 h at room temperature. The reaction was quenched with a drop of water and concentrated. It was then diluted with ethyl acetate and filtered. The filtrate was concentrated and chromatographed over silica gel using 100% CH_3Cl to isolate pure product as a white solid (70 mg, 14.2%), mp 230−233 °C. ^{1}H NMR (DMSO-d_6): δ 1.28 (d, J = 5.0 Hz, 1H), 4.50−4.65 (m, 1H), 6.8−8.0 (m, 12H), 9.17 (m, 1H), 13.0 (br s, 1H). Anal. ($C_{24}H_{21}Br_1N_4O_3 \cdot 0.92H_2O_1$) C, H, N, Br.

4-Bromobenzoic Acid *N′*-[3-(3-Isopropoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]hydrazide (14). To a mixture of 2-hydrazino-3-(3-isopropoxyphenyl)-3*H*-quinazolin-4-one (0.155 g, 0.5 mmol) and triethylamine (56 mg, 0.55 mmol) in CH_2Cl_2 (10 mL) was added 4-bromobenzoyl chloride (112 mg, 0.51 mmol) at room temperature. The reaction mixture was stirred overnight, diluted with 25 mL of CH_2Cl_2, and washed with water, saturated aqueous $NaHCO_3$, dilute HCl, and brine. After drying over $MgSO_4$ and concentration, it was chromatographed over silica gel (1:4, v/v, ethyl acetate−

hexane) to provide 110 mg (46%) of the title compound as a yellow solid, mp 120−122 °C. Anal. ($C_{24}H_{21}Br_1N_4O_3$) C, H, N, Br.

General Procedure for Synthesis of Hydrazinecarboxamides: *N*-(4-Bromophenyl)-2-[3,4-dihydro-3-[3-(1-methylethoxy)phenyl]-4-oxo-2-quinazolinyl]hydrazinecarboxamide (13). 2-Hydrazino-3-(3-isopropoxyphenyl)-3*H*-quinazolin-4-one (0.155 g, 0.5 mmol) was dissolved in 5.0 mL of CH_3CN, and 4-bromophenyl isocyanate (0.1 g, 0.5 mmol) was added at room temperature. The resulting reaction mixture was stirred at room temperature for 16 h. The white solid was separated which was filtered and washed with CH_3CN. The title compound was obtained as a white solid (0.12 g, 47.2%), mp 212 °C. ^{1}H NMR (DMSO-d_6): δ 1.30 (d, J = 6.0 Hz, 6H), 4.6−4.7 (m, 1H), 6.8−7.5 (m, 9H), 7.67 (m, 1H), 7.85 (m, 1H), 7.97 (d, J = 6.75 Hz, 1H), 8.26 (br s, 1H), 8.3 (br s, 1H), 10.5 (br s, 1H). Anal. ($C_{24}H_{22}Br_1N_5O_3$) C, H, N, Br.

Pharmacokinetic Protocol. The oral bioavailability and pharmacokinetics of **51** and **61** were evaluated in fasted Wistar rats. Groups of three male Wistar rats received either a single oral (po) nominal dose of 10 mg/kg or a single intravenous (iv) nominal dose of 5 mg/kg. Doses of **51** and **61** were prepared as a solution in 25:40:35 ethanol/PEG 400/5% dextrose water (v/v/v) and 10:40:50 dimethylacetamide/PEG 400/5% dextrose water, respectively. Heparinized plasma samples were collected from an implanted cannula in the jugular vein at serial times out to 24 h. Plasma samples were frozen until analysis. Plasma sample and dose solutions were assayed with validated HPLC-fluorescence methods for each respective candidate. Pharmacokinetic parameters were determined by standard noncompartmental methods. Absolute oral bioavailability was calculated as the dose-normalized ratio of the area under the curve following po dose to the area under the curve following iv dose.

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