Optimization of 3-(1*H*-Indazol-3-ylmethyl)-1,5-benzodiazepines as Potent, Orally Active CCK-A Agonists

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We previously described a series of 3-(1*H*-indazol-3-ylmethyl)-1,5-benzodiazepine CCK-A agonists exemplified by compound **1** (GW 5823), which is the first reported binding selective CCK-A full agonist demonstrating oral efficacy in a rat feeding model. In this report we describe analogs of compound **1** designed to explore changes to the C3 and N1 pharmacophores and their effect on agonist activity and receptor selectivity. Agonist efficacy in this series was affected by stereoelectronic factors within the C3 moiety. Binding affinity for the CCK-A vs CCK-B receptor showed little dependence on the structure of the C3 moiety but was affected by the nature of the second substituent at C3. Structure–activity relationships at the N1-anilidoacetamide "trigger" moiety within the C3 indazole series were also investigated. Both agonist efficacy and binding affinity within this series were modulated by variation of substituents on the N1-anilidoacetamide moiety. Evaluation of several analogs in an *in vivo* mouse gallbladder emptying assay revealed compound **1** to be the most potent and efficacious of all the analogs tested. The pharmacokinetic and pharmacodynamic profile of **1** in rats is also discussed.

Cholecystokinin (CCK) is a gastrointestinal hormone and neurotransmitter involved in a number of digestive processes such as contraction of the gall bladder, stimulation of pancreatic and biliary secretion, and modulation of gastric emptying.[1] In addition, CCK functions as a satiety signal by direct stimulation of vagal afferents that signal to feeding centers in the brain.[2] CCK is found in a number of molecular forms throughout peripheral tissues and the central nervous system, with the C-terminal octapeptide CCK-8 (Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-PheNH_2) being the minimal sequence required for bioactivity.[1b,c] The physiological actions of CCK are mediated via two G-protein-coupled seven transmembrane receptors. CCK-A receptors are localized primarily in peripheral tissues and appear to be the subtype which mediates the satiety effect of CCK,[3] while CCK-B receptors are located mainly in the CNS.[4] Exogenously administered CCK has been shown to reduce both duration and size of meals in several species, including lean[5] and obese[6] humans. In addition, administration of CCK-8 to patients on total parenteral nutrition suggests a role for CCK in the prevention of gallstones.[7] An orally active CCK-A selective agonist might therefore be useful as a satiety agent and may provide an alternative to current therapies for the treatment of obesity.[8]

We recently reported the identification of a series of 3-(indazol-3-ylmethyl)-1,5-benzodiazepines, exemplified by **1** (Figure 1), which are potent, selective CCK-A agonists *in vitro*.[9] Compound **1** (GW 5823) is the first reported CCK-A agonist which has demonstrated suppression of food intake when dosed orally in a rat feeding model. This paper provides a more complete account of the design, synthesis, and pharmacological activity of this series of 3-(indazol-3-ylmethyl)-1,5-benzodiazepine CCK-A agonists. The structure–activity relationships of both the C3 substituents and the N1-anilidoacetamide substituents are discussed. These substituents appear to be the key pharmacophores which modulate CCK-A agonist activity of this class of compounds. In addition, the *in vivo* pharmacodynamic and pharmacokinetic evaluation of compound **1** and several additional analogs is described.

Chemistry

The general synthetic route used to prepare most of the analogs is depicted in Scheme 1. This approach allows for easy variation of both the N1 and C3 substituents. Construction of the N1 substituent was effected via reductive amination[10] of a primary aniline with the appropriate ketone to afford the requisite secondary aniline, followed by acylation with bromoacetyl bromide (Scheme 1). Alkylation of *N*-phenyl-1,2-phenylenediamine with the appropriate bromoacetamide took place with complete chemoselectivity toward the primary aniline. Double acylation with malonyl dichloride then afforded the 1,5-benzodiazepine scaffold in rapid fashion. This cyclization reaction was effected simply by stirring the two reagents in a THF solution; interestingly, addition of an external base to the reaction afforded no cyclized material, possibly due to decomposition of the malonyl dichloride via ketene formation. Analogs which contain C3 alkyl substituents

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1 Asperlicin 2

Figure 1.

Scheme 1[a]

3a, c, e-g

4a, c, e-g

1,15-20, 22, 26-28, 29, 31-34, 36, 37, 39-41, 43

[a] Reagents: (i) $NaB(OAc)_3H$, AcOH, THF, 0 °C to room temperature; (ii) bromoacetyl bromide, Et_3N, CH_2Cl_2, 0 °C to room temperature; (iii) K_2CO_3, DMF, 60 °C, 18 h; (iv) malonyl dichloride, THF, 0 °C to room temperature, 18 h; (v) NaH, $NaN(TMS)_2$ or $KN(TMS)_2$, room temperature, DMF, 15 min and then addition of alkyl halide, DMF, room temperature, 2−5 h; (vi) $NaN(TMS)_2$ or $KN(TMS)_2$, room temperature, DMF, 15 min and then addition of R_3-X, DMF, room temperature, 2−5 h; (vii) deprotection (if necessary).

were synthesized via deprotonation using either NaH, $KN(TMS)_2$, or $NaN(TMS)_2$ as the base followed by addition of the requisite heteroaromatic alkyl halide, followed by deprotection if necessary (Scheme 1). Choice of base used for the deprotonation had no effect on either the yield or time course of the reaction; based on convenience, $NaN(TMS)_2$ was usually employed. Formation of the C3 quaternary analogs in which the second substituent was a methyl group was achieved by a second deprotonation and quenching with methyl iodide, again followed by deprotection if necessary. This sequence of alkylations could also be reversed without loss of yield; however, usually the alkylations were carried out in the order described above since it was a more efficient way to obtain both the C3-hydrogen and C3-methyl analogs containing a common C3 indazole derivative.

An alternative approach (Scheme 2) was also investigated and utilized in the synthesis of analogs **38**, **42**, **44**, and **45**. In this approach the 1,5-benzodiazepine ring was formed prior to attachment of the N1 moiety. Formation of the benzodiazepine ring was accomplished via a three-step procedure which involved acylation of 2-nitrodiphenylamine with methylmalonyl chloride, reduction of the aromatic nitro group with 10% palladium on carbon, and sodium ethoxide catalyzed ring closure. Alkylation of the N1 amide nitrogen was carried out by deprotonation of the N1 amide with NaH and addition of the requisite bromoacetamide (formed as in Scheme 1). Careful monitoring of both the amount of NaH utilized and the reaction time was needed in order to avoid byproducts originating from additional alkylation at the C3 position. Completion of the synthesis proceeded in a fashion identical to that outlined in Scheme 1. In general the route depicted in Scheme 1 is the preferred route to these analogs, based on ease of synthesis and higher yields.

Analogs **21** and **24**, which contain a C3 methoxy group, were synthesized by the route shown in Scheme 3. Dimethyl methoxymalonate was deprotonated using $NaN(TMS)_2$ and alkylated with the appropriate bromide, followed by saponification to the diacid and conversion to the diacid chloride. Cyclization of these disubstituted malonate derivatives with the appropriate diamine (constructed as in Scheme 1) required refluxing THF in order to effect cyclization, presumably due to the increased steric bulk around the acid chlorides. Deprotection then afforded analogs **21** and **24**.

The general synthetic route used in preparing several of the 3-bromoheterocyclic alkylating agents used in Schemes 1 and 2 is outlined in Scheme 4. The three-step sequence, starting from the corresponding known

Scheme 2[a]

[a] Reagents: (i) methylmalonyl chloride, toluene, 80 °C, 48 h; (ii) H_2, 10% Pd/C, EtOH/EtOAc; (iii) Na/EtOH; (iv) NaH, DMF, 0 °C then **3d,h–j**, room temperature; (v) NaH, $NaN(TMS)_2$ or $KN(TMS)_2$, DMF, room temperature, 15 min and then addition of alkyl halide, DMF room temperature, 2–5 h; (vi) $NaN(TMS)_2$ or $KN(TMS)_2$, DMF, room temperature, 15 min and then addition of R_3-X, DMF, room temperature, 2–5 h; (vii) deprotection (if necessary).

Scheme 3[a]

[a] Reagents: (i) $NaN(TMS)_2$, DMF, room temperature, 15 min; (ii) alkyl halide, DMF, room temperature, 2–5 h; (iii) NaOH, EtOH, room temperature; (iv) oxalyl chloride, cat. DMF, CH_2Cl_2, 0 °C to room temperature, 1 h; (v) THF, reflux, 4 h; (vi) 10% Pd/C, formic acid, EtOH, reflux, 6 h (R = benzyl).

Scheme 4[a]

[a] Reagents: (i) benzyl bromide or methyl iodide, K_2CO_3, DMF, room temperature; (ii) DIBAL-H, CH_2Cl_2, −78 °C to room temperature; (iii) PPh_3Br_2, CH_3CN or CCl_4, 0 °C.

Scheme 5[a]

[a] Reagents: (i) $NaNO_2$, NaOH, H_2O then H_2SO_4, $SnCl_2$; (ii) hydrazine, ethylene glycol, 0 °C for 4 h then reflux; (iii) $(BOC)_2O$, Et_3N, DMAP, CH_3CN; (iv) *N*-bromosuccinimide, cat. benzoyl peroxide, CCl_4, reflux.

3-carboxylic acid derivatives,[11] involves conversion to the methyl or benzyl ester, reduction of the ester to the corresponding alcohol using DIBAL-H, and conversion to the bromide with Ph_3PBr_2.[12] An additional NH protection step was needed in the indole and indazole series and was done prior to reduction of the ester. However, there were several problems with this general approach. Preparation of the requisite 3-carboxylic acids[11] was often a several-step procedure and tended to be cumbersome on large scale. In addition, poor (<50%) yields were also observed in many cases during attempted conversion of the alcohols to the bromides using Ph_3PBr_2 or other brominating agents. Finally, this synthetic route allowed for little flexibility in choice of protecting groups for the indazole or indole nitrogen; benzyl[13] was found to be the most robust but was often difficult to remove, resulting in incomplete conversion and poor yields in the final deprotection step.

An alternative route (Scheme 5) was developed in the indazole series which provided a shorter and more efficient method for construction of the desired bromides. Diazotization of the requisite *o*-aminoacetophenones followed by $SnCl_2$-mediated reduction provided the 3-methylindazole derivatives.[14] Protection of the N1 nitrogen by $(Boc)_2O$[13] followed by radical bromination with NBS[15] provided the protected indazole bromides in good yields. The desired bromide was always accompanied by unreacted starting material and dibrominated products, but fortunately in all cases these could be easily separated by silica gel chromatography. Compounds **18** and **28** were also synthesized in an analogous manner from their corresponding 3-methyl derivatives.[16] In cases where the desired *o*-aminoacetophenone was not readily available, an alternative procedure starting with the *o*-fluoroacetophenone analog

Scheme 6[a]

[a] Reagents: (i) ethyl propiolate, Et_3N, THF, room temperature; (ii) $Pd(OAc)_2$, PPh_3, $NaHCO_3$, DMF, 110 °C, 16 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C to room temperature; (iv) PPh_3Br_2, CCl_4, 0 °C.

Scheme 7[a]

[a] Reagents: (i) Tf_2O, Et_3N, CH_2Cl_2; (ii) $(PPh_3)_2PdCl_2$, CuI, 1-ethoxy-1-(trimethylstannyl)ethene, DMF, 75 0 °C; (iii) 2 N HCl, THF; (iv) H_2, 10% Pd/C, EtOH, room temperature.

Table 1. *In Vitro* Profile of 1,5-Benzodiazepine CCK-A Agonists

no.	structures[a] X	Y	functional assay[b] ED_{50} (nM)	%max	binding assay[c] CCK-A (pIC_{50})	CCK-B (pIC_{50})	A/BSel
CCK-8	–	–	2 ± 1 (5)	100	8.88 ± 0.22 (8)	9.46 ± 0.04 (8)	0.3
15	CH	NH	340 (1)	70 (4)	7.96 ± 0.14 (3)	5.28 ± 0.08 (3)	480
16	CH	O	–	40 (1)	–	–	–
17	CH	S	–	50 (1)	–	–	–
1	N	NH	109 ± 60 (4)	100 (6)	7.64 ± 0.12 (5)	6.00 ± 0.23 (4)	50
18	N	O	130 (1)	80 (2)	7.05 ± 0.15 (4)	3.76 ± 1.02 (3)	1980
19	N	S	–	30 (1)	–	–	–

[a] See figure. [b] Functional activity in the isolated guinea pig gall bladder following incubation with the test ligand for 30 min at 37 °C; ED_{50}, concentration at which 50% of the maximal contraction was observed ± SE (number of determinations); –, an ED_{50} was not determined; %max (number of determinations), relative efficacy as determined by the maximal contraction observed at 1 μM standardized to CCK-8 (1 μM) = 100%, all values ± 5%. [c] Binding affinity for human CCK-A and CCK-B receptors; pIC_{50}, −log of the concentration that displaced 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 ± SE (number of determinations); –, not determined; A/BSel, CCK-A receptor selectivity calculated from $IC_{50}(B)/IC_{50}(A)$.

was utilized (Scheme 5). Generation of the hydrazone with hydrazine hydrate followed by refluxing in ethylene glycol to effect intramolecular nucleophilic aromatic substitution provided the desired 3-methylindazole derivative.

The synthesis of 3-(bromomethyl)benzofuran is shown in Scheme 6. Michael addition of 2-bromophenol with ethyl propiolate followed by an intramolecular Heck[17] coupling afforded benzofuran-3-carboxylic acid ethyl ester. This material was then reduced with DIBAL-H and converted to the desired bromide with Ph_3PBr_2.

The synthesis of 3-(bromomethyl)-1-(*tert*-butoxycarbonyl)pyrazolo[4,3-*b*]pyridine, used in the formation of compound **29**, is outlined in Scheme 7. 2-Hydroxy-3-nitropyridine was converted into the corresponding triflate ester under standard conditions[18] and then coupled with 1-ethoxy-1-(trimethylstannyl)ethene[19] using methodology described by Stille[20] to afford, after hydrolysis, 1-(3-nitropyridin-2-yl)ethanone. The more direct approach utilizing a Heck coupling with butyl vinyl ether afforded no desired product with this substrate. Reduction of the nitro group with H_2 and 10% palladium provided the amino derivative which was converted into the desired bromide using the four-step sequence outlined in Scheme 5.

Biology

Analogs were initially evaluated for *in vitro* functional efficacy in inducing contraction of the isolated guinea pig gallbladder (GPGB) at a 1 μM concentration (Tables 1−4).[21] The activity of all compounds reported was reversed completely by addition of the CCK-A receptor selective antagonist MK-329[22] (0.5 μM). Full concentration−response curves on the GPGB and receptor binding affinities were obtained only for those compounds which induced ≥50% of the maximal contraction produced by CCK-8. Receptor binding affinities were measured on membrane preparations from CHO-K1 cell lines[23] stably transfected with cDNA from either human CCK-A[24] or CCK-B[25] receptors (Tables 1−4). IC_{50} values were

Table 2. *In Vitro* Profile of 1,5-Benzodiazepine CCK-A Agonists

no.	structures[a] R	X	Y	functional assay[b] ED50 (nM)	%max	binding assay[c] CCK-A (pIC50)	CCK-B (pIC50)	A/BSel
CCK-8	–	–	–	2 ± 1 (5)	100	8.88 ± 0.22	9.46 ± 0.04 (8)	0.3
15	H	CH	NH	340 (1)	70 (4)	7.96 ± 0.14 (3)	5.28 ± 0.08 (3)	480
20	CH_3	CH	NH	530 (1)	60 (3)	8.08 ± 0.24 (4)	4.76 ± 0.26 (5)	2090
21	OCH_3	CH	NH	150 (1)	60 (2)	7.86 ± 0.29 (3)	4.53 ± 0.48 (3)	2140
22	CH_3	CH	NCH_3	–	40 (2)	7.75 ± 0.11 (2)	–	–
1	H	N	NH	109 ± 60 (4)	100 (6)	7.64 ± 0.12 (5)	6.00 ± 0.23 (4)	50
23	CH_3	N	NH	320 (1)	80 (3)	7.88 ± 0.02 (3)	4.16 ± 0.23 (3)	5100
24	OCH_3	N	NH	70 (1)	70 (3)	7.84 ± 0.31 (3)	5.44 ± 0.17 (3)	250
25	H	N	NCH_3	70 ± 10 (2)	90 (3)	7.37 ± 0.43 (3)	5.62 ± 0.20 (3)	60
26	H	N	NCH_2Ph	340 (1)	40 (2)	6.51 ± 0.16 (5)	4.00 ± 0.01 (2)	320
27	CH_3	N	NCH_3	240 (1)	60 (2)	7.41 ± 0.01 (2)	–	–

[a] See figure. [b] Functional activity in the isolated guinea pig gall bladder following incubation with the test ligand for 30 min at 37 °C; ED_{50}, concentration at which 50% of the maximal contraction was observed ±SE (number of determinations); –, an ED_{50} was not determined; %max (number of determinations), relative efficacy as determined by the maximal contraction observed at 1 μM standardized to CCK-8 (1 μM) = 100%, all values ± 5%. [c] Binding affinity for human CCK-A and CCK-B receptors; pIC_{50}, –log of the concentration that displaced 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 ± SE (number of determinations); –, not determined; A/BSel, CCK-A receptor selectivity calculated from $IC_{50}(B)/IC_{50}(A)$.

determined using competitive radioligand binding with labeled CCK-8.

Selected compounds which induced ≥50% contraction of the GPGB relative to CCK-8 were also evaluated for *in vivo* activity in the mouse gallbladder emptying[26] (MBGE) assay at a single dose (0.1 μmol/kg, ip or 1 μmol/kg, po). The extent of CCK-A-mediated gallbladder emptying is measured 30 min after compound administration, thus providing a rapid measure of CCK-A-mediated peripheral agonist activity (Table 5). *In vivo* satiety effects were assessed following intraperitoneal (ip) administration in a rat feeding[21] model (Table 5). This model provides measurement of the anorectic activity of CCK-A agonists taking into account both vagally-mediated behavioral satiety effects in combination with effects through inhibition of gastric emptying.[27] The ED_{50} values in Table 5 represent the dose of test compound which produces a half-maximal response for that individual compound.

Results and Discussion

We had previously disclosed the identification of a series of 3-(phenylureido)-1,5-benzodiazepine CCK-A agonists.[21] To our knowledge, these compounds (exemplified by **2**, Figure 1) were the first reported non-peptide CCK-A agonists. Agonist efficacy within this series was modulated by variation of substituents on the N1-anilidoacetamide moiety, with minor structural modifications providing the "trigger" for interconversion between antagonist and agonist functional activity. Structure–activity relationships at this position revealed that a single methyl group confers agonist activity, with an *N*-isopropyl substituent providing optimal efficacy. Given this apparent sensitivity to agonist/antagonist interconversion at the N1 pharmacophore, we decided to focus our effort toward identifying *orally active* satiety agents by modifying the C3 moiety. The structure–activity relationships of both phenylurea and amide series of compounds at this C3 position was the focus of two recent reports from our laboratories.[28,29]

The strategy for modification of the C3 pharmacophore was suggested by structural analysis of the selective CCK-A antagonist natural product asperlicin (Figure 1),[30] which has been used by others as a template for the design of subtype-selective antagonists. The pioneering work at Merck[22,31] and later at Lilly[32] demonstrated that the 3-indolinylmethyl group embedded within the structure of asperlicin was an important element for bioactivity. In addition, this moiety is structurally similar to L-tryptophan, which is a key amino acid required for agonist activity in the peptide sequence of CCK and in various peptidomimetics of CCK.[33] The recurrence of the indole moiety in the reported CCK agonists and antagonists provided us with some degree of confidence that structure–activity relationships developed for the 1,4-benzodiazepine CCK-A and CCK-B receptor antagonists would be applicable to our 1,5-benzodiazepine CCK-A agonist series.

The structures and *in vitro* biological data are found in Tables 1–4 and fall into two broad categories: analogs in which the N1 substituent is an *N*-isopropyl-*N*-(4-methoxyphenyl)acetamide group while the C3 substituent is varied (Tables 1–3), and analogs in which the C3 substituent is a 3-indazol-3-ylmethyl group while the substituents on the N1-anilido nitrogen atom are changed (Table 4). Physical data for these compounds is presented in Table 7.

As the GPGB activity data in Table 1 shows, CCK-A agonist efficacy was modulated by the 5-membered ring structure embedded within the C3 heterocycle. Nitro-

Table 3. *In Vitro* Profile of 1,5-Benzodiazepine CCK-A Agonists

	structures[a]	functional assay[b]		binding assay[c]		
no.	R	ED_{50} (nM)	%max	CCK-A (pIC_{50})	CCK-B (pIC_{50})	A/BSel
CCK-8	—	2 ± 1 (5)	100	8.88 ± 0.22 (8)	9.46 ± 0.04 (8)	0.3
1		109 ± 60 (4)	100 (6)	7.64 ± 0.12 (5)	6.00 ± 0.23 (4)	50
28		40 (1)	90 (3)	6.95 ± 0.21 (3)	4.95 ± 0.44 (4)	100
29		—	40 (1)	—	—	—
30		300 (1)	80 (2)	6.89 ± 0.08 (3)	5.53 ± 0.05 (3)	20
31		70 (1)	100 (1)	7.76 ± 0.06 (3)	5.77 ± 0.05 (3)	100
32		40 (1)	90 (2)	7.37 ± 0.05 (3)	5.60 ± 0.08 (3)	60
33		40 (1)	100 (2)	7.53 ± 0.66 (4)	6.23 ± 0.10 (3)	20
34		20 (1)	90 (2)	7.68 ± 0.25 (4)	5.98 ± 0.11 (3)	50
35		—	20 (1)	—	—	—
36		—	20 (1)	—	—	—

[a] See figure. [b] Functional activity in the isolated guinea pig gall bladder following incubation with the test ligand for 30 min at 37 °C; ED_{50}, concentration at which 50% of the maximal contraction was observed ± SE (number of determinations); −, an ED_{50} was not determined; %max (number of determinations), relative efficacy as determined by the maximal contraction observed at 1 μM standardized to CCK-8 (1 μM) = 100%, all values ± 5%. [c] Binding affinity for human CCK-A and CCK-B receptors; pIC_{50}, −log of the concentration that displaced 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 ± SE (number of determinations); −, not determined; A/BSel, CCK-A receptor selectivity calculated from IC_{50}(B)/IC_{50}(A).

gen is the preferred heteroatom in both the 1- and 2-position of the 5-membered ring. The CCK-A agonist efficacy within this series increased in the order of benzothiophene ≈ benzisothiazole ≈ benzofuran < indole ≈ benzisoxazole < indazole, with analog **1** having efficacy equal to that of CCK-8 in the GPGB assay. Representation of the electrostatic potential surface mapped onto the electron density surface using SPARTAN[34] (data not shown) provides a qualitative explanation for the observed trend within this series. The increase in efficacy parallels the increase in negative electrostatic potential at the 2-position of the indole ring, suggesting that high electron density at this position is important for agonist activity. Table 2 shows the effects on CCK-A activity of altering the remaining C3 substituent and increasing steric bulk on the N1 nitrogen within the indole and indazole series. Replacement of the C3 hydrogen atom with either a methyl or methoxy substituent resulted in a small decrease in agonist activity (**15** vs **20** and **21**, **1** vs **23** and **24**). Methylation of the indole or indazole nitrogen also resulted in a small decrease in efficacy (**20** vs **22**, **1** vs **25**, **23** vs **27**), while *N*-benzyl analog **26** had substantially reduced agonist activity. Importantly, all compounds which showed ≥50% contraction in the GPGB assay also displayed submicromolar potencies ranging from 20 to 500 nM (Tables 1 and 2). Interpretations on potency differences within this series are precluded due to the lack of a significant number of full dose−response experiments for most entries.

Table 4. *In Vitro* Profile of 1,5-Benzodiazepine CCK-A Agonists

no.	structures[a] R1	structures[a] R2	functional assay[b] ED50 (nM)	functional assay[b] %max	binding assay[c] CCK-A (pIC50)	binding assay[c] CCK-B (pIC50)	binding assay[c] A/BSel
CCK-8	—	—	2 ± 1 (5)	100	8.88 ± 0.22 (8)	9.46 ± 0.04 (8)	0.3
1		OCH3	109 ± 60 (4)	100 (6)	7.64 ± 0.12 (5)	6.00 ± 0.23 (4)	50
37			140 (1)	90 (2)	7.06 ± 0.05 (3)	6.75 ± 0.10 (3)	2
38		F	60 (1)	100 (2)	6.86 ± 0.04 (4)	6.32 ± 0.11 (3)	5
39		CF3	230 (1)	80 (2)	6.18 ± 0.20 (4)	5.78 ± 0.04 (3)	5
40		OCH3	70 (1)	90 (2)	6.32 ± 0.10 (5)	6.72 ± 0.14 (3)	0.4
41		OCH3	830 ± 10 (2)	40 (3)	5.80 ± 0.05 (5)	6.89 ± 0.02 (3)	0.1
42			20 (1)	100 (2)	6.45 ± 0.06 (4)	6.14 ± 0.01 (3)	2
43		OCH3	40 (1)	90 (2)	7.77 ± 0.27 (3)	6.11 ± 0.04 (2)	50
44			20 (1)	70 (2)	6.28 ± 0.03 (3)	7.60 ± 0.05 (3)	0.05
45			110 (1)	90 (2)	6.05 ± 0.21 (3)	—	—

[a] See figure. [b] Functional activity in the isolated guinea pig gall bladder following incubation with the test ligand for 30 min at 37 °C; ED_{50}, concentration at which 50% of the maximal contraction was observed ± SE (number of determinations); −, an ED_{50} was not determined; %max (number of determinations), relative efficacy as determined by the maximal contraction observed at 1 μM standardized to CCK-8 (1 μM) = 100%, all values ± 5%. [c] Binding affinity for human CCK-A and CCK-B receptors; pIC_{50}, −log of the concentration that displaced 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 ± SE (number of determinations); −, not determined; A/BSel, CCK-A receptor selectivity calculated from $IC_{50}(B)/IC_{50}(A)$.

CCK receptor binding affinity and subtype selectivity were also modulated by the nature of the other substituent at C3 and steric bulk around the N1 nitrogen (Table 2). Replacement of the C3 hydrogen with either a methyl or methoxy group resulted in a 5−100-fold improvement in CCK-A/CCK-B binding selectivity (**15** vs **20** and **21**, **1** vs **23** and **24**). This improvement in selectivity was due primarily to loss of affinity for the CCK-B receptor, although modest improvement in CCK-A affinity was also observed. Several of these compounds displayed A/B selectivities >1000, the highest seen to date within the 1,5-benzodiazepine series. Interestingly, compound **18** (Table 1), which has a hydrogen at the C3 position, also displayed >1000-fold selectivity for the CCK-A receptor. The origin of this marked improvement in binding selectivity vs other compounds in this series with a C3 hydrogen is unclear. While methylation of the N1 nitrogen had little effect on CCK-A binding, *N*-benzyl analog **26** showed >10-fold loss in both CCK-A and CCK-B binding affinity, suggesting a lack of tolerance by the receptors for sterically demanding groups at this site.

The effect of changing both the steric bulk and stereoelectronics of the 6-membered ring portion of the C3 heterocycle was briefly examined, with the results shown in Table 3. On the basis of the efficacy in the GPGB assay, indazole was chosen as the 5-membered ring template for this investigation. Incorporation of a nitrogen in the 7-position to yield the 1*H*-pyrazolo[4,3-*b*]pyridin-7-yl derivative **28** which displayed similar efficacy to compound **1**; however, the 1*H*-pyrazolo[4,3-*b*]pyridin-4-yl analog **29** showed a large decrease in efficacy. In addition, the pyrazolo[4,3-*b*]pyridine derivatives showed a small reduction in binding affinity for the CCK-A receptor. Replacement of hydrogen with fluorine in the 4, 5, and 6 positions had little or no effect on either efficacy or affinity for the CCK receptors, while saturation of the phenyl ring (**33**) reduced both efficacy and binding affinity to a modest degree. The 5-methylpyrazole analog **35** in which the indazole phenyl ring is essentially removed was inactive, as was the 4-phenylpyrazole analog **36**. The drastic reduction in agonist activity of these two analogs suggests that the C3

Table 5. *In Vivo* Activity of Lead 1,5-Benzodiazepines

	MGBE[a]				anorexia[b]	
	ip		po		ip	
no.	ED_{50}	%max	ED_{50}	%max	ED_{50}	%max
CCK-8	0.03	95	ND	ND	30	95
1	0.2	97	10	89	50	98
15	3.8	90	100	74	ND	ND
20	0.8	91	380	46	ND	ND
21	ND	84	ND	54	ND	ND
23	ND	ND	ND	28	ND	ND
24	0.3	89	100	72	ND	52
25	0.8	83	30	84	220	98
27	10	ND	450	75	ND	ND

[a] *In vivo* mouse gall bladder emptying assay. Following overnight food deprivation, male CD-1 mice (10 animals per dose) were treated (ip or po) with vehicle (ethanol/propylene glycol/water, 2:3:5, 1 mL/kg) or test compound dissolved in vehicle (1 mL/kg). 30 min after drug treatment, animals were sacrificed (CO_2) and the gall bladders were dissected out and weighed. Gall bladder wet weights of the treated animals were normalized to the vehicle control group; 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; %max, maximal response at 0.5 μmol/kg, ip for CCK-8 and 10 μmol/kg, ip for test compound; ND, not determined.

Table 6. Rat Pharmacokinetic Data for Compounds **1**, **23**, **24**, and **27**

no.	route[a]	dose (mg/kg)[b]	C_{max} (ng/mL)[c]	$T_{1/2}$ (h)[d]	CL_{TOT} (mL/min/kg)[e]	V_{ss} (mL/kg)[f]	%F[g]
1	iv	6.3	2105	2.1	38	5175	NA
	po	6.2	20	–	–	–	8
	id	6.6	193	–	–	–	16
23	iv	5.2	3393	3.9	30	4313	NA
	id	5.2	30	–	–	–	15
24	iv	5.5	4900	3.4	35	7630	NA
	po	6.3	90	–	–	–	5
27	iv	6.5	3270	7.5	31	11050	NA
	po	6.5	20	–	–	–	4

[a] IV = intravenous, po = oral, id = intraduodenal. [b] Compound dosed as a solution in 5% DMSO/95% Molecusol solution (4:6, Molecusol:pH 7 buffer, w/v). [c] Maximum detected plasma concentration of parent drug in ng/mL. [d] Half-life of parent compound, h. [e] Total body clearance of parent compound in mL/min/kg, = $[(dose)_{iv}]/[(AUC)_{iv}]$. [f] Volume of distribution at steady state, mL/kg. [g] Oral bioavailability in Long–Evans rats, $[(AUC)_{po}]/[(AUC)_{iv}] \times 100$.

pharmacophore must occupy a fairly flat and narrow but relatively deep pocket within the CCK-A receptor.

Finally, a brief investigation of the N1-anilidoacetamide moiety was carried out within the C3 indazolylmethyl series. The results are displayed in Table 4. Previous work[21] in the C3 urea series had shown that hydrophilic electron-donating groups such as methoxy at the *para* position of the anilido ring were optimal for *in vitro* efficacy and A/B binding selectivity. Removal of the *p*-methoxy group (**37**) lowered efficacy only slightly in this series, but reduced A/B binding selectivity >10-fold. Interestingly, replacement of the *p*-methoxy group with electron-withdrawing groups (**38**, **39**) had only a modest reduction in efficacy, in contrast to the C3 phenylurea series.[21] The corresponding *o*- and *m*-methoxy isomers **40** and **41** were not only less efficacious than the *para* isomer **1** but also displayed a reversal in A/B binding selectivity, derived from both an increase in CCK-B affinity and a decrease in CCK-A affinity. The 3,4-methylenedioxy analog **42** was a full

Table 7. Physical Data for Compounds **1** and **15**–**45**

			HRMS molecular ion		
no.	formula	% purity[a]	theory	found	analysis[b]
1	$C_{35}H_{33}N_5O_4$	99	–	–	C,H,N
15	$C_{36}H_{34}N_4O_4$	97	586.2587	586.2580	C,H,N[c]
16	$C_{36}H_{33}N_3O_5$	100	588.2503	588.2498	–
17	$C_{36}H_{33}N_3O_4S$	97	604.2271	604.2270	–
18	$C_{35}H_{32}N_4O_5$	99	–	–	C,H,N
19	$C_{35}H_{32}N_4O_4S$	98	–	–	C,H,N
20	$C_{37}H_{36}N_4O_4$	100	–	–	C,H,N[d]
21	$C_{37}H_{36}N_4O_5$	100	616.2686	616.2675	–
22	$C_{38}H_{38}N_4O_4$	98	615.2968	615.2971	–
23	$C_{36}H_{35}N_5O_4$	96	602.2768	602.2767	C,H,N
24	$C_{36}H_{35}N_5O_5$	98	618.2719	618.2716	C,H,N[e]
25	$C_{36}H_{35}N_5O_4$	100	–	–	C,H,N
26	$C_{42}H_{39}N_5O_4$	97	678.3082	678.3080	–
27	$C_{37}H_{37}N_5O_4$	97	616.2920	616.2924	–
28	$C_{34}H_{32}N_6O_4$	95	–	–	C,H,N[f]
29	$C_{34}H_{32}N_6O_4$	98	–	–	C,H,N[g]
30	$C_{35}H_{37}N_5O_4$	100	–	–	C,H,N
31	$C_{35}H_{32}FN_5O_4$	95	606.2517	606.2506	–
32	$C_{35}H_{32}FN_5O_4$	97	606.2517	606.2517	–
33	$C_{35}H_{32}FN_5O_4$	96	606.2517	606.2516	–
34	$C_{35}H_{32}FN_5O_4$	97	606.2517	606.2510	–
35	$C_{32}H_{33}N_5O_4$	100	–	–	C,H,N
36	$C_{37}H_{35}N_5O_4$	100	–	–	C,H,N
37	$C_{34}H_{31}N_5O_3$	98	558.2505	558.2501	C,H,N[h]
38	$C_{34}H_{30}FN_5O_3$	99	576.2411	576.2404	–
39	$C_{35}H_{30}F_3N_5O_3$	98	–	–	C,H,N
40	$C_{35}H_{33}N_5O_4$	97	588.2611	588.2602	–
41	$C_{35}H_{33}N_5O_4$	94	588.2611	588.2604	–
42	$C_{35}H_{31}N_5O_5$	96	602.2403	602.2410	–
43	$C_{36}H_{33}N_5O_3$	96	584.2662	584.2660	–
44	$C_{34}H_{29}N_5O_3$	94	556.2349	556.2341	C,H,N
45	$C_{35}H_{33}N_5O_3$	98	–	–	C,H,N

[a] Purity values were obtained by reverse-phase analytical HPLC using a Waters 600E system equipped with a Waters 990 diode array spectrometer (λ range 200–400 nm). The stationary phase was a Vydac C-18 column (5 μm, 4.6 mm × 200 mm). The mobile phase employed 0.1% aqueous TFA with acetonitrile as the organic modifier and the flow rate was 1.0 or 1.5 mL/min (t_o = 3 min). [b] Combustion analyses are within ±0.4% of the calculated value unless otherwise indicated. [c] C, calc 73.70, found 72.70. [d] C, calc 73.98, found 73.27. [e] C, calc 70.00, found 69.10. [f] C, calc 69.37, found 68.69. [g] N, calc 14.28, found, 13.73. [h] C, calc 73.23, found 72.78.

agonist *in vitro* but showed a 10-fold reduction in CCK-A binding affinity vs compound **1**. Since previous investigations[21] had revealed the anilido nitrogen to be extremely sensitive to both steric and stereoelectronic perturbation, we chose to look at only three modifications at this site which had not been evaluated earlier. Replacement of the *N*-isopropyl group with cyclopentyl (**43**) led to a slight loss in efficacy with no change in binding affinity, while replacement with cyclopropyl (**44**) or *tert*-butyl (**45**) groups resulted in >10-fold decrease in CCK-A binding affinity. Overall, none of the modifications at the N1-anilido moiety resulted in compounds with an *in vitro* profile superior to that of **1**.

A subset of compounds which displayed good *in vitro* efficacy and A/B binding selectivity were characterized further for *in vivo* potency and efficacy (Table 5). All compounds tested were fully efficacious relative to CCK-8 following ip administration in the mouse gallbladder emptying (MGBE) assay, with potencies ranging from 10- to 100-fold less than that of CCK-8. However, only compounds **1**, **15**, **24**, **25**, and **27** displayed >50% maximal response when dosed orally in this assay. Of these five compounds, **1** and **25** were the most potent when dosed orally, with **1** being the most

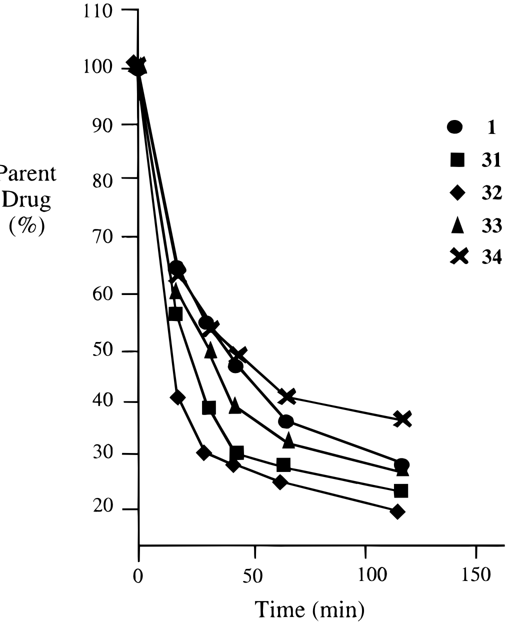

Figure 2. Test compound was incubated for 3 h with liver from normal (noninduced) Sprague–Dawley rats at 37 °C using 4 μM P450 concentrations in 0.1 M potassium phosphate buffer (pH 7.2) in a final volume of 1 mL. Analysis of the incubation mixture was carried out by analytical HPLC.

potent and efficacious of the compounds tested independent of the route of administration.

The potency and efficacy of analogs **1**, **24**, and **25** were also evaluated upon ip administration in the rat conditioned feeder assay (Table 5). Compound **24** was only a partial agonist in this assay, and an ED_{50} was not determined. Benzodiazepine **25**, although fully efficacious compared to CCK-8, was 10-fold less potent. Compound **1,** however, displayed potency and efficacy equal to that of CCK-8. The differences in potency and efficacy among the analogs tested in these two assays may reflect species differences in pharmacokinetics and/or pharmacodynamics of the various compounds.

The pharmacokinetic profiles of compound **1** and analogs in which the C3 substituent (**23**, **24**) and indazole N1 nitrogen (**27**) are altered were evaluated in the rat (Table 6). Compound **1** displayed fairly high total body clearance (CL_{TOT} = 38 mL/min/kg) and a short half-life ($t_{1/2}$ = 2.1 h) following iv administration. The oral bioavailability of a 10 μmol/kg (6 mg/kg) dose was 8%, with a C_{max} of only 20 ng/mL. Analogs **23**, **24**, and **27** also displayed similar pharmacokinetic profiles characterized by high total body clearance and poor oral bioavailability, although the half-life of these analogs were all longer than that seen with compound **1**.

To investigate the contribution of liver metabolism to the poor bioavailability and high clearance observed in these analogs, compound **1** was incubated with rat liver microsomes (37 °C, 5 μM **1**, 1 mg microsomal protein) for 3 h. The results indicate compound **1** was rapidly metabolized by rat liver microsomes, with a half-life of approximately 30 min (Figure 2). The fluorinated analogs **31**–**34**, which displayed potency and efficacy equal to that of **1** *in vitro*, were also incubated with rat liver microsomes. The fluorine substituents might serve to protect against any potential oxidative metabolism occurring in the indazole moiety and thus provide greater metabolic stability. Unfortunately these analogs also displayed similar *in vitro* lability in this assay (Figure 2), suggesting that the metabolic instability associated with these compounds is more complex than simple oxidation at the C3 indazole moiety.

CCK is reported to inhibit gastric emptying in a variety of species through CCK-A receptor-mediated contraction of the pyloric sphincter.[35] Therefore, gastric retention of drug may also contribute to the low oral bioavailability observed with **1**. Compound **1** was evaluated for its ability to inhibit gastric emptying in rats following both ip and po administration.[36] In this assay compound **1** was able to completely inhibit gastric emptying upon ip and po administration at a concentration of 0.1 and 1.0 μmol/kg, respectively (data not shown). Intraduodenal (id) administration of **1**, which bypasses the pyloric sphincter, resulted in a 2-fold increase in bioavailability over that seen upon oral dosing (Table 6). In addition, the C_{max} after id administration was 10-fold higher than that obtained via po administration. Taken together these results suggest that gastric retention of **1** is partially responsible for the low oral bioavailability. The clinical implications of the gastric retention observed with compound **1** are not well understood since there is considerable species variation in CCK-A receptor-mediated delayed gastric emptying, with humans reported to be less sensitive than rats.[37] A more detailed analysis of the pharmacokinetic and pharmacodynamic profiles of nonpeptide CCK-A agonists is the subject of a recent report from our laboratories.[38]

Despite the low oral bioavailability of compound **1**, on the basis of the overall *in vitro* and *in vivo* profile, this analog was evaluated for oral activity in the rat conditioned feeder model. The results (Figure 3) demonstrate indazole **1** was effective at reducing food intake to 40% of vehicle controls when given orally at a dose of 10 μmol/kg, with statistically significant reduction in food intake occurring at a dose of 1 μmol/kg after 180 min. At the higher dose the reduction in food intake could be seen up to 24 h after dosing (data not shown). Compound **1** was even more efficacious as an anorectic agent when dosed id, with a 10 μmol/kg dose reducing food intake to 30% of that seen with vehicle controls after just 30 min postdosing (Figure 3). This increase in efficacy is not surprising given the higher %F and C_{max} values obtained with id vs po administration (*vide supra*). The chronic effectiveness of **1** in this model has not been evaluated.

The potential for CCK-B agonist-mediated pharmacological side effects such as increased gastric acid secretion or enhanced anxiety would be unacceptable in a therapeutic agent for the treatment of obesity. The identification of **1** as an orally active analog in two *in vivo* models of CCK-A-mediated activity, coupled with the modest (50-fold) selectivity for CCK-A vs CCK-B receptors, prompted us to evaluate the CCK-B functional profile of this compound. The ability of **1** to mobilize intracellular calcium in stably transfected CHO-K1 cells expressing the hCCK-A or hCCK-B receptors and loaded with FURA2-AM was used to evaluate functional activity.[33d] 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.[29] Indazole **1** profiled as a potent, full agonist on the CHO cells expressing the

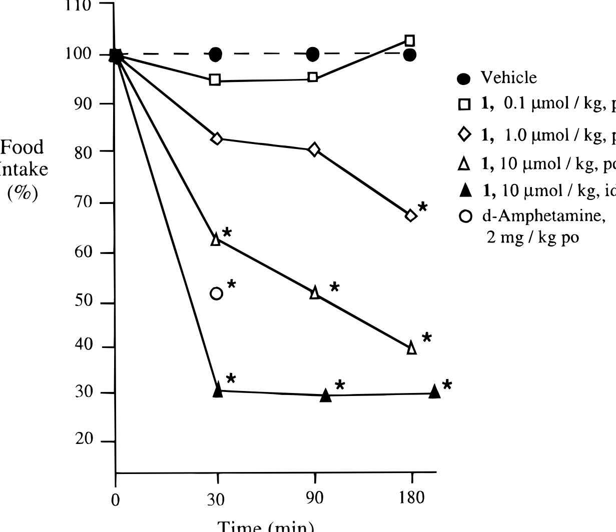

Figure 3. Male Long–Evans rats (225–300 g) were conditioned for 2 weeks to consume a palatable liquid diet (Bio-Serve F1657, Frenchtown, NJ) after a 2 h fast. On pretreatment day, rats were fasted (100 min) and injected po with drug vehicle (propylene glycol, PG, 1 mL/kg) and an oral preload of saline (0.9% NaCl, 8 mL/kg). Liquid diet access was provided 20 min later, and consumption was measured at 30, 90, and 180 min. To qualify for the drug treatment study, rats had to consume at least 8 mL of liquid diet within the first 30 min on the pretreatment day. The next day, following the 100 min deprivation, rats (8–10 animals per dose) were treated po or id with vehicle (PG, 1 mL/kg) or various doses (0.1–10 μmol/kg) of test compound dissolved in PG (1 mL/kg), immediately followed by the saline oral preload. Food access was again provided 20 min later and food intake was measured at 30, 90, and 180 min. All food intake data were normalized for each rat to the respective values from the pretreatment day. $*p < 0.05$ using Dunnett's multiple comparison test.

hCCK-A receptor (EC_{50} = 145 nM, n = 1) but was inactive at concentrations up to 10 μM on the CHO cells expressing the hCCK-B receptor. Although compound **1** was not tested for CCK-B antagonist activity in this assay, the lack of CCK-B agonist activity displayed by **1** provides additional evidence for the potential utility of **1** as a therapeutic agent.

Compound **1** was also resolved into its optical antipodes to evaluate the relationship between bioactivity and absolute stereochemistry at C3. Absolute stereochemistry at this position has been shown to modulate both CCK-A/CCK-B selectivity and potency in 1,4-benzodiazepine CCK antagonists.[31] Racemic **1** was separated on a Chiralpak AD column to afford the two enantiomers with >98% ee. The faster-eluting enantiomer was a potent (ED_{50} = 70 nM, n = 1) full agonist (%max = 105%, n = 1) at the CCK-A receptor *in vitro* (GPGB assay), while the other enantiomer was less potent (ED_{50} = 530 nM, n = 1) and efficacious (%max = 80%, n = 1). Surprisingly, the receptor binding selectivities for the two enantiomers were similar, with the faster eluting enantiomer having slightly better affinity for both receptor subtypes (CCK-A $pIC_{50} = 7.47 \pm 0.46$, CCK-B $pIC_{50} = 6.45 \pm 0.09$, n = 3) than its antipode (CCK-A $pIC_{50} = 6.67 \pm 0.37$, CCK-B $pIC_{50} = 6.02 \pm 0.15$, n = 3). It is possible that the N1-anilidoacetamide moiety overrides any influence on receptor binding selectivities attributed to the stereochemical disposition of the C3 substituent, as a similar effect has been reported in a 1,4-benzodiazepine CCK-B antagonist series.[39]

Summary

In our initial communication[9] we described a synopsis of the discovery of a series of 3-(1*H*-indazol-3-ylmethyl)-1,5-benzodiazepines which are binding-selective CCK-A full agonists. One of these compounds, **1** (GW 5823) was the first non-peptide CCK-A agonist to demonstrate suppression of food intake when given orally in a rat feeding model. In the present paper we detailed the design, synthesis, and structure–activity relationships within this series of 1,5-benzodiazepines. Modulation of efficacy in this series was dependent on the electronic nature of the C3 heterocyclic substituent and the steric bulk of both the second C3 substituent and the N1-indazolyl substituent. Modulation of receptor subtype binding affinity was achieved by altering the size of the second C3 substituent and by changing the N1-anilidoacetamide substituents. Several additional potent and selective CCK-A agonists from this series were discovered to have *in vivo* activity. None, however, displayed potency or efficacy equal to that of **1** in these assays. In addition, data suggests that GW 5823 is a CCK-B antagonist *in vitro*. The rat pharmacokinetic profiles of GW 5823 and several close analogs indicate these compounds suffer from poor oral bioavailability and relatively high clearance. This low bioavailability in the rat appears to be a consequence of both delayed gastric emptying and rapid metabolism by the liver. Despite the pharmacokinetic limitations, GW 5823 is a potent and efficacious anorectic agent when dosed both orally and intraduodenally in a rat conditioned feeding model and shows promise as an orally active satiety agent which may be useful for the treatment of obesity. It remains to be seen whether the low bioavailability and inhibition of gastric emptying observed with GW 5823 in rats will translate to humans. Efforts to further refine the pharmacological profile of this series of compounds are continuing and will be reported at a later date.

Experimental Section

General. All commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise specified. The following solvents and reagents have been abbreviated: tetrahydrofuran (THF), ethyl ether (Et_2O), dimethyl sulfoxide (DMSO), EtOAc (EtOAc), dichloromethane (DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), methanol (MeOH). All reactions except those in aqueous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60F-254, E. Merck) and visualized with UV light, iodine vapors, or 5% phosphomolybdic acid in 95% ethanol.

Final compounds were typically purified either by flash chromatography on silica gel (E. Merck 40–63 mm) as described by Still[40] or by preparative reverse 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 μm, 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 100 mL/min (t_o = 5 min). Analytical purity was assessed by RP-HPLC using a Waters 600E system equipped with a Waters 990 diode array spectrometer (λ range 200–400 nm). The stationary phase was a Vydac C-18 column (5 μm, 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_o = 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, a Varian Unity-400, 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 (Hz). 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, 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. MK-329[22] was obtained from Merck & Co. (Rahway, NJ). CCK-8 was purchased from Sigma (St. Louis, MO).

General Method for Reductive Amination of Anilines with Ketones/Aldehydes. Where appropriate secondary amines could not be procured from commercial sources, a primary amine was converted to the desired secondary amine via reductive amination with an appropriate aldehyde or ketone using the following method: To a stirring solution of the appropriate aniline in THF at 0 °C is added 1.0 equiv of the appropriate aldehyde or ketone, 1.0 equiv of acetic acid, and 1.5 equiv of sodium triacetoxyborohydride. The solution is stirred at room temperature for 15 h, cooled to 0 °C, and then quenched by careful addition of H_2O. The reaction mixture warmed to room temperature and is poured into EtOAc, the organic layer is separated, washed with brine (1 × 200 mL), and dried ($MgSO_4$), and the solvents are removed *in vacuo* to afford the crude compounds as yellow to brown oils which were used without further purification. Spectral data for representative compounds are as follows:

***N*-Isopropyl-*N*-(4-methoxyphenyl)amine (46a):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, 2H, J = 8.8), 6.57 (d, 2H, J = 9.1), 3.75 (s, 3H), 3.55 (m, 1H), 2.92 (bs, 1H), 1.18 (d, 6H, J = 6.1); TLC (EtOAc/Hex (2:3)) R_f = 0.72.

***N*-Isopropyl-*N*-(3-methoxyphenyl)amine (46b):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, 1H, J = 8.0), 7.01 (dt, 2H, J = 9.7, 1.9), 6.19 (s, 1H), 3.80 (s, 3H), 3.62 (m, 1H, J = 6.8), 1.06 (d, 6H, J = 6.8).

***N*-Isopropyl-*N*-(2-methoxyphenyl)amine (46c):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (t, 1H, J = 7.6), 7.01 (d, 1H, J = 7.6), 6.68 (t, 2H, J = 7.9), 3.88 (s, 3H), 3.66 (m, 1H, J = 6.8), 1.28 (d, 6H, J = 6.8).

***N*-Isopropyl-*N*-(3,4-(methylenedioxy)phenyl)amine (46d):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, 1H, J = 8.3), 6.43 (s, 1H), 6.29 (s, br, 1H), 5.91 (s, 2H), 3.53 (m, 1H, J = 6.8), 1.17 (m, 6H).

General Procedure for Acylation of Secondary Amines To Give 2-Bromoacetamides of General Formula 3. A solution of amine (1.0 equiv) and triethylamine (1.0 equiv) in CH_2Cl_2 was cooled to 0 °C. Bromoacetyl bromide (1.0 equiv) was dissolved in CH_2Cl_2 and was added dropwise over 45 min with stirring. The reaction mixture was stirred anywhere from 3 h to overnight at ambient temperature, washed successively with 0.3 N HCl (300 mL) and brine (300 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo*. The resultant oil was purified by silica gel flash column chromatography using the appropriate eluent, and the combined filtrates were evaporated *in vacuo* to give the corresponding 2-bromoacetamide in good yield (>85% typical) and high purity. Spectral data for representative compounds are as follows:

2-Bromo-*N*-isopropyl-*N*-phenylacetamide (3a). Chromatography eluting with EtOAc/hexane (1/1) afforded a brown oil which crystallized on standing (76% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 3H), 7.15 (m, 2H), 4.93 (m, 1H), 3.53 (s, 2H), 1.04 (d, 6H, J = 6.8).

2-Bromo-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (3b). Chromatography eluting with EtOAc/hexane (1/1) afforded a brown oil which crystallized on standing (82% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2H, J = 9.1), 6.93 (d, 2H, J = 9.1), 4.93 (m, 1H), 3.84 (s, 3H), 3.53 (s, 2H), 1.04 (d, 6H, J = 6.8); TLC (EtOAc/hexane (3/17)) R_f = 0.18.

2-Bromo-*N*-cyclopentyl-*N*-(4-methoxyphenyl)acetamide (3c). Chromatography using EtOAc/hexanes (3/17) as eluent gave an amber oil (87% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, 2H, J = 9.0), 6.90 (d, 2H, J = 9.0), 4.84 (m, 1H), 3.83 (s, 3H), 3.54 (s, 2H), 1.87 (m, 2H), 1.49 (m, 4H), 1.25 (m, 2H); TLC R_f = 0.65 (EtOAc/hexanes, 3/17).

2-Bromo-*N*-cyclopropyl-*N*-phenylacetamide (3d). Chromatography eluted successively with EtOAc/hexanes (1/9, 100 mL; 3/17, 300 mL) gave an amber oil (76% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 3H), 7.15 (m, 2H), 3.62 (s, br, 2H), 3.24 (m, 1H), 0.83 (m, 2H), 0.52 (m, 2H); TLC R_f = 0.18 (EtOAc/hexanes, 3/17).

2-Bromo-*N*-(4-(trifluoromethyl)phenyl)-*N*-isopropylacetamide (3e). Chromatography using EtOAc/hexanes (3/17) as eluent afforded an amber oil (81% yield): ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.26–7.09 (m, 4H), 4.85 (m, 1H), 3.51 (s, 2H), 1.05 (d, 6H, J = 6.9); low-resolution MS (FAB) m/e 274 (MH^+).

***N*-Isopropyl-*N*-(3-methoxyphenyl)bromoacetamide (3f).** Concentrated *in vacuo* to afford a dark mobile oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, 1H, J = 8.0), 7.01 (dd, 1H, J = 8.1, 2.2), 6.81 (d, 1H, J = 7.6), 6.79 (s, 1H), 4.95 (m, 1H, J = 6.8), 3.88 (s, 3H), 3.60 (s, 2H), 1.06 (d, 6H, J = 6.8).

***N*-Isopropyl-*N*-(2-methoxyphenyl)bromoacetamide (3g).** Concentrated *in vacuo* to afford a dark mobile oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dt, 1H, J = 7.8, 1.4), 7.20 (dd, 1H, J = 7.8, 1.4), 7.04 (m, 2H), 4.90 (m, 1H, J = 6.8), 3.85 (s, 3H), 3.60 (dd, 2H, J = 32.9, 11.5), 1.20 (d, 3H, J = 6.8), 0.97 (d, 3H, J = 6.8).

***N*-Isopropyl-*N*-(3,4-(methylenedioxy)phenyl)bromoacetamide (3h).** Concentrated *in vacuo* to afford a dark mobile oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, 1H, J = 8.2), 6.61 (m, 2H), 4.90 (m, 1H, J = 6.8), 3.58 (s, 2H), 1.07 (m, 6H).

2-Bromo-*N*-*tert*-butyl-*N*-phenylacetamide (3i). Purification via filtration through a pad of silica gel eluted with DCM: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.21 (m, 12H), 7.08 (t, 1H), 6.90 (m, 1H), 4.30 (d, 1H, J = 16.4), 3.85 (d, 1H, J = 16.6), 3.59 (d, 1H, J = 12.0), 3.49 (d, 1H, J = 11.9), 1.43 (s, 9H); TLC R_f = 0.24 (EtOAc/hexanes, 1/1).

General Procedure for Alkylation of *N*-Phenyl-*o*-phenylenediamine with Bromoacetamides 3a–g. To a stirring solution of *N*-phenyl-*o*-phenylenediamine in DMF at room temperature was added 1.1 equiv of K_2CO_3 followed by 1.0 equiv of the bromoacetamide. The resulting mixture was heated to 60 °C for 16 h and then cooled to room temperature. The mixture was filtered to remove the K_2CO_3 and then diluted with 800 mL of EtOAc and 200 mL of Et_2O. This solution was washed successively with H_2O (2 × 400 mL), brine (1 × 400 mL), 1 N HCl (2 × 400 mL), and H_2O (1 × 400 mL), and the organics were dried ($MgSO_4$) and concentrated to give a greenish-black oil. The resultant oil was purified either by trituration in the appropriate solvent or by silica gel flash column chromatography using the appropriate eluent and the combined filtrates evaporated *in vacuo* to give the corresponding acetamides. Spectral data for representative compounds are as follows:

***N*-Isopropyl-*N*-phenyl-2-((2-(phenylamino)phenyl)amino)acetamide (7a).** Chromatography using first $CHCl_3$, then hexane/EtOAc (2/1) as eluents gave a clear oil (62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–6.8 (m, 14H), 6.36 (m, 1H), 4.95 (m, 1H), 3.22 (s, 2H), 1.05 (d, 6H J = 6.8); MS m/e 360 (MH^+); TLC R_f = 0.18 ($CHCl_3$).

***N*-Isopropyl-*N*-(4-methoxyphenyl)-2-((2-(phenylamino)phenyl)amino)acetamide (7b).** Trituration with Et_2O/petroleum ether (1/4) gave a light gray solid which was dried under vacuum to afford the title compound (75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24–6.71 (m, 12H), 6.43 (d, 1H, J = 8.3), 4.96 (m, 1H), 3.92 (s, 3H), 3.44 (s, 2H), 1.05 (d, 6H, J = 6.9).

***N*-Cyclopentyl-*N*-(4-methoxyphenyl)-2-((6-(phenylamino)cyclohexa-2,4-dienyl)amino)acetamide (7c).** Chromatograhpy using EtOAc/hexanes (3/17) as eluent afforded a yellow oil (67%): ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.26–6.50 (m, 13H), 6.22 (d, 1H, J = 7.9), 5.29 (s, br, 1H), 4.82 (m, 1H), 3.87 (s, 3H), 3.41 (d, 2H, J = 4.4), 1.83 (m, 2H), 1.48 (m, 4H), 1.33 (m, 2H); TLC R_f = 0.14 (EtOAc/hexanes, 3/17).

***N*-Isopropyl-2-((2-(phenylamino)phenyl)amino)-*N*-(4-(trifluoromethyl)phenyl)acetamide (7e).** Chromatography using hexane/EtOAc (5/1) as eluent afforded a light tan solid (57%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 2H, J = 8.2), 7.26 (d, 2H, J = 8.2), 7.15 (m, 3H), 6.95 (dd, 1H, J = 7.7, 7.7), 6.80 (dd, 1H, J = 7.1, 7.1), 6.74 (d, 2H, J = 7.9), 6.68 (dd, 1H, J = 7.4, 7.4), 6.29 (d, 1H, J = 7.9), 5.20 (s, 1H), 5.00 (m, 1H), 3.40 (s, 2H), 1.06 (d, 6H, J = 6.6); low-resolution MS (FAB) m/e 427 (MH^+); high-resolution MS ($C_{24}H_{24}F_3N_3O$) calcd 427.1871, found 427.1871.

***N*-Isopropyl-*N*-(3-methoxyphenyl)-2-((2-(phenylamino)phenyl)amino)acetamide (7f).** Chromatography using EtOAc/hexane (1/4) as eluent gave a light brown foam (62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, 1H, J = 8.0), 7.3−7.1 (m, 3H), 7.02 (m, 2H), 6.9−6.6 (m, 7H), 6.36 (d, 1H, J = 7.8), 5.3 (s, br, 1H), 4.95 (m, 1H, J = 6.8), 3.88 (s, 3H), 3.53 (s, 2H), 1.06 (m, 6H).

***N*-Isopropyl-*N*-(2-methoxyphenyl)-2-((2-(phenylamino)phenyl)amino)acetamide (7g).** Chromatography using EtOAc/hexane (1/4) as eluent gave a light brown foam (71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (t, 1H, J = 7.9), 7.030−7.05 (m, 8H), 6.98 (t, 1H, J = 6.8), 6.84 (m, 2H), 6.70 (t, 1H, J = 7.6), 6.37 (d, 1H, J = 8.0), 5.4 (s, br, 1H), 4.95 (m, 1H, J = 6.8), 3.84 (s, 3H), 3.45 (dd, 2H, J = 23.2, 6.6), 1.20 (d, 3H, J = 6.8), 1.01 (d, 3H, J = 6.8).

General Procedure for Cyclization To Provide 1,5-Benzodiazepines of General Formula 4. To 100 mL of THF at 0 °C was added dropwise over 20 min *simultaneously* a solution of 8.0 g (1.0 equiv) of the requisite diaminoacetamide in 100 mL of THF and 2.40 mL (1.2 equiv) of malonyl dichloride in 100 mL of THF. The resulting solution was stirred at room temperature for 20 h and the solvent removed *in vacuo*. The resultant material was purified by silica gel flash column chromatography using the appropriate eluent, and the combined filtrates were evaporated *in vacuo* to give the corresponding acetamides. Spectral data for representative compounds are as follows:

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-isopropyl-*N*-phenylacetamide (4a). Chromatography (50−75% EtOAc/petroleum ether) followed by recrystallization from hot EtOAc/petroleum ether gave a white powder (56%): mp 199−200 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.6−7.2 (m, 12H), 7.09 (t, 1H, J = 8), 6.90 (d, 1H, J = 8), 5.05 (m, 1H), 4.38 (d, 1H, J = 17), 4.04 (d, 1H, J = 17), 3.54 (dd, 2H, J = 5, 22), 1.10 (d, 6H, J = 7); low-resolution MS (FAB) m/e 428 (MH^+).

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (4b). Chromatography using hexanes/EtOAc (1/1) as eluent afforded a light tan solid (60%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−6.86 (m, 13H), 5.02 (m, 1H), 4.38 (d, 1H, J = 16.6), 4.04 (d, 1H, J = 16.6), 3.84 (s, 3H), 2.55 (m, 2H), 1.10 (d, 6H, J = 6.8).

***N*-Cyclopentyl-2-(2,4-dioxo-5-phenyl-2,3,4,5,-tetrahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-(4-methoxyphenyl)-acetamide (4c).** Chromatography using EtOAc/hexanes (1/1) as eluent afforded a clear glass (48%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.20 (m, 8H), 7.09 (m, 2H), 6.97 (m, 3H), 4.95 (m, 1H), 4.38 (d, 1H, J = 16.4), 4.06 (d, 1H, J = 16.3), 3.84 (s, 3H), 3.59 (d, 1H, J = 12.0), 3.49 (d, 1H, J = 11.9), 1.90 (m, 2H), 1.52 (m, 4H), 1.35 (m, 2H); TLC R_f = 0.16 (EtOAc/hexanes, 1/1).

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-isopropyl-*N*-(4-(trifluoromethyl)phenyl)acetamide (4e). Chromatography using hexane/EtOAc (3/2) as eluent afforded a light tan solid (54%): mp 186−188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, 2H, J = 8.1), 7.42 (d, 2H, J = 8.1), 7.36 (m, 3H), 7.25 (m, 4H), 7.08 (ddd, 1H, J = 1.4, 8.4, 8.4), 6.90 (dd, 1H, J = 1.2, 8.2), 5.06 (m, 1H), 4.12 (dd, 2H, J = 14.4, 95.5), 3.52 (dd, 2H, J = 12.0, 34.5), 1.11 (d, 6H, J = 6.6); low-resolution MS (FAB) m/e 496 (MH^+), 293, 265. Anal. ($C_{27}H_{24}F_3N_3O_3$) Calcd: C, 65.45; H, 4.88; N, 8.48; Found: C, 65.16; H, 4.95; N, 8.33.

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-isopropyl-*N*-(3-methoxyphenyl)acetamide (4f). Chromatography using 3% MeOH in DCM as eluent afforded an amber foam (46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.1 (m, 10H), 7.02 (t, 1H, J = 7.2), 6.92 (dd 1H, J = 8.6, 2.4), 6.83 (d, 1H, J = 7.2), 4.95 (m, 1H, J = 6.8), 4.38 (m, 1H), 4.02 (m, 1H), 3.78 (s, 3H), 3.48 (dd, 2H, J = 39.3, 11.9), 1.06 (m, 6H).

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-isopropyl-*N*-(2-methoxyphenyl)acetamide (4g). Chromatography using 2% MeOH in DCM as eluent afforded a cream foam which exists as 3:2 mixture of rotamers (major rotamer recorded): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−6.90 (m, 13H), 5.05 (m, 1H, J = 6.9), 4.60−3.40 (m, 7H), 1.12 (m, 6H).

1-Phenyl-1,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-2,4-dione (5). 2-Nitrophenylenediamine (100 g, 1.0 equiv, 0.47 mol) is dissolved in 1 L of dry toluene and cooled to 0 °C with a ice/water bath. Methylmalonyl chloride (55 mL, 1.1 equiv, 0.51 mol) is added dropwise over 20 min. The reaction mixture is allowed to warm to room temperature and stirred 1 h, and at 80 °C for 2 days. The solvent is removed *in vacuo*, and the resulting solid is recrystallized from Et_2O/CH_2Cl_2/hexane to afford 110.6 g of *N*-(2-nitrophenyl)-*N*-phenylmalonamic acid methyl ester. A mixture of 55.6 g (1.0 equiv, 0.17 mol) of the above product and 5 g of 10% Pd/C is taken up in 4 L of ethanol and 200 mL of EtOAc, the reaction mixture is stirred under an atmosphere of hydrogen gas for 7 h and then filtered through Celite, and the solvent is removed *in vacuo* to afford 43.7 g of *N*-(2-aminophenyl)-*N*-phenylmalonamic acid methyl ester. The above amine (10 g, 1.0 equiv, 35.0 mmol) is dissolved in 220 mL of ethanol and cooled to 0 °C, and 1.2 g (56.0 mmol, 1.6 equiv) of Na dissolved in 180 mL of ethanol is added. The reaction mixture is warmed slowly to room temperature and stirred for 1 h followed by the removal of solvent *in vacuo*. The residue is acidified with 1 N HCl and extracted with EtOAc (2 × 500 mL). The organic layer is dried over $MgSO_4$, and the solvent is removed *in vacuo*. Trituration with Et_2O afforded 2.75 g of a white solid: ^{1}H NMR (DMSO, 300 MHz) δ 10.60 (s, 1H), 7.64−7.08 (m, 8H), 6.81 (d, J = 8.0, 1H), 3.61−3.11 (m, 2H); R_f = 0.44 (hexane/EtOAc, 1/2).

General Procedure for Alkylation of 1,5-Benzodiazepines with Bromoacetamides of Formula 2 To Provide Compounds of General Formula 4. To a stirred solution of 1.0 equiv of 1-phenyl-1,5,5a,9a-tetrahydrobenzo[*b*][1,4]-diazepine-2,4-dione in DMF is added 1.3 equiv of 60 wt % NaH in mineral oil at ambient temperature and the resulting reaction stirred 0.5 h. To this solution is added 1.0 equiv of the desired acetamide in 3 mL of DMF, and the resulting reaction is stirred 18 h at room temperature. The solvent is removed *in vacuo* and the residue taken into 50 mL of EtOAc, washed successively with H_2O (30 mL), 1 N HCl (30 mL), $NaHCO_3$ (30 mL), and brine (30 mL), dried ($MgSO_4$), and filtered, and solvents are removed *in vacuo*. The resultant material was purified by silica gel flash column chromatography using the appropriate eluent, and the combined filtrates were evaporated *in vacuo* to give the corresponding acetamides. Spectral data for representative compounds are as follows:

***N*-Cyclopropyl-2-(2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-(4-methoxyphenyl)-acetamide (4d).** Chromatography using EtOAc/hexanes (1/1) as eluent afforded a white foam (52%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.07 (m, 13H), 6.92 (d, 1H, J = 7.3), 3.60 (d, 1H, J = 11.9), 3.51 (d, 1H, J = 12.0), 3.30 (m, 1H), 0.86 (m, 2H), 0.60 (m, 2H); TLC R_f = 0.35 (EtOAc/hexanes, 2/1).

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-isopropyl-*N*-(3,4-(methylenedioxy)phenyl)acetamide (4h). Concentration of solvent afforded a brown glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.5−6.6 (m, 11H), 6.09 (s, 2H), 5.03 (m, 1H, J = 6.9), 4.46 (dd, 1H, J = 27.2, 12.6), 4.16 (dd, 1H, J = 27.2, 5.6), 3.58 (d, 1H, J = 15.8), 3.48 (d, 1H, J = 15.8), 1.08 (m, 6H).

***N*-*tert*-Butyl-2-(2,4-dioxo-5-phenyl-2,3,4,5,5a,9a-hexahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-phenylacetamide (4i).** Chromatography eluted successively with EtOAc/hexanes (2/3 to 1/1) afforded a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.21 (m, 12H), 7.08 (t, 1H), 6.90 (m, 1H), 4.30 (d, 1H, J = 16.4), 3.85 (d, 1H, J = 16.6), 3.59 (d, 1H, J =

12.0), 3.49 (d, 1H, J = 11.9), 1.43 (s, 9H); TLC R_f = 0.24 (EtOAc/hexanes, 1/1).

2-(2,4-Dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl)-*N*-(4-fluorophenyl)-*N*-isopropylacetamide (4j). Concentration of solvent afforded a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (s, 1H), 7.40–7.06 (m, 11H), 6.90 (m, 1H), 5.45 (m, 1H), 4.30 (d, 1H, J = 16.2), 4.00 (d, 1H, J = 16.2), 3.55 (m, 2H), 1.08 (d, 6H, J = 6.7); low-resolution MS (FAB) *m/e* 446 (MH^+).

General Procedure for Alkylation of 1,5 Benzodiazepines at C-3 followed by Deprotection (if Needed) To Afford 1, 15–19, 26, 28, 29, 31–34, 36–45 (Tables 1–4). To a stirring solution of 1.0 equiv of the desired 1,5-benzodiazepine substrate in 15 mL of DMF at 0 °C was added 1.1 equiv of the desired base (60% NaH in mineral oil, a 1.0 M solution of $NaN(TMS)_2$ in THF or a 0.5 M solution of KN-$(TMS)_2$ in toluene). The resulting solution was stirred 10–30 min, and then a solution of 1.1 equiv of the desired alkyl halide (normally a 3-(bromomethyl)indazole derivative) in 3 mL of DMF was added. The resulting solution was stirred 2 h at room temperature and then quenched with 5 mL of H_2O. The reaction mixture was then poured into 50 mL of EtOAc and extracted with H_2O (2 × 50 mL). The organic layer was separated and dried ($MgSO_4$), and the solvents were removed *in vacuo*. Deprotection, if needed, was carried out using one of the following two methods unless otherwise indicated.

Method A: To a stirring solution of the material obtained in the alkylation step described above in 10 mL of DCM was added 3 mL of TFA. The resulting solution was stirred for 2 h, and the solvents were removed *in vacuo*. The resultant material was purified by either silica gel flash column chromatography or reverse phase MPLC using the appropriate eluent, and the combined filtrates were evaporated *in vacuo* to give the desired analog.

Method B: The crude material obtained in the alkylation step described above was dissolved in 10 mL of 4 N HCl in dioxane, and the reaction mixture was stirred 6 h at room temperature. The reaction mixture was diluted with 40 mL of EtOAc and extracted with $NaHCO_3$ (1 × 30 mL) and H_2O (1 × 30 mL). The organic layer was dried ($MgSO_4$), and the solvents were removed *in vacuo*. The resultant material was purified by either silica gel flash column chromatography or reverse phase MPLC using the appropriate eluent, and the combined filtrates were evaporated *in vacuo* to give the desired analog. Spectral data and purification protocol for the representative compounds are as follows:

2-[3-(1*H*-Indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-terahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(4-methoxyphenyl)acetamide (1). Deprotection via method A, purification of the residue by chromatography using hexane/EtOAc (3/2 up to 2/3) as eluent followed by further purification via reverse phase MPLC using a C-18 column and 60% acetonitrile/40% H_2O as eluent and lyophilization afforded 62 mg of a white amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, 1H, J = 8.0), 7.41–6.90 (m, 17H), 5.00 (m, 1H), 4.23 (m, 3H), 3.84 (s, 3H), 3.79 (d, 1H, J = 7.9), 3.61 (dd, 1H, J = 5.8, 16.1), 1.06 (m, 6H); low resolution MS (FAB) *m/e* 588 (MH^+), 423, 223. Anal. ($C_{35}H_{33}N_5O_4$) C, H, N.

Racemic **1** (40 mg) was dissolved in 250 mL of a mixture of *i*-PrOH/$CHCl_3$/hexane (32%/8%/60%) and separated on Chiralpack AD column 20 mm × 25 cm using hexane/*i*-PrOH/$CHCl_3$ = 80%/16%/4% as eluent and a flow rate of 6 mL/min. Two fractions were collected at $t_R(1)$ = 39.4 min and $t_R(2)$ = 76.6 min. The solvent was removed *in vacuo* to afford 18 mg of one enantiomer (ee >99% by analytical HPLC) and 16 mg of the other (ee >98% by analytical HPLC).

2-[3-(1*H*-Indol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(4-methoxyphenyl)acetamide (15). Deprotection via method B and purification via silica gel chromatography using hexane/EtOAc (2/1) as eluent followed by further purification by reverse phase MPLC using a C-18 column and 65% acetonitrile/35% H_2O as eluent and lyophilization afforded 52 mg (54%) of a white amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.73 (s, 1H), 7.46–6.88 (m, 18H), 4.78 (m, 1H), 4.38 (d, 1H, J = 16.6), 4.17 (d, 1H, J = 16.6), 3.80 (s, 3H), 3.58 (t, 1H, J = 6.6), 3.22 (d, 2H, J = 6.6), 0.96 (m, 6H); low-resolution MS (FAB) *m/e* 587 (MH^+), 586 (M^+), 422, 293; high-resolution MS calcd 586.2587, found 586.2580. Anal. ($C_{36}H_{34}N_4O_4$) H, N, C: calcd, 73.70; found, 72.70.

2-[3-(Benzofuran-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (16). Purification by silica gel MPLC on an Si60 column using hexane/EtOAc (5/2) as eluent followed by lyophilization in acetonitrile/H_2O afforded 292 mg of a white amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (m, 2H), 7.43–6.86 (m, 16H), 5.05 (m, 1H), 4.40 (d, 1H, J = 16.6), 4.08 (d, 1H, J = 16.6), 3.85 (s,3H), 3.68 (t, 1H, J = 6.4), 3.47 (m, 2H), 1.11 (m, 6H); low-resolution MS (FAB) *m/e* 588 (MH^+); high-resolution MS calcd 588.2503, found 588.2498.

2-[3-(Benzo[*b*]thiophene-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (17). Purification by silica gel MPLC on an Si60 column using hexane/EtOAc (5/2) as eluent followed by lyophilization in acetonitrile/H_2O afforded 222 mg of a white amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (m, 2H), 7.44–6.93 (m, 15H), 6.88 (dd, 1H, J = 1.5, 8.1), 5.03 (m, 1H), 4.42 (d, 1H, J = 16.6), 4.09 (d, 1H, J = 16.6), 3.85 (s, 3H), 3.80 (t, 1H, J = 6.6), 3.61 (m, 2H), 1.10 (t, 6H, J = 6.8); low-resolution MS (FAB) *m/e* 604 (MH^+), 439; high-resolution MS calcd 604.2271, found 604.2270.

2-[3-(Benzo[*d*]isoxazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (18). Purification by silica gel chromatography using hexane/EtOAc (2/1) as eluent followed by lyophilization in acetonitrile/H_2O afforded 303 mg of a white amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, 1H, J = 7.8), 7.55–7.10 (m, 14H), 6.97 (m, 2H), 5.01 (m, 1H), 4.28 (m, 3H), 3.85 (m, 4H), 3.58 (dd, 1H, J = 5.1, 16.6), 1.07 (d, 6H, J = 6.6); low-resolution MS (FAB) *m/e* 589 (MH^+), 588 (M^+), 424, 396. Anal. ($C_{35}H_{32}N_4O_5$) C, H, N.

2-[3-(Benzo[*d*]isothiazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (19). Purification by silica gel MPLC on an Si60 column using hexane/EtOAc (2/1) as eluent afforded a white amorphous solid (76%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, 1H, J = 8.1), 7.84 (d, 1H, J = 8.1), 7.49–7.21 (m, 11H), 7.13 (m, 2H), 6.98 (m, 2H), 5.00 (m, 1H), 4.52 (dd, 1H, J = 5.0, 8.7), 4.26 (m, 2H), 3.96 (dd, 1H, J = 8.7, 17.1), 3.83 (s, 3H), 3.64 (dd, 1H, J = 5.0, 19.0), 1.06 (m, 6H); low-resolution MS (FAB) *m/e* 605 (MH^+), 604 (M^+), 440. Anal. ($C_{35}H_{32}N_4O_4S$) C, H, N.

***N*-Isopropyl-*N*-(4-methoxyphenyl)-2-[3-[(1-methyl-1*H*-indazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]acetamide (25).** Purification by silica gel chromatography using hexane/EtOAc (2/1) as eluent followed by further purification via silica gel MPLC using a Si60 column and hexane/EtOAc (1/1) as eluent and lyophilization in acetonitrile/H_2O afforded 100 mg of a white amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 1H, J = 8.3), 7.25–6.76 (m, 16H), 4.85 (m, 1H), 4.11 (s, br, 2H), 3.97 (dd, 1H, J = 5.6, 7.8), 3.77 (s, 3H), 3.70 (s, 3H), 3.63 (dd, 1H, J = 7.8, 15.9), 3.48 (dd, 1H, J = 5.6, 15.9), 0.92 (d, 6H, J = 6.8); low-resolution MS (FAB) *m/e* 602 (MH^+), 437. Anal. ($C_{36}H_{35}N_5O_4$) C, H, N.

2-[3-[(1-Benzyl-1*H*-indazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (26). Purification by silica gel flash column chromatography using hexane/EtOAc (3/2) as eluent followed by lyophilization in acetonitrile/H_2O afforded 620 mg a white amorphous solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 1H, J = 8.1), 7.40 (d, 1H, J = 7.9), 7.33–6.88 (m, 20H), 5.43 (s, 2H), 5.00 (m, 1H), 4.25 (m, 3H), 3.85 (m, 4H), 3.58 (dd, 1H, J = 5.1, 16.0), 1.06 (d, 6H, J = 6.6); low-resolution MS (FAB) *m/e* 678 (MH^+), 677 (M^+), 513; high-resolution MS calcd 678.3082, found 678.3080.

2-[2,4-Dioxo-5-phenyl-3-[(1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)methyl]-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(4-methoxyphenyl)acetamide (28). Deprotection via method B followed by purification by silica gel MPLC using hexane/EtOAc (1/3) as eluent afforded 89 mg of

a white solid: mp 156−158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.51 (s, br, 1H), 8.48 (dd, 1H, J = 1.2, 4.6), 8.25 (d, 1H, J = 7.0), 7.40−6.91 (m, 14H), 4.98 (m, 1H), 4.26 (m, 2H), 4.18 (dd, 1H, J = 5.8, 7.8), 3.83 (s, 3H), 3.79 (dd 1H, J = 7.8, 15.9), 3.60 (dd, 1H, J = 5.7, 15.9), 1.05 (d, 6H, J = 6.7); low-resolution MS (FAB) m/e 589 (MH^+), 424. Anal. ($C_{34}H_{32}N_6O_4$) H, N, C: calcd, 69.37; found, 68.69.

2-[2,4-Dioxo-5-phenyl-3-[(1*H*-pyrazolo[4,3-*b*]pyridin-7-yl)methyl]-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (29). Deprotection via method B followed by purification by silica gel MPLC using hexane/EtOAc (1/4) as eluent afforded 146 mg of a white solid: mp 173−176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.50 (s, br, 1H), 8.33 (d, 1H, J = 3.5), 7.59 (d, 1H, J = 8.5), 7.39−6.88 (m, 14H), 4.97 (m, 1H), 4.41 (dd, 1H, J = 6.8, 6.8), 4.28 (m, 2H), 3.92 (dd, 1H, J = 7.9, 16.6), 3.82 (s, 3H), 3.76 (dd 1H, J = 6.8, 16.6), 1.04 (d, 3H, J = 6.6), 0.99 (d, 3H, J = 6.9); low-resolution MS (FAB) m/e 589 (MH^+), 588 (M^+), 424. Anal. ($C_{34}H_{32}N_6O_4$) C, H, N: calcd, 14.28; found, 13.73.

2-[3-[(4-Fluoro-1*H*-indazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (31). Deprotection via method A followed by purification via silica gel column chromatography using hexane/EtOAc (2/1) as eluent afforded 140 mg of a white solid (64%): mp 232−234 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 7.43−6.90 (m, 16H), 5.02 (m, 1H), 4.32 (d, 1H, J = 15.6), 4.20 (m, 2H), 3.84 (s, 3H), 3.73 (dd, 1H, J = 7.9, 15.7), 3.51 (dd, 1H, J = 5.6, 16), 1.06 (t, 6H, J = 6.8); high-resolution MS (FAB) calcd 606.2517, found 606.2506.

2-[3-[(5-Fluoro-1*H*-indazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (32). Deprotection via method B followed by purification via silica gel column chromatography using hexane/EtOAc (2/1) as eluent afforded 170 mg of a white solid (44%): mp 216−219 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−6.90 (m, 16H), 5.02 (m, 1H), 4.32 (d, 1H, J = 15.6), 4.20 (m, 2H), 3.84 (s, 3H) 3.73 (dd, 1H, J = 7.9, 15.7), 3.51 (dd, 1H, J = 5.6, 16), 1.06 (t, 6H, J = 6.8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 166.6, 159.6, 144.3, 136.1, 131.4, 131.2, 129.6, 129.1, 128.2, 127.3, 126.6, 126.3, 126.0, 123.1, 114.7, 55.5, 46.5, 21.0, 20.7; high-resolution MS (FAB) m/e calcd 606.2517, found 606.2517.

2-[3-[(6-Fluoro-1*H*-indazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (33). Deprotection via method A afforded 240 mg of the title compound: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82−6.88 (m, 18H), 4.77 (m, 1H, J = 6.8), 4.45 (d, 1H, J = 16.8), 4.12 (m, 2H), 3.41 (m, 2H), 0.95 (t, 6H, J = 6.8); low-resolution MS (FAB) m/e 576 (MH^+); t_R = 10.31 min (HPLC column: Dynamax C-8 2 mL/min, 50−90% acetonitrile in aqueous TFA (0.1% v/v) over 15 min).

2-[3-[(7-Fluoro-1*H*-indazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (34). Deprotection via method A afforded a solid which was dissolved in EtOAc and triturated with hexane to afford a white, amorphous solid (59%): mp 270−272 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 3H), 7.20 (d, 1H, J = 8.2), 7.12 (t, 1H, J = 4.7), 7.01−6.89 (m, 9H), 5.02 (m, 1H), 4.28 (m, 3H), 4.20 (m, 2H), 3.84 (s, 3H), 3.797 (dd,1H J = 7.9, 16.3) 3.59 (dd, 1H, J = 5.6, 16.4), 1.06 (t, 6H, J = 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 166.5, 165.7, 159.6, 149.2, 144.9, 141.3, 136.2, 131.4, 130.7, 129.7, 128.2, 127.3, 126.6, 123.1, 120.9, 120.8, 116.6, 114.7, 111.1, 110.9, 55.5, 51.7, 47.7, 46.5, 23.0, 20.9, 20.8; high-resolution MS (FAB) calcd 606.2517, found 606.2510.

***N*-Isopropyl-*N*-(4-methoxyphenyl)-2-[3-[(4-phenyl-2*H*-pyrazol-3yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]acetamide (36).** Deprotection via method B followed by purification via silica gel MPLC using hexane/EtOAc (3/2) as eluent afforded a white solid: mp 160−164 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 1H), 7.39−7.15 (m, 14H), 7.06 (m, 1H), 6.97 (m, 2H), 6.87 (d, 1H, J = 8.1), 5.04 (m, 1H), 4.28 (AB quartet, 2H, J = 15.9), 3.85 (s, 3H), 3.54 (m, 3H), 1.09 (m, 6H); low-resolution MS (FAB) m/e 614 (MH^+). Anal. ($C_{35}H_{30}F_3N_5O_3$) C, H, N.

2-[3-(1*H*-Indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-phenylacetamide (37). Deprotection via method A followed by purification via silica gel flash column chromatography using MeOH 1%/$CHCl_3$ 99% as eluent afforded 240 mg of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, J = 8.4), 7.51−7.19 (m, 16H), 6.99 (m, 1H), 5.03 (m, 1H, J = 6.8), 4.29 (d, 1H, J = 16.4), 4.26 (d, 1H, J = 16.4), 4.14 (m, 1H), 3.89 (dd, 1H, J = 16.5, 6.4), 3.82 (dd, 1H, J = 16.5, 6.4), 1.08 (t, 6H, J = 6.8); low-resolution MS (FAB) m/e 558 (MH^+); t_R = 9.90 min (HPLC column: Dynamax C-8 2 mL/min, 50−90% acetonitrile in aqueous TFA (0.1% v/v) over 15 min). Anal. ($C_{34}H_{31}N_5O_3$) H, N, C: calcd, 73.23; found, 72.78.

***N*-(4-Fluorophenyl)-2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropylacetamide (38).** Deprotection via method B followed by purification via RP-HPLC (50−60% acetonitrile/H_2O over 30 min) afforded 87 mg of the title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 1H, J = 8.2), 7.43−7.09 (m, 15H), 6.96 (d, 1H, J = 8.3), 5.01 (m, 1H), 4.98 (m, 2H), 3.82 (m, 2H), 1.05 (m, 6H); low-resolution MS (FAB) m/e 576 (MH^+); RP-HPLC t_R = 5.5 min (40−60% acetonitrile/H_2O).

2-[3-(1*H*-Indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-[4-(trifluoromethyl)phenyl]acetamide (39). Deprotection via method B followed by purification via silica gel MPLC using hexane/EtOAc (3/2) as eluent afforded 189 mg of a white solid: mp 145−148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.75 (s, br, 1H), 7.82 (d, 1H, J = 8.0), 7.73 (d, 2H, J = 8.0), 7.42−7.07 (m, 13H), 6.93 (d, 1H, J = 7.2), 5.03 (m, 1H), 4.19 (m, 3H), 3.79 (dd, 1H, J = 7.5, 16.0), 3.61 (dd, 1H, J = 5.8, 16.0), 1.07 (d, 6H, J = 6.4); low-resolution MS (FAB) m/e 626 (MH^+), 625 (M^+), 423. Anal. ($C_{35}H_{30}F_3N_5O_3$) C, H, N.

2-[3-(1*H*-Indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(3-methoxyphenyl)acetamide (40). Deprotection via method B provided a viscous oil. Diethyl ether (40 mL) was added and the resultant mixture stirred vigorously for 20 min. The solids were allowed to settle, and the solvent was decanted. This procedure was repeated three times and the final solid dried by concentration *in vacuo* to afford 197 mg of a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H, J = 8.6), 7.76 (d, 1H, J = 8.5), 7.67 (t, 1H, J = 8.8), 7.5−7.2 (m, 12H), 7.16 (t, 1H, J = 6.3), 6.98 (t, 2H, J = 7.3), 5.05 (m, 1H, J = 6.9), 4.36 (s, br, 2H), 3.94 (t, 1H, J = 7.0), 3.82 (s, br, 2H), 3.74 (s, 3H), 1.16 (m, 6H); low-resolution MS (FAB) m/e 588 (M^+).

2-[3-(1*H*-Indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(2-methoxyphenyl)acetamide (41). Deprotection via method B provided a viscous oil. Diethyl ether (40 mL) was added and the resultant mixture stirred vigorously for 20 min. The solids were allowed to settle, and the solvent was decanted. This procedure was repeated three times and the final gum dried by concentration *in vacuo*. Recrystallization from 5% MeOH in EtOAc afforded 126 mg of a white solid, which exists as 3:2 mixture of rotamers (major rotamer recorded): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (t, 1H, J = 8.0), 7.70 (m, 1H), 7.61 (s, 1H), 7.40−6.90 (m, 15H), 5.05 (m, 1H, J = 6.9), 4.45 (d, 2H, J = 16.4), 4.25 (d, 1H, J = 17.5), 4.07 (d, 1H, J = 16.4), 3.74 (m, 5H), 1.16 (m, 6H); low-resolution MS (FAB) m/e 588 (M^+); t_R = 27.29 min (RP-HPLC, 100% A to 100% C, 30 min).

2-[3-(1*H*-Indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-[3,4-(methylenedioxy)phenyl]acetamide (42). Deprotection via method B provided a viscous oil. Diethyl ether (20 mL) was added and the resultant mixture stirred vigorously for 20 min. The solids were allowed to settle, and the solvent was decanted. This procedure was repeated three times and the final solid dried by concentration *in vacuo* to afford 106 mg of a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H, J = 8.3), 7.68 (d, 1H, J = 8.5), 7.59 (t, 1H, J = 6.8), 7.2−7.5 (m, 11H), 7.12 (t, 1H, J = 8.5), 6.94 (d, 1H, J = 8.2), 6.84 (dd, 1H, J = 15.8, 8.3), 6.03 (s, 2H), 5.00 (m, 1H, J = 6.9), 4.40 (m, 1H), 4.24 (t, 2H, J = 6.1), 3.92 (dd, 1H, J = 16.5, 7.7), 3.83

(dd, 1H, $J = 16.5, 5.8$), 1.08 (m, 6H); low-resolution MS (FAB) m/e 602 (M$^+$); t_R = 23.06 min (RP-HPLC, 70% A to 70% C, 30 min).

***N*-Cyclopentyl-2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5,5a,9a-hexahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-(4-methoxyphenyl)acetamide (43).** Deprotection via method A followed by purification via silica gel flash chromatography using EtOAc/hexanes (2/1) as eluent afforded 84 mg of a white foam: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.82 (d, 1H, $J = 8.0$), 7.41−7.06 (m, 13H), 6.93 (m, 3H), 4.94 (m, 1H), 4.24 (m, 3H), 3.84 (s, 3H), 3.80 (m, 1H), 3.62 (m, 1H), 1.88 (m, 2H), 1.51 (m, 4H), 1.29 (m, 2H); low-resolution MS (FAB) m/e 614.3 (MH$^+$).

***N*-Cyclopropyl-2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5,5a,9a-hexahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-phenylacetamide (44).** Deprotection via method B followed by silica gel flash chromatography eluted successively with EtOAc/hexanes (1/1, 200 mL) (3/2, 200 mL) afforded 328 mg of a white solid: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.86 (d, 1H, $J = 8.1$), 7.48−7.21 (m, 14H), 7.11 (m, 2H), 6.95 (m, 1H), 4.39 (m, 2H), 4.25 (m, 1H), 3.83 (m, 1H), 3.65 (m, 1H), 3.28 (m, 1H), 0.82 (m, 2H), 0.57 (m, 2H); low-resolution MS (FAB) m/e 556.0 (MH$^+$); TLC R_f = 0.18 (EtOAc/hexanes, 1/1).

***N*-*tert*-Butyl-2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5,5a,9a-hexahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-phenylacetamide (45).** Deprotection via method B followed by silica gel flash chromatography eluted successively with EtOAc/hexanes (1/2 to 1/1) afforded a white foam: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.82 (d, 1H, $J = 7.5$), 7.43−7.06 (m, 16H), 4.19 (m, 2H), 4.08 (m, 1H), 3.79 (m, 1H), 3.63 (m, 1H), 1.37 (s, 9H); low-resolution MS (FAB) m/e 572.2 (MH$^+$); TLC R_f = 0.41 (EtOAc/hexanes, 3/2); Anal. ($C_{35}H_{33}N_5O_3$) C, H, N.

General Procedure for Methylation of 1,5-Benzodiazepines at C3 followed by Deprotection (if Needed) To Afford C3 Quarternary Compounds 20, 22, and 27 (Table 2). To a stirring solution of 1.0 equiv of the desired 1,5-benzodiazepine substrate in 15 mL of DMF at 0 °C was added 1.1 equiv of the desired base (60% NaH in mineral oil, a 1.0 M solution of NaN(TMS)$_2$ in THF, or a 0.5 M solution of KN(TMS)$_2$ in toluene). The resulting solution was stirred 10−30 min, and then a solution of 1.5 equiv of methyl iodide was added. The resulting solution was stirred 2 h at room temperature and then quenched with 5 mL of H_2O. The reaction mixture was then poured into 50 mL of EtOAc and extracted with H_2O (2 × 50 mL). The organic layer was separated and dried (MgSO$_4$), and the solvents were removed *in vacuo*. Deprotection, if needed, was carried out using either method A or method B outlined above in the General Procedure for Alkylation of 1,5-Benzodiazepines at C3. Spectral data and purification protocol for the representative compounds are as follows:

2-[3-(1*H*-Indol-3-ylmethyl)-3-methyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (20). Deprotection via method B followed by purification via reverse phase MPLC using a C-18 column and 65% acetonitrile/35% H_2O as eluent followed by lyophilization afforded 82 mg of a white amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.56−6.84 (m, 18H), 4.83 (m, 1H), 4.27 (m, 2H), 3.80 (s, 3H), 2.78 (d, 1H, $J = 15.1$), 2.64 (d, 1H, $J = 15.0$), 1.26 (s, 3H), 0.98 (m, 6H); low-resolution MS (FAB) m/e 601 (MH$^+$), 600 (M$^+$). Anal. ($C_{37}H_{36}N_4O_4$) H, N, C: calcd, 73.98; found 73.27.

***N*-Isopropyl-*N*-(4-methoxyphenyl)-2-[3-[(1-methyl-1*H*-indazol-3-yl)methyl]-3-methyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-1-yl]acetamide (27).** Purification of the material by silica gel MPLC on an Si60 column using hexane/EtOAc (4/3) as eluent followed by lyophilization in acetonitrile/H_2O afforded 124 mg of a white amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.48−6.95 (m, 16H), 6.71 (d, 1H, $J = 7.3$), 4.78 (m, 1H), 4.21 (s, br, 2H), 3.95 (s, 3H), 3.74 (s, 3H), 2.79 (d, 2H, $J = 5.9$), 1.20 (s, 3H), 0.93 (m, 6H); low-resolution MS (FAB) m/e 616 (MH$^+$); high-resolution MS calcd 616.2920, found 616.2924.

2-[3-[(*N*-Methylindol-3-yl)methyl]-3-methyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(4-methoxyphenyl)acetamide (22). Purification via reverse phase MPLC using a C-18 column and 65% acetonitrile/35% H_2O as eluent followed by lyophilization afforded 51 mg of a white amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.61−6.88 (m, 18H), 4.86 (m, 1H), 4.28 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.71 (dd, 2H, $J = 14.9, 35.4$), 1.25 (s, 3H), 1.00 (m, 6H); low-resolution MS (FAB) m/e 615 (MH$^+$), 614 (M$^+$); high-resolution MS calcd 615.2968, found 615.2971.

2-(1*H*-Indol-3-ylmethyl)-2-methoxypropanedioic Acid Dimethyl Ester (6a). A suspension of 1.0 g (6.17 mmol) of dimethyl methoxymalonate, 1.07 g (6.17 mmol) of gramine, and 0.46 mL of tributylphosphine in 20 mL of acetonitrile was refluxed for 18 h. The solvent was removed *in vacuo* and the residue diluted with EtOAc (50 mL) and extracted with HCl (2 × 50 mL). The organic layer was separated and dried (MgSO$_4$) and the solvent removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 1.24 g of a clear, yellow oil which solidified on standing: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.06 (bs, 1H), 7.58 (m, 1H), 7.34−7.07 (m, 4H), 3.70 (s, 6H), 3.69 (s, 2H), 3.57 (s, 3H); low-resolution MS (FAB) m/e 292 (MH$^+$), 291 (M$^+$).

2-[3-(1*H*-Indol-3-ylmethyl)-3-methoxy-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (21). A solution of 1.23 g (4.22 mmol) of 2-(1*H*-indol-3-ylmethyl)-2-methoxypropanedioic acid dimethyl ester, 1.01 g (4.64 mmol, 1.1 equiv) of (BOC)$_2$O, and 570 mg (4.64 mmol, 1.1 equiv) of DMAP in 30 mL of acetonitrile was stirred at room temperature for 12 h. The solvent was removed *in vacuo* and the residue diluted with EtOAc (50 mL) and extracted with HCl (2 × 50 mL). The organic layer was separated and dried (MgSO$_4$) and the solvent removed *in vacuo*. This material was dissolved in 30 mL of a 9/1 solution of EtOH/H_2O and 10 mL of a solution of 713 mg (12.7 mmol) of KOH in 9/1 EtOH/H_2O was added dropwise. The resulting solution was stirred 18 h at room temperature, concentrated to remove the EtOH, diluted with H_2O (100 mL), and washed with EtOAc (2 × 20 mL). The aqueous extract was acidified to pH 2 with concentrated HCl and extracted with EtOAc (2 × 30 mL). The organic layer was separated and dried (MgSO$_4$) and the solvent removed *in vacuo* to afford a white foam. This material was dissolved in 30 mL of DCM and cooled to 0 °C, and 0.02 mL of DMF was added. To this solution was added dropwise 815 μL (9.80 mmol) of oxalyl chloride. The resulting solution was stirred 2 h at room temperature, and then the solvent and excess oxalyl chloride were removed *in vacuo* to yield the crude diacid chloride as an orange-red oil. This material was immediately dissolved in 30 mL of THF, and a solution of 763 mg (1.96 mmol) of *N*-isopropyl-*N*-(4-methoxyphenyl)-2-[[2-(phenylamino)phenyl]-amino]acetamide in 10 mL of THF was added dropwise over 2 min. The resulting solution was stirred 10 min at room temperature and then refluxed for 24 h. The solution was cooled to room temperature and the solvent removed *in vacuo*. Purification by silica gel flash column chromatography using hexane/EtOAc (2/1) as eluent followed by further purification by reverse phase MPLC using a C18 column and 75% MeOH/25% H_2O as eluent followed by lyophilization in acetonitrile/H_2O afforded 150 mg of a white amorphous solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.77 (s, 1H), 7.57 (d, 1H, $J = 8.0$), 7.45−6.91 (m, 15H), 6.69 (d, 1H, $J = 8.2$), 4.82 (m, 1H), 4.26 (m, 2H), 3.79 (s, 3H), 3.54 (AB quartet, 2H, $J = 6.3, 15.2$), 2.83 (s, 3H), 1.00 (m, 6H); low-resolution MS (FAB) m/e 617 (MH$^+$), 616 (M$^+$); t_R = 13.50 min (RP-HPLC, 50−100% acetonitrile, 30 min); high-resolution MS calcd 616.2686, found 616.2675.

2-[(1-Benzyl-1*H*-indazol-3-yl)methyl]-2-methoxypropanedioic Acid Dimethyl Ester (6b). To a stirring solution of 183 mg (1.13 mmol) of dimethyl methoxymalonate in 5 mL of DMF at 0 °C was added 1.35 mL (1.35 mmol, 1.2 equiv) of a 1.0 M solution of NaN(TMS)$_2$ in THF. The resulting solution was stirred 5 min, and then a solution of 340 mg (1.13 mmol, 1.0 equiv) of 1-benzyl-3-(bromomethyl)-1*H*-indazole in 2 mL of DMF was added. The reaction mixture was stirred 1 h at room temperature, then poured into 50 mL of Et$_2$O, and extracted with H_2O (2 × 50 mL). The organic layer was

separated and dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by silica gel flash column chromatography using hexane/EtOAc (4/1) as eluent afforded 350 mg of as a clear, colorless oil which solidifies on standing: mp 94−96 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, 1H, J = 8.0), 7.31−7.07 (m, 8H), 5.54 (s, 2H), 3.80 (s, 2H), 3.72 (s, 6H), 3.51 (s, 3H); low-resolution MS (FAB) *m/e* 383 (MH^+), 382 (M^+), 350, 221. Anal. ($C_{21}H_{22}N_2O_5$) Calcd: C, 65.96; H, 5.80; N, 7.33. Found: C, 66.06; H, 5.75; N, 7.29.

2-[(1-Benzyl-1*H*-indazol-3-yl)methyl]-2-methoxypropanedioic Acid (47). A solution of 350 mg (0.92 mmol) of 2-[(1-benzyl-1*H*-indazol-3-yl)methyl]-2-methoxypropanedioic acid dimethyl ester and 0.6 mL of 6 N NaOH in 10 mL of a 9/1/1 mixture of absolute EtOH/H_2O/THF was stirred 22 h at room temperature. The solvent was removed *in vacuo* and the residue dissolved in 15 mL of H_2O, cooled to 0 °C, and acidified to pH 1 with 1 N HCl. The reaction mixture was then extracted with EtOAc (2 × 30 mL), and the organic layers were washed with brine (1 × 30 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford 324 mg of a light pink solid: mp 144−145 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (d, 1H, J = 8.0), 7.52 (d, 1H, J = 8.6), 7.29−7.15 (m, 6H), 7.04 (dd, 1H, J = 7.5, 7.5), 5.55 (s, 2H), 3.58 (s, 2H), 3.33 (s, 3H); low-resolution MS (FAB) *m/e* 354 (MH^+), 353 (M^+), 310, 309, 295, 294. Anal. ($C_{19}H_{18}N_2O_5$) Calcd: C, 64.40; H, 5.12; N, 7.90. Found: C, 64.60; H, 5.15; N, 7.94.

2-[3-[(1-Benzyl-1*H*-indazol-3-yl)methyl]-3-methoxy-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (48). To a stirring solution of 320 mg (0.90 mmol) of 2-[(1-benzyl-1*H*-indazol-3-yl)methyl]-2-methoxypropanedioic acid and 7 μL of DMF in 8 mL of DCM at 0 °C was added dropwise 315 μL (3.61 mmol, 4.0 equiv) of oxalyl chloride. The resulting solution was stirred 2 h at room temperature, and then the solvent and excess oxalyl chloride were removed *in vacuo* to yield the crude diacid chloride as an orange-red oil. This material was immediately dissolved in 8 mL of THF and cooled to 0 °C, and a solution of 296 mg (0.76 mmol) of *N*-isopropyl-*N*-(4-methoxyphenyl)-2-[[2-(phenylamino)phenyl]amino)acetamide in 2 mL of THF was added dropwise over 2 min. The resulting solution was stirred 10 min at room temperature and then refluxed for 4 h. The solution was cooled to room temperature and the solvent removed *in vacuo*. Purification of the residue by silica gel flash column chromatography using hexane/EtOAc (2/1) as eluent followed by further purification by silica gel MPLC using an Si60 column and hexane/EtOAc (3/1) as eluent followed by lyophilization in acetonitrile/H_2O afforded 220 mg of a white amorphous solid: ^1H NMR (DMSO-d_6, 300 MHz) δ 7.91 (d, 1H, J = 8.1), 7.58 (d, 1H, J = 8.3), 7.44−7.00 (m, 19H), 6.65 (dd, 1H, J = 1.0, 8.3), 5.54 (s, 2H), 4.82 (m, 1H), 4.26 (s, br, 2H), 3.95 (d, 1H, J = 15.4), 3.82 (d, 1H, J = 15.4), 3.80 (s, 3H), 2.90 (s, 3H), 0.99 (m, 6H); low-resolution MS (FAB) *m/e* 708 (MH^+).

2-[3-(1*H*-Indazol-3-ylmethyl)-3-methoxy-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (24). To a stirring solution of 80 mg (0.11 mmol) of 2-[3-[(1-benzyl-1*H*-indazol-3-yl)methyl]-3-methoxy-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(4-methoxyphenyl)acetamide in 10 mL of a 10% solution of formic acid in absolute ethanol was added 70 mg of 10% palladium on carbon. The resulting black suspension was refluxed for 6 h and then cooled to room temperature. The reaction mixture was filtered through Celite to remove the catalyst and the solvent removed *in vacuo*. Purification of the residue via silica gel MPLC using an Si60 column and hexane/EtOAc (1/1) as eluent followed by lyophilization afforded 41 mg of a white amorphous solid: ^1H NMR (DMSO-d_6, 300 MHz) δ 7.83 (d, 1H, J = 8.3), 7.38−6.94 (m, 16H), 6.59 (d, 1H, J = 7.1), 4.76 (m, 1H), 4.19 (s, br, 2H), 3.85 (d, 1H, J = 15.7), 3.73 (m, 4H), 2.88 (s, 3H), 0.93 (m, 6H); low-resolution MS (FAB) *m/e* 618 (MH^+).

2-[3-(1*H*-Indazol-3-ylmethyl)-3-methyl-2,4-dioxo-5-phenyl-2,3,4,5-terahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (23). To a stirring solution of 190 mg (0.28 mmol) of 2-[3-[(1-benzyl-1*H*-indazol-3-yl)methyl]-3-methyl-2,4-dioxo-5-phenyl-2,3,4,5-terahydrobenzo-[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-N-(4-methoxyphenyl)acetamide in 15 mL of a 10% solution of formic acid in absolute ethanol was added 200 mg of 10% palladium on carbon. The resulting black suspension was refluxed for 6 h and then cooled to room temperature. The reaction mixture was filtered through Celite to remove the catalyst and the solvent removed *in vacuo*. Purification of the residue by silica gel flash column chromatography using hexane/EtOAc (3/2) as eluent followed by further purification via silica gel MPLC using an Si60 column and hexane/EtOAc (2/1) as eluent, and lyophilization afforded 30 mg of a white amorphous solid: ^1H NMR (DMSO-d_6, 300 MHz) δ 7.48−6.98 (m, 17H), 6.70 (d, 1H, J = 7.8), 4.86 (m, 1H), 4.27 (m, 2H), 3.81 (s, 3H), 2.87 (dd, 2H), 1.29 (s, 3H), 1.00 (m, 6H); low-resolution MS (FAB) *m/e* 602 (MH^+), 437, 279, 223.

2-[2,4-Dioxo-5-phenyl-3-[(4,5,6,7-tetrahydro-1-benzyl-1*H*-indazol-3-yl)methyl]-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (49). To a stirring solution of 164 mg (0.36 mmol) of 2-(2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl)-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide in 5 mL of DMF at 0 °C was added 0.430 mL (0.78 mmol, 1.2 equiv) of a 1.0 M solution of $NaN(TMS)_2$ in THF. The resulting solution was stirred 5 min, and a solution of 120 mg (0.39 mmol, 1.1 equiv) of 3-(bromomethyl)-4,5,6,7-tetrahydro-1-benzyl-1*H*-indazole in 2 mL of DMF was added. The resulting solution was stirred for 3 h at room temperature and then quenched with 5 mL of H_2O. The reaction mixture was poured into 50 mL of EtOAc and extracted with H_2O (2 × 50 mL). The organic layer was separated and dried ($MgSO_4$), and the solvents were removed *in vacuo*. Purification by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 175 mg of a white solid: mp 173−176 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−6.84 (m, 18H), 5.02 (s, 2H), 4.99 (m, 1H), 4.22 (s, br, 2H), 4.10 (dd, 1H, J = 5.3, 8.7), 3.823 (s, 3H), 3.36 (dd 1H, J = 8.6, 15.6), 3.09 (dd, 1H, J = 5.3, 15.6), 2.54−2.38 (m, 4H), 1.67 (m, 4H), 1.04 (d, 6H, J = 6.6); low-resolution MS (FAB) *m/e* 682 (MH^+).

2-[2,4-Dioxo-5-phenyl-3-[(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)methyl]-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide (30). To a stirring solution of 150 mg (0.22 mmol) of 2-[2,4-dioxo-5-phenyl-3-[(4,5,6,7-tetrahydro-1-benzyl-1*H*-indazol-3-yl)methyl]-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide in 10 mL of a 10% solution of formic acid in absolute ethanol was added 150 mg of 10% palladium on carbon. The resulting black suspension was refluxed for 3 h and then cooled to room temperature. The reaction mixture was filtered through Celite to remove the catalyst and the solvent removed *in vacuo*. Purification of the residue via silica gel MPLC using an Si60 column and hexane/EtOAc (1/5) as eluent afforded 105 mg of as a white solid: mp 170−173 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−6.88 (m, 13H), 5.03 (m, 1H), 4.34 (d, 1H, J = 16.8), 4.14 (d, 1H, J = 16.8), 3.84 (s, 3H), 3.58 (dd, 1H, J = 6.8, 6.8), 3.46 (dd, 1H, J = 7.0, 14. 0), 3.30 (dd, 1H, J = 7.5, 15.2), 2.60 (m, 2H), 2.36 (m, 2H), 1.70 (m, 4H), 1.08 (2 d, 6H, J = 6.6); low-resolution MS (FAB) *m/e* 592 (MH^+), 591 (M^+), 427. Anal. ($C_{35}H_{37}N_5O_4$) Calcd: C, 71.05; H, 6.30; N, 11.84. Found: C, 70.20; H, 6.47; N, 11.66.

***N*-Isopropyl-*N*-(4-methoxyphenyl)-2-[3-[(5-methyl-2*H*-pyrazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]acetamide (35).** To a stirring solution of 194 mg (0.30 mmol) of 2-[3-[(2-benzyl-5-methyl-2*H*-pyrazol-3-yl)methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(4-methoxyphenyl)acetamide in 10 mL of 5% formic acid (v/v) in absolute ethanol is added 190 mg of 10% palladium on carbon. The resulting mixture is heated to reflux for 2 h, cooled to room temperature, and filtered through a pad of Celite to remove the catalyst. The filtrate is concentrated, poured into 50 mL of EtOAc, and washed successively with 1 N NaOH (1 × 50 mL) and H_2O (1 × 50 mL). The organic layer is separated and dried ($MgSO_4$), and the solvents are removed *in vacuo*. Purification by silica gel MPLC using EtOAc/chloroform (8/1) as eluent afforded 112 mg of a white solid: mp 156−159 °C;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.18 (m, 9H), 7.14 (d, 1H, J = 8.7), 7.06 (t, 1H, J = 7.3), 6.96 (m, 2H), 6.86 (d, 1H, J = 7.6), 5.81 (s, 1H), 5.02 (m, 1H), 4.18 (dd, 2H, J = 16.5, 86.1), 3.83 (s, 3H), 3.59 (t, 1H, J = 6.8), 3.32 (ddd, 2H, J = 7.5, 15.2, 34.3), 2.19 (s, 3H), 1.08 (m, 6H); low-resolution MS (FAB) m/e 552 (MH^+), 551 (M^+), 387. Anal. ($C_{32}H_{33}N_5O_4$) Calcd; C, 69.67; H, 6.03; N, 12.70. Found: C, 69.61; H, 6.11; N, 12.44.

3-Methylindazole (10). To a stirring solution of 36.2 g (0.26 mol) of 2-fluoroacetophenone in 120 mL of ethylene glycol was added 8.6 mL (0.27 mol, 1.05 equiv) of hydrazine. The resulting solution was stirred 2 h at room temperature and then heated at 165 °C for 40 h. The solution was cooled to room temperature, poured into CH_2Cl_2 (200 mL), and extracted with H_2O (2 × 200 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by recrystallization form hexane/$CHCl_3$ afforded 26 g of a light tan solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, 1H, J = 8.1), 7.44 (m, 2H), 7.19 (dd, 1H, J = 7.0, 7.0), 2.67 (s, 3H).

1-(*tert*-Butoxycarbonyl)-3-methylindazole (50). To a stirring solution of 30.3 g (0.23 mol) of 3-methylindazole in 300 mL of CH_3CN was added 35.0 mL (0.25 mol, 1.1 equiv) of Et_3N and 5.77 g (47.2 mmol, 0.2 equiv) of DMAP, and the mixture was cooled to 0 °C. Next, 60.5 g (0.28 mol, 1.2 equiv) of $(BOC)_2O$ in 200 mL of CH_3CN was added dropwise with stirring at 0 °C, and the resultant reaction mixture stirred 3 h at room temperature. The solvent was removed *in vacuo* and the crude material partitioned between Et_2O (300 mL) and H_2O (100 mL). The pH was adjusted to 2.0 with 1 N HCl, and the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to an orange oil which was purified by filtration through a pad of silica gel using hexane/EtOAc (4/1) as eluent. The filtrate was concentrated *in vacuo* to give 53.4 g of a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, 1H, J = 7.8), 7.67 (d, 1H, J = 7.8), 7.56 (dd, 1H, J = 7.3, 7.3), 7.35 (dd, 1H, J = 7.3, 7.3), 2.62 (s, 3H), 1.77 (s, 9H); TLC R_f = 0.66 (EtOAc/hexane, 1/2).

3-(2-Bromophenoxy)acrylic Acid Ethyl Ester (11). To a stirring solution of 972 mg (11.56 mmol) of ethyl propiolate in 20 mL of THF at 0 °C was added a solution of 1.61 mL (11.56 mmol) of triethylamine in 5 mL of THF, followed by a solution of 2.0 g (11.56 mmol) of 2-bromophenol in 5 mL of THF. The resulting clear orange-brown solution was stirred 5 h at 0 °C, poured into 100 mL of Et_2O, and extracted with H_2O (1 × 100 mL). The organic layer was separated, washed with saturated Na_2CO_3 (1 × 100 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo* to provide 2.97 g of the title compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, 1H, J = 12.3), 7.61 (d, 1H, J = 7.4), 7.37−7.08 (m, 3H), 5.47 (d, 1H, J = 12.3), 3.72 (s, 3H).

Benzofuran-3-carboxylic Acid Ethyl Ester (12). A stirring solution of 2.43 g (9.45 mmol) of 3-(2-bromophenoxy)-acrylic acid ethyl ester, 1.98 g (7.56 mmol, 0.8 equiv) of triphenylphosphine, 794 mg (9.45 mmol, 1.0 equiv) of $NaHCO_3$, and 848 mg (3.78 mmol, 0.4 equiv) of palladium(II) acetate in 25 mL of DMF was heated to 110 °C for 16 h. After being cooled to room temperature, the reaction mixture was diluted with 100 mL of Et_2O, extracted with H_2O (1 × 100 mL), and dried ($MgSO_4$), and the solvents were removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography afforded 650 mg of a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 8.06 (m, 1H), 7.55 (m, 1H), 7.37 (m, 2H), 3.95 (s, 3H).

3-(Hydroxymethyl)benzofuran (51). To a stirring solution of 650 mg (3.69 mmol) of benzofuran-3-carboxylic acid ethyl ester in 25 mL of DCM at −78 °C was added dropwise over 5 min a solution of 9.22 mL (9.22 mmol, 2.5 equiv) of a 1.0 M solution of DIBAL-H in hexane. The resulting solution was allowed to slowly warm to room temperature over a 4 h period and then quenched by careful addition of 5 mL of H_2O. The reaction mixture was poured into 100 mL of EtOAc, extracted with 1 N HCl (1 × 100 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (4/1) as eluent afforded 444 mg of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, 1H), 7.60 (s, 1H), 7.49 (d, 1H), 7.29 (m, 2H), 4.82 (d, 2H), 1.70 (m, 1H).

(1-Methyl-1*H*-indazol-3-yl)methanol (52). To a stirring solution of 440 mg (2.31 mmol) of 1-methyl-1*H*-indazole-3-carboxylic acid methyl ester[41] in 10 mL of DCM at −78 °C was added dropwise over 5 min a solution of 5.8 mL (5.8 mmol, 2.5 equiv) of a 1.0 M solution of DIBAL-H in hexane. The resulting solution was allowed to slowly warm to room temperature over a 3 h period and then quenched by careful addition of 5 mL of H_2O. The reaction mixture was poured into 100 mL of EtOAc, extracted with 1 N HCl (1 × 100 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 340 mg of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, 1H), 7.42−7.12 (m, 3H), 5.02 (d, 2H), 4.00 (s, 3H), 2.27 (m, 1H).

3-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine (53). To a stirring suspension of 5.0 g (51.5 mmol) of 3-amino-5-methylpyrazole in 10.1 g (61.8 mmol, 1.2 equiv) of malonaldehyde dimethyl acetal was added approximately 8 g of polyphosphoric acid, and the resulting mixture was heated to 100 °C for 2 h. The resulting black oil was poured onto crushed ice, made basic by the addition of 3 N NaOH, and then extracted with EtOAc (2 × 100 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 160 mg of a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (dd, 1H, J = 1.1, 4.7), 8.04 (dd, 1H, J = 1.1, 8.0), 7.12 (dd, 1H, J = 4.7, 8.0), 2.60 (s, 3H); low-resolution MS (FAB) m/e 134 (MH^+).

3-Methyl-1-(*tert*-butoxycarbonyl)pyrazolo[3,4-*b*]pyridine (54). To a stirring solution of 160 mg (1.20 mmol) of 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine in 5 mL of acetonitrile at 0 °C was added 167 μL (1.20 mmol) of Et_3N and 145 mg (1.20 mmol) of DMAP. The resulting solution was stirred 2 min, and then a solution of 315 mg (1.44 mmol, 1.2 equiv) of di-*tert*-butyl dicarbonate in 1 mL of acetonitrile was added. The resulting solution was warmed to room temperature and stirred for 30 min. The reaction mixture was poured into 10 mL of EtOAc, extracted with brine (1 × 10 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 253 mg of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (dd, 1H, J = 1.5, 4.7), 7.99 (dd, 1H, J = 1.5, 8.0), 7.26 (dd, 1H, J = 4.7, 8.0), 2.59 (s, 3H), 1.71 (s, 9H).

1-(3-Nitropyridin-2-yl)ethanone (55). To a stirring solution of 4.40 g (16.05 mmol) of trifluoromethanesulfonic acid 3-nitropyridin-2-yl ester[17] in 30 mL of DMF was added 3.96 g (16.85 mmol, 1.05 equiv) of 1-ethoxy-1-(trimethylstannyl) ethene,[18] followed by 305 mg (1.61 mmol, 0.10 equiv) of copper(I) iodide and 560 mg (0.80 mmol, 0.05 equiv) of bis(triphenylphosphine)palladium(II) chloride. The resulting mixture was heated to 80 °C for 4 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was poured into 100 mL of EtOAc, extracted with H_2O (1 × 100 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (5/1) as eluent afforded 2.41 g of a pale yellow oil. This material was dissolved in 80 mL of THF, and 20 mL of 2 N HCl was added. The resulting solution was stirred at 35 °C for 6 h and then cooled to room temperature. The reaction was made basic by the addition of 2 N NaOH, extracted with diethyl ether (2 × 100 mL), and dried ($MgSO_4$), and the solvent removed *in vacuo* to afford 2.0 g of a light brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (dd, 1H, J = 1.2, 4.7), 8.20 (dd, 1H, J = 1.2, 8.3), 7.58 (dd, 1H, J = 4.7, 8.3), 2.69 (s, 3H).

1-(3-Aminopyridin-2-yl)ethanone (14). To a solution of 1.90 g (11.43 mmol) of 1-(3-nitropyridin-2-yl)ethanone in 60 mL of absolute ethanol was added 600 mg of 10% palladium on carbon. The resulting mixture was stirred at room temperature for 24 h over an atmosphere of H_2 gas (balloon). The reaction mixture was filtered through a pad of Celite to remove

the palladium catalyst and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 1.22 g of a pale yellow solid: mp 64−65 °C (lit. mp 66−67 °C); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.00 (dd, 1H, J = 1.5, 4.1), 7.18 (dd, 1H, J = 4.1, 8.4), 6.97 (dd, 1H, J = 1.5, 8.4), 6.14 (s, br, 2H), 2.70 (s, 3H).

3-Methyl-1*H*-pyrazolo[4,3-*b*]pyridine (56). To a cold (0 °C) solution of 570 mg (8.25 mmol, 1.05 equiv) of $NaNO_2$ in 15 mL of 2 N H_2SO_4 was added a cold (0 °C) solution of 1.07 g (7.86 mmol) of 1-(3-aminopyridin-2-yl)ethanone in 15 mL of 2 N H_2SO_4. The reaction mixture was stirred 30 min at 0 °C and then was warmed to room temperature and stirred for 15 min. The reaction mixture was then recooled to 0 °C, and a cold (0 °C) solution of 3.58 g (18.86 mmol, 2.4 equiv) of $SnCl_2$ in 10 mL of concentrated HCl was added dropwise over 5 min. The resulting orange suspension was stirred 20 min at 0 °C and then was warmed to room temperature and stirred 20 min. The reaction mixture was then poured into 75 mL of cold 3 N NaOH and extracted with a 1/1 mixture of EtOAc and diethyl ether (2 × 150 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/2) as eluent afforded 553 mg of a tan solid: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 10.21 (s, br, 1H), 8.58 (dd, 1H, J = 1.0, 4.3), 7.77 (dd, 1H, J = 1.0, 8.4), 7.28 (dd, 1H, J = 4.3, 8.4), 2.69 (s, 3H); low-resolution MS (FAB) m/e 134 (MH$^+$).

3-Methyl-1-(*tert*-butoxycarbonyl)pyrazolo[4,3-*b*]pyridine (57). To a stirring solution of 530 mg (3.98 mmol) of 3-methyl-1*H*-pyrazolo[4,3-*b*]pyridine in 15 mL of acetonitrile at 0 °C was added 582 μL (4.18 mmol, 1.05 equiv) of Et_3N and 486 mg (3.98 mmol) of DMAP. The resulting solution was stirred 2 min, and then a solution of 1.04 g (4.78 mmol, 1.2 equiv) of di-*tert*-butyl dicarbonate in 3 mL of acetonitrile was added. The resulting solution was warmed to room temperature and stirred for 90 min. The reaction mixture was poured into 40 mL of EtOAc, extracted with brine (1 × 40 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (12/1) as eluent afforded 854 mg of a white solid: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.65 (dd, 1H, J = 1.3, 4.4), 8.37 (d, 1H, J = 8.3), 7.41 (dd, 1H, J = 4.4, 8.3), 2.70 (s, 3H), 1.72 (s, 9H); low-resolution MS (FAB) m/e 234 (MH$^+$).

4,5,6,7-Tetrahydro-1-benzyl-1*H*-indazole-3-carboxylic Acid Ethyl Ester (8a). To a stirring solution of 2.0 g (10.30 mmol) of 4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylic acid ethyl ester[11c] in 50 mL of DMF was added 1.85 g (13.838 mmol, 1.3 equiv) of K_2CO_3, followed by 1.35 mL (11.33 mmol, 1.1 equiv) of benzyl bromide. The reaction mixture was stirred 15 min at room temperature and then heated at 60 °C for 16 h. The reaction was cooled to room temperature, poured into 100 mL of 1 N HCl, and extracted with Et_2O (2 × 100 mL). The organic layers were washed with H_2O (2 × 100 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using a gradient elution of hexane/EtOAc (6/1 to 3/1) afforded 1.05 g of a yellow oil which later solidified: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.37−7.23 (m, 3H), 7.13 (m, 2H), 5.31 (s, 2H), 4.39 (q, 2H, J = 7.2), 2.74 (m, 2H), 2.40 (m, 2H), 1.72 (m, 4H), 1.39 (t, 3H, J = 7.2).

(4,5,6,7-Tetrahydro-1-benzyl-1*H*-indazol-3-yl)methanol (58). To a stirring solution of 1.0 g (3.52 mmol) of 4,5,6,7-tetrahydro-1-benzyl-1*H*-indazole-3-carboxylic acid ethyl ester in 15 mL of THF at 0 °C was added dropwise over 5 min a solution of 5.3 mL (5.3 mmol, 1.5 equiv) of a 1.0 M solution of $LiAlH_4$ in THF. The resulting solution was stirred at room temperature for 30 min then heated to 50 °C for 1 h. The reaction mixture was cooled to 0 °C and worked up by carefully quenching first with 0.22 mL of H_2O, then 0.22 mL of 15% NaOH, and then 0.66 mL of H_2O. The resulting slurry was filtered and the filter cake triturated with 20 mL of EtOAc and refiltered. The filtrates were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by Kugelrohr distillation gave 740 mg of a pale yellow thick oil: bp 225 °C at 0.8 mm; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.32−7.24 (m, 3H), 7.10 (m, 2H), 5.17 (s, 2H), 4.62 (s, 2H), 2.46 (m, 4H), 1.72 (m, 4H); low-resolution MS (FAB) m/e 243 (MH$^+$).

1-Benzyl-1*H*-indazole-3-carboxylic Acid Benzyl Ester (8b). To a stirring solution of 750 mg (4.62 mmol) of 1*H*-indazole-3-carboxylic acid[14] in 20 mL of DMF was added 1.92 g (13.86 mmol, 3.0 equiv) of K_2CO_3, followed by 1.43 mL of benzyl bromide. The reaction mixture was stirred for 15 min at room temperature and then heated at 60 °C for 16 h. The reaction was cooled to room temperature, poured into 100 mL of 1 N HCl, and extracted with EtOAc (2 × 100 mL). The organic layers were washed with H_2O (2 × 100 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using a gradient elution of hexane/EtOAc (20/1 to 2/1) afforded 735 mg of a yellow oil which later solidified: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.20 (d, 1H), 7.55 (d, 2H), 7.40−7.18 (m, 11H), 5.70 (s, 2H), 5.57 (s, 2H).

(1-Benzyl-1*H*-indazol-3-yl)methanol (59). To a stirring solution of 735 mg (2.15 mmol) of 1-benzyl-1*H*-indazole-3-carboxylic acid benzyl ester in 15 mL of DCM at −78 °C was added dropwise over 5 min a solution of 5.4 mL (5.4 mmol, 2.5 equiv) of a 1.0 M solution of DIBAL-H in hexane. The resulting solution was allowed to slowly warm to room temperature over a 4 h period and then quenched by careful addition of 5 mL of H_2O. The reaction mixture was poured into 100 mL of EtOAc and extracted with 1 N HCl (1 × 100 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using hexane/EtOAc (1/1) as eluent afforded 448 mg of a pale yellow solid: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.80 (d, 1H), 7.40−7.08 (m, 8H), 5.50 (s, 2H), 5.04 (d, 2H), 2.24 (m, 1H).

5-Methyl-2*H*-pyrazole-3-carboxylic Acid Methyl Ester (60). To a stirring solution of 2.0 g (13.87 mmol) of methyl acetopyruvate in 40 mL of absolute ethanol at 0 °C was added 0.48 mL (15.27 mmol, 1.1 equiv) of hydrazine. The resulting solution was stirred for 1 h at room temperature and then heated to reflux for 3 h. The solution was then cooled to room temperature and the solvent removed *in vacuo* to give a clear yellow oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.61 (s, 1H), 3.97 (s, 3H), 2.40 (s, 3H).

2-Benzyl-5-methyl-2*H*-pyrazole-3-carboxylic Acid Methyl Ester (8c). To a stirring solution of 21.91 g (13.63 mmol) of 5-methyl-2*H*-pyrazole-3-carboxylic acid methyl ester in 50 mL of DMF was added 2.88 g (20.44 mmol, 1.5 equiv) of K_2CO_3, followed by 1.95 mL (16.35 mmol, 1.2 equiv) of benzyl bromide. The reaction mixture was stirred 15 min at room temperature and then heated at 50 °C for 20 h. The reaction was cooled to room temperature, poured into 100 mL of 1 N HCl, and extracted with Et_2O (2 × 100 mL). The organic layers were washed with H_2O (2 × 100 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by silica gel flash column chromatography using a gradient elution of hexane/EtOAc (10/1 to 1/1) afforded 833 mg of a yellow oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.42−7.25 (m, 5H), 6.68 (s, 2H), 5.74 (s, 2H), 3.86 (s, 3H), 2.34 (s, 3H).

(2-Benzyl-5-methyl-2*H*-pyrazol-3-yl)methanol (61). To a stirring solution of 833 mg (3.61 mmol) of 2-benzyl-5-methyl-2*H*-pyrazole-3-carboxylic acid methyl ester in 5 mL of THF at 0 °C was added dropwise over 5 min a solution of 5.5 mL (5.5 mmol, 1.5 equiv) of a 1.0 M solution of $LiAlH_4$ in THF. The resulting solution was stirred at room temperature for 48 h. The reaction mixture was cooled to 0 °C and worked up by carefully quenching first with 0.20 mL of H_2O, then 0.20 mL of 15% NaOH, and then 0.60 mL of H_2O. The resulting slurry was filtered and the filter cake triturated with 20 mL of EtOAc and refiltered. The filtrates were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material by Kugelrohr distillation gave 710 mg of a clear oil: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.41−7.29 (m, 3H), 7.16 (m, 2H), 6.07 (s, 1H), 5.37 (s, 2H), 4.55 (s, 2H), 2.30 (s, 3H); low-resolution MS (FAB) m/e 203 (MH$^+$).

General Procedure for Bromination of 3-Hydroxyindazole Derivatives To Provide Compounds of General Formula 9. To a stirring solution of 1.2 equiv of triphenylphosphine in CCl_4 at 0 °C was added 1.1 equiv of Br_2. The resulting orange-yellow suspension was stirred 10 min at 0 °C, and then a solution of the requisite alcohol in 5 mL of CCl_4 was added over 2 min. The resulting solution was stirred 1.5 h at room temperature, and the solvent was removed *in vacuo*. Purification of the crude material was achieved by silica gel flash column chromatography. Purification conditions and spectral data for representative compounds are as follows:

1-Benzyl-3-(bromomethyl)-4,5,6,7-tetrahydro-1*H*-indazole (9a). Chromatography using hexane/EtOAc (5/1) as eluent afforded a clear oil (39%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.24 (m, 3H), 7.10 (m, 2H), 5.17 (s, 2H), 4.49 (s, 2H), 2.48 (m, 4H), 1.74 (m, 4H); low-resolution MS (FAB) *m/e* 305 (MH^+).

1-Benzyl-3-(bromomethyl)-1*H*-indazole (9b). Chromatography using hexane/EtOAc (5/1) as eluent afforded 305 mg of a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, 1H), 7.40−7.16 (m, 8H), 5.59 (s, 2H), 4.90 (s, 2H).

1-Methyl-3-(bromomethyl)-1*H*-indazole (9c). Chromatography using hexane/EtOAc (5/1) as eluent afforded a yellow solid (72%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, 1H), 7.40 (m, 2H), 7.22 (m, 1H), 4.82 (s, 2H), 4.03 (s, 3H).

3-(Bromomethyl)-1-(*tert*-butoxycarbonyl)indole (9d). Purification by trituration with hexane, filtration of the solids, and removal of solvent *in vacuo* afforded a yellow solid (69%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, 1H, J = 7.8), 7.64 (m, 2H), 7.33 (m, 2H), 4.63 (s, 2H), 1.71 (s, 9H).

3-(Bromomethyl)benzoisothiazole (9e). Chromatography using hexane/EtOAc (10/1) as eluent afforded a clear colorless oil (51%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, 1H, J = 7.9), 7.94 (d, 1H, J = 7.9), 7.55 (m, 2H), 4.89 (s, 2H).

1-Benzyl-5-(bromomethyl)-3-methyl-1*H*-pyrazole (9f). Chromatography using hexane/EtOAc (5/1) as eluent afforded a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, 3H), 7.19 (m, 2H), 6.16 (s, 1H), 5.42 (s, 2H), 4.32 (s, 2H), 2.31 (s, 3H); low-resolution MS (FAB) *m/e* 265 (M^+).

3-(Bromomethyl)benzofuran (9g). Chromatography using hexane/EtOAc (20/1) as eluent afforded a clear, colorless oil (48%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (m, 2H), 7.50 (m, 1H), 7.37 (m, 2H), 4.62 (s, 2H).

General Procedure for Radical Bromination of Indazole Derivatives To Provide Compounds of General Formula 9. A stirring solution of a suitably protected indazole or analog thereof in CCl_4 was heated to reflux, and then a mixture of 1.1 equiv of *N*-bromosuccinimide and 0.1 equiv of benzoyl peroxide was added portionwise over 5 min as a solid. The resulting solution was heated at reflux for 4.5 h and then cooled to room temperature. The reaction mixture was filtered through a pad of Celite to remove the precipitated succinimide, and the solvent was removed *in vacuo*. Purification of the crude material was achieved by silica gel flash column chromatography. Purification conditions and spectral data for representative compounds are as follows:

3-(Bromomethyl)-1-(*tert*-butoxycarbonyl)indazole (9h). Chromatography using hexane/EtOAc (15/1) to hexane/EtOAc (3/1) as eluent afforded a white solid (60%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, 1H, J = 7.8), 7.88 (d, 1H, J = 7.8), 7.60 (dd, 1H, J = 7.3, 7.3), 7.41 (dd, 1H, J = 7.3, 7.3), 4.91 (s, 2H), 1.77 (s, 9H); TLC R_f = 0.56 (EtOAc/hexane, 1/5).

3-(Bromomethyl)-1-(*tert*-butoxycarbonyl)pyrazolo[3,4-*b*]pyridine (9i). Chromatography using hexane/EtOAc (3/1) as eluent afforded a white solid (54%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (dd, 1H, J = 1.4, 4.6), 8.21 (dd, 1H, J = 1.4, 8.0), 7.32 (dd, 1H, J = 4.6, 8.0), 4.74 (s, 2H), 1.70 (s, 9H).

3-(Bromomethyl)-6-fluoro-1-(*tert*-butoxycarbonyl)-1*H*-indazole (9j). Chromatography eluted successively with DCM/hexanes (1/2 to 1/1) afforded an amber oil (57%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (m, 2H), 7.13 (m, 1H), 4.76 (s, 2H), 1.72 (s, 9H); TLC R_f = 0.17 (EtOAc/hexanes, 1/19).

3-(Bromomethyl)benzisoxazole (9k). Chromatography using hexane/EtOAc (10/1) as eluent afforded a white solid (48%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, 1H, J = 8.3), 7.58 (m, 3H), 4.86 (s, 2H).

3-(Bromomethyl)-4-phenyl-1-(*tert*-butoxycarbonyl)-2*H*-pyrazole (9m). Chromatography using hexane/EtOAc (20/1) as eluent afforded a white solid (61%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1H), 7.53 (d, 2H, J = 7.2), 7.43 (m, 2H), 7.36 (m, 1H), 4.57 (s, 2H), 1.65 (s, 9H).

3-(Bromomethyl)-1-(*tert*-butoxycarbonyl)pyrazolo[4,3-*b*]pyridine (9n). Chromatography using hexane/EtOAc (4/1) as eluent afforded a white solid (43%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (dd, 1H, J = 1.4, 4.5), 8.40 (d, 1H, J = 8.3), 7.47 (dd, 1H, J = 4.5, 8.3), 4.90 (s, 2H), 1.73 (s, 9H); low-resolution MS (FAB) *m/e* 312 (MH^+).

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References

(1) (a) Crawley, J. N.; Corwin, R. L. Biological Actions of Cholecystokinin. *Peptides* **1994**, *4*, 731−755. (b) Larson, L.-I.; Rehfeld, J. F. Localisation and Molecular Heterogeneity of Cholocystokinin in the Central and Peripheral Nervous System. *Brain Res.* **1979**, *165*, 201−218. (c) Reeve, J. R., Jr.; Eysselein, V.; Walsh, J. H.; Ben Avram, C. M.; Shively, J. E. New Molecular Forms of Cholecystokinin. Microsequence Analysis of Forms Previously Characterized by Chromatographic Methods. *J. Biol. Chem.* **1986**, *261*, 16392−16397.

(2) Schwartz, G. J.; McHugh, P. R.; Moran, T. H. Gastric Loads and Cholecystokinin Synergistically Stimulate Rat Vagal Afferents. *Am. J. Physiol.* **1993**, *265*, R872−R876.

(3) Dourish, C. T.; Ruckert, A. C.; Tattersall, F. D.; Iversen, S. D. Evidence that Decreased Feeding Induced by Systemic Injection of Cholecystokinin is Mediated by CCK-A Receptors. *Eur. J. Pharmacol.* **1989**, *173*, 233−234.

(4) Dourish, C. T.; Hill, D. R. Classification and Function of CCK Receptors. *Trends Pharmacol. Sci.* **1987**, *8*, 207−208.

(5) Kissileff, H. R.; Pi-Sunyer, F. X.; Thornton, J.; Smith, G. P. C-Terminal Octapeptide of Cholecystokinin Decreases Food Intake in Man. *Am. J. Clin. Nutr.* **1981**, *34*, 154−160.

(6) Pi-Sunyer, F. X.; Kissileff, H. R.; Thornton, J.; Smith, G. P. C-Terminal Octapeptide of Cholecystokinin Decreases Food Intake in Obese Men. *Physiol. Behav.* **1982,** *29*, 627−630.

(7) (a) Sitzmann, J. V.; Pitt, H. A.; Steinborn, P. A.; Pasha, Z. R.; Sanders, R. C. Cholecystokinin Prevents Parenteral Nutrition Induced Biliary Sludge in Humans *Surg. Gynacol. Obstetrics* **1990,** *170*, 25−31. (b) Froehlich, F.; Gonvers, J. J.; Fried, M. Role of Nutrient Fat and Cholecystokinin in Regulation of Gallbladder Emptying in Man. *Dig. Dis. Sci.* **1995**, *40*, 529−533. (c) Roslyn, J. J.; DenBesten, L.; Pitt, H. A.; Kuchenbecker, S.; Polarek, J. W. Effects of Cholecystokinin on Gallbladder Stasis and Cholesterol Gallstone Formation. *J. Surg. Res.* **1981**, *30*, 200−204.

(8) Silverstone, T. In *Obesity: Theory and Therapy*; Stunkard, A. J., Wadden, T. A., Eds.; Raven Press, Ltd.: New York, 1993; pp 275−283.

(9) Henke, B. R.; Willson, T. M.; Sugg, E. E.; Croom, D. K.; Dougherty, R. W., Jr.; Queen, K. L.; Birkemo, L. S.; Ervin, G. N.; Grizzle, M. K.; Johnson, M. F.; James, M. K. 3-(1H-Indazol-3-ylmethyl)-1,5-benzodiazepines: CCK-A Agonists That Demonstrate Oral Activity as Satiety Agents. *J. Med. Chem.* **1996**, *39*, 2655−2658.

(10) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. Reductive Amination of Aldehydes and Ketones by Using Sodium Triacetoxyborohydride. *Tetrahedron Lett.* **1990**, *31*, 5595−5598.

(11) Indole-3-carboxylic acid is commercially available from the Aldrich Chemical Co. Leading references to the preparation of other derivatives include the following: (a) Indazole-3-carboxylic acid: Ferrari, M; Ripa, A; Ripa, G; Sisti, M. An improved synthesis of indazole-3-carboxylic acid. *J. Heterocycl. Chem.* **1989**, *26*, 531−532. (b) Benzothiophene-3-carboxylic acid: Bonjouklian, R. A direct synthesis of benzothiophene-3-carboxylic acid from benzothiophene. *Synth. Commun.* **1985**, *15*, 711−713. (c) 4,5,6,7-Tetrahydro-1*H*-indazole-3-carboxylic acid: Ainsworth, C. Indazole Analog of Tryptamine: A New Synthesis of Indazoles. *J. Am. Chem. Soc.* **1957**, *79*, 5242−5245. (d) Benzisoxazole- and benzisothiazole-3-carboxylic acid: Hrib, N. J.; Jurcak, J. G.; Burgher, K. L.; Conway, P. G.; Hartman, H. B.; Kerman, L. L.; Roehr, J. E.; Woods, A. T. Benzisoxazole- and Benzisothiazole-3-carboxamides as Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1994**, *37*, 2308−2314.

(12) Horner, L.; Oediger, H.; Hoffman, H. *Ann.* **1959**, *626*, 26−34.

(13) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons, Inc.: New York, 1991.

(14) Snyder, H. R.; Thompson, C. B.; Hinman, R. L. The Synthesis of an Indazole Analog of DL-Tryptophan. *J. Am. Chem. Soc.* **1952**, *74*, 2009−2012.

(15) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985; pp 608−626.

(16) (a) 3-Methylbenzisoxazole: Stokker, G. Preparation of 1,2-benzisoxazoles from Salicylaldoximes via trichloroacetyl isocyanate. *J. Org. Chem.* **1983**, *48*, 2613−15. (b) 3-Methyl-1*H*-pyrazolo[3,4-*b*]pyridine: Abignente, E.; De Caprariis, P.; Stein, M. L. New Isoxazolo[5,4-*b*]pyridine-3-acetic Acids. *Farmaco, Ed. Sci.* **1975**, *30*, 992−1000.

(17) Heck, R. F. Palladium Reagents in Organic Synthesis. In *Best Synthetic Methods*, 2nd ed.; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1985; pp 276−287.

(18) Etchevarren, A. M.; Stille, J. K. Palladium-Catalyzed Coupling of Aryl Triflates with Organostannanes *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.

(19) Gadwood, R. C.; Rubino, M. R.; Nagarajan, S. C.; Michel, S. T. Generation of (1-Alkoxycyclopropyl)lithium Reagents. *J. Org. Chem.* **1985**, *50*, 3255−3260.

(20) Kwan, H. B.; McKee, B. H.; Stille, J. K. Palladium-Catalyzed Coupling Reactions of (α-Ethoxyvinyl)trimethylstannane with Vinyl and Aryl Triflates. *J. Org. Chem.* **1990**, *55*, 3114−3118.

(21) Aquino, C. J.; Armour, D. R.; Berman, J. M.; Birkemo, L. S.; Carr, R. A. E.; Croom, D. K.; Dezube, M.; Dougherty, R. W.; Ervin, G. N.; Grizzle, M. K.; Head, J. E.; Hirst, G. C.; James, M. K.; Johnson, M. F.; Long, J. E.; Miller, L. J.; Queen, K. L.; Rimele, T. J.; Smith, D. N.; Sugg, E. E. Discovery of 1,5-Benzodiazepines with Peripheral Cholecystokinin (CCK-A) Receptor Agonist Activity I. Optimization of the Agonist "Trigger". *J. Med. Chem.* **1996**, *39*, 562−569.

(22) Evans, B. E.; Bock, M. G.; Rittle, K. E; Dipardo, R. M.; Whitter, W. L; Veber, D. L.; Anderson, P. S.; Freidinger, R. M. Design of Potent, Orally Effective, Nonpeptidyl Antagonists of the Peptide Hormone Cholecystokinin. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83,* 4918−4922.

(23) Sugg, E. E.; Kimery, M. J.; Ding, J. M.; Kenakin, D. C.; Miller, L. J.; Queen K. L.; Rimele, T. J. CCK-A Receptor Selective Antagonists Derived from the CCK-A Receptor Selective Tetrapeptide Agonist Boc-Trp-Lys(Tac)-Asp-MePhe-NH_2 (A-71623). *J. Med. Chem.* **1995**, *38*, 207−211.

(24) (a) Ulrich, C. D.; Ferber, I.; Holicky, E.; Hadac, E.; Buell, G.; Miller, L. J. Molecular Cloning and Functional Expression of the Human Gallbladder Cholecystokinin A Receptor. *Biochem. Biophys. Res. Commun.* **1993**, *193*, 204−211. (b) de Weerth, A.; Pisegna, J. R.; Huppi, K.; Wank, S. A. Molecular Cloning, Functional Expression and Chromosomal Localization of the Human Cholecystokinin Type A Receptor. *Biochem. Biophys. Res. Commun.* **1993**, *194*, 811−818.

(25) (a) Pisegna, J. R.; de Weerth, A.; Huppi, K.; Wank, S. A. Molecular Cloning of the Human Brain and Gastric Cholecystokinin Receptor: Structure, Functional Expression and Chromosomal Localization. *Biochem. Biophys. Res. Commun.* **1992**, *189*, 296−303. (b) Lee, Y. M.; Beinborn, M.; McBride, E. W.; Lu, M.; Kolakowski, L. F., Jr.; Kopin, A. S. The Human Brain Cholecystokinin-B/Gastrin Receptor. Cloning and Characterization. *J. Biol. Chem.* **1993**, *268*, 8164−8169.

(26) Makovec, F.; Bani, M.; Cereda, R.; Chiste, R.; Pacini, M. A.; Revel, L.; Rovati, L. C. Antispasmodic Activity on the Gallbladder of the Mouse of CR1409 (Lorglumide), a Potent Antagonist of Peripheral Chlolecystokinin. *Pharmacol. Res. Commun.* **1987,** *19,* 41−51.

(27) For the effects of CCK on rat feeding behavior by peripheral and centrally mediated pathways and gastric emptying, see: (a) Della-Fera, M. A.; Coleman, B. D.; Baile, C. A. CNS injection of CCK in rats: Effects on Real and Sham Feeding and Gastric Emptying. *Am. J. Physiol.* **1990**, *258*, R1165−R1169. (b) Crawley, J. Clarification of the Behavioral Functions of Peripheral and Central Cholecystokinin: Two Separate Peptide Pools. *Peptides* **1985**, *6*, 129−36. (c) Moran, T. H.; McHugh, P. R. Cholecystokinin Suppresses Food Intake by Inhibiting Gastric Emptying. *Am. J. Physiol.* **1982**, *242*, R491−R497.

(28) Willson, T. M.; Henke, B. R.; Momtahen, T. M.; Myers, P. L.; Sugg, E. E., Unwalla, R. J.; Croom, D. K.; Grizzle, M. K.; Johnson, M. F.; Queen, K. L.; Rimele, T. R.; Yingling, J. D.; James, M. K. 3-[2-(N-Phenylacetamide)]-1,5-benzodiazepines: Orally Active, Binding Selective CCK-A Agonists. *J. Med. Chem.* **1996**, *39*, 3030−3034.

(29) Hirst, G. C.; Aquino, C.; Birkemo, L.; Croom, D. K.; Dezube, M.; Dougherty, R.W.; Ervin, G. N.; Grizzle, M. K.; Henke, B.; James, M. K.; Johnson, M. F.; Momtahen, T.; Queen, K. L.; Sherrill, R. G.; Szewczyk, J.; Willson, T. M.; Sugg, E. E. Discovery of 1,5-Benzodiazepines with Peripheral Cholecystokinin (CCK-A) Receptor Agonist Activity (II): Optimization of the C3 Amino Substituent. *J. Med. Chem.* **1996**, *39*, 5236−5245.

(30) Chang, R. S.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schonberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D. A Potent Nonpeptide Cholecystokinin Antagonist Selective for Peripheral Tissues Isolated from Aspergillus Alliaceus. *Science* **1985**, *230*, 177−179.

(31) (a) Evans, B. E.; Bock, M. G. Promiscuity in Receptor Ligand Research: Benzodiazepine-based Cholecystokinin Antagonists. *Adv. Med. Chem.* **1993**, *2*, 111−52. (b) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Gould, N. P.; Lundell, G. F.; Homnick, C. F.; Veber, D.F.; Anderson, P.S.; Chang, R.S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; King, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. Design of Nonpeptidal Ligands for a Peptide Receptor: Cholecystokinin Antagonists. *J. Med. Chem.* **1987**, *30*, 1229−1239. (c) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; King, P. J.; Kunkel, K.A.; Springer, J. P.; Hirshfield, J. Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists. *J. Med. Chem.* **1988**, *31*, 2235−2246. (d) Bock, M. G.; Dipardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. Benzodiazepine Gastrin and Brain CCK Receptor Ligands: L365, 260. *J. Med. Chem.* **1989**, *32*, 13−16.

(32) (d) Yu, M. J.; Thrasher, K. J.; McCowan, J. R.; Mason, N. R.; Mendelsohn, L. G. Quinazoline Cholecystokinin-B Receptor Ligands. *J. Med. Chem.* **1991**, *34*, 1505−1508. (e) Yu, M. J.; McCowan, J. R.; Mason, N. R.; Deeter, J. B.; Mendelsohn, L. G. Synthesis and X-ray Crystallographic Analysis of Quinazoline Cholecystokinin/Gastrin Receptor Ligands. *J. Med. Chem.* **1992**, *35,* 2534−2542.

(33) (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; van der Werf-Pieters, J. M. L.; Broekkamp, C. L. E.; de Boer, T.; van Nispen, J. W. CCK-A Agonists: Endeavours Involving Structure-Activity Relationship Studies. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 95−106. (b) Shiosaki, K.; Lin, C. W.; Kopecka, H.; Craig, R.; Wagenaar, F. L.; Bianchi, B.; Miller, T.; Witte, D.; Nadzan, A. M. Development of CCK-Tetrapeptide Analogues as Potent and Selective CCK-A Receptor Agonists. *J. Med. Chem.* **1990**, *33*, 2950−2952. (c) Shiosaki, K.; Lin, C. W.; Kopecka, H.; Tufano, M. D.; Bianchi, B. R.; Miller, T. R.; Witte, D. G.; Nadzan, A. M. Boc-CCK-4 Derivatives Containing Side-Chain Ureas as Potent and Selective CCK-A Receptor Agonists. *J. Med. Chem.* **1991**, *34*, 2837−2842. (d) Dezube, M.; Sugg, E. E.; Birkemo, L. S.; Croom, D. K.; Dougherty, R. W., Jr.; Ervin, G. N.; Grizzle, M. K.; James, M. K.; Johnson, M. F.; Mosher, J.T.; Queen, K. L.; Rimele, T. J.; Sauls, H. R.; Triantafillou, J. A. Modification of Receptor Selectivity and Functional Activity in Cholecystokinin Peptoid Ligands. *J. Med. Chem.* **1995**, *38*, 3384−3390.

(34) SPARTAN, Version 3.5, Wavefunction, Inc. 18401 Von Karman Ave., #370, Irvine, CA 92715. The *ab initio* molecular orbital calculations were carried out using the SPARTAN program on a Silicon Graphics Indigo workstation on the C3 heterocyclic fragment only. The 3-21G* basis set was used, and full geometry optimizations were performed. Electrostatic potential surface color-coded onto the electron density was calculated in each case.

(35) (a) Grider, J. Role of cholecystokinin in the regulation of gastrointestinal motility *J. Nutr.* **1994**, *124*, 1334S−1339S. (b) Reidelberger, R. D.; Varga, G.; Liehr, R.-M.; Castellanos, D. A.; Rosenquist, G. L.; Wong, H. C.; Walsh, J. H. Cholecystokinin suppresses food intake by a nonendocrine mechanism in rats. *Am. J. Physiol.* **1994**, *267*, R901−R908.

(36) Scarpignato, C.; Capovilla, T.; Bertaccini, G. Action of caerulein on gastric emptying of the conscious rat. *Arch. Int. Pharmacodyn. Ther.* **1980**, *246*, 286−294.

(37) Liddle, R. A.; Gertz, B. J.; Kanayama, S.; Beccaria, L.; Coker, L. D.; Turnbull, T. A.; Morita, E. T. 1989, Effects of a novel cholecystokinin (CCK) receptor antagonist, MK-329, on gallbladder contraction and gastric emptying in humans. Implications for the physiology of CCK. *J. Clin. Invest.* **1989,** *84*, 1220−1225.

(38) Sugg, E. E.; Birkemo, L.; Gan, L.-S.; Tippin, T. K. Orally active nonpeptide CCK-A agonists. In *Integration of Pharmaceutical Discovery and Development: Case Histories*; Borchardt, R. T., Freidinger, R. M., Sawyer, T., Smith, P., Eds.; Plenum Publishing Corp.: New York, in press.

(39) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Garsky, V. M.; Gilbert, K. F.; Leighton, J. L.; Carson, K. L.; Melin, E. C.; Veber, D. F.; Chang, R. S. L.; Lotti, V. J.; Freedman, S. B.; Smith, A. J.; Patel, S.; Anderson, P. S.; Freidinger, R. M. Development of 1,4-Benzodiazepine Cholecystokinin Type B Antagonists. *J. Med. Chem.* **1993**, *36*, 4276−4292.

(40) Still, W. C.; Kahn, M.; Mitra, A. J. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(41) Fludzinski, P.; Evrard, D. A.; Bloomquist, W. E.; Lacefield, W. B.; Pfeifer, W.; Jones, N. D.; Deeter, J. B.; Cohen, M. L. Indazoles as Indole Bioisosteres: Synthesis and Evaluation of the Tropanyl Ester and Amide of Indazole-3-carboxylate as Antagonists at the Serotonin $5HT_3$ Receptor. *J. Med. Chem.* **1987**, *30*, 1535−1537.

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