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Bis(aminopyrrolidine)-derived ureas (APUs) as potent MCH_1 receptor antagonists

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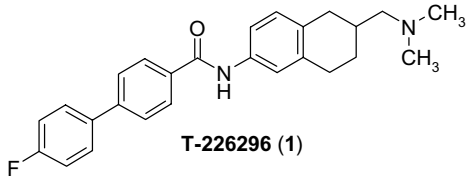
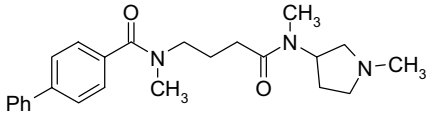
Abstract—Ureas derived from two substituted 3-aminopyrrolidine subunits were prepared as constrained analogs of a linear lead compound and tested as antagonists of the MCH_1 receptor. The series was optimized for substitution and stereochemistry to generate a functional antagonist with a K_i of 3.3 nM and IC_{50} of 12 nM (GTPγS).

In mammals, melanin-concentrating hormone (MCH) is believed to be a key neuropeptide responsible for balancing energy intake and expenditure.[1–4] This equilibrium is modulated by interaction of the hormone with one or more G-protein coupled receptors. In rodents, a single receptor (MCH_1) has been identified, and homozygous knockouts of this receptor have been generated.[5,6] These animals demonstrate a lean phenotype characterized by hyperphagia and increased energy expenditure. Acute and chronic infusion of MCH into the brains of wild type rats leads to increased feeding[7] and body weight,[8] respectively. Non-peptide MCH_1 receptor antagonists have demonstrated efficacy both in acute[9] and chronic feeding models.[10] In humans, at least two MCH receptors are present. Of the two, MCH_1 shares greater homology with the rodent receptors, and is more widely distributed in the human CNS.[11] This evidence is suggestive of a role for a selective MCH_1 antagonist in the treatment of human obesity, an epidemic of the developed world. There is also an



T-226296 (1)



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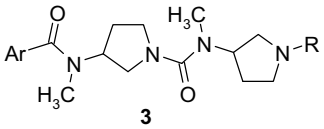

3

Keywords: Melanin-concentrating hormone; Obesity; Anxiety; Depression.
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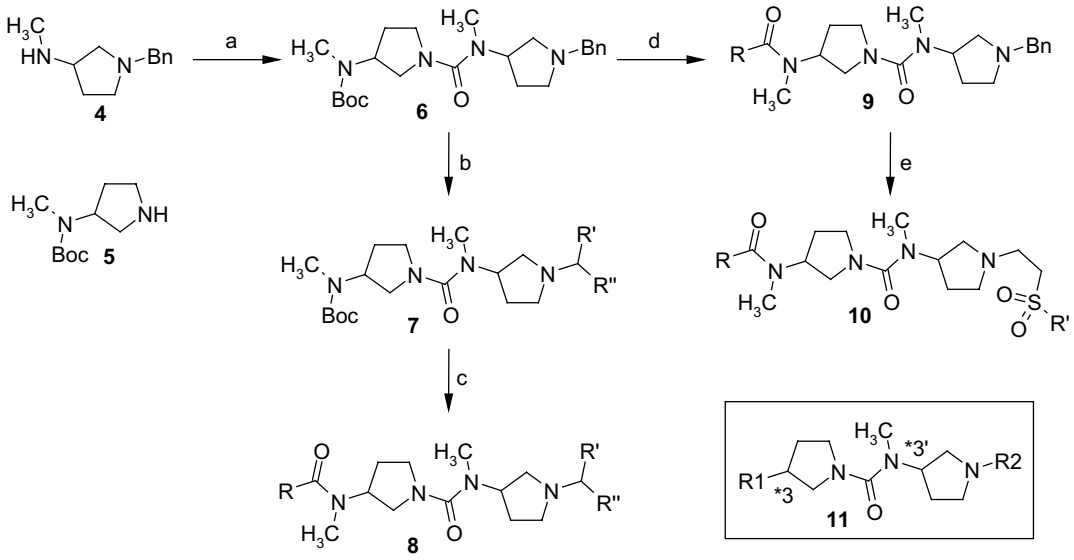


Scheme 1. Reagents and conditions: (a) (i) 4-nitrophenyl chlorocarbonate, THF; (ii) **5**, DMF, 100 °C (54–74%, two steps); (b) (i) ammonium formate, 10% Pd on carbon, ethanol, reflux; (ii) aldehyde or ketone, $NaBH_3CN$, methanol (21–86%, two steps); (c) (i) TFA, DCM; (ii) RCOCl, TEA, DCM or RCO_2H, HOBt, EDC, DCM (44–90%, two steps); (d) (i) TFA, DCM; (ii) RCOCl, TEA, DCM or RCO_2H, HOBt, EDC, DCM (90–100%, two steps); (e) (i) ammonium formate, 10% Pd on carbon, ethanol, reflux; (ii) vinyl sulfone or sulfonamide, ACN, 60 °C (12–27%, two steps).

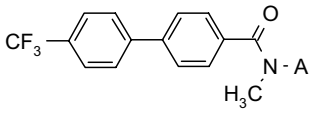
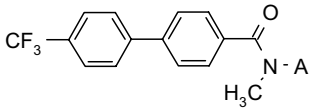
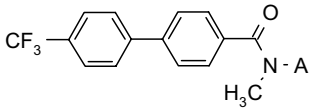
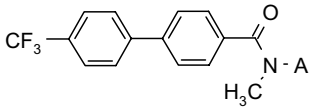
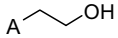
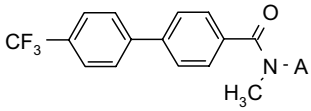
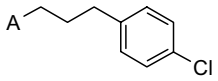
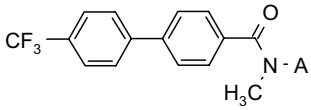
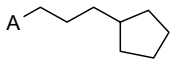
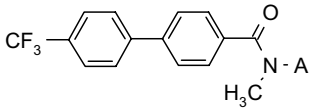
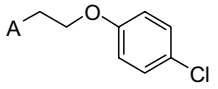
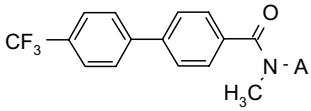
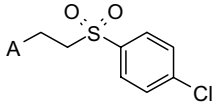
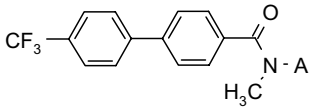
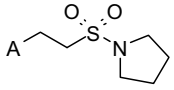
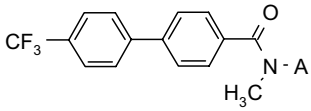
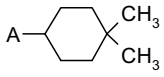
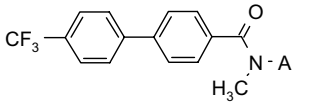
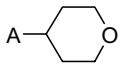
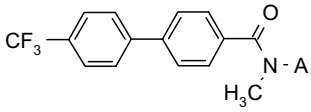
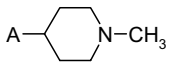
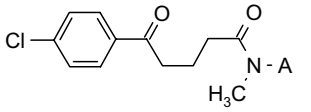
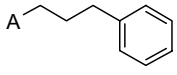
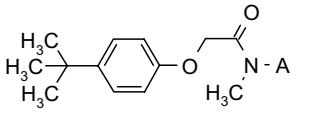
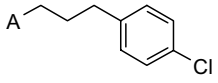
increasing body of evidence suggesting that an MCH_1 antagonist may have application in the treatment of anxiety and/or depression.[4,10]

Tetrahydronaphthalene-derived **T-226296** (**1**) is a potent MCH_1 receptor antagonist, which, when given orally, blocks the induced hyperphagia brought on by MCH injections into the lateral cerebral ventricle of rats.[9] During our investigation of the pharmacophore of MCH_1 antagonists related to **1**, we discovered a related series of compounds based on a γ-aminobutyramide (GABA) core. When the GABA scaffold is substituted with 3-aminopyrrolidine and biphenyl carboxamide groups, compounds with sub-micromolar binding affinities result (i.e., **2**).[12] Further optimization of the substitution on the pyrrolidine nitrogen atom produces compounds with binding constants below 10 nM. However, the flexible nature of the GABA molecules was a concern, both because the multitude of conformations available would likely cause selectivity issues, and also due to the negative impact of a large number of rotable bonds on pharmacokinetic parameters.[13] Therefore, in an attempt to develop a potent and selective MCH_1 antagonist, we sought to constrain the GABA-based lead compound **2** into a urea-linked compound containing two aminopyrrolidine units (i.e., **3**). Introduction of a second aminopyrrolidine unit offered additional opportunity to adjust the selectivity of the compounds, whilst relying on the same source of optically pure starting materials.

The synthesis of the bis(aminopyrrolidine)ureas (APUs) was performed as shown in Scheme 1. Benzyl-protected aminopyrrolidine **4** was converted to the *p*-nitrophenyl carbamate by treatment with the corresponding chloroformate. The carbamate was then heated with 3-(*N*-Boc-*N*-methylamino)pyrrolidine (**5**) to produce orthogonally protected **6**. Removal of the benzyl protecting group by transfer hydrogenation and reductive alkylation with a ketone or an aldehyde provided **7**. Removal of the Boc protecting group was effected by treatment with trifluoroacetic acid, and acylation of the resulting exocyclic amine group afforded the desired APU compounds **8**. Alternatively, for some examples it was preferable to remove the Boc protecting group and acylate to give compound **9**. At this stage, debenzylation and alkylation with various electrophiles, including α,β-unsaturated sulfones and sulfonamides, afforded compounds **10**.

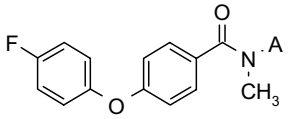
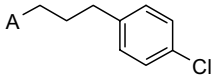
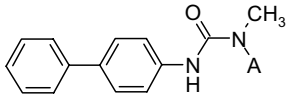
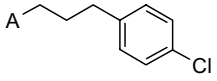
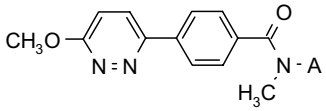
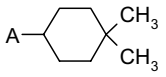
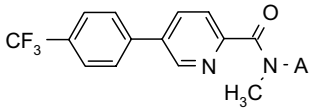
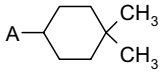
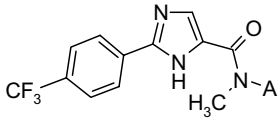
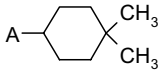
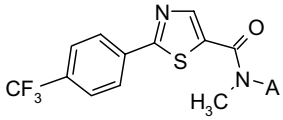
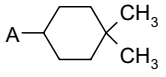
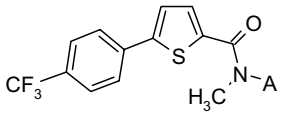
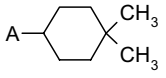
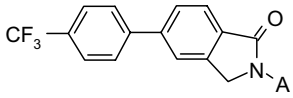
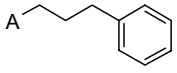
Preliminary experiments with the APU core indicated that the (3*S*,3′*R*)-stereochemistry was likely to produce the most potent examples (cf. annotation in **11**). When the (3*S*,3′*R*)-APU nucleus was substituted similarly to lead compound **2**, there was a modest increase in potency (**12**). This is consistent with previous observations that a restriction in the number of possible conformations of a ligand results in a concomitant entropic energy gain leading to an increase in binding potency.[14] In the GABA series, replacement of the *N*-methyl substituent of the pyrrolidine ring with more lipophilic groups enabled a 20-fold improvement in binding potency.[12] Hence, an attempt was made to impart a similar improvement in the affinity of the APU compounds by the analogous modifications. Conversion of the *N*-methyl group to hydrogen (**13**) or larger lipophilic (**14**) or hydrophilic (**15**) groups had little effect on binding potency. An exception was the introduction of lipophiles attached via a three-atom spacer, which inevitably led to potent compounds (**16** and **17**), one exhibiting a K_i of 7.3 nM. Attempts to modify the lipophile in order to lower the log *D* and attenuate the basicity of the pyrrolidine nitrogen atom, resulted in compounds that were 2- to 10-fold less potent than **16** (**18**–**20**). Dimethylcyclohexyl derivative **21** possesses lower affinity than **16**, but the compound was of interest due to the in-

Table 1. Binding affinities of **1**, **2**, and APU compounds **11** at the MCH_1 receptor[15]

Compd[a]	R1[b]	R2[b]	$K_i \pm SD$ (nM)[c]
1[d]	N.A.	N.A.	5.5
2[e]	N.A.	N.A.	142 ± 54
12		Me	57 ± 14
13		H	64 ± 62
14		*n*-Butyl	64 ± 38
15			96 ± 6
16			7.3 ± 2
17			20 ± 10
18			18 ± 9
19			14 ± 6
20			82 ± 6
21			31 ± 15
22			75 ± 23
23			83 ± 9
24			48 ± 11
25			67 ± 67

(*continued on next page*)

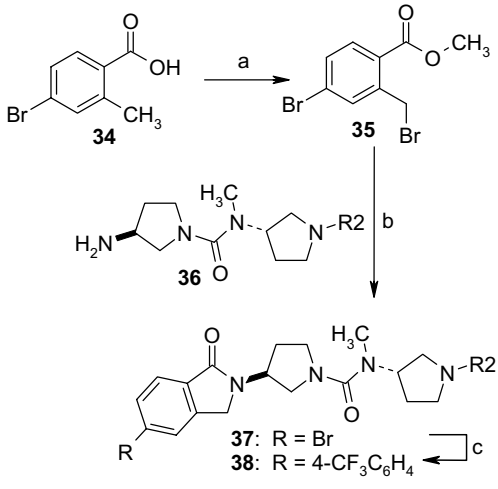
Table 1 (*continued*)

Compd[a]	R1[b]	R2[b]	$K_i \pm$ SD (nM)[c]
26			5.3 ± 3
27			22 ± 20
28			1043 ± 56
29			3.9 ± 1
30			1096 ± 584
31			456 ± 288
32			1.8 ± 0.2
33[f]			1019 ± 211

[a] (3*S*,3′*R*)-configuration unless otherwise specified.
[b] A: site of attachment to APU core.
[c] Values are averaged from at least two experiments.
[d] Ref. 9.
[e] Racemic.
[f] (3*S*,3′*S*)-configuration.

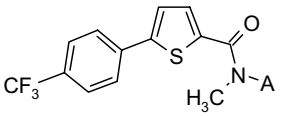
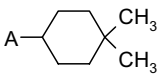
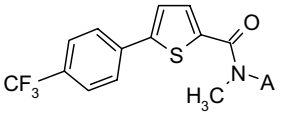
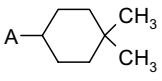
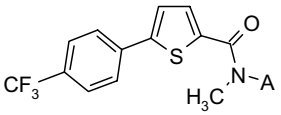
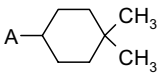
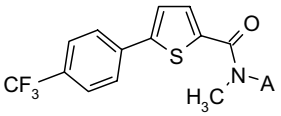
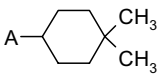
creased rigidity. More hydrophilic analogs of **21** showed a similar drop in potency (**22** and **23**), as was observed when similar changes were made to **16** (Table 1).

Considerable effort was also invested in modifying the biphenyl carboxamide group of the APU compounds. The replacement of the internal phenyl ring with other linkers led to less potent analogs (**24** and **25**). However, an ether linkage between the phenyl rings produced **26**, which was comparably potent to **16**. Introduction of a urea functional group to replace the carboxamide group led to a threefold drop in potency (**27**). Attempts to introduce nitrogen-containing heterocycles to replace either of the phenyl rings of the biphenyl moiety typically resulted in a substantial drop in potency (**28**, **30**, and **31**), although the pyridyl derivative **29** exhibited a K_i of 3.9 nM. The introduction of a thiophene replacement of the internal phenyl ring produced **32**, which is the most potent compound of the series with a K_i of 1.8 nM. Thiophene **32** was also shown to be a functional antagonist with an IC_{50} of 12 ± 8 nM ($n = 11$) in an MCH_1-derived GTPγS binding inhibition assay.[16] Preli-



Scheme 2. Reagents and conditions: (a) (i) trimethylsilyldiazomethane, DCM (100%); (ii) NBS, benzoyl peroxide, carbon tetrachloride, reflux (30%); (b) DIEA, methanol (45%); (c) 4-trifluoromethylbenzeneboronic acid, tetrakis(triphenylphosphine)palladium, 2 M sodium carbonate, toluene, ethanol, 100 °C, sealed tube (20%).

Table 2. Effect of stereochemistry of APU core on MCH_1 receptor binding[15]

Compd	R1[a]	R2[a]	Stereochemistry	$K_i \pm SD$ (nM)[b]
32			(3*S*,3′*R*)	1.8 ± 0.2
39			(3*R*,3′*R*)	338 ± 15
40			(3*S*,3′*S*)	27 ± 22
41			(3*R*,3′*S*)	1125 ± 784

[a] A: site of attachment to APU core.
[b] Values are averaged from at least two experiments.

minary screening showed this compound to have a K_i value for the human MCH_2 receptor greater than 10 μM.

Finally, in an attempt to remove the metabolically labile amide *N*-methyl group, a cyclized analog was prepared as shown in Scheme 2. Compound **36** was prepared in an analogous fashion to its methyl counterpart **7** of Scheme 1. This material was cyclized with the benzylic bromide **35** to afford **37**, which was subjected to Suzuki coupling conditions with 4-(trifluoromethyl)benzeneboronic acid to give **38**. Unfortunately, compounds of this class (i.e., **33**) were typically more than 100-fold less potent than their acyclic analogs.

In order to verify that the (3*S*,3′*R*)-stereochemistry was optimal for the current series of APU compounds, we synthesized the three stereoisomers of **32** using modifications of the chemistry described in Scheme 1. The binding affinities of these compounds are shown in Table 2. The (3*R*)-epimer **39** was 100-fold less potent than **32**, and the (3′*S*)-epimer **40** was 15-fold less potent. This confirms that the stereochemistry of the pyrrolidine ring residing closer to the carboxamide group is more critical for high affinity binding than is the analogous center on the right hand side of the molecule. Compound **41**, the enantiomer of **32**, is more than 600-fold less potent. This suggests that the decreased potency resulting from inverting the stereocenters of **32** is additive.

In this study, we discovered a new class of MCH_1 receptor ligands containing a urea moiety derived from two substituted 3-aminopyrrolidine subunits. With this new class of ligands, the MCH_1 receptor shows a strong stereochemical preference and an affinity for lipophilic substituents. Our attempts to circumvent the latter met with limited success; however, a potent, functional antagonist was discovered, which prompted its evaluation in vivo. Studies to determine the pharmacokinetics and activity of **32** and related compounds in animal models of obesity, anxiety, and depression will be reported in due course.

References and notes

1. Forray, C. *Curr. Opin. Pharmacol.* **2003**, *3*, 85.
2. Pissios, P.; Maratos-Flier, E. *Trends Endocrinol. Metabol.* **2003**, *14*, 243.
3. Collins, C. A.; Kym, P. R. *Curr. Opin. Invest. Drugs* **2003**, *4*, 386.
4. Hervieu, G. *Expert Opin. Ther. Targets* **2003**, *7*, 495.
5. Marsh, D. J.; Weingarth, D. T.; Novi, D. E.; Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Guan, X.-M.; Jiang, M. M.; Feng, Y.; Camacho, R. E.; Shen, Z.; Frazier, E. G.; Yu, H.; Metzger, J. M.; Kuca, S. J.; Shearman, L. P.; Gopal-Truter, S.; MacNeil, D. J.; Strack, A. M.; MacIntyre, D. E.; Van der Ploeg, L. H. T.; Qian, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3240.
6. Chen, Y.; Hu, C.; Hsu, C.-K.; Zhang, Q.; Bi, C.; Asnicar, M.; Hsiung, H. M.; Fox, N.; Slieker, L. J.; Yang, D. D.; Heinman, M. L.; Shi, Y. *Endocrinology* **2002**, *143*, 2469.
7. Qu, D.; Ludwig, D. S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M. A.; Cullen, M. J.; Mathes, W. F.; Przypek, J.; Kanarek, R.; Maratos-Flier, E. *Nature* **1996**, *380*, 243.
8. Della-Zuana, O.; Presse, F.; Ortola, C.; Duhault, J.; Nahon, J. L.; Levens, N. *Int. J. Obesity* **2002**, *26*, 1289.
9. Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; Kato, K.; Susuki, N.; Nishimura, O.; Fujino, M. *Eur. J. Pharmacol.* **2002**, *438*, 129.
10. Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nat. Med.* **2002**, *8*, 825.
11. Schlumberger, S. E.; Talke-Messerer, C.; Zumsteg, U.; Eberle, A. N. *J. Recept. Signal Transduc. Res.* **2002**, *22*, 509.

12. Details of the SAR of the GABA-based MCH_1 receptor antagonists will be reported elsewhere.
13. Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615.
14. Bohm, H.-J.; Klebe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2588.
15. Measuring displacement of [^{125}I]MCH from human MCH_1 receptor modified for optimal expression in HEK293 cells.
16. Measuring inhibition of MCH-stimulated G-protein/[^{35}S]GTPγS binding in CHO cells expressing human MCH_1 receptor.