Discovery of Orally Efficacious Melanin-Concentrating Hormone Receptor-1 Antagonists as Antiobesity Agents. Synthesis, SAR, and Biological Evaluation of Bicyclo[3.1.0]hexyl Ureas

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Melanin-concentrating hormone (MCH) is a cyclic, nonadecapeptide expressed in the CNS of all vertebrates that regulates feeding behavior and energy homeostasis via interaction with the central melanocortin system. Regulation of this interaction results in modulation of food intake and body weight gain, demonstrating significant therapeutic potential for the treatment of obesity. The MCH-1 receptor (MCH-R1) has been identified as a key target in MCH regulation, as small molecule antagonists of MCH-R1 have demonstrated activity in vivo. Herein, we document our research in a bicyclo[3.1.0]hexyl urea series with particular emphasis on structure−activity relationships and optimization of receptor occupancy, measured both in vitro and via an ex vivo binding assay following an oral dosing regimen. Several compounds have been tested in vivo and exhibit oral efficacy in relevant acute rodent feeding models. In particular, **24u** has proven efficacious in chronic rodent models of obesity, showing a statistically significant reduction in food intake and body weight over a 28 day study.

Introduction

The obesity epidemic has been recognized as a significant human health threat affecting cultures throughout the world. Identified by the World Health Organization (WHO) as one of the top 10 global health problems, current estimates hold that over 30% (∼60 million) of United States adults suffer from obesity, which is defined as a body mass index (BMI) greater than 30.[1] Additionally, 30% of U.S. adults are classified as overweight (BMI > 25) and are trending toward obesity. Similar disturbing trends have been observed in other industrialized countries, particularly those which have adopted a Western diet and sedentary lifestyle. Often mischaracterized as an aesthetic issue, obesity poses significant health risks including comorbidities such as type II diabetes, hypertension, coronary artery disease, stroke, osteoarthritis, and several forms of cancer.[2] Financial estimates of the direct and indirect costs of obesity exceed $117 billion in the U.S. and are increasing rapidly.[3] Though obesity-related cost estimates vary dramatically, the direct links between obesity and these comorbidities remain clear. Remediation of obesity via weight reduction has been suggested as a primary goal; however, long-term weight regulation remains difficult. Currently marketed weight reduction medications such as orlistat (Xenical) and sibutramine (Meridia) suffer from limited efficacy or undesirable side effects which limit patient compliance.[4] The pending FDA approval of rimonabant (Acomplia) may offer an alternative weight loss treatment.[5] Recent pharmacological approaches to induce weight loss have included modulation of several metabolic processes of which melanin-concentrating hormone (MCH) has been increasingly prominent.[6]

Melanin-concentrating hormone is a cyclic, nonadecapeptide which is expressed in the central nervous system of all vertebrates.[7] Interaction of MCH with the central melanocortin system plays a role in feeding behavior and energy homeostasis. Initial studies showed that central administration of MCH to rats induced hyperphagia and were followed by subchronic (7−14 day) murine studies in which central infusion of MCH also induced hyperinsulinemia, hyperleptinemia, and increased adiposity.[8] In contrast, MCH null mice present a lean phenotype characterized by hypophagia and increased energy expenditure.[9]

To date, two endogenous receptors for MCH have been identified as G-protein coupled receptors, designated as MCH-R1 and MCH-R2. MCH-R1 is expressed in hypothalamus of rodents and higher mammalian species, while MCH-R2 is expressed only in higher mammals such as ferrets, dogs, rhesus monkeys, and humans.[10] Due to this species-specific expression pattern, the pharmacological role of MCH-R2 in metabolic homeostasis is largely undefined. Conversely, the role of MCH-R1 in food intake and energy expenditure has been extensively studied. Specifically, MCH-R1 null mice are lean, have decreased leptin and insulin levels, and are resistant to diet-induced obesity.[11]

Antagonism of the MCH-R1 receptor has been the topic of several publications demonstrating the promise of this target in obesity therapy.[12] Orally active MCH-R1 antagonists demonstrating acute efficacy have been disclosed by several groups.[13] Subchronic efficacy in mice has been observed upon oral dosing with GW-856464 (**1**, Figure 1),[14] indazoles such as **2** and **3**,[15] and aminopiperidines exemplified by compounds **4**−**6**.[16] Recent publications from our laboratories have documented that biaryl urea **7** (hMCH-R1 K_i = 9 nM, K_b = 2 nM) was orally efficacious in a 28 day rodent obesity model, showing decreasing food intake and weight gain in addition to a selective decrease in fat mass relative to lean mass.[17] Though orally active in vivo, further studies with **7** were discontinued due to potential toxicity issues. The biaryl aniline substructure embedded in **7** provided a strongly positive result in an Ames assay, indicating the high mutagenic potential of the biaryl aniline. Though pharmacokinetic studies provided no evidence of metabolism of **7** in vivo

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1 (GW-856464)

2

3 **4** **5**

6 **7**

Figure 1. MCH-R1 antagonists exhibiting chronic oral efficacy.

NOE: H_1 - H_2

11, **16**

NOE: ortho H_{Ar} - H_1
ortho H_{Ar} - H_2
H_1 - H_2

23a

Figure 2. Diagnostic NOE observances for cyclopentanes **11**, **16**, and bicylohexane **23a**.

to produce the biaryl aniline, it was decided that any risk of biaryl aniline exposure to the target population, regardless of extent, was unacceptable in the context of antiobesity therapy. Herein, efforts aimed at reducing the liabilities of the biaryl urea **7** via modification of the central aryl ring to a bicyclic structure are chronicled. Central to this effort was the incorporation of an ex vivo binding assay to guide compound selection for further in vivo rodent studies. Oral efficacy of a resultant bicyclic urea in a chronic (**28d**) rodent model is demonstrated.[18]

Chemistry

The synthesis of the cyclopentenyl derivative and cyclopentyl derivatives proceeded according to Scheme 1. Aryl cyclopentenone **8**[18a] underwent reductive amination with 1-(2-aminoethyl)pyrrolidine, followed by treatment with 3,5-dichlorophenyl isocyanate to provide the racemic cyclopentenyl urea **9**. Hydroxyl-directed reduction of olefin **10**[18a] and careful chromatographic separation provided the pure *cis*- and *trans*-cyclopentanol isomers (**11** and **12**, respectively, in a 10:1 ratio). Conformational analysis via 2D-NOESY NMR confirmed the major product as the *cis*-isomer (Figure 2). Specifically, NOE observances between protons on the cyclopentyl ring of **11** were

Scheme 1. Preparation of Cyclopentenyl and Cyclopentyl Ureas[a]

8 → (a, b) → **9**: Ar = 3, 5-di Cl phenyl

10 → (c) → **11** + **12**

11 → (d, e) → **13** → (b) → **14:** Ar = 3-Cl, 4-F phenyl

11 → (f, e) → **15** → (b) → **16:** Ar = 3-Cl, 4-F phenyl

[a] (a) 1-(2-Aminoethyl)pyrrolidine, $NaB(OAc)_3H$; (b) aryl isocyanate, *i*-Pr_2NEt, CH_2Cl_2; (c) H_2, Pd/C, MeOH; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature; (e) 1-(3-aminopropyl)-4-methylpiperazine, K_2CO_3, CH_3CH_2CN, 100 °C; (f) Ph_3P, CBr_4, THF.

Scheme 2. Preparation of Bicyclo[3.1.0]hexyl Ureas: Stork Route[a]

21a: R_1 = *m*-CN
21b: R_1 = *m*-Br

24a: Ar = 3-Cl, 4-F phenyl

24b: R_1 = NHAc, Ar = 3-Cl, 4-F phenyl
24c: R_1 = $NHSO_2Me$, Ar = 3-Cl, 4-F phenyl

[a] (a) Butyllithium, THF, −78 °C, then **18**, −78 °C to −20 °C; (b) 1 N HCl; (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C to room temperature; (d) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C to room temperature; (e) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C to room temperature; (f) $H_2NCH_2CH_2R_2$, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (g) aryl isocyanate, *i*-Pr_2NEt, CH_2Cl_2; (h) TFA, CH_2Cl_2; (i) HCHO or *i*-BuCHO, $NaB(OAc)_3H$, CH_2Cl_2; (j) *tert*-butyl carbamate, *N*,*N*′-dimethylethylenediamine, CuI, K_2CO_3, toluene, 110 °C; (k) AcCl or MsCl, *i*-Pr_2NEt, CH_2Cl_2; (l) 4-aminobutanol, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (m) BOC_2O, Et_3N, CH_2Cl_2; (n) Ph_3P, CBr_4, THF, 0 °C to room temperature; (o) R_2NH, K_2CO_3, CH_3CN, 70 °C.

indicative. Formation of the mesylate of the *cis*-isomer and displacement using 1-(3-aminopropyl)-4-methylpiperazine provided the secondary amine **13**, which was treated with 3-chloro-4-fluorophenyl isocyanate to afford the *trans*-cyclopentyl urea **14**. Similarly, the *cis*-cyclopentanol **11** was brominated and alkylated in a sequence proceeding with double configurational inversion to give the *cis*-amine **15**, which underwent isocyanate treatment to provide the *cis*-cyclopentyl urea **16**. Configuration of the *cis*-cyclopentyl urea **16** was also confirmed via 2D-NOESY NMR studies (Figure 2).

The initial synthesis of the bicyclohexyl series is outlined in Scheme 2.[18a] Metal−halogen exhange of aryl bromides **17** followed by addition to 3-methoxy-2-cyclopenten-1-one and subsequent acidic workup provided the 3-aryl enones **19**. Direct cyclopropanation of these derivatives was highly desirable in the context of developing a streamlined synthesis. Several methods were employed in this effort such as Corey's sulfoxonium ylide,[19] diazomethane decomposition, and phase-transfer conditions with dichlorocarbene. Of these, the sulfoxonium ylide was most productive, though far from optimal (5−15% yield). Consequently, recourse was made to Luche reduction[20] and cyclopropanation of the resultant allylic alcohols, followed by Dess−Martin oxidation[21] to provide the desired bicyclic ketones **21**. The acid-sensitive nature of allylic alcohols derived from the reduction of **19** necessitated chromatographic purification via silica prewashed with triethylamine. Though circuitous, this method was reproducible and proceeded well on scale. Reductive amination of **21** using titanium tetraisopropoxide as a promotor followed by treatment with sodium borohydride provided exclusively the *trans*-isomers **22** with respect to the bicyclic core, as confirmed via 2D-NOESY NMR analysis of the fully elaborated target ureas (Figure 2). Treatment with the appropriate aryl isocyanate completed the synthesis of the bicyclohexyl ureas **23**. In cases where R_2 = BOC-piperazinyl, acid treatment to remove the carbamate was followed by derivatization to provide **23g** and **23h**.

Conversion of the bromo-derivative **21b** to protected amine **21c** was achieved via Buchwald amination.[22] Following side chain installation and urea formation, **24a** was treated with acid to generate the free aniline, which was subsequently derivatized to provide **24b** and **24c**.

To facilitate SAR studies of side chain extension, reductive amination of the bicyclic ketone was achieved using 4-aminobutanol to obtain amino-alcohol **25**. Protection of the amine (BOC_2O) was followed by bromination of the alcohol and subsequent displacement by various amines. Carbamate removal and isocyanate treatment proceeded uneventfully to afford **27**. Though suitable for SAR studies of the pendant side chain and aryl urea, the synthetic route was limited in applicability toward SAR of the aryl terminus. In this initial approach, commitment to the terminal aryl substituent was made in the first step of the synthesis via the metalated aryl species, with limited exception such as in conversion of **21b** to **21c**, which precluded the use of aryl groups containing substituents incompatible with metal−

Table 1. Representative Profile of Bicyclo[4.1.0]heptyl Urea MCH-R1 Antagonists

	(+)-**34**	(+)-**35**
MCH-R1 K_i (nM)[a]	15.1 ± 3.7	11.4 ± 2.2
MCH-R1 K_b (nM)[b]	11	7
rat $AUC_{(0-24h)}$ (μM·h)[c]	16.4	14
B/P (6 h)[c]	1.1	0.7
MCH-R1 ex vivo binding (6 h)[d]	73	58
DIO mouse food intake (24 h)[e]	active*	inactive

[a] Mean values (n = 3) ± SEM. Inhibition of [^{125}I]-MCH binding to h-MCH-R1 expressed in Chinese Hamster Ovary (CHO) cells. [b] Mean values (n = 3) of inhibition of MCH-mediated Ca^{2+} influx into cells expressing hMCH-R1 via FLIPR assay. [c] Mean values (n = 3); dosed at 10 mg/kg, po. [d] Expressed as % inhibition of MCH-ADO binding relative to vehicle control (n = 3); dosed at 30 mg/kg, po. [e] Dosed at 30 mg/kg, po. Asterisk (*) indicates value is significantly different from that of vehicle.

Scheme 3. Preparation of Bicyclo[3.1.0]hexyl Ureas: Suzuki Route[a]

[a] (a) $NaBH_4$, $CeCl_3$, MeOH, 0 °C to room temperature; (b) $ArB(OH)_2$, K_3PO_4, Pd(dppf)Cl_2, DME/H_2O (4:1), 80 °C; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C to room temperature; (d) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C to room temperature; or TPAP, NMO, CH_2Cl_2; (e) 1-(3-aminopropyl)-4-methylpiperazine, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (f) aryl isocyanate, *i*-Pr_2NEt, CH_2Cl_2; (g) TBSCl, imid., DMF; (h) Et_2Zn, $ClCH_2I$, DCE, −20 to 0 °C; (i) TBAF, THF.

halogen exchange conditions. As a solution, an alternative synthetic route was sought which would enable installation of various aryl boronic acids via a cross-coupling protocol.

In a revised approach, the brominated product of the enol tautomer of cyclopentane-1,3-dione (**28**)[23] underwent Luche reduction[20] to provide the key intermediate **29** (Scheme 3). Elaboration with various aryl groups was performed via Suzuki coupling, and the remainder of the synthesis was carried out similar to the previous route. With electron-rich aryl groups, the allylic alcohols **30** were particularly acid-sensitive (vide supra), and silylation of **29** prior to aryl installation was required. Cyclopropanation of the silyloxy-allyl derivatives **31** either under standard conditions (Et_2Zn, CH_2I_2) or with added ligands such as TFA[24] was unsuccessful. However, use of chloroiodomethane under Denmark[25] conditions proceeded smoothly. Deprotection of the hydroxyl and subsequent oxidation generated the bicyclic ketones **21**. Elaboration to the bicyclohexyl ureas proceeded according to the initial route (Scheme 2).

The monoalkylated piperazine derivative **32** was synthesized via reductive alkylation with amine **33**[26] and subsequent urea formation followed by carbamate removal (Scheme 4).

Scheme 4. Preparation of **32**[a]

[a] (a) **21u**, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH; (b) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, i-Pr_2NEt, CH_2Cl_2; (c) H_2, Pd/C, MeOH.

Results and Discussion

Previously, a series of central aryl ring modifications to reduce the mutagenic potential of biaryl urea **7** was described which resulted in the identification of an alternative bicyclo[4.1.0]heptane core.[18,27] Evidence that this core served as a viable alternative to the biaryl was coupled with inspection of various biological and structural models, indicating that further optimization would be useful. For example, similar in vitro and pharmacokinetic properties of structurally analogous bicyclo[4.1.0]heptyl derivatives (+)-**34** and (+)-**35** (Table 1) did not lead to similar in vivo efficacy in a diet-induced obese (DIO) mouse model.[27] This model was an acute feeding model in which oral dosing was followed by measurement of body weight gain and food intake relative to controls over 24 h. Given these results, it was sought to incorporate a high throughput assay which could guide SAR development, and to which one could relate in vivo efficacy. To this end, incorporation of an ex vivo

Figure 3. Cyclopentyl urea MCH-R1 antagonists.

Table 2. Initial Side Chain SAR of Bicyclohexanes

no.	R_2	R_4	h-MCH-R1 K_i (nM)[a]	Rat $AUC_{(0-6h)}$ (ng h mL^{-1})[b]	*Ex vivo* binding (6h)[c]
23a	pyrrolidin-1-yl	3, 5-diCl	15 ± 2	1491	69 ± 6
23b	pyrrolidin-1-yl	3-Cl, 4-F	18 ± 1	822	
(+)-**23c**[d]	3-hydroxypyrrolidin-1-yl	3-Cl, 4-F	13 ± 1	585	32 ± 3
(-)-**23d**[e]	3-hydroxypyrrolidin-1-yl	3-Cl, 4-F	22 ± 3	2404	57 ± 5
23e	3-hydroxypyrrolidin-1-yl	3-CF_3, 4-F	7.1 ± 1.1	2190	81 ± 6
23f	piperidin-1-yl	3-Cl, 4-F	4.1 ± 0.8	999	57 ± 10
23g	4-methylpiperazin-1-yl	3-CF_3, 4-F	30 ± 1	1457	53 ± 5
23h	4-isobutylpiperazin-1-yl	3-CF_3, 4-F	9 ± 0.5	140	40 ± 3
27a	2-(morpholin-4-yl)ethyl	3-CF_3, 4-F	2.5 ± 0.1	450	64 ± 3
27b	2-(4-methylpiperazin-1-yl)ethyl	3-CF_3, 4-F	2.2 ± 0.4	1675	85 ± 5
27c	2-(piperidin-1-yl)ethyl	3-CF_3, 4-F	1.6 ± 0.1	1161	72 ± 10

[a] Mean values ($n = 8$) ± SEM. Inhibition of [^{125}I]-MCH binding to h-MCH-R1 expressed in Chinese Hamster Ovary (CHO) cells. [b] Data from pooled samples as described in ref 29, dosed at 10 mg/kg, po. [c] Expressed as a percent inhibition of MCH-ADO binding relative to vehicle control ± SEM ($n = 3$; dosed at 30 mg/kg, po). [d] Single diastereomer, absolute stereochemical configuration of the bicyclic core is enantiomeric to that shown. [e] Single diastereomer, absolute stereochemical configuration of the bicyclic core is as shown.

binding assay served as an expedient surrogate measure of receptor occupancy.[18,27] In this assay, compounds (+)-**34** and (+)-**35** provided significantly different degrees of receptor occupancy upon oral dosing, which was found to correlate with the in vivo profile of each in the acute DIO mouse feeding model. In the present study, the ex vivo binding assay served as an indispensable tool for determining receptor occupancy of several small molecule antagonists while negating the requirement for radiolabeling each of the individual molecules, permitting rapid identification of compounds providing optimal receptor coverage at several time points postdose.

Though significant overlap of side chain trajectories between the biaryl (**7**) and bicyclo[4.1.0]heptyl [(+)-**34** and (+)-**35**] ureas was observed with models, the possibility of further constraining the central bicycloalkyl ring to improve binding was considered. The cyclopentyl core would have the additional benefit of modestly reduced molecular weight, a property which has been shown to favorably impact bioavailability.[28] Cyclopentyl derivatives were synthesized and tested for binding affinity to the MCH-1 receptor (Figure 3). Cyclopentenyl derivative **9** provided moderate binding affinity (K_i = 605 nM), in contrast to previous observations with cyclohexenyl derivatives, which were more potent by at least 2 orders of magnitude.[18a,27] Saturation of the cyclopentyl substructure provided the *trans*-**14** and *cis*-**16** derivatives, of which the *trans*-isomer was considerably more potent (K_i = 161 and 2190 nM respectively for **14** and **16**). Again, this general trend was similar to that observed in the cyclohexyl series, which was also amenable to incorporation of a bicyclo[4.1.0]heptyl core.[27]

As an extension, it was reasoned that conversion of **14** to a bicyclo[3.1.0]hexyl core might be tolerated. This hypothesis proved correct upon testing of **23a** (K_i = 15 nM, Figure 3), and it was decided to further develop this new series in order to probe the SAR differences, if any, between it and the bicyclo-[4.1.0]heptyl series. Many of the SAR trends generated in the previous biaryl series served as useful guidelines.[17] In particular, 3,4- or 3,5-disubstitution with electron-withdrawing substituents was required on the aryl urea. Halogens or trifluoromethyl groups on the aryl urea improved pharmacokinetic properties in the series. The incorporation of cyclic amines on the side chain terminus was important in order to provide selectivity for MCH-R1 over the serotonin reuptake transporter and muscarinic receptors such as M2.

Initial exploration of the side chain terminus in the bicyclo-[3.1.0]hexyl series was achieved by fixing the 3-cyanoaryl substituent on the bicyclic core, which had been previously shown to be optimal in the biaryl and bicyclo[4.1.0]heptyl series.[17,27] Representative variations of side chains are shown in Table 2. While excellent potency was observed with most substituents, extension of the side chain provided optimal potency (compare **23g** with **27b**). Pharmacokinetic parameters were screened according to an in-house rapid rat protocol,[29] which indicated that many of the compounds provided acceptable exposure in rodents. Further studies showed that the bicyclohexanes had improved ex vivo binding at the 6 h timepoint relative to the bicycloheptanes. In some cases (**23e** and **27b**), greater than 80% receptor occupancy was obtained. Ex vivo binding studies were performed for several compounds, establishing the general trend that >70% receptor occupancy @ 6 h correlated with in vivo efficacy.[18,27]

Initial SAR studies were performed on racemic bicycloalkyl cores in order to maintain simplicity. As a result, where chiral side chains were used, compounds were initially tested as a diastereomeric mixture and are reported as such. To define

Table 3. Representative Side Chain Basicity Requirements of Bicyclohexanes

no.	R_5	h-MCH-R1 K_i (nM)[a]
24d	3-(4-methylpiperazin-1-yl)propyl	9.3 ± 0.2
23i	2-(pyridin-2-yl)ethyl	>3000
23j	3-(2-oxopyrrolidin-1-yl)propyl	1615 ± 9
23k	(1-(methylsulfonyl)piperidin-4-yl)methyl (NSO$_2$Me)	974 ± 170

[a] Mean values (n = 8) ± SEM. Inhibition of [^{125}I]-MCH binding to h-MCH-R1 expressed in Chinese Hamster Ovary (CHO) cells.

properties related to absolute configuration of the bicyclic core,[30] diastereomers (+)-**23c** and (−)-**23d** were separated and tested individually (Table 2). Compound (+)-**23c** showed greater binding affinity than diastereomer (−)-**23d** at h-MCH-R1; however, pharmacokinetic properties such as rat AUC and degree of ex vivo binding were considerably improved with diastereomer (−)-**23d**. Subsequent biological studies were generally performed on racemic material in order to optimize throughput.

Focusing further on side chain structure, it was observed that basicity of the nitrogen atom was critical for activity at MCH-R1 (Table 3). Aliphatic amines proved optimal, while aryl amines such as **23i** resulted in diminution of affinity. Likewise, amides such as **23j** and nonbasic side chains as in **23k**[31] were significantly less active. These results reinforced previous observations regarding side chain SAR made in the biaryl series.[17]

Regarding the terminal aryl ring of the bicyclic core, it was discovered that simple, unsubstituted phenyl derivatives such as **24e** were suitable for potency (Table 4). This stood in stark contrast to SAR developed in the biaryl urea[17] and the bicyclo-[4.1.0]heptyl urea[27] series, wherein the position and nature of substitution were of paramount significance with regard to activity at MCH-R1. In these preceding studies, any divergence from *meta*-substitution of the terminal aryl ring resulted in significantly decreased activity, while the nitrile substituent offered significant pharmacokinetic advantages such as increased AUC and $T_{1/2}$. Upon the observation that aryl SAR in the bicyclohexyl series may be unique, a series of substituents was then incorporated in order to further probe the structural requirements at this position. It was discovered that simple alkyl substituents (**24n**) or electron-rich groups (**24j**) were tolerated well in terms of binding affinity. Further, emerging trends indicated that *para*-substituents provided receptor occupancy

Table 4. Aryl SAR of Bicyclohexanes

no.	R_6	R_4	h-MCH-R1 K_i (nM)[a]	rat $AUC_{(0-6h)}$ (ng h mL^{-1})[b]	ex vivo binding[c] 6 h	ex vivo binding[c] 24 h
24b	*m*-NHAcPh	3-Cl, 4-F	2.5 ± 0.2	251	18 ± 4	0 ± 2
24c	*m*-$NHSO_2$MePh	3-Cl, 4-F	394 ± 3			
24d	*p*-SO_2Me Ph	3-Cl, 4-F	9.3 ± 0.2	2336	8 ± 4	
24e	Ph	3-Cl, 4-F	8.9 ± 0.5	1129	79 ± 2	0 ± 2
24f	*m*-OCF_3Ph	3-Cl, 4-F	29 ± 2	504	39 ± 3	12 ± 3
24g	*p*-OCF_3Ph	3-Cl, 4-F	13 ± 1.5	578	96 ± 3	15 ± 1
24h	*m*-ClPh	3-Cl, 4-F	15 ± 0.5	436		
24i	*m*-SO_2MePh	3-Cl, 4-F	727 ± 70			
24j	*m*-NH_2Ph	3-Cl, 4-F	10 ± 3		37 ± 2	17 ± 2
24k	*m*-FPh	3-Cl, 4-F	3.3 ± 0.2	722	73 ± 1	0 ± 3
24l	*m*-FPh	3-CF_3, 4-F	2.3 ± 0.3	888	85 ± 2	10 ± 2
24m	*p*-FPh	3-CF_3, 4-F	1.8 ± 0.1	2169	100 ± 4	29 ± 4
24n	*m*-MePh	3-Cl, 4-F	33 ± 1		0 ± 3	4 ± 2
24o	3-thiophenyl	3-Cl, 4-F	13 ± 1		25 ± 2	12 ± 1
24p	3-pyridyl	3-Cl, 4-F	2 ± 0.7	1001	25 ± 1	11 ± 2
24q	*m*-OMePh	3-CF_3, 4-F	2.9 ± 0.2	571	73 ± 1	0 ± 2
24r	*p*-OMePh	3-CF_3, 4-F	2.8 ± 0.3	438	100 ± 2	7 ± 2
24s	3,5-diFPh	3-Cl, 4-F	7 ± 0.5	2735	65 ± 2	0 ± 4
24t	3,4-diFPh	3-Cl, 4-F	4.4 ± 0.3	1608	97 ± 1	0 ± 3
24u	*p*-CNPh	3-CF_3, 4-F	2.7 ± 0.2	642	99 ± 4	58 ± 7
24v	3-CN, 4-F Ph	3-CF_3, 4-F	4 ± 0.1	3081	81 ± 2	36 ± 5
24w	3-F, 4-CN Ph	3-CF_3, 4-F	3.5 ± 0.1	1659	100 ± 2	6 ± 4

[a] Mean values ($n = 8$) ± SEM. Inhibition of [^{125}I]-MCH binding to h-MCH-R1 expressed in Chinese Hamster Ovary (CHO) cells. [b] Data from pooled samples as described in ref 29, dosed at 10 mg/kg, po. [c] Expressed as a percent inhibition of MCH-ADO binding relative to vehicle control ± SEM ($n = 3$; dosed at 30 mg/kg, po).

Table 5. Functional Antagonism Data of Selected Compounds[a]

no.	h-MCH-R1 K_b (nM)
24m	15.0 ± 5.0
24q	8.0 ± 3.0
24r	9.0 ± 4.0
24u	1.9 ± 1.1
32	9.0 ± 2.0

[a] Inhibition of MCH-mediated Ca^{2+} influx into cells expressing hMCH-R1 via FLIPR assay. Mean values ($n = 3$) ± SEM.

Table 6. In Vivo Efficacy in DIO Mice[a]

no.	food intake at time indicated (% of vehicle) 2 h	6 h	24 h
23e[b]	65.7 ± 11.8*	68.2 ± 7.4*	80.8 ± 5.3*
24g	86.2 ± 6.3	80.5 ± 5.3*	85.9 ± 5.3*
24u	77.3 ± 6.9	76.0 ± 5.4*	78.1 ± 5.1*
27a	88.0 ± 4.3	83.4 ± 6.4*	94.1 ± 5.1
27b	81.1 ± 4.5*	81.6 ± 5.7*	89.1 ± 5.8
27c	92.0 ± 5.7	101.1 ± 4.5	102.0 ± 3.1

[a] Values expressed as a percent of vehicle ± SEM (dosed at 30 mg/kg, po). Asterisk (*) indicates value is significantly different from that of vehicle. [b] Denotes a mixture of diastereomers.

of >90% at 6 h postdose (Table 4). To exploit this trend, receptor occupancy was measured at 24 h postdose for several compounds. Notably, it was discovered that **24u** provided >50% receptor coverage after 24 h, which would be suitable for qd dosing.

Functional antagonism at MCH-R1 was previously confirmed in the structurally related biaryl and bicyclo[4.1.0]heptyl series;[17,18,27] thus, exhaustive functional data was not obtained for the current series. Rather, a set of compounds was tested for inhibition of MCH-mediated Ca^{2+} influx into cells expressing h-MCH-R1 via FLIPR assay (Table 5). As anticipated, all compounds tested displayed functional antagonism at MCH-R1 with low nanomolar activities.

Having established a means to achieve extended receptor coverage, the more promising compounds were dosed orally in the 24 h DIO mouse in order to determine efficacy (Table 6). Results of a representative set of compounds indicated that several provided a statistically significant reduction of food intake relative to vehicle controls. Consistent with the previous studies, receptor occupancy of >70% at 6 h translated into acute efficacy in the DIO mouse model. Importantly, compounds with low ex vivo binding lacked efficacy and served as controls for two reasons. Primarily, the lack of efficacy observed with these compounds validated our use of the ex vivo binding protocol as a preliminary screen. Second, these results indicated that changes in food intake were unlikely a function of inherent compound toxicity. Compounds **23e**, **24g**, and **24u** showed efficacy at the endpoint of the study, and **24u** was chosen for detailed evaluation on the basis of a superior overall profile relative to that of the others.

As a precursor to further studies, pharmacokinetic properties of **24u** were determined in rats (Table 7). Despite high receptor occupancy over 24 h and demonstrative activity in vivo, **24u** exhibited modest AUC and $T_{1/2}$ in rodents. Further studies using ^{3}H-**24u** indicated a major metabolite in the brain, which was subsequently identified as the product resulting from demethylation of the terminal piperazine nitrogen atom (**32**, Scheme 4). Importantly, it was discovered that following dosing with

Table 7. Rat Pharmacokinetic Profile of Compound **24u**[a]

oral $AUC_{(0-24h)}$ (μM h)	3.9
IV half-life (h)	4.0
IV clearance (mL min^{-1} kg^{-1})	21.8
V_d(ss) (L kg^{-1})	5.6
bioavailability, *F* (%)	27

[a] $n = 3$; dosed at 10 mg/kg, iv/po.

Table 8. Effect of **24u** in 5 day DIO Mice Feeding Studies[a]

	cumulative food intake (g)	body weight change (%)
vehicle	17.0 ± 0.4	0.79 ± 0.62
10 mg/kg **24u**	14.9 ± 0.7*	−2.26 ± 0.74*
30 mg/kg **24u**	11.7 ± 0.7*	−6.04 ± 0.88*

[a] Values expressed ± SEM measured at endpoint ($n = 11$/group, dosed po, qd). Asterisk (*) indicates value is significantly different from that of vehicle.

Table 9. Effect of **24u** in 28 Day DIO Mice Feeding Studies[a]

	cumulative food intake (g)	body weight change (%)
vehicle	96.6 ± 1.5	7.71 ± 1.24
10 mg/kg **24u**	87.0 ± 2.0*	−1.48 ± 2.04*
30 mg/kg **24u**	79.4 ± 1.6*	−9.83 ± 0.91*

[a] Values expressed ± SEM measured at endpoint ($n = 11$/group, dosed po, qd). Asterisk (*) indicates value is significantly different from that of vehicle.

24u, the brain concentration of **32** (340 ng/g) was 17-fold greater than that of the parent **24u** (20 ng/g) after 24 h. Independent analysis of **32** showed that despite similar binding affinity (K_i = 8 nM, K_b = 9.0 nM) and good exposure (rat AUC_{0-6h} = 3472 ng·h/mL), receptor occupancy was poor (ex vivo binding 27% @ 6 h, 0% @ 24 h) when dosed as parent. Though the ex vivo assay does not distinguish between parent and metabolite, it serves as a suitable measure of receptor occupancy. Feeding studies were not undertaken with **32** based on our experience with poor ex vivo binding translating to lack of efficacy in the feeding model. Additionally, the fact that compounds incapable of terminal *N*-demethylation have demonstrated efficacy (**23e**) supports the hypothesis that efficacy with **24u** is not driven mainly by the formation of metabolite **32**.

Counter-screening of **24u** against a panel of 103 receptors and enzymes was performed at CEREP,[32] which revealed no appreciable affinity to other targets related to weight loss such as CB_1, H_3, or the serotonin reuptake transporter.

Having demonstrated acute efficacy, **24u** was evaluated in a subchronic (5 day) DIO mouse study (Table 8). At oral dosages of 10 and 30 mg/kg (qd), **24u** significantly decreased cumulative food intake and body weight relative to vehicle controls. At the endpoint, brains were harvested from a subset of mice (n = 3/group) for ex vivo binding studies at 24 h post-last dose. Receptor occupancy >99% was observed at 30 mg/kg and >65% at 10 mg/kg, which is consistent with the in vivo activity observed at these doses. These results indicate that prolonged dosing significantly increased receptor occupancy relative to that seen during the acute studies (vide supra).

Similar effects were also seen upon chronic (28 day) oral dosing with **24u** to DIO mice (Table 9). Efficacy was observed at 10 and 30 mg/kg, as evidenced by statistically significant reductions in cumulative food intake and weight gain at the endpoint of the study. As in the previous studies, no evidence of adverse behavioral effects or compound toxicity was observed with any of the treated animals.

Conclusions

A structurally unique bicyclo[3.1.0]hexyl urea series has been discovered as MCH-R1 antagonists for potential treatment of obesity. Through a number of SAR studies on this and structurally related series, selectivity has been obtained over non-MCH mechanisms, and the bicyclic moiety has been established as an effective replacement for the previously identified mutagenic biaryl aniline. Structure−activity studies also enabled exploitation of terminal aryl ring variations in order to optimize receptor occupancy. Incorporation of ex vivo binding studies as a measure of receptor occupancy provided a means to delineate the unique advantages of the bicyco[3.1.0]hexyl ureas relative to prior series. Further, ex vivo binding was used as a means to predict efficacy in vivo, which in turn was extended to chronic (28 day) rodent models. Compound **24u** was shown to exhibit efficacy in these models, having positive effects on food intake and weight gain throughout the duration of the studies while exhibiting no toxicity or adverse behavorial effects. Further studies regarding adiposity, energy expenditure, and other metabolic parameters will be reported in due course.[33]

Experimental Section

General. All reagents and solvents were obtained from commercial suppliers and used without further purification. All reactions were carried out under an inert atmosphere of nitrogen unless otherwise noted. Silica gel chromatography was performed using prepacked silica gel cartridges (Biotage). ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini-300 (300 MHz, ^{1}H; 75.5 MHz, ^{13}C) or XL-400 (400 MHz, ^{1}H; 100 MHz, ^{13}C) spectrometer and are reported as ppm downfield from Me_4Si. Purity was checked via LCMS analysis, performed on an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Alltech platinum C18, 3 μm, 33 mm × 7 mm ID; gradient flow: 0 min- 10% CH_3CN, 5 min- 95% CH_3CN, 7 min- 95% CH_3CN, 7.5 min- 10% CH_3CN, 9 min- stop. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ, and were within 0.4% of calculated values unless otherwise noted.

In vitro and in vivo data given throughout the text and in Tables 1−6, with exception of **23j**, **23k**, **24n**, **24o**, **24q**, and **24r** were collected for the amorphous hydrochloride salts. The hydrochloride salts were prepared by mixing the final compound with an excess of 1.0 M hydrogen chloride solution in diethyl ether followed by evaporation of the solvent.

***N*-[3-(3-Cyanophenyl)-2-cyclopenten-1-yl]-*N'*-(3,5-dichlorophenyl)-*N*-[2-(1-pyrrolidinyl)ethyl]urea (9).** A solution of ketone **8**[18a] (120 mg, 0.66 mmol) in CH_2Cl_2 (7 mL) was treated with 1-(2-aminoethyl)pyrrolidine (110 μL, 0.86 mmol) followed by NaB-$(OAc)_3$H (212 mg, 1.0 mmol). After 18 h, the reaction mixture was diluted with a solution of saturated aqueous $NaHCO_3$ and extracted with EtOAc (2×). The combined organic phases were dried and concentrated in vacuo. The crude product was dissolved in DCE (5 mL) and treated with diisopropylethylamine (350 μL, 2.0 mmol) followed by 3,5-dichlorophenyl isocyanate (250 mg, 1.32 mmol). After 36 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (75% EtOAc/Hex), followed by filtration, an EtOH rinse, and concentration in vacuo, furnished **9** (11.5 mg, 4% over 2 steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.51 (s, 1 H), 7.71 (s, 1 H), 7.68 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.46 (dd, J = 7.7, 7.7 Hz, 1H), 7.32 (d, J = 1.6 Hz, 2 H), 6.94 (m, 1 H), 6.12 (m, 1 H), 5.67 (m, 1 H), 3.32−3.22 (m, 2H), 2.90−2.54 (m, 8 H), 2.09−1.54 (m, 6 H); LCMS: 469.4, rt = 5.61 min (M + H^+), 91.5% purity; HRMS (FAB) *m/z* 469.1568 $[(M + H)^+]$; calcd for $C_{25}H_{27}N_4OCl_2$: 469.1562].

***cis*-3-(3-Hydroxy-cyclopentyl)-benzonitrile (11) and (±)-*trans*-3-(3-Hydroxy-cyclopentyl)-benzonitrile (12).** A solution of **10**[18a] (1.45 g, 7.83 mmol) in MeOH (70 mL) was treated with Pd/C (1.5

g, 0.7 mmol; 50% in H_2O) and stirred under 1 atm H_2 via balloon. After 1 h, the reaction mixture was filtered through Celite, rinsed with MeOH, and concentrated in vacuo. Flash chromatography (25% EtOAc/Hex) provided **11** (R_f = 0.35, 1.0 g, 68%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.52 (m, 3 H), 7.45 (dd, J = 7.7, 7.7 Hz, 1H), 4.47 (m, 1 H), 3.07 (m, 1 H), 2.46 (ddd, J = 13.7, 8.8, 6.0 Hz, 1H), 2.09 (m, 1 H), 1.94−1.80 (m, 4 H), 1.63 (ddd, J = 13.2, 8.8, 4.4 Hz, 1 H); followed by **12** (R_f = 0.30, 120 mg, 8%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.45 (m, 3 H), 7.37 (m, 1H), 4.55 (m, 1 H), 3.41 (m, 1 H), 2.31−2.06 (m, 2 H), 1.90 (s, 1 H), 1.71−1.62 (m, 3 H), 1.54 (m, 1 H).

***trans*-3-{3-[3-(4-Methyl-piperazin-1-yl)-propylamino]-cyclopentyl}-benzonitrile (13).** A solution of alcohol **11** (220 mg, 1.18 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with Et_3N (350 μL, 2.5 mmol) followed by MsCl (140 μL, 1.80 mmol). After 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. The residue was dissolved in propionitrile (10 mL), treated with K_2CO_3 (830 mg, 6.0 mmol) followed by 1-(3-aminopropyl)-4-methylpiperazine (1.02 mL, 6.0 mmol), and heated to 100 °C. After 18 h, the reaction mixture was cooled to ambient temperature, diluted with H_2O, and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried and concentrated in vacuo. Flash chromatography (10% NH_4OH/MeOH (1:9), 90% CH_2Cl_2) provided **13** (200 mg, 52% over 2 steps) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.42 (m, 3 H), 7.35 (dd, J = 7.7, 7.7 Hz, 1H), 3.27 (m, 1 H), 2.62 (t, J = 7.1 Hz, 2 H), 2.37 (t, J = 7.1 Hz, 2 H), 2.40−2.26 (m, 11 H), 2.26 (s, 3 H), 2.16 (m, 1 H), 1.93 (ddd, J = 7.7, 4.5, 4.4 Hz, 1 H), 1.80−1.48 (m, 4 H).

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-3-(3-cyanophenyl)cyclopentyl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (14).** A solution of amine **13** (80 mg, 0.245 mmol) in CH_2Cl_2 (2 mL) was treated with diisopropylethylamine (87 μL, 0.5 mmol) followed by 3-chloro-4-fluorophenyl isocyanate (40 μL, 0.319 mmol). After 18 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (5% MeOH/CH_2Cl_2), followed by filtration, an EtOH rinse, and concentration in vacuo gave **14** (74 mg, 61%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 7.49−7.44 (m, 4 H), 7.39 (d, J = 7.7 Hz, 1H), 7.31 (m, 1 H), 7.05 (dd, J = 8.8, 8.8 Hz, 1 H), 4.23 (dddd, J = 8.8, 8.8, 8.5, 8.5 Hz, 1 H), 3.50 (dddd, J = 8.8, 8.8, 8.5, 8.5 Hz, 1 H), 3.37 (t, J = 4.9 Hz, 2 H), 2.32−2.22 (m, 9 H), 2.25 (s, 3 H), 2.11−1.54 (m, 7 H); LCMS: 498.1, rt = 4.09 min (M + H^+), >99% purity; HRMS (FAB) m/z 498.2440 [(M + H)$^+$; calcd for $C_{27}H_{34}ClFN_5O$: 498.2436].

***cis*-3-{3-[3-(4-Methyl-piperazin-1-yl)-propylamino]-cyclopentyl}-benzonitrile (15).** A solution of alcohol **11** (300 mg, 1.60 mmol) in THF (10 mL) at 0 °C was treated with Ph_3P (840 mg, 3.20 mmol) followed by CBr_4 (1.06 g, 3.2 mmol). After 1 h, the reaction mixture was diluted with Et_2O, filtered through Celite, and concentrated in vacuo. Flash chromatography (2→10% Et_2O/Hex) provided the bromide (340 mg, 85%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.40 (m, 4 H), 4.66 (m, 1 H), 3.63 (dddd, J = 8.2, 8.2, 8.2, 8.2 Hz, 1 H), 2.56−2.28 (m, 4 H), 2.14 (dddd, J = 8.2, 5.5, 5.2, 4.9 Hz, 1 H), 1.70 (m, 1 H).

The bromide from the previous step (340 mg, 1.36 mmol) was dissolved in propionitrile (10 mL) and treated with K_2CO_3 (940 mg, 6.8 mmol) followed by 1-(3-aminopropyl)-4-methylpiperazine (1.15 mL, 6.8 mmol) and heated to 100 °C. After 18 h, the reaction mixture was cooled to ambient temperature, diluted with H_2O, and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried and concentrated in vacuo. Flash chromatography (10% NH_4OH/MeOH (1:9), 90% CH_2Cl_2) provided **15** (376 mg, 85%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.46 (m, 3 H), 7.40 (dd, J = 7.7, 7.7 Hz, 1H), 4.67 (m, 1 H), 3.64 (m, 1 H), 3.25 (m, 1 H), 3.06 (m, 1 H), 2.68 (t, J = 7.1 Hz, 2 H), 2.55−2.40 (m, 9 H), 2.28 (s, 3 H), 2.19−1.98 (m, 3 H), 1.75−1.67 (m, 4 H).

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[*cis*-3-(3-cyanophenyl)cyclopentyl]-*N*-[3-(4 -methyl-1-piperazinyl)propyl]urea (16).** A solution of amine **15** (80 mg, 0.245 mmol) in CH_2Cl_2 (2 mL) was treated with diisopropylethylamine (87 μL, 0.5 mmol) followed by 3-chloro-4-fluorophenyl isocyanate (40 μL, 0.319 mmol). After 18 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (5% MeOH/ CH_2Cl_2), followed by filtration, an EtOH rinse, and concentration in vacuo, gave **16** (96 mg, 79%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1 H), 7.54−7.47 (m, 4 H), 7.38 (d, J = 7.7 Hz, 1H), 7.36 (m, 1 H), 7.06 (dd, J = 8.8, 8.8 Hz, 1 H), 4.34 (m, 1 H), 3.37 (t, J = 5.5 Hz, 2 H), 3.07 (m, 1 H), 2.59−2.40 (m, 9 H), 2.26 (s, 3 H), 2.26−1.79 (m, 7 H); LCMS: 498.1, rt = 4.03 min (M + H^+), >99% purity; HRMS (FAB) m/z 498.2431 [(M + H)$^+$; calcd for $C_{27}H_{34}ClFN_5O$: 498.2436].

General Synthesis of 21: Method A. (a) (3-Oxo-cyclopent-1-enyl)-benzonitrile (8). A solution of 3-bromobenzonitrile (26.8 g, 147.1 mmol) in THF (1000 mL) at −78 °C was treated with a solution of *n*-butyllithium (2.5 M in hexanes; 61.0 mL, 155 mmol) such that the reaction temperature remained less than or equal to −78 °C. After 15 min, a solution of 3-methoxy-2-cyclopenten-1-one (15 g, 134 mmol) in THF (80 mL) was added such that the reaction temperature remained less than or equal to −78 °C. The reaction mixture was warmed to −20 °C over 1.5 h, quenched with a solution of 1 N HCl, and concentrated in vacuo to remove THF. A solution of 1 N HCl (100 mL) was added, and then the solution was stirred for 45 min and extracted with EtOAc (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized at 0 °C from a solution of 1 N HCl, filtered, and rinsed with cold 1 N HCl, H_2O, and ether to provide **8** (14.4 g, 59%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 1.6 Hz, 1 H), 7.90 (d, J = 7.7 Hz, 1 H), 7.74 (d, J = 7.7 Hz, 1 H), 7.59 (d, J = 7.7 Hz, 1 H), 6.63 (d, J = 1.6 Hz, 1 H), 3.07−3.03 (m, 2 H), 2.65−2.62 (m, 2 H).

(b) 3-(3-Hydroxy-cyclopent-1-enyl)-benzonitrile (10). A solution of **8** (7.88 g, 43.0 mmol) in methanol (100 mL) at 0 °C was treated with $CeCl_3 \cdot 7H_2O$ (20.5 g, 55.0 mmol) followed portionwise by $NaBH_4$ (2.10 g, 55.0 mmol). The reaction was warmed to ambient temperature over 12 h, quenched with saturated aqueous NH_4Cl, and concentrated to remove MeOH. The concentrate was diluted with H_2O and extracted with EtOAc (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated in vacuo. Trituration (10% EtOAc/Hex) at 0 °C and filtration afforded the alcohol **10** (6.39 g, 80%) as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 7.7, 1.6 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 6.30 (dd, J = 3.8, 1.6 Hz, 1H), 5.05 (m, 1H), 2.90 (m, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 1.92 (m, 1H), 1.62 (br s, 1H).

(c) 3-(4-Hydroxy-bicyclo[3.1.0]hex-1-yl)-benzonitrile (20a: R_1 = *m*-CN). A solution of allylic alcohol **10** (0.50 g, 2.7 mmol) in CH_2Cl_2 (75 mL) was treated with Et_2Zn (1.0 M in hexanes; 14 mL, 14 mmol). After 10 min, the reaction mixture was cooled to 0 °C, treated with a solution of CH_2I_2 (1.13 mL, 14 mmol) in CH_2Cl_2 (10 mL) dropwise over 10 min, and allowed to warm to ambient temperature. After 48 h, the reaction mixture was quenched slowly with saturated aqueous NH_4Cl and stirred for 10 min. The reaction mixture was extracted with CH_2Cl_2 (2×), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried, and concentrated in vacuo. Flash chromatography (40% EtOAc/Hex) gave **20a** (500 mg, 93%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.32 (m, 4 H), 4.69 (ddd, J = 12.1, 7.7, 4.4 Hz, 1H), 2.20−1.85 (m, 4H), 1.80 (br s, 1H), 1.38−1.25 (m, 2H), 0.85 (dd, J = 8.2, 5.5 Hz, 1H).

(d) 3-(4-Oxo-bicyclo[3.1.0]hex-1-yl)-benzonitrile (21a). A solution of alcohol **20a** (0.50 g, 2.51 mmol) in CH_2Cl_2 (25 mL) at 0 °C was treated with pyridine (445 μL, 5.50 mmol) followed by Dess−Martin periodinane (2.12 g, 5.0 mmol) and warmed to ambient temperature. After 2 h, 3 drops of H_2O were added. After 30 min further, the reaction was quenched with saturated aqueous

$NaHCO_3$ and saturated aqueous Na_2SO_3 and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Flash chromatography (25% EtOAc/Hex) gave **21a** (440 mg, 89%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.52 (m, 2 H), 7.47−7.43 (m, 2H), 2.45 (m, 1H), 2.40−2.25 (m, 3H), 2.17 (dd, *J* = 9.3, 5.5 Hz, 1H), 1.61−1.52 (m, 2H).

(e) 5-(3-Bromo-phenyl)-bicyclo[3.1.0]hexan-2-one (21b). Following procedures similar to that described for the synthesis of **21a** and using *m*-dibromobenzene (51%, 4 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.37 (m, 2 H), 7.23−7.14 (m, 2 H), 2.47−2.24 (m, 5 H), 2.15 (dd, *J* = 9.3, 3.3 Hz, 1 H), 1.58 (dd, *J* = 8.8, 3.8 Hz, 1 H), 1.48 (dd, *J* = 4.9, 3.8 Hz, 1 H).

(f) [3-(4-Oxo-bicyclo[3.1.0]hex-1-yl)-phenyl]-carbamic Acid *tert*-Butyl Ester (21c). A tube purged with argon was charged with **21b** (875 mg, 3.48 mmol), *tert*-butyl carbamate (490 mg, 4.18 mmol), K_2CO_3 (962 mg, 6.96 mmol), and CuI (34 mg, 0.18 mmol), evacuated, and purged with argon. *N*,*N*′-dimethylethylenediamine (37 μL, 0.35 mmol) and toluene (3 mL) were added, and the tube was sealed and heated to 110 °C. After 18 h, the reaction mixture was cooled to ambient temperature, filtered through Celite, rinsed with EtOAc, and concentrated in vacuo. Flash chromatography (20% EtOAc/Hex) gave **21c** (450 mg, 45%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1 H), 7.23 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.15 (d, *J* = 8.7 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 6.56 (s, 1 H), 2.43−2.22 (m, 4 H), 2.11 (dd, *J* = 9.3, 3.3 Hz, 1 H), 1.46 (dd, *J* = 9.3, 4.9 Hz, 1 H), 1.51 (s, 9 H), 1.40 (m, 1 H).

General Synthesis of 21: Method B. (a) 3-Bromo-cyclopent-2-enol (29). A solution of 3-bromo-cyclopentenone[23] (21 g, 100 mmol) in methanol (200 mL) at 0 °C was treated with $CeCl_3·7H_2O$ (56.6 g, 152 mmol) followed portionwise by $NaBH_4$ (5.75 g, 152 mmol). The reaction was warmed to ambient temperature over 12 h, quenched with saturated aqueous NH_4Cl, and concentrated to remove MeOH. The concentrate was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried and concentrated in vacuo. Flash chromatography (15% EtOAc/Hex) afforded alcohol **29** (11.8 g, 70%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (m, 1 H), 4.79 (m, 1 H), 2.80 (m, 1 H), 2.60−2.35 (m, 2 H), 1.82 (m, 1 H), 1.65 (m, 1 H).

(b) 3-(4-Methanesulfonyl-phenyl)-cyclopent-2-enol (30d: Ar = *p*-MeO₂SPh). A solution of bromide **29** (1.04 g, 6.3 mmol) in 3:1:1 tol:EtOH:H_2O (300 mL) was treated with (4-methanesulfonyl)phenyl boronic acid (1.6 g, 8.19 mmol), Na_2CO_3 (2.0 g, 19.0 mmol), LiCl (0.40 g, 9.4 mmol), and $Pd(Ph_3P)_4$ (0.74 g, 0.64 mmol) and heated to 80 °C. After 1.5 h, the reaction was cooled to ambient temperature, diluted with CH_2Cl_2 and 0.5 mL of Et_3N, washed with aqueous $NaHCO_3$, dried, and concentrated in vacuo. Flash chromatography (35% EtOAc/Hex) afforded alcohol **30d** (0.61 g, 40%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2 H), 7.66−7.45 (m, 3 H), 6.40 (dd, *J* = 3.8, 1.6 Hz, 1H), 5.05 (m, 1H), 3.09 (d, *J* = 7.1 Hz, 1 H), 3.05 (s, 3 H), 2.90 (m, 1 H), 2.64 (m, 1H), 2.53 (m, 1 H), 1.96 (m, 1H), 1.71 (br s, 1 H).

(c) 5-(4-Methanesulfonyl-phenyl)-bicyclo[3.1.0]hexan-2-one (21d: Ar = *p*-MeO₂SPh). Following the procedure described for the synthesis of **21a** using **30d** (70%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2 H), 7.40 (d, *J* = 8.2 Hz, 2 H), 3.05 (s, 3 H), 2.56−2.11 (m, 4 H), 1.64−1.58 (m, 3 H).

General Synthesis of 21: Method C. (a) *tert*-Butyl-dimethyl-(3-*m*-tolyl-cyclopent-2-enyloxy)-silane (31n: Ar = *m*-MePh). A solution of **29** (1.55 g, 9.51 mmol) in DMF (5 mL) was treated with imidazole (647 mg, 9.51 mmol) and TBSCl (1.43 g, 9.51 mmol). After 5 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O (3×). The combined organic extracts were dried and concentrated in vacuo to provide the silyl ether (3.0 g, >99%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1 H), 4.73 (m, 1 H), 2.63 (m, 1 H), 2.46 (m, 1 H), 2.23 (m, 1 H), 1.69 (m, 1 H), 0.78 (s, 9 H), −0.03 (s, 6 H).

The silyl ether from the previous step (1.2 g, 4.35 mmol) in 3:1:1 tol:EtOH:H_2O (70 mL) was treated with (3-methyl)phenyl boronic acid (887 mg, 6.52 mmol), Na_2CO_3 (1.38 g, 13.0 mmol), LiCl (0.28 g, 6.52 mmol), and $Pd(Ph_3P)_4$ (0.50 g, 0.44 mmol) and heated to 80 °C. After 1.5 h, the reaction was cooled to ambient temperature, diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried, and concentrated in vacuo. Flash chromatography (2% Et_2O/Hex) afforded alcohol **31n** (745 mg, 60%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2 H), 7.24 (dd, *J* = 8.2, 7.1 Hz, 1 H), 7.10 (d, *J* = 7.1 Hz, 1 H), 6.12 (dd, *J* = 3.8, 2.2 Hz, 1 H), 5.08 (m, 1 H), 2.88 (m, 1 H), 2.60 (m, 1H), 2.40 (m, 1 H), 2.37 (s, 3 H), 1.87 (m, 1 H), 0.96 (s, 9 H), 0.15 (s, 6 H).

(b) 5-*m*-Tolyl-bicyclo[3.1.0]hexan-2-one (21n). A solution of Et_2Zn (1.0 M in hexanes; 1.6 mL, 1.6 mmol) in DCE (3.5 mL) at 0 °C was treated with $ClCH_2I$ (231 μL, 3.17 mmol) dropwise over 5 min. After an additional 10 min, a solution of **31n** (228 mg, 0.792 mmol) in DCE (0.5 mL) was added dropwise over 10 min and allowed to warm to ambient temperature. After 2 h, the reaction mixture was quenched slowly with saturated aqueous NH_4Cl and stirred for 10 min. The reaction mixture was extracted with CH_2Cl_2 (2×), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried, and concentrated in vacuo. A second iteration was performed using 517 mg, 1.80 mmol of **31n**, 3.6 mL of Et_2Zn, and 523 μL of $ClCH_2I$. Flash chromatography (2% Et_2O/Hex, pretreating the column with 2% Et_3N/Hex) of the combined crude products gave the cyclopropane (646 mg, 83%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 7.17−6.99 (m, 3 H), 4.68 (m, 1 H), 2.36 (s, 3 H), 2.17−1.90 (m, 3 H), 1.79 (ddd, *J* = 8.2, 4.4, 3.8 Hz, 1 H), 1.38−1.30 (m, 2 H), 0.96 (s, 9 H), 0.84 (dd, *J* = 7.7, 5.4 Hz, 1 H), 0.15 (s, 3 H), 0.13 (s, 3 H).

The cyclopropane from the previous step (646 mg, 2.14 mmol) was dissolved in THF (5 mL) and treated with TBAF (1.0 M in THF; 4.2 mL, 4.2 mmol). After 18 h, the reaction mixture was concentrated in vacuo. Flash chromatography (25% Et_2OAc/Hex) afforded the alcohol (394 mg, 98%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.8, 7.1 Hz, 1 H), 7.02−6.97 (m, 3 H), 4.71 (m, 1 H), 2.35 (s, 3 H), 2.19−2.03 (m, 3 H), 1.90 (ddd, *J* = 8.2, 4.4, 3.8 Hz, 1 H), 1.31−1.25 (m, 2 H), 0.85 (dd, *J* = 8.2, 5.5 Hz, 1 H).

A solution of alcohol from the previous step (394 mg, 2.09 mmol) in CH_2Cl_2 (2 mL) at 0 °C was treated with pyridine (375 μL, 4.59 mmol) followed by Dess−Martin periodinane (1.77 g, 4.18 mmol) and warmed to ambient temperature. After 2 h, 3 drops of H_2O were added. After 6 h further, the reaction was quenched with saturated aqueous $NaHCO_3$, saturated aqueous Na_2SO_3, and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Flash chromatography (10% EtOAc/Hex) gave **21n** (185 mg, 47%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.7, 7.7 Hz, 1 H), 7.08−7.04 (m, 3 H), 2.44−2.22 (m, 4 H), 2.36 (s, 3 H), 2.11 (dd, *J* = 9.3, 6.0 Hz, 1 H), 1.60 (dd, *J* = 9.3, 4.4 Hz, 1 H), 1.47 (dd, *J* = 4.4, 3.3 Hz, 1 H).

Representative Procedure for the Synthesis of Compounds 23a−k. (a) *N*-[5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-(3,5-dichlorophenyl)-*N*-[2-(1-pyrrolidinyl)ethyl]urea (23a). A solution of ketone **21a** (100 mg, 0.51 mmol) in CH_2Cl_2 (1 mL) was treated with 1-(2-aminoethyl)pyrrolidine (98 μL, 0.77 mmol) followed by titanium tetraisopropoxide (200 μL, 0.67 mmol). After 18 h, the reaction mixture was diluted with MeOH (1 mL) and sodium borohydride (38 mg, 1.0 mmol) was added. After 2 h further, the reaction mixture was diluted with a solution of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (4×). The combined organic phases were dried and concentrated in vacuo to provide the crude amine (140 mg). A portion of the crude product (66 mg) was dissolved in CH_2Cl_2 (2 mL) and treated with diisopropylethylamine (78 μL, 0.45 mmol) followed by 3,5-dichlorophenyl isocyanate (63 mg, 0.335 mmol). After 18 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (75% EtOAc/Hex), followed by filtration, an EtOH rinse, and concentration in vacuo, furnished **23a** (59 mg, 50% over 2 steps) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.24 (s, 1 H), 7.48−7.37 (m, 4 H), 7.29 (s, 2 H), 6.92 (s, 1 H), 5.06 (dddd, *J* = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 2.96−2.66 (m, 5 H), 2.18−1.89 (m, 8 H), 1.73 (ddd, *J* = 12.1, 8.2, 4.4 Hz, 1 H), 1.31−1.21 (m, 2 H), 0.95 (dd, *J* = 6.6,

6.6 Hz, 1H); LCMS: 483.3, rt = 5.50 min (M + H$^+$), 95.5% purity; HRMS (FAB) *m/z* 483.1722 [(M + H)$^+$; calcd for $C_{26}H_{29}Cl_2N_4O$: 483.1718]. Anal. ($C_{26}H_{28}Cl_2N_4O{\cdot}HCl{\cdot}0.5H_2O$): C, H, N.

Following procedures similar to those described for compound **23a**, we prepared the following compounds.

(b) *N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-cyanophenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[2-(1-pyrrolidinyl)ethyl]urea (23b). Using 3-chloro-4-fluorophenyl isocyanate (54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.96 (s, 1 H), 7.46−7.36 (m, 5 H), 7.14 (m, 1 H), 7.00 (dd, J = 8.8, 8.8 Hz, 1 H), 5.07 (dddd, J = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 3.49 (dd, J = 15.4, 7.1 Hz, 1 H), 3.39 (dd, J = 15.4, 5.5 Hz, 1 H), 2.94 (dd, J = 12.6, 7.1 Hz, 1 H), 2.94−2.73 (m, 4 H), 2.17−1.85 (m, 8 H), 1.71 (ddd, J = 12.1, 8.2, 4.4 Hz, 1 H), 1.28−1.20 (m, 2 H), 0.94 (dd, J = 6.6, 6.6 Hz, 1H); LCMS: 467.3, rt = 5.23 min (M + H$^+$), 93.5% purity; HRMS (FAB) *m/z* 467.2020 [(M + H)$^+$; calcd for $C_{26}H_{29}ClFN_4O$: 467.2014]. Anal. ($C_{26}H_{28}ClFN_4O{\cdot}HCl{\cdot}H_2O$): C, H, N.

(c) (+)-*N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-cyano-phenyl)bicyclo[3.1.0]h ex-2-yl]-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (23c) and (−)-*N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (23d). Using (*R*)-3-hydroxy-1-(2-aminoethyl)pyrrolidine[34] and 3-chloro-4-fluorophenyl isocyanate. Diastereomers were separated via preparative HPLC using a chiral AD column (25% *i*-PrOH/Hex, isocratic), flow rate 40 mL/min, to provide **(+)-23c** (16%, 2 steps): $[\alpha]^{25}_D$ +65.5° (*c* 1.0, $CHCl_3$); rt = 76 min, 100% purity; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1 H), 7.63 (dd, J = 6.6, 2.2 Hz, 1 H), 7.46−7.43 (m, 2 H), 7.40−7.36 (m, 2 H), 7.34 (m, 1 H), 6.98 (dd, J = 8.8, 8.8 Hz, 1 H), 5.02 (dddd, J = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 4.52 (m, 1 H), 3.48 (dd, J = 15.4, 7.1 Hz, 1 H), 3.39 (dd, J = 15.4, 5.5 Hz, 1 H), 3.10 (ddd, J = 8.2, 7.4, 6.6 Hz, 1 H), 2.93−2.73 (m, 4 H), 2.58 (m, 1 H), 2.29−1.81 (m, 6 H), 1.72 (ddd, J = 12.1, 8.2, 4.4 Hz, 1 H), 1.31−1.21 (m, 2 H), 0.94 (dd, J = 6.6, 6.6 Hz, 1H); LCMS: 483.1, rt = 4.85 min (M + H$^+$), >99% purity; HRMS (FAB) *m/z* 483.1960 [(M + H)$^+$; calcd for $C_{26}H_{29}ClFN_4O_2$: 483.1963]; and **(−)-23d** (20%, 2 steps): $[\alpha]^{25}_D$ −46.4° (*c* 1.0, $CHCl_3$); rt = 159 min, 100% purity; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1 H), 7.63 (dd, J = 6.6, 2.2 Hz, 1 H), 7.47−7.44 (m, 2 H), 7.41−7.37 (m, 2 H), 7.30 (m, 1 H), 6.99 (dd, J = 8.8, 8.8 Hz, 1 H), 5.05 (dddd, J = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 4.53 (m, 1 H), 3.50 (dd, J = 15.4, 7.1 Hz, 1 H), 3.39 (dd, J = 15.4, 5.5 Hz, 1 H), 3.17 (ddd, J = 8.2, 7.4, 6.6 Hz, 1 H), 2.99−2.74 (m, 4 H), 2.54 (m, 1 H), 2.27−1.84 (m, 6 H), 1.72 (ddd, J = 12.1, 8.2, 4.4 Hz, 1 H), 1.30−1.23 (m, 2 H), 0.95 (dd, J = 6.6, 6.6 Hz, 1H); LCMS: 483.1, rt = 4.84 min (M + H$^+$), >99% purity; HRMS (FAB) *m/z* 483.1960 [(M + H)$^+$; calcd for $C_{26}H_{29}ClFN_4O_2$: 483.1963]. Anal. ($C_{26}H_{28}ClFN_4O_2{\cdot}HCl$): C, H, N.

(d) *N*-[*trans*-5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[2-(3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (23e). Using (*R*)-3-hydroxy-1-(2-aminoethyl)-pyrrolidine and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (51%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.68 (d, J = 14.3 Hz, 1 H), 7.71−7.68 (m, 2 H), 7.46−7.36 (m, 4 H), 7.04 (dd, J = 9.9, 9.9 Hz, 1 H), 5.06 (ddd, J = 9.9, 7.1, 3.3 Hz, 1 H), 4.50 (m, 1 H), 3.50 (dd, J = 15.4, 7.1 Hz, 1 H), 3.41 (dd, J = 15.4, 7.1 Hz, 1 H), 3.13 (ddd, J = 15.9, 15.4, 8.2 Hz, 1 H), 2.98−2.71 (m, 4 H), 2.55 (ddd, J = 15.9, 15.9, 8.8 Hz, 1 H), 2.42 (br s, 1 H), 2.28−1.80 (m, 5 H), 1.72 (ddd, J = 7.7, 7.1, 3.3 Hz, 1 H), 1.34−1.19 (m, 2 H), 0.94 (dd, J = 7.1, 6.0 Hz, 1 H); LCMS: 517.1, rt = 4.50 min (M + H$^+$), 98.3% purity; HRMS (FAB) *m/z* 517.2250 [(M + H)$^+$; calcd for $C_{27}H_{29}N_4O_2F_4$: 517.2227]. Anal. ($C_{27}H_{28}N_4O_2F_4{\cdot}HCl{\cdot}0.5H_2O$): C, H, N.

(e) *N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-cyanophenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[2-(1-piperidinyl)ethyl]urea (23f). Using 1-(2-aminoethyl)piperidine and 3-chloro-4-fluorophenyl isocyanate (70%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1 H), 7.60 (dd, J = 6.6, 2.2 Hz, 1 H), 7.47−7.44 (m, 2 H), 7.38−7.37 (m, 2 H), 7.23 (m, 1 H), 7.03 (dd, J = 8.8, 8.8 Hz, 1 H), 5.07 (dddd, J = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 3.49 (dd, J = 15.4, 7.1 Hz, 1 H), 3.37 (dd, J = 15.4, 5.5 Hz, 1 H), 2.71−2.58 (m, 6 H), 2.18−1.94 (m, 3 H), 1.74−1.52 (m, 7 H), 1.29−1.23 (m, 2 H), 0.94 (dd, J = 6.6, 6.6 Hz, 1H); LCMS: 481.1, rt = 4.88 min (M + H$^+$), 97.7% purity; HRMS (FAB) *m/z* 481.2173 [(M + H)$^+$; calcd for $C_{27}H_{29}ClFN_4O$: 481.2170]. Anal. ($C_{27}H_{30}ClFN_4O{\cdot}HCl{\cdot}0.5H_2O$): C, H, N.

(f) *N*-[*trans*-5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[2-(4-methyl-1-piperazinyl)-ethyl]urea (23g). Using 1-(2-aminoethyl)-4-Boc-piperazine and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, the Boc-protected urea was obtained (29%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.66−7.38 (m, 6 H), 7.11 (dd, J = 9.9, 9.3 Hz, 1 H), 5.08 (dddd, J = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 3.59−3.43 (m, 6 H), 2.76−2.62 (m, 5 H), 2.17−1.97 (m, 4 H), 1.72 (ddd, J = 7.6, 4.4, 4.4 Hz, 1 H), 1.47 (s, 9 H), 1.27−0.97 (m, 2 H), 0.96 (dd, J = 7.1, 5.4 Hz, 1H).

A solution of the Boc-protected urea (0.45 g, 0.731 mmol) in CH_2Cl_2 (7 mL) at 0 °C was treated with TFA (1.5 mL) and warmed to ambient temperature. After 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo to give the free piperazine (370 mg, 98%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1 H), 7.71−7.37 (m, 6 H), 7.11 (dd, J = 9.8, 9.3 Hz, 1 H), 5.07 (dddd, J = 8.4, 8.4, 4.9, 4.9 Hz, 1 H), 3.56 (dd, J = 15.9, 6.0 Hz, 1 H), 3.40 (dd, J = 16.2, 6.0 Hz, 1 H), 2.99 (t, J = 4.9 Hz, 2 H), 2.78−2.61 (m, 6 H), 2.18−1.93 (m, 4 H), 1.72 (ddd, J = 7.7, 4.5, 4.4 Hz, 1 H), 1.36−1.23 (m, 2 H), 0.97 (dd, J = 7.7, 5.5 Hz, 1H).

A solution of the piperazine from the previous step (80 mg, 0.155 mmol) in CH_2Cl_2 (2 mL) was treated with a solution of formaldehyde (50 μL, 0.6 mmol; 37% in H_2O) followed by $NaB(OAc)_3H$ (160 mg, 0.75 mmol) and Na_2SO_4 (350 mg, 2.5 mmol). After 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (5% MeOH/CH_2Cl_2) provided **23g** (47 mg, 57%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1 H), 7.76 (m, 1 H), 7.62 (m, 1 H), 7.48−7.44 (m, 2 H), 7.39−7.37 (m, 2 H), 7.11 (dd, J = 8.8, 8.8 Hz, 1 H), 5.07 (dddd, J = 8.8, 8.8, 5.2, 5.2 Hz, 1 H), 3.53 (dd, J = 15.4, 7.1 Hz, 1 H), 3.41 (dd, J = 15.4, 5.5 Hz, 1 H), 2.79−2.55 (m, 10 H), 2.33 (s, 3 H), 2.19−1.93 (m, 3 H), 1.71 (ddd, J = 12.1, 8.2, 4.4 Hz, 1 H), 1.29−1.20 (m, 2 H), 0.96 (dd, J = 6.6, 6.6 Hz, 1H); LCMS: 530.1, rt = 4.85 min (M + H$^+$), 91.9% purity; HRMS (FAB) *m/z* 530.2538 [(M + H)$^+$; calcd for $C_{28}H_{32}F_4N_5O$: 530.2543]. Anal. ($C_{28}H_{31}F_4N_5O{\cdot}HCl{\cdot}H_2O$): C, H, N.

(g) *N*-[*trans*-5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[2-[4-(2-methylpropyl)-1-piperazinyl]ethyl]urea (23h). Following the procedure described for **23g** and using the piperazine intermediate from the synthesis of **23g** and isobutyraldehyde (65%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (s, 1 H), 7.75 (m, 1 H), 7.65 (m, 1 H), 7.48−7.45 (m, 2 H), 7.39−7.37 (m, 2 H), 7.11 (dd, J = 8.7, 8.7 Hz, 1 H), 5.08 (dddd, J = 8.7, 8.7, 5.1, 5.1 Hz, 1 H), 3.53 (dd, J = 15.3, 7.1 Hz, 1 H), 3.42 (dd, J = 15.3, 5.5 Hz, 1 H), 2.71−2.52 (m, 10 H), 2.19−1.93 (m, 5 H), 1.78−1.69 (m, 2 H), 1.30−1.24 (m, 3 H), 0.99 (dd, J = 6.6, 6.6 Hz, 6 H); LCMS: 572.1, rt = 5.12 min (M + H$^+$), 99% purity; HRMS (FAB) *m/z* 572.3020 [(M + H)$^+$; calcd for $C_{31}H_{38}F_4N_5O$: 572.3012]. Anal. ($C_{31}H_{37}F_4N_5O{\cdot}2HCl$): C, H, N.

(h) *N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-[4(methylsulfonyl)-phenyl]bicyclo[3.1.0]hex-2-yl]-*N*-[2-(2-pyridinyl)ethyl]urea (23i). Following procedures described for **23a** and using **21d** (synthesized according to method B), 2-(2-aminoethyl)pyridine and 3-chloro-4-fluorophenyl isocyanate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 8.65 (d, J = 4.4 Hz, 1 H), 7.85 (d, J = 8.2 Hz, 2 H), 7.75−7.67 (m, 2 H), 7.42 (m, 1 H), 7.38 (d, J = 8.2 Hz, 2 H), 7.25−7.22 (m, 2 H), 7.06 (dd, J = 8.8, 8.8 Hz, 1 H), 5.20 (dddd, J = 8.7, 8.7, 5.0, 5.0 Hz, 1 H), 3.93 (m, 1 H), 3.76 (m, 1 H), 3.23 (t, J = 6.6 Hz, 2 H), 3.05 (s, 3 H), 2.27−1.99 (m, 3 H), 1.86 (ddd, J = 12.2, 8.2, 4.5 Hz, 1 H), 1.48 (t, J = 4.9 Hz, 1 H), 1.37 (m, 1 H), 1.11 (dd, J = 7.7, 5.4 Hz, 1 H); LCMS: 528.1, rt = 4.39 min

(M + H$^+$), 92% purity; HRMS (FAB) *m/z* 528.1510 [(M + H)$^+$; calcd for $C_{27}H_{28}ClFN_3O_3S$: 528.1524].

(i) *N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-[4(methylsulfonyl)-phenyl]bicyclo[3.1.0]hex-2-yl]-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-urea (23j). Following procedures described for **23a** and using **21d** (synthesized according to method B), *N*-(3-aminopropyl)-2-pyrrolidinone and 3-chloro-4-fluorophenyl isocyanate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 7.60 (m, 1 H), 7.47 (m, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.03 (m, 1 H), 6.35 (s, 1 H), 4.81 (dddd, *J* = 8.8, 8.8, 4.9, 4.9 Hz, 1 H), 3.69−3.53 (m, 2 H), 3.04−3.00 (m, 6 H), 2.26−1.97 (m, 3 H), 1.73 (ddd, *J* = 12.2, 8.2, 4.5 Hz, 1 H), 1.44−1.31 (m, 1 H), 1.11 (dd, *J* = 7.7, 5.3 Hz, 1 H); LCMS: 548.1, rt = 4.51 min (M + H$^+$), 90% purity; HRMS (FAB) *m/z* 548.1772 [(M + H)$^+$; calcd for $C_{27}H_{32}ClFN_3O_4S$: 548.1786]. Anal. ($C_{27}H_{31}ClFN_3O_4S\cdot 3H_2O$): C, H, N.

(j) 4-[[[[(3-Chloro-4-fluorophenyl)amino]carbonyl][(*trans*-5-[4-(methylsulfonyl)phenyl]bicyclo[3.1.0]hex-2-yl]amino]methyl]-1-(methylsulfonyl)piperidine (23k). Following procedures described for **23a** and using **21d** (synthesized according to method B), *N*-methanesulfonyl-4-(1-aminomethyl)piperidine,[31] and 3-chloro-4-fluorophenyl isocyanate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.80 (m, 2 H), 7.54 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.33−7.30 (m, 2 H), 7.21 (m, 1 H), 7.04 (m, 1 H), 6.71 (m, 1 H), 4.75 (dddd, *J* = 8.8, 8.8, 4.9, 4.9 Hz, 1 H), 3.81 (d, *J* = 10.4 Hz, 2 H), 3.35 (dd, *J* = 14.8, 6.6 Hz, 1 H), 3.27 (m, 1 H), 3.03 (s, 3 H), 2.76 (s, 3 H), 2.64 (t, *J* = 9.9 Hz, 2 H), 2.24−1.81 (m, 7 H), 1.41−1.33 (m, 4 H), 1.11 (dd, *J* = 7.7, 5.3 Hz, 1 H); LCMS: 598.1, rt = 4.55 min (M + H$^+$), 96% purity; HRMS (FAB) *m/z* 598.1584 [(M + H)$^+$; calcd for $C_{27}H_{34}ClFN_3O_5S_2$: 598.1612]. Anal. ($C_{27}H_{33}ClFN_3O_5S_2\cdot 0.5H_2O$): C, H, N.

[3-(4-{3-(3-Chloro-4-fluoro-phenyl)-1-[3-(4-methyl-piperazin-1-yl)-propyl]-ureido}-bicyclo[3.1.0]hex-1-yl)-phenyl]-carbamic Acid *tert*-Butyl Ester (24a). Following procedures similar to those described for the synthesis of compound **23a** and using **21c**, 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (68%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1 H), 7.54 (m, 1 H), 7.38 (m, 1 H), 7.18−7.05 (m, 4 H), 6.86 (d, *J* = 7.7 Hz, 1 H), 6.52 (s, 1 H), 5.03 (dddd, *J* = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.45−3.32 (m, 2 H), 2.30−2.11 (m, 9 H), 2.25 (s, 3 H), 2.11−1.85 (m, 3 H), 1.65 (ddd, *J* = 7.6, 4.4, 4.4 Hz, 1 H), 1.51 (s, 9 H), 1.25−1.20 (m, 2 H), 0.93 (dd, *J* = 7.1, 5.4 Hz, 1 H).

***N*-[*trans*-5-(3-Aminophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (24j).** A solution of **24a** (640 mg, 1.07 mmol) in 20% TFA/CH_2Cl_2 (10 mL) was stirred at ambient temperature. After 12 h, the reaction mixture was concentrated in vacuo, diluted with CH_2Cl_2, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (2×). The combined organic phases were dried and concentrated in vacuo to provide **24j** (470 mg, 88%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1 H), 7.53 (dd, *J* = 6.6, 2.7 Hz, 1 H), 7.39 (m, 1 H), 7.07 (dd, *J* = 7.7, 2.2 Hz, 1 H), 7.06 (dd, *J* = 9.3, 4.9 Hz, 1 H), 6.60−6.51 (m, 4 H), 5.03 (dddd, *J* = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.62 (s, 2 H), 3.50−3.32 (m, 2 H), 2.70−2.33 (m, 10 H), 2.27 (s, 3 H), 2.11−1.82 (m, 5 H), 1.63 (ddd, *J* = 7.6, 4.4, 4.4 Hz, 1 H), 1.29−1.20 (m, 2 H), 0.91 (dd, *J* = 7.1, 5.4 Hz, 1 H); LCMS: 501.1, rt = 4.02 min (M + H$^+$), 94% purity; HRMS (FAB) *m/z* 500.2597 [(M + H)$^+$; calcd for $C_{27}H_{36}ClFN_5O$: 500.2592].

***N*-[3-[*trans*-4-[[[(3-Chloro-4-fluorophenyl)amino]carbonyl][3-(4-methyl-1-piperazinyl)propyl]amino]bicyclo[3.1.0]hex-1-yl]-phenyl]acetamide (24b).** A solution of **24j** (75 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with diisopropylethylamine (52 μL, 0.30 mmol) followed by acetyl chloride (17 μL, 0.23 mmol). After 12 h, diisopropylethylamine (52 μL, 0.30 mmol), acetyl chloride (17 μL, 0.23 mmol), and DMAP (5 mg) were added. After 18 h further, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (10% MeOH/CH_2Cl_2) furnished **24b** (30 mg, 37%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1 H), 7.54 (dd, *J* = 6.6, 2.2 Hz, 1 H), 7.41−7.26 (m, 3 H), 7.21 (dd, *J* = 8.2, 7.7 Hz, 1 H), 7.05 (dd, *J* = 8.8, 8.8 Hz, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 5.03 (dddd, *J* = 8.4, 8.4, 4.9, 4.9 Hz, 1 H), 3.51−3.29 (m, 2 H), 2.67−2.27 (m, 7 H), 2.26 (s, 3 H), 2.16 (s, 3 H), 2.15−1.72 (m, 8 H), 1.65 (ddd, *J* = 7.7, 4.5, 4.5 Hz, 1 H), 1.31−1.21 (m, 2 H), 0.93 (dd, *J* = 7.7, 5.5 Hz, 1 H); LCMS: 542.1, rt = 4.50 min (M + H$^+$), 99% purity; HRMS (FAB) *m/z* 542.2690 [(M + H)$^+$; calcd for $C_{29}H_{38}ClFN_5O_2$: 542.2698].

***N*-[3-[*trans*-4-[[[(3-Chloro-4-fluorophenyl)amino]carbonyl][3-(4-methyl-1-piperazinyl)propyl]amino]bicyclo[3.1.0]hex-1-yl]-phenyl]methanesulfonamide (24c).** Following the procedure used for the synthesis of **24b** and using **24j** and methanesulfonyl chloride (17%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 7.53 (dd, *J* = 6.8, 3.0 Hz, 1 H), 7.37 (m, 1 H), 7.22 (dd, *J* = 7.7, 7.1 Hz, 1 H), 7.09−6.98 (m, 4 H), 5.05 (dddd, *J* = 8.4, 8.4, 4.9, 4.9 Hz, 1 H), 3.54−3.31 (m, 2 H), 2.99 (s, 3 H), 2.69−2.29 (m, 11 H), 2.26 (s, 3 H), 2.15−1.87 (m, 4 H), 1.68 (ddd, *J* = 7.6, 4.4, 4.4 Hz, 1 H), 1.33−1.24 (m, 2 H), 0.93 (dd, *J* = 7.1, 5.4 Hz, 1 H); LCMS: 578.1, rt = 4.79 min (M + H$^+$), >99% purity; HRMS (FAB) *m/z* 578.2368 [(M + H)$^+$; calcd for $C_{28}H_{38}ClFN_5O_3S$: 578.2368].

***N*′-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-[4-(methylsulfonyl)phenyl]bicyclo[3.1.0]hex-2-yl]urea (24d).** Following the procedure used for the synthesis of **23a** and using **21d** (synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (24%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.40 (s, 1 H), 7.85 (d, *J* = 8.2 Hz, 2 H), 7.59 (m, 1 H), 7.39 (m, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.07 (dd, *J* = 8.8, 8.8 Hz, 1 H), 5.06 (dddd, *J* = 8.7, 8.7, 5.0, 5.0 Hz, 1 H), 3.53−3.29 (m, 2 H), 3.03 (s, 3 H), 2.78−2.30 (m, 12 H), 2.26 (s, 3 H), 2.15−1.82 (m, 3 H), 1.65−1.20 (m, 3 H), 0.92 (dd, *J* = 7.7, 5.5 Hz, 1 H); LCMS: 563.1, rt = 3.86 min (M + H$^+$), 90% purity; HRMS (FAB) *m/z* 563.2289 [(M + H)$^+$; calcd for $C_{28}H_{37}ClFN_4O_3S$: 563.2259].

***N*′-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-phenylbicyclo[3.1.0]hex-2-yl]urea (24e).** Following the procedure used for the synthesis of **23a** and using **21e** (Ar = phenyl, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (44%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1 H), 7.54 (dd, *J* = 6.6, 2.7 Hz, 1 H), 7.39 (m, 1 H), 7.31−7.26 (m, 2 H), 7.20−7.18 (m, 3 H), 7.06 (dd, *J* = 8.8, 8.8 Hz, 1 H), 5.07 (dddd, *J* = 8.8, 8.8, 4.9, 4.9 Hz, 1 H), 3.52−3.31 (m, 2 H), 2.70−1.85 (m, 15 H), 2.27 (s, 3 H), 1.66 (ddd, *J* = 12.1, 8.2, 4.4 Hz, 1 H), 1.32−1.23 (m, 2 H), 0.94 (dd, *J* = 8.2, 5.5 Hz, 1 H); LCMS: 485.1, rt = 4.94 min (M + H$^+$), 97% purity; HRMS (FAB) *m/z* 485.2478 [(M + H)$^+$; calcd for $C_{27}H_{35}ClFN_4O$: 485.2483].

***N*′-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-[3-(trifluoromethoxy)phenyl]bicyclo[3.1.0]-hex-2-yl]urea (24f).** Following the procedure used for the synthesis of **23a** and using **21f** (Ar = *m*-OCF_3Ph, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (31%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1 H), 7.45 (m, 1 H), 7.41 (dd, *J* = 7.1, 2.2 Hz, 1 H), 7.18 (d, *J* = 7.7 Hz, 1 H), 7.11−7.00 (m, 5 H), 5.06 (dddd, *J* = 8.8, 8.8, 4.9, 4.9 Hz, 1 H), 3.51−3.29 (m, 2 H), 2.68−2.29 (m, 10 H), 2.24 (s, 3 H), 2.19−1.82 (m, 5 H), 1.69 (ddd, *J* = 7.7, 4.4, 4.4 Hz, 1 H), 1.32−1.22 (m, 2 H), 0.94 (dd, *J* = 7.7, 5.5 Hz, 1 H); LCMS: 569.1, rt = 5.05 min (M + H$^+$), 93% purity; HRMS (FAB) *m/z* 569.2319 [(M + H)$^+$; calcd for $C_{28}H_{34}ClF_4N_4O_2$: 569.2306]. Anal. ($C_{28}H_{33}ClF_4N_4O_2\cdot 2HCl$): C, H, N.

***N*′-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-[4-(trifluoromethoxy)phenyl]bicyclo[3.1.0]-hex-2-yl]urea (24g).** Following the procedure used for the synthesis of **23a** and using **21g** (Ar = *p*-OCF_3Ph, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (76%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1 H), 7.52 (dd, *J* = 6.6, 2.2 Hz, 1 H), 7.36 (m, 1 H), 7.20−7.02 (m, 5 H), 5.06 (dddd, *J* = 8.8, 8.8, 4.9, 4.9 Hz, 1 H), 3.52−3.29 (m, 2 H), 2.68−2.30 (m, 11 H), 2.26 (s, 3 H), 2.15−1.84 (m, 4 H), 1.65 (ddd, *J* = 7.7, 4.4, 4.4 Hz, 1 H), 1.31−1.20 (m, 2 H), 0.92 (dd, *J* = 7.7, 5.5 Hz, 1 H); LCMS: 569.1, rt = 4.92 min (M + H$^+$), 90% purity; HRMS (FAB) *m/z* 569.2298 [(M +

H)$^+$; calcd for $C_{28}H_{34}ClF_4N_4O_2$: 569.2306]. Anal. ($C_{28}H_{33}ClF_4N_4O_2$·2HCl·0.5H_2O): C, H, N.

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-chlorophenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (24h).** Following the procedure used for the synthesis of **23a** and using **21h** (Ar = *m*-ClPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (70%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1 H), 7.53 (dd, J = 6.6, 2.2 Hz, 1 H), 7.37 (m, 1 H), 7.23−7.13 (m, 3 H), 7.08−7.02 (m, 2 H), 5.04 (dddd, J = 8.7, 8.7, 4.9, 4.9 Hz, 1 H), 3.51−3.29 (m, 2 H), 2.68−2.30 (m, 11 H), 2.26 (s, 3 H), 2.19−1.85 (m, 4 H), 1.68 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.32−1.26 (m, 2 H), 0.92 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 519.3, rt = 4.50 min (M + H$^+$), 97% purity; HRMS (FAB) *m/z* 519.2086 [(M + H)$^+$; calcd for $C_{27}H_{34}Cl_2FN_4O$: 519.2094].

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-[3-(methylsulfonyl)phenyl]bicyclo[3.1.0]hex-2-yl]urea (24i).** Following the procedure used for the synthesis of **23a** and using **21i** (Ar = *m*-SO_2MePh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (35%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1 H), 7.79−7.73 (m, 2 H), 7.53 (dd, J = 6.6, 2.2 Hz, 1 H), 7.49−7.47 (m, 2 H), 7.38 (m, 1 H), 7.06 (dd, J = 8.8, 8.8 Hz, 1 H), 5.07 (dddd, J = 8.7, 8.7, 4.9, 4.9 Hz, 1 H), 3.52−3.30 (m, 2 H), 3.05 (s, 3 H), 2.68−2.27 (m, 10 H), 2.26 (s, 3 H), 2.21−1.86 (m, 4 H), 1.78 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.40−1.30 (m, 2 H), 0.99 (dd, J = 7.1, 5.5 Hz, 1 H); LCMS: 563.1, rt = 4.43 min (M + H$^+$), 95% purity; HRMS (FAB) *m/z* 563.2282 [(M + H)$^+$; calcd for $C_{28}H_{37}ClFN_4O_3S$: 563.2259].

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-fluorophenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24k).** Following the procedure used for the synthesis of **23a** and using **21k** (Ar = *m*-FPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (24%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1 H), 7.54 (dd, J = 6.6, 2.2 Hz, 1 H), 7.41−7.20 (m, 2 H), 7.07 (dd, J = 8.2, 8.2 Hz, 1 H), 6.97 (d, J = 8.2 Hz, 1 H), 6.94−6.82 (m, 2 H), 5.03 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.56−3.30 (m, 2 H), 2.67−2.27 (m, 7 H), 2.26 (s, 3 H), 2.15−1.84 (m, 8 H), 1.69 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.38−1.23 (m, 2 H), 0.97 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 503.1, rt = 4.82 min (M + H$^+$), 96% purity; HRMS (FAB) *m/z* 503.2395 [(M + H)$^+$; calcd for $C_{27}H_{34}ClF_2N_4O$: 503.2389]. Anal. ($C_{27}H_{33}ClF_2N_4O$·2HCl·H_2O): C, H, N.

***N*-[*trans*-5-(3-fluorophenyl)bicyclo[3.1.0]hex-2-yl]-*N′*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24l).** Following the procedure used for the synthesis of **23a** and using **21l** (Ar = *m*-FPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 4-fluoro-3-(trifluoromethyl)-phenyl isocyanate (33%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1 H), 7.77 (m, 1 H), 7.60 (m, 1 H), 7.21 (m, 1 H), 7.14 (dd, J = 8.8, 8.8 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 1 H), 6.95−6.85 (m, 2 H), 5.05 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.56−3.30 (m, 2 H), 2.67−2.27 (m, 7 H), 2.24 (s, 3 H), 2.15−1.77 (m, 8 H), 1.64 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.38−1.23 (m, 2 H), 0.96 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 537.1, rt = 4.83 min (M + H$^+$), >99% purity; HRMS (FAB) *m/z* 537.2656 [(M + H)$^+$; calcd for $C_{28}H_{34}F_5N_4O$: 537.2653].

***N*-[*trans*-5-(4-fluorophenyl)bicyclo[3.1.0]hex-2-yl]-*N′*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24m).** Following the procedure used for the synthesis of **23a** and using **21m** (Ar = *p*-FPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (8%, 2 steps): ^{1}H NMR (300 MHz, CD_3OD) δ 7.82 (m, 1 H), 7.65 (m, 1 H), 7.28 (m, 1 H), 7.27 (dd, J = 8.2, 8.2 Hz, 2 H), 7.01 (dd, J = 8.2, 8.2 Hz, 2 H), 4.81 (dddd, J = 8.1, 8.1, 4.5, 4.5 Hz, 1 H), 3.90−3.61 (m, 8 H), 3.59−3.32 (m, 8 H), 3.00 (s, 3 H), 2.20−1.96 (m, 5 H), 1.86 (ddd, J = 7.1, 4.3, 4.3 Hz, 1 H), 1.51−1.43 (m, 2 H), 1.07 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 537.1, rt = 4.64 min (M + H$^+$), >99% purity; HRMS (FAB) *m/z* 537.2663-[(M + H)$^+$; calcd for $C_{28}H_{34}F_5N_4O$: 537.2653].

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3-methylphenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24n).** Following the procedure used for the synthesis of **23a** and using **21n** (Ar = *m*-CH_3Ph, synthesized via method C), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (31%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1 H), 7.52 (dd, J = 6.6, 2.7 Hz, 1 H), 7.36 (m, 1 H), 7.17 (dd, J = 7.7, 7.1 Hz, 1 H), 7.05 (dd, J = 9.3, 8.8 Hz, 1 H), 7.00−6.98 (m, 3 H), 5.04 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.51−3.30 (m, 2 H), 2.68−2.30 (m, 7 H), 2.32 (s, 3 H), 2.27−1.89 (m, 8 H), 1.64 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.33−1.23 (m, 2 H), 0.91 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 499.1, rt = 5.35 min (M + H$^+$), 96% purity; HRMS (FAB) *m/z* 499.2635 [(M + H)$^+$; calcd for $C_{28}H_{37}ClFN_4O$: 499.2640].

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-(3-thienyl)bicyclo[3.1.0]hex-2-yl]urea (24o).** Following the procedure used for the synthesis of **23a** and using **21o** (Ar = *3*-thienyl, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (47%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 7.53 (dd, J = 6.6, 2.7 Hz, 1 H), 7.35 (m, 1 H), 7.23 (dd, J = 4.9, 2.7 Hz, 1 H), 7.04 (dd, J = 8.8, 8.8 Hz, 1 H), 6.92 (m, 1 H), 6.82 (dd, J = 4.9, 1.1 Hz, 1 H), 4.99 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.45−3.33 (m, 2 H), 2.68−2.35 (m, 7 H), 2.27 (s, 3 H), 2.13−1.85 (m, 8 H), 1.57 (ddd, J = 7.1, 4.3, 4.3 Hz, 1 H), 1.33−1.17 (m, 2 H), 0.96 (dd, J = 7.1, 4.9 Hz, 1 H); LCMS: 491.1, rt = 4.35 min (M + H$^+$), >99% purity; HRMS (FAB) *m/z* 491.2057[(M + H)$^+$; calcd for $C_{25}H_{33}ClFN_4OS$: 491.2048].

***N′*-(3-Chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]-*N*-[*trans*-5-(3-pyridinyl)bicyclo[3.1.0]hex-2-yl]urea (24p).** Following the procedure used for the synthesis of **23a** and using **21p** (Ar = 3-pyridyl, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate 17%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1 H), 8.47−8.42 (m, 2 H), 7.53 (dd, J = 7.1, 2.7 Hz, 1 H), 7.49 (m, 1 H), 7.39 (m, 1 H), 7.22 (m, 1 H), 7.06 (dd, J = 8.8, 8.8 Hz, 1 H), 5.09 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.53−3.32 (m, 2 H), 2.70−2.32 (m, 11 H), 2.27 (s, 3 H), 2.16−1.85 (m, 4 H), 1.72 (ddd, J = 7.1, 4.5, 4.5 Hz, 1 H), 1.34−1.27 (m, 2 H), 0.96 (dd, J = 7.1, 5.5 Hz, 1 H); LCMS: 486.1, rt = 3.26 min (M + H$^+$), 91% purity; HRMS (FAB) *m/z* 486.2424 [(M + H)$^+$; calcd for $C_{26}H_{34}ClFN_5O$: 486.2436].

***N′*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[*trans*-5-(3-methoxyphenyl)bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (24q).** Following the procedure used for the synthesis of **23a** and using **21q** (Ar = *m*-OCH_3Ph, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (31%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1 H), 7.77 (m, 1 H), 7.62 (dd, J = 6.6, 2.7 Hz, 1 H), 7.20 (dd, J = 8.7, 7.7 Hz, 1 H), 7.12 (dd, J = 9.3, 9.3 Hz, 1 H), 6.79−6.71 (m, 2 H), 5.06 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.79 (s, 3 H), 3.54−3.32 (m, 2 H), 2.72−2.32 (m, 11 H), 2.25 (s, 3 H), 2.12−1.86 (m, 4 H), 1.66 (ddd, J = 7.1, 4.5, 4.5 Hz, 1 H), 1.34−1.20 (m, 2 H), 0.94 (dd, J = 7.1, 5.5 Hz, 1 H); LCMS: 549.1, rt = 4.55 min (M + H$^+$), 94% purity; HRMS (FAB) *m/z* 549.2862 [(M + H)$^+$; calcd for $C_{29}H_{37}F_4N_4O_2$: 549.2853].

***N′*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[*trans*-5-(4-methoxyphenyl)bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (24r).** Following the procedure used for the synthesis of **23a** and using **21r** (Ar = *p*-OCH_3Ph, synthesized via method C), 1-(3-aminopropyl)-4-methylpiperazine, and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (47%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 7.77 (m, 1 H), 7.62 (dd, J = 6.6, 2.7 Hz, 1 H), 7.15 (m, 1 H), 7.09 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 5.06 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.78 (s, 3 H), 3.51−3.33 (m, 2 H), 2.72−2.34 (m, 11 H), 2.25 (s, 3 H), 2.10−1.84 (m, 4 H), 1.57 (ddd, J = 7.1, 4.5, 4.5 Hz, 1 H), 1.28−1.18 (m, 2 H), 0.90 (dd, J = 7.1, 5.5 Hz, 1 H); LCMS: 549.1, rt = 4.51 min (M + H$^+$), 93% purity; HRMS (FAB) *m/z* 549.2861 [(M + H)$^+$; calcd for $C_{29}H_{37}F_4N_4O_2$: 549.2853].

***N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3, 5-difluorophenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24s).** Following the procedure used for the synthesis of **23a** and using **21s** (Ar = 3,5-diFPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (30%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1 H), 7.53 (dd, J = 6.6, 3.8 Hz, 1 H), 7.37 (m, 2 H), 7.06 (dd, J = 8.8, 8.8 Hz, 1 H), 6.67−6.58 (m, 3 H), 5.03 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.52−3.29 (m, 2 H), 2.70−2.36 (m, 7 H), 2.28 (s, 3 H), 2.12−1.86 (m, 8 H), 1.70 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.35−1.26 (m, 2 H), 0.93 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 521.1, rt = 4.44 min (M + H$^+$), >99% purity; HRMS (FAB) m/z 521.2310 [(M + H)$^+$; calcd for $C_{27}H_{33}ClF_3N_4O$: 521.2295]. Anal. ($C_{27}H_{32}ClF_3N_4O$·2HCl ·3H_2O): C, H, N.

***N*′-(3-Chloro-4-fluorophenyl)-*N*-[*trans*-5-(3, 4-difluorophenyl)-bicyclo[3.1.0]hex-2-yl]-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24t).** Following the procedure used for the synthesis of **23a** and using **21t** (Ar = 3, 4-diFPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 3-chloro-4-fluorophenyl isocyanate (43%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1 H), 7.52 (dd, J = 6.6, 2.7 Hz, 1 H), 7.37 (m, 1 H), 7.06 (dd, J = 8.8, 8.2 Hz, 1 H), 7.00 (dd, J = 8.2, 8.2 Hz, 1 H), 6.88 (m, 1 H), 5.06 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.51−3.26 (m, 2 H), 2.68−2.29 (m, 7 H), 2.26 (s, 3 H), 2.10−1.85 (m, 8 H), 1.63 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.31−1.24 (m, 2 H), 0.89 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 521.3, rt = 4.54 min (M + H$^+$), 99% purity; HRMS (FAB) m/z 521.2307 [(M + H)$^+$; calcd for $C_{27}H_{33}ClF_3N_4O$: 521.2295]. Anal. ($C_{27}H_{32}ClF_3N_4O$·2HCl·H_2O) C, H, N.

***N*-[*trans*-5-(4-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[3-(4-methyl-1-piperazinyl)propyl]-urea (24u).** Following the procedure used for the synthesis of **23a** and using **21u** (Ar = *p*-CNPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 4-fluoro-3-(trifluoromethyl)-phenyl isocyanate (47%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.93 (s, 1 H), 8.80 (s, 1 H), 7.99 (d, J = 4.4 Hz, 1 H), 7.87 (dd, J = 8.2, 4.4 Hz, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.36 (d, J = 8.2 Hz, 2 H), 5.06 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.78−3.17 (m, 8 H), 2.81 (m, 4 H), 2.48 (dd, J = 2.2, 1.6 Hz, 1 H), 2.15−1.98 (m, 6 H), 1.82 (ddd, J = 13.2, 11.5, 7.7 Hz, 1 H), 1.64 (dd, J = 4.9, 4.4 Hz, 1 H), 1.43 (m, 1 H), 1.08 (m, 1 H). LCMS: 544.1, rt = 4.45 min (M + H$^+$), > 99% purity; HRMS (FAB) m/z 544.2699 [(M + H)$^+$; calcd for $C_{29}H_{34}F_4N_5O$: 544.2699]. Anal. ($C_{29}H_{33}F_4N_5O$·2HCl·H_2O) C, H, N.

***N*-[*trans*-5-(3-Cyano-4-fluorophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (24v).** Following the procedure used for the synthesis of **23a** and using **21v** (Ar = 3-CN, 4-FPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (52%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1 H), 7.75 (m, 1 H), 7.62 (dd, J = 6.0, 2.2 Hz, 1 H), 7.42−7.38 (m, 2 H), 7.16−7.10 (m, 1 H), 5.06 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.56−3.31 (m, 2 H), 2.71−2.36 (m, 7 H), 2.26 (s, 3 H), 2.16−1.89 (m, 8 H), 1.69 (ddd, J = 7.7, 4.5, 4.4 Hz, 1 H), 1.34−1.26 (m, 1 H), 0.91 (dd, J = 7.7, 5.4 Hz, 1 H); LCMS: 562.3, rt = 4.18 min (M + H$^+$), 98% purity; HRMS (FAB) m/z 562.2609 [(M + H)$^+$; calcd for $C_{29}H_{33}F_5N_5O$: 562.2605].

***N*-[*trans*-5-(4-Cyano-3-fluorophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[3-(4-methyl-1-piperazinyl)propyl]urea (24w).** Following the procedure used for the synthesis of **23a** and using **21w** (Ar = 3-F, 4-CNPh, synthesized via method B), 1-(3-aminopropyl)-4-methylpiperazine, and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (54%, 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 7.74 (m, 1 H), 7.60 (m, 1 H), 7.50 (dd, J = 7.7, 7.1 Hz, 1 H), 7.12 (dd, J = 9.3, 9.3 Hz, 1 H), 7.00−6.95 (m, 2 H), 5.02 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.55−3.31 (m, 2 H), 2.69−2.35 (m, 7 H), 2.26 (s, 3 H), 2.14−1.90 (m, 8 H), 1.82 (ddd, J = 7.7, 4.5, 4.4 Hz, 1 H), 1.44−1.31 (m, 1 H), 1.01 (dd, J = 7.7, 5.4 Hz, 1 H); LCMS: 562.3, rt = 4.18 min (M + H$^+$), 98% purity; HRMS (FAB) m/z 562.2609 [(M + H)$^+$; calcd for $C_{29}H_{33}F_5N_5O$: 562.2605].

***trans*-3-[4-(4-Hydroxy-butylamino)-bicyclo[3.1.0]hex-1-yl]-benzonitrile (25a).** A solution of ketone **21a** (synthesized as in method A) (440 mg, 2.23 mmol) in CH_2Cl_2 (2 mL) was treated with 4-amino-1-butanol (247 μL, 2.68 mmol) followed by titanium tetraisopropoxide (800 μL, 2.68 mmol). After 18 h, the reaction mixture was diluted with MeOH (2 mL) and sodium borohydride (130 mg, 3.40 mmol) was added. After 1.5 h further, the reaction mixture was diluted with a solution of saturated aqueous sodium/potassium tartrate and CH_2Cl_2 and stirred vigorously. After 12 h, the solution was extracted with CH_2Cl_2 (4×). The combined organic phases were dried and concentrated in vacuo to provide **25a** (560 mg, 88%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.41 (m, 2 H), 7.39−7.29 (m, 2 H), 3.59 (t, J = 4.9 Hz, 2 H), 3.59−3.51 (m, 7 H), 2.81 (m, 1 H), 2.67 (m, 1 H), 2.15−2.00 (m, 3 H), 1.90 (ddd, J = 7.7, 4.5, 4.4 Hz, 1 H), 1.75−1.62 (m, 7 H), 1.20−1.12 (m, 2 H), 0.80 (dd, J = 8.2, 5.5 Hz, 1 H.

***trans*-(4-Bromo-butyl)-[5-(3-cyano-phenyl)-bicyclo[3.1.0]hex-2-yl]-carbamic Acid *tert*-Butyl Ester (26a).** A solution of amine **25a** (560 mg, 1.96 mmol) was dissolved in CH_2Cl_2 (4 mL) and treated with triethylamine (280 μL, 2.0 mmol) followed by di-*tert*-butyl carbonate (437 mg, 2.0 mmol). After 12 h, the reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl, $NaHCO_3$, and brine, dried, and concentrated in vacuo. Flash chromatography (50% EtOAc/Hex) gave the alcohol (700 mg, 92%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.41 (m, 2 H), 7.39−7.29 (m, 2 H), 4.78 (dddd, J = 8.3, 8.3, 5.2, 5.2 Hz, 1 H), 3.68 (t, J = 6.6 Hz, 2 H), 3.32 (m, 1 H), 3.14 (m, 1 H), 2.11 (dd, J = 12.0, 8.2 Hz, 1 H), 2.01−1.88 (m, 3 H), 1.74−1.54 (m, 5 H), 1.46 (s, 9 H), 1.31−1.24 (m, 2 H), 0.93 (dd, J = 7.7, 6.0 Hz, 1 H).

A solution of alcohol from the previous step (700 mg, 1.81 mmol) in THF (9 mL) at 0 °C was treated with carbon tetrabromide (1.2 g, 3.6 mmol) followed by triphenylphosphine (1.05 g, 4.0 mmol) and warmed to ambient temperature. After 45 min, the reaction mixture was diluted with diethyl ether, filtered through Celite, rinsed, and concentrated in vacuo. Flash chromatography (10% EtOAc/Hex) gave **26a** (770 mg, 95%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2 H), 7.39−7.37 (m, 2 H), 4.81 (dddd, J = 8.3, 8.3, 5.2, 5.2 Hz, 1 H), 3.45 (t, J = 6.6 Hz, 2 H), 3.42 (m, 1 H), 3.13 (m, 1 H), 2.15 (dd, J = 12.0, 8.2 Hz, 1 H), 2.02−1.70 (m, 7 H), 1.48 (s, 9 H), 1.33−1.26 (m, 2 H), 0.95 (dd, J = 7.7, 6.0 Hz, 1 H).

***N*-[*trans*-5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[4-(4-morpholinyl)butyl]urea (27a).** A solution of **26a** (150 mg, 0.333 mmol) in CH_3CN was treated with K_2CO_3 (70 mg, 0.50 mmol) and morpholine (32 μL, 0.367 mmol) and heated to 70 °C. After 12 h, the reaction mixture was cooled to ambient temperature, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc (3×). The combined organic extracts were washed with $NaHCO_3$ and brine, dried, and concentrated in vacuo to provide the morpholine as a clear oil.

A solution of crude morpholine derivative (≤0.333 mmol) in 20% TFA/CH_2Cl_2 (3.6 mL) was stirred at ambient temperature. After 12 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2×). The combined organic phases were dried and concentrated in vacuo to provide the free amine as a yellow oil. The residue was dissolved in CH_2Cl_2 (3 mL) and treated with diisopropylethylamine (87 μL, 0.50 mmol) followed by 3-(trifluoromethyl)-4-fluorophenyl isocyanate (57 μL, 0.40 mmol). After 12 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2×). The combined organic phases were dried and concentrated in vacuo. Preparative thin-layer chromatography (5% MeOH/CH_2Cl_2) furnished **27a** (136 mg, 75% over 3 steps) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 1 H), 7.57 (m, 1 H), 7.48−7.44 (m, 2 H), 7.39−7.37 (m, 2 H), 7.12 (dd, J = 8.8, 8.8 Hz, 1 H), 6.95 (s, 1 H), 5.00 (dddd, J = 8.8, 8.8, 5.1, 5.1 Hz, 1 H), 3.71−3.65 (m, 5 H), 3.47−3.25 (m, 2 H), 2.49−2.46 (m, 6 H), 2.20−1.94 (m, 2 H), 1.85−1.58 (m, 4 H), 1.36−1.31 (m, 2 H), 0.99 (dd, J = 7.1, 6.0 Hz, 1 H); LCMS: 546.1, rt = 5.37 min (M + H$^+$), 99% purity; HRMS (FAB) m/z 545.2543 [(M)$^+$; calcd for $C_{29}H_{32}F_4N_4O_2$: 545.2540]. Anal. ($C_{29}H_{32}F_4N_4O_2$·HCl·0.5H_2O): C, H, N.

***N*-[*trans*-5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N'*-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[4-(4-methyl-1-piperazinyl)butyl]-urea (27b).** Following the procedure described for **27a** and using piperazine (36%, 3 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 1 H), 7.57 (m, 1 H), 7.48−7.45 (m, 2 H), 7.39−7.37 (m, 2 H), 7.12 (dd, J = 8.8, 8.8 Hz, 1 H), 7.03 (s, 1 H), 5.03 (dddd, J = 8.7, 8.7, 5.0, 5.0 Hz, 1 H), 3.46−3.24 (m, 2 H), 2.64−2.40 (m, 8 H), 2.22 (s, 3 H), 2.20−1.95 (m, 6 H), 1.85−1.58 (m, 4 H), 1.39−1.30 (m, 2 H), 0.99 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 558.1, rt = 4.85 min (M + H$^+$), 90% purity; HRMS (FAB) *m/z* 558.2851 [(M + H)$^+$; calcd for $C_{30}H_{36}F_4N_5O$: 558.2856]. Anal. ($C_{30}H_{35}F_4N_5O$·2HCl): C, H, N.

***N*-[*trans*-5-(3-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N'*-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[4-(1-piperidinyl)butyl]urea (27c).** Following the procedure described for **27a** and using piperidine (65%, 3 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 1 H), 7.58 (m, 1 H), 7.47−7.44 (m, 2 H), 7.39−7.37 (m, 2 H), 7.25 (s, 1 H), 7.12 (dd, J = 8.8, 8.8 Hz, 1 H), 5.05 (dddd, J = 8.7, 8.7, 5.0, 5.0 Hz, 1 H), 3.47−3.23 (m, 2 H), 2.47−2.43 (m, 6 H), 2.19−1.94 (m, 3 H), 1.85−1.30 (m, 13 H), 0.98 (dd, J = 7.7, 5.5 Hz, 1 H); LCMS: 544.1, rt = 5.56 min (M + H$^+$), 97% purity; HRMS (FAB) *m/z* 543.2757 [(M)$^+$; calcd for $C_{30}H_{34}F_4N_4O$: 543.2747]. Anal. ($C_{30}H_{34}F_4N_4O$·HCl·0.5H_2O): C, H, N.

***N*-[*trans*-5-(4-Cyanophenyl)bicyclo[3.1.0]hex-2-yl]-*N'*-[4-fluoro-3-(trifluoromethyl)phenyl)-*N*-[3-(1-piperazinyl)propyl]urea (32).** A solution of 33[26] (418 mg, 1.5 mmol) in CH_2Cl_2 (3 mL) was treated with **21u** (250 mg, 1.27 mmol) followed by titanium tetraisopropoxide (440 μL, 1.5 mmol). After 18 h, the reaction mixture was diluted with EtOH (1 mL) and sodium borohydride (80 mg, 1.9 mmol) was added. After 2.5 h further, the reaction mixture was diluted with H_2O (2 mL). After 0.5 h further, the reaction mixture was filtered through Celite and washed with EtOH. The filtrate was concentrated in vacuo, diluted with a solution of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (2×). The combined organic phases were dried and concentrated in vacuo. The product from the previous step (400 mg, 0.87 mmol) was dissolved in CH_2Cl_2 (4 mL) and treated with diisopropylethylamine (300 μL, 1.73 mmol) followed by 4-fluoro-(3-trifluoromethyl)-phenyl isocyanate (200 μL, 1.30 mmol). After 18 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and concentrated in vacuo. Flash chromatography (35→100% EtOAc/Hex) furnished the urea (425 mg, 73%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1 H), 7.69 (dd, J = 6.0, 2.7 Hz, 1 H), 7.55 (d, J = 8.2 Hz, 2 H), 7.37−7.31 (m, 6 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.12 (dd, J = 9.8, 8.7 Hz, 1 H), 5.08 (s, 2 H), 5.06 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.52−3.38 (m, 7 H), 2.60−2.35 (m, 5 H), 2.18−1.90 (m, 5 H), 1.78 (ddd, J = 7.7, 4.5, 4.5 Hz, 1 H), 1.40−1.36 (m, 2 H), 0.99 (dd, J = 7.1, 5.5 Hz, 1 H).

The urea from the previous step (375 mg, 0.67mol) in MeOH (20 mL) was treated with 10% Pd/C (150 mg) and stirred under 1 atm H_2 via ballon. After 40 min, the reaction mixture was filtered through Celite, rinsed with MeOH, and concentrated in vacuo. Flash chromatography (5→10% MeOH/CH_2Cl_2) provided **32** (210 mg, 59%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1 H), 7.69−7.62 (m, 2 H), 7.56 (d, J = 8.2 Hz, 2 H), 7.23 (d, J = 8.2 Hz, 2 H), 7.22 (dd, J = 8.2, 8.2 Hz, 1 H), 5.08 (dddd, J = 8.2, 8.2, 4.9, 4.9 Hz, 1 H), 3.78−3.17 (m, 2 H), 2.81 (m, 4 H), 2.70−2.26 (m, 6 H), 2.21−1.60 (m, 6 H), 1.38−1.26 (m, 2 H), 1.02 (dd, J = 7.1, 5.5 Hz, 1 H); LCMS: 530.1, rt = 4.10 min (M + H$^+$), 96% purity; HRMS (FAB) *m/z* 530.2525 [(M + H)$^+$; calcd for $C_{28}H_{32}F_4N_5O$: 530.2543].

MCH Receptor Binding Assay. CHO cells expressing MCH-R1 (CHO-MCH-R1) were generated as described previously.[35] Membranes from these cells were prepared by lysing cells with 5 mM HEPES for 15 min at 4 °C followed by centrifugation of the cell lysates (12000 × g, 15 min). The pellet was resuspended in 5 mM HEPES by trituration with a 21 gauge needle. Binding of compound to MCH-R1 was determined using an SPA-based radioligand binding assay. CHO-MCH-R1 cell membranes (10 μg) were incubated with 100 μg of wheat germ agglutinin SPA beads (Amersham Life Science, Arlington Heights, IL), 125 pM [^{125}I]-MCH (New England Nuclear, Boston, MA), and 0.1−3000 nM compound in 200 μL of MCH-R1 binding buffer (25 mM Hepes, pH 7.4, 10 mM $MgCl_2$, 10 mM NaCl, 5 mM $MnCl_2$, 0.1% BSA) for 2 h at room temperature in 96-well plates. Nonspecific binding was determined by including 1 μM unlabeled MCH in the binding reaction. Following the binding incubation, plates were analyzed in a TOPCOUNT microplate scintillation counter (Packard) to measure radioactivity bound to MCH-R1. K_i values were determined using Prism (GraphPad software).

Functional Assays Measuring MCH-R1 Activity. The ability of compounds to functionally antagonize MCH-R1 was determined by measuring inhibition of MCH-stimulated increases in intracellular Ca^{2+} using a FLIPR instrument. CHO-MCH-R1 cells were grown in 384 well black/clear plates. Cells were washed with 50 μL of FLIPR buffer (Hank's BSS, 0.1% BSA, 20 mM HEPES, 2.5 mM probenecid) and loaded with FLIPR buffer containing 0.04% pluronic acid and 4 μM Fluo 3AM dye. Cells were then incubated for 1 h at 37 °C. Subsequently, cells were washed twice with FLIPR buffer and treated with 20 μL of vehicle (FLIPR buffer containing 2% DMSO) or compound. Cells were then stimulated with 30 nM MCH and the change in intracellular Ca^{2+} level was determined with a FLIPR instrument (Molecular Devices). K_b values were determined using the Cheng-Prusoff formula.

Ex Vivo Binding Assay. Receptor occupation in brain following oral dosing was determined using an ex vivo radioligand binding assay. Mice were orally administered vehicle (HPβCD) or 30 mg/kg of test compound and subsequently killed by CO_2 asphyxiation 6 or 24 h after dosing. The brains were removed and immediately frozen on dry ice. Sections (16 μm) of the caudate putamen were cut and thaw-mounted onto microscope slides. The tissue was exposed to MCH-R1 binding buffer containing 700 pM [^{125}I]-S36057 (NEN) for 30 min at room temperature. Nonspecific binding was determined by including 1 μM MCH in the binding buffer. The tissue was then washed with binding buffer and dried. Radiolabeled S36057 bound to the tissue was visualized using a Storm PhosphorImager (Molecular Dynamics) and quantified using ImageQuant Software.

Animal Care and Maintenance. Male C57Bl/6NCrl:BR (Charles River Inc., Wilmington, DE) mice were used for all experiments. Mice arrived at 4−6 weeks of age and were individually housed in polycarbonate cages with food (10% kcal as fat; D12450B; Research Diets Inc, New Brunswick, NJ) and water available ad libitum unless otherwise stated. They were maintained under a 12 h/12 h light/dark cycle at a temperature of 22 °C. Diet-induced obese (DIO) mice were generated by feeding C57Bl/6NCrl:BR mice a high fat diet (45% of calories from fat; D12451, Research Diets Inc.) for 8−12 weeks beginning at 4 weeks of age. All studies were conducted in an American Association for Laboratory Animal Care accredited facility following protocols approved by the Schering-Plough Research Institute Animal Care and Use Committee. The procedures were performed in accordance with the principles and guidelines established by the National Institutes of Health for the care and use of laboratory animals.

(a) Dosing. In all studies performed, mice were orally dosed with vehicle (5 or 10 mL/kg 20% hydroxypropyl-β-cyclodextrin (HPβCD, Cetestar, Indianapolis, IN)) for 2−3 days prior to study to acclimate them to handling and dosing. Compound was orally administered in a 20% HPβCD solution, while Sibutramine was orally administered as a suspension in 20% HPβCD.

(b) Feeding Studies. Two preweighed fresh 3−3.5 g food pellets were presented to mice on the floor of the home cage every day. Body weight (weighed to the nearest 0.1 g) and food intake (weighed to the nearest 0.01 g) were measured daily.

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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