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Bicyclic[4.1.0]heptanes as phenyl replacements for melanin concentrating hormone receptor antagonists

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Abstract—Melanin concentrating hormone (MCH) receptor antagonists have been proposed as potential treatments of obesity. MCH receptor antagonists with a biphenylamine subunit have been reported previously at Schering-Plough. Herein, we report the discovery of bicyclo[4.1.0]heptanes as replacements for the middle phenyl ring of the biphenylamine moiety in order to eliminate its potential mutagenic liability. Structure–activity relationships in this series were found to be very similar to those of the original biphenylamine series, suggesting that the two series have similar binding modes.

1. Introduction

Melanin concentrating hormone is a 19 amino acid cyclic peptide that is predominantly expressed in the lateral hypothalamus and zona incerta areas of the brain.[1,2] It has been reported to participate in a variety of processes including feeding, water balance, energy metabolism, memory and cognitive functions, and psychiatric disorders.[3–5] Based on the pattern of MCH expression in rodents, the role of MCH in feeding behavior and energy homeostasis has been suggested and demonstrated by a series of experiments and observations. Intracerebroventricular injection of MCH induces feeding in rats.[6,7] Mice with an ablation of the MCH gene are hypophagic, hypermetabolic, and lean,[8] while transgenic mice that overexpress MCH are hyperphagic and obese when maintained in high fat diet.[9] The effects of MCH are mediated via two G-protein-coupled receptors, MCH-R1[10] and MCH-R2,[11] although only MCH-R1 is functional in rodents and the role of the MCH-R2 receptor is unknown. MCH-R1 knock-out mice are hyperactive, hypermetabolic, have reduced fat mass, insulin and leptin levels, and are mildly hyperphagic.[12,13] Since the discovery of MCH and subsequent cloning of MCH-R1 receptor, there have been a number of publications and patent applications on the discovery of MCH-R1 antagonists as potential therapeutics for the treatment of obesity.[14,15] In vivo antiobesity activity for small molecule MCH-R1 antagonists was also observed in rats either via IP injection[16] or oral administration.[17] All these data provide compelling evidence for the hypothesis that blocking the effect of MCH will be effective in the treatment of obesity.

Screening of our proprietary compound collection followed by extensive medicinal chemistry work led to the discovery of a chemical series exemplified by compound **1**, a potent MCH-R1 antagonist which exhibited oral efficacy in chronic (28 days) rodent models, reducing cumulative food intake and body weight gain relative to vehicle controls[18] (see Fig. 1).

One crucial element of the pharmacophore for MCH-R1 activity in this chemical series is the biphenyl amine moiety **2**. Upon further studies, it was found that the biphenylamine is a very potent mutagenic agent as indicated by its strong positive result in an Ames test.[18] Although the final target compounds themselves are clean in the

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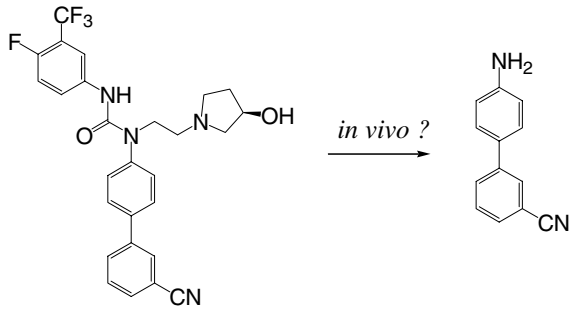


Figure 1. Biarylaniline MCH-R1 antagonist and potential mutagenic liability.

Ames assay and there is no evidence from the preliminary studies that the biphenylamine itself is formed in vivo, these compounds were deemed unsuitable for development because of the potential risk of exposure to such a highly mutagenic precursor. So a great effort was made to find potent MCH-R1 antagonists that do not have the mutagenic biphenylamine. Herein, we report the discovery of potent MCH-R1 antagonists that lack the undesired biphenylamine moiety and provide preliminary biological evaluation of these compounds.

Although compounds with the biphenylamine are not suitable for development, the vast SAR generated in the identification of **1** could be used to direct future research if a non-mutagenic functional group that closely resembled the biphenyl amine could be found. Two strategies for replacing biphenylamine were applied here: (1) replace the biphenylamine with non-mutagenic biarylamines, and (2) remove the mutagenic aniline moiety by replacing the middle phenyl ring with an alkyl group.

2. Chemistry

A survey of both the literature and data generated in-house suggested that substitution on the distal aryl ring has little or no effect on the relative mutagenicity of biarylamines, while changes in the aniline portion of the molecule could have a major impact on its mutagenic effects. For instance, both pyrazine and pyrimidine analogs of biphenylamine have tested negative in the Ames test. Since they closely resemble the original biphenylamine, they became the first choice of modification. Synthesis of these analogs was complicated by the poor nucleophilicities of the aminopyrazine and aminopyrimidine, so the procedures used in previous studies[18] were not feasible. Thus, an alternative synthesis of compounds **6** and **8** was accomplished via Scheme 1. The basic side chain was introduced first by reacting appropriate amines with chloropyrazine or chloropyrimidine. Bromination, followed by Suzuki coupling, introduced the distal phenyl ring with appropriate substitution. Due to the poor nucleophilicites of the pyrazine and pyrimidine amines, urea formation had to be aided by strong bases such as sodium hydride.

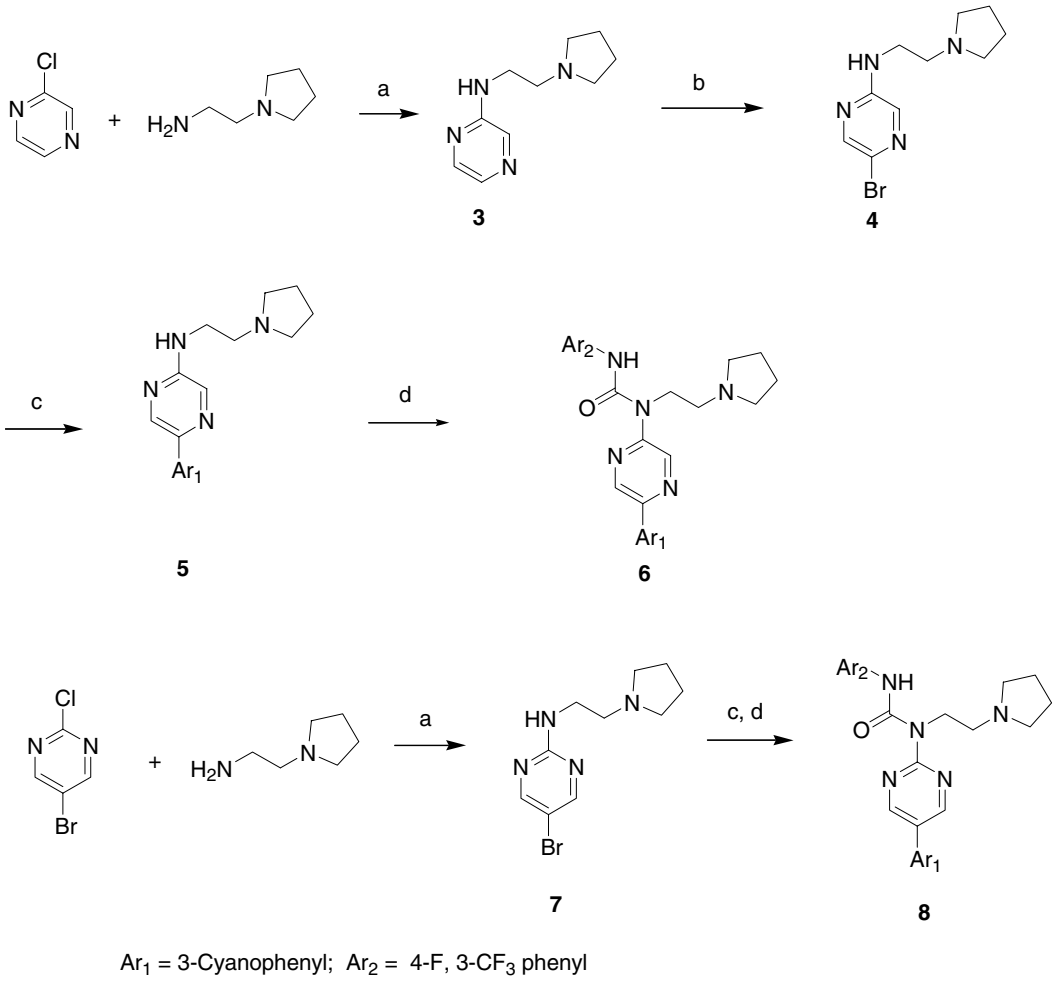
Replacing the middle phenyl group with a piperidine would eliminate the biarylaniline substructure. The synthesis of the piperidine series is shown in Scheme 2. Cyanoaniline reacted with 1-benzyl-1-methyl-4-oxopiperidine[19] to give piperidinone **9**. Reductive amination, followed by urea formation, provided compound **11**.

Fully saturating the central phenyl ring to a cyclohexyl derivative was also explored, which required the separation of *cis*- and *trans*-isomers (Schemes 3 and 4). 3-Cyanophenyl lithium was reacted with monoprotected 1,4-cyclohexanedione at −100 °C to give the hydroxycyclohexyl compound **12**. This intermediate could be progressed to three different series. Selective removal of the ketal group with toluenesulfonic acid in acetone, followed by reductive amination and urea formation, gave hydroxycyclohexyl derivative **15**. In order to remove the hydroxyl group, **15** was treated with triethylsilane and trifluoroacetic acid. However, the only product obtained from this reaction was the dehydration product **16**. It should be noted this dehydration reaction occurred smoothly in acidic medium without the addition of triethylsilane.

Alternatively, removal of the ketal group of **12** under strongly acidic conditions was accompanied by dehydration to provide enones **17** and **18**, resulting from migration of the olefin (Scheme 3). However, catalytic hydrogenation of the mixture reduced both the double bond and ketone concurrently. The resulting hydroxy compound was then oxidized to ketone **19** with Dess–Martin reagent. Reductive amination and urea formation yielded compounds **21** and **22**.

Dehydration of **12** with triethylamine and methanesulfonyl chloride left the ketal group intact and formed cyclohexene **23** (Scheme 5). Cyclopropanation of **23** could be achieved only by an improved Simmons–Smith method developed by Shi and co-workers.[20] The ketal protecting group was then removed, followed by reductive amination with appropriate pre-synthesized amine side chains. Inevitably, both *cis* and *trans* isomers were formed during the reductive amination reaction. The *cis*/*trans* selectivity of the reduction with different reducing reagents was studied. It was found that sodium borohydride gave the highest selectivity for the *trans* isomer (>9:1). Other reducing agents such as sodium cyanoborohydride and sodium triacetoxyborohydride gave a more equal mixture of *cis* and *trans* isomers. To prevent competitive reduction of the ketone during this reductive amination reaction, the ketone was initially treated with the appropriate amine in the presence of titanium isopropoxide, and sodium borohydride was then added to selectively afford the *trans* isomer over *cis* isomer in 9:1 ratio.

The bicyclic ketone **25** synthesized as described above was a racemic mixture. Chiral synthesis of **25** was not straightforward, so chiral HPLC separation was used as an alternative. After a survey of all synthetic intermediates using an array of different chiral columns, it was found that the ketone intermediate **25** gave the best enantiomeric separation. Thus, enantiomers of ketone



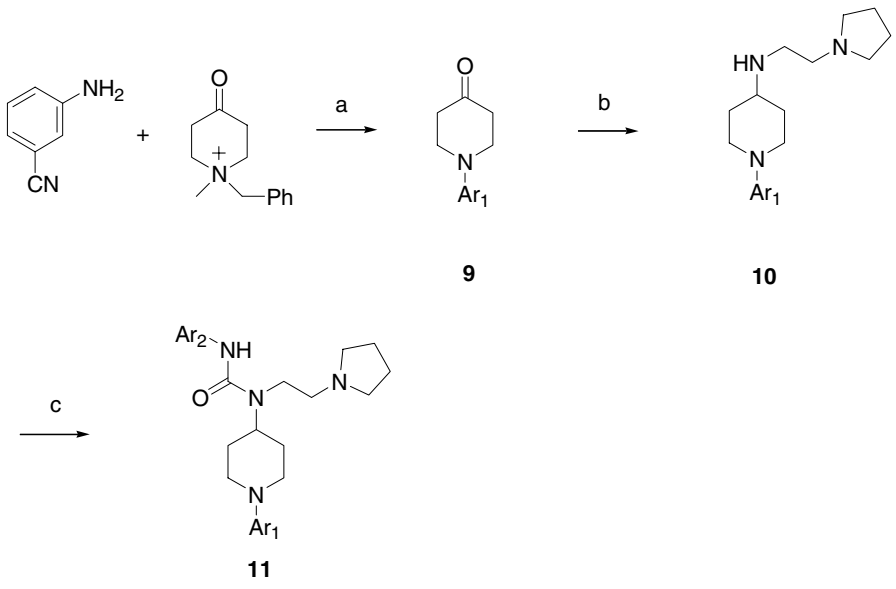
Scheme 1. Synthesis of pyrazine and pyrimidine series. Reagents and conditions (yields for **6**): (a) neat, 100 °C, 77%; (b) Br_2, Py, CH_2Cl_2, 35%; (c) 3-cyanophenylboronic acid, $PdCl_2(dppf)_2$, Na_2CO_3, ethylene glycol dimethyl ether/H_2O, 46%; (d) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, NaH, CH_2Cl_2, 50%.

25 were separated rapidly using a chiracel OD column with hexane/isopropanol (8/2) as solvent on multi-gram scale. One of optically pure isomers of ketone **25** was reduced to the corresponding alcohol, and *cis*/*trans* isomers were separated by conventional column chromatography. Mosher esters of the resulting *trans* hydroxy compound were subjected to NMR analysis to determine their absolute configurations. The optically pure isomers of **25** were then carried forward to yield compounds **51**–**54**, each as a single diastereomer. X-ray crystallography (Fig. 2) of **54** was obtained which further confirmed the designated absolute configuration of the final compounds.

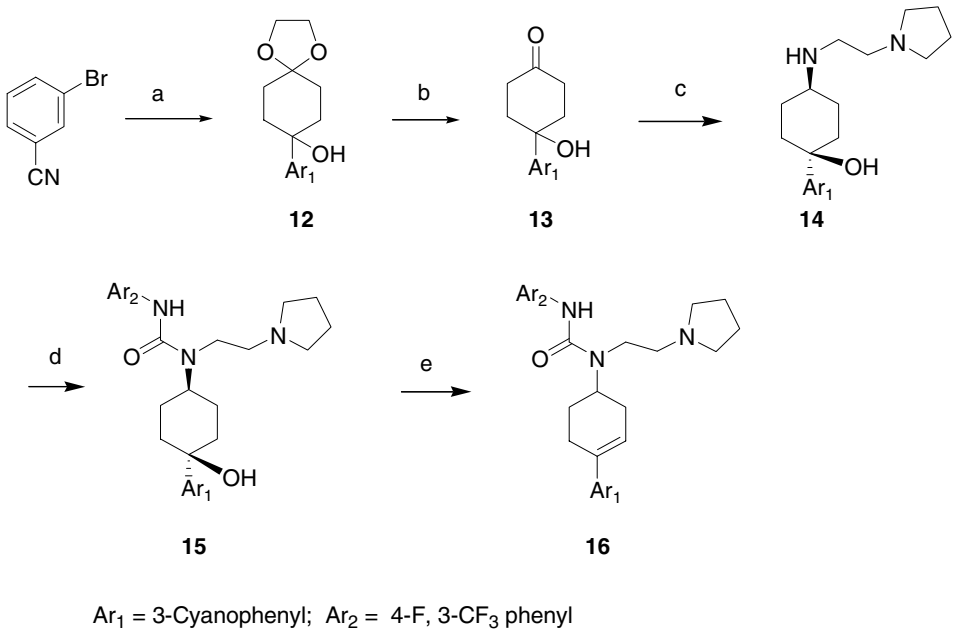
To probe the role of the cyclopropane moiety and also to remove one chiral center, the methylcyclohexane derivatives **33** and **34** were synthesized according to Scheme 6. Ketone **28** was condensed with ethyl chloroacetate in the presence of potassium *t*-butoxide. The resulting glycidic ester **29** was hydrolyzed and decarboxylated to give aldehyde **30**,[21] which was subsequently condensed with methyl vinyl ketone to form **31**. Hydrogenation of the olefin was accompanied by ketone reduction to the alcohol, which was then reoxidized to ketone **32** with Dess–Martin reagent. Ketone **32** was then progressed to compounds **33** and **34** as described previously.

3. Result and discussion

Pyrazine and pyrimidine analogs of biarylamines **6**–**8** were synthesized first due to their close resemblance to the original biphenylamine (**1**). However, these simple changes drastically reduced the MCH-R1 activities of the resulting compounds (Table 1). Changes at the distal aryl group, substitutions on the urea phenyl, and changes to the right-hand side amines did little to bring back the MCH-R1 activities. Changing the middle phenyl ring to piperidine (**11**) eliminated the aniline moiety. Unfortunately, this modification also reduced MCH-R1 activity drastically. Similarly, fully saturating the middle ring resulted in a loss of MCH-R1 activity, although the *trans* compound **22** was more potent than the corresponding *cis* compound **21**. One of the intermediates formed during synthesis of **21** and **22** was the cyclohexene compound **16**. Surprisingly, this compound was extremely active in the MCH-R1 binding assay. However, despite its good MCH-R1 activity, both the intrinsic metabolic liability associated with the styrene



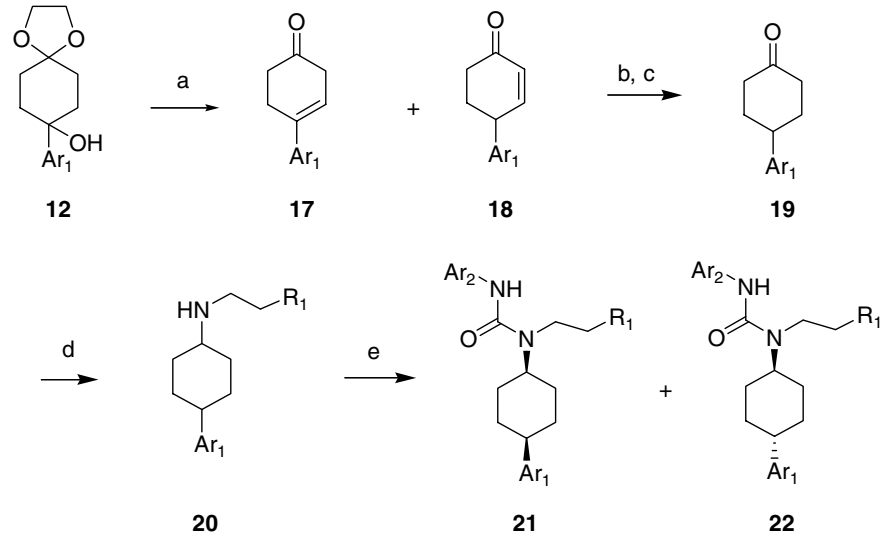
Scheme 2. Synthesis of piperidine series. Reagents and conditions: (a) K_2CO_3, Ce_2CO_3, H_2O/EtOH, 2.8%; (b) 2-aminoethylpyrrolidine, $NaBH_3CN$, CH_2Cl_2, quant.; (c) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, DMAP, CH_2Cl_2, 69%.



Scheme 3. Synthesis of cyclohexene series. Reagents and conditions: (a) butyllithium, THF, −100 °C, then 1,4-dioxaspiro[4,5]decan-8-one, −100 to −75 °C, 82%; (b) TsOH, acetone, quant.; (c) 1-(2-aminoethyl)-pyrrolidine, $NaCNBH_3$, DCM, 64%; (d) 4-fluoro-3-trifluoromethylphenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 80%; (e) DCM/TFA/Et_3SiH, 50%.

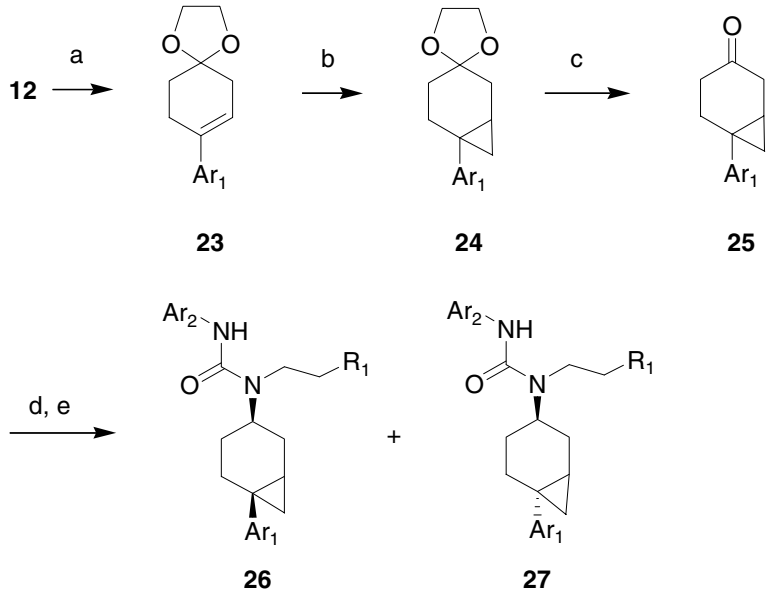
moiety of **16** and its potential for generating a biphenylamine via aromatization prompted exploration to discover more stable analogs of **16**. Cyclopropanation of the double bond to form a bicyclo[4.1.0]alkyl group achieved this goal. Similar to the cyclohexane series, *cis* and *trans* isomers were formed in this series. *Trans* isomers were found to be more active than the corresponding *cis* isomers. As shown by compound **27**, *trans* isomers of the bicycloheptane series gave comparable MCH-R1 activity to the corresponding biphenylamines. Interestingly, when the cyclopropyl ring of **27** was opened to form a methylcyclohexane, such as in compounds **33** and **34**, the MCH-R1 activity was significantly reduced.

Once the bicyclo[4.1.0]heptyl core was discovered, the SAR around this new core was fully studied. As shown in Table 2, structure–activity relationships in the bicycloheptane series paralleled very well with those of biphenylamine series.[18] The phenyl ring on the urea required one or two electron-withdrawing groups at the *meta* or *para* positions for potent MCH-R1 activity



Ar_1 = 3-Cyanophenyl; R_1 = (*R*)-3-OH pyrrolidinyl; Ar_2 = 4-F, 3-CF_3 phenyl

Scheme 4. Synthesis of cyclohexane series. Reagents and conditions: (a) TFA, 50 °C, 94%; (b) Pd/C, H_2, 45 psi, MeOH, 98%; (c) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt, 63%; (d) 1-(2-aminoethyl)-pyrrolidine, $NaBH(OAc)_3$, 48%; (e) 4-fluoro-3-trifluoromethylphenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 75%.



Ar_1 = 3-cyanophenyl; R_1 = (*R*)-3-OH pyrrolidinyl; Ar_2 = 4-F, 3-CF_3-phenyl

Scheme 5. Synthesis of the bicyclo[4.1.0]heptyl series. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 91%; (b) Et_2Zn, TFA, CH_2I_2, CH_2Cl_2, 0 °C, 57%; (c) 20% TFA/CH_2Cl_2, 85%; (d) 1-(2-aminoethyl) pyrrolidine, Ti(O-*i*-Pr)$_4$, 18 h, then $NaBH_4$, MeOH, 52%; (e) 4-fluoro-3-trifluoromethylphenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 50%.

as shown by compounds **35**–**38**. The tolerance for substitution on the distal phenyl ring was very limited, and 3-cyanophenyl was optimal for in vitro and in vivo activity. A few other *meta*-substituted phenyl groups, such as acetamide, gave compounds with good MCH-R1 activity (**42**), but their pharmacokinetic profiles were not as good as those of the 3-cyanophenyl compounds. The most tolerated position of this series in terms of MCH-R1 activity was the right-hand side amine, just as was the case in the biphenylamine series.[18] A variety of amines with extended carbon linkers gave active compounds as shown by **43**–**50**. Although compounds with three carbon linkers had the best MCH-R1 potency, their in vivo profiles were not as good as compounds with two carbon linkers. The basicity of the nitrogen side chain was also very important. As fluorine substitution on the cyclic amine decreased basicity of the nitrogen, the MCH-R1 activity of these compounds

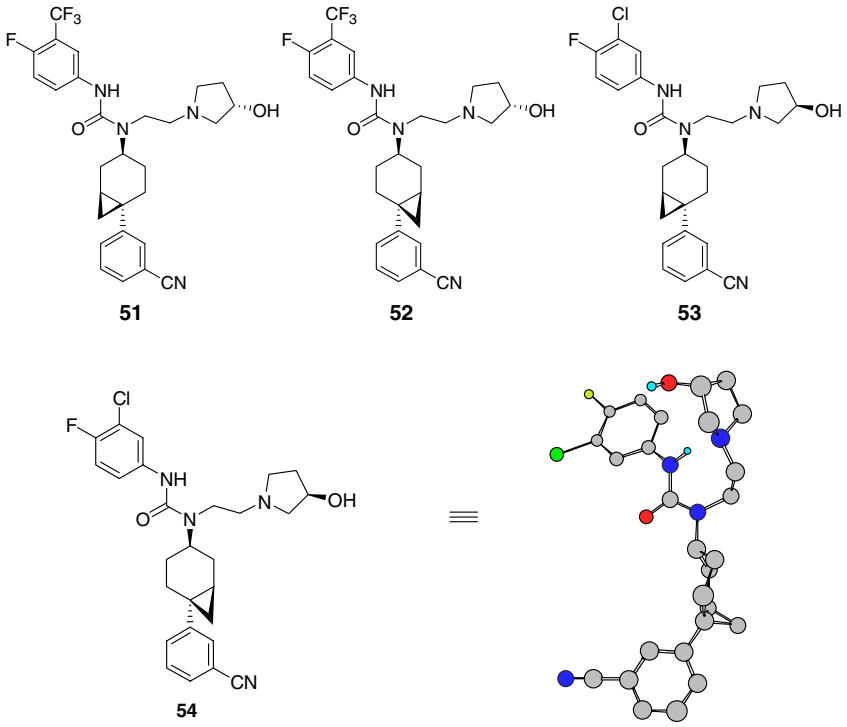
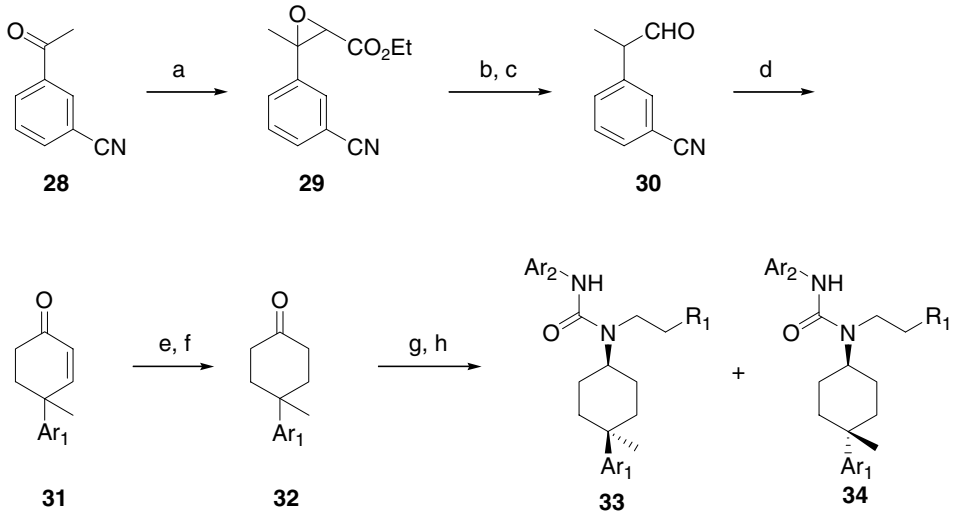


Figure 2. Lead compounds with absolute stereo chemistry and X-ray structure of **54**.

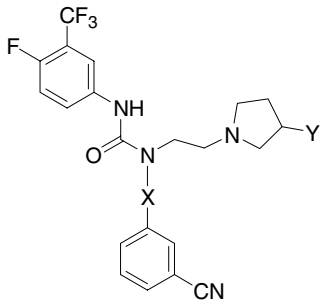


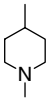
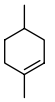
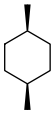
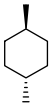
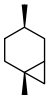
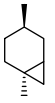
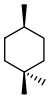
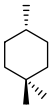
Scheme 6. Synthesis of methyl cyclohexane series. Reagents and conditions: (a) ethyl chloroacetate, K(O-*t*-Bu), *t*-BuOH, 79%; (b) NaOH, EtOH, %; (c) 2 N HCl, 100 °C, 14%; (d) methyl vinylketone, KOH, EtOH, H_2O; (e) H_2, Pt/C, MeOH; (f) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt, 77% for three steps; (g) 1-(2-aminoethyl)-(3)-*R*-hydroxypyrrolidine, $NaBH(OAc)_3$, CH_2Cl_2, 76%; (h) 4-fluoro-3-(trifluoromethyl)phenyl isocyanate, *i*-Pr_2NEt, CH_2Cl_2, 20%.

decreased accordingly (**43**–**45**). Overall, the compounds with two carbon linkers gave the best combined in vitro and in vivo properties.

Since many compounds in this series met the preliminary in vitro criteria for this project, several compounds were resolved to their enantiomerically pure form for further studies. After extensive medicinal chemistry optimization of the current series, four pure diastereomers, **51**–**54**, were identified and synthesized in large quantities. Interestingly, the two enantiomeric cyclopropanes **51**–**52** or **53**–**54** had almost identical MCH-R1 affinities as well as pharmacokinetic properties. Detailed biological studies were carried out and the results are listed in Table 3. All of these compounds showed good oral exposure as indicated by their rat AUC. These compounds were then dosed orally to fasted, diet induced obese mice, and the cumulative food intake was

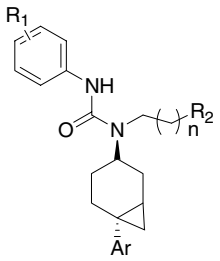
Table 1. Modification of middle phenyl ring

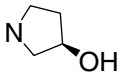
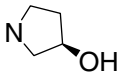
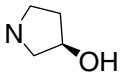
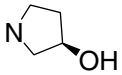
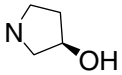
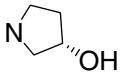
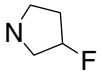
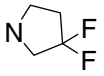
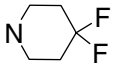
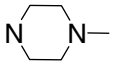
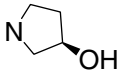
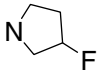
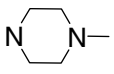


Compound	X	Y	MCH-R1 K_i (nM)[a]
1		H	2
6		H	292
8		H	1350
11		H	906
16		H	3
21		(*R*)-OH	3465
22		(*R*)-OH	297
26		H	739
27		H	12
33		(*R*)-OH	6% inhibition at 3 μM
34		(*R*)-OH	391

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

Table 2. SAR around the bicyclo[4.1.0]heptane core



Compound[a]	*n*	R_1	Ar	R_2	MCH-R1 K_i (nM)[b]	Rapid rat AUC[c] (h ng/ml)
35	1	3-Cl, 4-F	3-Cyanophenyl		9	10,019
36	1	3-CF_3, 4-F	3-Cyanophenyl		16	4,105
37	1	3, 4-di-Cl	3-Cyanophenyl		15	
38	1	3, 5-di-Cl	3-Cyanophenyl		13	26,000
39	1	3-Cl, 4-F	4-Cyanophenyl		95	
40	2	3-Cl, 4-F	3-Thiomethoxyphenyl		46	
41	1	3-Cl, 4-F	3-Fluorophenyl		3000	
42	1	3-Cl, 4-F	3-AcNH-phenyl		3	730
43	1	3-Cl, 4-F	3-Cyanophenyl		54	
44	1	3-Cl, 4-F	3-Cyanophenyl		1581	
45	1	3-Cl, 4-F	3-Cyanophenyl		348	
46	1	3-Cl, 4-F	3-Cyanophenyl		58	
47	2	3-Cl, 4-F	3-Cyanophenyl		3	665
48	2	3-Cl, 4-F	3-Cyanophenyl		7	64
49	2	3-Cl, 4-F	3-Cyanophenyl		3	401
50	2	3-Cl, 4-F	3-Cyanophenyl		4	661

[a] All compounds are racemic at the bicyclic core.
[b] Mean values ($n = 8$). Inhibition of [^{125}I]-MCH binding to h-MCH-R1 expressed in Chinese hamster ovary (CHO) cells.
[c] Data from pooled samples, dosed at 10 mpk, po.

Table 3. In vivo data for leading compounds

Compound[a]	MCH-R1 K_i[b] (nM)	Rapid rat AUC[c] (h ng/ml)	Mouse ex vivo binding (%)[d] at 6 h	24 h DIO mouse assay[e] at 6 h
51	8.6	1924	62	16 ± 6
52	15	2685	73	21 ± 8
53	8.9	2183	49	1 ± 6
54	11.4	2980	58	6 ± 6

[a] All compounds are pure diastereomers.
[b] Mean values ($n = 8$) of inhibition of [^{125}I]-MCH binding to h-MCH-R1 expressed in Chinese hamster ovary (CHO) cells.
[c] Data from pooled samples, dosed at 10 mpk, po.
[d] Expressed as a percent inhibition of MCH-ADO binding relative to vehicle control ±SEM ($n = 3$; dosed at 30 mpk, po).
[e] Expressed as a percent inhibition of accumulative food intake relative to vehicle control; dosed at 30 mpk, po.

measured up to 24 h to determine acute oral efficacy. The results showed that compounds **51** and **52** were active but **53** and **54** were inactive. In order to better understand this dichotomy, we developed an assay measuring ex vivo binding as an indicator of receptor occupancy in the brain.[22] As shown in Table 3, compounds **51** and **52** showed greater ex vivo binding than compounds **53** and **54**. In general, we have found that greater than 60% in ex vivo binding correlates well with activity in the DIO mouse model. These results have established ex vivo binding as one of the primary indicators of in vivo efficacy. Further studies were directed to improve the long-term ex vivo binding and oral efficacy and will be reported in due course.

4. Conclusion

We have discovered a series of MCH-R1 antagonists containing a bicyclo[4.1.0]heptane system. This new core was developed to replace biphenylamine of previous generation of MCH-R1 antagonists in order to circumvent the mutagenic liability of the biphenylamine. The SAR of the bicyclo[4.1.0]heptane series paralleled that of biphenylamine series, suggesting that the two series bind to the receptor in the same fashion. The bicyclo[4.1.0]heptane amine, which acted as the biphenylamine replacement, kept almost all of the in vitro and in vivo profile of biphenylamine moiety, but removed its mutagenic liability. Orally active compounds bearing bicycloheptane core were also identified in acute DIO mouse feeding studies.

5. Experimental

5.1. General

Silica gel chromatography was performed using prepacked silica gel cartridges (Biotage or Isco) on ISCO CombiFlash™ system. NMR spectra were obtained on a Varian Gemini-300 or XL-400 spectrometer in $CDCl_3$ 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: Altech 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. In vitro and in vivo data given throughout the text and in Tables 1–3 were gathered for the amorphous hydrochloride salts whenever there were basic amines on the compounds. 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.

5.1.1. Pyrazin-2-yl-[2-(1-pyrrolidinyl)ethyl] amine (3). 2-Chloropyrazine (10 g, 0.087 mol) and *N*-(2-aminoethyl)pyrrolidine (10 g, 0.087 mol) were heated to 100 °C overnight. The reaction was cooled to room temperature and then dissolved in 2 N hydrochloride solution (250 ml). The aqueous solution was washed with CH_2Cl_2 (2× 100 ml) and then adjusted to pH 10 with 50% NaOH solution. The product was extracted with 250 ml CH_2Cl_2. The organic layer was washed with brine (2× 100 ml), dried over Na_2SO_4, and concentrated. The product was used in next step without further purification (12.9 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (d, $J = 2.7$ Hz, 1H), 7.76 (d, $J = 2.7$ Hz, 1H), 5.28 (br, 1H), 3.42(m, 2H), 2.73 (t, $J = 6.6$ Hz, 2H), 2.55 (m, 4H), 1.79 (m, 4H).

5.1.2. 5-Bromopyrazin-2-yl-[2-(1-pyrrolidinyl)ethyl] amine (4). Compound **3** (12.9 g, 0.067 mole) and pyridine (6.3 g, 0.079 mol) were dissolved in 500 ml CH_2Cl_2 and the solution was cooled to 0 °C. Bromine (13.8 g, 0.086 mol) was added dropwise in 30 min. The reaction mixture was stirred overnight at room temperature. Three hundred milliliters of 2 N NaOH solution was added and the aqueous layer was extracted with CH_2Cl_2 (2× 200 ml). The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column using EtOAc/MeOH/NEt_3 (84/15/1) as the solvent (6.3 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.69 (s, 1H), 5.37 (br, 1H), 3.38 (m, 2H), 2.72 (t, $J = 5.5$ Hz, 2H), 2.55 (m, 4H), 1.80 (m, 4H).

5.1.3. [5-(3-Cyanophenyl)-pyrazin-2-yl]-[2-(1-pyrrolidinyl)ethyl] amine (5). Compound **4** (0.8 g, 3.0 mmol), 3-cyanophenylboronic acid (0.52 g, 3.5 mmol), $PdCl_2(dppf)_2$ (0.24 g, 0.3 mmol), and Na_2CO_3 (0.48 g, 0.45 mmol) were mixed with 100 ml ethylene glycol dimethyl ether and 20 ml water. The reaction mixture was refluxed for 2 h and then cooled to room temperature. One hundred milliliters of EtOAc was added and the organic layer was washed with brine (100 ml), dried over Na_2SO_4, and concentrated. The residue was purified by column using EtOAc/MeOH/NEt_3 (89/10/1) as the solvent (0.4 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.17 (s, 1H), 8.07 (d, $J = 7.7$ Hz, 1H), 7.98 (s, 1H), 7.57 (d, $J = 7.1$ Hz, 1 H), 7.51 (t, $J = 7.7$ Hz, 1H), 5.67 (br, 1H), 3.51 (m, 2H), 2.78 (t, $J = 5.49$ Hz, 2H), 2.59 (m, 4H), 1.82 (m, 4H).

5.1.4. *N*-[5-(3-Cyanophenyl)-pyrazin-2-yl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[2-(1-pyrrolidinyl)ethyl] urea (6). Compound **5** (20 mg, 0.068 mmol) and 4-fluoro-3-trifluorophenylisocyanate (25 mg, 0.12 mmol) were dis-

solved in 5 ml dry CH_2Cl_2. NaH (60% in oil, about 20 mg) was added and the mixture was stirred at room temperature over the weekend. Fifty milliliters of CH_2Cl_2 was added and the organic layer was washed with water (2× 30 ml), dried over Na_2SO_4, and concentrated. The product was purified by preparative TLC using EtOAc as the solvent (23 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.3 (s, 1H), 9.22 (s, 1H), 8.68 (s, 1H), 8.28 (s, 1H), 8.21 (d, J = 7.7 Hz, 1H), 7.52–7.80 (m, 4H), 7.18 (t, J = 9.3 Hz, 1H), 4.31 (t, J = 4.4 Hz, 2H), 2.95 (t, J = 4.4 Hz, 2H), 2.80 (m, 4H), 1.93 (m, 4H).

LCMS: 499.3, t_R = 5.15 min ($M+H^+$), >99% purity; HRMS (FAB) *m/z* 499.1865 ($M+H^+$); calcd. for $C_{25}H_{23}F_4N_6O$: 499.1864.

5.1.5. *N*-[5-(3-Cyanophenyl)-2-pyrimidinyl]-*N*′-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*-[2-(1-pyrrolidinyl)ethyl] urea (8). Obtained from 5-bromo-2-chloro-pyrimidine according to the synthetic procedure for **6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 2H), 7.62–7.88 (m, 6H), 7.18 (t, J = 9.9 Hz, 1H), 4.62 (t, J = 7.1 Hz, 2H), 2.95–3.14 (m, 6H), 1.95 (m, 4H). LCMS: 499.1, t_R = 5.43 min ($M+H^+$), 93% purity; HRMS (FAB) *m/z* 499.1865 ($M+H^+$); calcd. for $C_{25}H_{23}F_4N_6O$: 499.1864.

5.1.6. 3-(4-Oxo-1-piperidinyl)-benzonitrile (9). 3-Cyanoaniline (2.36 g, 20 mmol), K_2CO_3 (1 g, 7.2 mmol), Cs_2CO_3 (0.5 g, 1.5 mmol), and 40 ml EtOH were heated to 100 °C. Slurry of 1-benzyl-1-methyl-4-oxo-piperidinium iodide (7.3 g, 22 mmol) in 20 ml water was added and the solution was refluxed for 2 h. EtOH was removed under vacuum and the residue was partitioned between 100 ml CH_2Cl_2 and 100 ml water. The organic layer was washed with brine (50 ml), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography using EtOAc/hexane (25/75) as the solvent (0.11 g, 2.8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 1H), 7.15 (m, 3H), 3.65 (t, J = 6.0 Hz, 4H), 2.57 (t, J = 6.0 Hz, 4H).

5.1.7. 3-[4-[[2-(1-Pyrrolidinyl)ethyl]amino]-1-piperidinyl]benzonitrile (10). Compound **9** (0.11 g, 0.55 mmol), *N*-(2-aminoethyl)-pyrrolidine (0.094 g, 0.825 mmol), Ti(O-*i*-Pr)$_4$ (0.1 ml), and 10 ml CH_2Cl_2 were stirred at room temperature overnight. $NaCNBH_3$ (0.19 g, 3 mmol) and a few drops of MeOH were added and the reaction mixture was stirred at room temperature overnight. Five milliliters of saturated NH_4Cl solution and 50 ml CH_2Cl_2 were added and the solution was filtered though a Celite pad. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was used in next step without further purification (0.16 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.06 (m, 3H), 3.67 (d, J = 13.2 Hz, 1H), 2.55–2.90 (m, 13H), 2.00 (m, 2H), 1.80 (m, 4H), 1.48 (m, 2H).

5.1.8. *N*-[1-(3-Cyanophenyl)-4-piperidinyl]-*N*′-[4-fluoro-3-(trifluoromethyl)penyl]-*N*-(1-pyrrolidinyl)ethyl]urea (11). Compound **10** (11 mg, 0.037 mmol), 4-fluoro-3-trifluoromethyl-phenylisocyanate (35 mg, 0.17 mmol), and 10 mg DMAP were stirred in 5 ml CH_2Cl_2 at room temperature overnight. The reaction solution was diluted with 25 ml CH_2Cl_2, washed with brine (25 ml), dried over Na_2SO_4, and concentrated. The residue was purified with a preparative TLC plate using EtOAc/NEt_3 (90/10) as solvent (13 mg. 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.60 (m, 3H), 7.30 (m, 1H), 7.06 (m, 2H), 4.38 (m, 1H), 3.72 (m, 2H), 3.52 (m, 2H), 2.30–3.40 (m, 8 H), 1.70–2.10 (m, 8 H). LCMS: 504.1, t_R = 4.01 min ($M+H^+$), >90% purity.

5.1.9. 4-(3-Cyanophenyl)-4-hydroxycyclohexane-1-one ethylene ketal (12). 3-Bromobenzonitrile (20 g, 0.11 mol) was dissolved in 500 ml dry THF and the solution was cooled to −100 °C. *n*-Butyllithium (1.6 M in hexane, 68 ml, 0.11 mol) was added via an additional funnel in one hour. During this time, the temperature inside the reaction flask was kept below −95 °C. After *n*-butyllithium was added, the reaction mixture was stirred at −95 °C for 10 min. 1,4-Dioxaspiro[4, 5]decan-8-one (17.1 g, 0.11 mol) in 100 ml dry THF was added via another additional funnel in 1 h. During this time the reaction temperature was kept below −75 °C. The reaction mixture was stirred for 30 min and the temperature slowly rose to −25 °C. The reaction was then quenched by adding 200 ml water and 1000 ml EtOAc. The organic layer was washed with water (3× 400 ml), dried over Na_2SO_4 and the solvent was removed via vacuum. The residue was recrystallized from EtOAc/hexane mixture to afford 15.5 g pure product. The crude product from mother liquor was purified by column using hexane/EtOAc (70/30) as the solvent. Additional 8.0 g pure product was obtained (total yield: 23.5 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.76 (d, J = 7. 7 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 3.99 (t, J = 2.8 Hz, 4H), 2.00–2.21 (m, 4H), 1.60–1.81 (m, 4H).

5.1.10. 4-(3-Cyanophenyl)-4-hydroxycyclohexane-1-one (13). Compound **12** (1.5 g, 5.8 mmol) was dissolved in 100 ml acetone and toluenesulfonic acid monohydrate (0.2 g) was added. The reaction was refluxed for one hour. Acetone was removed and the residue was dissolved in 100 ml EtOAc. The organic layer was washed with water (3× 100 ml) and dried over Na_2SO_4. After the solvent was removed, the residue was the desired product and it was used in next step without further purification (1.2 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 2.92 (m, 2H), 2.10–2.46 (m, 6H).

5.1.11. *trans*-1-[2-(1-Pyrrolidinyl)ethylamino]-4-(3-cyanophenyl)-4- hydroxycyclohexane (14). Compound **13** (1.4 g, 6.5 mmol), 1-(2-aminoethyl)pyrrolidine (1.5 g, 13 mmol), and $NaCNBH_3$ (0.8 g, 13 mmol) were stirred in 100 ml CH_2Cl_2 at room temperature overnight. The organic layer was washed with water (3× 50 ml), dried over Na_2SO_4, and the solvent was removed. The residue was purified by column using EtOAc/MeOH/NEt_3 (65/34/1) as the eluent (0.91 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 2.80 (m, 1H), 2.68 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H),

2.48 (s, 4H), 2.22 (s, 2H), 1.93 (s, 2H), 1.73 (s, 4H), 1.51 (m, 4H). *Cis* isomer was also isolated from this column (0.40 g, 20%).

5.1.12. *N*′-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*-[*trans*-4-(3-cyanophenyl)-4-hydroxycyclohexyl]-*N*-[2-(1-pyrrolidinyl)ethyl]urea (15). Compound **14** (25 mg, 0.08 mmol) and 4-fluoro-3-trifluoromethyl phenylisocyanate (15 mg, 0.08 mmol) were stirred in 3 ml CH_2Cl_2 at room temperature overnight. The reaction solution was purified directly with a preparative TLC plate using EtOAc as the solvent (20 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.84 (s, 1H), 7.82 (d, J = 6.9 Hz, 1H), 7.50–7.64 (m, 3H), 7.41(dd, J = 6.2, 2.5 Hz 1H), 7.06 (t, J = 9.3 Hz, 1H), 4.36 (tt, J = 12, 3.7 Hz, 1H), 3.06 (t, J = 4.0 Hz, 2H), 2.50–2.70 (m, 8 H), 1.77–2.05 (m, 8 H), 1.28 (q, J = 12.4 Hz, 2H).

5.1.13. *N*′-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*-[4-(3-Cyanophenyl)-3-cyclohexen-1-yl]-*N*-[2-(1-pyrrolidinyl)ethyl]urea (16). Compound **15** (20 mg, 0.039 mmol) was dissolved in 5 ml mixture of CH_2Cl_2/TFA/Et_3SiH (5/5/1) and the reaction mixture was stirred at room temperature overnight. TFA was removed and the residue was partitioned between 60 ml EtOAc and 60 ml saturated $NaHCO_3$ solution. The organic layer was washed with water (2× 50 ml), dried over Na_2SO_4, and concentrated. The product was purified by preparative TLC using EtOAc as the eluent (12 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.09 (s, 1 H), 7.62 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38–7.52 (m, 3H), 7.15 (m, 1H), 7.01 (t, J = 8.9 Hz, 1H), 6.11 (t, J = 2.8 Hz, 1H), 4.50 (m, 1H), 3.32 (t, J = 4.1 Hz, 2H), 1.70–2.82 (m, 16H). LCMS: 501.1, t_R = 5.36 min ($M+H^+$), 99% purity; HRMS (FAB) *m/z* 501.2268 ($M+H^+$); calcd. for $C_{27}H_{29}F_4N_4O$: 501.2272.

5.1.14. 4-(3-Cyanophenyl)-3-cyclohexene-1-one (17) and 4-(3-cyanophenyl)-2-cyclohexene-1-one (18). Compound **12** (10 g, 39 mmol) was dissolved in 80 ml TFA. The mixture was heated to 50 °C for 4 h. TFA was removed under vacuum and the residue was partitioned between 200 ml EtOAc and 100 ml saturated $NaHCO_3$ solution. The organic layer was washed with water (2× 100 ml), dried over Na_2SO_4, and concentrated. The product was purified by column using hexane/EtOAc (85/15) as the eluent. Two products were obtained: **17** (3.1 g, 41%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.7 (m, 4H), 6.17 (t, J = 3.9 Hz, 1H). 3.11(s, 2H), 2.90 (t, J = 6.6 Hz, 2H), 2.67(t, J = 6.6 Hz, 2H) and **18** (4.0 g, 53%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.63 (m, 4H), 6.92 (d, J = 9.9 Hz, 1H), 6.23 (dd, J = 10.4, 2.7 Hz, 1H), 3.80(m, 1H), 2.31–2.59(m, 3H), 2.25(m, 1H).

5.1.15. 4-(3-Cyanophenyl)-cyclohexane-1-one (19). The mixture of **17** and **18** (total 1.8 g, 9.1 mmol) was dissolved in 50 ml EtOAc. Pt (10% on carbon, 0.5 g) was added and the mixture was shaken at 45 psi hydrogen overnight. The catalyst was filtered and the solvent was removed under vacuum. The residue was dissolved in 100 ml CH_2Cl_2 and Dess–Martin reagent (4.2 g, 10 mmol) was added. The mixture was stirred at room temperature for 5 h. The reaction solution was washed with water (3× 100 ml), dried over Na_2SO_4, and concentrated. The product was purified by column using hexane/EtOAc (85/15) as the eluent (1.1 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.60 (m, 4H), 3.10 (tt, J = 12.1, 3.3 Hz, 1H), 2.53(m, 4H), 2.3 (m, 2H), 1.94(m, 2H).

5.1.16. *N*′-(4-Fluoro-3-trifluoromethylphenyl)-*N*-[*cis*-4-(3-cyanophenyl)-cyclohexyl]-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (21) and *N*′-(4-fluoro-3-trifluoromethylphenyl)-*N*-[*trans*-4-(3-cyanophenyl)-cyclohexyl]-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (22). Compound **19** (0.7 g, 3.5 mmol), *N*-(2-aminoethyl)-3-(*R*)-hydroxy-pyrrolidine (1.36 g, 10.5 mmol), and $NaBH(OAc)_3$ (2.2 g, 10.5 mmol) were refluxed in 50 ml CH_2Cl_2 for 24 h. Fifty milliliters of water was added to quench the reaction. The organic layer was washed with water (3× 50 ml), dried over Na_2SO_4, and concentrated. The residue was used in next step without further purification. A portion of the above product (60 mg, 0.19 mmol) and 4-fluoro-3-trifluoromethyl phenylisocyanate (50 mg, 0.24 mmol) were stirred in 5 ml CH_2Cl_2 at room temperature overnight. The reaction mixture was purified directly by a preparative TLC plate using EtOAc/hexane(85/15) as the solvent. Two products were isolated. Compound **21** (35.9 mg HCl salt, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.57–7.71 (m, 4H), 7.42–7.53 (m, 2H), 7.03 (t, J = 9.8 Hz, 1H), 4.48 (m, 1H), 4.29 (tt, J = 12.0, 4.0 Hz, 1H), 3.00–3.17 (m, 4H), 2.66–2.85 (m, 4H), 1.76–2.52 (m, 8 H), 1.60–1.70 (m, 2H), 1.30–1.45 (m, 2H). LCMS: 519.1, t_R = 5.46 min ($M+H^+$), 98% purity; HRMS (FAB) *m/z* 519.2392 $(M+H)^+$; calcd. for $C_{27}H_{31}F_4N_4O_2$: 519.2378. Compound **22** (38.6 mg HCl salt, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.67–7.73 (m, 2H), 7.36–7.51 (m, 4H), 7.03 (t, J = 9.8 Hz, 1H), 4.51 (m, 1H), 4.24 (tt, J = 12.0, 4.0 Hz, 1H), 3.35 (t, J = 4.0 Hz, 2H), 3.10 (m, 1H), 2.75–2.90 (m, 4H), 2.52 (m, 2H), 2.22 (m, 1H), 1.80–2.00 (m, 6H), 1.45–1.70 (m, 4H). LCMS: 519.1, t_R = 5.46 min ($M+H^+$), 96% purity; HRMS (FAB) *m/z* 519.2387 $[(M+H)^+$; calcd. for $C_{27}H_{31}F_4N_4O_2$: 519.2378.

5.1.17. 4-(3-Cyanophenyl)-3-cyclohexene-1-one ethylene ketal (23). Compound **12** (20 g, 77 mmol) and NEt_3 (15.6 g, 154 mmol) were dissolved in 500 ml CH_2Cl_2. MsCl (9.7 g, 85 mmol) in 100 ml CH_2Cl_2 was then added dropwise in 1 h. The mixture was stirred at room temperature for 5 h. Additional NEt_3 and MsCl (same amount as the first time) were added, and the reaction mixture was stirred at room temperature for 1 h. Two hundred milliliters of saturated $NaHCO_3$ solution was added to quench excess MsCl. The organic layer was washed with water (2× 200 ml), dried over Na_2SO_4, and concentrated. The residue was recrystallized from EtOAc/hexane to afford 9.1 g pure product. Column purification of the compound in filtrate with EtOAc/hexane (80/20) gave additional 7.8 g pure product (total yield: 16.9 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 6.06 (m, 1H), 4.03 (s, 4H), 2.64 (m, 2H), 2.44 (m, 2H), 1.93 (t, J = 6.6 Hz, 2H).

5.1.18. 6-(3-Cyanophenyl)bicyclo[4.1.0]heptane-3-one ethylene ketal (24). Diethylzinc (1 M in hexane, 19 ml, 19 mmol) was mixed with 50 ml CH_2Cl_2 and the mixture was cooled to 0 °C. TFA (2.1 g, 19 mmol) in 20 ml CH_2Cl_2 was added. The mixture was stirred at 0 °C for 20 min. CH_2I_2 (5 g, 19 mmol) in 10 ml CH_2Cl_2 was then added, followed by **23** (1.5 g, 6.2 mmol) in 20 ml CH_2Cl_2. The mixture was stirred at room temperature overnight. Fifty milliliters of 1 N HCl solution was added to quench the reaction. The organic layer was washed with water (2× 50 ml) and dried over Na_2SO_4. The product was purified by column using EtOAc/hexane (10/90) as the eluent (0.8 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 3.9 (m, 4H), 2.10–2.35 (m, 2H), 1.4–1.9 (m, 4H), 1.25 (s, 1H), 1.05(m, 1H), 0.82 (t, J = 5.5 Hz, 1H).

5.1.19. 6-(3-Cyanophenyl)bicyclo[4.1.0]heptane-3-one (25). Compound **24** (0.8 g, 3.1 mmol) was stirred in 20 ml mixture of CH_2Cl_2/TFA (4/1) for 30 min. The solvent was removed and the residue was partitioned between 100 ml EtOAc and 100 ml saturated $NaHCO_3$ solution. The organic layer was washed with water (2× 50 ml), dried with Na_2SO_4, and concentrated. The product was purified by column using EtOAc/hexane (10/90) as the eluent (0.56 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.49–7.51 (m, 2H), 7.42 (t, J = 7.7 Hz, 1H), 2.62–2.92 (m, 2H), 2.39–2.52 (m, 2H), 2.18–2.32 (m, 2H), 1.48–1.57 (m, 1H), 1.10 (d, J = 7.7 Hz, 2H).

5.1.20. *N*-[*cis*-6-(3-Cyanophenylbicyclo[4.1.0]hept-3-yl]-*N*′-(4-fluoro-3-trifluoromethyl-phenyl)-*N*-[2-(1-pyrrolidinyl)ethyl]urea (26) and *N*-[*trans*-6-(3-cyanophenylbicyclo[4.1.0]hept-3-yl]-*N*′-(4-fluoro-3-trifluoromethyl-phenyl)-*N*-[2-(1-pyrrolidinyl)ethyl]urea (27). Obtained from **25** according to the same procedure as **21** and **22.**

Compound **26**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.65 (m, 1H), 7.32–7.58 (m, 5H), 7.08 (t, J = 9.6 Hz, 1H), 4.18 (tt, J = 11.5, 3.8 Hz, 1H), 3.17 (m, 2H), 2.66–2.84 (m, 6H), 1.35–2.35 (m, 11H), 1.10 (dd, J = 9.3, 4.9 Hz, 1H), 0.85 (t, J = 5.5 Hz, 1H). LCMS: 515.1, t_R = 5.56 min ($M+H^+$), 95% purity; HRMS (FAB) m/z 515.2432 ($M+H^+$); calcd. for $C_{28}H_{31}F_4N_4O$: 515.2428. Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.25–7.70 (m, 6H), 7.08 (t, J = 9.6 Hz, 1H), 4.24 (m, 1H), 3.27 (m, 2H), 2.74 (m, 6H), 1.20–2.40 (m, 11H), 1.00 (dd, J = 9.3, 4.9 Hz, 1H), 0.76 (t, J = 5.5 Hz, 1H). LCMS: 515.1, t_R = 5.56 min ($M+H^+$), >99% purity; HRMS (FAB) m/z 515.2427 ($M+H^+$); calcd. for $C_{28}H_{31}F_4N_4O$: 515.2428.

5.1.21. 3-(3-Cyano-phenyl)-3-methyl-oxirane-2-carboxylic acid ethyl ester (29). 3-Acetyl-benzonitrile (10.2 g, 70 mmol) was dissolved in 100 ml *t*-butanol. With stirring, KO-*t*-Bu (11.8 g, 105 mmol) was added portionwise and the reaction mixture was stirred for 0.5 h. Ethyl chloroacetate (9.4 g, 77 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. Two hundred milliliters of EtOAc was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column using EtOAc/hexane(30/70) as the solvent (4.9 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.80 (m, 4H), 4.20–4.40 (m, 1H), 3.86–4.00 (m, 1H), 3.70 (s, 0.5H), 3.41 (s, 0.5H), 1.78 (s, 1.5H), 1.76 (s, 1.5H), 1.34 (t, J = 7.1 Hz, 1.5H), 0.96 (t, J = 7.1 Hz, 1.5H).

5.1.22. 3-(1-Methyl-2-oxo-ethyl)-benzonitrile (30). Sodium (0.73 g, 32 mmol) was dissolved in 20 ml ethanol at room temperature and the reaction mixture was cooled to 0 °C. Compound **29** (4.9 g, 21.2 mmol) in 20 ml EtOH was added and the reaction was stirred for 0.5 h. Two milliliters of water was added and the reaction mixture was stirred at room temperature overnight. Ethanol was removed and 45 ml water and 8.4 ml concentrated HCl solution were added. The reaction mixture was heated to 100 °C for 1 h. It was then cooled to room temperature and then 100 ml CH_2Cl_2 was added. The organic layer was washed with 100 ml brine, dried over Na_2SO_4, and concentrated. The product was purified by column using EtOAc/hexane (30/70) as the solvent (yield 0.46 g, 14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.45–7.65 (m, 4H), 3.70 (q, J = 7.1 Hz, 1H), 1.49 (d, J = 7.1 Hz, 3H).

5.1.23. 3-(1-Methyl-4-oxo-cyclohex-2-enyl)-benzonitrile (31). Compound **30** (0.46 g, 2.9 mmol) was dissolved in 20 ml EtOH and 20 ml ether at 0 °C. A few milligrams of potassium hydroxide and methyl vinyl ketone (0.3 g, 4.35 mmol) was added, the reaction mixture was stirred at room temperature overnight. Solvent was removed and the residue was dissolved in 80 ml CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was used in next step without further purification. (Yield 0.91 g, impure, some solvent still existed.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.70 (m, 4H), 6.88 (d, J = 9.9 Hz, 1H), 6.17 (d, J = 9.9 Hz, 1H), 2.15–2.50 (m, 4H), 1.58 (s, 3H).

5.1.24. 3-(1-Methyl-4-oxo-cyclohexyl)-benzonitrile (32). Compound **31** (All the product from last step) was dissolved in 50 ml EtOAc. Pt/C (5%, 0.5 g) was added and the mixture was shaken at 45 psi hydrogen over the weekend. The catalyst was filtered and the solvent was removed. The residue was dissolved in 50 ml CH_2Cl_2 and Dess–Martin reagent (1.7 g) was added. The reaction mixture was stirred at room temperature overnight. The white precipitate was filtered and discarded. The filtrate was washed with 50 ml brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC using EtOAc/hexane (30/70) as the solvent. (0.36 g, 77% for three steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.76 (m, 4H), 2.36–2.50 (m, 4H), 2.18–2.32 (m, 2H), 1.92–2.08 (m, 2H), 1.34 (s, 3H).

5.1.25. *N*′-(4-Fluoro-3-trifluoromethylphenyl)-*N*-[*cis*-4-(3-cyanophenyl)-4-methyl-cyclohexyl]-*N*-[2-[3-(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (33) and *N*′-(4-fluoro-3-trifluoromethylphenyl)-*N*-[*trans*-4-(3-cyanophenyl)-4-methyl-cyclohexyl]-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (34). Obtained from **32** according to the same procedure as **21** and **22**.

Compound **33**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (s, 1H), 7.40–7.76 (m, 6H), 7.06 (t, J = 9.3 Hz, 1H), 4.48 (m, 1H), 4.29 (m, 1H), 1.16–3.12 (m, 18H), 1.14(s, 3H). LCMS: 533.1, t_R = 5.23 min. ($M+H^+$), >99% purity; HRMS (FAB) m/z 533.2547 ($M+H^+$), calcd for $C_{28}H_{33}F_4N_4O_2$: 533.2534. Compound **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (s, 1H), 7.4–7.8 (m, 6H), 7.06 (t, J = 9.3 Hz, 1H), 4.54 (m, 1H), 4.14 (m, 1H), 1.60–3.50 (m, 18H), 1.31 (s, 3H). LCMS: 533.1, t_R = 5.26 min. ($M+H^+$), >99% purity; HRMS (FAB) m/z 533.2547 ($M+H^+$), calcd for $C_{28}H_{33}F_4N_4O_2$: 533.2534.

5.1.26. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (35). Compound **25** (1.4 g, 6.6 mmol), 2-[3-(*R*)-hydroxy-1-pyrrolidinyl]ethylamine (1.3 g, 10 mmol), and Ti(O-*i*-Pr)$_4$ were stirred at room temperature overnight. $NaBH_4$ (0.5 g, 13 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. One hundred milliliters of 2 N HCl solution was added and the aqueous layer was washed with CH_2Cl_2 twice (50 ml each). Two hundred milliliters of CH_2Cl_2 was added to the aqueous layer and pH of the two layer solution was adjusted to **14** by adding 50% NaOH solution. The white precipitate was filtered and discarded. The organic layer of the filtrate was separated, washed with 50 ml brine, dried over Na_2SO_4, and concentrated. The residue (1.5 g, 4.6 mmol) was dissolved in 40 ml dry CH_2Cl_2 and 3-chloro-4-fluorophenyl isocyanate (1 g, 5.8 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was purified by column using EtOAc/7N NH_3 in MeOH (99/1) as the eluent. After the *cis* isomer came off the column completely, the *trans* isomer was collected as the major product (1.0 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.62–7.68 (m, 2H), 7.25–7.55 (m, 4H), 6.97 (t, J = 8.8 Hz, 1H), 4.52 (m, 1H), 4.19 (m, 1H), 3.25 (m, 2H), 3.07 (m, 1H), 2.73–2.91 (m, 4H), 2.54 (m, 1H), 1.50–2.40 (m, 7H), 1.32 (m, 2H), 0.99 (dd, J = 9.3, 4.9 Hz, 1H), 0.76 (t, J = 4.9 Hz, 1H). LCMS: 497.1, t_R = 5.11 min. ($M+H^+$), >99% purity; HRMS (FAB) m/z 497.2125 ($M+H^+$), calcd for $C_{27}H_{31}ClFN_4O_2$: 497.2114.

5.1.27. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(4-fluoro-3-trifluoromethylphenyl)-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (36). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (d, J = 6.6 Hz, 1H), 7.66–7.74 (m, 2H), 7.33–7.55 (m, 4H), 7.04 (t, J = 9.9 Hz, 1H), 4.51 (m, 1H), 4.21 (m, 1H), 3.26 (m, 2H), 3.09 (m, 1H), 2.70–2.91 (m, 4H), 2.53 (m, 1H), 1.50–2.60 (m, 7H), 1.32 (m, 2H), 1.00 (dd, J = 9.3, 5.4 Hz, 1H), 0.76 (t, J = 4.9 Hz, 1H). LCMS: 531.1, t_R = 5.16 min. ($M+H^+$), >99% purity; HRMS (FAB) m/z 531.2373 ($M+H^+$), calcd for $C_{28}H_{31}F_4N_4O_2$: 531.2378.

5.1.28. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3,4-dichloro-phenyl)-*N*-[2-[3(R)-hydroxy-1-pyrrolidinyl]ethyl]urea (37). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.70 (t, J = 2.4 Hz, 1H), 7.23–7.56 (m, 6H), 4.53 (m, 1H), 4.20 (m, 1H), 3.24 (m, 2H), 3.08 (m, 1H), 2.74–2.91 (m, 4H), 2.54 (m, 1H), 1.50-2.42 (m, 7H), 1.32 (m, 2H), 1.00 (dd, J = 9.3, 4.9 Hz, 1H), 0.76 (t, J = 5.5 Hz, 1H). LCMS: 513.1, t_R = 5.16 min. ($M+H^+$), >99% purity; HRMS (FAB) m/z 513.1828 ($M+H^+$), calcd for $C_{27}H_{31}Cl_2N_4O_2$: 513.1819.

5.1.29. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3, 5-dichloro-phenyl)-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (38). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.82 (d, J = 6.0 Hz, 1H), 7.33–7.55 (m, 6H), 6.89 (t, J = 1.9 Hz, 1H), 4.54 (m, 1H), 4.18 (m, 1H), 3.23 (m, 2H), 3.08 (m, 1H), 2.72–2.92 (m, 4H), 2.54 (m, 1H), 1.82–2.42 (m, 5H), 1.58 (m, 2H), 1.31 (m, 2 H), 0.99 (dd, J = 9.3, 4.9 Hz, 1H), 0.75 (t, J = 5.5 Hz, 1H). LCMS: 513.1, t_R = 5.26 min. ($M+H^+$), >99% purity; HRMS (FAB) m/z 513.1816 ($M+H^+$), calcd for $C_{27}H_{31}Cl_2N_4O_2$: 513.1819.

5.1.30. *N*-[*trans*-6-(4-cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (39). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.64 (dt, J = 7.1, 2.7 Hz, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.34 (m, 3H), 6.95 (t, J = 8.8 Hz, 1H), 4.54 (m, 1H), 4.20 (m, 1H), 3.26 (m, 2H), 3.09 (m, 1H), 2.74–2.92 (m, 4H), 2.55 (m, 1H), 2.03–2.45 (m, 4H), 1.20–1.94 (m, 5H), 1.02 (dd, J = 9.3, 4.9 Hz, 1H), 0.79 (t, J = 5.4 Hz, 1H). LCMS: 497.1, t_R = 5.28 min. ($M+H^+$), 100% purity; HRMS (FAB) m/z 497.2139 ($M+H^+$), calcd for $C_{27}H_{31}ClFN_4O_2$: 497.2114.

5.1.31. *N*-[*trans*-6-[3-(Thiomethoxy)phenyl]bicyclo[4.1.0]-hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[3-(1-pyrrolidinyl)propyl]urea (40). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.53 (m, 1H), 7.31 (m, 1H), 7.20 (m, 2H), 7.03 (m, 3H), 3.95 (m, 1H), 3.35 (m, 2H), 2.64 (m, 6H), 2.47(s, 3H), 2.30 (m, 2H), 2.08 (m, 1H), 1.74–1.94 (m, 7H), 1.60 (m, 2H), 1.28 (m, 1H), 0.97 (dd, J = 9.3, 4.9 Hz, 1H), 0.79 (t, J = 5.5 Hz, 1H). LCMS: 516.1, t_R = 5.66 min. ($M+H^+$), 97% purity; HRMS (FAB) m/z 516.2248 ($M+H^+$), calcd for $C_{28}H_{36}ClFN_3OS$: 516.2246.

5.1.32. *N*-[*trans*-6-(3-Fluorophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-[3(*S*)-hydroxy-1-pyrrolidinyl]ethyl]urea (41). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.66 (m, 1H), 7.12–7.36 (m, 3H), 6.92–7.07 (m, 3H), 4.53 (m, 1H), 4.27 (m, 1H), 3.27 (m, 2H), 3.10 (m, 1H), 2.76–2.93 (m, 4H), 2.57 (m, 1H), 1.82–2.44 (m, 8 H), 1.20–1.62 (m, 2H), 0.97 (dd, J = 9.3, 4.9 Hz, 1H), 0.68 (t, J = 4.9 Hz, 1H). LCMS: 490.3, t_R = 4.87 min. ($M+H^+$), 95% purity; HRMS (FAB) m/z 490.2080 ($M+H^+$), calcd for $C_{26}H_{31}ClF_2N_4O_2$: 490.2067.

5.1.33. *N*-[3-*trans*-4-[[[(3-Chloro-4-fluorophenyl)amino]carbonyl][2-(1-pyrrolidinyl)ethyl]amino]bicyclo[4.1.0]hept-1-yl]phenyl]acetamide (42). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.03 (s, 1H), 7.40–7.51(m, 2H), 7.12–7.32 (m, 3H), 6.96–7.04 (m, 2H), 4.22 (m, 1H), 3.25 (m, 2H), 2.72 (m, 6H), 2.00–2.4(m, 2H), 2.19 (s, 3H), 1.90 (m, 4H), 1.60 (m, 4H), 1.25 (m, 1H), 1.00 (dd, J = 4.4, 9.3 Hz, 1H), 0.64 (t, J = 5.5 Hz, 1H). LCMS: 513.1, t_R = 5.18 min. ($M+H^+$), 95% purity; HRMS (FAB) m/z 513.2440 ($M+H^+$), calcd for $C_{28}H_{35}ClFN_4O_2$: 513.2427.

5.1.34. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-(3-fluoro-1-pyrrolidinyl)ethyl]urea (43). Compound **35** (50 mg, 0.1 mmol) and DAST (100 mg, 0.62 mmol) were stirred in 5 ml CH_2Cl_2 at room temperature overnight. Forty milliliters of CH_2Cl_2 was added and the organic layer was washed with brine (50 ml), dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC using EtOAc/hexane (60/40) as the eluent (15 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.10–7.60 (m, 6H), 7.00 (t, J = 8.8 Hz, 1H), 5.35 (m, 0.5H), 5.16 (m, 0.5H), 4.20 (m, 1H), 3.12–3.34 (m, 4H), 2.71–2.86 (m, 2H), 2.02–2.82 (m, 8 H), 1.24–1.70(m, 3H), 1.01 (dd, J = 9.8, 4.4 Hz, 1H), 0.76 (t, J = 4.9 Hz, 1H). LCMS: 499.1, t_R = 5.28 min. (M+H$^+$), >99% purity.

5.1.35. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-(3,3-difluoro-1-pyrrolidinyl)ethyl]urea (44). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.33–7.57 (m, 5H), 7.10–7.17 (m, 1H), 7.01 (t, J = 8.8 Hz, 1H), 4.17 (m, 1H), 3.28 (m, 2H), 3.12 (td, J = 12.6, 3.3 Hz, 2H), 2.95 (t, J = 7.1 Hz, 2H), 2.80 (m, 2H), 2.36 (m, 4H), 2.11 (td, J = 13.2, 4.9 Hz, 1H), 1.25–1.67 (m, 3H), 1.01 (dd, J = 9.3, 4.9 Hz, 1H), 0.76 (t, J = 5.5 Hz, 1H). LCMS: 517.1, t_R = 5.25 min. (M+H$^+$), >99% purity; HRMS (FAB) m/z 517.1799 (M+H$^+$), calcd for $C_{27}H_{29}ClF_3N_4O$: 517.1976.

5.1.36. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-(4,4-difluoro-1-piperidinyl)ethyl]urea (45). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.42–7.59 (m, 4H), 7.37 (t, J = 7.7 Hz, 1H), 7.09 (m, 1H), 7.03 (t, J = 8.8 Hz, 1H), 4.19 (m, 1H), 3.29 (m, 2H), 2.77 (m, 4H), 2.66 (m, 2H), 2.32 (m, 2H), 1.96–2.17 (m, 5H), 1.58 (m, 2H),1.24–1.45 (m, 2H), 1.01 (dd, J = 9.3, 4.9 Hz, 1H), 0.76 (t, J = 5.5 Hz, 1H). LCMS: 531.1, t_R = 5.52 min. (M+H$^+$), >99% purity; HRMS (FAB) m/z 531.2130 (M+H$^+$), calcd for $C_{28}H_{31}ClF_3N_4O$: 531.2133.

5.1.37. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[3-[3(R)-hydroxy-1-pyrrolidinyl]propyl]urea (47). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, J = 23.1 Hz,1H), 7.64 (m, 1H), 7.32–7.55 (m, 5H), 6.98 (t, J = 8.8 Hz, 1H), 4.47 (m, 1H), 3.90 (m, 1H), 3.17–3.46 (m, 2H), 1.56–2.84 (m, 16H), 1.28 (m, 1H), 0.97 (m, 1H), 0.84 (m, 1H). LCMS: 511.1, t_R = 5.18 min. (M+H$^+$), 100% purity; HRMS (FAB) m/z 511.2283 (M+H$^+$), calcd for $C_{28}H_{33}ClFN_4O_2$: 511.2271.

5.1.38. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[3-(3-fluoro-1-pyrrolidinyl)-propyl]urea (48). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, J = 26.9 Hz, 1H), 7.28–7.64 (m, 6H), 6.98 (td, J = 8.8, 1.1 Hz, 1H), 5.32 (m, 0.5H), 5.13 (m, 0.5H), 3.90 (m, 1H), 1.48–3.47 (m, 18H), 1.29 (m, 1H), 0.98 (m, 1H), 0.85 (m, 1H). LCMS: 513.3, t_R = 5.05 min. (M+H$^+$), 100% purity; HRMS (FAB) m/z 513.2238 (M+H$^+$), calcd for $C_{28}H_{32}ClF_2N_4O$: 513.2227.

5.1.39. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[3-(1-pyrrolidinyl)propyl]urea (49). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.26–7.56 (m, 6H), 7.00 (t, J = 8.8 Hz, 1H), 3.88 (m, 1H), 3.33 (m, 2H), 2.54 (m, 6H), 2.31 (m, 2H), 1.60–2.13 (m, 10 H), 1.28 (m, 1H), 0.98 (dd, J = 9.9, 4.9 Hz, 1H), 0.86 (t, J = 5.4 Hz, 1H). LCMS: 495.1, t_R = 5.72 min. (M+H$^+$), 100% purity; HRMS (FAB) m/z 495.2331 (M+H$^+$), calcd for $C_{28}H_{33}ClFN_4O$: 495.2321.

5.1.40. *N*-[*trans*-6-(3-Cyanophenyl)bicyclo[4.1.0]hept-3-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[3-(4-methyl-1-piperazinyl)-propyl]urea (50). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.30–7.55 (m, 6H), 7.05 (t, J = 9.3 Hz, 1H), 3.90 (m, 1H), 3.30 (m, 2H), 1.56–2.60 (m, 21H), 1.29 (m, 1H), 0.98 (dd, J = 9.3, 4.4 Hz, 1H), 0.85 (t, J = 5.4 Hz, 1H). LCMS: 524.1, t_R = 5.56 min. (M+H$^+$), 99% purity; HRMS (FAB) m/z 524.2589 (M+H$^+$), calcd for $C_{29}H_{36}ClFN_5O$: 524.2587.

5.1.41. *N*-[6(*R*)-(3-Cyanophenyl)bicyclo[4.1.0]hept-3(*S*)-yl *N*′-(3-fluoro-4-trifluoromethyl-phenyl)-*N*-[2-[3(*S*)-hydroxyl-1-pyrrolidinyl]ethyl]urea (51). Compound (±)**25** was separated by a Chiralcel® OD column with hexane/isopropanol (8/2) as the solvent to two enantiomers: (+)**25**, 96.3% by Chiralcel® OD column, [α] +161.9 (*c* 1, MeOH) and (−)**25**, 97.5% by Chiralcel® OD column [α] −163.9 (*c* 1, MeOH). Using (−)**25** and the synthetic procedure for **35**, **51** was synthesized.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.76 (s, 1 H), 7.66–7.74 (m, 2H), 7.43–7.55 (m, 3H), 7.37 (t, J = 7.7 Hz, 1H), 7.0 (t, J = 9.3 Hz, 1H), 4.52 (m, 1H), 4.21 (m, 1H), 3.26 (m, 2H), 3.10 (m, 1H), 2.70–2.91 (m, 4H), 2.52 (m, 1H), 2.04-2.64 (m, 4H), 1.80–1.92 (m, 1H), 1.80-1.92 (m, 1H), 1.52–1.66 (m, 2H), 1.23–1.43 (m, 2H), 1.00 (dd, J = 9.3, 4.4 Hz, 1H), 0.76 (t, J = 5.5 Hz, 1H). HPLC (Chiralcel® AD column, Mobile phase: 77% hexane, 23% isopropanol, 1 ml/min.): t_R = 13.4 min. (M+H$^+$), >99% purity; [α] −35.2 (*c* 1, MeOH).

5.1.42. *N*-[6(*S*)-(3-Cyanophenyl)bicyclo[4.1.0]hept-3(*R*)-yl *N*′-(3-fluoro-4-trifluoromethyl-phenyl)-*N*-[2-[3(*S*)-hydroxyl-1- pyrrolidinyl]ethyl]urea (52). Obtained using (+)**25** according to the procedure for **35**.

HPLC (Chiralcel® AD column, Mobile phase: 92% hexane, 8% isopropanol, 1 ml/min), t_R = 15.5 min. (M+H$^+$), >99% purity; [α] +38.5 (*c* 1, MeOH).

5.1.43. *N*-[6(*R*)-(3-Cyanophenyl)bicyclo[4.1.0]hept-3(*S*)-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (53). Obtained using (−)**25** according to the procedure for **35**. ^{1}H NMR of **53** is the same as **35**. [α] −43.8 (*c* 1, MeOH).

5.1.44. *N*-[6(*S*)-(3-Cyanophenyl)bicyclo[4.1.0]hept-3(*R*)-yl]-*N*′-(3-chloro-4-fluorophenyl)-*N*-[2-[3(*R*)-hydroxy-1-pyrrolidinyl]ethyl]urea (54). Obtained using (+)**25** according to the procedure for **35**. ^{1}H NMR of **54** is the same as **35**. [α] 41.5 (*c* 1, MeOH).

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