Discovery of 1,5-Benzodiazepines with Peripheral Cholecystokinin (CCK-A) Receptor Agonist Activity (II): Optimization of the C3 Amino Substituent

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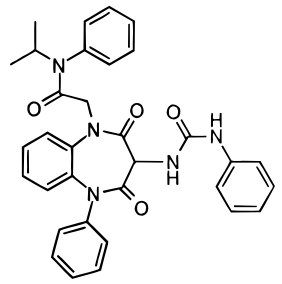
Analogs of the previously reported 1,5-benzodiazepine peripheral cholecystokinin (CCK-A) receptor agonist **1** were prepared which explore substitution and/or replacement of the C-3 phenyl urea moiety. Agonist efficacy on the isolated guinea pig gallbladder (GPGB) was retained with a variety of substituted ureas and amide analogs. Three compounds were identified which were orally active in the mouse gallbladder emptying assay (MGBE). The 2-indolamide (**52**) and *N*-(carboxymethyl)-2-indolamide (**54**) derivatives had improved affinity for the human CCK-A receptor but reduced agonist efficacy on the GPGB. Neither indolamide was orally active in a rat feeding assay. In contrast, the (3-carboxyphenyl)urea derivative (**29**, GW7854) had moderately increased affinity for the human CCK-B receptor but was a potent full agonist on the GPGB and was orally active in both the MGBE and rat feeding assays. GW7854 was a full agonist (EC_{50} = 60 nM) for calcium mobilization on CHO K1 cells expressing hCCK-A receptors and a potent antagonist of CCK-8 (pA_2 = 9.1) on CHO K1 cells expressing hCCK-B receptors. GW7854 is a potent mixed CCK-A agonist/CCK-B antagonist which is orally active in two *in vivo* models of CCK-A-mediated agonist activity.

Introduction

Cholecystokinin (CCK) is a gastrointestinal hormone and neurotransmitter involved in nutrient assimilation, including the secretion of bile and digestive enzymes and the regulation of enteric transit.[1] While a variety of endogenous molecular forms of CCK have been isolated, the C-terminal octapeptide (Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-PheNH_2, CCK-8) appears to be the minimum sequence required for bioactivity.[2−4] CCK is released from intestinal I cells primarily in response to fat and protein ingestion.[5] The physiological actions of CCK are mediated by two G-protein-coupled seven transmembrane receptor subtypes. CCK-A receptors predominate in the periphery (gallbladder, pancreas, pyloric sphincter, and vagal afferent fibers) but are also found in discrete regions of the brain.[6] CCK-B or gastrin receptors predominate in the brain and gastric glands.[7] Although CCK-A and CCK-B receptor sequences are highly conserved among species, considerable variation in receptor subtype distribution has been reported.[8] The utility of a CCK receptor agonist for the treatment of obesity is suggested by studies demonstrating that exogenous CCK can shorten meal duration and reduce meal size in several species, including lean[9] and obese[10] humans. Chronic administration of CCK-8 to patients on total parenteral nutrition has also demonstrated a role for CCK in the prevention of gallstones.[11] The relevant target for both effects is the CCK-A receptor.[12] An orally acting CCK-A agonist which enhanced satiety and decreased meal size could be a useful alternative to current centrally mediated (serotonergic and adrenergic) therapies for the treatment of obesity.[13]

We recently reported the discovery of a series of 1,5-benzodiazepines, exemplified by **1**, which were CCK-A receptor agonists *in vitro* (isolated guinea pig gallbladder) and *in vivo* (rat anorexia).[14] Despite good CCK-A



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agonist efficacy, these compounds had equivalent affinity for both human CCK-A and CCK-B receptors and, while some compounds were potent anorectics in the rat following intraperitoneal administration, none were orally active. We now report the synthesis and biological profile of analogs of **1** which explore both substitution and/or replacement of the C3-position phenyl urea moiety. The primary goal of this work was to identify compounds which were orally active satiety agents in a rat feeding model.

Chemistry

The key amine intermediate used in the preparation of analogs reported in Tables 1−5 was prepared as outlined in Scheme 1. *N*-Phenyl-1,2-phenylene diamine was alklated with bromoacetanilide **2**[14] and the substituted phenylene diamine **3** condensed with diacid

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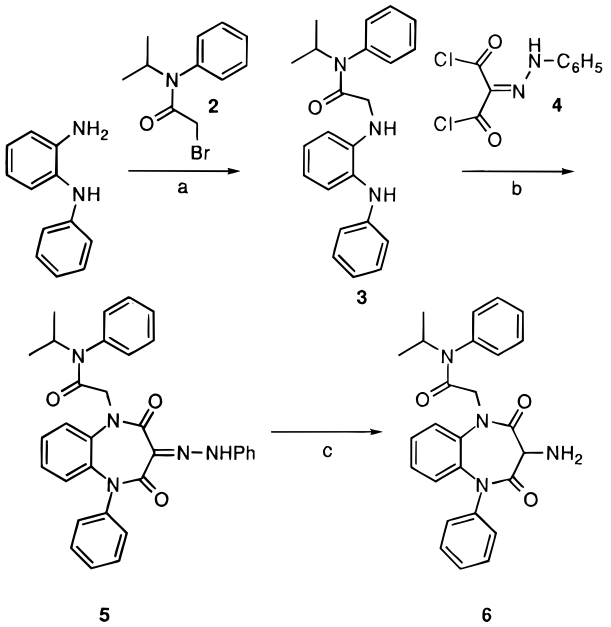
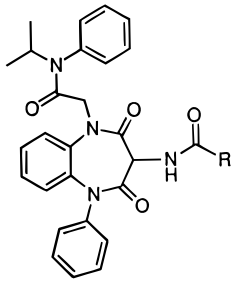
Scheme 1. Synthesis of Intermediate 6[a]



[a] (a) K_2CO_3, DMF; (b) THF; (c) Zn, CH_3COOH.

Table 1. *In Vitro* Functional Data for Unsubstituted Urea Analogs



no.	R	GPGB (30 μM)[a] % CCK-8
1	NHC_6H_5	86
17		ia
18	NH_2	ia
19	$NHCH_2C_6H_5$	1
20	$NHCH(CH_3)_2$	22

[a] Functional activity on the isolated guinea pig gallbladder following incubation with test ligand at 30 μM for 30 min at 37 °C; % CCK-8, percent contraction normalized to that for CCK-8 (1 μM); ia, inactive.

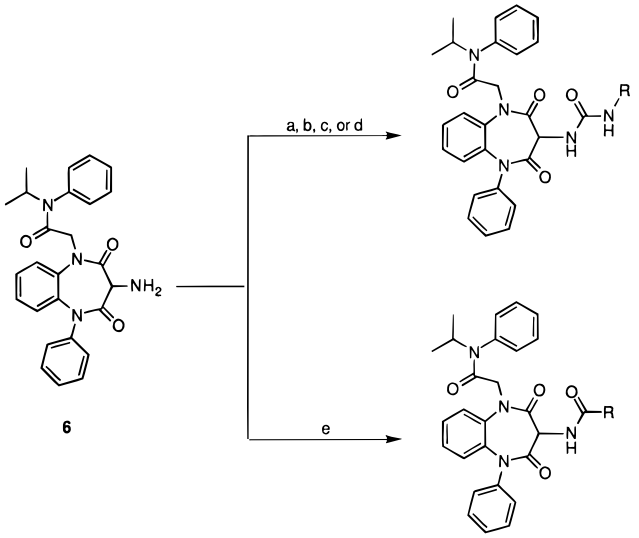
chloride **4**[14] to afford hydrazone **5.** Reduction of hydrazone **5** with zinc/acetic acid provided amine **6**.

Most of the ureas listed in Tables 1−3 were prepared by treatment of **6** with commercially available isocyanates (Scheme 2). Alternatively, anilines were converted to *p*-nitrophenyl carbamate derivatives[15] or activated *in situ* with triphosgene[16] or carbonyldiimidazole[17] prior to reaction with benzodiazepine **6**. Addition and removal of protecting groups followed standard practice.[18] Exceptions to these generalized approaches are noted below.

Condensation of benzoxazolinone with benzodiazepine **6** at 125 °C provided **22** (Table 2).

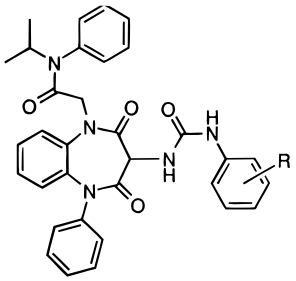
Triflamide **33** (Table 3) was prepared from the corresponding aniline **34** by treatment with triflic anhydride.

Scheme 2. Generalized Scheme for the Preparation of C-3 Analogs of **1**[a]



[a] (a) RNCO, CH_3CN; (b) $RNHCOO_2Ar$; (c) RNH_2, 1,1′-carbonyldiimidazole; (d) RNH_2, $(CCl_3O)_2CO$; (e) EDC or DCC, HOBt, RNH_2.

Table 2. *In Vitro* Functional Activity for Substituted Phenylurea Analogs



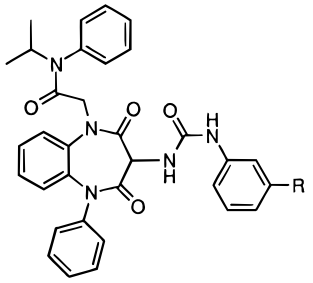
no.	R	GPGB[a] % CCK-8 30 μM	GPGB[a] % CCK-8 1 μM	pK_B
1	H	86	ND	
21	2-CH_3	34	ND	
22	2-OH	ND	16	5.5
23	4-CH_3	20	ND	
24	4-OCH_3	38	ND	
25	4-COOH	14	ND	
26	3-CH_3	5	ND	
27	3-OCH_3	78	ND	
28	3-OH	89	82	
29	3-COOH	100	95	

[a] Functional activity on the isolated guinea pig gallbladder following incubation with test ligand at 30 μM for 30 min or 1 μM for 60 min at 37 °C; % CCK-8, percent contraction normalized to that for CCK-8 (1 μM); pK_B, single dose pA_2 calculated from the fold shift of the CCK-8 concentration-response curve in the presence of test ligand (30 μM); ia, inactive.

Sulfone **36** was prepared by oxidation of the corresponding thioether **35** with *m*-CPBA.

The phenoxy-substituted derivatives **40**−**43** were prepared through the reaction of **6** with the anilines **12**−**15**, activated *in situ* with triphosgene. The anilines were prepared as outlined in Scheme 3. Alkylation of *m*-nitrophenol with *tert*-butyl bromoacetate afforded intermediate **7.** Deprotection of **7** provided phenoxyacetic acid **8**, which was converted to the imidiazolide *in situ* and treated with ammonia or morpholine to provide amides **9** and **10**. Direct alkylation of *m*-nitrophenol with *N*,*N*-dimethylchloroacetamide pro-

Table 3. *In Vitro* Functional Activity for 3-Substituted Phenylurea Analogs



		GPGB[a] % CCK-8	
no.	R	30 μM	1 μM
1	H	86	ND
30	$N(CH_3)_2$	58	29
31	CH_2OH	90	85
32	CN_4H	79	64
33	NHTf	89	87
34	NH_2	76	50
35	SCH_3	58	ND
36	SO_2CH_3	53	ND
37	CH_2COOH	89	ND
38	$CONH_2$	76	ND
39	Cl	ND	7
40	OCH_2CONH_2	95	ND
41	OCH_2CONMe_2	77	ND
42	OCH_2CO-morpholino	78	ND
43	OCH2COOH	98	85
44	$OCH_2CH_2NMe_2$	ND	2

[a] See Tables 1 and 2. ND, not determined.

vided intermediate **11**. Catalytic hydrogenation of **7** and **9**−**11** provided anilines **12**−**15**. Deprotection of the *tert*-butyl ester of **16** afforded the phenoxyacetic acid **43**.

The C-3 amide analogs listed in Table 4 were prepared through the reaction of **6** with commercially available carboxylic acids utilizing standard dehydrating protocols[19] (Scheme 2). Alkylation of indole **52** with *tert*-butyl bromoacetate or *tert*-butyl bromobutyrate, followed by treatment with HCl/dioxane, provided **54** and **55**, respectively.

All compounds reported in Tables 1−6 were purified to homogeneity (>97%) by RP-HPLC, and the resultant lyophile was characterized by analytical RP-HPLC, ^{1}H NMR spectroscopy, and high-resolution mass spectrometry or combustion analysis.

Biology

Analogs were initially evaluated for *in vitro* functional efficacy on the isolated guinea pig gallbladder (GPGB) at 30 or 1 μM concentrations (Tables 1−4).[14] The contractile activity of all compounds reported was reversed completely by addition of the CCK-A receptor selective antagonist MK-329[20] (0.5 μM). Compounds which did not produce contraction were evaluated for antagonist activity against a concentration−response curve for CCK-8 (10^{-11} to 10^{-6} M).[14]

Compounds which induced ≥40% contraction of the GPGB were subsequently evaluated for oral activity in the mouse gallbladder emptying[21] (MBGE) assay at a single dose (1 μmol/kg, po). Only compounds which demonstrated oral efficacy in the mouse were characterized in detail. Full concentration−response curves were obtained on the GPGB, as well as for calcium mobilization with CHO-K1 cells stably expressing the human CCK-A (hCCK-A) or CCK-B (hCCK-B) receptors.[22] Receptor binding affinities were measured on membrane preparations from the stably transfected CHO-K1 cells (Table 5).[23] *In vivo* efficacy was assessed following intraperitoneal (ip) or oral (po) administration in both MGBE[21] and rat feeding[14] models (Table 5). The reported ED_{50}'s represent the half-maximal response for test compound, relative to the highest dose tested.

Results

The single concentration screening data used to evaluate new compounds are provided in Tables 1−4. Of the simple urea replacements in Table 1, the phenyl moiety (**1**) was preferred over the piperazine derivative **17** or unsubstituted urea **18**. Homologation to a benzyl group (**19**) or replacement with an isopropyl moiety (**20**) also reduced agonist efficacy.

Within the phenylurea series, substitution of a methyl group at any position on the aromatic ring significantly reduced agonist efficacy (Table 2). However, the 3-hydroxy (**27**), 3-methoxy (**28**), and 3-carboxyl (**29**) derivatives were fully efficacious. These data suggested that substitution at the 3-position was preferred over either 2- or 4-substitution. Therefore, additional analogs were prepared to explore more fully the structure-activity relationships of these substituted phenyl ureas (Table 3).

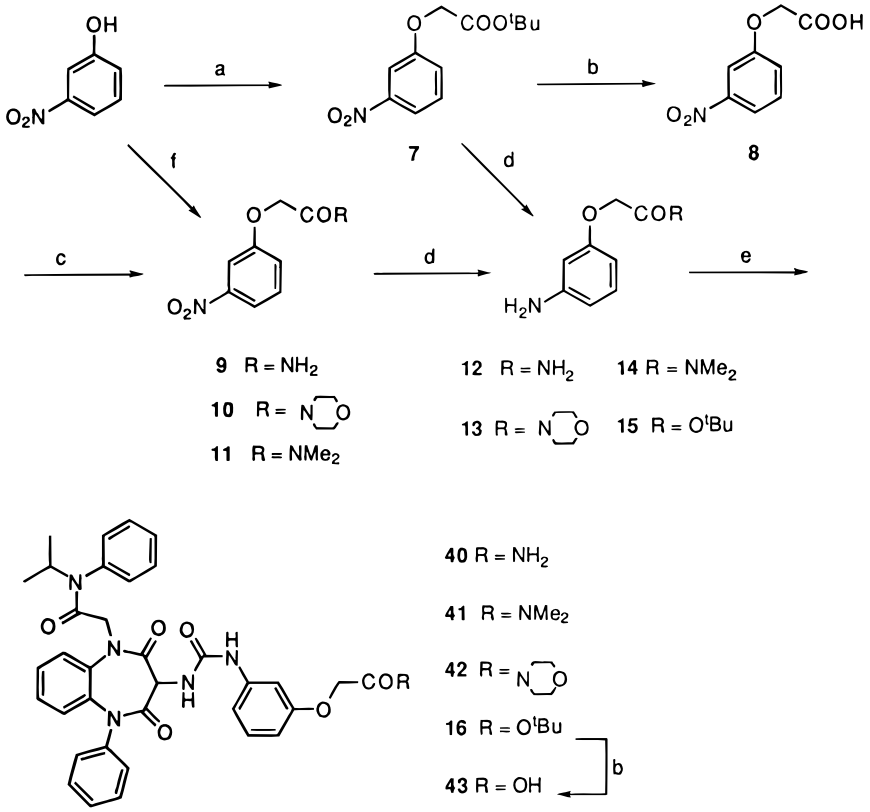
Full efficacy (≥75%) was observed with a variety of substitutents, including amines, acids, acid isosteres and even the phenoxy derivatives **40**−**43**. Partial efficacy (>50%) was observed with the *N*,*N*-dimethyl (**30**), thiomethyl (**35**), and methyl sulfoxide (**36**) derivatives. Only the 3-methyl (**26**), 3-chloro (**39**), and (*N*,*N*-dimethylamino)ethoxy (**44**) derivatives were poorly efficacious at the concentrations tested.

In contrast to the phenyl ureas, most of the C-3 amide analogs were consistently less efficacious (≤60%) at the concentrations tested (Table 4). The phenyl (**45**), pyridyl (**47**, **48**), or substituted phenyl (**49**, **50**) derivatives were equally efficacious on the GPGB. While the 3-indolamide (**51**) was weakly active, the 2-indolamide (**52**) had partial agonist efficacy. Only the *N*-(carboxymethyl)-indolamide derivative **54** appeared fully efficacious. Homologation to the *N*-carboxypropyl derivative (**55**) reduced efficacy.

All analogs which induced at least a 40% contractile response on the GPGB were evaluated at a single oral dose (1 μmol/kg) in the MGBE assay. Of the 25 compounds which met this criteria, three compounds (**29**, **52**, and **54**) were orally active in the mouse. These compounds were characterized further for both *in vitro* (Table 5) and *in vivo* (Table 6) potency and efficacy. Data for **1**[14] and CCK-8 are provided for comparative purposes.

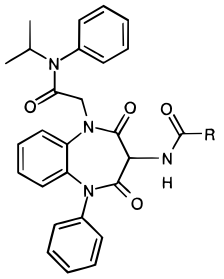
The (3-carboxyphenyl)urea (**29**), indolamide (**52**), and *N*-(carboxymethyl)indolamide (**54**) derivatives were approximately 30-fold, 2.5-fold, and 100-fold more potent, respectively, than **1** on the isolated GPGB (Table 5). These analogs were 100-fold (**29**), 1260-fold (**52**), and 32-fold (**54**) less potent than CCK-8 on this tissue. Again, only the ureas **1** and **29** were fully efficacious at the highest concentration tested (30 μM). The human CCK-A receptor binding affinities of **1** and **29** were 80-fold and 200-fold less than those for CCK-8. Both ureas had slightly better affinity for the human CCK-B receptor subtype. The indoles **52** and **54** had 200-fold

Scheme 3. Synthesis of Phenoxyaniline Derivatives **40**−**43**[a]



[a] (a) NaH, DMF, $BrCH_2COOtBu$; (b) HCl, dioxane; (c) 1,1′-carbonyldiimidazole, THF, amine; (d) H_2, Pd/C; (e) $(CCl_3O)_2CO$, $(C_2H_5)_3N$, THF, **6**; (f) NaH, DMF, $ClCH_2CONH(CH_3)_2$.

Table 4. *In vitro* Functional Activity for C-3 Amide Analogs



no.	R	GPGB[a] % CCK-8 30 μM	1 μM
45	phenyl	57	ND
46	benzyl	ND	28
47	3-pyridyl	43	ND
48	4-pyridyl	43	ND
49	3-carboxyphenyl	56	ND
50	2-carboxyphenyl	58	ND
51	3-indolyl	5	ND
52	2-indolyl	49	ND
53	2-benzofuran	35	ND
54	2-*N*-(carboxylmethyl)indolyl	73	63
55	2-*N*-(carboxypropyl)indolyl	44	ND

[a] See Tables 1−3.

and 25-fold reduced affinity for the human CCK-A receptor, compared to CCK-8. In contrast to the ureas, both indoles had slightly better affinity (20-fold) for the human CCK-A receptor subtype.

Analogs **29**, **52**, and **54** were potent, fully efficacious, and orally active in the MGBE assay (Table 6). These analogs were 40−200-fold less potent that CCK-8 following ip administration. While **54** was the most potent compound following ip administration (ED_{50} = 1.4 nmol/kg, 0.9 μg/kg), **29** was the most potent derivative following po administration (ED_{50} = 55 nmol/kg, 33 μg/kg).

Table 5. *In Vitro* Profile of Lead Benzodiazepines

no.	GPGB[a] pEC_{50}	% max	pIC_{50}[b] h-CCK-A	h-CCK-B	A/B
1	5.9 ± 0.4 (2)	86	7.3 ± 0.1 (3)	7.6 ± 0.1 (3)	0.4
29	7.4 ± 0.3 (3)	102	6.9 ± 0.1 (4)	8.0 ± 0.1 (4)	0.1
52	6.3 ± 0.1 (2)	49	7.8 ± 0.2 (3)	6.5 ± 0.3 (3)	20
54	7.9 ± 0.1 (3)	65	8.0 ± 0.1 (3)	6.7 ± 0.1 (3)	20
CCK-8	9.1 ± 0.2 (4)	100	9.2 ± 0.1 (3)	9.5 ± 0.4 (9)	0.8

[a] Potency and efficacy on the isolated guinea pig gallbladder. pEC_{50}, −log of the concentration that produces half-maximal contractile response; % max, maximal contractile response at 30 μM, normalized to CCK-8 (1 μM), ±SEM (number of determinations). [b] pIC_{50}, −log of the concentration displacing 50% of [125-I]Bolton−Hunter CCK-8 from membrane preparations isolated from CHO-K1 cells stably transfected with cDNA of human CCK-A and CCK-B receptors, ±SEM (number of determinations); A/B, IC_{50} CCK-A/IC_{50} CCK-B.

Analogs **29**, **52**, and **54** were 10−100 times more potent than **1** in the rat feeding assay following intraperitoneal (ip) administration. Since CCK-8 is 900-fold less potent in the rat feeding model, relative to the MGBE model, the potency of the benzodiazepine analogs was more comparable to that of CCK-8 in this assay. However, as seen with the isolated GPGB assay, only the phenylurea derivatives (**1** and **29**) were fully efficacious in this assay. Neither indole achieved >50% anorexia at the highest dose tested (10 μmol/kg, 6 mg/kg). While we have no explanation for these efficacy differences, which could reflect species, pharmacodynamic, or pharmacokinetic differences, these data serve to highlight the variability of animal models. When **29**, **52**, and **54** were screened for oral activity in the rat

Table 6. *In Vivo* Profile of Lead Benzodiazepines

	MGBE[a]				anorexia[b]		
	ip		po		ip		po
no.	ED_{50}	% max	ED_{50}	% max	ED_{50}	% max[c]	% max[d]
1	ND	78	ia	ia	950	96	ia
29	7.1	73	55	77	60	87	58
52	5.0	73	300	85	95	56	ia
54	1.4	88	600	74	10	44	ia
CCK-8	0.03	95	ND	ND	27	95	ND

[a] *In vivo* mouse gallbladder emptying assay; ED_{50}, dose of test compound that produces a half-maximal response of individual compounds, nmol/kg; % max, maximal response at 1 nmol/kg, ip for CCK-8, 0.1 μmol/kg ip or 1 μmol/kg po for test compounds. [b] Anorectic potency in rats conditioned to a palatable liquid diet and fasted for 2 h; ED_{50},dose of test compound that produces a half-maximal response, nmol/kg. [c] % max, maximal response at 0.5 μmol/kg, ip for CCK-8 and 10 μmol/kg, ip for test compound. [d] % max, maximal response at 10 μmol/kg po for test compound; ia, inactive; ND, not determined.

feeding model, only **29** was efficacious, inducing a 60% reduction in food intake following a 10 μmol/kg (6 mg/kg) dose.

The identification of **29** as an orally active analog in two *in vivo* models of CCK-A-mediated activity prompted us to explore further the functional selectivity of this analog. The ability of **29** to influence intracellular calcium was evaluated on the stably transfected CHO cells expressing the hCCK-A or hCCK-B receptors and loaded with FURA2-AM.[22] CCK-8 was a full agonist on both human CCK-A (EC_{50} = 0.1 nM) and CCK-B (EC_{50} = 0.05 nM) cell lines.[22] In contrast, analog **29** was a potent, full agonist on the CHO cells expressing the hCCK-A receptor (EC_{50} = 60 nM, n = 2), but inactive on the CHO cells expressing the hCCK-B receptor (up to 10 mM). Remarkably, **29** potently blocked the CCK-8 concentration response curve on the CHO cells expressing the hCCK-B receptor (pA_2 = 9.1). Thus **29** is a potent, mixed CCK-A agonist/CCK-B receptor antagonist which is orally active in two *in vivo* models of CCK-A-mediated agonist activity.

Discussion

While it was not intuitively obvious that structure−activity relationships developed for the 1,4-benzodiazepine CCK-A and CCK-B receptor antagonists would be applicable to these 1,5-benzodiazepine CCK-A agonists, the literature served as a valuable starting point for the optimization of **1**. Indeed, some parallels were observed. In both antagonist and agonist series, the C-3 phenylurea derivatives were CCK-B receptor selective, based on receptor affinity measurements.[15,24] Within both urea series, phenyl was preferred over benzyl- or alkylureas and substitution of the phenyl ring at the 3-position was generally favored over the 2- or 4-position. One striking difference between the agonist and antagonist series was the loss of agonist efficacy with the 3-methyl (**26**) or 3-chloro (**39**) derivatives. Both substitutions were optimal in the 1,4-benzodiazepine antagonist series.[15]

The 2-indolamide isomer was preferred over the 3-indolamide isomer in both agonist and antagonist series.[25] While the 2-indolamide substitution enhanced CCK-A receptor affinity and selectivity in the 1,4-benzodiazepine antagonists,[25] the improvement of CCK-A receptor affinity and selectivity of the 1,5-benzodiazepine agonists was less dramatic. The indolamide agonists **52** and **54** were not fully efficacious in all models of CCK-A functional activity.

In contrast to the N1-anilidoacetamide substituent, which primarily modulates the agonist efficacy[14] of these 1,5-benzodiazepines, the C-3 substituent seems to influence both receptor subtype affinity and agonist efficacy. That similar structural modifications at the C-3 position of either the 1,4-benzodiazepine antagonists[15,20,24,25] or 1,5-benzodiazepine agonists produced comparable changes in receptor affinity and subtype selectivity again suggests that these nonpeptide antagonists and agonists may share similar structural determinants for receptor recognition.[14]

The identification of compounds within this series of benzodiazepine agonists with improved CCK-A affinity and selectivity compared to **1** has been the focus of two recent reports.[26,27] However, the functional characterization of **29** as a potent mixed CCK-A agonist/CCK-B antagonist suggests that receptor selectivity based on affinity may not be a critical feature for this class of compounds. Since *in vivo* CCK-B agonist activity would be unacceptable in a therapeutic entity because of the potential for peripheral (enhanced gastric acid secretion) or central (enhanced anxiety) side effects, the mixed CCK-A agonist, CCK-B antagonist profile of **29** may actually be ideal. GW 7854 (**29**) was orally active in both *in vivo* models of gallbladder emptying and satiety. Efforts to enhance the oral activity of this class of compounds continue and will be reported at a later date.

Experimental Section

General. All chemicals and solvents are reagent grade unless otherwise specified. CCK-8 was purchased from Sigma (St. Louis, MO). MK-329 was obtained from Merck & Co. (Rahway, NJ). The following solvents and reagents have been abbreviated: tetrahydrofuran (THF), ethyl ether (Et_2O), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), dichloromethane (DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF). Reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60F-254, E. Merck) and visualized with UV light. Final compounds were typically purified by preparative reversed phase high-pressure liquid chromatography (RP-HPLC) using a Waters Model 3000 Delta Prep equipped with a Delta-pak radial compression cartridge (C-18, 300 A, 15 m, 47 mm × 300 mm) as the stationary phase. The mobile phase employed 0.1% aqueous TFA with acetonitrile as the organic modifier. Linear gradients were used in all cases, and the flow rate was usually 100 mL/min (t_0 = 5 min). Appropriate fractions were combined and lyophilized to obtain the target analogs. Analytical purity was assessed by RP-HPLC using a Waters 600E system equipped with a Waters 990 diode array spectrometer (l range 200−400 nm). The stationary phase was a Vydac C-18 column (5 m, 4.6 mm × 200 mm). The mobile phase was the same as above, and the flow rate was 1.0 or 1.5 mL/min (t_0 = 3 min). Analytical data is reported as retention time, t_R , in minutes (% acetonitrile, time, flow rate).

^{1}H NMR spectra were recorded on either a Varian VXR-300 or a Varian Unity-300 instrument. Chemical shifts are reported in parts per million (ppm, δ units). Coupling constants are reported in units of hertz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Low-resolution mass spectra (MS) were recorded on a JEOL JMS-AX505HA, a JEOL SX-102, or a SCIEX-APIiii spectrometers. High-resolution mass spectra were recorded on a AMD-604 (AMD Electra GmbH) high-resolution double-focusing mass spectrometer (Analytical Instrument Group, Raleigh, NC). Mass spectra were acquired in the positive ion mode under electrospray ionization (ESI)

or fast atom bombardment (FAB) methods. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

***N*-Isopropyl-*N*-phenyl-2-[[2-(phenylamino)phenyl]amino]acetamide (3).** Potassium carbonate (6.9 g, 50 mmol) was added to a solution of *N*-phenylphenylenediamine (9.2 g, 50 mmol) in DMF and 2-bromo-*N*-isopropyl-*N*-phenylacetamide, **2** (12.7 g, 50 mmol), in DMF (200 mL), and the mixture was stirred overnight. The DMF was evaporated *in vacuo*, and the residue was dissolved in ethyl acetate (400 mL) and washed exhaustively with aqueous 1 N HCl (4 × 250 mL). The organic layer was washed with water (2 × 200 mL), dried (Na_2SO_4), and evaporated to give the crude product. The oil was purified by chromatography on silica gel (600 g) using first $CHCl_3$ (8000 mL) and then hexane:ethyl acetate (2:1, 8000 mL) as eluents to give the titled compound (10.0 g) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, 6H), 3.22 (s, 2H), 4.95 (m, 1H), 6.36 (d, 1H), 7.42−6.8 (m, 14 H); LRMS (FAB) *m*/*z* 360 $(M + H)^+$; TLC $R_f = 0.18$ ($CHCl_3$).

2-[2,4-Dioxo-5-phenyl-3-(phenylhydrazono)-2,3,4,5-tetrahydro benzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (5). *N*-Isopropyl-*N*-phenyl-2-[[2-(phenylamino)-phenyl]amino]acetamide, **3** (10 g, 27.8 mmol), and 2-(phenylhydrazono)propanedioyl dichloride, **4** (6.83 g, 27.8 mmol), were each dissolved in THF (100 mL) and added simultaneously, with stirring, to a flask containing THF (100 mL) at 0 °C, under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The THF was evaporated *in vacuo*, and the residue was dissolved in ethyl acetate (200 mL). The ethyl acetate solution was washed with 10% aqueous sodium carbonate (2 × 200 mL) and water (2 × 200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residual foam was treated with diethyl ether (50 mL) to precipitate the title compound as a bright yellow solid (7.5 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (m, 6H), 4.4 (m, 2H), 5.05 (m, 1H), 7.6−6.8 (m, 19 H), 11.4 and 10.85 (s, 1H); LRMS (FAB) *m*/*z* 532 $(M + H)^+$; TLC $R_f = 0.19$ (hexane:ethyl acetate, 2:1).

2-(3-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo-[*b*][1,4]diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide (6). Zinc powder (9.1 g, 139 mmol) was added in portions to a slurry of 2-[2,4-dioxo-5-phenyl-3-(phenylhydrazono)-2,3,4,5-tetrahydrobenzo[b][1,4]-diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide, **16** (7.5 g, 14.1 mmol), in glacial acetic acid (30 mL), and the mixture was cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional hour. The solids were removed by filtration through a Celite pad, and the glacial acetic acid was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with 10% aqueous sodium carbonate (2 × 100 mL) and water (2 × 100 mL), dried (Na_2SO_4), and evaporated to a tan oil. Trituration with hexane/ethyl acetate (2:1) provided the title compound as a light tan powder (6.3 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, 6H), 4.3−4.0 (m, 3H), 5.05 (m, 1H), 7.6−6.8 (m, 14H); LRMS (FAB) *m*/*z* 448 $(M + H)^+$; TLC $R_f =$ 0.25 (chloroform:methanol, 9:1).

2-[2,4-Dioxo-5-phenyl-3-(3-phenylureido)-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (1). To a slurry of **6** (0.667 g, 1.49 mmol) in dichloromethane (5 mL) was added phenyl isocyanate (0.177 g, 1.49 mmol) with stirring at ambient temperature. The reaction mixture was stirred for 2 h, and the cream-colored precipitate was separated by filtration to afford the crude product which was purified by preparative RP-HPLC chromatography on a C-18 column with linear gradient elution from 40 to 60% acetonitrile in water with 0.1% TFA buffer over 30 min at a rate of 100 mL/min. Fractions containing the desired material were combined, frozen, and lyophilized to afford the titled product (0.181 g) as a white lyophile: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (d, 3H, J = 7.3 Hz), 0.98 (d, 3H, J = 7.3 Hz), 4.19 (d, 1H, J = 16.6 Hz), 4.48 (d, 1H, J = 16.9 Hz), 4.79 (m, 1H), 5.04 (d, 1H, J = 7.8 Hz), 6.87−6.92 (m, 1H), 6.95 (d, 1H, J = 7.6 Hz), 7.18−7.57 (m, 17H), 9.14 (s, 1H); HRMS calculated for $C_{33}H_{31}N_5O_4$ $(M + H)^+$ 562.2454, observed $(M + H)^+$ 562.2456; HPLC $t_R = 16.5$ min (51−60% CH_3CN, 30 min, 1.0 mL/min). Compounds **19**, **20**, **21**, **23**, **24**, **25**, **26**, **27**, **35,** and **39** were made in an analogous manner.

(3-Nitrophenoxy)acetic Acid *tert*-Butyl Ester (7). Sodium hydride (1.42 g, 35.9 mmol) was added to a 0 °C solution of 3-nitrophenol (5.00 g, 35.9 mmol) in DMF (20 mL), and the resultant solution stirred at 0 °C for 10 min. *tert*-Butyl bromoacetate (5.80 mL, 35.9 mmol) was added dropwise, and the resultant mixture allowed to attain room temperature overnight. The reaction mixture was poured into water (100 mL), and the resultant mixture extracted into ethyl acetate (3 × 50 mL). The combined organics were washed with saturated aqueous sodium carbonate (50 mL), water (2 × 50 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude intermediate **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 4.60 (s, 2H), 7.26 (m, 1H), 7.47 (t, J = 7.1 Hz, 1H), 7.69 (m, 1H), 7.83 (dd, J = 7.1, 0.8 Hz, 1H). Intermediate **7** was made in analogous manner.

(3-Nitrophenoxy)acetic Acid (8). A mixture of the above intermediate **7** (3.00 g, 11.8 mmol) and 4 N HCl in dioxane (10 mL) was stirred at room temperature for 2 h. Diethyl ether (50 mL) was added, and the solvents were decanted to leave a pale brown gum. Trituration with diethyl ether gave the desired product as a cream-colored solid (1.49 g): ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.82 (s, 2H), 7.40 (dd, J = 7.1, 0.8 Hz, 1H), 7.57 (t, J = 7.1 Hz, 1H), 7.69 (t, J = 0.8 Hz, 1H), 7.83 (dd, J = 7.1, 0.8 Hz, 1H).

(3-Nitrophenoxy)acetamide (9). A mixture of intermediate **8** (0.245 g, 1.24 mmol) and 1,1-carbonyldiimidazole (0.201 g, 1.24 mmol) in THF (5 mL) was stirred at room temperature for 3 h, ammonia (2.0 M in methanol, 2.48 mL, 4.96 mmol) was added, and the resultant solution was stirred at room temperature for 6 h. The solvents were removed *in vacuo*, and the residual solid was triturated with diethyl ether to afford the crude product which was recrystallized from ethyl acetate to afford the desired product (0.123 g) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2H), 7.28 (dd, J = 7.1, 0.8 Hz, 1H), 7.51 (t, J = 7.1 Hz, 1H), 7.80 (t, J = 0.8 Hz, 1H), 7.83 (dd, J = 7.1, 0.8 Hz, 1H). Intermediate **10** was also made in this manner.

(3-Aminophenoxy)acetamide (12). A mixture of intermediate **9** (0.123 g, 0.63 mmol) and 10% palladium on carbon (0.012 g) in ethyl acetate (10 mL) was stirred under an atmosphere of hydrogen for 1 h. The solids were removed by filtration, and the filtrate was concentrated *in vacuo* to afford the desired intermediate (0.100 g) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (s, 2H), 6.22 (dd, J = 7.1, 0.8 Hz, 1H), 6.37 (m, 2H), 7.08 (t, J = 0.8 Hz, 1H). Intermediates **13**, **14**, and **15** were made in this manner.

2-(2,4-Dioxo-5-phenyl-3-ureido-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide (18). To a stirring solution of intermediate **6** (200 mg, 0.45 mmol) in DCM (5 mL) was added (*S*)-(−)-α-methylbenzyl isocyanate (0.064 mL, 0.45 mmol). The reaction mixture was stirred for 12 h and then concentrated to dryness. The residue was triturated with methanol to give 131 mg of desired product. This crude urea (131 mg, 0.22 mmol) was dissolved in acetic acid (10 mL) and treated with 10% Pd/C (131 mg) under 50 psi of hydrogen. After 12 h the solids were removed by filtration through a pad of Celite, concentrated, and purified by RP-HPLC (42−60% acetonitrile, 30 min) to give the titled compound (0.036 g) as a white lyophile: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, J = 6.6 Hz, 6H); 4.12 (d, J = 17.0 Hz, 1H), 4.44 (d, J = 17.0 Hz, 1H), 4.83 (bs, 2H), 5.00 (m, 1H), 5.21 (d, J = 7.6 Hz, 1H), 6.14 (m, 1H), 6.97 (d, J= 7.9 Hz, 1H), 7.3 (m, 8H), 7.5 (m, 5H); MS $C_{22}H_{27}N_5O_4$ $(M + H)^+$ = 486.2141, observed $(M + H)^+$ = 486.2133; t_R= 26.5 min (42−60% acetonitrile, 30 min, t_0= 3 min).

2-[3-[3-(2-Hydroxyphenyl)ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (22). A solution of intermediate **6** (0.221 g, 0.5 mmol) and 2-benzoxazolinone (0.070 g, 0.5 mmol) in dry DMF (2 mL) was stirred at 125 °C for 48 h. The reaction mixture was poured into an ice−1 N HCl mixture, and the product was extracted with AcOEt. The solvent was removed *in vacuo*, and the product was purifed by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99), providing

the crude product. Trituration with methanol afforded the title compound (0.040 g) as a white amorphous solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (2d, J = 7 Hz, 6H), 4.17 (d, J = 16 Hz, 1H), 4.46 (d, J = 16 Hz, 1H), 4.79 (m, 1H), 5.07 (m, 1H), 6.60−7.00 (m, 3H), 7.21−7.82 (m, 16H), 8.65 (s, 1H), 9.72 (s, 1H); MS $C_{33}H_{32}N_5O_5$ $(M + H)^+$ = 578.2403, observed $(M + H)^+$ = 578.2388; RP-HPLC column Dynamax C-8, 2 mL/min (70% acetonitrile), t_R = 4.3 min.

***N*-Isopropyl-2-[3-[3-(3-hydroxyphenyl)ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-phenylacetamide (28).** A solution of 3-(benzyloxy)aniline (0.50 g, 2.51 mmol) and 1,1′-carbonyldiimidazole (0.434 g, 2.67 mmol) in methylene chloride (25 mL) was stirred at room temperature for 16 h, and the solvents were then removed *in vacuo*. A mixture of this crude product (0.245 g, 0.678 mmol) and 2-(3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*]-[1,4]diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide, **6** (0.150 g, 0.339 mmol), in DMF (15 mL) was heated at 90 °C for 6h. The reaction mixture was poured into water (30 mL), and the resultant mixture was extracted into ethyl acetate (3 × 30 mL). The combined organics were washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude intermediate. Purification by flash column chromatography (CH_2Cl_2:MeOH, 50:1) gave the pure intermediate *N*-isopropyl-2-[3-[3-[3-(benzyloxy)phenyl]ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-phenylacetamide (101 mg) as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (2d, J = 7.4 Hz, 6H), 4.15 (d, J = 14.4 Hz, 1H), 4.45 (d, J = 14.4 Hz, 1H), 5.00 (m, 3H), 5.40 (d, J = 7.4 Hz, 1H), 6.40 (br, 1H), 6.61 (dd, J = 7.4, 1.1 Hz, 1H), 6.8−7.4 (m, 24H). Compounds **30** and **37** were also made in this manner.

A mixture of *N*-isopropyl-2-[3-[3-[3-(benzyloxy)phenyl]ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-phenylacetamide (0.100 g, 0.150 mmol) and 10% palladium on carbon (0.010 g) in ethanol (10 mL) was stirred under an atmosphere of hydrogen at 50 psi for 2 h. The solids were removed by filtration, and the filtrate wasconcentrated *in vacuo* to afford the crude product. This was purified by preparative RP-HPLC (42−68% acetonitrile, 30 min) at a rate of 100 mL/min. Fractions containing the desired material were combined, frozen, and lyophilized to provide the titled compound as a white powder (26.2 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s × d, J = 7.3 Hz, 6H), 4.18 (d, J = 15.3 Hz, 1H), 4.52 (d, J = 15.3 Hz, 1H), 4.97 (sept, J = 7.3 Hz, 1H), 5.42 (d, J = 6.8 Hz, 1H), 6.42 (d, J = 6.7 Hz, 1H), 6.62 (d, J = 6.7 Hz, 1H), 6.85−7.0 (m, 2H), 7.14−7.55 (m, 17H); HRMS calculated for $C_{33}H_{31}N_5O_5$ $(M + H)^+$ = 578.2397, observed $(M + H)^+$ = 578.2383; RP-HPLC (42−68% CH_3CN, 30 min; 1 mL/min) t_R= 11.6 min.

3-[3-[1-[(Isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]ureido} **benzoic Acid (29).** A solution of 3-(ethoxycarbonyl)phenyl isocyanate (124 mg) in dichloromethane (3 mL) was added to a solution of 2-(3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide, **6** (288 mg), in dichloromethane (3 mL). The reaction mixture was allowed to stir at room temperature for 30 min. The dichloromethane was evaporated *in vacuo*, and the residue was suspended in acetonitrile and heated at reflux for 1 h with stirring. The product precipitated upon cooling to 0 °C and was washed with cold acetonitrile to give 3-[3-[1-[(Isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]ureido]benzoic acid ethyl ester as a white solid (312 mg): ^{1}H NMR (300 MHz, DMSO-d_6): d 0.96 (m, 6H), 1.27 (t, J = 7.2 Hz, 3H), 4.18 (d, J = 15.8 Hz, 1H), 4.3 (dd, J = 6.8 Hz, 2H), 4.48 (d, J = 16 Hz, 1H), 4.8 (m, 1H), 5.05 (d, J = 9 Hz, 1H), 7.6−6.9 (m, 18H), 8.05 (s, 1H), 9.4 (s, 1H); MS (FAB) m/z 634 $(M + H)^+$.

A solution of 3-[3-[1-[(Isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]ureido] benzoic acid ethyl ester (312 mg, 0.493 mol) in methanol (23 mL) and tetrahydrofuran (10 mL) was heated at reflux. Aqueous 5% potassium carbonate (6.5 mL) was added, and the reflux was maintained for 2.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was neutralized and triturated with 1 N HCl and water to give the crude product. The crude product was dissolved in ethyl acetate (20 mL), heated to reflux for 3 h and then cooled. The resulting precipitate was separated by filtration and dried under vacuum to provide the title compound (225 mg) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.96 (m, 6H), 4.18 (d, J = 15.8 Hz, 1H), 4.48 (d, J = 16 Hz, 1H), 4.8 (m, 1H), 5.05 (d, J = 9 Hz, 1H), 7.6−6.9 (m, 18H), 8.05 (s, 1H), 9.4 (s, 1H); MS (FAB) m/z 606 $(M + H)^+$. Anal. ($C_{34}H_{31}N_5O_6$·0.3TFA) C, H, N.

2-[3-[3-[3-(Hydroxymethyl)phenyl]ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (31). To a stirring solution of *m*-nitrobenzyl alcohol (2.0 g, 13.5 mmol) and triethylamine (2.0 mL, 14.3 mmol) in chloroform (20 mL) was added acetyl chloride (2 mL, 28.1 mmol) in chloroform (20 mL) at 0 °C. Stirring was continued at room temperature for 1 h, and the reaction mixture was washed successively with 1 N HCl, water, and saturated $NaHCO_3$ and dried, andthe solvent was evaporated *in vacuo*. The residue was dissolved in acetic acid (100 mL), and Zn powder (6 g, 91.7 mmol) was added. The resulting mixture was stirred for 3 h, the solids were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$, and the solvent was evaporated *in vacuo*. The residue was dissolved in chloroform (30 mL) at 0 °C, and pyridine (1 mL, 12.3 mmol) and *p*-nitrophenyl chloroformate (1 g, 4.97 mmol) in chloroform (10 mL) were added successively. The reaction mixture was stirred at room temperature for 1 h, and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and washed successively with 1 N HCl and saturated $NaHCO_3$. The product was recrystallized from ethyl acetate:hexane mixture providing 3-acetoxyaniline *p*-nitrophenyl carbamate (1.09 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 5.09 (s, 2H), 7.00−7.47 (m, 7H), 8.27 (d, J = 9 Hz, 2H).

A solution of intermediate **6** (663 mg, 1.5 mmol), 3-acetoxyaniline *p*-nitrophenyl carbamate (447 mg, 1.5 mmol), and triethylamine (0.21 mL) in acetonitrile (10 mL) was stirred at room temperature for 3 h. The product was removed by filtration and washed with methanol, providing the product (0.650 g) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 2.01 (s, 3H), 4.17 (d, J = 16 Hz, 1H), 4.46 (d, J = 16 Hz, 1H), 4.78 (m, 1H), 4.96 (s, 3H), 5.01 (d, J = 7.7 Hz, 1H), 6.84−6.96 (m, 3H), 7.16−7.58 (m, 16H), 9.19 (s, 1H); HRMS calculated for $C_{36}H_{36}N_5O_6$ $(M + H)^+$ = 634.2665, observed $(M + H)^+$ = 634.2650; RP-HPLC column, dynamax C-8, 2 mL/min (60% acetonitrile) t_R = 9.46 min.

The above intermediate (300 mg, 0.47 mmol) was suspended in methanol (50 mL) and 1 N aqueous NaOH (2 mL) added. The reaction mixture was stirred overnight, and the solvent was evaporated *in vacuo*. The residue was triturated with water, and the product was collected by filtration, affording the titled compound (250 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 4.17 (d, J = 16 Hz, 1H), 4.37 (s, 3H), 4.46 (d, J = 16 Hz, 1H), 4.78 (m , 1H), 5.01 (m, 1H), 6.80−6.96 (m, 3H), 7.10−7.56 (m, 16H), 9.09 (s, 1H); HRMS calculated for $C_{34}H_{34}N_5O_5$ $(M + H)^+$ = 592.2559, observed $(M + H)^+$ = 592.2556; RP-HPLC column, dynamax C-8, 2 mL/min (60% acetonitrile) t_R = 4.89 min.

2-[2,4-Dioxo-5-phenyl-3-[3-[3-(1H-tetrazol-5-yl)phenyl]-ureido]-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (32). To a vigorously stirring solution of 2-(3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide, **6** (0.070 g, 0.156 mmol), in tetrahydrofuran (3 mL) at ambient temperature was added 1,1′-carbonyldiimidazole (0.025 g, 0.169 mmol). The resulting mixture was stirred for 1.5 h at ambient temperature. 3-(2*H*-Tetrazol-5-yl)phenylamine hydrochloride (31.3 mg, 0.157 mmol) was added, and the reaction mixture was heated at reflux overnight. The solids were removed by filtration and the filtrate concentrated to a yellow oil. The oil was purified by preparative RP-HPLC (43−53% acetonitrile, 30 min) at a rate of 100 mL/min. Fractions containing the desired material were combined,

frozen, and lyophilized to provide the title compound as a white powder (50 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (d, J = 7.3 Hz, 3H), 0.98 (d, J = 7.3 Hz, 3H), 4.20 (d, J = 16.8 Hz, 1H), 4.49 (d, J = 17.1 Hz, 1H), 4.79 (m, 1H), 5.06 (d, J = 7.3 Hz, 1H), 6.98 (m, 2H), 7.24−7.55 (m, 17H), 8.17 (s, 1H), 9.44 (s, 1H); HRMS calculated for $C_{34}H_{32}N_9O_4$ $(M + H)^+$ = 630.2582, observed $(M + H)^+$ = 630.2577; RP-HPLC (43−53% CH_3CN, 30 min; 1 mL/min) t_R = 15 min (t_0= 3 min). Compounds **17** and **18** were prepared in this manner.

2-[3-[3-(3-Aminophenyl)ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (34). To a solution of **6** (0.300 g, 0.678 mmol) in dichloromethane (5 mL) under nitrogen was added 3-nitrophenyl isocyanate (0.111 g, 0.678 mmol) at ambient temperature. After 20 min of stirring, the reaction mixture was evaporated *in vacuo* to a tacky solid. The residue was combined with 10 mL of acetonitrile and brought to reflux. After 30 min of stirring, the slurry was cooled to 0−5 °C and filtered, washing with cold acetonitrile. The product was dried under high vacuum overnight under high vacuum to provide *N*-isopropyl-2-[3-[3-(3-nitrophenyl)ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-phenyl-acetamide as a white crystalline solid (335 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (m, 6H), 4.19 (d, 1H, J = 16.8 Hz), 4.49 (d, 1H, J = 16.8 Hz), 4.79 (m, 1H); 5.03 (m, 1H), 6.95 (d, 1H, J = 8.4 Hz), 7.03 (d, 1H, J = 7.3 Hz), 7.26 (m, 1H), 7.36 (m, 4H), 7.50 (m, 10H), 7.76 (m, 1H), 8.46 (s, 1H), 9.69 (s, 1H); LRMS (FAB) m/z 607.1 $(M + H)^+$; HPLC t_R = 23.24 min (48−60% CH_3CN, 30 min, 1.5 mL/min).

A suspension of *N*-isopropyl-2-[3-[3-(3-nitrophenyl)ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-*N*-phenylacetamide (0.280 g, 0.462 mmol) in absolute ethanol (25 mL) was combined with 10% palladium on carbon (100 mg) and hydrogenated on a Parr shaker at 50 psi for 88 h. The reaction mixture was filtered and then evaporated in vacuo to a residue. The crude product was purified on flash silica gel using 40−100% ethyl acetate in hexane in 100 mL increments of 20%. Fractions containing the desired product were combined and evaporated *in vacuo* to a solid (172 mg). A portion of the solid (122 mg) was purified on flash silica gel using 0−2% methanol in dichloromethane in 200 mL increments of 0.5%. Fractions containing the product were combined and evaporated *in vacuo* to a solid. The product was dried under high vacuum to provide the title compound (107 mg) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (m, 6H), 4.17 (d, 1H, J = 16.7 Hz), 4.47 (d, 1H, J = 16.7 Hz), 4.78 (m, 1H), 4.93 (bs, 2H), 5.00 (d, 1H, J = 7.9 Hz), 6.10 (d, 1H, J = 7.9 Hz), 6.48 (d, 1H, J = 7.8 Hz), 6.58 (bs, 1H), 6.80 (m, 2H), 6.93 (d, 1H, J = 7.9), 7.24 (m, 1H), 7.35 (m, 4H), 7.48 (m, 8H), 8.81 (s, 1H); LRMS (FAB) m/z $(M + H)^+$ = 576.9; HPLC t_R = 20.3 min (30−48% CH_3CN in water with 0.1% TFA, 30 min, 1.5 mL/min).

2-[2,4-Dioxo-5-phenyl-3-[3-[3-[[(trifluoromethyl)sulfonyl]amino)]phenyl]ureido]-2,3,4,5-tetrahydrobenzo[*b*]-[1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (33). A solution of **34** (0.190 g, 0.329 mmol) and triethylamine (50.6 mL, 0.362 mmol) in dichloromethane (5 mL) was cooled under nitrogen to −78 °C with a dry ice/acetone bath. Triflic anhydride (55.5 mL, 0.329 mmol) was added via micropipet, and the reaction mixture was allowed to warm to ambient temperature. Triethylamine was added (101.2 mL, 0.724 mmol), and the reaction mixture was cooled again to −78 °C. Triflic anhydride (111 mL, 0.658 mmol) was added, and the reaction was warmed again to ambient temperature forming a slurry. The slurry was filtered, washed with dichloromethane, and dried under high vacuum to provide the title compound as a white solid (0.069 g): ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (m, 6H), 4.18 (d, 1H, J = 16.6 Hz), 4.48 (d, 1H, J = 16.6 Hz), 4.78 (m, 1H), 5.02 (d, 1H, J = 7.8 Hz), 6.78 (d, 1H, J = 7.7 Hz), 6.89 (d, 1H, J = 7.2 Hz), 6.95 (d, 1H, J = 8.0), 7.13 (d, 1H, J = 8.1 Hz), 7.24 (m, 2H), 7.35 (m, 4H), 7.48 (m, 10H), 9.34 (s, 1H); LRMS (FAB) m/z 709.2 $(M + H)^+$; HPLC t_R = 27.1 min (42−60% CH_3CN, 30 min, 1.5 mL/min). Anal. ($C_{34}H_{31}N_6O_6S_1F_3 \cdot 0.3H_2O$) C, H, N.

***N*-Isopropyl-2-[3-[3-[3-(methylthio)phenyl]ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]-diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (35).** To a stirring solution of intermediate **6** (221 mg, 0.50 mmol) in DCM (5 mL) was added 3-(methylthio)phenyl isocyanate (83 mg, 0.50 mmol). The reaction mixture was stirred for 12 h, concentrated to dryness, and triturated with methanol (3 × 5 mL) to yield the titled compound (220.6 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (t, J = 7.4 Hz, 6H), 2.34 (s, 3H), 4.13 (d, J = 16.6 Hz, 1H), 4.43 (d, J = 16.6 Hz, 1H), 4.74 (m, 1H), 4.97 (d, J = 7.8 Hz, 1H), 6.73 (m, 1H), 6.89 (m, 3H), 7.13 (t, J = 8.0 Hz, 1H), 7.20 (m, 1H), 7.34 (m, 5H), 7.5 (m, 8H), 9.16 (s, 1H); MS $C_{34}H_{34}N_5O_4S$ $(M + H)^+$ = 608.2331; observed $(M + H)^+$ = 608.2325; t_R = 30.5 min (42−60% acetonitrile, 30 min), then 60−100% acetonitrile, 10 min, t_0= 3 min.

***N*-Isopropyl-2-[3-[3-[3-(methylsulfonyl)phenyl]ureido]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]-diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (36).** To a stirring solution of **35** (86 mg, 0.14 mmol) in DCM (5 mL) was added 50% *m*-CPBA (100 mg, 0.28 mmol). The reaction mixture stirred for 12 h at room temperature, then concentrated to dryness, and purified by RP-HPLC (42−60% acetonitrile, 30 min) to give the title product (63.4 mg) as a white lyophile: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.91 (t, J = 7.4 Hz, 6H), 2.34 (s, 3H), 4.17 (d, J = 16.6 Hz, 1H), 4.47 (d, J = 16.6 Hz, 1H), 4.78 (m, 1H), 5.02 (d, J = 7.8 Hz 1H), 6.96 (m, 2H), 7.24 (m, 1H), 7.34 (m, 14H), 7.89 (m, 1H), 8.06 (s, 1H), 9.57 (s, 1H); HRMS calculated for $C_{34}H_{33}N_5O_6S$ $(M + H)^+$ = 640.2230, observed $(M + H)^+$ = 640.2246; t_R = 31.75 min (42−60% acetonitrile, 30 min then 60−100% acetonitrile, 10 min, t_0 = 3 min).

2-[3-[3-[1-[(Isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]ureido]phenoxy]acetamide (40). Intermediate **12** (0.100 g, 0.602 mmol) was dissolved in THF (20 mL), triethylamine (0.182 mL, 1.19 mmol) was added, the resultant solution was cooled to 0 °C, and then triphosgene (0.0594 g, 0.2 mmol) was added. This mixture was stirred at 0 °C for 0.5 h prior to the addition of intermediate **6** (0.265 g, 0.602 mmol), and the resultant mixture was allowed to attain room temperature over 16 h. The solvents were concentrated *in vacuo* and the residue partitioned between ethyl acetate (50 mL) and 0.5 N hydrochloric acid (3 × 20 mL). The organics were washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the crude product (0.309 g). This was purified by preparative RP-HPLC (40−63% acetonitrile, 30 min) at a rate of 100 mL/min. Fractions containing the desired material were combined, frozen, and lyophilized to provide the title compound as a white powder (177 mg): ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (2d, J = 7.3 Hz, 6H), 4.18 (d, J = 15.3 Hz, 1H), 4.30 (s, 2H), 4.48 (d, J = 15.3 Hz, 1H), 4.80 (sept, J = 7.3 Hz, 1H), 5.02 (d, J = 6.8 Hz, 1H), 6.46 (d, J = 6.7 Hz, 1H), 6.85−7.0 (m, 4H), 7.14−7.55 (m, 17H), 9.20 (s, 1H); HPLC t_R = 17.9 min (30−70% CH_3CN, 30 min, 1.0 mL/min); HRMS calculated for $C_{35}H_{34}N_6O_6$ $(M + H)^+$ = 635.2761, observed $(M + H)^+$ = 635.2741. Compounds **41**−**44** and intermediate **16** were made in this manner.

1*H*-Indole-2-carboxylic Acid [1-[(Isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]amide 52. To a vigorously stirred solution of 2-(3-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide, **6** (0.116 g, 0.262 mmol), in *N*,*N*-dimethylformamide (5 mL) at ambient temperature was added indole-2-carboxylic acid (0.0423 g, 0.262 mmol), *N*-hydroxybenzotriazole (0.0354 g, 0.262 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.0503 g, 0.262 mmol) successively. Triethylamine (8 drops) was added dropwise to maintain the basicity (pH = 9) of the solution. The resultant mixture was stirred at ambient temperature for 5 h. The solvent was removed *in vacuo* and the crude product purified by preparative RP-HPLC (40−60% acetonitrile, 30 min) at a rate of 100 mL/min. Fractions containing the desired material were combined, frozen, and lyophilized to afford the titled product (0.141 g) as a white lyophile. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, J = 7.3 Hz, 3H), 1.09 (d, J = 7.3 Hz, 3H), 4.22 (d, J = 16.6 Hz, 1H), 4.40 (d, J = 16.4 Hz, 1H), 5.02 (m, 1H), 5.50 (d, J = 7.1 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 7.10−7.47 (m, 16H),

7.57 (d, J = 6.8 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 9.29 (br s, 1H); HRMS calculated for $C_{35}H_{31}N_5O_4$ $(M + H)^+$ = 586.2464, observed $(M + H)^+$ = 586.2461, TLC (EtOAc:hexane (2:3)) R_f = 0.16; RP-HPLC t_R = 19.5 min (51−60% CH_3CN 30 min; 1 mL/min). Compounds **45**−**51** were prepared in this manner.

[2-[[[1[[-(Isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]carbamoyl]indol-1-yl]acetic Acid (54). To a vigorously stirred solution of 1*H*-indole-2-carboxylic acid [1-[(isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]amide, **52** (0.101 g, 0.172 mmol), in *N*,*N*-dimethylformamide (3 mL) cooled to 0 °C was added sodium hydride (60% suspension in mineral oil) (0.0083 g, 0.172 mmol). After 20 min, *tert*-butyl bromoacetate (0.0336 g, 0.172 mmol) was added. The resultant mixture was stirred at 0 °C for 90 min followed by slow warming to ambient temperature and stirring overnight. The solvent was concentrated *in vacuo* to give a brown oil which was dissolved in dichloromethane (30 mL) and washed successively with saturated aqueous sodium bicarbonate (20 mL) and brine (20 mL). The resultant solution was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil (0.142 g) which was purified by flash chromatography on silica gel (9 g) with an eluant of a mixture of ethyl acetate and hexane (1:2, 200 mL) to give [2-[[1-[(isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]carbamoyl]indol-1-yl]acetic acid *tert*-butyl ester (0.092 g) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 4.9 Hz, 3H), 1.09 (d, J = 4.6 Hz, 3H), 1.37 (s, 9H), 4.17 (d, J = 16.6 Hz, 1H), 4.44 (d, J = 16.9 Hz, 1H), 5.01 (m, 1H), 5.18 (d, J = 17.1 Hz, 1H), 5.24 (d, J = 18 Hz, 1H), 5.47 (d, J = 7.6 Hz, 1H), 7.01 (dd, J = 1.2, 8.3 Hz, 1H), 7.13−7.51 (m, 17H), 7.57 (d, J = 7.3 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H); LRMS (FAB) m/z 700.2 $(M + H)^+$; RP-HPLC (60−70% CH_3CN; 30 min; 1 mL/min) t_R = 17.5 min.

To a solution of [2-[[1-[(isopropylphenylcarbamoyl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl]carbamoyl]indol-1-yl]acetic acid *tert*-butyl ester (0.072 g, 0.103 mmol) in dichloromethane (4 mL) at ambient temperature was added trifluoroacetic acid (1.5 mL) gradually with stirring. After 30 min, the solvents were concentrated *in vacuo* to afford a clear glass. The glass was purified by preparative RP-HPLC (45−55% acetonitrile, 30 min) at a rate of 100 mL/min. Fractions containing the desired material were combined, frozen, and lyophilized to afford the title compound (0.050 g) as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 4.4 Hz, 3H), 1.10 (d, J = 4.4 Hz, 3H), 4.23 (d, J = 16.6 Hz, 1H), 4.40 (d, J = 16.6 Hz, 1H), 5.01 (m, 1H), 5.06 (s, 2H), 5.44 (d, J = 7.1 Hz, 1H), 7.03 (dd, J = 8.1, 1.2 Hz, 1H), 7.17−7.52 (m, 17H), 7.67 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 7.1 Hz, 1H); HRMS calculated for $C_{37}H_{33}N_5O_6$ $(M + H)^+$ = 644.2653, observed $(M + H)^+$ = 644.2646; RP-HPLC (45−55% CH_3CN; 30 min; 1 mL/min) t_R= 22 min. Compound **55** was prepared in a similar manner.

Intracellular Calcium Measurements. CHO-K1 cells stably transfected with hCCK-A or hCCK-B receptors were grown on glass coverslips to 75−90% confluency. The cells were loaded for 50 min in serum-free culture medium containing 5 mM FURA2-AM and 2.5 mM probenecid. A JASCO CAF-102 calcium analyzer was used to measure changes in intracellular calcium concentration by standard ratiometric techniques using excitation wavelengths of 340 and 380 nm. Cells were perfused with increasing concentrations of CCK-8 (n = 2)[22] or compound **29** (n = 2) until a plateau in the 340/380 ratio was achieved. A washout/recovery period of at least 10 min was allowed between successive stimulations. The maximal response was normalized to the maximal response induced by CCK-8. EC_{50}'s were calculated at the concentration required to induce half-maximal response. In addition to the agonist concentration−response curves, the CHO-K1 cells expressing the human CCK-B receptor were perfused for 1 h with three concentrations of compound **29** (10^{-8}, 10^{-7}, 10^{-6} M, n = 2), concentration−reponse curves were acquired for CCK-8 (10^{-12} to 10^{-6}M), and the pA_2 for **29** was calculated by a Schild analysis.[28]

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