Identification and Optimization of Anthranilic Sulfonamides as Novel, Selective Cholecystokinin-2 Receptor Antagonists

Brett D. Allison, Victor K. Phuong, Laura C. McAtee, Mark Rosen, Magda Morton, Clodagh Prendergast,† Terry Barrett, Guy Lagaud, Jamie Freedman, Lina Li, Xiaodong Wu, Hariharan Venkatesan, Marna Pippel, Craig Woods, Michèle C. Rizzolio, Michael Hack, Kenway Hoey, Xiaohu Deng, Christopher King, Nigel P. Shankley, and Michael H. Rabinowitz*

Johnson & Johnson Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, California 92121

Received May 17, 2006

A high throughput screening approach to the identification of selective cholecystokinin-2 receptor (CCK-2R) ligands resulted in the discovery of a novel series of antagonists, represented by 1-[2-[(2,1,3-benzothiadiazol-4-ylsulfonyl)amino]-5-chlorobenzoyl]-piperidine (**1**; CCK-2R, pK_I = 6.4). Preliminary exploration of the structure−activity relationships around the anthranilic ring and the amide and sulfonamide moieties led to a nearly 50-fold improvement of receptor affinity and showed a greater than 1000-fold selectivity over the related cholecystokinin-1 receptor. Pharmacokinetic evaluation led to the identification of 4-[4-iodo-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-morpholine, **26d**, a compound that demonstrates promising pharmacokinetic properties in the rat and dog with respect to plasma clearance and oral bioavailability and is a potent inhibitor in vivo of pentagastrin-stimulated acid secretion in the rat when dosed orally.

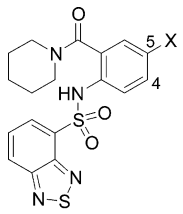
Introduction

In the past few years, there has been a renewed interest in cholecystokinin-2 (CCK-2; formerly gastrin/CCKB) receptor antagonists for the treatment of GI adenocarcinoma such as Barrett's metaplasia and pancreatic cancer based on evidence that gastrin, the cognate ligand for the CCK-2 receptor, is a potent trophic factor for these tumors.[1−3] The therapeutic potential of antigastrin strategies has been illustrated with encouraging clinical trial results with the gastrin vaccine, Gastrimmune.[4,5] In addition, although the widespread use of powerful inhibitors of acid secretion (e.g., proton pump inhibitors) has led to the perception of diminished medical need for new antisecretory agents, CCK-2 receptor antagonism remains a possible alternative/adjunct therapy for the treatment of gastroesophageal reflux disease and peptic ulcers.[6,7] This is because CCK-2 receptor antagonists have the potential to inhibit gastrin's trophic effect on the gastric mucosa decreasing acid secretory capacity, as evidenced in the acid rebound phenomenon associated with proton pump inhibitor withdrawal.[8]

It has been nearly twenty years since the first disclosures of nonpeptide cholecystokinin (CCK) receptor antagonists,[9] yet none have achieved their initial promise of becoming novel medicines for the treatment of gastrointestinal and CNS diseases. This failure has been largely associated with poor or variable pharmacokinetics (both with respect to gastrointestinal absorption as well as diffusion across the blood−brain barrier) and poor physicochemical properties of the drugs.[10,11] With this in mind, we initiated a program aimed at discovering small molecule CCK-2 receptor antagonists driven by structural novelty, developable biopharmaceutical properties, and, above all, evidence of good or optimizable pharmacokinetic properties.

A high throughput CCK-2 receptor binding assay carried out on the Johnson & Johnson corporate compound collection resulted in the identification of a number of novel structural types showing good affinity for the CCK-2 receptor. Of these, compound **1** (Figure 1, Table 1) exhibited submicromolar binding affinity (pK_I = 6.4) and good selectivity over the related CCK-1 receptor (pK_I < 5; upper concentration limit of quantitation in all binding assays is 10^{-5} M).

Pharmacokinetic analysis of **1** as representative of the structural class showed a promising half-life (0.35 ± 0.03 h) and low clearance (0.42 ± 0.01 L/kg/h) in the rat following iv administration. The biological activity garnered from compound **1**, along with related early analogues **2**−**7** (vide infra), prompted us to consider further analogue studies. Herein, we describe the



1: X = Cl
2: X = H
3: X = Br

Figure 1. Structures of initial high throughput screening hit (**1**) and selected early analogues.

Table 1. Human CCK-1 and CCK-2 Receptor Binding Affinities and Selected DMPK Parameters of Early Lead Compounds

compd	CCK-1R[a] (pK_I)	CCK-2R[a] (pK_I)
1	<5	6.4
2	ND[b]	<5[c]
3	ND[b]	6.1
4	<5[c]	7.4
5	<5[c]	7.6
6	<5[c]	<5[c]
7	<5[c]	<5[c]

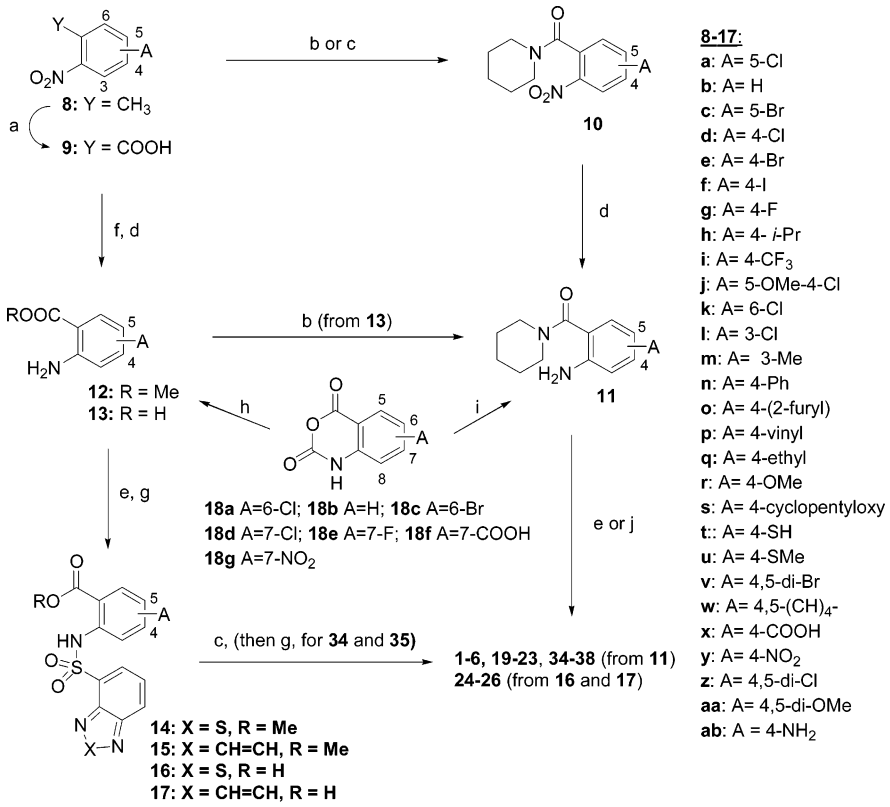
[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Not determined. [c] Affinity (K_I) greater than 10 μM.

* Corresponding author. Phone: (858) 450-2000. Fax: (858) 784-3267. E-mail: mrabinow@prdus.jnj.com.

† Present Address: Department of Physiology, University of Liverpool, Liverpool L69 3BX, United Kingdom.

10.1021/jm060590x CCC: $33.50
Published on Web 09/27/2006

Scheme 1[a]



[a] Reagents and conditions: (a) $KMnO_4$, H_2O or *n*-Bu_4NMnO_4, pyridine, rt, 5−18 h; (b) piperidine, EDC, DMF/MeCN, rt, 18 h; (c) $SOCl_2$, reflux, then piperidine, rt, 18 h; (d) $SnCl_2 \cdot 2H_2O$, EtOAc, CH_2Cl_2, rt; (e) $ArSO_2Cl$, pyridine or neat, 50 °C; (f) MeI, DBU, DMF, 0 °C to rt; (g) LiOH, MeOH, H_2O, rt, 5 h; (h) MeOH, reflux, 12 h; (i) piperidine, DMF, 60 °C, overnight; (j) 2,1,3-benzothiadiazole-4-carbonyl chloride, DCM, pyridine, rt.

evaluation of sulfonamide and amide analogues of **1** with an emphasis on optimizing CCK-2 receptor affinity and selectivity over the related CCK-1 receptor subtype. We also describe the preliminary investigations into pharmacokinetic parameters and in vivo pharmacodynamic activity of representative lead compounds.

Chemistry

m-Aminobenzoic acid-derived sulfonamide **7** was prepared in a two-step sequence (not shown) from 3-amino-4-chlorobenzoic acid via EDC-mediated amide coupling with piperidine, followed by sulfonylation with 2,1,3-benzothiadiazolesulfonyl chloride. Anthranilic acid-derived sulfonamides were prepared via any of four straightforward routes (Scheme 1). Thus, for noncommercially available *o*-nitrobenzoic acids and anthranilic acids, *o*-nitrotoluenes **8** were oxidized by either the action of $KMnO_4$ in water (yield 20−40%) or the treatment with tetrabutylammonium permanganate[12] in pyridine to provide benzoic acids **9** (yield 80−90%; *CAUTION*: We observed an induction period followed by a pronounced exotherm during this reaction, leading to rapid heating of solvent to its boiling point. This variable induction period was a function of the water content in the oxidant and could be controlled by warming of the solution of the substrate prior to addition of the oxidant). The resulting nitrobenzoic acids were then coupled with piperidine either as their acid chlorides or via the action of EDC to afford amides **10**. Nitro group reduction (stannous chloride dihydrate[13]) provided anthranilic amides **11**, which were sulfonylated with arylsulfonyl chlorides in either pyridine or in the absence of solvent, to afford target compounds **1**−**6**, **19**−**23**, and **34**−**37** (see Figures 2−4). This route allowed flexibility

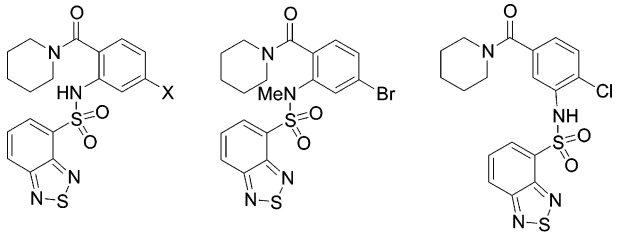


Figure 2. Structures of compounds **4**−**7**.

in evaluating the structure/activity relationship (SAR) around the sulfonamide moiety.

A second route, useful in our investigations of the amide group SAR, involved esterification of benzoic acids **9** (MeI, DBU), followed by nitro group reduction to anthranilic methyl esters **12**. Sulfonylation, as before, followed by saponification (LiOH), provided benzoic acids **16** and **17**, which were readily converted to target amides **24**−**26** via standard HATU[a,14] or acid-chloride couplings.

In a third route, either synthetic manifold could be accessed through isatoic anhydrides **18** via either methanolysis to provide methyl esters **12** or aminolysis to provide amides **11** directly.

In a fourth route, commercially available anthranilic acids **13** were coupled with piperidine (EDC) to provide directly

[a] Abbreviations: DCM, dichloromethane; DCE, dichloroethane; DMAP, *N*,*N*-(dimethylamino)pyridine; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; DMF, dimethyformamide; TFA, trifluoroacetic acid; EtOAc, ethyl acetate; THF, tetrahydrofuran; MPLC, medium-pressure liquid chromatography; Et_2O, diethyl ether; DIPEA, diisopropylethylamine.

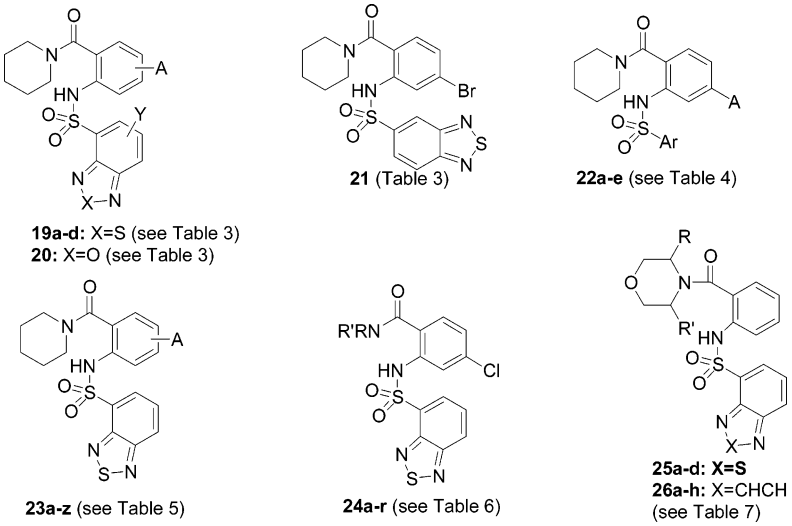


Figure 3. Structures of compounds **19**−**26**.

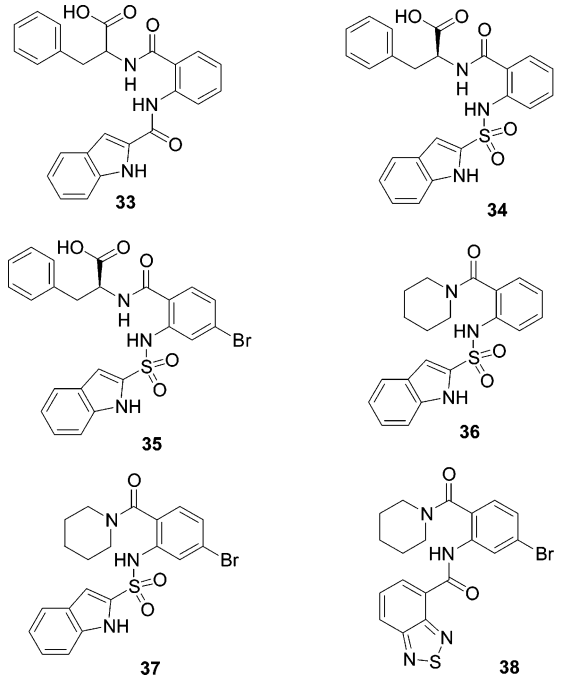


Figure 4. Indole-2-carboxamide, indole-2-sulfonamide, and 2,1,3-benzothidizole-4-carboxamide analogues.

anthranilic amides **11** that were converted to target compounds, as described above.

Amino and amido substitution at the C4 position was elaborated as follows: nitroarene **23y** was reduced with tin(II) chloride to aniline **23g** (Scheme 2), which was subsequently derivatized via reductive amination (**23d** and **23h**), condensation with 2,5-dimethoxytetrahydrofuran to furnish pyrrole **23i**, or acid-chloride couplings to provide amides **23p** and **23q**.

Quinoxaline-5-sulfonyl chloride, **29**, was prepared (Scheme 3) from 5-hydroxyquinoxaline[15] (**27**) via Newman−Kwart rearrangement[16,17] of the derived diethylthionocarbamate (prepared from **27** and *N*,*N*-diethylthiocarbamoyl chloride) to afford an intermediate diethylthiocarbamate **28**. Hydrolysis (KOH in methanol), followed by oxidation (Cl_2, formic acid in DCM/water), provided sulfonyl chloride **29** in 80% yield for the four steps. This same synthetic sequence was applied to 5-hydroxyquinoline (**30**) to provide quinoline-5-sulfonyl chloride, **32**. These sulfonyl chlorides were then incorporated into the synthetic routes depicted in Scheme 1 to provide **22c**, **22d**, and **26a**−**h**.

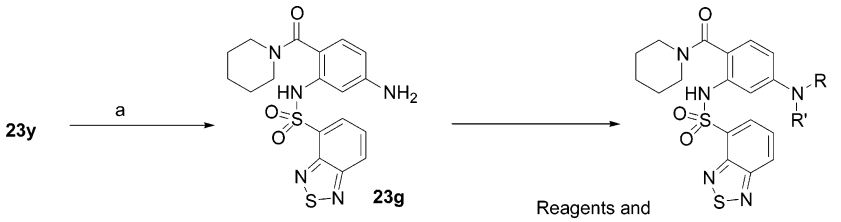
An alternate synthesis of quinoxaline compounds involved a two-step reductive desulfurization of the corresponding benzothiadiazole, followed by condensation with glyoxal.[18] Thus, benzothiadiazoles **25d** and **14g** (Scheme 3) were treated with zinc metal in acetic acid to provide unstable *o*-phenylenediamines that were immediately condensed with sodium glyoxal bisulfite in aqueous methanol to provide quinoxalines **26d** and **15g**.

Indole-2-sulfonamides **34**−**37** (Figure 4) were prepared from *N*-Boc-indole-2-sulfonyl chloride, **39**, synthesized using a variant of a previously described[19] procedure (Scheme 4), and anthranilic ester **12b** or **12e** to afford methyl anthranilates **40** and **41** (Scheme 5). Concomitant methyl ester and carbamate hydrolysis (aqueous LiOH) resulted in carboxylic acids **42** and **43**, which were coupled with either Phe−OMe or piperidine to provide **34**−**37**, after ester hydrolysis. Compound **38** was prepared via amide bond coupling between aniline **11e** and 2,1,3-benzothiadiazole-4-carbonyl chloride.

Results and Discussion

SARs were developed in this series using human CCK-1[20,21] and CCK-2[22] receptor cell-based radioligand binding assays. Initial SAR studies involved examination of the role of halogenation of the anthranilic ring. Removal of the chlorine atom of the lead compound **1** gave a compound, **2** (Table 1, Figure 1), that had low binding affinity in the CCK-2 receptor binding assay. However, replacement by Br (**3**) was tolerated. Moving the chlorine atom from the 5-position to the 4-position of the anthranilic ring resulted in a 10-fold improvement of binding affinity for the CCK-2 receptor, and substitution by a bromine atom at the 4-position (i.e., **5**) resulted roughly in an added improvement of similar magnitude. Investigation into some of the gross chemical features of the series revealed that the free NH of the sulfonamide moiety was required for activity (e.g., compound **6**, Table 1, Figure 2) and that the central anthranilic ring requires the *ortho*-aminobenzamide substitution pattern (*meta*-aminobenzamide **7**, Figure 2, Table 1, was found to be poorly active in all binding assays). Also, replacement of the sulfonamide moiety by an amide group resulted in the complete loss of activity (vide infra). In addition, replacement of the amide group in compounds of this series with analogous ester groups resulted in a complete loss of activity (data not shown).

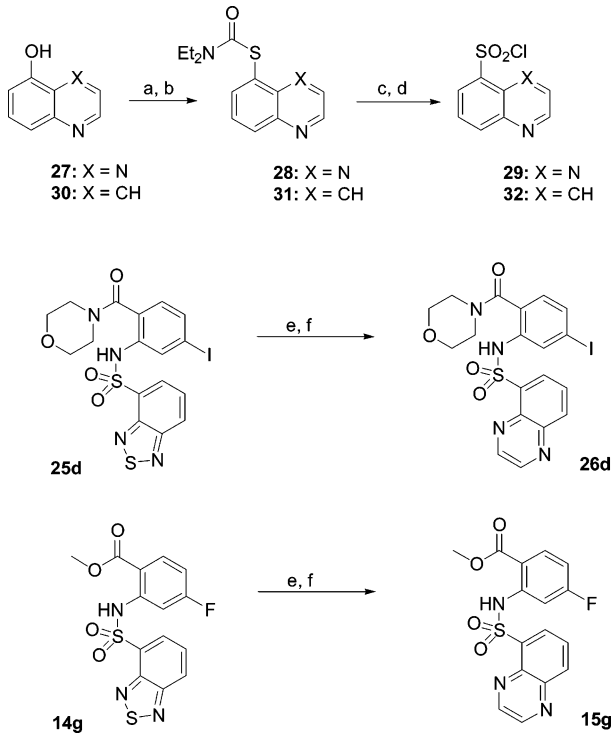
Scheme 2[a]



Reagents and conditions:[a]	Compound:
b	**23d**: R = H; R' = Bn
c	**23h**: R = R' = Me
d	**23i**: R = R' = -(CH)$_4$-
e	**23p**: R= H; R' = Bz
f	**23q**: R = H; R' = Ac

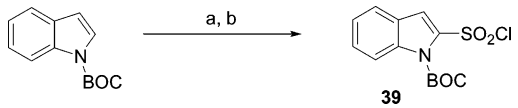
[a] Reagents and conditions: (a) $SnCl_2 \cdot 2H_2O$, EtOAc, DCM, rt; (b) PhCHO, $NaBH(OAc)_3$, AcOH; (c) CH_2O, $NaCNBH_3$, AcOH, rt; (d) 2,5-dimethoxytetrahydrofuran, AcOH, 120 °C; (e) BzCl, pyridine, DCM, rt; (f) AcCl, pyridine, DCM, rt.

Scheme 3[a]



[a] Reagents and conditions: (a) $ClC(S)NEt_2$, K_2CO_3, DMF, 95%; (b) 240 °C, neat, 95% (c) KOH, MeOH, reflux; (d) Cl_2, DCM, HCOOH, H_2O, 0 °C, 85% (two steps); (e) Zn, AcOH; (f) sodium glyoxal bisulfite, H_2O, MeOH, reflux, 60−80%.

Scheme 4[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C; (b) SO_2Cl_2, CH_2Cl_2, 0 °C to rt.

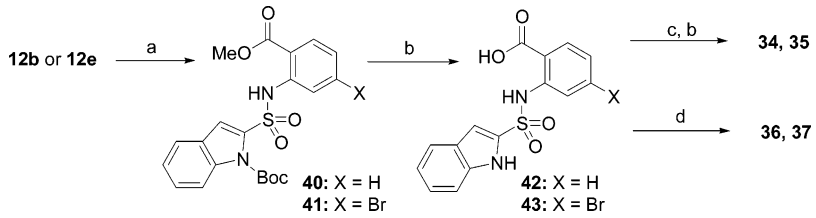
Preliminary investigations into in vitro predictors of ADME properties of **4** (Table 2) suggested the potential for a high degree of CYP_{450}-promoted oxidative metabolism in this chemical series, as predicted by incubation with pooled human liver microsome and S9 and rat and dog S9 preparations. Measurement of log D (pH 7.4) and permeability through Caco-2 monolayers suggested good GI absorption (1.8 and 23×10^{-6} cm s^{-1}, respectively) and that active efflux should not be important (Caco-2 P_{app} B−A/A−B ∼ 0.8). Similar results were observed for compound **5** (not shown).

Qualitative metabolite identification of compound **5** incubated in the presence of human liver microsomes suggested extensive metabolism of the benzothiadiazole ring system. In addition, oxidation of the piperidine ring was observed.[23] With these preliminary affinity and in vitro ADME data in hand, we set about to examine the following: (1) amide, sulfonamide, and anthranilic ring SAR, with the aim of improving binding affinity to the CCK-2 receptor, and (2) replacement groups for the oxidatively sensitive benzothiadiazole ring system.

The initial investigation into steric and electronic requirements around the sulfonamide group (Table 3) revealed that replacement of the 2,1,3-benzothiadiazole heterocyclic ring system by nearly any other ring system results in a dramatic loss of affinity for the CCK-2 receptor. Thus, moving the sulfonamide linker from the benzothiadiazole C4 to the C5 position (**21**) results in over a 100-fold loss in affinity with respect to **5**. However, this ring system was found to tolerate some degree of substitution, either alkylation or halogenation (**19a**−**d**). Most interestingly, replacement of the divalent sulfur atom of the 2,1,3-benzothiadiazole ring system of **4** with an oxygen atom results in a 50-fold drop in CCK-2R affinity (Table 3; **20**). This effect may be attributable to increased electronegativity of the oxygen atom (compared with the sulfur atom of **4**) of **20** and a change in the nitrogen atom lone pair geometries. Quantum mechanical density functional theory calculations at the B3LYP/6-31G** level[24] indicate C−C−N bond angles of 113.7° and 108.8°, with N−N interatomic distances of 2.53 Å and 2.29 Å, for the 2,1,3-benzothiadiazole and the 2,1,3-benzoxadiazole ring systems, respectively. These geometrical differences may play a role in the misalignment of interactions made to hydrogen bond donating groups of the receptor. At this same level of theory, Mulliken partial charge calculations[25] of these putative acceptor nitrogen atoms show values of −0.50 for the 2,1,3-benzothiadiazole and −0.17 for the 2,1,3-benzoxadiazole. Also, the pK_a values of the conjugate acids of the heterocyclic ring nitrogen atoms were calculated to be −2.29 for the benzothiadiazole and −3.81 for the benzozadiazole ring systems. These calculations together suggest the nitrogen atoms of the 2,1,3-benzoxadiazole ring system in **20** are far less competent hydrogen bond acceptors than are those in the corresponding benzothiadiazole ring system, lending credence to our hypothesis that one or both of the nitrogen atoms of compounds such as **4** make important hydrogen bond accepting interactions with the human CCK-2 receptor.

We have also measured an increase in the acidity of the sulfonamide NH group in compound **20** (pK_a = 6.18) with respect to compound **4** (pK_a = 5.47),[26] which further highlights distinct physicochemical differences between these two ring

Scheme 5[a]



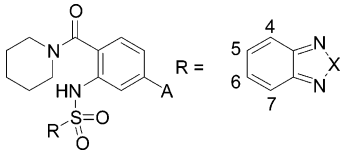
[a] Reagents and conditions: (a) **39**, pyridine, DCM, rt, 72 h; (b) LiOH·H_2O, THF, H_2O, rt, 16 h; (c) L-Phe-OMe·HCl, HATU, DIPEA, MeCN, 18 h, rt; (d) piperidine, HATU, DIPEA, MeCN, 18 h, rt.

Table 2. Preliminary ADME and PK Parameters for Compound **4**

log D[a]	HLM[b]	HS9[b]	RS9[b]	DS9[b]	caco-2[c] (cm s^{-1})	protein binding (% bound)
2.1 (pH 7.4)	19 (3.9)	69 (51)	78 (62)	78 (59)	22.7×10^{-6} (0.8)	77[d] >99.5[e] >99.5[f]

[a] Measured partition coefficient between water-saturated 1-octanol and buffer at the indicated pH. [b] Stability in the presence of human liver microsomes (HLM) or human, rat, or dog S9 liver fractions. Data indicate percentage of **4** remaining at 15 min (and 30 min). [c] Apparent apical (A) to basolateral (B) permeability (P_{app}) through caco-2 epithelial cell layers. Number in parentheses is P_{app} ratio B−A/A−B. [d] α-Glycoprotein. [e] Human plasma. [f] Human serum albumin.

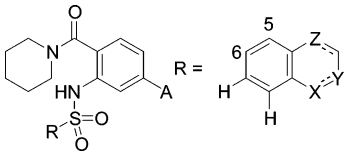
Table 3. Human CCK-1 and CCK-2 Receptor Binding Affinities: Effect of Benzothiadiazole Sulfonamide Group Variation



compd	A	X	**4**	**5**	**6**	**7**	CCK-1R pK_I[a]	CCK-2R pK_I[a]
19a	Br	S	-yl	Me	H	H	<5[b]	7.0
19b	Br	S	-yl	H	H	Me	<5[b]	7.0
19c	Br	S	-yl	H	H	Br	<5[b]	6.8
19d	Br	S	-yl	F	H	H	<5[b]	7.4
20	Cl	O	-yl	H	H	H	<5[b]	5.8
21	Br	S	H	-yl	H	H	<5[b]	<5[b]

[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Affinity (K_I) greater than 10 μM.

Table 4. Human CCK-1 and CCK-2 Receptor Binding Affinities: Effect of Carbocyclic and Heterocyclic Sulfonamide Group Variation



compd	A	X	Y	Z	**5**	**6**	CCK-1R pK_I[a]	CCK-2R pK_I[a]
22a	Br	CH	N	CH	-yl	H	<5[b]	<5[b]
22b	Cl	CH	CH	N	-yl	H	<5[b]	<5[b]
22c	Br	N	CH	CH	-yl	H	<5[b]	6.1
22d	Br	N	CH	N	-yl	H	<5[b]	7.2
22e	Br	CH	CH	CH	-yl	H	<5[b]	<5[b]

[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Affinity (K_I) greater than 10 μM.

systems that may provide an explanation for the observed differences in receptor affinities.

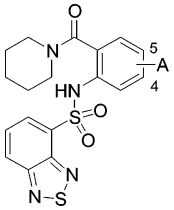
A more detailed analysis of the SAR around this ring system further demonstrated the exquisite sensitivity of binding affinity to alteration in this region (Table 4). Replacement of the sulfur atom and one of the nitrogen atoms of the 2,1,3-benzothiadiazole ring system by a CHCHCH group provided quinolin-8-yl and quinolin-5-yl analogues (**22b** and **22c**), displaying over 50-fold loss in activity for each compared to **4** and **5**, respectively. The greater CCK-2 receptor affinity of quinolin-5-yl analogue **22c** (pK_I = 6.1) over the related quinolin-8-yl **22b** (pK_I < 5)—assuming only a small contribution to the difference in receptor affinity as a result of the different anthranilic ring halogen atoms—points to a unequal contribution toward overall receptor affinity of the heterocyclic sulfonamide nitrogen atoms of **5** inasmuch as they each represent the contributions to receptor binding of the individual nitrogen atoms of the 2,1,3-benzothiadiazole parent. The low binding affinity observed for compound **22c** is reduced even further by transposition of the nitrogen atom to the adjacent position (i.e., isoquinoline **22a**, pK_I < 5). Removal of all heteroatoms from the sulfonamide bicyclic ring system (e.g., 1-naphthyl), as expected from the above discussion, results in a compound (**22e**) with no measurable receptor affinity under our assay conditions (Table 4).

We hypothesized from these series of studies that (1) both nitrogen atoms of the 2,1,3-benzothiadiazole ring system are required for high affinity CCK-2R binding, (2) receptor affinity in this series is highly dependent on the basicity of the nitrogen atom lone pairs, and (3) the 4-position connectivity of the sulfonamide moiety to the 2,1,3-benzothiadiazole ring is specifically required for the proper positioning of presumptive hydrogen bond acceptor atoms. Subsequent structural studies using NMR and X-ray diffraction techniques further supported this hypothesis and presented us with an interesting pharmacophore model, one involving a ground state/solution state conformation of the compounds in this series, consisting of a three-centered hydrogen bonding array between the amide carbonyl, the sulfonamide NH, and the N3 of the 2,1,3-benzothiadiazole ring.[27]

With this preliminary model in mind, we postulated that the quinoxaline-5-sulfonamido ring system would be a potentially useful heterocyclic replacement to the 2,1,3-benzothiadiazole-4-sulfonamido system in that the steric and electronic requirements of our pharmacophore hypothesis would largely be met. Indeed, substitution of the 2,1,3-benzothiadiazole-4-sulfonamido group of **5** by the novel quinoxaline-5-sulfonamido group resulted in a compound (**22d**) displaying a pK_I of 7.2 for the CCK-2 receptor (Table 4), with only a 2.5-fold lower affinity for this receptor compared to **5**.

Attention was turned to the analysis of substituent requirements around the central anthranilic ring (Table 5). We knew

Table 5. Human CCK-1 and CCK-2 Receptor Binding Affinities: Effect of Anthranilic Ring Substitution



compd	A	CCK-1R pK_I[a]	CCK-2R pK_I[a]
23a	3-chloro	<5[b]	<5[b]
23b	3-methyl	<5[b]	<5[b]
23c	6-chloro	<5[b]	6.0
23d	4-(*N*-benzylamino)	<5[b]	5.9
23e	4-methoxy	<5[b]	6.2
23f	4-cyclopentyloxy	<5[b]	6.8
23g	4-amino	<5[b]	5.1
23h	4-dimethylamino	<5[b]	6.5
23i	4-(1-pyrrolo)	<5[b]	6.3
23j	4-thiomethyl	<5[b]	7.0
23k	4-ethyl	<5[b]	6.6
23l	4-isopropyl	<5[b]	6.5
23m	4-phenyl	<5[b]	6.8
23n	4-(2-furyl)	<5[b]	6.9
23o	4,5-(−CHCHCHCH−)	<5[b]	6.9
23p	4-(*N*-benzoylamino)	5.6	5.1
23q	4-(*N*-acetylamino)	<5[b]	<5[b]
23r	4,5-dichloro	<5[b]	7.8
23s	4,5-dibromo	<5[b]	8.0
23t	4,5-dimethoxy	<5[b]	5.6
23u	4-chloro-5-methoxy	<5[b]	6.3
23v	4-fluoro		6.0
23w	4-iodo	<5[b]	8.3
23x	4-trifluoromethyl	<5[b]	7.2
23y	4-nitro	<5[b]	6.8
23z	4-carboxy	<5[b]	<5[b]

[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Affinity (K_I) greater than 10 μM.

from our earlier investigations that leaving this ring unsubstituted resulted in very poor CCK-2R binding affinity (cf. **2**, Table 1). Placing a substituent at the 3-position of the anthranilic ring (**23a** and **23b**) eliminates receptor binding affinity (pK_I < 5), while the 6-Cl analogue (**23c**) shows low but measurable activity (pK_I = 6.0). We, therefore, focused on substitution at the 4- and 5-position. A variety of substituents are tolerated at the 4-position with π-electron-donating substituents (methoxy (**23e**), cyclopentyloxy (**23f**), dimethylamino (**23h**), 1-pyrrolo (**23i**)), σ-electron-donating groups (thiomethyl (**23j**), ethyl (**23k**), isopropyl (**23l**), and 2-furyl (**23n**)), as well as inductively electron-withdrawing groups (CF_3 (**23x**) and nitro (**23y**)), imparting higher binding affinity to the CCK-2 receptor than the unsubstituted parent **2**. Fusing a benzene ring to the 4- and 5-position provides a naphthane analogue (**23o**) with a ~100 nM K_I value. Notable exceptions are highly polar groups such as amino (**23g**), amide-substituted compounds (**23p** and **23q**), and carboxy (**23z**) that show very low receptor affinity. Comparing **23h** and **23l**, the isosteric, but not isoelectronic, dimethylamino and isopropyl analogues, it is clear that, while neither is superior to a simple halogen substituent at the 4-position, the binding affinities are identical, suggesting the lack of strong electronic preference for substituents at this position.

Further examination of anthranilic ring halogenation demonstrates the effect of increasing receptor affinity in progressing from 4-F (**23v**, pK_I = 6.0) to 4-Cl (**4**, pK_I = 7.4), 4-Br (**5**, pK_I = 7.6), and 5-I (**23w**, pK_I = 8.3). Based on the electronic considerations discussed above, the effect of increasing binding affinity following the trend F → Cl → Br → I is not likely a function of decreasing electronegativity, but rather of increasing atomic radii (i.e., steric factors). Such steric effects on binding affinity have been observed with other cholecystokinin inhibitor classes.[28] Disubstitution at the 4- and 5-position, such as dichloro (**23r**) and dibromo (**23s**), suggests additive effects on binding (pK_i = 7.8 and 8.0, respectively). However, disubstitution involving a methoxy group (4,5-dimethoxy, **23t**, and 4-chloro-5-methoxy, **23u**) resulted in either unimproved or decreased receptor affinity with respect to either the 4-methoxy or 4-chloro substitution alone.

We also undertook a preliminary exploration of the SAR for CCK-2R binding of cyclic amides in comparison with compound **4** (Table 6). There is a clear trend of increasing receptor affinity with ring size (**24a**−**24d**, cf., **4**). Receptor binding is intolerant of charge (**24e**) and other polarity (**24f**, **24i**, **24m**, **24n**, and **24o**) in this region, however, lipophilic groups are tolerated (**24h**, **24l**, and **24q**). The methylated piperidine amides (**24k** and **24j**) reveal the steric limits of added lipophilicity in this region; while methylation at the C2 position acts to improve binding affinity (**24k**), 3,5-dimethylation is detrimental (**24j**). To underscore these observations, we found a modest correlation of compounds in Table 2 (R = 0.76) of CCK-2R affinity with clogP at pH 2. The loss in receptor affinity observed by substituting a benzyl amide for the piperidine-based amides of approximately 100-fold (i.e., **24q**) is reversed by *N*-methylation (i.e., **24r**).[29]

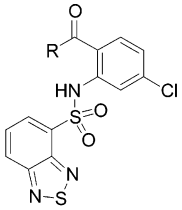
We were intrigued by the good CCK-2R affinity observed for morpholine amide **24p**, as we anticipated that the addition of the oxygen atom to the piperidine ring (of **4**, for example) would help diminish any amide ring metabolic oxidation that could explain the relatively high hepatic clearance of compounds in this series (e.g., **5**). We, therefore, examined optimizing the activity in the morpholine amide series.

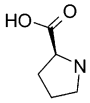
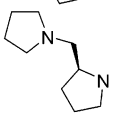
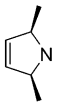
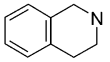
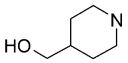
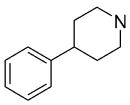
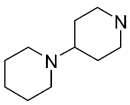
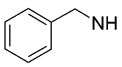
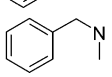
Table 7 shows more clearly the effect that halogen size at the anthranilic C4 position has on binding for compounds in this series. In these examples, both benzothiadiazole (**25a**−**25d**) and quinoxaline (**26a**−**26d**) sulfonamides show improvements in binding affinity of about 10-fold in progressing from 4-F to 4-Cl and 2.5− 4-fold further increases in progressing from chlorine to bromine to iodine. With respect to the parent morpholine amide (**26b**), the addition of an (*S*)-methyl group at the morpholine C2 position (**26e**) has the effect of lowering receptor affinity (pK_i = 6.1 vs 6.5), while the opposite effect of similar magnitude is observed for the (*R*)-configuration (**26f**). With respect to **26e**, the addition of a second (*S*)-methyl group at C6 (i.e., **26g**) dramatically lowers affinity (pK_I = 5.3 vs 6.1). Comparison with the *meso*-dimethyl analogue **26h**, C6 (*R*)-methylation (allowing C2 of the *meso*-ring to be (*S*), i.e., **26e**) has little effect on binding affinity (pK_I = 6.2 vs 6.1). However, comparison of the same *meso*-analogue, this time constraining C2 to be in the (*R*)-configuration, results in a significant decrease in affinity (pK_I = 6.2 vs 6.8).

As is shown in Tables 1−7, compounds in the series disclosed in the present work display little to no measurable affinity for the recombinant human CCK-1 receptor at concentrations up to 10 μM. Indeed, the highest affinity CCK-2 receptor antagonists display greater than 1000-fold selectivity for this receptor over the CCK-1 receptor. Evaluation of **5** against a panel of over 50 cloned receptors, ion channels, and enzymes showed no affinity of this compound for any of these selected pharmaceutical loci.

During the course of this work, researchers from the University of Trieste disclosed a related series of anthranilic

Table 6. Human CCK-1 and CCK-2 Receptor Binding Affinities: Effect of Heterocyclic Amide Variation

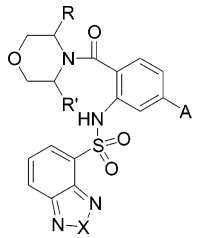


compd	R	CCK-1R pK_I[a]	CCK-2R pK_I[a]
24a		<5[b]	5.8
24b		<5[b]	6.6
24c		<5[b]	7.1
24d		<5[b]	7.2
24e		<5[b]	<5[b]
24f		<5[b]	<5[b]
24g	 (*meso*)	<5[b]	6.7
24h		<5[b]	6.0
24i		<5[b]	5.9
24j		<5[b]	5.9
24k		<5[b]	7.5
24l		<5[b]	7.2
24m		<5[b]	<5[b]
24n		<5[b]	5.6
24o		<5[b]	<5[b]
24p		<5[b]	6.5
24q		<5[b]	5.6
24r		<5[b]	7.5

[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Affinity (K_I) greater than 10 μM.

amides that were demonstrated to be highly selective for the CCK-1 receptor over the CCK-2 receptor in rat tissue preparations.[30−32] We confirmed the activity of the lead compound **33** (Figure 4) and also found it to be highly selective for the human CCK-1 receptor (Table 8). The reported SAR analysis of compounds such as **33** suggests the importance of an intramolecular hydrogen bond between the anthranilic amide carbonyl and the anthranilic NH group.[30] We independently identified the presence of this hydrogen bond in our sulfonamide series through X-ray, NMR, and molecular modeling studies.[33] The 2-indolyl amide ring system was identified as a so-called "needle" moiety that was found to be uniquely capable of imparting high affinity CCK-1 receptor binding in this series due to its postulated hydrogen bond donating capacity.[31,32] The authors prepared 1-naphthyl carboxamide and 1- and 2-naphthyl sulfonamide analogues of **33**[32] and found them to have no affinity for the CCK-1 receptor and weak affinity for the CCK-2 receptor, with little difference between carboxamide and sulfonamide affinities (CCK-2R, pK_I ~ 5.2). We found that replacing the sulfonamide group of compound **5** by a carboxamide group led to complete loss in binding affinity for the CCK-2 receptor (**38**, Table 8, Figure 4). To investigate whether an indole ring could act as a replacement group for our benthothiadiazole and quinoxaline sulfonamides, we prepared a number of chimeric compounds (**34**−**37**).

Table 7. Human CCK-1 and CCK-2 Receptor Binding Affinities: Effect of Anthranilic Ring Halogenation and Alkylation of Morpholine Amides



compd	R	R′	A	X	CCK-1R pK_I[a]	CCK-2R pK_I[a]
25a	H	H	H	S	<5[b]	<5[b]
25b	H	H	F	S	<5[b]	5.4
24p	H	H	Cl	S	<5[b]	6.5
25c	H	H	Br	S	<5[b]	6.9
25d	H	H	I	S	<5[b]	7.5
26a	H	H	F	CHCH	<5[b]	5.4
26b	H	H	Cl	CHCH	<5[b]	6.5
26c	H	H	Br	CHCH	<5[b]	7.2
26d	H	H	I	CHCH	<5[b]	7.5
26e	(*S*)-Me	H	Cl	CHCH	<5[b]	6.1
26f	(*R*)-Me	H	Cl	CHCH	<5[b]	6.8
26g	(*S*)-Me	(*S*)-Me	Cl	CHCH	<5[b]	5.3
26h	*meso*-2,6-di-Me		Cl	CHCH	<5[b]	6.2

[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Affinity (K_I) greater than 10 μM.

Table 8. Human CCK-1 and CCK-2 Receptor Binding Affinities of Indole-2-sulfonamide and 2,1,3-Benzothiadiazole-4-carboxamide Analogues

compd	CCK-1R pK_I[a]	CCK-2R pK_I[a]
33	7.5	<5[b]
34	5.5	5.3
35	6.7	5.7
36	5.1	<5[b]
37	5.7	5.7
38	<5[b]	<5[b]

[a] Negative logarithm of the antagonist equilibrium dissociation constant calculated from the concentration required to displace 50% ^{125}I-CCK-8S (pIC_{50}) by the method of Cheng and Prussoff.[44] All values are ±0.3 log units, unless otherwise stated. [b] Affinity (K_I) greater than 10 μM.

Table 9. Activities of Compounds **4** and **5** in Guinea Pig Fresh Tissue CCK-1R and CCK-2R Functional Assays

compd	GPGB pK_B[a]	GPGSM pK_B[b]
4	<5[c]	8.49 ± 0.09
5	<5[c]	8.80 ± 0.10

[a] Isolated CCK-8S-stimulated guinea pig gall bladder smooth muscle contraction. [b] Isolated penta-gastrin stimulated guinea pig gastric smooth muscle contraction. pK_B values determined via Schild analysis. [c] Affinity (K_B) greater than 10 μM.

Table 10. Liver Microsome Stability of Selected Compounds

compd	HLM[a] (%)	RLM[b] (%)
1	16	9
5	15	8
24d	11	2
24k	14	3
23r	8	8
22d	21	8
24r	2.2	
26d	60	46

[a] Percent remaining after 30 min in the presence of pooled human liver microsome preparations ($n = 20$). [b] Percent remaining after 30 min in the presence of pooled rat liver microsome preparations ($n = 20$). Standard deviation: ±15%. Compounds were evaluated using the same microsomal preparations under identical assay conditions on the same day.

In the event, replacement of the benzothiadiazole ring systems of **2** and **5** by the 2-indolyl group resulted in compounds with low affinity for both the CCK-1 and the CCK-2 receptor (**36** and **37**, Table 8). Converting the Varnavas indole amide (**33**) into a sulfonamide resulted in **34** (note that this compound as well as **35** are derived from L-Phe and not D/L-Phe), which again showed little measurable CCK-2 receptor binding (p$K_I = 5.3$, Table 8). Interestingly, the addition of a 4-bromo substituent to the anthranilic ring of **34** resulted in a compound (**35**) with submicromolar CCK-1R affinity (p$K_I = 6.7$, Table 8), with 10-fold selectivity over the CCK-2 receptor. One would anticipate, if the principle of additivity were operable, that 4-position halogenation of compounds such as **33** would result in greatly improved CCK receptor binding. Overall, these investigations indicate that, despite the superficial structural similarity of our CCK-2 receptor-selective anthranilic sulfonamides to the CCK-1 receptor-selective anthranilic amides, the two series remain largely distinct, with significantly divergent SAR, suggesting differing receptor binding modes.

To determine if compounds in this series behave as surmountable competitive antagonists of CCK-2 receptors, activity was measured in an isolated guinea pig gastric smooth muscle assay.[34] Inhibition of pentagastrin-stimulated contraction was associated with pK_B values of 8.5 for **4** and 8.8 for **5**, determined via Schild analysis (Table 9). In addition, evaluation of these compounds in the CCK-8S-stimulated guinea pig gall bladder contraction assay[35] (a CCK-1 receptor-mediated effect) demonstrated no antagonism at concentrations up to 10 μM (Table 9).

Human and rat liver microsome stability was assessed as a predictor of in vivo pharmacokinetic clearance. Table 10 shows that rapid degradation in vitro is observed for all of the compounds evaluated in the benzothiadiazole sulfonamide series (**1**, **5**, **24d**, **24k**, **23r**, and **24r**). Human and rat liver microsomes correlate in their prediction of a high degree of oxidative metabolism in both species. Neither the size of the heterocyclic amide ring nor its degree of substitution appears to protect against CYP_{450}-mediated degradation in this preparation (**24d** and **24k**), nor does the nature and extent of halogenation of the anthranilic ring (**1**, **5**, and **23r**). If anything, replacement of the cyclic amide by acyclic substitution (i.e., **24r**) results in even greater oxidative instability. In earlier studies (vide supra), we found that the benzothiadiazole ring of **4** was specifically oxidized in the presence of liver microsomes. While replacement of this ring system by a quinoxaline ring system per se did not impart greater resistance to degradation (e.g., **22d**), this ring system, when combined with a morpholine amide, results in a compound (**26d**) showing modest, but significantly improved, stability in the presence of both human and rat liver microsomes with respect the other compounds evaluated (assuming, as discussed above, little effect of anthranilic ring halogenation on changes in metabolic stability).

These structural changes effecting in vitro oxidative stability in human liver microsome preparations translate to some degree to pharmacokinetic clearance and half-life in the rat (Table 11). While oral bioavailability appears good for all compounds evaluated, plasma half-lives are low for compounds containing the piperidine amide or benzothiadiazole sulfonamide groups (entries 1−4). Half-lives, as well as clearance, are seen to improve by factors of 2 to 3 as a result of the enhanced metabolic stability imparted by a morpholino group replacing the piperidine ring coupled with inclusion of the quinoxaline heterocycle. Human liver microsome stabilities (Tables 2 and 10) predict for the reduced clearance and slightly improved plasma half-life in the rat gained by replacing a chlorine atom at C4 by a bromine atom (i.e., comparing compounds **4** and **5**). Predictably, half-lives are improved in the dog (entries 4 and 5), with a significantly reduced plasma clearance in this species for entry 5. Oral bioavailability in the dog is also good for compounds **5** and **26d** (Table 11).

Compounds in this series were found to be effective in vivo in rat models of gastric acid secretion. Thus, gastric acid secretion, as quantified by total acid output, stimulated by iv infusion of pentagastrin (100 nmol/kg/h, producing a near-maximal effect) in the anesthetized Ghosh and Schild[36] rat preparation, was reversed in a dose-dependent manner by iv infusions of compound **5**. A plot of percent increase in pH of intralumenal perfusate versus iv infusion rate (Figure 5A) revealed an ED_{50} of 0.6 mg/kg/h in this preparation. Pharmacokinetic/pharmacodynamic analysis (data not shown) indicated this effect to be associated with a plasma concentration of ~1.3 μM.

Table 11. Pharmacokinetic Parameters in the Rat and Dog for Selected Compounds

		rat[a]			dog[a]		
entry	compd	CL_{ss} (L/kg/h)	$T_{1/2}$ (h)	% F	CL_{ss} (L/kg/h)	$T_{1/2}$ (h)	% F
1	**1**	0.42 ± 0.01	0.35 ± 0.03				
2	**22d**	0.83 ± 0.27	0.34 ± 0.11	50 ± 16			
3	**4**	1.25 ± 0.26	0.16 ± 0.03	42 ± 7			
4	**5**	0.70 ± 0.06	0.26 ± 0.03	68 ± 8	0.7 ± 0.2	0.42 ± 0.03	33 ± 2
5	**26d**	0.36 ± 0.05	0.62 ± 0.06	55 ± 13	0.097 ± 0.02	1.5 ± 0.3	51 ± 14

[a] Calculated from at least three animals. Clearance values (CL_{ss}) and half-lives ($T_{1/2}$) measured from iv doses of 2 μmol/kg for rat and dog. Relative fraction absorbed (% F) measured from 2 μmol/kg (rat) and 20 μmol/kg (dog) po doses.

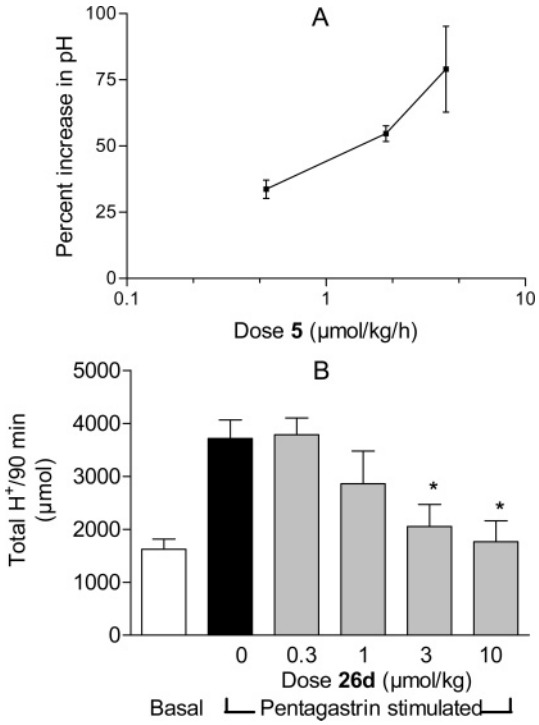


Figure 5. (A) Inhibition of pentagastrin-stimulated gastric acid secretion as a function of increasing iv infusion rates of compound **5** in the rat Ghosh and Schild model of acid hypersecretion. The ED_{50} was measured to be 0.6 mg/kg/h. (B) Inhibition of pentagastrin-stimulated gastric acid secretion in the rat by compound **26d** after po administration. Compound **26d** was dosed orally as a solution, and gastric acid was collected via a chronic stainless steel fistula. For both oral and intraveneous dosing, **26d** was freshly prepared in a 5% (v/v) pharmasolve in 20% HP-β-cyclodextrin solution. (* = $p < 0.05$).

Compound **26d** was evaluated for efficacy from the oral dose in a conscious, chronic gastric fistula rat model.[37,38] Thus, oral administration of solutions of **26d** were found to potently reverse pentagastrin-stimulated (30 nmol/kg, administered via subcutaneous injection 2 h after dosing of **26d**) gastric acid secretion in a dose-dependent manner in rats fitted with chronic stainless steel fistulae for the collection and quantification of gastric acid (Figure 5B). The total acid collected over 120 min was plotted versus basal acid secretion (white bar), control pentagastrin (black bar), and escalating doses of **26d** (0.30, 1.0, 3.0, and 10 μmol/kg, gray bars). The oral ED_{50} was calculated to be 0.57 mg/kg (1.1 μmol/kg). Thus, compound **26d** was found to be a potent inhibitor of gastric acid secretion in the rat when dosed orally.

Conclusion

We have described the identification and preliminary structural optimization of a novel series of highly selective cholecystokinin-2 receptor antagonists based on an anthranilic sulfonamide core. High affinity for the human CCK-2 receptor was shown to require a heterocyclic sulfonamide ring system possessing two nitrogen atoms—putative hydrogen bond accepting groups—situated *ortho* and *meta* around a phenylsulfonamide ring (e.g., 2,1,3-benzothiadiazole-4-sulfonyl or quinoxaline-5-sulfonyl ring systems).

Additionally, extensive SAR studies showed the importance of anthranilic ring halogenation and lipophilicity of the amide moiety to achieve high CCK-2 receptor affinity. Little to no affinity of these compounds for the related CCK-1 receptor was observed. In vitro measures of membrane permeability and log D predict that compounds in this series are expected to have good absorption from the oral dose in vivo, and pharmacokinetic studies in the rat and dog have borne this out. However, we found that stability toward liver microsome preparations of the compounds in the benzothiadiazole series predicts a high degree of phase I metabolism. This was supported by in vivo pharmacokinetic studies in the rat revealing relatively high clearance rates. Improvements in both in vivo clearance and half-life were achieved by replacing the benzothiadiazole and piperidine rings and varying the nature of the halogenation of compound **5** to give **26d**. These compounds were shown to be potent inhibitors of gastric acid secretion in the rat when dosed via either intravenous (compound **5**) or oral (**26d**) routes of administration. Further in vivo studies investigating reversal of the trophic actions of gastrin by compounds in this series are currently underway.

Structural studies of this series of compounds using X-ray, NMR, molecular modeling, and synthetic analysis have been undertaken and are the subjects of future disclosures from our laboratories, as are the results of further optimization toward reducing oxidative metabolism and in vivo efficacy studies.

Experimental Section

General. Except where indicated, materials and reagents were used as supplied. Reaction monitoring was performed with EMD Silica Gel 60 F_{254} 250 μm precoated TLC plates and visualized with UV light. Routine chromatographic purifications were performed via semiautomated MPLC, using prepacked RediSep 35−60 μm silica gel columns on ISCO Sg100 systems with UV peak detection. Semipreparative HPLC purification was performed on a Gilson automated HPLC system running Gilson Unipoint LC software with UV peak detection at 220 nm and fitted with a reverse phase YMC-Pack ODS-A 250 × 30 mm column; mobile-phase gradients consisted of mixtures of MeCN and water with 0.05% TFA and flow rates of 10−20 mL/min. Analytical LC spectra were collected on an Agilent/HP1100 LC system with diode array UV (220 and 254 nm) detection and either on a MeCN/water/0.1% HCOOH solvent gradient running on an Agilent Eclipse XDB-C8 5 μm column (HPLC-A) or on a Phenomenex Gemini, 5 m, C_{18} 4.6 × 150 mm column running a 1 to 99% gradient of MeCN and 20 mM aqueous NH_4OH over 7 min at 1.5 mL/min (HPLC-B). MS and LCMS spectra were recorded on a system identical to HPLC-A coupled with Agilent single quadrupole electrospray MSD mass detection. Proton NMR spectra were recorded at either 400 or 500 MHz using Bruker DPX-400 and DPX-500 spectrometers and were taken in $CDCl_3$ at ambient temperature unless otherwise noted. High-resolution mass spectra (HRMS) were determined on a Bruker microTOF instrument with internal calibration based on sodium formate ion clusters. Melting point determinations were made using a Stanford Research Systems OptiMelt system and are uncorrected. Combustion analyses were performed by NuMega Resonance Labs, Inc., San Diego, CA. Bioanalytical quantitation was performed via mass spectrometry using either a Finnigan Quantum Ultra system (Thermo Electron Corp.) or an API-4000 system (Applied Biosystems).

General Procedure for the Preparation of Anthranilic Piperidine Amides 11 from Isatoic Anhydrides 18. To a stirred solution of isatoic anhydride (**18**; 1 equiv) in 5:1 THF and DMF (0.2 M final concentration) was added DMAP (0.1 equiv) and piperidine (1 equiv). The reaction mixture was stirred at room temperature for 16 h. Ethyl acetate was added, and the organic layer was washed with H_2O (2×), dried (Mg_2SO_4), filtered, and concentrated in vacuo to yield crude anthranilic piperidine amide **11** and used directly without further purification.

General Procedure for Sulfonamide Formation, Method A: Purification by Silica Gel Chromatography. The sulfonyl chloride (1 equiv) was added to a solution of anthranilic piperidine amide **11** (1 equiv) and pyridine (1.1 equiv) in DCM or DCE (0.1 M final concentration). The mixture was left standing overnight at ambient

temperature. Then the volatiles were stripped in vacuo, and the resulting oil was taken up in EtOAc and washed with 1 N HCl. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified on silica gel (MPLC, hexanes/EtOAc) to provide sulfonamides.

General Procedure for Sulfonamide Formation, Method B: Purification by Resin Capture. To a solution of the aniline **11** (1 equiv) in DCM (0.2 M) and pyridine (5 equiv) was added arylsulfonyl chloride (2 equiv) in a 20 mL vial, and the sealed reaction mixture was shaken at room temperature for several hours until the reaction was complete, as indicated by TLC analysis. Excess sulfonyl chloride was removed by the addition of 5 equiv of PS-trisamine resin (tris-(2-aminoethyl)-amine polystyrene; 3.0 mmol/g; Biotage AB, Sweden), shaking for 1 h, followed by filtration to remove resin. The crude sulfonamide was purified by the addition of 5 equiv of TBD-methyl polystyrene resin (1,5,7-triazabicyclo[4.4.0]dec-5-ene polystyrene; Merck Biosciences AG; 2−3 mmol/g) in DCM, agitation for 1 h, filtration and washing of the resin with DCM (3×), and finally release of the purified sulfonamide product by treating the resin with a 10% trifluoroacetic acid solution in DCM for 30 min, followed by filtration and removal of solvent under reduced pressure.

General Procedure for HATU-Mediated Amide Bond Formation: Conversion of Benzoic Acids 16 and 17 to Sulfonamides 24−26. To a solution of carboxylic acid **16** or **17** in DMF (0.1−0.2 M) were added pyridine (3 equiv) and HATU (2 equiv). If the amine was in a salt form, DIPEA (2 equiv) was also added. The mixture was agitated for 1 h on a shaker. The desired amine (2 equiv) was then added. Agitation was continued for 1 h. After quenching with trifluoroacetic acid, the mixture was diluted with DMF and purified by preparative reversed-phase HPLC.

General Procedure for the Reduction of Nitroarenes to Anilines. A solution of the nitroarene (1 equiv) in EtOAc/DCM (3:1, 0.1 M) was treated with solid $SnCl_2 \cdot 2H_2O$ (5 equiv). The mixture was stirred at ambient temperature for 12 h and then poured cautiously into saturated aqueous $NaHCO_3$. The resulting gelatinous emulsion was filtered through a pad of Celite, and the biphasic filtrate was extracted with DCM (5×). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo, affording the anilines that were purified by silica gel chromatography (MPLC, EtOAc in hexanes, gradient).

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-5-chlorobenzoyl]-piperidine (1). The preparation from 1-(2-amino-5-chlorobenzoyl)piperidine (**11a**; 60 mg, 0.25 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol), as described in the general procedure for sulfonamide formation, method A, provided the product (41 mg, 0.094 mmol, 38%). MS (ESI): *m*/*z* 437/439 $[M + H]^+$, 459/461 $[M + Na]^+$. HPLC-A: $t_R = 9.56$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.68 (s, 1H), 8.25 (dd, $J = 8.8$, 1.0 Hz, 1H), 8.22 (dd, $J = 7.1$, 1.2 Hz, 1H), 7.69 (dd, $J = 8.8$, 7.1 Hz, 1H), 7.61 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.04 (d, $J = 2.4$ Hz, 1H), 3.6−2.8 (br m, 4H), 1.60 (br s, 2H), 1.45 (br m, 4H). Anal. ($C_{18}H_{17}ClN_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-benzoyl]-piperidine (2). Compound **2** was prepared from 1-(2-aminobenzoyl)-piperidine (**11b**; 51 mg, 0.25 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol) in 1.5 mL DCE, as described in the general procedure for sulfonamide formation (26 mg, 0.065 mmol; 26%). MS (ESI): *m*/*z* 403.2 $[M + H]^+$, 425.2 $[M + Na]^+$. HPLC-A: $t_R = 8.93$ min (96%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.84 (s, 1H), 8.20 (dd, $J = 4.0$, 1.0 Hz, 1H), 8.19 (dd, $J = 5.8$, 1.0 Hz, 1H), 7.64 (dd, $J = 7.0$, 8.8 Hz, 1H), 7.60 (d, $J = 8.2$ Hz, 1H), 7.27 (m, 2H), 7.01 (m, 2H), 3.6−2.8 (br m, 4H), 1.57 (m, 2H), 1.42 (br s, 4H). Anal. ($C_{18}H_{18}N_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-5-bromobenzoyl]-piperidine (3). Compound **3** was prepared from **11c** (71 mg, 0.25 mmol), pyridine (0.031 mL, 0.38 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol), as described in the general procedure for sulfonamide formation, method A, to provide the title sulfonamide as an amorphous solid (30 mg, 0.062 mmol, 25%). HPLC: $t_R = 9.67$ min (>99%). MS (ESI): *m*/*z* 481 $[M + H]^+$, 503 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.67 (s, 1H), 8.23 (dd, $J = 8.8$, 1.1 Hz, 1H), 8.21 (dd, $J = 7.0$, 1.1 Hz, 1H), 7.67 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.40 (dd, $J = 8.8$, 2.3 Hz, 1H), 7.17 (d, $J = 2.3$ Hz, 1H), 3.75−2.65 (br m, 4H), 1.90−1.30 (br m, 6H). Anal. ($C_{18}H_{17}BrN_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-piperidine (4). Compound **4** was prepared from **11d** (59 mg, 0.25 mmol), pyridine (0.030 mL, 0.38 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol), as described in the general procedure for sulfonamide formation, method A. The product was further purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% trifluoroacetic acid (TFA)) to provide **4** as a solid (31 mg, 0.071, 28%). Mp 142−145 °C. HPLC-A: $t_R = 9.63$ min (>99%). MS (ESI): *m*/*z* 437 $[M + H]^+$, 459 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.01 (s, 1H), 8.17 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.13 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.59 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.56 (dd, $J = 1.5$, 0.6 Hz, 1H), 6.89 (abx, $J = 8.0$, 1.5, 0.6 Hz, 2H), 3.70−2.70 (br s, 4H), 1.70−1.30 (br m, 6H). Anal. ($C_{18}H_{17}ClN_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-bromobenzoyl]-piperidine (5). Compound **5** was prepared from 4-bromo-2-aminobenzoic acid piperidine amide (**11e**; 145 mg, 0.51 mmol), pyridine (0.062 mL, 0.76 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (129 mg, 0.55 mmol), as described in the general procedure for sulfonamide formation to provide the title sulfonamide as an off-white solid (180 mg, 0.37 mmol, 74%). HPLC-A: $t_R = 9.68$ min (>99%). MS (ESI): *m*/*z* 481/483 $[M + H]^+$, 503 $[M + Na]^+$; negative ion *m*/*z* 479/481 $[M - H]^-$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.95 (s, 1H), 8.25 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.21 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.80 (d, $J = 1.8$ Hz, 1H), 7.68 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.14 (dd, $J = 8.2$, 1.8 Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 1H), 3.70−2.70 (br m, 4H), 1.80−1.30 (br m, 6H). Anal. ($C_{18}H_{17}BrN_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)methylamino]-4-bromobenzoyl]-piperidine (6). To a solution of **5** (24 mg, 0.050 mmol) in DMF (1 mL) was added Cs_2CO_3 (33 mg, 0.12 mmol) and MeI (0.01 mL, 0.16 mmol). The mixture was stirred 2 h at ambient temperature, poured into aqueous 1 N HCl, and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to provide the crude product as a white paste. The crude material was triturated with cold MeOH to give **6** (16 mg, 0.032 mmol, 64%) as a white powder, which was collected by suction filtration and air-dried. HPLC-A: $t_R = 9.40$ min (>99%). MS (ESI): *m*/*z* 496 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.30 (dd, $J = 8.8$, 1.0 Hz, 1H), 8.18 (dd, $J = 7.1$, 1.0 Hz, 1H), 7.72 (dd, $J = 8.8$, 7.1 Hz, 1H), 7.47 (dd, $J = 8.2$, 1.9 Hz, 1H), 7.14 (d, $J = 8.2$ Hz, 1H), 7.02 (d, $J = 1.9$ Hz, 1H), 3.94−3.85 (br m, 1H), 3.47 (s, 3H), 3.43−3.20 (br m, 3H), 3.43−3.20 (br m, 3H), 1.76−1.53 (br m, 5H), 1.52−1.39 (br m, 1H). Anal. ($C_{19}H_{19}BrN_4O_3S_2$) C, H, N.

1-[3-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-piperidine (7). To a stirred solution of 3-amino-4-chlorobenzoic acid (0.5 g, 2.91 mmol) in acetonitrile (10 mL) and DMF (10 mL) was added EDC (0.67 g, 3.50 mmol) and piperidine (0.34 mL, 3.50 mmol). The reaction mixture was stirred at room temperature for 16 h. NaOH (1 M) was added, and the aqueous layer was extracted with EtOAc. The organic layer was washed with H_2O (2×), dried (Mg_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified on silica gel to provide 1-(3-amino-4-chlorobenzoyl)-piperidine (0.31 g, 1.3 mmol, 45%). MS (ESI): *m*/*z* 239 $[M + H]^+$, 261 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 7.24 (d, $J = 8.1$ Hz, 1H), 6.79 (d, $J = 1.9$ Hz, 1H), 6.67 (dd, $J = 8.1$, 1.9 Hz, 1H), 4.13 (br s, 2H), 3.67 (br s, 2H), 3.34 (br s, 2H), 1.66 (br s, 4H), 1.50 (br s, 2H).

The title compound (**7**) was prepared from 2,1,3-benzothiadiazole-4-sulfonyl chloride (300 mg, 1.30 mmol) and 3-amino-4-chlorobenzoic acid piperidine amide (0.31 g, 1.3 mmol) and purified, as decribed in the general procedure for sulfonamide

preparation, method A, to provide the product as an amorphous solid (220 mg, 0.50 mmol, 38%). HPLC-B: t_R = 3.72 min (>99%). MS (ESI): *m/z* 437 $[M + H]^+$, 459 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.26−8.22 (m, 2H), 7.91 (s, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.66 (dd, J = 8.8, 7.0 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.01 (dd, J = 8.2, 1.8 Hz, 1H), 3.67 (br s, 2H), 3.27 (br s, 2H), 1.69 (br s, 4H), 1.53 (br s, 2H). HRMS (ESI): calcd for $C_{18}H_{17}N_4O_3S_2Cl$ $[M + H]^+$, 437.0503; found, 437.0503.

1-[4-Bromo-2-[5-methyl(2,1,3-benzothiadiazol-4-ylsulfonyl)-amino]-benzoyl]-piperidine (19a). Compound **19a** was prepared from **11e** (150 mg, 0.53 mmol), 5-methylbenzo[2,1,3]thiadiazole-4-sulfonyl chloride (130 mg, 0.53 mmol), and pyridine (0.22 mL, 0.22 mmol), as described in the general procedure for sulfonamide preparation, method A. This material was further purified by trituration with Et_2O to provide **19a** as a colorless solid (130 mg, 0.26 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.09 (s, 1H), 8.05 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.14 (dd, J = 6.5, 1.5 Hz, 1H), 6.93 (d, J = 6.5 Hz, 1H), 3.0−3.8 (br m, 4H), 2.93 (s, 3H), 1.44−1.65 (br m, 6H). MS (ESI): *m/z* 496.3 $(MH)^+$. Anal. ($C_{19}H_{19}BrN_4O_3S_2$) C, H, N.

1-[4-Bromo-2-[7-methyl(2,1,3-benzothiadiazol-4-ylsulfonyl)-amino]-benzoyl]-piperidine (19b). Compound **19b** was prepared from 7-methylbenzo[2,1,3]thiadiazole-4-sulfonyl chloride[39] (130 mg, 0.53 mmol) and **11e** (150 mg, 0.53 mmol), as described in the general procedure for sulfonamide preparation, method A. The product was further purified by trituration with ether providing **19b** as a light yellow solid (200 mg, 0.40 mmol, 75%). Mp 163−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 8.92 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 1.8 Hz, 1H), 7.42 (dd, J = 7.2, 1.0 Hz, 1H), 7.14 (dd, J = 8.2, 1.8 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 3.7−2.8 (br m, 4H), 2.80 (d, J = 1.0 Hz, 3H), 1.8−1.2 (br m, 6H). MS (ESI): *m/z* 496 $(MH)^+$. Anal. ($C_{21}H_{20}BrN_3O_3S$) C, H, N.

1-[2-[7-Bromo(2,1,3-benzothiadiazol-4-ylsulfonyl)amino]-4-bromobenzoyl]-piperidine (19c). Compound **19c** was prepared from 7-bromobenzo[2,1,3]thiadiazole-4-sulfonyl chloride[40] (0.28 g, 0.91 mmol) and **11e** (0.26 g, 0.91 mmol) and purified as described in the general procedure for sulfonamide preparation, method A, affording **19c** (120 mg, 0.21 mmol, 23%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.02 (s, 1H), 8.23 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.18 (dd, J = 8.2, 1.8 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 2.8−3.7 (br m, 4H), 1.58−1.65 (br m, 2H), 1.35−1.57 (br m, 4H). MS (ESI): *m/z* 560.8 $(MH)^+$. Anal. ($C_{18}H_{16}Br_2N_4O_3S_2$) C, H, N.

1-[4-Bromo-2-[5-fluoro(2,1,3-benzothiadiazol-4-ylsulfonyl)-amino]-benzoyl]-piperidine (19d). A solution of 5-fluorobenzo-[2,1,3]thiadiazole (1.0 g, 6.5 mmol) and chlorosulfonic acid (2 mL) was heated to 140 °C for 2 h. The dark mixture was then allowed to cool to 23 °C and was carefully poured over crushed ice. The resulting precipitate was collected and recrystallized from EtOAc/hexanes to provide 5-fluoro[2,1,3]thiadiazole-4-sulfonyl chloride as a tan solid (250 mg, 15%).

The sulfonyl chloride (0.15 g, 0.60 mmol) was immediately treated with **11e** (0.16 g, 0.57 mmol) and purified as described in the general procedure for sulfonamide formation, method A. The product was then triturated with Et_2O to provide **19d** as a colorless solid (180 mg, 0.35 mmol, 62%). Mp 164−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.24 (s, 1H), 8.20 (dd, J = 7.6, 3.7 Hz, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.53 (t, J = 9.9 Hz, 1H), 7.16 (dd, J = 8.2, 1.8 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 3.00−3.70 (br m, 4H), 1.45−1.70 (br m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 162.7, 160.5, 151.8, 150.1, 136.7, 128.9, 127.7, 127.6, 126.9, 124.8, 123.8, 123.6, 121.8, 121.6, 116.8, 116.7, 26.0, 24.3. HPLC-A: t_R = 9.45, >99%. HPLC-B: t_R = 4.08, >99%. HRMS (ESI): calcd for $C_{18}H_{17}BrFN_4O_3S_2$ $[M + H]^+$, 498.9904; found, 498.9884.

1-[2-[(2,1,3-Benzooxadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-piperidine (20). Compound **20** was prepared from **11d** (72 mg, 0.30 mmol), pyridine (0.036 mL, 0.45 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (69 mg, 0.31 mmol) and purified as described in the general procedure for sulfonamide formation, method A, to provide the product as a yellow oil, which solidified upon standing (90 mg, 0.21 mmol, 71%). HPLC-A: t_R = 9.69 min (>99%). MS (ESI): *m/z* 421 $[M + H]^+$, 443 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (br s, 1H), 8.04 (dd, J = 2.9, 0.7 Hz, 1H), 8.02 (dd, J = 5.2, 0.8 Hz, 1H), 7.68 (dd, J = 1.7, 0.5 Hz, 1H), 7.48 (dd, J = 9.1, 6.8 Hz, 1H), 7.01−6.95 (m, 2H), 3.36−3.00 (m, 4H), 1.62−1.54 (m, 2H), 1.47−1.34 (m, 4H). Anal. ($C_{18}H_{17}ClN_4O_4S\cdot0.1C_6H_{14}$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-5-ylsulfonyl)amino]-4-bromobenzoyl]-piperidine (21). Compound **21** was prepared from **11e** (50 mg, 0.18 mmol), 2,1,3-benzothiadiazole-5-sulfonyl chloride (85 mg, 353 mmol), and pyridine (0.10 mL, 1.2 mmol) and purified as described in the general procedure for sulfonamide formation, method B, to yield **21** as an amorphous solid (20 mg, 0.042 mmol, 24%). MS (ESI): *m/z* 481 $[M + H]^+$, 503 [M + Na]. HPLC-A: t_R = 9.69 min (>99%). HPLC-B: t_R = 4.07 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.01 (s, 1H), 8.58 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.98 (dd, J = 9.2, 1.8 Hz, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.23 (dd, J = 8.2, 1.8 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 3.15 (br s, 4H), 1.57−1.51 (br m, 6H). HRMS (ESI): calcd for $C_{18}H_{18}BrN_4O_3S_2$ $[M + H]^+$, 480.9998; found, 480.9981.

1-[4-Bromo-2-[(isoquinolin-5-ylsulfonyl)amino]-benzoyl]-piperidine (22a). Compound **22a** was prepared from **11e** (100 mg, 0.35 mmol), pyridine (0.14 mL, 1.8 mmol), and isoquinoline-5-sulfonyl chloride (160 mg, 0.70 mmol; prepared from isoquinoline-5-sulfonyl chloride hydrochloride, 0.18 g, and aqueous $NaHCO_3$, followed by extraction with DCM) and purified as described in the general procedure for the preparation of sulfonamides, method A, providing **22a** as a colorless solid (13 mg, 0.027 mmol, 8%). Mp 196−197 °C. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.34 (s, 1H), 9.21 (br s, 1H), 8.75 (d, J = 4.9 Hz, 1H), 8.42 (d, J = 6.0 Hz, 1H), 8.37 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 3.21 (br s, 2H), 2.53 (br s, 2H), 1.40−1.55 (br m, 3H), 0.90−1.15 (br m, 3H). MS (ESI): *m/z* 475.3 $(MH)^+$. Anal. ($C_{21}H_{20}BrN_3O_3S$) C, H, N.

1-[4-Chloro-2-[(quinolin-8-ylsulfonyl)amino]-benzoyl]-piperidine Trifluoroacetic Acid Salt (22b). Compound **22b** prepared from **11d** (50 mg, 0.21 mmol), pyridine (1.3 mmol, 0.10 mL), and quinoline-8-sulfonyl chloride (95 mg, 0.42 mmol), as described in the general procedure for sulfonamide formation, method B, to provide the title compound as a TFA salt (71 mg, 0.17 mmol, 80%). HPLC-A: t_R = 9.69 min (>97%). HPLC-B: t_R = 4.87 min (>99%). MS (ESI): *m/z* 430 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 10.70 (br s, NH + TFA), 9.39 (d, J = 4.1 Hz, 1H), 8.88 (d, J = 8.2 Hz, 1H), 8.47 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 8.2, 1H), 8.02 (dd, J = 5.0, 8.0 Hz, 1H), 7.83 (t_{app}, J = 7.8 Hz, 1H), 7.53 (br s, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 3.42 (br s, 2H), 3.16 (br s, 2H), 1.6−1.2 (m, 6H). HRMS (ESI): calcd for $C_{21}H_{20}ClN_3O_3S$ $[M + H]^+$, 430.0987; found, 430.0980.

1-[4-Bromo-2-[(quinolin-5-ylsulfonyl)amino]-benzoyl]-piperidine (22c). Compound **22c** prepared from **11e** (0.17 g, 0.69 mmol) and **32** (0.17 g, 0.76 mmol) and purified following the general procedure for the preparation of sulfonamides, method A, to afford **22c** as a colorless solid (260 mg, 0.55 mmol, 80%). Mp 181−182 °C. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 8.98−9.10 (m, 3H), 8.29 (d, J = 8.5 Hz, 1H), 8.21 (dd, J = 7.3, 0.8 Hz, 1H), 7.88 (d, J = 1.6 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.59−7.64 (m, 1H), 7.18 (dd, J = 8.1, 1.2 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 2.30−3.30 (br m, 4H), 1.05−1.55 (br m, 6H). MS (ESI): *m/z* 475.9 $(MH)^+$. Anal. ($C_{21}H_{20}BrN_3O_3S$) C, H, N.

1-[4-Bromo-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-piperidine (22d). Compound **22d** was prepared from **29** (0.15 g, 0.64 mmol) and **11e** (180 mg, 0.64 mmol) and purified as described in the general procedure for sulfonamide formation, method A, to provide **22d** as a pale yellow solid (0.049 g, 0.10 mmol, 16%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.07 (d, J =

1.8 Hz, 1H), 9.05 (br s, 1H), 9.00 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 7.0, 1.5 Hz, 1H), 8.34 (dd, J = 8.4, 1.4 Hz, 1H), 7.87 (dd, J = 8.4, 7.4 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.15 (dd, J = 8.0, 1.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 3.31 (br m, 2H), 2.86 (br m, 2H), 1.41 (br m, 6H). MS (ESI): m/z 475.3 $(MH)^+$, 497 $(M + Na)^+$. Anal. ($C_{20}H_{19}BrN_4O_3S$) C, H, N.

1-[4-Bromo-2-[[naphthalen-1-ylsulfonyl]amino]benzoyl]-piperidine (22e). Compound **22e** was prepared from **11e** (50 mg, 0.35 mmol), naphthalene-1-sulfonyl chloride (79 mg, 0.35 mmol), and pyridine (0.500 μL, 6.0 mmol) and purified as described in the general procedure for sulfonamide formation, method B, to yield **22e** as an amorphous solid (52 mg, 0.11 mmol, 31%). MS (ESI): m/z 473 $[M + H]^+$, 495 $[M + Na]^+$. HPLC-A: t_R = 10.26 min (>99%). HPLC-B: t_R = 4.36 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.01 (s, 1H), 8.65 (d, J = 8.6 Hz, 1H), 8.18 (dd, J = 7.3, 1.0 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.93−7.92 (m, 2H), 7.72 (dt, J = 7.0, 1.2 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.14 (dd, 1H, J = 8.2, 1.8 Hz), 6.82 (d, J = 8.2, 1H), 3.14 (br s, 2H), 2.40 (br s, 2H), 1.41−1.07 (br m, 6H). Anal. Calcd for $C_{22}H_{21}BrN_2O_3S$ (C, H, N): C, 55.82; H, 4.47; N, 5.92. Found: C, 55.45; H, 4.66; N, 6.11. HRMS (ESI): calcd for $C_{22}H_{22}BrN_2O_3S$ $[M + H]^+$, 473.0529; found, 473.0529.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-3-chlorobenzoyl]-piperidine (23a). Compound **23a** was prepared from aniline **11l** (0.25 mmol, 60 mg), pyridine (0.031 mL, 22 mg), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (0.26 mmol, 61 mg) and purified as described in the general procedure for sulfonamide formation, method B, to proved **20a** contaminated with about 10% of **11l** (2.9 mg, 0.0066 mmol, 3%). HPLC-A: t_R = 8.29 min (90%). HPLC-B: t_R = 3.58 min (91%). MS (ESI): m/z 437 $[M + H]^+$, 459 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J = 8.83, 1.05 Hz, 1H), 8.20 (dd, J = 7.02, 1.04 Hz, 1H), 7.75 (br s, 1H), 7.43 (d, J = 1.86 Hz, 1H), 7.41 (d, J = 1.86 Hz, 1H), 7.31−7.26 (m, 1H), 4.03−3.13 (m, 5H), 1.93−1.50 (m, 6H). HRMS (ESI): calcd for $C_{18}H_{17}ClN_4O_3S_2$ $[M + H]^+$, 437.0503; found, 437.0506.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-3-methylbenzoyl]-piperidine (23b). Compound **23b** was prepared from aniline **11m** (55 mg, 0.25 mmol), pyridine (0.031 mL, 22 mg), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol) and purified as described in the general procedure for sulfonamide formation, method B, to provide the title compound (21 mg, 0.050 mmol, 20%). HPLC-A: t_R = 8.59 min (>99%). HPLC-B: t_R = 3.94 min (98%). MS (ESI): m/z 417 $[M + H]^+$, 439 $[M + Na]^+$, 855 $[2M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 8.82, 1.06 Hz, 1H), 8.08 (dd, J = 6.99, 1.07 Hz, 1H), 8.06 (br s, 1H), 7.68 (dd, J = 8.81, 7.01 Hz, 1H), 7.30 (d, J = 1.06 Hz, 1H), 7.16 (t, J = 7.61, 7.61 Hz, 1H), 6.92 (dd, J = 7.52, 1.01 Hz, 1H), 3.6−3.0 (m, 4H), 2.41 (s, 3H), 1.72−1.49 (m, 2H), 1.45−1.28 (m, 4H). HRMS (ESI): calcd for $C_{19}H_{20}N_4O_3S_2$ $[M + H]^+$, 417.1050; found, 417.1052.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-6-chlorobenzoyl]-piperidine (23c). To a solution of 2-amino-6-chlorobenzoic acid (1.2 g, 7.0 mmol) in acetonitrile (17 mL) was added piperidine (0.63 mL, 6.3 mmol), followed by EDC (1.46 g, 7.6 mmol) and DMF (21 mL). The mixture was stirred at ambient temperature overnight. An additional 20 mol % piperidine and EDC was added, and the reaction mixture was stirred 3 h. The mixture was diluted with EtOAc and washed repeatedly with 1 N NaOH and then brine. The organic layer was dried (Na_2SO_4), filtered, and purified on silica gel (MPLC, hexanes/EtOAc, 15−70%) to provide **11k** as a white solid (0.21 g), which was used directly.

The title compound was prepared from amide **11k** (60 mg, 0.25 mmol), 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol), and pyridine (0.031 mL, 0.38 mmol) and purified as described in the general procedure for sulfonamide formation, method A, to provide the title sulfonamide as an off-white solid (3 mg, 0.007 mmol, 3%). HPLC-A: t_R = 9.15 min (>99%). MS (ESI): m/z 437 $[M + H]^+$, 459 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.24 (dd, J = 3.3, 1.0 Hz, 1H), 8.23 (dd, J = 1.6, 1.0 Hz, 1H), 7.71 (s, 1H), 7.68 (dd, J = 8.7, 7.2 Hz, 1H), 7.31 (dd, J = 8.1, 1.0 Hz, 1H), 7.16 (dd, J = 8.1, 8.1 Hz, 1H), 7.10 (dd, J = 8.1, 1.0 Hz, 1H), 3.67 (m, 1H), 3.54 (m, 1H), 3.16 (m, 1H), 3.02 (m, 1H), 1.65 (m, 5H), 1.48 (m, 1H). HRMS (ESI): calcd for $C_{18}H_{17}N_4ClO_3S_2$ $[M + H]^+$, 437.0503; found, 437.0518.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(benzylamino)benzoyl]-piperidine (23d). To a stirred solution of **23g** (50 mg, 0.12 mmol) in DCM (2 mL) was added benzaldehyde (18 μL, 0.18 mmol), acetic acid (28 μL, 0.48 mmol), and sodium triacetoxyborohydride (51 mg, 0.24 mmol). The reaction mixture was stirred at room temperature for 16 h. Saturated $NaHCO_3$ solution was added, and the aqueous layer was extracted with EtOAc (3×). The organic layer was removed, dried, and purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% TFA) to afford the title compound (26 mg, 0.051 mmol, 43%). Mp 168−170 °C. HPLC-A: t_R = 7.67 min (>99%). MS (ESI): m/z 508 $[M + H]^+$. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.61 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 7.0 Hz, 1H), 7.55 (dd, J = 8.7, 7.1 Hz, 1H), 7.37−7.31 (m, 5H), 6.92 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.20 (m, 1H), 4.33 (s, 2H), 3.18 (br s, 4H), 1.55 (br m, 3H), 1.42 (br s, 4H). Anal. ($C_{25}H_{25}N_5O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-methoxybenzoyl]-piperidine (23e). Compound **10r** (70 mg, 0.27 mmol) was reduced with $SnCl_2 \cdot 2H_2O$ (300 mg, 1.32 mmol) as described in the general procedure for nitroarene reduction to afford crude **11r** (49 mg, 0.21 mmol; MS (ESI): m/z 235 $[M + H]^+$, 257 $[M + Na]^+$), which was used directly in the next step. The title compound was prepared from **11r** (49 mg, 0.21 mmol), pyridine (0.034 mL, 0.32 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol), as described in the general procedure for the preparation of sulfonamides, method A, to give **23e** as a white solid (40 mg, 0.093 mmol, 44%). Mp 164−167 °C. MS (ESI): m/z 433 $[M + H]^+$, 455 $[M + Na]^+$. HPLC-A: t_R = 9.08 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.34 (s, 1H), 8.23 (dd, J = 7.0, 1.0 Hz, 2H), 7.66 (m, 1H), 7.22 (dd, J = 5.5, 2.5 Hz, 1H), 6.98 (d, J = 12 Hz, 1H), 6.53 (dd, J = 8.6, 2.5 Hz, 1H), 3.79 (s, 3H), 3.20−3.10 (br s, 4H), 1.63−1.58 (m, 2H), 1.43 (br s, 4H). Anal. ($C_{19}H_{20}N_4O_4S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(cyclopentyloxy)benzoyl]-piperidine (23f). Compound **10s** (60 mg, 0.19 mmol) in 1:1 DCM/EtOAc (8 mL), was reduced with $SnCl_2 \cdot 2H_2O$ (210 mg, 0.94 mmol) as described in the general procedure for nitroarene reduction to provide crude **11s** (40 mg, 0.14 mmol, 73%). This material was used directly in the subsequent reaction. The title compound was prepared from **11s** (40 mg, 0.14 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (40 mg, 0.17 mmol) and purified as described in the general preparation of sulfonamides, method A, to give **23f** as an amorphous solid (10 mg, 0.020 mmol, 15%). HPLC-A: t_R = 10.45 min (>99%). HPLC-B: t_R = 4.46 min (>99%). MS (ESI): m/z 487 $[M + H]^+$, 509 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.35 (s, 1H), 8.22 (dd, J = 7.0, 1.0 Hz, 2H), 7.66 (m, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.93 (d, J = 12 Hz, 1H), 6.48 (dd, J = 8.6, 2.5 Hz, 1H), 4.73−4.69 (m, 1H), 3.16 (br s, 4H), 2.04 (m, 2H), 1.76 (m, 4H), 1.60 (m, 4H), 1.42 (m, 4H). HRMS (ESI): calcd for $C_{23}H_{26}N_4O_4S_2$ $[M + H]^+$, 487.1468; found, 487.1475.

1-[4-Amino-2-[(2,1,3-benzothiadiazol-4-ylsulfonyl)amino]-benzoyl]-piperidine (23g). Compound **23g** was prepared via reduction of **23y** (0.99 g, 2.2 mmol) with $SnCl_2 \cdot 2H_2O$ (2.5 g, 11.1 mmol) and purified as described in the general procedure for the reduction of nitroarenes to provide **23g** (0.67 g, 1.61 mmol, 73%). MS (ESI): m/z 418 $[M + H]^+$, 440 $[M + Na]^+$. HPLC-A: t_R = 8.15 min (>99%). HPLC-B: t_R = 3.42 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.80 (s, 1H), 8.40 (dd, J = 8.8, 1.0 Hz, 1H), 8.15 (dd, J = 7.0, 1.0 Hz, 1H), 7.82 (dd, J = 8.8, 1.0 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.19 (dd, J = 8.4, 2.3 Hz, 1H), 5.75 (d, J = 2.3 Hz,

2H), 2.96 (br s, 4H), 1.45 (br s, 2H), 1.24 (br s, 4H). HRMS (ESI): calcd for $C_{18}H_{19}N_5O_3S_2$ $[M + H]^+$, 418.1002; found, 418.0999.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(dimethylamino)benzoyl]-piperidine (23h). To a stirred solution of **23g** (50 mg, 0.12 mmol) in DCM (2 mL) was added formaldehyde (37 wt % in water; 0.45 mL, 6.0 mmol), sodium cyanoborohydride (1.0 M in THF; 1.8 mL, 1.8 mmol), and acetic acid (68 μL). The reaction mixture was stirred for 3 h at room temperature. NaOH (1 M) was added until the solution became basic. The mixture was taken up in DCM and washed with water and brine. The organic layer was removed, dried, and purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% TFA) to afford the title compound (**23h**) as an amorphous solid (31 mg, 0.070 mmol, 58%). MS (ESI): *m/z* 446 $[M + H]^+$, 468 $[M + Na]^+$. HPLC-A: $t_R = 9.14$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.61 (s, 1H), 8.22 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.18 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.63 (dd, $J = 8.8$, 7.0 Hz, 1H), 6.95 (d, $J = 2.5$, 7.0 Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 6.26 (dd, 8.7, 2.5 Hz, 1H), 3.16 (s, 4H), 2.95 (s, 6H), 1.56 (m, 2H), 1.42 (m, 4H). Anal. ($C_{20}H_{23}N_5O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(1-pyrrolo)-benzoyl]-piperidine (23i). To a stirred solution of **23g** (25 mg, 0.060 mmol) in glacial acetic acid (3 mL) was added 2,5-dimethoxytetrahydrofuran (8 μL, 0.06 mmol). The reaction mixture was heated to 120 °C for 45 min after which it was cooled to room temperature. The mixture was taken up in 4 mL of DCM and washed with water. The organic layer was removed, dried, and purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% TFA) to afford the title compound as an amorphous solid (12 mg, 0.026 mmol, 43%). MS (ESI): *m/z* 468 $[M + H]^+$, 490 $[M + Na]^+$. HPLC-A: $t_R = 9.71$ min (>99%). HPLC-B: $t_R = 4.15$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.15 (s, 1H), 8.26 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.22 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.74 (d, $J = 2.1$ Hz, 1H), 7.67 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.10 (d, $J = 8.3$ Hz, 1H), 7.05 (m, 3H), 6.35 (t, $J = 2.2$ Hz, 2H), 3.23 (br s, 4H), 1.61 (m, 2H), 1.48 (br s, 4H). HRMS (ESI): calcd for $C_{22}H_{21}N_5O_3S_2$ $[M + H]^+$, 468.1159; found, 468.1138.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-thiomethylbenzoyl]-piperidine (23j). Compound **10u** (35 mg, 0.13 mmol) in 1:1 DCM/EtOAc (6 mL) was reduced with $SnCl_2 \cdot 2H_2O$ (141 mg, 0.62 mmol) as described in the general procedure for the reduction of nitroarenes to provide crude **11u** (30 mg, 0.12 mmol). This material was used directly in the subsequent reaction. The title compound was prepared from 2,1,3-benzothiadiazole-4-sulfonyl chloride (45 mg, 0.19 mmol) and crude **11u** (30 mg, 0.12 mmol) and purified as described in the general procedure for sulfonamide formation, method A, to provide **23j** as an amorphous solid (22 mg, 0.050 mmol, 42%). MS (ESI): *m/z* 449 $[M + H]^+$, 471 $[M + Na]^+$. HPLC-A: $t_R = 9.42$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.13 (s, 1H), 8.22 (m, 2H), 7.66 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.50 (d, $J = 1.8$ Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 1H), 6.85 (dd, $J = 8.2$, 1.8 Hz, 1H), 3.17 (br s, 4H), 2.45 (s, 3H), 1.61 (m, 2H), 1.43 (br s, 4H). Anal. ($C_{19}H_{20}N_4O_3S_3$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-ethylbenzoyl]-piperidine (23k). To a stirred solution of **10p** (98 mg, 0.39 mmol) and methanol (15 mL) was added Pd on carbon (10 wt %, 25 mg). The reaction mixture was maintained under ~1 atm H_2 and stirred for 12 h. The mixture was filtered through Celite and concentrated in vacuo to yield **10q**, which was immediately reduced with $SnCl_2 \cdot 2H_2O$ as described in the general procedure for nitroarene reduction to provide aniline **11q** as a yellow oil (90 mg, 0.39 mmol). This material was used directly in the subsequent reaction. The title compound was prepared from crude **11q** (90 mg, 0.39 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (180 mg, 0.78 mmol) and purified as decribed in the general procedure for sulfonamide formation, method A, to provide **23k** as an amorphous solid (120 mg, 0.28 mmol, 72%). MS (ESI): *m/z* 431 $[M + H]^+$, 453 $[M + Na]^+$. HPLC-A: $t_R = 9.52$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.95 (s, 1H), 8.21 (m, 2H), 7.65 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.47 (d, $J = 1.3$ Hz, 1H), 6.95 (d, $J = 7.8$ Hz, 1H), 6.85 (dd, $J = 7.9$, 1.6 Hz, 1H), 3.14 (br s, 4H), 2.60 (m, 2H), 1.61 (m, 2H), 1.43 (br s, 4H), 1.17 (t, $J = 7.6$ Hz, 3H). Anal. ($C_{20}H_{22}N_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(2-propyl)-benzoyl]-piperidine (23l). 4-Isopropyl-2-nitrobenzoic acid piperidine amide (**11h**; 0.217 g, 0.882 mmol) was coupled with 2,1,3-benzothiadiazole-4-sulfonyl chloride (0.248 g, 1.06 mmol) and pyridine (0.105 g, 1.32 mmol), and the product was purified as described in the general procedure for sulfonamide formation, method A, to provide the title sulfonamide as a solid, which was recrystallized from absolute ethanol (227 mg, 0.511 mmol, 60%). Mp 125−127 °C. MS (ESI): *m/z* 445 $[M + H]^+$, 467 $[M + Na]^+$, 911 $[2M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.22 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.20 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.65 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.49 (d, $J = 1.5$ Hz, 1H), 6.96 (d, $J = 7.9$ Hz, 1H), 6.87 (dd, $J = 7.9$, 1.5 Hz, 1H), 3.38 (br s, 4H), 2.84 (m, 1H), 1.57 (m, 3H), 1.44 (m, 3H), 1.18 (d, $J = 6.9$ Hz, 6H). Anal. ($C_{21}H_{24}N_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-phenylbenzoyl]-piperidine (23m). Compound **10n** (60 mg, 0.19 mmol) in 1:1 DCM/EtOAc (8 mL) was reduced with $SnCl_2 \cdot 2H_2O$ (218 mg, 0.97 mmol) as described in the general procedure for nitroarene reduction to provide **11n** (60 mg, 0.21 mmol), which was then taken directly to next step without further purification. The title compound was prepared from crude **11n** (60 mg, 0.21 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (50 mg, 0.21 mmol) and purified as described in the general procedure for sulfonamide formation, method A, to provide **23m** as a white solid (81 mg, 0.17 mmol, 80.%). Mp 174−177 °C. MS (ESI): *m/z* 479 $[M + H]^+$, 501 $[M + Na]^+$. HPLC-A: $t_R = 10.02$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.00 (s, 1H), 8.22 (m, 2H), 7.89 (d, $J = 1.61$ Hz, 1H), 7.65 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.52 (m, 2H), 7.44 (m, 2H), 7.37 (m, 1H), 7.25 (m, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 3.22 (br s, 4H), 1.60 (m, 2H), 1.47 (br s, 4H). Anal. ($C_{24}H_{22}N_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(2-furyl)-benzoyl]-piperidine (23n). Compound **10o** (20 mg, 0.066 mmol) was reduced with $SnCl_2 \cdot 2H_2O$ as described in the general procedure for nitroarene reduction to provide **11o** (17 mg, 0.063 mmol). This material was used directly in the subsequent reaction. The title compound was prepared from crude **11o** (17 mg, 0.063 mmol) and 2,1,3-benzothiadiazole-4-sulfonyl chloride (30 mg, 0.11 mmol) and purified as decribed in the general procedure for sulfonamide preparation to provide **23n** as an amorphous solid (12 mg, 0.026, 41%). HPLC-A: $t_R = 9.65$ min (>99%). HPLC-B: $t_R = 4.17$ min (>99%). MS (ESI): *m/z* 469 $[M + H]^+$, 491 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.01 (s, 1H), 8.26 (d, $J = 7.0$ Hz, 1H), 8.20 (d, $J = 8.8$ Hz, 1H), 7.96 (s, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.49 (s, 1H), 7.32 (d, $J = 8.0$, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.71 (d, $J = 3.2$ Hz, 1H), 6.48 (s, 1H), 3.14 (br s, 4H), 1.59 (m, 2H), 1.45 (br s, 4H). HRMS (ESI): calcd for $C_{22}H_{20}N_4O_4S_2$ $[M + H]^+$, 469.0999; found, 469.1029.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]naphthoyl]-piperidine (23o). Compound **23o** was prepared from **11w** (263 mg, 1.03 mmol), 2,1,3-benzothiadiazole-4-sulfonyl chloride (295 mg, 1.24 mmol), and pyridine (0.242 mL, 3 mmol) and purified as described in the general procedure for sulfonamide preparation, method A, to provide **23o** as an orange solid. Trituration and stirring with methanol at ambient temperature overnight provided **23o** as a white powder (310 mg, 0.68 mmol, 66%). MS (ESI): *m/z* 453 $[M + H]^+$, 475 $[M + Na]^+$. HPLC-A: $t_R = 9.7$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.88 (s, 1H), 8.26 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.19 (dd, $J = 8.8$, 1.0 Hz, 1H), 8.04 (s, 1H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.64 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.49 (arom m, 1H), 7.41 (arom m, 1H), 7.26 (s, 1H), *3*.70−2.70 (br m, 4H), 1.80−1.30 (br m, 6H). Anal. ($C_{22}H_{20}N_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-(benzoylamino)benzoyl]-piperidine (23p). To a stirred solution of **23g** (40

mg, 0.096 mmol) in DCM (2 mL) was added benzoyl chloride (22 μL, 0.19 mmol) and pyridine (16 μL, 0.19 mmol). The reaction mixture was stirred at room temperature for 16 h. Saturated $NaHCO_3$ solution was added, and the aqueous solution was extracted with DCM (3×). The organic layer was removed, dried, and purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% TFA) to afford the title compound as an amorphous solid (28 mg, 0.054, 56%). HPLC-A: t_R = 9.16 min (>99%). MS (ESI): *m/z* 522 $[M + H]^+$, 544 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.23 (s, 1H), 8.28 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.21 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.85 (m, 2H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.69−7.64 (m, 2H), 7.58−7.56 (m, 1H), 7.53−7.49 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 3.15 (br s, 4H), 1.58 (br s, 2H), 1.43 (br s, 4H). Anal. ($C_{25}H_{23}N_5O_4S_2$) C, H, N.

1-[4-Acetylamino-2-[(2,1,3-benzothiadiazol-4-ylsulfonyl)amino]benzoyl]-piperidine (23q). To a stirred solution of **23g** (30 mg, 0.072 mmol) in DCM (5 mL) was added acetyl chloride (10 μL, 0.14 mmol) and pyridine (12 μL, 0.14 mmol). The reaction mixture was stirred at room temperature for 16 h. Saturated $NaHCO_3$ solution was added, and the aqueous solution was extracted with DCM (3×). The organic layer was removed, dried, and purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% TFA) to afford the title compound as an amorphous solid (9 mg, 0.020 mmol, 27%). HPLC-A: t_R = 7.87 min (>99%). HPLC-B: t_R = 3.39 min (>99%). MS (ESI): *m/z* 460 $[M + H]^+$, 482 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.19 (s, 1H), 8.27−8.20 (m, 2H), 7.68 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 3.13 (br s, 4H), 2.18 (s, 3H), 1.57 (br s, 2H), 1.36 (br s, 4H). HRMS (ESI): calcd for $C_{20}H_{21}N_5O_4S_2$ $[M + H]^+$, 460.1108; found, 460.1101.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4,5-dichlorobenzoyl]-piperidine (23r). Prepared from aniline **11z** (5:1 mixture with 2-amino-4-chloro-5-(1-piperidino)benzoyl piperidine; 174 mg, 0.637 mmol), pyridine (0.10 mL, 0.955 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (0.179 g, 0.765 mmol) as described in the general procedure for sulfonamide formation, method A, to provide the title sulfonamide as a light yellow solid (0.115 g, 0.244 mmol, 25%, two steps). Mp 178−179 °C. MS (ESI): *m/z* ~471 $[M + H]^+$, ~493 $[M + Na]^+$. ^1H NMR (400 MHz, DMSO-d_6; rotameric broadening): δ 10.12 (br s, 1H), 8.41 (dd, *J* = 8.8, 1.0 Hz, 1H), 8.17 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.83 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 3.35 (br s, 2H), 2.88 (br s, 2H), 1.49 (m, 3H), 1.38−1.31 (m, 3H). Anal. ($C_{18}H_{16}Cl_2N_4O_3S_2$) C, H, N, S, Cl.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4,5-dibromobenzoyl]-piperidine (23s). [4,5-Dibromo-2-(piperidine-1-carbonyl)-phenyl]-carbamic acid *tert*-butyl ester (***N*-Boc-11v**; 150 mg, 0.32 mmol) was dissolved in TFA (2 mL) and allowed to stand at ambient temperature for 1 h. The TFA was removed in vacuo, and the resulting oil was taken up in DCM and washed with 5% aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the aniline as a crude oil, which was used directly without purification.

The crude aniline was coupled with 2,1,3-benzothiadiazole-4-sulfonyl chloride (91 mg, 0.39 mmol) and pyridine (0.16 mmol, 20 μL) and purified as described in the general procedure for sulfonamide formation, method A, to provide **23s** as an amorphous solid (34 mg, 0.061 mmol, 19%, two steps). HPLC-A: t_R = 10.15 min (>99%). HPLC-B: t_R = 4.28 min (>99%). MS (ESI): *m/z* 558/561/562 $[M + H]^+$, 581/582/584 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.81 (s, 1H), 8.27 (dd, *J* = 4.1, 1.0 Hz, 1H), 8.25 (dd, *J* = 6.0, 1.0 Hz, 1H), 7.95 (s, 1H), 7.71 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.28 (s, 1H), 3.3−2.8 (br s, 4H), 1.72 (m, 3H), 1.47 (m, 3H). HRMS (ESI): calcd for $C_{18}H_{16}Br_2N_4O_3S_2$ $[M + H]^+$, 558.9103; found, 558.9102.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4,5-dimethoxybenzoyl]-piperidine (23t). Compound **23t** was prepared from **11aa** (49 mg, 0.18 mmol), 2,1,3-benzothiadiazole-4-sulfonyl chloride (47 mg, 0.2 mmol), and pyridine (0.06 mL, 0.74 mmol) and purified as described in the general procedure for sulfonamide preparation, method A, to provide **23t** (3 mg, 0.007 mmol, 4%) as a colorless solid. MS (ESI): *m/z* 461 $[M - H]^-$. HPLC-A: t_R = 8.53 min (>99%). HPLC-B: t_R = 3.65 min (>99%). ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.75 (s, 1H), 8.21 (dd, *J* = 8.8, 1.1 Hz, 1H), 8.13 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.63 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.27 (s, 1H), 6.47 (s, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.15−2.85 (br m, 4H), 1.60−1.52 (br m, 2H), 1.42−1.33 (br m, 4H). HRMS (ESI): calcd for $C_{20}H_{22}N_4O_5S_2$ $[M + H]^+$, 463.1104; found, 463.1121.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chloro-5-methoxybenzoyl]-piperidine (23u). Compound **23u** was prepared from **11j** (0.11 g, 0.40 mmol), pyridine (0.070 mL, 0.60 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (0.11 g, 0.48 mmol) and purified as described in the general procedure for the preparation of sulfonamides, method A, to provide **23u** as a tan solid (0.090 g, 0.19 mmol, 48%). MS (ESI): *m/z* 467 $[M + H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.23 (dd, *J* = 8.81, 0.84 Hz, 1H), 8.18 (dd, *J* = 6.98, 0.85 Hz, 1H), 7.70−7.64 (m, 2H), 6.55 (s, 1H), 3.78 (s, 3H), 3.60−2.45 (m, 4H), 1.68−1.30 (m, 6H). Anal. ($C_{19}H_{19}ClN_4O_4S_2 \cdot 1/4H_2O$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-fluorobenzoyl]-piperidine (23v). Compound **23v** was prepared from **11g** (56 mg, 0.25 mmol), pyridine (0.031 mL, 0.38 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (61 mg, 0.26 mmol) as described in the general procedure for sulfonamide formation, method A, to provide the title sulfonamide as an off-white solid (23 mg, 0.054 mmol, 22%). HPLC-A: t_R = 9.30 min (>99%). MS (ESI): *m/z* 421 $[M + H]^+$, 443 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.18 (br s, 1H), 8.29 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.23 (dd *J* = 8.8, 1.0 Hz, 1H), 7.70 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.41 (dd, *J* = 10.8, 2.5 Hz, 1H), 7.05 (dd, *J* = 8.6, 6.1 Hz, 1H), 6.71 (dd, *J* = 8.6, 7.0, 2.5 Hz, 1H), 3.26−3.22 (br s, 4H), 1.62−1.57 (m, 2H), 1.47 (br s, 4H). Anal. ($C_{18}H_{17}FN_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-iodobenzoyl]-piperidine (23w). Compound **23w** was prepared from **11f** (190 mg, 0.58 mmol), pyridine (0.141 mL, 1.74 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (153 mg, 0.64 mmol) and purified as described in the general preparation of sulfonamides to provide **23w** as a white solid (230 mg, 0.43 mmol, 75%). HPLC-A: t_R = 9.79 min (>99%). MS (ESI): *m/z* 529 $[M + H]^+$, 551 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.90 (s, 1H), 8.27 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.24 (dd, *J* = 8.8, 1.0 Hz, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.71 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.70−2.70 (br m, 4H), 1.75−1.30 (br m, 6H). Anal. ($C_{18}H_{17}IN_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-trifluoromethylbenzoyl]-piperidine (23x). Compound **23x** was prepared from 2,1,3-benzothiadiazole-4-sulfonyl chloride (63 mg, 0.27 mmol), **11i** (70 mg, 0.26 mmol), and pyridine (0.030 mL, 0.36 mmol) and purified as described in the general procedure for the preparation of sulfonamides, method A, to afford the title compound as a white foam (46 mg, 0.098 mmol, 36%). MS (ESI): *m/z* 471 $[M + H]^+$, 493 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.86 (br s, 1H), 8.28 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.24 (dd *J* = 8.8, 1.0 Hz, 1H), 7.93 (s, 1H), 7.70 (dd, *J* = 8.8, 7.0 Hz, 1H), 7.30 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 3.49−3.44 (br s, 2H), 3.02−2.96 (br s, 2H), 1.62 (br s, 2H), 1.53−1.25 (br s, 4H). Anal. ($C_{19}H_{17}F_3N_4O_3S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-nitrobenzoyl]-piperidine (23y). Compound **23y** was prepared from **11y** (840 mg, 3.37 mmol), pyridine (0.41 mL, 5.06 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (1.02 g, 4.38 mmol) and purified as described in the general procedure for the preparation of sulfonamides to provide the product as a solid (990 mg, 2.2 mmol, 66%). HPLC-A: t_R = 9.11 min (>99%). HPLC-B: t_R = 3.93 min (>99%). MS (ESI): *m/z* 448 $[M + H]^+$, 470 $[M + Na]^+$. ^1H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.90 (s, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 8.38 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.27 (dd *J* = 8.8, 1.0 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.75 (dd, *J*

= 8.8, 7.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 3.80−3.30 (m, 2H), 3.30−2.80 (m, 2H), 1.75−1.40 (m, 6H). HRMS (ESI): calcd $C_{18}H_{17}N_5O_5S_2$ $[M + H]^+$, 448.0744; found, 448.0735.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-carboxybenzoyl]-piperidine (23z). To a stirred solution of 1,4-dihydro-2,4-dioxo-*2H*-3,1-benzoxazine-7-carboxylic acid (**18f**; 3.0 g, 14.5 mmol) in THF (100 mL) and DMF (20 mL) was added DMAP (0.18 g, 1.45 mmol) and piperidine (1.44 mL, 14.5 mmol). The reaction mixture was stirred at room temperature for 16 h. EtOAc was added, and the organic layer was washed with H_2O (2×), dried (Mg_2SO_4), filtered, and concentrated in vacuo to yield crude 3-amino-4-(piperidine-1-carbonyl)-benzoic acid (**11x**, 0.63 g) and taken directly to next step without further purification.

The title compound was prepared from crude **11x** (630 mg, 2.54 mmol), pyridine (0.31 mL, 3.81 mmol), and 2,1,3-benzothiadiazole-4-sulfonyl chloride (590 mg, 2.54 mmol) and purified as described in the general procedure for the preparation of sulfonamides, method A, to provide **23z** as an amorphous solid (130 mg, 0.30 mmol, 2.1%, two steps). HPLC-A: t_R = 7.92 min (>99%). HPLC−B: t_R = 2.64 min (>99%). MS (ESI): m/z 447 $[M + H]^+$, 469 $[M + Na]^+$. ^{1}H NMR (400 MHz, DMSO-d_6; rotameric broadening): δ 9.90 (s, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 7.0 Hz, 1H), 7,83−7.79 (m, 2H), 7.71 (dd, J = 8.0, 1.2 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 3.23 (br s, 2H), 2.88 (br s, 2H), 1.50 (br s, 2H), 1.39 (br s, 2H), 1.29 (br s, 2H). HRMS (ESI): calcd for $C_{19}H_{18}N_4O_5S_2$ $[M + H]^+$, 447.0791; found, 447.0798.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-azetidine (24a). This compound was prepared and purified according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), azetidine hydrochloride (26 mg, 0.28 mmol), DIPEA (0.049 mL, 0.28 mmol), and DMF (0.4 mL) to provide **24a** (38 mg, 0.093 mmol, 66%). MS (ESI): m/z 407 $[M - H]^-$. HPLC-A: t_R = 9.12 min (>99%). HPLC-B: t_R = 3.77 min (>99%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 10.97 (s, 1H), 8.34 (dd, J = 7.0, 1.0 Hz, 1H), 8.24 (dd, J = 8.8, 1.0 Hz, 1H), 7.72 (dd, J = 8.8, 7.1 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.93 (dd, J = 8.4, 2.0 Hz, 1H), 4.2−3.95 (br m, 4H), 2.28 (quint, J = 7.8 Hz, 2H). HRMS (ESI): calcd for $C_{16}H_{13}ClN_4O_3S_2$ $[M + H]^+$, 409.0190; found, 409.0189.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-pyrrolidine (24b). This compound was prepared and purified according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), pyrrolidine (0.023 mL, 0.28 mmol), and DMF (0.4 mL) to provide the title compound as an oil (32 mg, 0.076 mmol, 54%). MS (ESI): m/z 421 $[M - H]^-$. HPLC-A: t_R = 9.15 min (>99%). HPLC-B: t_R = 3.8 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.81 (s, 1H), 8.31 (dd, J = 7.0, 1.0 Hz, 1H), 8.24 (dd, J = 8.8, 1.0 Hz, 1H), 7.71 (dd, J = 8.8, 7.0, 1H), 7.66 (d, J = 8.8, 7.0 Hz, 1H), 7.14 (d, J = 11.2 Hz, 1H), 6.98 (dd, J = 8.4, 2.0 Hz, 1H), 3.47 (m, 2H), 3.12 (m, 2H), 1.90 (m, 2H), 1.65 (m, 2H). HRMS (ESI): calcd for $C_{17}H_{15}ClN_4O_3S_2$ $[M + H]^+$, 423.0347; found, 423.0341.

3-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-thiazolidine (24c). This compound was prepared and purified according to the general procedure for HATU-mediated peptide coupling using **16d** (30 mg, 0.08 mmol), pyridine (0.020 mL, 0.17 mmol), HATU (62 mg, 0.17 mmol), thiazolidine (0.014 mL, 0.16 mmol), and DMF (0.6 mL) to give **24c** (20 mg, 0.045 mmol, 56%). MS (ESI): m/z 441 $[M + H]^+$, 463 $[M + Na]^+$. HPLC-A: t_R = 9.24 min (>99%). HPLC-B: t_R = 3.96 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.52 (s, 1H), 8.31 (d, J = 7.0,1H), 8.26 (d, J = 8.8 Hz, 1H), 7.72 (m, 2H), 7.13 (d, J = 8.3 Hz, 1H), 7.01 (dd, J = 1.8, 8.3 Hz, 1H), 4.56 (br s, 1H), 4.21 (br s, 1H), 3.68 (br s, 2H), 2.84 (br s, 2H). HRMS (ESI): calcd for $C_{16}H_{13}ClN_4O_3S_3$ $[M + H]^+$, 440.9911; found, 440.9907.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]hexahydro-1*H*-azepine (24d). This compound was prepared and purified according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), hexahydro-1*H*-azepine (0.032 mL, 0.28 mmol), and DMF (0.4 mL) to give **24d** (15 mg, 0.033 mmol, 24%). MS (ESI): m/z 449 $[M - H]^-$. HPLC-A: t_R = 9.79 min (>99%). HPLC-B: t_R = 4.14 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.85 (s, 1H), 8.30 (dd, J = 7.0, 1.0 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.71 (dd, J = 8.8, 7.0 Hz, 1H), 7.64 (s, 1H), 7.01 (s, 2H), 3.47 (s, 2H), 2.99 (s, 2H), 1.75 (s, 2H), 1.57 (s, 2H), 1.49 (s, 4H). HRMS (ESI): calcd for $C_{19}H_{19}ClN_4O_3S_2$ $[M + H]^+$, 451.0660; found, 451.0667

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-proline (24e). This compound was prepared and purified according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), (*S*)-proline *tert*-butyl ester (0.048 mL, 0.28 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), and DMF (0.4 mL). The *tert*-butyl ester of **24e** was isolated as a white solid (25 mg, 0.048 mmol, 34%).

The *tert*-butyl ester (22 mg, 0.042 mmol) was stirred in a mixture of DCM (5 mL) and TFA (0.5 mL) at room temperature for 8 h. The mixture was concentrated in vacuo, and the residue was purified by preparative reversed-phase HPLC to provide **24e** as a white solid (10 mg, 0.021 mmol, 50%). MS (ESI): m/z 465 $[M - H]^-$. HPLC-A: t_R = 8.39 min (>99%). HPLC-B: t_R = 3.05 min (>99%). ^{1}H NMR (400 MHz, DMSO-d_6; rotameric broadening): δ 12.79 (br s, 1H), 10.04 (br s, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 7.0 Hz, 1H), 7.86 (dd, J = 8.6, 7.2 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.35−7.25 (m, 1H), 7.25−7.15 (m, 1H), 4.17 (dd, J = 8.0, 5.5 Hz, 1 H), 3.27−3.16 (br m, 1H), 3.09−2.98 (br m, 1H), 2.26−2.13 (br m, 1H), 1.90−1.70 (br m, 2H), 1.69−1.55 (br m, 1H). HRMS (ESI): calcd for $C_{18}H_{15}ClN_4O_5S_2$ $[M + H]^+$, 467.0245; found, 467.0244.

(*S*)-1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-2-[1-pyrrolidinylmethyl]pyrrolidine HCl Salt (24f). This compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), (*S*)-1-(2-pyrrolidinomethyl)pyrrolidine (0.046 mL, 0.28 mmol), and DMF (0.4 mL). The HCl salt was prepared by treatment of the purified product with 2 M HCl in Et_2O and concentration in vacuo (4×) to provide the title compound (10 mg, 0.018 mmol, 13%). MS (ESI): m/z 504 $[M - H]^-$. HPLC-A: t_R = 7.46 min (>99%). HPLC-B: t_R = 4.40 min (>99%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 11.61 (br s, 1H), 9.90−9.70 (br m, 1H), 8.42−8.30 (br m, 1H), 8.27 (bd, J = 7.8 Hz, 1H), 8.15−7.98 (br m, 1H), 7.70−7.60 (br m, 1H), 7.55−7.37 (br m, 2H), 7.15−6.97 (br m, 1H), 4.65−4.40 (br m, 1H), 4.20−3.90 (br m, 2H), 3.90−3.75 (m, 3H), 3.75−3.45 (br m, 3H), 3.40−2.80 (br m, 3H), 2.50−1.80 (br m, 4H), 1.65−1.05 (br m, 4H). HRMS (ESI): calcd for $C_{22}H_{25}ClN_5O_3S_2$ $[M + H]^+$, 506.1082; found, 506.1108.

***cis*-1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-2,5-dihydro-2,5-dimethyl-1*H*-pyrrole (24g).** The title compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), *cis*-2,5-dihydro-2,5-dimethyl-1*H*-pyrrole, (27 mg, 0.28 mmol), and DMF (0.4 mL) to give **24g** (10 mg, 0.024 mmol, 17%). MS (ESI): m/z 447 $[M - H]^-$. HPLC-A: t_R = 10.00 min (>99%). HPLC-B: t_R = 4.19 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.75 (s, 1H), 8.33 (dd, J = 7.0, 1.0 Hz, 1H), 8.20 (dd, J = 8.8, 1.0 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.69 (dd, J = 8.8, 7.0 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.97 (dd, J = 8.2, 2.0 Hz, 1H), 5.70 (d, J = 6.4 Hz, 1H), 5.42 (d, J = 4.6 Hz, 1H), 4.97 (m, 1H), 4.60 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H), 0.11 (d, J = 6.4 Hz, 3H). HRMS (ESI): calcd for $C_{19}H_{17}ClN_4O_3S_2$ $[M + H]^+$, 449.0503; found, 449.0519.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-1,2,3,4-tetrahydroisoquinoline (24h). The title compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (30 mg, 0.08 mmol), pyridine (0.020 mL, 0.17 mmol), HATU (62 mg, 0.17 mmol), 1,2,3,4-tetrahydroisoquinoline (0.018 mL, 0.16 mmol), and DMF (0.6 mL)

to give **24h** (23 mg, 0.047 mmol, 59%). MS (ESI): *m/z* 485 $[M + H]^+$. HPLC-A: $t_R = 9.93$ min (>99%). HPLC-B: $t_R = 4.34$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.24 (s, 1H), 8.28 (d, $J = 7.0$ Hz, 1H), 8.23−8.03 (br m, 1H), 7.74 (d, $J = 1.6$ Hz, 1H), 7.72−7.00 (br m, 1H), 7.25−6.99 (m, 6H), 4.90−4.00 (br m, 2H), 4.00−3.10 (br m, 2H), 3.10−2.40 (br m, 2H). HRMS (ESI): calcd for $C_{22}H_{17}ClN_4O_3S_2$ $[M + H]^+$, 485.0503; found, 485.0518.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-4-piperidinemethanol (24i). The title compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), 4-hydroxymethylpiperidine (32 mg, 0.28 mmol), and DMF (0.4 mL) to afford **24i** (14 mg, 0.030 mmol, 21%). MS (ESI): *m/z* 465 $[M - H]^-$. HPLC-A: $t_R = 7.99$ min (>99%). HPLC-B: $t_R = 3.65$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.00 (br s, 1H), 8.28 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.24 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.71 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.67−7.64 (m, 1H), 7.03−6.97 (m, 2H), 3.52 (br d, $J = 5.4$ Hz, 2H), 2.61−2.48 (m, 2H), 1.88−1.63 (br m, 3H), 1.63−1.42 (br m, 2H), 1.19−0.98 (br m, 2H). Anal. ($C_{19}H_{19}ClN_4O_4S_2$) C, H, N.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-3,5-dimethylpiperidine (24j). Compound **24j** was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (30 mg, 0.08 mmol), pyridine (0.020 mL, 0.17 mmol), HATU (62 mg, 0.17 mmol), 3,5-dimethylpiperdine (0.023 mL, 0.16 mmol), and DMF (0.6 mL) to provide the title compound (27 mg, 0.085 mmol, 72%) as a 4:1 mixture of diastereomers. MS (ESI): *m/z* 463 $[M - H]^-$. HPLC-A: $t_R = 10.23$ min (minor diastereomer), 10.34 min (major diastereomer). HPLC-B: $t_R = 4.32$ min (>99%). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening) δ 9.02 (br s, 1H), 8.29 (d, $J = 7.0$ Hz, 1H), 8.24 (d, $J = 8.8$ Hz, 1H), 7.71 (dd, $J = 8.8$, 7.1 Hz, 1H), 7.67 (d, $J = 1.6$ Hz, 1H), 7.03−6.94 (m, 2H), 4.80−3.80 (br m, 1H), 3.70−2.90 (br m, 1H), 2.15−1.90 (br m, 2H), 1.83−1.73 (br m, 1H), 1.60−1.25 (br m, 2H), 1.10−0.60 (br m, 7H). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening) δ 8.98 (br s, 1H), 8.31 (d, $J = 7.1$ Hz, 1H), 8.24 (d, $J = 8.8$ Hz, 1H), 7.72 (dd, $J = 8.8$, 7.1 Hz, 1H), 7.63 (d, $J = 1.4$ Hz, 1H), 7.03−6.94 (m, 2H), 3.70−2.90 (br m, 2H), 2.90−2.50 (br m, 1H), 2.15−1.9 (br m, 2H), 1.83−1.73 (br m, 1H), 1.60−1.25 (br m, 2H), 1.10−0.60 (br m, 7H). HRMS (ESI): calcd for $C_{20}H_{21}ClN_4O_3S_2$ $[M + H]^+$, 465.0816; found, 465.0821.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-2-methylpiperidine (24k). The title compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), 2-methylpiperidine (0.032 mL, 0.28 mmol), and DMF (0.4 mL) to give **24k** (21 mg, 0.047 mmol, 33%). MS (ESI): *m/z* 449 $[M - H]^-$. HPLC-A: $t_R = 9.88$ min (>99%). HPLC-B: $t_R = 4.16$ min (>99%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 8.89 (s, 1H), 8.33 (d, $J = 7.0$ Hz, 1H), 8.24 (d, $J = 8.8$ Hz, 1H), 7.72 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.62 (s, 1H), 7.00 (m, 2H), 4.45 (s, 1H), 3.49 (s, 1H), 2.89 (m, 1H), 1.64−1.54 (m, 5H), 1.26 (s, 1H), 1.16 (s, 3H). HRMS (ESI): calcd for $C_{19}H_{19}ClN_4O_3S_2$ $[M + H]^+$, 451.0660; found, 473.0521.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-4-phenylpiperidine (24l). The title compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), 4-phenylpiperidine (45 mg, 0.28 mmol), and DMF (0.4 mL) to give **24l** (5 mg, 0.01 mmol, 7%). MS (ESI): *m/z* 511 $[M - H]^-$. HPLC-A: $t_R = 10.31$ min (>99%). HPLC-B: $t_R = 4.63$ min (>99%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.02 (s, 1H), 8.30 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.24 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.71 (dd, $J = 8.8$, 7.1 Hz, 1H), 7.66 (d, $J = 1.7$ Hz, 1H), 7.33 (t, $J = 7.4$ Hz, 2H), 7.23 (m, 1H), 7.20 (m, 2H), 7.03 (m, 2H), 2.72−2.67 (m, 2H), 1.86 (br s, 2H), 1.59 (br s, 4H). HRMS (ESI): calcd for $C_{24}H_{21}ClN_4O_3S_2$ $[M + H]^+$, 513.0816; found, 513.0815.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-3-methylpiperazine (24m). This compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), 2-methylpiperazine (28 mg, 0.28 mmol), and DMF (0.4 mL). The HCl salt was prepared by treatment of the purified product with 2 M HCl in Et_2O and concentration in vacuo 4× to provide the title compound (12 mg, 0.027 mmol, 19%). MS (ESI): *m/z* 450 $[M - H]^-$. HPLC-A: $t_R = 6.76$ min (>99%). HPLC-B: $t_R = 3.61$ min (>99%). ^{1}H NMR (500 MHz, MeOH-d_4; rotameric broadening): δ 8.35 (dd, $J = 8.8$, 1.0 Hz, 1H), 8.25 (dd, $J = 7.0$, 1.0 Hz, 1H), 7.82 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.37 (d, $J = 8.2$ Hz, 1H), 7.28 (dd, $J = 8.3$, 2.0 Hz, 2H), 6.81 (br s, 1H), 4.80−4.30 (br m, 1H), 4.10−3.70 (br m, 1H), 3.62−3.35 (br m, 3H), 3.30−2.90 (br m, 2H), 1.50−1.20 (br m, 4H). HRMS (ESI): calcd for $C_{18}H_{18}ClN_5O_3S_2$ $[M + H]^+$, 452.0612; found, 452.0617.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-4-methylpiperazine (24n). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), 1-methylpiperazine (0.031 mL, 0.28 mmol), and DMF (0.4 mL) to give **24n** (23 mg, 0.051 mmol, 36%). MS (ESI): *m/z* 450 $[M - H]^-$. HPLC-A: $t_R = 6.74$ min (>99%). HPLC-B: $t_R = 3.70$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.57 (br s, 1H), 8.33 (br d, $J = 8.8$ Hz, 1H), 8.32 (br d, $J = 6.5$ Hz, 1H), 7.78 (dd, $J = 8.7$, 7.1 Hz, 1H), 7.27−7.23 (m, 1H), 7.17 (d, $J = 0.6$ Hz, 2H), 4.50−3.30 (br m, 6H), 3.10−2.92 (br m, 2H), 2.90 (s, 3H). HRMS (ESI): calcd for $C_{18}H_{18}ClN_5O_3S_2$ $[M + H]^+$, 452.0612; found, 452.0607.

1-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-4-(1-piperidinyl)piperidine (24o). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (50 mg, 0.14 mmol), pyridine (0.033 mL, 0.41 mmol), HATU (106 mg, 0.28 mmol), 4-(1-piperidinyl)-piperidine (48 mg, 0.28 mmol), and DMF (0.4 mL). The HCl salt was prepared by treatment of the purified product with 2 M HCl in Et_2O and concentration in vacuo 4× to provide the title compound (22 mg, 0.042 mmol, 30.%). MS (ESI): *m/z* 518 $[M - H]^-$. HPLC-A: $t_R = 7.02$ min (>99%). HPLC-B: $t_R = 4.21$ min (>99%). ^{1}H NMR (400 MHz, MeOH-d_4; rotameric broadening): δ 8.34 (dd, $J = 8.8$, 1.0 Hz, 1H), 8.24 (dd, $J = 7.1$, 1.0 Hz, 1H), 7.80 (dd, $J = 8.8$, 7.1 Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 1H), 7.24 (dd, $J = 8.2$, 1.9 Hz, 1H), 7.01 (br s, 1H), 3.90−3.55 (br m, 1H), 3.55−3.40 (br m, 3H), 3.15−2.10 (br m, 4H), 2.30−1.72 (br m, 10H), 1.60−1.45 (br m, 1H). HRMS (ESI): calcd for $C_{23}H_{26}ClN_5O_3S_2$ $[M + H]^+$, 520.1238; found, 520.1233.

4-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chlorobenzoyl]-morpholine (24p). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (30 mg, 0.08 mmol), pyridine (0.020 mL, 0.17 mmol), HATU (62 mg, 0.17 mmol), morpholine (0.015 mL, 0.16 mmol), and DMF (0.6 mL) to give **24p** (24 mg, 0.055 mmol, 68%). MS (ESI): *m/z* 439 $[M + H]^+$. HPLC-A: $t_R = 8.49$ min (>99%). HPLC-B: $t_R = 3.72$ min (>99%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.04 (s, 1H), 8.32 (dd, $J = 7.0$, 1.0 Hz, 1H), 8.26 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.73 (dd, $J = 8.8$, 7.0 Hz, 1H), 7.63 (s, 1H), 7.01 (m, 1H), 3.49 (m, 8H). HRMS (ESI): calcd for $C_{17}H_{15}ClN_4O_4S_2$ $[M + H]^+$, 439.0296; found, 439.0296.

2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chloro-*N*-(phenylmethyl)-benzamide (24q). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (30 mg, 0.08 mmol), pyridine (0.020 mL, 0.17 mmol), HATU (62 mg, 0.17 mmol), benzylamine (0.019 mL, 0.16 mmol), and DMF (0.6 mL) to give **24q** (30 mg, 0.065 mmol, 82%). MS (ESI): *m/z* 457 $[M - H]^-$. HPLC-A: $t_R = 9.92$ min (>99%). HPLC-B: $t_R = 4.23$ min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 11.67 (s, 1H), 8.37 (d, $J = 7.2$ Hz, 1H),

8.22 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.72 (dd, J = 8.7, 7.3 Hz, 1H), 7.42−7.27 (m, 5H), 7.23 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 8.4, 1.7 Hz, 1H), 6.26−6.17 (br m, 1H), 4.56 (d, J = 5.6 Hz, 2H). Anal. ($C_{20}H_{15}ClN_4O_3S_2$) C, H, N.

2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-chloro-*N*-methyl-*N*-(phenylmethyl)-benzamide (24r). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **16d** (18 mg, 0.05 mmol), pyridine (0.012 mL, 0.15 mmol), HATU (38 mg, 0.1 mmol), *N*-methylbenzylamine (0.013 mL, 0.1 mmol), and DMF (0.4 mL) to give **24r** (8 mg, 0.02 mmol, 30%). HPLC-A: t_R = 9.94 min (>99%). HPLC-B: t_R = 4.33 min (>99%). MS (ESI): m/z 471 $[M - H]^-$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.15 (br s, 1H), 8.32 (br d, J = 6.8 Hz, 1H), 8.29−8.18 (br m, 1H), 7.79−7.63 (br m, 2H), 7.48−7.26 (br m, 4H), 7.15−6.83 (br m, 2H), 7.02 (br d, J = 8.2 Hz, 1H), 4.65−4.37 (br s, 1.3H), 4.37−4.00 (br s, 0.7H), 3.15−2.70 (br s, 1.1H), 2.70−2.35 (br s, 1.9H). HRMS (ESI): calcd for $C_{21}H_{17}ClN_4O_3S_2$ $[M + H]^+$, 473.0503; found, 473.0529.

4-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]benzoyl]-morpholine (25a). The compound was prepared from morpholine (18 mL, 0.20 mmol), 2-(benzo[1,2,5]thiadiazole-4-sulfonylamino)-benzoic acid (**16b**; Fluorchem, Ltd., U.K.; 38 mg, 0.10 mmol), HATU (76 mg, 0.20 mmol), pyridine (24 mL, 0.30 mmol), and DMF (700 mL) as described in the general procedure for HATU-mediated amide preparation to give **25a** as a white solid (20 mg, 0.049 mmol, 49%). Mp 150−154 °C. HPLC-A: t_R = 7.66 min (>99%). HPLC-B: t_R = 3.33 min (>99%). MS (ESI): m/z 405 $[M + H]^+$, 427 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.67 (s, 1H), 8.27−8.24 (m, 2H), 7.70 (dd, J = 8.8, 7.0 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.31−7.27 (m, 1H), 7.10−7.08 (m, 2H), 3.63 (br s, 8H). HRMS (ESI): calcd for $C_{17}H_{17}N_4O_4S_2$ $[M + H]^+$, 405.0686; found, 405.0716.

4-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-fluorobenzoyl]-morpholine (25b). The compound was prepared from morpholine (18 μL, 0.20 mmol), **16g** (35 mg, 0.10 mmol), HATU (76 mg, 0.20 mmol), pyridine (24 μL, 0.30 mmol), and DMF (700 μL) and purified as described in the general procedure for HATU-mediated amide preparation to give **22b** as a white solid (25 mg, 0.059 mmol, 59%). Mp 165−168 °C. HPLC-A: t_R = 8.14 min (>99%). MS (ESI): m/z 423 $[M + H]^+$, 445 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.21 (s, 1H), 8.33 (dd, J = 7.0, 1.0 Hz, 1H), 8.26 (dd, J = 8.4, 1.0 Hz, 1H), 7.73 (dd, J = 8.8, 7.0 Hz, 1H), 7.37 (dd, J = 10.6, 2.4 Hz, 1H), 7.09−7.05 (m, 1H), 6.75−6.71 (m, 1H), 3.61 (br s, 4H), 3.42 (br s, 4H). Anal. ($C_{17}H_{15}FN_4O_4S_2$) C, H, N.

4-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-bromobenzoyl]-morpholine (25c). The compound was prepared from morpholine (18 μL, 0.20 mmol), **16e** (41 mg, 0.10 mmol), HATU (76 mg, 0.20 mmol), pyridine (24 μL, 0.30 mmol), and DMF (700 μL) and purified as described in the general procedure for HATU-mediated amide preparation to give **25c** as a white solid (23 mg, 0.048 mmol, 48%). Mp 185−188 °C. HPLC-A: t_R = 8.43 min (>99%). MS (ESI): m/z 483/484/485 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.97 (s, 1H), 8.32 (dd, J = 7.0, 1.0 Hz, 1H), 8.27 (dd, J = 8.8, 1.0 Hz, 1H), 7.78 (d, J = 1.8 Hz, 1H), 7.74 (dd, J = 8.8, 7.0 Hz, 1H), 7.18 (dd, J = 8.2, 1.8 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 3.7−3.18 (br m, 8H). Anal. ($C_{17}H_{15}BrN_4O_4S_2$) C, H, N.

4-[2-[(2,1,3-Benzothiadiazol-4-ylsulfonyl)amino]-4-iodobenzoyl]-morpholine (25d). The compound was prepared from morpholine (9 μL, 0.05 mmol), **16f** (23 mg, 0.05 mmol), HATU (38 mg, 0.10 mmol), pyridine (12 μL), and DMF (400 μL) and purified as described in the general procedure HATU-mediated amide preparation to give **25d** as a white amorphous solid (13 mg, 0.025 mmol, 50%). HPLC-A: t_R = 8.50 min (>99%). MS (ESI): m/z 531 $[M + H]^+$, 553 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.91 (s, 1H), 8.31 (dd, J = 7.0, 0.9 Hz, 1H), 8.27 (dd, J = 8.8, 0.9 Hz, 1H), 7.97 (d, J = 1.5 Hz, 1H), 7.74 (dd, J = 8.8, 7.0 Hz, 1H), 7.41 (dd, J = 8.1, 1.6 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 3.75−3.0 (br m, 8H). Anal. ($C_{17}H_{15}IN_4O_4S_2$) C, H, N.

4-[4-Fluoro-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-morpholine (26a). The compound was prepared from morpholine (12 μL, 0.14 mmol), **17g** (24 mg, 0.07 mmol), HATU (53 mg, 0.14 mmol), pyridine (17 μL, 0.21 mmol), and DMF (400 μL) as described in the general procedure for the HATU-mediated preparation of amides to give **26a** as a white amorphous solid (15 mg, 0.036 mmol, 52%). HPLC-A: t_R = 7.76 min (>99%). HPLC-B: t_R = 3.32 min (>99%). MS (ESI): m/z 417 $[M + H]^+$, 439 $[M + Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.22 (s, 1H), 9.07 (d, J = 1.8 Hz, 1H), 9.01 (d, J = 1.8 Hz, 1H), 8.53 (dd, J = 7.3, 1.4 Hz, 1H), 8.37 (dd, J = 8.5, 1.4 Hz, 1H), 7.90 (dd, J = 8.5, 7.4 Hz, 1H), 7.35 (dd, J = 10.7, 2.4 Hz, 1H), 7.05 (dd, J = 8.5, 6.1 Hz, 1H), 6.74−6.69 (m, 1H), 3.60−3.39 (br m, 8H). HRMS (ESI): calcd for $C_{19}H_{18}FN_4O_4S$ $[M + H]^+$, 417.1027; found, 417.1048.

4-[4-Chloro-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-morpholine (26b). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **17d** (17 mg, 0.050 mmol), pyridine (0.012 mL, 0.15 mmol), HATU (38 mg, 0.1 mmol), morpholine (0.009 mL, 0.1 mmol), and DMF (0.4 mL) to provide **26b** (20 mg, 0.046 mmol, 92%). MS (ESI): m/z 431 $[M - H]^-$. HPLC-A: t_R = 8.14 min. HPLC-B: t_R = 3.52 min. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.11 (br s, 1H), 9.06 (d, J = 1.8 Hz, 1H), 9.01 (d, J = 1.8 Hz, 1H), 8.52 (dd, J = 7.0, 1.5 Hz, 1H), 8.37 (dd, J = 8.4, 1.4 Hz, 1H), 7.90 (dd, J = 8.4, 7.4 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.00 (m, 2H), 3.55 (br m, 6H), 3.22 (br m, 2H). Anal. ($C_{19}H_{17}ClN_4O_4S$) C, H, N.

4-[4-Bromo-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-morpholine (26c). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **17e** (21 mg, 0.051 mmol), pyridine (0.012 mL, 0.15 mmol), HATU (38 mg, 0.1 mmol), morpholine (0.009 mL, 0.1 mmol), and DMF (0.4 mL) to provide **26c** (22 mg, 0.046 mmol, 92%). MS (ESI): m/z 475/477 $[M - H]^-$. HPLC-A: t_R = 8.23 min. HPLC-B: t_R = 3.58 min. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.08 (br s, 1H), 9.06 (d, J = 1.8 Hz, 1H), 9.01 (d, J = 1.8 Hz, 1H), 8.52 (dd, J = 7.0, 1.5 Hz, 1H), 8.37 (dd, J = 8.4, 1.4 Hz, 1H), 7.90 (dd, J = 8.4, 7.4 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.17 (dd, J = 8.0, 1.6 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 3.55 (br m, 6H), 3.22 (br m, 2H). Anal. ($C_{19}H_{17}BrN_4O_4S$) C, H, N.

4-[4-Iodo-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-morpholine (26d). The compound was prepared according to the general procedure for HATU-mediated peptide coupling using **17f** (23 mg, 0.050 mmol), pyridine (0.012 mL, 0.15 mmol), HATU (38 mg, 0.1 mmol), morpholine (0.009 mL, 0.1 mmol), and DMF (0.4 mL) to give **26d** (22 mg, 0.042 mmol, 84%). MS (ESI): m/z 523 $[M - H]^-$. HPLC-A: t_R = 8.32 min. ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.06 (d, J = 1.8 Hz, 1H), 9.02 (d, J = 1.8 Hz, 1H), 9.01 (br s, 1H), 8.51 (dd, J = 7.0, 1.5 Hz, 1H), 8.37 (dd, J = 8.4, 1.4 Hz, 1H), 7.96 (d, J = 1.5 Hz, 1H), 7.90 (dd, J = 8.4, 7.4 Hz, 1H), 7.38 (dd, J = 8.0, 1.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 3.50 (br m, 6H), 3.15 (br m, 2H). Anal. ($C_{19}H_{17}IN_4O_4S$) C, H, N.

(*S*)-4-[4-Chloro-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-3-methylmorpholine (26e). The title compound was prepared according to the general procedure for HATU-mediated peptide coupling using **17d** (18 mg, 0.050 mmol), pyridine (0.012 mL, 0.15 mmol), HATU (38 mg, 0.1 mmol), (*S*)-3-methylmorpholine[41] (0.010 mL, 0.1 mmol), and DMF (0.4 mL) to give **26e** (5 mg, 0.01 mmol, 20%). MS (ESI): m/z 445 $[M - H]^-$. HPLC-A: t_R = 8.44 min (>99%). HPLC-B: t_R = 3.60 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.05 (br s, 1H), 9.05 (d, J = 1.8 Hz, 1H), 9.00 (d, J = 1.8 Hz, 1H), 8.56 (dd, J = 7.3, 1.3 Hz, 1H), 8.37 (dd, J = 8.5, 1.3 Hz, 1H), 7.91 (dd, J = 8.5, 7.3 Hz, 1H), 7.57 (s, 1H), 7.03−6.98 (m, 2H), 4.70−3.40 (br m, 2H), 3.92−3.80 (br m, 1H), 3.75−3.58 (br m, 1H), 3.51 (dd, J = 11.7, 2.8 Hz, 1H), 3.40−3.15 (br m, 2H), 1.35−1.15 (br m, 3H). HRMS (ESI): calcd for $C_{20}H_{19}ClN_4O_4S$ $[M + H]^+$, 447.0888; found, 447.0893.

(*R*)-4-[4-Chloro-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-3-methylmorpholine (26f). The title compound was prepared ac-

cording to the general procedure for HATU-mediated peptide coupling using **17d** (18 mg, 0.050 mmol), pyridine (0.012 mL, 0.15 mmol), HATU (38 mg, 0.1 mmol), (*R*)-3-methylmorpholine[42] (0.010 mL, 0.1 mmol), and DMF (0.4 mL) to give **26f** (10 mg, 0.022 mmol, 45%). MS (ESI): *m*/*z* 445 $[M - H]^-$. HPLC-A: t_R = 8.54 min. HPLC-B: t_R = 3.73 min (>99%). ^{1}H NMR (500 MHz, $CDCl_3$; rotameric broadening): δ 9.05 (d, J = 1.8 Hz, 1H), 9.04 (br s, 1H), 9.00 (d, J = 1.8 Hz, 1H), 8.56 (dd, J = 7.0, 1.5 Hz, 1H), 8.37 (dd, J = 8.4, 1.4 Hz, 1H), 7.91 (dd, J = 8.4, 7.4 Hz, 1H), 7.56 (br m, 1H), 6.99 (m, 2H), 6.93 (d, J = 8.1 Hz, 1H), 4.30 (br m, 1H), 3.85 (m, 1H), 3.64 (m, 1H), 3.51 (dd, J = 11.5, 2.7 Hz, 1H), 3.30 (m, 3H), 1.23 (br m, 3H). HRMS (ESI): calcd for $C_{20}H_{19}ClN_4O_4S$ $[M + H]^+$, 447.0888; found, 447.0883.

(3*S*,5*S*)-4-[4-Chloro-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-3,5-dimethylmorpholine (26g). A suspension of **17d** (50 mg, 0.14 mmol) in thionyl chloride (5 mL) was heated at reflux for 30 min. The resulting homogeneous yellow mixture was cooled to room temperature and concentrated in vacuo. Final traces of thionyl chloride were removed by adding an aliquot of toluene to the crude acid chloride and concentrating in vacuo three times. To a solution of the acid chloride in toluene (5 mL) was added (*S*,*S*)-3,5-dimethylmorpholine[42] (50 mg, 0.43 mmol). The reaction was heated at 90 °C for 1 h, poured into 1 N HCl, and extracted three times with DCM. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography (4 g ISCO silica gel cartridge, EtOAc/hexanes gradient) to provide the title amide **26g** (32 mg, 0.069 mmol, 49%) as a white solid. MS (ESI): *m*/*z* 459 $[M - H]^-$. HPLC-A: t_R = 9.07 min (>99%). HPLC-B: t_R = 3.71 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.49 (br s, 1H), 9.04 (d, J = 1.8 Hz, 1H), 8.98 (d, J = 1.8 Hz, 1H), 8.60 (dd, J = 7.4, 1.4 Hz, 1H), 8.36 (dd, J = 8.5, 1.4 Hz, 1H), 7.91 (dd, J = 8.4, 7.4 Hz, 1H), 7.64 (d, J = 1.9 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.96 (dd, J = 8.3, 2.0 Hz, 1H), 3.86−3.72 (m, 4H), 3.44 (dd, J = 11.3, 5.5 Hz, 2H), 1.16 (d, J = 6.3 Hz, 6H). HRMS (ESI): calcd for $C_{21}H_{21}ClN_4O_4S$ $[M + H]^+$, 461.1045; found, 461.1044.

(3*R*,5*S*)-rel-4-[4-Chloro-2-[(5-quinoxalinylsulfonyl)amino]benzoyl]-3,5-dimethylmorpholine (26h). The compound was prepared from **17d** (50 mg, 0.14 mmol), thionyl chloride (5 mL), and (*S*,*R*)-*meso*-3,5-dimethylmorpholine[43] (50 mg, 0.43 mmol) as described for **26g** to provide the title amide **26h** as a white solid (32 mg, 0.069 mmol, 49%). MS (ESI): *m*/*z* 459 $[M - H]^-$. HPLC-A: t_R = 8.61 min (>99%). HPLC-B: t_R = 3.83 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 9.04 (d, J = 1.8 Hz, 1H), 9.00 (d, J = 1.8 Hz, 1H), 8.66 (br s, 1H), 8.57 (dd, J = 7.3, 1.4 Hz, 1H), 8.38 (dd, J = 8.5, 1.4 Hz, 1H), 7.93 (dd, J = 8.5, 7.3 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 7.02 (dd, J = 8.2, 1.8 Hz, 1H), 4.18−3.98 (br m, 2H), 3.75 (d, J = 11.7 Hz, 2H), 3.58 (dd, J = 11.7, 3.6 Hz, 2H), 1.35 (d, J = 7.0 Hz, 6H). HRMS (ESI): calcd for $C_{21}H_{21}ClN_4O_4S$ $[M + H]^+$, 461.1045; found, 461.1058.

***N*-[2-[(1*H*-Indol-2-ylsulfonyl)amino]benzoyl]-phenylalanine (34).** The methyl ester of the title compound was prepared from **42** (73.0 mg, 0.23 mmol), HATU (158 mg, 0.42 mmol), phenylalanine methyl ester hydrochloride (90 mg, 0.42 mmol), and DIPEA (0.20 mL, 1.15 mmol) and purified as described in the general procedure for HATU-mediated amide preparation (95 mg, 0.20 mmol, 86%). MS (ESI): *m*/*z* 476 $[M - H]^+$. HPLC-A (reversed-phase): t_R = 9.8 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.6 (s, 1H), 9.36 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.41−7.32 (arom m, 2H), 7.26−7.17 (arom m, 5H), 7.10 (t, J = 8.0 Hz, 1H), 7.0−6.98 (m, 4H), 6.49 (d, J = 7.2 Hz, 1H), 4.8 (q, J = 5.6 Hz, 1H), 3.7 (s, 3H), 3.1−3.09 (m, 2H).

To the methyl ester (70 mg, 0.15 mmol) in 1:1 THF/water (4 mL) was added $LiOH \cdot H_2O$ (19 mg, 0.44 mmol), and the mixture was stirred for 5 h. The reaction mixture was quenched with 10% HCl (10 mL), and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase HPLC (acetonitrile/water, 0.05% TFA) to afford **34** as a white solid (35 mg, 0.075 mmol, 50%). MS (ESI): *m*/*z* 462 $[M - H]^+$. HPLC-A: t_R = 9.1 min (>99%). HPLC-B: t_R = 6.7 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 7.74 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.45−7.41 (arom m, 2H), 7.4 (s, 1H), 7.32−7.28 (arom m, 5H), 7.17−7.13 (m, 3H), 7.1 (br s, 1H), 7.06−7.04 (t, J = 7.2 Hz, 1H), 4.83 (t, J = 6.6 Hz, 1H), 3.29 (dd, J = 14.4, 5.4 Hz, 1H), 3.18 (dd, J = 14.4, 6.6 Hz, 1H). Anal. ($C_{24}H_{21}N_3O_5S \cdot 1/3H_2O$) C, H, N, S.

(*S*)-*N*-[4-Bromo-2-[(1*H*-indol-2-ylsulfonyl)amino]benzoyl]-phenylalanine (35). The compound was prepared from **43** (57 mg, 0.14 mmol), phenylalanine methyl ester hydrochloride (62 mg, 0.29 mmol), DIPEA (126 μL, 0.72 mmol), and HATU (99 mg, 0.26 mmol) as described in the general procedure for HATU-mediated amide bond formation to afford the methyl ester of the title compound (65 mg, 0.12 mmol, 86%). MS (ESI): *m*/*z* 554 $[M - H]^+$. HPLC-A: t_R = 10.3 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.72 (s, 1H), 9.30 (s, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.6 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.28−7.23 (arom m, 4H), 7.13−7.10 (arom m, 2H), 7.01 (arom m, 1H), 7.03−6.98 (m, 3H), 6.47 (d, J = 7.2 Hz, 1H), 4.83 (q, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.14 (dd, J = 13.8, 5.4 Hz, 1H), 3.10 (dd, J = 13.8, 6.0 Hz, 1H).

The methyl ester (60 mg, 0.11 mmol) in 1:1 THF/water (4 mL) was treated with $LiOH \cdot H_2O$ (14 mg, 0.33 mmol) as described in the preparation of **34** to afford **35** as a white solid (35 mg, 0.064 mmol, 59%). MS (ESI): *m*/*z* 540 $[M-H]^+$. HPLC-A: t_R = 9.7 min (>99%). HPLC−B: t_R = 7.1 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 7.91 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.37−7.32 (arom m, 1H), 7.29−7.23 (arom m, 8H), 7.13−7.05 (arom m, 6H), 4.77 (q, J = 6 Hz, 1H), 3.25 (dd, J = 13.8, 5.4 Hz, 1H), 3.13 (dd, J = 13.8, 6.6 Hz, 1H). HRMS calcd for $C_{24}H_{20}BrN_3O_5S$, 540.0234 $[M - H]^+$; found, 540.0238. Anal. ($C_{24}H_{20}BrN_3O_5S \cdot 1H_2O$) C, H, N, S.

1-[2-[(1*H*-Indol-2-ylsulfonyl)amino]benzoyl]-piperidine (36). The compound was prepared from **42** (54.7 mg, 0.17 mmol), HATU (79 mg, 0.21 mmol), piperidine (34 μL, 0.34 mmol), DIPEA (90 μL, 0.52 mmol) as described in the general procedure for HATU-mediated amide formation to afford **36** (36 mg, 42%) as a white solid. MS (ESI): *m*/*z* 384 $[M + H]^+$, 406 $[M + Na]^+$. HPLC-A: t_R = 9.5 min (>99%). HPLC-B: t_R = 6.8 min (>99%). ^{1}H NMR (400 MHz, DMSO-d_6; rotameric broadening): δ 12.15 (s, 1H), 9.5 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.38−7.32 (arom m, 2H), 7.28−7.26 (arom m, 1H), 7.23−7.19 (arom m, 2H), 7.11−7.08 (t, J = 7.8 Hz, 1H), 6.92 (s, 1H), 3.46 (br m, 2H), 2.84 (br m, 2H), 1.49 (br m, 4H), 1.18 (br m, 2H). HRMS calcd for $C_{20}H_{21}N_3O_3S$, 382.1231 $[M - H]^+$; found, 382.1240. Anal. ($C_{20}H_{21}N_3O_3S \cdot 1/3H_2O$) C, H, N, S.

1-[4-Bromo-2-[(1*H*-indol-2-ylsulfonyl)amino]benzoyl]-piperidine (37). The compound was prepared from **43** (44 mg, 0.17 mmol), HATU (76 mg, 0.21 mmol), piperidine (22 μL, 0.22 mmol), and DIPEA (97 μL, 0.56 mmol) and purified as described in the general procedure for HATU-mediated amide bond formation to afford **37** as a white solid (23 mg, 0.050 mmol, 29%). MS (ESI): *m*/*z* 460 $[M - H]^+$. HPLC-A: t_R = 10.1 min (>99%). HPLC-B: t_R = 7.3 min (>99%). ^{1}H NMR (400 MHz, DMSO-d_6; rotameric broadening): δ 12.13 (s, 1H), 9.7 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.38 (dd, J = 7.8, 0.6 Hz, 1H), 7.35 (dd, J = 8.4, 2.4 Hz, 1H), 7.23−7.21 (arom m, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.06−7.03 (m, 1H), 6.9 (d, J = 1.2 Hz, 1H), 3.39 (br m, 2H), 2.78 (br m, 2H), 1.42−1.40 (br m, 4H), 1.12 (br m, 2H). HRMS calcd for $C_{20}H_{20}BrN_3O_3S$, 460.0336 $[M - H]^+$; found, 460.0337. Anal. ($C_{20}H_{20}BrN_3O_3S \cdot 1/3H_2O$) C, H, N, S.

1-[2-[(2,1,3-Benzothiadiazol-4-ylcarbonyl)amino]-4-bromobenzoyl]-piperidine (38). To a dry, one-necked round-bottom flask was added benzo[1,2,5]thiadiazole-4-carboxylic acid (31 mg, 0.17 μmol), followed by thionyl chloride (10 mL). The contents were heated at reflux overnight, then excess thionyl chloride was removed under reduced pressure, and the resulting oil was repeatedly stripped from toluene (3×). The crude acid chloride was taken up into dry DCM (10 mL) to which was added pyridine (45 μL, 0.50 mmol) and **11e** (57 mg, 0.20 mmol), and the reaction mixture was stirred

for 3 h, quenched with water, transferred to a separatory funnel, and washed with water and aqueous NaCl. The organic layer was dried (Mg_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified on silica gel (MPLC, hexanes/EtOAc) to afford **38** as a solid (15 mg, 0.033 mmol, 17%). MS (ESI): *m*/*z* 467 [M + Na]$^+$. HPLC-A: t_R = 9.78 min (>99%). HPLC-B: t_R = 7.81 min (>99%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric broadening): δ 8.77 (d, J = 1.8 Hz, 1H), 8.68 (dd, J = 7.1, 1.1 Hz, 1H), 8.24 (dd, J = 8.8, 1.1 Hz, 1H), 7.81 (dd, J = 8.8, 7.1 Hz, 1H), 7.35 (dd, J = 8.1, 1.8 Hz, 1H), 7.17 (d, J = 8.1, 1H), 3.78 (br s, 4H), 1.63−1.46 (br m, 6H). HRMS (ESI): calcd for $C_{19}H_{18}BrN_4O_2S$ [M + H]$^+$, 445.0328; found, 445.0329.

Human CCK-1 and Human CCK-2 Radioligand Binding Assays. The human CCK-1R and CCK-2R radioligand binding assays, the results of which are presented in Tables 1 and 3−8, were identical to those previously described.[20−22]

Guinea Pig Gallbladder and Gastric Smooth Muscle Functional Assays. Assays to measure the antagonism by compounds **4** and **5** (Table 9) of CCK-8S-stimulated guinea pig gallbladder contraction and penta-gastrin stimulated guinea pig gastric smooth muscle contraction were perfomed as previously described.[34,35]

Pharmacokinetics in the Rat and Dog. Compounds for iv administration (2 μmol/kg rat and dog) were freshly prepared as 5% (v/v) pharmasolve in 20% HP-beta-CD (cyclodextrin) solutions and adjusted to pH 9 by the addition of 1 N NaOH. For oral dosing (2 μmol/kg rat and 20 μmol/kg dog), the cyclodextrin vehicle was replaced by TPGS/PG/water (2:6:2).

Rat PK. The pharmacokinetic profiles were assessed in male Sprague−Dawley rats (230−350 g). The concentration of the compound in the plasma was determined at various time points after dosing in the La Jolla Bioanalytical group using a liquid chromatographic-triple quadrupole mass spectrometer assay procedure with a lower limit of quantification of 5−10 ng/mL. Rats in the oral dosing group were fasted 18 h prior to dosing, while those in the intravenous dosing group were not fasted. All animals were allowed water ad libitum, and fasted rats in the oral group were fed 4 h following dosing. Blood samples (250 μL) were obtained from the tail vein before dosing and at 0.5, 1, 2, 4, 6, 8, 24, and 26 h thereafter. Samples were stored on ice (<30 min) until such time that the plasma could be collected by centrifugation (10 min at 10 000 rpm). Plasma was collected and frozen at −20 or −80 °C until bioanalysis.

Dog PK. Male beagle dogs (6.1 to 8.0 kg at dose initiation) were dosed either via the iv or oral routes with compound solutions, as described above. Blood samples were collected from dogs via the jugular vein into tubes containing lithium heparin at predose, 0.5, 1, 2, 4, 8, and 24 h postdose. Plasma was separated by centrifugation and stored frozen at approximately −20 °C pending analysis. Plasma samples were analyzed for compound levels by the La Jolla Bioanalytical Group, as described above.

The pharmacokinetic parameters of all compounds evaluated were derived from noncompartmental analysis (WinNonlin, Pharsight Corporation, CA).

Inhibition of Penta-Gastrin Stimulated Gastric Acid Secretion in the Anesthetized Rat−Ghosh and Schild Preparation. The anesthetized rat preparation was developed using essentially the methods employed by Ghosh and Schild[36] with slight modification. Male rats (200−350 g) were anesthetized with isoflurane (1−3%) mixed with room air. Rats were allowed to breath spontaneously via a mask through which the anesthetic was delivered. The jugular vein and carotid artery were cannulated to allow measurement of blood pressure and the infusion of pentagastrin. The femoral vein was cannulated and used for bolus dosing of the test compounds. The stomach was cannulated and the lumen was washed with 20−60 mL of a nonbuffering solution (mucosal solution). The composition of the mucosal solution was (in mM) NaCl, 135; KCl, 4.8; $MgSO_4$, 1.2; $CaCl_2$, 1.3; and glucose, 31.6, maintained at 37 °C and gassed with 95% O_2 and 5% CO_2 (in order to modulate the pH to ∼6.6). The inflow cannula was inserted near the greater curvature of the stomach while the outflow cannula was inserted into the duodenum and back through the pyloric sphincter. The esophagus was ligated to prevent back flow of the mucosal solution. Care was taken not to damage the vagus nerve during the surgical procedure. For the whole period of the experiment, mucosal solution was continuously perfused through the stomach at the rate of 1 mL/min using a Carter multichannel precision pump (Manostat, IL). The perfusate was then passed over a pH electrode system (Beckman Instrument, Inc., CA) linked to a computer via a signal amplifier (ADinstruments, CO). The pH of the effluent was continuously monitored and recorded as a function of time.

Inhibition of Penta-Gastrin Stimulated Gastric Acid Secretion in the Conscious Gastric Fistula Rat. The protocol of Pare et al.[37] was followed with some modifications. Male Sprague−Dawley rats (n = 9), weighing 250−300 g at the start of experiment, were each fitted with a stainless steel cannula, which resembled a small spool, measuring 12 mm long with outer flanges 12 mm in diameter and an outside diameter of ∼7.5 mm. A 12 × 12 mm square piece of monofilament knitted polypropylene mesh was attached midway between the flanges to the barrel of the cannula with tissue glue (Vetbound, MN). The inner bore of the cannula was threaded to accept a screw-type plug, which functioned as an obturator. When gastric collections were made, the plugging screw was removed and replaced with a female luer joint (Instech, PA), which slipped over a small bushing with outside treads. The threaded bushing could be screwed into the cannula after the plugging screw has been removed. The female luer joint was connected to tubing (Manostat, IL) that drained the gastric secretion by gravity when the animal was placed in the metabolic cage. A 10 mL volumetric cylinder was placed underneath each cage as a collection vessel for the gastric juice over a 2 h period. The test compound was dosed orally as a solution at time 0, followed at 2 h by a subcutaneous injection of 30 nmol/kg pentagastrin. Gastric juice was collected by free drainage through the fistula in 30 min fractions over the next 2 h into a volumetric cylinder.

Acknowledgment. The authors thank Dr. Jiejun Wu, Ms. Heather McAllister, and Mr. David Tognarelli for analytical support and Ms. Veronica Moreno and Ms. Jayashree Pyati for assistance with assay development.

Supporting Information Available: Experimental details of the synthesis of noncommercially available intermediates as well as a table of combustion analysis/HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reubi, J. C.; Schaer, J. C.; Waser, B. Cholecystokinin(CCK)-A and CCK-B/gastrin receptors in human tumors. *Cancer Res.* **1997**, *57*, 1377−1386.
(2) Konturek, P. C.; Nikiforuk, A.; Kania, J.; Raithel, M.; Hahn, E. G.; Muhldorfer, S. Activation of NFkappaB represents the central event in the neoplastic progression associated with Barrett's esophagus: a possible link to the inflammation and overexpression of COX-2, PPARgamma and growth factors. *Dig. Dis. Sci.* **2004**, *49*, 1075−1083.
(3) Colucci, R.; Blandizzi, C.; Tanini, M.; Vassalle, C.; Breschi, M. C.; Del Tacca, M. Gastrin promotes human colon cancer cell growth via CCK-2 receptor-mediated cyclooxygenase-2 induction and prostaglandin E2 production. *Br. J. Pharmacol.* **2005**, *144*, 338−348.
(4) Durrant, L. G.; Spendlove, I. Cancer vaccines entering Phase III clinical trials. *Expert Opin. Emerging Drugs* **2003**, *8*, 489−500.
(5) Watson, S. A.; Gilliam, A. D. G17DT- -a new weapon in the therapeutic armoury for gastrointestinal malignancy. *Expert Opin. Biol. Ther.* **2001**, *1*, 309−317.
(6) Vakil, N. Review article: new pharmacological agents for the treatment of gastro-oesophageal reflux disease. *Aliment. Pharmacol. Ther.* **2004**, *19*, 1041−1049.
(7) Lehmann, F.; Hildebrand, P.; Beglinger, C. New molecular targets for treatment of peptic ulcer disease. *Drugs* **2003**, *63*, 1785−1797.
(8) Gillen, D.; McColl, K. E. Problems related to acid rebound and tachyphylaxis. *Best Pract. Res., Clin. Gastroenterol.* **2001**, *15*, 487−495.
(9) For a review see: Herranz, R. Cholecystokinin antagonists: pharmacological and therapeutic potential. *Med. Res. Rev.* **2003**, *23*, 559−605.

(10) Lin, J. H.; Storey, D. E.; Chen, I. W.; Xu, X. Improved Oral Absorption of L-365,260, a Poorly Soluble Drug. *Biopharm. Drug Dispos.* **1996**, *17*, 1−15.
(11) McDonald, I. M. CCK2 Receptor Antagonists. *Exp. Opin. Ther. Pat.* **2001**, *11*, 445−462.
(12) Karaman, H.; Barton, R. J.; Robertson, B. E.; Lee, D. G. Preparation and Properties of Quaternary Ammonium and Phosphonium Permanganates. *J. Org. Chem.* **1984**, *49*, 4509−4516.
(13) Bellamy, F. D.; Ou, K. Selective Reduction of Aromatic Nitro Compounds with Stannous Chloride in Nonacidic and Nonaqueous Medium. *Tetrahedron Lett.* **1984**, *25*, 839−842.
(14) Carpino, L. A. 1-Hydroxy-7-azabenzotriazole. An Efficient Peptide Coupling Additive. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.
(15) Lin, H.-S.; Richett, M. E. Quinoxaline-5,8-Dione Derivatives, Their Preparation, and Their Use as Anticancer Agents. WO 9952365 A1, 1999.
(16) Newman, M. S.; Karnes, H. A. Conversion of Phenols to Thiophenols Via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31*, 3980−3984.
(17) Kwart, H.; Evans, E. R. The Vapor Phase Rearrangement of Thionocarbonates and Thionocarbamates. *J. Org. Chem.* **1966**, *31*, 410−413.
(18) Sakurai, H.; Ritonga, M. T. S.; Shibatani, H.; Hirao, T. Synthesis and Characterization of *p*-Phenylenediamine Derivatives Bearing an Electron-Acceptor Unit. *J. Org. Chem.* **2005**, *70*, 2754−2762.
(19) Shankar, B. B.; Gilbert, E.; Rizvi, R. K.; Huang, C.; Kozlowski, J. A.; McCombie, S.; Shih, N.-Y. Preparation of Cannabinoid Receptor Ligands. WO 2006002133, 2006.
(20) 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.
(21) Morton, M. F.; Pyati, J.; Dai, H.; Li, L.; Moreno, V.; Shankley, N. P. Molecular Cloning, Expression and Pharmacological Characterization of the Canine Cholecystokinin 1 Receptor. *Br. J. Pharmacol.* **2005**, *145*, 374−384.
(22) Morton, M. F.; Liu, P. Q.; Reik, A.; de la Rosa, R.; Mendel, M.; Li, X. Y.; Case, C.; Pabo, C.; Moreno, V.; Pyati, J.; Shankley, N. P. Pharmacological Analysis of CCK2 Receptors Up-Regulated Using Engineered Transcription Factors. *Regul. Pept.* **2005**, *129*, 227−232.
(23) Rabinowitz, M. H.; Masucci, J. Unpublished results.
(24) *Jaguar Quantum Mechanics*, version 4.1; Ab initio density functional theory calculated using this application; Schrödinger, LLC: San Diego, CA.
(25) Mulliken, R. S. Electronic Population Analysis on LCAO-MO Molecular-Wave Functions. IV. Bonding and Antibonding In LCAO and Valence-Bond Theories. *J. Chem. Phys.* **1955**, *23*, 2343−2346.
(26) Aqueous pK_a measured with a Sirius GLpK_a automated computerized potentiometric system equipped with a pH electrode at 25 °C under argon gas (pION, Inc., Woburn, MA).
(27) Rosen, M.; Allison, B.; Rabinowitz, M. H. Manuscript in preparation.
(28) Low, C. M.; Buck, I. M.; Cooke, T.; Cushnir, J. R.; Kalindjian, S. B.; Kotecha, A.; Pether, M. J.; Shankley, N. P.; Vinter, J. G.; Wright, L. Scaffold Hopping With Molecular Field Points: Identification of a Cholecystokinin-2 (CCK2) Receptor Pharmacophore and its use in the Design of a Prototypical Series of Pyrrole- and Imidazole-Based CCK2 Antagonists. *J. Med. Chem.* **2005**, *48*, 6790−6802.
(29) This intriguing result suggests that a tertiary amide group is required in this series to realize high receptor affinity. This is not necessarily the case, and the results of further studies in this area will be the subject of future disclosures from these laboratories.
(30) Varnavas, A.; Valenta, V.; Berti, F.; Lassiani, L. Synthesis of *N*-Terminal Substituted Anthranilic Acid Dimer Derivatives for Evaluation on CCK Receptors. *Farmaco* **2001**, *56*, 555−564.
(31) Varnavas, A.; Lassiani, L.; Valenta, V.; Berti, F.; Tontini, A.; Mennuni, L.; Makovec, F. Anthranilic Acid Based CCK1 Antagonists: The 2-Indole Moiety May Represent a "Needle" According to the Recent Homonymous Concept. *Eur. J. Med. Chem.* **2004**, *39*, 85−97.
(32) Varnavas, A.; Lassiani, L.; Valenta, V.; Berti, F.; Mennuni, L.; Makovec, F. Anthranilic Acid Derivatives: A New Class of Non-Peptide CCK1 Receptor Antagonists. *Bioorg. Med. Chem.* **2003**, *11*, 741−751.
(33) These studies will be the subjects of future publications from our laboratories.
(34) Bishop, L. A.; Gerskowitch, V. P.; Hull, R. A.; Shankley, N. P.; Black, J. W. The Use of Receptor Desensitization to Analyse CCKA and CCKB/Gastrin Receptors Coupled to Contraction in Guinea-Pig Stomach Muscle. *Br. J. Pharmacol.* **1995**, *114*, 339−348.
(35) Hultman, E. H. A Method for the Standardization of Cholecystokinin In Vitro. *Acta Physiol. Scand.* **1955**, *33*, 291−295.
(36) Ghosh, M. N.; Schild, H. O. Continuous Recording of Acid Gastric Secretion in the Rat. *Br. J. Pharmacol. Chemother.* **1958**, *13*, 54−61.
(37) Pare, W. P.; Isom, K. E.; Vincent, G. P., Jr.; Glavin, G. B. Preparation of a Chronic Gastric Fistula in the Rat. *Lab Anim. Sci.* **1977**, *27*, 244−247.
(38) Brodie, D. A. *Neurogenic Factors in Experimental Peptic Ulceration*; McGill-Queens University Press: Montreal, 1963; pp 403−411.
(39) Pesin, V. G.; Muravnik, R. S. Studies on 2,1,3-thia- and selenadiazole. XXXVI. Sulfonation and Oxidation. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1965**, 223−232.
(40) Mikhailitsyn, F. S. Synthesis of 2,1,3-benzothiadiazole. I. New Sulfo Derivatives of 2,1,3-benzothiadiazole. *Khim. Geterotsikl. Soedin.* **1973**, 19−21.
(41) Bettoni, G.; Franchini, C.; Perrone, R.; Tortorella, V. Synthesis and Absolute Configuration of Substituted Morpholines. *Tetrahedron* **1980**, *36*, 409−415.
(42) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. (*S*,*S*)-3,5-Dimethylmorpholine, a Novel C2−Symmetric Auxiliary. First Application in [4+2]-cycloadditions Leading to 4-Oxohexahydropyridazine Derivatives. *Synthesis* **1994**, 66−72.
(43) Allison, B. D.; Hack, M. D.; Phuong, V. K.; Rabinowitz, M. H.; Rosen, M. D. Preparation of 5-[[(2-carbamoylphenyl)amino]sulfonyl]-quinoxaline compounds as cholecystokinin 2 modulators. U.S. Patent 2005038032, 20050217, 2005.
(44) Cheng, Y.; Prusoff, W. H. Relationship Between the Inhibition Constant (K1) and the Concentration of Inhibitorn Which Causes 50 Per Cent Inhibition (I50) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

JM060590X