Synthesis and Structure−Activity Relationships of Trisubstituted Phenyl Urea Derivatives as Neuropeptide Y5 Receptor Antagonists

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1-((1*R*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (**1**) was identified as a hit from the screening of the neuropeptide Y5 (NPY5) receptor. This lead was optimized for in vitro potency by changing the stereochemistry, the phenylethyl segment, the urea portion, and the 4-phenoxyphenyl group on the molecule. Over 40 analogues of **1** were prepared to study the structure−activity relationship for this series. The most potent compounds in this class have IC_{50}s less than 0.1 nM at the NPY5 receptor (e.g., **40f**, **44a**, and **47**). To determine the functional activity for this series of compounds, selected analogues were tested in a cellular assay measuring forskolin-induced cyclic AMP accumulation in 293 cells transfected with the human NPY5 receptor. All urea analogues tested in the functional assay acted as antagonists (e.g., **1**, **32**, **40a**, and **44e**).

Introduction

Neuropeptide Y receptors are a family of seven transmembrane G-protein coupled receptors that are expressed throughout the central and peripheral nervous systems.[1] They are implicated in several biological roles including vasoconstriction,[2] learning and memory,[3] and energy balance.[4] The endogenous peptide ligand for these receptors, neuropeptide Y (NPY), is a 36-amino acid C-amidated peptide and is known to interact with six pharmacologically distinct NPY receptor subtypes. NPY exerts a potent orexigenic affect when injected in the hypothalamus of rats.[5] The NPY5 receptor, located primarily in the hypothalamus, is believed to be one of the receptors that NPY interacts with to affect its feeding response.[6] Several scientific studies corroborate the role that NPY5 has on feeding;[7] however, the literature also shows that NPY1 may be involved in feeding behavior.[8] In this report, we focus on the preparation of non-peptide antagonists to the NPY5 receptor as part of our antiobesity program.

Three-dimensional computer modeling of the NPY5 receptor[9] has not provided the resolution necessary to guide de novo drug design. In light of this, we relied on the screening of our internal compound collection to provide us with leads for further optimization. One of the hits identified from the screening of the NPY5 receptor was the trisubstituted urea analogue **1** (Figure 1). Compound **1** provided us with a lead that differed significantly from the NPY5 antagonists reported in the literature (Chart 1).[10−15] In this report, we describe the synthesis and biological activity of analogues of **1** and describe our understanding of the structure−activity relationship for this series of compounds. In discussing the SAR around **1**, we have divided the lead into three segments: the phenylethyl region (segment A), the urea group (segment B), and the phenoxyphenyl portion (segment C) (Figure 1).

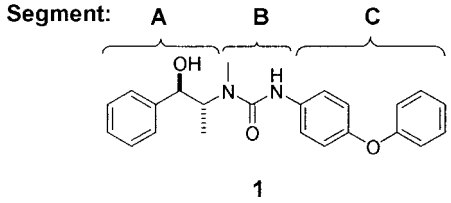

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Figure 1. Urea derivative identified from the screening of the NPY5 receptor (^{125}I-PYY binding to the human NPY5 receptor; SEM of two IC_{50}s determined over six dilutions).

Chemistry

Urea analogues **4** where segment A was modified were prepared by the addition of an amine **2** to 4-phenoxyphenyl isocyanate (**3**) (Scheme 1). When the required amines (**2**) were not commercially available, they were prepared by the methods illustrated in Table 1. A series of methylamines (**6**) (Table 1, eq 1) were prepared by reductive amination of ketones **5** with methylamine.[16] Alternatively, the desired methylamines **6** were prepared in three steps from primary amines **7** by using the method of Fukuyama.[17] Primary amines **7** were first converted to their corresponding 2-nitrobenezenesulfonamides, and these were subsequently alkylated with methyl iodide (Table 1, eq 2). The targeted methylamines **6** were isolated after the 2-nitrobenzenesulfonyl group was removed with thioacetic acid. Compound **9** (Table 1, eq 3) was prepared by reductive amination using acetaldehyde with (+)-norephedrine (**8**).[18]

To study the importance of the urea group (segment B), three analogues were prepared as alternatives to the central portion of the molecule: a cyanoguanidine, an amide, and a carbamate. Cyanoguanidine **15** was synthesized beginning with the addition of aniline **12** to diphenyl cyanocarbonimidate to give intermediate **13** (Scheme 2).[19] Amine **11**, prepared from the silyl protection of (+)-ephedrine (**10**), was added to intermediate

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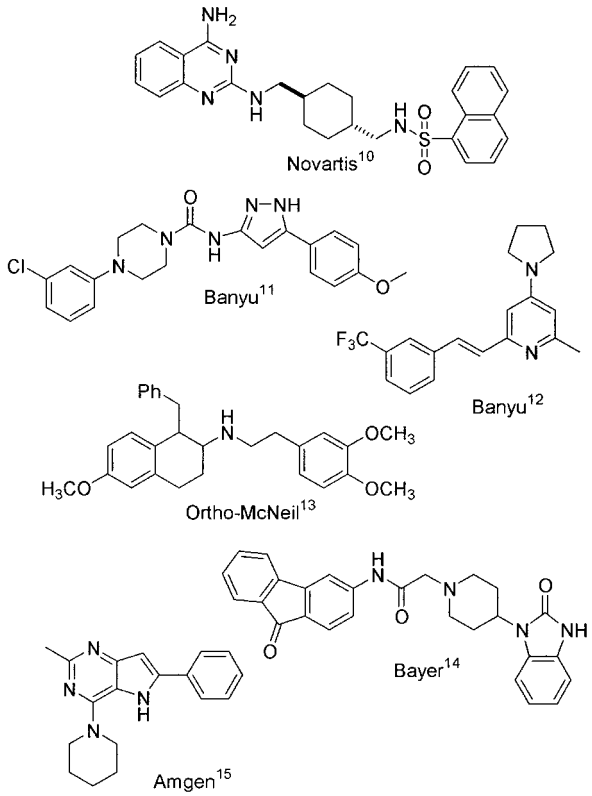
Chart 1. Examples of NPY5 Receptor Antagonists



Scheme 1. General Method for the Synthesis of Ureas: Modifications on Segment A

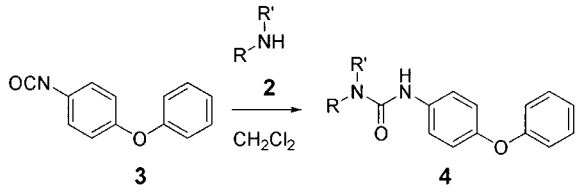
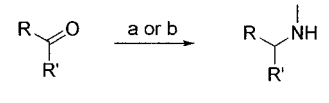
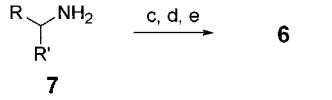
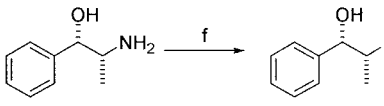


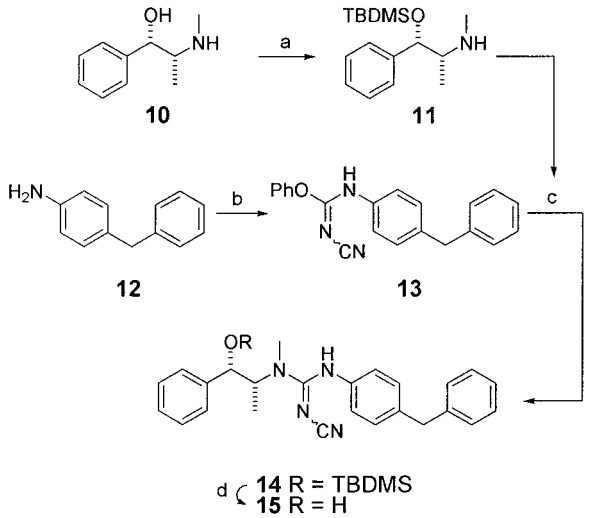
Table 1. Methods Used for Preparing Amines[a]

Reaction	Equation
	(1)
	(2)
	(3)

[a] Reagents: (a) Et_3N, CH_3NH_2·HCl, titanium(IV) isopropoxide, $NaBH_4$, ethanol, rt; (b) CH_3NH_2, $NaBH_4$, CH_3OH, H_2O, rt; (c) 2-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, rt; (d) CH_3I, K_2CO_3, DMF, rt; (e) mercaptoacetic acid, LiOH, DMF, rt; (f) acetaldehyde, BF_3·Et_2O, Na_2SO_4, ethanol, reflux, $NaBH_4$, rt.

13 to yield compound **14**. Deprotection of the silyl-protecting group on **14** provided the desired cyanoguanidine derivative **15**. Amide derivative **17** was prepared using a standard coupling procedure with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, acid **16**, and (+)-ephedrine (**10**) (Table 2, eq 1). Carbamate **19** was prepared from the chloroformate of **18** and (+)-ephedrine (**10**) (Table 2, eq 2).

Scheme 2. Synthesis of Cyanoguanidine Derivative[a]

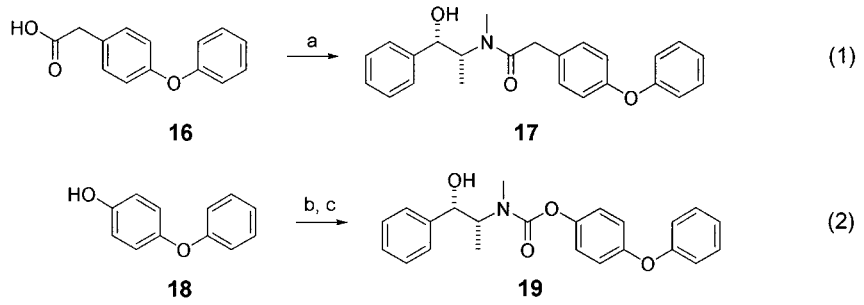


[a] Reagents: (a) *t*-Bu(Me)$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, rt; (b) diphenyl cyanocarbonimidate, CH_3CN, reflux; (c) **11**, 2-propanol, reflux; (d) TBAF, THF, 0 °C.

The majority of derivatives (**21**) modified at segment C were prepared by condensation of (+)-ephedrine (**10**) with a variety of isocyanates **20** (Table 3, eq 1). Ureas of general structure **23** were prepared by reacting (+)-ephedrine (**10**) with amines **22** that were activated with either triphosgene or phosgene (Table 3, eq 2). Anilines used in this study that were not commercially available were prepared by the methods outlined in Table 4. Substituted phenols **24** were treated with 1-fluoro-4-nitrobenzene to provide the corresponding nitroaryl intermediates, and these were reduced under catalytic hydrogenation conditions to give anilines **25** (Table 4, eq 1). Aniline **27** was prepared by adding 4-acetamidophenol (**26**) to 1-fluoro-3-nitrobenzene followed by removal of the acetyl group with concentrated hydrochloric acid (Table 4, eq 2). N-Alkylation of 4-nitrodiphenylamine **28** with ethyl iodide followed by reduction of the nitro group gave aniline **29** (Table 4, eq 3). Finally, benzylic amine **31** was prepared in two steps by adding phenol to 4-fluorobenzonitrile (**30**) followed by a reduction of the nitrile group with lithium aluminum hydride (Table 4, eq 4).[20]

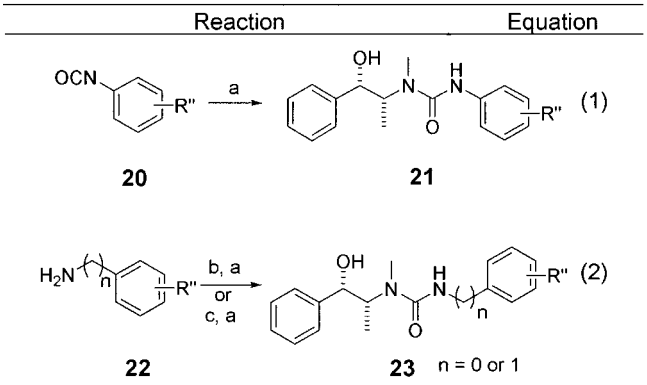
Other targeted urea analogues, **33**, **35**, and **39**, were prepared by modifying the compound after the urea bond had been assembled. Ketone **33** was synthesized through an oxidation of **32** with tetrapropylammonium perruthenate (Table 5, eq 1). The phenol analogue **35** was isolated after demethylation of the methoxy derivative **34** with boron tribromide (Table 5, eq 2). The *N*,*N*-dimethyl analogue **39** was prepared from (+)-norephedrine (**8**) in four steps (Table 5, eq 3). Treatment of (+)-norephedrine (**8**) with *tert*-butyldimethylsilyl chloride gave compound **36** which was subsequently reacted with 4-phenoxyphenylisocyanate to give urea **37**. Bisalkylation of **37** using methyl iodide and sodium hydride gave compound **38**. The silyl protecting group was removed with acetic acid to provide the desired dimethylated target **39**.

Table 2. Synthesis of Amide and Carbamate Derivatives[a]



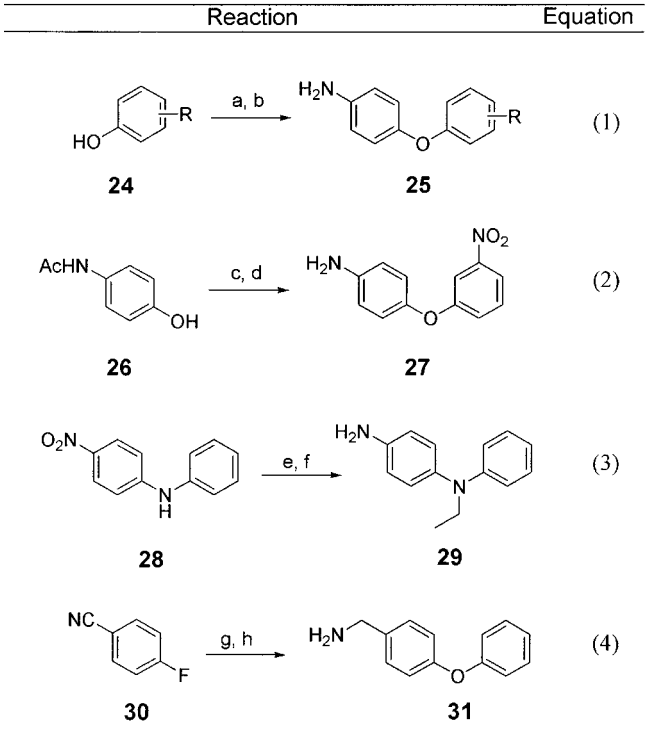
[a] Reagents: (a) **10**, EDC, CH_2Cl_2, rt; (b) triphosgene, *i*-Pr_2NEt, CH_2Cl_2, −23 °C to rt; (c) **10**, *i*-Pr_2NEt, CH_2Cl_2, rt.

Table 3. General Methods for the Synthesis of Ureas: Modifications on Segment C[a]



[a] Reagents: (a) **10**, CH_2Cl_2, rt; (b) triphosgene, *i*-Pr_2NEt, CH_2Cl_2, rt; (c) phosgene, 5% aq $NaHCO_3$, CH_2Cl_2, 0 °C.

Table 4. Methods Used for Preparing Anilines and Benzylamine **31**[a]



[a] Reagents: (a) 1-fluoro-4-nitrobenzene, K_2CO_3, DMF, 150 °C; (b) 20 psi H_2, 10% Pd−C, ethanol, rt; (c) 1-fluoro-3-nitrobenzene, K_2CO_3, DMF, 150 °C; (d) concentrated HCl, reflux; (e) ethyl iodide, tetrapropylammonium hydrogensulfate, benzene, 50% aq NaOH, rt; (f) H_2, 10% Pd−C, 10:1 ethanol−H_2O, rt; (g) phenol, DMF, K_2CO_3, DMF, 150 °C; (h) $LiAlH_4$, THF, rt.

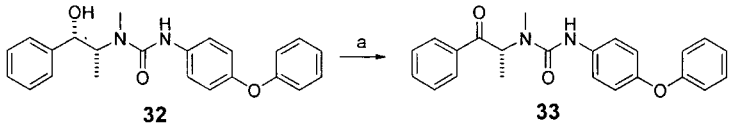
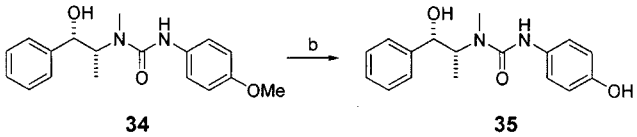
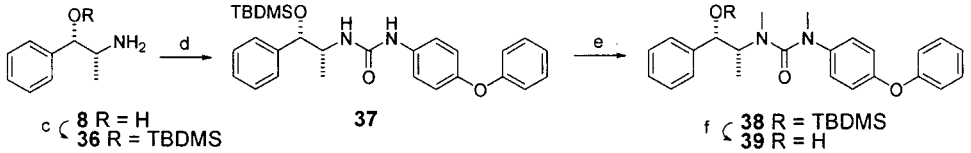
Results and Discussion

Structure−Activity Relationships (SAR). All analogues prepared were evaluated for binding affinity to the NPY5 receptor in a radioligand binding assay that employed ^{125}I-PYY as the ligand and membrane preparations of the human NPY5 receptor.[21] The IC_{50}s reported for these analogues are the standard errors of the mean (SEM) for two IC_{50} determinations that are measured over six different concentrations (10^{-5} M to 10^{-8} M) of the test compound.

We first examined analogues where segment A is modified (Table 6 and Figure 2). Looking at the other three diastereomers of the lead compound **1** we can see how the stereochemistry of this group influences activity. Compounds with R_3 groups in the (*R*) configuration are more potent than analogues with R_3 groups in the (*S*) configuration (cf. **1**, **32**, and **40c** with **40a**, **40b**, and **40o**). However, for the R_2 group, the (*S*)-hydroxyl is preferred when the R_3 group is (*R*)-methyl (cf. **32** to **1**), and the (*R*)-hydroxyl is preferred when the R_3 group is (*S*)-methyl (cf. **40a** and **40b**). These results suggest that the receptor favors an erythro configuration for these two chiral centers. When the R_3-methyl group is in the (*R*)-configuration, the R_2-hydroxyl group seems to be unnecessary (cf. **40c** to **32**). In the case where the R_3-methyl group is in the (*S*)-configuration, on the other hand, an R_2-hydroxyl group improves the potency (cf. **40a** and **40b** to **40o**). The R_3-methyl and the R_1-phenyl group also improve potency. When R_3 is a hydrogen rather than a methyl group (**40e**), or when R_1 is a methyl rather than a phenyl group (**40d**), the activity is ca. 10-fold lower than the corresponding analogue **40c**. Changing the R_2-hydroxyl group to a carbonyl is even more detrimental to activity since the ketone derivative **33** is more than 2 orders of magnitude less active than the parent compound **1**.

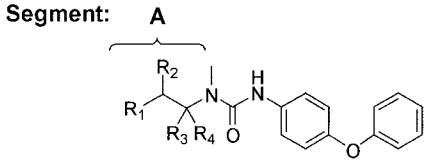
Racemic compounds **40f**−**n** were prepared to further study changes made to the R_3, R_4, and R_1 groups. For the R_3 group, the ethyl derivative **40f** has an IC_{50} less than 0.1 nM, but the added bulk of a phenyl group at this position (derivative **40g**) results in a slight loss in affinity (IC_{50} = 8 nM). More strikingly, the analogue where R_3 equals an *iso*-propyl group (**40h**) is more than 3000-fold less potent than the ethyl derivative **40f**. The compound where both the R_3 and R_4 groups are methyl (**40i**) is greater than 13 000-fold less potent than the ethyl derivative **40f**. Compounds with R_1-aryl rings having both electron donating and electron withdrawing

Table 5. Synthetic Modifications of Urea Analogues[a]

Reaction	Equation
	(1)
	(2)
	(3)

[a] Reagents: (a) 4-methylmorpholine *N*-oxide, 4 Å sieves, *n*-Pr_4NRuO_4, CH_2Cl_2, rt; (b) BBr_3, CH_2Cl_2, 0 °C; (c) *t*-Bu(Me)$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, rt; (d) 4-phenoxyphenyl isocyanate, CH_2Cl_2, rt; (e) NaH, CH_3I, DMF, 0 °C to rt; (f) 3:1:1 AcOH−THF−H_2O, 70 °C.

Table 6. In Vitro SAR: Variations on Segment A

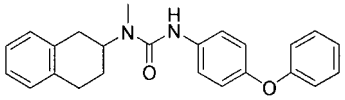


compd	R_1	R_2	R_3	R_4	hY5 receptor IC_{50} (nM)[a]
32	Ph	(*S*)OH	(*R*)CH_3	H	6.5 ± 3.5
1	Ph	(*R*)OH	(*R*)CH_3	H	45 ± 9.5
40a	Ph	(*R*)OH	(*S*)CH_3	H	127 ± 19
40b	Ph	(*S*)OH	(*S*)CH_3	H	507 ± 107
40c	Ph	H	(*R*)CH_3	H	3.1 ± 1
40o	Ph	H	(S)CH_3	H	5000 ± 1000
40d	H_3C	H	(*R*)CH_3	H	24 ± 8
40e	Ph	H	H	H	35 ± 15
33	Ph	=O	(*R*)CH_3	H	9500 ± 500
40f	Ph	H	CH_2CH_3	H	<0.1
40g	Ph	H	Ph	H	8 ± 0
40h	Ph	H	$CH(CH_3)_2$	H	380 ± 113
40i	Ph	H	CH_3	CH_3	1307 ± 165
40j	4-methoxyphenyl	H	CH_3	H	<0.1
40k	4-fluorophenyl	H	CH_3	H	<0.1
40l	4-chlorophenyl	H	CH_3	H	0.9 ± 0.1
40m	4-pyridyl	H	CH_3	H	0.5 ± 0.1
40n	cyclohexyl	H	CH_3	H	71 ± 17

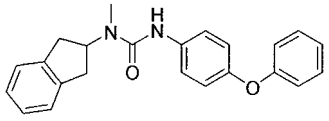
[a] ^{125}I-PYY binding to the human NPY5 receptor; SEM of two IC_{50}s determined over six dilutions.

groups (analogues **40j**, **40k**, and **40l**) have IC_{50}s less than 1 nM. Analogue **40m** has an R_1-pyridyl group, which has comparable activity to phenyl derivatives **40j**, **40k**, and **40l**. When the R_1 group is a cyclohexyl ring (**40n**), the potency decreases by more than 20-fold, indicating that the aromatic ring may be involved in a π-stacking interaction with the receptor. The conformationally constrained analogues (**41** and **42**) are less active than the more flexible analogue **40f**, demonstrating that segment A prefers a conformation different from those found in **41** and **42** (Figure 2).

Table 7 summarizes how changes in the urea group affect activity (segment B). Since compound **32** which contains the (+)-ephedrine group (segment A) was the most potent diastereomer of the initial lead **1**, (+)-



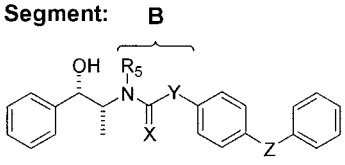
41
IC_{50} = 34 ± 3 nM



42
IC_{50} = 163 ± 33 nM

Figure 2. In vitro SAR: conformationally constrained variations on segment A (^{125}I-PYY binding to the human NPY5 receptor; SEM of two IC_{50}s determined over six dilutions).

Table 7. In Vitro SAR: Variations on Segment B

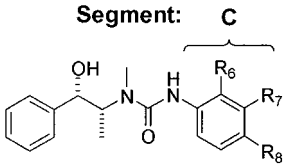


compd	R_5	X	Y	Z	hY5 receptor IC_{50} (nM)[a]
32	CH_3	O	NH	O	6.5 ± 3.5
43a	CH_2CH_3	O	NH	O	1230 ± 115
43b	H	O	NH	O	1650 ± 150
39	CH_3	O	NCH_3	O	>10000
43c	CH_3	S	NH	O	70 ± 10
15	CH_3	N-CN	NH	CH_2	282 ± 234
17	CH_3	O	CH_2	O	7500 ± 500
19	CH_3	O	O	O	9500 ± 500

[a] ^{125}I-PYY binding to the human NPY5 receptor; SEM of two IC_{50}s determined over six dilutions.

ephedrine analogues were prepared to study the SAR of segments B and C. Analogues that do not contain the group where $R_5 = CH_3$ have a lower affinity for the receptor. For example, analogue **43a**, where $R_5 = CH_2$-CH_3, and the derivative **43b**, where R_5 = H, are both ca. 200 times less potent than the parent **32**. The

Table 8. In Vitro SAR: Variations on Segment C



compd	R_6	R_7	R_8	hY5 receptor IC_{50} (nM)[a]
32	H	H	OPh	6.5 ± 3.5
44a	H	H	O(4-fluorophenyl)	<0.1
44b	H	H	O(3,4-dimethylphenyl)	<0.1
44c	H	H	O(3-nitrophenyl)	4 ± 2
44d	H	H	O(4-chlorophenyl)	5 ± 0
44e	H	H	OCH_2Ph	20 ± 2
34	H	H	OCH_3	2900 ± 100
35	H	H	OH	4500 ± 500
44f	H	H	H	>10000
44g	H	H	CH_2Ph	<0.1
44h	H	H	$N(CH_2CH_3)Ph$	<0.1
44i	H	OPh	H	9 ± 6
44j	OPh	H	H	>10000

[a] ^{125}I-PYY binding to the human NPY5 receptor; SEM of two IC_{50}s determined over six dilutions.

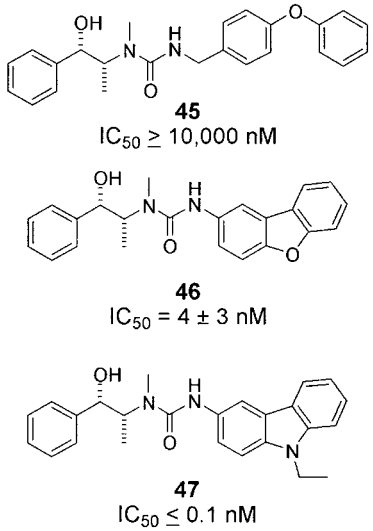


Figure 3. In vitro SAR: miscellaneous variations on segment C (^{125}I-PYY binding to the human NPY5 receptor; SEM of two IC_{50}s determined over six dilutions).

analogue where both nitrogens of the urea are substituted with a methyl group **39** ($R_5 = CH_3$, X = O, Y = NCH_3) has an even lower affinity for the receptor (IC_{50} greater than 10 000 nM). Derivatives that contain closely related functional groups in place of the urea (i.e., thiourea, cyanoguanidine, amide, and carbamate) are all less potent than the parent compound **32**. The thiourea analogue **43c** is ca. 10-fold less active, and the cyanoguanidine analogue **15** (Table 7) is greater than 1000 times less active than the corresponding urea analogue **44g** (Table 8). Amide **17** and carbamate **19** also have much lower affinity than the parent urea **32**. These results indicate that the receptor prefers the size of the R_5-methyl group, the hydrogen bond accepting property of the urea oxygen (X = O), and the hydrogen bond donating property of the 3-H (Y = NH) on the urea.

The SAR for segment C is summarized in Table 8 and Figure 3. Several derivatives were prepared where R_8 is a substituted aryloxy group. There are not clear SAR trends in this subset of compounds (**44a**−**d**). Analogue **44a**, where R_8 is the electron-poor 4-fluorophenoxy group, and analogue **44b**, where R_8 is the electron-rich 3,4-dimethylphenoxy group, are both greater than 60-fold more potent than the parent compound **32**. However, two other analogues where R_8 is an electron-poor aryloxy group, **44c** (R_8 = 3-nitrophenoxy) and **44d** (R_8 = 4-chlorophenoxy), are equipotent to the parent compound **32**. The analogue where R_8 is a benzyloxy group (**44e**) is ca. 3-fold less potent than parent urea **32**. Also, the compound where all of segment C is positioned one methylene group away from the urea (analogue **45**) has an IC_{50} of greater than 10 000 nM. When R_6 and R_7 are both H, the affinity is diminished in analogues where the R_8-aryloxy group is removed and replaced with smaller groups. The methoxy analogue **34**, the hydroxy analogue **35**, and the unsubstituted analogue **44f** all have IC_{50}s greater than 1000 nM. Adding lipophilicity by replacing the R_8 phenoxy group with a benzyl group (derivative **44g**) or an *N*-ethyl-*N*-phenylamino group (derivative **44h**) increases the potency by greater than 10-fold. The analogue where the phenoxy group is moved from the para to meta position (**44i**, R_7 = OPh) is as potent as the parent compound **32**. However, the analogue where the phenoxy is moved to the ortho position (**44j**, R_6 = OPh) has an IC_{50} greater than 10 000 nM, indicating either that the phenyl group is less proximal to the binding site or that the large group perturbs the conformation of the adjacent urea in a way that is unfavorable for binding. Conformationally constrained analogues **46** and **47** are equipotent to their nonconstrained counterparts (**32** and **44h**, respectively), suggesting that the receptor accepts a planar conformation for segment C.

Table 9. Receptor Selectivity Data and Functional Activity

compd	hY5 receptor IC_{50} (nM)[a]	hY1 receptor IC_{50} (nM)[a]	hY2 receptor IC_{50} (nM)[a]	hY5 functional K_i (nM)[b]
1	45 ± 9.5	>10000	2682 ± 900	477
32	6.5 ± 3.5	>10000	ND	24
40a	127 ± 19	ND	ND	515
40c	3.1 ± 1	>10000	>10,000	ND
40f	<0.1	>10000	>10,000	ND
40g	8 ± 0	>10000	>10,000	ND
40j	<0.1	>10000	>10,000	ND
40k	<0.1	>10000	>10,000	ND
40l	0.9 ± 0.1	>10000	>10,000	ND
44a	<0.1	>10000	>10,000	ND
44b	<0.1	>10000	>10,000	ND
44c	4 ± 2	>10000	>10,000	ND
44d	5 ± 0	>10000	>10,000	ND
44e	20 ± 2	>10000	>10,000	101
44h	<0.1	>10000	>10,000	ND
44i	9 ± 6	>10000	>10,000	ND
46	4 ± 3	>10000	>10,000	ND
47	<0.1	>10000	1101 ± 92	ND

[a] ^{125}I-PYY binding to the human NPY(1, 2, or 5) receptor; SEM of two IC_{50}s determined over six dilutions. [b] Reversal of NPY inhibition of forskolin stimulated cAMP production; single determinant K_i ascertained over six dilutions.

Screening at Receptor Subtypes and Functional Activity. Several or the most potent compounds were screened against the NPY receptor subtypes NPY1r and NPY2r. In all cases, the compounds are very selective for NPY5 receptor binding (see Table 9).

To determine the functional activity at the NPY5 receptor of some of the urea analogues, we used a forskolin induced cyclic AMP accumulation assay in 293 cells that were transfected with the human NPY5

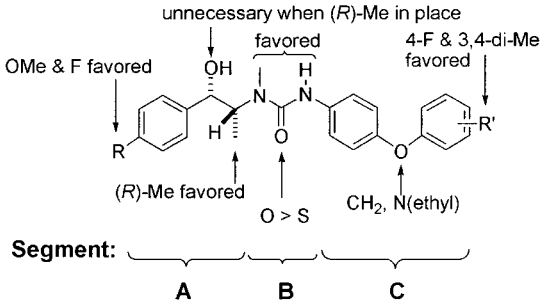


Figure 4. Summary of urea SAR.

receptor (see Experimental Section for details). Neuropeptide Y reverses the effects of forskolin, and as a result, the intracellular concentration of cAMP is lowered. Compounds **32**, **44e**, **1**, and **40a** showed a dose-dependent decrease in the percentage of NPY response (K_is = 24, 101, 477, and 515 nM, respectively, see Table 9) in this assay, indicating that they are acting as functional antagonists at the NPY5 receptor. The order of potency, **32** > **44e** > **1** > **40a**, is the same trend found in the binding affinity data.[22]

Conclusions

From our analysis of the urea lead **1**, we can conclude the following about the structure−activity relationship for this series of compounds (Figure 4). On segment A, an aryl substituent is necessary for high affinity binding to the receptor. The hydroxyl group is unnecessary, at least when the more favored (*R*)-methyl group is in place. The portion of the compound least tolerant to change is segment B. Any alterations to this core are detrimental to activity. Segment C prefers a phenyl-[O, CH_2, or NCH_2CH_3]-phenyl system directly attached to the urea group, and substitution on the distal aryl ring is tolerated. Our understanding of this series of compounds has led to the identification of several highly potent analogues with IC_{50}s less than 0.1 nM. These compounds should prove useful for further pharmacological characterization of the NPY5 receptor.

Experimental Section

General. All commercially available chemicals were reagent grade, and were used without further purification unless otherwise specified. ^{1}H NMR spectra were obtained on a Bruker DRX-500 (500 MHz) or a Bruker DRX-400 NMR (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. High resolution mass spectra (HRMS) were performed by Mass Consortium, La Jolla, CA. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a Buchi 535 capillary melting point apparatus and are uncorrected.

1-((1*R*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxy-phenyl)urea (1). To a 250 mL round-bottomed flask equipped with a magnetic stirring bar were added a solution of (−)-pseudoephedrine (7.9 g, 48 mmol) in CH_2Cl_2 (96 mL). Through a pipet was then added 4-phenoxyphenyl isocyanate (5 g, 24 mmol), and the reaction mixture was stirred for 18 h at room temperature. The contents of the reaction flask were then washed with 10% aqueous HCl (3 × 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Drying in the vacuum oven for 24 h at 60 °C afforded a white amorphous solid (6.8 g, 18 mmol, 75%).[23] ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.09 (d, 3H, J = 11 Hz), 2.90 (s, 3H), 3.7 (br s, 1H), 4.3 (quin, 1H, J = 7 Hz), 4.62 (dd, 1H, J = 5, 8 Hz), 6.76 (br s, 1H), 6.98 (d, 4H, J = 8 Hz), 7.07 (t, 1H, J = 7 Hz), 7.30−7.33 (m, 4H), 7.36−7.41(m, 5H). MS (ESI, pos. ion) *m*/*z*: 377 (M + 1); (ESI, neg. ion) 375 (M − 1). Anal. ($C_{23}H_{24}N_2O_3$·0.2H_2O) C, H, N.

(1*S*,2*R*)-2-(Ethylamino)-1-phenylpropan-1-ol (9). To a 50 mL round-bottomed flask equipped with a magnetic stirring bar were added (+)-norephedrine (3.0 g, 20 mmol) and acetaldehyde (1.7 mL, 30 mmol), followed by EtOH (20 mL). To the above solution were then added BF_3·Et_2O (10 drops) and Na_2SO_4 (0.5 g). The reaction mixture was heated at reflux for 15 h under N_2. After cooling to room temperature, the solid was filtered off and washed with EtOH (5 mL). To the filtrate cooled in an ice bath was then added $NaBH_4$ (1.3 g, 35 mmol) in one portion. The reaction was stirred at room temperature for 3 h, and then 10% HCl was added to adjust the pH to pH 2. The solvent was evaporated in vacuo, H_2O (100 mL) was added, and the residue was washed with Et_2O. After the aqueous layer was basified with 2 N NaOH to pH 9, a precipitate formed that was collected by filtration, washed with H_2O, and dried in a vacuum oven overnight. A light-yellow oil was obtained (1.8 g, crude) and used directly without further purification in the synthesis of **43a**. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.81 (d, 3H, J = 6.5 Hz), 1.11 (t, 3H, J = 7.1 Hz), 2.96−3.02 (m, 2H), 3.03−3.09 (m, 1H), 4.74 (d, 1H, J = 3.9 Hz), 7.32−7.34 (m, 5H). MS (ESI, pos. ion) *m*/*z*: 180 (M + 1).

Preparation of Cyanoguanidine Analogue (15). ((1*R*,2*S*)-2-((1,1-Dimethylethyl)dimethylsilyloxy)-1-methyl-2-phenylethyl)methylamine (11). To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added (+)-ephedrine hemihydrate (2.1 g, 13 mmol) (dissolved in benzene, placed over granular K_2CO_3 overnight, filtered and concentrated) and 40 mL of CH_2Cl_2. To the above solution were then added Et_3N (2.2 mL, 16 mmol), *tert*-butyldimethylsilyl chloride (2.3 g, 15 mmol), and 4-(dimethylamino)pyridine (77 mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 15 h. It was diluted with H_2O (50 mL) and separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 layers were dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (100:2.5 $CHCl_3$−MeOH) to give 2.6 g (9.3 mmol, 72%) of compound **11** as a colorless oil. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.20 (s, 3H), 0.24 (s, 3H), 1.09 (s, 9H), 1.21 (d, 3H, J = 6.4 Hz), 2.58 (s, 3H), 2.74−2.88 (m, 1H), 4.80 (d, 1H, J = 5 Hz), 7.47 (m, 5H). MS (ESI, pos. ion) *m*/*z*: 280 (M + 1).

***N*′-(Benzylphenyl)-*N*-cyanocabamimidic Acid Phenyl Ester (13).** To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added diphenyl cyanocarbonimidate (4.8 g, 20 mmol) and 4-aminodiphenylmethane (3.7 g, 20 mmol), followed by CH_3CN (40 mL). The reaction mixture was heated at reflux for 3 h. After cooling to room temperature, the precipitate formed was collected by filtration, washed with cold CH_3CN, and dried in a vacuum oven overnight to give 3.9 g (12 mmol, 60%) of the title compound as a light-yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.98 (s, 2H), 7.12−7.42 (m, 14H). MS (ESI, pos. ion) *m*/*z*: 328 (M + 1).

2-(4-Benzylphenyl)-3-cyano-1-((1*R*,2*S*)-2-((1,1-dimethylethyl)dimethylsilyloxy)-1-methyl-2-phenylethyl)-1-methylguanidine (14). To a 50 mL round-bottomed flask equipped with a magnetic stirring bar were added **13** (1.6 g, 5 mmol) and **11** (2.1 g, 7.5 mmol), followed by 2-propanol (15 mL). The reaction mixture was heated at reflux for 2 h under N_2. After cooling to room temperature, 10% HCl (50 mL) was added, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with 10% HCl, 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 2:1 EtOAc−hexanes as eluant to give a yellow residue. This material was obtained and used directly in the following step without purification. ^{1}H NMR ($CDCl_3$; 400 MHz): δ −0.01 (s, 3H), 0.18 (s, 3H), 0.94 (s, 9H), 1.36 (d, 3H, J = 6.8 Hz), 2.56 (s, 3H), 3.24−3.28 (m, 1H), 3.92 (s, 2H), 5.25 (d, 1H, J = 3.8 Hz), 6.84−7.42 (m, 14H). MS (ESI, pos. ion) *m*/*z*: 513 (M + 1).

2-(4-Benzylphenyl)-3-cyano-1-((1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl)-1-methylguanidine (15). To a 150 mL round-bottomed flask equipped with a magnetic stirring bar were added crude **14** and 80 mL of THF. The solution was cooled in an ice-bath, and Bu_4NF (1 M in THF, 10 mL, 10 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. The solvent was concentrated in vacuo, and the residue was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 layer was separated, dried over Na_2SO_4, and concentrated in vacuo to give a light-yellow foam. It was purified by flash chromatography on silica gel with 1:1 EtOAc−hexanes as eluant to give 49 mg (0.12 mmol, 2% based on **13**) of compound **15** as a colorless oil. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.30 (d, 3H, J = 7 Hz), 2.50 (s, 3H), 3.00 (br s, 1H), 3.93 (s, 2H), 4.34−4.43 (m, 1H), 4.85 (d, 1H, J = 4 Hz), 6.71−6.73 (m, 2H), 7.06−7.08 (m, 2H), 7.15−7.42 (m, 10H), 7.65 (br s, 1H). MS (ESI, pos. ion) m/z: 400 (M + 1); (ESI, neg. ion) 398 (M − 1); HRMS (MH^+): theoretical 399.2179; measured 399.2198.

***N*-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2-(4-phenoxyphenyl)ethanamide (17).** To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added a solution of (+)-ephedrine hemihydrate (1 g, 6 mmol) and 4-phenoxyphenylacetic acid (1.4 g, 6 mmol) in CH_2Cl_2 (30 mL). 1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (1.2 g, 6 mmol) was added, and the reaction mixture was stirred for 24 h at room temperature. CH_2Cl_2 (50 mL) was then added, and the organic layer was washed with 10% HCl (3 × 20 mL) and 5% $NaHCO_3$ (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (2:1 hexanes−EtOAc then 1:1 hexanes−EtOAc) provided the title compound as a white amorphous solid in a 58% yield (1.3 g, 3.5 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz) (chemical shifts of the minor rotamer are shown parenthetically): δ 1.23 (1.26) (d, 3H, J = 7.1 Hz), 2.72 (2.87) (s, 3H), 3.62, 3.64 (3.21, 3.35) (ABq, 2H, J = 15 Hz), 3.80 (d, 1H, J = 2.4 Hz), 4.03 (4.56) (quin, 1H, J = 6.9 Hz (dq, J = 4.2, 6.9 Hz)), 4.86 (4.66) (dd, 1H, J = 3.5, 3.6 Hz (dd, 1H, J = 2.7, 7.5 Hz)), 6.90−7.34(m, 14 H). MS (ESI, pos. ion) m/z: 376 (M + 1); (ESI, neg. ion) 374 (M − 1). Anal. ($C_{24}H_{25}NO_3$) C, H, N.

***N*-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-*O*-(4-phenoxyphenoxy)carbamate (19).** 4-Phenoxyphenol (1.0 g, 5.4 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to −23 °C in a dry ice−nitromethane bath. Triphosgene (0.74 g, 2.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 5 min to the heterogeneous mixture. *N*,*N*-Diisopropyethylamine (0.96 mL, 5.4 mmol) was added dropwise, and the reaction was stirred for 5 min at −23 °C. The reaction flask was then placed in an ice bath and stirred at 0 °C for 4 h and allowed to slowly warm to room temperature as the ice bath melted. After 16 h at room temperature, the reaction mixture was heated to reflux for 1.5 h, cooled to room temperature, and concentrated in vacuo. The resultant off-white solid was treated with dry THF, and the solids were removed by filtration. The filtrate was concentrated in vacuo to give a yellow oil (1.1 g) that was carried on without purification. This residue was stirred with (+)-ephedrine hemihydrate (2.0 g, 11.5 mmol) and *N*,*N*-diisopropylethylamine (0.8 mL, 4.5 mmol) in anhydrous CH_2Cl_2 (30 mL) for 18 h. The solids formed were then removed by filtration, and the filtrate was washed with 10% citric acid (2×). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a cloudy oil. Purification by column chromatography (1:3 EtOAc−hexanes) gave the title compound, 0.78 g (2.1 mmol, 39%) as a clear oil. ^{1}H NMR (DMSO-d_6; 500 MHz) (chemical shifts of the minor rotamer are shown parenthetically): δ 1.34 (1.42) (d, 3, J = 6.7), 2.97 (3.40) (s, 3), 4.23 (4.37) (quin, 1, J = 6.9), 4.74 (t, 1, J = 7.5), 5.61 (5.67) (d, 1, J = 4.9), 6.80 (d, 1, J = 8.6), 6.99 (d, 1, J = 8.7), 7.04−7.10 (m, 4), 7.24 (t, 1, J = 7.3), 7.37 (m, 1), 7.42−7.51 (m, 6)). MS m/z: 378 (M + 1). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

4-(3-Nitrophenoxy)phenylamine Hydrochloride (27). To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added 4-acetamidophenol (3.3 g, 22 mmol), 1-fluoro-3-nitrobenzene (2.8 g, 20 mmol), K_2CO_3 (3.0 g, 22 mmol), and DMF (40 mL). The reaction mixture was heated at 150 °C for 15 h under N_2. After cooling to room temperature, the reaction mixture was poured into 500 mL of ice-cold water and stirred for 0.5 h. The precipitate formed was collected by filtration, washed with water, and dried in a vacuum oven overnight to yield *N*-(4-(3-nitrophenoxy)phenyl)acetamide (4.8 g, 18 mmol, 82%) as a yellow solid. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 2.21 (s, 3), 7.03−7.06 (m, 2H), 7.22−7.56 (m, 4H), 7.75−7.77 (m, 1H), 7.91−7.93 (m, 1H). MS (ESI, pos. ion) m/z: 273 (M + 1); (ESI, neg. ion) 271 (M − 1). A portion of this sample (2.4 g, 8.8 mmol) was heated to 95 °C in 10 mL of 12 M HCl for 16 h. After the reaction mixture cooled to room temperature, the brown precipitate was collected by filtration and washed with both acetone and Et_2O to give the title compound (2.5 g crude yield). ^{1}H NMR (DMSO-d_6; 400 MHz): δ 7.24−7.27 (m, 2H), 7.40−7.43 (m, 2H), 7.51−7.54 (m, 1H), 7.69−7.73 (m, 2H), 8.01−8.03 (m, 1H). MS (ESI, pos. ion) m/z: 231 (M + 1).

(4-Aminophenyl)ethylphenylamine (29). To a 250 mL round-bottomed flask equipped with magnetic stirring bar were added a solution of 4-nitrodiphenylamine (20 g, 9.3 mmol) and ethyl iodide (1.9 g, 12 mmol) in benzene (50 mL). A 50% aqueous solution of NaOH (10 mL) was then added followed by the addition of tetrapropylammonium hydrogen sulfate (0.34 g, 1.2 mmol). After 17 h of stirring at room temperature, H_2O (150 mL) was added, and the mixture was extracted with EtOAc (120 mL). The organic layer was washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography ($CHCl_3$) provided ethyl(4-nitrophenyl)phenylamine (2.1 g, 8.7 mmol, 94%). ^{1}H NMR (DMSO-d_6; 500 MHz): δ 1.18 (t, 3H, J = 7 Hz), 3.84 (q, 2H, J = 7 Hz), 6.70 (d, 2H, J = 10 Hz), 7.30 (d, 2H, J = 8 Hz), 7.38 (t, 1H, J = 7 Hz), 7.53 (d, 2H, J = 7 Hz), 8.03 (d, 2H, J = 9 Hz). To a portion of this sample (0.35 g, 1.4 mmol) in 10:1 EtOH−H_2O (22 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirring bar and a three-way valve were added 10% palladium on carbon (180 mg, 0.17 mmol). The solution was placed under a vacuum through one part of the three-way valve and then filled with H_2. This process was repeated three times. Finally, a balloon of H_2 (ca. 500 mL) was placed on top of the flask, and the reaction mixture was stirred for 1.25 h. After the solution was filtered through Celite, the filtrate was concentrated in vacuo. Chloroform was added to dissolve the residue, and the solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide a gray oil (270 mg, 1.3 mmol, 93%) that was used without further purification for the synthesis of **44h**. ^{1}H NMR (DMSO-d_6; 500 MHz): δ 1.08 (t, 3H, J = 7 Hz), 3.56 (q, 2H, J = 7 Hz), 6.54−6.62 (m, 5H), 6.81 (m, 2H), 7.06 (t, 2H, J = 8 Hz).

4-Phenoxybenzylamine (31). To a 50 mL round-bottomed flask equipped with a magnetic stirring bar were added 4-fluorobenzonitrile (2.4 g, 20 mmol), phenol (2.1 g, 22 mmol), and DMF (20 mL). K_2CO_3 (3.0 g, 22 mmol) was then added to the above solution. The reaction mixture was heated at 150 °C under N_2 for 15 h. After cooling to room temperature, the reaction mixture was poured into 250 mL of ice-cold water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 3.7 g (19 mmol, 87%) of 4-phenoxybenzonitrile. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 7.01 (d, 2H, J = 8 Hz), 7.07 (d, 2H, J = 8 Hz), 7.22−7.26 (m, 1H), 7.4−7.45 (m, 2H), 7.59−7.62 (m, 2H). MS (ESI, pos. ion) m/z: 196 (M + 1). To a suspension of $LiAlH_4$ (1.25 g, 33 mmol) in anhydrous THF (60 mL) was added a solution of 4-phenoxybenzonitrile (3.7 g, 19 mmol) in 45 mL of THF at 0 °C. The reaction was then stirred at 0 °C for 1 h and then at room temperature for 5 h. NaF (0.17 g, 88 mmol) and water (2 mL) were then added, and the reaction was stirred for 45 min. After removing the insoluble material by filtration, the filtrate was concentrated in vacuo to give a white residue. Flash chromatography (100:2.5 CH_2Cl_2−MeOH) provided 4-phenoxybenzylamine (**31**) in 45% yield (1.7 g, 8.5 mmol) as a light-yellow oil. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 3.86 (s, 2H), 6.98−7.01 (m, 4H), 7.08−7.11 (m, 1H), 7.28−7.35 (m, 4H). MS (ESI, pos. ion) m/z: 200 (M + 1).

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (32). Following the procedure described for the synthesis of **1**, compound **32** was prepared from (+)-ephedrine hemihydrate (2.4 g, 14 mmol) and 4-phenoxyphenyl isocyanate (1 g, 4.7 mmol) in CH_2Cl_2 (28 mL) to afford a white amorphous solid (1.6 g, 4.3 mmol, 91%).[23] ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.26 (d, 3H, J = 7 Hz), 2.59 (s, 3 H), 3.64 (br s, 1H), 4.38 (dq, 1H, J = 3.1, 7 Hz), 4.87 (t, 1H, J = 3 Hz), 6.90 (br s, 1H), 6.98−6.96 (m, 3 H), 7.06 (t, 1H, J = 7 Hz), 7.29−7.41 (m, 10H). MS *m*/*z*: 377 (M + 1). Anal. ($C_{23}H_{24}N_2O_3 \cdot 0.2H_2O$) C, H, N.

1-((1*R*)-1-Methyl-2-oxo-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (33). To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added **32** (0.38 g, 1 mmol) in CH_2Cl_2 (2 mL), *N*-methylmorpholine-*N*-oxide (0.18 g, 1.5 mmol), and finely powdered 4 Å molecular sieves (0.5 g). Tetrapropylammonium perruthenate (0.017 g, 5 mol %) was added, and the mixture was stirred for 1 h at room temperature. The mixture was filtered through a 1 in. bed of silica using EtOAc as an eluant. The filtrate was treated with activated charcoal, filtered, and concentrated in vacuo to give a purple solid. Purification by flash chromatography (1:2 EtOAc−hexanes) gave the title compound as a white solid, 0.10 g (0.27 mmol, 27%). ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.11 (d, 3, J = 6.5), 2.79 (s, 3), 3.50 (q, 1, J = 6.5), 6.79 (d, 2, J = 6.9), 6.86 (s, 1), 6.87 (d, 2, J = 7.7), 7.09 (t, 1, J = 7.3), 7.21−7.36 (m, 7), 7.50 (d, 2, J = 7.2). MS *m*/*z*: 375 (M + 1). Anal. ($C_{23}H_{22}N_2O_3$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-methoxyphenyl)-1-methylurea (34). Following the procedure described for the synthesis of **1**, compound **34** was prepared from (+)-ephedrine hemihydrate (1 g, 6 mmol) and 4-methoxyphenyl isocyanate (0.26 mL, 2 mmol) in CH_2Cl_2 (12 mL). A white amorphous solid was isolated in 90% yield (580 mg, 1.8 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.26 (d, 3H, J = 7.1 Hz), 2.59 (s, 3H), 3.79 (s, 3H), 3.89 (br s, 1H), 4.39 (dq, 1H, J = 2.9, 7.1 Hz), 4.88 (dd, 1H, J = 3.0, 3.0 Hz), 6.60 (br s, 1H), 6.85 (d, 2H, J = 12 Hz), 7.21−7.41 (m, 7H). MS (ESI, pos. ion) *m*/*z*: 315 (M + 1); (ESI, neg. ion) 313 (M − 1). Anal. ($C_{18}H_{22}N_2O_3 \cdot 0.25H_2O$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-2-(4-hydroxyphenyl)-1-methylurea (35). Compound **34** (0.40 g, 1.3 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 °C in an ice bath. Boron tribromide (1.5 mL, 1.0 M in CH_2Cl_2, 1.5 mmol) was added dropwise, and the reaction was allowed to warm slowly to room temperature as the ice bath melted. After 48 h, the reaction was poured over ice (30 g). The aqueous mixture, which contained some solid precipitate, was neutralized with aqueous concentrated ammonia (10 mL). The layers were separated, and the aqueous layer was extracted with 3:1 chloroform−2-propanol (3 × 20 mL). The organic fractions were combined, dried over $MgSO_4$, and concentrated in vacuo to give the title compound, 0.14 g (0.45 mmol, 35%), as a beige foam. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 1.12 (d, 3, J = 6.8), 2.76 (s, 3), 4.35 (quin, 1, J = 6.6), 4.63 (t, 1, J = 5.5), 5.48 (d, 1, J = 4.7), 6.60 (d, 2, J = 8.7), 7.09 (d, 2, J = 8.7), 7.21 (t, 1, J = 7.4), 7.25−7.39 (m, 4), 7.80 (s, 1), 8.94 (s, 1). MS *m*/*z*: 301 (M + 1). Anal. ($C_{17}H_{20}N_2O_3 \cdot 0.5\ H_2O$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1,3-dimethyl-3-(4-phenoxyphenyl)urea (39). To a solution of (+)-norephedrine (5 g, 33 mmol) in CH_2Cl_2 (110 mL) contained in a 250 mL round-bottomed flask equipped with magnetic stirring were added triethylamine (5.7 mL, 41 mmol), 4-(dimethylamino)pyridine (210 mg, 1.7 mmol), and *tert*-butyldimethylsilyl chloride (6 g, 40 mmol). After being stirred at room temperature for 18 h, the reaction mixture was concentrated in vacuo. EtOAc (100 mL) was then added, and the organic layer was washed with 10% HCl, 10% Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was diluted in CH_2Cl_2 (30 mL) and added to a 100 mL round-bottomed flask equipped with magnetic stirring. 4-Phenoxyphenyl isocyanate (3.2 g, 15 mmol) was then added, and the reaction mixture was stirred for 18 h at room temperature. The contents of the reaction flask were diluted with EtOAc (100 mL) and washed with 10% citric acid, 10% Na_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (5:1 hexanes−EtOAc) was performed on the sample to provide 5.6 g of compound **37** as a white amorphous solid (12 mmol, 80%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ −0.18 (s, 3H), −0.04 (s, 3H), 0.89 (s, 9H), 0.96 (d, 3H, J = 6 Hz), 4.05 (m, 1H), 4.70 (br d, 1H, J = 9 Hz), 4.89 (d, 1H, J = 3 Hz), 6.18 (br s, 1H), 6.90 (m, 4H), 7.11 (m, 1H), 7.19−7.37 (m, 9H). MS *m*/*z*: 477 (M + 1). A solution of **37** (1.5 g, 3.1 mmol) in 10 mL of DMF was added to a 25 mL round-bottomed flask equipped with an ice bath, nitrogen atmosphere, and magnetic stirring. Sodium hydride (640 mg of a 60% dispersion in mineral oil, 16 mmol) was added to the reaction mixture, and vigorous gas evolution occurred. After 15 min of stirring, methyl iodide (1 mL, 16 mmol) was added. The reaction mixture was allowed to slowly warm to room temperature over 18 h, and then 1 mL of MeOH was added. Brine (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (4 × 25 mL). All organic fractions were combined and washed with 10% citric acid, 5% $NaHCO_3$, and brine (3×), dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (6:1 hexanes−EtOAc) was performed on the sample to provide 1.4 g of **38** as a white solid (2.8 mmol, 90%). Mp: 95−96 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.00 (s, 6H), 0.84 (s, 9H), 1.18 (d, 3H, J = 7 Hz), 2.39 (s, 3H), 3.05 (s, 3H), 4.23 (m, 1H), 4.73 (d, 1H, J = 7 Hz), 6.52 (dm, 2H, J = 9 Hz), 6.78 (dm, 2H, J = 9 Hz), 6.96 (dd, 2H, J = 1, 9 Hz), 7.11 (t, 1H, J = 7 Hz), 7.22−7.36 (m, 7H). MS *m*/*z*: 505 (M + 1). Anal. ($C_{30}H_{40}N_2O_3Si$) C, H, N. A solution of **38** (880 mg, 1.7 mmol) in 9 mL of 3:1:1 AcOH−THF−H_2O was heated to 70 °C in a 50 mL round-bottomed flask equipped with an oil bath and magnetic stirring bar. After 2 h, the reaction mixture was cooled to room temperature, poured into 400 mL of 5% $NaHCO_3$, and extracted with EtOAc (4 × 50 mL). The organic fractions were combined and washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (6:1 hexanes−EtOAc) was performed on the sample to provide 450 mg of **39** as an amorphous solid (1.2 mmol, 71% yield). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.19 (d, 3H, J = 7 Hz), 2.25 (s, 3 H), 3.19 (s, 3 H), 3.96 (dq, 1H, J = 4, 7 Hz), 4.84 (t, 1H, J = 3 Hz), 5.14 (br s, 1H), 6.86 (ABq with additional splitting, 4H), 6.98 (d, 2H, J = 8 Hz), 7.11 (t, 1H, J = 8 Hz), 7.24−7.40 (m, 7H). MS *m*/*z*: 391 (M + 1). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

1-((1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40a). Following the procedure described for the synthesis of **1**, compound **40a** was prepared from (−)-ephedrine (198 mg, 1.2 mmol) and 4-phenoxyphenyl isocyanate (250 mg, 1.2 mmol) in CH_2Cl_2 (4.5 mL) to yield a white amorphous solid (0.16 g, 0.43 mmol, 36%).[23] ^{1}H NMR ($CDCl_3$; 400 MHz): identical to (that for **32**. MS *m*/*z*: 377 (M + 1). Anal. ($C_{23}H_{24}N_2O_3$) C, H, N.

1-((1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40b). Following the procedure described for the synthesis of **1**, compound **40b** was prepared from (+)-pseudoephedrine (198 mg, 1.2 mmol) and 4-phenoxyphenyl isocyanate (250 mg, 1.2 mmol) in CH_2Cl_2 (4.5 mL) to yield a white amorphous solid (0.15 g, 0.40 mmol, 33%).[23] ^{1}H NMR ($CDCl_3$; 500 MHz): identical to that for **1**. MS (ESI, pos. ion) *m*/*z*: 377 (M + 1); (ESI, neg. ion) 375 (M − 1). Anal. ($C_{23}H_{24}N_2O_3$) C, H, N.

1-((1*R*)-1-Methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40c). Following the procedure described for the synthesis of **1**, **40c** was prepared from *R*(−)-methamphetamine (402 mg, 2.7 mmol) and 4-phenoxyphenyl isocyanate (510 mg, 2.4 mmol) in CH_2Cl_2 (10 mL). Drying in the vacuum oven for 24 h at 60 °C afforded a white amorphous solid (820 mg, 0.23 mmol, 96%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.25 (d, 3H, J = 7 Hz), 2.80 (m, 2 H), 2.86 (s, 3H), 4.56 (m, 1H), 5.78 (br s, 1H), 6.91 (d, 1H, J = 9 Hz), 6.95 (d, 1H, J = 8 Hz), 7.05 (t, 1H, J = 7 Hz), 7.09 (d, 1H, J = 8 Hz), 7.23−7.34 (m, 10H). MS *m*/*z*: 361 (M + 1). Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

1-((1*R*)-1-Methylpropyl)-1-methyl-3-(4-phenoxyphenyl)urea. (40d). To a 250 mL round-bottomed flask equipped with a magnetic stirring bar were added (*R*)-(−)-2-aminobutane (1.0 g, 14 mmol) in CH_2Cl_2 (50 mL) and triethylamine (2 mL, 14 mmol). The reaction flask was cooled in an ice bath, and 2-nitrobenzenesulfonyl chloride (2.8 g, 13 mmol), dissolved in 5 mL of CH_2Cl_2, was added over 5 min. After 10 h at room temperature, the reaction mixture was washed with 10% HCl (2×) and once with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to give ((1*R*)-1-methylpropyl) ((2-nitrophenyl)sulfonyl)amine as a brown solid, 3.1 g (12 mmol, 92%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.85 (t, 3H, J = 7 Hz), 1.10 (d, 3H, J = 7 Hz), 1.48 (quin, 2H, J = 7 Hz), 3.46 (dq, 1H, J = 7, 8 Hz), 5.10 (br d, 1H, J = 8 Hz), 7.73 (m, 2H), 7.86 (m, 1H), 8.17 (m, 1H). MS *m*/*z*: 259 (M + 1). This material was taken onto the next step without further purification. To a 250 mL round-bottomed flask equipped with a magnetic stirring bar were added ((1*R*)-1-methylpropyl) ((2-nitrophenyl)sulfonyl)-amine in DMF (40 mL), K_2CO_3 (2 g, 14 mmol), and iodomethane (1 mL, 16 mmol). After 10 h, additional portions of K_2CO_3 (2 g, 14 mmol) and iodomethane (1 mL, 16 mmol) were added to the reaction mixture. After 3 days of stirring, the reaction mixture was diluted with brine and extracted with Et_2O (3×). The combined organic fractions were washed with 10% HCl, 5% $NaHCO_3$, and with brine (3×), dried over Na_2SO_4, and concentrated in vacuo to give ((1*R*)-1-methylpropyl)-methyl((2-nitrophenyl)sulfonyl)amine as a brown solid (3.1 g, 11 mmol, 92%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.81 (t, 3H, J = 7 Hz), 1.09 (d, 3H, J = 7 Hz), 1.45 (m, 2H), 2.80 (s, 3H), 3.91 (dq, 1H, J = 2, 7 Hz), 7.61 (m, 1H), 7.66 (m, 2H), 8.04 (m, 1H). MS *m*/*z*: 273 (M + 1). This compound was carried onto the next step without further purification. To a 250 mL round-bottomed flask equipped with a magnetic stirring bar were added ((1*R*)-1-methylpropyl)methyl((2-nitrophenyl)sulfonyl)-amine in DMF (40 mL), LiOH monohydrate (2 g, 48 mmol), and mercaptoacetic acid (1.7 mL, 24 mmol). After 18 h, brine and 5 N NaOH were added, and the aqueous layer was extracted with Et_2O (3×). The combined organic fractions were washed with 5 N NaOH (2×) and brine (2×), dried over K_2CO_3, and filtered into a 250 mL round-bottomed flask. The flask was equipped with a magnetic stirring bar, and 4-phenoxyphenyl isocyanate (3 g, 14 mmol) was added. After 18 h, the white precipitate that had fallen out of solution was collected by filtration and washed with Et_2O. This solid was dissolved in 1:1 MeOH−EtOAc, filtered, and concentrated in vacuo. Column chromatography (4.5:1 hexanes−EtOAc, column pretreated with 1% triethylamine in 4.5:1 hexanes−EtOAc) provided the desired product **40d** as a light tan solid (1.2 g, 4.0 mmol, 36%). Mp: 104−107 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.90 (d, 3H, J = 7 Hz), 1.15 (d, 3H, J = 7 Hz), 1.50 (d quin, 2H, J = 2, 8 Hz), 2.83 (s, 3H), 4.33 (sext, 1H, J = 7 Hz), 6.25 (br s, 1H), 6.98 (m, 4H), 7.06 (t, 1H, J = 7 Hz), 7.30 (m, 2H), 7.37 (m, 2H). MS *m*/*z*: 299 (M + 1). Anal. ($C_{18}H_{22}N_2O_2$) C, H, N.

1-Methyl-3-(4-phenoxyphenyl)-1-(2-phenylethyl)urea (40e). The title compound was prepared according to the procedure described for the synthesis of **1** by using *N*-methylphenethylamine (0.41 mL, 2.8 mmol) and 4-phenoxyphenyl isocyanate (0.30 g, 1.4 mmol) in anhydrous CH_2Cl_2 (10 mL). The crude oil isolated after aqueous workup was dissolved in Et_2O and allowed to crystallize. The title compound was isolated as a white crystalline solid in 86% yield (0.40 g, 1.2 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 2.91 (t, 2, J = 6.8), 2.97 (s, 3), 3.60 (t, 2, J = 6.9), 5.84 (br s, 1), 6.91−7.36 (m, 14). MS *m*/*z*: 347 (M + 1). Anal. ($C_{22}H_{22}N_2O_2$) C, H, N.

1-(1-Benzylpropyl)-1-methyl-3-(4-phenoxyphenyl)urea (40f). To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added a solution of 1-phenyl-2-butanone (1.5 mL, 10 mmol) in EtOH (15 mL), triethylamine (2.8 mL, 20 mmol), methylamine hydrochloride (1.4 g, 20 mmol), and titanium(IV) isopropoxide (5.9 mL, 20 mmol). After 3 h, $NaBH_4$ (0.60 g, 16 mmol) was added, and the reaction mixture was stirred for an additional 3 h. Aqueous NH_3 was then added, and the white precipitate that fell out of solution was removed by filtration. Water was added to the filtrate, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic fractions were washed with 10% HCl, the layers were separated, and the aqueous layer was washed with CH_2Cl_2. The aqueous layer was neutralized with 2 N NaOH, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude methyl(benzylpropyl)amine as a clear oil (0.80 g crude yield, MS *m*/*z*: 164 (M + 1)). The title compound was prepared according to the procedure described in the synthesis of **1** by using the crude methyl-(benzylpropyl)amine (0.65 g, 4.8 mmol) and 4-phenoxyphenyl isocyanate (0.44 g, 2.1 mmol) in anhydrous CH_2Cl_2 (7 mL). After 2 h, the solution was partially concentrated in vacuo, cooled in a −20 °C freezer, and diluted with Et_2O. The resultant solids were collected by filtration and washed with cold Et_2O to give the title compound as a white solid (0.44 g, 1.2 mmol, 57%). Mp: 136.5−138.0 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.25 (t, 3, J = 6.7), 2.31 (s, 3), 2.75 (dq, 2, J = 6.1, 13.8), 2.75 (s, 2), 4.49 (m, 1), 5.74 (s, 1), 6.89−7.06 (m, 7), 7.12−7.28 (m, 7). MS *m*/*z*: 375 (M + 1). Anal. ($C_{24}H_{26}N_2O_2$) C, H, N.

1-(1,2-Diphenylethyl)-1-methyl-3-(4-phenoxyphenyl)-urea (40g). The title compound was prepared according to the procedure described for compound **1** by using 1,2-diphenylethyl-*N*-methylamine (1.0 g, 4.7 mmol) and 4-phenoxyphenyl isocyanate (0.58 mL, 3.2 mmol) in anhydrous CH_2Cl_2 (12 mL). The title compound was isolated after recrystallization from EtOAc and Et_2O to give a white solid (0.64 g, 1.5 mmol, 47%). ^{1}H NMR (DMSO-d_6; 400 MHz): δ 2.77 (s, 3), 3.21 (dd, 1, J = 10.3, 14.2), 3.37 (dd, 1, J = 6.2, 14.5), 5.92 (dd, 1, J = 5.0, 10.0), 6.91 (dd, 4, J = 7.3, 10.4), 7.23−7.45 (m, 15), 8.17 (s, 1). MS *m*/*z*: 423 (M + 1). Anal. ($C_{28}H_{26}N_2O_2$) C, H, N.

1-Methyl-1-(2-methyl-1-benzylpropyl)-3-(4-phenoxyphenyl)urea (40h). Methyl(2-methyl-1-benzylpropyl)amine was prepared according to the procedure described for the synthesis of methyl(benzylpropyl)amine (see the procedure for **40f**) by using benzyl isopropyl ketone (3.2 g, 20 mmol), titanium(IV) isopropoxide (12 mL, 40 mmol), methylamine hydrochloride (2.8 g, 40 mmol), triethylamine (5.6 mL, 50 mmol), EtOH (30 mL), and sodium borohydride (1.2 g, 32 mmol), to provide the intermediate amine as a clear oil (0.80 g crude yield, MS *m*/*z*: 178 (M + 1)). The title compound was prepared according to the procedure described for the synthesis of **1** by using methyl(2-methyl-1-benzylpropyl)amine (0.78 g, 4.4 mmol) and 4-phenoxyphenyl isocyanate (0.63 g, 3.0 mmol) in anhydrous CH_2Cl_2 (8 mL). The solution was cooled in a −20 °C freezer, and the solids were collected by filtration and washed with cold Et_2O to give the title compound as a white solid (0.88 g, 2.3 mmol, 77%). Mp: 173.0−174.5 °C. ^{1}H NMR (DMSO-d_6; 400 MHz): δ 0.84 (d, 3, J = 6.5), 1.05 (d, 3, J = 6.5), 1.85 (m, 1), 2.65 (m, 1), 2.98 (m, 1), 4.25 (br s, 1), 6.86−6.92 (m, 4), 7.06 (t, 1, J = 7.3), 7.12−7.35 (m, 9), 7.89 (s, 1). MS *m*/*z*: 389 (M + 1). Anal. ($C_{25}H_{28}N_2O_2$) C, H, N.

1-(1,1-Dimethyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40i). The title compound was prepared according to the procedure described for the synthesis of **1** by using mephentermine hemisulfate (0.65 g, 3.1 mmol) and 4-phenoxyphenyl isocyanate (0.30 g, 1.4 mmol) in anhydrous CH_2Cl_2 (10 mL) to yield **40i** as an opaque oil (0.41 g, 1.1 mmol, 79%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.50 (s, 6), 2.67 (s, 3), 3.25 (s, 2), 6.08 (s, 1), 7.01 (d, 4, J = 6.5), 7.09 (t, 1, J = 7.2), 7.23−7.35 (m, 9). MS *m*/*z*: 375 (M + 1). Anal.($C_{24}H_{26}N_2O_2 \cdot 0.25\ H_2O$) C, H, N.

1-(2-(4-Methoxyphenyl)-1-methylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40j). Methyl(2-(4-methoxyphenyl)-1-methylethyl)amine was prepared according to the procedure described for the synthesis of methyl(benzylpropyl)amine (see the procedure for **40f**) by using 4-methoxyphenylacetone (1.5 mL, 10 mmol), titanium(IV) isopropoxide (5.9 mL, 20 mmol), methylamine hydrochloride (1.4 g, 20 mmol), triethylamine (2.8 mL, 20 mmol), EtOH (15 mL), and sodium borohydride (0.60 g, 16 mmol). The intermediate amine was isolated upon workup as a clear oil and carried on without purification (0.73 g crude yield, MS *m*/*z*: 180 (M + 1)). The title compound was

prepared according to the procedure described in the synthesis of **1** by using methyl(1-methyl-2-(4-methoxyphenyl)ethylamine (0.71 g, 4.0 mmol) and 4-phenoxyphenyl isocyanate (0.69 g, 3.3 mmol) in anhydrous CH_2Cl_2 (10 mL). After 2 h, the solution was cooled in a −20 °C freezer and diluted with Et_2O. The resultant solids were collected by filtration and washed with cold Et_2O to give the title compound as a white solid (1.0 g, 2.8 mmol, 85%). Mp: 141.0−142.5 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.24 (d, 3, J = 6.7), 2.714, 2.777 (ABX, J_{ab} = 13.7, J_{ax} = 6.15, J_{bx} = 8.87), 2.85 (s, 3), 3.77 (s, 3), 4.50 (m, 1), 5.79 (s, 1), 6.85 (d, 2, J = 8.6), 6.91 (d, 2, J = 8.8), 6.95 (d, 2, J = 8.0), 7.05 (t, 1, J = 7.4), 7.10 (d, 2, J = 8.7), 7.14 (d, 2, J = 8.5), 7.29 (t, 2, J = 7.9). MS m/z: 391 (M + 1). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

1-(2-(4-Fluorophenyl)-1-methylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40k). Methyl(2-(4-fluorophenyl)-1-methylethyl)amine was prepared according to the procedure described for the synthesis of methyl(benzylpropyl)amine (see the procedure for **40f**) by using 4-fluorophenylacetone (1.5 g, 10 mmol), titanium(IV) isopropoxide (5.9 mL, 20 mmol), methylamine hydrochloride (1.4 g, 20 mmol), triethylamine (2.8 mL, 20 mmol), EtOH (15 mL), and sodium borohydride (0.60 g, 16 mmol). The intermediate amine was isolated upon workup as a clear oil and was carried on without purification (0.96 g, crude yield, MS m/z: 168 (M + 1)). The title compound was prepared according to the procedure described in the synthesis of **1** by using methyl(1-methyl-2-(4-fluorophenyl)-ethylamine (0.90 g, 5.4 mmol) and 4-phenoxyphenyl isocyanate (0.71 g, 3.4 mmol) in anhydrous CH_2Cl_2 (10 mL). The solution was cooled in a −20 °C freezer, and the solids were collected by filtration and washed with cold Et_2O to give the title compound as a white solid (0.98 g, 2.6 mmol, 76%). Mp: 174.5−176.0 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.22 (d, 3, J = 6.7), 2.772, 2.845 (ABX, J_{ab} = 13.7, J_{ax} = 6.74, J_{bx} = 8.27), 2.84 (s, 3), 4.64 (quin, 1, J = 6.0), 5.93 (s, 1), 6.93−7.18 (m, 11), 7.30 (t, 2, J = 7.6). MS m/z: 379 (M + 1). Anal. ($C_{23}H_{23}FN_2O_2$) C, H, N.

1-(2-(4-Chlorophenyl)-1-methylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40l). The title compound was prepared according to the procedure described for the synthesis of **1** by using dl-4-chloromethamphetamine hydrochloride (0.73 g, 3.3 mmol), triethylamine (0.46 mL, 3.3 mmol), and 4-phenoxyphenyl isocyanate (0.40 mL, 2.2 mmol) in anhydrous CH_2Cl_2 (10 mL) to give the title compound as a white solid (0.78 g, 2.0 mmol, 91%). Mp: 155.0−156.5 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.21 (d, 3, J = 6.7), 2.773, 2.847 (ABX, J_{ab} = 13.8, J_{ax} = 6.76, J_{bx} = 8.26), 2.83 (s, 3), 4.66 (q, 1, J = 7.0), 5.95 (s, 1), 6.95 (m, 4), 7.06 (t, 1, J = 7.5), 7.17 (t, 4, J = 8.6), 7.26−7.30 (m, 4). MS m/z: 395 (M + 1). Anal. ($C_{23}H_{23}ClN_2O_2$) C, H, N, Cl.

1-Methyl-3-(4-phenoxyphenyl)-1-(2-(4-pyridyl)-1-methylethyl)urea Hydrochloride (40m). Methyl(2-(4-pyridyl)1-methylethyl)amine was prepared according to the procedure described for the synthesis of methyl(benzylpropyl)amine (see the procedure for **40f**) by using 4-pyridylacetone (1.5 g, 10 mmol), titanium(IV) isopropoxide (5.9 mL, 20 mmol), methylamine hydrochloride (1.4 g, 20 mmol), triethylamine (2.8 mL, 20 mmol), EtOH (15 mL), and sodium borohydride (0.60 g, 16 mmol). The intermediate amine was isolated upon workup as a yellow oil and was carried on without purification (1.7 g crude yield, MS m/z: 151 (M + 1). The title compound was prepared according to the procedure described for the synthesis of **1** by using methyl(1-methyl-2-(4-pyridyl)ethyl)amine (0.85 g, 5.7 mmol) and 4-phenoxyphenyl isocyanate (0.76 g, 3.6 mmol) in anhydrous CH_2Cl_2 (8 mL). The crude product was purified by flash chromatography (EtOAc) to give the free base as a pure white solid. The free base was dissolved in MeOH and treated with ethereal HCl (0.95 mL, 1 M solution in Et_2O, 0.95 mmol) to give, upon concentration in vacuo and drying overnight in a vacuum oven, the title product as an off-white foam (0.38 g, 1.1 mmol, 31%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.22 (d, 3, J = 6.7), 3.027, 3.180 (ABX, J_{ab} = 14.3, J_{ax} = 5.36, J_{bx} = 9.64), 2.84 (s, 3), 4.64 (quin, 1, J = 6.0), 5.93 (s, 1), 6.93−7.18 (m, 11), 7.30 (t, 2, J = 7.6). MS m/z: 362 (M + 1). Anal. ($C_{22}H_{23}N_3O_2\cdot 0.8HCl\cdot H_2O$) C, H, N, Cl.

1-(2-Cyclohexyl-1-methylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40n). 2-Cyclohexylisopropylmethylamine was prepared according to the procedure described for the synthesis of methyl(benzylpropyl)amine (see the procedure for **40f**) by using cyclohexyl acetone (1.4 g, 10 mmol), titanium(IV) isopropoxide (5.9 mL, 20 mmol), methylamine hydrochloride (1.4 g, 20 mmol), triethylamine (2.8 mL, 20 mmol), EtOH (15 mL), and sodium borohydride (0.60 g, 16 mmol). The intermediate amine was isolated upon workup as a clear oil and carried on without purification (0.54 g crude yield, MS m/z: 156 (M + 1)). The title compound was prepared according to the procedure described in the synthesis of **1** by using 2-cyclohexylisopropylmethylamine (0.53 g, 3.1 mmol) and 4-phenoxyphenyl isocyanate (0.52 g, 2.5 mmol) in anhydrous CH_2Cl_2 (7 mL). After 1 h, crystals had formed in the reaction mixture. The solution was cooled in a −20 °C freezer, and the solids were collected by filtration and washed with cold Et_2O to give the title compound as a white solid (0.66 g, 1.8 mmol, 72%). Mp: 156.0−157.5 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 0.92 (m, 2), 1.12 (d, 3, J = 6.7), 1.14−1.27 (m, 5), 1.42 (m, 1), 1.66 (m, 4), 1.85 (m, 1), 2.81 (s, 3), 4.54 (m, 1), 6.22 (s, 1), 6.97 (d, 4, J = 7.9), 7.05 (t, 1, 7.3), 7.30 (t, 2, J = 8.0), 7.36 (d, 2, J = 8.9). MS m/z: 367 (M + 1). Anal. ($C_{23}H_{30}N_2O_2$) C, H, N.

1-((1*S*)-1-Methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)urea (40o). Following the procedure described for the synthesis of **1**, **40o** was prepared from *S*(+)-methamphetamine (62 mg, 0.42 mmol) and 4-phenoxyphenyl isocyanate (73 mg, 0.35 mmol) in CH_2Cl_2 (3 mL). Drying in the vacuum oven for 24 h at 48 °C afforded a white amorphous solid (96 mg, 0.27 mmol, 76%). ^{1}H NMR ($CDCl_3$; 400 MHz): identical to that for **40c**. MS m/z: 361 (M + 1). Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

1-Methyl-3-(4-phenoxyphenyl)-1-(1,2,3,4-tetrahydronaphth-2-yl)urea (41). *N*-Methyl-2-aminotetralin was prepared according to the procedure described for the synthesis of methyl(benzylpropyl)amine (see the procedure for **40f**) by using β-tetralone (0.37 g, 2.5 mmol), titanium(IV) isopropoxide (2.9 mL, 10 mmol), methylamine hydrochloride (0.68 g, 10 mmol), triethylamine (1.4 mL, 10 mmol), EtOH (7 mL), and $NaBH_4$ (0.28 g, 7.5 mmol). The intermediate amine was isolated upon workup as a dark green solid and carried on without purification (0.51 g crude yield. MS m/z: 162 (M + 1)). The title compound was prepared according to the procedure described for the synthesis of **1** by using *N*-methyl-2-aminotetralin (0.51 g, 2.5 mmol) and 4-phenoxyphenyl isocyanate (0.40 mL, 2.2 mmol) in anhydrous CH_2Cl_2 (10 mL). The resultant crude red-brown oil was purified by column chromatography (1:3 EtOAc−hexanes), decolorized with activated charcoal, filtered through Celite, and concentrated in vacuo to give the title compound as a red-brown oil (0.77 g, 2.1 mmol, 95%). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.91 (dq, 1, J = 6.0, 11.9), 2.01 (m, 1), 2.92−3.02 (m, 7), 4.62 (m, 1), 6.31 (s, 1), 6.94−7.15 (m, 9), 7.29−7.38 (m, 4). MS m/z: 373 (M + 1). Anal. ($C_{24}H_{24}N_2O_2\cdot 0.25\ H_2O$) C, H, N.

1-(Indan-2-yl)-1-methyl-3-(4-phenoxyphenyl)urea (42). To a 10 mL round-bottomed flask equipped with magnetic stirring were added a solution of 2-indanone (0.25 g, 1.9 mmol) in 2 mL of MeOH and methylamine (0.82 mL of a 40% solution in H_2O, 9.5 mmol). $NaBH_4$ (72 mg, 1.9 mmol) was then added to the reaction mixture over 5 min during which time vigorous gas evolution occurred. After 4 h of stirring at room temperature, K_2CO_3 (1 g) was added, and the reaction mixture was concentrated in vacuo. Water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined ethereal layers were washed with brine (50 mL), dried over K_2CO_3, filtered, and concentrated in vacuo to afford a brown oil (200 mg). The residue was dissolved in methyl *tert*-butyl ether, and 1 M ethereal HCl (1.4 mL, 1.4 mmol) was added. The resulting white precipitate was collected by decantation, washed with methyl *tert*-butyl ether (3 × 2 mL), washed with 1:1 Et_2O−pentane (3 × 3 mL), and dried under high vacuum for 30 min to give crude 2-methylaminoindan hydrochloride

as a green-yellow solid (190 mg). ^{1}H NMR (DMSO-d_6; 400 MHz): δ 2.58 (t, 3H, J = 5 Hz), 3.09 (dd, 2H, J = 7, 16 Hz), 3.28 (dd, 2H, J = 8, 17 Hz), 3.94 (sept, 1H, J = 7 Hz), 7.19 (m, 2H), 7.28 (m, 2H), 9.26 (br s, 2H). MS m/z: 148 (M + 1). Following the procedure described for the synthesis of **1**, compound **42** was prepared from 2-methylaminoindan (the HCl salt was converted to the neutral form prior to the reaction) (150 mg, 1.0 mmol) and 4-phenoxyphenyl isocyanate (192 mg, 0.91 mmol) in CH_2Cl_2 (4 mL). The crude sample was recrystallized from heptane and ethylene glycol dimethyl ether to afford the desired product as a white powder (200 mg, 0.56 mmol, 62%). Mp: 178−179 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 2.89 (s, 3H), 3.27 (dd, 2H, J = 6.5, 16 Hz), 3.27 (dd, 2H, J = 9, 16 Hz), 5.35 (d quin, 1H, J = 1, 8 Hz), 6.29 (s, 1H), 6.98 (d, 4H, J = 9 Hz), 7.07 (t, 1H, J = 7 Hz), 7.15−7.38 (m, 8H). MS m/z: 359 (M + 1). Anal. ($C_{23}H_{22}N_2O_2 \cdot 0.5H_2O$) C, H, N.

1-Ethyl-1-((1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl)-3-(4-phenoxyphenyl)urea (43a). Following the procedure described for the synthesis of **1**, compound **43a** was prepared from (1*S*,2*R*)-2-(ethylamino)-1-phenylpropan-1-ol (**9**) (1.8 g, crude) and 4-phenoxyphenyl isocyanate (0.70 g, 3.3 mmol) in CH_2Cl_2 (30 mL). After flash chromatography on silica gel with 1:1 EtOAc−hexanes as the eluant, a white solid was isolated in 10% yield (0.74 g, 1.9 mmol) based on (+)-norephedrine. Mp: 160−165 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.22 (t, 3H, J = 7.2 Hz), 1.31 (d, 3H, J = 7.1 Hz), 3.07−3.3 (m, 2H), 3.39−3.7 (m, 1H), 3.88−3.89 (m, 1H), 4.46 (br s, 1H), 5.06 (br s, 1H), 6.97−7.07 (m, 4H), 7.29−7.42 (m, 10H). MS (ESI, pos. ion) m/z: 391 (M + 1); (ESI, neg. ion) 389 (M − 1). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-phenoxyphenyl)urea (43b). Following the procedure described for **1**, **43b** was prepared from (1*S*,2*R*)-(+)-norephedrine (1 g, 6.6 mmol) and 4-phenoxyphenyl isocyanate (470 mg, 2.2 mmol) in CH_2Cl_2 (14 mL). A white amorphous solid was isolated in 91% yield (730 mg). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.02 (d, 3H, J = 7 Hz), 3.73 (br s, 1H), 4.26 (d quin, 1H, J = 3, 7 Hz), 4.68 (d, 1H, J = 7 Hz), 4.86 (s, 1H), 6.57 (br s, 1H), 6.96 (t, 4H, J = 9 Hz), 7.10 (t, 1H, J = 7 Hz), 7.23 (d, 2H, J = 9 Hz), 7.27−7.38 (m, 7H). MS (ESI, pos. ion) m/z: 363 (M + 1); (ESI, neg. ion) 361 (M − 1). Anal. ($C_{22}H_{22}N_2O_3$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenyl)thiourea (43c). Following the procedure described for the synthesis of **1**, compound **43c** was prepared from (1*S*,2*R*)-ephedrine hemihydrate (1 g, 6 mmol) and 4-phenoxyphenyl isothiocyanate (450 mg, 2 mmol) in CH_2Cl_2 (12 mL). A white amorphous solid was isolated in 90% yield (710 mg, 1.8 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.30 (d, 3H, J = 7.1 Hz), 2.66 (m, 1H), 2.88 (s, 3H), 5.04 (m, 1H), 5.40 (br s, 1H), 6.96−6.98 (m, 3H), 7.03 (d, 2H, J = 7 Hz), 7.11 (t, 1H, J = 8 Hz), 7.23 (d, 2H, J = 9 Hz), 7.34 (t, 2H, J = 8 Hz), 7.40 (t, 2H, J = 8 Hz), 7.47 (d, 2H, J = 8 Hz). MS (ESI, pos. ion) m/z: 393 (M + 1); (ESI, neg. ion) 391 (M − 1). Anal. ($C_{23}H_{24}N_2O_2S$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-(4-fluorophenoxy)phenyl)-1-methylurea (44a). To a 100 mL round-bottomed flask equipped with a magnetic stirring bar were added 1-fluoro-4-nitrobenzene (2.8 g, 20 mmol), 4-fluorophenol (2.5 g, 22 mmol), and DMF (40 mL). To the above solution was then added K_2CO_3 (3.0 g, 22 mmol). The reaction mixture was heated at 150 °C for 15 h under N_2. After cooling to room temperature, the reaction mixture was poured into 500 mL of ice cold water and stirred for 0.5 h. The precipitate that formed was collected by filtration, washed with water, and dried in a vacuum oven overnight to give 4-(4-fluorophenoxy)-1-nitrobenzene in a 90% yield (4.3 g, 18 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 6.97−7.00 (m, 2H), 7.06−7.17 (m, 4H), 8.19−8.23 (m, 2H). MS (ESI, pos. ion) m/z: 234 (M + 1). Into a pressure bottle was added a solution of 4-(4-fluorophenoxy)-1-nitrobenzene (1 g, 4.3 mmol) in 200 mL in EtOH with 10% Pd/C (0.6 g). The reaction mixture was agitated on a Parr shaker at 20 psi of H_2 for 1 h. The catalyst was filtered off through a pad of Celite, and the filtrate was concentrated in vacuo to give 93% of 4-(4-fluorophenoxy)phenylamine (0.81 g, 4.0 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 3.58 (br s, 2H), 6.65−6.70 (m, 2H), 6.82−6.91 (m, 4H), 6.94−7.00 (m, 2H). MS (ESI, pos. ion) m/z: 204 (M + 1). To a 250 mL round-bottomed flask equipped with stirring and an ice bath was added 4-(4-fluorophenoxy)phenylamine (1.0 g, 5 mmol) in CH_2Cl_2 (50 mL). A 5% solution of $NaHCO_3$ (50 mL) was then added, and the reaction mixture was stirred for 5 min. Stirring was stopped, and phosgene (5 mL of a 2 M solution in toluene, 10 mmol) was added directly to the organic layer through a syringe. After complete addition of phosgene, stirring was continued for 45 min. The organic layer was then separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). All organic fractions were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. This flask was equipped with magnetic stirring, and a solution of (1*S*,2*R*)-ephedrine hemihydrate (2.6 g, 15 mmol) in CH_2Cl_2 (30 mL) was added with vigorous stirring. After 24 h, 10% HCl (100 mL) was added, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with 10% HCl and 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (1:1 EtOAc−hexanes) was performed on the crude material and afforded an off-white foam in 73% yield (1.4 g). Mp: 117−119 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.26 (d, 3H, J = 7.2 Hz), 2.56 (s, 3H), 3.73 (br s, 1H), 4.38 (dq, 1H, J = 3.3, 7.1 Hz), 4.86 (dd, 1H, J = 2.5, 2.5 Hz), 6.84 (br s, 1H), 6.91−7.02 (m, 5H), 7.26−7.41 (m, 8H). MS (ESI, pos. ion) m/z: 395 (M + 1); (ESI, neg. ion) 393 (M − 1). Anal. ($C_{23}H_{23}FN_2O_3 \cdot 0.2H_2O$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-(3,4-dimethylphenoxy)phenyl)-1-methylurea (44b). Following the same procedure described for the synthesis of 4-(4-fluorophenoxy)-1-nitrobenzene (see procedure for **44a**), 4-(3,4-dimethylphenoxy)-1-nitrobenzene was prepared from 3,4-dimethylphenol (3 g, 11 mmol), 1-fluoro-4-nitrobenzene (1.4 g, 10 mmol), and K_2CO_3 (1.5 g, 11 mmol) in 20 mL of DMF. A yellow solid was obtained in 95% yield (2.3 g, 9.5 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 2.28 (s, 6), 6.81−6.88 (m, 2H), 6.96−7.00 (m, 2H), 7.17−7.19 (m, 1H), 8.16−8.20 (m, 2H). MS (ESI, pos. ion) m/z: 244 (M + 1). Following the same procedure described for the synthesis of 4-(4-fluorophenoxy)phenylamine (see procedure for **44a**), 4-(3,4-dimethylphenoxy)phenylamine was prepared from 4-(3,4-dimethylphenoxy)-1-nitrobenzene (2.3 g, 9.3 mmol) and 10% Pd/C (1.2 g) in 150 mL of EtOH. A brown solid was isolated in 91% yield (1.8 g, 8.5 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 2.20 (s, 3), 3.55 (br s, 2), 6.65−6.68 (m, 3H), 6.74−6.75 (m, 1H), 6.83−6.89 (m, 2H), 7.02−7.04 (m, 1H). MS (ESI, pos. ion) m/z: 214 (M + 1). Following the procedure described for the synthesis of **44a**, compound **44b** was prepared from 4-(3,4-dimethylphenoxy)phenylamine (0.85 g, 4 mmol), phosgene (4.0 mL of a 2 M solution in toluene, 8 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (1.4 g, 8 mmol). Flash chromatography (1:3 EtOAc−hexanes) afforded an off-white foam in 68% yield (1.1 g, 2.7 mmol). Mp: 64−67 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.25 (d, 3H, J = 7.2 Hz), 2.22 (s, 6H), 2.56 (s, 3H), 3.79 (br s, 1H), 4.38 (dq, 1H, J = 3.2, 7.1 Hz), 4.86 (dd, 1H, J = 2.9, 2.9 Hz), 6.71−6.79 (m, 2H), 6.92−6.95 (m, 2H), 7.18 (d, 2H, J = 8.2 Hz), 7.28−7.41 (m, 6H). MS (ESI, pos. ion) m/z: 405 (M + 1); (ESI, neg. ion) 403 (M − 1). Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-(3-nitrophenoxy)phenyl)urea (44c). Following the procedure described for the synthesis of **44a**, compound **44c** was prepared from 4-(3-nitrophenoxy)phenylamine (1.7 g, 7.4 mmol), phosgene (7.4 mL of a 2 M solution in toluene, 15 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (2.6 g, 15 mmol). Flash chromatography (1:3 EtOAc−hexanes) afforded a yellow foam in 68% yield (2.1 g, 5.0 mmol). Mp: 66−78 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.28 (d, 3H, J = 7.1 Hz), 2.57 (s, 3H), 3.48 (br s, 1H), 4.41 (dq, 1H, J = 3.1, 7.0 Hz), 4.88 (dd, 1H, J = 2.8, 2.8 Hz), 6.99−7.03 (m, 2H), 7.27−7.48 (m, 9H), 7.75−7.76 (m, 1H), 7.9 (d, 1H, J = 8.2 Hz). MS (ESI, pos. ion) m/z: 422 (M + 1); (ESI, neg. ion) 420 (M − 1). Anal. ($C_{23}H_{23}N_3O_5$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-(4-chlorophenoxy)phenyl)-1-methylurea (44d). Triphosgene (0.35 g, 1.2 mmol) was dissolved in anhydrous CH_2Cl_2 (12 mL) in a 100 mL round-bottomed flask equipped with magnetic stirring. A solution of 4-amino-4′-chlorodiphenyl ether (0.77 g, 3.5 mmol) and *N*,*N*-diisopropylethylamine (1.3 mL, 7.3 mmol) in CH_2Cl_2 (12 mL) was added to the reaction flask dropwise through a 25 mL addition funnel over 45 min. Five minutes after the addition, a solution of (1*S*,2*R*)-ephedrine hemihydrate (1.5 g, 8.6 mmol) in CH_2Cl_2 (12 mL) was added all at once to the stirring reaction mixture; a precipitate immediately formed in the solution. After 1 h, the reaction mixture was washed with 10% HCl (3 × 30 mL), dried over $MgSO_4$, and concentrated in vacuo to give a purple oil. Flash chromatography (1:3 then 1:2 EtOAc−hexanes) afforded the title compound as a clear oil in 17% yield (0.24 g, 0.59 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.27 (d, 3, J = 7.1), 2.58 (s, 3), 4.41 (dq, 1, J = 3.4, 7.0), 4.88 (s, 1), 6.90 (d, 2, J = 9.0), 6.96 (d, 2, J = 8.9), 7.25−7.40 (m, 9). MS *m*/*z*: 411 (M + 1). Anal. ($C_{23}H_{23}ClN_2O_3$) C, H, N, Cl.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-(4-phenylmethoxy)phenyl)urea (44e). Following the procedure described for the synthesis of **1**, compound **44e** was prepared from (1*S*,2*R*)-ephedrine hemihydrate (1 g, 6 mmol) and 4-benzyloxyphenyl isocyanate (450 mg, 2 mmol) in EtOH (6 mL). A white amorphous solid was isolated in a 60% yield (460 mg, 1.2 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.22 (d, 3H, J = 10 Hz), 2.53 (s, 3H), 4.14 (br s, 1H), 4.33 (m, 1H), 4.81 (m, 1H), 5.03 (s, 2H), 6.84 (br s, 1H), 6.90 (d, 2H, J = 9 Hz), 7.22 (d, 2H, J = 9 Hz), 7.30−7.5 (m, 10H). MS (ESI, pos. ion) *m*/*z*: 391 (M + 1); (ESI, neg. ion) 389 (M − 1). Anal. ($C_{24}H_{26}N_2O_3$·0.25H_2O) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-phenylurea (44f). Following the procedure described for the synthesis of **1**, compound **44f** was prepared from (1*S*,2*R*)-ephedrine hemihydrate (1 g, 6 mmol) and phenyl isocyanate (0.22 mL, 2 mmol) in EtOH (6 mL). A white amorphous solid was isolated in 80% yield (460 mg, 1.6 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.21 (d, 3H, J = 7 Hz), 2.5 (s, 3H), 4.1 (br s, 1H), 4.32 (m, 1H), 4.79 (m, 1H), 7.02 (t, 1H, J = 7 Hz), 7.2−7.4 (m, 9H). MS (ESI, pos. ion) *m*/*z*: 285 (M + 1); (ESI, neg. ion) 283 (M − 1). Anal. ($C_{17}H_{20}N_2O_2$·0.1H_2O) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-benzylphenyl)-1-methylurea (44g). Following the procedure for the synthesis of **44a**, compound **44g** was prepared from 4-aminodiphenylmethane (1 g, 5.5 mmol), phosgene (5 mL of a 2 M solution in toluene, 10 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (2.6 g, 15 mmol) to afford a white amorphous solid in 93% yield (1.9 g, 5.1 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.25 (d, 3H, J = 7 Hz), 2.56 (s, 3H), 3.81 (br s, 1H), 3.94 (s, 2H), 4.37 (m, 1H), 4.86 (m, 1H), 6.82 (br s, 1H), 7.11 (d, 2H, J = 8 Hz), 7.15−7.42 (m, 12H). MS (ESI, pos. ion) *m*/*z*: 375 (M + 1); (ESI, neg. ion) 373 (M − 1). Anal. ($C_{24}H_{26}N_2O_2$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(4-(ethylphenylamino)phenyl)-1-methylurea (44h). Following the procedure described for the synthesis of **44a**, compound **44h** was prepared from compound **29** (543 mg, 2.6 mmol), phosgene (2.6 mL of a 2 M solution in toluene, 5.1 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (1.3 g, 7.7 mmol). Flash chromatography (2:1 hexanes−EtOAc) afforded a brown amorphous solid in 32% yield (330 mg, 0.82 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.20 (t, 3H, J = 7 Hz), 1.27 (d, 3H, J = 7 Hz), 2.59 (s, 3H), 2.74 (q, 2H, J = 7 Hz), 3.75 (br s, 1H), 4.41 (dq, 1H, J = 3, 7 Hz), 4.89 (t, 1H, J = 3 Hz), 6.81 (t, 2H, J = 7 Hz), 6.89 (t, 2H, J = 7 Hz), 7.2 (m, 2H), 7.29−7.43 (m, 8H). MS *m*/*z*: 404 (M + 1). Anal. ($C_{25}H_{29}N_3O_2$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(3-phenoxyphenyl)urea (44i). Following the procedure described for the synthesis of **44a**, compound **44i** was prepared from 3-phenoxyaniline (170 mg, 0.91 mmol), phosgene (0.91 mL of a 2 M solution in toluene, 1.8 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (480 mg, 2.7 mmol). A white amorphous solid was isolated in a 76% yield (260 mg, 0.69 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.24 (d, 3H, J = 7.1 Hz), 2.53 (s, 3H), 3.52 (br s, 1H), 4.34 (dq, 1H, J = 3.3, 7.1 Hz), 4.83 (dd, 1H, J = 2.7, 2.7 Hz), 6.66 (ddd, 1H, J = 0.7, 1.5, 7.1 Hz), 7.01−7.38 (m, 13H). MS (ESI, pos. ion) *m*/*z*: 377 (M + 1); (ESI, neg. ion) 375 (M − 1). Anal. ($C_{23}H_{24}N_2O_3$·0.25H_2O) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(2-phenoxyphenyl)urea (44j). Following the procedure described for the synthesis of **1**, compound **44j** was prepared from (1*S*,2*R*)-ephedrine hemihydrate (1 g, 6 mmol) and 2-phenoxyphenyl isocyanate (420 mg, 2 mmol) in CH_2Cl_2 (6 mL). A white amorphous solid was isolated in a 95% yield (700 mg, 1.9 mmol). ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.19 (d, 3H, J = 7 Hz), 2.48 (s, 3H), 3.71 (br s, 1H), 4.37 (m, 1H), 4.82 (m, 1H), 6.8−7.4 (m, 14H), 8.22 (d, 1H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 377 (M + 1); (ESI, neg. ion) 375 (M − 1). Anal. ($C_{23}H_{24}N_2O_3$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-1-methyl-3-(4-phenoxyphenylmethyl)urea (45). Following the procedure described for the synthesis of **44a**, compound **45** was prepared from compound **31** (1.0 g, 5 mmol), phosgene (5 mL of a 2 M solution in toluene, 10 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (2.6 g, 15 mmol). Flash chromatography (1:1 EtOAc−hexanes) afforded an off-white foam in 66% yield (1.3 g, 3.3 mmol). Mp: 46−52 °C. ^{1}H NMR ($CDCl_3$; 400 MHz): δ 1.22 (d, 3H, J = 7.2 Hz), 2.50 (s, 3H), 4.25−4.42 (m, 4H), 4.78−4.82 (m, 2H), 6.96−7.02 (m, 4H), 7.09−7.13 (m, 1H), 7.23−7.38 (m, 9H). MS (ESI, pos. ion) *m*/*z*: 391 (M + 1); (ESI, neg. ion) 389 (M − 1). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(dibenzo[*b*,*d*]furan-2-yl)-1-methylurea (46). Following the procedure described for the synthesis of **44a**, compound **46** was prepared from 2-aminobenzofuran (purchased as the HCl salt and converted to the neutral form prior to the reaction) (170 mg, 0.91 mmol), phosgene (0.91 mL of a 2 M solution in toluene, 1.8 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (480 mg, 2.7 mmol). A white amorphous solid was isolated in 83% yield (280 mg, 0.75 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.30 (d, 3H, J = 7.1 Hz), 2.64 (s, 3H), 3.61 (br s, 1H), 4.46 (dq, 1H, J = 3.3, 7.1 Hz), 4.92 (dd, 1H, J = 2.8, 2.8 Hz), 7.05 (br s, 1H), 7.27 (m, 1H), 7.32 (t, 2H, J = 7.4 Hz), 7.38 (t, 2H, J = 7.4 Hz), 7.43−7.48 (m, 4H), 7.54 (d, 1H, J = 8.3 Hz), 7.93 (d, 1H, J = 7.6 Hz), 8.10 (d, 1H, J = 2.1 Hz). MS (ESI, pos. ion) *m*/*z*: 375 (M + 1); (ESI, neg. ion) 373 (M − 1). Anal. ($C_{23}H_{22}N_2O_3$·0.2H_2O) C, H, N.

1-((1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl)-3-(9-ethylcarbazol-3-yl)-1-methylurea (47). Following the procedure described for the synthesis of **44a**, compound **47** was prepared from 3-amino-9-ethylcarbazole (1.1 g, 4.8 mmol), phosgene (4.8 mL of a 2 M solution in toluene, 9.6 mmol), and (1*S*,2*R*)-ephedrine hemihydrate (2.4 g, 14 mmol). A brown amorphous solid was isolated in 88% yield (1.7 g, 4.2 mmol). ^{1}H NMR ($CDCl_3$; 500 MHz): δ 1.29 (d, 3H, J = 7.2 Hz), 1.42 (t, 3H, J = 7.1 Hz), 2.64 (s, 3H), 4.15 (br s, 1H), 4.35 (q, 2H, J = 7.3 Hz), 4.47 (dq, 1H, J = 3.9, 6.8 Hz), 4.92 (t, 1H, J = 2 Hz), 7.20 (t, 1H, J = 7.2 Hz), 7.30−7.47 (m, 10H), 8.07 (d, 1H, J = 7.2 Hz). MS (ESI, pos. ion) *m*/*z*: 402 (M + 1); (ESI, neg. ion) 400 (M − 1). Anal. ($C_{25}H_{27}N_3O_2$) C, H. N.

Biological Assay. The radioligand binding assay and membrane preparation for the NPY5 receptor are described in ref 21. The functional (cAMP) assay is described here. Human embryonic kidney cells (HEK 293) expressing the human Y5 receptor were seeded into 96-well fibronectin coated plates to a density of 75 000 cells/well. Plates were used for assay roughly 48 h after seeding. To start the assay, cells were preequilibrated in 100 μL of cAMP buffer (145 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 10 mM HEPES, 10 mM Glucose, 0.5% BSA, 250 μM IBMX**,** pH 7.4) for 5 min at 37 °C, then preincubated again for 5 min at room temperature with different concentrations of test compound over six log units (final concentration from 0.1 to 10 000 nM). NPY (10 μL, final concentration 5 nM) and forskolin (10 μL, final concentration 10 μM) were added and incubated for 1 h at 37 °C in 5% CO_2. Intracellular cAMP was extracted with 0.2 N HCl at room temperature for 15 min and quantified by radioimmunoassay

(Amersham, RPA 542). Nonlinear regression analysis of concentration response curves to determine K_i values was performed using GraphPad Prizm.

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(22) Reported Ki's were derived from $n = 1$ values and should therefore not be taken as absolute determinations of compound activity, but merely demonstrations of ability to antagonize NPY inhibition of forskolin stimulated cAMP production. A more detailed experiment to determine a pA2 value would be needed to assess antagonist activity.

(23) Compounds **1**, **32**, **40a**, and **40b** were analyzed by chiral HPLC (Chiracel OJ 25 cm × 4.6 mm, 90:10:0.2 hexanes−ethanol−diethylamine, UV detection at 254 nm). All four of these compounds had an optical purity of ≥97%.

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